

Supporting Information

**Dearomatization of Unactivated Arenes via Catalytic Hydroalkylation**

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<b>I.</b>	<b>General Information.....</b>	<b>S-1</b>
	I-A. General Reagent Information.....	S-1
	I-B. General Analytical Information.....	S-1
	I-C. Abbreviations.....	S-1
	I-D. General Photoredox Reaction Setup.....	S-2
<b>II.</b>	<b>General Procedures.....</b>	<b>S-3</b>
	II-A. General reductive amination procedure.....	S-3
	II-B. General acylation procedure.....	S-3
	II-C. General dearomative spirolactamization procedure 1.....	S-3
	II-C. General dearomative spirolactamization procedure 2.....	S-3
<b>III.</b>	<b>Optimization Details.....</b>	<b>S-4</b>
	III-A. Optimization Procedure.....	S-4
	III-B. Optimization Table.....	S-4
<b>IV.</b>	<b>Deuterium Labeling Study.....</b>	<b>S-5</b>
<b>V.</b>	<b>Electrochemical Measurements.....</b>	<b>S-5</b>
<b>VI.</b>	<b>Computational Details.....</b>	<b>S-8</b>
<b>VII.</b>	<b>Preparation of Starting Materials.....</b>	<b>S-21</b>
<b>VIII.</b>	<b>Preparation of Spirolactam Products.....</b>	<b>S-39</b>
	VIII-A. Derivatization.....	S-54
<b>IX.</b>	<b>NMR Spectra.....</b>	<b>S-58</b>

## I. General Information

### I-A. General Reagent Information

Solvents used in anhydrous reactions were purified by passing over activated alumina and storing under argon. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Combi-Blocks, Oakwood Chemicals, Astatech, and TCI America and used as received, unless stated otherwise. Organic solutions were concentrated under reduced pressure on a rotary evaporator using a water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on 230–400 mesh silica gel. Preparative thin-layer chromatography (PTLC) separations were carried out on 1000  $\mu\text{m}$  SiliCycle silica gel F-254 plates. Thin-layer chromatography (TLC) was performed on 250  $\mu\text{m}$  SiliCycle silica gel F-254 plates. Visualization of the developed chromatogram was performed by fluorescence quenching or staining using  $\text{KMnO}_4$ , p-anisaldehyde, or ninhydrin stains. All photoredox reactions were set up on the bench top and conducted under nitrogen atmosphere while subject to irradiation from blue LEDs, unless stated otherwise (LED wholesalers PAR38 Indoor Outdoor 16-Watt LED Flood Light Bulb, Blue; or Hydrofarm® PPB1002 PowerPAR LED Bulb-Blue 15W/E27 (available from Amazon)). Solvent was degassed by sonication under mild vacuum for 15 minutes. Photoredox catalysts 3DPAFIPN, 3DPA2FBN, 5CzBn, 4CzIPN, and  $[\text{Ir}(\text{ppy})_2\text{dtbbpy}]\text{PF}_6$  were prepared according to literature procedures.<sup>1,2</sup>

### I-B. General Analytical Information

Unless otherwise noted, all yields refer to chromatographically and spectroscopically ( $^1\text{H}$  NMR) homogenous materials. New compounds were characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and LRMS.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained from the Emory University NMR facility and recorded on a Bruker Avance III HD 600 equipped with cryo-probe (600 MHz), Bruker NEO 400 (400 MHz), INOVA 600 (600 MHz), INOVA 500 (500 MHz), INOVA 400 (400 MHz), or VNMR 400 (400 MHz) and are internally referenced to residual protio solvent signals. Data for  $^1\text{H}$  NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dtd = doublet of triplet of doublets, b = broad, etc.), coupling constant (Hz), integration, and assignment, when applicable. Data for decoupled  $^{13}\text{C}$  NMR are reported in terms of chemical shift and multiplicity when applicable. Gas Chromatography Mass Spectrometry (GCMS) was performed on an Agilent 5977A mass spectrometer with an Agilent 7890A gas chromatography inlet. Liquid Chromatography Mass Spectrometry (LCMS) was performed on an Agilent 6120 mass spectrometer with an Agilent 1220 Infinity liquid chromatography inlet.

### I-C. Abbreviations

CV = cyclic voltammogram

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM = dichloromethane

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<sup>1</sup> Speckmeier, E.; Fischer, T.; Zeitler, K. A Toolbox Approach to Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor-Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018**, *140*, 15354–15365.

<sup>2</sup> Slinker, J. D.; Gorodetsky, A. A.; Lowry, M. S.; Wang, J.; Parker, S.; Rohl, R.; Bernhard, S.; Malliaras, G. G. Efficient Yellow Electroluminescence from a Single Layer of a Cyclometalated Iridium Complex. *J. Am. Chem. Soc.* **2004**, *126*, 2763–2767.

DIPEA = diisopropylethylamine  
Et<sub>2</sub>O = diethyl ether  
EtOAc = ethyl acetate  
GCMS = gas chromatography mass spectrometry  
HPLC = high performance liquid chromatography  
LCMS = liquid chromatography mass spectrometry  
*m*CPBA = *meta*-chloroperoxybenzoic acid  
MeCN = acetonitrile  
MeOH = methanol  
SCE = saturated calomel electrode  
TFA = trifluoroacetic acid  
THF = tetrahydrofuran  
TLC = thin layer chromatography

#### I-D. General Photoredox Reaction Setup

To run multiple reactions (for optimization), an appropriately sized 3D printed carousel was used, which exposed the reactions to the blue light evenly (photo 1). A 15 W LED array lamp was used as a blue light source (photo 2,3). These lamps were routinely used for up to 12 reactions at a time (photo 2,3). The reactions were cooled with a line of compressed air (photo 2,3). The blue LEDs were positioned approximately 6 inches above the reaction vials to get good light coverage without overheating the reactions (photo 2,3). Reactions run at elevated temperatures were irradiated in a shallow oil bath (photo 4,5).

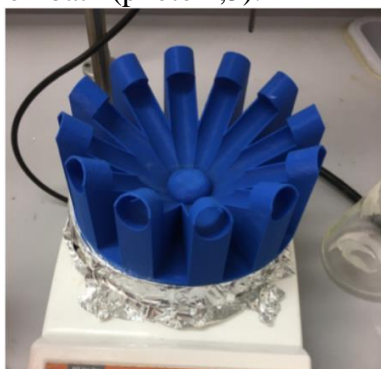


Photo 1



Photo 2



Photo 3

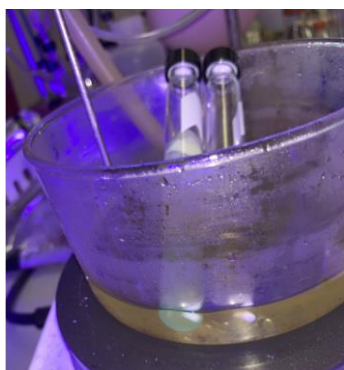


Photo 4



Photo 5

## II. General Procedures

### II-A. General Reductive Amination Procedure

To a round bottomed flask charged with benzaldehyde (1.0 equiv) was added MeOH (0.2 M) and primary amine. After stirring for 2-16 hours, NaBH<sub>4</sub> (1.5 equiv) was added slowly, and the resultant mixture was stirred until bubbling ceased. The reaction mixture was quenched with 1 M NaOH (aq) and extracted with EtOAc (3x). The combined organic layers were washed with 1 M HCl (aq), and the resulting aqueous layer was brought to pH 14 with 2 M NaOH (aq) or 50% KOH (aq) and extracted with EtOAc (3x). The combined organic layers were dried over MgSO<sub>4</sub> or Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to afford the desired product.

### II-B. General Acylation Procedure

To a round bottomed flask charged with secondary amine (1.0 equiv) was added CH<sub>2</sub>Cl<sub>2</sub> (0.1 M), Et<sub>3</sub>N (1.2 equiv), and chloroacetyl chloride (1.2 equiv). After stirring for 1-2 hours, the reaction mixture was quenched with MeOH, diluted with H<sub>2</sub>O, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x). The combined organic layers were dried over MgSO<sub>4</sub> or Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified on silica using the indicated solvent mixture, if necessary, to afford the desired product.

### II-C. General Dearomative Spirolactamization Procedure 1

A 20 mL screw-top test tube was charged with 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), and substrate (0.5 mmol, 1.0 equiv). The tube was equipped with a stir bar and sealed with a PTFE/silicon septa. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv) was added via syringe, followed by degassed solvent (5 mL of each MeCN and H<sub>2</sub>O to give a 0.05 M solution). The resulting mixture was stirred at 50 °C for 16 h under irradiation by blue LEDs, unless noted otherwise. The reaction was then extracted with EtOAc (3x), dried over MgSO<sub>4</sub> or Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude residue was purified as indicated to afford the desired product (1,4-diene products stain strongly with KMnO<sub>4</sub>).

### II-D. General Dearomative Spirolactamization Procedure 2

A 20 mL screw-top test tube was charged with 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), and substrate (0.5 mmol, 1.0 equiv). The tube was equipped with a stir bar and sealed with a PTFE/silicon septa. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv) was added via syringe, followed by degassed solvent (5 mL of each MeCN and H<sub>2</sub>O to give a 0.05 M solution). The resulting mixture was stirred at 50 °C for 16 h under irradiation by blue LEDs, unless noted otherwise. The reaction was then extracted with EtOAc (3x), dried over MgSO<sub>4</sub> or Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. In order to deprotect the HDH byproduct that is sometimes difficult to separate from the dearomatized product via chromatography, the crude residue was dissolved in 50% (v/v) TFA/CH<sub>2</sub>Cl<sub>2</sub> (0.1 M) for 16 hours. The reaction was quenched with saturated NaHCO<sub>3</sub> (aq) then extracted with EtOAc (3x), dried over MgSO<sub>4</sub> or Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude residue was purified as indicated to afford the desired product (1,4-diene products stain strongly with KMnO<sub>4</sub>).



### III. Optimization Details

#### III-A. Optimization Procedure

An 8 mL screw-top test tube was charged with photocatalyst (0.005 mmol, 5 mol%) and *N*-benzyl-*N*-(*tert*-butyl)-2-chloroacetamide (**S39**) (24.0 mg, 0.1 mmol, 1.0 equiv). The tube was equipped with a stir bar and sealed with a PTFE/silicon septa. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, DIPEA (52  $\mu$ L, 0.3 mmol, 3 equiv) was added via syringe, followed by degassed solvent. The resulting mixture was stirred at the indicated temperature for 16 h under irradiation by blue LEDs, unless noted otherwise. The reaction was then extracted with ethyl acetate (3x) and concentrated under reduced pressure. CDCl<sub>3</sub> and an internal standard of dibromomethane (7  $\mu$ L, 0.1 mmol) were added. The sample was analyzed by <sup>1</sup>H NMR (d1 = 5 s), and the integral values were used to calculate the data given in the Optimization Table.

#### III-B. Optimization Table

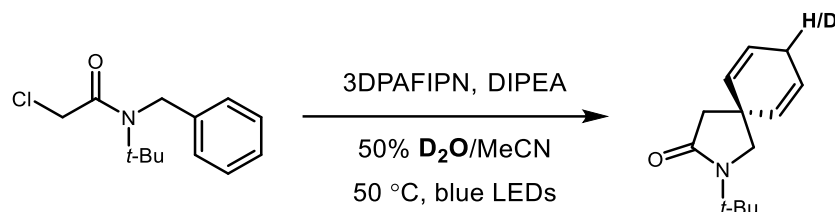
	<b>S39</b>		<b>19</b>	<b>HDH</b>	<b>Dimer</b>			
Entry	PC	Concentration	Temperature	% water	S39	19	HDH	Dimer
1	3DPAFIPN	0.05 M	23 °C	50%	-	74	25	-
2	3DPA2FBN	0.05 M	23 °C	50%	-	29	14	44
3	5CzBN	0.05 M	23 °C	50%	-	34	65	-
4	4CzIPN	0.05 M	23 °C	50%	78	16	7	-
5	[Ir(ppy) <sub>2</sub> dtbbpy]PF <sub>6</sub>	0.05 M	23 °C	50%	-	42	58	-
6	3DPAFIPN	0.1 M	23 °C	50%	-	67	31	-
7	3DPAFIPN	0.033 M	23 °C	50%	-	74	24	-
8	3DPAFIPN	0.05 M	0 °C	50%	-	52	50	-
9	3DPAFIPN	0.05 M	40 °C	50%	-	79	21	-
<b>10</b>	<b>3DPAFIPN</b>	<b>0.05 M</b>	<b>50 °C</b>	<b>50%</b>	-	<b>83</b>	<b>18</b>	-
								<b>optimized conditions</b>
11	3DPAFIPN	0.05 M	60 °C	50%	-	79	19	-
12	3DPAFIPN	0.05 M	50 °C	0%	-	42	57	-
13	3DPAFIPN	0.05 M	50 °C	10%	-	39	60	-
14	3DPAFIPN	0.05 M	50 °C	25%	-	54	44	-
<b>controls</b>								
15	-	0.05 M	23 °C	25%	100	-	-	-
								<b>no PC</b>
16	3DPAFIPN	0.05 M	23 °C	25%	97	-	-	-
								<b>no reductant</b>
17	3DPAFIPN	0.05 M	23 °C	25%	99	-	-	-
								<b>no light</b>

## VI. Deuterium Labeling Study

### General Deuterium Labeling Procedure

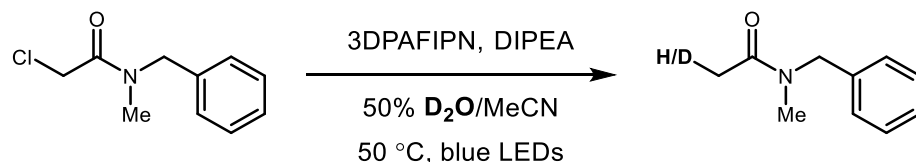
An 8 mL screw-top test tube was charged with 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%) and substrate (0.1 mmol, 1.0 equiv). The tube was equipped with a stir bar and sealed with a PTFE/silicon septa. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, degassed solvent was added via syringe (1 mL of each MeCN and **D**<sub>2</sub>O to give a 0.05 M solution), followed by DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv). The resulting mixture was stirred at 50 °C for 16 h under irradiation by blue LEDs. The reaction was then extracted with ethyl acetate (3x) and concentrated. CDCl<sub>3</sub> was added and the sample was analyzed by <sup>1</sup>H NMR (d1 = 5 s) to determine the % D incorporation at the indicated position.

### Experiment 1 – Deuterium incorporation in dearomatized spirolactam



*N*-benzyl-*N*-(*tert*-butyl)-2-chloroacetamide (**S39**) (24.0 mg) was subjected to the General Deuterium Labeling Procedure. <sup>1</sup>H NMR analysis showed >95% deuterium incorporation.

### Experiment 2 – Deuterium incorporation in hydrodehalogenation byproduct



*N*-benzyl-2-chloro-*N*-methylacetamide (**S39**) (24.0 mg) was subjected to the General Deuterium Labeling Procedure. <sup>1</sup>H NMR analysis showed 88% deuterium incorporation.

## V. Electrochemical Measurements

Electrochemical potentials were obtained with a standard set of conditions according to literature procedure.<sup>3</sup> Cyclic voltammograms (CVs) were collected with a VersaSTAT 4 Potentiostat. Samples were prepared with 0.05 mmol of substrate in 10 mL of 0.1 M tetra-*n*-butylammonium hexafluorophosphate in dry, degassed acetonitrile. Measurements employed a glassy carbon working electrode, platinum wire counter electrode, 3 M NaCl silver-silver chloride reference electrode, and a scan rate of 100 mV/s. Reductions were measured by scanning potentials in the negative direction and oxidations in the positive direction; the glassy carbon electrode was polished between each scan. Data was analyzed using Microsoft Excel by subtracting a background current prior to identifying the maximum current (*C*<sub>p</sub>) and determining the potential

<sup>3</sup> Roth, H. G.; Romero, N. A.; Nicewicz, D. A. Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single-Electron Redox Chemistry. *Synlett*. **2016**, 27, 714-723.

( $E_{p/2}$ ) at half this value ( $C_{p/2}$ ). The obtained value was referenced to Ag | AgCl and converted to SCE by subtracting 0.035 V.

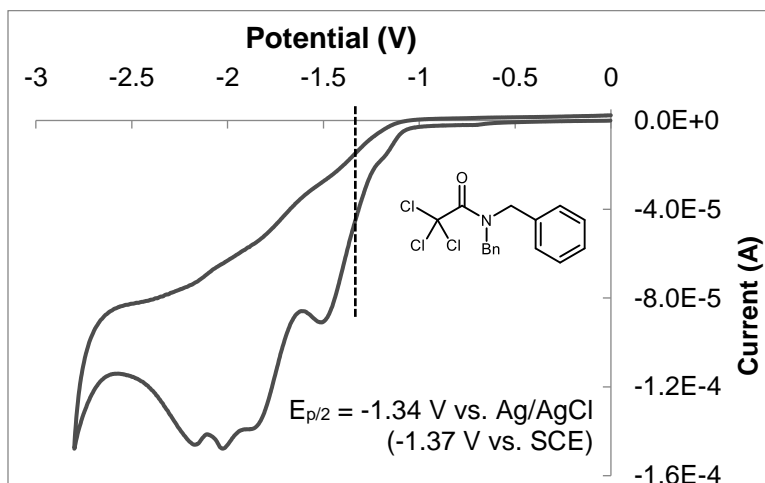


Figure S1: CV of *N,N*-dibenzyl-2,2,2-trichloroacetamide (S50)

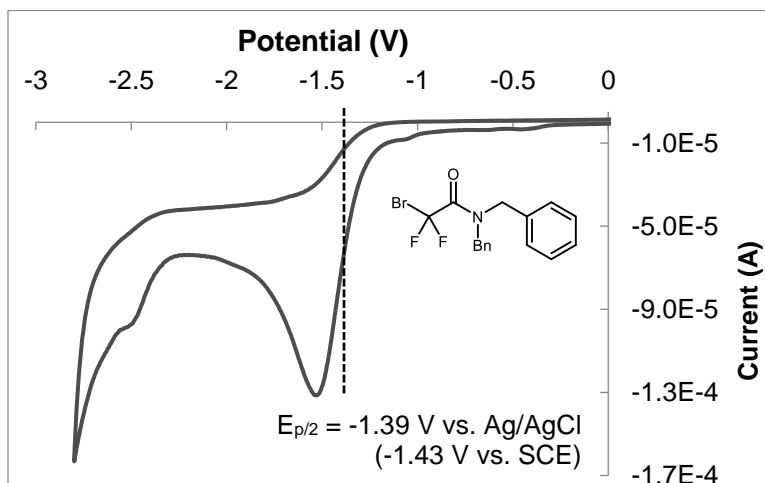


Figure S2: CV of *N,N*-dibenzyl-2-bromo-2,2-difluoroacetamide (S49)

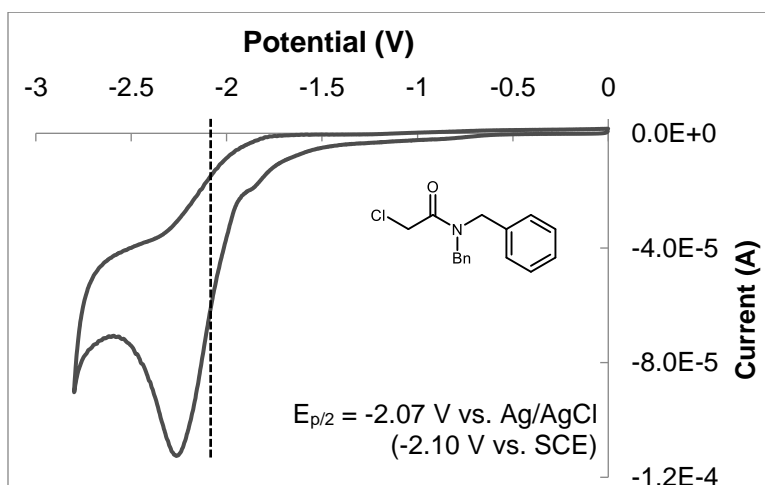
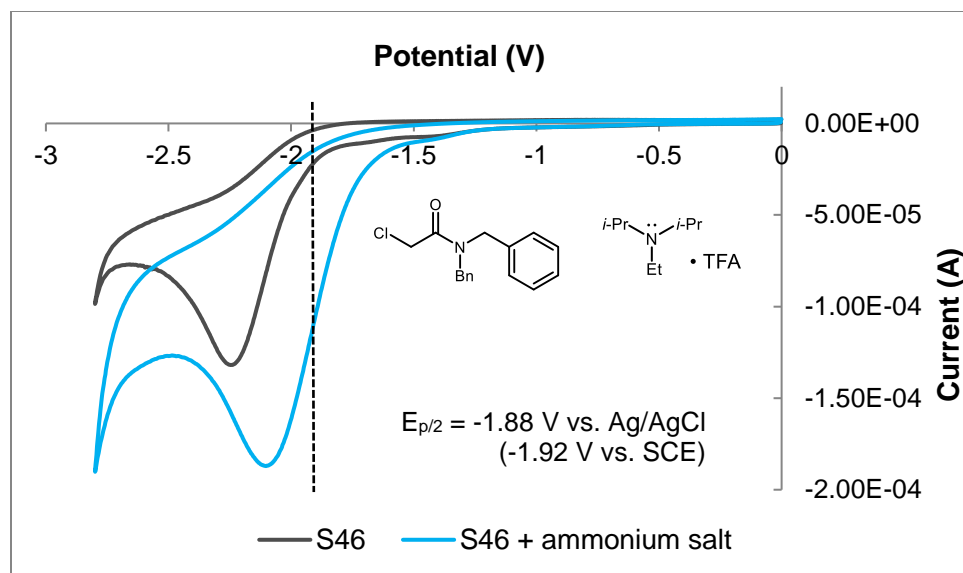
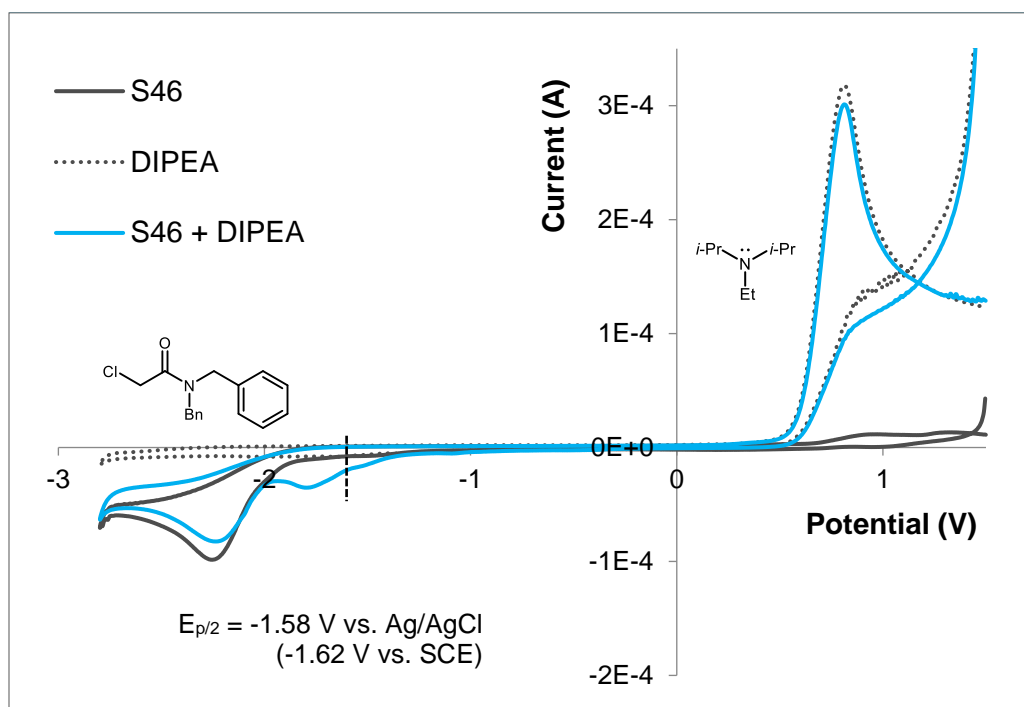


Figure S3: CV of *N,N*-dibenzyl-2-chloroacetamide (S46)



**Figure S4: CV of *N,N*-dibenzyl-2-chloroacetamide (S46) + *i*-Pr<sub>2</sub>NEt • TFA (3 equiv)**



**Figure S5: CV of *N,N*-dibenzyl-2-chloroacetamide (S46) + *i*-Pr<sub>2</sub>NEt (3 equiv)**

## VI. Computational Details

All DFT calculations were carried out using the Gaussian 9 software package<sup>4</sup> at the (U)B3LYP<sup>5</sup> or R(B3LYP)<sup>5</sup> level of theory with the 6-311+G(d,p)<sup>6</sup> basis set. The CPCM formalism for the Self Consistent Reaction Field (SCRF) model of solvation was employed in calculations to account for solvation in MeCN, and the default parameters as implemented in Gaussian were used.

Reduction potentials were calculated using a modified procedure as described by Nicewicz and coworkers.<sup>7</sup> Geometry optimizations were carried out for the reduced and neutral forms of each molecule, and frequency calculations were performed on the minimized structures to ensure no imaginary frequencies existed. Geometry optimizations that did not converge to an energy minimum upon the initial calculation were sequentially optimized using a tight convergence criteria. Gibbs free energies ( $G_{298}$ ) were obtained from the calculation and employed in the following equation:

$$E_{1/2}^{0,calc} = -\frac{(G_{298}[reduced] - G_{298}[oxidized])}{n_e \mathcal{F}} - E_{1/2}^{0,SHE} + E_{1/2}^{0,SCE}$$

Where  $n_e$  is the number of electrons transferred ( $n_e = 1$  for all calculations here),  $\mathcal{F}$  is the Faraday constant (value 23.061 kcal mol<sup>-1</sup> V<sup>-1</sup>),  $E_{1/2}^{0,SHE}$  is the absolute value for the standard hydrogen electrode (SHE, value = 4.281 V) and  $E_{1/2}^{0,SCE}$  is the potential of the saturated calomel electrode (SCE) relative to the SHE in MeCN (value = -0.141 V)<sup>8</sup>, and  $G_{298}[oxidized]$  and  $G_{298}[reduced]$  are the Gibbs free energies in MeCN obtained from DFT calculations.

Steric effects of the arene substituents on cyclization were observed from the minimized geometries of the relevant compounds. The structural minima were visualized using GaussView 5<sup>9</sup> allowing the interatomic distances between the two carbons which form the spirocyclic center to be obtained.

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<sup>4</sup>M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.

<sup>5</sup>(a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B*, **1988**, 37 (2), 785–789. (b) Becke, A. D. *J. Chem. Phys.* **1993**, 98 (7), 5648–5652.

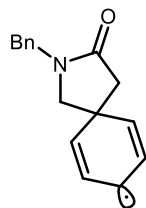
<sup>6</sup> McLean, A. D.; Chandler, G. S. Contracted Gaussian Basis Sets for Molecular Calculations. I. Second Row Atoms, Z=11–18. *J. Chem. Phys.* **1980**, 72, 5639–5648.

<sup>7</sup> Roth, H. G.; Romero, N. A.; Nicewicz, D. A. Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single Electron Redox Chemistry. *Synlett* **2016**, 27 (05), 714–723.

<sup>8</sup> Isse, A. A.; Gennaro, A. Absolute Potential of the Standard Hydrogen Electrode and the Problem of Interconversion of Potentials in Different Solvents. *J. Phys. Chem. B* **2010**, 114 (23), 7894–7899.

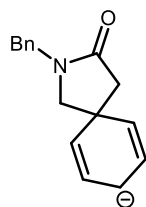
<sup>9</sup> Roy Dennington TK and JM. GaussView, Version 5, Semichem Inc, Shawnee Mission KS, **2009**.

Molecular coordinates of optimized structures:



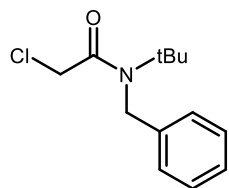
Charge: 0  
 Multiplicity: 2  
 Number of imaginary frequencies: 0  
 Solvation: MeCN  
 $G_{298} = -749.250858$  Hartree

C	-0.67021525	1.67383904	-3.52647222
C	1.62256455	1.29631778	-3.73626915
C	0.07672390	2.37458623	-2.38022356
H	-1.57793076	2.15145972	-3.83115408
H	-0.90383945	0.67001427	-3.23897339
H	1.48810123	0.31261662	-3.33733101
H	2.55355683	1.31829279	-4.26321362
O	-0.45691413	2.90442774	-1.37122951
N	1.53966646	2.32415369	-2.66562245
C	1.99332151	3.62922748	-3.16749843
H	1.41849308	3.89967664	-4.02850339
H	3.02787126	3.56890337	-3.43389629
C	1.80692420	4.69402465	-2.07065614
C	2.83996131	4.94875764	-1.15858849
C	0.60426554	5.40825710	-1.98459730
C	2.67034073	5.91772490	-0.16046362
H	3.75821850	4.40342648	-1.22429734
C	0.43464415	6.37722284	-0.98647109
H	-0.18448079	5.21376361	-2.68098190
C	1.46768203	6.63195728	-0.07440472
H	3.45908884	6.11222174	0.53591803
H	-0.48361187	6.92255620	-0.92076418
H	1.33817319	7.37178573	0.68768538
C	0.41715892	1.68130187	-4.58869847
C	0.60945176	3.15768691	-5.12274815
C	0.13949927	0.65242991	-5.75754249
C	0.94414182	3.32317391	-6.39869152
H	0.51126987	3.99542129	-4.46437028
C	-0.31675236	1.12588223	-6.91301264
H	0.27797525	-0.39785205	-5.60710243
C	0.27516439	2.42711245	-7.42686688
H	1.69198010	4.03440692	-6.68115480
H	-1.10493686	0.62654268	-7.43677329
H	0.22350066	2.69870937	-8.46053316



Charge: -1  
 Multiplicity: 1  
 Number of imaginary frequencies: 0  
 Solvation: MeCN  
 $G_{298} = -749.361362$  Hartree

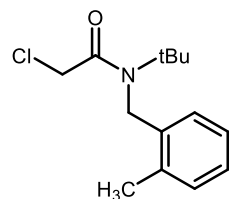
C	-0.67021525	1.67383904	-3.52647222
C	1.62256455	1.29631778	-3.73626915
C	0.07672390	2.37458623	-2.38022356
H	-1.57793076	2.15145972	-3.83115408
H	-0.90383945	0.67001427	-3.23897339
H	1.48810123	0.31261662	-3.33733101
H	2.55355683	1.31829279	-4.26321362
O	-0.45691413	2.90442774	-1.37122951
N	1.53966646	2.32415369	-2.66562245
C	1.99332151	3.62922748	-3.16749843
H	1.41849308	3.89967664	-4.02850339
H	3.02787126	3.56890337	-3.43389629
C	1.80692420	4.69402465	-2.07065614
C	2.83996131	4.94875764	-1.15858849
C	0.60426554	5.40825710	-1.98459730
C	2.67034073	5.91772490	-0.16046362
H	3.75821850	4.40342648	-1.22429734
C	0.43464415	6.37722284	-0.98647109
H	-0.18448079	5.21376361	-2.68098190
C	1.46768203	6.63195728	-0.07440472
H	3.45908884	6.11222174	0.53591803
H	-0.48361187	6.92255620	-0.92076418
H	1.33817319	7.37178573	0.68768538
C	0.41715892	1.68130187	-4.58869847
C	0.60945176	3.15768691	-5.12274815
C	0.13949927	0.65242991	-5.75754249
C	0.94414182	3.32317391	-6.39869152
H	0.51126987	3.99542129	-4.46437028
C	-0.31675236	1.12588223	-6.91301264
H	0.27797525	-0.39785205	-5.60710243
C	0.27516439	2.42711245	-7.42686688
H	1.69198010	4.03440692	-6.68115480
H	-1.10493686	0.62654268	-7.43677329
H	0.22350066	2.69870937	-8.46053316



Charge: 0  
 Multiplicity: 1  
 Solvation: MeCN  
 Number of imaginary frequencies: 0  
 Interatomic Distance: 3.49 Å

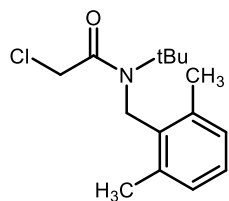
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N	-0.21375667	1.09002359	-0.41560538
C	-2.81505622	1.16126145	-0.25918986
H	-3.16450854	0.16432840	-0.42921214
H	-2.74146226	1.67760837	-1.19346486
Cl	-3.94504256	2.00781660	0.79155999
C	0.84595957	0.35633052	0.29121565
C	0.38046073	-1.08711028	0.55840376
H	1.15181881	-1.62115898	1.07289253
H	0.17044641	-1.57212133	-0.37195008
H	-0.50431405	-1.07096071	1.15991251
C	1.14822317	1.05438379	1.63022959
H	1.91958125	0.52033510	2.14471837
H	0.26344839	1.07053337	2.23173835
H	1.47165419	2.05729396	1.44458591
C	2.11937374	0.33308720	-0.57450723
H	2.89073182	-0.20096150	-0.06001846
H	2.44280476	1.33599736	-0.76015092
H	1.90935943	-0.15192384	-1.50486107
C	-0.50228101	0.42370000	-1.69375505
H	0.38249377	0.40755043	-2.29526381
H	-0.82571202	-0.57921016	-1.50811136
C	-1.61245993	1.19233084	-2.43423422
C	-2.48811378	0.50857202	-3.28841580
C	-1.74706889	2.57554372	-2.25388869
C	-3.49837493	1.20802651	-3.96225391
H	-2.38533832	-0.54754210	-3.42611180
C	-2.75733089	3.27499799	-2.92772574
H	-1.07848790	3.09760871	-1.60170192
C	-3.63298329	2.59123954	-3.78190911
H	-4.16695566	0.68596158	-4.61444100
H	-2.86010661	4.33111204	-2.79002943
H	-4.40433884	3.12528890	-4.29640101





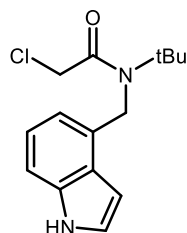
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 Number of imaginary frequencies: 0  
 Solvation: MeCN  
 Interatomic Distance: 3.42 Å

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N	1.03169377	-0.91818165	-0.01085634
C	-1.08513793	0.56414367	0.33270619
H	-1.23097314	1.11340606	-0.57390449
H	-0.44744177	1.12003940	0.98785774
Cl	-2.63967693	0.29771101	1.11374532
C	1.42013417	-1.96127084	-0.97105371
C	2.95439540	-2.09206871	-0.99417094
H	3.23713774	-2.85132411	-1.69309011
H	3.30449213	-2.35723106	-0.01845520
H	3.38756900	-1.15853001	-1.28702948
C	0.91625664	-1.57963532	-2.37535488
H	1.19899898	-2.33889072	-3.07427405
H	1.34943024	-0.64609662	-2.66821341
H	-0.14975603	-1.48875628	-2.35929291
C	0.79668805	-3.30486860	-0.54955638
H	1.07943039	-4.06412400	-1.24847556
H	-0.26932462	-3.21398956	-0.53349441
H	1.14678478	-3.57003094	0.42615936
C	1.62680143	0.36434348	-0.41319471
H	1.27670470	0.62950582	-1.38891045
H	2.69281410	0.27346444	-0.42925668
C	1.21986386	1.45710358	0.59272635
C	1.09241111	2.78690766	0.16928938
C	0.97700342	1.12171120	1.93155147
C	0.72209430	3.78131876	1.08467673
C	0.60668597	2.11612218	2.84693868
H	1.07431902	0.10637671	2.25485557
C	0.47923215	3.44592608	2.42350147
H	0.62478130	4.79665368	0.76137321
H	0.42125398	1.86004221	3.86916078
H	0.19648575	4.20518080	3.12241974
C	1.35929469	3.15547139	-1.30194613
H	1.72782650	4.15848454	-1.35716320
H	0.44934096	3.07862445	-1.85960082
H	2.08614872	2.48538517	-1.71129646



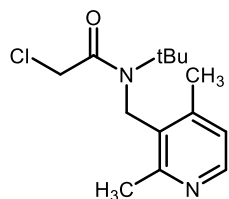
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 Interatomic Distance: 2.91 Å

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N	0.99291720	0.56343212	-0.01084802
C	-1.19361469	1.85342254	0.58186015
H	-1.48812414	2.38725389	-0.29745111
H	-0.53748551	2.46370861	1.16662114
Cl	-2.62102207	1.45127518	1.52969224
C	1.36083931	-0.44177984	-1.01836092
C	0.67065848	-0.10673774	-2.35365012
H	0.93846576	-0.83842258	-3.08700986
H	0.98458438	0.86123309	-2.68438097
H	-0.39061595	-0.11023476	-2.21732540
C	0.90902068	-1.83493418	-0.54235572
H	1.17682788	-2.56661908	-1.27571541
H	-0.15225374	-1.83843116	-0.40603096
H	1.38856193	-2.06772318	0.38541010
C	2.88828097	-0.43674675	-1.21456659
H	3.15608824	-1.16843160	-1.94792629
H	3.36782219	-0.66953570	-0.28680076
H	3.20220688	0.53122407	-1.54529744
C	1.42419860	1.89326126	-0.46521659
H	0.94465737	2.12605024	-1.39298246
H	2.48547299	1.89675826	-0.60154133
C	1.03875641	2.94634046	0.59027312
C	0.74834651	4.25951975	0.19638959
C	0.97841390	2.59146326	1.94465228
C	0.39759530	5.21782213	1.15688535
C	0.62766535	3.54976632	2.90514834
C	0.33725629	4.86294581	2.51126490
H	0.17586062	6.22046358	0.85614650
H	0.58159357	3.27880998	3.93924700
H	0.06944982	5.59463092	3.24462471
C	0.81465566	4.64949437	-1.29193930
H	1.08524402	5.68107847	-1.37863557
H	-0.14199254	4.49242142	-1.74476641
H	1.54678741	4.04593963	-1.78651457
C	1.29754143	1.14840803	2.37749085
H	1.70949193	1.15507812	3.36498888
H	2.00541810	0.72069865	1.69861295
H	0.39944568	0.56680505	2.3696092



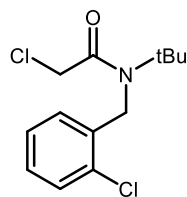
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 Interatomic Distance: 3.41 Å

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O	-1.15791776	0.45474692	0.09581049
N	0.95129954	1.44454317	0.50302599
C	-1.24076953	2.85467982	0.45156918
H	-1.29019019	3.31812571	-0.51158995
H	-0.70944740	3.49197138	1.12718464
Cl	-2.87111364	2.58623869	1.05780137
C	1.49214433	0.34225853	-0.30527808
C	1.15581445	0.58071586	-1.78906391
H	1.54949055	-0.22162741	-2.37742131
H	1.59051752	1.50449655	-2.10931771
H	0.09375155	0.62495983	-1.91139483
C	0.86649699	-0.98729501	0.15564797
H	1.26017309	-1.78963827	-0.43270941
H	-0.19556591	-0.94305104	0.03331709
H	1.10018077	-1.15297640	1.18659006
C	3.02072084	0.27858039	-0.12921309
H	3.41439695	-0.52376286	-0.71757049
H	3.25440467	0.11289902	0.90172898
H	3.45542381	1.20236111	-0.44946690
C	1.54850833	2.71366245	0.06305114
H	1.31482454	2.87934380	-0.96789094
H	2.61057125	2.66941854	0.18538202
C	0.98190907	3.86843687	0.90984587
C	0.85691106	5.15148359	0.38937984
C	0.57797504	3.66702136	2.24537631
C	0.28995697	6.17897067	1.08982434
C	0.07149149	4.75199263	3.00918067
H	0.65659470	2.69506976	2.68586357
C	-0.07451198	6.02921740	2.42534016
H	-0.20387837	4.59989838	4.03189215
H	-0.45919004	6.85348853	2.98881146
C	1.30281089	5.70566587	-0.95218599
H	1.77466013	5.16100102	-1.74313384
C	1.00986056	7.03255115	-0.94292059
H	1.35306981	7.73623853	-1.67225692
N	0.14972544	7.37497755	0.22779087
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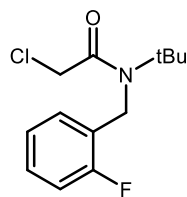
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 Number of imaginary frequencies: 0  
 Solvation: MeCN  
 Interatomic Distance: 2.95 Å

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O	2.78368334	0.66024971	-2.91772923
N	2.95555049	1.83421108	-0.87161220
C	0.65562940	1.05138115	-1.81704346
H	0.20600082	1.90176989	-2.28562977
H	0.37263454	1.02133901	-0.78558266
Cl	0.10916246	-0.41725914	-2.61833592
C	2.12875659	2.88700819	-0.26421602
H	2.68729115	3.38084986	0.50328614
H	1.84790004	3.59695636	-1.01387807
C	4.16382720	2.43521874	-1.45449914
C	5.02999225	1.33228845	-2.09081892
H	5.90948618	1.76975660	-2.51509717
H	4.47145770	0.83844672	-2.85832104
H	5.31084886	0.62234032	-1.34115685
C	3.75960369	3.45701324	-2.53345204
H	4.63909764	3.89448139	-2.95773029
H	3.15778772	4.22333495	-2.09133377
H	3.20106914	2.96317151	-3.30095416
C	4.96769935	3.14598163	-0.34986994
H	5.84719328	3.58344980	-0.77414818
H	5.24855595	2.43603351	0.39979215
H	4.36588336	3.91230333	0.09224833
C	0.86294285	2.25738114	0.34642737
C	-0.32966103	2.99049776	0.41391645
C	0.89268568	0.95148609	0.83775696
C	-0.27219432	0.41145146	1.38462852
C	-1.43705684	1.18968051	1.42674257
H	-0.27597075	-0.58743090	1.76819045
H	-2.33361790	0.78175801	1.84468694
N	-1.43592273	2.44433269	0.94602106
C	-0.37241114	4.43225234	-0.12563537
H	-1.09216047	4.99884195	0.42739004
H	-0.64768225	4.41814592	-1.15952455
H	0.59290631	4.88150770	-0.01965502
C	2.18814983	0.12097726	0.77752642
H	2.20814867	-0.56851182	1.59551472
H	3.03358497	0.77379063	0.84056721
H	2.22281108	-0.41938888	-0.14535116



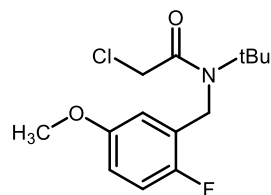
Charge: 0  
 Multiplicity: 1  
 Number of imaginary frequencies: 0  
 Solvation: MeCN  
 Interatomic Distance: 3.42 Å

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O	-1.62020267	-0.87186988	-0.43764791
N	0.46878452	0.16454722	-0.04231174
C	-1.76774614	1.50043808	0.05580161
H	-1.86432111	2.01469876	-0.87753071
H	-1.23465676	2.11684354	0.74917022
Cl	-3.36736441	1.14378531	0.69737794
C	1.01711452	-0.87224924	-0.92847612
C	0.62362710	-0.56330213	-2.38495109
H	1.02275166	-1.31797710	-3.02998230
H	1.01755263	0.39100131	-2.66606963
H	-0.44282009	-0.54827252	-2.47076771
C	0.45015628	-2.24573269	-0.52387561
H	0.84928084	-3.00040766	-1.16890682
H	-0.61629092	-2.23070308	-0.60969223
H	0.72355338	-2.46039075	0.48809077
C	2.55200114	-0.89388064	-0.80496435
H	2.95112570	-1.64855561	-1.44999557
H	2.82539824	-1.10853870	0.20700202
H	2.94592667	0.06042280	-1.08608289
C	1.00997194	1.47559960	-0.42852132
H	0.73657483	1.69025766	-1.44048770
H	2.07641913	1.46056999	-0.34270470
C	0.43553098	2.56176732	0.49984136
C	0.25787743	3.86791526	0.02409065
C	0.09044326	2.24403201	1.82040211
C	-0.26486135	4.85632852	0.86890149
C	-0.43229680	3.23244494	2.66521254
H	0.22608547	1.24675902	2.18364826
C	-0.60994818	4.53859343	2.18946253
H	-0.40050316	5.85360161	0.50565546
H	-0.69577712	2.98984744	3.67349056
H	-1.00906898	5.29326936	2.83449495
Cl	0.69126501	4.26695399	-1.63438555



Charge: 0  
 Multiplicity: 1  
 Number of imaginary frequencies: 0  
 Solvation: MeCN  
 Interatomic Distance: 3.43 Å

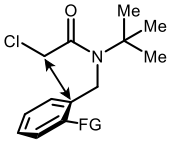
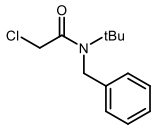
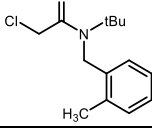
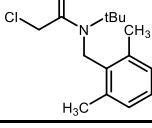
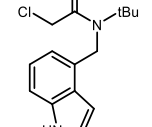
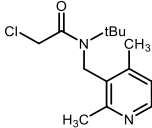
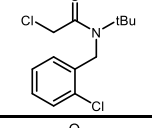
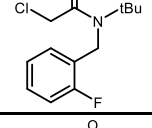
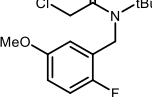
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O	-1.18280256	-0.82303094	0.78775079
N	0.85162121	0.35651459	0.53454962
C	1.42378791	-0.94638530	0.16579882
C	0.94481915	-1.33665208	-1.24483252
H	1.36129423	-2.28502138	-1.51324297
H	1.26359618	-0.59537172	-1.94753064
H	-0.12322293	-1.40072250	-1.25383794
C	0.96498733	-2.01327478	1.17715873
H	1.38146241	-2.96164409	0.90874829
H	-0.10305474	-2.07734521	1.16815331
H	1.29777731	-1.74211540	2.15727271
C	2.96096997	-0.85417179	0.17875989
H	3.37744504	-1.80254109	-0.08965056
H	3.29375994	-0.58301240	1.15887387
H	3.27974699	-0.11289143	-0.52393824
C	1.28956721	1.37490909	-0.43083939
H	0.95677723	1.10374971	-1.41095337
H	2.35760929	1.43897952	-0.42183398
C	-1.45885082	1.51205963	0.18421457
H	-1.63090453	1.55026933	-0.87117045
H	-0.93494532	2.39269024	0.49229369
Cl	-3.00121129	1.42191558	1.02718446
C	0.69015448	2.73985183	-0.04452903
C	0.40768852	3.68743915	-1.03761171
C	0.42715486	3.03436241	1.30009608
C	-0.13777457	4.92953807	-0.68606902
C	-0.11830950	4.27646080	1.65163863
H	0.64282365	2.31085836	2.05833672
C	-0.40077329	5.22404901	0.65855618
H	-0.35344298	5.65304227	-1.44430962
H	-0.31911375	4.50132690	2.67828993
H	-0.81724459	6.17241986	0.92696703
F	0.66103916	3.40372938	-2.33291948

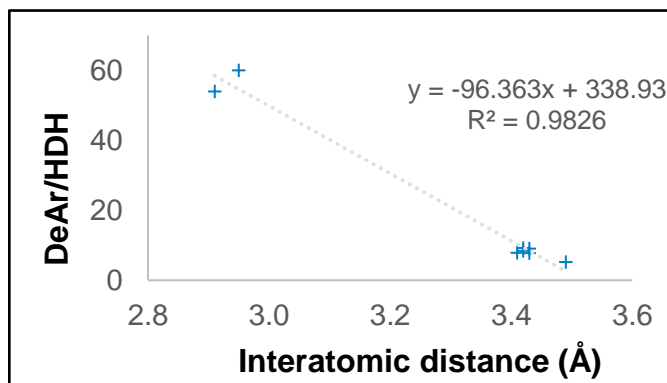


Charge: 0  
 Multiplicity: 1  
 Number of imaginary frequencies: 0  
 Solvation: MeCN  
 Interatomic Distance: 3.43 Å

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C	1.43849310	-0.90045013	0.20039280
C	0.85021447	-1.29270053	-1.16769633
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C	2.97463829	-0.85083005	0.10346084
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C	0.14701590	4.37918311	1.72402826
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C	0.17093435	6.10760855	3.29407287
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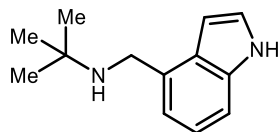
A screw-top test tube was charged with 3DPAFIPN (5 mol%) and the substrate (1.0 equiv). The tube was equipped with a stir bar and sealed with a PTFE/silicon septa. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, DIPEA (3 equiv) was added via syringe, followed by degassed solvent. The resulting mixture was stirred at 50 °C for 16 h under irradiation by blue LEDs. The reaction was then extracted with ethyl acetate (3x) and concentrated under reduced pressure. CDCl<sub>3</sub> and an internal standard of dibromomethane (1 equiv) were added. The sample was analyzed by <sup>1</sup>H NMR (d1 = 5 s), and the integral values were used to calculate the ratio of dearomatized product to hydrodehalogenation

Substrate	 Interatomic distance (Å)	DeAr/HDH ( <sup>1</sup> H NMR)
	3.49	5.2
	3.42	9.3
	2.91	54
	3.41	7.9
	2.95	60
	3.42	8.4
	3.43	9.1
	3.43	7.8





## VII. Preparation of Starting Materials



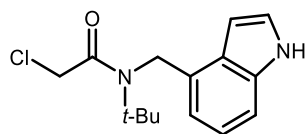
### ***N*-((1*H*-indol-4-yl)methyl)-2-methylpropan-2-amine (S1):**

Prepared according to General Reductive Amination Procedure. Indole-4-carboxaldehyde (435 mg, 3.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.38 mL, 3.6 mmol, 1.2 equiv) were stirred in MeOH (15 mL, 0.2 M) for 16 hours. After NaBH<sub>4</sub> (170 mg, 4.5 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 30 min. The title compound was obtained as a light-brown amorphous solid (607 mg, 100%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.24 (br s, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.18 – 7.08 (m, 2H), 6.65 (ddd, *J* = 3.2, 2.1, 1.0 Hz, 1H), 4.04 (s, 2H), 1.25 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>)  $\delta$  136.1, 133.3, 127.1, 124.0, 122.4, 119.40 110.0, 100.9, 51.0, 45.3, 29.3 ppm.

**LRMS (EI)** *m/z*: [M]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>, 202.2, found 202.2.



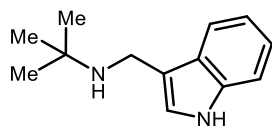
### ***N*-((1*H*-indol-4-yl)methyl)-*N*-(*tert*-butyl)-2-chloroacetamide (S2):**

Prepared according to General Acylation Procedure. *N*-((1*H*-indol-4-yl)methyl)-2-methylpropan-2-amine (S1) (474 mg, 2.3 mmol, 1.0 equiv), Et<sub>3</sub>N (0.39 mL, 2.8 mmol, 1.2 equiv), and chloroacetyl chloride (0.19 mL, 2.3 mmol, 1.0 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (23 mL, 0.1 M) for 30 minutes. Purification on silica gel (30% EtOAc/hexanes) afforded the title compound as a light-brown amorphous solid (535 mg, 83%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.41 (br s, 1H), 7.36 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.29 (dd, *J* = 3.3, 2.4 Hz, 1H), 7.21 (dd, *J* = 8.2, 7.3 Hz, 1H), 6.98 (dq, *J* = 7.2, 1.0 Hz, 1H), 6.56 (ddd, *J* = 3.1, 2.0, 1.0 Hz, 1H), 4.92 (s, 2H), 4.01 (s, 2H), 1.51 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>)  $\delta$  168.0, 135.9, 130.4, 124.7, 124.7, 122.6, 116.1, 110.6, 99.9, 58.8, 46.9, 44.5, 28.5 ppm.

**LRMS (EI)** *m/z*: [M]<sup>+</sup> calc'd. for C<sub>15</sub>H<sub>19</sub>ClN<sub>2</sub>O, 278.1, found 278.1.



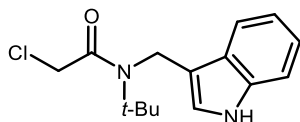
### ***N*-((1*H*-indol-3-yl)methyl)-2-methylpropan-2-amine (S3):**

Prepared according to General Reductive Amination Procedure. Indole-3-carbaldehyde (871 mg, 6.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.76 mL, 7.2 mmol, 1.2 equiv) were stirred in MeOH (30 mL, 0.2 M) for 16 hours. After NaBH<sub>4</sub> (340 mg, 9.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 4 hours. The title compound was obtained as an off-white amorphous solid (627 mg, 52%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 8.11 (br s, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 2.3 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 3.96 (s, 2H), 1.25 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 136.6, 127.2, 122.5, 122.2, 119.6, 118.9, 115.9, 111.4, 50.8, 38.1, 29.2 ppm.

**LRMS (APCI)** m/z: [M+1]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>, 203.2, found 203.2.

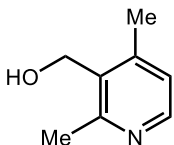


***N*-((1*H*-indol-3-yl)methyl)-*N*-(*tert*-butyl)-2-chloroacetamide (S4):**

Prepared according to General Acylation Procedure. *N*-((1*H*-indol-3-yl)methyl)-2-methylpropan-2-amine (**S3**) (506 mg, 2.5 mmol, 1.0 equiv), Et<sub>3</sub>N (0.35 mL, 2.5 mmol, 1.0 equiv), and chloroacetyl chloride (0.20 mL, 2.5 mmol, 1.0 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (25 mL, 0.1 M) for 18 hours. Purification on silica gel (30% EtOAc/hexanes) afforded the title compound as an off-white amorphous solid (534 mg, 77%).

**<sup>1</sup>H NMR** (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.55 (s, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.20 – 7.14 (m, 2H), 6.51 (s, 1H), 4.35 (s, 2H), 3.80 (s, 2H), 1.39 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, C<sub>6</sub>D<sub>6</sub>) δ 13C NMR (151 MHz, C<sub>6</sub>D<sub>6</sub>) δ 167.4, 137.2, 125.7, 123.0, 121.8, 120.1, 118.6, 114.7, 111.9, 58.1, 44.3, 41.8, 28.4 ppm.



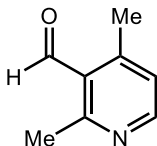
**(2,4-dimethylpyridin-3-yl)methanol (S5):**

Lithium aluminum hydride (4.0 M in ether, 7.5 mL, 10.0 mmol, 2.0 equiv) was added to cold, dry THF (12 mL). Ethyl 2,4-dimethylnicotinate (896.1 mg, 5.0 mmol, 1.0 equiv) was dissolved in dry THF (3 mL) and slowly added to the lithium aluminum hydride solution at 0°C. The reaction mixture was warmed to room temperature and stirred for 2 hours, then cooled to 0°C, diluted with water, quenched with 1 M NaOH (aq), filtered through a plug of celite, and extracted with EtOAc (3x). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to afford the title compound as a tan amorphous solid (519 mg, 76%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 8.26 (d, J = 5.0 Hz, 1H), 6.96 (d, J = 5.1 Hz, 1H), 4.77 (s, 2H), 2.63 (s, 3H), 2.42 (s, 3H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 157.7, 148.4, 147.0, 132.2, 124.0, 59.0, 22.4, 19.1 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>8</sub>H<sub>11</sub>NO, 137.1, found 137.0.



**2,4-dimethylnicotinaldehyde (S6):**

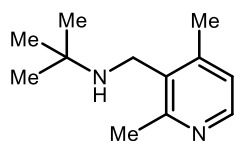
(2,4-dimethylpyridin-3-yl)methanol (**S5**) (478.8 mg, 3.5 mmol, 1.0 equiv), and manganese dioxide (1520 mg, 20.0 mmol, 5.0 equiv) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (32 mL, 0.15 M) and refluxed at 40°C

for 18 hours. The reaction mixture was cooled to room temperature and filtered through a plug of celite. Purification on silica gel (20-50% EtOAc/hexanes) afforded the title compound as a brown amorphous solid (263 mg, 56%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 10.64 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H), 7.06 (d, J = 5.2 Hz, 1H), 2.83 (s, 3H), 2.61 (s, 3H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 192.7, 160.9, 152.2, 150.1, 128.6, 125.3, 23.3, 20.4 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>8</sub>H<sub>9</sub>NO, 135.1, found 135.0.



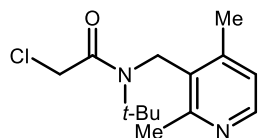
***N*-((2,4-dimethylpyridin-3-yl)methyl)-2-methylpropan-2-amine (S7):**

Prepared according to General Reductive Amination Procedure. 2,4-dimethylnicotinaldehyde (**S6**) (237 mg, 1.8 mmol, 1.0 equiv) and *tert*-butyl amine (0.28 mL, 2.6 mmol, 1.5 equiv) were stirred in MeOH (9 mL, 0.2 M) for 16 hours. After NaBH<sub>4</sub> (100 mg, 2.6 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 1 hour. The title compound was obtained as a white amorphous solid (316 mg, 94%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 8.22 (d, J = 5.0 Hz, 1H), 6.92 (d, J = 5.0 Hz, 1H), 3.72 (s, 2H), 2.61 (s, 3H), 2.38 (s, 3H), 1.20 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 157.2, 147.3, 146.4, 132.7, 123.7, 50.7, 40.4, 28.9, 22.1, 18.9 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>12</sub>H<sub>20</sub>N<sub>2</sub>, 192.2, found 192.2.



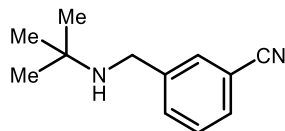
***N*-(*tert*-butyl)-2-chloro-*N*-((2,4-dimethylpyridin-3-yl)methyl)acetamide (S8):**

Prepared according to General Acylation Procedure. *N*-((2,4-dimethylpyridin-3-yl)methyl)-2-methylpropan-2-amine (**S7**) (289 mg, 1.5 mmol, 1.0 equiv), Et<sub>3</sub>N (0.23 mL, 1.7 mmol, 1.1 equiv), and chloroacetyl chloride (0.13 mL, 1.7 mmol, 1.1 equiv) were stirred in THF (15 mL, 0.1 M) for 3 hours. The title compound was afforded as a white amorphous solid (148 mg, 37%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 8.28 (d, J = 5.0 Hz, 1H), 6.94 (d, J = 4.9 Hz, 1H), 4.69 (s, 2H), 4.15 (s, 2H), 2.59 (s, 3H), 2.38 (s, 3H), 1.38 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 168.6, 155.9, 147.6, 145.4, 130.9, 125.2, 59.4, 46.0, 44.9, 28.4, 23.9, 20.5 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>21</sub>ClN<sub>2</sub>O, 268.1, found 268.1.



