Pd-Catalyzed Sequential β-C(sp^3)–H Arylation and Intramolecular Amination of δ-C(sp^2)–H Bonds to Synthesis of Quinolinones via a N,O-Bidentate Directing Group

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Supporting information

Table of Contents

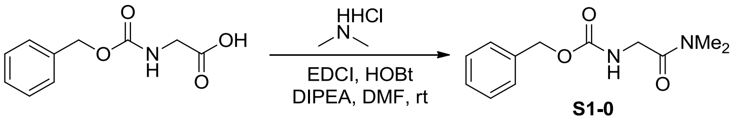
1. Reagents: Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Column chromatography purifications were performed using 300–400 mesh silica gel.

2. Instruments: NMR spectra were recorded on Varian Inova–400 MHz, Inova–300 MHz, Bruker DRX–400 or Bruker DRX–500 instruments and calibrated using residual solvent peaks as internal reference. Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, br = broad singlet, m = multiplet. HRMS analyses were carried out using a Bruker micrOTOF–Q instrument or a TOF–MS instrument.

3. Experimental section: Unless otherwide noted, all experiments were performed under air atmosphere. No reaction required anhydrous condition. All the glasswares used in the experiments were dried by vacuum oven.

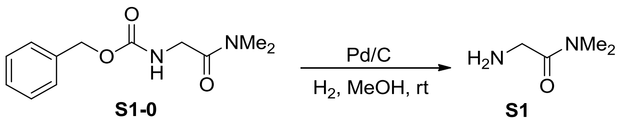
4. Preparation of glycine dimethylamide (S1)

4.1. Preparation of S1-0[1]

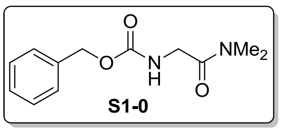


A mixture of acid (50 mmol, 1.0 equiv), amine (55 mmol, 1.1 equiv), EDCI (55 mmol, 1.1 equiv), HOBt (55 mmol, 1.1 equiv), and DIPEA (150 mmol, 3.0 equiv) in DMF (0.2 M) was stirred at rt overnight. Water was added and the mixture was extracted with DCM. The combined organic layers was washed with saturated ammonium chloride, sodium bicarbonate and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give **S1-0** as a white solid in 87% yield.

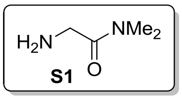
4.2. Preparation of S1



Compound **S1-0** (7.08 g, 30 mmol) was dissolved in methanol (150 mL) and 10% palladium-carbon (0.71 g) was added. The reaction mixture was shaked under hydrogen gas at room temperature over night. After removal of catalyst by filtration with aid of celite, the filtrate was concentrated under vacuum to give **S1** as pale yellow liquid in 95% yield. The crude product was used in the next step without any purification.



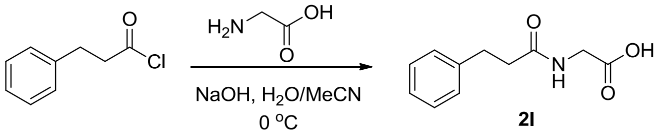
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H), 5.86 (br s, 1H), 5.10 (s, 2H), 3.98 (d, *J* = 4.1 Hz, 2H), 2.94 (d, *J* = 7.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.93, 156.29, 136.54, 128.53, 128.10, 128.04, 66.85, 42.69, 35.87, 35.62; HRMS Calcd for $C_{12}H_{17}N_2O_3$ [M+H$^+$]: 237.1239; Found: 237.1241.



^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 – 3.20 (m, 2H), 2.84 – 2.74 (m, 6H), 2.02 (br s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.41, 42.86, 35.55, 35.43; HRMS Calcd for $C_4H_{12}N_2O$ [M+H$^+$]: 103.0871; Found: 103.0874.

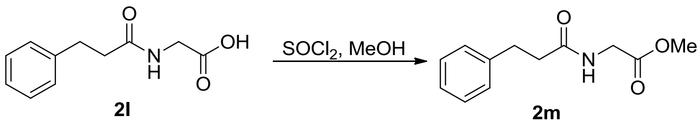
5. Preparation of various directing groups protected phenpropionic acid

5.1. Preparation of 2l



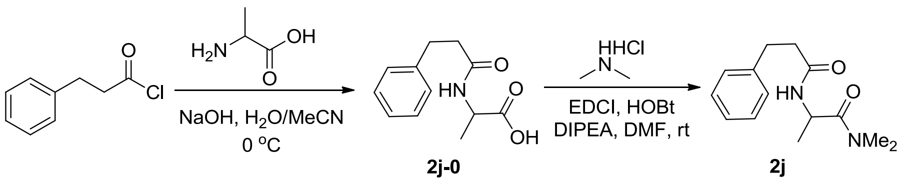
The glycine (30 mmol, 1.0 equiv) and NaOH (120 mmol, 4.0 equiv) were dissolved in water/acetonitrile (75/25, 0.3 M). After cooling to 0 °C, hydrocinnamoyl chloride (1.05 equiv) was added dropwise at this temperature. After the addition was complete, the mixture was stirred for additional 2 hours at 0 °C. Subsequently, the mixture was allowed to warm to RT and was stirred for one additional hour. All volatiles were then removed under reduced pressure before conc. HCl was added to cause precipitation. The mixture was filtered and the filter cake was washed with ice-cold diethylether to give **2l** as a white solid in 91% yield.

5.2. Preparation of 2m



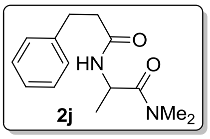
To a solution of **2l** (4.14 g, 20 mmol, 1.0 equiv) in MeOH (30 mL), at 0 °C, was added $SOCl_2$ (4.35 mL, 60 mmol, 3.0 equiv) dropwise. The resulting mixture was allowed to stir from 0 °C to room temperature overnight. The solvent was removed under reduced pressure afford a white solid **2m** 4.20 g, 95%.

5.3. Preparation of various directing groups protected phenpropionic acid 2j and 2k



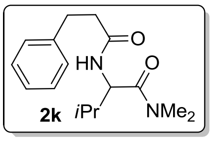
The racemic amino acid (20 mmol, 1 equiv) and NaOH (80 mmol, 4 equiv) were dissolved in water/acetonitrile (75/25, 0.3 M). After cooling to 0 °C, hydrocinnamoyl chloride (21 mmol, 1.05 equiv.) was added dropwise at this temperature. After the addition was complete, the mixture was stirred for additional 2 hours at 0 °C. Subsequently, the mixture was allowed to warm to RT and was stirred for one additional hour. All volatiles were then removed under reduced pressure before conc. HCl was added to cause precipitation. The mixture was filtered and the filter cake was washed with ice-cold diethylether to get a target compound. The crude product was used in the next step without any purification.

A mixture of acid (1.0 equiv), amine (1.1 equiv), EDCI (1.1 equiv), HOBt (1.1 equiv), and DIPEA (3.0 equiv) in DMF (0.2 M) was stirred at rt overnight. Water was added and the mixture was extracted with DCM. The combined organic layer was washed with saturated ammonium chloride, sodium bicarbonate and brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give white solid with >70% yield.



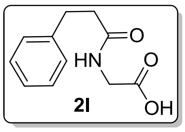
2j

H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 2H), 7.18 – 7.13 (m, 3H), 6.54 (br s, 1H), 4.89 – 4.82 (m, 1H), 3.02 (s, 3H), 2.97 – 2.93 (m, 5H), 2.51 – 2.42 (m, 2H), 1.22 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.45, 171.26, 140.88, 128.59, 128.47, 126.30, 45.24, 38.43, 37.05, 35.82, 31.75, 18.75; HRMS Calcd for $C_{14}H_{20}N_2O_2Na$ [M+Na$^+$]: 271.1422; Found: 271.1423.



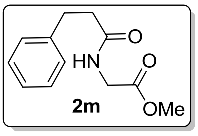
2k

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J=15.6 Hz, 1H), 7.49 – 7.47 (m, 2H), 7.38 – 7.31 (m, 3H), 6.85 (br s, 1H), 6.52 (d, J = 15.6 Hz, 1H), 4.96 (dd, J = 8.7, 6.9 Hz, 1H), 3.17 (s, 3H), 2.98 (s, 3H), 2.10 –2.01 (m,1H), 0.96 (dd, J = 13.3, 6.7 Hz, 6H), 0.90 – 0.78 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.20, 165.94, 141.25, 135.01, 129.72, 128.88, 127.91, 120.87, 53.79, 37.65, 35.81, 31.89, 19.65, 17.93; HRMS Calcd for $C_{16}H_{23}N_2O_2Na$ [M+Na$^+$]: 299.1735; Found: 299.1738.



2l

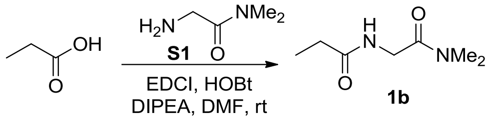
^{1}H NMR (400 MHz, DMSO) δ 12.49 (s, 1H), 8.20 (br s, 1H), 7.30 – 7.24 (m, 2H), 7.21 (d, J = 7.1 Hz, 2H), 7.17 (t, J = 7.1 Hz, 1H), 3.74 (d, J = 5.8 Hz, 2H), 2.81 (t, J = 7.8 Hz, 2H), 2.43 (t, J = 7.8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO) δ 171.81, 171.43, 141.32, 128.30, 128.23, 125.89, 40.60, 36.70, 30.96; HRMS Calcd for $C_{11}H_{14}NO_3$ [M+H$^+$]: 208.0974; Found: 208.0973.



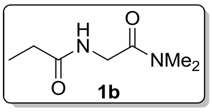
2m

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.22 (m, 2H), 7.17 – 7.15 (m, 3H), 5.93 (br s, 1H), 3.98 (d, J = 5.1 Hz, 2H), 3.70 (s, 3H), 2.96 – 2.91 (m, 2H), 2.54 – 2.48 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.39, 170.57, 140.77, 128.67, 128.43, 126.40, 52.51, 41.35, 38.10, 31.55; HRMS Calcd for $C_{12}H_{15}NO_3Na$ [M+Na$^+$]: 244.0950; Found: 244.0957.

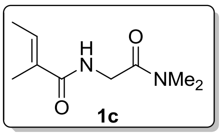
6. General procedures for the preparation of various carboxylic acid substrates 1b-1d, 1h-1i, 1l



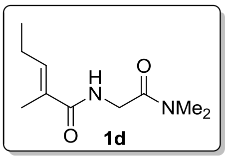
A mixture of carboxylic acid (1.0 equiv), **S1** (1.1 equiv), EDCI (1.1 equiv), HOBt (1.1 equiv), and DIPEA (3.0 equiv) in DMF (0.2 M) was stirred at rt overnight. Water was added and the mixture was extracted with DCM. The combined organic layer was washed with saturated ammonium chloride, sodium bicarbonate and brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give corresponding carboxylic acid substrates as white solid or colourless liquid with >85% yield.



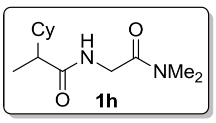
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (br s, 1H), 4.00 (d, *J*=4.0 Hz, 2H), 2.95 (s, 6H), 2.27 – 2.21 (m, 2H), 1.13 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.99, 168.24, 41.41, 36.04, 35.70, 29.63, 9.91; HRMS Calcd for $C_7H_{15}N_2O_2$ [M+H$^+$]: 159.1134; Found: 159.1138.



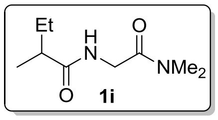
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (br s, 1H), 6.59 – 6.41 (m, 1H), 4.04 (d, *J* = 3.5 Hz, 2H), 2.96 (s, 6H), 1.83 (s, 3H), 1.71 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.08, 168.29, 131.60, 131.05, 41.56, 35.93, 35.57, 13.95, 12.22; HRMS Calcd for $C_9H_{17}N_2O_2$ [M+H$^+$]: 185.1290; Found: 185.1295.



^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.81 (br s, 1H), 6.31 (t, *J*=7.3 Hz, 1H), 3.98 (d, *J*=4.0 Hz, 2H), 2.90 (d, *J*=4.6 Hz, 6H), 2.09 – 2.01 (m, 2H), 1.76 (s, 3H), 0.92 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.00, 168.15, 138.24, 129.49, 41.39, 35.78, 35.39, 21.49, 13.12, 12.23; HRMS Calcd for $C_{10}H_{19}N_2O_2$ [M+H$^+$]: 199.1447; Found: 199.1446.

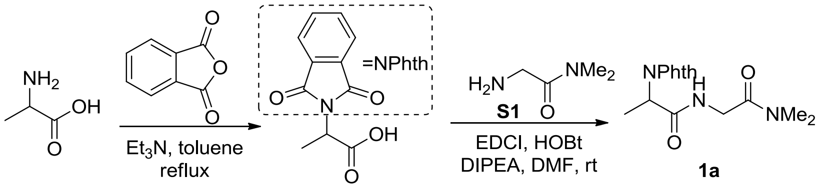


^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (br s, 1H), 6.55 (s, 1H), 4.03 (d, *J* = 3.9 Hz, 2H), 2.98 (d, *J* = 6.3 Hz, 6H), 2.98 (d, *J* = 6.3 Hz, 6H), 2.08 – 1.98 (m, 1H), 1.80 – 1.60 (m, 5H), 1.55 – 1.43 (m, 1H), 1.28 – 1.17 (m, 2H), 1.15 – 1.07 (m, 4H), 1.02 – 0.84 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.44, 168.27, 47.53, 41.24, 40.99, 35.99, 35.66, 31.58, 30.03, 26.49, 26.39, 26.37, 14.86; HRMS Calcd for $C_{13}H_{25}N_2O_2$ [M+H$^+$]: 241.1916; Found: 241.1918.



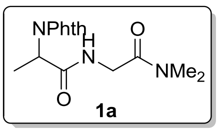
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (br s, 1H), 4.03 (d, *J* = 3.9 Hz, 2H), 2.98 (d, *J* = 6.3 Hz, 6H), 2.24 – 2.17 (m, 1H), 1.72 – 1.61 (m, 1H), 1.49 – 1.38 (m, 1H), 1.15 – 1.11 (m, 3H), 0.91 – 0.84 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.61, 168.29, 43.02, 41.28, 35.99, 35.65, 27.39, 17.48, 12.01; HRMS Calcd for $C_9H_{19}N_2O_2$ [M+H$^+$]: 187.1447; Found: 187.1445.

7. General procedures for the preparation of various amino acid substrates 1a, 1e-1g, 1j-1k, 1m

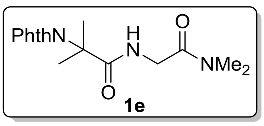


In RBF fitted with Dean-stark apparatus and a reflux condenser, phthalic acid anhydride (1.48 g, 10 mmol) and appropriate amino acids (10 mmol) were refluxed in toluene in the presence of 0.1 mL triethylamine for 3 hours. The organic solvents were removed under reduced pressure to get a sticky oily mass. Water was added to this oily mass and the mixture was acidified with hydrochloric acid, and stirred for 30 min to get a product. This product was filtered off, washed with water, and dried to get a target compound. The crude product was used in the next step without any purification.

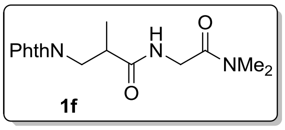
A mixture of acid (1.0 equiv), **S1** (1.1 equiv), EDCI (1.1 equiv), HOBt (1.1 equiv), and DIPEA (3.0 equiv) in DMF (0.2 M) was stirred at rt overnight. Water was added and the mixture was extracted with DCM. The combined organic layer was washed with saturated ammonium chloride, sodium bicarbonate and brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give corresponding carboxylic acid substratesas white solidor colourless liquid with >77% yield.



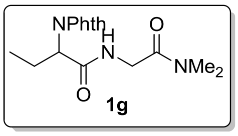
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.84 (m, 2H), 7.76 – 7.69 (m, 2H), 7.06 (br s, 1H), 5.00 – 4.95 (m, 1H), 4.06 (d, *J* = 3.8 Hz, 2H), 2.97 (d, *J* = 1.4, 6H), 1.73 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.01, 167.87, 167.72, 134.32, 132.04, 123.70, 49.14, 41.79, 35.99, 35.68, 15.40; HRMS Calcd for $C_{15}H_{18}N_3O_4$ [M+H$^+$]: 304.1297; Found: 304.1302.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.73 (m, 2H), 7.69 – 7.64 (m, 2H), 6.91 (br s, 1H), 4.05 (d, *J* = 3.8 Hz, 2H), 2.95 (d, *J* = 4.3 Hz, 6H), 1.84 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.89, 168.67, 167.93, 134.10, 131.94, 123.17, 61.28, 41.79, 35.90, 35.58, 24.78; HRMS Calcd for $C_{16}H_{20}N_3O_4$ [M+H$^+$]: 318.1454; Found: 318.1456.



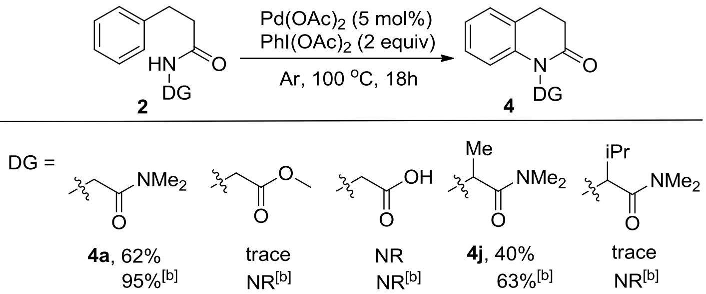
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.81 (m, 2H), 7.71 – 7.69 (m, 2H), 6.73 (br s, 1H), 4.03 (d, *J* = 3.9 Hz, 2H), 3.95 – 3.89 (m, 1H), 3.81 – 3.68 (m, 1H), 2.95 (s, 6H), 2.10 – 1.70 (m, 1H), 1.20 (d, *J* = 4.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.54, 168.34, 167.93, 134.05, 132.07, 123.44, 41.44, 41.21, 39.90, 35.97, 35.61, 15.57; HRMS Calcd for $C_{16}H_{20}N_3O_4$ [M+H$^+$]: 318.1454; Found: 318.1457.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 2H), 7.75 – 7.70 (m, 2H), 7.17 (br s, 1H), 4.81 – 4.74 (m, 1H), 4.05 (d, *J* = 3.3 Hz, 2H), 2.96 (d, *J* = 3.6 Hz, 6H), 2.39 – 2.29 (m, 1H), 2.28 – 2.79 (m, 1H), 0.96 – 0.89 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.79, 168.23, 167.71, 134.36, 131.83, 123.76, 55.96, 41.75, 35.98, 35.67, 22.31, 11.11; HRMS Calcd for $C_{16}H_{20}N_3O_4$ [M+H$^+$]: 318.1454; Found: 318.1460.

8. Screening of directing groups

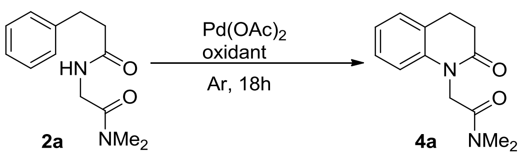
Table S1 Screening of directing groups[a]



[a] Reactions were carried out on a 0.2 mmol scale under argon (1 atm), using DCE (2 mL) as the solvent. Yields were based on GC-MS. [b] **2** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (2 equiv), HFIP (5 mL), 70 ^{o}C, Ar, 18 h.

9. Screening of reaction conditions of intramolecular δ-C(sp^2)–H amination

Table S2 Screening of reaction conditions[a]



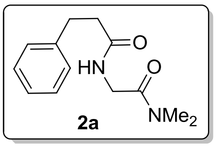
Entry	$Pd(OAc)_2$ (mol%)	Oxidant (equiv)	Solvent (mL)	Temperature (^{o}C)	Yield (%)
1	5	$PhI(OAc)_2$ (2)	DCE	100	61
2	5	$PhI(OAc)_2$ (2)	toluene	100	42
3	5	$PhI(OAc)_2$ (2)	HFIP	100	70
4	5	$PhI(OAc)_2$ (2)	HFIP	100	65

5	5	$PhI(OAc)_2$ (2)	HFIP	80	80
6	5	$PhI(OAc)_2$ (2)	HFIP	70	95 (**91**[b])
7	5	$PhI(OAc)_2$ (2)	HFIP	60	83
8	2.5	$PhI(OAc)_2$ (2)	HFIP	70	71
9	0	$PhI(OAc)_2$ (2)	HFIP	70	0
10	5	$PhI(OAc)_2$ (2)	HFIP	70	90[c]

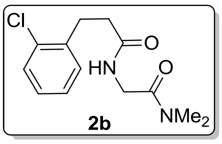
[a] Reactions were carried out on a 0.1 mmol scale under argon (1 atm), using HFIP (2.5 mL) as the solvent. Yield was based on GC using tridecane as the internal standard. [b] Isolated yield on a 0.2 mmol scale. [c] TEMPO (1 equiv) was added.

10. Palladium-catalyzed β-C(sp^3)–H arylation

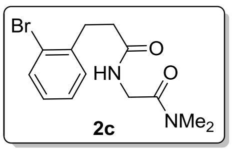
A mixture of carboxylic acid derivatives (0.2 mmol, 1.0 equiv), aryl iodide (1.5 equiv), $Pd(OAc)_2$ (2.2 mg, 0.05 equiv), AgOAc (33.4 mg, 2.0 equiv) and HFIP (1 mL) in a 25 mL glass vial (under air atmosphere, sealed with PTFE cap) was heated at 80 °C for 36 hours. The reaction mixture was cooled to rt, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give the arylation product.



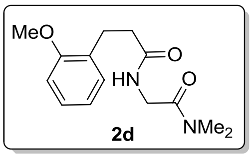
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 2H), 7.20 – 7.15 (m, 3H), 6.66 (br s, 1H), 4.01 (d, *J* = 3.9 Hz, 2H), 2.98 – 2.93 (m, 8H), 2.57 – 2.52 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.13, 168.01, 140.87, 128.54, 128.35, 126.22, 41.36, 38.06, 35.94, 35.60, 31.62; HRMS Calcd for $C_{13}H_{18}N_2O_2$ [M+H$^+$]: 235.1447; Found: 235.1448.



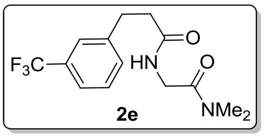
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 1H), 7.31 – 7.28 (m, 1H), 7.22 – 7.16 (m, 2H), 6.69 (br s, 1H), 4.07 (d, *J* = 3.9 Hz, 2H), 3.15 – 3.10 (m, 2H), 3.01 (s, 6H), 2.64 – 2.58 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.86, 167.99, 138.44, 133.97, 130.62, 129.61, 127.84, 126.99, 41.40, 36.02, 35.98, 35.63, 29.60; HRMS Calcd for $C_{13}H_{18}ClN_2O_2$ [M+H$^+$]: 269.1057; Found: 269.1065.



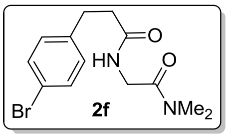
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 – 7.46 (m, 1H), 7.25 – 7.15 (m, 2H), 7.04 – 7.00 (m, 1.8, 1H), 6.70 (br s, 1H), 4.00 (d, *J* = 4.0 Hz, 2H), 3.09 – 3.03 (m, 2H), 2.93 (s, 6H), 2.57 – 2.51 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.72, 167.95, 140.11, 132.85, 130.54, 128.01, 127.59, 124.33, 41.34, 36.07, 35.92, 35.57, 32.03; HRMS Calcd for $C_{13}H_{18}BrN_2O_2$ [M+H$^+$]: 313.0552; Found: 313.0561.



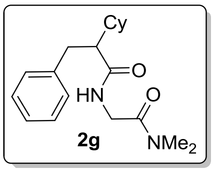
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.12 (m, 2H), 6.87 – 6.80 (m, 2H), 6.64 (br s, 1H), 4.01 (d, *J* = 3.9 Hz, 2H), 3.81 (s, 3H), 2.95 (d, *J* = 4.0 Hz, 6H), 2.94 – 2.91 (m, 2H), 2.57 – 2.49 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.76, 168.11, 157.45, 130.01, 129.08, 127.57, 120.48, 110.24, 55.23, 41.35, 36.39, 35.96, 35.59, 26.80; HRMS Calcd for $C_{14}H_{21}N_2O_3$ [M+H$^+$]: 265.2552; Found: 265.2553.



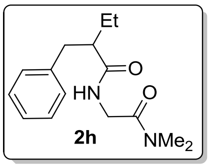
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.41 – 7.37 (m, 2H), 6.62 (br s, 1H), 4.01 (d, *J* = 4.0 Hz, 2H), 3.05 – 3.01 (m, 2H), 2.97 (d, *J* = 1.8 Hz, 6H), 2.59 – 2.54 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.57, 167.93, 141.87, 131.92 (d, $J_{C\text{-}F}$ = 1.0 Hz), 130.85 (q, $J_{C\text{-}F}$ = 32.0 Hz), 129.04, 125.21 (q, $J_{C\text{-}F}$ = 4.0 Hz), 124.28 (q, $J_{C\text{-}F}$ = 260.0 Hz), 123.23 (q, $J_{C\text{-}F}$ = 4.0 Hz), 41.41, 37.73, 35.98, 35.66, 31.37; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.59; HRMS Calcd for $C_{14}H_{18}F_3N_2O_2$ [M+H$^+$]: 303.1320; Found: 303.1357.



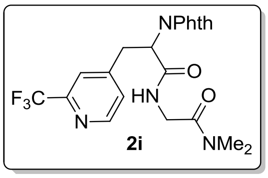
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.42 (m, 2H), 7.15 – 7.11 (m, 2H), 6.61 (br s, 1H), 4.06 (d, *J* = 3.9 Hz, 2H), 3.03 (d, *J* = 5.6 Hz, 6H), 3.00 – 2.96 (m, 2H), 2.61 – 2.56 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.71, 167.95, 139.90, 131.68, 130.26, 120.12, 41.44, 37.84, 36.01, 35.71, 31.00; HRMS Calcd for $C_{13}H_{18}BrN_2O_2$ [M+H$^+$]: 313.0552; Found: 313.0556.



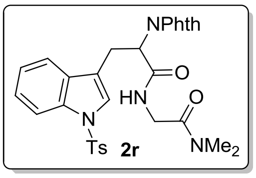
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 2H), 7.16 – 7.09 (m, 3H), 6.28 (br s, 1H), 4.02 (dd, *J* = 17.5, 4.4 Hz, 1H), 3.70 (dd, *J* = 17.5, 3.0 Hz, 1H), 2.90 (d, *J* = 11.2 Hz, 6H), 2.88 – 2.83 (m, 2H), 2.24 – 2.16 (m, 1H), 1.92 (d, *J* = 12.3 Hz, 1H), 1.78 – 1.63 (m, 4H), 1.29 – 1.11 (m, 4H), 1.08 – 0.98 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.25, 167.92, 140.49, 128.89, 128.37, 126.07, 56.37, 41.09, 40.37, 35.96, 35.88, 35.54, 31.15, 31.11, 26.49, 26.38; HRMS Calcd for $C_{19}H_{28}N_2O_2Na$ [M+Na$^+$]: 339.2048; Found: 339.2041.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.20 (m, 2H), 7.16 – 7.11 (m, 3H), 6.48 (br s, 1H), 4.04 (dd, *J* = 17.5, 4.4 Hz, 1H), 3.83 (dd, *J* = 17.5, 3.5 Hz, 1H), 2.95 – 2.89 (m, 7H), 2.70 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.38 – 2.31 (m, 1H), 1.71 – 1.60 (m, 1H), 1.54 – 1.45 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.93, 167.93, 139.86, 128.89, 128.34, 126.16, 51.27, 41.12, 38.80, 35.86, 35.50, 25.54, 12.03; HRMS Calcd for $C_{15}H_{22}N_2O_2Na$ [M+Na$^+$]: 285.1579; Found: 285.1582.



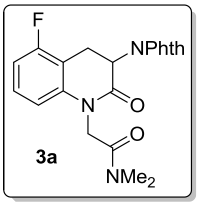
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.9 Hz, 1H), 7.76 – 7.71 (m, 2H), 7.70 – 7.64 (m, 2H), 7.49 (s, 1H), 7.42 (br s, 1H), 7.33 (d, *J* = 4.8 Hz, 1H), 5.28 – 5.23 (m, 1H), 4.06 – 3.94 (m, 2H), 3.75 – 3.62 (m, 2H), 2.91 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.68, 167.58, 167.43, 150.16, 148.65, 148.39 (q, $J_{C\text{-}F}$ = 34.0 Hz), 134.56, 131.24, 126.90, 123.74, 121.38 (q, $J_{C\text{-}F}$ = 272.0 Hz), 121.13 (q, $J_{C\text{-}F}$ = 3.0 Hz), 53.72, 41.58, 35.94, 35.53, 34.15; ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.15; HRMS Calcd for $C_{21}H_{19}F_3N_4O_4Na$ [M+Na$^+$]: 471.1256; Found: 471.1251.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.77 – 7.74 (m, 2H), 7.72 – 7.66 (m, 2H), 7.54 (t, *J* = 7.1, 3H), 7.35 (br s, 1H), 7.28 – 7.21 (m, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 2H), 5.29 – 5.22 (m, 1H), 4.06 (d, *J* = 3.7 Hz, 2H), 3.76 (dd, *J* = 15.2, 11.0 Hz, 1H), 3.63 (dd, *J* = 15.2, 5.1 Hz, 1H), 2.94 (d, *J* = 6.8 Hz, 6H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.04, 167.75, 167.51, 144.65, 135.11, 134.36, 131.52, 130.32, 129.77, 126.69, 124.96, 124.33, 123.74, 123.34, 119.40, 117.96, 113.67, 53.53, 41.75, 35.95, 35.63, 24.61, 21.60; HRMS Calcd for $C_{30}H_{29}N_4O_6S$ [M+H$^+$]: 573.1808; Found: 573.1818.

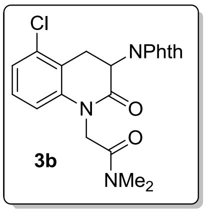
11. Synthesis of quinolinone from general acid derivatives with aryl idodies

A mixture of acid derivatives (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.05 equiv), AgOAc (33.4 mg, 2.0 equiv) and HFIP (1 mL) in a 25 mL glass vial (under air atmosphere, sealed with PTFE cap) was heated at 80 ^{o}C for 12 hours. The reaction mixture was cooled to rt, then $PhI(OAc)_2$ (160.5 mg, 2.5 equiv), PivOH (6.0 mg, 0.3 equiv) and HFIP (4 mL) were added in the 25 mL glass vial (purged with Ar, sealed with PTFE cap), which was heated at 70 ^{o}C for 18 hours. The reaction mixture was cooled to rt, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give the cyclized product.



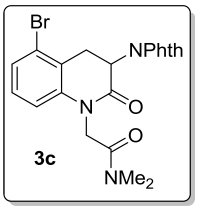
3a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.85 (m, 2H), 7.77 – 7.72 (m, 2H), 7.21 (dd, *J* = 14.7, 8.1 Hz, 1H), 6.82 (t, *J* = 8.5 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 5.21 (dd, *J* = 14.9, 6.4 Hz, 1H), 5.09 (d, *J* = 16.5 Hz, 1H), 4.36 (d, *J* = 16.5 Hz, 1H), 3.75 (t, *J* = 15.1 Hz, 1H), 3.33 (dd, *J* = 15.2, 6.4 Hz, 1H), 3.09 (s, 3H), 2.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.72, 166.35, 166.23, 159.64 (d, $J_{C\text{-}F}$ = 244.0 Hz), 140.88 (d, $J_{C\text{-}F}$ = 7.0 Hz), 134.34, 132.05, 129.00 (d, $J_{C\text{-}F}$ = 9.0 Hz), 123.70, 111.29 (d, $J_{C\text{-}F}$ = 3.0 Hz), 111.28 (d, $J_{C\text{-}F}$ = 21.0 Hz), 110.86 (d, $J_{C\text{-}F}$ = 22.0 Hz), 48.55, 45.92, 36.59, 36.00, 22.15 (d, $J_{C\text{-}F}$ = 4.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.56; HRMS Calcd for $C_{21}H_{18}FN_3O_4Na$ [M+Na$^+$]: 418.1179; Found: 418.1177.



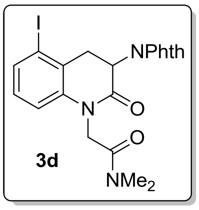
3b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.85 (m, 2H), 7.77 – 7.71 (m, 2H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 5.21 (dd, *J* = 14.9, 6.4 Hz, 1H), 5.10 (d, *J* = 16.5 Hz, 1H), 4.34 (d, *J* = 16.5 Hz, 1H), 3.83 (t, *J* = 15.2 Hz, 1H), 3.47 (dd, *J* = 15.5, 6.4 Hz, 1H), 3.09 (s, 3H), 2.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.71, 166.34, 166.21, 140.69, 134.34, 133.33, 132.05, 128.73, 124.69, 123.69, 122.10, 114.30, 48.56, 46.04, 36.61, 36.00, 26.72; HRMS Calcd for $C_{21}H_{18}ClN_3O_4Na$ [M+Na$^+$]: 434.0876; Found: 434.0876.



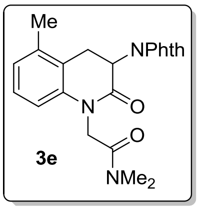
3c

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 2H), 7.77 – 7.70 (m, 2H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.11 (t, *J* = 8.1 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 5.21 (dd, *J* = 14.9, 6.3 Hz, 1H), 5.08 (d, *J* = 16.5 Hz, 1H), 4.33 (d, *J* = 16.5 Hz, 1H), 3.86 (t, *J* = 15.2 Hz, 1H), 3.45 (dd, *J* = 15.5, 6.3 Hz, 1H), 3.09 (s, 3H), 2.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.69, 166.33, 166.25, 140.62, 134.33, 132.04, 129.06, 127.89, 123.88, 123.68, 123.65, 115.00, 48.64, 46.05, 36.60, 36.00, 29.62; HRMS Calcd for $C_{21}H_{19}BrN_3O_4$ [M+H$^+$]: 456.0559; Found: 456.0553.



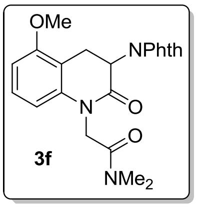
3d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.85 (m, 2H), 7.76 – 7.71 (m, 2H), 7.56 (d, *J* = 7.8 Hz, 1H), 6.95 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 5.22 (dd, *J* = 14.9, 6.2 Hz, 1H), 5.07 (d, *J* = 16.5 Hz, 1H), 4.32 (d, *J* = 16.5 Hz, 1H), 3.93 (t, *J* = 15.1 Hz, 1H), 3.31 (dd, *J* = 15.4, 6.3 Hz, 1H), 3.09 (s, 3H), 2.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.73, 166.40, 166.38, 139.78, 134.50, 134.35, 132.06, 129.48, 127.23, 123.71, 116.06, 99.79, 48.94, 46.07, 36.64, 36.03, 35.09; HRMS Calcd for $C_{21}H_{19}IN_3O_4$ [M+H$^+$]: 504.0420; Found: 504.0416.



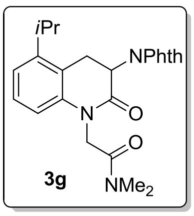
3e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.85 (m, 2H), 7.75 – 7.71 (m, 2H), 7.14 (t, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 5.20 (dd, *J* = 14.9, 6.2 Hz, 1H), 5.07 (d, *J* = 16.5 Hz, 1H), 4.38 (d, *J* = 16.4 Hz, 1H), 3.80 (t, *J* = 15.0 Hz, 1H), 3.12 (d, *J* = 6.3 Hz, 1H), 3.09 (s, 3H), 2.97 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.86, 166.72, 166.36, 139.31, 135.84, 134.24, 132.10, 127.65, 125.75, 123.60, 122.39, 113.66, 49.05, 45.99, 36.59, 35.98, 26.18, 19.73; HRMS Calcd for $C_{22}H_{22}N_3O_4$ [M+H$^+$]: 392.1610; Found: 392.1619.



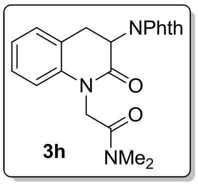
3f

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.84 (m, 2H), 7.77 – 7.66 (m, 2H), 7.19 (t, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 5.16 (dd, *J* = 14.8, 6.6 Hz, 1H), 5.05 (d, *J* = 16.5 Hz, 1H), 4.40 (d, *J* = 16.5 Hz, 1H), 3.82 (s, 3H), 3.59 (t, *J* = 15.1 Hz, 1H), 3.41 (dd, *J* = 15.3, 6.6 Hz, 1H), 3.09 (s, 3H), 2.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.79, 166.77, 166.60, 156.46, 140.24, 134.19, 132.14, 128.50, 123.58, 111.99, 108.41, 106.31, 55.80, 49.03, 45.93, 36.60, 35.99, 22.55; HRMS Calcd for $C_{22}H_{22}N_3O_5$ [M+H$^+$]: 408.1559; Found: 408.1560.



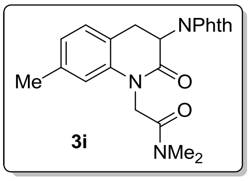
3g

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.86 (m, 2H), 7.77 – 7.70 (m, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 5.19 (dd, *J* = 14.9, 5.9 Hz, 1H), 5.10 (d, *J* = 16.5 Hz, 1H), 4.35 (d, *J* = 16.4 Hz, 1H), 3.84 (t, *J* = 14.9 Hz, 1H), 3.24 (dd, *J* = 15.0, 5.9 Hz, 1H), 3.15 – 3.05 (m, 4H), 2.98 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.92, 166.78, 166.53, 146.26, 139.44, 134.27, 132.16, 127.99, 123.64, 121.55, 120.84, 113.62, 49.25, 46.27, 36.63, 36.03, 29.50, 25.66, 23.33, 23.25; HRMS Calcd for $C_{24}H_{26}N_3O_4$ [M+H$^+$]: 420.1923; Found: 420.1922.



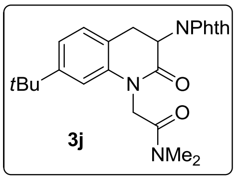
3h

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.85 (m, 2H), 7.74 – 7.72 (m, 2H), 7.27 – 7.23 (m, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 5.23 (dd, *J* = 15.1, 6.1 Hz, 1H), 5.07 (d, *J* = 16.4 Hz, 1H), 4.39 (d, *J* = 16.4 Hz, 1H), 4.07 (t, *J* = 14.9 Hz, 1H), 3.10 (s, 3H), 3.01 – 2.92 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.81, 166.63, 166.56, 139.25, 134.25, 132.10, 128.26, 123.72, 123.62, 115.59, 49.27, 45.76, 36.61, 35.99, 29.82; HRMS Calcd for $C_{21}H_{20}N_3O_4$ [M+H$^+$]: 378.1454; Found: 378.1444.



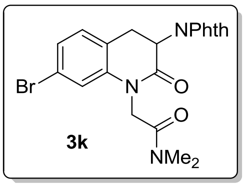
3i

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.84 (m, 2H), 7.73 – 7.71 (m, 2H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.67 (s, 1H), 5.20 (dd, *J* = 15.0, 6.1 Hz, 1H), 5.05 (d, *J* = 16.4 Hz, 1H), 4.36 (d, *J* = 16.4 Hz, 1H), 4.01 (t, *J* = 14.8 Hz, 1H), 3.10 (s, 3H), 2.98 (s, 3H), 2.92 (dd, *J* = 14.6, 6.1 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.83, 166.71, 166.68, 139.15, 138.10, 134.22, 132.11, 128.05, 124.42, 123.59, 120.75, 116.27, 49.45, 45.83, 36.62, 36.00, 29.46, 21.66; HRMS Calcd for $C_{22}H_{21}N_3O_4Na$ [M+Na$^+$]: 414.1430; Found: 414.1428.



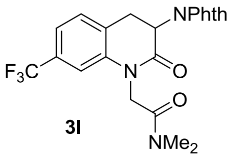
3j

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.84 (m, 2H), 7.75 – 7.69 (m, 2H), 7.14 – 7.05 (m, 2H), 6.96 (d, *J* = 1.4 Hz, 1H), 5.21 (dd, *J* = 15.0, 6.1 Hz, 1H), 4.96 (d, *J* = 16.2 Hz, 1H), 4.56 (d, *J* = 16.2 Hz, 1H), 4.02 (t, *J* = 14.6 Hz, 1H), 3.11 (s, 3H), 2.96 (s, 3H), 2.95 – 2.90 (m, 1H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.83, 166.95, 166.56, 151.50, 138.68, 134.22, 132.11, 127.84, 123.59, 120.82, 120.75, 113.06, 49.44, 45.79, 36.81, 36.06, 34.90, 31.35, 29.27; HRMS Calcd for $C_{25}H_{22}N_3O_4$ [M+H$^+$]: 434.2080; Found: 434.2084.



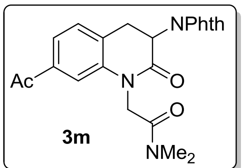
3k

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.85 (m, 2H), 7.74 – 7.72 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.98 (s, 1H), 5.21 (dd, *J* = 15.0, 6.1 Hz, 1H), 5.09 (d, *J* = 16.5 Hz, 1H), 4.27 (d, *J* = 16.5 Hz, 1H), 3.99 (t, *J* = 14.9 Hz, 1H), 3.10 (s, 3H), 2.99 (s, 3H), 2.94 (dd, *J* = 14.9, 6.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.73, 166.45, 166.04, 140.69, 134.34, 132.02, 129.54, 126.59, 123.69, 122.76, 121.64, 118.71, 48.91, 45.82, 36.60, 36.02, 29.44; HRMS Calcd for $C_{21}H_{19}BrN_3O_4$ [$M+H^+$]: 456.0559; Found: 455.0560.



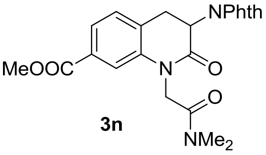
3l

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.87 (m, 2H), 7.76 – 7.74 (m, 2H), 7.32 (s, 2H), 7.07 (s, 1H), 5.25 (dd, *J* = 15.1, 6.0 Hz, 1H), 5.14 (d, *J* = 16.5 Hz, 1H), 4.34 (d, *J* = 16.5 Hz, 1H), 4.13 (t, *J* = 15.1 Hz, 1H), 3.13 (s, 3H), 3.05 (dd, *J* = 15.0, 6.0 Hz, 1H), 3.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.76, 166.44, 166.01, 140.03, 134.41, 132.03, 130.72 (q, J_{C-F} = 33.0 Hz), 128.82, 127.76 (d, J_{C-F} = 1.0 Hz), 123.90 (q, J_{C-F} = 270.0 Hz), 123.76, 120.57 (q, J_{C-F} = 4.0 Hz), 112.43 (q, J_{C-F} = 4.0 Hz), 48.73, 45.76, 36.67, 36.07, 29.82; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.44; HRMS Calcd for $C_{22}H_{19}F_3N_3O_4$ [$M+H^+$]: 446.1328; Found: 446.1326.



3m

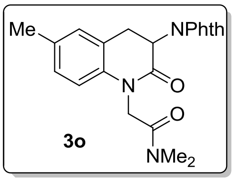
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.86 (m, 2H), 7.76 – 7.74 (m, 2H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.46 (s, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 5.23 (dd, *J* = 15.0, 6.0 Hz, 1H), 5.11 (d, *J* = 16.5 Hz, 1H), 4.48 (d, *J* = 16.5 Hz, 1H), 4.13 (t, *J* = 15.2 Hz, 1H), 3.13 (s, 3H), 3.07 (dd, *J* = 15.1, 6.0 Hz, 1H), 2.98 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.36, 167.68, 166.34, 166.05, 139.85, 137.24, 134.31, 131.98, 129.14, 128.48, 124.13, 123.64, 114.48, 48.71, 45.43, 36.57, 35.94, 29.94, 26.71; HRMS Calcd for $C_{23}H_{22}N_3O_5$ [$M+H^+$]: 420.1559; Found: 420.1561.



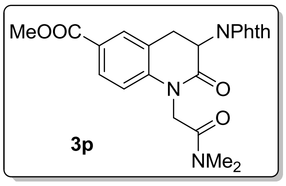
3n

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.86 (m, 2H), 7.76 – 7.71 (m, 3H), 7.49 (s, 1H), 7.27 (d, *J* = 5.7 Hz, 1H), 5.24 (dd, *J* = 15.1, 6.0 Hz, 1H), 5.12 (d, *J* = 16.5 Hz, 1H), 4.42 (d, *J* = 16.5 Hz, 1H), 4.13 (t, *J*

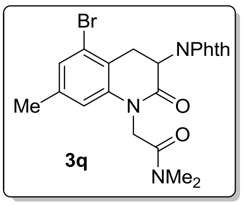
= 15.1 Hz, 1H), 3.90 (s, 3H), 3.12 (s, 3H), 3.05 (dd, *J* = 15.1, 6.0 Hz, 1H), 2.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.77, 166.63, 166.42, 166.12, 139.67, 134.35, 132.04, 130.31, 128.94, 128.46, 124.92, 123.72, 116.32, 52.46, 48.77, 45.56, 36.61, 36.03, 30.02; HRMS Calcd for $C_{23}H_{22}N_3O_6$ [M+H$^+$]: 436.1509; Found: 436.1513.



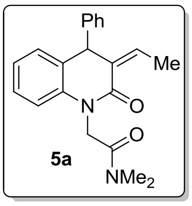
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.83 (m, 2H), 7.77 – 7.69 (m, 2H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.99 (s, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.20 (dd, *J* = 15.0, 6.1 Hz, 1H), 5.02 (d, *J* = 16.4 Hz, 1H), 4.40 (d, *J* = 16.4 Hz, 1H), 4.04 (t, *J* = 14.8 Hz, 1H), 3.09 (s, 3H), 2.96 (s, 3H), 2.90 (dd, *J* = 14.7, 6.1 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.82, 166.73, 166.40, 136.80, 134.21, 133.28, 132.10, 128.90, 128.63, 123.58, 123.51, 115.47, 49.34, 45.73, 36.60, 35.97, 29.79, 20.68; HRMS Calcd for $C_{22}H_{22}N_3O_4$ [M+H$^+$]: 392.1610; Found: 392.1620.



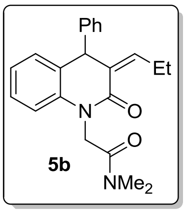
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.6 Hz, 1H), 7.89 – 7.87 (m, 3H), 7.75 – 7.73 (m, 2H), 6.90 (d, *J* = 8.5 Hz, 1H), 5.25 (dd, *J* = 15.1, 6.1 Hz, 1H), 5.14 (d, *J* = 16.5 Hz, 1H), 4.37 (d, *J* = 16.5 Hz, 1H), 4.08 (t, *J* = 14.9 Hz, 1H), 3.90 (s, 3H), 3.12 (s, 3H), 3.05 (dd, *J* = 14.9, 6.1 Hz, 1H), 2.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.73, 166.67, 166.45, 166.17, 143.20, 134.38, 132.06, 130.12, 129.69, 125.33, 123.75, 123.61, 115.40, 52.28, 48.93, 45.79, 36.64, 36.04, 29.65; HRMS Calcd for $C_{23}H_{22}N_3O_6$ [M+H$^+$]: 436.1509; Found: 436.1515.



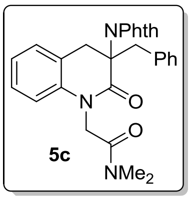
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.87 (m, 2H), 7.75 – 7.73 (m, 2H), 7.14 (s, 1H), 6.64 (s, 1H), 5.19 (dd, *J* = 14.8, 6.3 Hz, 1H), 5.07 (d, *J* = 16.5 Hz, 1H), 4.32 (d, *J* = 16.5 Hz, 1H), 3.82 (t, *J* = 15.1 Hz, 1H), 3.40 (dd, *J* = 15.4, 6.4 Hz, 1H), 3.11 (s, 3H), 2.99 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.77, 166.49, 166.42, 140.37, 139.35, 134.33, 132.10, 128.47, 123.71, 123.37, 120.96, 115.83, 48.86, 46.19, 36.68, 36.07, 29.33, 21.40; HRMS Calcd for $C_{22}H_{21}N_3O_4$ [M+H$^+$]: 470.0715; Found: 470.0707.



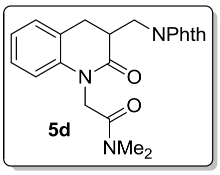
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H), 7.46 – 7.41 (m, 1H), 7.33 – 7.27 (m, 4H), 7.21 – 7.15 (m, 2H), 7.10 (d, *J* = 8.4 Hz, 1H), 5.25 (d, *J* = 16.4 Hz, 1H), 4.99 (d, *J* = 16.4 Hz, 1H), 4.55 – 4.49 (m, 1H), 3.14 (s, 3H), 2.98 (s, 3H), 1.61 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.59, 161.94, 144.80, 138.86, 137.36, 135.15, 129.81, 128.72, 128.48, 127.87, 126.33, 122.20, 120.71, 114.08, 44.36, 39.19, 36.57, 35.99, 20.49; HRMS Calcd for $C_{21}H_{23}N_2O_2$ [M+H$^+$]: 335.1760; Found: 335.1755.



