Functionalized Pyridylboronic acids and their Suzuki Cross-coupling Reactions to Yield Novel Heteroarylpyridines

P. R. Parry et al

Supporting Information

General Details. Column chromatography was carried out on silica (40-60 μ m mesh). Solvents used for chromatography were distilled prior to use. ^1H NMR Spectra were recorded on a Varian Mercury 200 at 200 MHz, Bruker AM 250 at 250 MHz, Varian Unity 300 at 300 MHz, a Varian VXR 400s at 400 MHz or a Varian Inova 500 at 500 MHz using the deuteriated solvent as lock. ^{13}C NMR Spectra were recorded on these spectrometers at 50, 63, 75, 100 and 125 MHz, respectively. Mass spectra were recorded on a Micromass Autospec spectrometer operating at 70 eV with the ionization mode as indicated. Elemental analyses were obtained on an Exeter Analytical Inc. CE-440 elemental analyzer. Melting points were recorded on a Stuart Scientific SMP3 melting point apparatus and are uncorrected.

2-Bromo-5-pyridylboronic acid (2a). To a solution of 2,5-dibromopyridine (10.0 g, 42.2 mmol) in anhydrous ether (30 mL) at -78°C was added nBuLi (1.6 M in hexane, 30.0 mL, 48.0 mmol) dropwise. The reaction mixture was stirred for 2 h at -78°C . Triisopropylborate (TPB) (18.6 g, 99.7 mmol) was then added quickly. The reaction mixture was stirred at -78°C for a further 2 h then allowed to warm to 20°C and was quenched with water (50 mL). The reaction mixture was stirred overnight. The organic solvent was evaporated *in vacuo* and the remaining aqueous layer was taken to pH 10 (with 5% NaOH), and was washed with ether (3x100 mL).

The aqueous layer was then carefully acidified to pH 4 (with 48% HBr) to give **2a** as a white solid (6.7 g, 79%), mp 167-169 °C (lit mp 198 °C)¹; ¹H NMR (200 MHz, DMSO-d₆) δ 8.63 (1H, d, *J* = 1.8 Hz), 8.47 (2H, OH, s), 7.99 (1H, dd, *J* = 2.2 Hz, *J* = 2.2 Hz), 7.61 (1H, d, *J* = 8.0 Hz); ¹³C NMR (50 MHz, DMSO-d₆) δ 156.51, 145.65, 144.52, 128.30. Anal. Calcd for C₅H₅BBrNO₂: C, 29.76; H, 2.50; N, 6.94. Found: C, 29.83; H, 2.60; N, 6.83. Crystals for X-ray analysis were grown from aqueous EtOH solution.

2-Chloro-5-pyridylboronic acid (2b). To a solution of 2-chloro-5-bromopyridine (742 mg, 3.9 mmol) and TPB (1.5 g, 7.8 mmol) in anhydrous THF (10 mL) at -78 °C was added nBuLi (1.6 M in hexane, 2.5 mL, 4.0 mmol), dropwise. The reaction mixture was stirred for 5 h at -78 °C then quenched with water (10 mL) and allowed to warm to 20 °C with stirring overnight. Workup as described for **2a** gave **2b** as a white solid (370 mg, 61%), mp 166-167 °C (lit mp 190 °C)¹; ¹H NMR (300 MHz, acetone-d₆) δ 8.76 (1H, d, *J* = 1.8 Hz), 8.17 (1H, dd, *J* = 2.1 Hz, *J* = 2.1 Hz), 7.61 (2H, OH, s), 7.43 (1H, d, *J* = 8.1 Hz); ¹³C NMR (75 MHz, acetone-d₆) δ 155.85, 152.76, 145.72, 124.26. Anal. Calcd for C₅H₅BClNO₂: C, 38.16; H, 3.20; N, 8.90. Found: C, 37.82; H, 3.28; N, 8.79. Crystals for X-ray analysis were grown from aqueous EtOH solution.

2-Methoxy-5-pyridylboronic acid (2c). To a solution of 5-bromo-2-methoxypyridine (727 mg, 3.9 mmol) in anhydrous ether (10 mL) at -78 °C was added nBuLi (1.6 M in hexane, 2.5 mL, 4.0 mmol), dropwise.

The reaction mixture was stirred for 1 h at $-78\text{ }^{\circ}\text{C}$ then TPB (1.5 g, 7.8 mmol) was added quickly. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for another 1 h, then quenched with water (15 mL) and allowed to warm to $20\text{ }^{\circ}\text{C}$ with stirring overnight. Workup as described for **2a** gave **2c** as a white solid (382 mg, 65%), mp $137\text{--}138\text{ }^{\circ}\text{C}$; ^1H NMR (250 MHz, acetone- d_6) δ 8.62 (1H, d, $J = 1.3\text{ Hz}$), 8.05 (1H, dd, $J = 2\text{ Hz}$, $J = 2\text{ Hz}$), 7.27 (2H, OH, s), 6.73 (1H, d, $J = 10.0\text{ Hz}$); ^{13}C NMR (100 MHz, acetone- d_6) δ 166.31, 154.23, 144.85, 110.49, 53.23. Anal. Calcd for $\text{C}_6\text{H}_8\text{BNO}_3$: C, 47.12; H, 5.27; N, 9.16. Found: C, 46.87; H, 5.30; N, 8.99.

