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Stereoselective Reactions. 28.[1] Effects of the Alkyl Group at the Amide Nitrogen of Chiral Bidentate Lithium Amides on Enantioselective Deprotonation Reaction

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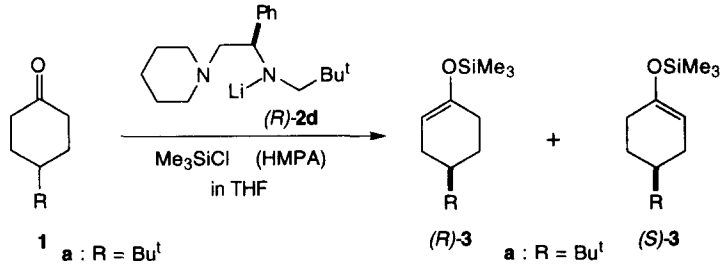
Abstract: Enantioselective deprotonation of 4-substituted cyclohexanones (**1a~d**) by chiral bidentate lithium amides ((*R*)-**2a~j**) having an alkyl- or a fluoroalkyl substituent at the amide nitrogen was examined. (*R*)-**2i** having a 2,2,2-trifluoroethyl group at the amide nitrogen was found to be an excellent chiral base for the present deprotonation reaction. Structures of (*R*)-**2i** in solution and solid state are discussed. © 1997 Elsevier Science Ltd.

INTRODUCTION

Enantioselective deprotonation of a prochiral cyclic ketone by a chiral lithium amide as a base and as a chiral auxiliary to give the corresponding chiral lithium enolate has received much attention in recent years.[3~5] We have previously reported enantioselective deprotonation of 4-substituted cyclohexanones (**1a~d**) by various chiral lithium amides such as a chiral bidentate lithium amide ((*R*)-**2d**) in the presence of excess trimethylsilyl chloride (TMSCl) (internal quench (IQ) method[6]) and isolation of the resulting chiral lithium enolates as their trimethylsilyl enol ethers (**3a~d**).[5]



1 **a** : R = Bu^t
b : R = Ph
c : R = Pr^i
d : R = Me

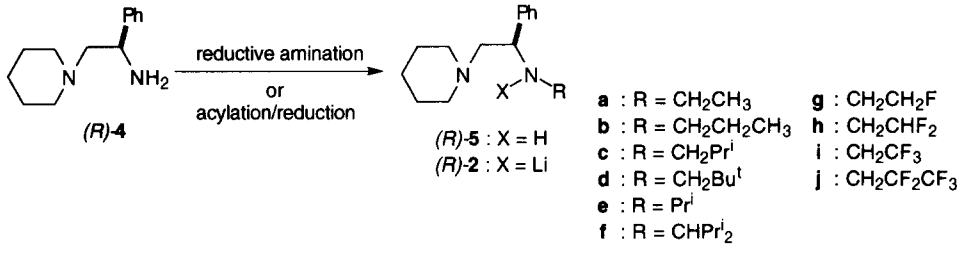
(*R*)-**3** (*S*)-**3**
a : R = Bu^t
b : R = Ph
c : R = Pr^i
d : R = Me

It is already shown that (*R*)-**2d** induces reasonably good enantioselectivity in the present deprotonation reaction of **1a~d** to give (*R*)-**3a~d** in excesses.[5b,5c,5h] In order to study structural requirements for bidentate chiral lithium amides to exhibit high enantioselectivity in deprotonation, we examined analogues of (*R*)-**2d** by substituting its neopentyl group at the amide nitrogen for other alkyl group ((*R*)-**2a~c, e~f**). Chiral lithium

amides (*(R)*-**2g~j**) having a fluorine-containing alkyl group were also examined, because of the possible interactions between the fluorine and the lithium.[7~11]

RESULTS AND DISCUSSION

***Synthesis of Chiral Bidentate Amines* (*(R)*-5a~j)** Chiral bidentate amines (*(R)*-**5a~j**) were all prepared from the known *(R)*-**4**[12] by reductive amination or acylation followed by reduction. Chiral lithium amides (*(R)*-**2a~j**) were prepared from these chiral amines by addition of butyllithium *in situ* as usual.



Deprotonation of* 1a~d *by (R)*-2a~j *in THF Deprotonation reactions of **1a~d** by *(R)*-**2a~j** were carried out in the presence of excess TMSCl in THF in the absence and in the presence of hexamethylphosphoric triamide (HMPA) at -78 °C. In the absence of HMPA, a solution of the ketone was added to a solution of the chiral lithium amide and TMSCl in THF (procedure IQ-1). However, in cases where the reactions were carried out by the same procedure in the presence of 1.2 equivalents of HMPA, chemical yields of the products (*(R)*-**3a~d**) dropped due to the formation of the *N*-silylated chiral amines. In these cases, a solution of the ketone and TMSCl in THF was added to a solution of the lithium amide in THF containing HMPA (procedure IQ-2). By this procedure, the products were obtained in reasonably good yields. The results are summarized in Table 1.

It is interesting to note that, for the lithium amides (*(R)*-**2a~d**) having an α-unbranched alkyl group, enantioselectivity of the reaction increases as the size at the β-position of the alkyl group increases (CH_2Me < CH_2Et < CH_2Pr^i < CH_2Bu^t) in the absence of HMPA (runs 1~4), while the difference in enantioselectivity is quite small in the presence of 1.2 equivalents of HMPA (runs 11~14). A similar phenomenon was observed for the lithium amides (*(R)*-**2g~j**) having a fluoroalkyl group at the amide nitrogen. Thus, enantioselectivity of the reaction increases as the number of fluorine atom at β- (and γ-) position(s) increases in the absence of HMPA (runs 7~10), while it is higher and remains rather constant in the presence of 1.2 equivalents of HMPA (runs 17~20). It is known that addition of HMPA deaggregates lithium amides in solution,[5b,5h] and it is shown that the existence of 1.2 equivalents of HMPA is enough to affect the enantioselectivity of the reaction (runs 21~23). On the other hand, enantioselectivity of the reaction is moderate by using chiral lithium amides (*(R)*-**2e~f**) having an α-branched alkyl group at the amide nitrogen in the absence and in the presence of HMPA (runs 5~6, and 15~16).

Since *(R)*-**2d, h~j** showed better results, reactions using these lithium amides were carried out at -100 °C as summarized in Table 2. Enantioselectivity of the reaction was improved as expected. By using *(R)*-**2i** in

THF in the presence of 1.2 equivalents of HMPA, 4-substituted cyclohexanones (**1a~d**) were converted to the corresponding *(R)*-**3a~d** in 93~95% ee,[13,14] irrespective of the size of the substituent at 4-position of **1**.

Table 1. Deprotonation of 1a by *(R)*-2a~j in THF at -78 °C to Give *(R)*-3a

	Chiral lithium amide				Product (*(R)*-**3a**)	
Run	*(R)*-**2**	R in **2**	HMPA (eq.)	Procedure[a]	Chem. y. (%)	Optical y. (%)
1	**2a**	CH_2CH_3	0	IQ-1	86	52
2	**2b**	$CH_2CH_2CH_3$	0	IQ-1	96	62
3	**2c**	CH_2Pr^i	0	IQ-1	92	81
4	**2d**	CH_2Bu^t	0	IQ-1	93	86
5	**2e**	Pr^i	0	IQ-1	87	65
6	**2f**	$CHPr^i_2$	0	IQ-1	97	59
7	**2g**	CH_2CH_2F	0	IQ-1	85	69
8	**2h**	CH_2CHF_2	0	IQ-1	93	77
9	**2i**	CH_2CF_3	0	IQ-1	88	84
10	**2j**	$CH_2CF_2CF_3$	0	IQ-1	79	85
11	**2a**	CH_2CH_3	1.2	IQ-2	93	78
12	**2b**	$CH_2CH_2CH_3$	1.2	IQ-2	97	80
13	**2c**	CH_2Pr^i	1.2	IQ-2	77	78
14	**2d**	CH_2Bu^t	1.2	IQ-2	94	84
15	**2e**	Pr^i	1.2	IQ-2	73	75
16	**2f**	$CHPr^i_2$	1.2	IQ-2	98	59
17	**2g**	CH_2CH_2F	1.2	IQ-2	67	85
18	**2h**	CH_2CHF_2	1.2	IQ-2	92	89
19	**2i**	CH_2CF_3	1.2	IQ-2	74	87
20	**2j**	$CH_2CF_2CF_3$	1.2	IQ-2	77	87
21	**2a**	CH_2CH_3	2.4	IQ-2	88	78
22	**2i**	CH_2CF_3	2.4	IQ-2	69	87
23	**2i**	CH_2CF_3	4.0	IQ-2	53	82

[a] See the text and experimental section.

