Use of Precatalysts Greatly Facilitate Palladium-Catalyzed Alkynylations in Batch and Continuous-Flow Conditions

Wei Shu and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139

Supporting Information

General Reagent Information

All reactions were carried out under an argon atmosphere. The 1,4-dioxane, dibutyl ether, 1,2-chloroethane, and DMSO were purchased from Aldrich Chemical Company in Sure-Seal bottles and were used as received. Toluene was purchased from J.T. Baker in CYCLE-TAINER® solvent delivery kegs and vigorously purged with argon for 2 h. The solvent was further purified by passing it under argon pressure through two packed columns of neutral alumina and copper (II) oxide. Aryl halides and alkynes were purchased from Aldrich Chemical Co., Alfa Aesar, Acros Organics or TCI America and were used as received without further purification. Aryl tosylate was synthesized using literature procedure.[1] Anhydrous cesium carbonate, cesium hydroxide, potassium hydroxide, sodium hydroxide were purchased from Aldrich Chemical Co. The bases were stored in a nitrogen-filled glovebox and were taken out in small quantities and stored on the bench for up to two weeks. Ligands 1a-1e were purchased from Strem Chemicals, Inc., Flash chromatography was performed using a Biotage SP4 instrument with prepacked silica cartridges.

General Analytical Information
All compounds were characterized by $^1$H NMR, $^{13}$C NMR, IR spectroscopy, as well as, in most instances, elemental analysis. Copies of the $^1$H and $^{13}$C spectra can be found at the end of the Supporting Information. Nuclear Magnetic Resonance spectra were recorded on a Varian 300 MHz instrument. All $^1$H NMR experiments are reported in $\delta$ 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 were taken on a Perkin–Elmer 2000 FTIR. All GC analyses were performed on an 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 Microlabs Inc., Norcross, GA.

**Experimental Procedures**

**General Procedure for Batch Reactions:** An oven-dried test tube, which was equipped with a magnetic stir bar, was charged with the Cs$_2$CO$_3$ (2.6 equiv). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and then the aryl halide (1.0 equiv), alkyne (1.3 equiv), and solvent (1.0 mL/mmoll) were added via syringe (aryl chlorides and alkynes that were solids were added with the base). The reaction mixture was heated to 90 °C until the starting material was completely consumed as monitored by GC. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate, washed with water and brine, concentrated in vacuo, and purified via the Biotage SP4.

![Chemical Structure](image)

**4-(5-Chloropent-1-yn-1-yl)benzonitrile.$^{[2]}$** Following the general procedure, a mixture of XPhos precatalyst 2a (1.9 mg, 0.0025 mmol), XPhos (1.2 mg, 0.0025 mmol), Cs$_2$CO$_3$ (847 mg, 2.6 mmol), 4-chlorobenzonitrile (137.6 mg, 1.0 mmol), 5-chloropent-1-ynyl (133 mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 2 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 20% EtOAc in hexane) to afford the title compound as clear oil (192 mg, 94%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.55 (d, $J = 8.4$ Hz, 2 H), 7.43 (d, $J = 8.4$ Hz, 2
H), 3.68 (t, J = 6.3 Hz, 2 H), 2.61 (t, J = 6.9 Hz, 2 H), 2.10-1.99 (m, 2 H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 132.2, 132.0, 128.6, 118.6, 111.1, 93.3, 80.3, 43.7, 31.1, 17.0; IR (neat, cm\(^{-1}\)): 2961, 2227, 1604, 1501, 1441, 1405, 1355, 1291, 1177, 1106.

**3-((2,6-Difluorophenyl)ethynyl)benzonitrile.** Following the general procedure, a mixture of XPhos precatalyst 2a (1.9 mg, 0.0025 mmol), XPhos (1.2 mg, 0.0025 mmol), Cs\(_2\)CO\(_3\) (847 mg, 2.6 mmol), 3-chlorobenzonitrile (138 mg, 1.0 mmol), 2-ethynyl-1,3-difluorobenzene (180 mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 6 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 20% EtOAc in hexane) to afford the title compound as colorless solid (174 mg, 73%), mp = 78-79 °C (hexane/EtOAc). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.79-7.68 (m, 2 H), 7.62-7.56 (m, 1 H), 7.53-7.40 (m, 2 H), 6.93-6.81 (m, 2 H) ppm. \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 162.9 (dd, J = 253.3, 11.1), 135.5, 134.7, 134.2 (dd, J = 9.8, 2.5 Hz), 131.6, 129.2, 124.1, 117.8, 112.8, 111.7 (dd, J = 22.0, 3.8 Hz), 107.2 (dd, J = 15.8, 4.0 Hz), 104.3 (dd, J = 25.9, 24.7 Hz), 91.4 (dd, J = 3.3, 1.8 Hz), 83.9 (d, J = 1.5 Hz) ppm. \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\): -105.8 ppm. IR (neat, cm\(^{-1}\)): 3073, 2230, 1614, 1586, 1572, 1506, 1424, 1292, 1264. Anal. Calcd. for C\(_{15}\)H\(_7\)F\(_2\)N: C, 75.31; H, 2.95. Found: C, 75.05; H, 2.96.

**3-Methyl-5-(phenylethynyl)pyridine.** Following the general procedure, a mixture of XPhos precatalyst 2a (2.0 mg, 0.0025 mmol), XPhos (1.2 mg, 0.0025 mmol), Cs\(_2\)CO\(_3\) (847 mg, 2.6 mmol), 3-bromo-5-methylpyridine (172 mg, 1.0 mmol), phenyl acetylene (133 mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 2 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 20% EtOAc in hexane) to afford the title compound as clear oil (149 mg, 77%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 8.57 (d, J = 1.5 Hz, 1 H), 8.38 (d, J = 1.5 Hz, 1 H),
7.61-7.57 (m, 1 H), 7.56-7.48 (m, 2 H), 7.36-7.29 (m, 3 H), 2.30 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 149.2, 149.1, 138.7, 132.5, 131.5, 128.6, 128.3, 122.5, 119.7, 92.1, 86.0, 18.1 ppm. IR (neat, cm$^{-1}$): 3023, 2921, 2867, 2214, 1600, 1565, 1492, 1443, 1416, 1383.

