A Hierarchy of Aryloxide Deprotection by Boron Tribromide

Sreenivas Punna, Stéphane Meunier and M. G. Finn*

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 N. Torrey Pines Rd., La Jolla, CA 92037 USA

Supporting Information

General: ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500, AMX-400, or Varian Mercury 200 spectrometer, using $CDCl_3$ or CD_3OD as solvents. Mass spectra were obtained on Agilent 1100 LC/MS spectrometer (model G1946A), Agilent-ESI-TOF, or Agilent 5973N GC/MS. Melting points were measured in a Mel-Temp II capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a MIDAC EM200 instrument with horizontal attenuated total reflectance accessory from Pike Instruments or in KBr pellets. Column chromatography was performed on EM Science silica gel, 60 Å and 40-63 μm. TLC analysis was facilitated by the use of phosphomolybdic acid or $KMnO_4/H_2O$ stains in addition to UV light with fluorescent-indicating plates. All commercially available reagents were purchased from Aldrich or Acros or TCI-America. Reactions requiring anhydrous conditions were performed under nitrogen. Anhydrous sodium sulfate was used for drying solutions.

Note: Compound numbers used here correspond to the entry numbers in Table 1 of the text, "a" representing the starting materials and "b" the products of treatment with BBr_3.

General propargylation procedure:
A mixture of the corresponding phenol (6.57 mmol), anhydrous potassium carbonate (19.71 mmol) and propargyl bromide (80 % in toluene, 7.88 mmol) in acetone (10 mL) was stirred overnight at room temperature. The solution was filtered, water was added, and the product was extracted three times with ether. The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography to afford the desired propargyl ether. The identities of compounds **1a**,[1] **3a**,[2] **5a**,[3] **6a**,[2] **7a**,[4] and **9a**[5] were confirmed by comparison to known spectra.

1-Methoxy-3-prop-2-ynyloxy-benzene (4a): the general protection procedure was applied to 3-methoxyphenol to afford **4a** (99 %) as a colorless liquid. ^{1}H NMR ($CDCl_3$) δ 2.53 (t, 1H, -CCH); 3.80 (s, 3 H, $-OCH_3$); 4.68 (d, J = 2.61 Hz, 2H, $-CH_2-$); 6.52-6.64 (m, 3H, Aryl); 7.14-7.30 (m, 1H, Aryl); ^{13}C NMR ($CDCl_3$) δ 55.0, 55.5, 75.2, 78.2, 101.2, 106.6, 106.9, 129.6, 158.5, 160.5; IR (thin film, cm^{-1}): 3312 (HCC-), 3002, 2954, 2833, 2122 (alkyne), 1594, 1280, 1260, 1195, 1151, 1047; GCMS *m/z* 162 (M), 161, 147, 95.

2-(3-Prop-2-ynyloxy-benzyloxy)-tetrahydro-pyran (8a): To a solution of 3-(2-propynyloxy)benzenemethanol (200 mg, 1.23 mmol)[6] in CH_2Cl_2 (10 mL) was added 3,4-dihydro-2*H*-pyran (0.17 mL, 1.85 mmol) and *p*-toluenesulfonic acid (20 mg, 0.1 mmol). The mixture was stirred overnight at room temperature, and then solid sodium bicarbonate was added to neutralize the acid. After filtration of the solid and evaporation under reduced pressure, the residue was purified by column chromatography (10% ethyl acetate / hexane) to afford 110 mg (36 %) of **8a** as a colorless liquid. ^{1}H NMR ($CDCl_3$; 200 MHz): δ 1.40-2.10 (m, 6H, THP); 2.52 (t, J = 2.40 Hz, -CCH); 3.45-3.65 (m, 1H, THP); 3.85-4.05 (m, 1H, THP); 4.49 (d, J = 12.4 Hz, 1H, Ar-CH_2-OTHP); 4.65-4.75 (m, 3H, THP, $-CH_2-$

[1] Ishii, H.;Ishikawa, T.; Takeda, S.; Ueki, S; Masahiro, S. *Chem. Pharm. Bull.* **1992**, *40*, 1148-1153.
[2] Pal, M.; Parasuraman, K.; Yleswarapu, K. R. *Org. Lett*. **2003**, *5*, 349-352.
[3] Atwal, K. S.; Grover, G. J.; Ferrara, F. N.; Ahmed, S. Z.; Sleph, P. G.; Dzwonczyk, S.; Normandin, D. E. *J. Med. Chem*. **1995**, *38*, 1966-1973.
[4] Ishikawa, T.; Nagai, K.; Ohkubo, N.; Ishii, H. *Heterocycles*, **1994**, *39*, 371-380.
[5] Schvartzapel, A. J.; Zhong, L.; Docampo, R.; Rodriguez, J. B.; Gros, E. G. *J. Med. Chem.* **1997**, *40*, 2314-2322.
[6] Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1996**, *61*, 2511-2516.

