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

Supporting Information for:

Palladium-Catalyzed β-(Hetero)Arylation of α,β-Unsaturated Valerolactams

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I. General Information

All reagents were obtained from commercial suppliers and used without further purification. All aryl halides were obtained from commercial suppliers and used without further purification. All solvents were purchased anhydrous (with a septum cap) and used as received. Silica gel chromatography was performed using medium pressure ISCO system employing pre-packaged ISCO columns. ^{1}H and ^{13}C NMR characterization data were collected at 300K on a Bruker AV-500 spectrometer operating at 500.1 and 125.8 MHz (respectively) with chemical shifts reported in parts per million relative to $CHCl_3$ (1H NMR; 7.26 ppm, 13C NMR; 77.16 ppm). Infrared data were recorded on a Nicolet Avatar 360 FT-IR. HPLC was performed on an Agilent 1100 system (XBridge C18 column, 4.6 x 150mm, 5 µm; 95% water/acetonitrile linear gradient to 5% water/acetonitrile over 4 min, hold at 5% water / 95% acetonitrile to 5.0 min, trifluoroacetic acid modifier (0.1%)). Liquid chromatography mass spectrometry (LCMS) was performed on an Agilent 1100 Series (Waters Atlantis C18 column, 4.6 x 50 mm, 5 µm; 95% water/acetonitrile linear gradient to 5% water/acetonitrile over 4 min, hold at 5% water / 95% acetonitrile to 5.0 min, trifluoroacetic acid modifier (0.05%); flow rate of 2.0 mL/ min). High resolution mass spectrometry was performed on an Agilent (6220) LC-MS TOF using an XBridge C18 2.5 µm 3.0 X 5.0 mm column at 60 °C; ammonium formate:water as mobile phase A1 and 50:50 methanol:acetonitrile as mobile phase B1.

Compounds **5a**,[1] **5b**,[2] **5c**,[3] **5d**,[1] **5e**,[4] **8**,[5] and **10**[6] were prepared according to reported procedures.

II. Reaction Optimization Procedure

Preparation of stock solution of base/lactam/aryl-bromide:

To a 20mL vial was added lactam (400mg), Cy_2NMe (0.888mL), DMF (8mL), pyridyl-bromide (0.36mL), the vial was sealed with a septum cap and the atmosphere was exchanged to N_2.

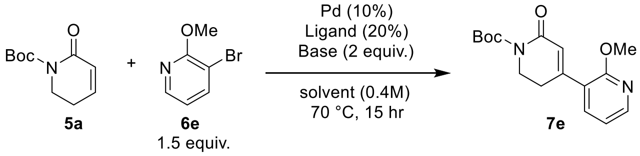
Total volume = ~ 9.65mL

Therefore, ~1.2mL goes into each rxn.

Rxn Setup:

To a 2-5mL microwave vial was added $Pd_2(dba)_3$ (23mg, 10mol%), the atmosphere was exchanged to N_2, then ligand (20 mol%), and the remainder of the reactants were added using the premixed stock solution (1.2mL) and the vial was heated to 70 degrees C on an aluminum block. After stirring for 15 hours an aliquot (0.010mL) was taken and added to an HPLC vial containing 0.50mL 1mg/mL mesitylene/MeOH and the mixture was analyzed by HPLC.

Table 1. Optimization of β-arylation of valeraolactam



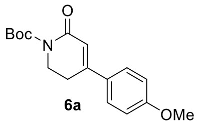
entry	L	Solvent	Base	Yield[c]
1	PPh_3	DMF	$MeNCy_2$	< 5 %
2	$P(tBu)_3$	DMF	$MeNCy_2$	91%
3	$P(Cy)_3$	DMF	$MeNCy_2$	< 5 %
4	Xphos	DMF	$MeNCy_2$	< 5 %
5	tBuXPhos	DMF	$MeNCy_2$	< 5 %
6	RuPhos	DMF	$MeNCy_2$	< 5 %
7	Amphos	DMF	$MeNCy_2$	95%
8	CataCXium A	DMF	$MeNCy_2$	< 5 %
9	Amphos	toluene	$MeNCy_2$	10%
10	Amphos	1,4-dioxane	$MeNCy_2$	10%
11	Amphos	THF	$MeNCy_2$	65%
12	Amphos	MeCN	$MeNCy_2$	62%
13	Amphos	THF/DMF[d]	$MeNCy_2$	64%
14	$Pd(OAc)_2$/Amphos	DMF	$MeNCy_2$	< 5 %
15	$PdCl_2Amphos_2$	DMF	$MeNCy_2$	< 5 %
16	PdAmphosGIII	DMF	$MeNCy_2$	< 5 %
17[e]	PdAmphosGIII	DMF	$MeNCy_2$	< 5 %
18	Amphos	DMF	Et_3N	10%
19	Amphos	DMF	K_2CO_3	< 5 %
20	Amphos	DMF	$NaHCO_3$	< 5 %
21	Amphos	DMF	Cs_2CO_3	< 5 %
22[a]	Amphos	DMF	$MeNCy_2$	55 %

[a] The reaction was run at 60 ˚C

III. General Procedure for the β-arylation of Boc-protected lactams

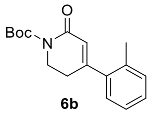
To a 2-5mL microwave vial was added $Pd_2(dba)_3$ (23mg, 0.025mmol, 5mol%), amphos (14mg, 0.050 mmol, 10mol%) and the atmosphere was exchanged to N_2 (evacuate/backfill 3x). To the vial was added a solution of lactam (100mg, 0.507mmol) in DMF (1.3mL, 0.40M), Cy_2NMe (0.222mL, 2equiv.), the atmosphere was once again evacuated/backfilled with N2 (~25mmHg vacuum), and arylbromide (1.01 mmol, 2equiv.) and the vial was heated to 70 degrees C on an aluminum block. After stirring for 15 hours the mixture was cooled to room temperature, diluted with EtOAc, washed with sat.NH_4Cl, brine, dried over Na_2SO_4 and concentrated. Purification over silica gel provided the desired arylated products.

IV. Preparation of β-aryl lactams and analytical data



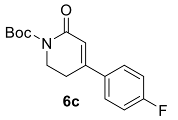
6a

Following the general procedure, **6a** (126mg, 82%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.25 (d, *J* = 1.3 Hz, 1H), 3.95 (t, *J* = 6.4 Hz, 2H), 3.82 (s, 3H), 2.77 (td, *J* = 6.5, 1.3 Hz, 2H), 1.54 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.69, 161.45, 152.73, 152.63, 128.89, 127.61, 118.62, 114.38, 82.93, 55.52, 43.52, 28.24, 26.91. **FTIR** (neat) cm^{-1} 2978, 1756, 1708, 1685, 1601, 1512, 1306, 1218, 1145, 1028, 830, 729. **HRMS** (ESI) calc'd for $C_{17}H_{21}NO_4Na$ [326.1363; M+Na] found m/z = 326.1364.



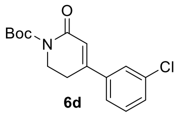
6b

Following the general procedure, **6b** (130mg, 89%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.32 – 7.16 (m, 3H), 7.14 (d, *J* = 1.5 Hz, 1H), 5.94 (t, *J* = 1.4 Hz, 1H), 3.99 (dd, *J* = 6.8, 6.0 Hz, 2H), 2.68 (ddd, *J* = 7.5, 6.1, 1.4 Hz, 2H), 2.34 (s, 3H), 1.58 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.06, 156.50, 152.75, 138.90, 134.49, 130.92, 128.81, 127.35, 126.16, 124.30, 83.14, 43.98, 30.13, 28.23, 20.39. **FTIR** (neat) cm^{-1} 2978, 1761, 1693, 1457, 1388, 1298, 1217, 1147, 755. **HRMS** (ESI) calc'd for $C_{17}H_{22}NO_3$ [288.1594; M+1] found m/z = 288.1583.



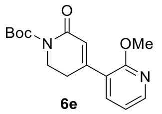
6c

Following the general procedure, **6c** (139mg, 94%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.54 – 7.45 (m, 2H), 7.09 (t, *J* = 8.6 Hz, 2H), 6.26 (t, *J* = 1.3 Hz, 1H), 3.97 (t, *J* = 6.4 Hz, 2H), 2.78 (td, *J* = 6.5, 1.3 Hz, 2H), 1.55 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.20, 164.23, 162.70, 152.60, 151.96, 132.90, 132.87, 128.05, 127.97, 120.49, 120.48, 116.19, 115.97, 83.13, 43.46, 28.20, 28.12, 27.11. **FTIR** (neat) cm^{-1} 2979, 1757, 1689, 1599, 1510, 1302, 1218, 1147, 836. **HRMS** (ESI) calc'd for $C_{16}H_{19}NO_3$ [292.1343; M+1] found m/z = 292.1339.



6d

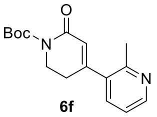
Following the general procedure **6d** (97mg, 62%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.47 (td, *J* = 1.8, 0.6 Hz, 1H), 7.42 – 7.31 (m, 3H), 6.30 (t, *J* = 1.4 Hz, 1H), 3.98 (dd, *J* = 6.8, 6.0 Hz, 2H), 2.78 (ddd, *J* = 7.5, 6.1, 1.4 Hz, 2H), 1.56 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.00, 152.61, 151.68, 138.74, 135.16, 130.28, 130.19, 126.26, 124.18, 121.76, 83.31, 43.48, 28.24, 27.05. **FTIR** (neat) cm^{-1} 2979, 1760, 1693, 1564, 1322, 1221, 1152, 786 ; **HRMS** (ESI) calc'd for $C_{16}H_{18}ClNO_3Na$ [330.0867; M+Na] found m/z = 330.0873.



6e

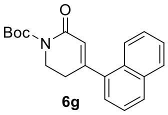
Following the general procedure, **6e** (147mg, 95%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.17 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.55 (dd, *J* = 7.4, 1.9 Hz, 1H), 6.93 (dd, *J* = 7.4, 5.0 Hz, 1H), 6.27 (t, *J* = 1.3 Hz, 1H), 3.97 (s, 3H), 3.94 (dd, *J*

= 6.8, 6.0 Hz, 2H), 1.56 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.19, 160.94, 152.64, 151.85, 147.91, 137.13, 124.25, 121.48, 117.05, 83.10, 53.75, 43.91, 28.28, 28.25. **FTIR** (neat) cm^{-1} 2979, 1758, 1688, 1574, 1462, 1403, 1297, 1148, 774 ; **HRMS** (ESI) calc'd for $C_{16}H_{20}N_2O_4Na$ [327.1315; M+Na] found m/z = 327.1319.



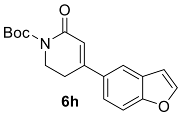
6f

Following the general procedure, **6f** (115mg, 79%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.54 (d, *J* = 4.9 Hz, 1H), 7.54 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.27 (m, 1H), 5.99 (t, *J* = 1.4 Hz, 1H), 4.02 (dd, *J* = 6.7, 6.0 Hz, 2H), 2.69 (td, *J* = 6.4, 1.4 Hz, 2H), 2.64 (s, 3H), 1.57 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.21, 154.07, 152.87, 152.51, 147.53, 137.02, 135.18, 126.02, 121.98, 83.63, 43.85, 29.70, 28.23, 22.50. **FTIR** (neat) cm^{-1} 3151, 2979, 1760, 1712, 1321, 1300, 1152, 1092. **HRMS** (ESI) calc'd for $C_{16}H_{21}N_2O_3$ [289.1552; M+1] found m/z = 289.1553.



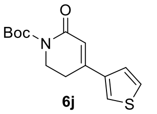
6g

Following the general procedure, **6g** (144mg, 88%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.97 – 7.78 (m, 3H), 7.59 – 7.42 (m, 3H), 7.34 (dd, *J* = 7.1, 1.2 Hz, 1H), 6.15 (t, *J* = 1.4 Hz, 1H), 4.10 (t, *J* = 6.4 Hz, 2H), 2.94 – 2.70 (m, 2H), 1.60 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.05, 155.46, 152.85, 137.17, 133.91, 130.04, 129.42, 128.85, 126.89, 126.43, 125.40, 125.33, 124.99, 124.88, 83.27, 44.14, 30.92, 28.29. **FTIR** (neat) cm^{-1} 2978, 1760, 1694, 1298, 1219, 1149, 802, 776. **HRMS** (ESI) calc'd for $C_{20}H_{21}NO_3Na$ [346.1414; M+Na] found m/z = 346.1413.



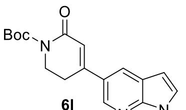
6h

Following the general procedure, **6h** (145mg, 91%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 2.1 Hz, 1H), 7.56 – 7.45 (m, 2H), 6.80 (dd, *J* = 2.2, 1.0 Hz, 1H), 6.34 (t, *J* = 1.2 Hz, 1H), 4.01 (td, *J* = 6.5, 1.8 Hz, 2H), 2.93 – 2.84 (m, 2H), 1.61 – 1.55 (m, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.52, 156.03, 153.64, 152.81, 146.34, 131.95, 128.13, 122.63, 120.21, 119.30, 112.00, 106.98, 83.10, 43.64, 28.29, 27.62. **FTIR** (neat) cm^{-1} 2979, 1758, 1688, 1470, 1316, 1152, 872. **HRMS** (ESI) calc'd for $C_{18}H_{20}NO_4$ [314.1387; M+1] found m/z = 314.1388.



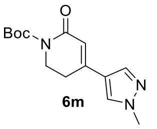
6j

Following the general procedure, **6j** (72mg, 51%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.51 (dd, *J* = 2.9, 1.4 Hz, 1H), 7.38 (dd, *J* = 5.1, 2.9 Hz, 1H), 7.33 (dd, *J* = 5.1, 1.4 Hz, 1H), 6.27 (t, *J* = 1.3 Hz, 1H), 3.97 (dd, *J* = 6.9, 6.1 Hz, 2H), 2.80 (ddd, *J* = 7.3, 6.1, 1.3 Hz, 2H), 1.56 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.88, 152.67, 147.47, 139.06, 127.25, 125.28, 125.09, 119.31, 83.11, 43.43, 28.26, 27.15. **FTIR** (neat) cm^{-1} 3099, 2978, 1755, 1709, 1687, 1318, 1151. **HRMS** (ESI) calc'd for $C_{14}H_{18}NO_3S$ [280.1007; M+1] found m/z = 280.1007.

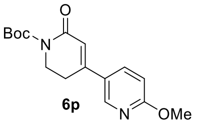


6l

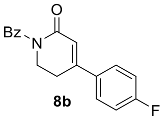
Following the general procedure, **6l** (147mg, 89%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.54 (d, *J* = 2.2 Hz, 1H), 8.05 (d, *J* = 2.2 Hz, 1H), 7.24 (d, *J* = 3.5 Hz, 1H), 6.51 (d, *J* = 3.5 Hz, 1H), 6.38 (t, *J* = 1.3 Hz, 1H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.92 (s, 3H), 2.90 (td, *J* = 6.5, 1.3 Hz, 2H), 1.57 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.36, 152.75, 152.10, 140.79, 130.94, 126.82, 124.76, 120.72, 119.72, 100.60, 83.13, 43.54, 31.79, 28.28, 27.38. **FTIR** (neat) cm^{-1} 2978, 1756, 1709, 1687, 1599, 1389, 1324, 1221, 1152, 725. **HRMS** (ESI) calc'd for $C_{18}H_{21}N_3O_3Na$ [350.1475; M+Na] found m/z = 350.1468.



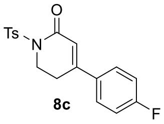
6m Following the general procedure, **6m** (30mg, 21%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.67 (s, 1H), 7.57 (s, 1H), 6.10 (d, *J* = 1.3 Hz, 1H), 3.92 (m, 5H), 2.71 – 2.58 (m, 2H), 1.54 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.80, 152.68, 145.88, 137.72, 128.81, 120.24, 116.56, 82.93, 43.26, 39.46, 28.22, 27.23. **HRMS** (ESI) calc'd for $C_{14}H_{20}N_3O_3$ [278.1499;M+1] found m/z = 278.1501.



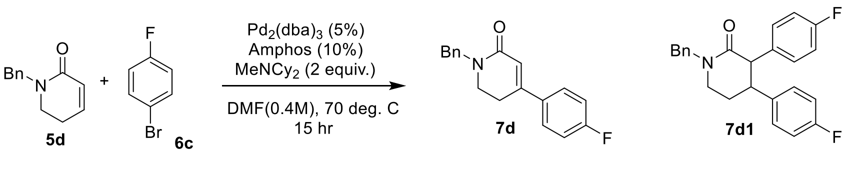
6p Following the general procedure, **6p** (123mg, 80%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.33 (dd, *J* = 2.6, 0.7 Hz, 1H), 7.72 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.77 (dd, *J* = 8.8, 0.7 Hz, 1H), 6.25 (t, *J* = 1.3 Hz, 1H), 4.00 – 3.95 (m, 2H), 3.95 (s, 3H), 2.78 (ddd, *J* = 7.4, 6.1, 1.3 Hz, 2H), 1.54 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.41, 164.16, 152.54, 150.11, 145.14, 136.02, 125.49, 119.49, 111.45, 83.12, 53.93, 43.35, 28.20, 26.58. **FTIR** (neat) cm^{-1} 2979, 1758, 1688, 1597, 1497, 1384, 1294, 1218, 1150, 1025, 832. **HRMS** (ESI) calc'd for $C_{17}H_{20}N_2O_4$ [305.1496; M+1] found m/z = 305.1497.



8b To a vial was added $Pd_2(dba)_3$ (12.5mg, 0.0137mmol, 5mol%), amphos (7.25mg, 0.027 mmol, 10mol%) and the atmosphere was exchanged to N_2 (evacuate/backfill 3x). To the vial was added a solution of lactam (55mg, 0.27mmol) in DMF (0.7mL, 0.40M), Cy_2NMe (0.12mL, 2equiv.), the atmosphere was once again evacuated/backfilled with N_2 (~25mmHg vacuum), and arylbromide (0.060mL, 0.547 mmol, 2equiv.) and the vial was heated to 70 degrees C on an aluminum block. After stirring for 15 hours the mixture was cooled to room temperature, diluted with EtOAc, washed with sat.NH_4Cl, brine, dried over Na_2SO_4 and concentrated. Purification over silica gel provided **8b** (69mg, 86%) as an off white solid. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.67 – 7.53 (m, 4H), 7.52 – 7.45 (m, 1H), 7.44 – 7.34 (m, 2H), 7.18 – 7.11 (m, 2H), 6.29 (d, *J* = 1.4 Hz, 1H), 4.12 (t, *J* = 6.4 Hz, 2H), 2.97 (td, *J* = 6.4, 1.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.80, 165.85, 165.44, 162.93, 153.87, 136.13, 132.74, 132.70, 131.73, 128.42, 128.24, 128.15, 128.13, 119.34, 119.33, 116.33, 116.32, 116.11, 43.26, 27.27. **FTIR** (neat) cm^{-1} 2888, 1666, 1597, 1509, 1296, 1216, 1159, 1020, 832, 727. **HRMS** (ESI) calc'd for $C_{18}H_{15}FNO_2$ [296.1081; M+1] found m/z = 296.1081.

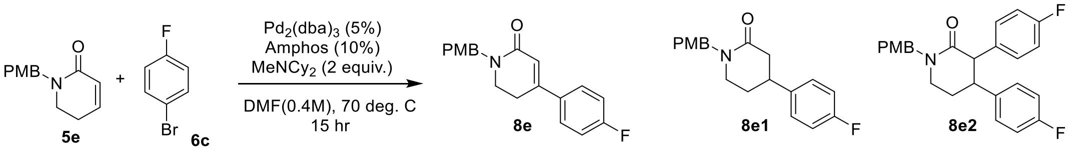


8c To a vial was added $Pd_2(dba)_3$ (11.4mg, 0.0125mmol, 5mol%), amphos (6.6mg, 0.025 mmol, 10mol%) and the atmosphere was exchanged to N_2 (evacuate/backfill 3x). To the vial was added a solution of lactam (63mg, 0.25mmol) in DMF (0.6mL, 0.40M), Cy_2NMe (0.110mL, 2equiv.), the atmosphere was once again evacuated/backfilled with N_2 (~25mmHg vacuum), and arylbromide (0.055mL, 0.50 mmol, 2equiv.) and the vial was heated to 70 degrees C on an aluminum block. After stirring for 15 hours the mixture was cooled to room temperature, diluted with EtOAc, washed with sat.NH_4Cl, brine, dried over Na_2SO_4 and concentrated. Purification over silica gel provided **8c** (68mg, 79%) as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.47 (dd, *J* = 8.9, 5.2 Hz, 1H), 7.38 – 7.28 (m, 1H), 7.10 (dd, *J* = 9.0, 8.3 Hz, 1H), 6.19 – 6.06 (m, 1H), 4.18 (dd, *J* = 6.8, 6.2 Hz, 2H), 2.93 (td, *J* = 6.5, 1.3 Hz, 2H), 2.43 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.45, 163.60, 162.94, 153.29, 144.95, 136.01, 132.58, 132.55, 129.56, 129.54, 128.72, 128.20, 128.11, 119.21, 119.19, 116.38, 116.16, 77.48, 44.00, 27.86, 21.82. **FTIR** (neat) cm^{-1} 3147, 3050, 1678, 1598, 1510, 1352, 1226, 1166, 894, 690. **HRMS** (ESI) calc'd for $C_{18}H_{17}FNO_3S$ [346.0908; M+1] found m/z = 346.0904.

