Preparation of Aryl-Alkyl Amines via Electrophilic Amination of Functionalized Arylazo Tosylates with Alkylzinc Reagents

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Supporting Information

All reactions were performed in flame dried glassware under argon atmosphere. Ethanol was distilled prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen atmosphere. Pre-coated silica gel 60F₂₅₄, Merck was used for thin layer chromatography (TLC) and silica gel 60 (0.040-0.063 nm), Merck was used for column chromatography. Reactions were monitored by TLC. Yields refer to isolated yields of analytically pure compounds. NMR spectra were recorded on 300 MHz NMR spectrometer. The ionization method used for mass spectrometry was electron impact (EI, 70 eV). Infrared spectroscopy was performed with Spectrum 1000 Perkin-Elmer FT-IR spectrometer.

Arylazo tosylates were prepared according to already reported procedures. The following organozinc compounds were prepared according to literature procedures: cyclopentylzinc iodide,¹ cyclohexylzinc iodide,¹ n-pentylzinc iodide,¹ octylzinc iodide,¹ dinorbornyl zinc,¹ dimyrtanylzinc,² bis[2-(ethoxycarbonyl)ethyl]zinc,³ bis[2-(2-methoxyphenyl)-1-cyclopentyl]-isopropylzinc,⁴ dicyclohexylzinc.⁵ Neophylzinc bromide was prepared by transmetalation of neophyllithium⁶ with anhydrous zinc bromide (solution in THF) at –75 °C, followed by slow warm up to 0 °C for 30 min.

Typical procedure (TP) for the synthesis of secondary amines:

In a flame dried argon flushed 25 mL two-neck round-bottom flask equipped with a magnetic stirrer and septum, the organozinc compound (1.2 mmol) was dissolved in dry THF (1 mL) and cooled to –20 °C. The arylazo tosylate (1 mmol) was dissolved in dry THF (2 mL) and added dropwise to the organozinc reagent. The reaction mixture was stirred at –20 °C until TLC analysis showed total consumption of the starting material as well as the formation of the new intermediate zinc hydrazide. The solvent was removed *in vacuo* and the residue was dissolved in ethanol (5 mL). Raney-Nickel (activated catalyst 50%, in water; Acros Chemical) (2.5 g) was added, and the reaction mixture was refluxed until full conversion could be observed. The reaction mixture was allowed to cool to room temperature and the Raney-Nickel residue was separated by filtration. Ethanol was removed *in vacuo* and the residue extracted with diethyl ether (2x10 mL), washed with brine (2x10 mL), and dried over sodium sulfate. The solvent removal under reduced pressure followed by flash chromatography over silica gel afforded the functionalized secondary amine.

1. Synthesis of 4-cyclopentylamino-benzoic acid ethyl ester (3a)

Cyclopentylzinc iodide (0.92 mL, 1.2 mmol, 1.31 M in THF) and 4-phenylazo tosylate ethyl ester (332 mg, 1.0 mmol) was stirred in 3 mL of dry THF at -20°C for 30 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (2.5 g) for 3 h. Standard workup and purification by flash chromatography (eluent: n-pentane/diethyl ether 95:5 v/v) yielded 166 mg (71% isolated yield) of **3a** as light-yellow viscous liquid.

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.84 (d, $J = 8.9$ Hz, 2H), 6.53 (d, $J = 8.9$ Hz, 2H), 4.30 (q, $J = 7.1$ Hz, 2H), 4.12 (br s, 1H), 3.86-3.78 (m, 1H), 2.09-1.97 (m, 2H), 1.77-1.57 (m, 4H), 1.52-1.41 (m, 2H), 1.34 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 166.9, 151.6, 131.4, 118.2, 111.7, 60.1, 54.2, 33.4, 24.0, 14.4.

MS (EI, 70 eV) m/z (%): 233 (64), 204 (100), 191 (29), 188 (20), 176 (11), 130 (16), 92 (7), 43 (8).

HRMS for $\text{C}_{14}\text{H}_{19}\text{NO}_2$: calcd. 233.1416, found 233.1401.

IR (film) (cm^{-1}): 3372, 2968, 2268, 1679, 1603, 1526, 1478, 1444, 1364, 1342, 1282, 1174, 1124, 1113, 1025, 841, 770, 703.

2. Synthesis of 4-cyclohexylamino-benzoic acid ethyl ester (3b)

Dicyclohexylzinc (0.28 mL, 0.55 mmol, 1.96 M in THF) and 4-phenylazo tosylate ethyl ester (166 mg, 0.50 mmol) was stirred in 3 mL of dry THF at -20°C for 30 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (1.25 g) for 3 h. Standard workup and purification by flash chromatography (eluent n-pentane/diethyl ether 99:1 v/v) yielded 85 mg (69% isolated yield) of **3b** as light-yellow viscous liquid.

