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A Novel Highly Effective Chiral Lithium Amide for Catalytic Enantioselective Deprotonation of *meso*-Epoxides

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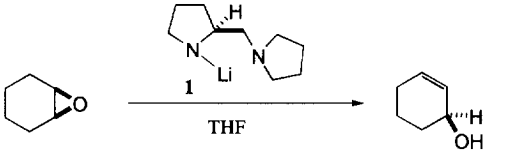
Abstract: A highly enantioselective deprotonation of *meso*-epoxides was achieved by a catalytic amount of a new chiral lithium amide, derived from (2*S*,3a*S*,7a*S*)-2-(pyrrolidin-1-ylmethyl)octahydroindole, in the presence of excess lithium diisopropylamide to afford the corresponding allylic alcohol derivatives up to 94% ee. © 1997 Elsevier Science Ltd.

Asymmetric reaction using chiral lithium amides has received much attention as a useful method for the preparation of non-racemic compounds from prochiral compounds.[1] In most cases, however, the procedures require more than a stoichiometric amount of chiral bases.[2] Thus, the development of an effective catalytic system using a chiral lithium amide is a significant challenge in synthetic organic chemistry since *N,N*-disubstituted lithium amide bases are widely employed in various synthetic reactions and a catalytic asymmetric reaction is of current interest.[3] We have been studying the enantioselective deprotonation of *meso*-epoxides using a chiral lithium amide, lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidide (**1**).[1d] The reaction was extended to a catalytic reaction using an excess of lithium diisopropylamide (LDA).[4] After the examination of the reaction conditions, the best result was obtained when the reaction was carried out using 20 mol% of **1** and 100 mol% of LDA in the presence of 6 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). However, the selectivity (75% ee) was still slightly lower than that achieved by using a stoichiometric amount of **1** (81% ee) in the reaction with cyclohexene oxide (eq. 1). DBU was found to be a crucial additive for the reaction, since the selectivity was decreased without DBU.



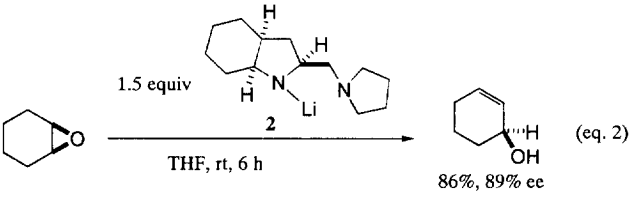
(eq. 1)

1.5 equiv **1** - 1.65 equiv DBU, rt, 12 h — 80%, 81% ee
20 mol% **1** - 100 mol% LDA - 6.0 equiv DBU, rt, 12 h — 71%, 75% ee

Herein we wish to report a novel chiral lithium amide **2**, prepared from (2*S*,3a*S*,7a*S*)-2-(pyrrolidin-1-ylmethyl)octahydroindole (**3**),[5] highly effective for the catalytic enantioselective deprotonation of *meso*-epoxides. The selectivity of the reaction was significantly improved and a high selectivity was achieved without an additive.

In our previous catalytic reaction, LDA was effective in regenerating **1** to afford (*S*)-2-cyclohexen-1-ol in 48% ee under the condition of 50 mol% of **1** and 150 mol% of LDA. However, lithium 2,2,6,6-tetramethylpiperidide (LTMP) in lieu of LDA afforded an almost racemic 2-cyclohexen-1-ol under the same conditions. This means that LDA is less reactive toward epoxides than **1**, while LTMP is more reactive than **1**. Thus it was anticipated that a bulkier chiral lithium amide would have a higher reactivity toward epoxides than **1**, and that it would show an interesting selectivity. Then we synthesized a new chiral diamine **3**, from (2*S*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid by the conventional method.[6] The pyrrolidin-1-yl substituent was selected on the basis of experimental results in our previous study using **1** and its derivatives.[6]

