Fragment Couplings via CO_2-Extrusion-Recombination: Expansion of a Classic Bond-Forming Strategy via Metallophotoredox

Chi "Chip" Le and David W. C. MacMillan*

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544

Supporting Information

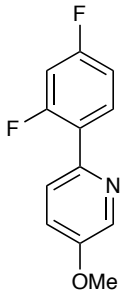
Table of Contents

1) General information S3
2) Preparation of Photocatalyst S4
3) Possible Mechanism for Oxidative Decarboxylation S7
4) Procedure for Optimization Studies S8
5) CO_2-Extrusion Recombination with Preformed Anhydrides S8
6) CO_2-Extrusion Recombination of (L)-Proline Mixed Anhydrides S10
7) CO_2-Extrusion Recombination of Hydrocinnamic Mixed Anhydrides S22
8) Observed Rearrangement with Cyclopropylacetic Mixed Anhydride S35
9) Control Experiments for Rearrangement Studies S37
10) Synthesis of ^{13}C-Labeled Starting Material S38
11) Labeling Experiments S42
12) Synthesis of (±)-Edivoxetine•HCl S46
13) References Cited S49
14) Spectral Data S50

1) General Information

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] All solvents were purified according to the method of Grubbs.[2] Acyl chlorides (if liquid) were distilled prior to use. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished by flash chromatography on Silicycle F60 silica gel according to the method of Still.[3] Thin-layer chromatography (TLC) was performed on Analtech 250 micron silica gel plates. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and peaks are reported in terms of frequency of absorption (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-II 500 (500 and 125 MHz) instrument, and are internally referenced to residual protic solvent signals (note: $CDCl_3$ referenced at δ 7.26 and 77.16 ppm respectively). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift and no special nomenclature is used for equivalent carbons. High-resolution mass spectra were obtained at Princeton University mass spectrometry facilities. Gas chromatography (GC) was performed on an Agilent 6890 Series chromatograph with split-mode capillary injection and FID detection.

2) Preparation of photocatalyst



2-(2,4-difluorophenyl)-5-methoxypyridine Under air, a three-neck round-bottom flask, equipped with a magnetic stir bar, was charged with 2,4-difluorobenzeneboronic acid (1.58 g, 10.0 mmol, 1 equiv), THF (30 mL) and Na_2CO_3 (1M aq, 15 mL, 1.5 equiv). The flask was equipped with a reflux condenser and placed under nitrogen before 2-bromo-5-methoxypyridine (2.07 g, 11.0 mmol, 1.1 equiv) and $Pd(PPh_3)_4$ (231 mg, 0.20 mmol, 0.02 equiv) were added. Nitrogen was bubbled through the solution with stirring for 30 mins then the reaction flask was placed under nitrogen. The orange mixture was heated to reflux for 12 hours then cooled to room temperature. Final mixture was diluted with Et_2O and the organic layer was separated from the aqueous layer. The ethereal solution was washed with water then brine, followed by drying over $MgSO_4$. Filtration and removal of volatile solvent yielded an orange oil. Column chromatography (silica gel, 30% DCM in hexanes) yielded the pure product as an off-white solid (1.77 g, 8.00 mmol, 80% yield)

IR (film) ν_{max} 3084, 3011, 2967, 2842, 1614, 1594, 1572, 1507, 1473, 1428, 1394, 1285, 1264, 1219 cm^{-1}.

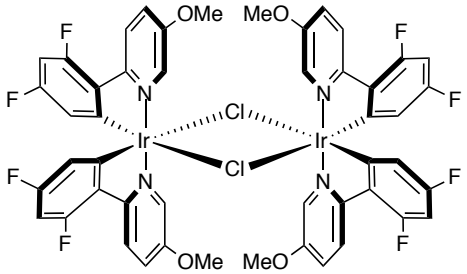
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (1H, d, *J* = 3.0 Hz), 7.95 (1H, td, *J* = 8.9, 6.7 Hz), 7.70 (1H, dd, *J* = 8.7, 2.1 Hz), 7.28-7.25 (1H, m), 7.00-6.96 (1H, m), 6.89 (1H, ddd, *J* = 11.3, 8.8, 2.5 Hz), 3.91 (3H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 163.6, 161.7, 161.6, 161.2, 161.1, 159.3, 159.2, 154.8, 144.9, 144.8, 137.5, 131.7, 131.6, 131.6, 124.4, 124.3, 123.6, 123.5, 123.4, 120.7, 111.9, 111.8, 111.7, 111.6, 104.5, 104.3, 104.2, 104.0, 55.68.

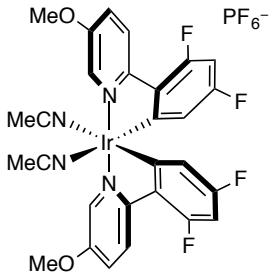
^{19}F NMR (282 MHz, $CDCl_3$) δ -110.5, -113.3.

HRMS (ESI-TOF) m/z calcd. $C_{12}H_{10}F_2NO$ ($[M+H]^+$) 222.0725, found 222.0721.

Synthesis of Ir[dF(OMe)ppy]$_2$-(dtbbpy)PF_6 (13)

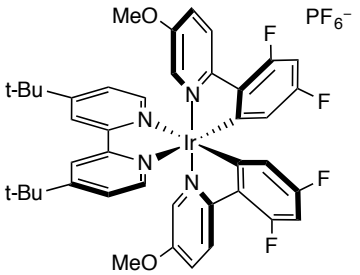


{Ir[dF(OMe)ppy]$_2$Cl}$_2$ Under air, a three-neck round-bottom flask, equipped with a Teflon coated magnetic stir bar, was charged with 2-(2,4-difluorophenyl)-5-methoxypyridine (1.70 g, 7.7 mmol, 2.2 equiv) and $IrCl_3$•H_2O (1.08 g, 3.4 mmol, 1.0 equiv) and 2/1 mixture of 2-ethoxyethanol/water (45 mL). The flask was equipped with a reflux condenser and nitrogen was bubbled through the solution with stirring for an hour before the mixture was heated at 120 ºC for 16 hours. Upon cooling to room temperature, water was added then the solid was isolated by filtration. Washing with cold Et_2O yielded {Ir[dF(OMe)ppy]$_2$Cl}$_2$ as a bright yellow solid (1.80 g, 1.34 mmol, 78% yield). This complex was carried over to the next step without purification.



Ir[dF(OMe)ppy]$_2$-(MeCN)$_2$$PF_6$ Under air, a round-bottom flask, equipped with a Teflon coated magnetic stir bar, was charged with {Ir[dF(OMe)ppy]$_2$Cl}$_2$ (1.00 g, 0.75 mmol, 1.0 equiv) and 5/1 mixture of DCM/MeCN (60 mL). $AgPF_6$ (0.40 g, 1.57 mmol, 2.1 equiv) was added in one portion. The reaction flask was protected from light with

aluminum foil, then stirred at room temperature for 12 hours. Filtration of AgCl, followed by concentrating the filtrate yielded Ir[dF(OMe)ppy]$_2$-(MeCN)$_2$PF$_6$ as a yellow solid. This complex was carried over to the next step without purification (800 mg, 0.93 mmol, 62% yield)



Ir[dF(OMe)ppy]$_2$-(dtbbpy)PF$_6$ (13) Under air, a round-bottom flask, equipped with a Teflon coated magnetic stir bar, was charged with Ir[dF(OMe)ppy]$_2$-(MeCN)$_2$PF$_6$ (0.30 g, 0.35 mmol, 1.0 equiv), 4,4'-di-tertbutyl-2,2'-bipyridine (0.10 g, 0.38 mmol, 1.1 equiv) and 3/1 mixture of DCM/EtOH (12 mL). The solution was stirred under air at room temperature for 12 hours. Evaporation of solvent yielded a yellow crystalline solid. Column chromatography (silica gel, 0 to 0.25% MeOH in DCM) yielded the pure product as a yellow crystalline solid (340 mg, 0.32 mmol, 93% yield)

IR (film) ν_{max} 3084, 3011, 2967, 2842, 1614, 1594, 1572, 1507, 1473, 1428, 1394, 1285, 1264, 1219 cm^{-1}.

^{1}H NMR (500 MHz, CD$_2$Cl$_2$) δ 8.40 (1H, d, *J* = 3.0 Hz), 7.95 (1H, td, *J* = 8.9, 6.7 Hz), 7.70 (1H, dd, *J* = 8.7, 2.1 Hz), 7.28-7.25 (1H, m), 7.00-6.96 (1H, m), 6.89 (1H, ddd, *J* = 11.3, 8.8, 2.5 Hz), 3.91 (3H, s).

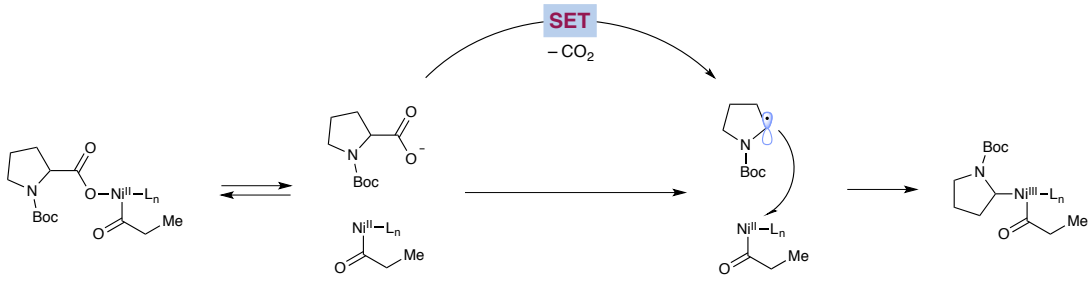
^{13}C NMR (125 MHz, CD$_2$Cl$_2$) δ 163.7, 163.6, 161.7, 161.6, 161.2, 161.1, 159.3, 159.2, 154.8, 144.9, 144.8, 137.5, 131.7, 131.6, 131.6, 124.4, 124.3, 123.6, 123.5, 123.4, 120.7, 111.9, 111.8, 111.7, 111.6, 104.5, 104.3, 104.2, 104.0, 55.68

^{19}F NMR (282 MHz, CD$_2$Cl$_2$) δ -72.1, -74.6, -108.4, -111.5

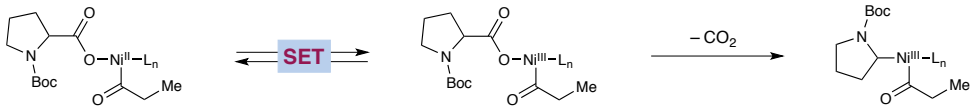
^{31}P NMR (282 MHz, CD_2Cl_2) δ -144.5

3) Possible Mechanisms for Oxidative Decarboxylation Step

1) Outer sphere decarboxylation mechanism



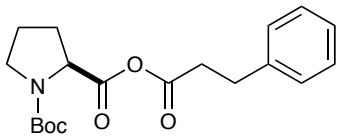
2) Inner sphere decarboxylation mechanism



4) Procedure for Optimization Studies

To an oven-dried 8 mL vial equipped with a stir bar was added $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1.1 mg, 1.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (1.1 mg, 5.0 μmol, 0.05 equiv.), bipyridine ligand (5.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (28.0 mg, 0.13 mmol, 1.3 equiv.) and MeCN (5.0 mL). The vial was sealed and placed under nitrogen before hydrocinnamoyl chloride (15.0 μL, 0.10 mmol, 1.0 equiv.) was added followed by base (0.13 mmol, 1.3 equiv.). The reaction mixture was degassed by sparging with nitrogen while stirring for 15 min before sealing the vial with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away, with cooling fan to keep the reaction temperature at 25 ºC) for 16 hours. The reaction was quenched by exposure to air. Methyl benzoate (internal standard, 12.65 μL, 0.10 mmol, 1.0 equiv.) was added then the reaction mixture was analyzed by GC and ^{1}H NMR.

5) CO_2-Extrusion Recombination of Preformed Mixed Anhydrides



Synthesis of amino acid anhydride: Under air, a round-bottom flask equipped with a stir bar was charged with *N*-Boc-(L)-Proline (1.08g, 5.00 mmol, 1.0 equiv.) then the flask was sealed, evacuated and backfilled with nitrogen three times. THF (50.0 mL) was added to the vial before the clear solution was cooled to 0 ºC. Hydrocinnamoyl chloride (0.74 mL, 5.00 mmol, 1.0 equiv.), triethylamine (0.76 mL, 5.50 mmol, 1.1 equiv.) were added in that order. The reaction mixture was stirred at 0 ºC for 30 minutes then warmed to room temperature over 3 hours. The reaction was cooled back to 0 ºC for 30 min before being filtered. The filtrate was concentrated to yield a clear oil. To ensure complete removal of triethylamine hydrochloride, the crude oil was dissolved in minimal amount of Et_2O, and then chilled in freezer for 2 hours. The ether solution was filtered over Celite to remove any precipitate. Volatile solvent was removed then the residual oil was placed on hi-vac overnight to afford the pure anhydride as a foamy solid (1.50g, 86% yield).

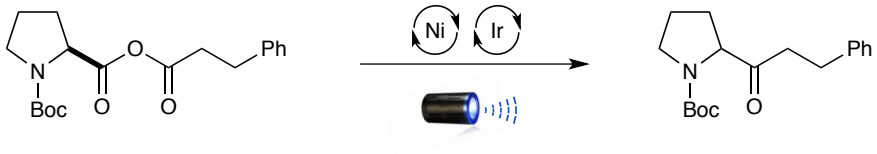
IR (film) ν_{max} 2976, 2881, 1820, 1752, 1696, 1391, 1365, 1256, 1162, 1118, 1029, 917, 771, 749, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (2H, m), 7.24-7.18 (3H, m), 4.40-4.23 (1H, m), 3.56-3.38 (2H, m), 3.01-2.94 (2H, m), 2.85-2,73 (2H, m), 2.28-1.85 (4H, m), 1.44 (9H, d, *J* = 1.44 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 168.0, 154.4, 153.5, 139.6, 139.4, 128.7, 128.6, 128.3, 126.6, 126.5, 80.6, 80.2, 59.6, 59.3, 46.6, 46.3, 37.0, 36.9, 30.4, 30.1, 29.3, 28.4, 28.2, 24.4, 23.7.

HRMS (ESI-TOF) m/z calcd. for $C_{19}H_{25}NNaO_5$ ($[M+Na]^+$) 370.1625, found 370.1628.

CO_2-Extrusion Recombination Preformed Mixed Anhydride

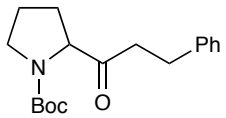


To an oven-dried 8 mL vial equipped with a stir bar was added Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (1.1 mg, 1.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (1.1 mg, 5.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridyl (1.1 mg, 5.0 μmol, 0.05 equiv.). The vial was sealed and placed under nitrogen before MeCN solution of the mixed anhydride (34.7 mg, 0.10 mmol, 1.0 equiv.) was added followed by DBU (0.03 mmol, 0.30 equiv.). The reaction mixture was degassed by sparging with nitrogen while stirring for 15 min before sealing the vial with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away, with cooling fan to keep the reaction temperature at 25 ºC) for 16 hours. The reaction was quenched by exposure to air. Methyl benzoate (internal standard, 12.65 μL, 0.10 mmol, 1.0 equiv.) was added then the reaction mixture was analyzed by GC and ^{1}H NMR.

DBU is thought to act as the terminal reductant for reduction from Ni(II) to Ni(0) to initiate the catalytic cycle

6) CO_2-Extrusion Recombination of (L)-Proline Mixed Anhydrides

To an oven-dried 40 mL vial equipped with a stir bar was added $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.) and MeCN (25.0 mL). The vial was sealed and placed under nitrogen before acyl chloride (0.50 mmol, 1.0 equiv.) was added followed by DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). The reaction mixture was degassed by sparging with nitrogen while stirring for 30 min before sealing the vial with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away, with cooling fan to keep the reaction temperature at 25 ºC) for 36 hours. The reaction was quenched by exposure to air and concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 to 20% EtOAc in hexanes) yielded the ketone product.



(±)-*tert*-butyl 2-(3-phenylpropanoyl)pyrrolidine-1-carboxylate (14)

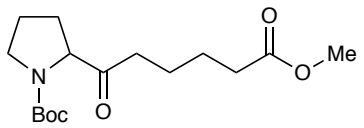
Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (130 mg, 0.43 mmol, 86% yield).

IR (film) ν_{max} 2974, 2931, 2878, 1715, 1690, 1496, 1478, 1453, 1390, 1364, 1253, 1160, 1115, 1086 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.17 (5H, m), 4.33 (0.42H, dd, *J* = 8.7, 4.7 Hz), 4.21 (0.58H, dd, *J* = 8.7, 5.5 Hz), 3.55-3.39 (2H, m), 2.93-2.88 (2H, m), 2.83-2.68 (2H, m), 2.15-2.00 (2H, m), 1.82-1.77 (2H, m), 1.70-1.64 (1H, m), 1.46 (3.8H, s), 1.39 (5.2H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.2, 154.6, 153.9, 141.3, 141.1, 128.3, 126.2, 80.1, 79.8, 65.4, 64.9, 46.9, 46.7, 40.8, 40.1, 29.8, 29.4, 28.5, 28.4, 28.3, 24.4, 23.7.

HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{25}NNaO_3$ ($[M+Na]^+$) 326.1727, found 326.1729.



(±)-*tert*-butyl 2-(6-methoxy-6-oxohexanoyl)pyrrolidine-1-carboxylate (15)

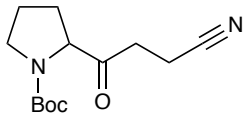
Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), methyl 6-chloro-6-oxohexanoate (78.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a yellow oil (121 mg, 0.38 mmol, 77% yield).

IR (film) ν_{max} 2964, 2878, 1731, 1690, 1478, 1436, 1391, 1365, 1252, 1160, 1115 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33 (0.42H, dd, *J* = 8.7, 4.5 Hz), 4.21 (0.58H, dd, *J* = 8.7, 5.2 Hz), 3.65 (3H, d, *J* = 3.8 Hz), 3.56-3.39 (2H, m), 2.51-2.29 (4H, m), 2.21-2.06 (1H, m), 1.88-1.77 (3H, m), 1.64-1.60 (4H, m), 1.44 (3.8H, s), 1.39 (5.2H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 173.9, 173.7, 154.6, 153.9, 80.1, 79.8, 65.2, 64.7, 51.6, 51.5, 46.9, 46.7, 38.7, 37.9, 33.8, 30.0, 28.9, 28.4, 28.3, 24.6, 24.4, 23.7, 22.8, 22.7.

HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{27}NNaO_5$ ($[M+Na]^+$) 336.1781, found 336.1784.



(±)-*tert*-butyl 2-(6-methoxy-6-oxohexanoyl)pyrrolidine-1-carboxylate (16)

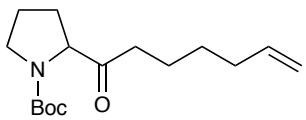
Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), 3-cyanopropanoyl chloride (58.8 mg, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as an orange oil (105 mg, 0.42 mmol, 83% yield).

IR (film) ν_{max} 2977, 2250, 1731, 1690, 1478, 1452, 1392, 1366, 1244, 1159, 1121, 1088, 1045 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35-4.24 (1H, m), 3.60-3.33 (2H, m), 2.91-2.58 (2H, m), 2.24-1.82 (4H, m), 1.47-1.40 (9H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 206.2, 154.8, 153.7, 119.1, 118.8, 80.8, 80.4, 65.0, 64.5, 59.2, 58.9, 47.1, 47.0, 46.8, 46.3, 34.7, 33.9, 30.0, 29.7, 28.9, 28.4, 28.3, 28.2, 24.6, 24.3, 23.9, 23.6, 11.4, 11.3.

HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{20}N_2NaO_3$ ($[M+Na]^+$) 275.1366, found 275.1369.



(±)-*tert*-butyl 2-(hept-6-enoyl)pyrrolidine-1-carboxylate (17)

Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), hept-6-enoyl chloride (75.0

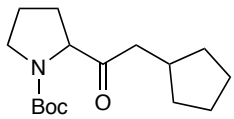
mg, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (120 mg, 0.43 mmol, 86% yield).

IR (film) ν_{max} 3076, 2975, 2931, 1692, 1478, 1390, 1365, 1161, 1115 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz), 5.01-4.91 (2H, m), 4.32 (0.36H, dd, *J* = 8.7, 4.3 Hz), 4.21 (0.64H, dd, *J* = 8.7, 5.0 Hz), 3.56-3.40 (2H, m), 2.50-2.37 (2H, m), 2.19-2.02 (3H, m), 1.87-1.77 (3H, m), 1.62-1.56 (2H, m), 1.45-1.36 (12H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 154.6, 153.9, 138.6, 138.4, 114.7, 114.5, 80.1, 79.7, 65.3, 64.7, 46.9, 46.7, 39.1, 38.1, 33.6, 30.0, 28.8, 28.6, 28.5, 28.4, 28.3, 24.3, 23.7, 22.8, 22.7.

HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{27}NNaO_3$ ($[M+Na]^+$) 304.1883, found 304.1885.



(±)-*tert*-butyl 2-(2-cyclopentylacetyl)pyrrolidine-1-carboxylate (18)

Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), 2-cyclopentylacetyl chloride (75.0 mg, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (116 mg, 0.41 mmol, 83% yield).

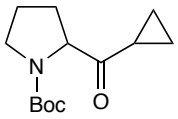
IR (film) ν_{max} 2980, 2936, 1689, 1406, 1240, 1365, 1364, 1253, 1155, 1114, 1077 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (0.36H, dd, *J* = 8.7, 4.1 Hz), 4.21 (0.64H, dd, *J* =

8.9, 4.5 Hz), 3.55-3.40 (2H, m), 2.52-2.39 (2H, m), 2.30-2.07 (2H, m), 1.86-1.81 (5H, m), 1.65-1.50 (4H, m), 1.45&1.40 (9H, s), 1.07-1.03 (2H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0, 209.9, 154.6, 154.0, 80.0, 79.7, 65.3, 64.7, 46.9, 46.7, 45.6, 44.7, 34.7, 32.8, 32.6, 29.9, 28.7, 28.5, 28.4, 28.3, 25.0, 25.0, 24.9, 24.9, 24.3, 23.6.

HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{27}NNaO_3$ ($[M+Na]^+$) 304.1883, found 304.1884.



(±)-*tert*-butyl 2-(cyclopropanecarbonyl)pyrrolidine-1-carboxylate (19)

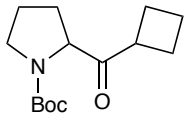
Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), cyclopropanecarbonyl chloride (45 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (85 mg, 0.35 mmol, 71% yield).

IR (film) ν_{max} 2975, 2878, 1691, 1478, 1451, 1388, 1365, 1253, 1160, 1117, 1063, 1022 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (0.42H, dd, *J* = 8.8, 4.3 Hz), 4.25 (0.58H, dd, *J* = 8.5, 5.5 Hz), 3.61-3.41 (2H, m), 2.26-2.14 (1H, m), 2.01-1.82 (4H, m), 1.45 (3.8H, s), 1.38 (5.2H, s), 1.06-1.01 (2H, m), 0.91-0.87 (2H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4, 209.6, 154.5, 154.1, 80.0, 79.6, 66.1, 65.4, 46.9, 30.4, 29.0, 28.3, 24.3, 23.8, 17.2, 16.0, 11.5, 11.1, 11.0.

HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{21}NNaO_3$ ($[M+Na]^+$) 262.1414, found 262.1416.



(±)-*tert*-butyl 2-(cyclobutanecarbonyl)pyrrolidine-1-carboxylate (20)

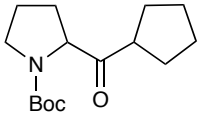
Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), cyclobutanecarbonyl chloride (57.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (85 mg, 0.43 mmol, 85% yield).

IR (film) ν_{max} 2975, 2875, 1691, 1748, 1452, 1390, 1364, 11246, 1160, 1116 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (0.42H, dd, *J* = 8.8, 3.8 Hz), 4.23 (0.58H, dd, *J* = 8.8, 4.9 Hz), 3.54-3.38 (3H, m), 2.35-1.95 (6H, m), 1.87-1.77 (4H, m), 1.45 (3.8H, s), 1.38 (5.2H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.8, 210.6, 154.4, 154.0, 80.0, 79.6, 64.1, 63.2, 46.9, 46.8, 30.1, 28.9, 28.5, 28.4, 25.5, 25.0, 24.4, 24.1, 23.6, 18.2, 18.0.

HRMS (ESI-TOF) m/z calcd. for $C_{14}H_{23}NNaO_3$ ($[M+Na]^+$) 276.1570, found 276.1569.



(±)-*tert*-butyl 2-(cyclopentanecarbonyl)pyrrolidine-1-carboxylate (21)

Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), cyclopentanecarbonyl chloride (61.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.).

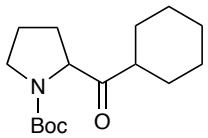
Purification by column chromatography yielded the pure product as a clear oil (106 mg, 0.40 mmol, 79% yield).

IR (film) ν_{max} 2960, 2871, 1719, 1691, 1478, 1451, 1390, 1364, 1253, 1161, 1112 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44 (0.42H, dd, *J* = 9.0, 3.5 Hz), 4.35 (0.58H, dd, *J* = 8.8, 4.0 Hz), 3.54-3.39 (2H, m), 3.02-2.95 (1H, m), 2.22-2.09 (1H, m), 1.85-1.56 (11H, m) 1.45 (3.8H, s), 1.38 (5.2H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 212.4, 212.3, 154.4, 154.0, 79.9, 79.5, 64.9, 64.2, 48.2, 47.3, 46.9, 46.8, 30.5, 29.9, 29.3, 28.8, 28.5, 28.4, 26.1, 24.2, 23.5.

HRMS (ESI-TOF) m/z calcd. for $C_{15}H_{25}NNaO_3$ ($[M+Na]^+$) 290.1727, found 290.1730.



(±)-*tert*-butyl 2-(cyclohexanecarbonyl)pyrrolidine-1-carboxylate (22)

Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), cyclohexanecarbonyl chloride (67.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (115 mg, 0.41 mmol, 82% yield).

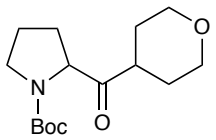
IR (film) ν_{max} 2979, 2928, 2856, 1714, 1683, 1478, 1449, 1398, 1362, 1255, 1244, 1163,1115, 1003 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (0.42H, dd, *J* = 8.8, 4.0 Hz), 4.40 (0.58H, dd, *J* = 8.9, 3.7 Hz), 3.54-3.36 (2H, m), 2.56-2.47 (1H, m), 2.20-2.05 (1H, m), 1.97-1.66 (8H, m),

1.44-1.39 (10H, m), 1.33-1.19 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 211.9, 154.3, 153.9, 79.8, 79.5, 63.7, 63.1, 48.2, 47.5, 46.9, 46.8, 29.8, 29.2, 28.8, 28.5, 28.4, 28.2, 28.1, 25.8, 25.8, 25.7, 25.6, 25.5, 24.2, 24.3.

HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{27}NNaO_3$ ($[M+Na]^+$) 304.1883, found 304.1884.



(±)-*tert*-butyl 2-(tetrahydro-2*H*-pyran-4-carbonyl)pyrrolidine-1-carboxylate (23)

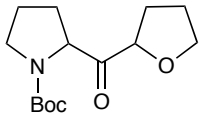
Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), tetrahydro-2*H*-pyran-4-carbonyl chloride (74.3 mg, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (110 mg, 0.39 mmol, 78% yield).

IR (film) ν_{max} 2955, 2846, 1719, 1689, 1478, 1444, 1391, 1364, 1255, 1240, 1161, 1111, 1018 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (0.50H, dd, *J* = 8.7, 4.3 Hz), 4.42 (0.50H, dd, *J* = 8.9, 4.3 Hz), 4.02-3.96 (2H, m), 3.53-3.39 (4H, m), 2.82-2.69 (1H, m), 2.22-2.09 (1H, m), 1.91-1.63 (7H, m), 1.43 (4.4H, s), 1.39 (4.6H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 211.1, 210.1, 154.4, 153.8, 80.1, 79.7, 67.3, 67.2, 67.1, 67.1, 63.5, 62.7, 46.9, 46.8, 45.2, 44.4, 30.0, 29.0, 28.8, 28.4, 28.3, 28.0, 24.4, 23.4.

HRMS (ESI-TOF) m/z calcd. for $C_{15}H_{25}NNaO_4$ ($[M+Na]^+$) 306.1676, found 306.1675.



(±)-*tert*-butyl 2-(tetrahydrofuran-2-carbonyl)pyrrolidine-1-carboxylate (24)

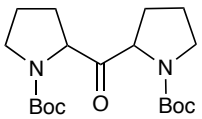
Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), tetrahydrofuran-2-carbonyl chloride (67.0 mg, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (88 mg, 0.32 mmol, 65% yield).

IR (film) ν_{max} 2975, 2877, 1728, 1690, 1478, 1453, 1396, 1365, 1254, 1163, 1116, 1074 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (0.49H, dd, *J* = 9.2, 3.8 Hz), 4.61 (0.51H, dd, *J* = 9.2, 4.3 Hz), 4.42 (1H, dt, *J* = 15.2, 7.6 Hz), 4.02-3.89 (2H, m), 3.55-3.36 (2H, m), 2.27-2.15 (3H, m), 2.04-1.79 (6H, m), 1.45 (4.7H, s), 1.41 (4.3H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 211.2, 210.2, 154.3, 153.9, 82.5, 81.8, 80.0, 79.5, 69.8, 69.5, 62.2, 61.2, 46.9, 46.7, 29.8, 29.6, 29.4, 28.8, 28.5, 28.4, 25.9, 25.7, 24.0, 23.1.

HRMS (ESI-TOF) m/z calcd. for $C_{14}H_{23}NNaO_4$ ($[M+Na]^+$) 292.1519, found 292.1520.



(±)-di-*tert*-butyl 2,2'-carbonylbis(pyrrolidine-1-carboxylate) (25)

Prepared using the following procedure:

Anhydride formation: Under air, an oven-dried 40-mL was charged with *N*-Boc-(L)-Proline (215.0 mg, 1.0 mmol, 1.0 equiv.) and DCM (10 mL). The clear solution was cooled to 0 °C before 1.3-Dicyclohexylcarbodiimide (103.0 mg, 0.5 mmol, 0.5 equiv)

was added in small portions. The reaction mixture was stirred under nitrogen for 5 hours at 0 °C. Upon warming to room temperature, precipitate was removed via filtration over celite. The clear filtrate was concentrated *in vacuo* to yield a clear oil. (IR confirmed anhydride formation).

IR (film) ν_{max} 2978, 2934, 2882, 1826, 1754, 1695, 1478, 1453, 1390, 1365, 1255, 1160, 1119, 1037, 1020 cm^{-1}.

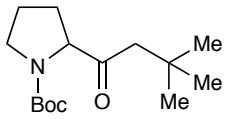
To this oil was added a MeCN solution (25 mL) of $Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.). DBU (22 μL, 0.65 mmol, 0.3 equiv.) was added then the solution was degassed by sparging with nitrogen while stirring for 30 mins before sealing the vial with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away, with cooling fan to keep the reaction temperature at 25 ºC) for 36 hours. Concentration in vacuo and purification by column chromatography yielded the pure product as a clear oil (129 mg, 0.35 mmol, 70% yield).

IR (film) ν_{max} 2977, 2928, 1726, 1687, 1481, 1451, 1393, 1364, 1252, 1161, 1097 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (2H, td, *J* = 9.2, 2.9 Hz), 3.60-3.31 (4H, m), 2.45-1.77 (8H, m), 1.44&1.41 (18H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 206.1, 154.3, 153.8, 80.1, 79.8, 79.6, 79.4, 62.7, 62.4, 61.9, 61.7, 46.9, 46.8, 46.7, 29.7, 29.2, 28.9, 28.4, 28.1, 27.9, 24.0, 23.9, 23.0, 22.8.

HRMS (ESI-TOF) m/z calcd. for $C_{19}H_{32}N_2NaO_5$ ($[M+Na]^+$) 391.2203, found 391.2209.



(±)-*tert*-butyl 2-(3.3-dimethylbutanoyl)pyrrolidine-1-carboxylate (26)

Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2$

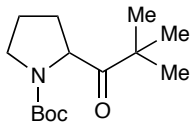
(dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), 3,3-dimethylbutanoyl chloride (70.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (110 mg, 0.30 mmol, 60% yield).

IR (film) ν_{max} 2954, 2872, 1724, 1693, 1478, 1454, 1391, 1364, 1251, 1163, 1115, 1067 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (0.41H, dd, *J* = 9.0, 3.3 Hz), 4.16 (0.59H, dd, *J* = 9.0, 4.0 Hz), 3.55-3.37 (2H, m), 2.44-2.05 (3H, m), 1.85-1.78 (3H, m), 1.45 (4.0H, s), 1.41 (5.0H, s), 1.03 (9.0H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.2, 208.7, 154.5, 154.0, 80.0, 79.6, 65.9, 65.6, 51.3, 50.5, 46.9, 46.7, 30.7, 30.3, 29.7, 29.6, 29.5, 28.5, 28.4, 28.3, 24.1, 23.5.

HRMS (ESI-TOF) m/z calcd. for $C_{15}H_{27}NNaO_3$ ($[M+Na]^+$) 292.1883, found 292.1882.



(±)-*tert*-butyl 2-pivaloylpyrrolidine-1-carboxylate (27)

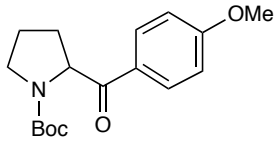
Prepared following the general procedure outlined above using Ir[dF(CF_3)ppy]$_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), pivaloyl chloride (62.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (40 mg, 0.16 mmol, 32% yield).

IR (film) ν_{max} 2973, 2875, 1713, 1693, 1479, 1455, 1395, 1365, 1254, 1163, 1123 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80-4.74 (1H, m), 3.55-3.38 (2H, m), 2.24-2.09 (1H, m),1.95-1.67 (3H, m), 1.43 (4.8H, s), 1.41 (4.2H, s), 1.22-1.21 (9.0H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 213.5, 154.0, 153.7, 79.9, 79.2, 60.2, 59.5, 47.0, 46.8, 43.5, 43.0, 30.7, 30.0, 28.6, 28.6, 28.5, 27.4, 27.1, 26.9, 24.1, 22.9.

HRMS (ESI-TOF) m/z calcd. for $C_{14}H_{25}NNaO_3$ ($[M+Na]^+$) 278.1727, found 278.1727.



(±)-*tert*-butyl 2-(4-methoxybenzoyl)pyrrolidine-1-carboxylate (28)[4]

Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), 4-methoxybenzoyl chloride (68.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the product as a white solid (110 mg, 0.36 mmol, 72% yield).

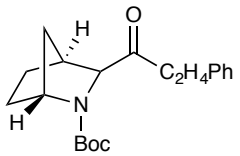
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (2H, dd, *J* = 14.2, 8.7 Hz), 6.93 (2H, dd, *J* = 15.4, 8.8 Hz), 5.29 (0.45H, dd, *J* = 9.3, 3.0 Hz), 5.14 (0.55H, dd, *J* = 8.8, 3.8 Hz), 3.87&3.85 (3H, s), 3.69-3.43 (2H, m), 2.32-2.24 (1H, m), 1.96-1.85 (3H, m), 1.45 (3.0H, s), 1.25 (6.0H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4, 196.8, 163.5, 154.5, 153.9, 130.8, 130.4, 128.2, 128.0, 113.9, 113.75, 79.6, 79.5, 61.0, 60.8, 55.5, 55.4, 46.8, 46.6, 31.0, 30.0, 28.5, 28.2, 24.2, 23.6.

7) CO_2-Extrusion Recombination of Hydrocinnamic Mixed Anhydride

Procedure A: To an oven-dried 40 mL vial equipped with a stir bar was added $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), amino acid (0.65 mmol, 1.3 equiv.) and MeCN (25.0 mL). The vial was sealed and placed under nitrogen before hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) was added followed by DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). The reaction mixture was degassed by sparging with nitrogen while stirring for 30 min before sealing the vial with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away, with cooling fan to keep the reaction temperature at 25 ºC) for 36 hours. The reaction was quenched by exposure to air. Reaction mixture was concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 to 20% EtOAc in hexanes) yielded the ketone product.

Procedure B: To an oven-dried 8 mL vial equipped with a stir bar was added $Ir[dF(OMe)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), carboxylic acid (0.50 mmol, 1.0 equiv.) and dioxane (5.0 mL). The vial was sealed and placed under nitrogen before hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) was added followed by DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). The reaction mixture was degassed by sparging with nitrogen while stirring for 30 min before sealing the vial with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away, with cooling fan to keep the reaction temperature at 25 ºC) for 36 hours. The reaction was quenched by exposure to air. Reaction mixture was filtered, then concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 to 20% EtOAc in hexanes) yielded the ketone product.



***tert*-butyl (1*R*,3*R*,4*S*)-3-(3-phenylpropanoyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (29)**

Prepared following general procedure A outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), (1R,3S,4S)-2-(tert-butoxycarbonyl)-2-azabicylo[2.2.1]heptane-3-carboxylic acid (157.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a white solid (115 mg, 0.35 mmol, 70% yield, single diastereomer).

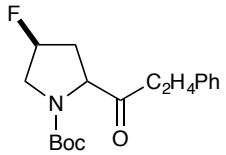
IR (film) ν_{max} 2973, 1727, 1694, 1497, 1477, 1454, 1398, 1365, 1308, 1256, 1161, 1103 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.17 (5H, m), 4.32 (0.5H, s), 4.18 (0.5H, s), 3.83 (0.5H, s), 3.73 (0.5H, s), 2.92-2.67 (4H, m), 2.52 (1H, dd, *J* = 17.1, 3.8 Hz), 1.74-1.60 (4H, m), 1.49-1.30 (10H, m) 1.41 (4.2H, s), 1.18-1.15 (1.0H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 207.6, 154.7, 153.4, 141.3, 141.1, 128.5, 128.4, 126.2, 126.0, 79.9, 79.8, 70.8, 70.5, 57.5, 56.4, 41.9, 41.7, 41.0, 35.2, 34.44, 30.5, 30.1, 29.4, 28.5, 28.3, 28.2, 27.9.

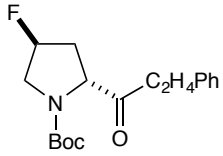
HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{27}NNaO_3$ ($[M+Na]^+$) 352.1883, found 352.1880.

$[\alpha]_D$ = -81.5° (c = 1.00, $CHCl_3$)



***tert*-butyl (4*S*)-4-fluoro-2-(3-phenylpropanoyl)-pyrrolidine-1-carboxylate (30)**

Prepared following general procedure A outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), (4S)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (157.0 mg, 0.65 mmol, 1.3 equiv.), MeCN (25.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (132 mg, 0.41 mmol, 82% yield, 8:1 dr)



(Major diastereomer)

IR (film) ν_{max} 2977, 2931, 1693, 1497, 1478, 1454, 1394, 1366, 1256, 1159, 1123, 1064 cm^{-1}.

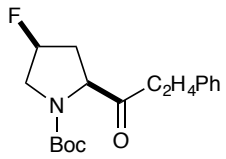
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.17 (5H, m), 5.17 (0.5H, s), 5.07 (0.5H, s), 4.53 (0.5H, dd, *J* = 9.4, 7.6 Hz), 4.44 (0.5H, dd, *J* = 9.9, 7.5 Hz), 3.95 (0.5H, ddd, *J* = 22.3, 13.2, 2.4 Hz), 3.81 (0.5H, ddd, *J* = 22.8, 13.1, 2.2 Hz), 3.57 (0.5H, ddd, *J* = 13.1, 6.8, 3.3 Hz), 3.50 (0.5H, ddd, *J* = 13.1, 5.9, 3.3 Hz), 2.93-2.78 (4H, m), 2.44-2.31 (1H, m), 1.78-1.63 (1H, m), 1.46 (4H, s), 1.39 (5H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2, 154.4, 153.9, 141.1, 140.9, 128.6, 128.5, 128.4, 126.3, 126.1, 92.6, 91.7, 91.2, 90.3, 80.9, 80.8, 63.4, 62.8, 53.7, 53.5, 53.3, 41.4, 40.4, 36.6, 36.4, 35.6, 35.4, 29.3, 28.4, 28.2.

^{19}F NMR (282 MHz, $CDCl_3$) δ -176.4, -177.1.

HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{24}FNNaO_3$ ($[M+Na]^+$) 344.1632, found 344.1635.

$[\alpha]_D$ = 73.2° (c = 1.00, $CHCl_3$)



(Minor diastereomer)

IR (film) ν_{max} 2976, 2931, 1729, 1695, 1497, 1478, 1454, 1391, 1365, 1251, 1168, 1119, 1066 cm^{-1}.

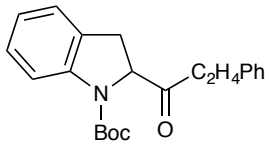
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.17 (5H, m), 5.24-5.12 (1H, m), 4.44-4.29 (1H, m), 3.85-3.56 (2H, m), 2.94-2.82 (4H, m), 2.45-2.20 (2H, m), 1.48 (4H, s), 1.40 (5H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.3, 209.9, 154.6, 153.9, 141.3, 141.2, 128.4, 126.1, 93.1, 92.2, 91.8, 90.9, 80.9, 80.7, 64.6, 64.1, 53.7, 53.5, 53.3, 39.5, 39.3, 37.5, 37.3, 36.5, 36.3, 29.7, 29.2, 28.4, 28.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ -171.1, -171.7.

HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{24}FNNaO_3$ ($[M+Na]^+$) 344.1632, found 344.1636.

$[\alpha]_D$ = -94.0° (c = 0.20, $CHCl_3$)



(±)-*tert*-butyl 2-(3-phenylpropanoyl)indoline-1-carboxylate (31)

Prepared following general procedure A outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), 1-(tert-butoxycarbonyl)indoline-2-carboxylic acid (171.0 mg, 0.65 mmol, 1.3 equiv.), MeCN

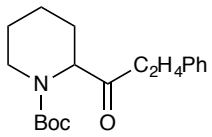
(25.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (141 mg, 0.40 mmol, 80% yield).

IR (film) ν_{max} 3028, 2975, 2930, 1704, 1602, 1483, 1464, 1454, 1383, 1367, 1317, 1255 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (0.6H, s), 7.50 (0.4H, s), 7.30-6.96 (8H, m), 4.93-4.81 (1H, m), 3.46-3.40 (1H, m), 2.96-2.74 (5H, m), 1.63&1.48 (9H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1, 152.6, 142.7, 140.8, 128.5, 128.4, 128.0, 126.2, 124.9, 124.5, 122.8, 114.8, 81.6, 66.6, 65.9, 39.9, 39.2, 31.5, 30.6, 29.3, 28.2.

HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{25}NNaO_3$ ($[M+Na]^+$) 374.1727, found 374.1724.



(±)-*tert*-butyl 2-(3-phenylpropanoyl)piperidine-1-carboxylate (32)

Prepared following general procedure B outlined above using $Ir[dF(OMe)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), 1-(tert-butoxycarbonyl)piperine-2-carboxylic acid (115.0 mg, 0.50 mmol, 1.0 equiv.), dioxane (5.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (120 mg, 0.38 mmol, 76% yield).

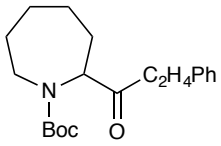
IR (film) ν_{max} 3007, 2975, 2931, 1709, 1673, 1602, 1475, 1451, 1407, 1361, 1338, 1270, 1250, 1163 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.17 (5H, m), 4.74-4.54 (1H, m), 4.06-3.88 (1H, m),

2.92-2.69 (5H, m), 2.15-2.12 (1H, m), 1.60-1.47 (15H, m), 1.25-1.18 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.2, 141.1, 128.5, 128.4, 126.1, 80.1, 61.4, 60.1, 42.8, 40.6, 29.6, 28.4, 29.6, 28.4, 25.0, 20.6.

HRMS (ESI-TOF) m/z calcd. for $C_{19}H_{27}NNaO_3$ ($[M+Na]^+$) 340.1883, found 340.1885.



(±)-*tert*-butyl 2-(3-phenylpropanoyl)azepane-1-carboxylate (33)

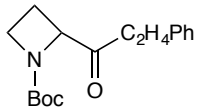
Prepared following general procedure B outlined above using $Ir[dF(OMe)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), 1-(tert-butoxycarbonyl)azepane-2-carboxylic acid (122.0 mg, 0.50 mmol, 1.0 equiv.), dioxane (5.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (114 mg, 0.34 mmol, 69% yield).

IR (film) ν_{max} 2927, 2855, 1685, 1604, 1453, 1403, 1365, 1157 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.16 (5H, m), 4.55 (0.55H, dd, *J* = 11.8, 6.4 Hz), 4.55 (0.45H, dd, *J* = 12.0, 5.5 Hz), 3.68-3.70 (1H, m), 3.01-2.70 (5H, m), 2.18-2.05 (1H, m), 1.87-1.64 (3H, m), 1.57-1.20 (13H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 156.1, 155.1, 141.2, 128.5, 128.4, 128.3, 126.1, 125.9, 80.3, 79.9, 66.2, 63.9, 44.4, 41.1, 40.3, 29.6, 29.5, 29.4, 29.4, 29.3, 29.0, 28.8, 28.4, 28.3, 26.2, 25.3.

HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{29}NNaO_3$ ($[M+Na]^+$) 354.2039, found 354.2038.



(±)-*tert*-butyl 2-(3-phenylpropanoyl)azetidine-1-carboxylate (34)

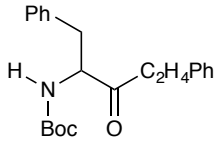
Prepared following general procedure B outlined above using Ir[dF(OMe)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), NiCl$_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), 1-(tert-butoxycarbonyl)azetidine-2-carboxylic acid (101.0 mg, 0.50 mmol, 1.0 equiv.), dioxane (5.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (57 mg, 0.20 mmol, 40% yield).

IR (film) ν_{max} 2974, 2931, 1698, 1498, 1478, 1454, 1390, 1365, 1134 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31-7.18 (5H, m), 4.62 (1H, dd, *J* = 9.8, 6.1 Hz), 3.91-3.82 (2H, m), 3.01-2.85 (4H, m), 2.43-2.36 (1H, m), 1.99-1.95 (1H, m), 1.42 (9H, m).

^{13}C NMR (125 MHz, CDCl$_3$) δ 208.3, 141.0, 140.2, 128.6, 128.5, 128.3, 128.2, 126.6, 126.1, 80.3, 35.3, 30.6, 29.1, 28.3, 20.2, 19.6.

HRMS (ESI-TOF) m/z calcd. for $C_{17}H_{23}NNaO_3$ ([M+Na]$^+$) 312.1570, found 312.1567.



(±)-*tert*-butyl (3-oxo-1,5-diphenylpentan-2-yl)carbamate (35)

Prepared following general procedure B outlined above using Ir[dF(OMe)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), NiCl$_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-phenylalanine (133.0 mg, 0.50 mmol, 1.0 equiv.), dioxane (5.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (97 mg,

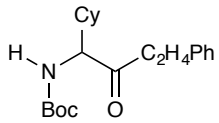
0.27 mmol, 55% yield).

IR (film) ν_{max} 3346, 3064, 3026, 2979, 2930, 1713, 1687, 1603, 1514, 1246, 1165 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.06 (10H, m), 5.08-4.79 (1H, m), 4.53-4.26 (1H, m), 3.02-2.62 (5H, m), 1.41 (9H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3, 155.2, 140.7, 136.1, 129.2, 128.7, 128.5, 128.4, 127.0, 126.1, 79.9, 60.1, 42.5, 37.8, 29.3, 28.3.

HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{27}NNaO_3$ ($[M+Na]^+$) 376.1883, found 376.1879.



(±)-*tert*-butyl (1-cyclohexyl-2-oxo-4-phenylbutyl)carbamate (36)

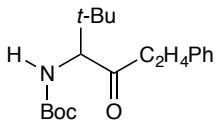
Prepared following general procedure B outlined above using $Ir[dF(OMe)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), 2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid (129.0 mg, 0.50 mmol, 1.0 equiv.), dioxane (5.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (100 mg, 0.29 mmol, 58% yield).

IR (film) ν_{max} 3316, 2979, 2926, 2854, 1720, 1682, 1534, 1363, 1248, 1169, 1059 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.20 (5H, m), 5.15-4.80 (1H, m), 4.27-3.99 (1H, m), 2.96-2.81 (4H, m), 1.76-1.63 (5H, m), 1.46 (9H, s), 1.30-0.92 (6H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 208.8, 156.9, 140.8, 128.5, 128.4, 126.2, 79.6, 63.9, 42.8, 40.1, 30.2, 29.4, 28.3, 27.2, 26.2, 26.0, 25.9.

HRMS (ESI-TOF) m/z calcd. for $C_{21}H_{31}NNaO_3$ ([M+Na]$^+$) 368.2196, found 368.2199.



(±)-*tert*-butyl (2,2-dimethyl-4-oxo-6-phenylhexan-3-yl)carbamate (37)

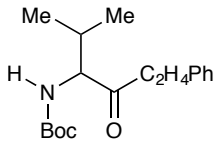
Prepared following general procedure B outlined above using Ir[dF(OMe)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), 2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid (116.0 mg, 0.50 mmol, 1.0 equiv.), dioxane (5.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (92 mg, 0.29 mmol, 59% yield).

IR (film) ν_{max} 3364, 2966, 1700, 1495, 1365, 1241, 1164, 1053 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.24 (5H, m), 5.20 (1H, d, *J* = 9.4 Hz), 4.22 (1H, d, *J* = 9.3 Hz), 3.00-2.93 (4H, m), 1.50 (9H, s), 1.00 (9H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0, 156.6, 140.8, 128.5, 128.4, 128.1, 79.7, 65.7, 45.9, 34.7, 29.4, 28.4, 27.1, 26.7.

HRMS (ESI-TOF) m/z calcd. for $C_{19}H_{29}NNaO_3$ ([M+Na]$^+$) 342.2039, found 342.2039.



(±)-*tert*-butyl (2-methyl-4-oxo-6-phenylhexan-3-yl)carbamate (38)

Prepared following general procedure B outlined above using Ir[dF(OMe)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05

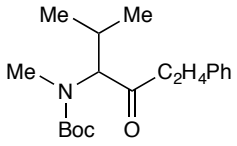
equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-valine (109.0 mg, 0.50 mmol, 1.0 equiv.), dioxane (5.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (97 mg, 0.32 mmol, 64% yield).

IR (film) ν_{max} 3350, 2969, 1720, 1686, 1520, 1497, 1454, 1364, 1247, 1172 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.17 (5H, m), 5.11-4.90 (1H, m), 4.27-3.99 (1H, m), 2.93-2.77 (4H, m), 2.15-2.08 (1H, m), 1.44 (9H, s), 0.97 (3H, d, *J* = 6.8 Hz), 0.70 (3H, d, *J* = 6.9 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 155.9, 140.8, 128.5, 128.4, 126.2, 79.7, 64.0, 42.4, 30.2, 29.5, 28.3, 19.9, 16.6.

HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{27}NNaO_3$ ($[M+Na]^+$) 328.1883, found 328.1885.



(±)-*tert*-butyl methyl(2-methyl-4-oxo-6-phenylhexan-3-yl)carbamate (39)

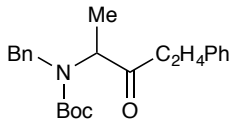
Prepared following general procedure B outlined above using $Ir[dF(OMe)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), 2-((tert-butoxycarbonyl)methylamino)-3-methylbutanoic acid (116.0 mg, 0.50 mmol, 1.0 equiv.), dioxane (5.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (120 mg, 0.37 mmol, 75% yield).

IR (film) ν_{max} 2966, 2931, 1718, 1688, 1604, 1454, 1382, 1366, 1302, 1254, 1157, 1130 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.16 (5H, m), 4.40 (0.6H, d, *J* = 10.7 Hz), 3.96 (0.4H, d, *J* = 10.3 Hz), 2.92-2.63 (4H, m), 2.62&2.45 (3H, s), 2.22-2.13 (1H, m) 1.46 (9H, s), 0.88-0.80 (6H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 206.5, 156.4, 155.4, 140.9, 128.5, 128.4, 128.3, 128.2, 126.0, 80.5, 80.1, 69.6, 67.1, 43.2, 42.8, 29.8, 29.6, 29.4, 28.4, 25.7, 25.1, 20.3, 19.8, 18.7, 18.3.

HRMS (ESI-TOF) m/z calcd. for $C_{19}H_{29}NNaO_3$ ($[M+Na]^+$) 342.2039, found 342.2042.



(±)-*tert*-butyl benzyl(3-oxo-5-phenylpentan-2-yl)carbamate (40)

Prepared following general procedure B outlined above using $Ir[dF(OMe)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), 2-(benzyl(tert-butoxycarbonyl)amino)propanoic acid (140.0 mg, 0.50 mmol, 1.0 equiv.), dioxane (5.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (147 mg, 0.40 mmol, 80% yield).

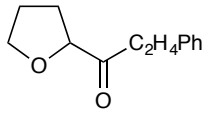
IR (film) ν_{max} 3063, 3028, 2977, 2933, 1720, 1688, 1604, 1495, 1453, 1419, 1366, 1246, 1156 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.06 (10H, m), 4.74-4.51 (1H, m), 4.30-3.53 (2H, m), 2.86-2.37 (4H, m), 1.46-1.44 (9H, m), 1.29-1.22 (3H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 207.3, 155.4, 154.9, 141.3, 141.0, 138.6, 137.8, 128.7, 128.6, 128.5, 128.4, 128.3, 127.8, 127.4, 127.3, 126.0, 125.9, 81.3, 80.8, 61.7,

60.7, 51.3, 49.9, 40.4, 39.8, 29.8, 28.2, 13.7, 13.4.

HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{25}NNaO_3$ ($[M+Na]^+$) 390.2039, found 390.2042.



(±)-3-phenyl-1-(tetrahydrofuran-2-yl)propan-1-one (41)

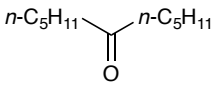
Prepared using conditions similar to general procedure B outlined above using $Ir[dF(OMe)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-di(*tert*-butyl)-2,2'-bipyridyl ligand (6.7 mg, 25.0 μmol, 0.05 equiv.), 2-tetrahydrofuranoic acid (58.0 mg, 0.50 mmol, 1.0 equiv.), dioxane (15.0 mL), hydrocinnamoyl chloride (74.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (66 mg, 0.32 mmol, 65% yield).

IR (film) ν_{max} 3028, 2950, 2871, 1712, 1603, 1496, 1453, 1401, 1361, 1287, 1068 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.20 (5H, m), 4.32 (1H, dd, *J* = 8.3, 5.9 Hz), 3.96-3.89 (2H, m), 2.98-2.80 (4H, m), 2.20-2.14 (1H, m), 1.93-1.81 (3H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6, 141.2, 128.5, 128.4, 126.1, 83.5, 69.4, 39.9, 29.2, 29.0, 25.6.

HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{16}NaO_2$ ($[M+Na]^+$) 227.1042, found 227.1041.



undecan-6-one (42)

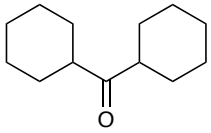
To an oven-dried 8 mL vial equipped with a stir bar was added $Ir[dF(OMe)ppy]_2(dtbbpy)PF_6$ (1.1 mg, 1.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (1.1 mg, 5.0 μmol, 0.05 equiv.), 2,2'-bipyridyl (0.8 mg, 5.0 μmol, 0.05 equiv.). The vial was sealed and placed under nitrogen before dioxane solution of hexanoic anhydride (24 mg, 0.10 mmol, 1.0

equiv.) was added followed by DBU (4.5 μL, 0.03 mmol, 0.30 equiv.). The reaction mixture was degassed by sparging with nitrogen while stirring for 15 min before sealing the vial with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away, with cooling fan to keep the reaction temperature at 25 ºC) for 36 hours. The reaction was quenched by exposure to air. Methyl benzoate (internal standard, 12.65 μL, 0.10 mmol, 1.0 equiv.) was added then the reaction mixture was analyzed by GC and ^{1}H NMR. The reaction was repeated three times to confirm the yield of the desired product.

Trial 1 46% yield

Trial 2 45% yield

Trial 3 48% yield



dicyclohexyl ketone (43)

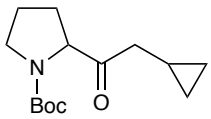
To an oven-dried 8 mL vial equipped with a stir bar was added Ir[dF(OMe)ppy]$_2$(dtbbpy)PF_6 (1.1 mg, 1.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (1.1 mg, 5.0 μmol, 0.05 equiv.), 2,2'-bipyridyl (0.8 mg, 5.0 μmol, 0.05 equiv.). The vial was sealed and placed under nitrogen before dioxane solution of cyclohexanecarboxylic anhydride (24 mg, 0.10 mmol, 1.0 equiv.) was added followed by DBU (4.5 μL, 0.03 mmol, 0.30 equiv.). The reaction mixture was degassed by sparging with nitrogen while stirring for 15 min before sealing the vial with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away, with cooling fan to keep the reaction temperature at 25 ºC) for 36 hours. The reaction was quenched by exposure to air. Methyl benzoate (internal standard, 12.65 μL, 0.10 mmol, 1.0 equiv.) was added then the reaction mixture was analyzed by GC and ^{1}H NMR. The reaction was repeated three times to confirm the yield of the desired product.

Trial 1 50% yield

Trial 2 47% yield

Trial 3 50% yield

8) Observed Rearrangement with Cyclopropylacetic Mixed Anhydride



Synthesis of (±)-*tert*-butyl 2-(2-cyclopropylacetyl)pyrrolidine-1-carboxylate

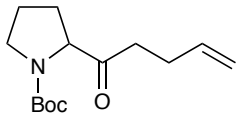
Under nitrogen, a round-bottom flask, equipped with a magnetic stir bar was charged with N-Boc-pyrrolidine (0.35 mL, 2.0 mmol, 1.0 equiv.), Et_2O (10 mL) and (-)-Lupinidine (0.59 mL, 2.6 mmol, 1.3 equiv.). The clear solution was cooled to -78 ºC before sec-BuLi (1.4M soln, 1.8 mL, 2.6 mmol, 1.3 equiv.) was added drop wise. The reaction mixture was stirred at -78 ºC for 5 hours. Separately, a fresh solution of CuCN•2LiCl in THF (0.3M) was prepared then added drop wise to the original reaction mixture (6.7 mL, 2.0 mmol, 1.0 equiv). The mixture was stirred at -78 ºC for 1 hour before cyclopropaneacetyl chloride was added in one portion (236 mg, 2.0 mmol, 1.0 equiv) and the reaction mixture was allowed to warm up to room temperature over night. H_2O was added to quench the reaction, followed by dilution with Et_2O. The organic layer was separated then washed with NH_4Cl (sat aq) and brine. Drying with Mg_2SO_4, followed by concentration *in vacuo* afford a crude oil. Column chromatography (silica gel, 5 to 20% EtOAc in hexanes) afforded the desired product as a clear oil. (300 mg, 1.2 mmol, 60% yield).

IR (film) ν_{max} 3080, 2975, 2879, 1690, 1478, 1454, 1389, 1364, 1253, 1160, 1113 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (0.4H, d, *J* = 8.9, 3.8 Hz), 4.28-4.25 (0.6H, m), 3.53-3.40 (2H, m), 2.40-2.31 (2H, m), 2.19-2.08 (1H, m), 1.87-1.80 (3H, m), 1.43&1.39 (9H, s), 1.01-1.00 (1H, m), 0.57-0.53 (2H, m), 0.09-0.06 (2H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0, 209.8, 154.6, 153.9, 80.0, 79.7, 64.9, 64.3, 46.9, 46.7, 44.8, 44.0, 29.9, 28.8, 28.4, 24.4, 23.7, 5.7, 4.7.

HRMS (ESI-TOF) m/z calcd. for $C_{14}H_{23}NNaO_3$ ($[M+Na]^+$) 276.1570, found 276.1571.



(±)-*tert*-butyl 2-(pent-4-enoyl)pyrrolidine-1-carboxylate

To an oven-dried 40 mL vial equipped with a stir bar was added $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 μmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.) and MeCN (25.0 mL). The vial was sealed and placed under nitrogen before 2-cyclopropylacetyl chloride (59.0 mg, 0.50 mmol, 1.0 equiv.) was added followed by DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). The reaction mixture was degassed by sparing with nitrogen while stirring for 30 min before sealing the vial with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away, with cooling fan to keep the reaction temperature at 25 ºC) for 36 hours. The reaction was quenched by exposure to air. An aliquot was taken for GC and NMR analysis. With an internal standard, GC analysis showed formation of unarranged product (<3%) and arranged product (84%)

Reaction mixture was concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 to 20% EtOAc in hexanes) yielded the ketone product as a clear oil (104 mg, 0.41 mmol, 82% yield).

IR (film) ν_{max} 2976, 2932, 2879, 1719, 1691, 1641, 1478, 1451, 1390, 1365, 1253, 1160, 1114 cm^{-1}.

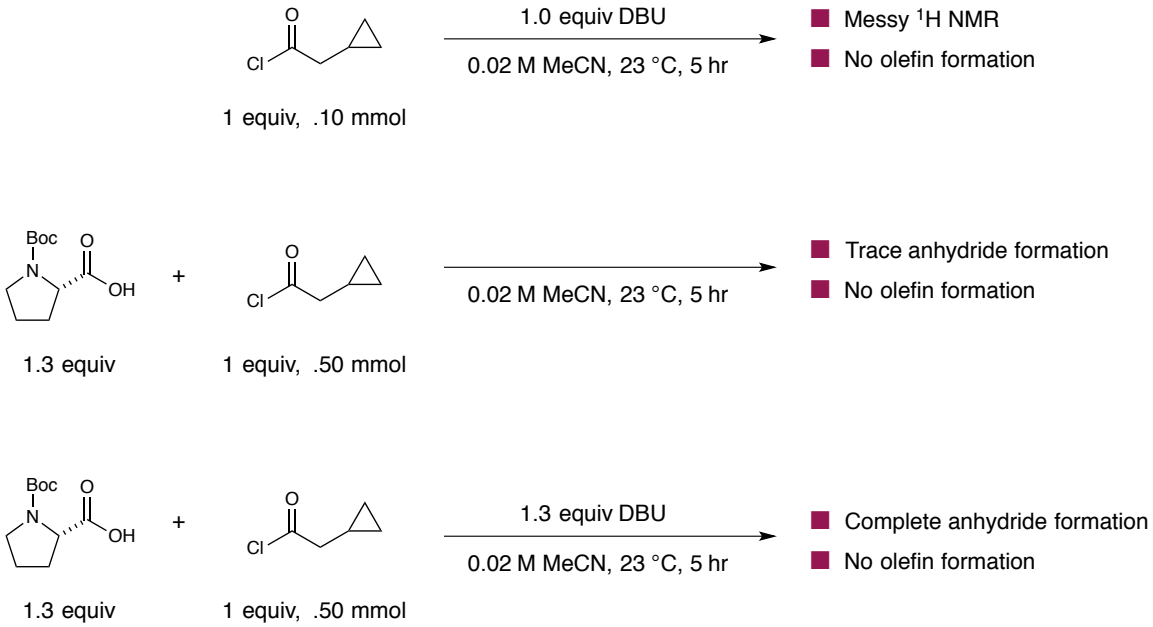
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82-5.76 (1H, m), 5.10-4.91 (2H, m), 4.33 (0.4H, d, *J* = 8.8, 4.2 Hz), 4.22 (0.6H, d, *J* = 8.7, 4.9 Hz), 3.55-3.40 (2H, m), 2.60-2.44 (2H, m), 2.35-2.30 (2H, m), 2.19-2.09 (1H, m), 1.88-1.78 (1H, m), 1.44 (4H, s), 1.39 (5H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 209.2, 154.6, 153.9, 137.2, 137.1, 115.4, 115.1, 80.1, 79.8, 65.3, 64.7, 46.9, 46.7, 38.4, 37.5, 29.9, 28.4, 28.3, 27.3, 27.3, 24.4, 23.7.

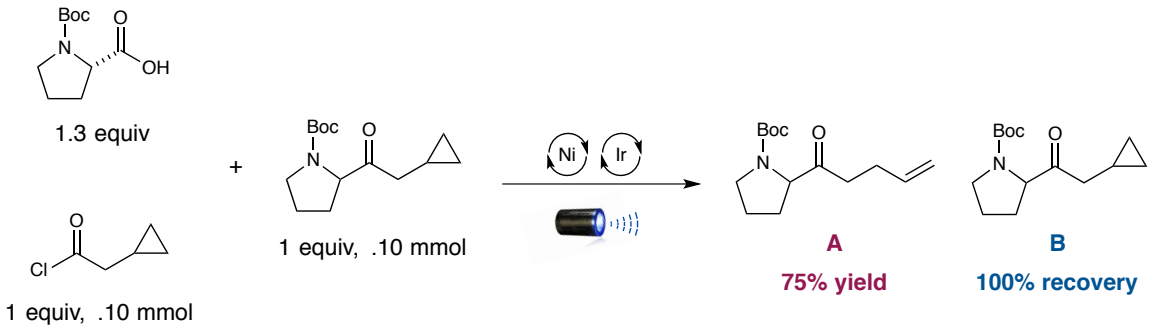
HRMS (ESI-TOF) m/z calcd. for $C_{14}H_{23}NNaO_3$ ($[M+Na]^+$) 276.1570, found 276.1571.

9) Control Experiments for Rearrangement Studies

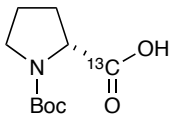
1) Monitoring rearrangement during the anhydride formation step



2) Monitoring rearrangement under reaction condition



10) Synthesis of ^{13}C-Labeled Starting Material

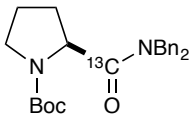


***[13]C-N*-Boc-(D)-Proline**

Under nitrogen, a round-bottom flask, equipped with a magnetic stir bar was charged with N-Boc-pyrrolidine (3.50 mL, 20.0 mmol, 1.0 equiv.), Et_2O (100 mL) and (-)-Lupinidine (5.90 mL, 26.0 mmol, 1.3 equiv.). The clear solution was cooled to -78 ºC before sec-BuLi (1.4M soln, 18.0 mL, 26.0 mmol, 1.3 equiv.) was added drop wise. The reaction mixture was stirred at -78 ºC for 5 hours. $^{13}CO_2$ was bubbled through the reaction mixture then the reaction was allowed to warm up to 23 ºC over 1 hour under an atmosphere of $^{13}CO_2$. H_2O followed by dilution with Et_2O. The aqueous layer was separated then washed with Et_2O. The aqueous layer was acidified to pH of 1 using 6M HCl then the product was extracted with Et_2O. Drying with $MgSO_4$, followed by concentration *in vacuo* yielded a clear oil, which solidified upon standing at room temperature under hi-vac over night. The crude solid was recrystallized by layering technique (hexanes over EtOAc at room temperature over night) to yield the pure desired product as a white crystalline solid (2.0 g, 9.25 mmol, 46% yield). ^{13}C incorporation was confirmed by Hi-Res MS (>99%) using the dibenzyl amide analog. Enantiomeric excess level (>99%) was determined by HPLC analysis on the dibenzyl amide analog.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36-4.26 (1H, m), 3.56-3.33 (2H, m), 2.45-1.90 (4H, m), 1.50-1.43 (9H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 172.7, 82.2, 47.3, 28.4, 27.7, 24.3.



***tert*-butyl (*R*)-2-(dibenzylcarbamoyl-*[13]C*)-pyrrolidine-1-carboxylate**

Under nitrogen, a round-bottom flask was charged with DMF (19 µL, 0.25 mmol, 2.0

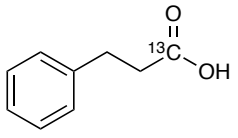
equiv.) and DCM (2.5 mL). The solution was cooled to 0 ºC before oxalyl chloride (22 µL, 0.25 mmol, 2.0 equiv.) was added, followed by pyridine (20 µL, 0.25 mmol, 2.0 equiv) was added. DCM solution of ^{13}C-*N*-Boc-(D)-Proline (54.0 mg, 0.25 mmol, 2.0 equiv.) was added in one portion and the solution was stirred at 0 ºC for 1 hour. At this point, dibenzylamine (24 µL, 0.12 mmol, 1.0 equiv) and triethylamine (17 µL, 0.12 mmol, 1.0 equiv) was added. The reaction mixture was stirred and allowed to warm up to room temperature over 3 hours. Final mixture was diluted with Et_2O and water. The organic layer was separated then washed with 1M HCl (aq) and brine. Drying with $MgSO_4$, followed by concentration *in vacuo* yielded a crude oil. Column chromatography (silica gel, 20% EtOAc in hexanes) yielded the pure desired product as a white solid (35 mg, 0.08 mmol, 70% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.14 (10H, m), 4.81-4.33 (5H, m), 3.63-3.34 (2H, m), 2.11-1.72 (4H, m), 1.43 (4.5H, s), 1.31 (4.5H, s).

HRMS (ESI-TOF)

m/z $(M+Na)^+$	*Abundance*
417	19473
418	123258

This mass distribution indicates >99% ^{13}C incorporation.[5]



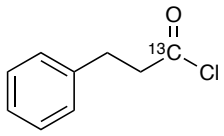
3-phenylpropanoic-1-*^{13}C* acid

Under nitrogen, a round-bottom flask equipped with a stir bar was charged with an Et_2O solution of phenylethylmagnesium bromide (Aldrich, 1.0M, 30.0 mmol). The solution was cooled to 0 ºC before $^{13}CO_2$ was bubbled through the solution. The mixture was allowed to warm up to room temperature over 1 hour under an atmosphere of $^{13}CO_2$. 1M

HCl was added followed by dilution with EtOAc. The organic layer was separated and washed with brine. Drying with $MgSO_4$, followed by concentration *in vacuo* yielded a clear oil. Column chromatography (silica gel, 30% EtOAc in hexanes) yielded the pure product as a white solid (1.6g, 10.6 mmol, 24% yield). ^{13}C incorporation was confirmed by Hi-Res MS of the dibenzyl amide analog (>99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.23 (5H, m), 3.00-2.71 (4H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 140.2, 140.1, 128.6, 128.3, 126.4, 35.7, 35.2, 30.6.

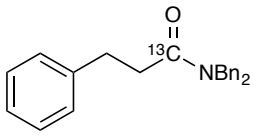


3-phenylpropanoyl-1-*^{13}C* chloride

Under nitrogen, a round-bottom flask equipped with a stir bar was charged with 3-phenylpropanoic-1-*^{13}C* acid (500 mg, 3.33 mmol, 1.0 equiv.) and DCM (10 mL). The solution was cooled to 0 ºC before oxalyl chloride (0.35 mL, 4.00 mmol, 1.2 equiv.) was added drop wise, followed by 2 drops of DMF. The solution was allowed to warm up to room temperature over 3 hours. Final solution was concentrate *in vacuo* to yield a yellow oil. Distillation under vacuum yielded the pure product as a clear oil (405 mg, 2.4 mmol, 72% yield). ^{13}C incorporation was confirmed by Hi-Res MS of the dibenzyl amide analog (>99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (2.0H, t, J = 7.5 Hz), 7.28-7.25 (1H, m), 7.23-7.22 (2H, m), 3.24 (2.0H, q, J = 7.6 Hz), 3.04 (2.0H, td, J = 7.5, 5.3 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 138.6, 138.5, 128.8, 128.3, 126.8, 48.7, 48.3, 31.0, 30.9.



***N,N*-dibenzyl-3-phenylpropanamide-1-^{13}C**

Under nitrogen, a round-bottom flask equipped with a stir bar was charged with 3-phenylpropanoyl-1-^{13}C chloride (44.0 μL, 0.3 mmol, 1.0 equiv.) and Et_2O (10 mL). The solution was cooled to 0 ºC before dibenzylamine (63.0 μL, 0.33 mmol, 1.1 equiv.) was added, followed by triethylamine (52.0 μL, 0.37 mmol, 1.2 equiv.). The solution was allowed to warm up to room temperature over 3 hours. Final solution was diluted with Et_2O and washed with 1M HCl. Drying with $MgSO_4$, followed by concentration *in vacuo* yielded a crude solid. Column chromatography (silica gel, 10% EtOAc in hexanes) yielded the pure product as a white solid (88 mg, 0.27 mmol, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.24 (8H, m), 7.21-7.18 (5H, m), 7.09-7.08 (2H, m), 4.60 (2.0H, d, *J* = 3.1 Hz), 4.37 (2.0H, d, *J* = 3.8 Hz), 3.05 (2.0H, td, *J* = 7.8, 3.4 Hz), 2.73 (2.0H, td, *J* = 7.8, 5.6 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 141.2, 141.1, 137.3, 136.4, 128.9, 128.6, 128.5, 128.4, 128.3, 127.6, 127.4, 126.3, 126.1, 49.9, 49.8, 48.3, 35.2, 34.8, 31.6.

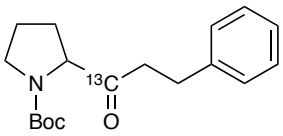
HRMS (ESI-TOF)

m/z $(M+H)^+$	*Abundance*
330	28090
331	1889610

This mass distribution indicates >99% ^{13}C incorporation.[5]

11) Labeling Experiments

General Procedure: To an oven-dried 8 mL vial equipped with a stir bar was added Ir[dF(CF_3)ppy]$_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 µmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 µmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine ligand (5.4 mg, 25.0 µmol, 0.05 equiv.), *^{13}C-N*-Boc-(D)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.) and MeCN (25.0 mL). The vial was sealed and placed under nitrogen before acyl chloride (0.10 mmol, 1.0 equiv.) was added followed by DBU (0.13 mmol, 1.3 equiv.). The reaction mixture was degassed by sparging with nitrogen while stirring for 30 min before sealing the vial with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away, with cooling fan to keep the reaction temperature at 25 ºC) for 36 hours. The reaction was quenched by exposure to air. Concentration *in vacuo* followed by column chromatography yielded the desire product. ^{13}C incorporation was analyzed by HR-MS.



***tert*-butyl 2-(3-phenylpropanoyl-1-^{13}*C*)pyrrolidine-1-carboxylate (45)**

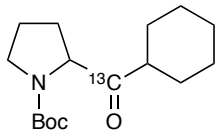
Prepared following the general procedure above using Ir[dF(CF_3)ppy]$_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 µmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 µmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine ligand (5.4 mg, 25.0 µmol, 0.05 equiv.), *^{13}C-N*-Boc-(D)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), hydrocinnamoyl chloride (74.0 µL, 0.50 mmol, 1.0 equiv.), and DBU (97.0 µL, 0.65 mmol, 1.3 equiv.) in MeCN (25 mL). Purification by column chromatography yielded the pure product as a clear oil (130 mg, 0.43 mmol, 86% yield).

HRMS (ESI-TOF)

m/z $(M+Na)^+$	*Abundance (Injection 1)*	*Abundance (Injection 2)*	*Abundance (Injection 3)*
326	486560	462922	617176

327	169052	161318	215922

This mass distribution indicates **15% ^{13}C incorporation**.[5]



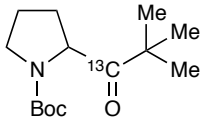
***tert*-butyl 2-(cyclohexanecarbonyl-1-^{13}*C*)pyrrolidine-1-carboxylate**

Prepared following the general procedure above using Ir[dF(CF_3)ppy]$_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine ligand (5.4 mg, 25.0 μmol, 0.05 equiv.), ^{13}*C*-*N*-Boc-(D)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), cyclohexanecarbonyl chloride (67.0 μL, 0.50 mmol, 1.0 equiv.), and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.) in MeCN (25 mL). Purification by column chromatography yielded the pure product as a clear oil (112 mg, 0.40 mmol, 80% yield).

HRMS (ESI-TOF)

m/z $(M+Na)^+$	*Abundance (Injection 1)*	*Abundance (Injection 2)*	*Abundance (Injection 3)*
304	255417	261944	352768
305	61615	62382	83838

This mass distribution indicates **6% ^{13}C incorporation**.[5]



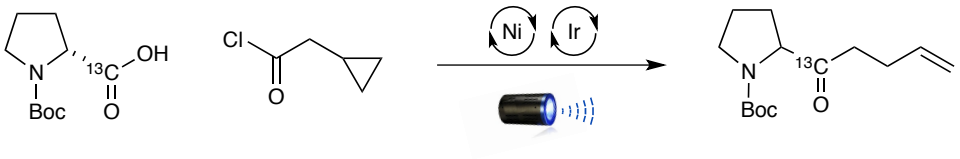
***tert*-butyl 2-(pivaloyl-1-^{13}*C*)pyrrolidine-1-carboxylate**

Prepared following the general procedure above using Ir[dF(CF_3)ppy]$_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 μmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine ligand (5.4 mg, 25.0 μmol, 0.05 equiv.), ^{13}*C*-*N*-Boc-(D)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), pivaloyl chloride (62.0 μL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 μL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (42 mg, 0.16 mmol, 35% yield).

HRMS (ESI-TOF)

m/z $(M+Na)^+$	*Abundance (Injection 1)*	*Abundance (Injection 2)*	*Abundance (Injection 3)*
278	218434	200445	163822
279	39622	36215	29606

This mass distribution indicates **3% ^{13}C incorporation**.[5]



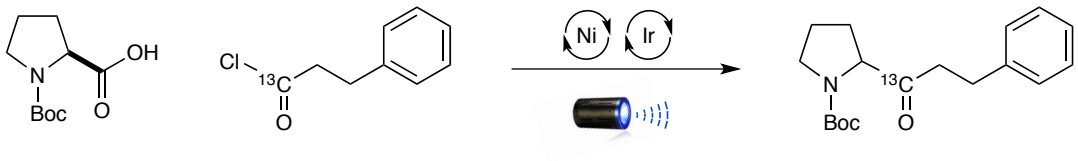
***tert*-butyl 2-(pent-4-enoyl-1-^{13}*C*)pyrrolidine-1-carboxylate (47)**

Prepared following the general procedure above using Ir[dF(CF_3)ppy]$_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 µmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 µmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine ligand (5.4 mg, 25.0 µmol, 0.05 equiv.), *^{13}C-N*-Boc-(D)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), 2-cyclopropylacetyl chloride (59.0 mg, 0.50 mmol, 1.0 equiv.) and DBU (97.0 µL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (102 mg, 0.40 mmol, 80% yield).

HRMS (ESI-TOF)

m/z $(M+Na)^+$	*Abundance (Injection 1)*	*Abundance (Injection 2)*	*Abundance (Injection 3)*
276	10804	8004	7142
277	3123	2453	2091

This mass distribution indicates **15% ^{13}C incorporation**.[5]



***tert*-butyl 2-(3-phenylpropanoyl-1-^{13}*C*)pyrrolidine-1-carboxylate**

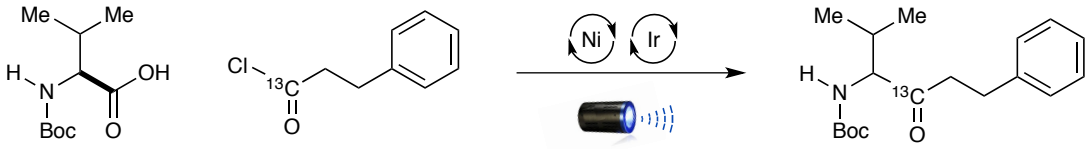
Prepared following the general procedure above using Ir[dF(CF_3)ppy]$_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 µmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 µmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine ligand (5.4 mg, 25.0 µmol, 0.05 equiv.), *N*-Boc-(L)-Proline (140.0 mg, 0.65 mmol, 1.3 equiv.), 3-phenylpropanoyl-1-*^{13}C* chloride (74.0 µL, 0.50

mmol, 1.0 equiv.), and DBU (97.0 µL, 0.65 mmol, 1.3 equiv.) in MeCN (25 mL). Purification by column chromatography yielded the pure product as a clear oil (125 mg, 0.41 mmol, 83% yield).

HRMS (ESI-TOF)

m/z $(M+Na)^+$	*Abundance (Injection 1)*	*Abundance (Injection 2)*	*Abundance (Injection 3)*
326	41438	39346	42936
327	247071	233698	256141

This mass distribution indicates **85% ^{13}C incorporation**.[5]



***tert*-butyl (2-methyl-4-oxo-6-phenylhexan-3-yl-4-^{13}*C*)carbamate**

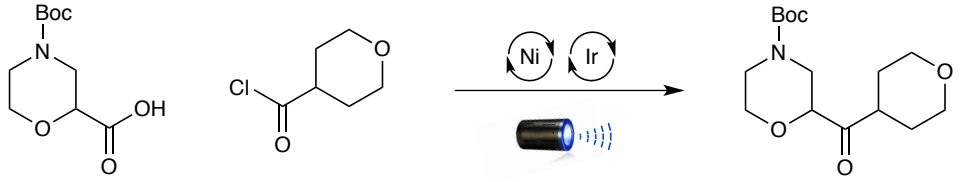
Prepared following general procedure outlined above using Ir[dF(OMe)ppy]$_2$(dtbbpy)PF_6 (5.6 mg, 5.0 µmol, 0.01 equiv.), $NiCl_2$•glyme (5.5 mg, 25.0 µmol, 0.05 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 25.0 µmol, 0.05 equiv.), *N*-Boc-(L)-valine (109.0 mg, 0.50 mmol, 1.0 equiv.), dioxane (5.0 mL), 3-phenylpropanoyl-1-^{13}*C* chloride (74.0 µL, 0.50 mmol, 1.0 equiv.) and DBU (97.0 µL, 0.65 mmol, 1.3 equiv.). Purification by column chromatography yielded the pure product as a clear oil (96 mg, 0.30 mmol, 60% yield).

