Stereoselective Reactions. XXXII.[1] Enantioselective Deprotonation of 4-*tert*-Butylcyclohexanone by Fluorine-Containing Chiral Lithium Amides Derived from 1-Phenylethylamine and 1-(1-Naphthyl)ethylamine

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Enantioselective deprotonation of 4-*tert*-butylcyclohexanone was examined using 1-phenylethylamine- and 1-(1-naphthyl)ethylamine-derived chiral lithium amides having an alkyl or a fluoroalkyl substituent at the amide nitrogen. The lithium amides having a 2,2,2-trifluoroethyl group on the amide nitrogen are easily accessible in both enantiomeric forms, and were found to induce good enantioselectivity in the present reaction.

Key words enantioselective deprotonation; 1-phenylethylamine; 1-(1-naphtyl)ethylamine; fluorine-containing alkyl group; chiral lithium amide

Lithium dialkylamides such as lithium diisopropylamide (LDA) are widely used in organic synthesis as strong bases with low nucleophilicity. In recent years, enantioselective deprotonation of prochiral carbonyl compounds by chiral lithium amides as a base and as a chiral auxiliary has received much attention to give the corresponding chiral lithium enolates.[3] We have previously reported enantioselective deprotonation of 4-*tert*-butylcyclohexanone (**1**) in the presence of excess trimethylsilyl chloride (TMSCl)[4] (internal quench (IQ) method) by a chiral chelated lithium amide ((*R*)-**2**) having a piperidino group as an internal ligation site for the lithium and 2,2,2-trifluoroethyl group on the amide nitrogen. High enantioselectivity was observed in tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME), or in THF, DME, toluene, and ether in the presence of hexamethylphosphoric triamide (HMPA).[5] Studies on the solution and solid structures[5b] have shown that (*R*)-**2** exists as a chelated monomer in THF and DME, as a chelated dimer in toluene and ether, while as a chelated monomer in these solvents in the presence of HMPA. In its monomeric form, it is shown that the piperidino group of (*R*)-**2** acts as a ligation site for the lithium to form a five-membered chelated ring, that the 2,2,2,-trifluoromethyl group exists away from the phenyl group on the five-membered chelated ring, and that one of the fluorine atoms exists in close proximity to the lithium due to electrostatic interaction.[5b] Thus, 2,2,2-trifluoroethyl group on the amide nitrogen plays a crucial role in forming a chiral amide nitrogen to induce high enantioselectivity in deprotonation reaction.[5]

In search of easily accessible chiral lithium amides that induce good enantioselectivity in the present kinetic deprotonation reaction, we designed 1-phenylethylamine-derived chiral lithium amides having an alkyl group, a fluorine-containing alkyl group, and a 2-(dimethylamino)ethyl group on the amide nitrogen, and their ability as chiral bases was examined.

Chiral secondary amines ((*R*)-**6c**—**h**) were prepared from commercially available (*R*)-1-phenylethylamine ((*R*)-**4a**) or (*R*)-1-(1-naphthyl)ethylamine ((*R*)-**4b**) by acylation to (*R*)-**5c**—**h** followed by reduction (Chart 2).[6] C_2-Symmetric chiral amine ((*R*,*R*)-**6i**) was prepared from (*R*)-2,2,2-trifluoro-1-phenylethylamine ((*R*)-**4c**)[7] *via* $LiAlH_4$ reduction of the corresponding imine ((*R*)-**8**) with trifluoroacetophenone followed by separation of the diastereomeric mixture ((*R*,*R*)-**6i** : *meso*-**6i** = 7 : 3) by column chromatography. Chiral amines (**6**) were converted to the corresponding chiral lithium amide (**7**) as usual.

Deprotonation reaction of **1** was carried out using 1.2 eq of **7** in a 50 mM concentration of lithium amide in the presence of 5 eq of TMSCl in the absence and in the presence of HMPA. In the absence of HMPA, a solution of the ketone was added to a solution of lithium amide and TMSCl (referred to as IQ-1). As shown previously,[5b] in cases where the reaction was carried out in the presence of HMPA using chiral lithium amides having a fluoroalkyl group on the amide nitrogen by IQ-1 procedure, chemical yields of the products