NN

MeO

3-(Cyclohex-1-en-1-ylethynyl)-6-methoxypyridazine. Following the general procedure, a mixture of XPhos precatalyst 2a (2.0 mg, 0.0025 mmol), XPhos (1.2 mg, 0.0025 mmol), Cs$_2$CO$_3$ (847 mg, 2.6 mmol), 3-chloro-6-methoxypyridazine (145 mg, 1.0 mmol), 1-ethynylcyclohex-1-ene (159 mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 12 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 30% EtOAc in hexane) to afford the title compound colorless solid (164 mg, 76%), mp = 84-85 °C (hexane/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.30 (d, $J = 9.0$ Hz, 1 H), 6.81 (d, $J = 9.0$ Hz, 1 H), 6.22-6.18 (m, 1 H), 4.01 (s, 3 H), 2.13-1.56 (m, 4 H), 1.57-1.46 (m, 4 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 162.8, 143.7, 137.3, 132.0, 119.6, 116.2, 93.7, 83.0, 54.6, 28.4, 25.5, 21.8, 21.0 ppm. IR (neat, cm$^{-1}$): 3053, 2940, 2208, 1587, 1539, 1461, 1408, 1329, 1287, 1008. Anal. Calcd. for C$_{13}$H$_{14}$N$_2$O: C, 72.87; H, 6.59. Found: C, 72.61; H, 6.66.

6-((3,5-Dimethoxyphenyl)ethynyl)picolinonitrile. Following the general procedure, a mixture of XPhos precatalyst 2a (1.9 mg, 0.0025 mmol), XPhos (1.2 mg, 0.0025 mmol), Cs$_2$CO$_3$ (847 mg, 2.6 mmol), 6-chloropicolinonitrile (183 mg, 1.0 mmol), 1-ethynyl-3,5-dimethoxybenzene (243 mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 6 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 20% EtOAc in hexane) to afford the title compound
colorless solid (260 mg, 98%), mp = 99-100 °C (hexane/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.82-7.75 (m, 1 H), 7.65 (dd, $J = 7.8$, 0.9 Hz, 1 H), 7.57 (dd, $J = 7.8$, 0.9 Hz, 1 H), 6.70-6.66 (m, 2 H), 6.46-6.43 (m, 1 H), 3.73 (s, 6 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 160.3, 144.6, 137.3, 133.7, 130.0, 127.0, 122.2, 116.4, 109.6, 102.8, 91.3, 86.2, 55.2 ppm. IR (neat, cm$^{-1}$): 3067, 2964, 2220, 1589, 1452, 1362, 1268, 1249, 1159.

Anal. Calcd. for C$_{16}$H$_{12}$N$_2$O$_2$: C, 72.72; H, 4.58. Found: C, 72.62; H, 4.52.

![Chemical Structure](Image)

**4-(4-(Cyclohex-1-en-1-ylethynyl)phenyl)morpholine.** Following the general procedure, a mixture of XPhos precatalyst 2a (1.9 mg, 0.0025 mmol), XPhos (1.2 mg, 0.0025 mmol), Cs$_2$CO$_3$ (847 mg, 2.6 mmol), 4-(4-bromophenyl)morpholine (242 mg, 1.0 mmol), 1-ethynyle cyclohex-1-ene (138 mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 4 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 10% EtOAc in hexane) to afford the title compound colorless solid (214 mg, 80%), mp = 133-134 °C (hexane/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.38-7.30 (m, 2 H), 6.81 (d, $J = 9.0$ Hz, 2 H), 6.18-6.14 (m, 1 H), 3.84 (t, $J = 4.8$ Hz, 4 H), 3.17 (t, $J = 4.8$ Hz, 4 H), 2.23-2.08 (m, 4 H), 1.72-1.54 (m, 4 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 150.3, 134.1, 132.4, 120.8, 114.7, 114.3, 89.7, 86.9, 66.6, 48.4, 29.3, 25.6, 22.3, 21.5 ppm. IR (neat, cm$^{-1}$): 2856, 1653, 1603, 1559, 1516, 1448, 1384, 1238, 1259, 1122. Anal. Calcd. for C$_{18}$H$_{21}$NO: C, 80.86; H, 7.92. Found: C, 80.57; H, 7.90.

![Chemical Structure](Image)

**4-(Pyridin-3-ylethynyl)benzonitrile.** Following the general procedure, a mixture of XPhos precatalyst 2a (1.9 mg, 0.0025 mmol), XPhos (1.2 mg, 0.0025 mmol), Cs$_2$CO$_3$ (847 mg, 2.6 mmol), 4-chlorobenzonitrile (138 mg, 1.0 mmol), 3-ethynylpyridine (134
mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 6 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 10% EtOAc in hexane) to afford the title compound colorless solid (195 mg, 95%), mp = 128-129 °C (hexane/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.72 (s, 1 H), 8.54-8.51 (m, 1 H), 7.78-7.74 (m, 1 H), 7.61-7.52 (m, 4 H), 7.28-7.23 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 152.0, 149.1, 138.4, 131.91, 131.87, 127.1, 122.9, 119.2, 118.1, 111.8, 90.5, 89.9 ppm. IR (neat, cm$^{-1}$): 3084, 2230, 1602, 1561, 1500, 1408, 1174, 1105, 1024, 844. Anal. Calcd. for C$_{14}$H$_8$N$_2$: C, 82.33; H, 3.95. Found: C, 82.38; H, 3.96.

