Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

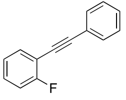
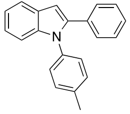
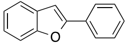
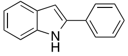
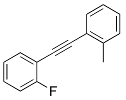
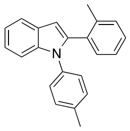
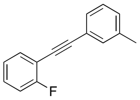
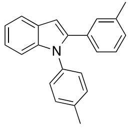
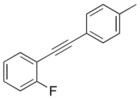
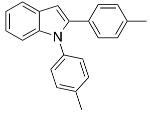
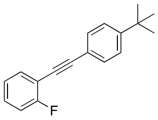
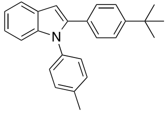
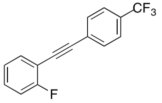
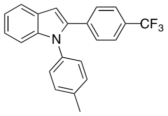
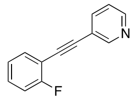
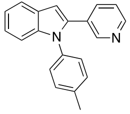
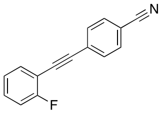
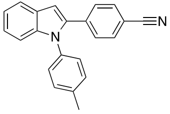
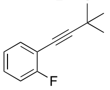
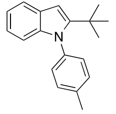
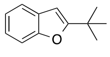
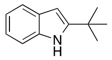
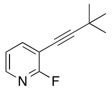
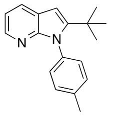
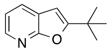
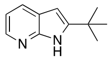
Synthesis of indoles, benzofurans, and related heterocycles via an acetylene-activated S_NAr/intramolecular cyclization cascade sequence in water or DMSO

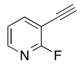
*Reuben Hudson,[a] Nicholas P. Bizier,[b] Kristin N. Esdale[a] and Jeffrey L. Katz[a]**

[a] Department of Chemistry, Colby College, 5754 Mayflower Hill Drive, Waterville, Maine, 04901, United States. [b] Division of Natural Sciences, Daemen College, 4380 Main St, Amherst, New York, 14226, United States

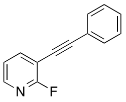
Supporting Information

Graphical Table of Contents with Compound Shorthand

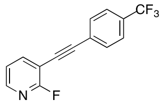
Electrophiles **1 (a-r)**	Indoles **2 (a-q)**	Benzofurans **3 (a-p)**	indoles **4 (a-p)**
 **1a**†	 **2a**†b	 **3a** – SI page 24‡	 **4a** – SI page 29‡
 **1b** – SI page 4‡	 **2b** – SI page 15‡		
 **1c** – SI page 4‡	 **2c** – SI page 15‡		
 **1d** – SI page 5‡	 **2d** – SI page 16‡		
 **1e** – SI page 5‡	 **2e** – SI page 16‡		
 **1f** – SI page 6‡	 **2f** – SI page 17‡		
 **1g** – SI page 7‡	 **2g** – SI page 18‡		
 **1h** – SI page 7‡	 **2h** – SI page 18‡		
 **1i**†	 **2i**†	 **3b** – SI page 24‡	 **4b** – SI page 29‡
 **1j** – SI page 8‡	 **2j –** SI page 19‡	 **3d** – SI page 25‡	 **4d** – SI page 30‡



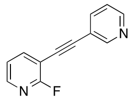
1k – SI page 8[‡]



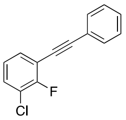
1l – SI page 9[‡]



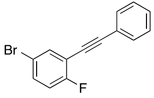
1m – SI page 10[‡]



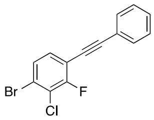
1n – SI page 10[‡]



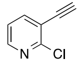
1o – SI page 11[‡]



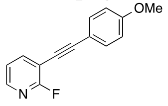
1p – SI page 12[‡]



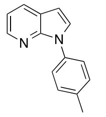
1q – SI page 12[‡]



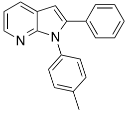
1r – SI page 13[‡][a]



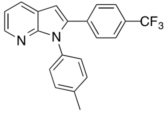
1s – SI page 13[‡]



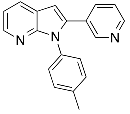
2k – SI page 19[‡][c]



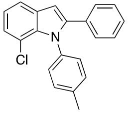
2l – SI page 20[‡]



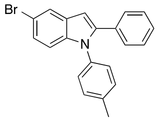
2m – SI page 21[‡]



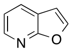
2n – SI page 21[‡]



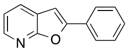
2o – SI page 22[‡]



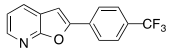
2p – SI page 23[‡]



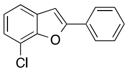
3e – SI page 25[‡][d]



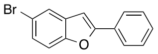
3c – SI page 26[‡]



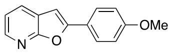
3g – SI page 26[‡]



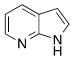
3j – SI page 27[‡]



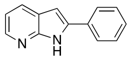
3k – SI page 28[‡]



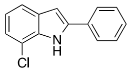
3h – SI page 27[‡]



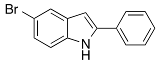
4e – SI page 30[‡]



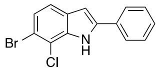
4c – SI page 31[‡]



4f – SI page 31[‡]



4g – SI page 32[‡]



4h – SI page 33[‡]

[†] synthesis and characterization data available in SI reference 1.

[‡] synthesis information and full characterization data (IR, TLC, HRMS, ^{1}H and ^{13}C NMR) available herein.

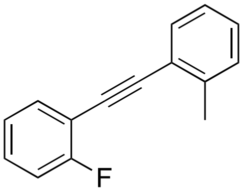
[a] ^{1}H NMR available for terminal-alkyne deuterated product (**1r-D**) on page 82.

[b] ^{1}H NMR available for C2-deuterated product (**2a-D**) on page 83.

[c] ^{1}H NMR available for C1,C2-deuterated product (**2k-D$_2$**) on page 84.

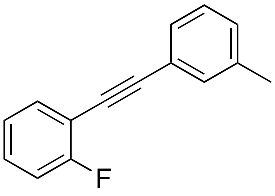
[d] ^{1}H NMR available for C1,C2-deuterated product (**3e-D$_2$**) on page 85.

Synthesis of 2-halo-arylacetylenes (1a-q)



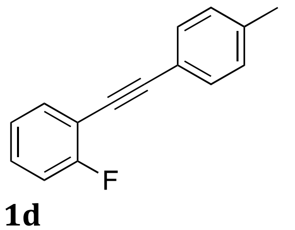
1b

In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol) and CuI (48 mg, 0.25 mmol). The mixture was purged with Argon for 5 minutes, and then degassed 2-fluoro-1-iodobenzene (1.0 mL, 8.75 mmol), degassed 2-ethynyltoluene (1.2 mL, 9.54 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes) gave 1.56 grams (7.43 mmol, 85 % yield) of product as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58-7.53 (td, J = 7.8 Hz, 1.9 Hz, 1H), 7.52-7.48 (d, J = 7.9 Hz, 2H), 7.36-7.30 (m, 1H), 7.21-7.19 (d, J = 7.8 Hz, 2H), 7.17-7.11 (q, 7.8 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ: 163.6, 161.6, 138.8, 131.6, 129.7, 129.6, 129.1, 123.9 (d, J = 3.8 Hz), 119.8, 115.6, 115.4, 94.6 (d, J = 3.3 Hz), 82.0, 21.5. TLC: R_f = 0.5 (hexanes). IR (ATR): 3031 (m), 2920 (m), 2216 (m), 1931 (m), 1800 (w), 1700 (m), 1600 (w), 1569 (m), 1486 (s), 1319 (w), 1271 (m), 1265 (s), 1221 (s). HRMS (DART): calculated for $[C_{15}H_{11}FH]^+$ 211.0918, measured 211.0921. ^{1}H and ^{13}C NMR spectra available on SI page 34.



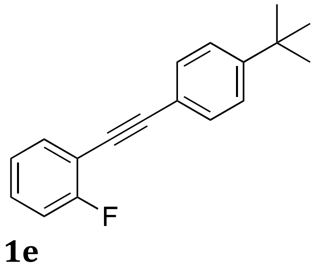
1c

In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol) and CuI (48 mg, 0.25 mmol). The mixture was purged with Argon for 5 minutes, and then degassed 2-fluoro-1-iodobenzene (1.0 mL, 8.75 mmol), degassed 3-ethynyltoluene (1.1 mL, 8.99 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes) gave 1.61 grams (7.66 mmol, 88 % yield) of product as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61-56 (td, J = 6.8 Hz, 1.9 Hz, 1H), 7.48-7.43 (d, J = 10.3 Hz, 2H), 7.38-7.29 (m, 2H), 7.25-7.21 (d, J = 7.8 Hz, 1H), 7.20-7.13 (q, *J* = 7.3 Hz, 2H), 7.42 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$): δ 163.7, 161.7, 138.1, 133.5 (d, *J* = 1.3 Hz), 132.3, 129.9 (d, *J* = 7.6 Hz), 129.6, 128.6 (d, *J* = 65.5 Hz), 124.0 (d, *J* = 3.8 Hz), 122.8, 115.6 (d, *J* = 21.4 Hz), 112.1 (d, *J* = 16.4 Hz), 94.8 (d, *J* = 2.5 Hz), 82.3, 21.2. TLC: R_f = 0.5 (hexanes). IR (ATR): 3038 (s), 2921 (s), 2212 (m), 1946 (w), 1793 (w), 1698 (w), 1598 (s), 1572 (s), 1495 (s), 1481 (s), 1380 (w), 1318 (w), 1264 (m), 1226 (s), 1205 (m), 1167 (w), 1155 (w), 1131 (w), 1098 (s), 1030 (m). HRMS (DART): calculated for $[C_{15}H_{11}FH]^+$ 211.0918, measured 211.0896. ^{1}H and ^{13}C NMR spectra available on SI page 35.



1d

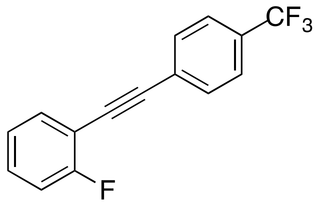
In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol) and CuI (48 mg, 0.25 mmol). The mixture was purged with Argon for 5 minutes, and then degassed 2-fluoro-1-iodobenzene (1.0 mL, 8.75 mmol), degassed 4-ethynyltoluene (1.2 mL, 9.46 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes) gave 1.65 grams (7.85 mmol, 90 % yield) of product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67-7.59 (m, 3H), 7.41-7.36 (m, 1H), 7.29-7.25 (d, *J* = 8 Hz, 2H), 7.24-7.18 (m, 2H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ: 163.6, 161.8, 138.8, 133.4 (d, *J* = 1.5 Hz), 131.6, 129.7 (d, *J* = 8.2 Hz), 129.1, 123.9 (d, *J* = 4.0 Hz), 119.8, 115.5 (d, *J* = 21.0 Hz), 112.1 (d, *J* = 15.6), 94.6 (d, *J* = 3.5 Hz), 21.5. TLC: R_f = 0.5 (hexanes). IR (ATR): 3027 (m), 2919 (m), 2219 (m), 1915 (m), 1805 (w), 1699 (m), 1662 (w), 1602 (w), 1566 (m), 1556 (m), 1542 (w), 1535 (w), 1509 (s), 1488 (s), 1444 (s), 1318 (w), 1276 (m), 1263 (s), 1219 (s), 1180 (m), 1139 (w), 1096 (m), 966 (w), 942 (m). HRMS (DART): calculated for $[C_{15}H_{11}FH]^+$ 211.0918, measured 211.0918. ^{1}H and ^{13}C NMR spectra available on SI page 36.



1e

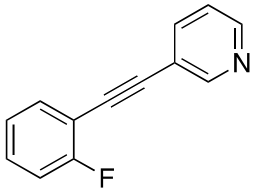
In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol) and CuI (48 mg, 0.25 mmol). The mixture was purged with Argon for 5 minutes, and then degassed 2-fluoro-1-iodobenzene (1.0 mL, 8.75 mmol), degassed 4-*tert*butylphenylacetylene (1.6 mL, 8.87

mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes) gave 1.91 grams (7.58 mmol, 87 % yield) of product as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.55-7.49 (m, 3H), 7.42-7.37 (d, J = 8.5 Hz, 2H), 7.34-7.28 (m, 1H), 7.16-7.08 (m, 2H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.5, 161.6, 151.9, 133.4, 131.4, 129.7 (d, J = 7.9 Hz), 125.4, 123.9 (d, J = 3.8 Hz), 120.0, 115.5 (d, J = 21.4 Hz), 112.2 (d, J = 15.8 Hz), 94.6 (d, J = 3.4 Hz), 34.8, 31.2. TLC: R_f = 0.5 (hexanes). IR (ATR): 2964 (s), 2860 (m), 2221 (w), 1918 (w), 1844 (w), 1733 (w), 1716 (w), 1698 (m), 1674 (w), 1616 (w), 1555 (m), 1567 (m), 1519 (m), 1502 (m), 1485 (s), 1450 (s), 1405 (w), 1362 (m), 1263 (s), 1213 (s), 1144 (w), 1094 (s), 1015 (m). HRMS (DART): calculated for $[C_{18}H_{17}FH]^+$ 253.1387, measured 253.1417. ^1H and ^{13}C NMR spectra available on SI page 37.



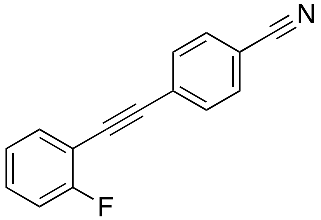
1f

In a sealed tube were added $PdCl_2(PPh_3)_2$ (89 mg, 0.13 mmol) and CuI (48 mg, 0.25 mmol). The mixture was purged with Argon for 5 minutes, and then degassed 2-fluoro-1-iodobenzene (1.0 mL, 8.75 mmol), degassed 1-ethynyl-4-(trifluoromethyl)benzene (1.5 mL, 9.19 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes) gave 1.61 grams (6.97 mmol, 80 % yield) of product as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.69-7.66 (d, J = 8.5 Hz, 2H), 7.64-7.61 (d, J = 8.5 Hz), 7.57-7.53 (td, J = 7.4 Hz, 1.8 Hz, 1H), 7.40-7.34 (m, 1H), 7.19-7.11 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ: 163.7, 161.7, 133.5 (d, J = 0.9 Hz), 131.9, 130.6 (d, J = 7.9 Hz), 126.7, 125.3 (q, J = 3.8 Hz), 124.9, 124.1 (d, J = 3.8 Hz), 115.6 (d, J = 20.5 Hz), 111.2 (d, J = 15.8 Hz), 92.8 (d, J = 3.2 Hz), 85.0. TLC: R_f = 0.5 (hexanes). IR (ATR): 3060 (w), 2928 (w), 2225 (m), 1927 (w), 1806 (w), 1698 (w), 1675 (w), 1615 (m), 1604 (s), 1555 (m), 1542 (m), 1521 (w), 1489 (s), 1449 (s), 1405 (m), 1324 (s), 1265 (s), 1223 (s), 1156 (s), 1104 (s). HRMS (DART): calculated for $[C_{15}H_8F_4H]^+$ 265.0635, measured 265.0661. ^1H and ^{13}C NMR spectra available on SI page 38.



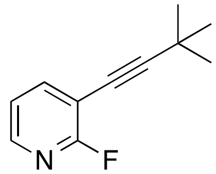
1g

In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol), CuI (48 mg, 0.25 mmol), and 3-ethynylpyridine (928 mg, 9.00 mmol). The mixture was purged with Argon for 5 minutes, and then degassed 2-fluoro-1-iodobenzene (1.0 mL, 8.75 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2, step gradient) gave 1.34 grams (6.80 mmol, 78 % yield) of product as a brown oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.60 (s, 1H), 7.84-7.80 (d, J = 7.5 Hz, 1H), 7.54-7.50 (td, J = 7.5 Hz, 1.7 Hz, 1H), 7.36-7.26 (m, 2H), 7.16-7.08 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.6, 161.6, 152.2, 149.7, 138.5, 133.4, 130.6 (d, J = 7.6 Hz), 124.1 (d, J = 3.8 Hz), 123.2, 115.6 (d, J = 21.4 Hz), 111.2 (d, J = 16.4 Hz), 90.2 (d, J = 2.9 Hz), 86.0. TLC: R_f = 0.4 (CH_2Cl_2). IR (ATR): 3421 (w), 3033 (m), 2226 (w), 1917 (w), 1844 (w), 1795 (w), 1733 (w), 1716 (w), 1698 (w), 1662 (w), 1612 (w), 1572 (m), 1561 (s), 1542 (w), 1524 (w), 1492 (s), 1473 (m), 1452 (m), 1406 (s), 1329 (w), 1264 (s), 1221 (s), 1187 (m), 1159 (w), 1145 (w), 1120 (w), 1098 (s), 1022 (s), 943 (w). HRMS (DART): calculated for $[C_{13}H_8FNH]^+$ 198.0714, measured 198.0697. ^1H and ^{13}C NMR spectra available on SI page 39.



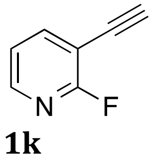
1h

In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol), CuI (48 mg, 0.25 mmol), and 4-ethynylbenzonitrile (1.144 g, 9.00 mmol). The mixture was purged with Argon for 5 minutes, and then degassed 2-fluoro-1-iodobenzene (1.0 mL, 8.75 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → EtOAc/hexanes, 1/9, step gradient) gave 290 mg (1.31 mmol, 15 % yield) of product as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.66-7.61 (m, 4H), 7.55-7.51 (td, J = 7.5 Hz, 1.7 Hz, 1H), 7.41-7.35 (m, 1H), 7.19-7.11 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.7, 161.7, 133.5, 132.1 (d, J =12.6 Hz), 130.9 (d, J = 7.6 Hz), 127.8, 124.1 (d, J = 15.0 Hz), 118.4, 115.7 (d, J = 85.0 Hz), 111.8, 111.0 (d, J = 17.6), 92.5 (d, J = 3.4), 87.0. TLC: R_f = 0.5 (EtOAc/hexanes, 1/9). IR (ATR): 3030 (w), 2924 (m), 2880 (w), 2221 (s), 1931 (m), 1796 (w), 1716 (w), 1698 (w), 1676 (w), 1600 (s), 1574 (m), 1555 (m), 1542 (w), 1535 (w), 1504 (s), 1485 (s), 1442 (m), 1409 (m), 1320 (w), 1263 9s), 1216 (s), 1179 (m), 1155 (w), 1136 (w), 1108 (w), 1096 (s), 1029 (m), 1017 (m). HRMS (DART): calculated for $[C_{15}H_8FNH]^+$ 222.0714, measured 222.0695. ^{1}H and ^{13}C NMR spectra available on SI page 40.



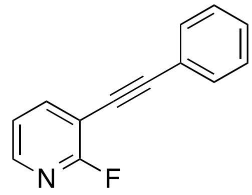
1j

In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol), CuI (48 mg, 0.25 mmol), and 2-fluoro-3-iodopyridine (1.95 g, 8.75 mmol). The mixture was purged with Argon for 5 minutes, and then degassed 3,3-dimethyl-1-butyne (1.1 mL, 8.93 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → EtOAc/hexanes, 1/9, step gradient) gave 1.02 g (5.76 mmol, 66 % yield) of product as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ: 8.10-8.07 (ddd, J = 4.9 Hz, 2.0 Hz, 1.0 Hz, 1H), 7.79-7.74 (dd, J = 7.5 Hz, 2.0 Hz, 1H), 7.13-7.09 (dd, J = 5.0 Hz, 1.8 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ: 163.7, 161.8, 145.7 (d, J = 14.5 Hz), 143.3 (d, J = 2.9 Hz), 120.8 (d, J = 4.5 Hz), 105.7 (d, J = 1.9 Hz), 71.0 (d, J = 4.6 Hz), 30.7, 28.2. TLC: R_f = 0.6 (EtOAc/hexanes, 1/9). IR (ATR): 3056 (m), 2223 (m), 1955 (w), 1884 (w), 1748 (w), 1716 (w), 1698 (w), 1674 (w), 1593 (m), 1562 (m), 1491 (s), 1430 (s), 1391 (w), 1316 (w), 1291 (w), 1278 (w), 1252 (s), 1212 (m), 1178 (w), 1151 (m), 1069 (m), 1027 (m). HRMS (DART): calculated for $[C_{11}H_{12}FNH]^+$ 178.1027, measured 178.1025. ^{1}H and ^{13}C NMR spectra available on SI page 41.



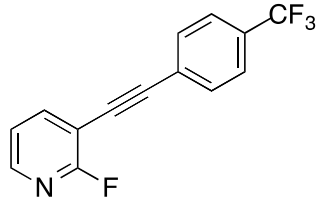
1k

In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol), CuI (48 mg, 0.25 mmol), and 2-fluoro-3-iodopyridine (1.95 g, 8.75 mmol). The mixture was purged with Argon for 5 minutes, and then degassed ethynyltrimethylsilane (1.3 mL, 9.20 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Deprotection (addition of tetrabutyl ammonium fluoride [1M in THF, 10 mL, 10 mmol], and stirring at room temperature for 30 minutes) followed an initial purification of the TMS protected product by silica gel flash column chromatography (CH_2Cl_2 → $MeOH/CH_2Cl_2$, 1/19, step gradient). The mixture was then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (CH_2Cl_2 → $MeOH/CH_2Cl_2$, 1/19) gave 854 mg (7.06 mmol, 81 % yield) of product as a yellow solid.^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22-8.17 (m, 1H), 7.92-7.87 (m, 1H), 7.20-7.16 (m, 1H), 3.38 (s, 1H).^{13}C NMR (126 MHz, $CDCl_3$): δ 164.2, 162.2, 147.3 (d, J = 14.5 Hz), 144.2 (d, J = 2.5 Hz), 120.1 (d, J = 3.8 Hz), 106.3 (d, J = 31.5 Hz), 84.1 (d, J = 2.0 Hz). TLC: R_f = 0.8 ($MeOH/CH_2Cl_2$, 1/19). IR (ATR): 3243 (s), 3096 (m), 3054 (m), 2926 (m), 2172 (w), 2109 (s), 1971 (m), 1938 (m), 1906 (m), 1765 (m), 1599 (s), 1566 (s), 1552 (m), 1443 (s), 1421 (s), 1325 (m), 1291 (s), 1252 (s), 1172 (s), 1107 (s). HRMS (DART): calculated for $[C_7H_4FNH]^+$ 122.0401, measured 122.0408. ^{1}H and ^{13}C NMR spectra available on SI page 42.



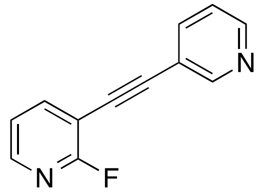
1l

In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol), CuI (48 mg, 0.25 mmol), and 2-fluoro-3-iodopyridine (1.95 g, 8.75 mmol). The mixture was purged with Argon for 5 minutes, and then degassed phenylacetylene (1.0 mL, 9.11 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → EtOAc/hexanes, 1/9, step gradient) gave 1.40 g (7.10 mmol, 81 % yield) of product as a brown solid.^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10-8.07 (dt, J = 5 Hz, 0.9 Hz, 1H), 7.84-7.79 (m, 1H), 7.53-7.48 (m, 2H), 7.33-7.28 (m, 3H), 7.11-7.07 (m, 1H).^{13}C NMR (126 MHz, $CDCl_3$): δ 163.4, 161.5, 146.5 (d, J = 13.8 Hz), 143.3 (d, J = 2.5 Hz), 131.7, 129.1, 128.5, 122.1, 121.1 (d, J = 4.3 Hz), 107.4 (d, J = 31.5 Hz), 96.0 (d, J = 1.9 Hz), 81.0 (d, J = 5.3 Hz). TLC: R_f = 0.4 (EtOAc/hexanes, 1/9). IR (ATR): 3057 (m), 2223 (m), 1955 (w), 1884 (w), 1748 (w), 1716 (w), 1698 (w), 1674 (w), 1593 (s), 1562 (s), 1491 (s), 1430 (s), 1391 (s), 1291 (w), 1278 (w), 1252 (s), 1212 (s), 1178 (w), 1151 (m), 1097 (s), 1069 (w), 1027 (m). HRMS (DART): calculated for $[C_{13}H_8FNH]^+$ 198.0714, measured 198.0714. ^{1}H and ^{13}C NMR spectra available on SI page 43.



1m

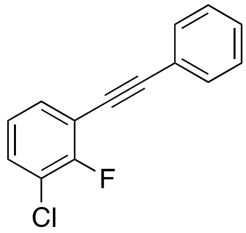
In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol), CuI (48 mg, 0.25 mmol), and 2-fluoro-3-iodopyridine (1.95 g, 8.75 mmol). The mixture was purged with Argon for 5 minutes, and then degassed 1-ethynyl-4-(trifluoromethyl)benzene (1.5 mL, 9.19 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → EtOAc/hexanes, 1/9, step gradient) gave 1.71 g (6.45 mmol, 74 % yield) of product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22-8.19 (dq, J = 5.0 Hz, 1.0 Hz, 1H), 7.96-7.91 (m, 1H), 7.69-7.60 (m, 4H), 7.24-7.20 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.6, 161.7, 147.2 (d, J = 13.9 Hz), 143.5 (d, J = 2.4 Hz), 132.0, 130.7 (q, J = 32.8 Hz), 126.0 (d, J = 1.4 Hz), 125.4 (q, J = 3.8 Hz), 121.1 (d, J = 4.4 Hz), 106.9 (d, J = 31.5), 94.3, 83.1 (d, J =5.3 Hz). TLC: R_f = 0.5 (EtOAc/hexanes, 1/9). IR (ATR): 3050 (w), 2890 (w), 1931 (w), 1748 (w), 1699 (w), 1675 (w), 1614 (w), 1595 (m), 1562 (m), 1524 (w), 1501 (w), 1456 (m), 1437 (s), 1403 (w), 1321 (s), 1255 (m), 1216 (w), 1184 (w), 1162 (s), 1125 (m), 1063 (s), 1013 (s). HRMS (DART): calculated for $[C_{14}H_7FNH]^+$ 266.0587, measured 266.0597. ^{1}H and ^{13}C NMR spectra available on SI page 44.



1n

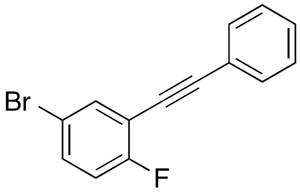
In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol), CuI (48 mg, 0.25 mmol), 2-fluoro-3-iodopyridine (1.95 g, 8.75 mmol), and 3-ethynylpyridine (928 mg, 9.00 mmol). The mixture was purged with Argon for 5 minutes, and then degassed triethylamine (12 mL) was added. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (CH_2Cl_2 → $MeOH/CH_2Cl_2$, 1/19, step gradient) gave 1.25 g (6.31 mmol, 72 % yield) of product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73-8.69 (d, J =

1.5 Hz, 1H), 8.53-8.50 (dd, *J* = 5.0 Hz, 1.5 Hz, 1H), 8.15-8.10 (dq, *J* = 5.0 Hz, 0.9 Hz, 1H), 7.89-7.84 (m, 1H), 7.78-7.75 (dt, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.26-7.22 (ddd, *J* = 8.0 Hz, 5.0 Hz, 0.8 Hz, 1H), 7.17-7.13 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.4, 161.6, 152.3, 149.3, 147.2 (d, *J* = 14.5 Hz), 143.4 (d, *J* = 2.4 Hz), 138.6, 123.1, 121.1 (d, *J* = 2.5 Hz), 119.4, 92.4 (d, *J* = 1.9 Hz), 84.1 (d, *J* = 12.6 Hz). TLC: R_f = 0.2 (CH_2Cl_2). IR (ATR): 3084 (w), 3028 (w), 2228 (w), 1907 (w), 1748 (w), 1716 (w), 1699 (w), 1675 (w), 1602 (m), 1563 (s), 1542 (m) 1501 (w), 1477 (s), 1433 (s), 1409 (m), 1318 (m), 1297 (w), 1250 (s), 1216 (m), 1188 (m), 1160 (w), 1118 (m), 1096 (s), 1033 (w), 1023 (m). HRMS (DART): calculated for $[C_{12}H_7FN_2H]^+$ 199.0666, measured 199.0664.^{1}H and ^{13}C NMR spectra available on SI page 45.



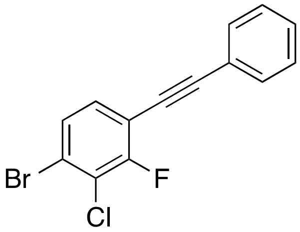
1o

In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol) and CuI (48 mg, 0.25 mmol). The mixture was purged with Argon for 5 minutes, and then degassed 1-chloro-2-fluoro-3-iodobenzene (2.24 g, 8.75 mmol), degassed phenylacetylene (1.0 mL, 9.11 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes) gave 1.56 grams (7.43 mmol, 85 % yield) of product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65-7.60 (m, 2H), 7.49-7.36 (m, 5H), 7.11-7.07 (td, *J* = 8.0 Hz, 1.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.3, 157.2, 131.8, 131.7, 130.6, 129.0, 128.5, 124.4 (d, *J* = 5.0 Hz), 122.6, 113.7 (d, *J* = 15.1), 95.7 (d, *J* = 3.8 Hz), 81.8. TLC: R_f = 0.7 (hexanes). IR (ATR): 3054 (m), 2197 (w), 1946 (w), 1869 (w), 1797 (w), 1747 (w), 1716 (w), 1698 (w), 1676 (w), 1603 (m), 1571 (m), 1556 (w), 1542 (w), 1524 (w), 1492 (s), 1464 (m), 1448 (s), 1314 (w), 1272 (w), 1239 (s), 1179 (w), 1156 (m), 1136 (m), 1061 (w), 1071 (m), 1027 (m). HRMS (DART): calculated for $[C_{14}H_8ClFH]^+$ 231.0371, measured 231.0377. ^{1}H and ^{13}C NMR spectra available on SI page 46.



1p

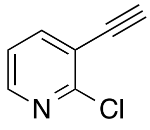
In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol) and CuI (48 mg, 0.25 mmol). The mixture was purged with Argon for 5 minutes, and then degassed 4-bromo-1-fluoro-2-iodobenzene (2.63 g, 8.75 mmol), degassed phenylacetylene (1.0 mL, 9.11 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes) gave 1.99 grams (7.26 mmol, 83 % yield) of product as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71-7.68 (dd, J = 6.5 Hz, 2.5 Hz, 1H), 7.65-7.60 (m, 2H), 7.46-7.38 (m, 4H), 7.04-6.99 (t, J = 9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.8, 160.8, 135.8, 132.8 (d, J = 7.6 Hz), 131.9, 129.0, 128.5, 122.5, 117.2 (d, J = 22.7 Hz), 116. 3(d, J = 3.8 Hz), 114.1 (d, J = 16.4 Hz), 95.6 (d, J = 3.3 Hz), 81.4. TLC: R_f = 0.7 (hexanes). IR (ATR): 3061 (m), 2222 (m), 1947 (w), 1877 (w), 1748 (w), 1716 (w), 1697 (w), 1675 (w), 1605 (w), 1572 (w), 1555 (w), 1541 (w), 1495 (s), 1479 (s), 1442 (m), 1392 (s), 1276 (w), 1255 (s), 1222 (s), 1178 (w), 1158 (w), 1144 (w), 1107 (s), 1069 (s), 1025 (m). HRMS (DART): calculated for $[C_{14}H_8BrFH]^+$ 274.9866, measured 274.9852. ^{1}H and ^{13}C NMR spectra available on SI page 47.



1q

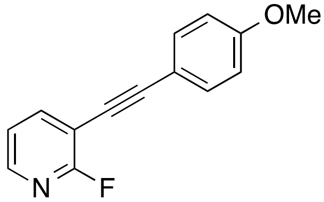
In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol) and CuI (48 mg, 0.25 mmol), The mixture was purged with Argon for 5 minutes, and then degassed 1-bromo-2-chloro-3-fluoro-4-iodobenzene (2.92 g, 8.75 mmol), degassed phenylacetylene (1.0 mL, 9.11 mmol), and triethylamine (12 mL) were added in that order. The mixture was stirred at room temperature for 2 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with Ethyl Acetate (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown liquid. Purification by silica gel flash column chromatography (hexanes) gave 1.97 grams (6.40 mmol, 73 % yield) of product as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62-7.56 (m, 2H), 7.44-7.22 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.7, 157.7, 132.5, 131.8, 131.3 (d, J = 1.6 Hz), 129.2 (d, J = 16.4 Hz), 128.5 (d, J = 1.5 Hz), 123.8, 122.3, 121.8, 112.6 (d, J

= 16.8), 95.6 (d, *J* = 3.8), 81.4 (d, *J* = 63 Hz). TLC: R_f = 0.7 (hexanes). IR (ATR): 3053 (m), 2538 (w), 2206 (m), 1951 (w), 1885 (w), 1795 (w), 1748 (w), 1716 (w), 1700 (w), 1670 (w), 1587 (m), 1571 (w), 1542 (w), 1525 (w), 1489 (s), 1458 (s), 1441 (m), 1411 (s), 1318 (w), 1260 (w), 1222 (m), 1182 (m), 1142 (w), 1157 (w), 1127 (w), 1069 (w), 1025 (w). HRMS (DART): calculated for $[C_{14}H_7BrClFH]^+$ 308.9476, measured 308.9473. ^{1}H and ^{13}C NMR spectra available on SI page 48.



1r

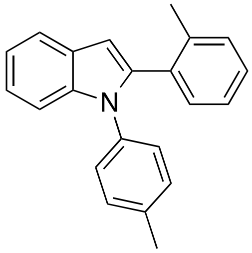
In a reaction vessel were added 2-chloro-3-trimethylsilanylethynyl-pyridine (0.5 g, 2.38 mmol) and tetrabutylammonium fluoride solution (1.0 M in THF, 4 mL, 4 mmol), in that order. The mixture was stirred at room temperature for 30 minutes and then diluted with ethyl acetate and water. The layers were separated and the aqueous phase extracted with ethyl acetate (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → EtOAc/hexanes, 3/7, step gradient) gave 0.32 g (2.33 mmol, 97 % yield) of product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33-8.29 (m, 1H), 7.81-7.77 (m, 1H), 7.20-7.16 (m, 1H) 3.48 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 152.5, 148.8, 142.1, 121.8, 119.4, 85.0, 78.2. TLC: R_f = 0.4 (EtOAc/hexanes, 1/9). IR (ATR): 3212 (s), 2106 (m), 1962 (w) 1926 (w), 1839 (w), 1748 (w), 1716 (w), 1698 (w), 1675 (w), 1646 (w), 1578 (m), 1556 (s), 1535 (m), 1501 (w), 1473 (w), 1440 (m), 1389 (s), 1275 (m), 1262 (m), 1125 (s), 1092 (w), 1077 (s), 1070 (s). HRMS (DART): calculated for $[C_7H_4ClNH]^+$ 138.0105, measured 138.0107. ^{1}H and ^{13}C NMR spectra available on SI page 49.



1s

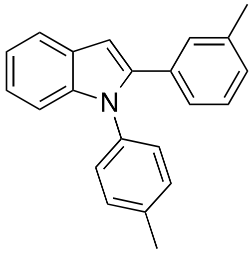
In a sealed tube were added $PdCl_2(PPh_3)_2$ (88 mg, 0.13 mmol), CuI (48 mg, 0.25 mmol), 2-fluoro-3-iodopyridine (1.95 g, 8.75 mmol), and 1-ethynyl-4-methoxybenzene (1.2 g, 9.00 mmol). The mixture was purged with Argon for 5 minutes, and then degassed triethylamine (12 mL) was added. The mixture was stirred at room temperature for 18 hours and then diluted with CH_2Cl_2 and aqueous NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 80 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes/CH_2Cl_2 1:1→ CH_2Cl_2, step gradient) gave 1.63 g (7.17 mmol, 82 % yield) of product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10-8.07 (dq, J = 5 Hz, 1H), 7.85-7.80 (ddd, J = 9.3 Hz, 7.5 Hz, 2 Hz, 1H), 7.47-7.43 (m, 2H), 7.14-7.10 (ddd, J = 7.5 Hz, 5 Hz, 2Hz, 1H), 6.86-6.82 (m, 2H), 3.77 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.4, 161.4, 160.2, 146.2-146.0 (d, J = 13.9 Hz) 143.1-143.0 (d, J = 2.5 Hz), 133.3, 121.1-121.0 (d, J = 4.4 Hz), 114.1, 108.0-107.3 (d, J = 125 Hz), 96.2 (d, J = 1.9 Hz), 79.8 (d, J = 5.0 Hz), 55.2. TLC: R_f = 0.5 (CH_2Cl_2). IR (ATR): 3056 (w), 3006 (w), 2962 (m), 2936 (m), 2838 (m), 2539 (m), 2221 (s), 2192 (m), 2015 (w), 1889 (w), 1607 (s), 1596 (s), 1561 (s), 1508 (s), 1456 (s), 1431 (s), 1319 (s), 1288 (s), 1247 (s), 1212 (s), 1174 (s), 1146 (s), 1107 (s), 1096 (s), 1027 (s). HRMS (DART): calculated for $[C_{14}H_{10}FNOH]^+$ 228.0819, measured 228.0820.^{1}H and ^{13}C NMR spectra available on SI page 50.

Synthesis of N-tolyl indoles (2a-p)



2b

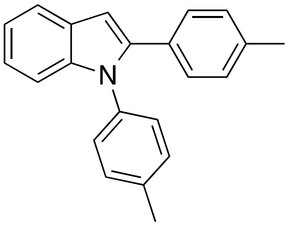
In a reaction flask under Ar, **1b** (105 mg, 0.5 mmol), p-toluidine (118 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (123 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2, step gradient) gave 101 mg (0.34 mmol, 68 % yield) of product as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.74-7.69 (m, 1H), 7.40-7.36 (m, 1H), 7.28-7.23 (m, 1H), 7.23-7.18 (m, 3H), 7.16-7.11 (m, 4H), 7.09-7.06 (m, 2H), 6.65 (s, 1H), 2.35 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.2, 137.7, 137.6, 136.4, 135.5, 132.7, 131.5, 129.9, 129.5, 128.2, 128.1, 127.1, 125.2, 121.9, 120.4, 120.4, 110.6, 104.0, 21.1, 20.4. TLC: $R_f = 0.5$ (CH_2Cl_2). IR (ATR): 3015 (s), 2221 (m), 2066 (w), 1634 (s), 1512 (s), 1488 (s), 1453 (s), 1262 (m), 1220 (m), 1097 (m), 1030 (w). HRMS (DART): calculated for $[C_{22}H_{19}NH]^+$ 298.1590, measured 298.1581. ^1H and ^{13}C NMR spectra available on SI page 51.



2c

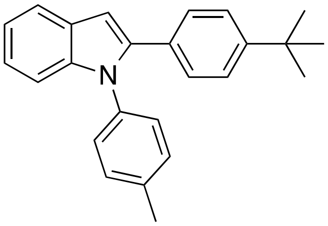
In a reaction flask under Ar, **1c** (105 mg, 0.5 mmol), p-toluidine (119 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (124 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2, step gradient) gave 107 mg (0.36 mmol, 72 % yield) of product as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ: 7.78-7.74

(m, 1H), 7.37-7.34 (m, 1H), 7.30-7.16 (m, 8H), 7.13-7.07 (m, 2H), 6.87 (d, *J* = 0.8 Hz), 2.47 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.0, 139.2, 137.8, 137.0, 136.0, 132.6, 129.9, 129.7, 128.3, 128.1, 128.0, 127.9, 126.1, 122.2, 120.6, 120.5, 110.7, 103.4, 21.5, 21.2. TLC: R_f = 0.5 (CH_2Cl_2). IR (ATR): 3031 (m), 2920 (m), 2862 (w), 1880 (w), 1606 (s), 1510 (s), 1483 (w), 1452 (s), 1376 (m), 1352 (m), 1316 (m), 1274 (w), 1261 (w), 1211 (m), 1173 (w), 1147 (w), 1108 (w), 1095 (w), 1078 (w), 1039 (w), 1014 (w). HRMS (DART): calculated for $[C_{22}H_{19}NH]^+$ 298.1590, measured 298.1598. ^{1}H and ^{13}C NMR spectra available on SI page 52.



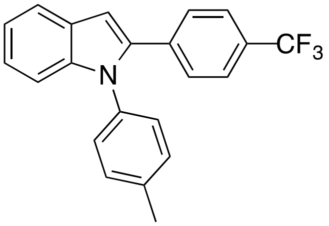
2d

In a reaction flask under Ar, **1d** (105 mg, 0.5 mmol), p-toluidine (117 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (125 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2/hexanes, 4/6, step gradient) gave 102 mg (0.35 mmol, 69 % yield) of product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74-7.70 (m, 1H), 7.33-7.29 (m, 1H), 7.28-7.17 (m, 8H), 7.12-7.09 (d, *J* = 8 Hz, 2H) 6.81 (d, *J* = 0.6 Hz, 1H), 2.45 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.9, 139.1, 137.1, 137.0, 136.0, 129.9, 129.8, 128.9, 128.8, 128.3, 127.9, 122.0, 120.5, 120.4, 110.7, 103.0, 21.2, 21.2. TLC: R_f = 0.2 (hexanes). IR (ATR): 3029 (m), 2960 (m), 1844 (w), 1749 (w), 1716 (w), 1699 (w), 1674 (w), 1606 (w), 1555 (w), 1542 (m), 1513 (s), 1500 (m), 1455 (s), 1412 (w), 1380 (m), 1357 (m), 1320 (w), 1307 (m), 1255 (w), 1187 (w), 1174 (w), 1147 (w), 1113 (w), 1021 (w). HRMS (DART): calculated for $[C_{22}H_{19}NH]^+$ 298.1590, measured 298.1573. ^{1}H and ^{13}C NMR spectra available on SI page 53.



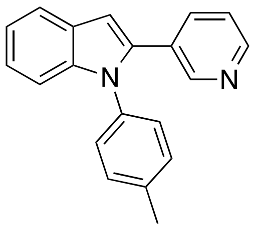
2e

In a reaction flask under Ar, **1e** (126 mg, 0.5 mmol), p-toluidine (118 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (123 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2/hexanes, 1/1, step gradient) gave 114 mg (0.34 mmol, 67 % yield) of product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73-7.68 (m, 1H), 7.32-7.23 (m, 7H), 7.21-7.16 (m, 4H), 6.81 (d, J = 0.8 Hz, 1H), 2.45 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.2, 140.8, 139.2, 137.0, 136.1, 129.9, 129.6, 128.4, 128.3, 127.9.2, 125.0, 122.0, 120.5, 120.3, 110.7, 103.0, 34.5, 31.3, 21.2. TLC: R_f = 0.2 (hexanes). IR (ATR): 3031 (w), 2960 (m), 2864 (w), 1844 (w), 1734 (w), 1716 (w), 1699 (w), 1675 (w), 1606 (w), 1564 (w), 1555 (w), 1541 (w), 1535 (w), 1513 (s), 1503 (m), 1473 (w), 1409 (w), 1378 (m), 1360 (w), 1347 (m), 1321 (m), 1259 (m), 1200 (m), 1175 (w), 1113 (m), 1017 (m). HRMS (DART): calculated for $[C_{25}H_{25}NH]^+$ 340.2060, measured 340.2037. ^{1}H and ^{13}C NMR spectra available on SI page 54.



