The Evolution of Titanium (IV) Alkoxides and Raney-Nickel for Asymmetric Reductive Amination of Prochiral Aliphatic Ketones

Thomas C. Nugent,* Vijay N. Wakchaure, Abhijit K. Ghosh, Rashmi R. Mohanty

*Department of Chemistry, School of Engineering and Science, International University Bremen,
Campus Ring 1, 28759 Bremen, Germany. E-mail: t.nugent@iu-bremen.de*

Supporting Information

General Experimental Details

NMR spectra were recorded on JEOL ECX 400 spectrometer, operating at 400 MHz (^1H) and 100 MHz (^{13}C) respectively. Chemical shifts (δ) were reported in parts per million (ppm) downfield from TMS (= 0) or in the scale relative to CHCl_3 (7.24 ppm) for ^1H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to CHCl_3 (77.0 ppm for ^{13}C NMR) as an internal reference. Multiplicities are abbreviated as: s, singlet; d, doublet; q, quartet; m, multiplet; br, broad. The coupling constants are measured in Hertz. FTIR spectra were obtained on Nicolet Avatar 370 spectrometer. Mass spectra were recorded on a Finnigan MAT 95 (EI) with an ionization potential of 70 eV. Elemental analyses were performed at Analytische Laboiratorien, Lindlar, Germany on an Elementar Vario EL III instrument. For amine products **2**, reaction progress and d.r. measurements were obtained using a Shimadzu GC-2010 instrument with a Rtx-5 amine column (Restec, 30m x 0.25mm); $T_{\text{inj}} = 300\text{ }^\circ\text{C}$ and $T_{\text{det}} = 300\text{ }^\circ\text{C}$ were always constant; Program A: 50 $^\circ\text{C}$ (1 min), 280 $^\circ\text{C}$ (14 $^\circ\text{C}/\text{min}$, then hold 5 min); Program B: 50 $^\circ\text{C}$ (1 min); 280 $^\circ\text{C}$ (20 $^\circ\text{C}/\text{min}$, then hold 2 min) and Program C: 50 $^\circ\text{C}$ (1 min), 130 $^\circ\text{C}$ (30 $^\circ\text{C}/\text{min}$), 170 $^\circ\text{C}$ (2 $^\circ\text{C}/\text{min}$), 280 $^\circ\text{C}$ (30 $^\circ\text{C}/\text{min}$, then hold 1 min). For hydrogenolyzed products primary amines **3**, the enantiomeric excess of the trifluoroacetamide derivative was determined by gas chromatography using a Shimadzu GC-2010 instrument on a Chiraldex B-DP column (Astec, 30m x 0.25mm); $T_{\text{inj}} = 200\text{ }^\circ\text{C}$, $T_{\text{det}} = 200\text{ }^\circ\text{C}$ and carrier gas He @ 23.6 psi were always constant; Program D: 160 $^\circ\text{C}$, isothermal, split ratio 100:1; Program E: 95 $^\circ\text{C}$, isothermal, split ratio 60:1. Column chromatography was performed using silica gel 60 (0.040 – 0.063 mm). Thin-layer chromatography (TLC) was performed using precoated plates of silica gel 60 F₂₅₄ and visualized under ultraviolet irradiation (254 nm). All reagents were obtained from Sigmaaldrich and used without further purification. 99.999% grade $\text{Ti}(\text{O}^i\text{Pr})_4$ was used for all screening reactions (2-5 mmol) and 97.0% grade $\text{Ti}(\text{O}^i\text{Pr})_4$ was used for all large scale

reactions (30-40 mmol). The (*R*)- or (*S*)- α -methylbenzylamine was of 98% chemical purity and 96% *ee*. The Raney-Nickel (in water) was purchased from Fluka (Catalog number, 83440). All reactions were performed under an argon or nitrogen atmosphere and under anhydrous conditions.

