Ligand Promoted *meta*-C–H Chlorination of Anilines and Phenols

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1. General Information

Solvents

Dry toluene, tetrahydrofuran, acetonitrile, cyclohexane, 1,4-dioxane, benzonitrile, and dimethylformamide were purchased from Sigma-Aldrich. Chloroform-d_1 and DMSO-$d_6$were purchased from Cambridge Isotope Laboratories.

Chromatography

Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light and Vogel's permanganate.

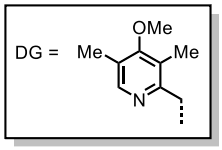
Spectroscopy and Instruments

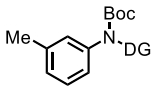
^{1}H NMR was recorded on Bruker DRX-600 instrument (600 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to 7.26 ppm of chloroform-*d* or referenced to the center line of a septet at 2.50 ppm of DMSO-d_6. ^{13}C NMR spectra were recorded on Bruker DRX-600 instrument (150 MHz), and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to either the center line of a triplet at 77.0 ppm of chloroform-*d* or referenced to the center line of a septet at 39.52 ppm of DMSO-d_6. ^{19}F NMR spectra were recorded on Bruker AMX-400 instrument (376 MHz), and were fully decoupled by broad band proton decoupling. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, sep = septet, m = multiplet, br = broad. Coupling constants, *J*, were reported in Hertz unit (Hz). High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

Starting materials

All substrates were used as received from commercial suppliers, unless otherwise stated. $Pd(PhCN)_2Cl_2$ and Ag_2CO_3 were purchased from Sigma-Aldrich. Methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate (NBE-CO_2Me) was synthesized following literature procedures.[1]

2. Substrate Structures





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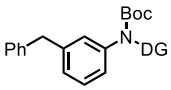

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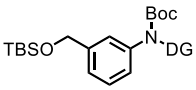

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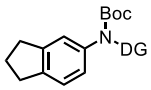

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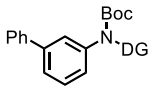

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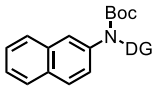

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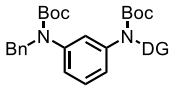

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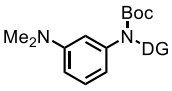

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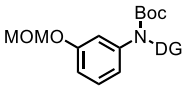

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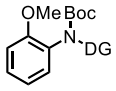

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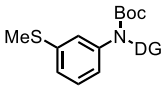

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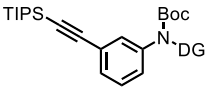

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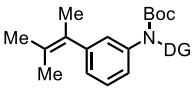

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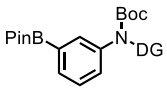

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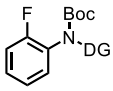

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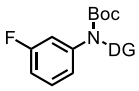

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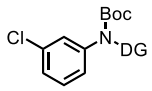

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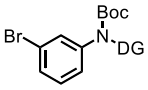

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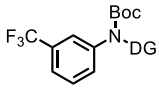

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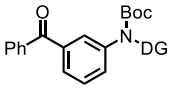

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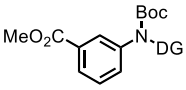

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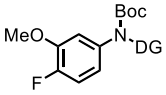

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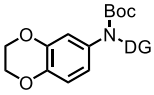

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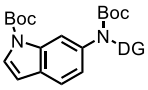

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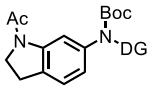

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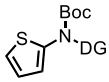

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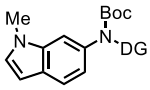

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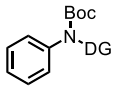

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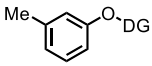

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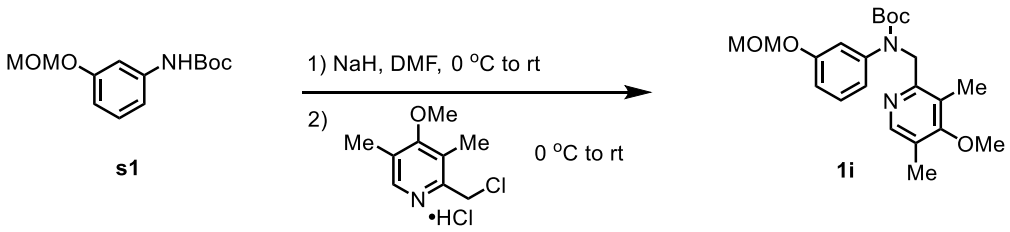
3. Experimental Section

3.1 Preparation of Substrates

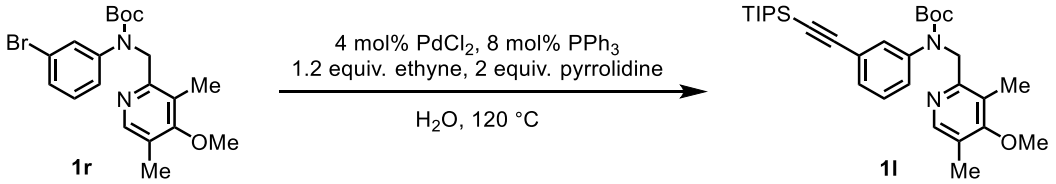
Substrates **2a**–**2h**, **2j**, **2k**, **2o**–**2ab**, and **3** were synthesized following the literature procedures.[2]



***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-(methoxymethoxy)phenyl)carbamate (1i)**

To a solution of *tert*-butyl (3-(methoxymethoxy)phenyl)carbamate **s1** (557 mg, 2.2 mmol, 1.1 equiv.) in DMF (10 mL) was added NaH (240 mg, 6 mmol, 3 equiv.) at 0 °C, and the resulting mixture was allowed to warm up to room temperature and stirred for 30 min. The mixture was cooled to 0 °C again, then 2-chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride (442 mg, 2 mmol, 1 equiv.) was added into the mixture slowly. The resulting mixture was allowed to warm up to room temperature and stirred for another 12 hours. After the reaction completed, EtOAc was added to dilute the reaction mixture, then the organic phase was washed with water, brine and dried over Na_2SO_4. After the organic solvent was concentrated by rotatory evaporation, the residue was purified by silica gel chromatography (hexanes/EtOAc = 5:1 v/v to 2:1 v/v) to afford 762 mg of compound **1i** as a yellow liquid (95% yield). R*f* = 0.30 (hexanes/EtOAc = 2:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.94 (s, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.79 (ddd, *J* = 8.4 Hz, *J* = 7.8 Hz, *J* = 3.0 Hz, *J* = 1.2 Hz, 1H), 5.09 (s, 2H), 4.89 (s, 2H), 3.72 (s, 3H), 3.42 (s, 3H), 2.20 (s, 6H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.61, 157.10, 154.97, 154.59, 148.91, 143.94, 128.83, 124.59, 123.64, 119.88, 114.84, 113.23, 94.45, 80.31, 59.79, 55.85, 53.41, 28.20, 13.16, 10.35. HRMS (ESI-TOF) *m/z* calc'd for $C_{22}H_{31}N_2O_5$ $[M+H]^+$: 403.2227; found: 403.2230.

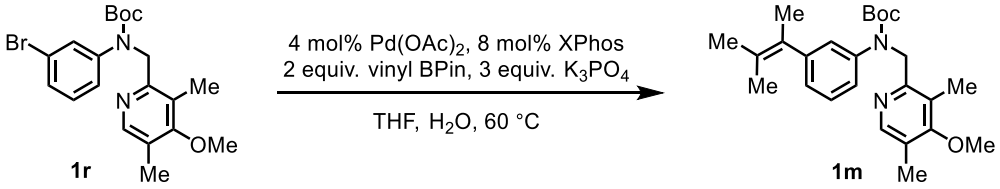


***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-((triisopropylsilyl)ethynyl)phenyl)carbamate (1l)**.

Aryl bromide **1r** (210 mg, 0.5 mmol, 1 equiv.), $PdCl_2$ (3.5 mg, 20 μmol, 4 mol%), and PPh_3 (10.5 mg, 40 μmol, 8 mol%) were added to a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. H_2O (2 mL), pyrrolidine (83.5 μL, 1 mmol, 2 equiv.), and ethynyltriisopropylsilane (137 μL, 0.6 mmol, 1.2 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 120 °C. After 2 h, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried with Na_2SO_4. After the organic solvent was concentrated by rotatory evaporation, the residue was purified by silica gel chromatography (hexanes/EtOAc = 8:1 v/v to 4:1 v/v) to afford 183 mg of compound **1l** as a yellow liquid (70% yield). R*f* = 0.66 (hexanes/EtOAc = 2:1 v/v).

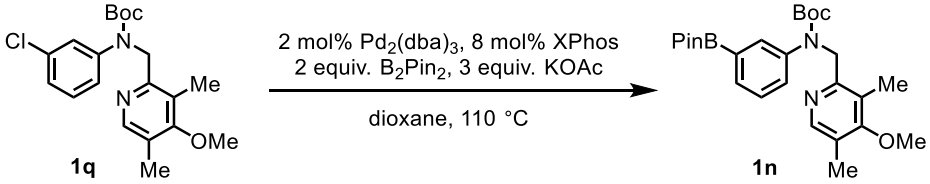
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.30 (s, 1H), 7.23–7.18 (m, 2H), 7.15 (t, *J* = 7.8 Hz, 1H), 4.90 (s, 2H), 3.72 (s, 3H), 2.20 (s, 6H), 1.40 (s, 9H), 1.10 (s, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.72, 154.79, 154.55, 148.97, 142.63, 130.10, 129.26, 128.19, 126.95, 124.75, 123.81, 123.59, 106.77, 90.37, 80.52, 59.83,

53.23, 26.21, 18.62, 13.17, 11.27, 10.43. HRMS (ESI-TOF) *m/z* calc'd for $C_{31}H_{47}N_2O_3Si$ $[M+H]^+$: 523.3350; found: 523.3347.



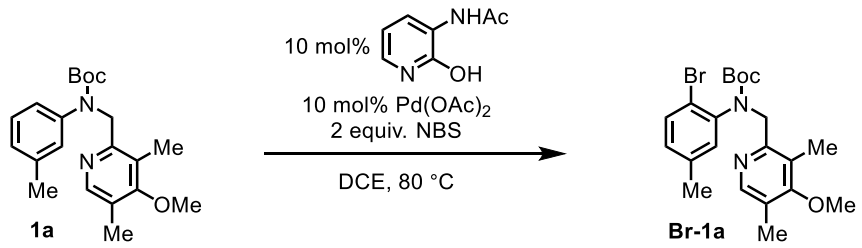
***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-(3-methylbut-2-en-2-yl)phenyl)carbamate (1m).**

Aryl bromide **1r** (210 mg, 0.5 mmol, 1 equiv.), $Pd(OAc)_2$ (4.5 mg, 20 μmol, 4 mol%), XPhos (19 mg, 40 μmol, 8 mol%), and aqueous K_3PO_4 (0.5 M, 3 mL, 1.5 mmol, 3 equiv.) were added to a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. THF (5 mL) and 4,4,5,5-tetramethyl-2-(3-methylbut-2-en-2-yl)-1,3,2-dioxaborolane (0.22 mL, 1 mmol, 2 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 60 °C. After 2 h, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried with Na_2SO_4. After the organic solvent was concentrated by rotatory evaporation, the residue was purified by silica gel chromatography (hexanes/EtOAc = 8:1 v/v to 2:1 v/v) to afford 193 mg of compound **1m** as a yellow liquid (94% yield). R*f* = 0.58 (hexanes/EtOAc = 2:1 v/v).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.88 (s, 1H), 6.85 (d, *J* = 7.4 Hz, 1H), 4.93 (s, 2H), 3.71 (s, 3H), 2.20 (s, 3H), 2.18 (s, 3H), 1.85 (s, 3H), 1.75 (s, 3H), 1.46 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.66, 155.18, 154.77, 148.88, 145.37, 142.04, 129.60, 127.91, 127.18, 127.11, 125.70, 124.63, 124.06, 123.70, 80.10, 59.78, 53.53, 28.27, 21.96, 20.62, 20.43, 13.15, 10.46. HRMS (ESI-TOF) *m/z* calc'd for $C_{25}H_{35}N_2O_3$ $[M+H]^+$: 411.2642; found: 411.2640.



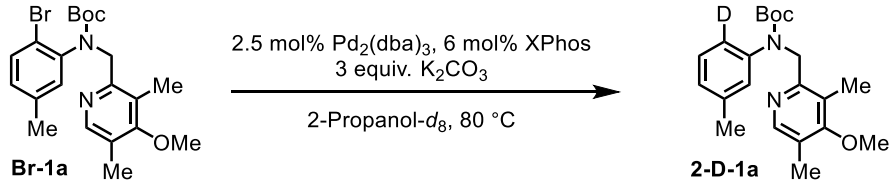
***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (1n).**

Aryl chloride **1q** (113 mg, 0.3 mmol, 1 equiv.), $Pd_2(dba)_3$ (5.5 mg, 6.0 μmol, 2 mol%), XPhos (11.4 mg, 24 μmol, 8 mol%), KOAc (88.3 mg, 0.9 mmol, 3 equiv.), and B_2Pin_2 (229 mg, 0.9 mmol, 3 equiv.) were added to a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Dioxane (1 mL) was added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 110 °C. After 1 h, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was poured into water (5 mL) and extracted with EtOAc (3 × 7 mL). The combined organic layers were dried with Na_2SO_4. After the solvent was concentrated by rotatory evaporation, the residue was purified by silica gel chromatography (hexanes/EtOAc = 4:1 v/v) to afford 77.3 mg of compound **1n** as a yellow liquid (55% yield). R*f* = 0.44 (hexanes/EtOAc = 2:1 v/v).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.60 (s, 1H), 7.54 (d, *J* = 7.3 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 4.92 (s, 2H), 3.71 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 1.39 (s, 9H), 1.31 (s, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.69, 155.17, 154.78, 148.88, 142.09, 132.79, 132.10, 130.03, 127.80, 124.62, 123.97, 83.71, 80.18, 59.81, 53.42, 28.25, 24.85, 13.16, 10.51. HRMS (ESI-TOF) *m/z* calc'd for $C_{26}H_{38}BN_2O_5$ $[M+H]^+$: 469.2868; found: 469.2858.



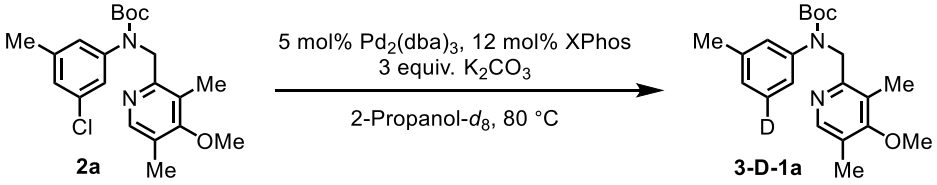
***tert*-Butyl (2-bromo-5-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (Br-1a).** Arene **1a** (1.07 g, 3 mmol, 1 equiv.), $Pd(OAc)_2$ (67.2 mg, 0.3 mmol, 10 mol%), *N*-(2-hydroxypyridin-3-yl)acetamide (45.6 mg, 0.3 mmol, 10 mol%), and NBS (1.07 g, 6 mmol, 2 equiv.) were added to a flame-dried Schlenk tube. DCE (30 mL) was added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 80 °C. After 14 h, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 15 mL). The filtrate was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/EtOAc = 6:1 v/v to 4:1 v/v) to afford 811 mg of compound **Br-1a** as a white solid (62% yield). R*f* = 0.54 (hexanes/EtOAc = 2:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.15 (s, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 4.86 (s, 2H), 3.73 (s, 3H), 2.30 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.70, 154.80, 154.48, 148.98, 142.00, 137.76, 131.96, 128.64, 125.54, 124.76, 123.68, 121.35, 80.53, 59.86, 53.32, 28.22, 22.93, 13.22, 10.39. HRMS (ESI-TOF) *m/z* calc'd for $C_{21}H_{28}BrN_2O_3$ $[M+H]^+$: 435.1278; found: 435.1275.



***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-methylphenyl-6-*d*)carbamate (2-D-1a).** Aryl bromide **Br-1a** (610 mg, 1.4 mmol, 1 equiv.), $Pd_2(dba)_3$ (32.1 mg, 35 μmol, 2.5 mol%), XPhos (40.1 mg, 84 μmol, 6 mol%), and K_2CO_3 (580 mg, 4.2 mmol, 3 equiv.) were added to a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. 2-Propanol-d_8 (4 mL) was added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 80 °C. After 14 h, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 8 mL). The filtrate was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/EtOAc = 8:1 v/v to 4:1 v/v) to afford 403 mg of compound **2-D-1a** as a white solid (81% yield). R*f* = 0.48 (hexanes/EtOAc = 2:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.06 (s, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 4.89 (s, 2H), 3.71 (s, 3H), 2.26 (s, 3H), 2.20 (s, 6H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.53, 155.10, 154.69, 148.82, 142.63, 137.84, 127.86, 126.87, 125.90 (t, *J* = 23.9 Hz), 124.48, 123.59, 123.41, 80.03, 59.73, 53.44, 28.16, 21.19, 13.10, 10.31. HRMS (ESI-TOF) *m/z* calc'd for $C_{21}H_{28}DN_2O_3$ $[M+H]^+$: 358.2235; found: 358.2230.

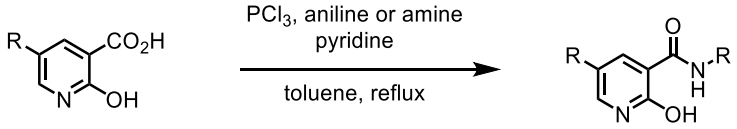


***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-methylphenyl-5-*d*)carbamate (3-D-1a).**

Aryl chloride **2a** (587 mg, 1.5 mmol, 1 equiv.), $Pd_2(dba)_3$ (68.7 mg, 75 μmol, 5 mol%), XPhos (85.9 mg, 180 μmol, 12 mol%), and K_2CO_3 (620 mg, 4.5 mmol, 3 equiv.) were added to a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. 2-Propanol-d_8 (4 mL) was added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 80 °C. After 24 h, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 8 mL). The filtrate was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/EtOAc = 15:1 v/v to 4:1 v/v) to afford 326 mg of compound **3-D-1a** as a white solid (61% yield). R*f* = 0.48 (hexanes/EtOAc = 2:1 v/v).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.06 (s, 1H), 7.01 (s, 1H), 6.91 (s, 1H), 4.90 (s, 2H), 3.72 (s, 3H), 2.27 (s, 3H), 2.20 (s, 6H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.64, 155.18, 154.79, 148.91, 142.68, 138.05, 127.79 (t, J = 24.6 Hz), 126.97, 126.21, 124.60, 123.73, 123.41, 80.17, 59.83, 53.52, 28.25, 21.34, 13.20, 10.41. HRMS (ESI-TOF) *m/z* calc'd for $C_{21}H_{28}DN_2O_3$ $[M+H]^+$: 358.2235; found: 358.2239.

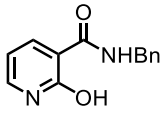
3.2 Preparation of Ligands

Ligand **6** was synthesized following the literature procedures.[3]



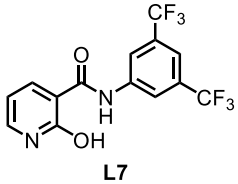
L5-L11

General procedure: Hydroxypyridine (1.65 mmol, 1.1 equiv) was added into a Schlenk tube. Toluene (5 mL), amine (1.5 mmol, 1.0 equiv), pyridine (1 drop) and PCl_3 (65 μL, 0.75 mmol, 0.5 equiv.) were added in sequence. The tube was sealed and immersed into a pre-heated oil bath at 115 °C. After 12 hours, the oil bath was removed, and the tube was allowed to cool to room temperature. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (5 × 15 mL). The combined organic layers were dried with Na_2SO_4. After the solvent was concentrated by rotatory evaporation, the residue was purified by silica gel chromatography to afford the desired ligands.



L5

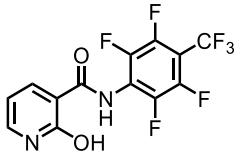
***N*-Benzyl-2-hydroxynicotinamide (L5)**
Purification by flash silica gel column chromatography (hexanes/EtOAc = 1:1 v/v to EA) afforded 0.203 g of compound **L5** as a white solid (59% yield). R*f* = 0.31 (EtOAc).
^{1}H NMR (600 MHz, DMSO-d_6) δ 12.51 (brs, 1H), 10.16 (t, *J* = 6.0 Hz, 1H), 8.41–8.30 (m, 1H), 7.71 (dd, *J* = 6.3, 2.2 Hz, 1H), 7.36–7.28 (m, 4H), 7.25 (t, *J* = 7.0 Hz, 1H), 6.49 (t, *J* = 6.6 Hz, 1H), 4.52 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 163.32, 162.32, 144.12, 139.50, 139.27, 128.44, 127.33, 126.91, 120.23, 106.34, 42.27. HRMS (ESI-TOF) *m/z* calc'd for $C_{13}H_{13}N_2O_2$ $[M+H]^+$: 229.0972; found: 229.0969.



L7

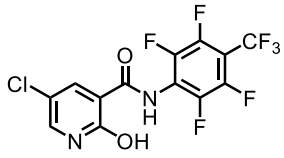
***N*-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxynicotinamide (L7)**

Purification by flash silica gel column chromatography (hexanes/EtOAc = 1:2 v/v) afforded 0.316 g of compound **L7** as a white solid (60% yield). R*f* = 0.21 (hexanes/EtOAc = 1:1 v/v).
^{1}H NMR (600 MHz, DMSO-d_6) δ 12.86 (brs, 1H), 12.62 (s, 1H), 8.49–8.39 (m, 1H), 8.39–8.27 (m, 2H), 7.90–7.80 (m, 1H), 7.79–7.67 (m, 1H), 6.63–6.53 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.47, 145.14, 141.01, 140.18, 130.88 (q, *J* = 32.7 Hz), 123.17 (q, *J* = 272.7 Hz), 119.72, 119.09, 116.47, 107.08; ^{19}F NMR (376 MHz, DMSO-d_6) δ −61.37. HRMS (ESI-TOF) *m/z* calc'd for $C_{14}H_9F_6N_2O_2$ $[M+H]^+$: 351.0563; found: 351.0554.



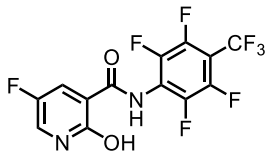
L8

2-Hydroxy-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)nicotinamide (L8)
Purification by flash silica gel column chromatography (hexanes/EtOAc = 1:1 v/v to EA) afforded 0.275 g of compound **L8** as a white solid (52% yield). R*f* = 0.57 (EtOAc).[4]
^{1}H NMR (600 MHz, DMSO-d_6) δ 12.96 (s, 1H), 12.22 (s, 1H), 8.48 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.92 (dd, *J* = 6.3, 2.2 Hz, 1H), 6.62 (dd, *J* = 7.2, 6.2 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.62, 161.40, 145.73, 141.63, 118.18, 107.23; ^{19}F NMR (376 MHz, DMSO-d_6) δ −54.73 (t, *J* = 21.1 Hz, 3H), −141.87–−142.27 (m, 2H), −142.64–−142.96 (m, 2H). HRMS (ESI-TOF) *m/z* calc'd for $C_{13}H_6F_7N_2O_2$ $[M+H]^+$: 355.0312; found: 355.0302.



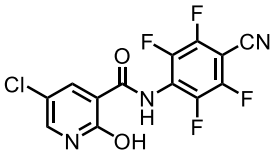
L9

5-Chloro-2-hydroxy-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)nicotinamide (L9)
Purification by flash silica gel column chromatography (hexanes/EtOAc = 2:1 v/v to EA) afforded 0.301 g of compound **L9** as a white solid (52% yield). R*f* = 0.44 (hexanes/EtOAc = 1:1 v/v). [4]
^{1}H NMR (600 MHz, DMSO-d_6) δ 13.36 (s, 1H), 12.04 (s, 1H), 8.37 (d, *J* = 3.0 Hz, 1H), 8.18 (d, *J* = 3.1 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.34, 160.31, 144.94, 139.82, 119.13, 112.30; ^{19}F NMR (376 MHz, DMSO-d_6) δ −54.77 (t, *J* = 21.2 Hz, 3H), −141.77–−142.02 (m, 2H), −142.50–−142.85 (m, 2H). HRMS (ESI-TOF) *m/z* calc'd for $C_{13}H_5ClF_7N_2O_2$ $[M+H]^+$: 388.9922; found: 388.9917.



L10

5-Fluoro-2-hydroxy-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)nicotinamide (L10)
Purification by flash silica gel column chromatography (hexanes/EtOAc = 2:1 v/v to EA) afforded 0.248 g of compound **L10** as a white solid (44% yield). R*f* = 0.34 (hexanes/EtOAc = 1:1 v/v). [4]
^{1}H NMR (600 MHz, DMSO-d_6) δ 13.13 (brs, 1H), 12.26 (s, 1H), 8.47–8.35 (m, 1H), 8.17 (t, *J* = 3.3 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.94, 160.54, 147.17 (d, *J* = 229.1 Hz), 135.01 (d, *J* = 23.6 Hz), 128.31 (d, *J* = 35.4 Hz), 118.25 (d, *J* = 5.7 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ −54.85 (t, *J* = 21.2 Hz, 3H), −141.84–−142.14 (m, 2H), −142.49–−142.94 (m, 2H), −146.68 (s, 1H). HRMS (ESI-TOF) *m/z* calc'd for $C_{13}H_5F_8N_2O_2$ $[M+H]^+$: 373.0218; found: 373.0212.



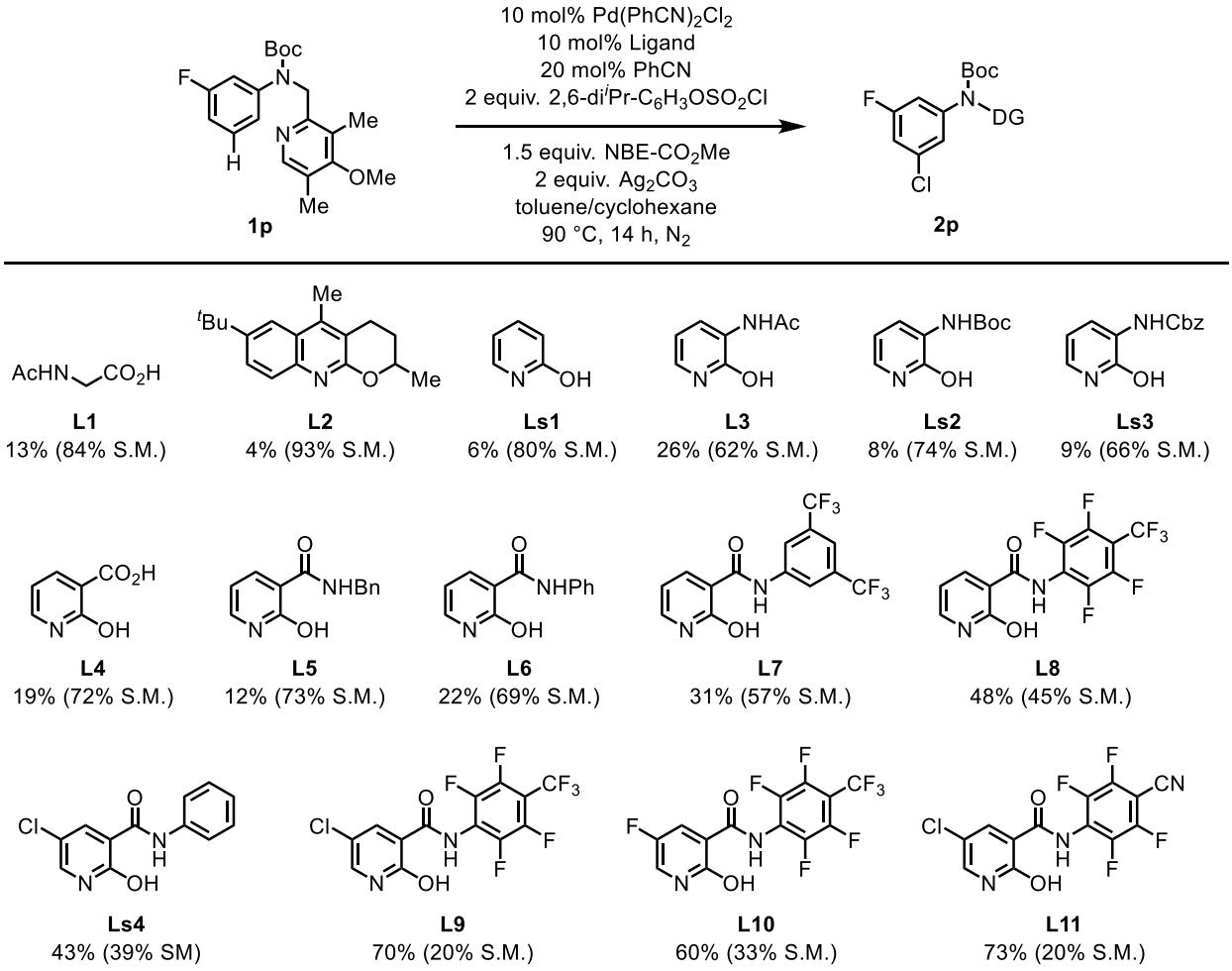
L11

5-Chloro-*N*-(4-cyano-2,3,5,6-tetrafluorophenyl)-2-hydroxynicotinamide (L11)

Purification by flash silica gel column chromatography (hexanes/EtOAc = 2:1 v/v to EA) afforded 0.29 g of compound **L11** as a white solid (56% yield). R*f* = 0.32 (hexanes/EtOAc = 1:1 v/v).

^{1}H NMR (600 MHz, DMSO-d_6) δ 13.37 (brs, 1H), 12.15 (s, 1H), 8.36 (s, 1H), 8.18 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.36, 160.28, 146.97 (dd, *J* = 256.3, 15.9 Hz), 141.31 (dd, *J* = 250.3, 12.9 Hz), 145.04, 139.97, 123.18 (t, *J* = 13.1 Hz), 119.05, 112.38, 108.24, 90.22 (t, *J* = 18.1 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ −134.39–−134.97 (m, 2H), −141.22–−141.70 (m, 2H). HRMS (ESI-TOF) *m/z* calc'd for $C_{13}H_5ClF_4N_3O_2$ $[M+H]^+$: 346.0001; found: 346.0007.

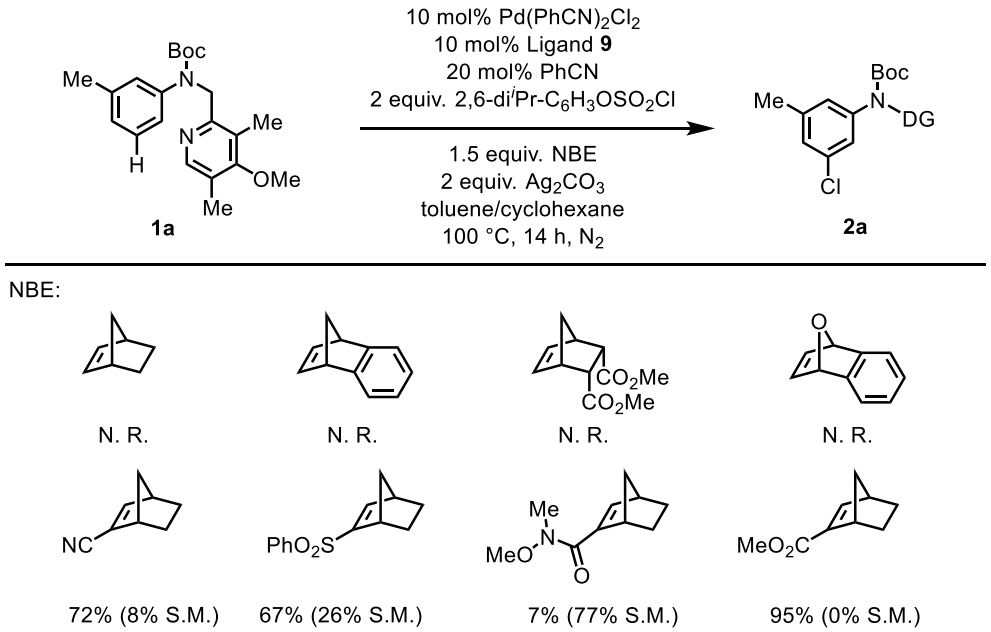
3.3 Ligand Screening



Procedure: Arene **1p** (36 mg, 0.10 mmol, 1.0 equiv), $Pd(PhCN)_2Cl_2$ (3.8 mg, 10 μmol, 10 mol%), Ligand (10 μmol, 10 mol%) and Ag_2CO_3 (55.1 mg, 0.20 mmol, 2.0 equiv.) were added into a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Toluene (1 mL), cyclohexane (1 mL), PhCN (2 μL, 20 μmol, 20 mol%), NBE-CO_2Me (23 μL, 0.15 mmol, 1.5 equiv.), and 2,6-di^{i}Pr-$C_6H_4OSO_2Cl$ (55 mg, 0.20 mmol, 2.0 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 90 °C. After 14 hours, the oil bath was removed, and the Schlenk tube was allowed to cool to room

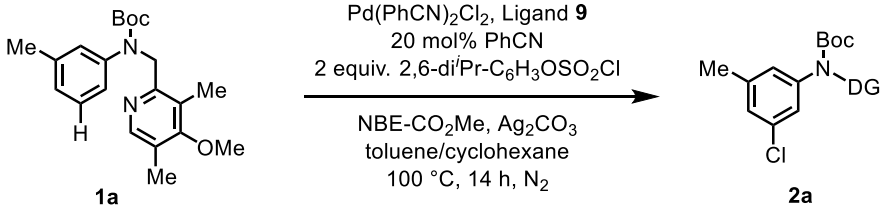
temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 2 mL). The filtrate was evaporated under reduced pressure. The yield was determined by ^{1}H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard.

3.4 Norbornene Derivatives Screening



Procedure: Arene **1a** (35.6 mg, 0.10 mmol, 1.0 equiv), $Pd(PhCN)_2Cl_2$ (3.8 mg, 10 μmol, 10 mol%), Ligand **9** (3.9 mg, 10 μmol, 10 mol%), and Ag_2CO_3 (55.1 mg, 0.20 mmol, 2.0 equiv.) were added into a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Toluene (1 mL), cyclohexane (1 mL), PhCN (2 μL, 20 μmol, 20 mol%), NBE derivative (0.15 mmol, 1.5 equiv.), and 2,6-di^{i}Pr-$C_6H_4OSO_2Cl$ (55 mg, 0.20 mmol, 2.0 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 100 °C. After 14 hours, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 2 mL). The filtrate was evaporated under reduced pressure. The yield was determined by ^{1}H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard.

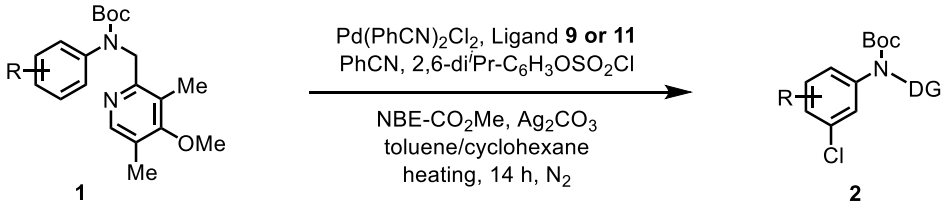
3.5 Loading Screening



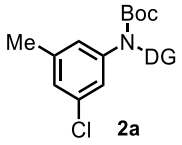
$Pd(PhCN)_2Cl_2$/ligand L9	NBE-CO_2Me	Ag_2CO_3	additional base	NMR yield
10 mol%	1.5 equiv.	2.0 equiv.	none	95%
5 mol%	1.5 equiv.	2.0 equiv.	none	72%
10 mol%	0.5 equiv.	2.0 equiv.	none	76%
10 mol%	1.5 equiv.	0.3 equiv.	none	16%
10 mol%	1.5 equiv.	0.3 equiv.	2.0 equiv. Li_2CO_3	34%
10 mol%	1.5 equiv.	0.3 equiv.	2.0 equiv. K_2CO_3	7%

Procedure: Arene **1a** (35.6 mg, 0.10 mmol, 1.0 equiv), $Pd(PhCN)_2Cl_2$, Ligand **9**, Ag_2CO_3, and additive were added into a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Toluene (1 mL), cyclohexane (1 mL), PhCN (2 μL, 20 μmol, 20 mol%), NBE-CO_2Me, and 2,6-di^{i}Pr-$C_6H_4OSO_2Cl$ (55 mg, 0.20 mmol, 2.0 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 100 °C. After 14 hours, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 2 mL). The filtrate was evaporated under reduced pressure. The yield was determined by ^{1}H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard.

3.6 *meta*-C–H Chlorination of Anilines



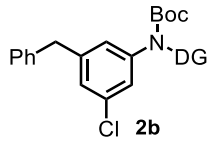
General procedure: Arene **1** (0.10 mmol, 1.0 equiv), $Pd(PhCN)_2Cl_2$ (3.8 mg, 10 μmol, 10 mol%), Ligand (10 μmol, 10 mol%) and Ag_2CO_3 (55 mg, 0.20 mmol, 2.0 equiv.) were added into a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Toluene (1 mL), cyclohexane (1 mL), PhCN (2 μL, 20 μmol, 20 mol%), NBE-CO_2Me (23 μL, 0.15 mmol, 1.5 equiv.) and 2,6-di^{i}Pr-$C_6H_4OSO_2Cl$ (55 mg, 0.20 mmol, 2.0 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 100 °C or 110 °C. After 14 hours, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 2 mL). The filtrate was evaporated under reduced pressure. Purification by preparative TLC chromatography afforded the title compound.



***tert*-Butyl (3-chloro-5-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2a)**

L9 (10 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 2:1 v/v) afforded 37.2 mg of compound **2a** as a yellow liquid (93% yield). R*f* = 0.19 (hexanes/EtOAc = 6:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.08 (s, 1H), 6.99 (s, 1H), 6.91 (s, 1H), 4.85 (s, 2H), 3.73 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.63, 154.69, 154.35, 148.99, 143.88, 139.40, 133.19, 126.19, 125.13, 124.68, 123.62, 123.44, 80.55, 59.83, 53.25, 28.14, 21.14, 13.17, 10.32. HRMS (ESI-TOF) *m/z* calc'd for $C_{21}H_{28}ClN_2O_3$ $[M+H]^+$: 391.1783; found: 391.1792.

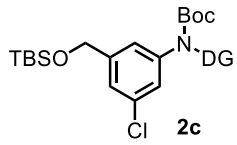


2b

***tert*-Butyl (3-benzyl-5-chlorophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2b)**

L9 (10 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 3:1 v/v) afforded 40.5 mg of compound **2b** as a colorless liquid (87% yield). R*f* = 0.59 (hexanes/EtOAc = 2:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.25 (t, *J* = 7.0 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.16–7.05 (m, 3H), 6.99 (s, 1H), 6.90 (d, *J* = 1.9 Hz, 1H), 4.85 (s, 2H), 3.87 (s, 2H), 3.71 (s, 3H), 2.21 (s, 3H), 2.17 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.69, 154.59, 154.33, 149.03, 143.99, 142.51, 139.99, 133.56, 128.89, 128.47, 126.26, 126.01, 125.45, 124.73, 124.09, 123.56, 80.69, 59.85, 53.23, 41.41, 28.17, 13.22, 10.35. HRMS (ESI-TOF) *m/z* calc'd for $C_{27}H_{32}ClN_2O_3$ $[M+H]^+$: 467.2096; found: 467.2105.

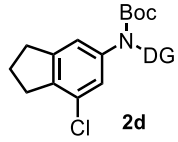


2c

***tert*-Butyl (3-(((tert-butyldimethylsilyl)oxy)methyl)-5-chlorophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2c)**

L9 (10 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 7:2 v/v) afforded 45.8 mg of compound **2c** as a colorless liquid (88% yield). R*f* = 0.75 (hexanes/EtOAc = 2:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.18 (s, 1H), 7.10 (s, 1H), 7.06 (s, 1H), 4.86 (s, 2H), 4.63 (s, 2H), 3.73 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 1.39 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.64, 154.58, 154.38, 149.07, 144.04, 143.21, 133.41, 124.92, 124.69, 123.38, 122.90, 121.70, 80.64, 64.04, 59.85, 53.24, 28.18, 25.85, 18.29, 13.19, 10.31, −5.38. HRMS (ESI-TOF) *m/z* calc'd for $C_{27}H_{42}ClN_2O_4Si$ $[M+H]^+$: 521.2597; found: 521.2603.

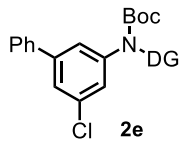


2d

***tert*-Butyl (7-chloro-2,3-dihydro-1H-inden-5-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2d)**

L11 (10 mol%), 110 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 3:1 v/v) afforded 30.0 mg of compound **2d** as a colorless liquid (72% yield). R*f* = 0.56 (hexanes/EtOAc = 2:1 v/v).

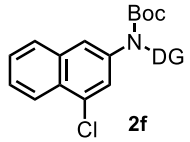
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.03 (s, 2H), 4.84 (s, 2H), 3.73 (s, 3H), 2.88 (p, *J* = 7.5 Hz 4H), 2.22 (s, 3H), 2.20 (s, 3H), 2.04 (p, *J* = 7.5 Hz, 2H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.66, 154.89, 154.68, 148.99, 145.90, 142.37, 139.68, 129.67, 124.67, 124.59, 123.57, 120.98, 80.40, 59.86, 53.59, 33.71, 31.76, 28.22, 24.56, 13.20, 10.38. HRMS (ESI-TOF) *m/z* calc'd for $C_{23}H_{30}ClN_2O_3$ $[M+H]^+$: 417.1939; found: 417.1956.



***tert*-Butyl (5-chloro-[1,1'-biphenyl]-3-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2e)**

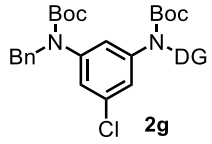
L9 (10 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 5:1 v/v) afforded 37.1 mg of compound **2e** as a yellow liquid (82% yield). R*f* = 0.71 (hexanes/EtOAc = 2:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$, compound exists as a 73:27 mixture of rotamers) δ 8.19 (s, 0.73H), 8.17 (s, 0.27H), 7.48 (d, *J* = 7.5 Hz, 1.5H), 7.44–7.24 (m, 6H), 7.22 (s, 0.25H), 7.17 (t, *J* = 1.7 Hz, 0.27H), 4.93 (s, 1.45H), 4.92 (s, 0.54H), 3.73 (s, 3H), 2.24–2.19 (m, 6H), 1.42 (s, 6.48H), 1.40 (s, 2.51H); ^{13}C NMR (150 MHz, $CDCl_3$, compound exists as a 73:27 mixture of rotamers) δ 163.72, 154.63, 154.55, 154.33, 149.07, 144.31, 143.71, 142.58, 140.49, 139.62, 138.90, 133.91, 133.24, 132.29, 131.15, 129.88, 128.94, 128.75, 127.78, 127.75, 127.04, 126.81, 126.44, 125.88, 125.53, 125.19, 124.83, 124.79, 124.24, 123.59, 80.79, 59.86, 53.27, 53.24, 28.22, 13.20, 10.39. HRMS (ESI-TOF) *m/z* calc'd for $C_{26}H_{30}ClN_2O_3$ $[M+H]^+$: 453.1939; found: 453.1946.



***tert*-Butyl (4-chloronaphthalen-2-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2f)**

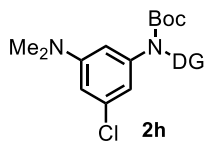
L9 (15 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 2:1 v/v) afforded 28.8 mg of compound **2f** as a yellow liquid (67% yield). R*f* = 0.49 (hexanes/EtOAc = 2:1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21–8.12 (m, 2H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.62 (s, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 5.00 (s, 2H), 3.73 (s, 3H), 2.24 (s, 3H), 2.21 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.72, 154.65, 154.48, 149.08, 140.30, 134.11, 131.10, 128.77, 128.12, 126.71, 126.48, 126.33, 124.81, 124.06, 123.61, 122.69, 80.85, 59.87, 53.46, 28.23, 13.20, 10.42. HRMS (ESI-TOF) *m/z* calc'd for $C_{24}H_{28}ClN_2O_3$ $[M+H]^+$: 427.1783; found: 427.1795.



***tert*-Butyl (3-(benzyl(tert-butoxycarbonyl)amino)-5-chlorophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2g)**

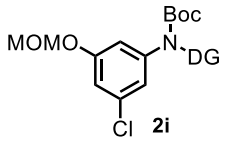
L9 (10 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 4:1 v/v) afforded 45.2 mg of compound **2g** as a colorless liquid (78% yield). R*f* = 0.52 (hexanes/EtOAc = 2:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.25 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.17–7.10 (m, 3H), 7.03 (s, 1H), 6.96 (s, 1H), 4.77 (s, 2H), 4.73 (s, 2H), 3.72 (s, 3H), 2.20 (s, 3H), 2.15 (s, 3H), 1.38 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.65, 154.40, 154.19, 154.15, 149.02, 144.21, 143.53, 138.17, 133.09, 128.37, 127.06, 124.69, 123.71, 123.32, 122.13, 80.94, 80.75, 59.86, 53.74, 53.14, 28.15, 28.14, 13.19, 10.28. HRMS (ESI-TOF) *m/z* calc'd for $C_{32}H_{41}ClN_3O_5$ $[M+H]^+$: 582.2729; found: 582.2739.

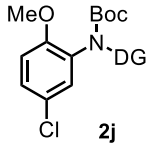


***tert*-Butyl (3-chloro-5-(dimethylamino)phenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2h)**

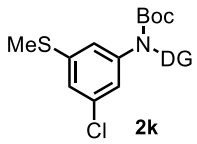
L9 (10 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 2:1 v/v) afforded 31.0 mg of compound **2h** as a yellow liquid (74% yield). R*f* = 0.40 (hexanes/EtOAc = 2:1 v/v).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H), 6.58 (s, 1H), 6.53 (s, 1H), 6.44 (t, *J* = 2.1 Hz, 1H), 4.86 (s, 2H), 3.72 (s, 3H), 2.85 (s, 6H), 2.21 (s, 3H), 2.19 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.63, 154.98, 154.55, 151.11, 148.93, 144.38, 134.09, 124.63, 123.67, 114.76, 109.78, 109.50, 80.35, 59.82, 53.43, 40.33, 28.25, 13.17, 10.39. HRMS (ESI-TOF) *m/z* calc'd for $C_{22}H_{31}ClN_3O_3$ $[M+H]^+$: 420.2048; found: 420.2058.



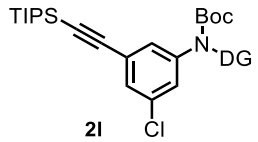
***tert*-Butyl (3-chloro-5-(methoxymethoxy)phenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2i)**
L9 (10 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 2:1 v/v) afforded 29.8 mg of compound **2i** as a yellow liquid (68% yield). R*f* = 0.40 (hexanes/EtOAc = 2:1 v/v).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 6.95 (s, 1H), 6.88 (s, 1H), 6.82 (t, *J* = 1.8 Hz, 1H), 5.08 (s, 2H), 4.85 (s, 2H), 3.73 (s, 3H), 3.42 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.67, 157.47, 154.55, 154.23, 149.04, 144.81, 133.92, 124.74, 123.45, 120.04, 113.60, 113.14, 94.50, 80.78, 59.86, 56.01, 53.22, 28.17, 13.20, 10.34. HRMS (ESI-TOF) *m/z* calc'd for $C_{22}H_{30}ClN_2O_5$ $[M+H]^+$: 437.1838; found: 437.1844.



***tert*-Butyl (5-chloro-2-methoxyphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2j)**
L9 (10 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 2:1 v/v) afforded 30.5 mg of compound **2j** as a colorless liquid (75% yield). R*f* = 0.34 (hexanes/EtOAc = 2:1 v/v).
^{1}H NMR (600 MHz, $CDCl_3$, compound exists as a 71:29 mixture of rotamers) δ 8.17–8.00 (m, 1H), 7.19 (s, 0.29H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.91 (s, 0.71H), 6.84–6.66 (m, 1H), 5.43–4.20 (m, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 1.47–1.32 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$, compound exists as a 71:29 mixture of rotamers) δ 163.80, 154.98, 154.90, 153.97, 148.78, 131.82, 130.46, 129.69, 127.78, 127.54, 125.08, 124.96, 124.80, 124.34, 112.62, 111.82, 80.43, 79.93, 59.79, 55.95, 55.52, 53.10, 52.27, 28.16, 13.17, 10.55. HRMS (ESI-TOF) *m/z* calc'd for $C_{21}H_{28}ClN_2O_4$ $[M+H]^+$: 407.1732; found: 407.1743.



***tert*-Butyl (3-chloro-5-(methylthio)phenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2k)**
L9 (10 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 3:1 v/v) afforded 36.8 mg of compound **2k** as a yellow liquid (87% yield). R*f* = 0.63 (hexanes/EtOAc = 2:1 v/v).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.08 (s, 2H), 6.96 (s, 1H), 4.84 (s, 2H), 3.73 (s, 3H), 2.40 (s, 3H), 2.22 (s, 3H), 2.19 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.69, 154.49, 154.19, 149.06, 144.34, 140.03, 133.92, 124.79, 123.44, 123.22, 122.93, 122.62, 80.84, 59.87, 53.14, 28.18, 15.66, 13.20, 10.35. HRMS (ESI-TOF) *m/z* calc'd for $C_{21}H_{28}ClN_2O_3S$ $[M+H]^+$: 423.1504; found: 423.1513.

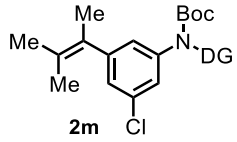


2l

***tert*-Butyl (3-chloro-5-((triisopropylsilyl)ethynyl)phenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2l)**

L9 (10 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 5:1 v/v) afforded 41.5 mg of compound **2l** as a yellow liquid (79% yield). R*f* = 0.80 (hexanes/EtOAc = 2:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.28 (s, 1H), 7.25 (s, 1H), 7.20 (t, *J* = 1.5 Hz, 1H), 4.85 (s, 2H), 3.73 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 1.40 (s, 9H), 1.10 (s, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.75, 154.38, 154.16, 149.07, 143.98, 133.44, 128.81, 128.20, 127.02, 124.85, 124.68, 123.54, 105.30, 92.04, 80.97, 59.87, 53.03, 28.16, 18.59, 13.19, 11.21, 10.38. HRMS (ESI-TOF) *m/z* calc'd for $C_{31}H_{46}ClN_2O_3Si$ $[M+H]^+$: 557.2961; found: 557.2976.

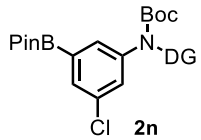


2m

***tert*-Butyl (3-chloro-5-(3-methylbut-2-en-2-yl)phenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2m)**

L9 (10 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 4:1 v/v) afforded 35.5 mg of compound **2m** as a yellow liquid (80% yield). R*f* = 0.58 (hexanes/EtOAc = 2:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.10 (s, 1H), 6.85 (s, 2H), 4.88 (s, 2H), 3.72 (s, 3H), 2.20 (s, 6H), 1.84 (s, 3H), 1.75 (s, 3H), 1.49 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.69, 154.72, 154.37, 149.01, 146.59, 143.41, 133.04, 128.59, 128.24, 125.64, 125.32, 124.74, 123.77, 80.55, 59.84, 53.31, 28.22, 22.00, 20.47, 20.43, 13.17, 10.40. HRMS (ESI-TOF) *m/z* calc'd for $C_{25}H_{34}ClN_2O_3$ $[M+H]^+$: 445.2252; found: 445.2270.

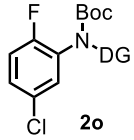


2n

***tert*-Butyl (3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2n)**

L9 (10 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 2:1 v/v) afforded 26.8 mg of compound **2n** as a colorless solid (53% yield). R*f* = 0.49 (hexanes/EtOAc = 2:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.52 (s, 1H), 7.52 (s, 1H), 7.37 (s, 1H), 4.88 (s, 2H), 3.72 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H), 1.31 (s, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.72, 154.71, 154.40, 149.01, 145.79, 143.57, 133.40, 131.71, 130.74, 129.86, 124.75, 123.70, 120.18, 84.08, 80.63, 59.85, 53.19, 28.19, 24.82, 13.18, 10.45. HRMS (ESI-TOF) *m/z* calc'd for $C_{26}H_{37}BClN_2O_5$ $[M+H]^+$: 503.2479; found: 503.2500.

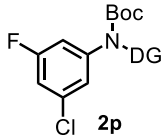


2o

***tert*-Butyl (5-chloro-2-fluorophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2o)**

L11 (10 mol%), 110 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 3:1 v/v) afforded 24.5 mg of compound **2o** as a yellow liquid (62% yield). R*f* = 0.62 (hexanes/EtOAc = 2:1 v/v).

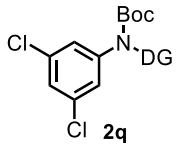
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.24 (brs, 1H), 7.13–7.05 (m, 1H), 6.93 (t, *J* = 9.3 Hz, 1H), 4.87 (s, 2H), 3.73 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.84 , 156.83 (d, *J* = 249.2 Hz), 154.27 , 153.92 , 148.93 , 131.17 (d, *J* = 14.3 Hz), 129.42 , 128.41 , 127.76 (d, *J* = 8.0 Hz), 125.10 , 124.73, 116.57 (d, *J* = 19.5 Hz), 80.97 , 59.83 , 52.60 , 28.05 , 13.20 , 10.46; ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.93. HRMS (ESI-TOF) *m/z* calc'd for $C_{20}H_{25}ClFN_2O_3$ $[M+H]^+$: 395.1532; found: 395.1547.



***tert*-Butyl (5-chloro-3-fluorophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2p)**

L9 (10 mol%), 110 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 7:2 v/v) afforded 33.1 mg of compound **2p** as a yellow liquid (84% yield). R*f* = 0.75 (hexanes/EtOAc = 2:1 v/v).

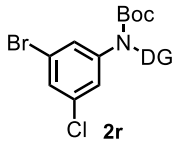
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.13 (s, 1H), 6.99 (dt, *J* = 10.3, 2.2 Hz, 1H), 6.84 (dt, *J* = 8.3, 2.1 Hz, 1H), 4.84 (s, 2H), 3.75 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.73 , 162.14 (d, *J* = 247.6 Hz), 154.20 , 153.98 , 149.15 , 145.40 (d, *J* = 11.2 Hz), 134.11 (d, *J* = 12.2 Hz), 124.88 , 123.30 , 122.09 , 112.97 (d, *J* = 24.9 Hz), 112.02 (d, *J* = 23.5 Hz), 81.18 , 59.91 , 53.06 , 28.13 , 13.23 , 10.31; ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.82. HRMS (ESI-TOF) *m/z* calc'd for $C_{20}H_{25}ClFN_2O_3$ $[M+H]^+$: 395.1532; found: 395.1546.



***tert*-Butyl (3,5-dichlorophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2q)**

L11 (10 mol%), 110 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 4:1 v/v) afforded 33.7 mg of compound **2q** as a yellow liquid (82% yield). R*f* = 0.61 (hexanes/EtOAc = 3:1 v/v).

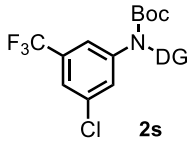
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.24 (s, 2H), 7.10 (t, *J* = 1.8 Hz, 1H), 4.83 (s, 2H), 3.75 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.72, 154.17, 153.95, 149.15, 145.09, 134.13, 125.32, 124.89, 124.73, 123.29, 81.18, 59.90, 53.01, 28.11, 13.22, 10.32. HRMS (ESI-TOF) *m/z* calc'd for $C_{20}H_{25}Cl_2N_2O_3$ $[M+H]^+$: 411.1237; found: 411.1249.



***tert*-Butyl (3-bromo-5-chlorophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2r)**

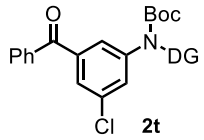
L11 (10 mol%), 110 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 4:1 v/v) afforded 36.0 mg of compound **2r** as a colorless liquid (79% yield). R*f* = 0.73 (hexanes/EtOAc = 2:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.39 (s, 1H), 7.28 (s, 1H), 7.25 (s, 1H), 4.83 (s, 2H), 3.74 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.74, 154.15, 153.94, 149.15, 145.20, 134.31, 128.07, 127.59, 125.22, 124.91, 123.33, 121.64, 81.21, 59.91, 53.00, 28.12, 13.23, 10.32. HRMS (ESI-TOF) *m/z* calc'd for $C_{20}H_{25}BrClN_2O_3$ $[M+H]^+$: 455.0732; found: 455.0744.



***tert*-Butyl (3-chloro-5-(trifluoromethyl)phenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2s)**

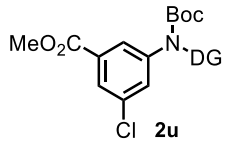
L11 (15 mol%), 110 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 5:1 v/v) afforded 34.5 mg of compound **2s** as a yellow liquid (80% yield). R*f* = 0.81 (hexanes/EtOAc = 2:1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.53 (s, 1H), 7.50 (s, 1H), 7.34 (s, 1H), 4.87 (s, 2H), 3.74 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.79 , 154.04 , 153.88 , 149.18 , 144.94 , 134.32 , 131.64 (q, *J* = 32.8 Hz), 129.26 , 125.00 , 123.37 , 123.15 (q, *J* = 272.9 Hz), 122.01 (q, *J* = 3.5 Hz), 121.62 , 81.42 , 59.90 , 52.88 , 28.09 , 13.22 , 10.33; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.14. HRMS (ESI-TOF) *m/z* calc'd for $C_{21}H_{25}ClF_3N_2O_3$ $[M+H]^+$: 445.1500; found: 445.1515.



2t

***tert*-Butyl (3-benzoyl-5-chlorophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2t)**

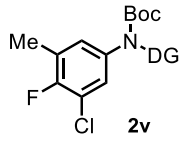
L11 (10 mol%), 100 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 3:1 v/v) afforded 35.0 mg of compound **2t** as a yellow liquid (73% yield). R*f* = 0.53 (hexanes/EtOAc = 2:1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.75 (d, *J* = 7.4 Hz, 2H), 7.65–7.53 (m, 3H), 7.50 (t, *J* = 1.7 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 4.89 (s, 2H), 3.73 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.73, 163.76, 154.21, 154.13, 149.07, 144.31, 138.76, 136.74, 133.85, 132.72, 130.16, 130.00, 128.34, 126.62, 125.91, 124.89, 123.43, 81.16, 59.89, 52.94, 28.14, 13.21, 10.34. R*f* = 0.53 (hexanes/EtOAc = 2:1 v/v). HRMS (ESI-TOF) *m/z* calc'd for $C_{27}H_{30}ClN_2O_4$ $[M+H]^+$: 481.1889; found: 481.1899.



2u

Methyl 3-((*tert*-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-5-chlorobenzoate (2u)

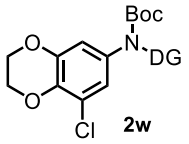
L11 (15 mol%), 110 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 2:1 v/v) afforded 30.8 mg of compound **2u** as a yellow liquid (71% yield). R*f* = 0.47 (hexanes/EtOAc = 2:1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.85 (s, 1H), 7.76 (t, *J* = 1.7 Hz, 1H), 7.54 (s, 1H), 4.88 (s, 2H), 3.88 (s, 3H), 3.74 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.63, 163.75, 154.26, 154.10, 149.14, 144.43, 133.88, 131.48, 130.81, 126.39, 125.69, 124.89, 123.45, 81.13, 59.90, 52.96, 52.38, 28.14, 13.22, 10.37. HRMS (ESI-TOF) *m/z* calc'd for $C_{22}H_{28}ClN_2O_5$ $[M+H]^+$: 435.1681; found: 435.1696.



2v

***tert*-Butyl (3-chloro-4-fluoro-5-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2v)**

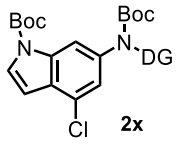
L11 (10 mol%), 110 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 3:1 v/v) afforded 33.0 mg of compound **2v** as a yellow liquid (81% yield). R*f* = 0.49 (hexanes/EtOAc = 3:1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.15 (s, 1H), 7.02 (s, 1H), 4.82 (s, 2H), 3.74 (s, 3H), 2.24–2.21 (m, 6H), 2.20 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.28, 154.50, 153.65, 149.01, 138.65, 127.97, 127.94 126.32, 125.88 (q, *J* = 18 Hz), 124.82, 119.92 (q, *J* = 18 Hz), 80.68, 59.87, 53.38, 28.18, 14.86 (q, *J* = 3.0 Hz), 13.21, 10.37; ^{19}F NMR (376 MHz, $CDCl_3$) δ −123.23. HRMS (ESI-TOF) *m/z* calc'd for $C_{21}H_{27}ClFN_2O_3$ $[M+H]^+$: 409.1689; found: 409.1704.



2w

***tert*-Butyl (8-chloro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2w)**

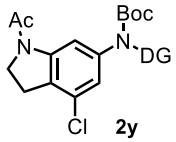
L11 (10 mol%), 110 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 2:1 v/v) afforded 30.9 mg of compound **2w** as a yellow liquid (71% yield). Rf = 0.39 (hexanes/EtOAc = 2:1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H), 6.88 (s, 1H), 6.76 (s, 1H), 4.80 (s, 2H), 4.36 – 4.25 (m, 2H), 4.25 – 4.14 (m, 2H), 3.73 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.66, 154.65, 149.00, 143.66, 137.95, 136.05, 124.70, 123.57, 121.01, 120.77, 114.64, 80.46, 64.74, 64.07, 59.85, 53.49, 28.20, 13.19, 10.34. HRMS (ESI-TOF) *m/z* calc'd for $C_{22}H_{28}ClN_2O_5$ $[M+H]^+$: 435.1681; found: 435.1696.



2x

***tert*-Butyl 6-((tert-butoxycarbonyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amino)-4-chloro-1H-indole-1-carboxylate (2x)**

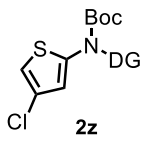
L11 (10 mol%), 110 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 3:1 v/v) afforded 42.8 mg of compound **2x** as a yellow liquid (72% yield). R*f* = 0.56 (hexanes/EtOAc = 2:1 v/v).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.92 (s, 1H), 7.56 (d, *J* = 3.7 Hz, 1H), 7.21 (s, 1H), 6.59 (d, *J* = 3.7 Hz, 1H), 4.94 (s, 2H), 3.73 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 1.59 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.71, 154.86, 154.74, 149.22, 148.99, 140.02, 135.26, 127.19, 126.65, 124.98, 124.73, 123.78, 122.25, 112.56, 105.09, 84.06, 80.46, 59.82, 53.96, 28.23, 28.00, 13.16, 10.44. HRMS (ESI-TOF) *m/z* calc'd for $C_{27}H_{35}ClN_3O_5$ $[M+H]^+$: 516.2260; found: 516.2273.



2y

***tert*-Butyl 2-(1-acetyl-4-chloroindolin-6-yl)-3-(4-methoxy-3,5-dimethylpyridin-2-yl)propanoate (2y)**

L11 (10 mol%), 110 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 1:2 v/v) afforded 32.9 mg of compound **2y** as a yellow liquid (72% yield). R*f* = 0.19 (hexanes/EtOAc = 1:1 v/v).
^{1}H NMR (600 MHz, $CDCl_3$, compound exists as a 84:16 mixture of rotamers) δ 8.15 (s, 1H), 8.05 (s, 0.84H), 7.13 (s, 0.16H), 7.06 – 6.89 (m, 1H), 4.85 (s, 2H), 4.15 – 3.98 (m, 2H), 3.72 (s, 3H), 3.11 (t, *J* = 8.5 Hz, 1.70H), 2.99 (t, *J* = 8.3 Hz, 0.28H), 2.31–2.12 (m, 9H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$, compound exists as a 84:16 mixture of rotamers) δ 168.62, 168.29, 163.67, 154.74, 154.48, 148.94, 143.75, 143.71, 129.19, 126.81, 124.66, 123.67, 122.13, 121.46, 114.22, 112.09, 80.59, 59.84, 53.39, 48.86, 47.95, 28.19, 27.06, 24.12, 13.19, 10.41. HRMS (ESI-TOF) *m/z* calc'd for $C_{24}H_{31}ClN_3O_4$ $[M+H]^+$: 460.1998; found: 460.2007.

