Asymmetric Trasformation of Symmetrical Epoxides to Allylic Alcohols by Lithium (*S*)-2-(*N*,*N*-Disubstituted aminomethyl)pyrrolidide

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Enantioselective deprotonation of symmetrical epoxides was studied by using chiral lithium amide, prepared from (*S*)-2-(*N*,*N*-disubstituted aminomethyl)pyrrolidine and butyllithium. Chiral allylic alcohols were obtained with moderate to high enantiomeric excesses (ee's) (41—92% ee) from several cyclic and acyclic epoxides employing lithium (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidide in tetrahydrofuran (THF) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Asymmetric synthesis is a potentially direct and effective method for the construction of chiral framework and extensive effort has been devoted to find new and efficient methodology.[1,2] Asymmetric reactions are classified into six categories, that is enantioface-, enantiotopos-, enantiomer-, diastereoface-, diastereotopos-, and diastereomer-differentiating reaction, according to the classification proposed by Izumi and Tai.[2] Most of highly stereoselective asymmetric reactions reported to date are classified into diastereoface- or enantioface-differentiating reaction and only a limited number of highly diastereotopos- or enantiotopos-differentiating reactions are known[3,5c,6e,f,i,7] leaving asymmetric reactions using enzymes out of account.

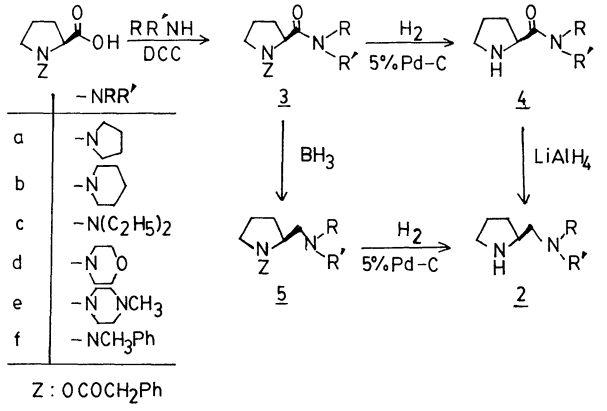
We have been studying highly stereoseletive asymmetric reactions by the use of chiral diamines prepared from (*S*)-proline based on the fundamental idea of using conformationally restricted cis-fused five-membered ring structure in asymmetric raction,[4] and developed highly enantioface-,[5a] and diastereoface-[5b] differentiating reactions. Furthermore, a highly diastereotopos-differentiating reaction was also achieved by using (*R*)-2-amino-2-phenylethanol.[5c]

Thus we started to explore the selective deprotonation of enantiotopically related protons in symmetrical epoxides leading to chiral allylic alcohols using chiral lithium amide as an example of the enantiotopos-differentiating reaction. Such type of the reaction was first reported by Whitesell and Felman in 1980 only for cyclohexene oxide, but the selectivity was not high (≤31% enantioneric excess (ee)).[6a] In 1984 we found that lithium (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidide (**1a**) showed high selectivity for cyclohexene oxide,[7a] and the reaction was further extended to other symmetrical epoxides.[7b] Herein we describe the results in detail.

Results and Discussion

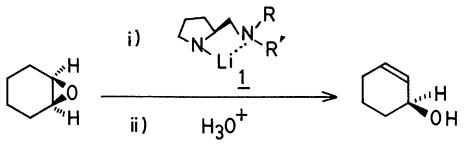
Chiral diamines, (*S*)-2-(*N*,*N*-disubstituted aminomethyl)pyrrolidine (**2a—f**) employed in the present study are derived from commercially available (*S*)-*N*-(benzyloxycarbonyl)proline (Scheme 1). (*S*)-*N*-(Benzyloxycarbonyl)proline was coupled with several kinds of amines using dicyclohexylcarbodiimide (DCC) as the condensing reagent in dichloromethane to afford corresponding amides (**3a—f**), respectively. Catalytic hydrogenolysis of **3a—e** under a hydrogen atmosphere in the presence of catalytic amount of 5% Pd–C in methanol gave *N*,*N*-disubstituted (*S*)-prolinamides (**4a—e**), which were then reduced with lithium aluminium hydride ($LiAlH_4$) to give chiral diamines **2a—e**. Chiral diamine **2f** was prepared by selective reduction of amide carbonyl of **3f** with diborane to (*S*)-1-benzyloxycarbonyl-2-(*N*-methylanilinomethyl)pyrrolidine (**5f**) followed by removal of benzyloxycarbonyl group by catalytic hydrogenolysis, because (*S*)-prolinol was obtained as a major product by the reduction of (*S*)-*N*-methylprolinanilide (**4f**) with $LiAlH_4$.

In the first place, the asymmetric transformation of cyclohexene oxide was examined using chiral lithium amide **1a—f**, prepared in situ from diamine **2a—f** and butyllithium. The reaction was carried out as follows: To a tetrahydrofuran (THF) solution of diamine **2** (3.3 mmol) was added a hexane solution of butyllithium (3.0 mmol) at 0 °C. After 30 min, the reaction mixture was cooled to −78 °C and a THF solution of cyclohexene oxide (2.0 mmol) was added. The reaction temperature was gradually warmed to room temperature and the reaction mixture was stirred



Scheme 1.

