Copper-in-Charcoal (Cu/C) Promoted Diaryl Ether Formation

Bruce H. Lipshutz*, John B. Unger, and Benjamin R. Taft
Department of Chemistry & Biochemistry
University of California
Santa Barbara, CA 93106

Supporting Information

General. Reactions were performed in oven-dried Biotage[®] 2-5 mL microwave vials under an argon atmosphere containing a Teflon coated stir bar and sealed with a Teflon lined septum. Solvents were freshly distilled from Na[°]/benzophenone ketyl prior to use. Cu/C was stored and weighed out as a black powder on the bench top. All aryl halides were obtained commercially and used as received; phenols were obtained commercially and recrystallized prior to use. All microwave experiments were performed using a Personal Chemistry (now Biotage[®]) Emrys Optimizer. GC analyses were carried out using an HP-5 capillary column (0.25 μ m x 30 m; cross-linked 5% PH-ME siloxane) and a time program beginning with 5 min at 50 °C followed by 20 °C/min ramp to 280 °C, then 20 min at this temp. Column chromatography was performed using Davisil Grade 633 Type 60_ silica gel. TLC analyses were performed on commercial Kieselgel 60 F₂₅₄ silica gel plates. NMR spectra were obtained on Varian Inova systems using CDCl₃ as solvent, with proton and carbon resonances at 400 and 100 MHz, respectively. IR spectra were obtained on an JASCO FT/IR-430 series spectrometer neat on NaCl plates or in a KBr pellet and are reported in cm⁻¹. Mass spectral data were acquired on a VF Autospec or an analytical VG-70-250 HF instrument.

Preparation of Cu/C: Darco KB activated carbon (15.0 g, 100 mesh, 25 % H₂O content) was added to a 300-mL round-bottom flask containing a stir bar. A solution of Cu(NO₃)₂•3H₂O (Acros Organics, 5.00 g, 20.7 mmol) in deionized H₂O (100 mL) was added to activated carbon, and additional deionized H₂O (125 mL) was added to wash down the sides of the flask. The flask was purged under argon and stirred vigorously for 30 min. The flask was submerged in an ultrasonic bath under a positive argon flow for 1 hour. The flask was attached to an argon-purged distillation setup and placed in a preheated 175-180 °C sand bath with stirring plate. As the distillation ended, the flask temperature began to rise and was held *below* 210 °C for an additional 15 min. Upon cooling to rt, toluene (75 mL) was added to wash down the sides of the flask. The flask was again placed into a hot sand bath until the toluene/H₂O azeotrope had distilled. Once the distillation was finished, the azeotropic distillation was repeated a second time. Upon cooling to room temperature, the black solid was washed with toluene (2_50 mL) under argon into a predried 150-mL coarse-fritted funnel (*in vacuo*). The fritted funnel was turned upside down under vacuum for 5 h until the Cu/C fell from the frit into the collection flask. The collection flask was then heated *in vacuo* in a 110-115 °C sand bath for 18 h to further

dry the catalyst. The impregnated charcoal (*ca.* 13 g) was transferred to, and stored in, an amber vial.

Simplified Preparation of Cu/C: Darco KB activated carbon (50.0 g, 100 mesh, 25 % H₂O content) was added to a 500-mL round-bottom flask containing a stir bar. A solution of Cu(NO₃)₂·3 H₂O (Acros Organics, 11.114 g, 46.0 mmol) in deionized H₂O (100 mL) was added to the flask and deionized H₂O (100 mL) was further added to wash down the sides of the flask. The flask was loosely capped and stirred under air for 30 min, then submerged in an ultrasonic bath for 7 h. Subsequent washing with toluene (2 x 50 mL) and air drying (3 h) by vacuum filtration yielded *ca.* 85 grams of “wet” Cu/C. The catalyst was then further dried *in vacuo* at 120 °C overnight to yield 41 grams of “dry” Cu/C. The impregnated charcoal was transferred to, and stored in, an amber bottle.