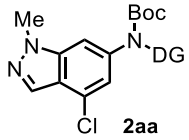


2z

***tert*-Butyl 2-(4-chlorothiophen-2-yl)-3-(4-methoxy-3,5-dimethylpyridin-2-yl)propanoate (2z)**

L11 (10 mol%), 110 °C. Purification by preparative TLC chromatography (hexanes/EtOAc = 5:1 v/v)

afforded 24.1 mg of compound **2z** as a yellow solid (63% yield). R*f* = 0.71 (hexanes/EtOAc = 2:1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 6.98 (s, 1H), 6.68 (s, 1H), 4.84 (s, 2H), 3.74 (s, 3H), 2.22 (s, 3H), 2.19 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.75, 154.43, 154.01, 149.10, 139.87, 127.89, 124.86, 124.78, 123.52, 113.34, 81.09, 59.92, 52.99, 28.22, 13.24, 10.30. HRMS (ESI-TOF) *m/z* calc'd for $C_{18}H_{24}ClN_2O_3S$ $[M+H]^+$: 383.1191; found: 383.1205.

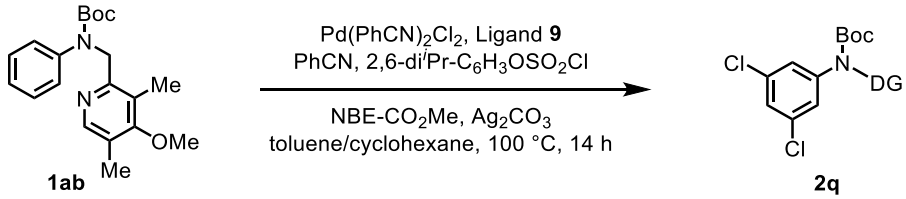


2aa

***tert*-Butyl 2-(4-chloro-1-methyl-1H-indazol-6-yl)-3-(4-methoxy-3,5-dimethylpyridin-2-yl)propanoate (2aa)**

L11 (10 mol%), 110 °C. Purijjfication by preparative TLC chromatography (hexanes/EtOAc = 2:3 v/v) afforded 32.0 mg of compound **2aa** as a yellow solid (74% yield). R*f* = 0.27 (hexanes/EtOAc = 1:1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.94 (d, *J* = 0.9 Hz, 1H), 7.29 (s, 1H), 7.11 (s, 1H), 4.94 (s, 2H), 3.98 (s, 3H), 3.73 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.78, 154.64, 154.52, 148.99, 142.04, 140.49, 131.24, 125.57, 124.91, 123.71, 121.27, 120.51, 105.36, 80.89, 59.88, 53.74, 35.86, 28.20, 13.22, 10.44. HRMS (ESI-TOF) m/z calc'd for $C_{22}H_{28}ClN_4O_3$ $[M+H]^+$: 431.1844; found: 431.1853.

3.7 *meta*-C–H Dichlorination of Aniline 1ab

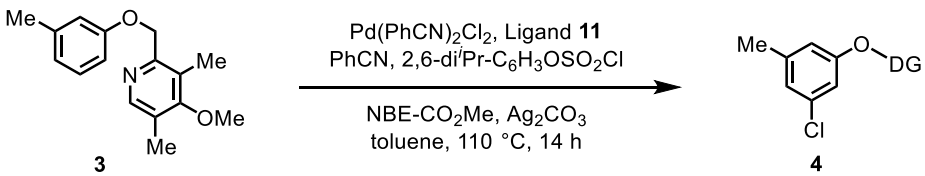


1ab **2q**

***tert*-Butyl (3,5-dichlorophenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2q)**

Arene **1ab** (34.2 mg, 0.10 mmol, 1.0 equiv), $Pd(PhCN)_2Cl_2$ (3.8 mg, 10 μmol, 10 mol%), Ligand **9** (3.9 mg, 11 μmol, 10 mol%) and Ag_2CO_3 (55 mg, 0.20 mmol, 2.0 equiv.) were added into a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Toluene (1 mL), cyclohexane (1 mL), PhCN (2 μL, 20 μmol, 20 mol%), NBE-CO_2Me (23 μL, 0.15 mmol, 1.5 equiv.) and 2,6-di^{i}Pr-$C_6H_4OSO_2Cl$ (69 mg, 0.25 mmol, 2.5 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 100 °C. After 14 hours, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 2 mL). The filtrate was evaporated under reduced pressure. Purification by preparative TLC chromatography (hexanes/EtOAc = 4:1 v/v) afforded 31.8 mg of compound **2q** as a yellow liquid (77% yield). R*f* = 0.61 (hexanes /EtOAc = 3/1 v/v).

3.8 *meta*-C–H Chlorination of Phenol 3



3 **4**

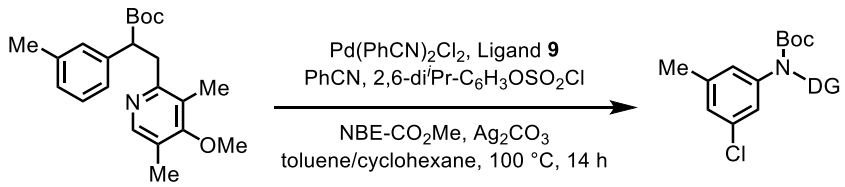
2-((3-Chloro-5-methylphenoxy)methyl)-4-methoxy-3,5-dimethylpyridine (4)

Arene **3** (25.7 mg, 0.10 mmol, 1.0 equiv), $Pd(PhCN)_2Cl_2$ (3.8 mg, 10 μmol, 10 mol%), Ligand **11** (3.5 mg, 11 μmol, 10 mol%) and Ag_2CO_3 (55 mg, 0.20 mmol, 2.0 equiv.) were added into a flame-dried Schlenk tube. The

Schlenk tube was evacuated and back-filled with nitrogen. Toluene (2 mL), PhCN (2 µL, 20 µmol, 20 mol%), NBE-CO_2Me (23 µL, 0.15 mmol, 1.5 equiv.) and 2,6-di^{i}Pr-$C_6H_4OSO_2Cl$ (69 mg, 0.25 mmol, 2.5 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 110 °C. After 14 hours, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 2 mL). The filtrate was evaporated under reduced pressure. Purification by preparative TLC chromatography (toluene/EtOAc = 10:1 v/v) afforded 17.5 mg of compound **4** as a yellow liquid (60% yield). R*f* = 0.41 (toluene/EtOAc = 10:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.08 (s, 1H), 6.99 (s, 1H), 6.91 (s, 1H), 4.85 (s, 2H), 3.73 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.63, 154.69, 154.35, 148.99, 143.88, 139.40, 133.19, 126.19, 125.13, 124.68, 123.62, 123.44, 80.55, 59.83, 53.25, 28.14, 21.14, 13.17, 10.32. HRMS (ESI-TOF) *m/z* calc'd for $C_{16}H_{19}ClNO_2$ $[M+H]^+$: 292.1099; found: 292.1096.

3.9 Gram-Scale *meta*-C–H Chlorination of Aniline 1a

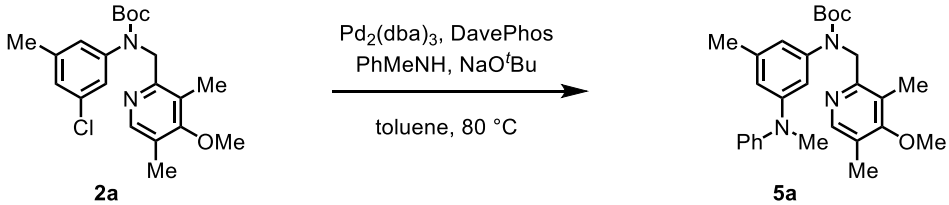


1a **2a**, 1.19 g, 87%

***tert*-Butyl (3-chloro-5-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate (2a)**

Arene **1a** (1.25 g, 3.5 mmol, 1.0 equiv), $Pd(PhCN)_2Cl_2$ (134 mg, 0.35 mmol, 10 mol%), Ligand **9** (136 mg, 0.35 µmol, 10 mol%) and Ag_2CO_3 (818 mg, 4.9 mmol, 1.4 equiv.) were added into a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Toluene (35 mL), PhCN (72.1 µL, 0.7 mmol, 20 mol%), NBE-CO_2Me (532 mg, 3.5 mmol, 1 equiv.), 2,6-di^{i}Pr-$C_6H_4OSO_2Cl$ (1.94 g, 7 mmol, 2 equiv.) and cyclohexane (35 mL) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 100 °C. After 14 hours, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 30 mL). The filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (Hexane/EtOAc = 6:1 v/v to 3:1 v/v) afforded 1.19 g of compound **2a** as a yellow liquid (87% yield).

3.10 Diversification of *meta*-Chloro Aniline 2a

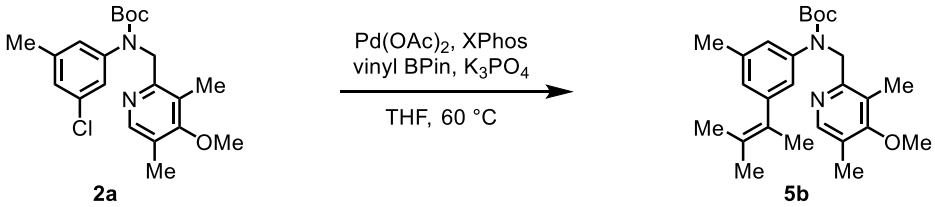


2a **5a**

***tert*-Butyl ((4-methoxy-3,5dimethylpyridin-2-yl)methyl)(3-methyl-5-(methyl(phenyl)amino)phenyl)carbamate (5a)**

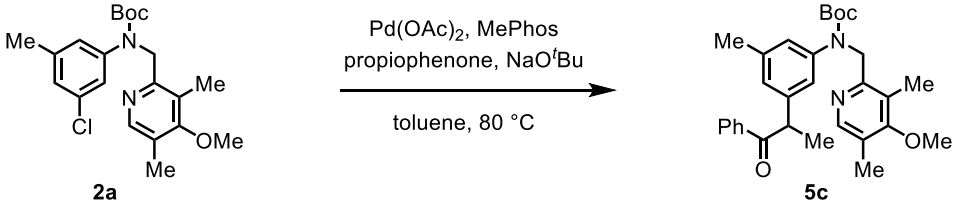
Arene **2a** (39.0 mg, 0.1 mmol, 1 equiv.), $Pd_2(dba)_3$ (2.7 mg, 3 µmol, 3 mol%), Davephos (3.5 mg, 9 µmol, 9 mol%), and NaO^{t}Bu (13.4 mg, 0.14 mmol, 1.4 equiv.) were added to a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Toluene (0.4 mL) and *N*-methylaniline (16 µL, 0.15 mmol, 1.5 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 80 °C. After 18 h, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 2 mL). The filtrate was evaporated

under reduced pressure. Purification by preparative TLC chromatography (hexane/EtOAc = 2:1 v/v) afforded 39.8 mg of compound **5a** as a yellow liquid (86% yield). R*f* = 0.33 (hexanes/EtOAc = 2:1 v/v).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.21 (t, *J* = 7.8 Hz, 2H), 6.92–6.82 (m, 3H), 6.70 (d, *J* = 7.8 Hz, 2H), 6.61 (s, 1H), 4.88 (s, 2H), 3.70 (s, 3H), 3.21 (s, 3H), 2.21 (s, 6H), 2.19 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.66, 155.16, 154.71, 148.96, 148.84, 148.65, 143.41, 138.84, 126.96, 124.57, 123.80, 120.62, 120.49, 119.48, 119.38, 117.24, 80.14, 59.79, 53.55, 40.13, 28.27, 21.50, 13.20, 10.42. HRMS (ESI-TOF) *m/z* calc'd for $C_{28}H_{36}N_3O_3$ $[M+H]^+$: 462.2751; found: 462.2749.



***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-methyl-5-(3-methylbut-2-en-2-yl)phenyl)carbamate** (**5b**).

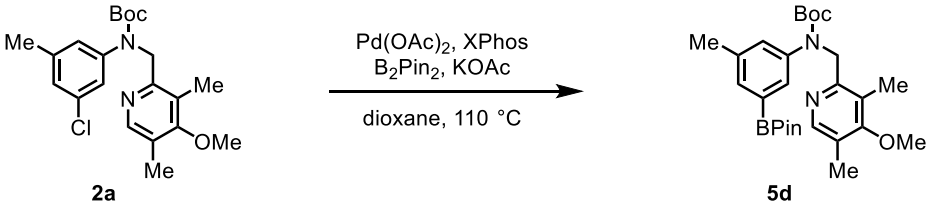
Arene **2a** (39.0 mg, 0.1 mmol, 1 equiv.), $Pd(OAc)_2$ (0.9 mg, 4 μmol, 4 mol%), XPhos (3.8 mg, 8 μmol, 8 mol%), and K_3PO_4 aqueous solution (0.5 M, 600 μL, 0.3 mmol, 3 equiv.) were added to a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. THF (1 mL) and 4,4,5,5-tetramethyl-2-(3-methylbut-2-en-2-yl)-1,3,2-dioxaborolane (44 μL, 0.2 mmol, 2 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 60 °C. After 4 h, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. Water (3 mL) was added into the Schlenk. The reaction mixture was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried with Na_2SO_4. After the organic solvent was concentrated by rotatory evaporation, the residue was purified by preparative TLC chromatography (hexane/EtOAc = 3:1 v/v) to afford 37.2 mg of compound **5b** as a yellow liquid (88% yield). R*f* = 0.48 (hexanes/EtOAc = 3:1 v/v).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (s, 1H), 6.86 (s, 1H), 6.68–6.65 (m, 2H), 4.91 (s, 2H), 3.71 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H), 1.83 (s, 3H), 1.74 (s, 3H), 1.46 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.64, 155.27, 154.79, 148.83, 145.14, 141.95, 137.55, 129.69, 126.90, 126.45, 124.59, 124.22, 80.03, 59.77, 53.59, 28.28, 21.99, 21.33, 20.64, 20.39, 13.18, 10.46. HRMS (ESI-TOF) *m/z* calc'd for $C_{26}H_{37}N_2O_3$ $[M+H]^+$: 425.2799; found: 425.2796.



***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-methyl-5-(1-oxo-1-phenylpropan-2-yl)phenyl)carbamate** (**5c**).

Arene **2a** (39.0 mg, 0.1 mmol, 1 equiv.), $Pd(OAc)_2$ (1.1 mg, 5 μmol, 5 mol%), MePhos (3.6 mg, 10 μmol, 10 mol%), and NaO^{t}Bu (12.4 mg, 0.13 mmol, 1.3 equiv.) were added to a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Toluene (0.2 mL) and propiophenone (16 μL, 0.12 mmol, 1.2 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 80 °C. After 18 h, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 2 mL). The filtrate was evaporated under reduced pressure. Purification by preparative TLC chromatography (hexane/EtOAc = 2:1 v/v) afforded 37.1 mg of compound **5c** as a yellow liquid (76% yield). R*f* = 0.40 (hexanes/EtOAc = 2:1 v/v).

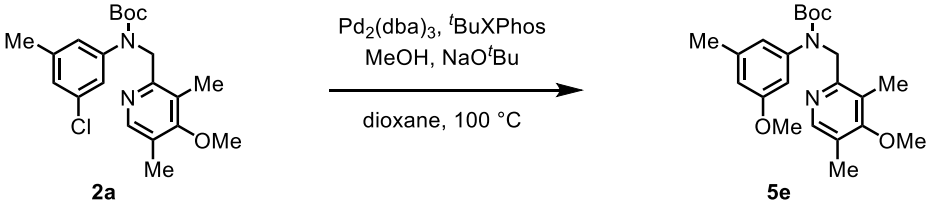
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 6.93 (s, 1H), 6.88 (s, 1H), 6.82 (s, 1H), 4.85 (s, 2H), 4.54 (q, *J* = 6.6 Hz, 1H), 3.70 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.34 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.06, 163.62, 155.00, 154.55, 148.80, 143.07, 141.14, 138.79, 136.46, 132.61, 128.72, 128.33, 125.46, 124.95, 124.57, 123.72, 123.42, 80.2, 59.79, 53.37, 47.70, 28.18, 21.33, 19.44, 13.17, 10.36. HRMS (ESI-TOF) *m/z* calc'd for $C_{30}H_{37}N_2O_4$ $[M+H]^+$: 489.2748; found: 489.2739.



***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (5d)**

Arene **2a** (39.0 mg, 0.1 mmol, 1 equiv.), $Pd(OAc)_2$ (1.1 mg, 5 μmol, 5 mol%),, XPhos (4.8 mg, 10 μmol, 10 mol%), KOAc (29.4 mg, 0.3 mmol, 3 equiv.), and B_2Pin_2 (50.7 mg, 0.2 mmol, 2 equiv.) were added to a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Dioxane (0.4 mL) was added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 110 °C. After 1 h, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 2 mL). After evaporated under reduced pressure, the residue was purified by silica gel chromatography (hexanes/EtOAc = 10:1 to 3:1 v/v) to afford 34.0 mg of compound as a white solid (71% yield). R*f* = 0.32 (hexanes/EtOAc = 3:1 v/v).

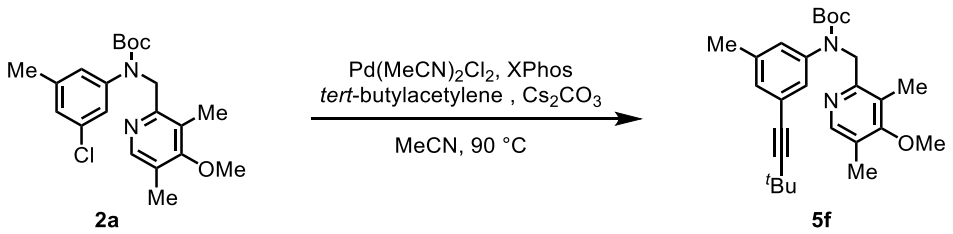
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.39 (s, 1H), 7.37 (s, 1H), 7.15 (s, 1H), 4.89 (s, 2H), 3.71 (s, 3H), 2.25 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H), 1.38 (s, 9H), 1.30 (s, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.62, 155.24, 154.72, 148.80, 142.06, 137.39, 132.74, 130.48, 129.80, 124.50, 123.85, 83.59, 80.03, 59.75, 53.44, 28.19, 24.79, 21.02, 13.11, 10.46. HRMS (ESI-TOF) *m/z* calc'd for $C_{27}H_{40}BN_2O_5$ $[M+H]^+$: 483.3025; found: 483.3020.



***tert*-Butyl ((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)(3-methoxy-5-methylphenyl)carbamate (5e)**

Arene **2a** (39.0 mg, 0.1 mmol, 1 equiv.), $Pd_2(dba)_3$ (2.7 mg, 3 μmol, 3 mol%), ^{t}BuXPhos (5.1 mg, 12 μmol, 12 mol%), and NaO^{t}Bu (13.4 mg, 0.14 mmol, 1.4 equiv.) were added to a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Dioxane (0.4 mL) and MeOH (41 μL, 1.0 mmol, 10 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 100 °C. After 4 h, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 2 mL). The filtrate was evaporated under reduced pressure. Purification by preparative TLC chromatography (hexane/EtOAc = 3:1 v/v) afforded 33.1 mg of compound **5e** as a yellow liquid (86% yield). R*f* = 0.43 (hexanes/EtOAc = 3:1 v/v).

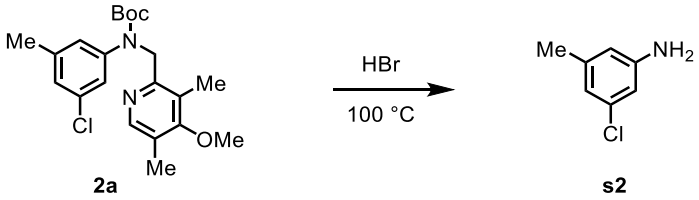
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H), 6.67 (s, 1H), 6.62 (d, 1H), 6.48 (s, 1H), 4.87 (s, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 2.24 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.62, 159.33, 155.10, 154.68, 148.87, 143.76, 138.92, 124.57, 123.62, 119.51, 112.13, 109.48, 80.20, 59.82, 55.16, 53.51, 28.25, 21.53, 13.18, 10.37. HRMS (ESI-TOF) *m/z* calc'd for $C_{22}H_{31}N_2O_4$ $[M+H]^+$: 387.2278; found: 387.2283.



***tert*-Butyl (3-(3,3-dimethylbut-1-yn-1-yl)-5-methylphenyl)((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)carbamate** (**5f**).

Arene **2a** (39.0 mg, 0.1 mmol, 1 equiv.), $Pd(MeCN)_2Cl_2$ (1.6 mg, 6.0 μmol, 6 mol%), XPhos (8.9 mg, 18 μmol, 18 mol%), Cs_2CO_3 (81.5 mg, 0.25 mmol, 2.5 equiv.) were added to a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. MeCN (0.4 mL) was added to the mixture. After stirring for 30 minutes at room temperature, 3,3-dimethylbut-1-yne (17.5 μL, 0.14 mmol, 1.4 equiv.) was added to the reaction mixture. The Schlenk tube was immersed into a pre-heated oil bath at 90 °C. After 6 h, the oil bath was removed, and the Schlenk tube was allowed to cool to room temperature. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 2 mL). The filtrate was evaporated under reduced pressure. Purification by preparative TLC chromatography (hexane/EtOAc = 3:1 v/v) afforded 41.2 mg of compound **5f** as a yellow liquid (94% yield). R*f* = 0.61 (hexanes/EtOAc = 3:1 v/v).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.05 (s, 1H), 6.97 (s, 2H), 4.92 (s, 2H), 3.72 (s, 3H), 2.21 (d, *J* = 3.4 Hz, 6H), 2.20 (s, 3H), 1.38 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.64, 155.05, 154.60, 148.94, 142.52, 137.90, 129.65, 126.77, 126.69, 124.61, 123.84, 123.72, 97.96, 80.24, 76.86, 59.82, 53.40, 31.01, 28.22, 27.84, 21.08 13.18, 10.43. HRMS (ESI-TOF) *m/z* calc'd for $C_{27}H_{37}N_2O_3$ $[M+H]^+$: 437.2799; found: 437.2790.



3-Chloro-5-methylaniline (**s2**).

HBr aqueous solution (48 wt%, 0.5 mL) was added to arene **2a** (39.0 mg, 0.1 mmol, 1 equiv.) in a round flask. The reaction mixture was stirred at 100 °C overnight. Then the flask was allowed to cool to room temperature. Saturated $NaHCO_3$ aqueous solution (10 mL) was added to the mixture and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with Na_2SO_4. After the organic solvent was concentrated by rotatory evaporation, the residue was purified by preparative TLC chromatography (hexane/EtOAc = 5:1 v/v) afforded 13.5 mg of compound **s2** as a yellow liquid (95% yield). R*f* = 0.31 (hexanes/EtOAc = 6:1 v/v).

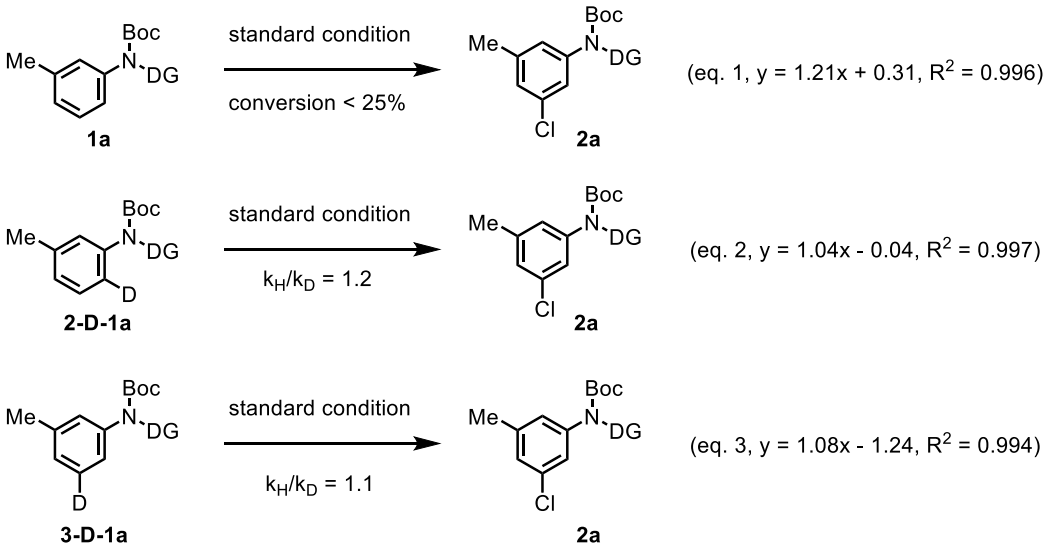
3.11 KIE Studies and Competition Experiments

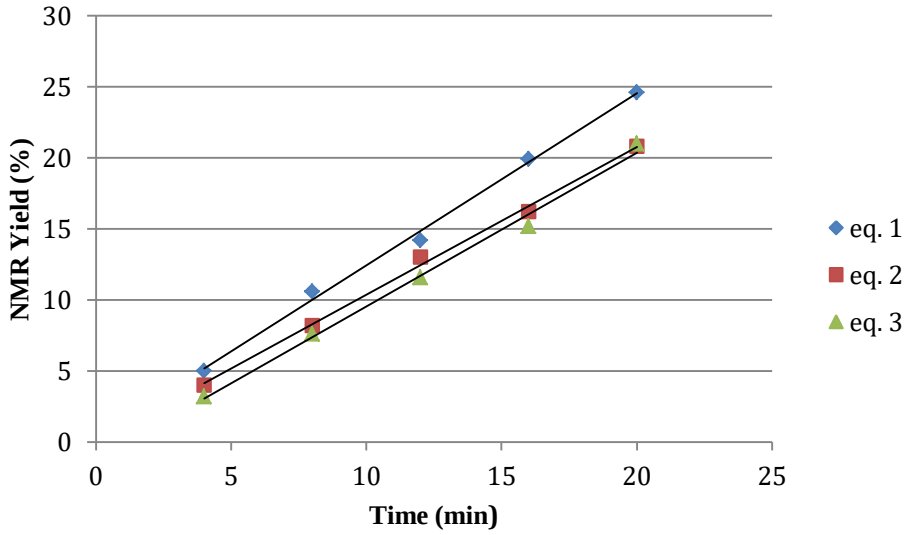
A. Measurement of the Kinetic Isotope Effect

Kinetic studies on the *meta*-chlorination of **1a**, **2-D-1a**, and **3-D-1a** were conducted in separate vessels.

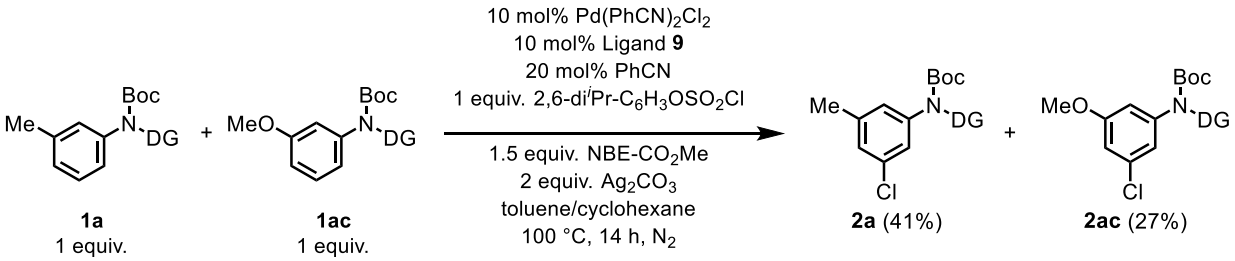
Arene (0.05 mmol, 1.0 equiv), $Pd(PhCN)_2Cl_2$ (1.9 mg, 5 μmol, 10 mol%), Ligand **9** (2.0 mg, 5 μmol, 10 mol%) and Ag_2CO_3 (27.6 mg, 0.10 mmol, 2.0 equiv.) were added into a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Toluene (0.5 mL), cyclohexane (0.5 mL), PhCN (1 μL, 10 μmol, 20 mol%), NBE-CO_2Me (12 μL, 0.075 mmol, 1.5 equiv.) and 2,6-di^{i}Pr-$C_6H_4OSO_2Cl$ (27.7 mg, 0.10 mmol, 2.0 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 100 °C. After indicated time, the oil bath was removed, and the Schlenk tube was cooled by ice water. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 2 mL). The filtrate was evaporated

under reduced pressure. The yield was determined by ^{1}H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard.





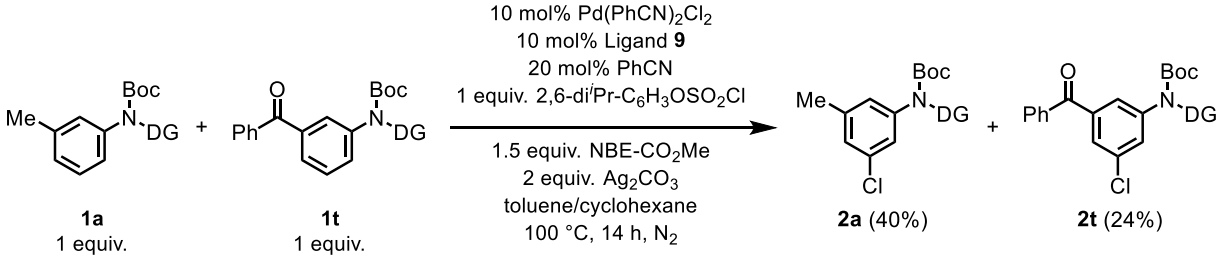
B. Competition Experiments



Arenes **1a** (35.6 mg, 0.10 mmol, 1.0 equiv), arenes **1ac** (37.2 mg, 0.10 mmol, 1.0 equiv), $Pd(PhCN)_2Cl_2$ (3.8 mg, 10 μmol, 10 mol%), Ligand **9** (3.9 mg, 10 μmol, 10 mol%) and Ag_2CO_3 (55.1 mg, 0.20 mmol, 2.0 equiv.) were added into a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Toluene (1 mL), cyclohexane (1 mL), PhCN (2 μL, 20 μmol, 20 mol%), NBE-CO_2Me (23 μL, 0.15 mmol, 1.5 equiv.) and 2,6-di^{i}Pr-$C_6H_4OSO_2Cl$ (27.7 mg, 0.10 mmol, 1.0 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 100 °C. After indicated time, the oil bath was removed, and the Schlenk tube was cooled by ice water. The reaction mixture was filtered through Celite and eluted with

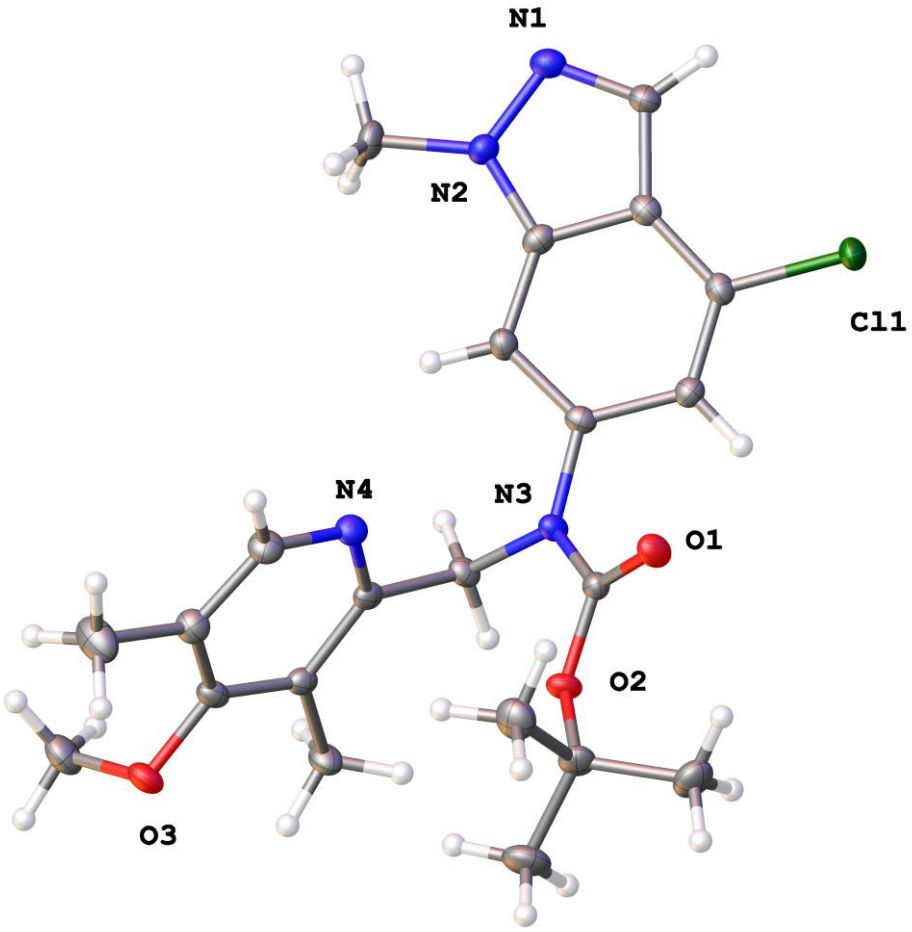
EtOAc (3 × 2 mL). The filtrate was evaporated under reduced pressure. Purification by preparative TLC chromatography afforded the corresponding products **2a** (16 mg, 41%) and **2ac** (11 mg, 27%).

2ac: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 6.90 (s, 1H), 6.77 (s, 1H), 6.66 (s, 1H), 4.85 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.26, 160.48, 155.18, 154.86, 149.64, 145.47, 134.57, 125.32, 124.03, 119.65, 111.98, 111.68, 81.32, 60.46, 56.08, 53.85, 28.78, 13.79, 10.93. HRMS (ESI-TOF) *m/z* calc'd for $C_{21}H_{28}ClN_2O_4$ $[M+H]^+$: 407.1732; found: 407.1739.



Arenes **1a** (35.6 mg, 0.10 mmol, 1.0 equiv), arenes **1t** (44.7 mg, 0.10 mmol, 1.0 equiv), $Pd(PhCN)_2Cl_2$ (3.8 mg, 10 μmol, 10 mol%), Ligand **9** (3.9 mg, 10 μmol, 10 mol%) and Ag_2CO_3 (55.1 mg, 0.20 mmol, 2.0 equiv.) were added into a flame-dried Schlenk tube. The Schlenk tube was evacuated and back-filled with nitrogen. Toluene (1 mL), cyclohexane (1 mL), PhCN (2 μL, 20 μmol, 20 mol%), NBE-CO_2Me (23 μL, 0.15 mmol, 1.5 equiv.) and 2,6-di^{i}Pr-$C_6H_4OSO_2Cl$ (27.7 mg, 0.10 mmol, 1.0 equiv.) were added to the mixture. The Schlenk tube was immersed into a pre-heated oil bath at 100 ℃. After indicated time, the oil bath was removed, and the Schlenk tube was cooled by ice water. The reaction mixture was filtered through Celite and eluted with EtOAc (3 × 2 mL). The filtrate was evaporated under reduced pressure. Purification by preparative TLC chromatography afforded the corresponding products **2a** (15.6 mg, 40%) and **2t** (11.6 mg, 24%).

4. X-ray Crystallographic Data of Compound 2aa



2aa

Table 1. Crystal data and structure refinement.

Report date	2016-08-01	
Identification code	Yu_SH160727-1	
Empirical formula	C22 H27 Cl N4 O3	
Molecular formula	C22 H27 Cl N4 O3	
Formula weight	430.92	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 14.7646(4) Å	□= 90°.
	b = 8.9396(2) Å	□= 90.0910(10)°.
	c = 16.5413(4) Å	□ = 90°.

Volume	2183.28(9) $Å^3$
Z	4
Density (calculated)	1.311 Mg/m^3
Absorption coefficient	1.803 mm^{-1}
F(000)	912
Crystal size	0.2 x 0.12 x 0.12 mm^3
Crystal color, habit	colorless block
Theta range for data collection	5.348 to 68.292°.
Index ranges	-17<=h<=17, -10<=k<=9, -19<=l<=19
Reflections collected	20152
Independent reflections	3973 [R(int) = 0.0405]
Completeness to theta = 67.500°	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.5210 and 0.4208
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3973 / 0 / 278
Goodness-of-fit on F^2	1.063
Final R indices [I>2sigma(I)]	R1 = 0.0370, wR2 = 0.0908
R indices (all data)	R1 = 0.0382, wR2 = 0.0915
Extinction coefficient	n/a
Largest diff. peak and hole	0.475 and -0.328 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	5863(1)	2590(1)	9193(1)	23(1)
O(1)	6023(1)	1526(1)	6281(1)	21(1)
O(2)	7169(1)	1774(1)	5370(1)	18(1)
O(3)	7820(1)	5663(1)	2896(1)	22(1)
N(1)	5412(1)	7631(1)	8744(1)	21(1)
N(2)	5746(1)	7597(1)	7976(1)	19(1)
N(3)	6998(1)	3528(1)	6302(1)	16(1)

N(4)	6324(1)	5184(1)	5003(1)	18(1)
C(1)	5480(1)	6251(2)	9021(1)	18(1)
C(2)	5864(1)	5282(2)	8438(1)	16(1)
C(3)	6090(1)	3769(2)	8377(1)	16(1)
C(4)	6474(1)	3218(2)	7688(1)	16(1)
C(5)	6610(1)	4164(2)	7007(1)	15(1)
C(6)	6385(1)	5665(2)	7031(1)	17(1)
C(7)	6028(1)	6201(2)	7764(1)	17(1)
C(8)	5790(1)	8931(2)	7485(1)	22(1)
C(9)	6666(1)	2198(2)	6003(1)	15(1)
C(10)	6847(1)	591(2)	4816(1)	21(1)
C(11)	7601(1)	546(2)	4190(1)	32(1)
C(12)	6769(1)	-897(2)	5253(1)	28(1)
C(13)	5956(1)	1088(2)	4439(1)	28(1)
C(14)	7620(1)	4412(2)	5799(1)	16(1)
C(15)	7214(1)	4895(1)	4997(1)	15(1)
C(16)	7758(1)	5028(1)	4307(1)	15(1)
C(17)	7331(1)	5541(2)	3606(1)	17(1)
C(18)	6405(1)	5863(2)	3593(1)	20(1)
C(19)	5939(1)	5641(2)	4311(1)	20(1)
C(20)	5935(1)	6405(2)	2840(1)	32(1)
C(21)	8248(1)	7093(2)	2804(1)	27(1)
C(22)	8748(1)	4597(2)	4292(1)	21(1)

Table 3. Bond lengths [Å] and angles [°].

Cl(1)-C(3)	1.7459(14)	N(1)-C(1)	1.3197(19)
O(1)-C(9)	1.2150(17)	N(2)-C(7)	1.3617(18)
O(2)-C(9)	1.3401(16)	N(2)-C(8)	1.4433(18)
O(2)-C(10)	1.4765(16)	N(3)-C(5)	1.4194(17)
O(3)-C(17)	1.3838(16)	N(3)-C(9)	1.3773(17)
O(3)-C(21)	1.4340(19)	N(3)-C(14)	1.4700(17)
N(1)-N(2)	1.3638(17)	N(4)-C(15)	1.3391(17)

N(4)-C(19)	1.3414(19)	C(18)-C(19)	1.388(2)
C(1)-H(1)	0.9500	C(18)-C(20)	1.505(2)
C(1)-C(2)	1.4161(19)	C(19)-H(19)	0.9500
C(2)-C(3)	1.397(2)	C(20)-H(20A)	0.9800
C(2)-C(7)	1.4057(19)	C(20)-H(20B)	0.9800
C(3)-C(4)	1.3662(19)	C(20)-H(20C)	0.9800
C(4)-H(4)	0.9500	C(21)-H(21A)	0.9800
C(4)-C(5)	1.4229(19)	C(21)-H(21B)	0.9800
C(5)-C(6)	1.3826(19)	C(21)-H(21C)	0.9800
C(6)-H(6)	0.9500	C(22)-H(22A)	0.9800
C(6)-C(7)	1.4072(19)	C(22)-H(22B)	0.9800
C(8)-H(8A)	0.9800	C(22)-H(22C)	0.9800
C(8)-H(8B)	0.9800		
C(8)-H(8C)	0.9800	C(9)-O(2)-C(10)	120.65(10)
C(10)-C(11)	1.522(2)	C(17)-O(3)-C(21)	113.06(11)
C(10)-C(12)	1.518(2)	C(1)-N(1)-N(2)	106.06(11)
C(10)-C(13)	1.521(2)	N(1)-N(2)-C(8)	121.47(11)
C(11)-H(11A)	0.9800	C(7)-N(2)-N(1)	111.73(11)
C(11)-H(11B)	0.9800	C(7)-N(2)-C(8)	126.79(12)
C(11)-H(11C)	0.9800	C(5)-N(3)-C(14)	120.22(11)
C(12)-H(12A)	0.9800	C(9)-N(3)-C(5)	119.73(11)
C(12)-H(12B)	0.9800	C(9)-N(3)-C(14)	118.92(11)
C(12)-H(12C)	0.9800	C(15)-N(4)-C(19)	117.87(11)
C(13)-H(13A)	0.9800	N(1)-C(1)-H(1)	124.3
C(13)-H(13B)	0.9800	N(1)-C(1)-C(2)	111.38(12)
C(13)-H(13C)	0.9800	C(2)-C(1)-H(1)	124.3
C(14)-H(14A)	0.9900	C(3)-C(2)-C(1)	137.52(13)
C(14)-H(14B)	0.9900	C(3)-C(2)-C(7)	117.85(12)
C(14)-C(15)	1.5169(19)	C(7)-C(2)-C(1)	104.63(12)
C(15)-C(16)	1.4022(18)	C(2)-C(3)-Cl(1)	118.86(10)
C(16)-C(17)	1.396(2)	C(4)-C(3)-Cl(1)	120.54(11)
C(16)-C(22)	1.5112(18)	C(4)-C(3)-C(2)	120.60(12)
C(17)-C(18)	1.3971(19)	C(3)-C(4)-H(4)	119.8

C(3)-C(4)-C(5)	120.35(12)	C(10)-C(12)-H(12B)	109.5
C(5)-C(4)-H(4)	119.8	C(10)-C(12)-H(12C)	109.5
N(3)-C(5)-C(4)	118.05(12)	H(12A)-C(12)-H(12B)	109.5
C(6)-C(5)-N(3)	120.63(12)	H(12A)-C(12)-H(12C)	109.5
C(6)-C(5)-C(4)	121.31(12)	H(12B)-C(12)-H(12C)	109.5
C(5)-C(6)-H(6)	121.8	C(10)-C(13)-H(13A)	109.5
C(5)-C(6)-C(7)	116.50(12)	C(10)-C(13)-H(13B)	109.5
C(7)-C(6)-H(6)	121.8	C(10)-C(13)-H(13C)	109.5
N(2)-C(7)-C(2)	106.21(12)	H(13A)-C(13)-H(13B)	109.5
N(2)-C(7)-C(6)	130.45(13)	H(13A)-C(13)-H(13C)	109.5
C(2)-C(7)-C(6)	123.30(13)	H(13B)-C(13)-H(13C)	109.5
N(2)-C(8)-H(8A)	109.5	N(3)-C(14)-H(14A)	108.8
N(2)-C(8)-H(8B)	109.5	N(3)-C(14)-H(14B)	108.8
N(2)-C(8)-H(8C)	109.5	N(3)-C(14)-C(15)	113.69(11)
H(8A)-C(8)-H(8B)	109.5	H(14A)-C(14)-H(14B)	107.7
H(8A)-C(8)-H(8C)	109.5	C(15)-C(14)-H(14A)	108.8
H(8B)-C(8)-H(8C)	109.5	C(15)-C(14)-H(14B)	108.8
O(1)-C(9)-O(2)	126.16(12)	N(4)-C(15)-C(14)	115.74(11)
O(1)-C(9)-N(3)	124.73(12)	N(4)-C(15)-C(16)	123.58(12)
O(2)-C(9)-N(3)	109.11(11)	C(16)-C(15)-C(14)	120.68(11)
O(2)-C(10)-C(11)	101.87(11)	C(15)-C(16)-C(22)	123.15(12)
O(2)-C(10)-C(12)	110.90(11)	C(17)-C(16)-C(15)	116.42(12)
O(2)-C(10)-C(13)	108.76(12)	C(17)-C(16)-C(22)	120.40(12)
C(12)-C(10)-C(11)	110.94(13)	O(3)-C(17)-C(16)	119.61(12)
C(12)-C(10)-C(13)	112.64(13)	O(3)-C(17)-C(18)	118.88(12)
C(13)-C(10)-C(11)	111.20(13)	C(16)-C(17)-C(18)	121.43(12)
C(10)-C(11)-H(11A)	109.5	C(17)-C(18)-C(20)	121.92(13)
C(10)-C(11)-H(11B)	109.5	C(19)-C(18)-C(17)	116.36(13)
C(10)-C(11)-H(11C)	109.5	C(19)-C(18)-C(20)	121.72(13)
H(11A)-C(11)-H(11B)	109.5	N(4)-C(19)-C(18)	124.30(12)
H(11A)-C(11)-H(11C)	109.5	N(4)-C(19)-H(19)	117.9
H(11B)-C(11)-H(11C)	109.5	C(18)-C(19)-H(19)	117.9
C(10)-C(12)-H(12A)	109.5	C(18)-C(20)-H(20A)	109.5

C(18)-C(20)-H(20B)	109.5	H(21A)-C(21)-H(21C)	109.5
C(18)-C(20)-H(20C)	109.5	H(21B)-C(21)-H(21C)	109.5
H(20A)-C(20)-H(20B)	109.5	C(16)-C(22)-H(22A)	109.5
H(20A)-C(20)-H(20C)	109.5	C(16)-C(22)-H(22B)	109.5
H(20B)-C(20)-H(20C)	109.5	C(16)-C(22)-H(22C)	109.5
O(3)-C(21)-H(21A)	109.5	H(22A)-C(22)-H(22B)	109.5
O(3)-C(21)-H(21B)	109.5	H(22A)-C(22)-H(22C)	109.5
O(3)-C(21)-H(21C)	109.5	H(22B)-C(22)-H(22C)	109.5
H(21A)-C(21)-H(21B)	109.5		

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	30(1)	19(1)	19(1)	6(1)	8(1)	4(1)
O(1)	25(1)	18(1)	20(1)	-1(1)	5(1)	-6(1)
O(2)	22(1)	17(1)	16(1)	-5(1)	4(1)	-1(1)
O(3)	25(1)	26(1)	15(1)	-1(1)	6(1)	-1(1)
N(1)	22(1)	21(1)	19(1)	-3(1)	2(1)	2(1)
N(2)	24(1)	15(1)	18(1)	-1(1)	2(1)	2(1)
N(3)	18(1)	14(1)	14(1)	-1(1)	4(1)	-2(1)
N(4)	15(1)	18(1)	19(1)	0(1)	3(1)	-1(1)
C(1)	18(1)	19(1)	16(1)	-1(1)	2(1)	1(1)
C(2)	14(1)	20(1)	15(1)	0(1)	-1(1)	-1(1)
C(3)	15(1)	19(1)	15(1)	2(1)	0(1)	-1(1)
C(4)	16(1)	15(1)	18(1)	0(1)	0(1)	0(1)
C(5)	14(1)	17(1)	14(1)	-2(1)	0(1)	-1(1)
C(6)	19(1)	16(1)	15(1)	1(1)	0(1)	-2(1)
C(7)	15(1)	14(1)	20(1)	-2(1)	-2(1)	0(1)
C(8)	27(1)	14(1)	23(1)	6(1)	-1(1)	-1(1)
C(9)	18(1)	14(1)	13(1)	1(1)	1(1)	2(1)
C(10)	28(1)	18(1)	17(1)	-7(1)	0(1)	-1(1)

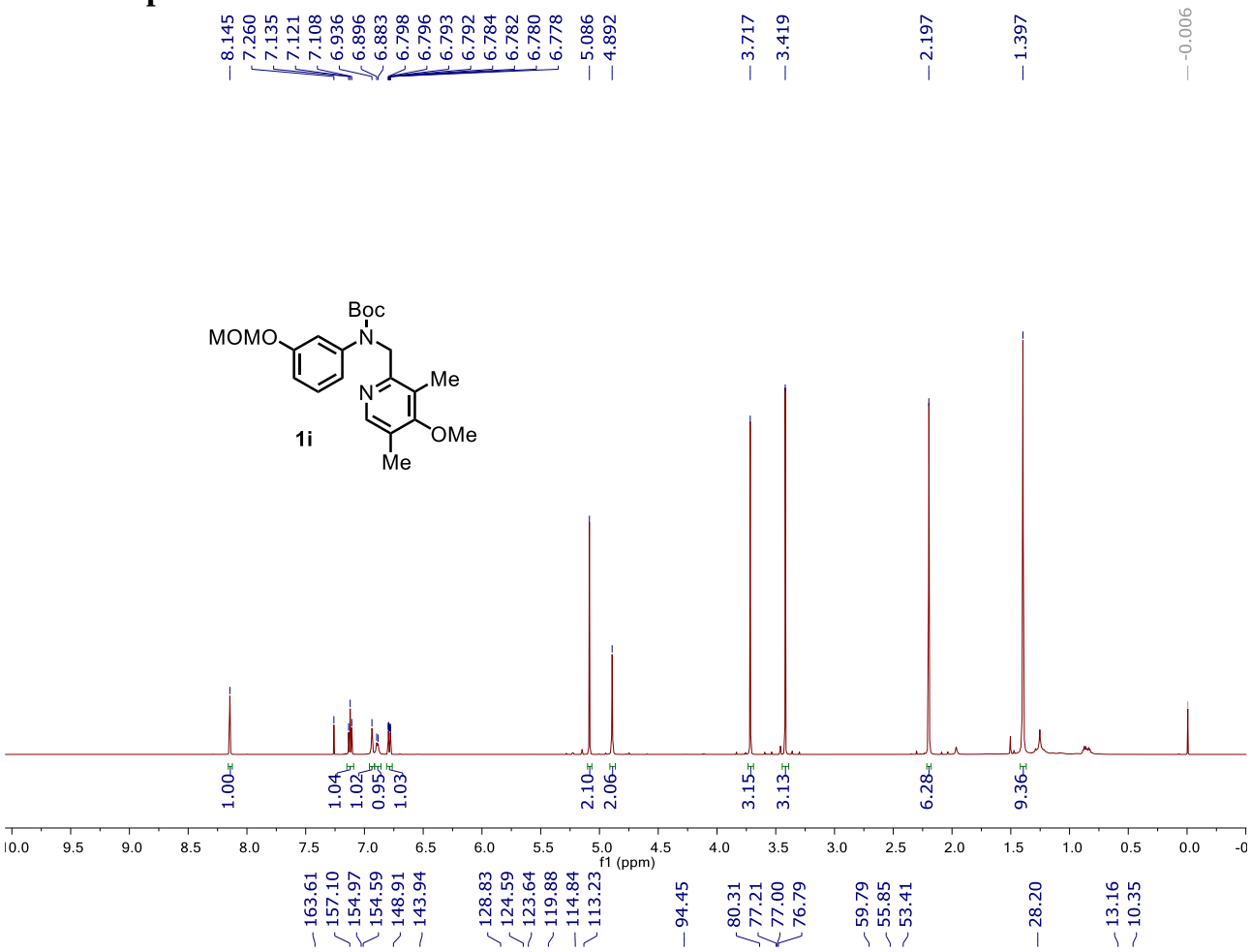
C(11)	37(1)	35(1)	23(1)	-12(1)	7(1)	1(1)
C(12)	38(1)	17(1)	30(1)	-5(1)	-2(1)	2(1)
C(13)	32(1)	32(1)	21(1)	-2(1)	-5(1)	-1(1)
C(14)	16(1)	18(1)	16(1)	0(1)	3(1)	-3(1)
C(15)	16(1)	11(1)	17(1)	-2(1)	2(1)	-2(1)
C(16)	16(1)	13(1)	18(1)	-2(1)	2(1)	-2(1)
C(17)	19(1)	16(1)	15(1)	-3(1)	4(1)	-3(1)
C(18)	18(1)	21(1)	19(1)	-1(1)	-2(1)	-2(1)
C(19)	14(1)	23(1)	23(1)	0(1)	1(1)	-1(1)
C(20)	22(1)	50(1)	24(1)	6(1)	-3(1)	1(1)
C(21)	28(1)	33(1)	21(1)	3(1)	6(1)	-6(1)
C(22)	17(1)	26(1)	20(1)	2(1)	4(1)	2(1)

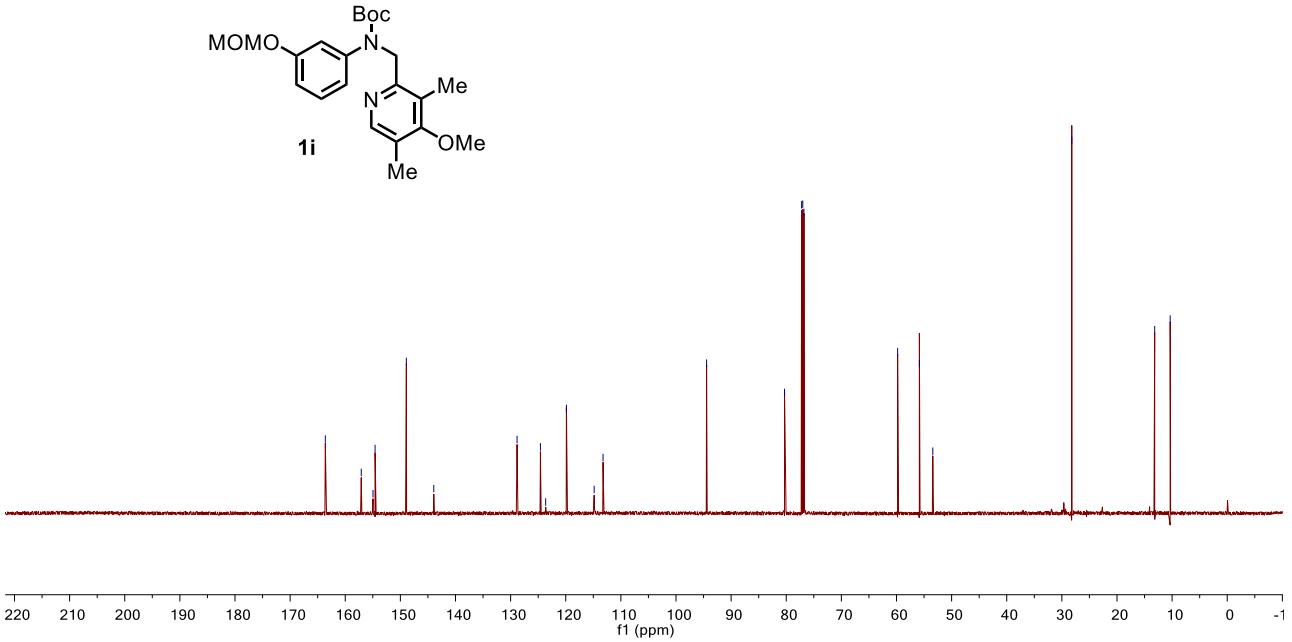
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3).