5-Chloro-2-methoxy-4-pyridylboronic acid (4). To a solution of 5-chloro-2-methoxypyridine (437 mg, 3.0 mmol) in anhydrous THF (10 mL) at $-78\text{ }^{\circ}\text{C}$ was added LDA (2.0 M in heptane/THF/ethylbenzene, 1.8 mL, 3.6 mmol), dropwise. The reaction mixture was stirred for 4 h then TPB (1.4 mL, 6.1 mmol) was added quickly. The reaction mixture was stirred for a further 3 h then quenched with water (10 mL) at $-78\text{ }^{\circ}\text{C}$ and allowed to warm to $20\text{ }^{\circ}\text{C}$ with stirring overnight. Workup as described for **2a** gave **4** as a white solid (275 mg, 48%), mp $123\text{--}125\text{ }^{\circ}\text{C}$; ^1H NMR (250 MHz, acetone- d_6) δ 8.07 (1H, s), 7.72 (2H, OH, s), 6.89 (1H, s), 3.86 (3H, OMe, s); ^{13}C NMR (63 MHz, acetone- d_6) δ 163.42, 145.94, 127.58, 116.35, 54.07. Anal. Calcd for $\text{C}_6\text{H}_7\text{BClNO}_3$: C, 38.46; H, 3.77; N, 7.47. Found: C, 38.22; H, 3.64; N, 7.43.

General Procedure for the Cross-Coupling Reactions. The boronic acid, the halide and tetrakis(triphenylphosphino)palladium (5 mol% relative to the boronic acid) were added sequentially to degassed DMF (10 mL) and the mixture was stirred at 20 °C for 30-60 min. Degassed aqueous Na₂CO₃ solution was added and the reaction mixture was heated under N₂ at 80 °C until tlc monitoring showed that the reaction was complete (22 – 70 h). Solvent was evaporated *in vacuo* and ethyl acetate was added. Then the organic layer was washed with brine, separated and dried over MgSO₄. The product was purified by column chromatography on silica gel.

3-(6-Bromo-pyridin-3-yl)-quinoline (5). Compound **2a** (222 mg, 1.1 mmol), 3-bromoquinoline (153 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (56 mg), DMF and Na₂CO₃ (1 M, 3.5 mL); reaction time 43 h; eluent petroleum ether (bp 40-60 °C):EtOAc 3:2 v/v gave compound **5** as a white solid (63 mg, 32%), mp 178-179 °C; ¹H NMR (500 MHz, CDCl₃) δ 9.13 (1H, d, *J* = 2.0 Hz), 8.74 (1H, d, *J* = 2.5 Hz), 8.33 (1H, d, *J* = 2.5 Hz), 8.18 (1H, d, *J* = 8.5 Hz), 7.93 (1H, d, *J* = 8.0 Hz), 7.89 (1H, dd, *J* = 2.5 Hz, *J* = 3.0 Hz), 7.80 (1H, t, *J* = 7.0 Hz), δ 7.67-7.63 (2H, m); ¹³C NMR (125 MHz, CDCl₃) δ 150.40, 148.97, 147.99, 142.17, 137.33, 134.03, 133.20, 130.56, 129.59, 128.69, 128.32(3C), 127.95, 127.85; MS (EI) *m/z* 286 (M⁺, 100%). HRMS (EI) calcd for C₁₄H₉BrN₂ (M⁺) 283.9950, found 283.9949.

6'-Bromo-[2,3']bipyridinyl (6). Compound **2a** (222 mg, 1.1 mmol), 2-bromopyridine (163 mg, 0.7 mmol), tetrakis(triphenylphosphino) palladium (56 mg), DMF and Na₂CO₃ (1 M, 3.5 mL); reaction time 43 h; eluent petroleum ether (bp 40-60 °C):EtOAc 3:2 v/v gave compound **6** as a white solid (18 mg, 11%), mp 78-82.5 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.94 (1H, s), 8.77 (1H, s), 8.31 (1H, d, *J* = 8.0 Hz), 7.92 (1H, t, *J* = 7.0 Hz), 7.81 (1H, d, *J* = 7.5 Hz), 7.64 (1H, d, *J* = 8.0 Hz), δ 7.50-7.34 (1H, m); ¹³C NMR (125 MHz, CDCl₃) δ 153.00, 149.20, 148.53, 143.23, 138.41, 137.16, 128.32, 123.56(2C), 121.08; MS (EI) *m/z* 234 (M⁺, 100%). HRMS(EI) calcd for C₁₀H₇BrN₂ (M⁺) 233.9793, found 233.9795.

5-(6-Bromo-pyridin-3-yl)-pyrimidine (7). Compound **2a** (162 mg, 0.8 mmol), 5-bromopyridine (111 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (40 mg), DMF and Na₂CO₃ (1 M, 2.5 mL); reaction time 22 h; eluent petroleum ether (bp 40-60 °C): EtOAc 1:4 v/v gave compound **7** as a white solid (16 mg, 10%), mp 178-179 °C; ¹H NMR (500 MHz, CDCl₃) δ 9.32 (1H, s), 8.97 (2H, s), 8.63 (1H, s), 7.78 (1H, dd, *J* = 2.0 Hz, *J* = 2.5 Hz), 7.69 (1H, d, *J* = 8.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 158.82, 155.05, 148.38, 143.32, 136.94, 130.66, 129.77, 129.01; MS (EI) *m/z* 235 (M⁺, 100%). HRMS(EI) calcd for C₉H₆BrN₃ (M⁺) 234.9746, found 233.9744.