Table 1. Asymmetric Transformation of Cyclohexene Oxide by Chiral Lithium Amides **1a—f**[a]



	Diamine	Yield/%[b]	$[\alpha]_D$ (temp, $c(CHCl_3)$)	ee/%
1	**2a**	78	−100.8° (18, 0.65)	90(*S*)[c]
2	**2b**	71	−90.6° (20, 0.61)	81(*S*)[c]
3	**2c**	69	−93.3° (18, 0.61)	83(*S*)[c]
4	**2d**	70	−95.9° (17, 0.61)	86(*S*)[c]
5	**2e**	67	−76.3° (17, 0.60)	68(*S*)[c]
6	**2f**	55	−53.0° (18, 0.54)	47(*S*)[c]

a) The reaction was carried out using 1.5 equivalent of chiral lithium amide **1** in THF at −78 °C to room temperature overnight. b) Isolated yield as 2-cyclohexenyl benzoate. c) Absolute configuration.

Table 2. Effects of Solvent and Reaction Temperature on Asymmetric Transformation of Cyclohexene Oxide by Lithium Amide **1a**[a]

	Solvent	Yield/%[b]	$[\alpha]_D$ (temp, $c(CHCl_3)$)	ee/%
1	THF	78	−100.8° (18, 0.65)	90
2	THF[c]	77	−102.6° (20, 0.61)	92
3	Ether	71	−62.1° (18, 0.95)	55
4	DME	72	−89.0° (18, 1.05)	71
5	Benzene[d]	29	−24.8° (28, 0.60)	22

a) The reaction was carried out using 1.5 equiv of **1a** at −78 °C to room temperature overnight unless otherwise noted. b) Isolated yield as 2-cyclohexenyl benzoate. c) The reaction was carried out at 0 °C to room temperature. d) The reaction was carried out under reflux for 2 h.

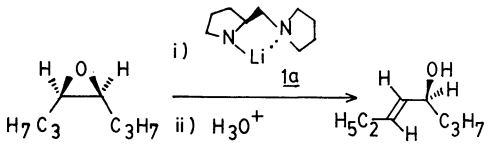
overnight. After the reaction mixture was worked up in usual manner (see Experimental section), the resulting alcohol was converted to 2-cyclohexenyl benzoate to determine the yield. The absolute configuration and ee were determined by comparing the optical rotation of 2-cyclohexen-1-ol with reported value[8] ($[\alpha]_D$ −112° (*c* 0.6, $CHCl_3$) for optically pure (*S*)-2-cyclohexen-1-ol) after hydrolysis of the benzoate and bulb-to-bulb distillation. High selectivity was achieved in cases the diamine **2a**, **2b**, **2c**, or **2d** was used while the selectivity decreased when the diamine **2e** or **2f** was used as shown in Table 1.

Next, the effect of the reaction solvent and temperature on the selectivity was examined. The transformation of cyclohexene oxide was carried out in THF, ether, 1,2-dimethoxyethane (DME), and benzene using **1a** as chiral lithium amide. As shown in Table 2, THF gave the best result. The reaction was supposed to take place near room temperature because the similar result was obtained even when the reaction was carried out at 0 °C to room temperature in THF (Entry 2). The reaction did not proceed at room temperature when benzene was used as solvent, thus the reaction mixture was refluxed for 2 h. The reaction, however, gave poor yield (29%) and poor selectivity (22% ee).

As high selectivity was actually realized for cyclohexene oxide, the reaction was applied to an acyclic symmetrical epoxide, (*Z*)-4-octene oxide. (*E*)-5-Octen-4-ol[9] was obtained in 52% yield using chiral lithium amide **1a** in refluxing THF for 2 h. The ee of the alcohol was determined to be 52% by ^1H NMR spectrum of the corresponding acetate using tris[3-heptafluorobutyryl-*d*-camphorato]europium(III) (Eu(hfbc)$_3$) as chiral shift reagent. The absolute configuration was determined by the conversion of the alcohol to (*S*)-1,2-pentanediol ($[\alpha]_D^{30}$ −8.66° (*c* 3.65, EtOH); lit,[10] $[\alpha]_D^{20}$ +16.2° (*c* 8.00, C_2H_5OH) for (*R*)-1,2-pentanediol) by benzoylation followed by oxidative cleavage of the double bond and reduction with $LiAlH_4$. Then several kinds of additives which coordinate to the lithium cation of lithium amide **1a** were examined to improve the ee. Bicyclic amidine bases, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), were effective and the ee was increased to 60%. The results are summarized in Table 3.

Then the reaction was applied to (*Z*)-2-butene oxide, cyclopentene oxide, and cyclooctene oxide using **1a** in THF in the presence of DBU. As shown in Table 4, all epoxides examined gave the corresponding alcohol having *S*-configuration with moderate to good selectivities (41—70% ee). In the case of cyclopentene oxide, the reaction was carried out in refluxing THF for 1.5 h as the reaction did not proceed at room temperature.