Table 2. Deprotonation of 1 by *(R)*-2d, h~j in THF at -100 °C to Give *(R)*-3

		Chiral lithium amide				Product		
Run	Ketone	*(R)*-**2**	R in **2**	HMPA (eq.)	Procedure[a]	*(R)*-**3**	Chem. y. (%)	Optical y. (%)
1	**1a**	**2d**	CH_2Bu^t	0	IQ-1	**3a**	61	92
2	**1a**	**2h**	CH_2CHF_2	0	IQ-1	**3a**	75	85
3	**1a**	**2i**	CH_2CF_3	0	IQ-1	**3a**	82	91
4	**1a**	**2j**	$CH_2CF_2CF_3$	0	IQ-1	**3a**	77	90
5	**1a**	**2d**	CH_2Bu^t	1.2	IQ-2	**3a**	78	89
6	**1a**	**2h**	CH_2CHF_2	1.2	IQ-2	**3a**	70	92
7	**1a**	**2i**	CH_2CF_3	1.2	IQ-2	**3a**	88	93
8	**1a**	**2j**	$CH_2CF_2CF_3$	1.2	IQ-2	**3a**	84	92
9	**1b**	**2i**	CH_2CF_3	1.2	IQ-2	**3b**	95	93
10	**1c**	**2i**	CH_2CF_3	1.2	IQ-2	**3c**	92	95
11	**1d**	**2i**	CH_2CF_3	1.2	IQ-2	**3d**	76	94

[a] See the text and experimental section.

Dependence of Enantioselectivity on Solvent and HMPA in the Deprotonation of 1a by (R)-2i Since *(R)*-**2i** was found to be an excellent base in deprotonation of **1** in THF in the absence and in the presence of HMPA as shown in Tables 1 and 2, examinations were made on the effects of solvent and HMPA to the reaction. The results of the deprotonation of **1a** are summarized in Table 3.

Table 3. Deprotonation of 1a by *(R)*-2i in Several Solvents at -78 °C to Give *(R)*-3a

	Without HMPA[a]			With HMPA (1.2 eq.)[b]		
Solvent	Run	Chem. y. (%)	Optical y. (%)	Run	Chem. y. (%)	Optical y. (%)
THF	1	88	84	5	74	87
DME	2	84	71	6	71	85
ether	3	59	67	7	78	84
toluene	4[c]	30	35	8	71	87

[a] Reactions were carried out by IQ-1 procedure. [b] Reactions were carried out by IQ-2 procerure.
[c] Reaction was carried out at -78 °C for 40 min, at -45 °C for 1.5 hr, and then at 0 °C for 17 hr.

It is shown that deprotonation of **1a** in the absence of HMPA depends upon the solvent used. Chemical yield and ee of the product (*(R)*-**3a**) change from higher to lower as the solvent is changed from THF to DME, to ether, and to toluene (runs 1~4). In the presence of HMPA (1.2 equivalents), however, they are almost the same in these solvents (runs 5~8). This phenomenon is similar to that observed by using *(R)*-**2d** as a chiral lithium amide.[5b,5i]

^{6}Li, ^{15}N, and ^{19}F-NMR Spectral Studies on [^{6}Li,$^{15}N_2$]-(R)-2i in the Absence of HMPA-d_{18} [$^{15}N_2$]-*(R)*-**5i** was prepared from [$^{15}N_2$]-*(R)*-**4**[5i] by the reported method.[12] Solutions of [^{6}Li,$^{15}N_2$]-*(R)*-**2i** in THF-d_8, DME-toluene-d_8 (4:1), ether-toluene-d_8 (4:1), and toluene-d_8 were prepared by the method reported previously.[5i] ^{6}Li-, ^{15}N-, and ^{19}F-NMR spectra are shown in Figure 1.[15,16]

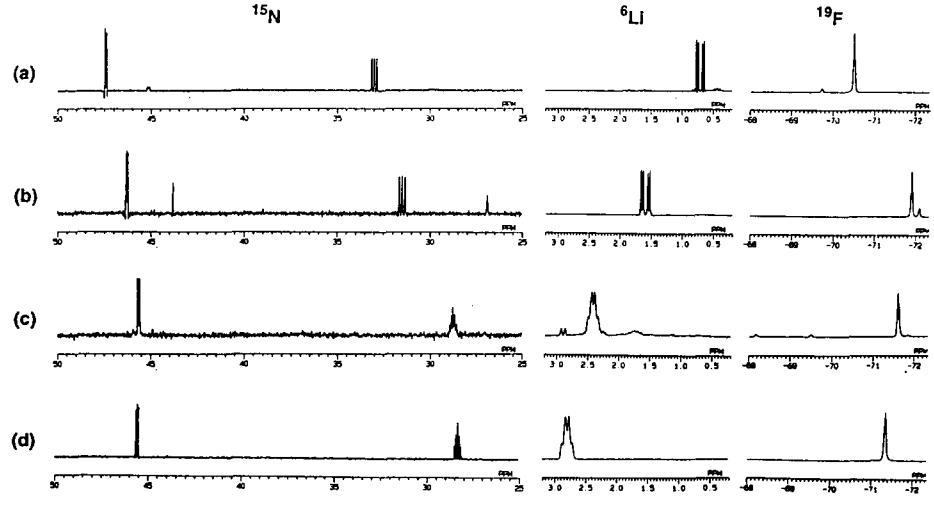
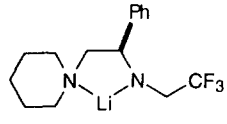


Figure 1. ^{6}Li-, ^{15}N-, and ^{19}F-NMR spectra of a ca. 0.07*M* solution of [^{6}Li,$^{15}N_2$]-*(R)*-**2i** recorded at -80 °C. (a) in THF-d_8; (b) in DMF-toluene-d_8 (4:1); (c) in ether-toluene-d_8 (4:1); (d) in toluene-d_8.

In THF-d_8 and DME-toluene-d_8 (4:1) (Figure 1, (a) and (b)), the ^{15}N-NMR spectrum of [^{6}Li,$^{15}N_2$]-*(R)*-**2i** shows two sets of triplets (1:1:1), indicating that each nitrogen atom couples to one neighboring ^{6}Li nucleus. The ^{6}Li spectrum displays a doublet of doublets, indicative of coupling to two neighboring ^{15}N nuclei. The ^{19}F spectrum shows simply a triplet (1:2:1), indicating that fluorine atoms are equivalent and couple only to the neighboring methylene protons, and that coupling between fluorine atom and ^{6}Li nucleus is not observed.

