

Efficient Pd-Catalyzed Amination of Heteroaryl Halides

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Supporting Information

General Considerations: Tris(dibenzylideneacetone) dipalladium was purchased from Strem Chemical Company. Sodium *tert*-butoxide was purchased from Aldrich and stored in a glovebox, portions were removed and stored in a dessicator for up to 2 weeks. Lithium bis (trimethylsilylamide) solution in THF was purchased from Aldrich. K_3PO_4 (anhydrous) was purchased from Riedel-de Haen and was stored on the bench. Ligands **1**, **2** and **4** were purchased from Strem Chemical Company. Unless otherwise stated all reagents were commercially available and used without further purification. Flash column chromatography was performed with EM science silica gel (230-400 mesh). Melting points were recorded on a Mel-Temp II, Laboratory Devices, Inc. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. IR spectra were recorded on an ASI ReactIR™ 1000 and were obtained by placing the samples directly on the DiComp probe. 1H and ^{13}C NMR were obtained on a Bruker Avance 400 MHz instrument with chemical shifts reported relative to solvent (7.26 ppm for residual $CHCl_3$) or TMS as an internal standard.

General procedure 1. For the Pd-Catalyzed Amination of Pyrimidines, Thiophenes, Benzoxazoles and Benzothiazoles.

An oven dried schlenk tube containing a magnetic stirrer bar was evacuated and backfilled with argon. The tube was then charged with Pd_2dba_3 , the appropriate ligand, base, aryl halide and amine in cases where these reagents were solids. The tube was evacuated and argon backfilled once and capped with a septa. The aryl halide and amine were added using a syringe in cases where these reagents were liquids followed by toluene. The tube was sealed under a positive pressure of argon with a teflon screw cap and placed into a pre-heated oil bath at the indicated temperature for the appropriate period of time. The tube was removed from the oil bath and allowed to cool to room temperature. Dodecane was added as an internal standard and the reaction mixture was analyzed by gas chromatography or thin layer chromatography. The contents of the tube were filtered through a pad of celite, washing with ethyl acetate until all of the product had eluted, as judged by thin layer chromatography. The organics were evaporated and purified by flash column chromatography to provide the products.

General procedure 2. For the Pd-Catalyzed Amination of Indoles

An oven dried schlenk tube containing a magnetic stirrer bar was evacuated and backfilled with argon. The tube was then charged with Pd_2dba_3 , the appropriate ligand and aryl halide. The tube was evacuated, argon backfilled three times and capped with a septa. The amine was added using a syringe followed by a 1 M solution of LiHMDS in THF. The tube was sealed under a positive pressure of argon with a teflon screw cap and

placed into a pre-heated oil bath at 65 °C for the appropriate period of time. The tube was removed from the oil bath and allowed to cool to room temperature. To the tube was added 1 M HCl (2 mL), the contents of the tube were stirred for 5 minutes and then poured into a separatory funnel containing a saturated aqueous sodium bicarbonate solution (20 mL). The organics were extracted with ethyl acetate (3x20 mL), washed with brine (40 mL), dried over magnesium sulfate and filtered. Dodecane was added as an internal standard and the reaction mixture was analyzed by gas chromatography or thin layer chromatography. The organics were evaporated under reduced pressure and the residue was purified by flash column chromatography.

2-(1-Phenyl-ethyl)-thiophene (Table 1, Entry 1). Following general procedure 1, a mixture of 2-chlorothiophene (0.118 g, 0.092 mL, 1.00 mmol), *N*-methylaniline (0.128 g, 0.130 mL, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **2** (16.4 mg, 0.04 mmol, 4 mol%), Pd(OAc)₂ (4.4 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 85 °C for 19 h. The crude reaction mixture was purified by flash column chromatography using 1:20 ethyl acetate:hexane, to yield the title compound as a yellow oil (0.155 g, 82%). ¹H NMR (400 MHz CDCl₃): δ 7.31-7.27 (m, 2H), 7.00-6.98 (m, 3H), 6.94-6.90 (m, 2H), 6.92 (dd, *J* = 3.6 Hz, 1.3 Hz, 1H), 3.37 (s, 3H). ¹³C NMR (100 MHz CDCl₃): δ 153.7, 149.4, 129.1, 125.9, 120.0, 119.7, 118.9, 116.4, 42.1. IR (thin film cm⁻¹) 3105, 3091, 2944, 2879, 2811, 1598, 1542, 1495, 1474, 1441, 1420, 1318, 1297, 1245, 1200, 1111, 1059, 1017. Anal. Calcd for C₁₁H₁₁NS: C, 69.80. H, 5.86. Found C, 69.65. H, 5.73.

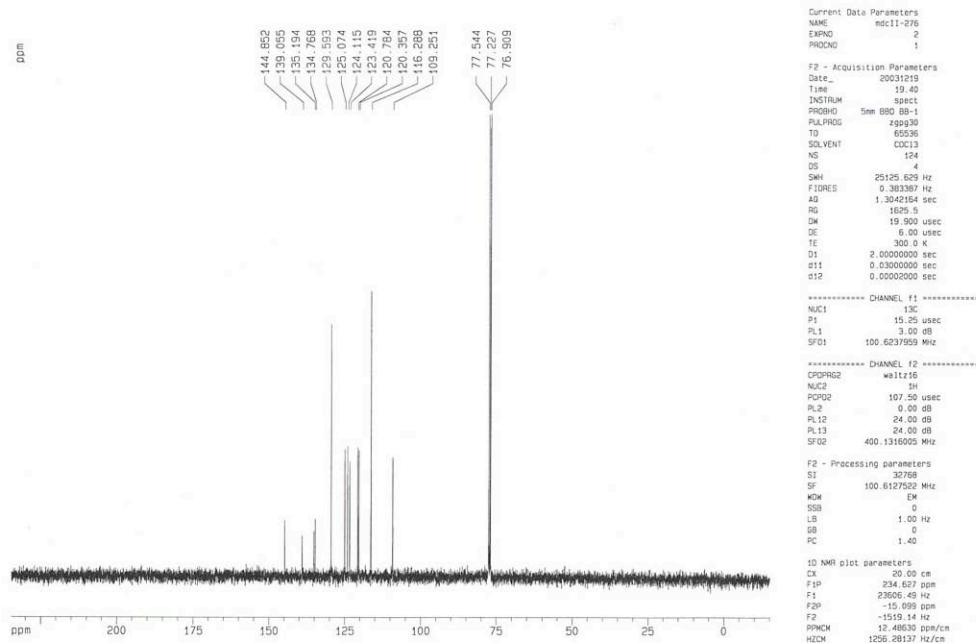
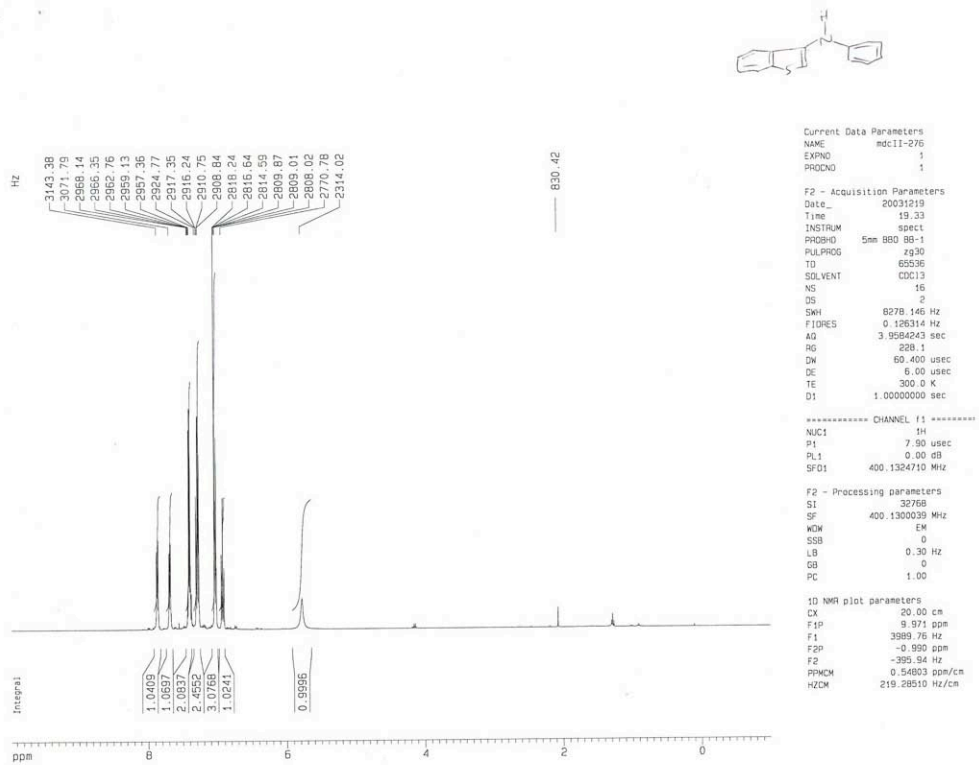
Methyl-phenyl-thiophen-3-yl-amine (Table 1, Entry 2).¹ Following general procedure 1, a mixture of 3-chlorothiophene (0.118 g, 0.092 mL, 1.00 mmol), *N*-methylaniline (0.128 g, 0.130 mL, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **3** (9.3 mg, 0.02 mmol, 2 mol%), Pd₂dba₃ (4.5 mg, 0.005 mmol, 0.5 mol%) and toluene (2 mL) was stirred at 100 °C for 17 h. The crude reaction mixture was purified by flash column chromatography using 1:20 ethyl acetate:hexane, to yield the title compound as a light brown oil (0.187 g, 99%). ¹H NMR (400 MHz CDCl₃): δ 7.31-7.24 (m, 3H), 7.06-7.04 (m, 2H), 6.97-6.94 (m, 1H), 6.92 (dd, *J* = 5.2 Hz, 1.4 Hz, 1H), 6.61 (dd, *J* = 3.1 Hz, 1.4 Hz, 1H), 3.34 (s, 3H). ¹³C NMR (100 MHz CDCl₃): δ 149.4, 148.5, 129.2, 125.1, 123.4, 120.9, 118.9, 107.9, 41.2. IR (thin film cm⁻¹) 3107, 3089, 3037, 3027, 2933, 2879, 1598, 1536, 1493, 1387, 1318, 1189, 1127, 1088, 1063, 1028, 941, 874, 746. Anal. Calcd for C₁₁H₁₁NS: C, 69.80. H, 5.86.