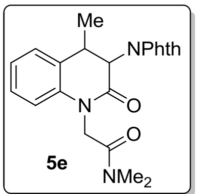
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.0 Hz, 2H), 7.27 (d, *J* = 9.2 Hz, 2H), 7.20 – 7.18 (m, 1H), 7.17 – 7.15 (m, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 5.24 (d, *J* = 16.4 Hz, 1H), 4.96 (d, *J* = 16.4 Hz, 1H), 4.25 (dd, *J* = 9.1, 6.2 Hz, 1H), 3.11 (s, 3H), 2.97 (s, 3H), 2.13 – 2.06 (m, 1H), 2.02 – 1.94 (m, 1H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.56, 162.08, 143.16, 138.79, 136.37, 134.99, 129.76, 128.70, 128.47, 128.39, 126.33, 122.17, 120.73, 114.07, 46.67, 44.42, 36.53, 35.96, 27.52, 12.75; HRMS Calcd for $C_{22}H_{25}N_2O_2$ [M+H$^+$]: 349.1916; Found: 349.1921.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 4H), 7.35 – 7.29 (m, 2H), 7.15 – 7.11 (m, 4H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.86 (t, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 5.23 (d, *J* = 16.4 Hz, 1H), 4.47 (d, *J* = 16.4 Hz, 1H), 4.31 (d, *J* = 15.7 Hz, 1H), 3.80 (d, *J* = 13.8 Hz, 1H), 3.50 (d, *J* = 13.8 Hz, 1H), 3.21 (d, *J* = 15.6 Hz, 1H), 3.08 (s, 3H), 2.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.08, 167.86, 166.99, 139.36, 136.09, 134.03, 131.16, 131.12, 129.02, 128.12, 127.73, 126.92, 124.81, 123.35, 123.05, 114.64, 62.25, 45.30, 39.74, 36.54, 35.94, 35.15; HRMS Calcd for $C_{22}H_{26}N_3O_4$ [M+H$^+$]: 468.1923; Found: 468.1931.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.82 (m, 2H), 7.74 – 7.68 (m, 2H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.1 Hz, 1H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 4.98 (d, *J* = 16.5 Hz, 1H), 4.44 (d, *J* = 16.5 Hz, 1H), 4.29 (dd, *J* = 14.0, 5.8 Hz, 1H), 3.87 (dd, *J* = 14.1, 9.0 Hz, 1H), 3.25 – 3.16 (m, 1H), 3.11 (s, 3H), 2.97 (s, 3H), 2.88 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.49, 168.39, 166.76, 139.59, 134.11, 132.12, 128.27, 127.81, 124.83, 123.46, 123.23, 114.96, 44.68, 39.30, 38.27, 36.51, 35.95, 29.41; HRMS Calcd for $C_{22}H_{22}N_3O_4$ [M+H$^+$]: 392.1610; Found: 392.1617.

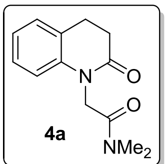


5e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.93 (m, 2H), 7.81 – 7.79 (m, 2H), 7.39 – 7.33 (m, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 6.99 – 6.96 (m, 1H), 5.13 (d, *J* = 16.4 Hz, 1H), 4.91 (d, *J* = 14.0 Hz, 1H), 4.49 (d, *J* = 16.4 Hz, 1H), 4.17 – 4.09 (m, 1H), 3.16 (s, 3H), 3.03 (s, 3H), 1.42 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.12, 166.67, 166.55, 138.87, 134.30, 132.08, 128.68, 128.25, 125.41, 124.08, 123.71, 115.60, 55.39, 45.97, 36.68, 36.05, 31.75, 14.32; HRMS Calcd for $C_{22}H_{22}N_3O_4$ [M+H$^+$]: 392.1610; Found: 392.1616.

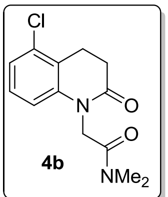
12. Palladium-catalyzed Intramolecularδ-C(sp^2)–H amination

A mixture of derivatives **2** (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.05 equiv), $PhI(OAc)_2$ (128.8 mg, 2.0 equiv) and HFIP (5 mL) in a 25 mL glass vial (purged with Ar, sealed with PTFE cap) was heated at 70 ^{o}C for 18 hours. The reaction mixture was cooled to rt,and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give the cyclized product.



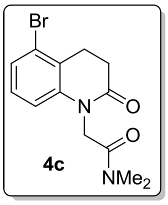
4a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.13 (m, 2H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 4.69 (s, 2H), 3.12 (s, 3H), 2.98 (s, 3H), 2.96 – 2.91 (m, 2H), 2.73 – 2.68 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.98, 166.91, 140.12, 127.85, 127.52, 126.36, 123.01, 114.93, 44.58, 36.51, 35.94, 31.59, 25.49; HRMS Calcd for $C_{13}H_{17}N_2O_2$ [M+H$^+$]: 233.1290; Found: 233.1284.

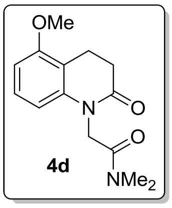


4b

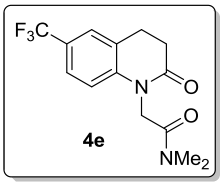
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 6.9 Hz, 1H), 6.67 (d, *J* = 7.1 Hz, 1H), 4.69 (s, 2H), 3.12 (s, 3H), 3.11 – 3.06 (m, 2H), 2.99 (s, 3H), 2.76 – 2.69 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.53, 166.67, 141.70, 133.23, 128.07, 124.61, 124.04, 113.70, 44.89, 36.56, 36.01, 30.79, 22.40; HRMS Calcd for $C_{13}H_{16}ClN_2O_2$ [M+H$^+$]: 267.0900; Found: 267.0907.



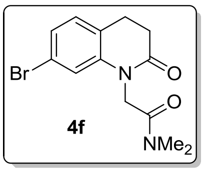
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.1 Hz, 1H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 4.67 (s, 2H), 3.11 (s, 3H), 3.09 – 3.03 (m, 2H), 2.97 (s, 3H), 2.74 – 2.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.51, 166.60, 141.54, 128.37, 127.16, 126.32, 123.57, 114.36, 44.85, 36.50, 35.94, 30.85, 25.32; HRMS Calcd for $C_{13}H_{16}BrN_2O_2$ [M+H$^+$]: 311.0395; Found: 311.0405.



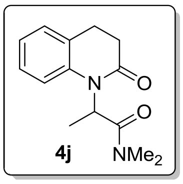
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 8.3 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 6.41 (d, *J* = 8.2 Hz, 1H), 4.70 (s, 2H), 3.83 (s, 3H), 3.12 (s, 3H), 2.98 (s, 3H), 2.96 – 2.91 (m, 2H), 2.70 – 2.64 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.07, 167.10, 156.47, 141.28, 127.79, 114.61, 108.00, 105.81, 55.78, 44.79, 36.54, 35.99, 31.07, 18.05; HRMS Calcd for $C_{14}H_{19}N_2O_3$ [M+H$^+$]: 263.1396; Found: 263.1388.



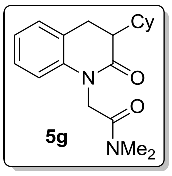
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 10.6 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 4.72 (s, 2H), 3.14 (s, 3H), 3.03 – 2.98 (m, 5H), 2.77 – 2.74 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.70, 166.42, 143.12 (d, J_{C-F} = 1.0 Hz), 128.44 (q, J_{C-F} = 54.0 Hz), 126.77, 124.95 (q, J_{C-F} = 4.0 Hz), 124.89 (q, J_{C-F} = 4.0 Hz), 124.03 (q, J_{C-F} = 269.0 Hz), 114.97, 44.50, 36.56, 36.00, 31.17, 25.41; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.03; HRMS Calcd for $C_{14}H_{16}F_3N_2O_2$ [M+H$^+$]: 301.1164; Found: 301.1163.



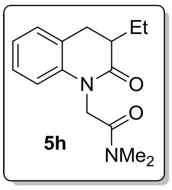
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 1.7 Hz, 1H), 4.65 (s, 2H), 3.13 (s, 3H), 3.00 (s, 3H), 2.91 – 2.87 (m, 2H), 2.72 – 2.68 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.70, 166.37, 141.65, 129.16, 125.84, 125.39, 120.88, 118.10, 44.62, 36.55, 36.00, 31.34, 25.15; HRMS Calcd for $C_{13}H_{16}BrN_2O_2$ [M+H$^+$]: 311.0395; Found: 311.0399.



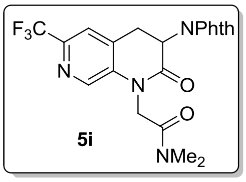
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 5.9 Hz, 1H), 7.20 – 7.14 (m, 2H), 7.00 (t, *J* = 7.4 Hz, 1H), 5.78 – 5.71 (m, 1H), 2.92 – 2.85 (m, 2H), 2.82 (d, *J* = 8.0 Hz, 6H), 2.72 – 2.59 (m, 2H), 1.56 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.72, 170.05, 138.16, 128.17, 127.66, 126.94, 123.53, 116.38, 50.22, 36.92, 36.52, 32.27, 25.66, 15.57; HRMS Calcd for $C_{14}H_{28}N_2O_2Na$ [M+Na$^+$]: 269.1266; Found: 269.1269.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 6.97 (t, *J* = 7.3 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 4.79 (d, *J* = 16.4 Hz, 1H), 4.57 (d, *J* = 16.4 Hz, 1H), 3.12 (s, 3H), 2.99 (s, 3H), 2.95 – 2.92 (m, 1H), 2.91 – 2.83 (m, 2H), 2.44 (dd, *J* = 12.5, 6.9 Hz, 1H), 1.75 (d, *J* = 11.8 Hz, 2H), 1.65 (dd, *J* = 29.1, 11.1 Hz, 4H), 1.26 – 1.17 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.59, 167.08, 139.89, 128.09, 127.43, 126.00, 122.93, 114.66, 46.47, 44.80, 36.53, 36.03, 35.99, 31.34, 29.66, 27.68, 26.48, 26.41, 26.35; HRMS Calcd for $C_{19}H_{27}N_2O_2$ [M+H$^+$]: 315.2073; Found: 315.2076.

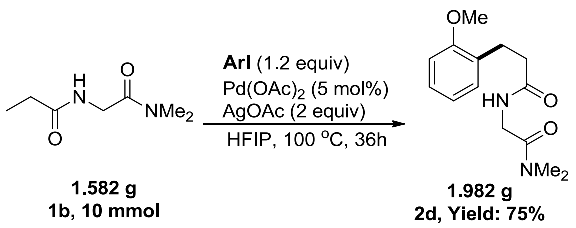


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.14 (m, 2H), 6.98 (t, *J* = 7.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 4.69 (s, 2H), 3.13 (s, 3H), 3.03 (dd, *J* = 15.6, 5.5 Hz, 1H)., 2.99 (s, 3H), 2.75 (dd, *J* = 15.4, 9.0 Hz, 1H), 2.59 – 2.52 (m, 1H), 1.92 – 1.86 (m, 1H), 1.53 – 1.45 (m, 1H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.25, 167.05, 139.87, 128.24, 127.50, 125.66, 122.93, 114.65, 44.72, 42.07, 36.53, 35.99, 30.29, 22.68, 11.62; HRMS Calcd for $C_{15}H_{21}N_2O_2$ [M+H$^+$]: 261.1603; Found: 261.1608.



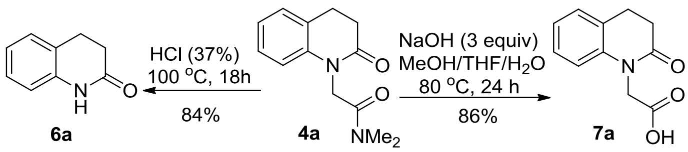
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.90 – 7.88 (m, 2H), 7.78 – 7.76 (m, 2H), 7.54 (s, 1H), 5.28 (dd, *J* = 15.0, 6.3 Hz, 1H), 5.21 (d, *J* = 16.6 Hz, 1H), 4.42 (d, *J* = 16.6 Hz, 1H), 4.17 (t, *J* = 15.2 Hz, 1H), 3.17 – 3.09 (m, 4H), 3.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.56, 166.17, 165.32, 143.29 (q, $J_{C\text{-}F}$ = 33.0 Hz), 138.29 (d, $J_{C\text{-}F}$ = 1.0 Hz), 136.58, 134.57, 133.06, 131.96, 123.91, 122.49 (q, $J_{C\text{-}F}$ = 272.0 Hz), 119.84 (q, $J_{C\text{-}F}$ = 2.0 Hz), 47.86, 45.01, 36.57, 36.08, 29.37; ^{19}F NMR (376 MHz, CDCl$_3$) δ -67.40; HRMS Calcd for $C_{21}H_{19}F_3N_4O_4$ [M+H$^+$]: 447.1280; Found: 447.1288.

13. Gram scale reaction



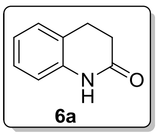
A mixture of **1b** (1.582 g, 10 mmol, 1.0 equiv), Pd(OAc)$_2$ (55.0 mg, 0.025 equiv), AgOAc (3.34 g, 2 equiv) and HFIP (25 mL) in a 100 mL glass vial (purged with Ar, sealed with PTFE cap) was heated at 100 °C for 36 hours. The reaction mixture was cooled to rt, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give **2d** as yellow solid in 75% yield.

14. The removal and transformation of directing group



14.1. The removal of directing group

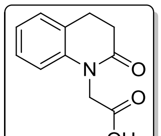
A mixture of the cyclized product **4a** (0.2 mmol, 1.0 equiv) and hydrochloric acid (1 mL) in a 15 mL glass vial (under air atmosphere, sealed with PTFE cap) was heated at 100 °C for 18 hours. The reaction mixture was cooled to rt. Water was added and the mixture was extracted with DCM. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give the product **7a**.



^{1}H NMR (400 MHz, CDCl$_3$) δ 8.54 (br s, 1H), 7.17 (t, *J* = 7.7 Hz, 2H), 7.04 (t, *J* = 7.0 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 2.99 – 2.95 (m, 2H), 2.66 – 2.63 (m, 2H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.98, 137.37, 128.11, 127.67, 123.81, 123.24, 115.53, 30.87, 25.48; HRMS Calcd for C_9H_9NONa [M+Na$^+$]: 170.0582; Found: 170.0581.

14.2. The transformation of directing group

A mixture of the cyclized product **4a** (0.2 mmol, 1.0 equiv) and NaOH (1.0 mmol, 5.0 equiv) were dissolved in MeOH/THF/water/ (1/1/1, 2/15 M) in a 15 mL glass vial (under air atmosphere, sealed with PTFE cap) was heated at 80 °C for 24 hours. The reaction mixture was cooled to rt. HCl was added dropwise until pH =2 and the mixture was extracted with DCM. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give the product **8a**.

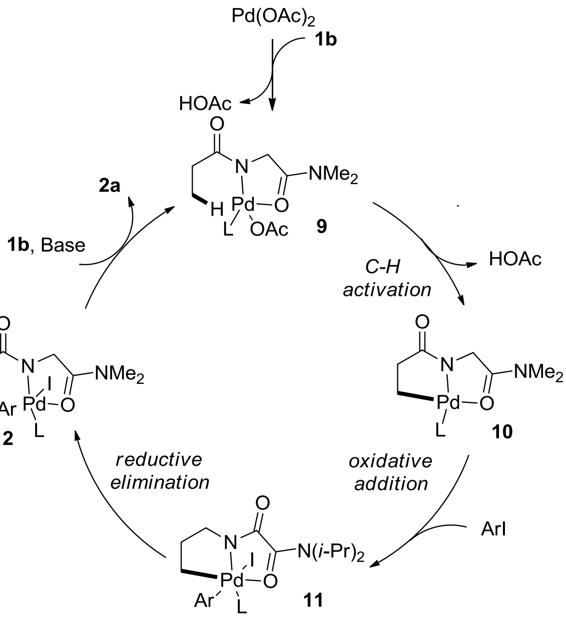


7a

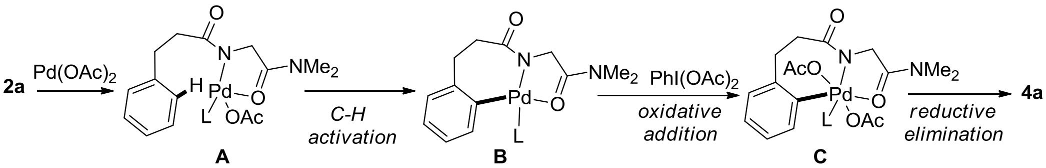
[1]H NMR (400 MHz, DMSO) δ 7.20 (t, *J* = 7.2 Hz, 2H), 6.98 (t, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 4.50 (s, 2H), 2.87 (t, *J* = 7.1 Hz, 2H), 2.59 – 2.51 (m, 2H); [13]C NMR (101 MHz, DMSO) δ 169.56, 139.80, 127.69, 127.21, 125.96, 122.43, 114.85, 44.40, 31.07, 24.69; HRMS Calcd for $C_{11}H_{13}NO_3$ $[M+H^+]$: 206.0817; Found: 206.0815.

15. Proposed reaction mechanism

15.1. Proposed catalytic cycle for Palladium-catalyzed β-C(sp^3)–H arylation[3]



14.2. Proposed reaction mechanism for Palladium-catalyzed intramolecular δ-C(sp^2)–H amination[2]



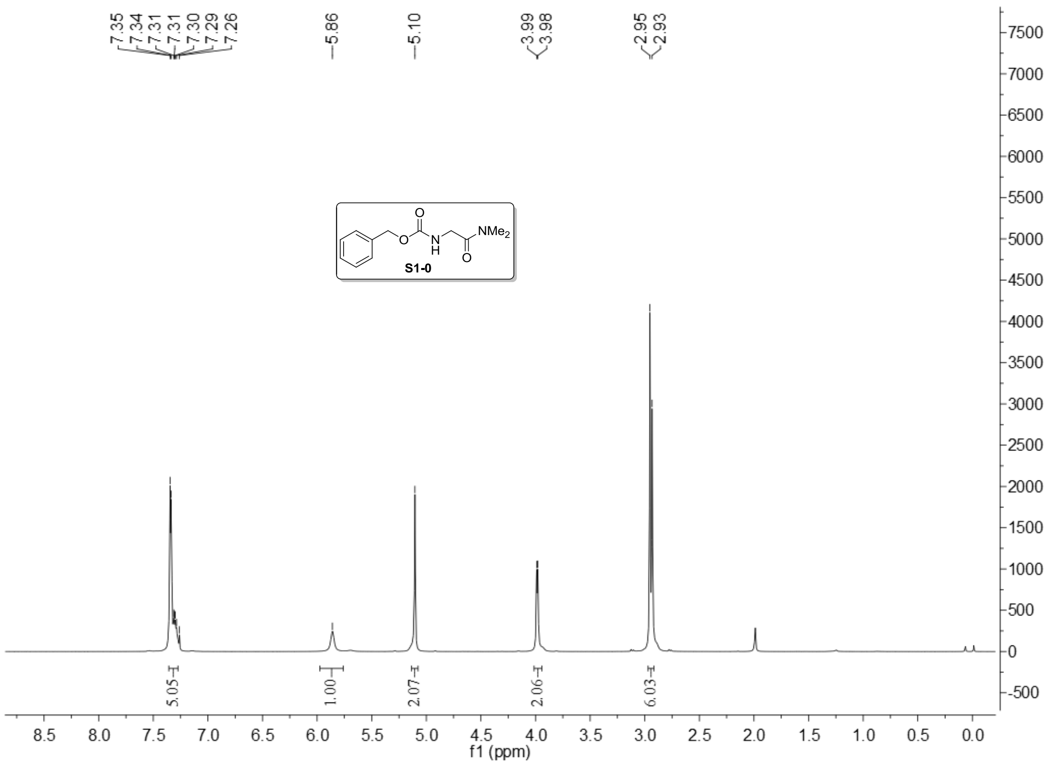
16. References

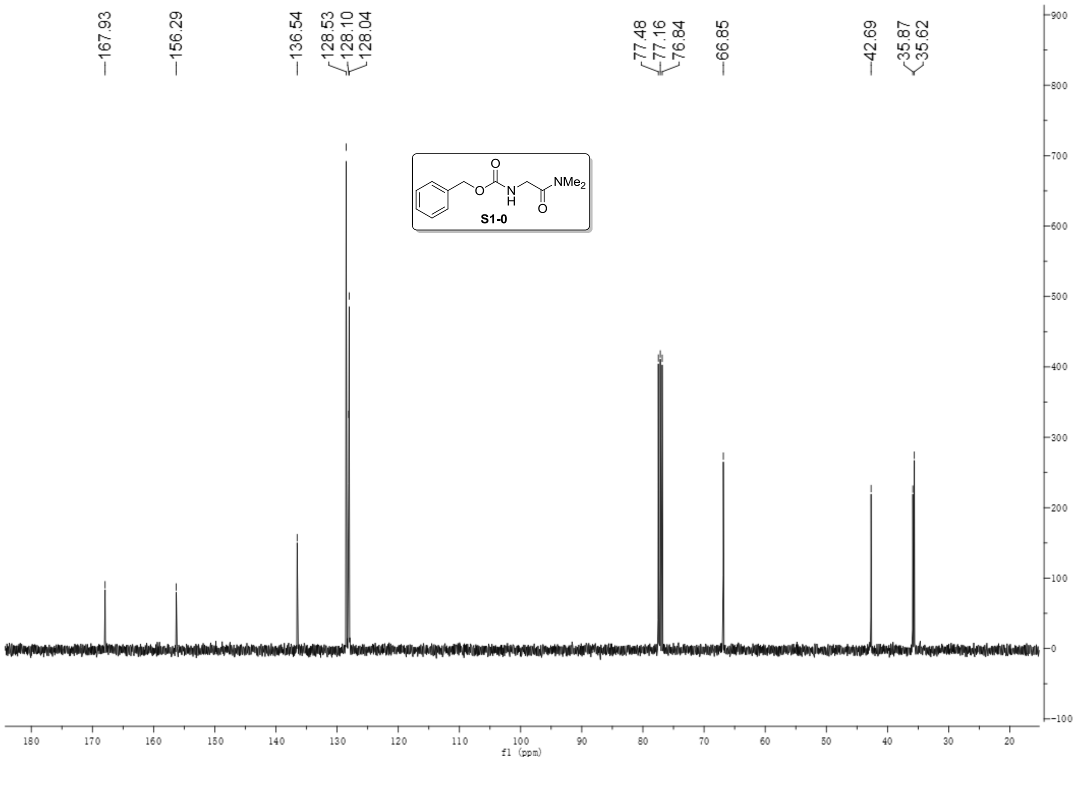
[1] Y. Zhao, G. Chen, *Org. Lett.* **2011**, *13*, 4850.

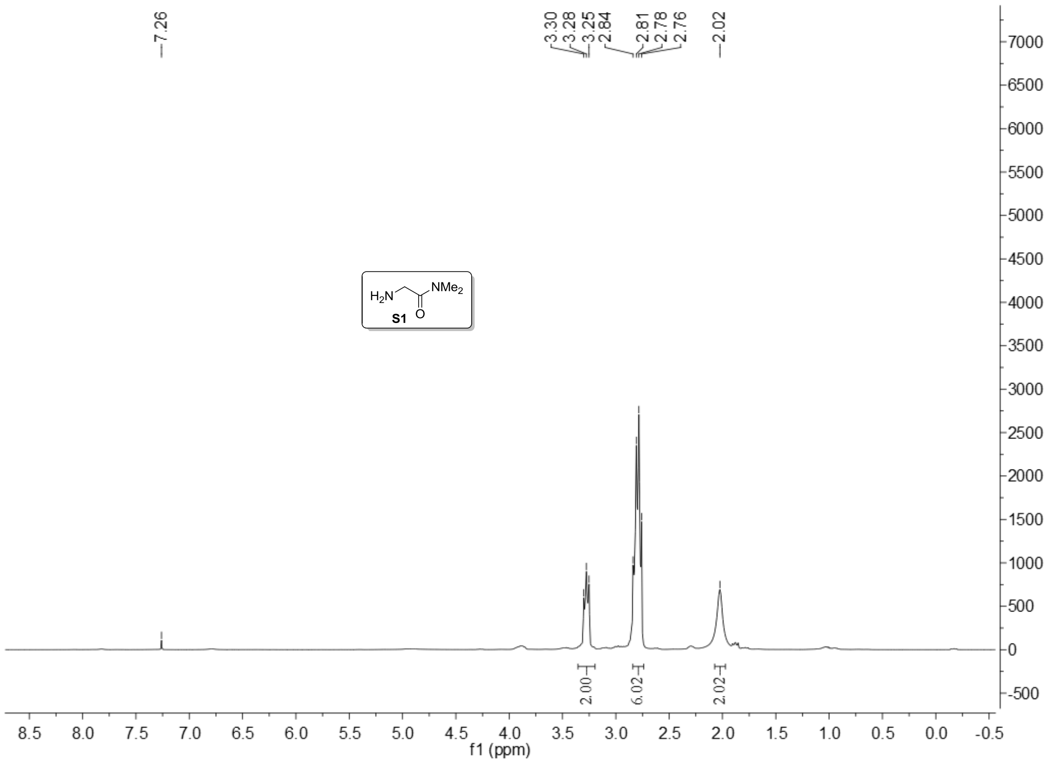
[2] G. He, C.-X. Lu, Y.-S. Zhao, W. A. Nack, G. Chen, *Org. Lett.* **2012**, *14*, 2944.

[3] J. Han, Y.-X. Zheng, C. Wang, Y. Zhu, D.-Q. Shi, R.-S. Zeng, Z.-B. Huang, Y.-S. Zhao, *J. Org. Chem.* **2015**, *80*, 9297.

17. NMR spectra



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3.25
2.84
2.81
2.78
2.76
2.02
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NMe2
O
S1
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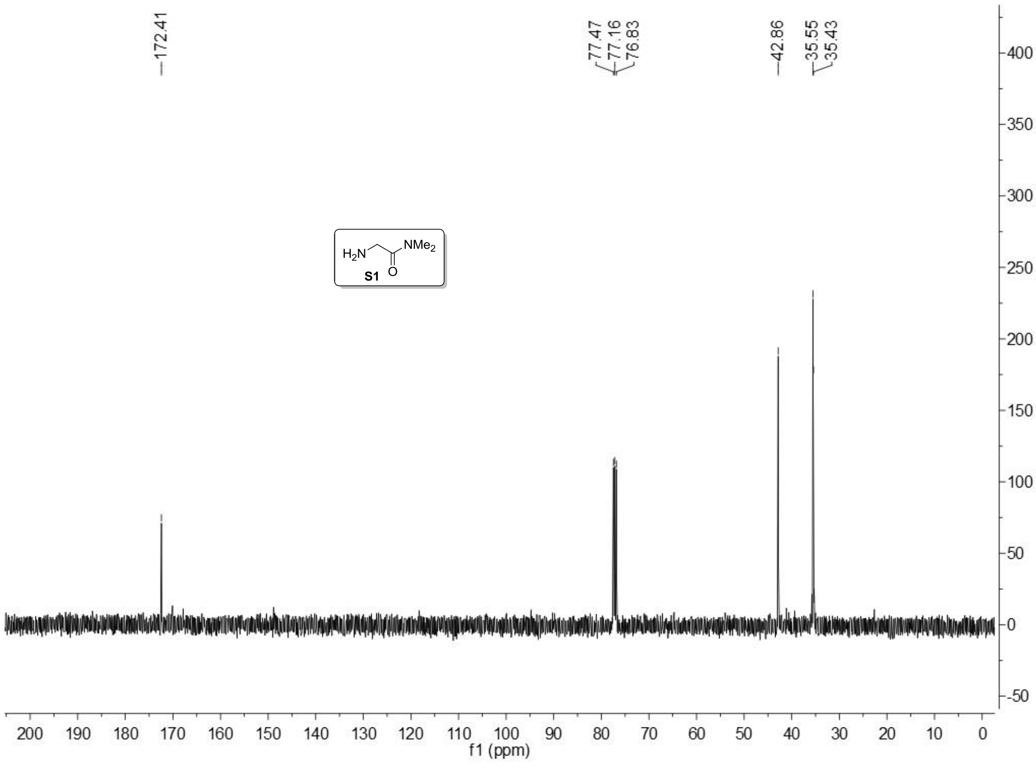
6.02
2.02
f1 (ppm)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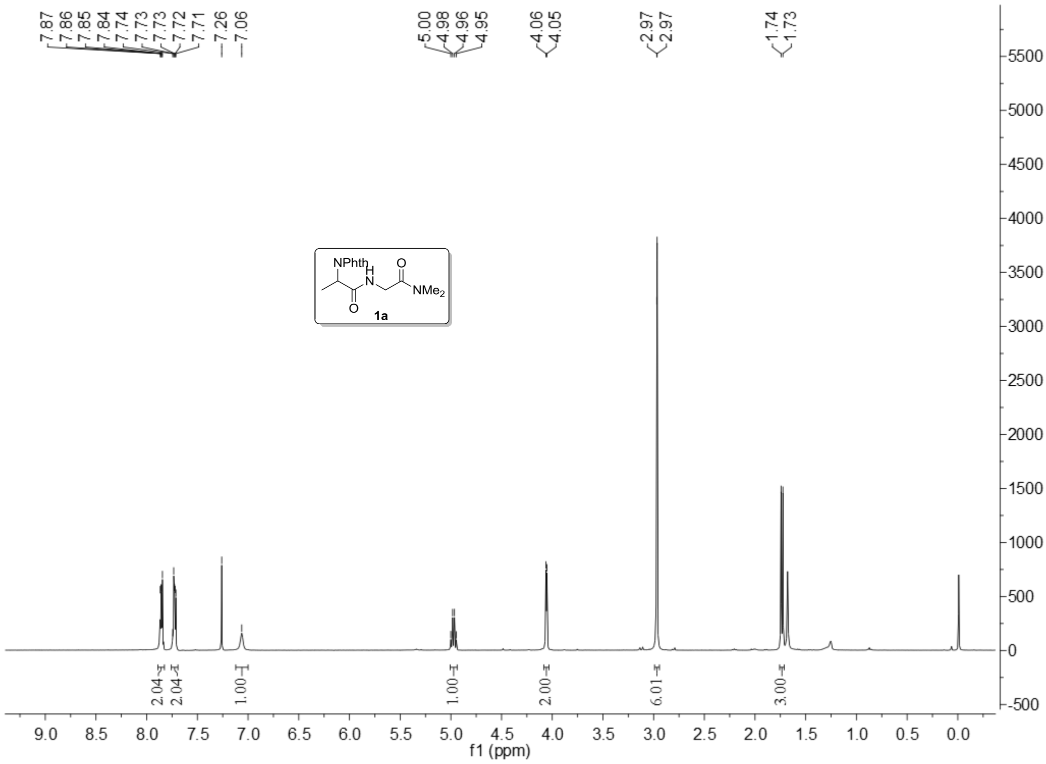
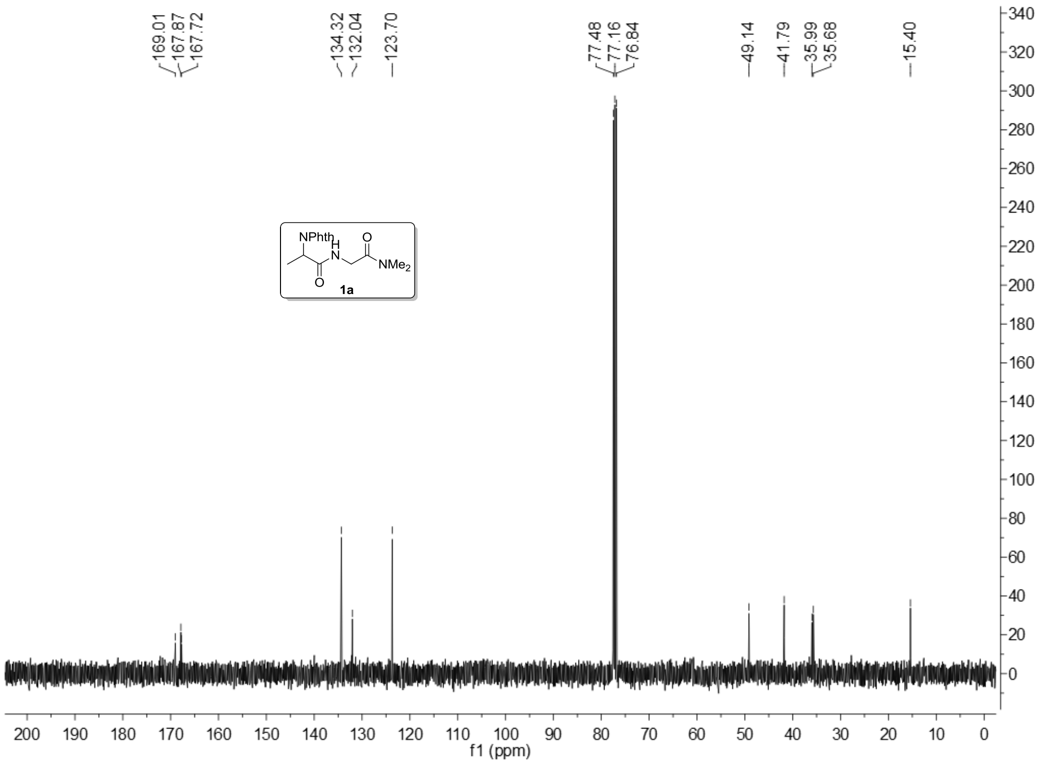
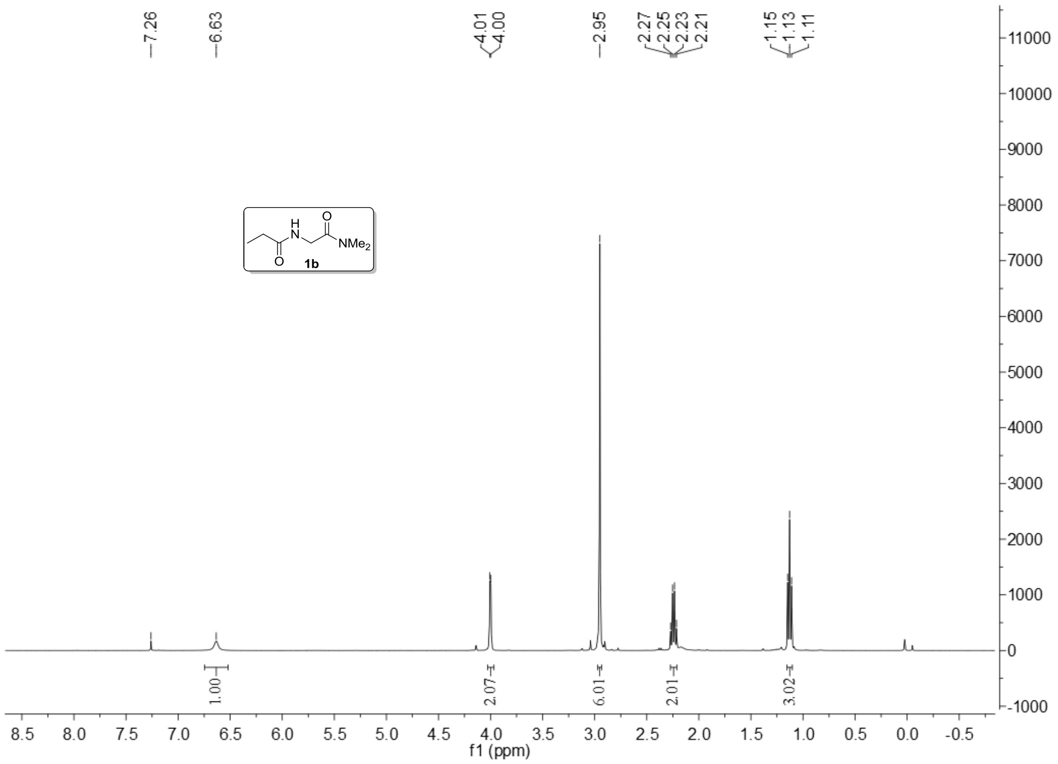
O
S1
f1 (ppm)







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4.00
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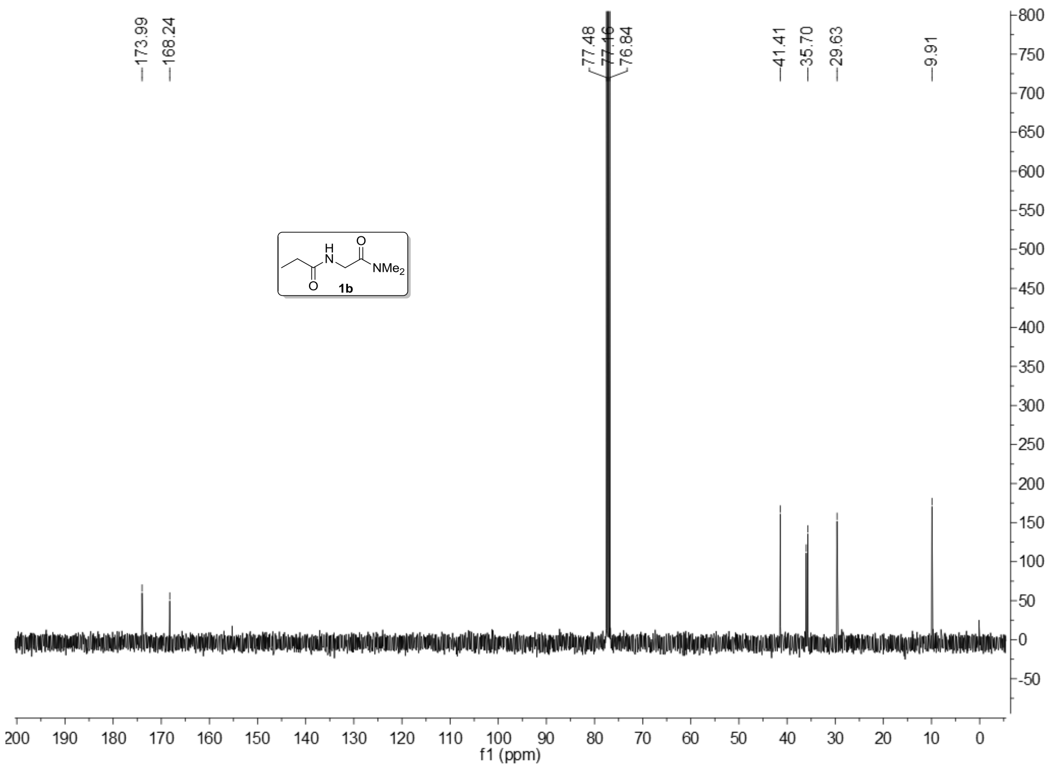
3.02
f1 (ppm)



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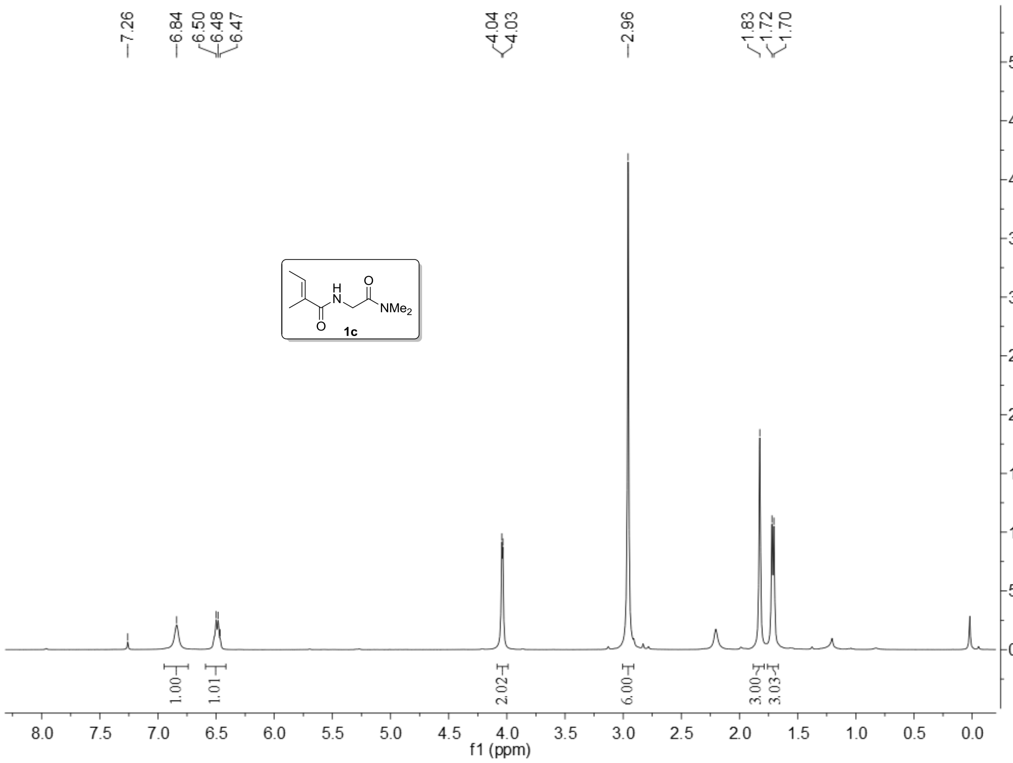
f1 (ppm)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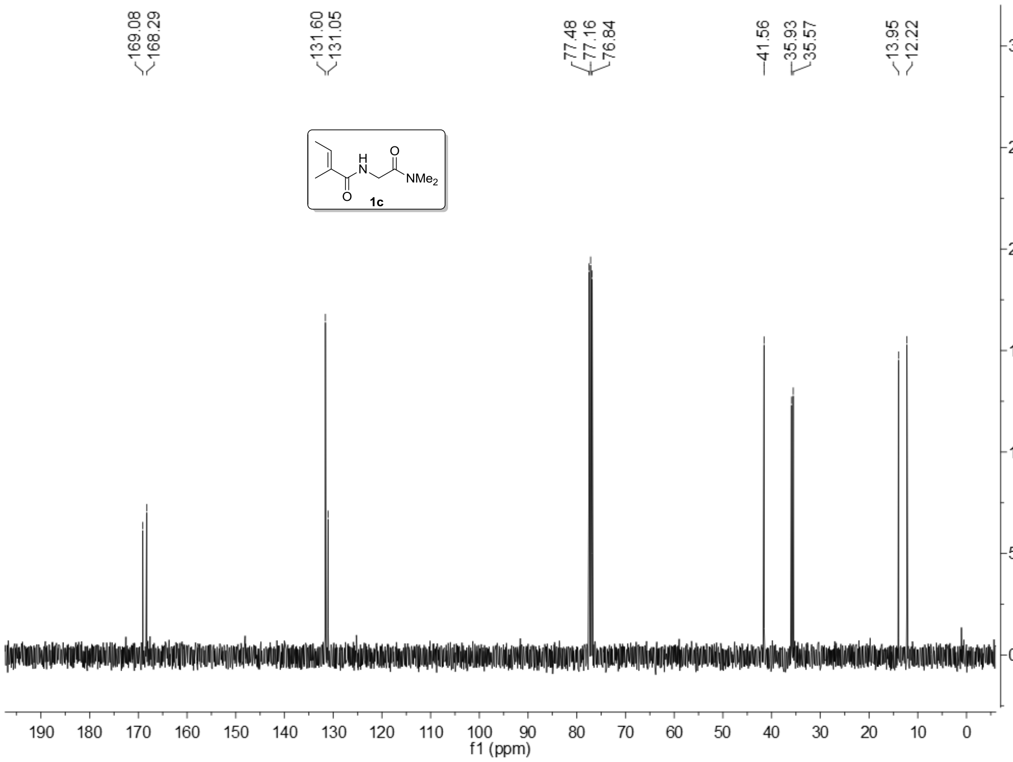
3.03
f1 (ppm)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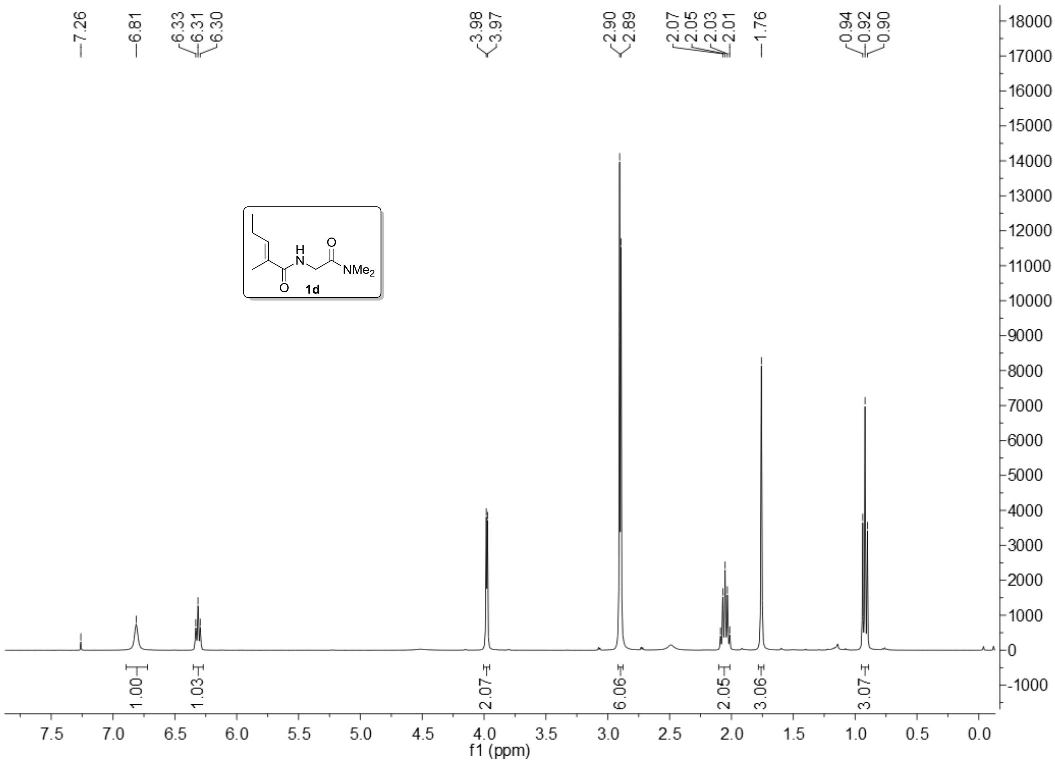

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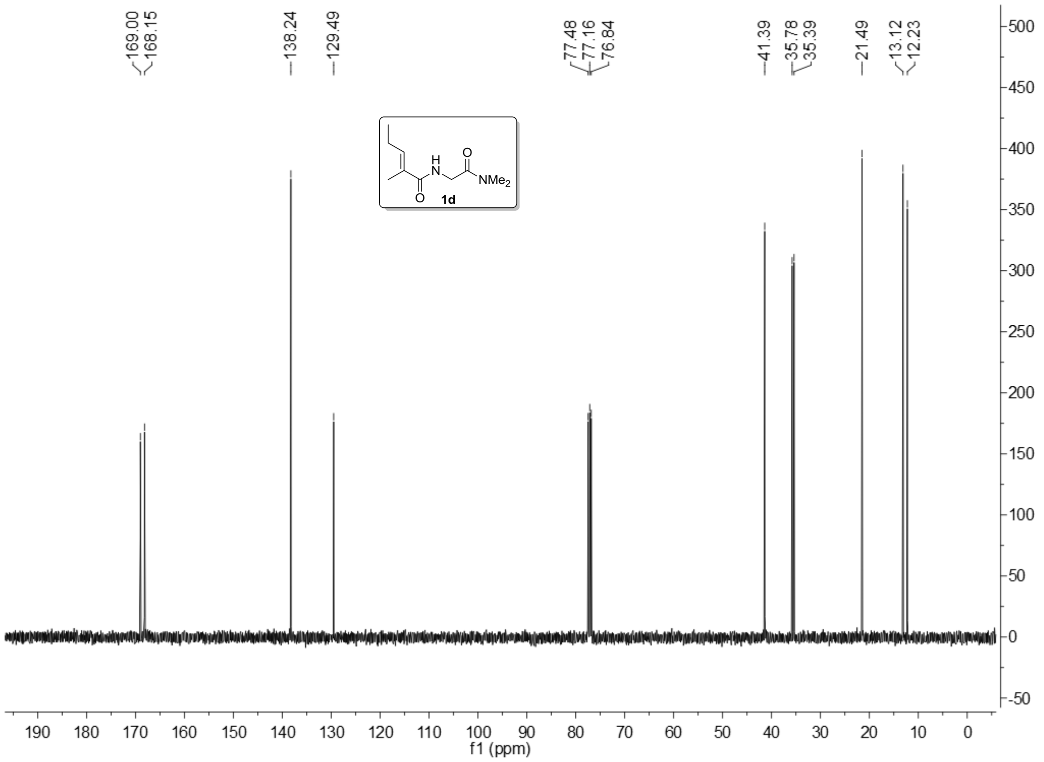