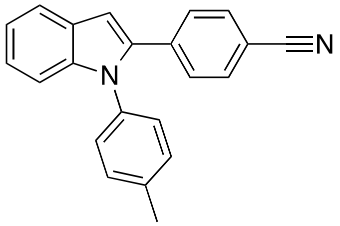
2f

In a reaction flask under Ar, **1f** (132 mg, 0.5 mmol), p-toluidine (117 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (123 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2/hexanes 1/1, step gradient) gave 142 mg (0.41 mmol, 81 % yield) of product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72-7.49 (m, 1H), 7.53-7.38 (d, J = 8.5 Hz, 2H), 7.30-7.17 (m, 7H), 7.16-7.12 (dt, J = 8.5 Hz, 2 Hz, 2H). 6.88 (d, J = 0.7 Hz), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.5, 139.0, 137.5, 136.1, 135.5, 130.2, 128.8, 128.0, 127.7, 125.1 (q, J = 3.8 Hz), 123.1, 122.9, 120.8 (d, J = 12.6 Hz), 110.8, 104.7, 29.7, 21.1. TLC: R_f = 0.3 (hexanes). IR (ATR): 3034 (m), 2920 (m), 1617 (s), 1514 (s), 1474 (w), 1453 (s), 1412 (m), 1379 (m), 1320 (s), 1257 (w), 1212 (m), 1165 (s), 1123 (s), 1109 (s), 1079 (s), 1063 (s), 1016 (s). HRMS (DART): calculated for $[C_{22}H_{16}F_3NH]^+$ 352.1313, measured 352.1317. ^{1}H and ^{13}C NMR spectra available on SI page 55.



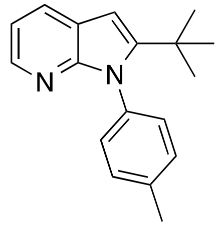
2g

In a reaction flask under Ar, **2g** (99 mg, 0.5 mmol), p-toluidine (118 mg, mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (123 mg, mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2, step gradient) gave 112 mg (0.4 mmol, 79 % yield) of product as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65-8.62 (m, 1H), 8.48-8.44 (m, 1H), 7.72-7.68 (m, 1H), 5.54-5.50 (m, 1H), 7.27-7.11 (m, 8H), 6.87 (s, 1H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.5, 148.1, 139.7, 137.6, 137.2, 135.6, 135.5, 130.0, 128.9, 128.2, 122.7, 120.8, 120.7, 110.7, 104.4, 20.9. TLC: $R_f = 0.6$ (CH_2Cl_2). IR (ATR): 3029 (m), 2920 (m), 1920 (w), 1771 (w), 1697 (w), 1661 (w), 1607 (m), 1571 (m), 1555 (w), 1541 (w), 1535 (w), 1510 (s), 1448 (s), 1421 (m), 1376 (m), 1364 (m), 1350 (m), 1324 (m), 1310 (m), 1254 (m), 1208 (m), 1173 (m), 1143 (w), 1127 (w), 1108 (w), 1104 (m), 1038 (w), 1024 (m), 1016 (m). HRMS (DART): calculated for $[C_{20}H_{16}N_2H]^+$ 285.1386, measured 285.1362. ^{1}H and ^{13}C NMR spectra available on SI page 56.



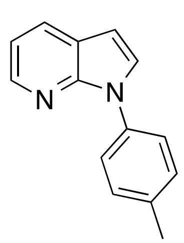
2h

In a reaction flask under Ar, **1h** (111 mg, mmol), p-toluidine (116 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (124 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown solid. Purification by silica gel flash column chromatography (CH_2Cl_2 → MeOH/CH_2Cl_2, 1/39, step gradient) gave 123 mg (0.4 mmol, 80 % yield) of product as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72-7.68 (m, 3H), 7.38-7.34 (dt, J = 8.8 Hz, 2 Hz, 2H), 7.30-7.28 (m, 1H), 7.25-7.22 (m, 2H), 7.22-7.17 (m, 2H), 7.15-7.12 (m, 2H), 6.89 (d, J = 0.8 Hz), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.9, 139.5, 137.4, 136.3, 135.6, 131.6, 130.1, 128.7, 128.0, 127.7, 127.7, 122.9, 120.8, 120.7, 110.8, 104.5, 21.2. TLC: R_f = 0.1 (CH_2Cl_2), 0.4 ($MeOH/CH_2Cl_2$, 1/39). IR (ATR): 3480 (m), 3365 (w), 3149 (s), 2922 (w), 1905 (w), 1793 (w), 1680 (s), 1663 (s), 1605 (s), 1563 (m), 1541 (w), 1535 (w), 1472 (w), 1453 (m), 1411 (w), 1380 (s), 1352 (m), 1321 (m), 1282 (m), 1259 (m), 1210 (m), 1139 (m), 1106 (m), 1017 (m). HRMS (DART): calculated for $[C_{22}H_{16}N_2H]^+$ 309.1386, measured 309.1380. ^1H and ^{13}C NMR spectra available on SI page 57.



2j

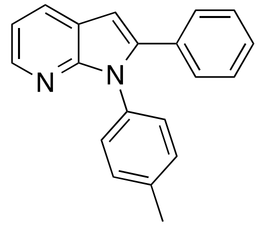
In a reaction flask under Ar, **1j** (89 mg, 0.5 mmol), p-toluidine (118 mg, mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (123 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown solid. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2, step gradient) gave 90 mg (0.34 mmol, 68 % yield) of product as a brown solid. ^1H NMR (500 MHz, $CDCl_3$): δ 8.22-8.19 (dd, *J* = 4.7 Hz, 1.5 Hz, 1H), 7.86-7.83 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.34-7.31 (d, *J* = 2Hz, 2H), 7.29-7.25 (m, 2H), 7.04-7.00 (dd, *J* = 8 Hz, 4.5 Hz, 1H), 6.41 (s, 1H), 2.46 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 151.6, 151.2, 142.8, 138.7, 136.2, 130.5, 129.7, 127.3, 119.5, 116.0, 96.9, 33.5, 30.7, 21.4. TLC: R_f = 0.6 (CH_2Cl_2), 0.7 ($MeOH/CH_2Cl_2$, 1/19), 0.2 (CH_2Cl_2/hexanes, 1/1). IR (ATR): 3041 (m), 2958 (s), 2924 (s), 2869 (s), 1593 (m), 1574 (m), 1525 (s), 1515 (s), 1470 (m), 14010 (s), 1393 (m), 1361 (s), 1311 (s), 1285 (s), 1246 (s), 1216 (m), 1199 (m), 1132 (w), 1107 (m), 1041 (w), 1023 (w). HRMS (DART): calculated for $[C_{18}H_{20}N_2H]^+$ 265.1705, measured 265.1703. ^1H and ^{13}C NMR spectra available on SI page 58.



2k

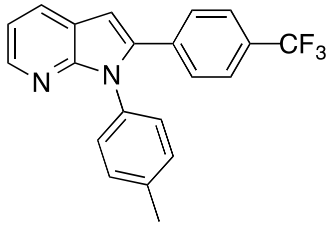
In a reaction flask under Ar, **1k** (61 mg, 0.5 mmol), p-toluidine (118 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (123 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 80˚C for 48 hr.

The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown solid. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2/hexanes 1/1, step gradient) gave 53 mg (0.26 mmol, 51 % yield) of product as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39-8.36 (d, J = 4.5 Hz, 1H), 7.99-7.96 (d, J = 9 Hz), 7.64-7.61 (d, J = 8 Hz, 2H), 7.51-7.48 (d, J = 3.5 Hz, 1H), 7.35-7.32 (d, J = 8.5 Hz, 2H), 7.15-7.11 (ddd, J = 8.0 Hz, 4.5 Hz, 0.7 Hz, 1H), 6.63-6.61 (dd, 3.8 Hz, 0.7 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.5, 136.2, 135.9, 129.9, 128.0, 124.0, 116.5, 108.2, 107.7, 101.2, 21.0. TLC: R_f = 0.8 (CH_2Cl_2), 0.4 (CH_2Cl_2/hexanes, 1/1). IR (ATR): 2923 (s), 1594 (s), 1530 (s), 1476 (m), 1424 (s), 1359 (m), 1323 (s), 1269 (m), 1235 (m), 1210 (w), 1147 (w), 1110 (m), 1039 (w). HRMS (DART): calculated for $[C_{14}H_{12}N_2H]^+$ 209.1079, measured 209.1083. ^{1}H and ^{13}C NMR spectra available on SI page 59.



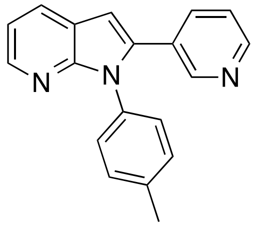
2l

In a reaction flask under Ar, **1l** (99 mg, 0.5 mmol), p-toluidine (118 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (124 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100°C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown solid. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2, step gradient) gave 111 mg (0.39 mmol, 78 % yield) of product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36-8.33 (dd, J = 4.5 Hz, 1.6 Hz, 1H), 7.99-7.96 (dd, J = 8.0 Hz, 1.7 Hz, 1H), 7.35-7.27 (m, 5H), 7.26-7.21 (m, 4H), 7.15-7.12 (dd, 8.0 Hz, 4.8 Hz, 1H), 6.74 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.0, 143.7, 141.1, 137.1, 134.3, 132.2, 129.7, 128.8, 128.3, 128.2, 128.1, 127.7, 120.8, 116.9, 101.1, 21.2. TLC: R_f = 0.7 (CH_2Cl_2), 0.4 (EtOAc/hexanes, 1/9). IR (ATR): 3058 (w), 3034 (w), 2917 (w), 1920 (w), 1884 (w), 1845 (w), 1734 (w), 1699 (w), 1675 (w), 1604 (w), 1589 (m), 1567 (m), 1541 (m), 1512 (s), 1489 (w), 1473 (m), 1447 (w), 1417 (s), 1371 (s), 1315 (m), 1297 (m), 1277 (m), 1241 (m), 1211 (w), 1195 (w), 1183 (m), 1108 (m), 1073 (w), 1028 (m). HRMS (DART): calculated for $[C_{20}H_{16}N_2H]^+$ 285.1386, measured 285.1396. ^{1}H and ^{13}C NMR spectra available on SI page 60.



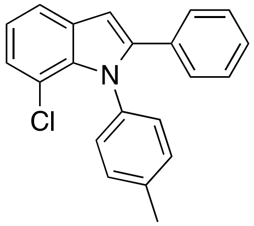
2m

In a reaction flask under Ar, **1m** (133 mg, 0.5 mmol), p-toluidine (118 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (124 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown solid. Purification by silica gel flash column chromatography (hexanes → EtOAc/hexanes, 1/9, step gradient) gave 148 mg (0.42 mmol, 84 % yield) of product as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39-8.36 (dd, *J* = 4.6 Hz, 1.6 Hz, 1H), 8.02-7.98 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.56-7.53 (d, *J* = 8.0 Hz, 2H), 7.45-7.41 (d, *J* = 8.0 Hz, 2H), 7.28-7.25 (d, *J* = 8.0 Hz, 2H), 7.23-7.19 (dt, *J* = 9.0 Hz, 2.2 Hz, 2H), 7.18-7.14 (dd, *J* = 7.5 Hz, 4.8 Hz, 1H), 6.81 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.3, 144.3, 139.3, 137.7, 135.7, 134.0, 130.0, 129.6, 129.4, 128.9, 128.8, 128.1, 125.2 (q, *J* = 3.8 Hz), 120.6, 117.2, 102.4, 21.2. TLC: R_f = 0.8 (CH_2Cl_2), 0.4 (EtOAc/hexanes, 1/9). IR (ATR): 3006 (w), 2990 (w), 1844 (w), 1738 (w), 1716 (w), 1699 (w), 1674 (w), 1617 (w), 1555 (w), 1542 (w), 1513 (w), 1501 (w), 1473 (w), 1456 (w), 1403 (w), 1325 (s), 1275 (s), 1260 (s), 1160 (s), 1122 (s), 1109 (s), 1084 (m), 1063 (m), 1018 (m). HRMS (DART): calculated for $[C_{21}H_{15}F_3NH]^+$ 353.1260, measured 353.1239. ^{1}H and ^{13}C NMR spectra available on SI page 61.



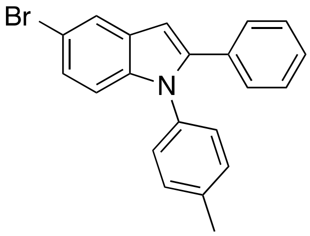
2n

In a reaction flask under Ar, **1n** (99 mg, 0.5 mmol), p-toluidine (118 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (124 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown solid. Purification by silica gel flash column chromatography (CH_2Cl_2 → MeOH/CH_2Cl_2, 1/9, step gradient) gave 125 mg (0.44 mmol, 88 % yield) of product as a brown solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.66 (s, 1H), 8.51 (s, 1H), 8.37-8.35 (dd, J = 4.5 Hz, 1.5 Hz, 1H), 8.01-7.98 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 7.53-7.49 (dt, J = 8.0 Hz, 2.0 Hz, 1H), 7.26-7.23 (d, J = 8.0 Hz, 2.0 Hz, 1H), 7.26-7.23 (d, J = 8.0 Hz, 2H), 7.22-7.17 (m, 3H), 7.17-7.14 (dd, J = 7.8 Hz, 4.5 Hz, 1H), 6.8 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 150.2, 149.5, 148.7, 144.3, 137.8, 137.4, 135.8, 133.8, 130.0, 128.7 128.1, 123.0, 120.5, 117.2, 109.8, 101.9, 21.2. TLC: R_f = 0.1 (CH$_2$Cl$_2$), 0.2 (MeOH/CH$_2$Cl$_2$, 1/19). IR (ATR): 3037 (m), 2923 (m), 2855 (m), 1897 (w), 1693 (m), 1592 (m), 1567 (m), 1512 (s), 1462 (m), 1430 (s), 1403 (s), 1371 (m), 1316 (s), 1294 (s), 1247 (m), 1211 (w), 1178 (m), 1110 (m), 1023 (m). HRMS (DART): calculated for $[C_{19}H_{15}N_3H]^+$ 286.1344, measured 286.1344. ^{1}H and ^{13}C NMR spectra available on SI page 62.



2o

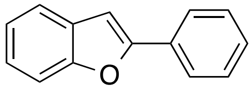
In a reaction flask under Ar, **1o** (115 mg, 0.5 mmol), p-toluidine (117 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (125 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100°C for 18 hr. The reaction was quenched by dilution with ethyl acetate and addition of NH$_4$Cl. The layers were separated and the aqueous phase extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with H$_2$O (80 mL) and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH$_2$Cl$_2$/hexanes, 1/4, step gradient) gave 116 mg (0.37 mmol, 73 % yield) of product as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.65-7.62 (dd, J = 7.8 Hz, 1.1 Hz, 1H), 7.32-7.25 (m, 5H), 7.25-7.21 (dt, J = 8.5 Hz, 2.0 Hz, 2H), 7.21-7.19 (dd, J = 7.7 Hz, 1.1 Hz, 1H), 7.18-7.15 (m, 2H), 7.14-7.10 (t, J = 7.8 Hz, 1H), 6.8 (s, 1H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 143.3, 138.1, 136.2, 134.0, 132.4, 130.9, 130.3, 129.5, 128.7, 128.0, 127.6, 124.0, 120.8, 119.3, 117.4, 103.5, 21.3. TLC: R_f = 0.6 (hexanes). IR (ATR): 3064 (w), 3038 (w), 2924 (m), 2853 (w), 1897 (w), 1785 (w), 1609 (m), 1581 (m), 1513 (w), 1491 (m), 1470 (s), 1456 (m), 1443 (m), 1422 (s), 1377 (w), 1351 (w), 1322 (w), 1289 (s), 1272 (w), 1256 (w), 1236 (m), 1206 (w), 1192 (m), 1169 (m), 1143 (s), 1107 (w), 1097 (w), 1071 (w), 1050 (w), 1038 (m), 1020 (s). HRMS (DART): calculated for $[C_{21}H_{16}ClNH]^+$ 318.1044, measured 318.1045. ^{1}H and ^{13}C NMR spectra available on SI page 63.



2p

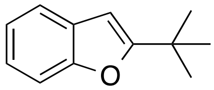
In a reaction flask under Ar, **1p** (137 mg, 0.5 mmol), p-toluidine (118 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (124 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with ethyl acetate and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2/hexanes, 1/4, step gradient) gave 137 mg (0.38 mmol, 76 % yield) of product as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.83-7.81 (d, J = 1.8 Hz, 1H), 7.31-7.22 (m, 8H), 7.16-7.11 (m, 3H), 6.74 (d, J = 0.6 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.9, 137.5, 135.4, 132.1, 130.0, 129.8, 128.9, 128.2, 127.7, 127.6, 124.9, 122.8, 113.6, 112.2, 102.6, 21.2. TLC: R_f = 0.4 (hexanes). IR (ATR): 3033 (m), 2923 (s), 2855 (m), 1902 (w), 1602 (m), 1514 (s), 1486 (m), 1456 (s), 1441 (s), 1378 (s), 1324 (m), 1302 (w), 1285 (w), 1255 (w), 1204 (m), 1170 (m), 1109 (w), 1077 (w), 1052 (m), 1029 (m). HRMS (DART): calculated for $[C_{21}H_{16}BrNH]^+$ 362.0539, measured 362.0538. ^1H and ^{13}C NMR spectra available on SI page 64.

Synthesis of benzofurans (3a-g)



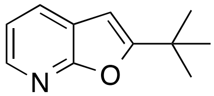
3a

In a reaction flask under Ar, **1a** (98 mg, 0.5 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of NaOH (25 mg, 0.6 mmol). The reaction was stirred on an aluminum heating block at 100°C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown solid. Purification by silica gel flash column chromatography (hexanes) gave 89 mg (0.46 mmol, 92 % yield) of product as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94-7.91 (m, 2H), 7.65-7.62 (ddd, J = 7.7 Hz, 1.4 Hz, 0.7 Hz, 1H), 7.60-7.57 (dq, J = 8.0 Hz, 0.8 Hz, 1H), 7.52-7.47 (m, 2H), 7.43-7.38 (tt, J = 7.4 Hz, 1.3Hz, 1H), 7.37-7.32 (m, 1H), 7.31-7.27 (m, 1H), 7.07-7.06 (d, J = 1.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.9, 154.9, 130.5, 129.2, 128.8, 128.6, 124.9, 124.3, 123.0, 120.9, 111.2, 101.2. TLC: R_f = 0.5 (hexanes). IR (ATR): 3034 (m), 1896 (w), 1673 (w), 1604 (w), 1587 (w), 1561 (m), 1490 (m), 1470 (m), 1455 (s), 1440 (s), 1350 (w), 1333 (w), 1321 (w), 1304 (w), 1295 (w), 1272 (w), 1257 (m), 1207 (m), 1168 (m), 1105 (m), 1073 (m), 1038 (m), 1019 (m). HRMS (DART): calculated for $[C_{14}H_{10}OH]^+$ 195.0804, measured 195.0776. ^1H and ^{13}C NMR spectra available on SI page 65.



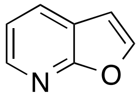
3b

In a reaction flask under Ar, **1i** (88 mg, 0.5 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of NaOH (24 mg, 0.6 mmol). The reaction was stirred on an aluminum heating block at 150°C for 72 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes) gave 77 mg (0.45 mmol, 89 % yield) of product as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.51-7.48 (m, 1H), 7.45-7.42 (m, 1H), 7.24-7.16 (m, 2H), 6.37-6.36 (d, J = 0.9 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.4, 154.6, 128.9, 123.0, 122.2, 120.3, 110.8, 98.9, 33.0, 28.9. TLC: R_f = 0.7 (hexanes). IR (ATR): 2924 (s), 2854 (m), 1844 (w), 1734 (m), 1716 (m), 1699 (s), 1674 (m), 1647 (w), 1555 (m), 1523 (s), 1498 (m), 1456 (m), 1260 (m). HRMS (DART): calculated for $[C_{12}H_{14}OH]^+$ 175.1117, measured 175.1115. ^1H and ^{13}C NMR spectra available on SI page 66.



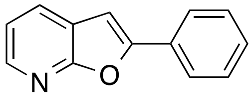
3d

In a reaction flask under Ar, **1j** (89 mg, 0.5 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of NaOH (27 mg, 0.6 mmol). The reaction was stirred on an aluminum heating block at 100°C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2/hexanes, 1/1, step gradient) gave 79 mg (0.40 mmol, 90 % yield) of product as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26-8.20 (d, J = 4.0 Hz, 1H), 7.82-7.79 (dd, J = 7.5 Hz, 1.7 Hz, 1H), 7.18-7.15 (dd, J = 7.5 Hz, 5.0 Hz, 1H), 6.37 (s, 1H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.3, 161.8, 142.7, 128.9, 121.1, 118.9, 98.1, 33.1, 28.6. TLC: R_f = 0.7 (CH_2Cl_2), 0.3 (CH_2Cl_2/hexanes, 1/1). IR (ATR): 2926 (s), 1580 (s), 1460 (m), 1403 (s), 1364 (m), 1341 (m), 1286 (s), 1252 (s), 1224 (m), 1203 (s), 1166 (m), 1115 (m), 1086 (s). HRMS (DART): calculated for $[C_{11}H_{13}NOH]^+$ 176.1075, measured 176.1075. ^{1}H and ^{13}C NMR spectra available on SI page 67.



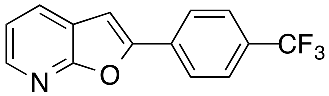
3e

In a reaction flask under Ar, **1k** (61 mg, 0.5 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of NaOH (24 mg, 0.6 mmol). The reaction was stirred on an aluminum heating block at 80°C for 48 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2, step gradient) gave 37 mg (0.31 mmol, 61 % yield) of product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37-8.34 (dd, J = 5.0 Hz, 2.0 Hz, 1H), 7.98-7.95 (dd, J = 7.5 Hz, 1.5 Hz, 1H), 7.74-7.72 (d, J = 2.5 Hz, 1H), 7.27-7.23 (dd, J = 8.0 Hz, 4.5 Hz, 1H), 6.81-6.79 (d, J = 2.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.0, 144.7, 144.2, 130.1, 119.2, 106.0, 103.8. TLC: R_f = 0.6 (CH_2Cl_2). IR (ATR): 2923 (s), 2880 (m), 1288 (s), 1135 (s). HRMS (DART): calculated for $[C_{11}H_{13}NOH]^+$ 176.1070, measured 176.1070. ^{1}H and ^{13}C NMR spectra available on SI page 68.



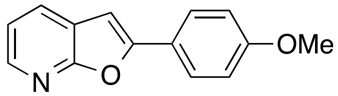
3c

In a reaction flask under Ar, **1l** (99 mg, 0.5 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of NaOH (25 mg, 0.6 mmol). The reaction was stirred on an aluminum heating block at 100°C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2, step gradient) gave 91 mg (0.47 mmol, 93 % yield) of product as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33-8.30 (dd, *J* = 5 Hz, 1.3 Hz, 1H), 7.95-7.91 (m, 3H), 7.51-7.46 (m, 2H), 7.43-7.39 (tt, *J* = 7.5 Hz, 1.3 Hz, 1H), 7.26-7.22 (dd, *J* = 8.0 Hz, 4.9 Hz, 1H), 7.03 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.9, 155.7, 143.9, 129.7, 129.5, 129.3, 128.9, 128.5, 125.2, 119.5, 100.0. TLC: R_f = 0.6 (CH_2Cl_2). IR (ATR): 3056 (w), 2974 (m), 2927 (w), 1952 (w), 1888 (w), 1734 (w), 1688 (m), 1657 (m), 1596 (m), 1585 (m), 1562 (m), 1542 (w), 1535 (w), 1491 (m), 1471 (w), 1446 (m), 1431 (m), 1416 (w), 1401 (s), 1363 (m), 1334 (m), 1305 (w), 1297 (m), 1277 (w), 1243 (s), 1170 (s), 1112 (m), 1071 (w), 1037 (w), 1045 (w), 1020 (s), 1000 (w). HRMS (DART): calculated for $[C_{13}H_9NOH]^+$ 196.0757, measured 196.0732. ^{1}H and ^{13}C NMR spectra available on SI page 69.



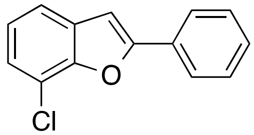
3g

In a reaction flask, 1s (133 mg, 0.5 mmol), and H_2O (1 mL) were added. The reaction was started with the addition of NaOH (59 mg, 1.5 mmol). The reaction was stirred on an aluminum heating block at 125°C for 48 hr. The reaction was quenched by dilution with ethyl acetate and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a yellow oil. Purification by silica gel flash column chromatography (hexanes/CH_2Cl_2, 1:1 → CH_2Cl_2) gave 128 mg (0.49 mmol, 97 % yield) of product as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37-8.35 (dd, *J* = 5 Hz, 1.5 Hz, 1H), 8.04-8.01 (d, *J* = 8.5 Hz, 2H), 7.98-7.95 (m, 1H), 7.76-7.72 (d, *J* = 8.5 Hz, 2H), 7.29-7.25 (m, 1H), 7.14 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 162,0, 153.9, 144.7, 130.1, 126.0-125.8 (q, *J* = 3.8 Hz), 125.3, 121.1, 119.8, 102.0, 29.7. TLC: R_f = 0.6 (CH_2Cl_2). IR (ATR): 2924 (m), 2852 (m), 1930 (w), 1732 (m), 1615 (m), 1596 (s), 1562 (s), 1511 (w), 1456 (m), 1438 (s), 1415 (w), 1403 (m), 1324 (s), 1295 (s), 1255 (s), 1216 (s), 1186 (m), 1162 (s), 1128 (m), 1120 (s), 1067 (s), 1031 (w), 1014 (s). HRMS (DART): calculated for $[C_{14}H_8F_3NOH]^+$ 264.0631, measured 264.0631. ^{1}H and ^{13}C NMR spectra available on SI page 70.



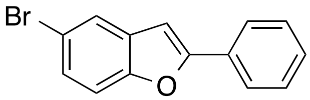
3h

In a reaction flask, **1s** (114 mg, 0.5 mmol), and H_2O (1 mL) were added. The reaction was started with the addition of NaOH (60 mg, 1.5 mmol). The reaction was stirred on an aluminum heating block at 125˚C for 48 hr. The reaction was quenched by dilution with ethyl acetate and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a yellow oil. Purification by silica gel flash column chromatography (CH_2Cl_2) gave 107 mg (0.48 mmol, 95 % yield) of product as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.28-8.25 (dd, J = 4.8 Hz, 1.5 Hz, 1H), 7.89-7.84 (m, 3H), 7.3-7.19 (dd, J = 7 Hz, 5 Hz, 1H), 7.02-6.99 (m, 2H), 6.88 (s, 1H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.5, 155.8, 143.2, 141.2, 129.0, 126.7, 121.2, 119.4, 110.0, 98.3, 55.4. TLC: R_f = 0.3 (CH_2Cl_2). IR (ATR): 2920 (s), 2855 (s), 1735 (s), 1615 (s), 1598 (s), 1507 (s), 1256 (s), 1037 (s). HRMS (DART): calculated for $[C_{14}H_{11}NO_2H]^+$ 226.0863, measured 226.0864. ^1H and ^{13}C NMR spectra available on SI page 71.



3j

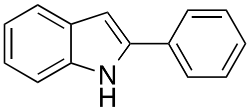
In a reaction flask under Ar, **1o** (115 mg, 0.5 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of NaOH (24 mg, 0.6 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with ethyl acetate and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes) gave 91 mg (0.40 mmol, 80 % yield) of product as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94-7.90 (m, 2H), 7.50-7.46 (m, 3H), 7.43-7.38 (tt, J = 7.5 Hz, 2 Hz, 1H), 7.32-7.29 (dd, J = 7.8 Hz, 0.9 Hz, 1H), 7.20-7.15 (t, J = 7.8 Hz, 1H), 7.04 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.8, 150.6, 130.8, 129.8, 129.0, 128.8, 125.1, 124.4, 123.8, 119.4, 116.6, 101.7. TLC: R_f = 0.5 (hexanes). IR (ATR): 3063 (w), 1609 (m), 1580 (m), 1491 (m), 1470 (s), 1447 (w), 1422 (s), 1351 (w), 1322 (w), 1288 (s), 1236 (s), 1192 (m), 1170 (s), 1143 (s), 1097 (w), 1071 (w), 1050 (w), 1038 (m), 1020 (s). HRMS (DART): calculated for $[C_{14}H_9ClOH]^+$ 229.0420, measured 229.0428. ^1H and ^{13}C NMR spectra available on SI page 72.



3k

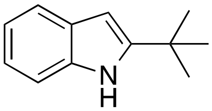
In a reaction flask under Ar, **1p** (137 mg, 0.5 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of NaOH (25 mg, 0.6 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with ethyl acetate and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes) gave 112 mg (0.41 mmol, 82 % yield) of product as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.89-7.85 (m, 2H), 7.73-7.71 (m, 2H), 7.51-7.46 (m, 2H), 7.45-7.37 (m, 3H), 6.96 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.2, 153.6, 131.2, 129.9, 129.0, 128.8, 127.1, 125.1, 123.5, 112.6, 100.7. TLC: R_f = 0.3 (hexanes). IR (ATR): 3091 (w), 3060 (w), 3030 (w), 2926 (w), 2601 (w), 2545 (w), 2237 (w), 2079 (w), 1959 (w), 1889 (w), 1871 (w), 1831 (w), 1740 (w), 1684 (w), 1604 (m), 1577 (s), 1490 (m), 1449 (s), 1437 (s), 1428 (s), 1326 9m), 1275 (m), 1260 (s), 1206 (m), 1156 (m), 1116 (m), 1072 (m), 1050 (s), 1037 (s), 1020 (m), 1001 (w). HRMS (DART): calculated for $[C_{14}H_9BrOH]^+$ 272.9910, measured 272.9921. ^1H and ^{13}C NMR spectra available on SI page 73.

Synthesis of N-H indoles (4a-g)



4a

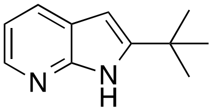
In a reaction flask under Ar, **1a** (98 mg, 0.5 mmol), acetamide (65 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (124 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2/hexanes, 1/1, step gradient) gave 66 mg (0.34 mmol, 68 % yield) of product as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.71-7.63 (m, 3H), 7.49-7.41 (m, 3H), 7.37-7.32 (tt, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.24-7.19 (m, 1H), 7.16-7.12 (m, 1H), 6.86-6.85 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 137.9, 136.8, 132.4, 129.3, 129.0, 127.7, 125.1, 122.3, 120.7, 120.3, 101.8, 100.0. TLC: R_f = 0.9 (CH_2Cl_2), 0.5 (EtOAc/hexanes, 1/9). IR (ATR): 3445 (s), 3050 (m), 2924 (m), 2853 (m), 1891 (w), 1686 (m), 1616 (m), 1542 (w), 1481 (m), 1457 (s), 1447 (s), 1403 (m), 1352 (m), 1339 (w), 1299 (s), 1241 (w), 1189 (w), 1148 (w), 1114 (w), 1074 (w), 1050 (w), 1028 (w). HRMS (DART): calculated for $[C_{14}H_{11}NH]^+$ 194.0964, measured 194.0965. ^1H and ^{13}C NMR spectra available on SI page 74.



4b

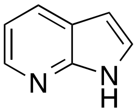
In a reaction flask under Ar, **1i** (88 mg, 0.5 mmol), acetamide (65, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (123 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 150˚C for 48 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2/hexanes, 1/1, step gradient) gave 44 mg (0.26 mmol, 51 % yield) of product as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.57-7.54 (m, 1H), 7.35-7.32 (m, 1H), 7.16-7.12 (m, 1H), 7.11-7.06 (m, 1H), 6.29-6.27 (dd, *J* = 2.5 Hz, 1.0 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.7, 135.7, 128.5, 121.1, 120.0, 119.6, 110.3, 97.0, 31.8, 30.3. TLC: R_f = 0.9 (CH_2Cl_2), 0.6 (EtOAc/hexanes, 1/9). IR (ATR): 3406 (s), 2957 (s), 2925 (s), 2863 (m), 1702 (w), 1612 (w), 1582 (w), 1542 (m), 1488 (w), 1458 (s), 1407 (s), 1394 (m), 1365 (s), 1348 (s), 1290 (s), 1246 (w), 1231 (w), 1202 (w), 1189 (w), 1148 (w), 1116 (w), 1012 (s). HRMS

(DART): calculated for $[C_{12}H_{15}NH]^+$ 174.1277, measured 174.1277. ^{1}H and ^{13}C NMR spectra available on SI page 75.



4d

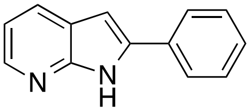
In a reaction flask under Ar, **1j** (89 mg, 0.5 mmol), acetamide (65 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (123 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (CH_2Cl_2 → $MeOH/CH_2Cl_2$, 2/23, step gradient) gave 58 mg (0.34 mmol, 67 % yield) of product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.76 (s, 1H), 8.28-8.26 (dd, J = 5.0 Hz, 1.5 Hz, 1H), 7.87-7.83 (ddd, J = 7.5 Hz, 1.5 Hz, 0.5 Hz, 1H), 7.07-7.03 (dd, J = 7.5 Hz, 5.0 Hz, 1H), 6.23-6.21 (d, J = 2.5 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.2, 149.1, 141.4, 127.9, 127.7, 121.2, 94.7, 32.2, 30.1. TLC: R_f = 0.1 ($MeOH/CH_2Cl_2$, 1/19), 0.5 ($MeOH/CH_2Cl_2$, 2/23). IR (ATR): 3157 (m), 3088 (m), 2964 (s), 2869 (m), 1647 (m), 1605 (m), 1588 (s), 1540 (m), 1494 (w), 1417 (s), 1363 (s), 1326 (m), 1276 (s), 1226 (w), 1173 (s), 1109 (w), 1027 (w). HRMS (DART): calculated for $[C_{11}H_{14}N_2H]^+$ 175.1235, measured 175.1236. ^{1}H and ^{13}C NMR spectra available on SI page 76.



4e

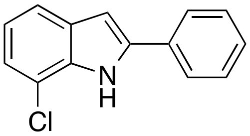
In a reaction flask under Ar, **1k** (61 mg, 0.5 mmol), acetamide (66 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (124 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 80˚C for 48 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (CH_2Cl_2 → $MeOH/CH_2Cl_2$, 2/23, step gradient) gave 31 mg (0.26 mmol, 52 % yield) of product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.49 (s, 1H), 8.36-8.30 (dd, J = 5.0 Hz, 1.3 Hz, 1H), 7.98-7.95 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 7.36-7.33 (dd, J = 3.5 Hz, 1.5 Hz, 1H), 7.12-7.09 (dd, J = 8.0 Hz, 4.5 Hz, 1H), 6.54-6.52 (dd, J = 3.5 Hz, 1.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.5, 143.0, 129.0, 124.8, 120.1, 116.0, 101.0. TLC: R_f = 0.4 ($MeOH/CH_2Cl_2$, 2/23). IR (ATR): 3070 (m), 3061 (m), 2922 (s), 1584 (s), 1421 (s), 1279 (s). HRMS (DART): calculated for

$[C_7H_6N_2H]^+$ 119.0609, measured 119.0614. ^{1}H and ^{13}C NMR spectra available on SI page 77.



4c

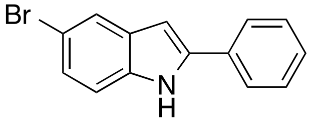
In a reaction flask under Ar, **1l** (67 mg, 0.5 mmol), acetamide (67 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (124 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (CH_2Cl_2 → MeOH/CH_2Cl_2, 1/39, step gradient) gave 67 mg (0.35 mmol, 69 % yield) of product as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.55 (s, 1H), 8.34-8.31 (d, J = 4.0 Hz, 1H), 8.00-7.97 (dd, J = 7.5 Hz, 1.5 Hz, 1H), 7.94-7.90 (m, 2H), 7.57-7.52 (m, 2H), 7.45-7.40 (tt, J = 7.5 Hz, 1.0 Hz, 1H), 7.15-7.10 (dd, J = 8.0 Hz, 4.5 Hz, 1H), 6.82 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.0, 142.0, 139.5, 132.4, 129.0, 128.7, 128.2, 125.9, 122.4, 116.1, 97.4. TLC: R_f = 0.8 (MeOH/CH_2Cl_2, 1/19), 0.4 (MeOH/CH_2Cl_2, 1/39). IR (ATR): 3160 (s), 3032 (s), 2972 (m), 2787 (m), 1904 (w), 1870 (w), 1833 (w), 1716 (w), 1698 (w), 1675 (w), 1588 (m), 1541 (m), 1486 (m), 1456 (m), 1431 (m), 1410 (m), 1363 (m), 1330 (m), 1280 (s), 1223 (w), 1195 (m), 1111 (m), 1074 (w), 1045 (w), 1029 (w). HRMS (DART): calculated for $[C_{13}H_{10}N_2H]^+$ 195.0917, measured 195.0895. ^{1}H and ^{13}C NMR spectra available on SI page 78.



4f

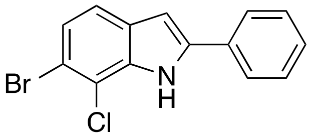
In a reaction flask under Ar, **1o** (115 mg, 0.5 mmol), acetamide (66 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (123 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with ethyl acetate and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2/hexanes, 1/1, step gradient) gave 76 mg (0.34 mmol, 67 % yield) of product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (s, 1H), 7.74-7.71 (m, 2H), 7.58-7.55 (dt, J = 8.0 Hz, 0.5 Hz, 1H), 7.52-7.47 (m, 2H), 7.41-7.37 (m, 1H), 7.24-7.21 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 7.12-7.07 (t, J =

7.5 Hz, 1H), 6.89-6.88 (d, J = 2.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.7, 134.0, 131.8, 130.6, 129.1, 128.2, 125.3, 121.6, 121.0, 119.2, 116.3, 100.8. TLC: R_f = 0.1 (hexanes), 0.7 (CH_2Cl_2/hexanes, 1/1). IR (ATR): 3854 (w), 3748 (w), 3673 (w), 3650 (w), 3438 (s), 3067 (w), 3038 (w), 1957 (w), 1879 (w), 1834 (w), 1771 (w), 1685 (w), 1617 (w), 1602 (m), 1568 (m), 1542 (w), 1485 (s), 1451 (s), 1431 (s), 1391 (s), 1352 (s), 1324 (s), 1299 (s), 1244 (s), 1195 (s), 1163 (w), 1141 (m), 1097 (w), 1073 (w), 1050 (w), 1028 (w). HRMS (DART): calculated for $[C_{14}H_{10}ClNH]^+$ 228.0580, measured 228.0589. ^{1}H and ^{13}C NMR spectra available on SI page 79.



4g

In a reaction flask under Ar, **1p** (137 mg, 0.5 mmol), acetamide (66 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (123 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100°C for 18 hr. The reaction was quenched by dilution with ethyl acetate and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2/hexanes, 1/1, step gradient) gave 84 mg (0.31 mmol, 62 % yield) of product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.78-7.76 (q, J = 1.0 Hz), 7.69-7.65 (m, 2H), 7.50-7.45 (tt, J = 7.0 Hz, 2.0 Hz, 2H), 7.40-7.35 (tt, J = 7.0 Hz, 1.0 Hz, 1H), 7.30-7.28 (d, J = 1.0 Hz, 2H), 6.79-6.77 (d, J = 2.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.1, 135.4, 131.8, 131.0, 129.1, 128.2, 125.3, 125.1, 123.1, 113.4, 112.3, 99.5. TLC: R_f = 0.7 (CH_2Cl_2/hexanes, 1/1). IR (ATR): 3436 (s), 3082 (w), 3060 (w), 3037 (w), 2923 (w), 2853 (w), 1570 (w), 1488 (m), 1453 (s), 1393 (m), 1310 (m), 1282 (m), 1180 (w), 1128 (w), 1053 (m). HRMS (DART): calculated for $[C_{14}H_{10}BrNH]^+$ 272.0075, measured 272.0083. ^{1}H and ^{13}C NMR spectra available on SI page 80.