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.83 (d, $J = 8.9$ Hz, 2H), 6.51 (d, $J = 8.9$ Hz, 2H), 4.29 (q, $J = 7.1$ Hz, 2H), 4.05 (br s, 1H), 3.35-3.26 (m, 1H), 2.05-2.00 (m, 2H), 1.86-1.61 (m, 3H), 1.44-1.10 (m, 8H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 166.8, 151.0, 131.5, 118.0, 111.5, 60.0, 51.2, 33.1, 25.7, 24.8, 14.4.

MS (EI, 70 eV) m/z (%): 247 (46), 204 (100), 191 (9), 174 (18), 146 (10), 130 (16), 120 (14), 77 (6), 44 (13).

HRMS for $\text{C}_{15}\text{H}_{21}\text{NO}_2$: calcd. 247.1572, found 247.1562.

IR (film) (cm^{-1}): 3368, 2979, 2931, 2854, 1694, 1606, 1526, 1451, 1421, 1368, 1338, 1310, 1149, 1106, 1023, 888, 837, 771, 700.

3. Synthesis of 4-pentylamino-benzoic acid ethyl ester (3c)

n-Pentylzinc iodide (0.43 mL, 0.55 mmol, 1.29 M in THF) and 4-phenylazo tosylate ethyl ester (166 mg, 0.50 mmol) was stirred in 3 mL of dry THF at -20°C for 30 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (1.25 g) for 3 h. Standard workup and purification by flash chromatography (eluent *n*-pentane/diethyl ether 99:1 v/v) yielded 64 mg (55% isolated yield) of **3c** as light-yellow viscous liquid.

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.86 (d, $J = 8.8$ Hz, 2H), 6.53 (d, $J = 8.8$ Hz, 2H), 4.30 (q, $J = 7.1$ Hz, 2H), 4.08 (br s, 1H), 3.14 (t, $J = 7.1$ Hz, 2H), 1.64-1.60 (m, 2H), 1.39-1.32 (m, 7H), 0.93-0.89 (m, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 166.9, 152.1, 131.5, 118.4, 111.3, 60.1, 43.3, 29.2, 29.0, 22.4, 14.4, 14.0.

MS (EI, 70 eV) m/z (%): 235 (21), 190 (10), 178 (100), 150 (24), 105 (4), 58 (4), 43 (1).

HRMS for $\text{C}_{14}\text{H}_{21}\text{NO}_2$: calcd. 235.1572, found 235.1588.

IR (film) (cm^{-1}): 3369, 2979, 2929, 2860, 1681, 1603, 1533, 1478, 1422, 1366, 1344, 1311, 1287, 1273, 1176, 1126, 1116, 1025, 840, 769, 701.

4. Synthesis of 4-octylamino-benzoic acid ethyl ester (3d)

n-Octylzinc iodide (1.0 mL, 1.2 mmol, 1.2 M in THF) and 4-phenylazo tosylate ethyl ester (332 mg, 1.0 mmol) was stirred in 3 mL of dry THF at -20°C for 45 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (2.5 g) for 3 h. Standard workup and purification by flash chromatography (eluent: *n*-pentane/diethyl ether 90:10 v/v) yielded 144 mg (52% isolated yield) of **3d** as white solid.

Mp.: 81°C .

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.84 (d, $J = 8.8$ Hz, 2H), 6.51 (d, $J = 8.8$ Hz, 2H), 4.29 (q, 2H), 4.06 (br s, 1H), 3.14 (t, $J = 7.1$ Hz, 2H), 1.65-1.56 (m, 2H), 1.39-1.27 (m, 13 H), 0.88 (m, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 166.9, 152.0, 131.5, 118.4, 111.3, 60.1, 43.4, 31.8, 29.3, 29.2, 27.1, 22.6, 14.4, 14.1.

MS (EI, 70 eV) m/z (%): 277 (19), 232 (8), 178 (100), 150 (17), 105 (5), 77 (2), 41 (3).

HRMS for $\text{C}_{17}\text{H}_{27}\text{NO}_2$: calcd. 277.2042, found 277.2007.

IR (film) (cm^{-1}): 3371, 2930, 1682, 1605, 1367, 1278, 1173, 772.