4-Thiophen-3-yl-morpholine (Table 1, Entry 3). Following general procedure 1, a mixture of 3-chlorothiophene (0.118 g, 0.092 mL, 1.00 mmol), morpholine (0.104 g, 0.105 mL, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **2** (16.4 mg, 0.04 mmol, 4 mol%), Pd₂dba₃ (9.1 mg, 0.01 mmol, 1 mol%) and toluene (2 mL) was stirred at 100 °C for 24 h. The crude reaction mixture was purified by flash column chromatography using 1:4 ethyl acetate:hexane, to yield the title compound as a white solid (0.134 g, 79%), mp 86-88 °C. ¹H NMR (400 MHz CDCl₃): δ 7.28 (dd, *J* = 5.2 Hz, 3.1 Hz, 1H), 6.88 (dd, *J* = 5.2 Hz, 1.5 Hz, 1H), 6.22 (dd, *J* = 3.0 Hz, 1.5 Hz, 1H), 3.87 (t, *J* = 4.8 Hz, 4H), 3.11 (t, *J* = 4.8 Hz, 4H). ¹³C NMR (100 MHz CDCl₃): δ 152.6, 125.8, 119.8, 100.6, 66.8, 50.9. IR (thin film cm⁻¹) 2964, 2856, 2833, 1544, 1457, 1268, 1233,

1189, 1162, 1111, 1081, 1065, 962, 924, 872, 771. Anal. Calcd for $C_8H_{11}NOS$: C, 56.77. H, 6.55. Found C, 56.89. H, 6.55.

Phenyl-thiophen-3-yl-amine (Table 1, Entry 4).¹ Following general procedure 1, a mixture of 3-bromothiophene (0.163 g, 0.093 mL, 1.00 mmol), aniline (0.111 g, 0.109 mL, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **3** (37.3 mg, 0.08 mmol, 8 mol%), Pd_2dba_3 (18.3 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 85 °C for 14 h. The crude reaction mixture was purified by flash column chromatography using 1:9 ethyl acetate:hexane, to yield the title compound as a brown solid (0.138 g, 79%), mp 43-44 °C. 1H NMR (400 MHz $CDCl_3$): δ 7.30-7.25 (m, 3H), 7.01 (m, 1H), 6.99 (m, 1H), 6.94 (dd, J = 5.1 Hz, 1.4 Hz, 1H), 6.90 (m, 1H), 6.76 (dd, J = 3.0 Hz, 1.4 Hz, 1H), 5.73 (s, br, 1H). ^{13}C NMR (100 MHz $CDCl_3$): δ 144.7, 141.6, 129.5, 125.3, 123.0, 120.0, 115.7, 106.6. IR (thin film cm^{-1}) 3394, 1600, 1555, 1532, 1497, 1445, 1430, 1314, 1252, 1171, 744. Anal. Calcd for $C_{10}H_9NS$: C, 68.53. H, 5.18.

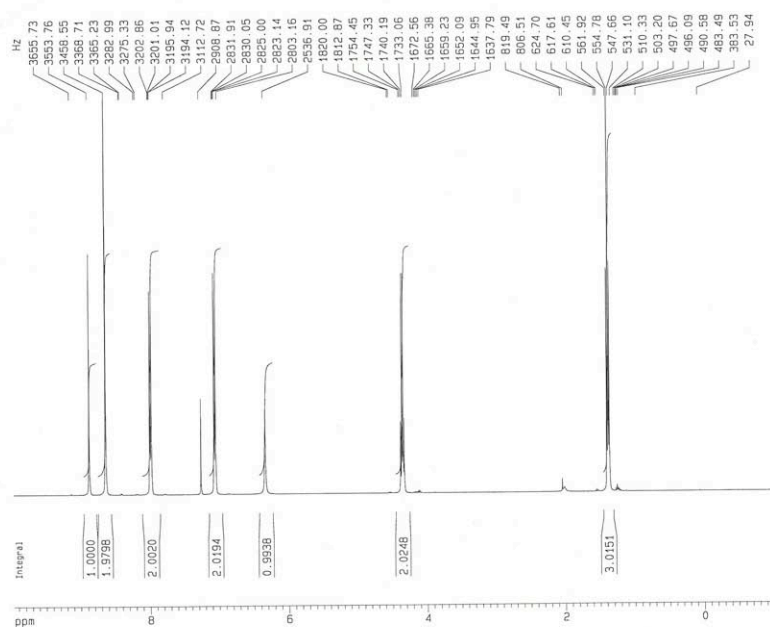
4-Benzo[*b*]thiophen-3-yl-phenyl-amine (Table 1, Entry 5). Following general procedure 1, a mixture of 3-bromothiophene (0.213 g, 0.130 mL, 1.00 mmol), aniline (0.111 g, 0.109 mL, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **1** (38.0 mg, 0.08 mmol, 8 mol%), Pd_2dba_3 (18.2 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 100 °C for 18 h. The crude reaction mixture was purified by flash column chromatography using 1:9 ethyl acetate:hexane to yield the title compound as a dark red solid (0.185 g, 82%), mp 79-80 °C. 1H NMR (400 MHz $CDCl_3$): δ 7.87-7.85 (m, 1H), 7.69-7.67 (m, 1H), 7.41-7.39 (m, 2H), 7.30-7.26 (m, 2H), 7.04-7.01 (m, 3H), 6.92 (t, J = 7.3 Hz, 1H), 5.78 (s, br, 1H). ^{13}C NMR (100 MHz $CDCl_3$): δ 144.8, 139.0, 135.9, 134.7, 129.5, 125.0, 124.1, 123.4, 120.7, 120.3, 116.2, 109.2. IR (thin film cm^{-1}) 3390, 1602, 1573, 1526, 1511, 1495, 1432, 1343, 1245, 750, 719. Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63. H, 4.92.



4-Benzo[*b*]thiophen-3-yl-morpholine (Table 1, Entry 6). Following general procedure 1, a mixture of 3-bromothiophene (0.213 g, 0.130 mmol), morpholine (0.104 g, 0.105 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **3** (37.3 mg, 0.08 mmol, 8 mol%), Pd₂dba₃ (18.3 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 80 °C for 16 h. The crude reaction mixture was purified by flash column chromatography using 1:9 ethyl acetate:hexane, to yield the title compound as a pale yellow solid (0.155 g, 71%), mp 59-60 °C. ¹H NMR (400 MHz CDCl₃): δ 7.84-7.79 (m, 1H), 7.78-7.74 (m, 1H), 7.40-7.33 (m, 2H), 6.65 (s, 1H), 3.95 (t, *J* = 4.6 Hz, 4H), 3.15 (t, *J* = 4.6 Hz, 4H). ¹³C NMR (100 MHz CDCl₃): δ 146.9, 139.5, 134.5, 124.8, 123.8, 123.5, 121.9, 107.4, 67.3, 53.0. IR (thin film cm⁻¹) 2966, 2861, 2825, 1519, 1449, 1432, 1368, 1356, 1281, 1256, 1192, 1111, 1065, 1017, 899, 860. Anal. Calcd for C₁₂H₁₃NOS: C, 65.72. H, 5.97. Found C, 66.06. H, 6.02.

