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CYCLOPROPANE RING FORMATION THROUGH ENANTIOSELECTIVE DEPROTONATION OF C*s*-SYMMETRIC CYCLOHEPT-4-ENONE OXIDES

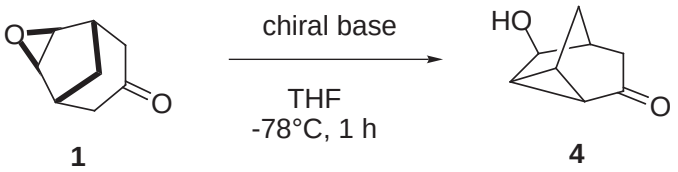
Hitoshi Abe,*,[a] Takenori Tsujino,[a] Daisuke Tsuchida,[a] Setsuo Kashino,[b] Yasuo Takeuchi,[a] and Takashi Harayama*,[a]

a) Faculty of Pharmaceutical Sciences, Okayama University, Okayama 700-8530, Japan
b) Department of Chemistry, Faculty of Science, Okayama University, Okayama 700-8530, Japan

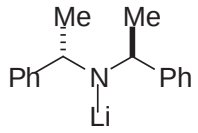
Abstract – Using a chiral lithium amide base, the asymmetric deprotonation reaction of C_S-symmetric cyclohept-4-enone oxides was examined to form an optically active cyclopropane compound.

Cyclopropanes are important compounds in organic chemistry because several classes of natural and non-natural products containing a cyclopropane ring exhibit biologically interesting activities, and because its highly reactive property based on its small ring strain can be utilized for various synthetic transformations.[1] Numerous methods for the enantioselective construction of the cyclopropane ring have been developed over the past decade.[2] The asymmetric Simons-Smith reaction,[3] as well as other carbenoid reactions using a diazo compound in the presence of both a chiral ligand and transition metal,[4] is one of the most popular scheme for the formation of optically active cyclopropane compounds. Enzymatic optical resolution is also useful for the large scale preparation of cyclopropane derivatives.[5]
As a unique method for cyclopropanation, although it is not an asymmetric version, the nucleophilic transannular C-C bond formation of cyclic epoxy ketone has been reported.[6] We considered that this method could be applied to the enantioselective preparation of ring-fused cyclopropane derivatives from prochiral epoxy ketones. Recently, the enantioselective deprotonation reaction of C_S-symmetric cyclic ketone with an optically active amide base has been well documented for non-racemic enolate formation.[7] In this report, we describe a novel asymmetric formation of a cyclopropane ring with *meso* epoxy ketone compounds by utilizing the enantioselective deprotonation strategy.
Using the C_S-symmetric epoxy ketone (**1**), we examined the asymmetric deprotonation with chiral amide bases (**2**) and (**3**) [8] to obtain the non-racemic keto alcohol (**4**) which had the newly formed C-C bond for the cyclopropane ring. These results are summarized in Table 1. When the chiral lithium amide (**2**) was used under salt-free conditions, **4** was formed in 66% yield with 22% ee (Entry 1). Fortunately, LiCl as an additive promoted the stereoselectivity, forming **4** in high ee (Entry 2). On the other hand, when chiral amide base (**3**) was employed in the presence of HMPA, only poor ee of the product was observed (Entry 3).

Table 1



1 **4**



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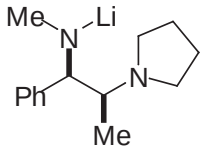

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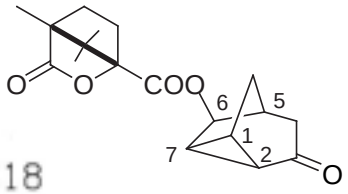
Entry	Base	Product	Yield (%)	ee (%)[a]
1	**2**	**4**	66	22
2	**2**[b]	**4**	71	88
3	**3**[c]	***ent*-4**	67	14

a) E.e (%) was determined by ^{1}H-NMR analysis of the corresponding (*R*)-MTPA ester.
b) LiCl was used as an additive.
c) HMPA was used as an additive.

