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Stereoselective Reactions. 25.[1] Enantioselective Deprotonation of Prochiral 4-Substituted Cyclohexanones by Chiral Chelated Lithium Amides

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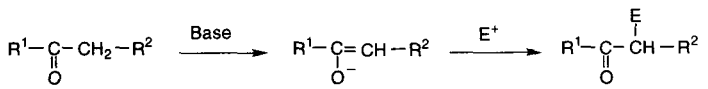
Abstract: Enantioselective deprotonation of prochiral 4-substituted cyclohexanones (**4a~d**) by chiral chelated lithium amides (**8a~k**) in the presence of excess trimethylsilyl chloride was realized to give the corresponding chiral silyl enol ethers (**6a~d**) in up to 89% ee. It is shown that enantioselectivity of the reaction is dependent on the solvent used, but becomes almost independent on the solvent in the presence of HMPA. The sense of asymmetric induction can be correlated to the configuration at the chiral carbon bearing amide nitrogen of the lithium amide. © 1997 Elsevier Science Ltd.

INTRODUCTION

Deprotonation of carbonyl compounds (**1**) by bases is the most fundamental and widely used reaction in synthetic organic chemistry, because the resulting enolate anions (**2**) can further react with various electrophiles to undergo many synthetically important reactions such as alkylation, aldolization, acylation, halogenation, protonation, etc. Lithium dialkylamides such as lithium diisopropylamide (LDA) are currently used as bases of choice for this purpose, because they are strong bases with low nucleophilicity, and are easily prepared by treating the corresponding secondary amines with alkyllithiums in aprotic solvents.



1 **2** **3**

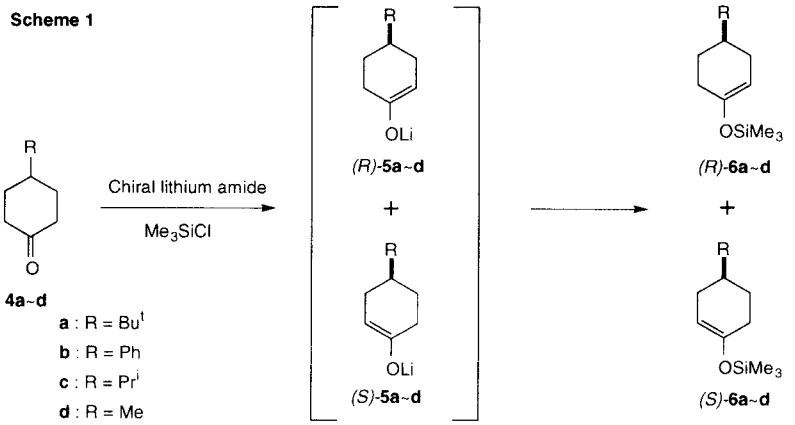
One of the first examples of enantioselective deprotonation reaction using chiral lithium amides was reported in 1980 by Whitesell, who studied the conversion of prochiral cyclohexene oxide to chiral 2-cyclohexenol.[2] The result clearly demonstrates that chiral lithium amides can recognize enantiotopic protons of prochiral molecules under kinetically controlled conditions.

In early 1986, approaches to enantioselective deprotonation reaction of prochiral cyclohexanone derivatives having a plane of symmetry by chiral lithium amides[3] were first reported by us[4a] and by Simpkins,[4b] independently. Since then, studies on enantioselective deprotonation reaction of carbonyl compounds and their applications to the synthesis of optically active compounds have been extensively carried out.[5]

We initiated our studies by using 4-substituted cyclohexanones (**4a~d**) as substrates. Although **4a~d** are achiral molecules having a plane of symmetry, the corresponding enolate anions (**5a~d**) are chiral

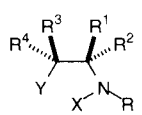
molecules, because the plane of symmetry is lost by enolization as shown in Scheme 1. Therefore, if abstraction of a proton from **4a~d** occurs enantioselectively by chiral lithium amides, optically active **5a~d** should be formed, and should be isolated as optically active silyl enol ethers (**6a~d**).

Scheme 1



RESULTS AND DISCUSSION

Design and Preparation of Chiral Chelated Lithium Amides Based on our earlier studies on diastereoselective asymmetric alkylation of chiral chelated lithioenamines,[6] we designed and synthesized chiral lithium amides (**8a~k**) having the structures shown.[7] We expected that 1) they should exist and react in a five-membered chelated form, 2) the amide nitrogen of these lithium amides should be chiral, because the substituent (R) on the amide nitrogen would orient itself exclusively *trans* to the substituent on the neighboring chiral carbon in the chelated ring, 3) they should form aggregates in solution to satisfy the valency of the lithium, and the degree of aggregation should be dependent on the solvent used, and 4) strongly coordinating additives such as hexamethylphosphoric triamide (HMPA) would promote deaggregation in solution.