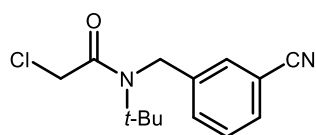
**3-((*tert*-butylamino)methyl)benzonitrile (S9):**

Prepared according to General Reductive Amination Procedure. 3-formylbenzonitrile (525 mg, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.73 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20

mL, 0.2 M) for 12 hours. After NaBH<sub>4</sub> (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 2 hours. The title compound was obtained as a colorless oil (694 mg, 92%).  
**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.65 (s, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 3.73 (s, 2H), 1.14 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 143.4, 132.7, 131.8, 130.5, 129.1, 119.1, 112.3, 50.9, 46.5, 29.2 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>, 188.1, found 188.2.



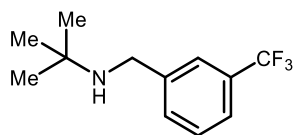
***N*-(*tert*-butyl)-2-chloro-*N*-(3-cyanobenzyl)acetamide (S10):**

Prepared according to General Acylation Procedure. 3-((*tert*-butylamino)methyl)benzonitrile (**S9**) (377 mg, 2.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.31 mL, 2.2 mmol, 1.1 equiv), and chloroacetyl chloride (0.18 mL, 2.2 mmol, 1.1 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (20 mL, 0.1 M) for 3 hours. The title compound was afforded as a tan solid (526 mg, 99%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.59 (d, J = 7.6 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.47 (d, J = 7.7 Hz, 1H), 4.69 (s, 2H), 3.92 (s, 2H), 1.43 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 167.7, 140.7, 131.4, 130.1, 130.0, 129.2, 118.5, 113.5, 59.1, 48.4, 44.0, 28.6 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>17</sub>ClN<sub>2</sub>O, 264.1, found 264.1.



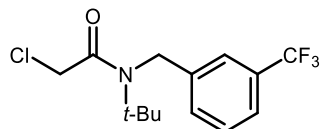
**2-methyl-*N*-(3-(trifluoromethyl)benzyl)propan-2-amine (S11):**

Prepared according to General Reductive Amination Procedure. 3-(trifluoromethyl)benzaldehyde (0.54 mL, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.50 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 26 hours. After NaBH<sub>4</sub> (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 30 min. The title compound was obtained as a light-yellow oil (590 mg, 86%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.62 (s, 1H), 7.54 (d, J = 7.3 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.44 – 7.39 (m, 1H), 3.79 (s, 2H), 1.18 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) 142.5, 131.7, 130.7 (q, <sup>2</sup>J<sub>C-F</sub> = 32.1 Hz), 128.8, 125.0 (q, <sup>3</sup>J<sub>C-F</sub> = 3.9 Hz), 124.3 (q, <sup>1</sup>J<sub>C-F</sub> = 272.2 Hz), 123.7 (q, <sup>3</sup>J<sub>C-F</sub> = 3.9 Hz), 50.9, 46.8, 29.2 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>12</sub>H<sub>16</sub>F<sub>3</sub>N, 231.1, found 231.2.



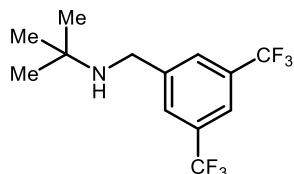
***N*-(*tert*-butyl)-2-chloro-*N*-(3-(trifluoromethyl)benzyl)acetamide (S12):**

Prepared according to General Acylation Procedure. 2-methyl-*N*-(3-(trifluoromethyl)benzyl)propan-2-amine (**S11**) (490 mg, 3.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.50 mL, 3.6 mmol, 1.2 equiv), and chloroacetyl chloride (0.29 mL, 3.6 mmol, 1.2 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub>

(30 mL, 0.1 M) for 1 hour. The title compound afforded as a light-yellow amorphous solid (685 mg, 95%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.57 (d, J = 7.7 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.47 (s, 1H), 7.42 (d, J = 7.6 Hz, 1H), 4.73 (s, 2H), 3.94 (s, 2H), 1.46 (s, 9H) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>9</sup>



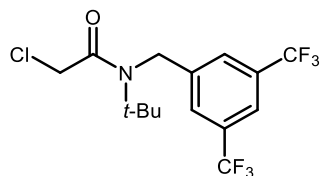
***N*-(3,5-bis(trifluoromethyl)benzyl)-2-methylpropan-2-amine (S13):**

Prepared according to General Reductive Amination Procedure. 3,5-bis(trifluoromethyl)benzaldehyde (0.66 mL, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.50 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 17 hours. After NaBH<sub>4</sub> (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 30 min. The title compound was obtained as a colorless oil (164 mg, 14%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.84 (s, 2H), 7.74 (s, 1H), 3.86 (s, 2H), 1.18 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 131.6 (q, <sup>2</sup>J<sub>C-F</sub> = 33.1 Hz), 128.6, 123.6 (q, <sup>1</sup>J<sub>C-F</sub> = 272.5 Hz), 121.0, 51.4, 46.5, 29.2 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>15</sub>F<sub>6</sub>N, 299.1, found 299.1.



***N*-(3,5-bis(trifluoromethyl)benzyl)-*N*-(*tert*-butyl)-2-chloroacetamide (S14):**

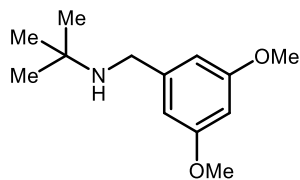
Prepared according to General Acylation Procedure. *N*-(3,5-bis(trifluoromethyl)benzyl)-2-methylpropan-2-amine (S13) (157 mg, 0.52 mmol, 1.0 equiv), Et<sub>3</sub>N (84 μL, 0.62 mmol, 1.2 equiv), and chloroacetyl chloride (49 μL, 0.62 mmol, 1.2 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (5 mL, 0.1 M) for 1 hour. The title compound afforded as a light-yellow amorphous solid (180 mg, 92%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.83 (s, 1H), 7.69 (s, 2H), 4.80 (s, 2H), 3.92 (s, 2H), 1.45 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 167.8, 142.0, 132.8 (q, <sup>2</sup>J<sub>C-F</sub> = 33.5 Hz), 125.9 (q, <sup>3</sup>J<sub>C-F</sub> = 3.8 Hz), 123.2 (q, <sup>1</sup>J<sub>C-F</sub> = 272.9 Hz), 121.8 (hept, <sup>3</sup>J<sub>C-F</sub> = 3.8 Hz), 59.2, 48.6, 43.8, 28.6 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>15</sub>H<sub>16</sub>ClF<sub>6</sub>NO, 375.1, found 375.1.

<sup>9</sup> Yanagita, H.; Urano, E.; Matsumoto, K.; Ichikawa, R.; Takaesu, Y.; Ogata, M.; Murakami, T.; Wu, H.; Chiba, J.; Komano, J.; Hoshino, T. Structural and biochemical study on the inhibitory activity of derivatives of 5-nitro-furan-2-carboxylic acid for RNase H function of HIV-1 reverse transcriptase. *Bioorg. Med. Chem.* **2011**, *19*, 816-825.

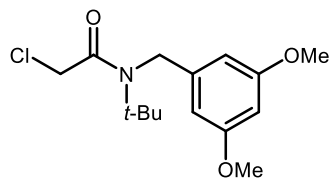


***N*-(3,5-dimethoxybenzyl)-2-methylpropan-2-amine (S15):**

Prepared according to General Reductive Amination Procedure. 3,5-dimethoxybenzaldehyde (665 mg, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.50 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 2 hours. After NaBH<sub>4</sub> (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 1 hour. The title compound was obtained as a white amorphous solid (701 mg, 78%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.51 (d, *J* = 2.1 Hz, 2H), 6.34 (t, *J* = 2.3 Hz, 1H), 3.79 (s, 6H), 3.67 (s, 2H), 1.17 (s, 9H) ppm.

<sup>1</sup>H NMR is consistent with reported values.<sup>10</sup>

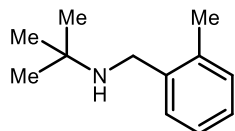


***N*-(*tert*-butyl)-2-chloro-*N*-(3,5-dimethoxybenzyl)acetamide (S16):**

Prepared according to General Acylation Procedure. *N*-(3,5-dimethoxybenzyl)-2-methylpropan-2-amine (S15) (670 mg, 3.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.50 mL, 3.6 mmol, 1.2 equiv), and chloroacetyl chloride (0.29 mL, 3.6 mmol, 1.2 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (30 mL, 0.1 M) for 1 hour. The title compound was obtained as a light-brown amorphous solid (899 mg, 100%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.36 (t, *J* = 2.2 Hz, 1H), 6.34 (d, *J* = 2.2 Hz, 2H), 4.59 (d, *J* = 0.8 Hz, 2H), 3.97 (s, 2H), 3.78 (s, 6H), 1.47 (s, 9H) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>11</sup>



**2-methyl-*N*-(2-methylbenzyl)propan-2-amine (S17):**

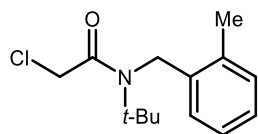
Prepared according to General Reductive Amination Procedure. 2-methylbenzaldehyde (0.46 mL, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.73 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 3 hours. After NaBH<sub>4</sub> (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 2 hours. The title compound was obtained as a white amorphous solid (546 mg, 77%).

<sup>1</sup>H NMR (400 MHz, cdcl3) δ 7.33 – 7.24 (m, 1H), 7.21 – 7.11 (m, 3H), 3.70 (s, 2H), 2.37 (s, 3H), 1.20 (s, 9H) ppm.

<sup>10</sup> Padwa, A.; Kuethe, J. T. Additive and Vinylogous Pummerer Reactions of Amido Sulfoxides and Their Use in the Preparation of Nitrogen Containing Heterocycles. *J. Org. Chem.* **1998**, 63, 4256-4268.

<sup>11</sup> Hamada, T.; Okuno, Y.; Ohmori, M.; Nishi, T.; Yonemitsu, O. Photochemical Synthesis of 1,2,3,4-Tetrahydroisoquinolin-3-ones and Oxindoles from *N*-Chloroacetyl Derivatives of Benzylamines and Anilines. Role of Intramolecular Exciplex Formation and *cis* Conformation of Amide Bonds. *Chem. Pharm. Bull.* **1981**, 29, 128-136.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>12</sup>



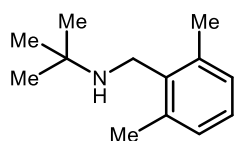
***N*-(*tert*-butyl)-2-chloro-*N*-(2-methylbenzyl)acetamide (S18):**

Prepared according to General Acylation Procedure. 2-methyl-*N*-(2-methylbenzyl)propan-2-amine (**S17**) (319 mg, 1.8 mmol, 1.0 equiv), Et<sub>3</sub>N (0.28 mL, 2.0 mmol, 1.1 equiv), and chloroacetyl chloride (0.16 mL, 2.0 mmol, 1.1 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (18 mL, 0.1 M) for 3.5 hours, which afforded the title compound as a white amorphous solid (401 mg, 88%).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.25 – 7.15 (m, 4H), 4.54 (s, 2H), 3.89 (s, 2H), 2.29 (s, 3H), 1.46 (s, 9H) ppm.

<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 167.8, 136.3, 134.3, 130.7, 127.3, 127.3, 126.7, 124.6, 58.6, 46.7, 44.1, 28.3, 19.1 ppm.

LRMS (EI) *m/z*: [M]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>20</sub>ClNO, 253.1, found 253.2.

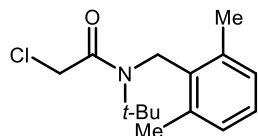


***N*-(2,6-dimethylbenzyl)-2-methylpropan-2-amine (S19):**

Prepared according to General Reductive Amination Procedure. 2,6-dimethylbenzaldehyde (537 mg, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (1.20 mL, 8.0 mmol, 2.0 equiv) were stirred in MeOH (20 mL, 0.2 M) for 6 hours. After NaBH<sub>4</sub> (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 1.5 hours. The title compound was obtained as a white amorphous solid (708 mg, 93%).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.07 – 6.98 (m, 3H), 3.72 (s, 2H), 2.39 (s, 6H), 1.45 (s, 1H), 1.21 (s, 9H).

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>12</sup>



***N*-(*tert*-butyl)-2-chloro-*N*-(2,6-dimethylbenzyl)acetamide (S20):**

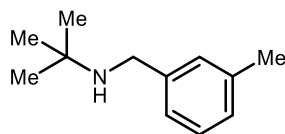
Prepared according to General Acylation Procedure. *N*-(2,6-dimethylbenzyl)-2-methylpropan-2-amine (**S19**) (574 mg, 3.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.46 mL, 3.3 mmol, 1.1 equiv), and chloroacetyl chloride (0.26 mL, 3.3 mmol, 1.1 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (30 mL, 0.1 M) for 14 hours, which afforded the title compound as a yellow amorphous solid (654 mg, 81%).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.08 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 2H), 4.65 (s, 2H), 4.11 (s, 2H), 2.36 (s, 6H), 1.39 (s, 9H) ppm.

<sup>12</sup> Franchi, P.; Casati, C.; Mezzina, E.; Lucarini, M. Kinetic control of the direction of inclusion of nitroxide cyclodextrines. *Org. Biomol. Chem.*, **2011**, 9, 6396-6401.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 168.6, 136.0, 134.8, 130.1, 127.4, 59.5, 46.8, 45.2, 28.3, 28.3, 21.1 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>15</sub>H<sub>22</sub>ClNO, 267.1, found 267.1.

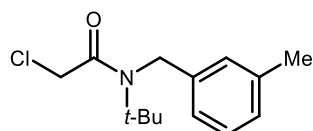


**2-methyl-N-(3-methylbenzyl)propan-2-amine (S21):**

Prepared according to General Reductive Amination Procedure. 3-methylbenzaldehyde (0.71 mL, 6.0 mmol, 1.0 equiv) and *tert*-butyl amine (1.10 mL, 7.2 mmol, 1.2 equiv) were stirred in MeOH (30 mL, 0.2 M) for 15 hours. After NaBH<sub>4</sub> (340 mg, 9.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 2 hours. The title compound was obtained as a light-yellow oil (990 mg, 93%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.23 – 7.10 (m, 3H), 7.04 (d, J = 7.5 Hz, 1H), 3.69 (s, 2H), 2.34 (d, J = 0.7 Hz, 3H), 1.18 (s, 9H) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>13</sup>



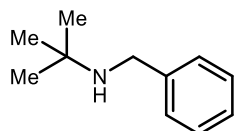
**N-(*tert*-butyl)-2-chloro-N-(3-methylbenzyl)acetamide (S22):**

Prepared according to General Reductive Amination Procedure. 2-methyl-N-(3-methylbenzyl)propan-2-amine (S21) (443 mg, 2.5 mmol, 1.0 equiv) Et<sub>3</sub>N (0.38 mL, 2.8 mmol, 1.1 equiv), and chloroacetyl chloride (0.22 mL, 2.8 mmol, 1.1 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (25 mL, 0.1 M) for 1 hour, which afforded the title compound as a white amorphous solid (593 mg, 94%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.21 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.97 (s, 1H), 6.96 (d, J = 8.5 Hz, 1H), 4.59 (s, 2H), 3.95 (s, 2H), 2.31 (s, 3H), 1.42 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 167.5, 138.7, 138.4, 128.9, 128.1, 126.0, 122.3, 58.6, 48.6, 44.2, 28.3, 21.4 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>20</sub>ClNO, 253.1, found 253.2.



**N-benzyl-2-methylpropan-2-amine (S23):**

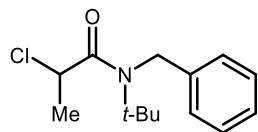
Prepared according to General Reductive Amination Procedure. Benzaldehyde (1.02 mL, 10.0 mmol, 1.0 equiv) and *tert*-butyl amine (1.26 mL, 12.0 mmol, 1.2 equiv) were stirred in MeOH (50 mL, 0.2 M) for 4 hours. After NaBH<sub>4</sub> (567 mg, 15.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 1 hour. The title compound was obtained as a colorless oil (1061 mg, 100%).

<sup>13</sup> Jankowski, K.; Harvey, R. A general one-pot, three-component mono N-alkylation of amines and amine derivatives in lithium perchlorate/diethyl ether solution. *Synthesis*, **2005**, 4, 627-633.



**<sup>1</sup>H NMR** (400 MHz, cdcl<sub>3</sub>) δ 7.38 – 7.28 (m, 4H), 7.25 – 7.20 (m, 1H), 3.73 (s, 2H), 1.18 (s, 9H) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>14</sup>



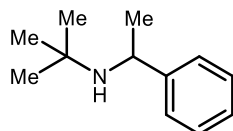
**N-benzyl-N-(tert-butyl)-2-chloropropanamide (S24):**

Prepared according to General Acylation Procedure. *N*-benzyl-2-methylpropan-2-amine (**S23**) (264 mg, 1.6 mmol, 1.0 equiv), Et<sub>3</sub>N (0.26 mL, 1.9 mmol, 1.2 equiv), and 2-chloropropionyl chloride (0.18 mL, 1.9 mmol, 1.2 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (16 mL, 0.1 M) for 1 hour. Purification on silica gel (10% EtOAc/hexanes) afforded the title compound as a white amorphous solid (276 mg, 68%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.38 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 2H), 4.82 (d, *J* = 18.9 Hz, 1H), 4.62 (d, *J* = 18.9 Hz, 1H), 4.32 (q, *J* = 6.4 Hz, 1H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.45 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 170.5, 139.2, 129.1, 127.3, 125.3, 58.5, 52.1, 48.3, 28.4, 21.4 ppm.

**LRMS (EI)** *m/z*: [M]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>20</sub>ClNO, 253.1, found 253.2.



**2-methyl-N-(1-phenylethyl)propan-2-amine (S25):**

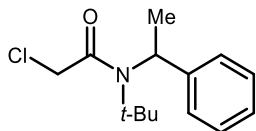
To a round bottomed flask charged with (1-bromoethyl)benzene (0.41 mL, 3.0 mmol, 1.0 equiv) was added MeCN (15 mL, 0.2 M), *tert*-butylamine (0.38 mL, 3.6 mmol, 1.2 equiv), and K<sub>2</sub>CO<sub>3</sub> (829 mg, 6.0 mmol, 2.0 equiv). The resulting suspension was heated at reflux for 16 hours. After cooling to room temperature, the reaction was quenched with H<sub>2</sub>O and extracted with EtOAc (3x). The combined organic layers were washed with 1 M HCl (aq), and the resulting aqueous layer was brought to pH 14 with 2 M NaOH (aq) extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to afford the title compound as a colorless oil (363 mg, 68%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.41 – 7.33 (m, 2H), 7.33 – 7.23 (m, 2H), 7.23 – 7.14 (m, 1H), 3.95 (q, *J* = 6.7 Hz, 1H), 1.31 (d, *J* = 6.7 Hz, 3H), 1.02 (s, 9H) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>15</sup>

<sup>14</sup> Niu, Z.; Zhang, W.; Lan, P. C.; Aguila, B.; Ma, S. Promoting frustrated lewis pairs for heterogeneous chemoselective hydrogenation via the tailored pore environment within metal-organic frameworks. *Angew. Chem. Int. Ed.* **2019**, 58, 7420-7424.

<sup>15</sup> Cliffe, I. A.; Crossley, R.; Shepherd, R. G. Sterically Hindered Lithium Dialkylamides; A Novel Synthesis of Lithium Dialkylamides from *N*-*t*-Alkyl-*N*-benzylideneamines and the Isolation of Highly Hindered *s*-Alkyl-*t*-alkylamines. *Synthesis* **1985**, 12, 1138-1140.



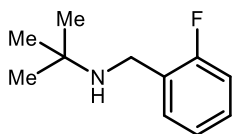
***N*-(*tert*-butyl)-2-chloro-*N*-(1-phenylethyl)acetamide (S26):**

Prepared according to General Acylation Procedure. 2-methyl-*N*-(1-phenylethyl)propan-2-amine (S25) (266 mg, 1.5 mmol, 1.0 equiv), Et<sub>3</sub>N (0.25 mL, 1.8 mmol, 1.2 equiv), and chloroacetyl chloride (0.14 mL, 1.8 mmol, 1.2 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (15 mL, 0.1 M) for 4 hours. Purification on silica gel (30% EtOAc/hexanes) afforded the title compound as a light-yellow oil (292 mg, 77%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.38 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.33 – 7.26 (m, 3H), 5.13 (q, *J* = 7.0 Hz, 1H), 3.76 (d, *J* = 12.7 Hz, 1H), 3.45 (d, *J* = 11.9 Hz, 1H), 1.79 (d, *J* = 7.1 Hz, 3H), 1.56 (s, 9H) ppm.

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 169.0, 143.1, 129.3, 127.3, 125.6, 60.0, 53.0, 44.7, 29.4, 21.0 ppm.

LRMS (EI) *m/z*: [M]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>20</sub>ClNO, 253.1, found 253.1.



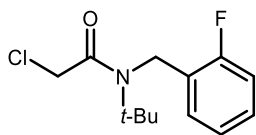
***N*-(2-fluorobenzyl)-2-methylpropan-2-amine (S27):**

Prepared according to General Reductive Amination Procedure. 2-fluorobenzaldehyde (0.42 mL, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.73 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 3 hours. After NaBH<sub>4</sub> (227 mg, 4.8 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 1.5 hours. The title compound was obtained as a colorless oil (508 mg, 70%).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.39 (td, *J* = 7.6, 1.8 Hz, 1H), 7.21 (tdd, *J* = 7.5, 5.2, 1.8 Hz, 1H), 7.09 (td, *J* = 7.5, 1.2 Hz, 1H), 7.01 (ddd, *J* = 9.8, 8.2, 1.2 Hz, 1H), 3.78 (s, 2H), 1.19 (s, 9H) ppm.

<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 161.3 (d, <sup>1</sup>*J*<sub>C-F</sub> = 245.0 Hz), 130.6 (d, <sup>3</sup>*J*<sub>C-F</sub> = 4.9 Hz), 128.6 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.9 Hz), 128.5, 124.3 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.5 Hz), 115.4 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.9 Hz), 51.0, 40.9 (d, <sup>3</sup>*J*<sub>C-F</sub> = 3.5 Hz), 29.3 ppm.

LRMS (EI) *m/z*: [M]<sup>+</sup> calc'd. for C<sub>11</sub>H<sub>16</sub>FN, 181.1, found 181.2.



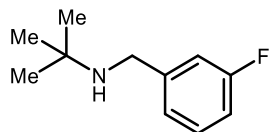
***N*-(*tert*-butyl)-2-chloro-*N*-(2-fluorobenzyl)acetamide (S28):**

Prepared according to General Acylation Procedure. *N*-(2-fluorobenzyl)-2-methylpropan-2-amine (S27) (399 mg, 2.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.31 mL, 2.2 mmol, 1.1 equiv), and chloroacetyl chloride (0.16 mL, 2.0 mmol, 1.1 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (20 mL, 0.1 M) for 3 hours. Purification on silica gel (30% EtOAc/hexanes) afforded the title compound as a white amorphous solid (473 mg, 92%).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.29 (dtd, *J* = 7.4, 6.3, 5.2, 1.8 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.21 – 7.15 (t, *J* = 7.2 Hz, 1H), 7.08 (ddd, *J* = 10.3, 8.2, 1.2 Hz, 1H), 4.69 (s, 2H), 3.98 (s, 2H), 1.46 (s, 9H) ppm.

**$^{13}\text{C}$  NMR** (151 MHz,  $\text{CDCl}_3$ )  $\delta$  167.77, 159.79 (d,  $^1J_{\text{C-F}} = 245.8$  Hz), 129.21 (d,  $^3J_{\text{C-F}} = 7.9$  Hz), 127.06 (d,  $^3J_{\text{C-F}} = 3.8$  Hz), 125.87 (d,  $^2J_{\text{C-F}} = 13.9$  Hz), 124.74 (d,  $^4J_{\text{C-F}} = 3.8$  Hz), 115.80 (d,  $^2J_{\text{C-F}} = 20.8$  Hz), 58.89, 44.15, 42.99 (d,  $^3J_{\text{C-F}} = 5.9$  Hz), 28.40.

**LRMS (EI)**  $m/z$ :  $[\text{M}]^+$  calc'd. for  $\text{C}_{13}\text{H}_{17}\text{ClFNO}$ , 257.1, found 257.1.



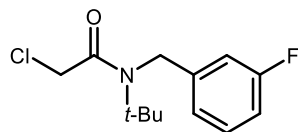
***N*-(3-fluorobenzyl)-2-methylpropan-2-amine (S29):**

Prepared according to General Reductive Amination Procedure. 3-Fluorobenzaldehyde (0.42 mL, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.50 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 3 hours. After  $\text{NaBH}_4$  (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 14 hours. The title compound was obtained as a white amorphous solid (633 mg, 87%).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 – 7.23 (m, 1H), 7.19 – 7.10 (m, 2H), 6.96 – 6.88 (m, 1H), 3.75 (s, 2H), 1.20 (s, 9H) ppm.

**$^{13}\text{C}$  NMR** (151 MHz,  $\text{CDCl}_3$ )  $\delta$  163.1 (d,  $^1J_{\text{C-F}} = 245.6$  Hz), 130.0 (d,  $^3J_{\text{C-F}} = 8.3$  Hz), 124.3, 122.4 (d,  $^4J_{\text{C-F}} = 2.9$  Hz), 115.7 (d,  $^2J_{\text{C-F}} = 21.4$  Hz), 114.1 (d,  $^2J_{\text{C-F}} = 21.2$  Hz), 64.7, 46.7, 28.9 ppm.

**LRMS (EI)**  $m/z$ :  $[\text{M}]^+$  calc'd. for  $\text{C}_{11}\text{H}_{16}\text{FN}$ , 181.1, found 181.0.



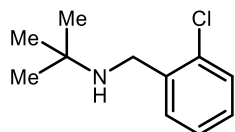
***N*-(*tert*-butyl)-2-chloro-*N*-(3-fluorobenzyl)acetamide (S30):**

Prepared according to General Acylation Procedure. *N*-(3-fluorobenzyl)-2-methylpropan-2-amine (S29) (544 mg, 3.0 mmol, 1.0 equiv),  $\text{Et}_3\text{N}$  (0.50 mL, 3.6 mmol, 1.2 equiv), and chloroacetyl chloride (0.29 mL, 3.6 mmol, 1.2 equiv) were stirred in  $\text{CH}_2\text{Cl}_2$  (30 mL, 0.1 M) for 2 hours. Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a white amorphous solid (601 mg, 78%).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 (td,  $J = 8.0, 5.8$  Hz, 1H), 7.03 – 6.95 (m, 2H), 6.95 – 6.87 (m, 1H), 4.65 (s, 2H), 3.95 (s, 2H), 1.45 (s, 9H) ppm.

**$^{13}\text{C}$  NMR** (151 MHz,  $\text{CDCl}_3$ )  $\delta$  167.7, 163.5 (d,  $^1J_{\text{C-F}} = 247.7$  Hz), 141.7 (d,  $^3J_{\text{C-F}} = 6.6$  Hz), 130.9 (d,  $^3J_{\text{C-F}} = 8.3$  Hz), 121.1 (d,  $^4J_{\text{C-F}} = 2.8$  Hz), 114.6 (d,  $^2J_{\text{C-F}} = 21.1$  Hz), 112.7 (d,  $^2J_{\text{C-F}} = 22.3$  Hz), 59.0, 48.6 (d,  $^4J_{\text{C-F}} = 2.0$  Hz), 44.2, 28.6 ppm.

**LRMS (EI)**  $m/z$ :  $[\text{M}]^+$  calc'd. for  $\text{C}_{13}\text{H}_{17}\text{ClFNO}$ , 257.1, found 257.1.



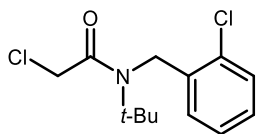
***N*-(2-chlorobenzyl)-2-methylpropan-2-amine (S31):**

Prepared according to General Reductive Amination Procedure. 2-chlorobenzaldehyde (0.45 mL, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.73 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 3 hours. After  $\text{NaBH}_4$  (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction

was stirred for an additional 4 hours. The title compound was obtained as a colorless oil (515 mg, 65%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.45 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.33 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.22 (td, *J* = 7.5, 1.4 Hz, 1H), 7.17 (td, *J* = 7.6, 1.8 Hz, 1H), 3.82 (s, 2H), 1.20 (s, 9H) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>16</sup>



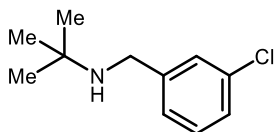
***N*-(*tert*-butyl)-2-chloro-*N*-(2-chlorobenzyl)acetamide (S32):**

Prepared according to General Acylation Procedure. *N*-(2-chlorobenzyl)-2-methylpropan-2-amine (S31) (395 mg, 2.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.31 mL, 2.2 mmol, 1.1 equiv), and chloroacetyl chloride (0.18 mL, 2.2 mmol, 1.1 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (20 mL, 0.1 M) for 3.5 hours. Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a light yellow oil (435 mg, 79%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.40 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.29 – 7.23 (m, 2H), 4.67 (s, 2H), 3.92 (s, 2H), 1.46 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 167.8, 136.0, 132.1, 130.1, 128.9, 127.5, 126.8, 59.0, 47.0, 44.1, 28.4 ppm.

**LRMS (EI)** *m/z*: [M]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>17</sub>Cl<sub>2</sub>NO, 273.1, found 273.1.

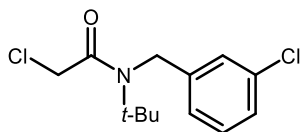


***N*-(3-chlorobenzyl)-2-methylpropan-2-amine (S33):**

Prepared according to General Reductive Amination Procedure. 3-chlorobenzaldehyde (0.45 mL, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.73 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 4.5 hours. After NaBH<sub>4</sub> (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 1.5 hours. The title compound was obtained as a light-yellow oil (744 mg, 94%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.36 (s, 1H), 7.24 – 7.14 (m, 3H), 3.70 (s, 2H), 1.17 (s, 9H) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>17</sup>



***N*-(*tert*-butyl)-2-chloro-*N*-(3-chlorobenzyl)acetamide (S34):**

Prepared according to General Acylation Procedure. *N*-(3-chlorobenzyl)-2-methylpropan-2-amine (S33) (395 mg, 2.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.15 mL, 2.2 mmol, 1.1 equiv), and chloroacetyl

<sup>16</sup> Franchi, P.; Casati, C.; Mezzina, E.; Lucarini, M. Kinetic control of the direction of inclusion of nitroxide cyclodextrines. *Org. Biomol. Chem.*, **2011**, 9, 6396-6401.

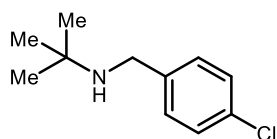
<sup>17</sup> Jiang, G.; Chen, J.; Huang, J.-S.; Che, C.-M. Highly efficient oxidation of amines to imines by singlet oxygen and its application in ugi-type reactions. *Org. Lett.*, **2009**, 11, 4568-4571.

chloride (0.18 mL, 2.2 mmol, 1.1 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (20 mL, 0.1 M) for 3.5 hours, which afforded the title compound as a white amorphous solid (436 mg, 72%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.36 – 7.23 (m, 2H), 7.19 (s, 1H), 7.09 (d, J = 7.8 Hz, 1H), 4.64 (s, 2H), 3.95 (s, 2H), 1.45 (s, 9H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 167.6, 140.9, 135.2, 130.4, 127.8, 125.7, 123.5, 58.9, 48.4, 44.0, 28.4 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>17</sub>Cl<sub>2</sub>NO, 273.1, found 273.1.



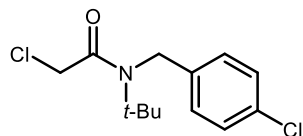
***N*-(4-chlorobenzyl)-2-methylpropan-2-amine (S35):**

Prepared according to General Reductive Amination Procedure. 4-Chlorobenzaldehyde (562 mg, 4.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.50 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 17 hours. After NaBH<sub>4</sub> (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 30 min. The title compound was obtained as a white amorphous solid (676 mg, 85%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.29 – 7.26 (m, 4H), 3.70 (s, 2H), 1.17 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 140.2, 132.6, 129.8, 128.6, 51.0, 46.7, 29.3 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>11</sub>H<sub>16</sub>ClN, 197.1, found 197.1.

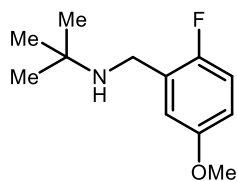


***N*-(*tert*-butyl)-2-chloro-*N*-(4-chlorobenzyl)acetamide (S36):**

Prepared according to General Acylation Procedure. *N*-(4-chlorobenzyl)-2-methylpropan-2-amine (S35) (593 mg, 3.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.50 mL, 3.6 mmol, 1.2 equiv), and chloroacetyl chloride (0.29 mL, 3.6 mmol, 1.2 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (30 mL, 0.1 M) for 1 hour. The title compound was obtained as a yellow oil (823 mg, 100%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.38 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 4.65 (s, 2H), 3.97 (s, 2H), 1.46 (s, 9H) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>18</sup>



***N*-(2-fluoro-5-methoxybenzyl)-2-methylpropan-2-amine (S37):**

Prepared according to General Reductive Amination Procedure. 2-fluoro-5-methoxybenzaldehyde (0.25 mL, 2.0 mmol, 1.0 equiv) and *tert*-butyl amine (0.41 mL, 2.4 mmol, 1.2 equiv) were stirred in MeOH (4 mL, 0.5 M) for 14 hours. After NaBH<sub>4</sub> (114 mg, 3.0 mmol, 1.5 equiv) was added, the

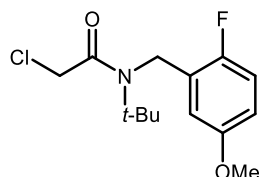
<sup>18</sup> Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. Access to β-Lactams by Enantioselective Palladium(0)-Catalyzed C(sp<sup>3</sup>)—H Alkylation. *Angew. Chem. Int. Ed.* **2014**, 53, 9064-9067.

reaction was stirred for an additional 1 hour. The title compound was obtained as a light-yellow oil (386 mg, 46%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 6.95 – 6.86 (m, 2H), 6.69 (ddd, J = 8.9, 4.0, 3.2 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 2H), 1.17 (s, 9H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 155.8 (d, <sup>4</sup>J<sub>C-F</sub> = 2.0 Hz), 155.5 (d, <sup>1</sup>J<sub>C-F</sub> = 237.4 Hz), 129.1 (d, <sup>2</sup>J<sub>C-F</sub> = 16.8 Hz), 115.7 (d, <sup>2</sup>J<sub>C-F</sub> = 23.8 Hz), 115.4 (d, <sup>3</sup>J<sub>C-F</sub> = 4.7 Hz), 113.2 (d, <sup>3</sup>J<sub>C-F</sub> = 8.2 Hz), 55.8, 50.9, 41.0 (d, <sup>3</sup>J<sub>C-F</sub> = 2.9 Hz), 29.1 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>12</sub>H<sub>18</sub>FNO, 211.1, found 211.2.



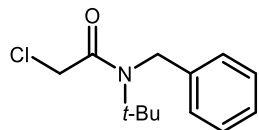
***N*-(tert-butyl)-2-chloro-*N*-(2-fluoro-5-methoxybenzyl)acetamide (S38):**

Prepared according to General Acylation Procedure. *N*-(2-fluoro-5-methoxybenzyl)-2-methylpropan-2-amine (**S37**) (211 mg, 1.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.15 mL, 1.1 mmol, 1.1 equiv), and chloroacetyl chloride (0.09 mL, 1.1 mmol, 1.1 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (10 mL, 0.1 M) for 4.5 hours, which afforded the title compound as a tan amorphous solid (263 mg, 91%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 6.99 (t, J = 9.1 Hz, 1H), 6.80 – 6.72 (m, 1H), 6.76 – 6.70 (m, 1H), 4.64 (s, 2H), 3.98 (s, 2H), 3.76 (s, 3H), 1.46 (s, 9H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 167.8, 156.4 (d, <sup>4</sup>J<sub>C-F</sub> = 2.0 Hz), 154.0 (d, <sup>1</sup>J<sub>C-F</sub> = 238.2 Hz), 126.8 (d, <sup>2</sup>J<sub>C-F</sub> = 15.7 Hz), 116.4 (d, <sup>2</sup>J<sub>C-F</sub> = 22.9 Hz), 113.3 (d, <sup>3</sup>J<sub>C-F</sub> = 7.9 Hz), 112.6 (d, <sup>3</sup>J<sub>C-F</sub> = 3.8 Hz), 58.9, 55.9, 44.1, 43.2 (d, <sup>3</sup>J<sub>C-F</sub> = 5.1 Hz), 28.4 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>19</sub>ClFNO<sub>2</sub>, 287.1, found 287.1.



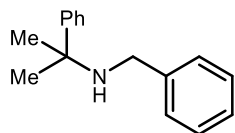
***N*-benzyl-*N*-(tert-butyl)-2-chloroacetamide (S39):**

Prepared according to General Acylation Procedure. *N*-benzyl-2-methylpropan-2-amine (**S23**) (688 mg, 4.2 mmol, 1.0 equiv), Et<sub>3</sub>N (0.64 mL, 4.6 mmol, 1.1 equiv), and chloroacetyl chloride (0.37 mL, 4.6 mmol, 1.1 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (42 mL, 0.1 M) for 3.5 hours. The title compound was afforded as a white amorphous solid (946 mg, 99%).

**<sup>1</sup>H NMR** (400 MHz, cdcl<sub>3</sub>) δ 7.38 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 7.20 (d, J = 6.9 Hz, 2H), 4.66 (s, 2H), 3.98 (s, 2H), 1.46 (s, 9H) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>19</sup>

<sup>19</sup> Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. Access to β-Lactams by Enantioselective Palladium(0)-Catalyzed C(sp<sup>3</sup>)-H Alkylation. *Angew. Chem. Int. Ed.* **2014**, 126, 9210-9213.

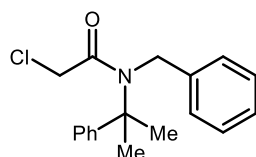


***N*-benzyl-2-phenylpropan-2-amine (S40):**

Prepared according to General Reductive Amination Procedure. Benzaldehyde (0.20 mL, 2.0 mmol, 1.0 equiv) and 2-phenylpropan-2-amine (0.35 mL, 2.4 mmol, 1.2 equiv) were stirred in MeOH (10 mL, 0.2 M) for 14 hours. After NaBH<sub>4</sub> (114 mg, 3.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 2 hours. The title compound was obtained as a colorless oil (414 mg, 92%).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.49 (d, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.22 (m, 4H), 7.21 – 7.15 (m, 2H), 3.44 (s, 2H), 1.49 (s, 6H) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>20</sup>



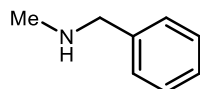
***N*-benzyl-2-chloro-*N*-(2-phenylpropan-2-yl)acetamide (S41):**

Prepared according to General Acylation Procedure. *N*-benzyl-2-phenylpropan-2-amine (S40) (225 mg, 1.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.15 mL, 1.1 mmol, 1.1 equiv), and chloroacetyl chloride (0.09 mL, 1.1 mmol, 1.1 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (10 mL, 0.1 M) for 16 hours. Purification on silica gel (10% EtOAc/hexanes) afforded the title compound as a white amorphous solid (138 mg, 46%).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.40 (t, *J* = 7.5 Hz, 2H), 7.32 (dd, *J* = 9.4, 5.9 Hz, 7H), 7.22 (hept, *J* = 4.2 Hz, 1H), 4.92 (s, 2H), 3.89 (s, 2H), 1.70 (s, 6H) ppm.

<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 167.9, 148.1, 138.7, 129.2, 128.7, 127.7, 126.8, 126.4, 124.4, 63.1, 49.5, 43.7, 29.4 ppm.

LRMS (EI) *m/z*: [M]<sup>+</sup> calc'd. for C<sub>18</sub>H<sub>20</sub>ClNO, 301.1, found 301.1.



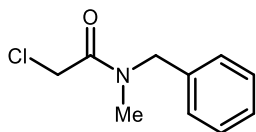
***N*-methyl-1-phenylmethanamine (S42):**

Prepared according to General Reductive Amination Procedure. Benzaldehyde (0.41 mL, 4.0 mmol, 1.0 equiv) and methanamine (0.37 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 2 hours. After NaBH<sub>4</sub> (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 30 min. The title compound was obtained as a white amorphous solid (479 mg, 99%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.36 – 7.30 (m, 4H), 7.29 – 7.22 (m, 1H), 3.75 (s, 2H), 2.46 (s, 3H), 1.59 (s, 1H) ppm.

<sup>20</sup> Milburn, R. R.; Snieckus, V. *ortho*-Anisylsulfonyl as a protecting group for secondary amines: mild Ni<sup>0</sup>-catalyzed hydrodesulfonylation. *Angew. Chem. Int. Ed.* **2004**, 43, 892-893.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>21</sup>

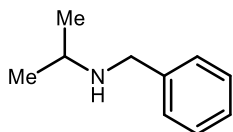


***N*-benzyl-2-chloro-*N*-methylacetamide (S43):**

Prepared according to General Acylation Procedure. *N*-methyl-1-phenylmethanamine (**S42**) (364 mg, 3.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.46 mL, 3.3 mmol, 1.1 equiv), and chloroacetyl chloride (0.26 mL, 1.1 mmol, 1.1 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (30 mL, 0.1 M) for 30 min. Purification on silica gel (10-30% EtOAc/hexanes) afforded the title compound as a colorless oil (401 mg, 68%).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.40 – 7.26 (m, 3H), 7.26 – 7.24 (m, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 4.60 (s, 2H), 4.12 (d, *J* = 22.3 Hz, 2H), 2.99 (d, *J* = 16.5 Hz, 3H) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>22</sup>

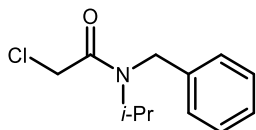


***N*-benzylpropan-2-amine (S44):**

Prepared according to General Reductive Amination Procedure. Benzaldehyde (0.41 mL, 4.0 mmol, 1.0 equiv) and propan-2-amine (0.39 mL, 4.8 mmol, 1.2 equiv) were stirred in MeOH (20 mL, 0.2 M) for 2 hours. After NaBH<sub>4</sub> (227 mg, 6.0 mmol, 1.5 equiv) was added, the reaction was stirred for an additional 30 min. The title compound was obtained as a yellow amorphous solid (557 mg, 93%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.32 (d, *J* = 4.4 Hz, 4H), 7.26 – 7.22 (m, 1H), 3.78 (s, 2H), 2.85 (h, *J* = 6.2 Hz, 1H), 1.10 (d, *J* = 6.2 Hz, 6H) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>23</sup>



***N*-benzyl-2-chloro-*N*-isopropylacetamide (S45):**

Prepared according to General Acylation Procedure. *N*-benzylpropan-2-amine (**S44**) (448 mg, 3.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.46 mL, 3.3 mmol, 1.1 equiv), and chloroacetyl chloride (0.26 mL, 3.3 mmol, 1.1 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (30 mL, 0.1 M) for 30 min. Purification on silica gel (10-30% EtOAc/hexanes) afforded the title compound as a colorless oil (414 mg, 61%). Mixture of rotamers (H\* denotes major rotamer and H denotes minor rotamer).

<sup>21</sup> Ji, P.; Manna, K.; Lin, Z.; Feng, X.; Urban, A.; Song, Y.; Lin, W. Single-site cobalt catalysts at new Zr<sub>12</sub>(μ<sub>3</sub>-O)<sub>8</sub>(μ<sub>3</sub>-OH)<sub>8</sub>(μ<sub>2</sub>-OH)<sub>6</sub> metal-organic framework nodes for highly active e hydrogenation of nitroarenes, nitriles and isocyanides. *J. Am. Chem. Soc.* **2017**, *139*, 7004-7011.

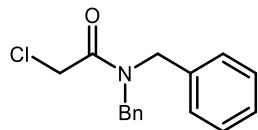
<sup>22</sup> Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. Access to β-Lactams by Enantioselective Palladium(0)-Catalyzed C(sp<sup>3</sup>)-H Alkylation. *Angew. Chem. Int. Ed.* **2014**, *126*, 9210-9213.

<sup>23</sup> Rauser, M.; Eckert, R.; Gerbershagen, M.; Niggemann, M. Catalyst-free reductive coupling of aromatic and aliphatic nitro compounds with organohalides. *Angew. Chem. Int. Ed.* **2019**, *58*, 6713-6717.



**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.36 (t, J = 7.6 Hz, 2(H+H\*)), 7.29 (t, J = 7.7 Hz, 4(H+H\*)), 7.22 (t, J = 8.1 Hz, 4(H+H\*)), 4.79 (spt, J = 6.8 Hz, 1H\*), 4.54 (m, 4(H+H\*)), 4.22 (spt, J = 6.8 Hz, 1H), 4.20 (s, 2H\*), 3.91 (s, 2H), 1.20 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.8 Hz, 3H\*) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>22</sup>

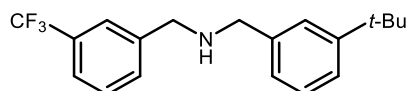


***N,N*-dibenzyl-2-chloroacetamide (S46):**

Prepared according to General Acylation Procedure. Dibenzylamine (0.22 mL, 2.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.31 mL, 2.2 mmol, 1.1 equiv), and chloroacetyl chloride (0.18 mL, 2.2 mmol, 1.1 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (20 mL, 0.1 M) for 20 min. Purification on silica gel (10-30% EtOAc/hexanes) afforded the title compound as a colorless oil. (307 mg, 56%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.42 – 7.27 (m, 6H), 7.23 (d, J = 6.4 Hz, 2H), 7.18 – 7.15 (d, J = 6.4 Hz, 2H), 4.62 (s, 2H), 4.52 (s, 2H), 4.15 (s, 2H).

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>24</sup>



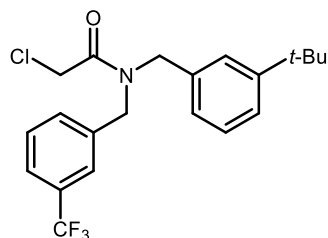
***N*-(3-(*tert*-butyl)benzyl)-1-(3-(trifluoromethyl)phenyl)ethanamine (S47):**

3-(trifluoromethyl)benzylamine (0.29 mL, 2.0 mmol, 1.0 equiv) was dissolved in DCM (8 mL, 0.25 M). 3-*tert*-butylbenzaldehyde (324 mg, 2.0 mmol, 1.0 equiv), AcOH (0.11 mL, 2.0 mmol, 1.0 equiv), and sodium triacetoxyborohydride (593 mg, 2.8 mmol, 1.4 equiv) were added and reaction was stirred for 16 hours. NaBH<sub>4</sub> (76 mg, 2.0 mmol, 1.0 equiv) was added and the reaction was stirred for an additional 4 hours. The reaction was quenched with 1 M NaOH (aq), extracted with DCM (3x), washed with brine, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. Purification on silica gel (50% EtOAc/hexanes) afforded the title compound as a colorless oil (361 mg, 56%).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.64 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.35 (s, 1H), 7.32 – 7.27 (m, 2H), 7.16 (dt, J = 7.0, 1.7 Hz, 1H), 3.88 (s, 2H), 3.81 (s, 2H), 1.33 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 151.6, 141.5, 139.7, 131.7, 130.9 (q, <sup>2</sup>J<sub>C-F</sub> = 32.0 Hz), 129.0, 128.4, 125.5, 125.3, 125.3 (q, <sup>1</sup>J<sub>C-F</sub> = 272.0 Hz), 125.1 (q, <sup>3</sup>J<sub>C-F</sub> = 3.8 Hz), 124.3, 124.0 (q, <sup>3</sup>J<sub>C-F</sub> = 3.8 Hz), 53.6, 52.7, 34.9, 31.6 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>19</sub>H<sub>22</sub>F<sub>3</sub>N, 321.2, found 321.3.



<sup>24</sup> Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. Access to β-Lactams by Enantioselective Palladium(0)-Catalyzed C(sp<sup>3</sup>)-H Alkylation. *Angew. Chem. Int. Ed.* **2014**, 126, 9210-9213.

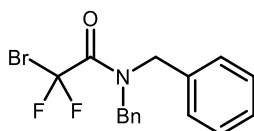
***N*-(3-(*tert*-butyl)benzyl)-2-chloro-*N*-(3-(trifluoromethyl)benzyl)acetamide (S48):**

Prepared according to General Acylation Procedure. *N*-(3-(*tert*-butyl)benzyl)-1-(3-(trifluoromethyl)phenyl)methanamine (S47) (321 mg, 1.0 mmol, 1.0 equiv), Et<sub>3</sub>N (0.17 mL, 1.2 mmol, 1.2 equiv), and chloroacetyl chloride (0.10 mL, 1.2 mmol, 1.2 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (10 mL, 0.1 M) for 16 hours. The title compound was obtained as a colorless oil (390 mg, 98%). Mixture of rotamers (\* denotes major rotamer # denotes minor isomer).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.62 – 7.27<sup>(\*+)</sup> (m, 6H), 7.16<sup>(\*+)</sup> (d, J = 27.3 Hz, 1H), 7.00<sup>(\*+)</sup> (dd, J = 23.3, 7.5 Hz, 1H), 4.65\* (s, 1H), 4.61<sup>#</sup> (s, 1H), 4.58<sup>#</sup> (s, 1H), 4.54\* (s, 1H), 4.18\* (s, 1H), 4.13<sup>#</sup> (s, 1H), 1.30\* (s, 9H), 1.29<sup>#</sup> (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 167.7\*, 167.4<sup>#</sup>, 152.6\*, 152.1<sup>#</sup>, 137.8\*, 137.2<sup>#</sup>, 135.7<sup>#</sup>, 135.0\*, 131.7\*, 131.3<sup>#</sup>, 130.0<sup>#</sup>, 129.8<sup>#</sup>, 129.5\*, 129.1\*, 128.8<sup>#</sup>, 125.5<sup>#</sup>, 125.4\*, 125.4<sup>#</sup>, 125.1 (m), 124.67 (q, <sup>3</sup>J<sub>C-F</sub> = 3.8 Hz), 123.9\*, 123.7\*, 51.4\*, 50.2<sup>#</sup>, 49.1<sup>#</sup>, 48.6\*, 41.4<sup>(\*+)</sup>, 34.9\*, 34.8<sup>#</sup>, 31.5<sup>(\*+)</sup> ppm.

**LRMS (APCI)** m/z: [M+H]<sup>+</sup> calc'd. for C<sub>21</sub>H<sub>24</sub>F<sub>3</sub>NO, 398.1, found 398.2.

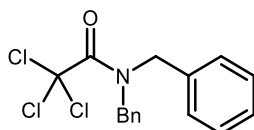
***N,N*-dibenzyl-2-bromo-2,2-difluoroacetamide (S49):**

An oven-dried reaction vial was cooled under N<sub>2</sub>. Dibenzylamine (0.19 mL, 1.0 mmol, 1.0 equiv), ethyl bromodifluoroacetate (0.15 mL, 1.2 mmol, 1.2 equiv), and La(OTf)<sub>3</sub> (59 mg, 0.1 mmol, 10 mol %) were added sequentially. The reaction was stirred for 20 hours then quenched with 1 M HCl (aq), extracted with EtOAc (3x), filtered through a plug of silica with EtOAc, and concentrated under reduced pressure. The crude residue was purified on silica gel (20% EtOAc/hexanes) to afford the title compound as a white amorphous solid (104 mg, 29%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.43 – 7.29 (m, 6H), 7.19 (ddd, J = 7.4, 5.5, 1.6 Hz, 4H), 4.63 (s, 2H), 4.55 (s, 2H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 160.1 (t, <sup>2</sup>J<sub>C-F</sub> = 26.3 Hz), 135.5, 134.8, 129.2, 129.1, 128.4, 128.4, 128.2, 127.5, 111.3 (t, <sup>1</sup>J<sub>C-F</sub> = 315.1 Hz), 50.6 (t, <sup>4</sup>J<sub>C-F</sub> = 3.8 Hz), 48.8 ppm.

**LRMS (EI)** m/z: [M]<sup>+</sup> calc'd. for C<sub>16</sub>H<sub>14</sub>BrF<sub>2</sub>NO, 353.0, found 353.1.

***N,N*-dibenzyl-2,2,2-trichloroacetamide (S50):**

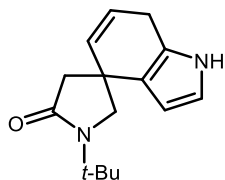
Prepared according to General Acylation Procedure. Dibenzylamine (0.66 mL, 3.3 mmol, 1.1 equiv), Et<sub>3</sub>N (0.46 mL, 3.3 mmol, 1.1 equiv), and trichloroacetyl chloride (0.33 mL, 3.0 mmol, 1.0 equiv) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (30 mL, 0.1 M) for 23 hours. Purification on silica gel (0-10% EtOAc/hexanes) afforded the title compound as a white amorphous solid (654 mg, 64%).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.43 – 7.30 (m, 6H), 7.24 (d, J = 6.9 Hz, 2H), 7.16 (d, J = 6.9 Hz, 2H), 4.91 (s, 2H), 4.58 (s, 2H) ppm.

<sup>1</sup>H NMR spectrum is consistent with reported values.<sup>25</sup>

<sup>25</sup> Diaba, F.; Montiel, J.A.; Martínez-Laporta, A.; Bonjoch, J. Dearomative radical spirocyclization from *N*-benzyltrichloroacetamides revisited using a copper(I)-mediated atom transfer reaction leading to 2-azaspiro[4.5]decanes. *Tetrahedron Lett.* **2013**, *54*, 2619-2622.

## VIII. Preparation of Spirolactam Products



### 1'-(*tert*-butyl)-1,7-dihydrospiro[indole-4,3'-pyrrolidin]-5'-one (1):

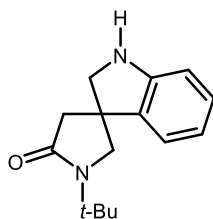
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-((1*H*-indol-4-yl)methyl)-*N*-(*tert*-butyl)-2-chloroacetamide (**S2**) (139 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 10% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (0-10% acetone/CH<sub>2</sub>Cl<sub>2</sub>) afforded the title compound as a yellow oil (96.3 mg, 79%).

**R<sub>f</sub>**: 0.21 (5% acetone/DCM)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.91 (s, 1H), 6.72 (dd, *J* = 3.0, 2.4 Hz, 1H), 6.16 (t, *J* = 2.7 Hz, 1H), 5.86 (dt, *J* = 10.0, 3.0 Hz, 1H), 5.81 (dt, *J* = 10.0, 1.8 Hz, 1H), 3.59 (d, *J* = 9.6 Hz, 1H), 3.44 (d, *J* = 9.7 Hz, 1H), 3.28 – 3.22 (m, 2H), 2.64 (d, *J* = 16.4 Hz, 1H), 2.48 (d, *J* = 16.5 Hz, 1H), 1.43 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 174.1, 132.4, 124.1, 122.6, 120.9, 117.3, 104.4, 59.9, 54.2, 48.7, 37.3, 28.0, 24.1 ppm.

**HRMS (APCI)** *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>15</sub>H<sub>21</sub>N<sub>2</sub>O, 245.16484, found 245.16491.



### 1'-(*tert*-butyl)spiro[indoline-3,3'-pyrrolidin]-5'-one (2):

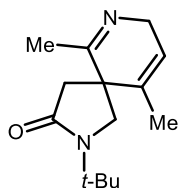
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-((1*H*-indol-3-yl)methyl)-*N*-(*tert*-butyl)-2-chloroacetamide (**S4**) (56 mg, 0.2 mmol, 1.0 equiv), 3DPAFIPN (6.5 mg, 0.01 mmol, 5 mol%), DIPEA (0.10 mL, 0.6 mmol, 3.0 equiv), cyclohexanethiol (1.2 μL, 0.01 mmol, 5 mol%), and 50% H<sub>2</sub>O/MeCN (4 mL, 0.05 M). Purification on silica gel (10-50% EtOAc/hexanes) afforded the title compound as a yellow oil (34.4 mg, 70%).

**R<sub>f</sub>**: 0.15 (30% EtOAc/hexanes)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.15 (d, *J* = 7.4 Hz, 1H), 7.14 – 7.08 (m, 1H), 6.83 – 6.77 (m, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 3.63 (d, *J* = 9.8 Hz, 1H), 3.58 (d, *J* = 9.1 Hz, 1H), 3.51 (d, *J* = 9.1 Hz, 1H), 3.49 (d, *J* = 9.8 Hz, 1H), 2.80 (d, *J* = 16.7 Hz, 1H), 2.52 (d, *J* = 16.7 Hz, 1H), 1.42 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 173.6, 150.4, 133.3, 128.8, 122.4, 119.9, 110.5, 60.2, 57.7, 54.4, 45.6, 45.5, 28.0 ppm.

**HRMS (APCI)** *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>15</sub>H<sub>21</sub>N<sub>2</sub>O, 245.16484, found 245.16487.



**2-(tert-butyl)-6,10-dimethyl-2,7-diazaspiro[4.5]deca-6,9-dien-3-one (3):**

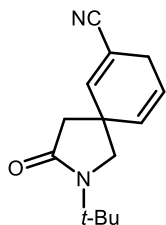
Prepared according to General Dearomative Spirolactamization Procedure 1 using N-(tert-butyl)-2-chloro-N-((2,4-dimethylpyridin-3-yl)methyl)acetamide (**S8**) (26.9 mg, 0.1 mmol, 1.0 equiv), 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (0.05 mL, 0.3 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (2 mL, 0.05 M). Purification on silica gel (50-70% acetone/DCM) afforded the title compound as a white amorphous solid (23 mg, 97%).