In order to clarify the absolute configuration, **4** was converted to the (*S*)-camphanate (**5**), and an X-Ray analysis was carried out. As shown in Figure 1, it was found that the stereostructure of **4** was 1*S*, 2*S*, 5*S*, 6*S*, and 7*R* configuration.[9]

Figure 1. ORTEP drawing of (*S*)-camphanate **5**



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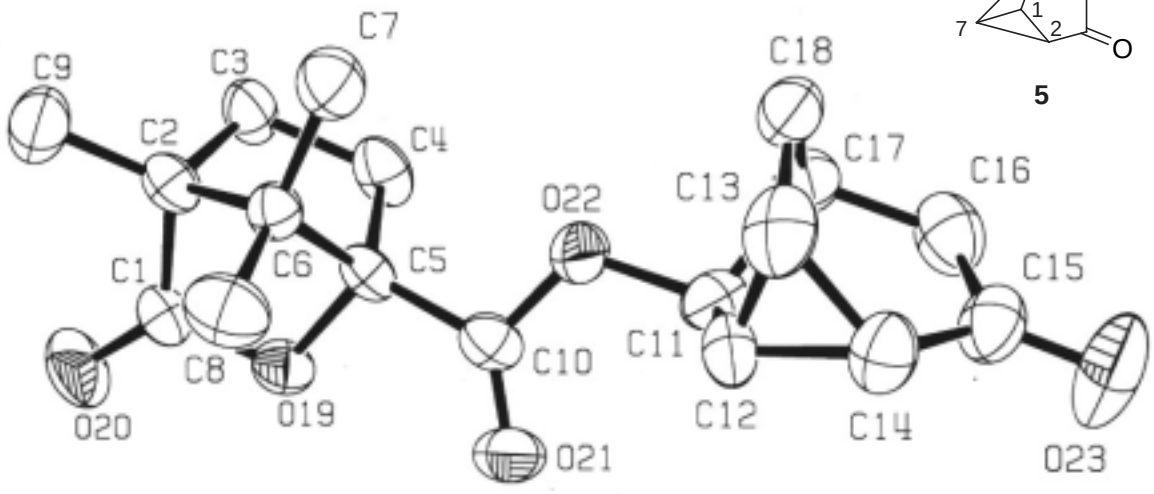
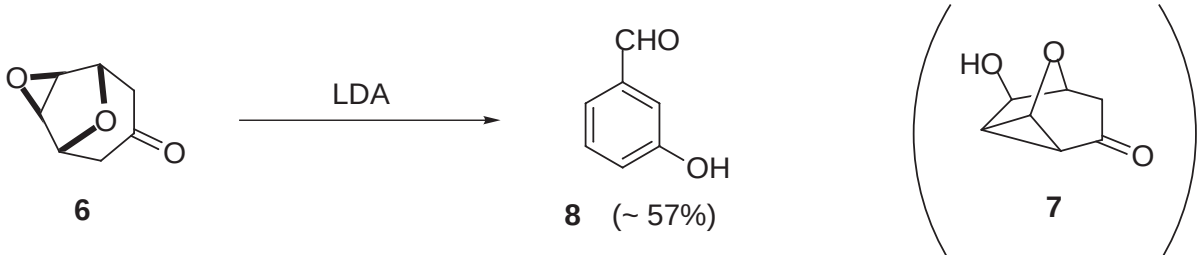