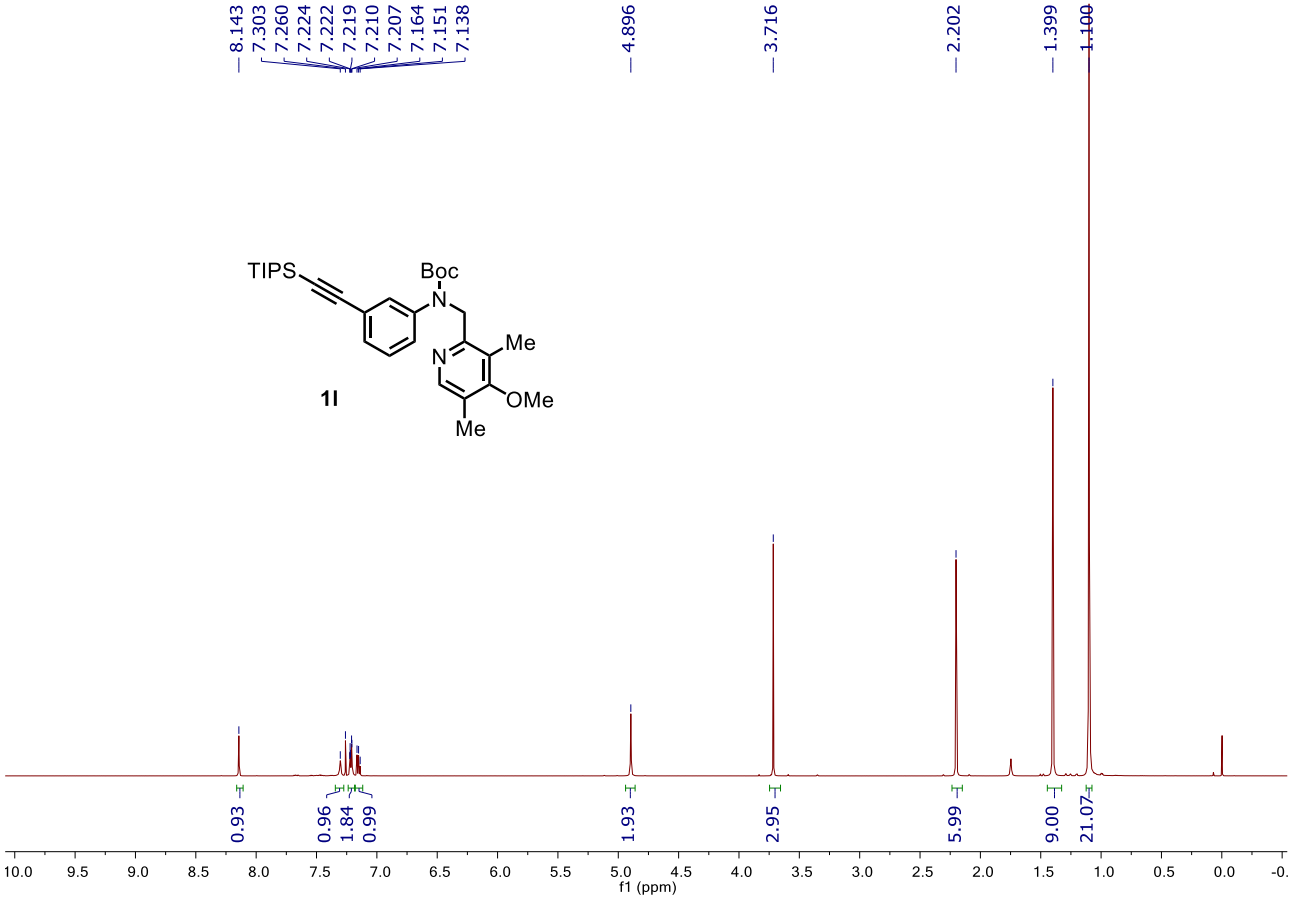
	x	y	z	U(eq)
H(1)	5294	5947	9546	21
H(4)	6652	2197	7663	19
H(6)	6469	6300	6577	20
H(8A)	5557	9783	7794	32
H(8B)	5424	8792	6997	32
H(8C)	6421	9123	7333	32
H(11A)	7683	1546	3958	48
H(11B)	7440	-160	3761	48
H(11C)	8166	225	4449	48
H(12A)	7311	-1058	5586	43
H(12B)	6715	-1706	4856	43
H(12C)	6232	-887	5600	43
H(13A)	5500	1210	4864	43
H(13B)	5751	331	4052	43
H(13C)	6044	2043	4160	43
H(14A)	8170	3813	5693	20
H(14B)	7806	5314	6104	20

H(19)	5305	5824	4312	24
H(20A)	5979	5639	2418	48
H(20B)	6225	7328	2652	48
H(20C)	5296	6602	2960	48
H(21A)	8642	7074	2327	41
H(21B)	8611	7313	3286	41
H(21C)	7785	7867	2735	41
H(22A)	9112	5417	4513	31
H(22B)	8933	4397	3733	31
H(22C)	8839	3696	4620	31

5. NMR Spectra



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1.399
1.100
TIPS
Boc
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Me
N
OMe
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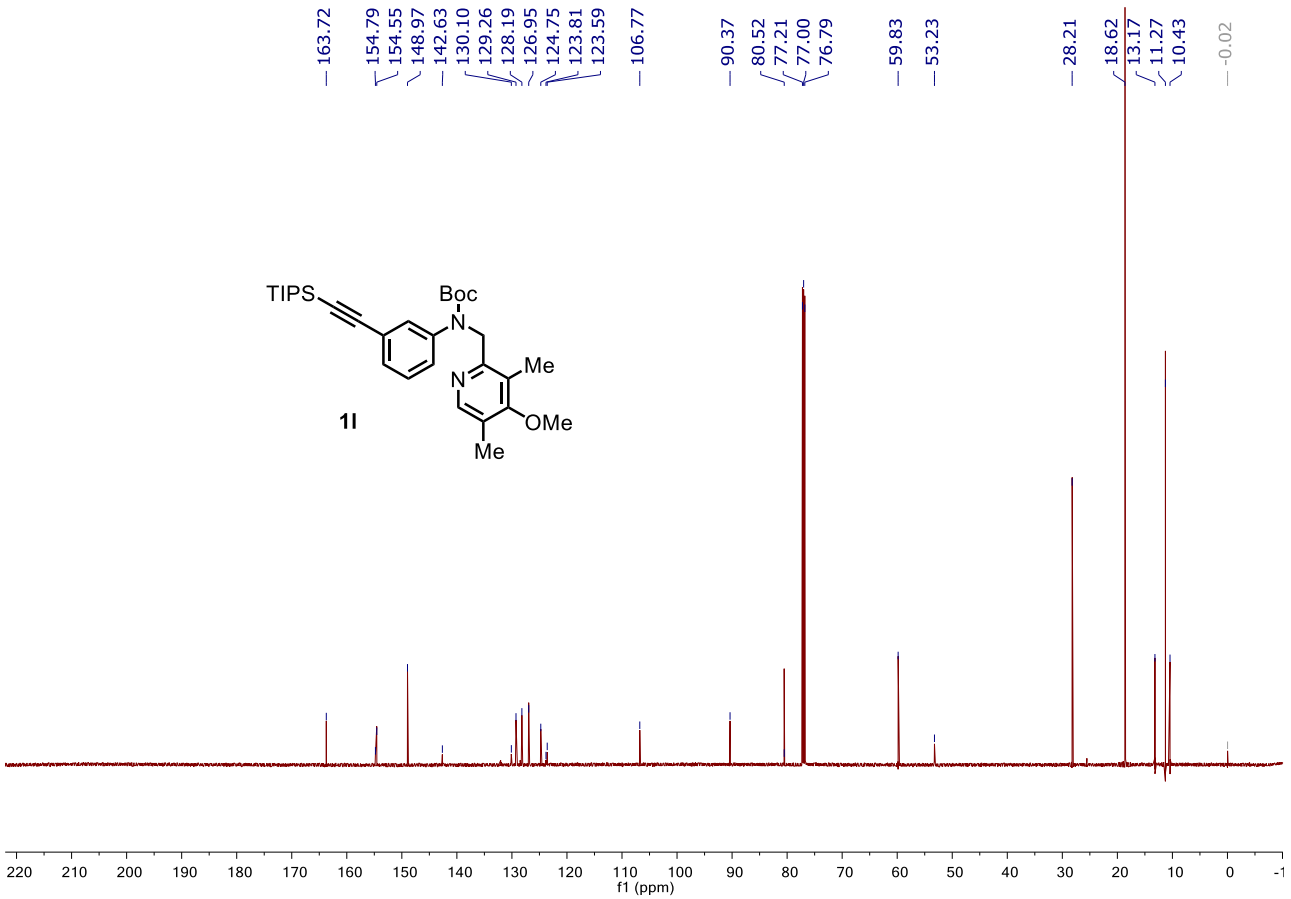
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Me
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OMe
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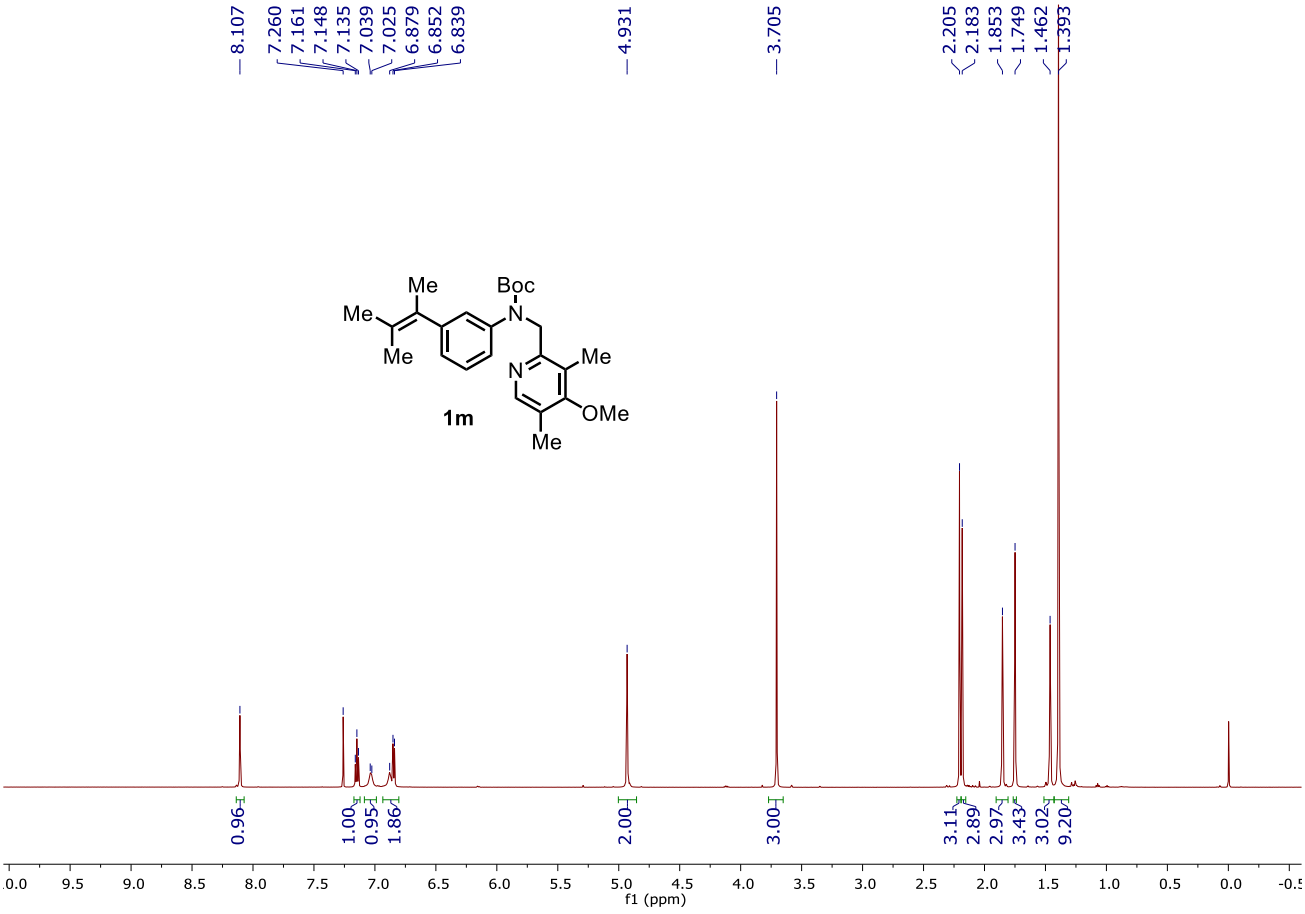
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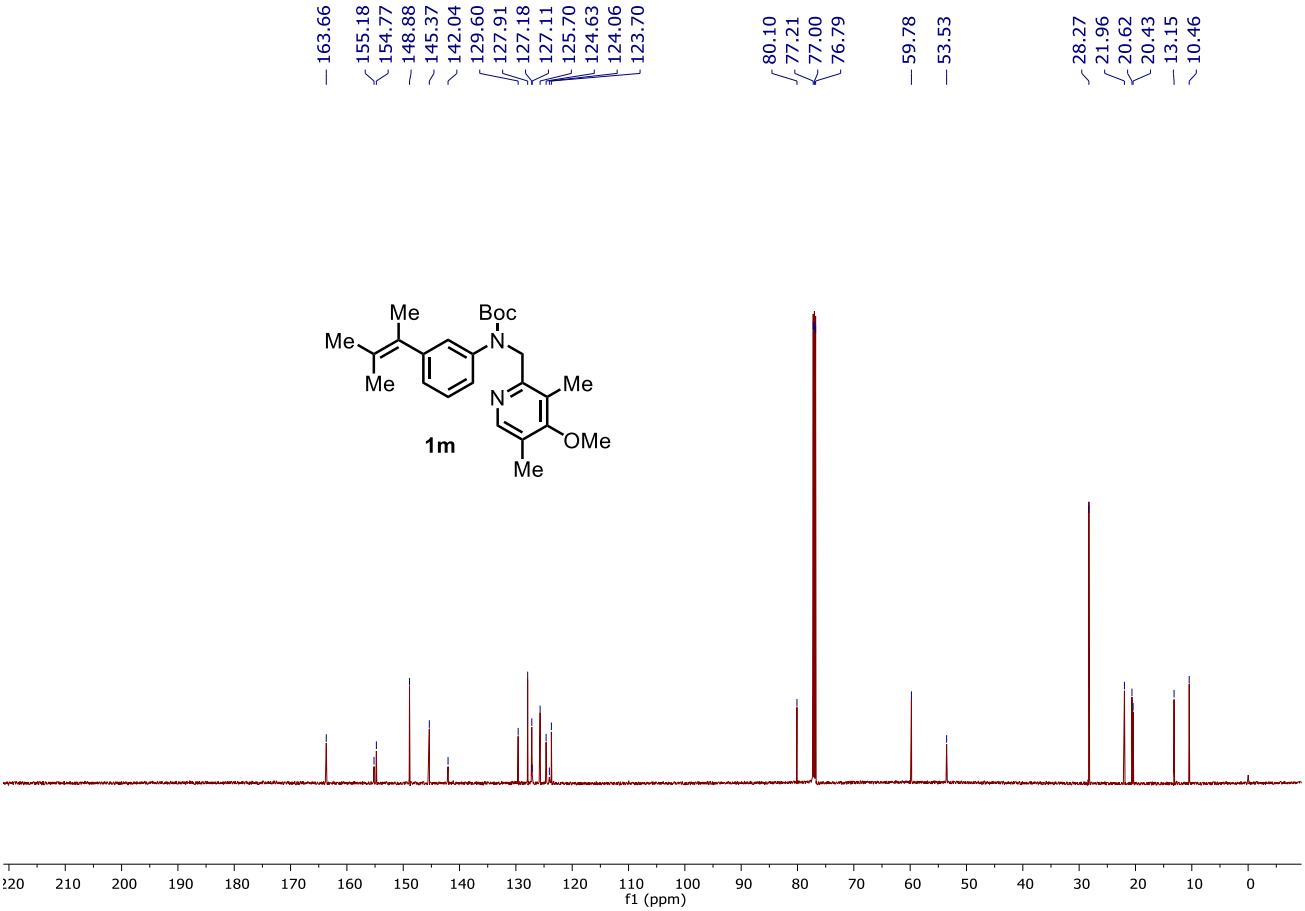
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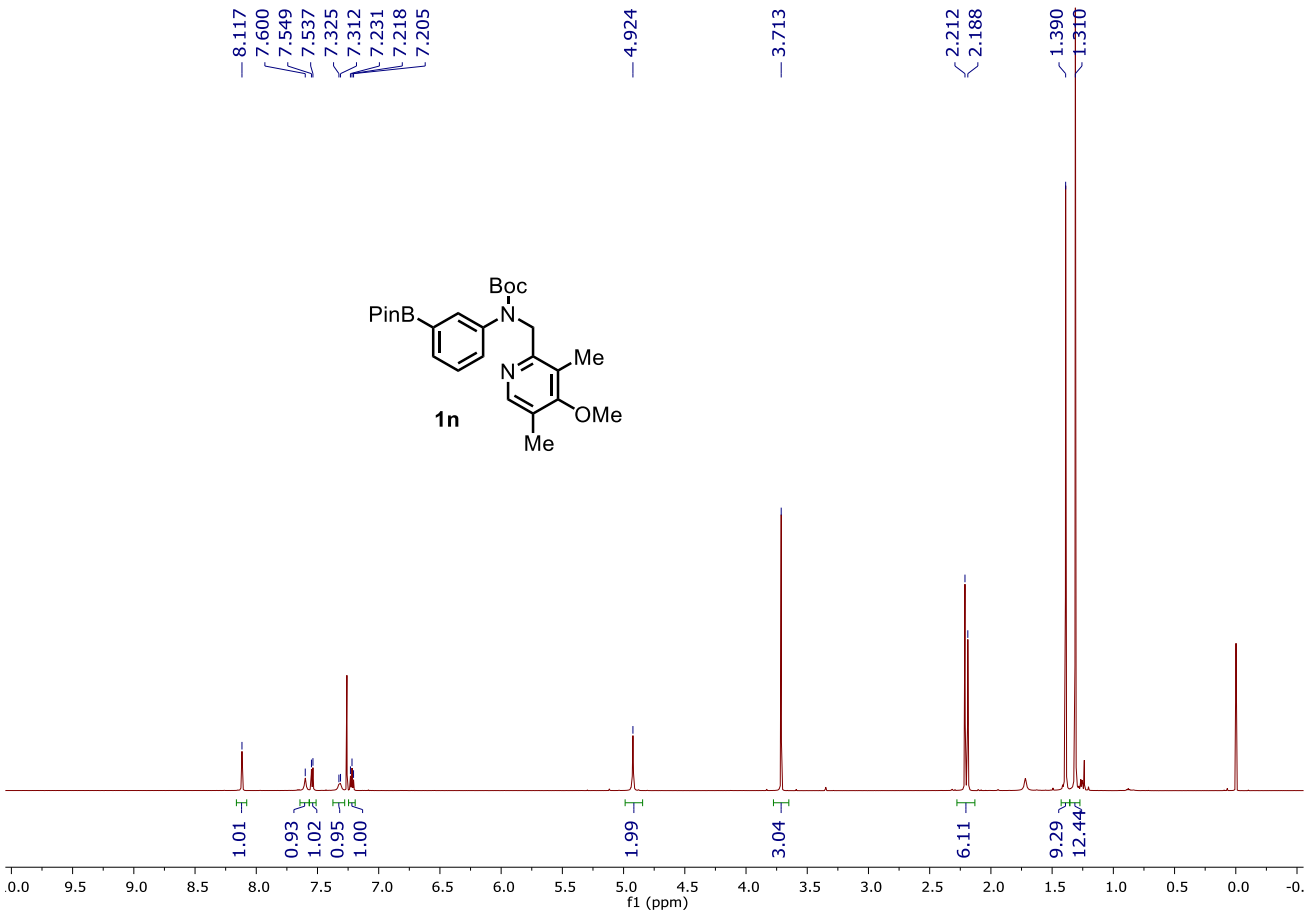
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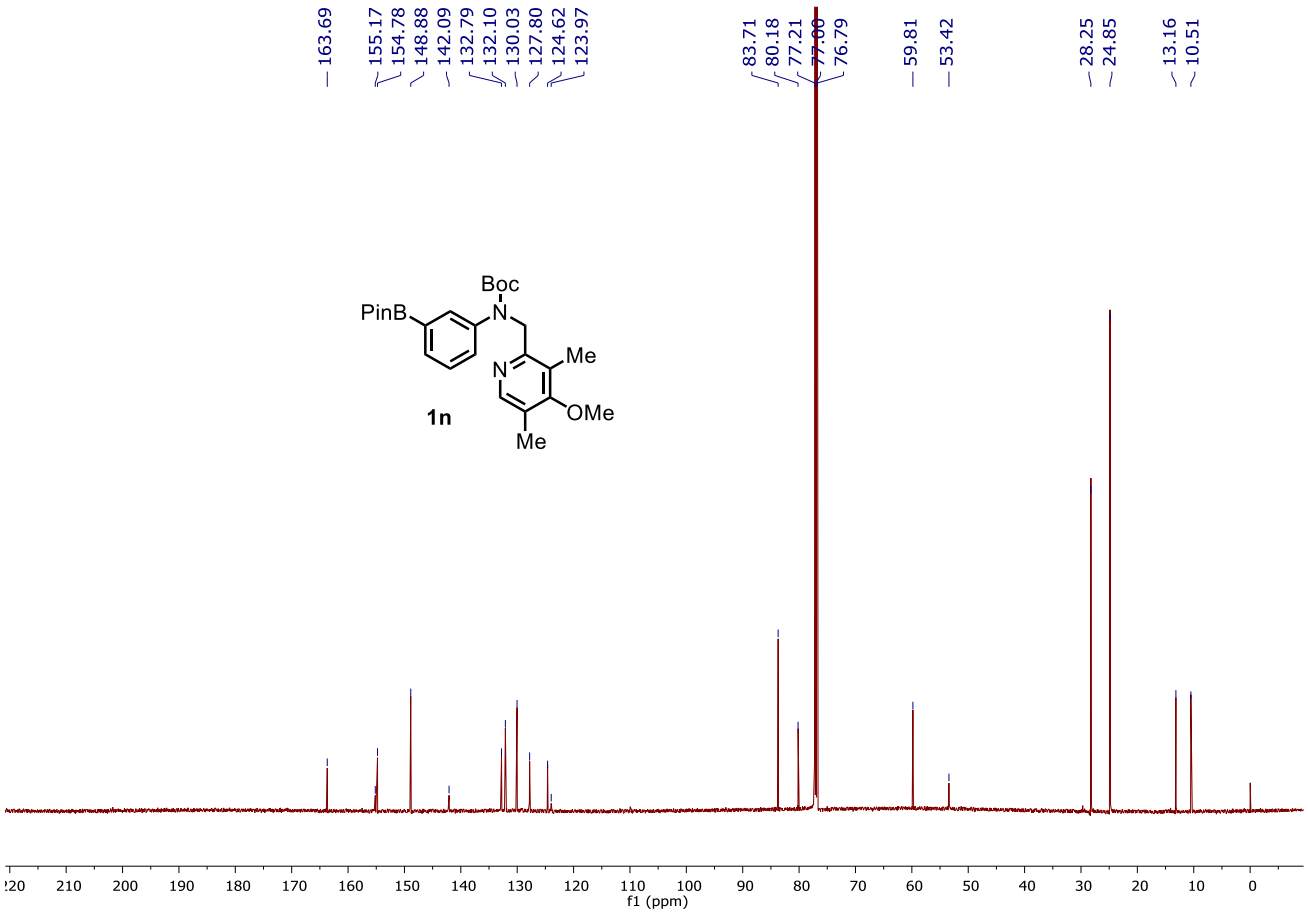
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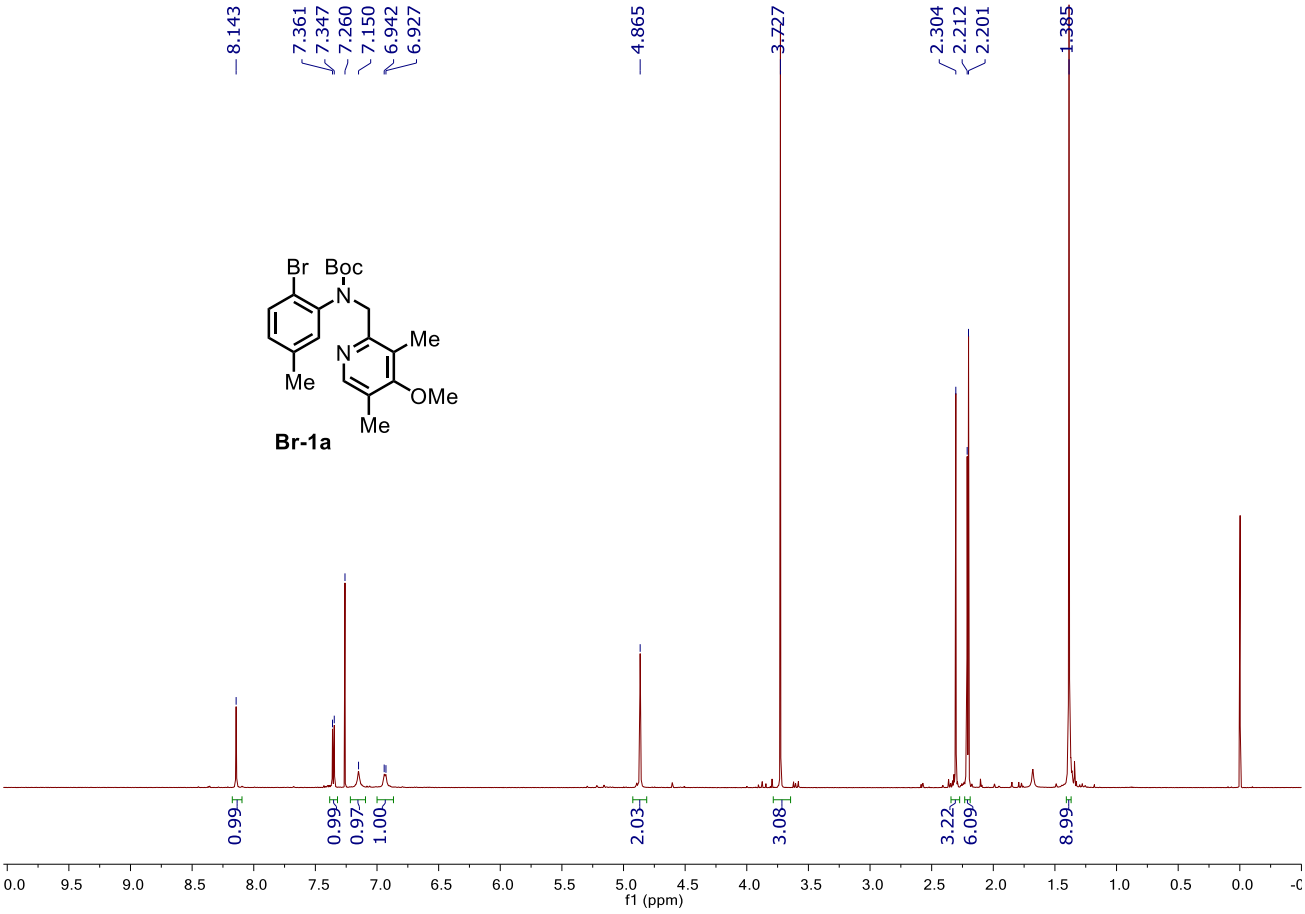
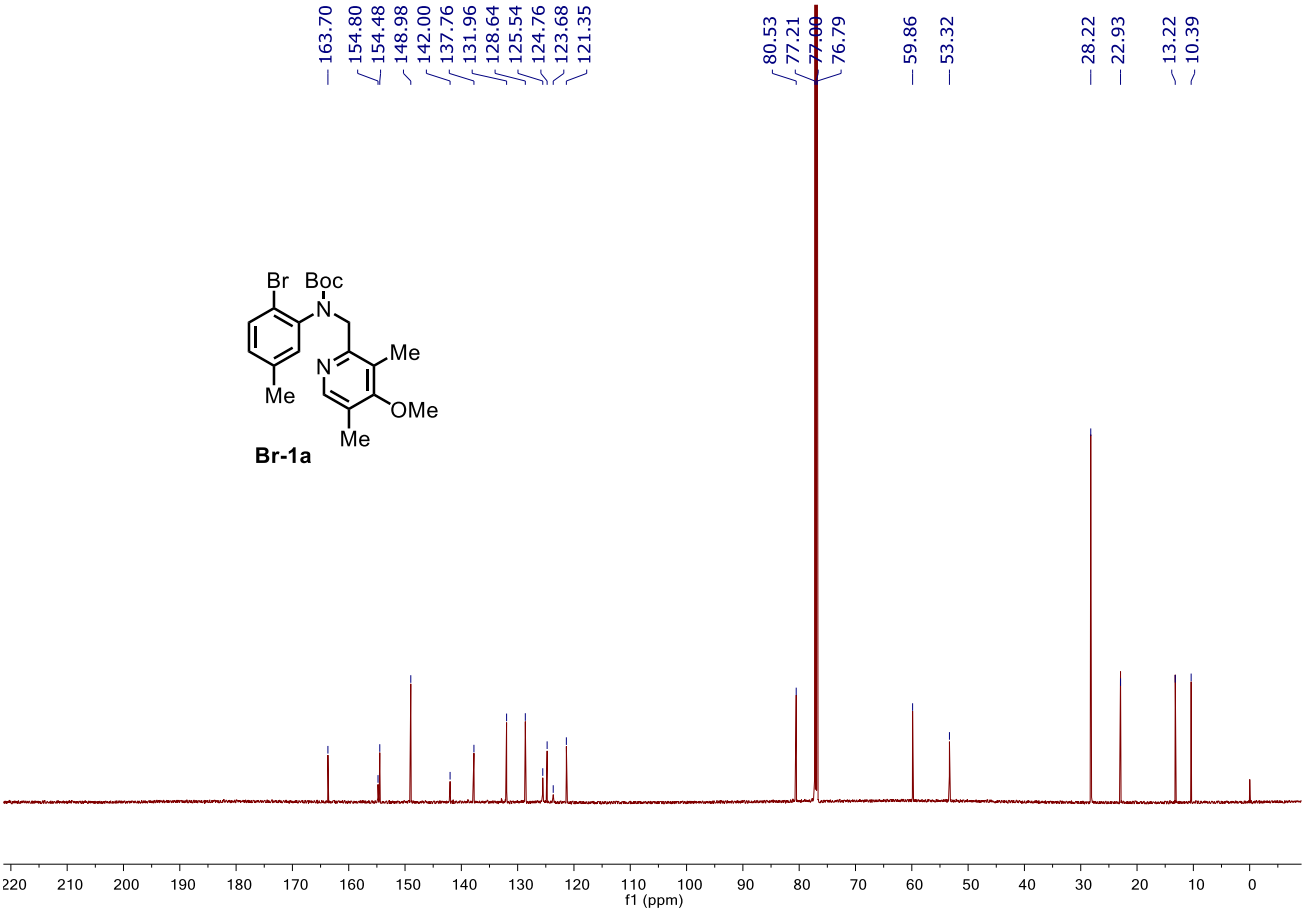
28.25
24.85
13.16
10.51
Boc
PinB
N
Me
N
OMe
Me
1n
f1 (ppm)


8.143
7.361
7.347
7.260
7.150
6.942
6.927
4.865
3.727
2.304
2.212
2.201
1.385
Br
Boc
N
Me
N
Me
OMe
Me
Br-1a
0.99
0.99
0.97
1.00
2.03
3.08
3.22
6.09
8.99
f1 (ppm)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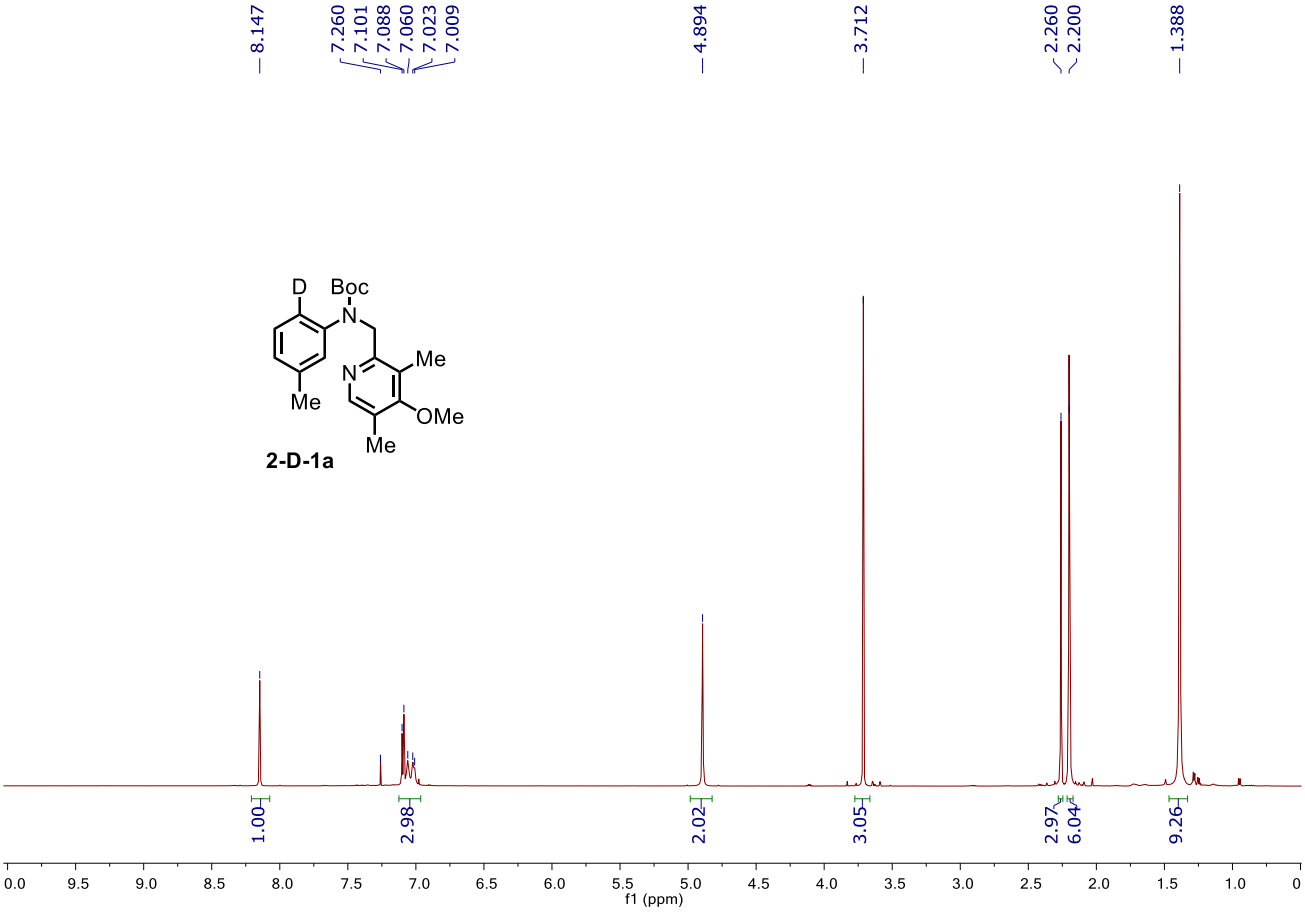
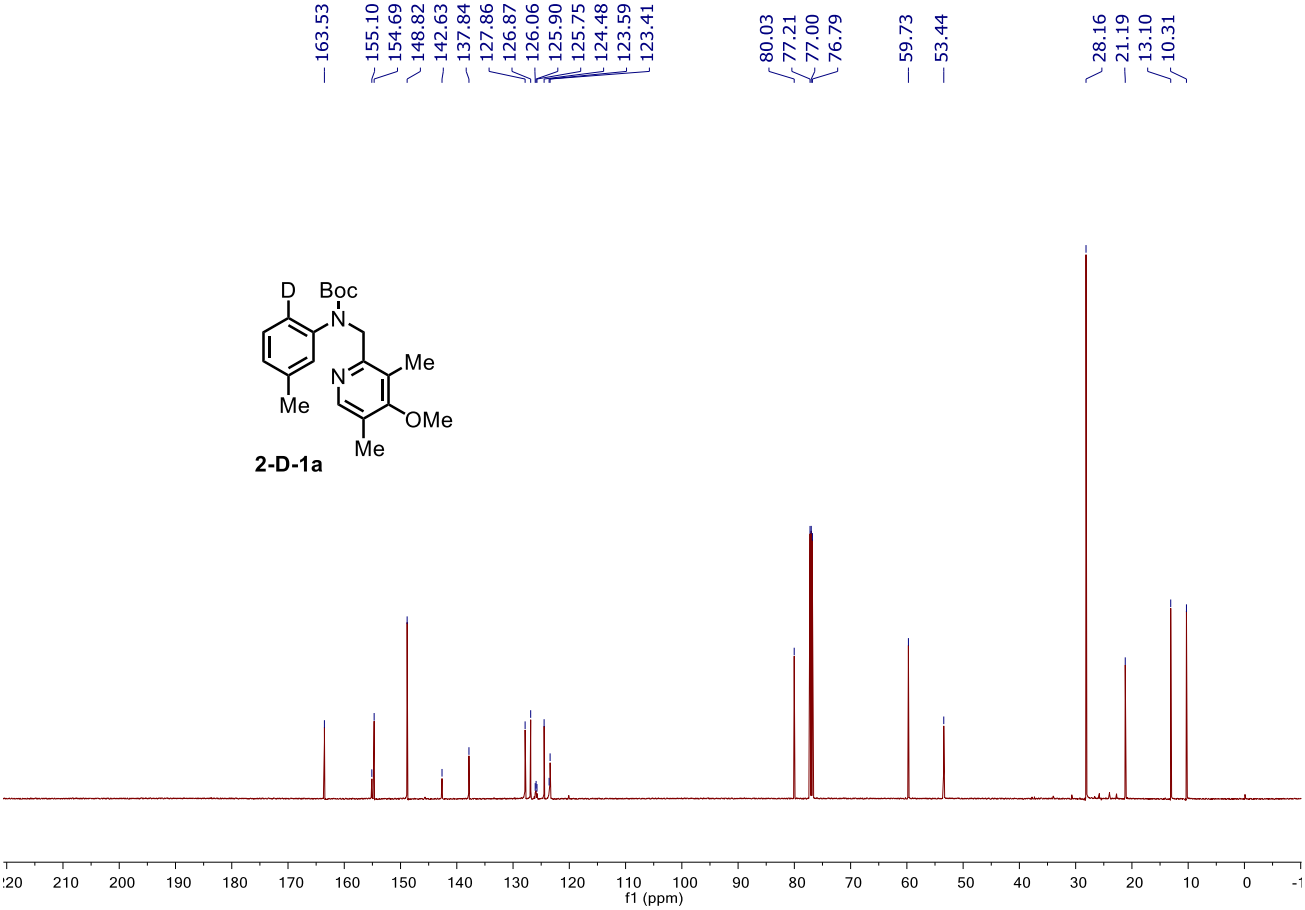
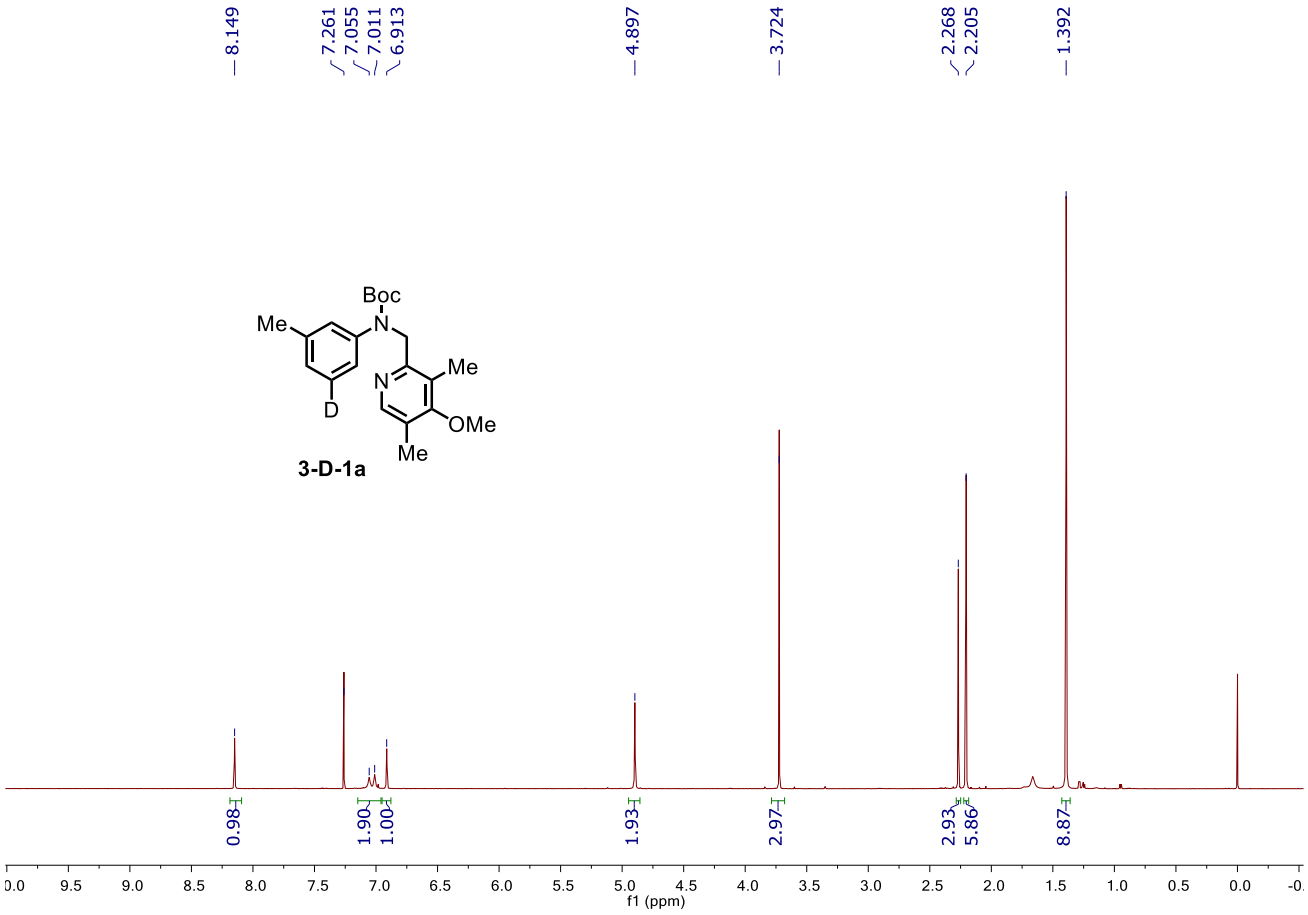
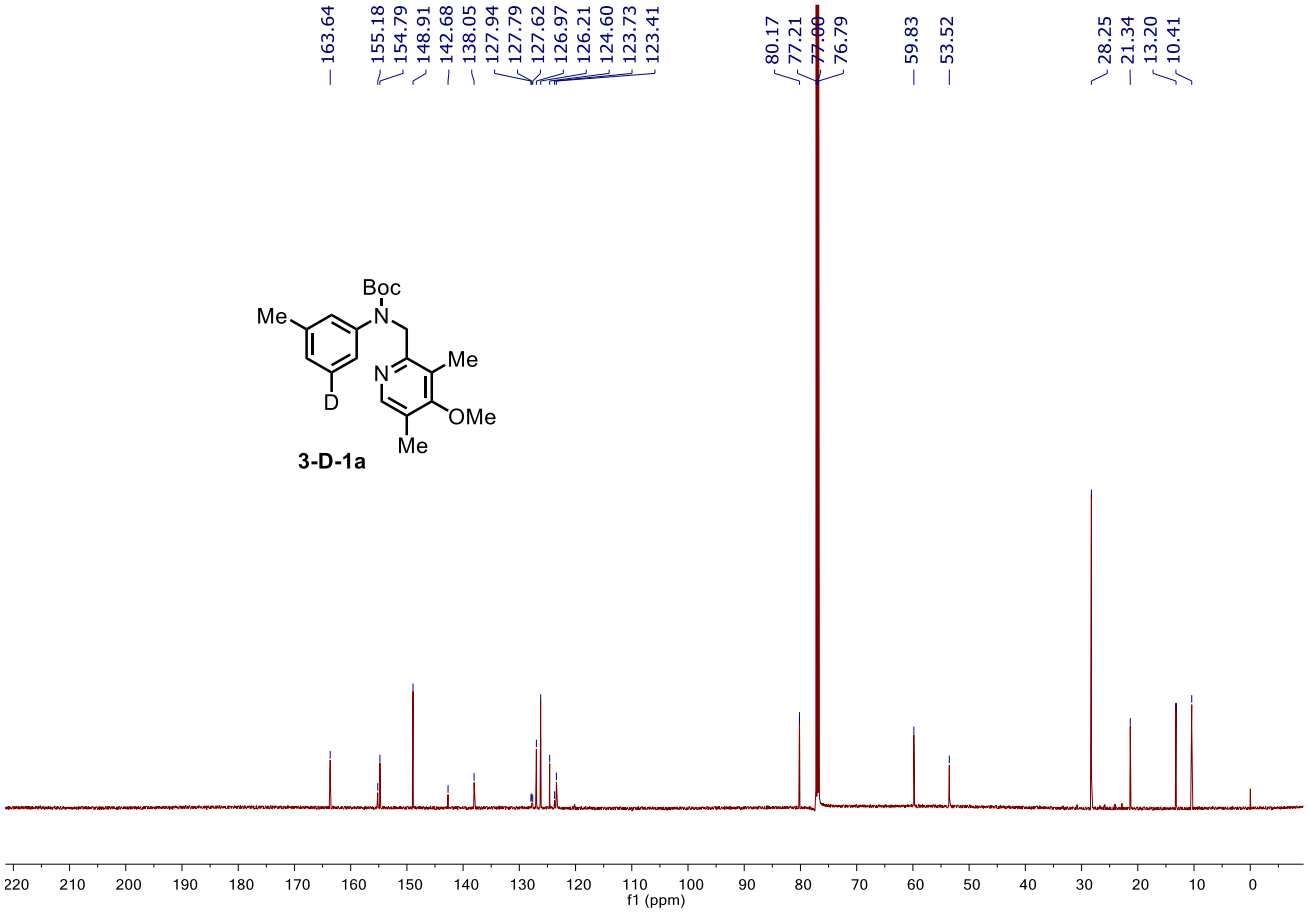
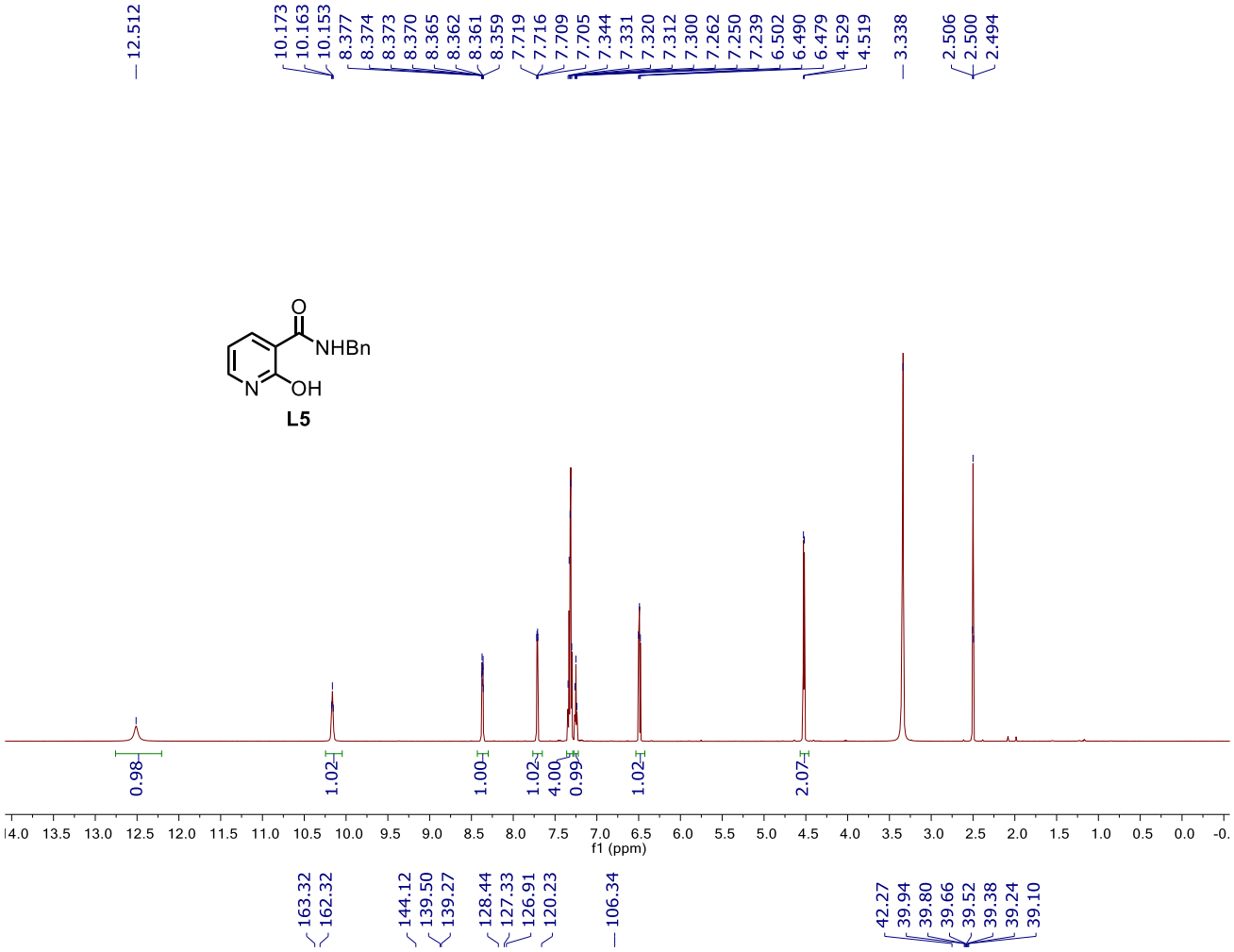
154.80
154.48
148.98
142.00
137.76
131.96
128.64
125.54
124.76
123.68
121.35
80.53
77.21
77.00
76.79
59.86
53.32
28.22
22.93
13.22
10.39
Br
Boc
N
Me
N
Me
OMe
Me
Br-1a
f1 (ppm)

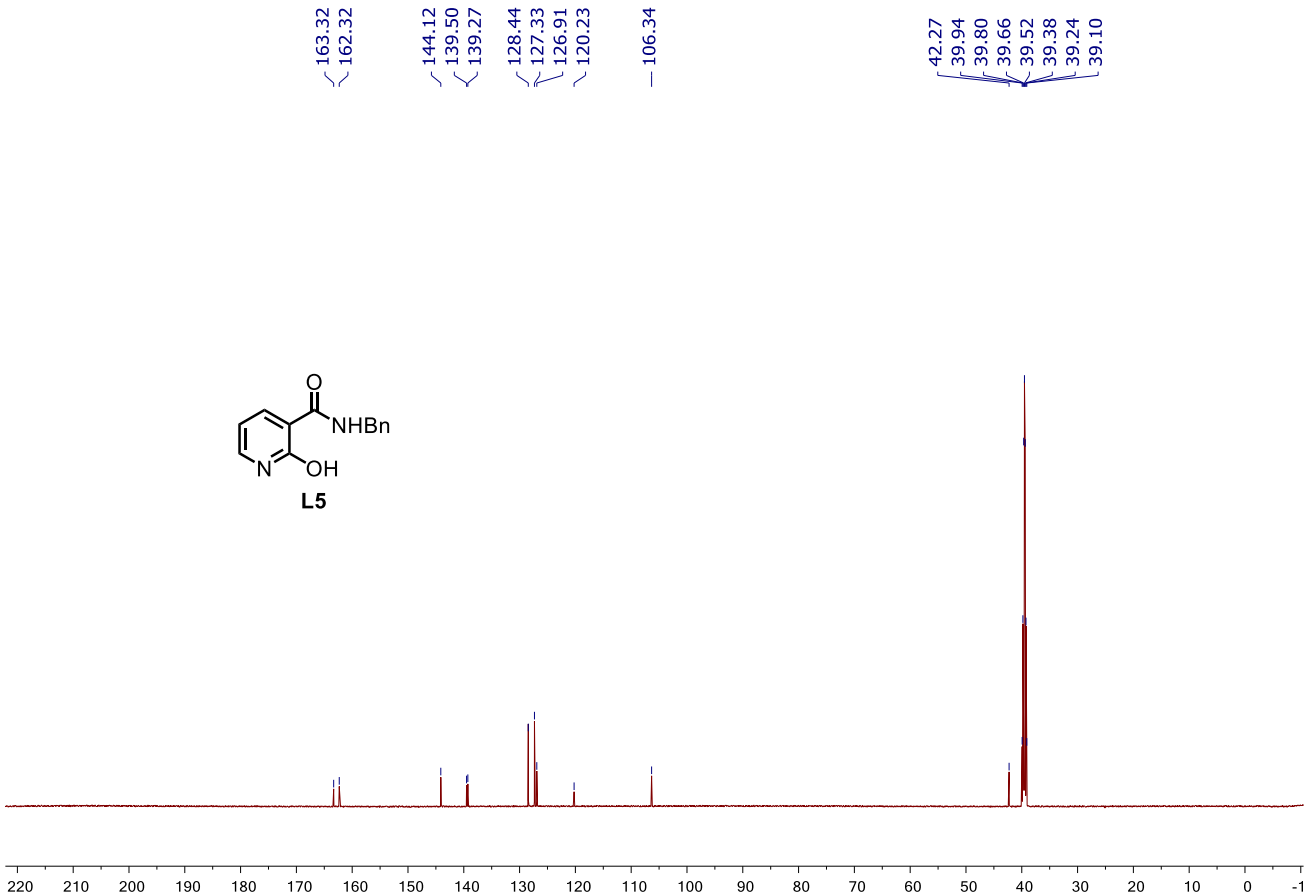

8.147
7.260
7.101
7.088
7.060
7.023
7.009
4.894
3.712
2.260
2.200
1.388
D
Boc
N
Me
N
Me
OMe
Me
2-D-1a
1.00
2.98
2.02
3.05
2.97
6.04
9.26
f1 (ppm)


163.53
155.10
154.69
148.82
142.63
137.84
127.86
126.87
126.06
125.90
125.75
124.48
123.59
123.41
80.03
77.21
77.00
76.79
59.73
53.44
28.16
21.19
13.10
10.31
D
Boc
N
Me
N
Me
OMe
Me
2-D-1a
f1 (ppm)

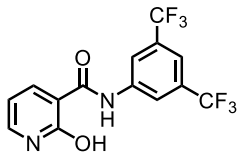

8.149
7.261
7.055
7.011
6.913
4.897
3.724
2.268
2.205
1.392
Boc
N
Me
D
N
Me
OMe
Me
3-D-1a
0.98
1.90
1.00
1.93
2.97
2.93
5.86
8.87
f1 (ppm)


163.64
155.18
154.79
148.91
142.68
138.05
127.94
127.79
127.62
126.97
126.21
124.60
123.73
123.41
80.17
77.21
77.00
76.79
59.83
53.52
28.25
21.34
13.20
10.41
Boc
N
Me
D
N
Me
OMe
Me
3-D-1a
f1 (ppm)

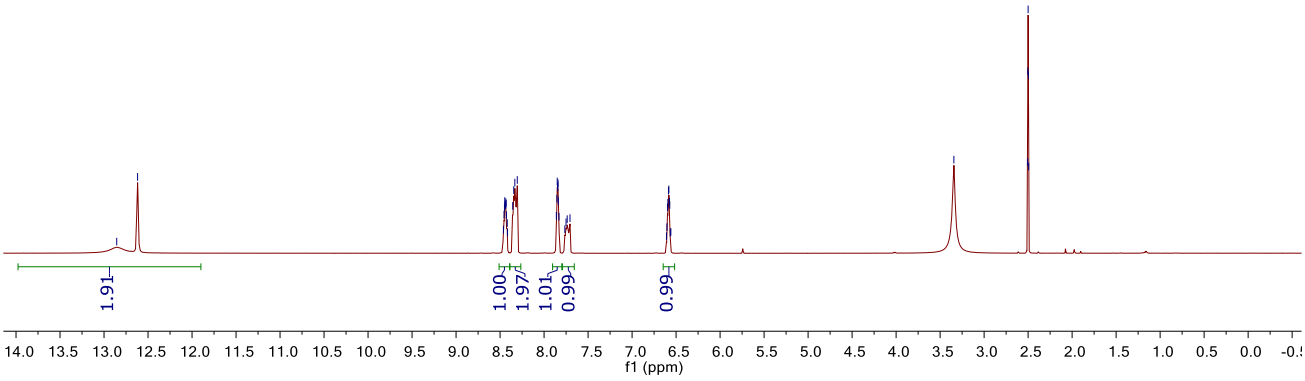

12.512
10.173
10.163
10.153
8.377
8.374
8.373
8.370
8.365
8.362
8.361
8.359
7.719
7.716
7.709
7.705
7.344
7.331
7.320
7.312
7.300
7.262
7.250
7.239
6.502
6.490
6.479
4.529
4.519
3.338
2.506
2.500
2.494
NHBn
OH
N
O
L5
0.98
1.02
1.00
1.02
4.00
0.99
1.02
2.07
f1 (ppm)

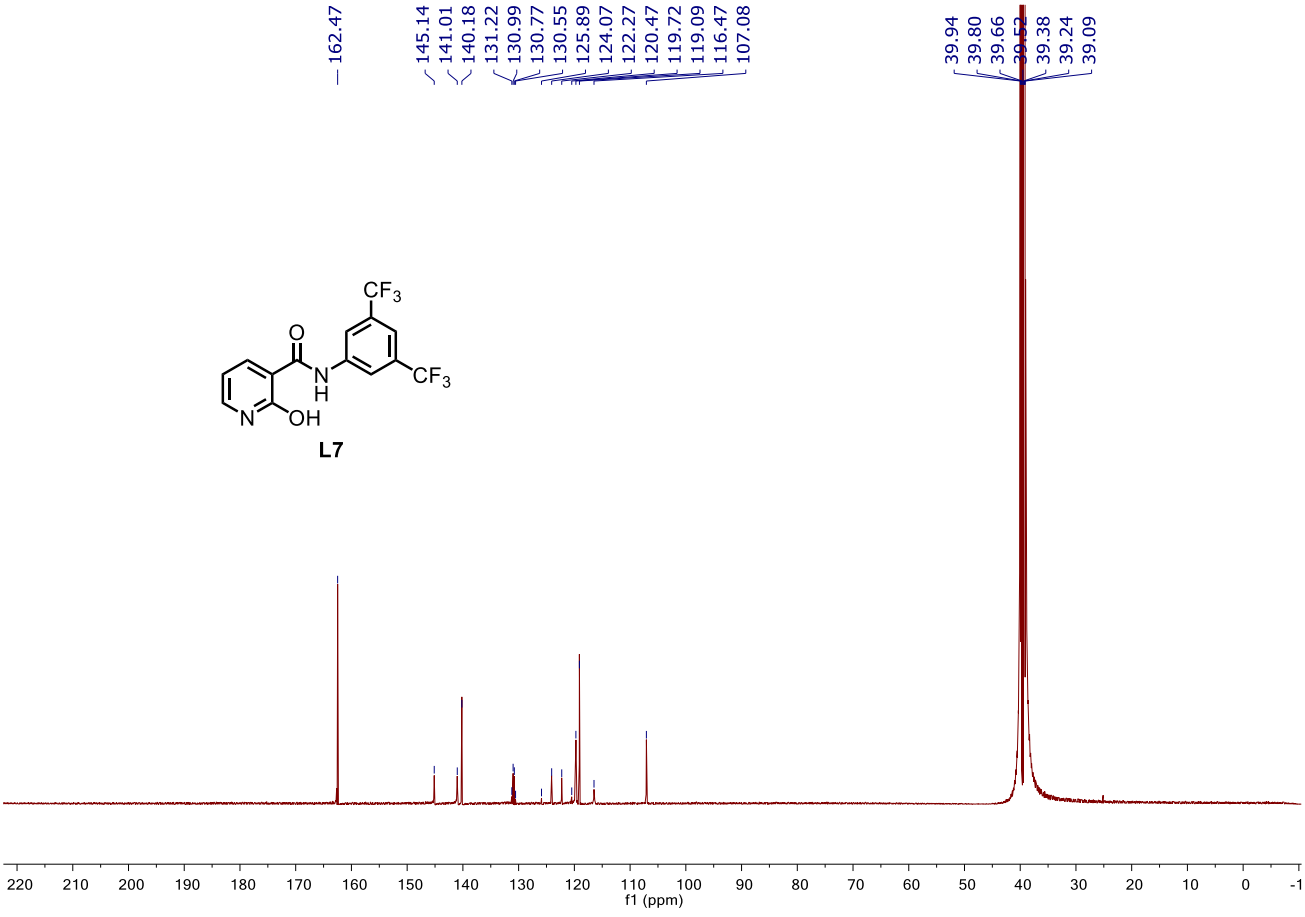

163.32
162.32
144.12
139.50
139.27
128.44
127.33
126.91
120.23
106.34
42.27
39.94
39.80
39.66
39.52
39.38
39.24
39.10
NHBn
OH
N
O
L5
f1 (ppm)


12.619
8.455
8.450
8.447
8.443
8.437
8.435
8.431
8.427
8.419
8.356
8.344
8.332
8.305
7.861
7.854
7.851
7.846
7.844
7.841
7.838
7.831
7.764
7.750
7.737
6.604
6.597
6.593
6.586
6.582
6.575
6.572
6.565
6.560
3.344
2.506
2.503
2.500
2.497
2.494


CF3
O
N
H
CF3
N
OH

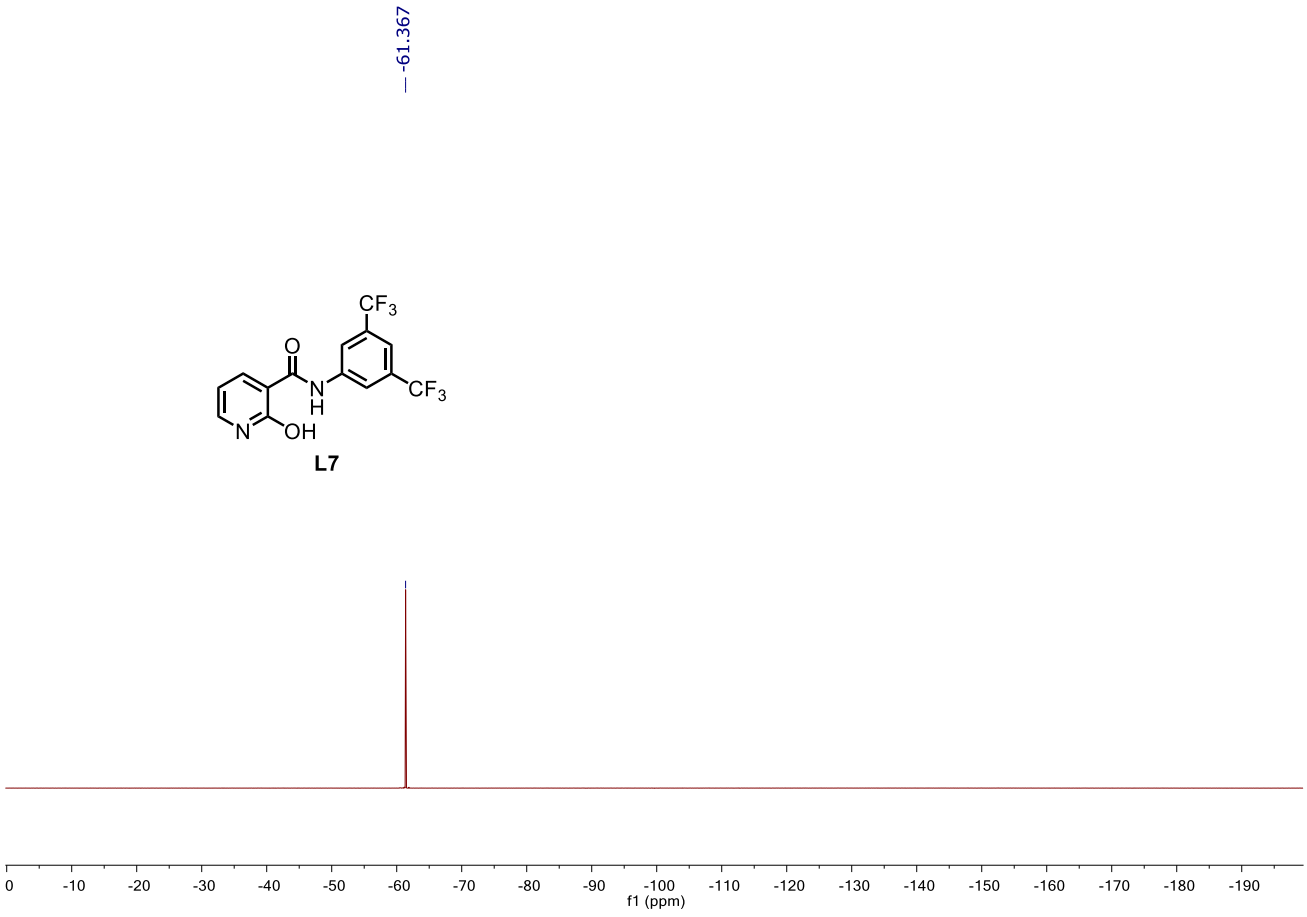
L7

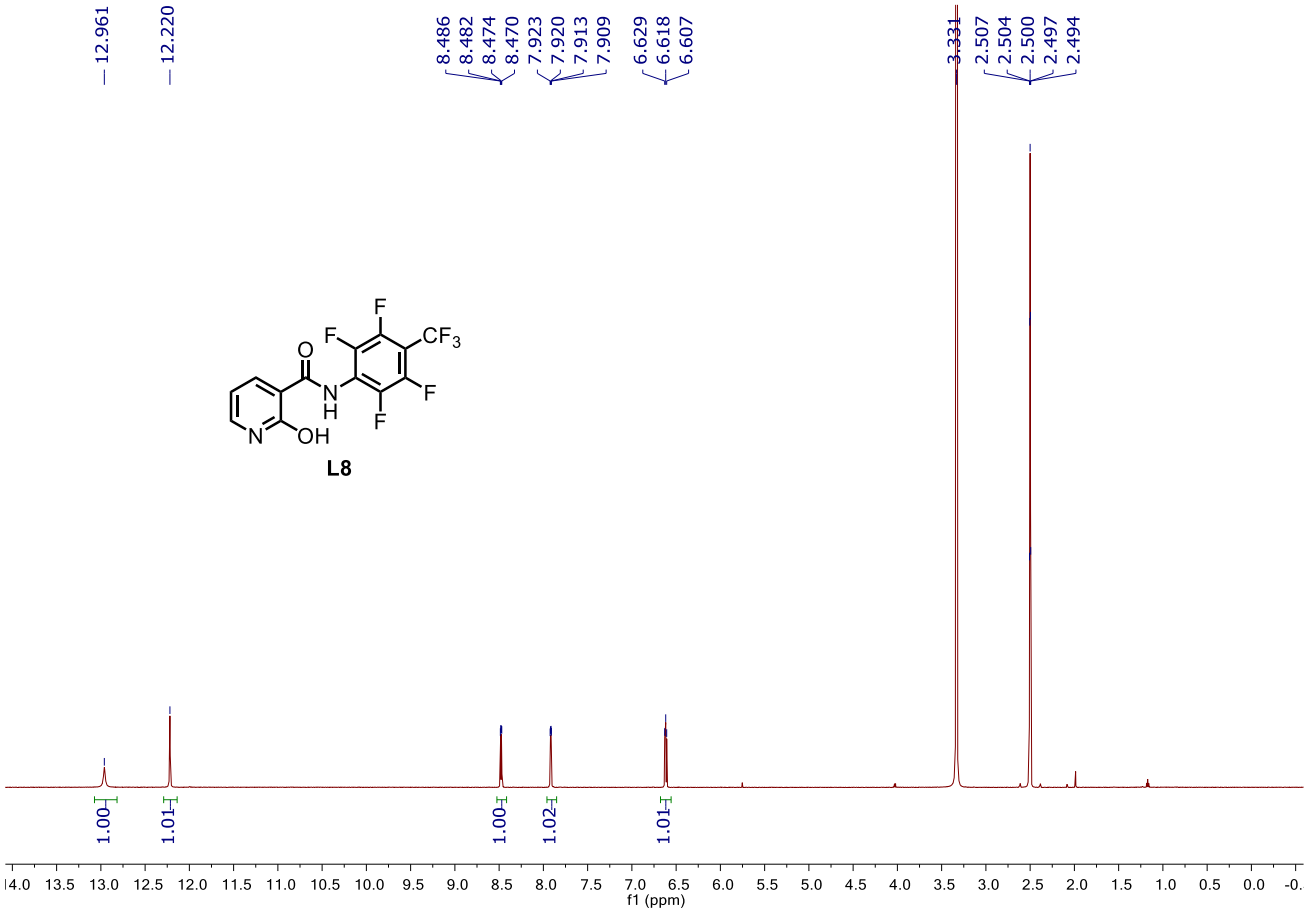

1.91
1.00
1.97
1.01
0.99
0.99
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

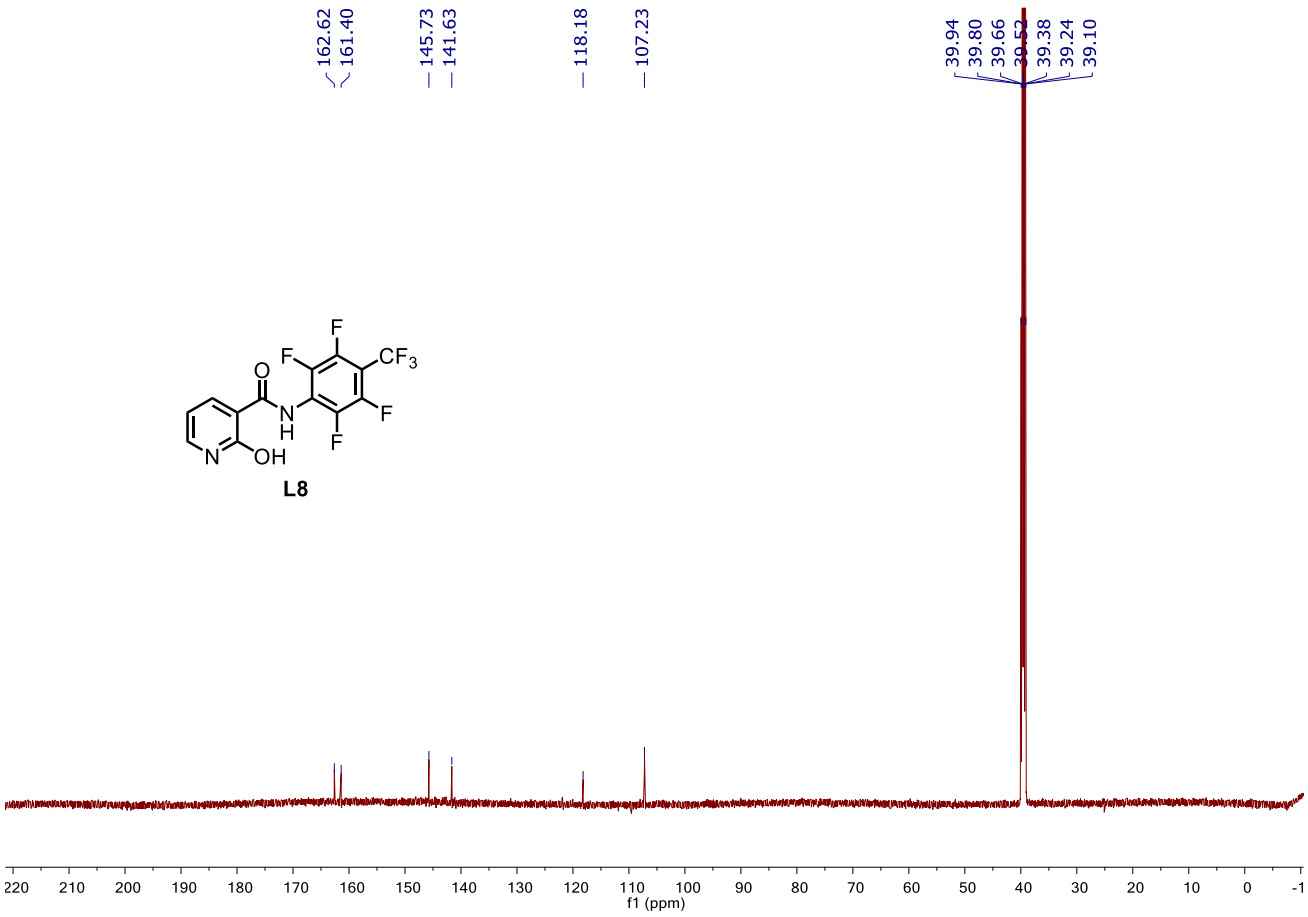

162.47
145.14
141.01
140.18
131.22
130.99
130.77
130.55
125.89
124.07
122.27
120.47
119.72
119.09
116.47
107.08
39.94
39.80
39.66
39.52
39.38
39.24
39.09
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