**R<sub>f</sub>**: 0.24 (50% acetone/DCM)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 5.55 (dq, J = 3.1, 1.5 Hz, 1H), 4.16 – 4.08 (m, 2H), 3.49 (d, J = 10.9 Hz, 1H), 3.42 (d, J = 10.9 Hz, 1H), 2.55 (d, J = 9.6 Hz, 2H), 2.06 (d, J = 1.8 Hz, 3H), 1.73 (t, J = 1.8 Hz, 3H), 1.42 (s, 9H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 173.0, 167.0, 131.7, 121.4, 54.7, 54.3, 50.3, 41.6, 39.1, 27.8, 22.3, 18.2 ppm.

**HRMS (APCI)** m/z: [M+H]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>23</sub>N<sub>2</sub>O, 235.18049, found 235.18090.



**2-(tert-butyl)-3-oxo-2-azaspiro[4.5]deca-6,9-diene-7-carbonitrile (4):**

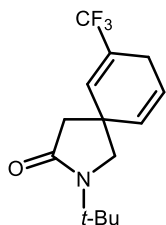
Prepared according to General Dearomative Spirolactamization Procedure 2 using N-(tert-butyl)-2-chloro-N-(3-cyanobenzyl)acetamide (**S10**) (132.4 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (0-30% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (73 mg, 63%).

**R<sub>f</sub>**: 0.13 (20% EtOAc/hexanes)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 6.50 (q, J = 2.0 Hz, 1H), 5.77 (dt, J = 10.3, 3.4 Hz, 1H), 5.67 (dq, J = 10.2, 2.2 Hz, 1H), 3.33 (q, J = 12 Hz, 2H), 2.85 (dq, J = 3.4, 1.7 Hz, 2H), 2.35 (d, J = 1.6 Hz, 2H), 1.37 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 172.0, 145.4, 145.4, 128.8, 122.6, 122.6, 118.5, 110.8, 57.3, 54.4, 46.7, 37.6, 27.8, 27.8, 27.8, 27.7 ppm.

**HRMS (APCI)** m/z: [M+H]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>19</sub>N<sub>2</sub>O, 231.14919, found 231.14940.



**2-(tert-butyl)-7-(trifluoromethyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (5):**

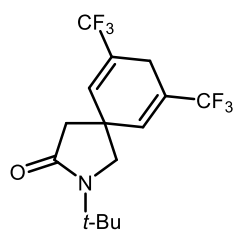
Prepared according to General Dearomative Spirolactamization Procedure 2 using *N*-(*tert*-butyl)-2-chloro-*N*-(3-(trifluoromethyl)benzyl)acetamide (**S12**) (120 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (75 mg, 55%).

**R<sub>f</sub>**: 0.27 (20% EtOAc/hexanes)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 6.26 (p, *J* = 1.7 Hz, 1H), 5.83 (dt, *J* = 10.1, 3.4 Hz, 1H), 5.70 (dq, *J* = 10.0, 2.1 Hz, 1H), 3.36 (d, *J* = 10.1 Hz, 1H), 3.33 (d, *J* = 10.3 Hz, 1H), 2.84 – 2.77 (m, 2H), 2.38 (s, 2H), 1.40 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 72.7, 132.1 (q, <sup>3</sup>*J*<sub>C-F</sub> = 5.6 Hz), 129.2, 126.6 (q, <sup>2</sup>*J*<sub>C-F</sub> = 31.2 Hz), 123.5 (q, <sup>1</sup>*J*<sub>C-F</sub> = 272.1 Hz), 122.8, 57.7, 54.4, 47.0, 37.0, 27.9, 23.7 ppm.

**HRMS (APCI)** *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>19</sub>F<sub>3</sub>NO, 274.14133, found 274.14162.



**2-(*tert*-butyl)-7,9-bis(trifluoromethyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (6):**

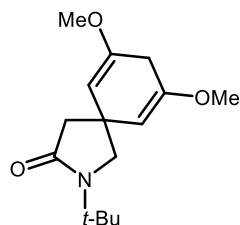
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(3,5-bis(trifluoromethyl)benzyl)-*N*-(*tert*-butyl)-2-chloroacetamide (**S14**) (174 mg, 0.46 mmol, 1.0 equiv), 3DPAFIPN (14.9 mg, 0.023 mmol, 5 mol%), DIPEA (0.24 mL, 1.38 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (9 mL, 0.05 M). Purification on silica gel (10% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (103 mg, 66%).

**R<sub>f</sub>**: 0.46 (20% EtOAc/hexanes)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 6.30 (p, *J* = 1.8 Hz, 2H), 3.41 (s, 2H), 2.97 (s, 2H), 2.45 (s, 2H), 1.41 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 171.6, 131.2 (q, <sup>3</sup>*J*<sub>C-F</sub> = 5.4 Hz), 125.4 (q, <sup>2</sup>*J*<sub>C-F</sub> = 31.8 Hz), 123.0 (q, <sup>1</sup>*J*<sub>C-F</sub> = 272.4 Hz), 56.7, 54.7, 46.1, 37.8, 27.8, 21.4 ppm.

**HRMS (APCI)** *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>15</sub>H<sub>18</sub>F<sub>6</sub>NO, 342.12871, found 342.12899.



**2-(*tert*-butyl)-7,9-dimethoxy-2-azaspiro[4.5]deca-6,9-dien-3-one (7):**

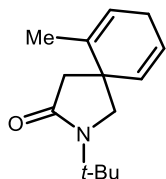
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(3,5-dimethoxybenzyl)-2-methylpropan-2-amine (**S16**) (60 mg, 0.2 mmol, 1.0 equiv), 3DPAFIPN (6.5 mg, 0.01 mmol, 5 mol%), DIPEA (0.10 mL, 0.6 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (4 mL, 0.05 M). Purification by preparatory TLC (20% acetone/hexanes eluent) afforded the title compound as an off-white amorphous solid (28 mg, 54%).

**R<sub>f</sub>**: 0.29 (20% acetone/hexanes)

**<sup>1</sup>H NMR** (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 4.45 (t, J = 1.3 Hz, 2H), 3.13 (s, 6H), 3.03 (s, 2H), 2.95 (qt, J = 8.0, 1.3 Hz, 2H), 2.35 (s, 2H), 1.40 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, C<sub>6</sub>D<sub>6</sub>) δ 173.3, 152.9, 98.4, 60.1, 54.0, 53.6, 49.5, 39.4, 32.0, 28.0 ppm.

**HRMS (APCI)** m/z: [M+H]<sup>+</sup> calc'd. for C<sub>15</sub>H<sub>24</sub>NO<sub>3</sub>, 266.17507, found 266.17541.



**2-(tert-butyl)-6-methyl-2-azaspiro[4.5]deca-6,9-dien-3-one (8):**

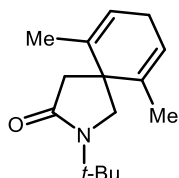
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(tert-butyl)-2-chloro-*N*-(2-methylbenzyl)acetamide (**S18**) (126.6 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (5-10% acetone/hexanes) afforded the title compound as a yellow oil (72 mg, 66%).

**R<sub>f</sub>**: 0.27 (10% acetone/hexanes)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 5.70 (dtd, J = 9.8, 3.3, 1.5 Hz, 1H), 5.57 (dt, J = 9.9, 2.1 Hz, 1H), 5.46 (tt, J = 3.4, 1.6 Hz, 1H), 3.45 (d, J = 10.2 Hz, 1H), 3.21 (d, J = 10.2 Hz, 1H), 2.59 (tq, J = 3.7, 1.9 Hz, 2H), 2.49 (d, J = 17.1 Hz, 1H), 2.23 (d, J = 17.1 Hz, 1H), 1.72 (q, J = 1.8 Hz, 3H), 1.37 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 173.7, 134.7, 131.9, 123.6, 121.6, 57.4, 54.2, 45.8, 37.9, 27.8, 27.0, 19.0 ppm.

**HRMS (APCI)** m/z: [M+H]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>22</sub>NO, 220.16959, found 220.16959.



**2-(tert-butyl)-6,10-dimethyl-2-azaspiro[4.5]deca-6,9-dien-3-one (9):**

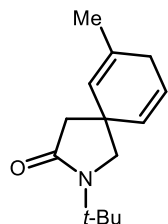
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(tert-butyl)-2-chloro-*N*-(2,6-dimethylbenzyl)acetamide (**S20**) (133.9 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (10-15% acetone/hexanes) afforded the title compound as a yellow oil (98 mg, 84%).

**R<sub>f</sub>**: 0.24 (10% acetone/hexanes)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 5.47 (t, J = 3.5 Hz, 2H), 3.39 (s, 2H), 2.59 (tt, J = 3.7, 1.9 Hz, 2H), 2.47 (s, 2H), 1.75 – 1.72 (m, 6H), 1.41 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 174.1, 134.8, 121.3, 55.6, 54.5, 42.5, 39.8, 27.8, 27.3, 18.9 ppm.

**HRMS (APCI)** m/z: [M+H]<sup>+</sup> calc'd. for C<sub>15</sub>H<sub>24</sub>NO, 234.18524, found 234.18562.



**2-(tert-butyl)-7-methyl-2-azaspiro[4.5]deca-6,9-dien-3-one (10):**

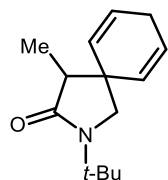
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(tert-butyl)-2-chloro-*N*-(3-methylbenzyl)acetamide (**S22**) (126.9 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a yellow oil (65 mg, 59%).

**R<sub>f</sub>**: 0.34 (20% EtOAc/hexanes)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 5.74 (dt, *J* = 10.0, 3.3 Hz, 1H), 5.65 (dq, *J* = 10.0, 2.1 Hz, 1H), 5.35 (s, 1H), 3.24 (s, 2H), 2.54 – 2.50 (m, 2H), 2.26 (s, 2H), 1.69 (s, 3H), 1.37 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 173.8, 132.1, 130.2, 125.0, 124.3, 58.7, 54.0, 47.9, 37.6, 31.2, 27.9, 23.2 ppm.

**HRMS (APCI)** *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>22</sub>NO, 220.16959, found 220.16966.



**2-(tert-butyl)-4-methyl-2-azaspiro[4.5]deca-6,9-dien-3-one (11):**

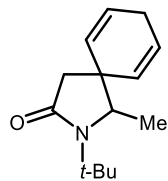
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-benzyl-*N*-(tert-butyl)-2-chloropropanamide (**S24**) (127 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (2-3% acetone/hexanes) afforded the title compound as an off-white amorphous solid (94 mg, 85%).

**R<sub>f</sub>**: 0.26 (5% acetone/hexanes)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.93 – 5.81 (m, 2H), 5.55 (dq, *J* = 9.6, 1.9 Hz, 1H), 5.48 (dq, *J* = 10.0, 2.1 Hz, 1H), 3.24 (d, *J* = 9.7 Hz, 1H), 3.19 (d, *J* = 9.8 Hz, 1H), 2.70 – 2.62 (m, 1H), 2.24 (q, *J* = 7.3 Hz, 1H), 1.38 (s, 9H), 0.94 (d, *J* = 7.3 Hz, 3H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 175.9, 130.0, 127.2, 127.0, 125.8, 56.6, 53.9, 49.3, 41.9, 27.9, 26.8, 9.7 ppm.

**HRMS (APCI)** *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>22</sub>NO, 220.16959, found 220.16969.



**2-(tert-butyl)-1-methyl-2-azaspiro[4.5]deca-6,9-dien-3-one (12):**

Prepared according to General Dearomative Spirolactamization Procedure 2 using *N*-(tert-butyl)-2-chloro-*N*-(1-phenylethyl)acetamide (**S26**) (254 mg, 1.0 mmol, 1.0 equiv), 3DPAFIPN (32.4 mg,

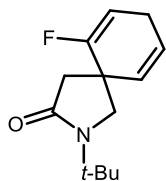
0.05 mmol, 5 mol%), DIPEA (0.52 mL, 3.0 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (20 mL, 0.05 M). Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (89.7 mg, 41%).

**R<sub>f</sub>**: 0.45 (20% EtOAc/hexanes)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.88 (dtd, J = 10.3, 3.4, 1.7 Hz, 1H), 5.81 (dq, J = 10.2, 2.0 Hz, 1H), 5.72 (dtd, J = 10.2, 3.3, 1.7 Hz, 1H), 5.60 (dq, J = 10.3, 2.1 Hz, 1H), 3.49 (q, J = 6.5 Hz, 1H), 2.64 (m, 2H), 2.51 (d, J = 16.6 Hz, 1H), 2.11 (d, J = 16.6 Hz, 1H), 1.43 (s, 9H), 1.20 (d, J = 6.4 Hz, 3H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 73.0, 131.3, 127.9, 127.0, 123.3, 64.9, 54.2, 45.5, 40.2, 28.4, 26.7, 17.7 ppm.

**HRMS (APCI)** m/z: [M+H]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>22</sub>NO, 220.16959, found 220.16983.



**2-(*tert*-butyl)-6-fluoro-2-azaspiro[4.5]deca-6,9-dien-3-one (13):**

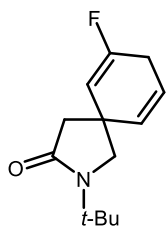
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(*tert*-butyl)-2-chloro-*N*-(2-fluorobenzyl)acetamide (**S28**) (128.6 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (0-20% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (81 mg, 72%).

**R<sub>f</sub>**: 0.32 (20% EtOAc/hexanes)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 5.72 – 5.64 (m, 2H), 5.33 (dt, J = 17.5, 3.9 Hz, 1H), 3.71 (d, J = 9.8 Hz, 1H), 3.27 (d, J = 9.9 Hz, 1H), 2.83 – 2.77 (m, 3H), 2.25 (d, J = 16.7 Hz, 1H), 1.40 (d, J = 0.8 Hz, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 172.6, 158.4 (d, <sup>1</sup>J<sub>C-F</sub> = 254.7 Hz), 130.2 (d, <sup>3</sup>J<sub>C-F</sub> = 6.4 Hz), 123.2 (d, <sup>4</sup>J<sub>C-F</sub> = 2.7 Hz), 101.7 (d, <sup>2</sup>J<sub>C-F</sub> = 17.2 Hz), 55.4, 54.4, 43.6, 37.8 (d, <sup>2</sup>J<sub>C-F</sub> = 23.2 Hz), 27.8, 26.4 (d, <sup>3</sup>J<sub>C-F</sub> = 7.0 Hz) ppm.

**HRMS (APCI)** m/z: [M+H]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>19</sub>FNO, 224.14452, found 224.14472.



**2-(*tert*-butyl)-7-fluoro-2-azaspiro[4.5]deca-6,9-dien-3-one (14):**

Prepared according to General Dearomative Spirolactamization Procedure 2 using *N*-(*tert*-butyl)-2-chloro-*N*-(3-fluorobenzyl)acetamide (**S30**) (129 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (84.7 mg, 76%).

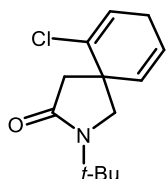
**R<sub>f</sub>**: 0.26 (20% EtOAc/hexanes)



**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 5.69 (ddt, J = 9.9, 7.8, 3.3 Hz, 1H), 5.64 (ddq, J = 9.8, 3.7, 1.9 Hz, 1H), 5.24 (dq, J = 17.0, 1.5 Hz, 1H), 3.34 (dd, J = 9.9, 1.1 Hz, 1H), 3.32 (d, J = 9.9 Hz, 1H), 2.86 – 2.82 (m, 2H), 2.36 (d, J = 1.0 Hz, 1H), 2.35 (d, J = 16.6 Hz, 1H), 1.39 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 173.2, 158.5 (d, <sup>1</sup>J<sub>C-F</sub> = 256.0 Hz), 130.5 (d, <sup>4</sup>J<sub>C-F</sub> = 2.8 Hz), 121.9 (d, <sup>3</sup>J<sub>C-F</sub> = 10.6 Hz), 106.3 (d, <sup>2</sup>J<sub>C-F</sub> = 15.0 Hz), 58.4 (d, <sup>4</sup>J<sub>C-F</sub> = 2.6 Hz), 54.2, 47.6 (d, <sup>4</sup>J<sub>C-F</sub> = 2.0 Hz), 39.5 (d, <sup>3</sup>J<sub>C-F</sub> = 7.8 Hz), 27.9, 27.2 (d, <sup>2</sup>J<sub>C-F</sub> = 26.4 Hz) ppm.

**HRMS (APCI)** m/z: [M+H]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>19</sub>FNO, 224.14452, found 224.14468.



**2-(tert-butyl)-6-chloro-2-azaspiro[4.5]deca-6,9-dien-3-one (15):**

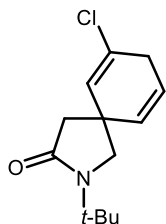
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(tert-butyl)-2-chloro-*N*-(2-chlorobenzyl)acetamide (**S32**) (137.1 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (5-10% acetone/hexanes) afforded the title compound as a yellow oil (57 mg, 47%).

**R<sub>f</sub>**: 0.22 (10% acetone/hexanes)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 5.93 (t, J = 3.7 Hz, 1H), 5.75 – 5.67 (m, 2H), 3.79 (d, J = 10.1 Hz, 1H), 3.27 (d, J = 10.1 Hz, 1H), 2.92 (d, J = 17.0 Hz, 1H), 2.79 (dq, J = 4.0, 2.4, 2.0 Hz, 2H), 2.27 (d, J = 16.9 Hz, 1H), 1.41 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 172.8, 134.4, 130.9, 124.8, 122.0, 56.82, 54.5, 45.2, 40.4, 28.5, 27.8 ppm.

**HRMS (APCI)** m/z: [M+H]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>19</sub>ClNO, 240.11497, found 240.11541.



**2-(tert-butyl)-7-chloro-2-azaspiro[4.5]deca-6,9-dien-3-one (16):**

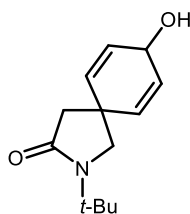
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(tert-butyl)-2-chloro-*N*-(3-chlorobenzyl)acetamide (**S34**) (137.1 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (10% EtOAc/hexanes) afforded the title compound as a yellow amorphous solid (84 mg, 70%).

**R<sub>f</sub>**: 0.31 (20% EtOAc/hexanes)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 5.78 (q, J = 1.8 Hz, 1H), 5.69 (dt, J = 10.0, 3.3 Hz, 1H), 5.63 (dq, J = 10.0, 2.0 Hz, 1H), 3.30 (dd, J = 18.0, 12.0 Hz, 2H), 2.89 (dt, J = 3.4, 2.0 Hz, 2H), 2.33 (d, J = 1.9 Hz, 2H), 1.36 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 173.0, 131.0, 129.4, 127.2, 123.4, 57.9, 54.3, 47.1, 40.0, 33.6, 27.8 ppm.

**HRMS (APCI)** m/z: [M+H]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>19</sub>ClNO, 240.11497, found 240.11508.



**2-(*tert*-butyl)-8-hydroxy-2-azaspiro[4.5]deca-6,9-dien-3-one (17):**

Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(*tert*-butyl)-2-chloro-*N*-(4-chlorobenzyl)acetamide (**S36**) (137 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (50-75% EtOAc/hexanes) afforded the title compound (72.2 mg, 65%, 1:1 d.r.).

**Diastereomer 1 (elutes first, 36.2 mg, yellow amorphous solid):**

**R<sub>f</sub>:** 0.30 (75% EtOAc/hexanes)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.93 (dq, *J* = 10.3, 3.0 Hz, 2H), 5.88 (dd, *J* = 10.3, 1.3 Hz, 2H), 4.54 (s, 1H), 3.33 (s, 2H), 2.32 (s, 2H), 1.39 (s, 9H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 173.0, 132.9, 128.1, 62.3, 56.5, 54.3, 46.2, 37.2, 27.9 ppm.

**HRMS (APCI)** *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>20</sub>NO<sub>2</sub>, 222.14886, found 222.14877.

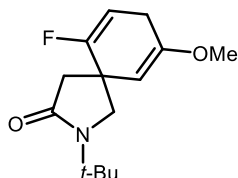
**Diastereomer 2 (elutes second, 36.0 mg, yellow amorphous solid):**

**R<sub>f</sub>:** 0.22 (75% EtOAc/hexanes)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.94 (dq, *J* = 10.3, 3.1 Hz, 2H), 5.87 (dq, *J* = 10.2, 1.5 Hz, 2H), 4.51 (s, 1H), 3.28 (s, 2H), 2.37 (s, 2H), 1.39 (s, 9H) ppm.

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 173.2, 132.9, 128.2, 62.2, 57.0, 54.3, 45.7, 37.2, 27.9 ppm.

**HRMS (APCI)** *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>20</sub>NO<sub>2</sub>, 222.14886, found 222.14897.



**2-(*tert*-butyl)-6-fluoro-9-methoxy-2-azaspiro[4.5]deca-6,9-dien-3-one (18):**

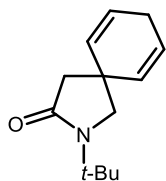
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(*tert*-butyl)-2-chloro-*N*-(2-fluoro-5-methoxybenzyl)acetamide (**S38**) (143.9 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a yellow oil (88 mg, 69%).

**R<sub>f</sub>:** 0.26 (20% EtOAc/hexanes)

**<sup>1</sup>H NMR** (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 4.86 (dt, *J* = 16.1, 3.7 Hz, 1H), 4.36 (d, *J* = 7.3 Hz, 1H), 3.52 (dd, *J* = 9.6, 1.0 Hz, 1H), 3.01 (s, 3H), 2.95 (d, *J* = 9.6 Hz, 1H), 2.87 (d, *J* = 16.5 Hz, 1H), 2.61 – 2.48 (m, 2H), 2.23 (d, *J* = 16.5 Hz, 1H), 1.32 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, C<sub>6</sub>D<sub>6</sub>) δ 172.0, 159.1 (d, <sup>1</sup>*J*<sub>C-F</sub> = 254.5 Hz), 153.3 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.8 Hz), 99.8 (d, <sup>2</sup>*J*<sub>C-F</sub> = 20.1 Hz), 98.5 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.4 Hz), 56.39, 54.2, 44.7, 38.8 (d, <sup>2</sup>*J*<sub>C-F</sub> = 23.8 Hz), 28.3 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.2 Hz), 27.7 ppm.

**HRMS (APCI)** *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>21</sub>FNO<sub>2</sub>, 254.15508, found 254.15549.



**2-(*tert*-butyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (19):**

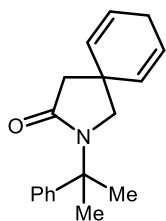
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-benzyl-*N*-(*tert*-butyl)-2-chloroacetamide (**S39**) (120 mg, 0.5 mmol, 1.0 equiv), 3DPAFIPN (16.2 mg, 0.025 mmol, 5 mol%), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (10 mL, 0.05 M). Purification on silica gel (10% EtOAc/hexanes) afforded the title compound as a white amorphous solid (103 mg, 73%).

**R<sub>f</sub>**: 0.28 (20% EtOAc/hexanes)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 5.77 (dt, *J* = 10.1, 3.3 Hz, 2H), 5.66 (dt, *J* = 10.3, 2.1 Hz, 2H), 3.28 (s, 2H), 2.63 (p, *J* = 2.7 Hz, 2H), 2.31 (s, 2H), 1.38 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 173.7, 130.3, 124.7, 58.8, 54.1, 48.0, 36.4, 27.9, 26.4 ppm.

**HRMS (APCI)** *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>20</sub>NO, 206.15394, found 206.15423.



**2-(2-phenylpropan-2-yl)-2-azaspiro[4.5]deca-6,9-dien-3-one (S51):**

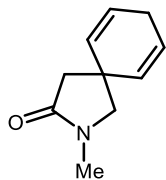
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-benzyl-2-chloro-*N*-(2-phenylpropan-2-yl)acetamide (**S41**) (121 mg, 0.4 mmol, 1.0 equiv), 3DPAFIPN (13.0 mg, 0.020 mmol, 5 mol%), DIPEA (0.21 mL, 1.2 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (8 mL, 0.05 M). Purification on silica gel (10-20% EtOAc/hexanes) afforded the title compound as a white amorphous solid (63 mg, 59%).

**R<sub>f</sub>**: 0.36 (20% EtOAc/hexanes)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 7.37 – 7.28 (m, 4H), 7.23 (tt, *J* = 6.6, 2.1 Hz, 1H), 5.78 (dt, *J* = 10.3, 3.3 Hz, 2H), 5.70 (dt, *J* = 10.3, 2.1 Hz, 2H), 3.22 (s, 2H), 2.63 (dh, *J* = 7.4, 2.2 Hz, 2H), 2.36 (s, 2H), 1.75 (s, 6H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 173.5, 146.7, 130.2, 128.5, 126.9, 125.2, 124.8, 59.6, 59.0, 47.9, 36.7, 27.9, 26.4.

**HRMS (APCI)** *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>18</sub>H<sub>22</sub>NO, 268.16959, found 268.17006.

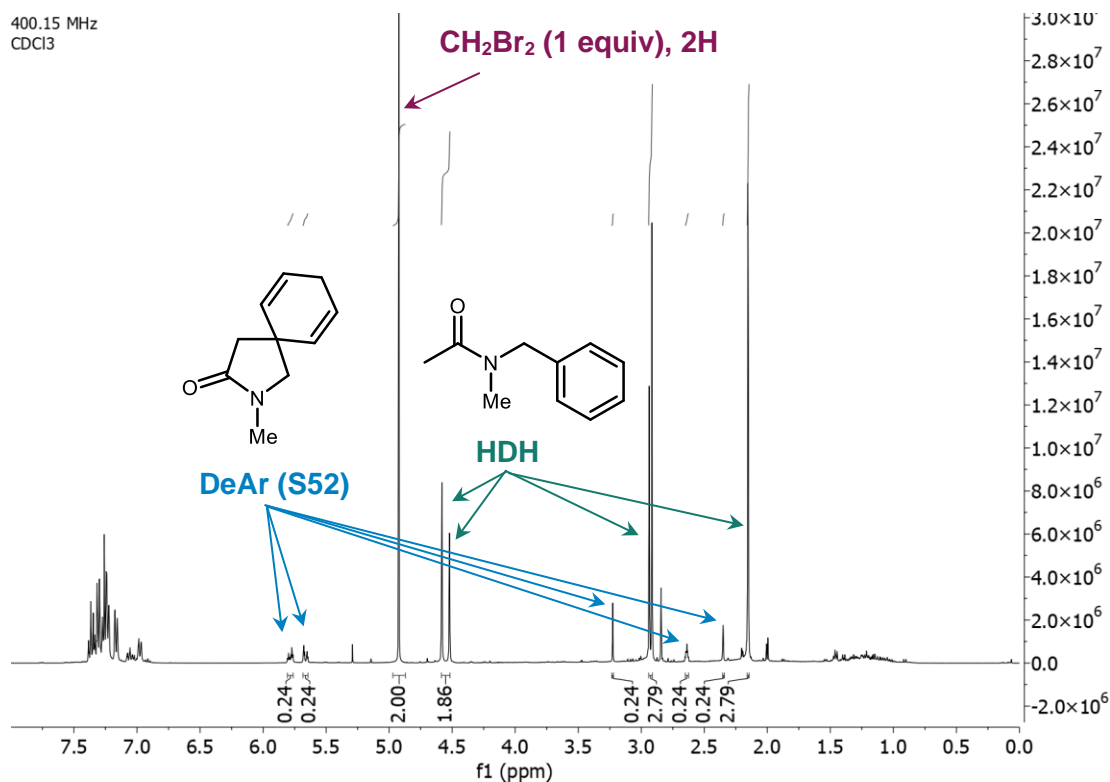


### 2-methyl-2-azaspiro[4.5]deca-6,9-dien-3-one (S52):

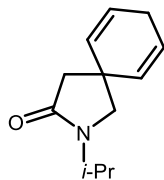
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-benzyl-2-chloro-*N*-methylacetamide (S43) (20 mg, 0.1 mmol, 1.0 equiv), 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (52  $\mu$ L, 0.3 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (2 mL, 0.05 M). CDCl<sub>3</sub> and an internal standard of dibromomethane (7  $\mu$ L, 0.1 mmol) were added to the crude residue. The sample was analyzed by <sup>1</sup>H NMR (d1 = 5 s), and the integral values were used to calculate the yield of the title compound (12%) and the hydrodehalogenation byproduct (93%). <sup>1</sup>H NMR spectrum of HDH byproduct is consistent with reported values.<sup>26</sup>

#### Characteristic peaks

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.82 – 5.75 (m, 2H), 5.66 (dt, *J* = 10.3, 2.0 Hz, 2H), 3.23 (s, 2H), 2.84 (t, *J* = 0.8 Hz, 3H), 2.64 (ddd, *J* = 5.4, 3.4, 2.0 Hz, 2H), 2.35 (d, *J* = 0.9 Hz, 2H) ppm.



<sup>26</sup> Rauser, M.; Ascheberg, A.; Niggemann, M. Direct Reductive *N*-Functionalization of Aliphatic Nitro Compounds. *Chem. Eur. J.* **2018**, *24*, 3970-3974.

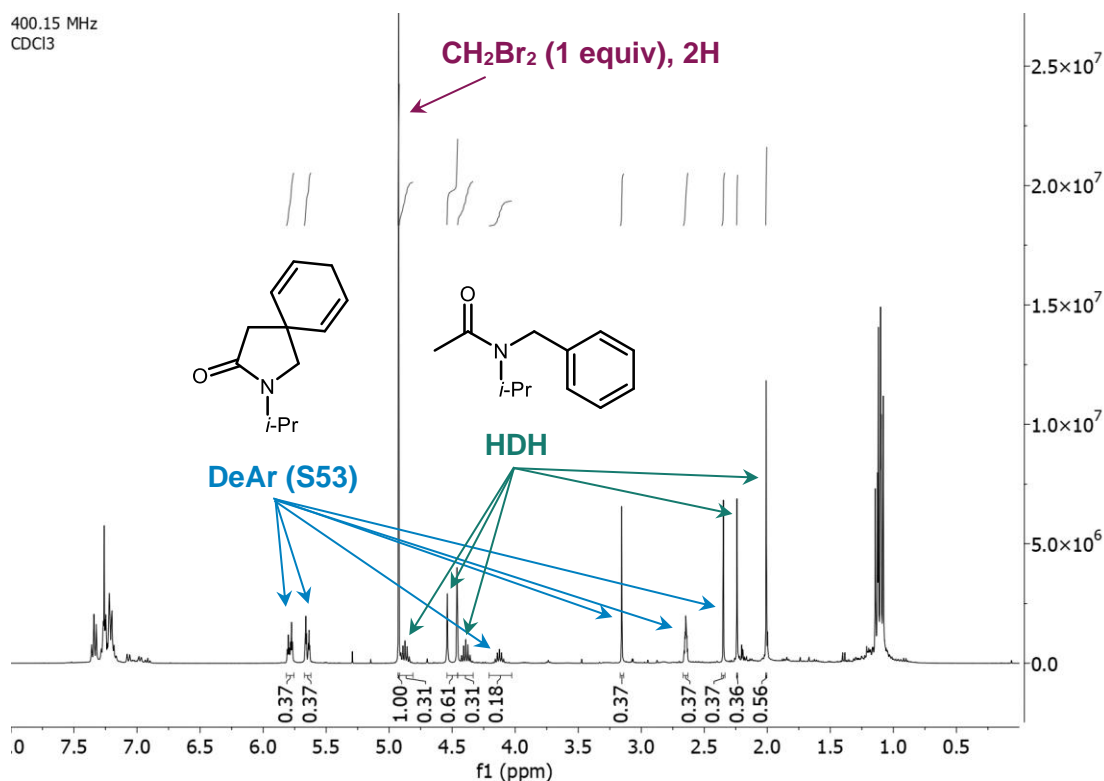


### 2-isopropyl-2-azaspiro[4.5]deca-6,9-dien-3-one (S53):

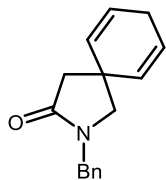
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-benzyl-2-chloro-*N*-isopropylacetamide (**S45**) (23 mg, 0.1 mmol, 1.0 equiv), 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (52  $\mu$ L, 0.3 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (2 mL, 0.05 M). CDCl<sub>3</sub> and an internal standard of dibromomethane (7  $\mu$ L, 0.1 mmol) were added to the crude residue. The sample was analyzed by <sup>1</sup>H NMR (d1 = 5 s), and the integral values were used to calculate the yield of the title compound (37%) and the hydrodehalogenation byproduct (61%). <sup>1</sup>H NMR spectrum of HDH byproduct is consistent with reported values.<sup>27</sup>

#### Characteristic peaks

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.86 – 5.74 (m, 2H), 5.65 (dt, *J* = 10.4, 2.0 Hz, 2H), 4.12 (p, *J* = 6.7 Hz, 1H), 3.15 (s, 2H), 2.65 (tt, *J* = 3.4, 2.0 Hz, 2H), 2.35 (s, 2H) ppm.



<sup>27</sup> Rauser, M.; Ascheberg, A.; Niggemann, M. Direct Reductive *N*-Functionalization of Aliphatic Nitro Compounds. *Chem. Eur. J.* **2018**, *24*, 3970-3974.

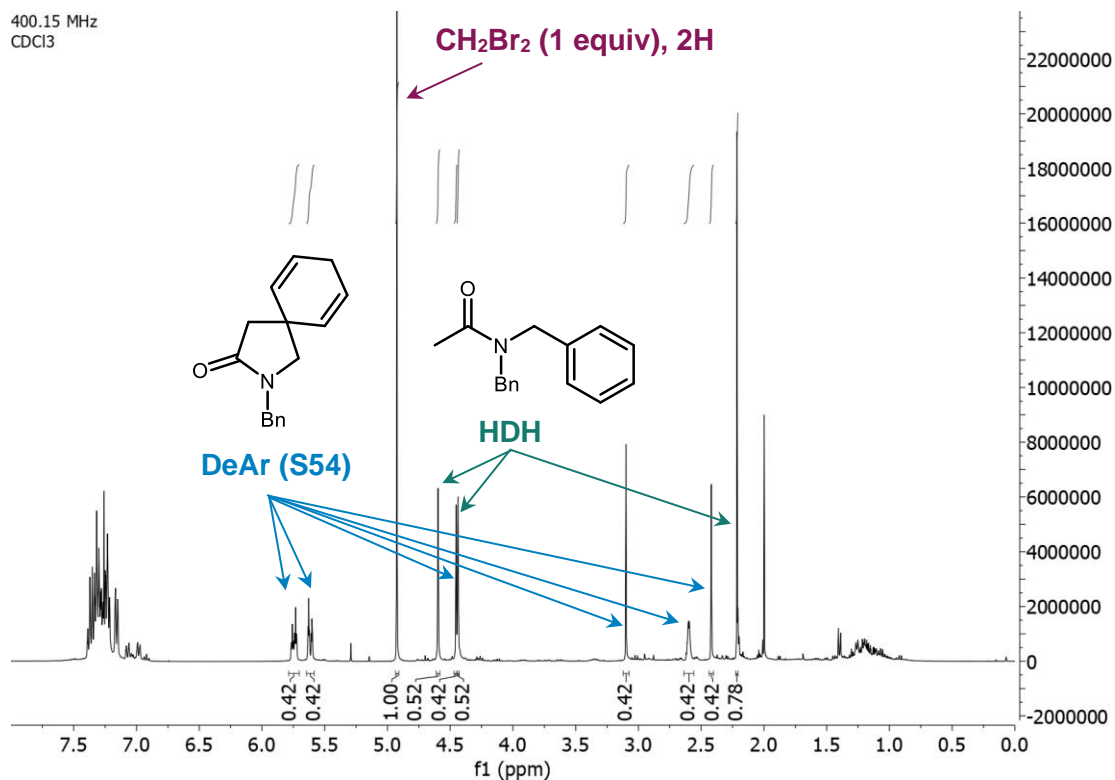


### 2-benzyl-2-azaspiro[4.5]deca-6,9-dien-3-one (S54):

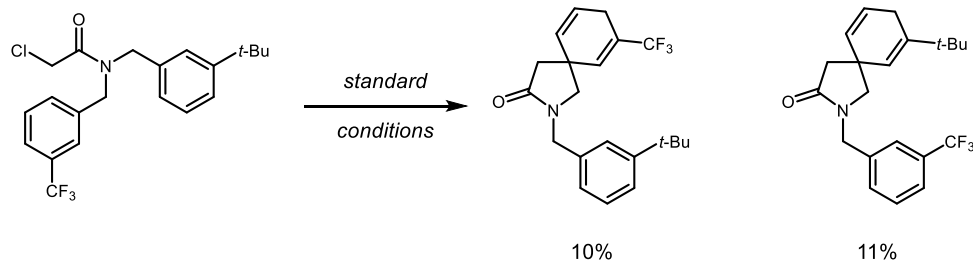
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N,N*-dibenzyl-2-chloroacetamide (**S46**) (27 mg, 0.1 mmol, 1.0 equiv), 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (52  $\mu$ L, 0.3 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (2 mL, 0.05 M). CDCl<sub>3</sub> and an internal standard of dibromomethane (7  $\mu$ L, 0.1 mmol) were added to the crude residue. The sample was analyzed by <sup>1</sup>H NMR (d1 = 5 s), and the integral values were used to calculate the yield of the title compound (42%) and the hydrodehalogenation byproduct (52%). <sup>1</sup>H NMR spectrum of HDH byproduct is consistent with reported values.<sup>28</sup>

#### Characteristic peaks

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.77 – 5.69 (m, 2H), 5.61 (dt, *J* = 10.4, 2.0 Hz, 2H), 4.45 (s, 2H), 3.10 (s, 2H), 2.60 (dtt, *J* = 4.1, 3.3, 2.1 Hz, 2H), 2.42 (s, 2H) ppm.



<sup>28</sup> Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. A Convenient and General Iron-Catalyzed Reduction of Amides to Amines. *Angew. Chem. Int. Ed.* **2009**, 48, 9507-9510.



**2-(3-*tert*-butylbenzyl)-7-(trifluoromethyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (S55) and 7-*tert*-butyl-2-(3-(trifluoromethyl)benzyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (S56):**

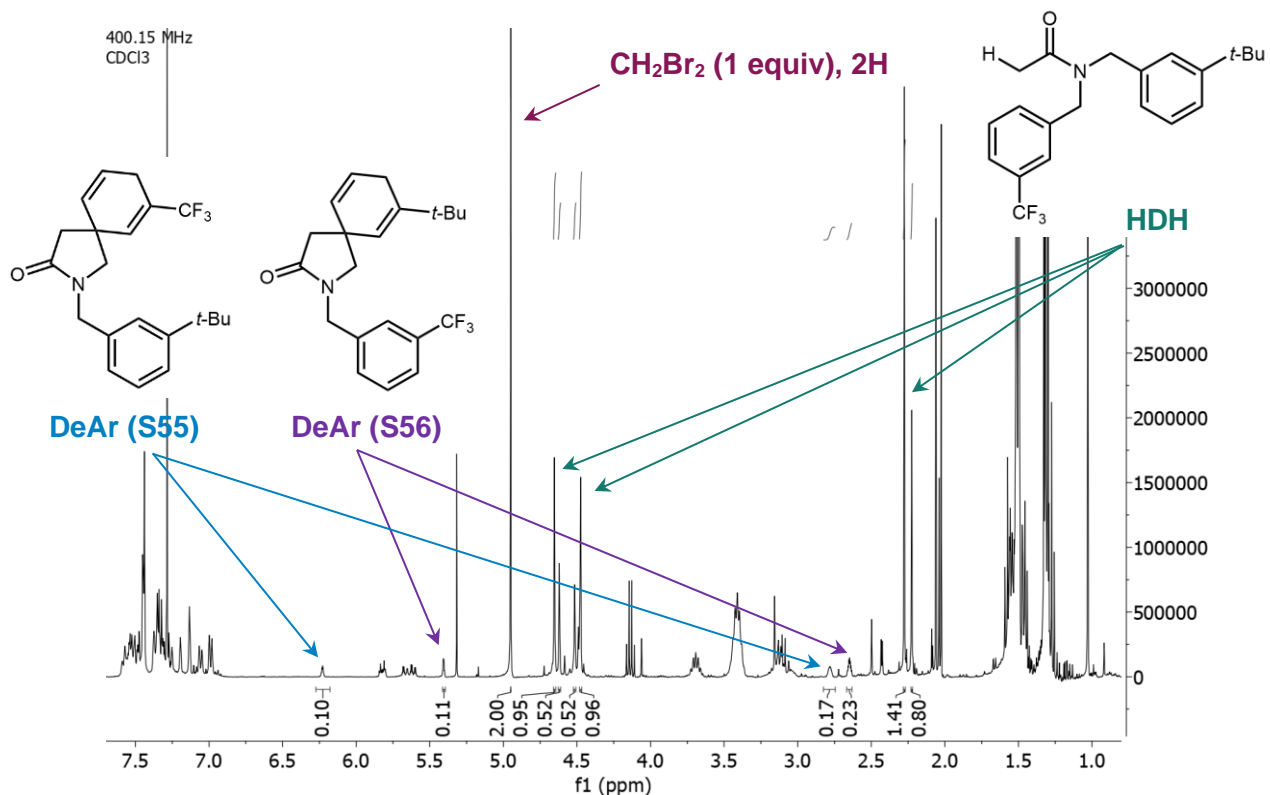
Prepared according to General Dearomative Spirolactamization Procedure 1 using *N*-(3-(*tert*-butyl)benzyl)-2-chloro-*N*-(3-(trifluoromethyl)benzyl)acetamide (**S48**) (39.8 mg, 0.1 mmol, 1.0 equiv), 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (52  $\mu$ L, 0.3 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (2 mL, 0.05 M). CDCl<sub>3</sub> and an internal standard of dibromomethane (7  $\mu$ L, 0.1 mmol) were added to the crude residue. The sample was analyzed by <sup>1</sup>H NMR (d1 = 5 s), and the integral values were used to calculate the yield of the title compounds (10%, 11%) and the hydrodehalogenation byproduct (74%).

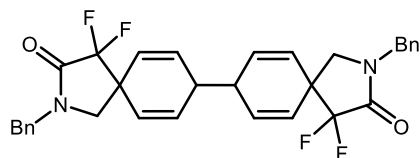
**S55 (characteristic peaks):**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.26 – 6.18 (m, 1H), 2.81 – 2.74 (m, 2H) ppm.

**S56 (characteristic peaks):**

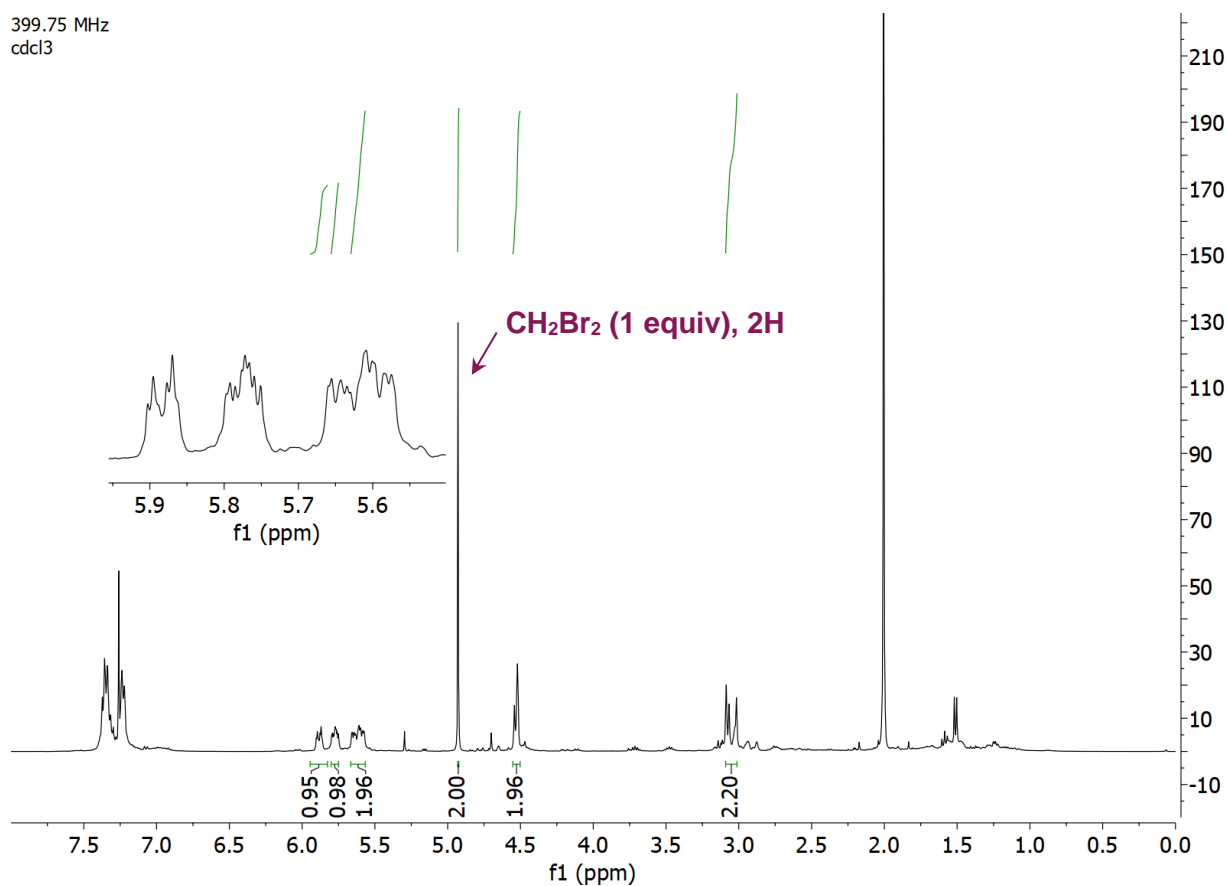
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.41 (q, *J* = 1.7 Hz, 1H), 2.65 (tt, *J* = 3.8, 1.9 Hz, 2H) ppm.



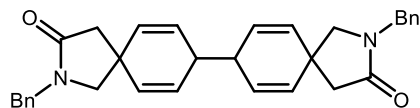


**2,2'-dibenzyl-4,4,4',4'-tetrafluoro-2,2'-diazab[8,8'-bispiro[4.5]decane-6,6',9,9'-tetraene]-3,3'-dione (S57):**

Prepared according to General Dearomative Spirolactamization Procedure 1 using *N,N*-dibenzyl-2-bromo-2,2-difluoroacetamide (**S49**) (35.4 mg, 0.1 mmol, 1.0 equiv), 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (52  $\mu$ L, 0.3 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (2 mL, 0.05 M). CDCl<sub>3</sub> and an internal standard of dibromomethane (7  $\mu$ L, 0.1 mmol) were added to the crude residue. The sample was analyzed by <sup>1</sup>H NMR (d1 = 5 s), and the integral values were used to calculate the yield of the title compound (98%).

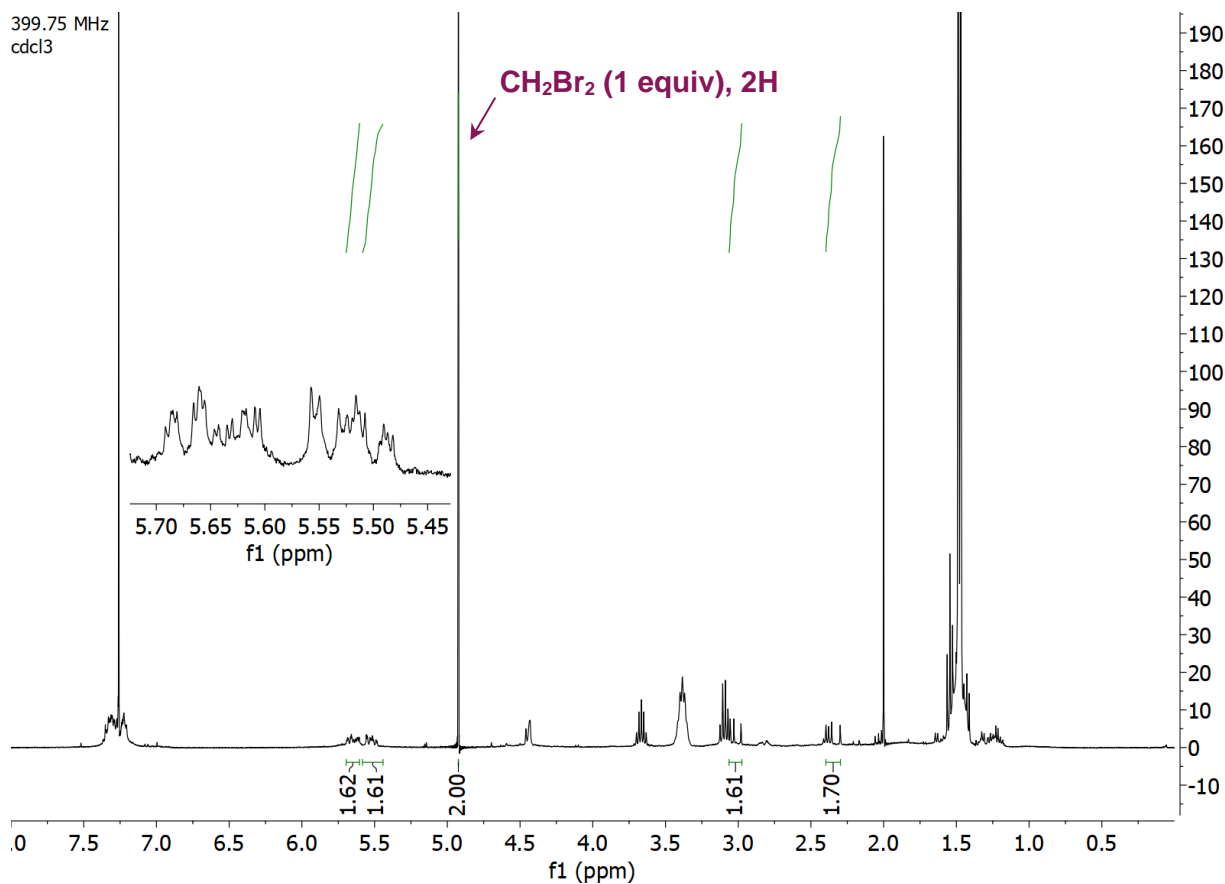




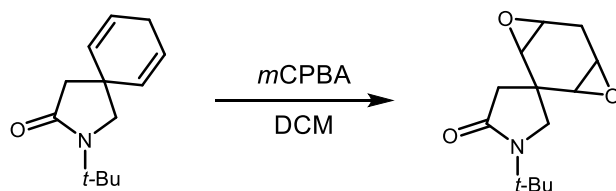


**2,2'-dibenzyl-2,2'-diazab[8,8']-bisp[4.5]decane-6,6',9,9'-tetraene-3,3'-dione (S58):**

Prepared according to General Dearomative Spirolactamization Procedure 1 using *N,N*-dibenzyl-2,2,2-trichloroacetamide (**S50**) (34.3 mg, 0.1 mmol, 1.0 equiv), 3DPAFIPN (3.2 mg, 0.005 mmol, 5 mol%), DIPEA (52  $\mu$ L, 0.3 mmol, 3.0 equiv), and 50% H<sub>2</sub>O/MeCN (2 mL, 0.05 M). CDCl<sub>3</sub> and an internal standard of dibromomethane (7  $\mu$ L, 0.1 mmol) were added to the crude residue. The sample was analyzed by <sup>1</sup>H NMR (d1 = 5 s), and the integral values were used to calculate the yield of the title compound (81%).

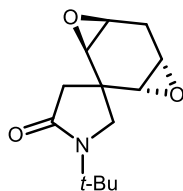


## VIII-A. Derivatization



### 1-(*tert*-butyl)-4',8'-dioxaspiro[pyrrolidine-3,2'-tricyclo[5.1.0.0<sup>3,5</sup>]octan]-5-one (**20**):

To an reaction vial charged with 2-(*tert*-butyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (**19**) (62 mg, 0.3 mmol, 1.0 equiv) cooled to 0 °C was added CH<sub>2</sub>Cl<sub>2</sub> (6 mL, 0.05 M) and *m*CPBA (75%, 172 mg, 0.75 mmol, 2.5 equiv). The resulting solution was allowed to stir at 23 °C for 17 hours. The precipitate was filtered and washed with CH<sub>2</sub>Cl<sub>2</sub> and 1 M NaOH (aq). The filtrate was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x), washed with brine, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The crude residue was purified on silica gel (10-50% acetone/hexanes) to yield the title compound (57.0 mg, 82%, 5:6:1 d.r.; diastereomers **2** and **3** isolated as a mixture).



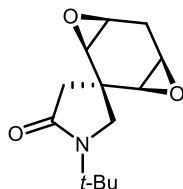
**Diastereomer 1** (elutes first, 23.8 mg, white amorphous solid): (1'*R*,3'*R*,5'*S*,7'*S*)-1-(*tert*-butyl)-4',8'-dioxaspiro[pyrrolidine-3,2'-tricyclo[5.1.0.0<sup>3,5</sup>]octan]-5-one:

R<sub>f</sub>: 0.55 (50% acetone/hexanes)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.68 (d, *J* = 10.5 Hz, 1H), 3.37 (d, *J* = 10.5 Hz, 1H), 3.18 (tq, *J* = 4.0, 1.8 Hz, 2H), 2.94 (dt, *J* = 5.8, 2.9 Hz, 2H), 2.71 (d, *J* = 17.0 Hz, 1H), 2.42 (d, *J* = 16.9 Hz, 1H), 2.34 (t, *J* = 2.3 Hz, 2H), 1.43 (s, 9H) ppm.

<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 172.8, 56.5, 55.9, 54.5, 52.4, 51.0, 50.8, 41.6, 34.8, 27.9, 23.9 ppm.

HRMS (APCI) *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>20</sub>NO<sub>3</sub>, 238.14377, found 238.14375.



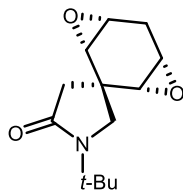
**Diastereomer 2** (elutes second, 29.0 mg, white amorphous solid): (1'*R*,3'*r*,3'*S*,5'*R*,7'*S*)-1-(*tert*-butyl)-4',8'-dioxaspiro[pyrrolidine-3,2'-tricyclo[5.1.0.0<sup>3,5</sup>]octan]-5-one:

R<sub>f</sub>: 0.35 (50% acetone/hexanes)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.78 (s, 2H), 3.23 (ddd, *J* = 4.1, 2.9, 1.2 Hz, 2H), 3.05 – 3.01 (m, 2H), 2.76 (dt, *J* = 17.3, 1.3 Hz, 1H), 2.43 (s, 2H), 2.24 (dt, *J* = 17.3, 3.0 Hz, 1H), 1.44 (s, 9H) ppm.

<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 172.0, 55.8, 54.7, 53.1, 51.3, 41.0, 34.4, 27.9, 23.0 ppm.

HRMS (APCI) *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>20</sub>NO<sub>3</sub>, 238.14377, found 238.14384.



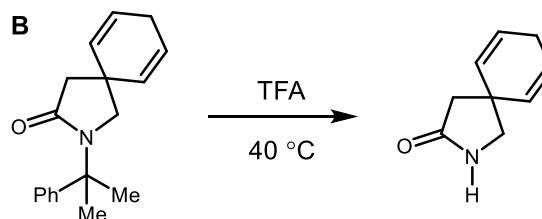
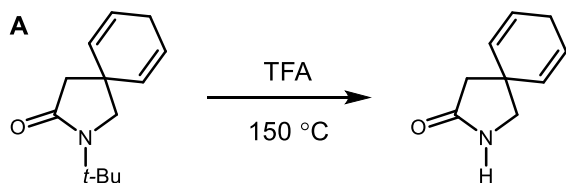
**Diastereomer 3** (elutes second, 5.1 mg, white amorphous solid): (1'*R*,3*s*,3'*S*,5'*R*,7'*S*)-1-(*tert*-butyl)-4',8'-dioxaspiro[pyrrolidine-3,2'-tricyclo[5.1.0.0<sup>3,5</sup>]octan]-5-one (characteristic peaks):

**R<sub>f</sub>**: 0.35 (50% acetone/hexanes)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 3.43 (s, 2H), 3.20 (ddd, *J* = 3.9, 2.9, 1.2 Hz, 2H), 3.01 – 2.99 (m, 2H), 2.79 (s, 2H), 2.21 (dt, *J* = 17.2, 3.0 Hz, 2H), 1.43 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 172.8, 56.0, 54.5, 52.0, 41.6, 34.2, 27.9 ppm.

**HRMS** (APCI) *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>20</sub>NO<sub>3</sub>, 238.14377, found 238.14384.



## 2-azaspiro[4.5]deca-6,9-dien-3-one (21):

**Procedure A:** Dissolved 2-(*tert*-butyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (**19**) (20.5 mg, 0.1 mmol, 1.0 equiv) in TFA (4 mL). The reaction was heated to 150 °C in a pressure tube. After 16 hours, quenched with 1 M NaOH (aq), extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x) and concentrated under reduced pressure. The crude residue was purified on silica gel (10-100% ethyl acetate/hexanes) to yield the title compound as an off-white amorphous solid (14.9 mg, 100%).

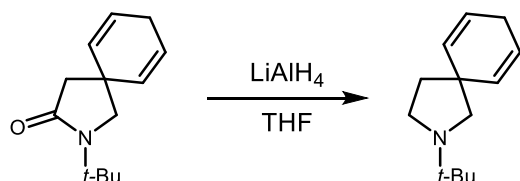
**Procedure B:** Dissolved 2-(2-phenylpropan-2-yl)-2-azaspiro[4.5]deca-6,9-dien-3-one (**S51**) (57.8 mg, 0.22 mmol, 1.0 equiv) in TFA (1 mL). The reaction was heated to 40 °C. After 2 hours, quenched with 1 M NaOH (aq), extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x) and concentrated under reduced pressure. The crude residue was purified on silica gel (20-100% ethyl acetate/hexanes) to yield the title compound as an off-white amorphous solid (19.0 mg, 59%).

**R<sub>f</sub>**: 0.29 (100% EtOAc)

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>) δ 6.55 (s, 1H), 5.78 (dt, *J* = 10.4, 3.3 Hz, 2H), 5.72 (dt, *J* = 10.4, 2.0 Hz, 2H), 3.24 (s, 2H), 2.64 (tt, *J* = 3.5, 1.9 Hz, 2H), 2.28 (s, 2H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 177.3, 130.1, 124.7, 55.4, 45.3, 39.9, 26.3 ppm.