3-(6-Chloro-pyridin-3-yl)-quinoline (8). Compound **2b** (100 mg, 0.6 mmol), 3-bromoquinoline (153 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (37 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 70 h; eluent DCM: EtOAc 3:7 v/v gave compound **8** as a white solid (84 mg, 55%), mp 180-181 °C; ¹H NMR (300 MHz, acetone-d₆) δ 9.13 (1H, d, *J* = 2.4 Hz), 8.77 (1H, d, *J* = 2.1 Hz), 8.55 (1H, d, *J* = 1.8 Hz), 8.20 (1H, dd, *J* = 2.7 Hz, *J* = 2.7 Hz), 7.99-7.92 (2H, m), 7.72-7.66 (1H, m), 7.60-7.50 (2H, m); ¹³C NMR (125 MHz, CDCl₃) δ 151.29, 148.88, 148.17, 147.48, 137.34, 133.71(2C), 132.60, 130.22, 129.38, 128.05, 127.68, 127.51, 124.59; MS (EI) *m/z* , 240 (M⁺, 100%). Anal. Calcd for C₁₄H₉ClN₂: C, 69.86; H, 3.77; N, 11.64. Found: C, 69.40; H, 3.80; N, 11.53.

6'-Chloro-[2,3']bipyridinyl (9). Compound **2b** (100 mg, 0.6 mmol), 2-bromopyridine (163 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (37 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 70 h; eluent DCM:EtOAc 7:3 v/v gave compound **9** as a white solid (75 mg, 61%), mp 71-72 °C; ¹H NMR (300 MHz, acetone-d₆) δ 9.10 (1H, d, *J* = 2.4 Hz), 8.73-8.71 (1H, m), 8.51 (1H, dd, *J* = 2.4 Hz, *J* = 2.4 Hz), 8.03 (1H, dd, *J* = 0.9 Hz, *J* = 0.9 Hz), 7.96-7.90 (1H, m), 7.57 (1H, d, *J* = 8.4 Hz), 7.44-7.39 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 153.42, 151.53, 150.27, 148.31, 137.54, 137.44, 134.19, 124.40, 123.60, 120.71; MS (EI) *m/z* 192 ([M+2]⁺, 41%), 190 (M⁺, 100%). Anal. Calcd for C₁₀H₇ClN₂: C, 63.01; H, 3.70; N, 14.70. Found: C, 63.19; H, 3.84; N, 14.45.

5-(6-Chloropyridin-3-yl)-pyrimidine (10). Compound **2b** (50 mg, 0.3 mmol), 5-bromopyrimidine (115 mg, 0.7 mmol), tetrakis(triphenylphosphino) palladium (37 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 70 h; eluent petroleum ether (bp 40-60 °C) : EtOAc 2:3 v/v gave compound **10** as a white solid (24 mg, 38%), mp 177-178.5 °C; ¹H NMR (400 MHz, acetone-d₆) δ 9.22 (1H, s), 9.16 (2H, s), 8.84 (1H, d, *J* = 2.4 Hz), 8.28 (1H, dd, *J* = 2.4 Hz, *J* = 2.8 Hz), 7.66 (1H, dd, *J* = 0.8 Hz, *J* = 0.8 Hz); ¹³C NMR (100 MHz, acetone-d₆) δ 158.42, 155.25 (2C), 151.68, 148.36, 138.08, 130.49, 130.00, 124.85; MS (EI) *m/z* 193 ([*M*+2]⁺, 33%), 191 (*M*⁺, 100%). Anal. Calcd for C₉H₆ClN₃: C, 56.41; H, 3.16; N, 21.93. Found: C, 56.48; H, 3.33; N, 21.43.

2-Chloro-4-(6-chloropyridin-3-yl)-pyrimidine (11). Compound **2b** (91 mg, 0.6 mmol), 2,4-dichloropyrimidine (75 mg, 0.5mmol), tetrakis(triphenylphosphino) palladium (34 mg) and Na₂CO₃ (1M, 2.0 mL); reaction time 65 h; eluent DCM:EtOAc; 4:1 v/v gave compound **11** as a white solid (26 mg, 23%), mp 188-190°C; ¹H NMR (200 MHz, acetone-d₆) δ 9.06 (1H, d, *J* = 1.8 Hz), 8.74 (1H, d, *J* = 5.4 Hz), 8.48 (1H, dd, *J* = 2.6 Hz, *J* = 2.6 Hz), 8.04 (1H, d, *J* = 5.2 Hz), 7.56 (1H, d, *J* = 8.4 Hz); ¹³C NMR (100 MHz, acetone-d₆) δ 163.91, 161.64, 161.54, 154.17, 149.17, 138.21, 130.61, 124.94, 116.42; MS (EI) *m/z* 226 ([*M*+2]⁺, 70%), 224 (*M*⁺, 100%). HRMS(EI) calcd for C₉H₅Cl₂N₃ (*M*⁺) 224.9861, found 224.9861.