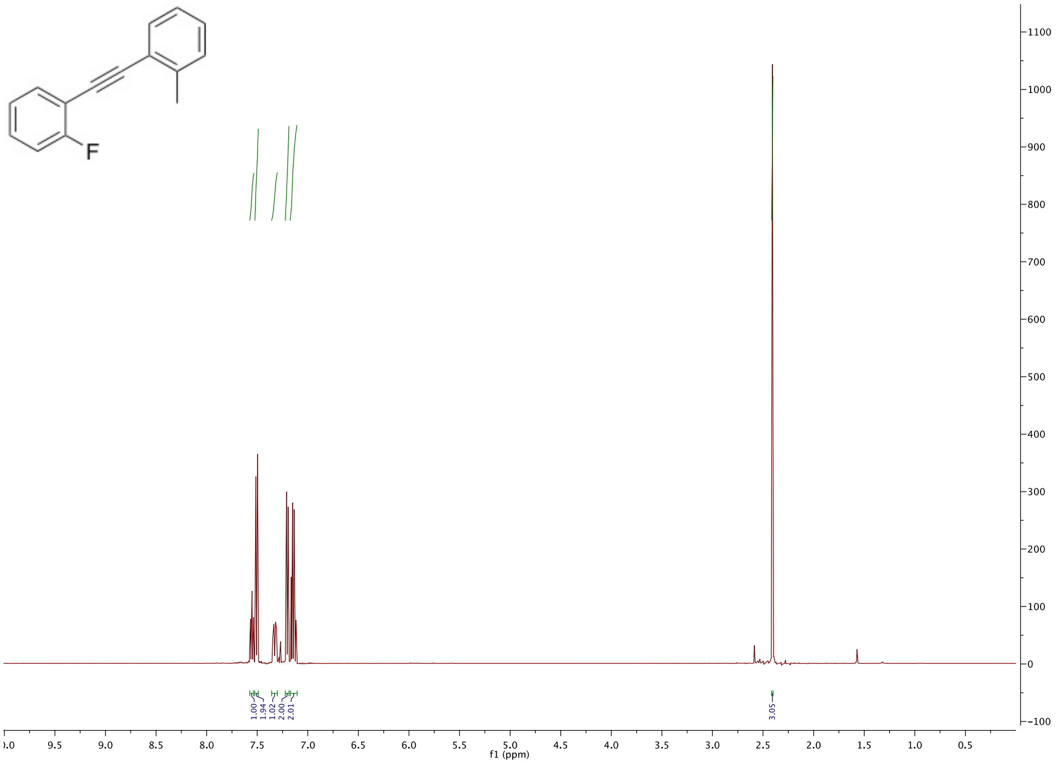


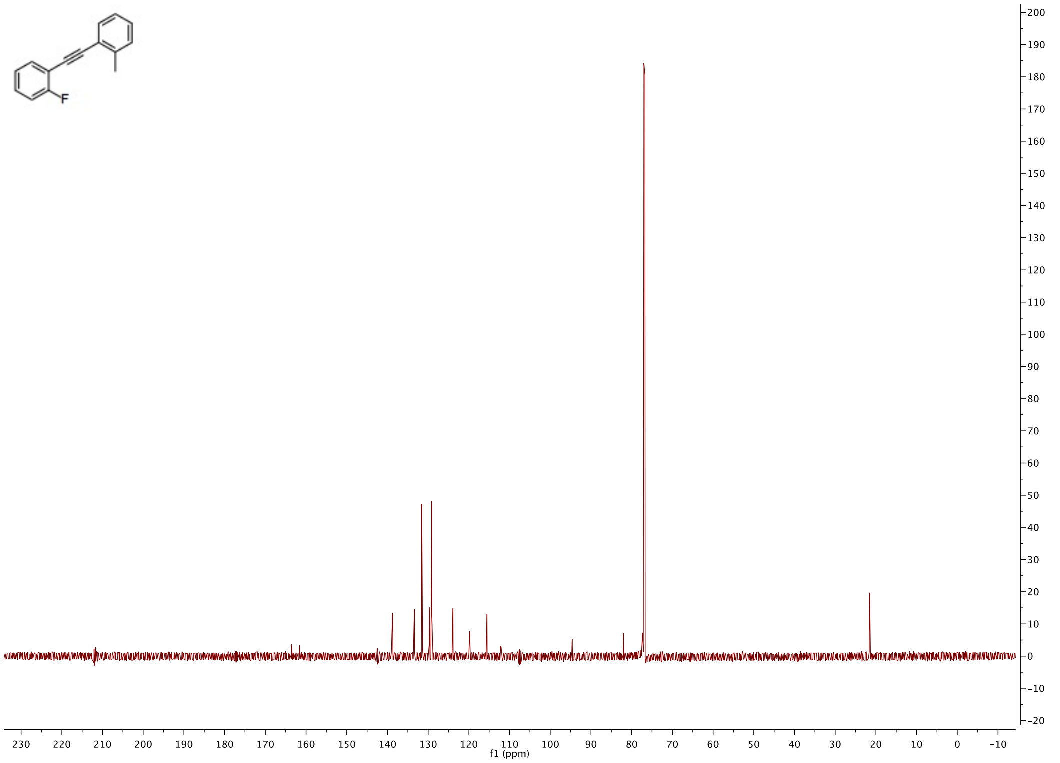
4h

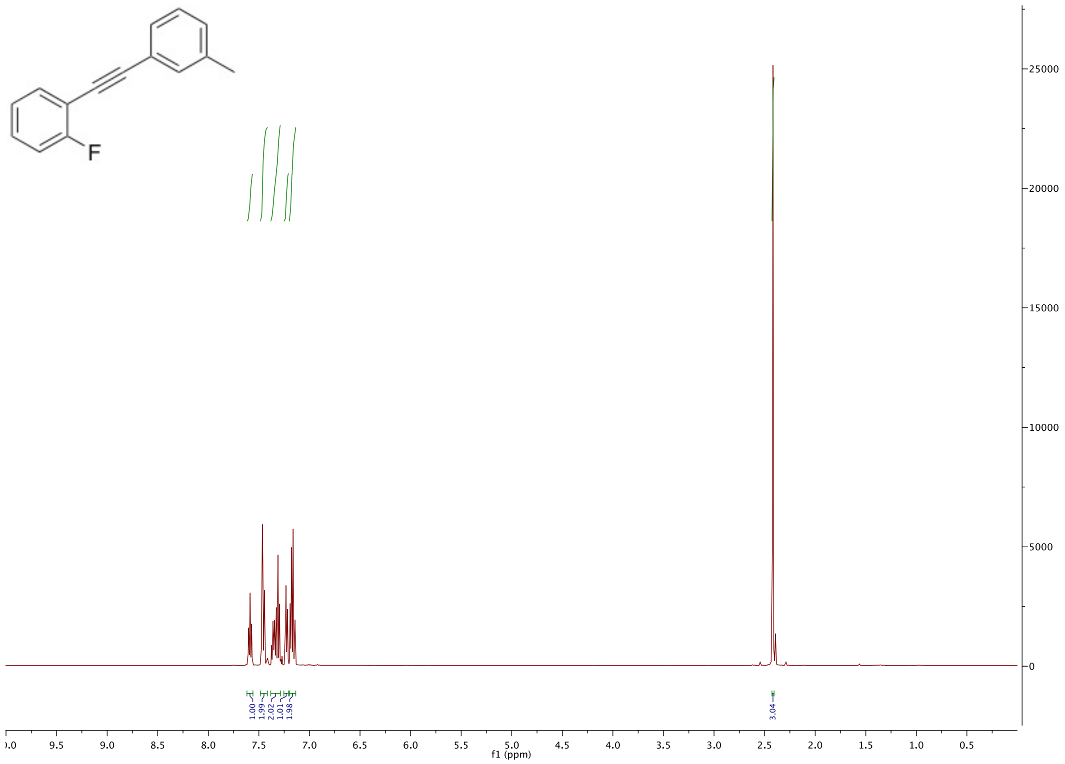
In a reaction flask under Ar, **1q** (154 mg, 0.5 mmol), acetamide (66 mg, 1.1 mmol), and DMSO (1.0 mL) were added. The reaction was started with the addition of KO*t*Bu (123 mg, 1.1 mmol). The reaction was stirred on an aluminum heating block at 100°C for 18 hr. The reaction was quenched by dilution with ethyl acetate and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2/hexanes, 1/1, step gradient) gave 90 mg (0.30 mmol, 59 % yield) of product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.71-7.67 (m, 2H), 7.51-7.46 (m, 2H), 7.42-7.37 (m, 2H), 7.36-7.33 (d, J = 8.5 Hz, 1H), 6.84-6.82 (d, J = 2.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.3, 134.9, 131.4, 129.3, 129.2, 128.4, 125.3, 125.0, 120.0, 116.6, 115.0, 100.9. TLC: R_f = 0.1 (hexanes), 0.7 (CH_2Cl_2/hexanes, 1/1). IR (ATR): 3426 (s), 3080 (m), 3057 (m), 3036 (m), 2924 (m), 2854 (m), 1939 (w), 1866 (w), 1735 (w), 1604 (m), 1567 (m), 1488 (s), 1473 (s), 1450 (s), 1432 (s), 1375 (s), 1338 (s), 1309 (m), 1296 (m), 1273 (w), 1227 (s), 1182 (w), 1153 (s), 1119 (w), 1097 (w), 1050 (w), 1029 (w), 1000 (w). HRMS (DART): calculated for $[C_{14}H_9BrClNH]^+$ 305.9685, measured 305.9697. ^{1}H and ^{13}C NMR spectra available on SI page 81.

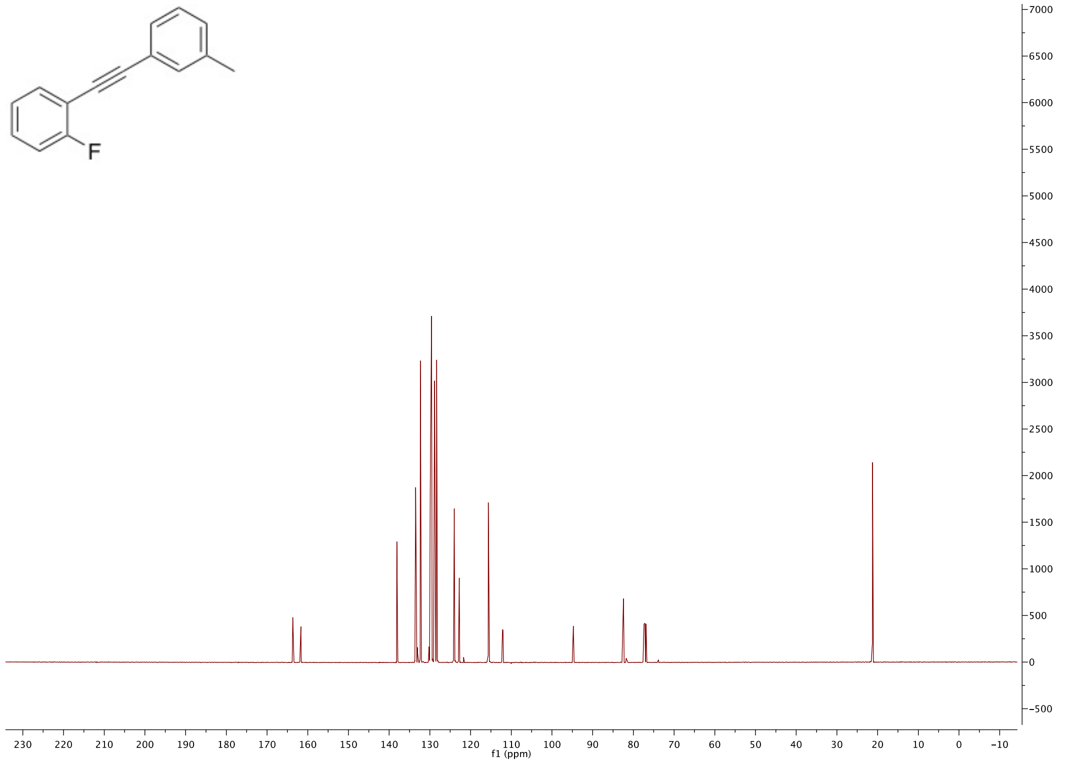
Hydroxide/p-tolylamide competition reaction

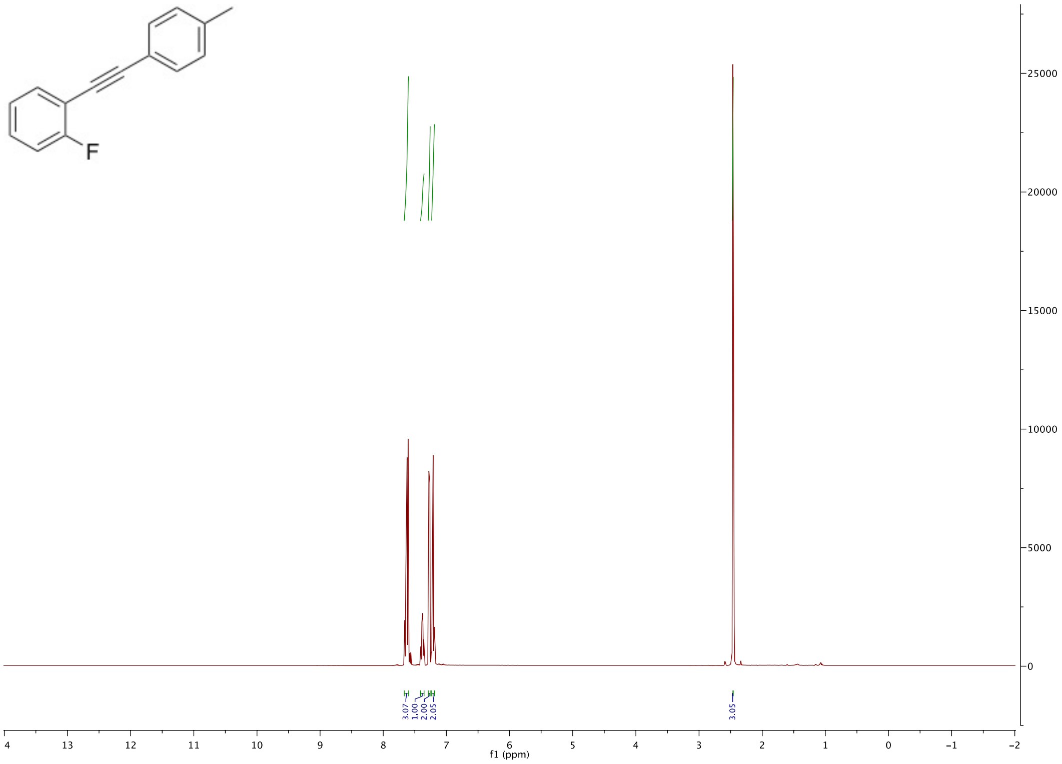
In a reaction flask under Ar, **1a** (212 mg, 1.1 mmol), p-toluidine (236 mg, 2.2 mmol), water (39.6 µL, 2.2 mmol) and DMSO (2.0 mL) were added. The reaction was started with the addition of KO*t*Bu (494 mg, 4.4 mmol). The reaction was stirred on an aluminum heating block at 100˚C for 18 hr. The reaction was quenched by dilution with CH_2Cl_2 and addition of NH_4Cl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with H_2O (80 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil. Purification by silica gel flash column chromatography (hexanes → CH_2Cl_2, step gradient) gave 191.4 mg (0.99 mmol) **3a** and 14.7 mg (0.05 mmol) **2a**.

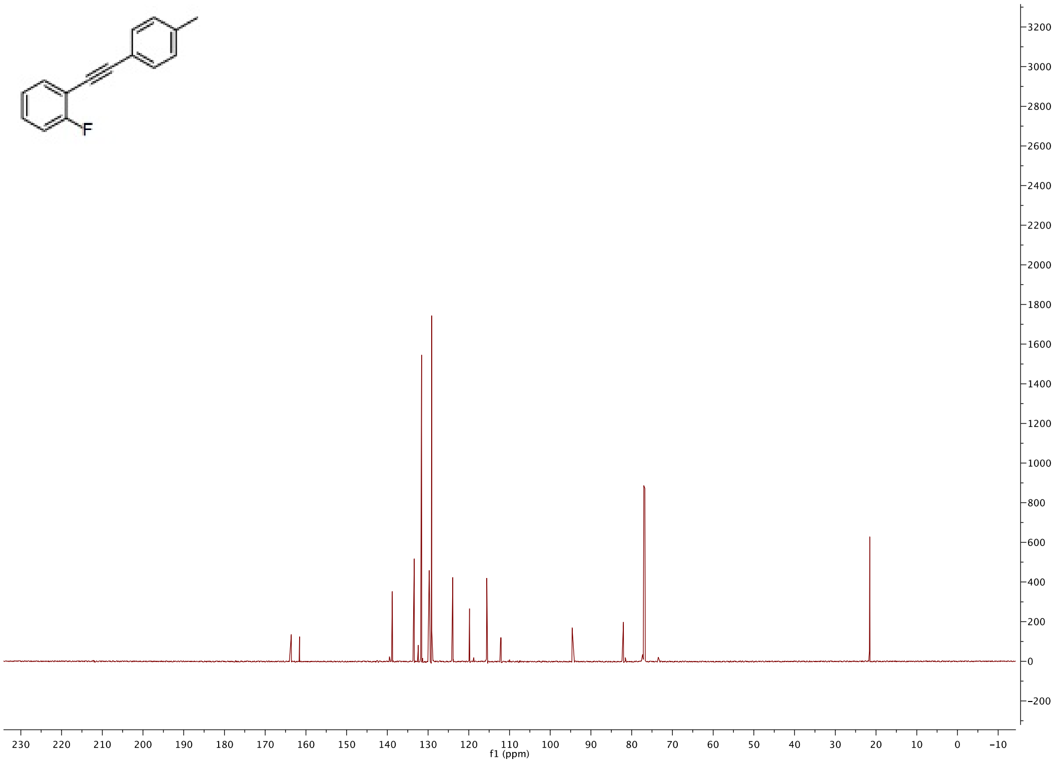

F
1.00
1.94
1.02
2.00
2.01
3.05
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

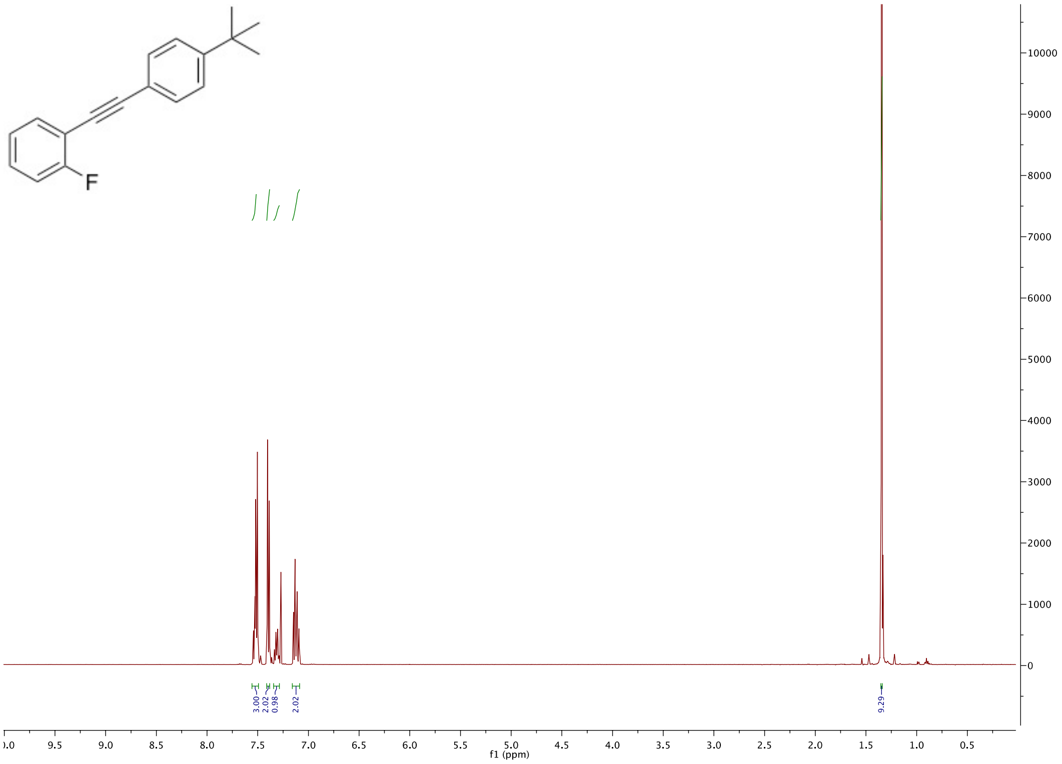

F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

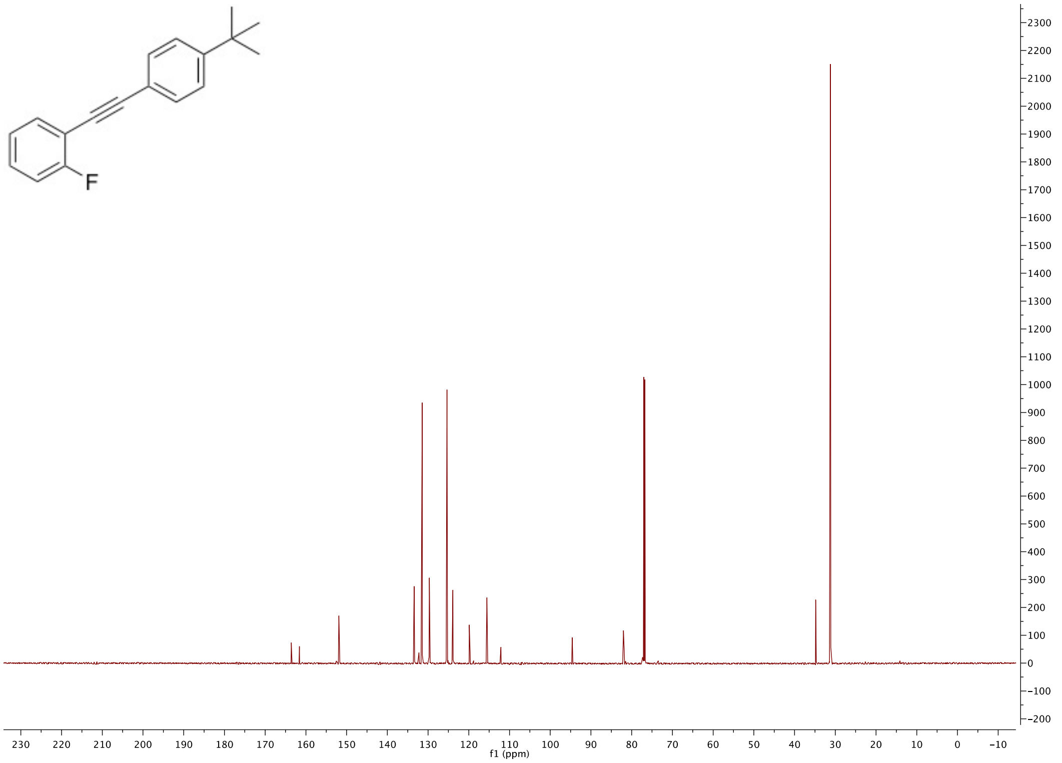

F
1.00
1.99
2.02
1.01
1.98
3.04
25000
20000
15000
10000
5000
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

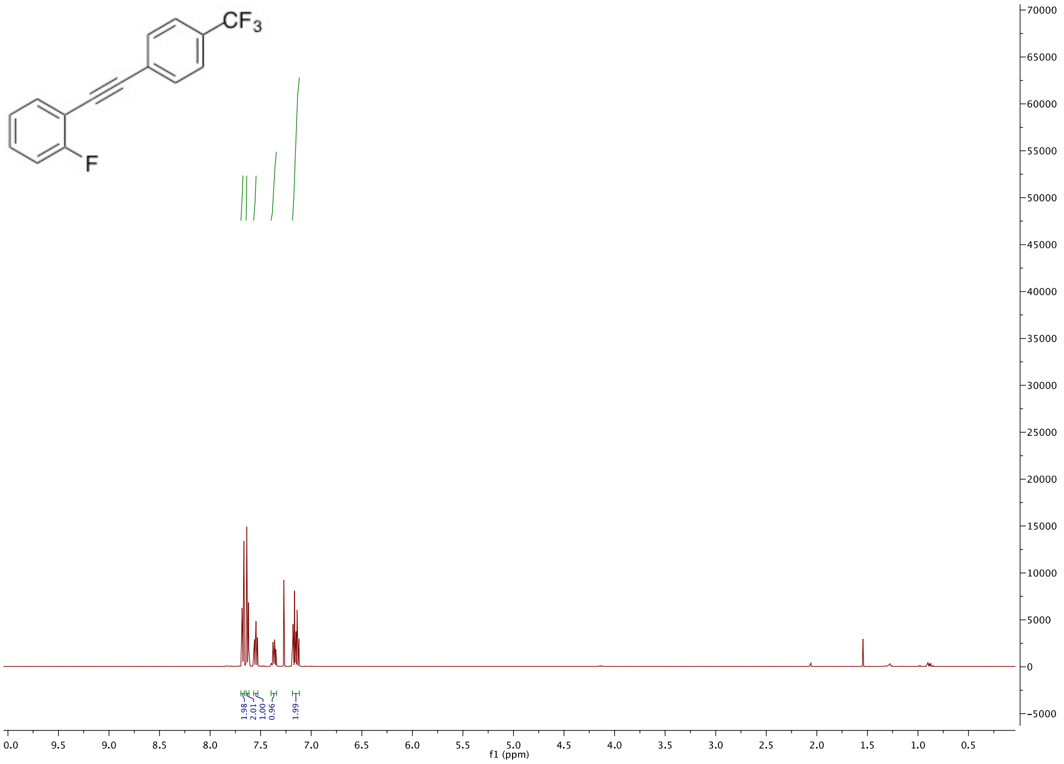

F
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

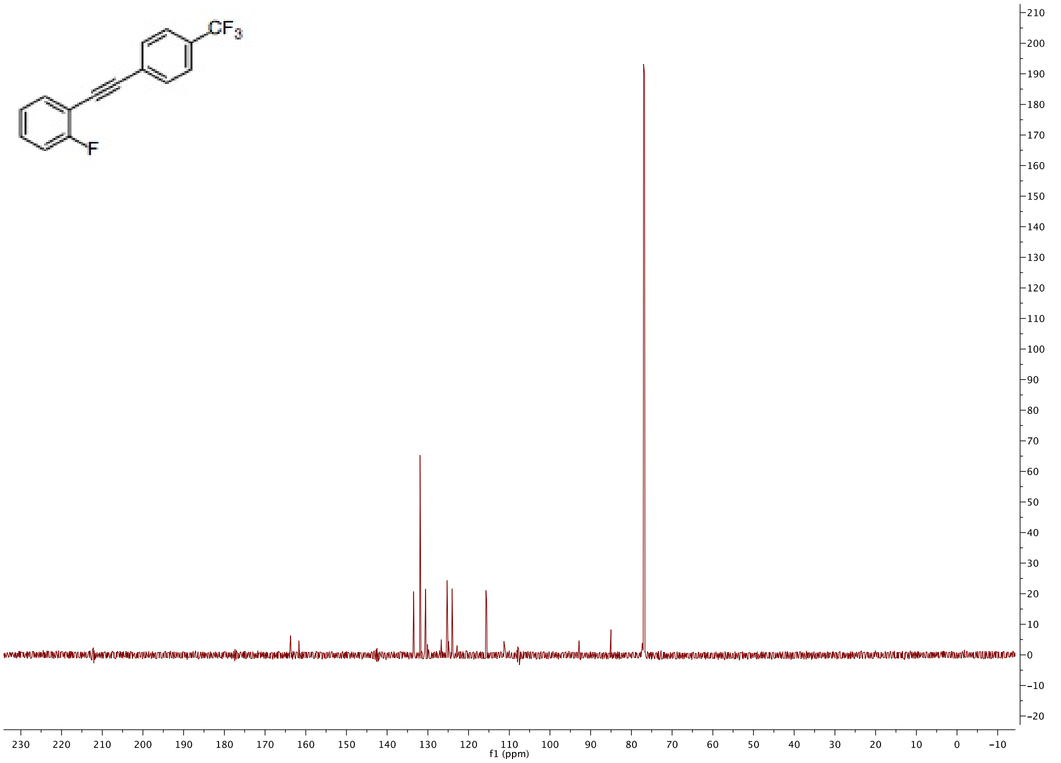

F
25000
20000
15000
10000
5000
0
3.07
1.00
2.00
2.05
3.05
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

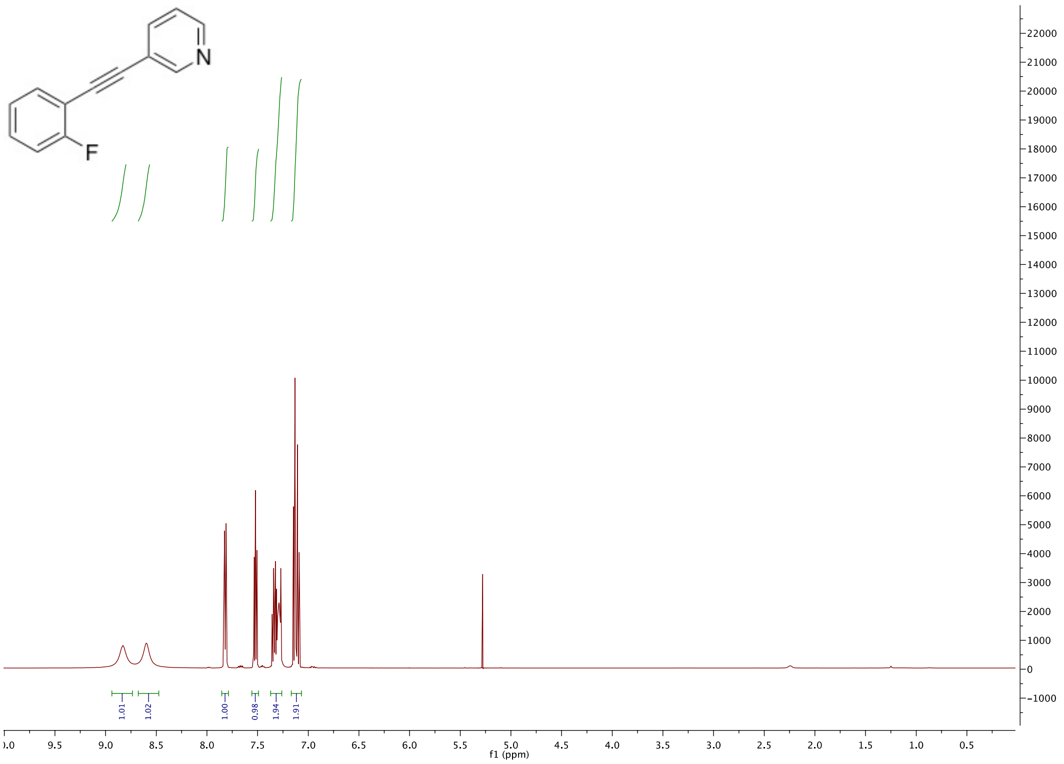

F
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

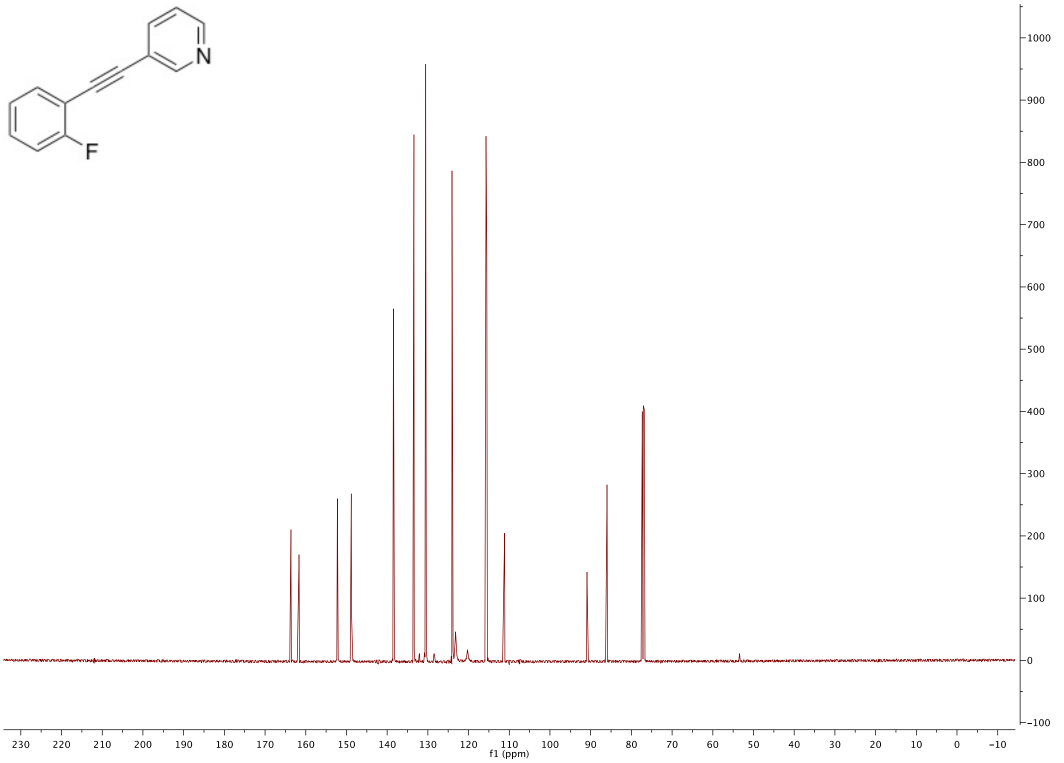

F
3.00
2.02
0.98
2.02
9.29
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


F
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
−200
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

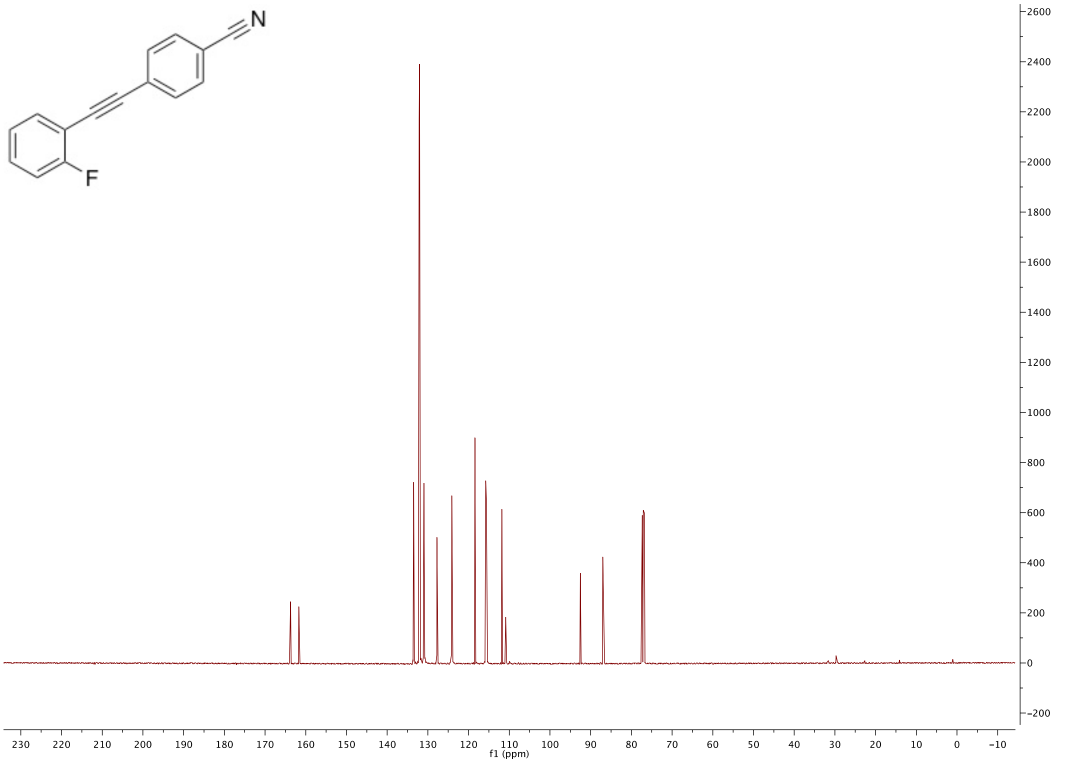

CF3
F
1.98
2.01
1.00
0.96
1.99
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
−5000
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

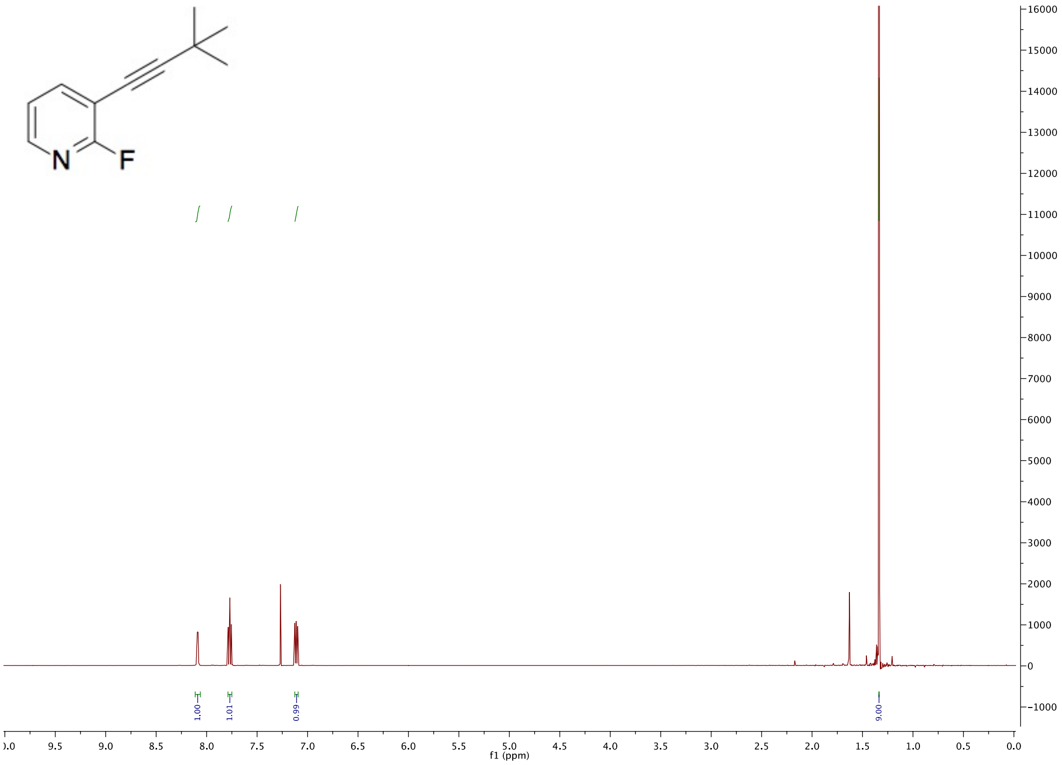

CF3
F
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

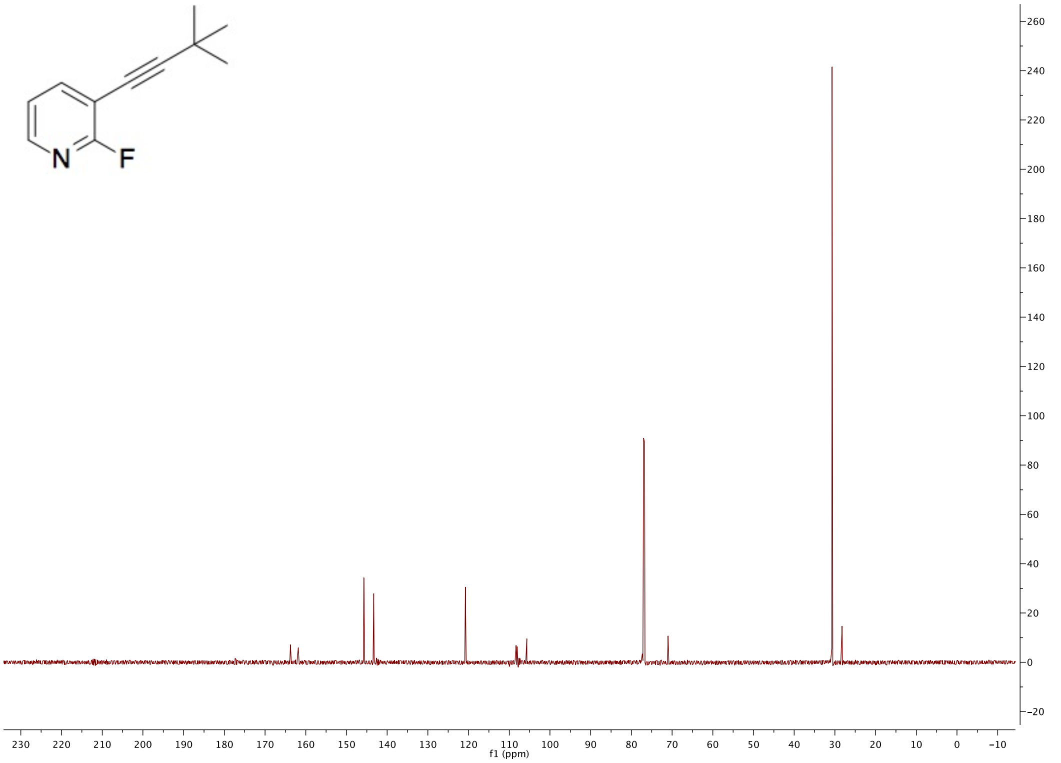

N
F
1.01
1.02
1.00
0.98
1.94
1.91
f1 (ppm)

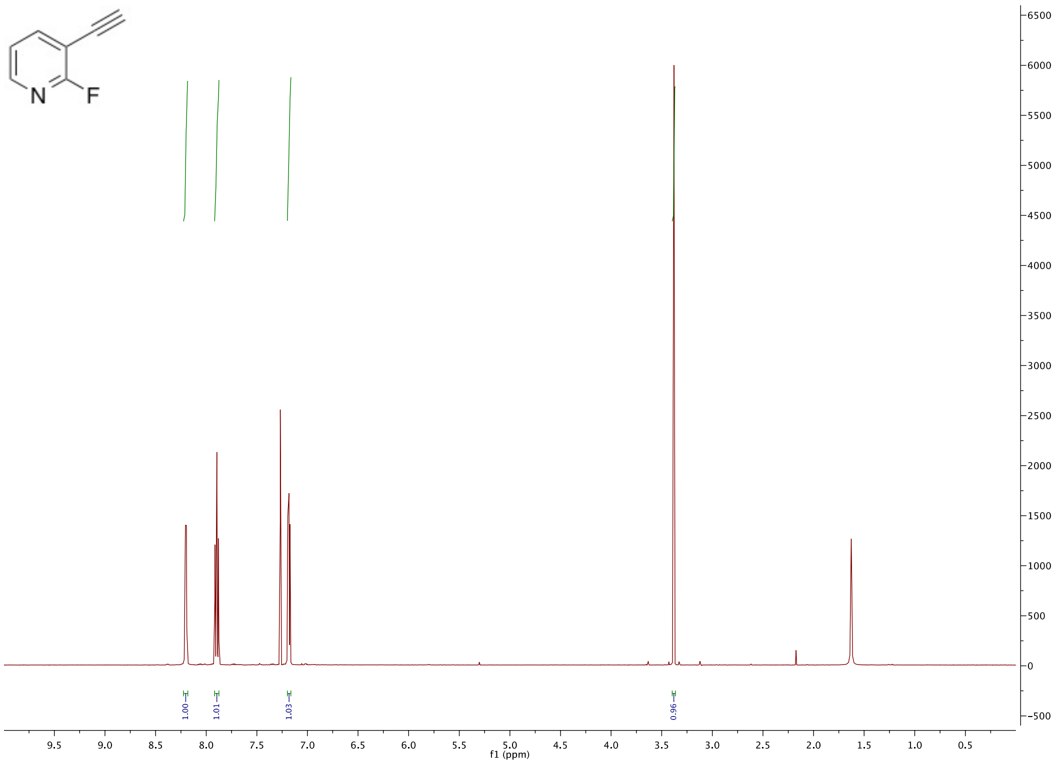

N
F
f1 (ppm)

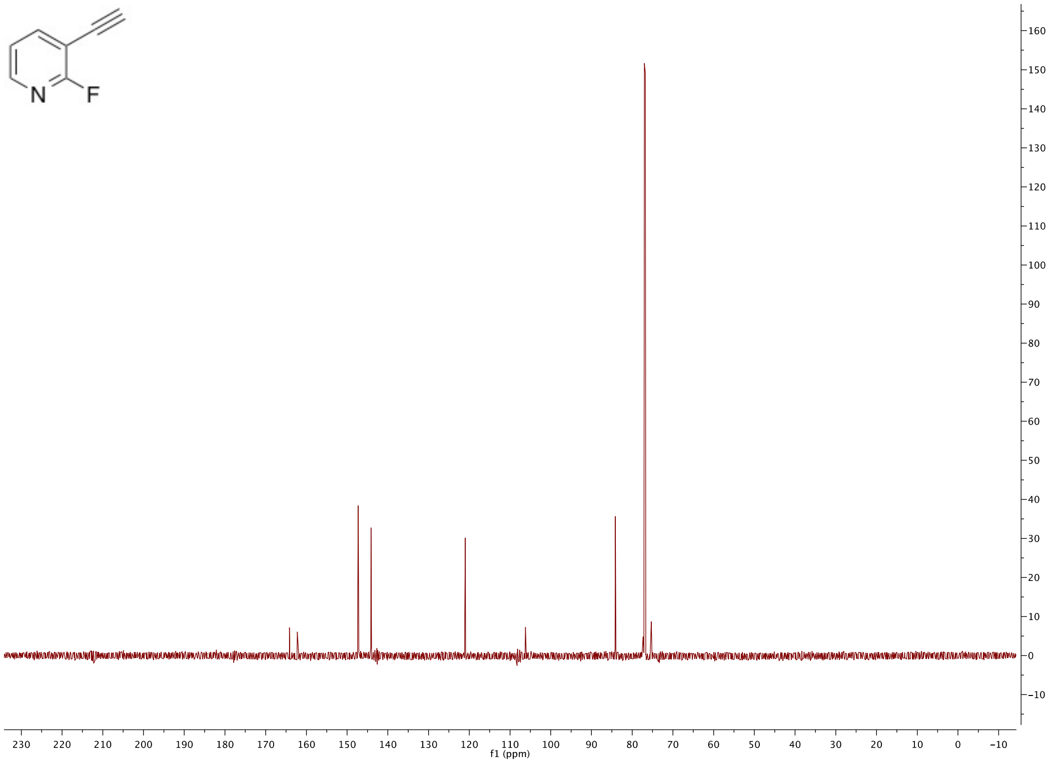

N
F
4.02
1.00
0.95
1.99
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
−10000