5. Synthesis of cyclohexyl-(4-fluoro-phenyl)-amine (3e)

Cyclohexylzinc iodide (1.41 mL, 1.2 mmol, 0.85 M in THF) and 4-fluoro phenylazo tosylate (278 mg, 1.0 mmol) was stirred in 3 mL of dry THF at -20°C for 35 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (2.5 g) for 3 h. Standard workup and purification by flash chromatography (eluent: n-pentane/diethyl ether 97:3 v/v) yielded 145 mg (75% isolated yield) of **3e** as light-yellow viscous liquid.

^1H NMR (300 MHz, CDCl_3) δ (ppm): 6.85 (m, 2H), 6.51 (m, 2H), 3.35 (br s, 1H), 3.16 (m, 1H), 2.06-2.00 (m, 2H), 1.78-1.71 (m, 1 H), 1.68-1.59 (m, 1H), 1.42-1.05 (m, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 153.9, 143.7, [115.7, 115.5], [114.1, 114.0], 52.5, 33.5, 25.9, 25.0.

MS (EI, 70 eV) m/z (%): 193 (32), 150 (100), 137 (10), 124 (7), 111 (13), 95 (5), 55 (4).

HRMS for $\text{C}_{12}\text{H}_{16}\text{FN}$: calcd. 193.1267, found 193.1249.

IR (film) (cm^{-1}): 2929, 2854, 1612, 1506, 1219, 818, 769.

6. Synthesis of bicyclo[2.2.1]hept-2-yl-(4-methoxyphenyl)-amine (3f)

Dinorbornyl zinc (1.9 mL, 1.2 mmol, 0.62 M in THF) and 4-methoxy phenylazo tosylate (290 mg, 1.0 mmol) was stirred in 3 mL of dry THF at -20°C for 40 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (2.5 g) for 1.5 h. Standard workup and purification by flash chromatography (eluent: n-pentane/diethyl ether 95:5 v/v) yielded 154 mg (71% isolated yield, diastereomeric ratio 80:20) of **3f** as colorless viscous liquid.

^1H NMR (300 MHz, CDCl_3) δ (ppm): (*major isomer*) 6.75 (m, 2H), 6.55 (m, 2H), 3.73 (s, 3H), 3.15 (m, 1H), 2.25 (m, 2H), 1.76 (m, 1H), 1.67-1.33 (m, 4H), 1.25-1.13 (m, 3H). δ (ppm): (*minor isomer*) 6.75 (m, 2H), 6.55 (m, 2H), 3.73 (s, 3H), 3.61(m, 1H), 2.47 (m, 2H), 2.12 (m, 1H), 1.67-1.33 (m, 4H), 1.25-1.13 (m, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 151.8, [142.6, 141.9] (*major+minor*), 114.9, [114.4, 114.3] (*major+minor*), 57.4, [55.8, 55.5] (*major+minor*), [41.1, 41.0, 39.8, 38.9, 38.1, 36.8, 35.6, 35.2, 29.9, 28.4, 26.4, 21.1] (*major+minor isomer for 2 CH and 4 CH₂*).

MS (EI, 70 eV) m/z (%): 217 (100), 188 (12), 162 (31), 149 (85), 136 (45), 108 (21), 67 (14).

HRMS for $\text{C}_{14}\text{H}_{19}\text{NO}$: calcd. 217.1467, found 217.1449.

IR (film) (cm^{-1}): 3399, 2951, 2869, 1512, 1234, 1039, 817.

7. Synthesis of cyclopentyl-(3,5-dimethylphenyl)-amine (3g)

Cyclopentylzinc iodide (0.92 mL, 1.2 mmol, 1.31 M in THF) and 3,5-dimethyl phenylazo tosylate (288 mg, 1.0 mmol) was stirred in 3 mL of dry THF at -20°C for 30 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (2.5 g) for 1.5 h. Standard workup and purification by flash chromatography (eluent: n-pentane/diethyl ether 99:1 v/v) yielded 144 mg (76% isolated yield) of **3g** as light-yellow viscous liquid.

^1H NMR (300 MHz, CDCl_3) δ (ppm): 6.36 (m, 1H), 6.26 (m, 2H), 3.79 (m, 1H), 3.32 (br s, 1H), 2.25 (s, 6H), 2.00 (m, 2H), 1.75-1.59 (m, 4H), 1.47 (m, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 148.1, 138.8, 118.9, 111.1, 54.6, 33.6, 24.0, 21.5.

MS (EI, 70 eV) m/z (%): 189 (61), 160 (100), 147 (31), 132 (15), 121 (10), 77 (8).