Table 3. Asymmetric Transformation of (*Z*)-4-Octene Oxide by Lithium Amide **1a** in the Presence of Additive[a)]



	Additive	Yield/%[b)]	$[\alpha]_D$ (temp, c($CHCl_3$))	ee/%
1	—	52	−2.76° (29, 3.30)	52
2	Pyridine	63	−3.33° (31, 3.24)	56
3	$(C_2H_5)_3N$	66	−3.39° (31, 3.36)	56
4	TMEDA[c)]	64	−3.32° (30, 3.28)	56
5	HMPA[d)]	59	−2.67° (29, 3.75)	50
6	DBN	66	−3.53° (30, 3.40)	58
7	DBU	64	−3.53° (29, 3.23)	60
8	DBU[e)]	66	−3.63° (28, 2.96)	60

a) The reaction was carried out using 1.5 equivalent of lithium amide **1a** and additive in THF under reflux for 1—3 h unless otherwise noted. b) Isolated yield. c) *N,N,N′,N′*-Tetramethylethylenediamine. d) Hexamethylphosphoric triamide. e) The reaction was carried out at room temperature overnight.

Table 4. Asymmetric Transformation of Symmetrical Epoxides by Lithium Amide **1a**[a)]

	Epoxide	Yield/%	ee/%
1	(*Z*)-4-Octene oxide	66[b)]	60(*S*)[c)]
2	(*Z*)-2-Butene oxide	60[d)]	72(*S*)[c)]
3	Cyclopentene oxide[e)]	53[d)]	41(*S*)[c)]
4	Cyclooctene oxide	45[b,f)]	58(*S*)[c)]
5	Cyclooctene oxide[e)]	84[b)]	50(*S*)[c)]

a) The reaction was carried out using 1.5 equivalent of chiral lithium amide **1a** and DBU in THF at room temperature overnight unless otherwise noted. b) Isolated yield. c) Absolute configuration. d) Isolated yield after benzoylation. e) The reaction was carried out under reflux for 2 h. f) Cyclooctene oxide was recovered (50%).

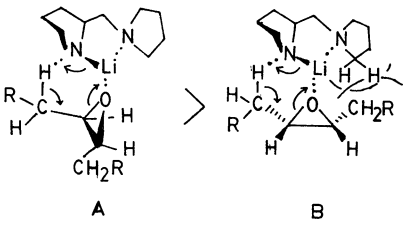


Fig. 1. Transition states model for the reaction by chiral lithium amide **1a**.

2-Cycloocten-1-ol was obtained in 45% yield with 58% ee and 50% of the starting material was recovered by the reaction of cyclooctene oxide at room temperature overnight (Entry 4). The yield was improved to 84% when the reaction was carried out in refluxing THF for 2 h, but ee decreased to 50% (Entry 5). The ee's and absolute configurations were determined as follows, respectively. 3-Buten-2-ol was converted to 1,2-propanediol by benzoylation followed by ozonolysis and reduction with $LiAlH_4$. The absolute configuration and ee were determined by comparing its optical rotation ($[\alpha]_D^{27}$ +14.5° (*c* 2.4, H_2O)) with the reported value[11] ($[\alpha]_D^{23}$ +20.1° (*c* 7.5, H_2O) for (*S*)-1,2-propanediol). For 2-cyclopenten-1-ol and 2-cycloocten-1-ol, ee's were determined by the conversion to the corresponding acetates and measurements of their ^1H NMR spectra using Eu(hfbc)$_3$ as chiral shift reagent. The absolute configurations were determined by comparing optical rotations of the alcohols and the acetates with literature values.[12–15]

We assume the following stereochemical course for this asymmetric reaction as all epoxides examined gave alcohols having *S*-configuration preferentially. Conformationally restricted cis-fused five-membered ring structure is formed in chiral lithium amide **1** by an intramolecular chelation of the nitrogen atom on the side chain to the lithium cation. The rigid structure will play an important role to achieve high selectivity, and less selectivity with diamine **2f** may be attributed to less basicity of the nitrogen atom on the side chain. Two transition states depicted in Fig. 1 are possible for the reaction as lithium amide promoted transformation of epoxides to allylic alcohols is supposed to proceed in a cyclic concerted manner.[16] Transition state **B** is disfavored because of steric interaction between chiral lithium amide **1a** and epoxide, so that the alcohols having *S*-configuration are obtained via transition state **A**. The additive may serve to increase the steric interaction between chiral lithium amide **1a** and epoxide in transition state **B** by coordinating to the lithium cation.

Although a few studies of enatioselective deprotonation of enantiotopic protons in symmetrical compounds have been reported using chiral lithium amides,[6a,e,f,i)] none of those has succeeded in realizing selectivity for acyclic compounds. It is noteworthy

that enantioselective deprotonation of acyclic symmetrical epoxides as well as cyclic ones has been achieved with moderate to high selectivities (41—92%) by chiral lithium amide **1a**.

