Selective Amination of Polyhalo-pyridines Catalyzed by Palladium - Xantphos Complex

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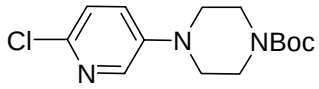
Experimental Procedures, Analytical Instrumentation and Data. ^{1}H NMR spectra were recorded on GE QE-300 (300 MHz) and Bruker AMX-400 (400 MHz) spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from TMS as an internal standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublets of doublets, m=multiplet, br=broad), coupling constant(s), integration and peak assignment. ^{13}C NMR spectra were recorded on a GE QE-300 (75 MHz) spectrometers using broad band proton decoupling. Chemical shifts are reported in parts per million (ppm) down field from TMS, using the middle resonance of $CDCl_3$ (77.0 ppm) as an internal standard. Mass spectra were acquired on a Jeol JMS-SX-102 spectrometer. HPLC analyses were carried out on Hitachi system model D-7000. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, New Jersey.

General Procedure for Ligand Screen on Amination of 5-Bromo-2-chloro pyridine (1a) with 1-*N*-Boc piperazine (2a): Condition A: 5-Bromo-2-chloropyridine (**1a**) (192.4 mg, 1 mmol, 1.0 equiv.) and 1-*N*-Boc piperazine (**2a**) (186.3 mg, 1 mmol, 1.0 equiv.) were combined in the reaction flask. Dry toluene (10 mL) was added, followed by ^{t}BuONa (144.0 mg, 1.5 mmol, 1.5 equiv.), $Pd_2(dba)_3$ (18.3 mg, 0.02 mmol, 0.02 equiv.) and the ligand (0.06 mmol, 0.06 equiv.). The mixture was evacuated and

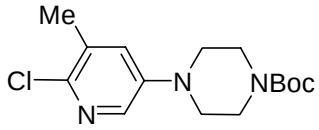
purged with N_2 (3 cycles), then heated to 95-100 °C under N_2 for 3 hours. The yield and selectivity were determined by HPLC analysis. (HPLC conditions: HPLC (Column: Zorbax-RX-C8. Solvent: 0.2% $HClO_{4(aq)}$- CH_3CN, 90 : 10 to 10 : 90 over 15 min. UV detection at 250 nM). The product 1-*N*-Boc-4-(6-chloropyridin-3-yl)-piperazine (**3a**) elutes at 15.2 min. The byproduct 1-*N*-Boc-4-(5-bromopyridin-2-yl)-piperazine (**4a**) elutes at 13.4 min., 2,5-di-(1-*N*-Boc-4-piperazinyl)-pyridine **5a** at 12.6 min., starting material 5-bromo-2-chloropyridine at 13.7 min. **Condition B:** 5-Bromo-2-chloropyridine (**1a**) (250.1 mg, 1.3 mmol, 1.3 equiv.) and 1-*N*-Boc piperazine (**2a**) (186.3 mg, 1 mmol, 1.0 equiv.) were combined in the reaction flask. Dry toluene (10 mL) was added, followed by ^{t}BuONa (144.0 mg, 1.5 mmol, 1.5 equiv.), $Pd_2(dba)_3$ (18.3 mg, 0.02 mmol, 0.02 equiv.) and the ligand (0.06 mmol, 0.06 equiv.). The mixture was evacuated and purged with N_2 (3 cycles), then heated to 95-100 °C under N_2 for 3 hours. The yield and selectivity were determined by HPLC analysis.