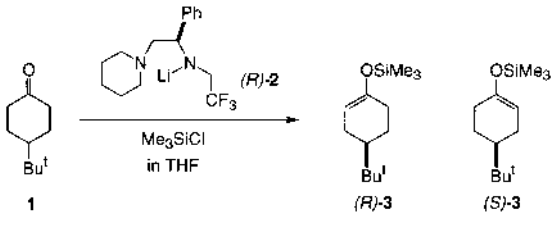

Chart 1

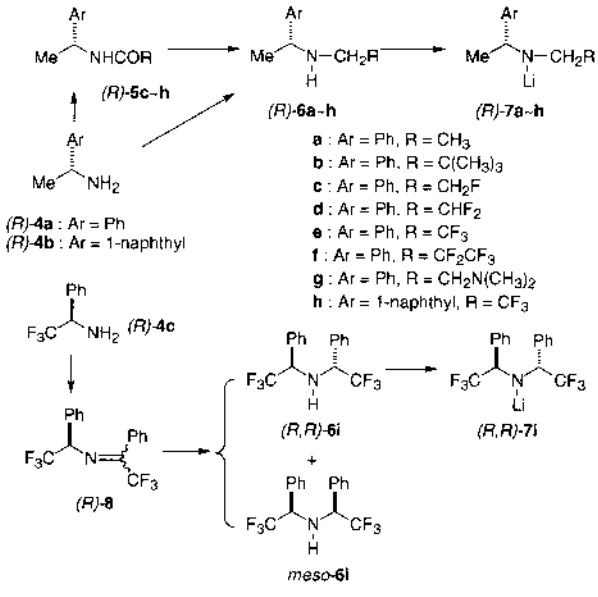

Chart 2

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Table 1. Enantioselective Deprotonation of **1** Using **7**[a)]

Run	7	Temp. (°C)	Solvent	Additive (eq)	Procedure	Product		
						3	Chem. y. (%)	Ee (%)
1	(*R*)-**7a**	−78	THF	—	IQ-1	(*S*)-**3**	55	41
2	(*R*)-**7b**	−78	THF	—	IQ-1	(*S*)-**3**	94	32
3	(*R*)-**7c**	−78	THF	—	IQ-1	(*S*)-**3**	61	43
4	(*R*)-**7d**	−78	THF	—	IQ-1	(*S*)-**3**	66	59
5	(*R*)-**7e**	−78	THF	—	IQ-1	(*S*)-**3**	98	89
6	(*R*)-**7e**	−100	THF	—	IQ-1	(*S*)-**3**	86	92
7	(*S*)-**7e**	−100	THF	—	IQ-1	(*R*)-**3**	83	92
8	(*R*)-**7e**	−78	Ether	—	IQ-1	(*S*)-**3**	15	38
9	(*R*)-**7e**	−78	Ether	HMPA (1.2)	IQ-2	(*S*)-**3**	82	36
10	(*R*)-**7e**	−78—−20	Toluene	—	IQ-1	(*S*)-**3**	6	16
11	(*R*)-**7e**	−78	Toluene	HMPA (1.2)	IQ-2	(*R*)-**3**	56	8
12	(*R*)-**7f**	−78	THF	—	IQ-1	(*S*)-**3**	92	83
13	(*R*)-**7g**	−78	THF	—	IQ-1	(*S*)-**3**	92	18
14	(*R*)-**7h**	−78	THF	—	IQ-1	(*S*)-**3**	95	86
15	(*R*,*R*)-**7i**	−78—−20	THF	HMPA (1.2)	IQ-2	(*R*)-**3**	72	16

a) For general procedure, see Experimental.

dropped due to the partial conversion of chiral lithium amides to their corresponding *N*-silylated amines. Therefore, in such cases, a solution of the ketone and TMSCl was added to a solution of the chiral lithium amide containing HMPA (referred to as IQ-2). The results are summarized in Table 1.

It is shown that the results depend heavily on the substituent on the amide nitrogen. Thus, the amides ((*R*)-**7a**, **b**) having an alkyl group gave (*S*)-**3** in low optical yields (runs 1, 2). Among the amides ((*R*)-**7c**—**e**) having a fluorine-containing alkyl group, chemical and optical yields of (*S*)-**3** increased as the number of the fluorine atoms increased (runs 3, 4, 5). The amide ((*R*)-**7e**) having a 2,2,2-trifluoroethyl group gave (*S*)-**3** in high chemical and optical yields in THF (run 5),[8)] while in low chemical and optical yields in ether and toluene (runs 8, 10) under the IQ-1 procedure. Chemical yields of the product were improved in ether and toluene in the presence of HMPA under the IQ-2 procedure, but optical yields were still low (runs 9, 11). By using the amide ((*R*)-**7f**) having a 2,2,3,3,3-pentafluoropropyl group, enantioselectivity of the reaction slightly goes declined (run 12). The amide ((*R*)-**7h**), having a 1-naphthyl group instead of a phenyl group on the chiral carbon and a 2,2,2-trifluoroethyl group on the amide nitrogen, also showed good enantioselectivity (run 14), similar to that by (*R*)-**7e** (run 5). However, the amide ((*R*,*R*)-**7i**) gave (*S*)-**3** in low optical yield (run 15). Based on the assumption that one of the fluorine atoms and the lithium in (*R*)-**7e** should be forced to come in close proximity due to the electrostatic interaction, as was observed in (*R*)-**2**,[5,9)] (*R*)-**7g** was designed with the expectation that the dimethylamino group will also orient itself in close proximity to the lithium by coordination to form a five-membered chelated ring. However, it is shown that (*R*)-**7g** gave (*S*)-**3** in quite low enantioselectivity (run 13).