In ether-toluene-d_8 (4:1) and toluene-d_8 (Figure 1, (c) and (d)), the ^{15}N-NMR spectrum of [^{6}Li,$^{15}N_2$]-*(R)*-**2i** shows a triplet (1:1:1) and a quintet (1:2:3:2:1), indicating that one nitrogen couples to one ^{6}Li nucleus, while the other nitrogen couples to two ^{6}Li nuclei. The ^{6}Li spectrum displays a doublet of triplets, indicative of coupling to three ^{15}N nuclei. The ^{19}F spectrum shows a triplet (1:2:1), indicating that three equivalent fluorine atoms couple only to the methylene protons.

These coupling patterns are quite similar to those observed for *(R)*-**2d** in these solvents,[5b,i] and suggest that *(R)*-**2i** exists as a chelated monomer (**6**) in THF and DME, while as a chelated dimer (**7**) in ether and toluene.



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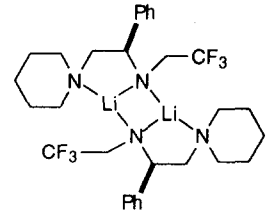

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^{6}Li, ^{15}N, and ^{19}F-NMR Spectral Studies on [^{6}Li,$^{15}N_2$]-(R)-2i in the Presence of HMPA-d_{18} ^{6}Li-, ^{15}N-, and ^{19}F-NMR spectral studies on [^{6}Li,$^{15}N_2$]-*(R)*-**2i** were carried out in THF-d_8, DME-toluene-d_8, and ether-toluene-d_8 in the presence of 2 equivalents of HMPA-d_{18}.[17] The spectra are shown in Figure 2.[16]

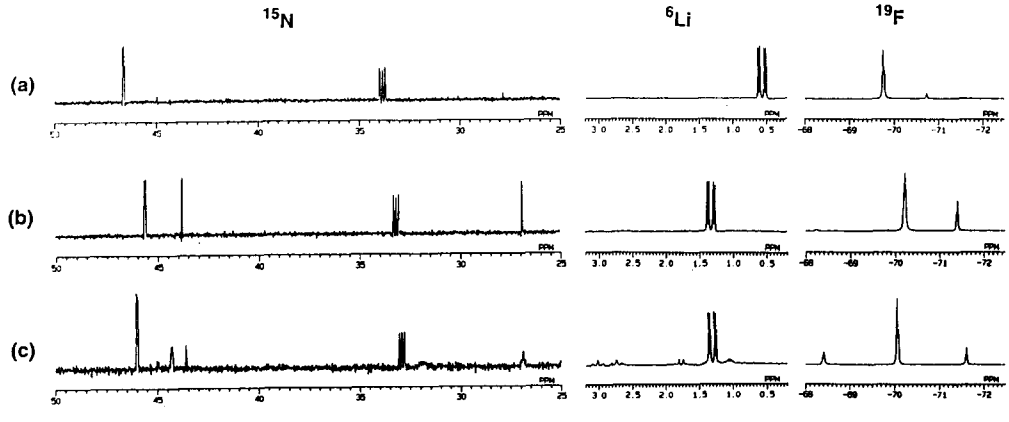

Figure 2. ^{6}Li-, ^{15}N-, and ^{19}F-NMR spectra of a ca. 0.07*M* solution of [^{6}Li,$^{15}N_2$]-*(R)*-**2i** in the presence of 2.0 equivalents of HMPA-d_{18} recorded at -80 °C. (a) in THF-d_8; (b) in DME-toluene-d_8 (4:1); (c) in ether-toluene-d_8 (4:1).

It is shown that the coupling patterns of the major signals of [^{6}Li,$^{15}N_2$]-*(R)*-**2i** are those of the chelated monomer (**6**) in all of these solvents. Thus, ^{15}N-NMR spectra show two sets of triplets (1:1:1), while ^{6}Li spectra show a doublet of doublets, and ^{19}F-NMR spectra show a triplet. These observations clearly demonstrate that, the monomer (**6**) still holds in THF and DME-toluene (4:1) by addition of HMPA, while deaggregation from the dimer (**7**) to the monomer (**6**) occurs in ether-toluene (4:1) by addition of HMPA. This phenomenon is similar to that observed for *(R)*-**2d**.[5b,i]

X-Ray Analysis of Crystalline (R)-2i Isolated from THF-Solution Crystalline *(R)*-**2i** was isolated from THF solution as air-sensitive colorless prisms, and was subjected to X-ray analysis at -40 °C.[18] The structure is shown in Figure 3.

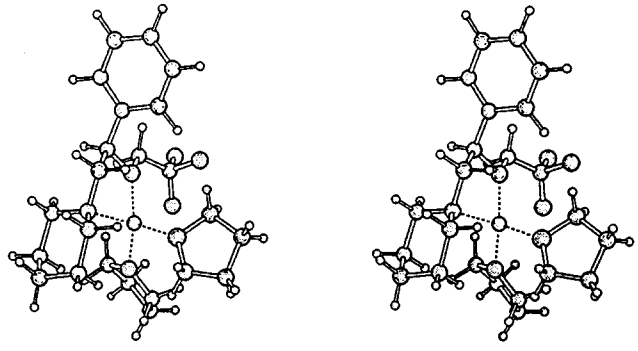

Figure 3. Crystal structure (stereoview) of *(R)*-**2i** obtained from THF solution.

As predicted by NMR spectral studies in THF (Figure 1(a)), the X-ray structure of crystalline *(R)*-**2i** isolated from THF solution is the chelated monomeric form solvated by 2 molecules of THF. The lithium is tetra-coordinated, and the amide nitrogen is nearly planar. The trifluoromethyl group exists away from the phenyl group, and the distance between one of the fluorine atoms and the lithium is very close (3.10Å).

Effect of Fluoroalkyl Group at the Amide Nitrogen It is reported that effective van der Waals radius (in Å) of fluorine (1.47) is larger than that of hydrogen (1.20) but smaller than that of methyl (1.80), while that of trifluoromethyl (2.2) is larger than that of methyl, almost comparable to that of isopropyl (2.2), but reasonably smaller than that of *tert*-butyl (3.6).[19] Conformational energy (in kcal/mole) of fluorine (0.25~0.42) is larger than that of hydrogen (0) but smaller than that of methyl (1.74), while that of trifluoromethyl (2.4~2.5) is larger than that of methyl, almost comparable to that of isopropyl (2.2), but reasonably smaller than that of *tert*-butyl (4.7~4.9).[20]

It is found that chiral lithium amides (*(R)*-**2g~j**) having a fluorine-containing ethyl or propyl group at the amide nitrogen are distinctly superior to *(R)*-**2a** or *(R)*-**2b** having an ethyl or propyl group there. For example, in Table 1, it is shown that *(R)*-**2g** having a monofluoroethyl group at the amide nitrogen induces higher enantioselectivity than *(R)*-**2b** having a propyl group there (runs 7 vs. 2, runs 17 vs. 12). It is also shown that *(R)*-**2i** having a trifluoroethyl group induces higher enantioselectivity than *(R)*-**2c** having an isobutyl group there (runs 9 vs. 3, runs 19 vs. 13), while induces almost the same enantioselectivity as *(R)*-**2d** having a neopentyl group there (runs 9 vs. 4, runs 19 vs. 14). It is thus clear that the superiority of chiral lithium amides having a fluoroalkyl group is not ascribable to the difference in the bulkiness of the alkyl group on the amide nitrogen. It is conceivable that electrostatic interaction between the fluorine and the lithium is responsible.

CONCLUSION

It is experimentally shown that enantioselectivity of the deprotonation reactions of 4-substituted cyclohexanones (**1**) by chiral bidentate lithium amides (*(R)*-**2**) depends upon the alkyl substituent at the amide nitrogen of *(R)*-**2**. To get higher enantioselectivity, the alkyl substituent should be bulky at the β-position of the alkyl group such as *(R)*-**2d**, or the alkyl substituent should have fluorine atoms at β- (and γ-) positions such as *(R)*-**2i**.