Methyl-phenyl-pyrimidin-5-yl-amine (Table 2, Entry 1). Following general procedure 1, a mixture of 5-bromopyrimidine (0.158 g, 1.00 mmol), *N*-methyl aniline (0.128 g, 0.130 mmol, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **1** (38.0 mg, 0.08 mmol, 8 mol%), Pd₂dba₃ (18.3 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 100 °C for 15 h. The crude reaction mixture was purified by flash column chromatography using ethyl acetate to yield the title compound as a pale brown solid (0.175 g, 95%), mp 74-75 °C. ¹H NMR (400 MHz C₆D₆): δ 9.10 (s, 1H), 8.32 (s, 2H), 7.11 (t, *J* = 7.7 Hz, 2H), 6.97 (m, 1H), 6.81 (dd, *J* = 7.6 Hz, 0.9 Hz, 2H), 2.66 (s, 3H). ¹³C NMR (100 MHz C₆D₆): δ 150.5, 146.9, 144.6, 142.9, 130.2, 124.9, 124.0, 39.0. IR (thin film cm⁻¹) 1569, 1542, 1495, 1441, 1424, 1356, 1273, 1196, 1069, 866, 775, 702. Anal. Calcd for C₁₁H₁₁N₃: C, 71.33. H, 5.99. Found C, 70.94. 6.02.

4-(Pyrimidin-5-ylamino)-benzoic acid ethyl ester (Table 2, Entry 2). Following general procedure 1, a mixture of 5-bromopyrimidine (0.158 g, 1.00 mmol), ethyl-4-aminobenzoate (0.198 g, 1.20 mmol), K₃PO₄ (0.297 g, 1.40 mmol), **1** (38.0 mg, 0.08 mmol, 8 mol%), Pd₂dba₃ (18.3 mg, 0.02 mmol, 2 mol%), and toluene (2 mL) was stirred 100 °C for 19 h. The crude reaction mixture was purified by flash column chromatography using ethyl acetate to yield the title compound as a white solid 0.218 g, 90%), mp 161-162 °C. ¹H NMR (400 MHz CDCl₃): δ 8.88 (s, 1H), 8.64 (s, 2H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.34 (s, br, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz CDCl₃): δ 166.3, 152.5, 147.3, 145.6, 136.8, 131.8, 123.9, 115.9, 61.0, 14.5. IR (thin film cm⁻¹) 3242, 3054, 1715, 1607, 1576, 1563, 1420, 1328, 1291, 1279, 1179, 1115, 1106, 764, 721. Anal. Calcd for C₁₃H₁₃N₃O₂: C, 61.14. H, 5.86.



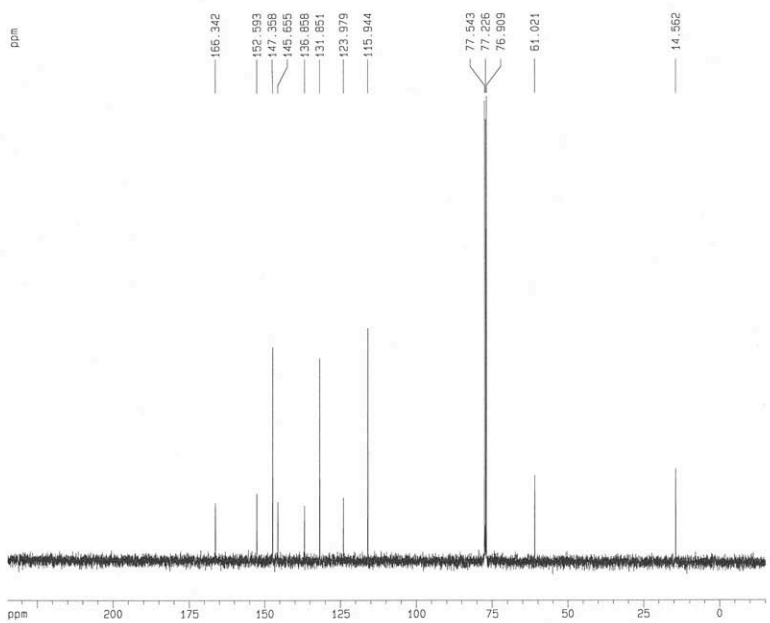
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3-(Pyrimidin-5-ylamino-benzonitrile (Table 2, Entry 3). Following general procedure 1, a mixture of 5-bromopyrimidine (0.158 g, 1.00 mmol), 4-aminobenzonitrile (0.141 g, 1.20 mmol), K_3PO_4 (0.297 g, 1.40 mmol), **1** (38.0 mg, 0.08 mmol, 8 mol%), Pd_2dba_3 (18.3 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 100 °C for 15 h. The crude reaction mixture was purified by flash column chromatography using ethyl acetate to yield the title compound as a white solid (0.121 g, 62%), mp 189-190 °C. 1H NMR (400 MHz d_6 -DMSO): δ 8.89 (s, 1H), 8.75 (s, 1H), 8.64 (s, 2H), 7.55-7.38 (m, 3H), 7.34-7.26 (m, 1H). ^{13}C NMR (100 MHz d_6 -DMSO): δ 151.7, 146.3, 143.6, 138.1, 131.6, 125.1, 122.2, 119.8, 119.6, 113.7. IR (thin film cm^{-1}) 3365, 1571, 1530, 1493, 1422, 1333, 1277, 1192, 849, 791, 717. Anal. Calcd for $C_{11}H_8N_4$: C, 67.34. H, 4.11. Found C, 67.06. H, 4.15.

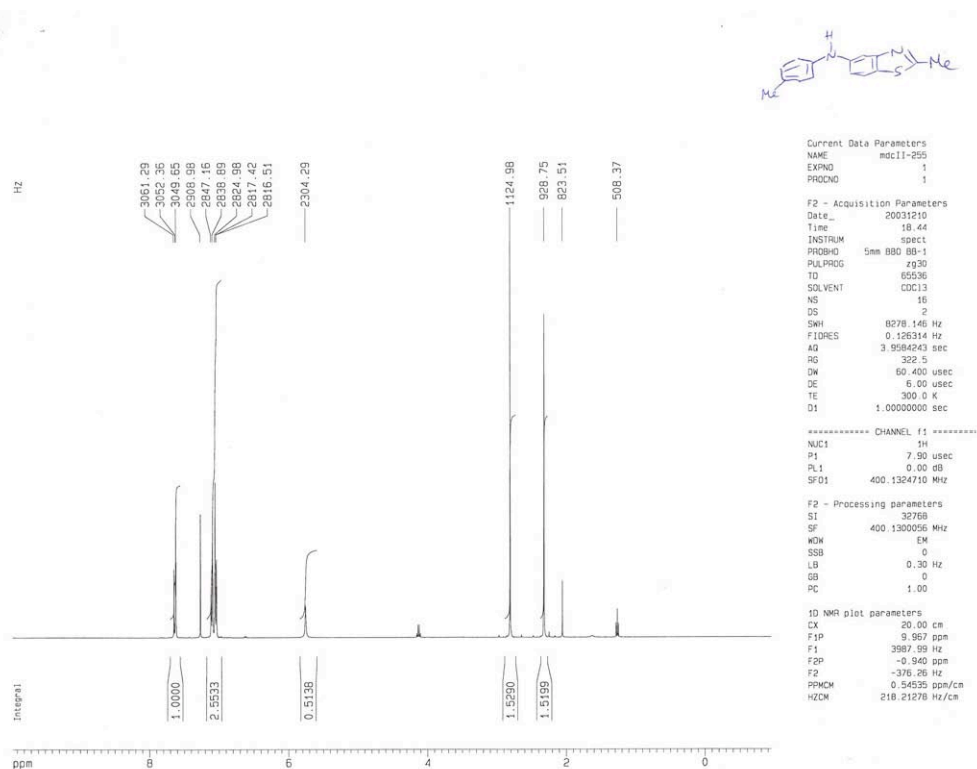
Pyrimidin-5-yl-(4-trifluoromethyl-phenyl)-amine (Table 2, Entry 4). Following general procedure 1, a mixture of 5-bromopyrimidine (0.158 g, 1.00 mmol), 4-aminobenzotrifluoride (0.193 g, 0.150 mL, 1.20 mmol), K_3PO_4 (0.297 g, 1.40 mmol), **1** (38.0 mg, 0.08 mmol, 8 mol%), Pd_2dba_3 (18.3 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 100 °C for 15 h. The crude reaction mixture was purified by flash column chromatography, ethyl acetate, to yield the title compound as a white solid (0.210 g, 88%), mp 157-158 °C. 1H NMR (400 MHz $CDCl_3$): δ 8.89 (s, 1H), 8.62 (s, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 6.00 (s, br, 1H). ^{13}C NMR (100 MHz $CDCl_3$): δ 152.5, 147.1, 144.4, 137.0, 127.35, 127.31, 127.2, 125.6, 124.4, 124.0, 122.9, 116.7, observed complexity due to ^{19}F splitting. IR (thin film cm^{-1}) 3244, 3095, 3051, 1605, 1567, 1538, 1420, 1329, 1318, 1189, 1140, 1075, 889, 849, 719. Anal. Calcd for $C_{11}H_8F_3N_3$: C, 55.23. H, 3.37. Found C, 55.11. H, 3.44.