General Procedure on Amination of Bromo-2-chloropyridine with Cycloamine (2): Scope of Pyridines and Amines: 5-Bromo-2-chloropyridine (**1a**) (250.1 mg, 1.3 mmol, 1.3 equiv.) and 1-*N*-Boc piperazine (**2a**) (186.3 mg, 1 mmol, 1.0 equiv.) were combined in the reaction flask. Dry toluene was added, followed by ^{t}BuONa (144.0 mg, 1.5 mmol, 1.5 equiv.), $Pd_2(dba)_3$ (18.3 mg, 0.02 mmol, 0.02 equiv.) and Xantphos (34.7 mg, 0.06 mmol, 0.06 equiv.). The mixture was evacuated and purged with N_2 (3 cycles), then heated to 95-100 °C under N_2 for 3 hours. The conversion and selectivity were determined by HPLC analysis. After the reaction went to completion, the reaction mixture was then cooled down to room temperature, diluted with EtOAc (20 mL) and washed with water (5 mL). The organic solution was concentrated under

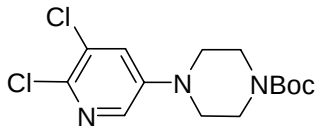
reduced pressure, and the residue was purified by chromatography on silica gel using hexane/EtOAc (v. 50/50) for **3a**-**3g**, **9** and **10**, hexane/EtOAc (v. 80/20) for **3j**-**3m**, and CH_2Cl_2/MeOH(with v. 2% $NH_3 \cdot H_2O$) (v. 90/10) for **3h**, **3i**.



1-*N*-Boc-4-*N*-(6-chloropyridin-3-yl)-piperazine (**3a**): R_f=0.5. ^{1}H NMR (CD_3OD) δ 8.01 (d, *J*=3.1 Hz, 1H), 7.43 (dd, *J*=8.8, 3.1 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 3.58 (t, *J*=5.4 Hz, 4H), 3.19 (t, *J* = 5.1 Hz, 4H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 154.3, 146.1, 141.8, 137.9, 126.2, 124.0, 80.2, 48.7, 28.4. MS (DCI/NH_3) *m/z* 298 (M + H^+), 300 (M + H^+). Anal. Cacld. for $C_{14}H_{20}ClN_3O_2$: C, 56.47; H, 6.77; N, 14.11. Found: C, 56.67; H, 6.45; N, 14.00.

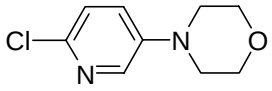


1-*N*-Boc-4-*N*-(6-chloro-5-methyl-pyridin-3-yl)-piperazine (**3b**): R_f=0.6. ^{1}H NMR (CD_3OD) δ 7.86 (d, *J*=3.0 Hz, 1H), 7.37 (d, *J*=3.2 Hz, 1H), 3.57 (t, *J*=5.1 Hz, 4H), 3.18 (t, *J* = 5.1 Hz, 4H), 2.35 (s, 3H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 154.3, 146.3, 142.2, 135.3, 132.0, 127.0, 80.1, 48.8, 28.4, 19.8. MS (DCI/NH_3) *m/z* 312 (M + H^+), 314 (M + H^+). Anal. Cacld. for $C_{15}H_{22}ClN_3O_2$: C, 57.78; H, 7.11; N, 13.48. Found: C, 58.11; H, 7.26; N, 13.26.

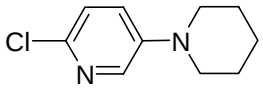


1-*N*-Boc-4-*N*-(5,6-dichloropyridin-3-yl)-piperazine (**3c**): R_f=0.7. ^{1}H NMR (CD_3OD) δ 8.01 (d, *J*=2.7 Hz, 1H), 7.57 (d, *J*=2.7 Hz, 1H), 3.57 (t, *J*=5.4 Hz, 4H), 3.24

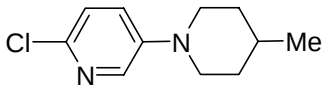
(t, *J* = 5.1 Hz, 4H), 1.50 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 154.4, 146.8, 138.6, 135.4, 130.2, 125.2, 80.3, 48.2, 28.4. MS (DCI/NH_3) *m/z* 332 ($M + H^+$), 334 ($M + H^+$), 336 ($M + H^+$). Anal. Cacld. for $C_{14}H_{19}Cl_2N_3O_2$: C, 50.61; H, 5.76; N, 12.34. Found: C, 50.41; H, 5.49; N, 12.38.