EXPERIMENTAL SECTION

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 on a JEOL GSX-400 (400 MHz), a JEOL EX-270 (270 MHz), or a JEOL FX-100 (100 MHz) spectrometer. Chemical shifts are given in δ (ppm) values using THF-d_8 (δ = 3.60) or toluene-d_8 (δ = 6.98) as an internal standard. ^{13}C NMR spectra were recorded on a JEOL GSX-400 (100 MHz) or a JEOL EX-270 (67.5 MHz). Chemical shifts are given in δ (ppm) values using the central peak of $CDCl_3$ (δ = 77.0) as an internal standard. ^{6}Li-, ^{15}N- and ^{19}F-NMR spectra were recorded on a JEOL GSX-500 spectrometer operating at 73.45, 50.55 and 470.40 MHz, respectively. ^{6}Li chemical shifts are given in δ (ppm) values using ^{6}LiCl (0.3 *M* in THF-d_8 or 0.07 *M* in MeOH-toluene-d_8 (7/1 v/v) (δ = 0.00)) as an external standard. ^{15}N chemical shifts are given in δ (ppm) values using [^{15}N]aniline (0.16 *M* in THF-d_8 or toluene-d_8 (δ = 52.00)) as an external standard. ^{19}F chemical shifts are given in δ (ppm) values using $CFCl_3$ (in THF-d_8 or toluene-d_8 (δ = 0.00)) as an external standard. Data are reported as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (hertz), and assignments where relevant. Low resolution mass spectra (LRMS) were recorded on a JEOL JMS-01 mass spectrometer, and high resolution mass spectra (HRMS) were recorded on a DX-300 mass spectrometer under electron impact (EI) conditions. Optical rotations were measured on a JASCO DIP-370 digital polarimeter in the solvent indicated. For anhydrous reactions, THF was freshly distilled from sodium/benzophenone ketyl and HMPA was distilled from CaH_2. *(R)*-**4**, *(R)*-**5d**, *(R)*-**5e**, and *(R)*-**5i** were prepared by the reported method.[12]

***(R)*-*N*-Ethyl-1-phenyl-2-piperidinoethylamine (*(R)*-5a)** Acetic anhydride (0.95 mL, 9.9 mmol) was added dropwise to a solution of (*R*)-**4** (1.69 g, 8.27 mmol) and triethylamine (2.32 mL, 16.5 mmol) in CH_2Cl_2 (17 mL) under cooling, and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was mixed with water (5 mL) and 10 % aqueous NaOH (20 mL), and then the whole was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried (K_2CO_3), filtered, and concentrated *in vacuo* to give (*R*)-*N*-(1-phenyl-2-piperidinoethyl)acetamide (1.84 g, 90 %) as a pale yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): 1.4–1.7 (6 H, br, $NCH_2(CH_2)_3CH_2$), 2.01 (3 H, s, CH_3), 2.2–2.4 (2 H, br, $NCH_2(CH_2)_3CH_2$), 2.4–2.6 (2 H, br, $NCH_2(CH_2)_3CH_2$), 2.47 (1 H, dd, *J* = 6, 13 Hz, NCH_2CHPh), 2.55 (1 H, dd, *J* = 10, 13 Hz, NCH_2CHPh), 4.90 (1 H, ddd, *J* = 5, 10, 10 Hz, $CHPh$), 6.7 (1 H, br, $NHCO$), 7.1–7.3 (5 H, m, C_6H_5). IR (neat) cm^{-1}: 3320, 1660, 1560. MS *m/z*: 245 (M^+–1). A solution of this amide (1.89 g, 7.67 mmol) in THF (2 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.91 g, 23 mmol) in THF (15 mL) at 0 °C, and

the mixture was stirred at room temperature for 13.5 h and then heated under refluxed for 1.5 h. While stirring and cooling with an ice bath, water (0.9 mL), 15 % aqueous NaOH (0.9 mL), water (2.7 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 then the solvent was evaporated *in vacuo* to give a pale yellow oil. Purification by column chromatography (Al_2O_3, 4:1 hexane/ether) gave a colorless oil (1.35 g). A solution of this oil in MeOH was mixed with a 38 % solution of HCl in MeOH (7.5 mL) at 0 °C. The solvent was evaporated *in vacuo*, 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 EtOH/ether (20 mL/10 mL) gave *(R)*-**5a**·2HCl (1.41 g, 60 %) as colorless needles of mp 236–238 °C (dec). $[\alpha]_D^{25}$ = –9.5 (*c* 0.99, MeOH). Anal. Calcd for $C_{15}H_{26}N_2Cl_2$: C, 59.01; H, 8.52; N, 9.18. Found: C, 58.86; H, 8.59; N, 8.94. This salt (1.25 g) was dissolved in 10 % aqueous NaOH (20 mL) at 0 °C and then the solution was extracted with hexane (3 x 40 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), and concentrated to dryness *in vacuo* to give (*R*)-**5a** (0.95 g, quantitative) as a colorless oil. $[\alpha]_D^{25}$ = –81.8 (*c* 1.18, MeOH). ^{1}H NMR (100 MHz, $CDCl_3$): 1.09 (3 H, t, *J* = 7 Hz, C*H*$_3$), 1.25–1.80 (6 H, m, $CH_2(CH_2)_3CH_2$), 2.10–2.70 (9 H, m, 4 x NC*H*$_2$, N*H*), 3.77 (1 H, dd, *J* = 4, 10 Hz, PhC*H*CH$_2$), 7.1–7.5 (5 H, m, C$_6$*H*$_5$). ^{13}C NMR (100 MHz, $CDCl_3$) : 15.3, 24.3, 26.0, 41.9, 54.4, 59.9, 66.4, 126.7, 127.1, 128.0, 143.2. MS *m/z*: 233 (M^++1), 231 (M^+–1).

(*R*)-*N*-Propyl-1-phenyl-2-piperidinoethylamine ((*R*)-5b) Propionaldehyde (1.63 mL, 22.5 mmol) was mixed with an ice-cooled solution of (*R*)-**4** (4.00 g, 19.6 mmol) in benzene (80 mL), and the whole was stirred at room temperature for 30 min. The reaction mixture was dried (Na_2SO_4), filtered, and concentrated to dryness *in vacuo* to obtain the corresponding imine (4.79 g, quantitative) as a pale yellow oil. ^{1}H NMR (270 MHz, C_6D_6): 1.11 (3 H, t, *J* = 8 Hz, C*H*$_3$), 1.3–1.9, 2.2–2.8 (14 H, m, $NCH_2(CH_2)_3CH_2$, NC*H*$_2$ x 3, C*H*$_2$CH$_3$), 4.22 (1 H, dd, *J* = 4, 9 Hz, C*H*Ph), 7.1–7.4 (5 H, m, C$_6$*H*$_5$), 7.68 (1 H, t, *J* = 5 Hz, N=C*H*). IR (neat) cm^{-1}: 1665. $NaBH_4$ (1.48 g, 39.2 mmol) was added in small portions to a solution of this imine (4.79 g) in EtOH (80 mL) at 0 °C, and the resulting solution was stirred at room temperature for 50 min. Evaporation of the solvent *in vacuo* gave a residue, which was mixed with saturated aqueous $NaHCO_3$, and the whole was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a pale yellow oil. Purification by column chromatography (Al_2O_3, 4:1 hexane/ether) gave a colorless oil, which was converted to the corresponding HCl salt as described above. Recrystallization from $CHCl_3$ gave *(R)*-**5b**·2HCl as colorless needles of mp 254–255 °C (dec). $[\alpha]_D^{25}$ = –8.7 (*c* 0.92, MeOH). By a similar procedure described above, the free amine (*(R)*-**5b**) (3.88 g, 80 %) was obtained from this salt as a colorless oil. An analytical sample was obtained by bulb-to-bulb distillation as a colorless oil of $bp_{0.3}$ 170–180 °C (bath temperature). $[\alpha]_D^{25}$ = –87.0 (*c* 0.99, MeOH). ^{1}H NMR (270 MHz, $CDCl_3$): 0.89 (3 H, t, *J* = 7 Hz, C*H*$_3$), 1.4–1.6 (8 H, m, $NCH_2(CH_2)_3CH_2$, C*H*$_2$CH$_3$), 2.2–2.6 (9 H, m, NC*H*$_2$ x 4, N*H*), 3.74 (1 H, dd, *J* = 4, 11 Hz, C*H*), 7.2–7.4 (5 H, m, C$_6$*H*$_5$). ^{13}C NMR (67.5 MHz, $CDCl_3$) : 11.7, 23.1, 24.5, 26.2, 49.8, 54.6, 60.0, 66.6, 126.8, 127.3, 128.1, 143.4. MS *m/z*: 247 (M^++1), 245 (M^+–1), 217 (M^+–29). Anal. Calcd for $C_{16}H_{26}N_2$: C, 78.00; H, 10.64; N, 11.37. Found: C, 77.95; H, 10.79; N, 11.46.