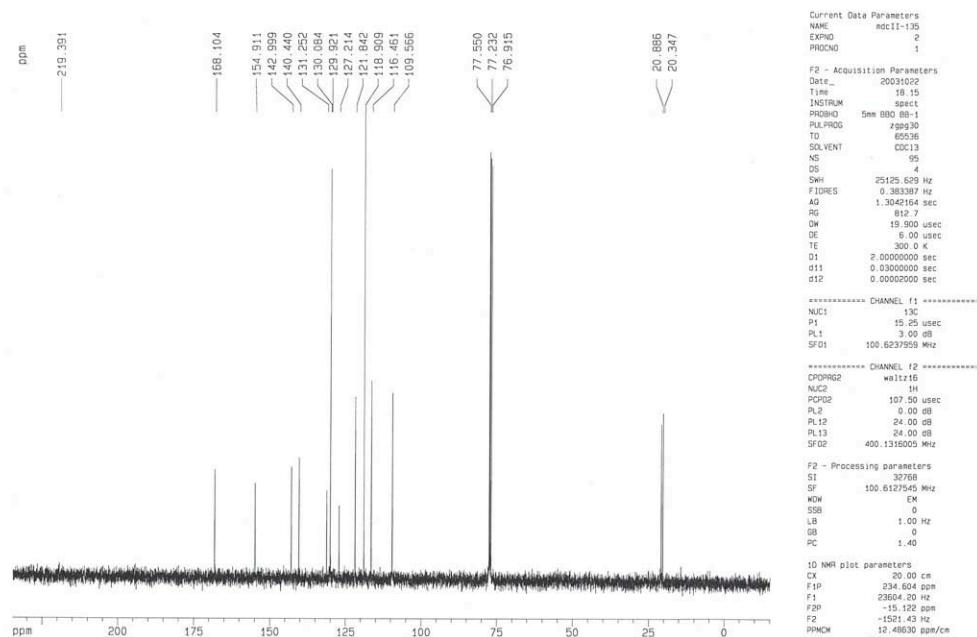
4-Pyrimidin-5-yl-morpholine (Table 2, Entry 5). Following general procedure 1, a mixture of 5-bromopyrimidine (0.158 g, 1.00 mmol), morpholine (0.104 g, 0.105 mL, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **2** (32.8 mg, 0.08 mmol, 8 mol%), Pd_2dba_3 (18.3 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 100 °C for 15 h. The crude reaction mixture was purified by flash column chromatography using 98:2 ethyl acetate:Et₃N to yield the title compound as a light brown solid (0.130 g, 75%), mp 38-39 °C. 1H NMR (400 MHz d_6 -DMSO): δ 8.61 (s, 1H), 8.49 (s, 2H), 3.75 (t, J = 4.8 Hz, 4H), 3.23 (t, J = 4.8 Hz, 4H). ^{13}C NMR (100 MHz d_6 -DMSO): δ 149.7, 144.9, 143.7, 66.5, 47.4. IR (thin film cm^{-1}) 2956, 2944, 2927, 2865, 2852, 1569, 1557, 1542, 1443, 1272, 1245, 1119, 924, 719. Anal. Calcd for $C_8H_{11}N_3O$: C, 58.17. H, 6.71. Found C, 58.28. H, 6.81.

5-Pyrrolidin-1-yl-pyrimidine (Table 2, Entry 6). Following general procedure 1, a mixture of 5-bromopyrimidine (0.158 g, 1.00 mmol), pyrrolidine (0.085 g, 0.100 mL, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.4 mmol), **1** (38.0 mg, 0.08 mmol, 8 mol%), Pd_2dba_3 (18.3 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 100 °C for 15 h. The crude reaction mixture was purified by flash column chromatography using ethyl acetate to yield the title compound as a pale yellow solid (0.070 g, 48%), mp 73-75 °C. 1H NMR (400 MHz $CDCl_3$): δ 8.54 (s, 1H), 8.04 (s, 2H), 3.31 (t, J = 6.5 Hz, 4H), 2.05 (m, 4H). ^{13}C NMR (100 MHz $CDCl_3$): δ 146.8, 141.3, 139.5, 47.0, 25.5. IR (thin film cm^{-1})

¹) 2850, 1569, 1437, 1337, 1198, 1156, 868, 727. Anal. Calcd for C₈H₁₁N₃: C, 64.40. H, 7.43. Found C, 64.73. H, 7.32.

(2-Methyl-benzothiazol-5-yl)-*p*-tolyl-amine (Table 3, Entry 1). Following general procedure 1, a mixture of 2-methyl-5-chlorobenzothiazole (0.183 g, 1.00 mmol), 4-methyl aniline (0.128 g, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **1** (38.0 mg, 0.08 mmol, 8 mol%), Pd₂dba₃ (18.3 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 90 °C for 18 h. The crude reaction mixture was purified by flash column chromatography using 1:1 ethyl acetate:hexane to yield the title compound as a pale brown solid (0.250 g, 98%), mp 157-158 °C. ¹H NMR (400 MHz CDCl₃): δ 7.65-7.62 (m, 2H), 7.11-7.03 (m, 5H), 5.75 (s, br, 1H), 2.81 (s, 3H), 2.32 (s, 3H). ¹³C NMR (100 MHz CDCl₃): δ 168.1, 154.9, 142.9, 140.4, 131.2, 130.0, 127.2, 121.8, 118.9, 116.4, 109.5, 20.8, 20.3. IR (thin film cm⁻¹) 3292, 3116, 1617, 1600, 1530, 1515, 1457, 1339, 1314, 1301, 1241, 1179, 1167, 814, 791. Anal. Calcd for C₁₅H₁₄N₂S: C, 70.83. H, 5.55.





2-Methyl-5-morpholin-4-yl-benzothiazole (Table 3, Entry 2). Following general procedure 1, a mixture of 2-methyl-5-chlorobenzothiazole (0.183 g, 1.00 mmol), morpholine (0.104 g, 0.105, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **1** (38.0 mg, 0.08 mmol, 8 mol%), Pd₂dba₃ (18.3 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 90 °C for 15 h. The crude reaction mixture was purified by flash column chromatography using 1:1 ethyl acetate:hexane to yield the title compound as a white solid (0.152 g, 65%), mp 95-96 °C. ¹H NMR (400 MHz CDCl₃): δ 7.66 (d, *J* = 8.8 Hz, 1H), 7.44 (d, *J* = 2.2 Hz, 1H), 7.03 (dd, *J* = 8.8 Hz, 2.3 Hz, 1H), 3.89 (t, *J* = 4.7 Hz, 4H), 3.19 (t, *J* = 4.7 Hz, 4H), 2.79 (s, 3H). ¹³C NMR (100 MHz CDCl₃): δ 168.0, 154.9, 150.7, 127.1, 121.6, 115.7, 108.6, 67.0, 50.2, 20.3. IR (thin film cm⁻¹) 2964, 2954, 2852, 1470, 1459, 1445, 1268, 1250, 1189, 1169, 1115, 1040, 957, 891, 847, 814, 796. Anal. Calcd for C₁₂H₁₄N₂OS: C, 61.51. H, 6.02. Found C, 61.49. H, 6.05.

2-Piperidin-1-yl-benzothiazole (Table 3, Entry 3). Following general procedure 1, a mixture of 2-chlorobenzothiazole (0.169 g, 0.130 mL, 1.00 mmol), piperidine (0.102 g, 0.118 mL, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **2** (8.2 mg, 0.02 mmol, 2 mol%), Pd₂dba₃ (4.5 mg, 0.005 mmol, 0.5 mol%) and toluene (2 mL) was stirred at 25 °C for 24 h. The crude reaction mixture was purified by flash column chromatography using 1:1 ethyl acetate:hexane to yield the title compound as a white solid (0.205 g, 94%), mp 93-94 °C. ¹H NMR (400 MHz CDCl₃): δ 7.59 (dd, *J* = 7.8 Hz, 0.8 Hz, 1H), 7.55-7.53 (m, 1H), 7.30-7.26 (m, 1H), 7.05 (m, 1H), 3.60 (m, 4H), 1.70 (s, 6H). ¹³C NMR (100 MHz CDCl₃): δ 169.1, 153.1, 130.8, 126.0, 121.2, 120.7, 118.9, 49.8,

25.5, 24.4. IR (thin film cm^{-1}) 2941, 2921, 2850, 1534, 1524, 1333, 1287, 1258, 1239, 1212, 1121, 1009, 901, 760. Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{S}$: C, 66.02. H, 6.46. Found C, 65.84. H, 6.45.