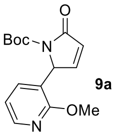


To a microwave vial was added $Pd_2(dba)_3$ (11.2mg, 0.0123 mmol, 5mol%), amphos (6.5mg, 0.025 mmol, 10mol%) and the atmosphere was exchanged to N_2 (evacuate/backfill 3x). To the vial was added a solution of lactam (46mg, 0.25mmol) in

DMF (0.6mL, 0.40M), Cy_2NMe (0.108mL, 0.49 mmol, 2equiv.), the atmosphere was once again evacuated/backfilled with N2 (~25mmHg vacuum), and arylbromide (0.055mL, 0.49mmol, 2equiv.) and the vial was heated to 70 degrees C on an aluminum block. After stirring for 15 hours the mixture was cooled to room temperature, diluted with EtOAc, washed with sat.NH_4Cl, brine, dried over Na_2SO_4 and concentrated. Silica gel chromatography provided an inseperable mixture of **7d** and **7d1**(**7d** / **7d1** = 1.5/1; 43mg): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.45 – 7.33 (m, 2H), 7.32 – 7.18 (m, 6H), 7.05 – 6.93 (m, 2H), 6.81 (dddd, *J* = 12.5, 8.8, 7.5, 4.7 Hz, 5H), 6.25 (d, *J* = 1.4 Hz, 1H), 4.66 (d, *J* = 14.3 Hz, 1H), 4.60 (s, 2H), 4.56 (d, *J* = 14.4 Hz, 1H), 3.59 (d, *J* = 10.4 Hz, 1H), 3.49 – 3.32 (m, 3H), 3.28 (ddd, *J* = 12.4, 4.9, 3.6 Hz, 1H), 3.03 (td, *J* = 10.4, 4.3 Hz, 1H), 2.63 (td, *J* = 7.1, 1.3 Hz, 2H), 2.09 – 1.96 (m, 1H). **LCMS** (ES+) **7d1**: 0.99 min calc'd for $C_{24}H_{22}F_2NO$ [378.16; M+1] found m/z = 378.7. **7d**: 0.90 min, calc'd for $C_{18}F_{17}FNO$ [282.12; M+1] found m/z = 282.7.

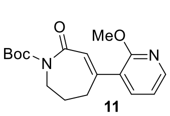


To a microwave vial was added $Pd_2(dba)_3$ (10.5mg, 0.0115mmol, 5mol%), amphos (6.1mg, 0.023 mmol, 10mol%) and the atmosphere was exchanged to N_2 (evacuate/backfill 3x). To the vial was added a solution of lactam (50mg, 0.23mmol) in DMF (0.58mL, 0.40M), Cy_2NMe (0.101mL, 0.46 mmol, 2equiv.), the atmosphere was once again evacuated/backfilled with N2 (~25mmHg vacuum), and arylbromide (0.051mL, 0.46mmol, 2equiv.) and the vial was heated to 70 degrees C on an aluminum block. After stirring for 15 hours the mixture was cooled to room temperature, diluted with EtOAc, washed with sat.NH_4Cl, brine, dried over Na_2SO_4 and concentrated. Purification over silica gel provided the arylated products. Bis-arylated **8e2** (24mg, 26%) was obtained as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.32 – 7.27 (m, 2H), 6.90 (dt, *J* = 8.4, 2.9 Hz, 10H), 4.72 – 4.54 (m, 2H), 3.83 (s, 3H), 3.66 (d, *J* = 10.3 Hz, 1H), 3.54 – 3.43 (m, 1H), 3.36 (dt, *J* = 12.3, 4.3 Hz, 1H), 3.10 (td, *J* = 10.0, 5.4 Hz, 1H), 2.14 – 2.03 (m, 2H). **LCMS** 0.98 min (ES+) calc'd [407.17; M+1] observed [m/z 408.3]. β-arylated **8e** and reduced product **8e1** were obtained as an inseperable mixture (**8d** / **8d1** = 1 /2; 24mg, 34%). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.51 – 7.43 (m, 2H), 7.25 – 7.18 (m, 4H), 7.17 – 7.11 (m, 3H), 7.08 (t, *J* = 8.6 Hz, 2H), 7.04 – 6.96 (m, 3H), 6.87 (dd, *J* = 8.8, 2.6 Hz, 5H), 6.31 (d, *J* = 1.3 Hz, 1H), 4.66 (d, *J* = 14.4 Hz, 2H), 4.62 (s, 2H), 4.49 (d, *J* = 14.3 Hz, 2H), 3.80 (s, 7H), 3.43 (t, *J* = 7.1 Hz, 2H), 3.26 (dt, *J* = 9.9, 4.0 Hz, 3H), 3.07 (tdd, *J* = 11.1, 5.2, 3.2 Hz, 2H), 2.78 (ddd, *J* = 17.4, 5.3, 2.1 Hz, 2H), 2.70 (td, *J* = 7.1, 1.3 Hz, 2H), 2.52 (dd, *J* = 17.4, 11.0 Hz, 2H), 2.11 – 1.98 (m, 1H), 1.96 – 1.80 (m, 2H). **LCMS** (ES+) 0.88min calc'd for $C_{19}H_{19}FNO_2$ [312.13; 2M+] observed m/z = 312.2. 0.93 min calc'd for $C_{19}H_{21}FNO_2$ [314.15; M+1] found m/z = 314.2.



9a

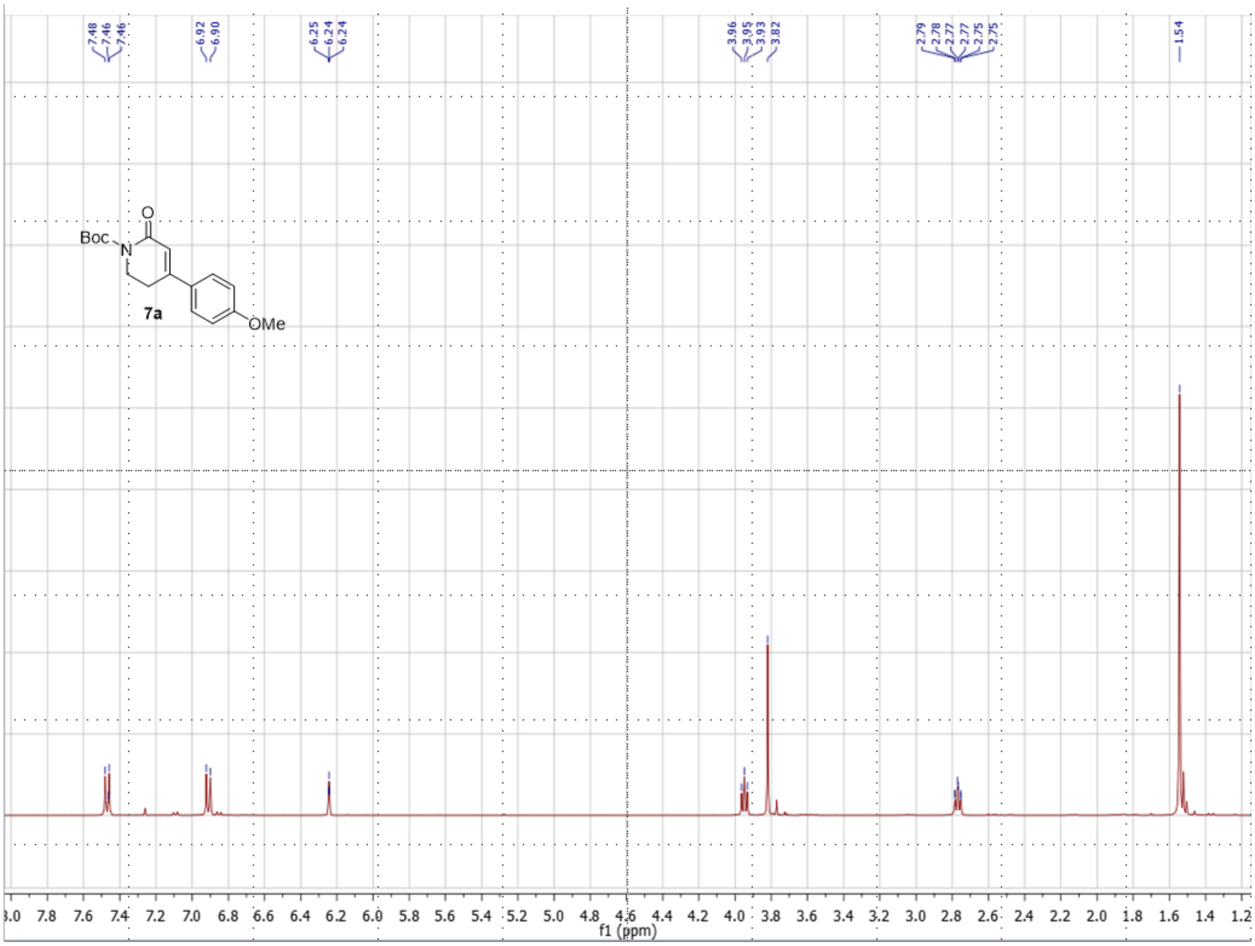
To a vial was added $Pd_2(dba)_3$ (50mg, 0.055mmol, 10 mol%), lactam (100mg, 0.55mmol), and the atmosphere was exchanged to N_2 (evacuate/backfill 3x). To the sealed vial was added $P(tBu)_3$ (0.110 mL, 1M in toluene, 0.11 mmol, 20 mol%), DMF (2.2 mL, 0.40M), Cy_2NMe (0.24 mL, 2equiv.), arylbromide (0.074mL, 0.63 mmol, 2equiv.) and the vial was heated to 70 degrees C on an aluminum block. After stirring for 15 hours the mixture was cooled to room temperature, diluted with EtOAc, washed with sat.NH_4Cl, brine, dried over Na_2SO_4 and concentrated. Purification over silica gel provided **9a** (116mg, 73%) as a yellow oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.12 (dd, *J* = 5.0, 1.7 Hz, 1H), 7.30 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.13 (dd, *J* = 6.0, 2.1 Hz, 1H), 6.87 (dd, *J* = 7.4, 5.0 Hz, 1H), 6.14 (dd, *J* = 6.0, 1.7 Hz, 1H), 5.93 (t, *J* = 1.9 Hz, 1H), 4.00 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (151 MHz, cdcl$_3$) δ 169.95, 160.89, 149.31, 148.69, 146.61, 134.35, 125.77, 118.89, 117.19, 83.12, 60.32, 53.81, 27.90. **FTIR** (neat) cm^{-1} 2979, 2902, 1778, 1741, 1717, 1466, 1334, 1157. **HRMS** (ESI) calc'd for $C_{15}H_{19}N_2O_4$ [291.1345; M+1] found m/z = 291.1346.



11

To a microwave vial containing lactam (106mg, 0.502mmol) and $Pd_2(dba)_3$ (46mg, 10 mol%) under N_2 was added DMF (2mL) and $PtBu_3$ (1M in toluene, 0.10 mL, 20mol%), followed by addition of pyridyl bromide (0.120 mL, 1.01mmol) and Cy_2NMe (0.220 mL, 1.01mmol) and the vial was heated to 70 degrees C in an aluminum block. After stirring for 15 hours the mixture was cooled to room temperature, diluted with EtOAc, washed with sat.NH_4Cl, brine, dried over Na_2SO_4 and concentrated. Purification over silica gel provided **11** (46mg, 30%) as a yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.14 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.50 (dd, *J* = 6.8, 2.0 Hz, 1H), 6.90 (dd, *J* = 7.6, 5.2 Hz, 1H), 6.07 (s, 1H), 3.97 (s, 3H), 3.88 (t, *J* = 6.0 Hz, 2H), 2.62 (t, *J* = 8.0Hz, 2H), 2.12 (m, 2H), 1.55 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.9, 160.5, 152.1, 149.2, 147.0, 137.3, 126.7, 125.4, 117.0, 82.8, 53.6, 43.8, 28.6, 28.1, 26.9. **HRMS** (ESI) calc'd for $C_{17}H_{22}N_2O_4Na$ [341.1472; M+Na] found m/z = 341.1470.