5-(Cyclohex-1-en-1-ylethynyl)-2-methylbenzo[d]thiazole. Following the general procedure, a mixture of XPhos precatalyst 2a (7.9 mg, 0.01 mmol), XPhos (4.8 mg, 0.01 mmol), Cs$_2$CO$_3$ (847 mg, 2.6 mmol), 5-chloro-2-methylbenzo[d]thiazole (184 mg, 1.0 mmol), 1-ethynylcyclohex-1-ene (138 mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 8 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 20% EtOAc in hexane) to afford the title compound colorless solid (208 mg, 82%), mp = 114-116 °C (hexane/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ: 7.92 (dd, $J$ = 1.2 Hz, 1 H), 7.65 (d, $J$ = 8.4 Hz, 1 H), 7.33 (dd, $J$ = 8.4, 1.2 Hz, 1 H), 6.23-6.18 (m, 1 H), 2.76 (s, 3 H), 2.26-2.17 (m, 2 H), 2.12-2.08 (m, 2 H), 1.69-1.52 (m, 4 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 167.6, 153.2, 135.3, 135.0, 127.7, 124.9, 121.4, 121.0, 120.5, 91.2, 86.4, 29.0, 25.6, 22.2, 21.3, 20.0 ppm. IR (neat, cm$^{-1}$): 2921, 2853, 2200, 1919, 1533, 1455, 1384, 1172, 1157, 919. Anal. Calcd. for C$_{16}$H$_{15}$NS: C, 75.85; H, 5.97. Found: C, 75.72; H, 5.92.

5-(Dodec-1-yn-1-yl)-1,2,3-trimethoxybenzene. Following the general procedure, a mixture of XPhos precatalyst 2a (1.9 mg, 0.0025 mmol), XPhos (1.2 mg, 0.0025 mmol), Cs$_2$CO$_3$ (847 mg, 2.6 mmol), 5-bromo-1,2,3-trimethoxybenzene (247 mg, 1.0 mmol), 1-
dodecyne (216 mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 3 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 10% EtOAc in hexane) to afford the title compound clear oil (316 mg, 95%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 6.60 (s, 2 H), 3.80 (s, 9 H), 2.36 (t, $J = 6.9$ Hz, 2 H), 1.61-1.51 (m, 2 H), 1.48-1.19 (m, 14 H), 0.85 (t, $J = 6.9$ Hz, 3 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 152.8, 138.0, 119.1, 108.5, 89.4, 80.3, 60.7, 55.9, 31.8, 29.5, 29.4, 29.2, 29.0, 28.8, 28.7, 22.5, 19.2, 14.0 ppm. IR (neat, cm$^{-1}$): 2921, 2852, 1575, 1508, 1462, 1410, 1235, 1184, 1130, 993. Anal. Calcd. for C$_{21}$H$_{32}$O$_3$: C, 75.86; H, 9.70. Found: C, 75.94; H, 9.54.

3-(Dec-1-yn-1-yl)-6-methoxypyridazine. Following the general procedure, a mixture of XPhos precatalyst 2a (1.9 mg, 0.0025 mmol), XPhos (1.2 mg, 0.0025 mmol), Cs$_2$CO$_3$ (847 mg, 2.6 mmol), 3-chloro-6-methoxypyridazine (145 mg, 1.0 mmol), 1-decyne (179 mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 6 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 20% EtOAc in hexane) to afford the title compound colorless solid (212 mg, 86%), mp = 35-37 °C (hexane/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.35 (d, $J = 9.0$ Hz, 1 H), 6.87 (d, $J = 9.0$ Hz, 1 H), 4.12 (s, 3 H), 2.44 (t, $J = 7.2$ Hz, 2 H), 1.68-1.57 (m, 2 H), 1.50-1.38 (m, 2 H), 1.37-1.21 (m, 8 H), 0.87 (t, $J = 7.2$ Hz, 3 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 163.2, 144.0, 132.2, 116.5, 94.1, 77.3, 54.9, 31.8, 29.13, 29.06, 28.9, 28.2, 22.6, 19.4, 14.1 ppm. IR (neat, cm$^{-1}$): 3062, 2924, 2851, 2225, 1595, 1508, 1466, 1413, 1326, 1292. Anal. Calcd. for C$_{15}$H$_{22}$N$_2$O: C, 73.13; H, 9.00. Found: C, 73.13; H, 8.95.

F$_3$C
MeS

(4-((2,6-Bis(trifluoromethyl)phenyl)ethynyl)phenyl)(methyl)sulfane. Following the general procedure, a mixture of XPhos precatalyst 2a (1.9 mg, 0.0025 mmol), XPhos (1.2
mg, 0.0025 mmol), Cs₂CO₃ (847 mg, 2.6 mmol), 4-bromothioanisole (203 mg, 1.0 mmol), 2-ethynyl-1,3-bis(trifluoromethyl)benzene (310 mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 4 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 2% EtOAc in hexane) to afford the title compound colorless solid (328 mg, 91%), mp = 91-93 °C (hexane/EtOAc). ¹H NMR (300 MHz, CDCl₃) δ: 7.94 (s, 2 H), 7.81 (s, 1 H), 7.50-7.44 (m, 2 H), 7.26-7.20 (m, 2 H), 2.51 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 141.0, 132.0, 131.8 (q, J = 33.6 Hz), 131.2 (q, J = 3.6 Hz), 125.7, 125.6, 123.0 (q, J = 272.9 Hz), 121.3 (hept, J = 3.8 Hz), 117.8, 92.7, 86.4, 14.9 ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -63.6 ppm. IR (neat, cm⁻¹): 2926, 2227, 2202, 1614, 1589, 1497, 1441, 1386, 1287, 1180. Anal. Calcd. for C₁₇H₁₀F₆S: C, 56.67; H, 2.80. Found: C, 56.61; H, 2.65.

