Stereoselective Reactions. XXXIII.[1] Design and Synthesis of Chiral Bidentate Amines Having a Bulky Group on the Chiral Carbon

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Based on the solution structures of chiral bidentate lithium amides ((*R*)-3a,b) having a phenyl group on the chiral carbon, chiral bidentate amines ((*R*)-5a,b—8a,b and (*S*)-9a,b) having a bulkier group instead of a phenyl group on the chiral carbon were designed and synthesized.

Key words chiral amine; chiral lithium amide; chiral amide nitrogen; enantioselective deprotonation

Conversion of carbonyl compounds into their enolates is a fundamental and widely used process in synthetic organic chemistry, because enolates play a central role as carbon nucleophiles to undergo reactions with various electrophiles.[2] In recent years, enantioselective deprotonation of prochiral cyclic ketones by chiral lithium amides to give the corresponding chiral lithium enolates has become one of the useful methods for asymmetric synthesis.[3] We have previously reported enantioselective deprotonation of prochiral 4-substituted cyclohexanones (**1**) using chiral lithium amides in the presence of excess trimethylsilyl chloride (TMSCl)[4] to isolate the corresponding lithium enolates as trimethylsilyl enol ethers (**2**).[1,5] Among various chiral lithium amides examined, it is shown that the bidentate amides ((*R*)-**3a**,**b**) having a phenyl group on the chiral carbon and a neopentyl or trifluoroethyl group on the amide nitrogen gave the products ((*R*)-**2**) in high ee's.[5b,c,i,l] By X-ray and NMR studies, it is also shown that these amides ((*R*)-**3a**,**b**) exist almost entirely as a chelated monomeric form (**4**) having a chiral amide nitrogen in tetrahydrofuran (THF) or dimethoxyethane (DME), and in THF, DME, ether, or toluene in the presence of 2 equivalents of hexamethylphosphoric triamide (HMPA).[5b,c,i,l] Assuming that the substituent on the amide nitrogen and the phenyl group on the chiral carbon in the chelated ring are *trans* due to steric repulsion between them, bidentate lithium amides (**5**—**9**) having a bulkier substituent instead of a phenyl group on the chiral carbon would be more effective as a chiral base for enantioselective deprotonation. Based on this consideration, the present paper describes the synthesis of chiral diamines ((*R*)-**5a**,**b**—(*R*)-**8a**,**b** and (*S*)-**9a**,**b**) for the preparation of their corresponding lithium amides to use for enantioselective deprotonation.

Chiral diamines ((*R*)-**5a**,**b**—(R)-**7a**,**b** and (*S*)-**9a**,**b**) were prepared as shown in Chart 2. Thus, *Z*-derivatives ((*R*)-**10**—

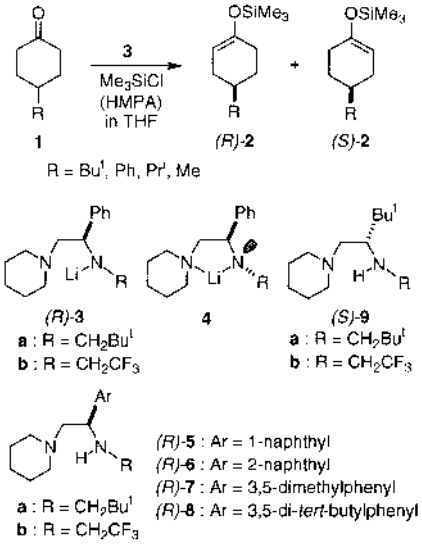

Chart 1

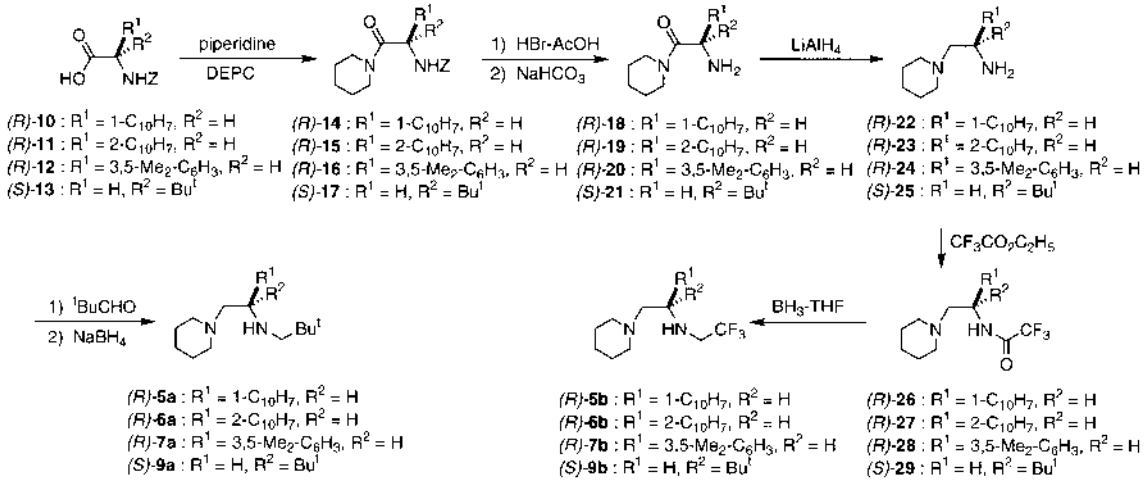

Chart 2

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(*R*)-**12**, (*S*)-**13**) of the corresponding optically active amino acids were condensed with piperidine to give the amides ((*R*)-**14**—(*R*)-**16**, (*S*)-**17**). After deprotection, the products ((*R*)-**18**—(*R*)-**20**, (*S*)-**21**) were reduced with lithium aluminum hydride to the corresponding diamines ((*R*)-**22**—(*R*)-**24**, (*S*)-**25**). Monoalkylation at the primary amino nitrogen of these diamines was carried out by reductive alkylation using pivalaldehyde to give the corresponding *N*-neopentyl derivatives ((*R*)-**5a**—(*R*)-**7a**, (*S*)-**9a**), while trifluoroacetylation followed by reduction gave the corresponding *N*-trifluoroethyl derivatives ((*R*)-**5b**—(*R*)-**7b**, (*S*)-**9b**).

(*R*)-3,5-Dimethylphenylglycine ((*R*)-**31**) used for the synthesis of (*R*)-**12** was prepared as shown in Chart 3. Racemic 3,5-dimethylphenylglycine, prepared from 3,5-dimethylbenzaldehyde[6] by the Bucherer–Berges reaction, was resolved *via* its *N*-trifluoroacetyl derivative with cinchonine. (*R*)-**30** thus obtained was hydrolyzed to give (*R*)-**31**. The absolute configuration of this amino acid was determined by X-ray analysis of the salt of its methyl ester with (*S*)-10-camphorsulfonic acid.[7]

Syntheses of (*R*)-**8a** and (*R*)-**8b** were carried out as shown in Chart 4. (*R*)-**32**[8] was converted to its phthaloyl derivative ((*R*)-**33**), and was treated with *tert*-butyl chloride and aluminum trichloride to give (*R*)-**34**. Dephthaloylation gave the amine ((*R*)-**35**), which was converted to (*R*)-**8a** and (*R*)-**8b** as described above.