IV. Spectra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2.78
2.77
2.77
2.75
2.75
1.54
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O
7a
OMe
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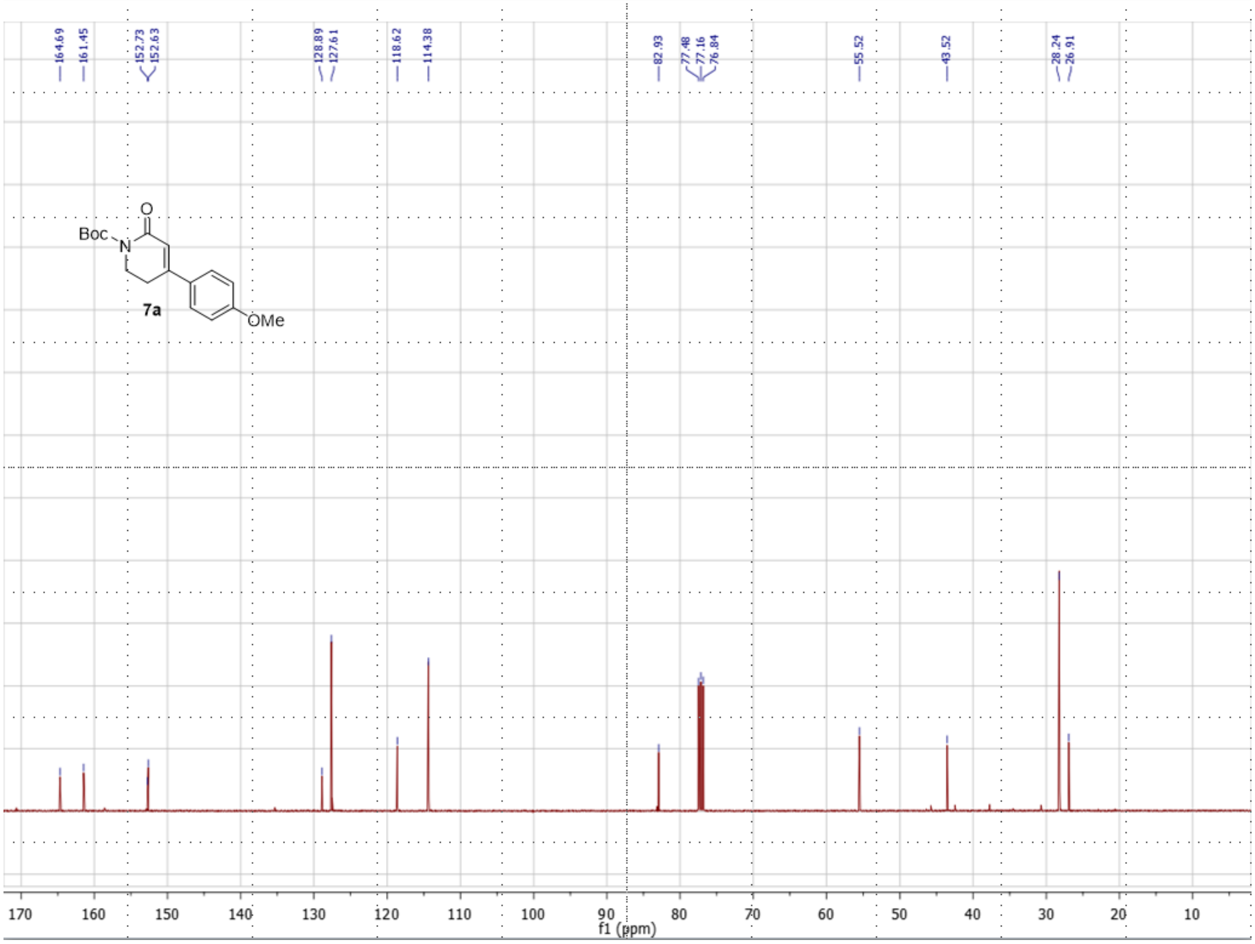
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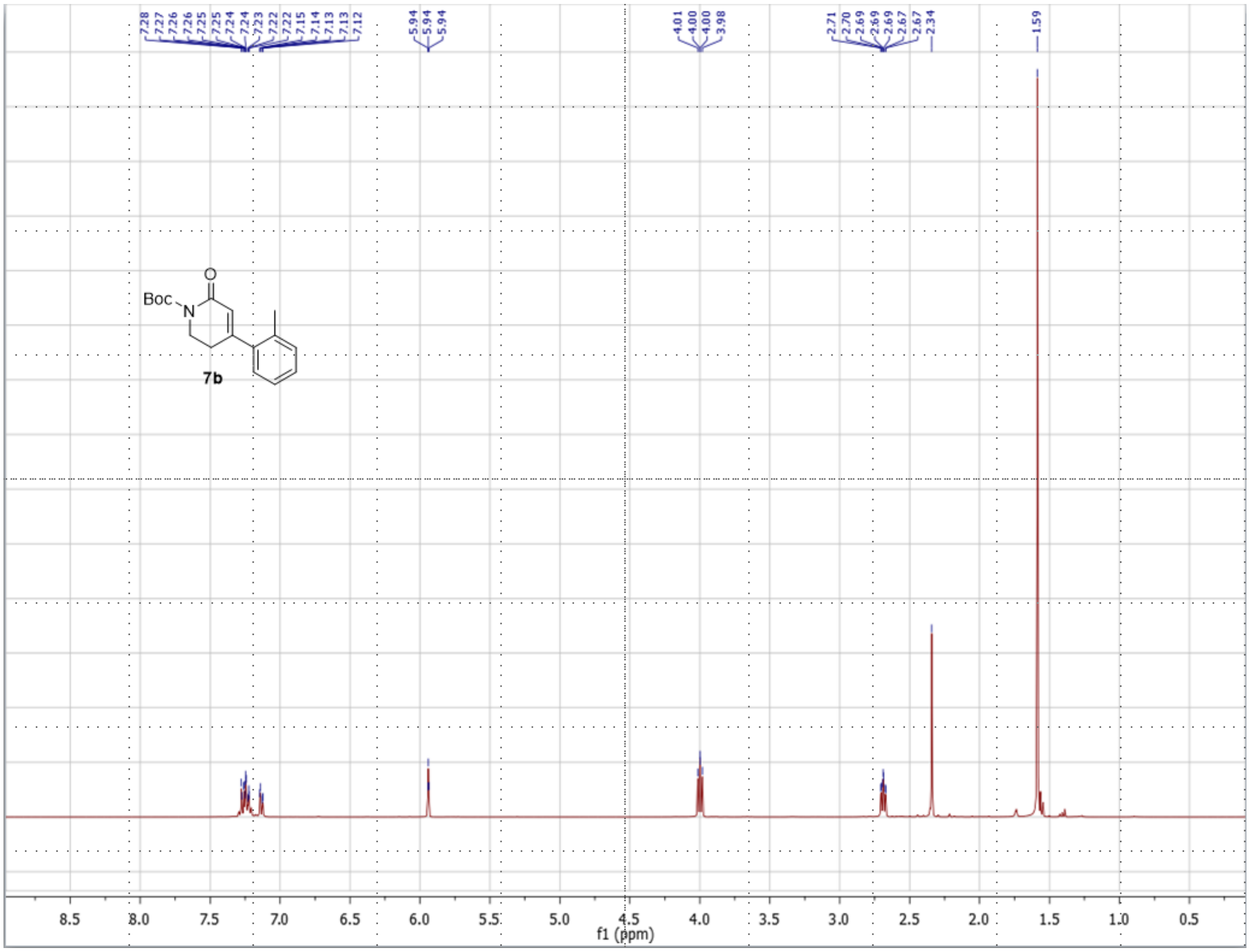
f1 (ppm)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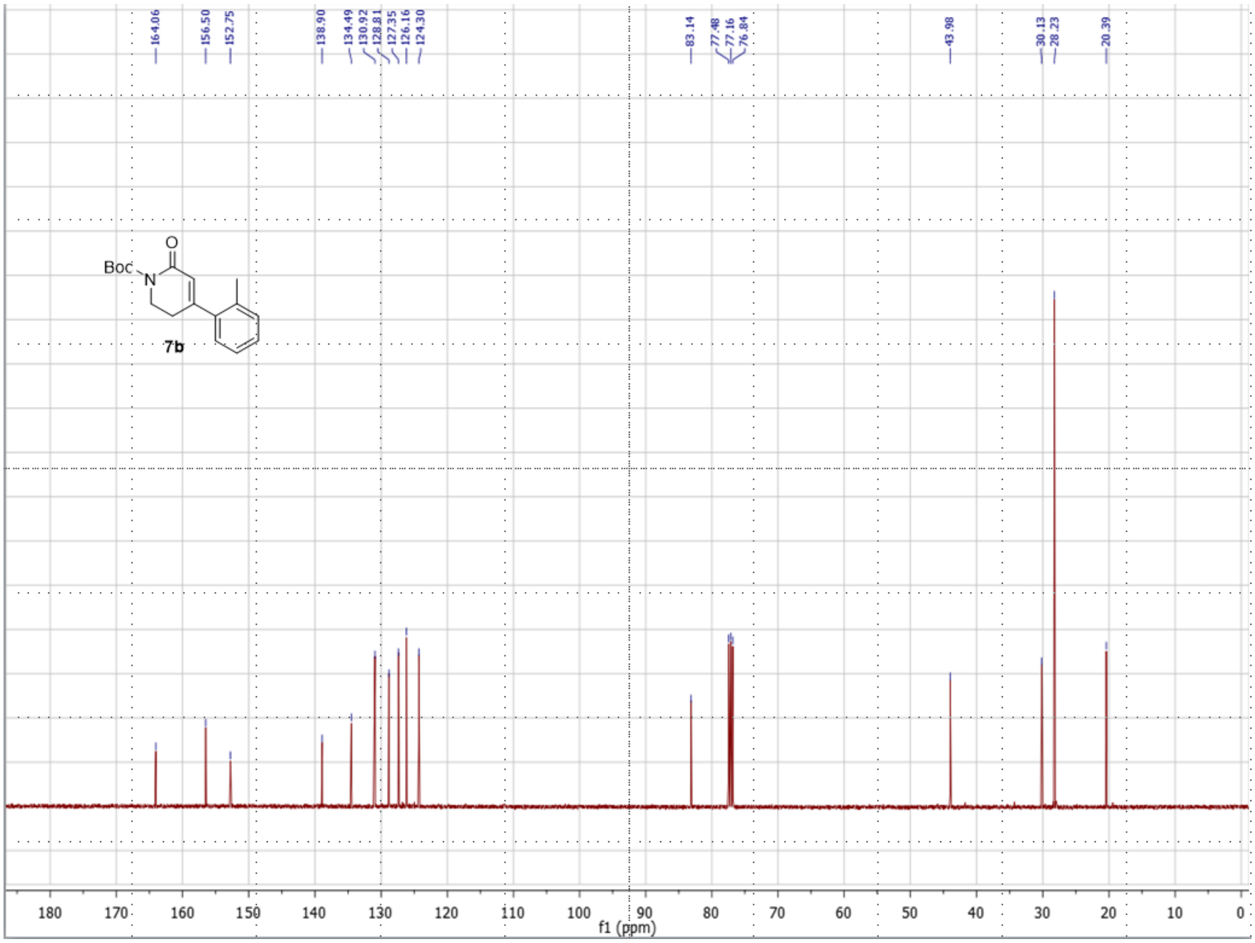
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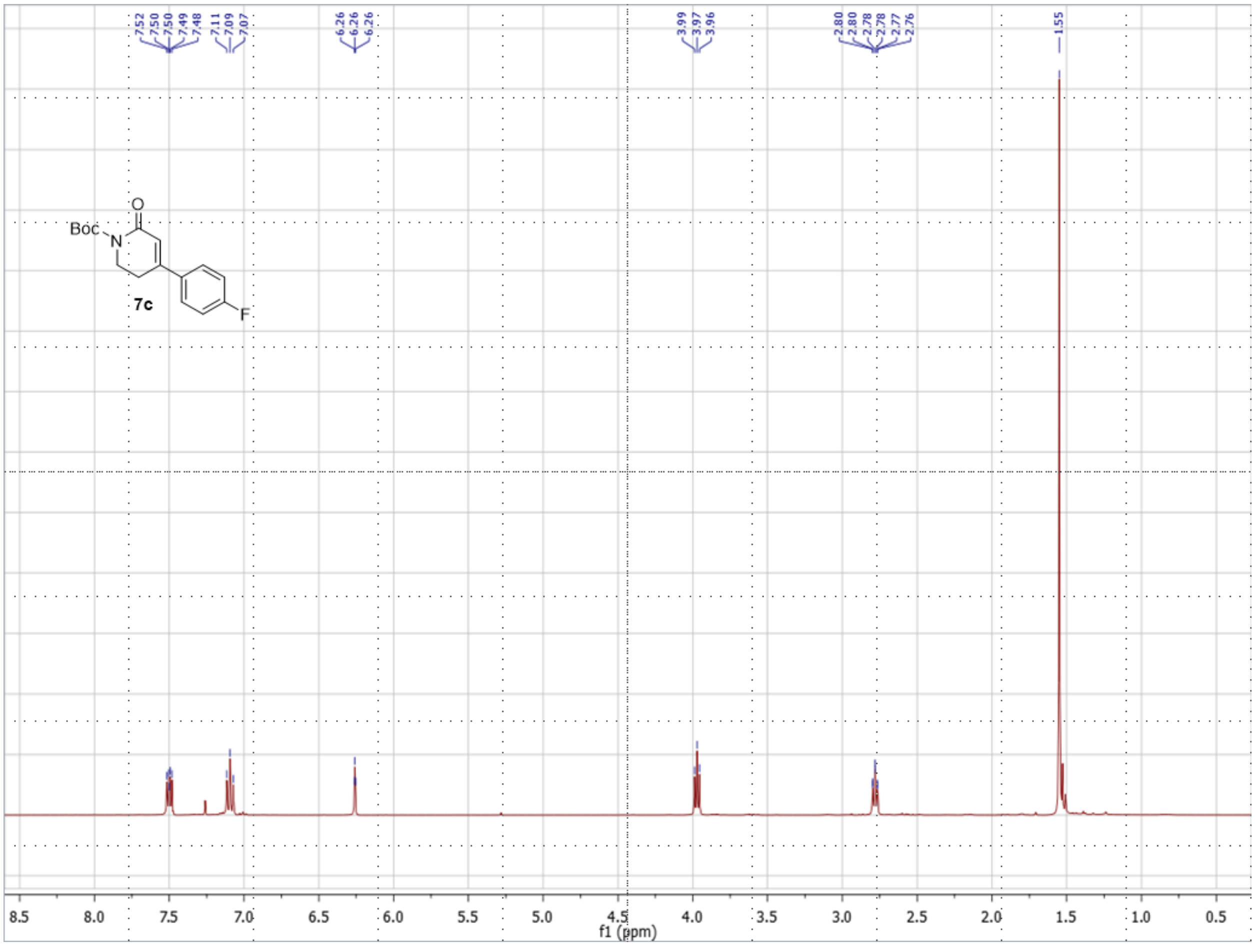
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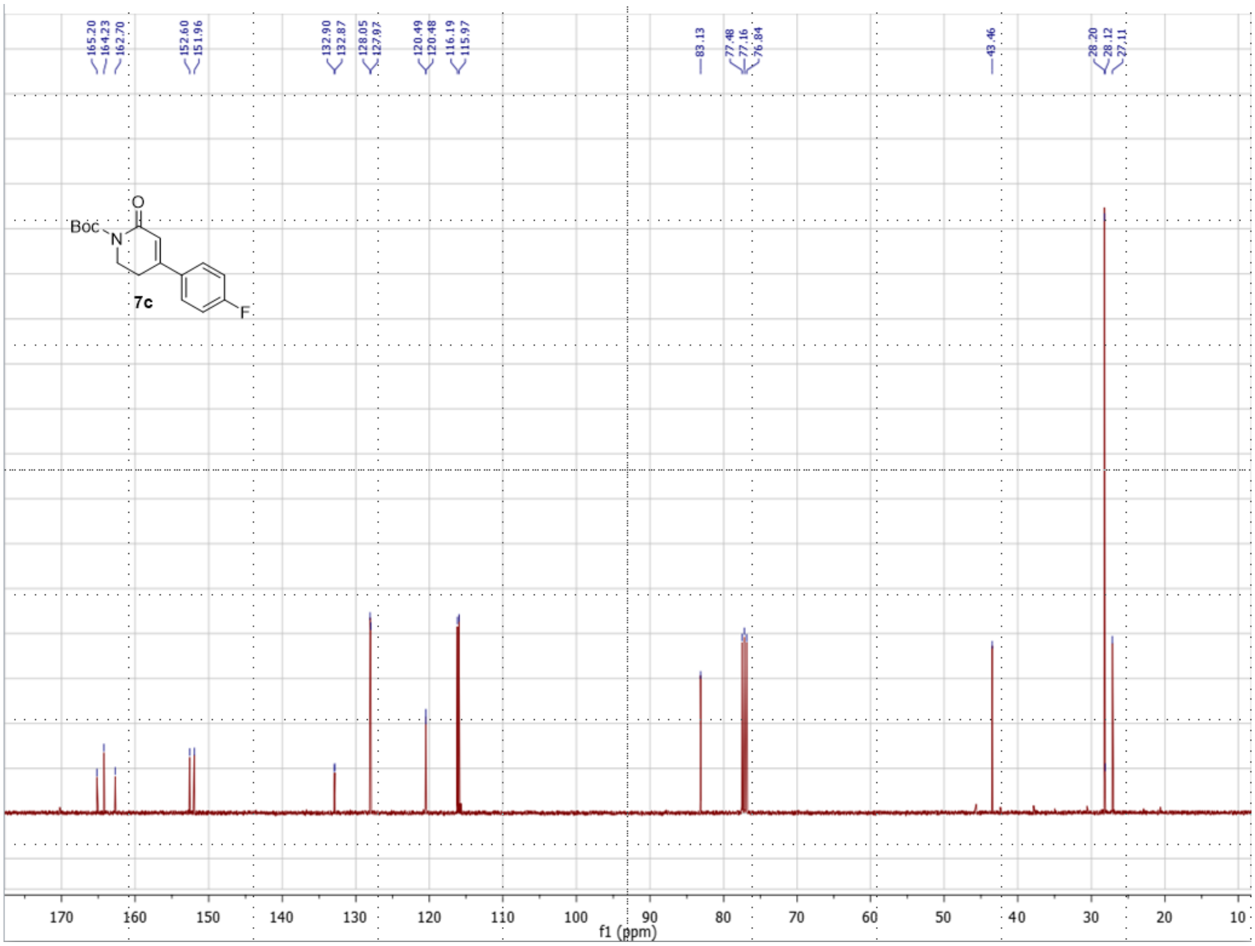
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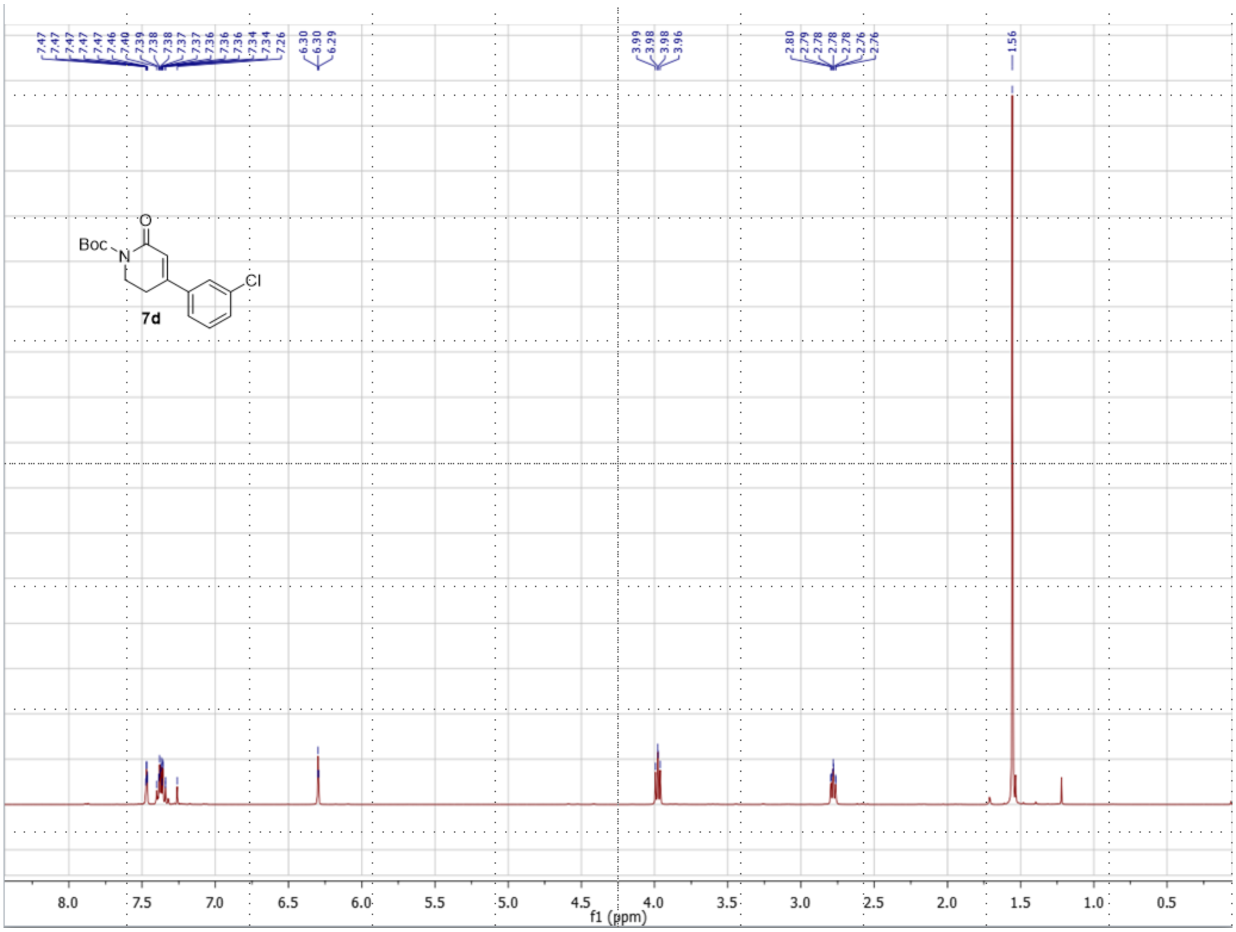
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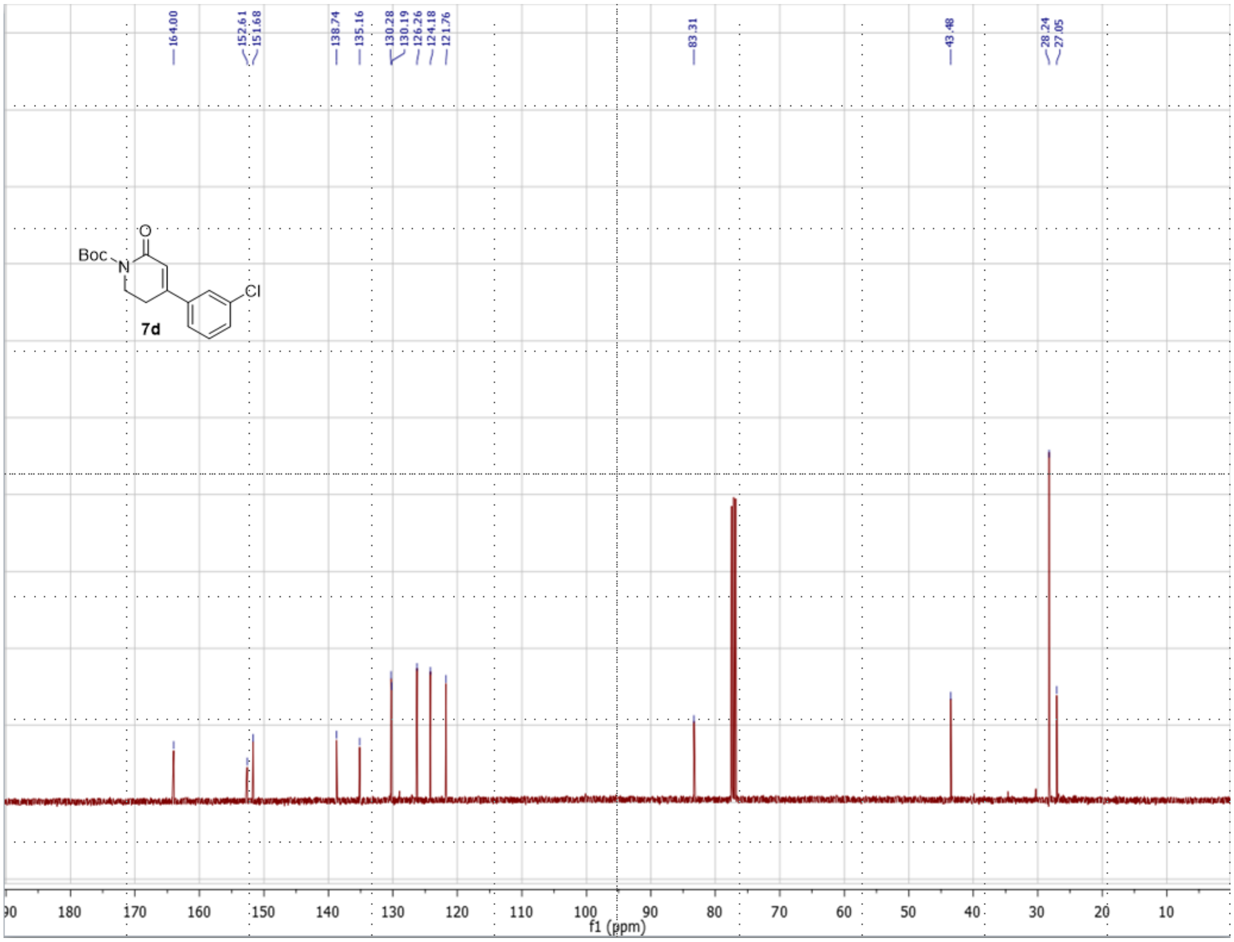
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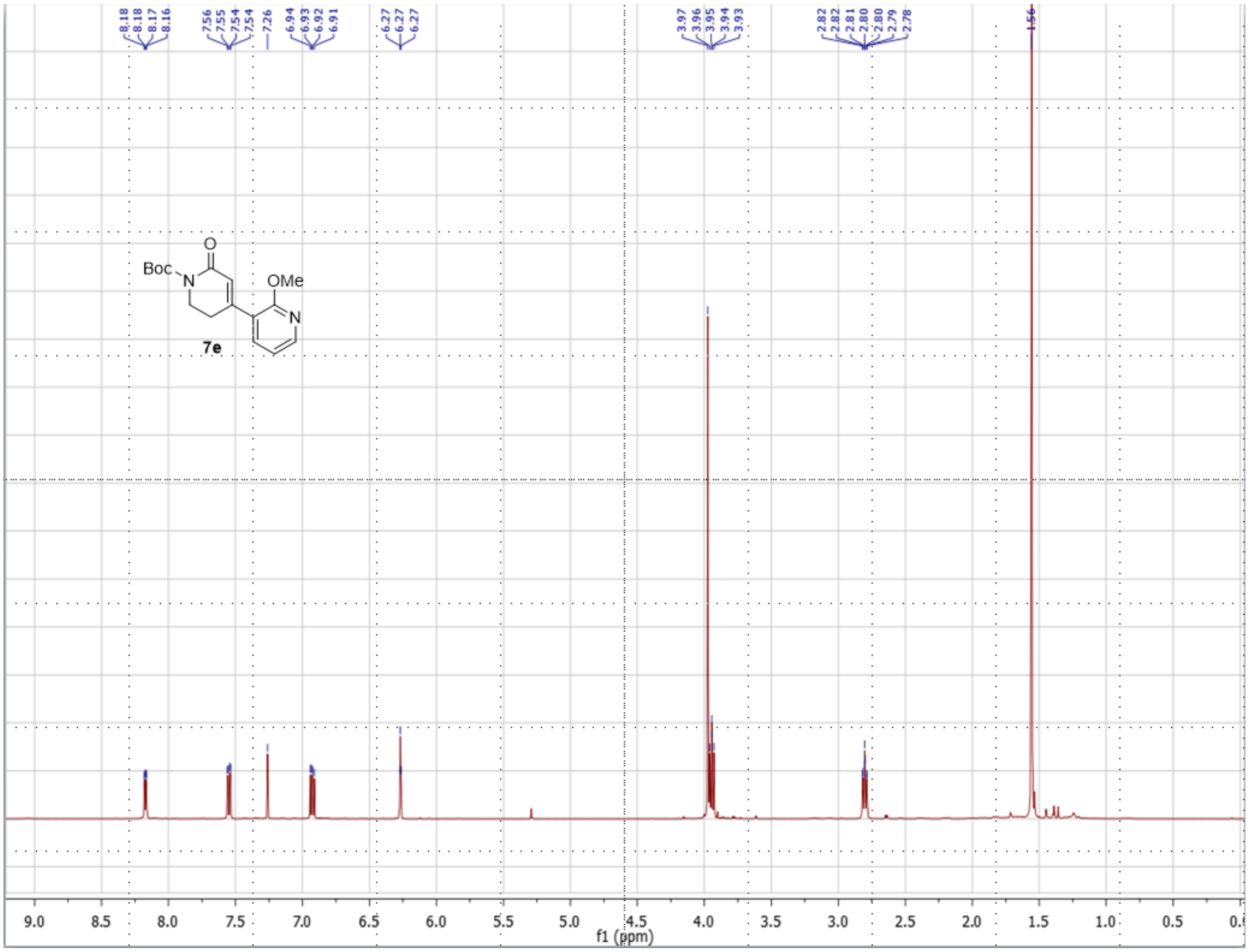
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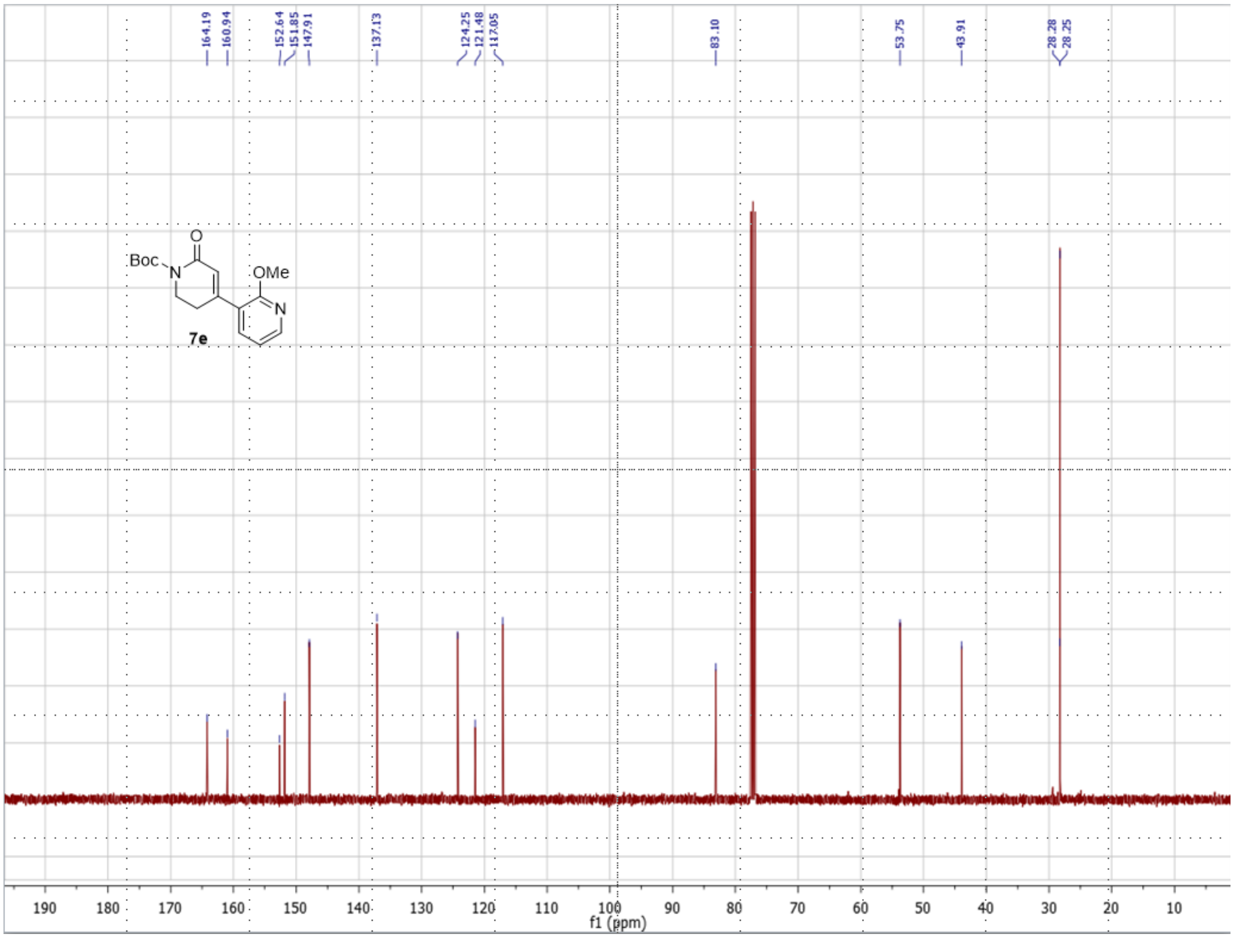
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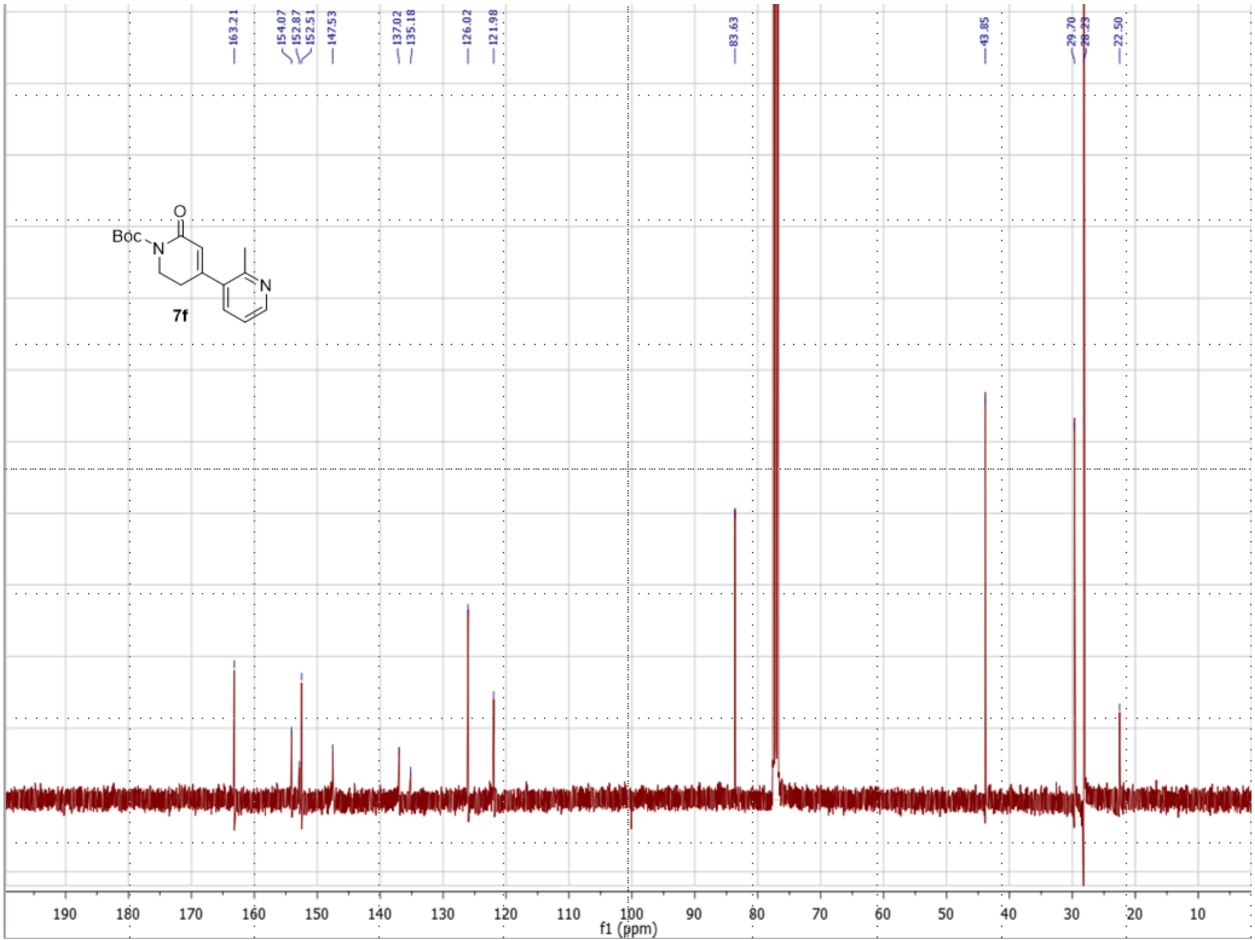
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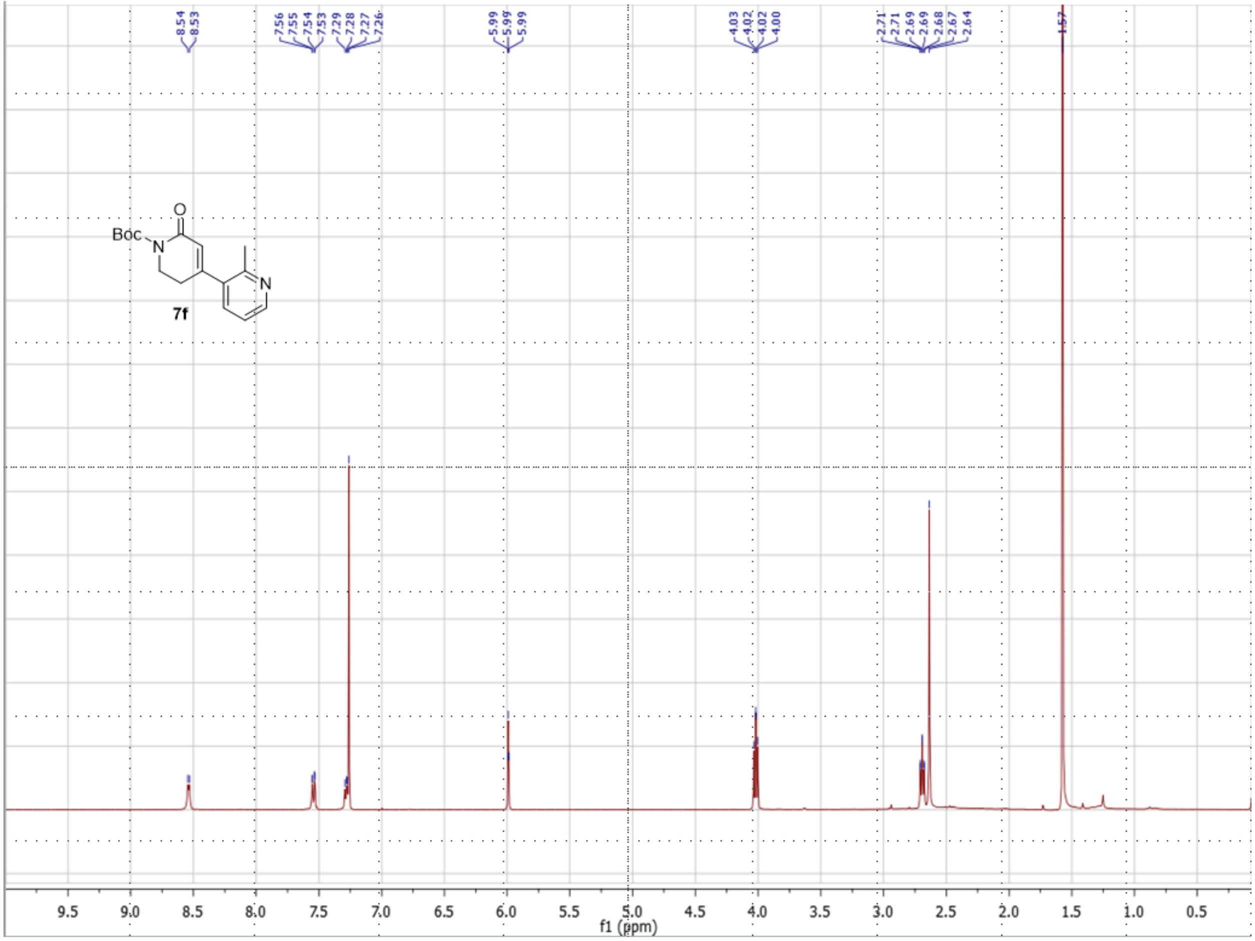
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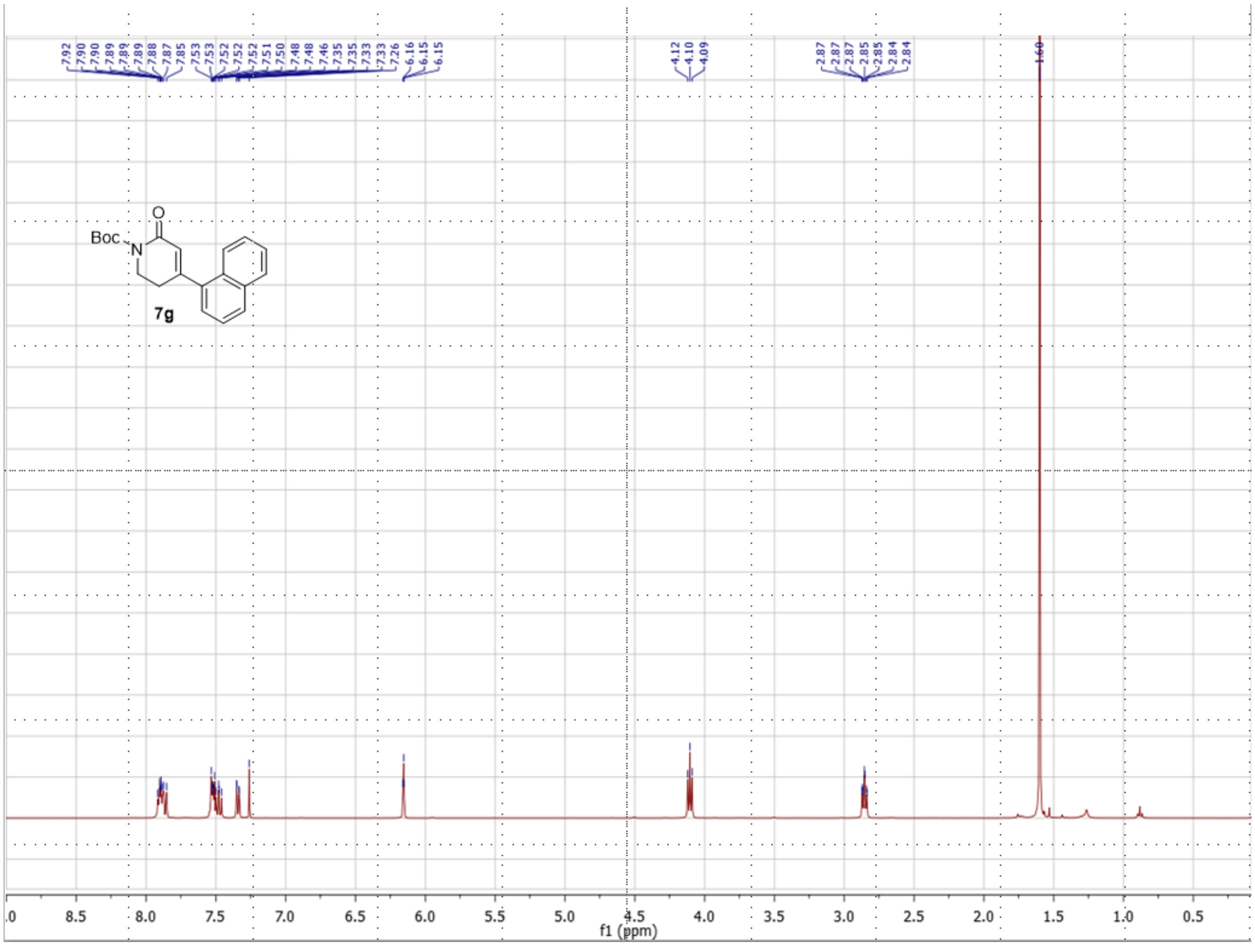
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2.84
1.60
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O