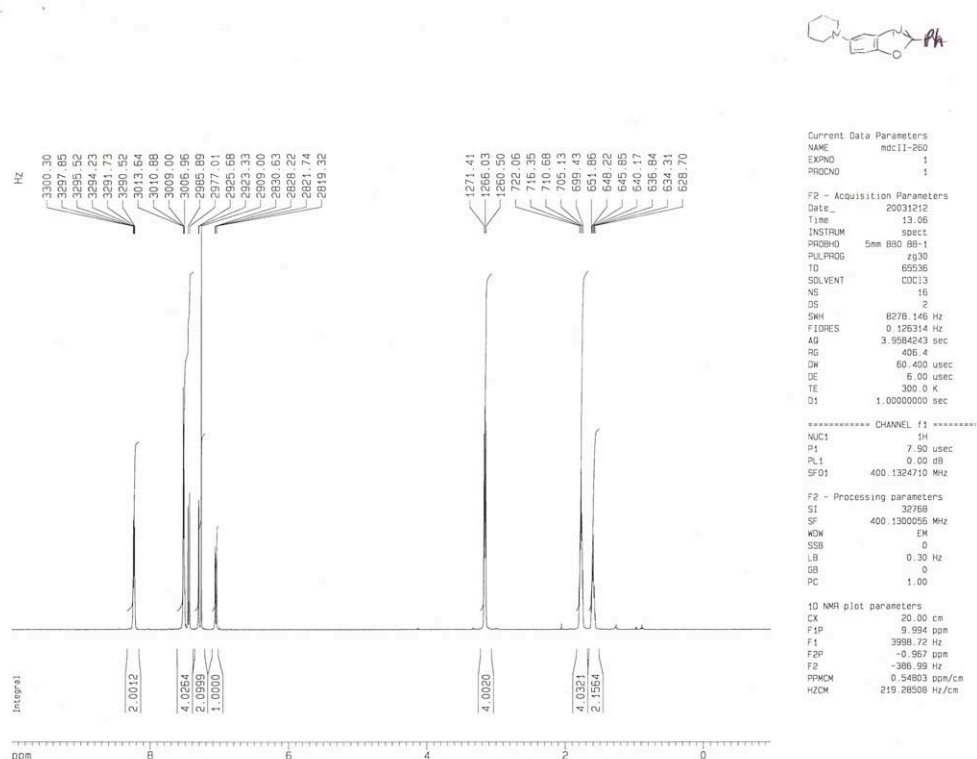
Benzothiazol-2-yl-dibutyl-amine (Table 3, Entry 4).² Following general procedure 1, a mixture of 2-chlorobenzothiazole (0.169 g, 0.130 mL, 1.00 mmol), di-*n*-butylamine (0.155 g, 0.202 mL, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **3** (37.3 mg, 0.08 mmol, 8 mol%), Pd_2dba_3 (18.2 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 80 °C for 16 h. The crude reaction mixture was purified by flash column chromatography using 1:20 ethyl acetate:hexane to yield the title compound as a yellow oil (0.242 g, 93%). ^1H NMR (400 MHz CDCl_3): δ 7.57 (dd, $J = 7.8$ Hz, 0.8 Hz, 1H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.29-7.25 (m, 1H), 7.05-7.01 (m, 1H), 3.51 (t, $J = 7.5$ Hz, 4H), 1.73 (m, 4H), 1.40 (sextet, $J = 14.9$ Hz, 7.4 Hz, 4H), 0.98 (t, $J = 7.3$ Hz, 6H). ^{13}C NMR (100 MHz CDCl_3): δ 168.0, 153.5, 130.8, 125.9, 120.7, 120.6, 118.6, 51.1, 29.8, 20.3, 14.1. IR (thin film cm^{-1}) 2958, 2931, 2871, 1598, 1563, 1536, 1455, 1443, 1372, 1316, 1279, 1210, 1123, 1111, 1067, 1017, 748. Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{S}$: C, 68.66. H, 8.45.

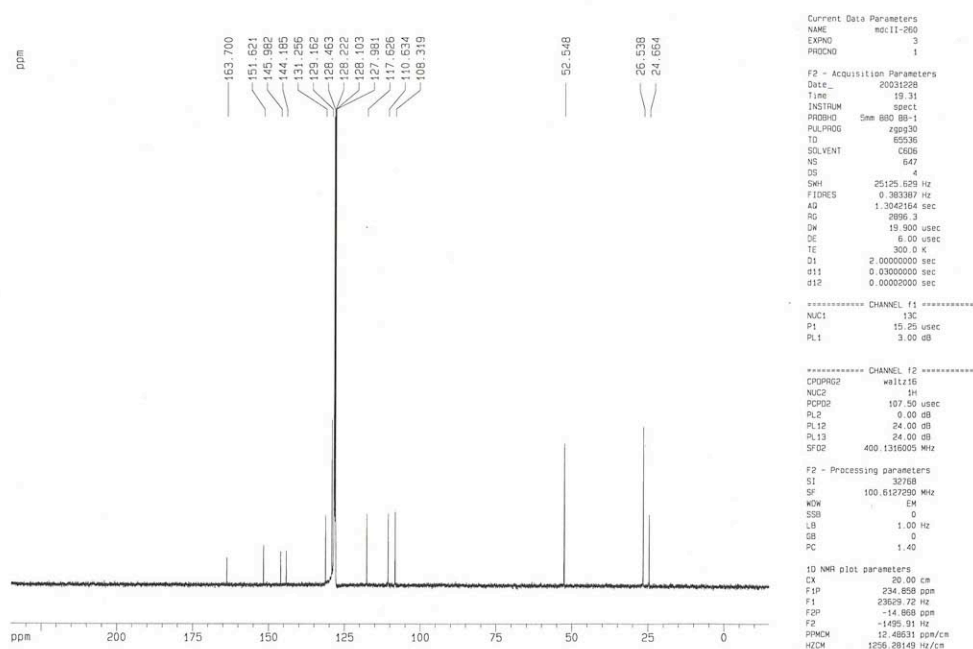
2-Indol-1-yl-benzothiazole (Table 3, Entry 5). Following general procedure 1, a mixture of 2-chlorobenzothiazole (0.169 g, 0.130 mL, 1.00 mmol), indole (0.140 g, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **1** (19.0 mg, 0.04 mmol, 4 mol%), Pd_2dba_3 (9.1 mg, 0.01 mmol, 1 mol%) and toluene (2 mL) was stirred at 70 °C for 15 h. The crude reaction mixture was purified by flash column chromatography using 1:9 ethyl acetate:hexane to yield the title compound as a white solid (0.190 g, 76%), mp 107-108 °C. ^1H NMR (400 MHz CDCl_3): δ 8.51 (d, $J = 8.3$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.69 (d, $J = 7.9$ Hz, 1H), 7.57-7.54 (m, 2H), 7.39-7.31 (m, 2H), 7.24-7.13 (m, 2H), 6.64 (d, $J = 3.2$ Hz, 1H). ^{13}C NMR (100 MHz CDCl_3): δ 159.0, 151.4, 135.6, 131.6, 130.5, 126.7, 126.6, 124.6, 124.4, 122.9, 122.1, 121.4, 121.3, 114.5, 108.3. IR (thin film cm^{-1}) 1528, 1472, 1449, 1439, 1351, 1333, 1206, 1140, 1013, 916. Anal. Calcd for $\text{C}_{15}\text{H}_{10}\text{N}_2\text{S}$: C, 71.97. H, 4.03. Found C, 71.66. H, 4.05.

Methyl-(2-methyl-benzooxazol-5-yl)phenyl-amine (Table 3, Entry 6). Following general procedure 1, a mixture of 2-methyl-5-chlorobenzoxazole (0.167 g, 1.00 mmol), *N*-methylaniline (0.128 g, 0.130 mL, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **1** (38.0 mg, 0.08 mmol, 8 mol%), Pd_2dba_3 (18.3 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 100 °C for 15 h. The crude reaction mixture was purified by flash column chromatography using 1:4 ethyl acetate:hexane to yield the title compound as a brown oily solid (0.181 g, 79%). ^1H NMR (400 MHz CDCl_3): δ 7.30 (d, $J = 2.1$ Hz, 1H), 7.28 (d, $J = 8.7$ Hz, 1H), 7.15-7.10 (m, 2H), 6.95 (dd, $J = 8.6$ Hz, 2.2 Hz, 1H), 6.79-6.74 (m, 3H), 3.23 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (100 MHz CDCl_3): δ 164.7, 149.7, 147.5, 146.1, 142.7, 129.2, 121.2, 119.7, 117.5, 114.3, 110.6, 41.0, 14.7. IR (thin film cm^{-1}) 3062, 3037, 3027, 2948, 2875, 2809, 1598, 1576, 1495, 1453, 1341, 1297, 1256, 1200, 1169, 1113, 1057, 943. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$: C, 75.61. H, 5.92. Found C, 75.80. H, 5.84.