HRMS for $\text{C}_{13}\text{H}_{19}\text{N}$: calcd. 189.1517, found 189.1503.

IR (film) (cm^{-1}): 2955, 2867, 1605, 1473, 1339, 1195, 821.

8. Synthesis of 4-(2-methyl-2-phenyl-propylamino)-benzoic acid ethyl ester (3h)

Neophylzinc bromide prepared *in situ* from the reaction of neophyllithium (0.9 mL, 1.25 mmol, 1.34 M in ether) and anhydrous zinc bromide (0.83 mL, 1.25 mmol, 1.5 M in THF), was stirred in 3 mL of dry THF with 4-phenylazo tosylate ethyl ester (332 mg, 1.0 mmol) at -20°C for 35 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (2.5 g) for 3 h. Standard workup and purification by flash chromatography (eluent: n-pentane/diethyl ether 92:8 v/v) yielded 235 mg (79% isolated yield) of **3h** as yellow viscous liquid.

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.84 (d, $J = 8.8$ Hz, 2H), 7.41-7.36 (m, 4H), 7.30-7.23 (m, 1H), 6.49 (d, $J = 8.8$ Hz, 2H), 4.32 (q, 2H), 3.81 (br s, 1H), 3.37 (s, 2H), 1.45 (s, 6H), 1.38 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 166.8, 152.2, 146.2, 131.4, 128.6, 126.4, 125.9, 118.5, 111.4, 60.1, 54.9, 38.9, 27.2, 14.4.

MS (EI, 70 eV) m/z (%): 297 (3), 252 (3), 178 (100), 150 (29), 105 (9), 77 (6).

HRMS for $\text{C}_{19}\text{H}_{23}\text{NO}_2$: calcd. 297.1729, found 297.1737.

IR (film) (cm^{-1}): 3390, 1698, 1606, 1527, 1277, 1106, 770.

9. Synthesis of bicyclo[2.2.1]hept-2-yl-quinolin-3-yl-amine (**3i**)

Dinorbornyl zinc (1.9 mL, 1.2 mmol, 0.62 M in THF) and 3-quinoline azo tosylate (311 mg, 1.0 mmol) was stirred in 3 mL of dry THF at -20°C for 25 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (2.5 g) for 2 h. Standard workup and purification by flash chromatography (eluent: n-pentane/diethyl ether 80:20 v/v) yielded 148 mg (62% isolated yield, diastereomeric ratio 80:20) of **3i** as colorless viscous liquid.

^1H NMR (300 MHz, CDCl_3) δ (ppm): (*major isomer*) 8.37 (m, 1H), 7.89 (m, 1H), 7.58 (m, 1H), 7.42-7.34 (m, 2H), 6.94 (m, 1H), 3.87 (br s, 1H), 3.31 (m, 1H), 2.34 (s, 2H), 1.94-1.86 (m, 1H), 1.63-1.48 (m, 4H), 1.30-1.19 (m, 3H). δ (ppm): (*minor isomer*) 8.42 (m, 1H), 7.89 (m, 1H), 7.58 (m, 1H), 7.42-7.34 (m, 2H), 6.98 (m, 1H), 4.12 (br s, 1H), 3.73 (m, 1H), 2.61 (s, 2H), 2.23 (m, 1H), 1.63-1.48 (m, 4H), 1.30-1.19 (m, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 143.7, 141.9, 140.8, 128.9, 126.8, 125.9, 124.6, 110.4, 56.5, [40.9, 40.8] (*major+minor*), [35.6, 35.5] (*major+minor*), 28.4, 26.4.

MS (EI, 70 eV) m/z (%): 238 (100), 209 (16), 183 (11), 170 (79), 144 (75), 128 (20), 95 (10).

HRMS for $\text{C}_{16}\text{H}_{18}\text{N}_2$: calcd. 238.1470, found 238.1462.

IR (film) (cm^{-1}): 3436, 2953, 1609, 1474, 747.

10. Synthesis of (6,6-dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-(4-methoxyphenyl)-amine (**3j**)

Dimyrtanylzinc (0.8 mL, 1.2 mmol, 1.5 M in THF) and 4-methoxy phenylazo tosylate (290 mg, 1.0 mmol) was stirred in 3 mL of dry THF at -20°C for 30 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (2.5 g) for 1.5 h. Standard workup and purification by flash chromatography (eluent: n-pentane/diethyl ether 96:4 v/v) yielded 174 mg (67% isolated yield) of **3j** as colorless viscous liquid.