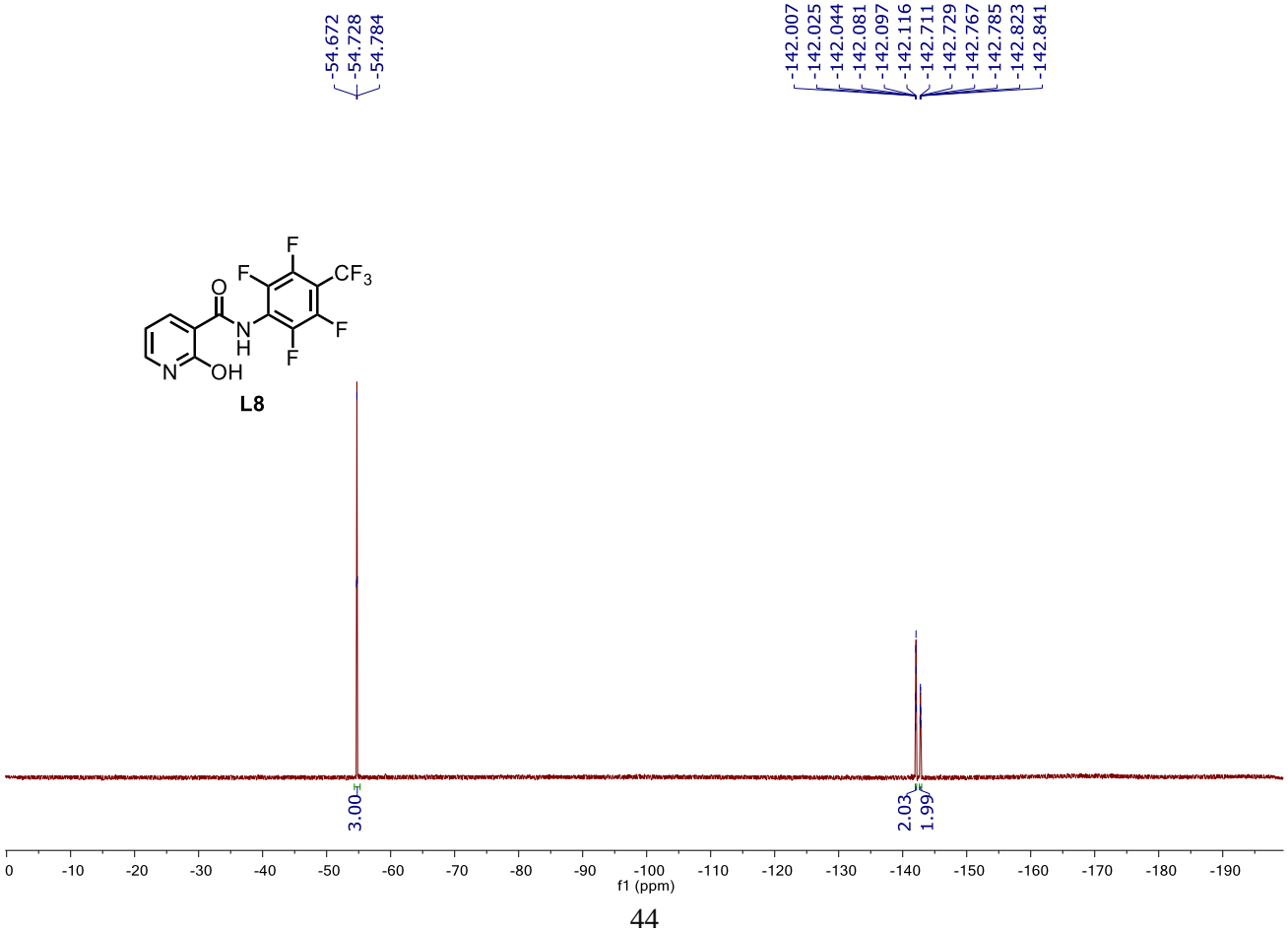
CF3
O
N
H
CF3
N
OH

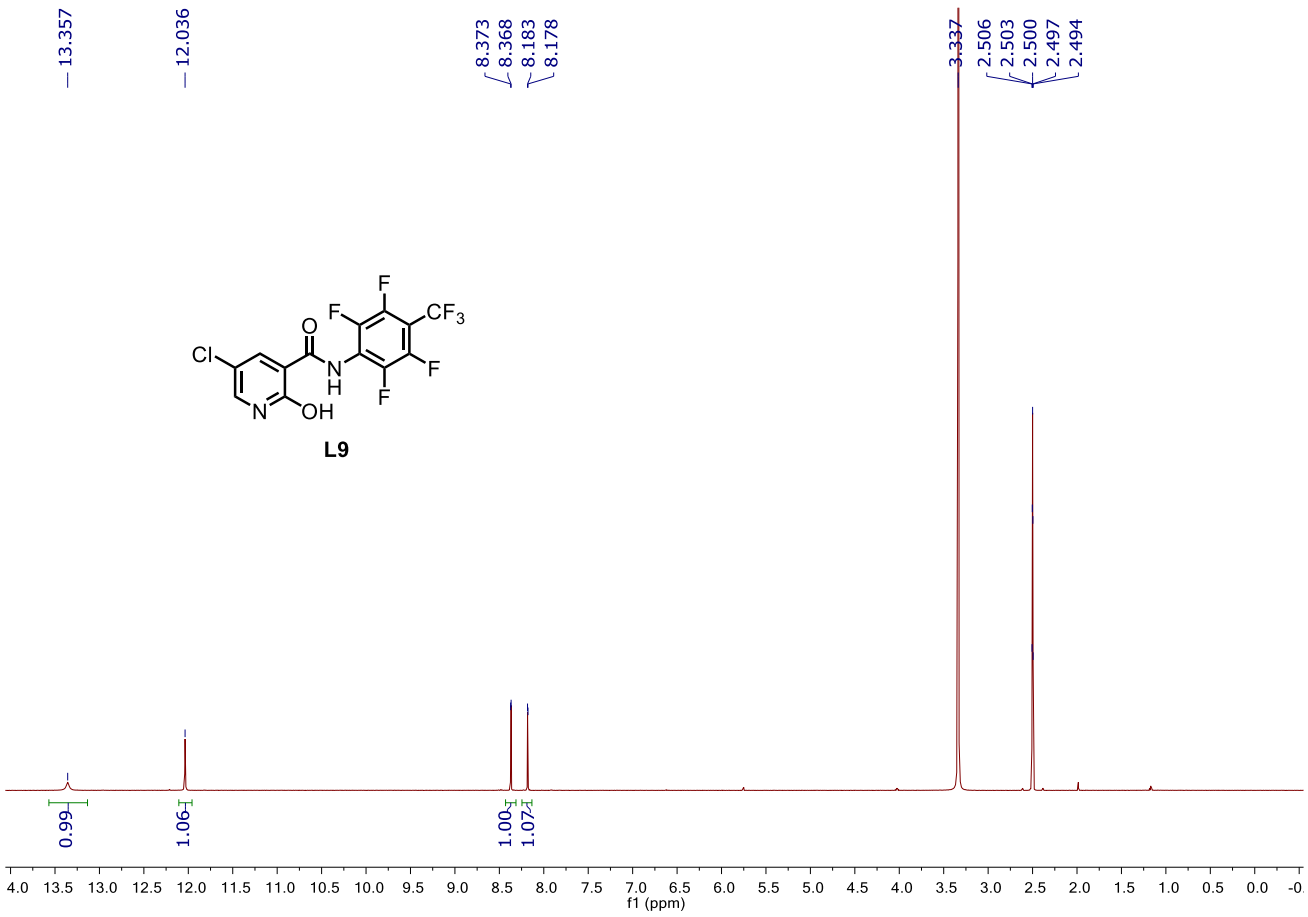
L7


-61.367
CF3
O
N
H
CF3
N
OH
L7
f1 (ppm)


12.961
12.220
8.486
8.482
8.474
8.470
7.923
7.920
7.913
7.909
6.629
6.618
6.607
3.331
2.507
2.504
2.500
2.497
2.494
F
F
CF3
O
F
N
H
F
N
OH
L8
1.00
1.01
1.00
1.02
1.01
f1 (ppm)

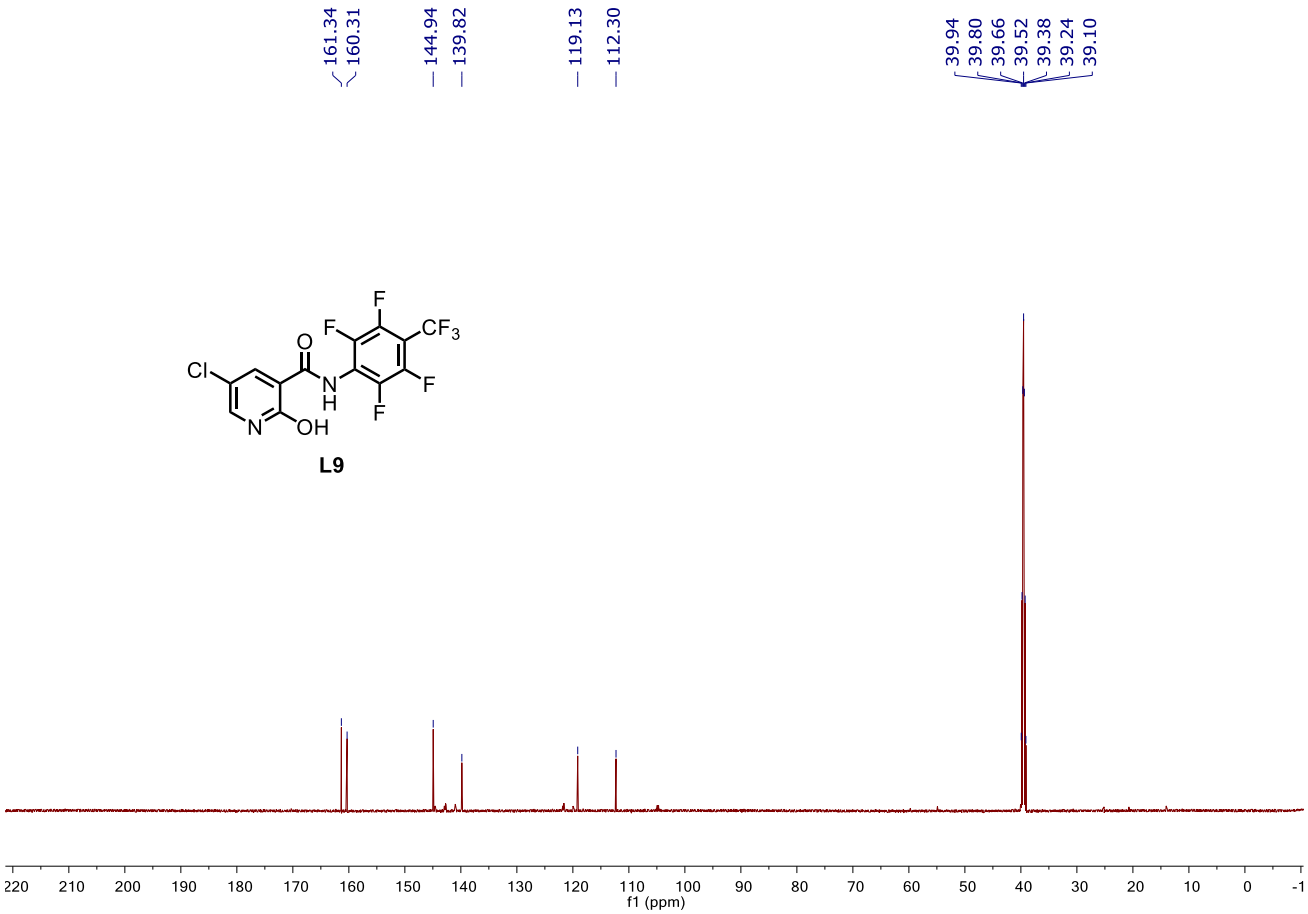

162.62
161.40
145.73
141.63
118.18
107.23
39.94
39.80
39.66
39.52
39.38
39.24
39.10
F
F
CF3
O
N
H
F
N
OH
L8
f1 (ppm)


-54.672
-54.728
-54.784
-142.007
-142.025
-142.044
-142.081
-142.097
-142.116
-142.711
-142.729
-142.767
-142.785
-142.823
-142.841
F
F
CF3
O
N
H
F
F
N
OH
L8
3.00
2.03
1.99
f1 (ppm)


13.357
12.036
8.373
8.368
8.183
8.178
3.337
2.506
2.503
2.500
2.497
2.494
0.99
1.06
1.00
1.07
f1 (ppm)

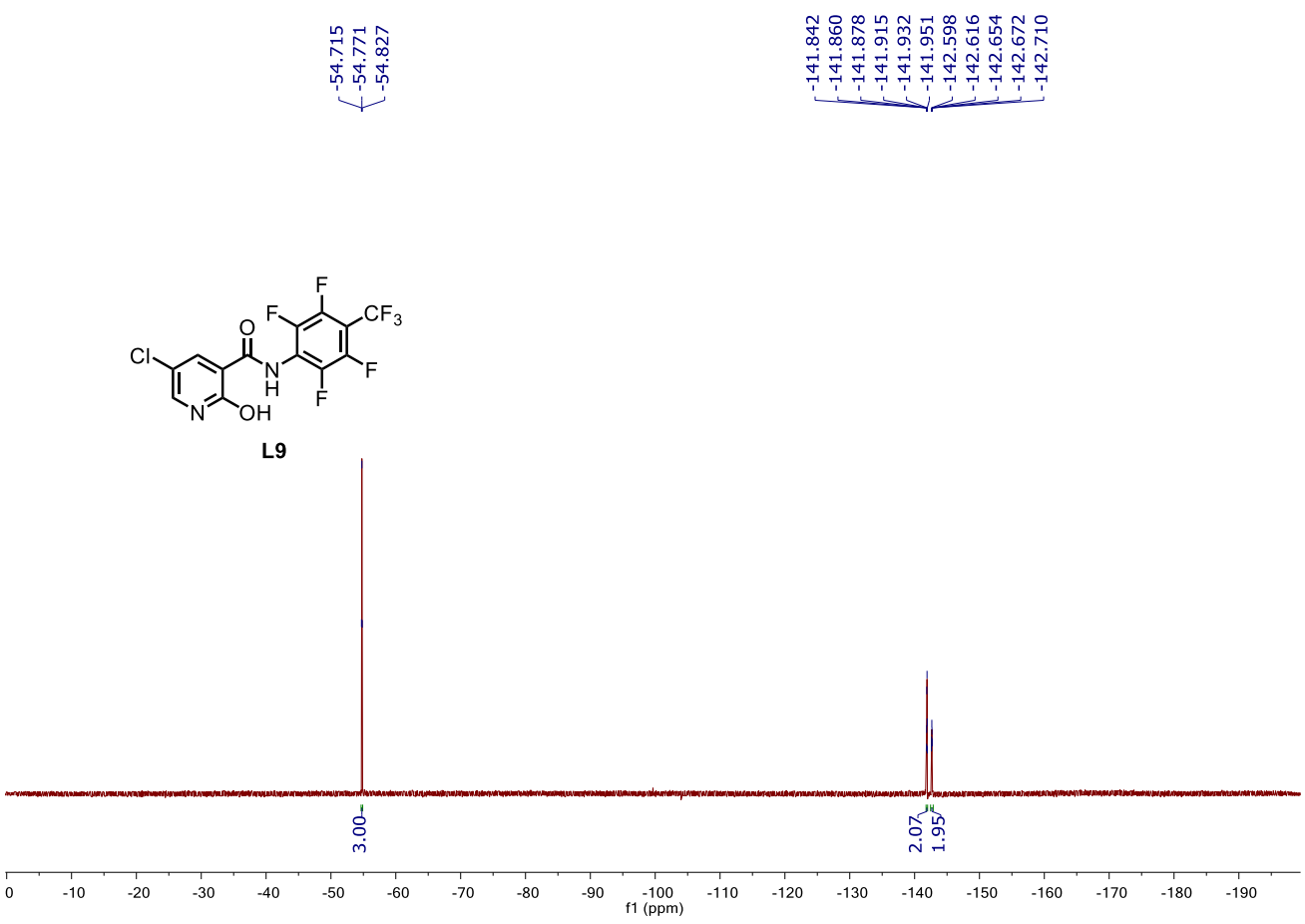
F
F
CF3
O
Cl
N
H
F
F
N
OH

L9

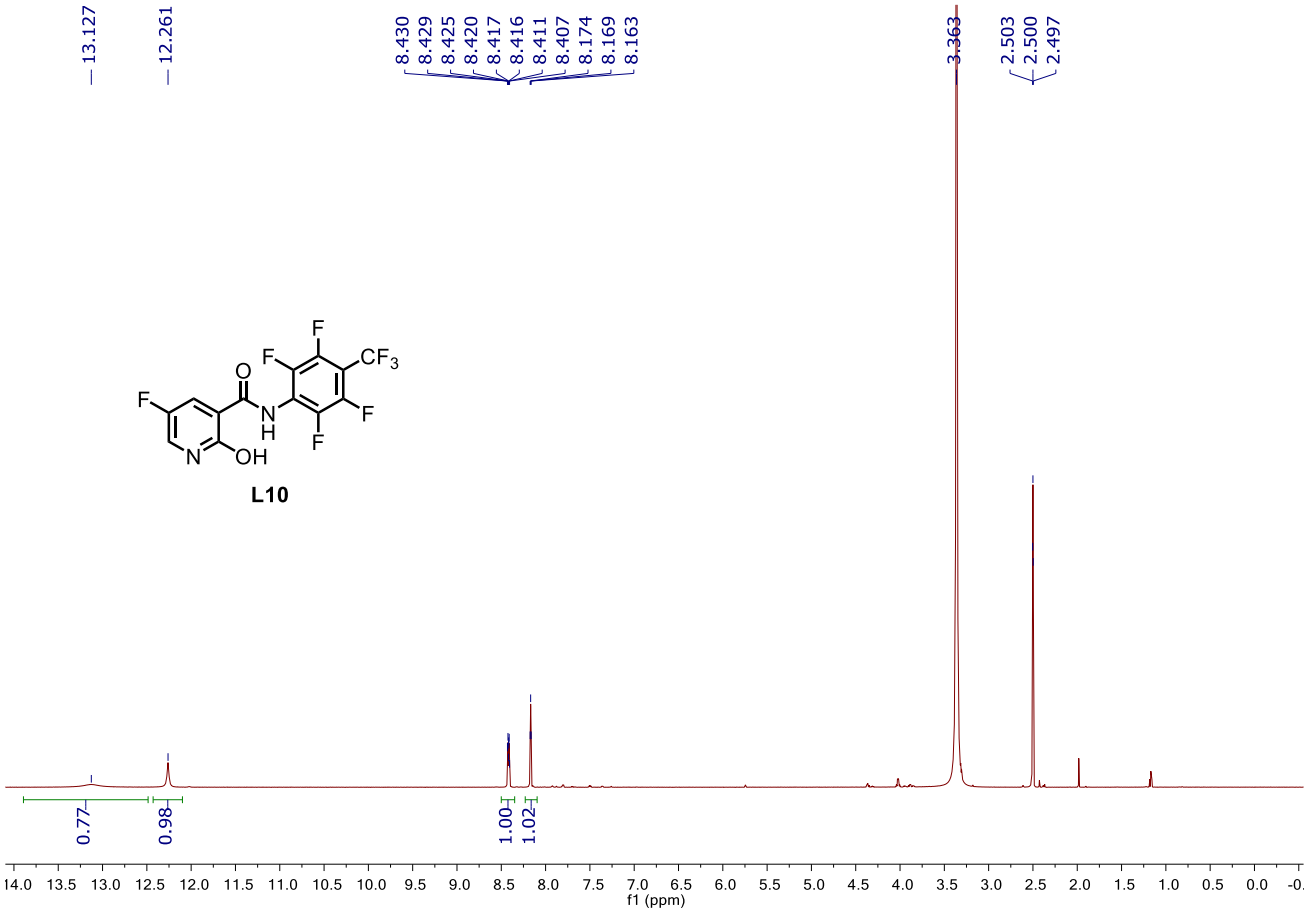

161.34
160.31
144.94
139.82
119.13
112.30
39.94
39.80
39.66
39.52
39.38
39.24
39.10
f1 (ppm)

F
F
CF3
O
Cl
N
H
F
F
N
OH

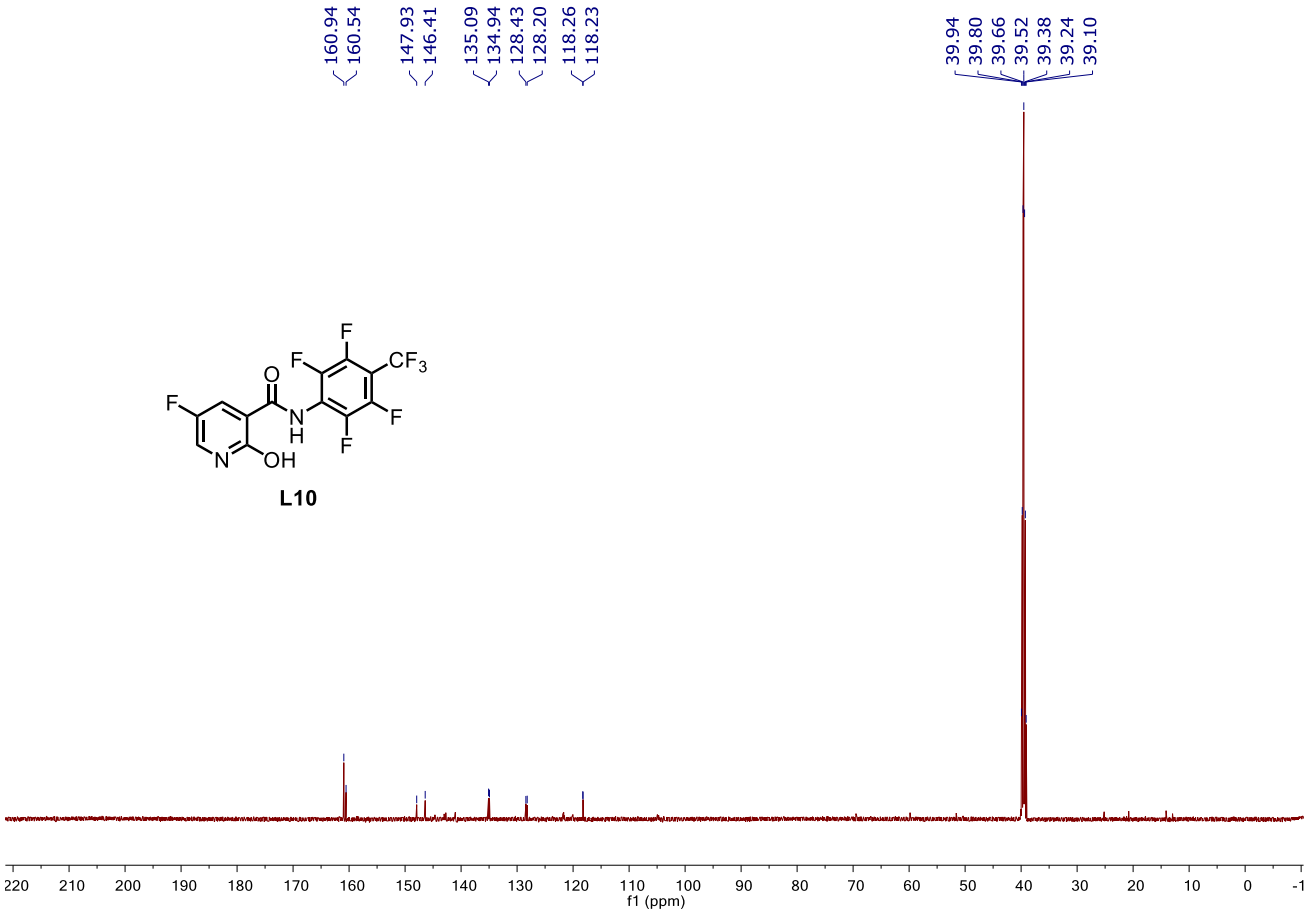
L9

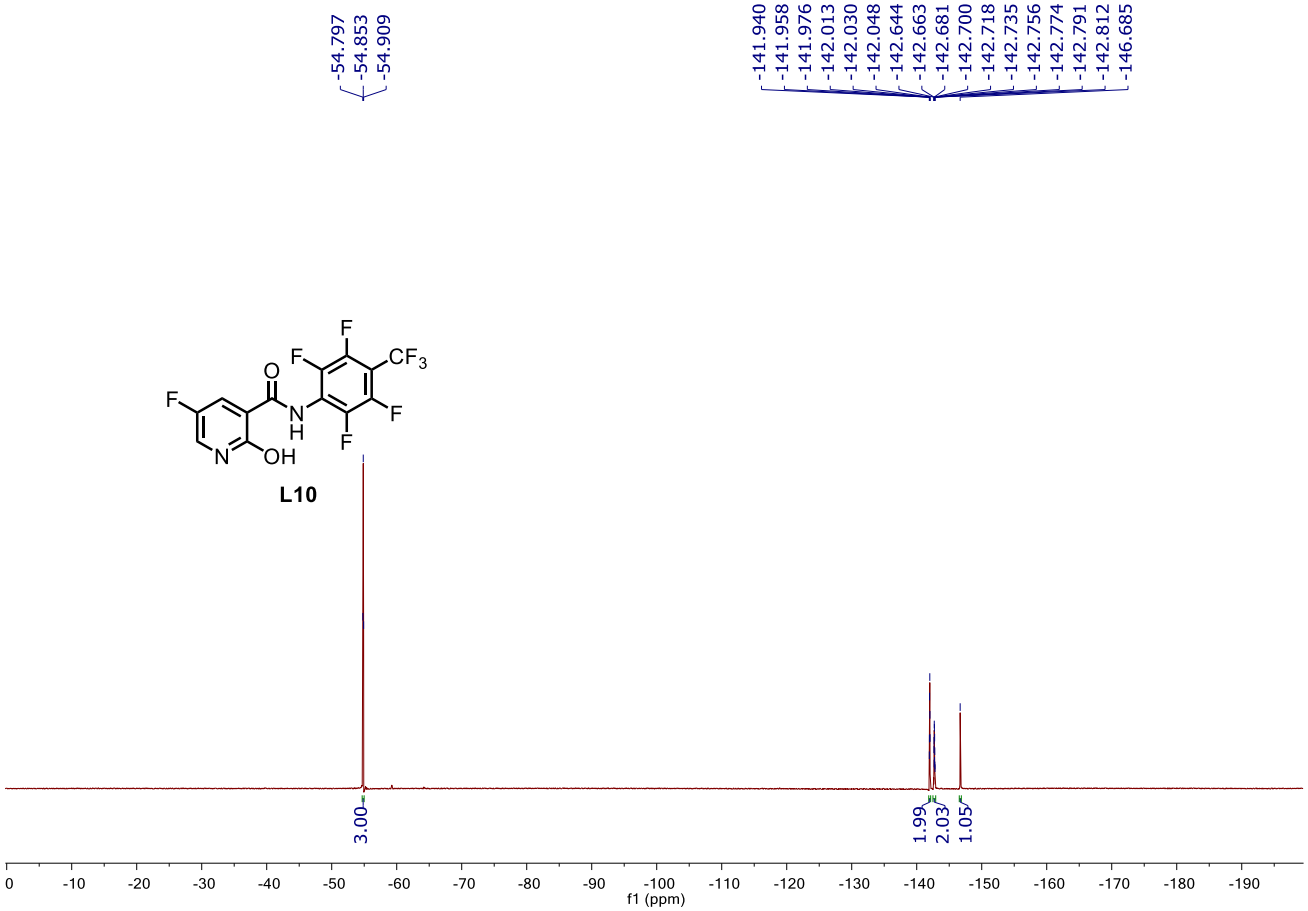

-54.715
-54.771
-54.827
-141.842
-141.860
-141.878
-141.915
-141.932
-141.951
-142.598
-142.616
-142.654
-142.672
-142.710
F
F
CF3
O
Cl
N
H
F
F
N
OH
3.00
2.07
1.95
f1 (ppm)

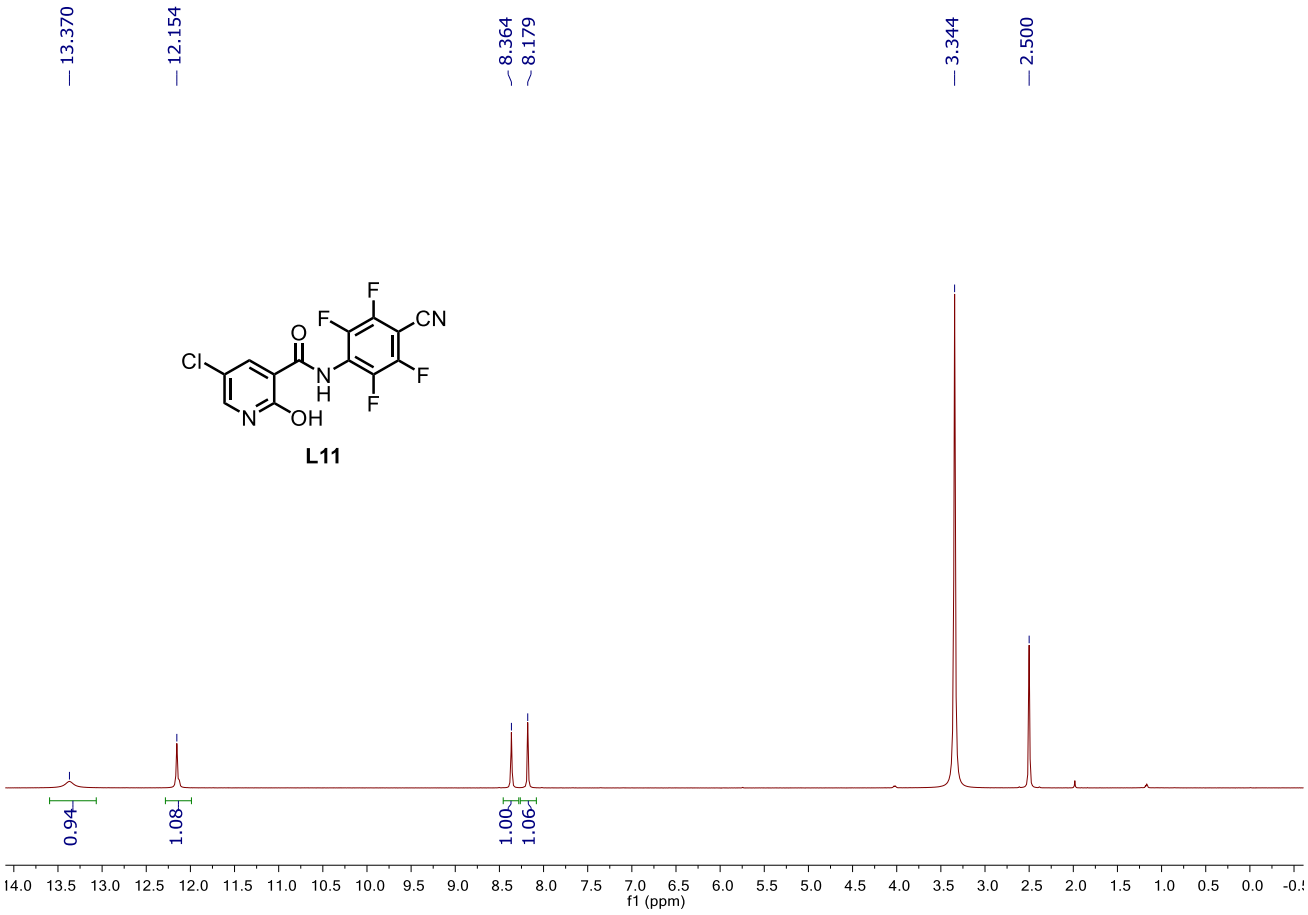
L9

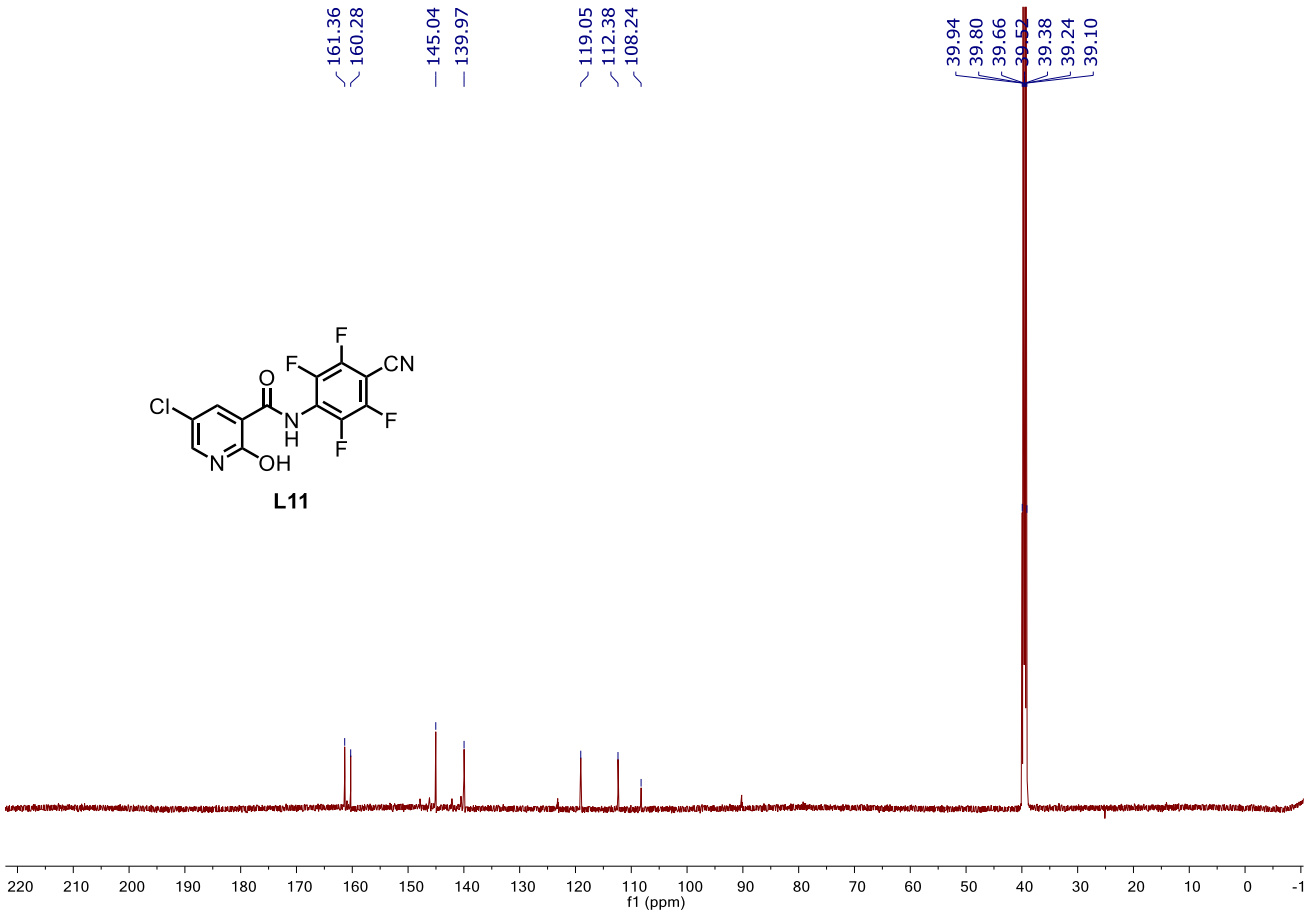

13.127
12.261
8.430
8.429
8.425
8.420
8.417
8.416
8.411
8.407
8.174
8.169
8.163
3.363
2.503
2.500
2.497
F
F
CF3
O
F
N
H
F
F
N
OH
0.77
0.98
1.00
1.02
f1 (ppm)

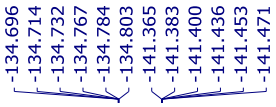
L10

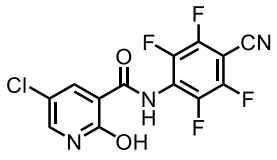

160.94
160.54
147.93
146.41
135.09
134.94
128.43
128.20
118.26
118.23
39.94
39.80
39.66
39.52
39.38
39.24
39.10
F
F
CF3
O
N
H
F
F
F
N
OH
L10
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


-54.797
-54.853
-54.909
-141.940
-141.958
-141.976
-142.013
-142.030
-142.048
-142.644
-142.663
-142.681
-142.700
-142.718
-142.735
-142.756
-142.774
-142.791
-142.812
-146.685
F
F
CF3
O
N
H
F
F
F
N
OH
L10
3.00
1.99
2.03
1.05
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

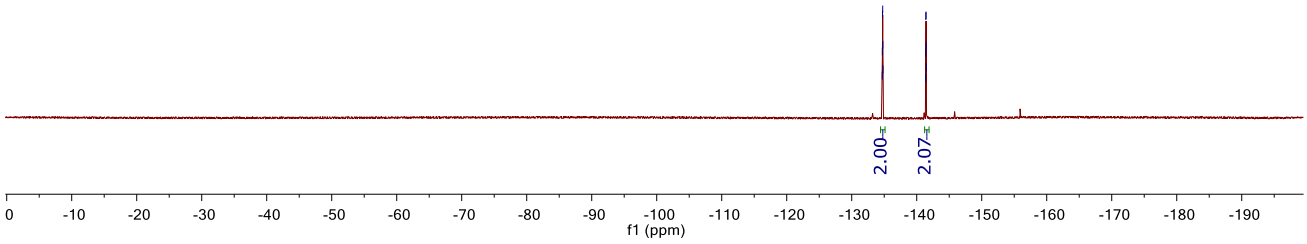

13.370
12.154
8.364
8.179
3.344
2.500
F
F
CN
O
Cl
N
H
F
F
N
OH
L11
0.94
1.08
1.00
1.06
f1 (ppm)


161.36
160.28
145.04
139.97
119.05
112.38
108.24
39.94
39.80
39.66
39.52
39.38
39.24
39.10
F
F
CN
O
Cl
N
H
F
F
N
OH
L11
f1 (ppm)

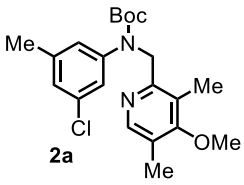




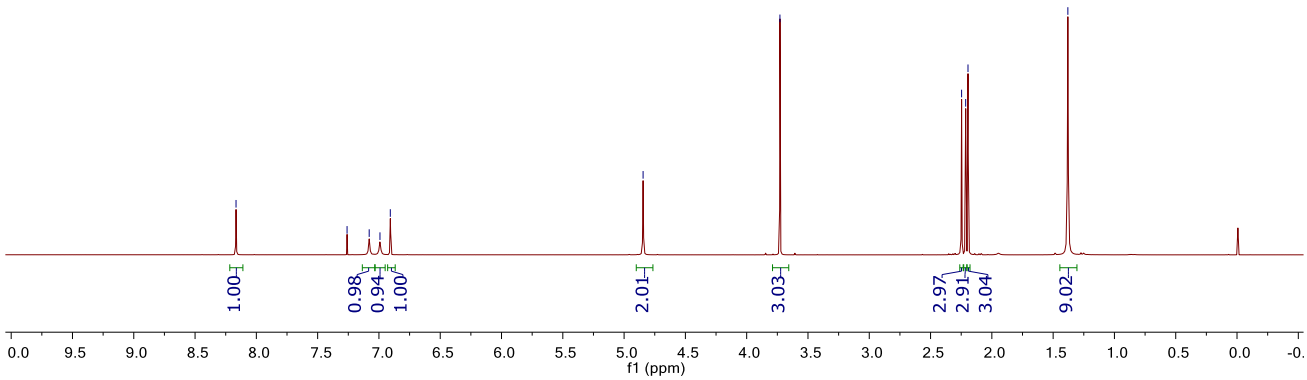
L11

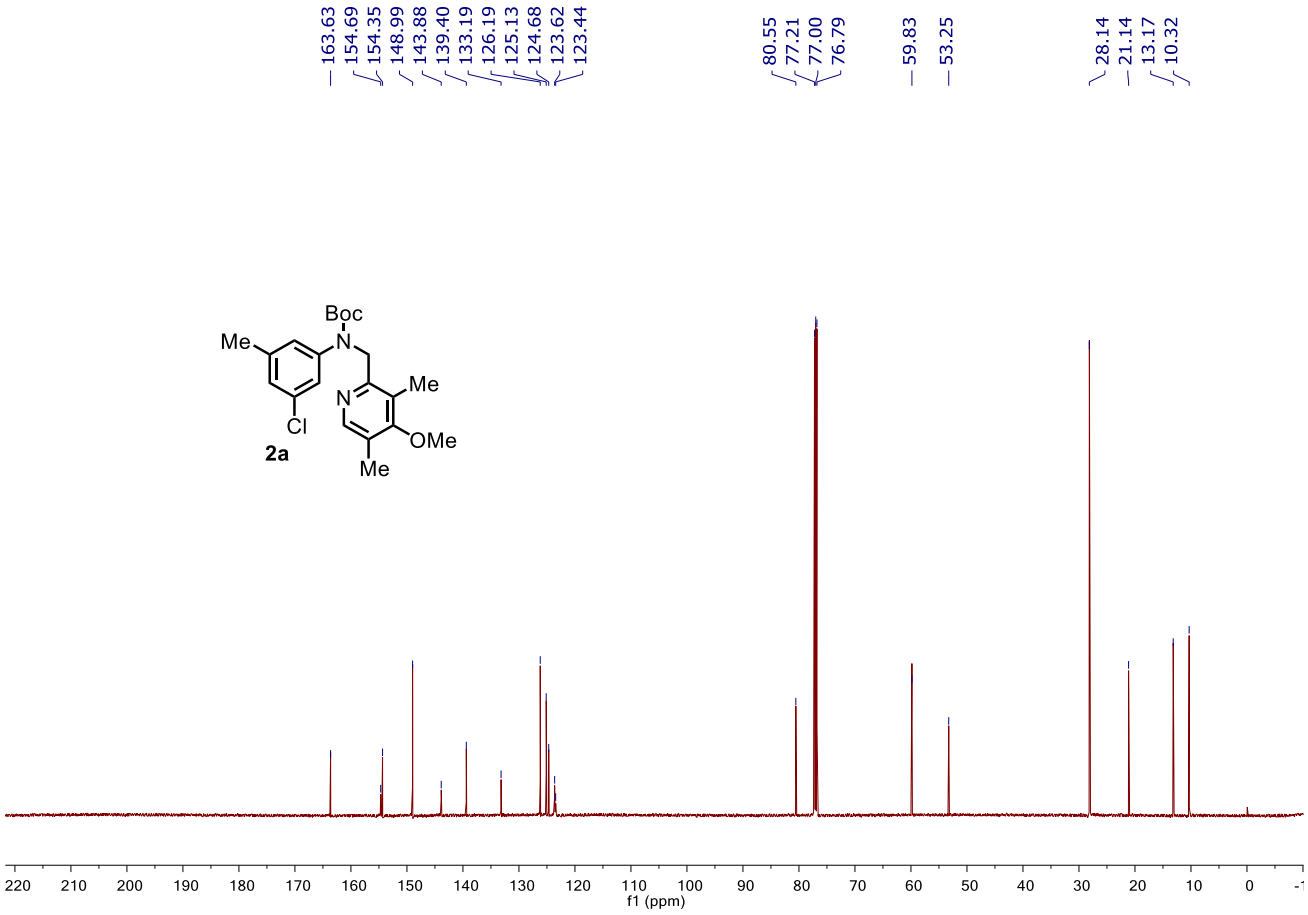


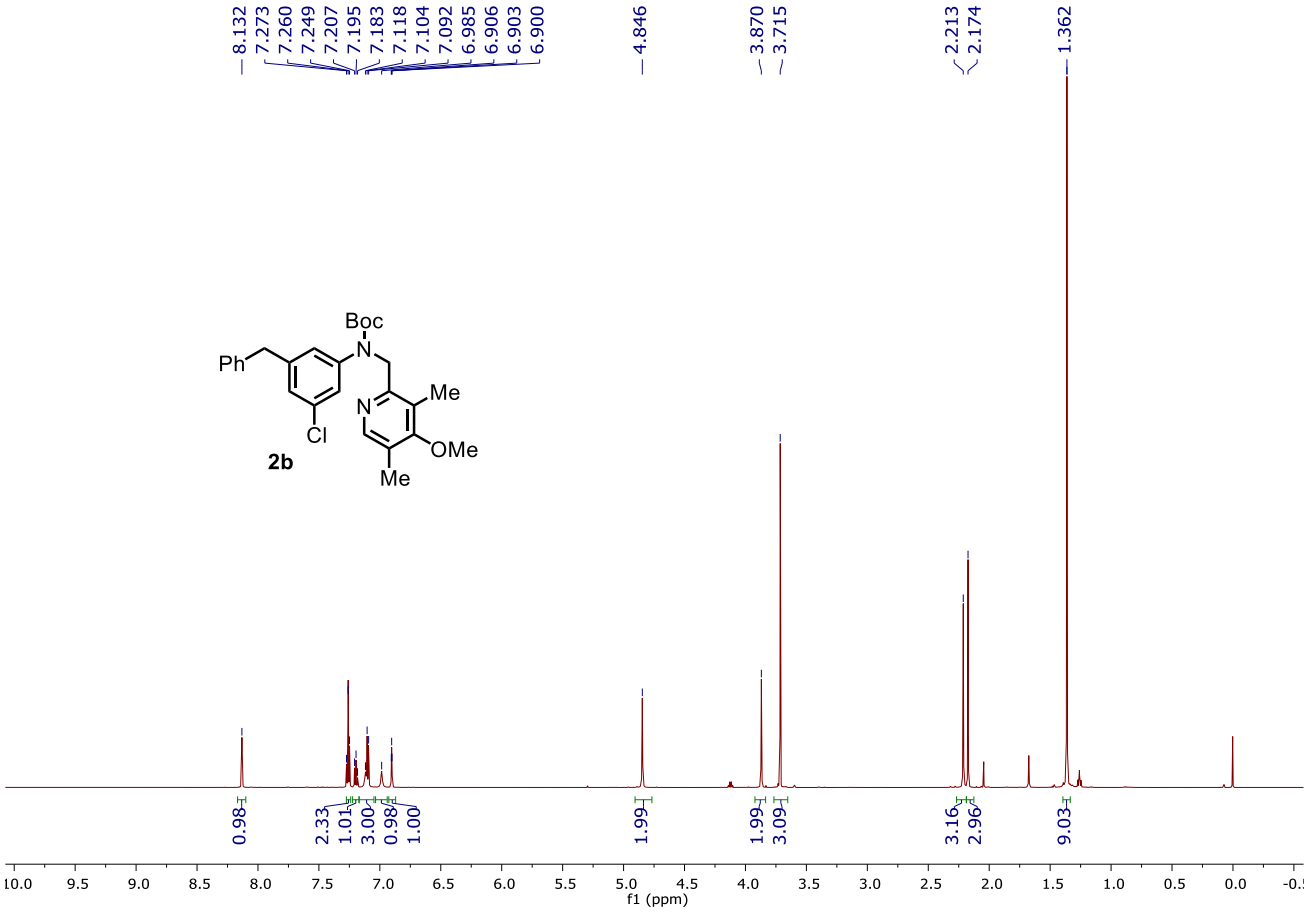
8.166
7.260
7.079
6.992
6.907
4.845
3.729
2.247
2.213
2.195
1.380

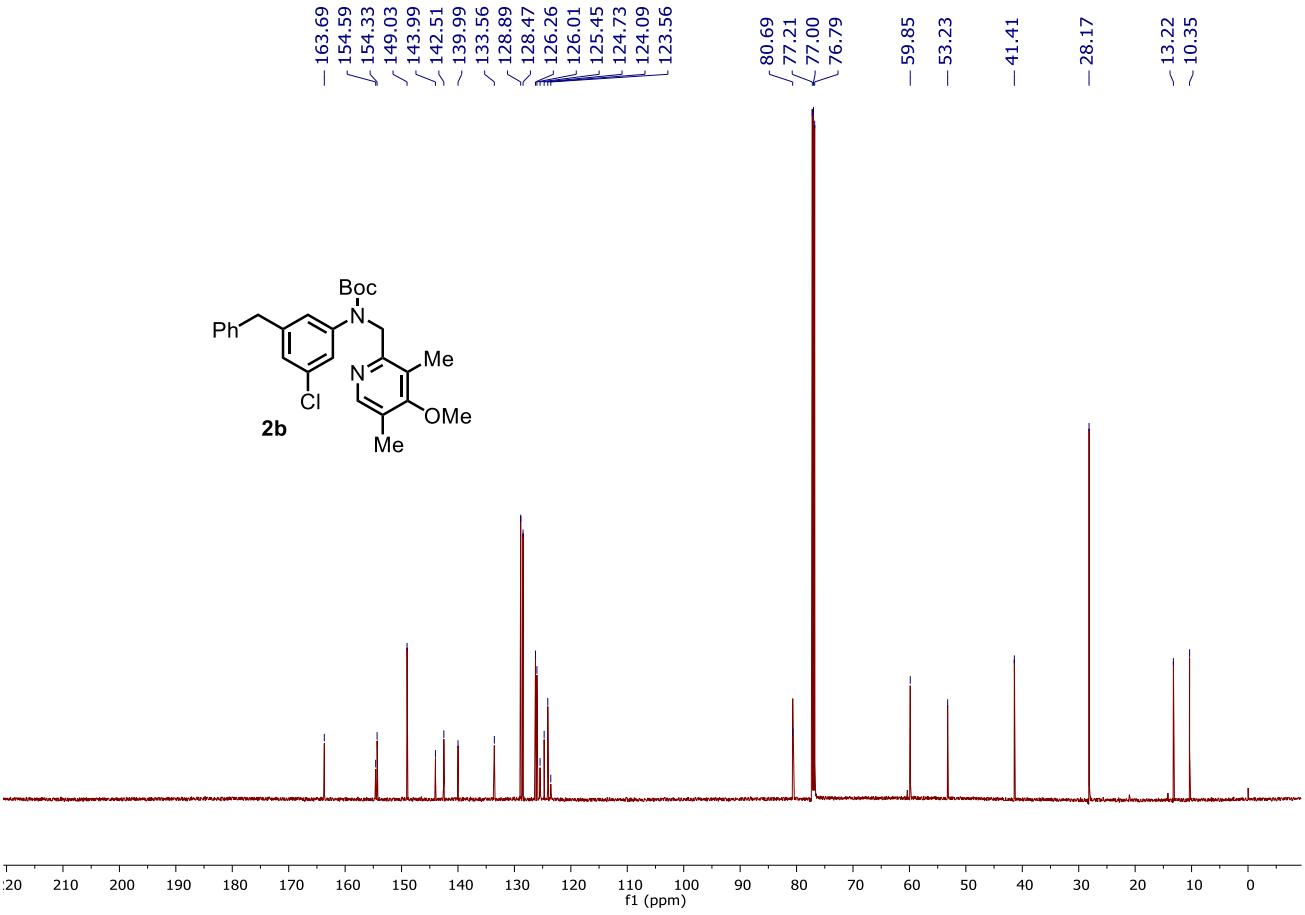


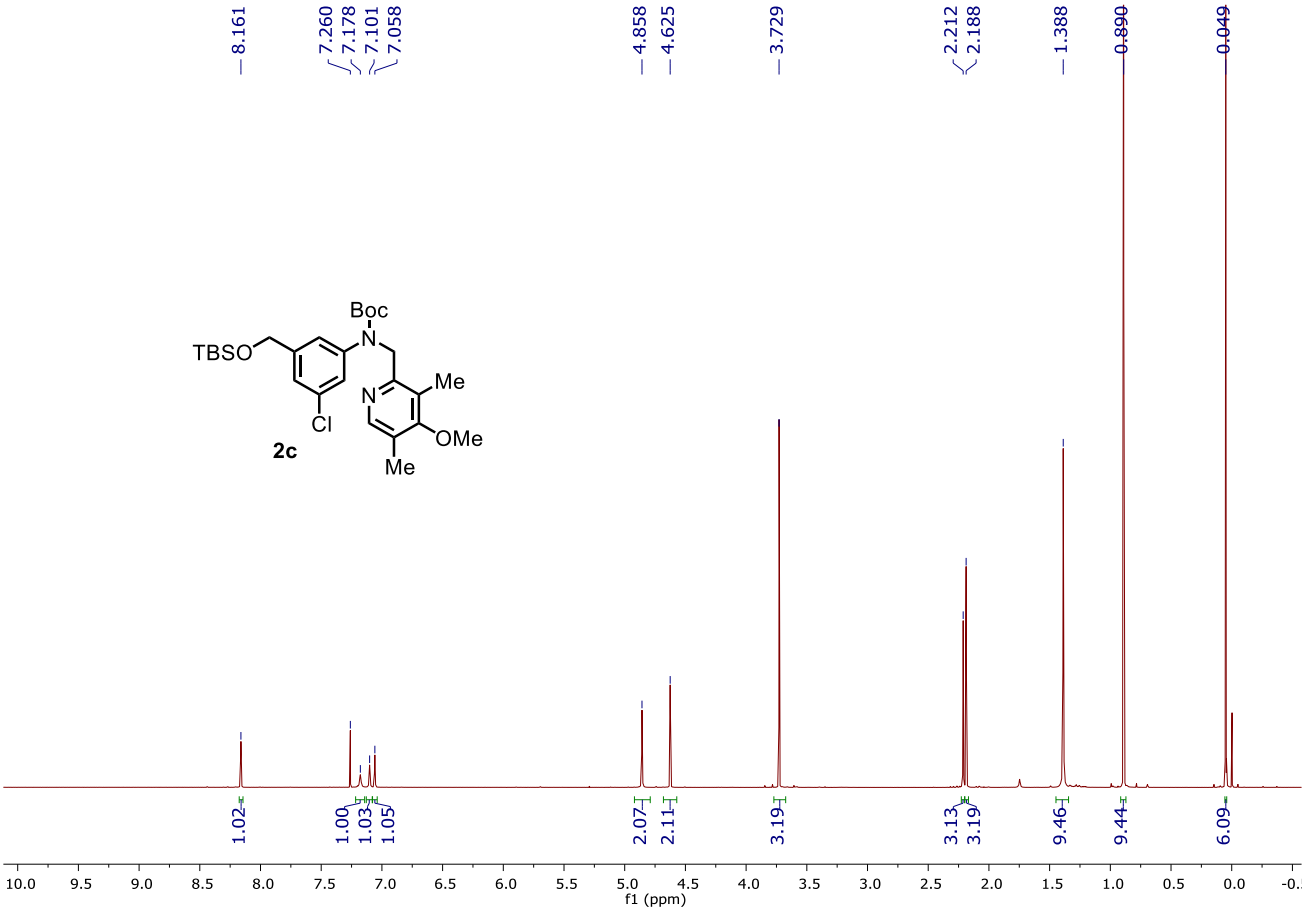
2a




163.63
154.69
154.35
148.99
143.88
139.40
133.19
126.19
125.13
124.68
123.62
123.44
80.55
77.21
77.00
76.79
59.83
53.25
28.14
21.14
13.17
10.32
Boc
Me
N
Me
Cl
OMe
Me
2a
f1 (ppm)


8.132
7.273
7.260
7.249
7.207
7.195
7.183
7.118
7.104
7.092
6.985
6.906
6.903
6.900
4.846
3.870
3.715
2.213
2.174
1.362
Boc
Ph
N
Me
Cl
OMe
Me
2b
0.98
2.33
1.01
3.00
0.98
1.00
1.99
1.99
3.09
3.16
2.96
9.03
f1 (ppm)