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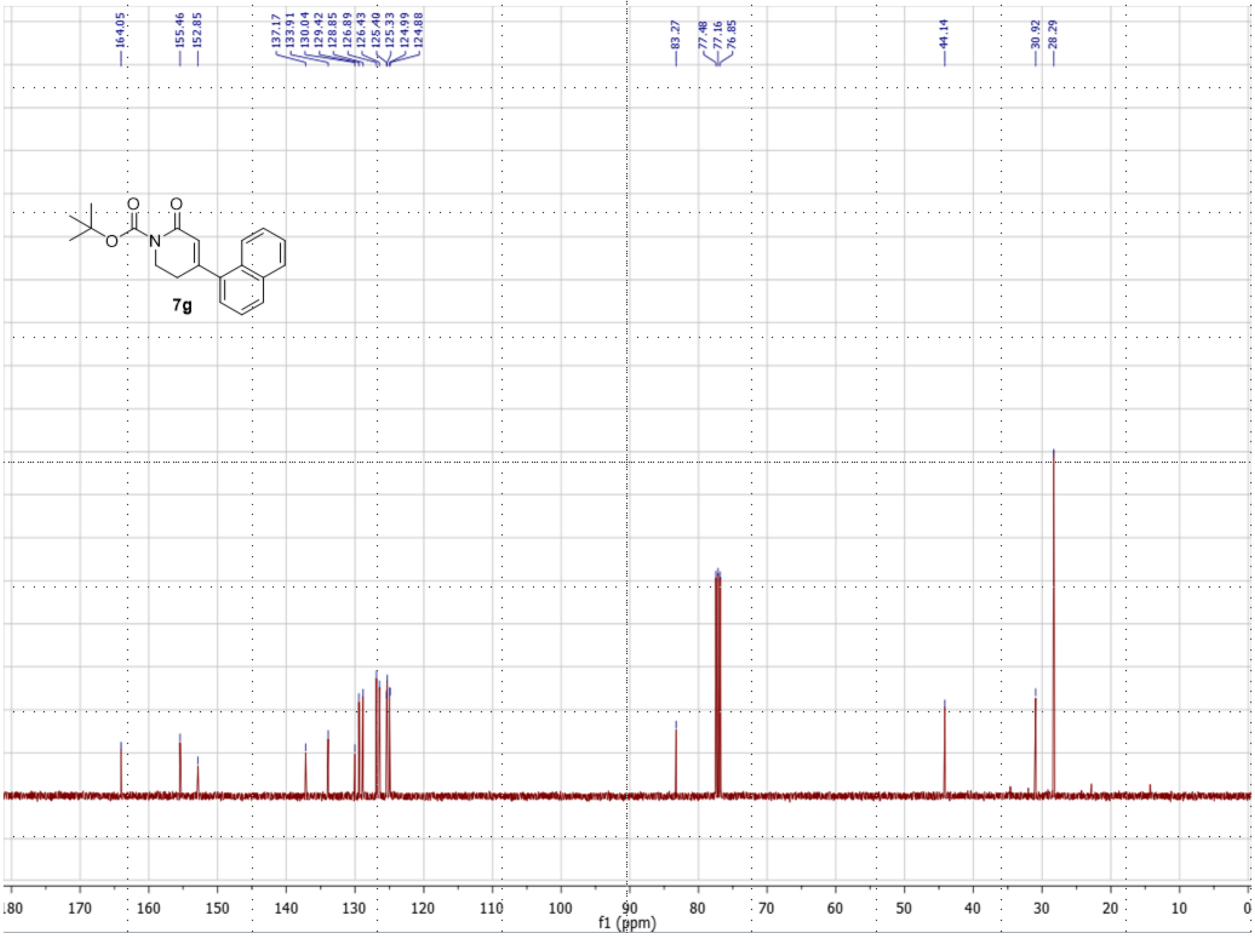
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76.85
44.14
30.92
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O
O
N
7g
180
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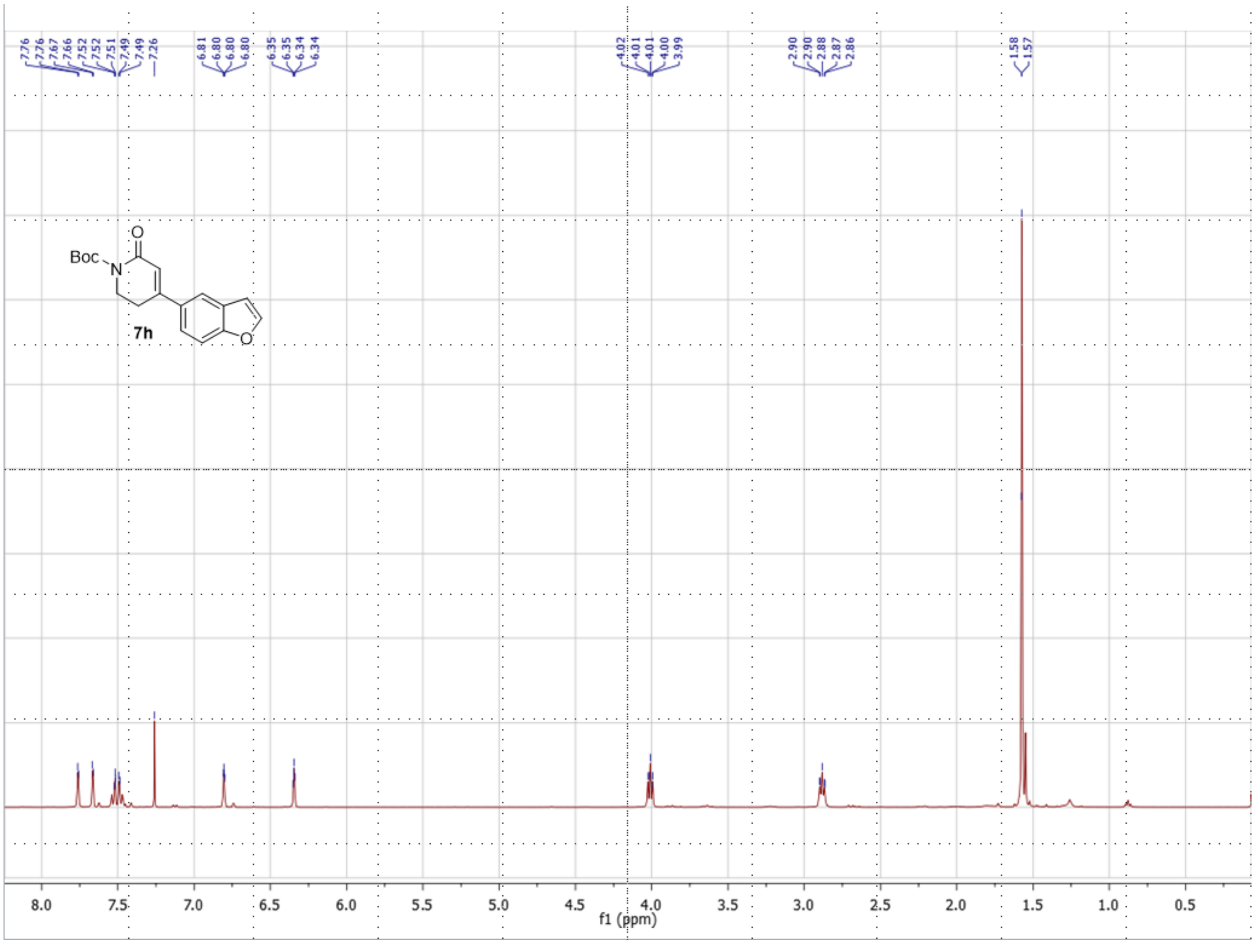
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6.34
6.34
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4.01
4.00
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2.90
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1.57
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6.0
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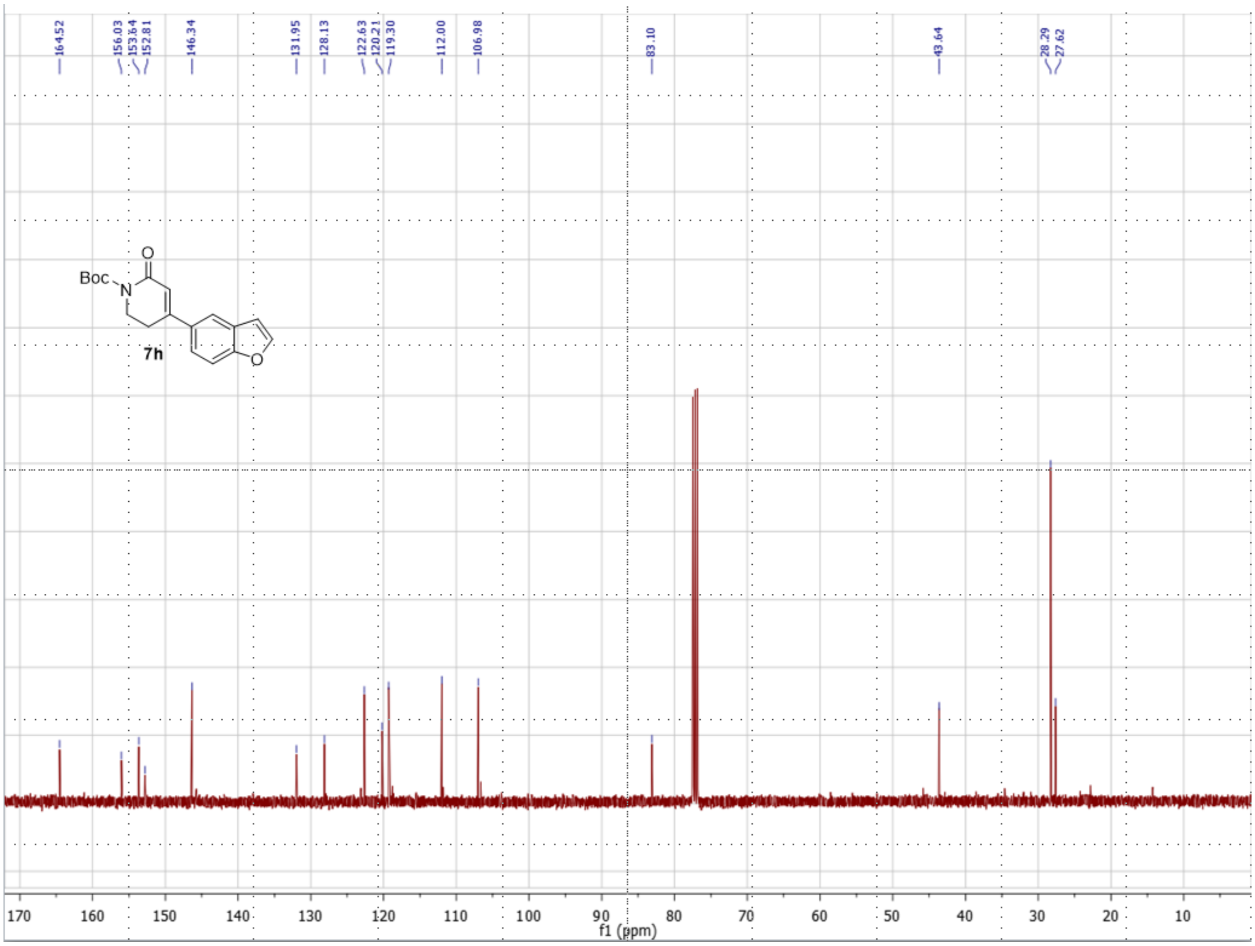
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43.64
28.29
27.62
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O
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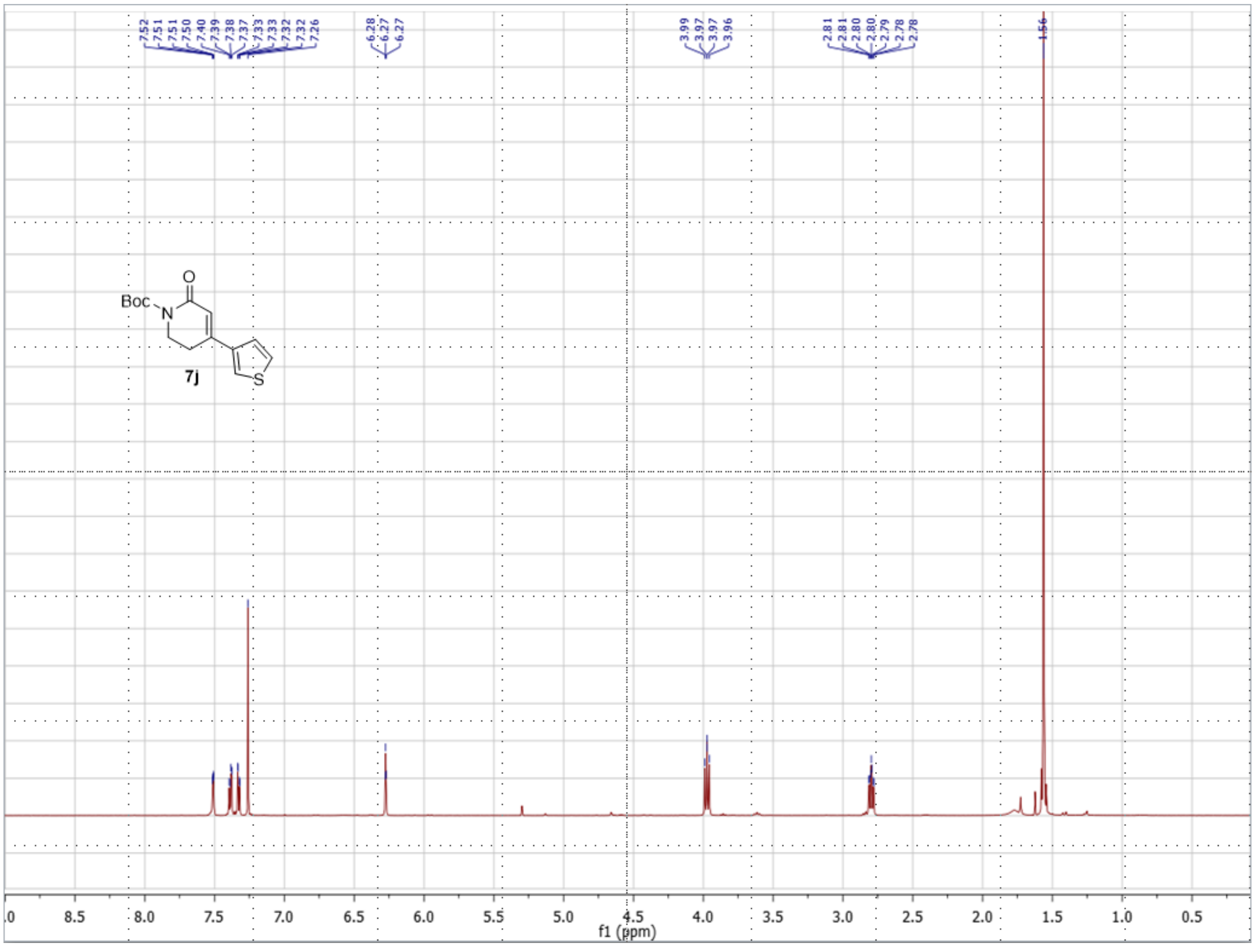
f1 (ppm)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6.27
6.27
3.99
3.97
3.97
3.96
2.81
2.81
2.80
2.80
2.79
2.78
2.78
1.56
Boc
N
O
S
7j
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8.0
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6.5
6.0
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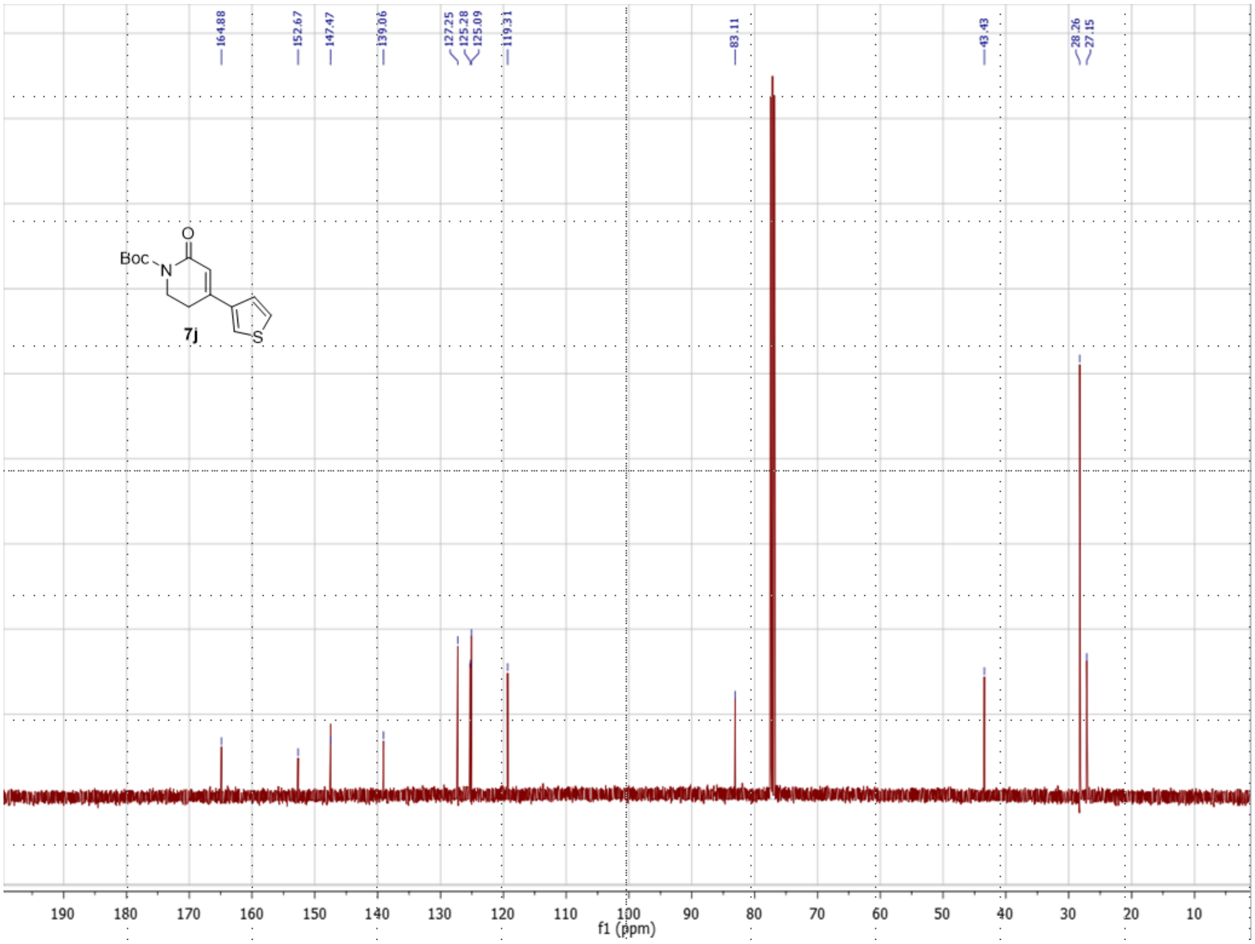
f1 (ppm)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O
S
7j
190