2-Chloro-5-(5-nitrothien-2-yl)-pyridine (12). Compound **2b** (100 mg, 0.6 mmol), 2-bromo-5-nitrothiophene (115 mg, 0.6 mmol), tetrakis(triphenylphosphino) palladium (37 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 70 h; eluent DCM gave compound **12** as a yellow solid (132 mg, 53%), mp 190-191 °C; ¹H NMR (500 MHz, acetone-d₆) δ 8.74 (1H, d, *J* = 3.0 Hz), 8.13 (1H, dd, *J* = 2.5 Hz, *J* = 2.5 Hz), 7.98 (1H, d, *J* = 4.5 Hz), 7.60 (1H, d, *J* = 4.0 Hz), 7.49 (1H, d, *J* = 8.5 Hz); ¹³C NMR (125 MHz, acetone-d₆) δ 152.16, 147.40, 146.38, 137.10(2C), 130.43, 127.89, 125.42, 125.05, 122.95; MS (EI) *m/z* 242 ([M+2]⁺, 38%), 240 (M⁺, 100%). Anal. Calcd for C₉H₅ClN₂O₂S: C, 44.92; H, 2.09; N, 11.64. Found: C, 44.81; H, 2.19; N, 11.38.

3-(6-Methoxypyridin-3-yl)-quinoline (13). Compound **2c** (122 mg, 0.8 mmol), 3-bromoquinoline (307 mg, 1.1mmol), tetrakis(triphenylphosphino)palladium (56 mg), DMF and Na₂CO₃ (1 M, 2.5 mL); reaction time 70 h; eluent petroleum ether (bp 40-60 °C):EtOAc 3:7 v/v gave compound **13** as a white solid (144 mg, 76%), mp 125-126 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.13 (1H, d, *J* = 2.4 Hz), 8.52 (1H, d, *J* = 2.4 Hz), 8.26 (1H, d, *J* = 1.8 Hz), 8.14 (1H, d, *J* = 8.7 Hz), 7.94-7.88 (2H, m), 7.76-7.71 (1H, m), 7.62-7.57 (1H, m), 4.02 (3H, OMe, s); ¹³C NMR (100 MHz, CDCl₃) δ 164.11, 149.32, 147.29, 145.43, 137.54, 132.70, 130.70, 129.51, 129.27, 127.95, 127.89, 127.19, 126.89, 111.37, 53.70; MS (EI) *m/z* 236 (M⁺, 100%). Anal. Calcd for C₁₅H₁₂N₂O: C, 76.25; H, 5.12; N, 11.86. Found: C, 75.99; H, 5.08; N, 11.64.

6'-Methoxy-[2,3']bipyridinyl (14). Compound **2c** (50 mg, 0.3 mmol), 2-bromopyridine (163 mg, 1.0 mmol), tetrakis(triphenylphosphino)palladium (26 mg), DMF and Na₂CO₃ (1 M, 1.0 mL); reaction time 22 h; eluent petroleum ether (bp 40-60 °C):EtOAc 7:3 v/v gave compound **14** as a dark red oil (28 mg, 50%). ¹H NMR (300 MHz, CDCl₃) δ 8.73 (1H, d, *J* = 2.4 Hz), 8.68-8.66 (1H, m), 8.24 (1H, dd, *J* = 2.7 Hz, *J* = 2.4 Hz), 7.78-7.72 (1H, m), 7.66 (1H, d, *J* = 7.8 Hz), 7.25-7.20 (1H, m), δ 6.84 (1H, d, *J* = 8.4 Hz), 3.99 (3H, OMe, s); ¹³C NMR (125 MHz, D₂O) δ 167.48, 157.45, 152.59, 148.43, 139.99, 131.33, 125.02(2C), 122.29, 113.35, 55.76; MS (EI) *m/z* 186 (M⁺, 100%); HRMS(EI) calcd for C₁₁H₁₀N₂O (M⁺) 186.0793, found 186.0795.

6-Methoxy-[3,3']-bipyridinyl (15). Compound **2c** (100 mg, 0.7 mmol), 3-bromopyridine (162 mg, 1.0 mmol), tetrakis(triphenylphosphino)palladium (56 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 48 h; eluent EtOAc gave compound **15** as a white solid (71 mg, 58%), mp 62-63 °C; ¹H NMR (300 MHz, acetone-d₆) δ 8.86 (1H, d, *J* = 2.4 Hz), 8.57 (1H, d, *J* = 4.8 Hz), 8.49 (1H, d, *J* = 2.4 Hz), 8.02 (1H, dd, *J* = 1.8 Hz, *J* = 1.8 Hz), 7.48-7.43 (1H, m), 6.90 (1H, d, *J* = 8.4 Hz), 3.95 (3H, OMe, s); ¹³C NMR (63 MHz, acetone-d₆) δ 165.23, 149.65, 148.76, 146.30, 138.62, 134.75, 134.44, 128.00, 124.83, 112.06, 54.00; MS (EI) *m/z* 186 (M⁺, 100%). Anal. Calcd for C₁₁H₁₀N₂O: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.52; H, 5.32; N, 15.05.

6,6'-Dimethoxy-[3,3']bipyridinyl (16). Compound **2c** (150 mg, 1.0 mmol), 5-bromo-2-methoxypyridine (145 mg, 0.8 mmol), tetrakis(triphenylphosphino) palladium (50 mg), DMF and Na₂CO₃ (1 M, 3.0 mL); reaction time 65 h; eluent used, petroleum ether (bp 40-60 °C):EtOAc 4:1 v/v gave compound **16** as a white solid (138 mg, 83%), mp 104.5-106 °C (lit. mp 104-105 °C)²; ¹H NMR (300 MHz, CDCl₃) δ 8.33 (2H, d, *J* = 2.1 Hz), 7.72 (2H, dd, *J* = 2.4 Hz, *J* = 2.4 Hz), 6.83 (2H, d, *J* = 8.7 Hz), 3.98 (6H, OMe, s); ¹³C NMR (75 MHz, CDCl₃) δ 163.86(2C), 144.76(2C), 137.70(2C), 127.17(2C), 111.33(2C), 53.83(2C); MS (EI) *m/z* 216 (M⁺, 100%). Anal. Calcd for C₁₂H₁₂N₂O₂: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.42; H, 5.62; N, 12.97.