5-(Dec-1-yn-1-yl)-2-methylbenzo[d]thiazole. Following the general procedure, a mixture of XPhos precatalyst 2a (7.9 mg, 0.01 mmol), XPhos (4.8 mg, 0.01 mmol), Cs₂CO₃ (847 mg, 2.6 mmol), 5-chloro-2-methylbenzo[d]thiazole (184 mg, 1.0 mmol), 1-decyne (180 mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 6 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 2% EtOAc in hexane) to afford the title compound colorless solid (256 mg, 90%), mp = 52-53 °C (hexane/EtOAc). ¹H NMR (300 MHz, CDCl₃) δ: 7.93 (d, J = 1.2 Hz, 1 H), 7.63 (d, J = 8.1 Hz, 1 H), 7.30 (dd, J = 8.1, 1.2 Hz, 1 H), 2.75 (s, 3 H), 2.38 (t, J = 6.9 Hz, 2 H), 1.63-1.51 (m, 2 H), 1.46-1.19 (m, 10 H), 0.85 (t, J = 6.6 Hz, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 167.4, 153.2, 134.8, 127.9, 125.1, 121.8, 120.9, 90.5, 80.1, 31.7, 29.1, 29.0, 28.8, 28.6, 22.5, 19.9, 19.3, 14.0 ppm. IR (neat, cm⁻¹): 3053, 2956, 2921, 2851, 2228, 1183, 1749, 1538, 1455, 1417. Anal. Calcd. for C₁₈H₂₃NS: C, 75.74; H, 8.12. Found: C, 75.65; H, 8.32.
1,3-Di-tert-butyl-5-(cyclohex-1-en-1-ylethynyl)benzene. Following the general procedure, a mixture of XPhos precatalyst 2a (1.9 mg, 0.0025 mmol), XPhos (1.2 mg, 0.0025 mmol), Cs$_2$CO$_3$ (847 mg, 2.6 mmol), 1-bromo-3,5-di-tert-butylbenzene (269 mg, 1.0 mmol), 1-ethynylcyclohex-1-ene (138 mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 7 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, hexane) to afford the title compound colorless solid (213 mg, 72%), mp = 106-108 °C (hexane/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ: 7.26 (d, $J =$ 1.8 Hz, 1 H), 7.20 (d, $J =$ 1.8 Hz, 2 H), 6.18-6.15 (m, 1 H), 2.18-2.14 (m, 2 H), 2.12-2.04 (m, 2 H), 1.64-1.48 (m, 4 H), 1.234 (s, 18 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 150.5, 134.7k 125.7, 122.6, 122.1, 120.8, 89.9, 87.8, 34.7, 31.3, 29.3, 25.7, 22.3, 21.5 ppm. IR (neat, cm$^{-1}$): 3060, 3026, 2963, 2097, 1590, 1493, 1478, 1452, 1427, 1363. Anal. Calcd. for C$_{22}$H$_{30}$: C, 89.73; H, 10.27. Found: C, 89.70; H, 10.24.

3-(Phenanthren-9-ylethynyl)pyridine. Following the general procedure, a mixture of XPhos precatalyst 2a (1.9 mg, 0.0025 mmol), XPhos (1.2 mg, 0.0025 mmol), Cs$_2$CO$_3$ (847 mg, 2.6 mmol), 9-bromophenanthrene (257 mg, 1.0 mmol), 3-ethynylpyridine (134 mg, 1.3 mmol), and 2 mL MeCN was heated to 90 °C for 9 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 10% EtOAc in hexane) to afford the title compound colorless solid (234 mg, 84%), mp = 110-111 °C (hexane/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ: 8.94 (d, $J =$ 1.2 Hz, 1 H), 8.61-8.42 (m, 4 H), 8.01 (s, 1 H), 7.86-7.75 (m, 2 H), 7.71-7.49 (m, 4 H),
7.26-7.17 (m, 1 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 152.0, 148.4, 138.1, 132.1, 130.7, 130.5, 130.1, 129.8, 128.4, 127.4, 126.89, 126.86, 126.7, 126.4, 122.8, 122.6, 122.3, 120.2, 118.5, 90.9, 90.1 ppm. IR (neat, cm$^{-1}$): 3059, 2211, 1594, 1560, 1492, 1477, 1451, 1406, 1383, 1184. Anal. Calcd. for C$_{21}$H$_{13}$N: C, 90.29; H, 4.69. Found: C, 89.99; H, 4.61.

5-(Oct-1-yn-1-yl)benzo[d][1,3]dioxole. Following the general procedure, a mixture of XPhos precatalyst 2a (7.9 mg, 0.01 mmol), XPhos (4.8 mg, 0.01 mmol), Cs$_2$CO$_3$ (647 mg, 2.0 mmol), benzo[d][1,3]dioxol-5-yl 4-methylbenzenesulfonate (146 mg, 0.5 mmol), 1-octyne (83 mg, 0.75 mmol), and 1 mL MeCN was heated to 90 °C for 15 h and then was cooled to room temperature. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column, 5% EtOAc in hexane) to afford the title compound clear oil (78 mg, 68%). $^1$H NMR (300 MHz, CDCl$_3$) δ: 6.91 (dd, $J = 8.1$, 1.5 Hz, 1 H), 6.85 (d, $J = 1.5$ Hz, 1 H), 6.72 (d, $J = 8.1$ Hz, 1 H), 5.94 (s, 2 H), 2.37 (t, $J = 6.9$ Hz, 2 H), 1.63-1.53 (m, 2 H), 1.50-1.25 (m, 6 H), 0.91 (t, $J = 6.6$ Hz, 3 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 147.2, 147.1, 125.8, 117.4, 111.6, 108.2, 101.1, 88.6, 80.2, 31.3, 28.7, 28.6, 22.5, 19.3, 14.0 ppm. IR (neat, cm$^{-1}$): 2930, 2858, 1603, 1504, 1490, 1441, 1327, 1246, 1211, 1041. Anal. Calcd. for C$_{15}$H$_{18}$O$_2$: C, 78.23; H, 7.88. Found: C, 78.40; H, 7.93.