At the outset, we evaluated the new chiral lithium amide **2** in the stoichiometric deprotonation of cyclohexene oxide. The reaction was carried out in the presence of 1.5 equiv of **2**, prepared from **3** and butyllithium, in THF at rt for 6 h, and (*S*)-2-cyclohexen-1-ol was obtained in 86% yield with 89% ee (eq. 2). As the selectivity of the reaction was considerably enhanced compared with the case in which **1** was



used, we then applied **2** to the catalytic reaction. The results are summarized in Table 1. Initially, the reaction was carried out using 20 mol% of **2** and 180 mol% of LDA in THF at rt for 6 h, and (*S*)-2-cyclohexen-1-ol was obtained in high yield (95%) with almost the same ee (88% ee, Entry 1) as in the case where a stoichiometric amount of **2** was used. In contrast to the case in which **1** was used, when **2** was employed, the selectivity was decreased by the reaction using an additive such as hexamethylphosphoric triamide (HMPA), DBU, or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (*N*,*N*'-dimethylpropyleneurea, DMPU) (Entries 2–4). Next, the influence of the amount of **2** upon the ee of the product was examined. There was no change in the selectivity, even when the amount of **2** was reduced to 10 mol% (Entry 5). Relatively high ee was achieved with only 3-5 mol% of **2** (Entries 6-8). The reaction was then carried out at lower temperatures. Although the yield and the ee of the alcohol were not increased by the reaction at 0 °C using 10 mol% or 5 mol% of **2** (Entries 10,11), the selectivity was improved when the reaction was carried out at lower temperatures using 20 mol% of **2** (Entries 9,12,13). Finally, the reaction at 0 °C using 20 mol% of **2** afforded (*S*)-2-cyclohexen-1-ol of 94% ee in 89% yield (Entry 9).

As the high selectivity was achieved in the reaction with cyclohexene oxide employing the new chiral lithium amide **2**, we next examined the reaction of **2** with other *meso*-epoxides. With cyclooctene oxide, it was necessary to carry out the reaction at rt for 41 h using 20 mol% of **2** and 180 mol% of LDA to obtain

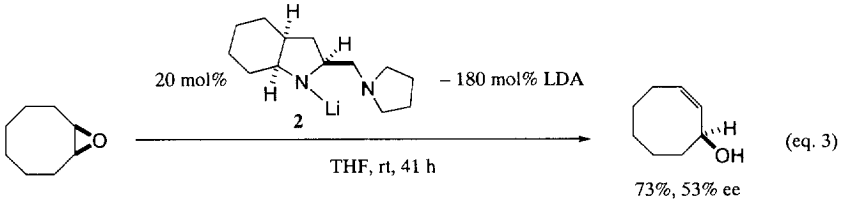
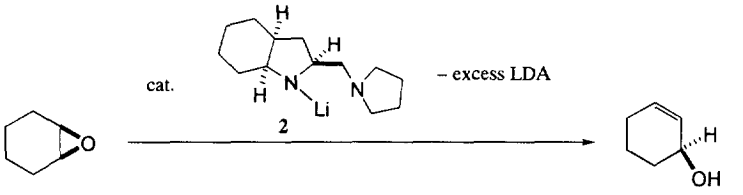


Table 1. Enantioselective Deprotonation of Cyclohexene Oxide by a Catalytic Amount of **2**[a]

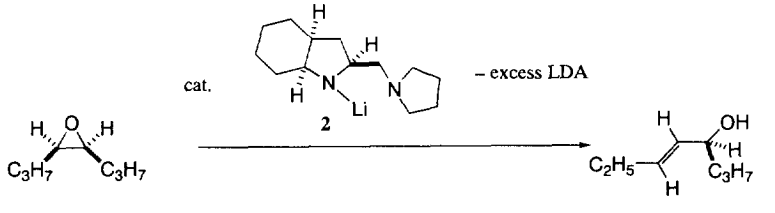


Entry	2/mol%	Temp.	Time/h	Yield/%[b]	Ee/%[c]
1	20	rt	6	95	88
2[d]	20	rt	6	66	76
3[e]	20	rt	6	68	78
4[f]	20	rt	6	74	80
5	10	rt	12	97	88
6	5	rt	12	93	85
7	3	rt	18	92	79
8	1	rt	18	74	60
9	20	0 °C	18	89	94
10	10	0 °C	24	74	89
11	5	0 °C	42	51	81
12	20	–5 °C	24	84	94
13	20	–15 °C	72	73	93

[a] The total amount of lithium amides (2+LDA) was 2.0 equiv to cyclohexene oxide. [b] Isolated yield after benzoylation. [c] Determined by HPLC analysis (Opti-Pak TA, Waters, Ltd.) of the benzoate ester of the product. [d] The reaction was carried out in the presence of 2.0 equiv of HMPA. [e] The reaction was carried out in the presence of 2.0 equiv of DBU. [f] The reaction was carried out in the presence of 2.0 equiv of DMPU.