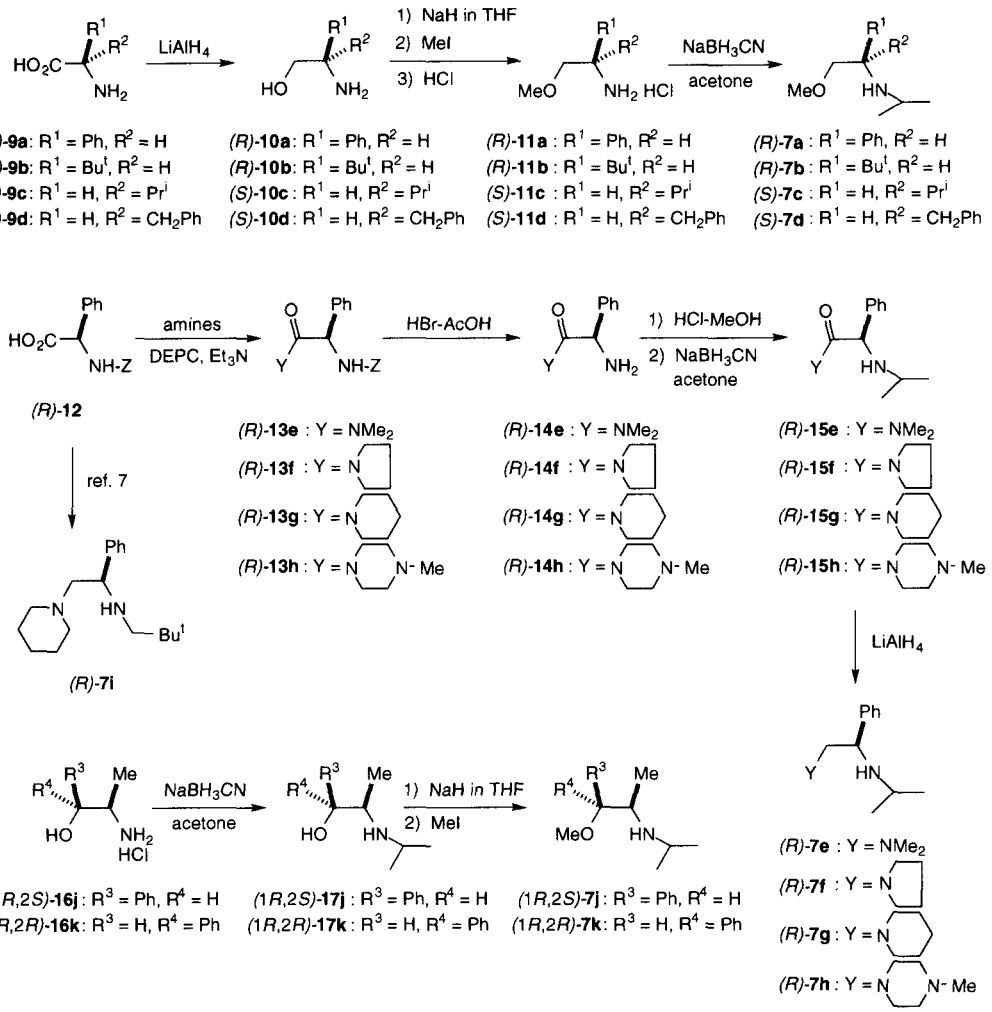
7a~k: X = H
8a~k: X = Li

	R^1	R^2	R^3	R^4	R	Y	Confign.
a	Ph	H	H	H	Pr^i	OMe	*R*
b	Bu^t	H	H	H	Pr^i	OMe	*R*
c	H	Pr^i	H	H	Pr^i	OMe	*S*
d	H	CH_2Ph	H	H	Pr^i	OMe	*S*
e	Ph	H	H	H	Pr^i	NMe_2	*R*
f	Ph	H	H	H	Pr^i	1-pyrrolidyl	*R*
g	Ph	H	H	H	Pr^i	1-piperidyl	*R*
h	Ph	H	H	H	Pr^i	1-(4-methylpiperazyl)	*R*
i	Ph	H	H	H	CH_2Bu^t	1-piperidyl	*R*
j	Me	H	Ph	H	Pr^i	OMe	1*R*,2*S*
k	Me	H	H	Ph	Pr^i	OMe	1*R*,2*R*

It is known that lithium amide is actively involved in the transition state of the deprotonation reaction of a carbonyl compound.[8] We expected that the use of chiral lithium amide might show enantioselectivity in deprotonation reaction of **4a~d** under kinetically controlled conditions.

The chiral amines (**7a~k**) were prepared as shown in Scheme 2, and were converted to the corresponding lithium amides (**8a~k**) as usual using butyllithium.

Scheme 2



Deprotonation Reaction of 4a by (R)-8a Deprotonation of 4-*tert*-butylcyclohexanone (**4a**) was first examined by using *(R)*-**8a** as a base in several solvents in the absence and in the presence of HMPA (2 equiv.) at -78 °C . To trap the resulting enolate anion as quickly as possible, the reaction was carried out in the presence of excess trimethylsilyl chloride (TMSCl) from the beginning of the reaction (Corey's internal quench method[9]), and the product was isolated as its trimethylsilyl enol ether (**6a**). Determination of the absolute

configurations[4a] and maximum rotations[10,11] of *(R)*-**6a~d** has already been reported. The results are summarized in Table 1.

It is shown that enantioselective deprotonation actually occurs, and that the chemical yields, stereochemistry, and ee's of **6a** depend heavily upon the solvent used (runs 1~4). Based on one of our hypotheses discussed above, HMPA (2 equiv) was added to the reaction mixture from the beginning of the reaction for the purpose of controlling the degree of aggregation of *(R)*-**8a** in solution. It was found that *(R)*-**6a** was obtained in almost the same ee's in these solvents in the presence of HMPA (runs 5~8). These facts suggest that the solution structure of *(R)*-**8a** is dependent on the solvents used, but becomes independent on these solvents in the presence of HMPA.

Table 1. Enantioselective Deprotonation of 4a by *(R)*-8a to Give Optically Active 6a

Run	Solvent	Additive (equiv.)	Reaction time (min)	Product (**6a**)		
				Isolated y. (%)	E. e. (%)	Confign.
1	THF	-	1	87	6	*S*
2	ether	-	1	5	12	*R*
3	DME	-	1	90	25	*R*
4	toluene	-	1500	31	14	*R*
5	THF	HMPA (2.0)	10	90	43	*R*
6	ether	HMPA (2.0)	10	88	42	*R*
7	DME	HMPA (2.0)	10	90	40	*R*
8	toluene	HMPA (2.0)	75	27	41	*R*

Deprotonation Reaction of 4-Substituted Cyclohexanaones (4a~d) by Chiral Lithium Amides (8a~k) Based on the results in Table 1, all reactions were carried out in THF in the presence of HMPA and excess TMSCl. The results are shown in Table 2.