4-*N*-(6-Chloropyridin-3-yl)-morpholine (**3d**): R_f=0.4. ^{1}H NMR (CD_3OD) δ 8.00 (d, *J*=3.1 Hz, 1H), 7.43 (dd, *J*=8.8, 3.1 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 3.83 (t, *J*=4.8 Hz, 4H), 3.19 (t, *J* = 4.8 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 146.1, 141.6, 137.1, 125.4, 123.9, 66.5, 48.6. MS (DCI/NH_3) *m/z* 199 ($M + H^+$), 201 ($M + H^+$). Anal. Cacld. for $C_9H_{11}ClN_2O$: C, 54.42; H, 5.58; N, 13.93. Found: C, 54.45; H, 5.51; N, 13.93.

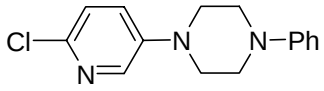


1-*N*-(6-Chloropyridin-3-yl)-piperidine (**3e**): R_f=0.8. ^{1}H NMR (CD_3OD) δ 7.96 (d, *J*=3.1 Hz, 1H), 7.38 (dd, *J*=8.8, 3.0 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 3.21(t, *J*=5.1 Hz, 4H), 1.58-1.80 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 146.8, 140.4, 137.6, 125.9, 123.7, 49.8, 25.4, 23.9. MS (DCI/NH_3) *m/z* 199 ($M + H^+$), 201 ($M + H^+$). Anal. Cacld. for $C_{10}H_{13}ClN_2$: C, 61.07; H, 6.66; N, 14.24. Found: C, 60.92; H, 6.84; N, 14.17.

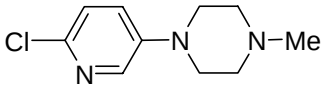


1-*N*-(6-Chloropyridin-3-yl)-4-methyl-piperidine (**3f**): R_f=0.8. ^{1}H NMR (CD_3OD) δ 7.97 (d, *J*=3.4 Hz, 1H), 7.39 (dd, *J*=8.8, 3.4 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 3.70(dt, *J*=12.5, 2.7 Hz, 2H), 2.74 (td, *J*=12.2, 2.7 Hz, 2H), 1.75 (dt, *J*=13.2, 2.4 Hz, 2H), 1.54 (m, 1H), 1.35 (dd, *J*=12.5, 4.1 Hz, 1H), 1.29 (dd, *J*=12.1, 4.1 Hz, 1H), 0.98 (d, *J*=6.8 Hz,

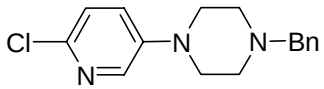
3H). ^{13}C NMR ($CDCl_3$) δ 146.5, 140.4, 137.6, 125.9, 123.7, 49.2, 33.6, 30.4, 21.7. MS (DCI/NH_3) *m/z* 213 (M + H^+), 215 (M + H^+). Anal. Cacld. for $C_{10}H_{15}ClN_2$: C, 61.07; H, 6.66; N, 14.24. Found: C, 60.92; H, 6.84; N, 14.17.



1-*N*-(6-Chloropyridin-3-yl)-4-*N*-phenyl-piperazine (**3g**): R_f=0.6. ^{1}H NMR (CD_3OD) δ 8.05 (d, *J*=3.1 Hz, 1H), 7.48 (dd, *J*=8.8, 3.0 Hz, 1H), 7.20-7.31 (m, 3H), 7.03 (d, *J*=8.1 Hz, 2H), 6.87 (t, *J*=7.4Hz, 1H), 3.30-3.50 (m, 8H). ^{13}C NMR (CD_3OD) δ 150.9, 146.0, 141.5, 137.6, 129.2, 125.9, 123.9, 120.5, 116.5, 49.2, 48.7. MS (DCI/NH_3) *m/z* 274 (M + H^+), 276 (M + H^+). Anal. Cacld. for $C_{15}H_{16}ClN_3$: C, 65.81; H, 5.89; N, 15.35. Found: C, 65.72; H, 5.85; N, 15.15.