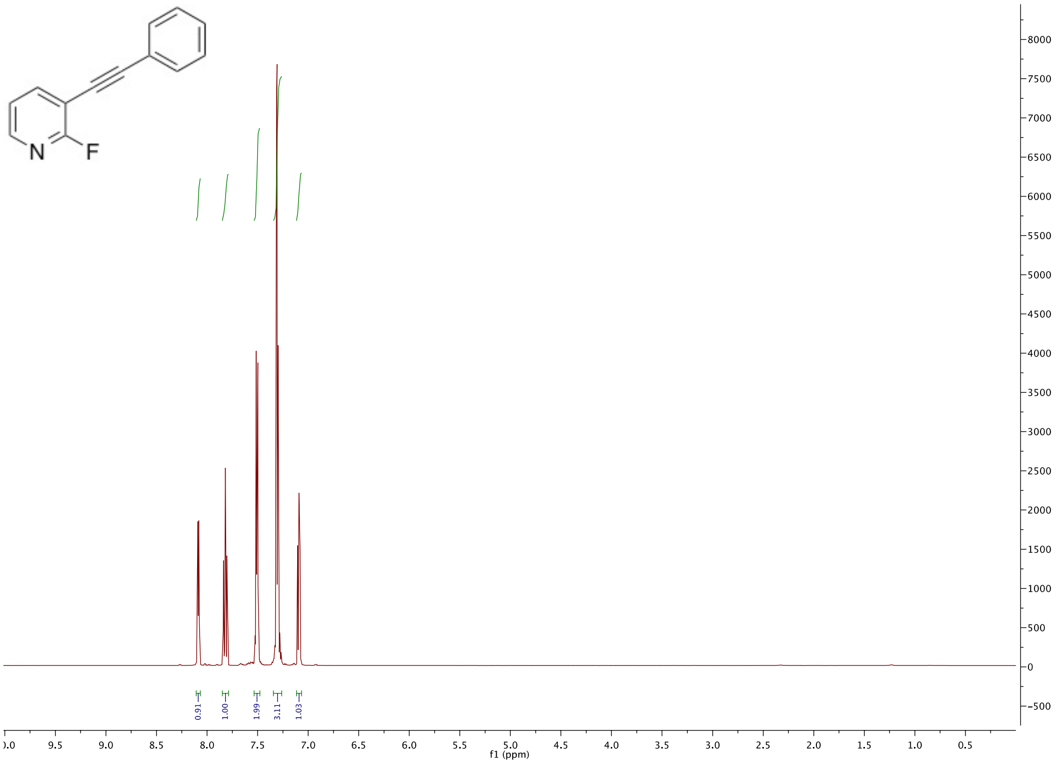

N
F
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200

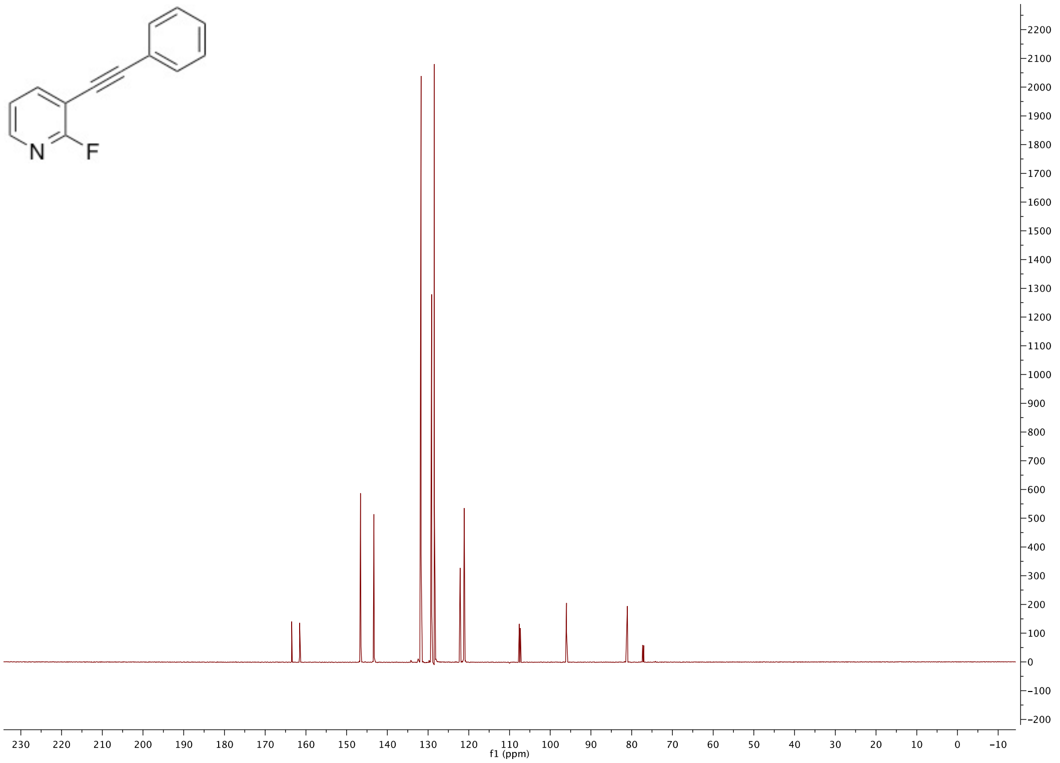

N
F
1.00
1.01
0.99
9.00
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
).0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

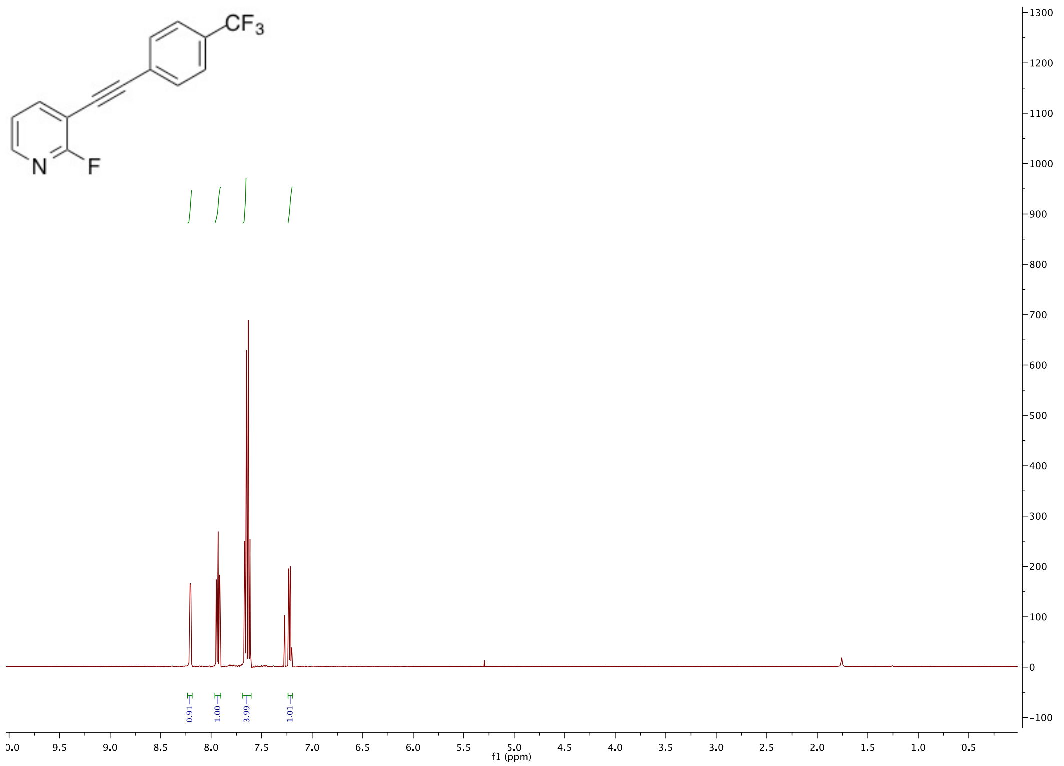

N
F
260
240
220
200
180
160
140
120
100
80
60
40
20
0
−20
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

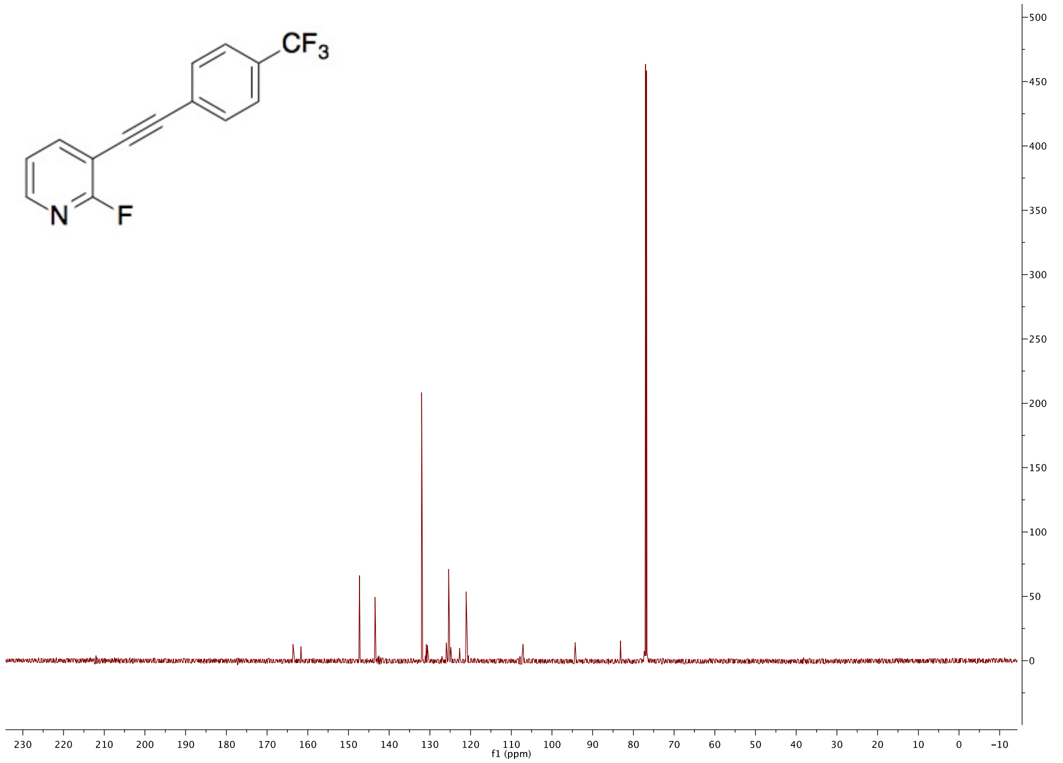

N
F
1.00
1.01
1.03
0.96
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 −500

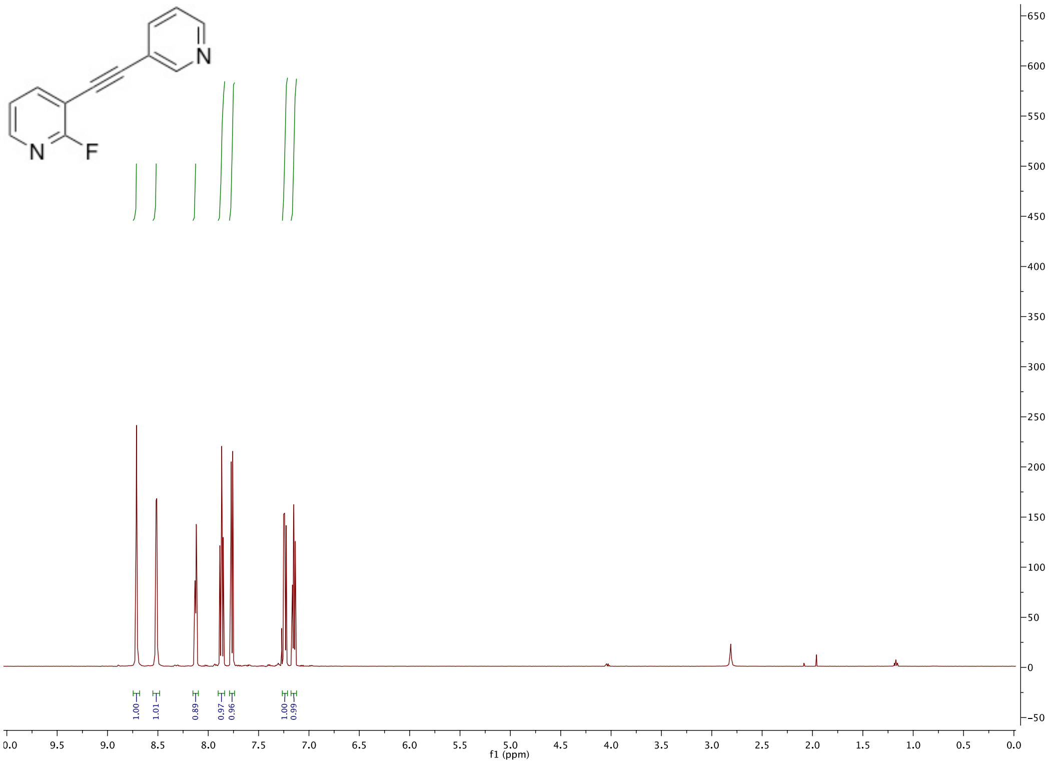

N
F
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

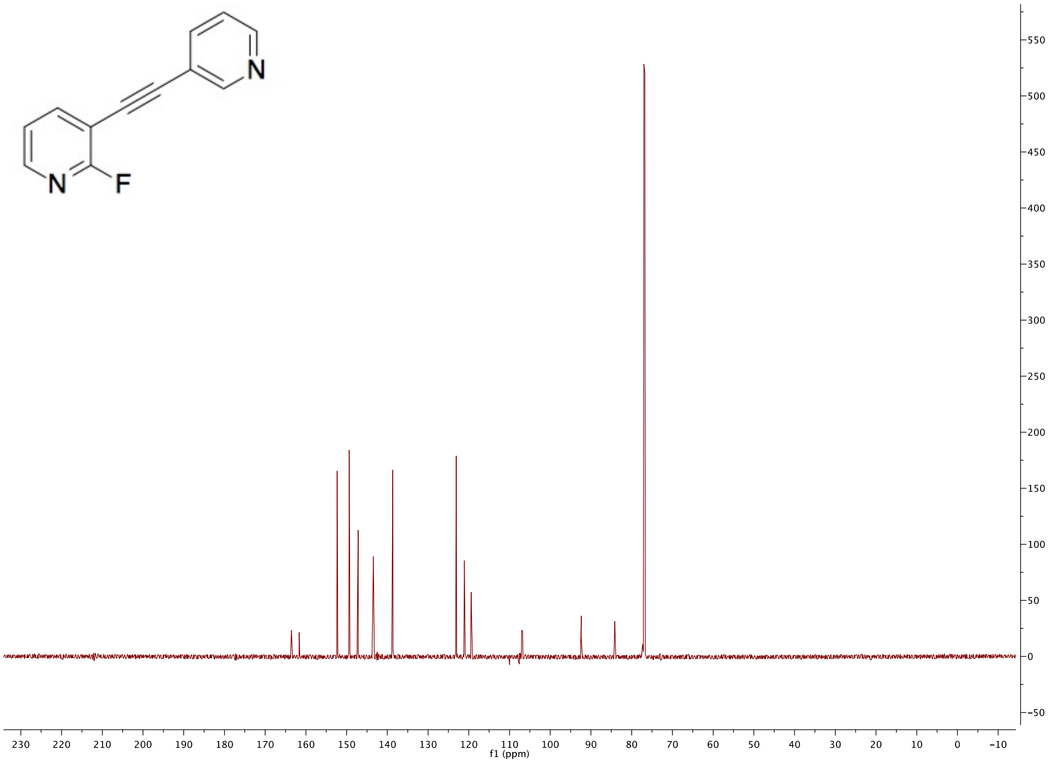

N
F
0.91
1.00
1.99
3.11
1.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500

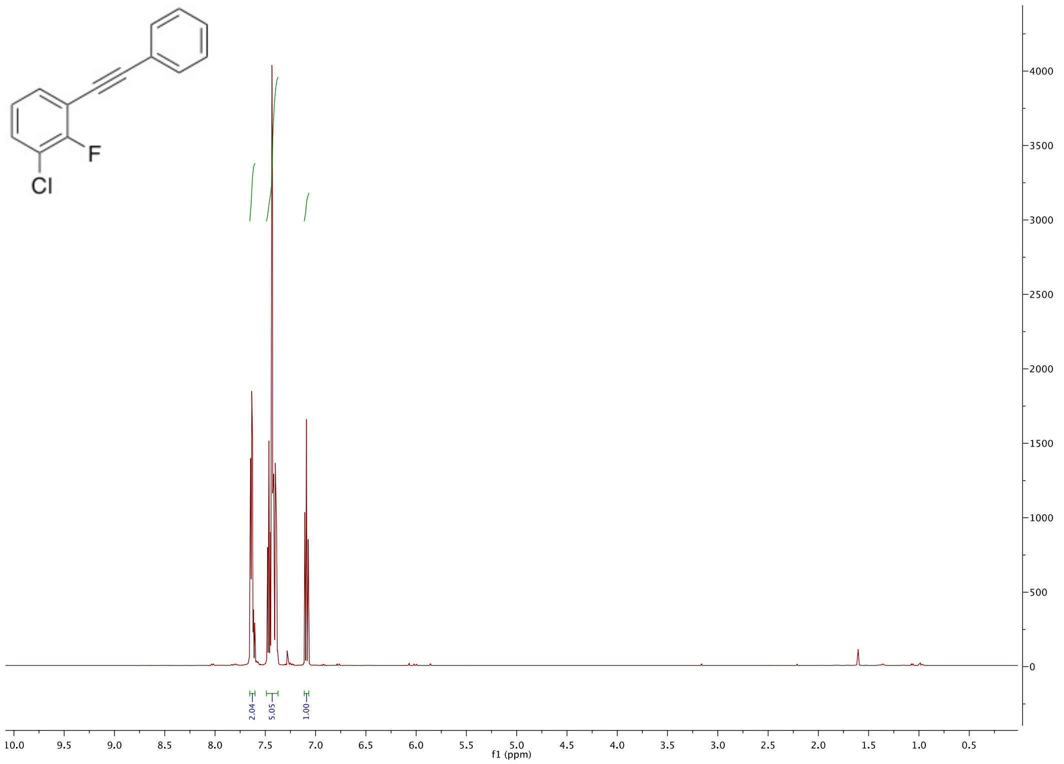

N
F
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
−200

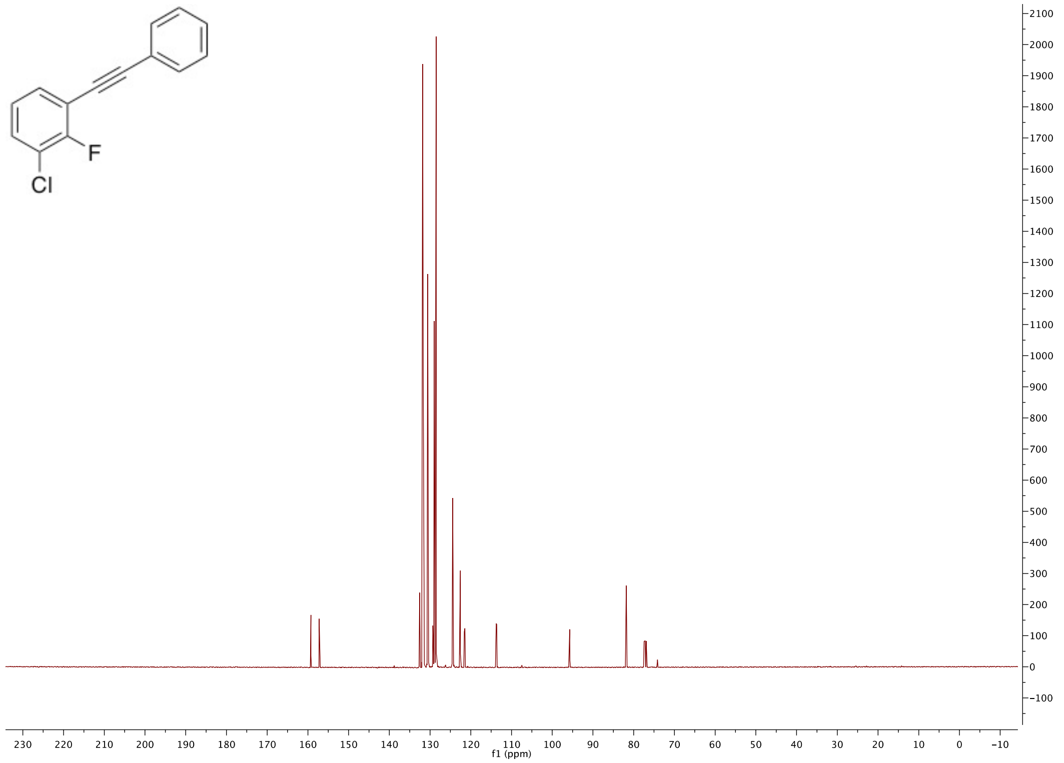

CF3
N
F
0.91
1.00
3.99
1.01
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

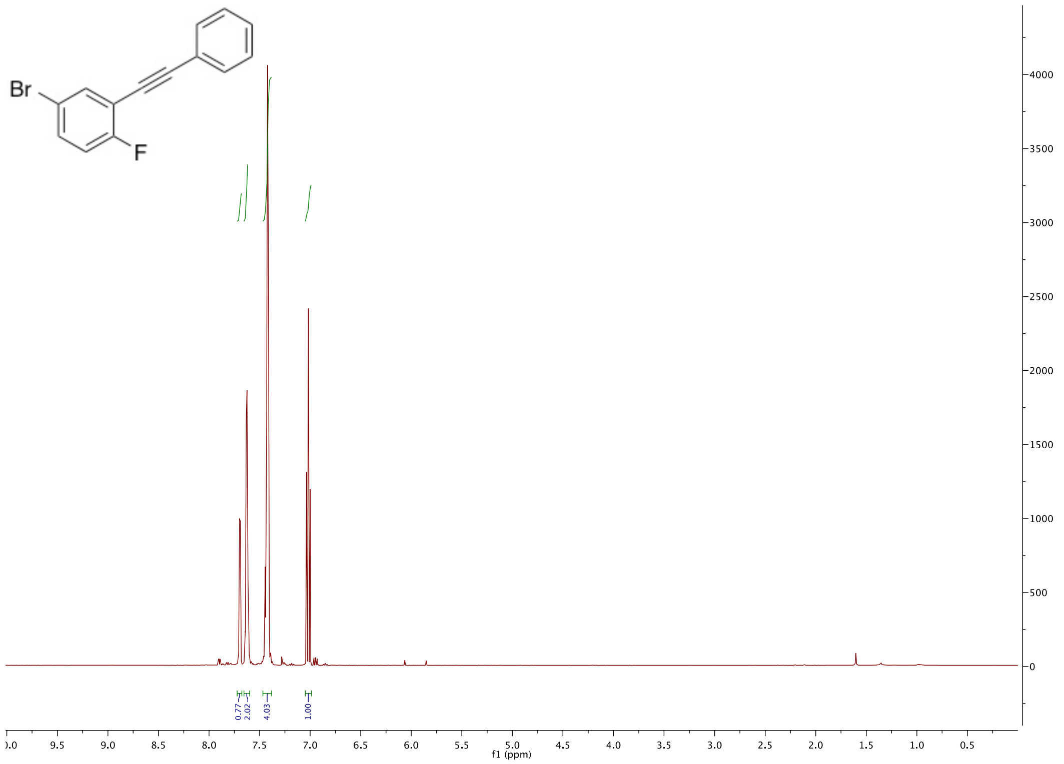

CF3
N
F
500
450
400
350
300
250
200
150
100
50
0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

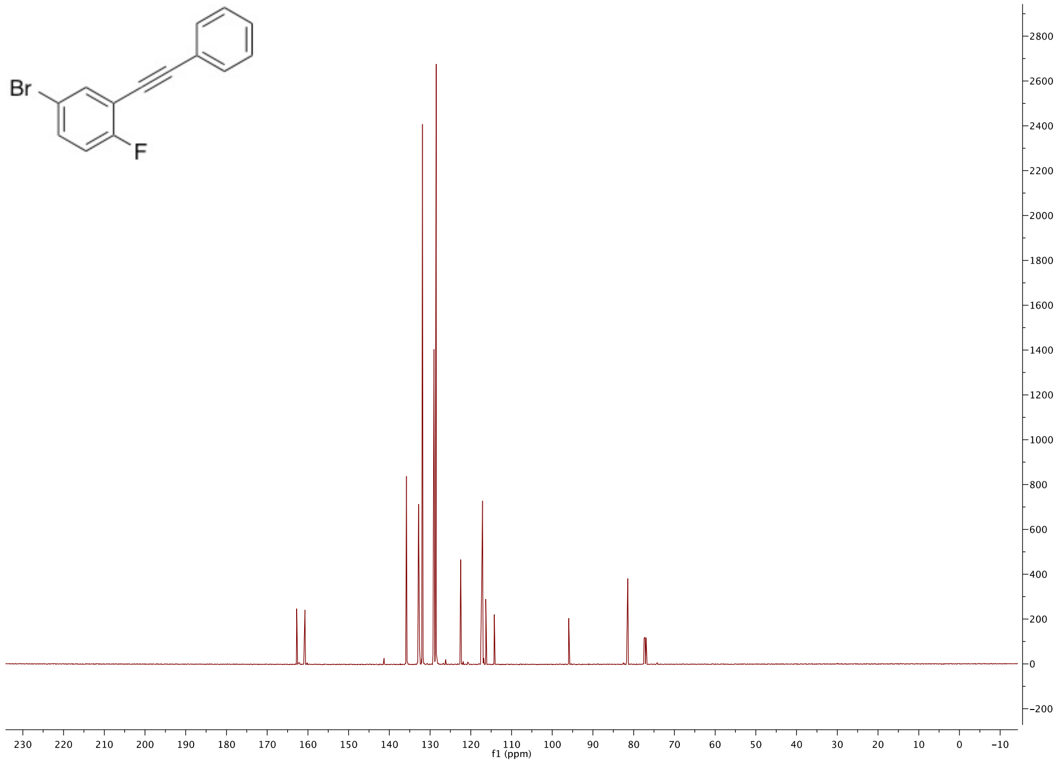

N
N
F
1.00
1.01
0.89
0.97
0.96
1.00
0.99
f1 (ppm)

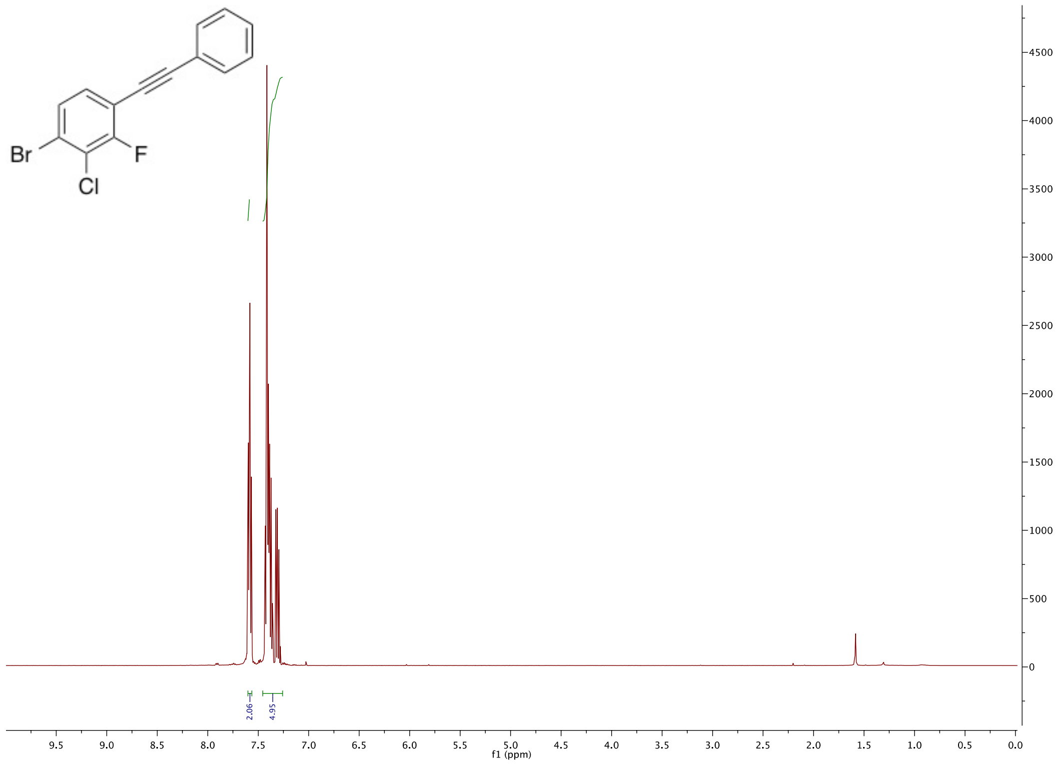

N
N
F
f1 (ppm)

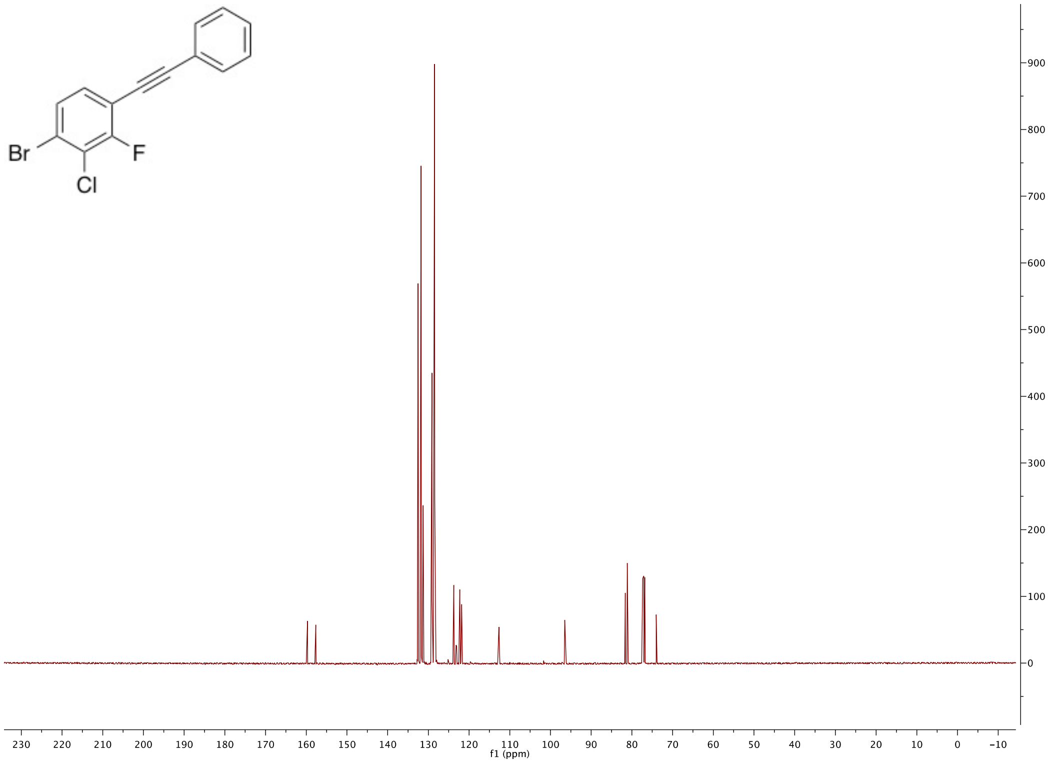

F
Cl
2.04
5.05
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
4000
3500
3000
2500
2000
1500
1000
500
0

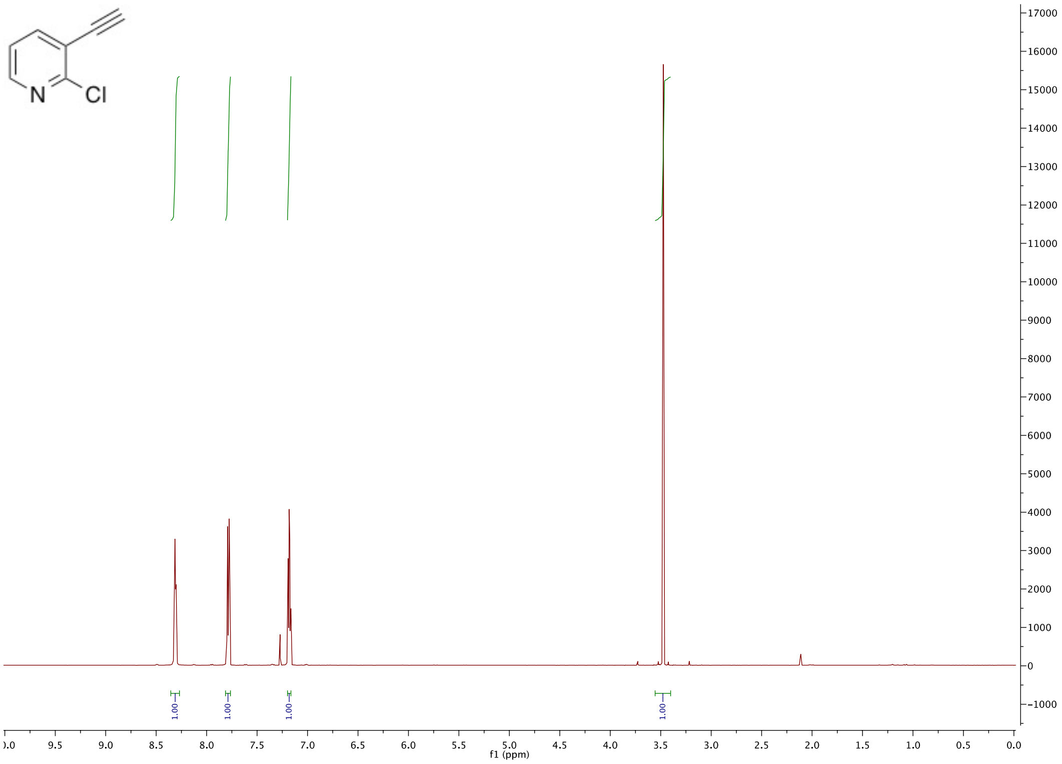

F
Cl
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100

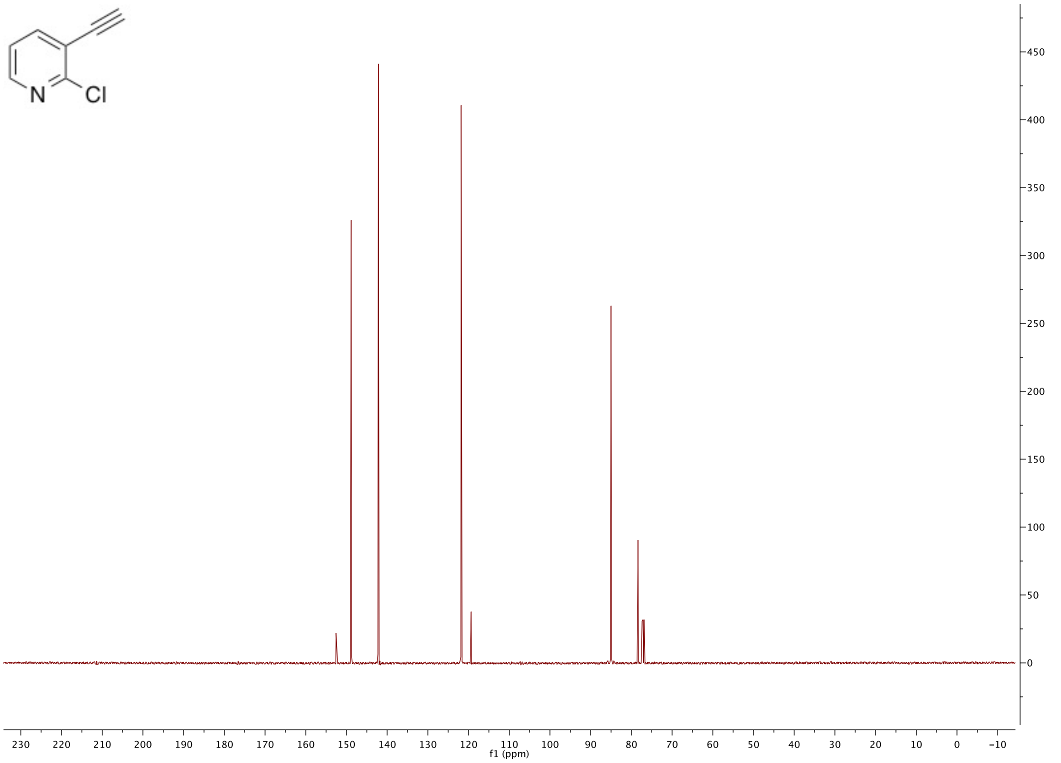

Br
F
0.77
2.02
4.03
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
4000
3500
3000
2500
2000
1500
1000
500
0

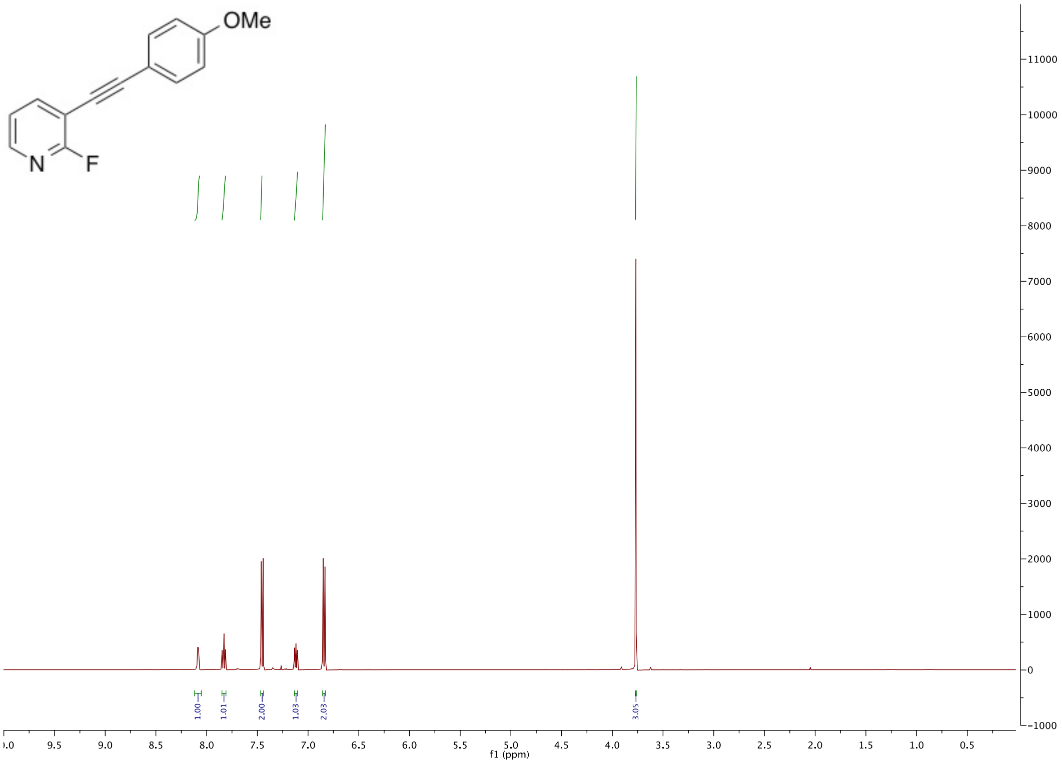

Br
F
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200

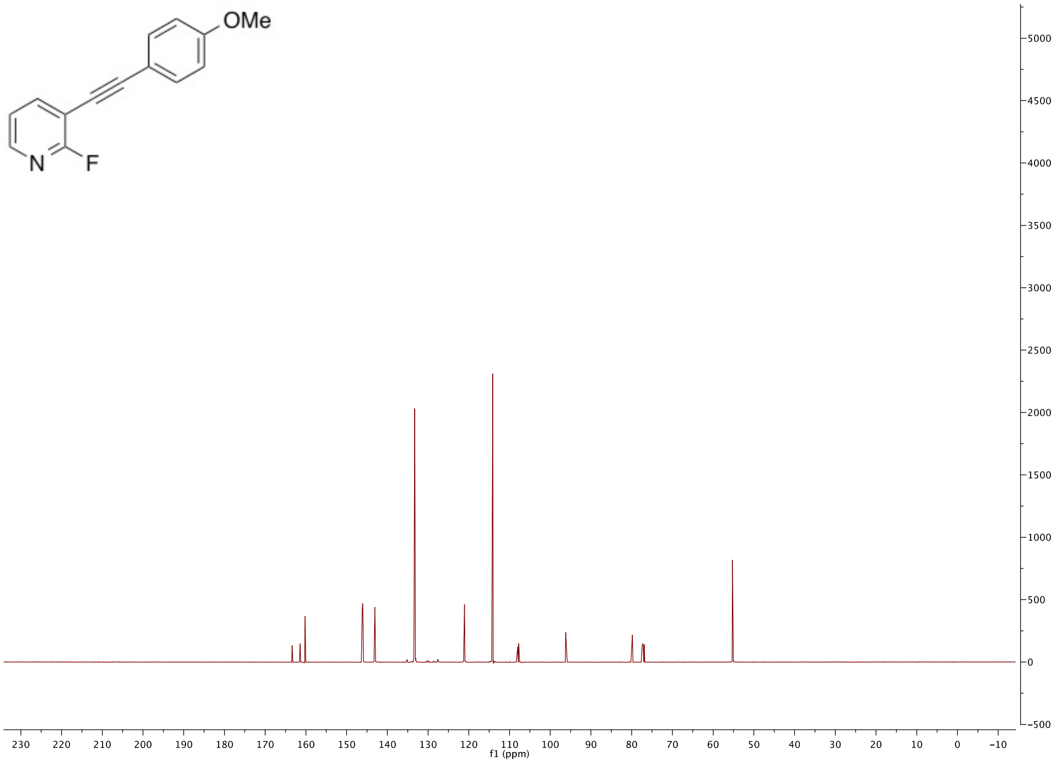

Br
F
Cl
4500
4000
3500
3000
2500
2000
1500
1000
500
0
2.06
4.95
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