In conclusion, 1-phenylethylamine- and 1-(1-naphthyl)ethylamine-derived chiral lithium amides (**7e**, **7h**) having a 2,2,2-trifluoroethyl group on the amide nitrogen are easily accessible in both enantiomeric forms, and are excellent bases for the present enantioselective deprotonation reaction.

Experimental

General All melting and boiling points are uncorrected. IR spectra were recorded on a Jasco IRA-1 or a Jasco IR Report-100 spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a JEOL EX-270 spectrometer. Chemical shifts are given in δ (ppm) using tetramethylsilane as an internal standard. Low resolution mass spectra (MS) were recorded on a JEOL JMS-01 mass spectrometer, and high resolution mass spectra (HR-MS) were recorded on a JEOL DX-300 mass spectrometer under electron impact (EI) conditions. Optical rotations were measured on a JASCO DIP-370 digital polarimeter in the solvent indicated. Enantiomeric excesses of the products (**3**) were calculated based on datum that optically pure (*R*)-**3** should show $[\alpha]_{365}^{25}$ +237° (benzene).[10)] For anhydrous solvents, THF, toluene, and ether were distilled from sodium/benzophenone ketyl, and HMPA was distilled from CaH_2. (*R*)-**6a**[11)] and (*R*)-**6b**[12)] were prepared by the reported methods.

(*R*)-*N*-Fluoroacetyl-1-phenylethylamine ((*R*)-5c) A solution of (*R*)-**4a** (9.00 g, 74.3 mmol), ethyl fluoroacetate (14.1 g, 132 mmol) and NaOMe (96%, 1.25 g, 22.2 mmol) in MeOH (50 ml) was heated under reflux for 4.5 d. The solvent was evaporated to dryness *in vacuo*, the residue was mixed with saturated aqueous NH_4Cl (50 ml), and the whole was extracted with CH_2Cl_2 (100 ml×3). The combined organic extracts were washed with brine (50 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give colorless fine needles. Recrystallization from hexane gave (*R*)-**5c** (9.70 g, 72%) as colorless fine needles of mp 79—80 °C. $[\alpha]_D^{25}$ +138° (*c*=0.91, MeOH). IR (KBr) cm^{-1}: 1655, 1545. ^{1}H-NMR: 1.54 (3H, d, *J*=7 Hz, CH_3), 4.74 (1H, dd, *J*=14, 48 Hz, CH_2F), 4.81 (1H, dd, *J*=14, 48 Hz, CH_2F), 5.20 (1H, dq, *J*=7, 7 Hz, PhCHN), 6.75 (1H, br, NH), 7.25—7.4 (5H, m, C_6H_5). MS *m*/*z*: 182 (M^++1), 181 (M^+), 180 (M^+−1). *Anal*. Calcd for $C_{10}H_{12}FNO$: C, 66.28; H, 6.67; N, 7.73. Found: C, 66.10; H, 6.70; N, 7.79.

(*R*)-*N*-Difluoroacetyl-1-phenylethylamine ((*R*)-5d) A solution of (*R*)-**4a** (6.00 g, 49.5 mmol) in MeOH (100 ml) was mixed with ethyl difluoroacetate (8.9 g, 72 mmol) and NaOMe (96%, 0.90 g, 15 mmol), and the whole was stirred at room temperature for 4 d. The reaction mixture was evaporated *in vacuo*, the residue was mixed with satd aqueous NH_4Cl (50 ml), and the whole was extracted with CH_2Cl_2 (100 ml×3). The combined organic extracts were washed with brine (50 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a colorless solid. Recrystallization from hexane (190 ml) gave (*R*)-**5d** (8.34 g, 85%) as colorless fine needles of mp 60—61 °C. $[\alpha]_D^{25}$ +147° (*c*=0.95, MeOH). IR (KBr) cm^{-1}: 1680, 1540. ^{1}H-NMR: 1.53 (3H, d, *J*=7 Hz, CH_3), 5.12 (1H, dq, *J*=7, 7 Hz, PhCHN), 5.82 (1H, t, *J*=54 Hz, CHF_2), 6.87 (1H, br, NH), 7.2—7.4 (5H, m, C_6H_5). MS *m*/*z*: 200 (M^++1), 199 (M^+), 198 (M^+−1). *Anal*. Calcd for $C_{10}H_{11}F_2NO$: C, 60.30; H, 5.57; N, 7.03. Found: C, 60.56; H, 5.68; N, 7.05.

