Chemoselectivity in the Cu-catalyzed O-Arylation of Phenols and Aliphatic Alcohols

Debabrata Maiti

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA

dmaiti@chem.iitb.ac.in

Supporting Information

General Reagent Information

All reactions were carried out under an argon atmosphere. Dimethylsulfoxide (DMSO) and dimethylformamide (DMF) were purchased from Aldrich Chemical Co. in Sure-Seal bottles and were used as received. Copper(I) iodide (98%) was purchased from Strem. Powdered K_3PO_4 was purchased from Riedel-de Haën. Both sodium *tert*-butoxide (NaO*t*-Bu) and potassium carbonate were purchased from Aldrich Chemical Co. *Anhydrous finely powdered* Cs_2CO_3 was a generous gift from Chemetall. The bulk of the base was stored under nitrogen in a Vacuum Atmospheres glovebox. Small portions (~2 g) were removed from the glovebox in glass vials, stored in the air in a desiccator filled with anhydrous calcium sulfate, and weighed in the air. Alcohols were purchased from commercial sources and used without further purification. Aryl iodides were purchased from commercial sources and, when necessary, filtered through neutral alumina or distilled prior to use. Flash column chromatography was performed using a Biotage SP4 Flash Purification System using KP-Sil silica cartridges. In all cases, dichloromethane was used to transfer the crude reaction material onto the silica gel samplet. A gradient elution using hexane and ethyl acetate was performed, based on the recommendation from the Biotage TLC Wizard.

General Analytical Information. All compounds were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy. Copies of the ^{1}H NMR, ^{13}C NMR can be found at the end of the Supporting Information. Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz instrument. All ^{1}H NMR experiments are reported in units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm) in the deuterated solvent, unless otherwise stated. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), unless otherwise stated, and all were obtained

with ^{1}H decoupling. All IR spectra was taken on a Perkin – Elmer 2000 FTIR. All GC analyses were performed on a Agilent 6890 gas chromatograph with an FID detector using a J & W DB-1 column (10 m, 0.1 mm I.D.). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA 30091.

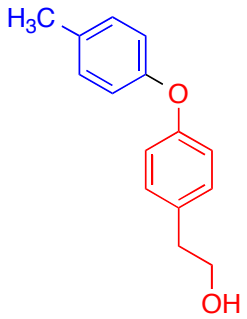
Experimental Procedure.

General procedure A for the Cu-catalyzed C-O bond formation between Phenol (ArOH) and Aryl Iodide

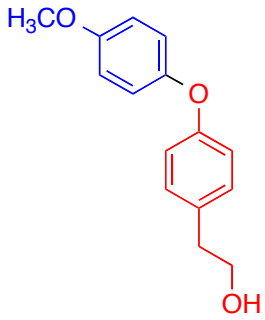
An oven-dried screw cap test tube was charged with a magnetic stir-bar, copper(I) iodide (9.5 mg, 0.05 mmol, 5 mol%), picolinic acid, **1** (12.3 mg, 0.1 mmol, 10 mol%), aryl iodide (if solid; 1 mmol), alkyl aryl diols (if solid; 1.2 mmol) and K_3PO_4 (424 mg, 2 mmol). The tube was then evacuated and back-filled with argon. The evacuation/backfill sequence was repeated two additional times. Under a counterflow of argon, remaining liquid reagents were added, followed by dimethylsulfoxide (2 mL) by syringe. The tube was placed in a preheated oil bath at 80 ºC and the reaction mixture was stirred vigorously for 21 h. The reaction mixture was cooled to room temperature. Dichloromethane (10 mL) and H_2O (1 mL) were added and the mixture was stirred. The organic layer was separated and the aqueous layer was extracted twice more with dichloromethane (10 mL). Combined organic layer was dried over Na_2SO_4 and filtered through the pad of silica gel. The filtrate was concentrated and the resulting residue was purified via the Biotage SP4 (silica- packed SNAP cartridge, KP-Sil, 10 g) using hexane: ethyl acetate (3:1).