Table 2. Enantioselective Deprotonation of 4a~d to Give Optically Active 6a~d

Run	4	8	HMPA (equiv.)	Temp (°C)	Product		
					6	Isolated y. (%)	E. e. (%)
1	**4a**	*(R)*-**8a**	2.0	-78	*(R)*-**6a**	90	43
2	**4a**	*(R)*-**8b**	2.0	-78	*(R)*-**6a**	91	36
3	**4a**	*(S)*-**8c**	2.0	-78	*(S)*-**6a**	88	23
4	**4a**	*(S)*-**8d**	2.0	-78	*(S)*-**6a**	65	33
5	**4a**	*(R)*-**8e**	2.0	-78	*(R)*-**6a**	35	46
6	**4a**	*(R)*-**8f**	2.0	-78	*(R)*-**6a**	52	67
7	**4a**	*(R)*-**8g**	2.0	-78	*(R)*-**6a**	67	77
8	**4a**	*(R)*-**8h**	1.0	-78	*(R)*-**6a**	87	77
9	**4a**	*(R)*-**8h**	1.0	-105	*(R)*-**6a**	51	89
10	**4a**	*(R)*-**8i**	2.0	-78	*(R)*-**6a**	82	82
11	**4a**	*(1R,2S)*-**8j**	2.0	-78	*(R)*-**6a**	74	33
12	**4a**	*(1R,2R)*-**8k**	2.0	-78	*(R)*-**6a**	32	40
13	**4b**	*(R)*-**8h**	1.0	-78	*(R)*-**6b**	93	75
14	**4c**	*(R)*-**8h**	1.0	-78	*(R)*-**6c**	85	78
15	**4d**	*(R)*-**8h**	1.0	-78	*(R)*-**6d**	68	46

It is shown that the enantioselectivity of the reaction is dependent on the structure of the chiral lithium amide used, and that the sense of asymmetric induction is correlated to the configuration at the chiral carbon bearing amide nitrogen of the lithium amide. Thus, among the chiral lithium amides (**8a~i**) having only one chiral center at the carbon bearing amide nitrogen, *(R)*-lithium amide gives *(R)*-product (runs 1,2,5~10, 13~15), while *(S)*-lithium amide gives *(S)*-product (runs 3,4). Among the chiral lithium amides (**8j~k**) having two chiral carbons, it is shown that the chiral carbon bearing amide nitrogen determines the stereochemical course of the reaction (runs 11,12).

Among the chiral lithium amides (**8a~i**) having one chiral carbon, the amides (**8e~i**) whose internal ligation site for the lithium is amine nitrogen gave the product (**6**) in higher ee, compared with those (**8a~d**) whose ligation site is ether oxygen. This result may be ascribed to the fact that amine nitrogen is superior to ether oxygen as the ligation site for the lithium to form a five-membered chelated ring.

The method outlined above represents an enantioselective asymmetric synthesis of chiral silyl enol ethers, which are equivalent to enolate anions from the synthetic viewpoint, and should be useful as chiral building blocks for the synthesis of various optically active compounds.

EXPERIMENTAL SECTION

General All melting and boiling points are uncorrected. IR spectra were recorded on a JASCO IRA-1 or a JASCO DS-402G spectrometer. ^{1}H-NMR spectra were recorded on a Hitachi R-24B (60 MHz) or a JNM-PS 100 (100 MHz) spectrometer. The chemical shifts are given in δ (ppm) values using tetramethylsilane as an internal standard unless otherwise stated. Coupling constants (*J*) are given in hertz. The following abbreviations are used: br=broad, s=singlet, d=doublet, dd=doublet of doublets, t=triplet, m=multiplet. Mass spectra (MS) were recorded on a JEOL JMS-01 SG-Z spectrometer. Optical rotations were measured by a JASCO DIP-370 digital polarimeter.

***(R)*-O-Methyl-*tert*-leucinol Hydrochloride (*(R)*-11b)** Under argon atmosphere, NaH in oil (60%, 5.5 g, 138 mmol) was washed with hexane (30 mL) twice, and the residue was mixed with THF (260 mL). After addition of *(R)*-*tert*-leucinol[12] (*(R)*-**10b**) (13.0 g, 111 mmole), the resulting mixture was stirred at room temperature for 30 min, and was heated under reflux for 30 min. After ice-cooling, methyl iodide (7.26 mL, 117 mmol) was added, and the whole was stirred at room temperature for 3 hr. The reaction mixture was quenched with MeOH, and the whole was evaporated under reduced pressure. The residue was mixed with brine (200 mL) and water (200 mL), and the whole was extracted with ether (100 mL) five times. The ethereal extracts were combined, dried over anhydrous K_2CO_3, and evaporated under reduced pressure. The residue was dissolved in EtOH (20 mL), and was then mixed with saturated ethanolic HCl (30 mL) under ice-cooling. Evaporation of the solvent gave a solid, which was recrystallized from EtOH-ether to give *(R)*-**11b** (10.8 g, 58%) as colorless needles of mp 203-205 °C. IR (nujol) cm^{-1}: 3200. ^{1}H-NMR (D_2O/DSS): 1.00 (9H, s), 3.17 (1H, dd, *J*=4 and 10), 3.35 (3H, s), 3.49 (1H, t, *J*=10), 3.78 (1H, dd, *J*=4 and 10). $[\alpha]_D^{25}$ -21.7 (*c*=0.46, EtOH). Anal. Calcd. for $C_7H_{18}NOCl$: C, 50.14; H, 10.82; N, 8.35. Found: C, 50.31; H, 11.03; N, 8.13.