HRMS (ESI-TOF)

m/z $(M+Na)^+$	*Abundance (Injection 1)*	*Abundance (Injection 2)*	*Abundance (Injection 3)*
328	19983	14345	14447
329	247156	176982	176659

This mass distribution indicates **92% ^{13}C incorporation**.[5]

12) Synthesis of (±)-Edivoxetine•HCl



***(±)tert*-butyl 2-(tetrahydro-2*H*-pyran-4-carbonyl)morpholine-4-carboxylate (54)**

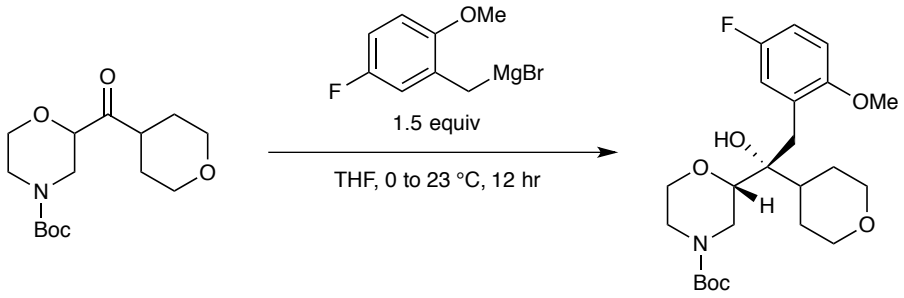
To an oven-dried 40 mL vial equipped with a stir bar was added Ir[dF(OMe)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv.), NiCl$_2$•glyme (5.5 mg, 25.0 µmol, 0.05 equiv.), 4,4'-di(*tert*-butyl)-2,2'-bipyridyl ligand (6.7 mg, 25.0 µmol, 0.05 equiv.), 4-(tert-butoxycarbonyl)morpholine-2-carboxylic acid (116.0 mg, 0.50 mmol, 1.0 equiv.) and dioxane (15.0 mL). The vial was sealed and placed under nitrogen before tetrahydro-2*H*-pyran-4-carbonyl chloride (74 mg, 0.50 mmol, 1.0 equiv.) was added followed by DBU (97.0 µL, 0.65 mmol, 1.3 equiv.). The reaction mixture was degassed by sparing with nitrogen while stirring for 30 min before sealing the vial with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away, with cooling fan to keep the reaction temperature at 25 ºC) for 36 hours. The reaction was quenched by exposure to air. Reaction mixture was filtered, then concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 to 40% EtOAc in hexanes) yielded the ketone product (102 mg, 0.34 mmol, 68% yield).

IR (film) ν_{max} 2958, 2926, 2852, 1694, 1415, 1366, 1238, 1162, 1126, 1087 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$) δ 4.16-3.95 (6H, m), 3.58-3.42 (3H, m), 3.07-2.55 (3H, m), 1.88-1.64 (5H, m), 1.46 (9H, s).

^{13}C NMR (125 MHz, CDCl$_3$) δ 178.5, 154.6, 80.5, 78.9, 67.2, 67.0, 66.7, 43.1, 39.6, 29.7, 28.4, 28.3, 27.9, 27.4.

HRMS (ESI-TOF) m/z calcd. for $C_{15}H_{25}NNaO_5$ ([M+Na]$^+$) 322.1625, found 322.1623.



(±)*tert*-butyl 2-(2-(5-fluoro-2-methoxyphenyl)-1-hydroxy-1-(tetrahydro-2*H*-pyran-4-yl)ethyl)morpholine-4-carboxylate

Under nitrogen, a round-bottom flask equipped with a magnetic stir bar and a reflux condenser was charged with Mg (55 mg, 2.25 mmol, 4.5 equiv.), THF (5 mL) and catalytic amount of I_2. A separate THF solution (5 mL) of 2-(bromomethyl)-4-fluoro-1-methoxybenzene (165 mg, 0.75 mmol, 1.5 equiv.) was added to the Mg mixture drop wise. The reaction mixture was heated to reflux for 1 hour then cooled to room temperature.

In a separate round-bottom flask, under nitrogen, was added (±)*tert*-butyl 2-(tetrahydro-2*H*-pyran-4-carbonyl)morpholine-4-carboxylate (150 mg, 0.50 mmol, 1 equiv.) and THF (10 mL) before the solution was cooled to 0 °C. The Grignard solution was added to the ketone solution drop wise. Once the addition was complete, the reaction mixture was allowed to warm up to room temperature over 12 hours. The reaction was quenched by the addition of NH_4Cl, followed by Et_2O. The organic layer was separated then washed with additional NH_4Cl and brine. Drying with $MgSO_4$, followed by concentration in vacuo yielded a crude solid. Column chromatography (silica gel, 10 to 30% EtOAc in hexanes) yielded the pure product (176 mg, 0.40 mmol, 80% yield). Diastereomeric ratio was determined by GC and HPLC - 17 : 1.

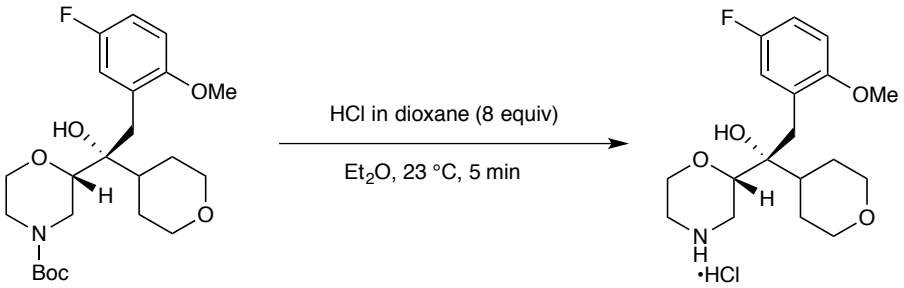
IR (film) ν_{max} 3498, 2957, 2848, 2374, 2246, 1688, 1497, 1453, 1420, 1365, 1252, 1236, 1169, 1103 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (1H, d, *J* = 9.2, 3.1 Hz), 4.22 (1H, ddd, *J* = 8.9, 7.9, 3.1 Hz), 6.76 (1H, d, *J* = 9.0, 4.5 Hz), 4.03-3.97 (3H, m), 3.83-3.75 (5H, m), 3.40-3.24 (5H, m), 3.00 (1H, d, *J* = 14.0 Hz), 2.86-2.68 (3H, m), 1.77-1.55 (5H, m), 1.45 (9H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 155.8, 154.8, 153.8, 128.3, 119.5, 119.3, 113.5, 113.3, 110.9, 110.8, 79.9, 79.1, 75.9, 68.6, 68.3, 66.5, 55.9, 43.3, 42.4, 34.1, 28.4, 27.6, 27.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ -123.8, -124.1.

HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{34}FNNaO_6$ ($[M+Na]^+$) 462.2262, found 462.2266.



(±)-Edivoxetine•HCl

Under air, an oven-dried 25 mL vial equipped with a magnetic stir bar was charged with *tert*-butyl 2-(2-(5-fluoro-2-methoxyphenyl)-1-hydroxy-1-(tetrahydro-2*H*-pyran-4-yl)ethyl)morpholine-4-carboxylate (120 mg, 0.27 mmol, 1 equiv) and Et_2O, 2 mL. HCl in dioxane (4.0 M, 0.55 mL, 2.2 mmol, 8 equiv) was added drop wise. After 5 min, the precipitate was isolated by filtration and washed with addition Et_2O. Drying the solid under hi-vac at 60 °C for 12 hours yielded the desired product as a white solid (97 mg, 0.26 mmol, 95% yield). Spectra data matched those previously reported.[6]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (2H, s), 7.15 (1H, dd, *J* = 10.0, 3.2 Hz), 7.01 (1H, td, *J* = 8.5, 3.2 Hz), 7.15 (1H, dd, *J* = 9.0, 4.8 Hz), 4.63 (1H, s), 3.98 (1H, dd, *J* = 12.5, 3.8 Hz), 3.85-3.69 (7H, m), 3.33-2.87 (8H, m), 2.69 (1H, d, *J* = 14.2 Hz), 1.60-1.24 (5H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 155.3, 154.3, 128.2, 128.1, 119.3, 119.1, 113.7, 113.5, 112.0, 111.9, 76.1, 75.7, 68.3, 67.9, 63.6, 56.2, 43.3, 42.8, 42.5, 31.2, 28.1, 27.0.

HRMS (ESI-TOF) m/z calcd. for (M-HCl) 339.1846, found 339.1845.

13) References Cited

1) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals* (Pergamon Press, Oxford, 1988) ed 3.

2) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

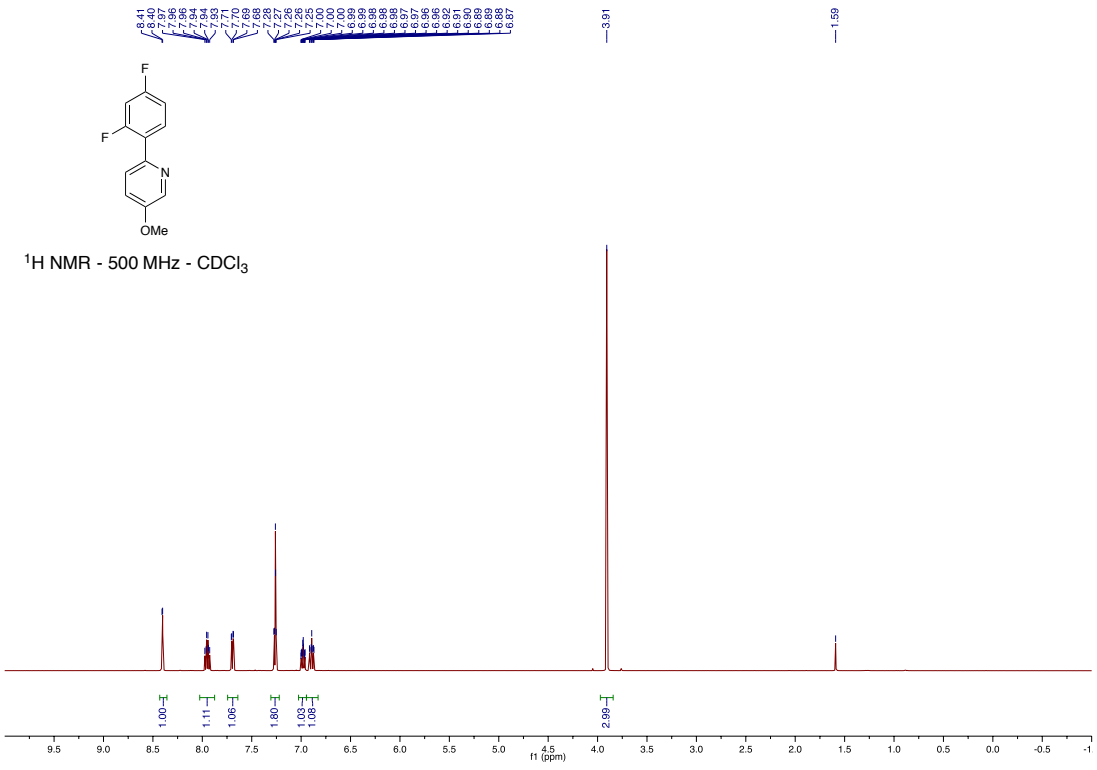
3) Still, W. C.; Kahn, M. ; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

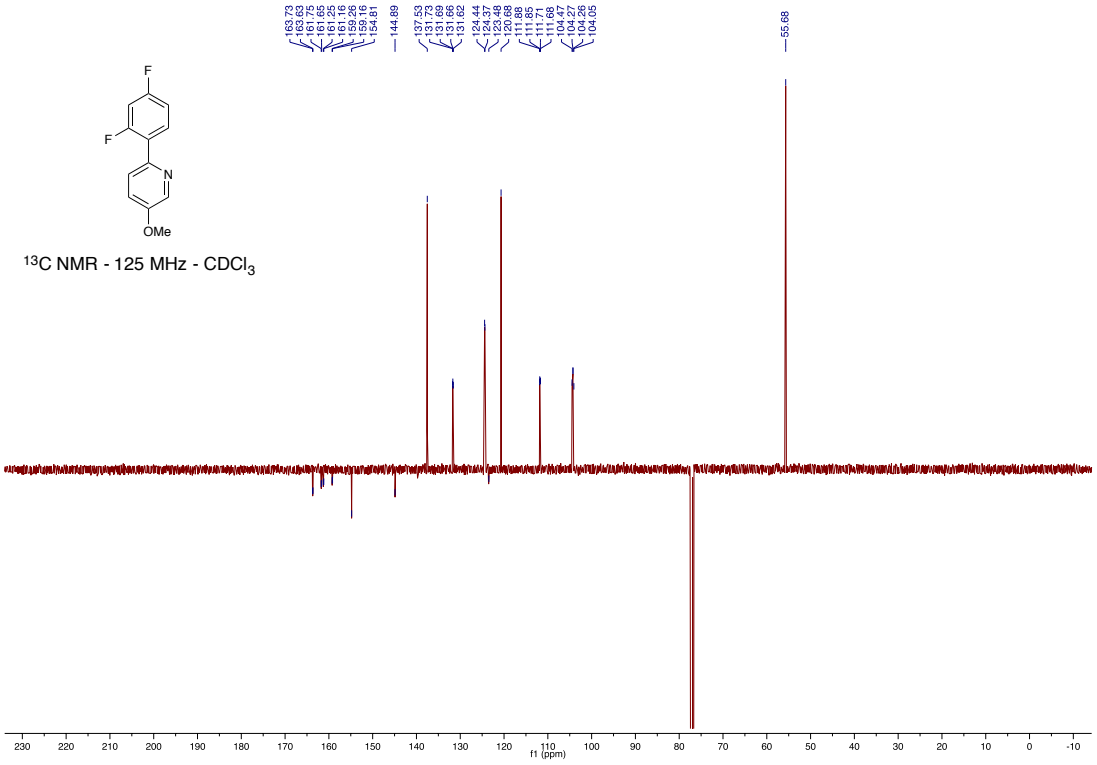
4) Dieter, R. K.; Topping, C. M.; Nice, L. E. *J. Org. Chem.* **2001,** *66*, 2302.

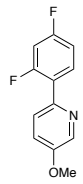
5) Patiny, L.; Borel, A. *J. Chem. Inf. Model.* **2013**, *53*, 1223.

6) Campell, G. I.; Cases-Thomas, M. J.; Man, T.; Masters, J. J.; Eugenie Rudyk, H. C.; Walter, M. W. U.S. Patent Appl. 2007/0083046 A1, 2007.