**HRMS** (APCI) *m/z*: [M+H]<sup>+</sup> calc'd. for C<sub>9</sub>H<sub>12</sub>NO, 150.09134, found 150.09157.



## 2-(*tert*-butyl)-2-azaspiro[4.5]deca-6,9-diene (22):

To an oven-dried reaction vial charged with 2-(*tert*-butyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (**19**) (20.5 mg, 0.1 mmol, 1.0 equiv) was added THF (1 mL, 0.1 M). The solution was cooled to 0 °C and LiAlH<sub>4</sub> (1 M in THF, 0.25 mL, 0.25 mmol, 2.5 equiv) was added dropwise. The resulting

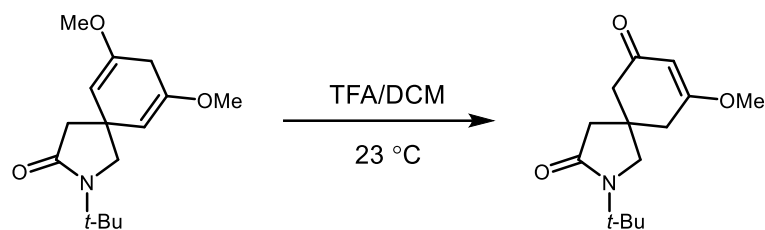
solution was allowed to warm to 23 °C and stir for 20 hours. The reaction was cooled to 0 °C and diluted with Et<sub>2</sub>O. Then 0.01 mL H<sub>2</sub>O, 0.01 mL 15% NaOH (aq), and 0.03 mL H<sub>2</sub>O were added sequentially, and the resulting solution was stirred for 15 minutes at 23 °C. Anhydrous MgSO<sub>4</sub> was added and the resulting suspension was stirred for an additional 15 minutes. After filtration and concentration under reduced pressure, the title compound was obtained as a white amorphous solid (19.1 mg, 100%).

**Rf:** 0.19 (5% MeOH/DCM)

**<sup>1</sup>H NMR** (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 5.83 (dt, J = 10.4, 2.1 Hz, 2H), 5.60 (dt, J = 10.2, 3.3 Hz, 2H), 2.66 (t, J = 7.0 Hz, 2H), 2.63 (s, 2H), 2.49 (tt, J = 3.5, 2.1 Hz, 2H), 1.75 (t, J = 7.0 Hz, 2H), 1.00 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, C<sub>6</sub>D<sub>6</sub>) δ 134.2, 122.0, 60.8, 52.0, 45.6, 42.1, 41.3, 26.8, 26.2 ppm.

**HRMS (APCI)** m/z: [M+H]<sup>+</sup> calc'd. for C<sub>13</sub>H<sub>22</sub>N, 192.17468, found 192.17484.



**2-(tert-butyl)-9-methoxy-2-azaspiro[4.5]dec-8-ene-3,7-dione (24):**

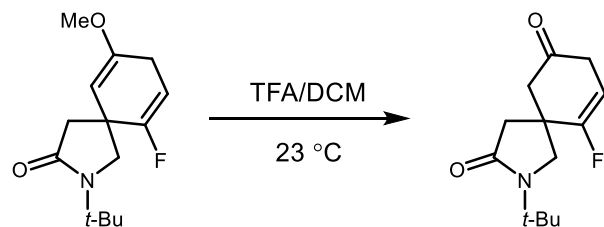
Dissolved 2-(tert-butyl)-7,9-dimethoxy-2-azaspiro[4.5]deca-6,9-dien-3-one (**7**) (2.8 mg, 0.011 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) and added TFA (0.1 mL). After 18 hours, quenched with saturated NaHCO<sub>3</sub> (aq), extracted with EtOAc (3x) and concentrated under reduced pressure to obtain the title compound as a yellow oil (2.7 mg, 100%).

**Rf:** 0.14 (20% EtOAc/hexanes)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.48 (s, 1H), 3.75 (s, 3H), 3.34 (s, 2H), 2.60 – 2.43 (m, 4H), 2.47 (s, 2H), 1.39 (s, 9H) ppm.

**<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>) δ 197.6, 176.6, 174.2, 102.2, 56.7, 56.5, 55.3, 47.2, 44.9, 40.0, 36.2, 27.9 ppm.

**HRMS (APCI)** m/z: [M+H]<sup>+</sup> calc'd. for C<sub>14</sub>H<sub>22</sub>NO<sub>3</sub>, 252.15942, found 252.15975.



**2-(tert-butyl)-10-fluoro-2-azaspiro[4.5]dec-9-ene-3,7-dione (25):**

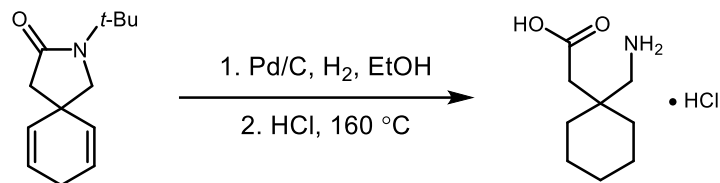
Dissolved 2-(tert-butyl)-6-fluoro-9-methoxy-2-azaspiro[4.5]deca-6,9-dien-3-one (**18**) (6.0 mg, 0.024 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) and added TFA (0.2 mL). After 16 hours, quenched with 1M NaOH (aq), extracted with DCM (3x) and concentrated under reduced pressure to obtain the title compound as a yellow oil (5.7 mg, 100%).

**Rf:** 0.58 (100% EtOAc)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.40 (dt, J = 15.5, 3.9 Hz, 1H), 3.58 (dt, J = 10.0, 0.8 Hz, 1H), 3.21 (dt, J = 10.1, 0.6 Hz, 1H), 3.05 (ddd, J = 20.9, 5.5, 3.6 Hz, 1H), 2.93 (d, J = 16.6 Hz, 1H), 2.89 (dt, J = 20.9, 4.6 Hz, 1H), 2.77 – 2.62 (m, 2H), 2.19 (d, J = 16.6 Hz, 1H), 1.38 (s, 9H) ppm.

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  204.6 (d,  $^4J_{\text{C-F}} = 2.5$  Hz), 171.8, 158.6 (d,  $^1J_{\text{C-F}} = 260.1$  Hz), 101.8 (d,  $^2J_{\text{C-F}} = 22.2$  Hz), 54.6, 53.4 (d,  $^3J_{\text{C-F}} = 1.5$  Hz), 50.0 (d,  $^3J_{\text{C-F}} = 5.3$  Hz), 42.2 (d,  $^3J_{\text{C-F}} = 2.5$  Hz), 40.6 (d,  $^2J_{\text{C-F}} = 23.9$  Hz), 37.4 (d,  $^3J_{\text{C-F}} = 8.1$  Hz), 27.8 ppm.

**HRMS (APCI)**  $m/z$ :  $[\text{M}+\text{H}]^+$  calc'd. for  $\text{C}_{13}\text{H}_{19}\text{FNO}_2$ , 240.13943, found 240.13983.



**2-(1-(aminomethyl)cyclohexyl)acetic acid hydrochloride (23):**

Dissolved 2-(tert-butyl)-2-azaspiro[4.5]deca-6,9-dien-3-one (**19**) (102.6 mg, 0.50 mmol, 1.0 equiv) in methanol (20 mL, 0.025 M). Added palladium (5% on carbon, wet basis, 5 mg), and evacuated and backfilled with hydrogen. After 16 hours, the reaction mixture was filtered through a plug of celite to afford a white solid, which was added to a microwave vial with hydrochloric acid (37% in water, 5 mL), and microwaved at 160°C for 16 hours. The resulting reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (4x) and  $\text{Et}_2\text{O}$  (1x). The aqueous phase was azeotroped with acetonitrile under reduced pressure. The resulting white solid was sonicated in  $\text{Et}_2\text{O}$  and vacuum filtered to afford the title compound as a white solid (103 mg, 52%).

**$^1\text{H}$  NMR** (600 MHz,  $\text{D}_2\text{O}$ )  $\delta$  3.12 (s, 2H), 2.56 (s, 2H), 1.57 – 1.35 (m, 10H) ppm.

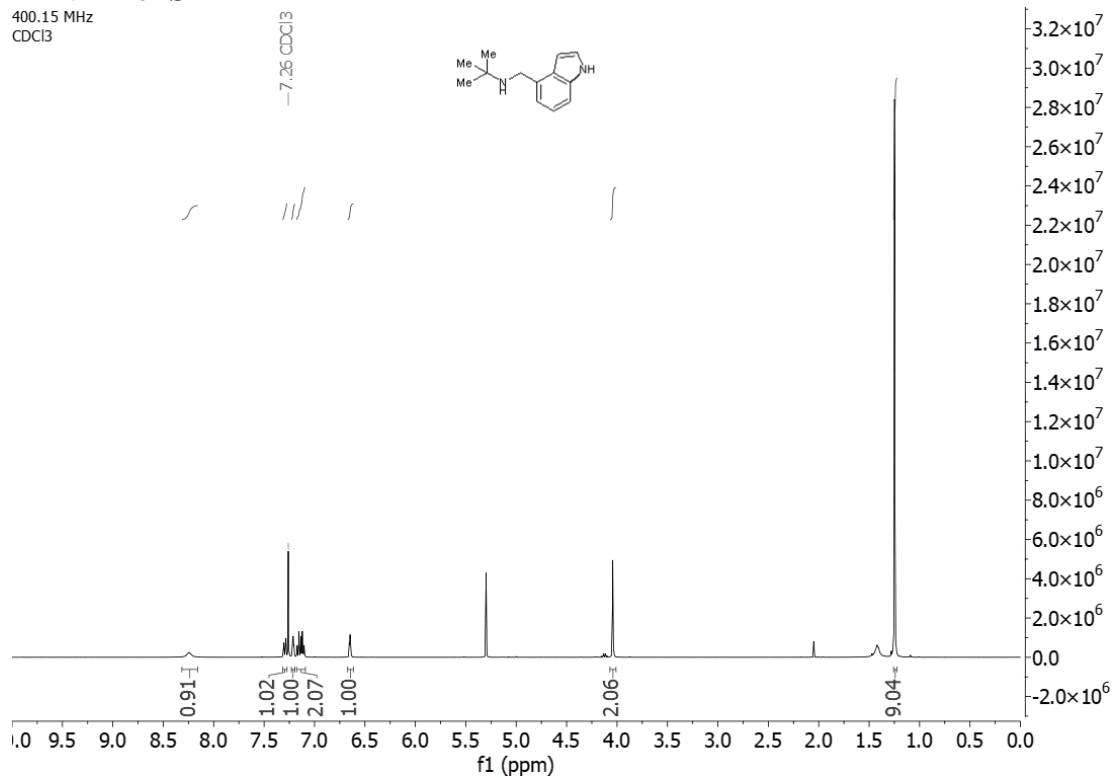
$^1\text{H}$  NMR spectrum is consistent with reported values.<sup>29</sup>

<sup>29</sup> Nagatomo, M.; Nishiyama, H.; Fujino, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 1537-1541.