General procedure B for the Cu-catalyzed C-O bond formation between Aliphatic Alcohols (ArOH) and Aryl Iodide

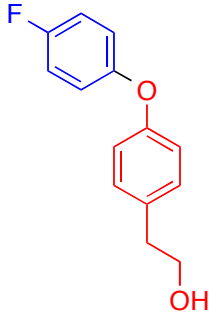
An oven-dried screw cap test tube was charged with a magnetic stir-bar, copper(I) iodide (19 mg, 0.1 mmol, 10 mol%), aryl iodide (if solid; 1 mmol), alkyl aryl diols (if solid; 1.1 mmol) and NaO*t*-Bu (212 mg, 2.2 mmol). The tube was then evacuated and back-filled with argon. The evacuation/backfill sequence was repeated two additional times. Under a counterflow of argon, remaining liquid reagents were added, followed by DMF (1.5 mL) by syringe. The tube was placed in a preheated oil bath at 70 ºC and the reaction mixture was stirred vigorously for 21 h. The reaction mixture was cooled to room temperature. Dichloromethane (10 mL) and H_2O (1 mL) were added and the mixture was stirred. The organic layer was separated and the aqueous layer was extracted twice more with dichloromethane (10 mL). Combined organic layer was dried over Na_2SO_4 and filtered through the pad of silica gel. The filtrate was concentrated and the resulting residue was purified via the Biotage SP4 (silica- packed SNAP cartridge, KP-Sil, 10 g) using hexane: ethyl acetate (3:1).



2-(4-(*p*-tolyloxy)phenyl)ethanol (Table 1, entry 1). The general procedure A was followed. Isolation and biotage purification afforded the title compound as a white solid (194 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17-7.11 (m, 4H), 6.92 (m, 4H), 3.81 (t, 2H, J = 8), 2.81 (t, 2H, J = 8), 2.33 (s, 3H), 2.13 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.6, 155.1, 133.2, 133.1, 130.5, 130.4, 119,2, 118.7, 63.9, 38.6, 20.9. IR (KBr disc, cm^{-1}): 3297, 2934, 1508, 1264, 1198, 1105, 1057, 818. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.69; H, 6.96. m.p. 35 ºC.

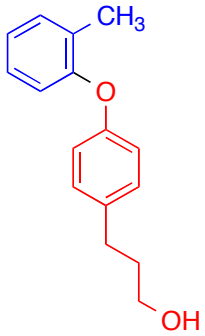


2-(4-(4-methoxyphenoxy)phenyl)ethanol (Table 1, entry 2). The general procedure A was followed. Isolation and biotage purification afforded the title compound as a white solid (220 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (d, 2H, J = 8), 6.95 (d, 2H, J = 8), 6.86 (t, 4H, J = 8), 3.81 (t, 2H, J = 6), 3.77 (s, 3H), 2.81 (t, 2H, J = 8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.1, 155.8, 150.2, 132.4, 130.2, 120.7, 117.8, 114.8, 63.7, 55.68, 38.38. IR (KBr disc, cm^{-1}): 3302, 2930, 1653, 1559, 1508, 1456, 1384, 1032, 840, 698. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.82; H, 6.78. m.p. 58-61 ºC.

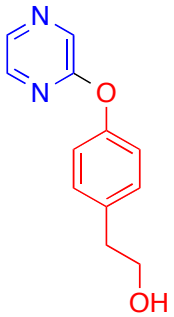


2-(4-(4-fluorophenoxy)phenyl)ethanol (Table 1, entry 3). The general procedure A was followed. Isolation and biotage purification afforded the title compound as a colorless liquid (183 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15 (d, 2H, J = 8),

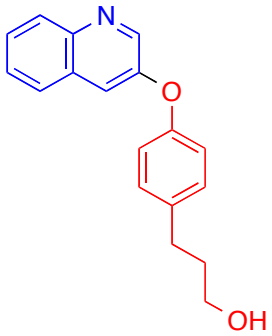
7.01-6.85 (m, 6H), 3.81 (t, 2H, J = 4), 2.79 (t, 2H, J = 12), 1.72 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.9, 157.6, 156.3, 153.1, 133.3, 130.3, 120.4, 120.3, 118.5, 116.4, 116.2, 63.7, 38.4. IR (KBr disc, cm^{-1}): 3359, 2931, 1653, 1615, 1558, 1496, 1249, 1211, 1191, 1045. Anal. Calcd for $C_{14}H_{13}FO_2$: C, 72.40; H, 5.64. Found: C, 71.98; H, 5.60.