(*R*)-*N*-Trifluoroacetyl-1-phenylethylamine ((*R*)-5e) Ethyl trifluoroacetate (17.6 g, 124 mmol) was added dropwise to (*R*)-**4a** (10.0 g, 82.5 mmol) over a period of 5 min at 0 °C. The resulting mixture solidified after stirring at room temperature for 3 min. Benzene (30 ml) was added, and the whole was concentrated to dryness *in vacuo*. This process was repeated three times. The residue was recrystallized from hexane (450 ml) to give (*R*)-**5e** (16.0 g, 89%) as colorless needles of mp 93—93.5 °C. $[\alpha]_D^{25}$ +145° (*c*=0.90, MeOH). IR (KBr) cm^{-1}: 1700, 1545. ^{1}H-NMR: 1.60 (3H, d, *J*=7 Hz, CH_3), 5.15 (1H, dq, *J*=7, 7 Hz, PhCHN), 6.42 (1H, br, NH), 7.3—

7.4 (5H, m, C_6H_5). MS *m/z*: 217 (M^+), 216 (M^+-1). *Anal*. Calcd for $C_{10}H_{10}F_3NO$: C, 55.30; H, 4.64; N, 6.45. Found: C, 55.33; H, 4.63; N, 6.65.

(*R*)-*N*-Pentafluoropropionyl-1-phenylethylamine ((*R*)-5f) By a procedure similar to the preparation of (*R*)-**5e** described above, addition of methyl pentafluoropropionate (8.8 g, 50 mmol) to (*R*)-**4a** (5.00 g, 41.3 mmol) followed by recrystallization of the resulting solid from hexane afforded (*R*)-**5f** (8.40 g, 76%) as colorless needles of mp 101—101.5 °C. $[\alpha]_D^{25}$ +126° (*c*=0.64, MeOH). IR (KBr) cm^{-1}: 1695, 1540. ^{1}H-NMR: 1.59 (3H, d, *J*=7 Hz, CH_3), 5.18 (1H, dq, *J*=7, 7 Hz, PhCHN), 6.56 (1H, br, NH), 7.2—7.4 (5H, m, C_6H_5). MS *m/z*: 267 (M^+), 266 (M^+-1), 148 ($M^+-CF_2CF_3$). *Anal*. Calcd for $C_{11}H_{10}F_5NO$: C, 49.45; H, 3.77; N. 5.24. Found: C, 49.51; H, 3.57; N. 5.52.

(*R*)-*N*-Dimethylaminoacetyl-1-phenylethylamine ((*R*)-5g) Triethylamine (12 ml, 86 mmol) was added dropwise over a period of 20 min to a solution of (*R*)-**4a** (4.67 g, 41.0 mmol), diethyl phosphorocyanidate (DEPC)[13] (90%, 8.16 g, 45.0 mmol) and *N*,*N*-dimethylglycine (86.00 g, 43.0 mmol) in *N*,*N*-dimethylformamide (DMF) (120 ml), and the whole was stirred at room temperature for 3 h. The resulting solution was diluted with a mixture of benzene (300 ml) and ethyl acetate (600 ml), and then the whole was washed with 1.5% aqueous $NaHCO_3$ (600 ml×3). The aqueous layer was extracted with a mixture of benzene (100 ml) and ethyl acetate (200 ml). The organic layers were combined and extracted with 2.5% aqueous HCl (500 ml×2, 250 ml). The aqueous extracts were combined, neutralized with solid $NaHCO_3$, and extracted with ether (300 ml×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give (*R*)-**5g** (5.62 g, 66%) as a pale yellow powder. This sample was used for the next step without further purification. An analytical sample was obtained by recrystallization of a part of this product (210 mg) from hexane (6 ml) as colorless needles (110 mg) of mp 54—55 °C. $[\alpha]_D^{25}$ +102° (*c*=0.39, MeOH). IR (KBr) cm^{-1}: 1655, 1510. ^{1}H-NMR: 1.50 (3H, d, *J*=7 Hz, CH_3), 2.27 (6H, s, $N(CH_3)_2$), 2.95 (2H, m, CH_2N), 5.17 (dq, *J*=7, 8.4 Hz, PhCHN), 7.4 (1H, br, NH), 7.2—7.4 (5H, m, C_6H_5). MS *m/z*: 206 (M^+), 191 (M^+-15). *Anal*. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.79; N, 13.58. Found: C, 69.60; H, 8.93; N, 13.44.