(*R*)-*N*-(2-Methylpropyl)-1-phenyl-2-piperidinoethylamine ((*R*)-5c) By a similar procedure described above, condensation of (*R*)-**4** (3.50 g, 17.1 mmol) with isobutyraldehyde (1.3 g, 18 mmol) gave the corresponding imine (4.41 g, quantitative) as a colorless oil. ^{1}H NMR (270 MHz, C_6D_6): 1.01

(3 H, d, J = 7 Hz, CH_3), 1.07 (3 H, d, J = 7 Hz, CH_3), 1.2–1.6 (6 H, m, $NCH_2(CH_2)_3CH_2$), 2.2–2.5 (5 H, m, NCH_2 x 2, $CH(CH_3)_2$), 2.49 (1 H, dd, J = 4, 13 Hz, NCH_2CHPh), 2.68 (1 H, dd, J = 9, 13 Hz, NCH_2CHPh), 4.16 (1 H, dd, J = 4, 9 Hz, $CHPh$), 7.1-7.3 (3 H, m, C_6H_5), 7.43 (1 H, d, J = 5 Hz, N=CH), 7.57 (2 H, m, C_6H_5). IR (neat) cm^{-1}: 1665. This imine (4.40 g, 17 mmol) was treated with $NaBH_4$ (1.3 g, 34 mmol) in EtOH, and worked up as described above to give a colorless oil, which was converted to the corresponding HCl salt as described above. Recrystallization from *iso*-PrOH/ether (10 mL/50 mL) gave *(R)*-**5c**·2HCl (5.24 g, 92 %) as colorless needles of mp 213–215 °C. IR (KBr) cm^{-1}: 2950, 2700, 2650, 1560, 1450, 1440, 1000. By a similar procedure described above, the free amine (*(R)*-**5c**) (3.22 g) was obtained from this salt as a colorless oil. An analytical sample was obtained by bulb-to-bulb distillation as a colorless oil of $bp_{0.3}$ 160–170 °C (bath temperature). $[\alpha]_D^{25}$ = –90.8 (*c* 0.78, MeOH). ^1H NMR (270 MHz, $CDCl_3$): 0.89 (3 H, t, J = 7 Hz, CH_3), 0.90 (3 H, t, J = 7 Hz, CH_3), 1.4–1.7 (6 H, m, $NCH_2(CH_2)_3CH_2$), 1.75 (1 H, septet, J = 7 Hz, $CH(CH_3)_2$), 2.2–2.6 (9 H, m, NCH_2 x 4, NH), 3.71 (1 H, dd, J = 4, 11 Hz, CH), 7.2–7.4 (5 H, m, C_6H_5). ^{13}C NMR (67.5 MHz, $CDCl_3$): 20.6, 20.7, 24.5, 26.2, 28.1, 54.5, 56.2, 60.0, 66.6, 126.8, 127.3, 128.2, 143.5. MS *m/z*: 259 (M^+–1), 188 (M^+–72). Anal. Calcd for $C_{17}H_{28}N_2$: C, 78.41; H, 10.84; N, 10.76. Found: C, 78.25; H, 10.73; N, 10.64.

(*R*)-*N*-[3-(2.4-dimethylpentyl)]-1-phenyl-2-pipridinoethylamine ((*R*)-5f) 2,4-Dimethyl-3-pentanone (20.5 mL, 145 mmol) and 1 drop of conc. HCl were added to a stirred solution of *(R)*-**4**·2HCl[12] (8.00 g, 28.9 mmol) in MeOH (125 mL). Then, $NaBH_3CN$ (95 %, 9.6 g, 145 mmol) was added in small portions at 0 °C. After stirring for 61 h at room temperature, the solvent was removed *in vacuo*. The residue was mixed with 10 % aqueous NaOH (50 mL) and the whole was extracted with ether (3 x 50 mL). The organic extracts were combined, and were mixed with 5 % aqueous HCl (100 mL) at 0 °C. After shaking vigorously, the aqueous layer was washed with ether (3 x 50 mL) and was basified with 5 % aqueous NaOH (120 mL) at 0 °C. The resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic extracts were washed with brine (60 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain a solid of mp 66–68 °C. Recrystallization from MeOH (32 mL) gave *(R)*-**5f** (5.50g, 63 %) as colorless prisms of mp 81–82 °C. $[\alpha]_D^{25}$ = –101 (*c* 0.94, benzene). ^1H NMR (270 MHz, $CDCl_3$): 0.76 (6 H, dd, J = 7, 16 Hz, $CH(CH_3)_2$), 0.95 (6 H, dd, J = 7, 12 Hz, $CH(CH_3)_2$), 1.4–2.1 (10 H, m, $NCH_2(CH_2)_3CH_2$, NH, $CH(CH_3)_2$, $CH(^iPr)_2$), 2.3 (2 H, br, NCH_2), 2.6 (2 H, br, NCH_2), 2.21 (1 H, dd, J = 3, 12 Hz, NCH_2CHPh), 2.45 (1 H, dd, J = 11, 12 Hz, NCH_2CHPh), 3.87 (1 H, dd, J = 3, 11 Hz, $CHPh$), 7.1–7.4 (5 H, m, C_6H_5). ^{13}C NMR (67.5 MHz, $CDCl_3$): 19.0, 19.3, 19.8, 21.6, 24.5, 26.3, 29.5, 29.6, 55.0, 58.5, 64.2, 67.1, 126.8, 127.9, 128.2, 144.4. MS *m/z*: 303 (M^++1), 301 (M^+–1). Anal. Calcd for $C_{20}H_{34}N_2$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.27; H, 11.39; N, 9.14.