); 4.77 (d, *J* = 12.4 Hz, 1H, Ar-C*H*$_2$-OTHP); 6.85-7.10 (m, 3H, Aryl); 7.20-7.35 (m, 1H, Aryl); ^{13}C NMR ($CDCl_3$) δ 19.4, 25.6, 30.7, 55.9, 62.2, 68.6, 75.6, 78.7, 97.8, 114.2, 121.0, 129.5, 140.2, 157.8; IR (thin film, cm^{-1}): 3289 (HCC-), 2935, 2862, 2118 (alkyne), 1446, 1341, 1264, 975, 902, 866; ESMS *m/z* (relative intensity) 269 $(M+Na)^+$ (62), 121 (100); HRMS calcd for $C_{15}H_{18}O_3Na$ 269.1154, found 269.1058.

1-Allyloxy-4-prop-2-ynyloxy-benzene (10a): the general protection procedure was applied to 4-allyloxyphenol,[7] to afford **10a** (75 %) as a white solid. Mp 47-48 °C; ^{1}H NMR ($CDCl_3$; 200 MHz): δ 2.52 (t, *J* = 2.4 Hz, 1H, -CCH); 4.50 (d, *J* = 5.4 Hz, 2H, -CH_2-); 4.64 (d, *J* = 2.4 Hz, 2H, -CH_2-); 5.20-5.50 (m, 2H, -CH=C*H*$_2$); 5.95-6.20 (m, 1H, -C*H*=CH_2); 6.80-7.00 (m, 4H, Aryl); ^{13}C NMR ($CDCl_3$) δ 56.3, 69.1, 75.0, 78.6, 115.3, 115.8, 117.2, 133.2, 151.5, 153.2; IR (KBr, cm^{-1}): 3273 (HCC-), 3023 (-C=C-H), 2990, 2914, 2858, 2133 (alkyne), 2045, 1860, 1630 (-C=C-), 1505, 1215, 1020, 825, 795; GCMS *m/z* 188 (M), 147, 91; Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.73; H, 6.47.

1-Benzyloxy-4-prop-2-ynyloxy-benzene (11a): the general protection procedure was applied to 4-(benzyloxy)phenol to afford **11a** (99 %) as a white solid. Mp 45-46 °C; ^{1}H NMR ($CDCl_3$; 200 MHz): δ 2.52 (t, *J* = 2.4 Hz; 1H, -CCH); 4.65 (d, *J* = 2.4 Hz, 2H, -CH_2-CC); 5.04 (s, 2H, -OC*H*$_2$-Ar); 6.94 (s, 4H, -O-C_6H_4-O-); 7.25-7.55 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 56.2, 70.3, 75.2, 78.7, 115.2, 115.8, 127.2, 127.7, 128.3, 137.0, 151.6, 153.4; IR (KBr, cm^{-1}): 3280 (HCC-), 2902, 2861, 2117 (alkyne), 1847, 1509, 1453, 1377, 1227, 1034, 1010, 813; ESMS *m/z* (relative intensity) 261 $(M+Na)^+$ (50), 105 (100); Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 81.01; H, 6.05.

4-Methoxy-benzoic acid prop-2-ynyl ester (12a): To a solution of 4-methoxybenzoic acid (1.0 g, 6.57 mmol) in CH_2Cl_2 (20 mL) was added propargyl alcohol (0.38 mL, 6.57 mmol), DMAP (80 mg, 0.66 mmol) and DCC (2.0 g, 9.85 mmol). The mixture was stirred for 10 hours at room temperature, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (20 % ethyl acetate / hexane) to afford 762 mg (63 %) of **12a** as a white solid. Mp 40-41 °C; ^{1}H NMR ($CDCl_3$; 200 MHz): δ 2.48-2.54 (m, 1H, -CCH); 3.82 (s, -OCH_3); 4.84-4.92 (m, 2H, -OCH_2-CC); 6.89 (d, *J* = 9.20 Hz, 2H, Aryl); 7.98 (d, *J* = 9.20 Hz, 2H, Aryl); ^{13}C NMR ($CDCl_3$) δ 52.3, 55.6, 75.1, 78.2, 113.8, 121.9, 132.0, 163.8, 165.4; IR (KBr, cm^{-1}): 3240 (HCC-), 2934, 2841, 2121 (alkyne), 1710 (-C=O), 1602, 1509, 1264, 1167, 1095, 1022, 845, 786; GCMS *m/z* 190 (M).