(*R*)-*N*-Trifluoroacetyl-1-(1-naphthyl)ethylamine ((*R*)-5h) By a procedure similar to the preparation of (*R*)-**5e** described above, the reaction of (*R*)-**4b** (11.0 g) with ethyl trifluoroacetate (12.9 g) gave a pale brown powder. Three recrystallizations from ether/hexane gave (*R*)-**5h** (7.46 g, 46%, 99.8% ee by HPLC analysis using Waters Opti-Pak XC; hexane/iso-PrOH=10/1) as slightly pink needles of mp 112—112.5 °C. $[\alpha]_D^{25}$ +63.0° (*c*=0.49, MeOH). IR (KBr) cm^{-1}: 1690. ^{1}H-NMR: 1.74 (3H, d, *J*=7 Hz, CH_3), 5.93 (1H, dq, *J*=7, 7 Hz, ArCHN), 6.6 (1H, br, NH), 7.2—7.7 (4H, m, ArH), 7.8—8.1 (3H, m, ArH). MS *m/z*: 267 (M^+), 252 (M^+-15). *Anal*. Calcd for $C_{14}H_{12}F_3NO$: C, 62.92; H, 4.53; N, 5.24. Found: C, 63.02; H, 4.53; N, 5.51.

(*R*)-*N*-(2′,2′,2′-Trifluoro-1′-phenethylidene)-2,2,2-trifluoro-1-phenylethylimine ((*R*)-8) A solution of BuLi in hexane (1.64 N, 18.5 ml, 30.3 mmol) was added to a stirred solution of (*R*)-**4c**[7] (5.30 g, 30.3 mmol) in THF (200 ml) at −78 °C under argon atmosphere. The resulting solution was stirred for 20 min at −78 °C. After addition of TMSCl (4.03 ml, 31.8 mmol), the reaction mixture was warmed to room temperature, stirred for 45 min, and then cooled to −78 °C. A solution of BuLi in hexane (1.64 N, 18.5 ml, 30.3 mmol) was added, and the resulting mixture was stirred for 30 min. Trifluoroacetophenone (4.54 ml, 33.3 mmol) was added dropwise over a period of 5 min at −78 °C, and the whole was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (200 ml), and the whole was extracted with ether (300 ml×3). The combined organic extracts were washed with brine (50 ml), dried (Na_2SO_4), and concentrated in vacuo to give a semisolid residue, which was purified by column chromatography (silica gel, hexane/ether=20/1) to give (*R*)-**8** as a pale yellow semisolid (8.07 g, 81%), followed by bulb-to-bulb distillation to give a colorless oil of $bp_{0.8}$ 180 °C (bath temperature). $[\alpha]_D^{25}$ −173° (*c*=0.87, MeOH). *Anal*. Calcd for $C_{16}H_{11}F_6N$: C, 58.01; H, 3.35; N, 4.23. Found: C, 57.74; H, 3.24, N, 4.48.

(*R*)-*N*-(2-Fluoroethyl)-1-phenylethylamine ((*R*)-6c) A solution of (*R*)-**5c** (6.90 g, 38.1 mmol) in THF (50 ml) was mixed with a solution of borane-THF complex in THF (1.0 M, 115 ml, 115 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 3 h. After addition of MeOH (30 ml), the solvent was evaporated *in vacuo*. The residue was dissolved in MeOH (30 ml), and was mixed with a solution of HCl in MeOH (38%, 20 ml) at 0 °C. The solvent was evaporated *in vacuo*, and the residue was suspended in benzene, and the benzene was evaporated *in vacuo*. This process was repeated three times to give a colorless solid. Recrystallization from iso-PrOH (150 ml) gave (*R*)-**6c**·HCl (5.96 g, 77%) as colorless fine needles of mp 219—220 °C (sublimation in the sealed capillary). $[\alpha]_D^{25}$ +14.9° (*c*=0.95, MeOH). *Anal*. Calcd for $C_{10}H_{15}ClFN$: C, 58.97; H, 7.42; N, 6.88. Found: C, 58.73; H, 7.72; N, 6.96. This salt (3.75 g, 18.4 mmol) was dissolved in 10% aqueous NaOH (30 ml) at 0 °C, and the resulting solution was extracted with hexane (100 ml×3). The combined organic extracts were washed with brine (50 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give (*R*)-**6c** (2.98 g, 97% recovery) as a colorless oil, which was subjected to bulb-to-bulb distillation to give a colorless oil of bp_5 170—180 °C (bath temperature). $[\alpha]_D^{25}$ +45.5° (*c*=0.96, MeOH). ^{1}H-NMR: 1.37 (3H, d, *J*=7 Hz, CH_3), 1.65 (1H, br, NH), 2.6—2.9 (2H, m, NCH_2), 3.81 (1H, q, *J*=7 Hz, PhCHN), 4.3—4.7 (2H, m, CH_2F), 7.2—7.4 (5H, m, C_6H_5). MS *m/z*: 168 (M^++1), 167 (M^+), 166 (M^+-1).