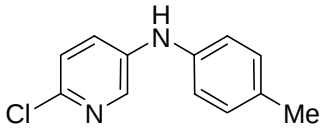


1-*N*-(6-Chloropyridin-3-yl)-4-*N*-Methyl-piperazine (**3h**): R_f=0.2. ^{1}H NMR (CD_3OD) δ 8.00 (d, *J*=3.0 Hz, 1H), 7.40 (dd, *J*=8.8, 3.4 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 3.27 (t, *J*=5.1 Hz, 4H), 2.61 (t, *J*=5.5 Hz, 4H), 2.35(S, 3H) ^{13}C NMR ($CDCl_3$) δ 146.0, 141.1, 137.3, 125.5, 123.8, 54.6, 48.4, 46.1. MS (DCI/NH_3) *m/z* 212 (M + H^+), 214 (M + H^+). Anal. Cacld. for $C_{10}H_{14}ClN_3$: C, 56.74; H, 6.67; N, 19.85. Found: C, 56.55; H, 6.69; N, 19.53.

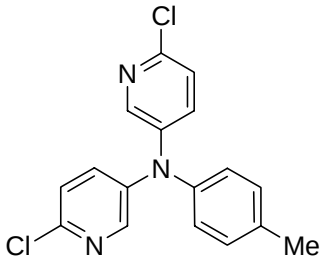


4-*N*-Benzyl-1-*N*-(6-chloropyridin-3-yl)-piperazine (**3i**): R_f=0.3. ^{1}H NMR (CD_3OD) δ 7.98 (d, *J*=3.1 Hz, 1H), 7.30-7.42 (m, 6H), 7.24 (d, *J* = 8.8 Hz, 1H), 3.58(s, 2H), 3.24 (t, *J*=5.1 Hz, 4H), 2.62 (t, *J*=5.4 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 146.1, 140.9,

137.7, 137.2, 129.0, 128.2, 127.2, 125.4, 123.7, 62.9, 52.5, 54.6, 48.4. MS (DCI/NH_3) *m/z* 288 ($M + H^+$), 290 ($M + H^+$). Anal. Cacld. for $C_{16}H_{18}ClN_3$: C, 66.78; H, 6.30; N, 14.60. Found: C, 66.68; H, 6.34; N, 14.52.

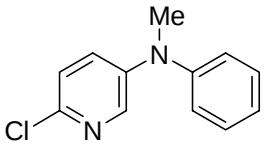


N-(6-Chloropyridin-3-yl)-4-methylaniline[1] (**3j**): R_f=0.5. ^{1}H NMR (CD_3OD) δ 7.87 (d, *J*=3.1 Hz, 1H), 7.28 (dd, *J*=8.9, 3.1 Hz, 1H), 7.06 (d, *J*=8.9 Hz, 1H), 6.98 (d, *J*=8.0 Hz, 2H), 6.89 (d, *J*=8.3 Hz, 2H), 2.10 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 142.7, 140.4, 140.3, 137.7, 133.1, 130.9, 126.3, 125.4, 120.6, 20.8. MS (DCI/NH_3) *m/z* 219 ($M + H^+$), 221 ($M + H^+$).

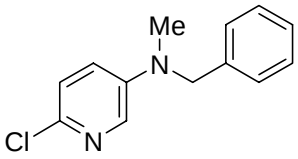


N, N-Bis(6-chloropyridin-3-yl)-4-methylaniline: R_f=0.7. ^{1}H NMR (CD_3OD) δ 8.01 (d, *J*=3.0 Hz, 2H), 7.48 (dd, *J*=8.6, 3.1 Hz, 2H), 7.32 (d, *J*=8.6 Hz, 2H), 7.23 (d, *J*=7.9 Hz, 4H), 7.05 (d, *J*=7.6 Hz, 4H), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 145.3, 144.7, 144.3, 143.9, 137.3, 134.2, 132.1, 126.9, 126.1, 21.0. MS (DCI/NH_3) *m/z* 330 ($M + H^+$), 332 ($M + H^+$), 334 ($M + H^+$). Anal. Cacld. for $C_{17}H_{13}Cl_2N_3$•HCl•H_2O: C, 53.08; H, 4.19; N, 10.92. Found: C, 53.32; H, 3.89; N, 10.73.