General procedure for asymmetric reductive amination

In an anhydrous solvent (0.50-0.83 M) a prochiral ketone (2.5 or 5.0 mmol) (**1**), titanium tetrakisopropoxide (1.25 equiv), and (*R*)- α -methylbenzylamine (1.05-1.10 equiv) were combined and stirred at room temperature for 30 min. Raney-Ni (70-100 wt %; the catalyst was first triturated with EtOH (twice) and then with the reaction solvent (twice) before addition to the reaction) was then added and the vessel pressurized at 120 psi (8.3 bar) of hydrogen. At complete conversion (<1 area % of ketone by GC), the reaction mixture was stirred with aqueous NaOH (1.0 M, 10 mL) for 1 h. The heterogeneous mixture was then filtered through a bed of celite and the celite subsequently washed with CH₂Cl₂ or EtOAc. The filtrate was concentrated (rotary evaporator) to remove the low boiling organics and the remaining aqueous solution was then extracted with CH₂Cl₂ (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and then concentrated (rotary evaporator) to give the crude product. *Des* were determined by analysis of the crude product. The diastereomeric yield was determined by flash chromatography. The major (*R,R*) diastereomer was isolated in pure form after further flash chromatography.

(1*R*)-N((*R*)-1-cyclohexylethyl)-1-phenylethanamine (**2a**)

(*R,R*)-**2a**

Reaction details: 5.00 mmol scale, 0.70 M; solvent: methyl tert-butyl ether (7.0 mL); reaction time: 11 h; 98% *de*. The mixture of diastereomers was isolated as a colorless oil (1.04 g, 90% yield) using flash chromatography (cyclohexane/EtOAc/NH₄OH = 83:15:2). The major diastereomer (*R,R*)-**2a** was obtained by further flash chromatography (cyclohexane/diethyl ether/NH₄OH = 97:1:2 to 92:6:2). GC (program A, see General Experimental Details) retention time [min]: major (*R,R*)-**2a** isomer, 15.0; minor (*S,R*)-**2a** isomer, 14.8.

Major (*R,R*)-2a: *R*_f = 0.49 (cyclohexane:EtOAc:NH₄OH = 75:20:5) [*R*_f of (*S,R*)-**2a** diastereomer = 0.38]; ¹H NMR (400 MHz, CDCl₃): δ 7.33–7.19 (m, 5H), 3.85 (q, *J* = 6.4 Hz, 1H), 2.39 (m, 1H), 1.72 (m, 4H), 1.57 (m, 1H), 1.39 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.16 (m, 3H), 0.98 (m, 2H), 0.87 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100MHz, CDCl₃): δ 146.8, 128.3, 126.6, 126.58, 55.3, 54.7, 42.1,

30.2, 27.3, 26.9, 26.8, 26.6, 24.5, 17.5; IR (KBr): $\nu_{\max}$ 3423, 2924, 1602, 1492, 1450, 1370 cm^{-1} ; LRMS (EI): m/z (%): 231 (30) [M^+], 216 (25), 160 (16), 148 (100), 105 (85), 44 (42); Anal. Calcd (%) for $\text{C}_{16}\text{H}_{25}\text{N}$: C, 83.06; H, 10.89; N, 6.05; Found: C, 83.09; H, 10.91; N, 6.07.

(2*R*)-3-Methyl-N-((*R*)-1-phenylethyl) butan-2-amine (2b)

Reaction details: 5.00 mmol scale, 0.83 M; solvent: hexane (6.0 mL); reaction time: 10 h; 98% *de*. The mixture of diastereomers was isolated as a pale yellow viscous oil (0.74 g, 78% yield) using flash chromatography (heptane/EtOAc/ NH_4OH = 92.5:3.5:4). Both the diastereomers were separately obtained by further flash chromatography (heptane/EtOAc/ NH_4OH = 93:3:4). Note that this amine is considered semi-volatile and is preferably not kept under high vacuum (defined as 0.5 mm Hg) for longer than 10 h. GC (program A, see General Experimental Details) retention time [min]: major (*R,R*)-2b isomer, 11.4; minor (*S,R*)-2b isomer, 11.2.