Results of the deprotonation reaction of **1** using chiral lithium amides prepared from these chiral bidentate amines will be reported separately.

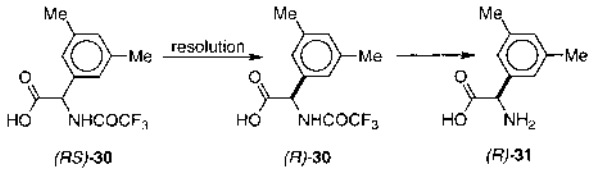

Chart 3

Experimental

General All melting and boiling points are uncorrected. IR spectra were recorded on a JASCO IRA-1 or a JASCO FT/IR-300E spectrometer. ^{1}H-NMR spectra were recorded on a JEOL GSX-400 (400 MHz), a JEOL EX-270 (270 MHz), or a JEOL EX-90 (90 MHz) spectrometer. All spectra were recorded in $CDCl_3$, unless otherwise stated. The chemical shifts are given in δ (ppm) using tetramethylsilane as an internal standard. Coupling constants (J) are given in hertz (Hz). The following abbreviations are used: br=broad, s=singlet, d=doublet, dd=doublet of doublets, t=triplet, q=quartet, m=multiplet. High resolution mass spectra (HR-MS) were recorded on a Hitachi M-2000 spectrometer (EI) or a JEOL GCmate (FAB). Optical rotations were measured on a JASCO DIP-370 digital polarimeter.

(*R*)-1-[*N*-(Benzyloxycarbonyl)-2-(1-naphthyl)glycyl]piperidine ((*R*)-14) Triethylamine (4.25 g, 42 mmol) was added dropwise during 15 min to an ice-cooled solution of (*R*)-**10** (13.4 g, 40 mmol), piperidine (3.75 g, 44 mmol), and DEPC[10] (7.98 g, 44 mmol) in *N*,*N*-dimethylformamide (DMF) (96 ml), and the whole was stirred under ice-cooling for 30 min, and then at room temperature overnight. The solution was diluted with a mixture of ethyl acetate (400 ml) and benzene (200 ml), and the whole was washed successively with water (400 ml×4), 2.5% aqueous HCl (200 ml×3), water (400 ml), saturated aqueous $NaHCO_3$ (200 ml×3), water (200 ml), and brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give a residue, which was purified by column chromatography (silica gel, hexanes/AcOEt=2/1) to give (*R*)-**14** (15.5 g, 96%) as a colorless oil. IR (film) cm^{-1}: 3290, 1714, 1642. $[\alpha]_D^{25}$ −182° (c=1.31, $CHCl_3$). ^{1}H-NMR: 1.23—1.62 (6H, m, $CH_2CH_2CH_2$), 2.99—3.17 (2H, m, half of CH_2NCH_2), 3.42—3.83 (2H, m, half of CH_2NCH_2), 5.10 (2H, q, $PhCH_2$), 6.09 (1H, d, J=9 Hz, NH), 6.34 (1H, d, J=9 Hz, Ar-CH), 7.28—8.43 (12H, m, aromatic H). *Anal.* Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.77; H, 6.59; N, 6.77.

(*R*)-1-[*N*-(Benzyloxycarbonyl)-2-(2-naphthyl)glycyl]piperidine ((*R*)-15) By a procedure similar to the preparation of (*R*)-**14** described above, (*R*)-**15** was synthesized from (*R*)-**11** as a pale yellow oil in 91% yield. IR (film) cm^{-1}: 3400, 3300, 1717, 1641. $[\alpha]_D^{25}$ −148° (c=1.04, $CHCl_3$). ^{1}H-NMR: 0.85—1.50 (6H, m, $CH_2CH_2CH_2$), 3.20—3.74 (4H, m, CH_2NCH_2), 4.99, 5.12 (2H, q, J=12 Hz, $PhCH_2$), 5.75 (1H, d, J=7 Hz, ArCH), 6.35 (1H, d, J=7 Hz, NH), 7.23—7.95 (12H, m, aromatic H). HR-MS m/z: 403.2024 (MH^+) (Calcd for $C_{25}H_{27}N_2O_3$: 403.2021).

(*R*)-1-[*N*-(Benzyloxycarbonyl)-2-(3,5-dimethylphenyl)glycyl]piperidine ((*R*)-16) By a procedure similar to the preparation of (*R*)-**14** described above, (*R*)-**16** was synthesized from (*R*)-**12** as a colorless oil in 97% yield. IR (film) cm^{-1}: 3300, 1713, 1635. $[\alpha]_D^{25}$ −133° (c=1.14, $CHCl_3$). ^{1}H-NMR: 1.32—1.66 (6H, m, $CH_2CH_2CH_2$), 2.26 (6H, s, two CH_3), 3.18—3.72 (4H, m, CH_2NCH_2), 5.06 (2H, $PhCH_2$), 5.52 (1H, d, J=7 Hz, ArCHN), 6.37 (1H, d, J=7 Hz, NH), 6.93—7.32 (8H, m, aromatic H). HR-MS m/z: 380.2118 (M^+) (Calcd for $C_{23}H_{28}N_2O_3$: 380.2098).

(*S*)-1-[(*N*-Benzyloxycarbonyl)-2-(*tert*-butyl)glycyl]piperidine ((*S*)-17) By a procedure similar to the preparation of (*R*)-**14** described above, (*S*)-**17** was synthesized from (*S*)-**13** as a colorless oil in 94% yield. IR (film) cm^{-1}: 3300, 1710, 1630. $[\alpha]_D^{25}$ +13.3° (c=1.22, MeOH). ^{1}H-NMR: 0.98 (9H, s, $(CH_3)_3C$), 1.4—1.8 (6H, m, $CH_2CH_2CH_2$), 3.46—3.63 (4H, m, CH_2NCH_2), 4.61 (1H, d, J=10 Hz, *tert*-BuCHN), 5.05 (1H, d, J=12 Hz, half of $PhCH_2O$), 5.12 (1H, d, J=12 Hz, half of $PhCH_2O$), 5.65 (1H, d, J=10 Hz, NHCO), 7.2—7.4 (5H, m, C_6H_5). *Anal.* Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.53; H, 8.53; N, 8.22.