Experimental

General. Melting and boiling points are uncorrected. ^{1}H NMR spectra were recorded on a Hitachi R-24B spectrometer with tetramethylsilane as internal standard. IR spectra were taken on a Shimadzu IR-440 spectrophotometer. High-resolution mass spectra were obtained on a Hitachi M-80 GC-MC spectrometer operating with an ioniztion energy (70 eV). Optical rotations were measured on a JASCO DIP-SL or a JASCO DIP-181 polarimeter. All solvents used were purified according to the standard procedure.

Preparation of *N,N*-Disubstituted N^{α}-(Benzyloxycarbonyl)-prolinamide (3). To a dichloromethane (30 ml) solution of (*S*)-*N*-(benzyloxycarbonyl)proline (24.9 g, 100 mmol) was added a dichloromethane (60 ml) solution of DCC (20.6 g, 100 mmol) at 0 °C under a nitrogen atmosphere. After stirring for 30 min, a dichloromethane (40 ml) solution of amine (100 mmol) was slowly added to the mixture at 0 °C and the mixture was slowly warmed to room temperature and further stirred overnight. After removal of the precipitate by filtration, the filtrate was washed successively with 2% HCl solution, 4% $NaHCO_3$ solution, water, and brine and dried over anhyd Na_2SO_4. The solvent was evaporated in vacuo, and the crude product was purified by recrystallization or column chromatography to afford **3**. The treatment with 2% HCl solution was omitted in the preparation of **3e**.

(*S*)-1-[*N*-(Benzyloxycarbonyl)prolyl]pyrrolidine (3a): Yield 63%; mp 130—132 °C (ethyl acetate)(lit,[17] 130—133 °C (acetone)); $[\alpha]_D^{29}$ −13.0° (*c* 1.67, CH_3OH)(lit, [17] $[\alpha]_D^{22}$ −14.1° (*c* 1.61, CH_3OH)); IR(KBr): 2950, 2880, 1710, 1640, 1415, 1355, 1125, 1090, 765, 735, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.4—2.1 (m, 8H), 3.1—4.1 (m, 6H), 4.2—4.7 (m, 1H), 4.8—5.4 (m, 2H), and 7.32 (d, 5H). Found: C, 67.24; H, 7.25; N, 9.25%. Calcd for $C_{17}H_{22}O_3N_2$: C, 67.32; H, 7.33; N, 9.27%.

(*S*)-1-[*N*-(Benzyloxycarbonyl)prolyl]piperidine (3b): Yield 63%; mp 90—91 °C (ethyl acetate); $[\alpha]_D^{29}$ −14.3° (*c* 2.00, C_2H_5OH); IR(KBr): 2940, 2890, 2860, 1705, 1640, 1440, 1420, 1350, 1130, 770, 740, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.1—2.5 (m, 10H), 3.1—3.9 (m, 6H), 4.5—5.0 (m, 1H), 5.0—5.3 (m, 1H), and 7.30 (d, 5H). Found: C, 68.23; H, 7.63; N, 8.95%. Calcd for $C_{18}H_{24}O_3N_2$: C, 68.33; H, 7.65; N, 8.85%.

(*S*)-*N,N*-Diethyl-N^{α}-(benzyloxycarbonyl)prolinamide (3c): Yield 52%; viscous oil (silica gel/ethyl acetate); $[\alpha]_D^{29}$ −20.0° (*c* 2.30, C_2H_5OH); IR(neat): 2950, 2870, 1705, 1690, 1660, 1640, 1410, 1350, 1255, 1115, 765, 735, and 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.7—2.6 (m, 10H), 2.7—2.9 (m, 6H), 4.2—4.8 (m, 1H), 4.9—5.2 (m, 2H), and 7.30 (s, 5H). Found: *m/z* 304.1760. Calcd for $C_{17}H_{24}O_3N_2$: M, 304.1785.

(*S*)-4-[*N*-(Benzyloxycarbonyl)prolyl]morpholine (3d): Yield 73%; mp 141—142 °C (ethyl acetate); $[\alpha]_D^{28}$ −16.5° (*c* 2.00, C_2H_5OH); IR (KBr): 2950, 2840, 1690, 1640, 1420, 1350, 1265, 1230, 1105, 765, 735, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.6—2.4 (m, 4H), 3.0—4.0 (m, 10H), 4.3—4.9 (m, 1H), 4.9—5.3 (m, 2H), and 7.27 (s, 5H). Found: C, 64.00; H, 6.94; N, 8.79%. Calcd for: $C_{17}H_{22}O_4N_2$: C, 64.13; H, 6.97; N, 8.80%.

(*S*)-4-Methyl-1-[*N*-(benzyloxycarbonyl)prolyl]piperazine (3e): Yield 53%; mp 92—93 °C (ethyl acetate–hexane); $[\alpha]_D^{29}$ −11.0° (*c* 2.00, C_2H_5OH); IR (KBr): 2990, 2940, 2890, 2790, 1695, 1440, 1410, 1350, 765, 735, and 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.6—2.9 (m, 11H), 3.1—3.9 (m, 6H), 4.4—4.9 (m, 1H), 4.9—5.3 (m, 2H), and 7.30 (d, 5H). Found: C, 65.15; H, 7.59; N, 12.39%. Calcd for $C_{18}H_{25}O_3N_3$: C, 65.23; H, 7.60; N, 12.68%.