## IX. NMR Spectra

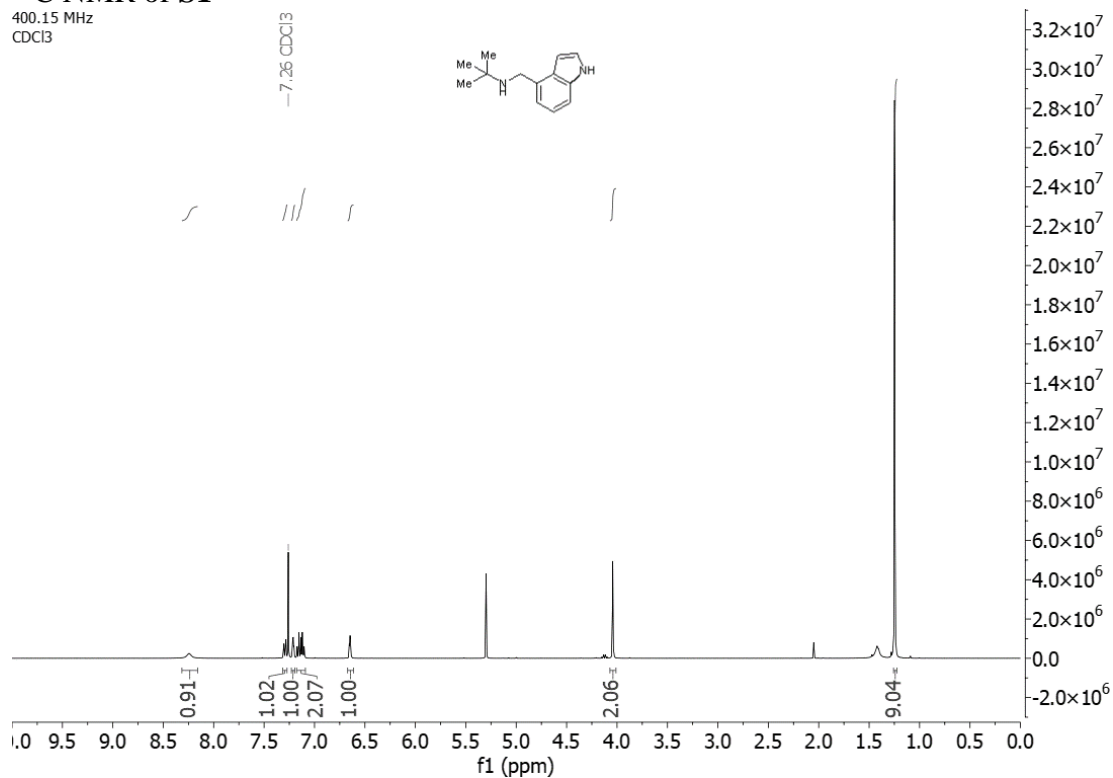
### <sup>1</sup>H NMR of S1

400.15 MHz  
CDCl<sub>3</sub>



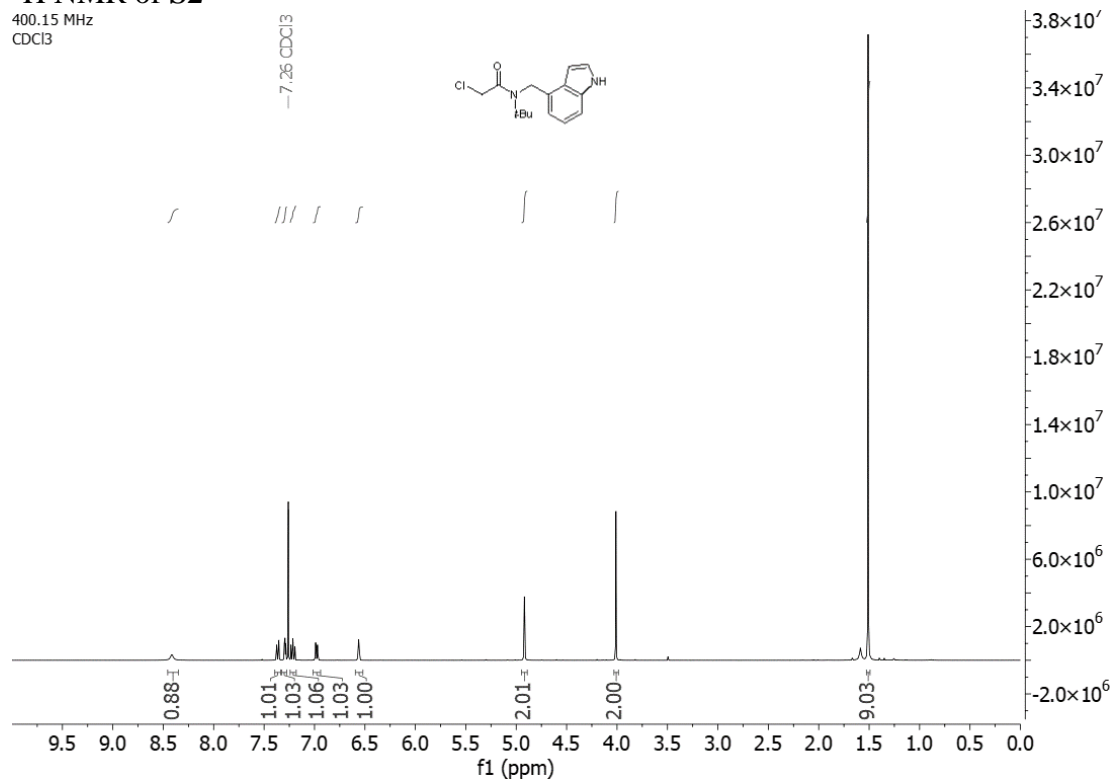
### <sup>13</sup>C NMR of S1

400.15 MHz  
CDCl<sub>3</sub>



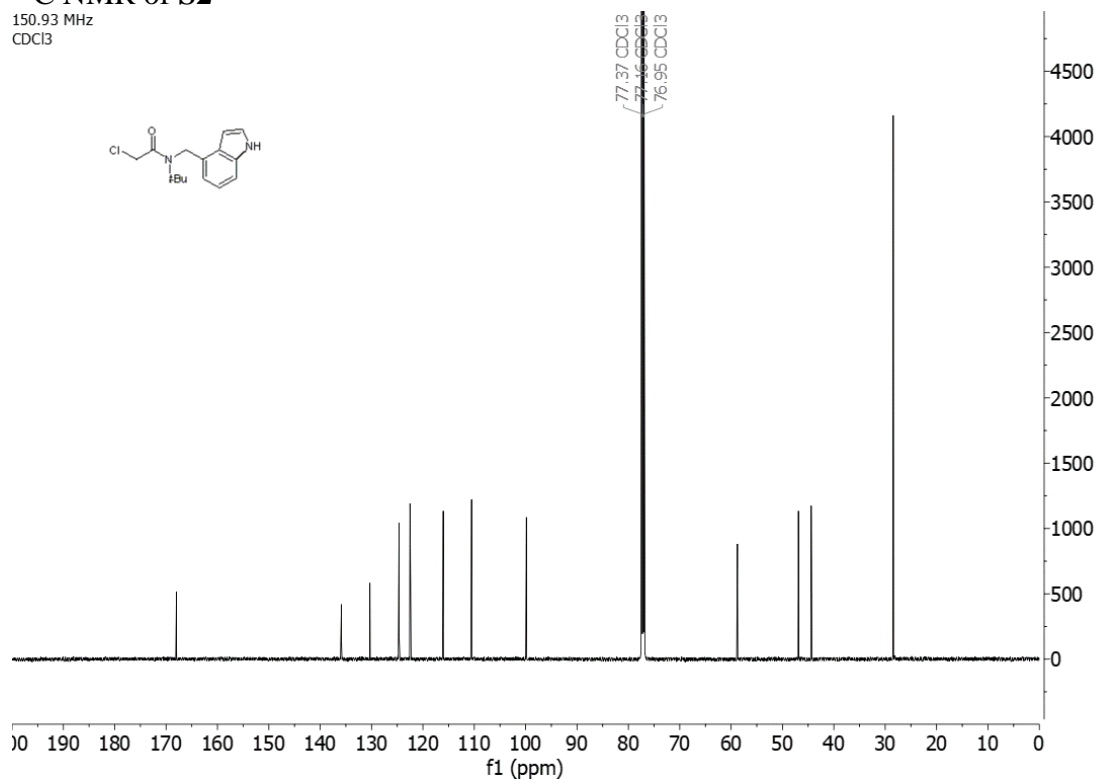
# <sup>1</sup>H NMR of S2

400.15 MHz  
CDCl<sub>3</sub>



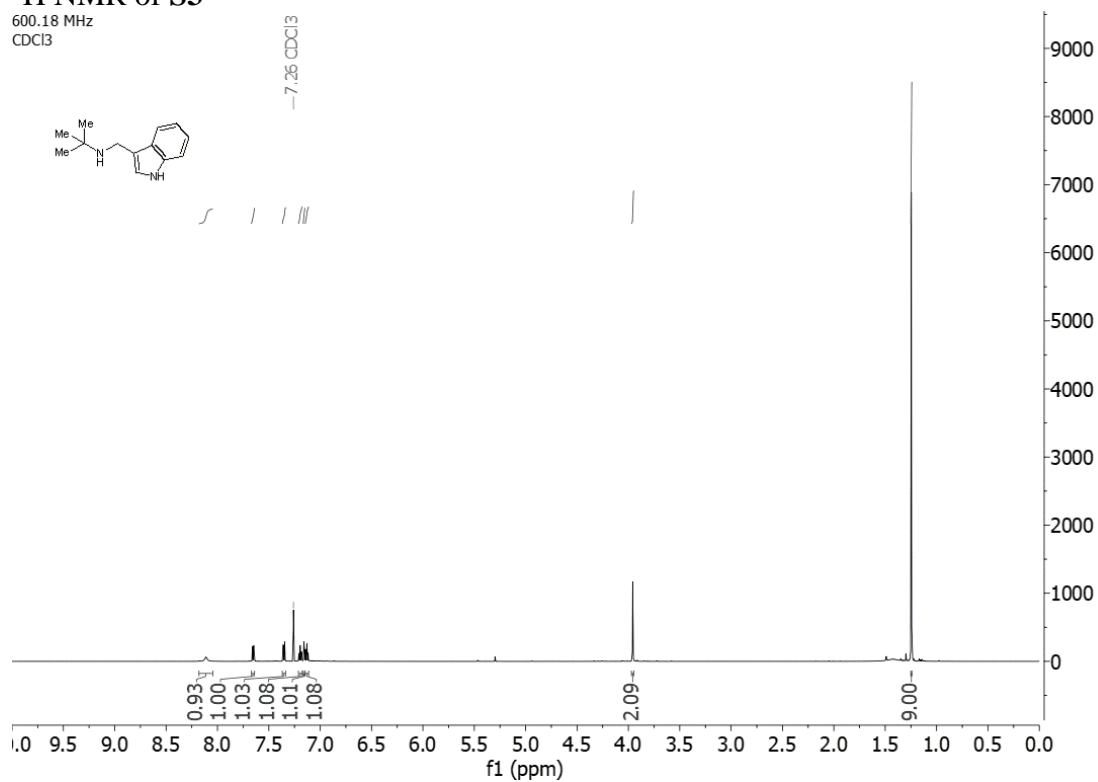
# <sup>13</sup>C NMR of S2

150.93 MHz  
CDCl<sub>3</sub>



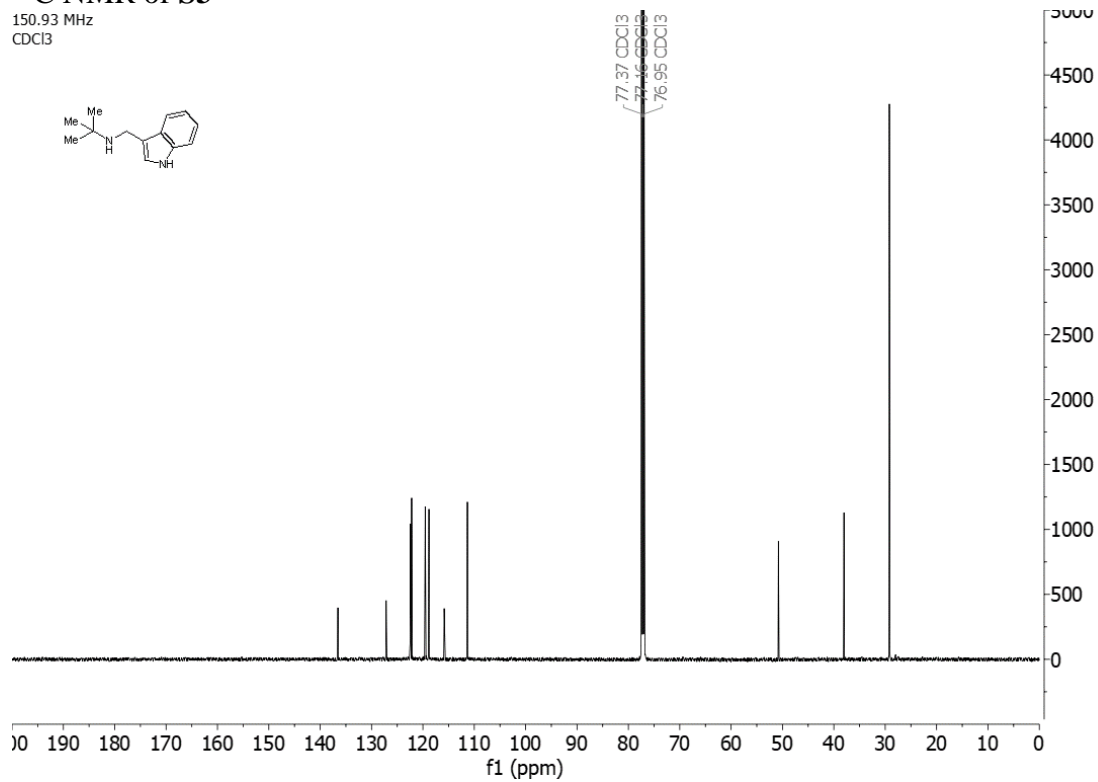
# <sup>1</sup>H NMR of S3

600.18 MHz  
CDCl<sub>3</sub>



# <sup>13</sup>C NMR of S3

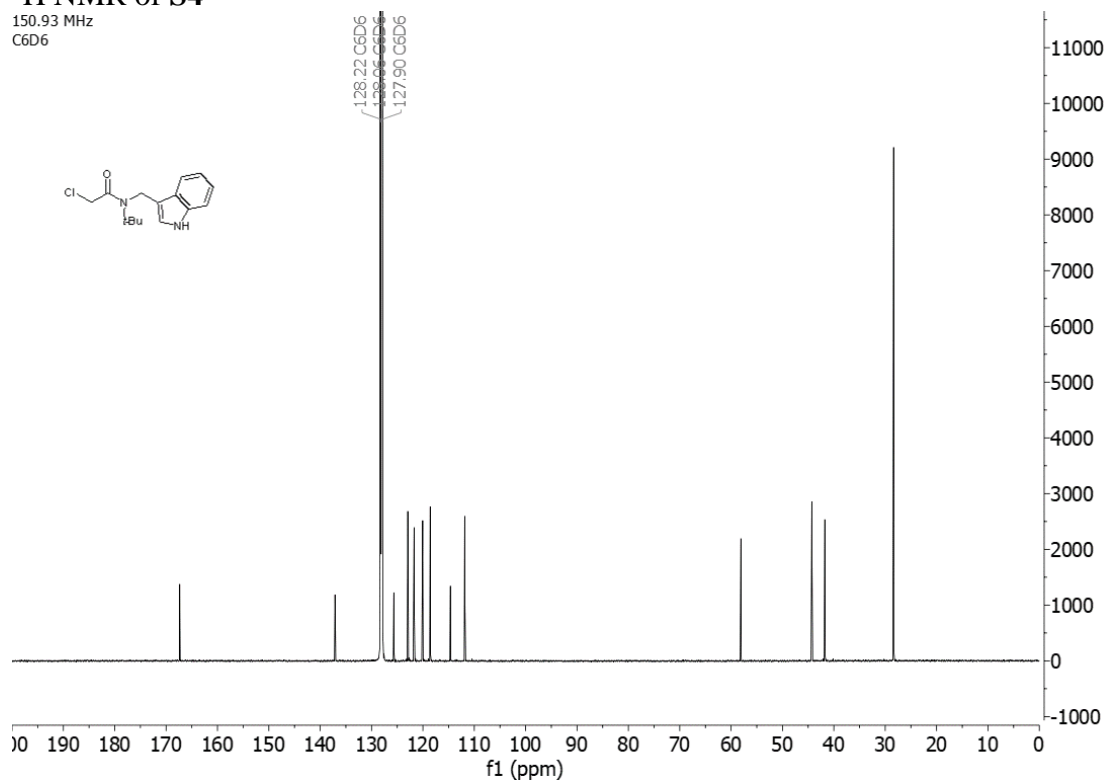
150.93 MHz  
CDCl<sub>3</sub>





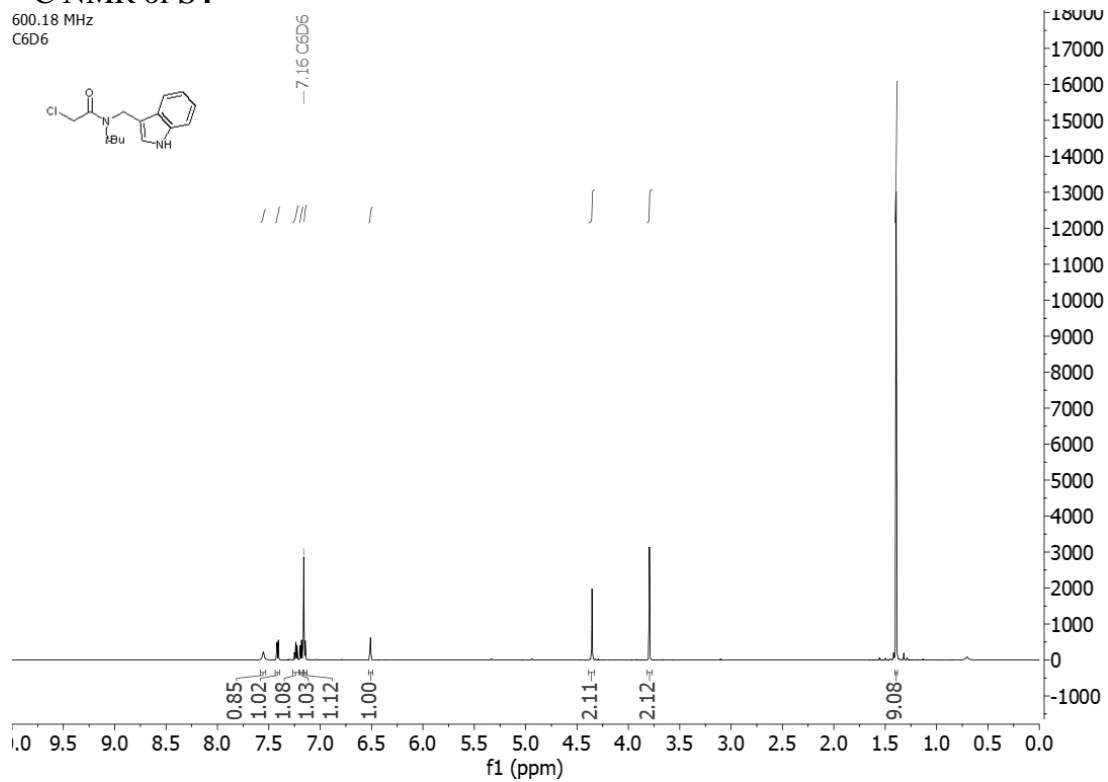
# <sup>1</sup>H NMR of S4

150.93 MHz  
C6D6



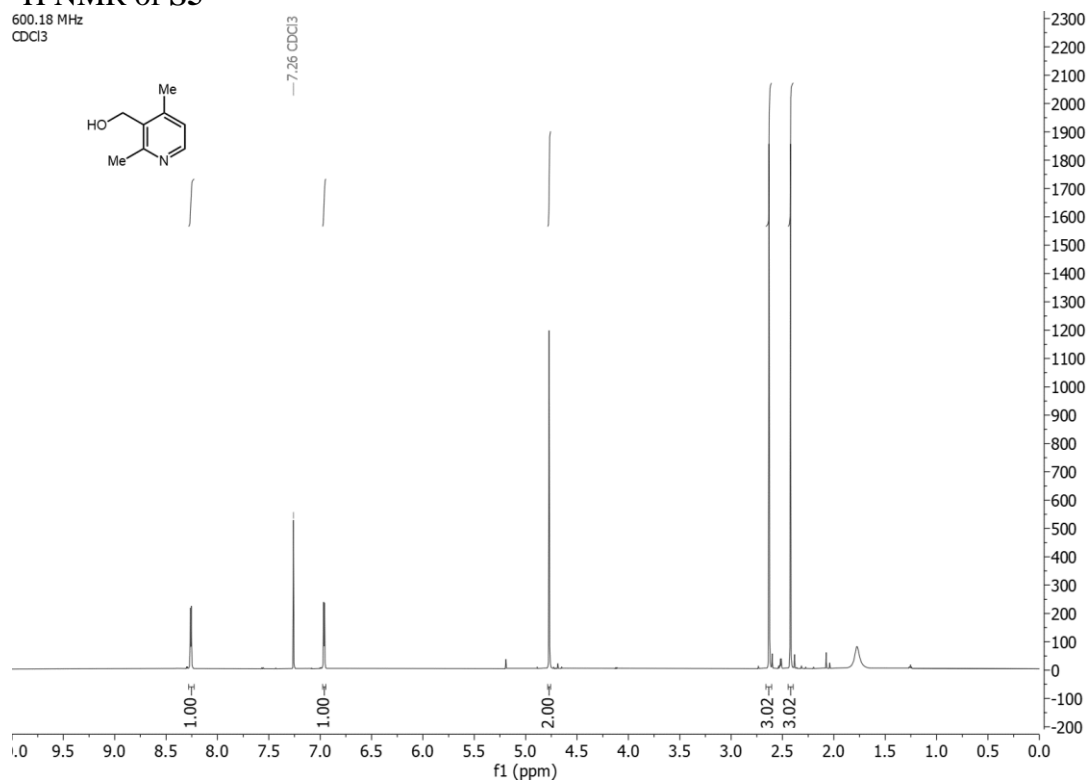
# <sup>13</sup>C NMR of S4

600.18 MHz  
C6D6



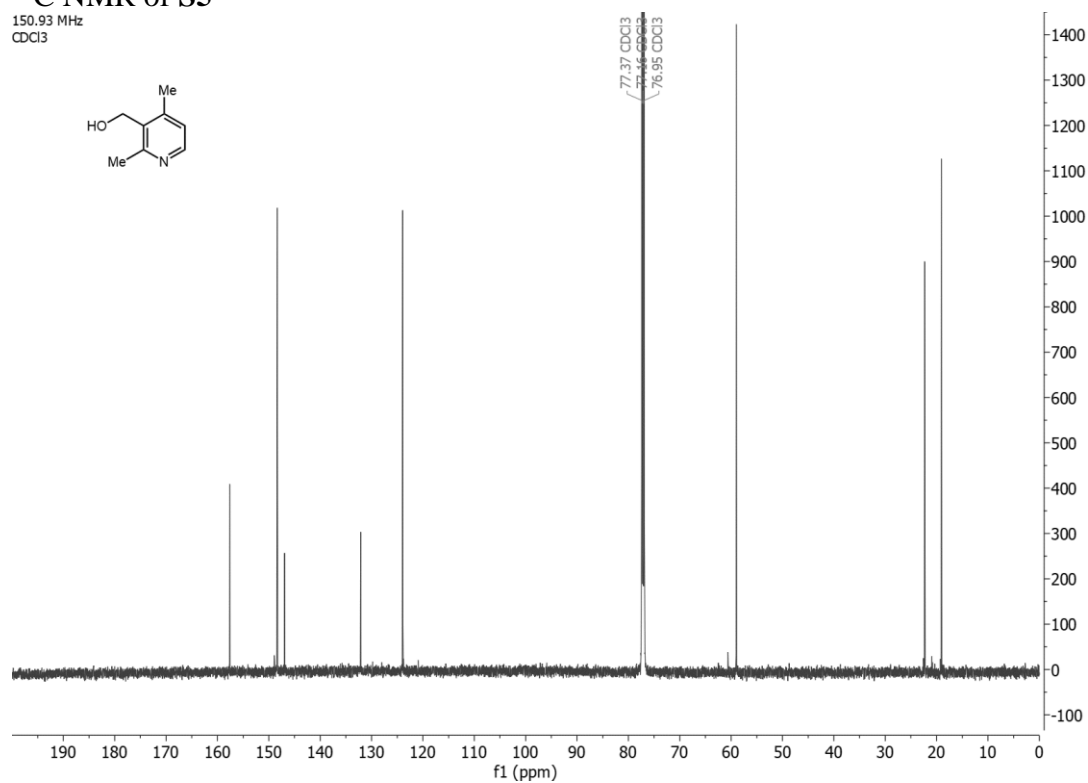
# <sup>1</sup>H NMR of S5

600.18 MHz  
CDCl<sub>3</sub>



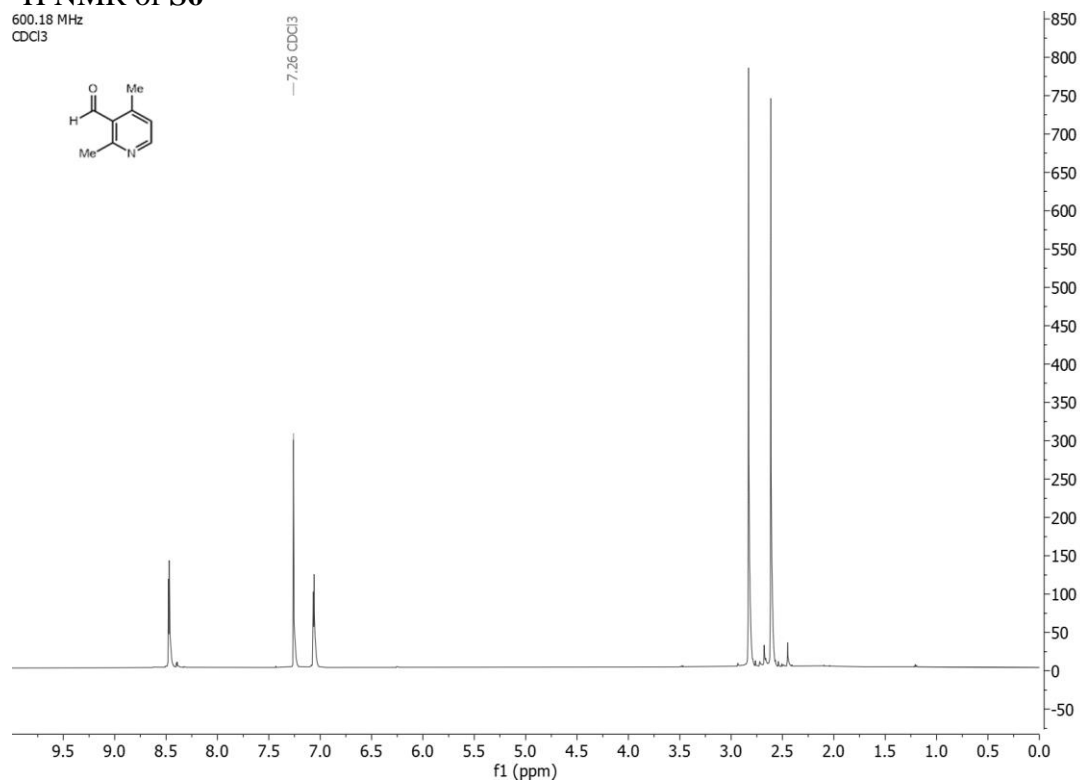
# <sup>13</sup>C NMR of S5

150.93 MHz  
CDCl<sub>3</sub>



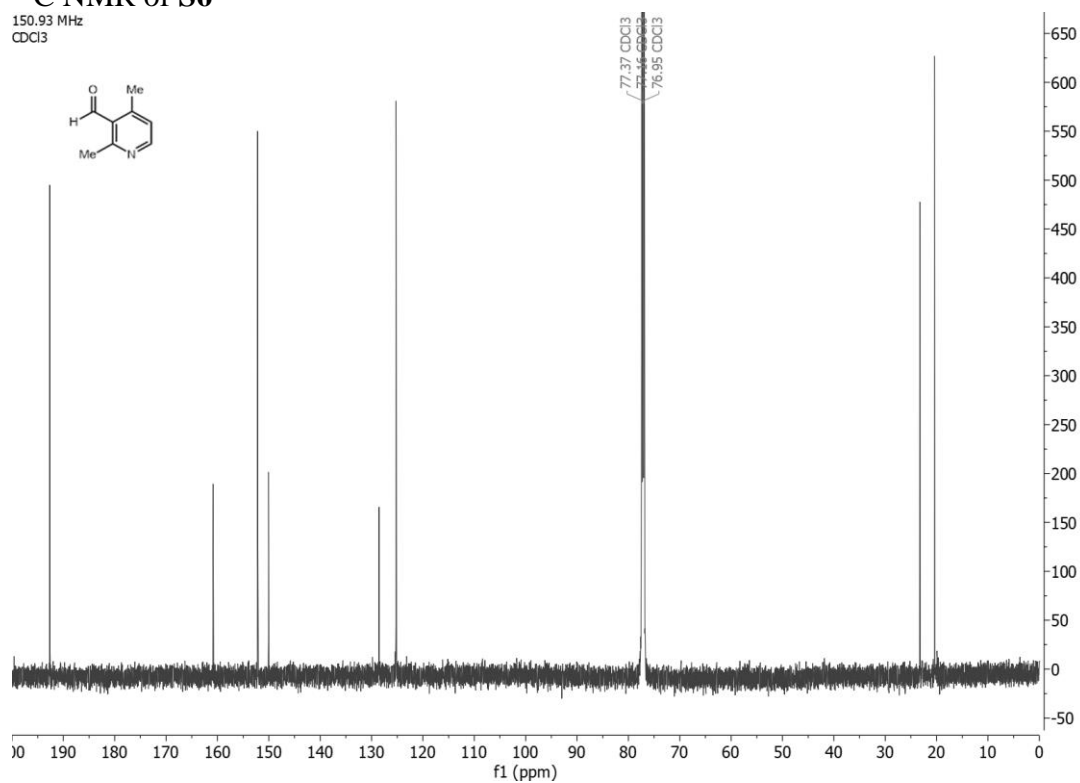
# <sup>1</sup>H NMR of S6

600.18 MHz  
CDCl<sub>3</sub>



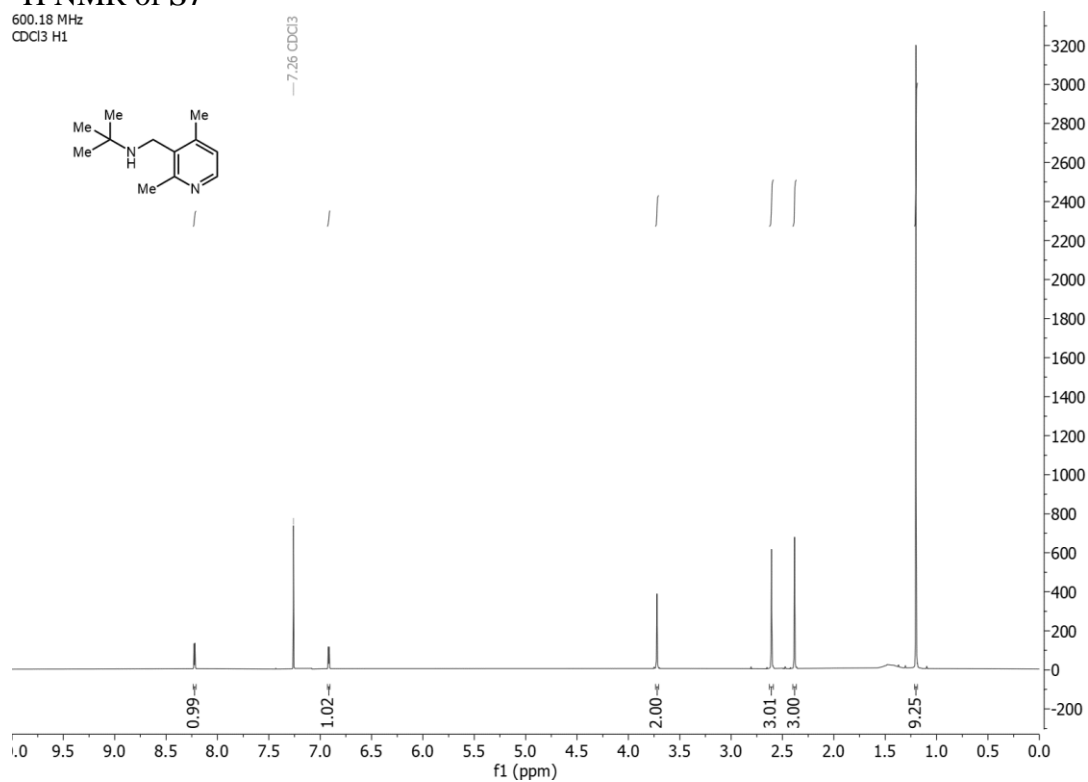
# <sup>13</sup>C NMR of S6

150.93 MHz  
CDCl<sub>3</sub>



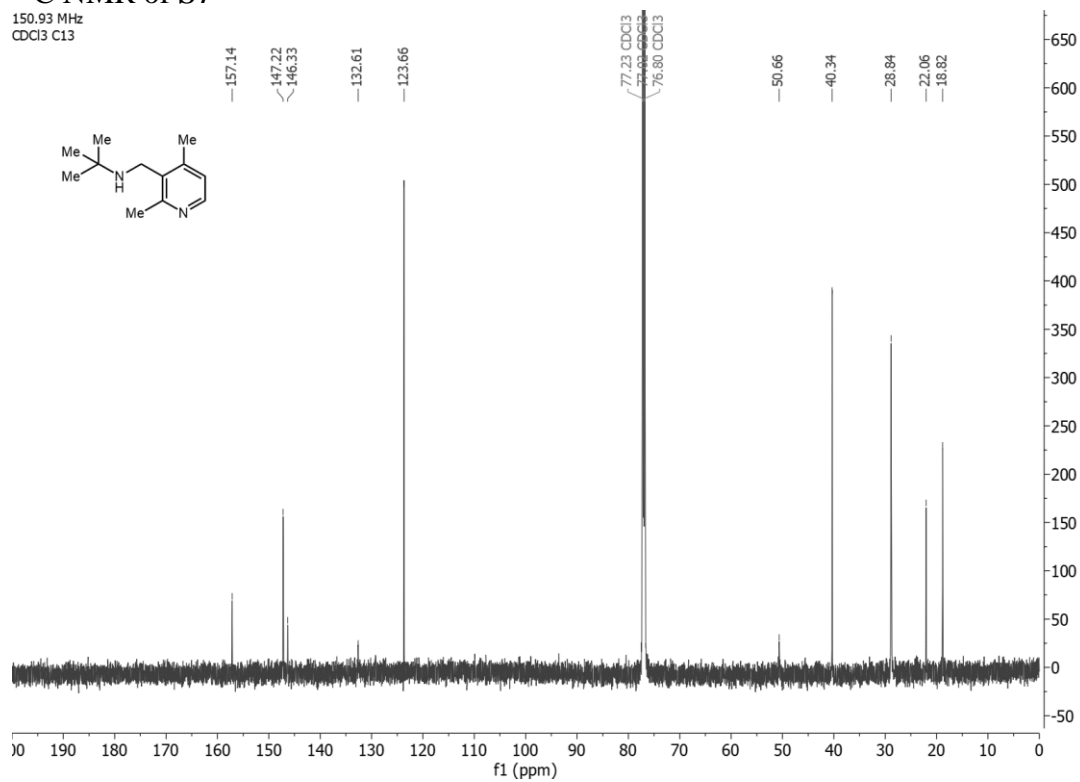
# <sup>1</sup>H NMR of S7

600.18 MHz  
CDCl<sub>3</sub> H1



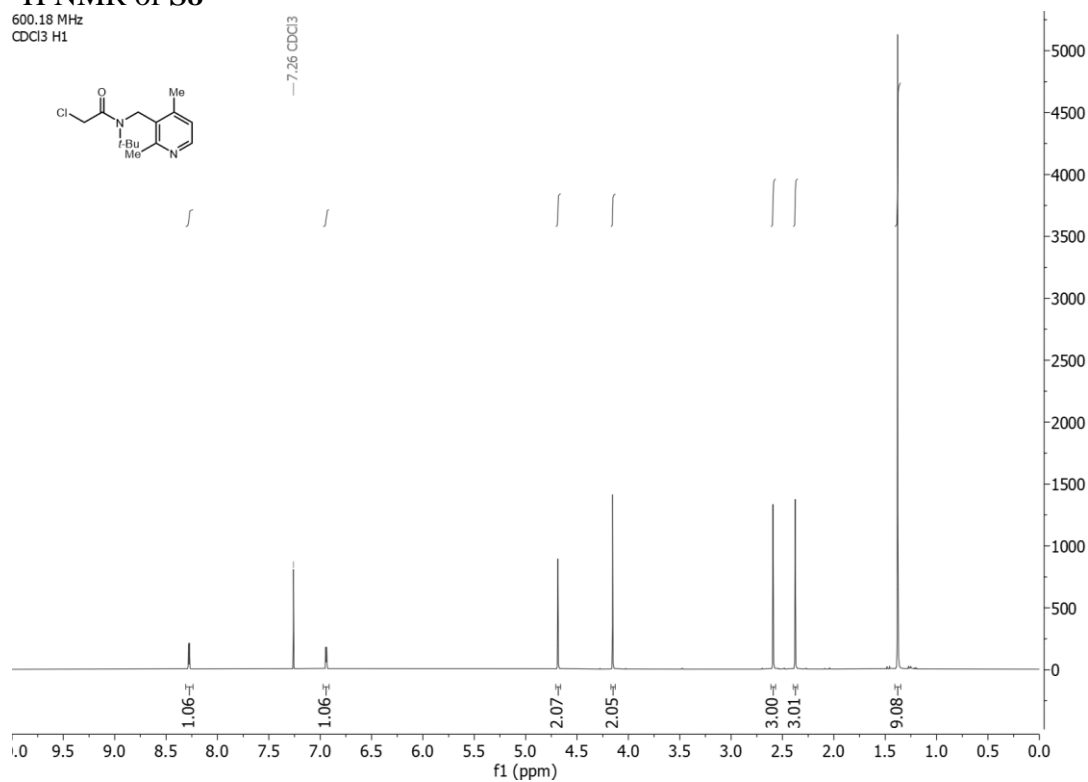
# <sup>13</sup>C NMR of S7

150.93 MHz  
CDCl<sub>3</sub> C13



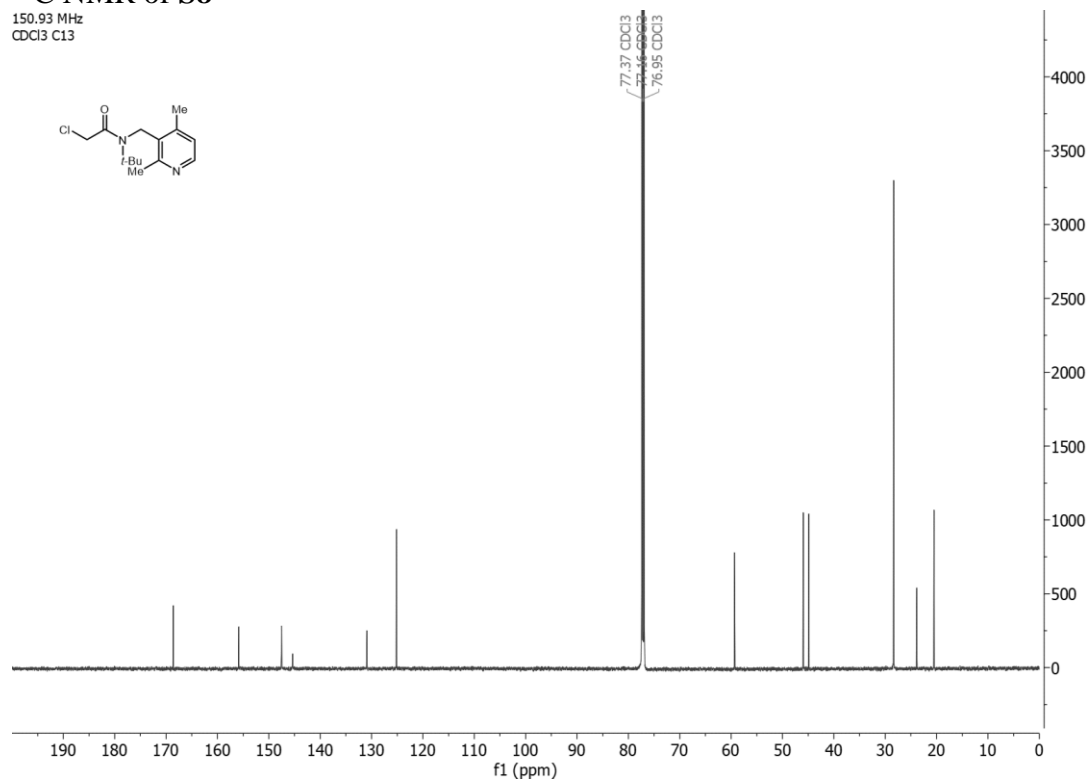
# <sup>1</sup>H NMR of S8

600.18 MHz  
CDCl<sub>3</sub> H1



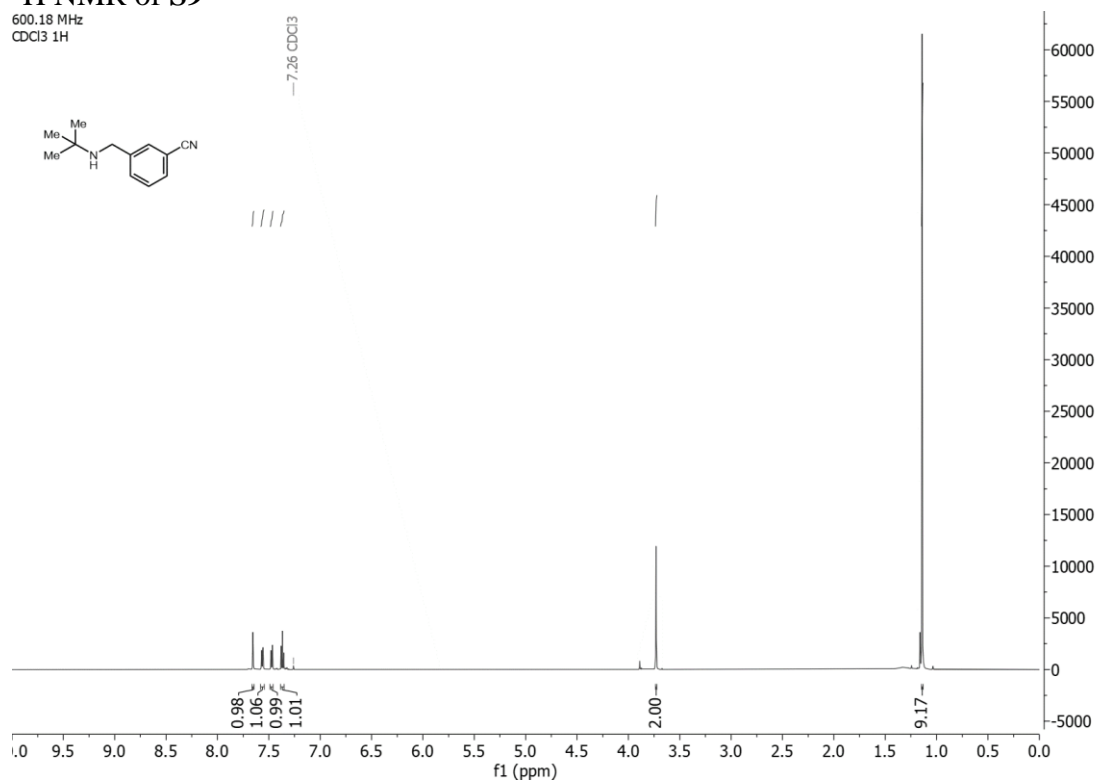
# <sup>13</sup>C NMR of S8

150.93 MHz  
CDCl<sub>3</sub> C13



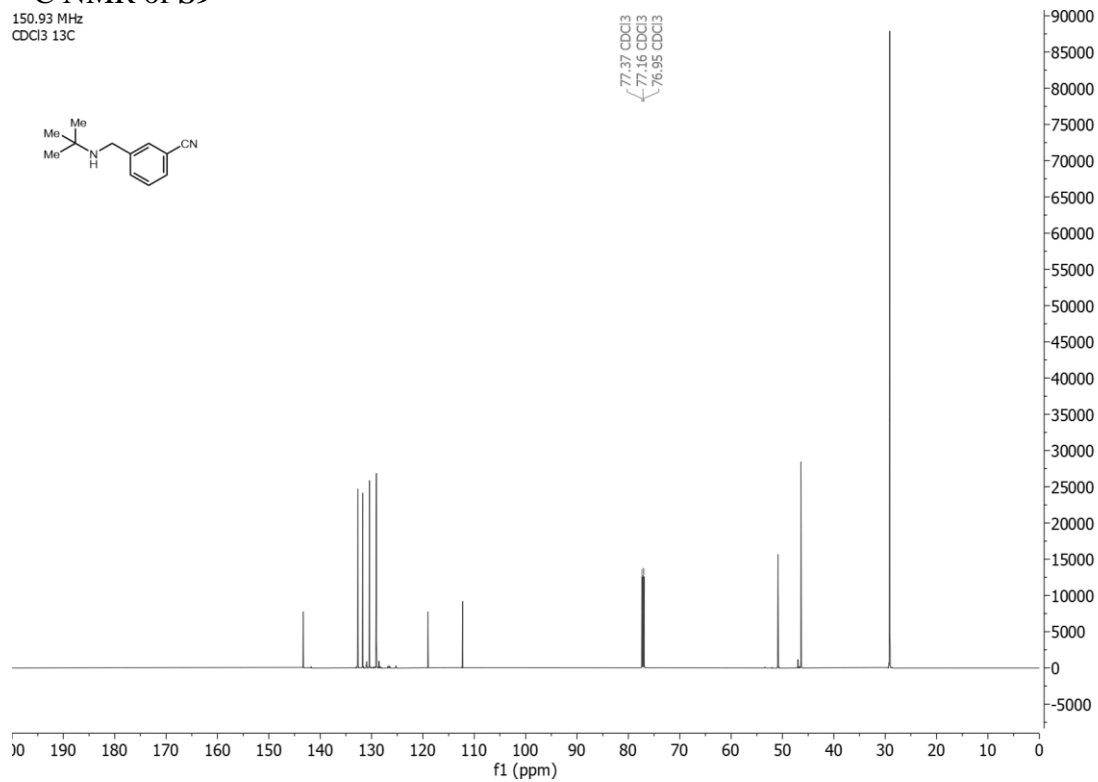
# <sup>1</sup>H NMR of S9

600.18 MHz  
CDCl<sub>3</sub> 1H



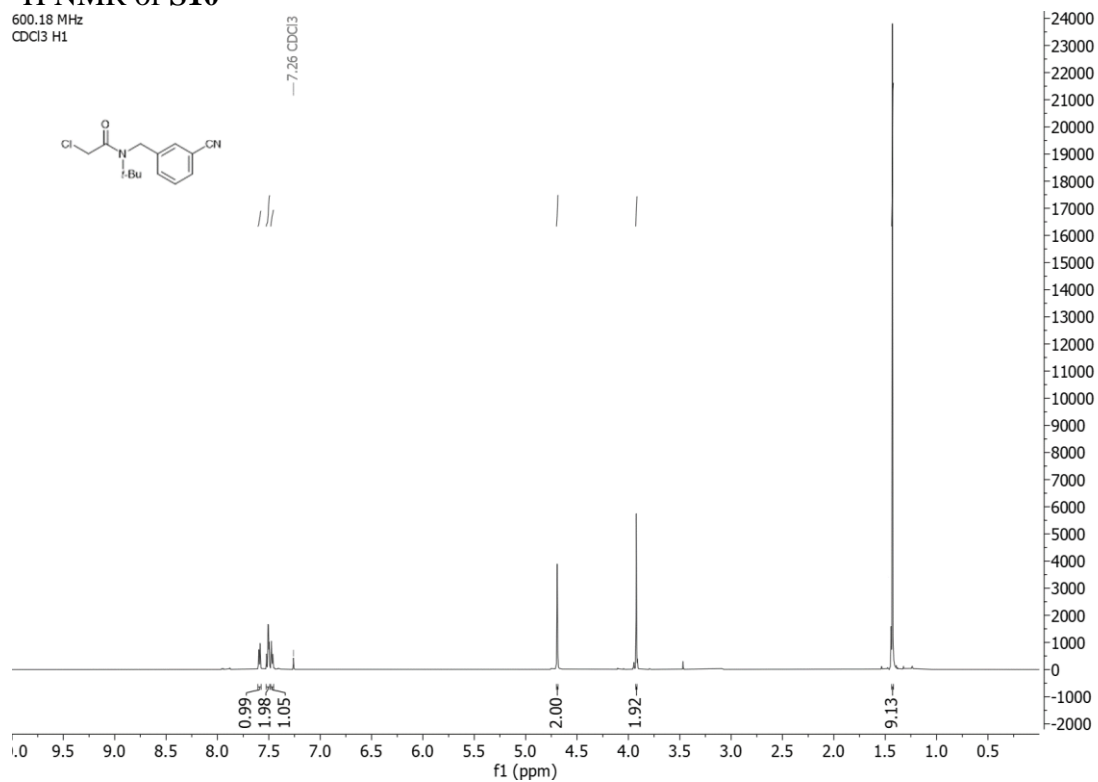
# <sup>13</sup>C NMR of S9

150.93 MHz  
CDCl<sub>3</sub> 13C



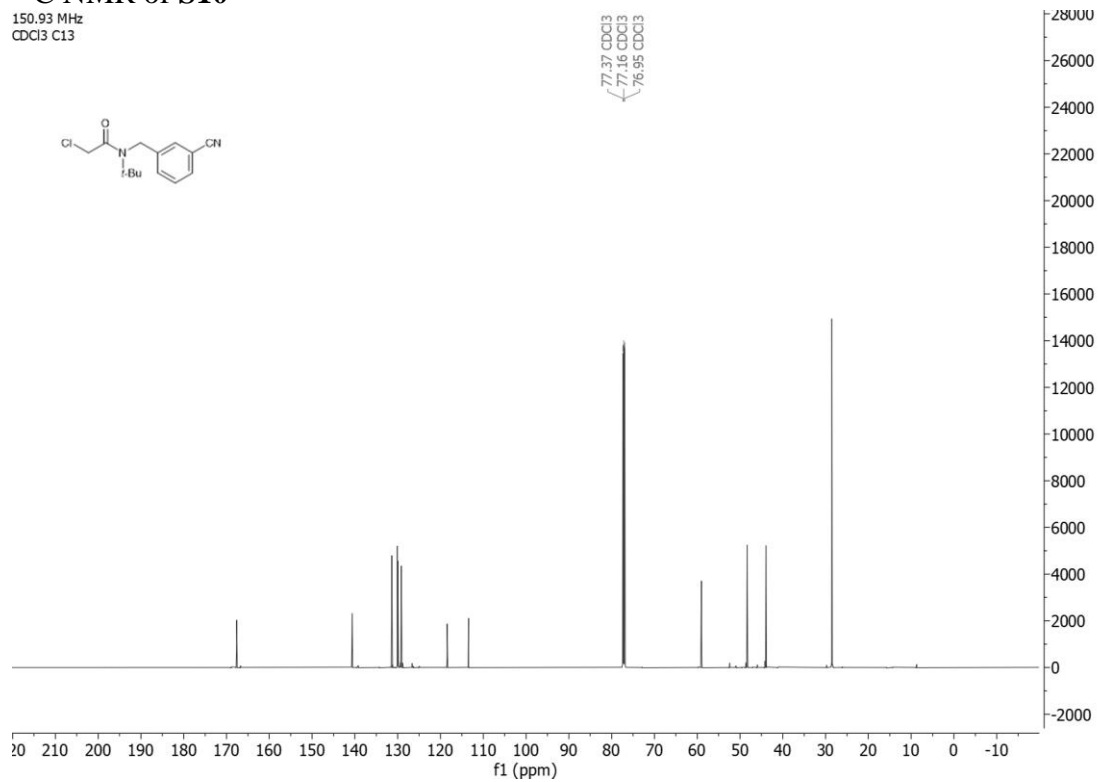
# <sup>1</sup>H NMR of S10

600.18 MHz  
CDCl<sub>3</sub> H1



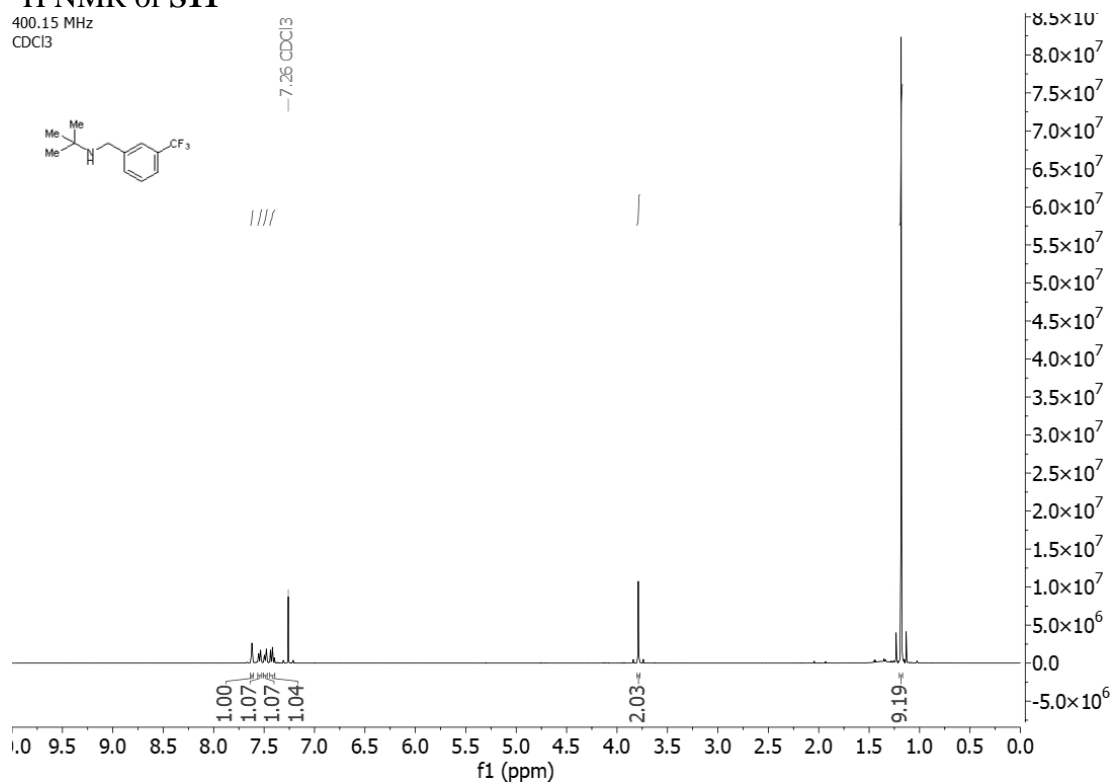
# <sup>13</sup>C NMR of S10

150.93 MHz  
CDCl<sub>3</sub> C13



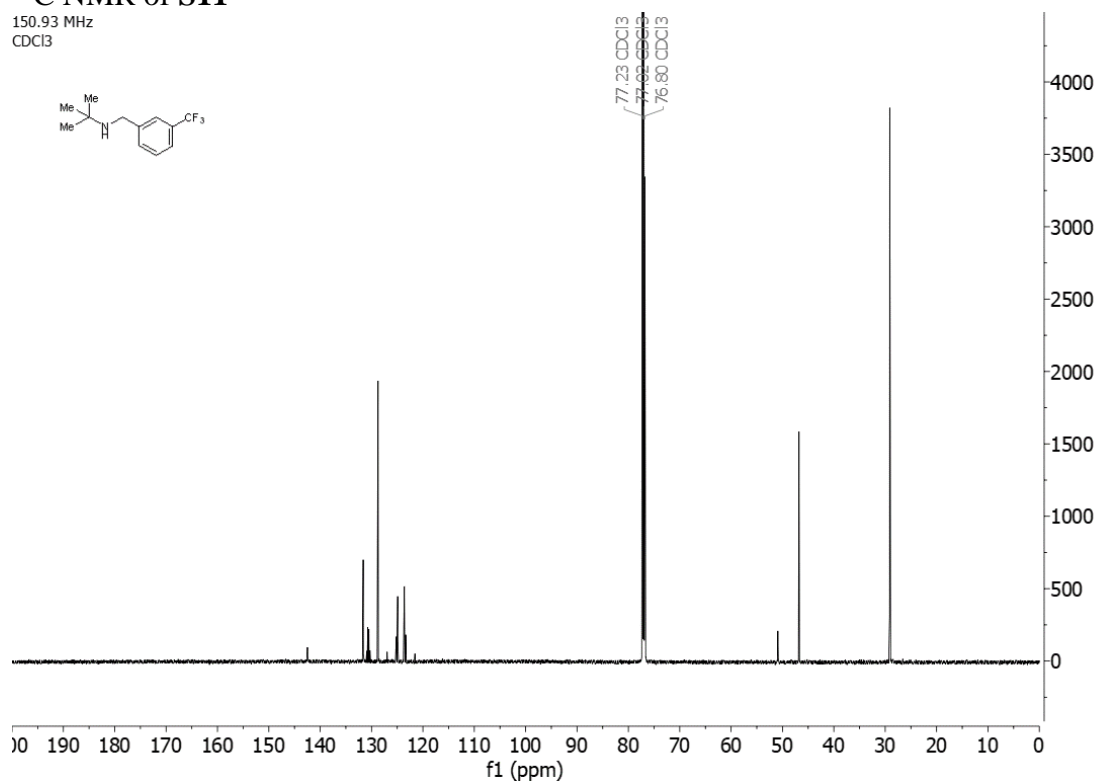
# <sup>1</sup>H NMR of S11

400.15 MHz  
CDCl<sub>3</sub>



# <sup>13</sup>C NMR of S11

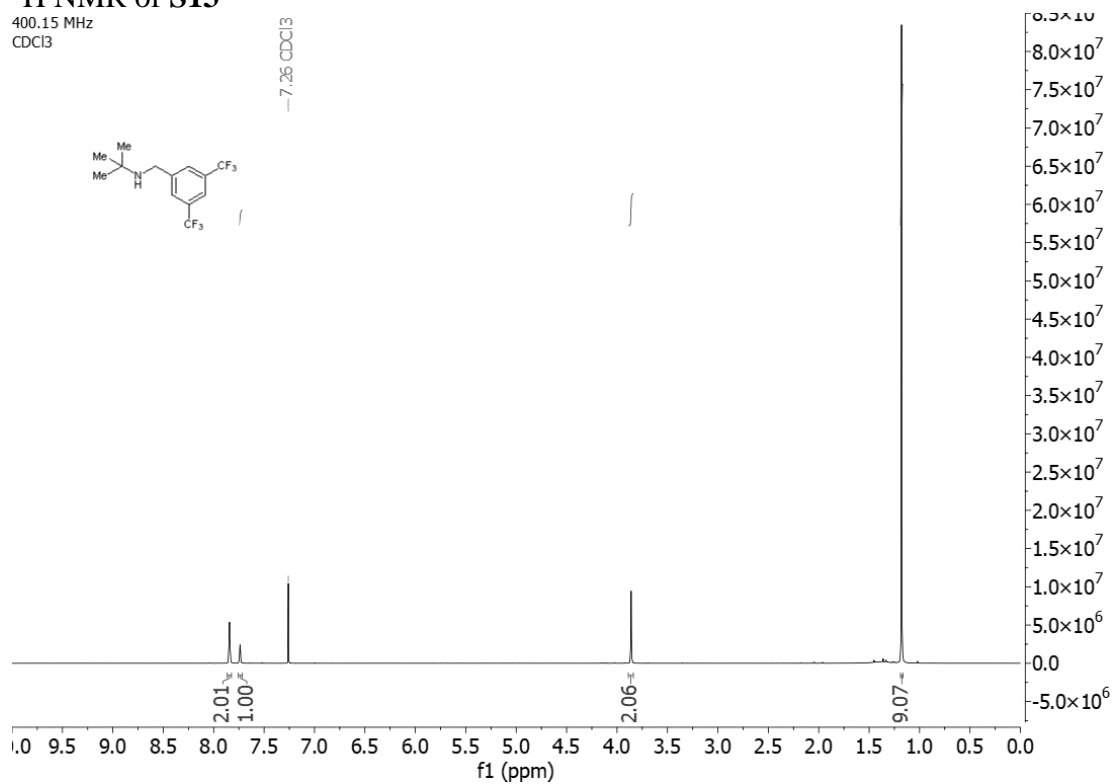
150.93 MHz  
CDCl<sub>3</sub>





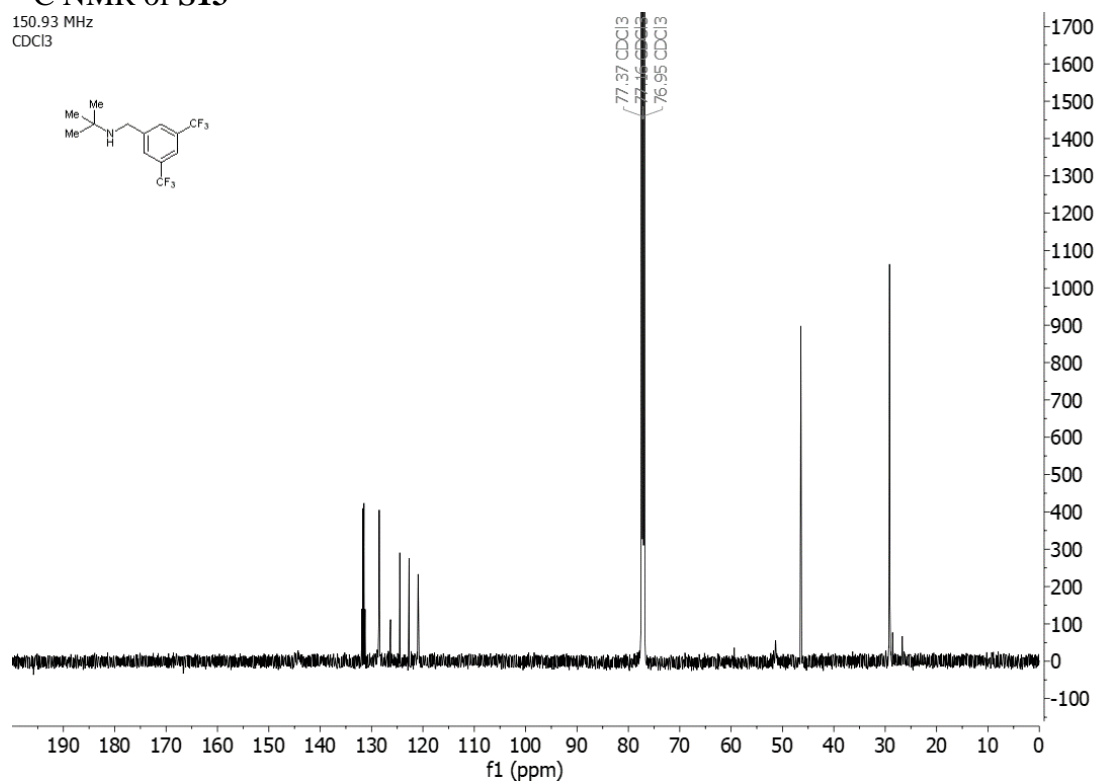
# <sup>1</sup>H NMR of S13

400.15 MHz  
CDCl<sub>3</sub>



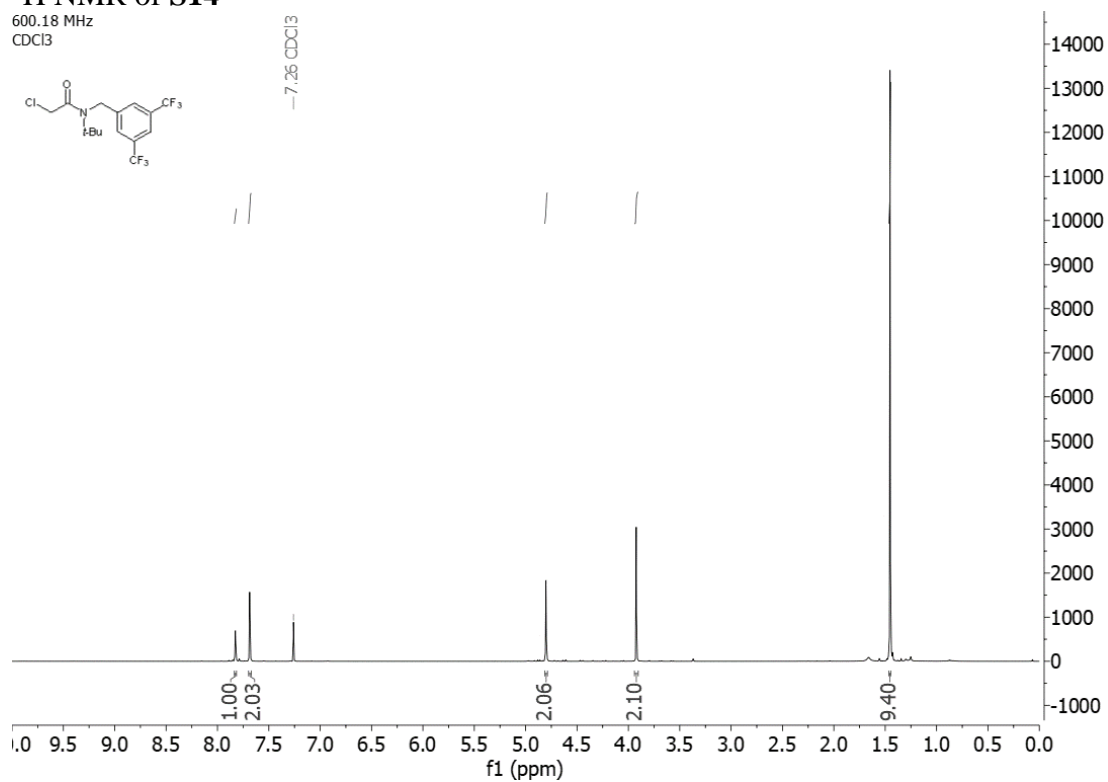
# <sup>13</sup>C NMR of S13

150.93 MHz  
CDCl<sub>3</sub>