(*R*)-*N*-(2,2,-Difluoroethyl)-1-phenylethylamine ((*R*)-6d) Reduction of (*R*)-**5d** (8.00 g) by borane-THF and conversion of the product to the corresponding hydrochloride by the procedure similar to that for the preparation of (*R*)-**6c**·HCl described above gave (*R*)-**6d**·HCl (7.06 g, 80%) as colorless fine needles of mp 240—241 °C (sublimation in the sealed capillary). $[\alpha]_D^{25}$ +17.8° (*c*=0.81, MeOH). *Anal*. Calcd for $C_{10}H_{14}ClF_2N$: C, 54.18; H, 6.37; N, 6.32. Found: C, 54.18; H, 6.44; N, 6.53. Conversion of this salt (4.00 g) to the free amine as described above for the preparation of (*R*)-**6c** gave (*R*)-**6d** (3.17 g, 95% recovery) as a colorless oil, which was subjected to bulb-to-bulb distillation as a colorless oil of bp_5 170—180 °C (bath temperature). $[\alpha]_D^{25}$ +50.3° (*c*=1.05, MeOH). ^{1}H-NMR: 1.37 (3H, d, *J*=7 Hz, CH_3), 1.50 (1H, br, NH), 2.7—2.9 (2H, m, NCH_2CHF_2), 3.82 (1H, q, *J*=7 Hz, PhCHN), 5.77 (1H, tt, *J*=57, 4 Hz, CHF_2), 7.2—7.4 (5H, m, C_6H_5). MS *m/z*: 185 (M^+), 184 (M^+-1).

(*R*)-*N*-(2,2,2-Trifluoroethyl)-1-phenylethylamine ((*R*)-6e) A solution of borane-THF complex in THF (1.0 M, 800 ml, 0.8 mol) was added to a stirred solution of (*R*)-**5e** (44.0 g, 203 mmol) in THF (250 ml) at 0 °C, and the resulting mixture was refluxed for 10 h. MeOH (200 ml) was added to the reaction mixture, and the whole was concentrated *in vacuo*. The residue was dissolved in MeOH (200 ml), and then a solution of HCl in MeOH (20%, 200 ml) was added at 0 °C. The resulting mixture was heated under reflux for 3 h. After removal of the solvent *in vacuo*, the residue was treated by the procedure similar to that for the preparation of (*R*)-**6c**·HCl described above to give (*R*)-**6e**·HCl (46.1 g, 95%) as colorless needles of mp 235—236 °C (sublimation in the sealed capillary). $[\alpha]_D^{25}$ +17.0° (*c*=1.06, MeOH). *Anal*. Calcd for $C_{10}H_{13}ClF_3N$: C, 50.12; H, 5.05; N, 5.84. Found: C, 49.99; H, 5.30; N, 5.85. This salt (4.00 g) was dissolved in saturated aqueous $NaHCO_3$ (50 ml), and the resulting aqueous mixture was extracted with hexane (100 ml×3). The combined organic extracts were washed with brine (60 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give (*R*)-**6e** (3.35 g, 99% recovery) as a colorless oil, which was subjected to bulb-to-bulb distillation as a colorless oil of bp_5 170—180 °C (bath temperature). $[\alpha]_D^{25}$ +54.9° (*c*=0.98, MeOH). ^{1}H-NMR: 1.37 (3H, d, *J*=7 Hz, CH3), 1.62 (1H, br, NH), 3.01 (2H, q, *J*=10 Hz, CH_2CF_3), 3.91 (1H, q, *J*=7 Hz, PhCHN), 7.2—7.4 (5H, m, C_6H_5).