(*R*)-*N*-(2-Fluoroethyl)-1-phenyl-2-piperidinoethylamine ((*R*)-5g) Ethyl fluoroacetate (1.6 mL, 16.6 mmol) and sodium methoxide (96 %, 160 mg, 2.85 mmol) were added to a solution of *(R)*-**4** (1.90 g, 9.30 mmol) in ethanol (40 mL), and the resulting solution was heated under reflux for 47 h. The solvent was evaporated *in vacuo*, and saturated aqueous NH_4Cl (2 mL) was added to the residue. The aqueous layer was basified by addition of saturated aqueous $NaHCO_3$, and was then extracted with CH_2Cl_2 (3 x 70 mL). The combined organic extracts were washed with brine (40 mL), dried (K_2CO_3), filtered, and concentrated *in vacuo* to give a pale yellow oil. This crude oil was treated with a 35 % solution of HCl in EtOH (6 mL) and worked up as described for the preparation of *(R)*-**5a**·2HCl to give a colorless amorphous solid. Recrystallization from EtOH/ether (3 mL/15 mL) gave the mono-hydrochloride salt of *(R)*-*N*-(1-phenyl-2-piperidinoethyl)-

fluoroacetamide (2.07g, 74%) as colorless prisms of mp 152.5–153 °C. $[\alpha]_D^{25}$ = –65.8 (*c* 1.03, EtOH). IR (KBr) cm^{-1}: 1690, 1550. By a similar procedure for the preparation of *(R)*-**5a**, this salt (1.85 g) was converted to *(R)*-*N*-(1-phenyl-2-piperidinoethyl)fluoroacetamide (1.45 g, 89%) as a colorless oil. $[\alpha]_D^{25}$ –73.1 (*c* 0.98, EtOH). ^1H NMR (100 MHz, $CDCl_3$): 1.1–1.7 (6 H, br, $NCH_2(CH_2)_3CH_2$), 2.0–2.6 (6 H, br m, NCH_2 x 3), 4.80 (2 H, d, *J* = 48 Hz, CH_2F), 4.95 (1 H, dd, *J* = 6.6, 7.4 Hz, CHPh), 7.3 (5 H, m, C_5H_6), 7.3–7.4 (1 H, br, NHCO). IR (neat) cm^{-1}: 1660, 1550. MS *m/z*: 265 (M^++1), 263 (M^+–1), 231 (M^+–CH_2F), 188 (M^+–$NHCOCH_2F$). To obtain an analytical sample, this oil (140 mg) was dissolved in ether and a 60 % solution of $HClO_4$ in water (0.19 g) was added at 0 °C. The colorless precipitates deposited were collected by filtration, and recrystallized from ethanol (1.5 mL) to give the perchlorate salt of *(R)*-*N*-(1-phenyl-2-piperidinoethyl)fluoroacetamide as colorless needles of mp 173–174 °C. IR (KBr) cm^{-1}: 1680, 1520. Anal. Calcd for $C_{15}H_{22}N_2O_5ClF$: C, 49.39; H, 6.08; N, 7.68. Found: C, 49.17; H, 6.05; N, 7.58. A solution of the free amide (2.07 g, 7.83 mmol) in THF (10 mL) was added to a 1.0 *M* solution of borane-tetrahydrofuran complex in THF (47 mL, 47 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 4 h . The reaction was quenched with MeOH (50 mL) and then conc. HCl (50 mL) was added at the same temperature. The mixture was stirred for 38 h at room temperature. After removal of the solvent *in vacuo*, MeOH (100 mL) was added to the residue and the solvent was concentrated *in vacuo*. This process was repeated three times. A pale yellow residue was washed with ether (2 x 40 mL) and was then dissolved in water (50 mL). Solid $NaHCO_3$ (33 g) was added to this solution and the aqueous layer was extracted with ether (3 x 60 mL). The combined organic extracts were washed with brine (30 mL), dried (K_2CO_3), filtered, and concentrated *in vacuo* to give a yellow oil (2.66 g). Purification by column chromatography (silica gel, 20:1 $CHCl_3$/MeOH) gave a yellow oil, which was converted to the corresponding dihydrochloride salt by a procedure similar to that for the preparation of *(R)*-**5a**·2HCl described above. Recrystallization from EtOH (17 mL) gave *(R)*-**5g**·2HCl (1.81 g, 72 %) as colorless needles of mp 217–219 °C. $[\alpha]_D^{25}$ = –3.4 (*c* 0.94, MeOH). Anal. Calcd for $C_{15}H_{25}N_2Cl_2F$: C, 55.73; H, 7.79; N, 8.67. Found: C, 55.72; H, 7.83; N, 8.40. This salt was converted to the free amine by a similar procedure described above give (*R*)-**5g** as a colorless oil. $[\alpha]_D^{25}$ = –79.4 (*c* 0.96, MeOH). ^1H NMR (100 MHz, $CDCl_3$): 1.0–1.8 (6 H, m, $NCH_2(CH_2)_3CH_2$), 1.8–2.9 (9 H, m, NCH_2 x 4 and NH), 3.80 (1 H, dd, *J* = 4, 11 Hz, CHPh), 4.46 (2 H, ddd, *J* = 5, 5, 47 Hz, CH_2F), 6.9–7.6 (5 H, m, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$): 24.3, 26.0, 47.4(t, J_{CF} = 19 Hz), 54.4, 59.4, 66.3, 83.3 (t, J_{CF} = 166 Hz), 127.0, 127.2, 128.2, 142.6. MS *m/z*: 251 (M^++1), 250 (M^+), 249 (M^+–1).

(*R*)-*N*-(2,2-Difluoroethyl)-1-phenyl-2-piperidinoethylamine ((*R*)-5h) Ethyl difluoroacetate (3.40 mL, 34.0 mmol) and sodium methoxide (96 %, 0.35 g, 6.0 mmol) were added to a solution of (*R*)-**4** (4.09 g, 20.0 mmol) in EtOH (70 mL), and the whole was stirred at room temperature for 16 h. The solvent was evaporated *in vacuo*, and the residue was mixed with saturated aqueous NH_4Cl (5 mL). The aqueous mixture was basified by addition of saturated $NaHCO_3$, and the whole was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a pale yellow viscous oil. Purification by column chromatography (silica gel, 3:1 ethyl acetate/benzene) gave (*R*)-*N*-(1-phenyl-2-piperidinoethyl)difluoroacetamide (5.05g, quantitative) as a pale yellow viscous oil. $[\alpha]_D^{25}$ = –84.6 (*c* 0.97, MeOH). ^1H NMR (100 MHz, $CDCl_3$): 1.0–1.7 (6 H, br, $NCH_2(CH_2)_3CH_2$), 2.0–2.6 (4 H, br m, $NCH_2(CH_2)_3CH_2$), 2.59 (2 H, d, *J* = 8 Hz, NCH_2CHPh), 4.8 (1 H, br, CHPh), 5.89 (1 H, t, J_{HF}= 55 Hz, CHF_2), 7.0–7.3 (5 H, m, C_6H_5), 7.45 (1 H, br, NHCO). IR ($CHCl_3$) cm^{-1}: 1700, 1520. MS *m/z*: 281 (M^+–1), 231 (M^+–CF_2H). Anal. Calcd for $C_{15}H_{20}N_2OF_2$: C, 63.82; H,

7.14; N, 9.92. Found: C, 63.53; H, 7.15; N, 9.66. Reduction of this amide (5.69 g) by borane-THF and conversion of the product to the corresponding dihydrochloride salt by the procedure similar to that for the preparation of *(R)*-**5g**·2HCl described above gave *(R)*-**5h**·2HCl as a colorless powder of mp 148-149 °C. Conversion of this salt to the free amine was carried out as described above, and purification by column chromatography (silica gel, 1:1 hexane/ether) followed by distillation gave (*R*)-**5h** (4.41 g, 82 %) as a colorless oil of $bp_{0.4\sim0.5}$ 110–112 °C. $[\alpha]_D^{25}$ = –78.2 (*c* 1.14, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): 1.3–1.7 (6 H, m, $NCH_2(CH_2)_3CH_2$), 2.2–3.0 (9 H, m, NCH_2 x 4 and N*H*), 3.82 (1 H, dd, *J* = 4, 11 Hz, C*H*Ph), 5.77 (1 H, dddd, *J* = 3, 5, 56, 57 Hz, CF_2H), 7.2–7.4 (5 H, m, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$) : 24.4, 26.1, 49.3 (t, J_{CF} = 23 Hz), 54.5, 59.4, 66.3, 116.0 (t, J_{CF} = 239 Hz), 127.3, 128.4, 142.1. MS *m/z*: 267 (M^+–1), 249 (M^+–F), 217 (M^+–CF_2H). Anal. Calcd for $C_{15}H_{22}N_2F_2$: C, 67.14; H, 8.26; N, 10.44. Found: C, 66.97; H, 8.31; N, 10.17.