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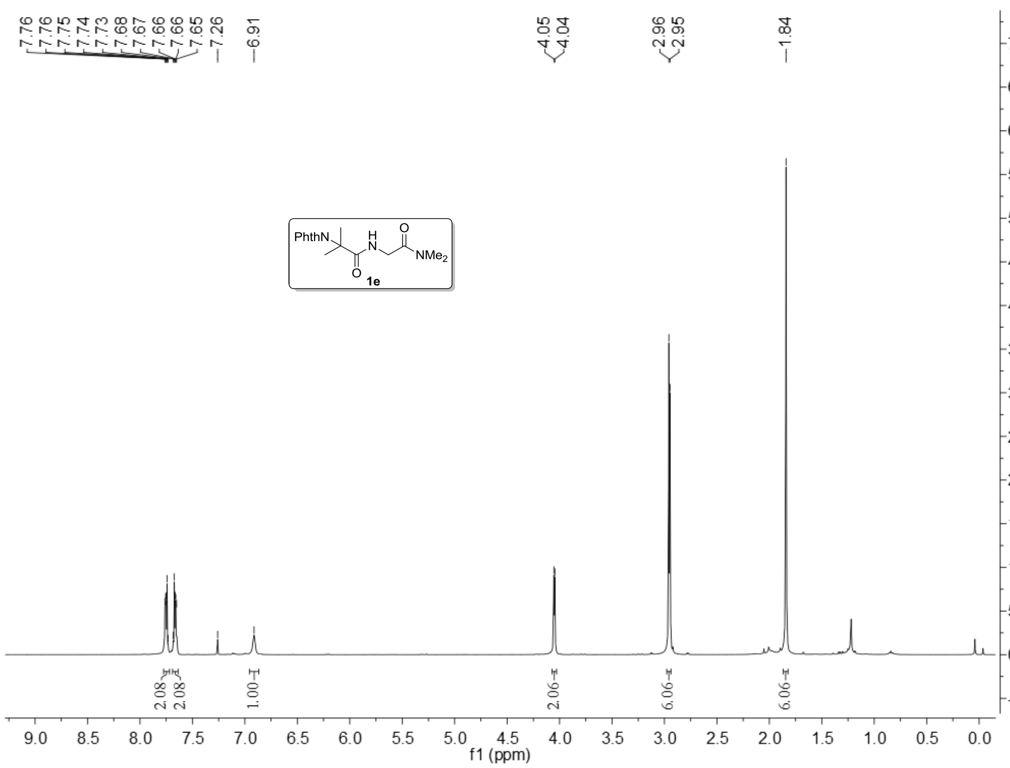
1d
f1 (ppm)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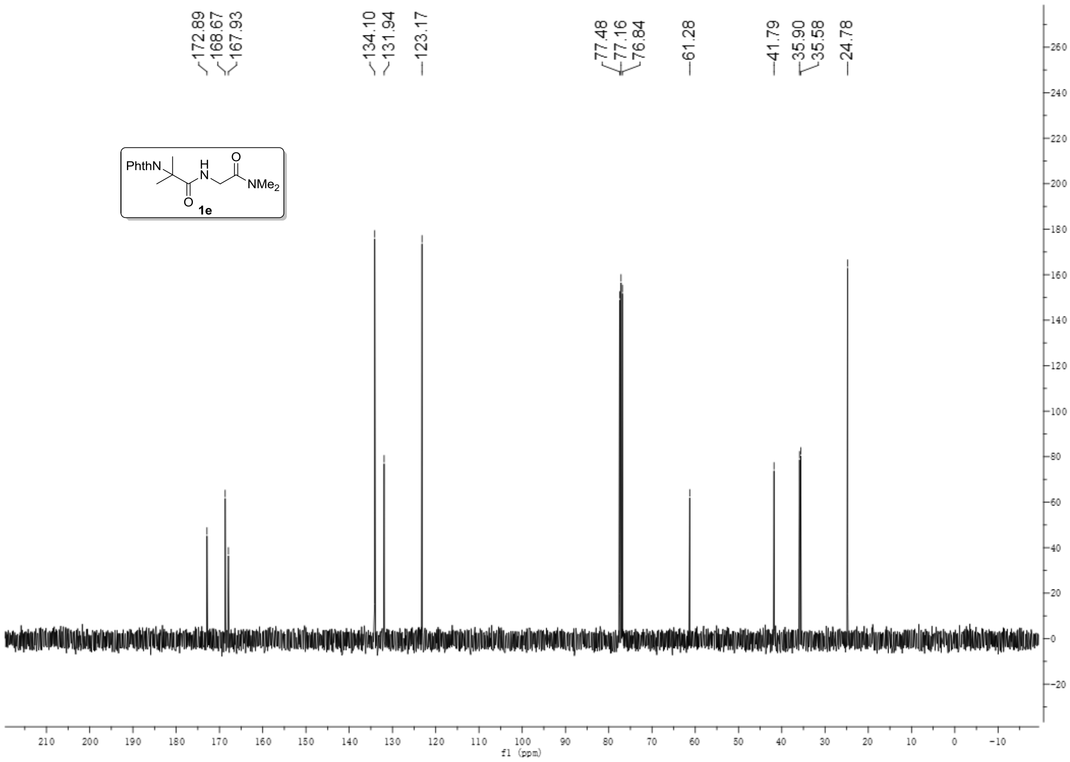
6.06
f1 (ppm)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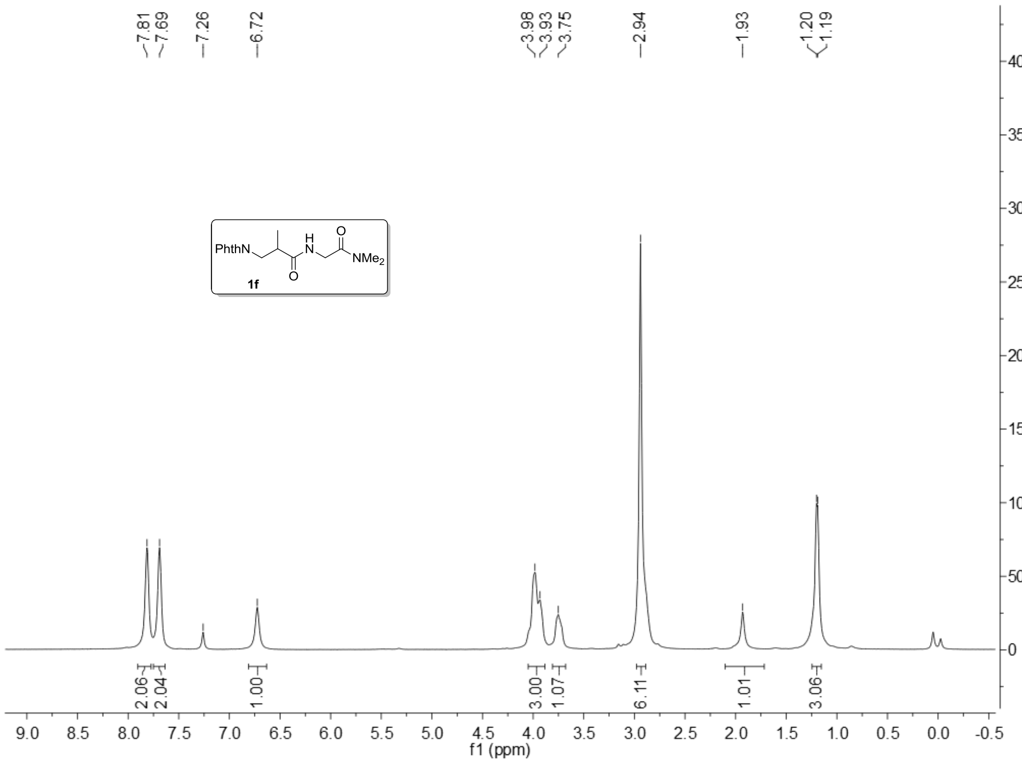
1e
f1 (ppm)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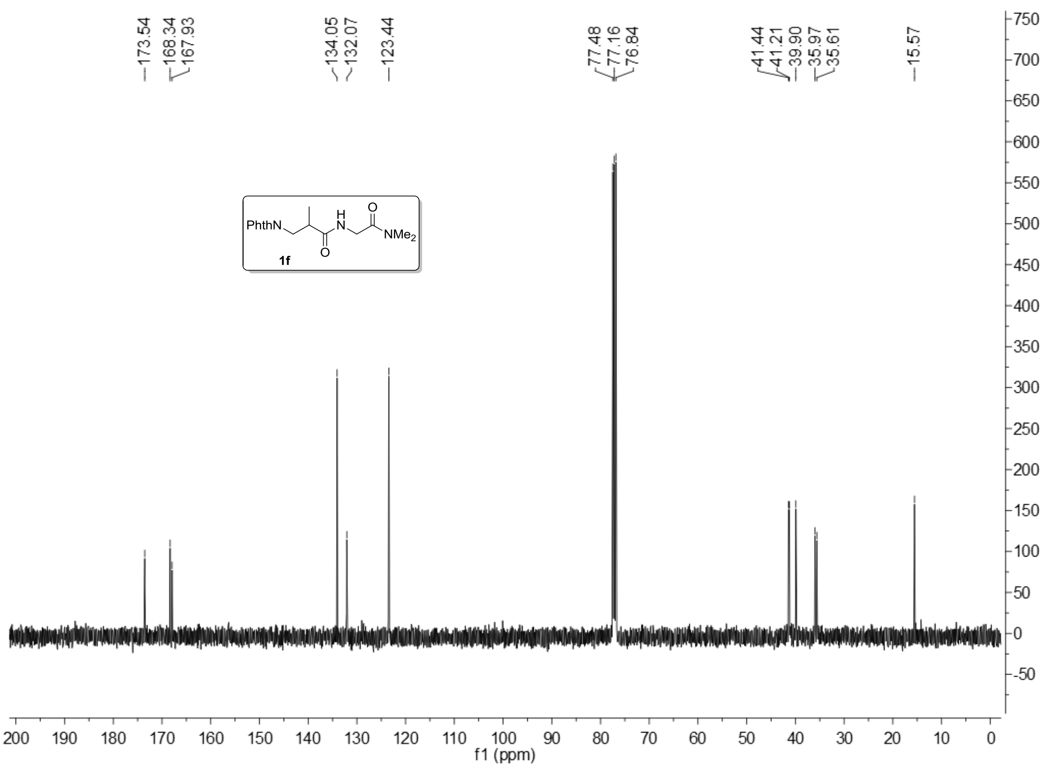
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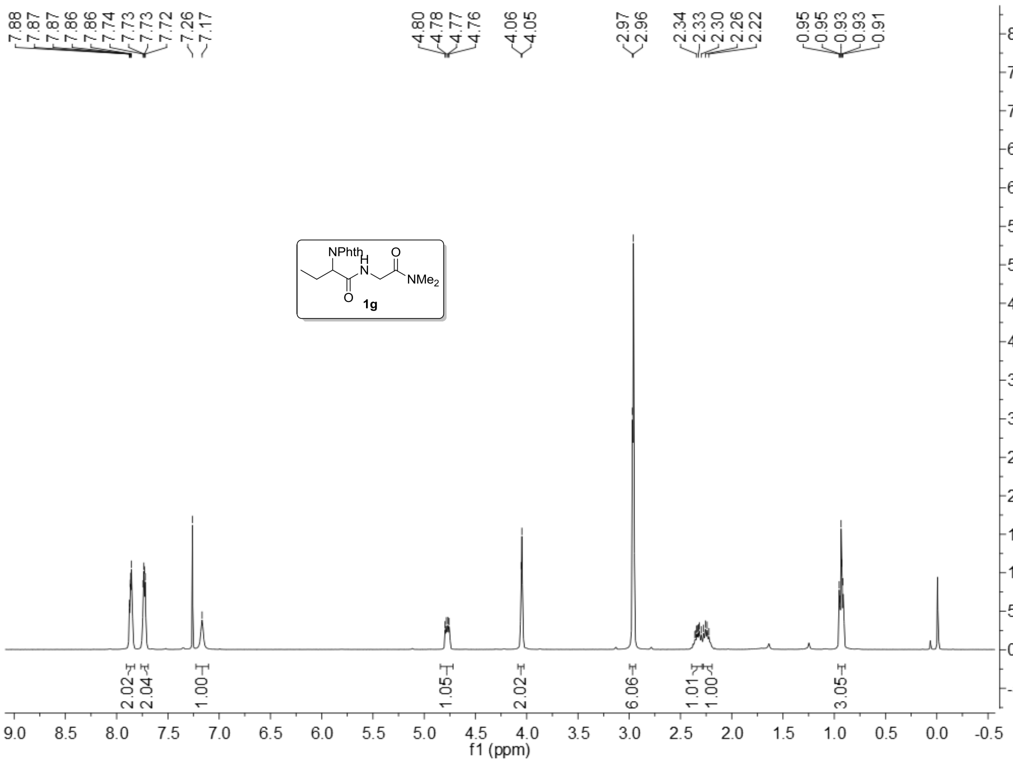
f1 (ppm)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0.91
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NMe2
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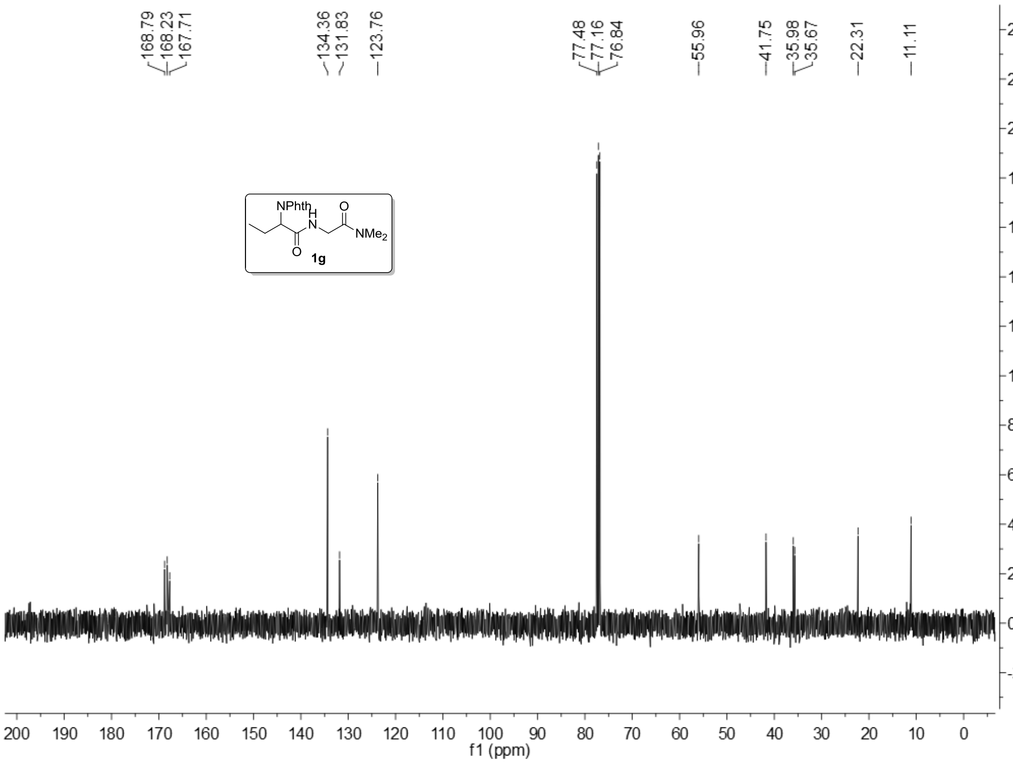
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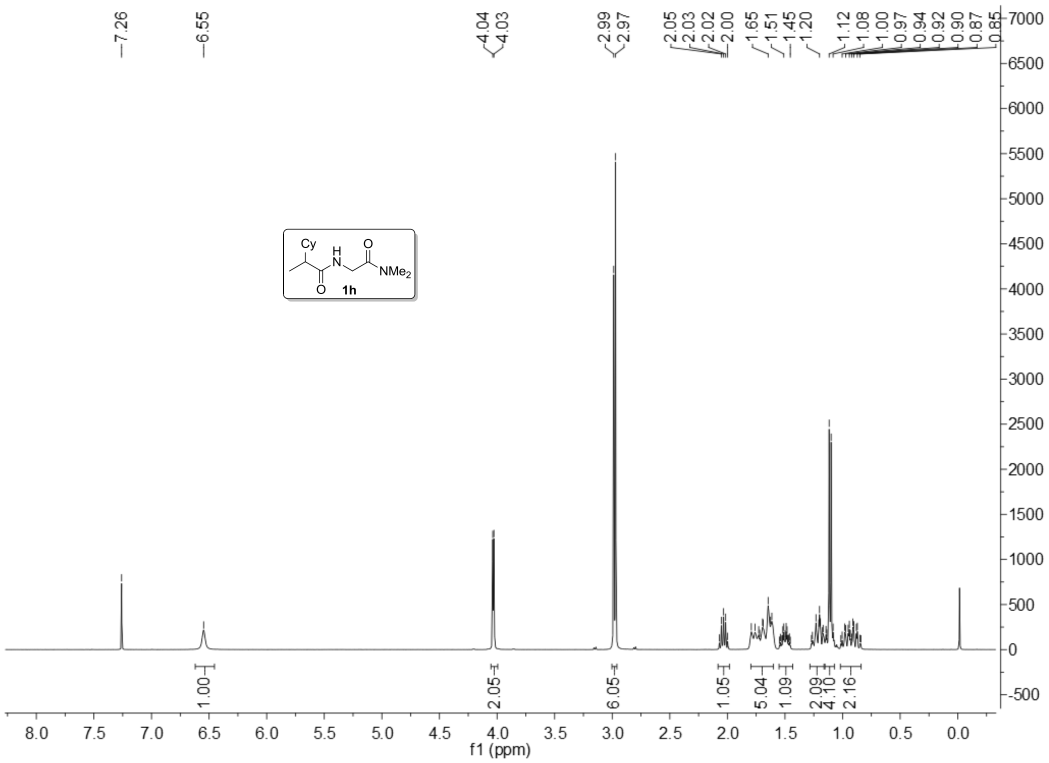
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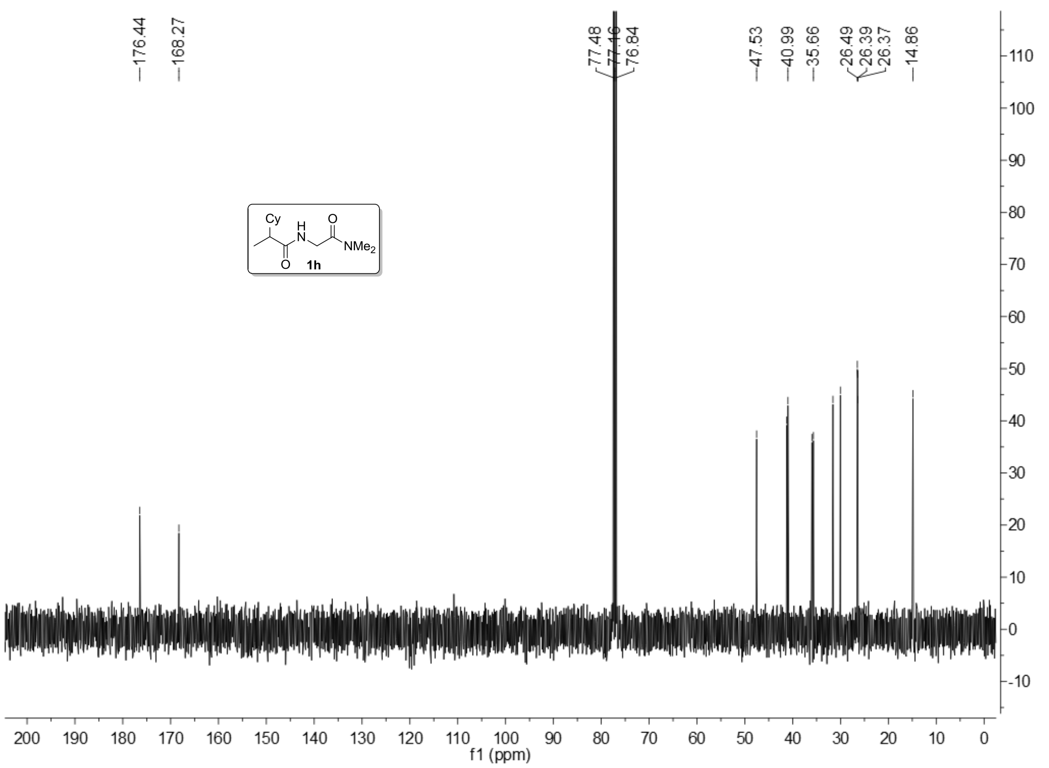
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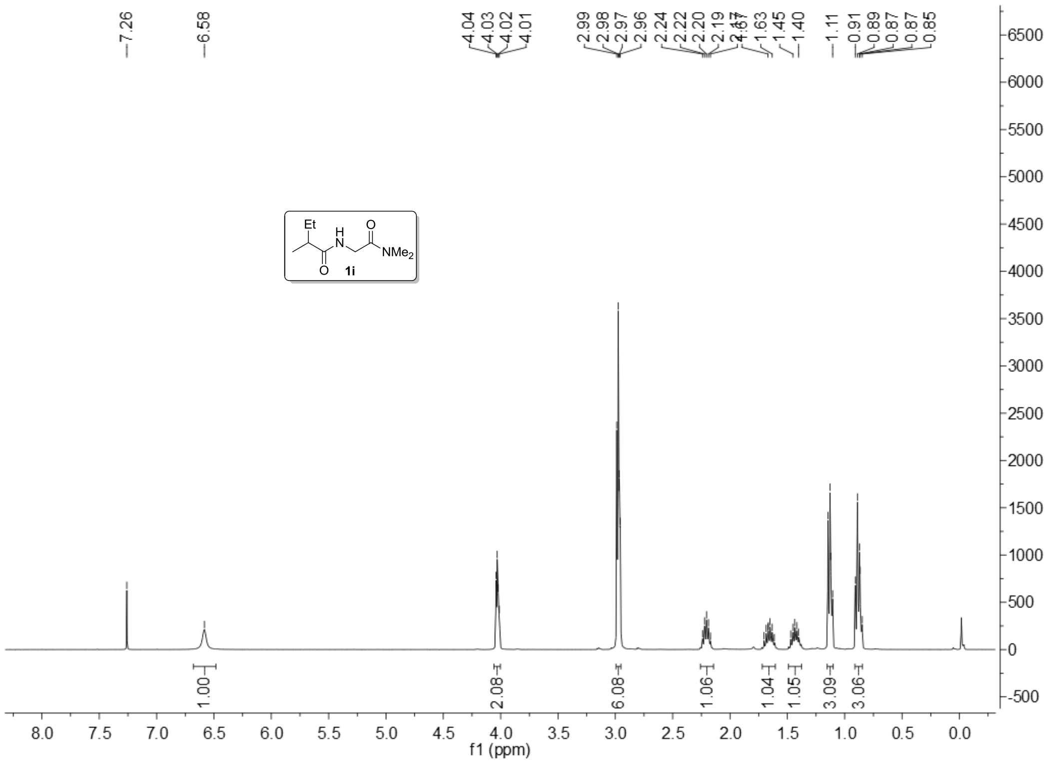
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2.98
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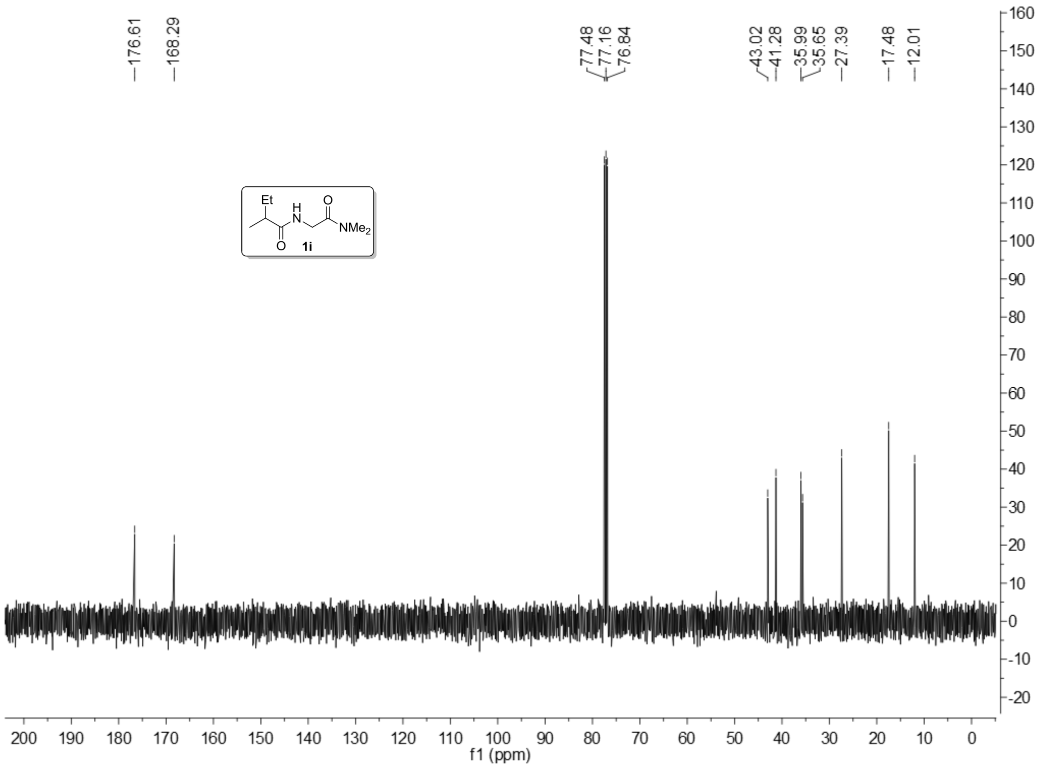
2.96
2.24
2.22
2.20
2.19
1.63
1.45
1.40
1.11
0.91
0.89
0.87
0.87
0.85
Et
H
N
O
NMe2
O
1i
1.00
2.08
6.08
1.06
1.04
1.05
3.09
3.06
f1 (ppm)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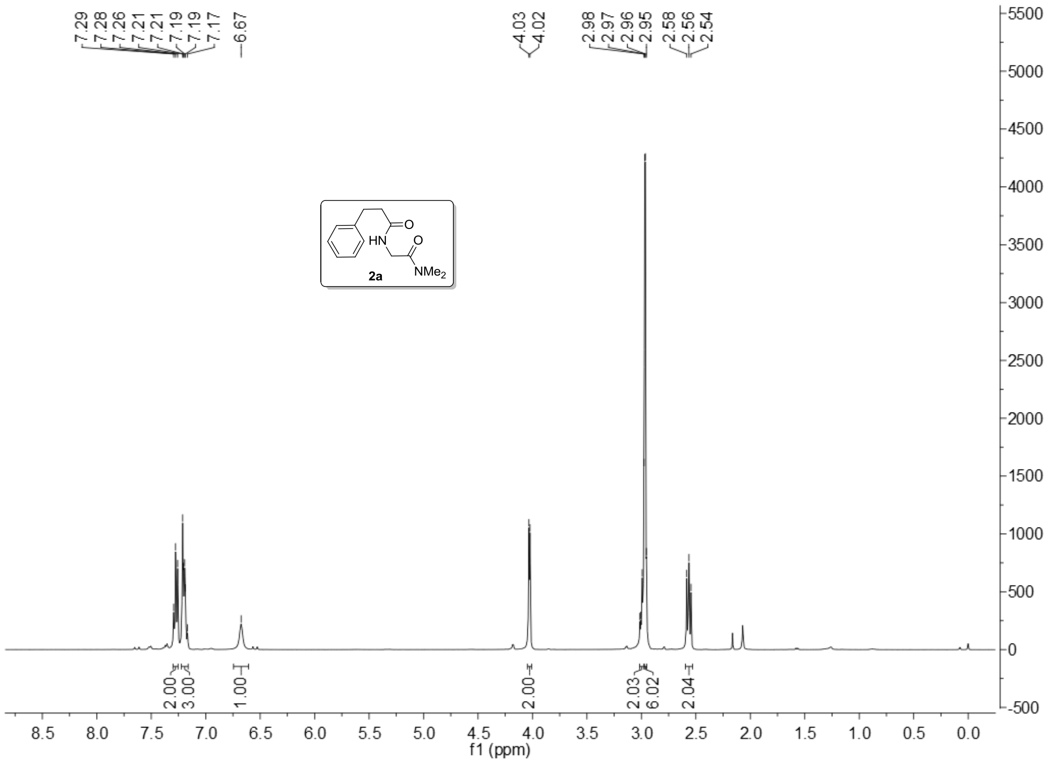
N
O
NMe2
O
1i
f1 (ppm)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7.17
6.67
4.03
4.02
2.98
2.97
2.96
2.95
2.58
2.56
2.54
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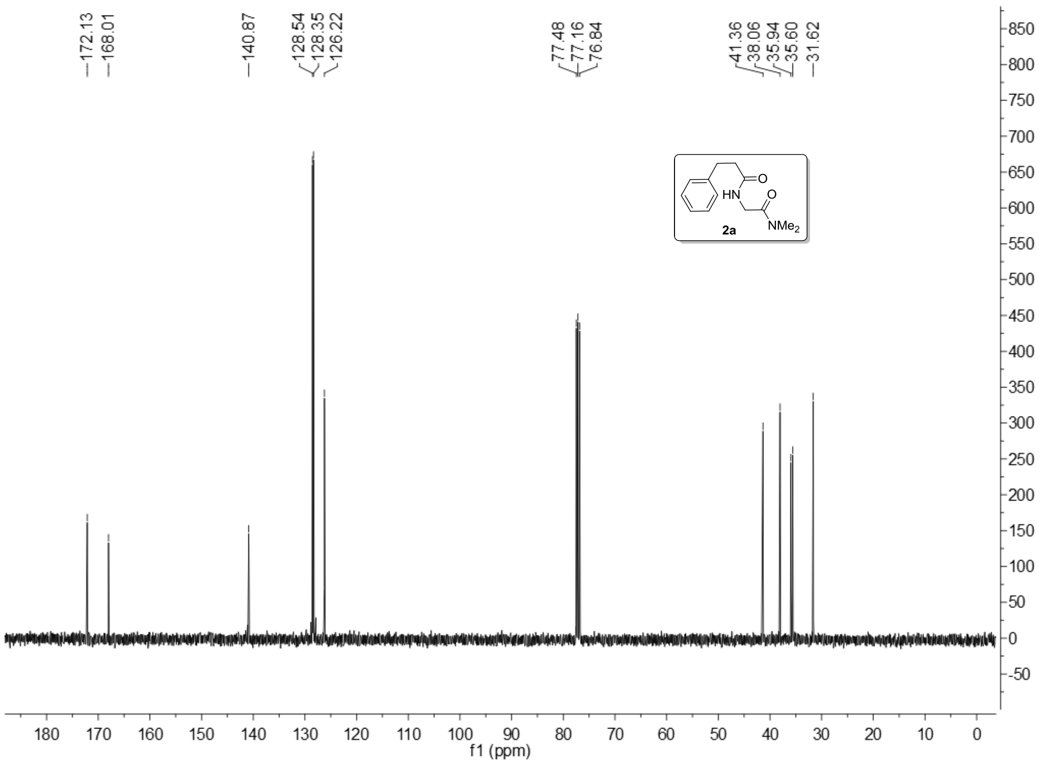
O
O
NMe2
2a
2.00
3.00
1.00
2.00
2.03
6.02
2.04
f1 (ppm)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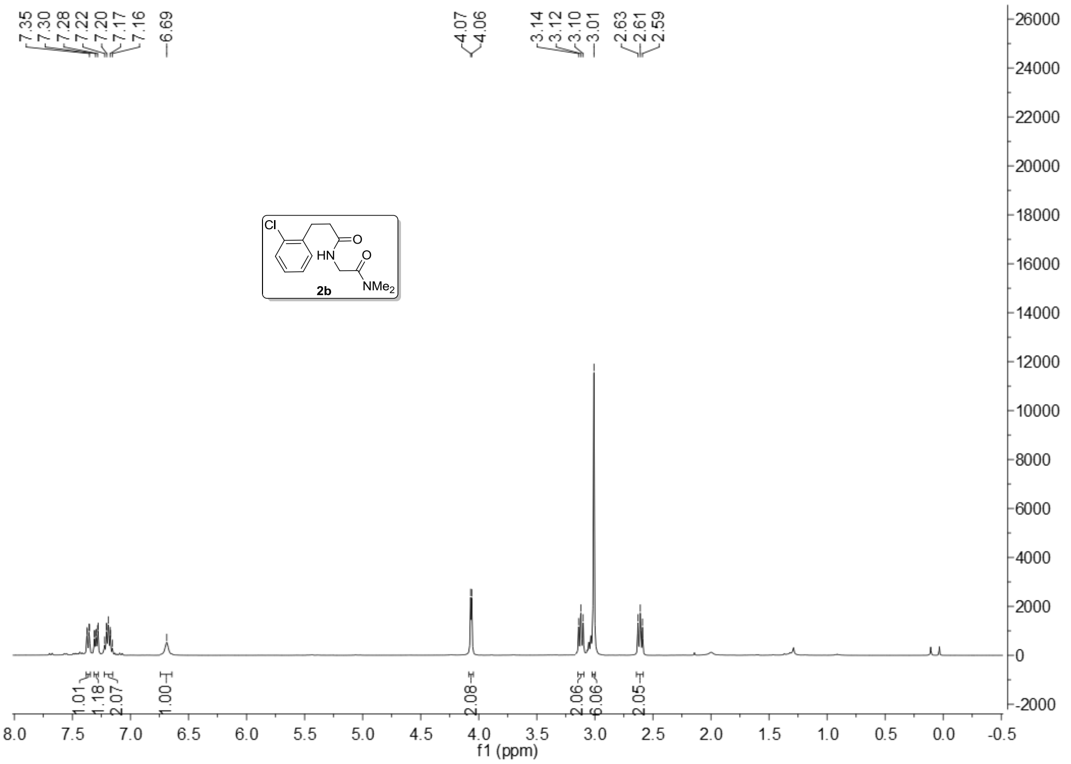
2a
f1 (ppm)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3.10
3.01
2.63
2.61
2.59
Cl
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2.06
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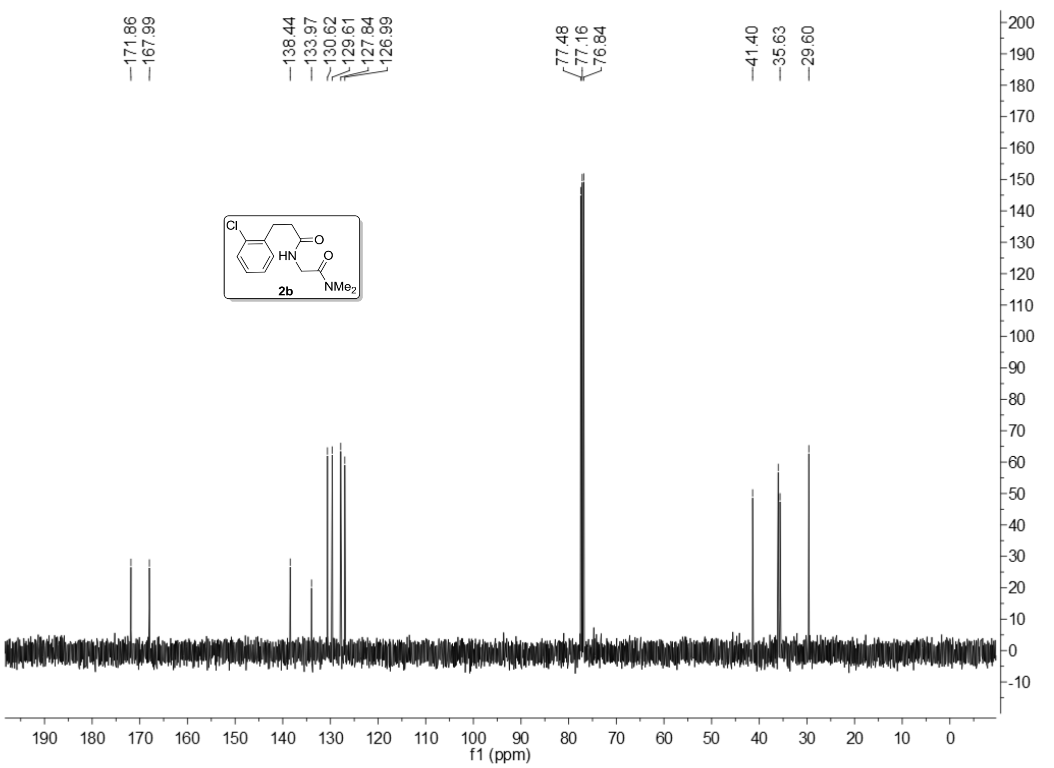
2.05
f1 (ppm)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35.63
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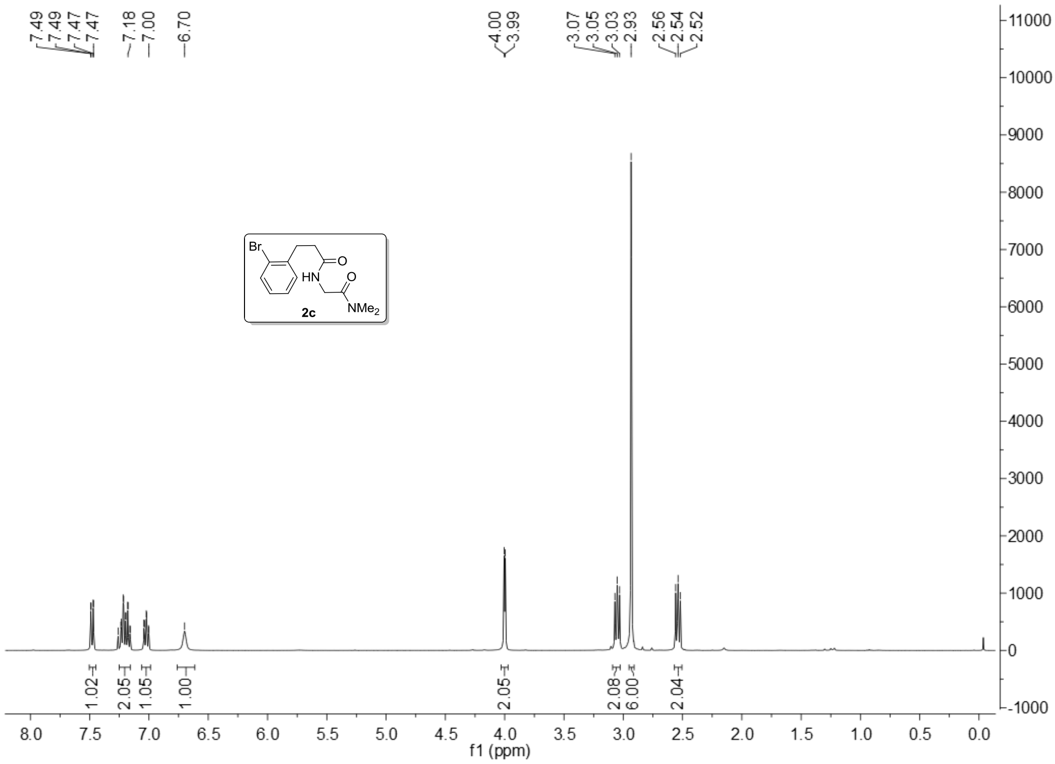
Cl
HN
O
NMe2
2b
f1 (ppm)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4.00
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3.03
2.93
2.56
2.54
2.52
Br
HN
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1.05
1.00
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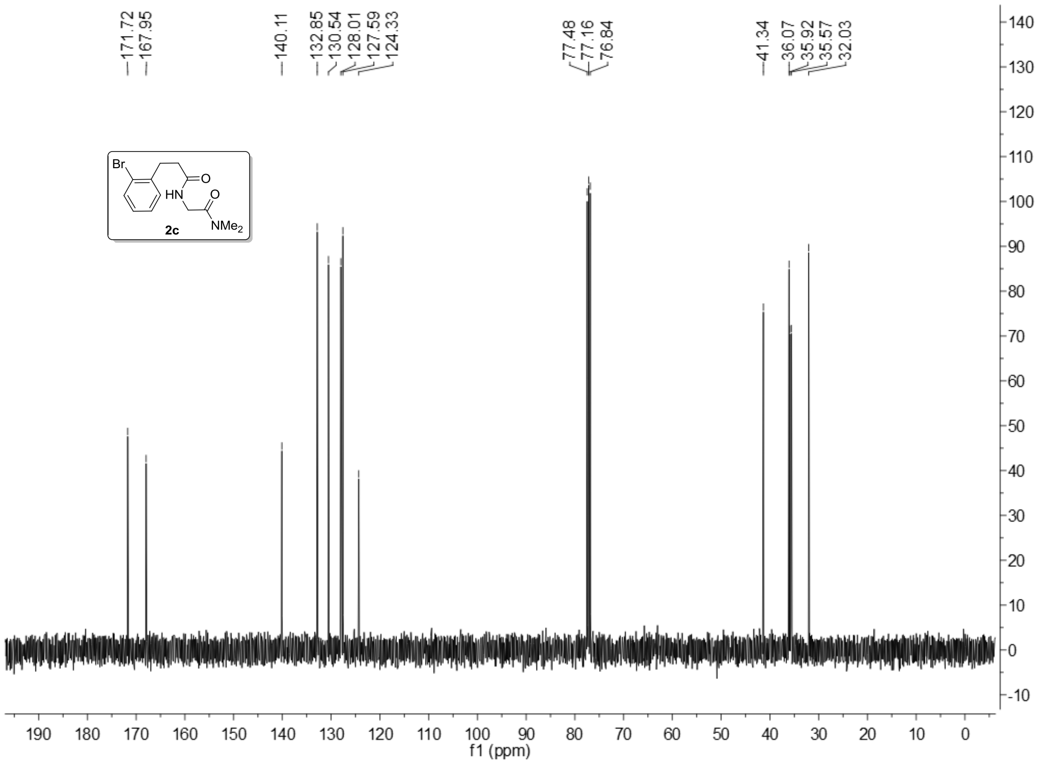
2.04
f1 (ppm)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32.03
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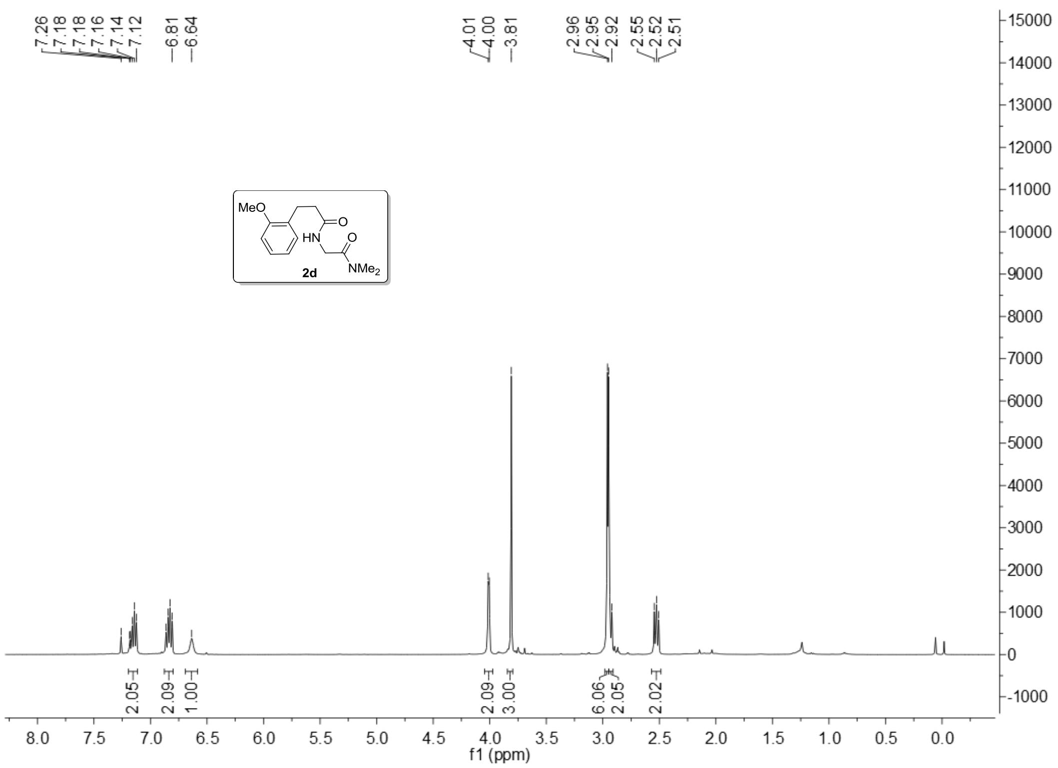
HN
O
O
NMe2
2c
f1 (ppm)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6.64
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4.00
3.81
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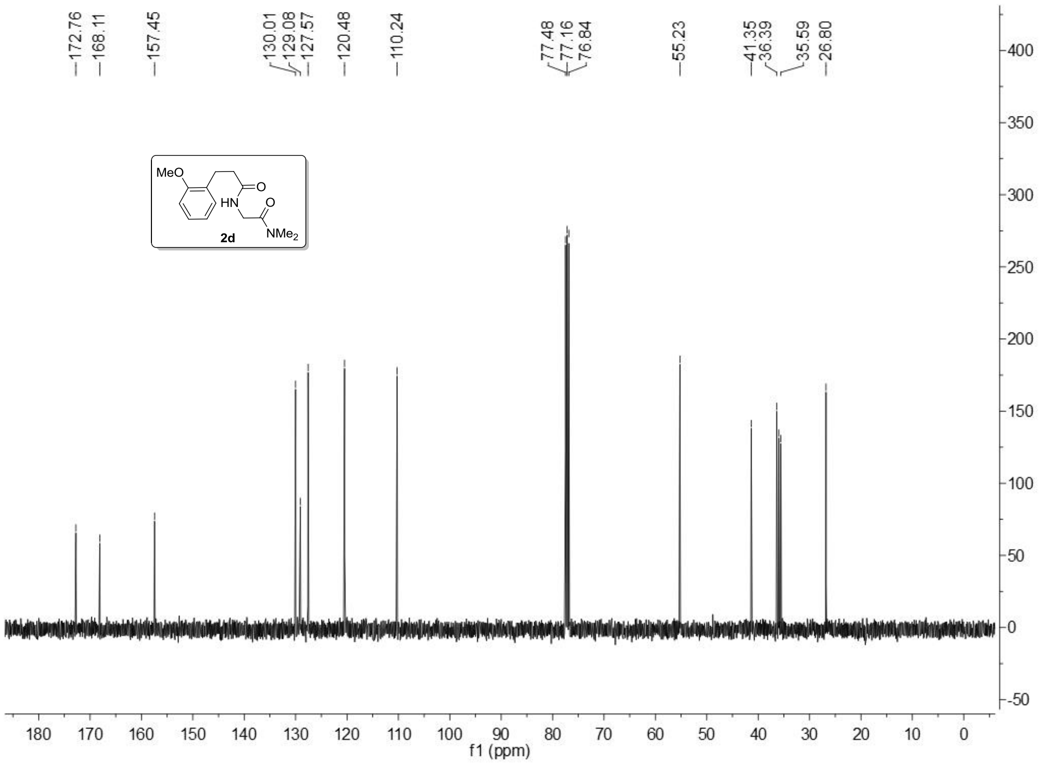
2.95
2.92
2.55
2.52
2.51
MeO
HN
O
O
NMe2
2d
2.05
2.09
1.00
2.09
3.00
6.06
2.05
2.02
f1 (ppm)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110.24
77.48
77.16
76.84
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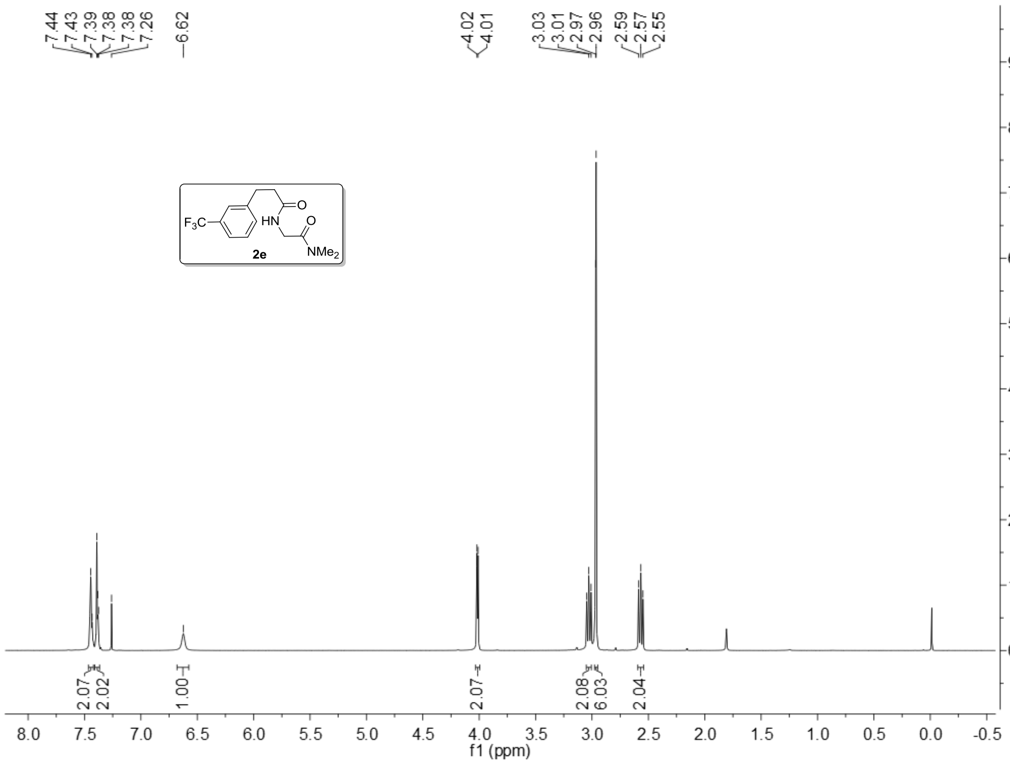
41.35
36.39
35.59
26.80
MeO
HN
O
O
NMe2
2d
f1 (ppm)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7.26
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4.01
3.03
3.01
2.97
2.96
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2.57
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2e
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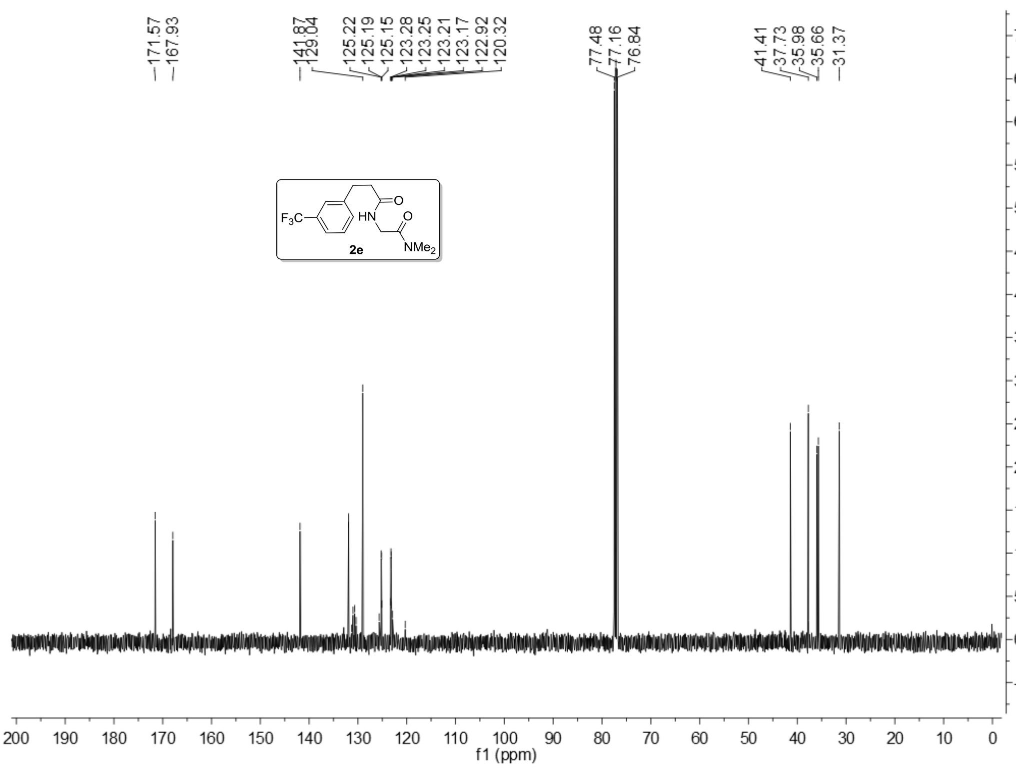
2.02
1.00
2.07
2.08
6.03
2.04
f1 (ppm)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123.17
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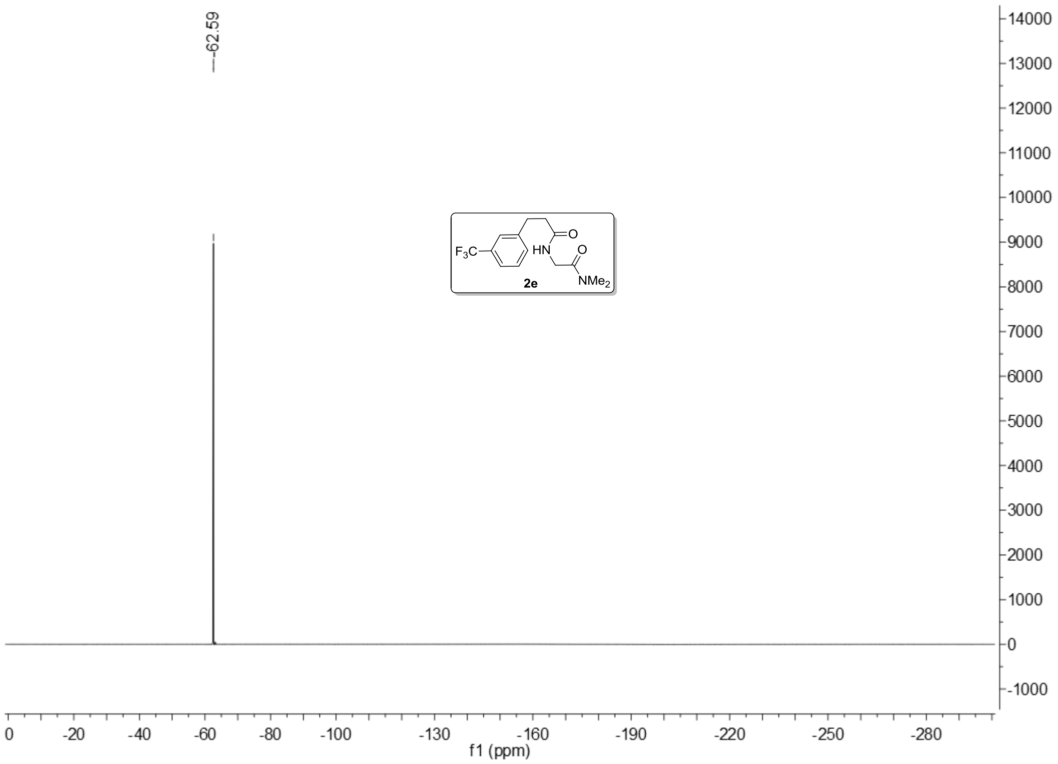
31.37
2e
f1 (ppm)