Representative procedure for the microwave assisted Cu/C-catalyzed Ullmann aryl ether coupling; compound 2, Scheme 2. Cu/C (30 mg, 0.05 mmol, 1.8 mmol/g), 1,10-phenanthroline (90 mg, 0.50 mmol), cesium carbonate (390 mg, 1.2 mmol), and estrone (271 mg, 1.0 mmol) were added to a oven-dried Biotage[®] 2-5 mL process vial under argon at rt. Dry dioxane (2.0 mL) was added by syringe and the slurry allowed to stir at rt for 30 min. 3-Bromopyridine (0.145 mL, 1.5 mmol) was added via micro-syringe and the resulting heterogeneous mixture was heated in the microwave with the following settings; *Temperature:* 220 °C, *Time:* 1800 sec., *Fixed hold time:* On, *Sample Absorption:* Normal, *Pre-stirring:* 10 sec. After cooling to rt, the crude reaction mixture was filtered through Celite[®] and the filter cake was further rinsed with ethyl acetate. Volatiles were removed on a rotary evaporator and the crude product was then purified by flash chromatography on silica gel, (3/2 Hexanes/Ethyl Acetate) R_f = 0.25, to yield 299 mg (86%) as a colorless solid.

Compound Characterization Data. Aryl ethers: in Table 1, and Table 2 entries 1 and 5, are known compounds; spectral data correspond to that in the literature.^[1]

(Scheme 2, compound 2). Colorless amorphous solid, mp = 146-147 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.39-8.30 (m, 2H), 7.29-7.19 (m, 3H), 6.77 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.72 (s, 1H), 2.89-2.81 (m, 2H), 2.47 (dd, *J* = 19.2, 8.8 Hz, 1H), 2.42-1.89 (m, 6H), 1.65-1.35 (m, 6H), 0.88 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 220.9, 154.2, 144.2, 141.4, 138.7, 135.8, 127.0, 125.3, 124.1, 119.2, 116.5, 50.5, 48.1, 44.2, 38.2, 35.9, 31.6, 29.6, 26.5, 25.9, 21.7, 13.9. IR (KBr pellet): 3074, 3044, 2932, 2888, 2854, 1736, 1605, 1570, 1492, 1471, 1422, 1276, 1259, 1228, 1187 cm⁻¹. MS (EI): *m/z* (%): 348(25), 347(100), 290(11), 223(11), 128(10), 97(10). HREIMS calcd. for C₂₃H₂₅NO₂ [*M*⁺] = 347.1885, found 347.1870.

(Table 2, entry 2). Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 9.91 (s, 1H), 7.83 (m, 2H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.08 (dt, *J* = 0.4, 7.2 Hz, 1H), 6.96 (m, 2H), 6.88 (dt, 0.4, 8.0 Hz, 1H), 2.34 (s, 3H), 2.10 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 191.0, 163.9, 152.7, 139.6, 132.2, 130.9, 129.4, 127.2, 126.9, 119.0, 116.5, 20.3, 12.4. IR (neat NaCl plate): 3054, 3023, 2921, 2827, 2734, 1696, 1602, 1468, 1246, 1155, 1062, 834 cm⁻¹. MS (EI): *m/z* (%): 226(100), 197 (7), 105(20), 77(16), 51(6). HREIMS calcd. for C₁₅H₁₄O₂Na [*M*+Na] = 249.0891, found 249.0897.

(Table 2, entry 3). Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.88 (dd, $J = 2.4, 8.4$ Hz, 1H), 7.66 (d, $J = 2.4$ Hz, 1H), 7.40 (m, 3H), 6.94 (m, 2H), 2.41 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 156.4, 153.7, 147.4, 137.2, 131.6, 127.2, 118.6, 118.0, 112.4, 34.6, 31.7, 16.9. IR (neat NaCl plate): 3039, 2963, 2868, 1600, 1522, 1347, 1239, 833, 741 cm^{-1} . MS (EI): m/z (%): 285(22), 270(100), 224(5), 97(7). HREIMS calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}_3$ [M^+] = 285.1365, found 285.1372.