6-Methoxy-6'-nitro-[3,3']bipyridinyl (17). Compound **2c** (100 mg, 0.7 mmol), 5-bromo-2-nitropyridine (140 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (30 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 65 h; eluent petroleum ether (bp 40-60 °C):EtOAc 3:2 v/v gave compound **17** as a yellow solid (150 mg, 66%), mp 191-192 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.81 (1H, d, *J* = 1.8 Hz), 8.48 (1H, d, *J* = 2.1 Hz), 8.36 (1H, d, *J* = 8.7 Hz), δ 8.16 (1H, dd, *J* = 2.4 Hz, *J* = 2.1 Hz), 7.86 (1H, dd, *J* = 2.7 Hz, *J* = 2.4 Hz), 6.93 (1H, d, *J* = 8.4 Hz), 4.02 (3H, OMe, s); ¹³C NMR (75 MHz, CDCl₃) δ 165.31, 156.35, 146.71, 146.08, 139.68, 137.50, 137.21, 124.60, 118.62, 112.13, 54.17; 53.83(2C); MS (EI) *m/z* 231 (M⁺, 100%). Anal. Calcd for C₁₁H₉N₃O₃: C, 57.14; H, 3.92; N, 18.17. Found: C, 56.94; H, 3.97; N, 17.92.

6'-Methoxy-5-trifluoromethyl-[2,3']-bipyridinyl (18). Compound **2c** (100 mg, 0.7 mmol), 2-bromo-5-(trifluoromethyl)pyridine (170 mg, 0.8 mmol), tetrakis(triphenylphosphino)palladium (38 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 70 h; eluent DCM:EtOAc 9:1 v/v gave compound **18** as a yellow solid (53 mg, 32%), mp 78-80 °C; ¹H NMR (400 MHz, acetone-d₆) δ 8.98 (2H, dd, *J* = 0.8 Hz, *J* = 0.8 Hz), 8.47 (1H, dd, *J* = 2.8 Hz, *J* = 2.4 Hz), 8.23-8.15 (2H, m), 6.93 (1H, dd, *J* = 0.8 Hz, *J* = 0.8 Hz), 3.98 (3H, OMe, s); ¹³C NMR (100 MHz, acetone-d₆) δ 166.76, 158.56, 146.61, 137.74, 134.60(2C), 127.28, 119.62(2C), 111.04, 53.31; MS (EI) *m/z* 253 (M⁺, 100%). Anal. Calcd for C₁₂H₉F₃N₂O: C, 56.70; H, 3.57; N, 11.02. Found: C, 56.78; H, 3.61; N, 10.72.

5-(6-Methoxy-pyridin-3-yl)-pyrimidine (19). Compound **2c** (50 mg, 0.3 mmol), 5-bromopyrimidine (60 mg, 0.4 mmol), tetrakis(triphenylphosphine) palladium (26 mg), DMF and Na₂CO₃ (1 M, 1.0 mL); reaction time 70 h; eluent petroleum ether (bp 40-60 °C):EtOAc 1:9 v/v gave compound **19** as a white solid (20 mg, 35%), mp 162-164 °C; ¹H NMR (300 MHz, acetone-d₆) δ 9.14 (1H, s), 9.07 (1H, s), 8.57 (1H, d, *J* = 1.8 Hz), 8.10 (1H, dd, *J* = 2.7 Hz, *J* = 2.7 Hz), 6.95 (1H, dd, *J* = 0.6 Hz, *J* = 0.6 Hz), 3.96 (3H, OMe, s); ¹³C NMR (75 MHz, acetone-d₆) δ 164.66, 157.53, 154.58(2C), 145.61, 137.66, 131.42, 123.77, 111.41, 53.22; MS (EI) *m/z* 187 (M⁺, 100%). HRMS(EI) calcd for C₁₀H₉N₃O (M⁺) 187.0746, found 187.0746.

2-(6-Methoxy-pyridin-3-yl)-pyrimidine (20). Compound **2c** (100 mg, 0.7 mmol), 2-bromopyrimidine (105 mg, 0.7 mmol), tetrakis(triphenylphosphino) palladium (56 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 70 h; eluent petroleum ether (bp 40-60 °C):EtOAc 3:2 v/v gave compound **20** as a white solid (34 mg, 28%), mp 70-71 °C; ¹H NMR (400 MHz, acetone-d₆) δ 9.09 (1H, d, *J* = 2.4 Hz), 8.72 (2H, d, *J* = 4.8 Hz), 8.51 (1H, dd, *J* = 2.4 Hz, *J* = 2.0 Hz), 7.25 (1H, t, *J* = 5.2 Hz), 6.77-6.75 (1H, m), 3.85 (3H, OMe, s); ¹³C NMR (100 MHz, acetone-d₆) δ 166.22, 163.20, 158.02(2C), 148.12, 138.58, 127.55, 119.96, 110.91, 53.56; MS (EI) *m/z* 186 (M⁺, 100%). Anal. Calcd for C₁₀H₉N₃O: C, 64.16; H, 4.85; N, 22.45. Found: C, 63.79; H, 4.89; N, 22.19.