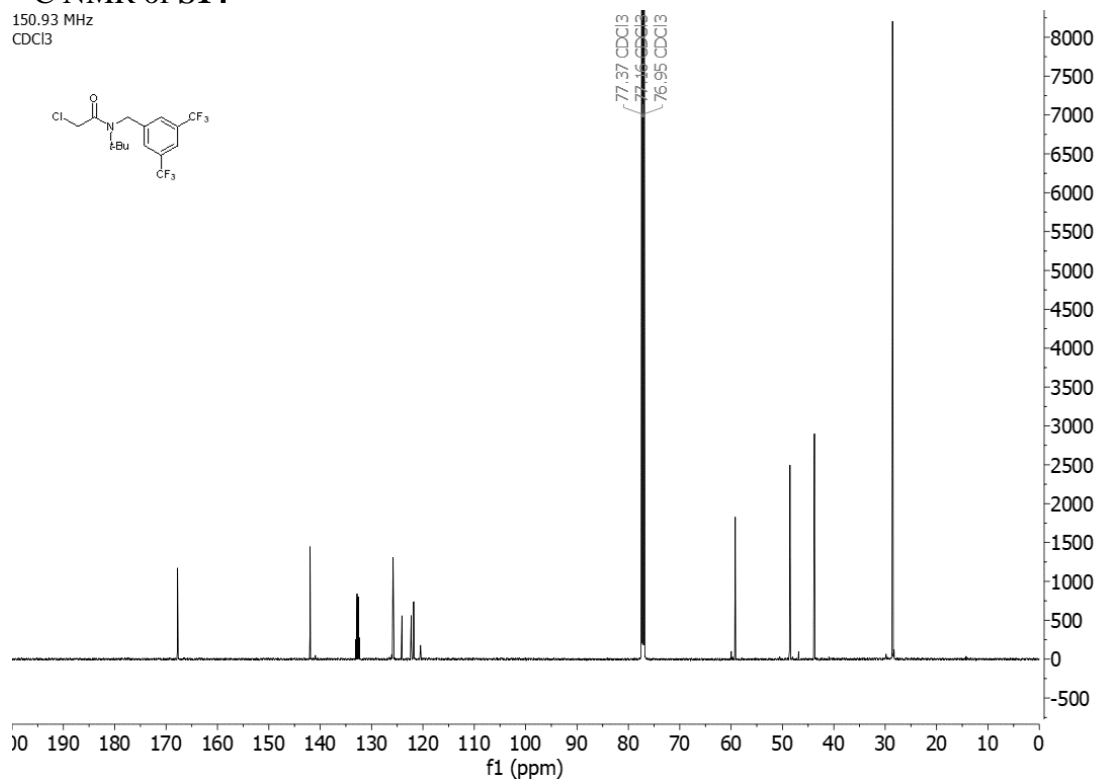
# <sup>1</sup>H NMR of S14

600.18 MHz  
CDCl<sub>3</sub>



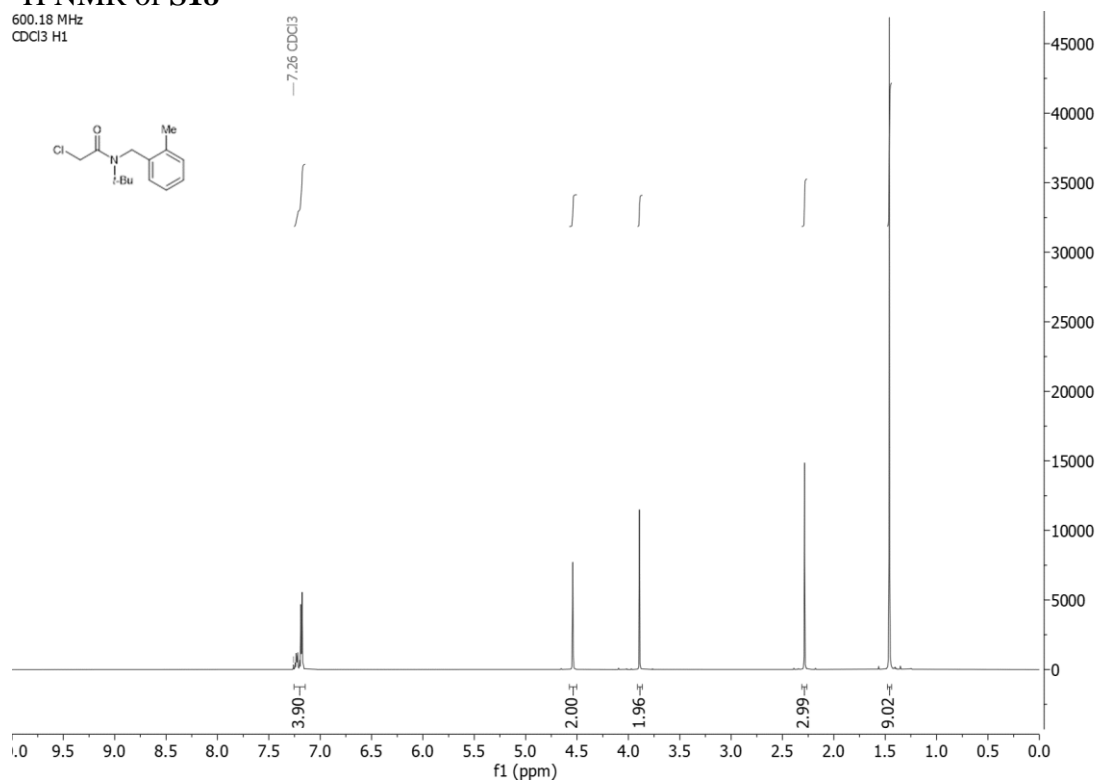
# <sup>13</sup>C NMR of S14

150.93 MHz  
CDCl<sub>3</sub>



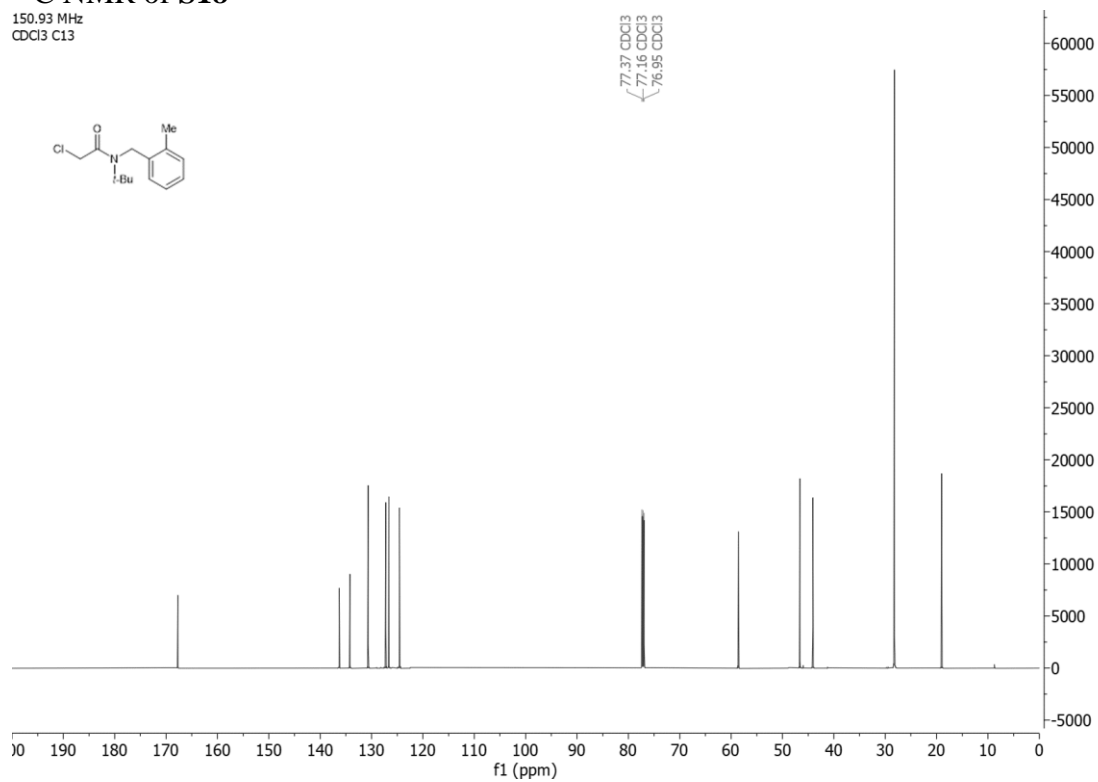
# <sup>1</sup>H NMR of S18

600.18 MHz  
CDCl<sub>3</sub> H1



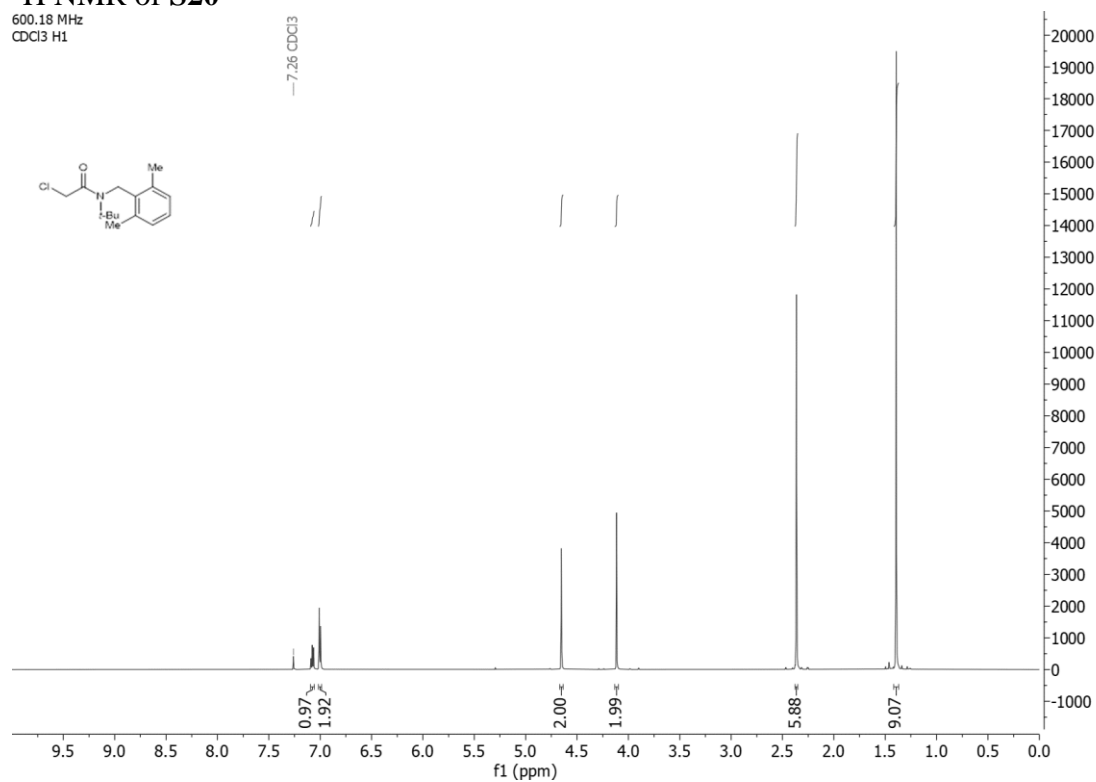
# <sup>13</sup>C NMR of S18

150.93 MHz  
CDCl<sub>3</sub> C13



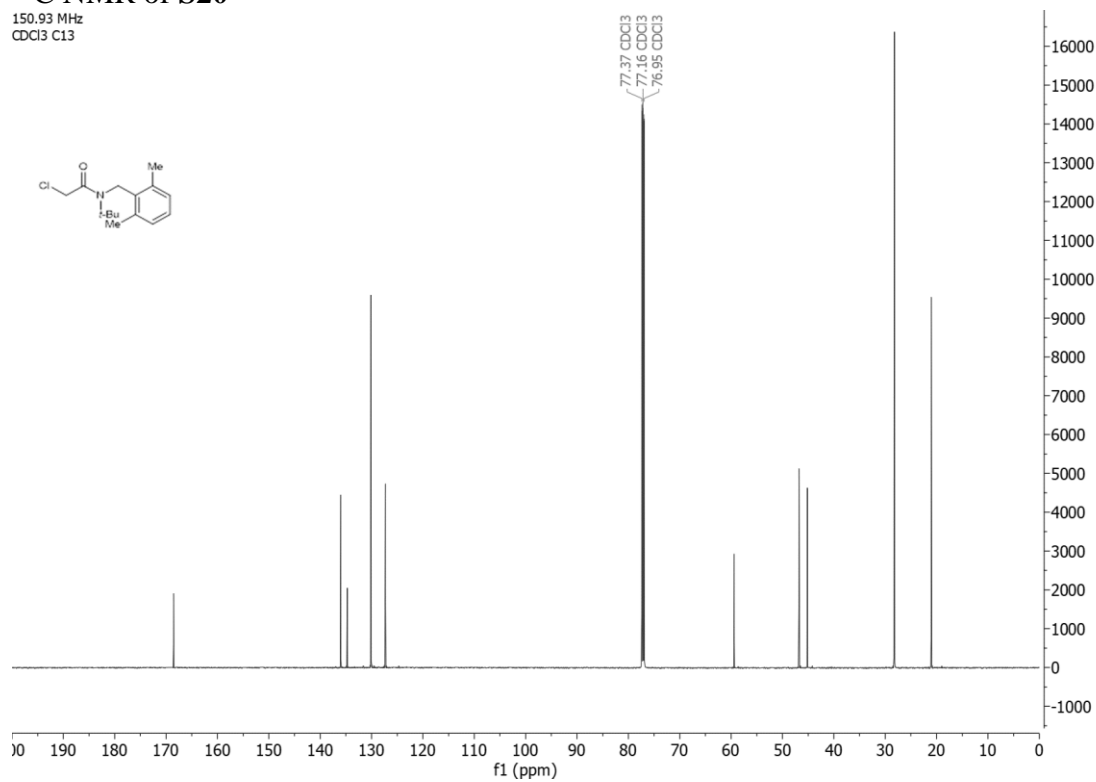
# <sup>1</sup>H NMR of S20

600.18 MHz  
CDCl<sub>3</sub> H1



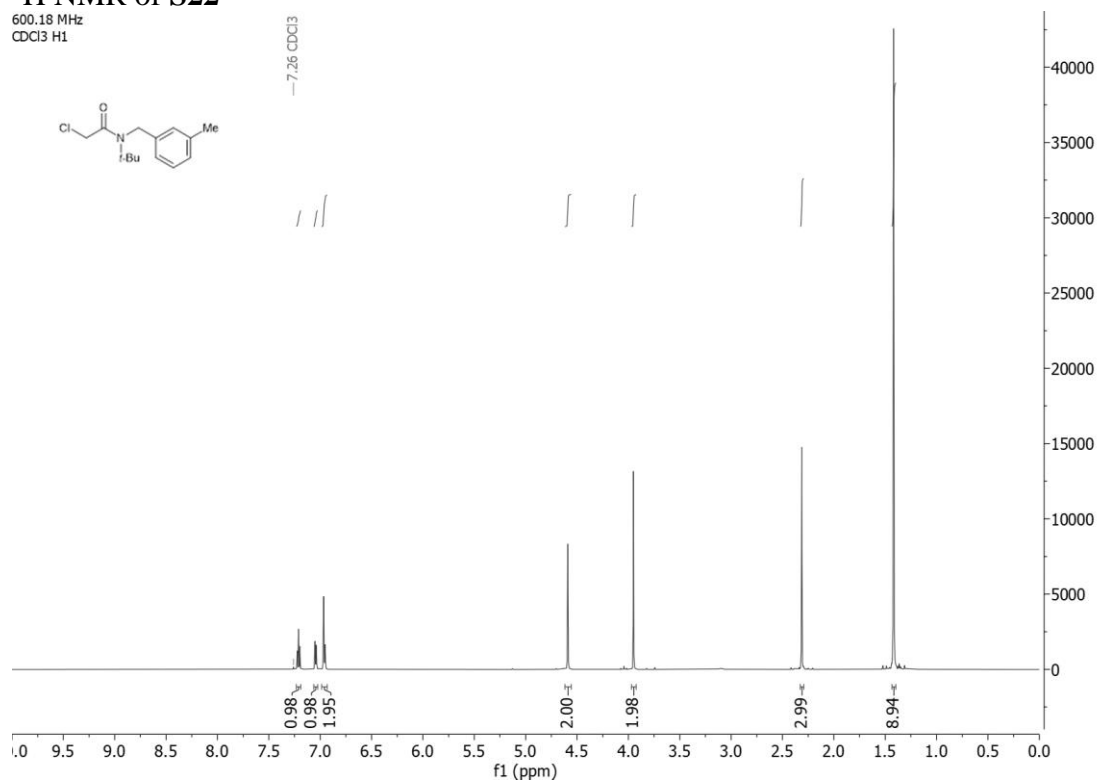
# <sup>13</sup>C NMR of S20

150.93 MHz  
CDCl<sub>3</sub> C13



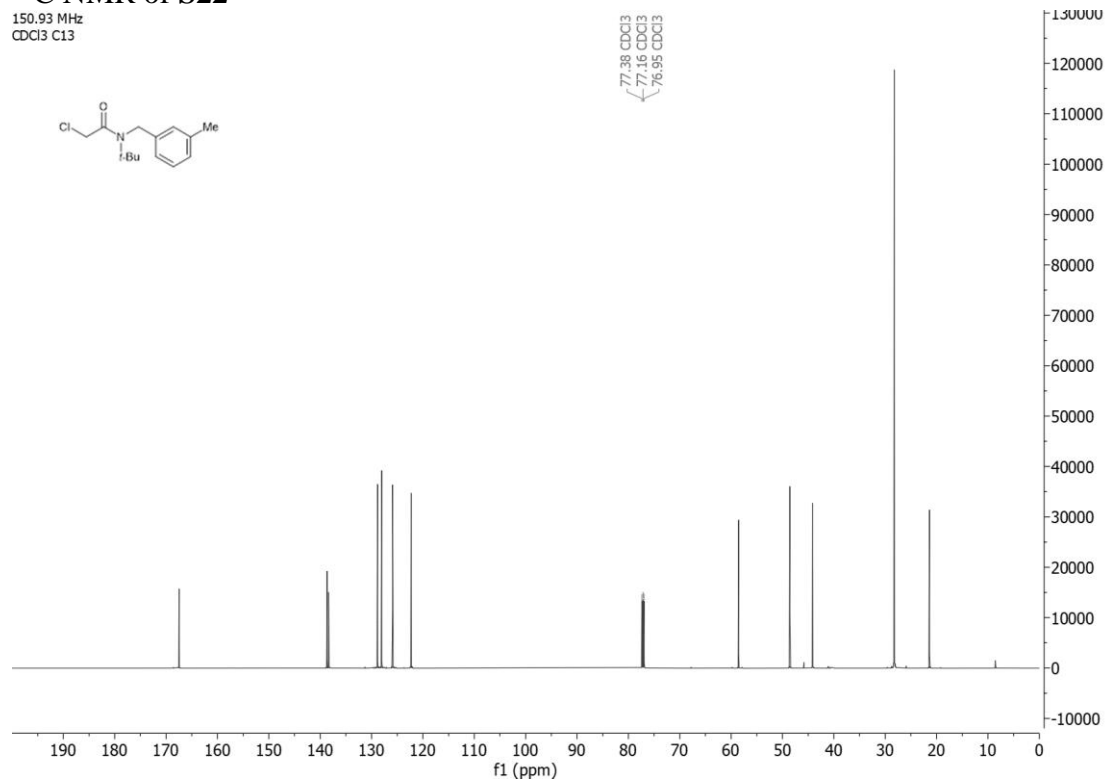
# <sup>1</sup>H NMR of S22

600.18 MHz  
CDCl<sub>3</sub> H1



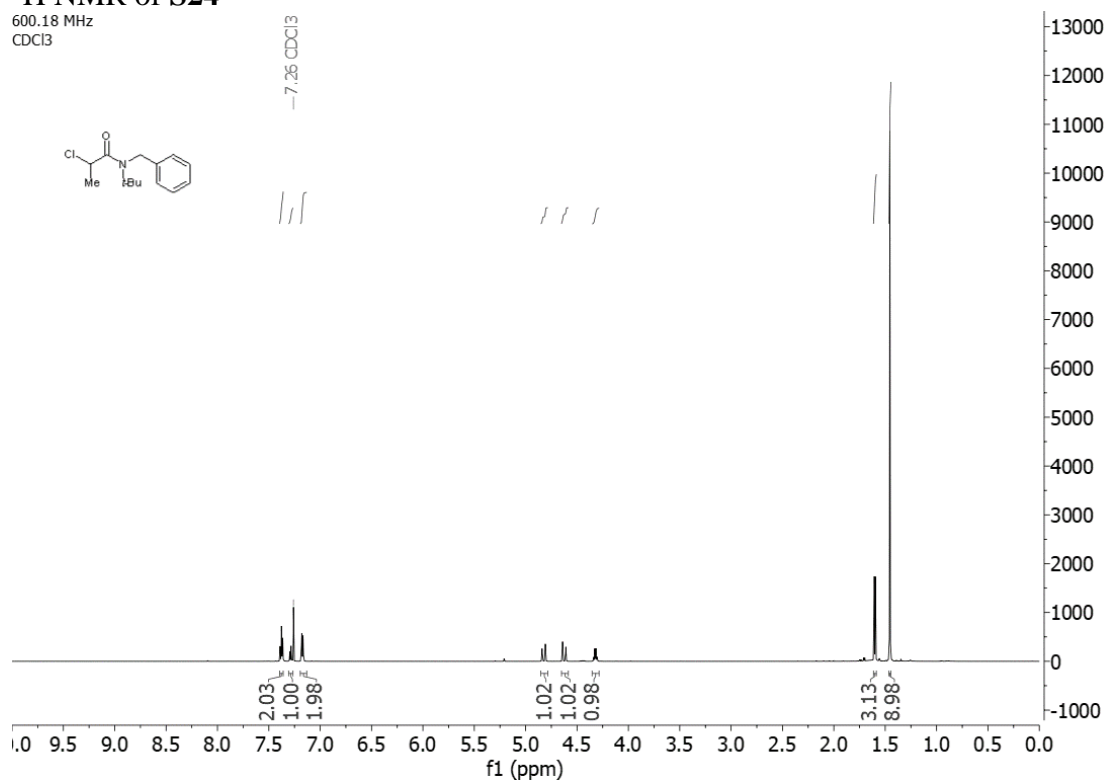
# <sup>13</sup>C NMR of S22

150.93 MHz  
CDCl<sub>3</sub> C13



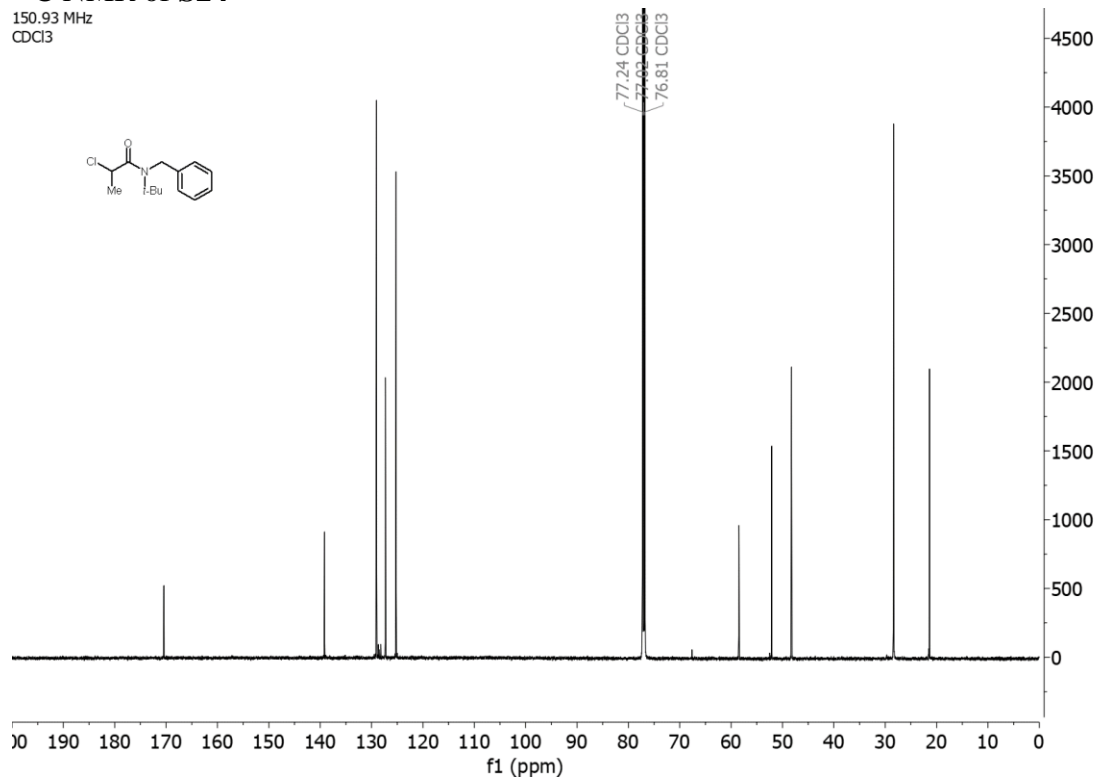
# <sup>1</sup>H NMR of S24

600.18 MHz  
CDCl<sub>3</sub>



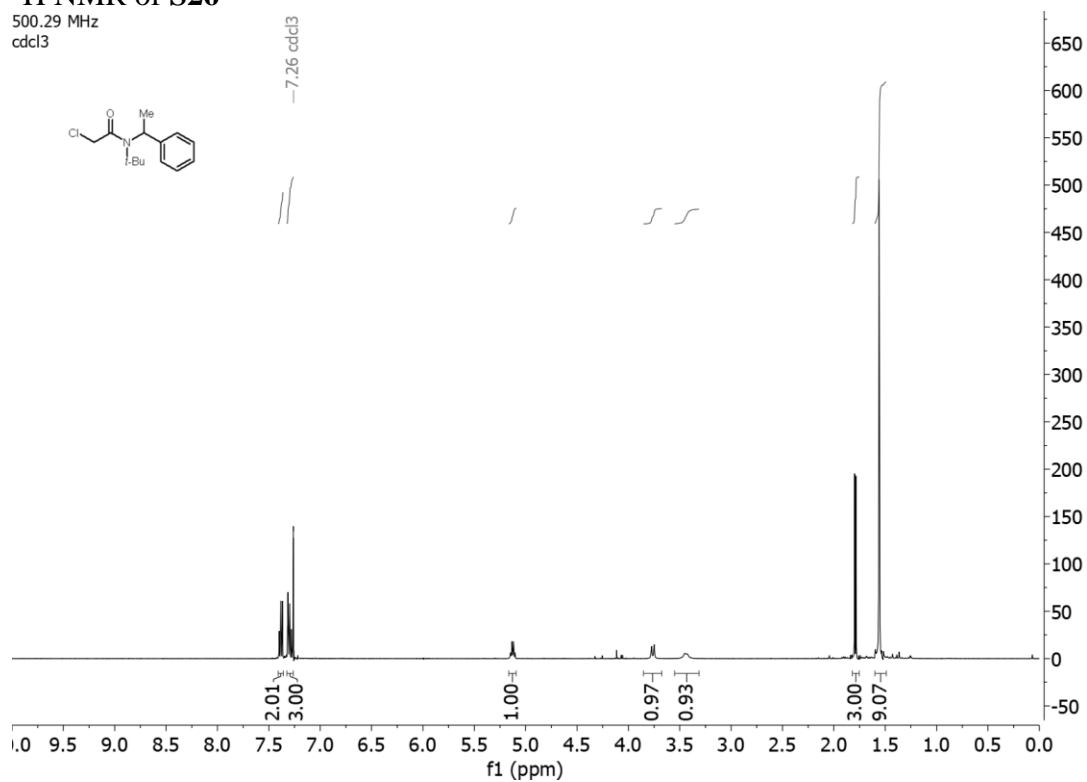
# <sup>13</sup>C NMR of S24

150.93 MHz  
CDCl<sub>3</sub>



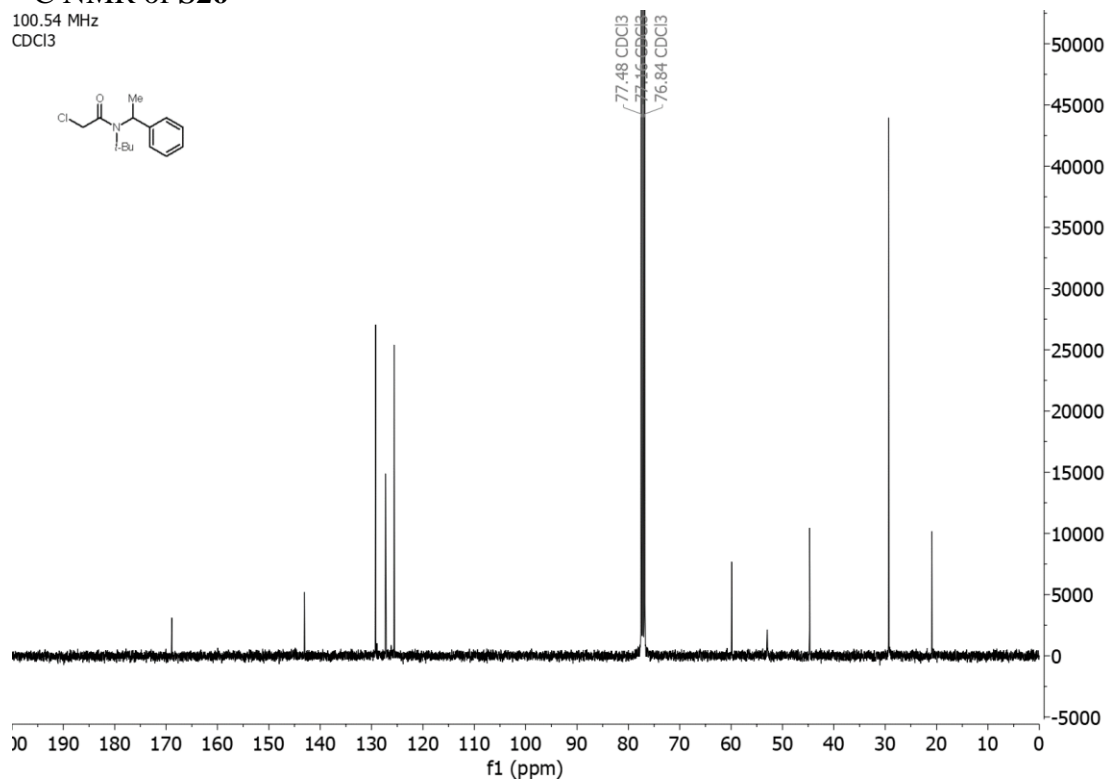
# <sup>1</sup>H NMR of S26

500.29 MHz  
cdcl<sub>3</sub>



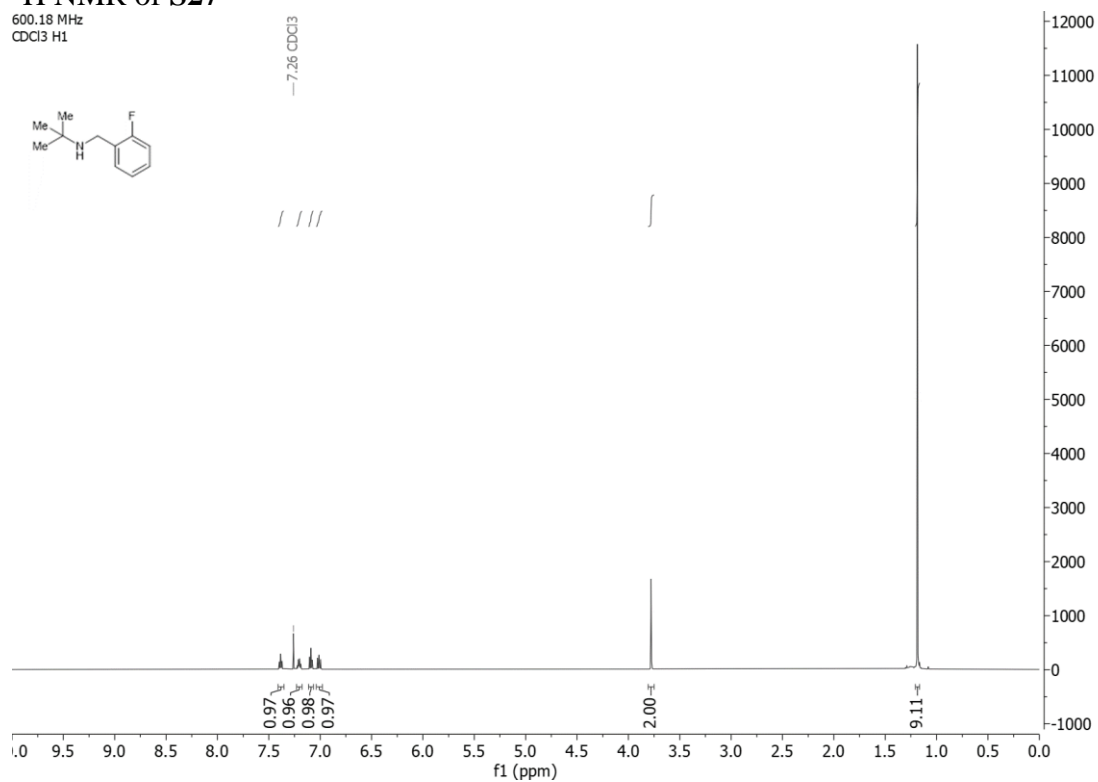
# <sup>13</sup>C NMR of S26

100.54 MHz  
CDCl<sub>3</sub>



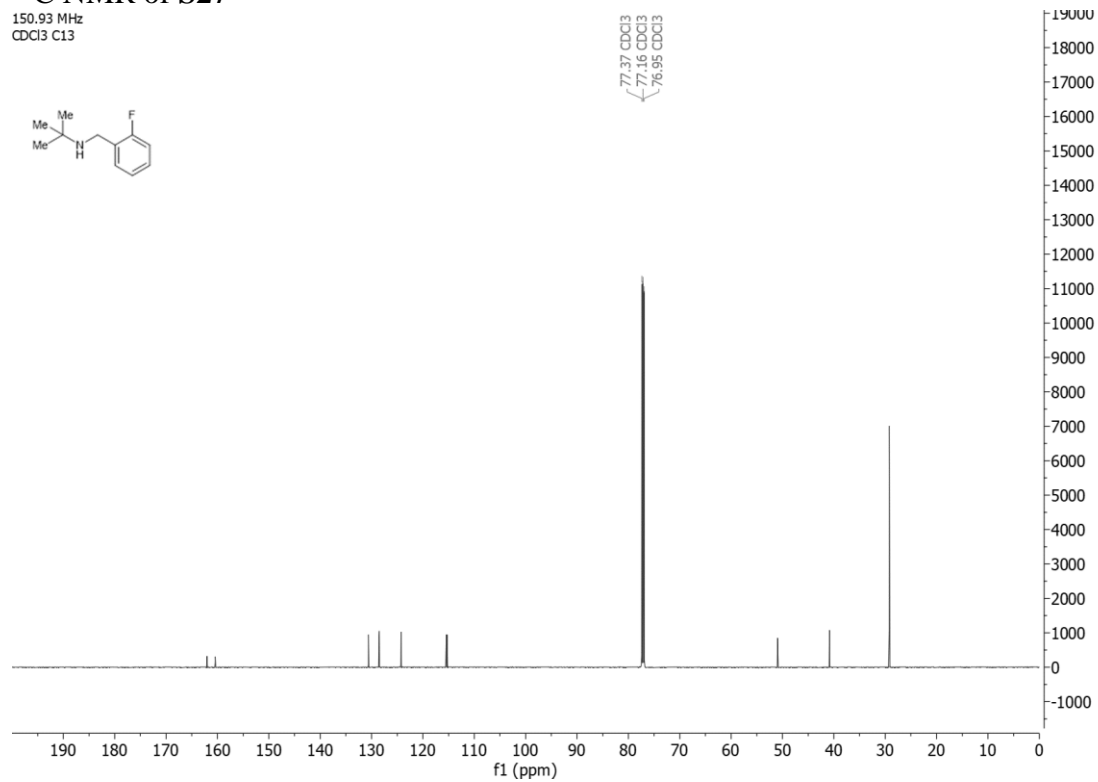
# <sup>1</sup>H NMR of S27

600.18 MHz  
CDCl<sub>3</sub> H1



# <sup>13</sup>C NMR of S27

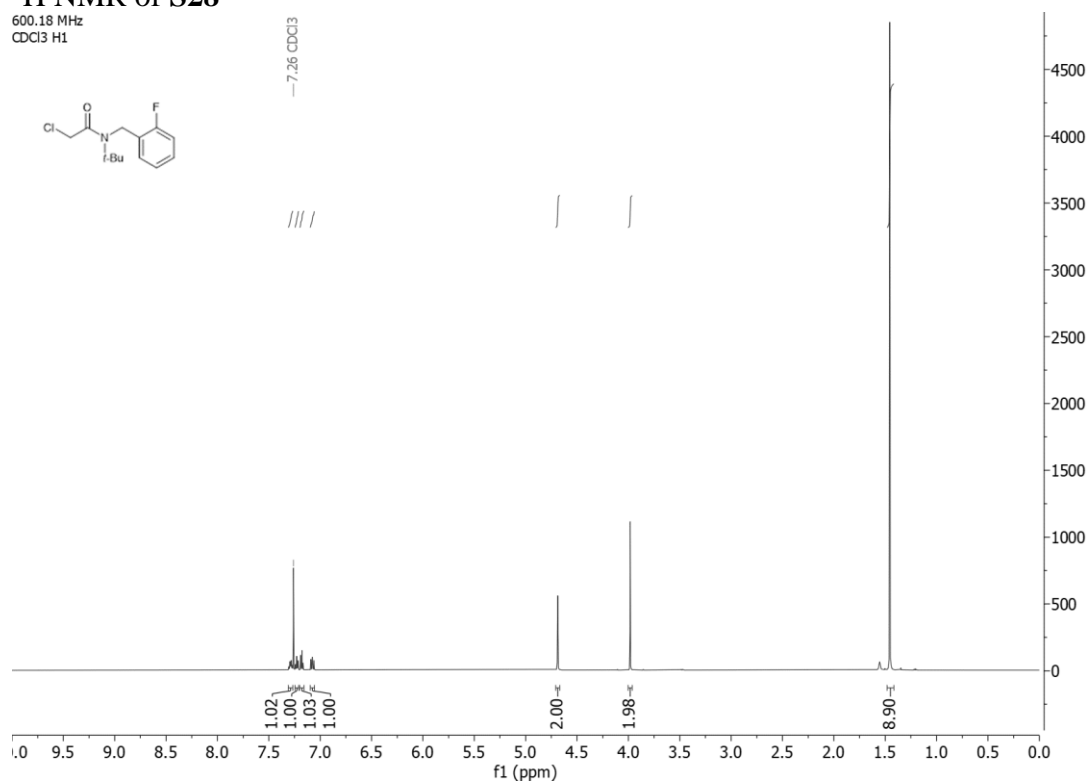
150.93 MHz  
CDCl<sub>3</sub> C13





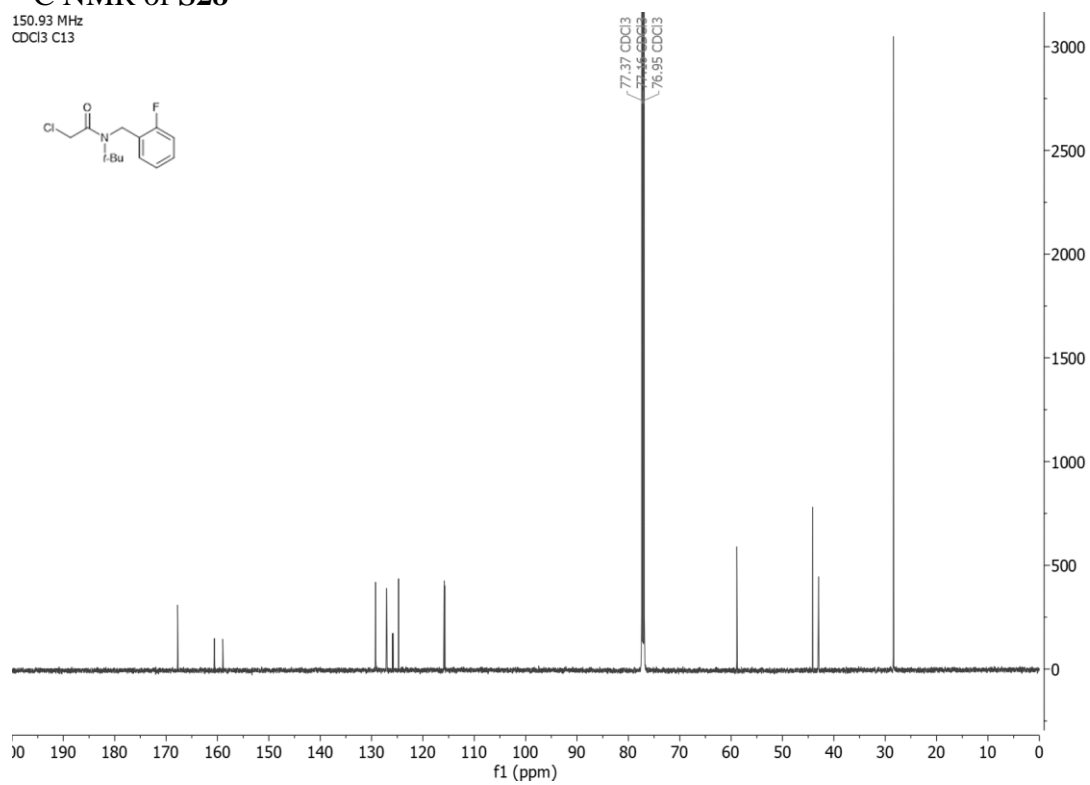
# <sup>1</sup>H NMR of S28

600.18 MHz  
CDCl<sub>3</sub> H<sub>1</sub>



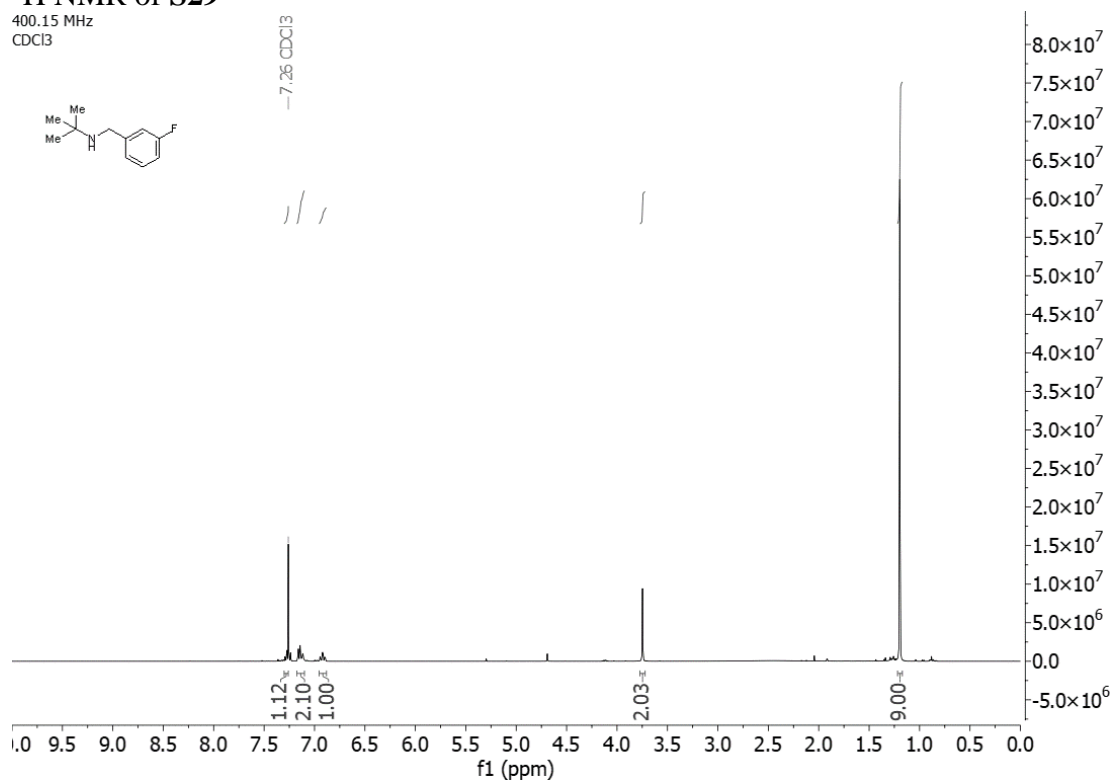
# <sup>13</sup>C NMR of S28

150.93 MHz  
CDCl<sub>3</sub> C13



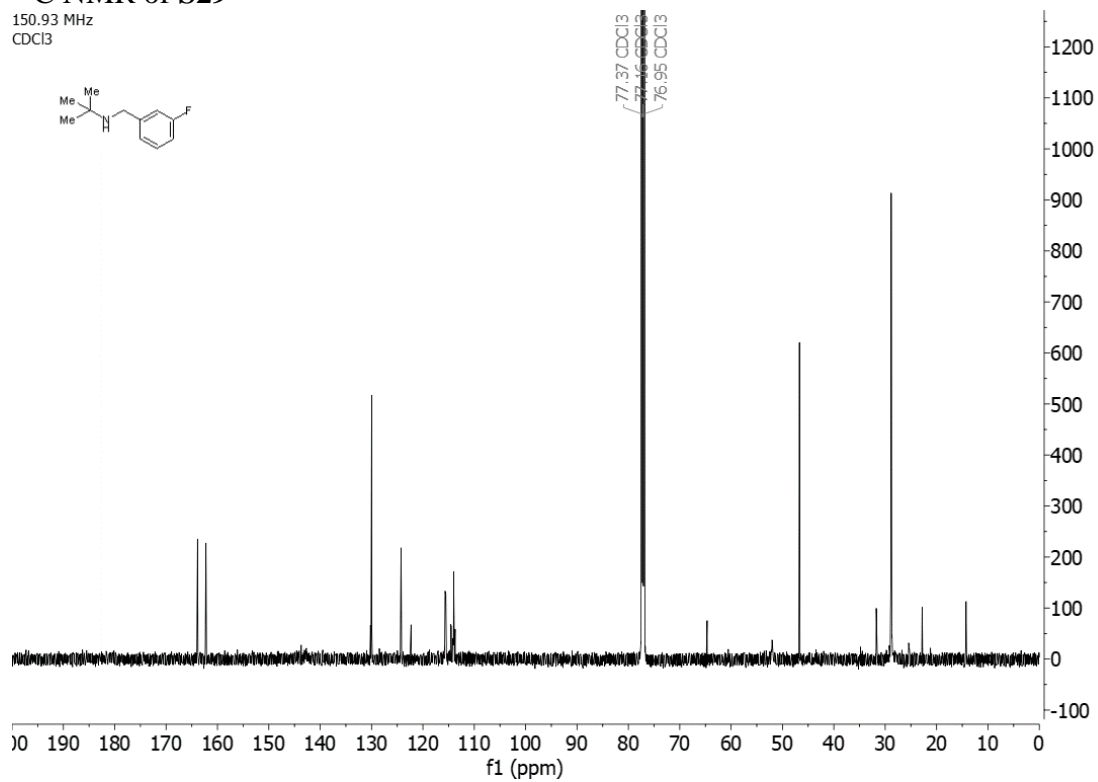
# <sup>1</sup>H NMR of S29

400.15 MHz  
CDCl<sub>3</sub>



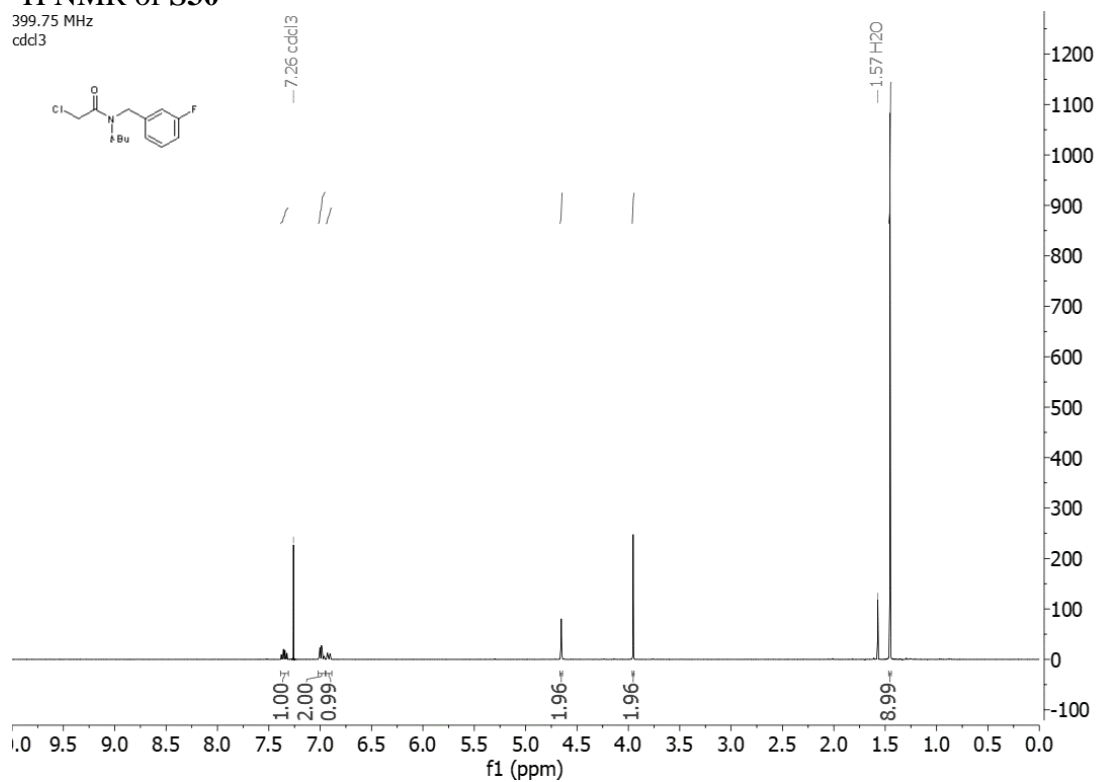
# <sup>13</sup>C NMR of S29

150.93 MHz  
CDCl<sub>3</sub>



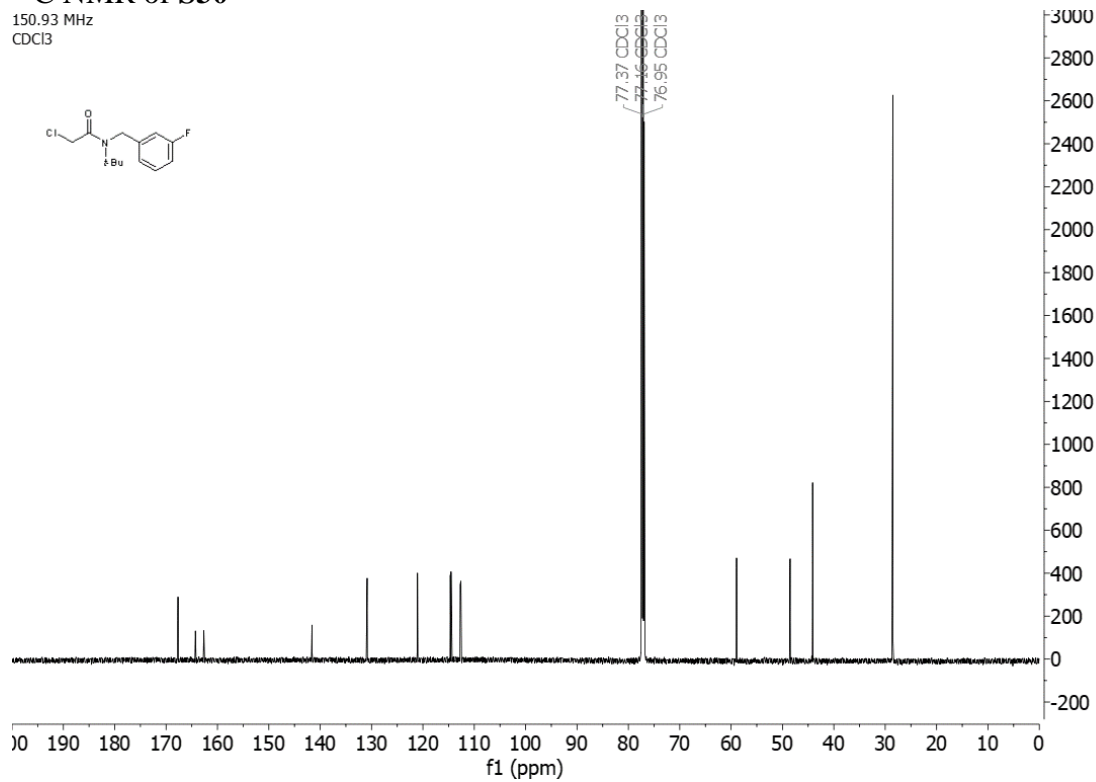
# <sup>1</sup>H NMR of S30

399.75 MHz  
cdcl3



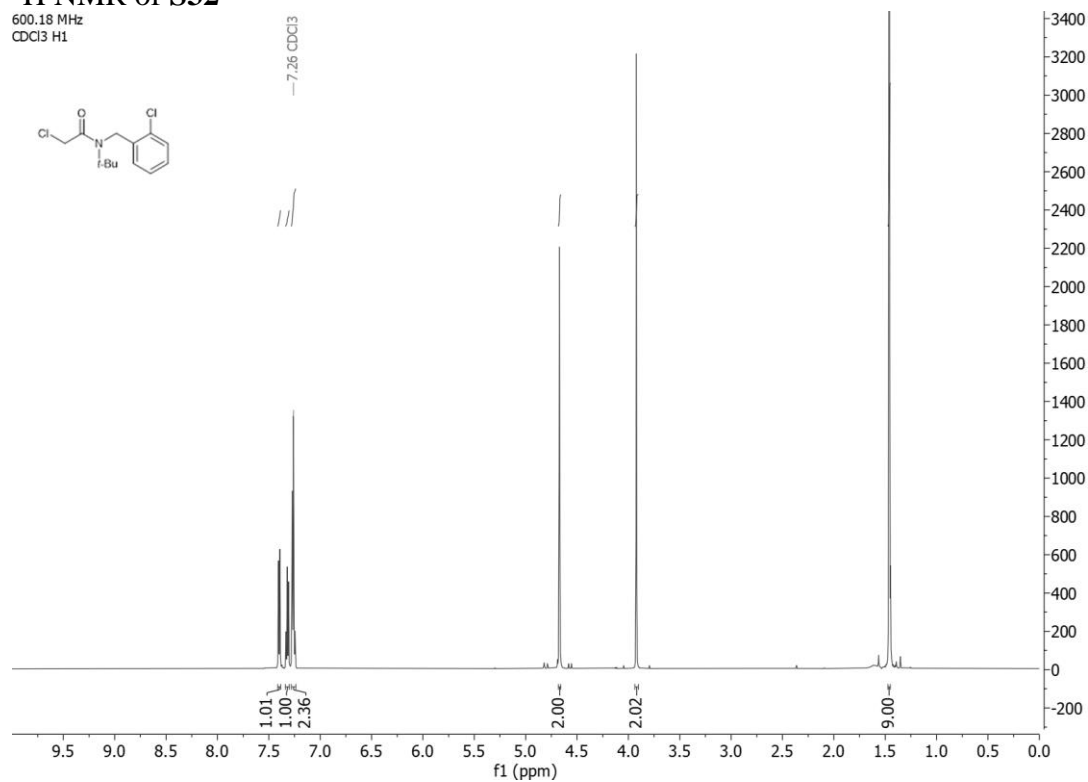
# <sup>13</sup>C NMR of S30

150.93 MHz  
CDCl3



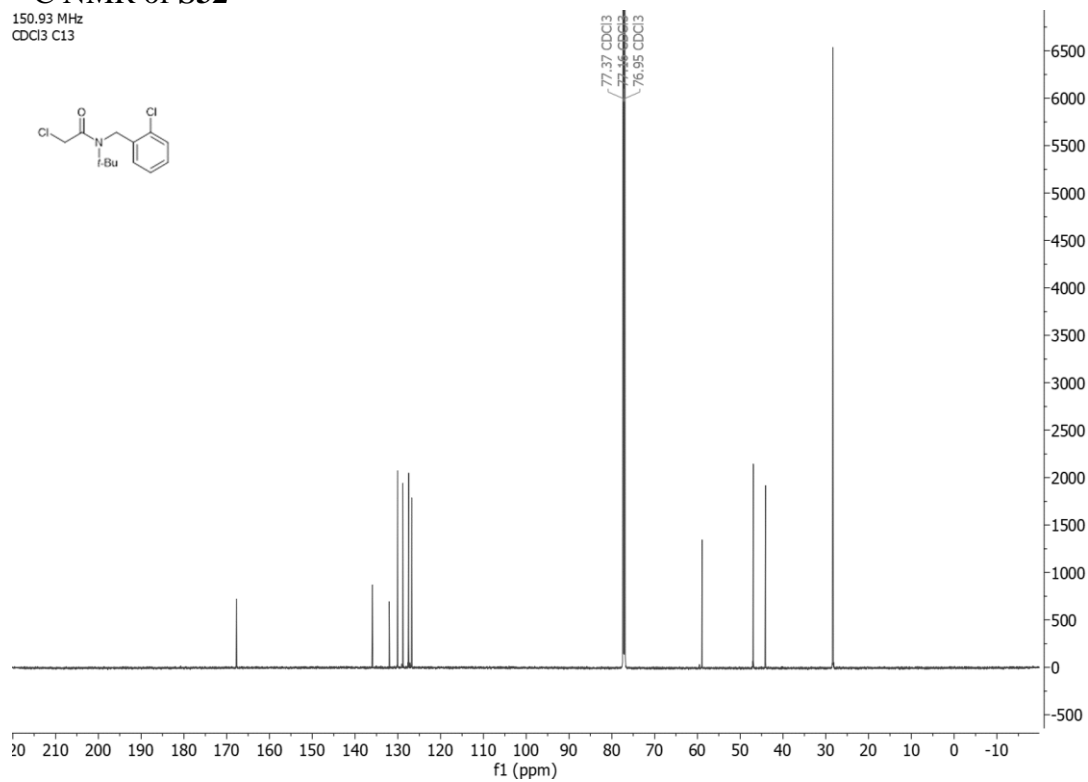
# <sup>1</sup>H NMR of S32

600.18 MHz  
CDCl<sub>3</sub> H1



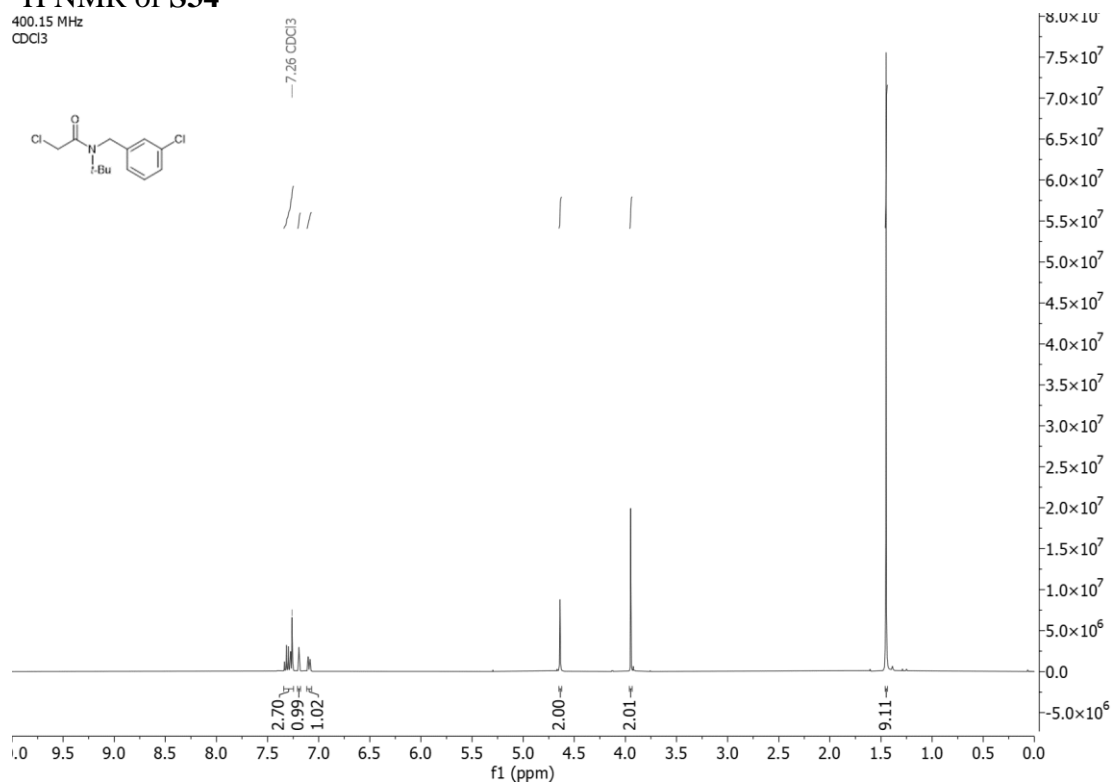
# <sup>13</sup>C NMR of S32

150.93 MHz  
CDCl<sub>3</sub> C13



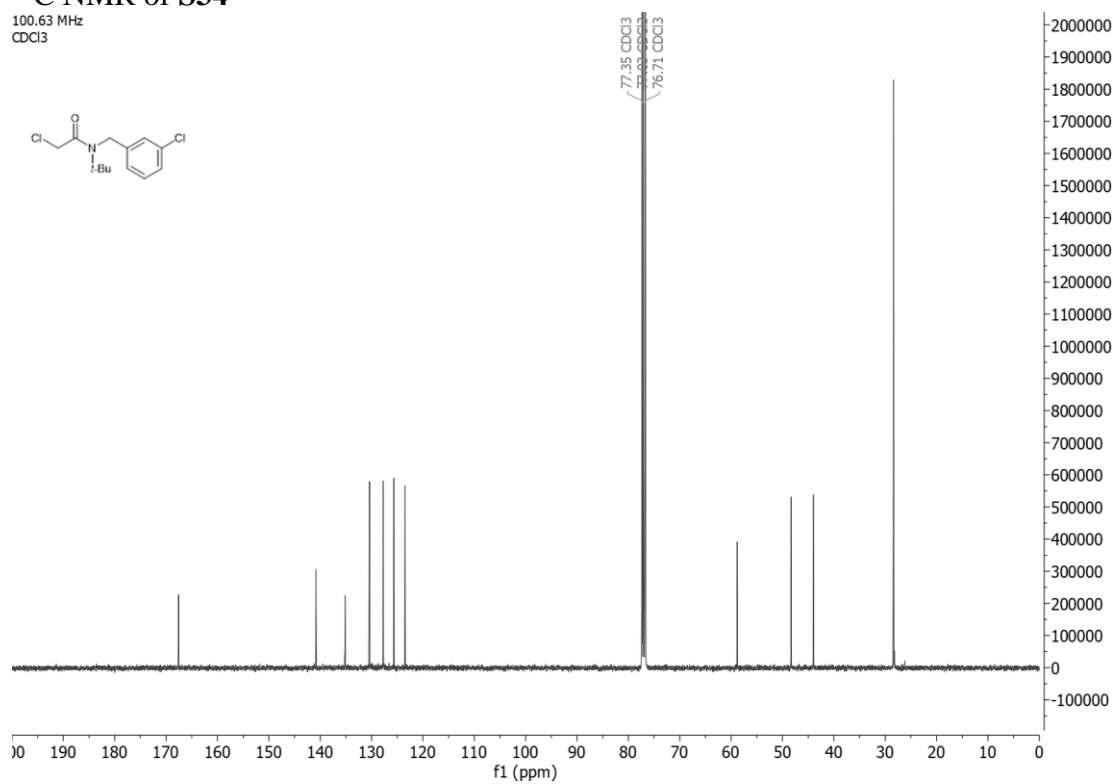
# <sup>1</sup>H NMR of S34

400.15 MHz  
CDCl<sub>3</sub>



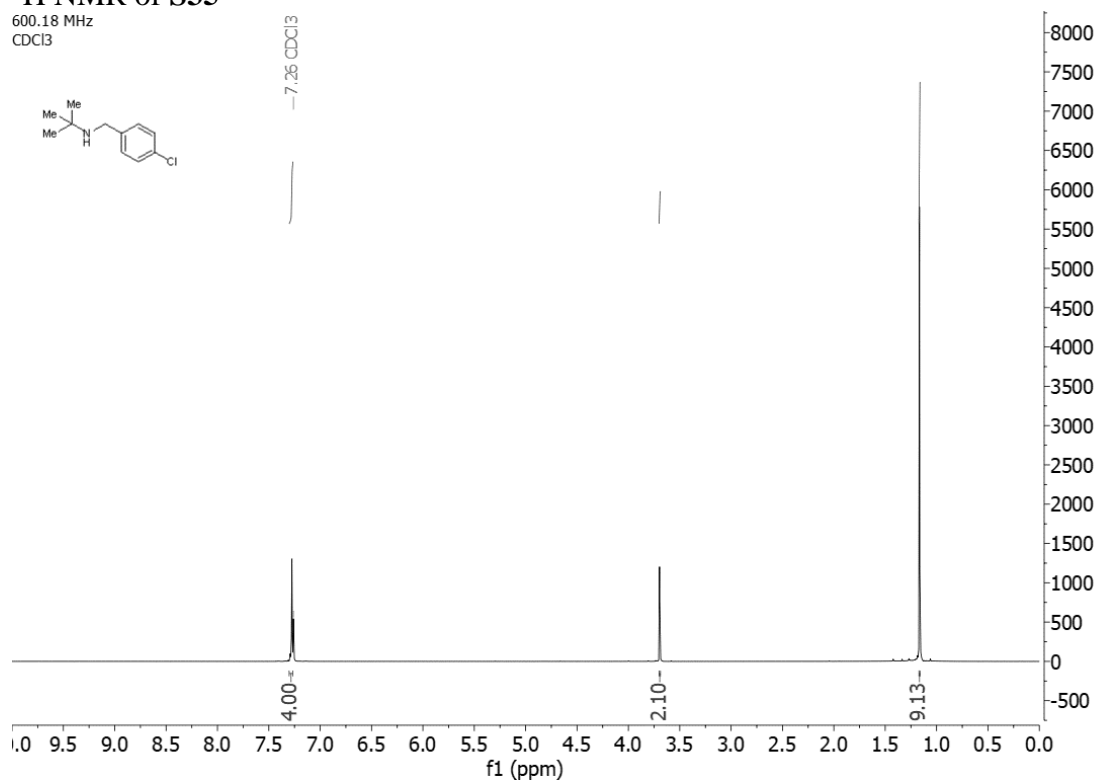
# <sup>13</sup>C NMR of S34

100.63 MHz  