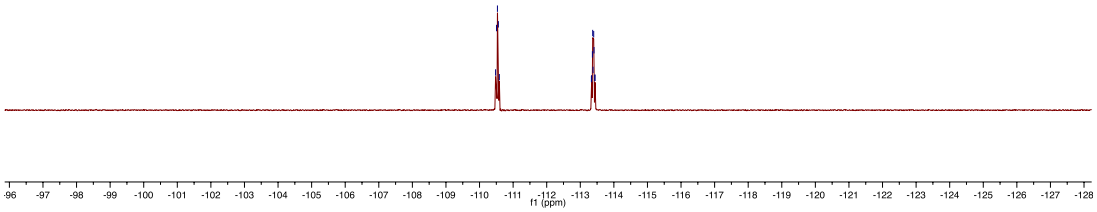
14) Spectral Data

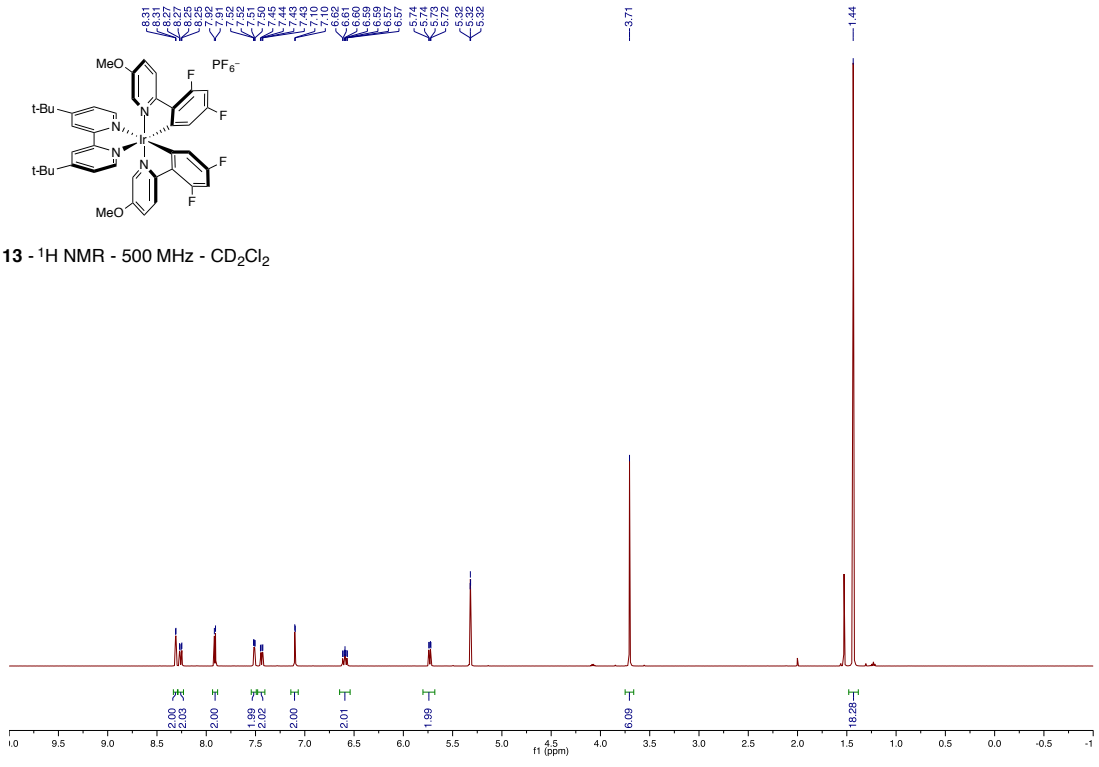




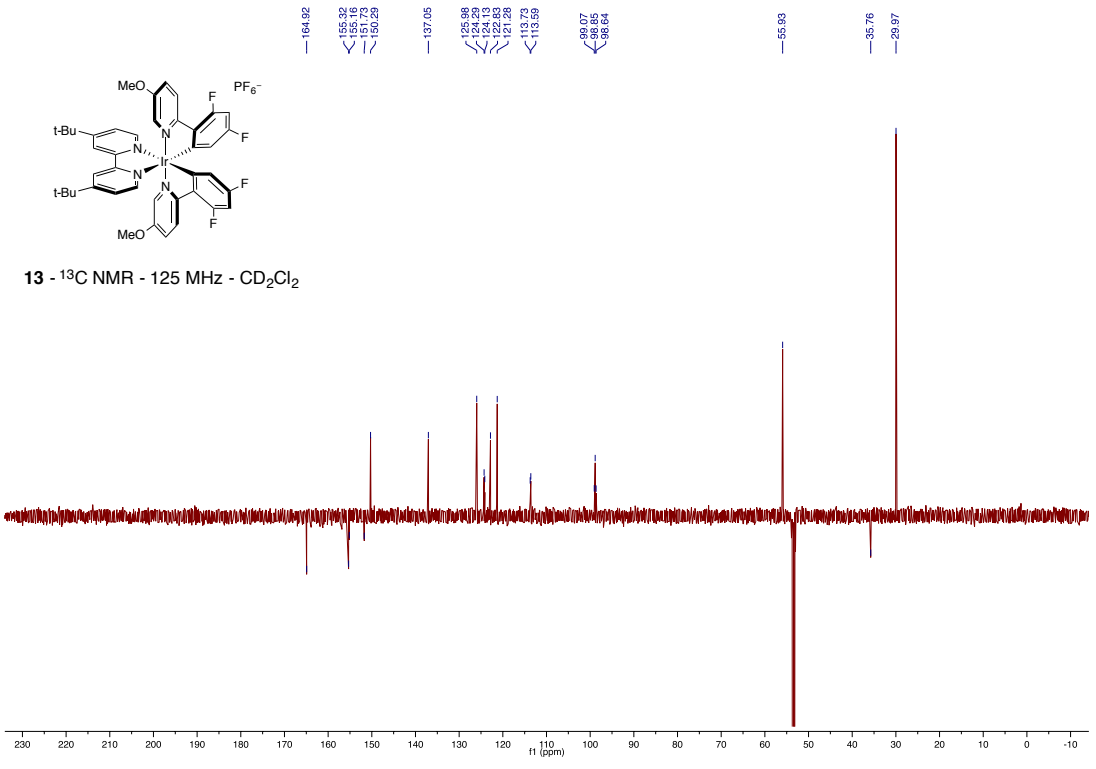


^{19}F NMR - 282 MHz - $CDCl_3$

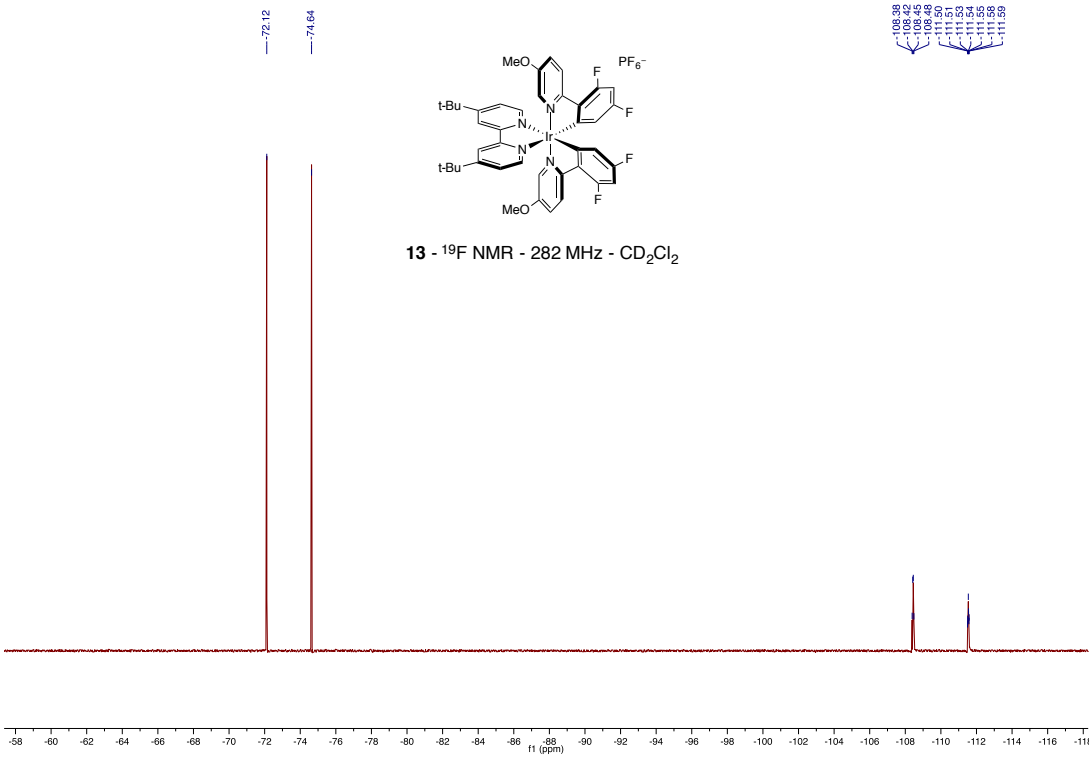




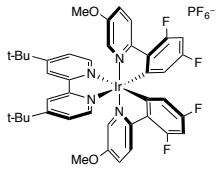
13 - ^{1}H NMR - 500 MHz - CD_2Cl_2



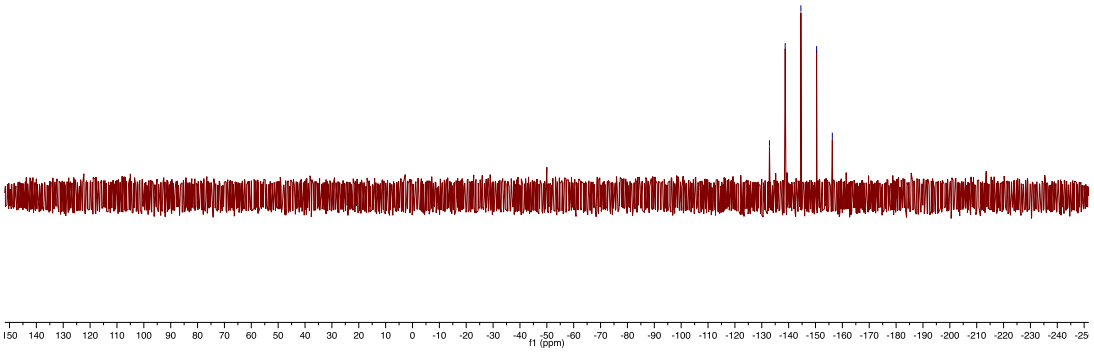
13 - ^{13}C NMR - 125 MHz - CD_2Cl_2

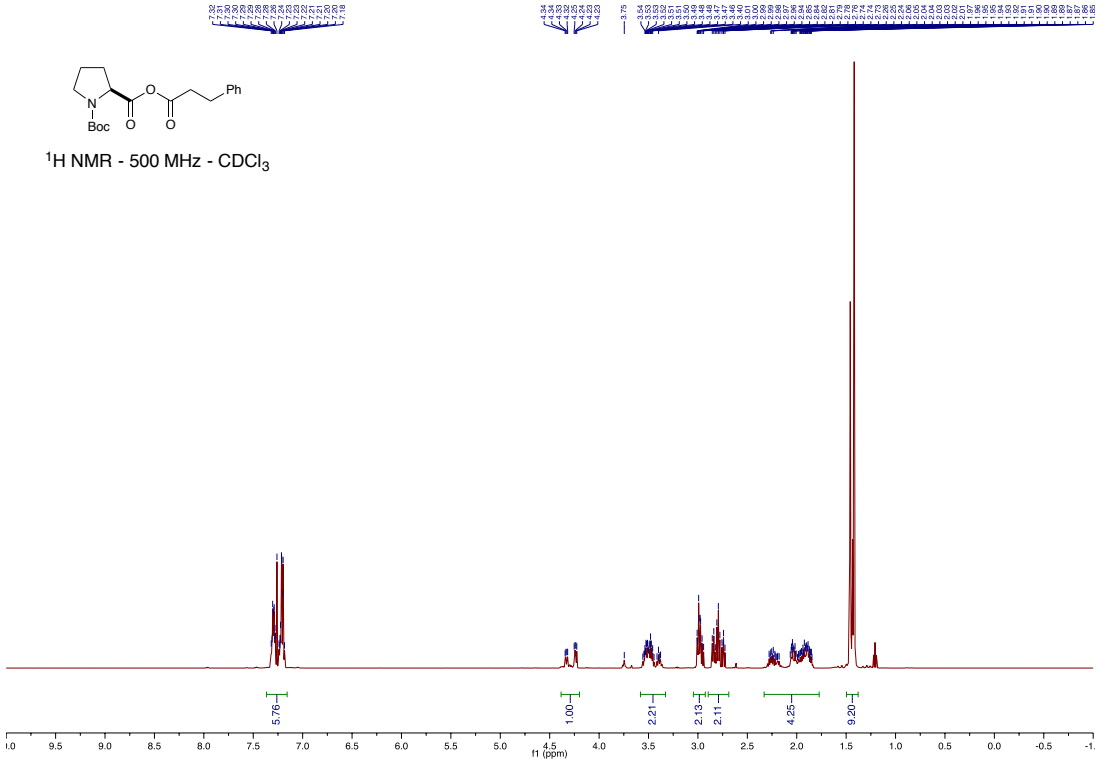


13 - ^{19}F NMR - 282 MHz - CD_2Cl_2

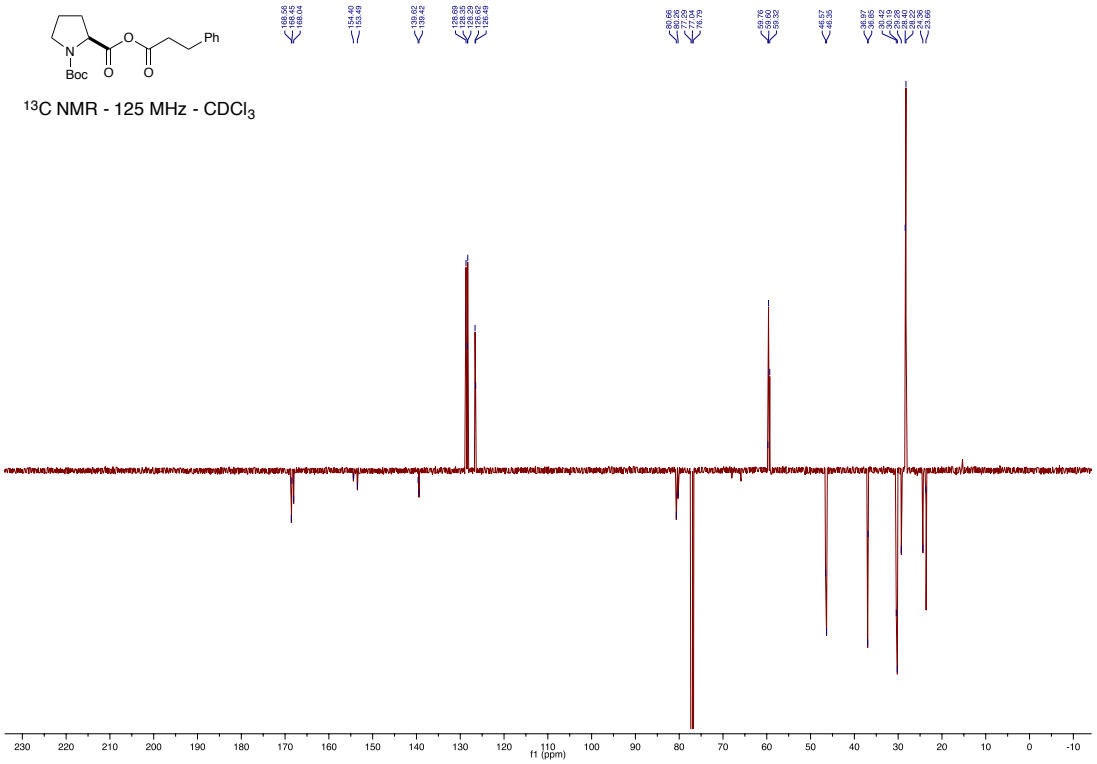


13 - ^{31}P NMR - 282 MHz - CD_2Cl_2

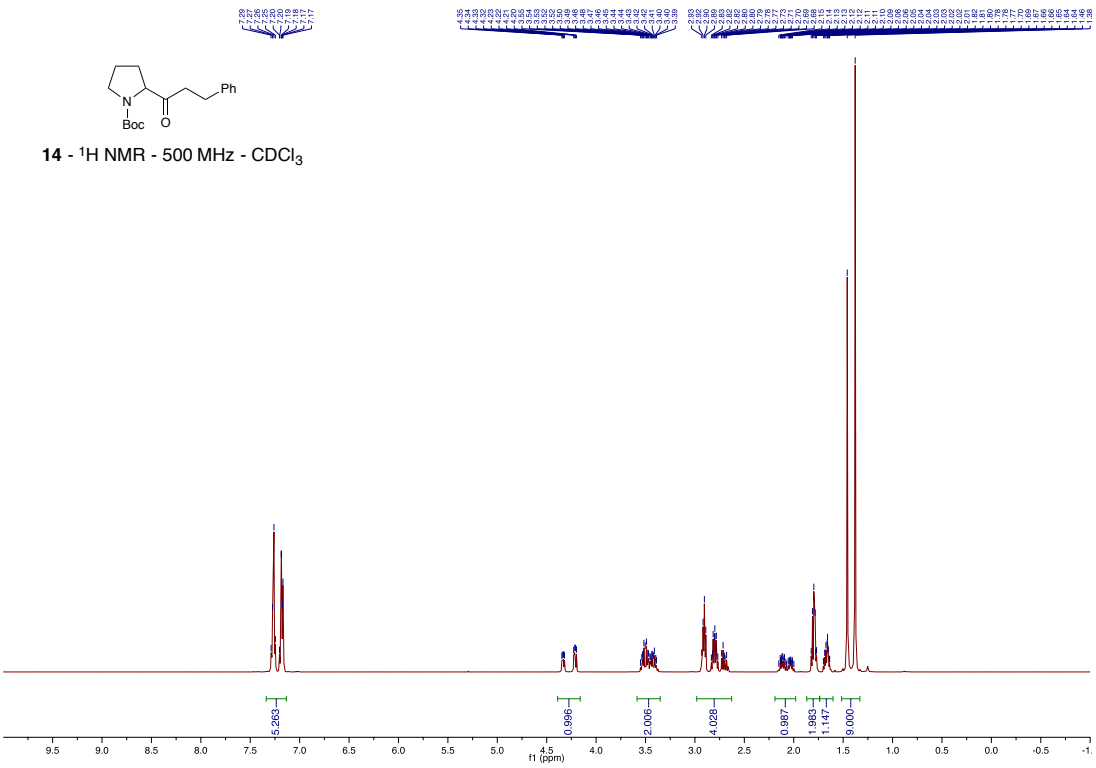




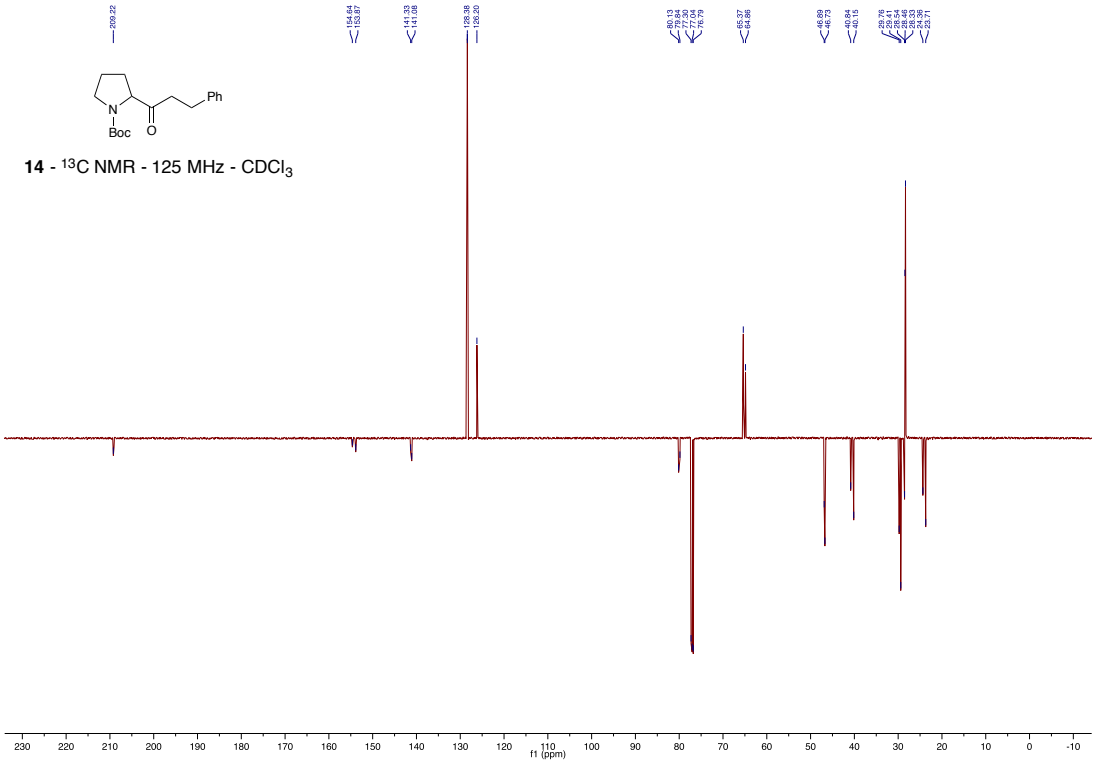
^{1}H NMR - 500 MHz - $CDCl_3$



^{13}C NMR - 125 MHz - $CDCl_3$

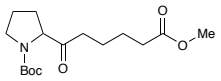


14 - ^{1}H NMR - 500 MHz - $CDCl_3$



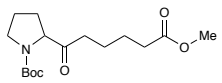
14 - ^{13}C NMR - 125 MHz - $CDCl_3$

CCL1-519-CDCl3.10.fid —



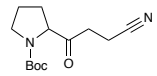
15 - ^{1}H NMR - 500 MHz - $CDCl_3$

CCL1-519-CDCl3.11.fid —



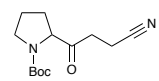
15 - ^{13}C NMR - 125 MHz - $CDCl_3$

CCL1-565-P-CDCl3.10.fid —

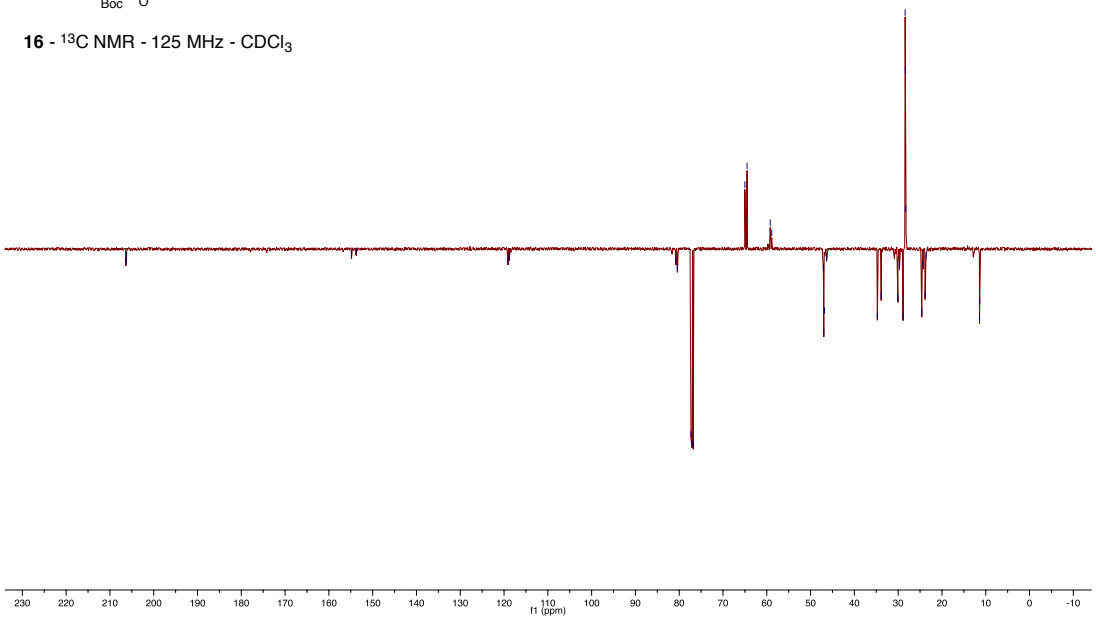


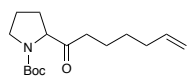
16 - ^{1}H NMR - 500 MHz - $CDCl_3$

CCL1-565-P-CDCl3.11.fid —

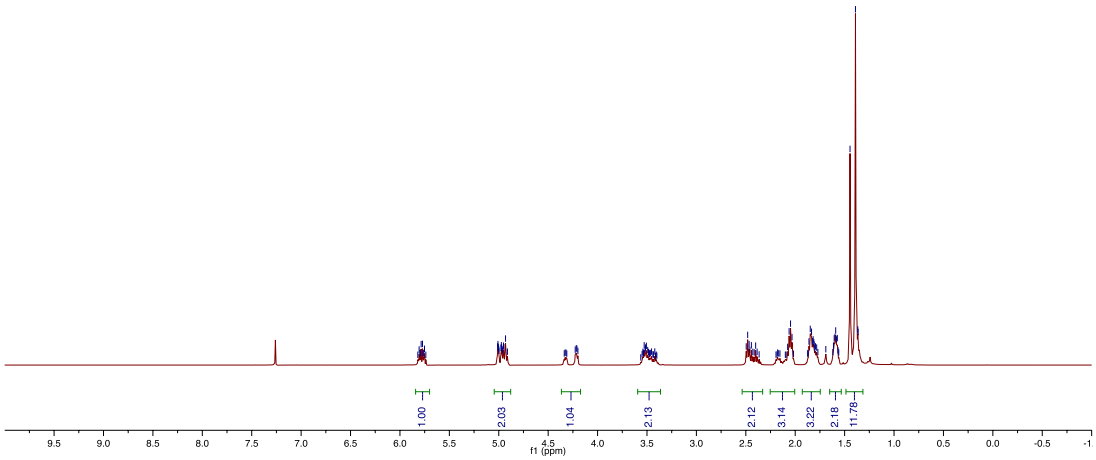


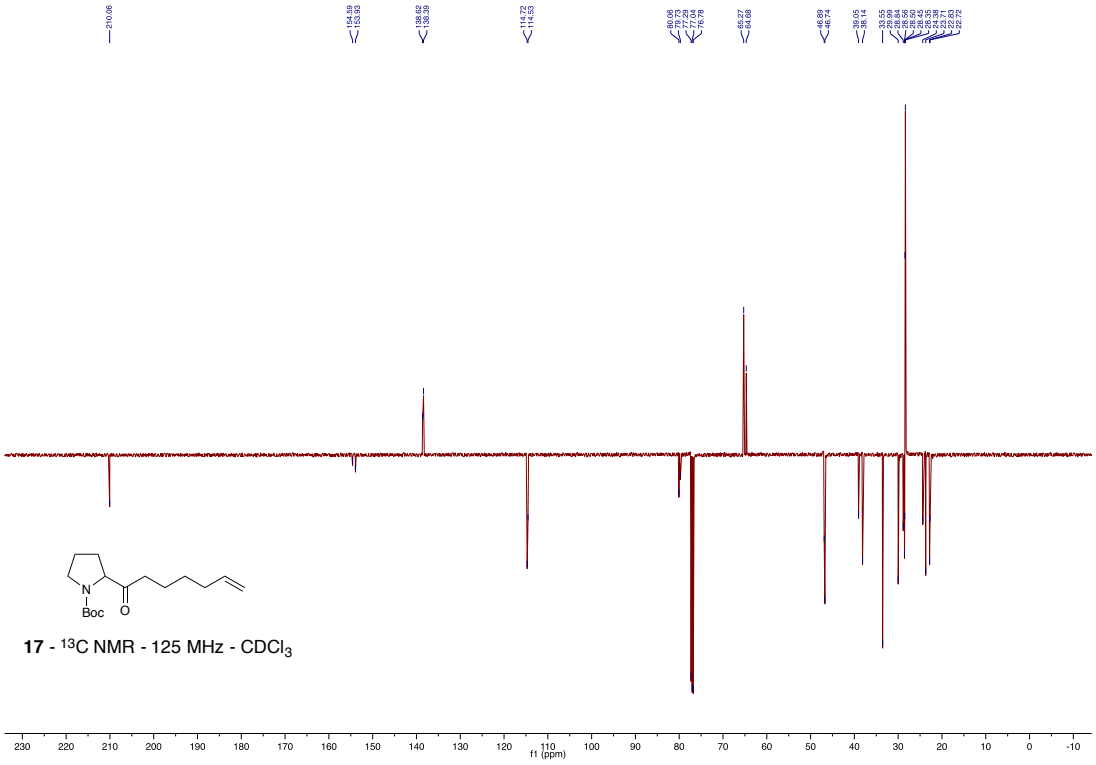
16 - ^{13}C NMR - 125 MHz - $CDCl_3$



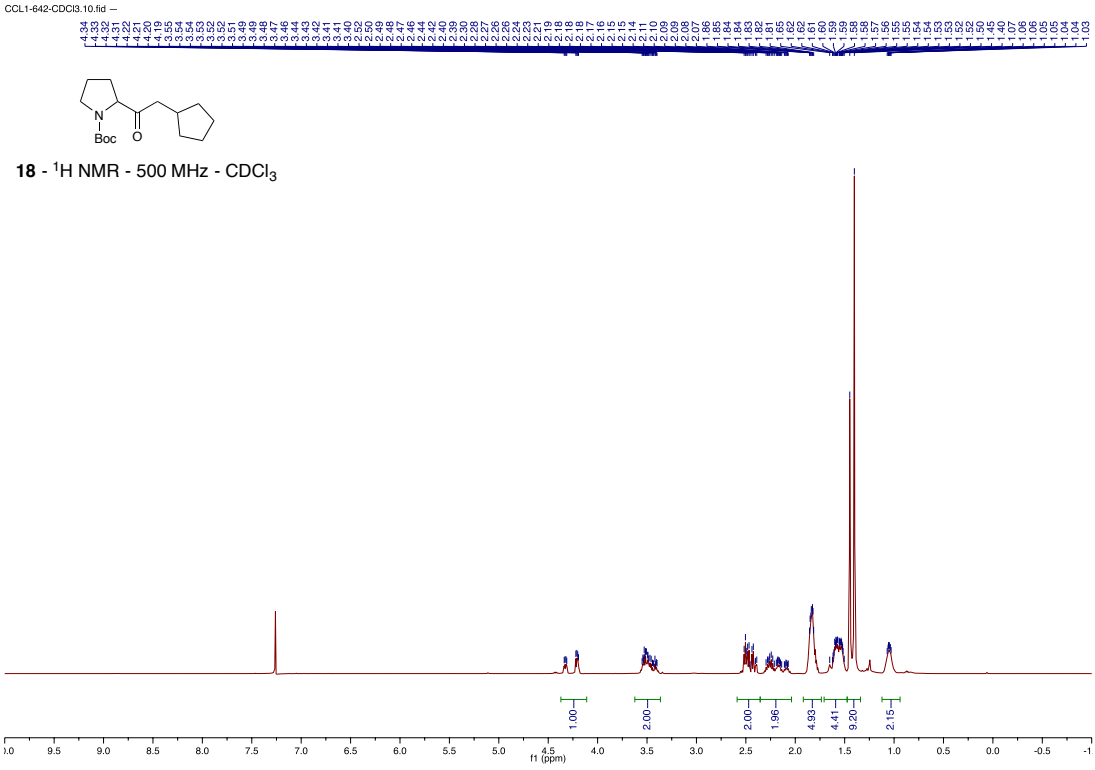


17 - ^{1}H NMR - 500 MHz - $CDCl_3$

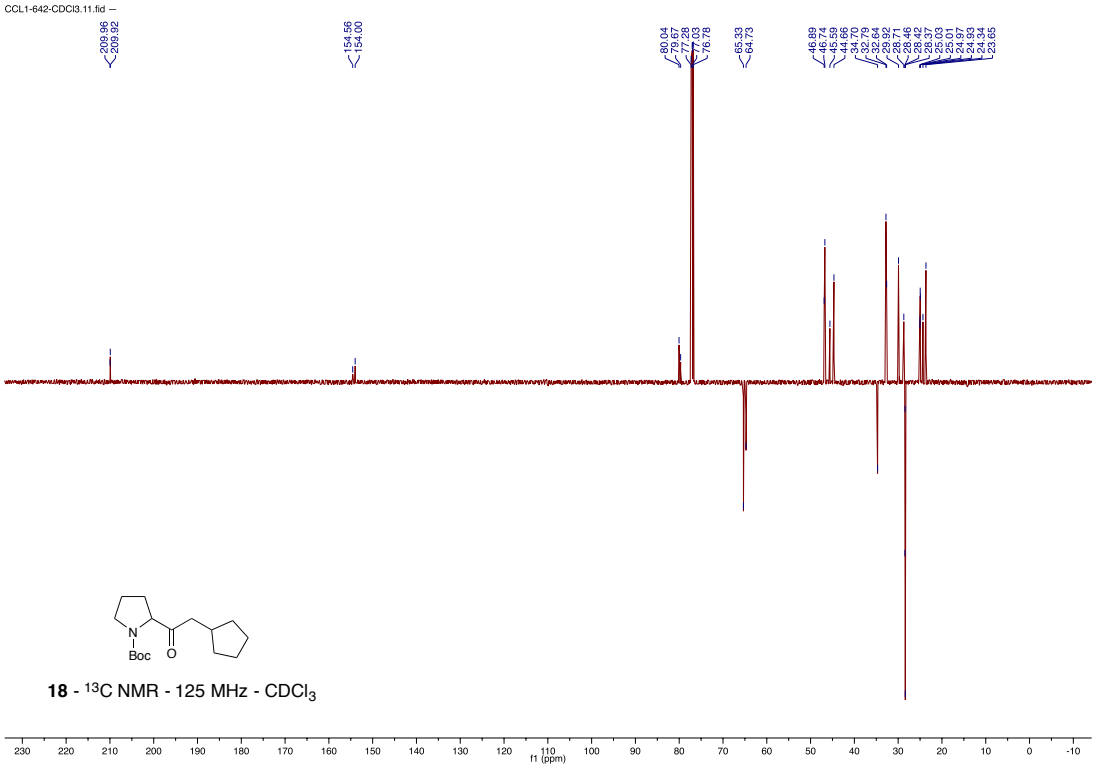




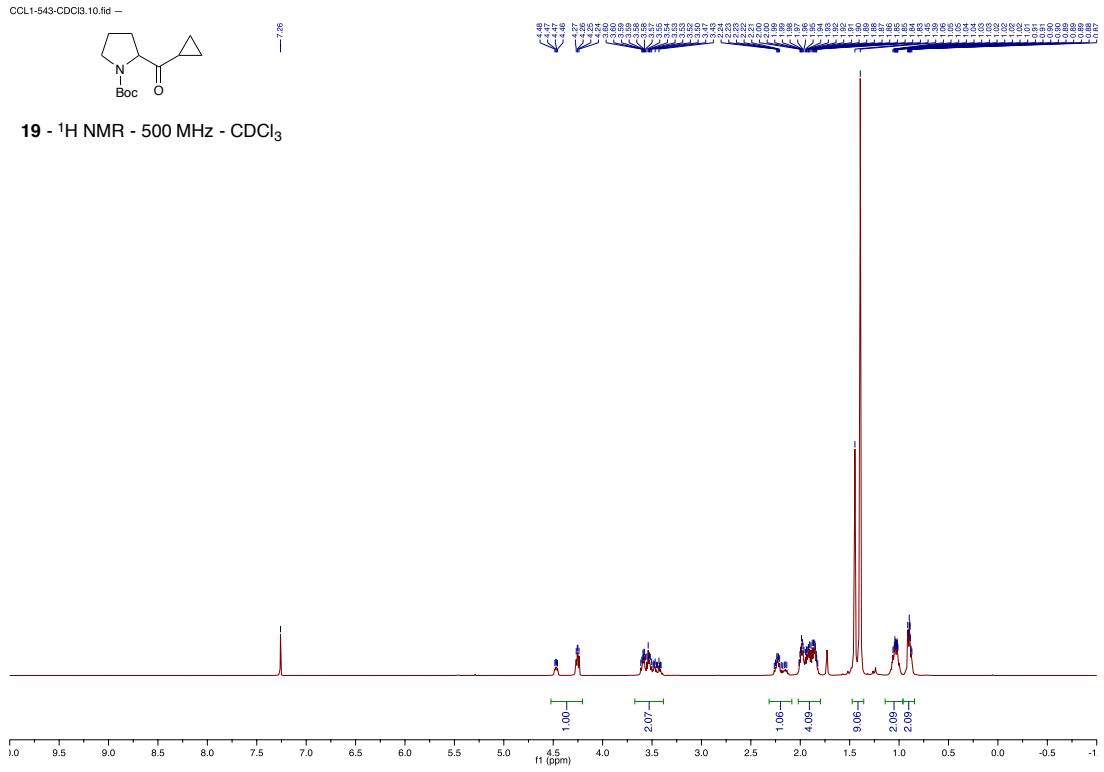
17 - ^{13}C NMR - 125 MHz - $CDCl_3$



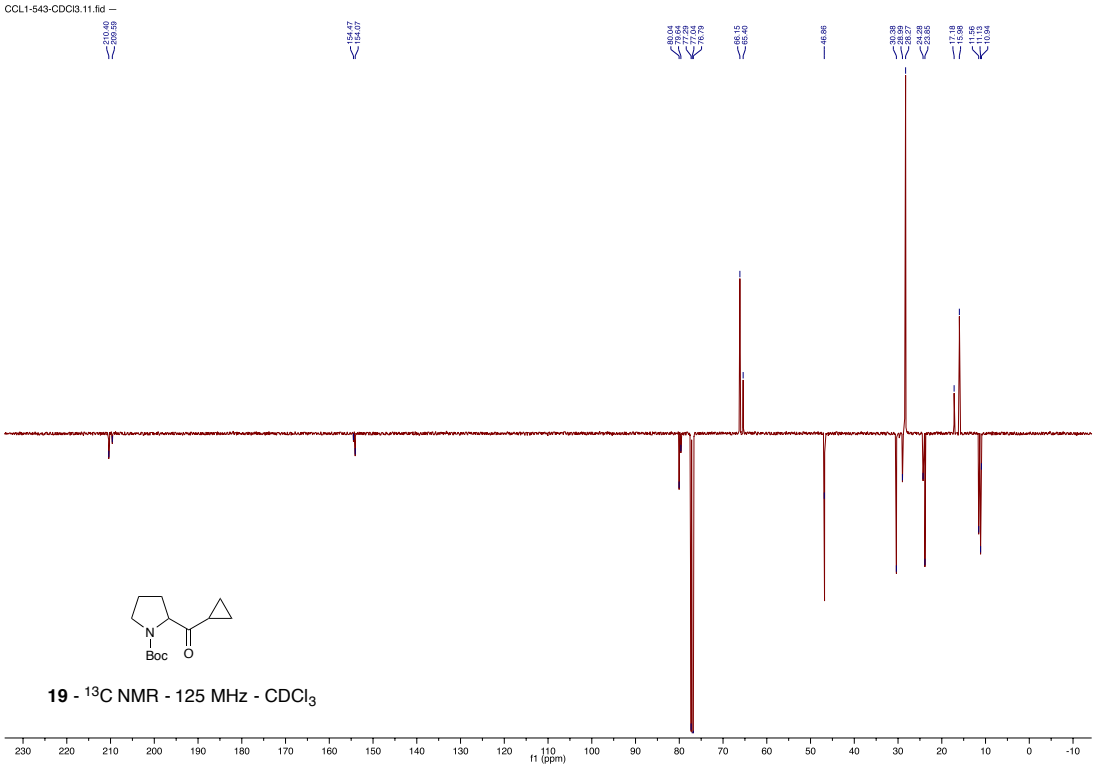
18 - ^{1}H NMR - 500 MHz - $CDCl_3$



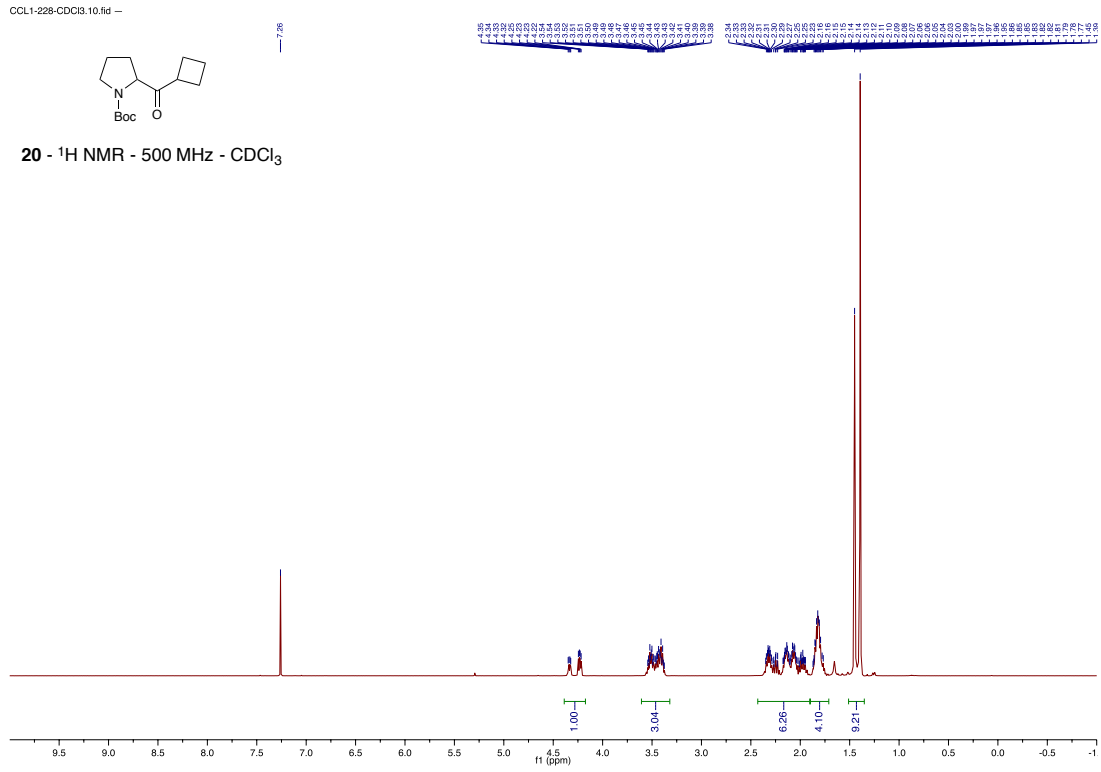
18 - ^{13}C NMR - 125 MHz - $CDCl_3$



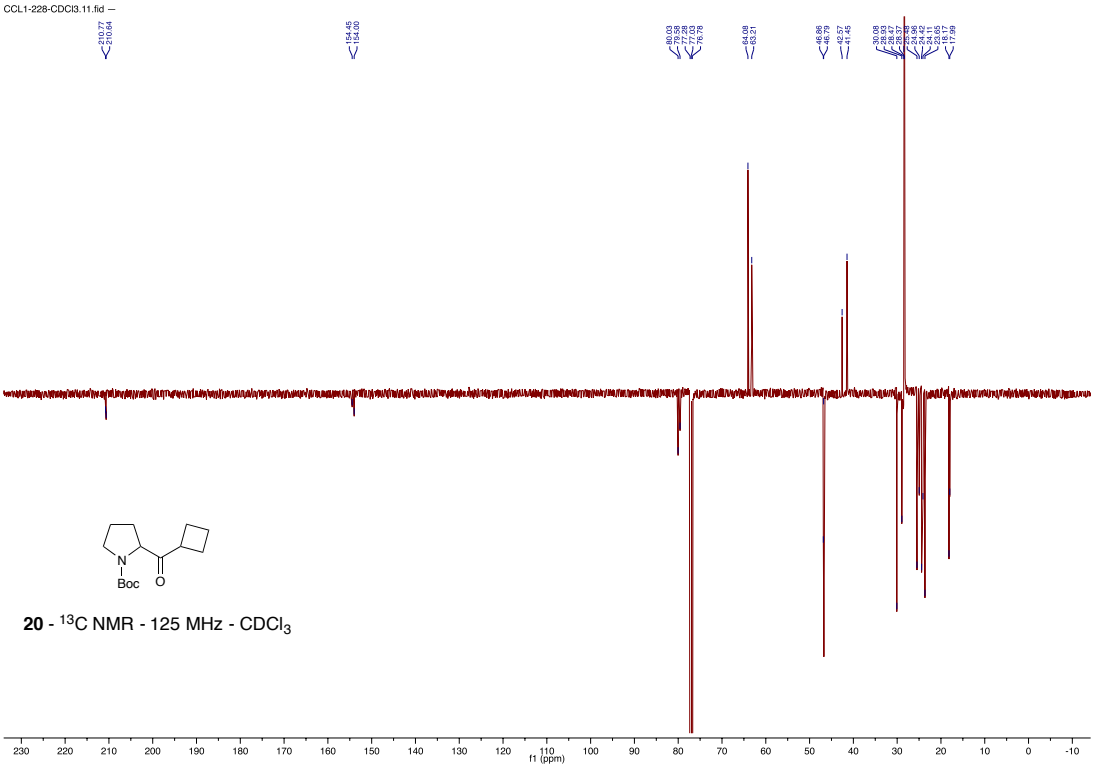
19 - ^{1}H NMR - 500 MHz - $CDCl_3$



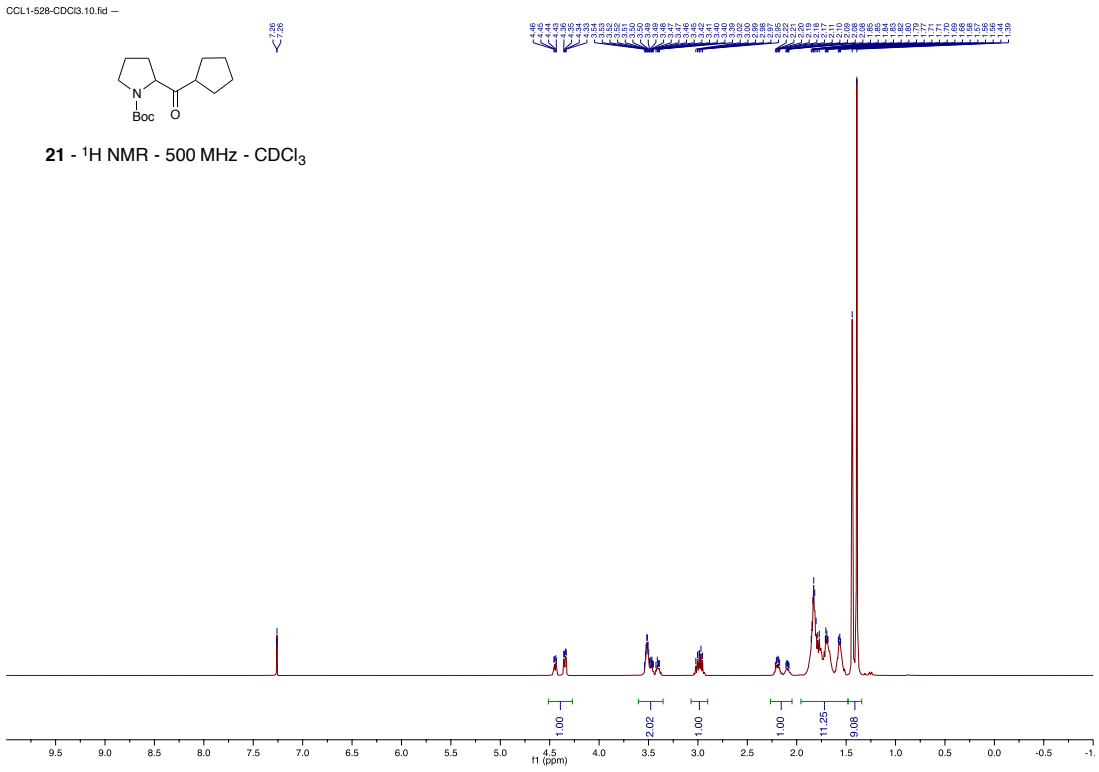
19 - ^{13}C NMR - 125 MHz - $CDCl_3$



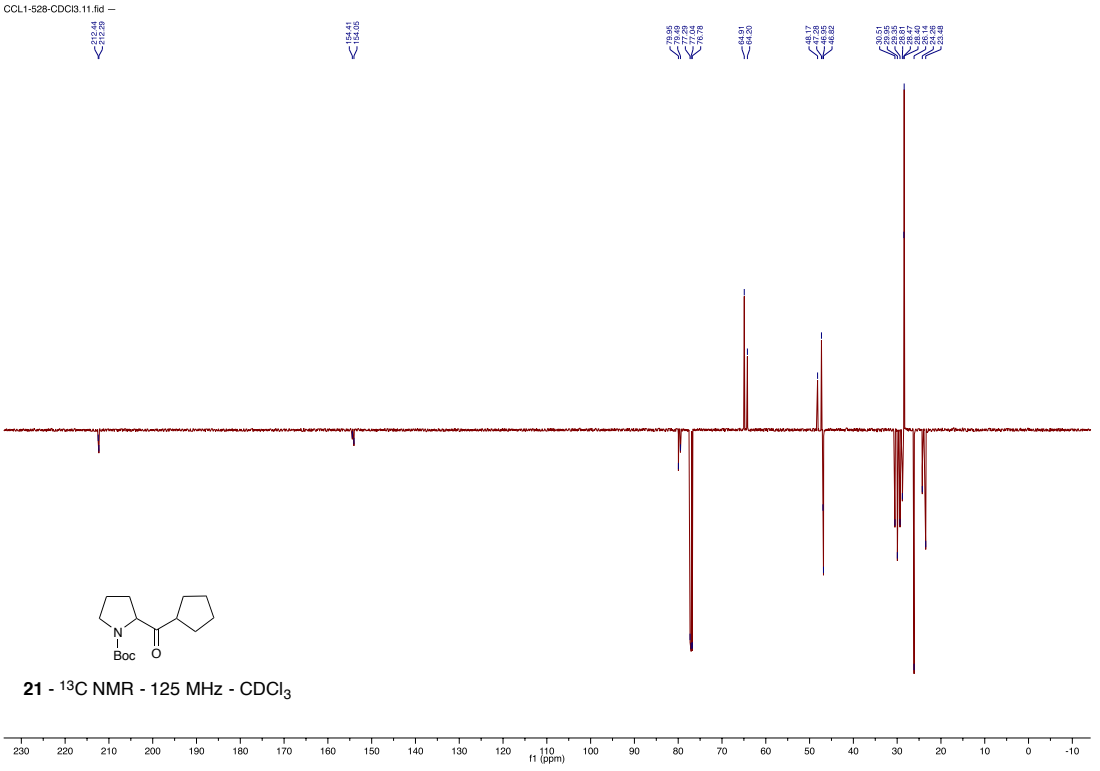
20 - ^{1}H NMR - 500 MHz - $CDCl_3$



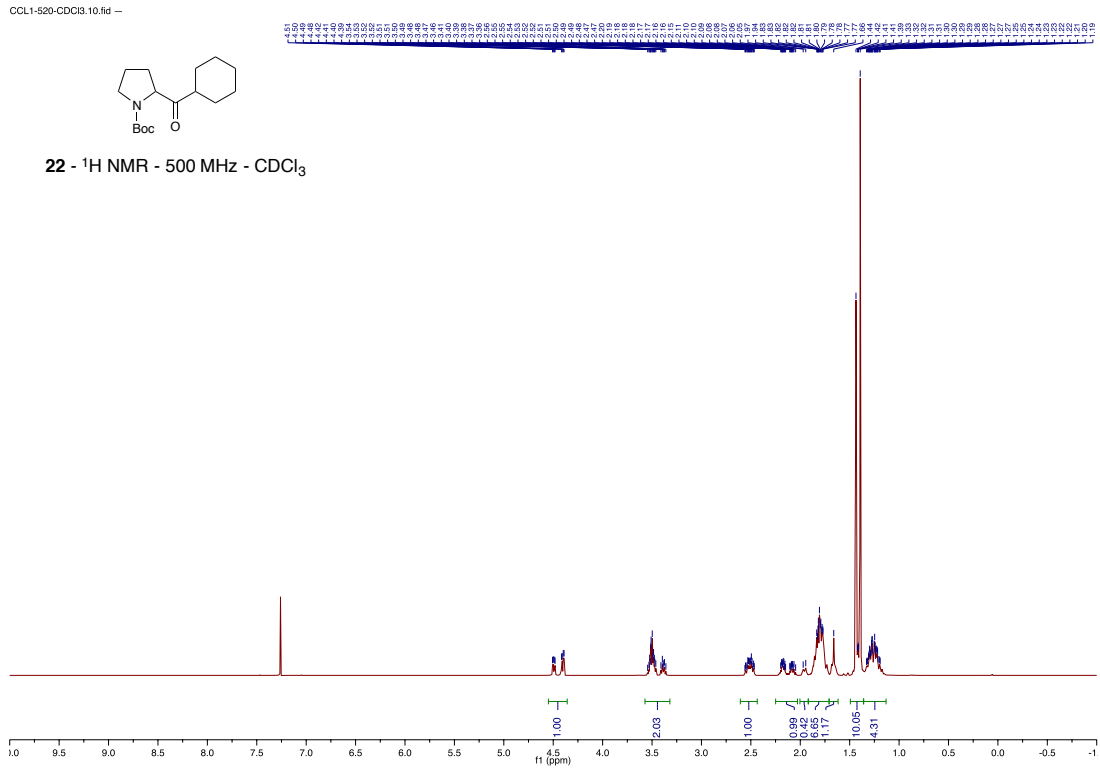
20 - ^{13}C NMR - 125 MHz - $CDCl_3$



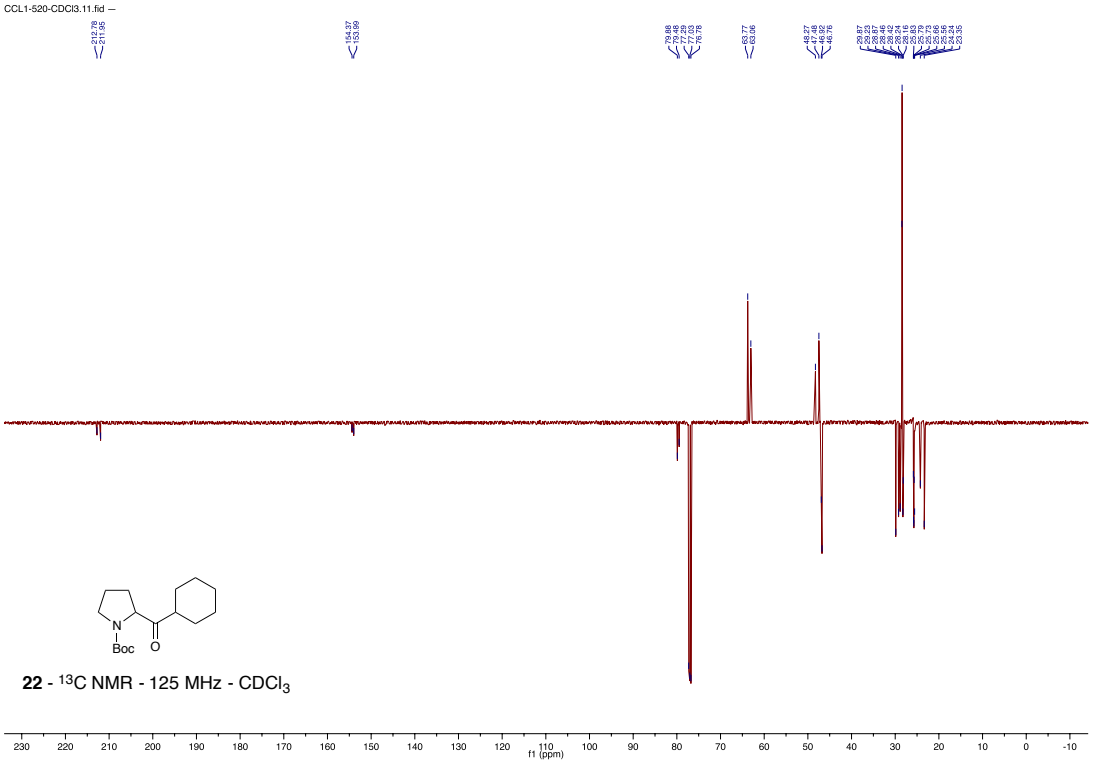
21 - ^{1}H NMR - 500 MHz - $CDCl_3$



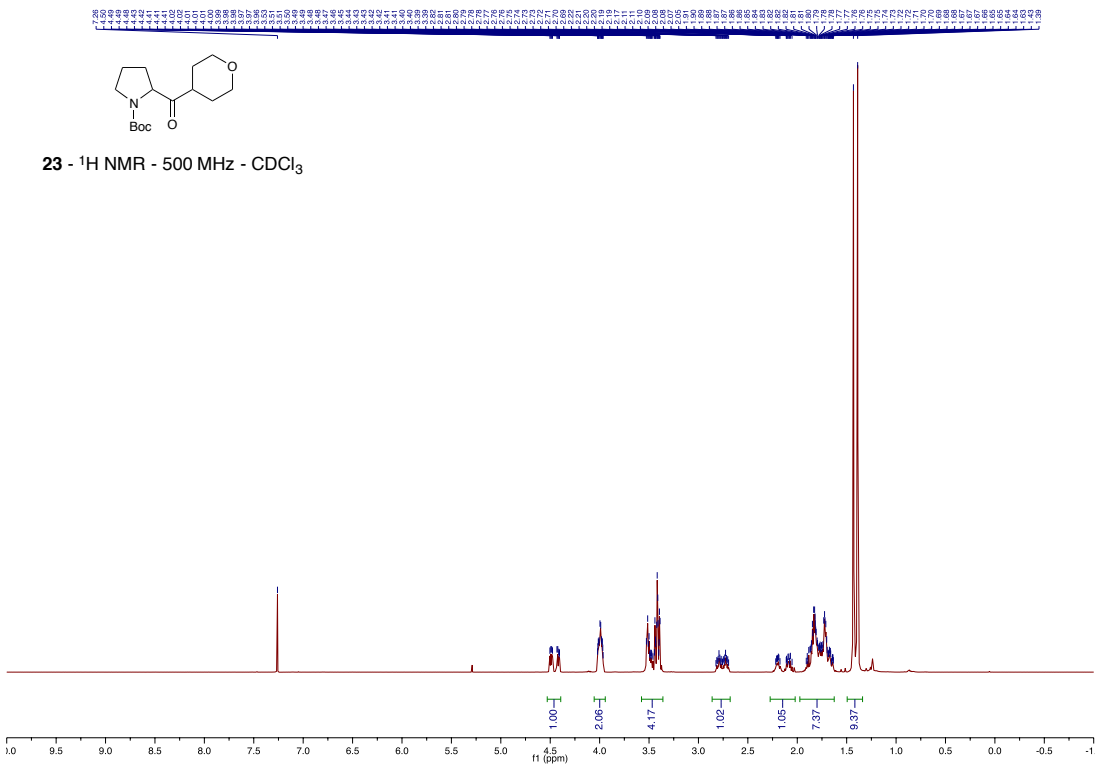