^1H NMR (300 MHz, CDCl_3) δ (ppm): 6.75 (d, $J = 8.8$ Hz, 2H), 6.54 (d, $J = 8.8$ Hz, 2H), 3.73 (s, 3H), 3.05 (m, 2H), 2.38-2.25 (m, 2H), 2.01-1.85 (m, 5H), 1.54 (m, 1H), 1.20 (s, 3H), 1.03 (s, 3H), 0.89 (m, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 151.9, 142.9, 114.9, 113.9, 55.9, 51.1, 44.2, 41.5, 41.2, 38.7, 33.4, 28.0, 26.2, 23.3, 20.5.

MS (EI, 70 eV) m/z (%): 259 (22), 136 (100), 121 (2), 41 (2).

HRMS for $\text{C}_{17}\text{H}_{25}\text{NO}$: calcd. 259.1936, found 259.1912.

IR (film) (cm^{-1}): 3401, 2907, 2830, 1514, 1234, 1040, 817.

11. Synthesis of 4-[(6,6-dimethyl-bicyclo[3.1.1]hept-2-ylmethyl)-amino]-benzoic acid ethyl ester (**3k**)

Dimyrtanylzinc (0.8 mL, 1.2 mmol, 1.5 M in THF) and 4-phenylazo tosylate ethyl ester (332 mg, 1.0 mmol) was stirred in 3 mL of dry THF at -20°C for 55 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (2.5 g) for 6 h. Standard workup and purification by flash chromatography (eluent: n-pentane/diethyl ether 96:4 v/v) yielded 151 mg (50% isolated yield) of **3k** as white solid.

Mp.: 84°C .

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.83 (d, $J = 8.8$ Hz, 2H), 6.50 (d, $J = 8.8$ Hz, 2H), 4.29 (q, 2H), 4.12 (br s, 1H), 3.14 (m, 2H), 2.41-2.27 (m, 2H), 2.01-1.86 (m, 5H), 1.54 (m, 1H), 1.34 (t, $J = 7.1$ Hz, 3H), 1.20 (s, 3H), 1.04 (s, 3H), 0.90 (m, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 166.9, 152.1, 131.5, 112.6, 111.3, 60.1, 49.3, 44.9, 41.4, 41.1, 38.7, 33.4, 28.0, 26.0, 23.3, 20.2, 14.5.

MS (EI, 70 eV) m/z (%): 301 (16), 256 (6), 178 (100), 150 (15), 105 (4), 43 (9).

HRMS for $\text{C}_{19}\text{H}_{27}\text{NO}_2$: calcd. 301.2042, found 301.2032.

IR (film) (cm^{-1}): 3389, 2916, 1684, 1601, 1529, 1279, 1172, 770.

12. Synthesis of 3-(4-methoxy-phenylamino)-propionic acid ethyl ester (**3l**)

Bis[2-(ethoxycarbonyl)ethyl]zinc synthesized from (1-ethoxy-cyclopropoxy)-trimethylsilane (1.93 mL, 9.6 mmol) and anhydrous zinc chloride (545 mg, 4.0 mmol), was stirred with 4-methoxy phenylazo tosylate (290 mg, 1.0 mmol) in 3 mL of dry THF at 0°C for 45 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (2.5 g) for 2 h. Standard workup and purification by flash chromatography (eluent: n-pentane/diethyl ether 75:25 v/v) yielded 100 mg (45% yield) of **3l** as yellow viscous liquid.

^1H NMR (300 MHz, CDCl_3) δ (ppm): 6.76 (d, $J = 8.8$ Hz, 2H), 6.57 (d, $J = 8.8$ Hz, 2H), 4.13 (q, 2H), 3.73 (s, 3H), 3.38 (t, $J = 6.3$ Hz, 2H), 2.58 (t, $J = 6.3$ Hz, 2H), 1.25 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 172.4, 152.4, 141.8, 114.9, 114.6, 60.5, 55.7, 40.5, 33.9, 14.2.

MS (EI, 70 eV) m/z (%): 223 (38), 208 (3), 136 (100), 120 (13), 108 (3).

HRMS for $\text{C}_{12}\text{H}_{17}\text{NO}_3$: calcd. 223.1208, found 223.1213.

IR (film) (cm^{-1}): 3390, 2930, 1731, 1514, 1375, 1236, 1035, 821.