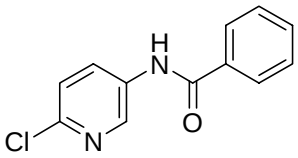
[1] Maes, B. U. W.; Loones, K. T. J.; Jonckers, T. H. M.; Lemière, G. L. F.; Dommisse, R. A.; Haemers, A. *Synlett* **2002**, 1995.



N-(6-Chloropyridin-3-yl)-*N*-methylaniline (**3k**): R_f=0.6. ^{1}H NMR (CD_3OD) δ 7.87 (d, *J*=3.0 Hz, 1H), 7.25 (m, 2H), 7.10 (dd, *J*=8.9, 3.1 Hz, 1H), 7.04 (m, 4H), 3.15 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 148.6, 146.2, 140.8, 137.9, 131.0, 127.6, 126.0, 125.4, 125.2, 40.5. MS (DCI/NH_3) *m/z* 219 (M + H^+), 221 (M + H^+). Anal. Cacld. for $C_{12}H_{11}ClN_2$•HCl: C, 56.49; H, 4.74; N, 10.98. Found: C, 56.35; H, 4.37; N, 10.86.



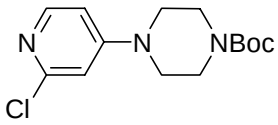
N-(6-Chloropyridin-3-yl)-*N*-methylbenzylamine (**3l**): R_f=0.6. ^{1}H NMR (CD_3OD) δ 7.64 (t, *J*=1.8 Hz, 1H), 7.18 (m, 2H), 7.10 (m, 4H), 7.02 (d, *J*=1.8 Hz, 1H), 4.40 (s, 2H), 2.96(s, 3H). ^{13}C NMR ($CDCl_3$) δ 149.0, 146.2, 139.0, 134.1, 129.7, 128.2, 127.7, 125.1, 123.9, 56.9, 39.1. MS (DCI/NH_3) *m/z* 233 (M + H^+), 235 (M + H^+). Anal. Cacld. for $C_{13}H_{13}ClN_2$: C, 67.10; H, 5.63; N, 12.04. Found: C, 66.92; H, 5.83; N, 11.98.



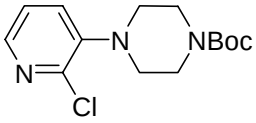
N-(6-Chloropyridin-3-yl)-benzamide[2] (**3m**): R_f=0.5. ^{1}H NMR (CD_3OD) δ 8.62 (d, *J*=2.7 Hz, 1H), 8.13 (dd, *J*=8.6, 2.2 Hz, 1H), 7.84 (d, *J*=7.4 Hz, 2H), 7.49 (t, *J*=7.4 Hz, 1H), 7.41 (t, *J*= 7.5 Hz, 2H), 7.33 (d, *J*=8.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 168.9, 146.5, 142.8, 136.6, 135.4, 133.3, 132.6, 129.7, 128.7, 125.4. MS (DCI/NH_3) *m/z* 233

[2] McNaughton-Smith, G.; Fritch, C.; Amato, G. S. U.S. Patent 0 049 444, 2001.

($M + H^+$), 235 ($M + H^+$). Anal. Cacld. for $C_{12}H_9ClN_2O$•HCl: C, 53.55; H, 3.75; N, 10.41. Found: C, 53.38; H, 3.47; N, 10.13.



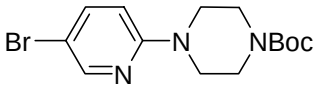
1-*N*-Boc-4-*N*-(2-chloropyridin-4-yl)-piperazine (**9**): R_f=0.5. ^{1}H NMR (CD_3OD) δ 7.92 (d, *J*=6.1 Hz, 1H), 6.86 (d, *J*=2.7 Hz, 1H), 6.80 (dd, *J*=6.5, 2.7 Hz, 1H), 3.50-3.57 (m, 4H), 3.40-3.45 (m, 4H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 156.3, 154.5, 152.8, 149.6, 107.5, 80.4, 45.8, 28.4. MS (DCI/NH_3) *m/z* 298 ($M + H^+$), 300 ($M + H^+$). Anal. Cacld. for $C_{14}H_{20}ClN_3O_2$: C, 56.47; H, 6.77; N, 14.11. Found: C, 56.31; H, 6.67; N, 13.83.