Major (*R,R*)-2b: R_f = 0.60 (heptane:EtOAc: NH_4OH = 86:10:4); ^1H NMR (400 MHz, CDCl_3): δ 7.20-7.31 (m, 5H), 3.85 (q, J = 6.8 Hz, 1H), 2.41 (m, 1H), 1.77 (m, 1H), 1.30 (d, J = 6.8 Hz, 3H), 0.82-0.86 (m, 9H); ^{13}C NMR (100 MHz, CDCl_3): δ 146.7, 128.2, 126.6, 126.5, 55.1, 54.9, 31.0, 24.6, 19.5, 16.4, 16.3; IR (KBr): $\nu_{\max}$ 3424, 3025, 2959, 1492, 1451, 1369 cm^{-1} ; LRMS (EI): m/z (%): 191 (5) [M^+], 176 (50), 148 (58), 105 (100), 44 (40); Anal. Calcd (%) for $\text{C}_{13}\text{H}_{21}\text{N}$: C, 81.61; H, 11.06; N, 7.32; Found: C, 81.46; H, 11.10; N, 7.31.

Minor (*S,R*)-2b: R_f = 0.52 (heptane:EtOAc: NH_4OH = 86:10:4); ^1H NMR (400 MHz, CDCl_3): δ 7.20-7.31 (m, 5H), 3.88 (q, J = 6.8 Hz, 1H), 2.20 (m, 1H), 1.53 (m, 1H), 1.32 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H), 0.80-0.85 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 146.2, 128.2, 126.7, 126.6, 54.9, 54.7, 33.3, 25.2, 19.0, 18.0, 16.0; IR (KBr): $\nu_{\max}$ 3432, 2959, 2872, 1450 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{13}\text{H}_{21}\text{N}$ [$\text{M}-15$] $^+$ 176.14392, found 176.14392.

(2*R*)-4-methyl-N-((*R*)-1-phenylethyl)pentan-2-amine (2c)

Reaction details: 5.00 mmol scale, 0.83 M; solvent: hexane (6.0 mL); hydrogen pressure, 60 psi (4.1 bar); reaction time: 9 h; 93% *de*. The mixture of diastereomers was isolated as a colorless viscous oil (0.81 g, 79% yield) using flash chromatography (heptane/EtOAc/NH₄OH = 87:9:4). The major diastereomer (*R,R*)-**2c** was obtained by further flash chromatography (heptane/EtOAc/NH₄OH = 93:3:4). Note that this amine is considered semi-volatile and is preferably not kept under high vacuum (defined as 0.5 mm Hg) for longer than 13 h. GC (program A, see General Experimental Details) retention time [min.]: major (*R,R*)-**2c** isomer, 12.01; minor (*S,R*)-**2c** isomer, 11.78.

Major (*R,R*)-2c: *R*_f = 0.60 (heptane/EtOAc/NH₄OH = 76:20:4) [*R*_f of (*S,R*)-**2c** diastereomer = 0.49]; ¹H NMR (400 MHz, CDCl₃): δ 7.19-7.33 (m, 5H), 3.87 (q, *J* = 6.5 Hz, 1H), 2.58 (m, 1H), 1.60 (m, 1H), 1.39 (m, 1H), 1.32 (d, *J* = 6.5 Hz, 3H), 1.09 (m, 1H), 0.93 (d, *J* = 6.3 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.76 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 146.5, 128.5, 126.6, 126.5, 55.1, 48.3, 66.6, 25.0, 24.3, 23.5, 22.3, 21.6; IR (KBr): ν_{max} 3423, 2957, 2867, 1468, 1368 cm⁻¹; LRMS (EI): *m/z* (%): 205 (3) [*M*⁺], 190 (14), 148 (54), 105 (100), 79 (12), 44 (84); Anal. Calcd (%) for C₁₄H₂₃N: C, 81.89; H, 11.29; N, 6.82; Found: C, 81.93; H, 11.39; N, 6.75.

(2*R*)-4-phenyl-N-((*R*)-1-phenylethyl)butan-2-amine (2d)

Reaction details: 5.00 mmol scale, 0.70 M; solvent, dichloromethane (7.0 mL); reaction time, 11 h; 80% *de*. The mixture of diastereomers was isolated as a colorless oil (1.13 g, 89% yield) using flash chromatography (cyclohexane/EtOAc/NH₄OH = 83:15:2). Both the diastereomers were separately obtained by further flash chromatography (cyclohexane/diethyl ether/NH₄OH = 87:8:5 to 80:15:5). GC (program A, see General Experimental Details) retention time [min]: major (*R,R*)-**2d** isomer, 16.5; minor (*S,R*)-**2d** isomer, 16.4.