21 - ^{13}C NMR - 125 MHz - $CDCl_3$



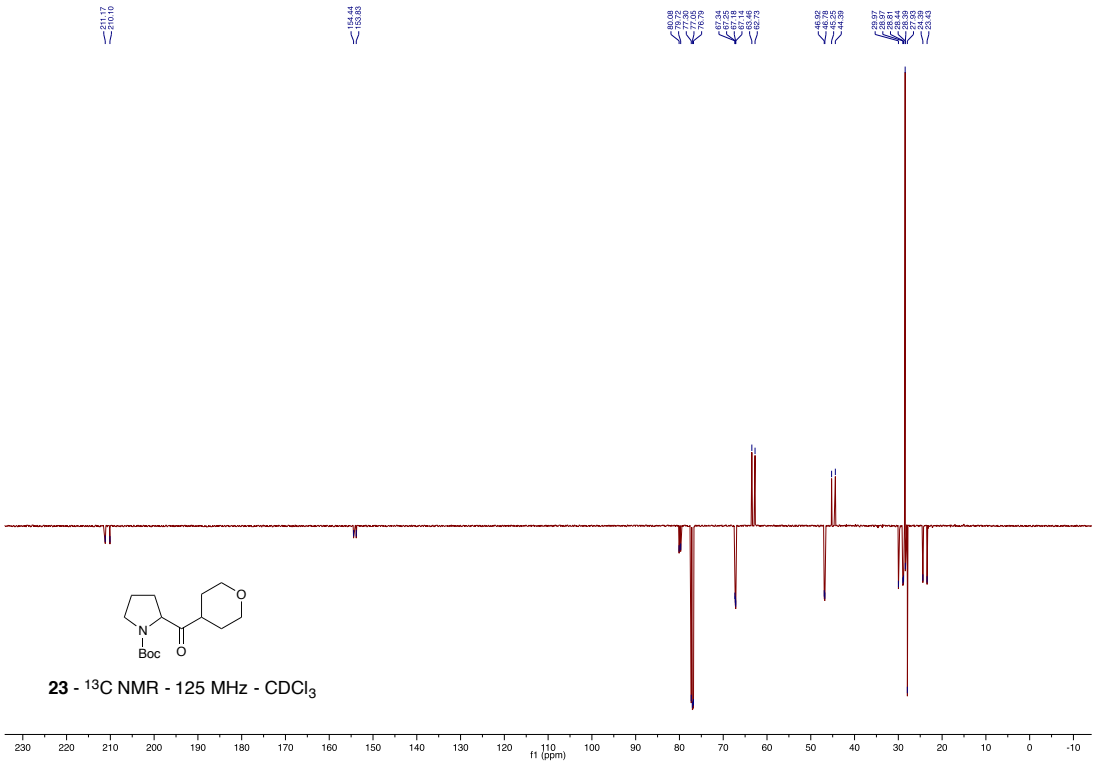
22 - ^{1}H NMR - 500 MHz - $CDCl_3$



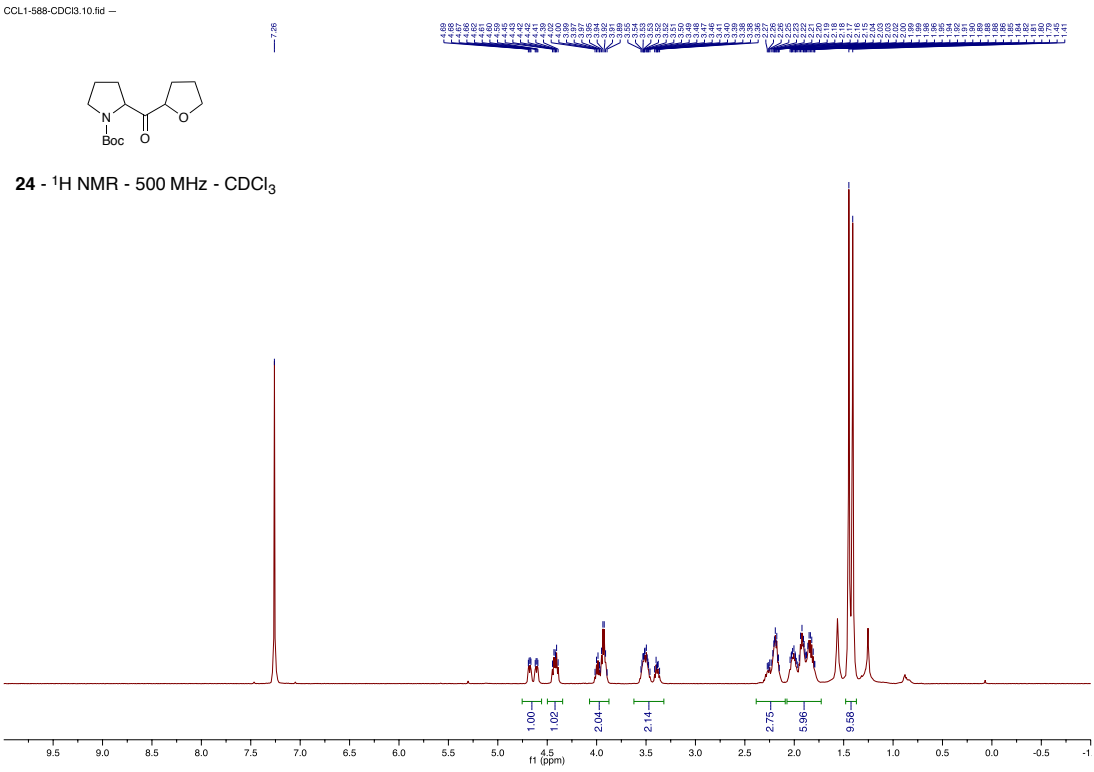
22 - ^{13}C NMR - 125 MHz - $CDCl_3$



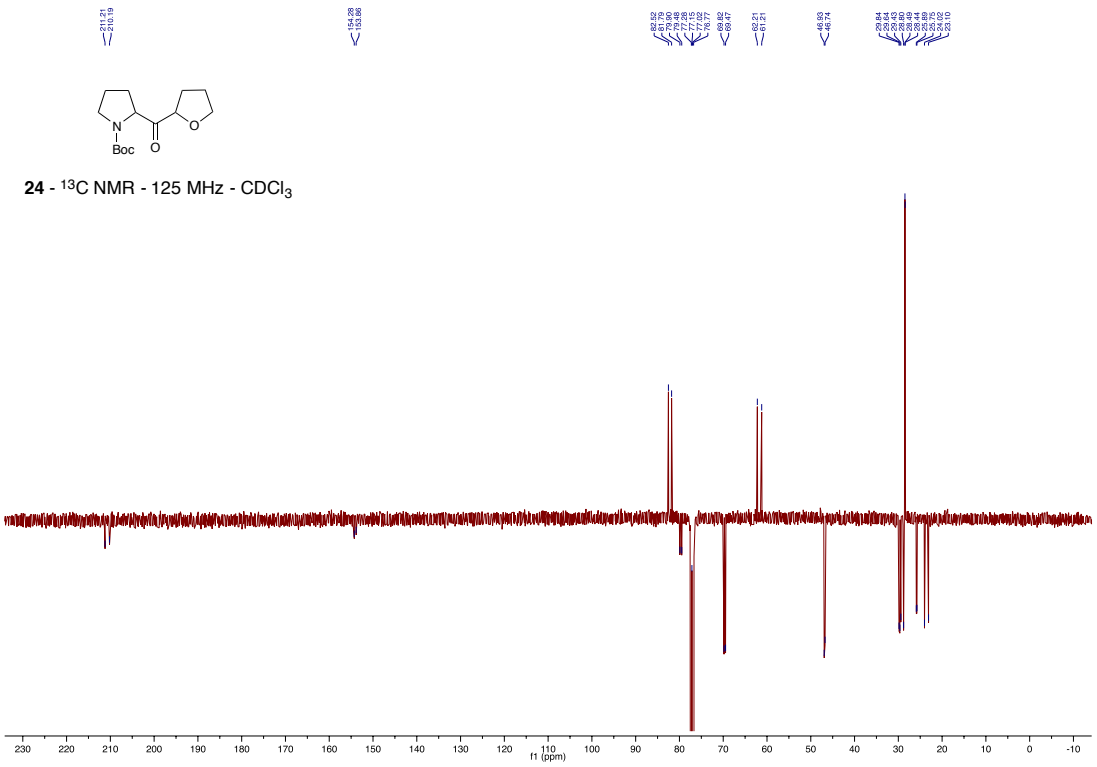
23 - ^{1}H NMR - 500 MHz - $CDCl_3$



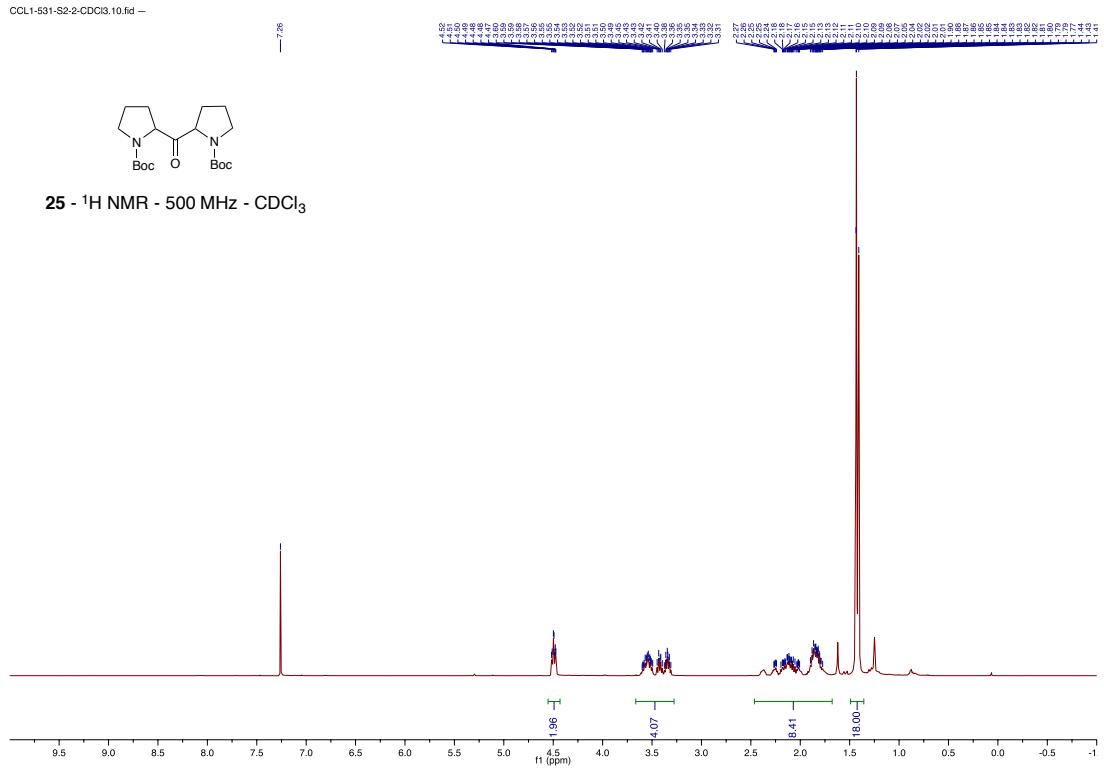
23 - ^{13}C NMR - 125 MHz - $CDCl_3$



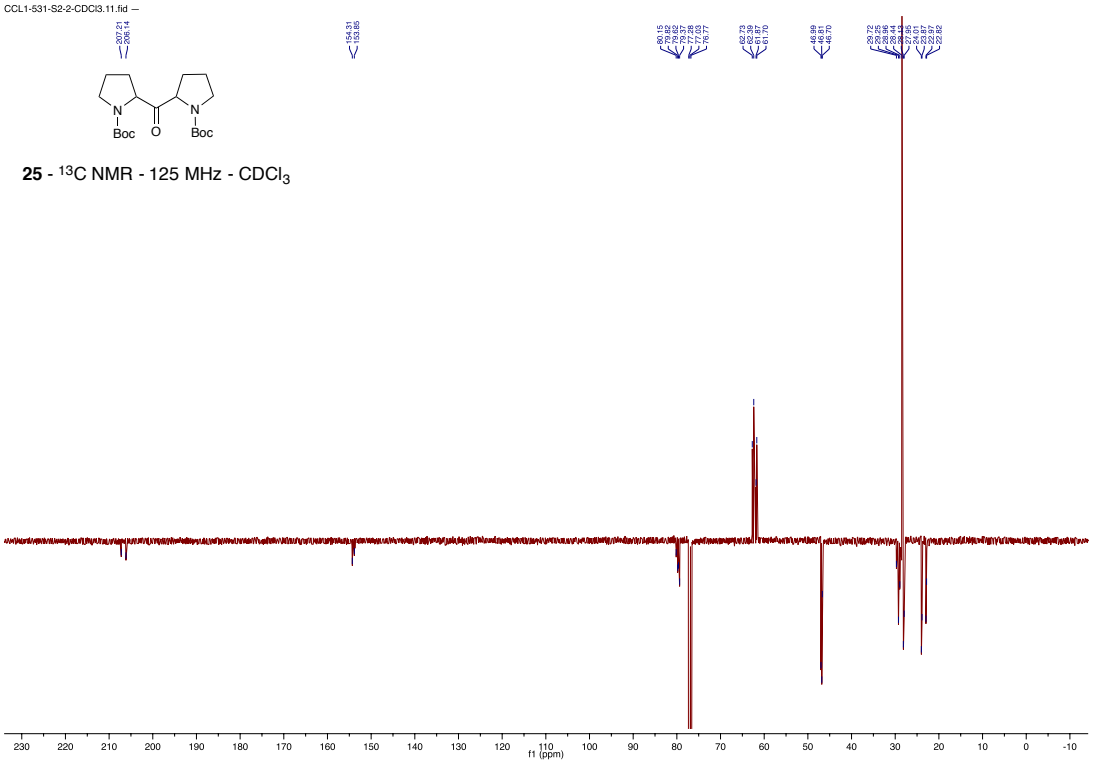
24 - ^{1}H NMR - 500 MHz - $CDCl_3$



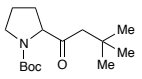
24 - ^{13}C NMR - 125 MHz - $CDCl_3$



25 - ^{1}H NMR - 500 MHz - $CDCl_3$



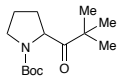
25 - ^{13}C NMR - 125 MHz - $CDCl_3$



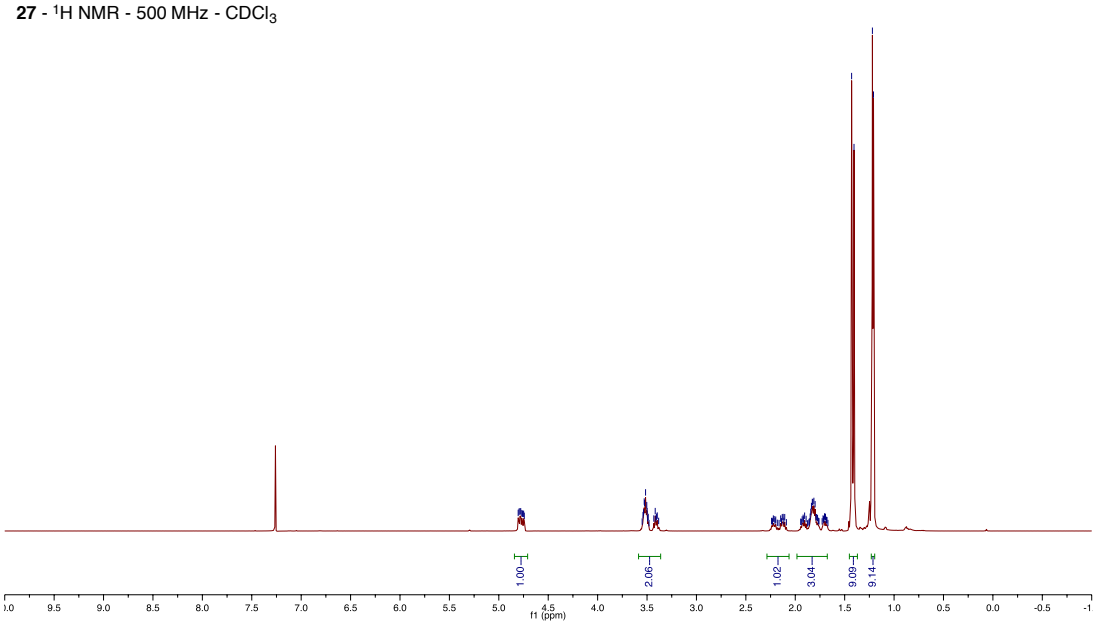
26 - ^{1}H NMR - 500 MHz - $CDCl_3$

26 - ^{13}C NMR - 125 MHz - $CDCl_3$

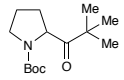
CCL1-576-CDCl3.10.fid —



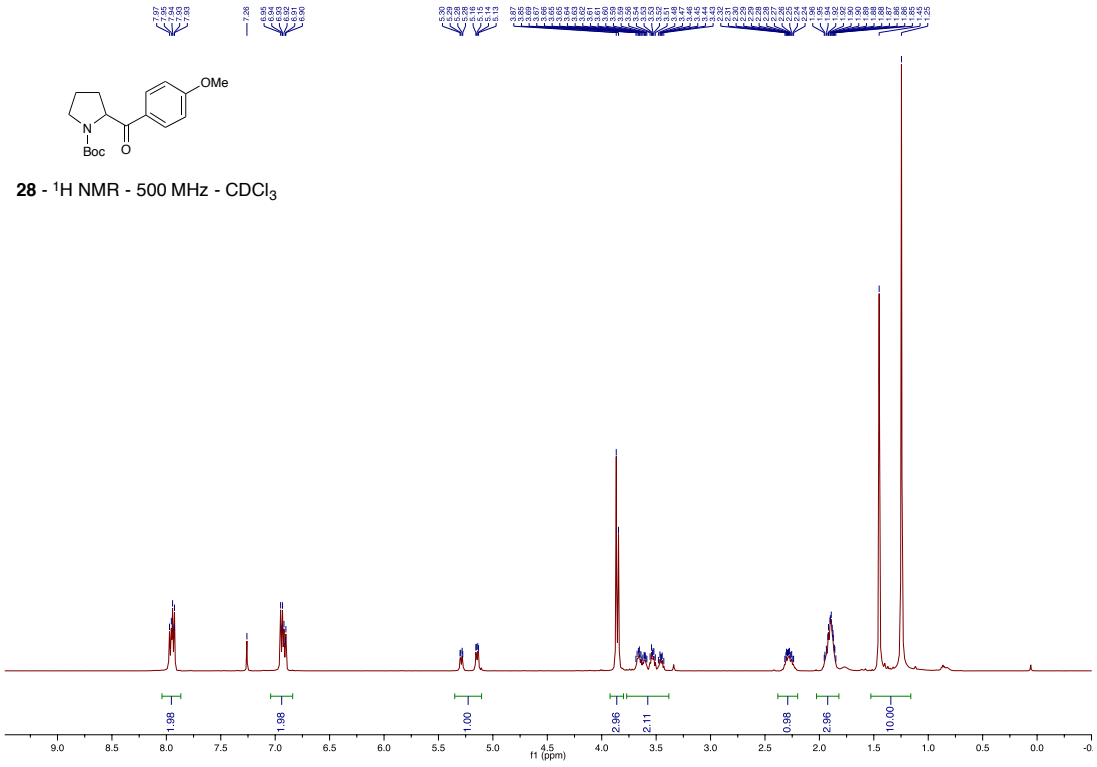
27 - ^{1}H NMR - 500 MHz - $CDCl_3$



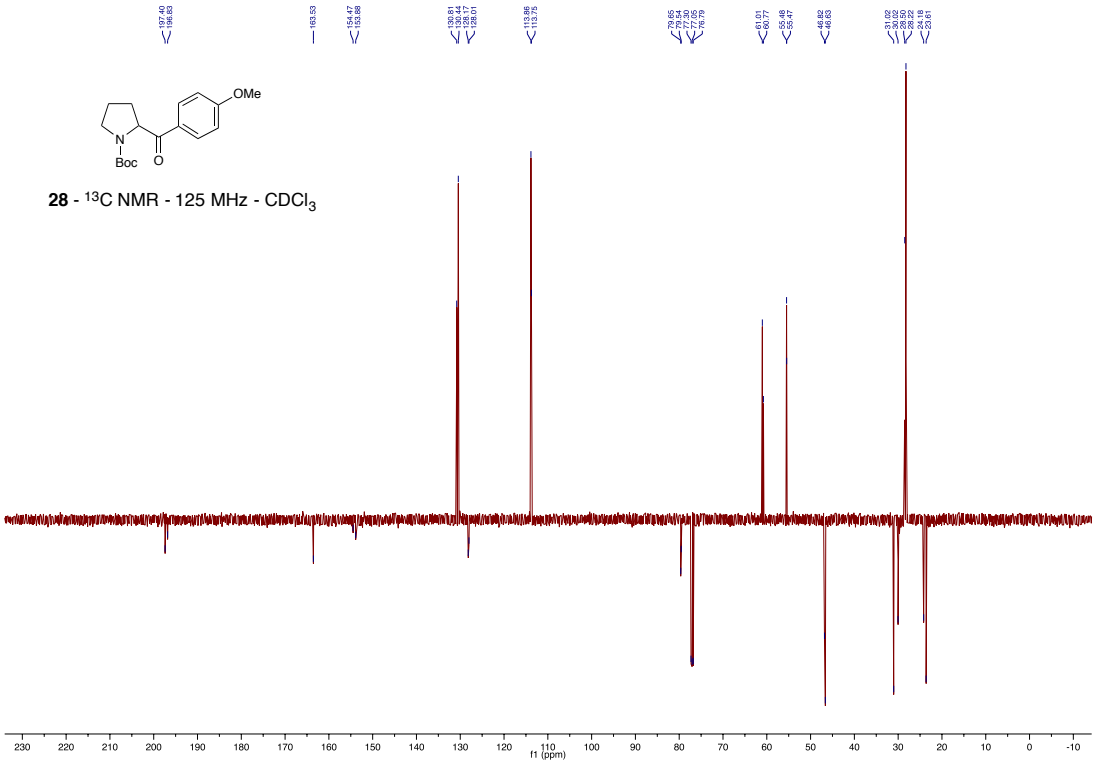
CCL1-576-CDCl3.11.fid —



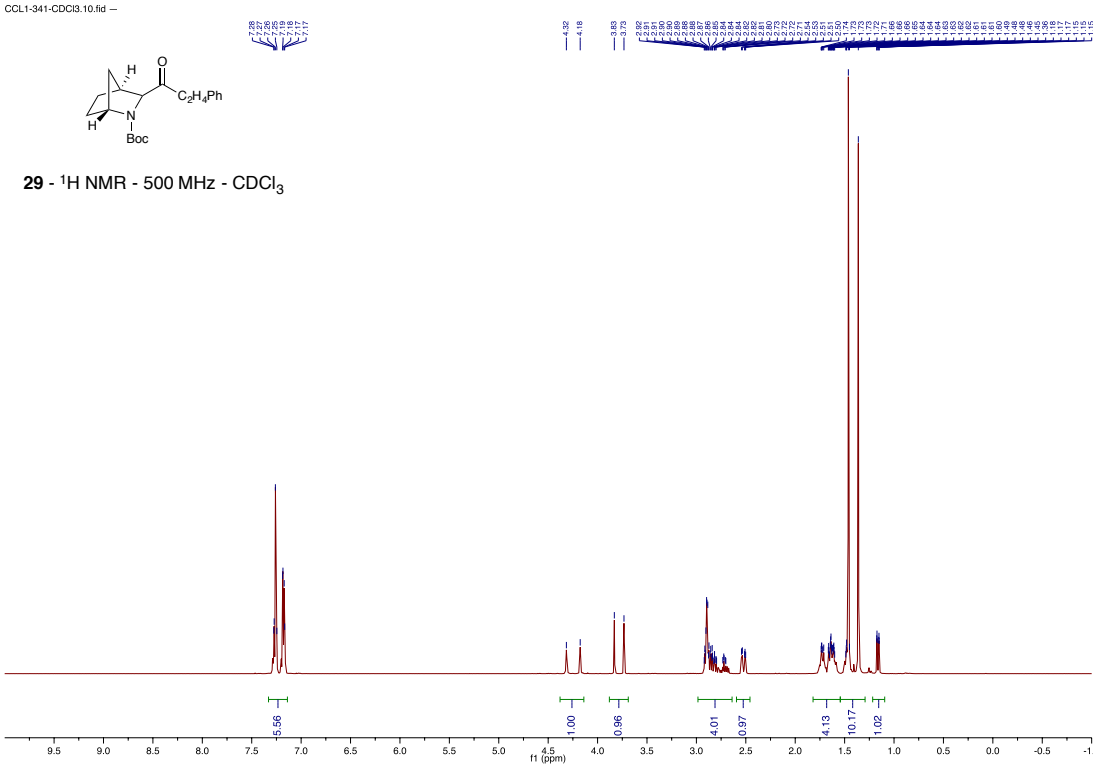
27 - ^{13}C NMR - 125 MHz - $CDCl_3$



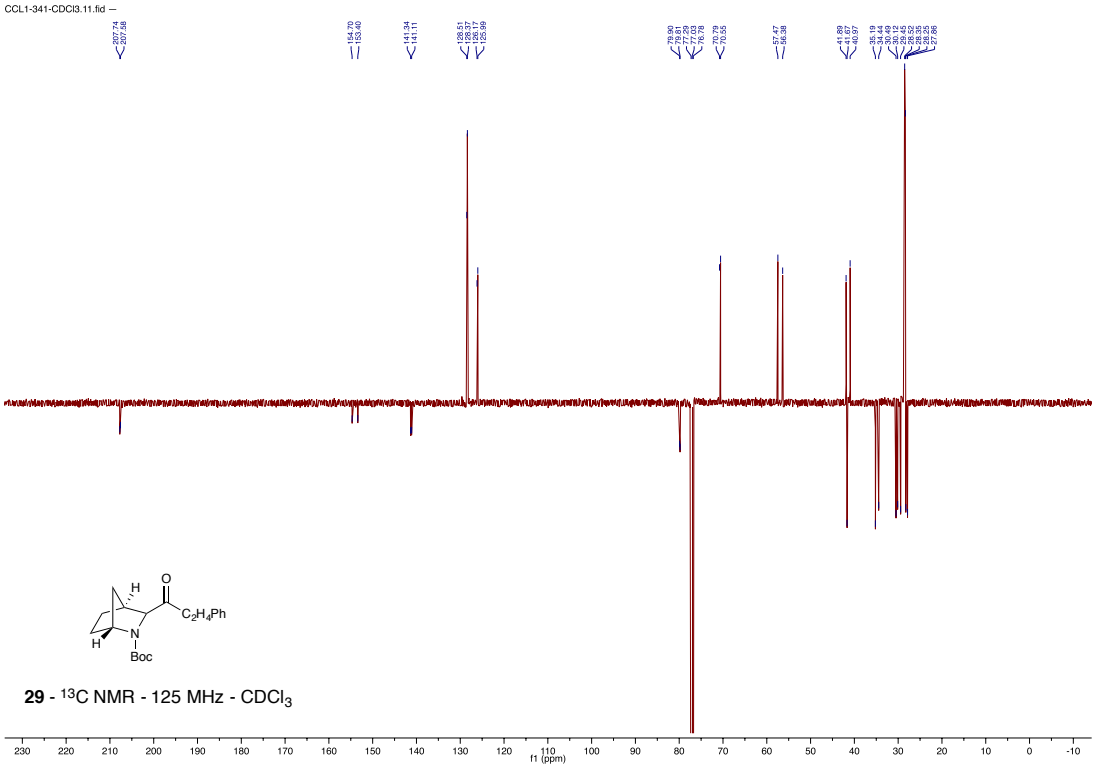
28 - ^{1}H NMR - 500 MHz - $CDCl_3$



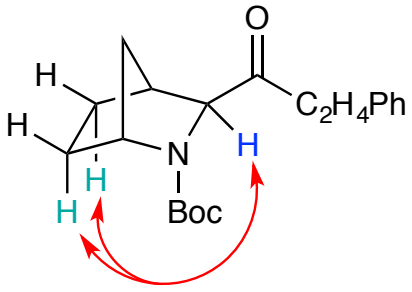
28 - ^{13}C NMR - 125 MHz - $CDCl_3$

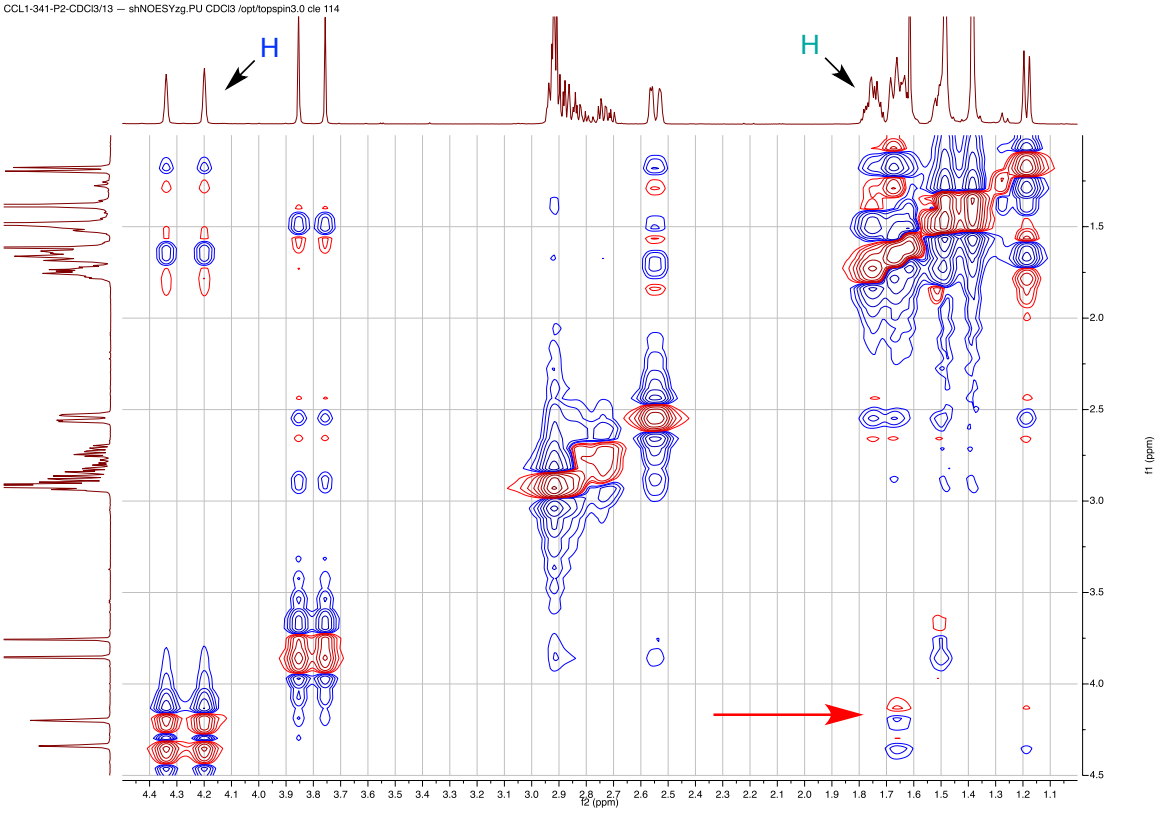


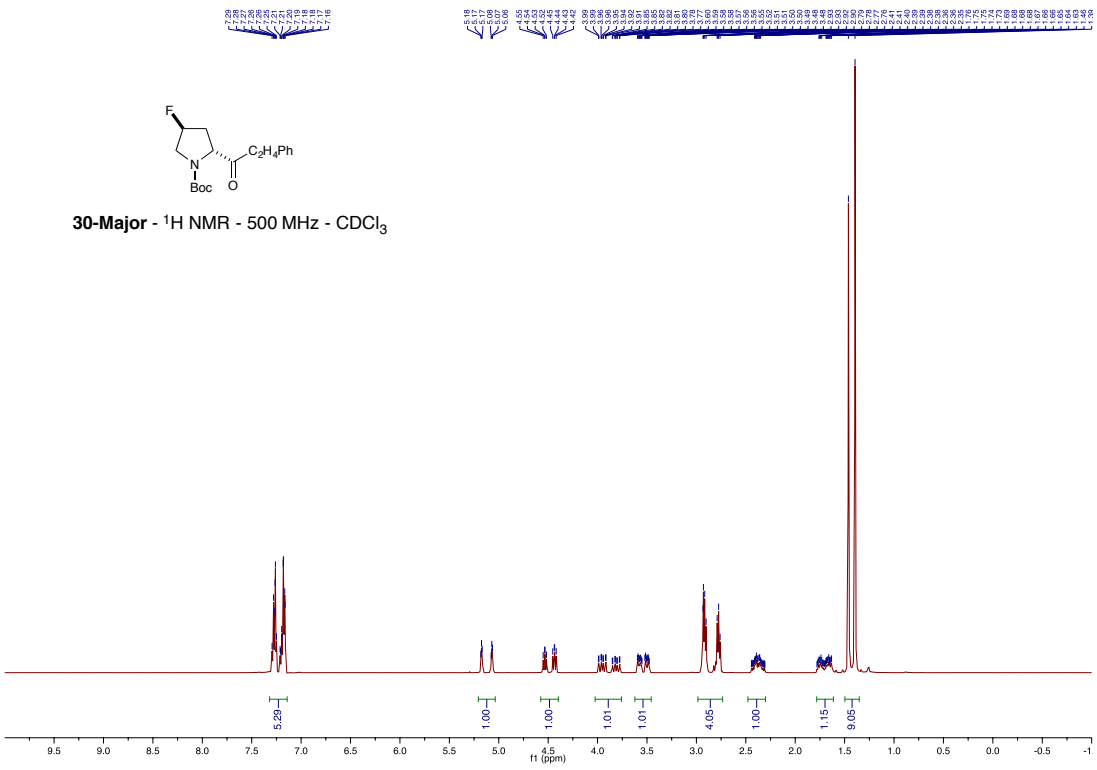
29 - ^{1}H NMR - 500 MHz - $CDCl_3$



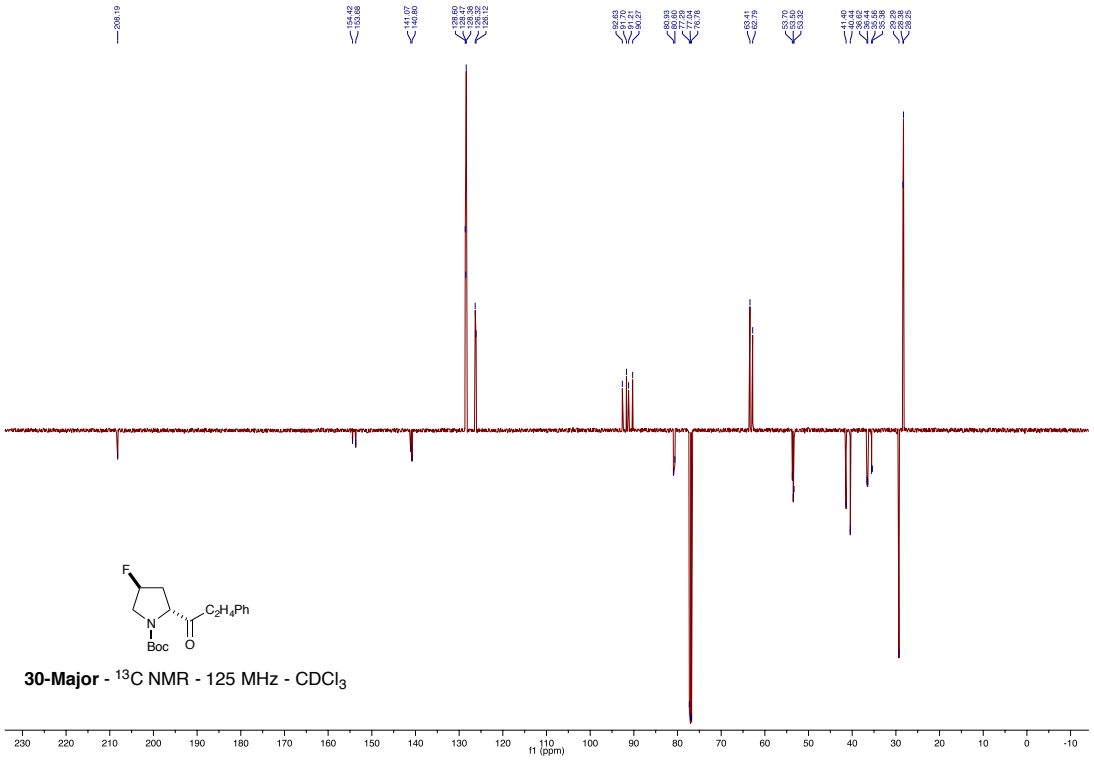
29 - ^{13}C NMR - 125 MHz - $CDCl_3$


O
H
H
C2H4Ph
N
H
H
H
Boc

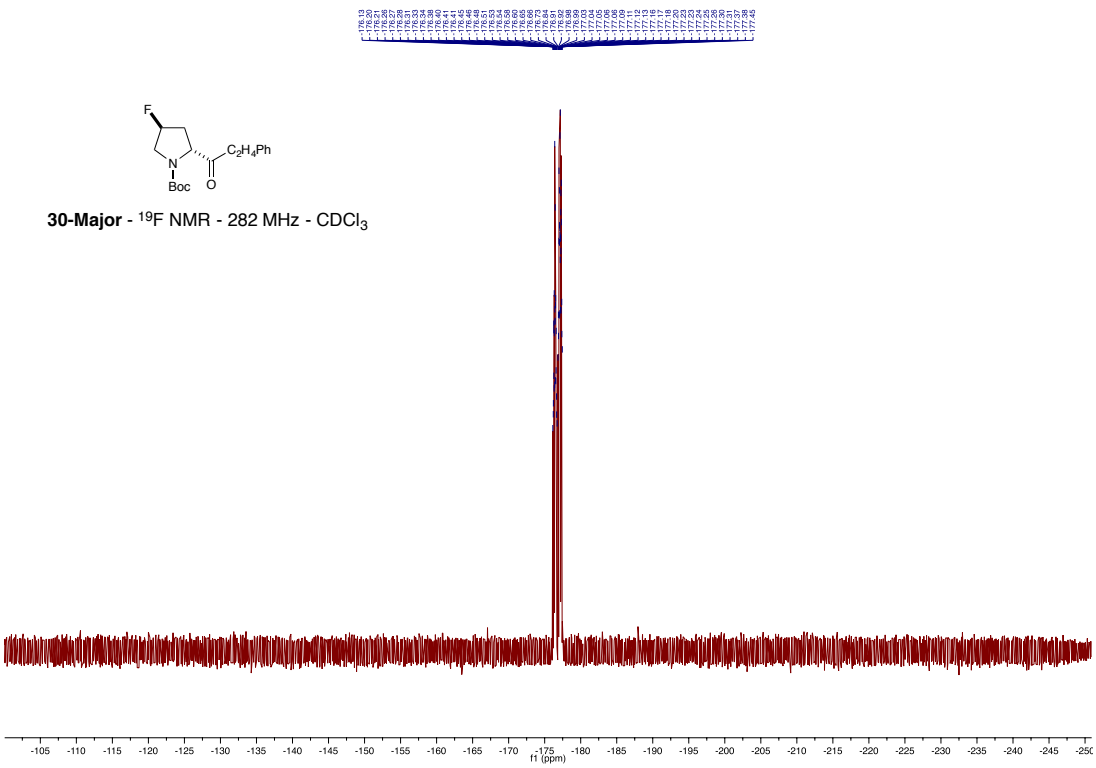

CCL1-341-P2-CDCl3/13 — shNOESYzg.PU CDCl3 /opt/topspin3.0 cle 114
H
H
f2 (ppm)
f1 (ppm)



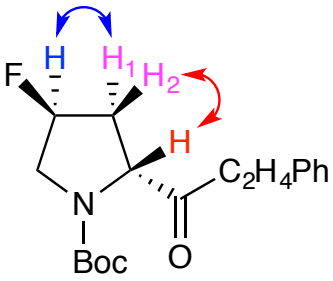
30-Major - ^{1}H NMR - 500 MHz - $CDCl_3$

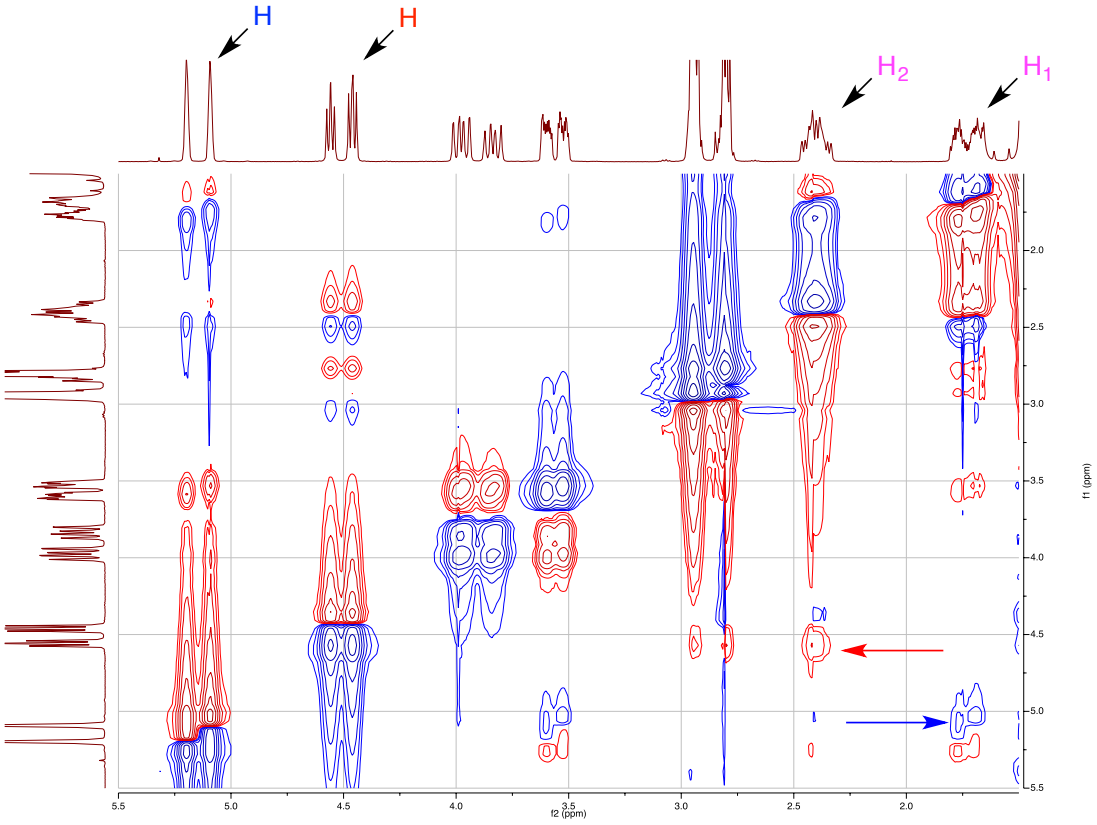


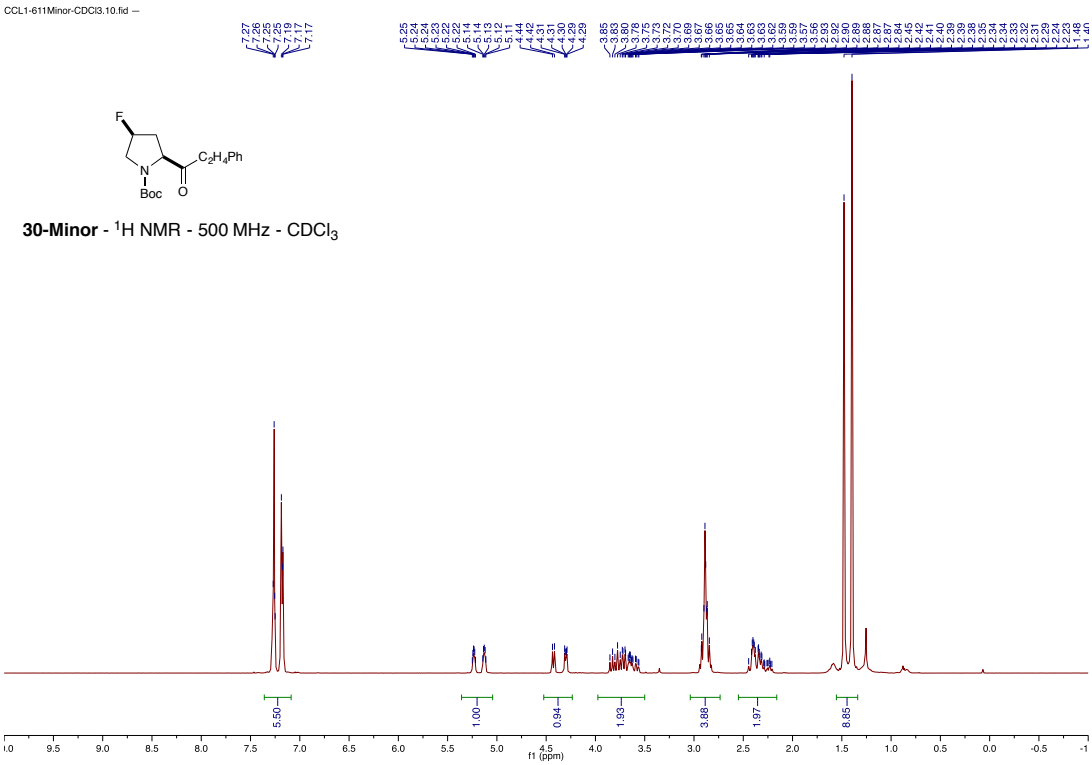
30-Major - ^{13}C NMR - 125 MHz - $CDCl_3$



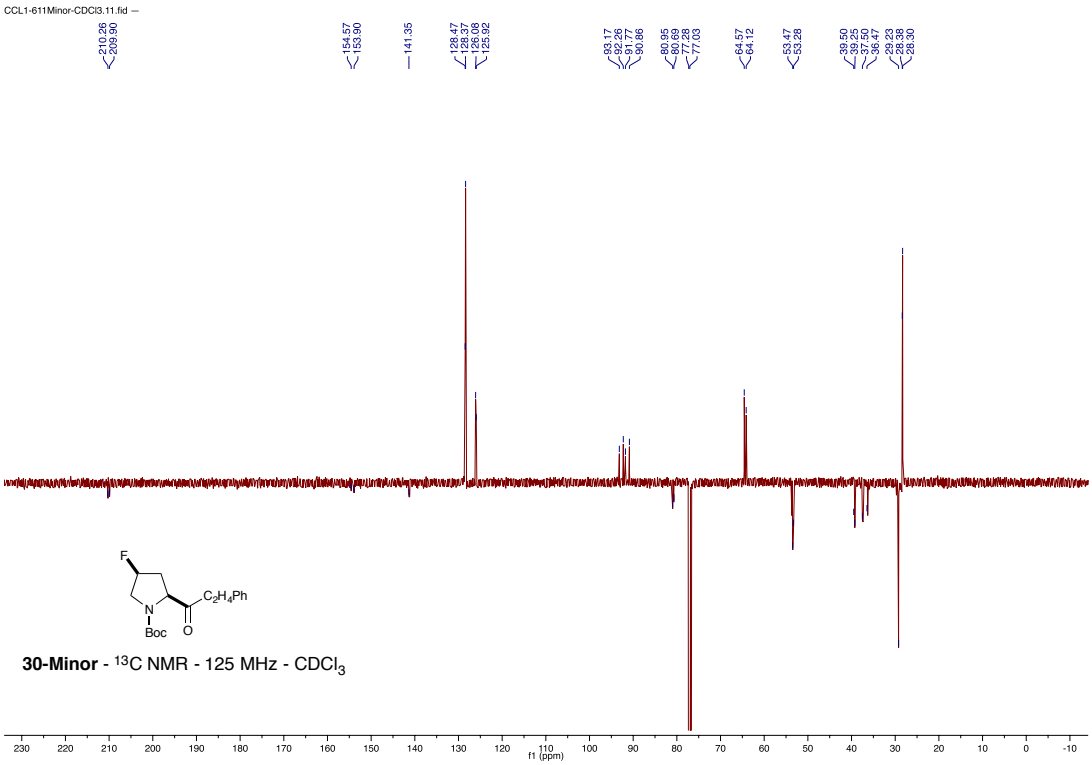
30-Major - ^{19}F NMR - 282 MHz - $CDCl_3$


H
H1
H2
F
H
C2H4Ph
N
Boc
O


H
H
H2
H1
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f2 (ppm)
f1 (ppm)

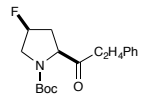


30-Minor - ^{1}H NMR - 500 MHz - $CDCl_3$

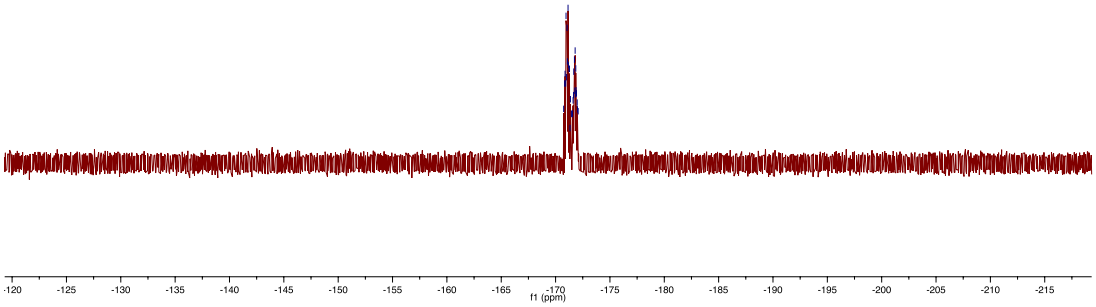


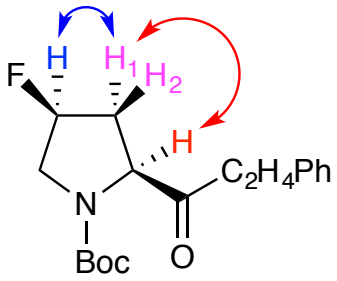
30-Minor - ^{13}C NMR - 125 MHz - $CDCl_3$