(*R*)-1-[2-(1-Naphthyl)glycyl]piperidine ((*R*)-18) A solution of (*R*)-**14** (15.7 g) in AcOH (7 ml) was mixed with a solution of 33% HBr in AcOH (21 ml) under ice-cooling, and the whole was stirred at room temperature overnight. The solution was poured into ice-water (200 ml), and washed with ether (200 ml×3). The aqueous layer was basified by addition of $NaHCO_3$,

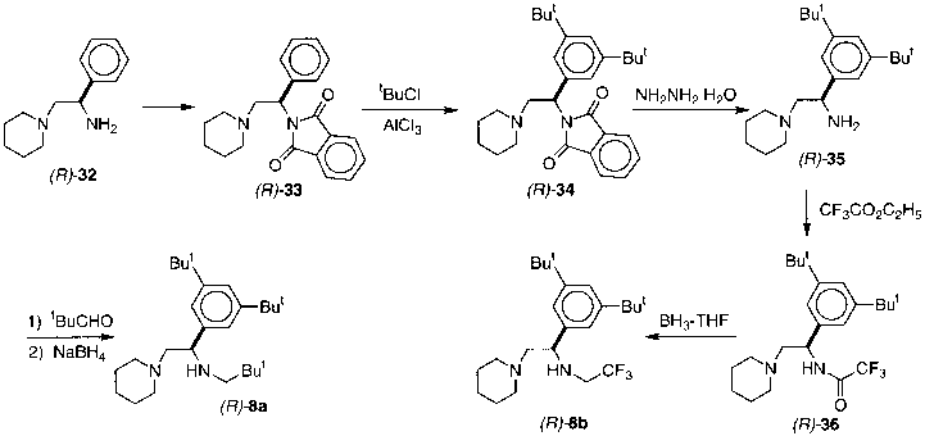

Chart 4

and was extracted with $CHCl_3$ (200 ml×3). The organic extracts were combined, washed with brine, dried over K_2CO_3, and evaporated to dryness *in vacuo* to give a residue, which was purified by column chromatography (silica gel, $CHCl_3$/MeOH=9/1) to give (*R*)-**18** (10.1 g, 97%) as a colorless oil. IR (film) cm^{-1}: 3360, 1640. $[\alpha]_D^{25}$ −167.5° (*c*=1.37, EtOH). ^{1}H-NMR: 0.80—1.56 (6H, m, $CH_2CH_2CH_2$), 2.04 (2H, s, NH_2), 2.88—3.12 (2H, m, half of CH_2NCH_2), 3.52—3.82 (2H, m, half of CH_2NCH_2), 5.41 (1H, s, ArCHCO), 7.26—8.28 (7H, m, aromatic H). HR-MS *m/z*: 269.1666 (MH^+) (Calcd for $C_{17}H_{21}N_2O$: 269.1654).

(*R*)-1-[2-(2-Naphthyl)glycyl]piperidine ((*R*)-19) By a procedure similar to the preparation of (*R*)-**18** described above, (*R*)-**19** was synthesized from (*R*)-**15** and was recrystallized from hexanes–ether as pale yellow crystals of mp 80.5—81.0 °C in 90% yield. IR (KBr) cm^{-1}: 3365, 1635. $[\alpha]_D^{25}$ −128.5° (*c*=1.06, EtOH). ^{1}H-NMR: 0.86—1.60 (6H, m, $CH_2CH_2CH_2$), 2.08 (2H, s, NH_2), 3.17—3.77 (4H, m, CH_2NCH_2), 4.90 (1H, s, ArCHCO), 7.44—7.88 (7H, m, aromatic H). HR-MS *m/z*: 269.1653 (MH^+) (Calcd for $C_{17}H_{21}N_2O$: 269.1654).

(*R*)-1-[2-(3,5-Dimethylphenyl)glycyl]piperidine ((R)-20) By a procedure similar to the preparation of (*R*)-**18** described above, (*R*)-**20** was synthesized from (*R*)-**16** as a pale yellow oil in 91% yield. IR (film) cm^{-1}: 3360, 1637. $[\alpha]_D^{25}$ −96.9° (*c*=1.17, EtOH). ^{1}H-NMR: 0.90—1.64 (6H, m, $CH_2CH_2CH_2$), 2.01 (2H, s, NH_2), 2.29 (6H, s, two CH_3), 3.13—3.72 (4H, m, CH_2NCH_2), 4.64 (1H, s, ArCHCO), 6.91 (3H, s, aromatic H). HR-MS *m/z*: 247.1810 (MH^+) (Calcd for $C_{15}H_{23}N_2O$: 247.1810).

(*S*)-1-[2-(*tert*-Butyl)glycyl]piperidine ((*S*)-21) By a procedure similar to the preparation of (*R*)-**18** described above, (*S*)-**21** was synthesized from (*S*)-**17** as a pale yellow oil in 99%. An analytical sample was obtained by bulb-to-bulb distillation to give a colorless oil of $bp_{1.0}$ 210—220 °C (bath temperature). IR (film) cm^{-1}: 1625. $[\alpha]_D^{25}$ +79.7° (*c*=1.04, MeOH). ^{1}H-NMR: 0.99 (9H, s, $(CH_3)_3C$), 1.5—2.0 (8H, m, $CH_2CH_2CH_2$, NH_2), 3.4—3.8 (5H, m, CH_2NCH_2, *t*-BuCHN). HR-MS *m/z*: 198.1688 (M^+) (Calcd for $C_{11}H_{22}N_2O$: 198.1727).

(*R*)-1-(1-Naphthyl)-2-(1-piperidino)ethylamine ((*R*)-22) A solution of (*R*)-**18** (10.0 g, 37.3 mmol) in THF (20 ml) was added dropwise during 20 min to a suspension of $LiAlH_4$ (6.10 g, 149 mmol) in THF (80 ml), and the whole was stirred under reflux for 2 h. Under stirring and ice-cooling, water (6.1 ml), 15% aqueous NaOH (6.1 ml) and water (18.3 ml) 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. The oil was dissolved in EtOH, and then excess HCl–EtOH was added. The crystals deposited were collected and recrystallized from EtOH to give (*R*)-**22**·2HCl (11.1 g, 91%) as colorless plates of mp 188—189 °C. IR (KBr) cm^{-1}: 3308, 1598. $[\alpha]_D^{25}$ −19.4° (*c*=1.37, EtOH). This salt (3.27 g) was dissolved in water, and the resulting solution was basified to pH 8 using $NaHCO_3$. The whole was extracted with ether (80 ml×3). The ethereal extracts were combined, washed with brine, dried over K_2CO_3, and evaporated to dryness *in vacuo* to give a residue, which was recrystallized from hexane to give (*R*)-**22** (2.30 g, 90%) as colorless plates of mp 88—89 °C. IR (nujol) cm^{-1}: 3380. $[\alpha]_D^{25}$ −130.0° (*c*=1.25, MeOH). ^{1}H-NMR: 1.44—1.72 (6H, m, $CH_2CH_2CH_2$), 1.94 (2H, s, NH_2), 2.39—2.70 (6H, m, $(CH_2)_2NCH_2$), 5.02 (1H, dd, *J*=3, 10 Hz, ArCH), 7.44—8.11 (7H, m, aromatic H). *Anal.* Calcd for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found: C, 80.53; H, 8.96; N, 10.92.