***(R)*-N-Isopropyl-*O*-methylphenylglycinol (*(R)*-7a)** A solution of *(R)*-*O*-methylphenylglycinol[13] (7.9 g, 52.3 mmol) was converted to its hydrochloride, and was dissolved in a mixture of MeOH (150 mL) and acetone (50 mL). Under ice-cooling, $NaBH_3CN$ (95%, 4.2 g, 66.7 mmol) was added, and the whole was stirred under ice-cooling for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was made alkaline by addition of aqueous ammonia. The resulting mixture was extracted with $CHCl_3$ (100 mL) three times. The organic extracts were combined, washed with brine, dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo*. The residue was purified by distillation to give *(R)*-**7a** (7.7 g, 78%) as a colorless oil of bp 95-98 °C (7 mmHg). IR (film) cm^{-1}: 3330. ^{1}H-NMR ($CDCl_3$): 0.93 (3H, d, *J*=7), 0.97 (3H, d, *J*=7), 1.66 (1H, br), 2.59 (1H, m), 3.23 (3H, s), 3.30 (2H, d, *J*=8), 3.94 (1H, dd, *J*=5 and 8), 7.16 (5H, s). $[\alpha]_D^{25}$ -78.5 (*c* =1.1, $CHCl_3$). *(R)*-**7a** hydrochloride (mp 197-198 °C from AcOEt) : Anal. Calcd. for $C_{12}H_{20}NOCl$: C, 62.73; H, 8.77; N, 6.10. Found: C, 62.48; H, 8.84; N, 5.85.

***(R)*-*N*-Isopropyl-*O*-methyl-*tert*-leucinol *(R)*-7b)** Treatment of *(R)*-**11b** (5.0 g, 29.9 mmol) with $NaBH_3CN$ (95%, 2.4 g, 36.2 mmol) and acetone (30 mL) in MeOH (90 mL) according to the procedure described above for the preparation of *(R)*-**7a** gave an oil, which was purified by distillation to give *(R)*-**7b** (3.04 g, 59%) as a colorless oil of bp 96-98 °C (60 mmHg). IR (film) cm^{-1}: 3350. ^{1}H-NMR ($CDCl_3$): 0.90 (9H, s), 1.00 (3H, d, *J*=6), 1.05 (3H, d, *J*=6), 2.27 (1H, m), 2.86 (1H, m), 3.29 (3H, s), 3.12~3.63 (2H, m). $[\alpha]_D^{25}$ +25.6 (*c*=1.02, EtOH). *(R)*-**7b** hydrochloride (mp 196-197 °C): Anal. Calcd. for $C_{10}H_{24}NOCl$: C, 57.26; H, 11.53; N, 6.68. Found: C, 57.50; H, 11.80; N, 6.45.

***(S)*-*N*-Isopropyl-*O*-methylvalinol *((S)*-7c)** Treatment of *(S)*-**11c**[13] (4.8 g, 31.3 mmol) with $NaBH_3CN$ (95%, 2.5 g, 37.7 mmol) and acetone (30 mL) in MeOH (90 mL) according to the procedure described above for the preparation of *(R)*-**7a** gave an oil, which was purified by distillation to give *(S)*-**7c** (3.6 g, 72%) as a colorless oil of bp 90-92 °C (65 mmHg). IR (film) cm^{-1}: 3350. ^{1}H-NMR ($CDCl_3$): 0.88 (6H, d, *J*=7), 1.02 (6H, d, *J*=7), 1.5-2.1 (2H, m), 2.4-3.0 (2H, m), 3.2-3.4 (1H, m), 3.30 (3H, s). $[\alpha]_D^{25}$ -6.8 (*c*=1.09, EtOH). *(S)*-**7c** hydrochloride (mp 126-128 °C): Anal. Calcd. for $C_9H_{22}NOCl$: C, 55.23; H, 11.33; N, 7.16. Found: C, 55.25; H, 11.33; N, 6.86.

***(S)*-*N*-Isopropyl-*O*-methylphenylalaninol *((S)*-7d)** Treatment of *(S)*-**11d**[13] (10.0 g, 49.6 mmol) with $NaBH_3CN$ (95%, 4.8 g, 72.4 mmol) and acetone (60 mL) in MeOH (180 mL) according to the procedure described above for the preparation of *(R)*-**7a** gave an oil, which was purified by distillation to give *(S)*-**7d** (8.3 g, 81%) as a colorless oil of bp 95-96 °C (3 mmHg). IR (film) cm^{-1}: 3330. ^{1}H-NMR ($CDCl_3$): 1.00 (3H, d, *J*=6), 1.09 (3H, d, *J*=6), 1.20 (1H, br), 2.60-3.22 (6H, m), 3.33 (3H, s), 7.24 (5H, s). $[\alpha]_D^{25}$ +8.62 (*c*=1.09, EtOH).

***(R)*-*N*-[*N*-(Benzyloxycarbonyl)-2-phenylglycyl]dimethylamine *((R)*-13e)** Triethylamine (30.8 mL, 221 mmol) was added dropwise during 10 min to an ice-cooled solution of *(R)*-**12**[14] (30.0 g, 105 mmol), dimethylamine hydrochloride (9.44 g, 116 mmol), and DEPC[15] (90%, 21.0 g, 116 mmol) in DMF (250 mL), and the whole was stirred at room temperature for 4 hr. Benzene (500 mL) and ethyl acetate (1 L) were added, and the whole was washed with water (1 L) five times, with brine (1 L) three times, and was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave *(R)*-**13e** (31.7 g, 97%) as a pale yellow oil, which was used for the next step without further purification. IR (film) cm^{-1}: 1710, 1640. ^{1}H-NMR ($CDCl_3$): 2.88 (3H, s), 2.98 (3H, s), 5.18 (2H, s), 5.58 (1h, br), 6.35 (1H, br), 7.30 (5H, s), 7.35 (5H, s). MS *m/z* : 312 (M^+). $[\alpha]_D^{25}$ -163.6 (*c*=1.21, $CHCl_3$).