Terephthalic acid 1-methyl ester 4-prop-2-ynyl ester (13a): To a solution of mono-methyl terephthalate (0.5 g, 2.77 mmol) in DMF (6 mL) was added potassium carbonate (1.15 g, 8.32 mmol) and propargyl bromide (80 % in toluene, 0.62 mL, 5.55 mmol). The mixture was stirred overnight at 70°C. A saturated solution of ammonium chloride was added, and the mixture was extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (10 % ethyl acetate / hexane) to afford 595 mg (98 %) of **13a** as a white solid. Mp 81-82 °C; ^{1}H NMR ($CDCl_3$; 200 MHz): δ 2.54 (t, *J* = 2.2 Hz, 1H, -CCH); 3.94 (s, 3H, -OCH_3); 4.94 (d, *J* = 2.2 Hz, -CH_2-CC); 8.11 (s, 4H, Aryl); ^{13}C NMR ($CDCl_3$) δ 52.1, 52.5, 75.1, 77.1, 129.1, 129.20, 129.23, 129.39, 132.7, 132.8, 164.5, 165.7, IR (KBr, cm^{-1}): 3253 (HCC-), 2963, 2126 (alkyne), 1720 (-C=O), 1438, 1406, 1276, 1111, 955, 721, 673; GCMS *m/z* 218 (M), 63, 135; Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.01; H, 4.69.

4-Methoxy-*N*-prop-2-ynyl-benzamide (14a): To a solution of 4-methoxybenzoic acid (1.0 g, 6.57 mmol) in CH_2Cl_2 (20 mL) was added propargylamine (0.42 mL, 6.57 mmol), DMAP (80 mg, 0.66 mmol) and DCC (2.0 g, 9.85 mmol). The mixture was stirred for 10 hours at room temperature, filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (40 % ethyl acetate / hexane) to afford 849 mg (68 %) of **14a** as a white solid. Mp 124-125 °C; ^{1}H NMR ($CDCl_3$; 200 MHz): δ 2.25-2.30 (m, 1H, -CCH); 3.83 (s, 1H, –OCH_3); 4.15-4.28 (m, 2H, -NH-C*H*$_2$-); 6.56 (brs., 1H, -NH-); 6.90 (d, *J* = 8.80 Hz, 2H, Aryl); 7.76 (d, *J* = 8.80 Hz, 2H, Aryl); ^{13}C NMR ($CDCl_3$) δ

[7] Lee, K. C.; Moon, B. S.; Lee, J. H.; Chung, K. H.; Katzenellenbogen, J. A.; Chi, D. Y. *Bioorg. Med. Chem.* **2003**, *11*, 3649-3658.

29.9, 55.6, 71.8, 80.0, 113.9, 126.2, 129.1, 162.5, 166.9; IR (KBr, cm^{-1}): 3264 (HCC-), 2930, 2837, 2120 (alkyne), 1892, 1634 (-C=O), 1494, 1409, 1300, 1258, 1179, 1030, 835, 765; ESMS *m/z* (relative intensity) 212 $(M+Na)^+$ (90), 190 $(M+1)^+$ (100); Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.68; H, 6.09; N, 7.58.

4-Methoxy-*N*-methyl-*N*-prop-2-ynyl-benzamide (15a): To a solution of *p*-anisic acid acid (0.5 g, 3.28 mmol) in CH_2Cl_2 (10 mL) was added *N*-methylpropargylamine (0.30 mL, 3.61 mmol) and DCC (746 mg, 3.61 mmol). The mixture was stirred overnight at room temperature. DCU was filtered, the filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography (30 % ethyl acetate / hexane) to afford 458 mg (68 %) of **15a** as a pale yellow syrup. ^{1}H NMR ($CDCl_3$; 200 MHz): δ 2.27-2.35 (m, 1H, -CCH); 3.10 (s, 3H, $-NCH_3$); 3.82 (s, 3H, $-OCH_3$); 4.05-4.30 (m, 2H, $-OCH_2$-CC); 6.90 (d, *J* = 8.8 Hz, 2H, Aryl); 7.46 (d, *J* = 8.8 Hz, 2H, Aryl); ^{13}C NMR ($CDCl_3$+CD_3OD) δ 32.5, 40.2, 53.9, 71.2, 77.0, 112.6, 125.8, 127.8, 160.3, 171.0, 171.06, 172.4; IR (KBr, cm^{-1}): 3284 (HCC-), 2926, 2845, 2117 (alkyne), 1622 (-C=O), 1389, 1296, 1252, 1172, 1066, 1026, 837, 769; ESMS *m/z* (relative intensity) 226 $(M+Na)^+$ (78), 204 $(M+1)^+$ (100); HRMS calcd for $C_{12}H_{13}NO_2$ 204.1019, found 204.1015.