Major (*R,R*)-2d: *R*_f = 0.41 (cyclohexane/diethyl ether/NH₄OH = 55:40:5); ¹H NMR (400 MHz, CDCl₃): δ 7.32 – 7.16 (m, 10H), 3.87 (q, *J* = 6.4 Hz, 1H), 2.66 (m, 1H), 2.55 (m, 2H), 1.82 (m, 1H), 1.60 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (100MHz, CDCl₃): δ 146.3, 142.6, 128.4, 128.3, 126.7, 126.5, 125.6, 55.0, 49.7, 38.0, 32.0, 24.5, 21.2 ; IR (KBr): ν_{max} 3441, 2960, 1603, 1494, 1453 cm⁻¹; LRMS (EI): *m/z* (%): 253 (5) [*M*⁺], 238 (16), 148 (78), 105 (100), 44 (42); Anal. Calcd (%) for C₁₈H₂₃N: C, 85.32; H, 9.15; N, 5.53; Found: C, 85.29; H, 9.18; N, 5.49.

Minor (*S,R*)-2d: $R_f = 0.48$ (cyclohexane:diethyl ether: $\text{NH}_4\text{OH} = 55:40:5$); ^1H NMR (400 MHz, CDCl_3): δ 7.34 – 7.07 (m, 10H), 3.91 (q, $J = 6.4$ Hz, 1H), 2.65 (m, 1H), 2.50 (m, 2H), 1.61 (m, 2H), 1.34 (d, $J = 6.8$ Hz, 3H), 1.06 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 146.0, 142.5, 128.4, 128.3, 128.2, 126.7, 126.6, 125.6, 54.9, 49.6, 39.8, 32.4, 25.1, 20.2; IR (KBr): ν_{max} 3445, 2960, 1603, 1494, 1452 cm^{-1} ; LRMS (EI): m/z (%): 253 (8) [M^+], 238 (20), 148 (78), 105 (100), 44 (40); HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{23}\text{N}$ [M^+] 253.183, found 253.183.

(2*R*)-N-((*R*)-1-phenylethyl)octan-2-amine (2e)

(*R,R*)-2e

Reaction details: 2.50 mmol scale, 0.50 M; solvent, THF (5.0 mL); reaction time, 6 h, 72% *de*. The mixture of diastereomers was isolated as a pale yellow liquid (0.42 g, 72% yield) using flash chromatography (cyclohexane/diethyl ether/ $\text{NH}_4\text{OH} = 58:40:2$). The major diastereomer (*R,R*)-2e was obtained by further flash chromatography (cyclohexane/diethyl ether/ $\text{NH}_4\text{OH} = 78:20:2$). GC (program B, see General Experimental Details) retention time [min]: major (*R,R*)-2e isomer, 11.13; minor (*S,R*)-2e isomer, 11.0.

Major (*R,R*)-2e: $R_f = 0.54$ (cyclohexane/diethyl ether/ $\text{NH}_4\text{OH} = 58:40:2$) [R_f of (*S,R*)-2e diastereomer = 0.58]; ^1H NMR (400 MHz, CDCl_3): δ 7.22–7.34 (m, 5H), 3.88 (q, $J = 6.4$ Hz, 1H), 2.49 (m, 1H), 1.32 (d, $J = 6.8$ Hz, 3H), 1.25 (br, 10H), 0.95 (d, $J = 6.4$ Hz, 3H), 0.88 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 146.5, 128.3, 126.4, 55.1, 50.1, 36.3, 31.8, 29.5, 25.6, 24.6, 22.6, 21.3, 14.1; IR (KBr): ν_{max} 3440, 1600, 1495, 1448, cm^{-1} ; LRMS (EI): m/z (%): 233 (5) [M^+], 218 (85), 148 (84), 106 (16), 105(100), 44 (42); HRMS (EI) m/z calcd for $\text{C}_{16}\text{H}_{27}\text{N}$ [M^+] 233.21436, found 233.21385; Anal. Calcd (%) for $\text{C}_{16}\text{H}_{27}\text{N}$: C, 82.34; H, 11.66; N, 6.0; Found: C, 81.90; H, 11.24; N, 5.63.