(*S*)-*N*-Methyl-N^{α}-(benzyloxycarbonyl)prolinanilide (3f): Yield 71%; viscous oil (silica gel/ether); $[\alpha]_D^{29}$ +123.6° (*c* 2.10, C_2H_5OH); IR (neat) 3030, 2940, 2860, 1720, 1705, 1690, 1660, 1590, 1400, 1340, 1110, 760, 700, and 600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.5—2.2 (m, 4H), 3.14 (d, 3H), 3.3—3.8 (m, 2H), 3.8—4.5 (m, 1H), 5.0—5.2 (m, 2H), and 7.33 (s, 5H). Found: *m/z* 338.1635. Calcd for $C_{20}H_{22}O_3N_2$: M, 338.1629.

Preparation of (*S*)-2-(*N,N*-Disubstituted aminomethyl)-pyrrolidine (2a—e). *N,N*-Disubstituted (*S*)-*N*-(benzyloxycarbonyl)prolinamide **3a—e** (70 mmol) and 5% Pd–C catalyst (1.3 g) were stirred vigorously in methanol (100 ml) under a hydrogen atmosphere overnight. Then the reaction mixture was filtered through celite and the filtrate was concentrated in vacuo to give crude *N,N*-disubstituted (*S*)-prolinamide (**4a—e**) as viscous oil. Crude **4a—e** in THF (75 ml) was slowly added to a THF (75 ml) suspension of $LiAlH_4$ (9.1 g, 240 mmol) at 0 °C under a nitrogen atmosphere and the mixture was refluxed for 20 h. Then saturated Na_2SO_4 solution was added to the mixture at 0 °C. After removal of the inorganic material by decantation and removal of the solvent in vacuo, fractional distillation under reduced pressure afforded **2a—e** as colorless oil.

(*S*)-2-(1-Pyrrolidinylmethyl)pyrrolidine (2a): Yield 69%; bp 84 °C/5 mmHg (lit,[18] 99—101 °C/12 mmHg; 1 mmHg= 133.322 Pa); $[\alpha]_D^{29}$ +8.2° (*c* 2.38, C_2H_5OH) (lit,[18] $[\alpha]_D^{20}$ +8.5 ° (*c* 2.40, C_2H_5OH)); IR (neat): 3250, 2950, 2860, 2780, 1460, 1400, 1345, 1310, 1290, 1140, and 870 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.0—2.1 (m, 8H), 1.96 (s, 1H), and 2.1—3.4 (m, 9H). Compound **2a** gave a dipicrate which showed mp 168—170 °C (lit,[18] 170 °C). Found: C, 41.03; H, 3.95; N, 18.28%. Calcd for $C_{21}H_{24}O_{14}N_8$: C, 41.18; H, 3.95; N, 18.30%.

(*S*)-2-(Piperidinomethyl)pyrrolidine (2b): Yield 69%; bp 95 °C/6 mmHg (lit,[19] 100 °C/1 mmHg); $[\alpha]_D^{30}$ +18.6° (*c* 9.85, C_2H_5OH), $[\alpha]_D^{28}$ +19.1° (*c* 1.04, C_2H_5OH) (lit,[19] $[\alpha]_D^{25}$ +14° (*c* 10, C_2H_5OH)); IR (neat): 3300, 2940, 2850, 2800, 1440, 1300, 1155, 1120, 1040, 860, and 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.0—2.0 (m, 10H), 2.0—3.0 (m, 9H), and 3.22 (t, 1H, *J*=6 Hz). Compound **2b** gave a dipicrate which showed mp 153—155 °C. Found: C, 41.98; H, 4.12; N, 17.72%. Calcd for $C_{22}H_{26}O_{14}N_8$: C, 42.17; H, 4.18; N, 17.89%.

(*S*)-2-(Diethylaminomethyl)pyrrolidine (2c): Yield 61%; bp 68 °C/7 mmHg (lit,[18] 103—105 °C/56 mmHg); $[\alpha]_D^{28}$+ 14.5° (*c* 1.10, C_2H_5OH) (lit,[18] $[\alpha]_D^{20}$ +13.4° (*c* 1.14, C_2H_5OH)): IR (neat): 3300, 2960, 2860, 2800, 1450, 1380, 1285, 1200, 1150, 1060, and 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.00 (t, 6H, *J*=7 Hz), 1.2—2.0 (m, 4H), 2.14 (s, 1H), 2.36 (q, 4H, *J*=7 Hz), and 2.0—3.4 (m, 5H). Compound **2c** gave a dipicrate which showed mp 133—134 °C. Found: C, 41.01; H, 4.25; N, 18.00%. Calcd for $C_{21}H_{26}O_{14}N_8$: C, 41.04; H, 4,26; N, 18.24%.