**Experimental Setup**

The equipment configuration that was used for the continuous-flow of Sonogashira cross-coupling reaction is described in Figure S1. Two Harvard Apparatus PHD2000 syringe pumps were used to deliver reagents from Harvard Apparatus stainless syringes to the reactor. The packed bed reactor had a volume of 450 µL (11.25 cm length, 0.381 cm ID, packing 60-125 µm stainless steel spheres) and was assembled according to a literature procedure.$^{[4]}$ The tubing from the syringes to the reactor was made out of PFA capillary tubing (1/16” OD x 500 µm ID) and all fluidic connections were made using either 1/4-28 flat bottomed flangeless fittings or 10-32 coned fittings (IDEX Health and Science).
The mixing tee’s used in this work were made out of TEFZEL® (ETFE) (500 µm ID) and purchased from IDEX Health and Science. The backpressure regulator was purchased from IDEX Health and Science. The packed bed reactor was submerged in an oil bath. The bath temperature was monitored via a thermocouple and maintained with a Waage immersion heater controlled by a J-KEM Scientific Gemini PID controller. Upon exiting the reactor and through the backpressure regulator, the reaction stream was quenched by a stream of H2O and EtOAc. These two streams were delivered the third Harvard Apparatus PHD2000 syringe pump. The diluted reaction stream was collected.

**Figure S1.** Microreactor setup for the continuous-flow synthesis of aryl alkynes.

**General procedure for continuous-flow:** An oven-dried screw-top volumetric flask (25.0 mL) that was fitted with a Teflon screw-cap, was charged with aryl bromide (8.33 mmol), biphenyl (1.284 g, 8.33 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and alkyne (10.83 mmol) and PEG 200 (1.3 mL) were added via syringe and dioxane was added to make the solution volume 25 mL. A second oven-dried screw-top volumetric flask (5.00 mL) that was fitted with a Teflon screw-cap, was charged with XPhos precatalyst 2a (39.3 mg, 0.05 mmol) and XPhos (23.9 mg, 0.05 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and dioxane was added to make the solution volume 5 mL. The first solution and aqueous KOH (0.87 M) were loaded into 20 mL Harvard Apparatus stainless syringes and fitted to a first syringe pump. The solution of precatalyst was loaded into 8 mL Harvard Apparatus stainless syringe and fitted to a second syringe pump. As diagrammed in Figure S1, different flow rates gave different residence times. When exiting the reactor and passing through the backpressure regulator, the reaction was quenched with ethyl acetate and water. The flow rate of the ethyl acetate stream and water stream are both 100 µL/min. Typically, each experiment is preceded by
a flush (about 4 reactor-volume) in order to ensure steady-state data collection. When the aryl bromide was completely consumed monitored by GC, a sample was collected in order to obtain exactly 1 mmol of product. The organic layer was separated and the aqueous layer was diluted with ethyl acetate, washed with water and brine, dried over Na₂SO₄, concentrated in vacuo and purified by column chromatography via Biotage SP4 (silica-packed 25 g snap column; eluting with hexanes and 0-20% ethylacetate).

![C₁₀H₂₁](attachment:image.png)

**1-(Dodec-1-yn-1-yl)-4-methylbenzene.** Follow the general procedure, a first syringe was loaded with 4-bromotoluene (0.33 M), 1-dodecyne (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 64.3 µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 64.3 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 21.4 µL/min). A sample was collected for 47 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes) to give the title compound as clear oil (233 mg, 93 %). ¹H NMR (300 MHz, CDCl₃) δ: 7.30 (d, J = 8.1 Hz, 2 H), 7.09 (d, J = 8.1 Hz, 2 H), 2.40 (t, J = 6.9 Hz, 2 H), 2.34 (s, 3 H), 1.64-1.54 (m, 2 H), 1.50-1.38 (m, 2 H), 1.37-1.20 (m, 12 H), 0.90 (t, J = 6.6 Hz, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 137.4, 131.4, 128.9, 121.0, 89.6, 80.5, 31.9, 29.59, 29.55, 29.33, 29.17, 28.9, 28.8, 22.7, 21.4, 19.4, 14.1 ppm. IR (neat, cm⁻¹): 2925, 2855, 1653, 1559, 1510, 1457, 816. Anal. Calcd. for C₁₉H₂₈: C, 88.99; H, 11.01. Found: C, 89.03; H, 10.99.

![MeS](attachment:image.png)

**(4-((4-Fluorophenyl)ethynyl)phenyl)(methyl)sulfane.** Follow the general procedure, a first syringe was loaded with 4-bromothioanisole (0.33 M), 1-ethynyl-4-fluorobenzene (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 113.4 µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 113.4 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 21.4 µL/min). A sample was collected for 47 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with hexanes) to give the title compound as clear oil (233 mg, 93 %). ¹H NMR (300 MHz, CDCl₃) δ: 7.30 (d, J = 8.1 Hz, 2 H), 7.09 (d, J = 8.1 Hz, 2 H), 2.40 (t, J = 6.9 Hz, 2 H), 2.34 (s, 3 H), 1.64-1.54 (m, 2 H), 1.50-1.38 (m, 2 H), 1.37-1.20 (m, 12 H), 0.90 (t, J = 6.6 Hz, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 137.4, 131.4, 128.9, 121.0, 89.6, 80.5, 31.9, 29.59, 29.55, 29.33, 29.17, 28.9, 28.8, 22.7, 21.4, 19.4, 14.1 ppm. IR (neat, cm⁻¹): 2925, 2855, 1653, 1559, 1510, 1457, 816. Anal. Calcd. for C₁₉H₂₈: C, 88.99; H, 11.01. Found: C, 89.03; H, 10.99.
µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 113.4 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 37.8 µL/min). A sample was collected for 27 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 5% EtOAc in hexanes) to give the title compound as a colorless solid (196 mg, 81%), mp = 95-96 °C (hexane/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.55-7.41 (m, 4 H), 7.24-7.18 (m, 2 H), 7.09-7.00 (m, 2 H), 2.49 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 162.3 (d, $J = 249.5$ Hz), 139.4, 133.3 (d, $J = 8.3$ Hz), 131.7, 125.7, 119.3 (d, $J = 3.5$ Hz), 119.2, 115.5 (d, $J = 22.1$ Hz), 88.8 (d, $J = 1.6$ Hz), 88.3, 15.2 ppm. $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$: -111.3 ppm. IR (neat, cm$^{-1}$): 2917, 1904, 1661, 1604, 1584, 1516, 1400, 1243, 1091, 836. Anal. Calcd. for C$_{15}$H$_{11}$FS: C, 74.35; H, 4.58. Found: C, 74.31; H, 4.63.