***(R)*-1-[*N*-(Benzyloxycarbonyl)-2-phenylglycyl]pyrrolidine *((R)*-13f)** Triethylamine (15.4 mL, 111 mmol) was added dropwise during 20 min to an ice-cooled solution of *(R)*-**12**[13] (20.0 g, 105 mmol), pyrrolidine (8.22 g, 116 mmol), and DEPC[15] (90%, 21.0 g, 116 mmol) in DMF (250 mL), and the whole was stirred at room temperature for 4 hr. Work-up as described above for the preparation of *(R)*-**13e** gave *(R)*-**13f** (30.1 g, 85%) as a colorless oil, which was used for the next step without further purification. IR (film) cm^{-1}: 1720, 1640. ^{1}H-NMR ($CDCl_3$): ~1.8 (4H, m), 2.80-3.80 (4H, m), 5.02 (2H, s), 5.34 (1H, d, *J*=7), 6.35 (1H, br), 7.24 (5H, s), 7.28 (5H, s). MS *m/z*: 338 (M^+). $[\alpha]_D^{25}$ -123 (*c*=1.06, $CHCl_3$).

***(R)*-*N*-(2-Phenylglycyl)dimethylamine *((R)*-14e)** A solution of *(R)*-**13e** (31.6 g, 101 mmol) in AcOH (20 mL) was mixed with 25% HBr-AcOH (98.4 g, 304 mmol) under ice-cooling, and the whole was stirred at room temperature for 2 hr. The solution was poured into ice-water (300 mL), and was washed with ether (300 mL) three times. The aqueous layer was basified by addition of $NaHCO_3$, and then extracted with $CHCl_3$ (200 mL) three times. The organic extracts were combined, washed with brine (300 mL), dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo* to give *(R)*-**14e** (10,4 g, 58%) as a pale yellow oil. This sample was used for the next step without further purification. IR (film) cm^{-1}: 1640. ^{1}H-NMR ($CDCl_3$): 2.13 (2H, br), 2.87 (3H, s), 3.00 (3H, s), 4.75 (1H, s), 7.32 (5H, s).

***(R)*-1-(2-Phenylglycyl)pyrrolidine *((R)*-14f)** Prepared from *(R)*-**13f** by a similar procedure for the preparation of *(R)*-**14e** described above to give *(R)*-**14f** as a pale yellow oil. This sample was used for the next step without further purification. IR (film) cm^{-1}: 1640. ^{1}H-NMR ($CDCl_3$): 1.68-2.00 (4H, m), 2.10 (2H, br), 2.90-3.70 (4H, m), 4.57 (1H, s), 7.43 (5H, s).

***(R)*-*N*-(*N*-Isopropyl-2-pyenylglycyl)dimethylamine *((R)*-15e)** Under ice-cooling, $NaBH_3CN$ (95%, 4.39 g, 69.7 mmol) was added to a solution of *(R)*-**14e** (10.4 g, 58.1 mmol) and conc. HCl (4.8 mL,

57.6 mmol) in acetone (50 mL) and MeOH (150 mL), and the whole was stirred at room temperature for 50 hr. Evaporation of the solvent gave a residue, which was mixed with saturated aqueous $NaHCO_3$ (200 mL), and the whole was extracted with $CHCl_3$ (200 mL) twice. The organic extracts were combined, washed with brine, and dried over anhydrous K_2CO_3. Evaporation of the solvent gave *(R)*-**15e** (12.4 g, 97%) as a pale yellow solid. Recrystallization from hexane gave colorless needles of mp 99.5-102.5 °C. IR (nujol) cm^{-1}: 1640. ^1H-NMR ($CDCl_3$): 1.17 (6H, d, *J*=7), 2.50 (1H, br), 2.67 (1H, m), 2.97 (6H, s), 4.62 (1H, s), 7.32 (5H, s). $[\alpha]_D^{25}$ -146 (*c*=1.05, EtOH). Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.57; H, 9.15; N, 12.61.

***(R)*-1-(*N*-Isopropyl-2-phenylglycyl)pyrrolidine (*(R)*-15f)** Prepared from *(R)*-**14f** by a similar procedure for the preparation of *(R)*-**15e** described above to give *(R)*-**15f** as a pale yellow solid. Recrystallization from hexane gave colorless needles of mp 112-114 °C. IR (nujol) cm^{-1}: 1640. ^1H-NMR ($CDCl_3$): 1.07 (6H, d, *J*=7), 1.7-2.1 (4H, m), 2.66 (1H, m), 2.72 (1H, br), 3.0-3.8 (4H, m), 4.47 (1H, s), 7.30 (5H, s). $[\alpha]_D^{25}$ -102 (*c*=1.09, EtOH). Anal. Calcd. for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.06; H, 9.07; N, 11.33.

***(R)*-1-(*N*-Isopropyl-2-phenylglycyl)piperidine (*(R)*-15g)** Prepared from *(R)*-**14g**[7] by a similar procedure for the preparation of *(R)*-**15e** described above to give *(R)*-**15g** as a pale yellow solid. Recrystallization from hexane gave colorless needles of mp 86-88 °C. IR (nujol) cm^{-1}: 1620. ^1H-NMR ($CDCl_3$): 1.08 (6H, d, *J*=6), 1.51 (6H, m), 2.67 (1H, m), 3.16-3.76 (5H, m), 4.61 (1H, s), 7.27 (5H, s). Anal. Calcd. for $C_{16}H_{24}N_2O$: C, 73.81; H, 9.29; N, 10.76. Found: C, 73.91; H, 9.45; N, 10.70.