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F3C
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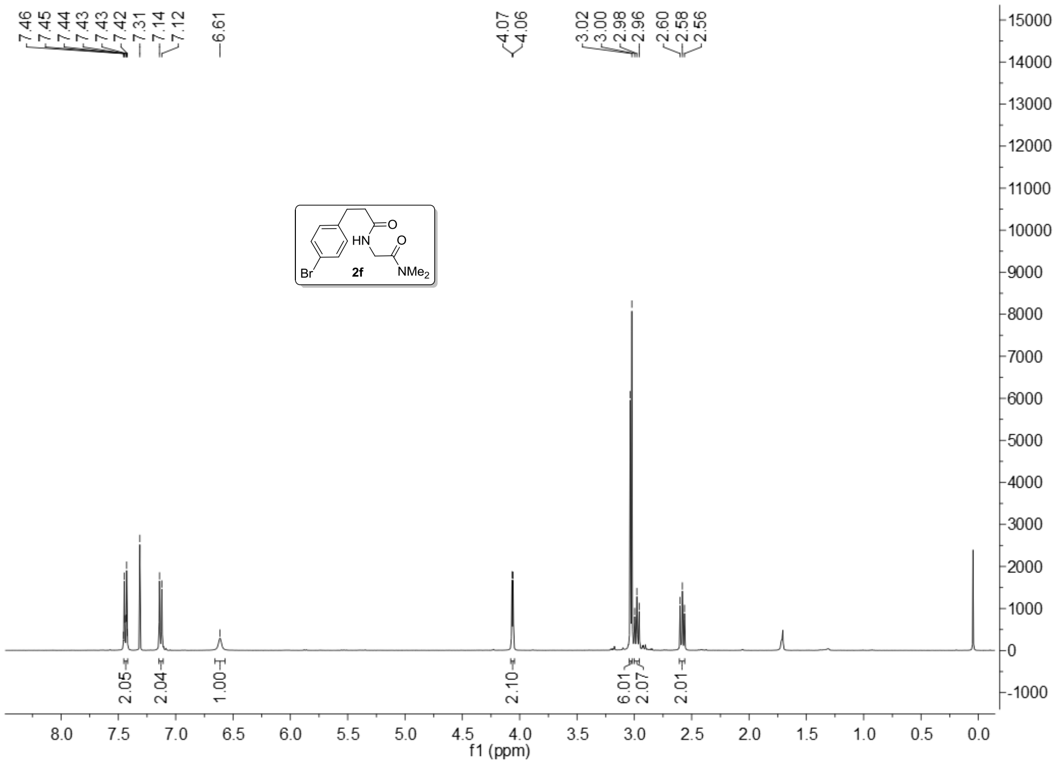
2e
NMe2
f1 (ppm)



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7.42
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7.14
7.12
6.61
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4.06
3.02
3.00
2.98
2.96
2.60
2.58
2.56
HN
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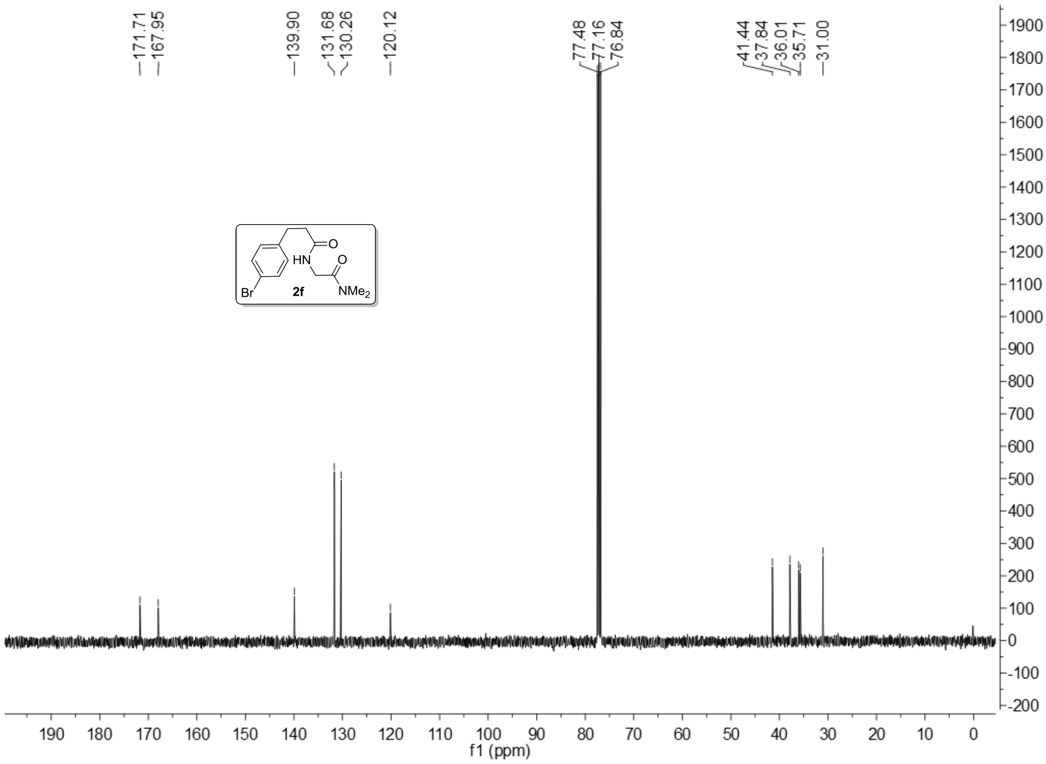
O
Br
2f
NMe2
2.05
2.04
1.00
2.10
6.01
2.07
2.01
f1 (ppm)



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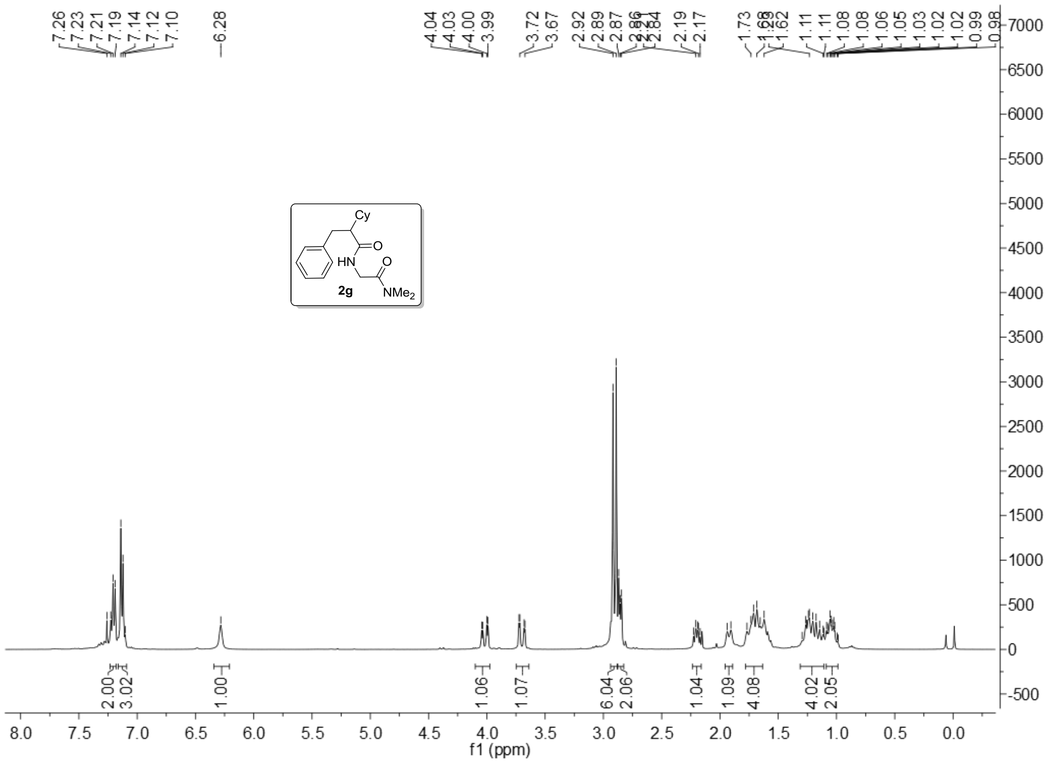
31.00
2f
f1 (ppm)



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2.17
1.73
1.62
1.11
1.11
1.08
1.08
1.06
1.05
1.03
1.02
1.02
0.99
0.98
Cy
2g
2.00
3.02
1.00
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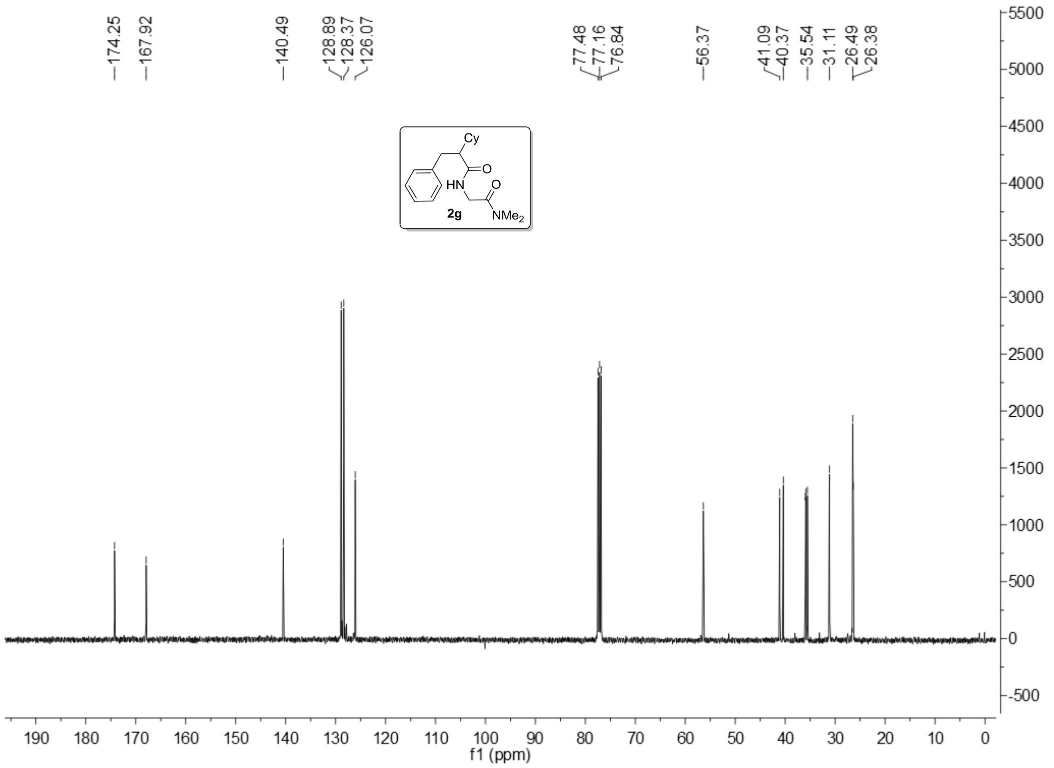
1.07
6.04
2.06
1.04
1.09
4.08
4.02
2.05
f1 (ppm)



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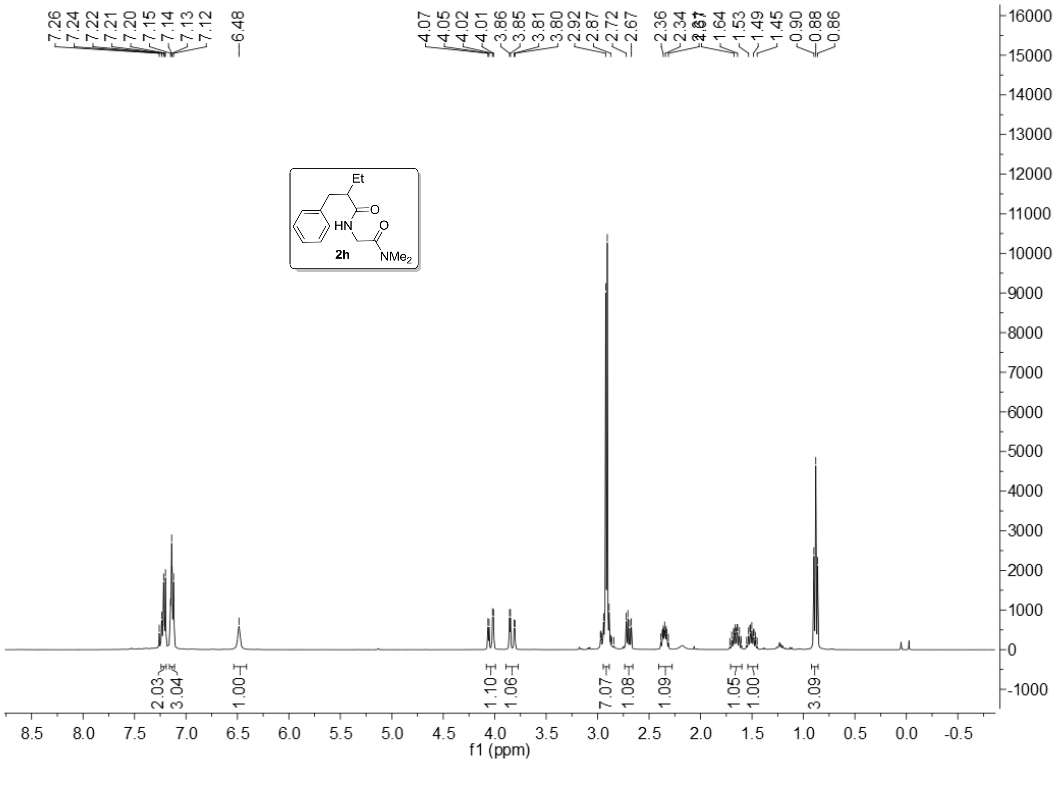
35.54
31.11
26.49
26.38
Cy
HN
O
O
NMe2
2g
f1 (ppm)



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7.13
7.12
6.48
4.07
4.05
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4.01
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3.81
3.80
2.92
2.87
2.72
2.67
2.36
2.34
1.64
1.53
1.49
1.45
0.90
0.88
0.86
Et
HN
O
O
NMe2
2h
2.03
3.04
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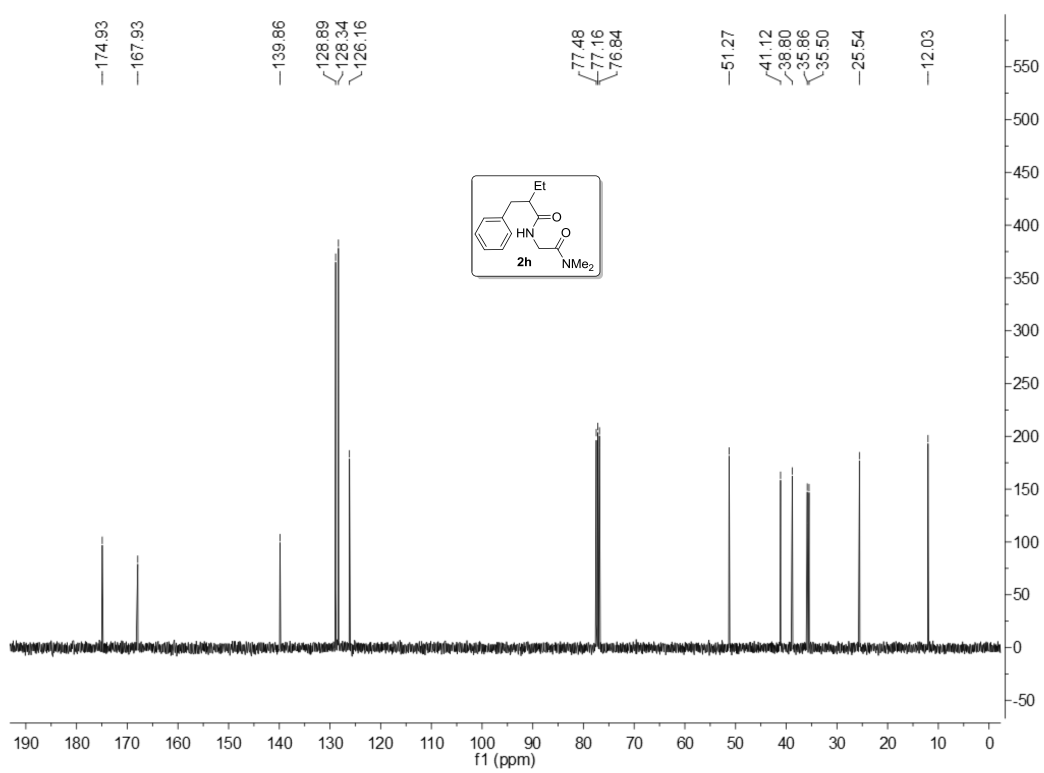
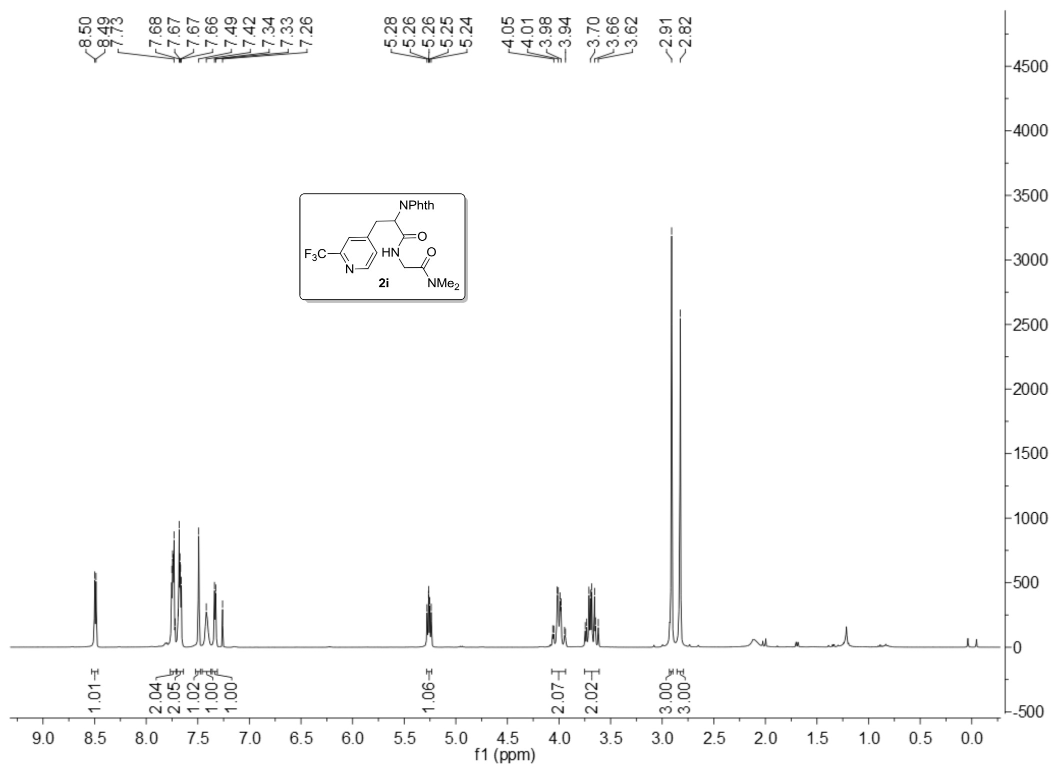
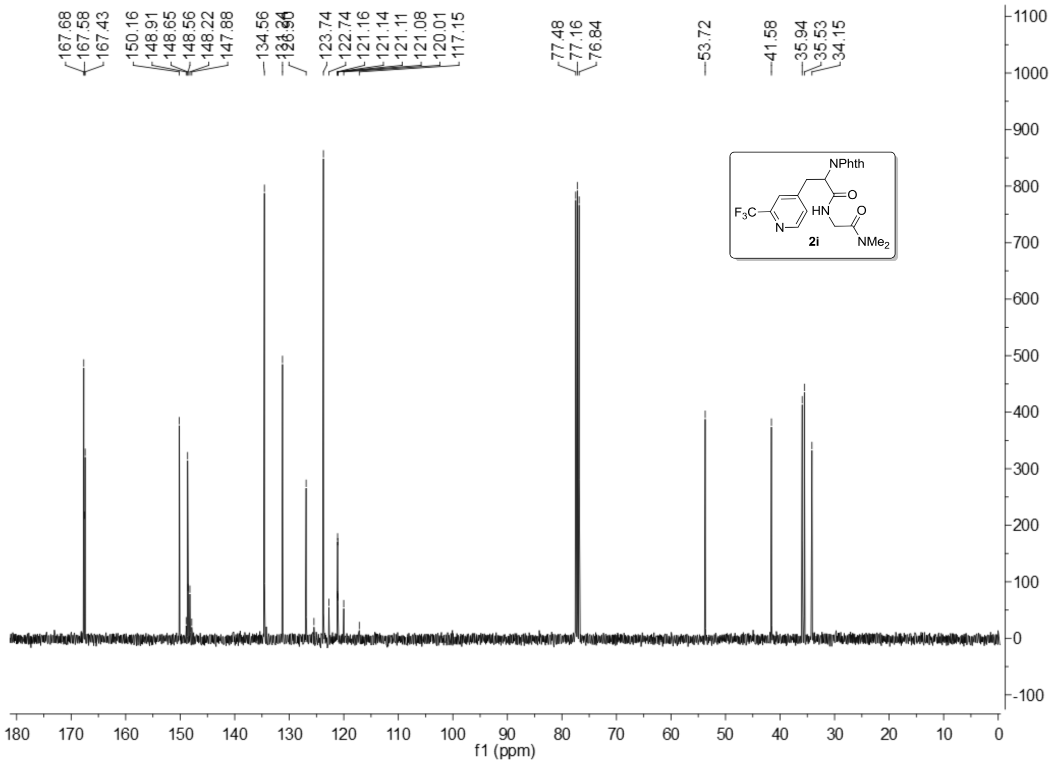
1.10
1.06
7.07
1.08
1.09
1.05
1.00
3.09
f1 (ppm)



2h
NMe2
Et
HN
O
f1 (ppm)



2i
NPhth
F3C
N
HN
O
NMe2
f1 (ppm)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122.74
121.16
121.14
121.11
121.08
120.01
117.15
77.48
77.16
76.84
53.72
41.58
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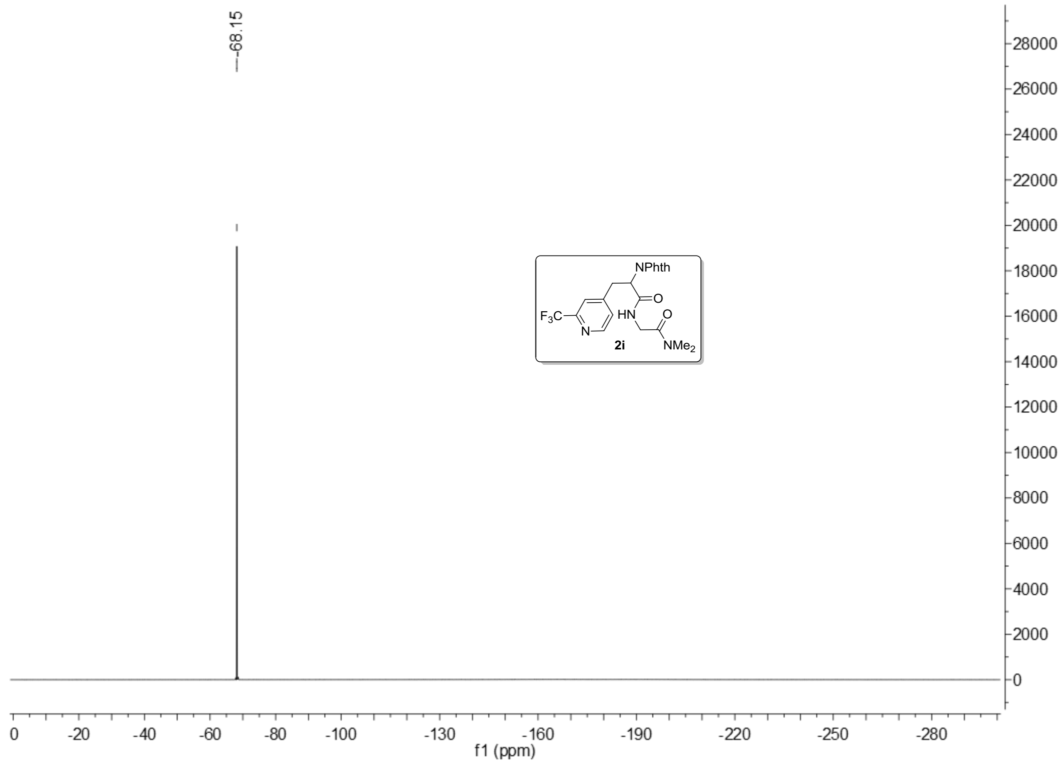
35.53
34.15
NPhth
F_3C
HN
O
N
2i
NMe_2
f1 (ppm)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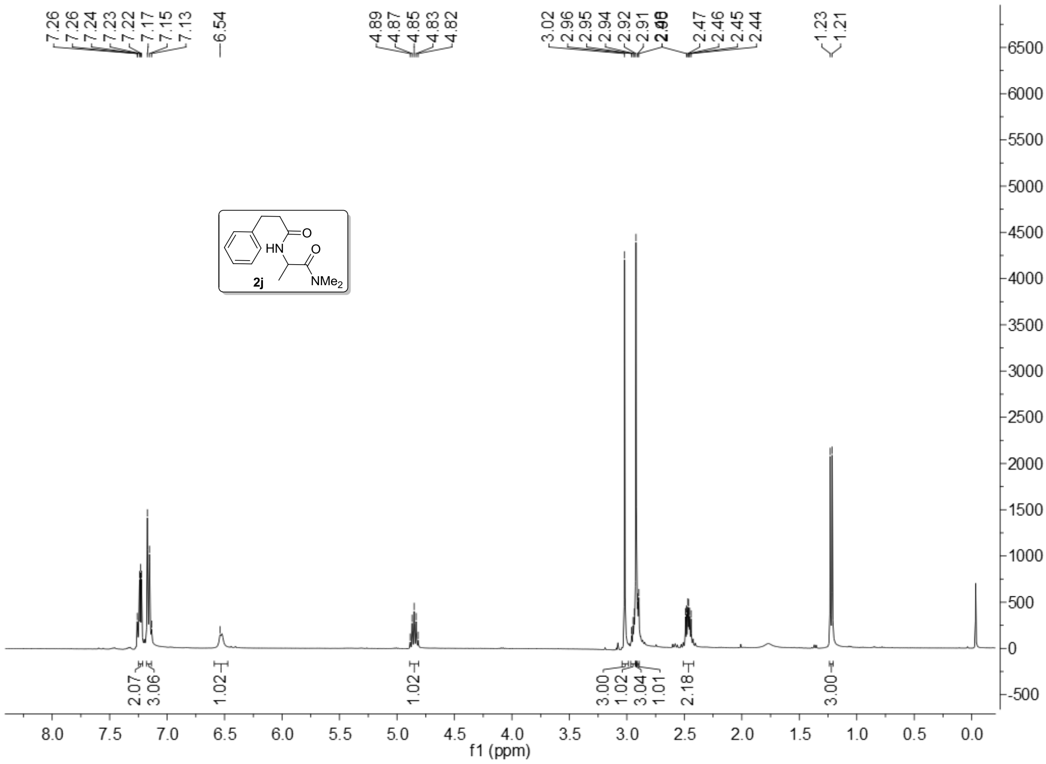

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7.13
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4.87
4.85
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4.82
3.02
2.96
2.95
2.94
2.92
2.91
2.47
2.46
2.45
2.44
1.23
1.21
HN
O
O
NMe2
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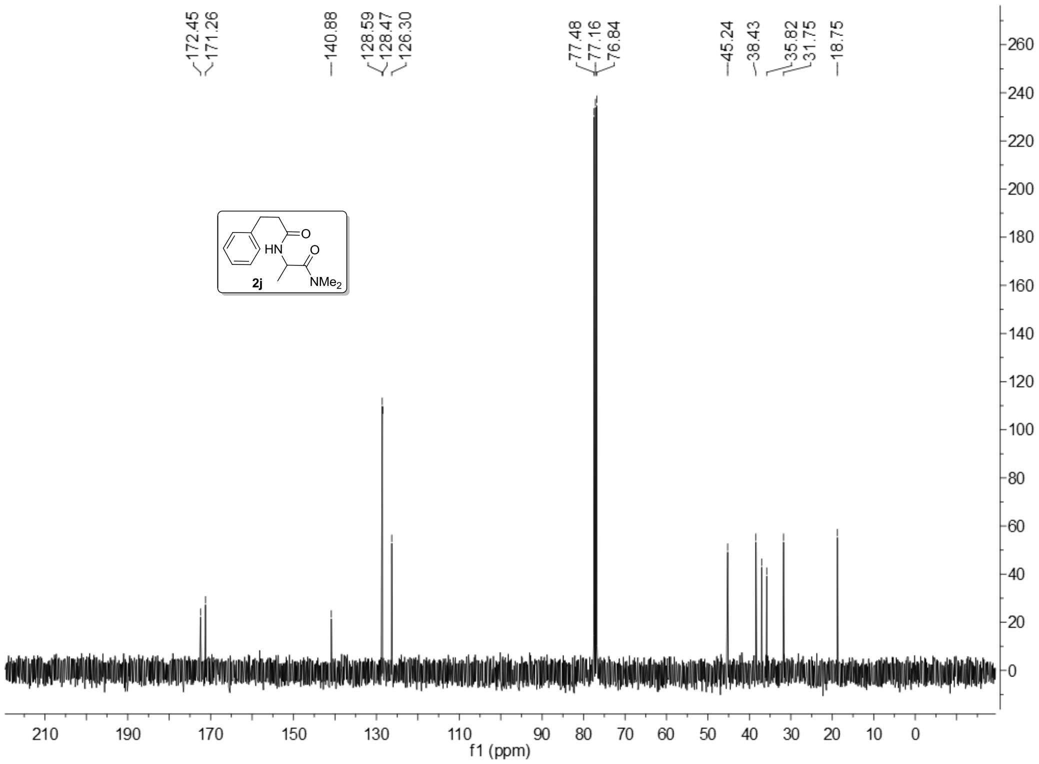
3.00
1.02
3.04
1.01
2.18
3.00
f1 (ppm)



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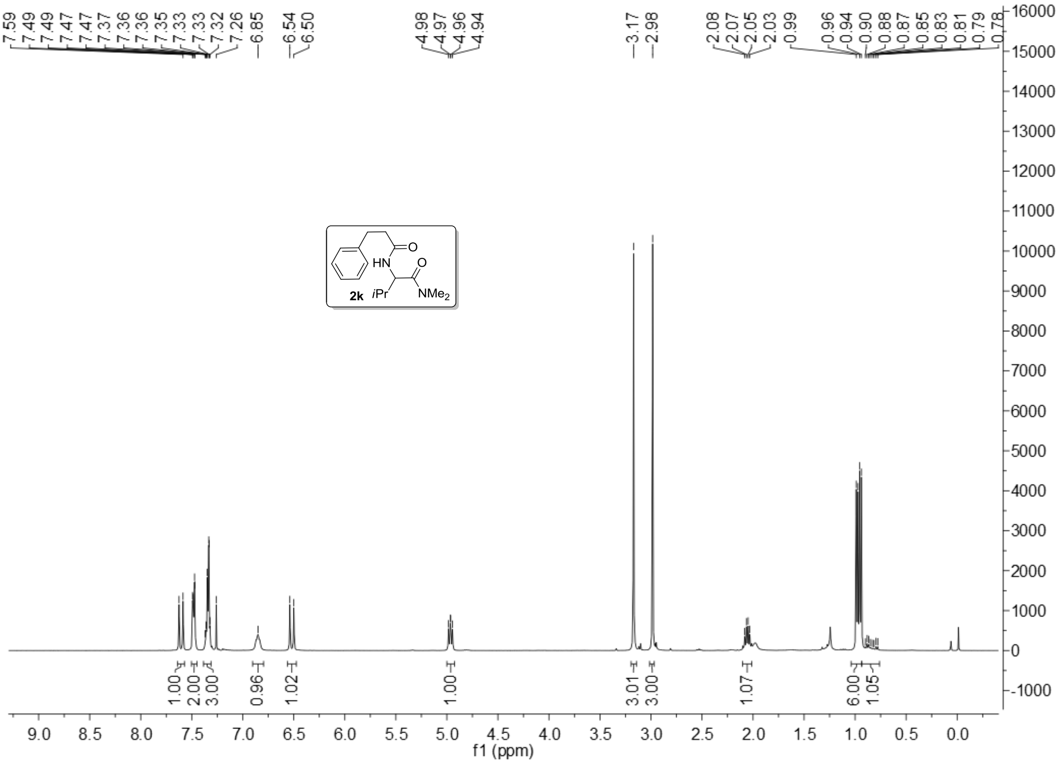
HN
O
O
NMe2
2j
f1 (ppm)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6.54
6.50
4.98
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4.96
4.94
3.17
2.98
2.08
2.07
2.05
2.03
0.99
0.96
0.94
0.90
0.88
0.87
0.85
0.83
0.81
0.79
0.78
2k
iPr
HN
O
O
NMe2
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2.00
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1.00
3.01
3.00
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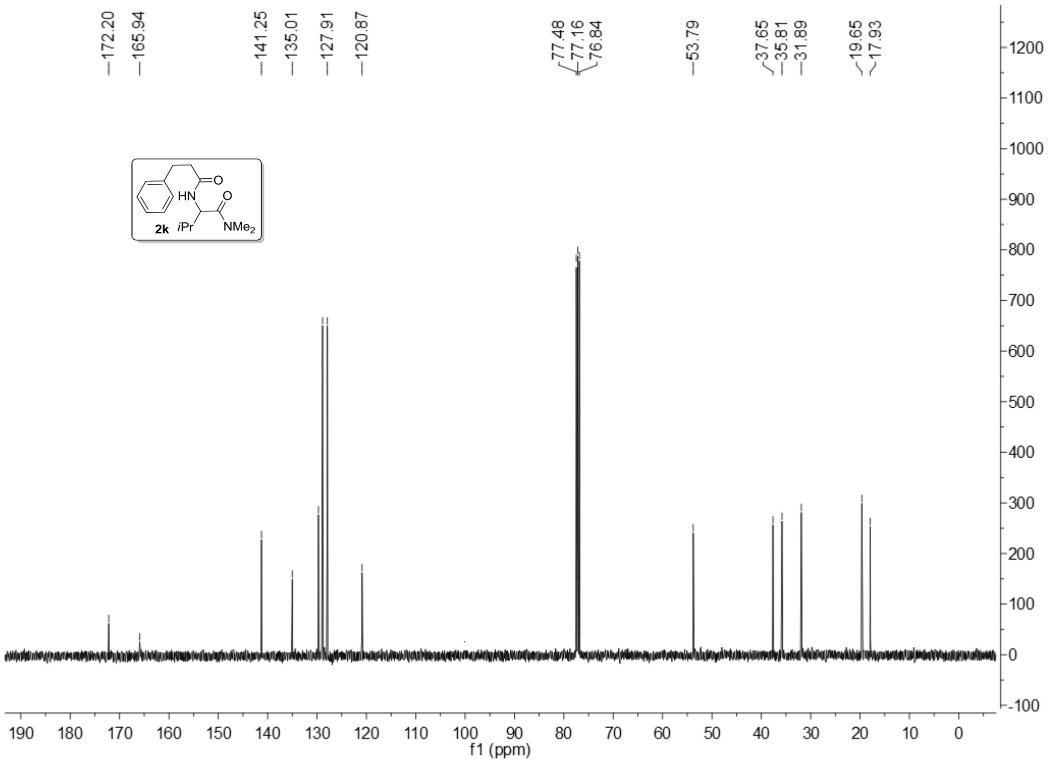
1.05
f1 (ppm)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19.65
17.93
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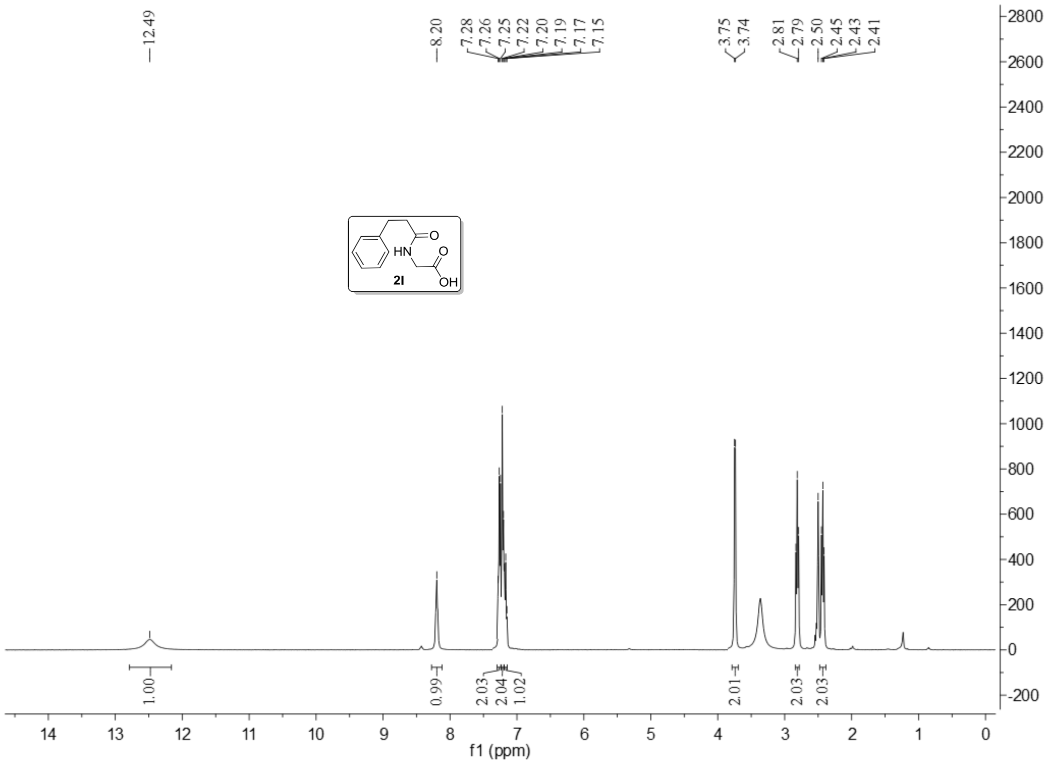
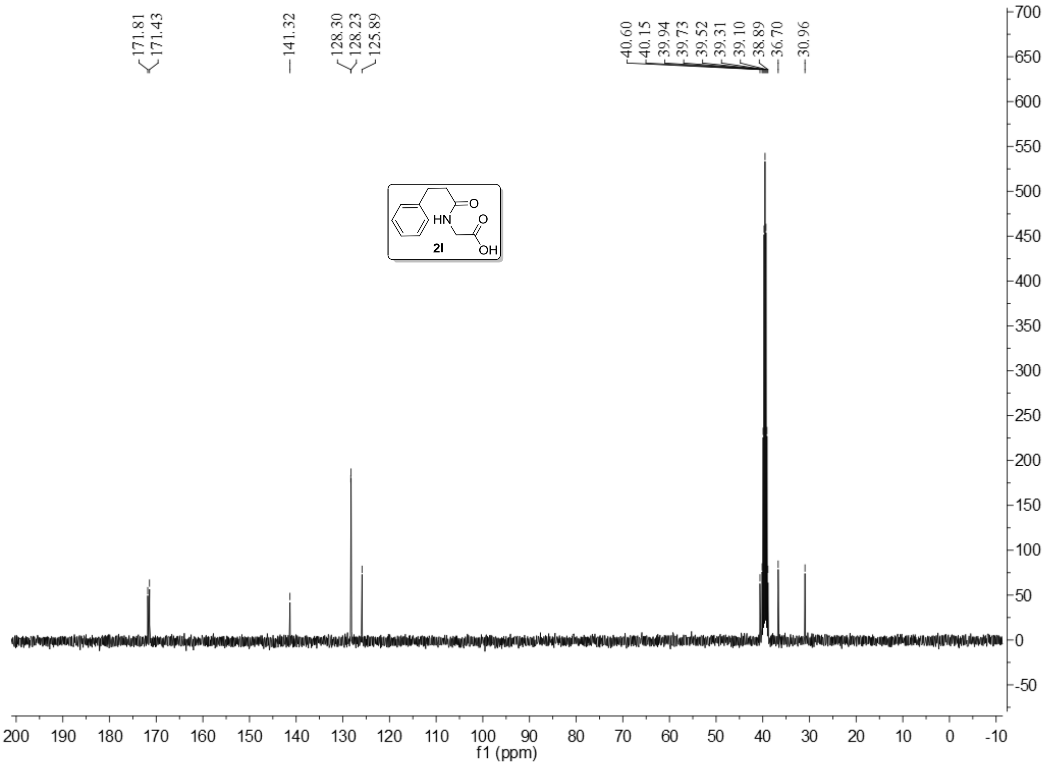
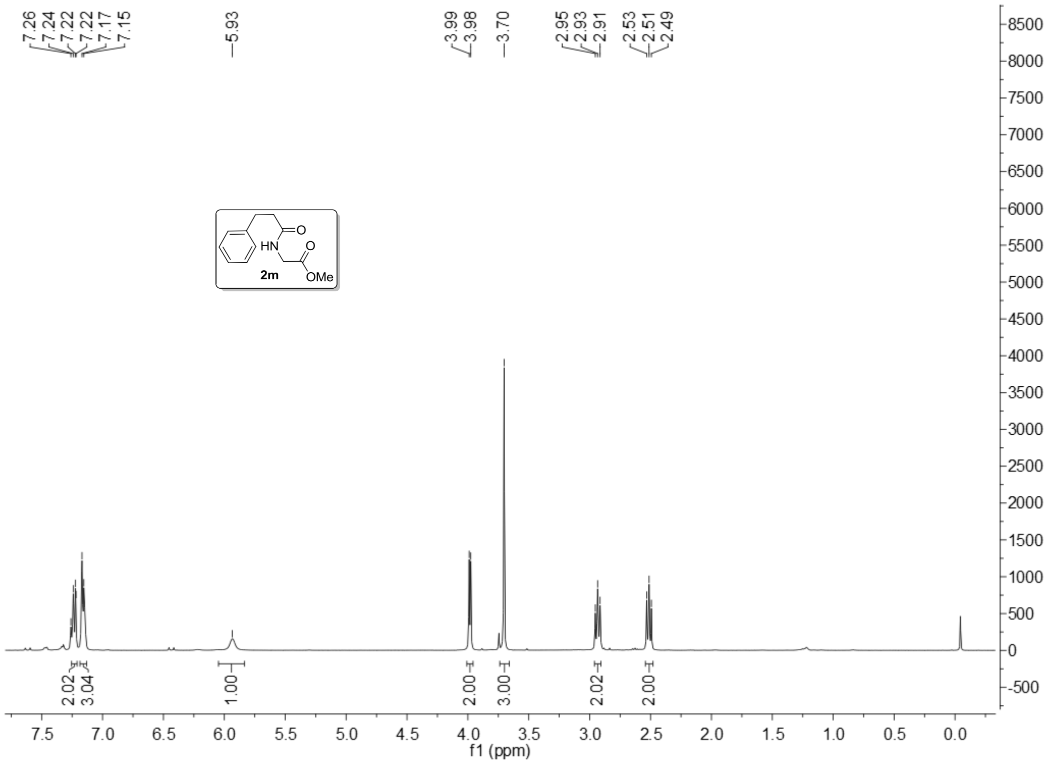
NMe2
f1 (ppm)