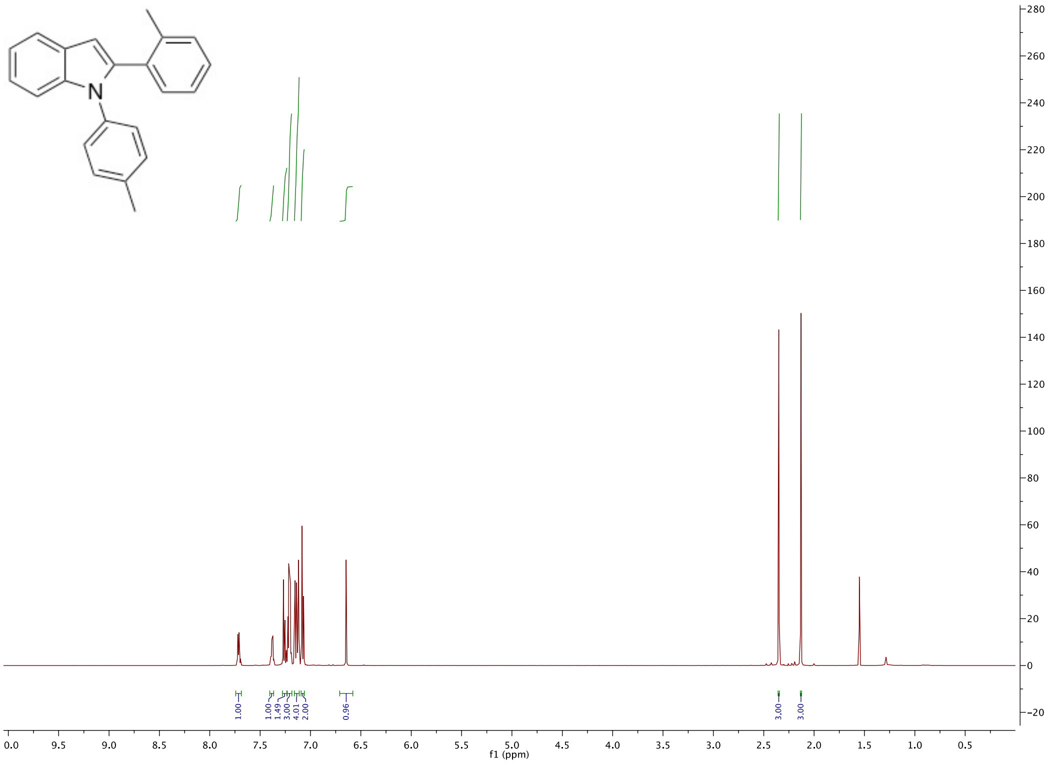

Br
F
Cl
900
800
700
600
500
400
300
200
100
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

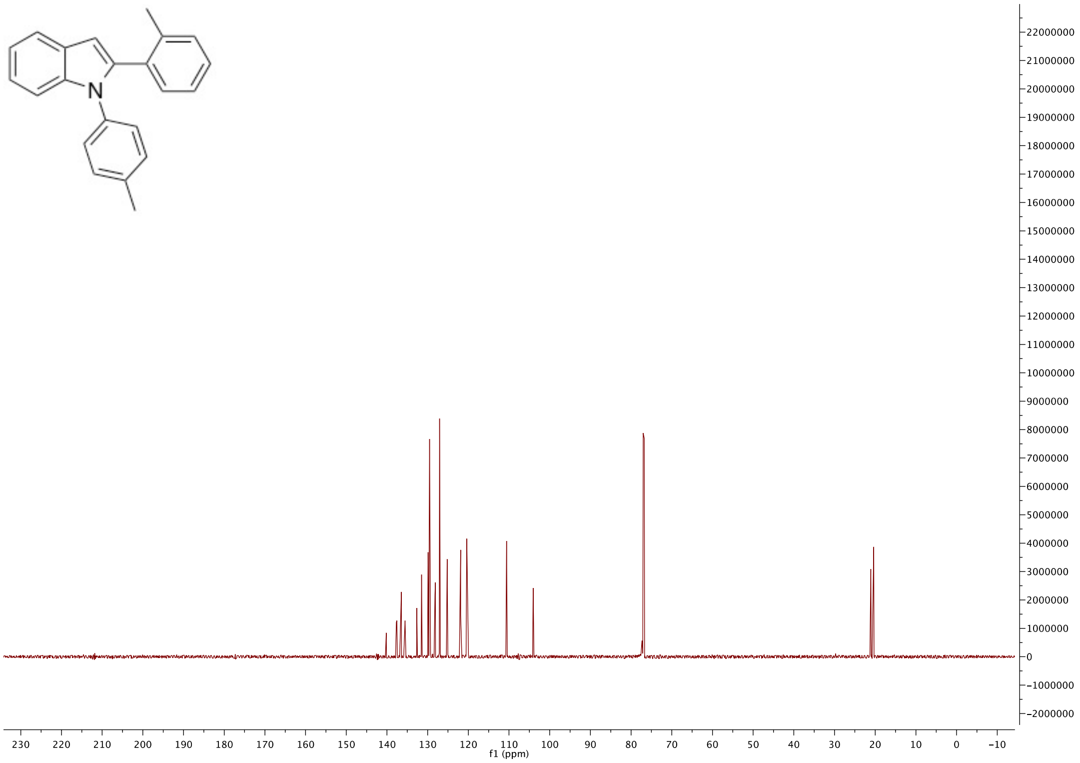

N
Cl
1.00
1.00
1.00
1.00
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

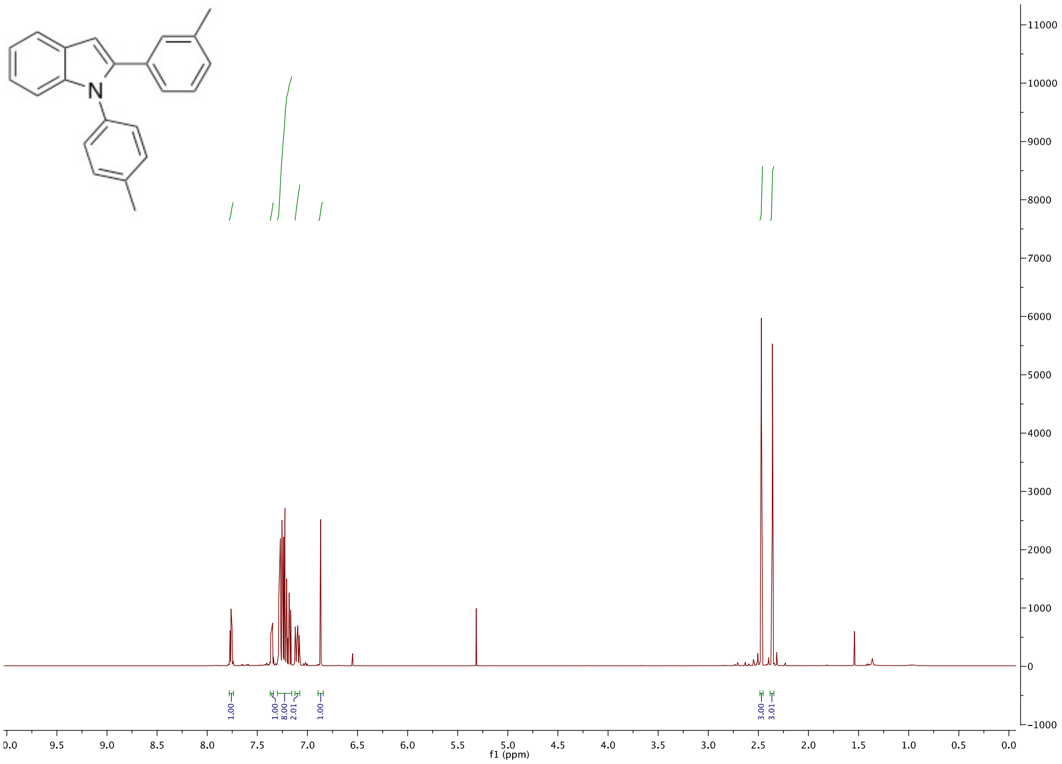

N
Cl
450
400
350
300
250
200
150
100
50
0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

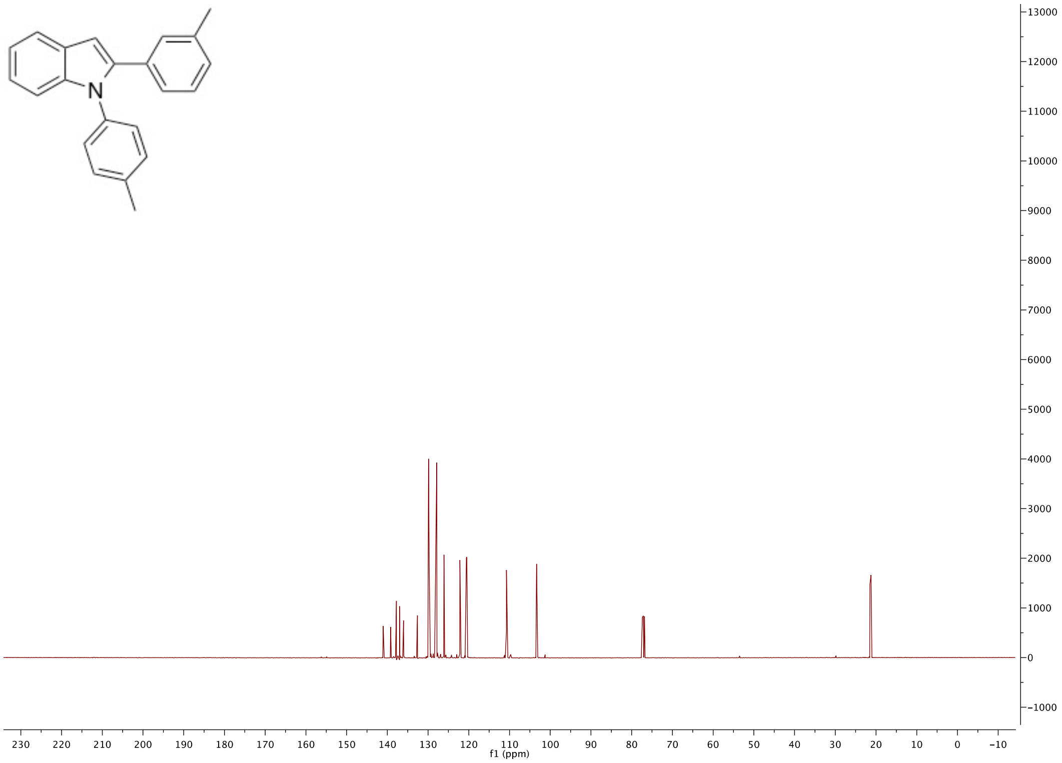

OMe
N
F
1.00
1.01
2.00
1.03
2.03
3.05
f1 (ppm)
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

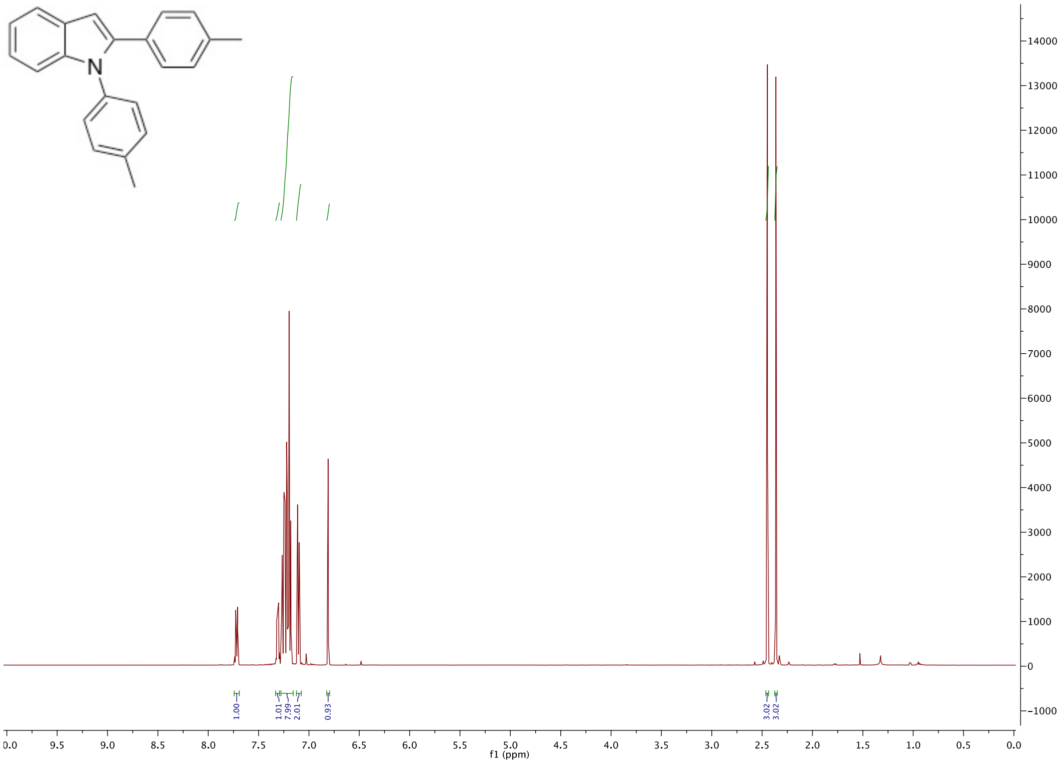

OMe
N
F
f1 (ppm)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

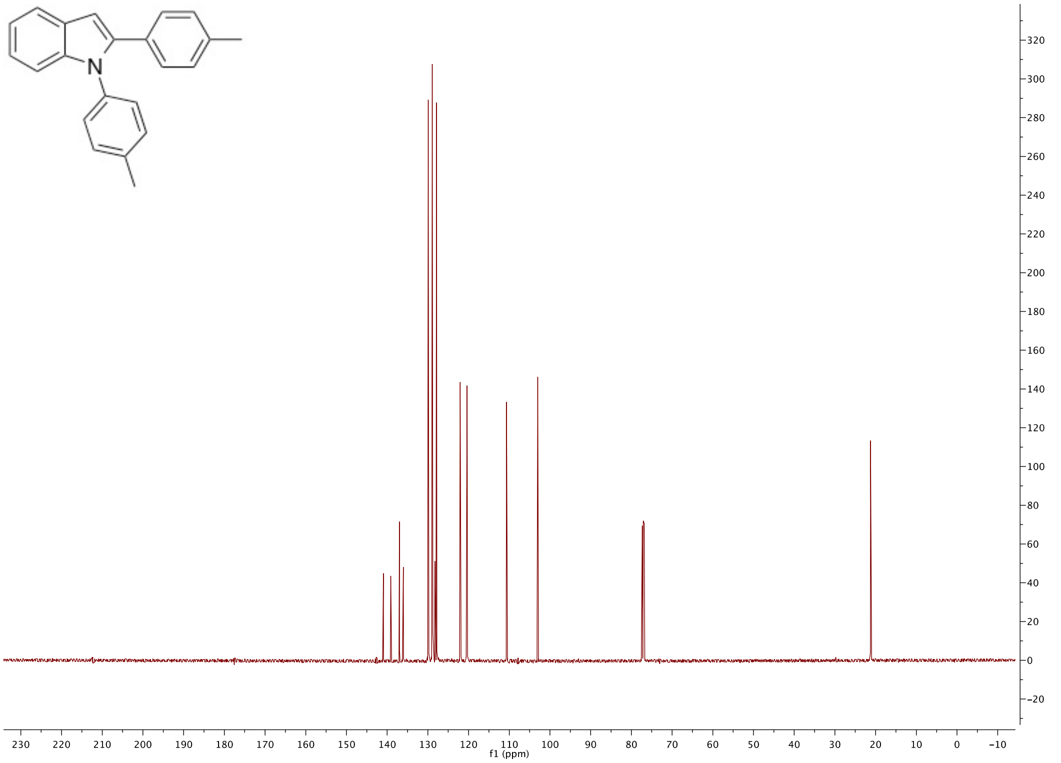

N
1.00
1.00
1.49
3.00
4.01
2.00
0.96
3.00
3.00
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 −20

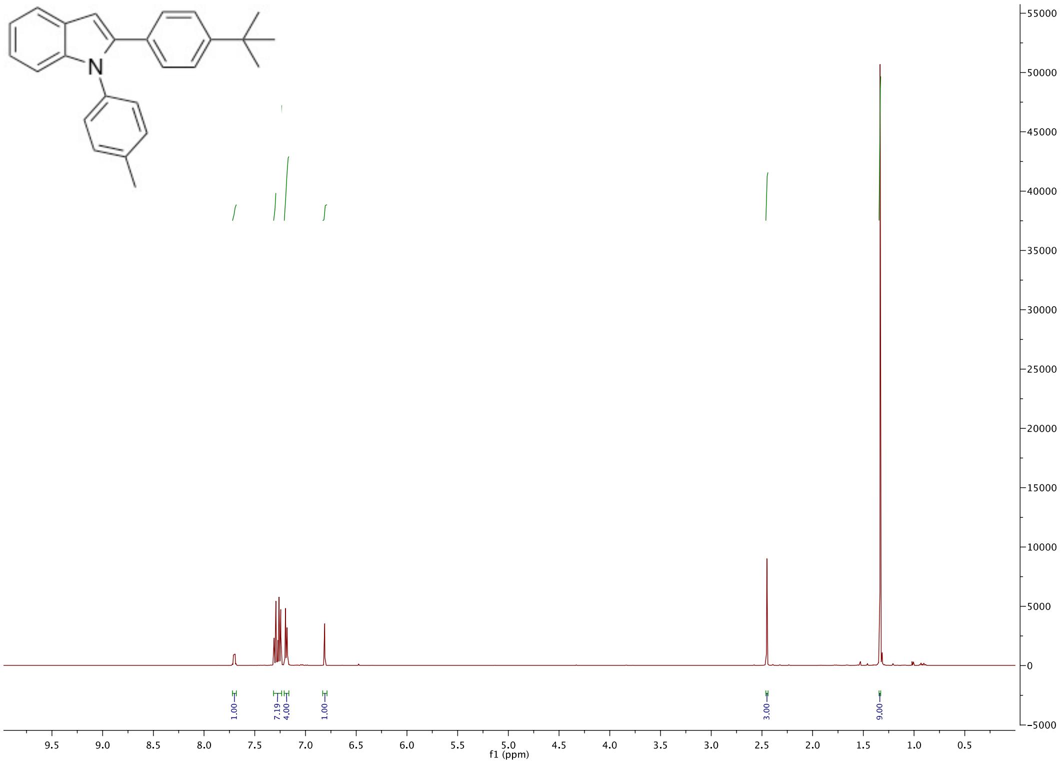

N
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)
22000000 21000000 20000000 19000000 18000000 17000000 16000000 15000000 14000000 13000000 12000000 11000000 10000000 9000000 8000000 7000000 6000000 5000000 4000000 3000000 2000000 1000000 0 −1000000 −2000000

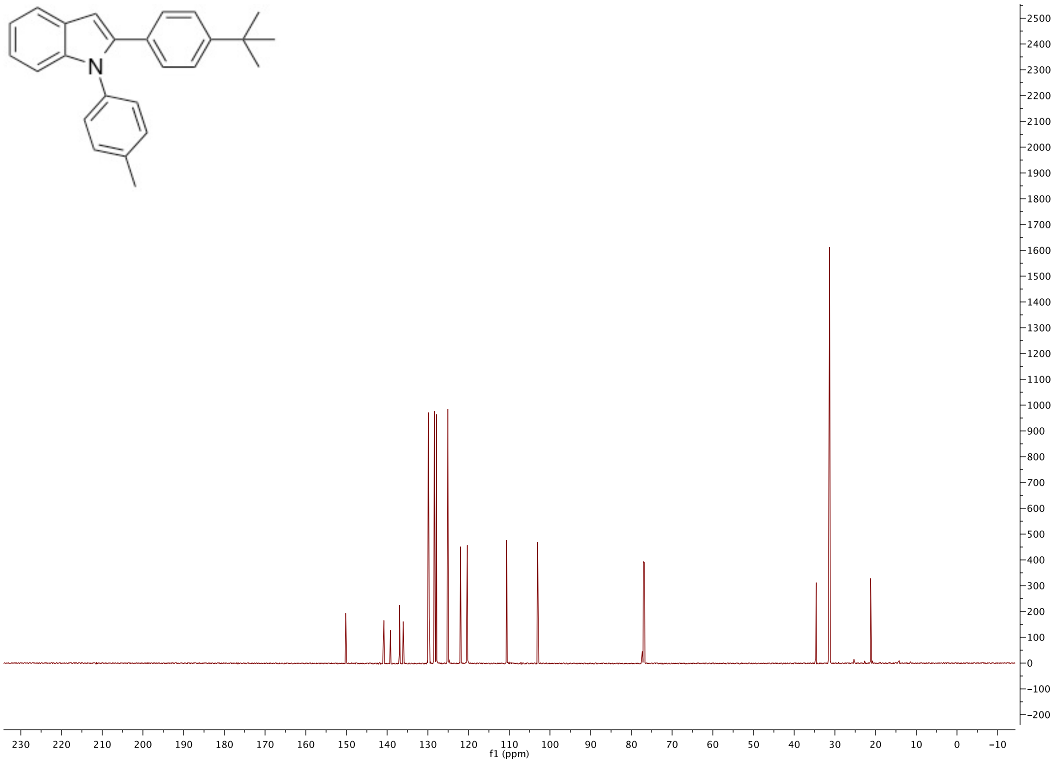

N
1.00
1.00
8.00
2.01
1.00
3.00
3.01
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

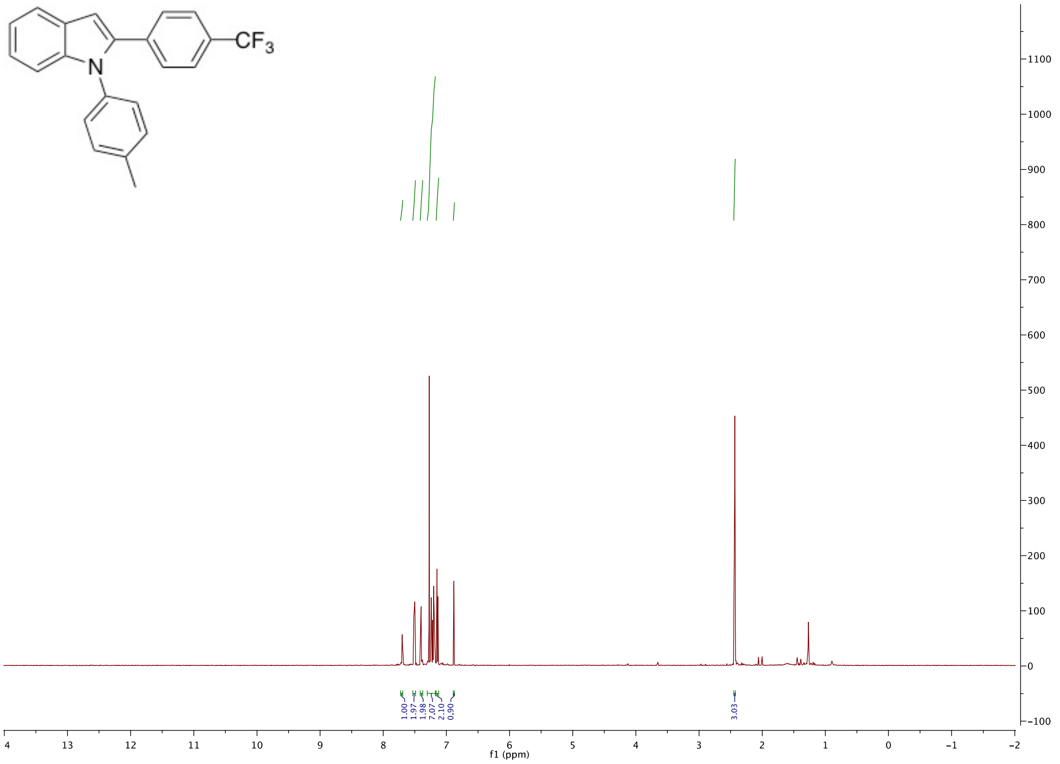

N
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

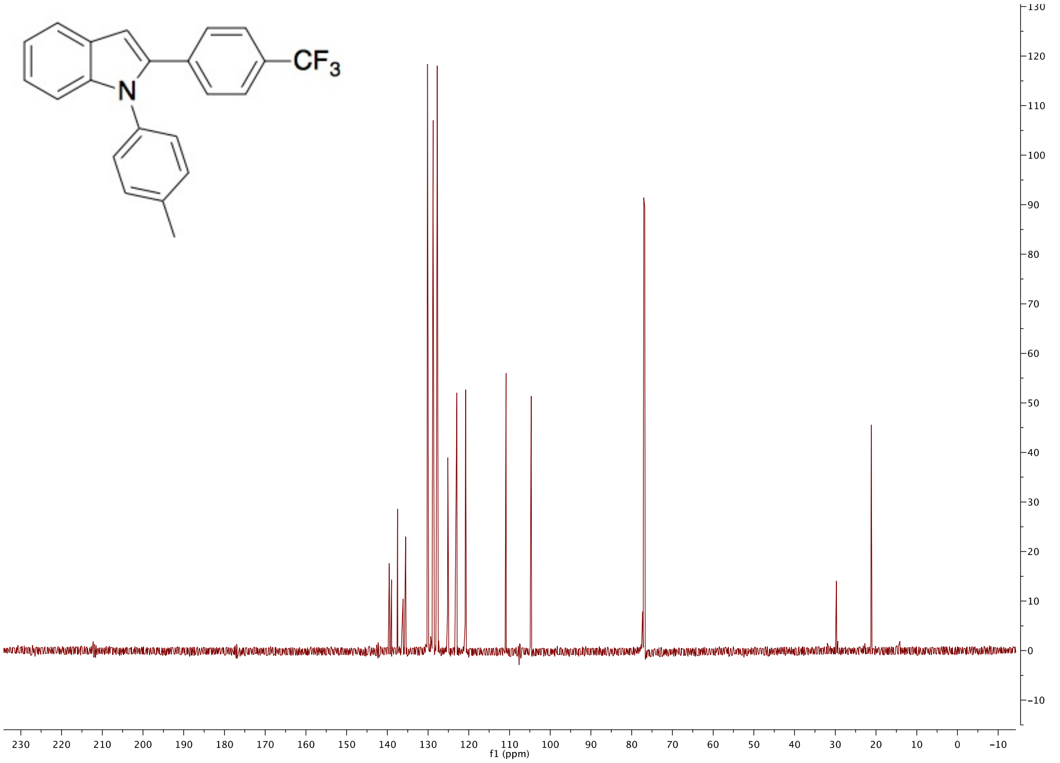

N
1.00
1.01
7.99
2.01
0.93
3.02
3.02
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

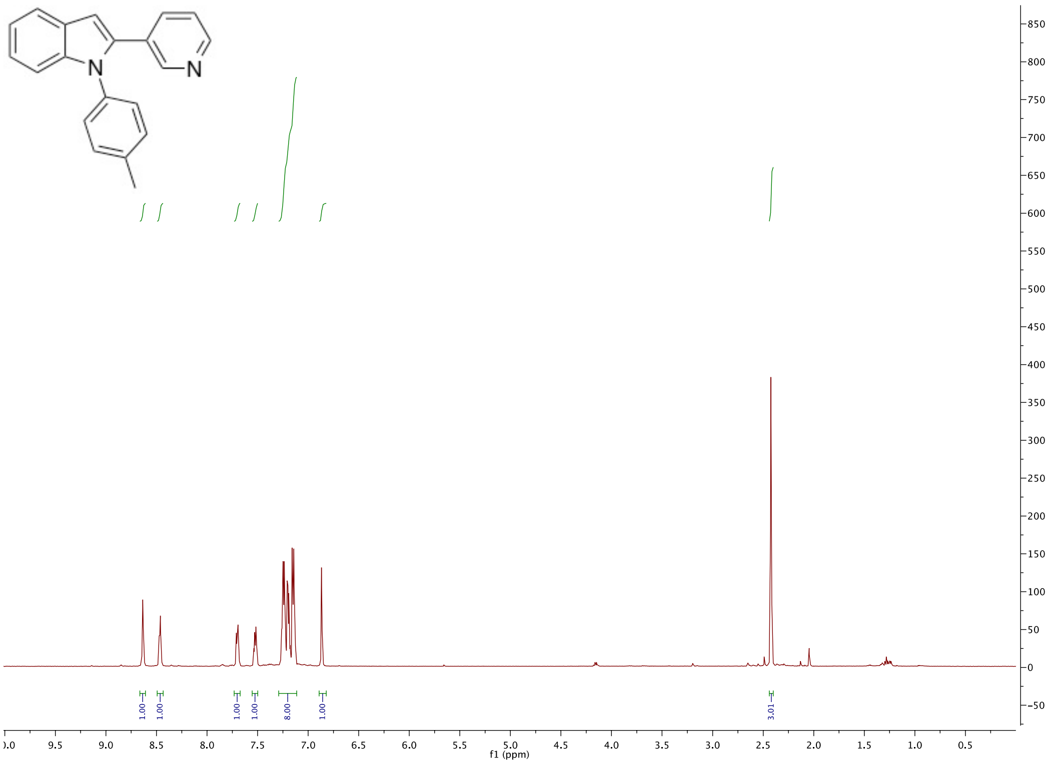

N
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
−20
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

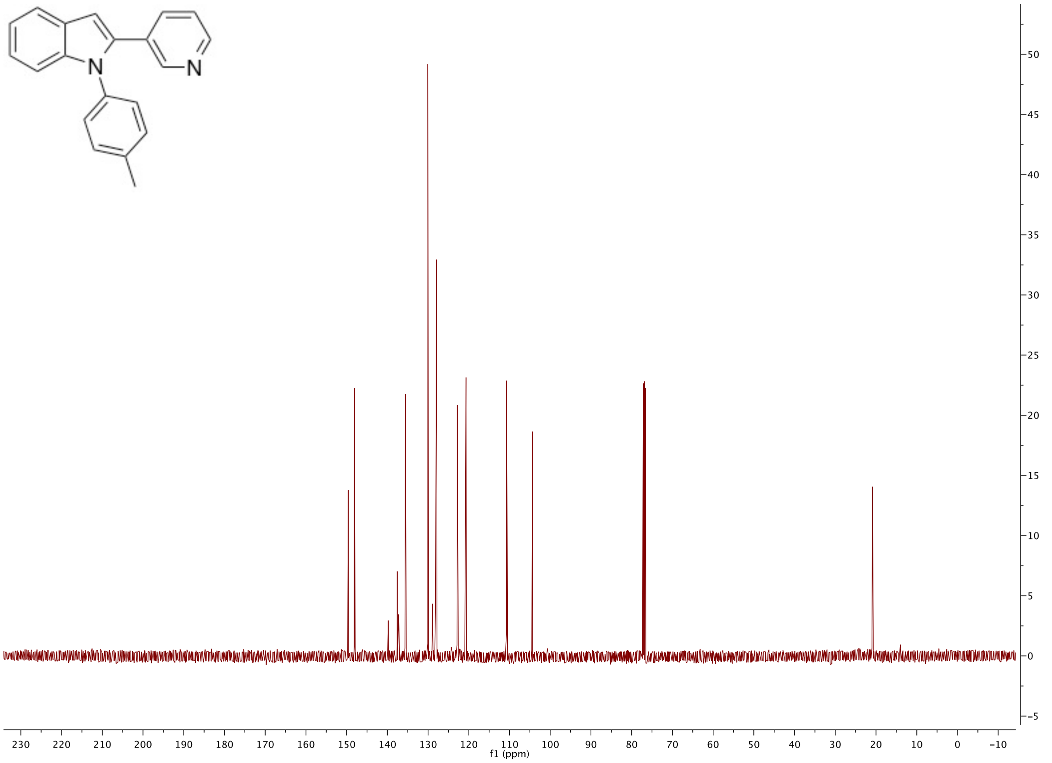

N
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
1.00
7.19
4.00
1.00
3.00
9.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

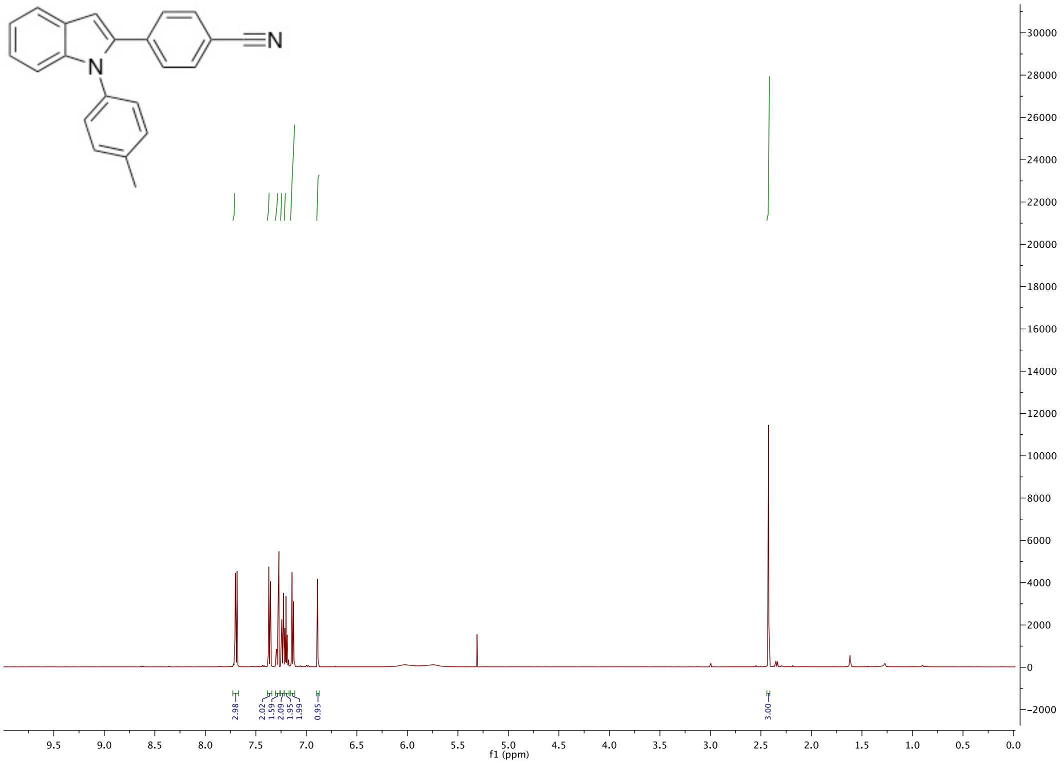

N
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

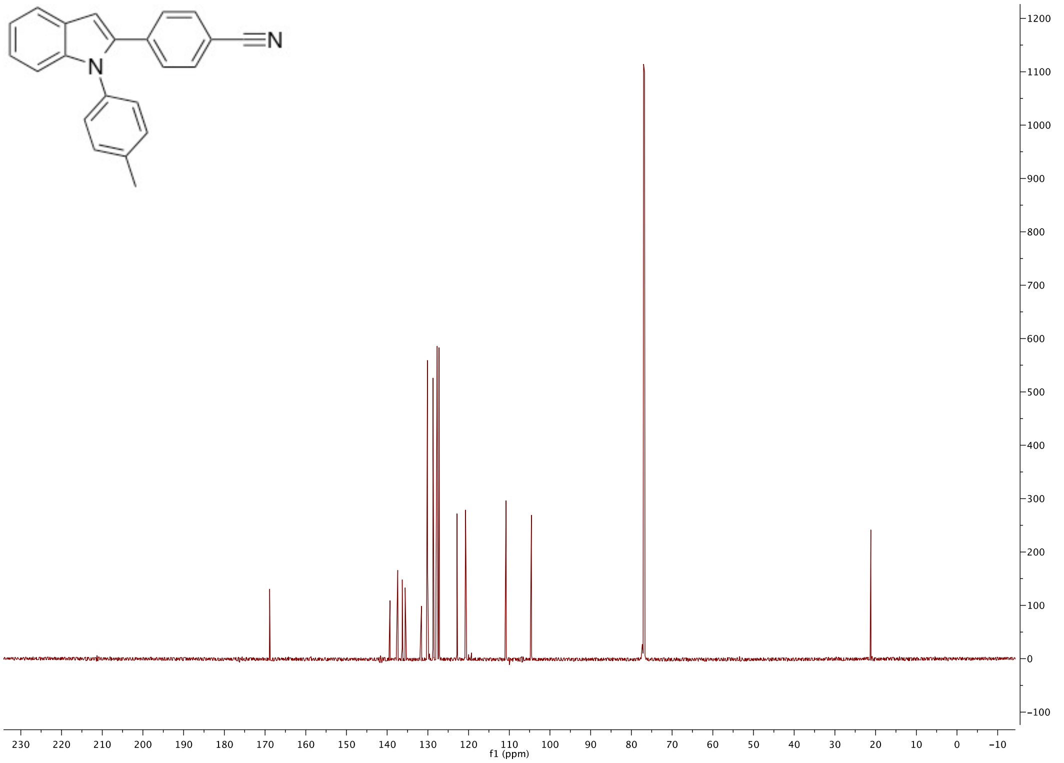

CF3
N
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
1.00
1.97
1.98
7.07
2.10
0.90
3.03
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

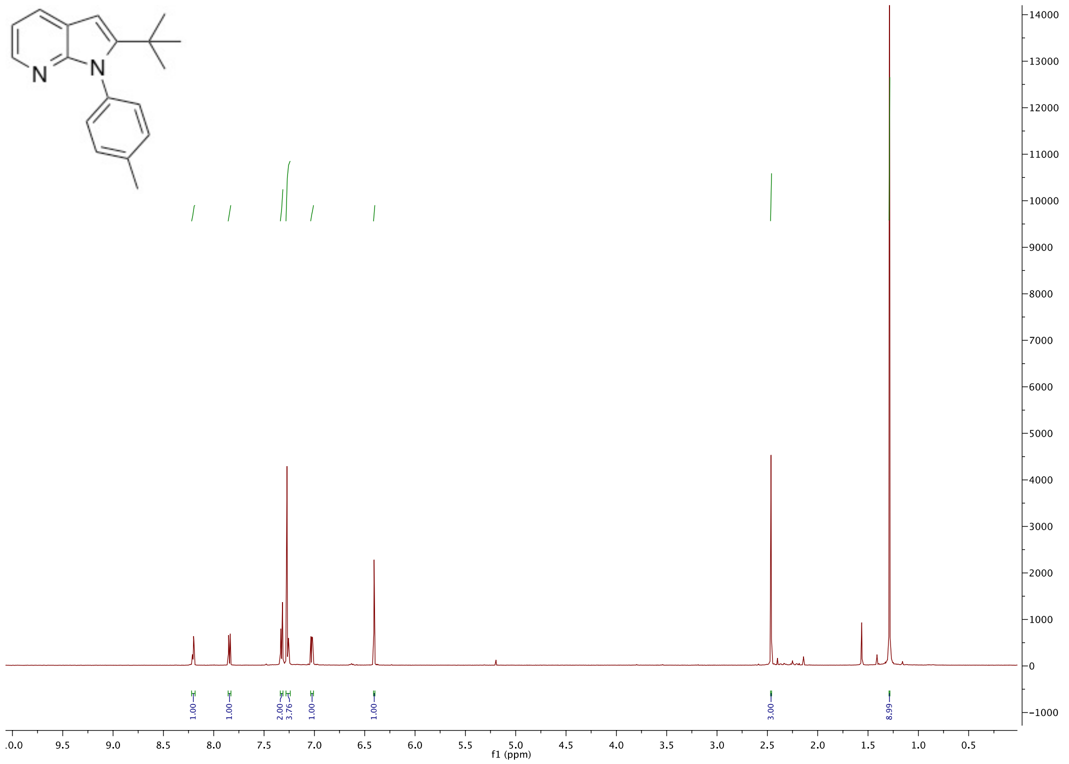

CF3
N
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

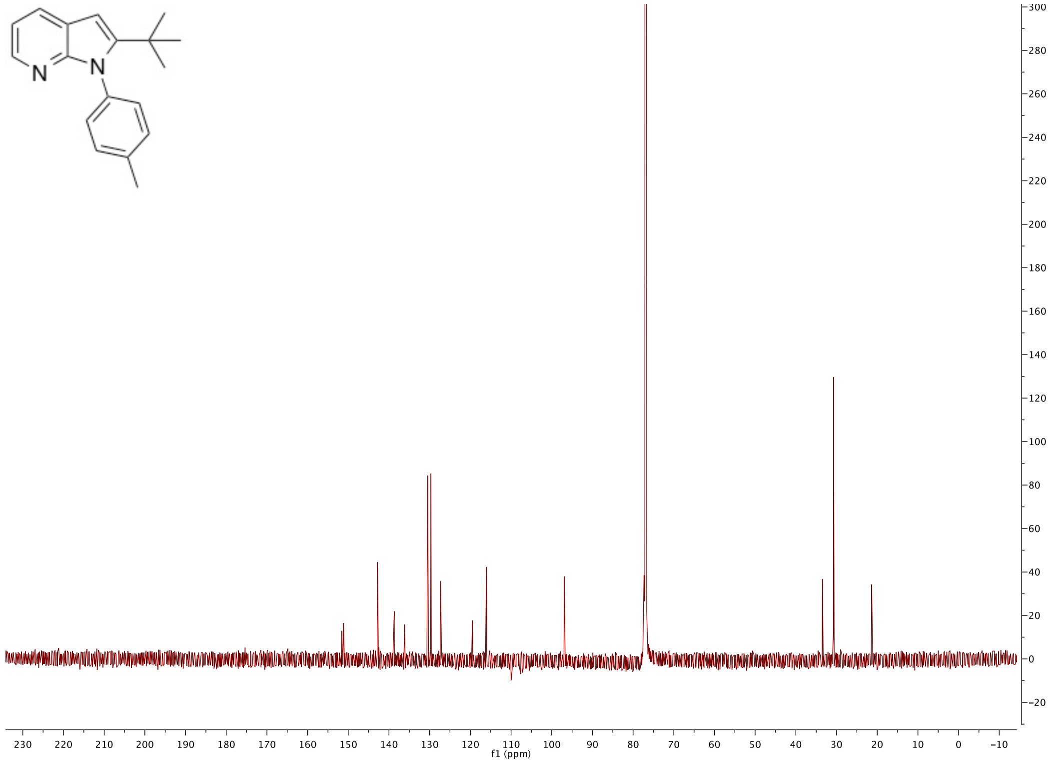

N
N
1.00
1.00
1.00
1.00
8.00
1.00
3.01
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
−50
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

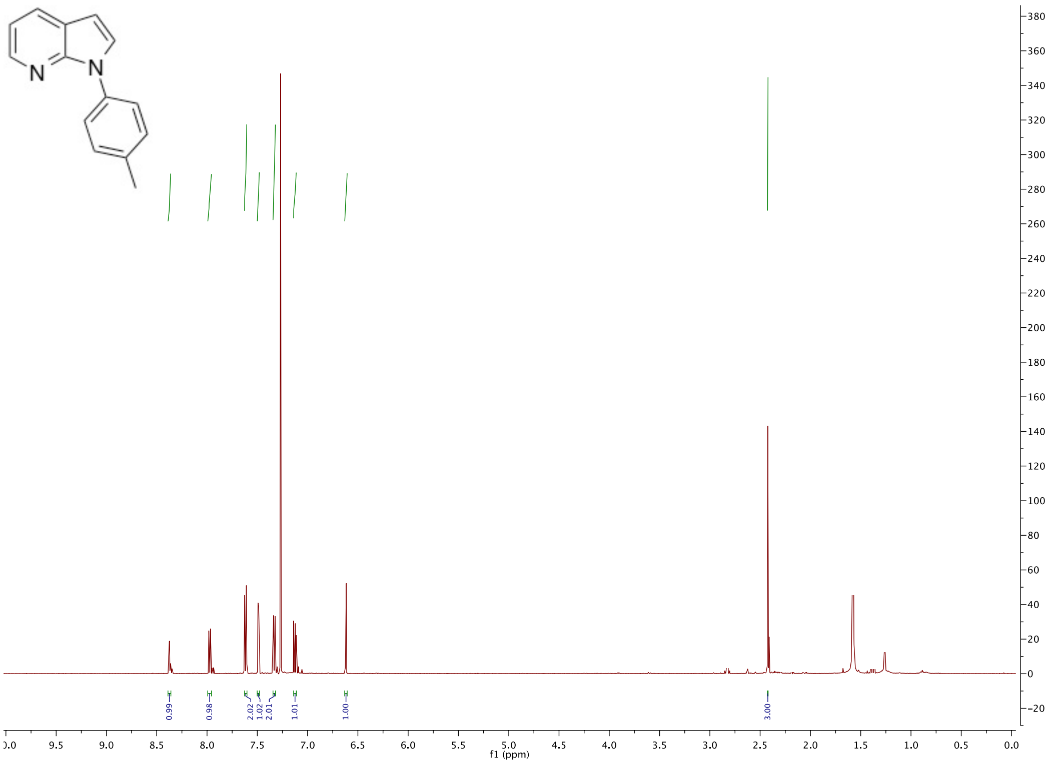

N
N
50
45
40
35
30
25
20
15
10
5
0
−5
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