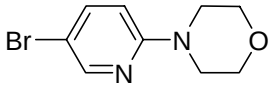
1-*N*-Boc-4-*N*-(2-chloropyridin-3-yl)-piperazine (**10**): R_f=0.6. ^{1}H NMR (CD_3OD)δ 8.03 (dd, *J*=4.4, 1.7 Hz, 1H), 7.57 (dd, *J*=7.9, 1.7 Hz, 1H), 7.34 (dd, *J*=8.1, 4.8 Hz, 1H), 3.60 (t, *J*=5.1 Hz, 4H), 3.03 (t, *J*=5.0 Hz , 4H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 154.7, 146.5, 145.8, 143.1, 128.2, 123.0, 80.0, 50.8, 28.4. MS (DCI/NH_3) *m/z* 298 ($M + H^+$), 300 ($M + H^+$). Anal. Cacld. for $C_{14}H_{20}ClN_3O_2$: C, 56.47; H, 6.77; N, 14.11. Found: C, 56.28; H, 6.82; N, 13.75.

General Procedure on Amination of 2,5-Dibromopyridine (1f): 2,5-Dibromopyridine (**1f**) (308.0 mg, 1.3 mmol, 1.3 equiv.) and corresponding cyclic amine **2** (see Table 3, 1.0 mmol, 1.0 equiv.) were combined in the reaction flask. Dry toluene (10 mL) was added, followed by ^{t}BuONa (144.0 mg, 1.5 mmol, 1.5 equiv.), $Pd_2(dba)_3$ (18.3

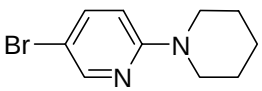
mg, 0.02 mmol, 0.02 equiv.) and Xantphos (34.7 mg, 0.06 mmol, 0.06 equiv.). The mixture was evacuated and purged with N_2 (3 cycles), then heated to 95-100 °C under N_2 for 3 hours. The reaction was monitored by HPLC analysis. After the reaction was completed, it was cooled down to room temperature and diluted with EtOAc (20 mL). It was then washed with water (5 mL). The organic solution was concentrated under reduced pressure. The residue was purified by chromatography on silica gel using hexane/EtOAc (v. 80/20) for **4a**-**4e** and CH_2Cl_2/MeOH(with v. 2% $NH_3 \cdot H_2O$) (v. 90/10) for **4f** and **4g**.



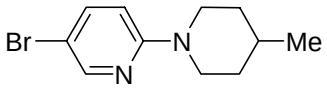
1-*N*-Boc-4-*N*-(5-bromopyridin-2-yl)-piperazine (**4a**): R_f=0.5. ^{1}H NMR (CD_3OD) δ 8.12 (d, *J*=2.7 Hz, 1H), 7.64 (dd, *J*=8.8, 2.4 Hz, 1H), 6.77 (d, *J* = 8.9 Hz, 1H), 3.52 (m, 8H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 159.7, 159.3, 149.2, 141.2, 110.3, 108.8, 81.4, 46.1, 28.7. MS (DCI/NH_3) *m/z* 342 ($M + H^+$), 344 ($M + H^+$). Anal. Cacld. for $C_{14}H_{20}BrN_3O_2$: C, 49.13; H, 5.89; N, 12.28. Found: C, 49.41; H, 5.73; N, 12.12.