***(R)*-1-(*N*-Isopropyl-2-phenylglycyl)-4-methylpiperazine (*(R)*-15h)** Prepared from *(R)*-**14h**[7] by a similar procedure for the preparation of *(R)*-**15e** described above to give *(R)*-**15h** as a pale yellow oil. This sample was used for the next step without further purification. IR (film) cm^{-1}: 1635. ^1H-NMR ($CDCl_3$): 1.07 (6H, d, *J*=6), 2.20 (3H, s), ~2.3 (4H, m), ~2.7 (1H, m), 3.2-3.8 (4H, m), 4.61 (1H, s), 7.30 (5H, s).

***(R)*-2-Dimethylamino-*N*-isopropyl-1-phenylethylamine (*(R)*-7e)** A solution of *(R)*-**15e** (12.0 g, 54.5 mmol) in THF (200 mL) was added dropwise during 10 min to a stirred suspension of $LiAlH_4$ (4.14 g, 109 mmol) in THF (400 mL), and the whole was stirred under reflux for 2 hr. Under stirring and ice-cooling, water (4.1 mL), 15% aqueous NaOH (4.1 mL) and water (12.4 mL) were added successively, and the whole was filtered. The filtrate and THF washings were combined, dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo* to give a pale yellow oil. By mixing a solution of this oil in ether with a solution of picric acid (25.2 g, 110 mmol) in ether, *(R)*-**7e** dipicrate (31.9 g, 88%) was obtained as a yellow powder of mp 185.5-186.5 °C. Recrystallizations from MeOH gave yellow needles of mp 187-188 °C. $[\alpha]_D^{25}$ -73.0 (*c*=1.08, acetone). Anal. Calcd. for $C_{25}H_{28}N_8O_{14}$: C, 45.19, H, 4.25; N, 16.86. Found: C, 45.18; H, 4.18; N, 16.71.

The above recrystallized *(R)*-**7e** dipicrate (6.0 g) was mixed with saturated aqueous Na_2CO_3 (100 mL) and water (600 mL), and the whole was extracted with ether (200 mL) three times. The ethereal extracts were combined, washed with water (30 mL) three times, and then with brine (100 mL), dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo* to give an oil. Purification by bulb-to-bulb distillation gave *(R)*-**7e** (1.80 g, 97%) as a colorless oil of bp 120-130 °C (bath temperature) (5 mmHg). IR (film) cm^{-1}: 3310. $[\alpha]_D^{25}$ -94.7 (*c*=1.13, EtOH). ^1H-NMR ($CDCl_3$): 1.00 (3H, d, *J*=7), 1.08 (3H, d, *J*=7), 1.91 (1H, br), 2.25 (6H, s), 2.05-2.85 (2H, m), 2.83 (1H, dd, *J*=4 and 10), 7.30 (5H, s).

***(R)*-*N*-Isopropyl-1-phenyl-2-(1-pyrrolidino)ethylamine (*(R)*-7f)** Reduction of *(R)*-**15f** by $LiAlH_4$ was carried out by a similar procedure to that for the preparation of *(R)*-**7e** described above, and the product was converted to *(R)*-**7f** dihydrochloride in almost quantitative yield. Recrystallization from EtOH-ether gave hygroscopic colorless needles of mp 150-152 °C (decomp.) $[\alpha]_D^{25}$ +9.3 (*c*=1.03, EtOH). Anal. Calcd. for $C_{15}H_{25}N_2Cl_2$ 1/2 H_2O: C, 57.32; H, 8.66; N, 8.91. Found: C, 57.71; H, 8.58; N, 8.40.

The above recrystallized *(R)*-**7f** dihydrochloride was converted to the free amine in the usual manner and was purified by bulb-to-bulb distillation to give *(R)*-**7f** as a colorless oil of bp 150 °C (bath temperature) (2 mmHg). ^1H-NMR ($CDCl_3$): 0.97 (3H, d, *J*=7), 1.05 (3H, d, *J*=7), 1.6-3.0 (11H, m), 3.80 (1H, dd, *J*=4 and 11), 7.30 (5H, s). $[\alpha]_D^{25}$ -72.0 (*c*=1.10, EtOH).

***(R)*-*N*-Isopropyl-1-phenyl-2-(1-piperidino)ethylamine (*(R)*-7g)** Reduction of *(R)*-**15g** by $LiAlH_4$ was carried out by a similar procedure to that for the preparation of *(R)*-**7e**, and the product was

converted to *(R)*-**7g** dipicrate in 92% net yield. Recrystallization from MeOH gave yellow needles of mp 190-192 °C. $[\alpha]_D^{25}$ -41.6 (*c*=0.49, acetone). Spectra data are identical to those reported.[7]

The above recrystallized *(R)*-**7g** dipicrate was converted to the free amine by a similar procedure for the preparation of *(R)*-**7e** described above, and was purified by bulb-to-bulb distillation to give *(R)*-**7g** as a colorless oil of bp 150-160 °C (bath temperature) (0.5mmHg) in 93% yield. $[\alpha]_D^{25}$ -90.0 (*c*=1.09, EtOH). Spectral data are identical to those reported.[7]

***(R)*-*N*-Isopropyl-1-phenyl-2-(4-methyl-1-piperazino)ethylamine (*(R)*-7h)** Reduction of *(R)*-**15h** by $LiAlH_4$ was carried out by a similar procedure to that for the preparation of *(R)*-**7e** described above, and the product was converted to *(R)*-**7h** trihydrochloride by a similar procedure to that for the preparation of *(R)*-**11b** hydrochloride described above. Recrystallization from EtOH gave hygroscopic colorless needles of 224-226 °C (decomp.) $[\alpha]_D^{25}$ -25.9 (*c*=1.44, EtOH). Anal. Calcd. for $C_{16}H_{30}N_3Cl_3$ 1/2H_2O: C, 50.60; H, 8.23; N, 11.06. Found: C, 50.32; H, 8.21; N, 10.90.