[$^{15}N_2$]-*(S)*-*N*-(2,2,2-Trifluoroethyl)-1-phenyl-2-piperidinoethylamine ([$^{15}N_2$]-*(S)*-5i) [$^{15}N_2$]-*(S)*-**5i** was prepared from [$^{15}N_2$]-*(S)*-**4**,[5i] and was purified by recrystallization of its 2HCl salt from isopropanol by the reported method.[12] The free amine ([$^{15}N_2$]-*(S)*-**5i**) was obtained as colorless oil of $bp_{0.3}$ 150-160 °C (bath temperature) after by bulb-to-bulb distillation. Spectral data agree with those reported.[12] $[\alpha]_D^{25}$ = +81.2 (*c* 1.03, MeOH) (reported[12] $[\alpha]_D^{25}$ = -82.7 (*c* 1.20, MeOH) for *(R)*-**5i**). HRMS Calcd for $C_{15}H_{21}{}^{15}N_2F_3$: 288.1590. Found: 288.1630. ^{13}C NMR (67.5 MHz, $CDCl_3$): 22.4, 26.1, 47.8 (dq, J_{CF} = 30, J_{15NC} = 5 Hz), 54.5, 58.1 (d.J_{15NC} = 6 Hz), 66.3 (d, J_{15NC} = 2 Hz), 125.9 (q, J_{CF} = 279 Hz), 127.5, 128.5, 141.5.

(*R*)-*N*-(2,2,3,3,3-Pentafluoropropyl)-1-phenyl-2-piperidinoethylamine ((*R*)-5j) Pentafluoropropionic anhydride (0.13 mL, 0.68 mmol) was added to a solution of (*R*)-**4** (92 mg, 0.45 mmol) and triethylamine (0.07 mL, 0.68 mmol) in CH_2Cl_2 (0.5 mL) at –10 °C, and the resulting mixture was stirred at room temperature for 1.5 h. Saturated aqueous $NaHCO_3$ (5 mL) was added to the reaction mixture, and the whole was extracted with CH_2Cl_2 (15 mL, 2 x 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography (silica gel, 8:1 benzene/acetone) gave (*R*)-*N*-(1-phenyl-2-piperidinoethyl)pentafluoropropionamide (157 mg, 99 %) as brown needles of mp 37–38 °C. $[\alpha]_D^{25}$ = –67.7 (*c* 0.91, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): 1.45–1.61 (6 H, m, $NCH_2(CH_2)_3CH_2$), 2.31 (2 H, br, $NCH_2(CH_2)_3CH_2$), 2.51 (2 H, br, $NCH_2(CH_2)_3CH_2$), 2.60 (2 H, d, *J* = 8 Hz, NCH_2CHPh), 4.84 (1 H, dd, *J* = 8, 8 Hz, C*H*Ph), 7.2–7.4 (5 H, m, C_6H_5), 7.90 (1 H, br, N*H*CO). ^{13}C NMR (100 MHz, $CDCl_3$): 24.1, 25.9, 51.7, 54.2, 63.2, 106.9 (tq, J_{CF} = 264, 39 Hz), 117.9 (tq, J_{CF} = 285, 35 Hz), 125.9, 127.7, 128.7, 139.4, 157.5 (t, J_{CF} = 25 Hz). IR (KBr) cm^{-1}: 1700. MS *m/z*: 349 (M^+–1), 231 (M^+–CF_2CF_3). Anal. Calcd for $C_{16}H_{19}N_2OF_5$: C, 54.86; H, 5.47; N, 8.00. Found: C, 54.66; H, 5.38; N, 8.22. Reduction of this amide (3.94 g) by borane-THF and conversion of the product to the corresponding dihydrochloride salt by the procedure similar to that for the preparation of *(R)*-**5g**·2HCl described above gave *(R)*-**5j**·2HCl (4.03 g) as a colorless powder. This salt (3.96 g) was converted to the free amine, and purified by column chromatography (silica gel, 10:1 hexane/ether) gave (*R*)-**5j** (3.07 g, 81 %) as a colorless oil. An analytical sample was obtained by bulb-to-bulb distillation as a colorless oil of $bp_{0.5}$ 180-190 °C (bath temperature). $[\alpha]_D^{25}$ = –77.7 (*c* 1.12, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): 1.3–1.7 (6 H, m, $NCH_2(CH_2)_3CH_2$), 2.29 (1 H, dd, *J* = 4, 12 Hz, NCH_2CHPh), 2.2–2.35 (2 H, br, $NCH_2(CH_2)_3CH_2$), 2.42 (1 H, dd, *J* = 12, 13 Hz, NCH_2CHPh), 2.5–2.65 (2 H, br, $NCH_2(CH_2)_3CH_2$), 2.96 (1 H, br, N*H*), 3.07 (2 H, m, NCH_2CF_3), 3.93 (1 H, dd, *J* = 4, 12 Hz,

C*H*Ph), 7.2–7.4 (5 H, m, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$) : 24.4, 26.2, 45.9 (t, J_{CF} = 22 Hz), 54.6, 58.8, 66.5, 115.0 (tq, J_{CF} = 285, 35 Hz), 120.5 (tq, J_{CF} = 285, 35 Hz), 127.4, 128.5, 141.5. MS *m/z*: 335 (M^+–1) 317 (M^+–19), 238 (M^+–98). HRMS Calcd for $C_{16}H_{21}N_2F_5$: 336.1542. Found: 336.1608.

A Typical Procedure for Deprotonation Reaction in the Absence of HMPA (IQ-1) (Table 2, Run 3) A solution of *n*-butyllithium in hexane (1.46 *N*, 1.65 mL, 2.4 mmol) was added to a stirred solution of (*R*)-**5i** (716 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 **1a** (308 mg, 2.0 mmol) in THF (4 mL) was added dropwise over a period of 6 min. After stirring at –100 °C for 25 min, the reaction mixture was quenched with 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 (3 x 50 mL). The combined organic extracts were washed successively with water (2 x 20 mL), 0.1 *N* aqueous citric acid (2 x 100 mL, 3 x 50 mL), water (20 mL), saturated $NaHCO_3$ (20 mL) and brine (40 mL), then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography (silica gel, hexane), followed by bulb-to-bulb distillation gave (*R*)-**3a** (371 mg, 82 %) as a colorless oil of $bp_{0.5}$ 150 °C (bath temperature). $[\alpha]_{365}^{25}$ = +215 (*c* 1.44, benzene), corresponding to 91 % ee.[13,14]

A Typical Procedure for Deprotonation Reaction in the Presence of HMPA (IQ-2) (Table 2, Run 7) A solution of *n*-butyllithium in hexane (1.46 *N*, 1.65 mL, 2.4 mmol) was added to a stirred solution of (*R*)-**5i** (716 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. After addition of HMPA (0.50 mL, 2.9 mmol), the reaction mixture was stirred at –78 °C for 20 min and was then cooled to –100 °C. A solution of TMSCl (1.27 mL, 10 mmol) and **1a** (308 mg, 2.0 mmol) in THF (4 mL) was added dropwise over a period of 6 min. After stirring at –100 °C for 35 min, the reaction mixture was quenched with triethylamine (4 mL) and saturated aqueous $NaHCO_3$ (10 mL), and the whole was allowed to warm to room temperature. Work-up, purification by column chromatography followed by bulb-to-bulb distillation as described above afforded (*R*)-**3a** as a colorless oil (400 mg, 88 %): $bp_{0.5}$ 150 °C (bath temperature). $[\alpha]_{365}^{25}$ = +220 (*c* 1.33, benzene), corresponding to 93 % ee.[13,14]