***N*-(3,5-Bis-prop-2-ynyloxy-benzyl)-2-chloro-terephthalamic acid methyl ester (16a):** Compound **16a** was prepared as part of an independent study and its detailed synthesis will be reported separately. White solid; ^{1}H NMR ($CDCl_3$; 200 MHz): δ 2.48-2.54 (m, 2H, -CCH); 3.93 (s, 3H, $-OCH_3$); 4.53 (d, *J* = 5.4 Hz, 2H, $-CH_2$-N); 4.60-4.67 (m, 4H, $-CH_2$-CC); 6.50-6.60 (m, 3H, Aryl); 6.83 (t, *J* = 6.1 Hz, 1H, -NH-); 7.64-7.72 (m, 1H, Aryl); 7.78-7.88 (m, 2H, Aryl). IR (KBr, cm^{-1}): 3261 (HCC-), 2951, 2118 (alkyne), 1720 (-C=O), 1627, 1587, 1466, 1289, 1245, 1156, 1044, 826, 754.

(2-Prop-2-ynyloxy-ethyl)-benzene (17a): To a solution of phenethyl alcohol (1.0 g, 8.18 mmol) in THF (15 mL) at 0°C was added sodium hydride (0.36 g, 8.99 mmol) followed by propargyl bromide (80 % in toluene, 1.37 mL, 12.27 mmol) after 5 min. The mixture was stirred overnight at room temperature. Water was added, and extracted three times with ether. The combined organic layers were dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (10 % ethyl acetate / hexane) to afford 917 mg (70 %) of **17a** as a yellow syrup. ^{1}H NMR ($CDCl_3$; 200 MHz): δ 2.42-2.48 (m, 1H, -CCH); 2.94 (t, I = 7.0 Hz; 2H, Ar-CH_2-); 3.77 (t, *J* = 7. 0 Hz, $-CH_2$-O-); 4.14-4.20 (m, 2H, $–CH_2$-CCH); 7.20-7.40 (m, 5H, Aryl); ^{13}C NMR ($CDCl_3$) δ 35.5, 57.5, 70.2, 74.1, 79.4, 125.8, 127.9, 128.4, 138.2; IR (KBr, cm^{-1}): 3313 (HC-), 2946, 2855, 2121 (alkyne), 1558, 1357, 1256, 1095; ESMS *m/z* (relative intensity) 183 $(M+Na)^+$ (38), 105 (100).

1-But-2-ynyloxy-4-methoxy-benzene (18a): To a solution of *p*-methoxyphenol (1.0 g, 8.05 mmol) in acetone (10 mL) was added potassium carbonate (3.34 g, 24.15 mmol) followed by 1-bromo-2-butyne (0.78 mL, 8.86 mmol). The mixture was stirred for 6h at 60°C. Water was added, and the mixture was extracted three times with ether. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (5 % ethyl acetate / hexane) to afford **18a** (1.42 g, 99 %) as a colorless liquid. ^{1}H NMR ($CDCl_3$; 200 MHz): δ 1.84-1.90 (m, 3H, $-CCH_3$); 3.77 (s, 3H, $-OCH_3$); 4.56-4.64 (m, 2H, $-CH_2$-CC); 6.80-6.96 (m, 4H, Aryl); ^{13}C NMR ($CDCl_3$) δ 55.6, 57.1, 74.8, 83.5, 114.7, 116.0, 152.1, 154.4; IR (KBr, cm^{-1}): 3000, 2151, 2837, 2226 (alkyne), 1739, 1497, 1441, 1364, 1211, 1042; GCMS *m/z* 176 (M), 161, 123, 95.