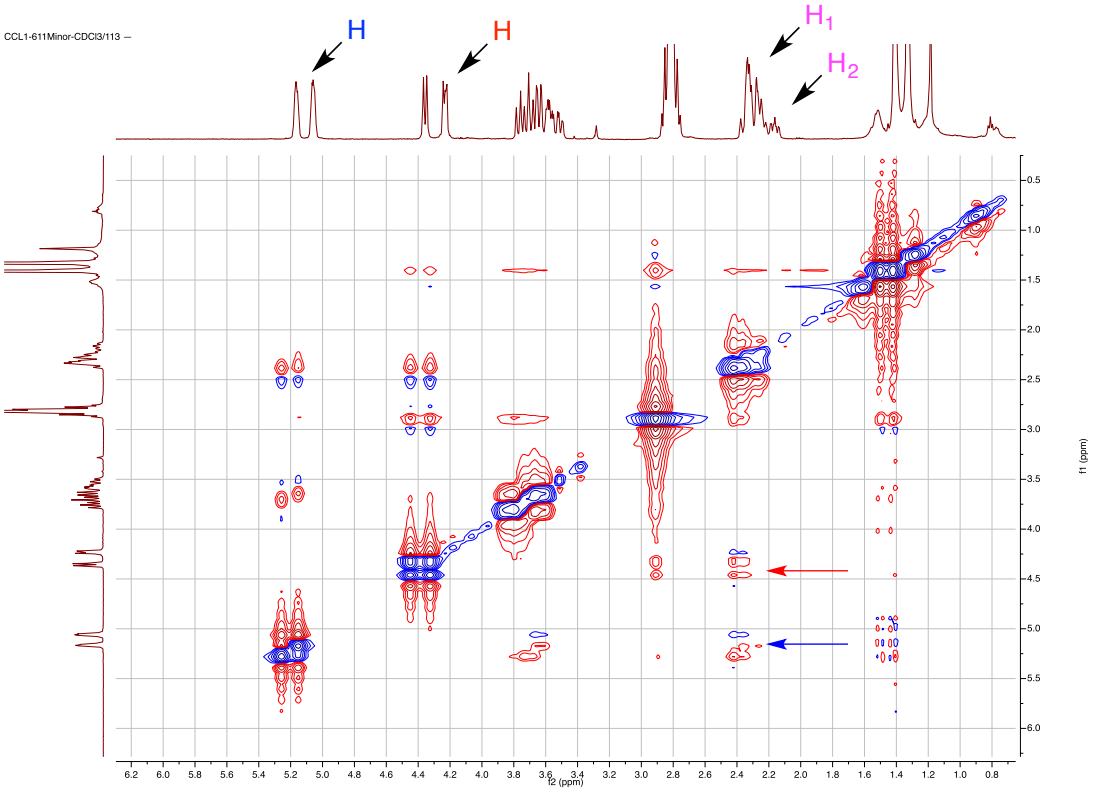
CCL1-611Minor-19F300-CDCl3.10.fid —

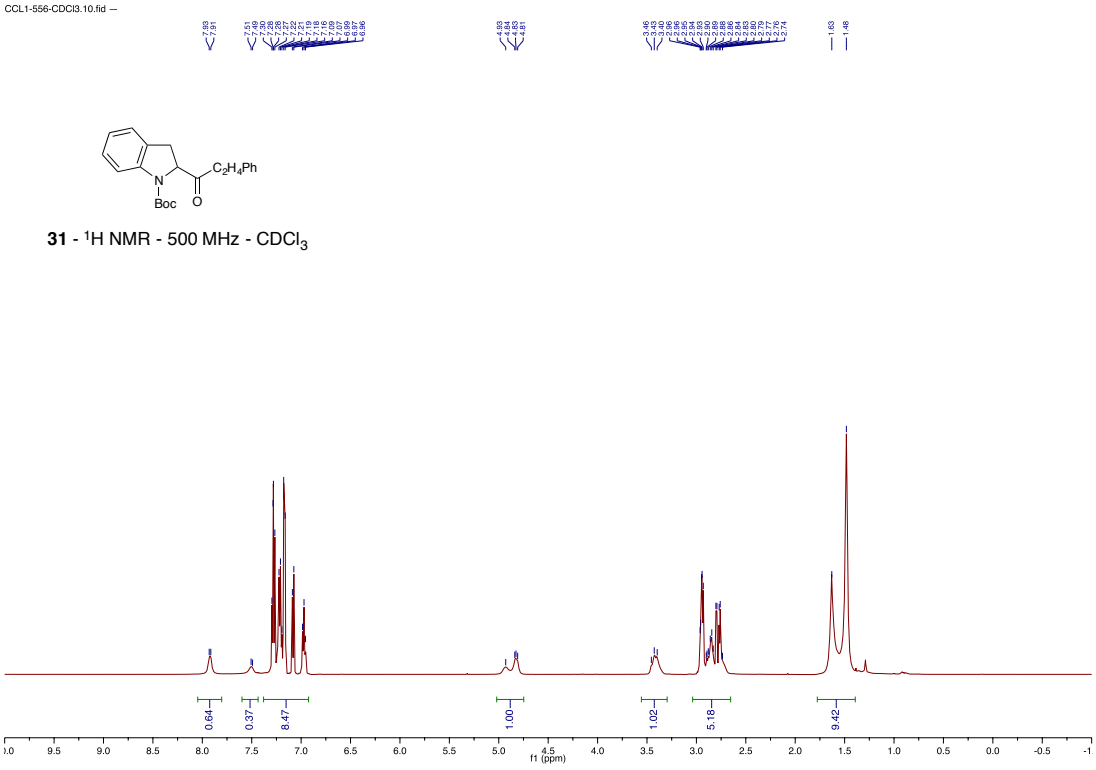


30-Minor - ^{19}F NMR - 282 MHz - $CDCl_3$

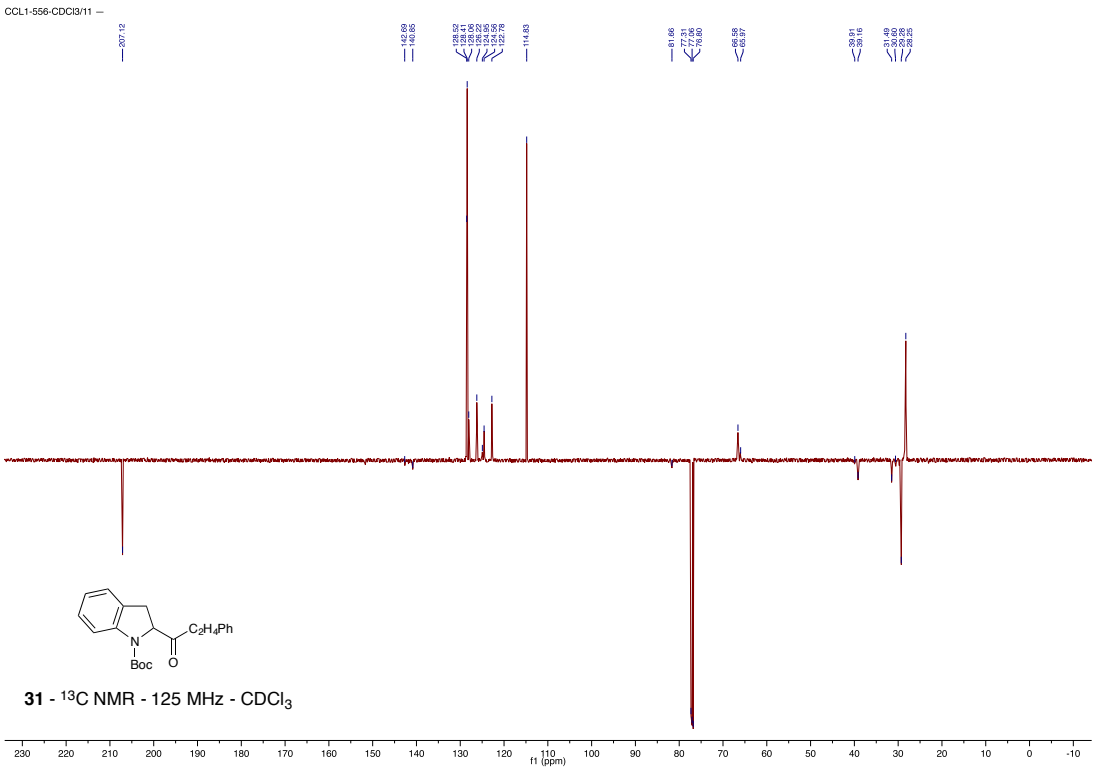



F
H
H1
H2
H
C2H4Ph
N
Boc
O


CCL1-611Minor-CDCl3/113 —
H
H
H1
H2
f2 (ppm)
f1 (ppm)