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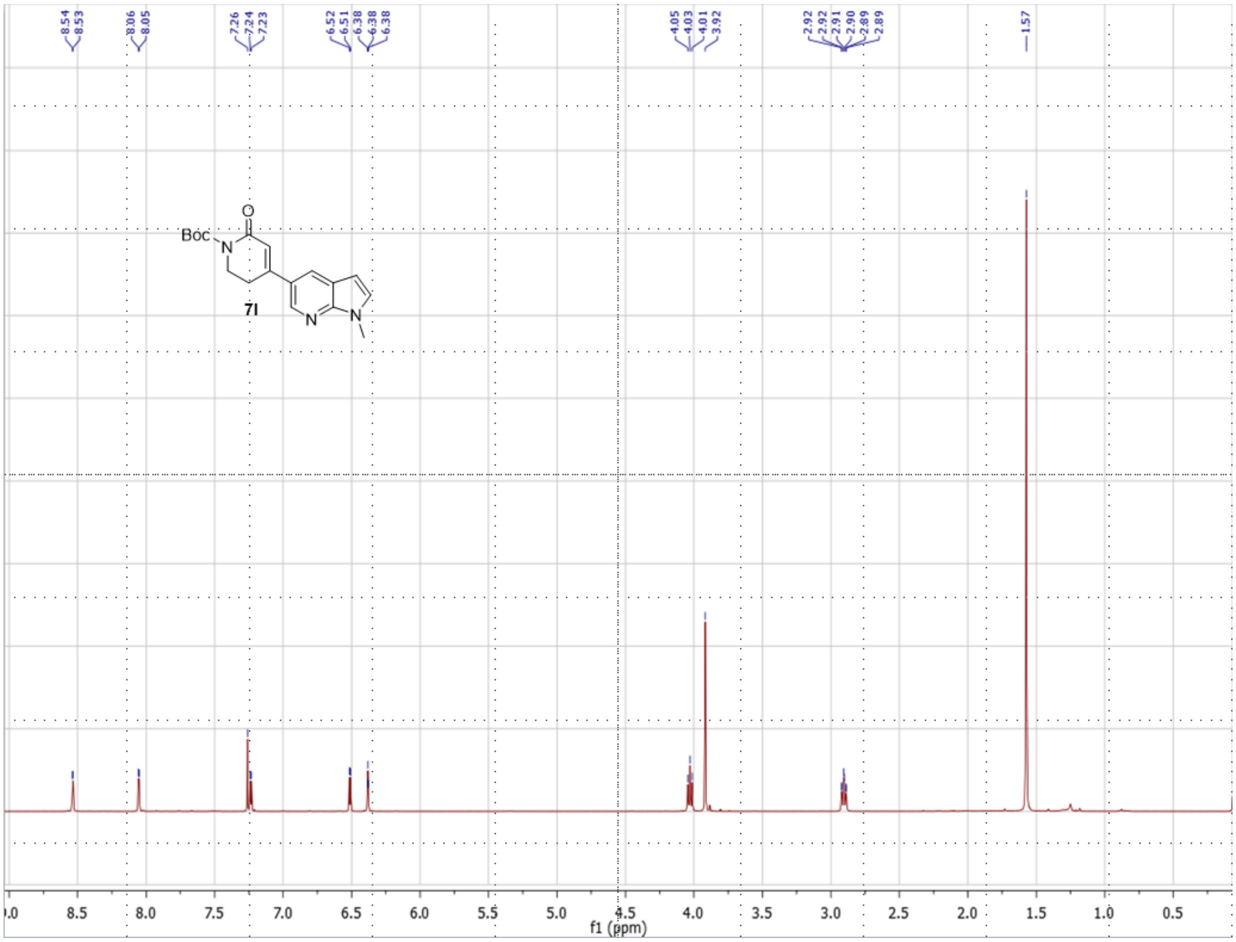
f1 (ppm)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4.05
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4.01
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2.89
1.57
Boc
O
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N
N
7l
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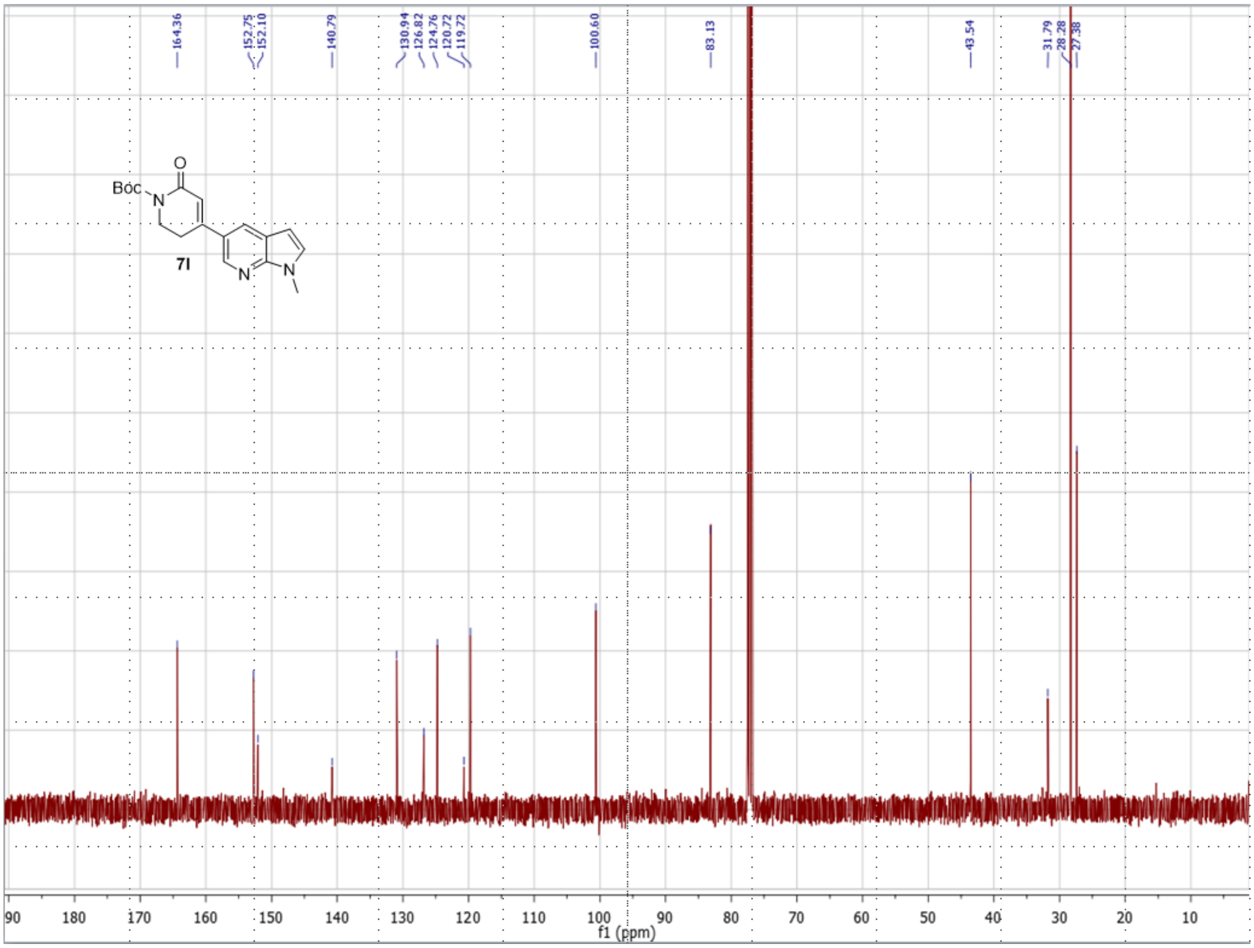
f1 (ppm)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27.38
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N
N
7l
190
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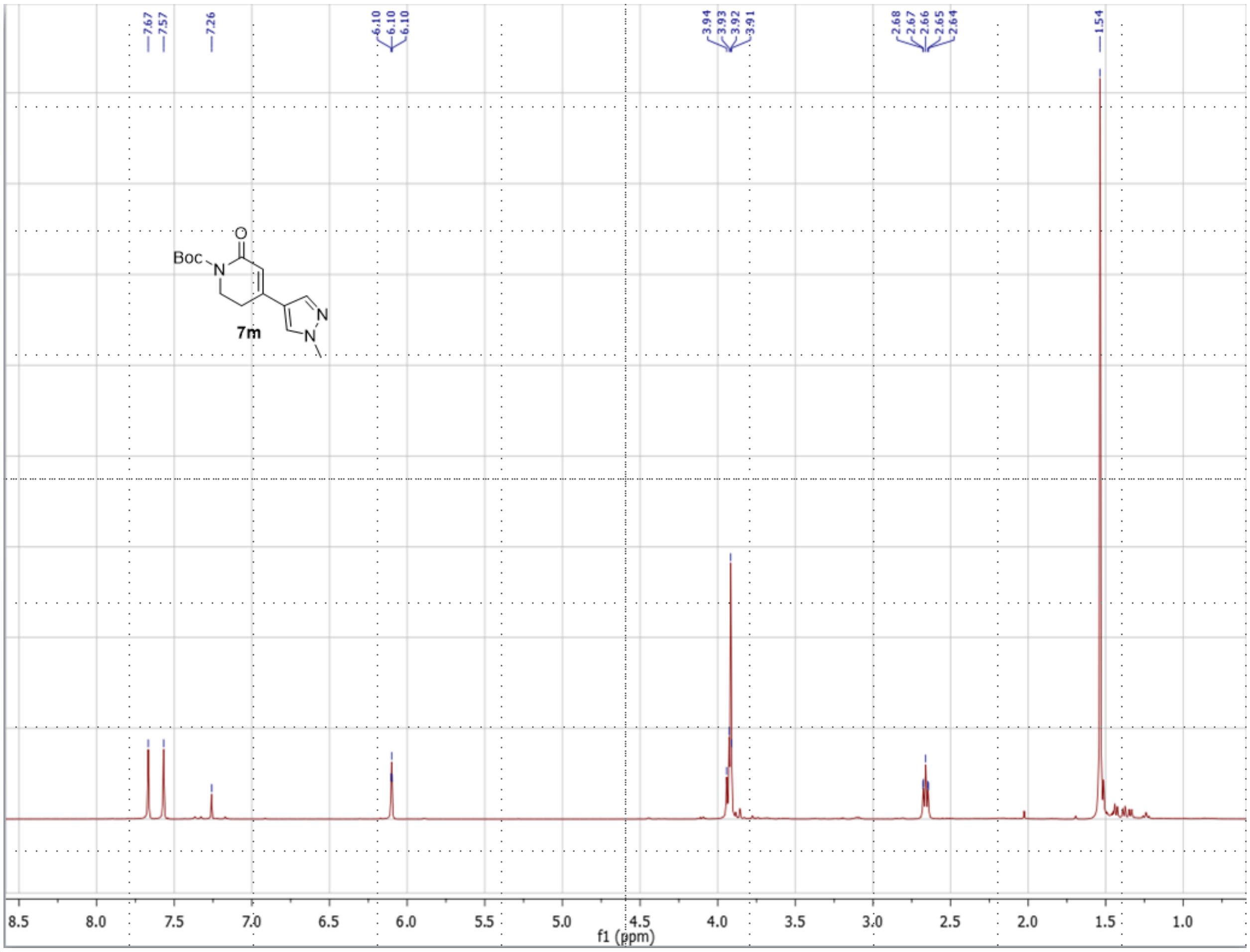
f1 (ppm)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1.54
Boc
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N
7m
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7.0
6.5
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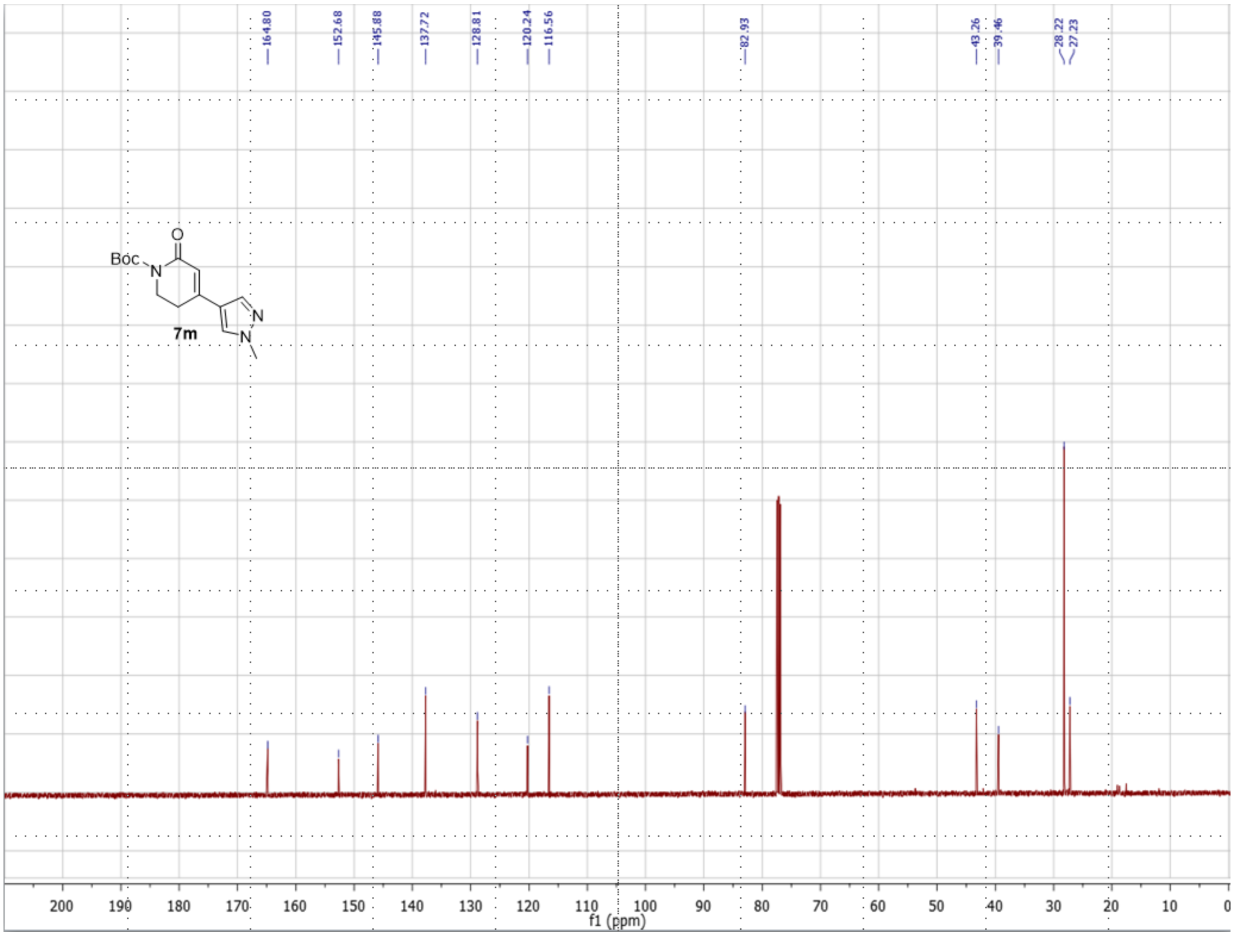
1.0
f1 (ppm)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O
N
N
7m
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190
180
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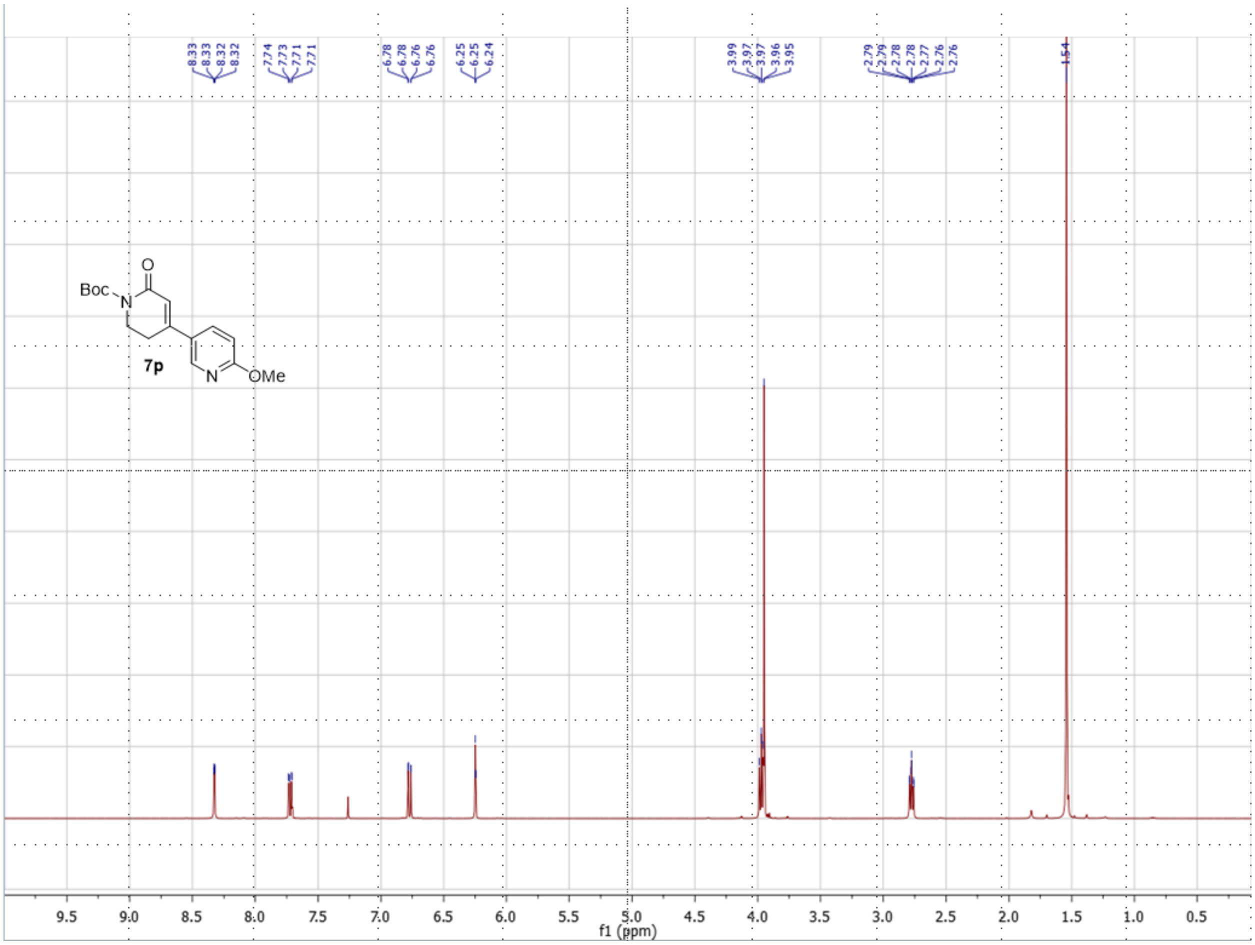
f1 (ppm)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6.25
6.24
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3.97
3.96
3.95
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2.79
2.78
2.78
2.77
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2.76