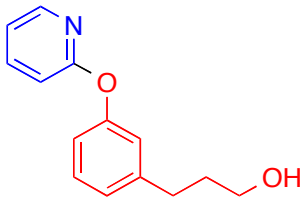
3-(4-(*o*-tolyloxy)phenyl)propan-1-ol (Table 1, entry 4). The general procedure A was followed with copper(I) iodide (19 mg, 0.1 mmol, 10 mol%), picolinic acid, **1** (24.6 mg, 0.2 mmol, 20 mol%) at 120 ºC. Isolation and biotage purification afforded the title compound as a colorless liquid (210 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (d, 1H, J = 8), 7.17-6.84 (m, 7H), 3.67 (t, 2H, J = 4), 2.69 (t, 2H, J = 8), 2.26 (s, 3H), 2.16 (s, 1H), 1.87 (pent, 2H, J = 5.6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.9, 154.8, 135.9, 131.4, 129.8, 129.6, 127.8, 127.2, 123.8, 119.9, 119.4, 117.6, 117.3, 62.1, 34.4, 31.3, 16.3. IR (KBr disc, cm^{-1}): 3343, 3029, 2938, 2863, 1890, 1604, 1585, 1506, 1489, 1457, 1379, 1238, 1210, 1183, 1167, 1112, 1042, 1014, 913, 876, 841, 815, 777, 753. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.10; H,7.58.



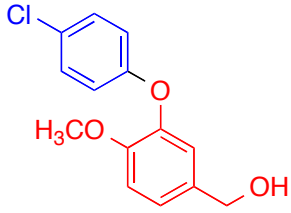
2-(4-(pyrazin-2-yloxy)phenyl)ethanol (Table 1, entry 5). The general procedure A was followed. Isolation and biotage purification afforded the title compound as a white solid (179 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (d, 1H), 8.21 (d, 1H, J = 4), 8.06-8.03 (m, 1H), 7.26 (d, 2H, J = 8), 7.07 (d, 2H, J = 8), 3.85 (q, 2H, J = 8), 2.85 (t, 2H, J = 4), 1.75 (t, 1H, J = 4). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.4, 151.7, 141.2, 138.5, 136.1, 136.1, 130.6, 121.5, 63.7, 38.8. IR (KBr disc, cm^{-1}): 3317, 2943, 1531, 1509, 1465, 1405, 1288, 1179, 1149, 1106, 1047, 1006, 886, 850. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59. Found: C, 66.51; H, 5.53. m.p. 75 ºC



3-(4-(quinolin-3-yloxy)phenyl)propan-1-ol (Table 1, entry 6). The general procedure A was followed with copper(I) iodide (19 mg, 0.1 mmol, 10 mol%), picolinic acid, **1** (24.6 mg, 0.2 mmol, 20 mol%), aryl bromide (1 mmol) at 110 ºC. Isolation and biotage purification afforded the title compound as a colorless liquid (190 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, 1H, J = 8), 7.63-7.44 (m, 4H), 7.20 (d, 2H, J = 8), 6.99 (d, 2H, J = 12), 3.67 (t, 2H, J = 4), 2.69 (t, 2H, J = 8), 2.26 (s, 1H), 1.87 (pent, 2H, J = 5.6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.1, 151.5, 145.1, 144.4, 138.2, 130.1, 129.4, 129.1, 128.6, 128.1, 127.8, 127.4, 127.3, 127.1, 120.4, 119.7, 119.4, 119.3, 61.9, 34.33, 31.4. IR (KBr disc, cm^{-1}): 3339, 2937, 1598, 1505, 1464, 1424, 1342, 1273, 1226, 1170, 1139, 1058, 1016, 985, 911, 850, 782, 752. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13. Found: C, 77.44; H, 6.05.