4-(Cyclohex-1-en-1-ylethynyl)-2-fluoro-1-methoxybenzene. Follow the general procedure, a first syringe was loaded with 4-bromothioanisole (0.33 M), 1-ethynyl-4-fluorobenzene (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 28.13 µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 28.13 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 9.38 µL/min). A sample was collected for 108 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 5% EtOAc in hexanes) to give the title compound as clear oil (226 mg, 98%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.17-7.10 (m, 2 H), 6.89-6.82 (m, 1 H), 6.21-6.15 (m, 1 H), 3.87 (s, 3 H), 2.24-2.09 (m, 4 H), 1.72-1.55 (m, 4 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 151.8 (d, $J = 246.2$ Hz), 147.8 (d, $J = 10.7$ Hz), 135.3, 128.1 (d, $J = 3.5$ Hz), 120.7, 119.1 (d, $J = 19.4$ Hz), 116.5 (d, $J = 8.4$ Hz), 113.1 (d, $J = 2.5$ Hz), 90.7, 85.7 (d, $J = 2.8$ Hz), 56.3, 29.3, 25.9, 22.5, 21.7 ppm. $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$: -135.7 ppm. IR (neat, cm$^{-1}$): 2937, 2193, 1723, 1667, 1613, 1574, 1516, 1443, 1308, 1271.
3-(6-Chlorohex-1-yn-1-yl)-4-methylpyridine. Follow the general procedure, a first syringe was loaded with 3-bromo-4-methylpyridine (0.33 M), 1-ethynylcyclohex-1-ene (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 56.72 µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 56.72 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 18.91 µL/min). A sample was collected for 54 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 10% EtOAc in hexanes) to give the title compound as clear oil (161 mg, 82%). ¹H NMR (300 MHz, CDCl₃) δ: 8.44 (s, 1 H), 8.24 (d, J = 5.1 Hz, 1 H), 6.99 (d, J = 5.1 Hz, 1 H), (m, 1 H), 3.50 (t, J = 6.3 Hz, 2 H), 2.42 (t, J = 6.9 Hz, 2 H), 2.29 (s, 3 H), 1.93-1.81 (m, 2 H), 1.74-1.62 (m, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 151.9, 148.3, 147.5, 123.8, 120.8, 96.2, 76.6, 44.2, 31.3, 25.6, 19.9, 18.6 ppm. IR (neat, cm⁻¹): 2952, 2868, 2231, 1590, 1483, 1475, 123.8, 120.8, 96.2, 76.6, 44.2, 31.3, 25.6, 19.9, 18.6 ppm.

Ethyl 4-(dec-1-yn-1-yl)benzoate. Follow the general procedure, a first syringe was loaded with ethyl 4-bromobenzoate (0.33 M), 1-decyne (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 33.75 µL/min). A second syringe was loaded with aqueous K₃PO₄ (0.87 M) (flow rate: 33.75 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 11.25 µL/min). A sample was collected for 90 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 5% EtOAc in hexanes) to give the title compound as clear oil (217 mg, 76%). ¹H NMR (300 MHz, CDCl₃) δ: 7.99-
7.92 (m, 2 H), 7.46-7.41 (m, 2 H), 4.36 (q, $J = 7.2$ Hz, 2 H), 2.41 (t, $J = 6.9$ Hz, 2 H),
1.65-1.55 (m, 2 H), 1.50-1.22 (m, 13 H), 0.88 (t, $J = 7.2$ Hz, 3 H) ppm. $^{13}$C NMR (75
MHz, CDCl$_3$) $\delta$: 166.1, 131.4, 129.3, 129.1, 128.8, 93.9, 80.1, 61.0, 31.8, 29.2, 29.1,
28.9, 28.5, 22.6, 19.5, 14.3, 14.1 ppm. IR (neat, cm$^{-1}$): 2929, 2856, 2234, 1720, 1607,
Found: C, 79.43; H, 9.25.

3-(Cyclohex-1-en-1-ylethynyl)-4-methoxybenzonitrile. Follow the general procedure, a
first syringe was loaded with 3-bromo-4-methoxybenzonitrile (0.33 M), 1-ethynlylcyclohex-1-ene (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 84.38 µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 84.38 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 28.13 µL/min). A sample was collected for 36 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 20% EtOAc in hexanes) to give the title compound as light yellow oil (214 mg, 90%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.60 (d, $J = 2.1$ Hz, 1 H), 7.49 (dd, $J = 8.7$, 2.1 Hz, 1 H), 6.88 (d, $J = 8.7$ Hz, 1 H), 6.24-6.20 (m, 1 H), 3.88 (s, 3 H), 2.23-2.07 (m, 4 H), 1.69-1.53 (m, 4 H) ppm. $^{13}$C NMR (75 MHz,
CDCl$_3$) $\delta$: 162.4, 136.5, 136.3, 133.0, 120.2, 118.3, 114.5, 110.9, 103.8, 97.2, 80.5, 56.0,
28.8, 25.6, 22.0, 21.2 ppm. IR (neat, cm$^{-1}$): 2934, 2859, 2227, 1597, 1497, 1460, 1441,
1292, 1277, 1020.