(*S*)-2-(Morpholinomethyl)pyrrolidine (2d): Yield 57%; bp 106 °C/7 mmHg; $[\alpha]_D^{30}$ +17.6° (*c* 9.98, C_2H_5OH), $[\alpha]_D^{27}$ +17.8° (*c* 1.28, C_2H_5OH) (lit,[19] $[\alpha]_D^{25}$ +10.4° (*c* 10, C_2H_5OH)): IR (neat): 3300, 2940, 2840, 2800, 1435, 1285, 1265, 1135, 1115, 1100, 910, and 860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.0—2.0 (m,

4H), 2.0—2.6 (m, 7H), 2.6—3.1 (m, 2H), 3.20 (t, 1H, J=7 Hz), and 3.60 (t, 4H, J=5 Hz). Compound **2d** gave a dipicrate which showed mp 170—171 °C. Found: C, 39.95; H, 3.83; N, 17.92%. Calcd for $C_{21}H_{24}O_{15}N_8$: C, 40.13; H, 3.85; N, 17.83%.

(*S*)-2-[(4-Methyl-1-piperazinyl)methyl]pyrrolidine (2e): Yield 55%; bp 117 °C/8 mmHg; $[\alpha]_D^{27}$ +17.8° (c 1.28, C_2H_5OH); IR (neat): 3250, 2920, 2850, 2790, 1450, 1365, 1290, 1160, 1140, 1100, 1010, 920, and 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.1—2.1 (m, 4H), 2.1—3.2 (m, 9H), 2.23 (s, 3H), and 3.20 (t, 1H, J=6 Hz). Compound **2e** gave a tripicrate which showed mp 241—243 °C. Found: C, 38.50; H, 3.48; N, 19.06%. Calcd for $C_{28}H_{30}O_{21}N_{12}$: C, 38.62; H, 3.47; N, 19.31%.

(*S*)-2-(*N*-Methylanilinomethyl)pyrrolidine (2f). To a THF (5 ml) solution of diborane (5.0 mmol) was added a THF (4 ml) solution of **3f** (1.015 g, 3.0 mmol) at 0 °C. After refluxing for 1 h, 2 M (M=mol dm^{-3}) HCl (3 ml) was added to the reaction mixture and THF was removed. Sodium hydroxide was added until the solution became alkaline and the mixture was extracted with ether. After removal of the solvent, the resulting viscous oil (crude **5f**) and 5% Pd–C catalyst (0.2 g) were stirred vigorously in methanol (5 ml) under a hydrogen atmosphere overnight. Then the reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. The resulting oil was purified by bulb-to-bulb distillation to afford (*S*)-2-(*N*-methylanilinomethyl)pyrrolidine **2f** (0.435 g, 76%) as a slightly yellow oil: bp 190 °C (oven temperature)/1.2 mmHg; $[\alpha]_D^{26}$ +3.1° (c 1.07, C_2H_5OH); IR (neat): 3300, 3080, 3040, 3000, 2940, 2850, 1595, 1565, 1500, 1440, 1360, 1245, 1210, 1190, 1115, 1080, 990, 745, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.1—2.1 (m, 4H), 1.88 (s, 1H), 2.7—3.1 (m, 2H), 2.93 (s, 3H), 3.1—3.7 (m, 3H), 6.4—6.9 (m, 3H), and 7.0—7.4 (m, 2H). Compound **2f** gave a *p*-hydroxycinnamate which showed mp 164—166 °C. Found: C, 69.12; H, 7.30; N, 8.58%. Calcd for $C_{19}H_{24}O_3N_2$: C, 69.49; H, 7.37; N, 8.53%.

Asymmetric Transformation of Cyclohexene Oxide. To (*S*)-2-(*N*,*N*-disubstituted aminomethyl)pyrrolidine **2** (3.3 mmol) in solvent (10 ml) was added a hexane solution of butyllithium (2.0 ml, 3.0 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 30 min and cyclohexene oxide (2.0 mmol) in solvent (5 ml) was added to the reaction mixture at 0 °C or −78 °C. The reaction temperature was gradually warmed to room temperature and the reaction mixture was stirred overnight. Saturated ammonium chloride solution was added to the reaction mixture and it was extracted with ether. The organic layer was washed successively with 2% HCl (10 ml) solution, water, and brine, and dried over anhyd Na_2SO_4. The solvent was removed at atmospheric pressure and the resulting crude 2-cyclohexen-1-ol was benzoylated with benzoyl chloride (4 mmol), pyridine (8 mmol), and catalytic amount of 4-dimethylaminopyridine in dichloromethane (5 ml) for several hours. After addition of water and ether, the organic layer was washed with 2 M HCl (10 ml), water, and brine. After drying (anhyd Na_2SO_4) and evaporation of the solvent in vacuo, the oily substance was purified by preparative TLC or column chromatography (silica gel/hexane–ether) to give 2-cyclohexenyl benzoate; IR (neat): 3070, 3040, 2940, 1710, 1650, 1600, 1585, 1490, 1450, 1315, 1270, 1175, 1110, 1070, 1050, 1025, 1010, 920, and 710 cm^{-1}; ^1H NMR (CCl_4) δ=1.3—2.5 (m, 6H), 5.1—5.6 (m, 1H), 5.6—6.1 (m, 2H), 6.9—7.6 (m, 3H), and 7.6—8.3 (m, 2H).