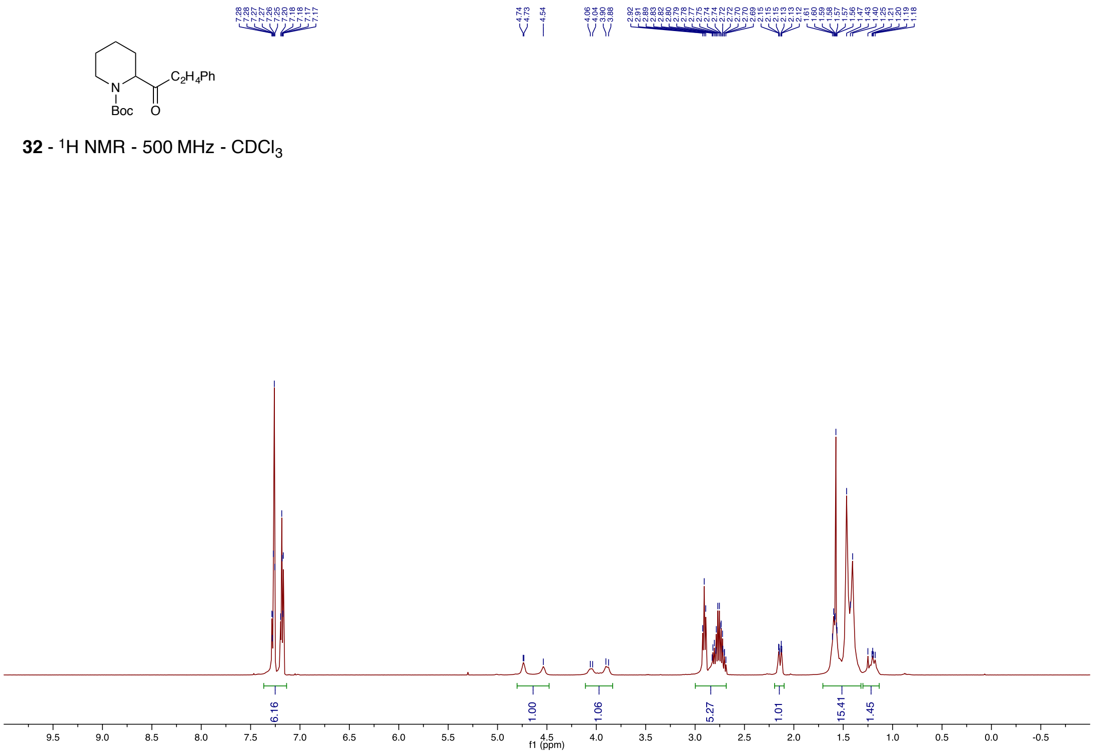


31 - ^{1}H NMR - 500 MHz - $CDCl_3$

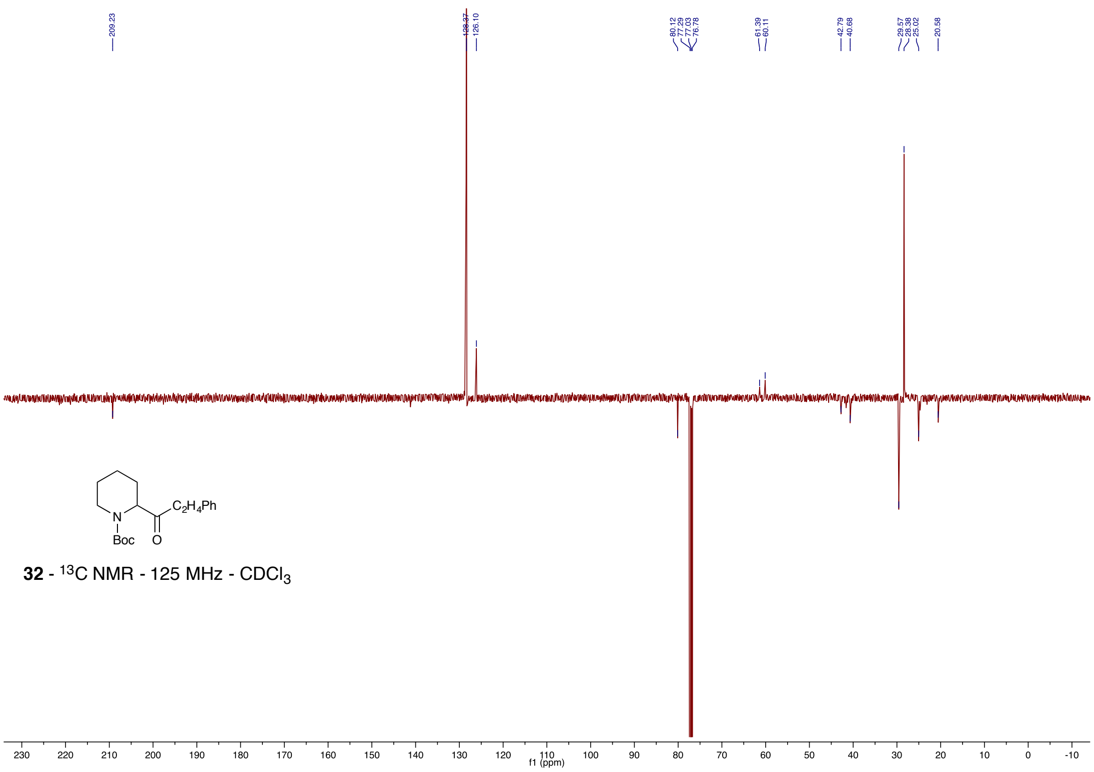


31 - ^{13}C NMR - 125 MHz - $CDCl_3$

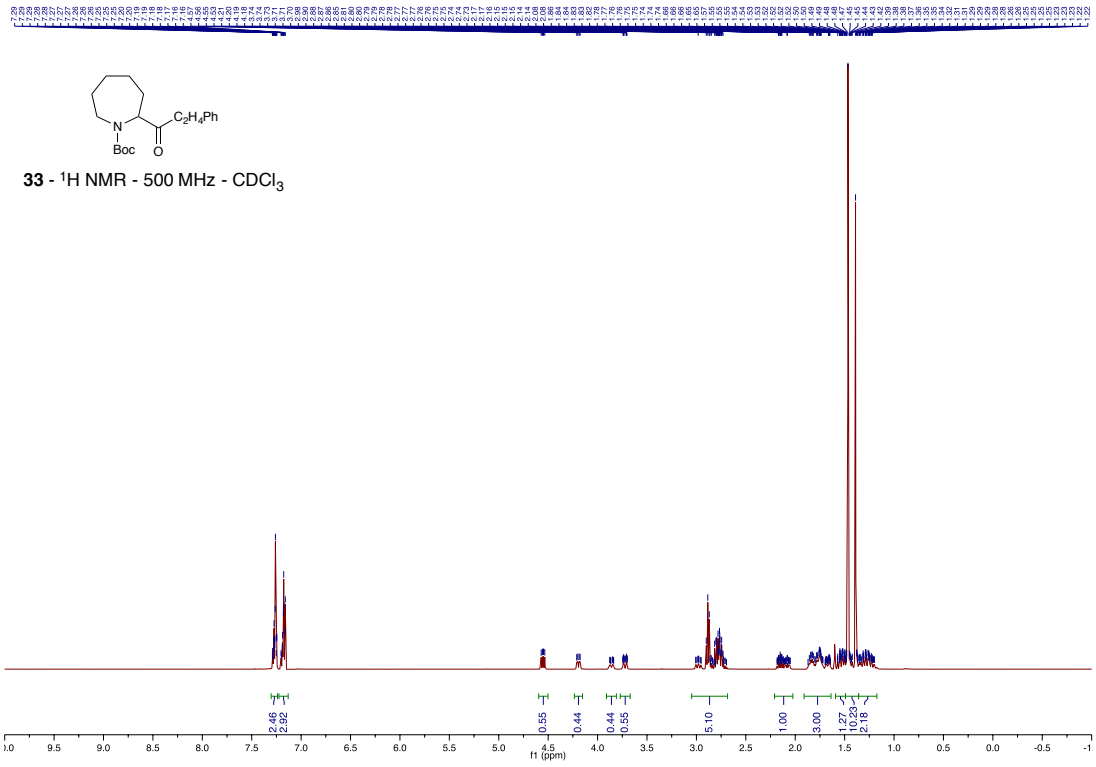
CCL1-411-Pure2-CDCl3.10.fid —



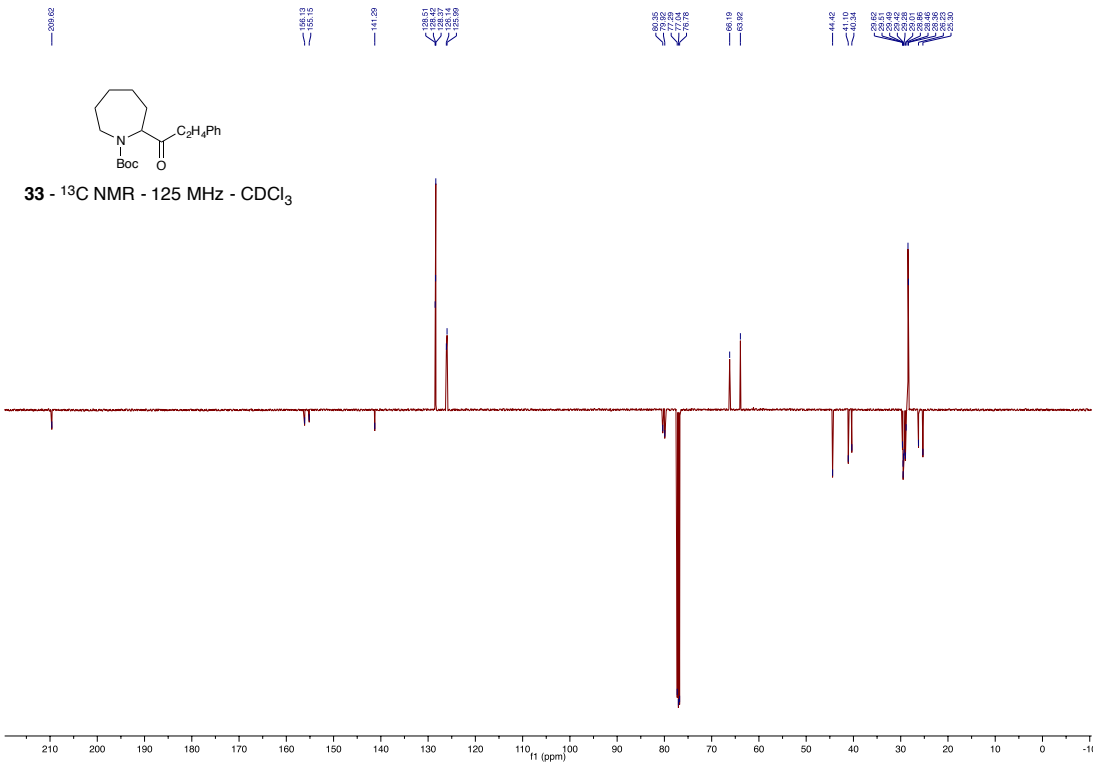
32 - ^{1}H NMR - 500 MHz - $CDCl_3$



32 - ^{13}C NMR - 125 MHz - $CDCl_3$

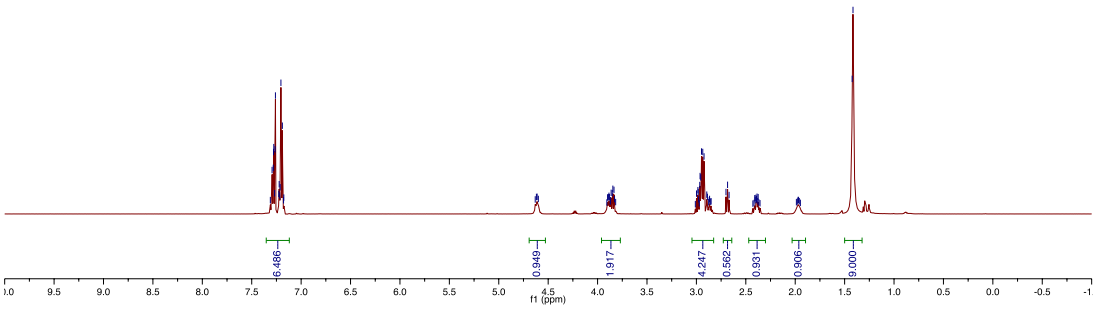


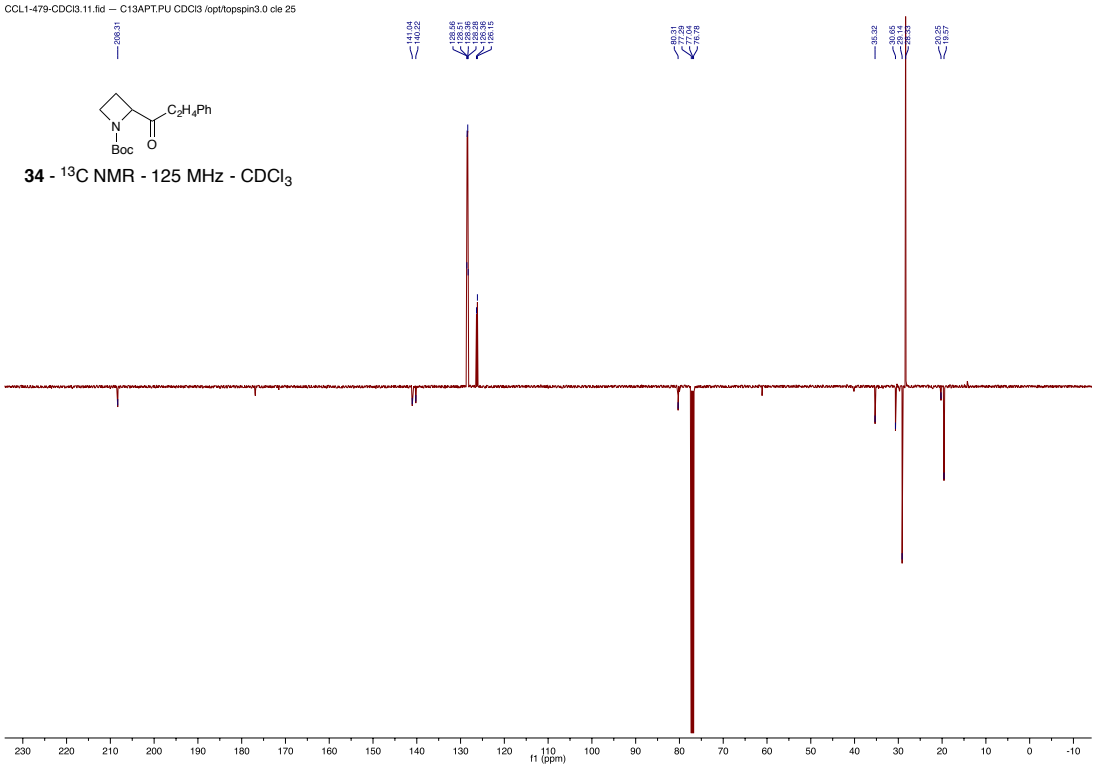
33 - ^{1}H NMR - 500 MHz - $CDCl_3$



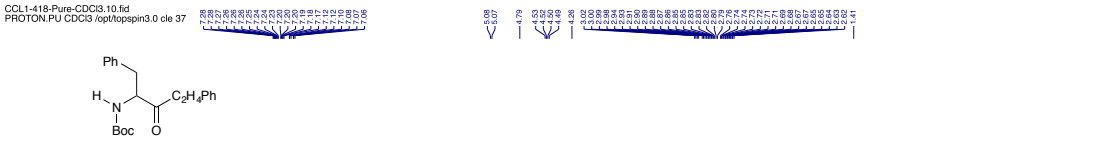
33 - ^{13}C NMR - 125 MHz - $CDCl_3$

34 - ^{1}H NMR - 500 MHz - $CDCl_3$

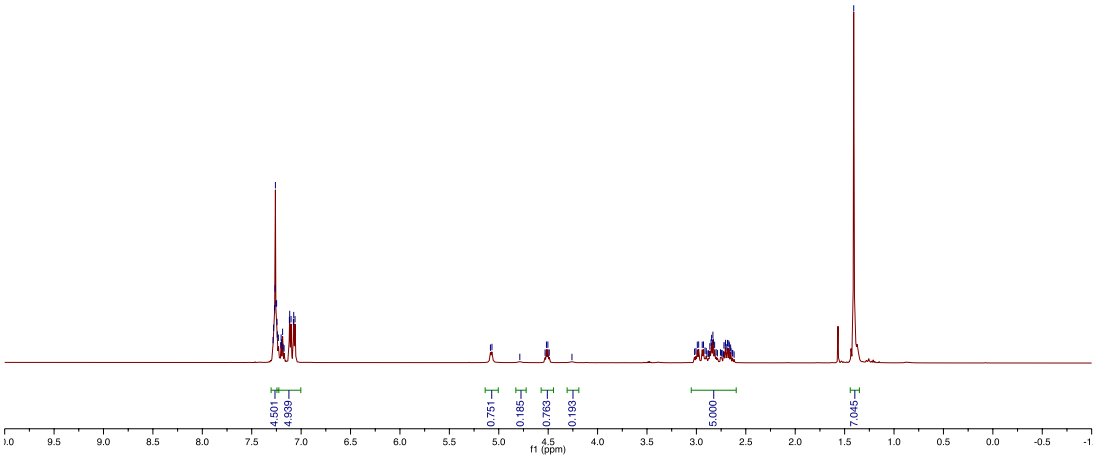


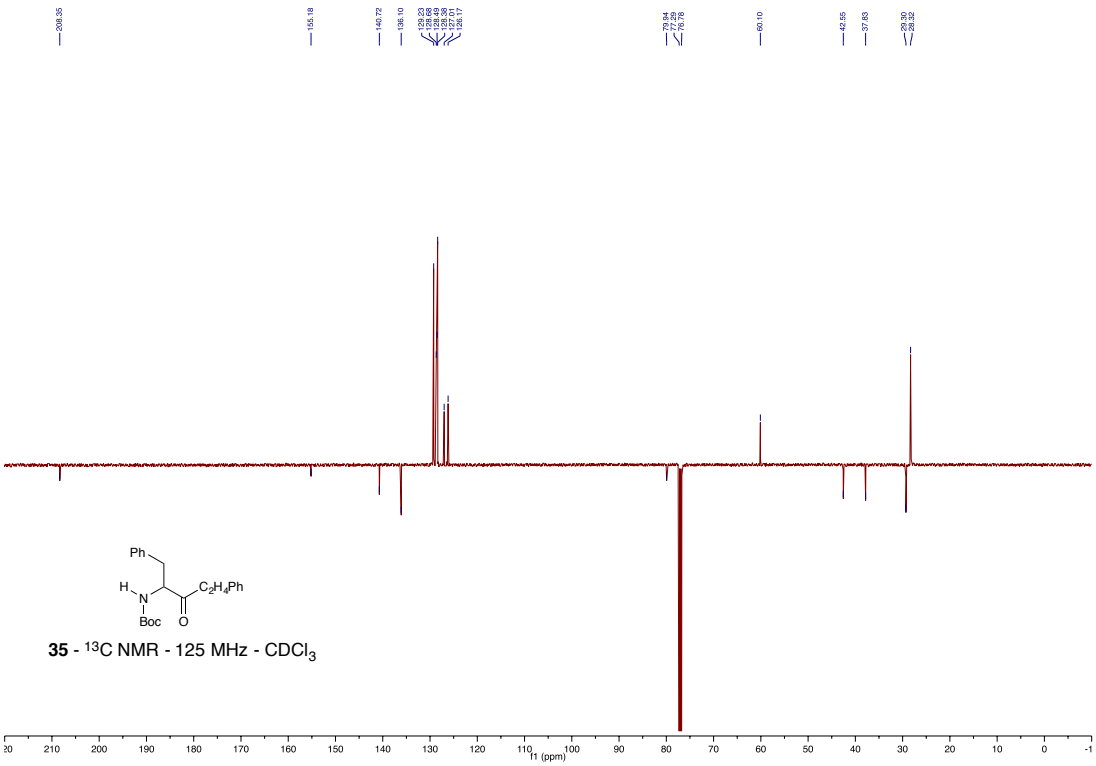


34 - ^{13}C NMR - 125 MHz - $CDCl_3$

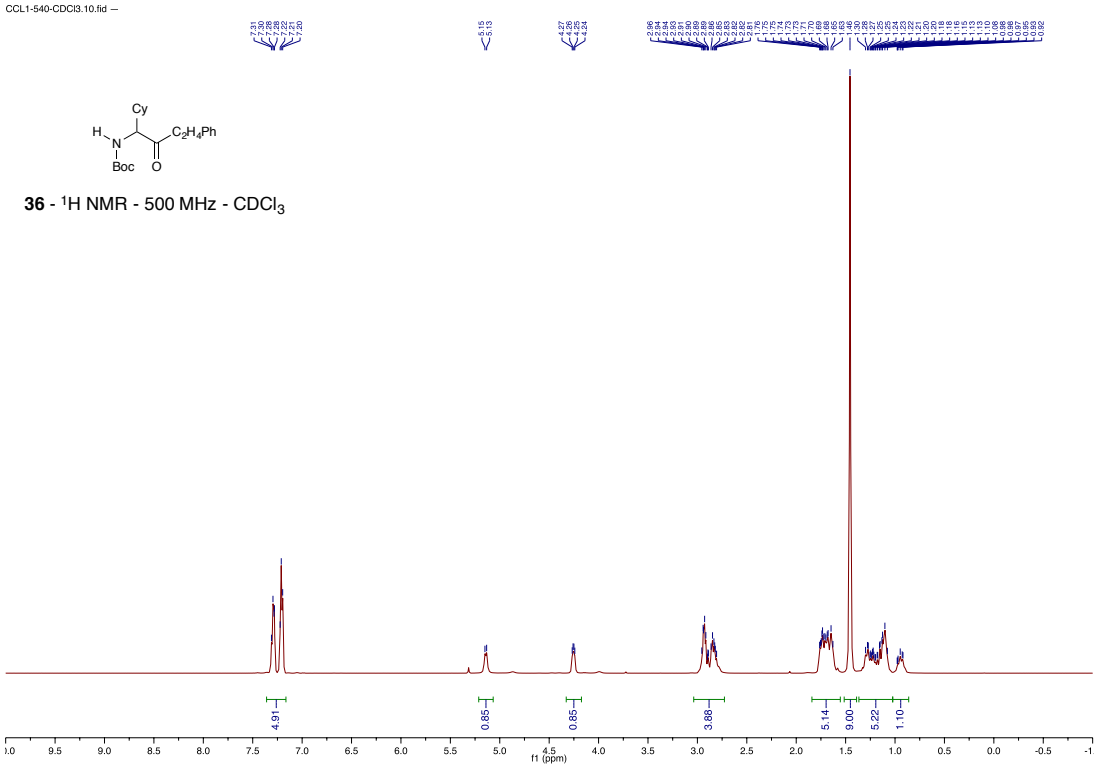


35 - ^{1}H NMR - 500 MHz - $CDCl_3$

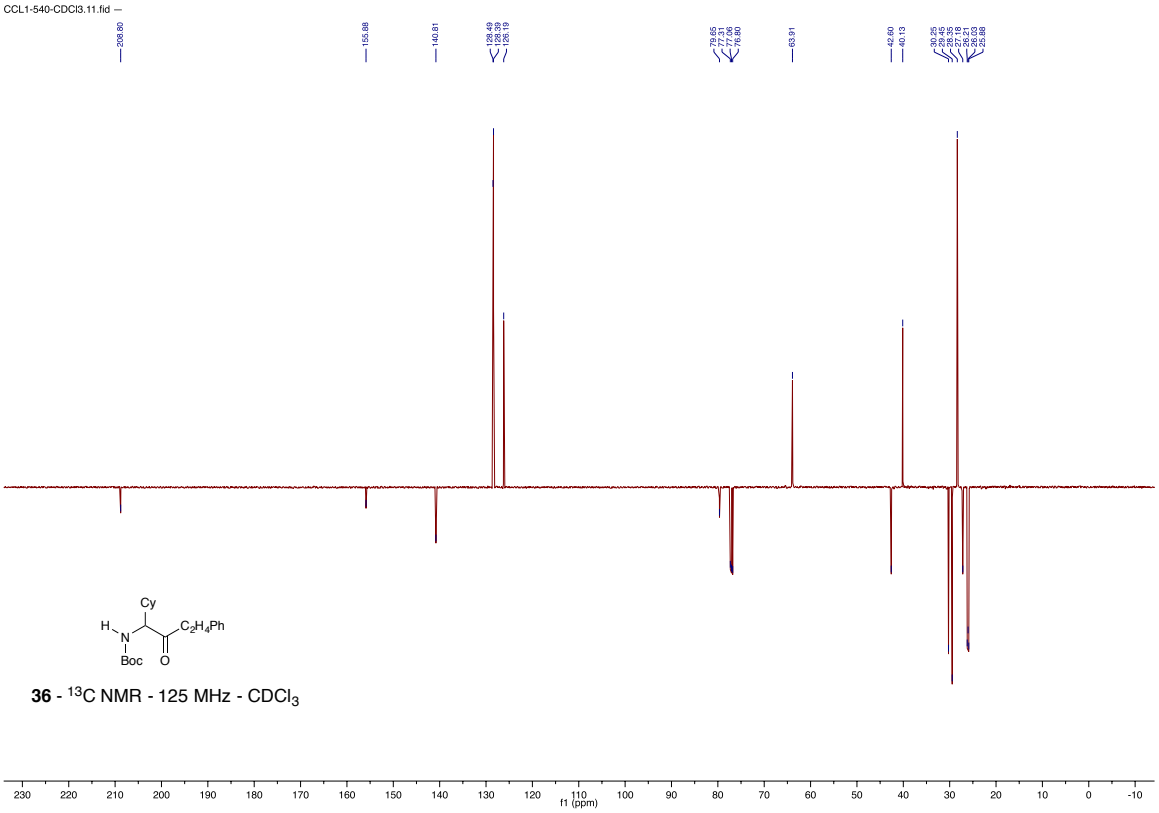




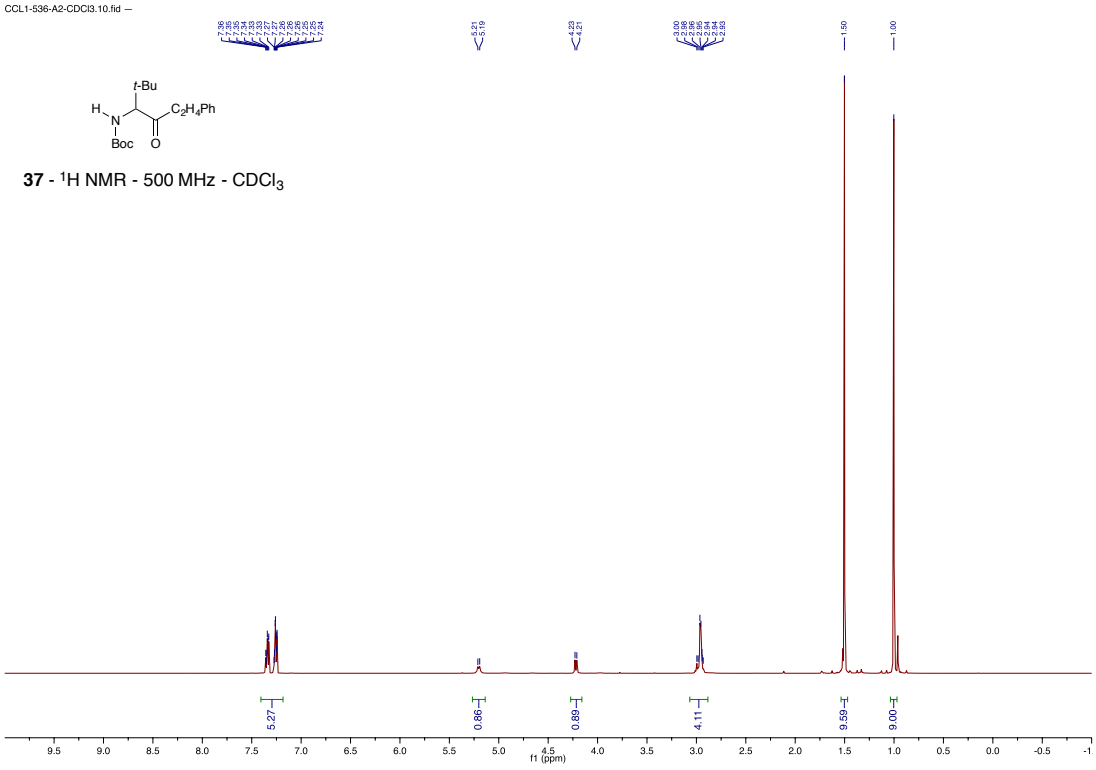
35 - ^{13}C NMR - 125 MHz - $CDCl_3$



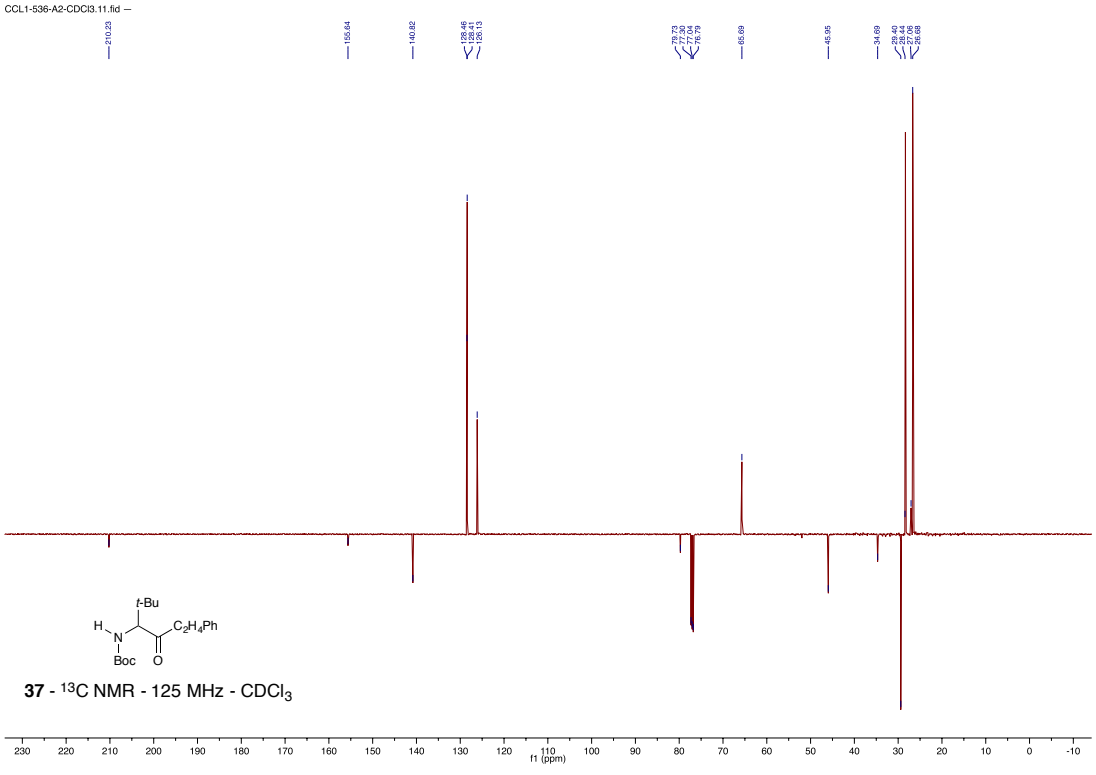
36 - ^{1}H NMR - 500 MHz - $CDCl_3$



36 - ^{13}C NMR - 125 MHz - $CDCl_3$

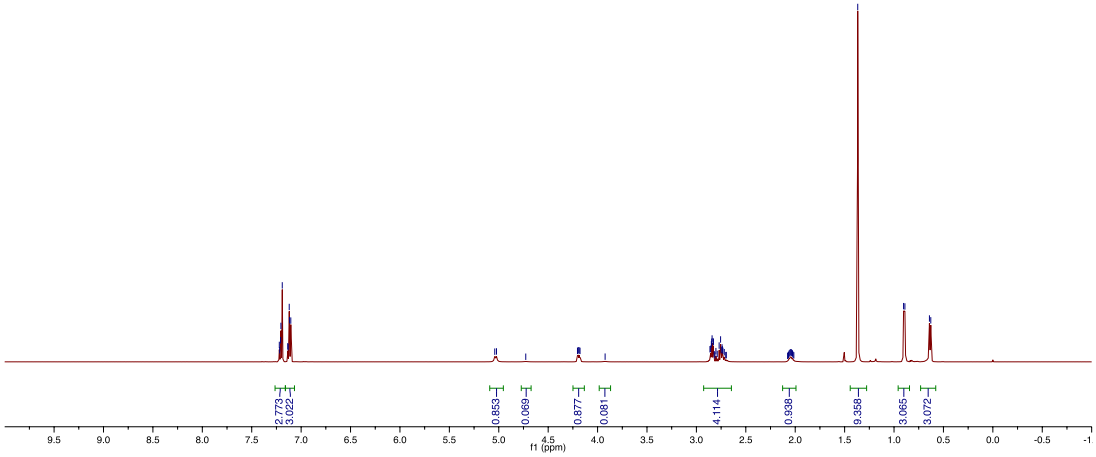


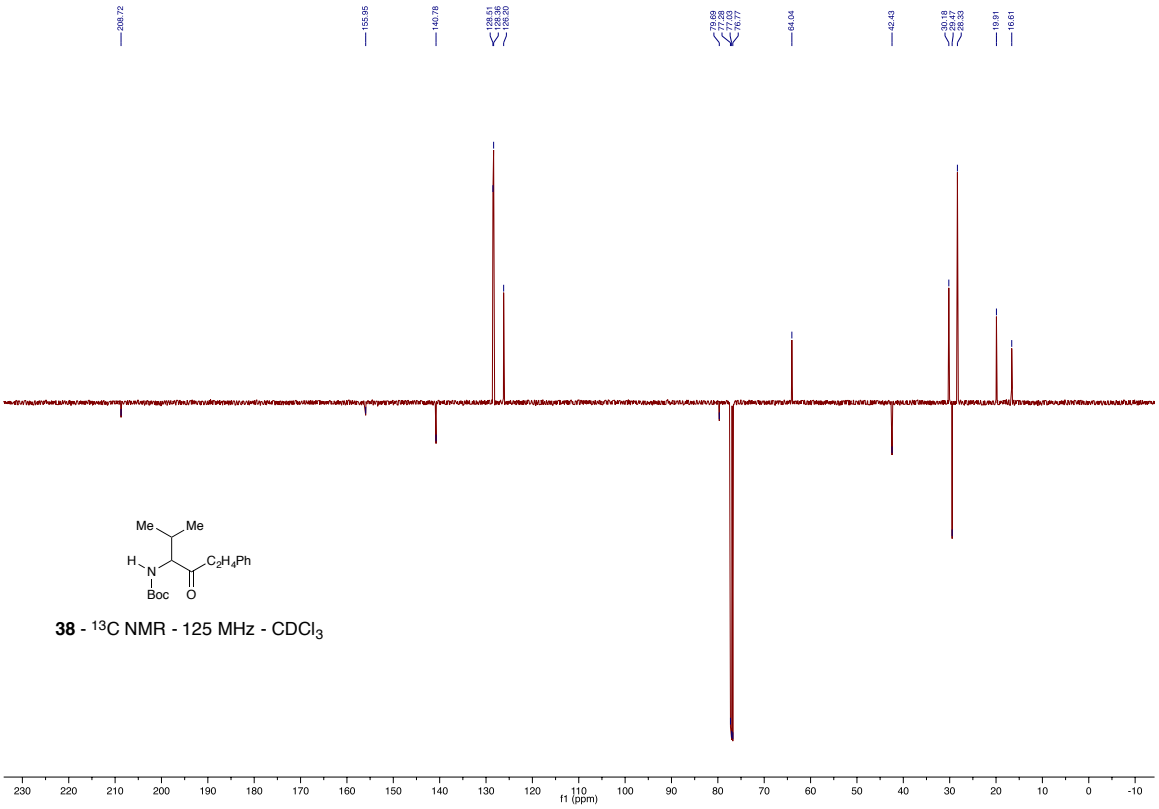
37 - ^{1}H NMR - 500 MHz - $CDCl_3$



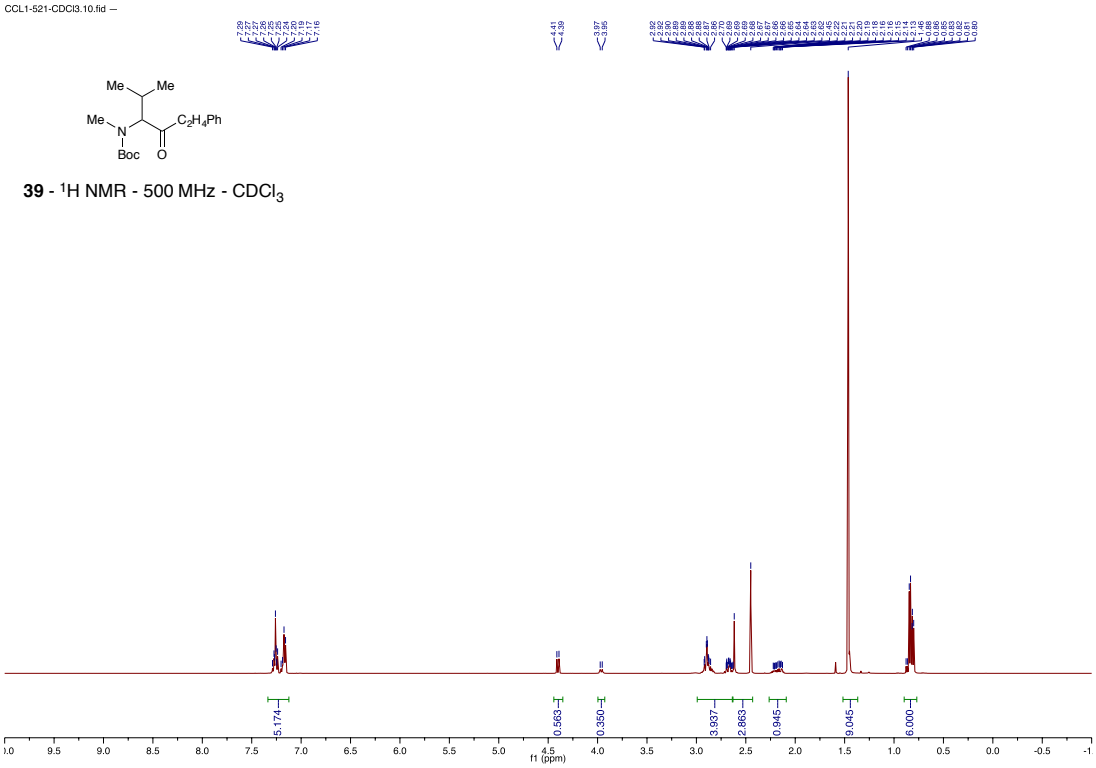
37 - ^{13}C NMR - 125 MHz - $CDCl_3$

38 - ^{1}H NMR - 500 MHz - $CDCl_3$

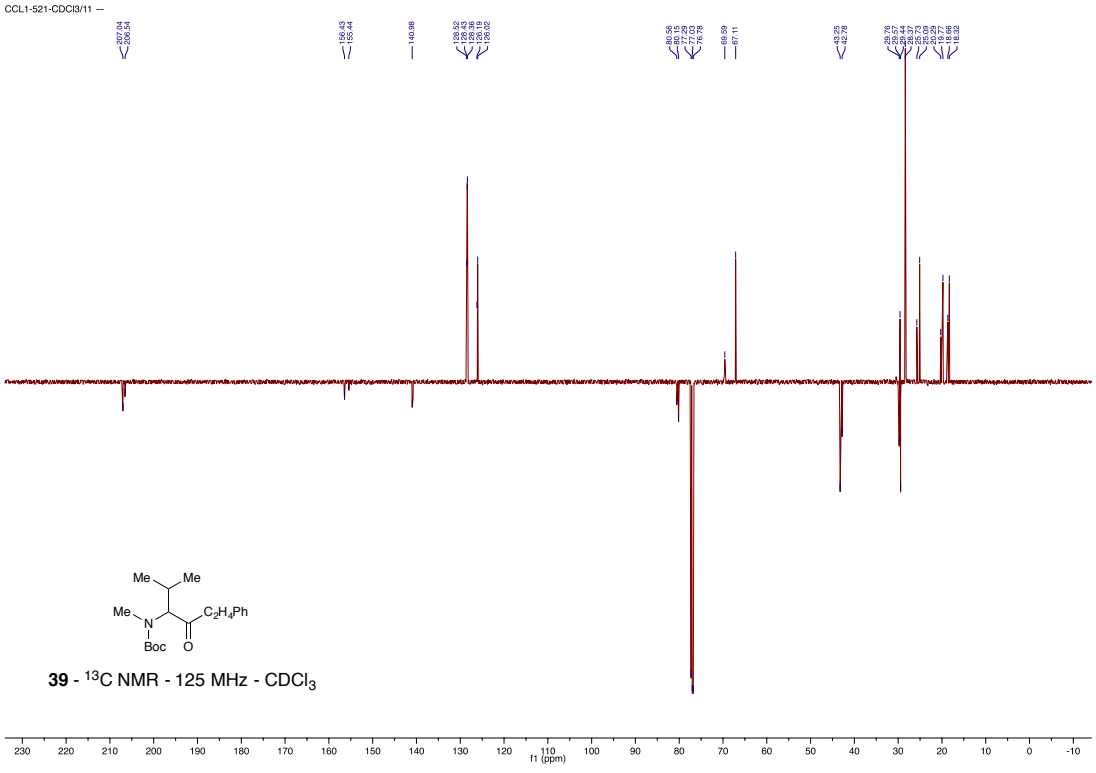




38 - ^{13}C NMR - 125 MHz - $CDCl_3$

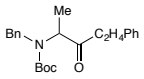


39 - ^{1}H NMR - 500 MHz - $CDCl_3$

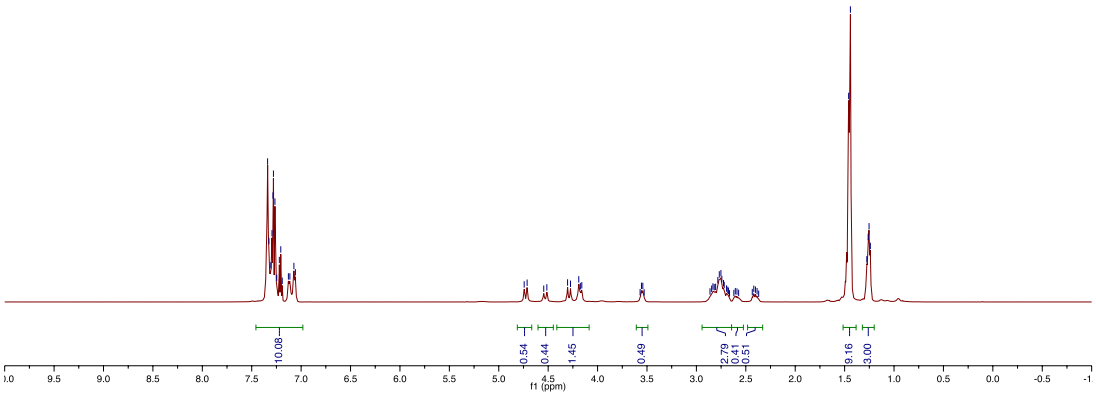


39 - ^{13}C NMR - 125 MHz - $CDCl_3$

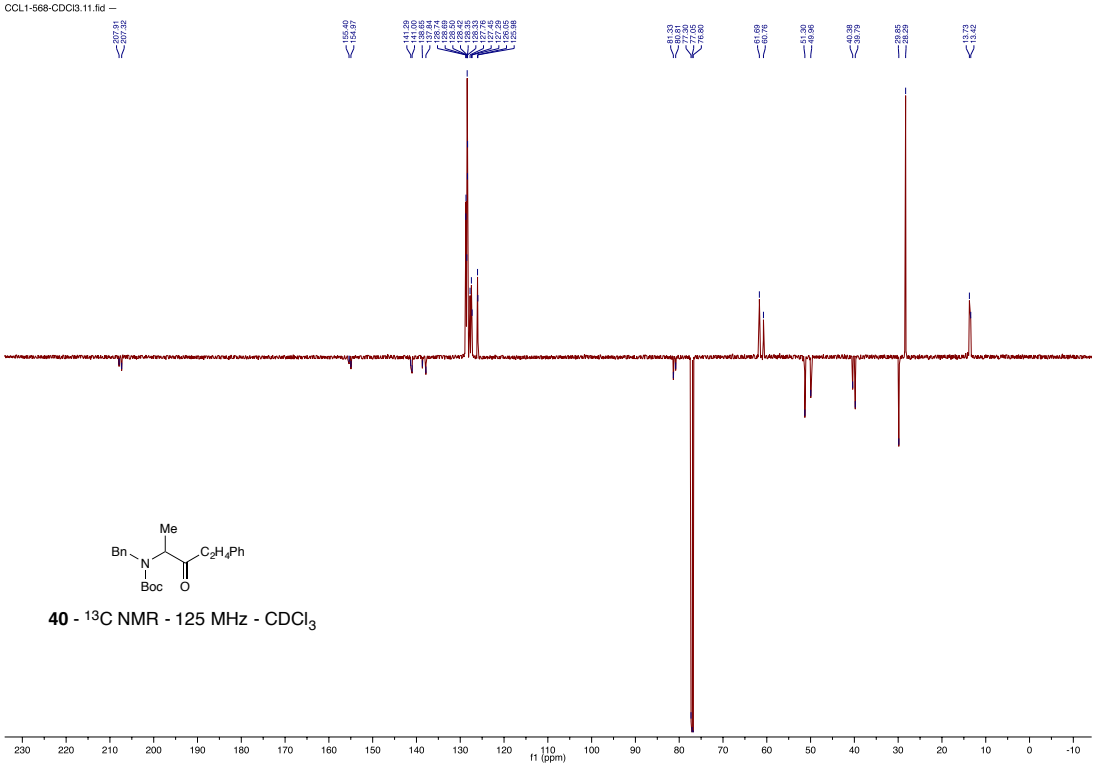
CCL1-568-CDCl3.10.fid —



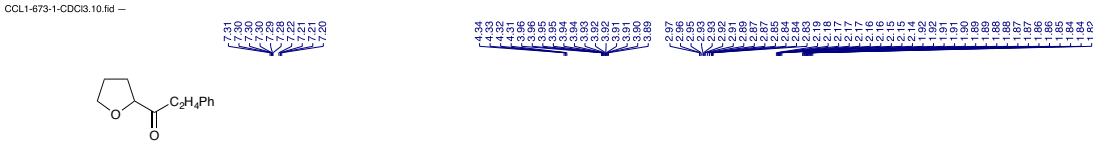
40 - ^{1}H NMR - 500 MHz - $CDCl_3$



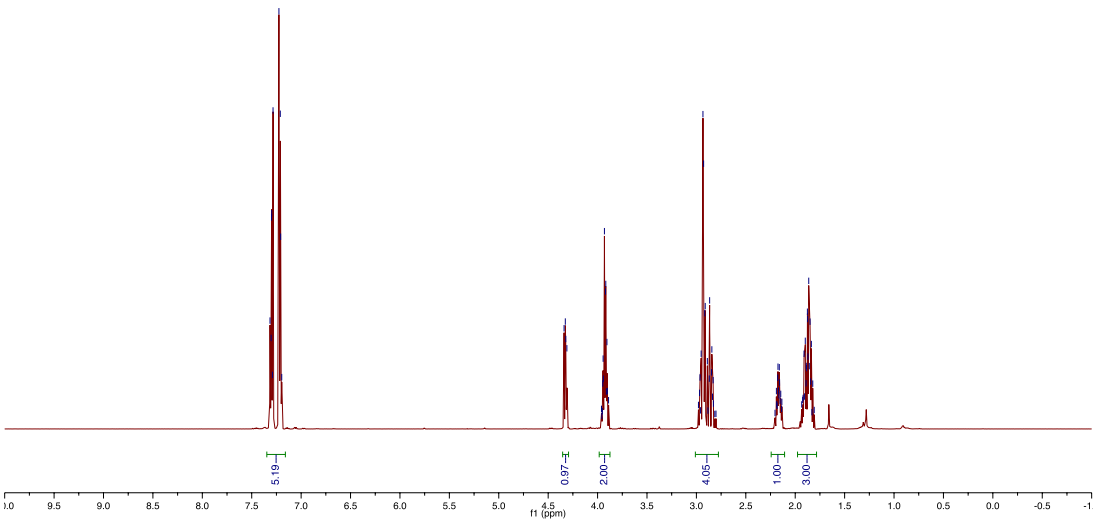
CCL1-568-CDCl3.11.fid —

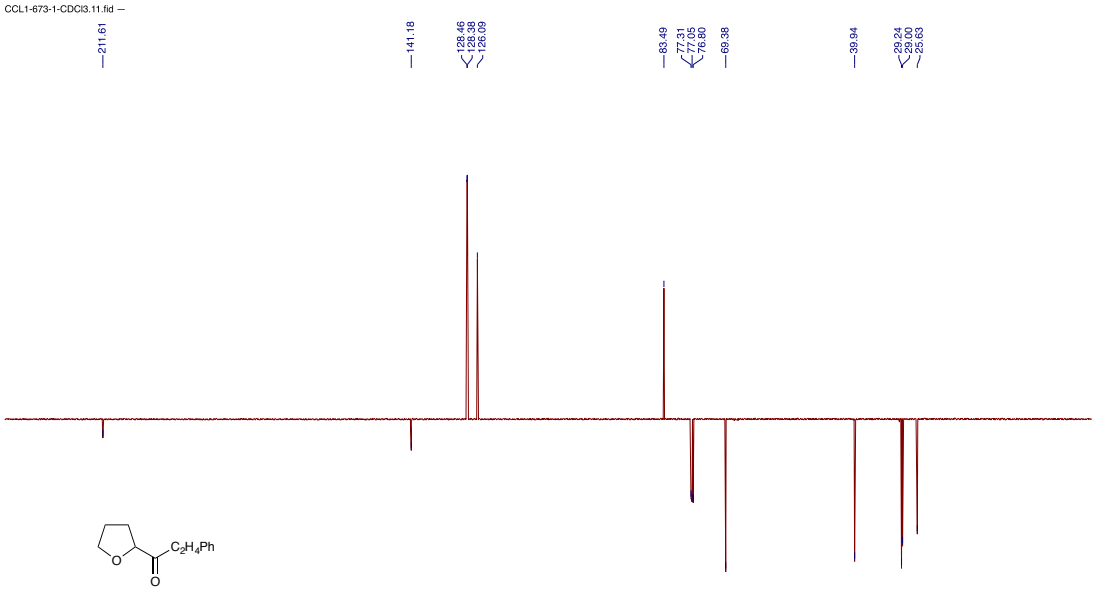


40 - ^{13}C NMR - 125 MHz - $CDCl_3$



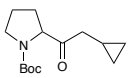
41 - ^{1}H NMR - 500 MHz - $CDCl_3$





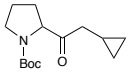
41 - ^{13}C NMR - 125 MHz - $CDCl_3$

CCL1-594-CDCl3.10.fid —

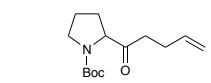


^{1}H NMR - 500 MHz - $CDCl_3$

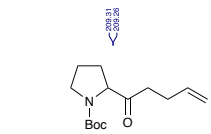
CCL1-594-CDCl3.11.fid —



^{13}C NMR - 125 MHz - $CDCl_3$

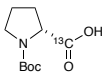


^{1}H NMR - 500 MHz - $CDCl_3$



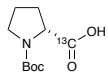
^{13}C NMR - 125 MHz - $CDCl_3$

CCL1-316-Rec1-CDCl3.10.fid — PROTON.PU CDCl3 /opt/topspin3.0 cle 107

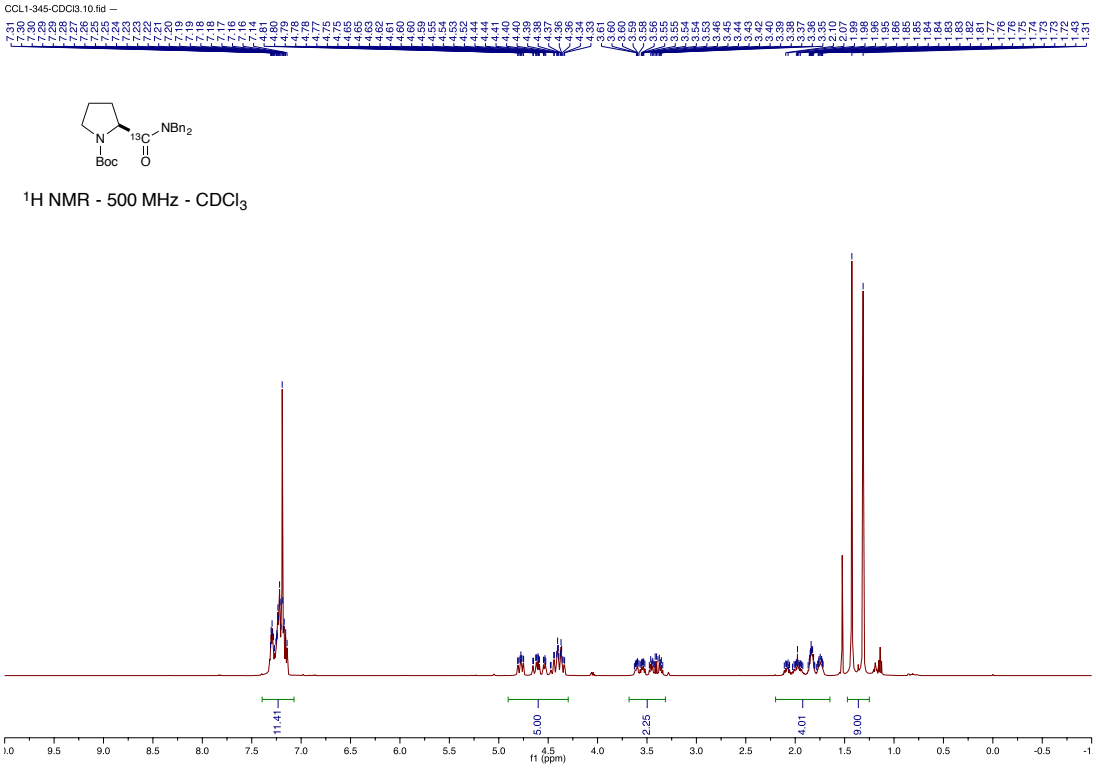


^{1}H NMR - 500 MHz - $CDCl_3$

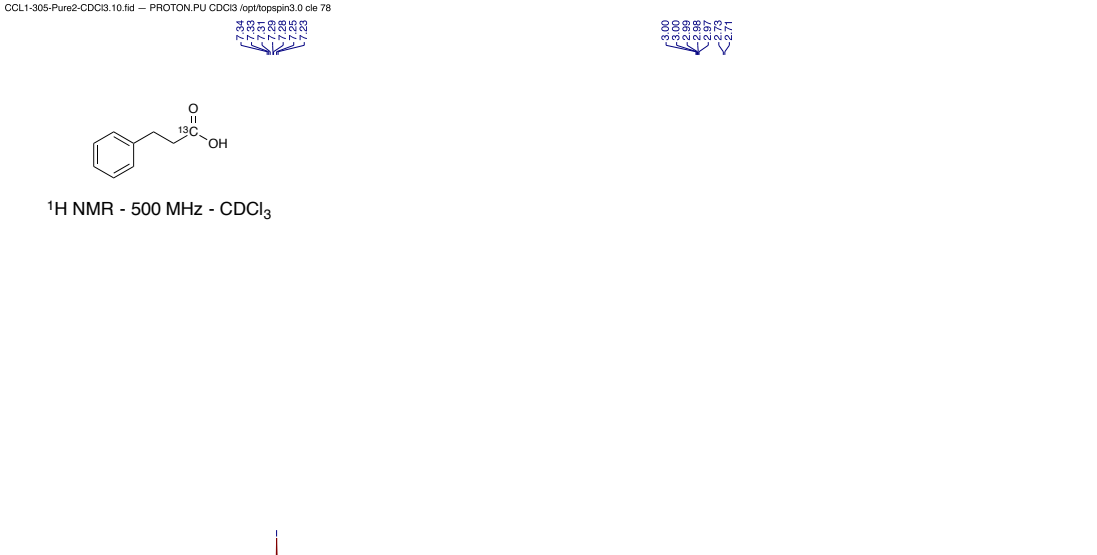
CCL1-316-Rec1-CDCl3.11.fid — C13CPDp1.PU CDCl3 /opt/topspin3.0 cle 107



^{13}C NMR - 125 MHz - $CDCl_3$

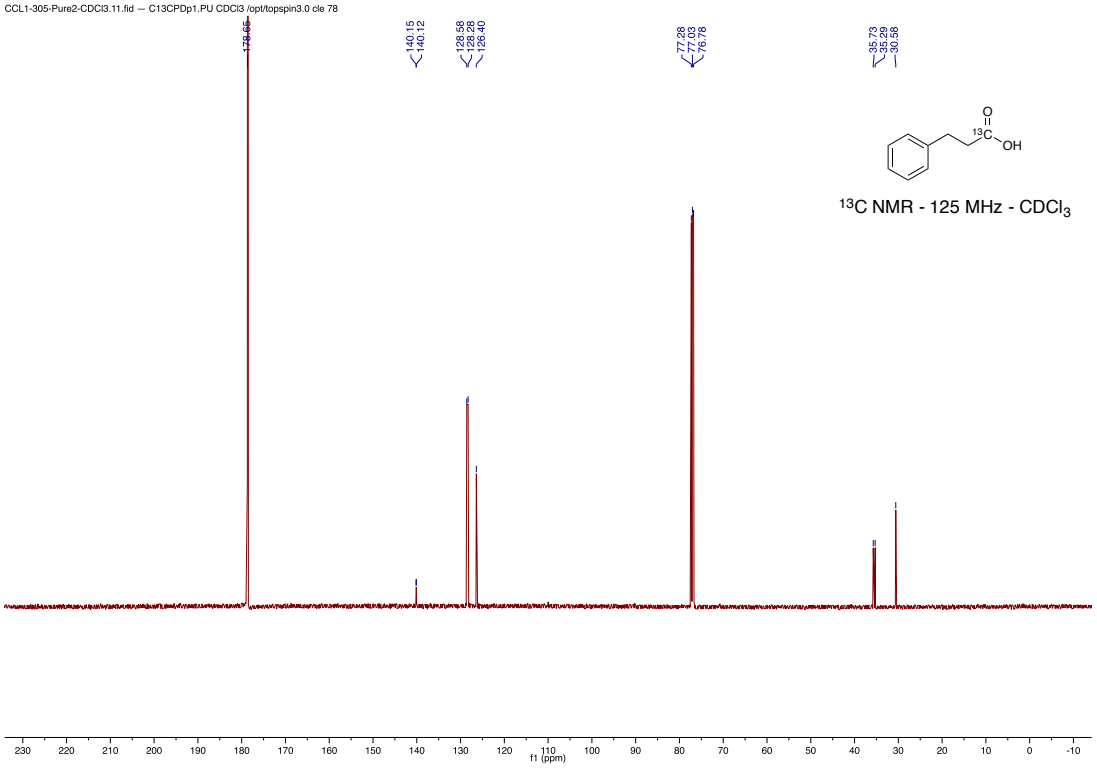

CCL1-345-CDCl3.10.fid
NBn2
13C
N
Boc
O
1H NMR - 500 MHz - CDCl3
11.41
5.00
2.25
4.01
9.00
f1 (ppm)

CCL1-305-Pure2-CDCl3.10.fid — PROTON.PU CDCl3 /opt/topspin3.0 cle 78



^{1}H NMR - 500 MHz - $CDCl_3$

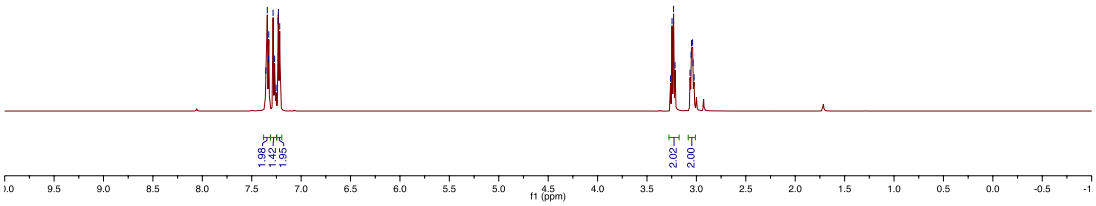
CCL1-305-Pure2-CDCl3.11.fid — C13CPDp1.PU CDCl3 /opt/topspin3.0 cle 78