4-Methoxy-2-methyl-1-(phenylethynyl)benzene.$^{[5]}$ Follow the general procedure, a first
syringe was loaded with 1-bromo-4-methoxy-2-methylbenzene (0.33 M), phenyl
acetylene (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow
rate: 48.21 µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 48.21 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 16.07 µL/min). A sample was collected for 36 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 5% EtOAc in hexanes) to give the title compound as colorless solid (191 mg, 86%), mp = 82-83 °C (hexane/EtOAc). ¹H NMR (300 MHz, CDCl₃) δ: 7.58-7.53 (m, 2 H), 7.47 (d, J = 8.7 Hz, 1 H), 7.41-7.32 (m, 3 H), 6.82-6.79 (m, 1 H), 6.75 (dd, J = 8.7, 2.4 Hz, 1 H), 3.83 (s, 3 H), 2.53 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 159.5, 141.9, 133.1, 131.3, 128.3, 127.8, 123.8, 115.2, 115.1, 111.2, 91.9, 88.4, 55.2, 21.0 ppm. IR (neat, cm⁻¹): 3013, 2934, 2837, 2207, 1603, 1593, 1568, 1499, 1462, 1440. Anal. Calcd. for C₁₆H₁₄O: C, 86.45; H, 6.35. Found: C, 86.52; H, 6.42.

2-(Dec-1-yn-1-yl)-6-methoxypyridine. Follow the general procedure, a first syringe was loaded with 2-bromo-6-methoxypyridine (0.33 M), 1-decyne (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 66.50 µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 66.50 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 22.17 µL/min). A sample was collected for 46 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 10% EtOAc in hexanes) to give the title compound as light yellow oil (198 mg, 80%). ¹H NMR (300 MHz, CDCl₃) δ: 6.45 (dd, J = 8.1, 7.2 Hz, 1 H), 6.97 (d, J = 7.2 Hz, 1 H), 6.64 (d, J = 8.1 Hz, 1 H), 3.93 (s, 3 H), 2.42 (t, J = 7.2 Hz, 2 H), 1.66-1.55 (m, 2 H), 1.49-1.19 (m, 10 H), 0.87 (t, J = 6.6 Hz, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 163.7, 140.8, 138.3, 120.2, 110.3, 90.5, 80.4, 53.4, 31.8, 29.13, 29.06, 29.0, 28.4, 22.6, 19.4, 14.0 ppm. IR (neat, cm⁻¹): 2928, 2856, 2230, 1584, 1571, 1462, 1431, 1405, 1315, 1241. Anal. Calcd. for C₁₆H₂₃NO: C, 78.32; H, 9.45. Found: C, 78.49; H, 9.52.
Phenyl-(4-(phenylethynyl)phenyl)methanone. Follow the general procedure, a first syringe was loaded with (4-bromophenyl)phenylmethanone (0.33 M), phenyl acetylene (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 175.3 µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 175.3 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 58.4 µL/min). A sample was collected for 18 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 5% EtOAc in hexanes) to give the title compound as colorless solid (260 mg, 92%), mp = 119-121 °C (hexane/EtOAc). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.84-7.78 (m, 4 H), 7.67-7.54 (m, 5 H), 7.54-7.46 (m, 2 H), 7.42-7.35 (m, 3 H) ppm. \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 195.9, 137.3, 136.7, 132.5, 131.7, 131.4, 130.0, 129.9, 128.7, 128.4, 128.3, 127.5, 122.6, 92.4, 88.6 ppm. IR (neat, cm\(^{-1}\)): 1646, 1602, 1441, 1385, 1286, 1070, 854, 793, 755, 745. Anal. Calcd. for C\(_{21}\)H\(_{14}\)O: C, 89.34; H, 5.00. Found: C, 89.17; H, 4.89.

1-(Dec-1-yn-1-yl)-2-methoxynaphthalene. Follow the general procedure, a first syringe was loaded with 1-bromo-2-methoxynaphthalene (0.33 M), 1-decyne (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 67.5 µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 67.5 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 22.5 µL/min). A sample was collected for 45 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 10% EtOAc in hexanes) to give the title compound as clear oil (224 mg, 76%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 8.29 (d, \(J = 8.4\) Hz, 1 H), 7.77 (d, \(J = 9.0\) Hz, 2 H), 7.57-7.50 (m, 1 H), 7.41-7.33 (m, 1
5-(Cyclohex-1-en-1-ylethynyl)-1,2,3-trimethoxybenzene. Follow the general procedure, a first syringe was loaded with 5-bromo-1,2,3-trimethoxybenzene (0.33 M), 1-ethynylcyclohex-1-ene (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 33.75 µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 33.75 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 11.25 µL/min). A sample was collected for 90 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 20% EtOAc in hexanes) to give the title compound as clear oil (242 mg, 89%). $^1$H NMR (300 MHz, CDCl$_3$) δ: 6.64 (s, 2 H), 6.21-6.17 (m, 1 H), 3.82 (s, 9 H), 2.23-2.09 (m, 4 H), 1.68-1.56 (m, 4 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 152.9, 138.2, 135.1, 120.5, 118.7, 108.4, 90.2, 86.6, 60.8, 56.0, 29.1, 25.7, 22.2, 21.4 ppm. IR (neat, cm$^{-1}$): 2936, 2838, 1575, 1504, 1464, 1410, 1337, 1269, 1237, 1175. Anal. Calcd. for C$_{17}$H$_{20}$O$_3$: C, 74.94; H, 7.40. Found: C, 74.66; H, 7.38.