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2.91
2.53
2.51
2.49
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OMe
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3.00
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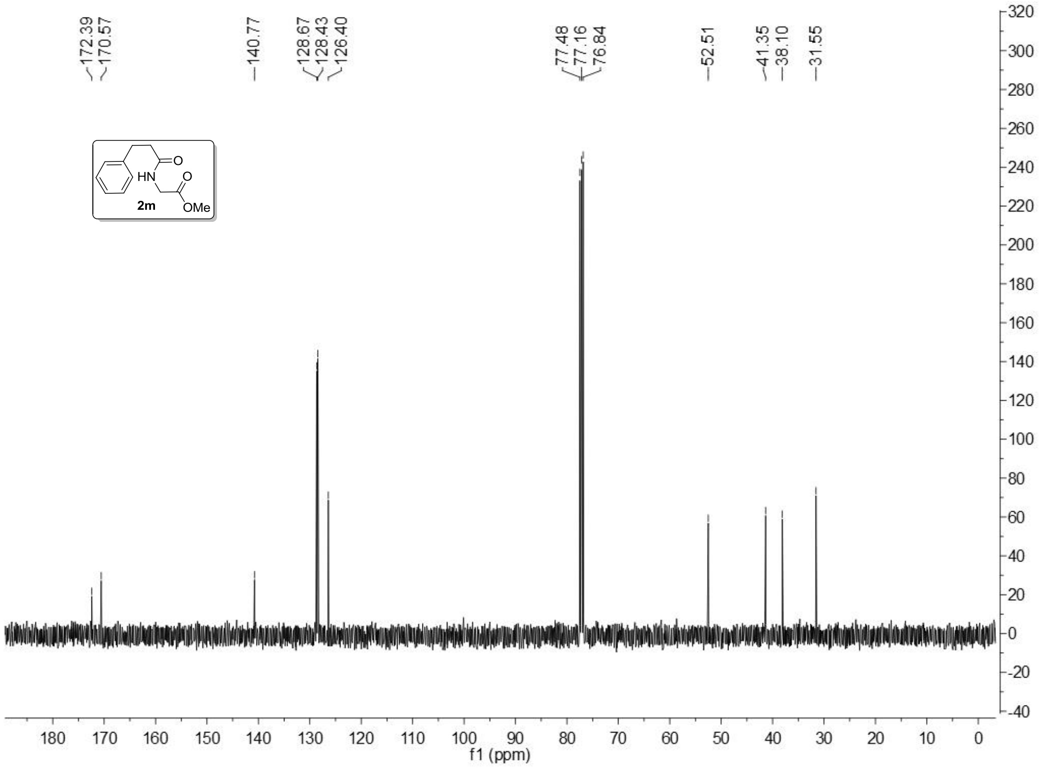
2.00
f1 (ppm)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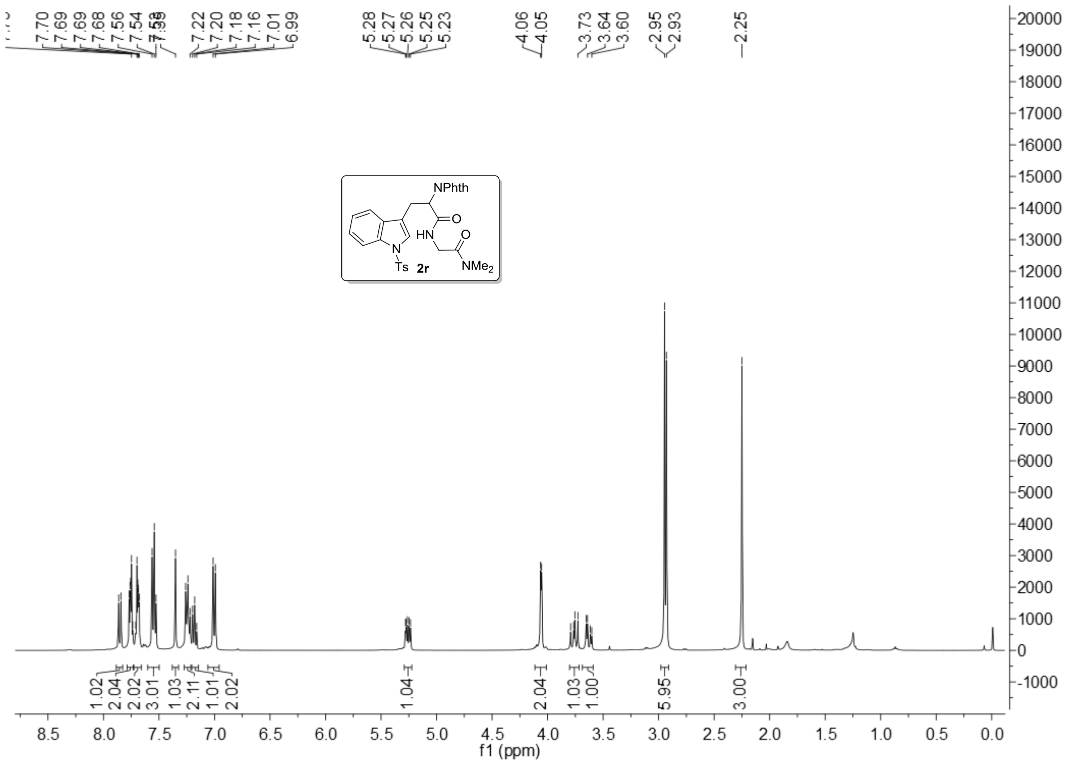
OMe
f1 (ppm)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5.25
5.23
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3.64
3.60
2.95
2.93
2.25
NPhth
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HN
N
O
Ts
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NMe2
1.02
2.04
2.02
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2.02
1.04
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1.00
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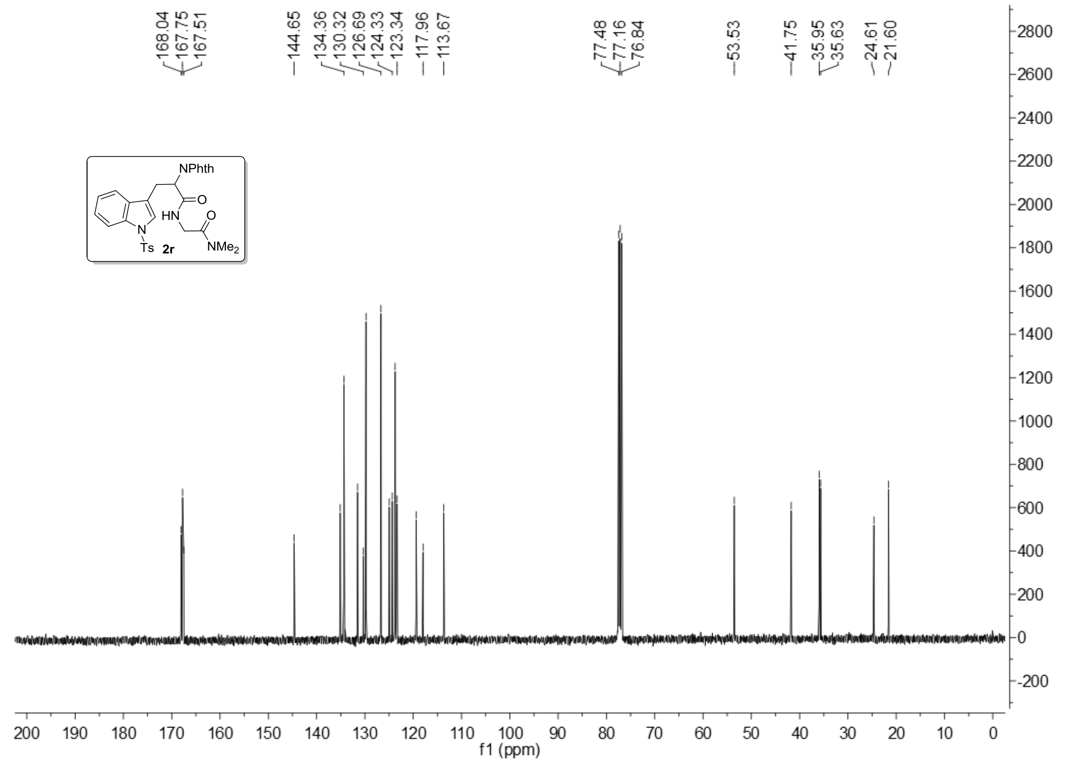
3.00
f1 (ppm)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77.16
76.84
53.53
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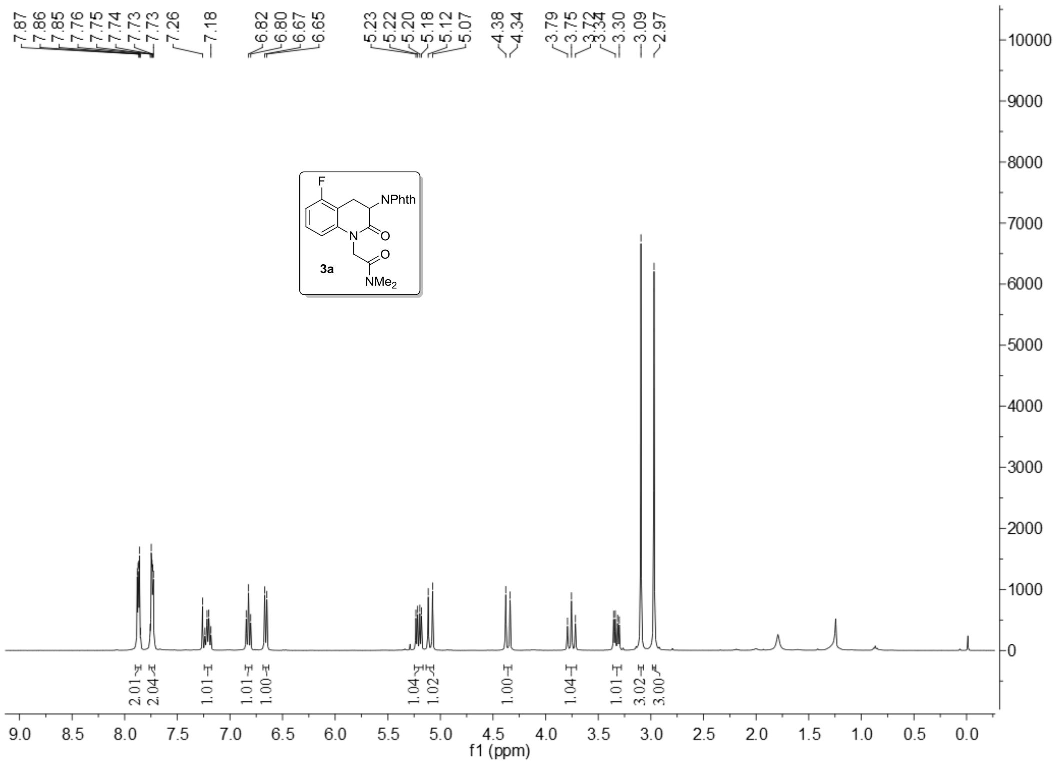
24.61
21.60
NPhth
O
HN
N
O
Ts
2r
NMe2
f1 (ppm)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5.07
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4.34
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3.75
3.72
3.34
3.30
3.09
2.97
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NPhth
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O
O
3a
NMe2
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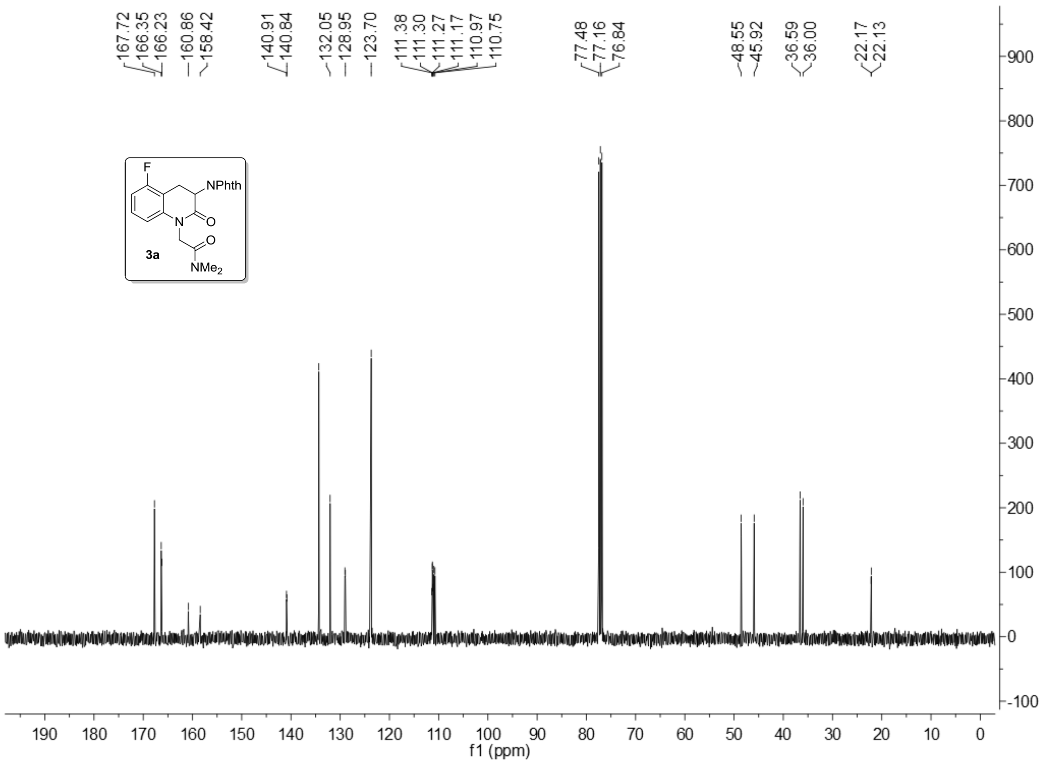
1.04
1.02
1.00
1.04
1.01
3.02
3.00
f1 (ppm)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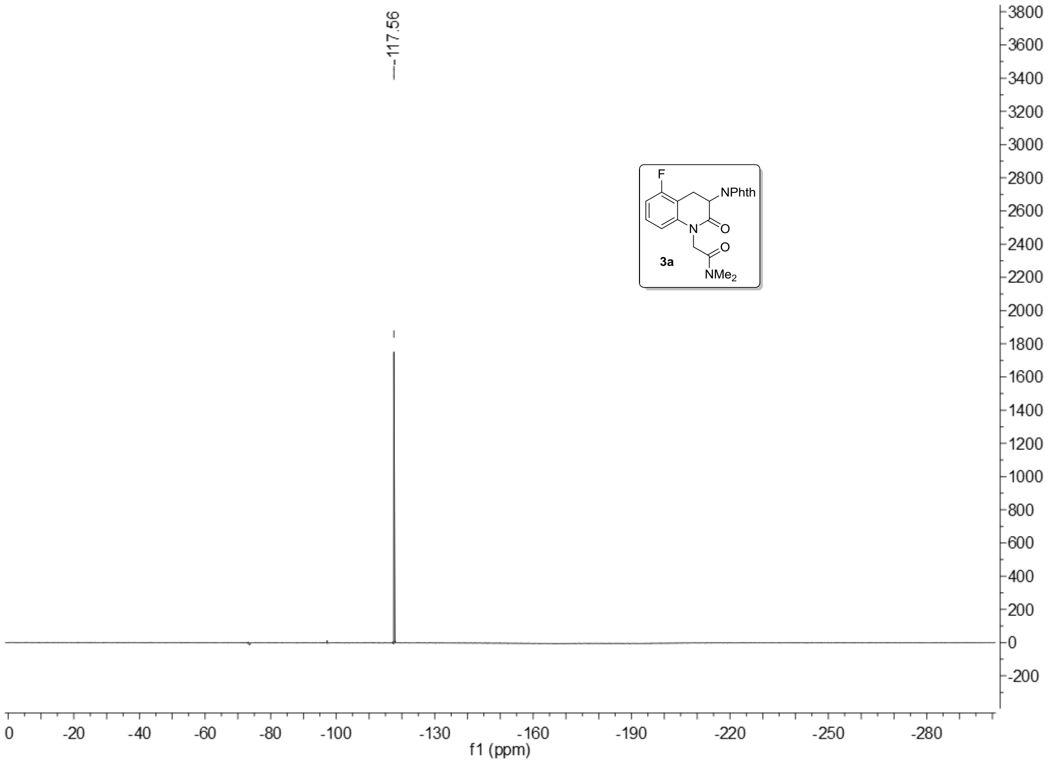
f1 (ppm)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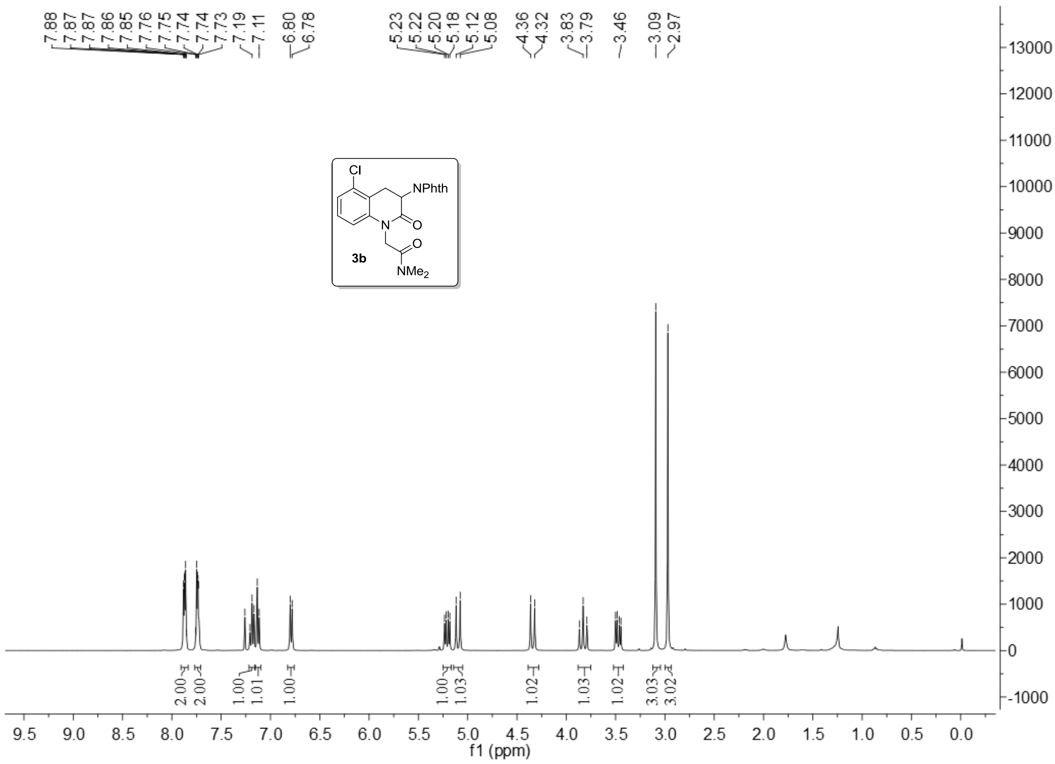
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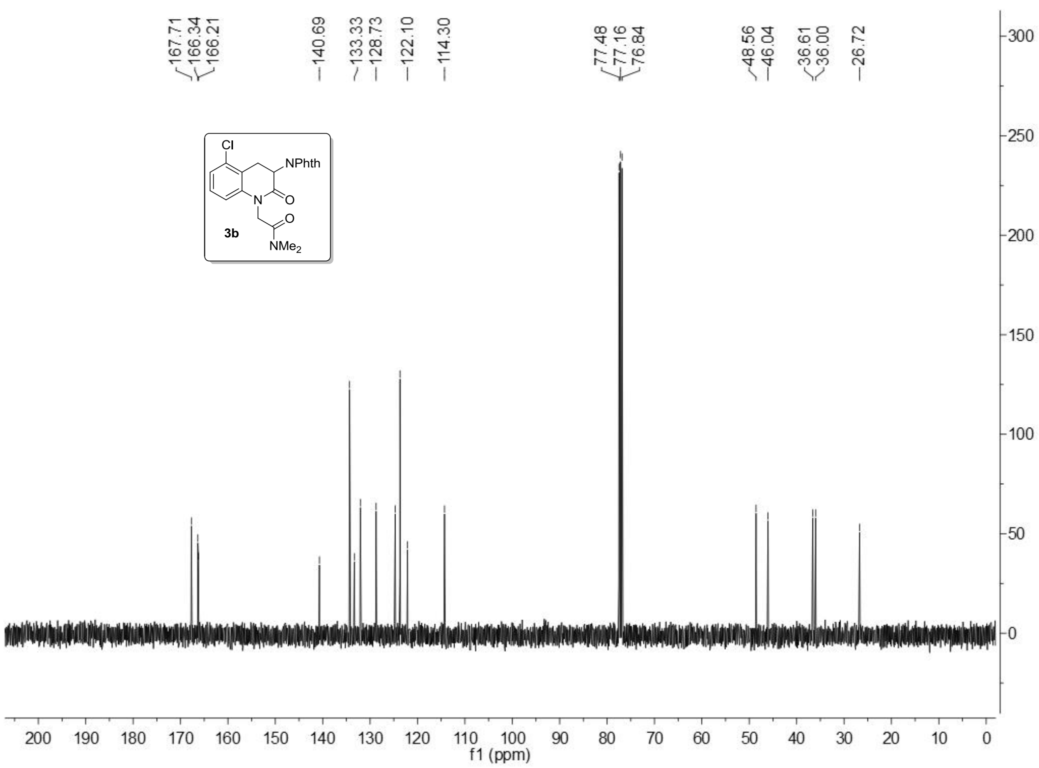

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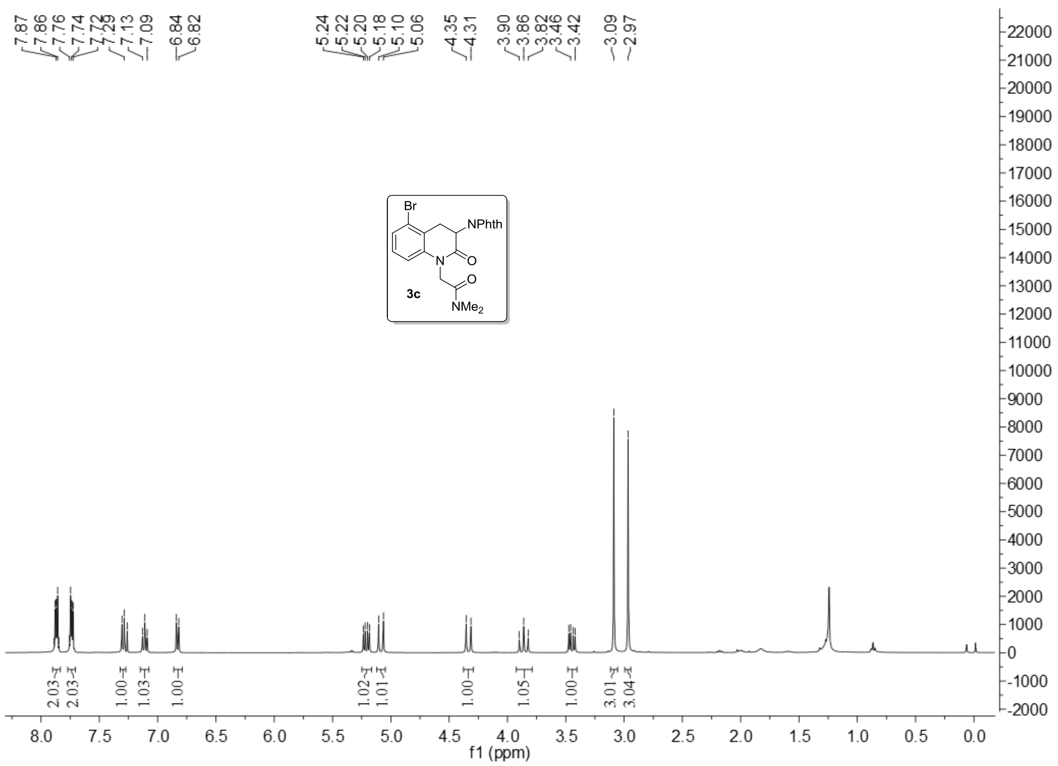
f1 (ppm)



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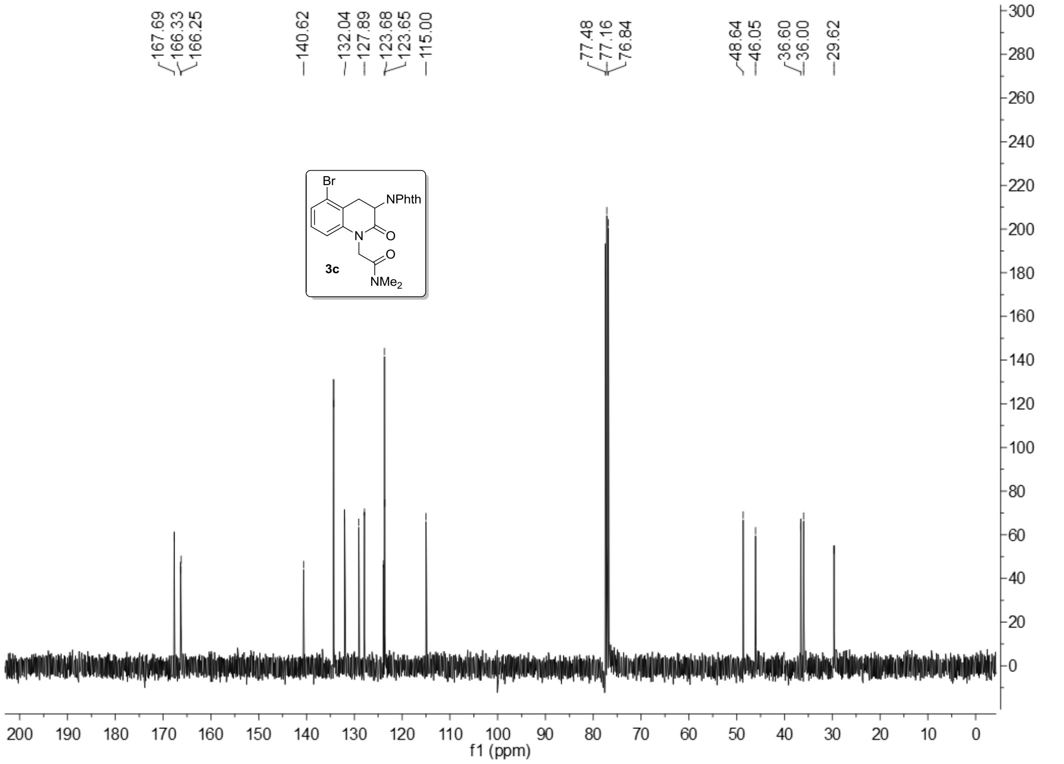

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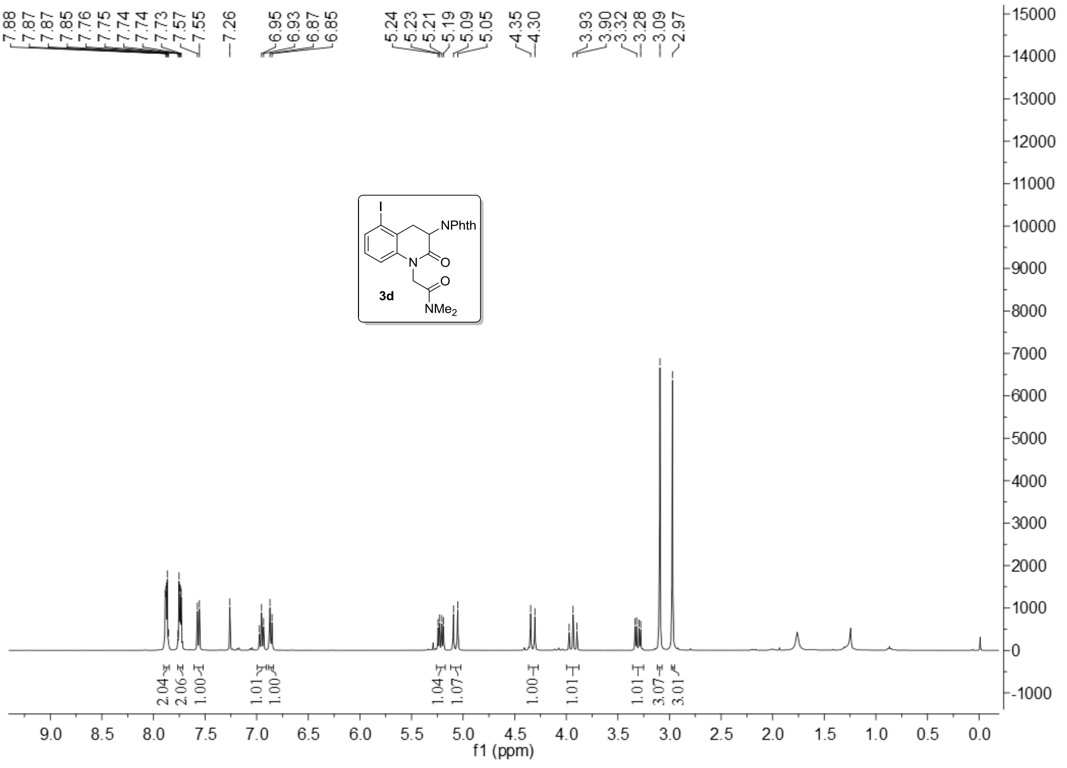
f1 (ppm)