(*R*)-1-(2-Naphthyl)-2-(1-piperidino)ethylamine ((*R*)-23) By a procedure similar to the preparation of (*R*)-**22** described above, crude (*R*)-**23** (8.62 g) synthesized from (*R*)-**19** (10.2 g, 38 mmol) was mixed with L-tartaric acid (5.09 g, 33.9 mmol) in EtOH. The precipitates were collected by filtration. Recrystallization from EtOH gave (*R*)-**23**·tartarate salt (11.0 g, 72%) as colorless crystals of mp 129—130 °C. IR (KBr) cm^{-1}: 3320. $[\alpha]_D^{25}$ +28.4° (*c*=1.04, H_2O). (*R*)-**23** was obtained from this salt as a pale yellow oil, which solidified (mp 57.5—58 °C). IR (film) cm^{-1}: 3370, 3290. $[\alpha]_D^{25}$ −37.7° (*c*=1.08, MeOH). ^{1}H-NMR: 1.37—1.70 (6H, m, $CH_2CH_2CH_2$), 2.08 (2H, s, NH_2), 2.27—2.70 (6H, m, $(CH_2)_2NCH_2$), 4.30 (1H, dd, *J*=4, 10 Hz, ArCH), 7.40—7.88 (7H, m, aromatic H). HR-MS *m/z*: 255.1860 (MH^+) (Calcd for $C_{17}H_{23}N_2$: 255.1861).

(*R*)-1-(3,5-Dimethylphenyl)-2-(1-piperidino)ethylamine ((*R*)-24) By a procedure similar to the preparation of (*R*)-**23** described above, (*R*)-**24**·L-tartarate salt was synthesized from (*R*)-**20** as colorless crystals of mp 106—107 °C (from EtOH) in 75% yield. IR (nujol) cm^{-1}: 3375. $[\alpha]_D^{25}$ −6.8° (*c*=1.14, MeOH). (*R*)-**24** was obtained from this salt as a colorless solid of mp 52—53 °C. IR (nujol) cm^{-1}: 3330. $[\alpha]_D^{25}$ −44.2° (*c*=1.26, MeOH). ^{1}H-NMR: 1.40—1.70 (6H, m, $CH_2CH_2CH_2$), 1.99 (2H, s, NH_2), 2.31 (6H, s, two $ArCH_3$), 2.20—2.50 (4H, m, CH_2NCH_2), 2.52—2.63 (2H, m, NCH_2), 4.62 (1H, dd, *J*=4, 10 Hz, ArCH), 6.88 (1H, s, aromatic H), 6.99 (2H, s, aromatic H). HR-MS *m/z*: 233.2020 (MH^+) (Calcd for $C_{15}H_{25}N_2$: 233.2018).

(*S*)-1-*tert*-Butyl-2-(1-piperidino)ethylamine ((*S*)-25) By a procedure similar to the preparation of (R)-**22** described above, crude (*S*)-**25** (13.3 g) synthesized from (*S*)-**21** (14.7 g, 74.1 mmol) was mixed with picric acid (*ca.* 80%, 45.5 g, *ca.* 160 mmol) in EtOH. The precipitates were collected by filtration. Recrystallization from MeOH (1.2 l) gave (*S*)-**25**·dipicrate (37.3 g, 78%) as yellow prisms of mp 192—193 °C. $[\alpha]_D^{25}$ +72.0° (*c*=0.74, acetone). *Anal.* Calcd for $C_{23}H_{30}N_8O_{14}$: C, 42.99; H, 4.71; N, 17.44. Found: C, 43.26; H, 4.71; N, 17.62. (*S*)-**25** was obtained from this salt as a colorless oil of $bp_{1.0}$ 160—180 °C (bath temperature) after bulb-to-bulb distillation. $[\alpha]_D^{25}$ +90.0° (*c*=1.08, MeOH). ^{1}H-NMR: 0.88 (9H, s, $(CH_3)_3C$), 1.35—1.7 (8H, m, $CH_2CH_2CH_2$, NH_2), 2.06 (1H, dd, *J*=11, 12 Hz, half of CH_2N), 2.22 (1H, dd, *J*=2.7, 12 Hz, half of CH_2N), 2.1—2.55 (4H, m, CH_2NCH_2), 2.62 (1H, dd, *J*=2.7, 12 Hz, *tert*-BuCH). HR-MS *m/z*: 185.2025 (M^+) (Calcd for $C_{11}H_{25}N_2$: 185.2018).

(*R*)-*N*-[1-(1-Naphthyl)-2-(1-piperidino)ethyl]trifluoroacetamide ((*R*)-26) A solution of (*R*)-**22** (2.04 g, 8 mmol) and ethyl trifluoroacetate (1.71 g, 12 mmol) in MeOH (10 ml) was stirred at room temperature overnight. The reaction mixture was evaporated *in vacuo* to dryness, and the residue was subjected to column chromatography (silica gel, hexanes/AcOEt=2/1) to give (*R*)-**26** (2.55 g, 91%) as a pale yellow oil. IR (film) cm^{-1}: 3310, 1703. $[\alpha]_D^{25}$ −42.5° (*c*=1.03, MeOH). ^{1}H-NMR: 1.46—1.67 (6H, m, $CH_2CH_2CH_2$), 2.37—2.74 (4H, m, CH_2NCH_2), 2.89 (2H, d, *J*=6 Hz, NCH_2), 5.77 (1H, t, *J*=7 Hz, ArCH), 7.44—8.02 (7H, m, aromatic H), 7.90—8.20 (1H, br, NH). HR-MS *m/z*: 351.1687 (MH^+) (Calcd for $C_{19}H_{22}F_3N_2O$: 351.1684).