(*R*)-*N*-(2,2,3,3,3-Pentafluoropropyl)-1-phenylethylamine ((*R*)-6f) Reduction of (*R*)-**5f** (8.20 g) by borane-THF and conversion of the product to the corresponding hydrochloride by the procedure similar to that for the preparation of (*R*)-**6e**·HCl described above gave (*R*)-**6f**·HCl, which was recrystallized from iso-PrOH (150 ml) as colorless fine needles (6.53 g, 73%). It was not possible to measure mp of this compound in a sealed capillary because of sublimation. *Anal*. Calcd for $C_{11}H_{13}ClF_5N$: C, 45.61; H, 4.52; N, 4.84. Found: C, 45.86; H, 4.48; N, 4.90. By a procedure similar to that described above, this salt (4.00 g) was converted to (*R*)-**6f** (3.41 g, 98% recovery) as a colorless oil, which was subjected to bulb-to-bulb distillation to give a colorless oil of bp_5 180 °C (bath temperature). $[\alpha]_D^{25}$ +49.7° (*c*=1.58, MeOH). ^{1}H-NMR: 1.37 (3H, d, *J*=7 Hz, CH_3), 1.52 (1H, br, NH), 3.04 (2H, t, *J*=15 Hz, NCH_2), 3.88 (1H, q, *J*=7 Hz, PhCHN), 7.2—7.5 (5H, m, C_6H_5). MS *m/z*: 253 (M^+), 252 (M^+-1).

(*R*)-*N*-(2-(*N*′,*N*′-Dimethylamino)ethyl)-1-phenylethylamine ((*R*)-6g) A solution of (*R*)-**5g** (5.45 g, 26.4 mmol) in THF (25 ml) was added over a period of 20 min to a stirred suspension of $LiAlH_4$ (6.00 g, 158 mmol) in THF (60 ml), and the whole was stirred under reflux for 7 d. Under stirring, water (6 ml), 15% aqueous NaOH (18 ml), water (6 ml), and K_2CO_3 were added successively to the reaction mixture, and the whole was filtered. The filtrate and THF washings were combined, and evaporated to dryness *in vacuo* to give a pale yellow oil. A solution of this oil in MeOH (10 ml) was mixed with a solution of oxalic acid (5.28 g, 59 mmol) in MeOH (50 ml). The white powder, which precipitated immediately, was recrystallized from MeOH (2.7 l) to give oxalic acid salt of (*R*)-**6g** (8.06 g, 82%) as colorless fine needles of mp 208—208.5 °C. To a suspension of the above salt (5.00 g) in CH_2Cl_2 (50 ml) was added 10% aqueous NaOH (20 ml). After dissolution of the salt, the organic layer was separated, and the aqueous layer was ex-

tracted with CH_2Cl_2 (50 ml×2). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give (*R*)-**6g** (2.53 g, 98% recovery) as a colorless oil, which was subjected to bulb-to-bulb distillation as a colorless oil of $bp_{0.6}$ 170—180 °C (bath temperature). $[\alpha]_D^{25}$ +48.4° (*c*=0.94, MeOH). ^{1}H-NMR: 1.18 (3H, d, *J*=7 Hz, CH_3), 1.8 (1H, br, NH), 2.15 (6H, s, $N(CH_3)_2$), 2.2—2.6 (4H, m, NCH_2CH_2N), 3.73 (1H, q, *J*=7 Hz, PhCHN), 7.1—7.3 (5H, m, C_6H_5). MS *m*/*z*: 192 (M^+). HR-MS *m*/*z*: Calcd for $C_{12}H_{20}N_2$: 192.1626. Found: 192.1626.

(*R*)-*N*-(2,2,2-Trifluoroethyl)-1-(1-naphthyl)ethylamine ((*R*)-6h) Reduction of (*R*)-**5h** (9.00 g) by borane-THF and conversion of the product to the corresponding hydrochloride by the procedure similar to that for the preparation of (*R*)-**6e**·HCl described above, followed by recrystallization from EtOH gave (*R*)-**6h**·HCl (6.72 g, 69%) as colorless needles of mp *ca*. 210 °C (sublimation in a sealed capillary). $[\alpha]_D^{25}$ −11.7° (*c*=0.45, MeOH) *Anal*. Calcd for $C_{14}H_{15}ClF_3N$: C, 58.04; H, 5.22; N, 4.83. Found: C, 58.18; H, 5.11; N, 5.09. By a procedure similar to that described above, this salt was converted to the free amine ((*R*)-**6h**) as a pale yellow oil in almost quantitative yield, and was subjected to bulb-to-bulb distillation as a colorless oil of $bp_{0.4}$ 175—185 °C (bath temperature). $[\alpha]_D^{25}$ +75.8° (*c*=0.98, MeOH). ^{1}H-NMR: 1.48 (3H, d, *J*=7 Hz, CH_3), 1.70 (1H, br, NH), 3.08 (2H, dq, *J*=3, 10 Hz, CH_2CF_3), 4.75 (1H, q, *J*=7 Hz, ArCHN), 7.1—8.2 (7H, m, ArH). MS *m*/*z*: 235 (M^+), 238 (M^+−15).