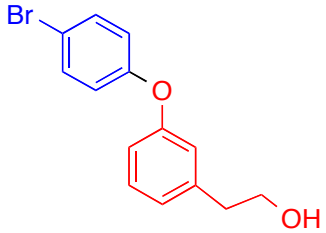


3-(3-(pyridin-2-yloxy)phenyl)propan-1-ol (Table 1, entry 7). The general procedure A was followed at 90 ºC. Isolation and biotage purification afforded the title compound as a colorless liquid (199 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (d, 1H, J = 8), 7.61 (t, 1H, J = 10), 7.24 (t, 1H, J = 8), 6.88-6.99 (m, 4H), 6.81 (d, 1H, J = 8), 3.58 (t, 2H, J = 4), 2.64 (s, 1H), 2.64 (t, 2H, J = 8), 2.26 (s, 1H), 1.87 (pent, 2H, J = 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 154.2, 147.2, 144.1, 143.5, 139.6, 129.6, 124.9, 121.1, 118.5, 118.4, 111.5, 61.8, 33.9, 31.9. IR (KBr disc, cm^{-1}): 3362, 2939, 2864, 1587, 1571, 1486, 1468, 1428, 1267, 1247, 1143, 1056, 992, 958, 840, 778, 696.

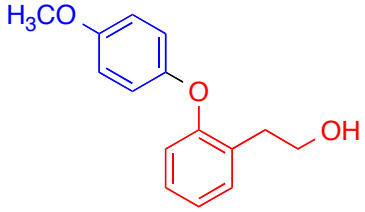


(3-(4-chlorophenoxy)-4-methoxyphenyl)methanol (Table 1, entry 8). The general procedure A was followed with copper(I) iodide (19 mg, 0.1 mmol, 10 mol%), picolinic acid, **1** (24.6 mg, 0.2 mmol, 20 mol%) at 90 ºC. Isolation and biotage purification afforded the title compound as a white solid (169 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19-7.23 (m, 2H), 7.08 (d, 1H, J = 8), 6.82-6.95 (m, 4H), 4.54 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.8, 144.6, 134.1, 129.5, 127.5, 123.8, 119.9, 118.4, 112.7, 64.6, 56.1. IR (KBr disc, cm^{-1}): 3344, 1580, 1511, 1485, 1425, 1268, 1224,

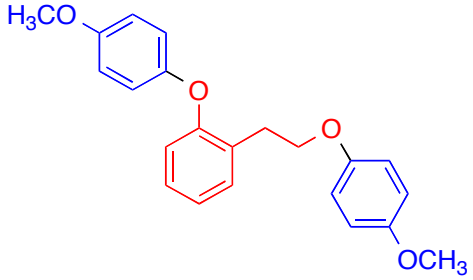
1123, 1091, 1026, 825. Anal. Calcd for $C_{14}H_{13}ClO_3$: C, 63.52; H, 4.95. Found: C, 63.24; H, 4.90. m.p. 75 ºC.



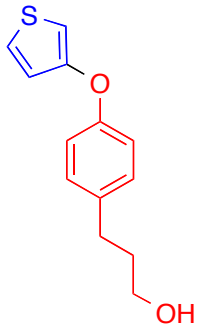
2-(3-(4-bromophenoxy)phenyl)ethanol (Table 1, entry 9). The general procedure A was followed with copper(I) iodide (19 mg, 0.1 mmol, 10 mol%), picolinic acid, **1** (24.6 mg, 0.2 mmol, 20 mol%) at 90 ºC. Isolation and biotage purification afforded the title compound as brown liquid (213 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, 2H, J = 8), 7.26 (d, 1H, J = 8), 6.97 (d, 1H, J = 8), 6.82-6.68 (m, 4H), 3.78 (t, 2H, J = 6), 2.79 (t, 2H, J = 6), 1.98 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.3, 156.9, 156.8, 156.4, 140.9, 138.7, 132.7, 129.9, 124.5, 124.4, 120.9, 120.6, 119.7, 119.6, 117.1, 116.9, 115.7, 86.1, 63.4, 39.1. IR (KBr disc, cm^{-1}): 3347, 2945, 2876, 1608, 1576, 1481, 1446, 1248, 1216, 1165, 1141, 1068, 1045, 1008, 948, 908, 825, 785, 694.



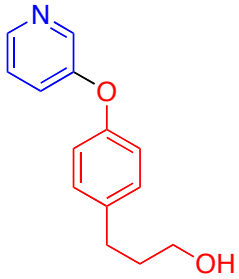
2-(2-(4-methoxyphenoxy)phenyl)ethanol (Table 1, entry 10). The general procedure A was followed. Isolation and biotage purification afforded the title compound as a colorless liquid (159 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.02-7.26 (m, 3H), 6.74-7.01 (m, 5H), 3.87 (m, 2H), 3.77 (s, 3H), 2.94 (t, 2H, J = 8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.4, 155.8, 150.8, 131.6, 129.2, 128.1, 123.2, 120.1, 117.8, 115.1, 62.9, 55.8, 34.2. IR (KBr disc, cm^{-1}): 3360, 2952, 1585, 1505, 1488, 1453, 1228, 1204, 1179, 1105, 1038, 882, 841, 756. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.68; H, 6.57.