Then the resulting 2-cyclohexenyl benzoate was hydrolyzed with sodium hydroxide (0.4 g) in methanol (10 ml) by stirring overnight at room temperature. After removal of 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 Na_2SO_4. The solvent was removed at atmospheric pressure, and the resulting crude 2-cyclohexen-1-ol was purified by bulb-to-bulb distillation (180 °C (bath temperature)/70 mmHg) to measure the optical rotation. The yields, the optical rotations, and ee's are summarized in Tables 1 and 2.

Asymmetric Transformation of (*Z*)-4-Octene Oxide. To a THF (2.5 ml) solution of **2a** (254 mg, 1.65 mmol) was added a hexane (1.0 ml) solution of butyllithium (1.5 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 30 min and a THF (2.5 ml) solution of additive (1.65 mmol) was added at this temperature. After 30 min, a THF (2.5 ml) solution of (*Z*)-4-octene oxide (128 mg, 1.0 mmol) was added and the reaction mixture was refluxed for 1—3 h or stirred overnight at room temperature. Saturated ammonium chloride solution was added to the reaction mixture and it was extracted with ether. The organic layer was washed with 2% HCl solution (10 ml), water, and brine, then dried over anhyd Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (silica gel/hexane–ether) to afford (*E*)-5-octen-4-ol.[9] IR (neat): 3320, 2970, 2930, 2880, 1665, 1460, 1375, 1120, 1060, 1020, 1000, and 970 cm^{-1}; ^1H NMR (CCl_4) δ=0.6—2.3 (m, 13H), 3.6—4.1 (m, 1H), and 5.0—5.6 (m, 2H). The yields, the optical rotations, and ee's are summarized in Table 3.

Benzoylation of (*E*)-5-octen-4-ol ($[\alpha]_D^{29}$ −2.76° (c 3.30, $CHCl_3$) (139 mg, 1.1 mmol) was conducted with benzoyl chloride (305 mg, 2.2 mmol), pyridine (342 mg, 4.3 mmol), and catalytic amount of 4-dimethylaminopyridine in CH_2Cl_2 at room temperature overnight. After the reaction mixture was worked up in a similar manner as described for 2-cyclohexenyl benzoate, 232 mg of (*E*)-1-propyl-2-pentenyl benzoate (92%) was obtained. $[\alpha]_D^{25}$ +11.8° (c 2.15, $CHCl_3$); IR (neat): 3050, 2980, 2950, 2890, 1720, 1600, 1585, 1450, 1315, 1270, 1175, 1110, 1070, 1030, 970, 940, and 715 cm^{-1}; ^1H NMR (CCl_4) δ=0.7—2.3 (m, 12H), 5.0—6.1 (m, 3H), 7.0—7.5 (m, 3H), and 7.6—8.1 (m, 2H). Found: m/z 232.1438. Calcd for $C_{15}H_{20}O_2$: M, 232.1461. To a solution of the benzoate (232 mg, 1 mmol) in H_2O (1.1 ml) and 1,4-dioxane (3.3 ml) was added osmium tetraoxide (5 mg). After stirring for 5 min, sodium periodate (0.9 g, 4.2 mmol) was added to the reaction mixture in several portions during 30 min. After 1.5 h, ether was added to the reaction mixture and the organic layer was dried over anhyd Na_2SO_4. After removal of the solvent in vacuo, resulting oily substance was reduced with excess $LiAlH_4$ in ether (5 ml) at 0 °C to afford 1,2-pentanediol (40 mg) in 36% yield from the benzoate after purification by column chromatography (silica gel/ethyl acetate). $[\alpha]_D^{30}$ −8.66° (c 3.65, C_2H_5OH).

Acetylation of (*E*)-5-octen-4-ol was conducted with acetic anhydride (2 equiv), pyridine (4 equiv), and catalytic amount of 4-dimethylaminopyridine in dichloromethane at room temperature for several hours. (*E*)-1-Propyl-2-pentenyl acetate was obtained after the reaction was worked up in a similar manner as above. IR (neat): 2960, 2940, 2870, 1735, 1665, 1460, 1370, 1015, 965, 940, and 820 cm^{-1}; ^1H NMR

(CCl_4) δ=0.7—1.7 (m, 10H), 1.7—2.2 (m, 2H), 1.94 (s, 3H), and 5.0—6.0 (m, 3H). Found: *m/z* 170.1276. Calcd for $C_{10}H_{18}O_2$: M, 170.1305. The ee was determined on the basis of ^{1}H NMR taken with Eu(hfbc)$_3$ which exhibited the acetoxyl methyl signals at the different chemical shifts depending upon the enantiomers.

Asymmetric Transformation of (*Z*)-2-Butene Oxide. The reaction was carried out in a similar manner as described for (*Z*)-4-octene oxide using DBU as additive and the reaction mixture was stirred at room temperature overnight. After drying the organic layer over anhyd Na_2SO_4, the solvent was removed at atmospheric pressure and resulting crude 3-buten-2-ol was benzoylated in a similar manner as described for 2-cyclohexen-1-ol to afford 1-methyl-2-propenyl benzoate in 60% yield form (*Z*)-2-butene oxide after purification by preparative TLC. $[\alpha]_D^{27}$ +32.3° (*c* 1.01, $CHCl_3$) (lit,[20] $[\alpha]_D^{20}$ +48.03° (C_2H_5OH) for 92% ee of (*S*)-1-methyl-2-propenyl benzoate).