(*R*)-*N*-[1-(2-Naphthyl)-2-(1-piperidino)ethyl]trifluoroacetamide ((*R*)-27) By a procedure similar to the preparation of (*R*)-**26** described above, (*R*)-**27** was synthesized from (*R*)-**23** in 88% yield after column chromatography (silica gel, hexanes/AcOEt=2/1) followed by recrystallization from hexanes as colorless needles of mp 106—106.5 °C. IR (KBr) cm^{-1}: 3336, 1702. $[\alpha]_D^{25}$ −109.5° (*c*=1.06, MeOH). ^{1}H-NMR: 1.35—1.70 (6H, m, $CH_2CH_2CH_2$), 2.25—2.60 (4H, m, CH_2NCH_2), 2.68 (2H, d, *J*=8 Hz, CH_2N), 4.99 (1H, t, *J*=8 Hz, ArCH), 7.36—7.86 (7H, m, aromatic H), 7.69—7.86 (1H, br, NH). HR-MS *m/z*: 351.1686 (MH^+) (Calcd for $C_{19}H_{22}F_3N_2O$: 351.1684).

(*R*)-*N*-[1-(3,5-Dimethylphenyl)-2-(1-piperidino)ethyl]trifluoroacetamide ((*R*)-28) By a procedure similar to the preparation of (*R*)-**26** described above, (*R*)-**28** was synthesized from (*R*)-**24** as a colorless oil in 99% yield. IR (film) cm^{-1}: 3300, 1700. $[\alpha]_D^{25}$ −80.9° (*c*=1.73, MeOH). ^{1}H-NMR: 1.40—1.70 (6H, m, $CH_2CH_2CH_2$), 2.29 (6H, s, two $ArCH_3$), 2.33 (2H, d, CH_2N), 2.45—2.70 (4H, m, CH_2NCH_2), 4.73 (1H, t, *J*=8 Hz, ArCHN), 6.85 ((2H, s, aromatic H), 6.90 (1H, s, aromatic H), 7.6—7.9 (1H, br, NH). HR-MS *m/z*: 328.1757 (M^+) (Calcd for $C_{17}H_{23}F_3N_2O$: 328.1760).

(*R*)-*N*-(2,2-Dimethylpropyl)-1-(1-naphthyl)-2-(1-piperidino)ethylamine ((*R*)-5a) A solution of (*R*)-**22** (2.28 g, 8.96 mmol) and pivalaldehyde (0.97 g, 11.2 mmol) in benzene was stirred at room temperature for 1 h. The reaction mixture was dried over K_2CO_3 and evaporated to dryness *in vacuo*, and the residue was dissolved in EtOH (36 ml). Under ice-cooling, $NaBH_4$ (0.68 g, 17.9 mmol) was added, and the whole was stirred at room temperature for 30 min. Evaporation of the solvent *in vacuo* gave a residue, which was mixed with saturated aqueous $NaHCO_3$ (30 ml), and the whole was extracted with hexanes (80 ml×3). The organic extracts were combined, washed with brine, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, benzene/ether=10/1) followed by bulb-to-bulb distillation to give (*R*)-**5a** (2.60 g, 89%) as a colorless oil of $bp_{0.4}$ 230 °C (bath temperature). IR (film) cm^{-1}: 3320. $[\alpha]_D^{25}$ −148.8° (*c*=1.09, MeOH). ^{1}H-NMR: 0.96 (9H, s, $(CH_3)_3C$), 1.44—1.66 (6H, m, $CH_2CH_2CH_2$), 2.18—2.66 (9H, m, $NHCH_2$Bu-*t*, $(CH_2)_2NCH_2$), 4.57 (1H, dd, *J*=3, 11 Hz, ArCH), 7.3—8.2 (7H, m, aromatic H). HR-MS *m/z*: 325.2650 (MH^+) (Calcd for $C_{22}H_{33}N_2$: 325.2644).

(*R*)-*N*-(2,2-Dimethylpropyl)-1-(2-naphthyl)-2-(1-piperidino)ethylamine ((*R*)-6a) By a procedure similar to the preparation of (*R*)-**5a** described above, (*R*)-**6a** was synthesized from (*R*)-**23** in 85% yield as colorless needles of mp 104.5—105 °C after recrystallization from MeOH. IR (KBr) cm^{-1}: 3290. $[\alpha]_D^{25}$ −94.2° (*c*=1.03, MeOH). ^{1}H-NMR: 0.93 (9H, s, $(CH_3)_3C$), 1.30—1.68 (6H, m, $CH_2CH_2CH_2$), 2.12 (1H, br, NH), 2.21 (1H, d, *J*=11 Hz, half of CH_2Bu-*t*), 2.26 (1H, *J*=11 Hz, half of CH_2Bu-*t*), 2.26—2.40 (2H, m, half of CH_2NCH_2), 2.35 (1H, dd, *J*=4, 12 Hz, half of CH_2N), 2.43—2.65 (2H, m, half of CH_2NCH_2), 2.49 (1H, dd, *J*=11, 12 Hz, half of CH_2N), 3.84 (1H, dd, *J*=4, 11 Hz, ArCH), 7.37—7.90 (7H, m, aromatic H). HR-MS *m/z*: 325.2642 (MH^+) (Calcd for $C_{22}H_{33}N_2$: 325.2644).

(*R*)-*N*-(2,2,Dimethylpropyl)-1-(3,5-dimethylphenyl)-2-(1-piperidino)-ethylamine ((*R*)-7a) By a procedure similar to the preparation of (*R*)-**5a**

described above, (*R*)-**7a** was synthesized from (*R*)-**24** in 73% yield after bulb-to-bulb distillation as a colorless oil of bp_3 270 °C (bath temperature). IR (film) cm^{-1}: 3310. $[\alpha]_D^{25}$ −92.6° (*c*=1.07, MeOH). ^{1}H-NMR: 0.93 (9H, s, $(CH_3)_3C$), 1.40—1.70 (6H, m, $CH_2CH_2CH_2$), 2.30 (6H, s, two $ArCH_3$), 2.05—2.65 (9H, m, $NHCH_2$Bu-*t*, $(CH_2)_2NCH_2$), 3.61 (1H, dd, *J*=4, 11 Hz, ArCH), 6.86 (1H, s, aromatic H), 7.00 (2H, s, aromatic H). *Anal.* Calcd for $C_{20}H_{34}N_2$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.59; H, 11.32; N, 9.42.

(*S*)-*N*-(2,2-Dimethylpropyl)-1-*tert*-butyl-2-(1-piperidino)ethylamine ((*S*)-9a) By a procedure similar to the preparation of (*R*)-**5a** described above, (*S*)-**9a** was synthesized from (*S*)-**25** in 77% yield after recrystallization from MeOH as colorless needles of mp 30—30.5 °C, which were further purified by bulb-to-bulb distillation. IR (KBr) cm^{-1}: 3316. $[\alpha]_D^{25}$ +79.0° (*c*=1.13, MeOH). ^{1}H-NMR: 0.86 (9H, s, $(CH_3)_3C$), 0.91 (9H, s, $(CH_3)_3C$), 1.32—1.62 (7H, m, $CH_2CH_2CH_2$, NH), 2.06—2.56 (9H, m, $(CH_2)_2NCH_2$, *tert*-BuCHNCH$_2$). HR-MS *m*/*z*: 255.2799 (MH^+) (Calcd for $C_{16}H_{35}N_2$: 255.2800).