163.69
154.59
154.33
149.03
143.99
142.51
139.99
133.56
128.89
128.47
126.26
126.01
125.45
124.73
124.09
123.56
80.69
77.21
77.00
76.79
59.85
53.23
41.41
28.17
13.22
10.35
Boc
N
Ph
Me
N
Cl
OMe
Me
2b
f1 (ppm)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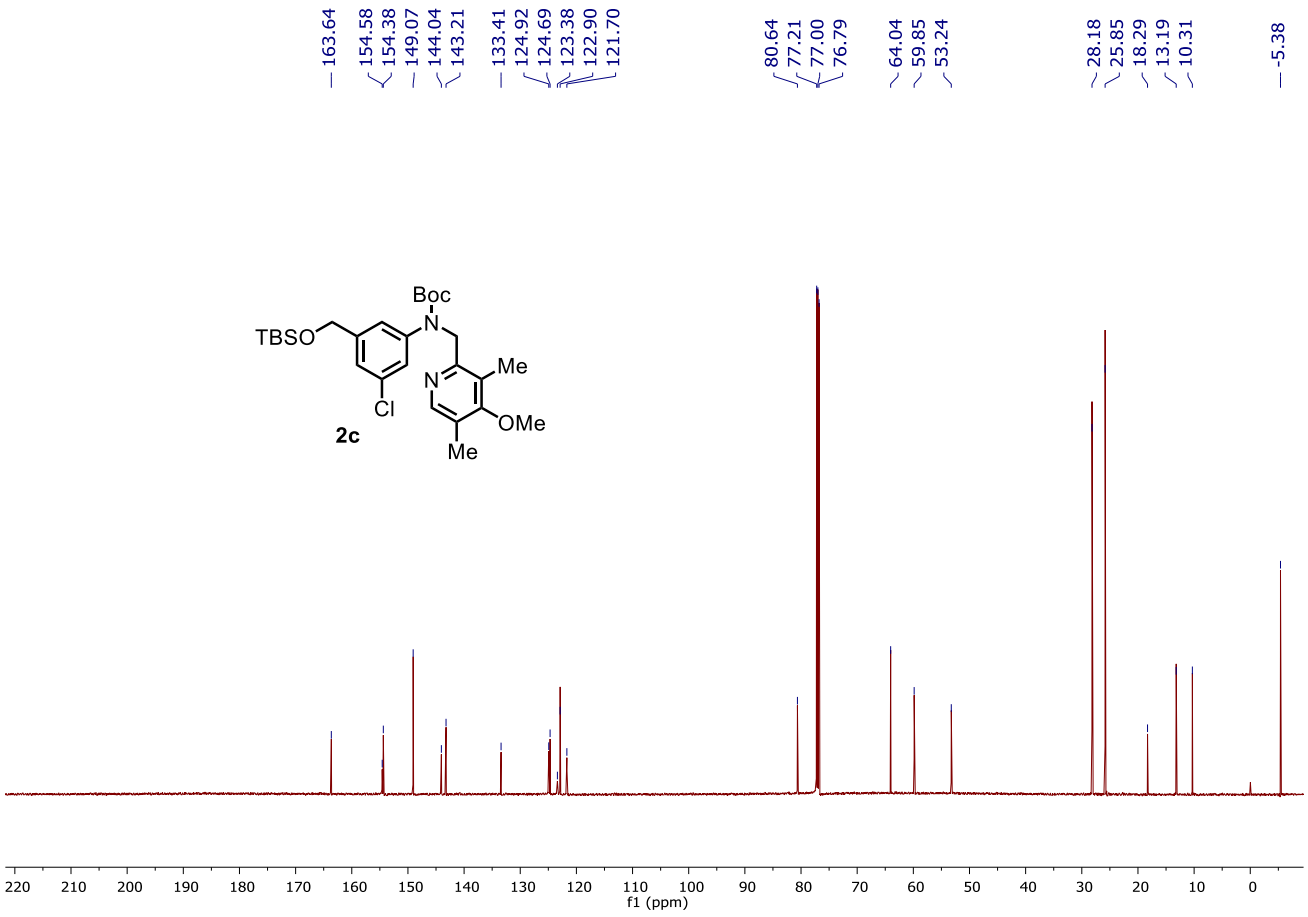
7.260
7.178
7.101
7.058
4.858
4.625
3.729
2.212
2.188
1.388
0.890
0.049
Boc
N
TBSO
Me
N
Cl
OMe
Me
2c
1.02
1.00
1.03
1.05
2.07
2.11
3.19
3.13
3.19
9.46
9.44
6.09
f1 (ppm)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154.38
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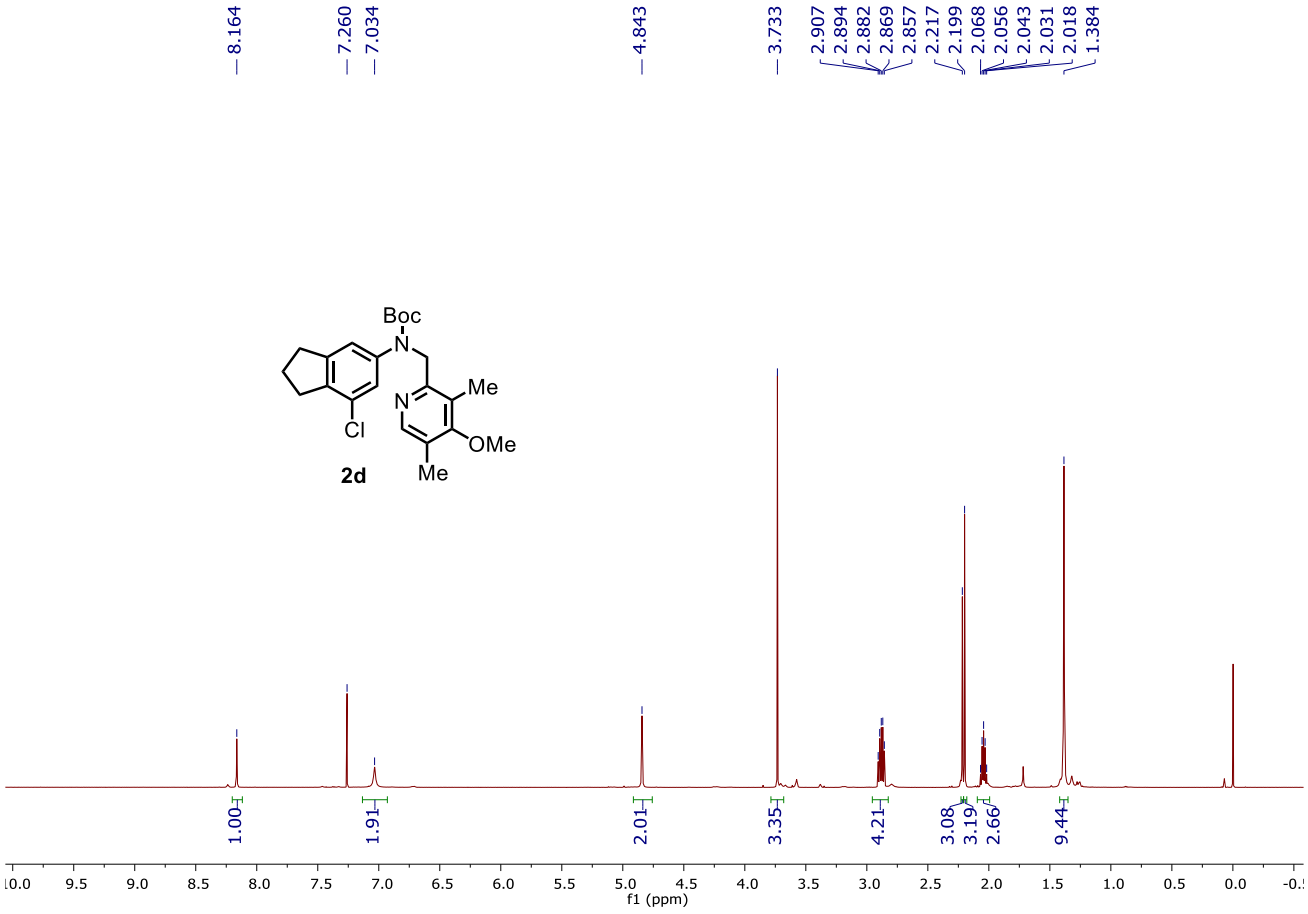
144.04
143.21
133.41
124.92
124.69
123.38
122.90
121.70
80.64
77.21
77.00
76.79
64.04
59.85
53.24
28.18
25.85
18.29
13.19
10.31
-5.38
Boc
TBSO
N
Me
N
Cl
OMe
Me
2c
f1 (ppm)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7.034
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3.733
2.907
2.894
2.882
2.869
2.857
2.217
2.199
2.068
2.056
2.043
2.031
2.018
1.384
Boc
N
Me
N
Cl
OMe
Me
2d
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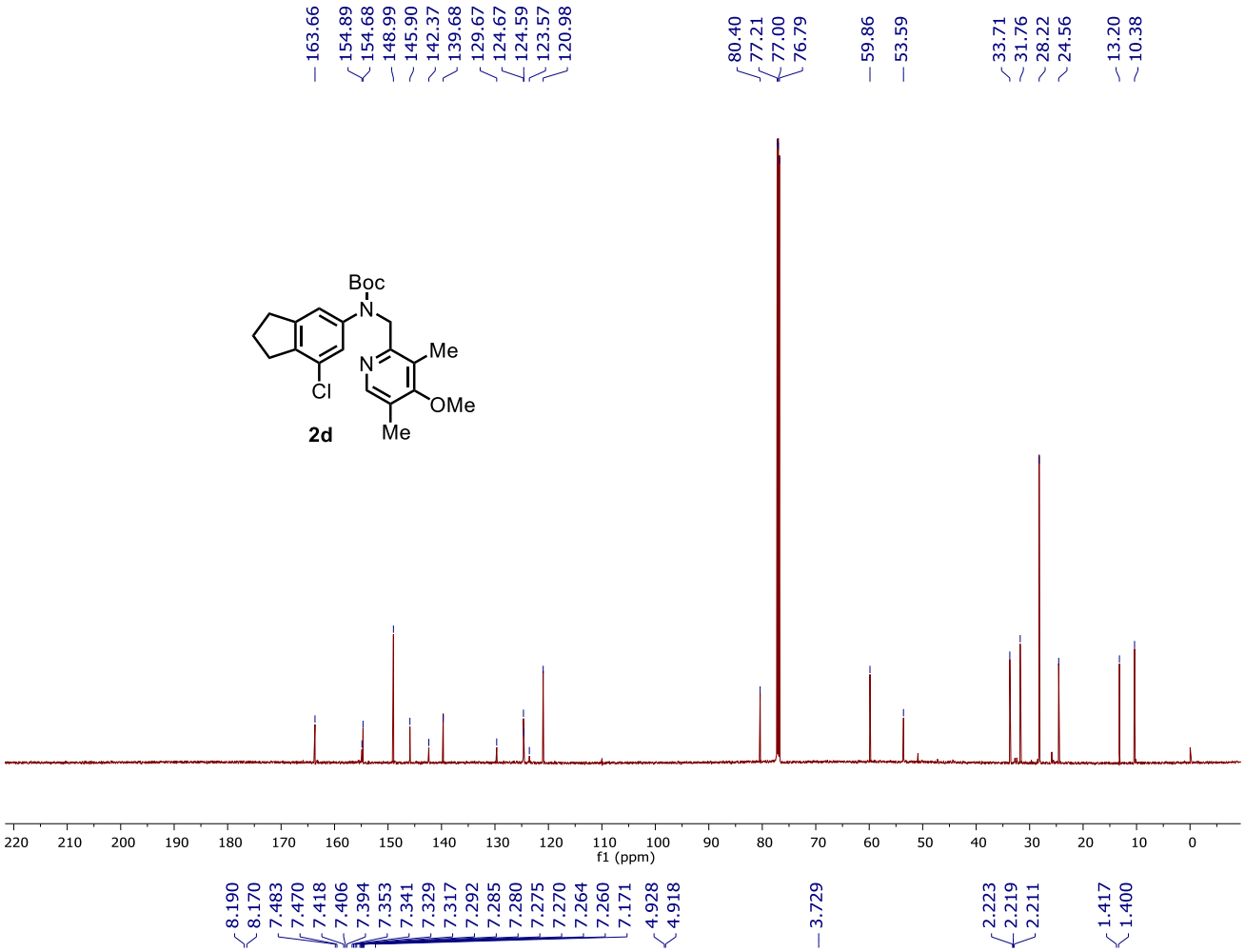
1.91
2.01
3.35
4.21
3.08
3.19
2.66
9.44
f1 (ppm)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139.68
129.67
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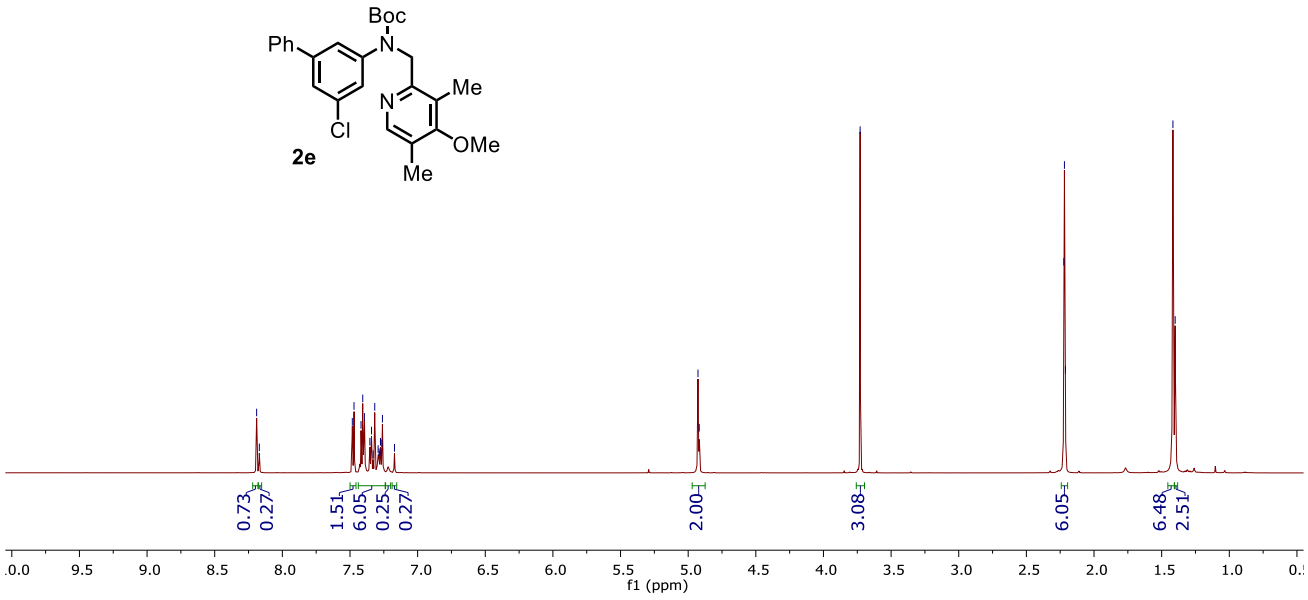
123.57
120.98
80.40
77.21
77.00
76.79
59.86
53.59
33.71
31.76
28.22
24.56
13.20
10.38
Boc
N
Me
N
Cl
OMe
Me
2d
f1 (ppm)
8.190
8.170
7.483
7.470
7.418
7.406
7.394
7.353
7.341
7.329
7.317
7.292
7.285
7.280
7.275
7.270
7.264
7.260
7.171
4.928
4.918
3.729
2.223
2.219
2.211
1.417
1.400


Boc
Ph
N
Me
N
Cl
OMe
Me
2e
f1 (ppm)
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1.51
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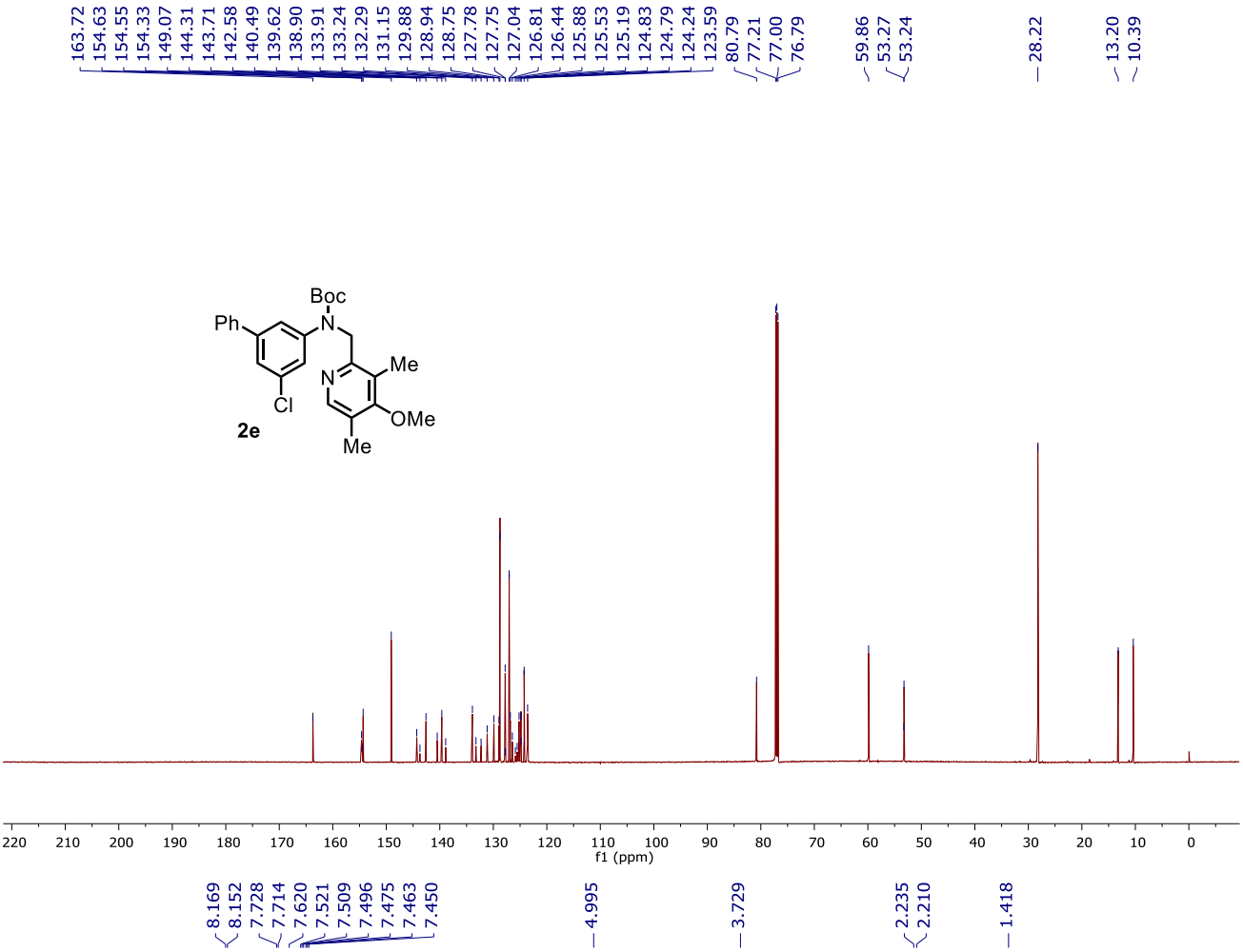
0.25
0.27
2.00
3.08
6.05
6.48
2.51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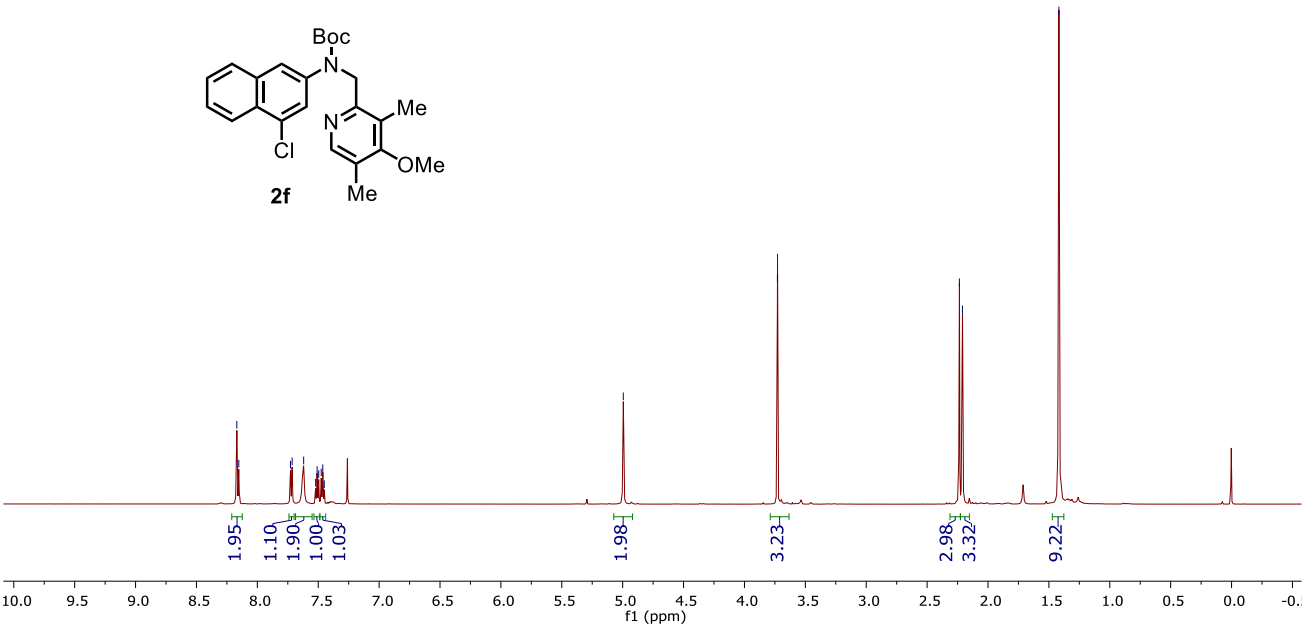
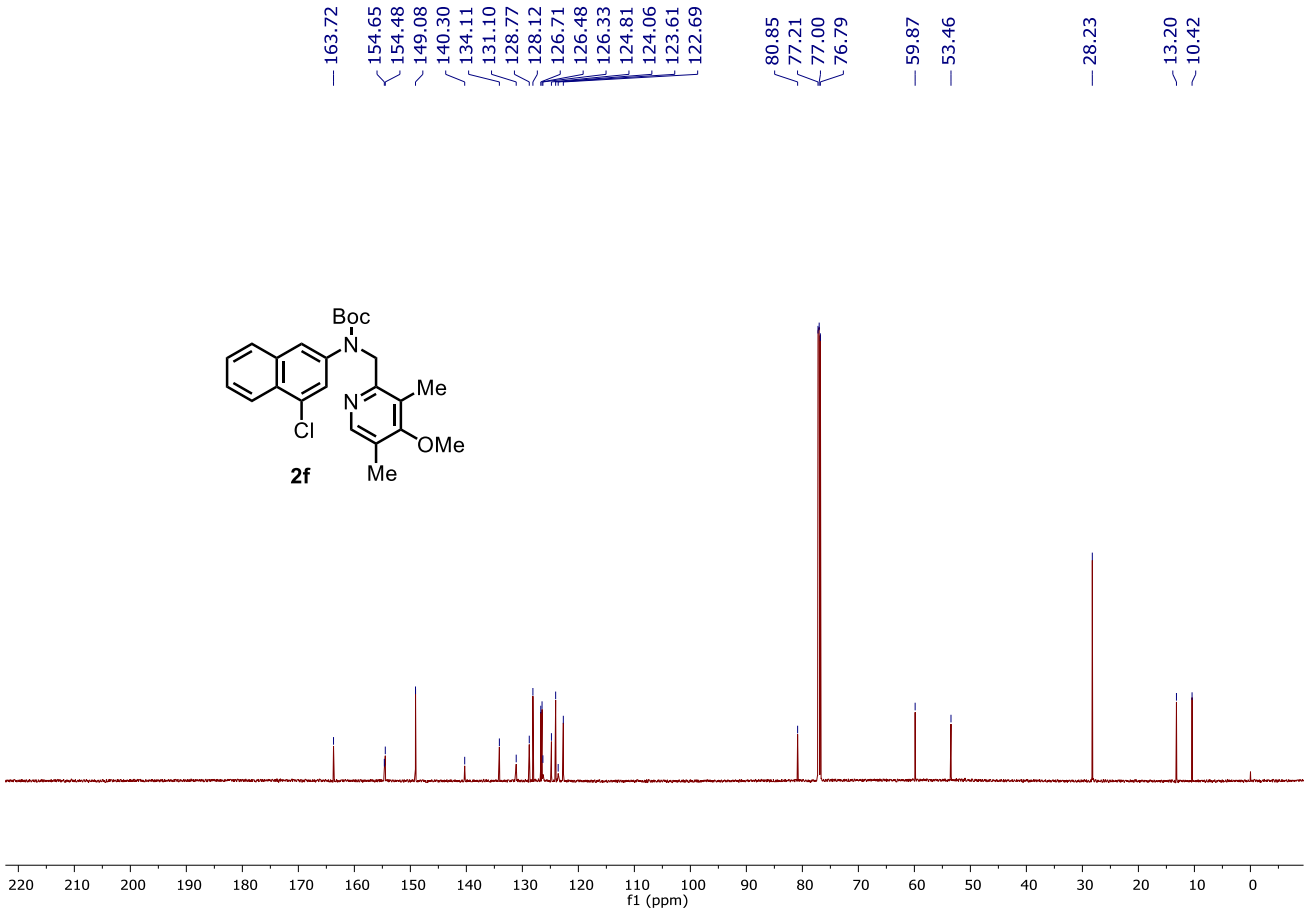
143.71
142.58
140.49
139.62
138.90
133.91
133.24
132.29
131.15
129.88
128.94
128.75
127.78
127.75
127.04
126.81
126.44
125.88
125.53
125.19
124.83
124.79
124.24
123.59
80.79
77.21
77.00
76.79
59.86
53.27
53.24
28.22
13.20
10.39
Boc
Ph
N
Me
N
Cl
OMe
Me
2e
f1 (ppm)
8.169
8.152
7.728
7.714
7.620
7.521
7.509
7.496
7.475
7.463
7.450
4.995
3.729
2.235
2.210
1.418
1.95
1.10
1.90
1.00
1.03
1.98
3.23
2.98
3.32
9.22
f1 (ppm)


Boc
N
Me
N
Cl
OMe
Me
2f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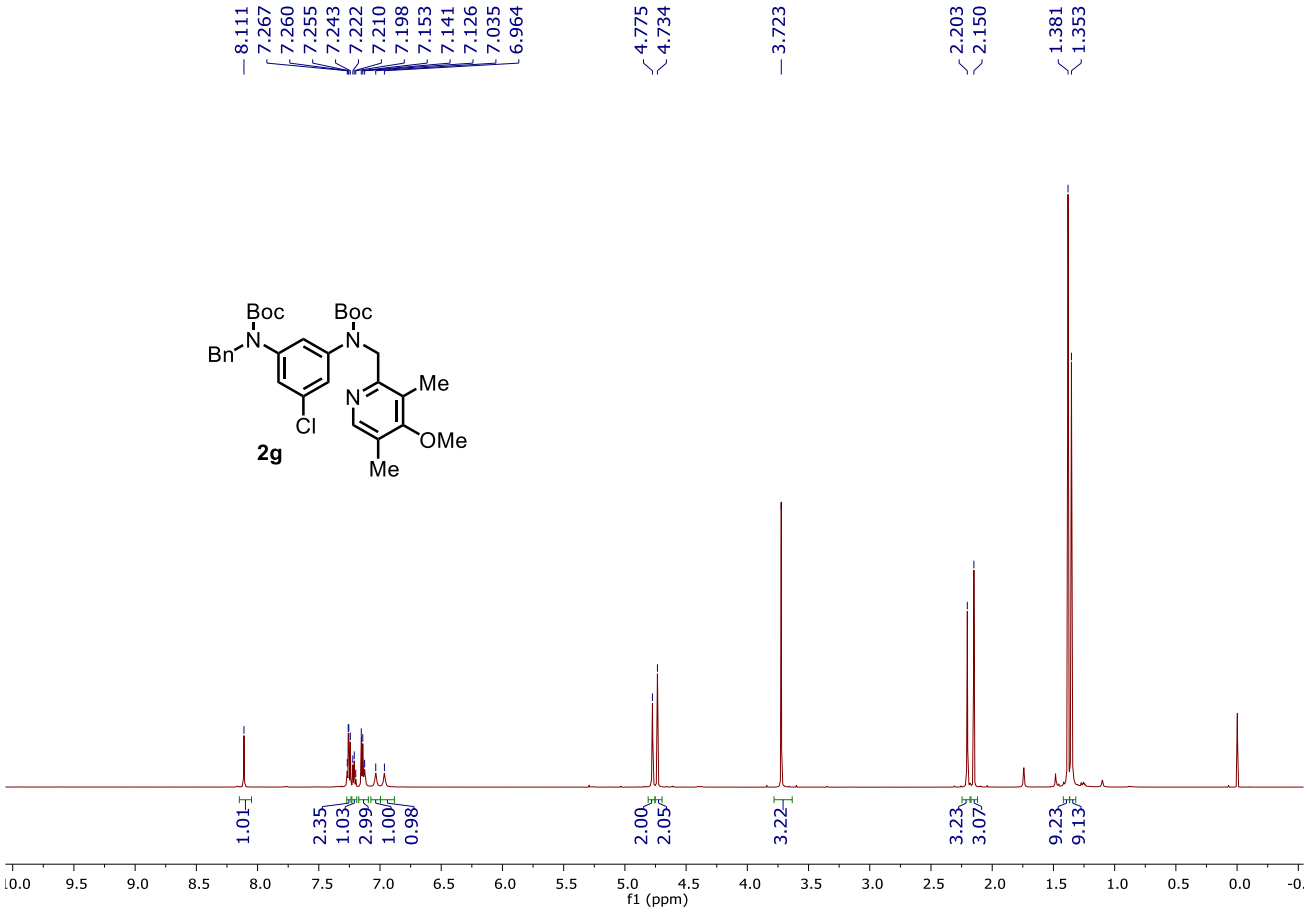
154.48
149.08
140.30
134.11
131.10
128.77
128.12
126.71
126.48
126.33
124.81
124.06
123.61
122.69
80.85
77.21
77.00
76.79
59.87
53.46
28.23
13.20
10.42
Boc
N
Me
N
Cl
OMe
Me
2f
f1 (ppm)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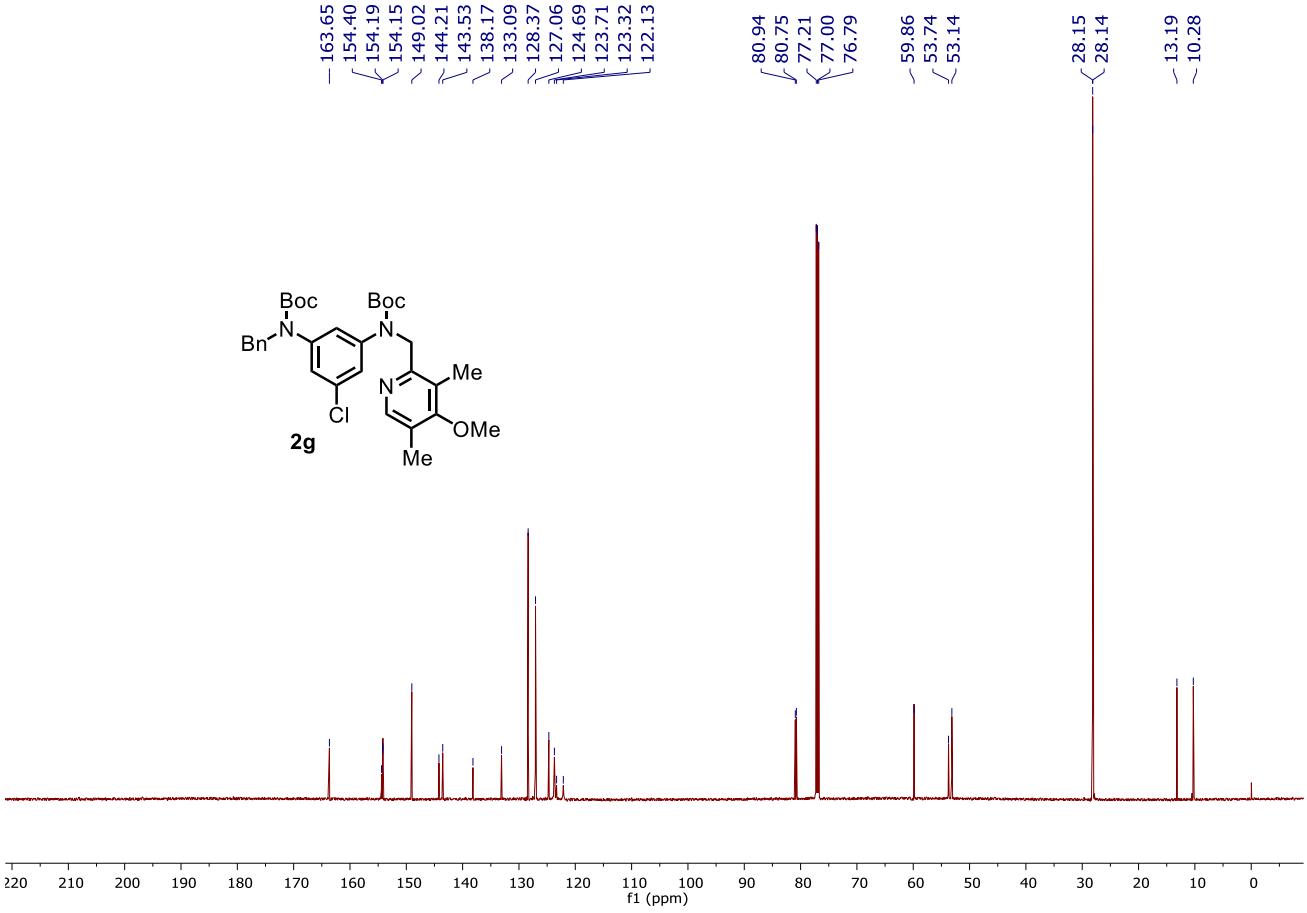
7.267
7.260
7.255
7.243
7.222
7.210
7.198
7.153
7.141
7.126
7.035
6.964
4.775
4.734
3.723
2.203
2.150
1.381
1.353
Boc
Boc
Bn
N
N
Me
N
Cl
OMe
Me
2g
1.01
2.35
1.03
2.99
1.00
0.98
2.00
2.05
3.22
3.23
3.07
9.23
9.13
f1 (ppm)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154.19
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144.21
143.53
138.17
133.09
128.37
127.06
124.69
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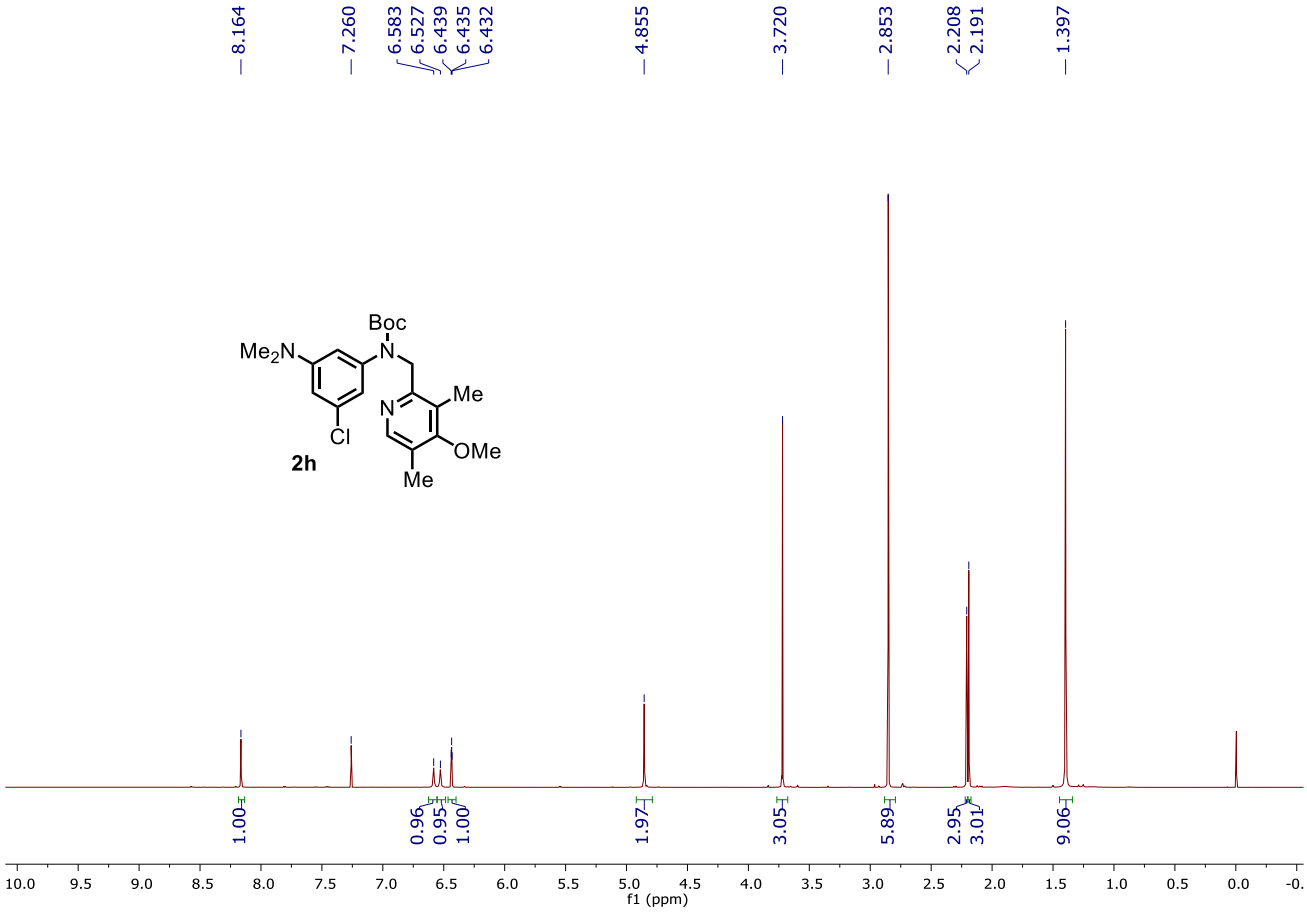
123.32
122.13
80.94
80.75
77.21
77.00
76.79
59.86
53.74
53.14
28.15
28.14
13.19
10.28
Boc
Boc
Bn
N
N
Me
N
Cl
OMe
Me
2g
f1 (ppm)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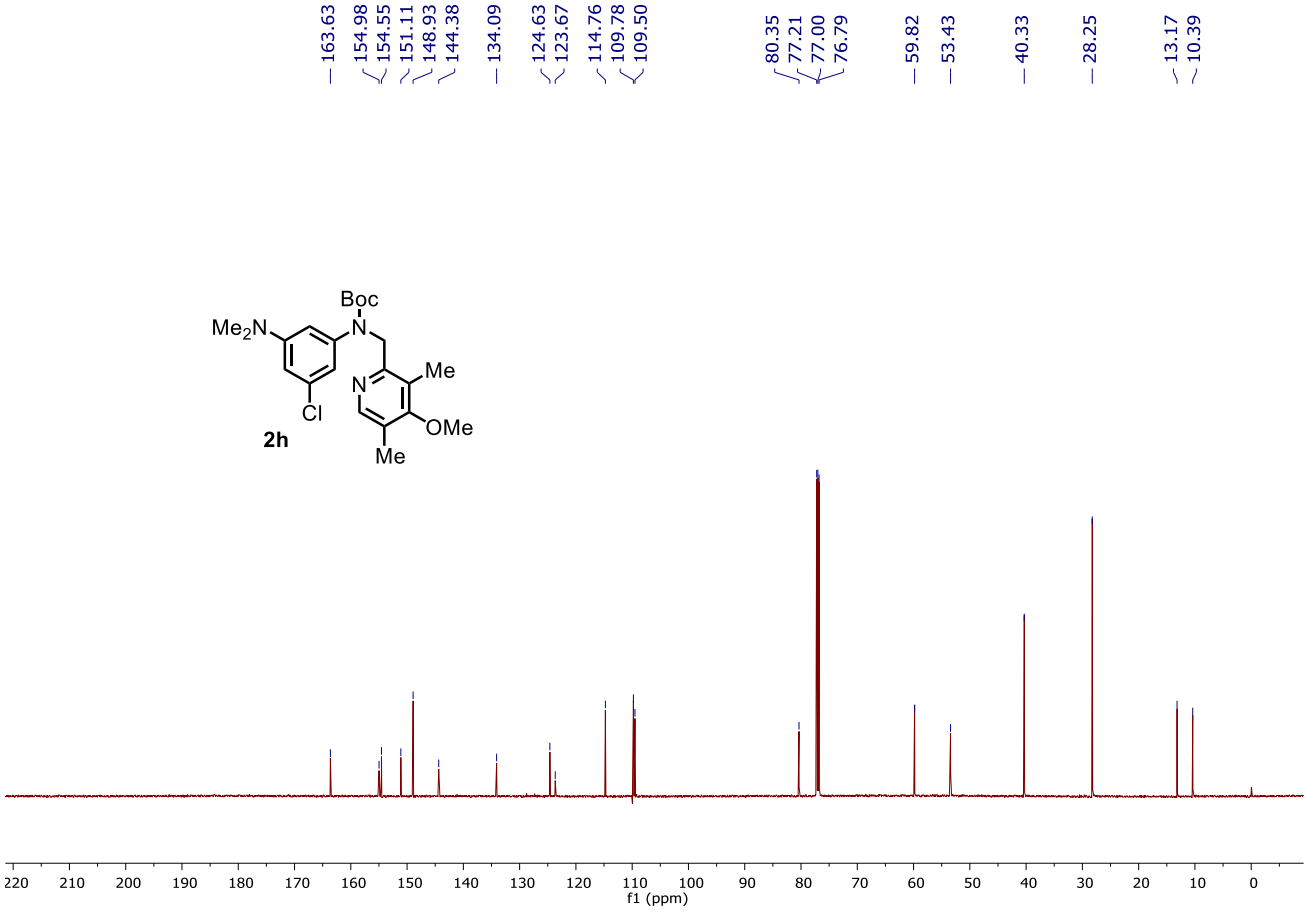
6.439
6.435
6.432
4.855
3.720
2.853
2.208
2.191
1.397
Boc
Me2N
N
Me
N
Cl
OMe
Me
2h
1.00
0.96
0.95
1.00
1.97
3.05
5.89
2.95
3.01
9.06
f1 (ppm)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151.11
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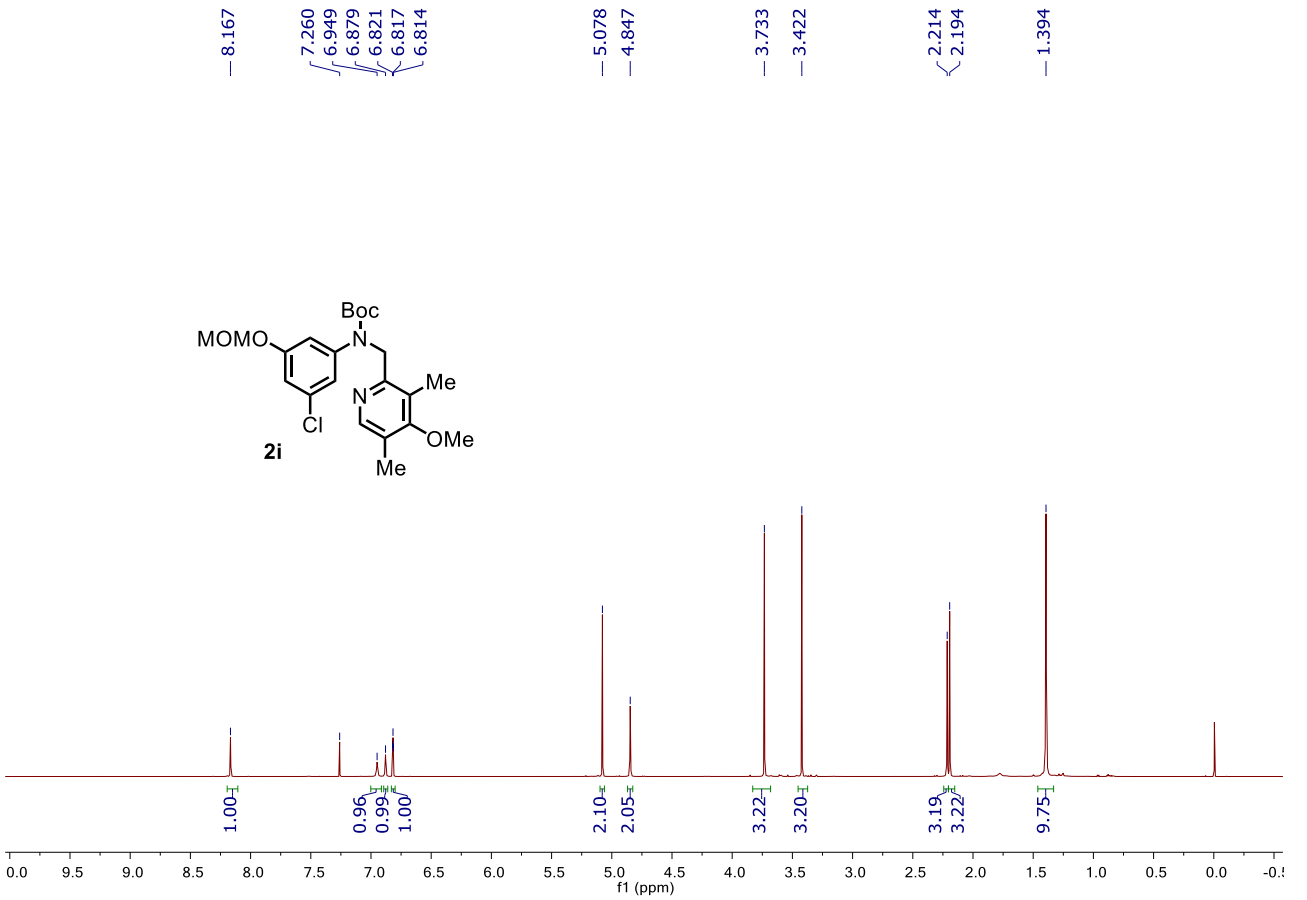
144.38
134.09
124.63
123.67
114.76
109.78
109.50
80.35
77.21
77.00
76.79
59.82
53.43
40.33
28.25
13.17
10.39
Boc
Me2N
N
Me
N
Cl
OMe
Me
2h
f1 (ppm)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6.879
6.821
6.817
6.814
5.078
4.847
3.733
3.422
2.214
2.194
1.394
Boc
MOMO
N
Me
N
Cl
OMe
Me
2i
1.00
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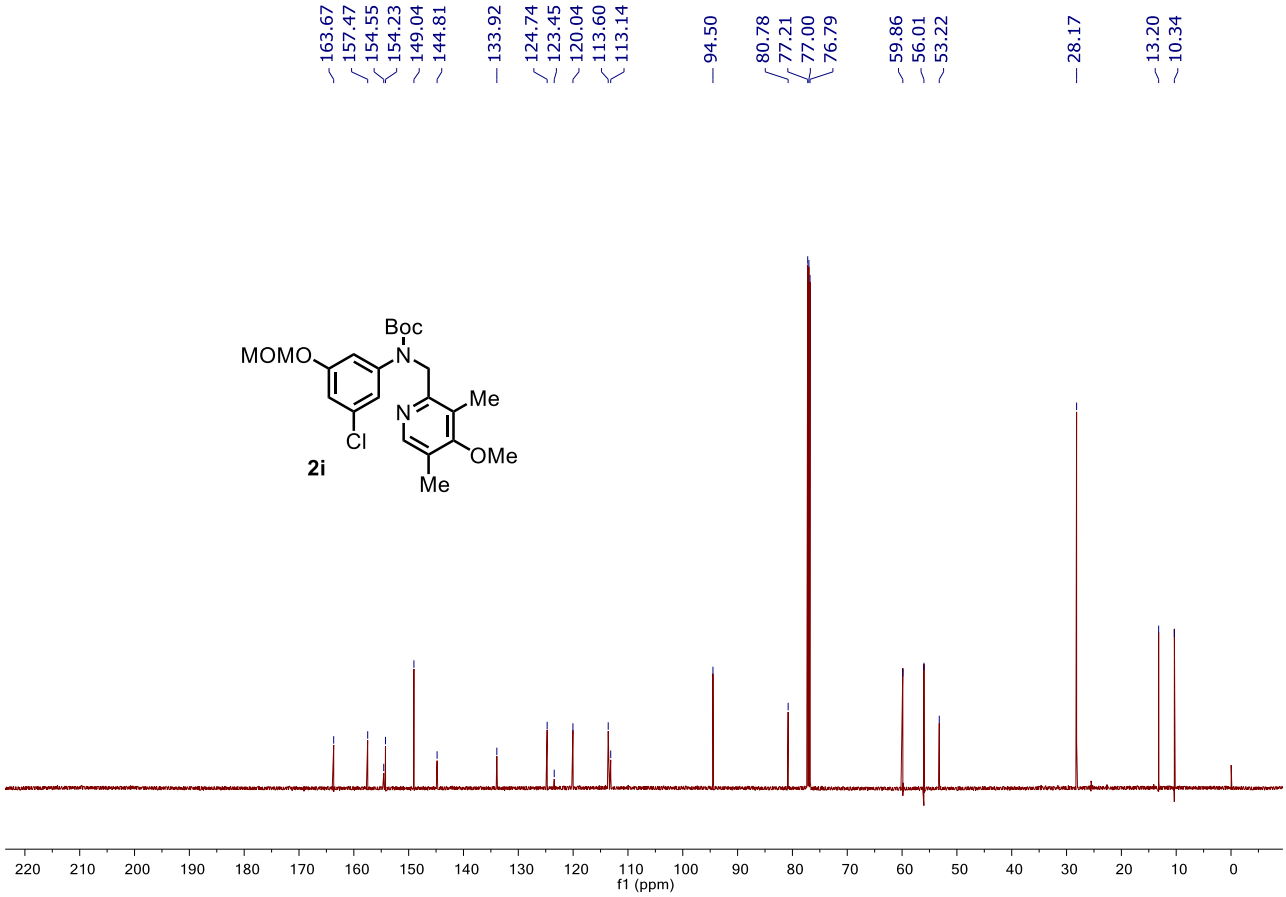
0.99
1.00
2.10
2.05
3.22
3.20
3.19
3.22
9.75
f1 (ppm)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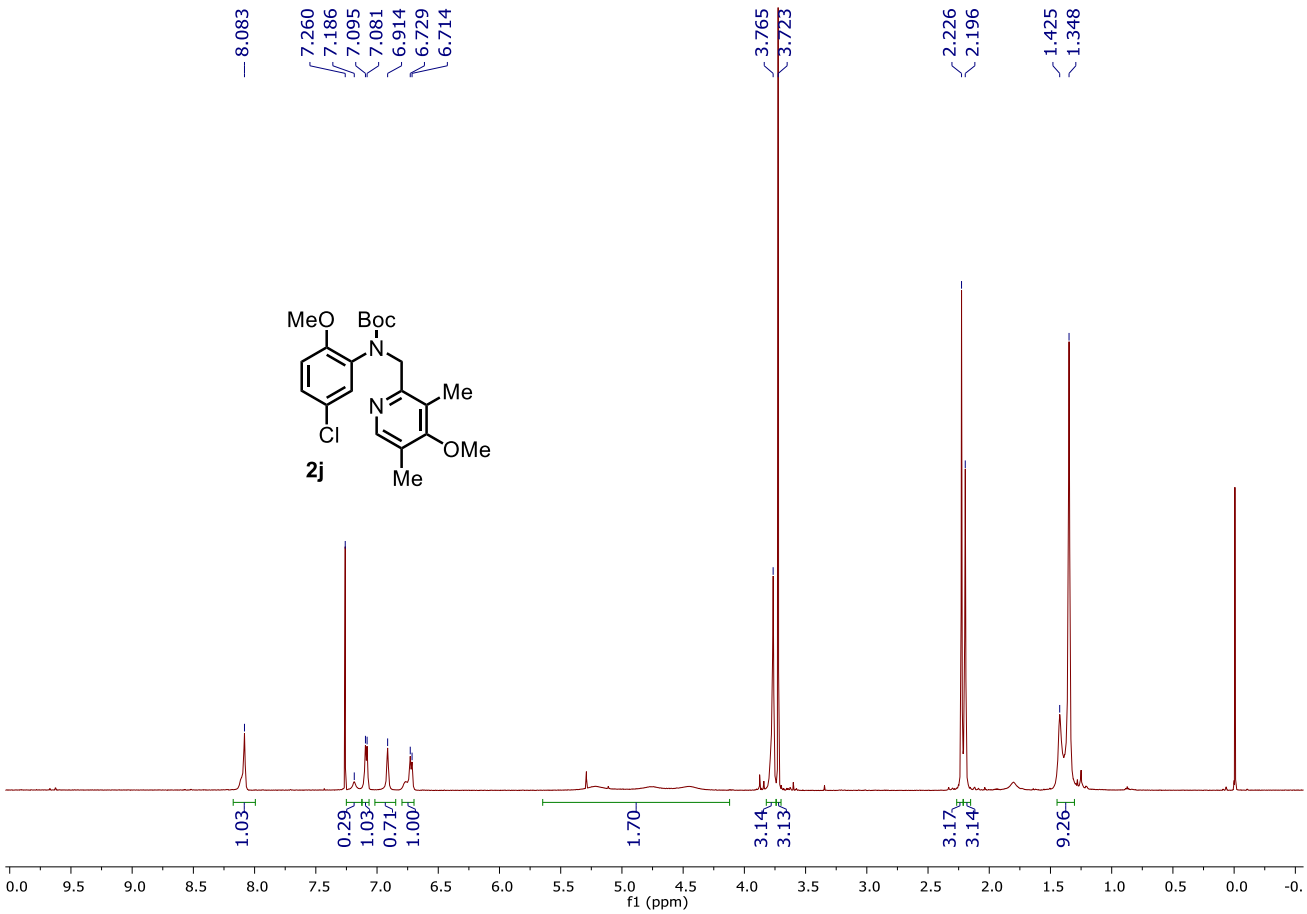
154.23
149.04
144.81
133.92
124.74
123.45
120.04
113.60
113.14
94.50
80.78
77.21
77.00
76.79
59.86
56.01
53.22
28.17
13.20
10.34
Boc
MOMO
N
Me
N
Cl
OMe
Me
2i
f1 (ppm)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7.095
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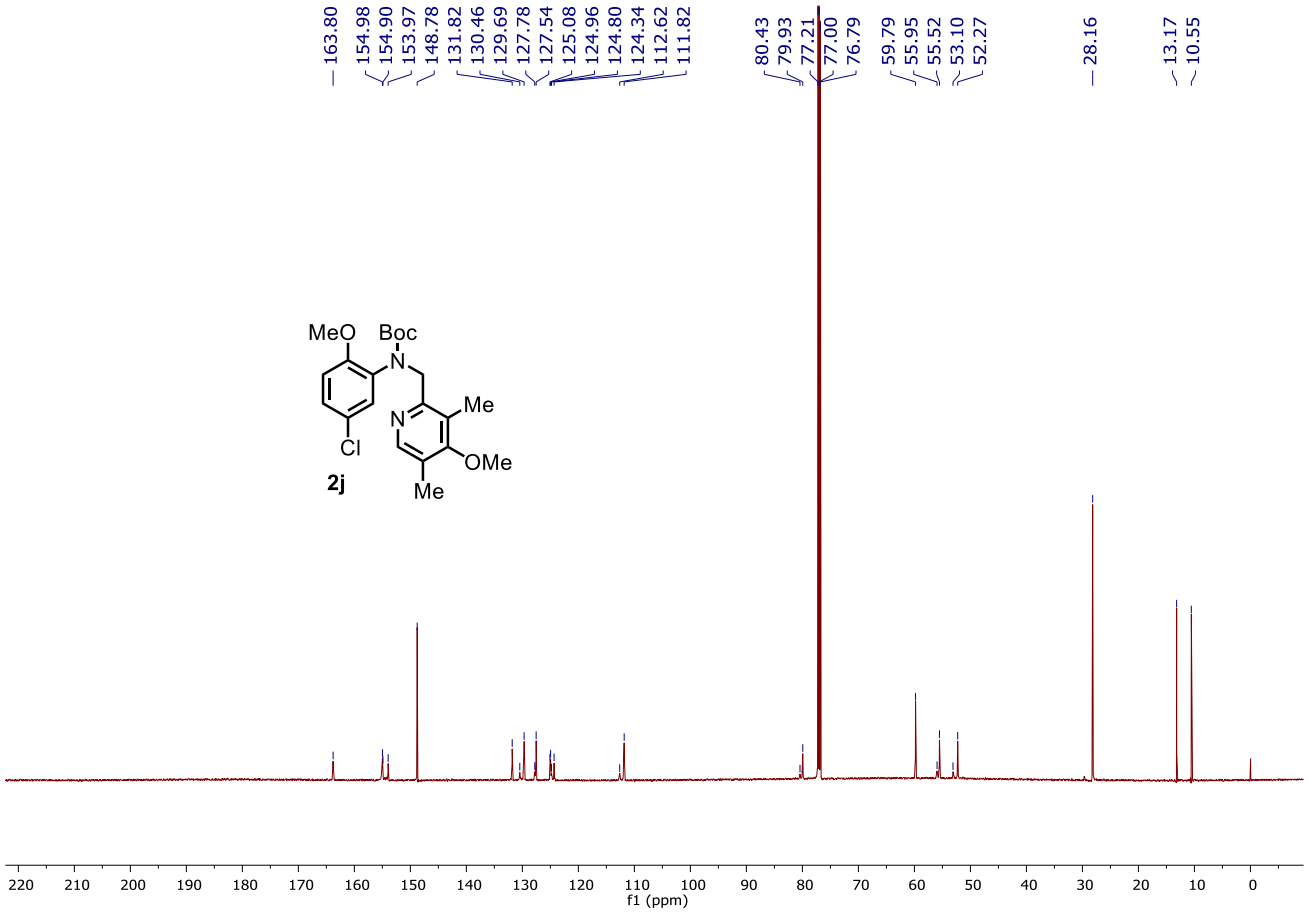
6.914
6.729
6.714
3.765
3.723
2.226
2.196
1.425
1.348
MeO
Boc
N
Me
N
Cl
OMe
Me
2j
1.03
0.29
1.03
0.71
1.00
1.70
3.14
3.13
3.17
3.14
9.26
f1 (ppm)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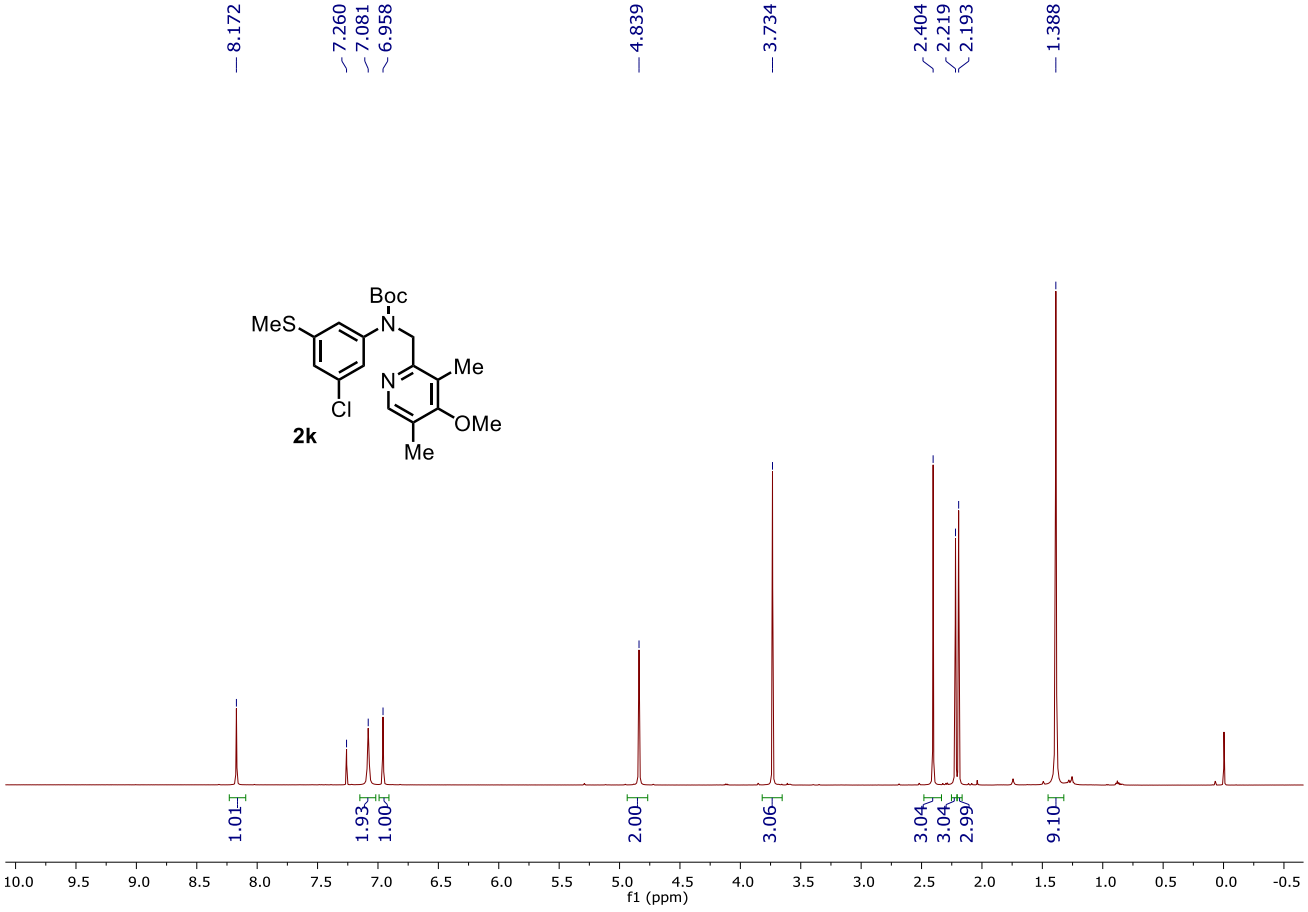
131.82
130.46
129.69
127.78
127.54
125.08
124.96
124.80
124.34
112.62
111.82
80.43
79.93
77.21
77.00
76.79
59.79
55.95
55.52
53.10
52.27
28.16
13.17
10.55
MeO
Boc
N
Me
N
Cl
OMe
Me
2j
f1 (ppm)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7.081
6.958
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3.734
2.404
2.219
2.193
1.388
Boc
MeS
N
Me
N
Cl
OMe
Me
2k
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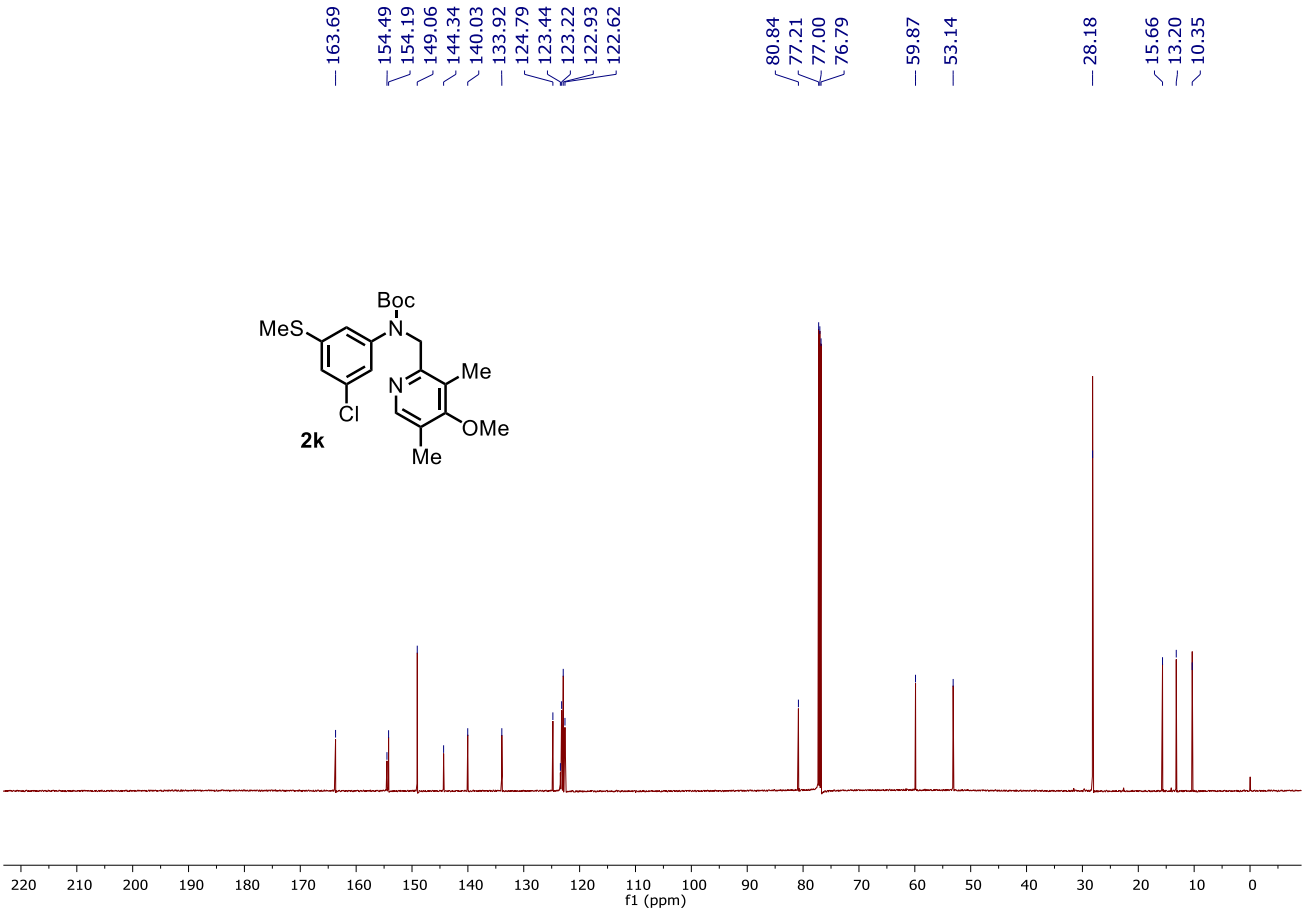
1.93
1.00
2.00
3.06
3.04
3.04
2.99
9.10
f1 (ppm)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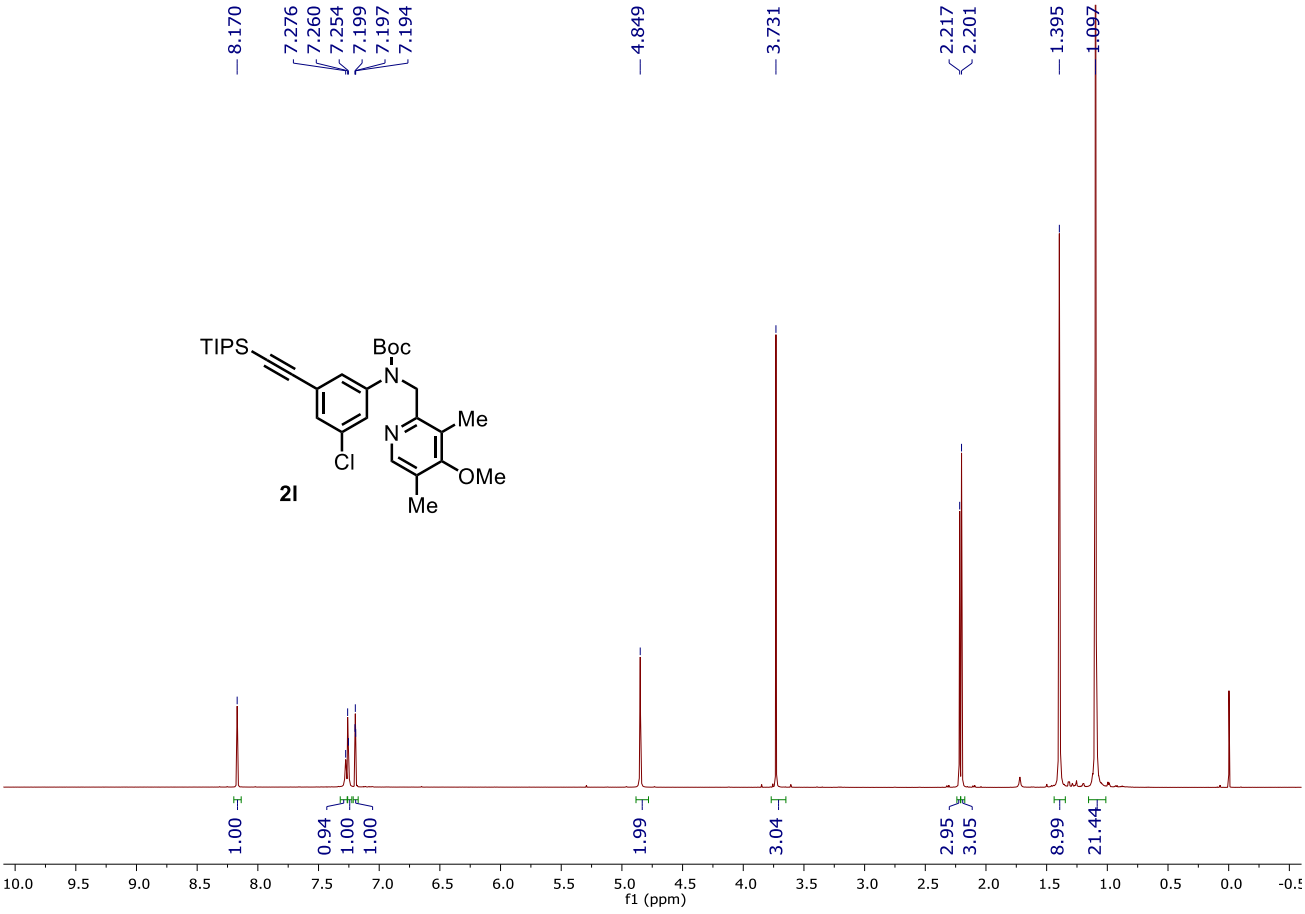
140.03
133.92
124.79
123.44
123.22
122.93
122.62
80.84
77.21
77.00
76.79
59.87
53.14
28.18
15.66
13.20
10.35
Boc
MeS
N
Me
N
Cl
OMe
Me
2k
f1 (ppm)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7.197
7.194
4.849
3.731
2.217
2.201
1.395
1.097
TIPS
Boc
N
Me
N
Cl
OMe
Me
2l
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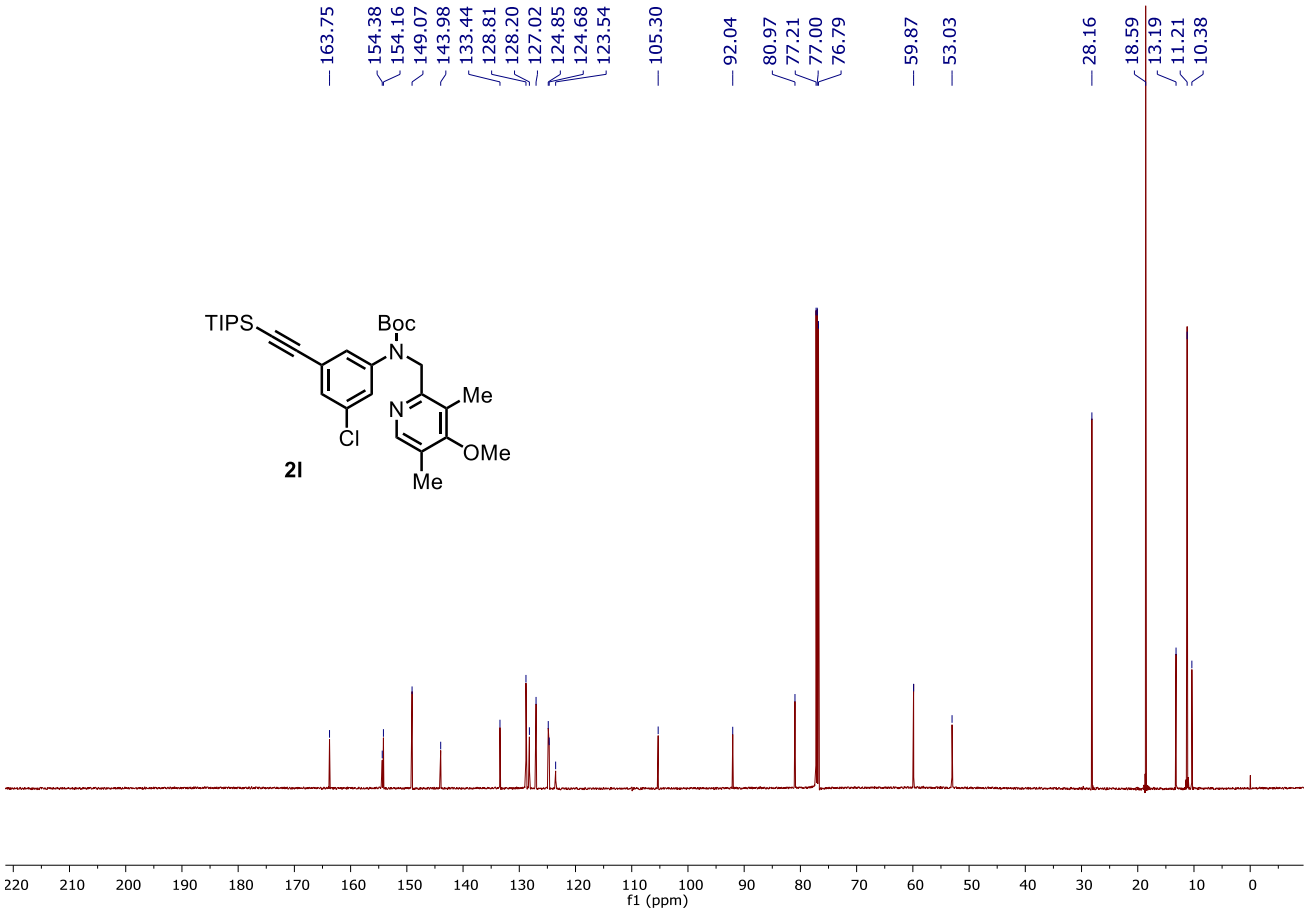
1.00
1.00
1.99
3.04
2.95
3.05
8.99
21.44
f1 (ppm)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154.16
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143.98
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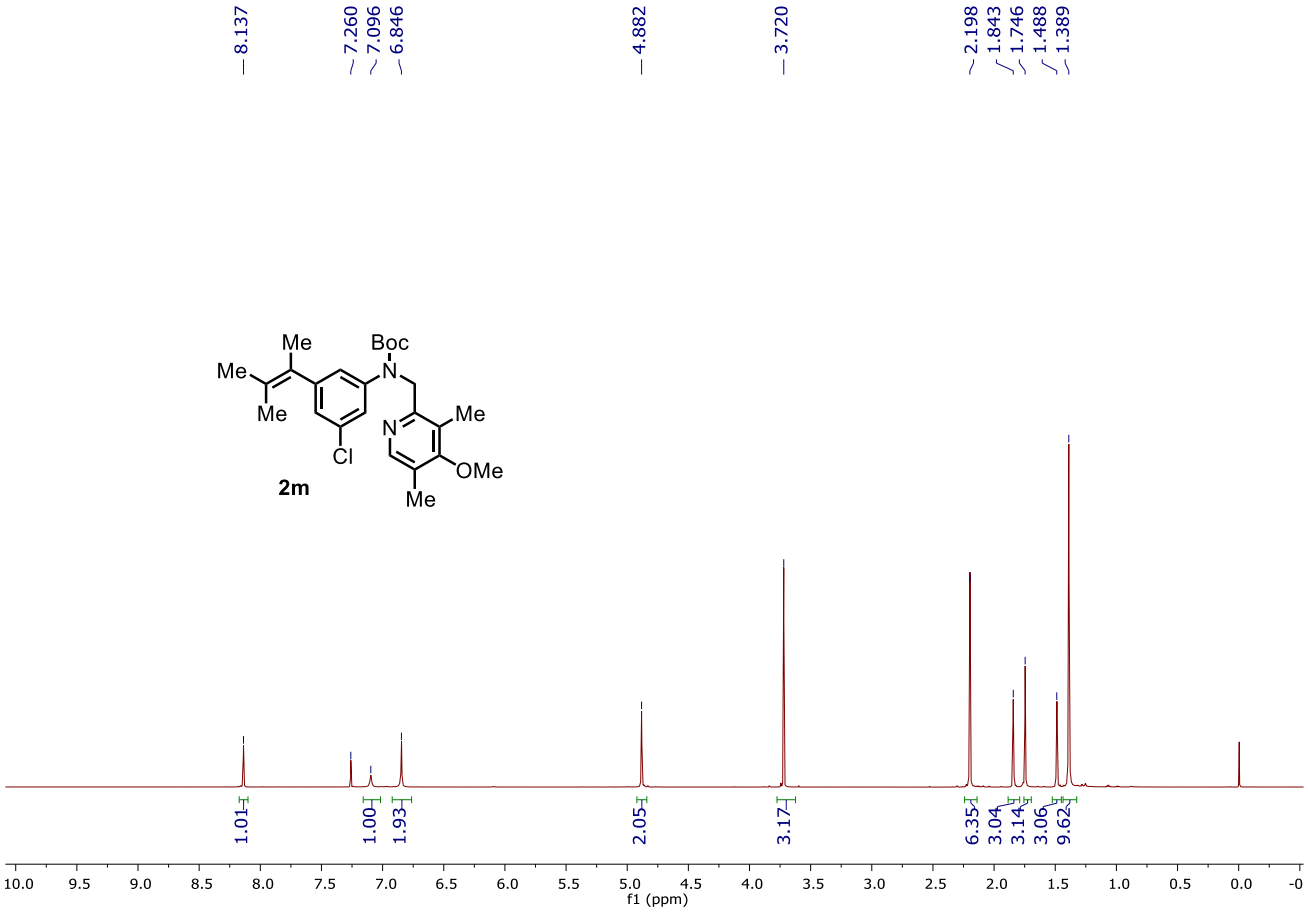
128.81
128.20
127.02
124.85
124.68
123.54
105.30
92.04
80.97
77.21
77.00
76.79
59.87
53.03
28.16
18.59
13.19
11.21
10.38
TIPS
Boc
N
Me
N
Cl
OMe
Me
2l
f1 (ppm)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1.488
1.389
Me
Boc
Me
Me
N
Me
Cl
OMe
Me
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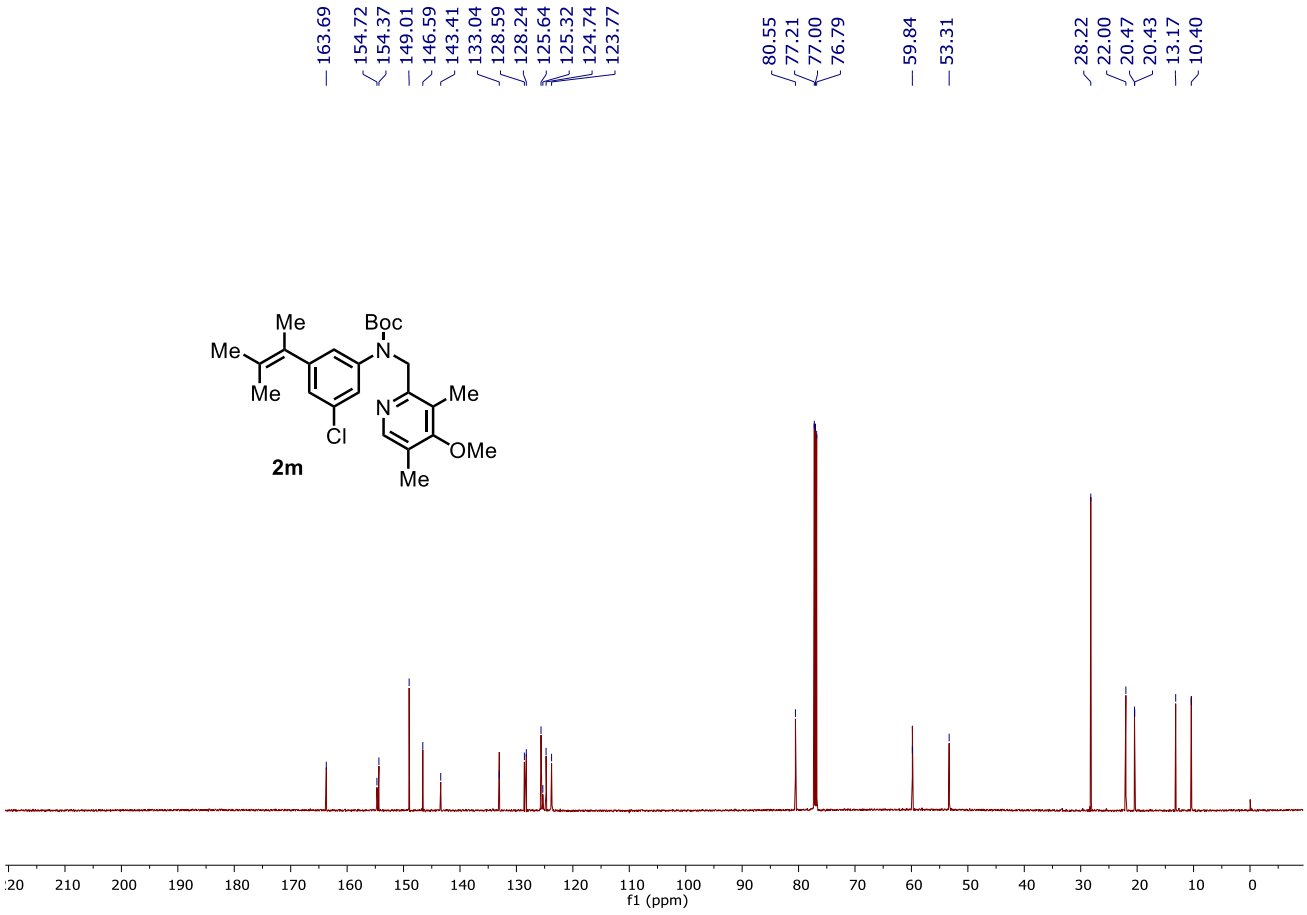
1.00
1.93
2.05
3.17
6.35
3.04
3.14
3.06
9.62
f1 (ppm)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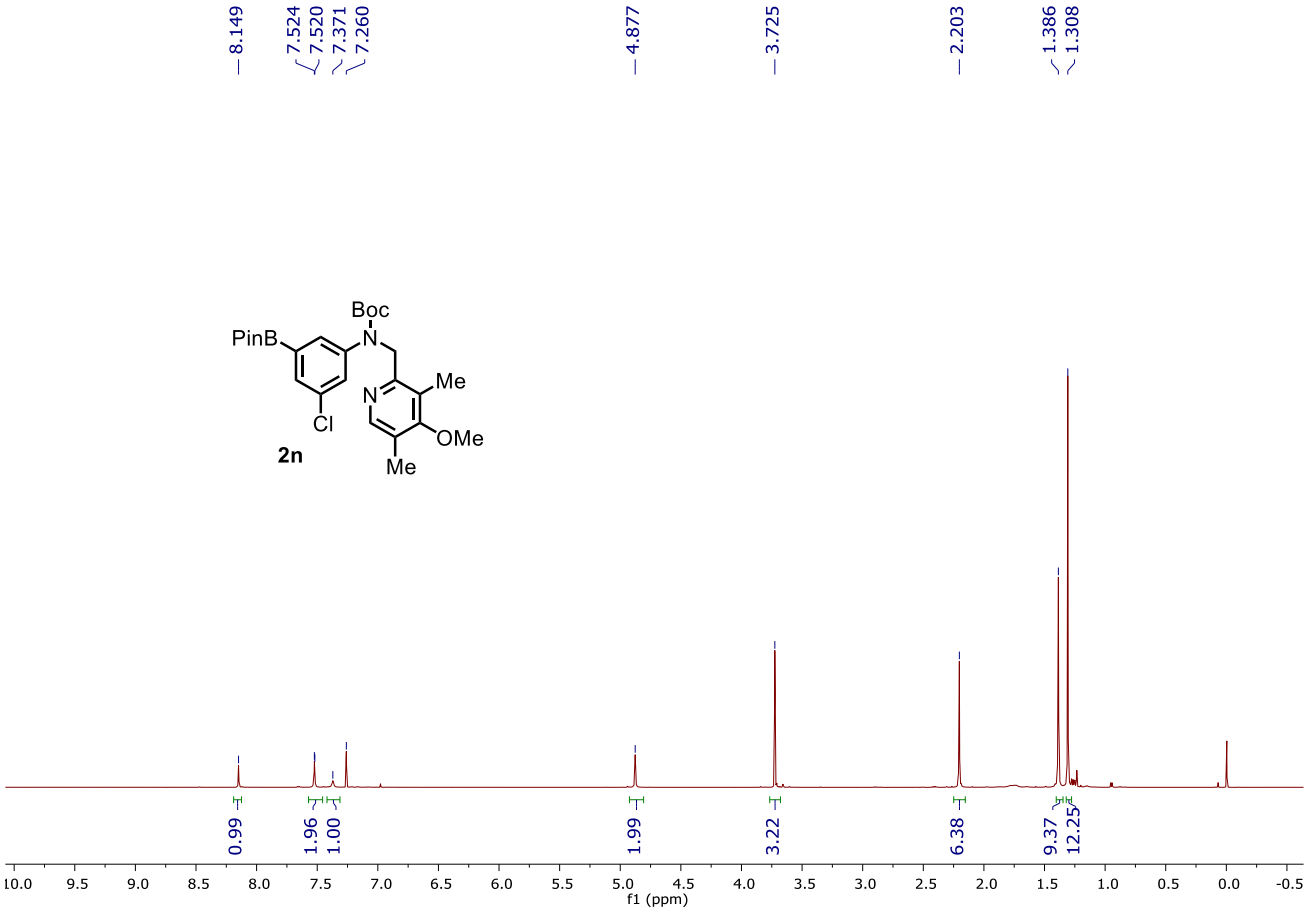
146.59
143.41
133.04
128.59
128.24
125.64
125.32
124.74
123.77
80.55
77.21
77.00
76.79
59.84
53.31
28.22
22.00
20.47
20.43
13.17
10.40
Me
Boc
Me
N
Me
Me
N
Cl
OMe
Me
2m
f1 (ppm)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7.260
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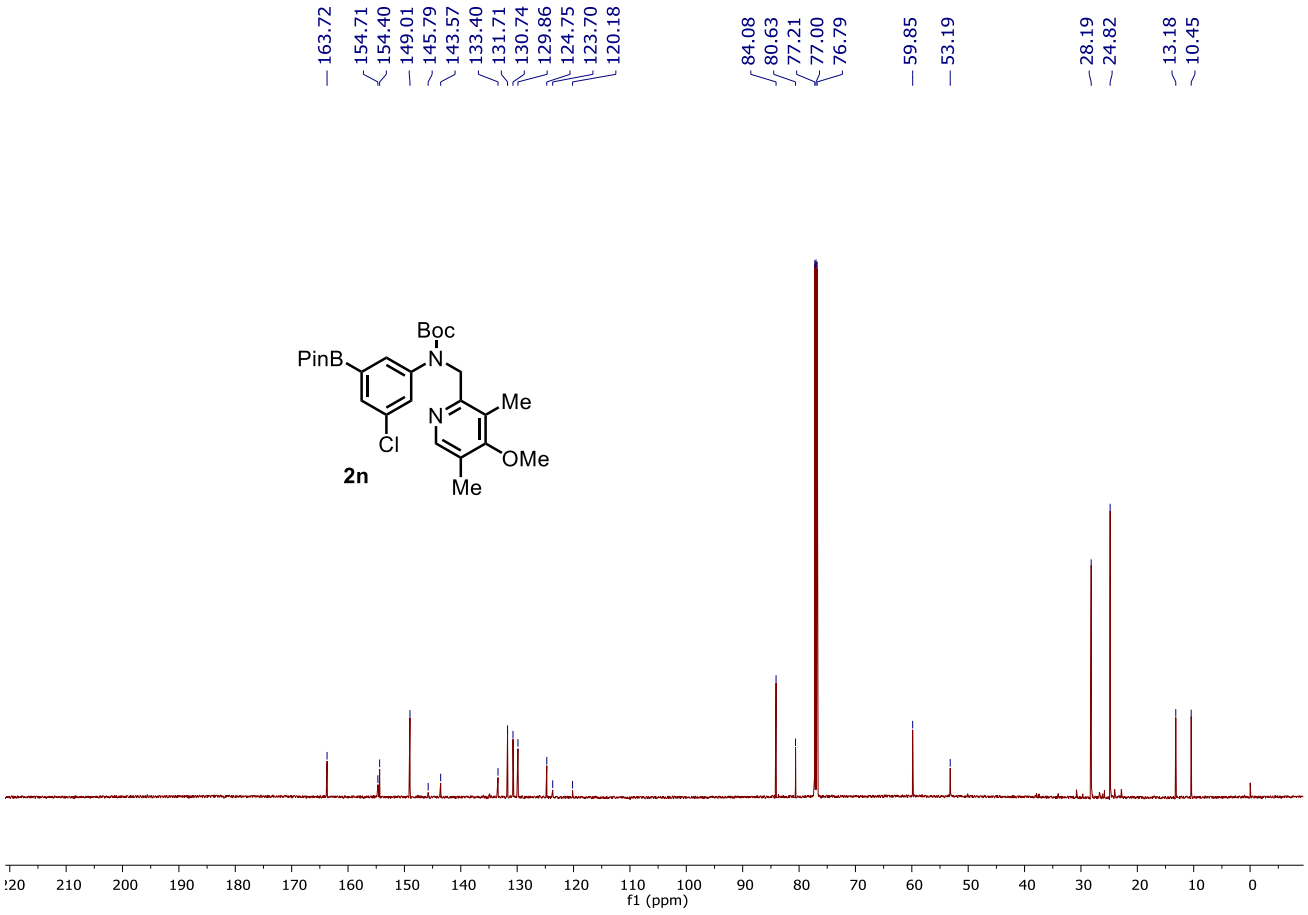
3.725
2.203
1.386
1.308
Boc
PinB
N
Me
N
Cl
OMe
Me
2n
0.99
1.96
1.00
1.99
3.22
6.38
9.37
12.25
f1 (ppm)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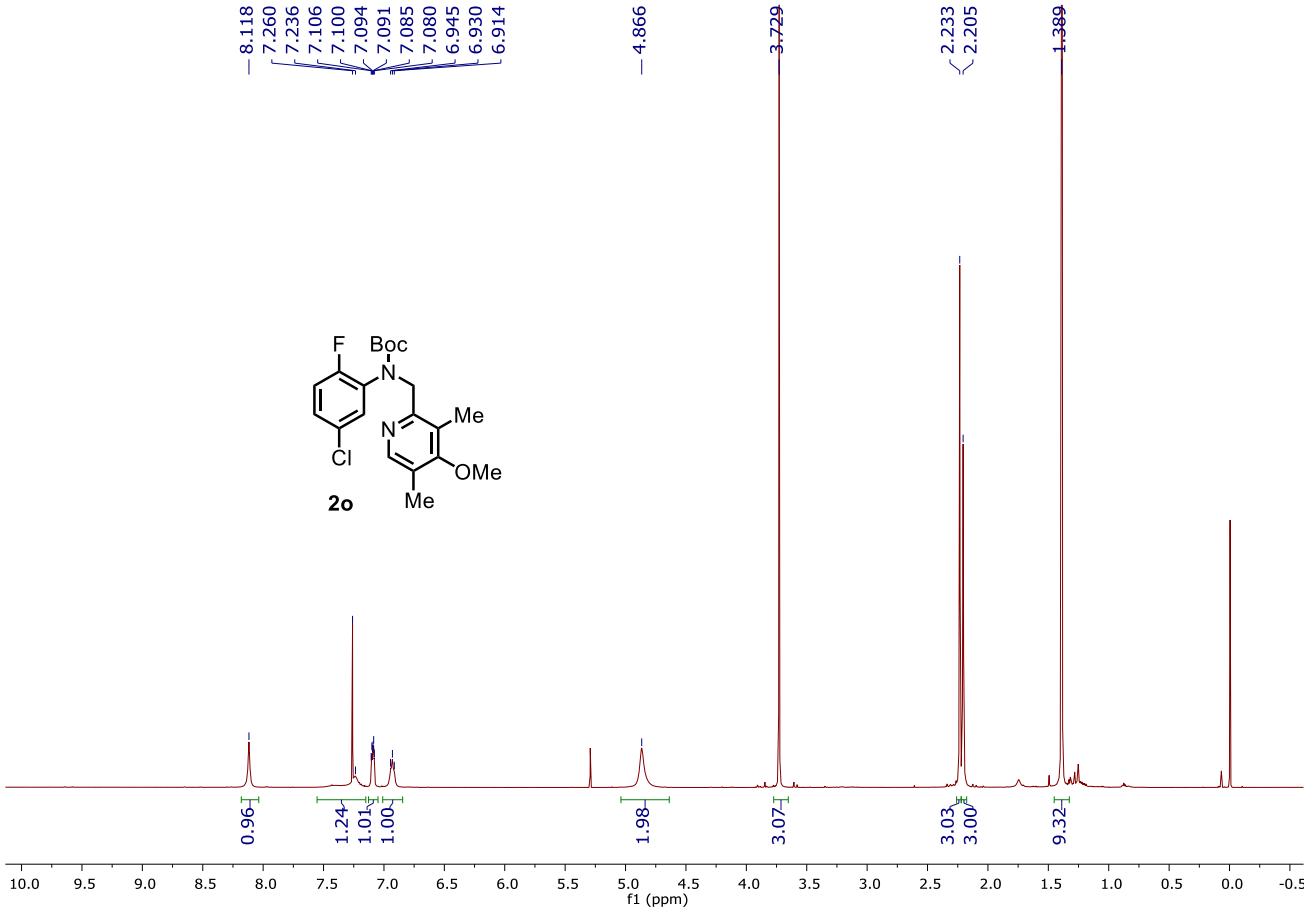
143.57
133.40
131.71
130.74
129.86
124.75
123.70
120.18
84.08
80.63
77.21
77.00
76.79
59.85
53.19
28.19
24.82
13.18
10.45
Boc
PinB
N
Me
N
Cl
OMe
Me
2n
f1 (ppm)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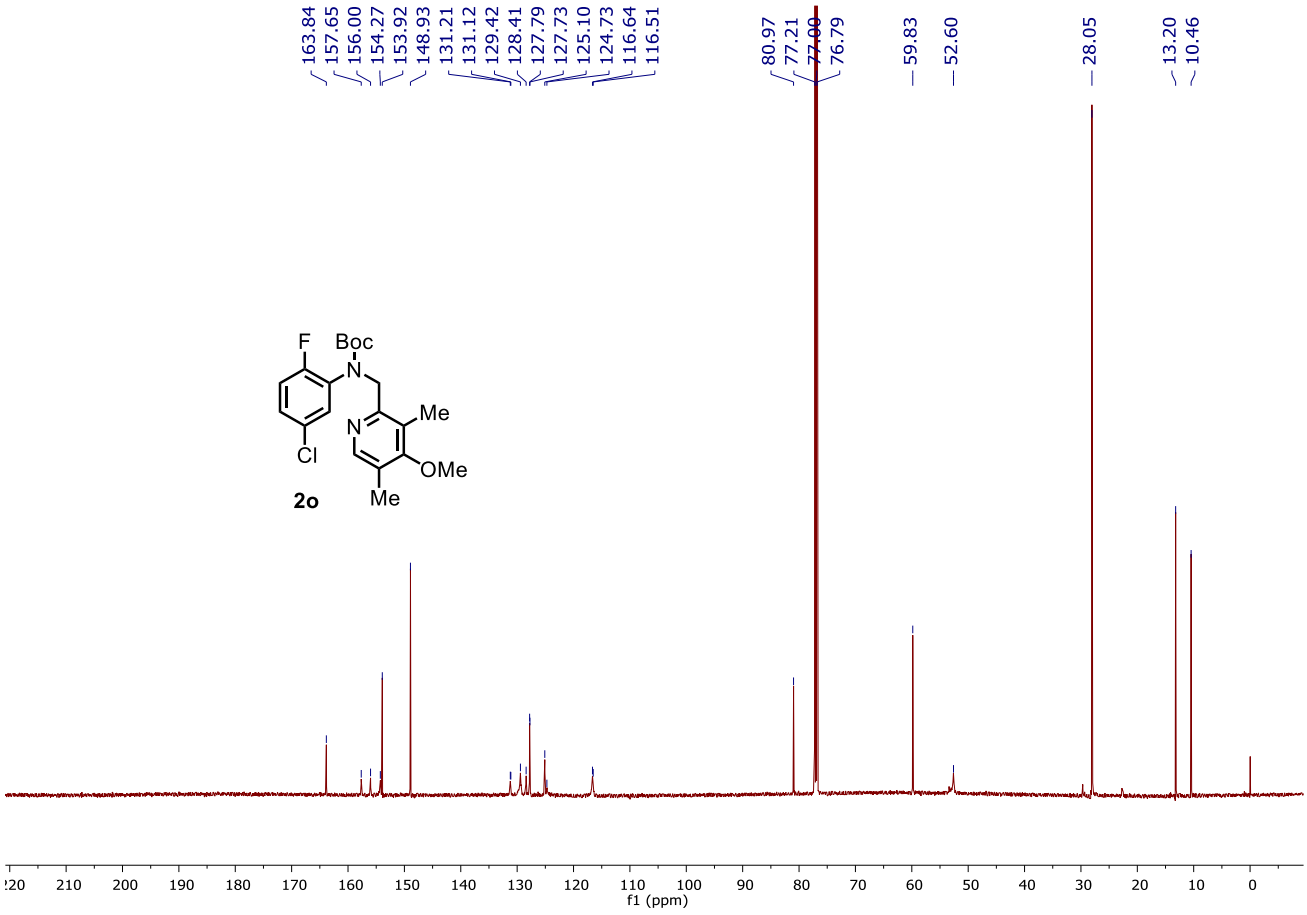
7.091
7.085
7.080
6.945
6.930
6.914
4.866
3.729
2.233
2.205
1.389
F
Boc
N
Me
N
Cl
OMe
Me
2o
0.96
1.24
1.01
1.00
1.98
3.07
3.03
3.00
9.32
f1 (ppm)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153.92
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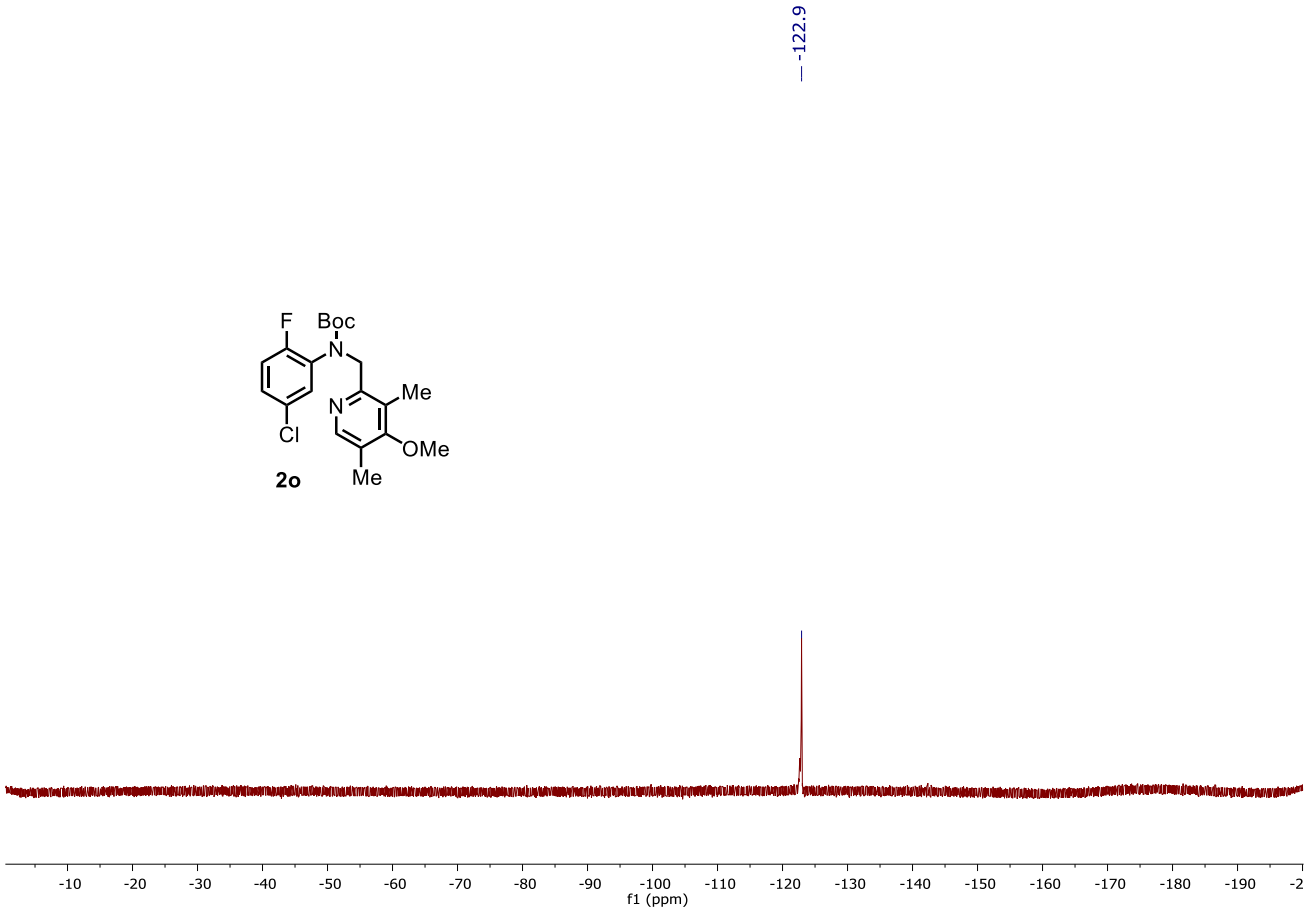
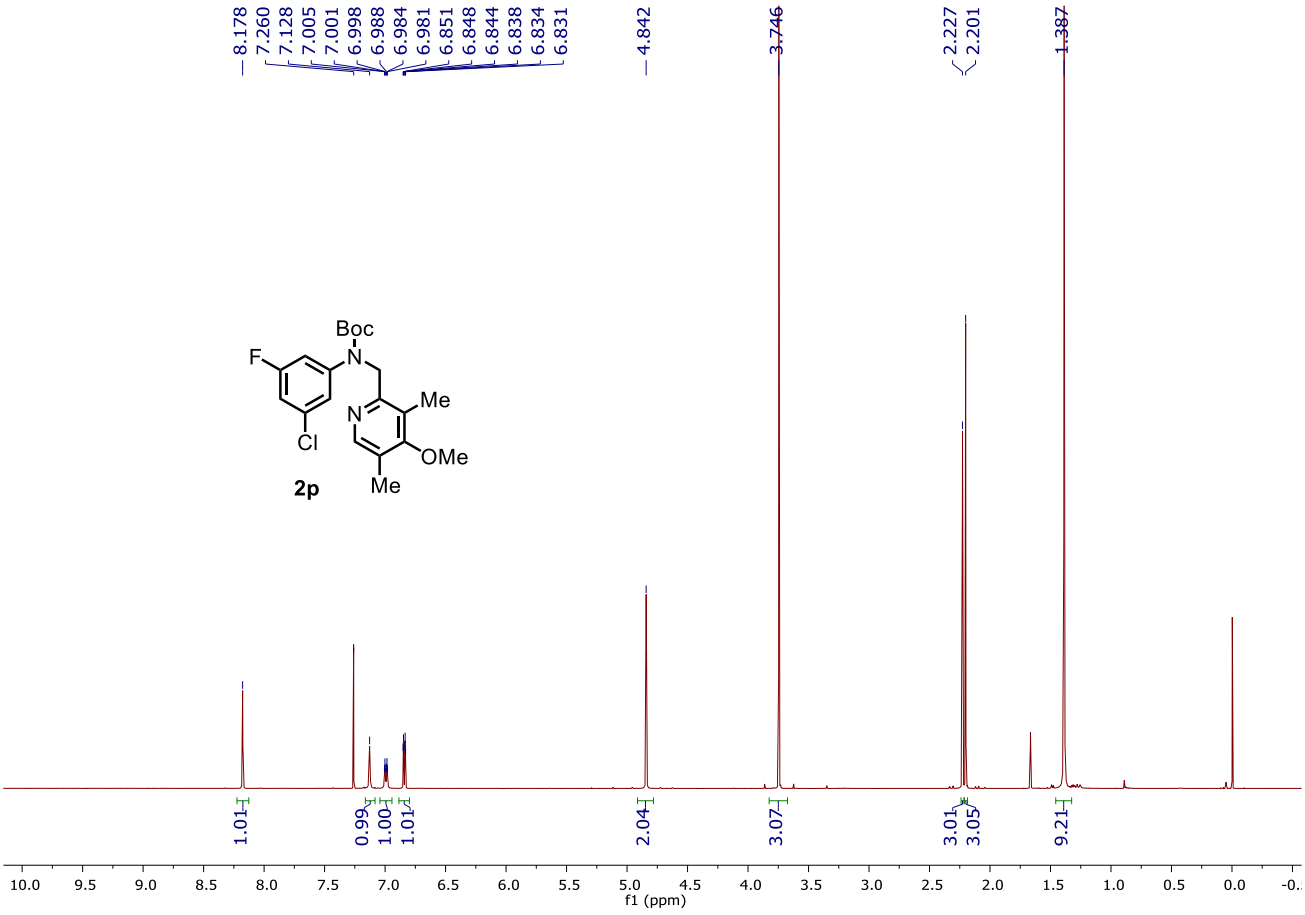
131.21
131.12
129.42
128.41
127.79
127.73
125.10
124.73
116.64
116.51
80.97
77.21
77.00
76.79
59.83
52.60
28.05
13.20
10.46
F
Boc
N
Me
N
Cl
OMe
Me
2o
f1 (ppm)