(Table 2, entry 4). Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.70 (dd, $J = 1.2, 7.6$ Hz, 1H), 7.44 (dt, $J = 1.2, 7.2$ Hz 1H), 7.39 (m, 2H), 7.15 (t, $J = 7.6$ Hz, 1H), 6.99 (m, 2H), 6.95 (d, $J = 8.4$ Hz, 1H), 1.344 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 154.1, 147.3, 133.4, 127.3, 127.3, 127.0, 122.5, 119.3, 118.9, 34.6, 31.7. IR (neat NaCl plate): 3042, 2965, 2870, 1609, 1491, 1322, 1248, 1137, 759 cm^{-1} . MS (EI): m/z (%): 294(23), 279(100), 251(5), 199(5), 125(5), 118 (5), 57(5). HREIMS calcd. for $\text{C}_{17}\text{H}_{17}\text{F}_3\text{O}$ [M^+] = 294.1231, found 294.1243.

(Table 2, entry 6). Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.35 (m, 2H), 7.27 (m, 2H), 6.95 (m, 2H), 2.49 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.9, 154.9, 146.4, 132.0, 129.4, 126.8, 119.6, 118.4, 34.5, 31.7, 17.5. IR (neat NaCl plate): 3042, 2962, 2868, 1588, 1487, 1363, 1240, 1012, 827 cm^{-1} . MS (EI): m/z (%): 272(78), 257(100), 139(17), 129(6), 115(15), 91(5), 77(7). HREIMS calcd. for $\text{C}_{17}\text{H}_{20}\text{OS}$ [M^+] = 272.1235, found 272.1232.

(Table 2, entry 7). Colorless needlelike crystals, mp = 142-143 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.22 (m, 5H), 7.18 (dt, J = 1.2, 7.2 Hz, 1H), 7.02 (m, 1H), 6.88 (m, 2H), 6.58 (d, J = 8.4 Hz, 2H), 3.68 (s, 6H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 158.2, 155.8, 145.3, 133.0, 129.0, 128.6, 126.4, 126.1, 122.9, 119.2, 118.4, 104.0, 55.9, 31.7. IR (KBr pellet): 3064, 2962, 2835, 1590, 1505, 1470, 1249, 1109, 730 cm^{-1} . MS (EI): m/z (%): 362(81), 347(100), 214 (7), 198(17), 183(11), 174(5), 155(12), 91(5), 57(5). HREIMS calcd. for $\text{C}_{24}\text{H}_{26}\text{O}_3$ [M^+] = 362.1882, found 362.1894.

(Table 2, entry 8). Colorless solid, mp = 68-69 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.84 (m, 2H), 7.72 (dd, J = 0.4, 8.0 Hz, 1H), 7.48-7.37 (m, 4H), 7.30 (m, 2H), 7.03 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.6, 154.8, 146.5, 134.5, 130.2, 130.0, 127.9, 127.3, 126.8, 126.6, 124.8, 120.2, 118.8, 113.9, 34.6, 31.7. IR (neat NaCl plate): 3057, 2962, 2904, 2868, 1631, 1597, 1505, 1464, 1251, 1176, 963, 842, 750 cm^{-1} . MS (EI): m/z (%): 276(44), 261(100), 130(6), 127(10), 116(17), 115(20), 77(5). HREIMS calcd. for $\text{C}_{20}\text{H}_{20}\text{O}$ [M^+] = 276.1514, found 276.1517.

(Table 2, entry 9). Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.41 (d, J = 2.4 Hz, 1H), 8.35 (dd, J = 1.6, 4.4 Hz, 1H), 7.39 (m, 2H), 7.31-7.23 (m, 2H), 6.97 (m, 2H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 154.5, 154.0, 147.3, 144.2, 141.4, 127.1, 125.3, 124.2, 118.8, 34.6, 31.7.