Conversion of the benzoate to 1,2-propanediol was conducted as follows. Ozone was bubbled into a methanol (3 ml) solution of the benzoate (266 mg, 1.5 mmol) at −78 °C for several minutes and excess $NaBH_4$ was added to the solution. After addition of ether and water to the reaction mixture, the organic layer was separated and washed with water and brine. After drying over anhyd Na_2SO_4 and removal of the solvent, excess $LiAlH_4$ was added to an ether (5 ml) solution of the resulting oily substance (201 mg) at 0 °C. After the reaction mixture was gradually warmed to room temperature was added saturated Na_2SO_4 solution to the reaction mixture. The resulting inorganic material was removed by decantation and the solvent was removed in vacuo. The resulting oil was purified by column chromatography (silica gel/ethyl acetate) to afford 1,2-propanediol (36 mg) in 43% yield from the benzoate. $[\alpha]_D^{27}$ +14.5° (*c* 2.4, H_2O).

Asymmetric Transformation of Cyclopentene Oxide. The reaction was carried out in a similar manner as described for (*Z*)-2-butene oxide and the reaction mixture was refluxed for 2 h. After a similar treatment of the reaction mixture, 2-cyclopentenyl benzoate was obtained in 63% yield from cyclopentene oxide. $[\alpha]_D^{25}$ −98.9° (*c* 2.05, $CHCl_3$); IR (neat): 3080, 2940, 2850, 1710, 1600, 1585, 1450, 1340, 1315, 1270, 1175, 1110, 1070, 1030, 940, 885, and 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.7—2.8 (m, 4H), 5.5—6.2 (m, 3H), 7.0—7.6 (m, 3H), and 7.6—8.1 (m, 2H).

The hydrolysis of the benzoate was conducted under similar conditions used for 2-cyclohexenyl benzoate to afford 2-cyclopenten-1-ol in 57% yield. $[\alpha]_D^{27}$ −57.4° (*c* 2.35, CCl_4) (lit,[12] $[\alpha]_D^{21}$ +22.8° (*c* 5, CCl_4) for (*R*)-2-cyclopenten-1-ol).

2-Cyclopenten-1-ol was then converted to the corresponding acetate in a similar manner as described for (*E*)-5-octen-4-ol, and 2-cyclopentenyl acetate was obtained in 80% yield after purification by column chromatography (silica gel/pentane–ether). $[\alpha]_D^{25}$ −83.8° (*c* 1.09, CH_2Cl_2) (lit,[14] $[\alpha]_D$+5.7° ($CHCl_3$) for (*R*)-2-cyclopentenyl acetate). IR (neat): 3050, 2940, 2850, 1725, 1430, 1370, 1360, 1240, 1160, 1110, 1030, 960, 915, 900, 880, and 730 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.5—2.7 (m, 4H), 1.90 (s, 3H), and 5.2—6.0 (m, 3H). The ee was determined to be 41% on the basis of ^{1}H NMR taken with Eu(hfbc)$_3$ which exhibited the acetoxyl methyl signals at the different chemical shifts depending upon the enantiomers.

Asymmetric Transformation of Cyclooctene Oxide. The reaction was carried out in a similar manner as described for (*Z*)-4-octene oxide using DBU as additive and the reaction mixture was refluxed for 2 h. After a similar treatment of the reaction mixture, 2-cycloocten-1-ol was obtained in 84% yield after purification by column chromatography (silica gel/hexane–ether). $[\alpha]_D^{28}$ +28.0° (*c* 0.89, $CHCl_3$) (lit,[13] $[\alpha]_D$−48° (*c* 0.8, CH_2Cl_2) for (*R*)-2-cycloocten-1-ol).

2-Cycloocten-1-ol was converted to the corresponding acetate in a similar manner as described for (*E*)-5-octen-4-ol, and 2-cyclooctenyl acetate was obtained in 89% yield after purification by column chromatography (silica gel/pentane–ether). $[\alpha]_D^{29}$ +47.0° (*c* 5.01, hexane) (lit,[15] $[\alpha]_D^{25}$ −50.5° (*c* 5.08, hexane) for (*R*)-2-cyclooctenyl acetate). IR (neat): 3010, 2920, 2840, 1730, 1445, 1365, 1240, 1025, 960, 900, 760, and 710 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.1—2.5 (m, 10H), 1.92 (s, 3H), and 5.1—5.9 (m, 3H). Found: *m/z* 168.1155. Calcd for $C_{10}H_{16}O_2$: M, 168.1149. The ee was determined to be 50% on the basis of ^{1}H NMR taken with Eu(hfbc)$_3$ which exhibited the acetoxyl methyl signals at the different chemical shifts depending upon the enantiomers.

The yield was 45% and ee was 58% ($[\alpha]_D^{22}$ +30.4° (*c* 1.14, $CHCl_3$)) when the reaction was carried out at room temperature overnight.

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