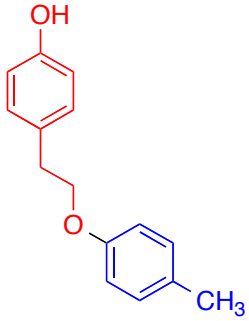
1-(4-methoxyphenoxy)-2-(2-(4-methoxyphenoxy)ethyl)benzene. Light-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, 1H, J = 8). 7.15 (t, 1H, J = 8), 7.04 (t, 1H, J = 8), 6.77-6.93 (m, 9H), 4.17 (t, 2H, J = 8), 3.79 (s, 3H), 3.74 (s, 3H), 3.15 (t, 2H, J = 6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.2, 155.6, 153.7, 152.9, 150.7, 131.4, 128.7, 127.9, 123.1, 119.9, 117.7, 115.5, 114,9, 114.6, 68.1, 55.7, 55.7, 30.5, 30.4. IR (KBr disc, cm^{-1}): 1506, 1228, 1038, 826. Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.3. Found: C, 75.68; H, 6.36.



3-(4-(thiophen-3-yloxy)phenyl)propan-1-ol (Table 1, entry 11). The general procedure A was followed with copper(I) iodide (19 mg, 0.1 mmol, 10 mol%), picolinic acid, **1** (24.6 mg, 0.2 mmol, 20 mol%) at 120 ºC. Isolation and biotage purification afforded the title compound as light-yellow liquid (110 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20-7.23 (m, 1H), 7.12 (d, 2H, J = 8), 6.95 (d, 2H, J = 8), 6.82 (dd, 1H), 6.52 (dd, 1H), 3.65 (t, 2H, J = 8), 2.66 (t, 2H, J = 8), 1.83-1.87 (m, 2H), 1.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.1, 154.8, 136.8, 129.6, 125.1, 120.7, 118.1, 106.2, 62.2, 34.3, 31.3. IR (KBr disc, cm^{-1}): 3346, 3112, 2938, 1609, 1536, 1504, 1390, 1235, 1211, 1169, 1067, 956, 817, 762. Anal. Calcd for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.02. Found: C, 66.34; H, 6.17.

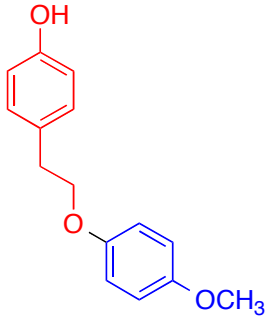


3-(4-(pyridin-3-yloxy)phenyl)propan-1-ol (Table 1, entry 12). The general procedure A was followed. Isolation and biotage purification afforded the title compound as a colorless liquid (220 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (t, 1H, J = 8), 7.23 (d, 1H, J = 8), 7.19-6.92 (m, 6H), 3.67 (t, 2H, J = 6), 2.67 (t, 2H, J = 8), 1.91-1.84 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.43, 154.0, 143.7, 140.7, 138.1, 129.9, 125.1, 124.2, 119.2, 61.7, 34.4, 31.4.

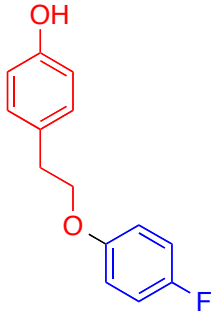


4-(2-(*p*-tolyloxy)ethyl)phenol (Table 2, entry 1). The general procedure B was followed. Isolation and biotage purification afforded the title compound as a brown liquid (192 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15 (d, 2H, J = 8), 7.11 (d, 2H, J = 8), 6.85 (d, 2H, J = 8), 6.79 (d, 2H, J =8), 5.55-5.59 (br, 1H), 4.14 (t, 2H, J = 6), 3.03 (t,

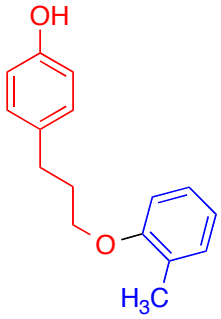
2H, J = 6), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.8, 154.3, 130.63, 130.5, 130.4, 130.3, 130.2, 115.6, 115.6, 115.6, 114.8, 69.4, 35.1, 20.7. IR (KBr disc, cm^{-1}): 3384, 2922, 1653, 1615, 1507, 1472, 1386, 1234, 1108, 1030, 819, 735.