(*R*,*R*)-Bis(2,2,2-trifluoro-1-phenylethyl)amine ((*R*,*R*)-6i) A solution of (*R*)-**8** (6.40 g, 19.3 mmol) in THF (38 ml) was added to a stirred suspension of $LiAlH_4$ (2.2 g, 58.0 mmol) in THF (12 ml) at −20 °C under argon atmosphere. The resulting mixture was stirred at −20 °C for 15 min. Usual workup gave a mixture of crude amine (6.37 g), whose diastereomeric ratio was 7 : 3 by gas chromatography (SE-30, 150 °C), Purification by column chromatography (silica gel, hexane/benzene=50/1) gave (*R*,*R*)-**6i** (3.39 g, 53%) as colorless prisms of mp 66.5—67.5 °C. $[\alpha]_D^{25}$ −153° (*c*=1.14, MeOH). ^{1}H-NMR: 2.55 (1H, t, *J*=7 Hz, NH), 3.92 (2H, dq, *J*=7, 7 Hz, PhCHN), 7.2—7.5 (10 H, C_6H_5). MS *m*/*z*: 333 (M^+). *Anal*. Calcd for $C_{16}H_{13}F_6N$: C, 57.66; H, 3.93; N, 4.20. Found: C, 57.68; H, 3.83; N, 4.50. meso-**6i** (0.71 g, 10%) was also isolated as a colorless oil. ^{1}H-NMR: 2.36 (1H, t, *J*=7 Hz, NH), 4.25 (2H, dq, *J*=7, 7 Hz, PhCHN), 7.2—7.4 (10H, m, C_6H_5). MS *m*/*z*: 333 (M^+). *Anal*. Calcd for $C_{16}H_{13}F_6N$: C, 57.66; H, 3.93; N, 4.20. Found: C, 57.36; H, 3.63; N, 4.46.

A Typical Procedure for the Deprotonation Reaction in the Absence of HMPA (IQ-1) (Table 1, Run 6) A solution of BuLi in hexane (1.55 N, 1.55 ml, 2.4 mmol) was added to a stirred solution of (*R*)-**6e** (508 mg, 2.5 mmol) in THF (50 ml) at −78 °C under argon atmosphere. The resulting solution was stirred at −78 °C for 30 min, and then cooled to −100 °C. After addition of TMSCl (1.27 ml, 10 mmol), a solution of **1** (308 mg, 2.0 mmol) in THF (4 ml) was added dropwise during a period of 6 min. After stirring at −100 °C for 50 min, the reaction mixture was quenched by addition of triethylamine (4 ml) and saturated aqueous $NaHCO_3$ (10 ml), and the whole was allowed to warm to room temperature. After addition of water (15 ml), the mixture was extracted with hexane (50 ml×3). The combined organic extracts were washed successively with water (20 ml×2), 0.1 N aqueous citric acid (100 ml×2, 50 ml×3), water (20 ml), saturated aqueous $NaHCO_3$ (20 ml) and brine (40 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give a yellow oil. Purification by column chromatography (silica gel, hexane) followed by bulb-to-bulb distillation gave (*S*)-**3** (388 mg, 86%) as a colorless oil of $bp_{0.5}$ 150 °C (bath temperature). $[\alpha]_D^{25}$ −217° (*c*=1.49, benzene), corresponding to be 92% ee.[10]

Rotational Values of 3 Obtained by the Reactions (Table 1) Run 1: $[\alpha]_{365}^{25}$ −97° (*c*=1.59, benzene); run 2: $[\alpha]_{365}^{25}$ −76° (*c*=1.50, benzene); run 3: $[\alpha]_{365}^{25}$ −103° (*c*=1.38, benzene); run 4: $[\alpha]_{365}^{25}$ −141° (*c*=1.42, benzene); run 5: $[\alpha]_{365}^{25}$ −211° (*c*=1.44, benzene); run 7: $[\alpha]_{365}^{25}$ +217° (*c*=1.49, benzene); run 8: $[\alpha]_{365}^{25}$ −89° (*c*=1.29, benzene); run 9: $[\alpha]_{365}^{25}$ −86° (*c*=1.45, benzene); run 10: $[\alpha]_{365}^{25}$ −37° (*c*=0.90, benzene); run 11: $[\alpha]_{365}^{25}$ −18° (*c*=1.70, benzene); run 12: $[\alpha]_{365}^{25}$ −197° (*c*=1.64, benzene); run 13: $[\alpha]_{365}^{25}$ −44° (*c*=1.48, benzene); run 14: $[\alpha]_{365}^{25}$ −203° (*c*=1.58, benzene); run 15: $[\alpha]_{365}^{25}$ +9.3° (*c*=1.00, benzene).

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References and Notes

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