1,3-Dimethyl-2,5-bis-prop-2-ynyloxy-benzene (19a): To a solution of 2,6-dimethylhydroquinone (1.0 g, 7.2 mmol) in DMF (10 mL) was added potassium carbonate (6.0 g, 43.5 mmol) followed by propargyl bromide (3.2 mL, 22 mmol, 80% in toluene). The mixture was stirred for overnight at 80°C. Water was added, and the mixture was extracted three times with ether. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (15 % ethyl acetate / hexane) to afford **19a** (1.1 g, 73 %) as white solid. Mp 45-46 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 6H, Ar-CH_3), 2.54 (t, *J* = 2.40 Hz, 2H, -CCH), 4.45, 4,61 (2d, *J* = 2.40 Hz, 4H, -CH_2-CC), 6.62 (s, 2H, Aryl); ^{13}C NMR ($CDCl_3$) δ 17.1, 56.2, 60.2, 75.4, 75.7, 79.2, 79.8, 109.9, 115.0, 132.3, 150.0, 153.8; IR (KBr, cm^{-1}): 3317 (HCC-), 3265, 2931, 2874, 2126 (alkyne), 1997, 1606, 1369, 1196, 838; ESMS *m/z* (relative intensity) 237 $(M+Na)^+$ (15), 215 $(M+1)^+$.

5-Methoxy-1,3-dimethyl-2-prop-2-ynyloxy-benzene (20a): Compound **19b** (the major product obtained from **19a** by treatment with one equivalent of BBr_3 was alkylated with MeI to afford **20a** (75% yield) as colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 6H, Ar-CH_3), 2.58 (t, *J* = 2.0 Hz, 1H, -CCH), 3.76 (s, 3H, Ar-OCH_3), 4.70 (d, *J* = 2.0 Hz, 2H, -CH_2-), 6.70 (s, 2H, Aryl); ^{13}C NMR ($CDCl_3$) δ 16.2, 55.8, 59.7, 75.0, 78.7, 114.6, 131.6, 151.3, 153.1; IR (thin film, cm^{-1}): 3289 (HCC-), 2926, 2862, 2371, 2126 (alkyne), 1598, 1486, 1321, 1220, 1180, 1152, 1055, 858; ESMS *m/z* (relative intensity) 213 $(M+Na)^+$ (20), 189 (40), 159 (25).

1,3-Di-*tert*-butyl-5-methoxy-2-prop-2-ynyloxy-benzene (21a): Compound **21a** was prepared using the method described for **19a** in 32 % yield (~50% of starting material recovered) as a colorless liquid. ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 18H, -$C(CH_3)_3$), 2.53 (t, *J* = 2.40 Hz, -CCH), 3.78 (s, 3H, Ar-OCH_3), 4.35 (d, *J* = 2.6 Hz, -CH_2-CC), 6.80 (s, 2H, Aryl); IR (thin film, cm^{-1}): 3296 (HCC-), 2692, 2910, 2870, 2371, 2129 (alkyne), 1590, 1433, 1356, 1199, 1062, 869, 764; ^{13}C NMR ($CDCl_3$) δ 29.4, 29.9, 31.8, 35.7, 55.0, 63.3, 74.3, 79.0, 111.7, 144.4, 150.3, 154.6; GCMS *m/z* 274 (M, low), 235.

General BBr_3-mediated propargyl deprotection procedure: To a solution of propargyl ether (1 mmol) in dry CH_2Cl_2 (3 mL) under N_2 atmosphere was added BBr_3 (1 M in CH_2Cl_2, 1 mmol) dropwise at room temperature. The reaction mixture was monitored by TLC; upon completion, ice-water was added and the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography to afford the desired product.

The isolated yields of pure compounds obtained from this procedure are reported in Table 1. The following compounds were displayed identical spectroscopic properties to authentic samples: **1b**, **2b**, **3b**, **4b**, **5b**, **6b**, **7b**, **12b**, **13b**, **17b**.

2-Allyl-4-methoxy-phenol (9b): the general deprotection procedure was applied on **9a** to afford **9b** (98 %) as a colorless oil. ^{1}H NMR ($CDCl_3$; 200 MHz): δ 3.32-3.60 (m, 2H, Ar-CH_2-); 3.79 (s, 3H, -OCH_3); 5.10-5.24 (m, 2H, -CH=CH_2); 5.40 (brs., 1H, -OH); 5.90-6.16 (m, 1H, -C*H*=CH_2); 6.60-6.90 (m, 3H, Aryl); ^{13}C NMR ($CDCl_3$) δ 34.7, 55.5, 112.3, 114.6, 115.7, 116.1, 126.6, 135.9, 147.6, 153.3; IR (thin film, cm^{-1}): 3333 (b, OH), 2834, 1820, 1606 (-C=C-), 1216, 910, 737; ESMS *m/z* (relative intensity) 183 $(M+1)^+$ (16), 121 (100); HRMS calcd for $C_{10}H_{13}O_2$ 165.0910, found 165.0907.