13. Synthesis of N'-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-N'-(2-methyl-2-phenylpropyl)-benzenesulfonohydrazide (3m)

Neophylzinc bromide prepared in situ from the reaction of neophyllthium (0.9 mL, 1.25 mmol, 1.34 M in ether) and anhydrous zinc bromide (0.83 mL, 1.25 mmol, 1.5 M in THF), was stirred with 3,5-bis (trifluoromethane)phenylazo tosylate (396 mg, 1.0 mmol) in 3 mL of dry THF at -20 °C for 40 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (2.5 g) for 3.5 h. Standard workup and purification by flash chromatography (eluent: n-pentane/diethyl ether 95:5 v/v) yielded 217 mg (41% isolated yield) of **3m** as yellow viscous liquid.

¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.48 (d, *J*= 8.0 Hz, 2H), 7.44-7.38 (m, 2H), 7.34-7.29 (m, 3H), 7.10 (d, *J*= 8.0 Hz, 2H), 7.06 (s, 1H), 6.97 (s, 2H), 5.33 (s, 1H), 3.99 (s, 2H), 2.31 (s, 3H), 1.30 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm): 149.2, 145.9, 144.8, 135.5, 132.1, 131.7, 129.6, 129.3, 127.9, 127.3, 125.9, 125.0, 112.8, 112.6, 111.9, 63.1, 40.9, 21.4.

MS (EI, 70 eV) *m/z* (%): 530 (20), 411 (9), 375 (50), 257 (82), 213 (17), 133 (46), 91 (100).

HRMS for C₂₅H₂₄F₆N₂O₂S: calcd. 530.1463, found 530.1484.

IR (film) (cm⁻¹): 3278, 2969, 1616, 1476, 1338, 1277, 1163, 1132, 869.

14. Synthesis of 4-[2-(2-methoxy-phenyl)-cyclopentylamino]-benzoic acid ethyl ester (3n)

[2-(2-methoxyphenyl)-1-cyclopentyl]-isopropylzinc was prepared accordingly: 1-(2-methoxyphenyl)-cyclopentene (523 mg, 3.0 mmol) was stirred with (-)IPcBH₂ (2.5 mL, 3.0 mmol, 1.2 M in THF) at -40 °C for 48 h, followed by the addition of diethyl borane dimethyl sulfide complex (2.5 mL, 18.0 mmol, 7.3 M) and further stirred at 25 °C for 16 h. Then diisopropylzinc (1.8 mL, 9.0 mmol, 5.0 M in THF) was added to the reaction mixture and allowed to stir for 5 h at 25 °C for the complete formation of organozinc compound. 4-Phenylazo tosylate ethyl ester (332 mg, 1.0 mmol) was added and stirred in 3 mL of dry THF at -20 °C for 30 min to form the corresponding zinc hydrazide. The addition product was refluxed with Raney-Nickel (2.5 g) for 12 h. Standard workup and purification by flash chromatography (eluent: n-pentane/diethyl ether 88:12 v/v) yielded 136 mg (40% yield) of **3n** as colorless viscous liquid.

HPLC: column Chiralcel OD (0.46 cm x 25 cm), heptane: ⁱPrOH = 90:10, 0.5 ml/min, *t_R* (major) = 20.95 min, *t_R* (minor) = 17.07 min; 85% ee. Diastereoselectivity >98%.

¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.76 (d, *J*= 8.8 Hz, 2H), 7.22-7.14 (m, 2H), 6.93-6.84 (m, 2H), 6.42 (d, *J*= 8.8 Hz, 2H), 4.64 (br s, 1H), 4.27 (q, 2H), 3.85 (s, 3H), 3.75 (m, 1H), 3.37 (m, 1H), 2.33 (m, 1H), 2.05 (m, 1H), 1.92-1.78 (m, 3H), 1.58 (m, 1H), 1.33 (t, *J*= 7.1 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm): 166.9, 157.4, 151.9, 131.3, 130.9, 127.5, 126.9, 120.9, 117.9, 111.7, 110.6, 60.9, 60.0, 55.4, 45.7, 33.1, 30.8, 23.2, 14.4.

MS (EI, 70 eV) m/z (%): 339 (65), 308 (34), 204 (100), 178 (75), 130 (17), 91 (13).

HRMS for C₂₁H₂₅NO₃: calcd. 339.1834, found 339.1813.

IR (film) (cm⁻¹): 3370, 2956, 2872, 1698, 1605, 1275, 1105, 771.

[α]_D²⁰ = +6.4 (c = 0.25, acetone).