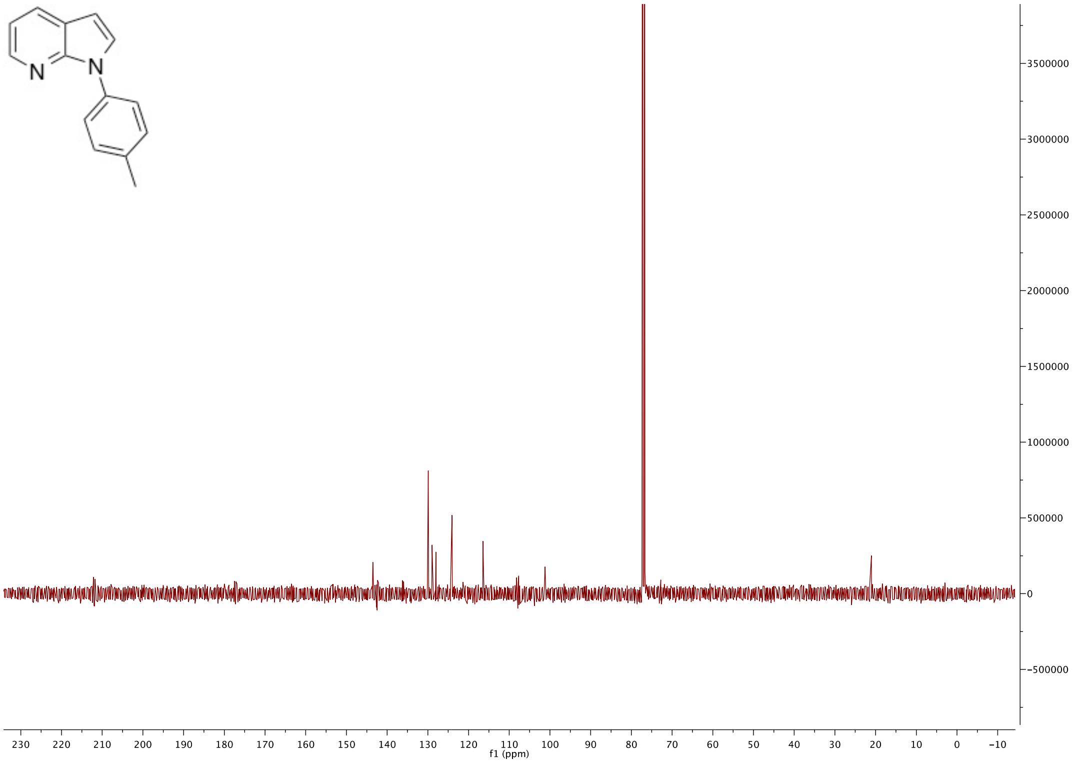

N
2.98
2.02
1.59
2.09
1.95
1.99
0.95
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
30000 28000 26000 24000 22000 20000 18000 16000 14000 12000 10000 8000 6000 4000 2000 0 −2000


N
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)
1200 1100 1000 900 800 700 600 500 400 300 200 100 0 −100

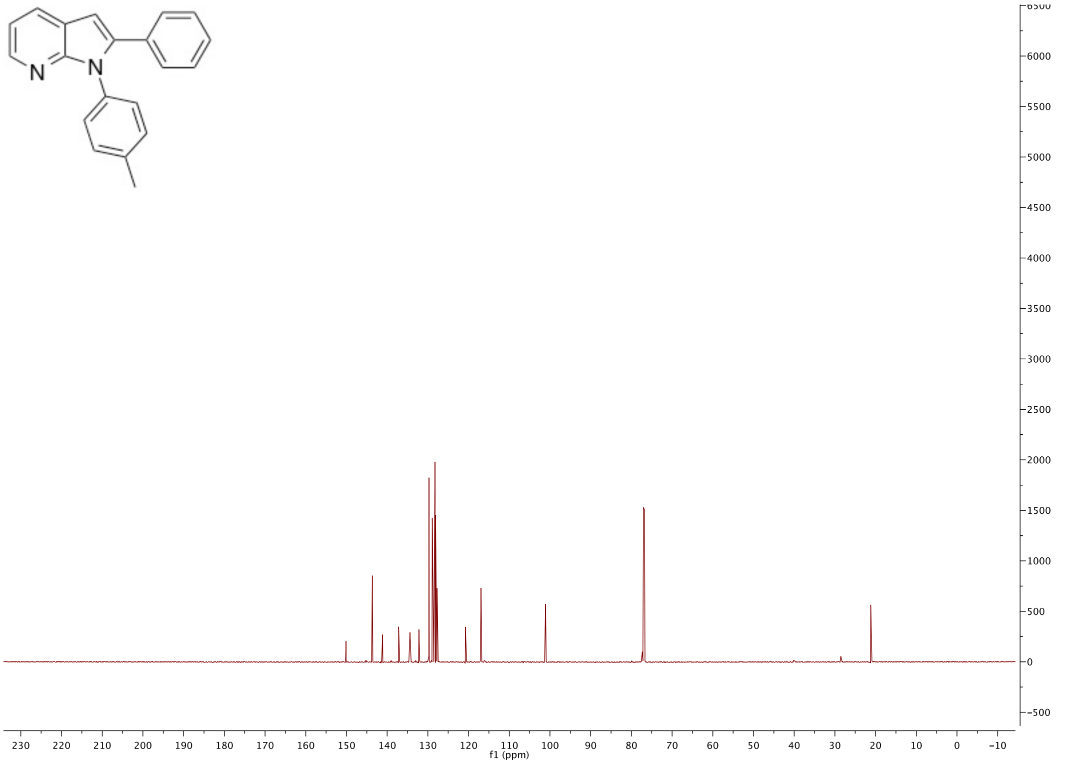

N
N
1.00
1.00
2.00
3.76
1.00
1.00
3.00
8.99
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
.0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

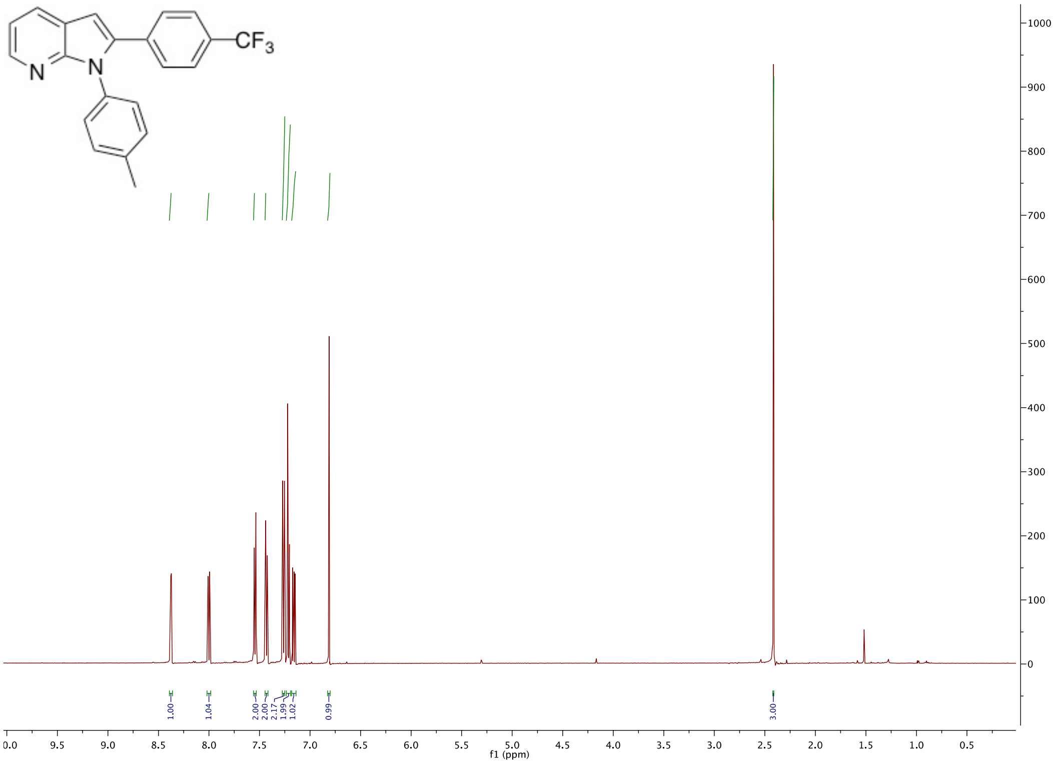

N
N
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
−20
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)


N
N
0.99
0.98
2.02
1.02
2.01
1.01
1.00
3.00
f1 (ppm)
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 −20

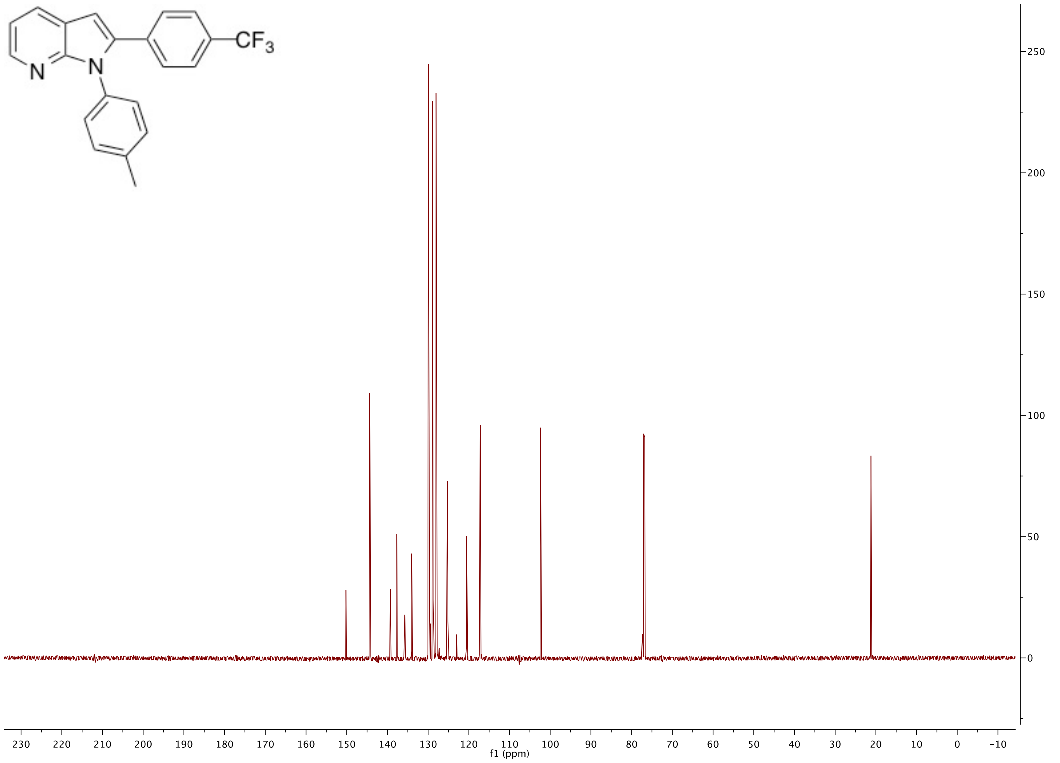

N
N
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
3500000 3000000 2500000 2000000 1500000 1000000 500000 0 −500000


N
N
1.00
1.05
5.41
4.06
1.17
1.01
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
200000
190000
180000
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
−10000

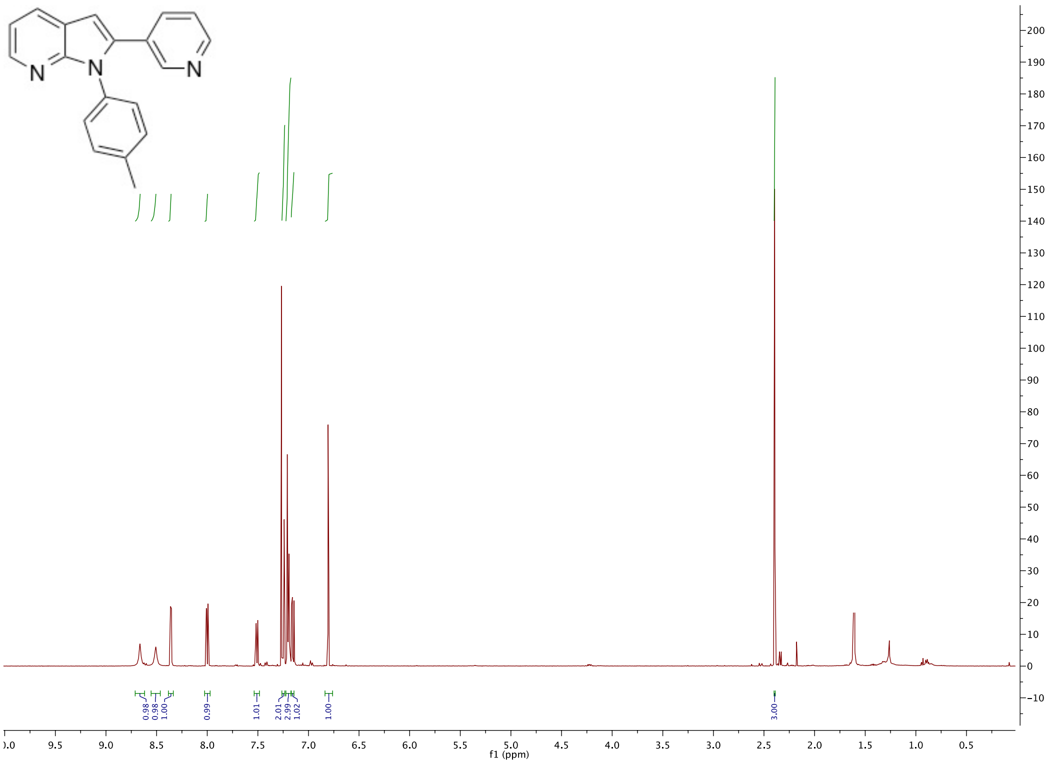

N
N
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500

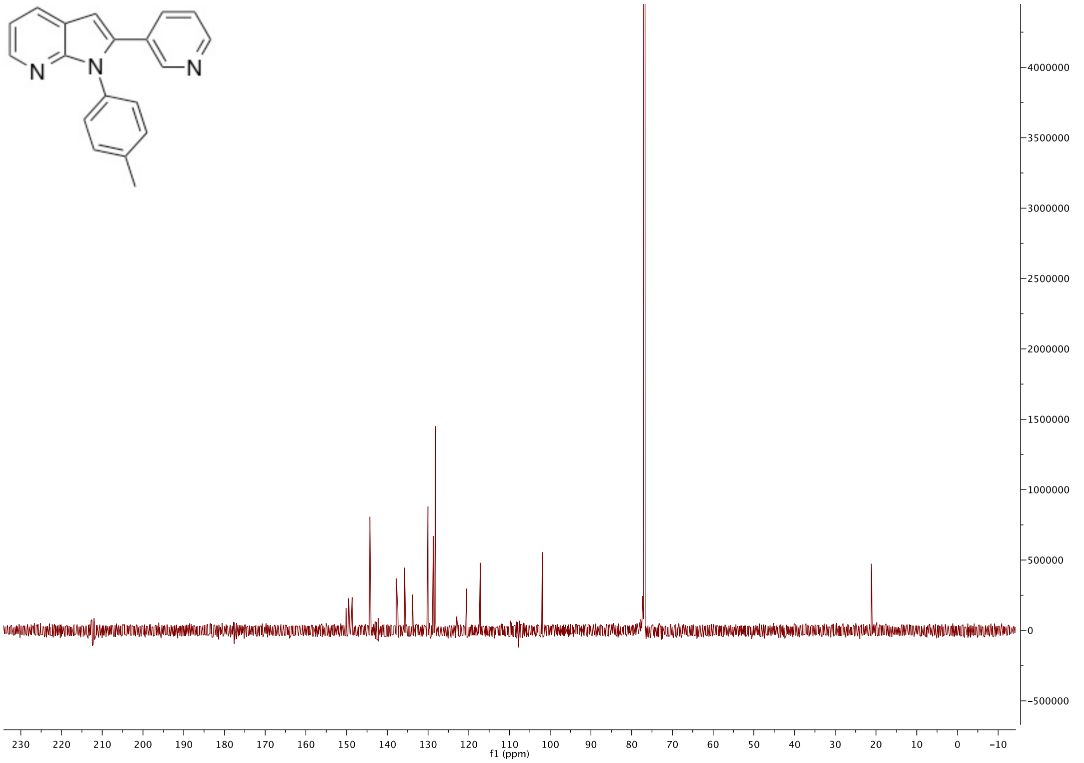


N
N
CF3
1.00
1.04
2.00
2.00
2.17
1.99
1.02
0.99
3.00
1000
900
800
700
600
500
400
300
200
100
0
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

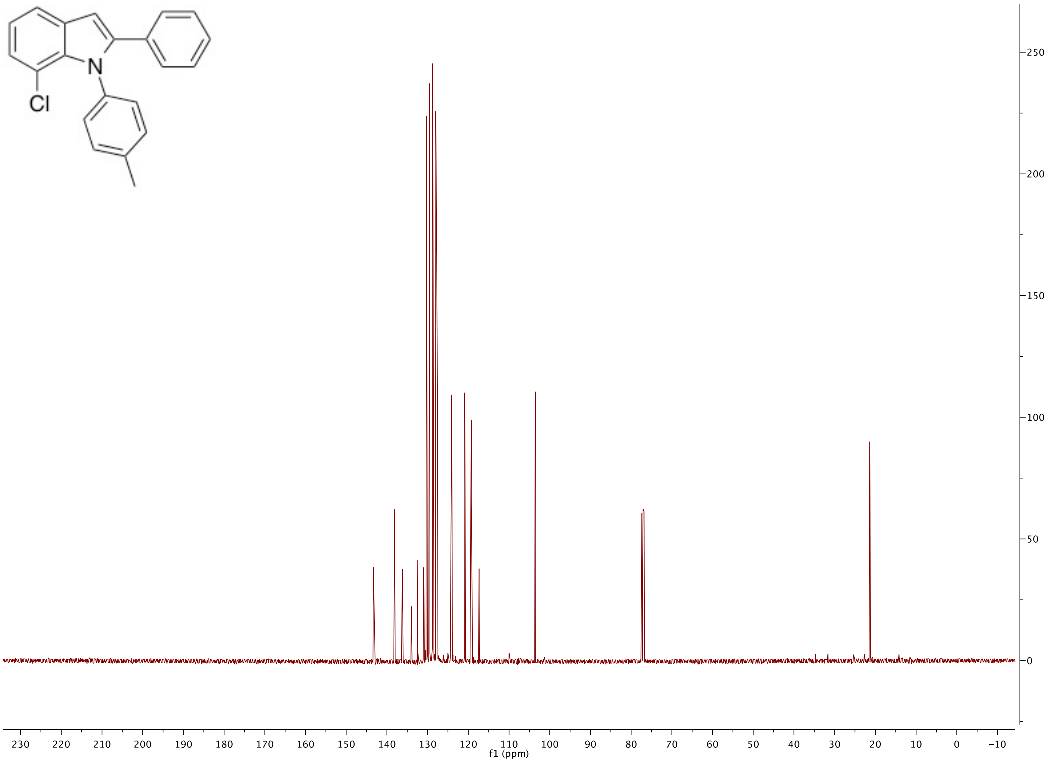


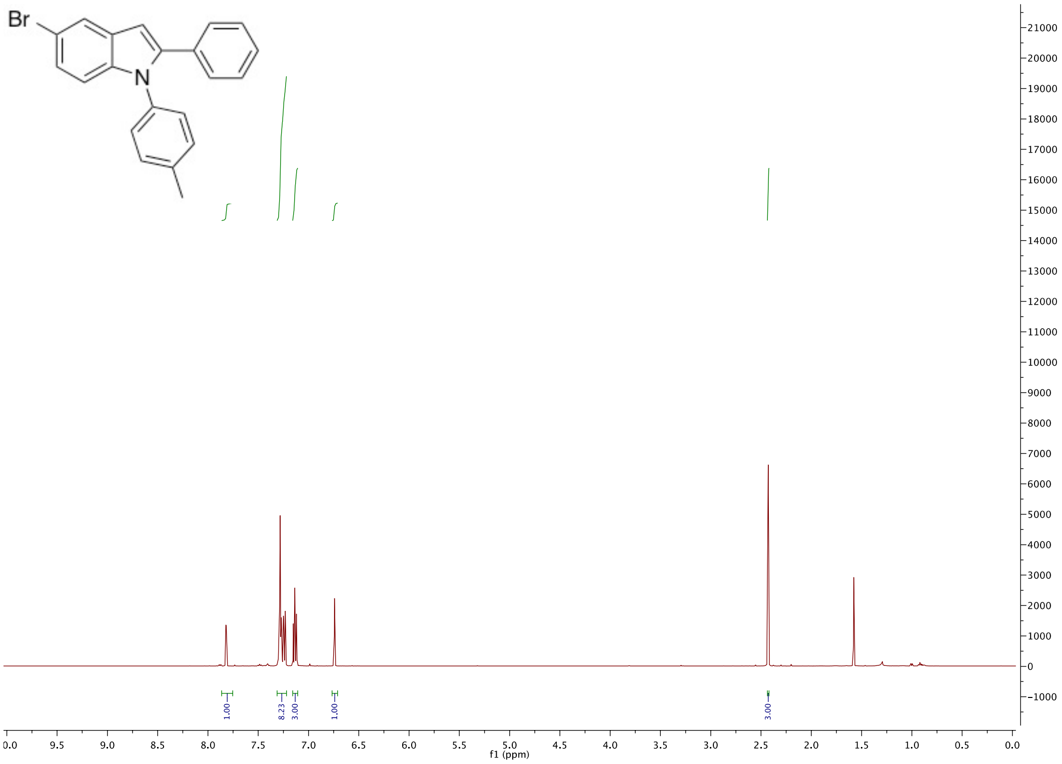
N
N
CF3
250
200
150
100
50
0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

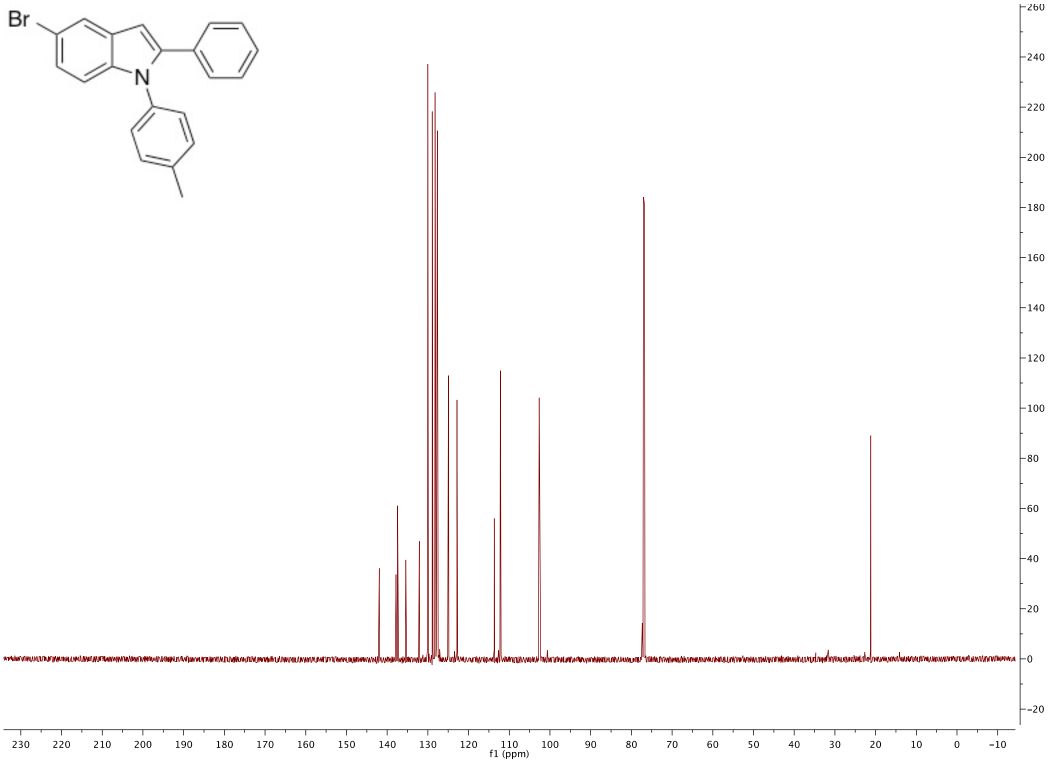

N
N
N
0.98
0.98
1.00
0.99
1.01
2.01
2.99
1.02
1.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10

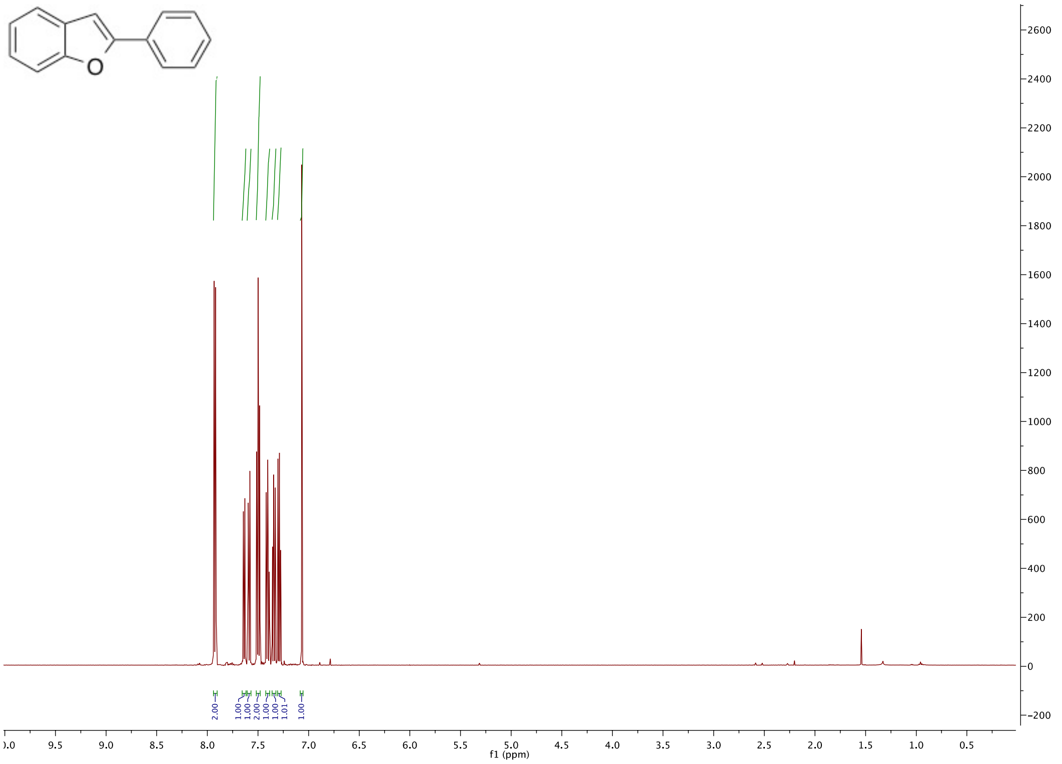

N
N
N
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
−500000

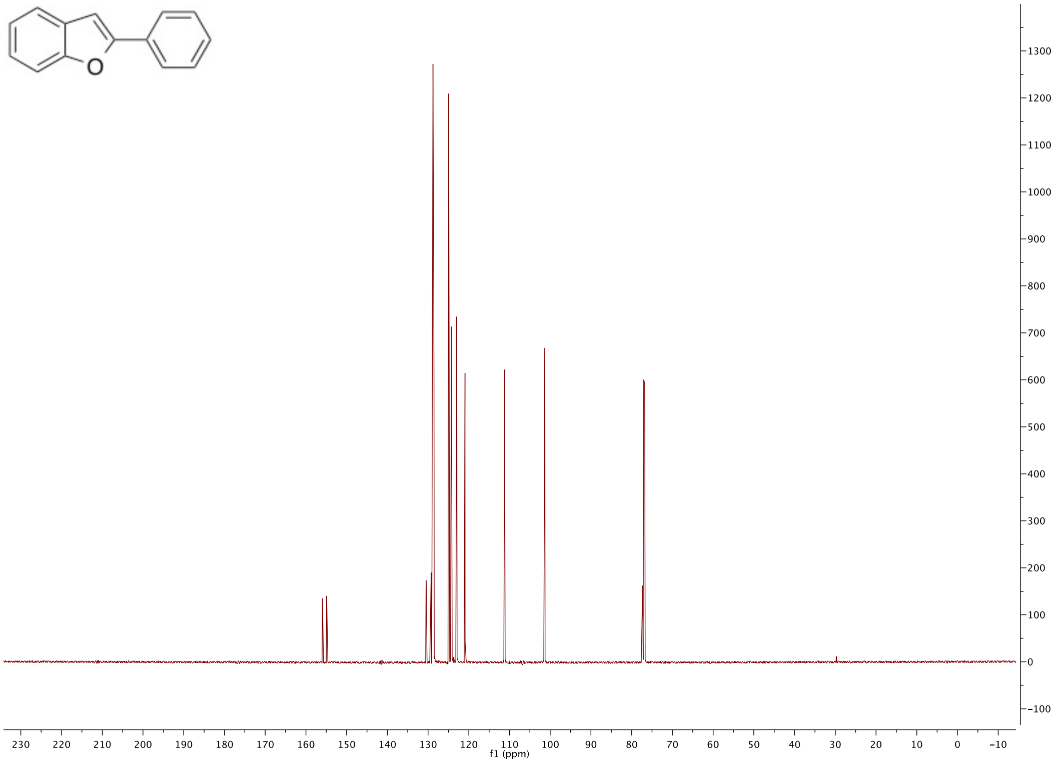

Cl
N
1.00
5.23
2.01
0.97
2.00
1.00
1.00
3.03
f1 (ppm)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
−2000

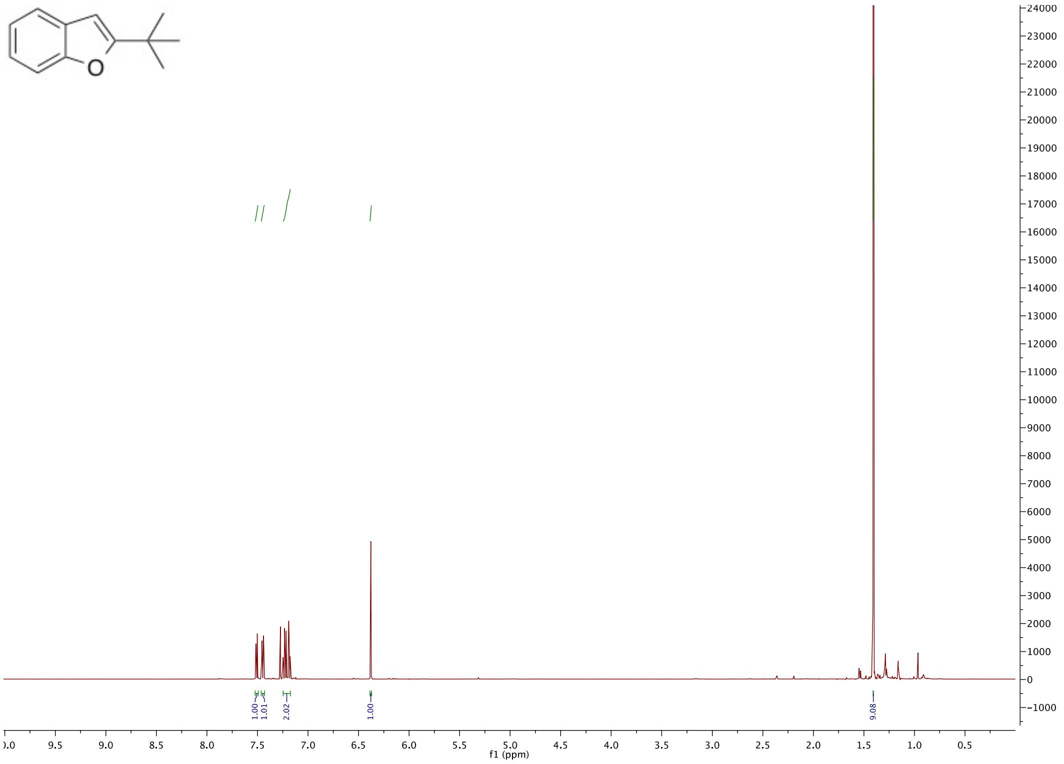

Cl
N
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
250
200
150
100
50
0

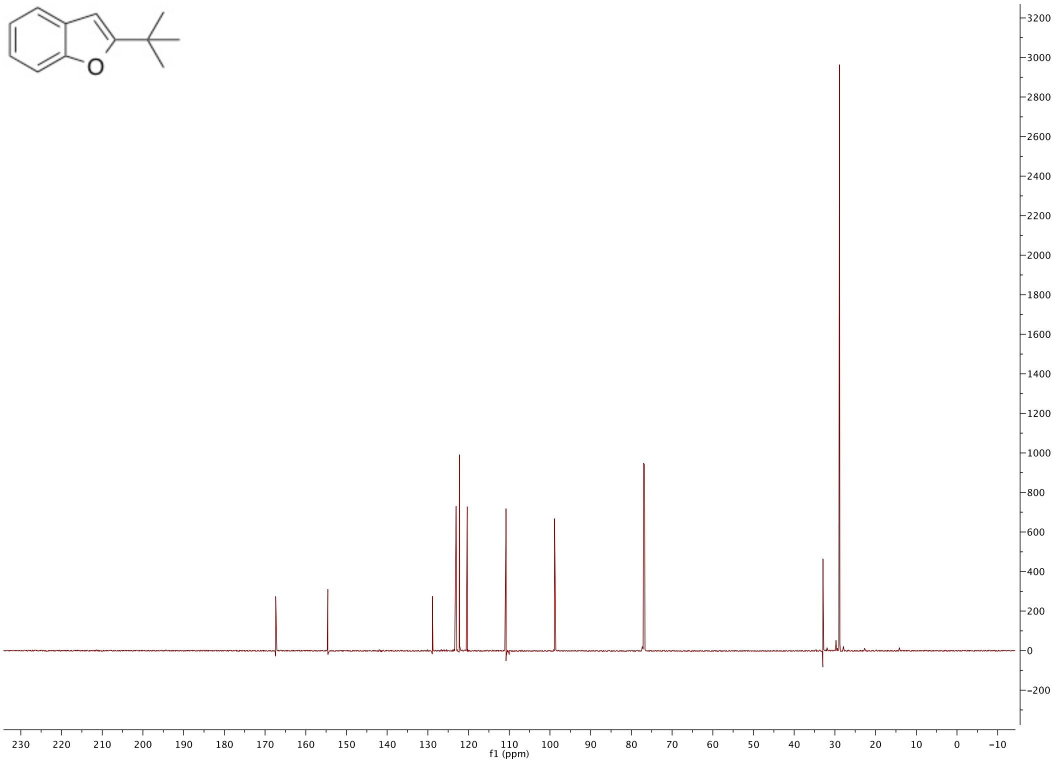

Br
N
1.00
8.23
3.00
1.00
3.00
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
21000 20000 19000 18000 17000 16000 15000 14000 13000 12000 11000 10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0 −1000

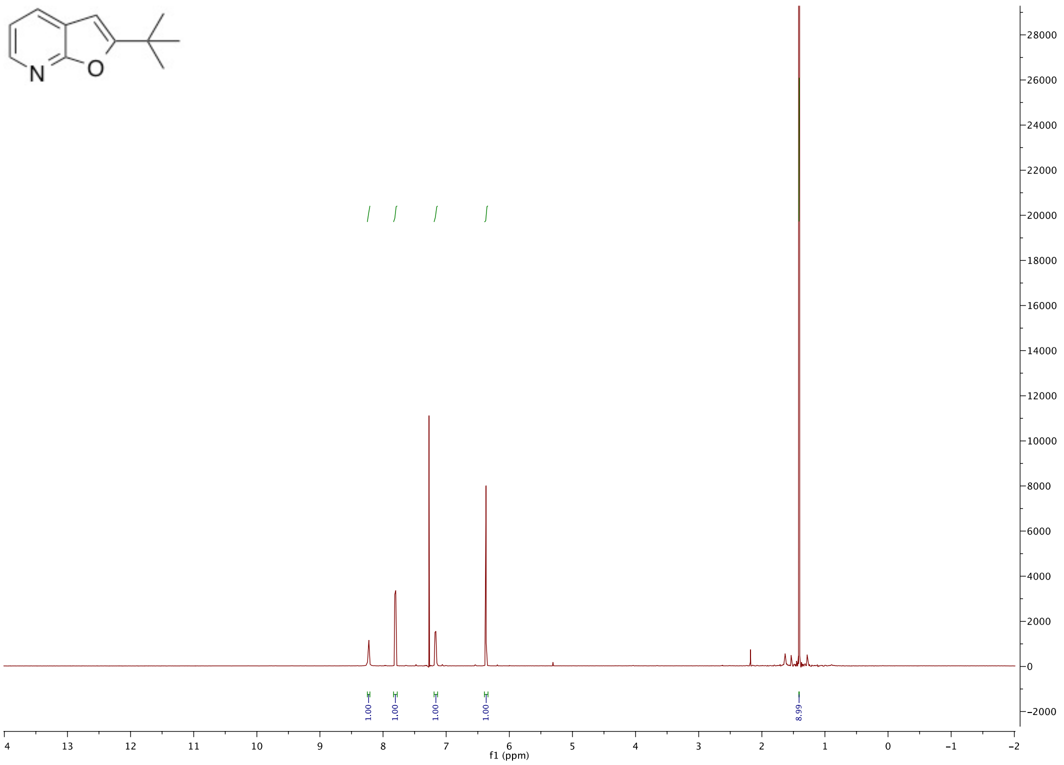

Br
N
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)
260 240 220 200 180 160 140 120 100 80 60 40 20 0 −20

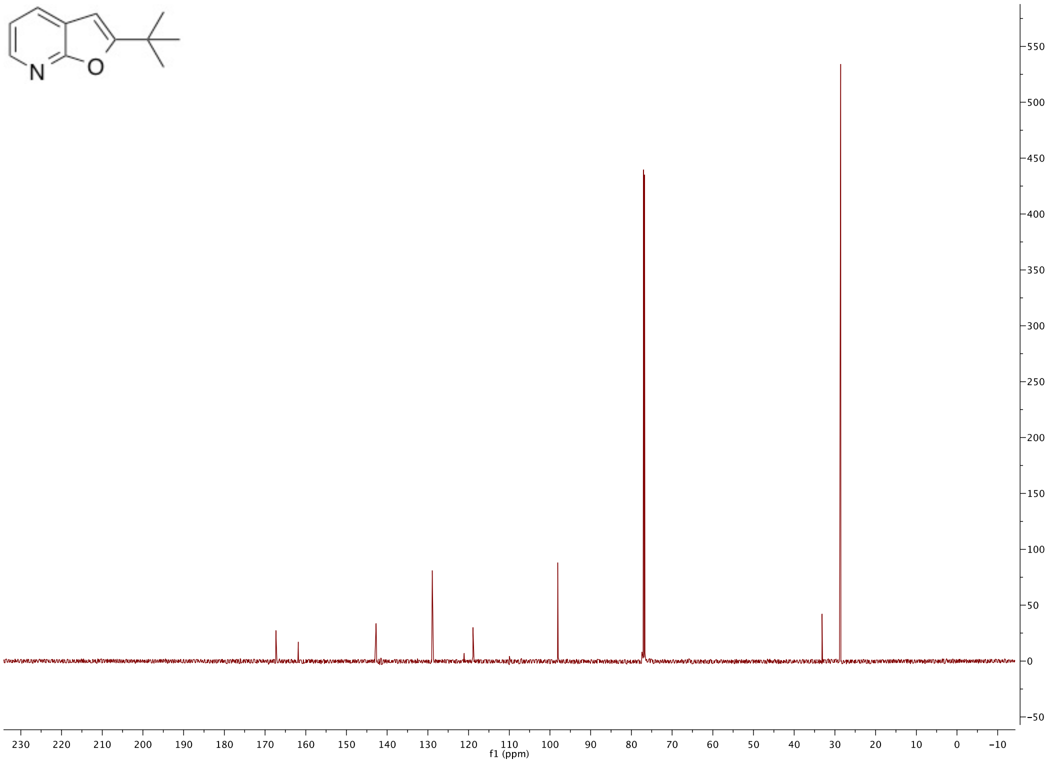

O
2.00
1.00
1.00
2.00
1.00
1.00
1.01
1.00
f1 (ppm)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0 −200