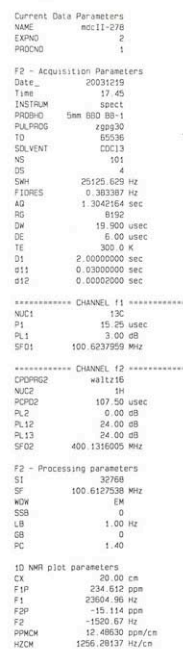
2-Phenyl-5-piperidin-1-yl-benzooxazole (Table 3, Entry 7). Following general procedure 1, a mixture of 2-phenyl-5-chlorobenzoxazole (0.229 g, 1.00 mmol), piperidine

(0.102 g, 0.118 mL, 1.20 mmol), sodium *tert*-butoxide (0.134 g, 1.40 mmol), **1** (38.0 mg, 0.08 mmol, 8 mol%), Pd₂dba₃ (18.3 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 70 °C for 15 h. The crude reaction mixture was purified by flash column chromatography using 1:9 ethyl acetate:hexane to yield the title compound as a white solid (0.260 g, 94%), mp 130-131 °C. ¹H NMR (400 MHz CDCl₃): δ 8.25-8.21 (m, 2H), 7.54-7.51 (m, 3H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.30 (d, *J* = 2.3 Hz, 1H), 7.06 (dd, *J* = 8.9 Hz, 2.4 Hz, 1H), 3.16 (t, *J* = 5.4 Hz, 4H), 1.80-1.74 (m, 4H), 1.62-1.57 (m, 2H). ¹³C NMR (100 MHz C₆D₆): δ 163.7, 151.6, 145.9, 144.1, 131.2, 129.1, 128.3, 128.1, 117.6, 110.6, 108.3, 52.5, 26.5, 24.6. IR (thin film cm⁻¹) 2931, 2912, 1551, 1478, 1449, 1439, 1219, 1204, 1177, 1119, 1057, 1025, 926. Anal. Calcd for C₁₈H₁₈N₂O: C, 77.67. H, 6.52.

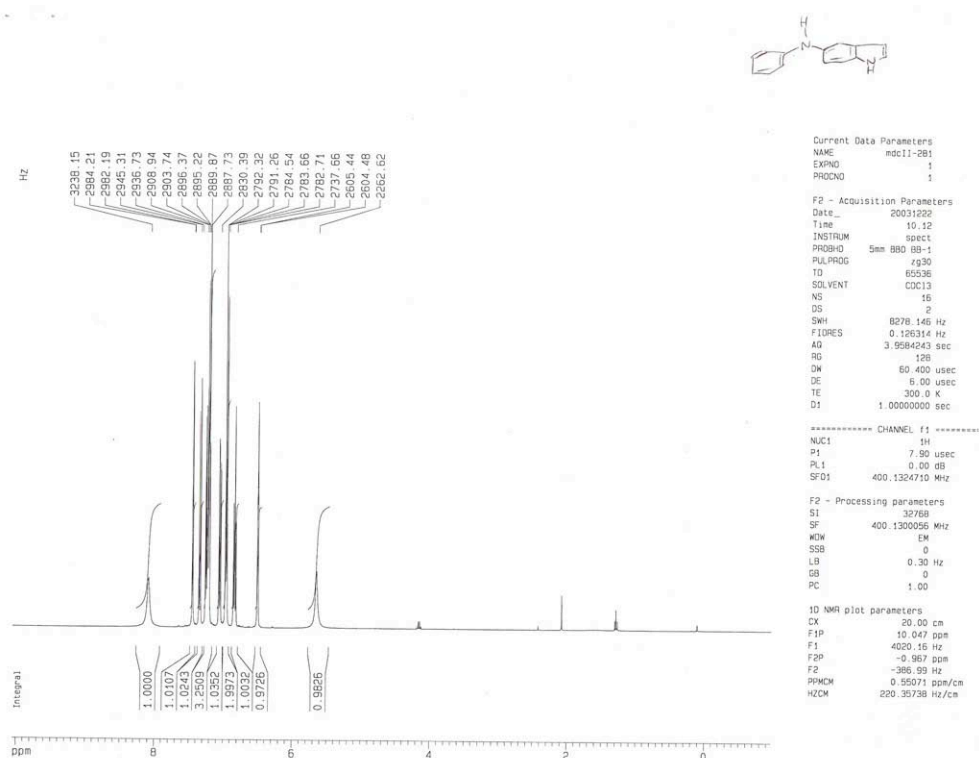


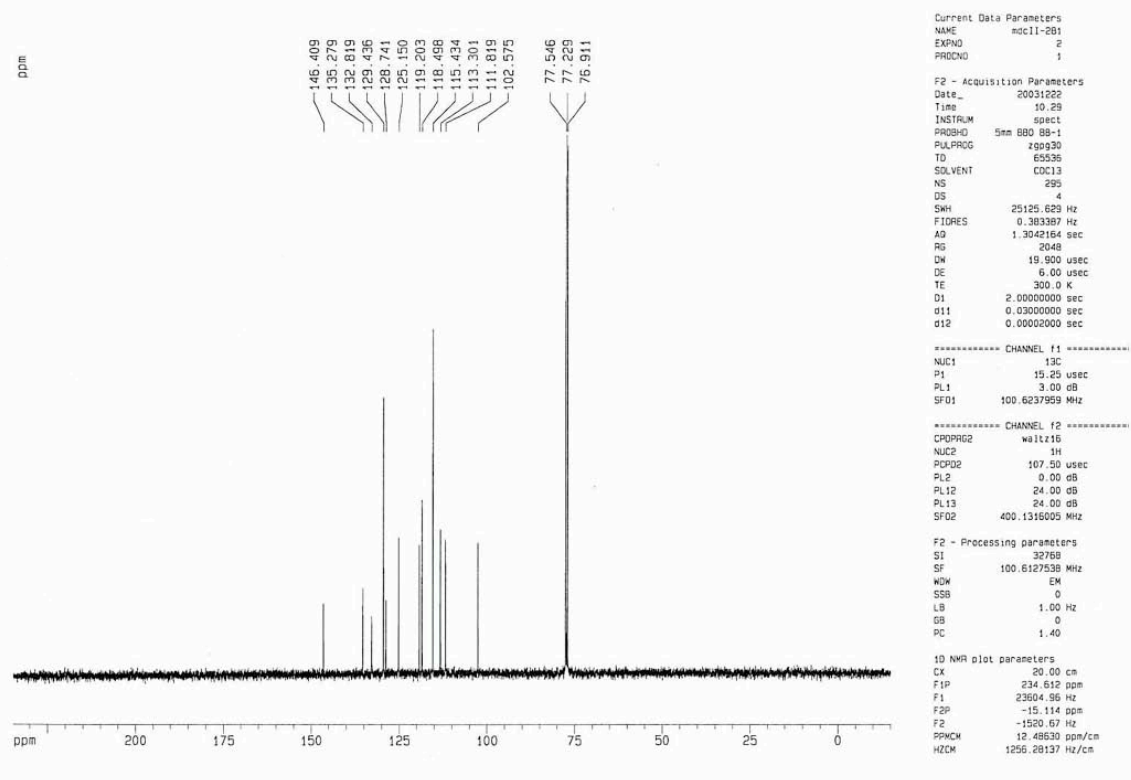


3-(2-Methyl-benzooxazol-5-ylamino)-benzonitrile (Table 3, Entry 8). Following general procedure 1, a mixture of 2-methyl-5-chlorobenzoxazole (0.167 g, 1.00 mmol), 3-aminobenzonitrile (0.141 g, 1.20 mmol), K_3PO_4 (0.297 g, 1.40 mmol), **1** (38.0 mg, 0.08 mmol, 8 mol%), Pd_2dba_3 (18.3 mg, 0.02 mmol, 2 mol%) and toluene (2 mL) was stirred at 100 °C for 15 h. The crude reaction mixture was purified by flash column chromatography using 1:1 ethyl acetate:hexane to yield the title compound as a white solid (0.147 g, 60%), mp 133-134 °C. 1H NMR (400 MHz $CDCl_3$): δ 7.43-7.40 (m, 2H), 7.27 (t, J = 7.8 Hz, 1H), 7.16-7.06 (m, 4H), 6.02 (s, br, 1H), 2.63 (s, 3H), ^{13}C NMR (100 MHz $CDCl_3$): δ 165.2, 147.8, 145.8, 142.8, 137.6, 130.3, 123.2, 119.7, 119.2, 119.1, 117.9, 113.2, 112.3, 111.0, 14.8. IR (thin film cm^{-1}) 3928, 1603, 1574, 1559, 1490, 1478, 1437, 1343, 1275, 1187, 1171, 937. Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.28. H, 4.45.