5-(6-Methoxy-pyridin-3-yl)-pyrazine-2-ylamine (21). Compound **2c** (100 mg, 0.7 mmol), 2-bromo-5-aminopyrazine³ (63 mg, 0.5 mmol), tetrakis(triphenylphosphino)palladium (38 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 70 h; eluent EtOAc gave compound **21** as an off-white solid (33 mg, 26%), mp 164-165 °C (from toluene); ¹H NMR (300 MHz, acetone-d₆) δ 8.70 (1H, d, *J* = 2.4 Hz), 8.46 (1H, s), 8.20 (1H, dd, *J* = 2.7 Hz, *J* = 2.7 Hz), 8.05 (1H, s), 6.82 (1H, d, *J* = 8.4 Hz), 5.92 (2H, NH₂, br s), 3.92 (3H, OMe, s); ¹³C NMR (125 MHz, D₂O) δ 166.58, 163.20, 157.76, 146.52, 141.49, 141.17, 138.64, 134.48, 129.83, 113.32, 55.60; MS (EI) *m/z* 202 (M⁺, 100%). HRMS(EI) calcd for C₁₀H₁₀N₄O (M⁺) 202.0855, found 202.0857.

2-Methoxy-5-thiazol-2-yl-pyridine (22). Compound **2c** (100 mg, 0.7 mmol), 2-bromothiazole (184 mg, 0.6 mmol), tetrakis(triphenylphosphino)palladium (38 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 70 h; eluent petroleum ether (bp 40-60 °C):EtOAc 7:3 v/v gave compound **22** as an off-white solid (107 mg, 85%), mp 76-79 °C; ¹H NMR (300 MHz, acetone-d₆) δ 8.75 (1H, d, *J* = 2.1 Hz), 8.23 (1H, dd, *J* = 2.7 Hz, *J* = 2.7 Hz), 7.87 (1H, d, *J* = 3.0 Hz), 7.61 (1H, d, *J* = 3.0 Hz), 6.89 (1H, d, *J* = 8.7 Hz), 3.95 (3H, OMe, s); ¹³C NMR (63 MHz, acetone-d₆) δ 166.21, 146.20, 144.88, 137.87, 124.95, 122.77, 120.14, 112.20, 54.26; MS (EI) *m/z* 192 (M⁺, 100%). Anal. Calcd for C₉H₈N₂OS: C, 56.23; H, 4.19; N, 14.57. Found: C, 56.10; H, 4.31; N, 14.23.

2-Methoxy-5-thien-2-yl-pyridine (23). Compound **2c** (229 mg, 1.5 mmol), 2-bromothiophene (170 mg, 1.0 mmol), tetrakis(triphenylphosphino)palladium (30 mg), DMF and Na₂CO₃ (1 M, 4.5 mL); reaction time 65 h; eluent petroleum ether (bp 40-60 °C):EtOAc 9:1 v/v gave compound **23** as a yellow oil (174 mg, 87%). ¹H NMR (300 MHz, CDCl₃) δ 8.41 (1H, d, *J* = 2.1 Hz), 7.73 (1H, dd, *J* = 2.4 Hz, *J* = 2.7 Hz), 7.24 (1H, dd, *J* = 0.6 Hz, *J* = 0.9 Hz), 7.18 (1H, dd, *J* = 0.6 Hz, *J* = 0.6 Hz), 7.05-7.03 (1H, m), 6.74 (1H, dd, *J* = 0.6 Hz, *J* = 0.3 Hz), 3.95 (3H, OMe, s); ¹³C NMR (75 MHz, CDCl₃) δ 163.75, 144.15, 140.97, 136.70, 128.30, 124.88, 124.31, 123.14, 111.17, 53.82; MS (EI) *m/z* 191 (M⁺, 100%). Anal. Calcd for C₁₀H₉NOS: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.54; H, 4.77; N, 7.33.

2-Methoxy-5-(5-nitrothien-2-yl)-pyridine (24). Compound **2c** (50 mg, 0.3 mmol), 2-bromo-5-nitrothiophene (115 mg, 0.7 mmol), tetrakis(triphenylphosphino)palladium (37 mg), DMF and Na₂CO₃ (1 M, 2.0 mL); reaction time 63 h; eluent DCM:MeOH (99:1 v/v) gave compound **24** as a yellow solid (109 mg, 94%), mp 186-187 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.48 (1H, d, *J* = 2.1 Hz), 7.91 (1H, dd, *J* = 0.6 Hz, *J* = 0.6 Hz), 7.79 (1H, dd, *J* = 2.1 Hz, *J* = 2.4 Hz), 7.16 (1H, d, *J* = 4.2 Hz), 6.84 (1H, d, *J* = 8.7 Hz), 4.00 (3H, OMe, s); ¹³C NMR (125 MHz, CDCl₃) δ 165.34, 148.94, 145.12, 136.64, 130.01, 122.12, 111.98, 111.94, 54.21; MS (EI) *m/z* 236 (M⁺, 100%). Anal. Calcd for C₁₀H₈N₂O₃S: C, 50.84; H, 3.41; N, 11.86. Found: C, 50.61; H, 3.41; N, 11.90.