Scale-up reaction of [(2*R*)-N-((*R*)-1-phenylethyl)octan-2-amine] (2e)

To a mixture of 2-octanone **1e** (1.0 equiv, 39.0 mmol, 6.1 mL), (*R*)- α -methylbenzylamine (1.1 equiv, 43.0 mmol, 5.50 mL) and titaniumtetrakisopropoxide (97% grade) (1.25 equiv, 49.0 mmol, 14.4 mL) in dry THF (75 mL) was added Raney Nickel (1.0 g). The reaction was then pressurized with 120 psi (8.3 bar) of hydrogen with vigorous overhead stirring (900 rpm) at room temperature. The reaction was monitored by GC using temperature gradient program B (see General

Experimental Details). At complete conversion, 17 h, the reaction mixture was treated with an aqueous solution of 3.0 M NaOH (20 mL) and CH₂Cl₂ (20 mL) and stirred for 1 h. The solution was then filtered through celite, the celite washed with CH₂Cl₂ (3 x 30 mL) and the organic solvents striped (rotary evaporator) from the filtrate. The remaining aqueous solution was then extracted with CH₂Cl₂ (3 x 50 mL). The combined extracts were dried (Na₂SO₄), filtered and evaporated to dryness and kept under high vacuum to remove excess (*R*)- α -methylbenzylamine. The resulting oil was then dissolved in EtOAc (30 mL) and this solution was extracted with 2.0 M HCl (2 x 20 mL). The combined acidic extracts were then neutralized with aqueous NaOH (4.0 M) to pH 10-12 and the free amine **2e** extracted into EtOAc (3 x 50 mL). The organic extracts were combined, dried over Na₂SO₄ and concentrated under reduced pressure. The secondary amine **2e** was then treated with ethereal HCl (1.0 M) to afford 9.40 g (90% yield, 72% *de*) of the HCl salt.

4-Phenylbutan-2-amine hydrochloride (**3d**)

The diastereomeric amine mixture **2d** (2.0 mmol, 0.51 g) was dissolved in methanol (5.0 mL) and hydrogenolysis was carried out in presence of 5 wt% Pd/C (12.0 mol%, 0.511 g) at 4.1 bar (60 psi) of hydrogen pressure at room temperature. After 25 h, the catalyst was filtered through celite and the celite washed with methanol (2 x 10 mL). 1.0 M ethereal HCl (2.5 mL) was added to the combined filtrate and concentrated. To the resulting sticky solid was added Et₂O, precipitation of the free flowing HCl salt was initiated and immediate upon spatula scratching. Removal of the Et₂O under reduced pressure, followed by high vacuum drying, gave a white solid (0.326 g, 88%) in qualitative purity (GC temperature program A, retention time of **3d** = 10.6 min, >99% pure; ¹H NMR and ¹³C NMR of **3d**·HCl salt). The trifluoroacetyl derivative of **3d** has an 80% *ee* (chiral GC program D, see General Experimental Details). GC retention time [min]: major (*R*)-**3d** trifluoroacetamide isomer, 21.7; minor (*S*)-**3d** trifluoroacetamide isomer, 20.4.

3d·HCl salt: ¹H NMR (400 MHz, CDCl₃): δ 8.5 (br s, 3H), 7.27 – 7.16 (m, 5H), 3.3 (m, 1H), 2.76 (t, *J* = 8.0 Hz, 2H), 2.16 (m, 1H), 1.93 (m, 1H), 1.43 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 140.0, 128.6, 128.4, 126.3, 47.9, 36.5, 31.6, 18.8; IR (KBr): ν_{max} 3441, 2922, 1602, 1516 cm⁻¹; LRMS (EI): *m/z* (%): 149 (11) [*M*⁺ - HCl], 132 (10), 117 (07), 91 (17), 44 (100), 36 (09); Anal. Calcd (%) for C₁₀H₁₆NCl: C, 64.68; H, 8.68; N, 7.54; Cl, 19.09; Found: C, 64.53; H, 8.67; N, 7.39; Cl, 18.92.