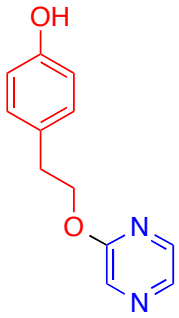
4-(2-(4-methoxyphenoxy)ethyl)phenol (Table 2, entry 2). The general procedure B was followed. Isolation and biotage purification afforded the title compound as a white solid (234 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (d, 2H, J = 8), 6.83-6.75 (m, 6H), 5.92 (s, 1H), 4.09 (t, 2H, J = 8), 3.80 (s, 3H), 2.98 (t, 2H, J = 8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154,4, 153.7, 152.9, 130.2, 130.1, 115.7, 115.4, 114.7, 69.8, 55.8, 35.0. IR (KBr disc, cm^{-1}): 3410, 2918, 2861, 1653, 1614, 1600, 1513, 1467, 1344, 1244, 1106, 1067, 1027, 822, 740. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.75; H, 6.44. m.p. 58-61 ºC.



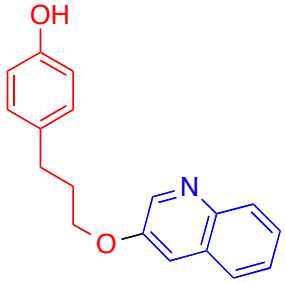
4-(2-(4-fluorophenoxy)ethyl)phenol (Table 2, entry 3). The general procedure B was followed. Isolation and biotage purification afforded the title compound as a colorless liquid (186 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.12 (d, 2H, J = 8), 6.93 (t, 2H, J = 8), 6.83-6.75 (M, 4H), 4.07 (t, 2H, J = 6), 2.99 (t, 2H, J = 8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.5, 156.1, 154.9, 154.8, 154.2, 130.3, 130.2, 115.9, 115.7, 115.6, 115.5, 115.4, 69.6, 36.9. IR (KBr disc, cm^{-1}): 3385, 2936, 1614, 1506, 1472, 1385, 1245, 1216, 1097, 1028, 827, 739.



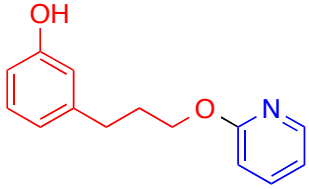
4-(3-(*o*-tolyloxy)propyl)phenol (Table 2, entry 4). The general procedure B was followed. Isolation and biotage purification afforded the title compound as an off-white solid (191 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (d, 2H, J = 4), 7.11 (d, 2H, J = 8), 6.94 (t, 1H, J = 4), 6.83 (d, 1H, J = 8), 6.79 (d, 2H, J = 8), 5.62 (s, 1H), 4.02 (t, 2H, J = 8), 2.81 (t, 2H, J = 8), 2.34 (s, 3H), 2.13 (pent, 2H, J = 8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.1, 153.6, 133.9, 130.8, 129.8, 126.9, 126.9, 120.4, 115.4, 111.2, 66.9, 31.4, 31.3, 16.4. IR (KBr disc, cm^{-1}): 3364, 3023, 2945, 1599, 1514, 1495, 1461, 1386, 1308, 1288, 1245, 1121, 1048, 946, 828, 751, 713. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.16; H,7.51. m.p. 53 ºC.