CDCl<sub>3</sub>



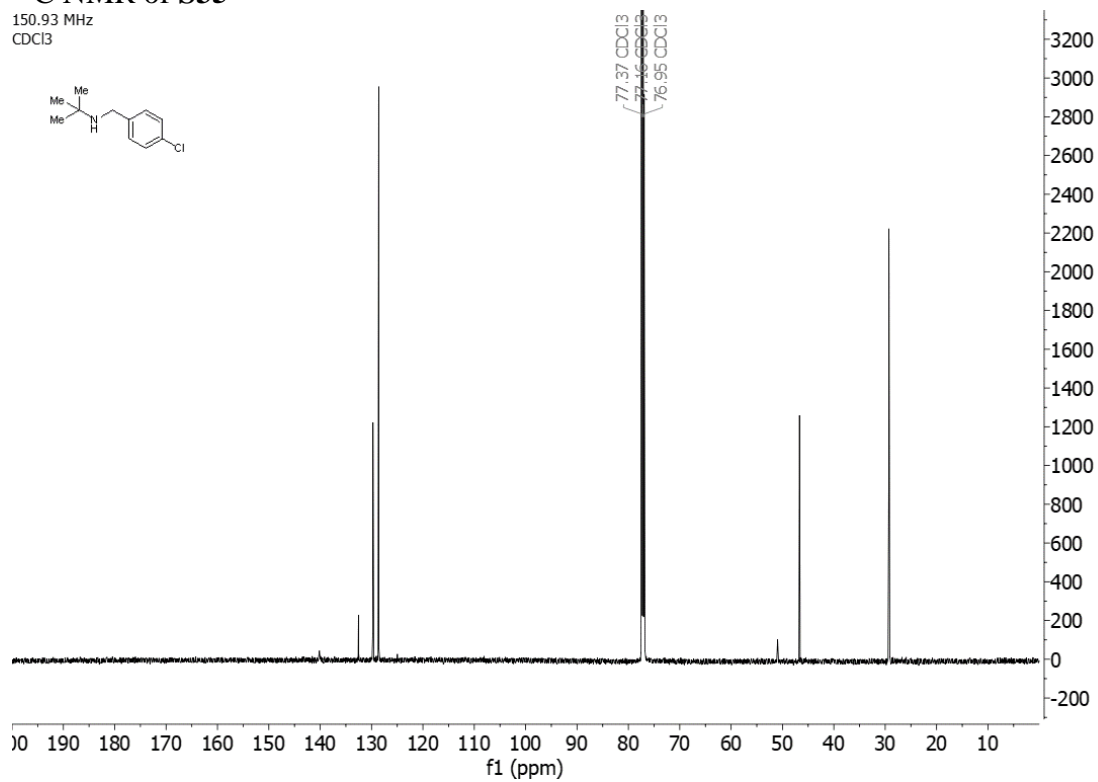
# <sup>1</sup>H NMR of S35

600.18 MHz  
CDCl<sub>3</sub>



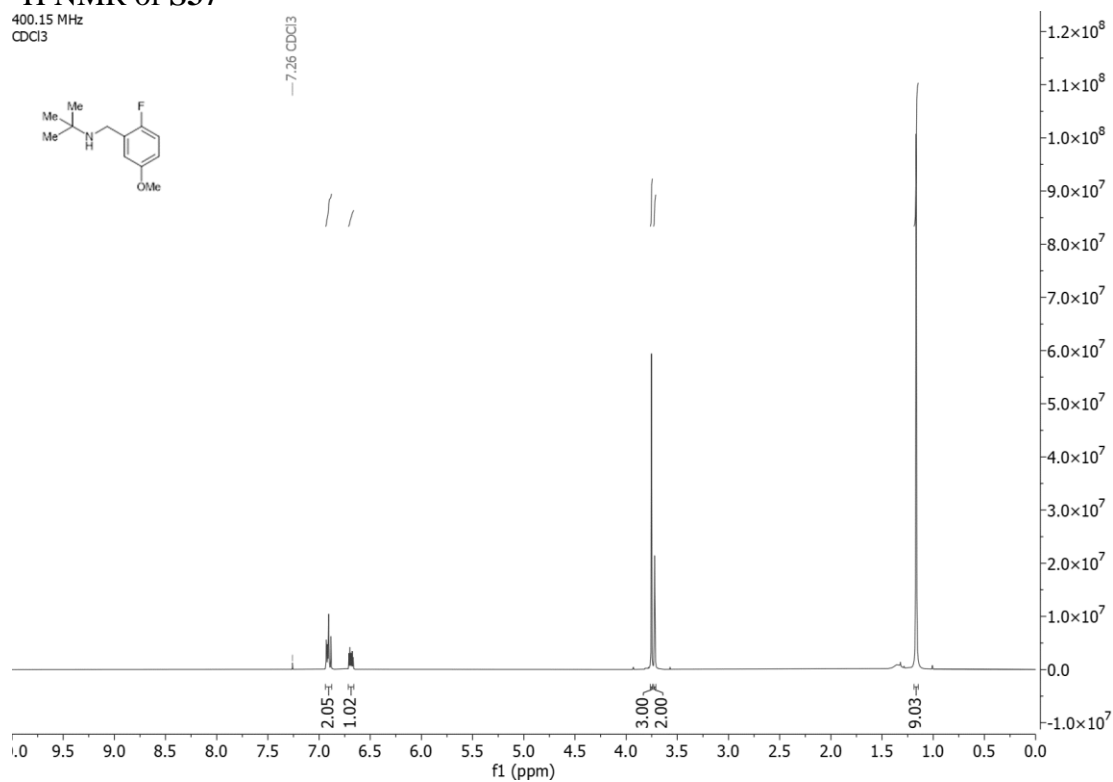
# <sup>13</sup>C NMR of S35

150.93 MHz  
CDCl<sub>3</sub>



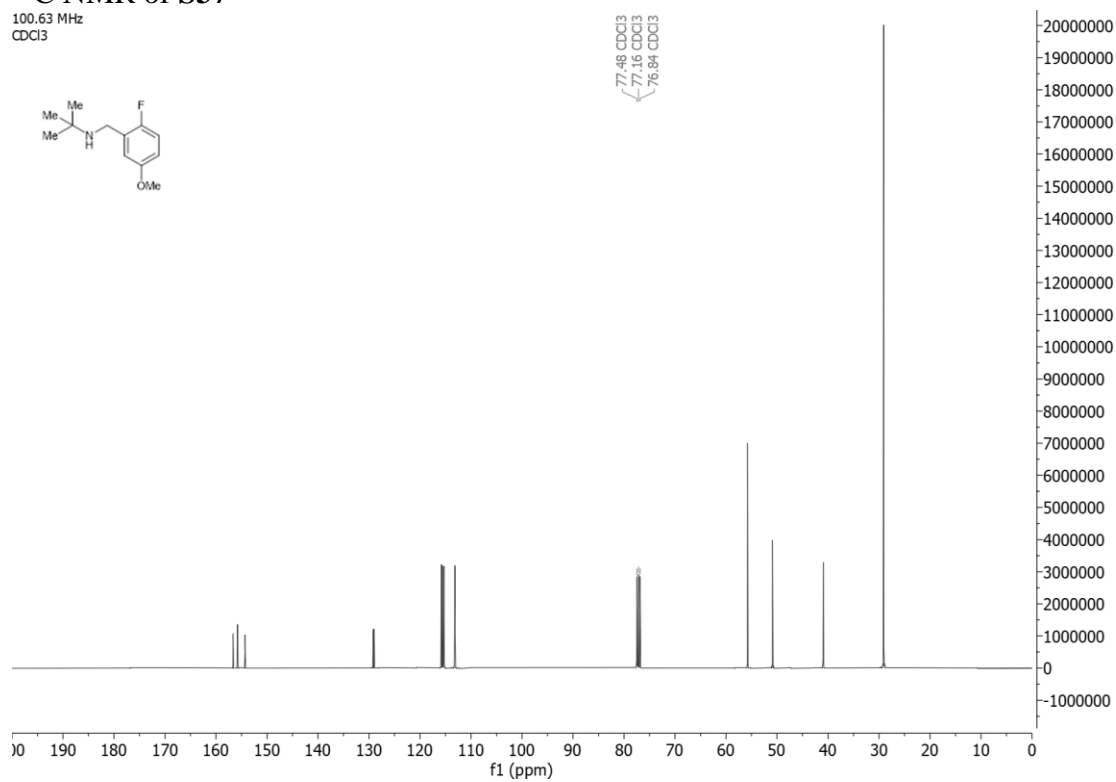
# <sup>1</sup>H NMR of S37

400.15 MHz  
CDCl<sub>3</sub>



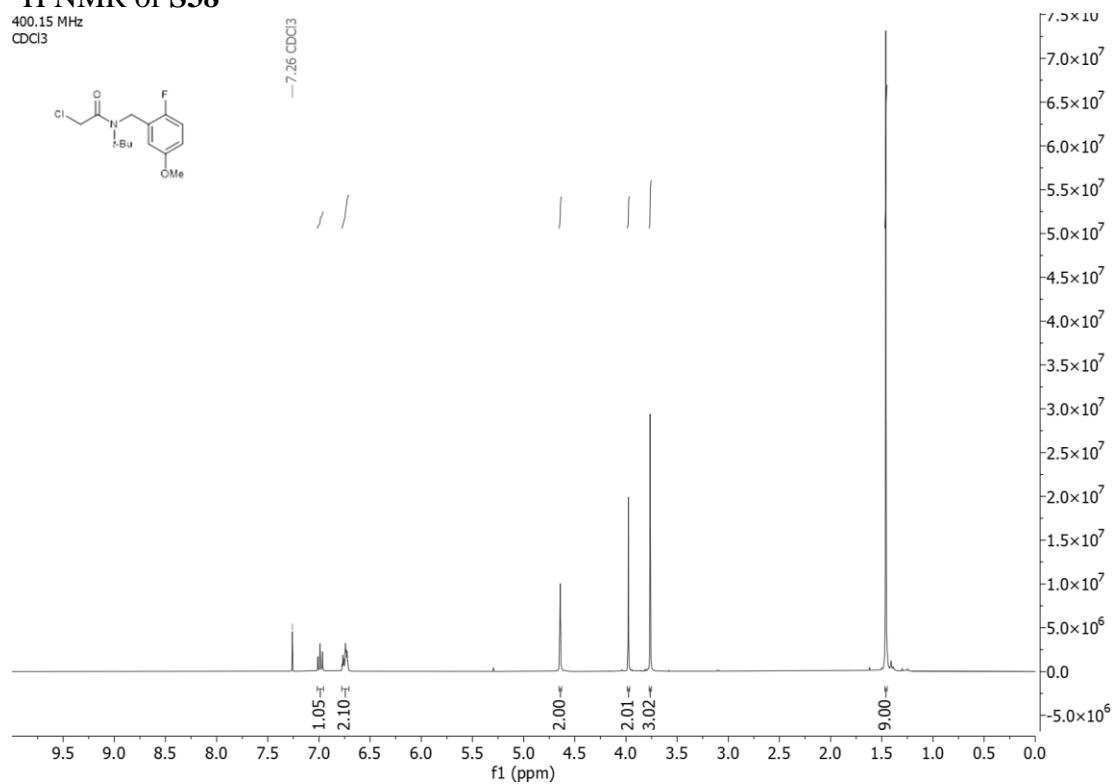
# <sup>13</sup>C NMR of S37

100.63 MHz  
CDCl<sub>3</sub>



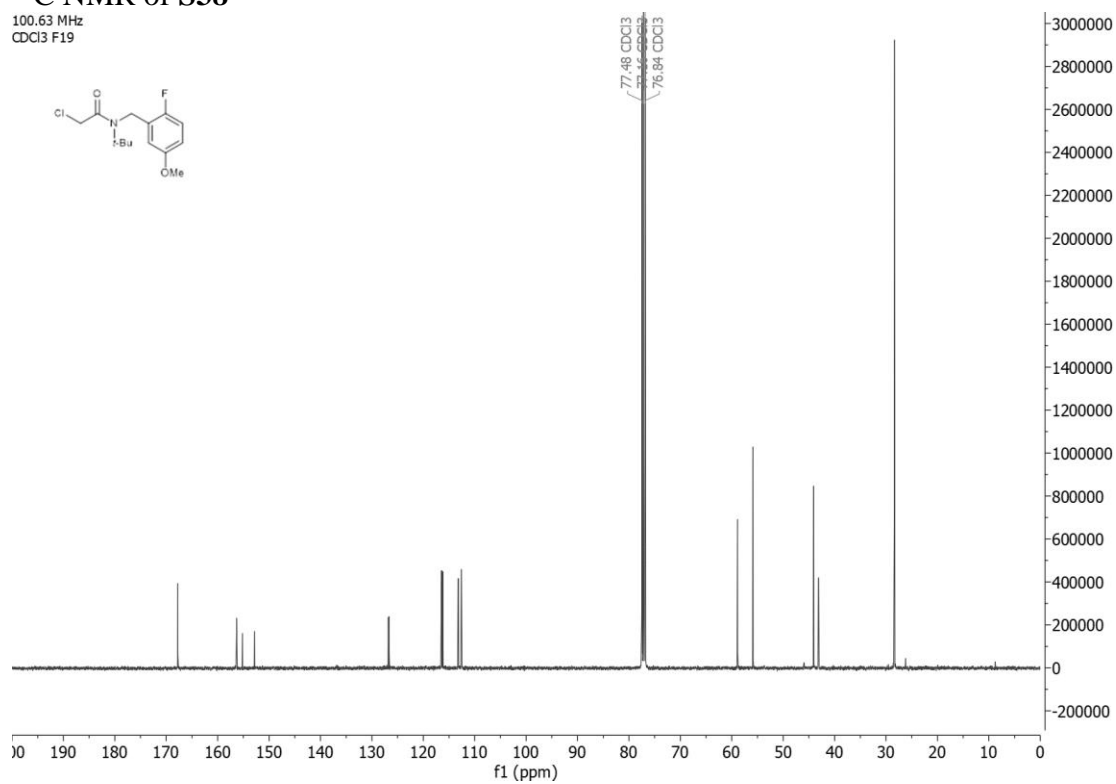
# <sup>1</sup>H NMR of S38

400.15 MHz  
CDCl<sub>3</sub>



# <sup>13</sup>C NMR of S38

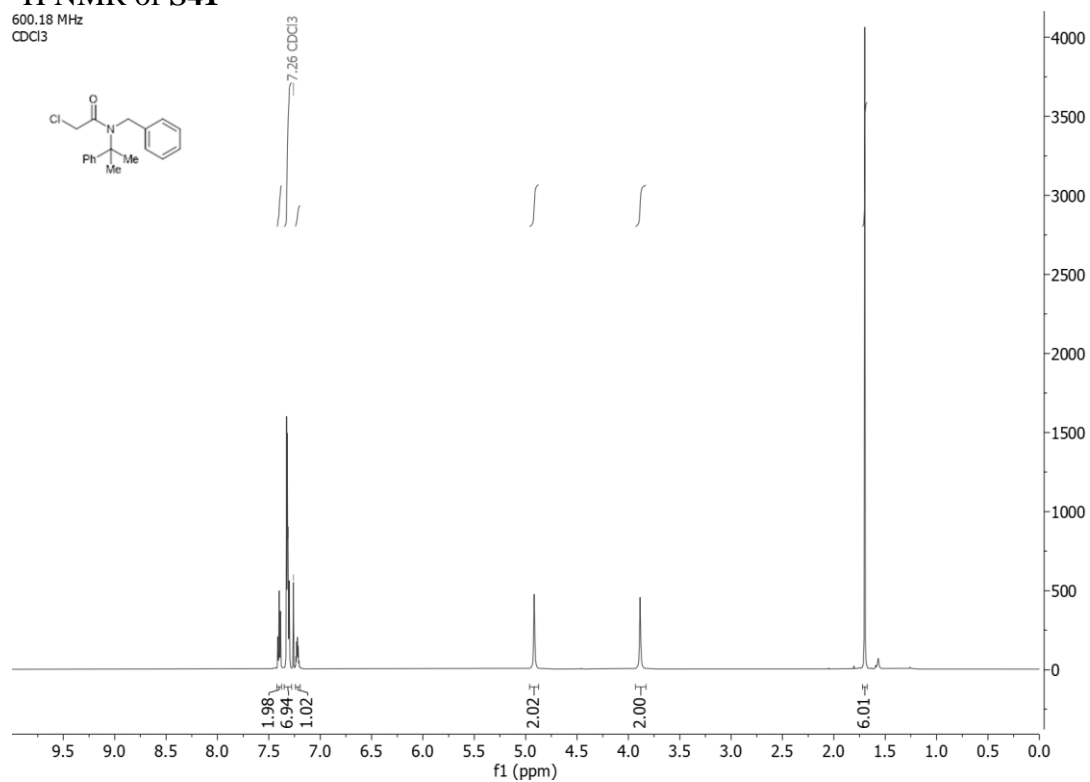
100.63 MHz  
CDCl<sub>3</sub> F19





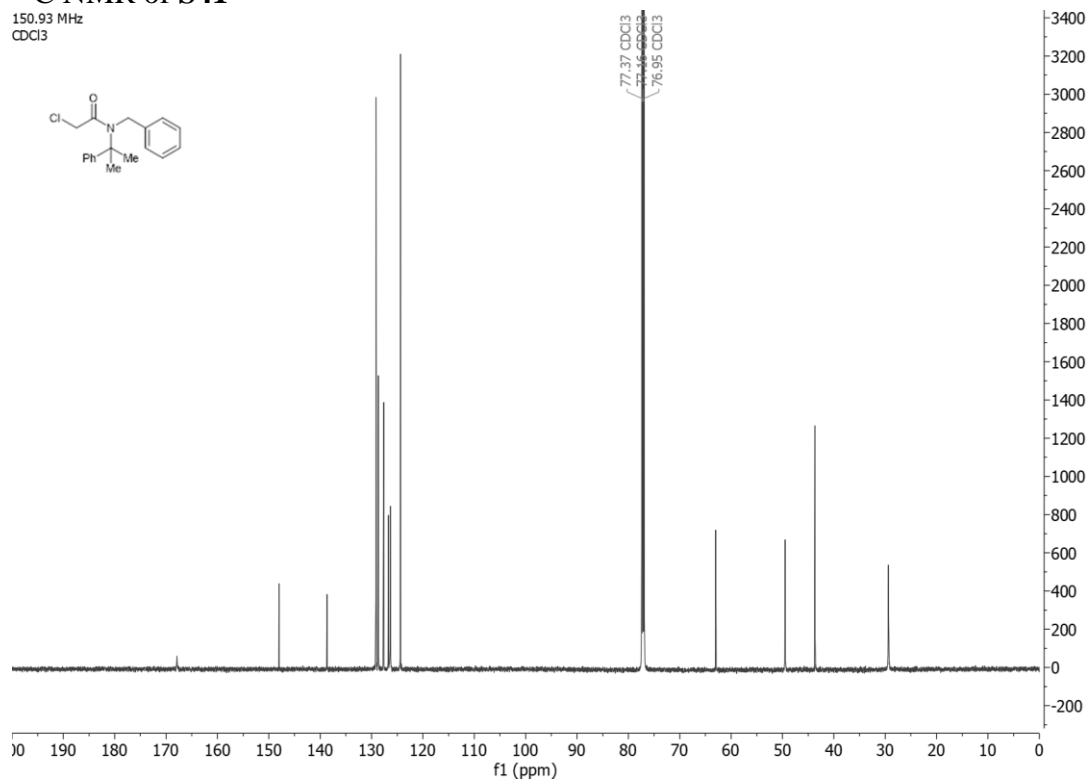
# <sup>1</sup>H NMR of S41

600.18 MHz  
CDCl<sub>3</sub>



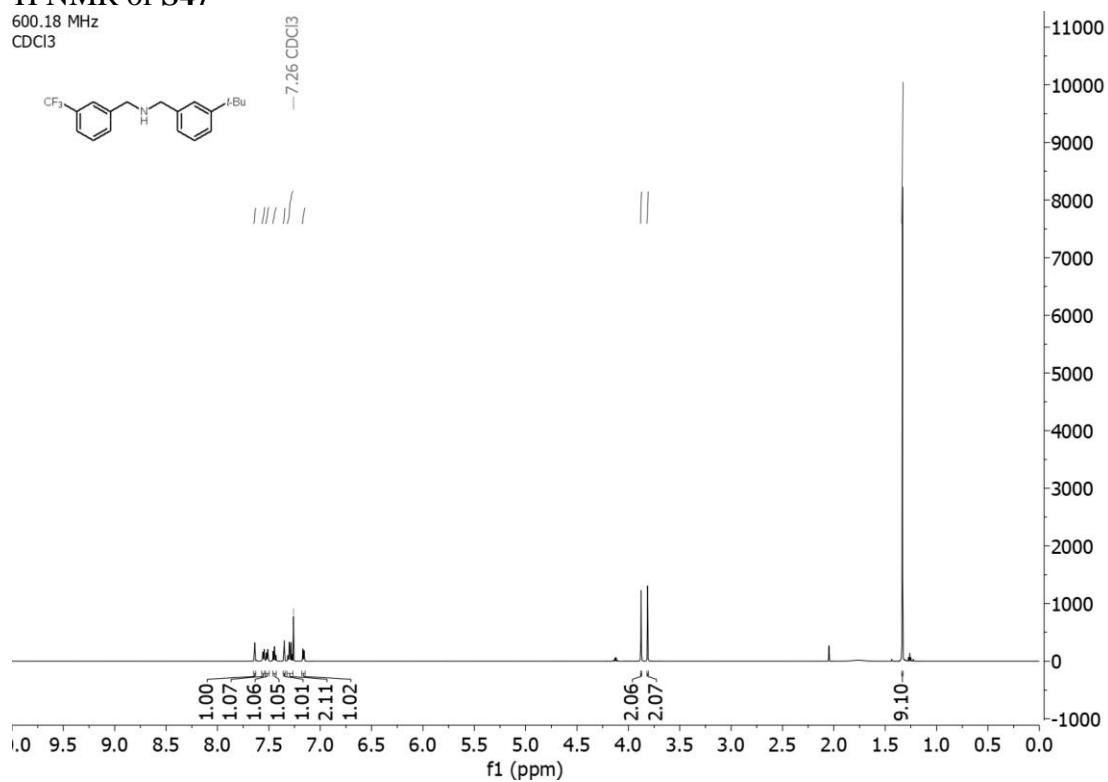
# <sup>13</sup>C NMR of S41

150.93 MHz  
CDCl<sub>3</sub>



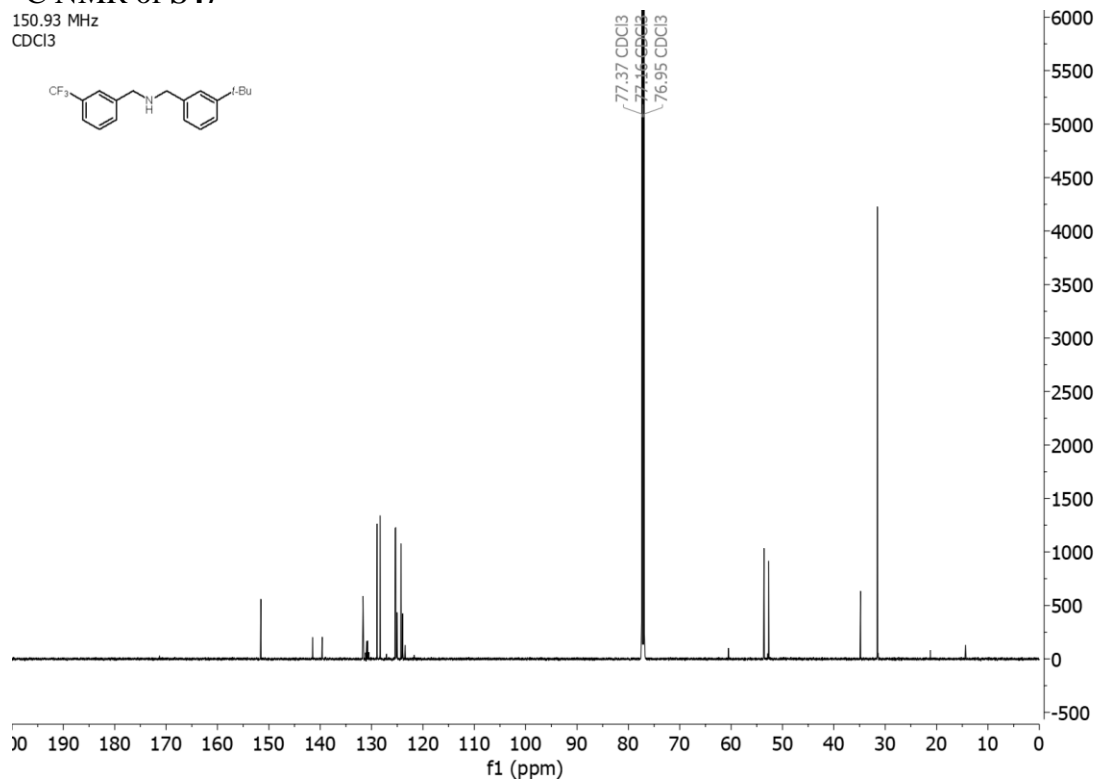
# <sup>1</sup>H NMR of S47

600.18 MHz  
CDCl<sub>3</sub>



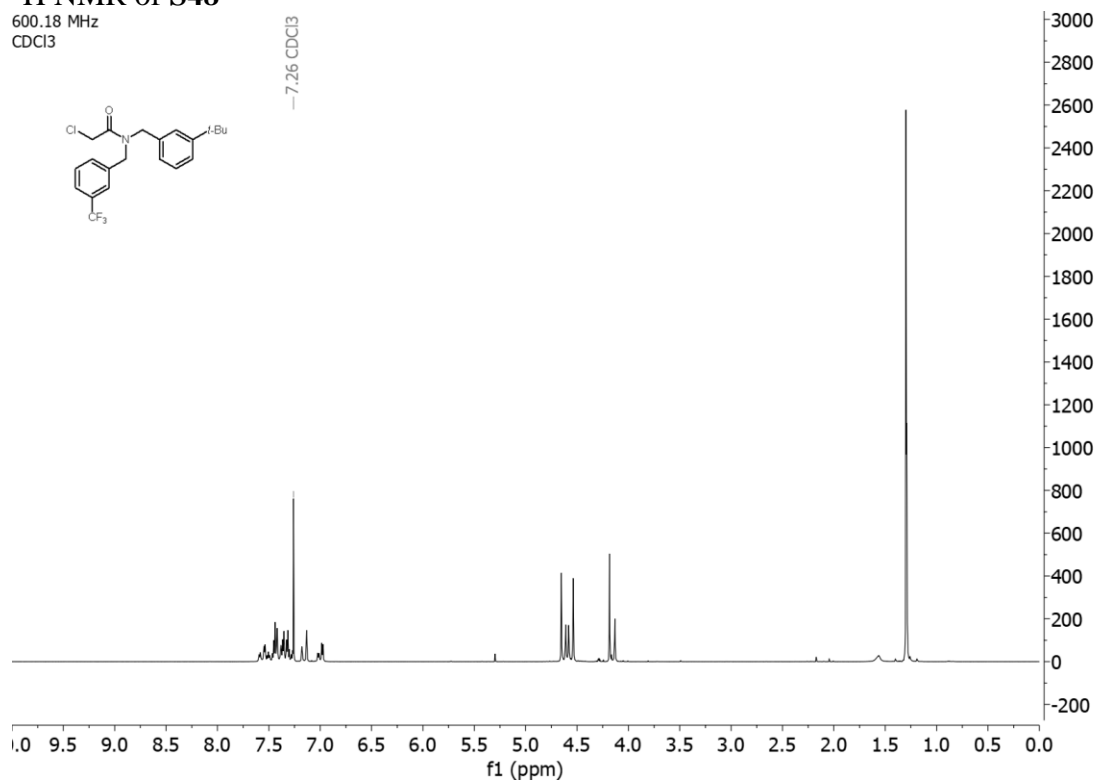
# <sup>13</sup>C NMR of S47

150.93 MHz  
CDCl<sub>3</sub>



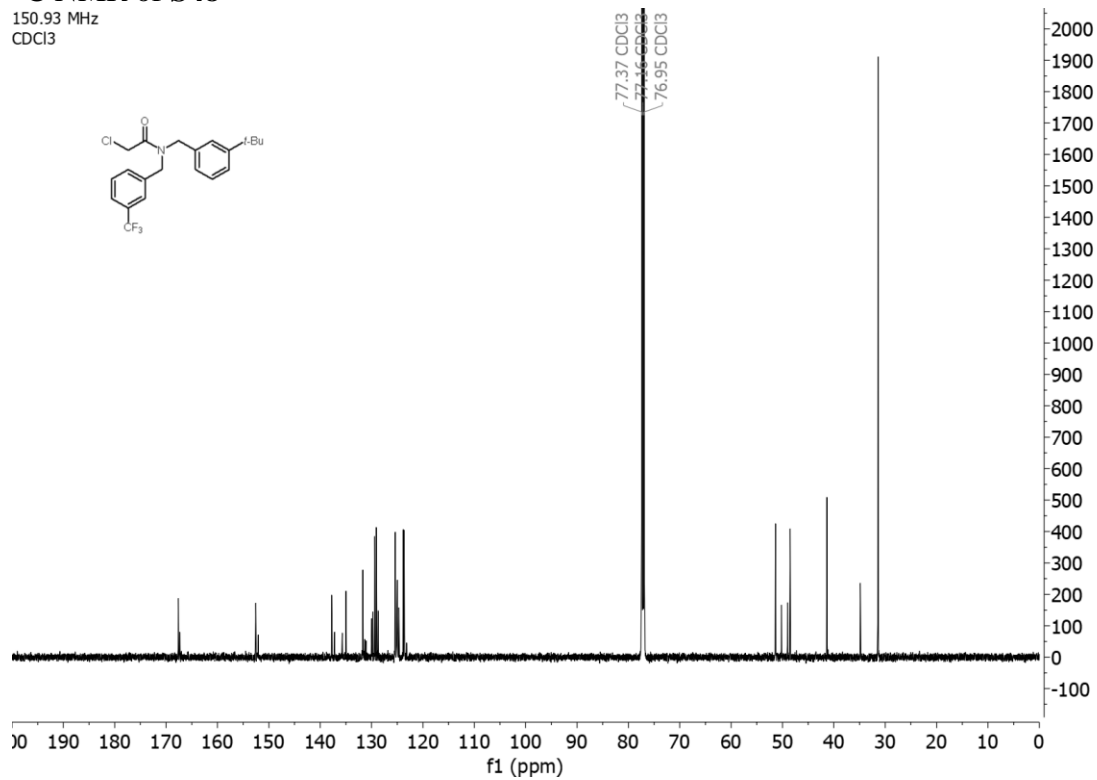
# <sup>1</sup>H NMR of S48

600.18 MHz  
CDCl<sub>3</sub>



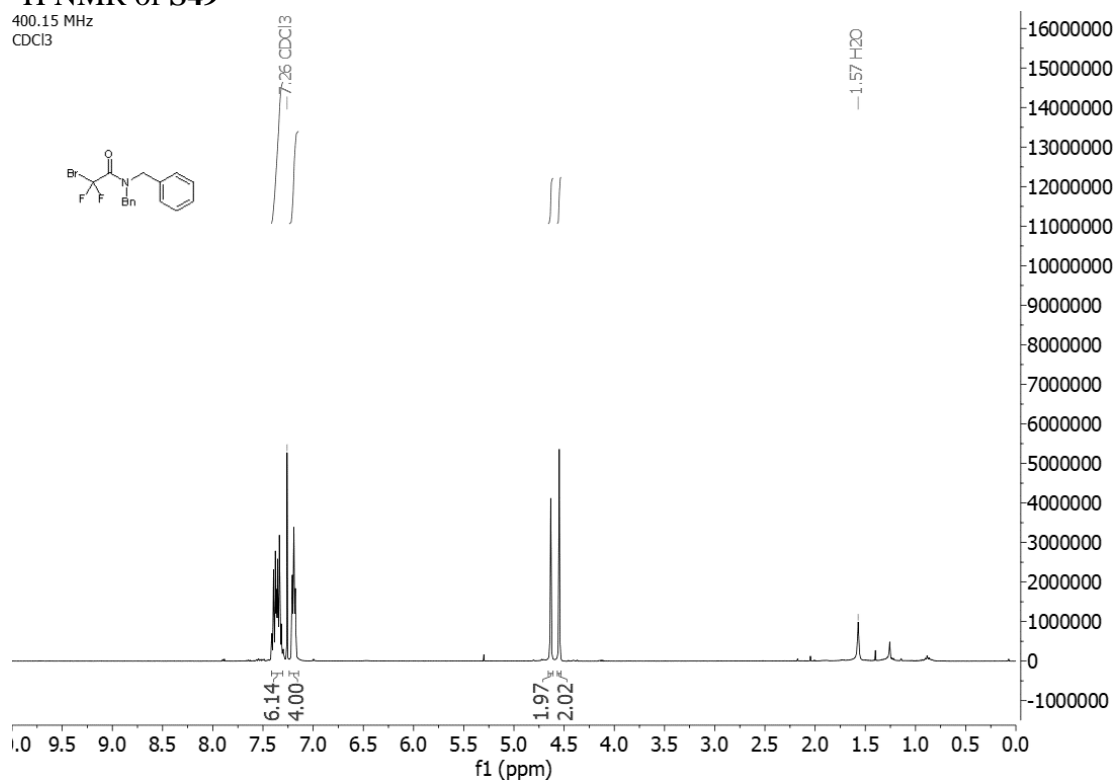
# <sup>13</sup>C NMR of S48

150.93 MHz  
CDCl<sub>3</sub>



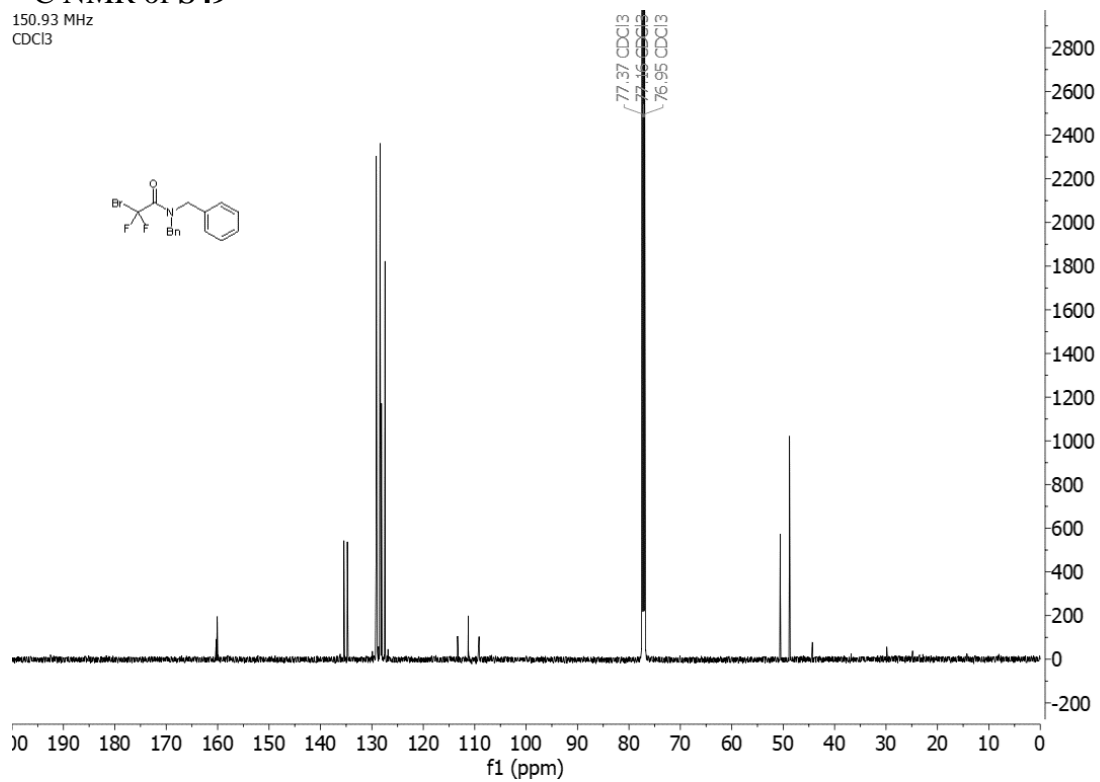
# <sup>1</sup>H NMR of S49

400.15 MHz  
CDCl<sub>3</sub>



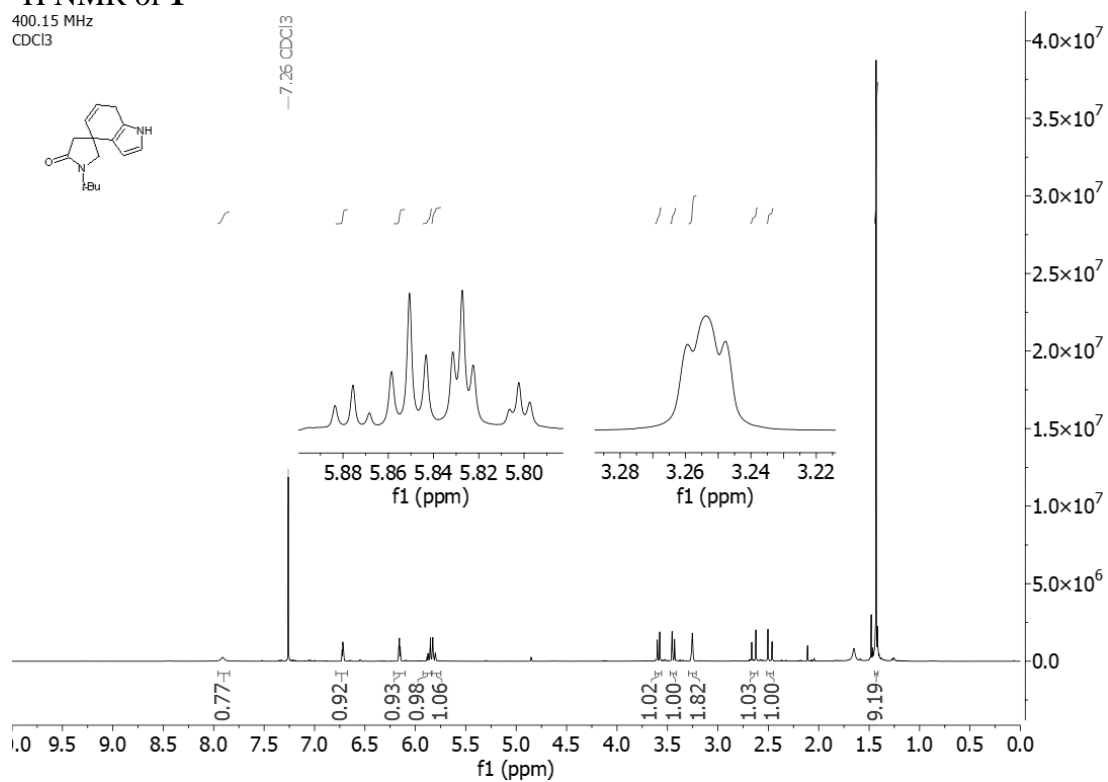
# <sup>13</sup>C NMR of S49

150.93 MHz  
CDCl<sub>3</sub>



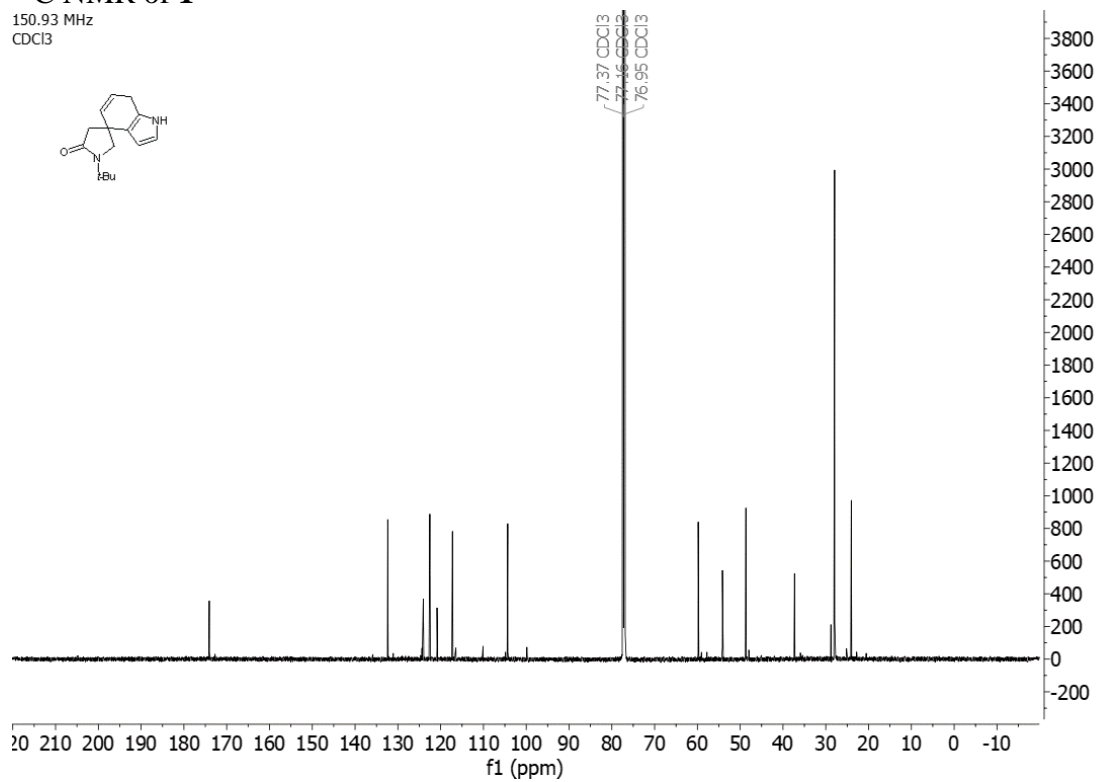
# <sup>1</sup>H NMR of **1**

400.15 MHz  
CDCl<sub>3</sub>



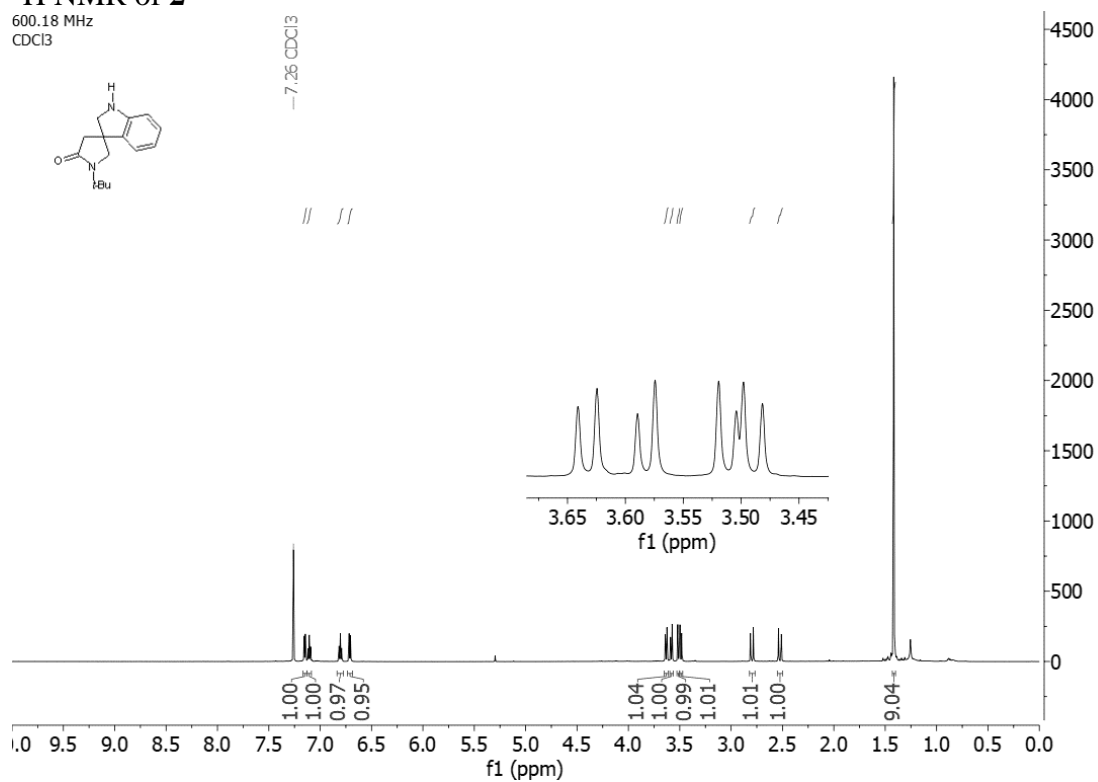
# <sup>13</sup>C NMR of **1**

150.93 MHz  
CDCl<sub>3</sub>



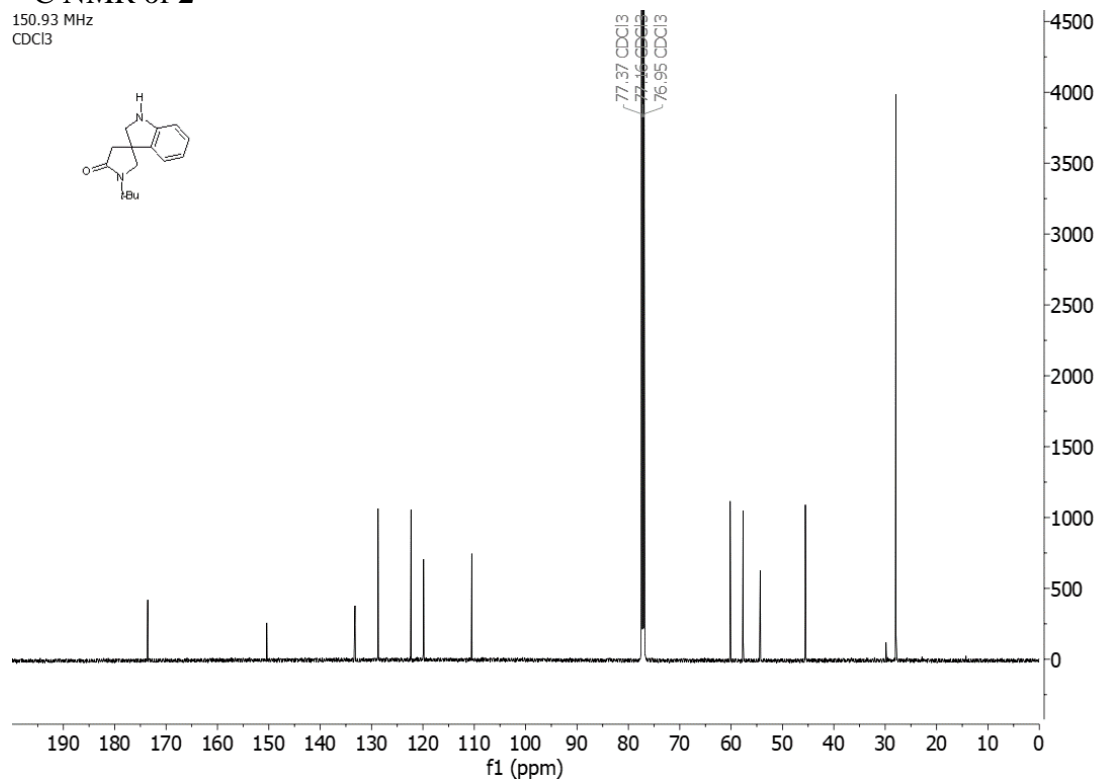
# <sup>1</sup>H NMR of **2**

600.18 MHz  
CDCl<sub>3</sub>



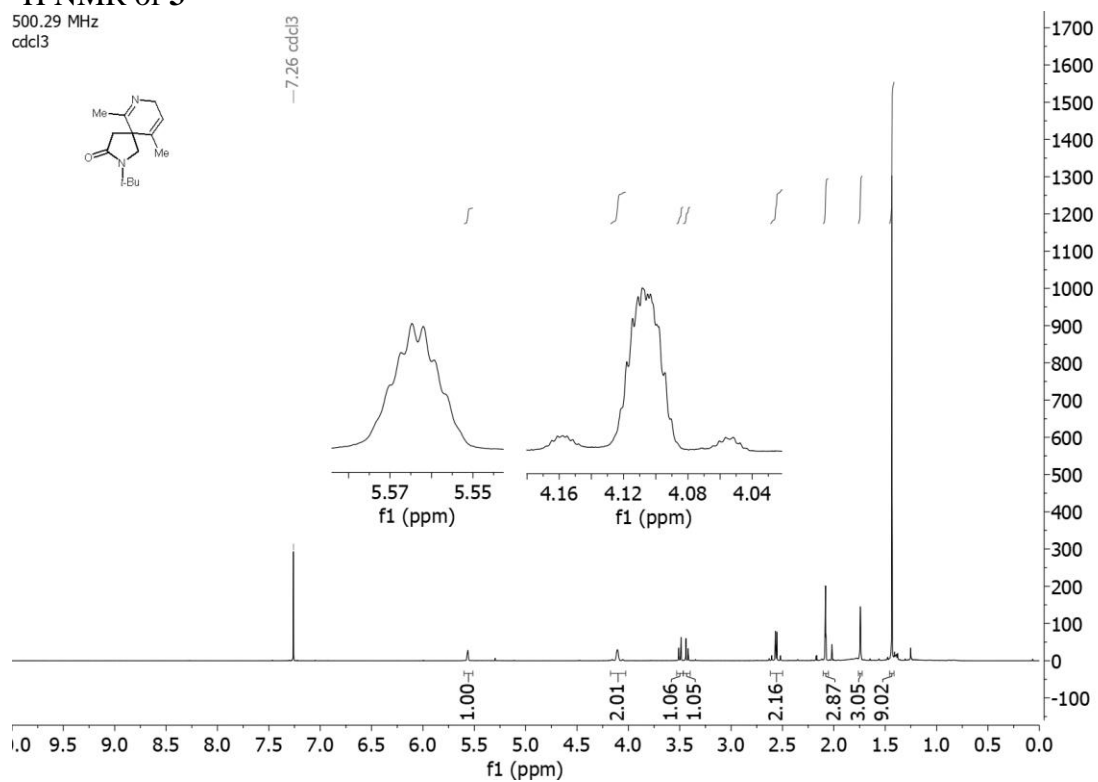
# <sup>13</sup>C NMR of **2**

150.93 MHz  
CDCl<sub>3</sub>



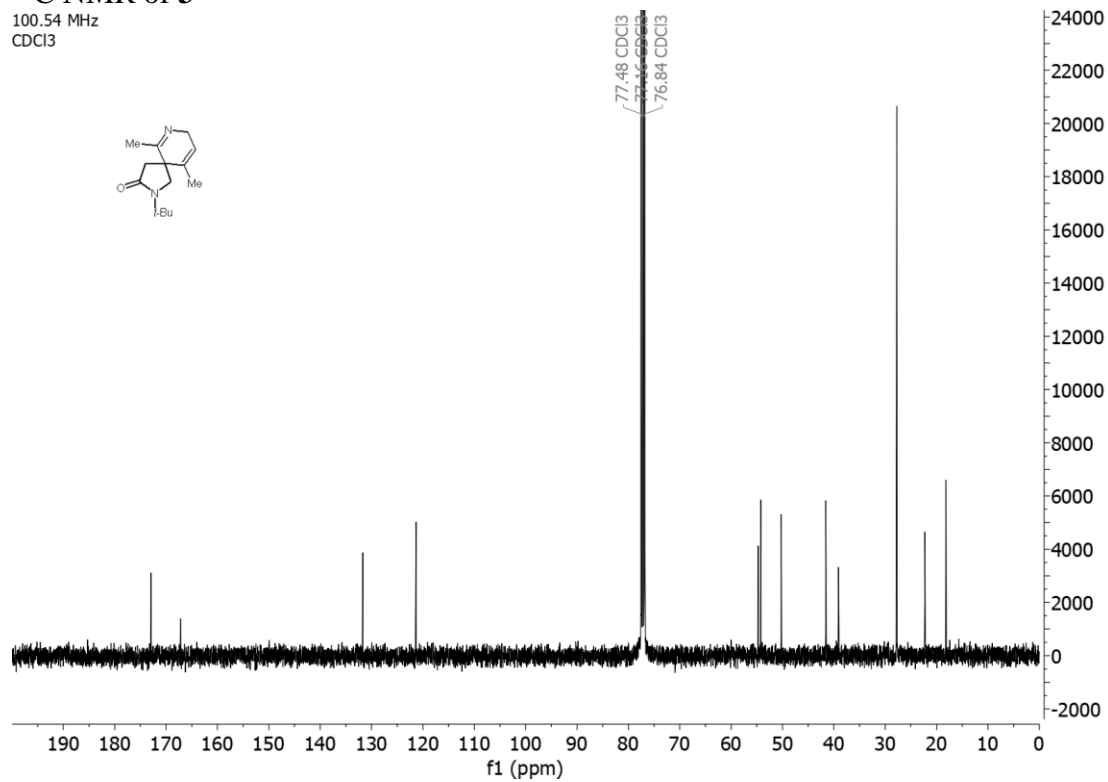
# <sup>1</sup>H NMR of **3**

500.29 MHz  
cdcl<sub>3</sub>



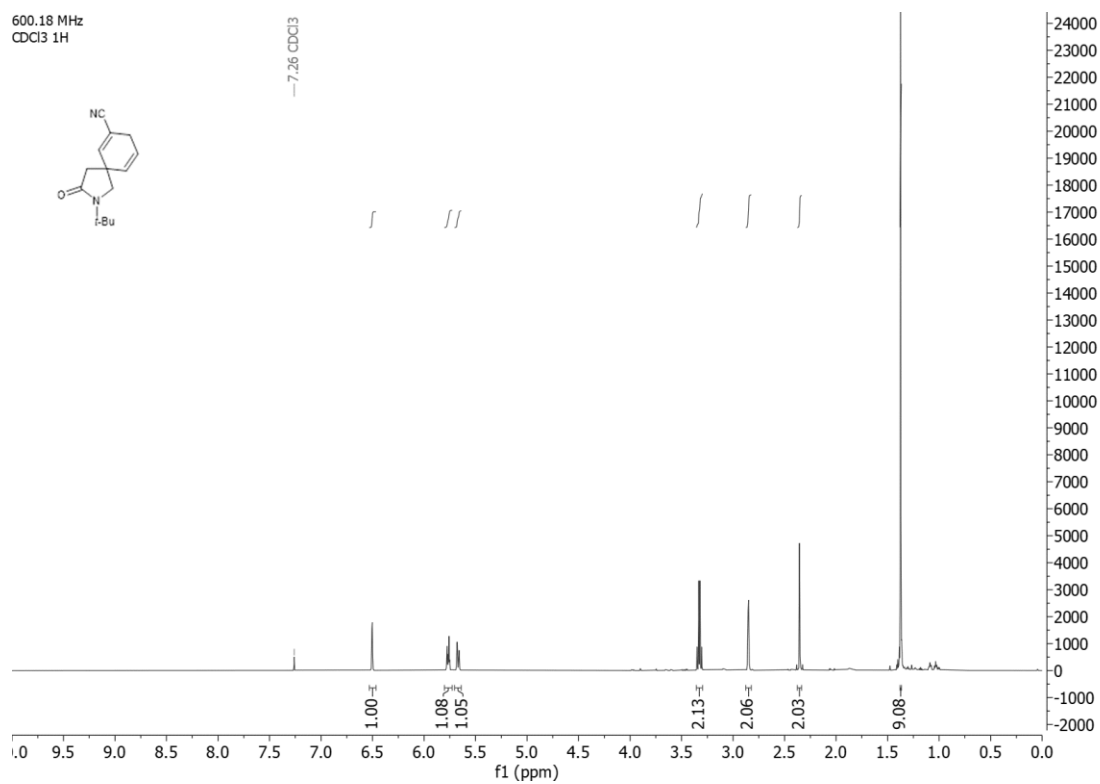
# <sup>13</sup>C NMR of **3**

100.54 MHz  
CDCl<sub>3</sub>



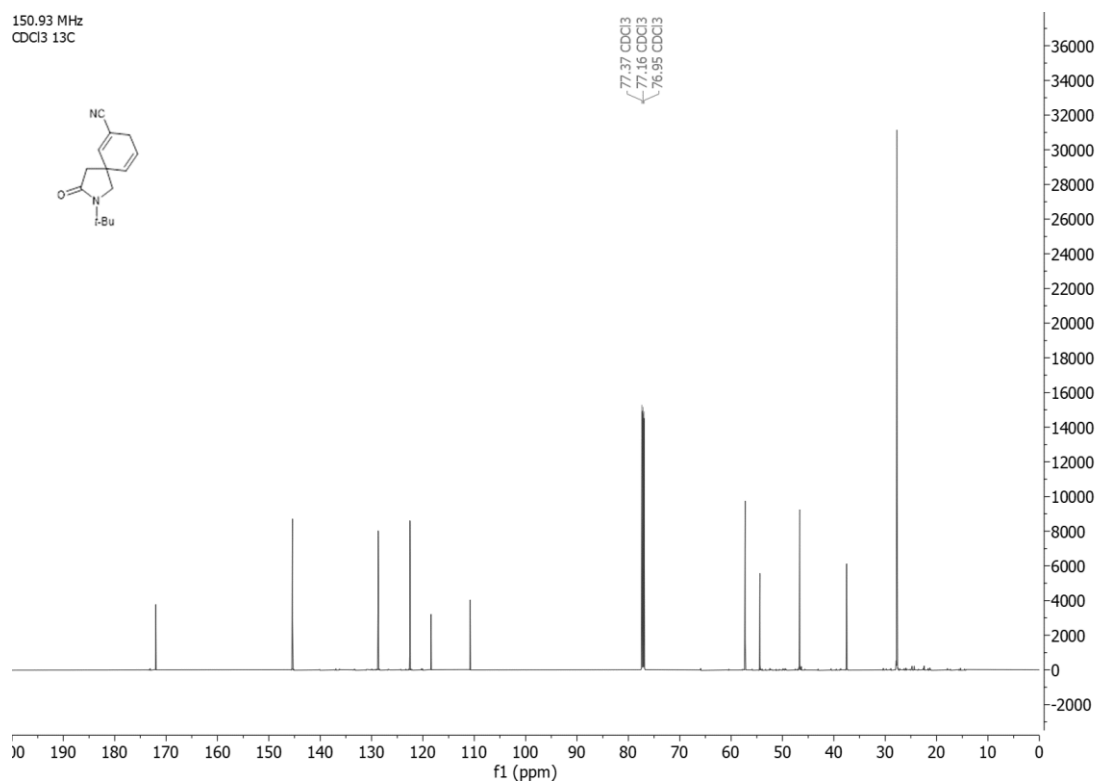
# <sup>1</sup>H NMR of **4**

600.18 MHz  
CDCl<sub>3</sub> 1H



# <sup>13</sup>C NMR of **4**

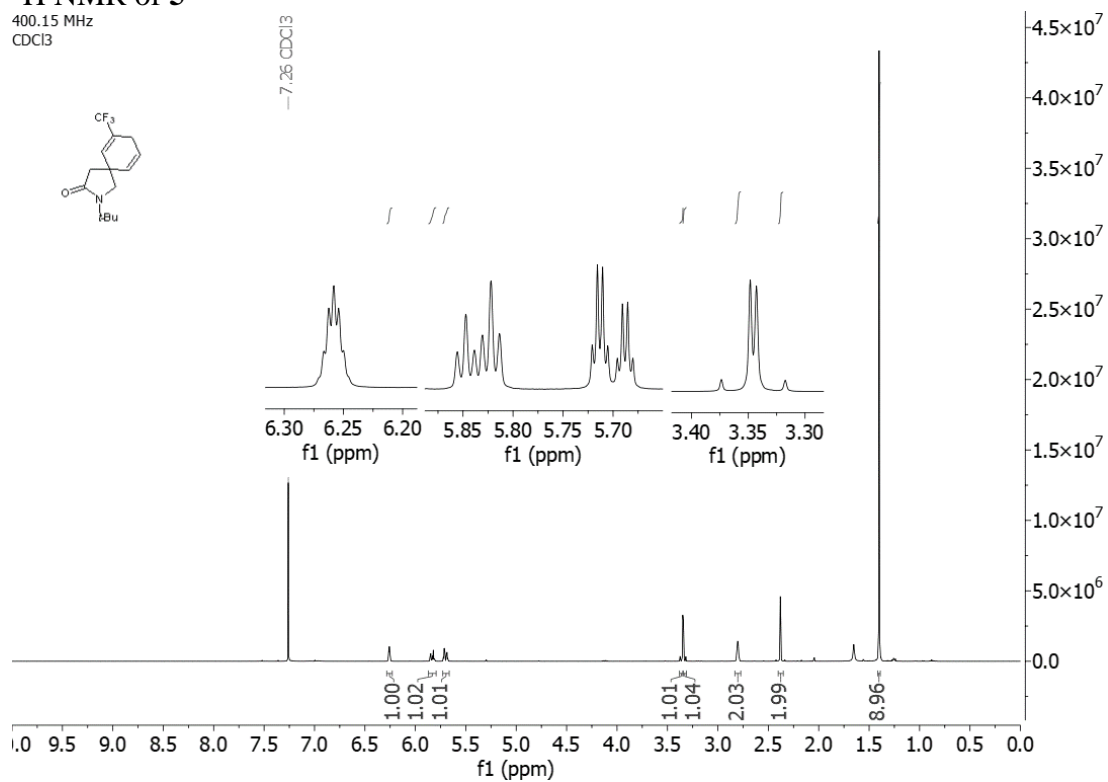
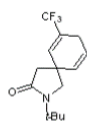
150.93 MHz  
CDCl<sub>3</sub> 13C





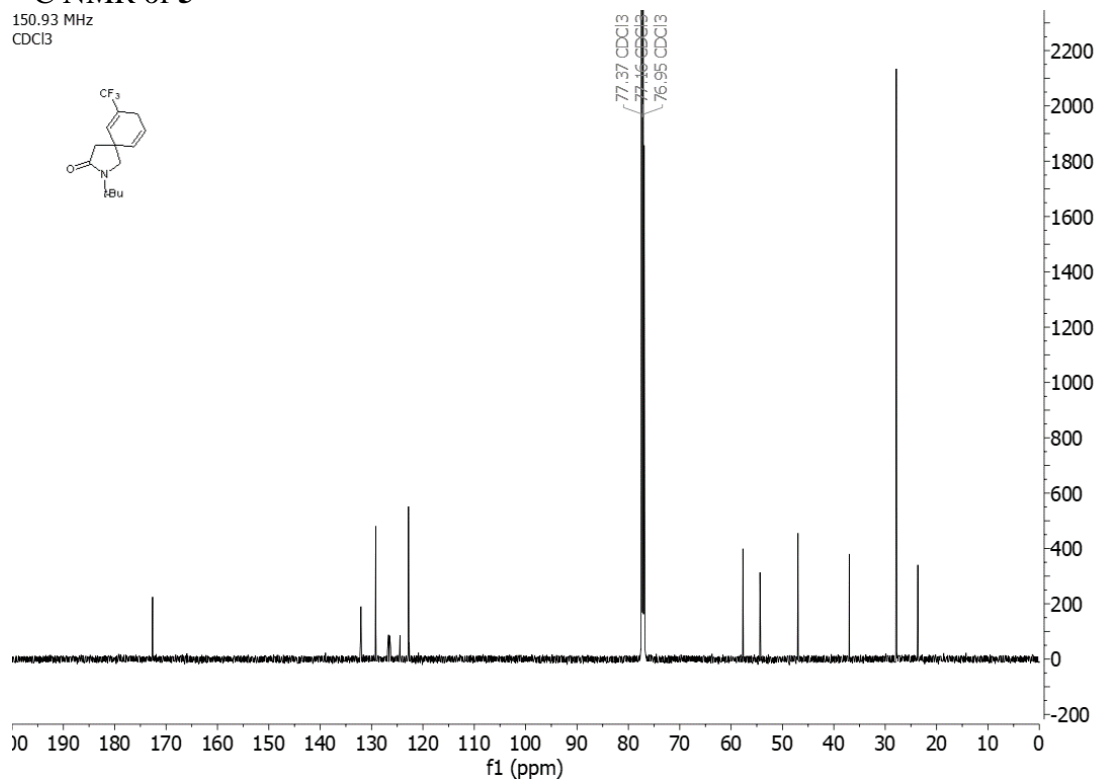
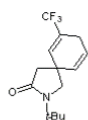
# <sup>1</sup>H NMR of **5**