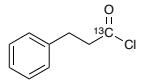
^{13}C NMR - 125 MHz - $CDCl_3$

CCL1-309-CDCl3.10.fid — PROTON.PU CDCl3 /opt/topspin3.0 cle 103

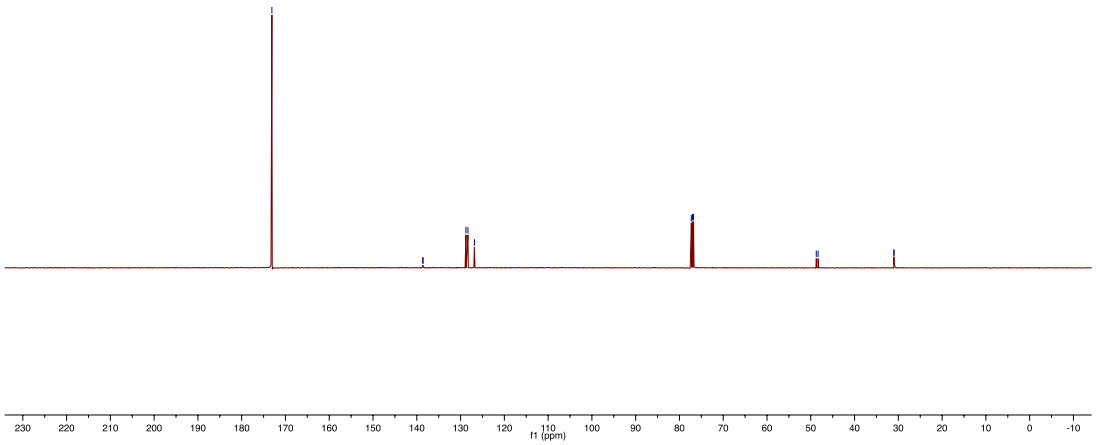
^{1}H NMR - 500 MHz - $CDCl_3$

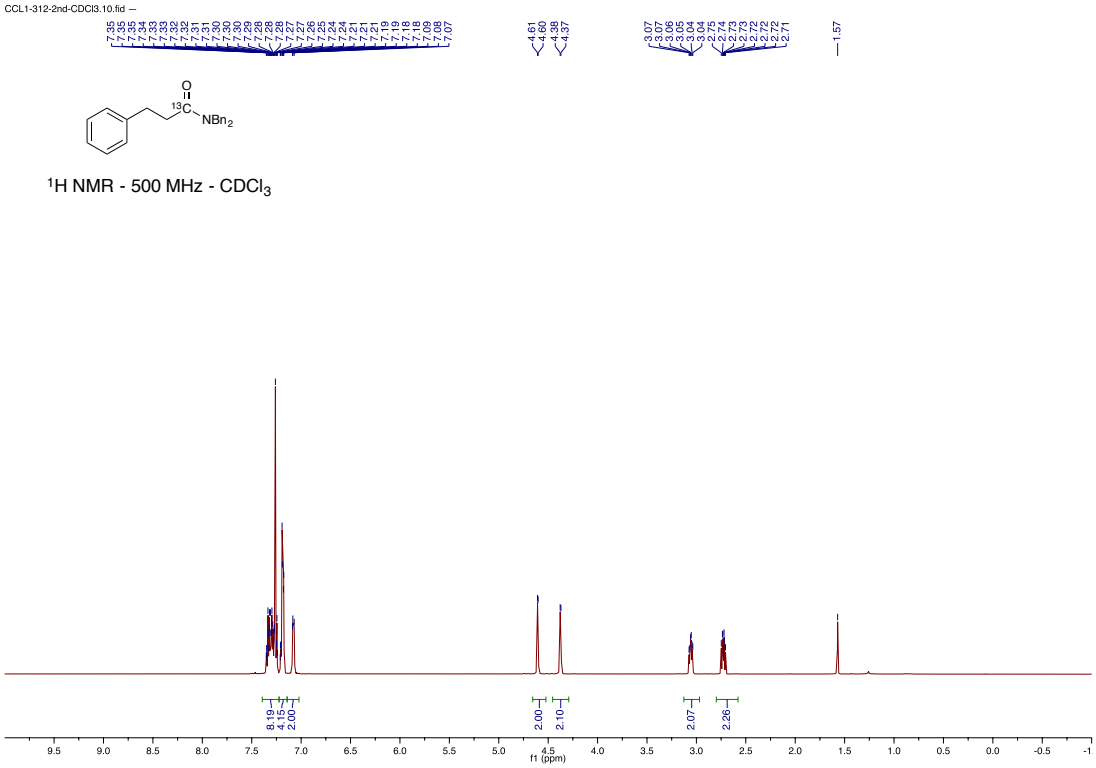


CCL1-309-CDCl3.11.fid — C13CPDp1.PU CDCl3 /opt/topspin3.0 cle 103

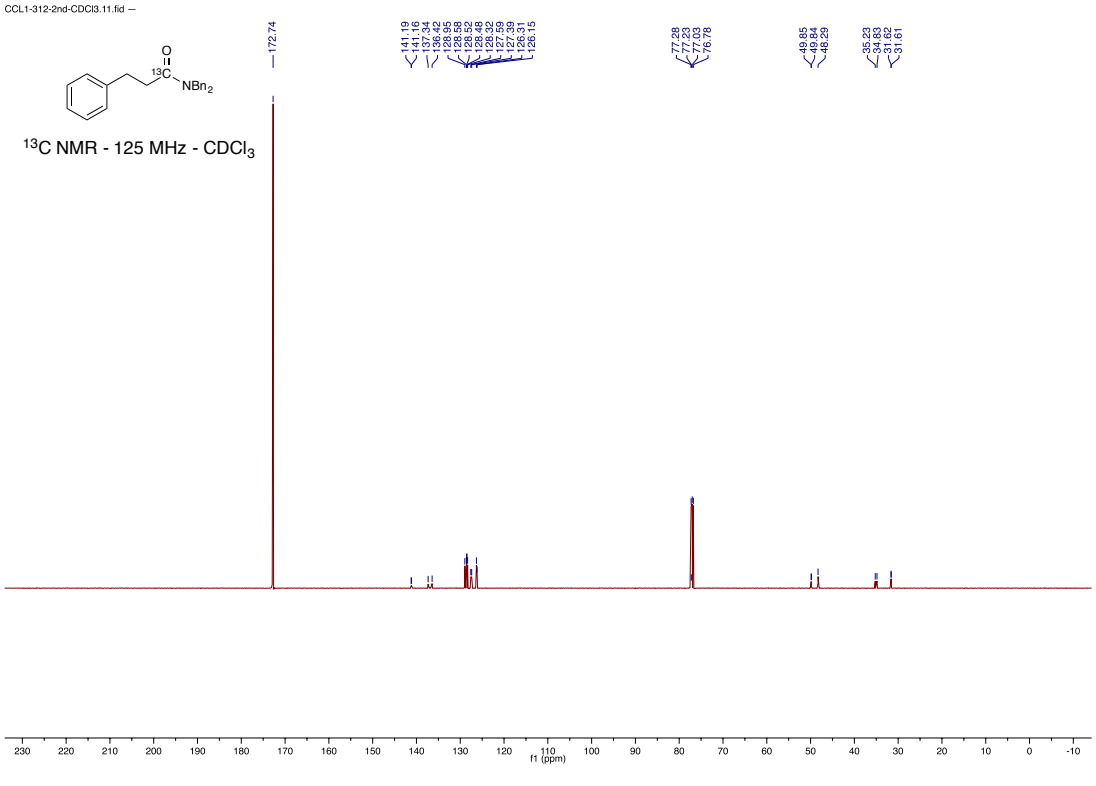


^{13}C NMR - 125 MHz - $CDCl_3$

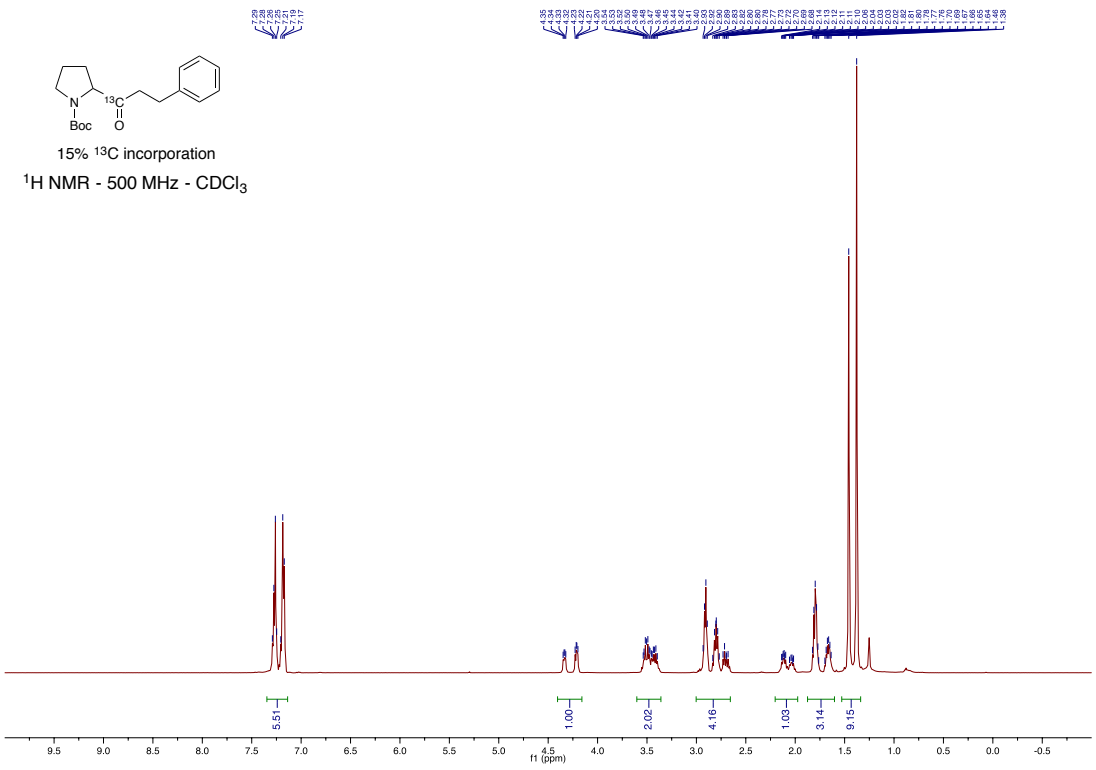


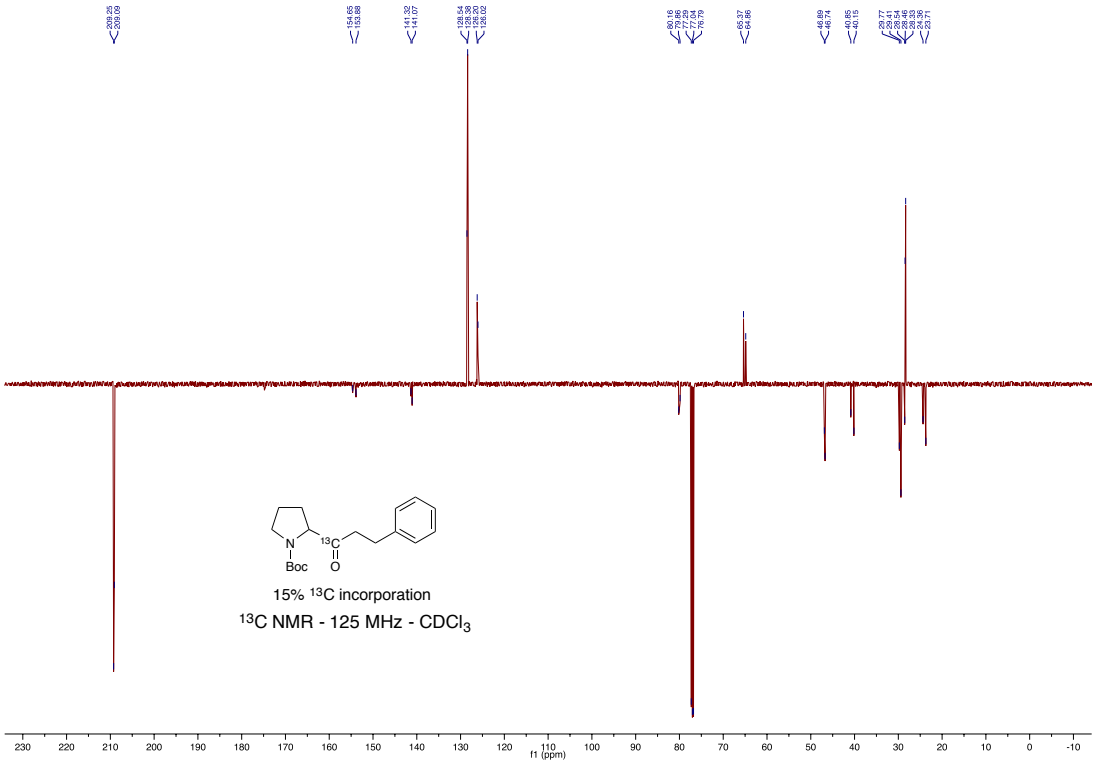


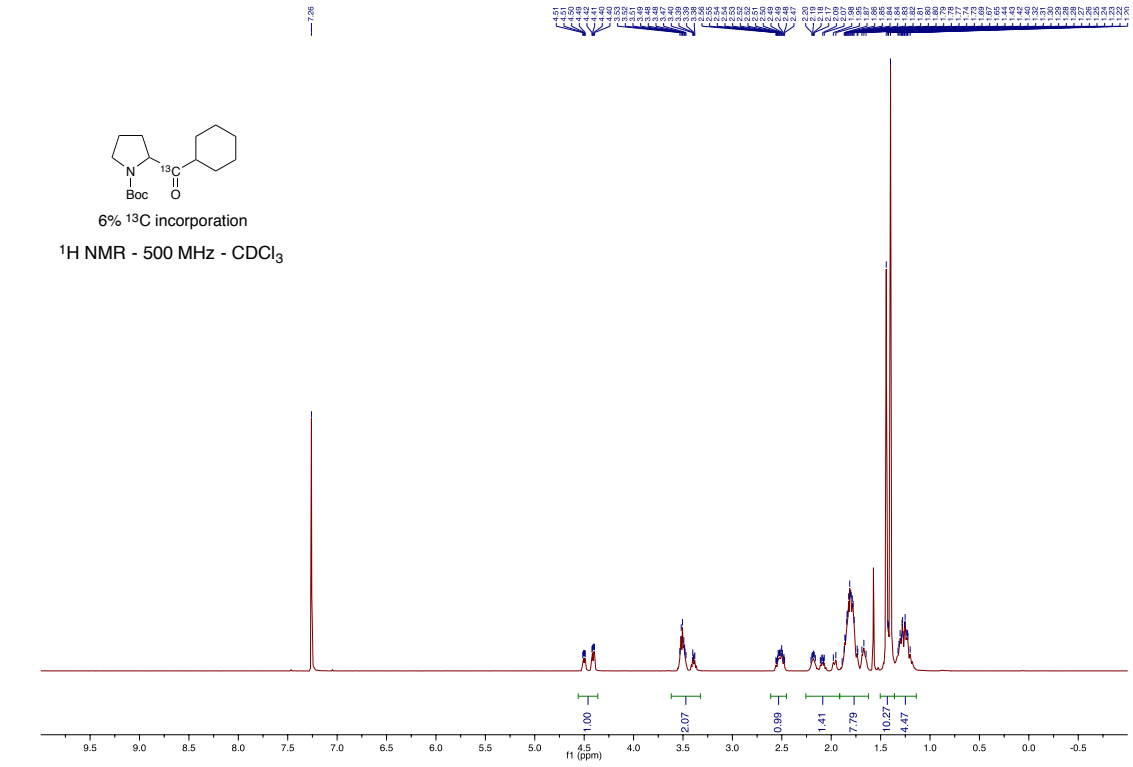
^{1}H NMR - 500 MHz - $CDCl_3$

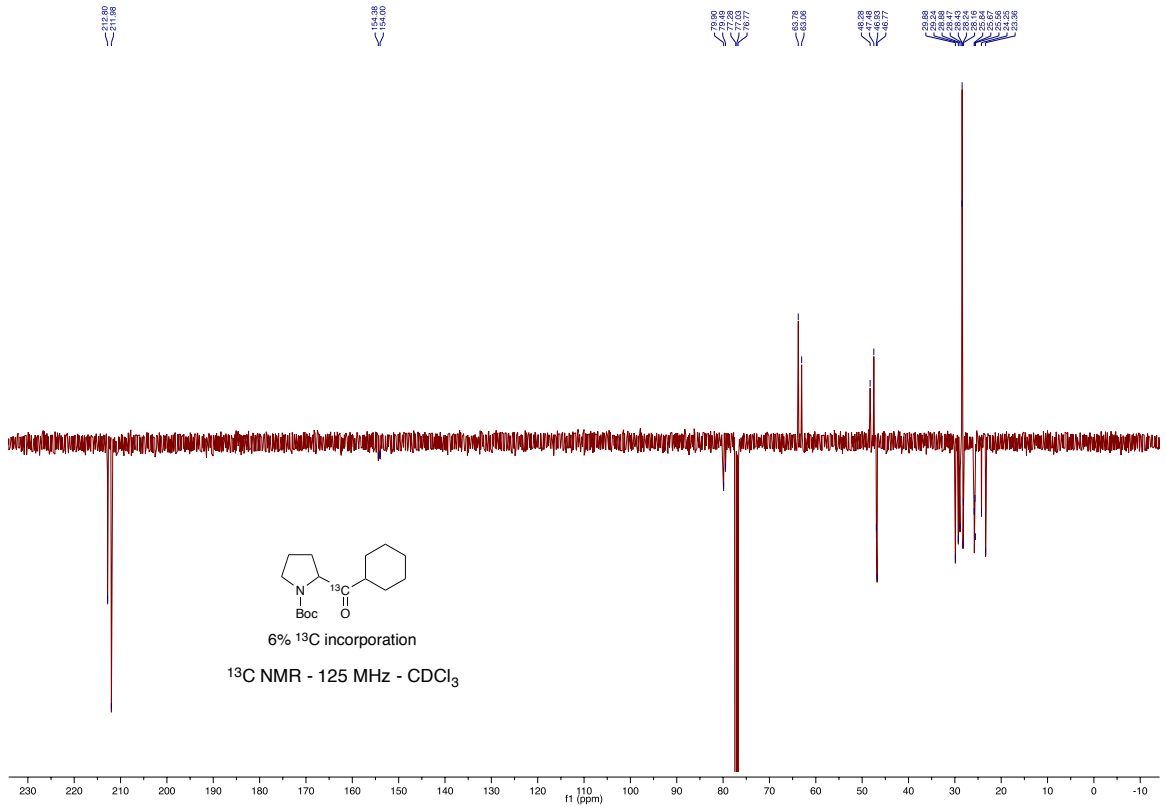


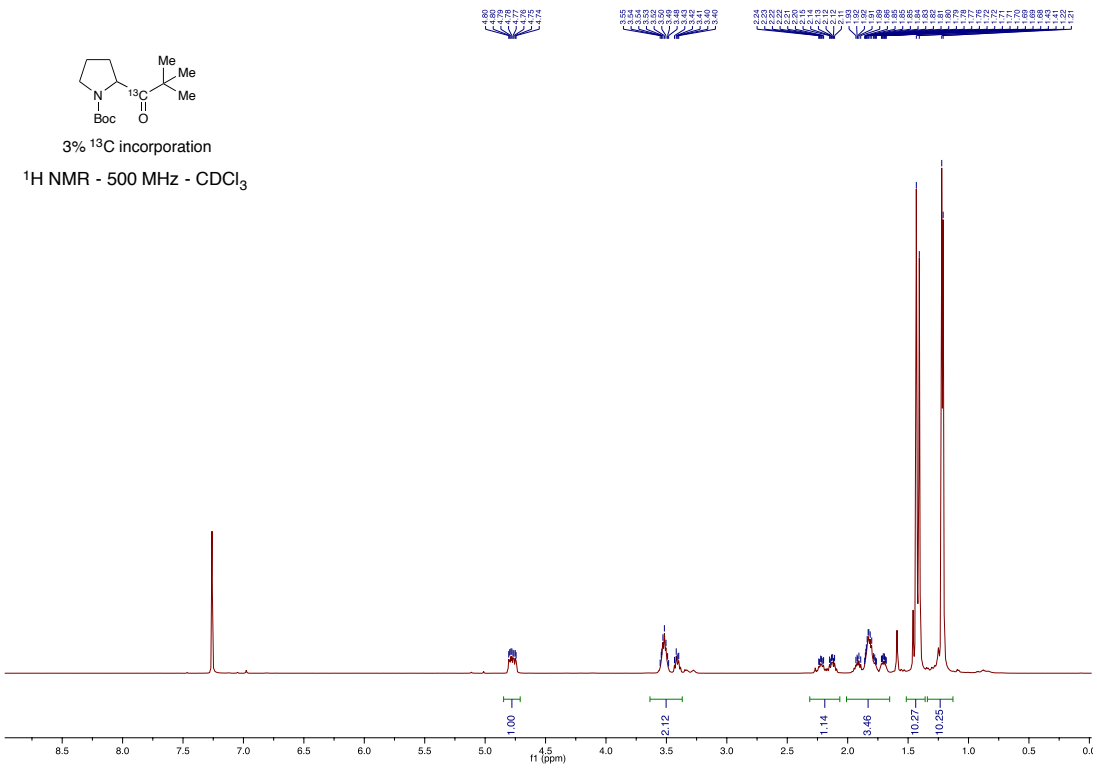
^{13}C NMR - 125 MHz - $CDCl_3$

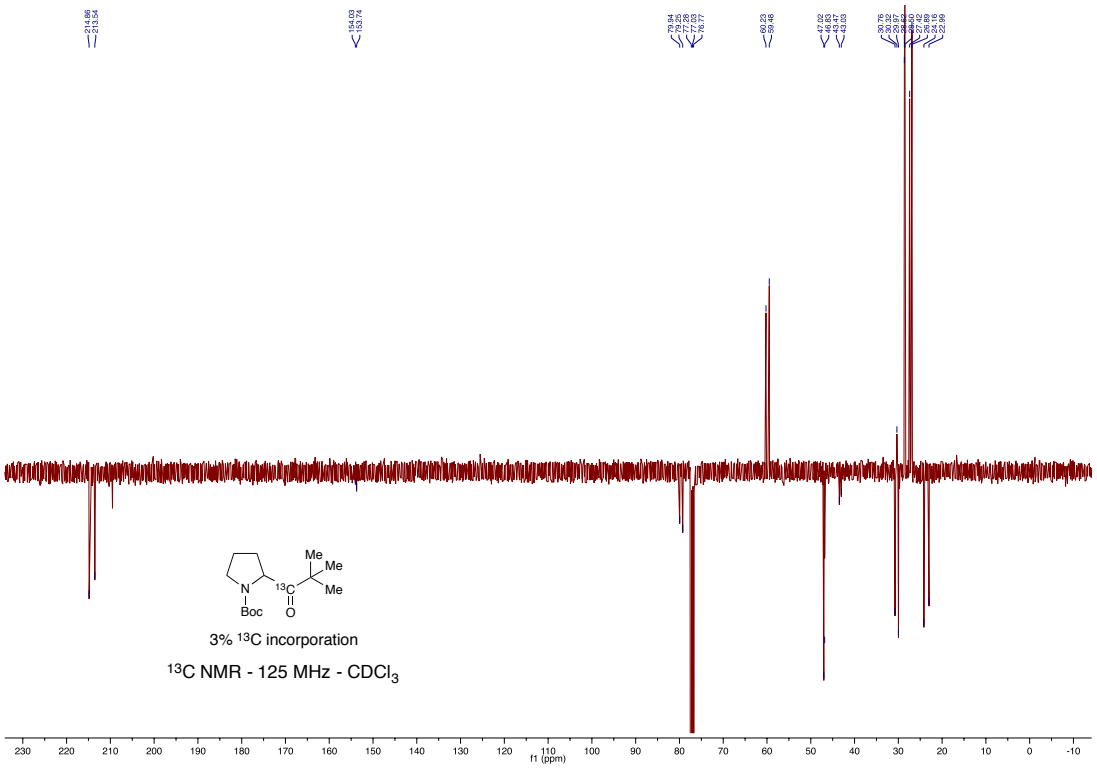

15% ^{13}C incorporation
^{1}H NMR - 500 MHz - $CDCl_3$

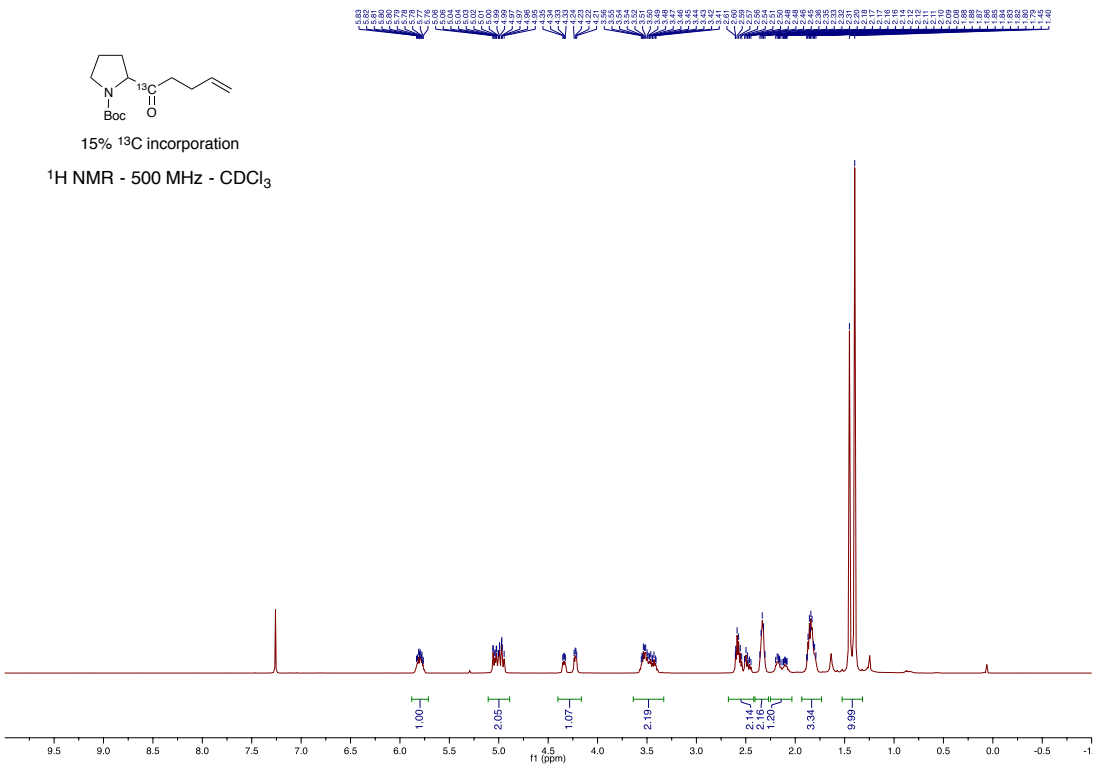

15% ^{13}C incorporation
^{13}C NMR - 125 MHz - $CDCl_3$

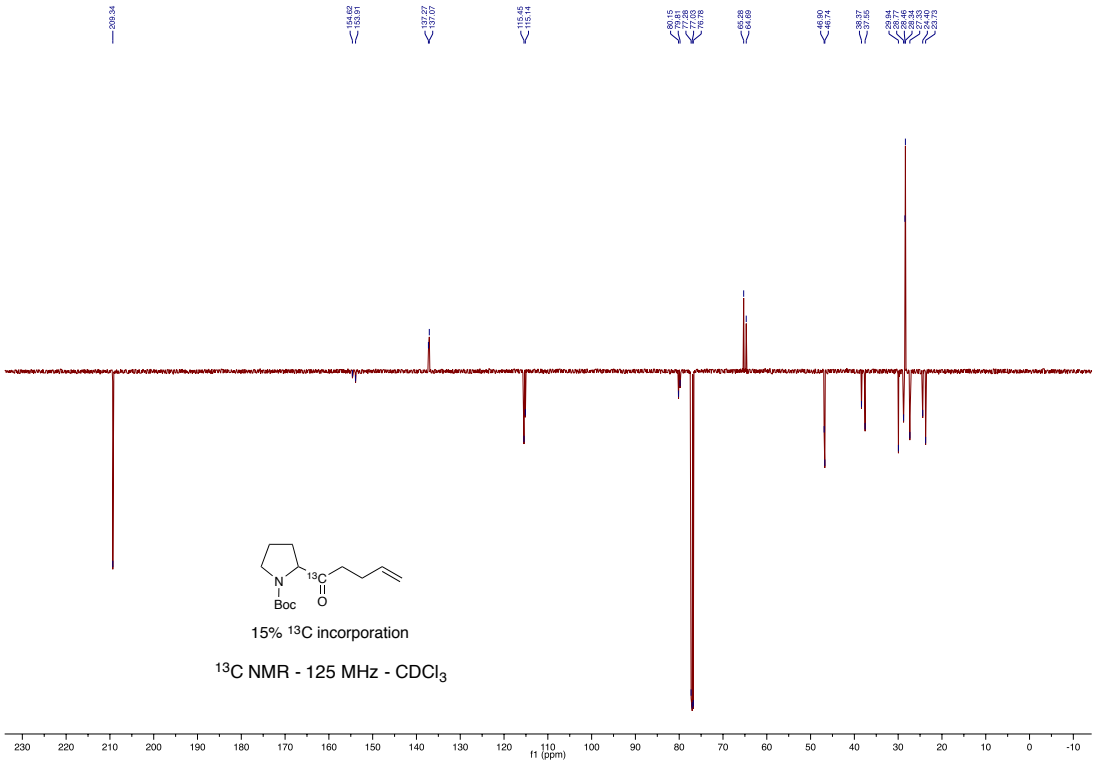

Boc
6% 13C incorporation
1H NMR - 500 MHz - CDCl3
f1 (ppm)

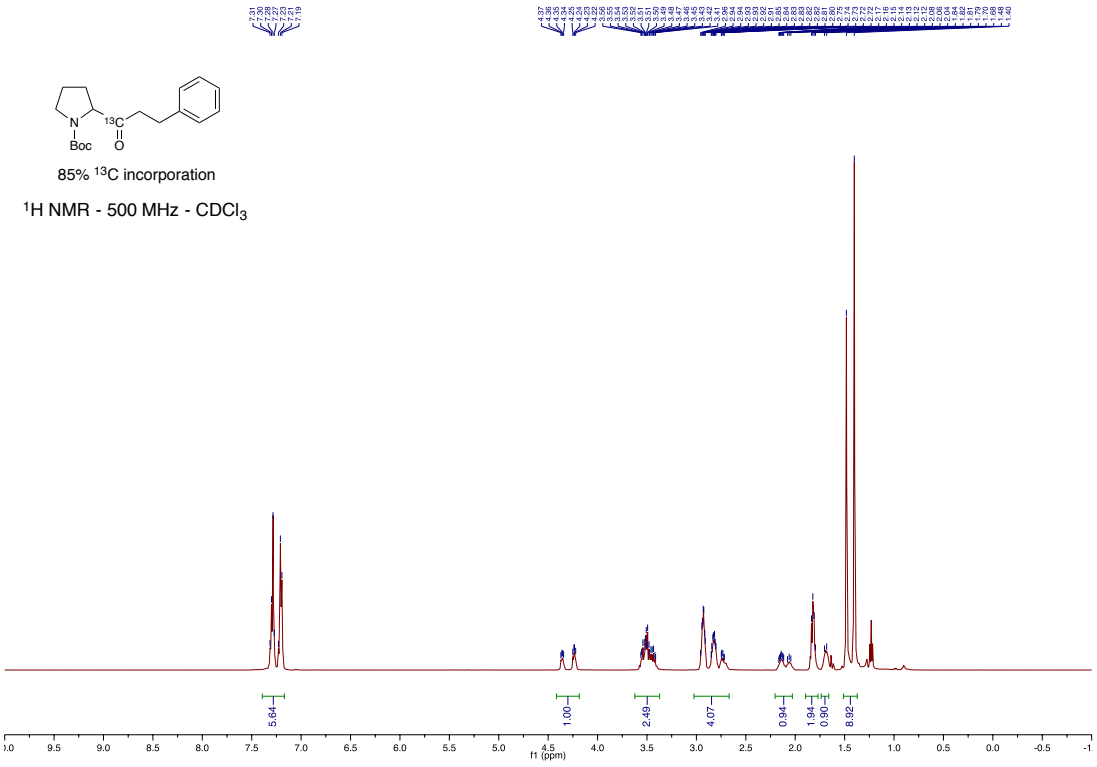

Boc
6% 13C incorporation
13C NMR - 125 MHz - CDCl3
f1 (ppm)

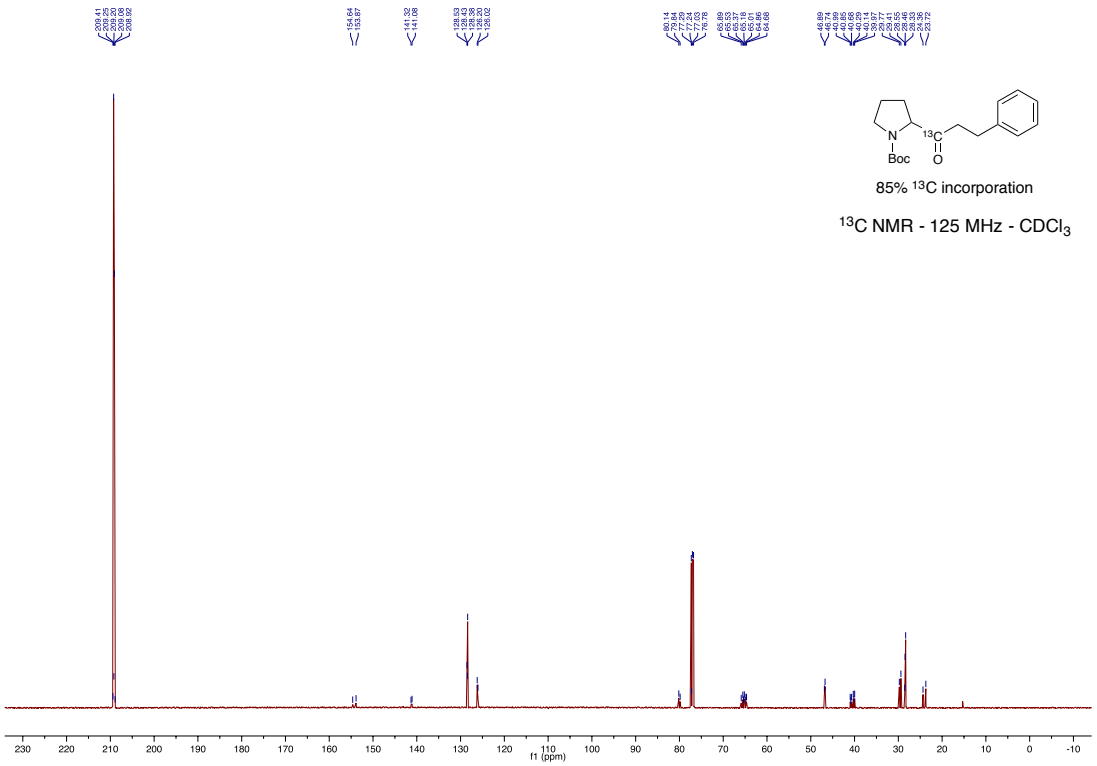

Me
Me
Me
N
13C
O
Boc
3% 13C incorporation
1H NMR - 500 MHz - CDCl3
1.00
2.12
1.14
3.46
10.27
10.25
f1 (ppm)

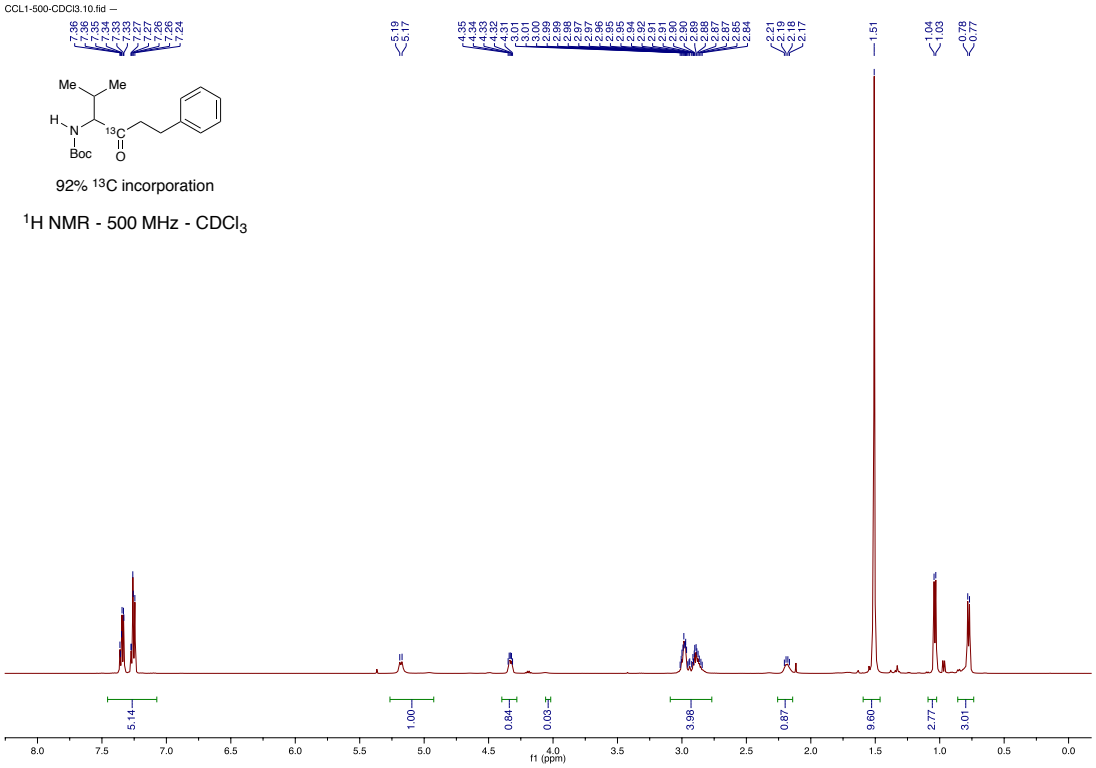

Me
Me
Me
N
13C
O
Boc
3% 13C incorporation
13C NMR - 125 MHz - CDCl3
f1 (ppm)

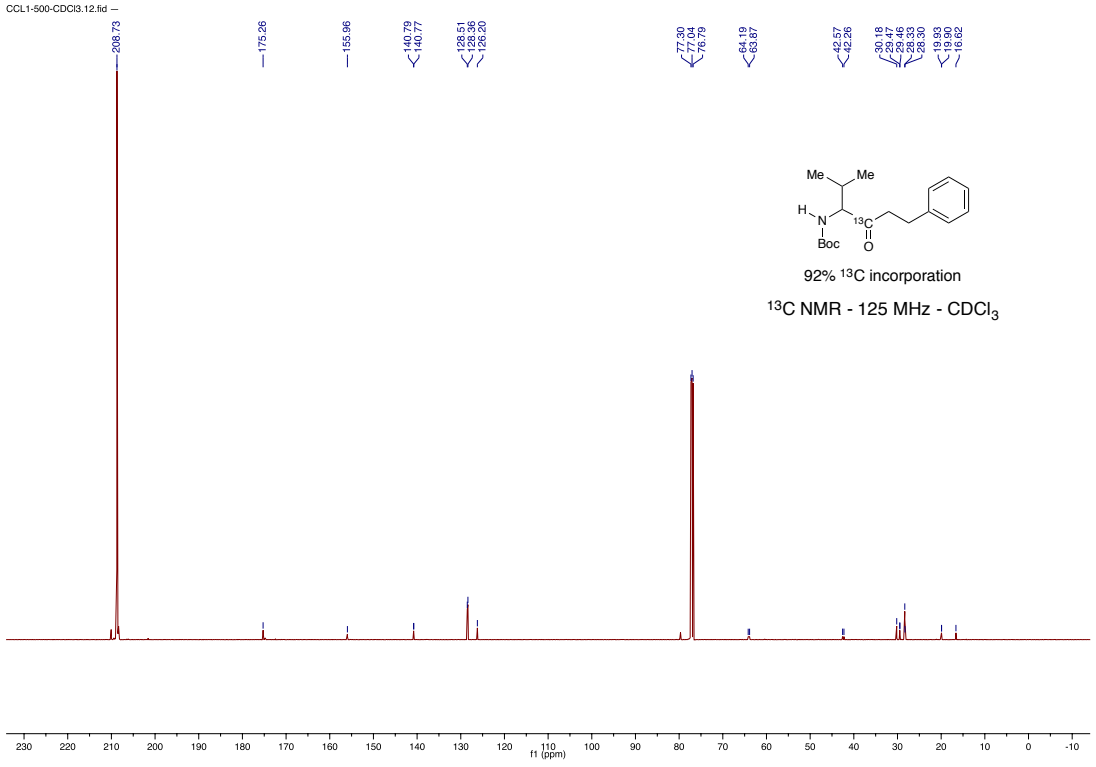

Boc
15% 13C incorporation
1H NMR - 500 MHz - CDCl3
1.00
2.05
1.07
2.19
2.14
2.16
1.20
3.34
9.99
f1 (ppm)

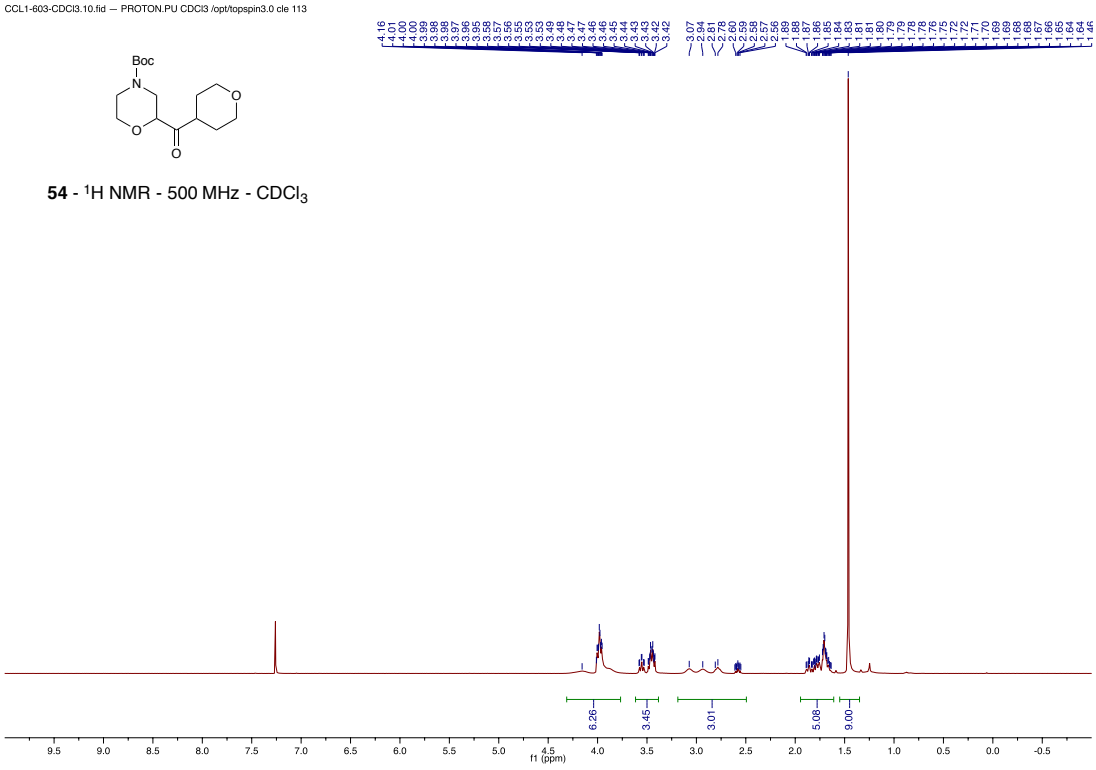

Boc
15% 13C incorporation
13C NMR - 125 MHz - CDCl3
f1 (ppm)


Boc
85% 13C incorporation
1H NMR - 500 MHz - CDCl3
5.64
1.00
2.49
4.07
0.94
1.94
0.90
8.92
f1 (ppm)

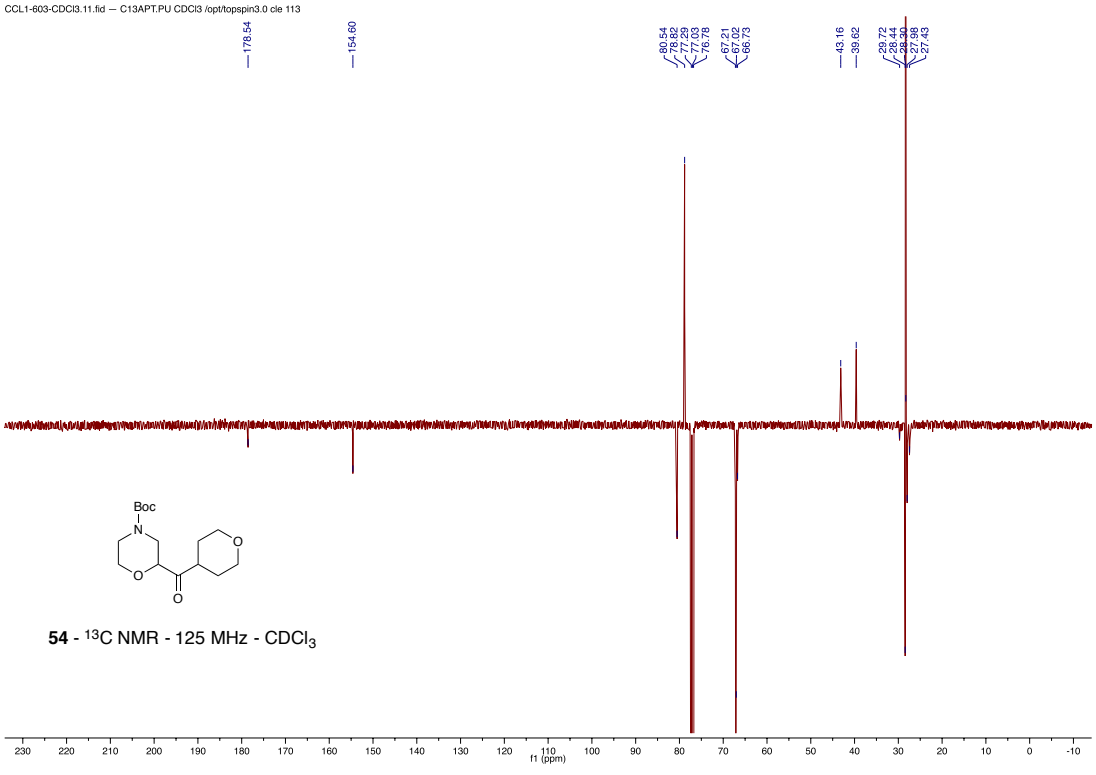

Boc
85% 13C incorporation
13C NMR - 125 MHz - CDCl3
f1 (ppm)


CCL1-500-CDCl3.10.fid
Me
Me
H
N
Boc
13C
O
92% 13C incorporation
1H NMR - 500 MHz - CDCl3
f1 (ppm)

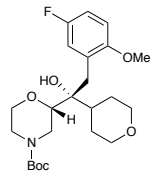

CCL1-500-CDCl3.12.fid
Me
Me
H
N
Boc
13C
O
92% 13C incorporation
13C NMR - 125 MHz - CDCl3
f1 (ppm)



54 - ^{1}H NMR - 500 MHz - $CDCl_3$

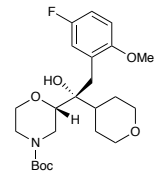


54 - ^{13}C NMR - 125 MHz - $CDCl_3$



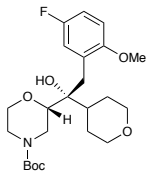
racemic

^{1}H NMR - 500 MHz - $CDCl_3$



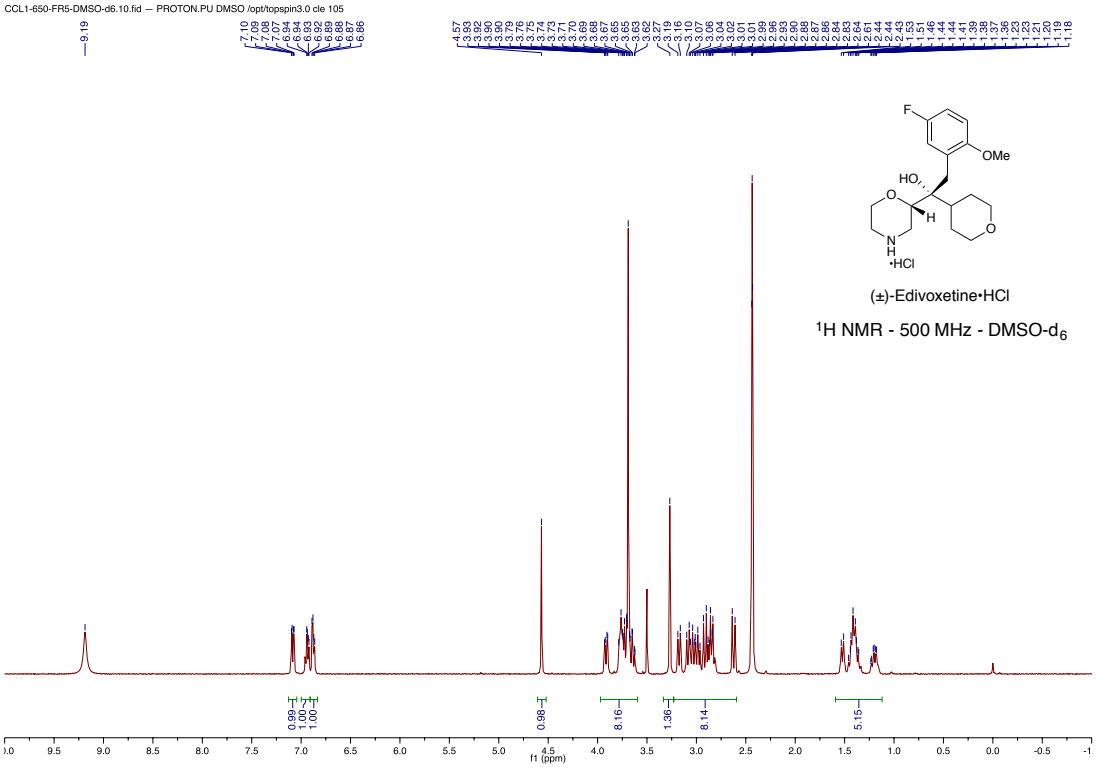
racemic

^{13}C NMR - 125 MHz - $CDCl_3$



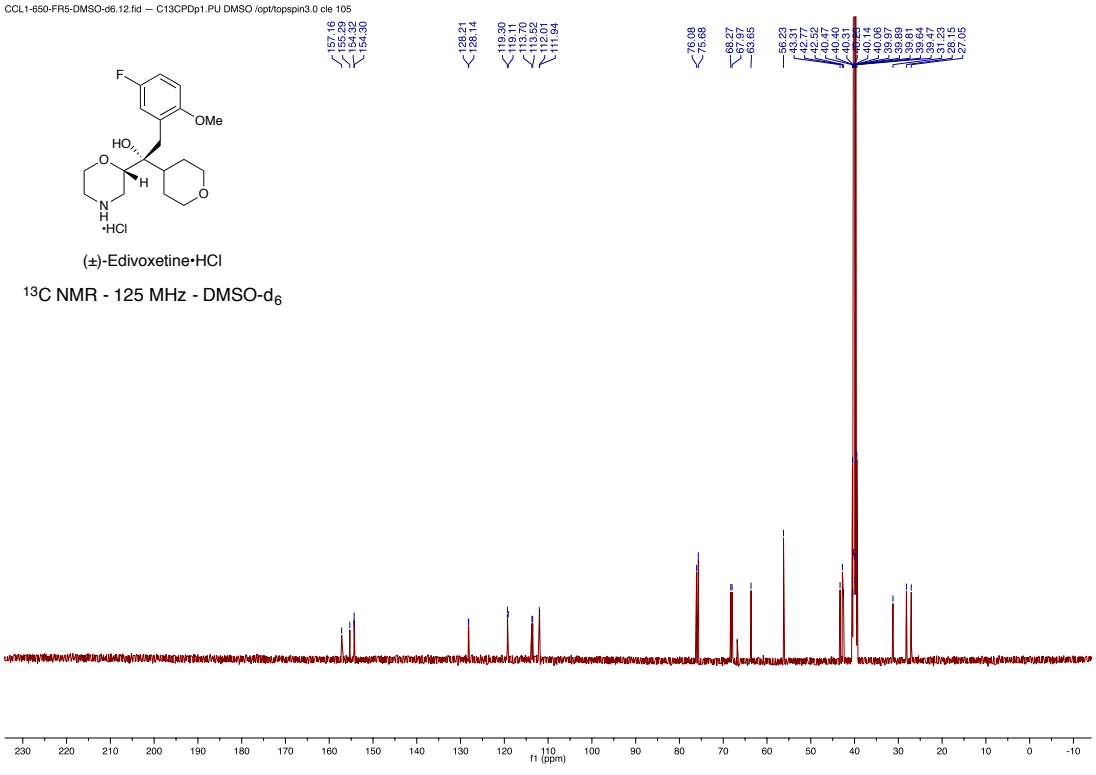
racemic

^{19}F NMR - 282 MHz - $CDCl_3$



(±)-Edivoxetine•HCl

^{1}H NMR - 500 MHz - DMSO-d_6



(±)-Edivoxetine•HCl

^{13}C NMR - 125 MHz - DMSO-d_6