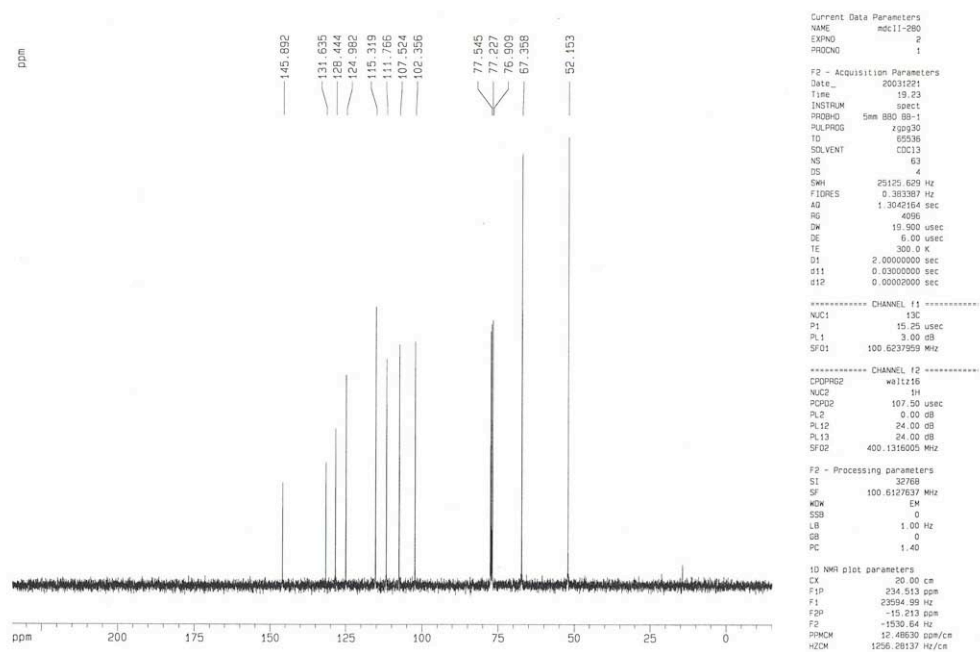


(1*H*-Indol-5-yl)-phenyl-amine (Table 4, Entry 1). Following general procedure 2, a mixture of 5-bromoindole (0.196 g, 1.00 mmol), aniline (0.111 g, 0.109 mL, 1.20 mmol), lithium bis(trimethylsilyl)amide (2.20 mL, 1.0 M solution in THF, 2.20 mmol), **4** (9.4 mg, 0.024 mmol, 2.4 mol%), Pd₂dba₃ (9.1 mg, 0.01 mmol, 1 mol%) and THF (1 mL) was stirred at 65 °C for 24 h. The crude reaction mixture was purified by flash column chromatography using 1:3 ethyl acetate:hexane to yield the title compound as a grey solid (0.201 g, 97%), mp 97-98 °C. ¹H NMR (400 MHz CDCl₃): δ 8.09 (s, br, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.26-7.20 (m, 3H), 7.06 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 6.97-6.95 (m, 2H), 6.86-6.82 (m, 1H), 6.51-6.50 (m, 1H), 5.65 (s, br, 1H). ¹³C NMR (100 MHz CDCl₃): δ 146.4, 135.2, 132.8, 129.4, 128.7, 125.1, 119.2, 118.4, 115.4, 113.3, 111.8, 102.5. IR (thin film cm⁻¹) 3411, 3398, 3384, 3371, 1600, 1520, 1495, 1459, 1306, 1285, 1154, 876, 746. Anal. Calcd for C₁₄H₁₂N₂: C, 80.74. H, 5.81.

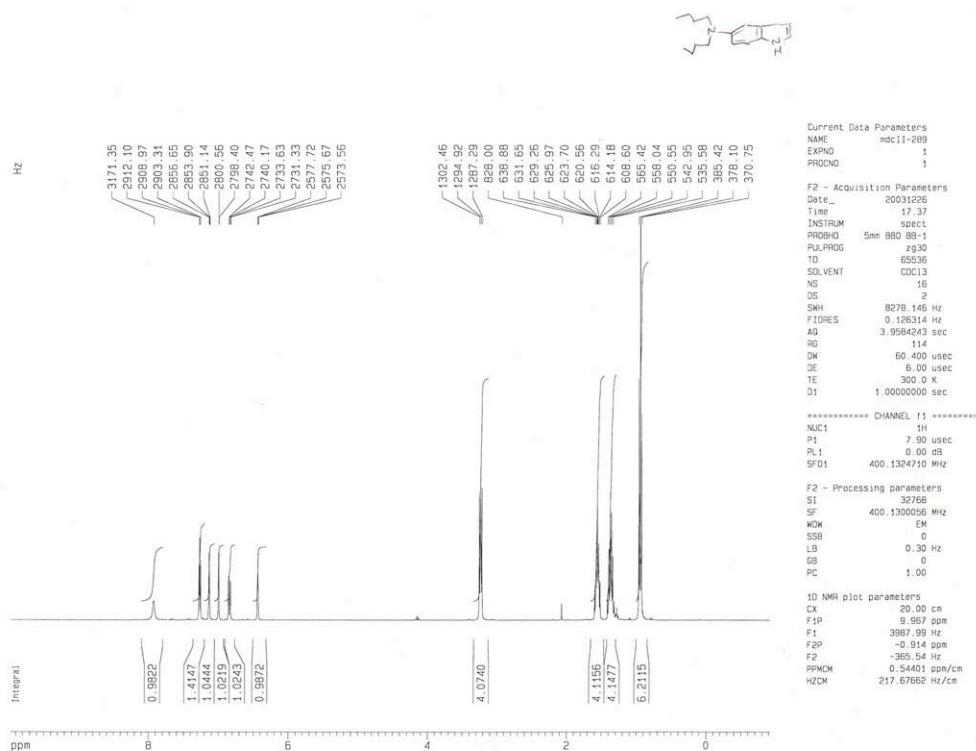


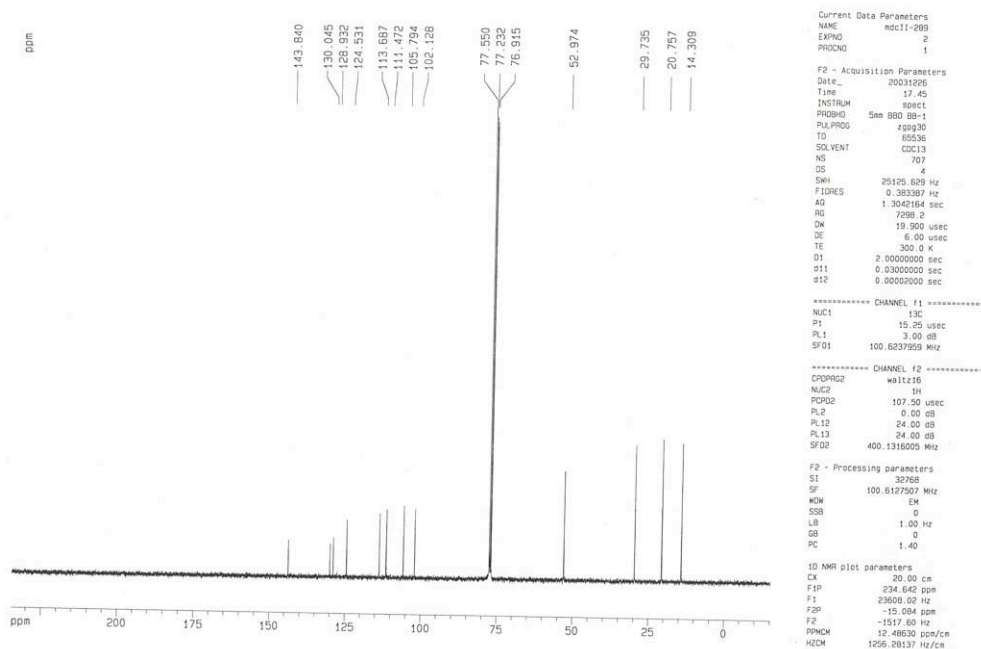


5-Morpholin-4-yl-1H-indole (Table 4, Entry 2). Following general procedure 2, a mixture of 5-bromoindole (0.196 g, 1.00 mmol), morpholine (0.104 g, 0.105 mL, 1.20 mmol), lithium bis(trimethylsilyl)amide (2.20 mL, 1.0 M solution in THF, 2.20 mmol), **4** (9.4 mg, 0.024 mmol, 2.4 mol%), Pd₂dba₃ (9.1 mg, 0.01 mmol, 1 mol%) and THF (1 mL) was stirred at 65 °C for 24 h. The crude reaction mixture was purified by flash column chromatography using 3:1 ethyl acetate:hexane to yield the title compound as a white solid (0.190 g, 94%), mp 134–135 °C. ¹H NMR (400 MHz CDCl₃): δ 8.31 (s, br, 1H), 7.33 (d, *J* = 8.79 Hz, 1H), 7.19–7.18 (m, 2H), 6.97 (dd, *J* = 8.7 Hz, 1.9 Hz, 1H), 6.49 (s, 1H), 3.92 (t, *J* = 4.3 Hz, 4H), 3.15 (t, *J* = 4.4 Hz, 4H). ¹³C NMR (100 MHz CDCl₃): δ 145.8, 131.6, 128.4, 124.9, 115.3, 111.7, 107.5, 102.3, 67.3, 52.1. IR (thin film cm⁻¹) 3346, 2815, 1476, 1447, 1304, 1275, 1260, 1227, 1165, 1111, 1067, 1044, 960, 893, 837, 758. Anal. Calcd for C₁₂H₁₄N₂O: C, 71.26. H, 6.98.