2-Allyl-4-prop-2-ynyloxy-phenol (10b): the general deprotection procedure was applied to **10a** to afford the Claisen-rearranged product **10b** (84 %) as a colorless oil. ^{1}H NMR ($CDCl_3$; 200 MHz): δ 2.51 (t, *J* = 2.2 Hz, 1H, -CCH); 3.39 (dt, *J* = 5.8 and 1.6 Hz, 2H, Ar-CH_2-); 4.63 (d, *J* = 2.2 Hz, 2H, -CH_2-CC); 4.86 (brs., 1H, -OH); 5.10-5.24 (m, 2H, -CH=CH_2); 5.90-6.12 (m, 1H, –C*H*=CH_2); 6.74-6.82 (m, 3H, Aryl); ^{13}C NMR ($CDCl_3$) δ 34.5, 55.9, 74.6, 78.2, 113.3, 115.7, 116.0, 116.7, 125.9, 135.3, 148.0, 151.0; IR (thin film, cm^{-1}): 3400 (b, OH), 3289 (HCC-), 2910, 2114 (alkyne), 1832, 1602 (-C=C-), 1200, 906; GCMS *m/z* 188 (M), 149.

4-Prop-2-ynyloxy-phenol (11b): the general deprotection procedure was applied on **11a** to afford **11b** (61 %) as a colorless oil. ^{1}H NMR ($CDCl_3$; 200 MHz): δ 2.51 (t, *J* = 2.4, 1H, -CCH); 4.62 (d, J = 2.4 Hz, 2H, -CH_2-CC); 5.66 (brs., 1H, -OH); 6.72-6.92 (m, 4H, Aryl); ^{13}C NMR ($CDCl_3$) δ 56.4, 75.0, 78.5, 115.7, 116.0, 150.1, 151.3; IR (thin film, cm^{-1}): 3350 (b, -OH), 3289 (HCC-), 2117 (alkyne), 1501, 1445, 1195, 1026, 821; GCMS *m/z* 148 (M), 109.

4-Hydroxy-*N*-prop-2-ynyl-benzamide (14b): the general deprotection procedure was applied to **14a** using 3.0 eq. BBr_3 to afford **14b** (35 %) as a colorless oil. ^{1}H NMR ($CDCl_3$; 200 MHz): δ 2.56 (t, *J* = 2.2 Hz, 1H, -CCH); 4.12-4.18 (m, 2H, -CH_2-CC); 6.81 (d, *J* = 8.6 Hz, 2H, Aryl); 7.69 (d, *J* = 8.6 Hz, 2H, Aryl); 8.50-8.65 (m, 1H, -NH); ^{13}C NMR (CD_3OD) δ 26.6, 67.0, 72.0, 81.1, 114.8, 116.2, 127.2, 130.4, 162.1, 164.1; IR (thin film, cm^{-1}): 3293 (b, -OH and HCC-), 2938, 1602 (-C=O), 1276, 1231, 1175, 1046,

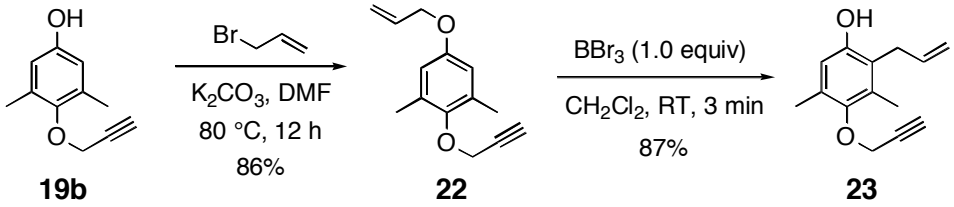
921, 845, 760; ESMS *m/z* (relative intensity) 198 $(M+Na)^+$ (9), 176 $(M+1)^+$ (7); HRMS calcd for $C_{10}H_{10}NO_2$ 176.0706, found 176.0706.