References:

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3a

26 May 2006

Acquisition Time (sec)	9.0440	Comment	Ak Knochel	Date	16/06/2004 13:09:00	Frequency (MHz)	300.13
Nucleus	¹ H	Original Points Count	32768	Points Count	32768	Sweep Width (Hz)	3623.19
						Temperature (grad C)	0.000

3a

26 May 2006

Acquisition Time (sec)	3.4079	Comment	Ak Knochel	Date	16/06/2004 14:09:20	Frequency (MHz)	75.47
Nucleus	¹³ C	Original Points Count	65536	Points Count	65536	Sweep Width (Hz)	19230.77
						Temperature (grad C)	0.000

No.	Annotation	(ppm)
1	Chloroform-d	77.00

3b

26 May 2006

Acquisition Time (sec)	9.0440	Comment	Ak Knochel	Date	13/08/2004 19:55:28	Frequency (MHz)	300.13
Nucleus	¹ H	Original Points Count	32768	Points Count	32768	Sweep Width (Hz)	3623.19
						Temperature (grad C)	0.000

3b

26 May 2006

Acquisition Time (sec)	3.4079	Comment	Ak Knochel	Date	13/08/2004 20:55:38	Frequency (MHz)	75.47
Nucleus	¹³ C	Original Points Count	65536	Points Count	65536	Sweep Width (Hz)	19230.77
						Temperature (grad C)	0.000

No.	Annotation	(ppm)
1	Chloroform-d	77.00

3c

26 May 2006

Acquisition Time (sec)	9.0440	Comment	Ak Knochel	Date	16/08/2004 14:40:26	Frequency (MHz)	300.13
Nucleus	¹ H	Original Points Count	32768	Points Count	32768	Sweep Width (Hz)	3623.19
						Temperature (grad C)	0.000

3c

26 May 2006

Acquisition Time (sec)	3.4079	Comment	Ak Knochel	Date	16/08/2004 15:25:28	Frequency (MHz)	75.47
Nucleus	¹³ C	Original Points Count	65536	Points Count	65536	Sweep Width (Hz)	19230.77
						Temperature (grad C)	0.000

No.	Annotation	(ppm)
1	Chloroform-d	77.00

3d

3e

Acquisition Time (sec)	2.2610	Comment	Imported from UXNMR.		Date	06/02/2006 20:24:14		Frequency (MHz)	300.13
Nucleus	1H	Number of Transients	64	Original Points Count	8192	Points Count	8192	Solvent	CDCI3
Temperature (grad C)	17.000							Sweep Width (Hz)	3623.19

Acquisition Time (sec)	1.7039	Comment	Imported from UXNMR.		Date	06/02/2006 22:24:18	
Frequency (MHz)	75.48	Nucleus	13C	Number of Transients	2048	Original Points Count	32768
Solvent	CDCl3	Sweep Width (Hz)	19230.77	Temperature (grad C)	27.000	Points Count	32768

3f

Acquisition Time (sec)	2.2610	Comment	Imported from UxNMR.	Date	03/06/2005 09:02:20	Frequency (MHz)	300.13
Nucleus	¹ H	Number of Transients	64	Original Points Count	8192	Points Count	8192
Temperature (grad C)	17.000	Solvent	CDCl ₃	Sweep Width (Hz)			3623.19

Acquisition Time (sec)	1.7039	Comment	Imported from UxNMR.	Date	03/06/2005 10:45:32	Frequency (MHz)	75.48
Nucleus	¹³ C	Number of Transients	2048	Original Points Count	32768	Points Count	32768
Solvent	CDCl ₃	Sweep Width (Hz)	19230.77	Temperature (grad C)	27.000

3g

Acquisition Time (sec)	2.2610	Comment	Imported from UXNMR.	Date	13/06/2005 18:46:06	Frequency (MHz)	300.13
Nucleus	¹ H	Number of Transients	64	Original Points Count	8192	Points Count	8192
Temperature (grad C)	17.000	Solvent	CDCl ₃	Sweep Width (Hz)	3623.19

Acquisition Time (sec)	1.7039	Comment	Imported from UXNMR.	Date	13/06/2005 19:46:30
Frequency (MHz)	75.48	Nucleus	¹³ C	Number of Transients	1024
Solvent	CDCl ₃	Sweep Width (Hz)	19230.77	Original Points Count	32768
		Temperature (grad C)	27.000	Points Count	32768

3h

Acquisition Time (sec)	2.2610	Comment	Imported from UXNMR.			Date	22/05/2005 14:15:28		Frequency (MHz)	300.13	
Nucleus	1H	Number of Transients	64	Original Points Count	8192	Points Count	8192	Solvent	CDCI3	Sweep Width (Hz)	3623.19
Temperature (grad C)	17.000