(3*R*)-2-methyl-N-((*R*)-1-phenylethyl)hexan-3-amine (6)

A mixture of 2-methyl-3-hexanone **5** (1.00 equiv, 5.00 mmol, 0.69 mL), (*R*)- α -methylbenzylamine (1.05 equiv, 5.25 mmol, 0.67 mL) and titanium tetraisopropoxide (2.00 equiv, 10.0 mmol, 2.93 mL) was prestirred for 2 h under argon at room temperature. Dry 1,2-dichloroethane (0.83 M, 6.0 mL) and Raney Nickel (0.57 g) were added. The reaction vessel was then pressurized with hydrogen at 120 psi (8.3 bar) and vigorously stirred at 60 °C. The reaction course was monitored by GC (temperature program C, see General Experimental Details). At 24 h, 6 area % of the ketone remained; the reaction mixture was then treated with an aqueous solution of 1.0 M NaOH (10 mL). After stirring for 1 h, the solution was diluted with CH₂Cl₂ (30 mL), filtered through celite and the celite washed with CH₂Cl₂ (2 x 25 mL). The organic layer was removed from the filtrate and the aqueous layer further extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and evaporated. Purification using flash chromatography (cyclohexane/EtOAc/NH₄OH = 95:1:4) afforded the pure diastereomers as a pale yellow viscous oil (0.71 g, 65% yield, 87% *de*). The major (*R,R*)-**6** diastereomer was obtained by further flash chromatography (cyclohexane/EtOAc/NH₄OH = 95.5:0.5:4). GC retention time [min.]: major (*R,R*)-**6** isomer, 18.29; minor (*S,R*)-**6** isomer, 18.65. Note the stereochemistry of the major product has not been determined, but is assumed, based on precedent, to have the (*R,R*) configuration.

Major (*R, R*)-6: R_f = 0.51 (cyclohexane/EtOAc/NH₄OH = 90:6:4) [R_f of (*S,R*)-**2e** diastereomer = 0.40]; ¹H NMR (400 MHz, CDCl₃): δ 7.18-7.38 (m, 5H), 3.84 (q, J = 6.5 Hz, 1H), 2.16 (m, 1H), 1.86 (m, 1H), 1.26 (d, J = 6.5 Hz, 3H), 1.13 (m, 4H), 0.85 (m, 3H), 0.78 (m, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 146.5, 128.1, 126.7, 126.6, 58.7, 55.0, 32.4, 28.8, 24.8, 19.6, 18.9, 16.7, 14.2; IR (KBr): $\nu_{\max}$ 3432, 2957, 1462, 1360 cm⁻¹; LRMS (EI): m/z (%): 218 (6) [M^+], 205 (18), 204 (62), 105 (100), 72 (79); Anal. Calcd (%) for C₁₅H₂₅N: C, 82.13; H, 11.49; N, 6.39; Found: C, 82.01; H, 11.40; N, 6.51.

Scale up reaction of (3*R*)-2-methyl-N-((*R*)-1-phenylethyl)hexan-3-amine (6)

A mixture of 2-methyl-3-hexanone **5** (1.00 equiv, 30.00 mmol, 4.15 mL), (*R*)- α -methylbenzylamine (1.05 equiv, 31.5 mmol, 4.07 mL) and titanium tetraisopropoxide (97% grade) (3.00 equiv, 90.0 mmol, 26.6 mL) in dry 1,2-dichloroethane (20 mL) were stirred at 900 rpm under argon at 40 °C for 2 h. Raney Nickel (2.8 g) suspended in 1,2-dichloroethane (10 mL) was added and the whole