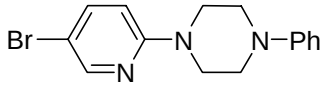
4-*N*-(5-Bromopyridin-2-yl)-morpholine (**4b**): R_f=0.4. ^{1}H NMR (CD_3OD) δ 8.13 (d, *J*=2.8 Hz, 1H), 7.64 (dd, *J*=8.8, 2.4 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 3.77 (t, *J*=5.0 Hz, 4H), 3.45 (t, *J* = 4.7 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 158.1, 148.5, 139.8, 108.2, 66.6, 45.5. MS (DCI/NH_3) *m/z* 243 ($M + H^+$), 245 ($M + H^+$). Anal. Cacld. for $C_9H_{11}BrN_2O$: C, 44.47; H, 4.56; N, 11.52. Found: C, 44.58; H, 4.56; N, 11.39.



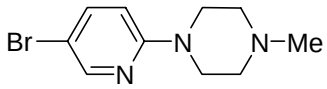
1-*N*-(5-Bromopyridin-2-yl)-piperidine (**4c**): R_f=0.8. ^{1}H NMR (CD_3OD) δ 8.06 (d, *J*=2.4 Hz, 1H), 7.56 (dd, *J*=9.1, 2.4 Hz, 1H), 6.73 (d, *J* = 9.2 Hz, 1H), 3.50 (t, *J*=4.8 Hz, 4H), 1.58-1.80 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 148.4, 139.5, 128.1, 108.4, 106.5, 46.3, 28.5, 25.4, 24.6. MS (DCI/NH_3) *m/z* 241 (M + H^+), 243 (M + H^+). Anal. Cacld. for $C_{10}H_{13}BrN_2$: C, 49.81; H, 5.43; N, 11.62. Found: C, 49.99; H, 5.22; N, 11.64.



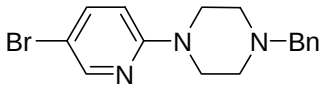
1-*N*-(5-Bromopyridin-2-yl)-4-methyl-piperidine (**4d**): R_f=0.8. ^{1}H NMR (CD_3OD) δ 8.05 (d, *J*=2.7 Hz, 1H), 7.56 (dd, *J*=9.2, 2.7 Hz, 1H), 6.74 (d, *J* = 9.1 Hz, 1H), 4.20 (dt, *J*=13.2, 2.3 Hz, 2H), 2.82 (td, *J*=13.2, 2.7 Hz, 2H), 1.54-17.75 (m, 3H), 1.22 (dd, *J*=12.8, 3.8 Hz, 1H), 1.13 (dd, *J*=12.7, 3.4 Hz, 1H), 0.96 (d, *J*=6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 148.4, 139.5, 128.1, 108.4, 106.6, 45.7, 33.6, 31.1, 28.5, 21.9. MS (DCI/NH_3) *m/z* 255 (M + H^+), 257 (M + H^+). Anal. Cacld. for $C_{10}H_{15}BrN_2$: C, 51.78; H, 5.93; N, 10.98. Found: C, 51.46; H, 5.92; N, 10.61.



1-*N*-(5-Bromopyridin-2-yl)-4-*N*-phenyl-piperazine (**4e**): R_f=0.6. ^{1}H NMR (CD_3OD) δ 8.14 (d, *J*=2.7 Hz, 1H), 7.64 (dd, *J*=9.2, 2.7 Hz, 1H), 7.25 (m, 2H), 7.01 (d, *J*=8.2 Hz, 2H), 6.86 (t, *J*=7.1Hz, 1H), 6.82 (d, *J*=8.8 Hz, 1H), 3.67 (t, *J*=5.1 Hz, 4H), 3.25 (t, *J*=5.5Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 157.8, 151.1, 148.5, 139.7, 129.2, 120.1, 116.4, 108.4, 107.9, 49.0, 45.2. MS (DCI/NH_3) *m/z* 318 (M + H^+), 320 (M + H^+). Anal. Cacld. for $C_{15}H_{16}BrN_3$: C, 56.62; H, 5.07; N, 13.21. Found: C, 56.39; H, 5.07; N, 12.88.