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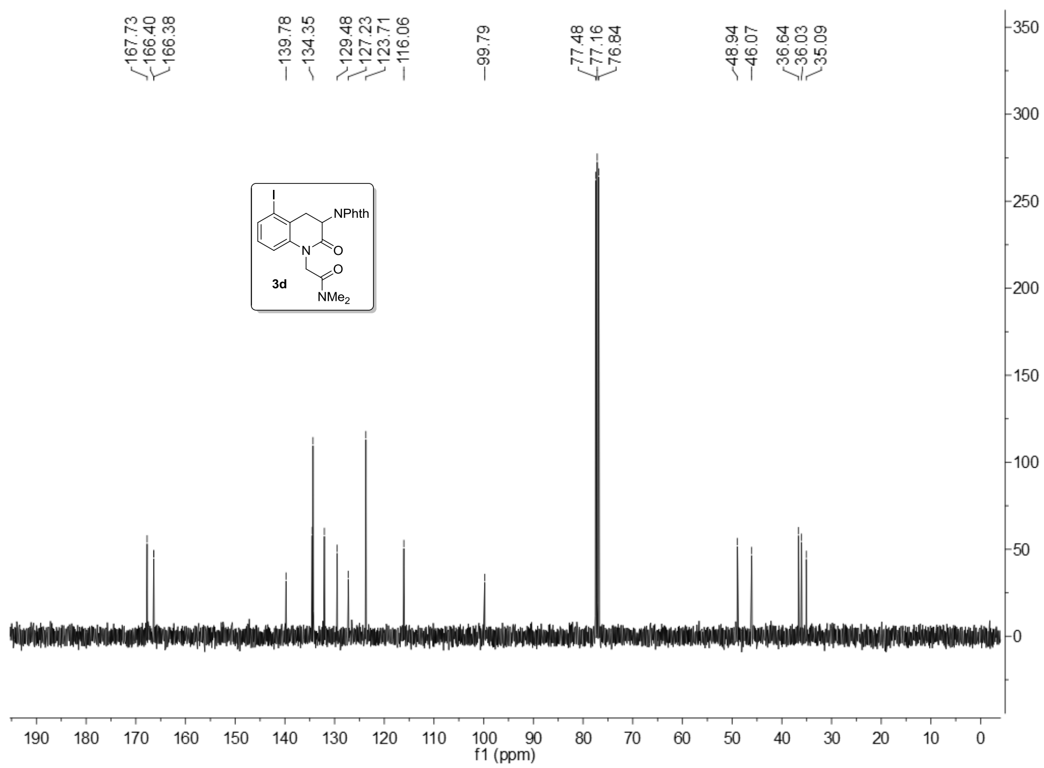
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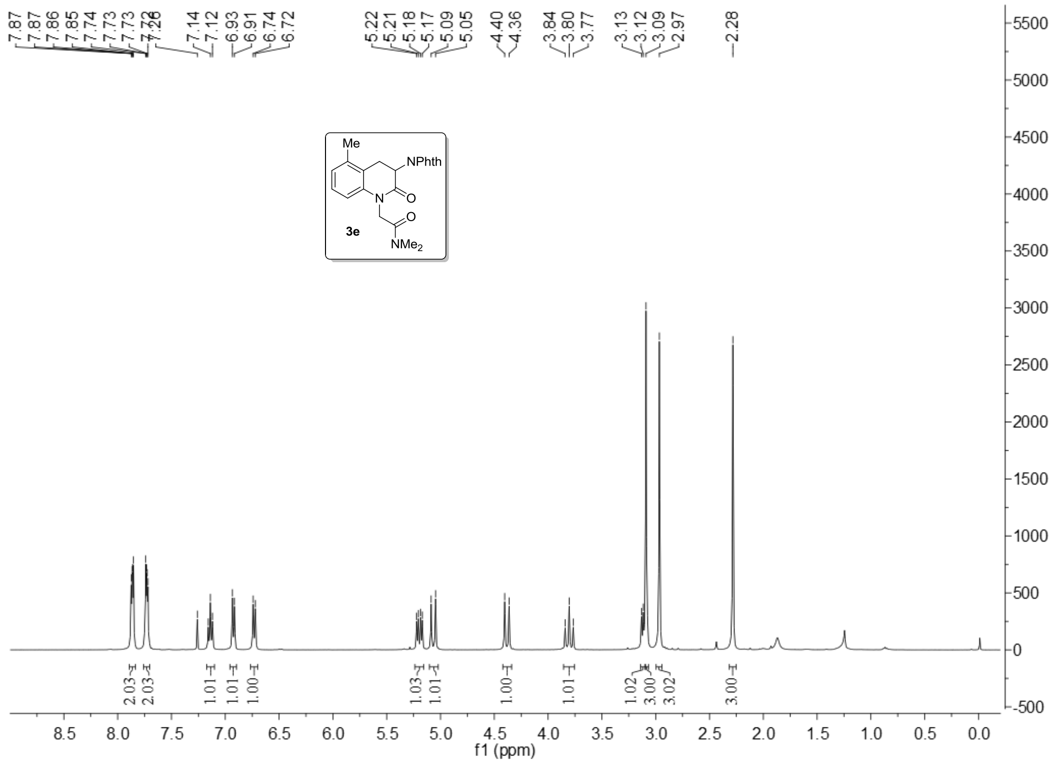
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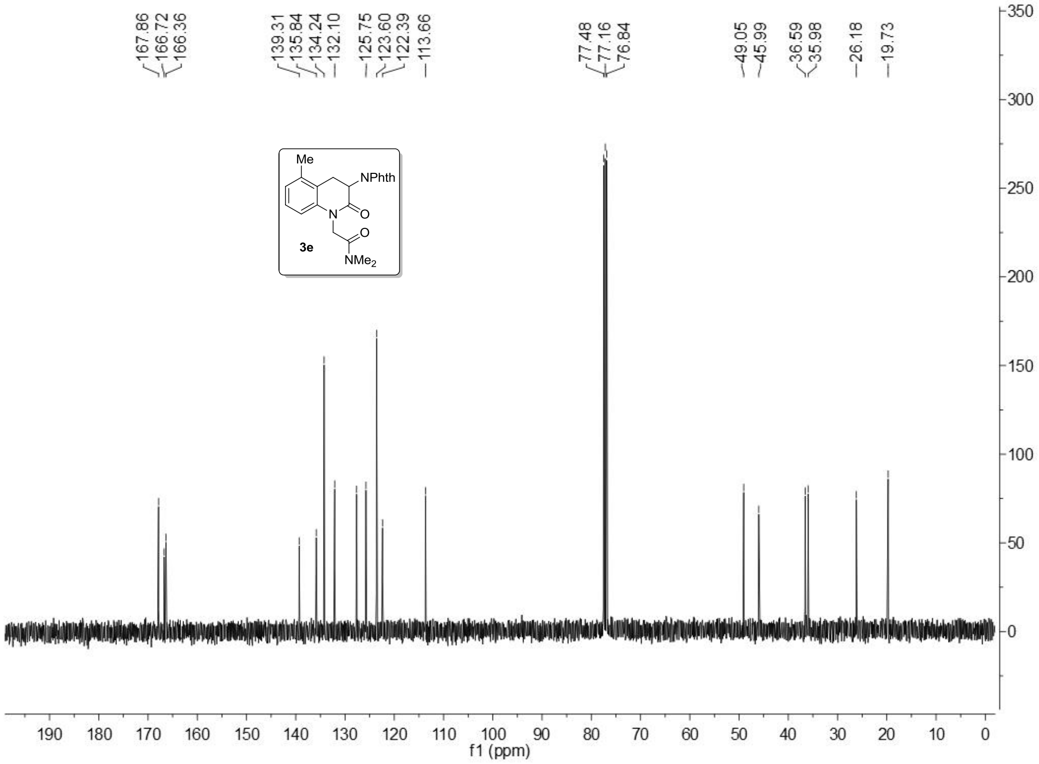
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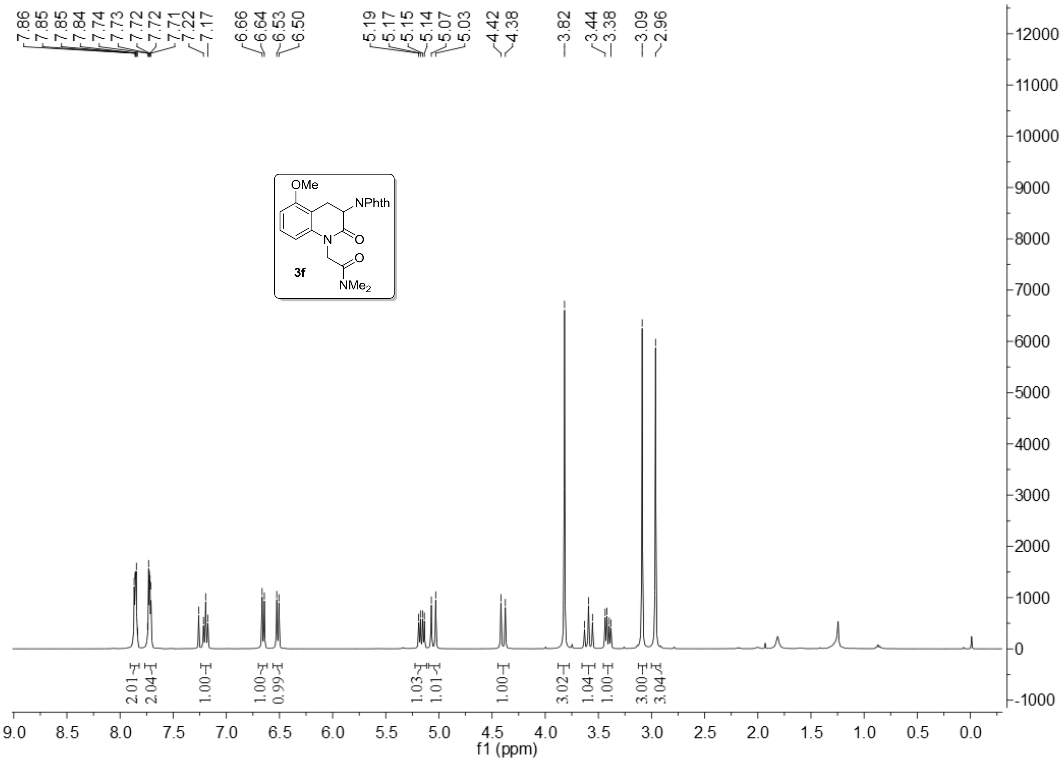
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NPhth
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O
O
3f
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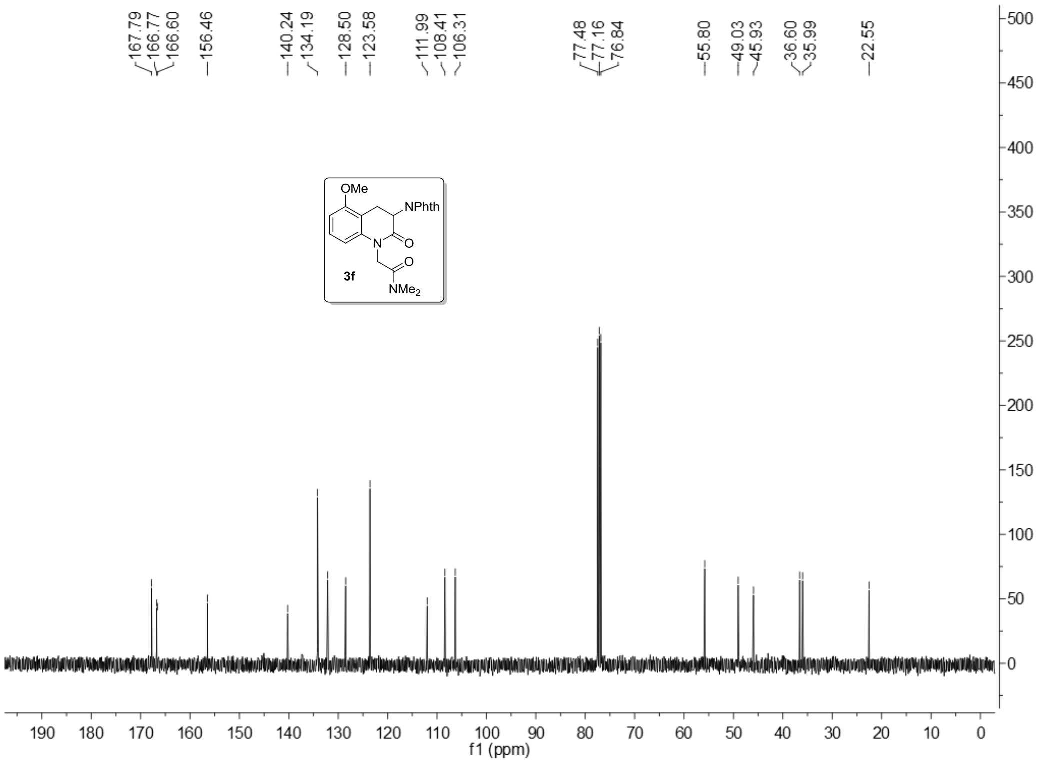
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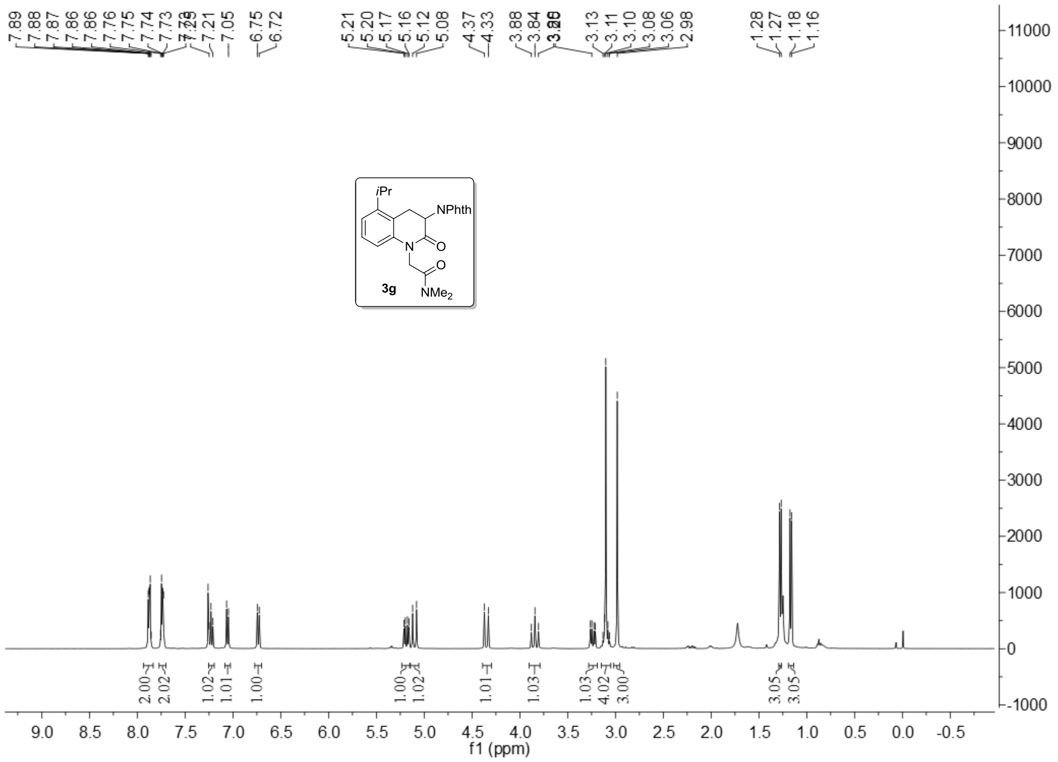
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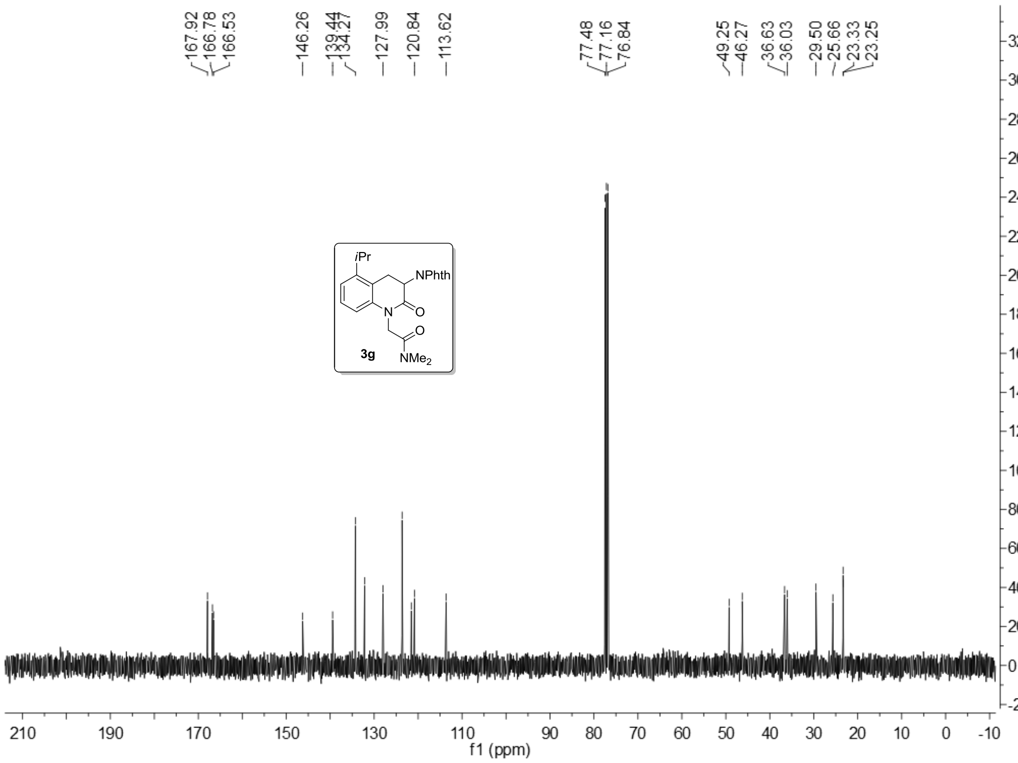
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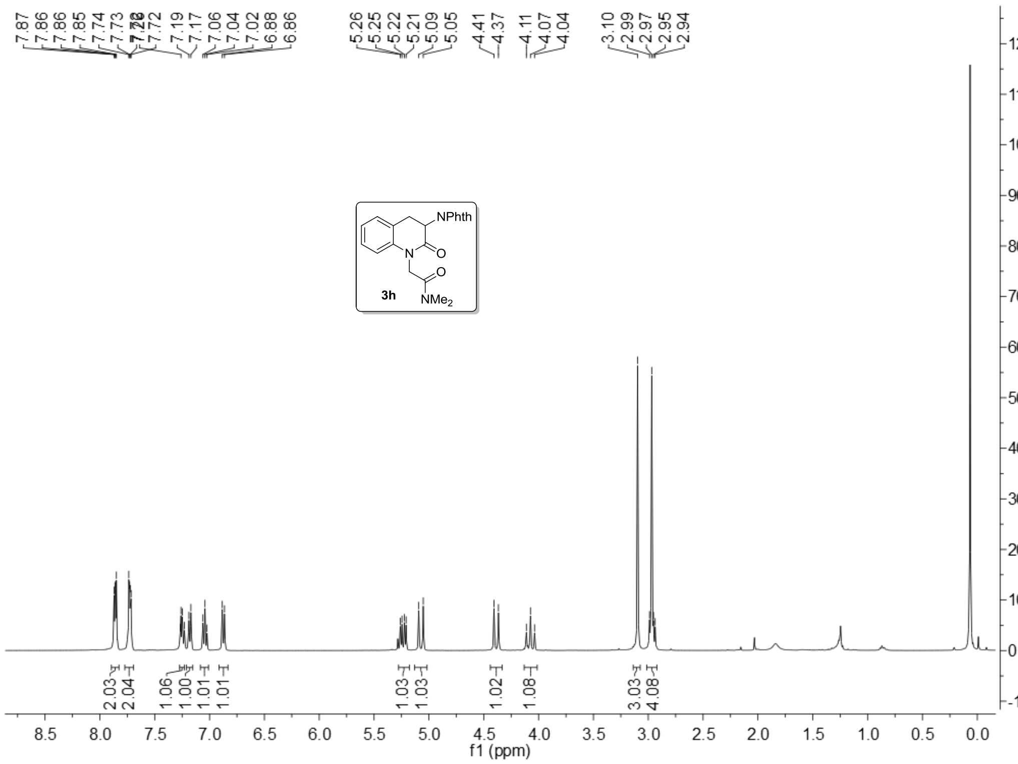
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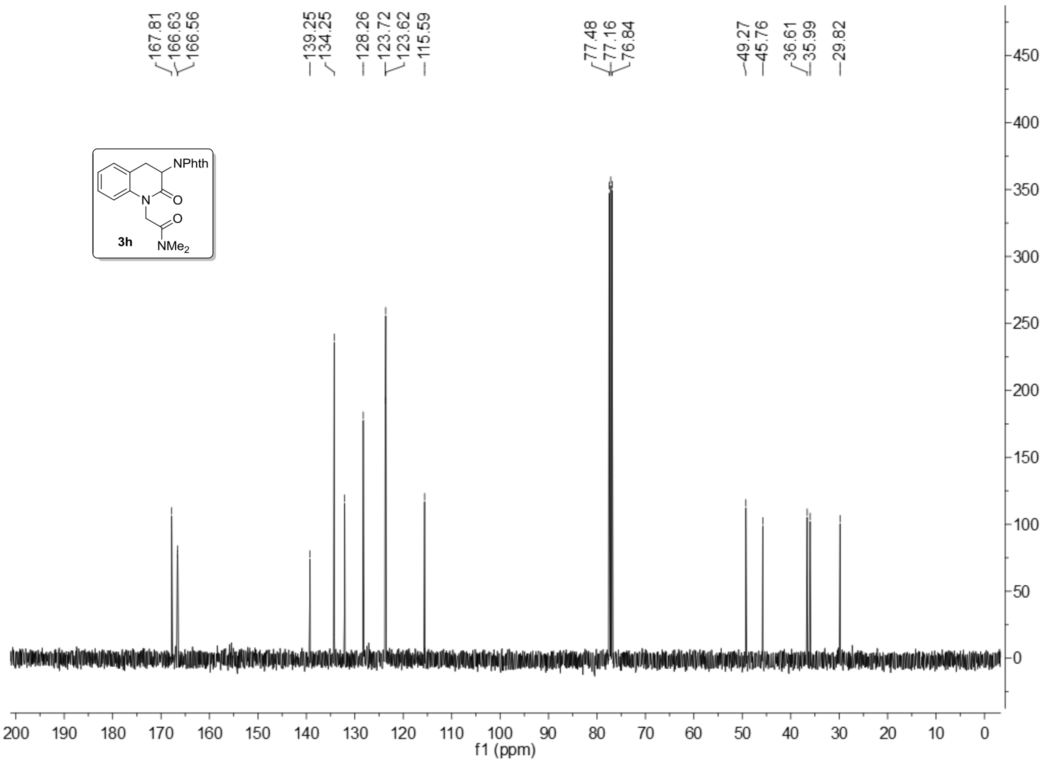
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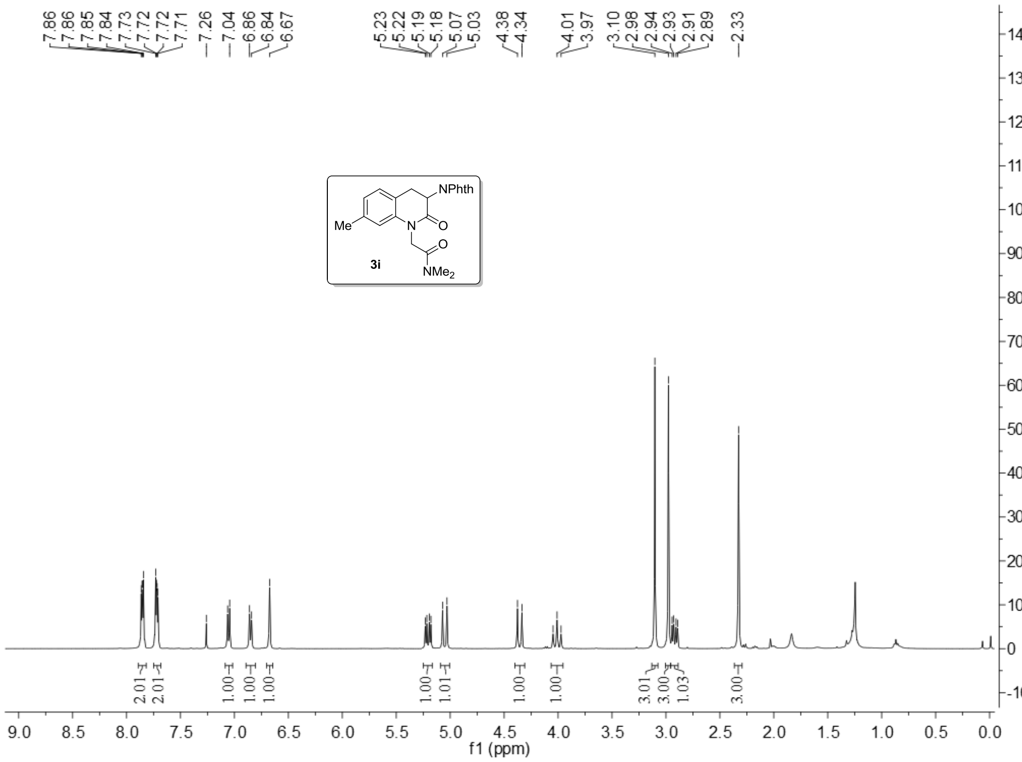
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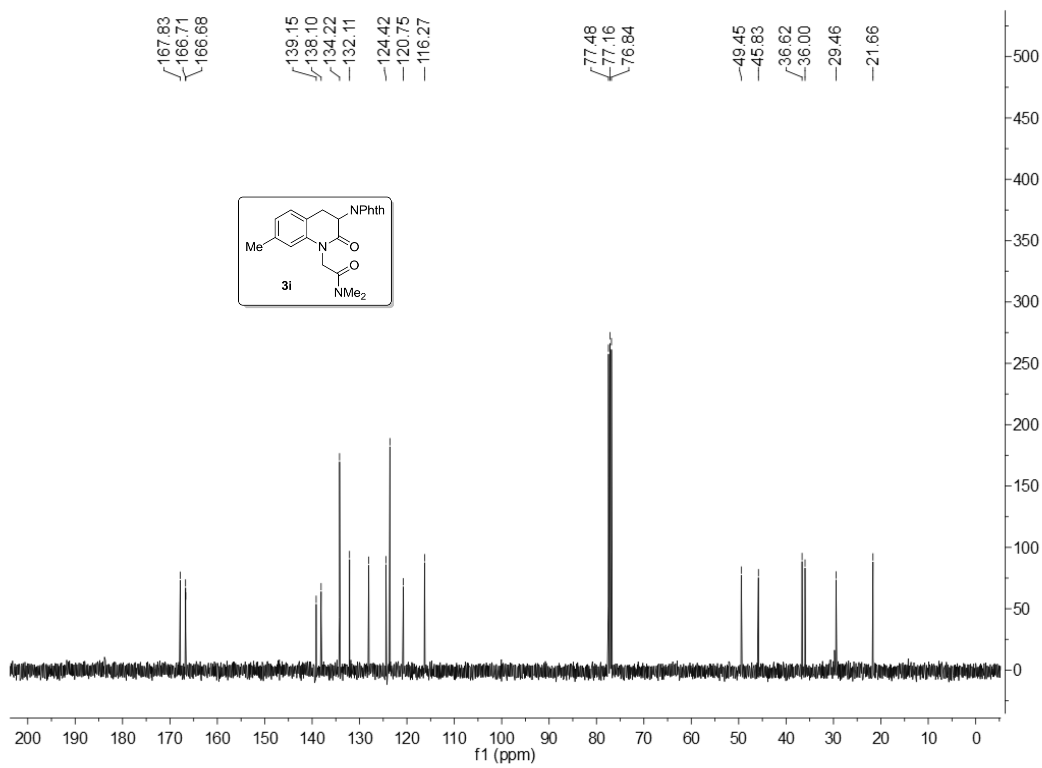
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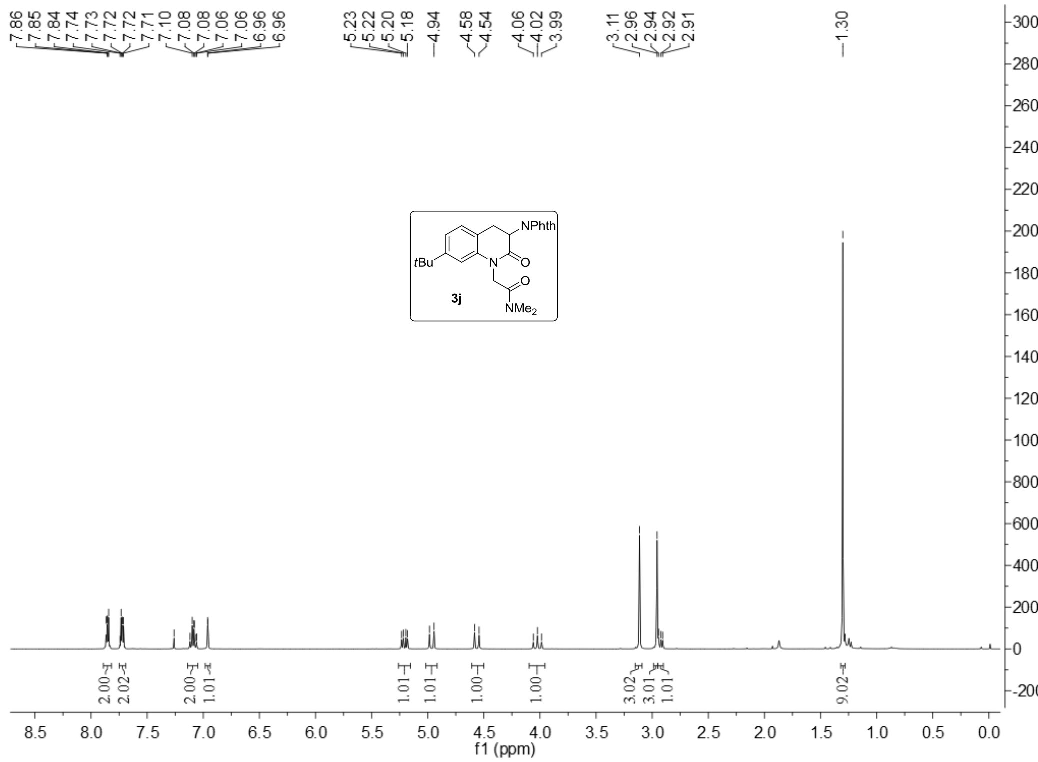
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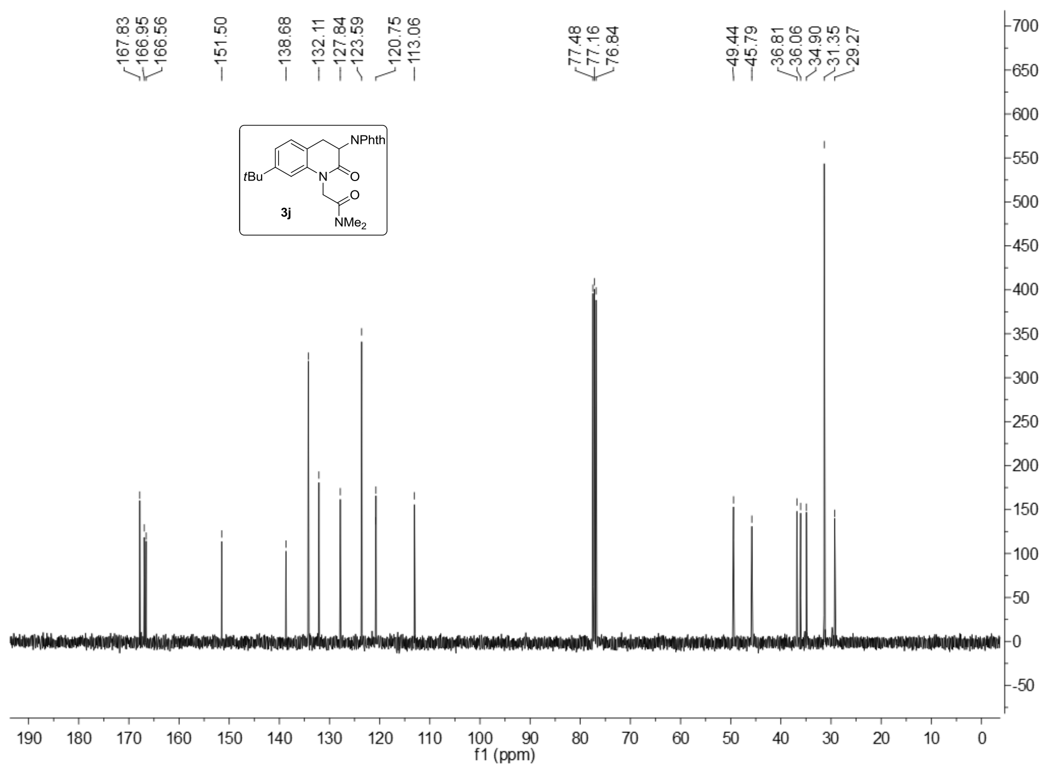
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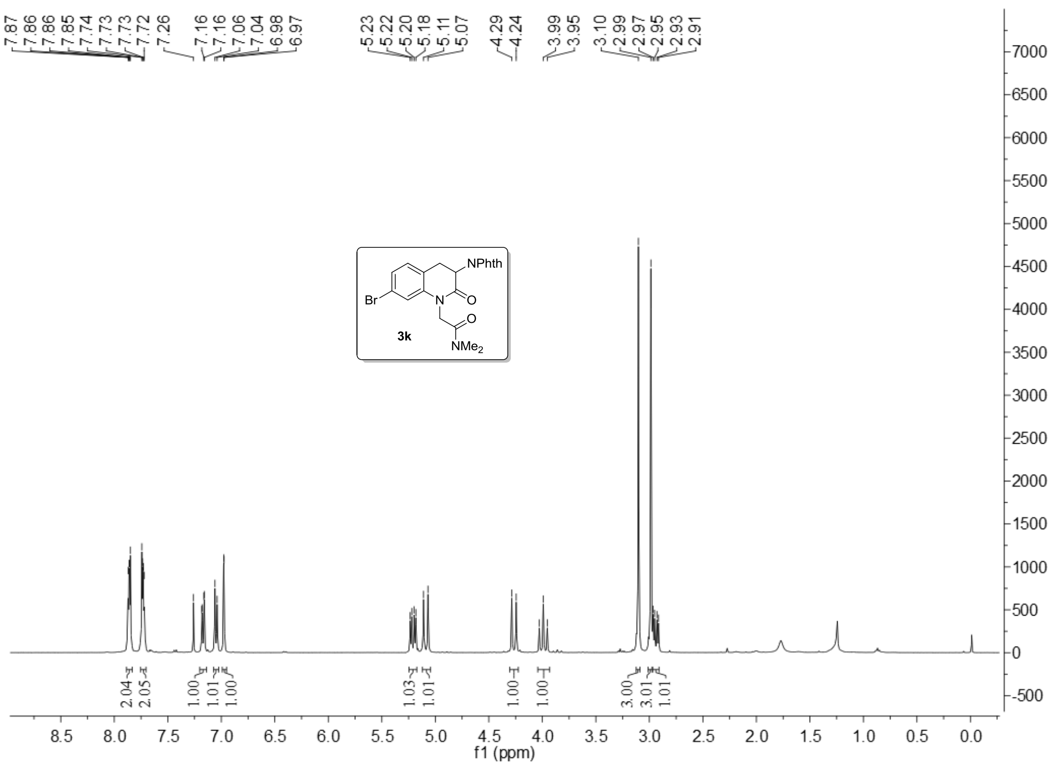
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O
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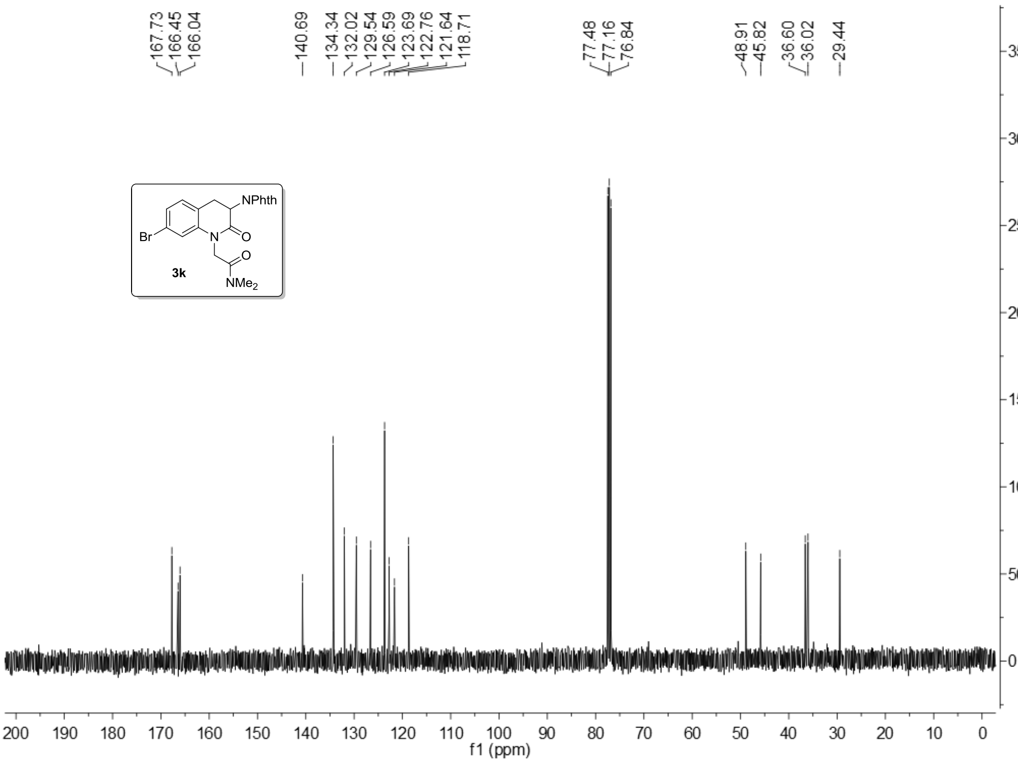
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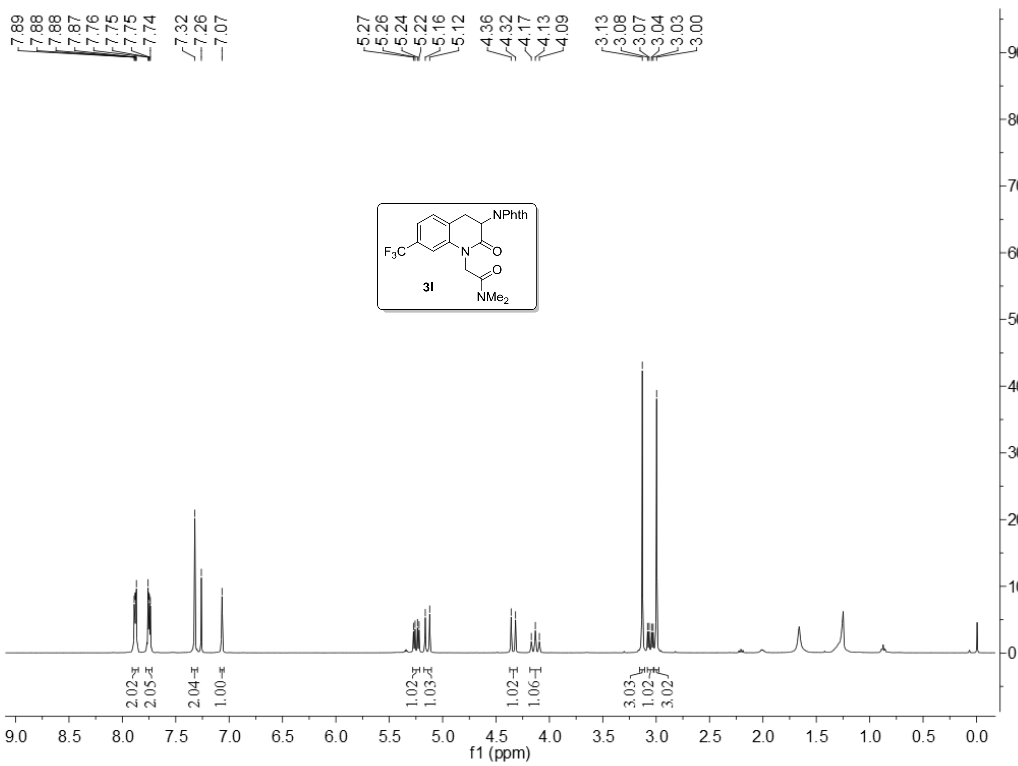
f1 (ppm)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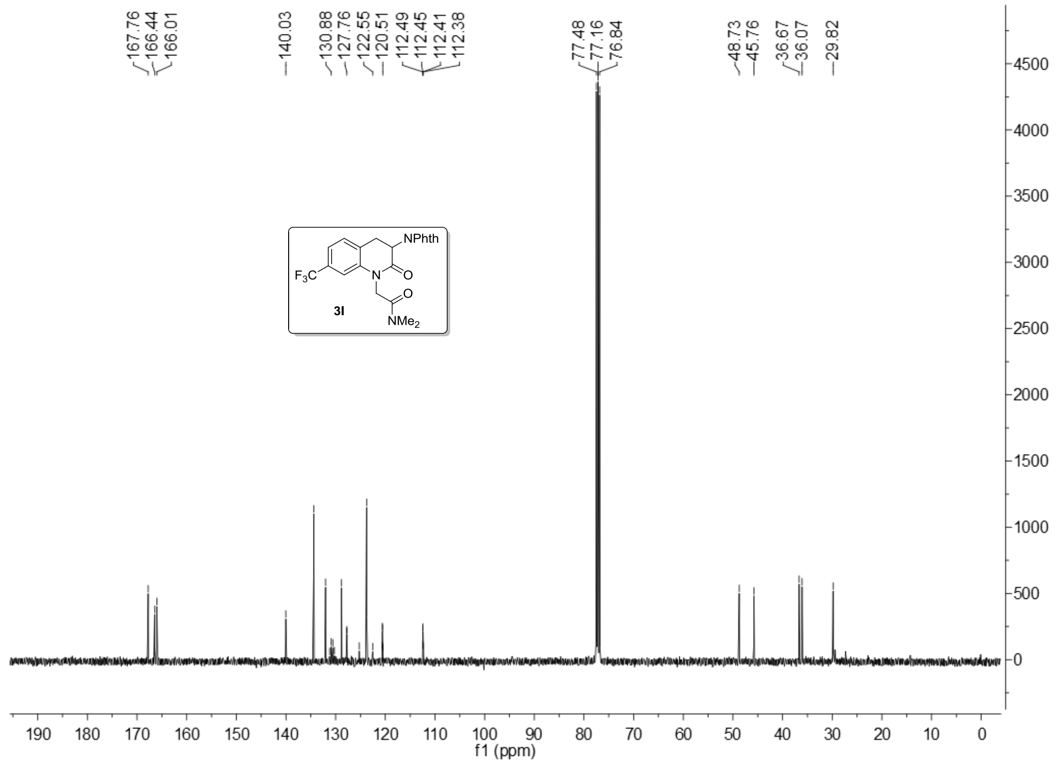