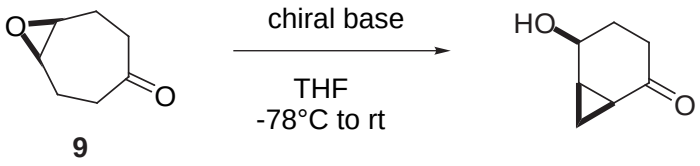
As a second substrate, we prepared the oxygen-bridged compound (**6**).[10] In our preliminary experiments, it was found that when LDA was employed as a base under various conditions, no desired product (**7**) was formed at all, but *m*-hydroxybenzaldehyde (**8**) was obtained in up to 57% yield (Scheme 1).[11]

Scheme 1



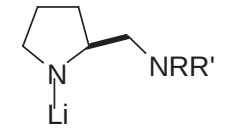
Finally, we examined a reaction of simple epoxy ketone (**9**), which was easily derived from cycloheptene-5-one[12] by treatment with *m*-CPBA. Although the chiral lithium amide bases (**2**, **3**, and **10**-**13**[13]) were attempted, high enantioselectivity was not observed in each reaction (Table 2). We considered, based on the results observed in Table 2, that conformational rigidity of the substrate is important for realizing a high stereoselectivity in this reaction.

Table 2

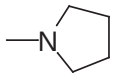


Entry	Base	Time (h)	Yield (%)	ee (%)[a, b]
1	**2**[c]	2	53	0
2	**3**[d]	6	12	7
3	**10**[d]	4	48	1
4	**11**[d]	4	61	3
5	**12**[d]	4	47	6
6	**13**[e]	21	34	8

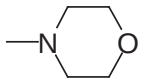
a) E.e (%) was determined by HPLC using chiral column (Daicel Chiralpak AD) after conversion to the corresponding benzoyl ester.
b) Absolute configuration was not determined.
c) LiCl was used as an additive.
d) HMPA was used as an additive.
e) No additive was used.

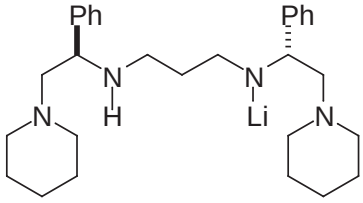


-NRR'

10: 

11: —NEt_2

12: 



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In conclusion, a novel enantioselective deprotonation reaction of C_S-symmetric cyclohept-4-enone oxides with a chiral lithium amide to form a cyclopropane ring was demonstrated. Good enantioselectivity was accomplished in the case of the conformationally rigid substrate. The oxygen-bridged substrate, however, gave no desired cyclopropane compound because it was easy to aromatize.

ACKNOWLEDGMENT

We are grateful to the SC-NMR Laboratory and the X-Ray Laboratory of Okayama University for the use of their facilities.

EXPERIMENTAL

General: Melting points were measured using a Yanagimoto micro melting point hot-plate apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 or FTIR-350 spectrophotometer. NMR spectra were taken with a Varian VXR-500 or VXR-200 instrument with the chemical shifts being reported as δ ppm and couplings expressed in Hertz. FAB-MS were obtained with a VG-70SE instrument using *m*-nitrobenzyl alcohol as the matrix. Silica gel column chromatography was carried out with Wako-gel C-200. Merck Silica-gel 60 F254 plates (No. 5744) were used for the preparative TLC. All reactions were carried out under argon atmosphere.

Substrates: Chiral amide bases (**3**,[8] **10**,[13a] **11**,[13a] **12**,[13a] and **13**[14]) were prepared by the literature methods. (*S*,*S*)-Bis(α-methylbenzyl)amine (NH amine of **2**, HCl salt) was purchased from Aldrich chemical company.