(*S*)-2-cycloocten-1-ol in good yield (73%). The selectivity achieved was 53% ee (eq. 3).

The striking feature of the new lithium amide **2** is the high selectivity shown in the reaction with *meso*-epoxide prepared from acyclic olefin, for which only moderate selectivity was obtained using **1** (54%, 60% ee for (*Z*)-4-octene oxide). (*S*)-5-Octen-4-ol was obtained in 85% with 83% ee from (*Z*)-4-octene oxide when the reaction was carried out at rt for 24 h using 20 mol% of **2** and 180 mol% of LDA. Almost the same result was obtained even when the amount of **2** was reduced to 10 mol%. The selectivity was further improved to 86% ee by the reaction at 0 °C (84%, 20 mol% of **2**, 48 h) (eq. 4).



(eq. 4)

20 mol% **2** - 180 mol% LDA, rt, 24 h — 85%, 83% ee
10 mol% **2** - 190 mol% LDA, rt, 24 h — 85%, 82% ee
20 mol% **2** - 180 mol% LDA, 0 °C, 48 h — 84%, 86% ee

In summary, a novel chiral lithium amide **2** has been developed, and successfully employed in the catalytic enantioselective deprotonation of *meso*-epoxides. The high selectivity was achieved not only for cyclohexene oxide but also for epoxide prepared from acyclic olefin. Although the roles of the fused cyclohexane ring and the new chiral center adjacent to the reaction center have not yet been fully elucidated, both of them must have been effective for enhancing the reactivity and selectivity of the reagent. Further applications of this catalytic system to the enantioselective deprotonation of various *meso*-epoxides and other asymmetric reactions are now in progress .

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2. There have been two recent reports[1h,1j] on the catalytic enantioselective deprotonation by the use of chiral lithium amides other than our previous report.[4]
3. (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993.
4. Asami, M.; Ishizaki, T.; Inoue, S. *Tetrahedron: Asymmetry* **1994**, *5*, 793-796.
5. **3**: colorless viscous oil; bp (bulb-to-bulb distillation) 190–195 °C (oven temperature)/2.0 mmHg: $[\alpha]_D^{20}$ +2.09 (*c* 2.39, EtOH); IR (neat) ν: 2900, 2775, 1650, 1440, 1140, 870, 790 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.19–2.08 (m, 17H), 2.40–2.65 (m, 5H), 3.05 (dt, *J*=5.28, 5.28 Hz, 1H), 3.31 (m, 1H); ^{13}C-NMR (67.94 MHz, $CDCl_3$) δ: 64.5, 57.5, 56.6, 54.6, 38.0, 36.2, 29.6, 28.6, 23.6, 23.4, 22.2; Anal. Calcd for $C_{25}H_{30}N_8O_{14}$ (dipicrate of **3**; mp 170.6-171.8 °C): C, 45.05; H, 4.54; N, 16.81. Found; C, 44.83; H, 4.54; N, 16.59.
6. Asami, M. *Bull. Chem. Soc. Jpn.*, **1990**, *63*, 721-727.
7. A typical experimental procedure is as follows: To a mixture of diisopropylamine (1.8 mmol) and **2** (0.2 mmol) in THF (5 ml) was added a hexane solution (1.3 ml) of butyllithium (2.0 mmol) at 0 °C under an atmosphere of argon. After 0.5 h, cyclohexene oxide (1 mmol) in THF (2.5 ml) was added. The reaction mixture was stirred for 18 h at 0 °C, and saturated NH_4Cl was added to quench the reaction. The organic layer was washed with 1N HCl and brine, and was dried over $MgSO_4$. After the removal of the solvent at atmospheric pressure, crude 2-cyclohexen-1-ol was directly converted to the benzoate ester with benzoyl chloride (2.6 mmol), pyridine (4.9 mmol), and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine in dichloromethane (5.0 ml) at room temperature for 6 h. *N*,*N*-Dimethyl-1,3-propanediamine (0.5 ml) was added to the reaction mixture to destroy excess benzoyl chloride. After 0.5 h, water was added to the reaction mixture and the organic layer was washed with 1N HCl and brine. The organic layer was dried over anhydrous $MgSO_4$ and then concentrated *in vacuo*. The crude product was chromatographed on silica gel to give (*S*)-2-cyclohexenyl benzoate. The ee was determined by HPLC using a chiral column. Pure 2-cyclohexen-1-ol was obtained by the hydrolysis of the benzoate ester with sodium hydroxide in methanol.

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