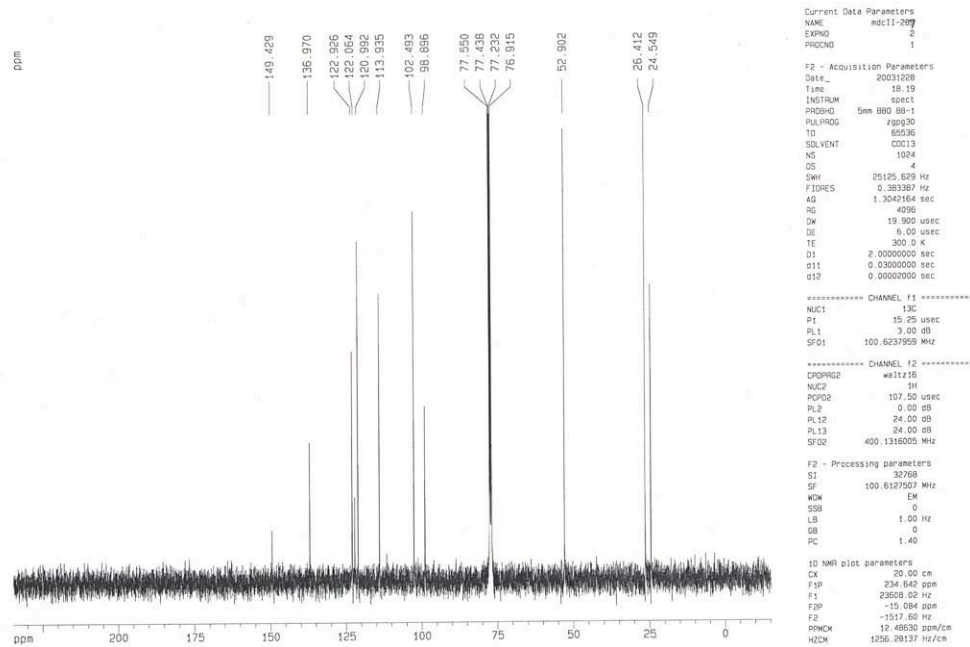
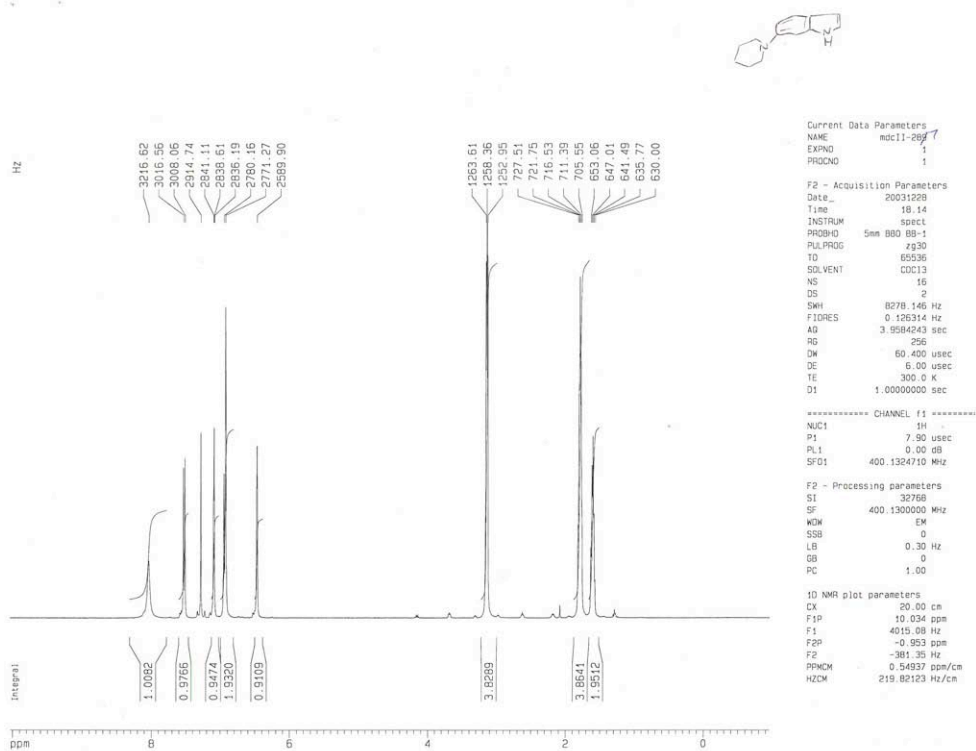


Dibutyl-(1*H*-indol-5-yl)-amine (Table 4, Entry 3). Following general procedure 2, a mixture of 5-bromoindole (0.098 g, 0.50 mmol), di-*n*-butylamine (0.077 g, 0.101 mL, 0.60 mmol), lithium bis(trimethylsilyl)amide (1.10 mL, 1.0 M solution in THF, 1.10 mmol), **1** (5.7 mg, 0.012 mmol, 1.2 mol%), Pd₂dba₃ (4.6 mg, 0.005 mmol, 0.5 mol%) and THF (1 mL) was stirred at 65 °C for 24 h. The crude reaction mixture was purified by flash column chromatography using 1:4 ethyl acetate:hexane + 2% Et₃N to yield the title compound as a dark yellow oil (0.065 g, 53%). ¹H NMR (400 MHz CDCl₃): δ 7.92 (s, br, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 7.13 (t, *J* = 2.7 Hz, 1H), 6.99 (d, *J* = 2.1 Hz, 1H), 6.84 (dd, *J* = 8.7 Hz, 2.3 Hz, 1H), 6.44-6.43 (m, 1H), 3.23 (t, *J* = 7.5 Hz, 4H), 1.59-1.52 (m, 4H), 1.36 (sextet, *J* = 14.9 Hz, 7.4 Hz, 4H), 0.94 (t, *J* = 7.3 Hz, 6H). ¹³C NMR (100 MHz CDCl₃): δ 143.8, 130.0, 128.9, 124.5, 113.6, 111.4, 105.7, 102.1, 52.9, 29.7, 20.7, 14.3. IR (thin film cm⁻¹) 3483, 3408, 2958, 2933, 2873, 1627, 1576, 1513, 1472, 1368, 1219, 1179, 1131, 904, 721. Anal. Calcd for C₁₆H₂₄N₂: C, 78.64. H, 9.90.





6-Piperidin-1-yl-1H-indole (Table 4, Entry 4). Following general procedure 2. a mixture of 6-chloroindole (0.151 g, 1.00 mmol), piperidine (0.102 g, 0.118 mL, 1.20 mmol), lithium bis(trimethylsilyl)amide (2.20 mL, 1.0 M solution in THF, 2.20 mmol), **1** (11 mg, 0.024 mmol, 2.4 mol%), Pd₂dba₃ (9.1 mg, 0.01 mmol, 1 mol%) and THF (1 mL) was stirred at 65 °C for 24 h. The crude reaction mixture was purified by flash column chromatography using 3:7 ethyl acetate:hexane followed by trituration with diisopropyl ether yielded the title compound as a white solid (0.125 g, 63%), mp 153-154 °C. ¹H NMR (400 MHz CDCl₃): δ 8.03 (s, br, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.10-7.08 (m, 1H), 6.94-6.92 (m, 2H), 6.47 (s, 1H), 3.14 (t, *J* = 5.3 Hz, 4H), 1.81-1.76 (m, 4H), 1.63-1.57 (m, 2H). ¹³C NMR (100 MHz CDCl₃): δ 149.4, 136.9, 122.9, 122.0, 120.9, 113.9, 102.4, 98.8, 52.9, 26.4, 24.5. IR (thin film cm⁻¹) 3161, 3130, 3118, 2935, 2860, 2811, 1598, 1576, 1497, 1482, 1447, 1256, 1026, 1171, 1129, 1094, 1059, 1027, 849.0, 771.8, 708.1. Anal. Calcd for C₁₃H₁₆N₂: C, 77.96. H, 8.05.



(1) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861-2873.

(2) D'Amico, J. J.; Webster, S. T.; Campbell, R. H.; Twine, C. E. *J. Org. Chem.* **1965**, *30*, 3618-3625.