-122.9
F
Boc
N
Me
N
Cl
OMe
Me
2o
f1 (ppm)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7.001
6.998
6.988
6.984
6.981
6.851
6.848
6.844
6.838
6.834
6.831
4.842
3.746
2.227
2.201
1.387
Boc
N
F
Cl
N
Me
OMe
Me
2p
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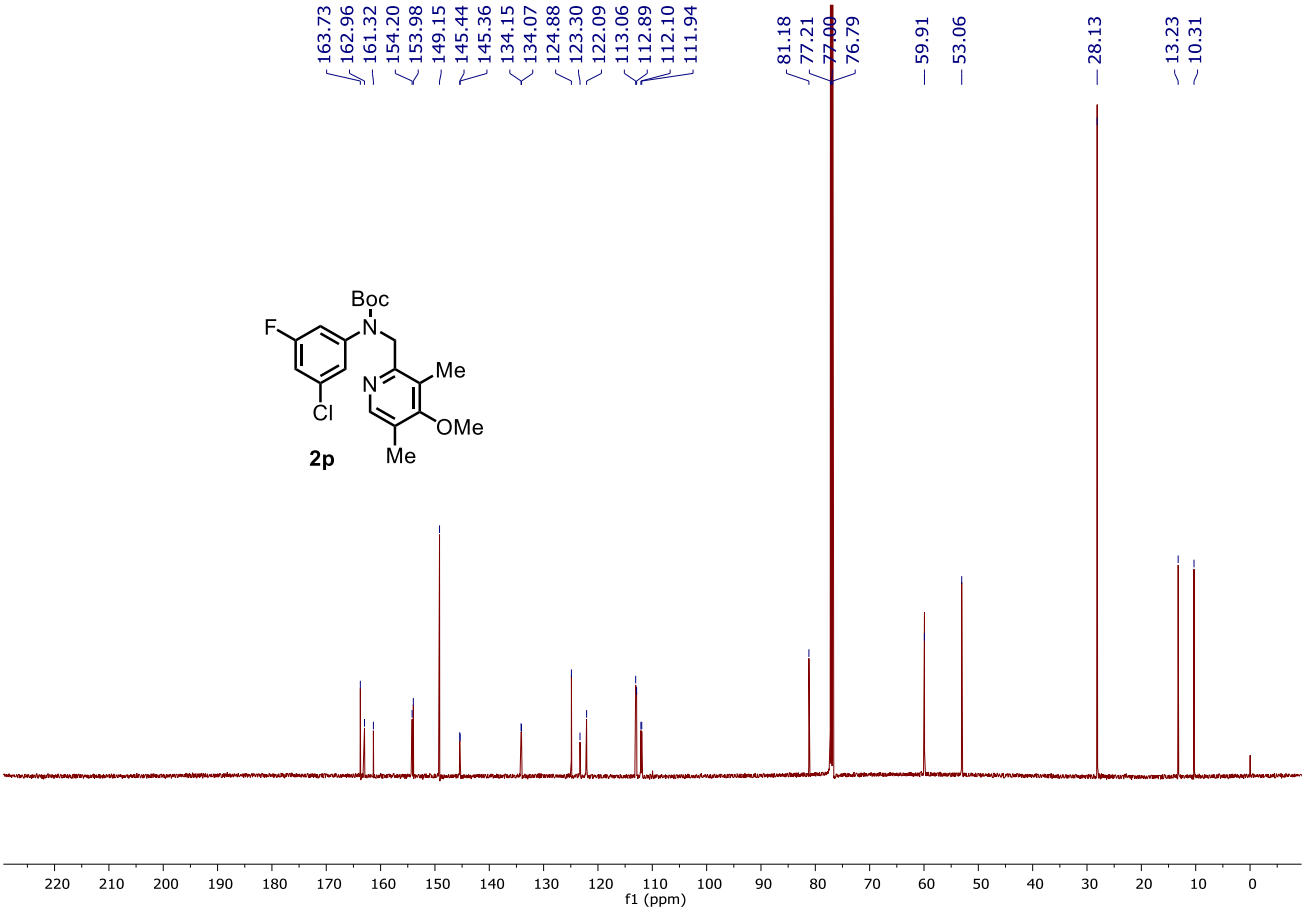
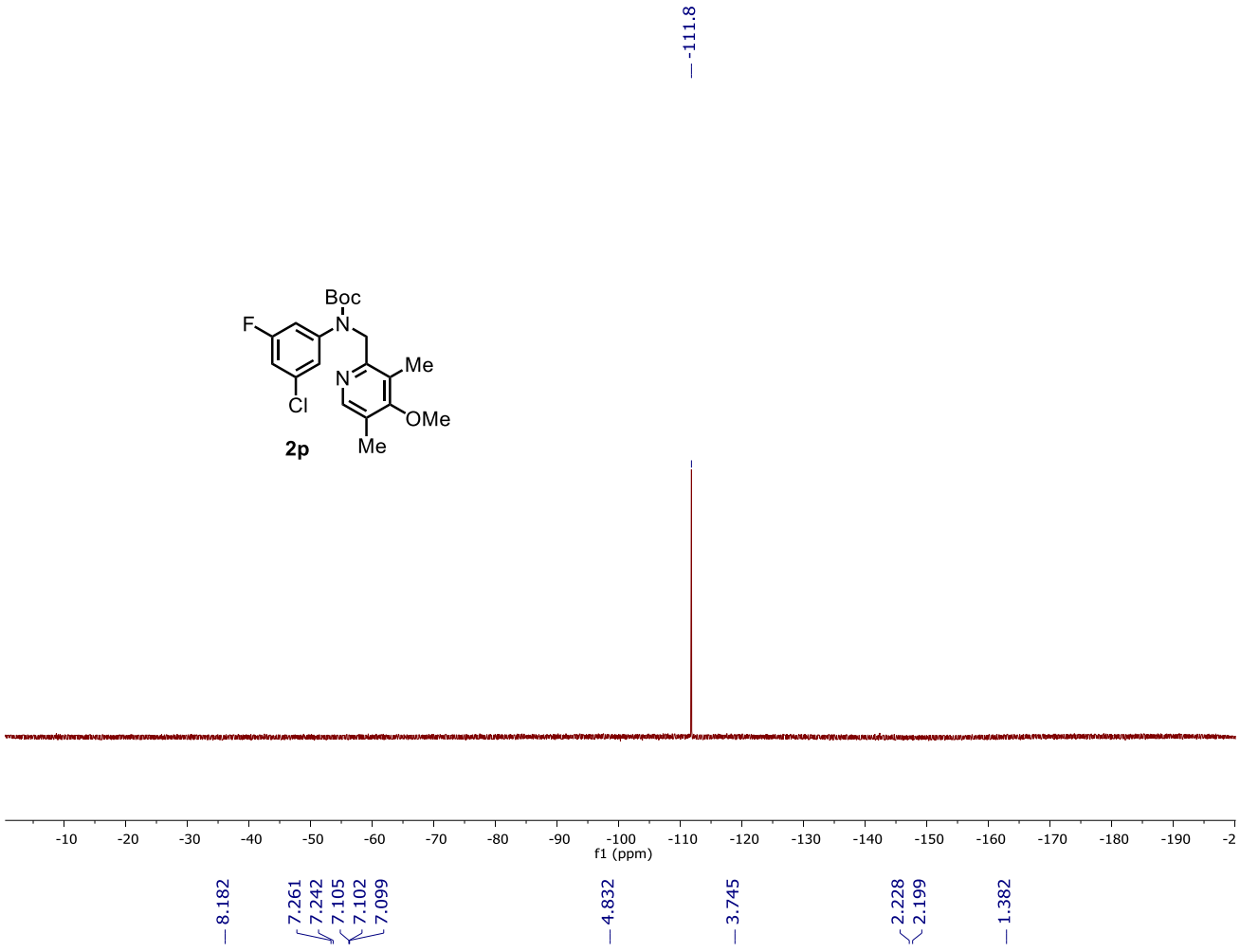
0.99
1.00
1.01
2.04
3.07
3.01
3.05
9.21
f1 (ppm)


163.73
162.96
161.32
154.20
153.98
149.15
145.44
145.36
134.15
134.07
124.88
123.30
122.09
113.06
112.89
112.10
111.94
81.18
77.21
77.00
76.79
59.91
53.06
28.13
13.23
10.31
Boc
N
F
Cl
N
Me
OMe
Me
2p
f1 (ppm)


-111.8
Boc
F
N
Cl
N
Me
OMe
Me
2p
f1 (ppm)
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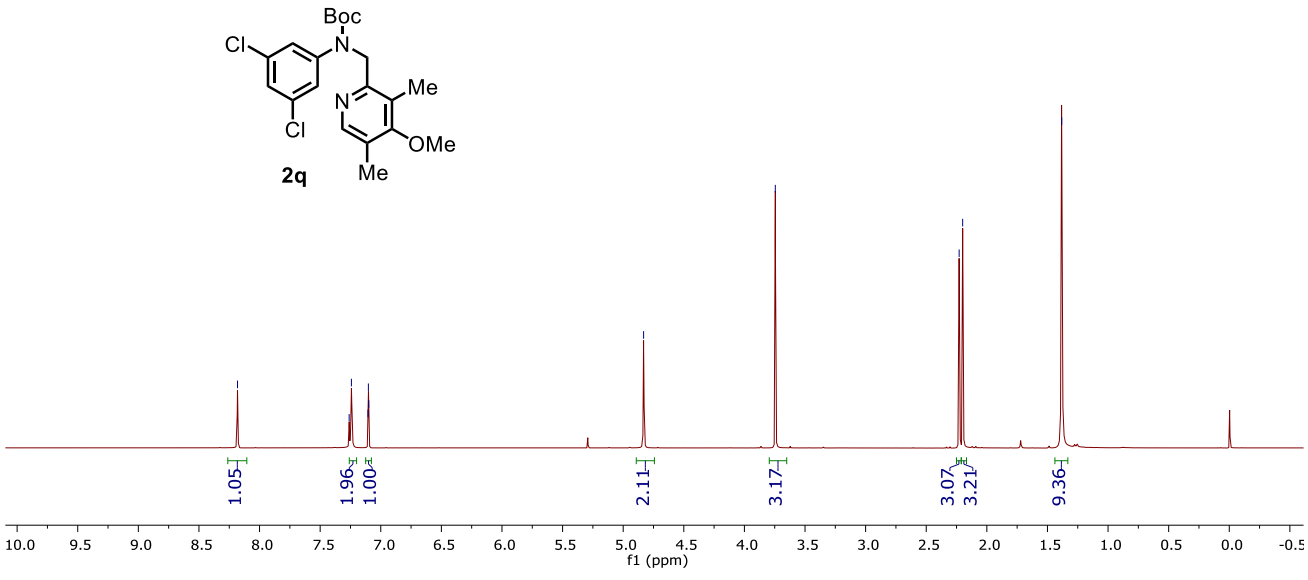
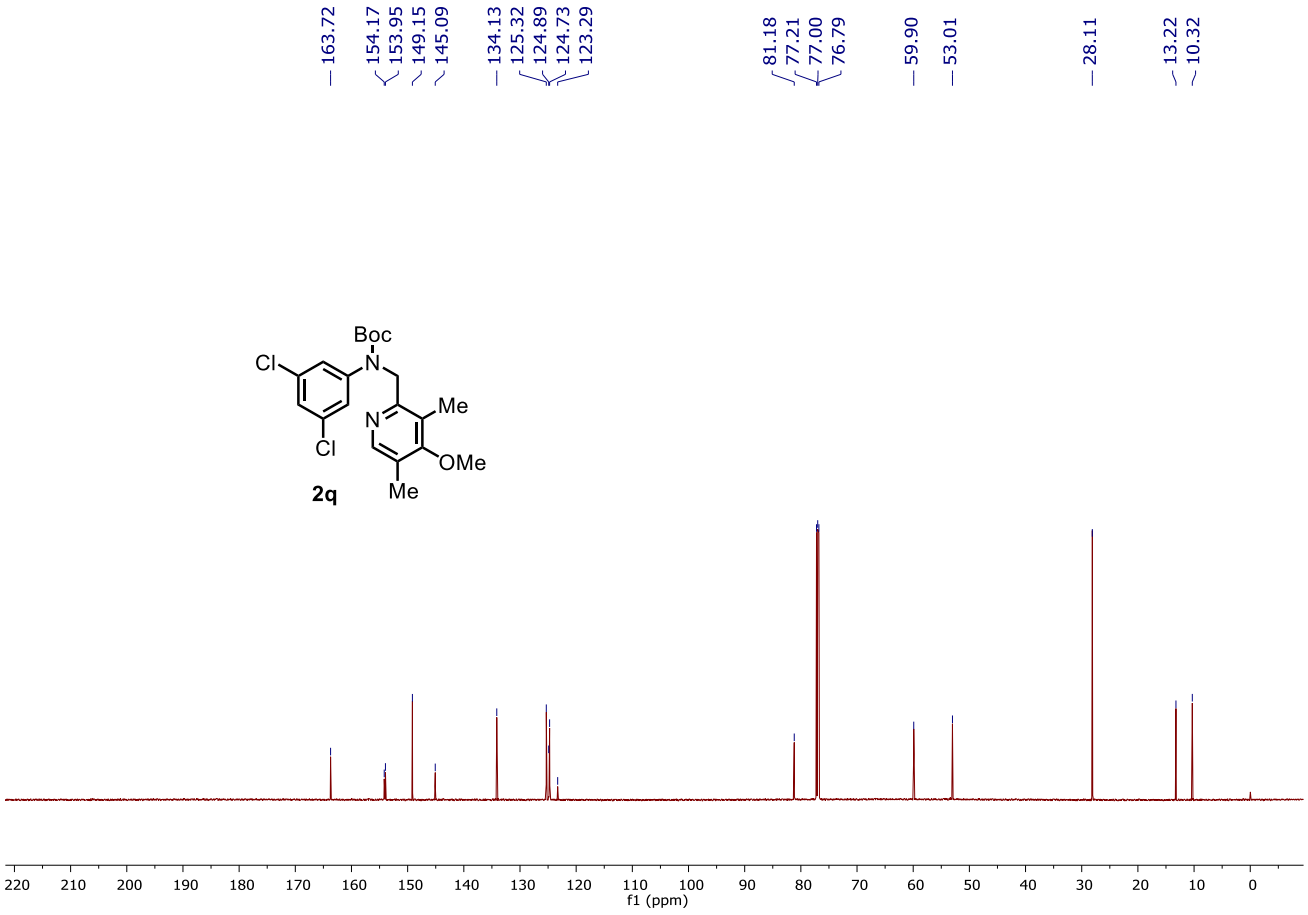
7.261
7.242
7.105
7.102
7.099
4.832
3.745
2.228
2.199
1.382


Boc
Cl
N
Cl
N
Me
OMe
Me
2q
f1 (ppm)
1.05
1.96
1.00
2.11
3.17
3.07
3.21
9.36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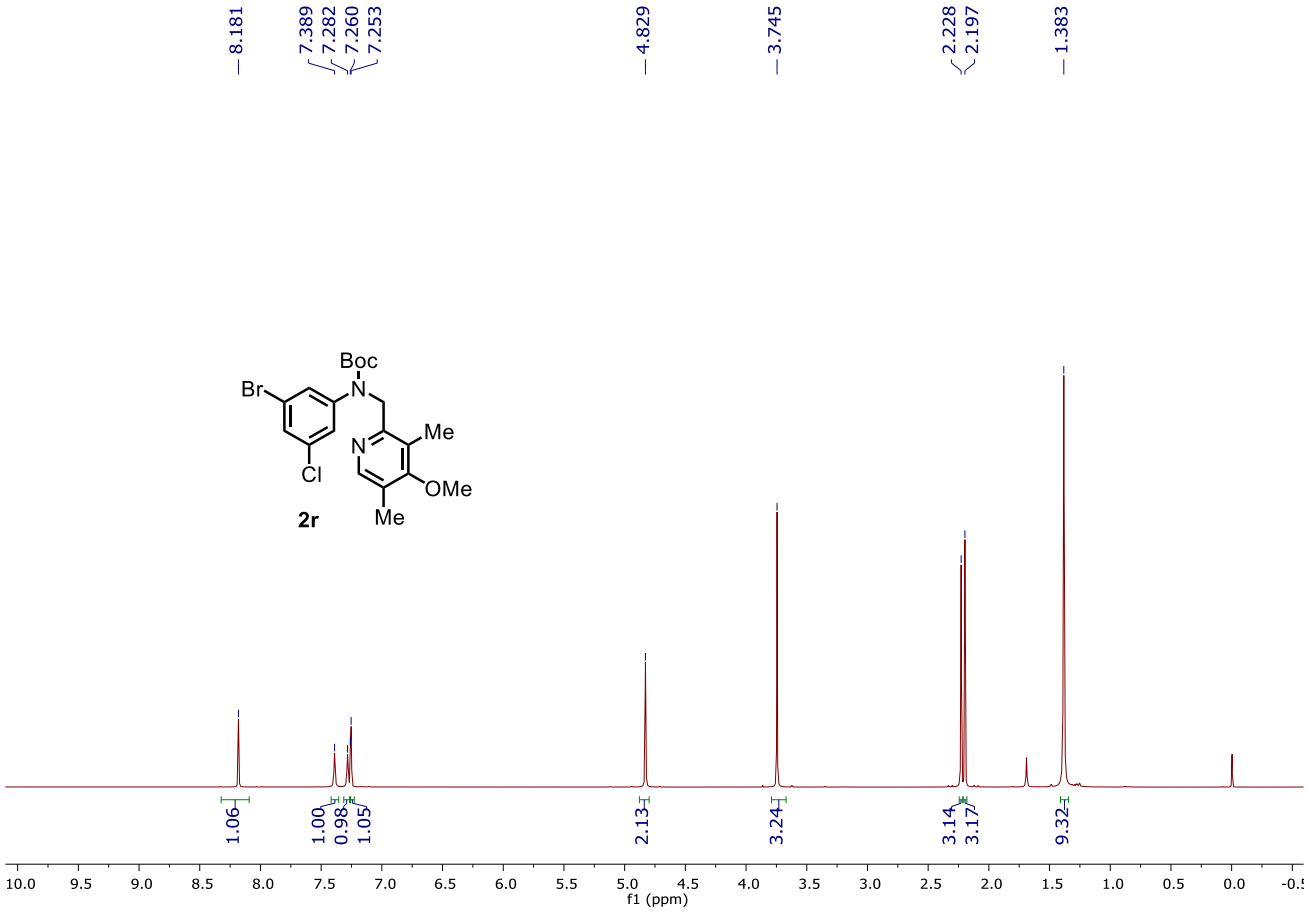
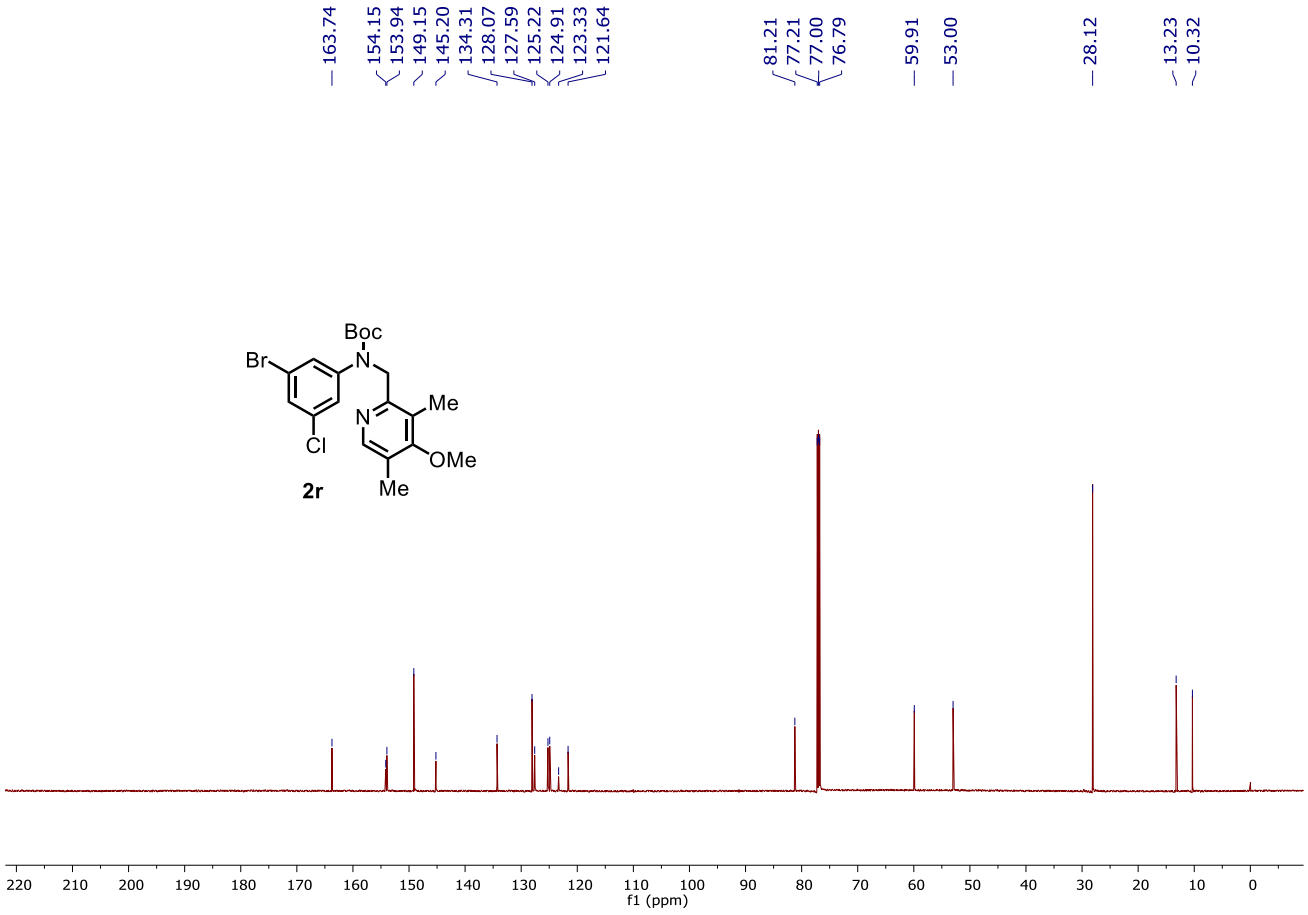
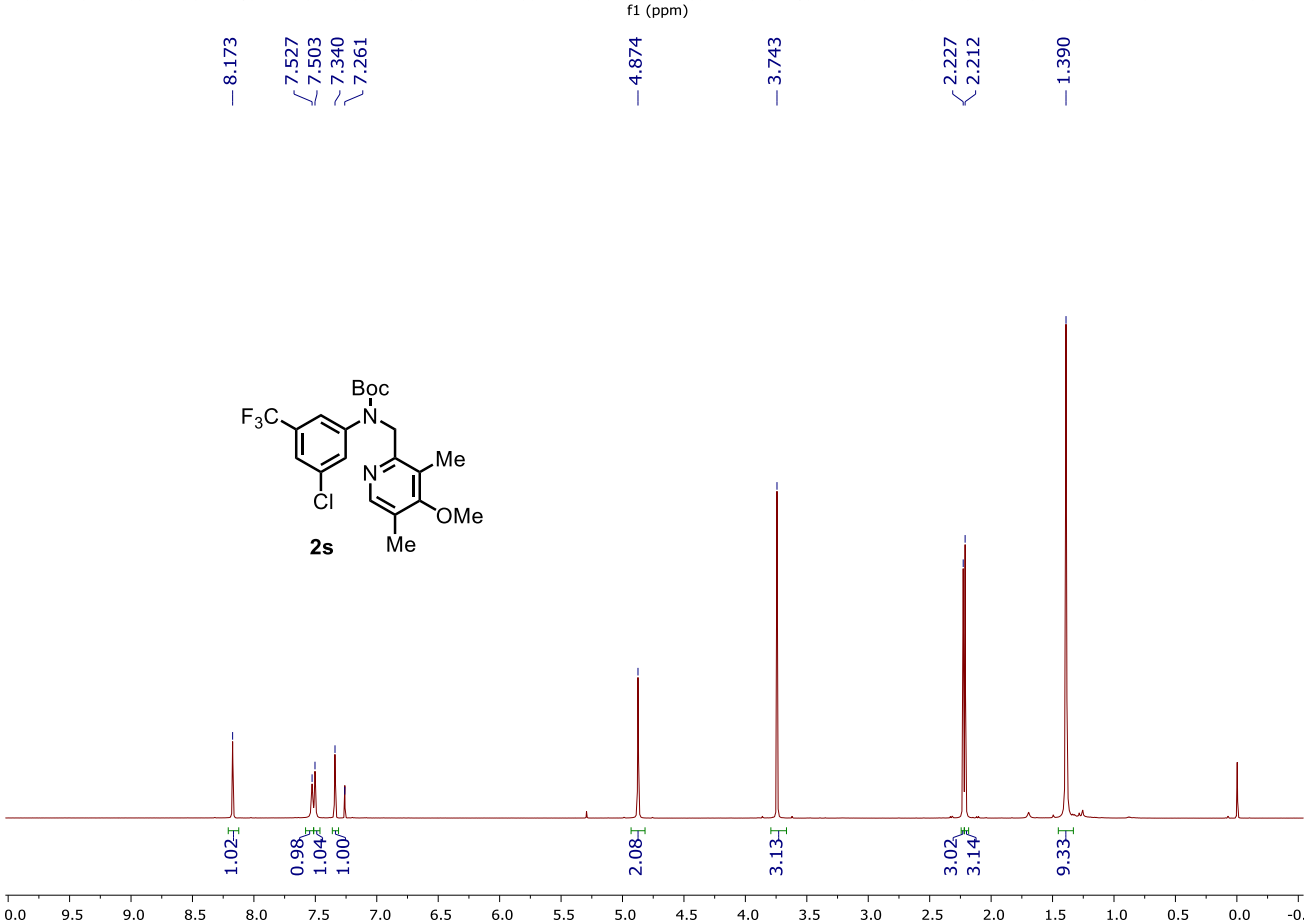
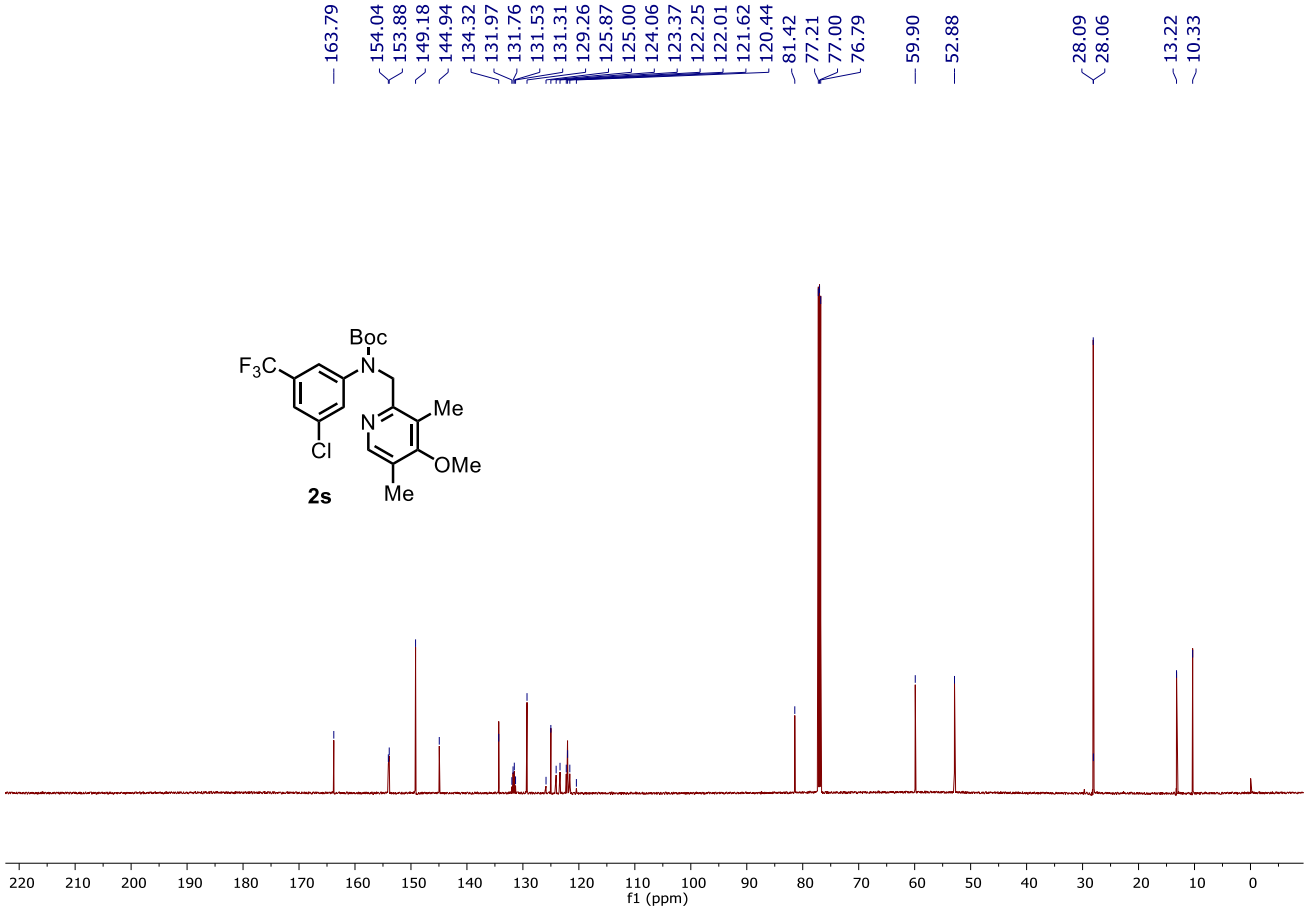
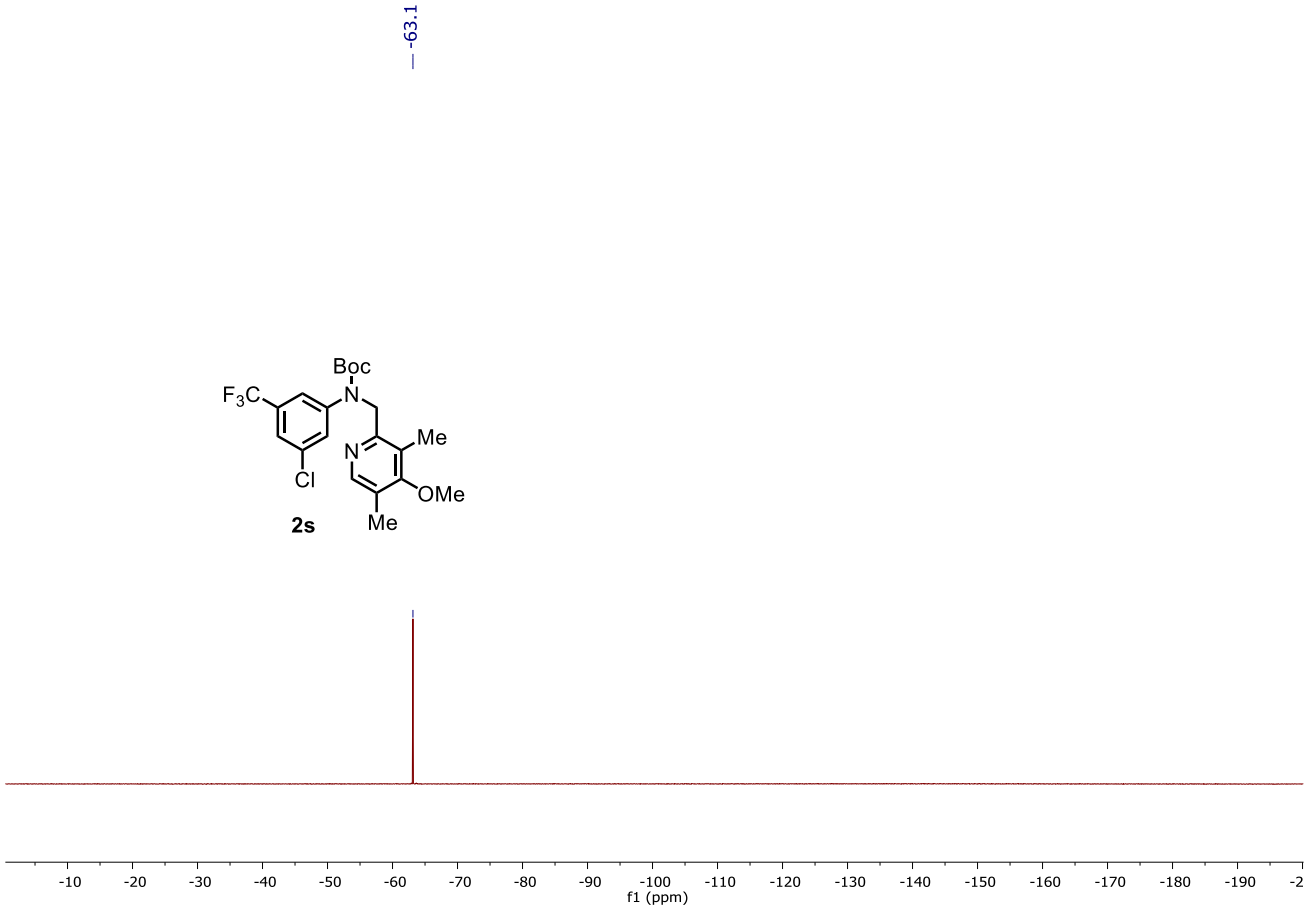
153.95
149.15
145.09
134.13
125.32
124.89
124.73
123.29
81.18
77.21
77.00
76.79
59.90
53.01
28.11
13.22
10.32
Boc
N
Cl
Cl
N
Me
OMe
Me
2q
f1 (ppm)