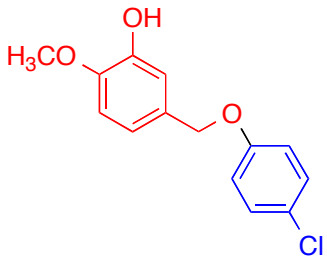
4-(2-(pyrazin-2-yloxy)ethyl)phenol (Table 2, entry 5). The general procedure B was followed. Isolation and biotage purification afforded the title compound as a white solid (159 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (s, 1H), 8.1 (s, 2H), 7.11 (d, 2H, J = 8), 6.77 (m, 3H), 4.48 (t, 2H, J = 6), 2.99 (t, 2H, J = 8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.4, 154.8, 140.9, 135.7, 130.2, 129.7, 115.5, 67.3, 34.4. IR (KBr disc, cm^{-1}): 3157, 1614, 1592, 1536, 1479, 1417, 1381, 1299, 1240, 1194, 1152, 1067, 1008, 992. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59. Found: C, 66.38; H, 5.53. m.p. 114 ºC.



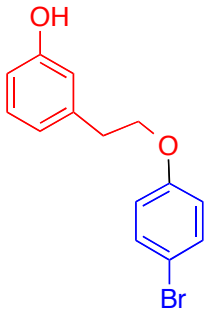
4-(3-(quinolin-3-yloxy)propyl)phenol (Table 2, entry 6). The general procedure B was followed. Isolation and biotage purification afforded the title compound as a white solid (220 mg, 79%). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 9.3 (s, 1H), 8.7 (s, 1H), 8.01 (d, 1H, J = 8) 7.88 (d, 1H, J = 8), 7.71 (s, 1H), 7.57-7.62 (m, 2H), 7.07 (d, 2H, J = 8), 6.74 (d, 2H, J = 8), 4.13 (t, 2H, J = 6), 2.72 (t, 2H, J = 8), 2.11 (pent, 2H, J = 5.6). ^{13}C NMR (100 MHz, d_6-DMSO) δ: 160.8, 157.5, 149.6, 148.2, 136.6, 134.6, 134.1, 133.9, 132.4, 132.4, 132.3, 131.9, 120.5, 118.5, 72.5, 35.9, 35.8. IR (KBr disc, cm^{-1}): 3385, 2360, 2257, 2130, 1653, 1517, 1230, 1025. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13. Found: C, 77.12; H, 5.99. m.p. 164 ºC.



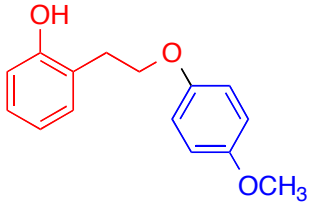
3-(3-(pyridin-2-yloxy)propyl)phenol (Table 2, entry 7). The general procedure A was followed at 90 ºC. Isolation and biotage purification afforded the title compound as a colorless liquid (206 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (dd, 1H, J = 8 and 4), 7.74 (s, 1H), 7.61 (dt, 1H, J = 8 and 4), 7.08 (t, 1H, J = 8), 6.86 (dt, 1H, J = J = 8 and 4) 6.66-6.82 (m, 4H), 4.24 (t, 2H, J = 4), 2.67 (t, 2H, J = 8), 2.06 (pent, 2H, J = 8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1, 156.6, 146.8, 143.6, 139.3, 129.7, 120.6, 117.1, 115.8, 113.3, 111.3, 65.8, 56.8, 32.3, 30.7. IR (KBr disc, cm^{-1}): 3010, 1600, 1550, 1500, 1480, 1305.



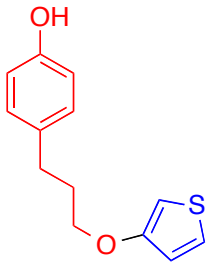
5-((4-chlorophenoxy)methyl)-2-methoxyphenol (Table 2, entry 8). The general procedure B was followed at 110 ºC. Isolation and biotage purification afforded the title compound as a white solid (166 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (d, 2H, J = 8), 7.08 (d, 1H, J = 8), 6.82-6.95 (m, 5H), 5.68 (s, 1H), 4.90 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.3, 146.5, 145.7, 129.8, 129.3, 125.7, 119.5, 116.2, 114.1, 110.6, 70.1, 56.1. IR (KBr disc, cm^{-1}): 3535, 1593, 1514, 1492, 1442, 1384, 1281, 1240, 1172, 1132, 1000, 882, 834, 797, 762, 672. Anal. Calcd for $C_{14}H_{13}ClO_3$: C, 63.52; H, 4.95;. Found: C, 63.47; H, 4.97. m.p. 95 ºC.