(*R*)-*N*-(2,2,2-Trifluoroethyl)-1-(1-naphthyl)-2-(1-piperidino)ethylamine ((*R*)-5b) A 1 M solution of BH_3 in THF (20 ml, 20 mmol) was added dropwise to a solution of (*R*)-**26** (1.66 g, 4.74 mmol) in THF (6 ml), and the whole was heated under reflux for 8 h. The reaction mixture was quenched with MeOH (16 ml) under ice-cooling, and was then evaporated to dryness *in vacuo*. The residue was mixed with 37% HCl–MeOH (20 ml), and the whole was stirred at room temperature for 1 h. Evaporation of the solvent gave a residue, which was mixed with saturated aqueous $NaHCO_3$, and the whole was extracted with hexanes (80 ml×3). The organic extracts were combined, washed with brine, dried over Na_2SO_4, and evaporated to dryness *in vacuo* to give an oil. Purification by column chromatography (silica gel, hexanes/ether=5/1) followed by bulb-to-bulb distillation gave (*R*)-**5b** (1.45 g, 91%) as a colorless oil of $bp_{0.1}$ 210 °C (bath temperature). IR (film) cm^{-1}: 3310. $[\alpha]_D^{25}$ −149.2° (*c*=1.13, MeOH). ^{1}H-NMR: 1.44—1.73 (6H, m, $CH_2CH_2CH_2$), 2.35—2.68 (6H, m, $(CH_2)_2NCH_2$), 3.07—3.16 (3H, m, $NHCH_2CF_3$), 4.86 (1H, dd, *J*=3, 10 Hz, ArCH), 7.44—8.13 (7H, m, aromatic H). *Anal.* Calcd for $C_{19}H_{23}F_3N_2$: C, 67.84; H, 6.89; N, 8.33. Found: C, 68.03; H, 6.81; N, 8.47.

(*R*)-*N*-(2,2,2-Trifluoroethyl)-1-(2-naphthyl)-2-(1-piperidino)ethylamine ((*R*)-6b) By a procedure similar to the preparation of (*R*)-**5b** described above, (*R*)-**6b** was synthesized from (*R*)-**27** and was recrystallized from MeOH as colorless crystals of mp 98.5—99 °C in 89% yield. IR (KBr) cm^{-1}: 3295. $[\alpha]_D^{25}$ −81.7° (*c*=1.03, MeOH). ^{1}H-NMR: 1.40—1.70 (6H, m, $CH_2CH_2CH_2$), 2.20—2.40 (2H, m, half of CH_2NCH_2), 2.35 (1H, dd, *J*=3, 12 Hz, half of CH_2N), 2.51 (1H, dd, *J*=11, 12 Hz, half of CH_2N), 2.55—2.70 (2H, m, half of CH_2NCH_2), 2.90—3.08 (1H, br, NH), 3.09 (2H, q, *J*=10 Hz, CH_2CF_3), 4.12 (1H, dd, *J*=3, 11 Hz, ArCH), 7.42—7.93 (7H, m, aromatic H). HR-MS *m*/*z*: 337.1894 (MH^+) (Calcd for $C_{19}H_{24}F_3N_2$: 337.1891).

(*R*)-*N*-(2,2,2-Trifluoroethyl)-1-(3,5-dimethylphenyl)-2-(1-piperidino)-ethylamine ((*R*)-7b) By a procedure similar to the preparation of (*R*)-**5b** described above, (*R*)-**7b** was synthesized from (*R*)-**28** as a colorless oil of bp_3 230 °C (bath temperature) in 88% yield. IR (film) cm^{-1}: 3315. $[\alpha]_D^{25}$ −77.0° (*c*=1.26, MeOH). ^{1}H-NMR: 1.35—1.70 (6H, m, $CH_2CH_2CH_2$), 2.31 (6H, s, two $ArCH_3$), 2.10—2.65 (6H, m, $(CH_2)_2NCH_2$), 3.06 (2H, q, *J*=10, CH_2CF_3), 2.80—3.10 (1H, br, NH), 3.88 (1H, dd, *J*=3, 11 Hz, ArCH), 6.90 (1H, s, aromatic H), 6.97 (2H, s, aromatic H). HR-MS *m*/*z*: 314.1956 (M^+) (Calcd for $C_{17}H_{25}F_3N_2$: 314.1968).

(*S*)-*N*-(2,2,2-Trifluoroethyl)-1-*tert*-butyl-2-(1-piperidino)ethylamine ((*S*)-9b) By a procedure similar to the preparation of (*R*)-**5b** described above, (*S*)-**9b** was synthesized from (*S*)-**29** as a colorless oil of $bp_{1.5}$ 160 °C (bath temperature) in 87% yield. $[\alpha]_D^{25}$ +66.4° (*c*=0.90, MeOH). ^{1}H-NMR: 0.89 (9H, s, $(CH_3)_3C$), 1.35—1.63 (6H, m, $CH_2CH_2CH_2$), 1.66 (1H, br, NH), 2.12 (1H, dd, *J*=10, 12 Hz, half of *tert*-BuCCH$_2$N), 2.15—2.27 (2H, m, half of CH_2NCH_2), 2.28—2.40 (2H, m, CH_2N and half of *tert*-BuCCH$_2$N), 2.40—2.57 (2H, m, half of CH_2NCH_2), 3.21 (1H, dq, *J*=10, 14 Hz, half of CH_2CF_3), 3.42 (1H, dq, *J*=10, 14 Hz, half of CH_2CF_3). HR-MS *m*/*z*: 266.1931 (M^+) (Calcd for $C_{13}H_{25}F_3N_2$: 266.1964).

(*RS*)-*N*-(Trifluoroacetyl)-2-(3,5-dimethylphenyl)glycine ((*RS*)-30) A solution of (*RS*)-3,5-dimethylphenylglycine (88.8 g, 0.496 mol), triethylamine (100.4 g, 0.99 mol), and ethyl trifluoroacetate (84.6 g, 0.595 mol) in MeOH (600 ml) was stirred at room temperature for 24 h. Evaporation of the solvent gave a residue, which was mixed with 5% aqueous HCl (400 ml), and the whole was extracted with ether (300 ml×3). The organic extracts were combined, washed with 5% aqueous HCl (100 ml), water (100 ml×3), and brine. The organic phase was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give a residue, which was recrystallized from benzene–ether to give (*RS*)-**30** (105.5 g, 77%) as colorless crystals of mp 173.5—174.5 °C. IR (KBr) cm^{-1}: 3342, 1723, 1689. ^{1}H-NMR: 2.32 (6H, s, two $ArCH_3$), 5.50 (1H, s, ArCH), 6.98 (2H, s, aromatic H), 7.03 (1H, s, aromatic H), 7.16 (1H, br, NH), 6.80—7.40 (1H, br, CO_2H). *Anal.* Calcd for $C_{12}H_{12}F_3NO_3$: C, 52.37; H, 4.39; N, 5.09. Found: C, 52.42; H, 4.28; N, 5.20.