3-Oxatricyclo[3.3.1.0^{2,4}]nonan-7-one (**1**)

A mixture of bicyclo[3.2.1]oct-6-en-3-one[15] (94.1 mg, 0.770 mmol), *m*-chloroperoxybenzoic acid (*m*CPBA, 70-75%, 285 mg, *ca.* 1.16 mmol) and dry $CHCl_3$ (5 mL) was heated under reflux for 1 h. After cooling, the reaction mixture was washed with sat. aq. Na_2CO_3 (10 mL) and sat. aq. $Na_2S_2O_3$ (10 mL). The organic phase was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by silica gel column chromatography eluting with ether-hexane (1:1) to give **1** (107 mg, 99%) as colorless needles, mp 97-110°C (decomp) (CH_2Cl_2). IR ($CHCl_3$) cm^{-1}: 1710. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.41 (1H, d, *J* = 12.0), 1.73-1.79 (1H, m), 2.37-2.41 (2H, m), 2.45 (2H, dd, *J* = 4.0, 18.0), 2.61-2.64 (2H, m), 3.37 (2H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 27.5, 33.0, 44.1, 54.9, 209.3. *Anal.* Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.37; H, 7.17.

3,9-Dioxatricyclo[3.3.1.0^{2,4}]nonan-7-one (**6**)

A mixture of 8-oxabicyclo[3.2.1]oct-6-en-3-one[16] (2.12 g, 17.1 mmol), *m*CPBA, (70-75%, 4.42 g, *ca.* 17.9 mmol) and dry CH_2Cl_2 (50 mL) was heated under reflux for 11 h. After cooling, the reaction mixture was poured into sat. aq. Na_2CO_3 (100mL), and the precipitated materials were removed by filtration. The filtrate was extracted with CH_2Cl_2 and the organic phase was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by silica gel column chromatography eluting with ether-hexane (5:1) to give **6** (1.93 g, 81%) as colorless needles, mp 97-98.5°C (ethyl acetate) [lit.,[10] 93°C (CCl_4)]. IR ($CHCl_3$) cm^{-1}: 1720. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.37 (2H, d, *J* = 18.0), 2.73 (2H, dd, *J* = 5.5, 18.0), 3.63 (2H, s), 4.55 (2H, d, *J* = 5.5). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 43.0, 53.6, 70.8, 204.2. *Anal.* Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 59.85; H, 5.62.

8-Oxabicyclo[5.1.0]octan-4-one (**9**)

A mixture of cyclohept-4-enone[12] (5.13 g, 46.6 mmol), *m*CPBA, (70-75%, 12.8 g, *ca.* 51.9 mmol) and dry CH_2Cl_2 (200 mL) was stirred for 1 h at rt. The reaction mixture was poured into sat. aq. Na_2CO_3

and extracted with CH_2Cl_2. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by silica gel column chromatography eluting with ethyl acetate-hexane (1:2) to give **9** (4.14 g, 71%) as a colorless oil, bp 76-78°C / 1.0 mmHg. IR (neat) cm^{-1}: 1700. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.13-2.18 (4H, m), 2.28 (2H, ddd, *J* = 5.5, 6.5, 14.5), 2.48 (2H, ddd, *J* = 6.0, 7.5, 14.5), 3.15-3.18 (2H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 23.4, 37.7, 55.0, 212.3. FAB-MS *m/z*: 149 $(M+Na)^+$. *Anal.* Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.57; H, 8.00.

Typical procedure for asymmetric deprotonation reaction (**Table 1**, **Entry 2**)

n-BuLi (1.48 M solution in hexane, 743 μL, 1.10 mmol) was added to a stirred solution of (*S*,*S*)-bis(α-methylbenzyl)amine hydrochloride (154.5 mg, 0.590 mmol) in dry THF (3 mL) at 0°C. After 30 min, the mixture was cooled to -78°C. A solution of **1** (54.3 mg, 0.393 mmol) in THF (4 mL) was added dropwise *via* cannula. After 1 h, the reaction mixture was neutralized by addition of acetic acid, and then passed through a short column of florisil with ether as an eluent. The combined elution was evaporated *in vacuo* to give a residue which was purified by silica gel column chromatography. Elution with ether afforded **4** (38.4 mg, 71%, 88% ee) as colorless prisms.

In a large scale examination, **4** (1.10 g, 63%, 80% ee) was obtained from **1** (1.75 g, 12.7 mmol) by a similar way described above.