5'-Chloro-2'-methoxy-[2,4']bipyridinyl (25). Compound **2d** (100 mg, 0.5 mmol), 2-bromopyridine (163 mg, 0.6 mmol), tetrakis(triphenylphosphine)palladium (31 mg), DMF and Na₂CO₃ (1 M, 1.5 mL); reaction time 65 h; eluent DCM:EtOAc 9:1 v/v gave compound **25** as a white solid (41 mg, 35%), mp 76.5-78 °C; ¹H NMR (400 MHz, acetone-d₆) δ 8.58-8.56 (1H, m), 8.26 (1H, d, *J* = 2.4 Hz), 8.08 (1H, d, *J* = 2.4 Hz), 8.03-8.01 (1H, m), 7.76-7.71 (1H, m), 7.26-7.22 (1H, m), 3.90 (3H, OMe, s); ¹³C NMR (100 MHz, acetone-d₆) δ 159.90, 152.21, 149.90, 145.05, 138.70, 136.56, 124.63, 124.50, 123.97, 123.22, 53.72; MS (EI) *m/z* 222 ([M+2]⁺, 10%), 220 (M⁺, 30%). Anal. Calcd for C₁₁H₉ClN₂O: C, 59.88; H, 4.11; N, 12.70. Found: C, 60.12; H, 4.32; N, 12.53.

5-Chloro-2-methoxy-4-(5-nitrothien-2-yl)-pyridine (26). Compound **2d** (100 mg, 0.5 mmol), 2-bromo-5-nitrothiophene (129 mg, 0.6 mmol), tetrakis(triphenylphosphino)palladium (31 mg), DMF and Na₂CO₃ (1 M, 1.5 mL); reaction time 65 h; eluent DCM:petroleum ether (bp 40-60 °C) 9:1 v/v gave compound **26** as a yellow solid (40 mg, 28%), mp 177-200 °C; ¹H NMR (400 MHz, acetone-d₆) δ 8.32 (1H, d, *J* = 2.4 Hz), 8.13 (1H, d, *J* = 2.4 Hz), 7.95 (1H, d, *J* = 4.4 Hz), 7.80 (1H, d, *J* = 4.4 Hz), 4.04 (3H, OMe, s); ¹³C NMR (125 MHz, acetone-d₆) δ 174.68, 158.08, 146.02, 142.76, 135.92, 128.85, 125.79, 124.83, 116.78, 54.30; MS (EI) *m/z* 272 ([*M*+2]⁺, 18%), 270 (*M*⁺, 40%). Anal. Calcd for C₁₀H₇ClN₂O₃S: C, 44.37; H, 2.61; N, 10.35. Found: C, 43.88; H, 2.63; N, 9.91.

2,5-Bis(2-methoxy-4-pyridyl)thiophene (27). Compound **2c** (324 mg, 2.1 mmol), 2,5-dibromothiophene (215 mg, 0.5 mmol), tetrakis(triphenylphosphino) palladium (244 mg), DMF and Na₂CO₃ (1 M, 7.0 mL); reaction time 70 h; eluent DCM:EtOAc 9:1 v/v gave compound **27** as a yellow solid (53 mg, 34%), mp 126-127 °C (from cyclohexane). ¹H NMR (200 MHz, acetone-d₆) δ 8.36 (2H, d, *J* = 2.3 Hz), 7.85 (2H, dd, *J* = 3.3 Hz, *J* = 3.3 Hz), 7.29 (2H, s), 6.72 (2H, d, *J* = 10.8 Hz), 3.80 (6H, OMe, s); ¹³C NMR (100 MHz, CDCl₃) δ 163.83(2C), 143.96(2C), 140.13(2C), 136.45(2C), 124.10(2C), 111.29(2C), 53.90(2C); MS (EI) *m/z* 298 (*M*⁺, 100%). Anal. Calcd for C₁₆H₁₄N₂O₂S: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.50; H, 4.84; N, 9.20.

Crystal structures

A survey of the April 2002 version of the Cambridge Crystallographic Database⁴ found 17 structures containing a $C(sp^2)-B(OH)_2$ fragment, viz. $PhB(OH)_2$ ⁵ and its various derivatives, including $4-BrC_6H_4B(OH)_2$,⁶ but no heterocyclic derivatives. In all of them, the boron atom has a nearly planar trigonal coordination. In the absence of bulky substituents in the *ortho* positions, the CBO_2 plane is often coplanar with the benzene ring, but occasionally the twist around the C–B bond (τ) can be as large as 28°. The two independent molecules in the structure of $PhB(OH)_2$ display widely different τ of 6.6° and 21.4°. Thus the rotation around the C–B bond is not much hindered.

The crystal structures of **2a** (Figure 1) and **2b** (Figure 2) are substantially different, notwithstanding the similar size of the Cl and Br atoms (van der Waals radii 1.76 and 1.87 Å, respectively⁷), which often produce isomorphous derivatives. Compound **2a** has the same structure at 295 and 120 K, i.e. there is no evidence that the crystallographic difference between **2a** and **2b** is linked to temperature-dependent polymorphism.