(*R*)-*N*-(Trifluoroacetyl)-2-(3,5-dimethylphenyl)glycine ((*R*)-30) A solution of (*RS*)-**30** (137.6 g, 0.50 mol) and cinchonine (147.2 g, 0.50 mol) in EtOH (800 ml) was heated under reflux for 30 min, and the whole was evaporated to dryness *in vacuo*. The residue was recrystallized from ether to give a colorless solid (125.3 g), which was recrystallized from benzene–ether to give colorless crystals (88.5 g, 62%) of mp 178.5—179.5 °C. $[\alpha]_D^{25}$ +25.7° (*c*=1.66, EtOH). This salt was mixed with 2.5% aqueous HCl (400 ml), and the whole was extracted with ether (200 ml×3). The organic extracts were combined, washed with water (100 ml×2), brine, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was recrystallized from benzene–ether to give (*R*)-**30**[7] (38.4 g, 56%) as colorless crystals of mp 146—147 °C. $[\alpha]_D^{25}$ −170.2° (*c*=1.27, MeOH). ^{1}H-NMR spectral data were identical to those of (*RS*)-**30** described above. Methyl ester: A solution of CH_2N_2 in ether was added to a solution of (*R*)-**30** (83 mg) in ether (1 ml) until the color of the resulting solultion was kept pale yellow. After addition of acetic acid to decompose excess CH_2N_2, ether (30 ml) was added. The resulting solution was washed successively with saturated aqueous $NaHCO_3$ (5 ml×2), water (5 ml), brine, and dried over Na_2SO_4. Evaporation of the solvent gave the methyl ester of (*R*)-**30** (85 mg, 98%) as a colorless solid of mp 98—98.5 °C. Optical purity of this sample was found to be 96.3% by HPLC analysis using a Daicel CHIRALPAC AD column. IR (nujol) cm^{-1}: 3325, 1732, 1712. ^{1}H-NMR: 2.32 (6H, s, $Ar(CH_3)_2$), 3.77 (3H, s, OCH_3), 5.47 (1H, d, *J*=7 Hz, ArCH), 6.95 (2H, s, aromatic H), 7.00 (1H, s, aromatic H), 7.29 (1H, br, NH). HR-MS *m*/*z*: 289.0927 (M^+) (Calcd for $C_{13}H_{14}F_3NO_3$: 289.0926).

(*R*)-*N*-2-(3,5-Dimethylphenyl)glycine ((*R*)-31) A mixture of (*R*)-**30** (37.5 g) and 10% aqueous HCl (540 ml) was heated under reflux for 1 h. Under ice-cooling, 10% aqueous NaOH was added to the resulting solution to pH 6.0. The precipitates were collected by filtration and washed with water, EtOH, and ether successively to give (*R*)-**31** (19.6 g, 80%) as a colorless powder of mp >220 °C. $[\alpha]_D^{25}$ −135.3° (*c*=1.25, 1 N HCl). ^{1}H-NMR (DMSO-d_6): 2.25 (6H, s, two $ArCH_3$), 4.18 (1H, s, ArCH), 6.93 (1H, s, aromatic H), 7.01 (2H, s, aromatic H). HR-MS *m*/*z*: 180.1027 (MH^+) (Calcd for $C_{10}H_{14}NO_2$: 180.1024).

(*R*)-*N*-Phthaloyl-1-phenyl-2-(1-piperdino)ethylamine ((*R*)-33) A solution of (*R*)-328) (22.2 g, 109 mmol) and phthalic anhydride (19.3 g, 130 mmol) in AcOH (135 ml) was heated under reflux for 2.5 h. After cooling, AcOEt (200 ml) was added, and the whole was extracted with 5% aqueous HCl (550 ml×3, 100 ml×2). The aqueous extracts were combined, made alkaline by addition of K_2CO_3, and the whole was extracted with AcOEt (200 ml×3). The organic extracts were combined, washed with water (200 ml×3), brine, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/AcOEt=2/1), followed by recrystallization from hexanes to give (*R*)-**33** (27.3 g, 75%) as pale yellow crystals of mp 84.5—85 °C. IR (nujol) cm^{-1}: 1770, 1712. $[\alpha]_D^{25}$ −38.4° (*c*=1.22, $CHCl_3$). ^{1}H-NMR: 1.20—1.53 (6H, m, $CH_2CH_2CH_2$), 2.25—2.66 (4H, m, CH_2NCH_2), 2.76 (1H, dd, *J*=5, 13 Hz, half of $PhCCH_2N$), 3.67 (1H, dd, *J*=12, 13 Hz, half of $PhCCH_2N$), 5.56 (1H, dd, *J*=5, 12 Hz, PhCH), 7.23—7.85 (9H, m, aromatic H). *Anal.* Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.43; H, 6.70; N, 8.39.

(*R*)-*N*-Phthaloyl-1-(3,5-di-*tert*-butylphenyl)-2-(1-piperidino)ethylamine ((*R*)-34) Under ice-cooling, $AlCl_3$ (60.0 g, 450 mmol) was added in portions during 30 min to a solution of (*R*)-**33** (15.1 g, 45 mmol) in *tert*-BuCl (300 ml), and the whole was stirred for 1 h. After addition of 5% aqueous HCl (400 ml) under ice-cooling, the whole was washed with hexanes (200 ml×3). The aqueous layer and insoluble precipitates were combined, made alkaline by addition of aqueous NaOH, and the whole was extracted with AcOEt (200 ml×2). The organic extracts were combined, washed with water (200 ml×3) and brine, and dried over K_2CO_3. Evaporation of the solvent gave a residue, which was purified by column chromatography (silica gel, hexanes/AcOEt=4/1) to give (*R*)-**34** (7.2 g, 36%) as a pale yellow oil. This was used for the next step without further purification. IR (film) cm^{-1}: 1767, 1710. $[\alpha]_D^{25}$ −20.9° (*c*=1.13, $CHCl_3$). ^{1}H-NMR: 1.32 (18H, s, two $(CH_3)_3C$), 1.02—1.46 (6H, m, $CH_2CH_2CH_2$), 2.26—2.64 (4H, m, CH_2NCH_2), 2.69 (1H, dd, *J*=5, 13 Hz, half of $ArCCH_2N$), 3.75 (1H, dd, *J*=12, 13 Hz, half of $ArCCH_2N$), 5.53 (1H, dd, *J*=5, 12 Hz, ArCH), 7.34—7.83 (7H, m, aromatic H). HR-MS *m*/*z*: 447.3010 (MH^+) (Calcd for $C_{29}H_{39}N_2O_2$: 447.3011).