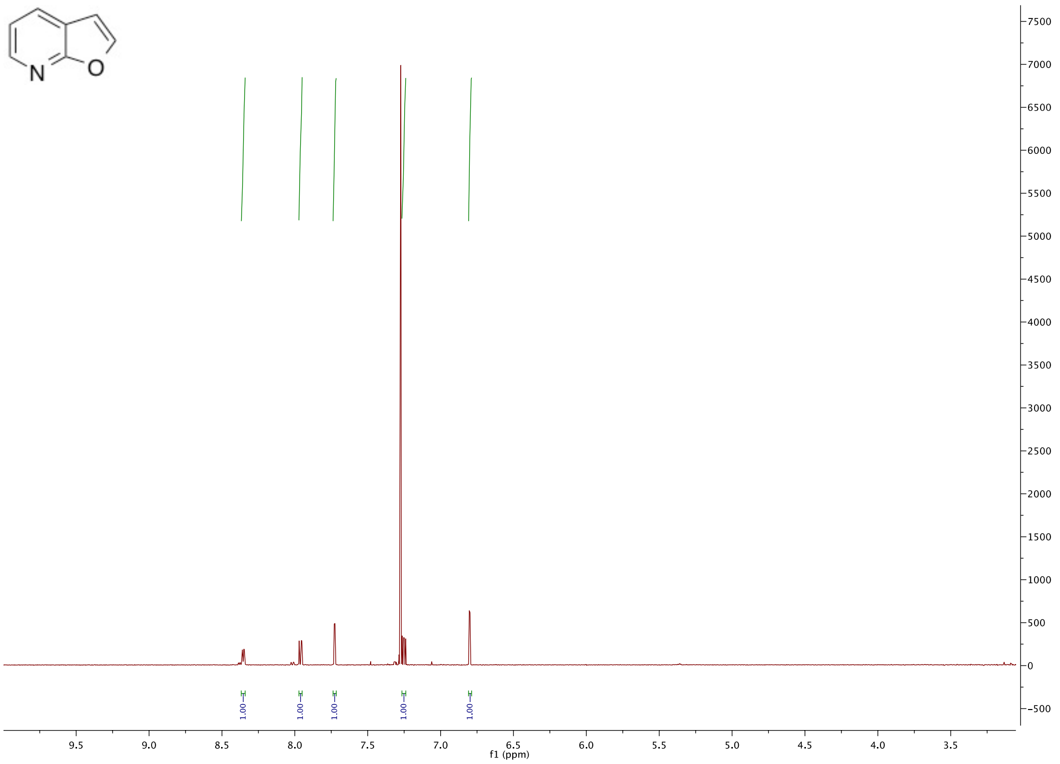

O
f1 (ppm)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 −100

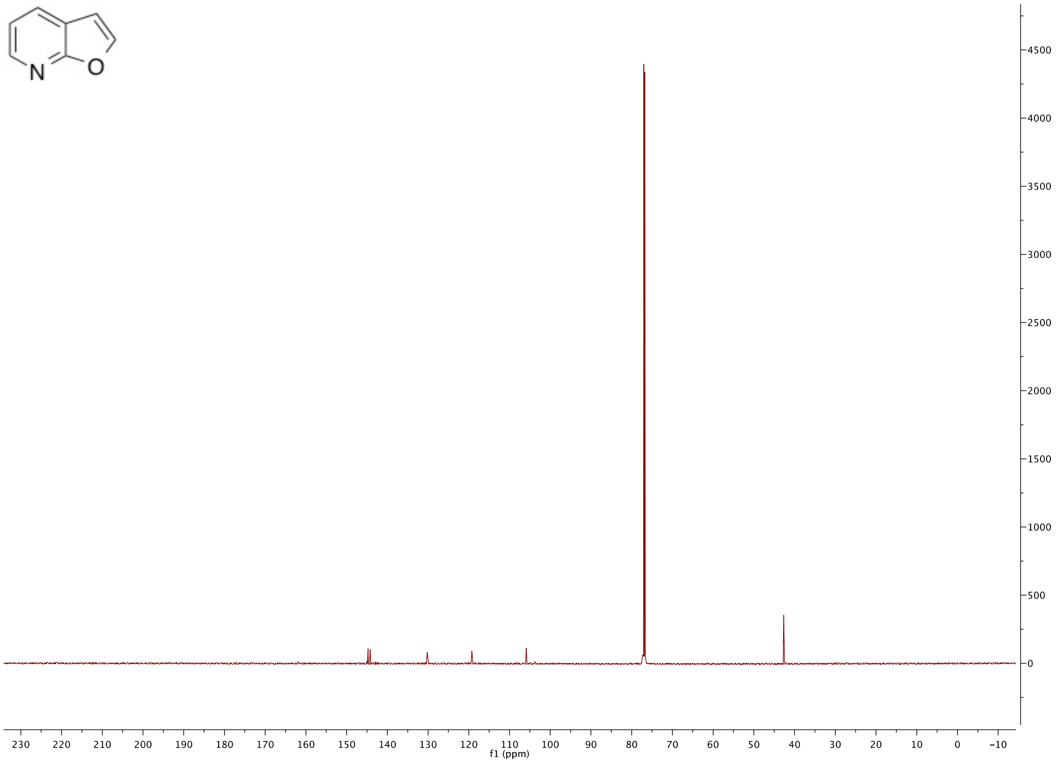

O
1.00
1.01
2.02
1.00
9.08
f1 (ppm)
24000
0
−1000
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

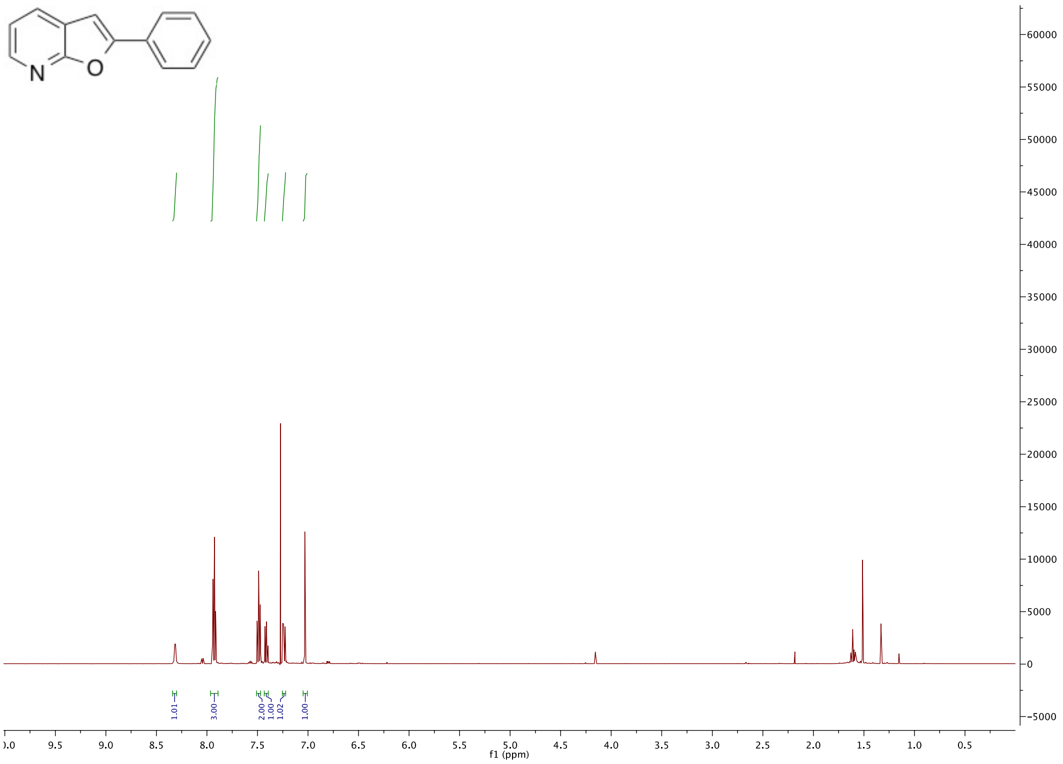

O
f1 (ppm)
3200
0
−200
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10

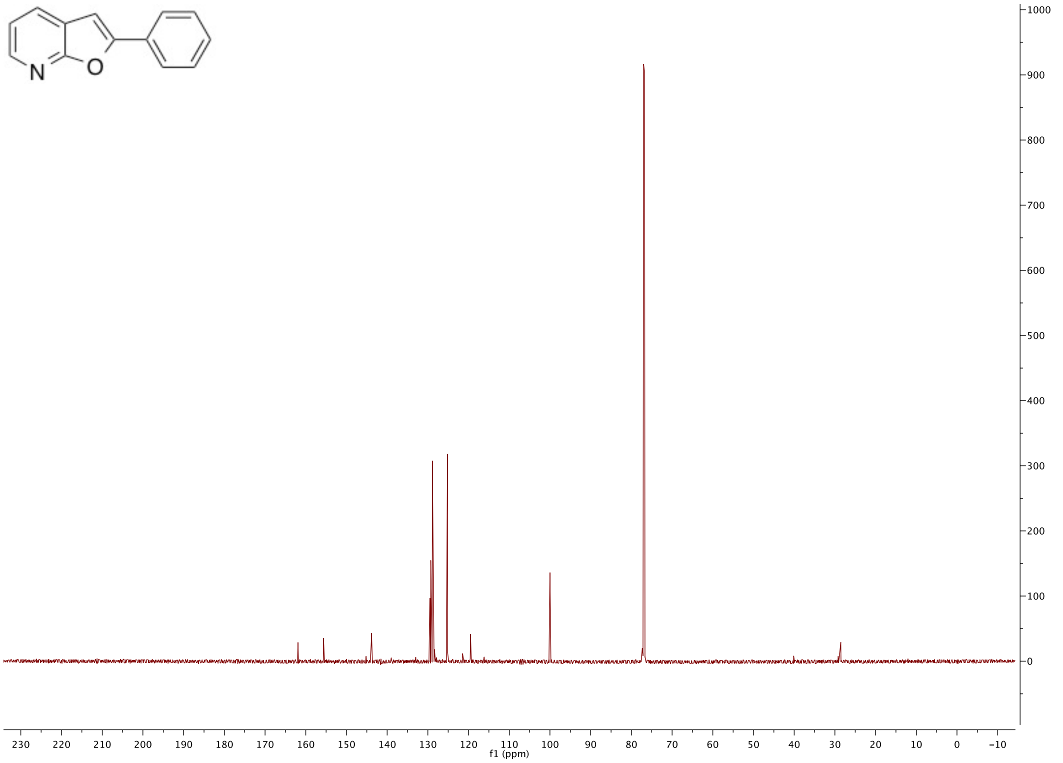

N
O
1.00
1.00
1.00
1.00
8.99
f1 (ppm)
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000

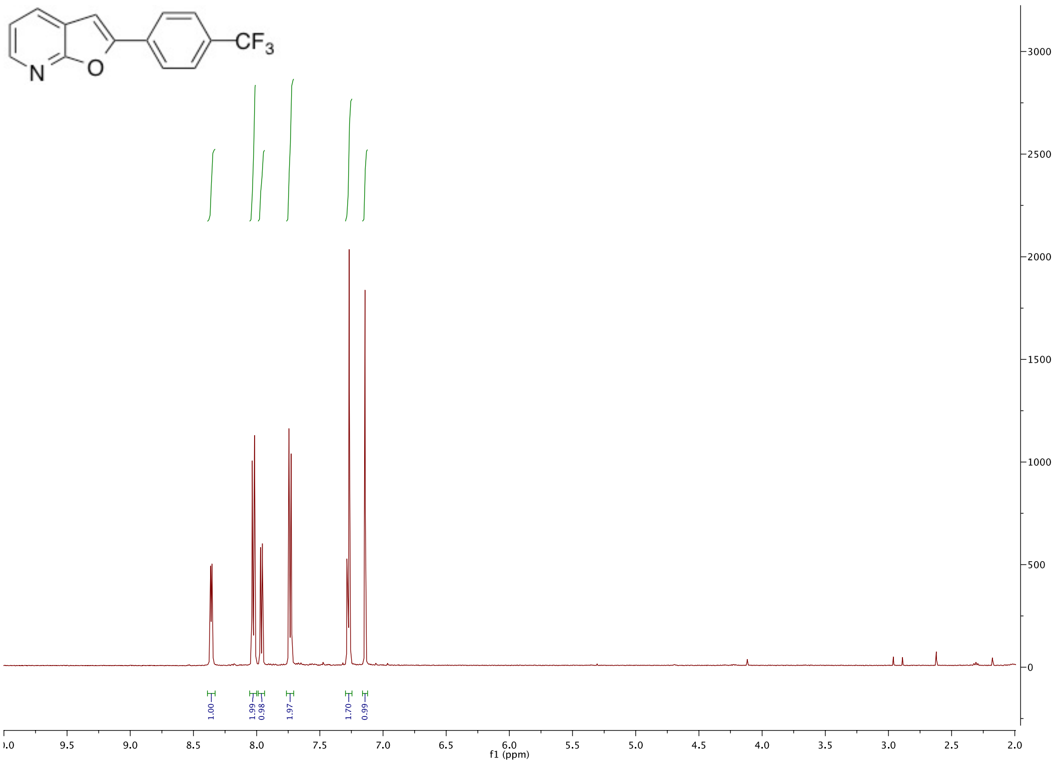

N
O
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
550
500
450
400
350
300
250
200
150
100
50
0
-50

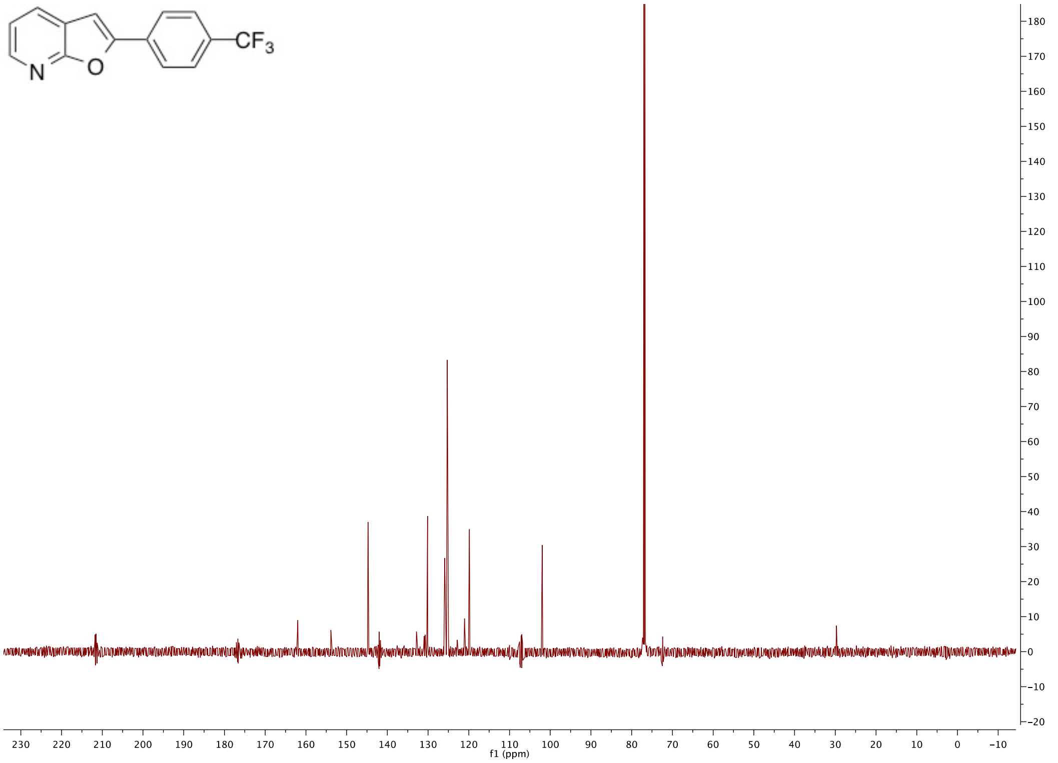

N
O
1.00
1.00
1.00
1.00
1.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f1 (ppm)
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

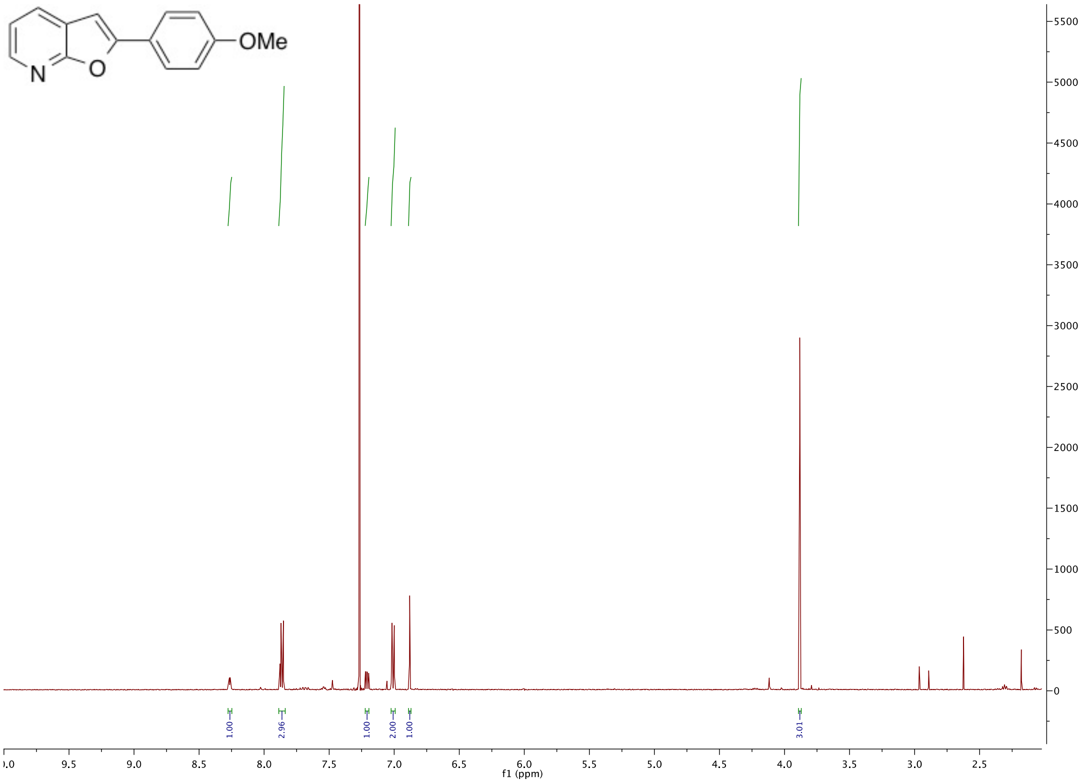

N
O
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
4500
4000
3500
3000
2500
2000
1500
1000
500
0

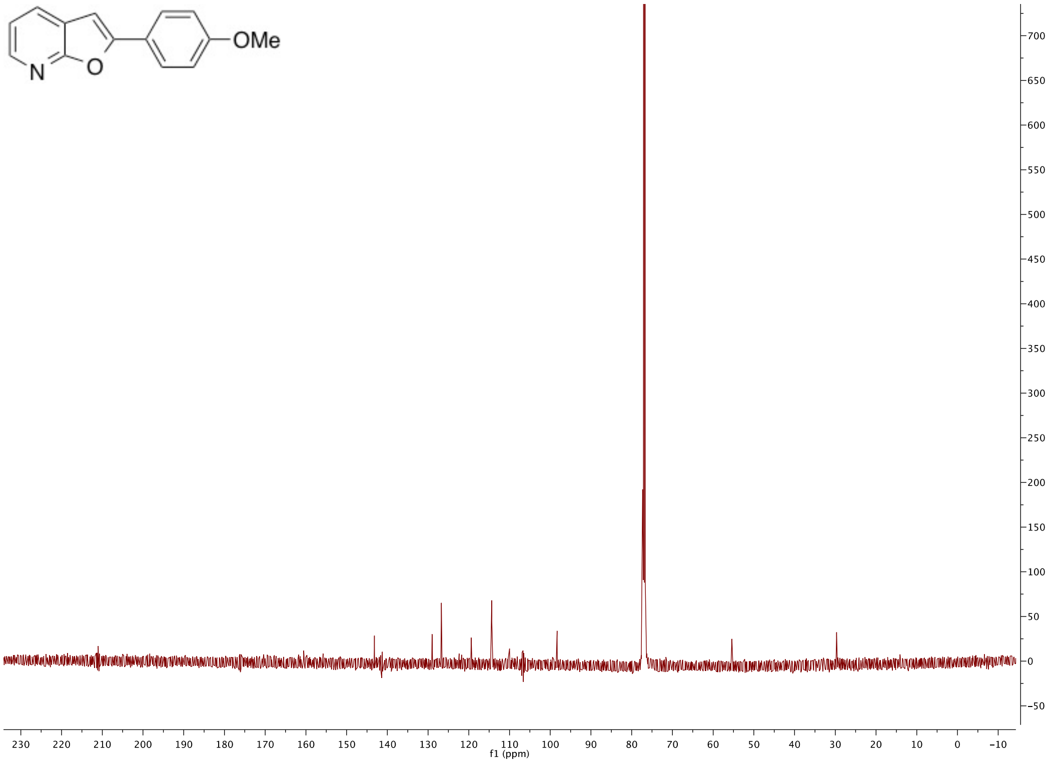

N
O
1.01
3.00
2.00
1.00
1.02
1.00
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
−5000
).0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

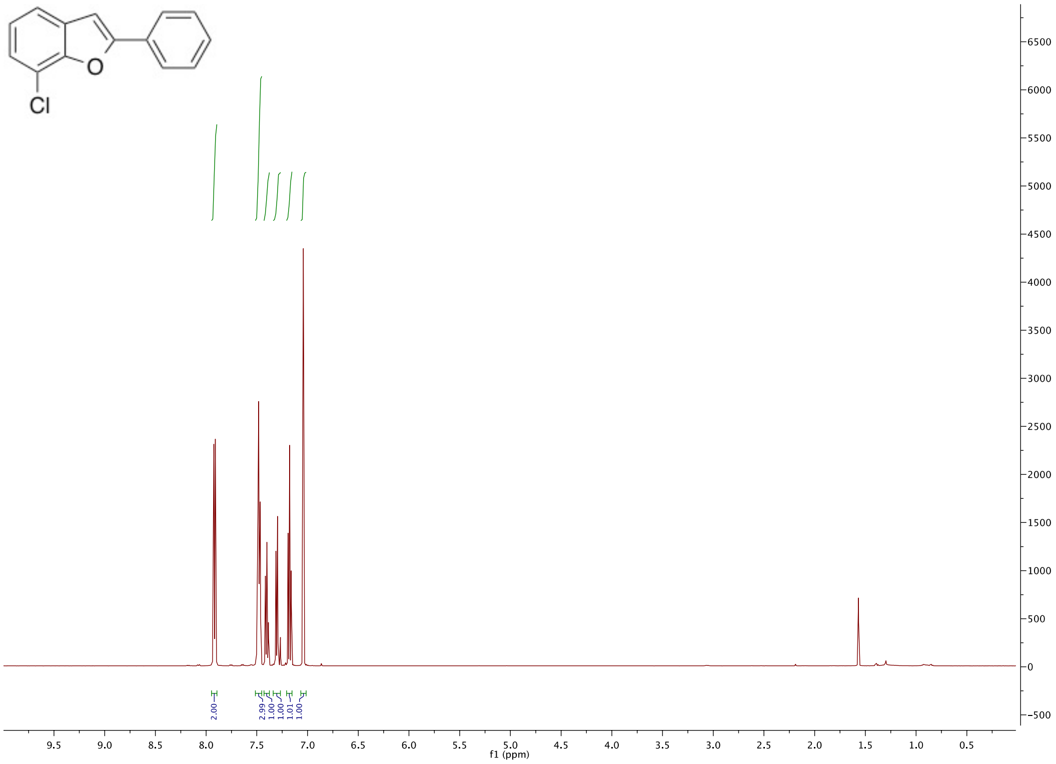

N
O
1000
900
800
700
600
500
400
300
200
100
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

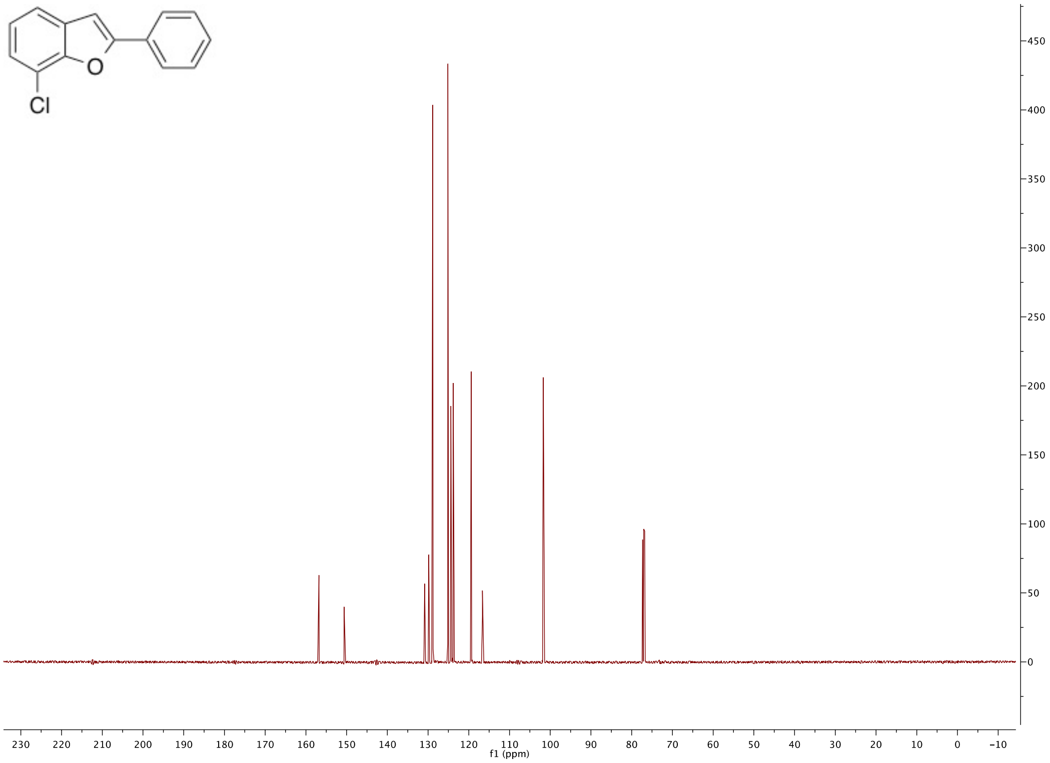

N
O
CF3
1.00
1.99
0.98
1.97
1.70
0.99
3000
2500
2000
1500
1000
500
0
.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

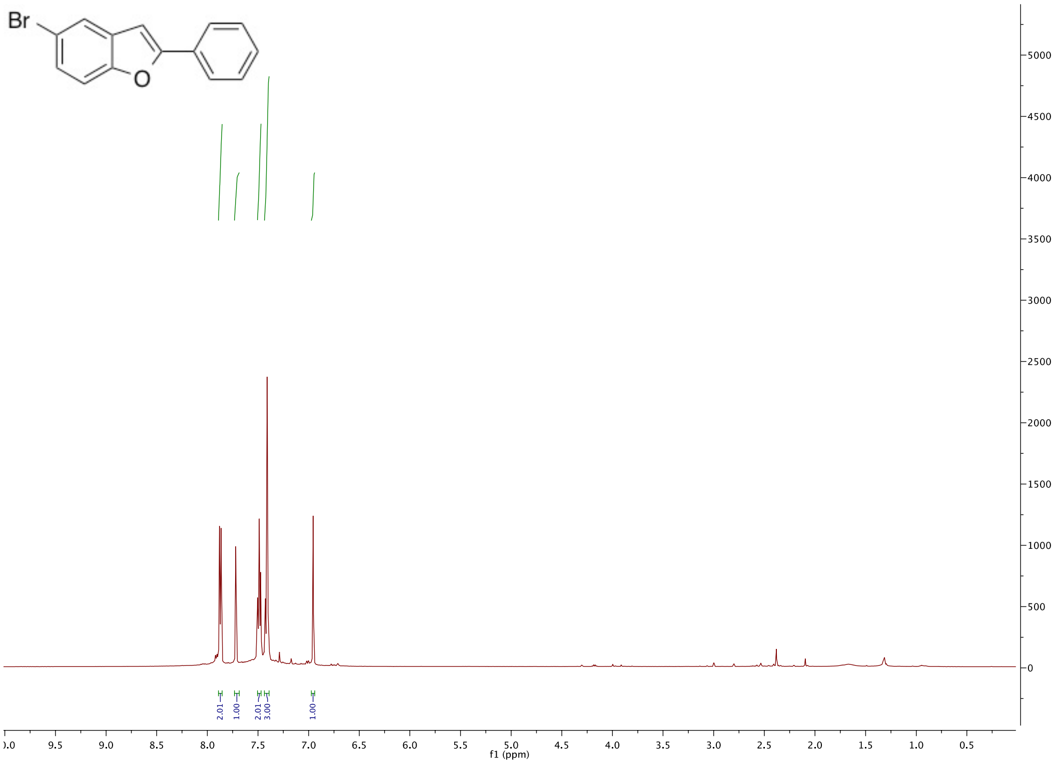

N
O
CF3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

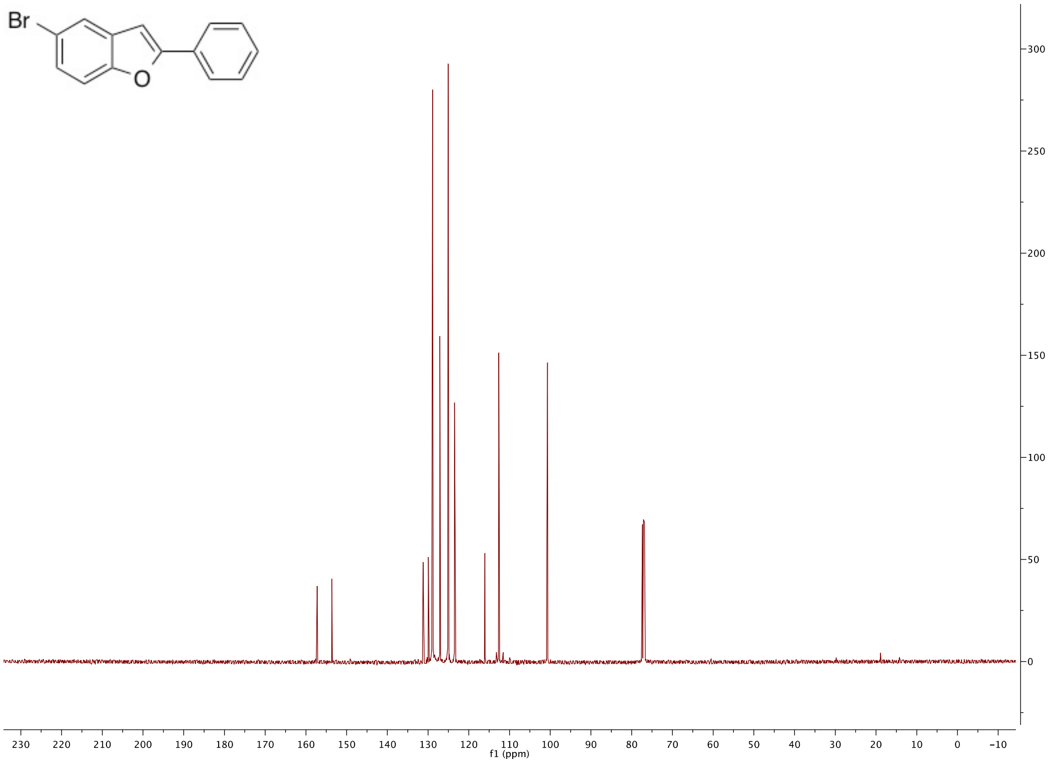

OMe
N
O
1.00
2.96
1.00
2.00
1.00
3.01
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)

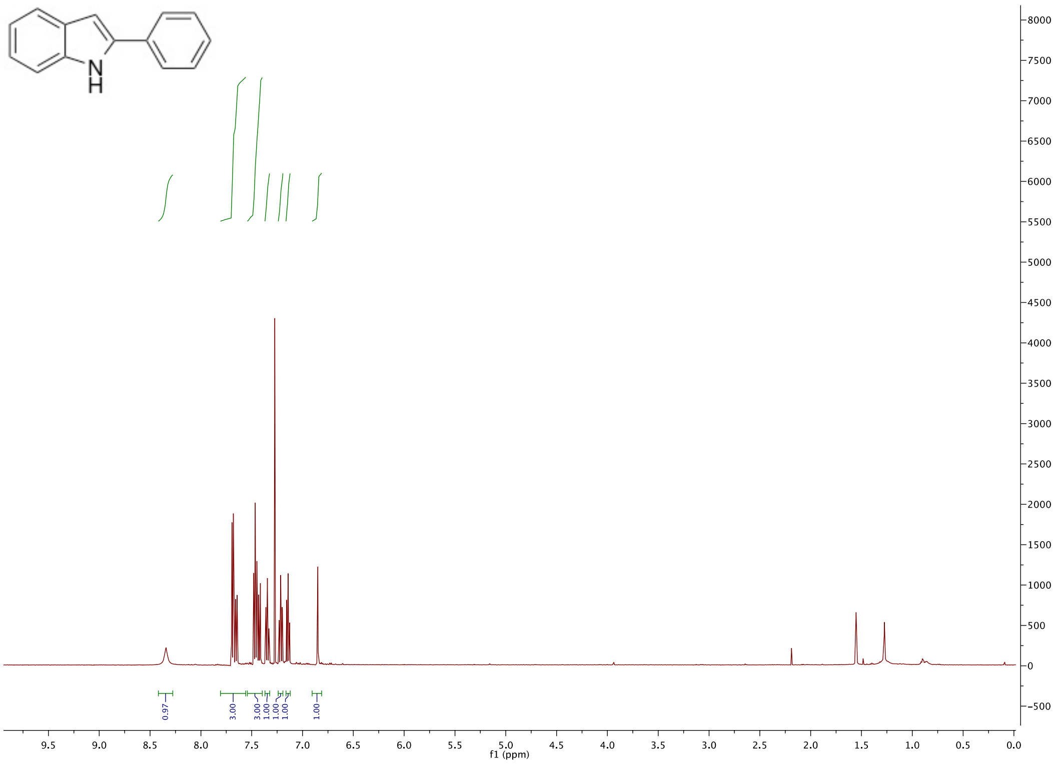

OMe
N
O
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
−50
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

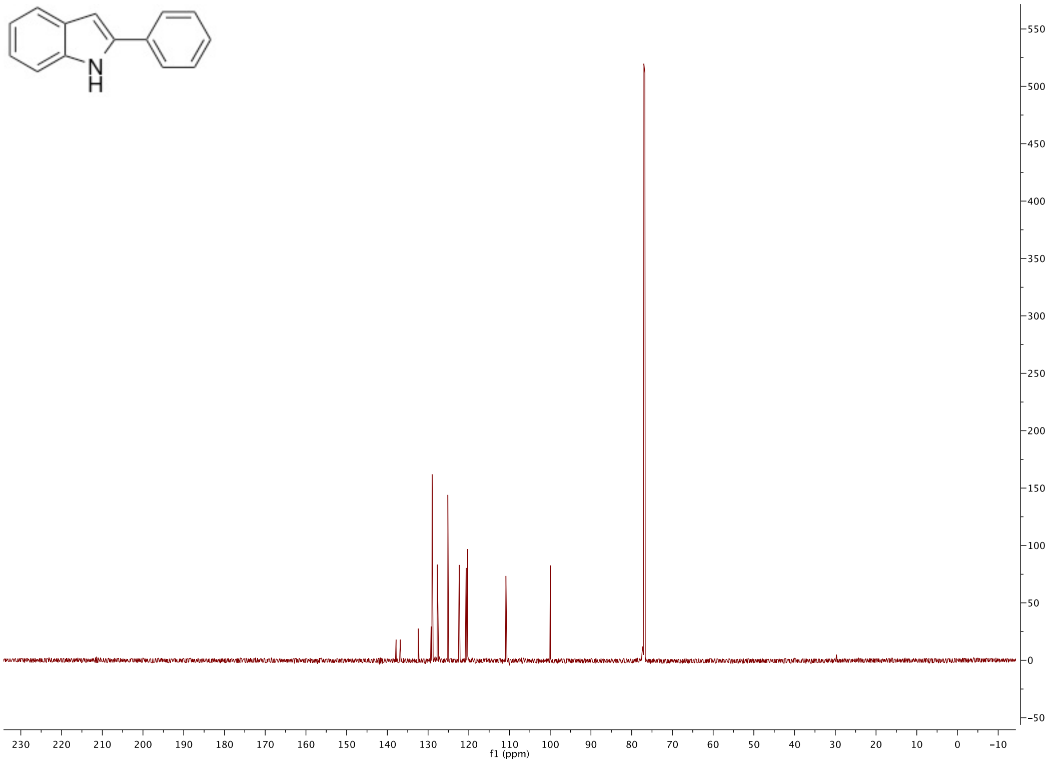

O
Cl
2.00
2.99
1.00
1.00
1.01
1.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500

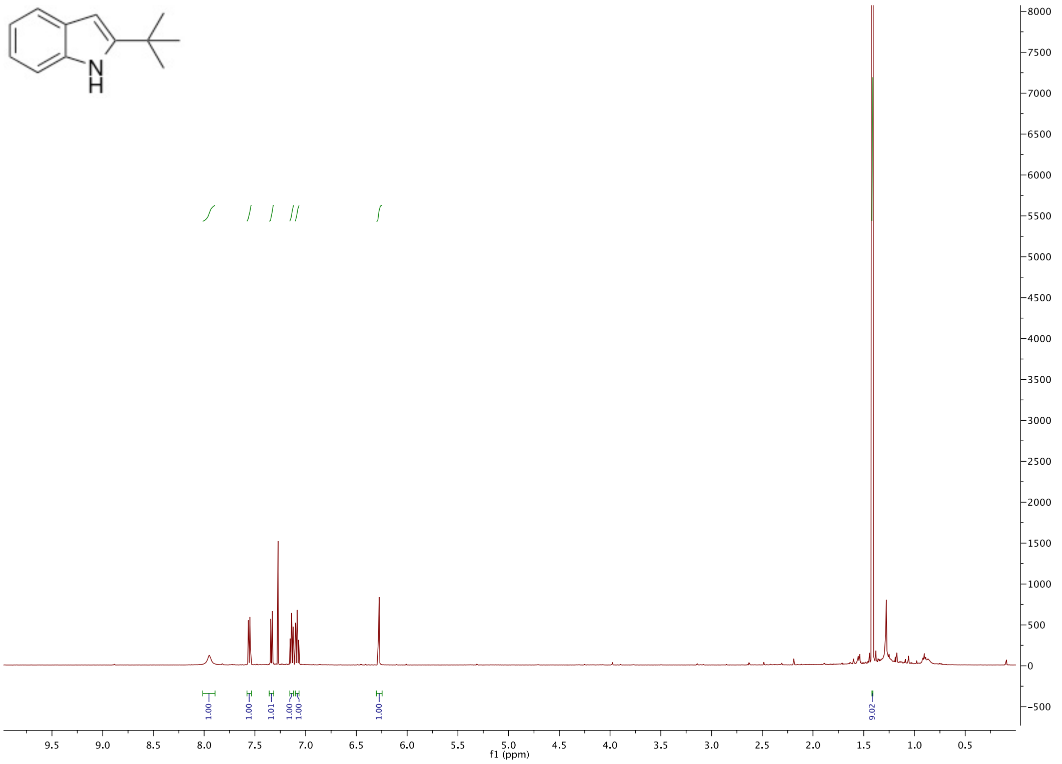

O
Cl
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)
450
400
350
300
250
200
150
100
50
0

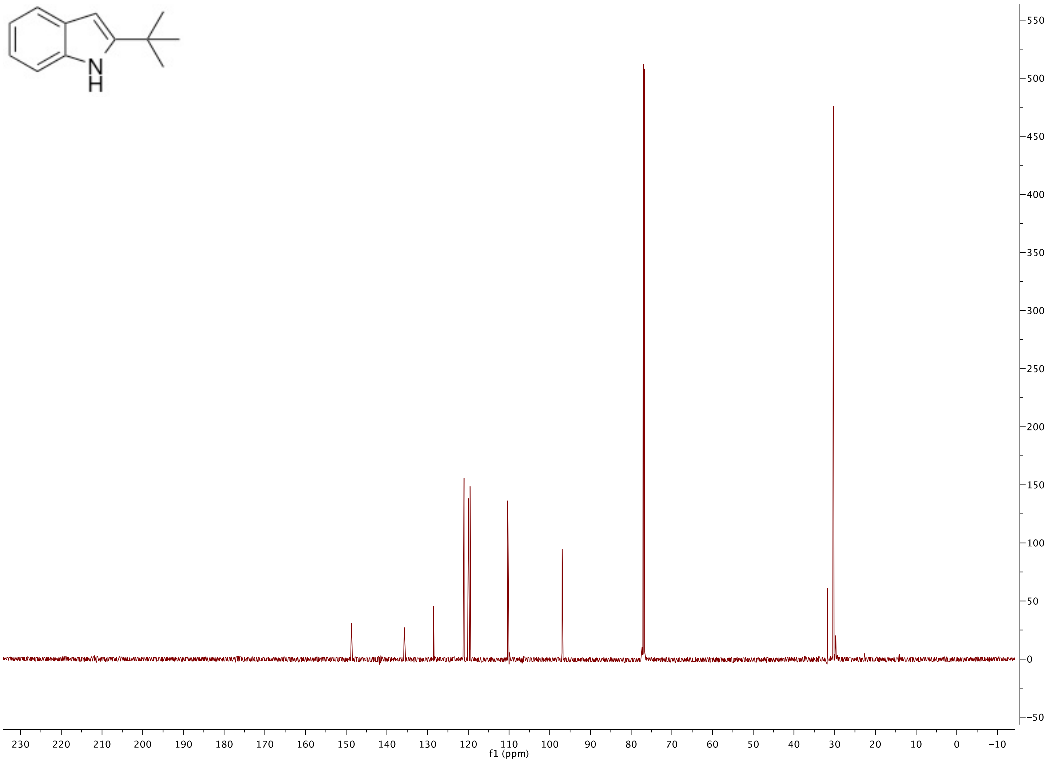

Br
O
2.01
1.00
2.01
3.00
1.00
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0

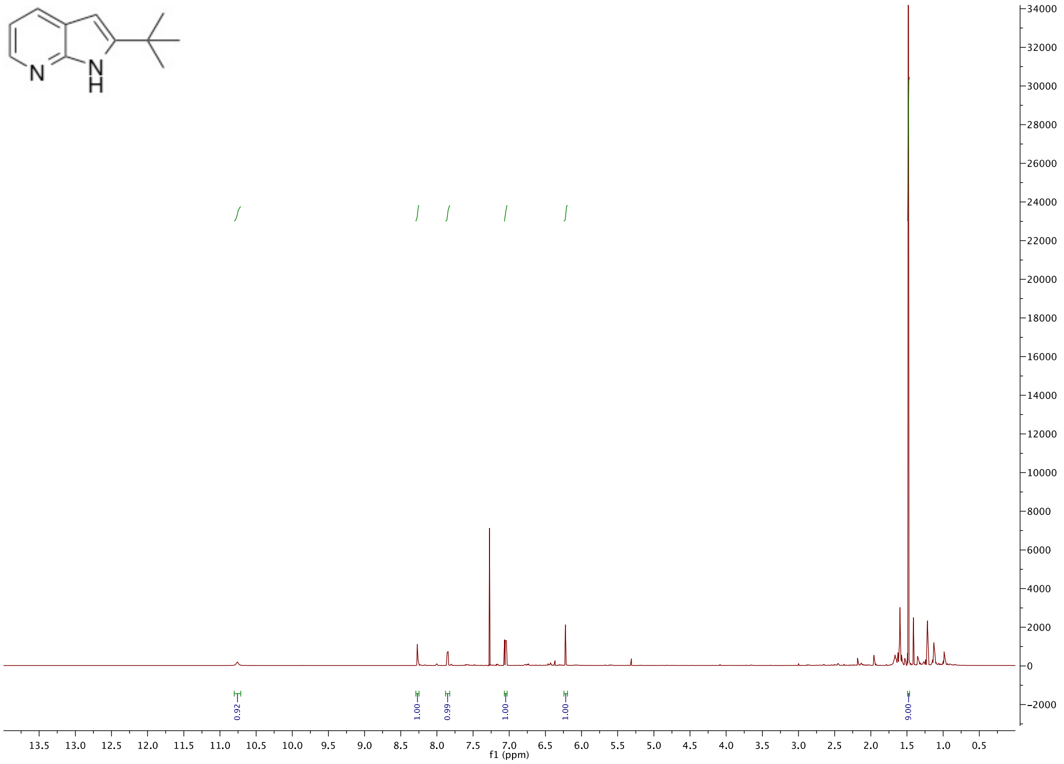

Br
O
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
300
250
200
150
100
50
0