4-Hydroxy-*N*-methyl-*N*-prop-2-ynyl-benzamide (15b): the general deprotection procedure was applied on **15a** using 2.0 eq. BBr_3 to afford **15b** (41 %) as a colorless oil. ^1H NMR ($CDCl_3$; 200 MHz): δ 2.77 (brs., 1H, -CCH); 3.10 (s, 3H, -N-CH_3); 4.21 (brs., 2H, -CH_2-CC); 6.83 (d, *J* = 8.4 Hz, 2H, Aryl); 7.36 (d, *J* = 8.4 Hz, 2H, Aryl); IR (thin film, cm^{-1}): 3289 (b, -OH and HCC-), 2802, 2114 (alkyne), 1605 (-C=O), 1272, 1232, 1168, 1067, 934, 846, 757; ESMS *m/z* (relative intensity) 212 $(M+Na)^+$ (10), 190 $(M+1)^+$ (30); HRMS calcd for $C_{11}H_{11}NO_2$ 188.0717, found 188.0715.

2-Chloro-*N*-(3-hydroxy-5-prop-2-ynyloxy-benzyl)-terephthalamic acid methyl ester (16b): the general deprotection procedure was applied to **16a** using 2.0 eq. BBr_3 to afford **16b** (71 %) as `a colorless oil. ^1H NMR ($CDCl_3$; 200 MHz): δ 2.89 (t, *J* = 2.4 Hz, 1H, -CCH); 3.92 (s, 3H, –OCH_3); 4.46-4.60 (m, 2H, -CH_2-N); 4.65 (d, *J* = 2.4 Hz, 2H, -CH_2-CCH); 6.30-6.36 (m, 1H, Aryl); 6.40-6.48 (m, 2H, Aryl); 7.76-7.90 (m, 2H, Aryl); 7.94-7.98 (m, 1H, Aryl); 9.09 (brt., J = 5.2 Hz, 1H, -NH);). IR (thin film, cm^{-1}): 3289 (-OH, HCC-), 2955, 2126 (alkyne), 1961, 1723 (–C=O), 1635, 1595, 1542, 1333, 1297, 1244, 1150, 1047, 842, 750.

3,5-Dimethyl-4-prop-2-ynyloxy-phenol (19b): the general deprotection procedure was applied to **19a** to afford **19b** (55%) as white solid. Mp 72-73 °C. ^1H NMR ($CDCl_3$) δ 2.23 (s, 6H, Ar-CH_3), 2.50 (t, *J* = 2.4 Hz, 1H, -CCH), 4.46 (s, 1H, Ar-OH), 4.61 (d, J = 2.4 Hz, 2H, -CH_2-CC), 6.63 (s, 2H, Aryl); ^{13}C NMR ($CDCl_3$) δ 15.6, 55.8, 74.5, 78.4, 114.5, 123.5, 146.2, 150.2; IR (KBr, cm^{-1}): 3405 (b, HCC-, -OH), 3309, 2931, 2351, 2126 (alkyne), 1647, 1345, 1196, 1095, 826; ESMS *m/z* (relative intensity) 199 $(M+Na)^+$ (30), 177 $(M+1)^+$ (80); HRMS calcd for $C_{11}H_{13}O_2$ 177.091, found 177.091.

The regiochemistry of deprotection was confirmed by the sequence of reactions shown below. Allylation was followed by rapid BBr_3-induced Claisen rearrangement to afford **23** in high yield. Such a rearrangement would not have been possible with the other potential regioisomer of **22**, since the *ortho* and *para* positions would be blocked.