(*R*)-1-(3,5-Di-*tert*-butylphenyl)-2-(1-piperidino)ethylamine ((*R*)-35) A solution of (*R*)-**34** (13.4 g, 30 mmol) and hydrazine hydrate (2.63 g, 42 mmol) in EtOH (270 ml) was heated under reflux for 1.5 h. After cooling, 6 N aqueous HCl (22 ml) was added, and the whole was heated under reflux

for 30 min. The precipitates were filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residue was mixed with water (100 ml), and washed with $CHCl_3$ (50 ml×3). The aqueous layer was basified by addition of aqueous ammonia, and extracted with $CHCl_3$ (80 ml×4). The organic extracts were combined, washed with brine, dried over K_2CO_3, and evaporated to dryness *in vacuo*. The residue was subjected to column chromatography (silica gel, $CHCl_3$/MeOH=9/1) to give a pale yellow solid. This solid was treated with HCl–MeOH to give a solid, which was recrystallized from EtOH–ether to give (*R*)-**35**·2HCl (9.2 g, 79%) as colorless crystals of mp 214—215 °C. $[\alpha]_D^{25}$ +10.2° (*c*=1.06, MeOH). This salt (7.90 g) was dissolved in water, and the resulting solution was basified by addition of K_2CO_3, and the whole was extracted with ether (80 ml×3). The organic extracts were combined, washed with water (80 ml×2) and brine, dried over K_2CO_3, and evaporated to dryness *in vacuo*. The residue was recrystallized from hexanes to give (*R*)-**35** (4.94 g, 77% recovery) as colorless plates of mp 74—75 °C. IR (KBr) cm^{-1}: 3380. $[\alpha]_D^{25}$ −30.8° (*c*=1.12, MeOH). ^{1}H-NMR: 1.33 (18H, s, two $(CH_3)_3C$), 1.40—1.70 (6H, m, $CH_2CH_2CH_2$), 1.94 (2H, s, NH_2), 2.30—2.50 (4H, m, CH_2NCH_2), 2.53—2.70 (2H, m, $ArCCH_2N$), 4.13 (1H, dd, *J*=4, 11 Hz, ArCH), 7.22 (2H, d, *J*=1.8 Hz, aromatic H), 7.31 (1H, s, aromatic H). HR-MS *m*/*z*: 317.2959 (MH^+) (Calcd for $C_{21}H_{37}N_2$: 317.2955).

(*R*)-*N*-[1-(3,5-Di-*tert*-butylphenyl)-2-(1-piperidino)ethyl]trifluoroacetamide ((*R*)-36) A solution of (*R*)-**35** (3.12 g, 9.86 mmol) and ethyl trifluoroacetate (2.10 g, 14.8 mmol) in MeOH (30 ml) was stirred at room temperature for 4 h, and the whole was evaporated to dryness *in vacuo*. The residue was subjected to column chromatography (silica gel, hexanes/AcOEt=4/1) to give a colorless oil, which was recrystallized from hexanes to give (*R*)-**36** (3.21 g, 77%) as colorless needles of mp 115—116 °C. IR (KBr) cm^{-1}: 3300, 1703. $[\alpha]_D^{25}$ −77.7° (*c*=1.16, MeOH). ^{1}H-NMR: 1.31 (18H, s, two $(CH_3)_3C$), 1.40—1.67 (6H, m, $CH_2CH_2CH_2$), 2.23—2.37 (2H, m, $ArCCH_2N$), 2.42—2.66 (4H, m, CH_2NCH_2), 4.85 (1H, dd, *J*=6, 9 Hz, ArCH), 7.05 (2H, d, *J*=1.8 Hz, aromatic H), 7.32 (1H, t, *J*=1.8 Hz, aromatic H), 7.50—7.74 (1H, br, CONH). *Anal.* Calcd for $C_{23}H_{35}F_3N_2O$: C, 66.96; H, 8.55; N, 6.79. Found: C, 67.09; H, 8.71; N, 6.76.

(*R*)-*N*-(2,2-Dimethylpropyl)-1-(3,5-di-*tert*-butylphenyl)-2-(1-piperidino)-ethylamine ((*R*)-8a) By a procedure similar to the preparation of (*R*)-**5a** described above, (*R*)-**8a** was synthesized from (*R*)-**35** as colorless needles (from MeOH) of mp 96—97 °C in 79% yield. IR (KBr) cm^{-1}: 3318. $[\alpha]_D^{25}$ −83.7° (*c*=1.02. MeOH). ^{1}H-NMR: 0.94 (9H, s, $(CH_3)_3C$), 1.32 (18H, s, two $(CH_3)_3CAr$), 1.40—1.67 (6H, m, $CH_2CH_2CH_2$), 2.14—2.60 (9H, m, CH_2NCH_2, $ArCCH_2N$, *tert*-$BuCH_2N$, NH), 3.67 (1H, dd, *J*=4, 11 Hz, ArCH), 7.23 (2H, d, *J*=1.8 Hz, aromatic H), 7.27 (1H, t, *J*=1.8 Hz, aromatic H). *Anal.* Calcd for $C_{26}H_{46}N_2$: C, 80.76; H, 11.99; N, 7.25. Found: C, 81.00; H, 12.14; N, 7.26.

(*R*)-*N*-(2,2,2-Trifluoroethyl)-1-(3,5-di-*tert*-butylphenyl)-2-(1-piperidino)-ethylamine ((*R*)-8b) By a procedure similar to the preparation of (*R*)-**5b** described above, (*R*)-**8b** was synthesized from (*R*)-**36** as a colorless oil of $bp_{0.2}$ 230 °C (bath temperature) in 94% yield. IR (film) cm^{-1}: 3322. $[\alpha]_D^{25}$ −69.3° (*c*=1.24, MeOH). ^{1}H-NMR: 1.32 (18H, s, two $(CH_3)_3C$), 1.40—1.70 (6H, m, $CH_2CH_2CH_2$), 2.20—2.70 (6H, CH_2NCH_2, $ArCCH_2N$), 2.85—3.16 (3H, m, CH_2CF_3, NH), 3.91 (1H, dd, *J*=3, 11 Hz, ArCH), 7.20 (2H, d, *J*=1.8 Hz, aromatic H), 7.32 (1H, t, *J*=1.8 Hz, aromatic H). HR-MS *m*/*z*: 399.2986 (MH^+) (Calcd for $C_{23}H_{38}F_3N_2$: 399.2987).

References and Notes

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