IR (neat NaCl plate): 3041, 2962, 1574, 1508, 1474, 1422, 1248, 707 cm^{-1} . MS (EI): m/z (%): 227(29), 212(100), 184(6), 172(5), 118(6), 91(5), 78(8), 51(7). HREIMS calcd. for $\text{C}_{15}\text{H}_{17}\text{NO}$ $[\text{M}^+] = 227.1310$, found 227.1308.

(Table 2, entry 10). Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.94 (s, 1H), 8.46 (s, 2H), 7.41 (m, 2H), 6.99 (m, 2H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 153.1, 152.9, 152.8, 148.3, 146.9, 127.3, 118.9, 34.6, 31.6. IR (neat NaCl plate): 3039, 2963, 2869, 1560, 1508, 1408, 1261, 1174, 1014, 837, 721, 616 cm^{-1} . MS (EI): m/z (%): 228(33), 213(100), 185(11), 173 (5), 118(7). HREIMS calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}$ $[\text{M}^+] = 228.1263$, found 228.1258.

(Scheme 3). Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.94 (m, 2H), 7.41 (m, 2H), 7.00 (m, 4H), 2.58 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 197.0, 162.5, 153.1, 147.8, 131.8, 130.8, 127.1, 119.9, 117.2, 34.7, 31.7, 26.7. IR (neat NaCl plate): 3043, 2963, 2871, 1682, 1592, 1500, 1244, 1172, 835 cm^{-1} . MS (EI): m/z (%): 268(29), 253(100), 117(6), 105(7), 91(6), 77(6), 43(21). HREIMS calcd. for $\text{C}_{18}\text{H}_{20}\text{O}_2$ $[\text{M}^+] = 268.1463$, found 268.1471.

(Table 3, entry 4). Colorless solid, mp = 53-54 $^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 7.83 (m, 2H), 7.70 (dd, $J = 0.8, 8.0$ Hz, 1H), 7.44 (m, 2H), 7.32-7.24 (m, 4H), 7.03 (m, 2H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.3, 155.3, 134.5, 132.8, 130.3, 130.1, 129.3, 127.9, 127.3, 126.8, 124.9, 120.1, 120.0, 113.9, 17.2. IR (neat NaCl plate): 3056, 2919, 1631, 1587, 1487,

1356, 1250, 1170, 963, 812, 750 cm^{-1} . MS (EI): m/z (%): 266(100), 223(10), 191(8), 179(5), 127(16). HREIMS calcd. for $\text{C}_{17}\text{H}_{14}\text{OS}$ [M^+] = 266.0765, found 266.0760.

(Table 3, entry 5). Colorless waxy solid, mp = 39-40 $^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 6.95-6.91 (m, 2H), 6.87-6.78 (m, 4H), 6.69 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.2, 151.6, 150.7, 144.1, 134.0, 121.4, 119.6, 118.9, 114.7, 113.6, 56.0, 55.7, 21.4. IR (neat NaCl plate): 3044, 3000, 2935, 2833, 1593, 1500, 1463, 1410, 1285, 1220, 1152, 1125, 1102, 1036 cm^{-1} . MS (EI): m/z (%): 245(16), 244(100), 229(12). HREIMS calcd. for $\text{C}_{15}\text{H}_{16}\text{O}_3$ [M^+] = 244.1099, found 244.1105.

References:

- (1) (a) Samuelson, A. G.; Ghosh, R. *New J. Chem.* **2004**, 28, 1390. (b) Reider, P.; Volante, R. P.; Dormer, P. G.; Tschaen, D.; Song, J. Z.; Buck, E. *Org. Lett.* **2002**, 4, 1623. (c) Ma, D.; Cai, Q. *Org. Lett.* **2003**, 5, 3799.