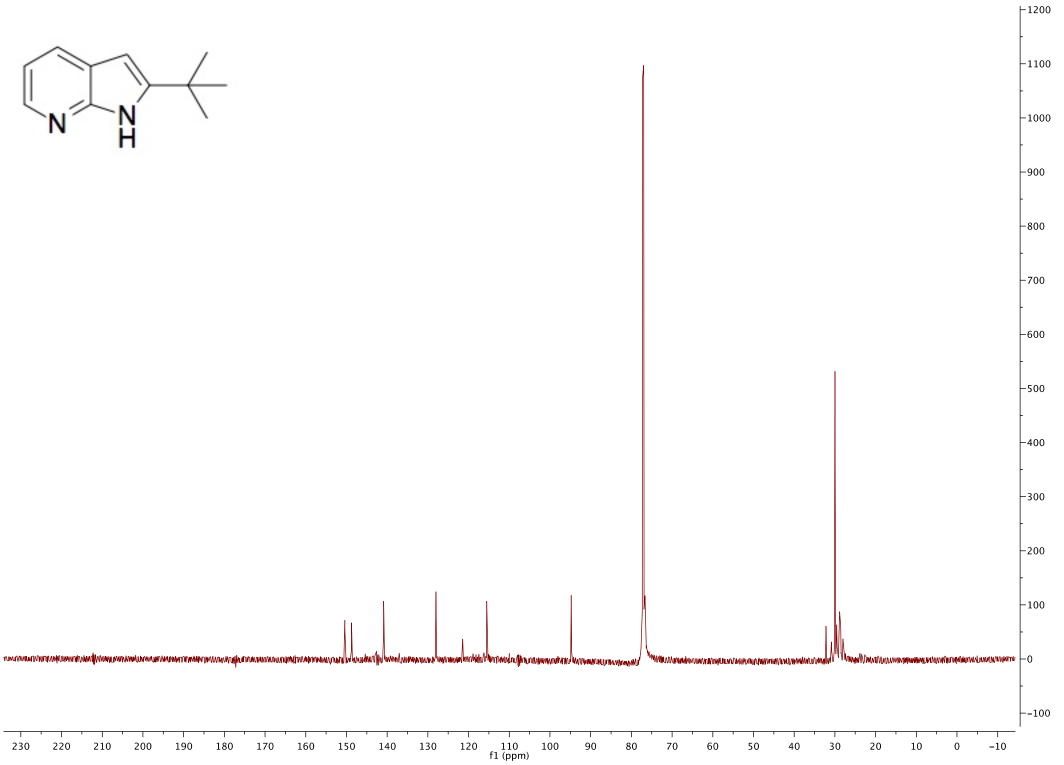

N
H
0.97
3.00
3.00
1.00
1.00
1.00
1.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

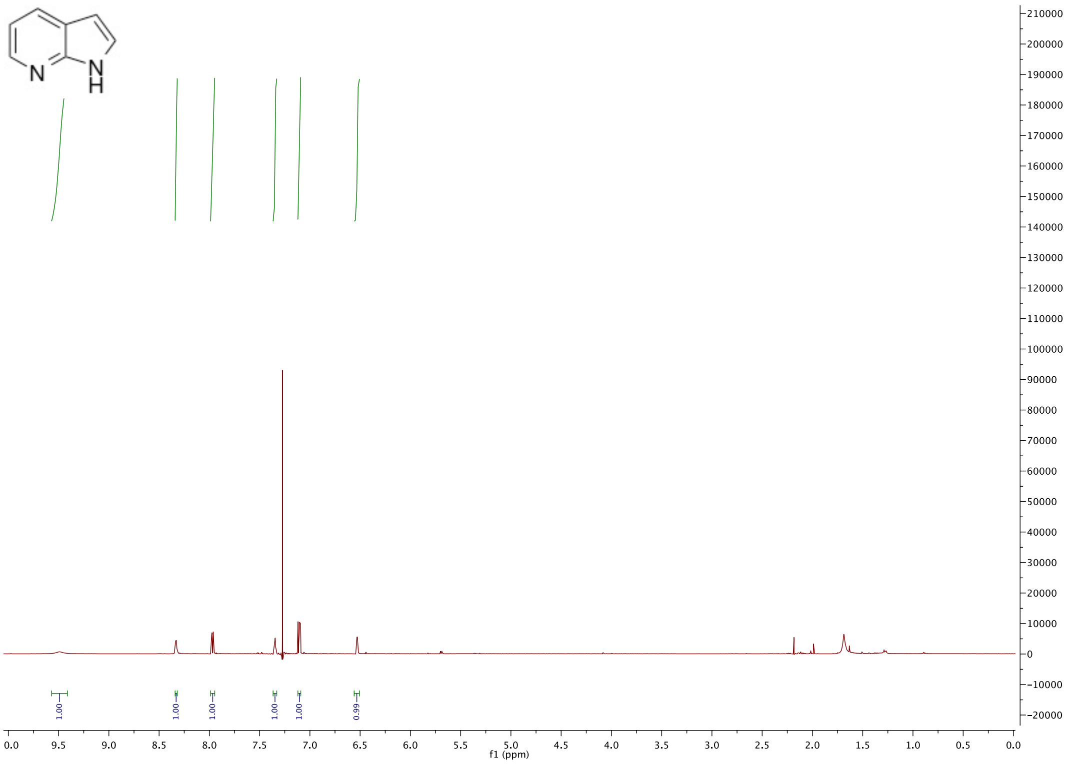

N
H
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
550
500
450
400
350
300
250
200
150
100
50
0
-50

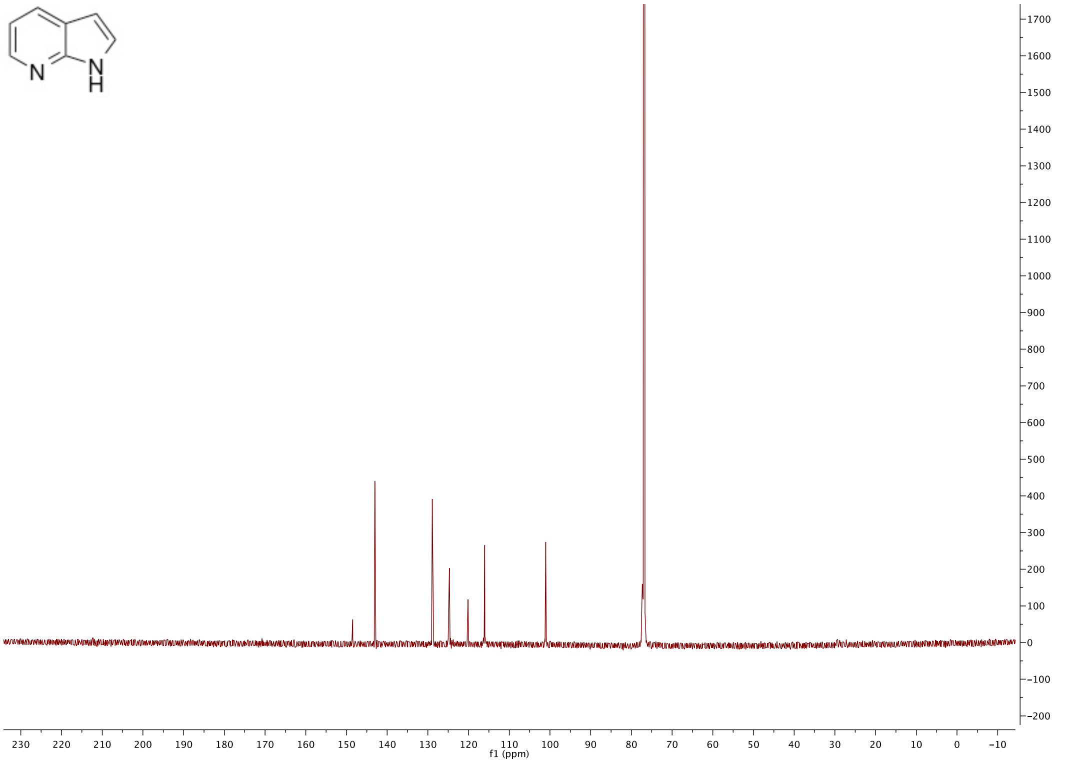

N
H
1.00
1.00
1.01
1.00
1.00
1.00
9.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
8000 7500 7000 6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500

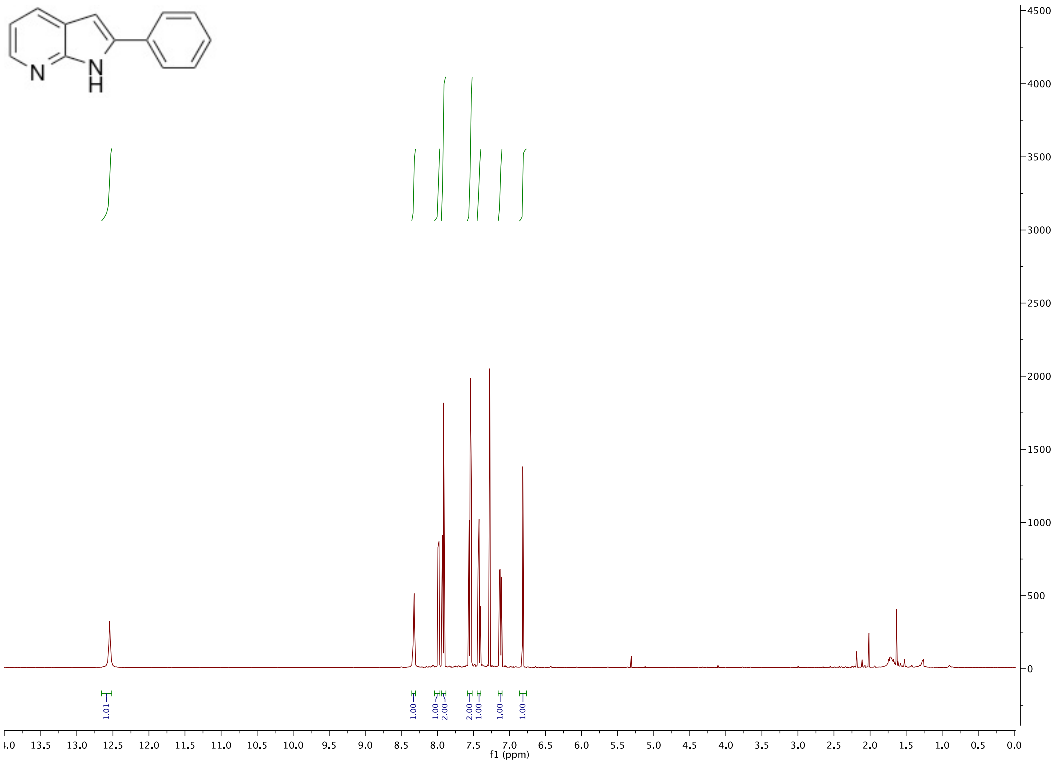

N
H
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
550 500 450 400 350 300 250 200 150 100 50 0 -50

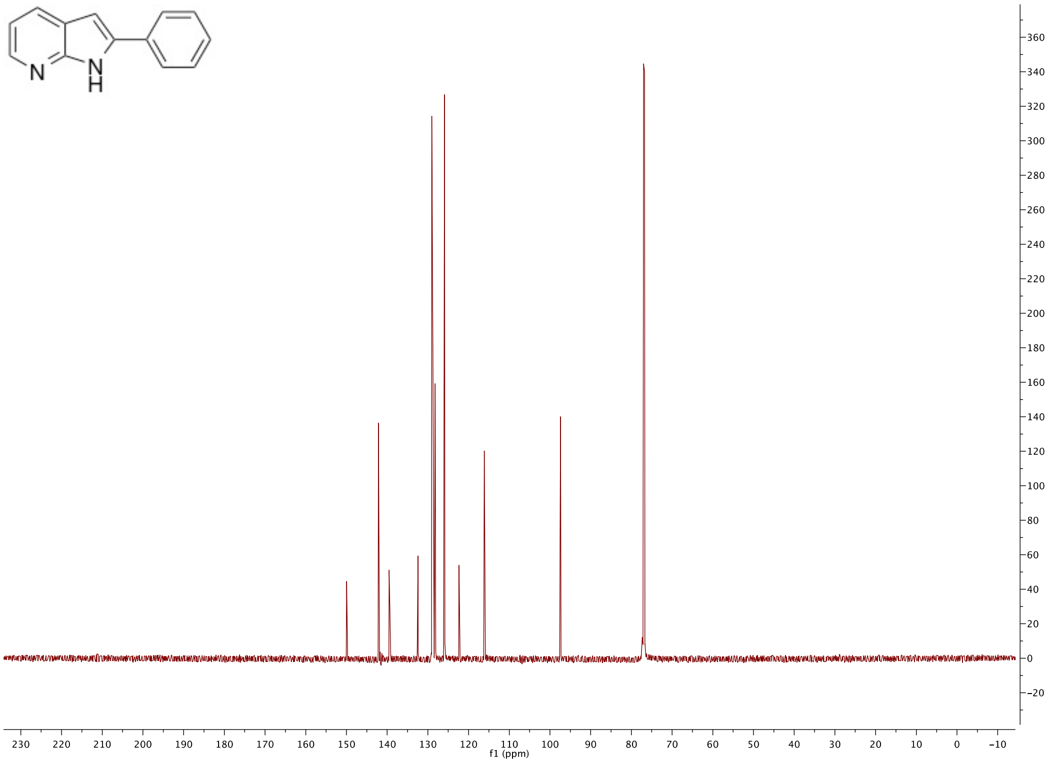

N
N
H
0.92
1.00
0.99
1.00
1.00
9.00
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
−2000
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

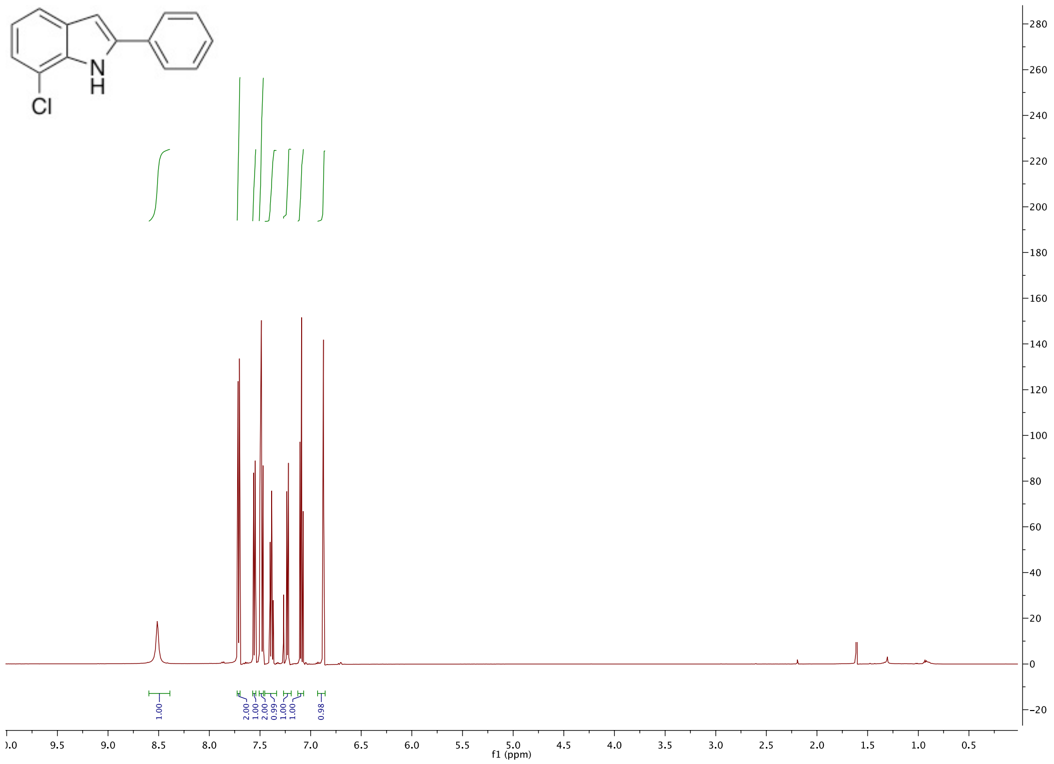

N
N
H
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

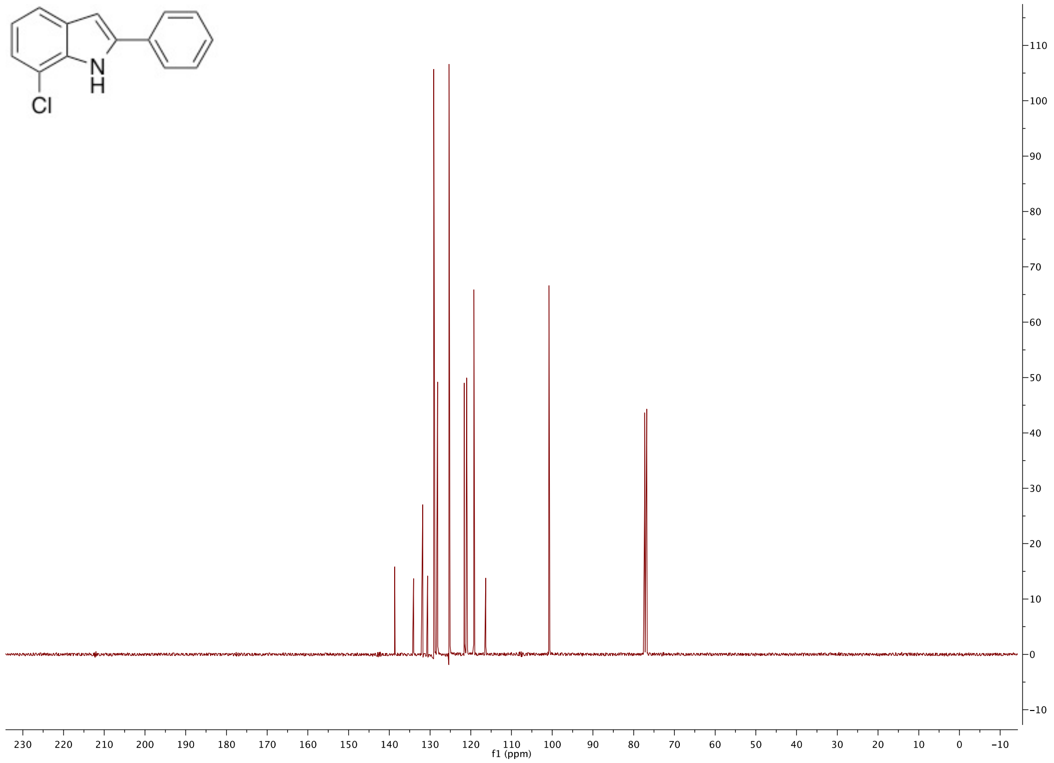

N
N
H
1.00
1.00
1.00
1.00
1.00
0.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
210000 200000 190000 180000 170000 160000 150000 140000 130000 120000 110000 100000 90000 80000 70000 60000 50000 40000 30000 20000 10000 0 −10000 −20000

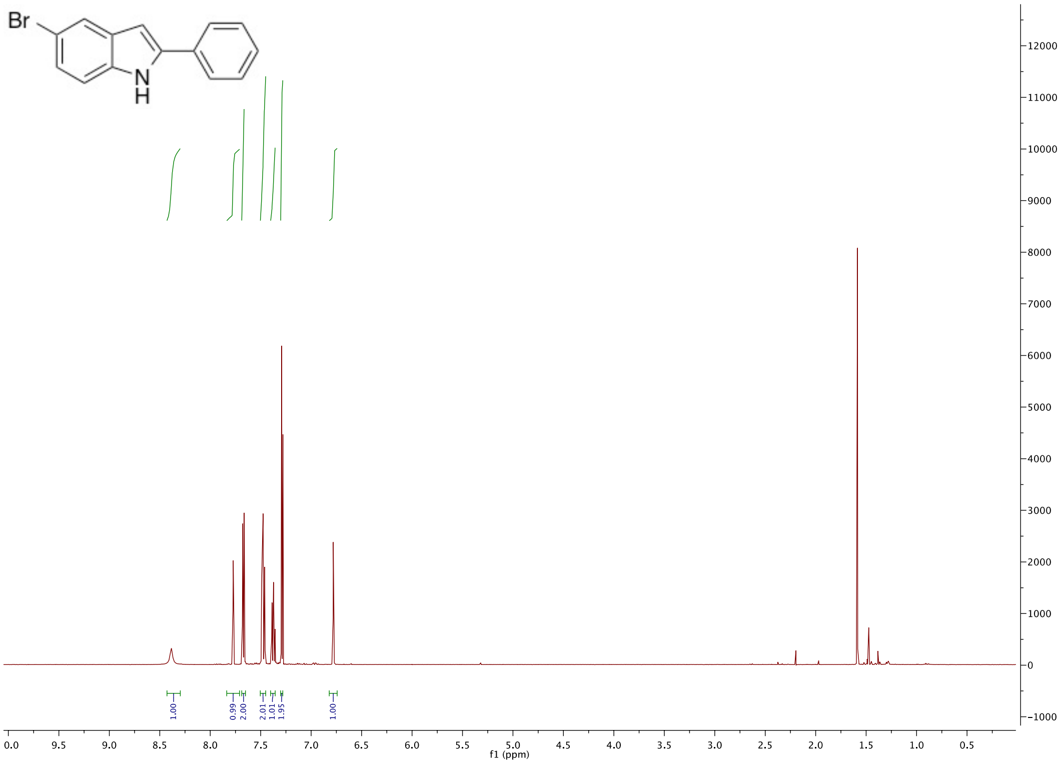

N
N
H
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)
1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 −100 −200


N
H
N
1.01
1.00
1.00
2.00
2.00
1.00
1.00
1.00
f1 (ppm)
4500
4000
3500
3000
2500
2000
1500
1000
500
0
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

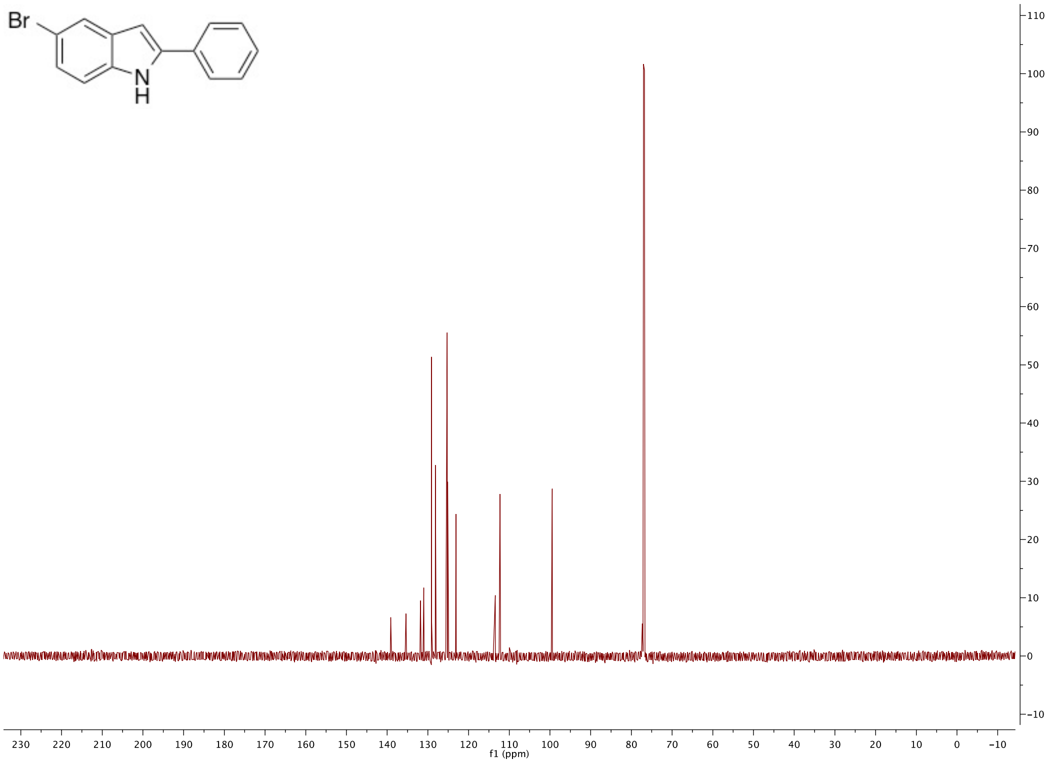

N
H
N
f1 (ppm)
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
−20
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10


Cl
N
H
1.00
2.00
1.00
2.00
0.99
1.00
1.00
0.98
f1 (ppm)

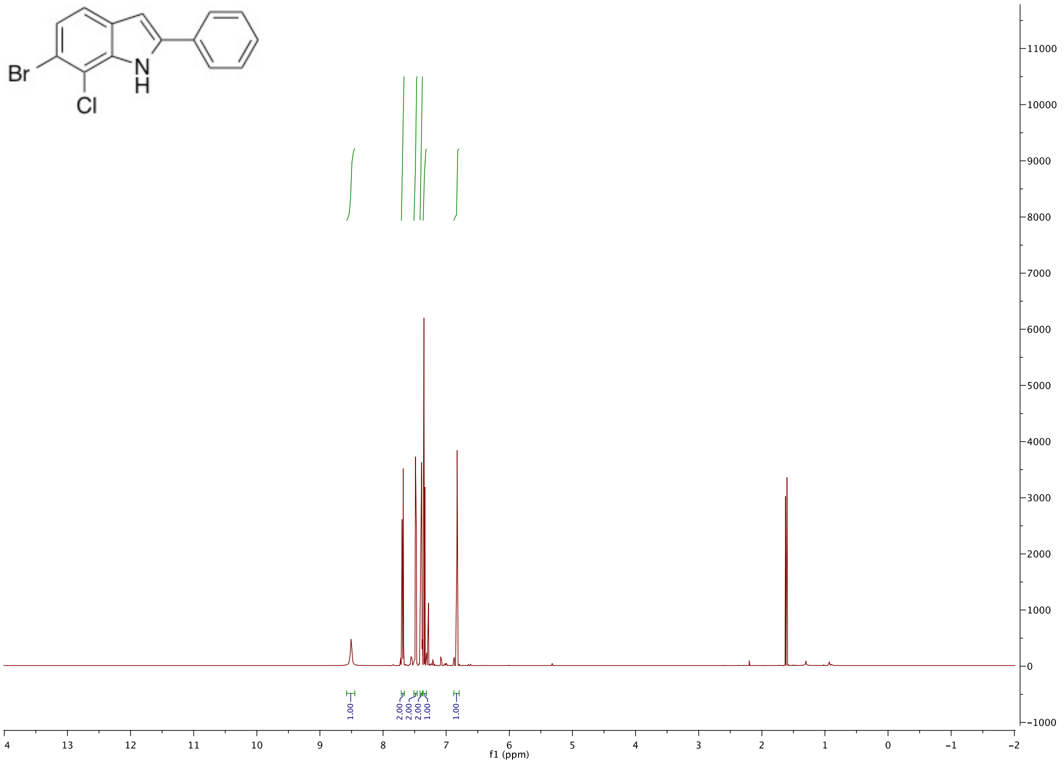

Cl
N
H
f1 (ppm)

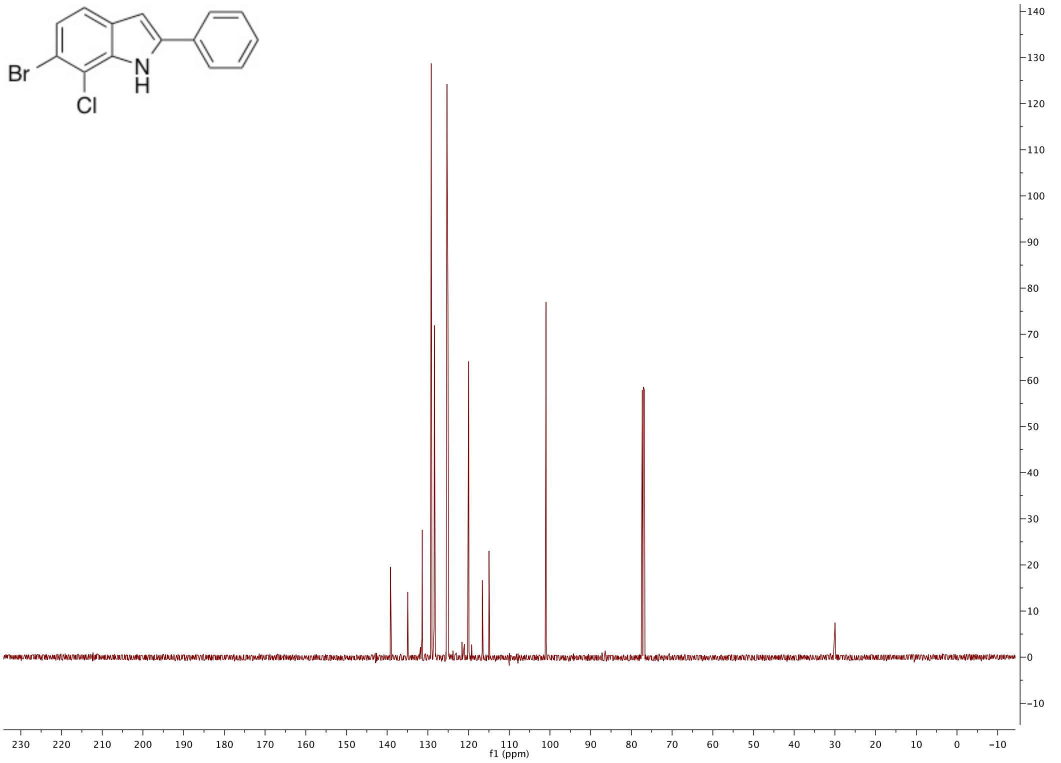


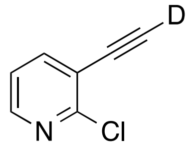
Br
N
H
1.00
0.99
2.00
2.01
1.01
1.95
1.00
f1 (ppm)



Br
N
H
f1 (ppm)


Br
Cl
N
H
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
1.00
2.00
2.00
2.00
1.00
1.00
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
f1 (ppm)

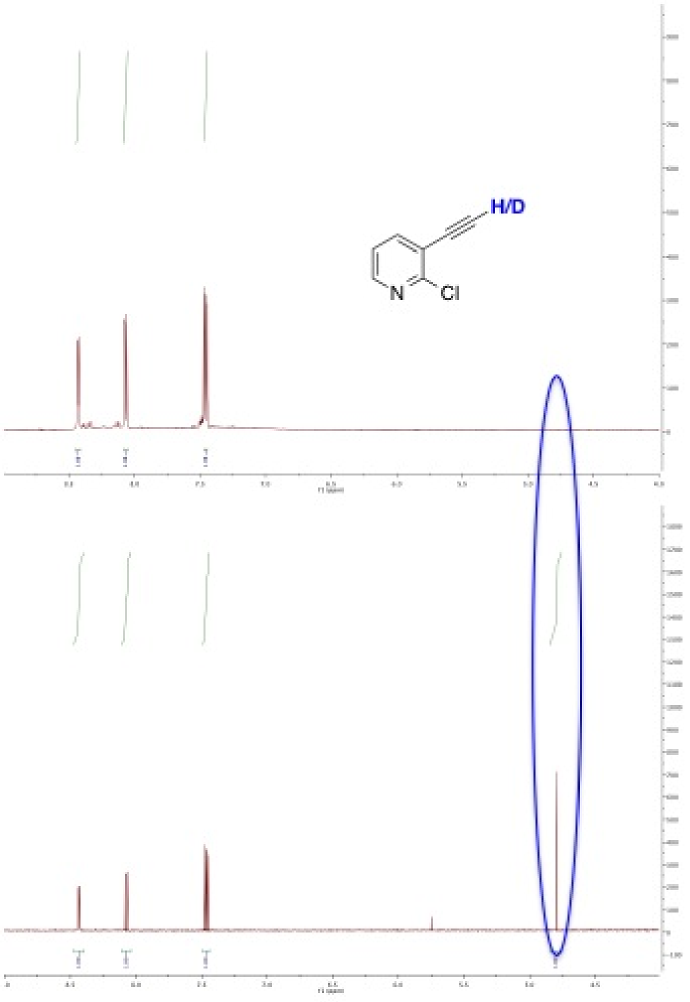

Br
Cl
N
H
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

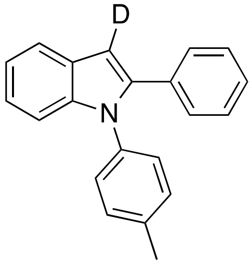


1r-D

^{1}H NMR (500 MHz, DMSO-D6): δ 8.44-8.41 (dd, J = 5.0 Hz, 2.0 Hz, 1H), 8.08-8.05 (dd, J = 7.5 Hz, 2.0 Hz, 1H), 7.48-7.44 (dd, J = 8.0 Hz, 4.5 Hz, 1H).

The relevant portion of the deuterated spectrum appears above that of the non-deuterated spectrum. The terminal acetylene peak is circled to indicate the level of deuteration. No residual ^{1}H peak could be detected in the deuterated compound.

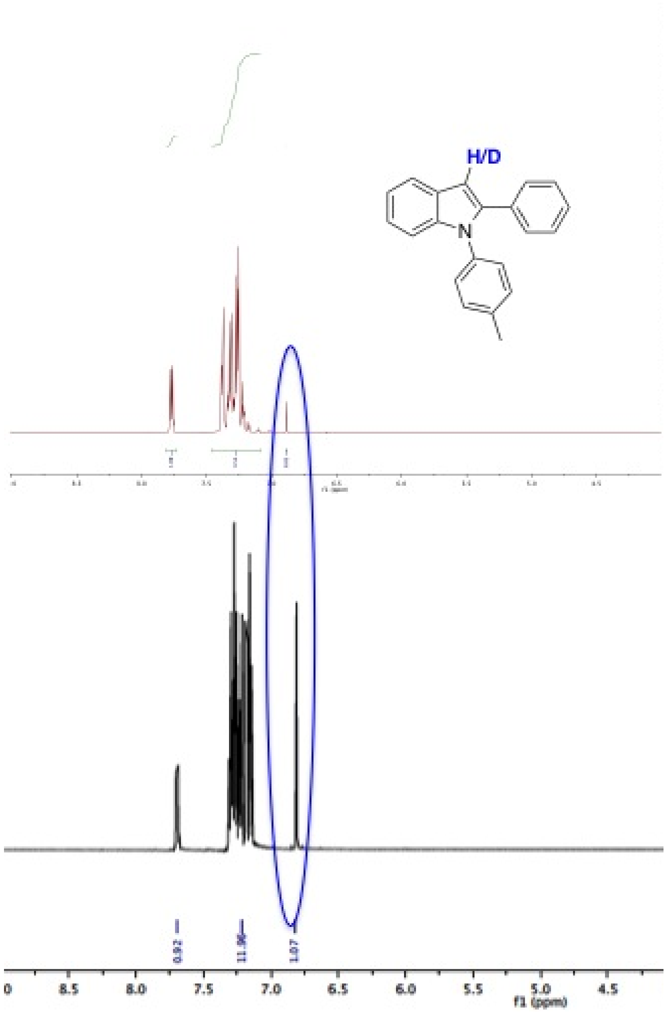


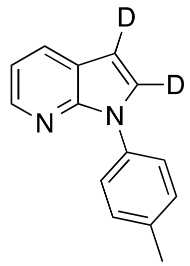


2a-D

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.79-7.75 (m, 1H), 7.40-7.15 (m, 12H), 6.89 (s, 0.05H), 2.43 (s, 3H).

The relevant portion of the deuterated spectrum appears above that of the non-deuterated spectrum. The C2 proton peak is circled to indicate the level of deuteration. The residual ^{1}H peak at the C2 position integrates to 5% intensity relative to the other peaks.

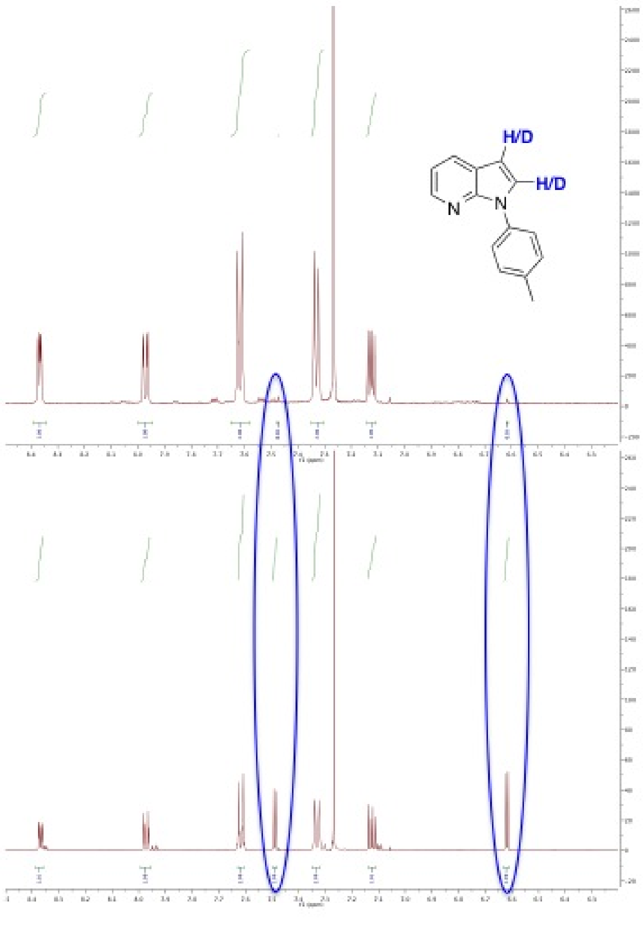


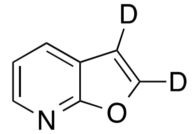


2k-D_2

^{1}H NMR (500 MHz, CDCl$_3$): δ 8.39-8.36 (d, J = 4.5 Hz, 1H), 7.99-7.96 (d, J = 9 Hz), 7.64-7.61 (d, J = 8 Hz, 2H), 7.51-7.48 (d, J = 3.5 Hz, 0.03H), 7.35-7.32 (d, J = 8.5 Hz, 2H), 7.15-7.11 (ddd, J = 8.0 Hz, 4.5 Hz, 0.7 Hz, 1H), 6.63-6.61 (dd, 3.8 Hz, 0.7 Hz, 0.03H), 2.43 (s, 3H).

The relevant portion of the deuterated spectrum appears above that of the non-deuterated spectrum. The C1 and C2 proton peaks are circled to indicate the level of deuteration. The residual ^{1}H peaks at the C1 and C2 positions both integrate to 3% intensity relative to the other peaks.

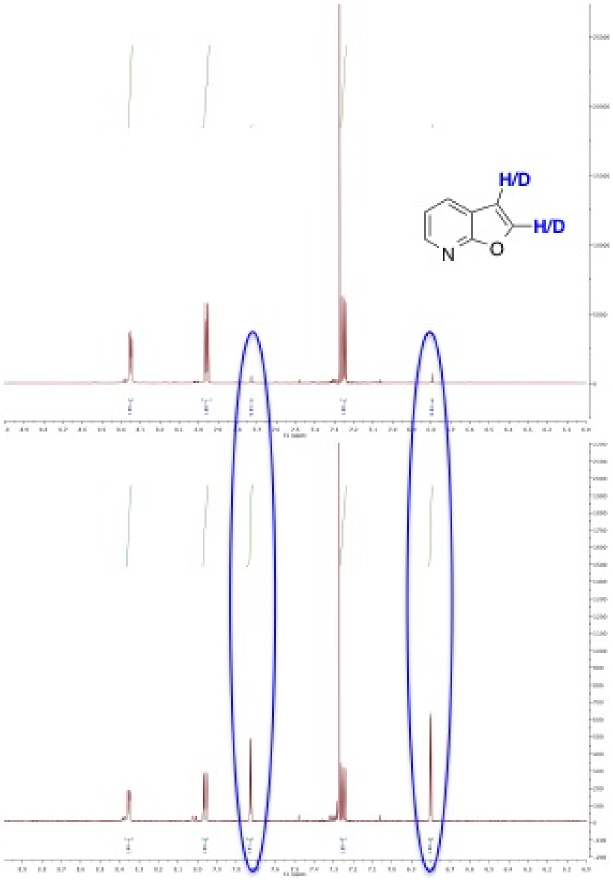




3e-D_2

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37-8.34 (dd, J = 5.0 Hz, 1.5 Hz, 1H), 7.98-7.94 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.73 (s, 0.05H), 7.27-7.23 (dd, J = 8.0 Hz, 4.5 Hz, 1H), 6.79 (s, 0.05H).

The relevant portion of the deuterated spectrum appears above that of the non-deuterated spectrum. The C1 and C2 proton peaks are circled to indicate the level of deuteration. The residual ^{1}H peaks at the C1 and C2 positions both integrate to 5% intensity relative to the other peaks.



Reagent sourcing, purity and aftermarket purification

All reagents and materials were purchased from the following suppliers with the indicated purity, and used as received unless otherwise specified:

phenylacetylene (Acros Organics, 98%), 2-ethynyltoluene (Sigma Aldrich, 97%), 3-ethynyltoluene (Sigma Aldrich, 97%), 4-ethynyltoluene (Sigma Aldrich, 97%), 4-*tert*-butylphenylacetylene (Sigma Aldrich, 96%), 4-Ethynyl-*α,α,α*-trifluorotoluene (Sigma Aldrich, 97%), 3-Ethynylpyridine (Sigma Aldrich, 98%), 4-Ethynylbenzonitrile (Sigma Aldrich, 97%), 3,3-dimethyl-1-butyne (TCI, 96%), trimethylsilylacetylene (Acros Organics, 98%), 4-Ethynylanisole (Sigma Aldrich, 97%), 2-Fluoroiodobenzene (Sigma Aldrich, 99%, contains copper as stabilizer), 2-fluoro-3-iodopyridine (Synthonix, 98%), 2-chloro-3-trimethylsilanylethynylpyridine (Sigma Aldrich), 1-chloro-2-fluoro-3-iodobenzene (Combi Blocks, 98%), 4-bromo-1-fluoro-2-iodobenzene (Combi Blocks, 98%), 4-bromo-3-chloro-1-fluoro-2-iodobenzene (Combi Blocks, 98%), copper (I) iodide (Strem Chemicals, 98%), bis(triphenylphosphine)palladium(II) dichloride (Sigma Aldrich, ≥99.99% trace metals basis), triethylamine (Fischer, reagent grade) – purified by distillation prior to use, tetrabutylammonium fluoride, 1.0 M in THF (TCI), p-toluidine (Acros Organics, 99%) – purified by sublimation prior to use
sodium hydroxide (Fischer, reagent grade) – finely ground with mortar and pestle prior to use, acetamide (Sigma Aldrich, 99%) – purified by sublimation prior to use, dimethyl sulfoxide (Acros, extra dry with molecular sieves, water < 50 ppm), dimethyl sulfoxide-D6 (Cambridge Isotope, D, 99.9%), chloroform-D (Cambridge Isotope, D, 99.9%), dichloromethane (Pharmco-Aaper), hexanes (Pharmco-Aaper), methanol (Honeywell) ethyl acetate (Honeywell), sodium sulfate, anhydrous (Fischer, ACS grade), silica gel, premium rf (Sorbtech, porosity: 60Å, particle size: 200x400 mesh)

Instrument specifications

All ^{1}H and ^{13}C NMR spectra were collected on a Varian 500 MHz NMR. HRMS data were obtained from an Agilent Technologies 6230 TOF LC/MS with an Ion Sense DART 100 ionization interface. All IR spectra were recorded on a Perkin Elmer FT-IR spectrum one instrument.

Supporting Information references

1. N. P. Bizier, J. W. Wackerly, E. D. Braunstein, M. Zhang, S. T. Nodder, S. M. Carlin and J. L. Katz, *J. Org. Chem.* , 2013, **78**, 5987.