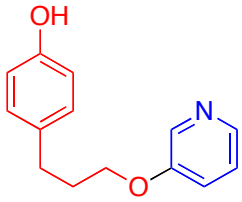
3-(2-(4-bromophenoxy)ethyl)phenol (Table 2, entry 9). The general procedure B was followed. Isolation and biotage purification afforded the title compound as a brown solid (202 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, 2H, J = 8), 7.16 (t, 1H, J = 8), 6.67-6.91 (m, 5H), 4.83 (s, 1H), 4.15 (t, 2H, J = 6), 3.02 (t, 2H, J = 6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8, 155.6, 139.9, 132.3, 129.8, 121.5, 116.4, 115.9, 113.5, 112.9, 68.7, 35.5. IR (KBr disc, cm^{-1}): 3367, 1653, 1589, 1558, 1540, 1488, 1241, 1156, 1029, 821. Anal. Calcd for $C_{14}H_{13}BrO_2$: C, 57.36; H, 4.47. Found: C, 57.46; H, 4.47. m.p. 70 ºC.



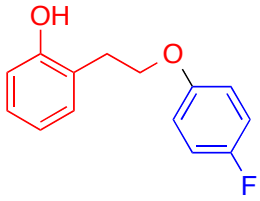
2-(2-(4-methoxyphenoxy)ethyl)phenol (Table 2, entry 10). The general procedure B was followed. Isolation and biotage purification afforded the title compound as a white solid (171 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.10-7.21 (m, 2H), 6.74-7.01 (m, 6H), 4.19 (t, 2H, J = 8), 3.74 (s, 3H), 3.08 (t, 2H, J = 6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.2, 154.5, 151.9, 131.1, 128.5, 125.8, 120.7, 116.9, 115.7, 114.7, 70.8, 55.7, 32.1. IR (KBr disc, cm^{-1}): 3385, 1594, 1508, 1456, 1384, 1230, 1109, 1040, 825, 754. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.75; H, 6.44. m.p. 72 ºC.



4-(3-(thiophen-3-yloxy)propyl)phenol (Table 2, entry 11). The general procedure B was followed at 120 ºC. Isolation and biotage purification afforded the title compound as a white solid (101 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (q, 1H, J = 4), 7.04-7.12 (m, 2H), 6.71-6.77 (m, 3H), 6.19 (q, 1H, J = 4), 4.99 (s, 1H), 3.92 (t, 2H, J = 6), 2.71 (t, 2H, J = 8), 1.99-2.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8, 153.6, 133.7, 129.7, 124.7, 119.5, 115.3, 97.3, 69.2, 31.2, 31.1. IR (KBr disc, cm^{-1}): 3383, 2943, 1597, 1543, 1512, 1442, 1377, 1227, 1182, 1112, 1069, 1041, 1020, 948, 824, 753. Anal. Calcd for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.02. Found: C, 66.42; H, 6.04. m.p. 98 ºC.



4-(3-(pyridin-3-yloxy)propyl)phenol (Table 2, entry 12). The general procedure B was followed. Isolation and biotage purification afforded the title compound as a white solid (146 mg, 64%). ^{1}H NMR (400 MHz, d_6-acetone) δ: 8.29-8.10 (m, 2H), 7.29-7.26 (m, 2H), 7.04-6.97 (m, 2H), 6.71-6.69 (d, 2H, J = 8), 4.10 (t, 2H, J = 12), 2.85 (s, 1H), 2.52 (t, 2H, J = 8), 2.01 (m, 2H). ^{13}C NMR (100 MHz, d_6-acetone) δ: 205.3, 155.6, 141.7, 138.1, 132.1, 129.3, 123.8, 120.4, 115.2, 67.1, 31.1, 29.3.



2-(2-(4-fluorophenoxy)ethyl)phenol (Scheme 2). The general procedure B was followed. Isolation and biotage purification afforded the title compound as a colorless liquid (116 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11-7.17 (m, 2H), 6.81-7.12 (m, 7H), 4.99 (s, 1H), 3.92 (t, 2H, J = 6), 2.71 (t, 2H, J = 8), 1.99-2.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.9, 156.5, 154.9, 153.9, 138.4, 131.1, 128.6, 128.5, 125.5,

120.9, 116.9, 116.8, 70.52, 31.80. IR (KBr disc, cm^{-1}): 3396, 1700, 1653, 1558, 1506, 1457, 1218, 827, 752.