Compounds **2a** and **2b** adopt slightly twisted conformations: in **2a** $\tau=10.5^\circ$ (295 K) and 10.9° (120 K), in **2b** $\tau=4.0^\circ$. The C–B bond distances in **2a** and **2b** are equal [1.573(2) Å at 120 K] and close to that in $PhB(OH)_2$ after libration correction [1.565(3) Å]. As with the latter structure, molecules of **2a** (**2b**) related by an inversion centre, form hydrogen-bonded dimers, broadly similar to those existing in the crystals of organic acids. The hydroxyl H atoms not engaged in dimerization, form hydrogen bonds with the O atoms of adjacent dimers in $PhB(OH)_2$ and with heterocyclic N atoms in **2a** (**2b**). Due to the latter bonds, the crystal architecture of **2a** (**2b**) is quite

different from that of 4-BrC₆H₄B(OH)₂, which crystallizes in the hexagonal space group *P6/mcc*. In both **2a** and **2b**, the O(1) atom acts as both as a donor *and* an acceptor of hydrogen bonds, and O(2) as a donor only. Correspondingly, the B–O(1) bond is marginally longer than B–O(2): 1.363(2) vs. 1.357(2) Å in **2a**, 1.362(2) vs. 1.352(2) Å in **2b**, cf. the average of 1.371(7) Å in PhB(OH)₂, where both O atoms act like O(1).

However, the two OH...N bonds (donated and accepted) by the same molecule, in **2a** are in *cis*, and in **2b** in *trans* orientation with respect to the B...Br(Cl) axis of the molecule (see Figures). In **2a** these bonds link the molecules symmetrically related by an *n* glide plane, in **2b** those related by a 2₁ axis, giving rise to rather different crystal packing patterns.

Experimental. X-ray diffraction experiments were carried out on SMART 3-circle diffractometers with CCD area detectors, using graphite-monochromated Mo-*K*α radiation ($\lambda = 0.71073$ Å) and a Cryostream (Oxford Cryosystems) open-flow N₂ gas cryostat. A hemisphere of reciprocal space was covered by a combination of 4 sets of ω scans, each set at different ϕ and/or 2θ angles. For absorption correction was performed. The structures were solved by direct methods and refined by full-matrix least squares against F^2 of all data, using SHELXTL software.⁸ Crystal data and experimental details are summarized in Table 1; full structural information has been deposited with the Cambridge Crystallographic Data Centre.

Table 1. Crystal data and experimental details

S18

Compound	2a	2a	2b
CCDC	184781	184782	184783
<i>T</i> , K	120	295	120
Formula	$C_5H_5BBrNO_2$		$C_5H_5BClNO_2$
Formula weight	201.82		157.36
Symmetry	Monoclinic		Monoclinic
Space group	$P2_1/c$ (# 14)		$P2_1/n$ (# 14)
<i>Z</i>	4		4
<i>a</i> , Å	7.346(1)	7.535(2)	8.906(1)
<i>b</i> , Å	6.938(1)	6.941(1)	7.277(1)
<i>c</i> , Å	13.727(1)	13.877(3)	10.389(1)
β , °	96.62(1)	96.81(4)	96.55(1)
<i>V</i> , Å ³	694.95(15)	720.7(3)	668.91(14)
<i>D</i> , g cm ⁻³	1.929	1.860	1.563
μ , cm ⁻¹	5.84	5.64	0.50
Crystal size, mm	0.32×0.25×0.05	0.55×0.30×0.07	0.36×0.07×0.05
CCD detector	6K	1K	6K
Reflections, total	8589	6245	8991
Max. 2θ , °	30	29	30
Reflections, unique	2023	1913	1945
Transmission, min/max	0.2679, 0.7345	0.2191, 0.6639	0.8944, 0.9801
<i>R</i> _{int}	0.150, 0.029*	0.163, 0.060*	0.032, 0.024*
Refls $F^2 > 2\sigma(F^2)$	2236	1314	1693
$R[F^2 > 2\sigma(F^2)]$	0.019	0.036	0.029
$wR(F^2)$, all data	0.050	0.082	0.084
$\Delta\rho$, e Å ⁻³	0.42, -0.25	0.43, -0.43	0.49, -0.17

* After absorption correction

References for the Supporting Information

- (1) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885.
- (2) For an alternative route to **16** see Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Synthesis*, **1984**, 736.
- (3) Chen, J. J.; Hinkley, J. M.; Wise, D. S.; Townsend, L. B. *Synth. Commun.* **1996**, *26*, 617. Ellingson, R. C.; Henry, R. L. *J. Am. Chem. Soc.* **1949**, *71*, 2798.
- (4) Allen, F. H.; Kennard, O. *Chem. Des. Autom. News* **1993**, *8*, 1 & 31.
- (5) Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1977**, *55*, 3071.
- (6) Zvonkova, Z. V.; Glushkova, V. P. *Kristallografiya* **1958**, *3*, 559.
- (7) Rowland, R. S.; Taylor, R. *J. Phys. Chem.* **1996**, *100*, 7384.
- (8) Bruker AXS. *SHELXTL*, Version 5.1. Madison, Wisconsin, USA, 1997.

Fig. 1. X-ray structure of **2a**, at 120 K (top) and 295 K (bottom), showing 50% thermal ellipsoids and hydrogen bonds. Atoms generated by an n plane are primed, those generated by an inversion center double-primed.

Fig. 2. X-ray structure of **2b**, showing 50% thermal ellipsoids and hydrogen bonds. Atoms generated by a 2_1 axis are primed, those generated by an inversion center double-primed.

Fig. 3. NOESY Spectrum of compound **11**

S21

Fig. 1

Fig. 2

Fig. 3