1.54
Boc
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O
N
OMe
7p
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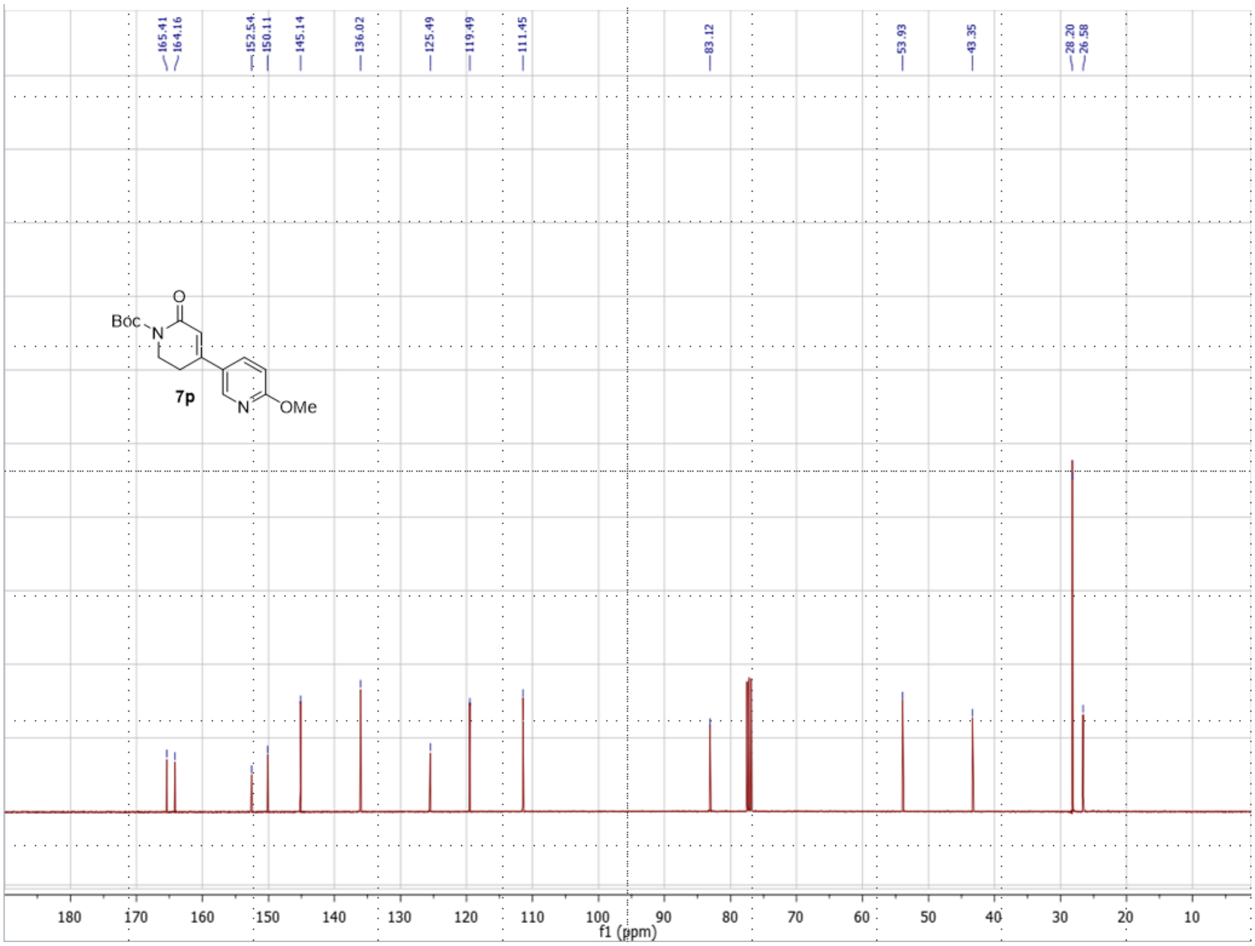
f1 (ppm)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26.58
Boc
N
O
N
OMe
7p
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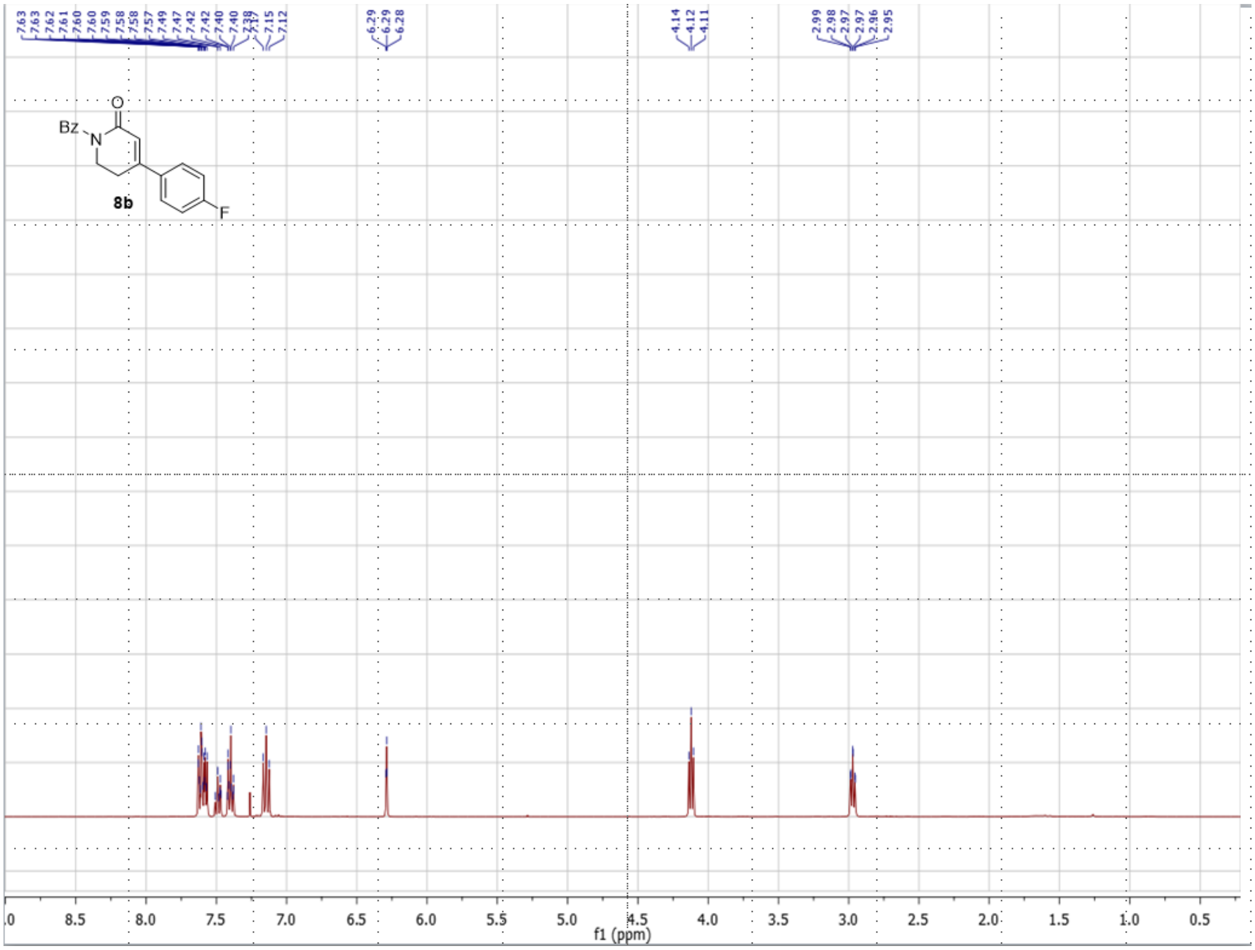
f1 (ppm)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7.38
7.17
7.15
7.12
6.29
6.29
6.28
4.14
4.12
4.11
2.99
2.98
2.97
2.97
2.96
2.95
Bz
N
O
F
8b
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7.0
6.5
6.0
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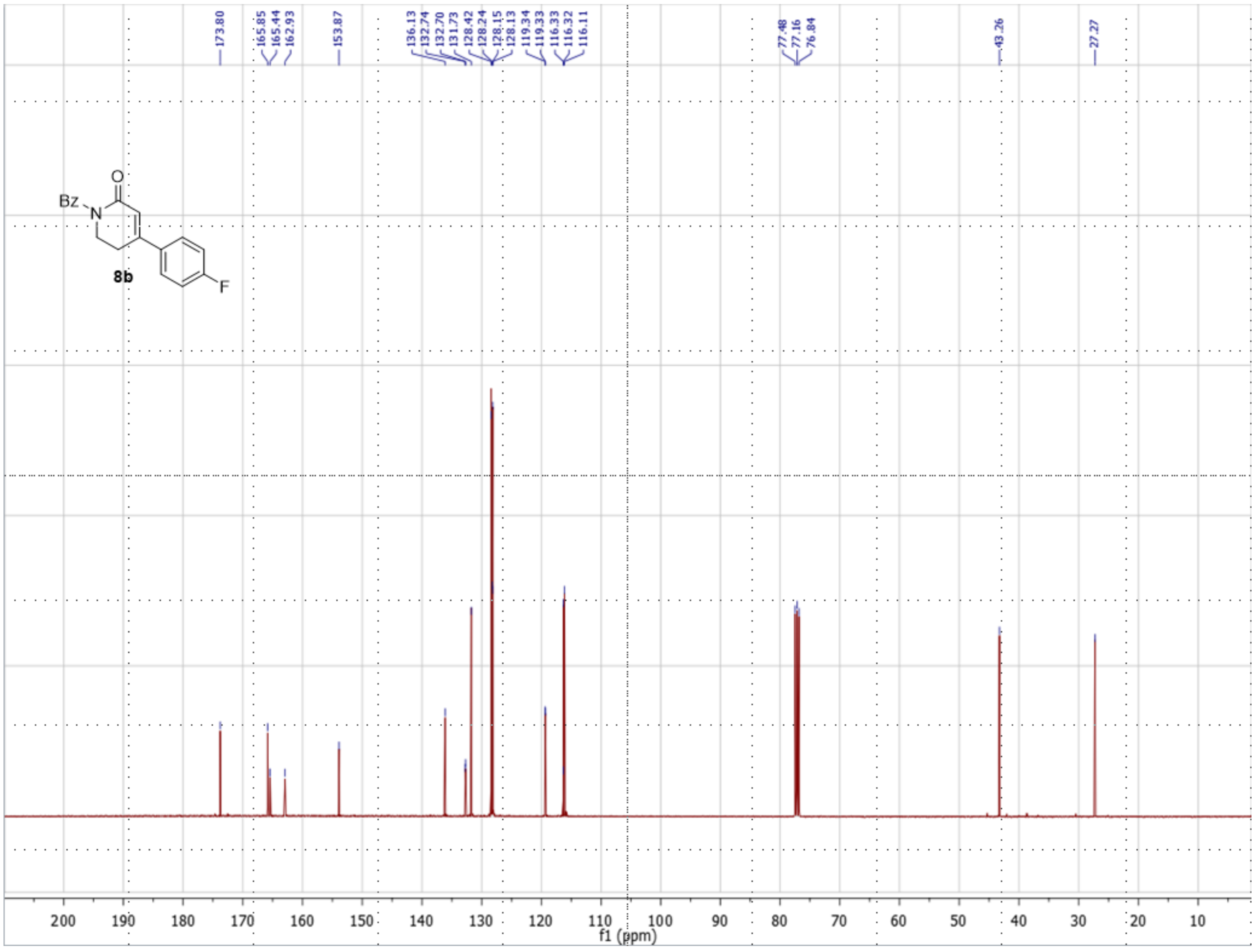
f1 (ppm)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77.48
77.16
76.84
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27.27
Bz
N
O
F
8b
200
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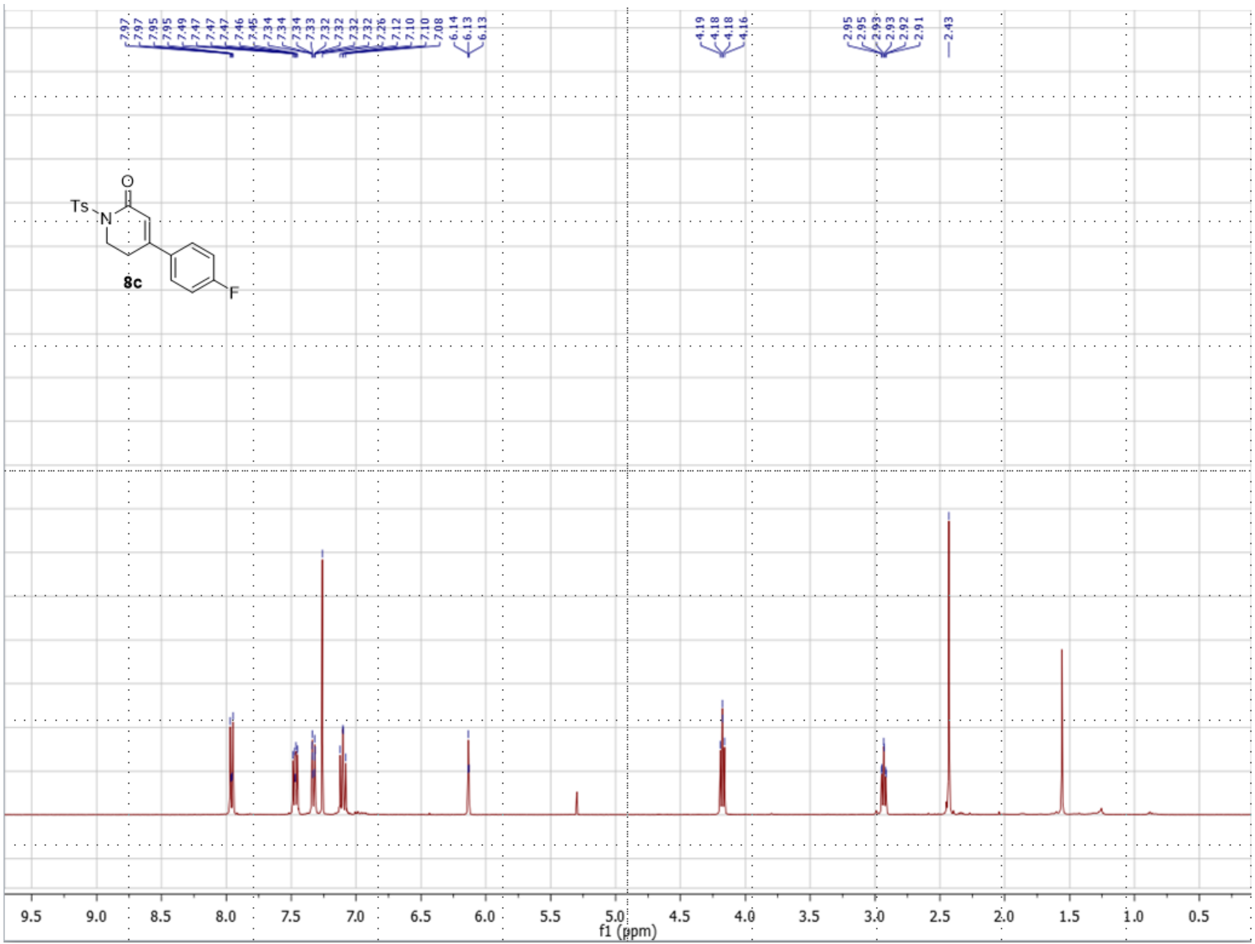
f1 (ppm)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4.16
2.95
2.95
2.93
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2.91
2.43
Ts
N
O
F
8c
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6.5
6.0
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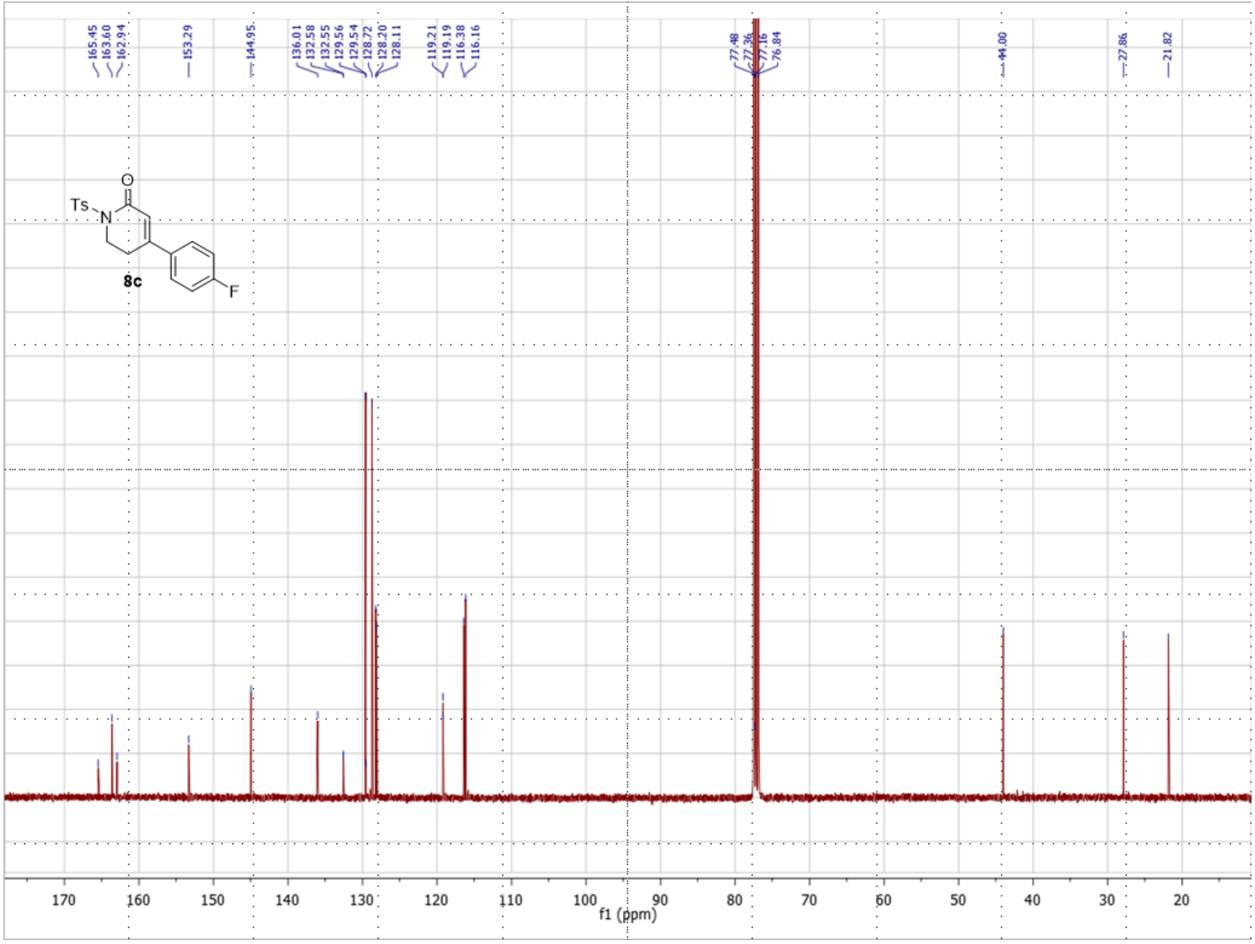
f1 (ppm)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77.16
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44.00
27.86
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Ts