The recrystallized *(R)*-**7h** trihydrochloride was converted to the free amine in the usual manner, and was purified by bulb-to-bulb distillation to give *(R)*-**7h** as a colorless oil of bp 170-180 °C (bath temperature) (0.5 mmHg). $[\alpha]_D^{25}$ -81.7 (*c*=1.29, EtOH). ^{1}H-NMR ($CDCl_3$): 0.97 (3H, d, *J*=6), 1.04 (3H, d, *J*=6), 2.11 (iH, br), 2.29 (3H, s), 12.2-3.0 (11H, m), 3.87 (1H, dd, *J*=5 and 10), 7.27 (5H, s).

***(1R,2S)*-*N*-Isopropylnorephedrine (*(1R,2S)*-17j)** Under ice-cooling, $NaBH_3CN$ (95%, 430 mg, 6.48 mmol) was added to a solution of *(1R,2S)*-norephedrine hydrochloride (*(1R,2S)*-**16j**) (1.0 g, 3.33 mmol) in acetone (5 mL) and MeOH (15 mL), and the whole was stirred at room temperature for 15 hr. Evaporation of the solvent gave a residue, which was mixed with conc. ammonia, and the whole was extracted with $CHCl_3$ (20 mL) three times. The organic extracts were combined, washed with brine (10 mL), and dried over anhydrous K_2CO_3. Evaporation of the solvent gave a colorless solid, which was recrystallized from hexane to give *(1R,2S)*-**17j** (0.83 g, 81%) as colorless needles of mp 105.5-106.5 °C. IR (film) cm^{-1}: 3120. ^{1}H-NMR ($CDCl_3$-D_2O): 0.80 (3H, d, *J*=7), 1.09 (6H, d, *J*= 7), ~3.0 (2H, m), 4.69 (1H, d, *J*=4), 7.22 (5H, s). $[\alpha]_D^{25}$ +9.60 (*c*=2.02, $CHCl_3$). Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.41; H, 10.09; N, 6.99.

***(1R,2R)*-*N*-Isopropylnorpseudoephedrine (*(1R,2R)*-17k)** Prepared from *(1R,2S)*-norpseudoephedrine hydrochloride (*(1R,2R)*-**16k**) in a similar procedure to that for the preparation of *(1R,2S)*-**17j** described above to give *(1R,2R)*-**17k** as a colorless oil. This sample was used for the next step without further purification. IR (film) cm^{-1}: 3400. ^{1}H-NMR ($CDCl_3$-D_2O): 0.93 (3H, d, *J*=7), 1.07 (3H, d, *J*=6), 1.10 (3H, d, *J*=6), 2.6-3.1 (2H, m), 4.04 (1H, d, *J*=8), 7.30 (5H, s).

***(1R,2S)*-*N*-Isopropyl-*O*-methylnorephedrine (*(1R,2S)*-7j)** Under argon atmosphere, NaH in oil (60%, 3.24 g, 81.0 mmol) was added to a solution of *(1R,2S)*-**17j** (13.0 g, 67.4 mmol) in THF (260 mL), and the whole was stirred at room temperature for 1 hr, and then heated under reflux for 30 min. After ice-cooling, methyl iodide (5.04 mL, 80.9 mmol) was added, and the whole was stirred at room temperature for 1 hr, and then at 50 °C for 30 min. The reaction mixture was quenched with saturated aqueous Na_2SO_4, and dried over anhyd. K_2CO_3. After filtration, the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in ether, and the whole was extracted with 10% aqueous HCl (100 mL) three times. The aqueous extracts were combined, made alkaline using aqueous ammonia, and the whole was extracted with ether (100 m) three times. The organic extracts were combined, washed with brine (20 mL), dried over anhydrous K_2CO_3, and evaporated to dryness to give a pale yellow oil, which was purified by distillation to give *(1R,2S)*-**7j** (11.9 g, 85%) as a colorless oil of bp 90-101 °C (7 mmHg). IR (film) cm^{-1}: 3330. ^{1}H-NMR ($CDCl_3$-D_2O): 0.94 (3H, d, *J*=7), 0.96 (3H, d, *J*=7), 1.04 (3H, d, *J*=7), 2.7-3.1 (2H, m), 3.26 (3H, s), 4.16 (1H, d, *J*=5), 7.25 (5H, s). $[\alpha]_D^{25}$ +57.5 (*c*=1.08, $CHCl_3$). MS *m/z*: 208 (M^++1). The hydrochloride (mp 141.5-142.5 °C) was prepared in a usual manner. Anal. Calcd. for $C_{13}H_{22}NOCl$: C, 64.05; H, 9.10; N, 5.75. Found: C, 64.13; H, 9.38; N, 5.68.

***(1R,2R)*-*N*-Isopropyl-*O*-methylnorpseudoephedrine (*(1R,2R)*-7k)** Prepared from *(1R,2R)*-**17k** in a similar procedure to that for the preparation of *(1R,2S)*-**7j** described above to give crude *(1R,2R)*-**7k** as a pale yellow oil. The acetic acid salt was prepared in the usual manner. Recrystallizations from ethyl acetate-hexane gave colorless crystals of mp 84-85 °C. $[\alpha]_D^{25}$ -88.4 (*c*=1.05, $CHCl_3$). Anal. Calcd. for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.69; N, 5.24. Found: C, 67.14, H, 9.69; N, 5.10. The recrystallized acetic acid salt was converted to the free amine in the usual manner. Purification by bulb-to-bulb distillation gave *(1R,2R)*-**7k** as a colorless oil of bp 130 °C (bath temperature) (5 mmHg). IR (film) cm^{-1}: 3370. $[\alpha]_D^{25}$

-108.8 (c=2.02, $CHCl_3$). ^{1}H-NMR ($CDCl_3$-D_2O): 0.77 (3H, d, J=6), 1.06 (3H, d, J=7), 1.12 (3H, d, J=7), 2.8-3.2 (2H, m), 3.20 (3H, s), 3.90 (1H, d, J=8), 7.26 (5H, s).