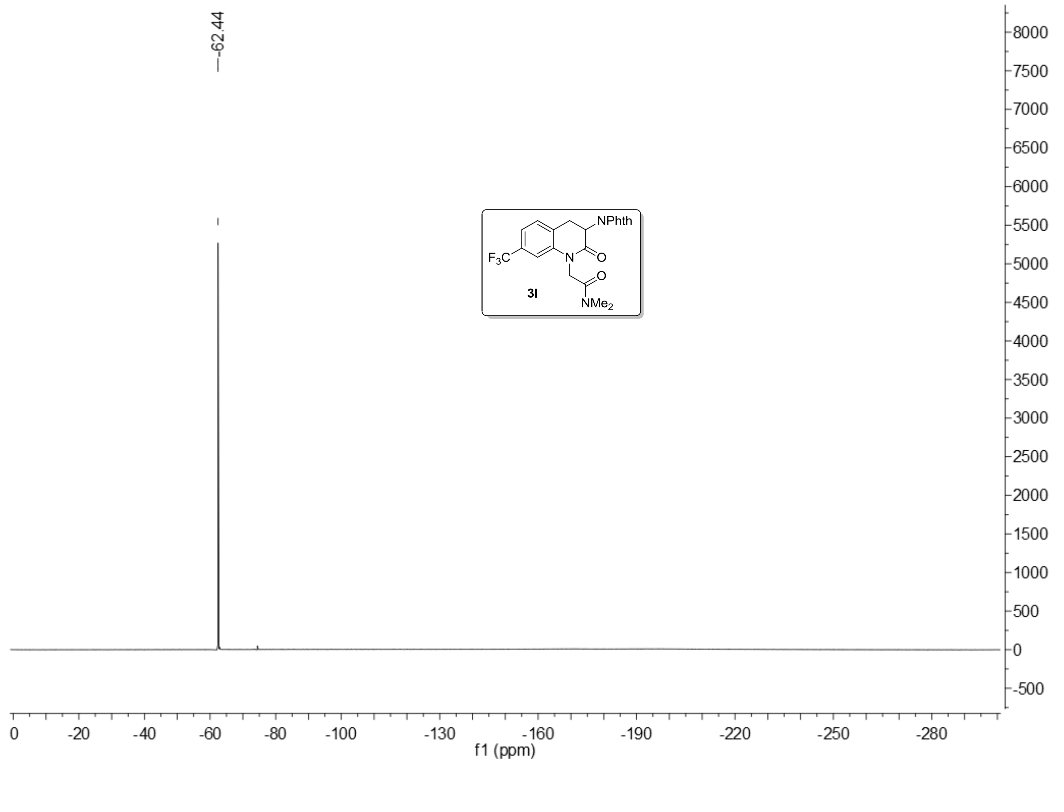

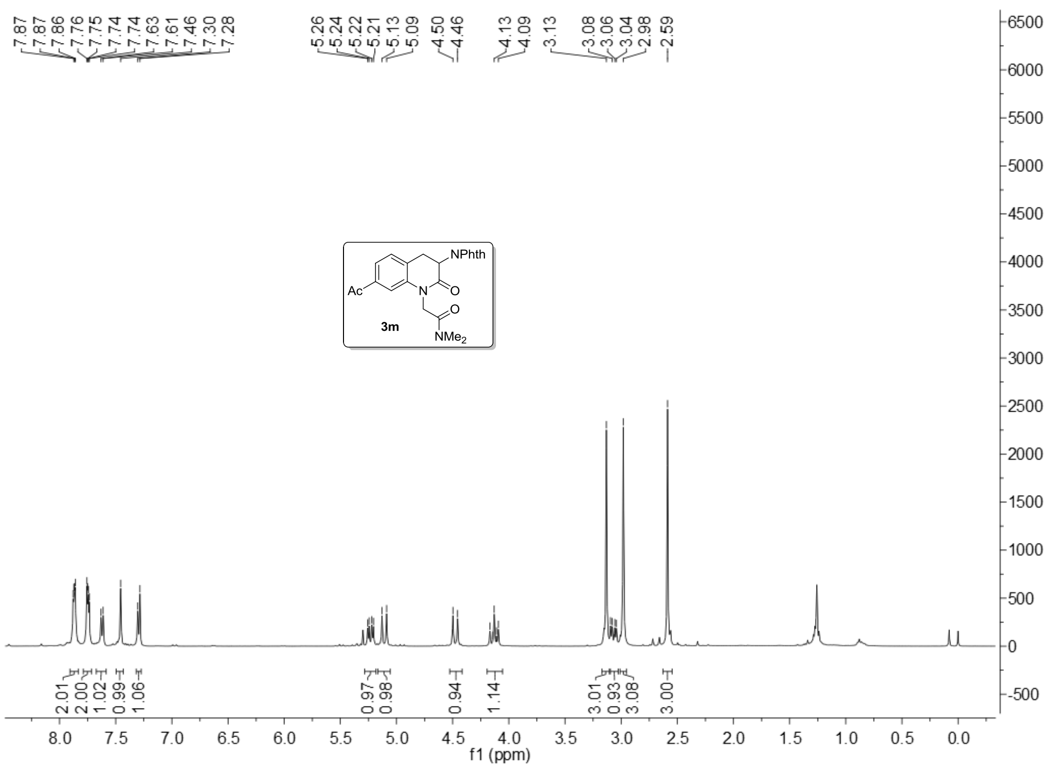

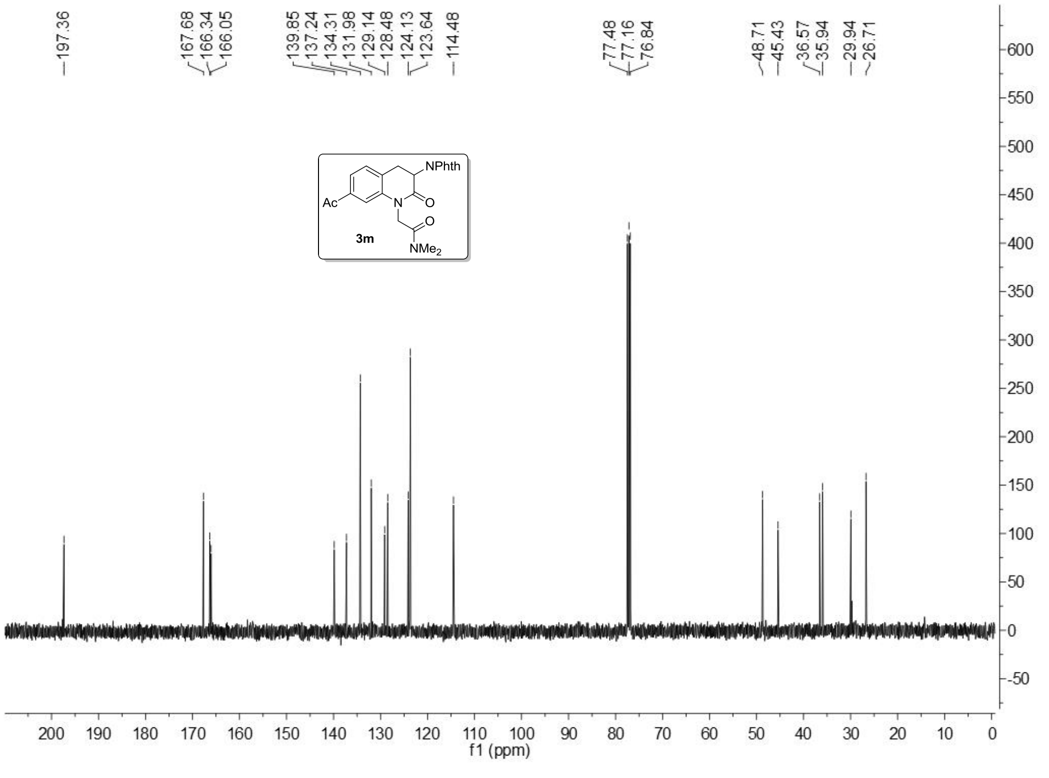

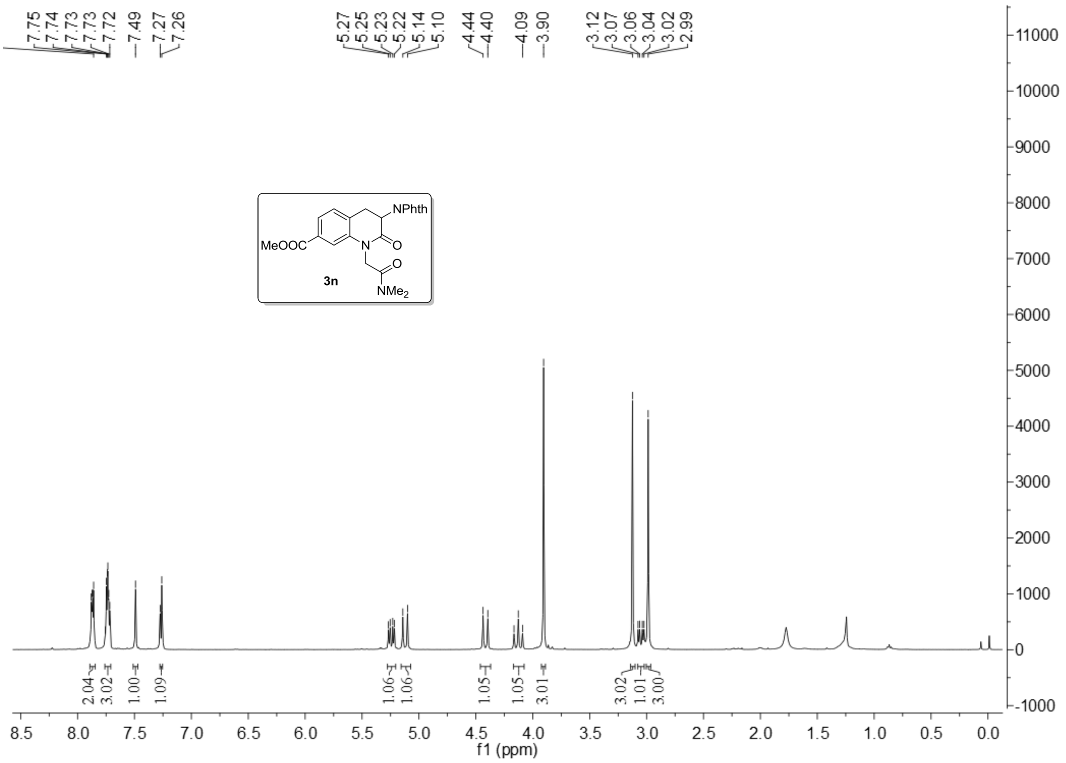

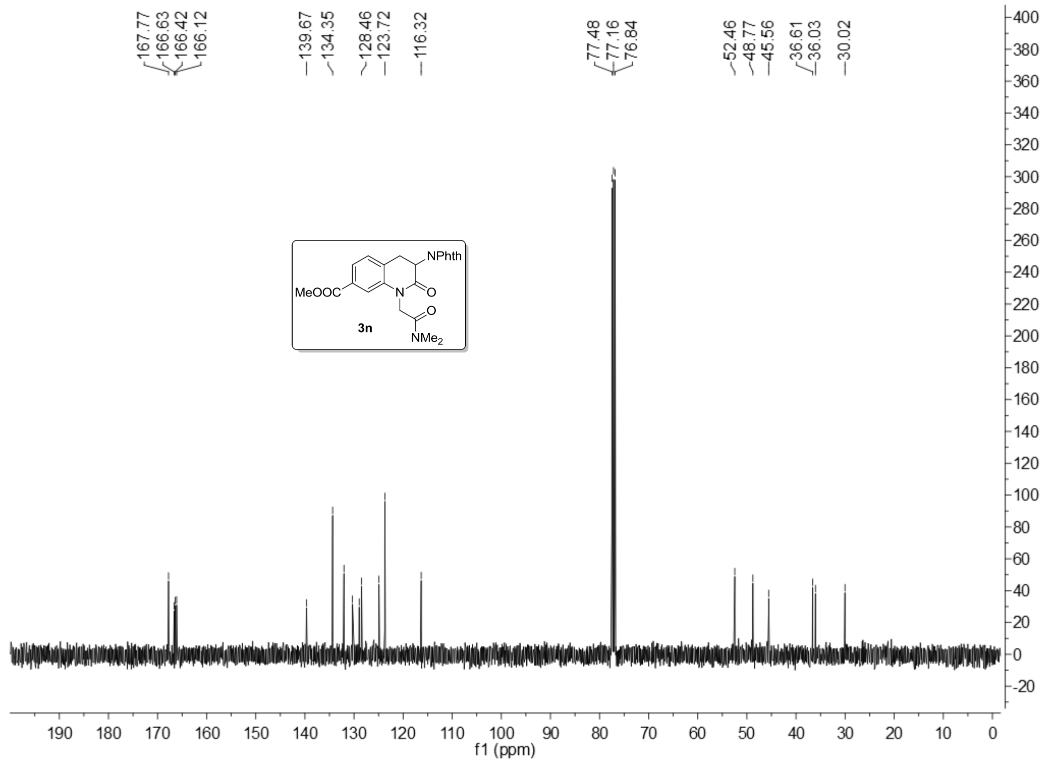

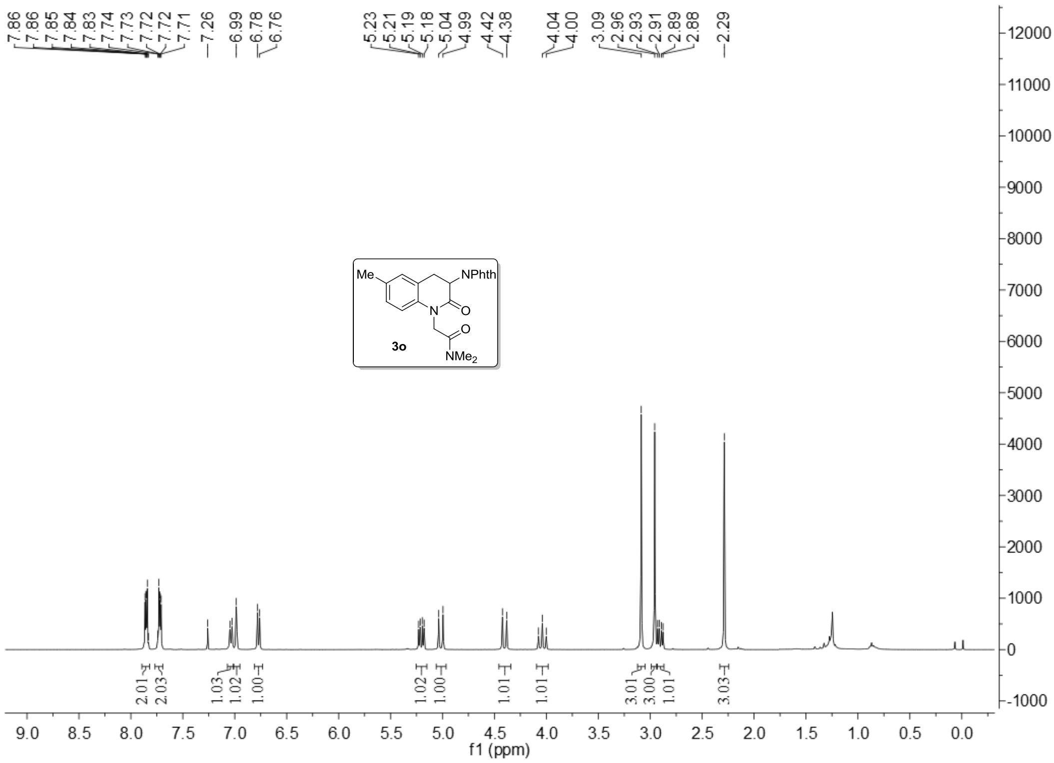
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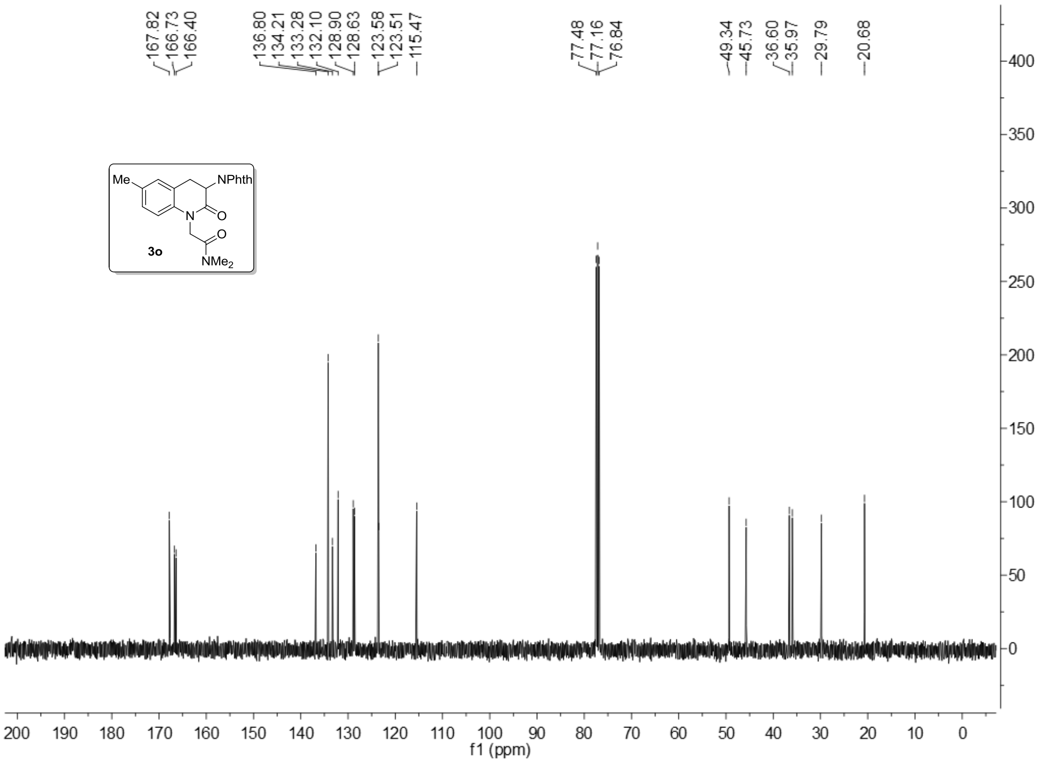
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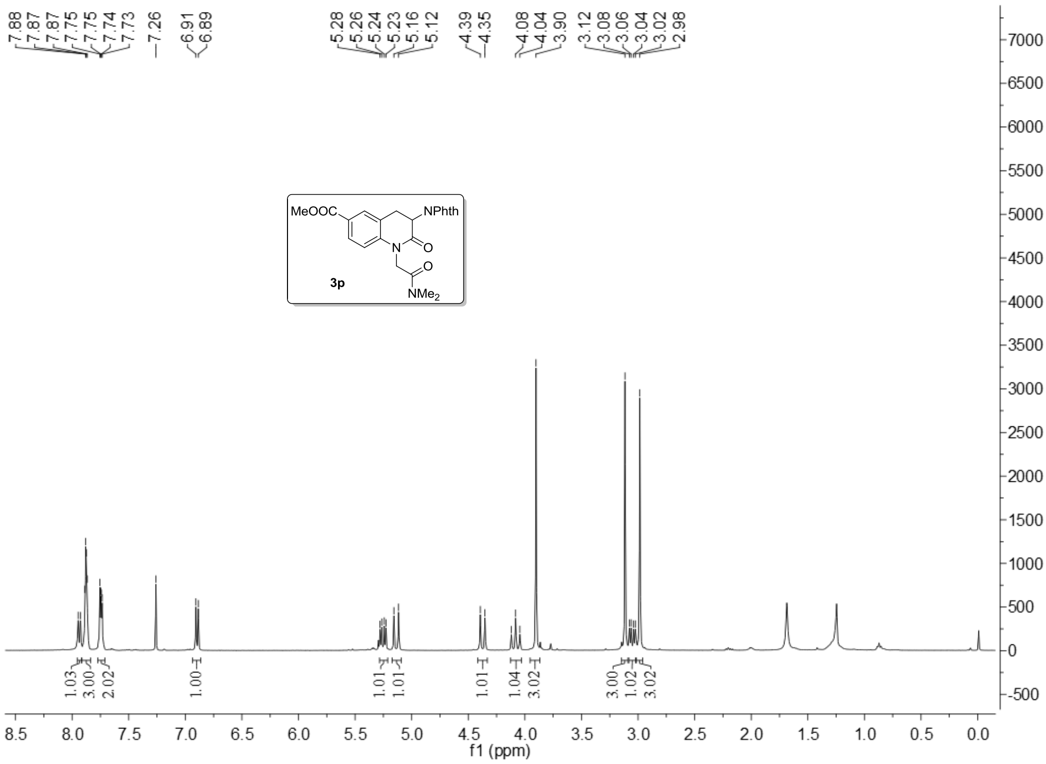
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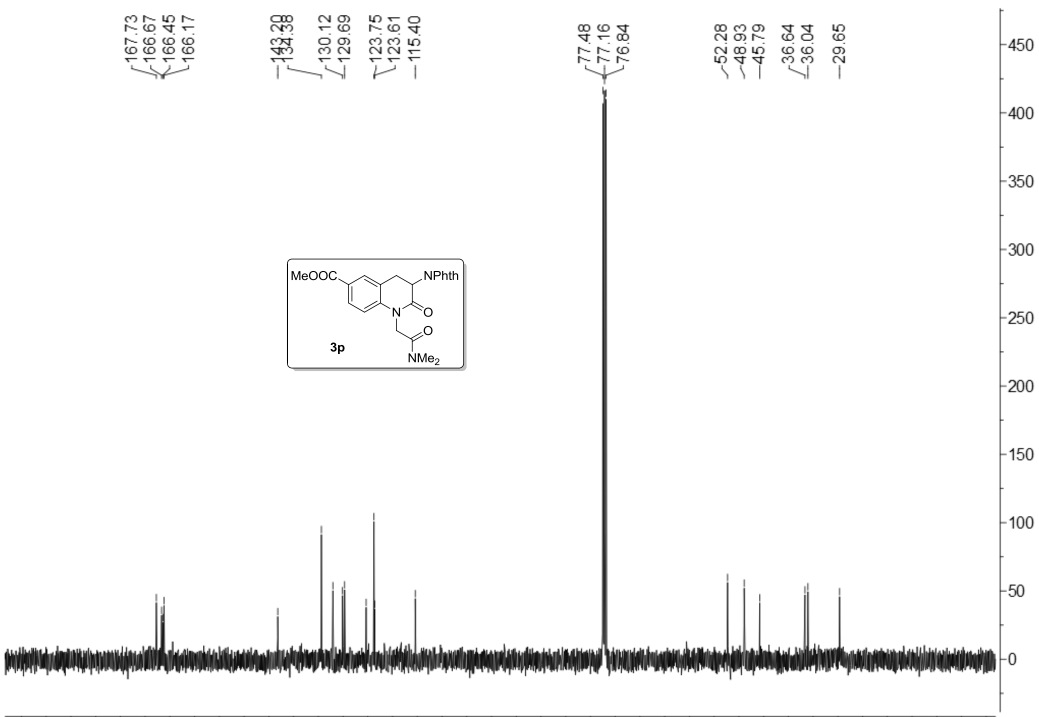
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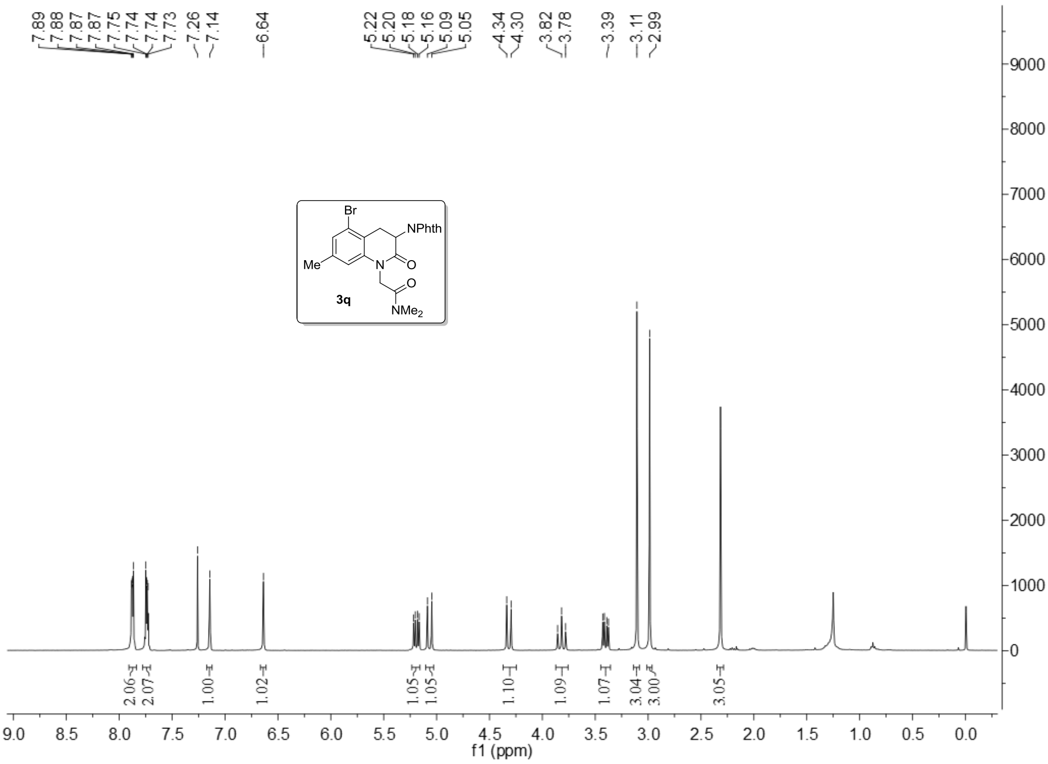
f1 (ppm)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3.82 3.78
3.39
3.11 2.99
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NPhth
Me
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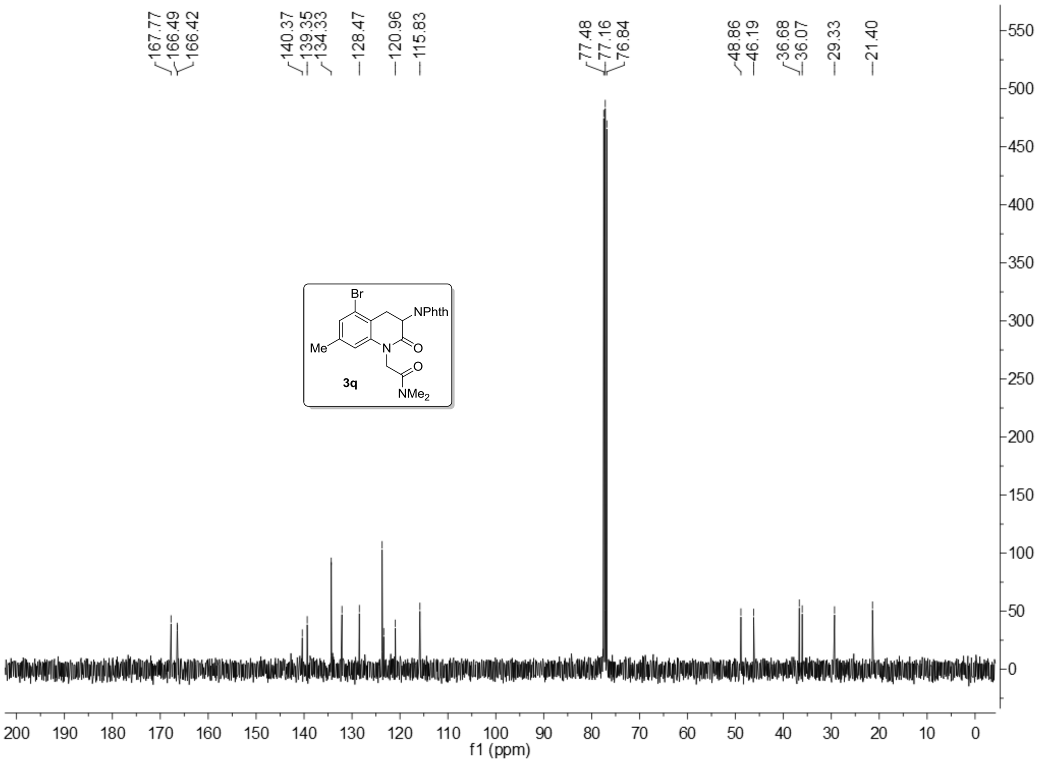
f1 (ppm)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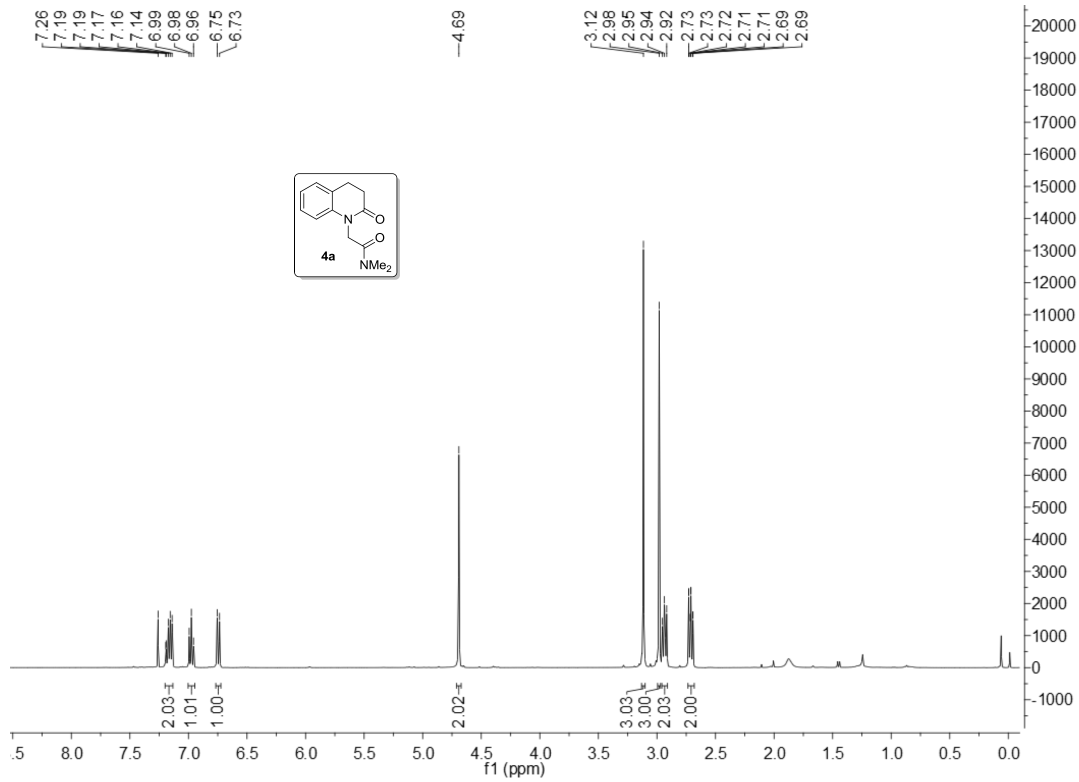
f1 (ppm)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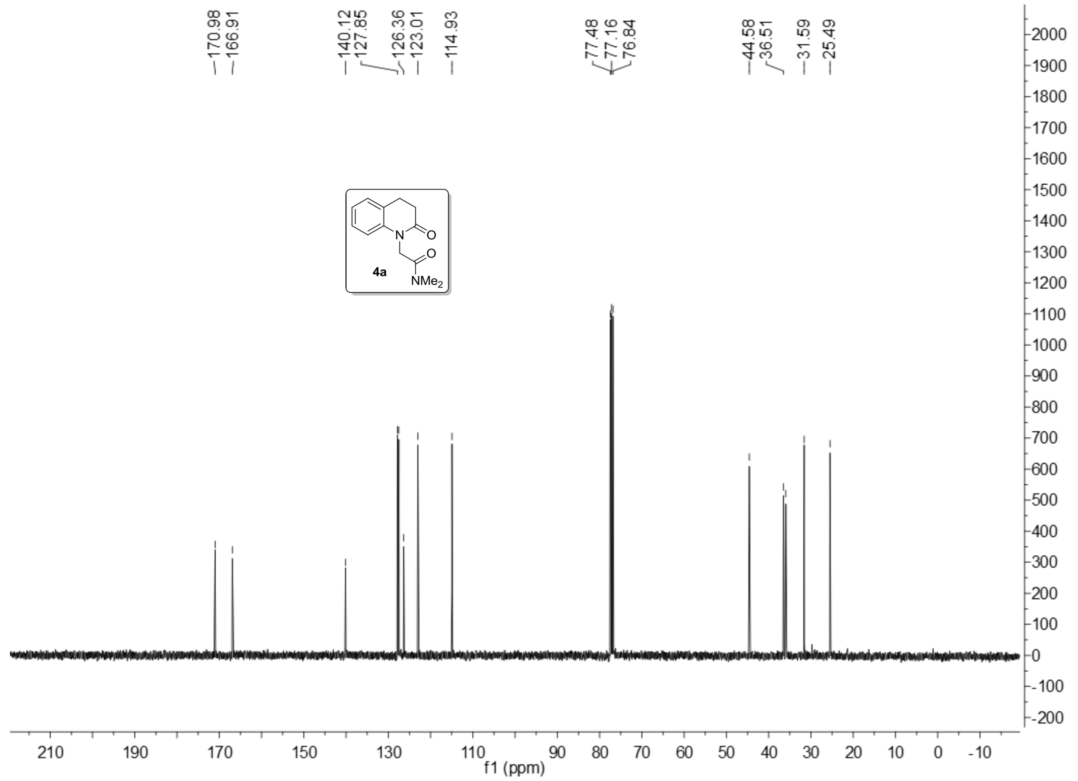
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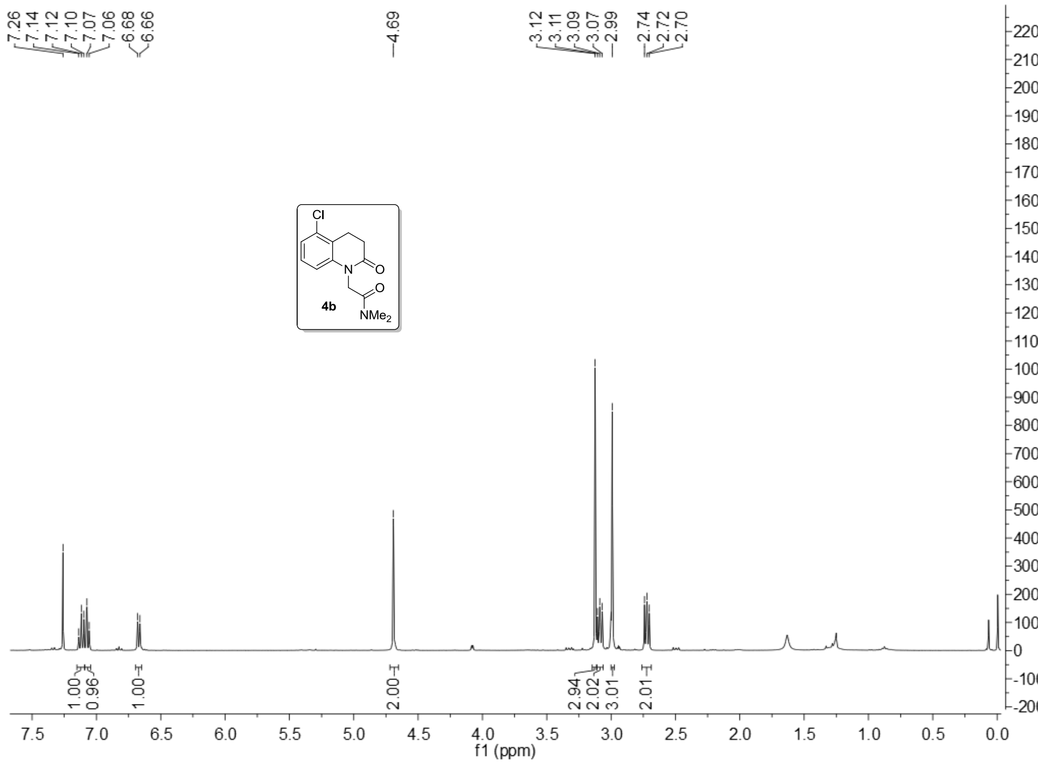
f1 (ppm)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3.09
3.07
2.99
2.74
2.72
2.70
Cl
N
O
O
NMe2
4b
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0.96
1.00
2.00
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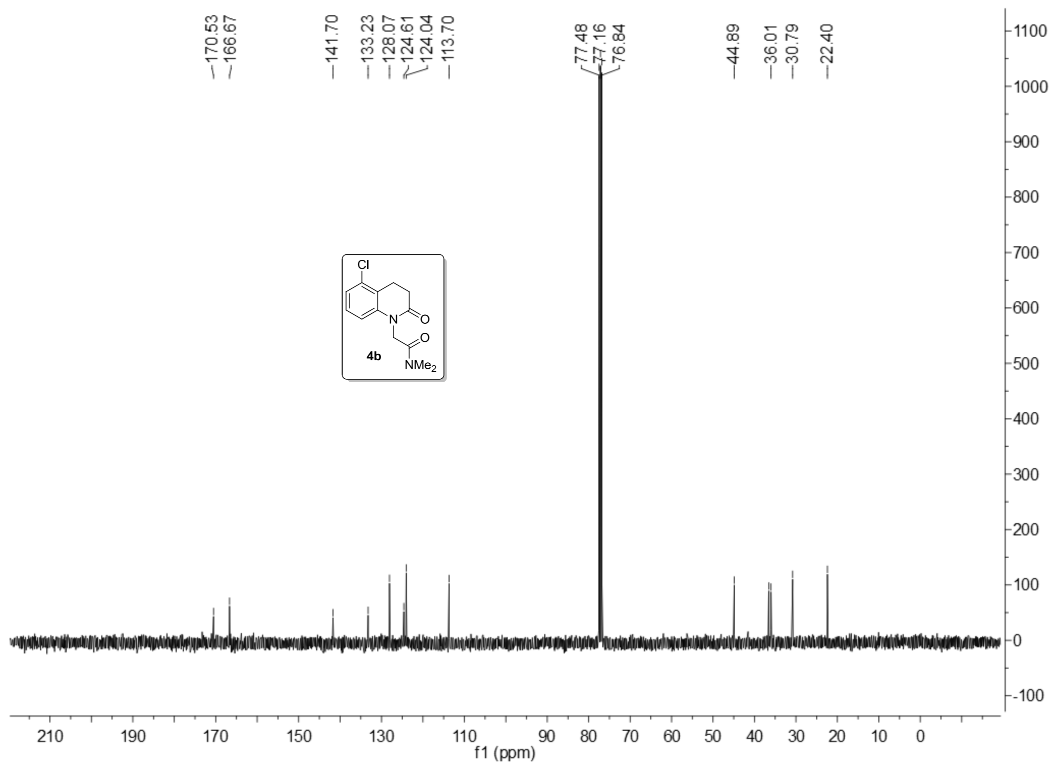
2.02
3.01
2.01
f1 (ppm)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113.70
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30.79
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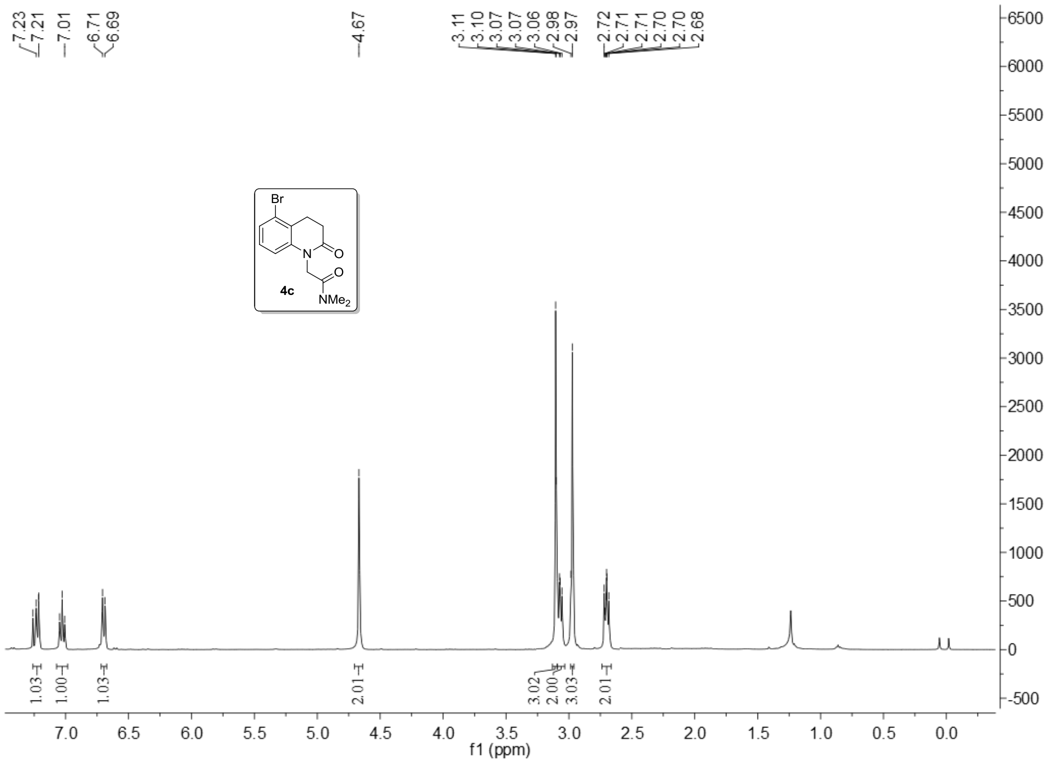
O
O
NMe2
4b
f1 (ppm)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3.06
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2.72
2.71
2.71
2.70
2.70
2.68
Br
N
O
O
4c
NMe2
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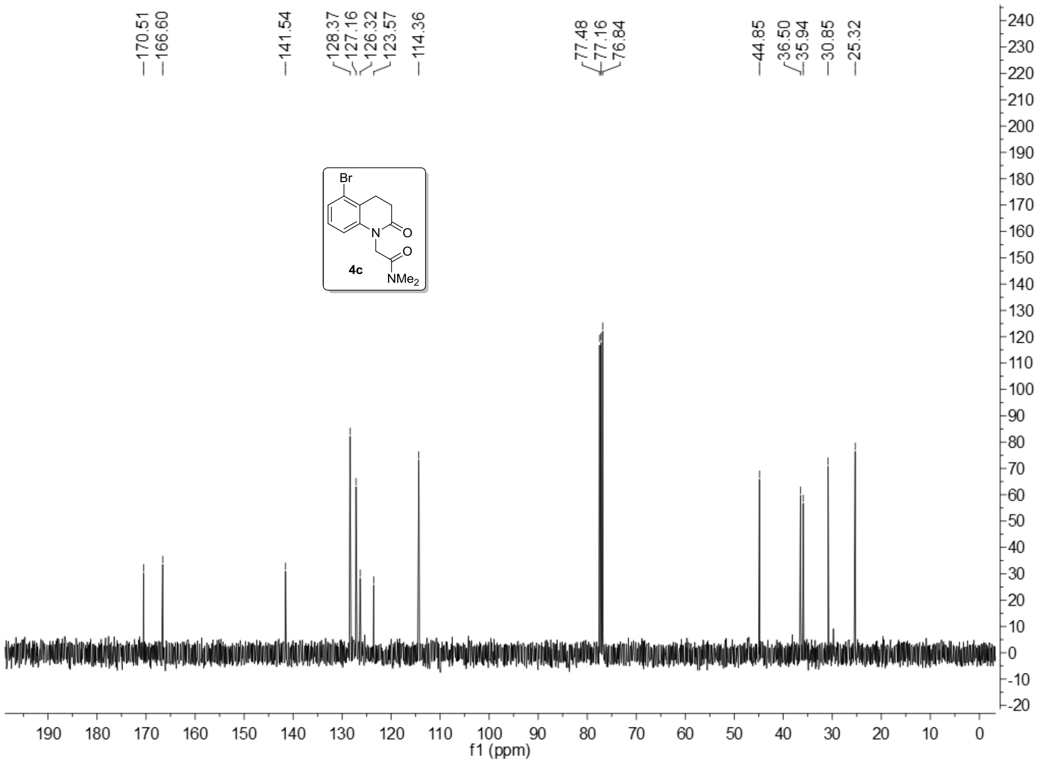
1.00
1.03
2.01
3.02
2.00
3.03
2.01
f1 (ppm)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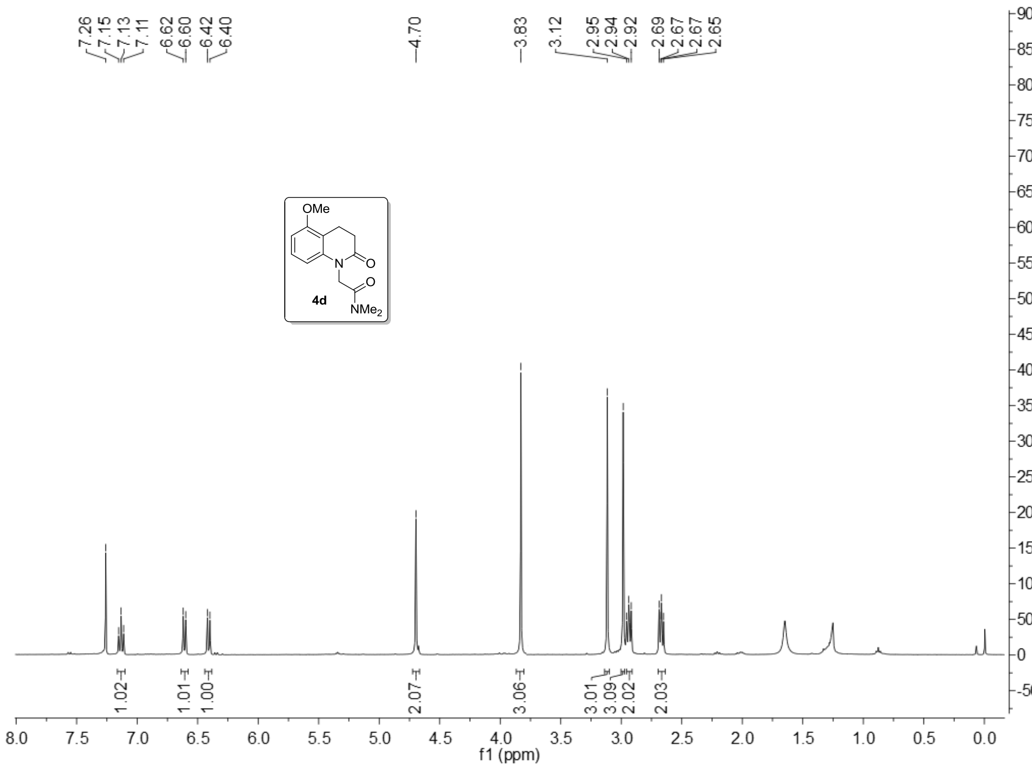
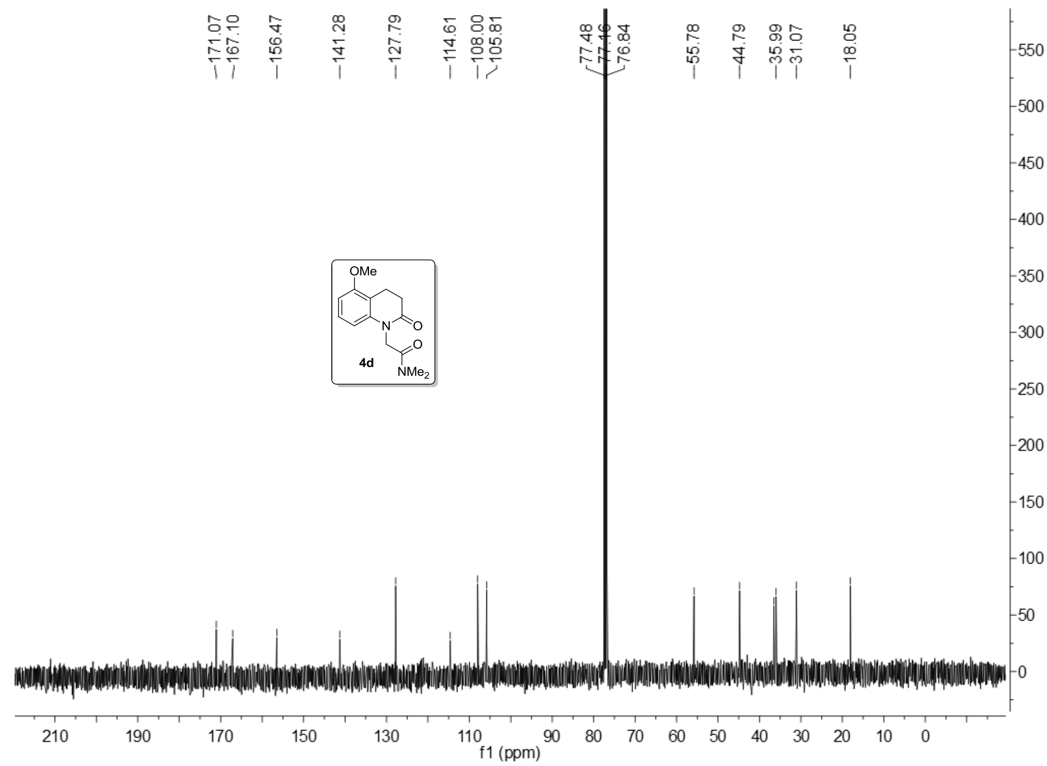
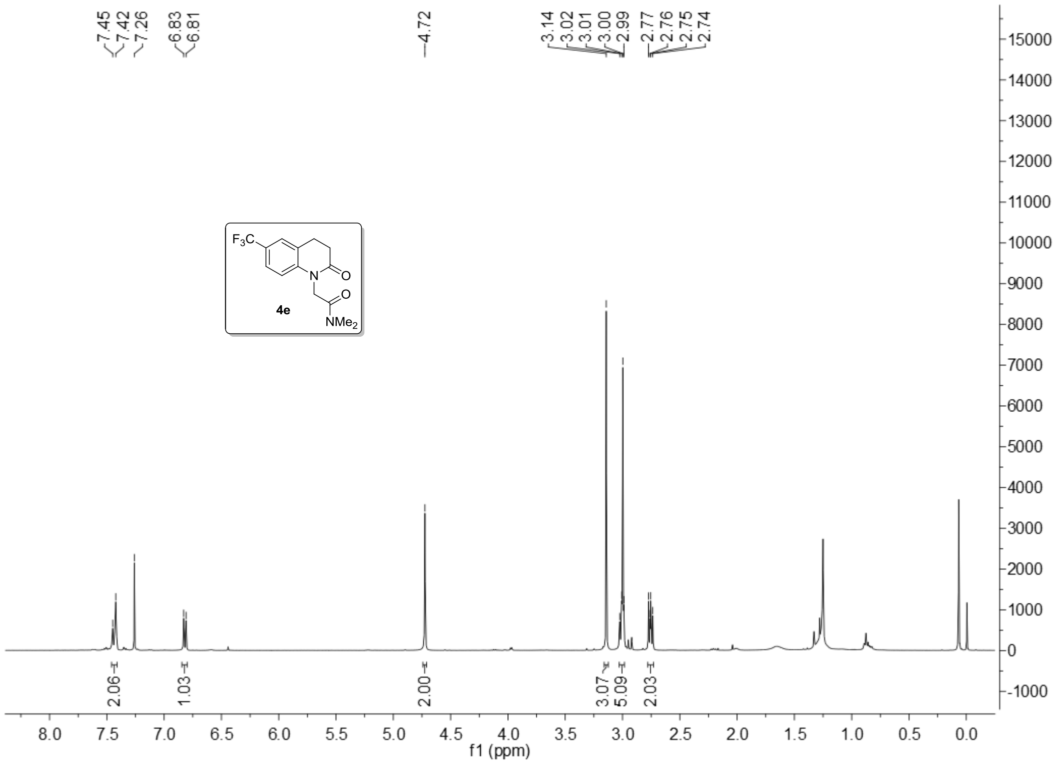
N
O
O
4c
NMe2
f1 (ppm)



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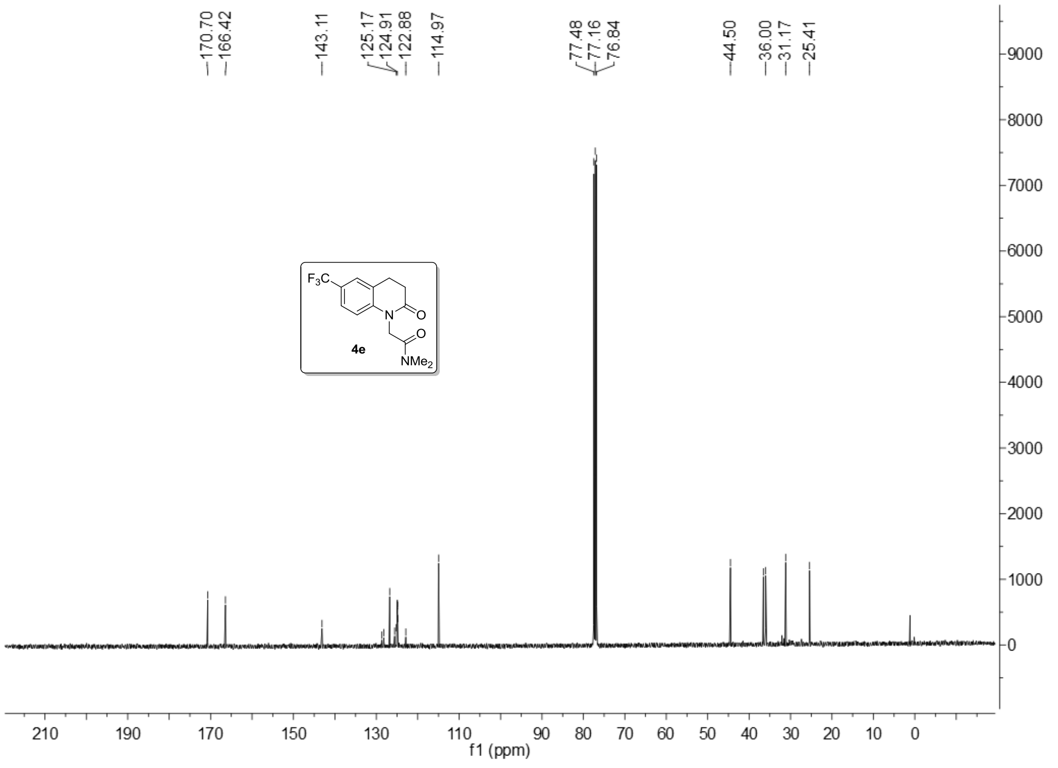
4e
2.06 1.03 2.00 3.07 5.09 2.03
f1 (ppm)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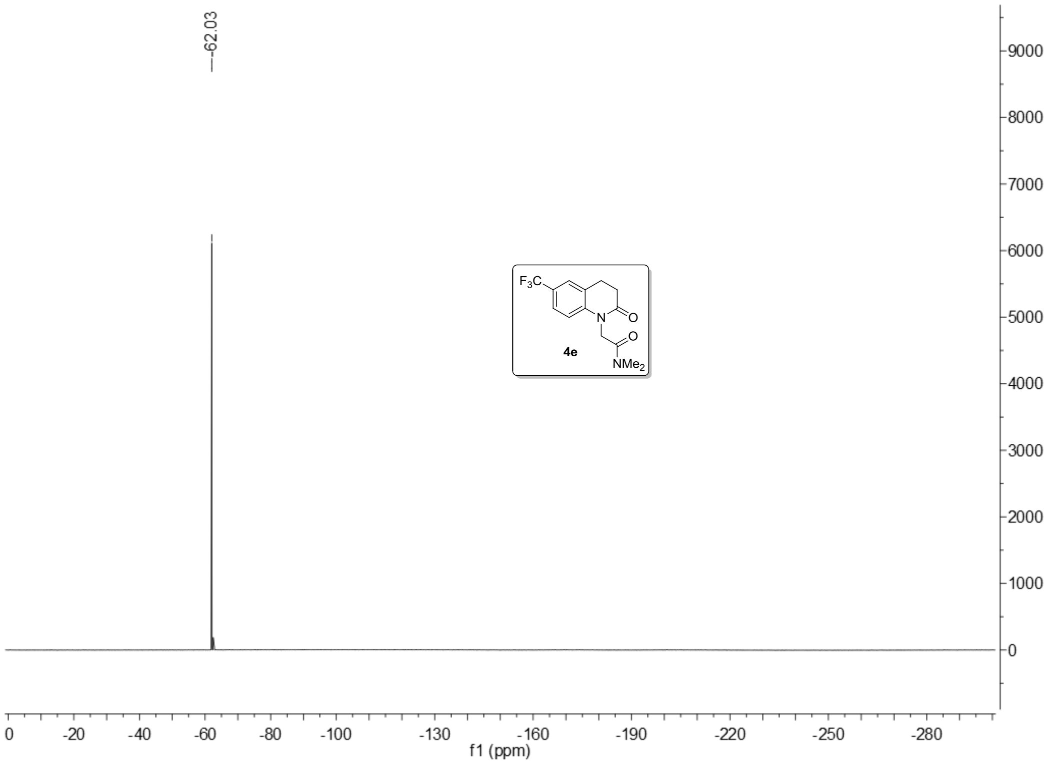
f1 (ppm)



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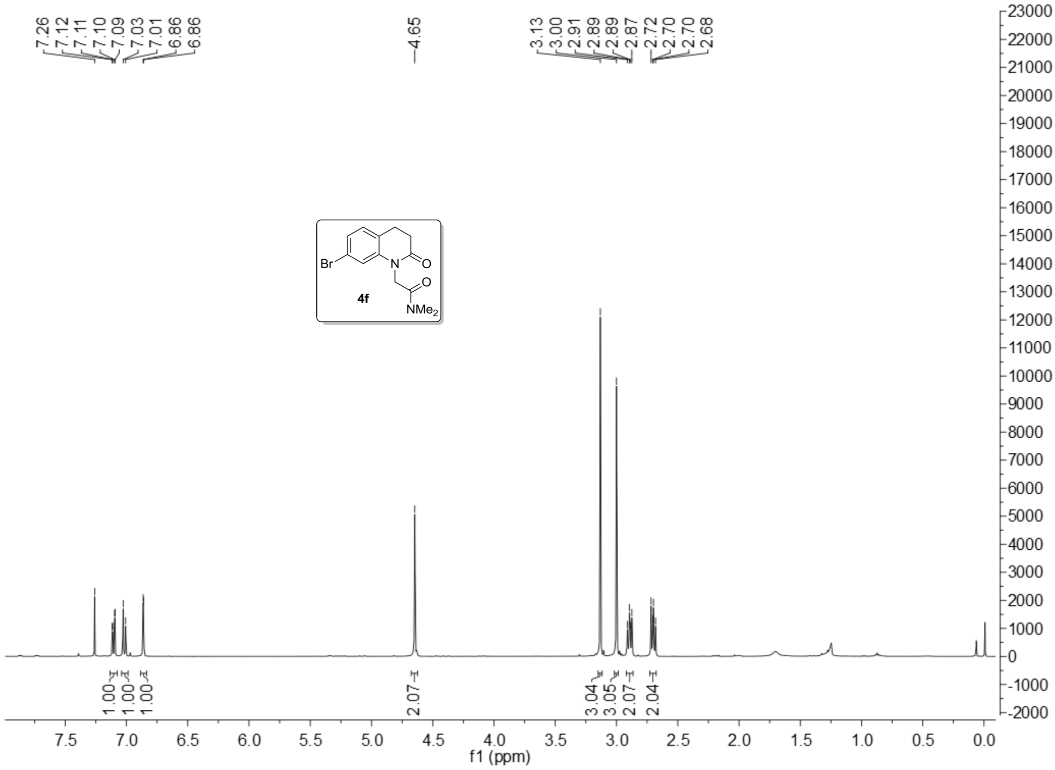
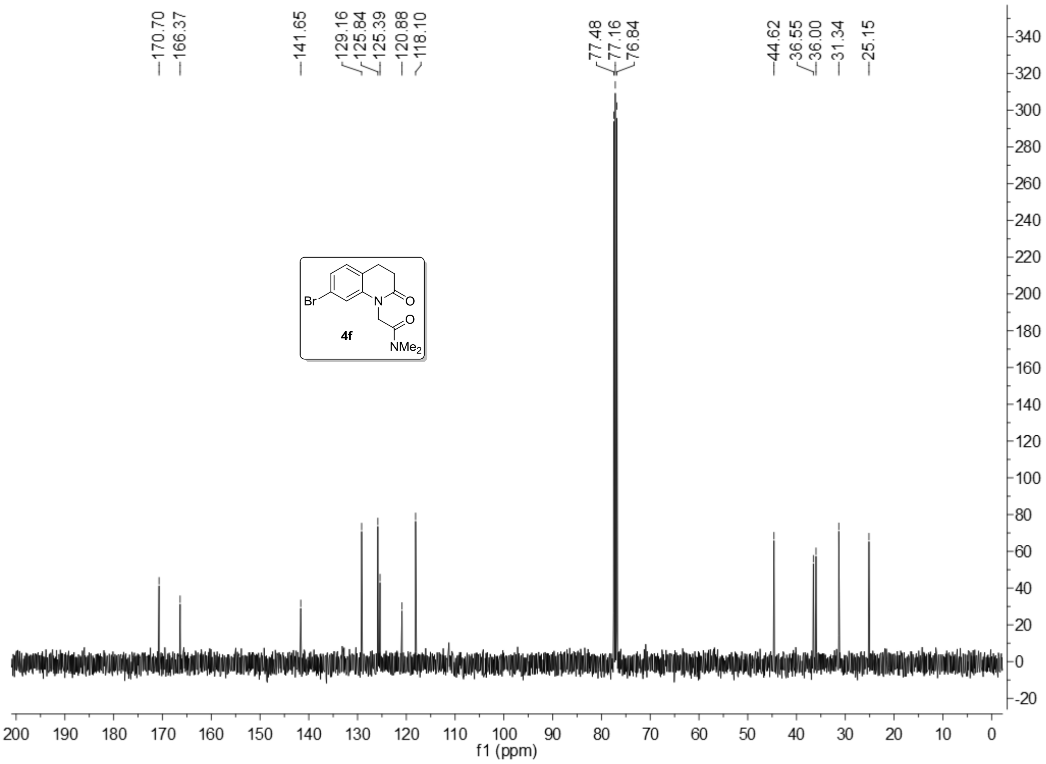


4f
f1 (ppm)



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125.39
120.88
118.10
77.48
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31.34
25.15
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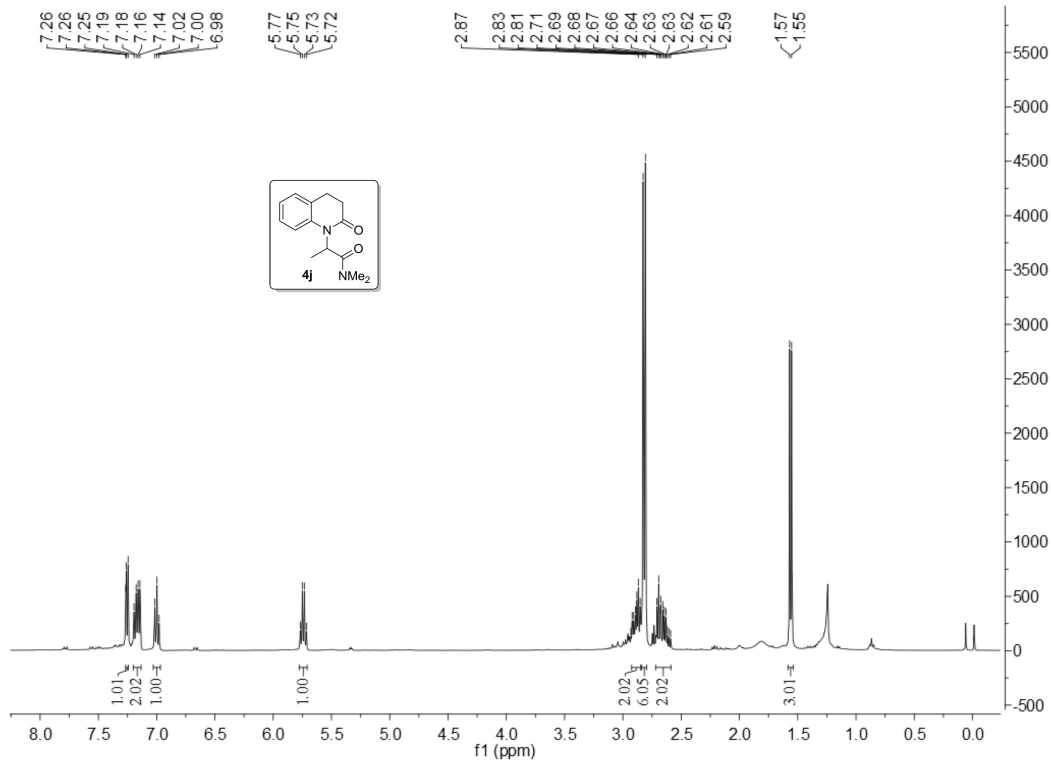
O
O
4f
NMe2
f1 (ppm)



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5.75
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2.68
2.67
2.66
2.64
2.63
2.63
2.62
2.61
2.59
1.57
1.55
N
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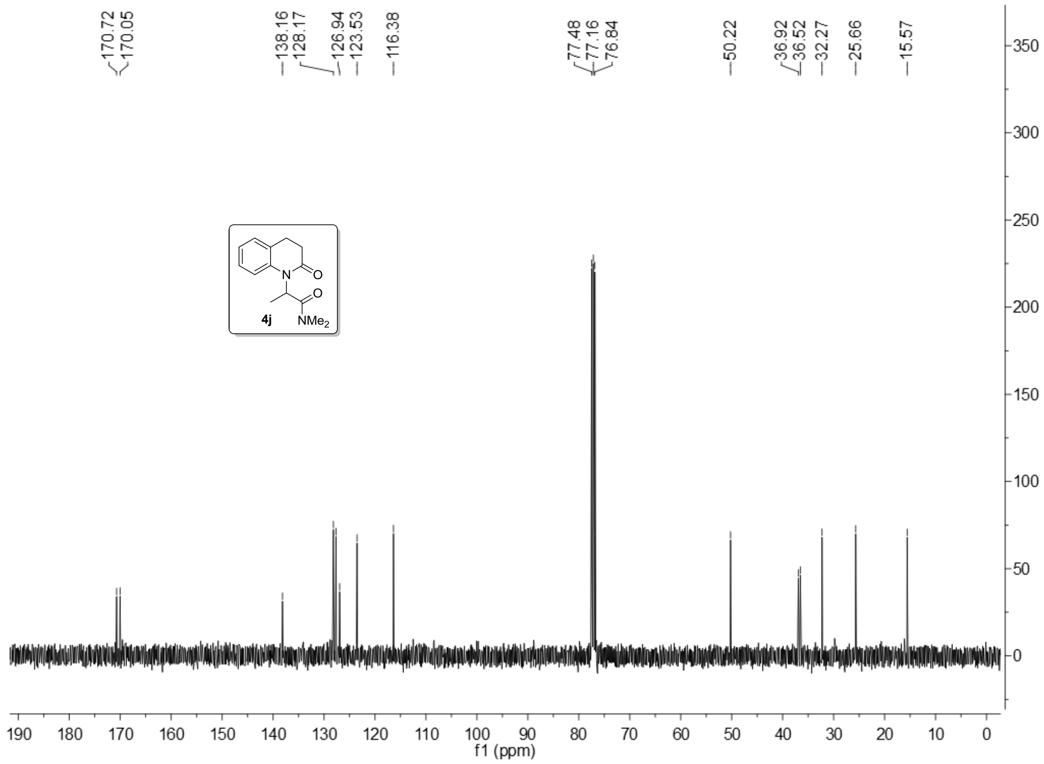
6.05
2.02
3.01
f1 (ppm)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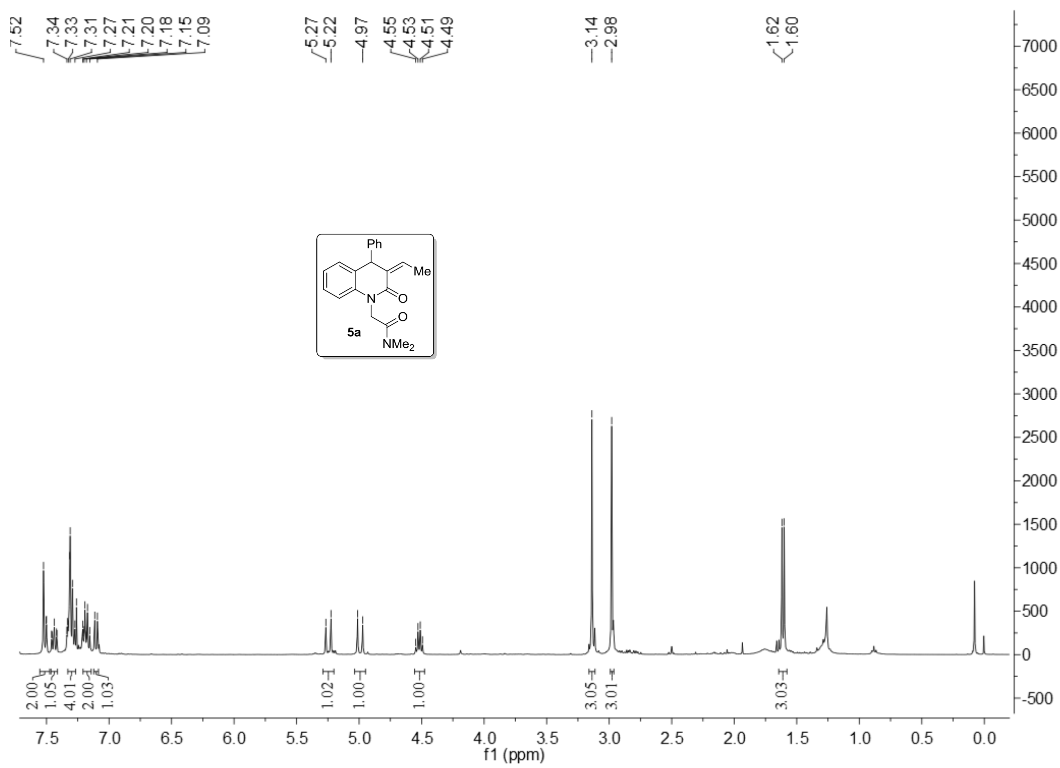
4j
NMe2
f1 (ppm)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7.09
5.27
5.22
4.97
4.55
4.53
4.51
4.49
3.14
2.98
1.62
1.60
Ph
Me
5a
NMe2
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2.00
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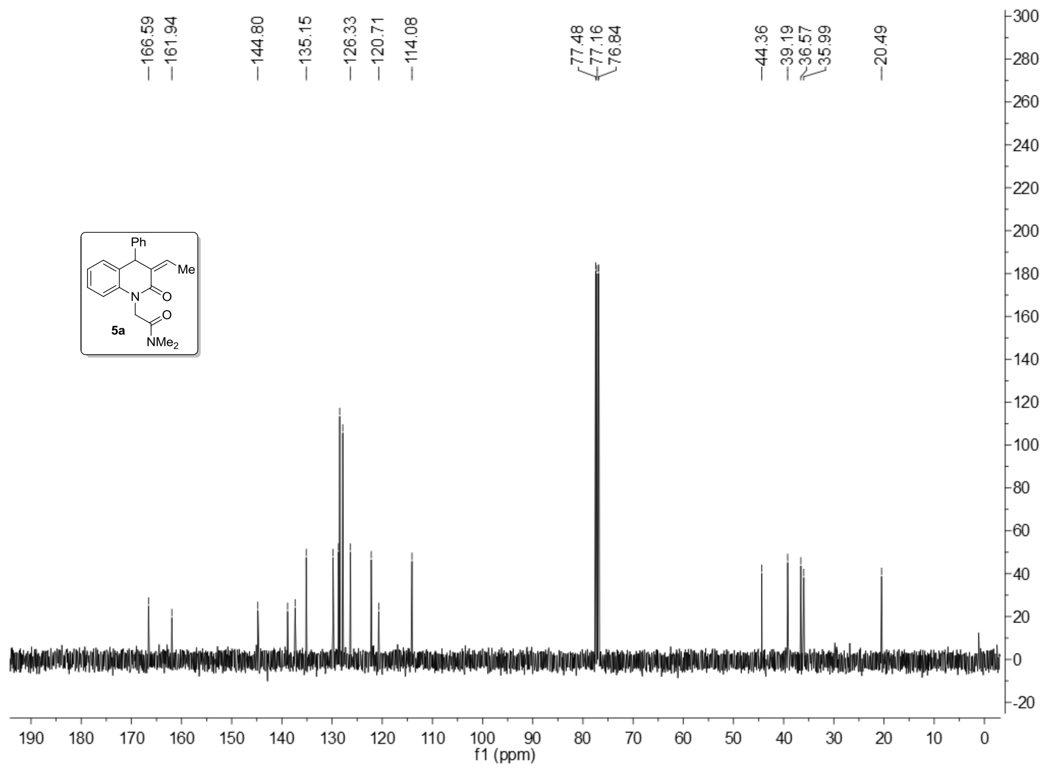
1.02
1.00
1.00
3.05
3.01
3.03
f1 (ppm)



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20.49
Ph
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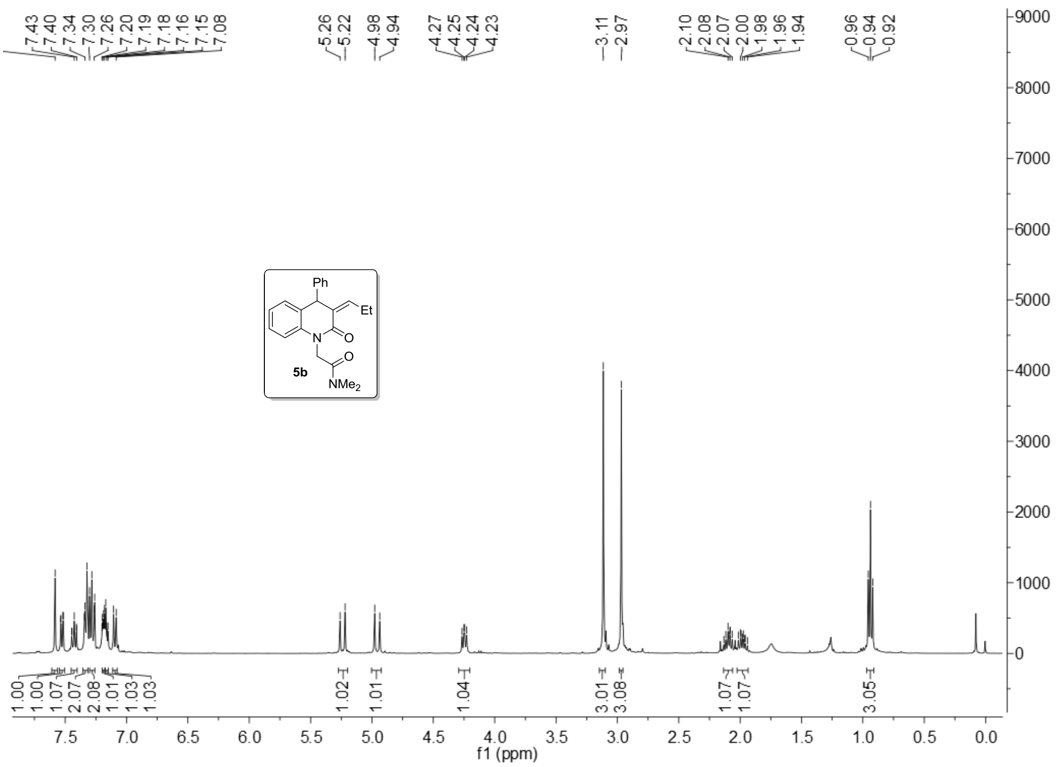
O
5a
NMe2
f1 (ppm)