N
O
F
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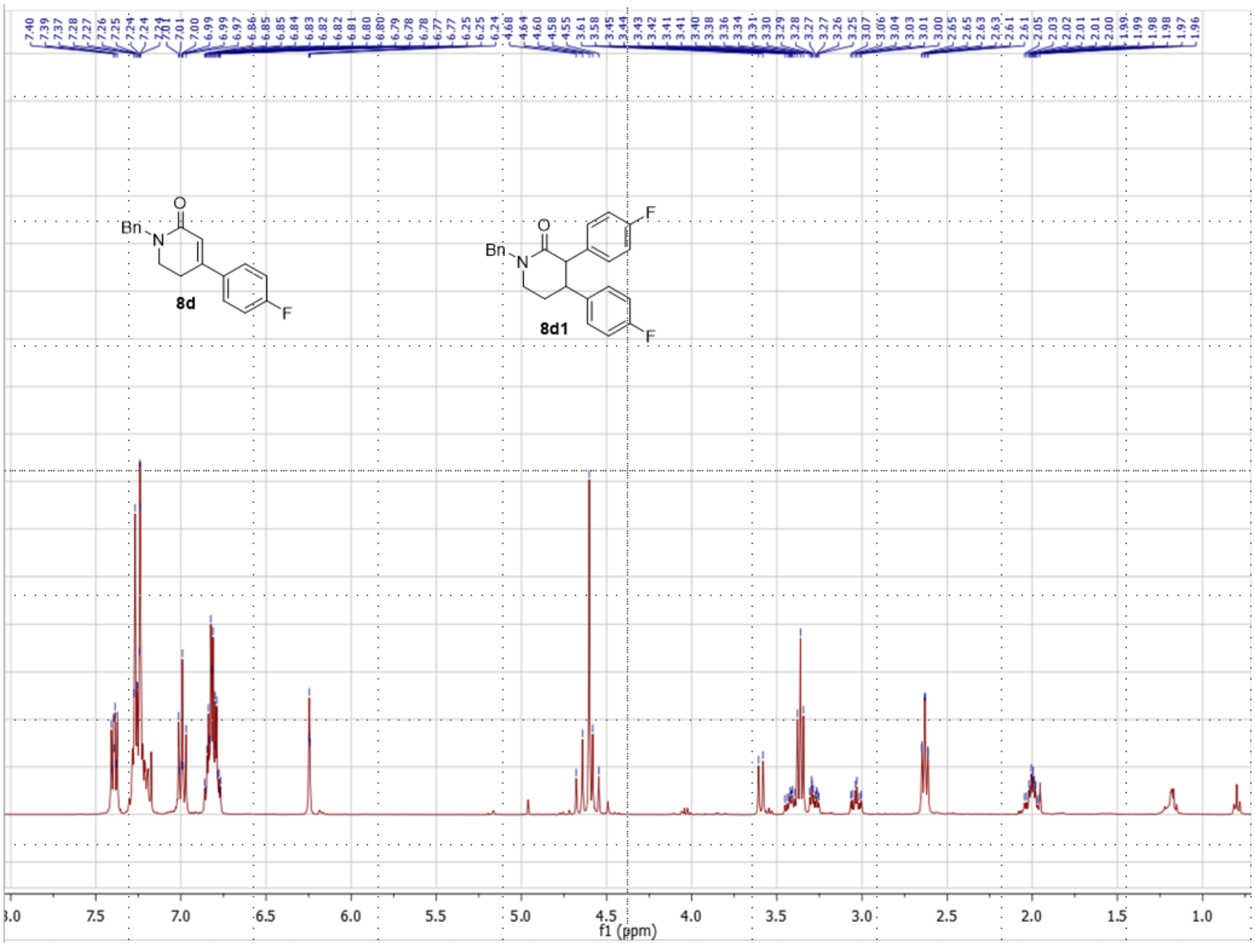
f1 (ppm)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Bn
N
O
F
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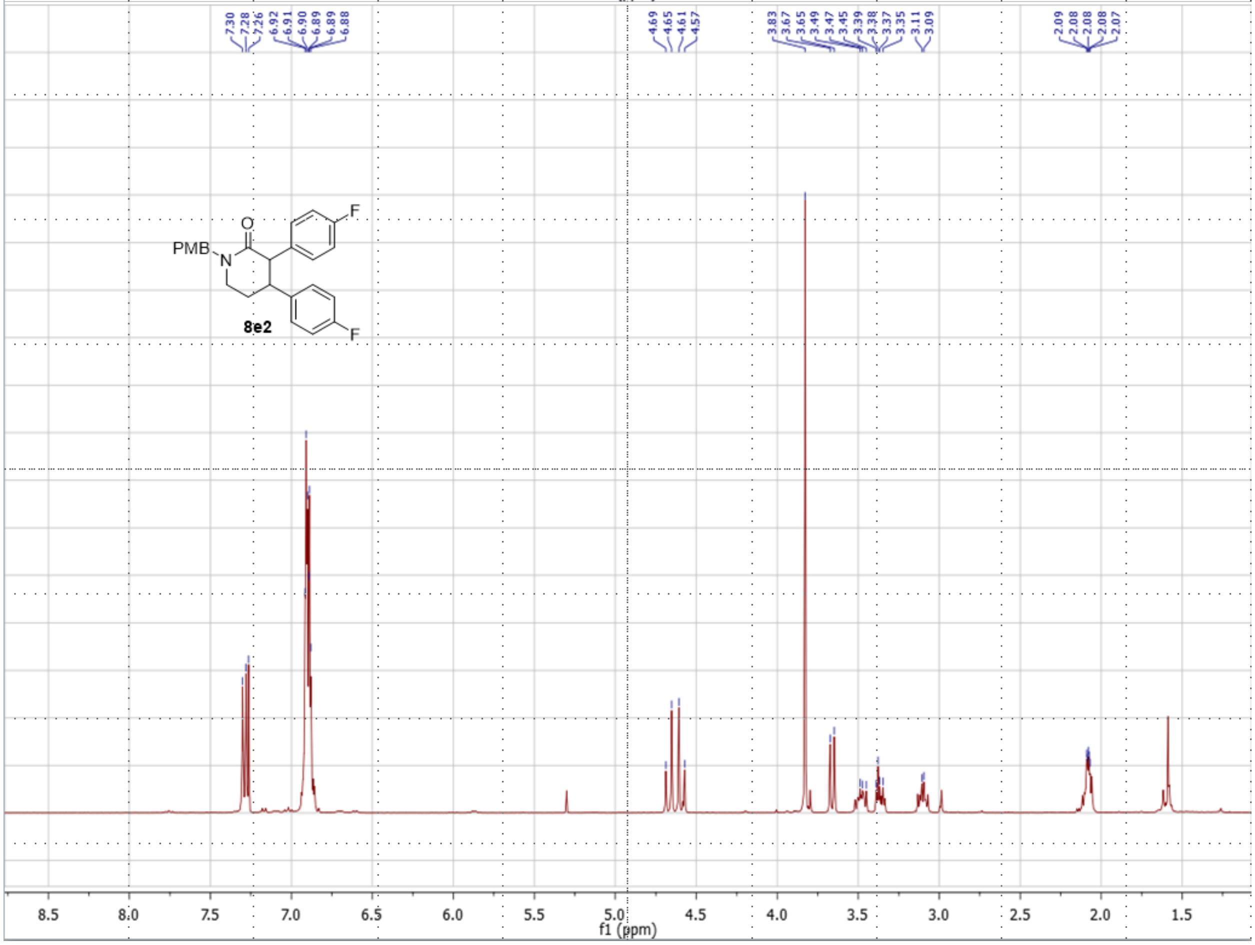
f1 (ppm)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2.09 2.08 2.08 2.08 2.07
PMB
N
O
F
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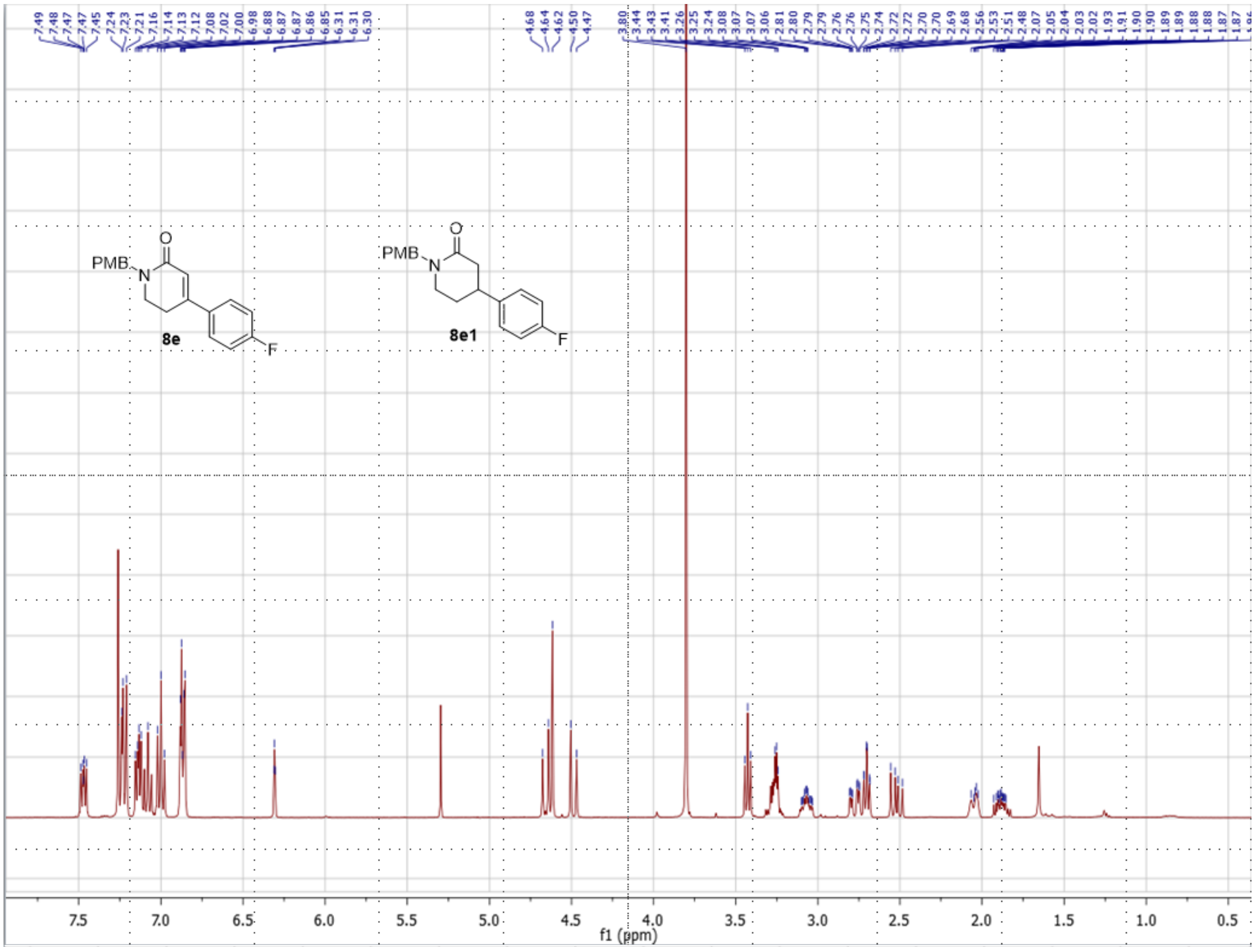
f1 (ppm)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4.68 4.64 4.62 4.50 4.47
3.80 3.44 3.43 3.41 3.26 3.25 3.24 3.08 3.07 3.07 3.06 2.81 2.80 2.79 2.79 2.76 2.75 2.74 2.72 2.72 2.70 2.70 2.69 2.68 2.56 2.53 2.51 2.48 2.07 2.05 2.04 2.03 2.02 1.93 1.91 1.90 1.89 1.89 1.88 1.88 1.87 1.87
PMB
N
O
F
8e
8e1
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6.0
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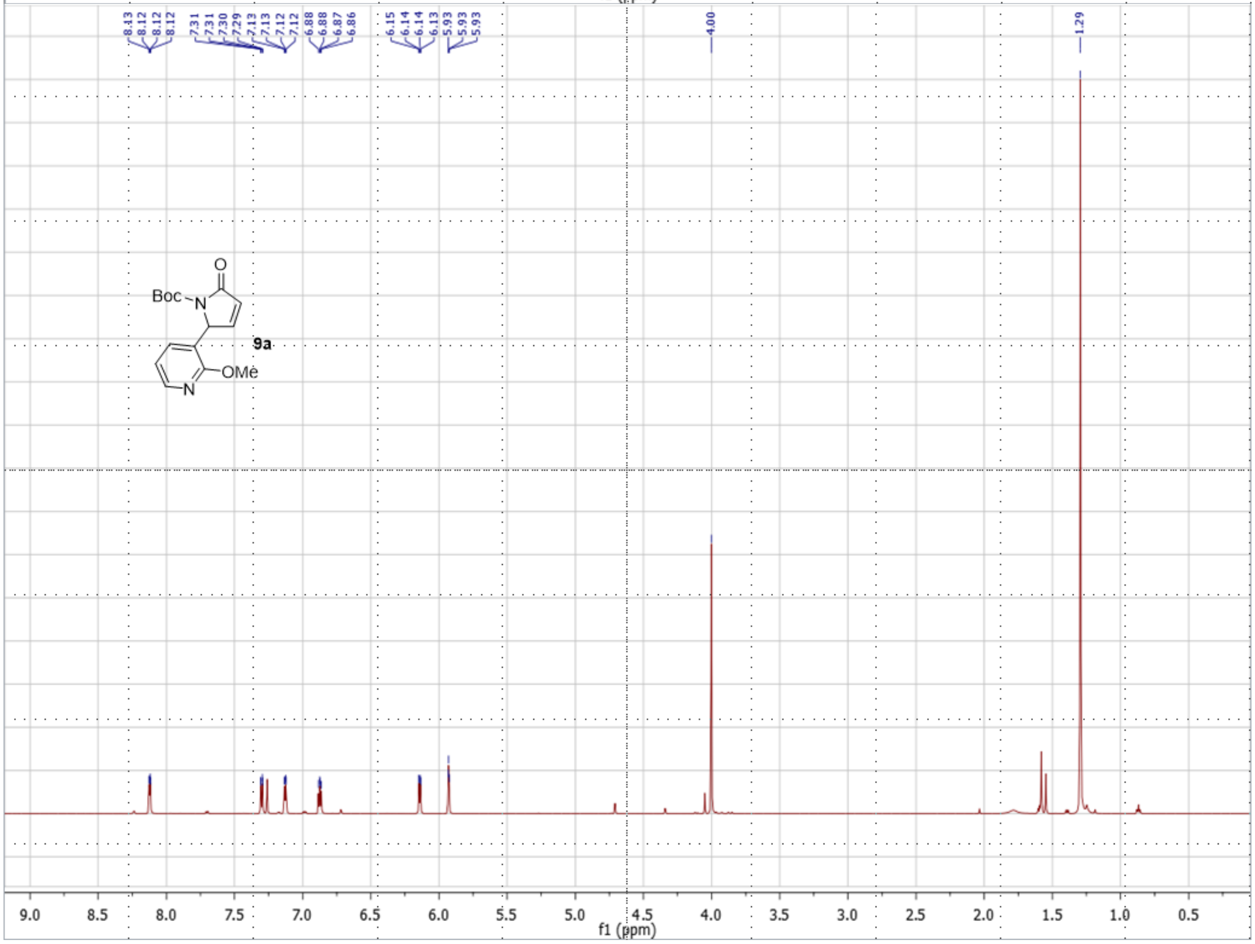
f1 (ppm)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4.00
1.29
Boc
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O
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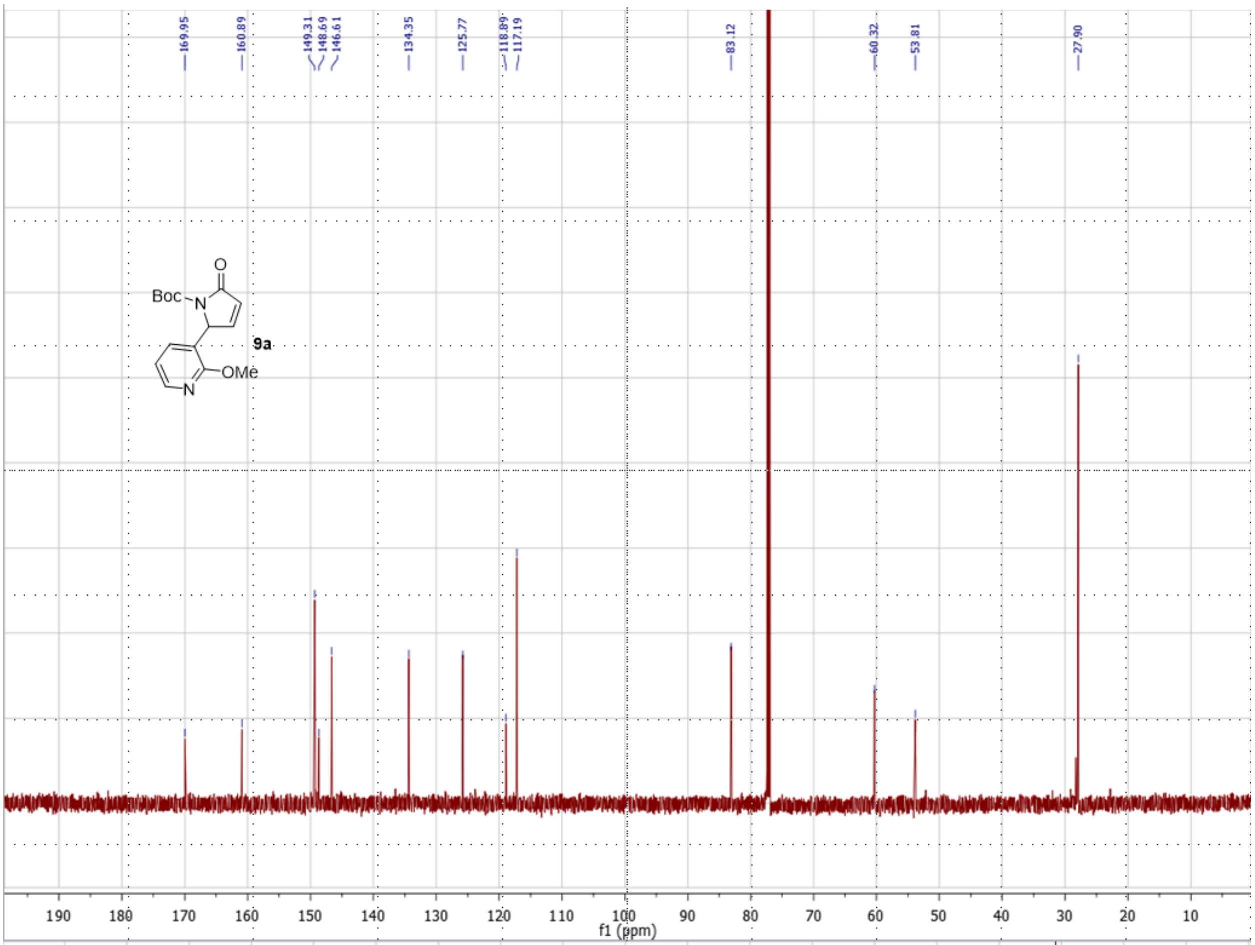
f1 (ppm)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27.90
Boc
N
O
OMe
N
190
180
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100
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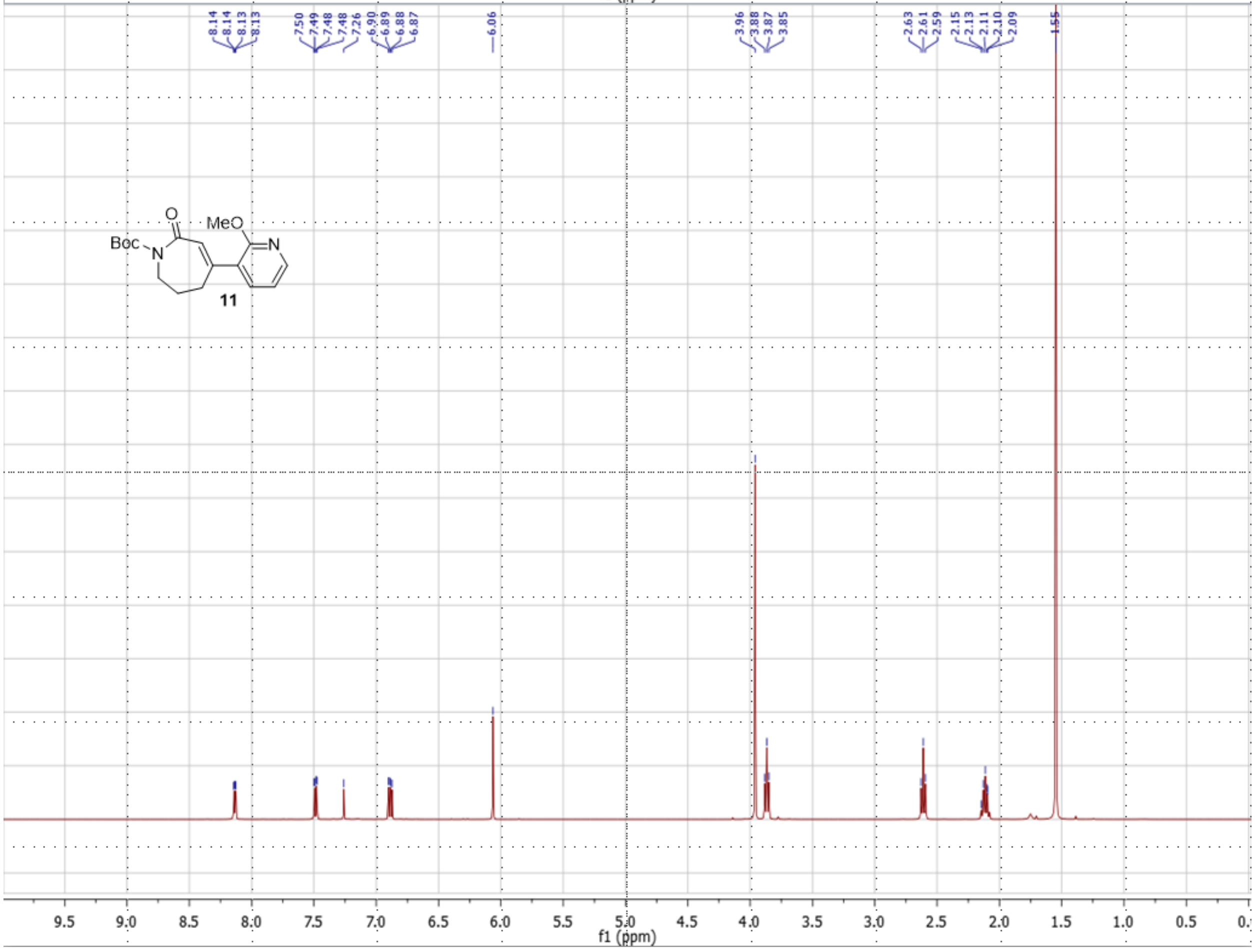
50
40
30
20
10
f1 (ppm)