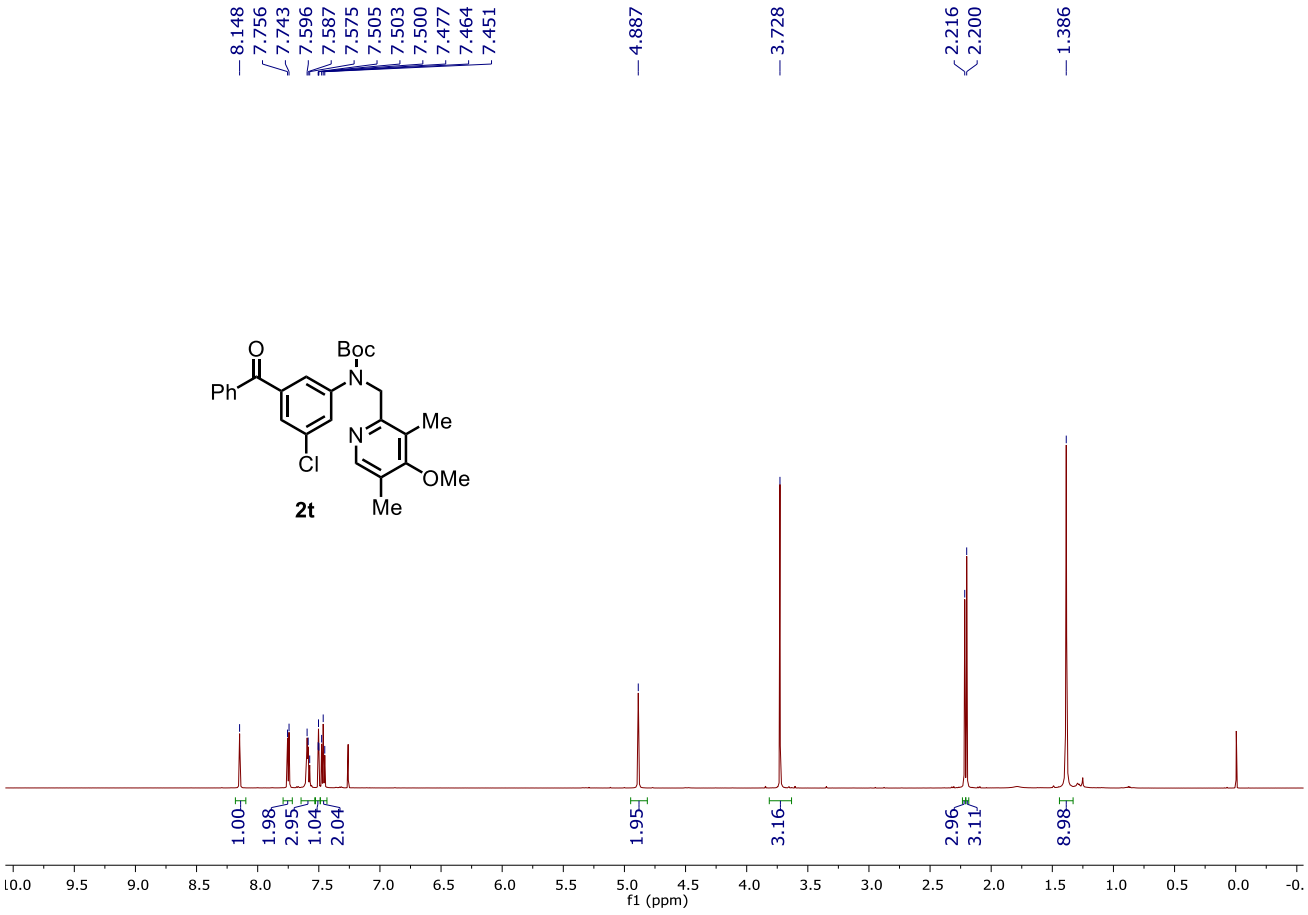

8.181
7.389
7.282
7.260
7.253
4.829
3.745
2.228
2.197
1.383
Boc
N
Br
Cl
N
Me
OMe
Me
2r
1.06
1.00
0.98
1.05
2.13
3.24
3.14
3.17
9.32
f1 (ppm)


163.74
154.15
153.94
149.15
145.20
134.31
128.07
127.59
125.22
124.91
123.33
121.64
81.21
77.21
77.00
76.79
59.91
53.00
28.12
13.23
10.32
Boc
Br
N
Me
N
Cl
OMe
Me
2r
f1 (ppm)


8.173
7.527
7.503
7.340
7.261
4.874
3.743
2.227
2.212
1.390
Boc
F3C
N
Me
N
Cl
OMe
Me
2s
1.02
0.98
1.04
1.00
2.08
3.13
3.02
3.14
9.33
f1 (ppm)


163.79
154.04
153.88
149.18
144.94
134.32
131.97
131.76
131.53
131.31
129.26
125.87
125.00
124.06
123.37
122.25
122.01
121.62
120.44
81.42
77.21
77.00
76.79
59.90
52.88
28.09
28.06
13.22
10.33
Boc
F3C
N
Me
N
OMe
Cl
Me
2s
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-63.1
Boc
F3C
N
Me
N
OMe
Cl
Me
2s
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -2
f1 (ppm)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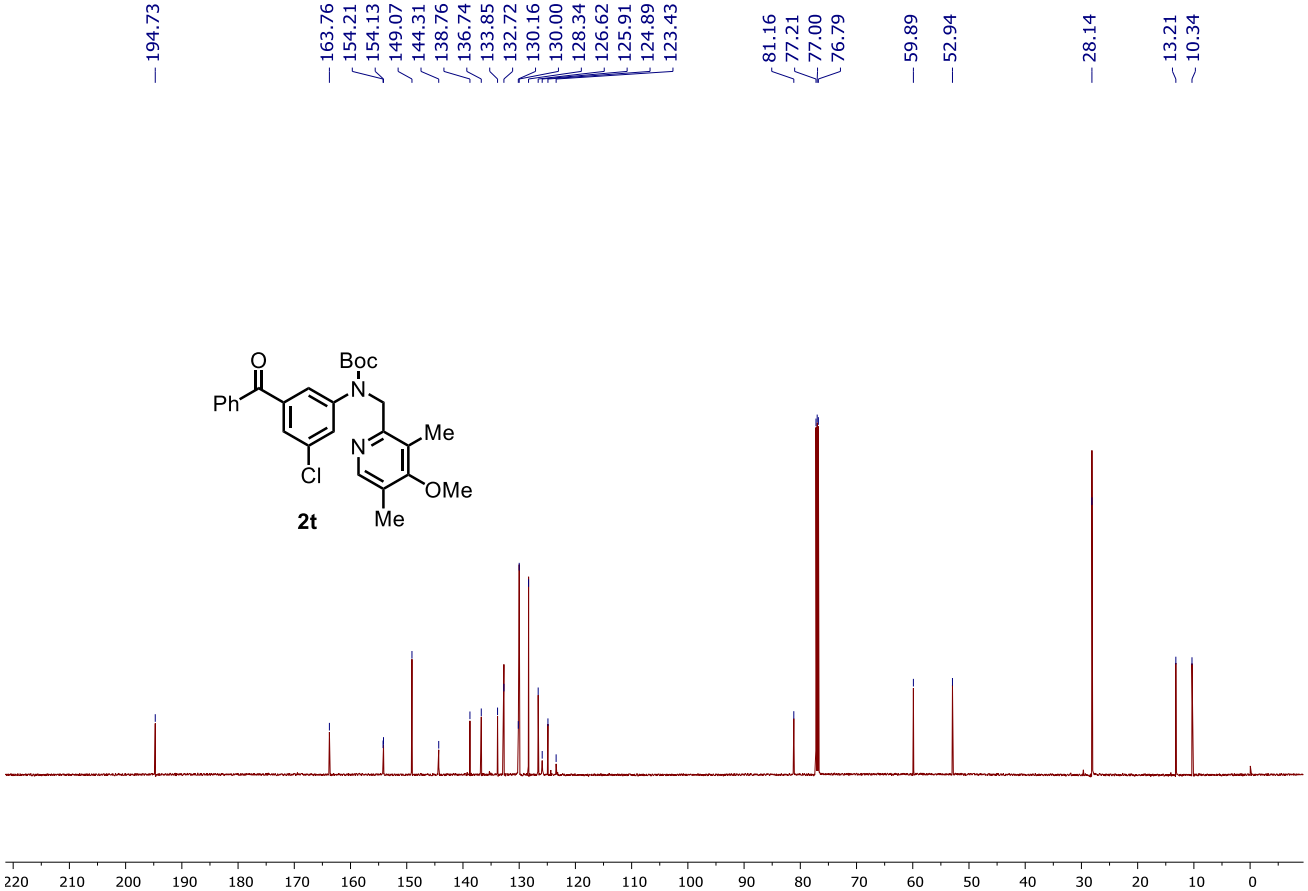
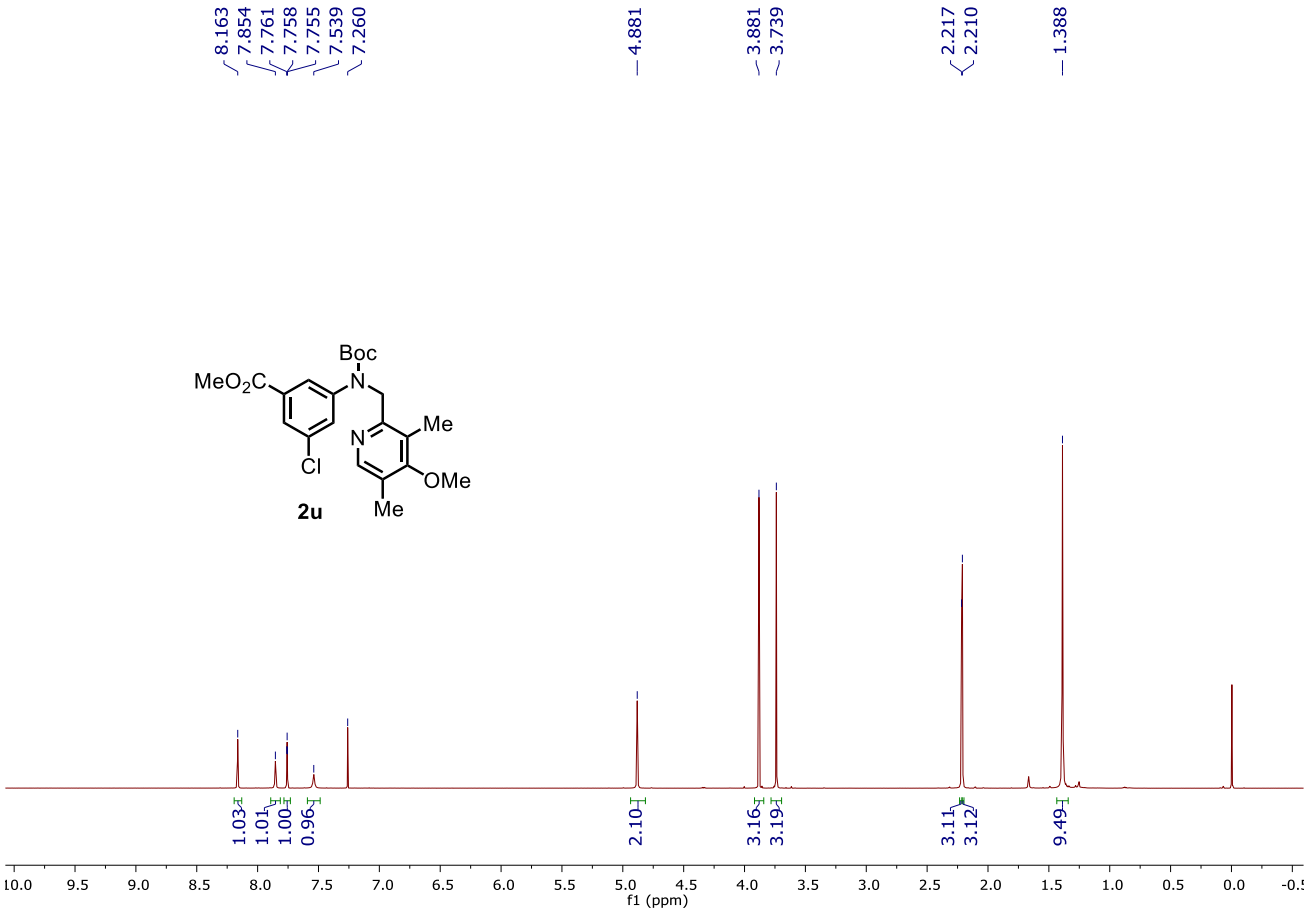
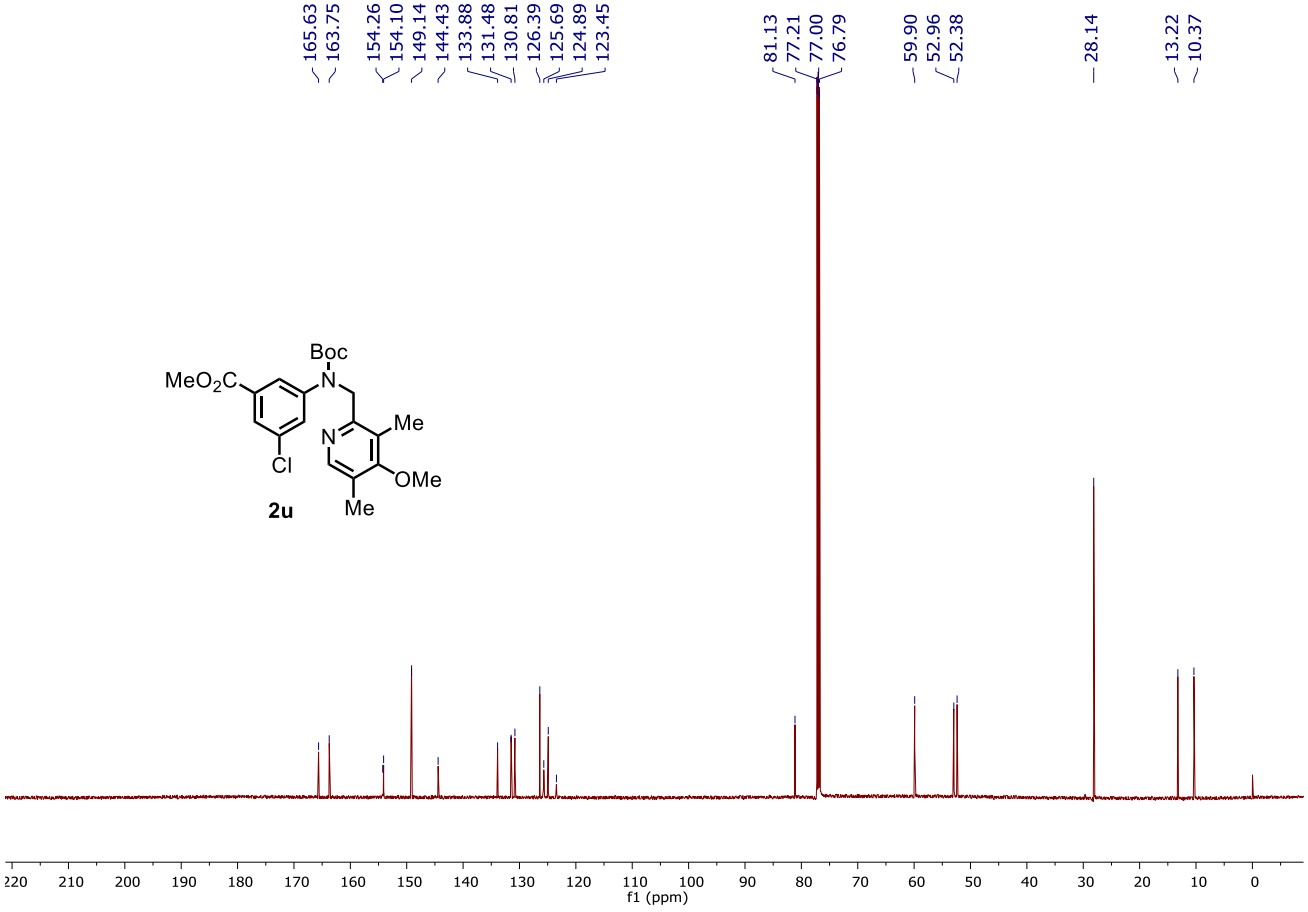
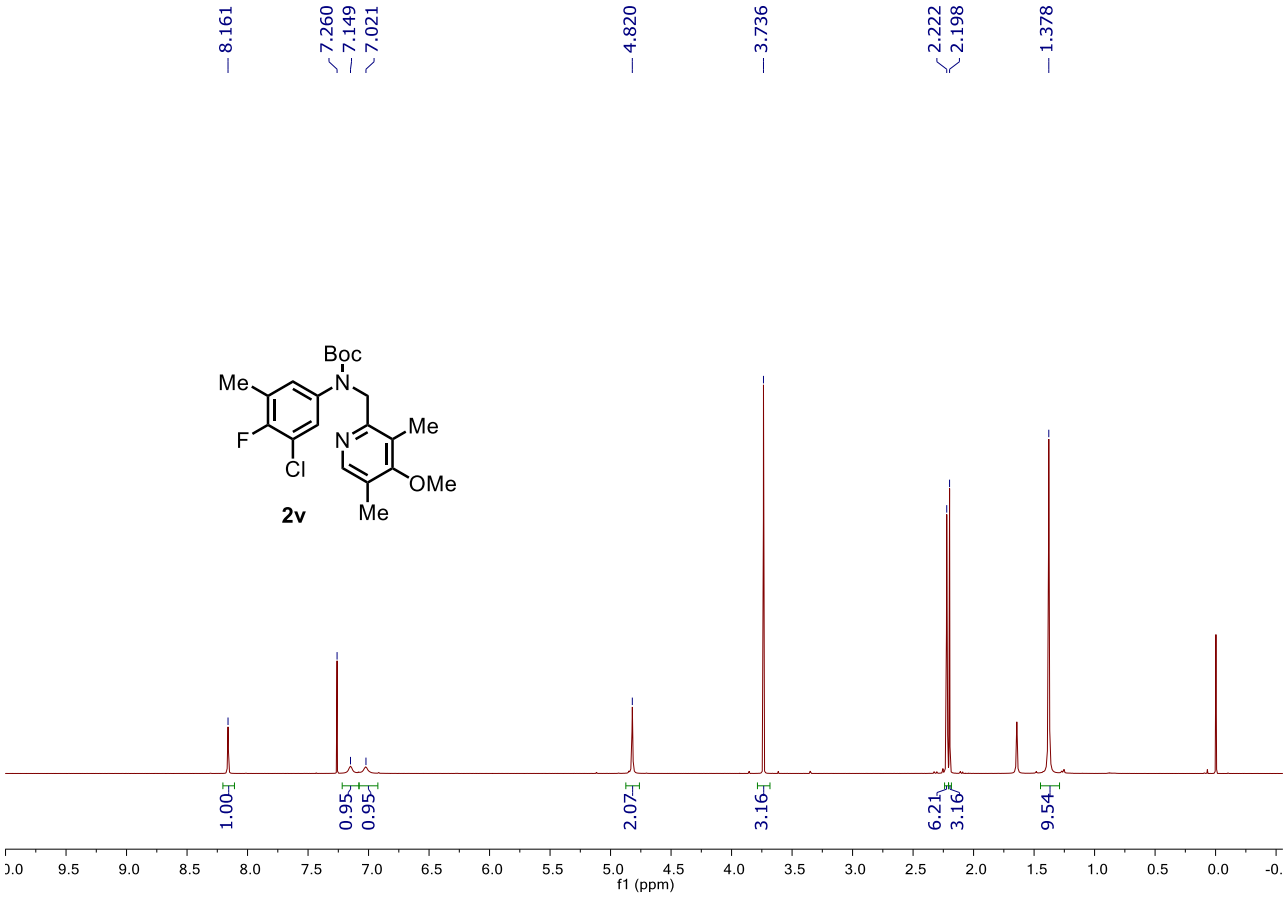
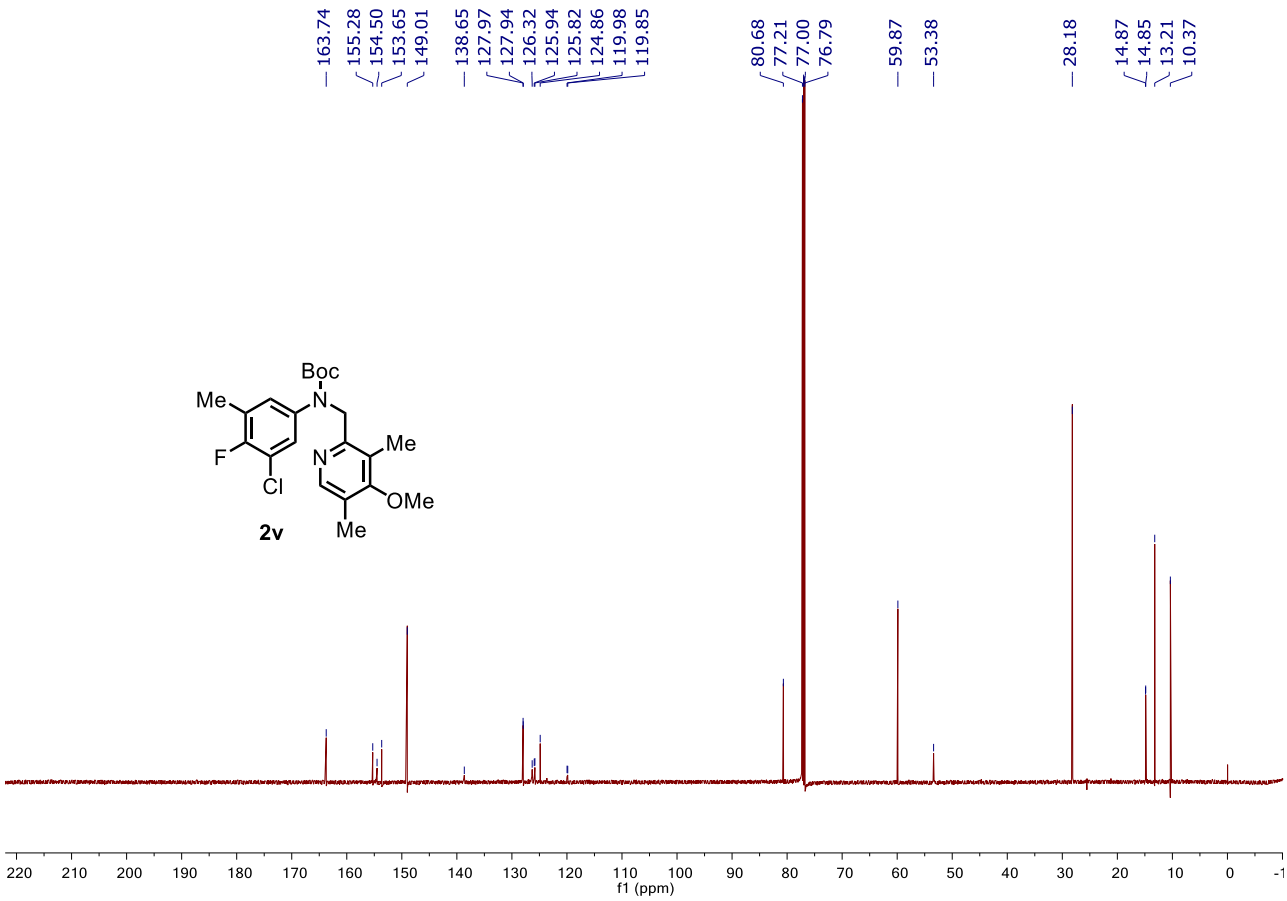
7.756
7.743
7.596
7.587
7.575
7.505
7.503
7.500
7.477
7.464
7.451
4.887
3.728
2.216
2.200
1.386
Boc
Ph
O
N
Me
N
Cl
OMe
Me
2t
1.00
1.98
2.95
1.04
2.04
1.95
3.16
2.96
3.11
8.98
f1 (ppm)

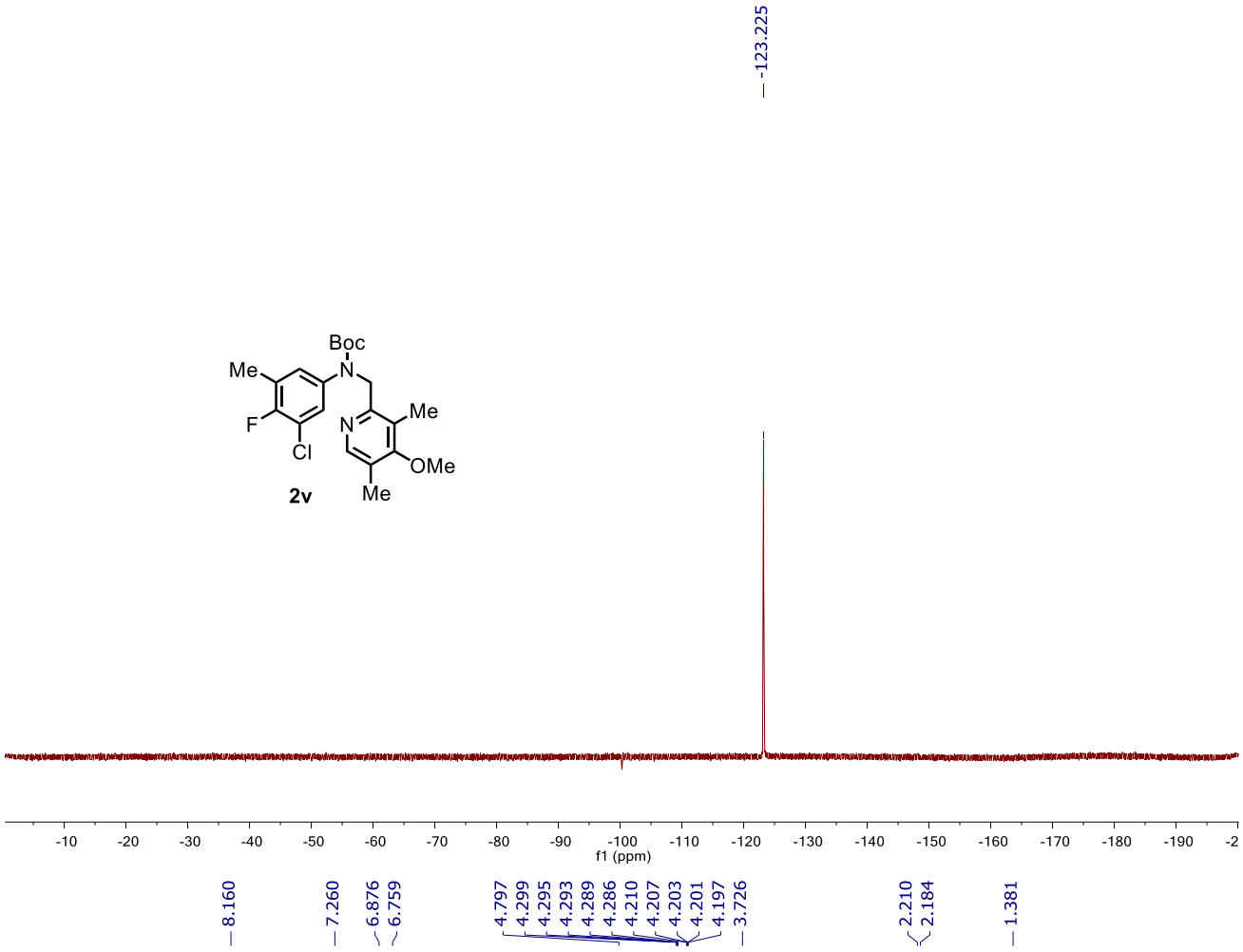

194.73
163.76
154.21
154.13
149.07
144.31
138.76
136.74
133.85
132.72
130.16
130.00
128.34
126.62
125.91
124.89
123.43
81.16
77.21
77.00
76.79
59.89
52.94
28.14
13.21
10.34
Boc
Ph
O
N
Me
N
Cl
OMe
Me
2t
f1 (ppm)

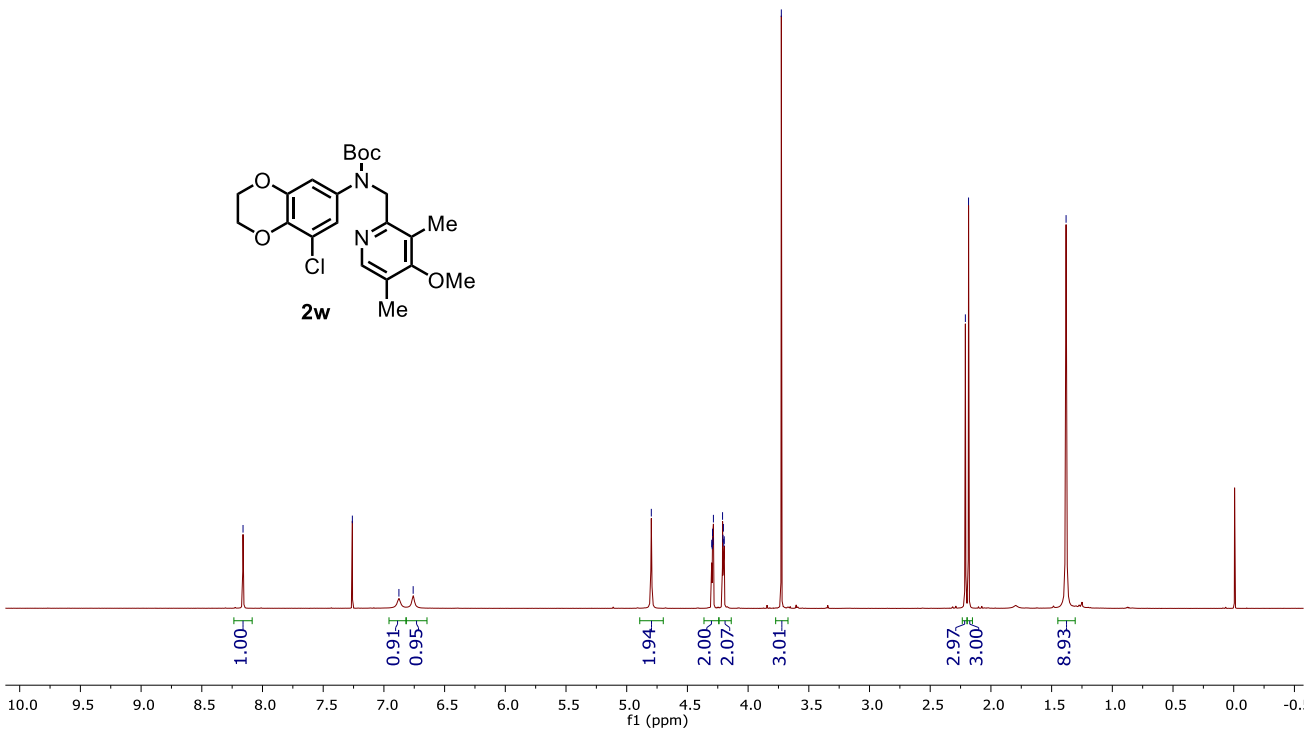

8.163
7.854
7.761
7.758
7.755
7.539
7.260
4.881
3.881
3.739
2.217
2.210
1.388
Boc
MeO2C
N
Me
N
Cl
OMe
Me
2u
1.03
1.01
1.00
0.96
2.10
3.16
3.19
3.11
3.12
9.49
f1 (ppm)

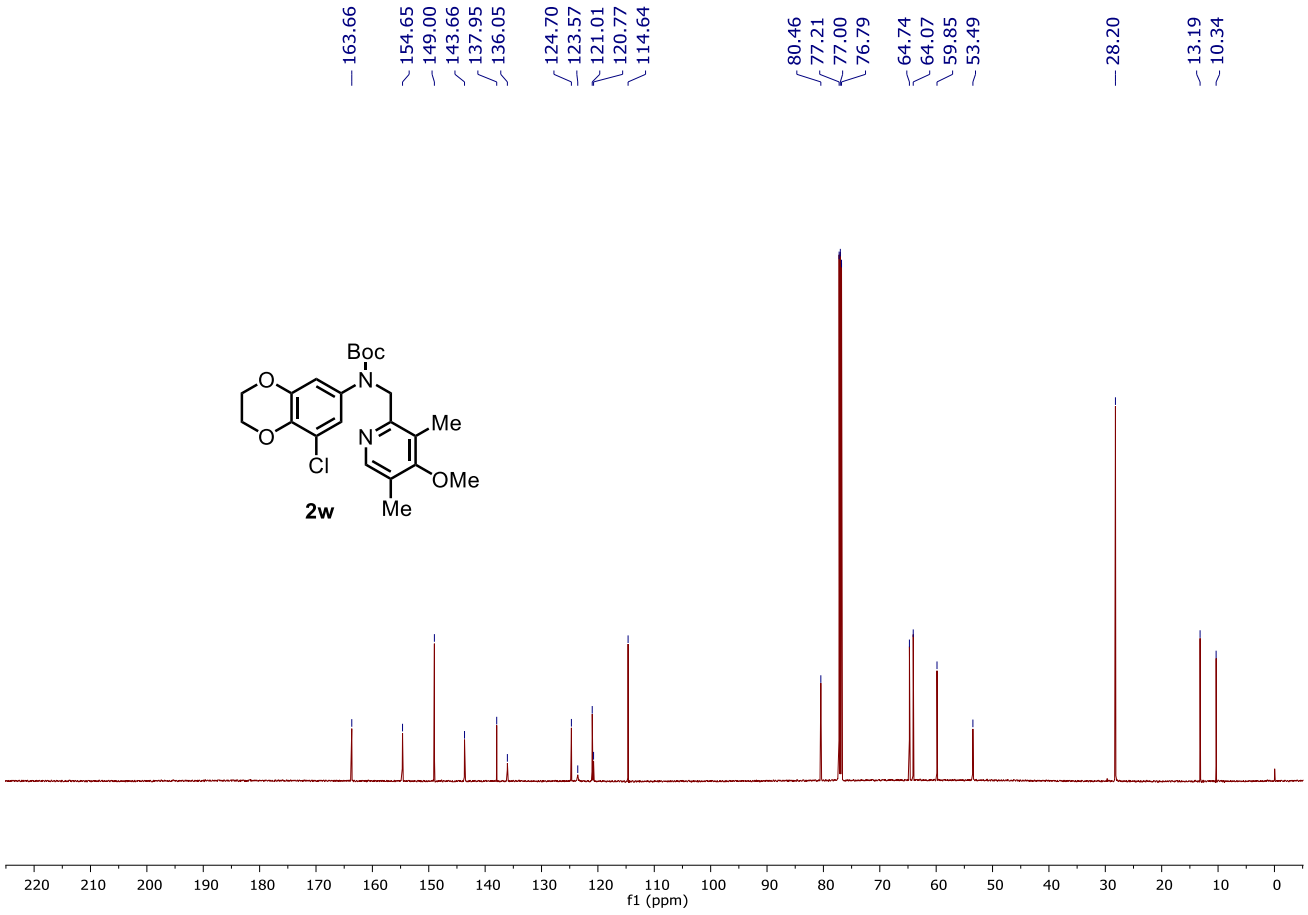

165.63
163.75
154.26
154.10
149.14
144.43
133.88
131.48
130.81
126.39
125.69
124.89
123.45
81.13
77.21
77.00
76.79
59.90
52.96
52.38
28.14
13.22
10.37
Boc
MeO2C
N
Me
N
Cl
OMe
Me
2u
f1 (ppm)


8.161
7.260
7.149
7.021
4.820
3.736
2.222
2.198
1.378
Boc
N
Me
F
Cl
N
Me
OMe
Me
2v
1.00
0.95
0.95
2.07
3.16
6.21
3.16
9.54
f1 (ppm)


163.74
155.28
154.50
153.65
149.01
138.65
127.97
127.94
126.32
125.94
125.82
124.86
119.98
119.85
80.68
77.21
77.00
76.79
59.87
53.38
28.18
14.87
14.85
13.21
10.37
Boc
N
Me
F
Cl
N
Me
OMe
Me
2v
f1 (ppm)


-123.225
Boc
Me
N
F
Cl
N
Me
OMe
Me
2v
f1 (ppm)
8.160
7.260
6.876
6.759
4.797
4.299
4.295
4.293
4.289
4.286
4.210
4.207
4.203
4.201
4.197
3.726
2.210
2.184
1.381


Boc
O
O
N
Cl
N
Me
OMe
Me
2w
f1 (ppm)
1.00
0.91
0.95
1.94
2.00
2.07
3.01
2.97
3.00
8.93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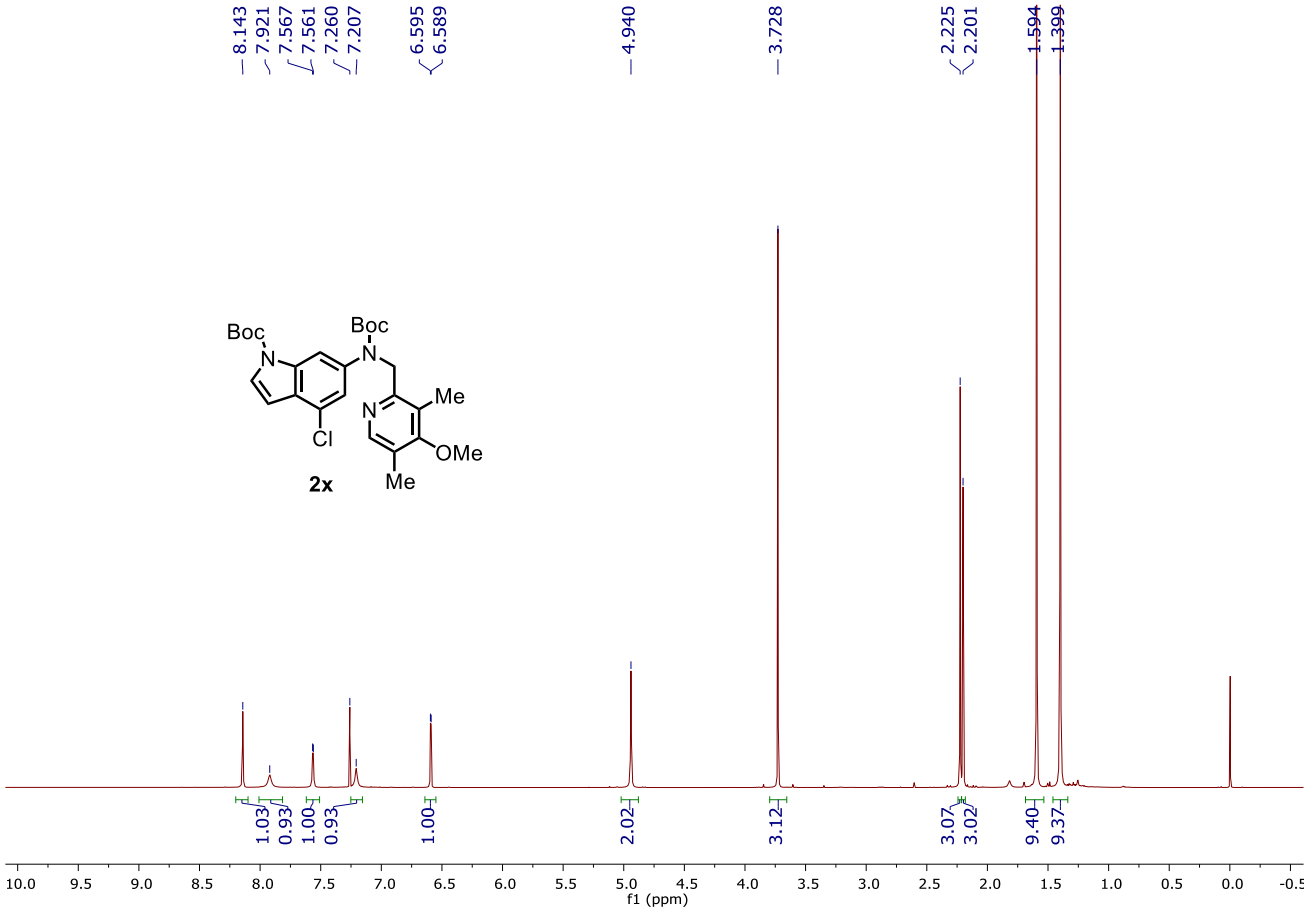
143.66
137.95
136.05
124.70
123.57
121.01
120.77
114.64
80.46
77.21
77.00
76.79
64.74
64.07
59.85
53.49
28.20
13.19
10.34
Boc
N
O
O
Cl
N
Me
OMe
Me
2w
f1 (ppm)


8.143
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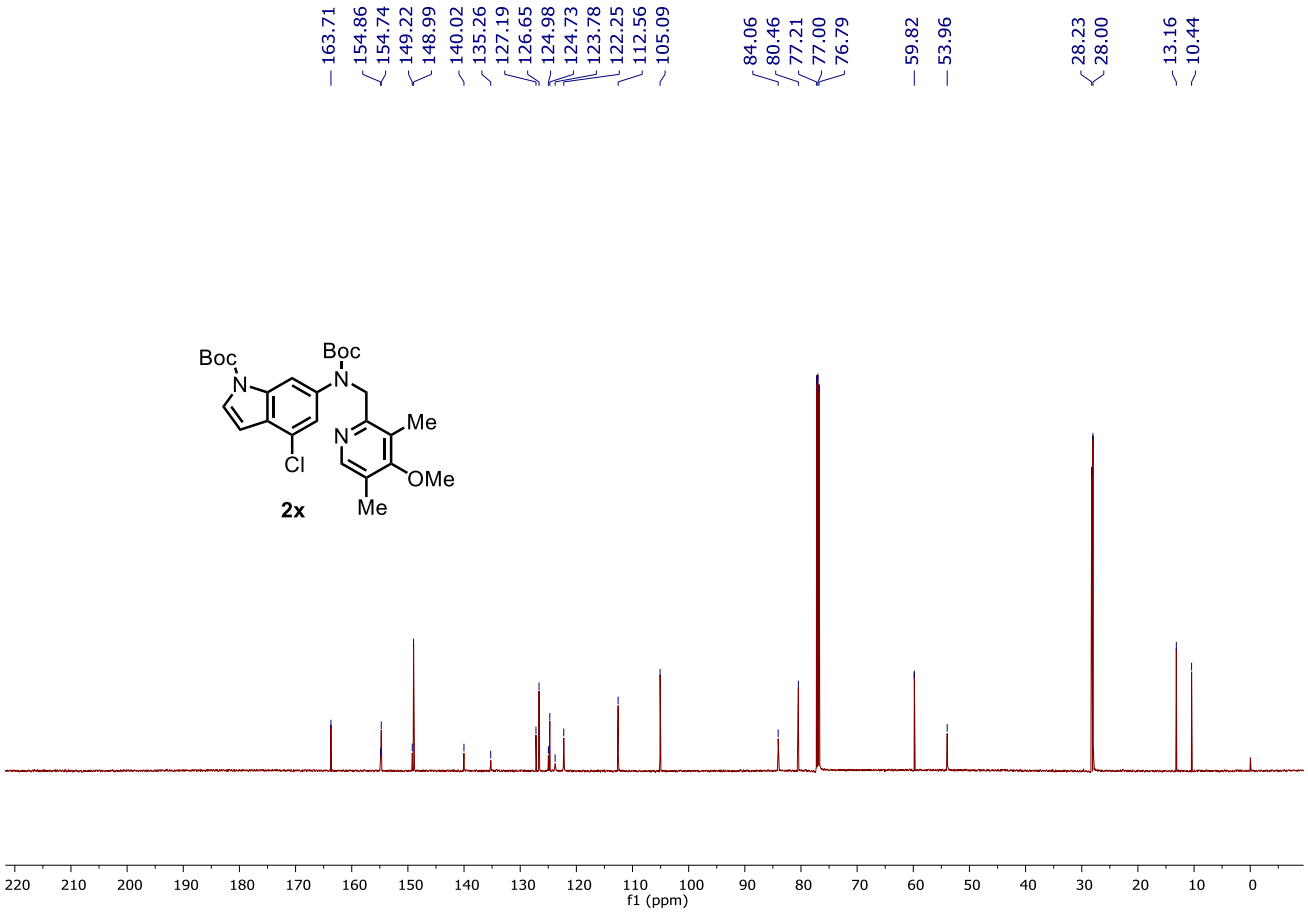
7.567
7.561
7.260
7.207
6.595
6.589
4.940
3.728
2.225
2.201
1.594
1.399
Boc
Boc
N
N
Cl
N
Me
OMe
Me
2x
1.03
0.93
1.00
0.93
1.00
2.02
3.12
3.07
3.02
9.40
9.37
f1 (ppm)


163.71
154.86
154.74
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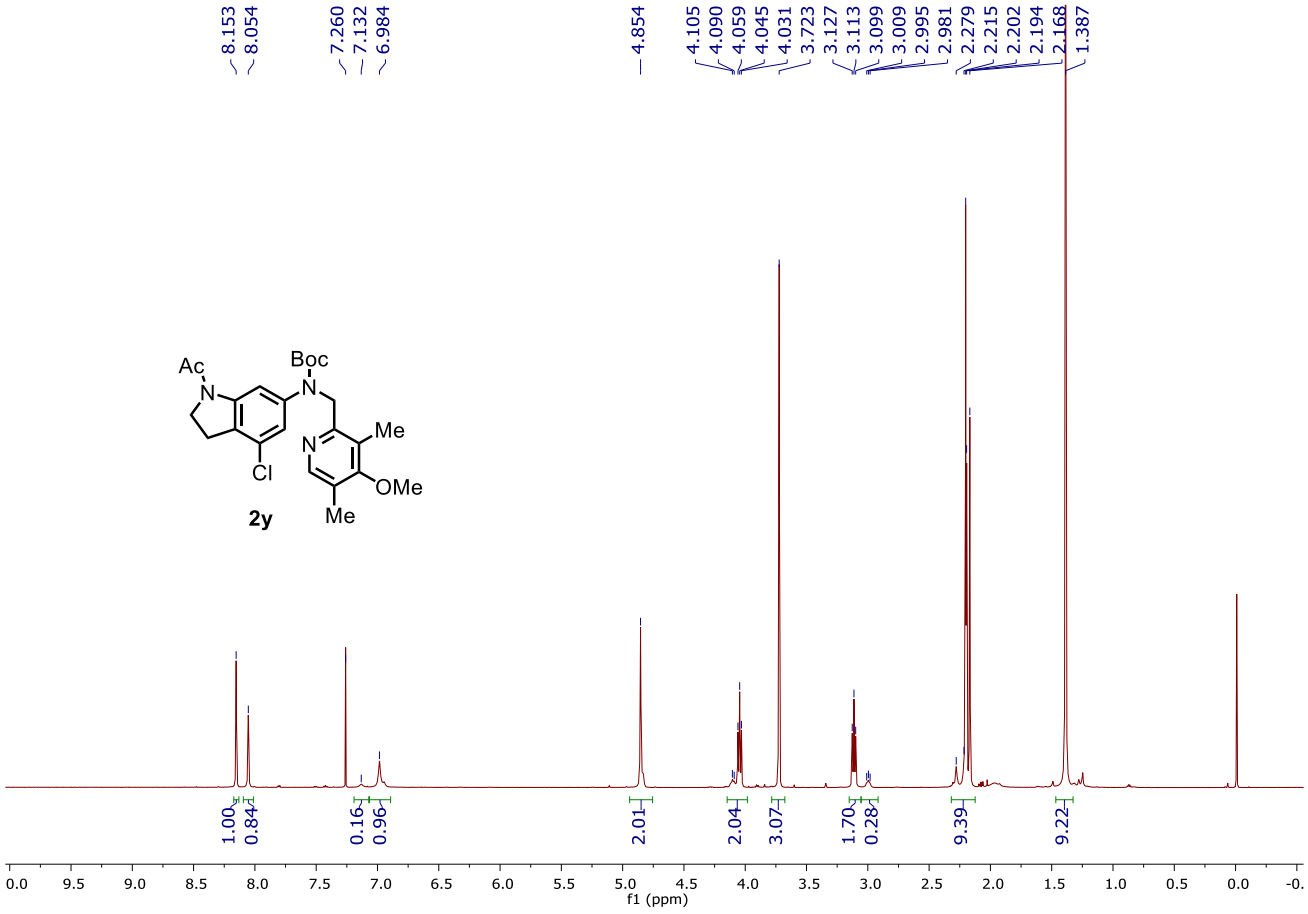
140.02
135.26
127.19
126.65
124.98
124.73
123.78
122.25
112.56
105.09
84.06
80.46
77.21
77.00
76.79
59.82
53.96
28.23
28.00
13.16
10.44
Boc
Boc
N
N
Me
N
Cl
OMe
Me
2x
f1 (ppm)


8.153
8.054
7.260
7.132
6.984
4.854
4.105
4.090
4.059
4.045
4.031
3.723
3.127
3.113
3.099
3.009
2.995
2.981
2.279
2.215
2.202
2.194
2.168
1.387
Ac
Boc
N
N
Me
N
Cl
OMe
Me
2y
1.00
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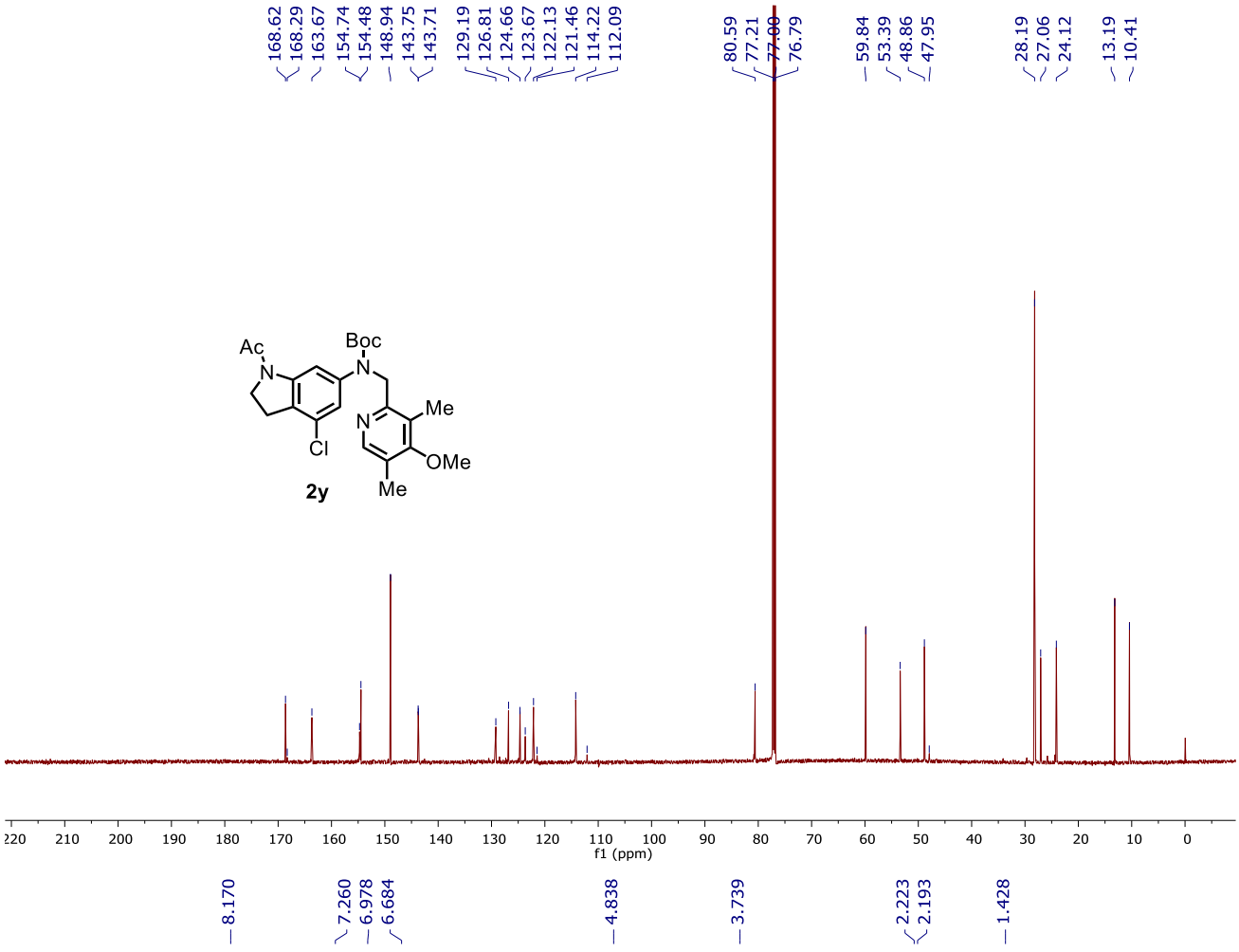
0.16
0.96
2.01
2.04
3.07
1.70
0.28
9.39
9.22
f1 (ppm)


168.62
168.29
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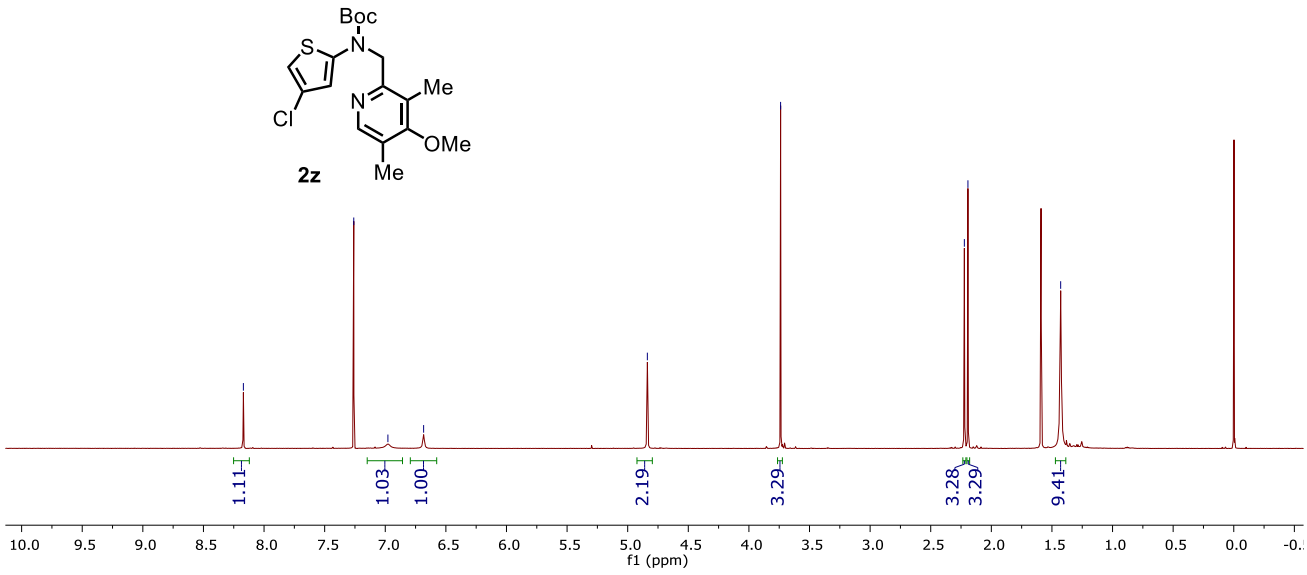
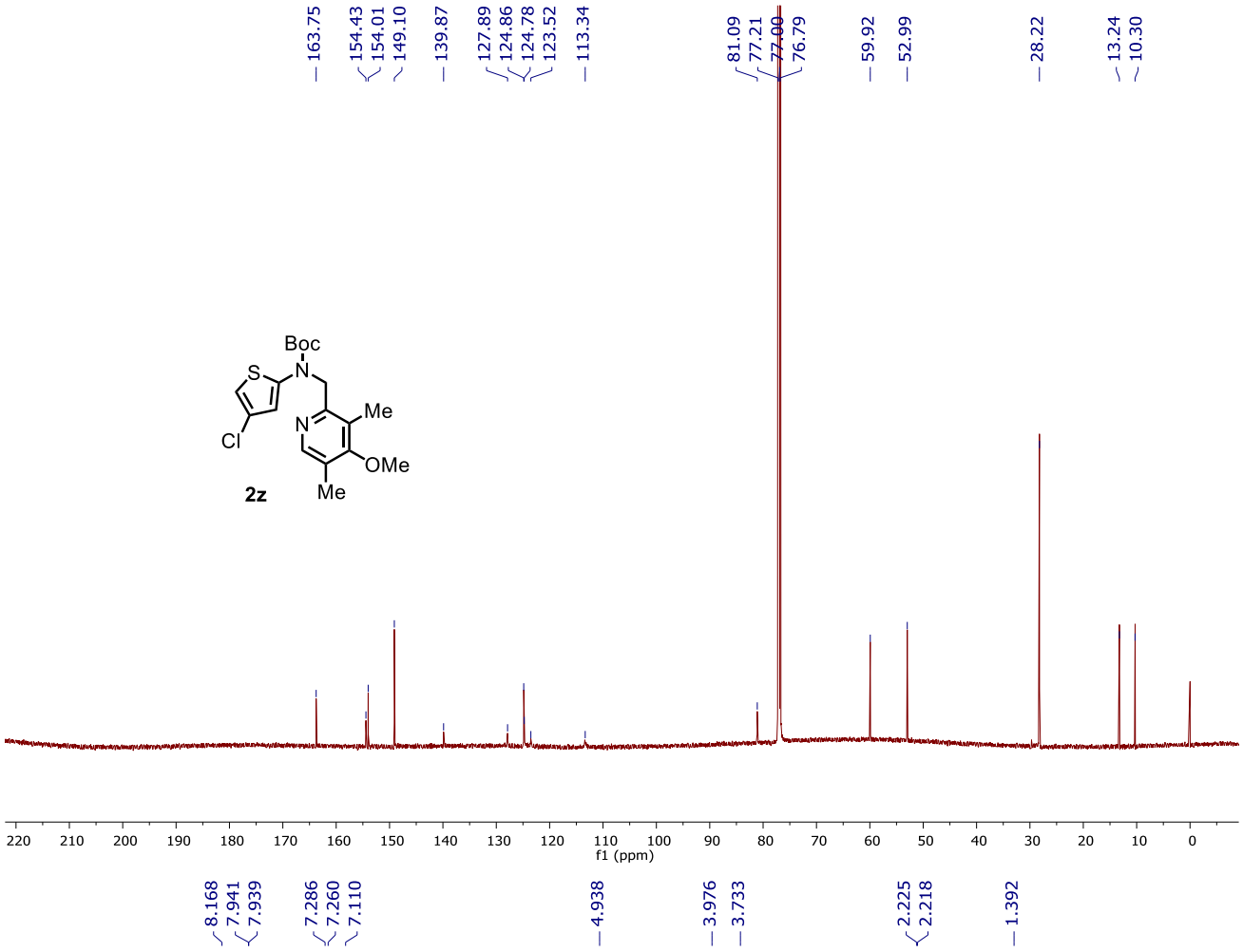
154.74
154.48
148.94
143.75
143.71
129.19
126.81
124.66
123.67
122.13
121.46
114.22
112.09
80.59
77.21
77.00
76.79
59.84
53.39
48.86
47.95
28.19
27.06
24.12
13.19
10.41
Ac
Boc
N
N
Me
N
Cl
OMe
Me
2y
f1 (ppm)
8.170
7.260
6.978
6.684
4.838
3.739
2.223
2.193
1.428