(1*S*, 2*S*, 5*S*, 6*S*, 7*R*)-6-Hydroxytricyclo[3.2.1.0^{2,7}]octan-3-one (**4**): Colorless prisms, mp 56.5-59°C (Et_2O). $[\alpha]_D^{26}$ = -6.17° (c 1.00, $CHCl_3$) [80% ee]. IR ($CHCl_3$) cm^{-1}: 3400, 1690. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.68 (1H, d, *J* = 12.5), 1.88 (1H, t, *J* = 7.5), 2.07 (2H, d, *J* = 3.0), 2.11-2.20 (3H, m), 2.34 (1H, ddd, *J* = 3.0, 5.0, 12.5), 4.13 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 22.8, 28.0, 28.8, 33.7, 35.3, 41.8, 74.5, 208.6. *Anal.* Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.70; H, 7.45.

3-Hydroxybenzaldehyde (**8**): Pale yellow needles, mp 104.5-106°C (ethyl acetate). This compound is known (commercially available).

5-Hydroxybicyclo[4.1.0]heptan-2-one: Pale yellow oil. The data of this compound were previously reported.[17]

(1*S*, 2*S*, 5*S*, 6*S*, 7*R*)-6-Tricyclo[3.2.1.0^{2,7}]octan-3-on-6-yl (-)-camphanate (**5**)

(-)-Camphanic acid (1.65 g, 8.32 mmol) and DMAP (132 mg, 1.08 mmol) were added to a solution of **4** (80% ee, 768 mg, 5.56 mmol) in dry CH_2Cl_2 (80 mL). The mixture was cooled to 0°C, then DCC (2.29 g, 11.1 mmol) was added. The reaction mixture was stirred for 2 h at rt and the solvent was evaporated off. Purification by silica gel column chromatography eluting with hexane-ether (1:5) afforded **5** (80% de, 1.77 g, 100%) as colorless prisms which was recrystallized from CH_2Cl_2-pentane, mp 162-163.5°C. $[\alpha]_D^{27}$ = -51.2° (c 1.23, $CHCl_3$) [87% de]. IR (KBr) cm^{-1}: 2960, 2940, 2880, 1790, 1750, 1700, 1170, 1110. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.97 (3H, s), 1.07 (3H, s), 1.13 (3H, s), 1.71 (1H, ddd, *J* = 4.0, 9.5, 13.5), 1.75 (1H, d, *J* = 11.5), 1.94 (1H, ddd, *J* = 4.5, 10.5, 13.5), 1.97 (1H, t, *J* = 7.5), 2.06 (1H, ddd, *J* = 4.5, 9.5, 13.5), 2.13 (1H, dd, *J* = 4.0, 19.0), 2.19-2.34 (5H, m), 2.44 (1H, ddd, *J* = 4.0, 10.5, 13.5), 5.15 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 9.5, 16.5, 16.6, 22.6, 25.7, 28.6, 28.7, 30.4, 33.2, 33.4, 41.5, 54.2, 54.6, 78.6, 90.7, 166.9, 177.9, 205.6. FAB-MS *m/z*: 319 $(M+1)^+$. *Anal.*

Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.84; H, 7.12. Crystal data: $C_{18}H_{22}O_5$, M = 318.37, orthorhombic, *a* = 10.969 (3), *b* = 20.531 (4), *c* = 7.201 (2) Å, *V* = 1621.7 (6) $Å^3$, *T* = 298 K, space group $P2_12_12_1$, *Z* = 4, μ(Mo-Kα) = 0.094 mm^{-1}. Of the 2872 reflections which were collected, 2172 were unique (R_{int} = 0.049). Least-squares refinements were carried out by fixing the H atom parameters and using 1803 reflections with $I > 0.01\sigma(I)$. The final *R* = 0.073, *wR* (F^2) = 0.084.

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