Deprotonation of 4a by *(R)*-8a in the Absence of HMPA (Table 1, run 1) A solution of lithium amide (*(R)*-**8a**) was prepared under argon atmosphere by adding a 1.47 *N* solution of butyllithium in hexane (1.63 mL, 2.4 mmol) to a solution of *(R)*-**7a** (483 mg, 2.5 mmol) in THF (50 mL) under stirring at -78 °C. After 30 min, TMSCl (1.27 mL, 10 mmol) was added, and then **4a** (308 mg, 2.0 mmol) in THF (4 mL) was added dropwise during 2 min. Stirring was continued at -78 °C for 1 min. After addition of triethylamine (4 mL) and saturated aqueous $NaHCO_3$ (20 mL), the reaction mixture was extracted with pentane (50 mL) three times. The organic extracts were combined, washed with water(100 mL), 0.1 *N* aqueous citric acid (50 ml) six times, brine (50 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave a pale yellow oil, which was purified by column chromatography (silica gel, pentane) followed by bulb-to-bulb distillation to give **6a** (394 mg, 87%) as a colorless oil of bp 110 °C (bath temperature) (3 mmHg). $[\alpha]_{365}^{25}$ -15.7 (c=1.50, benzene), corresponding to be 6% ee (*S*).[10]

Deprotonation of 4a by *(R)*-8a in the Presence of HMPA (Table 1, run 5) A solution of lithium amde (*(R)*-**8a**) was prepared under argon atmosphere by adding a 1.47 *N* solution of butyllithium in hexane (1.63 mL. 2.4 mmol) to a solution of *(R)*-**7a** (483 mg, 2.5 mmol) in THF (50 mL) under stirring at -78 °C. After 10 min, HMPA (0.83 mL, 4.8 mmol) was added, and the mixture was warmed to 0 °C, and was then cooled down to -78 °C. TMSCl (1.27 mL, 10 mmol) and then **4a** (308 mg, 2.0 mmol) in THF (4 mL) were added dropwise during 3 min. Stirring was continued at -78 °C for 10 min. After addition of triethylamine (4 mL) and saturated aqueous $NaHCO_3$ (20 mL), **6a** was isolated by the work-up and purification as described above for the reaction of Table1, run 1, to give **6a** (404 mg, 90%) as a colorless oil of bp 110 °C (bath temperature) (3 mmHg). $[\alpha]_{365}^{25}$ +103 (c=1.53, benzene), corresponding to be 43% ee (*R*).[10]

Rotational Values of 6a Obtained in Table 1 All reactions were carried out by the procedure for run 1 described above for the reactions in the absence of HMPA, and for run 5 described above for the reactions in the presence of HMPA, and the products (**6a**) were purified as described above for run 1. Chemical yields of **6a** are written in Table 1, and rotational velues of **6a** were as follows. run 2: $[\alpha]_{365}^{25}$ +27.5 (c=1.53, benzene); run 3: $[\alpha]_{365}^{25}$ +58.8 (c=1.48, benzene); run 4: $[\alpha]_{365}^{25}$ +32.3 (c=0.99, benzene); run 6: $[\alpha]_{365}^{25}$ +98.6 (c=2.03, benzene); run 7: $[\alpha]_{365}^{25}$ +95.2 (c=1.96, benzene); run 8: $[\alpha]_{365}^{25}$ +97.2 (c=1.67, benzene).

Rotational Values of 6a~d Obtained in Table 2 All reactions were carried out and the products (**6a~d**) were purified as described above for the reaction of Table 1, run 5. Chemical yields of **6a** are written in Table 2, and rotational values of **6a** obtained in runs 1~12 were as follows. run 1: $[\alpha]_{365}^{25}$ +103 (c=1.53, benzene); run 2: $[\alpha]_{365}^{25}$ +84.6 (c=1.57, benzene); run 3: $[\alpha]_{365}^{25}$ -55.3 (c=1.50, benzene); run 4: $[\alpha]_{365}^{25}$ -78.7 (c=1.51, benzene); run 5: $[\alpha]_{365}^{25}$ +109 (c=1.56, benzene); run 6: $[\alpha]_{365}^{25}$ +158 (c=1.49, benzene); run 7: $[\alpha]_{365}^{25}$ +182 (c=1.70, benzene); run 8: $[\alpha]_{365}^{25}$ +182 (c=1.76, benzene); run 9: $[\alpha]_{365}^{25}$ +210 (c=1.70, benzene); run 10: $[\alpha]_{365}^{25}$ +195 (c=1.09, benzene); run 11: $[\alpha]_{365}^{25}$ +79.0 (c=1.78, benzene); run 12: $[\alpha]_{365}^{25}$ +95.0 (c=1.52, benzene). Rotational value of **6b** obtained in run 13 was $[\alpha]_{365}^{25}$ +110 (c=1.55, benzene). Rotational value of **6c** obtained in run 14 was $[\alpha]_{365}^{25}$ +178 (c=1.52, benzene). Rotational value of **6d** obtained in run 15 was $[\alpha]_{365}^{25}$ +152 (c=1.83, benzene). Absolute configuration and ee's of **6a~d** obtained were determined by these data.[10]

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10. Reinvestigation[11] showed that maximum rotations of *(R)*-**6a**, *(R)*-**6b**, *(R)*-**6c**, and *(R)*-**6d** should be $[\alpha]_{365}^{25}$ +237 (benzene), $[\alpha]_{365}^{25}$ +146 (benzene), $[\alpha]_{365}^{25}$ +228 (benzene), and $[\alpha]_{365}^{25}$ +238 (benzene), respectively. Since enantiomers of **6a~d** could not be separated by chiral columns using HPLC and GC, ee's of **6a~d** were determined polarimetrically using these values.
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