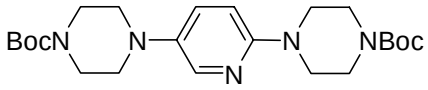
1-*N*-(5-Bromopyridin-3-yl)-4-*N*-methyl-piperazine (**4f**): R_f=0.3. ^{1}H NMR (CD_3OD) δ 8.12 (d, *J*=2.4 Hz, 1H), 7.62 (dd, *J*=9.1, 2.4 Hz, 1H), 6.76 (d, *J* = 9.1 Hz, 1H), 3.54(t, *J*=5.4 Hz, 4H), 2.54 (t, *J*=5.1 Hz, 4H), 2.34 (S, 3H) ^{13}C NMR ($CDCl_3$) δ 157.9, 148.5, 140.0, 108.4, 107.7, 54.7, 46.1, 45.1. MS (DCI/NH_3) *m/z* 256 (M + H^+), 258 (M + H^+). Anal. Cacld. for $C_{10}H_{14}BrN_3$: C, 46.89; H, 5.51; N, 16.41. Found: C, 46.92; H, 5.35; N, 15.87.



4-*N*-Benzyl-1-*N*-(5-bromopyridin-2-yl)-piperazine (**4g**): R_f=0.3. ^{1}HNMR (CD_3OD) δ 8.11 (d, *J*=2.4 Hz, 1H), 7.60 (dd, *J*=9.1, 2.7 Hz, 1H), 7.26-7.37 (m, 5H), 6.73 (d, *J* = 9.2 Hz, 1H), 3.57 (s, 2H), 3.51 (t, *J*=5.5 Hz, 4H), 2.55 (t, *J*=5.1 Hz, 4H). ^{13}CNMR ($CDCl_3$) δ 158.0, 148.5, 139.6, 137.9, 129.2, 128.3, 127.2, 108.3, 107.5, 63.1, 52.7, 45.2. MS (DCI/NH_3) *m/z* 332 (M + H^+), 334 (M + H^+). Anal. Cacld. for $C_{16}H_{18}BrN_3$: C, 57.84; H, 5.46; N, 12.65. Found: C, 58.17; H, 5.54; N, 12.56.

Procedure for Diamination of 5-Bromo-2-chloropyridine (1a): Under N_2, 5-bromo-2-chloropyridine (**1a**) (192.4 mg, 1 mmol, 1.0 equiv.) and 1-*N*-Boc piperazine (**2a**) (465.8mg, 2.5 mmol, 2.5 equiv.) were combined in the reaction flask. Dry toluene (10 mL) was added, followed by ^{t}BuONa (240 mg, 2.5 mmol, 2.5 equiv.), $Pd_2(dba)_3$ (18.3 mg, 0.02 mmol, 0.02 equiv.) and Xantphos (34.7 mg, 0.06 mmol, 0.06 equiv.). The mixture was evacuated and purged with N_2 (3 cycles), then heated to 95-100 °C under N_2 for 3 hours. The reaction was monitored by HPLC analysis. After the reaction went to completion, it was cooled down to room temperature and diluted with EtOAc (20 mL). It was then washed with water (5 mL). The organic solution was concentrated under

reduced pressure. The residue was purified by chromatography on silica gel using hexane/EtOAc (v. 50/50).



2,5-Di-(1-*N*-Boc-4-piperazinyl)-pyridine (**5a**): R_f=0.3. ^{1}H NMR (CD_3OD) δ 7.86 (d, *J*=2.3 Hz, 1H), 7.38 (dd, *J*=9.1, 3.0 Hz, 1H), 6.83 (d, *J* =9.5 Hz, 1H), 3.54 (m, 8H), 3.37 (m, 4H), 3.00 (t, *J*=5.1 Hz, 4H), 1.32 (s, 18H). ^{13}C NMR ($CDCl_3$) δ 154.8, 154.6, 140.3, 137.5, 128.7, 108.1, 79.9, 50.7, 46.1, 28.4. MS (DCI/NH_3) *m/z*, 448 ($M + H^+$). Anal. Cacld. for $C_{23}H_{37}N_5O_4$: C, 61.72; H, 8.33; N, 14.30. Found: C, 61.83; H, 8.20; N, 14.40.