Boc
S
N
Me
N
Cl
OMe
Me
2z
1.11
1.03
1.00
2.19
3.29
3.28
3.29
9.41
f1 (ppm)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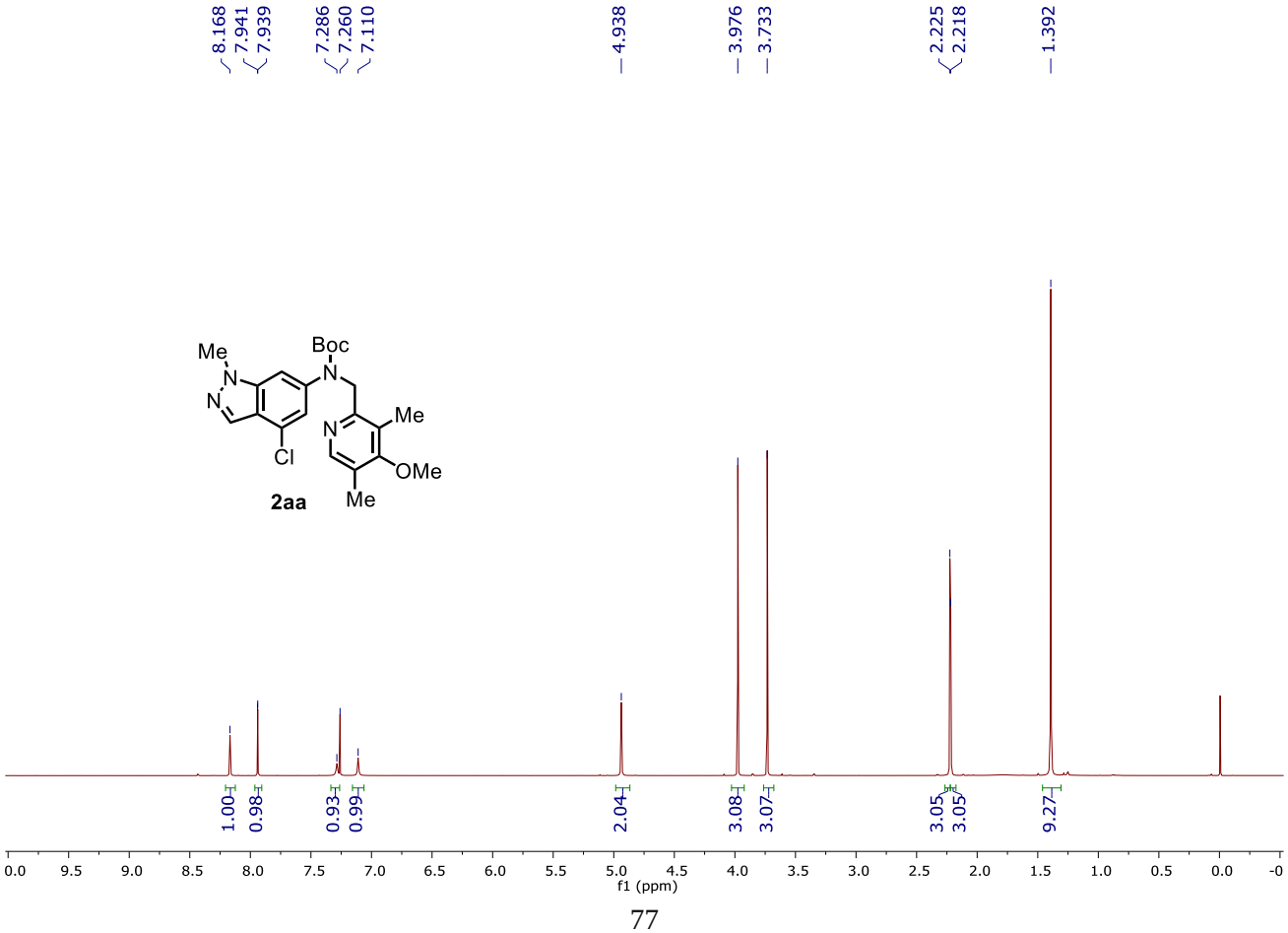
149.10
139.87
127.89
124.86
124.78
123.52
113.34
81.09
77.21
77.00
76.79
59.92
52.99
28.22
13.24
10.30
Boc
S
N
Cl
N
Me
OMe
Me
2z
f1 (ppm)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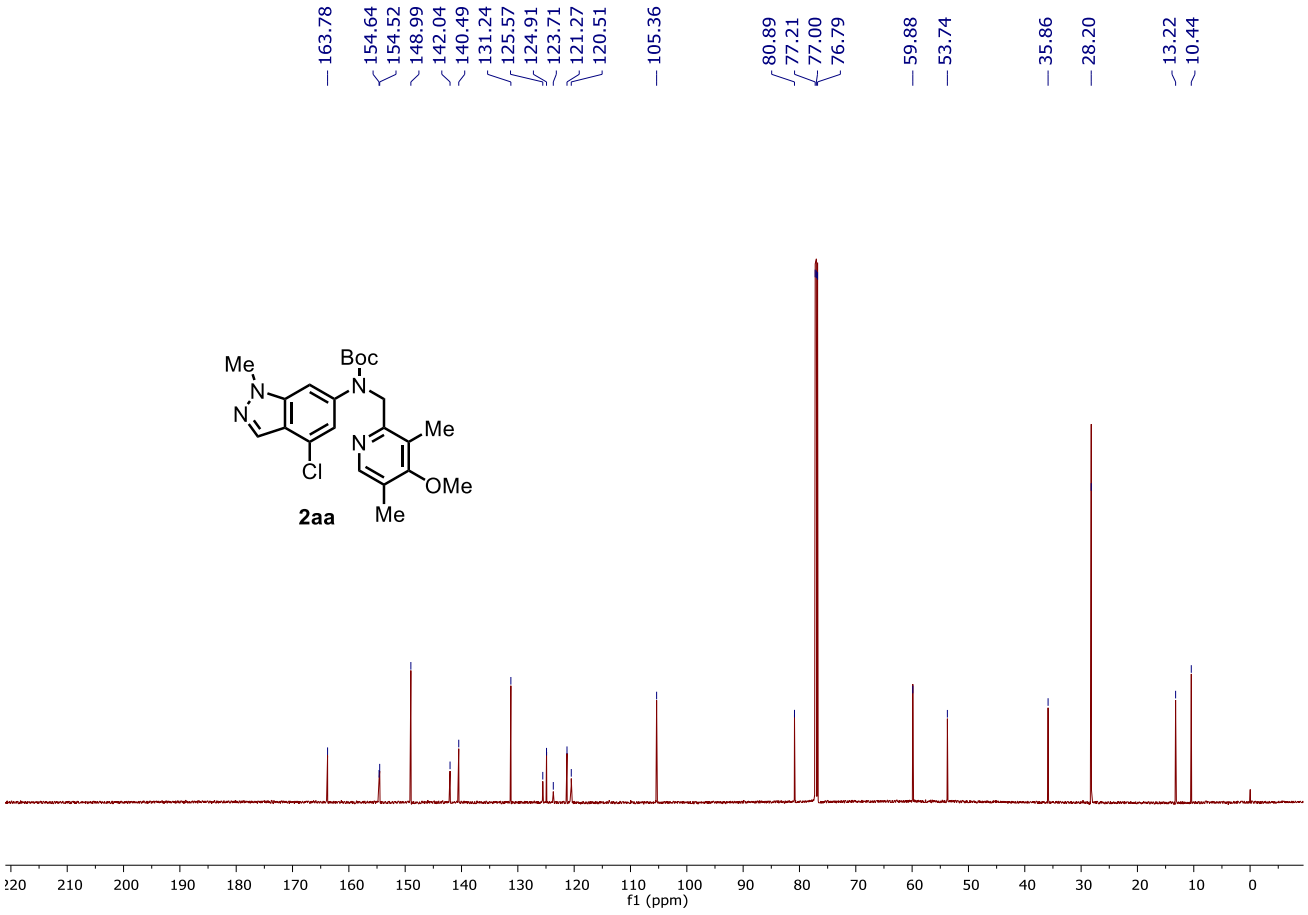
7.941
7.939
7.286
7.260
7.110
4.938
3.976
3.733
2.225
2.218
1.392
Me
N
N
Boc
N
Cl
N
Me
OMe
Me
2aa
1.00
0.98
0.93
0.99
2.04
3.08
3.07
3.05
3.05
9.27
f1 (ppm)


163.78
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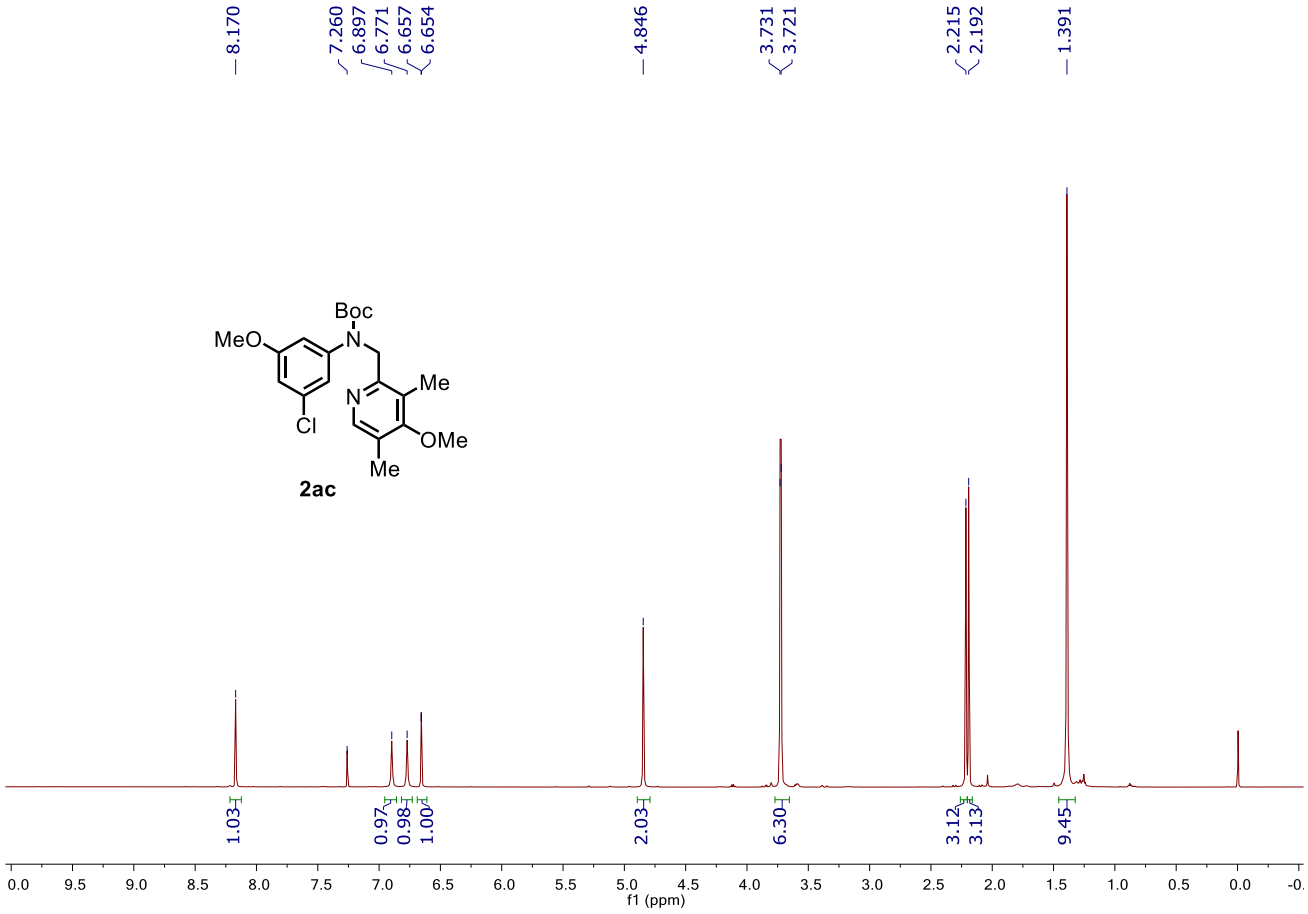
154.52
148.99
142.04
140.49
131.24
125.57
124.91
123.71
121.27
120.51
105.36
80.89
77.21
77.00
76.79
59.88
53.74
35.86
28.20
13.22
10.44
Me
Boc
N
N
Cl
N
Me
OMe
Me
2aa
f1 (ppm)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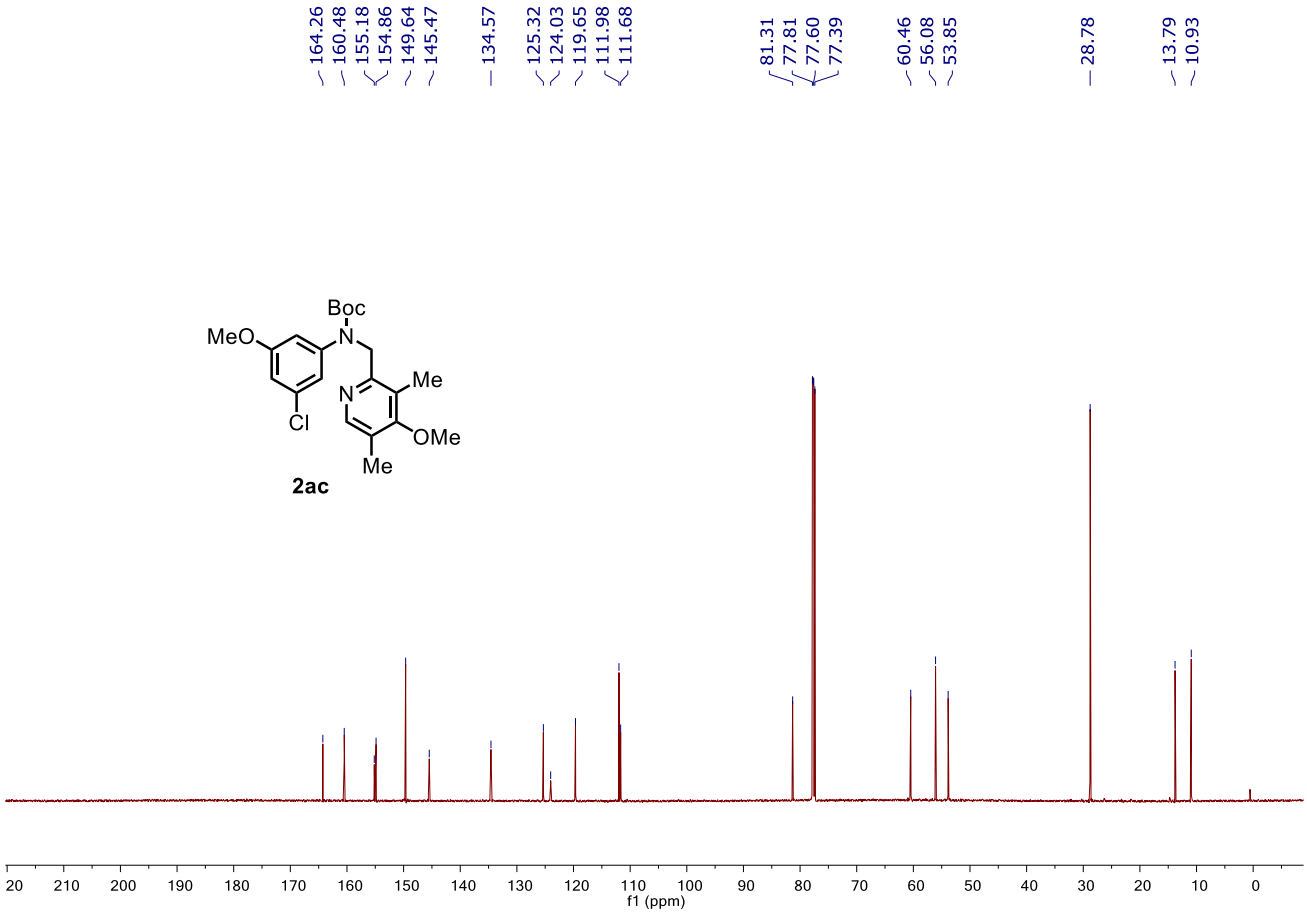
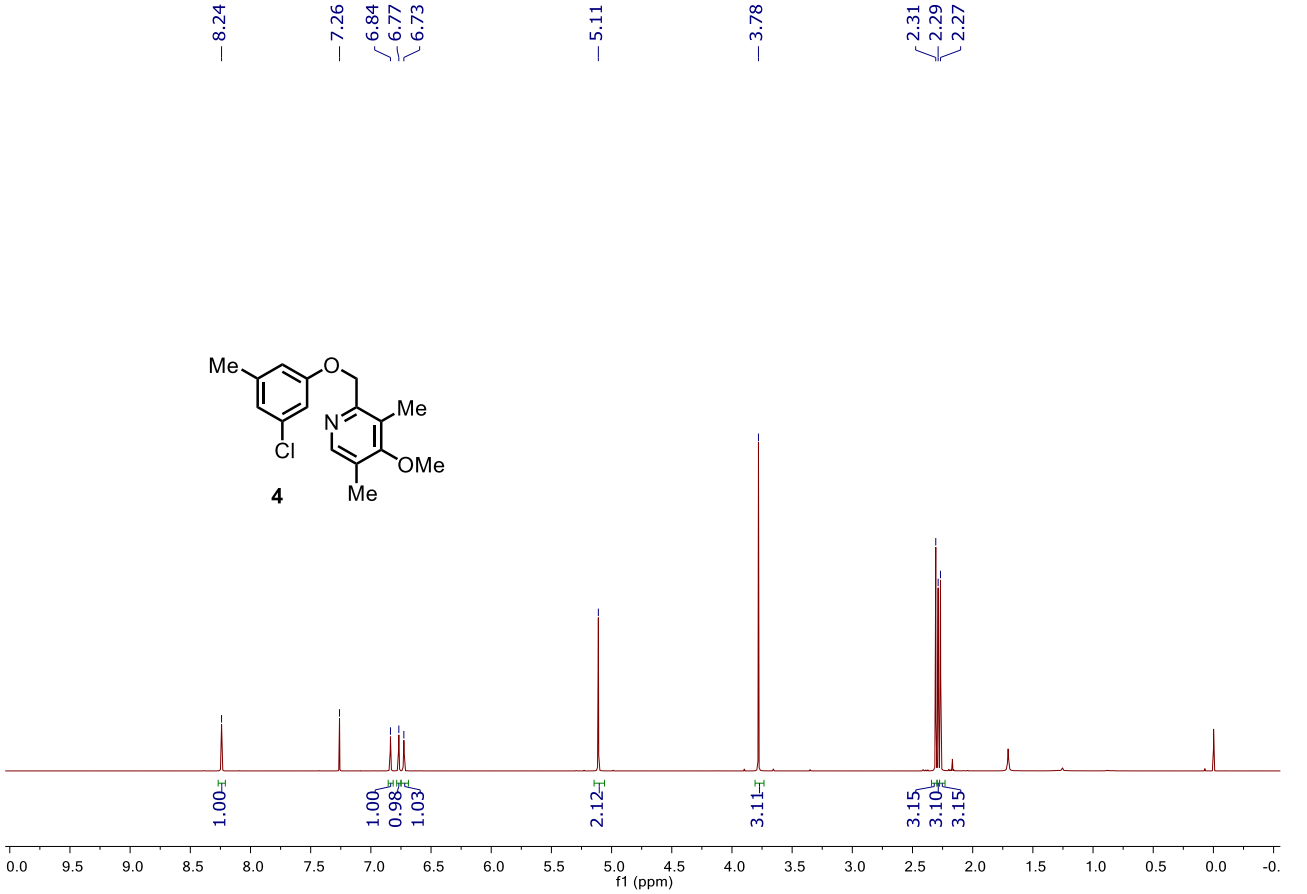
6.897
6.771
6.657
6.654
4.846
3.731
3.721
2.215
2.192
1.391
MeO
Boc
N
Cl
N
Me
OMe
Me
2ac
1.03
0.97
0.98
1.00
2.03
6.30
3.12
3.13
9.45
f1 (ppm)


164.26
160.48
155.18
154.86
149.64
145.47
134.57
125.32
124.03
119.65
111.98
111.68
81.31
77.81
77.60
77.39
60.46
56.08
53.85
28.78
13.79
10.93
Boc
MeO
N
Me
N
Cl
OMe
Me
2ac
f1 (ppm)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6.77
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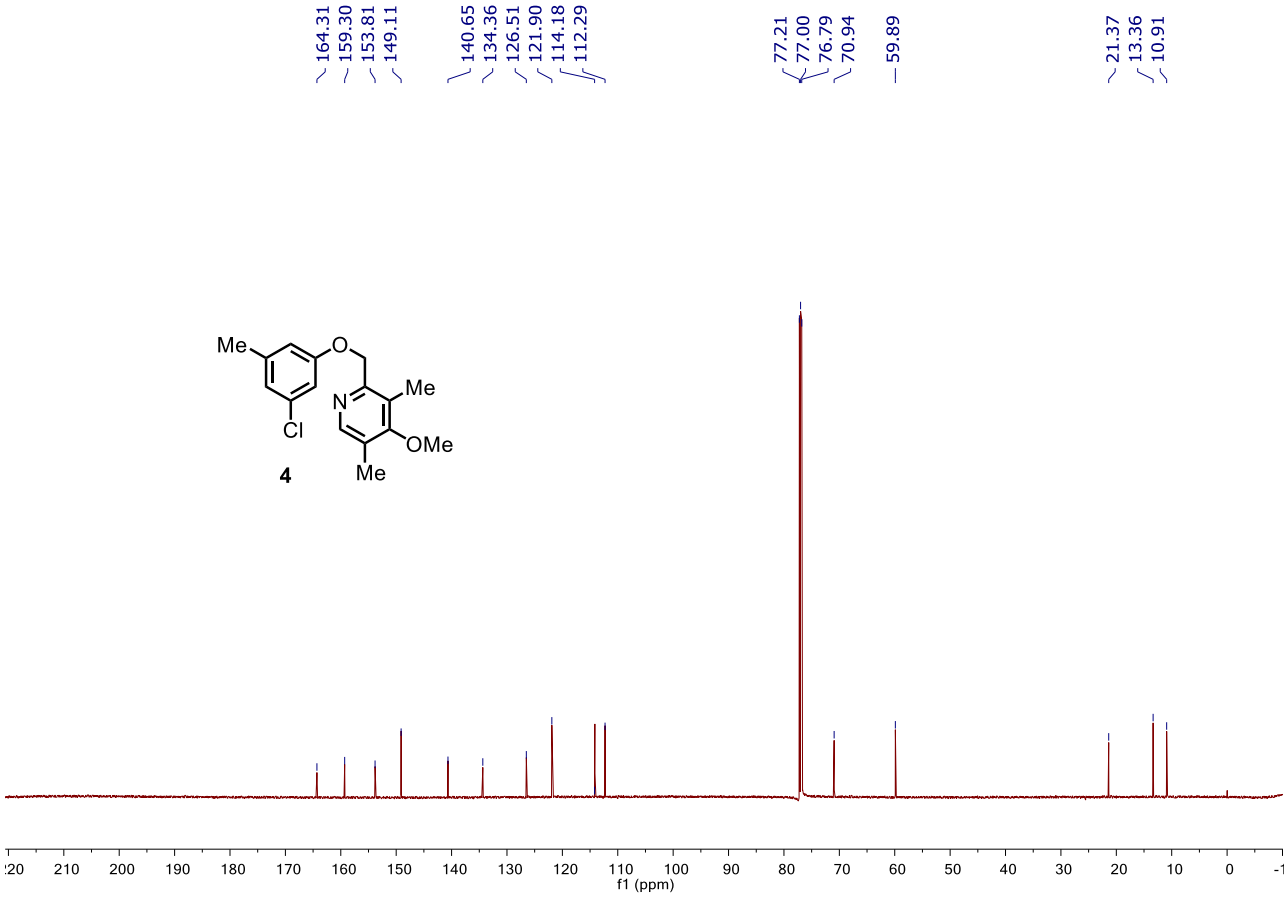
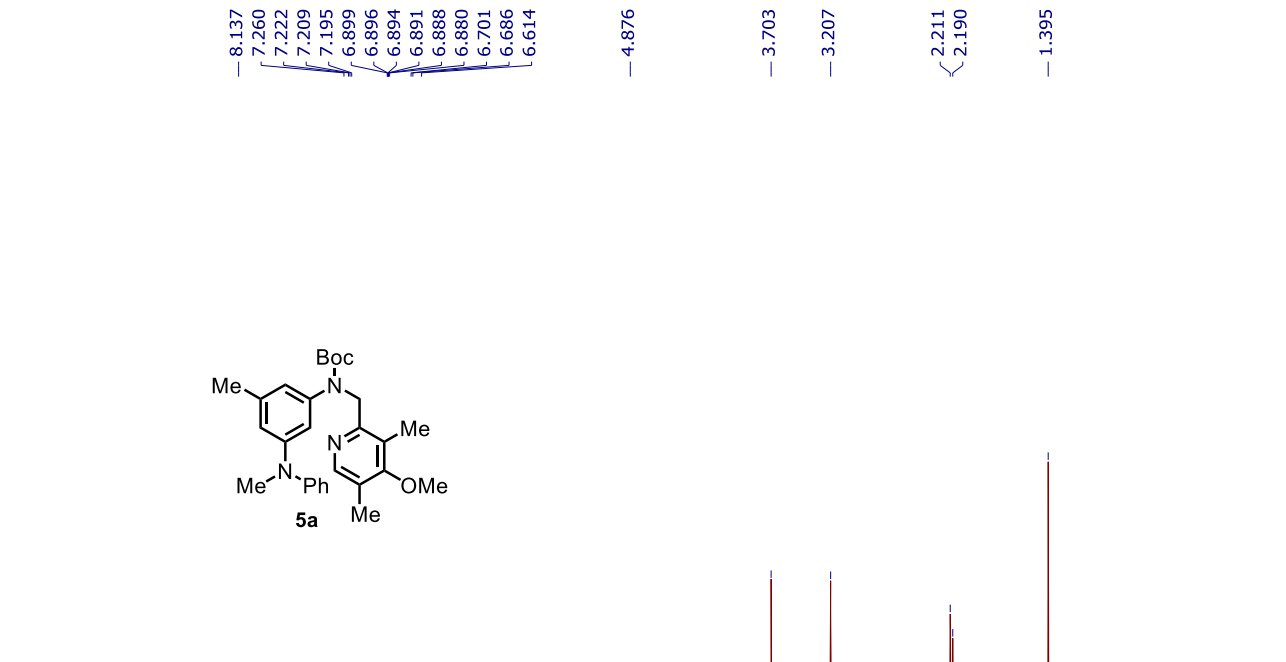
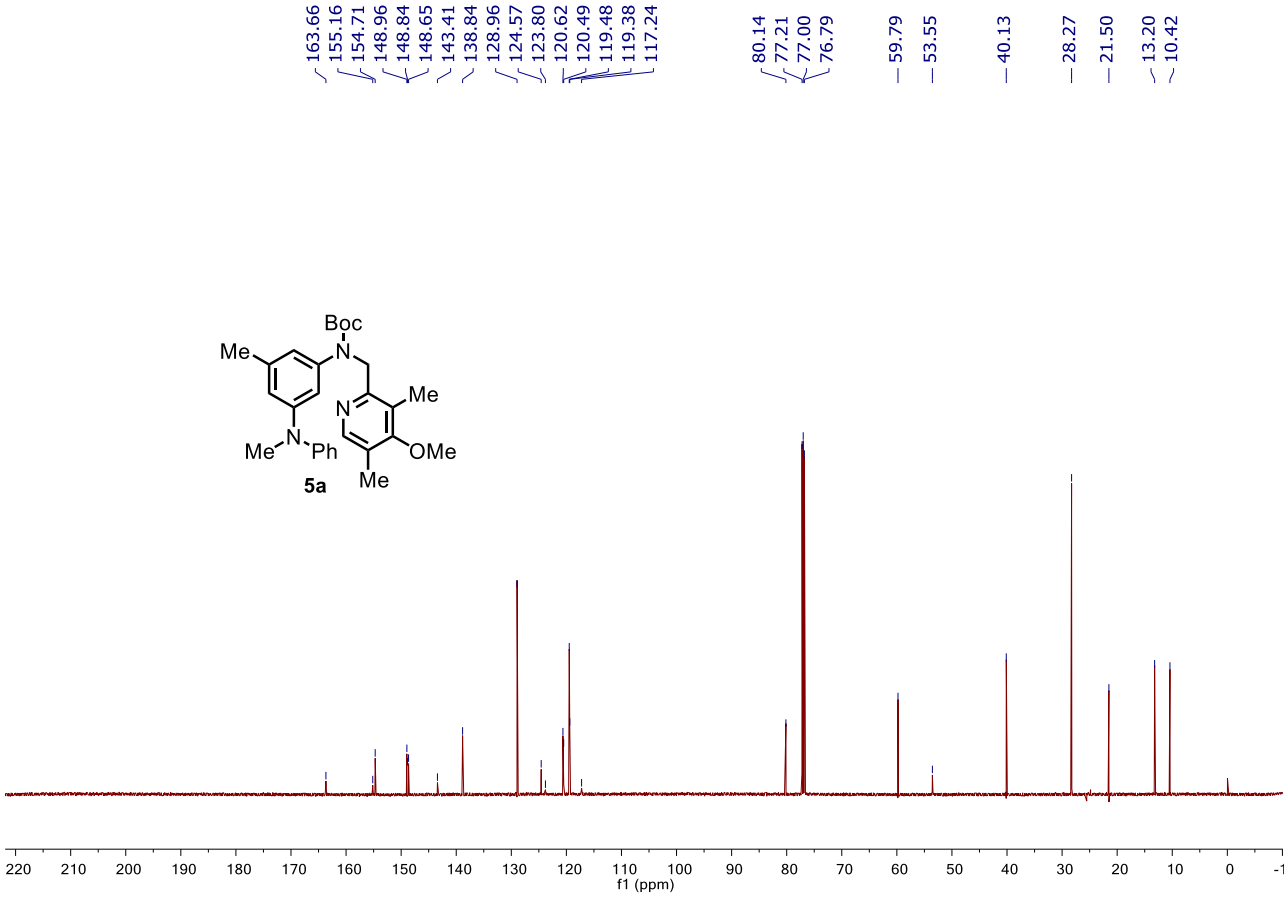
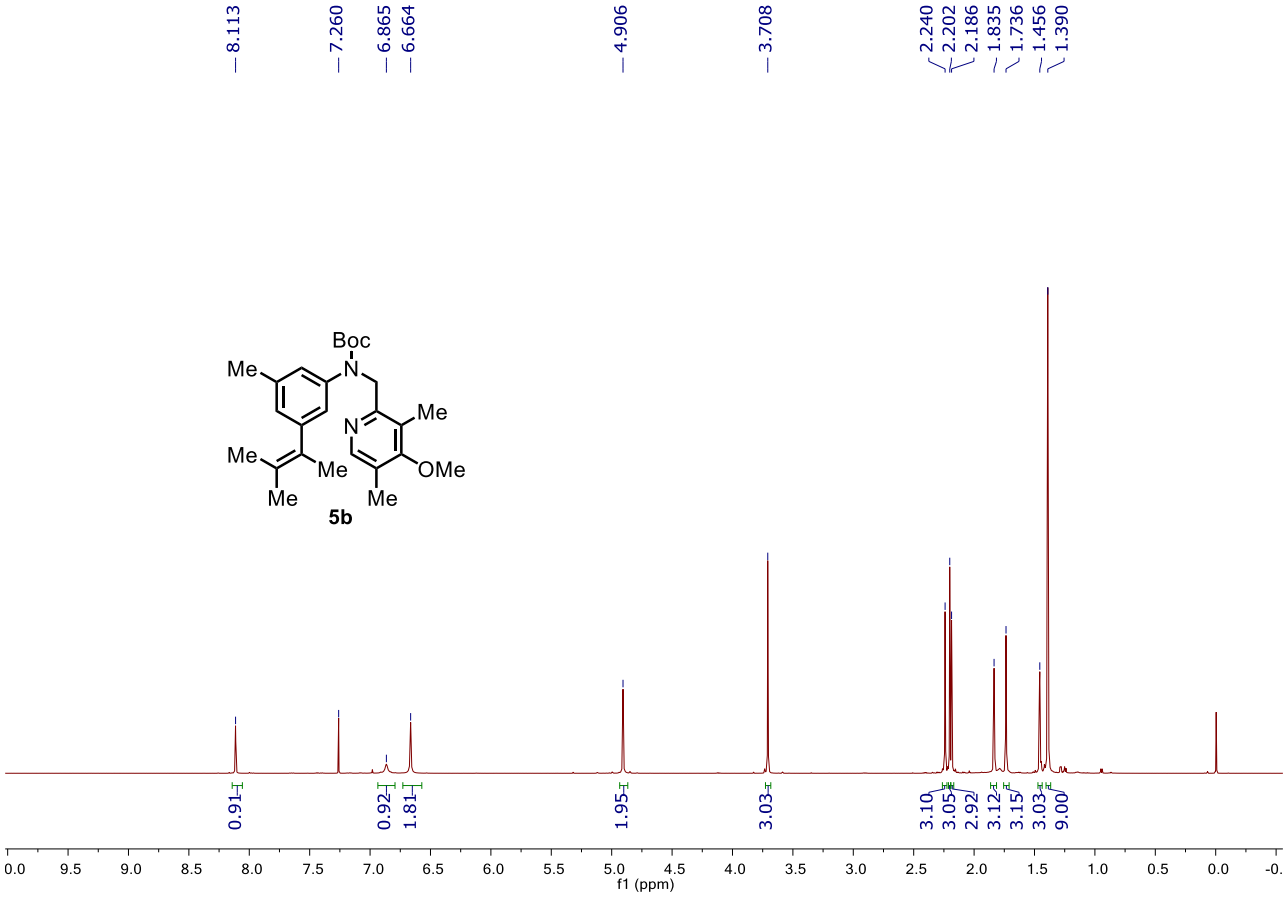
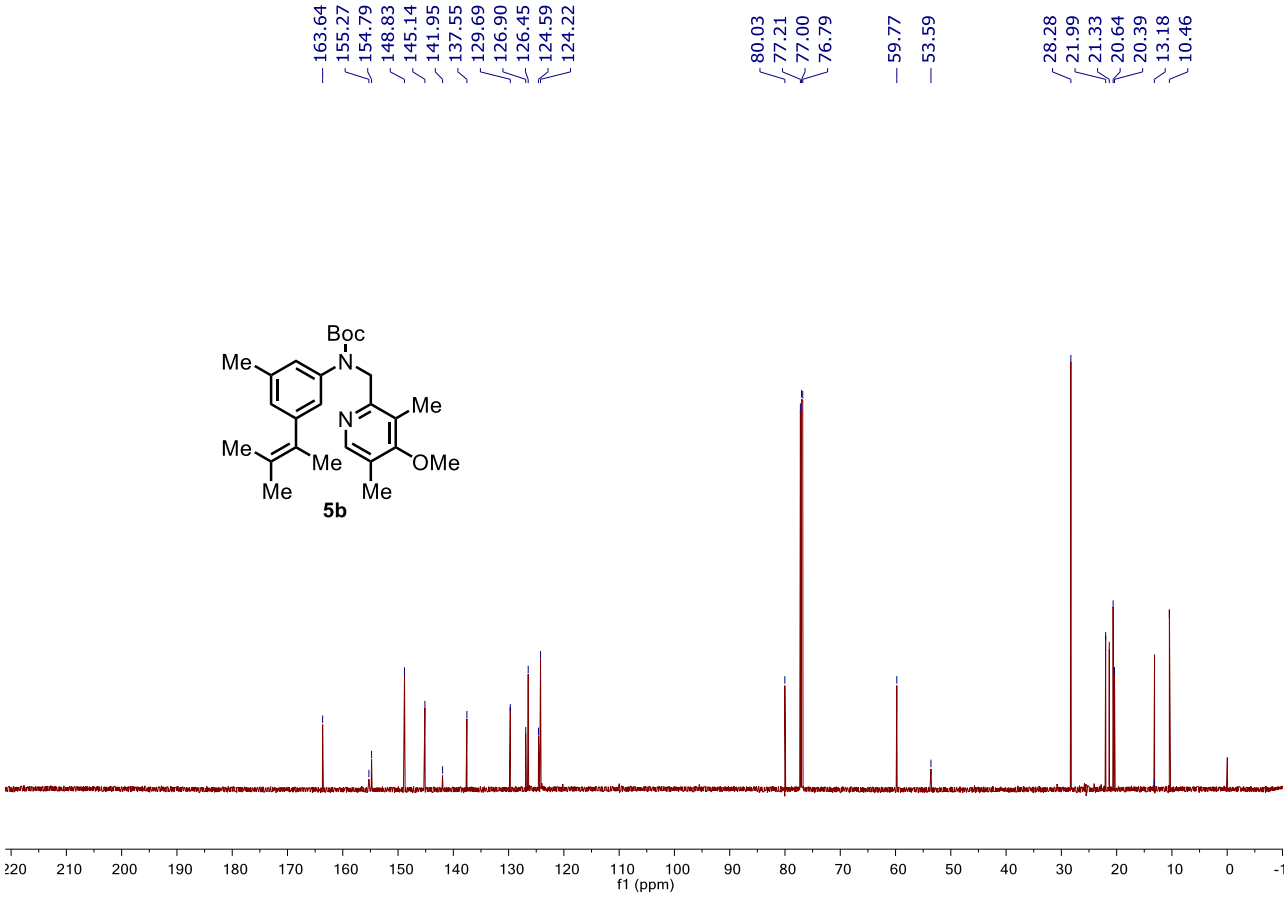
5.11
3.78
2.31
2.29
2.27
Me
O
Me
N
Cl
OMe
Me
4
1.00
1.00
0.98
1.03
2.12
3.11
3.15
3.10
3.15
f1 (ppm)

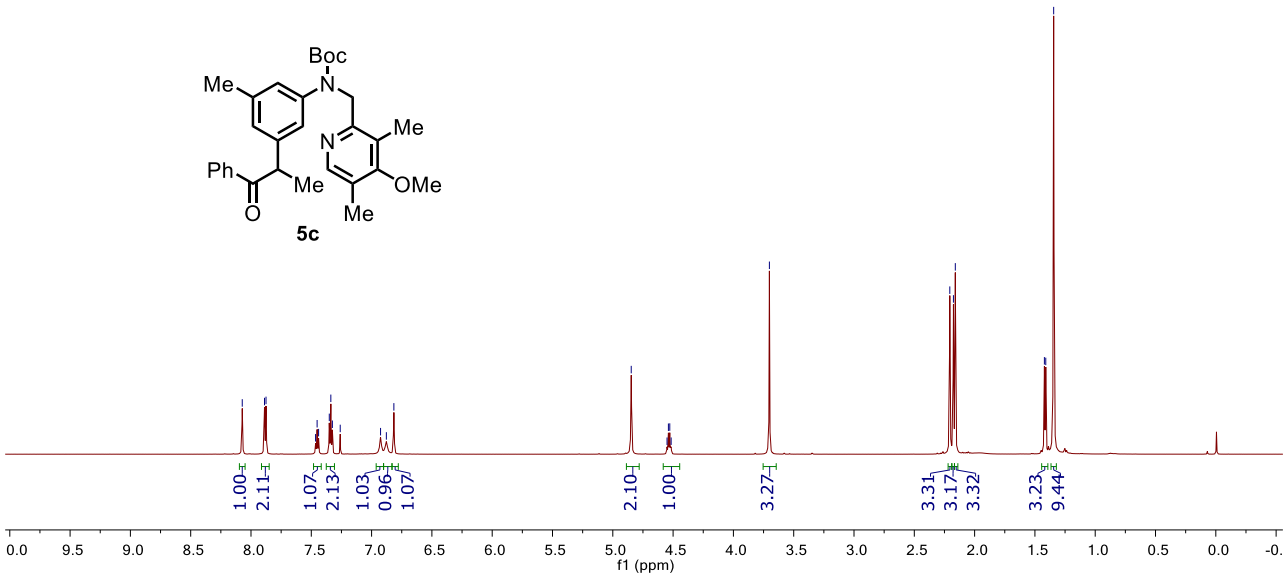

164.31
159.30
153.81
149.11
140.65
134.36
126.51
121.90
114.18
112.29
77.21
77.00
76.79
70.94
59.89
21.37
13.36
10.91
Me
O
Me
N
Cl
OMe
Me
4
f1 (ppm)


8.137
7.260
7.222
7.209
7.195
6.899
6.896
6.894
6.891
6.888
6.880
6.701
6.686
6.614
4.876
3.703
3.207
2.211
2.190
1.395
Boc
Me
N
Me
N
Me
Ph
OMe
Me
5a
1.00
2.07
3.11
1.88
1.06
2.03
3.22
3.14
6.24
3.04
9.67
f1 (ppm)


163.66
155.16
154.71
148.96
148.84
148.65
143.41
138.84
128.96
124.57
123.80
120.62
120.49
119.48
119.38
117.24
80.14
77.21
77.00
76.79
59.79
53.55
40.13
28.27
21.50
13.20
10.42
Boc
Me
N
Me
N
Me
N
Ph
OMe
Me
5a
f1 (ppm)


8.113
7.260
6.865
6.664
4.906
3.708
2.240
2.202
2.186
1.835
1.736
1.456
1.390
Boc
Me
N
Me
N
Me
Me
Me
OMe
Me
Me
5b
0.91
0.92
1.81
1.95
3.03
3.10
3.05
2.92
3.12
3.15
3.03
9.00
f1 (ppm)


163.64
155.27
154.79
148.83
145.14
141.95
137.55
129.69
126.90
126.45
124.59
124.22
80.03
77.21
77.00
76.79
59.77
53.59
28.28
21.99
21.33
20.64
20.39
13.18
10.46
Boc
N
Me
Me
N
Me
Me
Me
Me
OMe
Me
5b
f1 (ppm)
8.072
7.888
7.875
7.465
7.452
7.439
7.351
7.338
7.325
7.260
6.926
6.878
6.815
4.847
4.550
4.539
4.528
4.516
3.702
2.206
2.176
2.160
1.421
1.410
1.344


Boc
N
Me
Me
N
Ph
Me
OMe
O
Me
5c
1.00
2.11
1.07
2.13
1.03
0.96
1.07
2.10
1.00
3.27
3.31
3.17
3.32
3.23
9.44
f1 (ppm)

200.06
163.62
155.00
154.55
148.80
143.07
141.14
138.79
136.46
132.61
128.72
128.33
125.46
124.95
124.57
123.72
123.42
80.22
77.21
77.00
76.79
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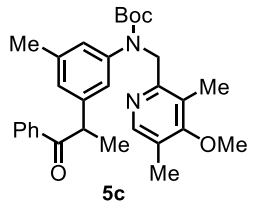
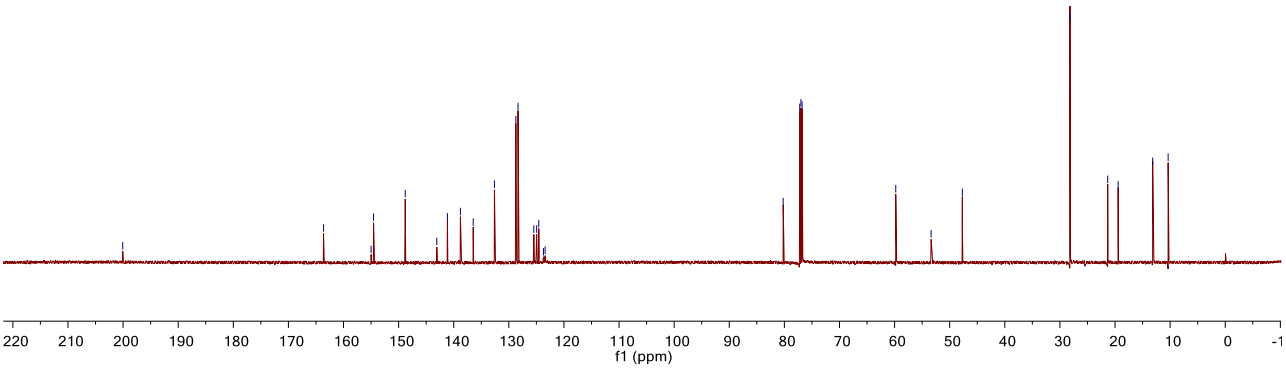
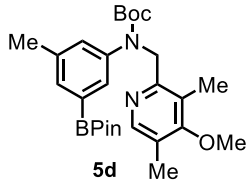
53.37
47.70
28.18
21.33
19.44
13.17
10.36



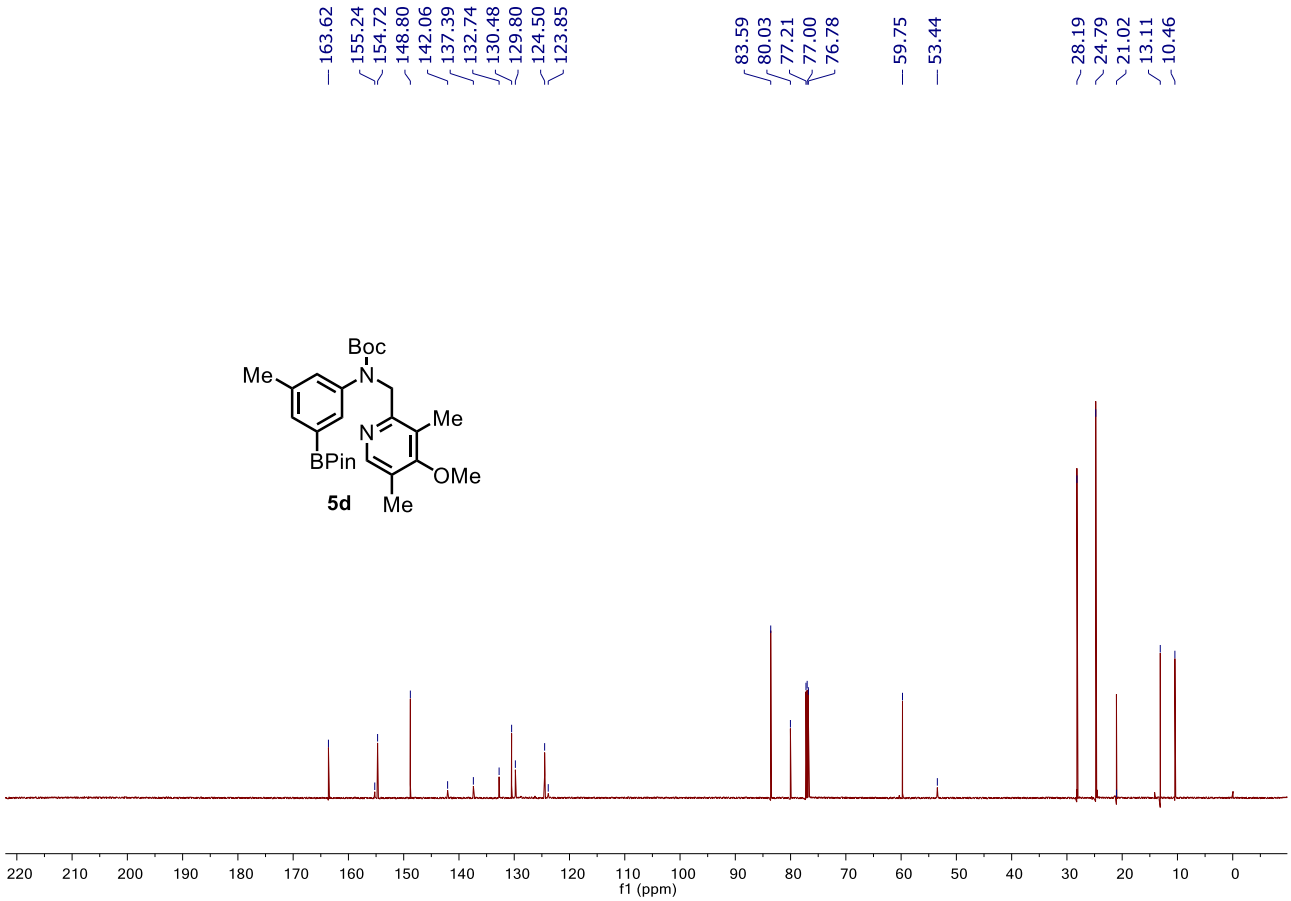
5c

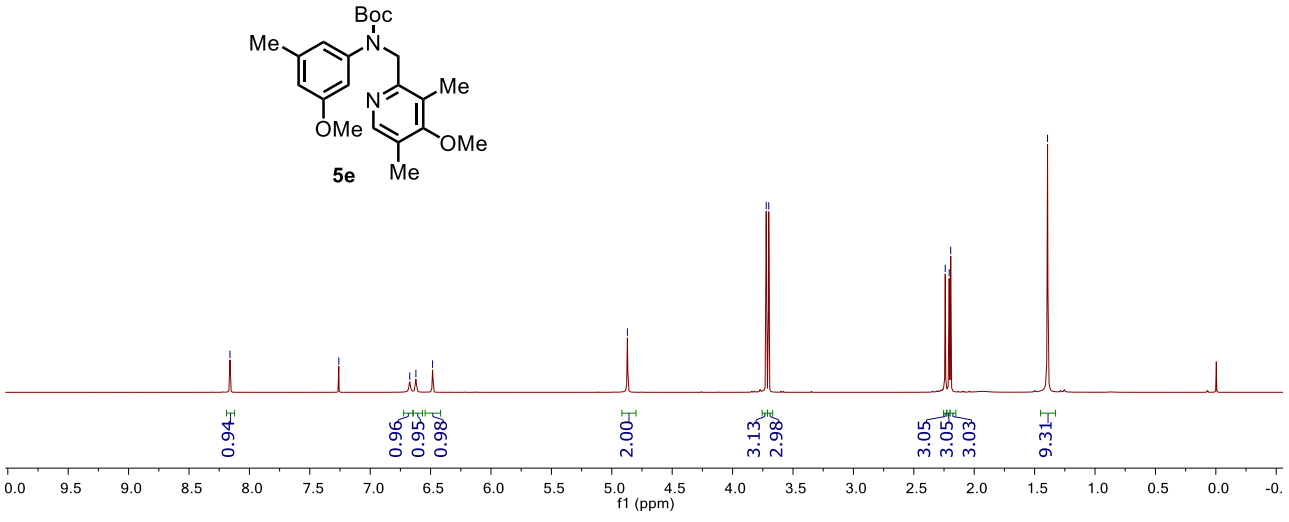


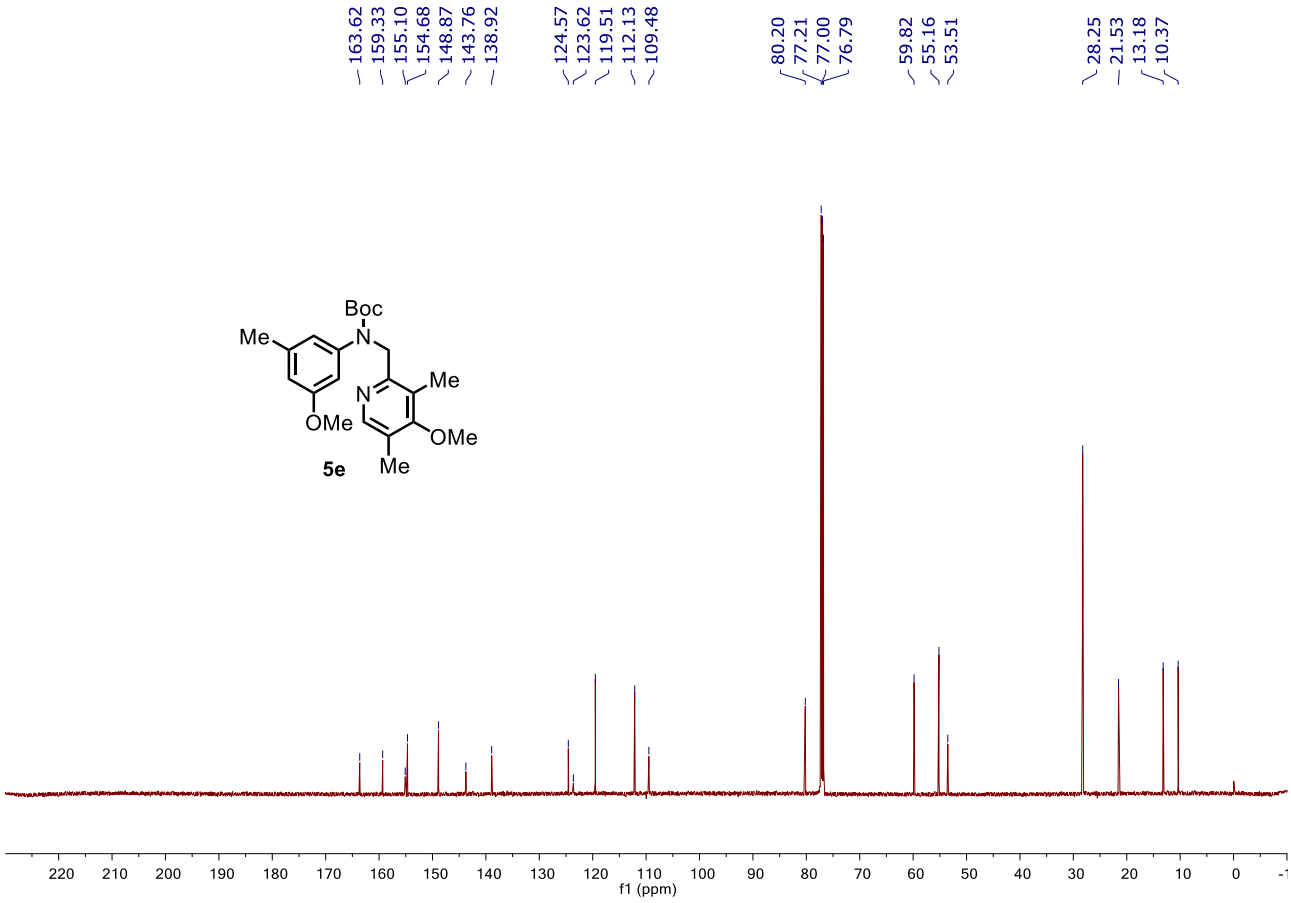
8.121
7.393
7.365
7.260
7.149
4.893
3.708
2.247
2.204
2.185
1.379
1.296

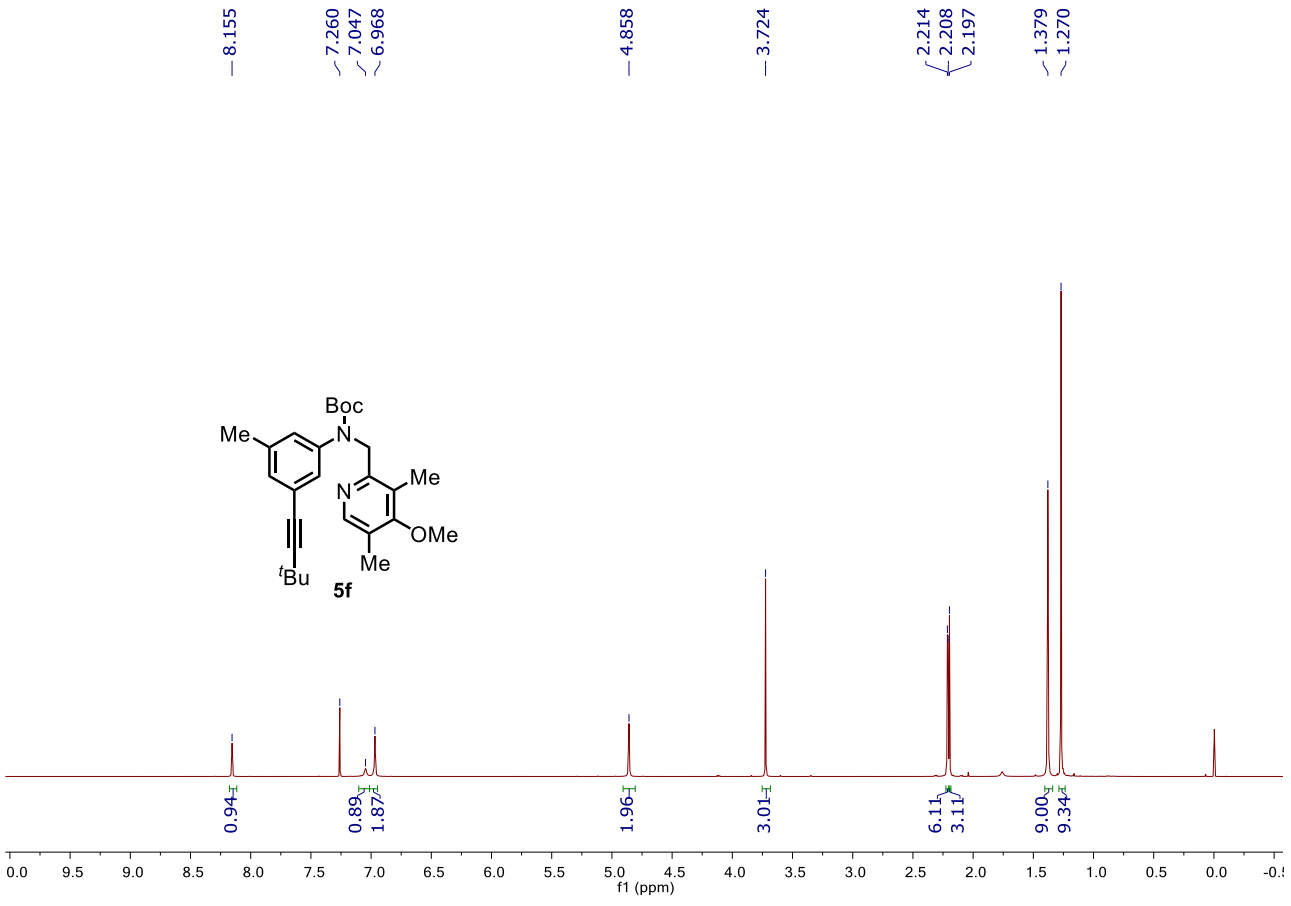


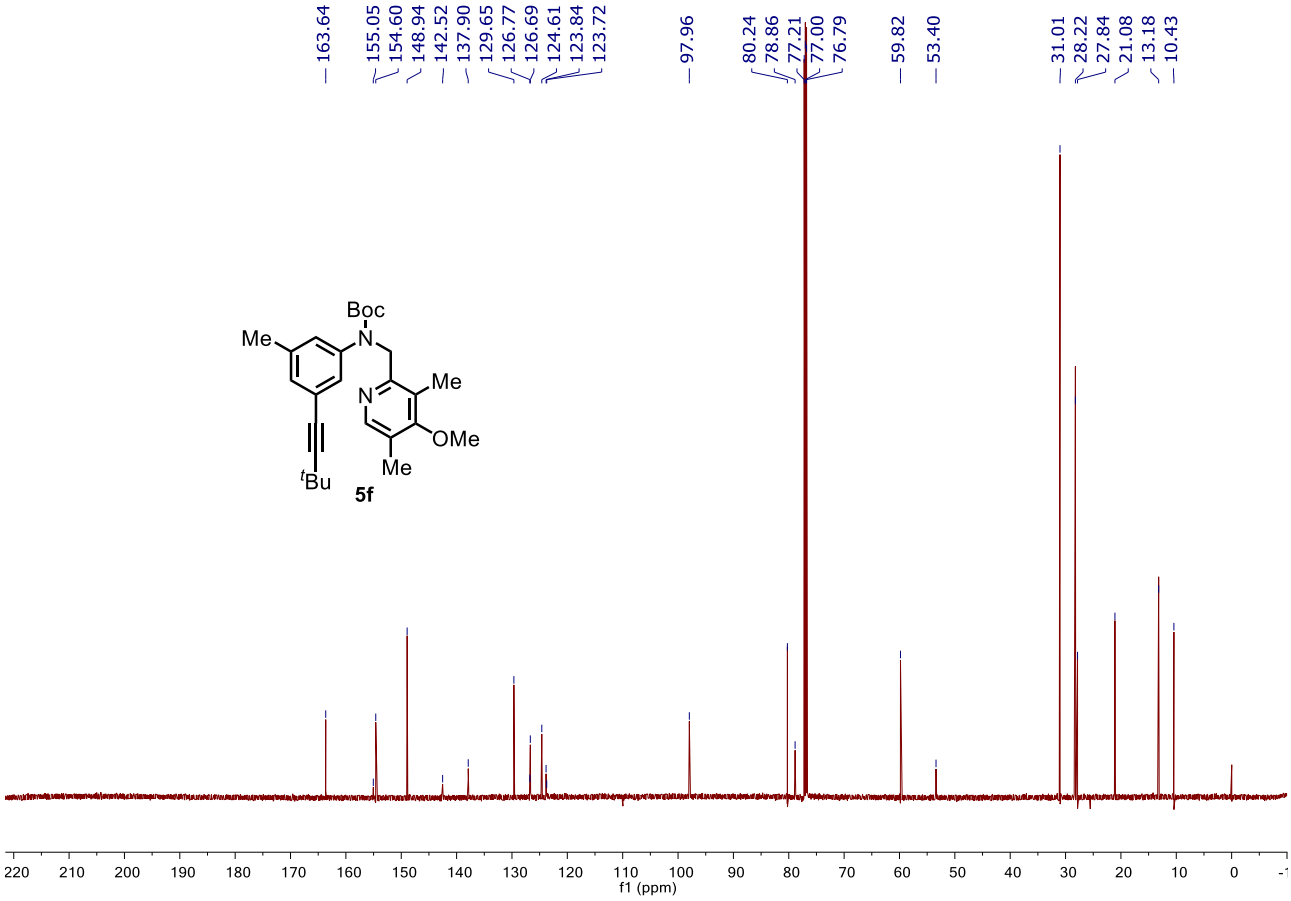
5d


163.62
155.24
154.72
148.80
142.06
137.39
132.74
130.48
129.80
124.50
123.85
83.59
80.03
77.21
77.00
76.78
59.75
53.44
28.19
24.79
21.02
13.11
10.46
Boc
Me
N
Me
N
BPin
OMe
Me
5d
f1 (ppm)
8.161
7.260
6.673
6.622
6.484
4.871
3.722
3.701
2.240
2.207
2.195
1.393


Boc
Me
N
Me
N
OMe
OMe
Me
5e
f1 (ppm)
0.94
0.96
0.95
0.98
2.00
3.13
2.98
3.05
3.05
3.03
9.31


163.62
159.33
155.10
154.68
148.87
143.76
138.92
124.57
123.62
119.51
112.13
109.48
80.20
77.21
77.00
76.79
59.82
55.16
53.51
28.25
21.53
13.18
10.37
Boc
Me
N
Me
N
OMe
OMe
Me
5e
f1 (ppm)


8.155
7.260
7.047
6.968
4.858
3.724
2.214
2.208
2.197
1.379
1.270
Boc
Me
N
Me
N
OMe
Me
tBu
5f
0.94
0.89
1.87
1.96
3.01
6.11
3.11
9.00
9.34
f1 (ppm)


163.64
155.05
154.60
148.94
142.52
137.90
129.65
126.77
126.69
124.61
123.84
123.72
97.96
80.24
78.86
77.21
77.00
76.79
59.82
53.40
31.01
28.22
27.84
21.08
13.18
10.43
Boc
N
Me
Me
N
OMe
Me
tBu
5f
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

References

1. Shen, P.-X.; Wang, X.-C.; Wang, P.; Zhu, R.-Y.; Yu, J.-Q. *J. Am. Chem. Soc*. **2015**, *137*, 11574.

2. Wang, P.; Farmer, M. E.; Huo, X.; Jain, P.; Shen, P.-X.; Ishoey, M.; Bradner, J. E.; Wisniewski, S. R.; Eastgate, M. D.; Yu, J.-Q. *J. Am. Chem. Soc*. **2016**, *138*, 9269.

3. Cativiela, C.; Fernandez, J.; Melendez, E. *J. Heterocycl. Chem.* **1982**, *19*, 1093.

4. Due to the high number of fluorine atoms, the ^{13}C peaks of heptafluoro-tolyl group were difficult to observe.