hydrogenated at 120 psi (8.3 bar) with vigorous stirring (1200 rpm) at 60 °C. The reaction course was monitored by GC (temperature program C, see General Experimental Details). At 24 h, 13 area % of the starting material remained. At 35 h, 3 area % of the starting material remained and the reaction mixture was quenched with aqueous NaOH (30 mL, 2.5 M). After stirring for 2 h, the solution was diluted with CH₂Cl₂ (50 mL), filtered through celite and the celite washed with CH₂Cl₂ (3 x 70 mL). The organic layer was removed from the filtrate and the aqueous layer further extracted with CH₂Cl₂ (2 x 20 mL), the combined organic extracts were dried over Na₂SO₄, filtered and evaporated to dryness and kept under high vacuum to remove excess (*R*)- α -methylbenzylamine. The resulting oil, secondary amine **6**, was then treated with ethereal HCl (4.0 M, 15 mL) to afford 5.82 g (76% yield, 87% *de*) of the HCl salt after filtration and drying.

(*R*)-2-methyl-3-hexyl amine hydrochloride (7)

The secondary amine **6** (2.00 mmol, 0.438 g) was dissolved in methanol (5.0 mL) and hydrogenolysis was carried out in the presence of 5 wt% Pd/C (5 mol%, 0.212 g) at 2.8 bar (40 psi) of hydrogen pressure at room temperature. After 165 min, the reaction mixture was filtered through celite and the celite further washed with methanol (2 x 5.0 mL). The combined filtrate was treated with 4.0 M ethereal HCl (1.0 mL), stirred for 15 min, and evaporated to dryness to obtain a white solid (0.28 g, 93%) in qualitative purity (GC temperature program C, see General Experimental Details, retention time of **7** = 4.45 min, >99% pure; ¹H NMR and ¹³C NMR of **7**·HCl salt). A small amount of the salt was converted to the trifluoroacetamide derivative of **7**. Using chiral GC temperature program E, the *ee* of the trifluoroacetamide was determined (87% *ee*). GC retention time [min]: major (*R*)-**7** trifluoroacetamide isomer, 28.97; minor (*S*)-**7** trifluoroacetamide isomer, 27.81.

7·HCl salt: ¹H NMR (400 MHz, CDCl₃): δ 8.32 (bs, 3H), 3.04 (bs, 1H), 2.03-2.11 (m, 1H), 1.41-1.72 (m, 4H), 0.93-1.09 (m, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 57.7, 31.8, 30.0, 19.0, 18.3, 17.9, 13.8; IR (KBr): ν_{max} 3441, 2961, 2647, 1604, 1516, 1466, 1392 cm⁻¹; LRMS (EI): *m/z* (%): 114 (06) [*M*⁺ - HCl], 100 (6), 72 (100), 55 (11), 36 (11), 30 (35); Anal. Calcd (%) for C₇H₁₈NCl: C, 55.43; H, 11.96; N, 9.23; Found: C, 55.24; H, 11.92; N, 9.09.

Peak Table - Channel 1

Peak#	Ret. Time	Area	Height	Conc.	Units
1	16.400	142835	83271	10,050	
2	16.537	1278477	706377	89,950	
Total		1421312	789648

Chromatogram Chiral- TFA-Rec-4-P2Butanamine D:\GC data Dr.Rashmi\Jan-Jun2005\RM-I-159.gcd - Channel 1

Peak Table - Channel 1

Peak#	Ret. Time	Area	Height	Conc.	Units
1	20.405	139635	14325	53,531	
2	21.721	121213	11497	46,469	
Total		260848	25822

Peak Table - Channel 1

Peak#	Ret. Time	Area	Height	Conc.	Units
1	20.402	20125	2014	10.026	
2	21.699	180594	17091	89.974	
Total		200719	19105

Peak Table - Channel 1

Peak#	Ret. Time	Area	Height	Conc.	Units
1	18.359	6171691	958461	93.356	
2	18.645	439263	98220	6.644	
Total		6610954	1056681

Peak Table - Channel 1

Peak#	Ret. Time	Area	Height	Conc.	Units
1	27.956	94516	4499	50.323	
2	29.348	93301	4228	49.677	
Total		187817	8727

Peak Table - Channel 1

Peak#	Ret. Time	Area	Height	Conc.	Units
1	27.816	59184	2931	6.239	
2	28.973	889461	38211	93.761	
Total		948645	41142		