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7.08
5.26
5.22
4.98
4.94
4.27
4.25
4.24
4.23
3.11
2.97
2.10
2.08
2.07
2.00
1.98
1.96
1.94
0.96
0.94
0.92
Ph
Et
N
O
O
5b
NMe2
1.00
1.00
1.07
2.07
2.08
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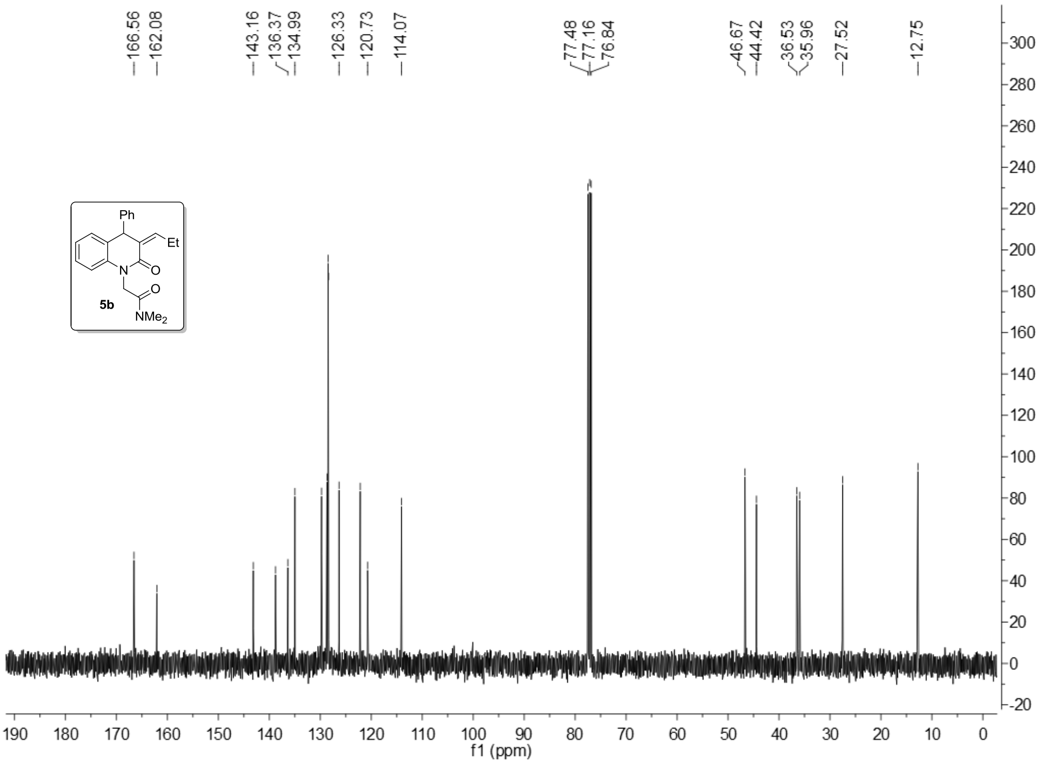
1.07
3.05
f1 (ppm)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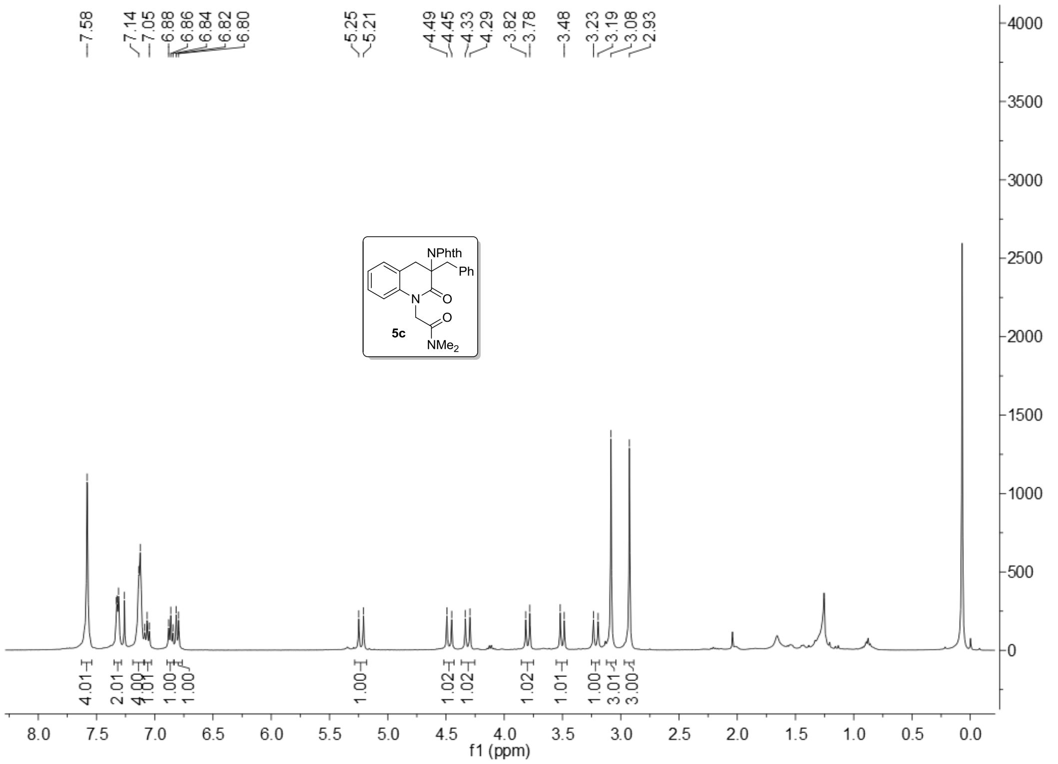
f1 (ppm)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4.29
3.82
3.78
3.48
3.23
3.19
3.08
2.93
NPhth
Ph
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O
O
5c
NMe2
4.01
2.01
4.00
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1.00
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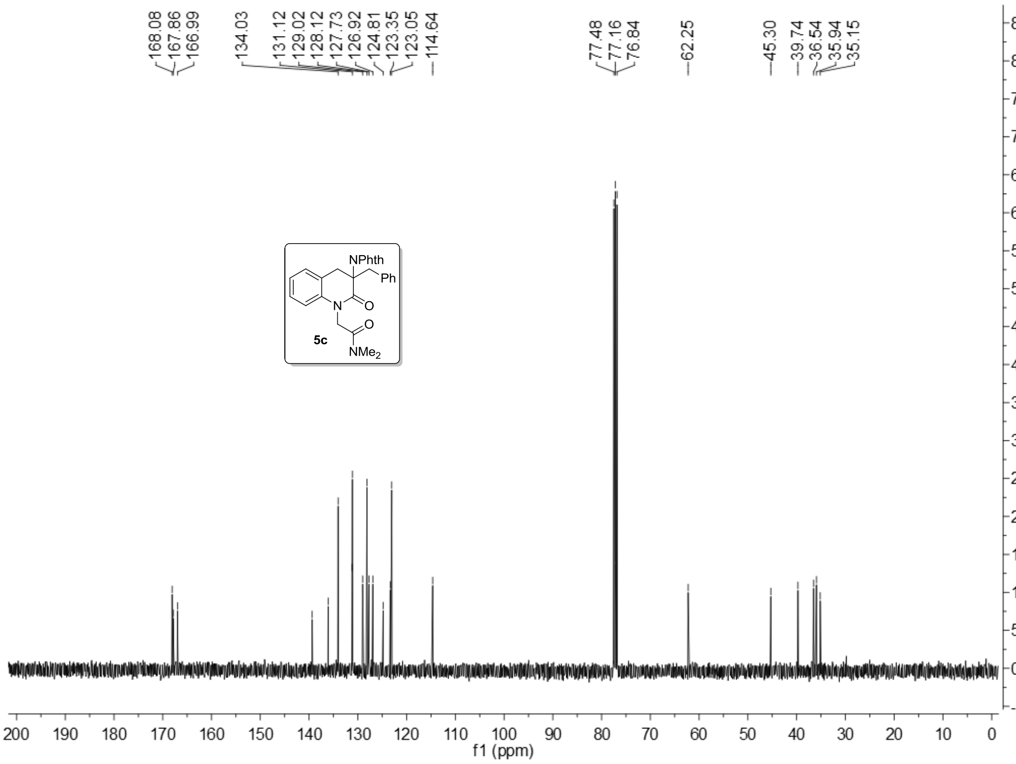
3.00
f1 (ppm)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77.48
77.16
76.84
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N
O
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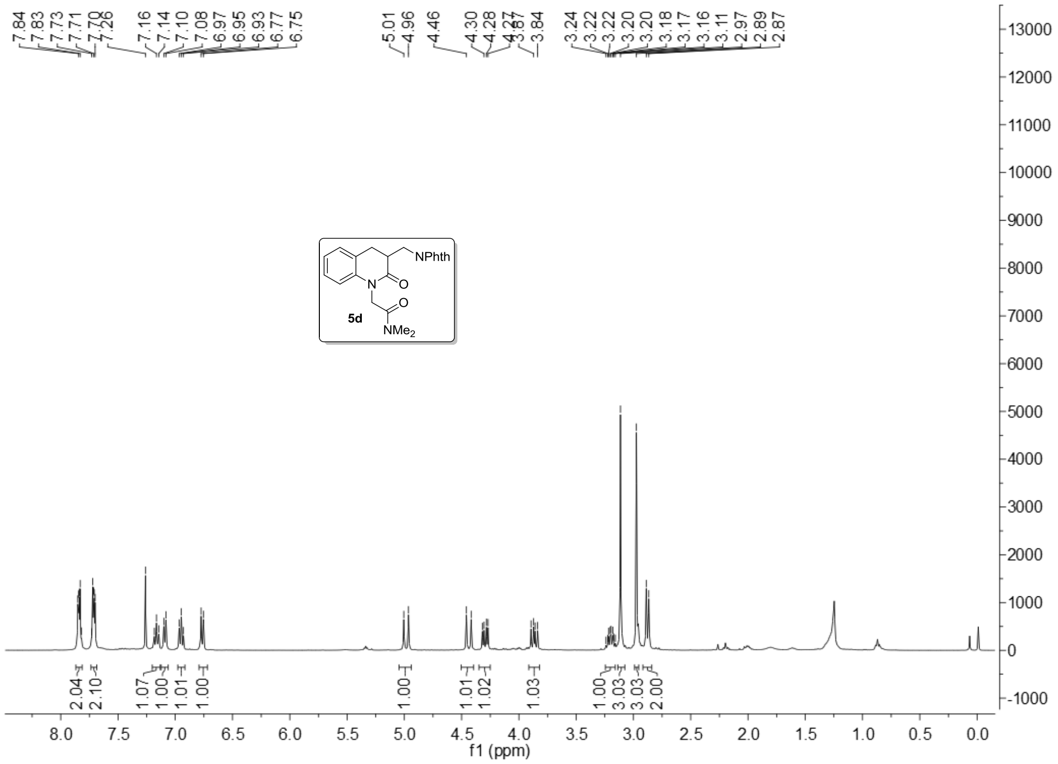
NMe2
f1 (ppm)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5.01
4.96
4.46
4.30
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4.27
3.87
3.84
3.24
3.22
3.22
3.20
3.20
3.18
3.17
3.16
3.11
2.97
2.89
2.87
NPhth
N
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O
5d
NMe2
2.04
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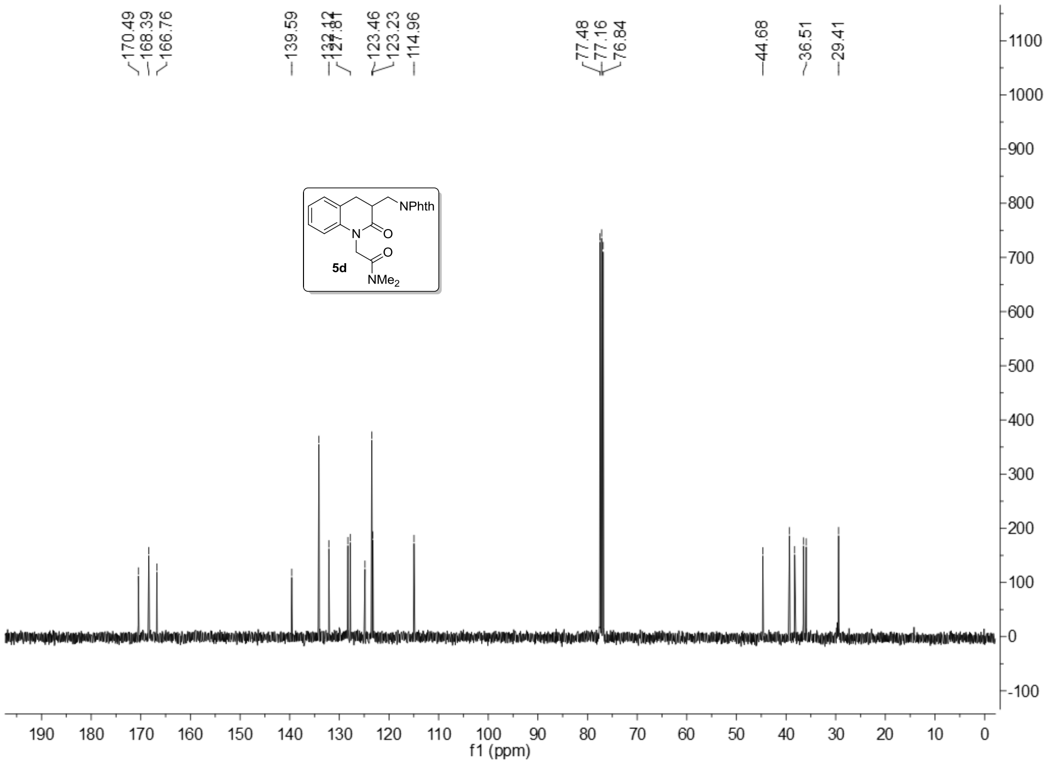

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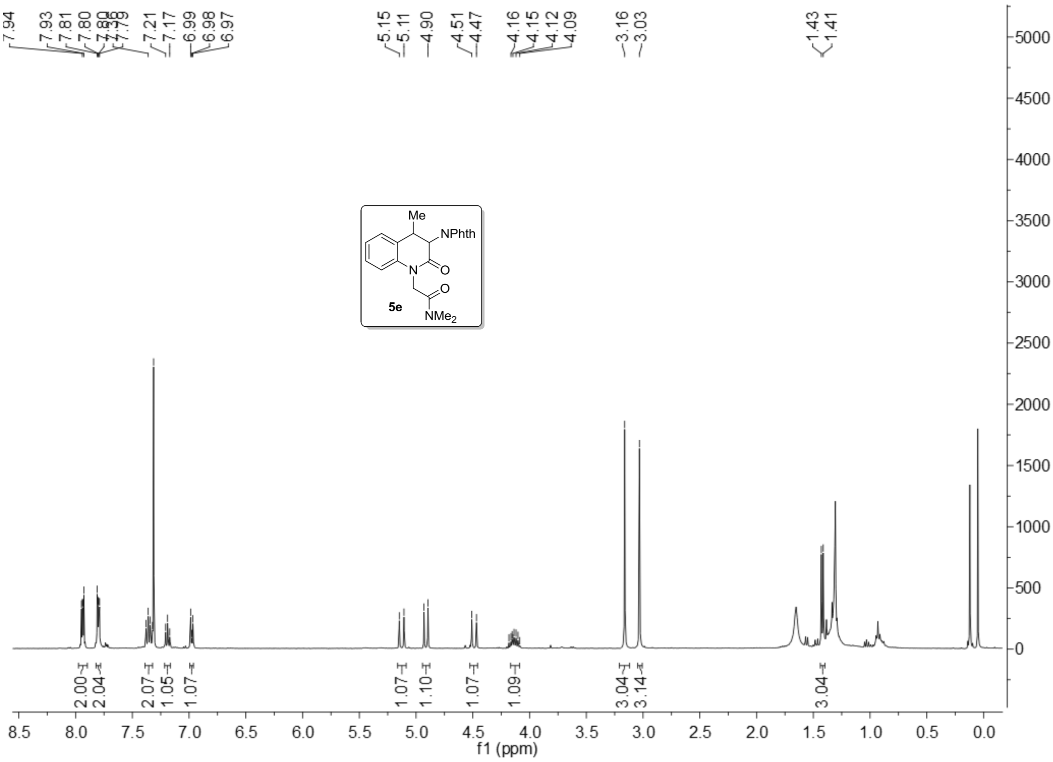
f1 (ppm)



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4.47
4.16
4.15
4.12
4.09
3.16
3.03
1.43
1.41
Me
NPhth
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O
O
5e
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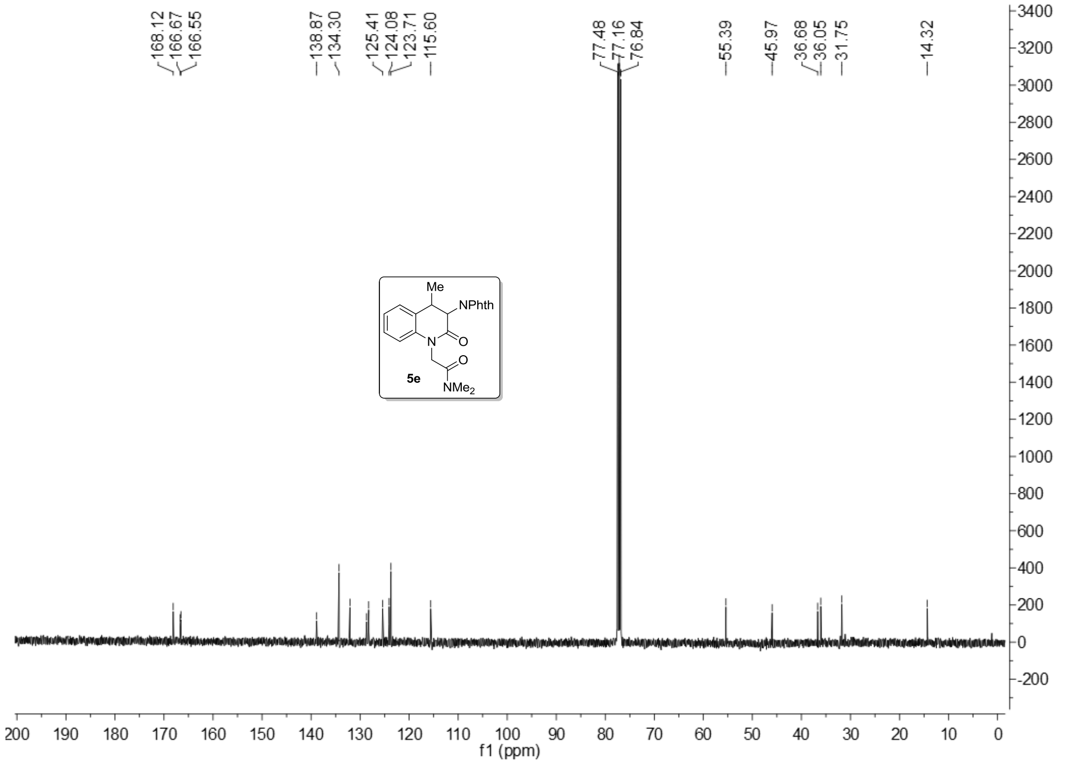

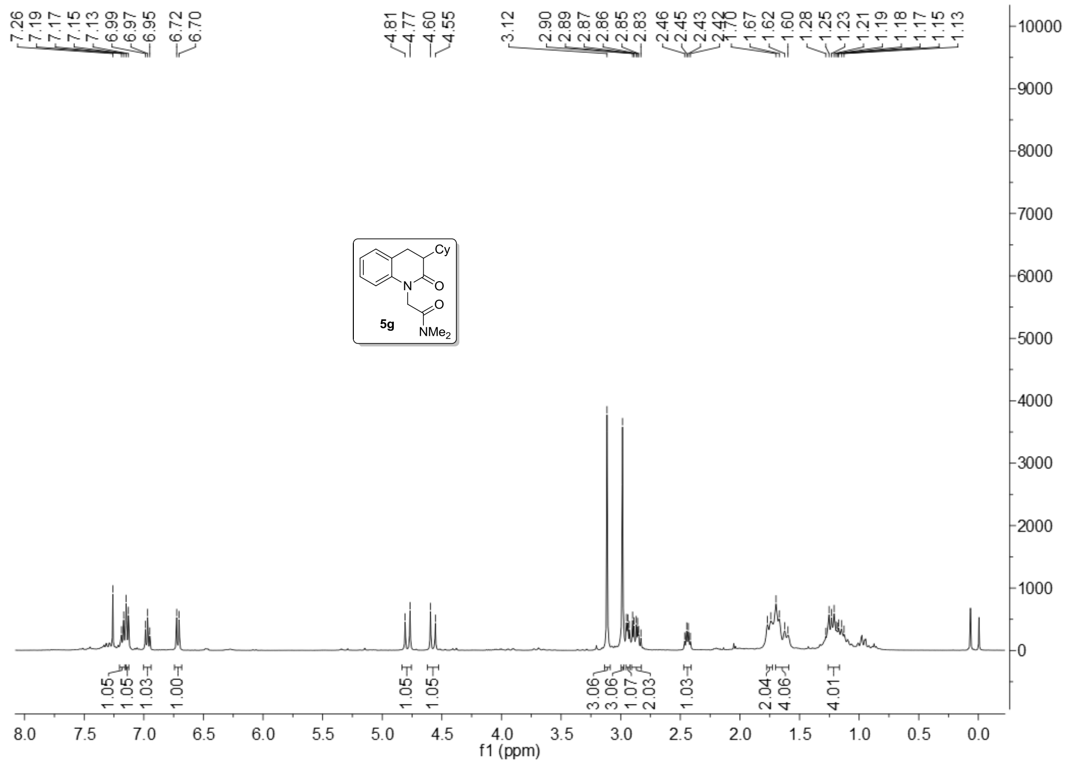

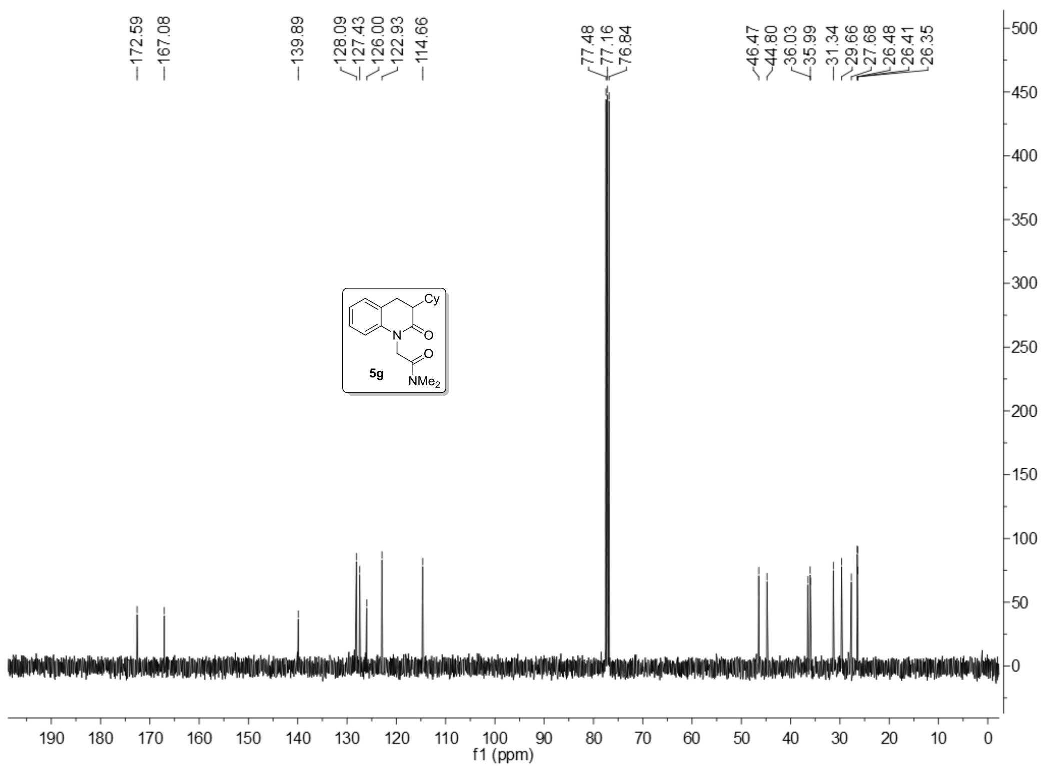
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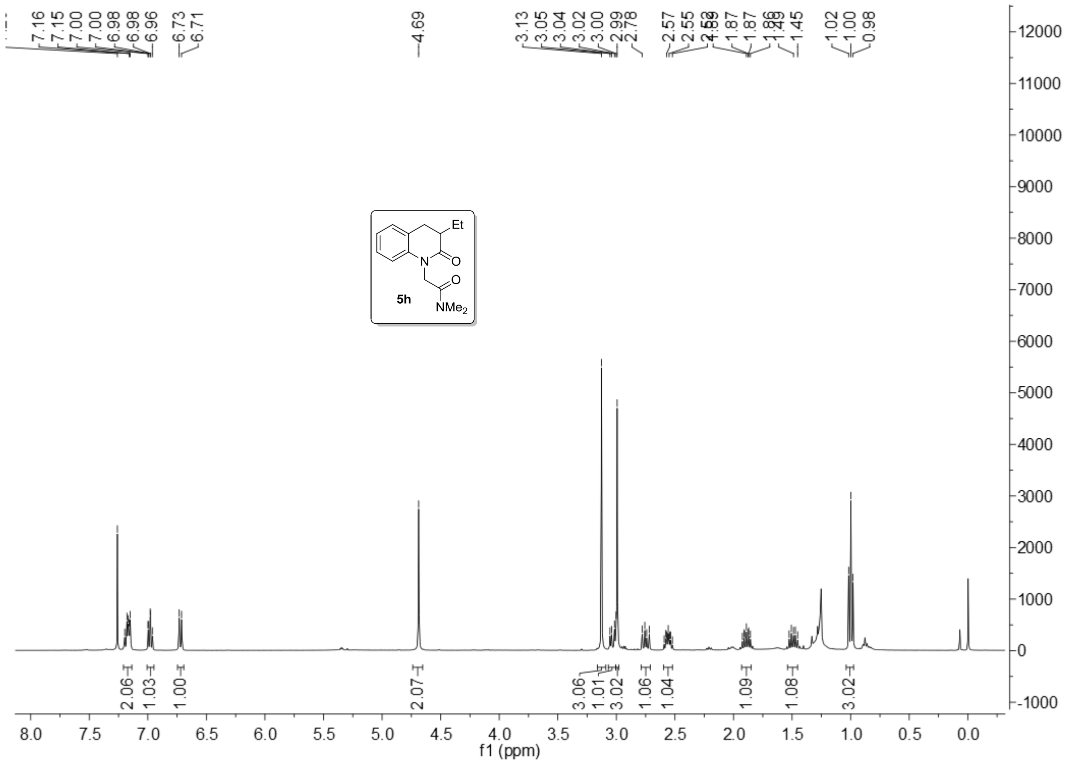
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3.00
2.99
2.78
2.57
2.55
1.87
1.87
1.45
1.02
1.00
0.98
Et
N
O
O
5h
NMe2
2.06
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3.06
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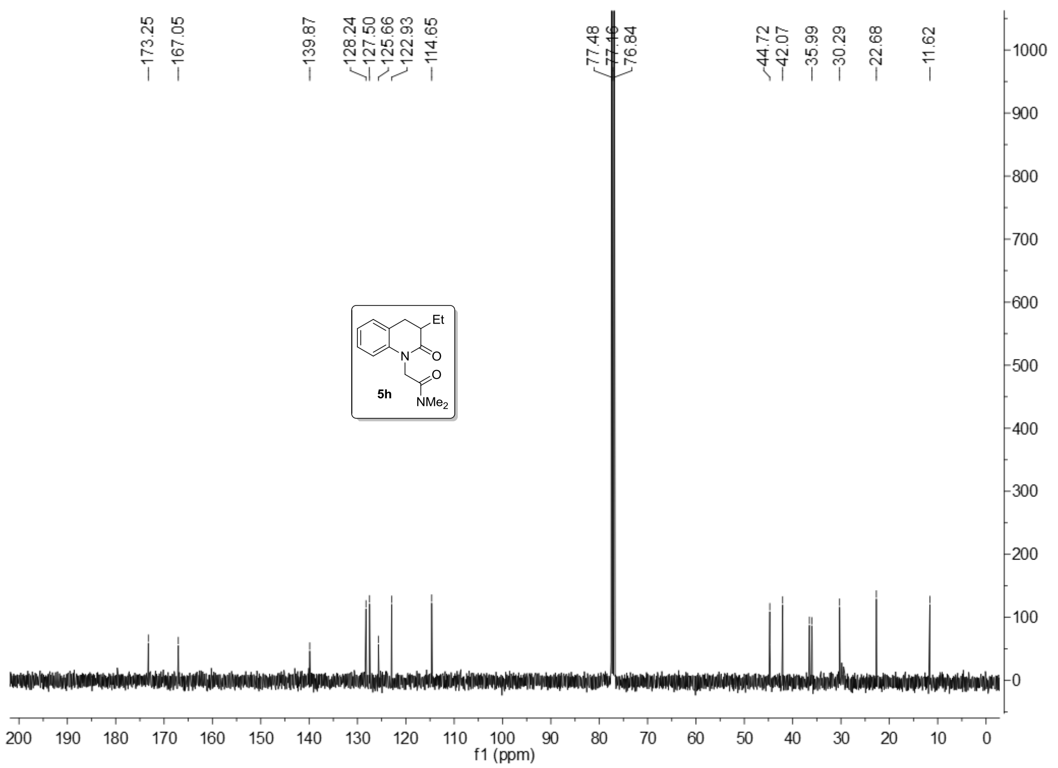
3.02
1.06
1.04
1.09
1.08
3.02
f1 (ppm)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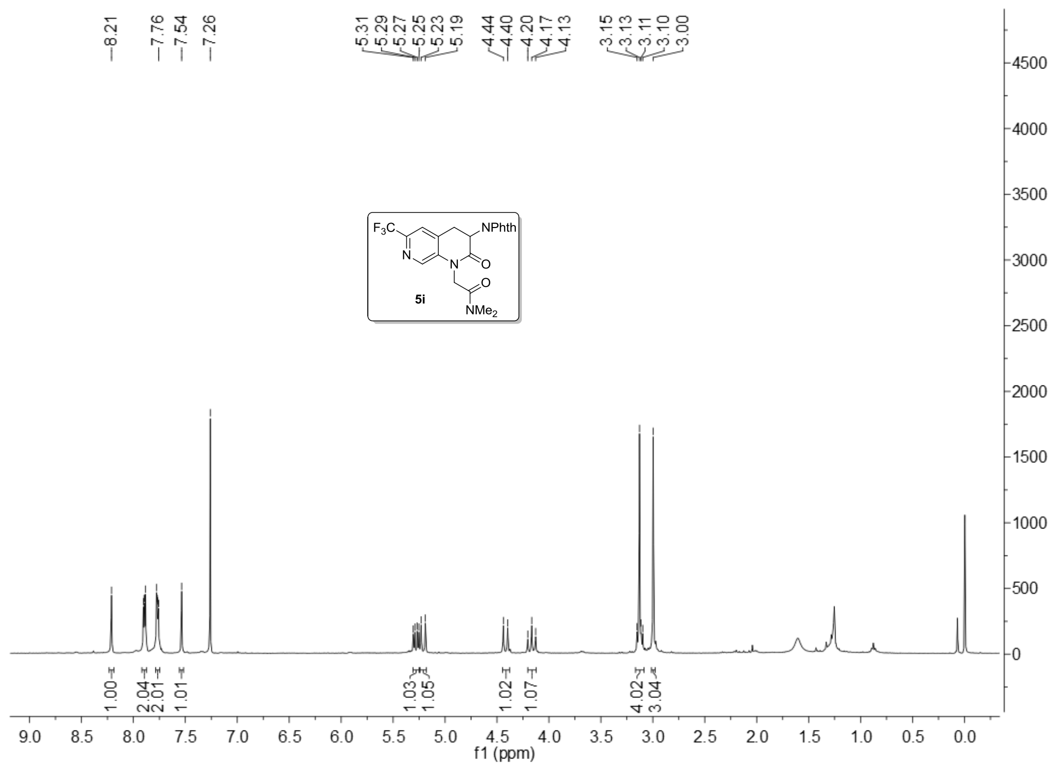
f1 (ppm)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4.20
4.17
4.13
3.15
3.13
3.11
3.10
3.00
F3C
NPhth
N
O
5i
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1.01
1.03
1.05
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1.07
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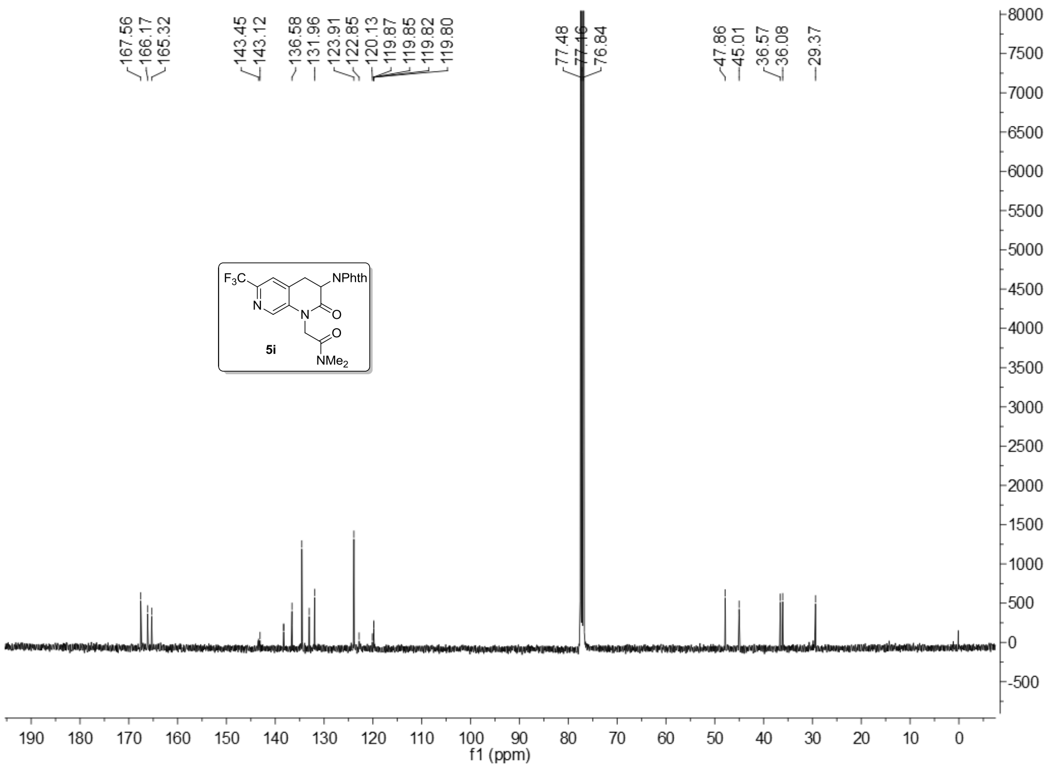
f1 (ppm)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N
O
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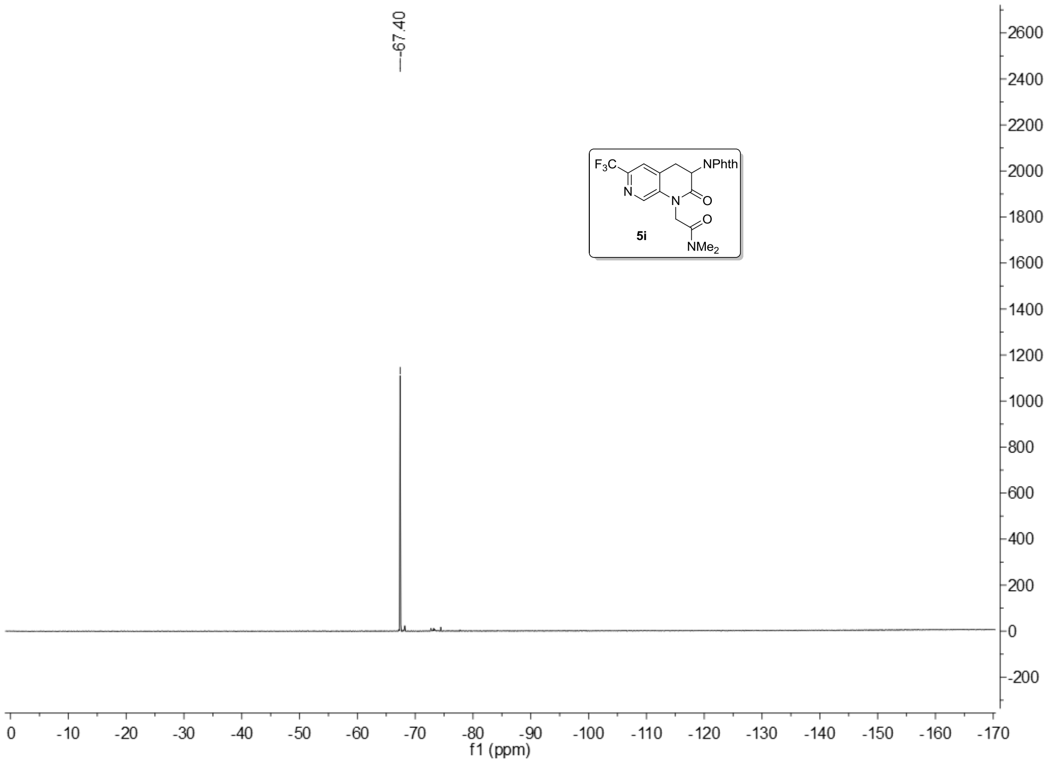
NMe2
f1 (ppm)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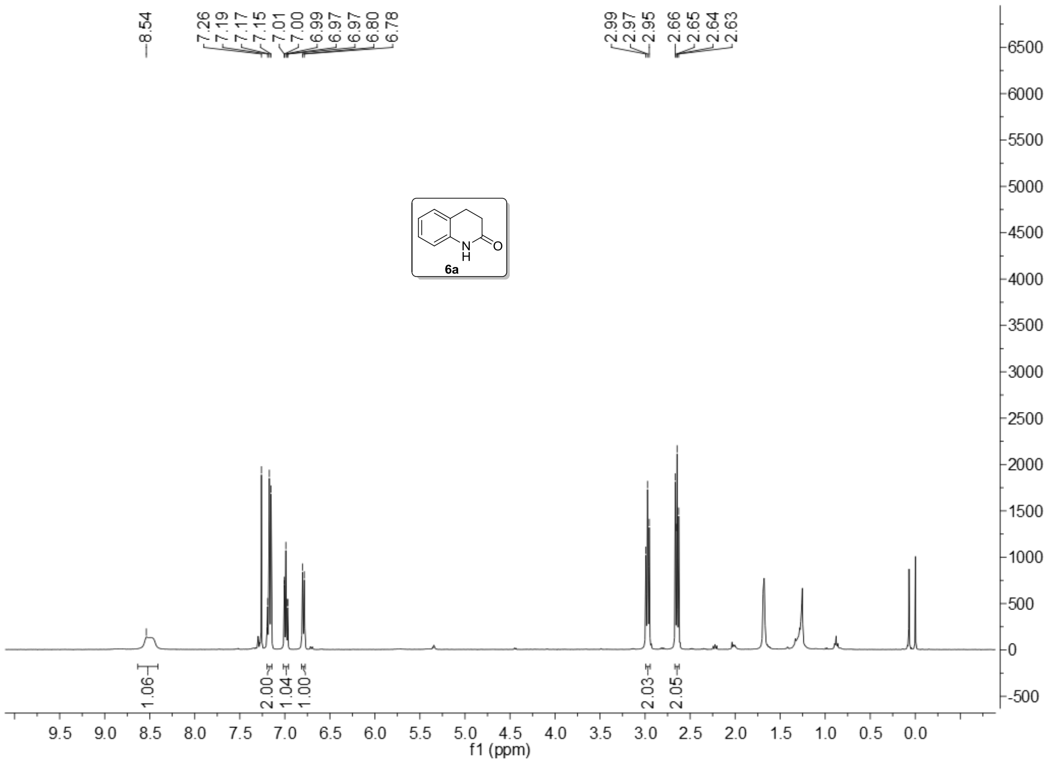
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2.97
2.95
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1.00
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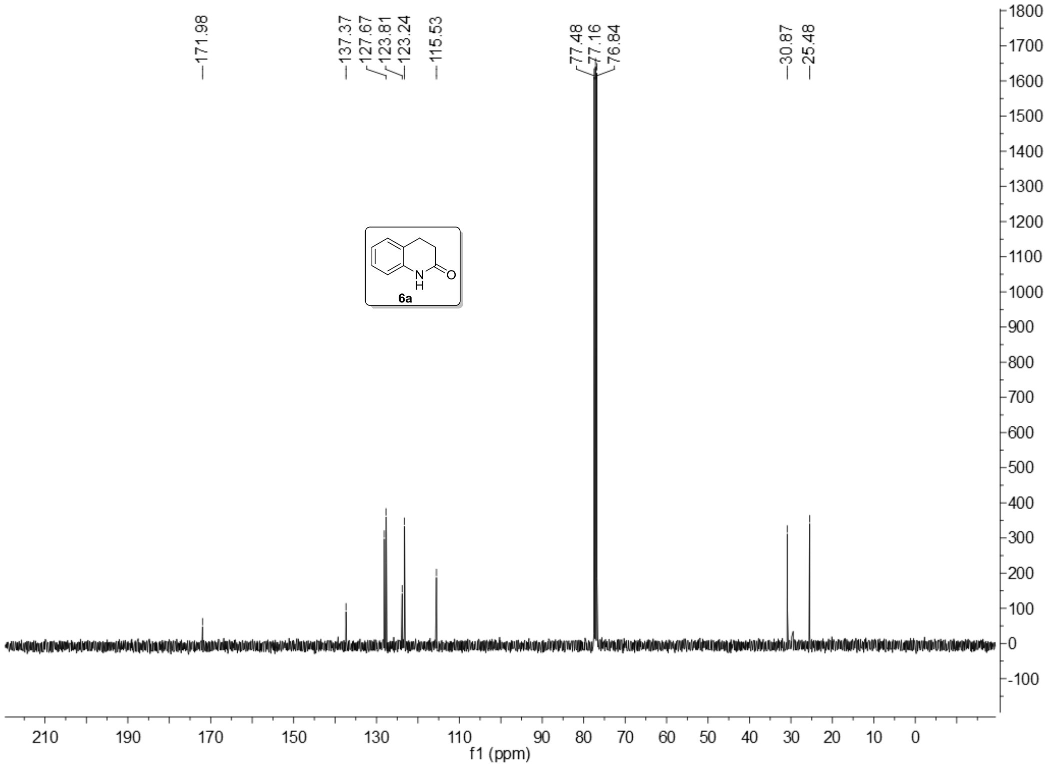
2.05
f1 (ppm)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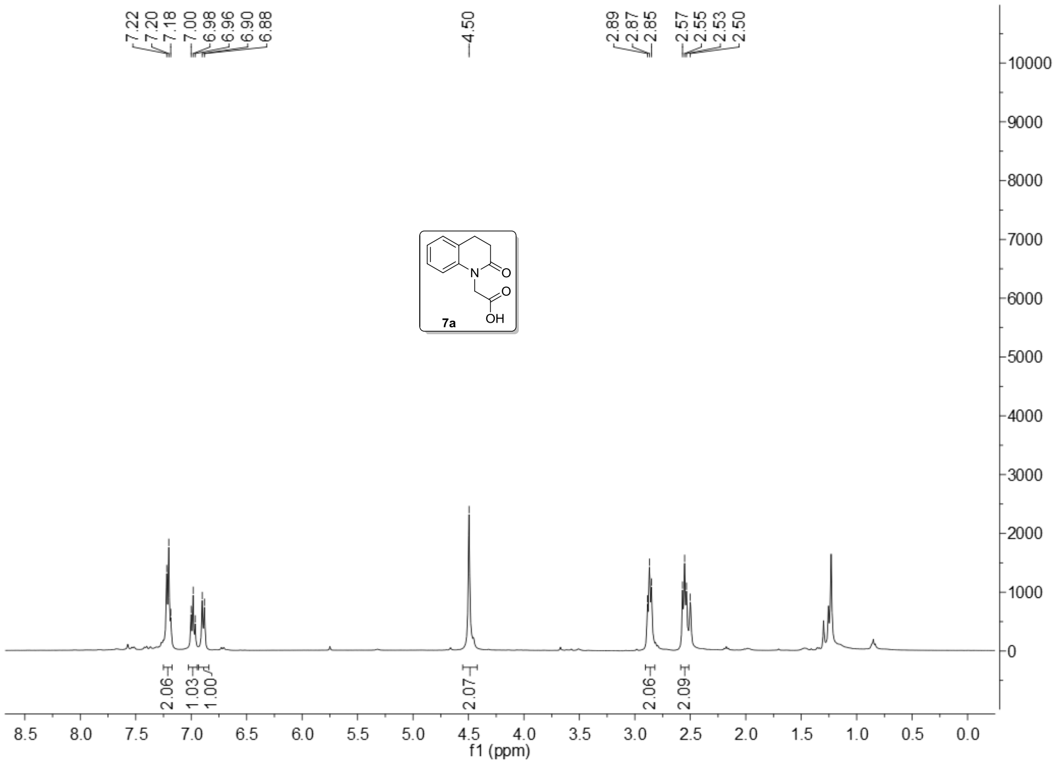
f1 (ppm)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2.57
2.55
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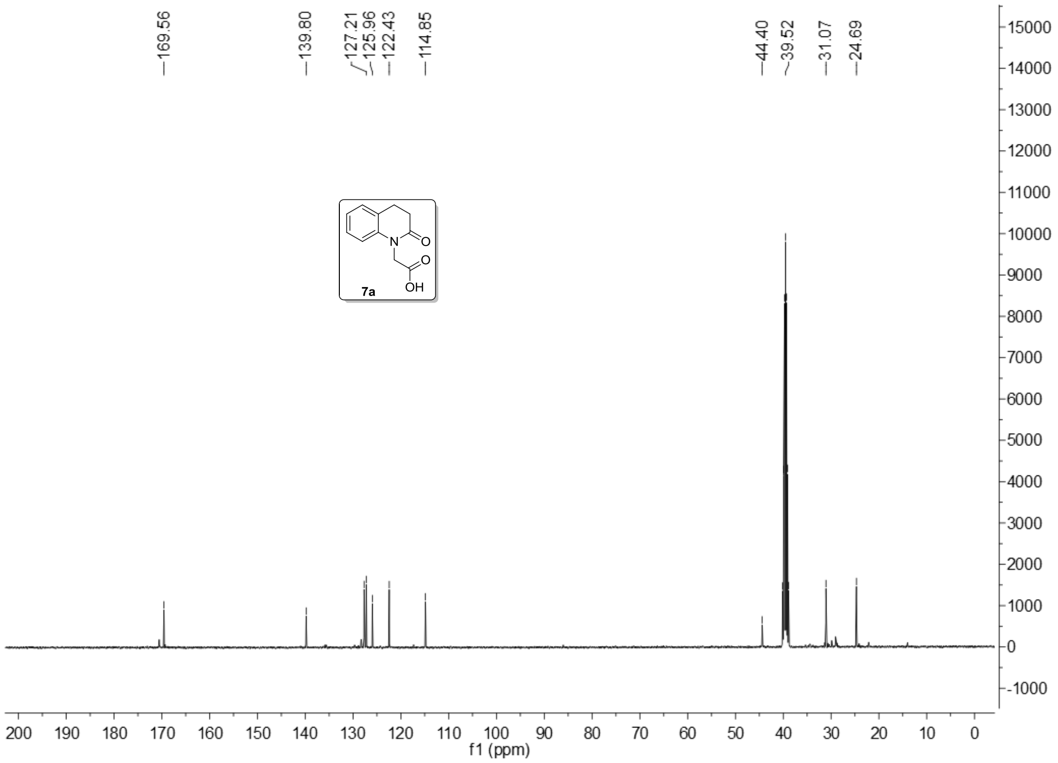
2.09
f1 (ppm)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24.69
7a
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O
f1 (ppm)