9a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3.85
2.63
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2.59
2.15
2.13
2.11
2.10
2.09
1.55
Boc
N
O
MeO
N
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8.0
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1.0
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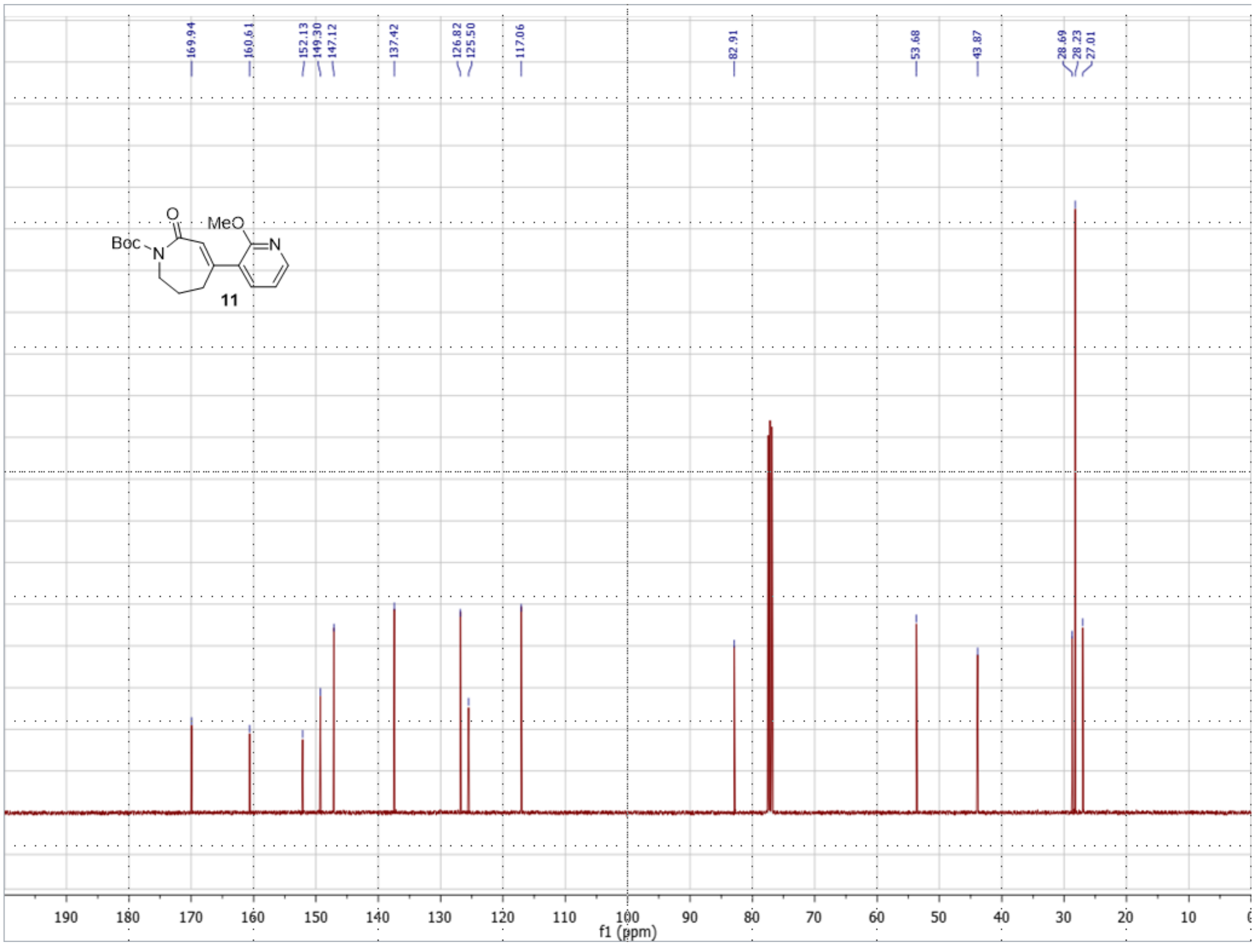
0.
f1 (ppm)

11



VI. References

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2. Pineschi, M.; Del Moro, F.; Gini, F.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004,** (10), 1244-1245.
3. Dake, G. R.; Fenster, M. D. B.; Hurley, P. B.; Patrick, B. O. *J. Org. Chem.* **2004,** *69* (17), 5668-5675.
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6. Álvarez, S.; Domínguez, G.; Gradillas, A.; Pérez-Castells, J. *Eur. J. Org. Chem.* **2013,** *2013* (15), 3094-3102.