4-(Cyclohex-1-en-1-ylethynyl)isoquinoline. Follow the general procedure, a first syringe was loaded with 4-bromoisoquinoline (0.33 M), 1-ethynylcyclohex-1-ene (0.43
M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 66.50 µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 66.50 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 22.17 µL/min). A sample was collected for 46 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 10% EtOAc in hexanes) to give the title compound as clear oil (185 mg, 79%). 1H NMR (300 MHz, CDCl3) δ: 9.11 (s, 1 H), 8.64 (s, 1 H), 8.20 (d, J = 8.4 Hz, 1 H), 7.92 (d, J = 7.8 Hz, 1 H), 7.75-7.68 (m, 1 H), 7.62-7.54 (m, 1 H), 6.36-6.31 (m, 1 H), 2.36-2.28 (m, 2 H), 2.22-2.13 (m, 2 H), 1.76-1.58 (m, 4 H) ppm. 13C NMR (75 MHz, CDCl3) δ: 151.3, 146.0, 136.2, 135.4, 130.7, 127.7, 127.6, 127.5, 125.0, 120.5, 116.3, 98.7, 81.7, 29.1, 25.7, 22.2, 21.4 ppm. IR (neat, cm⁻¹): 3024, 2931, 2858, 2201, 1620, 1564, 1496, 1448, 1435, 1391.

6-(Dec-1-yn-1-yl)-3-fluoro-2-methylpyridine. Follow the general procedure, a first syringe was loaded with 6-bromo-3-fluoro-2-methylpyridine (0.33 M), 1-decyne (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 83.85 µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 83.85 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 27.95 µL/min). A sample was collected for 36 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 10% EtOAc in hexanes) to give the title compound as clear oil (210 mg, 85%). 1H NMR (300 MHz, CDCl3) δ: 7.19-7.11 (m, 2 H), 2.46-2.29 (m, 5 H), 1.60-1.47 (m, 2 H), 1.41-1.10 (m, 10 H), 0.80 (t, J = 6.3 Hz, 3 H) ppm. 13C NMR (75 MHz, CDCl3) δ: 158.3, 154.9, 147.0, 146.7, 138.8, 138.7, 125.5, 125.4, 122.3, 122.0, 90.0, 79.3, 31.6, 29.0, 28.9, 28.8, 28.2, 22.5, 19.1, 17.8, 13.9 ppm. 19F NMR (282 MHz, CDCl3) δ: -124.8 ppm. IR
(neat, cm$^{-1}$): 2928, 2856, 2234, 1594, 1461, 1384, 1237, 1164, 1113, 832. Anal. Calcd. for C$_{16}$H$_{22}$FN: C, 77.69; H, 8.96. Found: C, 77.78; H, 9.00.

6-(Dodec-1-yn-1-yl)-2-methylquinoline. Follow the general procedure, a first syringe was loaded 6-bromo-2-methylquinoline (0.33 M), 1-dodecyne (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 48.21 µL/min). A second syringe was loaded with aqueous KOH (0.87 M) (flow rate: 48.21 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 16.07 µL/min). A sample was collected for 63 minutes (1 mmol). The mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 10% EtOAc in hexanes) to give the title compound as clear oil (245 mg, 80%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.98-7.88 (m, 2 H), 7.80 (d, $J = 1.2$ Hz, 1 H), 7.64 (dd, $J = 8.7, 1.8$ Hz, 1 H), 7.25 (d, $J = 7.8$ Hz, 1 H), 2.72 (s, 3 H), 2.44 (t, $J = 6.9$ Hz, 2 H), 1.66-1.57 (m, 2 H), 1.50-1.25 (m, 14 H), 0.87 (t, $J = 6.3$ Hz, 3 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 159.0, 146.8, 135.4, 132.3, 130.2, 128.4, 126.0, 122.2, 121.3, 91.3, 80.2, 31.8, 29.5, 29.4, 29.2, 29.0, 28.8, 28.6, 25.2, 22.5, 19.3, 13.8 ppm. IR (neat, cm$^{-1}$): 2925, 2854, 1597, 1560, 1490, 1466, 1384, 1341, 1309, 1221. Anal. Calcd. for C$_{22}$H$_{29}$N: C, 85.94; H, 9.51. Found: C, 85.86; H, 9.46.

1-(4-(Cyclohex-1-en-1-ylethynyl)phenyl)ethanone.$^{[7]}$ Follow the general procedure, a first syringe was loaded 4-bromoacetophenone (0.33 M), 1-ethynycyclohex-1-ene (0.43 M), biphenyl (0.33 M), and PEG 200 (1.3 mL in 25 mL solution) (flow rate: 38.57 µL/min). A second syringe was loaded with aqueous K$_3$PO$_4$ (0.87 M) (flow rate: 38.57 µL/min). A third syringe was loaded with XPhos precatalyst (0.01 M) and XPhos (0.01 M) (flow rate: 12.85 µL/min). A sample was collected for 79 minutes (1 mmol).
mixture was diluted with ethyl acetate, and the organic layer washed with water and brine, concentrated in vacuo and purified by column chromatography (silica gel, eluting with 10% EtOAc in hexanes) to give the title compound as clear oil (183 mg, 82%). $^1$H NMR (300 MHz, CDCl$_3$) δ: 7.86 (d, $J = 8.4$ Hz, 2 H), 7.46 (d, $J = 8.4$ Hz, 2 H), 6.27-6.21 (m, 1 H), 2.56 (s, 3 H), 2.40-2.09 (m, 4 H), 1.71-1.55 (m, 4 H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 197.4, 136.7, 135.8, 131.6, 128.9, 128.3, 120.6, 94.9, 86.3, 29.2, 26.7, 26.0, 22.4, 21.5 ppm. IR (neat, cm$^{-1}$): 2932, 2859, 2200, 1684, 1599, 1555, 1435, 1403, 1359, 1264.

References:
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2011
SI-23
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2011