Rotational Values of *(R)*-3a Obtained by the Reactions (Table 1) run 1: $[\alpha]_{365}^{25}$ = +122 (*c* 1.82, benzene); run 2: $[\alpha]_{365}^{25}$ = +147 (*c* 1.66, benzene); run 3: $[\alpha]_{365}^{25}$ = +191 (*c* 1.69, benzene); run 4: $[\alpha]_{365}^{25}$ = +205 (*c* 1.50, benzene); run 5: $[\alpha]_{365}^{25}$ = +154 (*c* 1.89, benzene); run 6: $[\alpha]_{365}^{25}$ = +140 (*c* 1.54, benzene); run 7: $[\alpha]_{365}^{25}$ = +163 (*c* 1.59, benzene); run 8: $[\alpha]_{365}^{25}$ = +184 (*c* 1.43, benzene); run 9: +198 (*c* 1.59, benzene); run 10; $[\alpha]_{365}^{25}$ = +201 (*c* 1.51, benzene); run 11: $[\alpha]_{365}^{25}$ = +184 (*c* 1.51, benzene); run 12: $[\alpha]_{365}^{25}$ = +190 (*c* 1.45, benzene); run 13: $[\alpha]_{365}^{25}$ = +185 (*c* 1.69, benzene); run 14: $[\alpha]_{365}^{25}$ = +198 (*c* 1.51, benzene); run 15: $[\alpha]_{365}^{25}$ = +178 (*c* 1.59, benzene); run 16: $[\alpha]_{365}^{25}$ = +139 (*c* 1.43, benzene): run 17: $[\alpha]_{365}^{25}$ = +201 (*c* 1.42, benzene); run 18: $[\alpha]_{365}^{25}$ = +210 (*c* 1.61, benzene); run 19: $[\alpha]_{365}^{25}$ = +206 (*c* 1.42, benzene); run 20: $[\alpha]_{365}^{25}$ = +206 (*c* 1.48, benzene); run 21: $[\alpha]_{365}^{25}$ = +185 (*c* 1.56, benzene); run 22: $[\alpha]_{365}^{25}$ = +207 (*c* 1.70, benzene); run 23: $[\alpha]_{365}^{25}$ = +195 (*c* 1.69, benzene).

Rotational Values of *(R)*-3a~d Obtained by the Reactions (Table 2) run 1: *(R)*-**3a** of $[\alpha]_{365}^{25}$ = +218 (*c* 1.41, benzene); run 2: *(R)*-**3a** of $[\alpha]_{365}^{25}$ = +203 (*c* 1.45, benzene); run 4: *(R)*-**3a** of $[\alpha]_{365}^{25}$ = +214 (*c* 1.47, benzene); run 5: *(R)*-**3a** of $[\alpha]_{365}^{25}$ = +212 (*c* 1.47, benzene); run 6: *(R)*-**3a** of $[\alpha]_{365}^{25}$ = +218 (*c* 1.45, benzene); run 8: $[\alpha]_{365}^{25}$ = +217 (*c* 1.65, benzene); run 9: *(R)*-**3b** of $[\alpha]_{365}^{25}$ = +136 (*c* 1.50, benzene); run 10: *(R)*-**3c** of $[\alpha]_{365}^{25}$ = +217 (*c* 1.45, benzene); run 11: *(R)*-**3d** of $[\alpha]_{365}^{25}$ = +224 (*c* 1.50, benzene).

Rotational Values of *(R)*-3a Obtained by the Reactions (Table 3) run 2: $[\alpha]_{365}^{25}$ = +168 (*c* 1.56, benzene); run 3: $[\alpha]_{365}^{25}$ = +158 (*c* 1.39, benzene); run 4: $[\alpha]_{365}^{25}$ = +83.8 (*c* 1.44, benzene); run 6: $[\alpha]_{365}^{25}$ = +202 (*c* 1.49, benzene); run 7: $[\alpha]_{365}^{25}$ = +200 (*c* 1.69, benzene); run 8: $[\alpha]_{365}^{25}$ = +206 (*c* 1.63, benzene).

^{6}Li-, ^{15}N-, and ^{19}F-NMR Spectral Data for [^{6}Li,$^{15}N_2$]-*(S)*-2i (Figure 1) A procedure for the preparation of samples for NMR spectral measurement is reported.[5i] (a) ^{6}Li: 0.72 (dd, *J* = 2.4, 7.0); ^{15}N: 33.0 (t, *J* = 7.0), 47.4 (t, *J* = 2.4); ^{19}F: -70.5 (t, *J* = 11). (b) ^{6}Li: 1.60 (dd, *J* = 2.4, 7.9); ^{15}N: 31.5 (t, *J* = 7.9), 46.3 (t, *J* = 2.5); ^{19}F: -71.9 (br t). (c) ^{6}Li: 2.43 (dt, *J* = 3.0, 4.6); ^{15}N: 28.8 (quint, *J* = 4.3), 45.7 (t, *J* = 3.0); ^{19}F: -71.6 (br). (d) ^{6}Li: 2.80 (br dt, *J* = 4.0, 4.3); ^{15}N: 28.3 (quint, *J* = 4.6), 45.6 (t, *J* = 3.3); ^{19}F: -71.3 (br).

^{6}Li-, ^{15}N-, and ^{19}F-NMR Spectral Data for [^{6}Li,$^{15}N_2$]-*(S)*-2i (Figure 2) (a) ^{6}Li: 0.57 (dd, *J* = 2.1, 6.7); ^{15}N: 33.8 (t, *J* = 6.7), 46.6 (t, *J* = 2.2); ^{19}F: -69.8 (t, *J* = 11). (b) ^{6}Li: 1.33 (dd, *J* = 2.1, 6.7); ^{15}N: 33.2 (t, *J* = 6.4), 45.6 (t, *J* = 2.1); ^{19}F: -70.2 (br t). (c) ^{6}Li: 1.30 (dd, *J* = 2.1, 6.3); ^{15}N: 33.0 (t, *J* = 6.4), 46.0 (t, *J* = 1.8); ^{19}F: -70.1 (t, *J* = 11).

Preparation of Crystalline *(R)*-2i from THF Solution and X-Ray Analysis A solution of *(R)*-**5i** (105 mg, 0.37 mmol) in THF (0.18 mL) was prepared in a dry glass tube under argon atmosphere. A solution of BuLi in hexane (9.7 *N*, 46μL, 0.44 mmol) was added, and the whole was mixed well by shaking. The sealed glass tube was dipped in liquid nitrogen, and then dipped in dry ice-acetone bath. This process was repeated several times until colorless crystals deposited. The glass tube was warmed by hands until almost all crystals disappeared, and then allowed to stand at -20 °C overnight. Colorless prisms appeared.

In a dry box placed in a cold room, the glass tube was cut under argon atmosphere. High vacuum pump oil was sprinkled over the colorless prisms immediately. A prism covered by pump oil was placed in a capillary. The capillary was sealed by pump oil, taken off from the dry box, sealed with a flame immediately, and was kept by dipping in dry ice-acetone bath until required for analysis at -40 °C on the X-ray diffractometer (AFC-5R, RIGAKU).

Crystal data: $C_{23}H_{36}N_2F_3LiO_2$, $P3_1$ with unit cell parameters *a* = 9.329 (3) Å, *b* = 9.329 (3) Å, *c* = 24.057 (3) Å, and D_{calcd} = 1.199 g/cm^3. A total of 1826 reflections were observed using CuK_α radiation, and the temperature of the crystal was kept at 233K during the data acquisition. The structure was solved by direct methods using the computer program SIR 85 [21] and the difference Fourier method. The final values are *R* = 0.0650 and R_w = 0.0700. The X-ray structure (stereoview) is shown in Figure 3.[18]

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