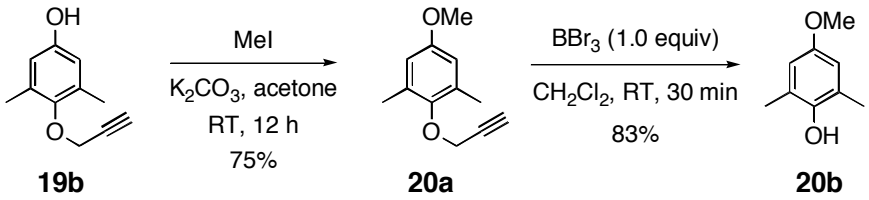


5-Allyloxy-1,3-dimethyl-2-prop-2-ynyloxy-benzene (22): the general protection procedure was applied to **19b** using allyl bromide to afford **22** (86%) as colorless oil. ^1H NMR ($CDCl_3$) δ 2.27(s, 6H, Ar-CH_3), 2.51 (t, *J* = 2.0 Hz, 1H, -CCH), 4.26 (d, *J* = 5.6 Hz, 2H, -CH_2-), 4.63 (d, *J* = 1.8 Hz, 2H, -CH_2-CC), 5.24-5.47 (m, 2H, -HC=C*H*$_2$), 6.01-6.21 (m, 1H, -C*H*=CH_2), 6.63 (s, 2H, Aryl); ^{13}C NMR ($CDCl_3$) δ 16.5, 55.8, 73.1, 75.1, 78.7, 114.5, 116.9, 131.8, 134.0, 150.2, 153.1; IR (thin film, cm^{-1}): 3293 (HCC-), 3087, 3023 (-C=C-H), 2927, 2866, 2363, 2335, 2126 (alkyne), 1719, 1651 (-C=C-), 1598, 1482, 1208, 1059, 987, 793; ESMS *m/z* (relative intensity) 239 $(M+Na)^+$ (100), 149 (50), 102 (43).

2-Allyl-3,5-dimethyl-4-prop-2-ynyloxy-phenol (23): the general deprotection procedure was applied to compound **22** to afford Claisen-rearranged product **23** (87%) as a white solid. Mp 73-74 °C; ^1H NMR ($CDCl_3$) δ 2.17, 2.24 (2s, 6H, Ar-CH3), 2.46 (t, *J* = 2.41 Hz, 1H, -CCH), 3.42 (d, *J* = 5.62 Hz, -CH_2-), 4.33 (s, 1H, Ar-OH), 4.62 (d, *J* = 2.41 Hz, -CH_2-CC), 4.86-4.99 (m, 2H, -C*H*$_2$=CH-), 5.83-5.97 (m, 1H, -CH_2=C*H*-), 6.68 (s, 1H, Aryl); ^{13}C NMR ($CDCl_3$) δ 11.9, 16.4, 30.6, 31.0, 57.4, 74.9, 78.1, 113.6, 114.6, 121.0, 123.7, 136.4, 149.3; IR (KBr, cm^{-1}): 3417 (b, HCC-, -OH), 3289, 3091, 2931, 2870, 2118 (alkyne), 1675 (-C=C-), 1478, 1305, 1212, 1111, 910, 838; ESMS *m/z* (relative intensity) 239 $(M+Na)^+$ (27), 217 $(M+1)^+$ (17).

4-Methoxy-2,6-dimethyl-phenol (20b): the general deprotection method was applied to compound **20a** to afford **20b** (83%) as a white solid. Mp 65-66 °C; ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 6H, Ar-CH_3), 3.66 (s, 3H, Ar-OCH_3), 4.74 (s, 1H, Ar-OH), 6.47 (s, 2H, Aryl); ^{13}C NMR ($CDCl_3$) δ 15.8, 59.6, 114.7, 131.6, 150.4, 150.9; IR (KBr, cm^{-1}): 3510 (b, -OH), 2667, 2351, 2162, 1606, 1478, 1321, 1216, 1007, 858; ESMS *m/z* (relative intensity) 151 $(M-1)^-$ (13), 113 (100).

The regiochemistry of **20b** was determined from **19b** by the sequence shown here:



19b **20a** **20b**

3,5-Di-*tert*-butyl-4-prop-2-ynyloxy-phenol (21b): the general deprotection procedure was applied to **21a** to afford **21b** (68 %) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 18H, -$C(CH_3)_3$), 2.43 (t, J = 2.1 Hz, 1H, -CCH), 4.35 (d, J = 2.1 Hz, -CH_2-CC), 5.22 (br s., 1H, Ar-OH), 6.74 (s, 2H, Aryl); ^{13}C NMR ($CDCl_3$) δ 31.6, 35.6, 79.2, 113.3, 118.4, 137.1, 144.4, 149.2, 150.6; IR (thin film, cm^{-1}): 33305 (HCC-, -OH), 2967, 2906, 2870, 2254 (alkyne), 1715, 1639, 1586, 1325, 1204, 1003, 962, 854; ESMS *m/z* (relative intensity) 261 $(M+1)^+$ (80), 257 (20); HRMS calcd for $C_{17}H_{25}O_2$ 261.1855, found 261.1313.

Examination of reaction mixture by deuterium NMR

Monodeuterated **1a** was prepared and its reaction with a slight deficiency of BBr_3 at room temperature in CH_2Cl_2 (containing 5% $CDCl_3$ for reference and spectrometer locking) was examined by ^{2}H NMR, as shown in Figure S1.

Figure S1. ^{2}D NMR of a the deprotection reaction of **1a**-d_1. Bromoallene is expected to give a resonance at approximately 5.9 ppm.