Acquisition Time (sec)	1.7039	Comment	Imported from UXNMR.		Date	22/05/2005 16:15:24	
Frequency (MHz)	75.48	Nucleus	13C	Number of Transients	2048	Original Points Count	32768
Solvent	CDCl3	Sweep Width (Hz)	19230.77	Temperature (grad C)	27.000	Points Count	32768

3i

Acquisition Time (sec)	2.2610	Comment	Imported from UXNMR.		Date	22/06/2005 00:01:20		Frequency (MHz)	300.13
Nucleus	1H	Number of Transients	64	Original Points Count	8192	Points Count	8192	Solvent	CDCl3
Temperature (grad C)	17.000							Sweep Width (Hz)	3623.19

Acquisition Time (sec)	1.7039	Comment	Imported from UXNMR.		Date	22/06/2005 02:01:48	
Frequency (MHz)	75.48	Nucleus	13C	Number of Transients	2048	Original Points Count	32768
Solvent	CDCl3	Sweep Width (Hz)	19230.77	Temperature (grad C)	27.000	Points Count	32768

3j

Acquisition Time (sec)	2.2610	Comment	Imported from UXMNR.	Date	09/06/2005 13:01:30	Frequency (MHz)	300.13
Nucleus	1H	Number of Transients	64	Original Points Count	8192	Points Count	8192
Temperature (grad C)	17.000	Solvent	CDCl3	Sweep Width (Hz)	3623.19

Acquisition Time (sec)	1.7039	Comment	Imported from UXMNR.	Date	09/06/2005 14:31:28	Frequency (MHz)	75.48
Nucleus	13C	Number of Transients	1418	Original Points Count	32768	Points Count	32768
Solvent	CDCl3	Sweep Width (Hz)	19230.77	Temperature (grad C)	27.000

3k

Acquisition Time (sec)	2.2610	Comment	Imported from UXNMR.		Date	09/06/2005 14:46:12		Frequency (MHz)	300.13
Nucleus	1H	Number of Transients	64	Original Points Count	8192	Points Count	8192	Solvent	CDCI3
Temperature (grad C)	17.000							Sweep Width (Hz)	3623.19

Acquisition Time (sec)	1.7039	Comment	Imported from UXNMR.		Date	09/06/2005 15:46:22			
Frequency (MHz)	75.48	Nucleus	13C	Number of Transients	1024	Original Points Count	32768	Points Count	32768
Solvent	CDCl3	Sweep Width (Hz)	19230.77	Temperature (grad C)	27.000

3l

Acquisition Time (sec)	2.2610	Comment	Imported from UxNMR	Date	08/08/2005 10:05:34	Frequency (MHz)	300.13
Nucleus	¹ H	Number of Transients	64	Original Points Count	8192	Points Count	8192
Temperature (grad C)	17.000			Solvent	CDCl ₃	Sweep Width (Hz)	3623.19

Acquisition Time (sec)	1.7039	Comment	Imported from UxNMR	Date	08/08/2005 09:50:48
Frequency (MHz)	75.48	Nucleus	¹³ C	Number of Transients	1024
Solvent	CDCl ₃	Sweep Width (Hz)	19230.77	Original Points Count	32768
		Temperature (grad C)	27.000	Points Count	32768

21

3m

Acquisition Time (sec)	2.2610	Comment	Imported from UXNMR.	Date	08/06/2005 02:31:08	Frequency (MHz)	300.13
Nucleus	¹ H	Number of Transients	64	Original Points Count	8192	Points Count	8192
Temperature (grad C)	17.000	Solvent	CDCl ₃	Sweep Width (Hz)	3623.19

Acquisition Time (sec)	1.7039	Comment	Imported from UXNMR.	Date	08/06/2005 04:30:56
Frequency (MHz)	75.48	Nucleus	¹³ C	Number of Transients	2048
Solvent	CDCl ₃	Sweep Width (Hz)	19230.77	Original Points Count	32768
Temperature (grad C)	27.000	Points Count	32768

3n

Acquisition Time (sec)	2.2610	Comment	Imported from Uxnmr		Date	07/07/2005 05:31:56		Frequency (MHz)	300.13
Nucleus	¹ H	Number of Transients	64	Original Points Count	8192	Points Count	8192	Solvent	CDCl ₃
Temperature (grad C)	17.000							Sweep Width (Hz)	3623.19

Acquisition Time (sec)	1.7039	Comment	Imported from Uxnmr		Date	07/07/2005 07:32:12	
Frequency (MHz)	75.48	Nucleus	¹³ C	Number of Transients	2048	Original Points Count	32768
Solvent	CDCl ₃	Sweep Width (Hz)	19230.77	Temperature (grad C)	27.000	Points Count	32768