400.15 MHz  
CDCl<sub>3</sub>



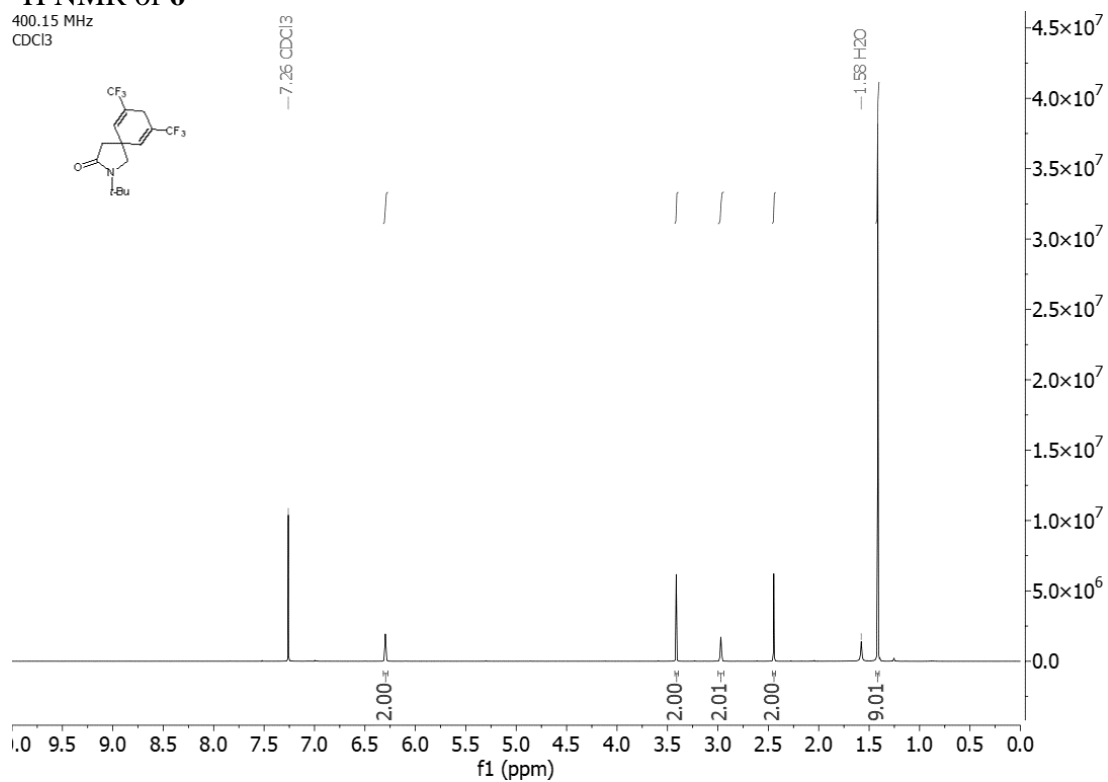
# <sup>13</sup>C NMR of **5**

150.93 MHz  
CDCl<sub>3</sub>



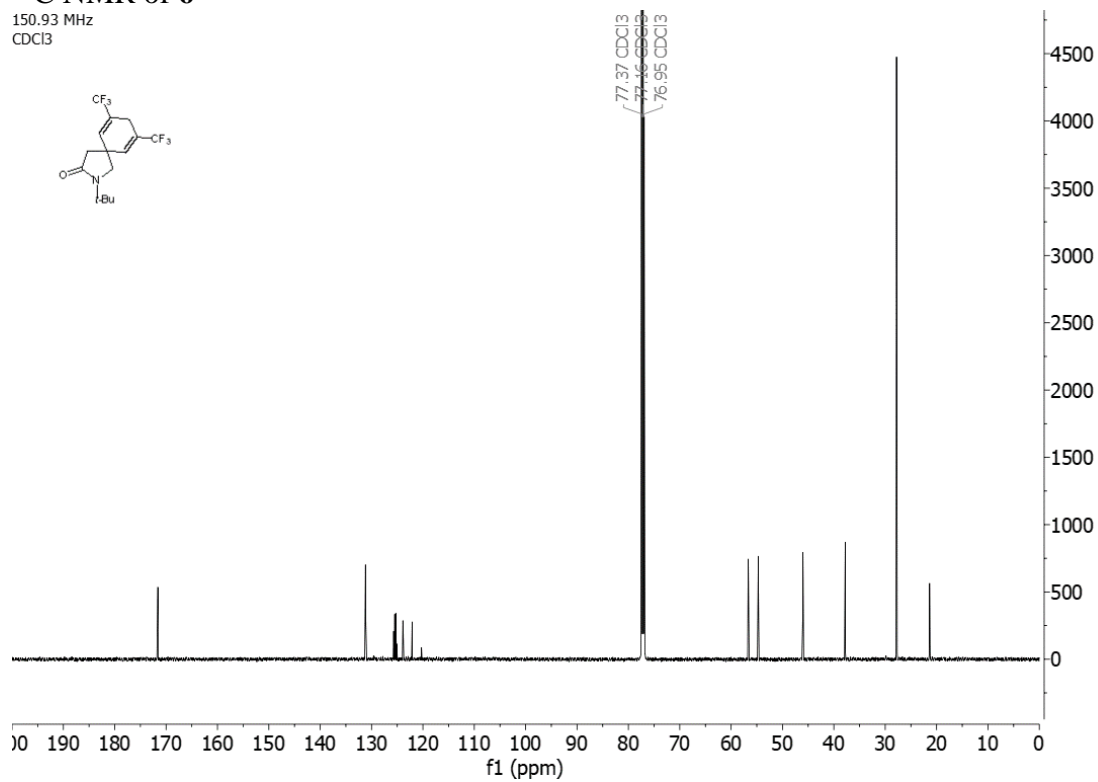
# <sup>1</sup>H NMR of **6**

400.15 MHz  
CDCl<sub>3</sub>



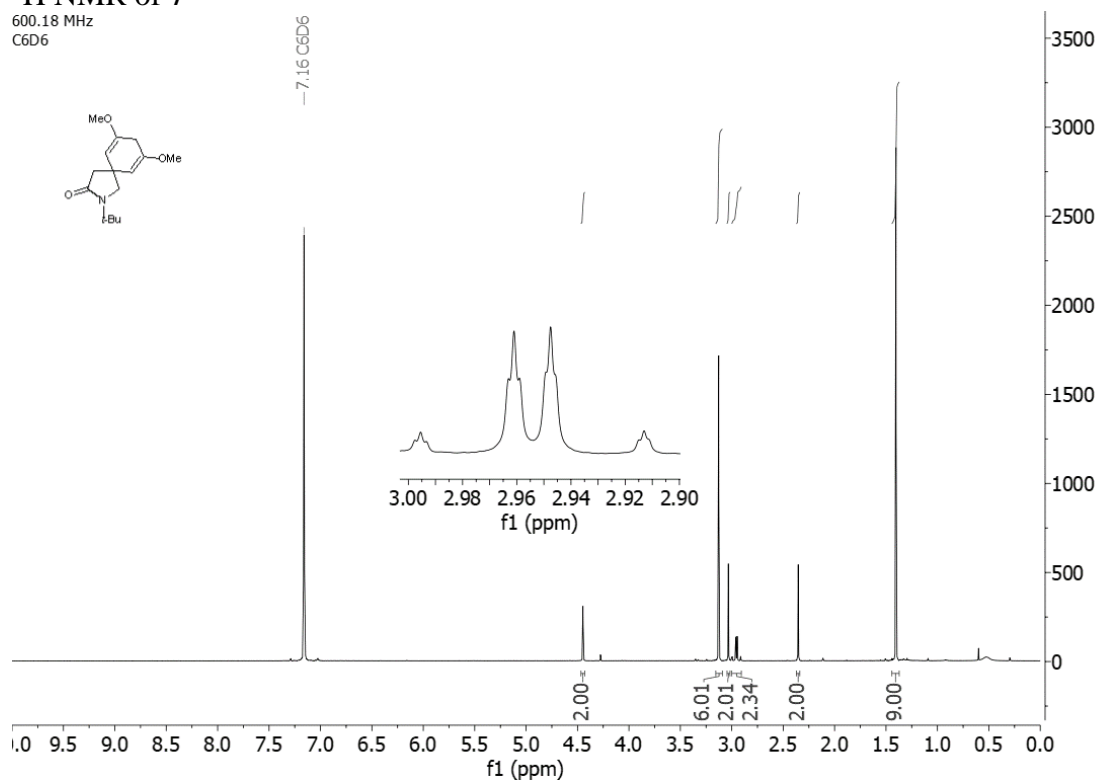
# <sup>13</sup>C NMR of **6**

150.93 MHz  
CDCl<sub>3</sub>



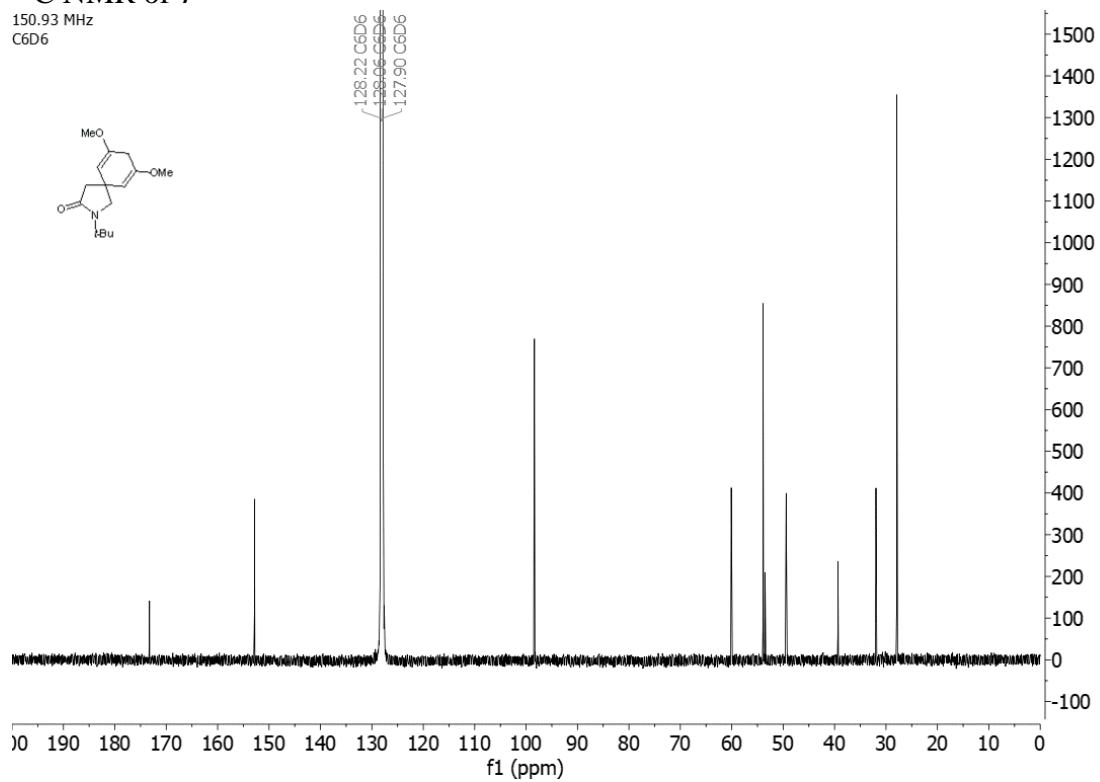
# <sup>1</sup>H NMR of **7**

600.18 MHz  
C6D6



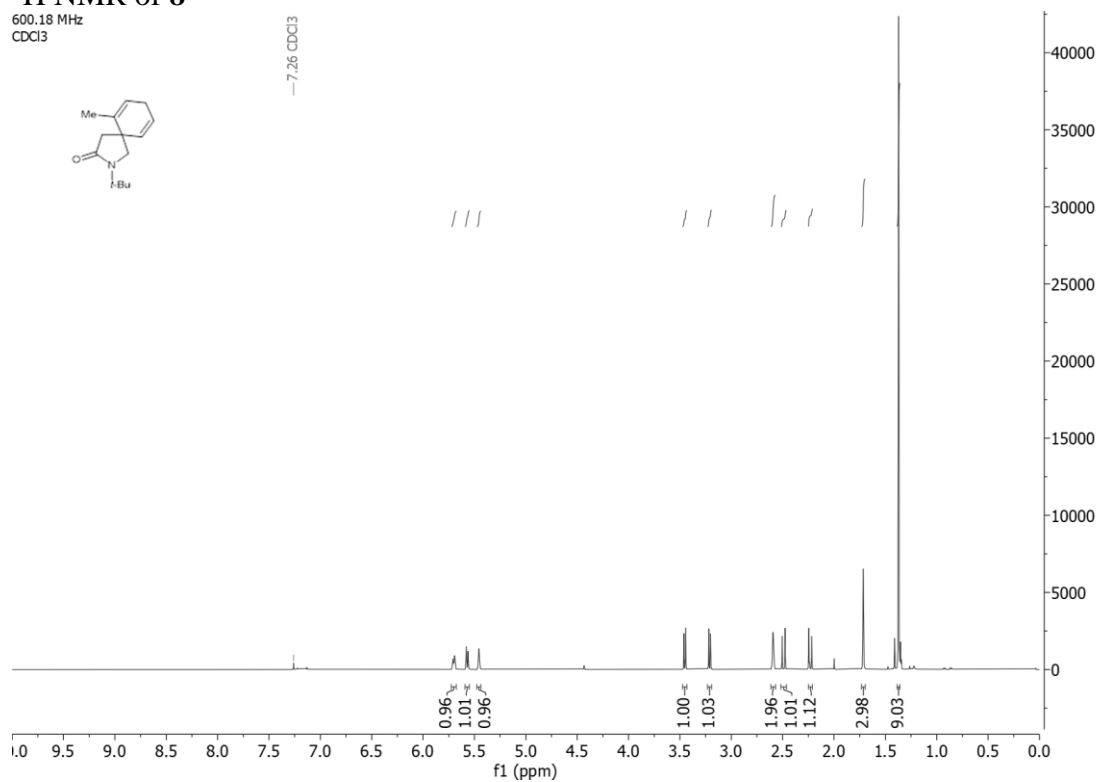
# <sup>13</sup>C NMR of **7**

150.93 MHz  
C6D6



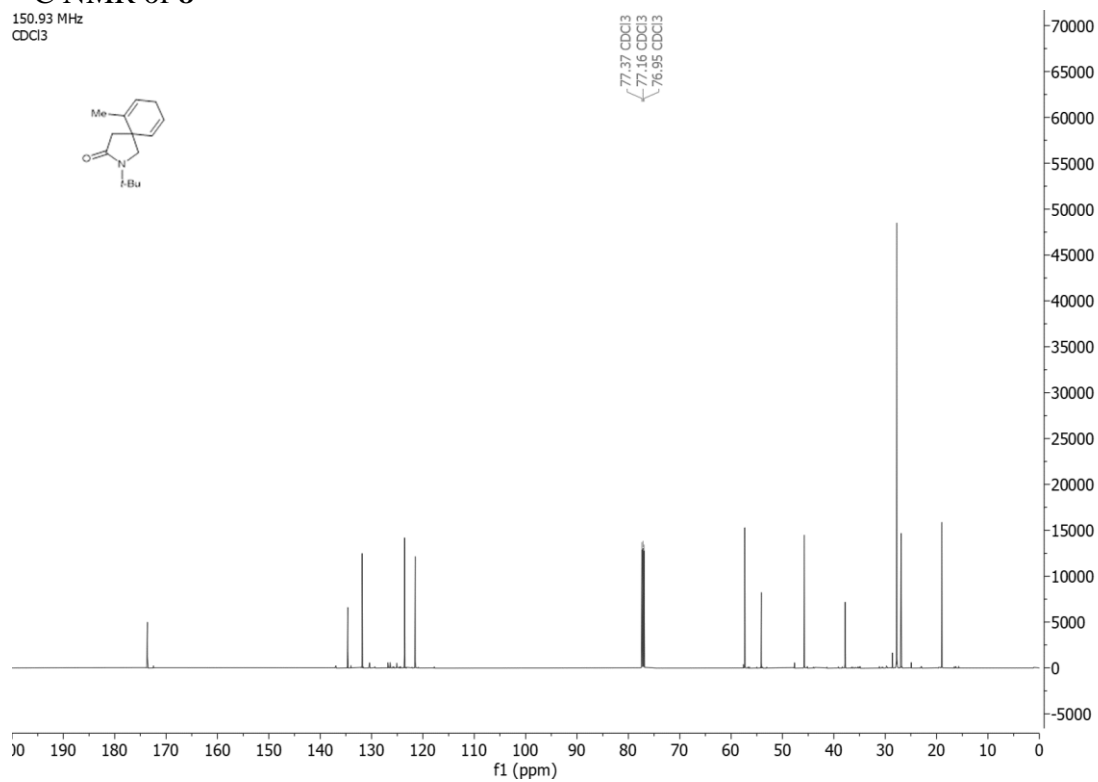
# <sup>1</sup>H NMR of **8**

600.18 MHz  
CDCl<sub>3</sub>



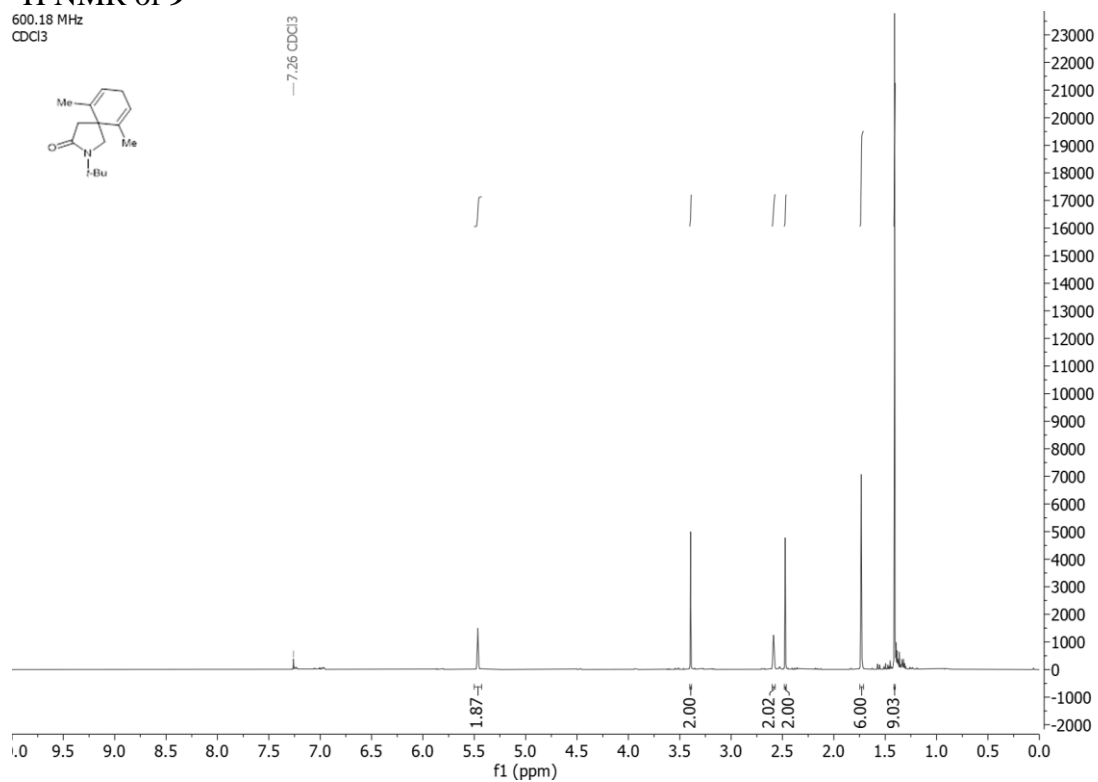
# <sup>13</sup>C NMR of **8**

150.93 MHz  
CDCl<sub>3</sub>



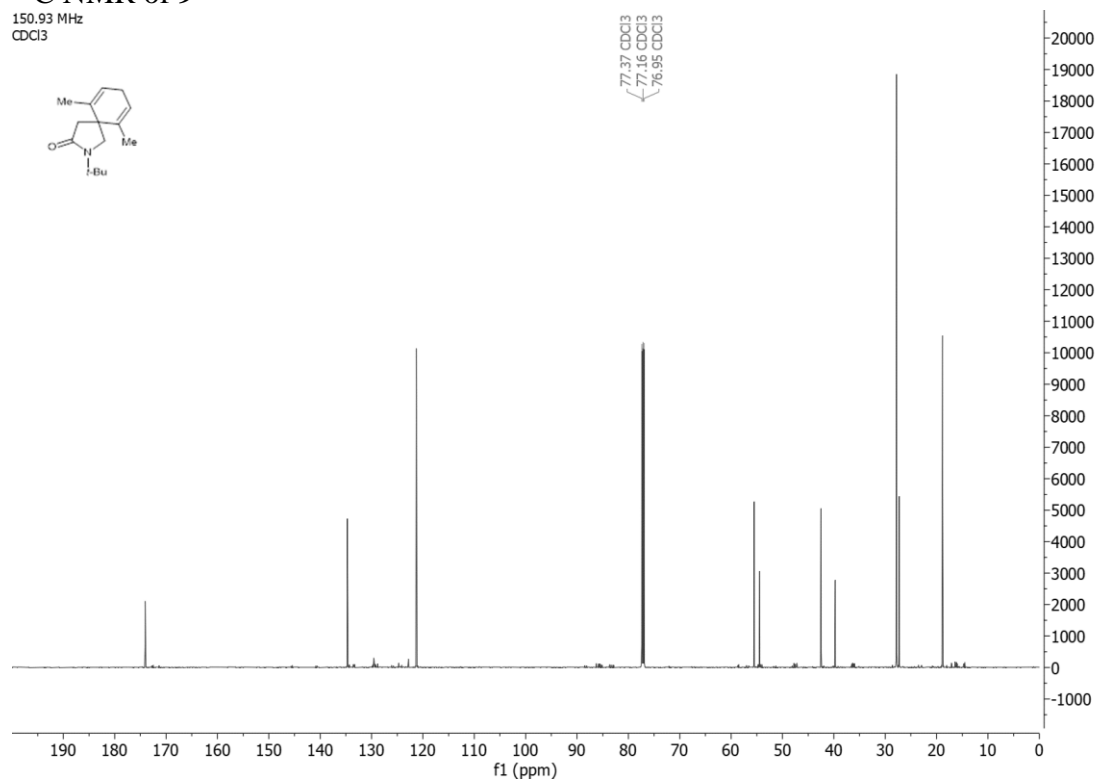
# <sup>1</sup>H NMR of **9**

600.18 MHz  
CDCl<sub>3</sub>



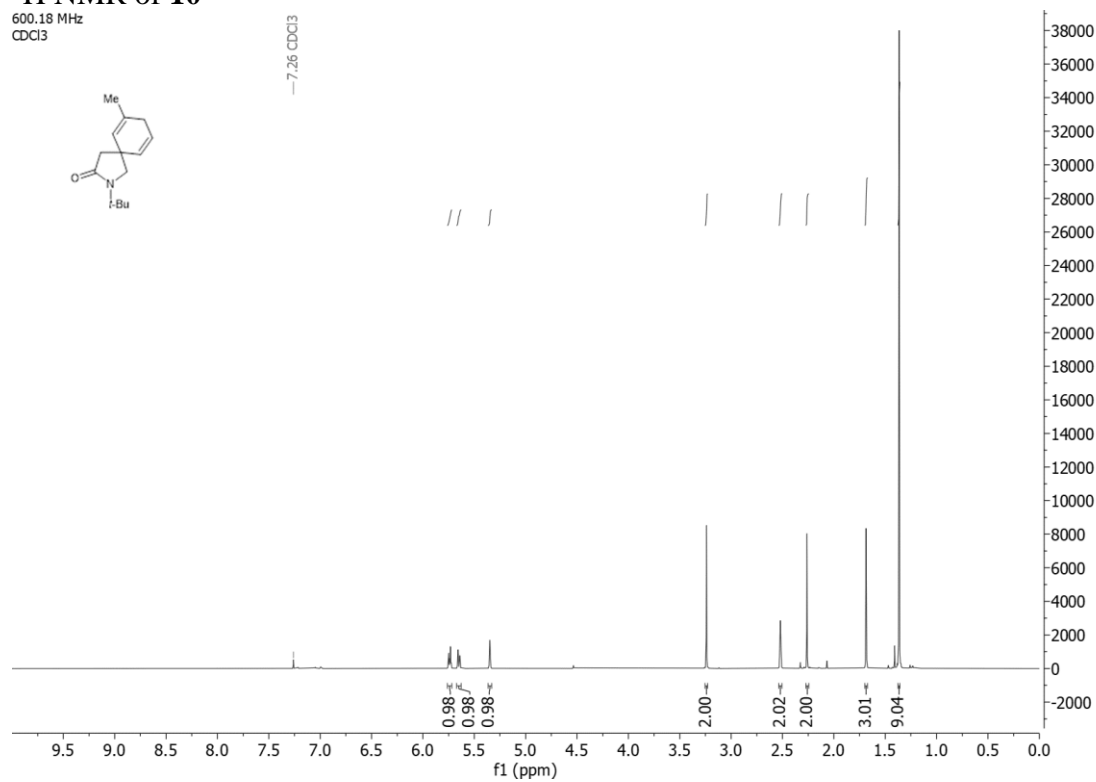
# <sup>13</sup>C NMR of **9**

150.93 MHz  
CDCl<sub>3</sub>



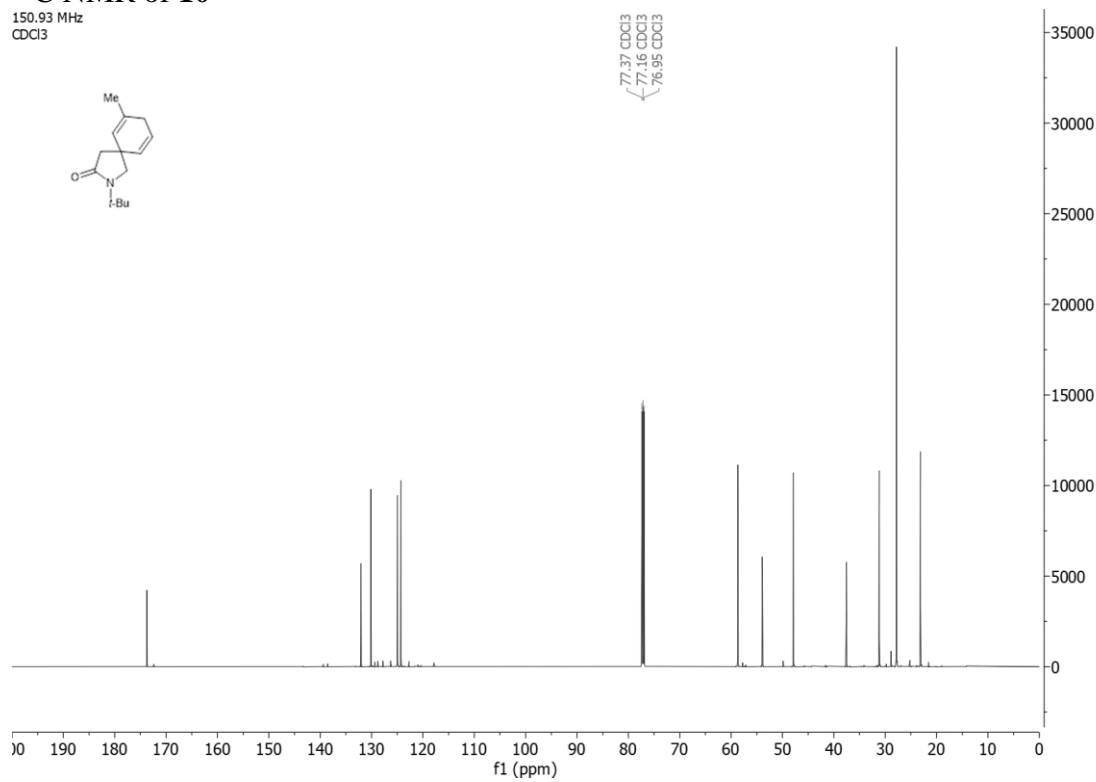
# <sup>1</sup>H NMR of **10**

600.18 MHz  
CDCl<sub>3</sub>



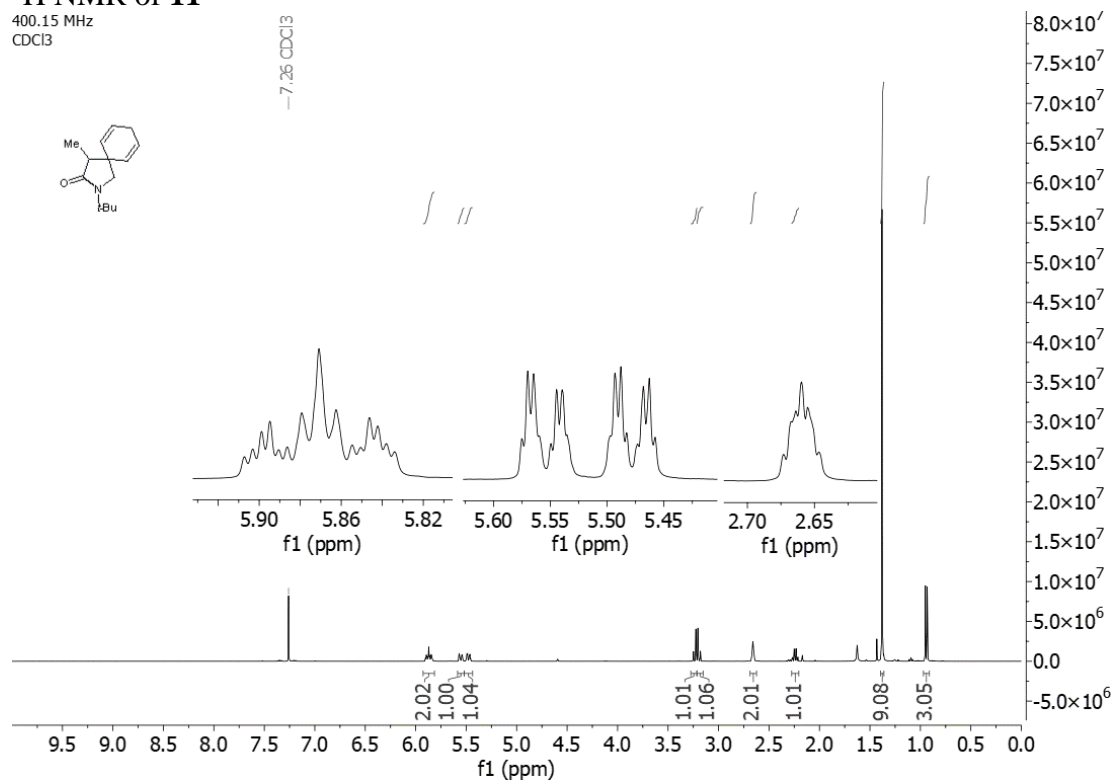
# <sup>13</sup>C NMR of **10**

150.93 MHz  
CDCl<sub>3</sub>



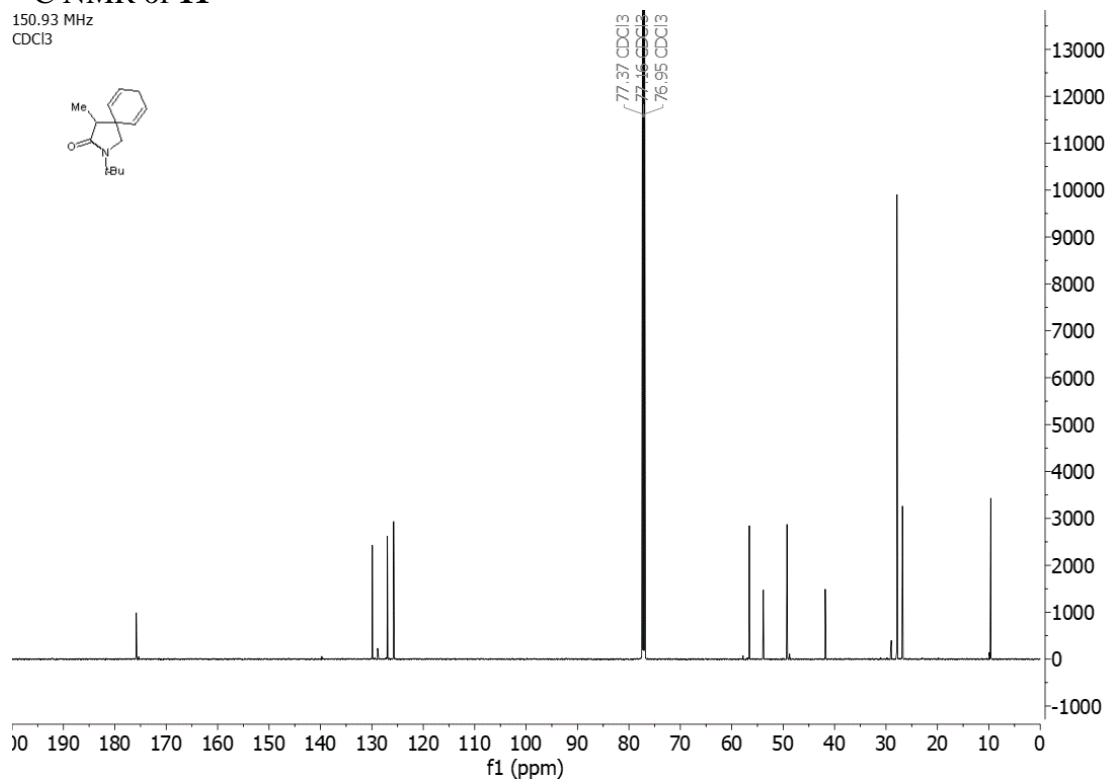
# <sup>1</sup>H NMR of **11**

400.15 MHz  
CDCl<sub>3</sub>



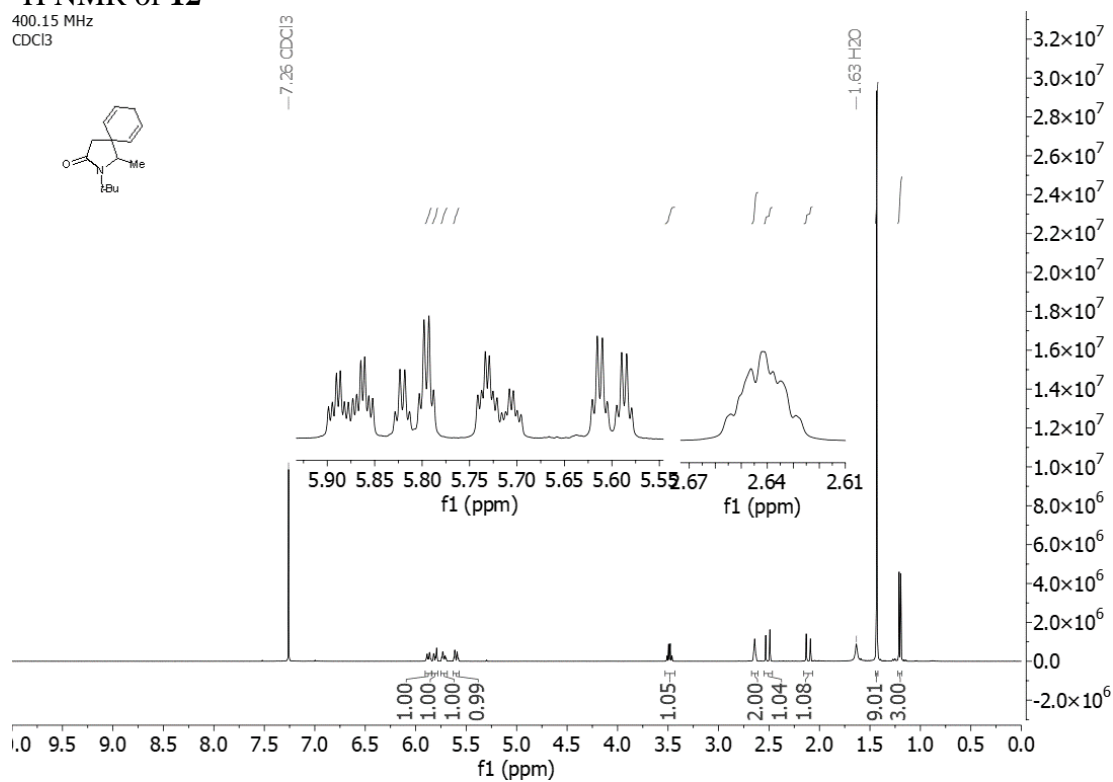
# <sup>13</sup>C NMR of **11**

150.93 MHz  
CDCl<sub>3</sub>



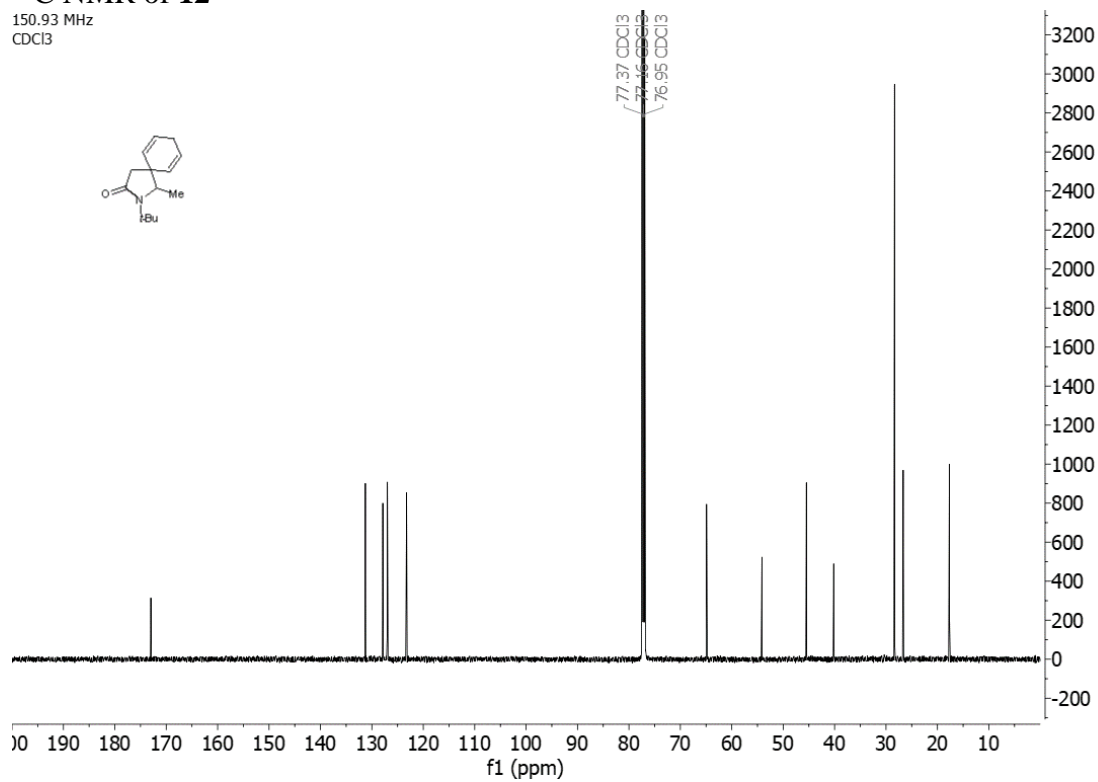
# <sup>1</sup>H NMR of **12**

400.15 MHz  
CDCl<sub>3</sub>



# <sup>13</sup>C NMR of **12**

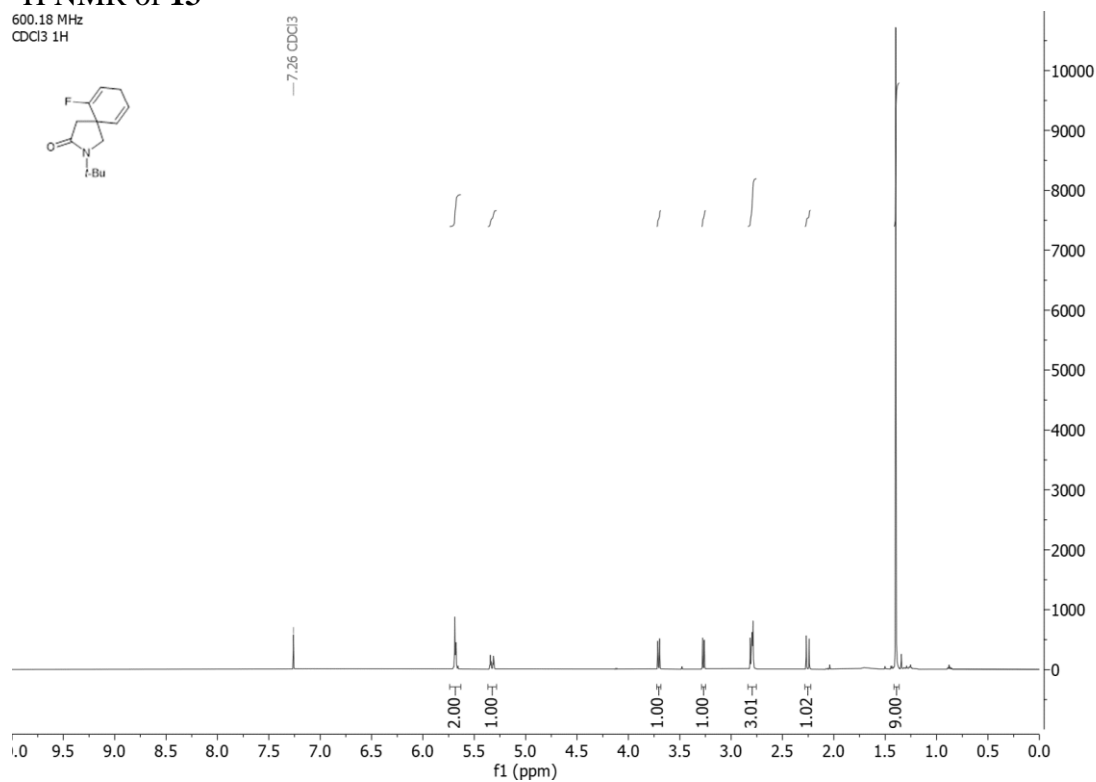
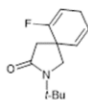
150.93 MHz  
CDCl<sub>3</sub>





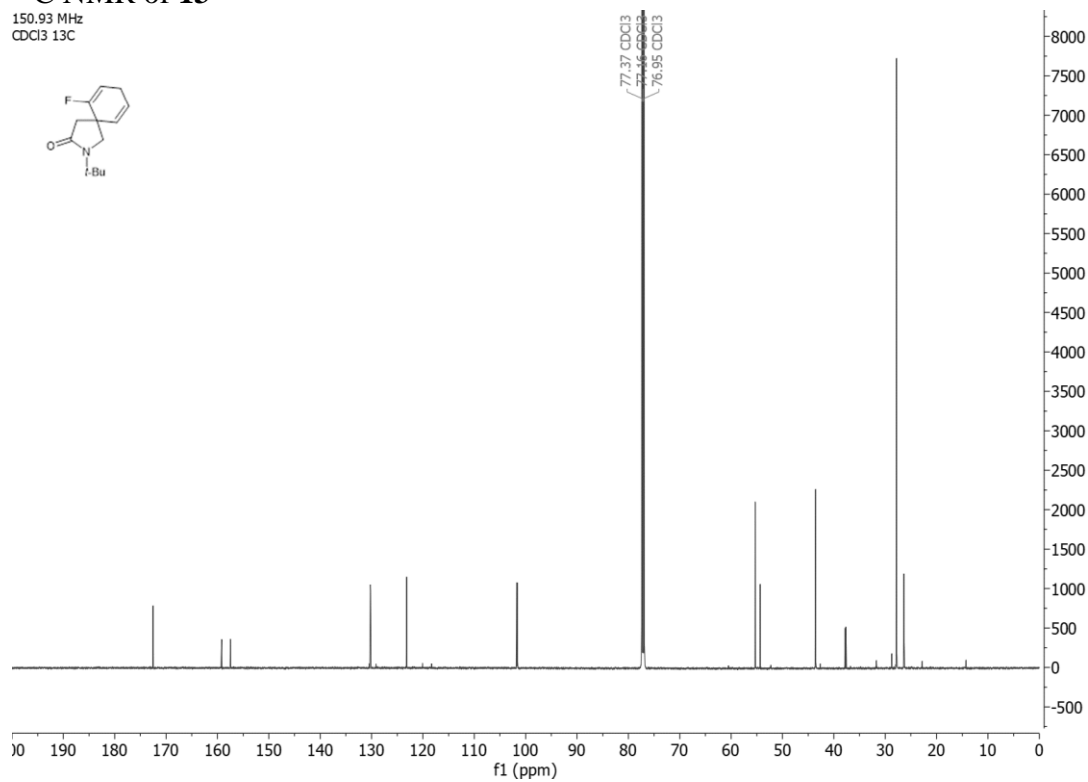
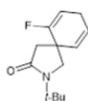
# <sup>1</sup>H NMR of **13**

600.18 MHz  
CDCl<sub>3</sub> 1H



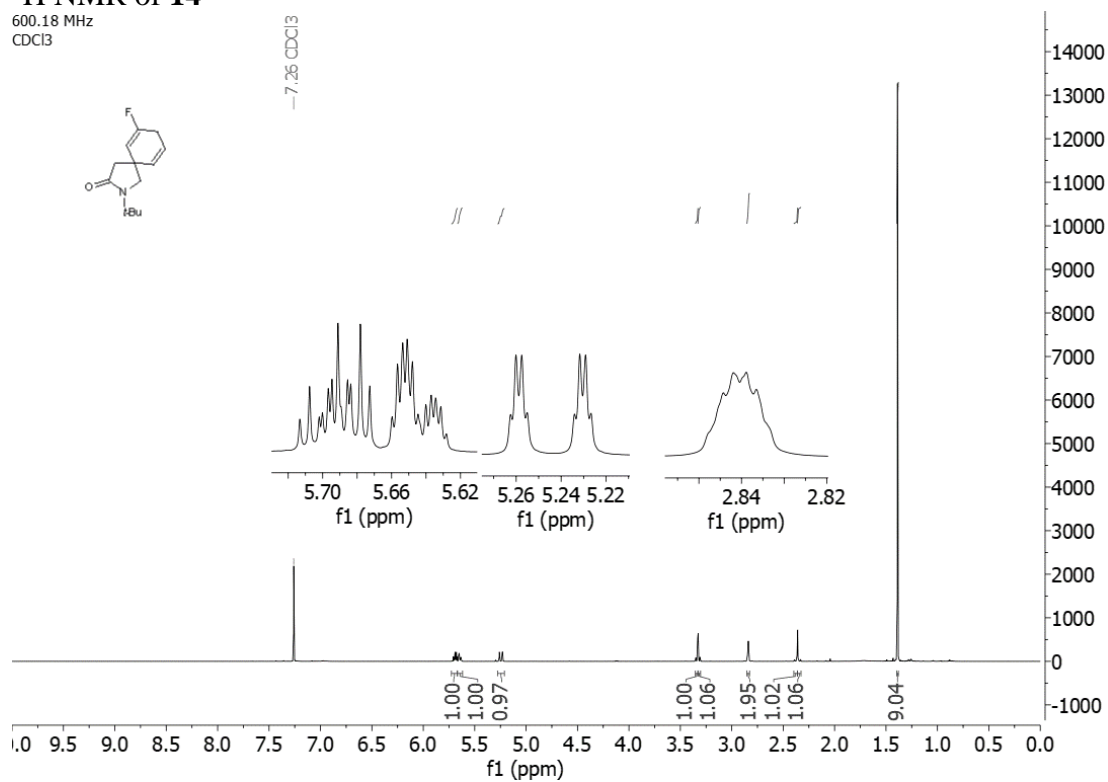
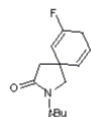
# <sup>13</sup>C NMR of **13**

150.93 MHz  
CDCl<sub>3</sub> 13C



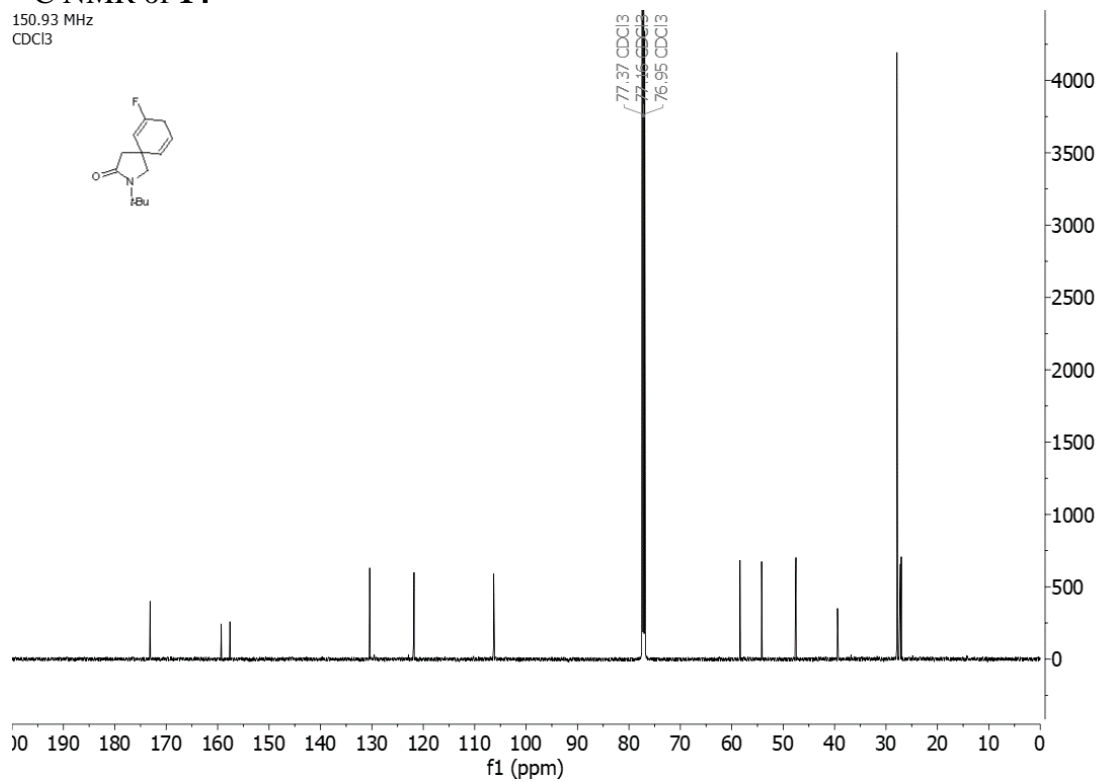
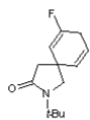
# <sup>1</sup>H NMR of **14**

600.18 MHz  
CDCl<sub>3</sub>



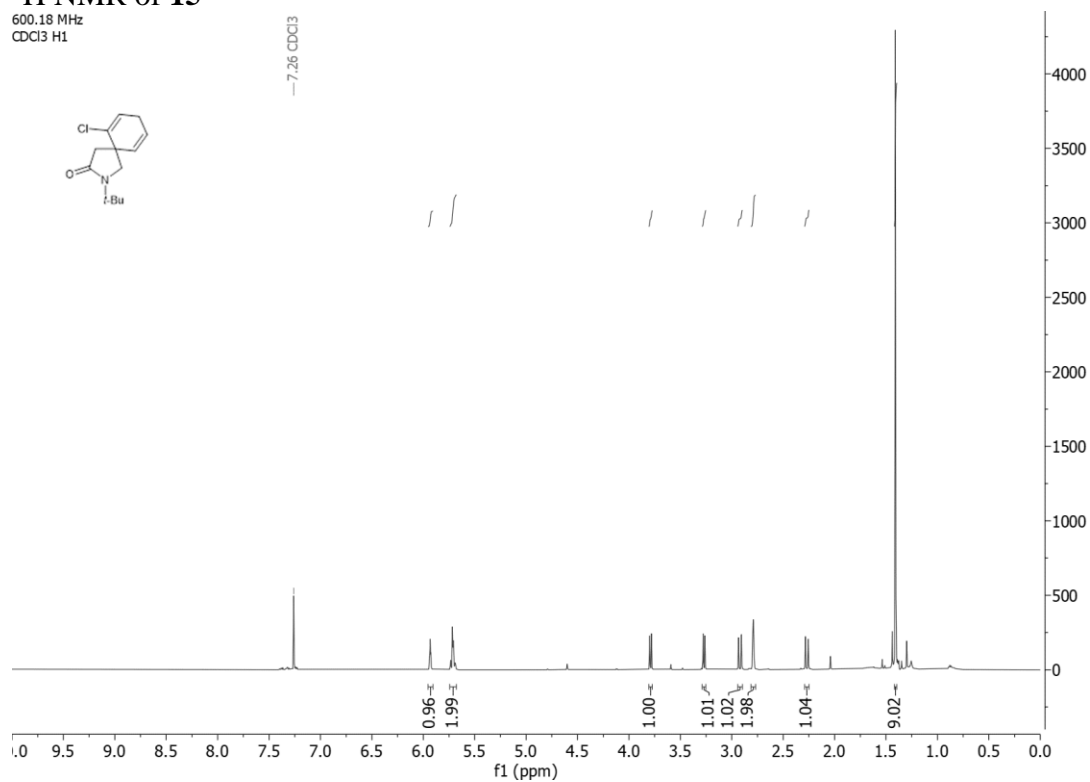
# <sup>13</sup>C NMR of **14**

150.93 MHz  
CDCl<sub>3</sub>



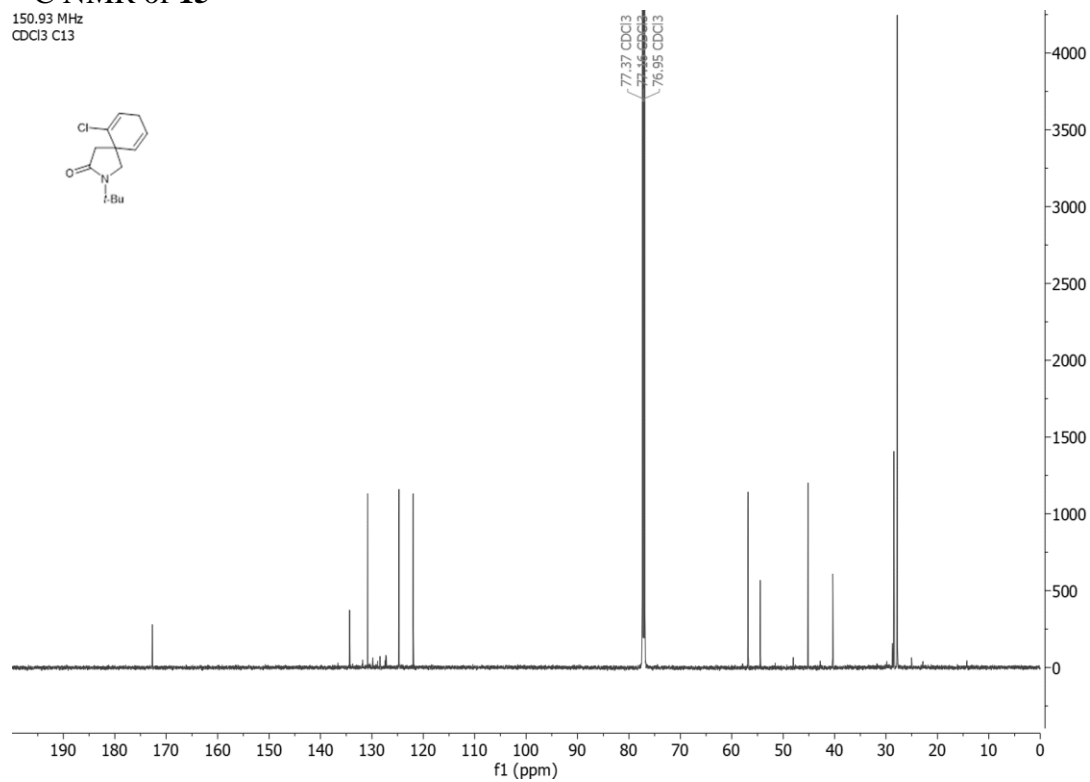
# <sup>1</sup>H NMR of **15**

600.18 MHz  
CDCl<sub>3</sub> H1



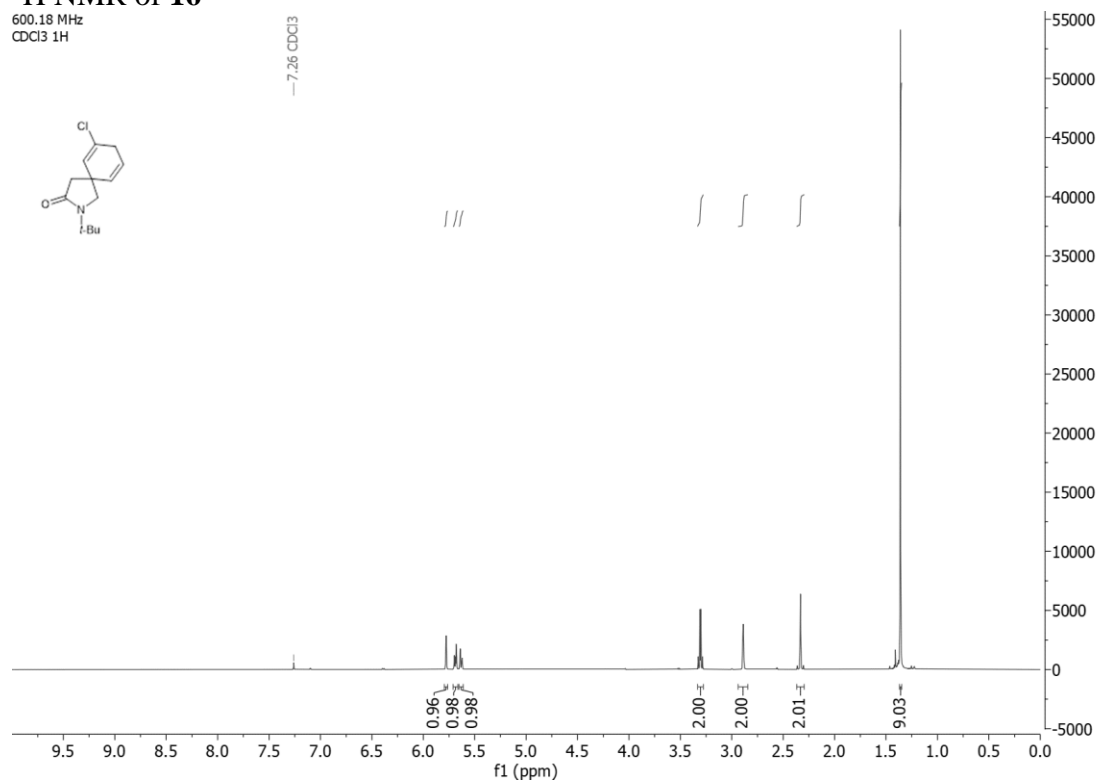
# <sup>13</sup>C NMR of **15**

150.93 MHz  
CDCl<sub>3</sub> C13



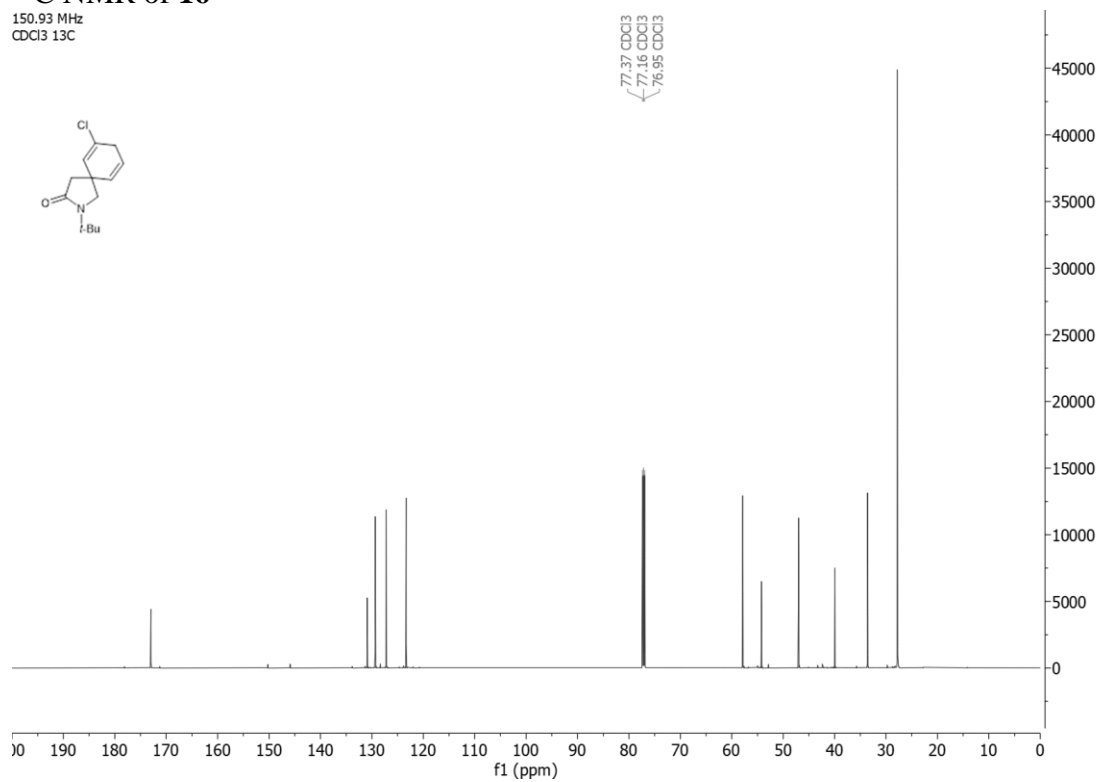
# <sup>1</sup>H NMR of **16**

600.18 MHz  
CDCl<sub>3</sub> 1H



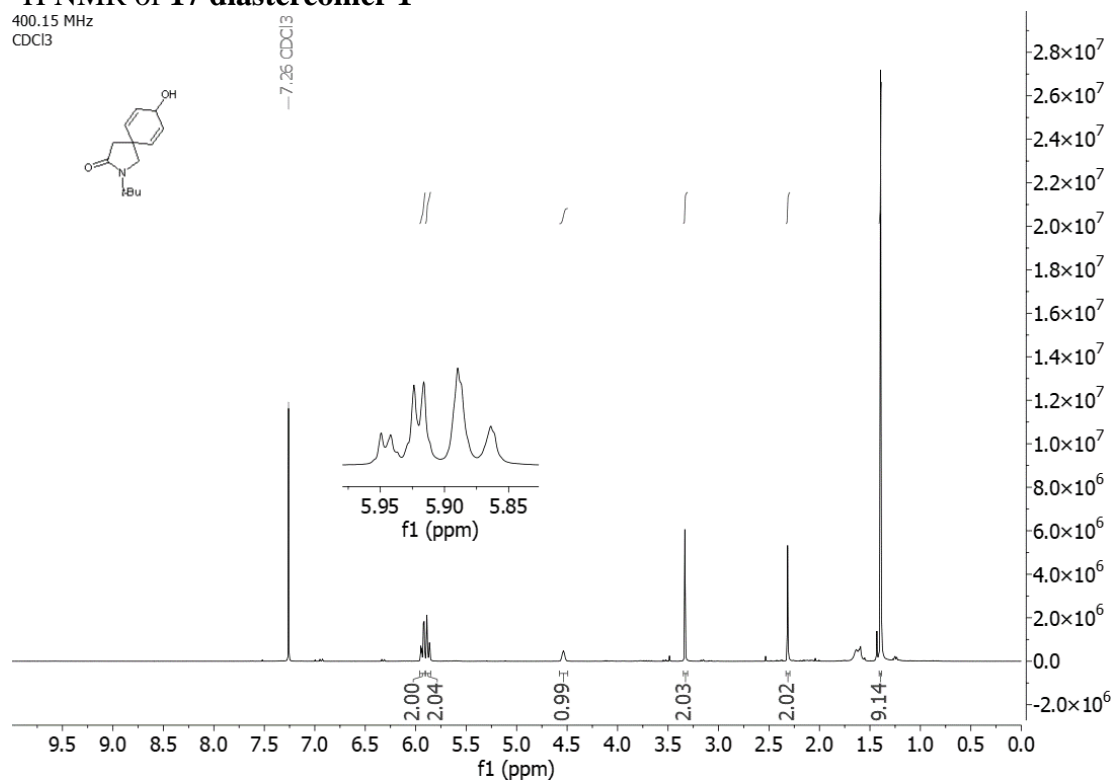
# <sup>13</sup>C NMR of **16**

150.93 MHz  
CDCl<sub>3</sub> 13C



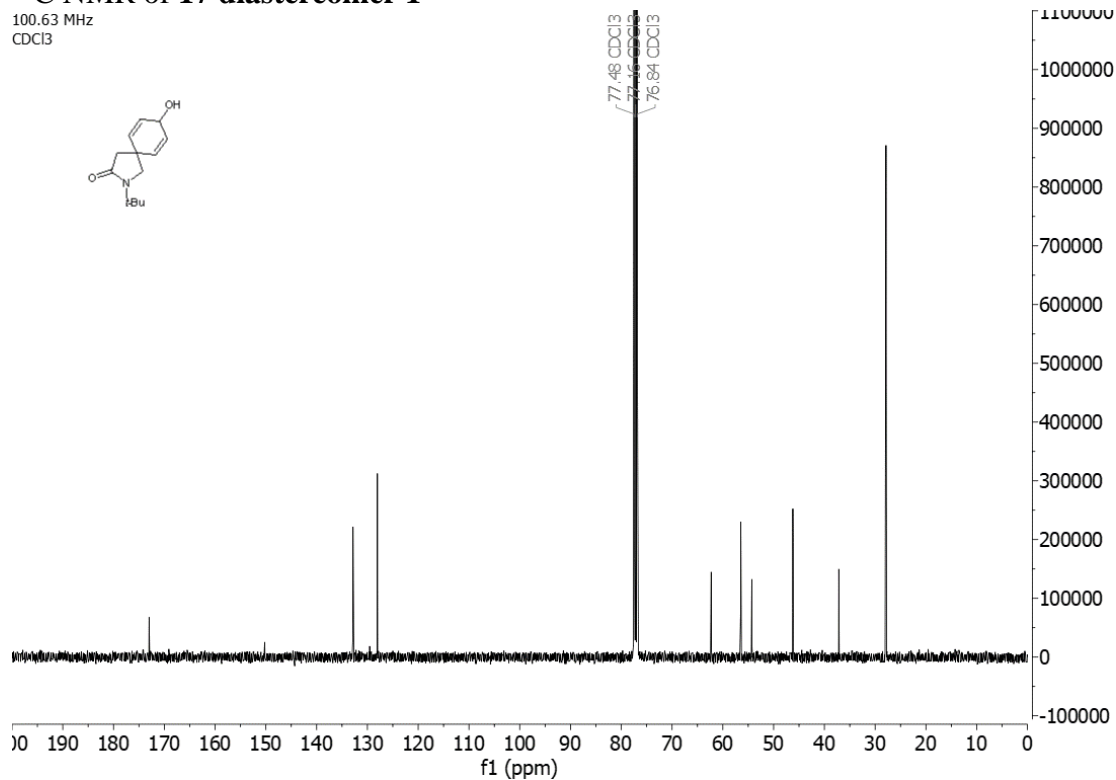
# <sup>1</sup>H NMR of **17** diastereomer **1**

400.15 MHz  
CDCl<sub>3</sub>



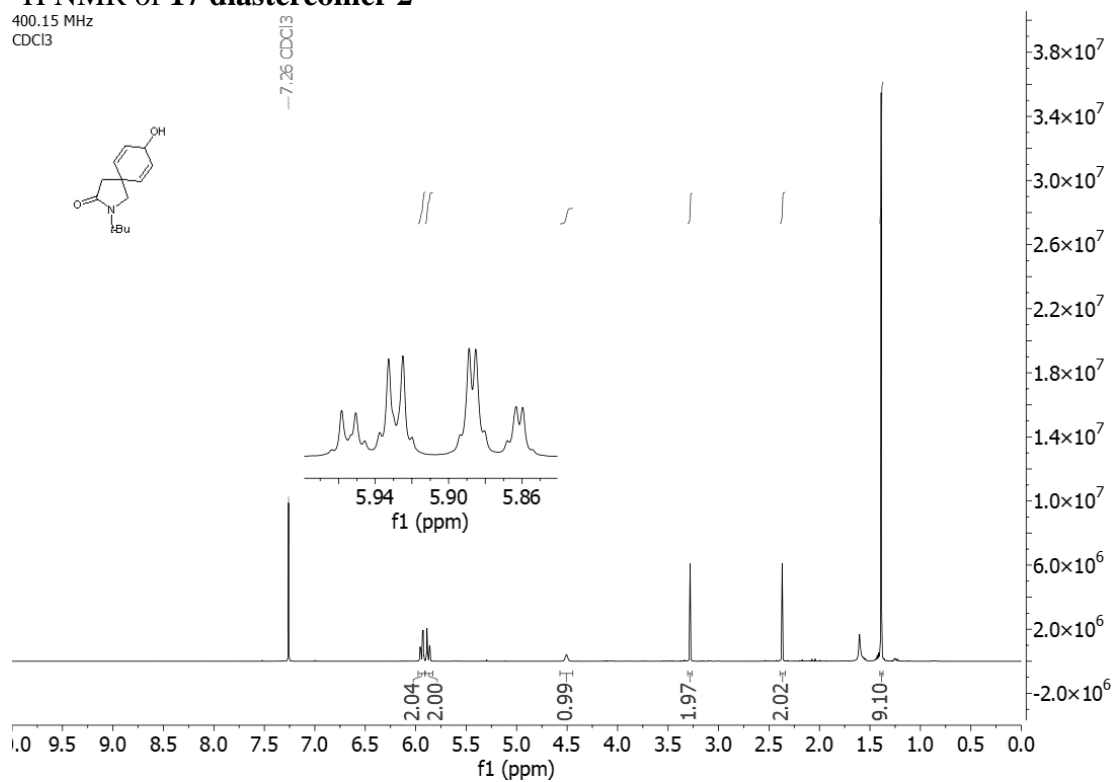
# <sup>13</sup>C NMR of **17** diastereomer **1**

100.63 MHz  
CDCl<sub>3</sub>



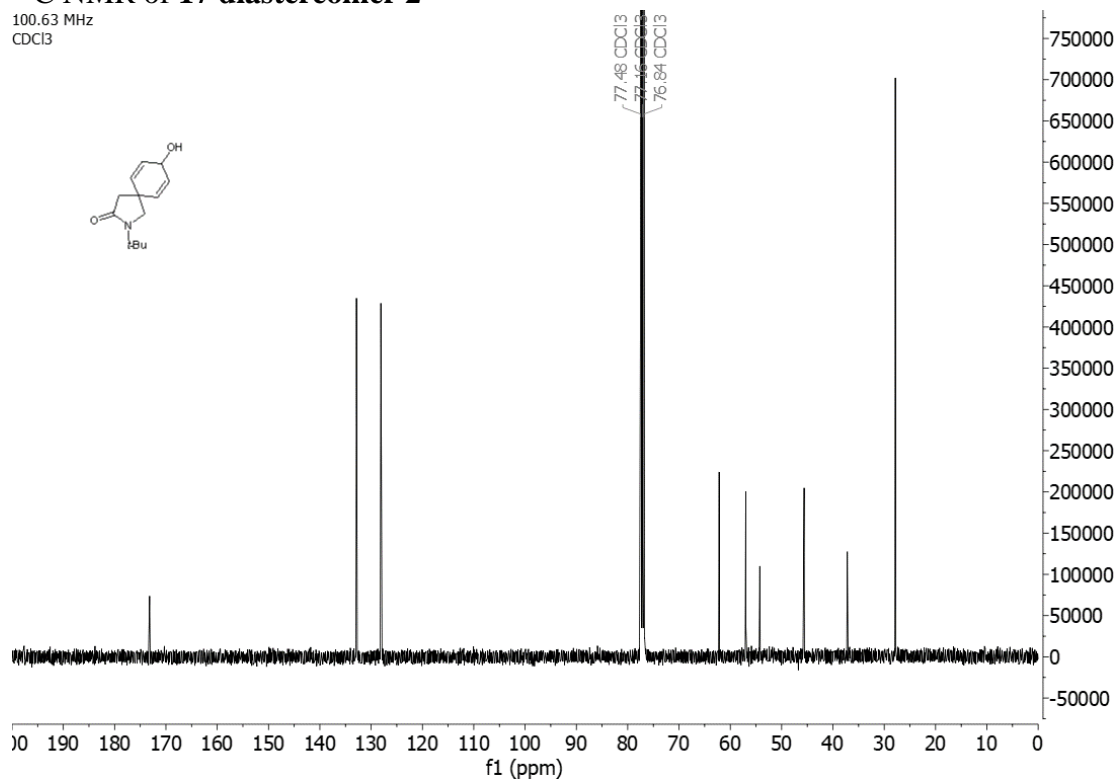
# <sup>1</sup>H NMR of **17** diastereomer **2**

400.15 MHz  
CDCl<sub>3</sub>



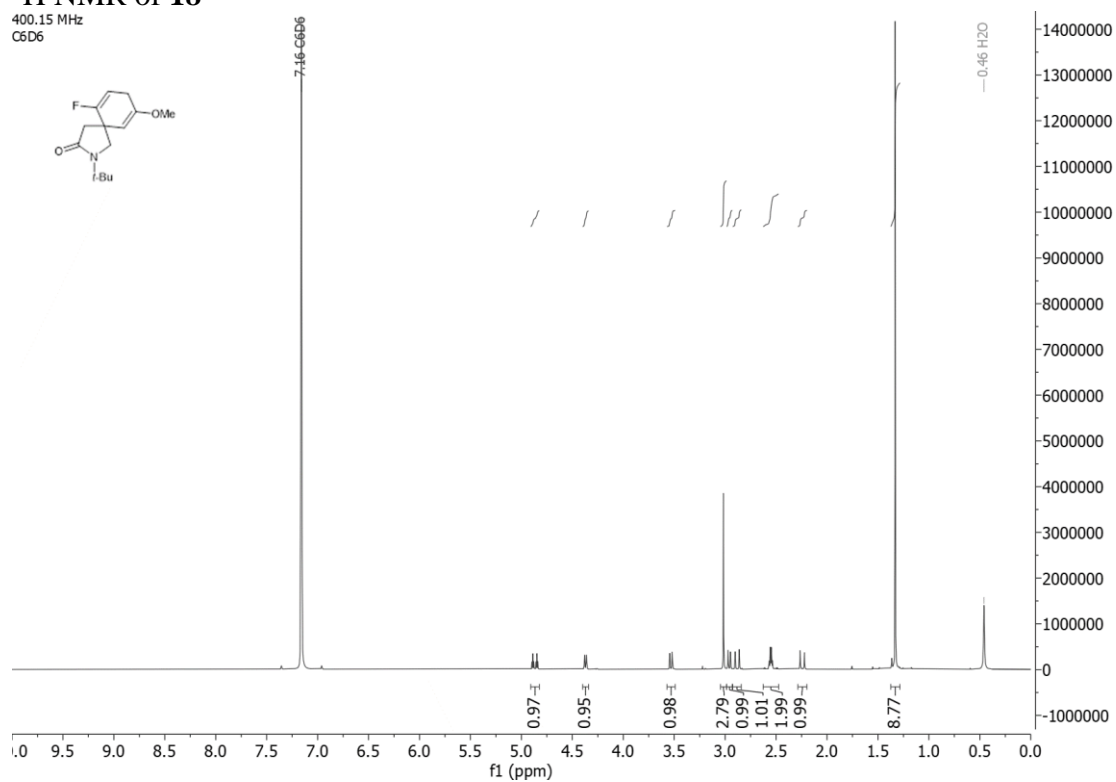
# <sup>13</sup>C NMR of **17** diastereomer **2**

100.63 MHz  
CDCl<sub>3</sub>



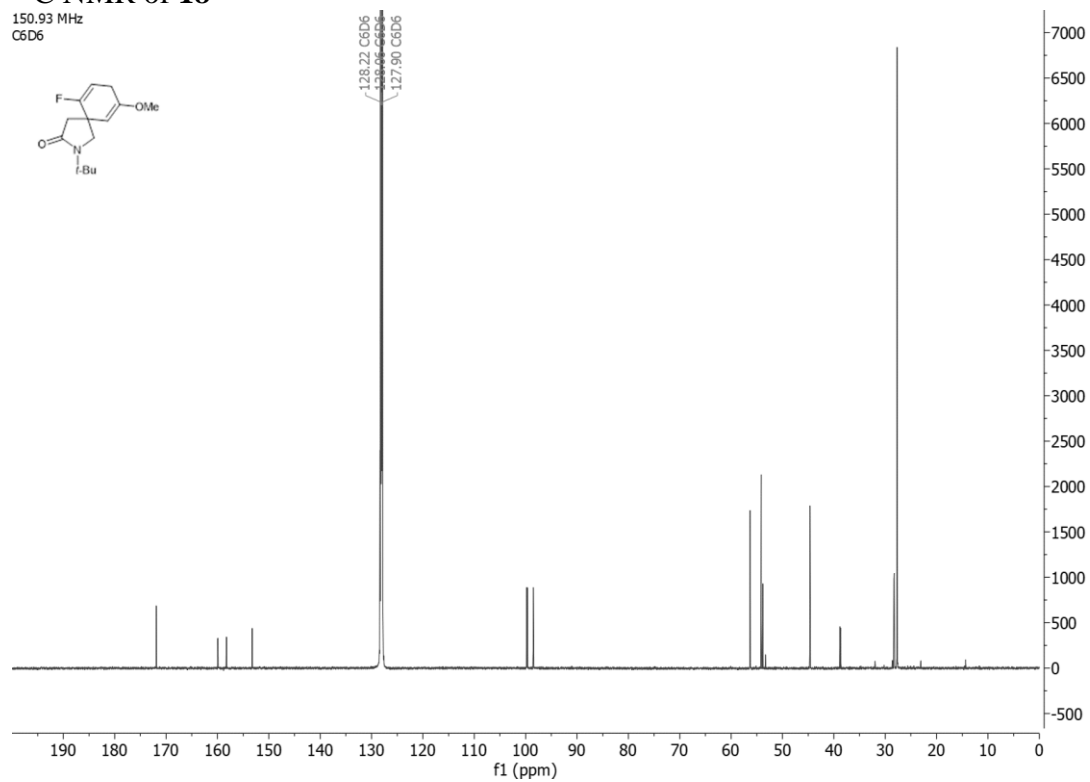
# <sup>1</sup>H NMR of **18**

400.15 MHz  
C6D6



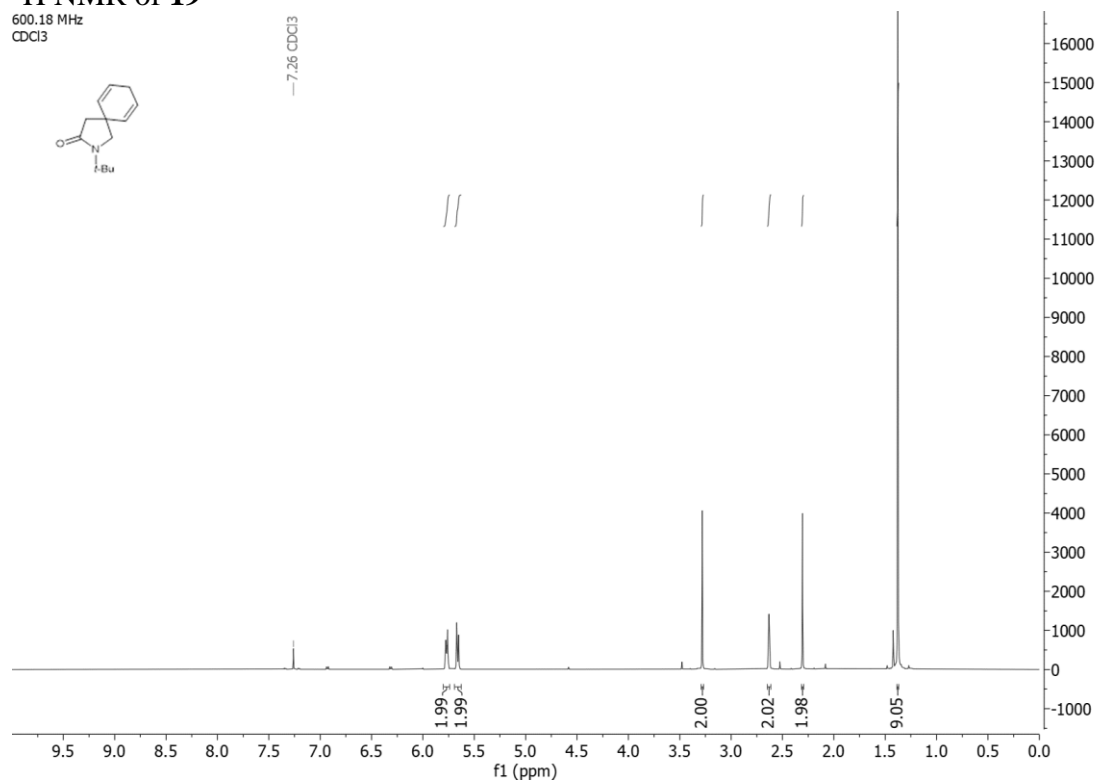
# <sup>13</sup>C NMR of **18**

150.93 MHz  
C6D6



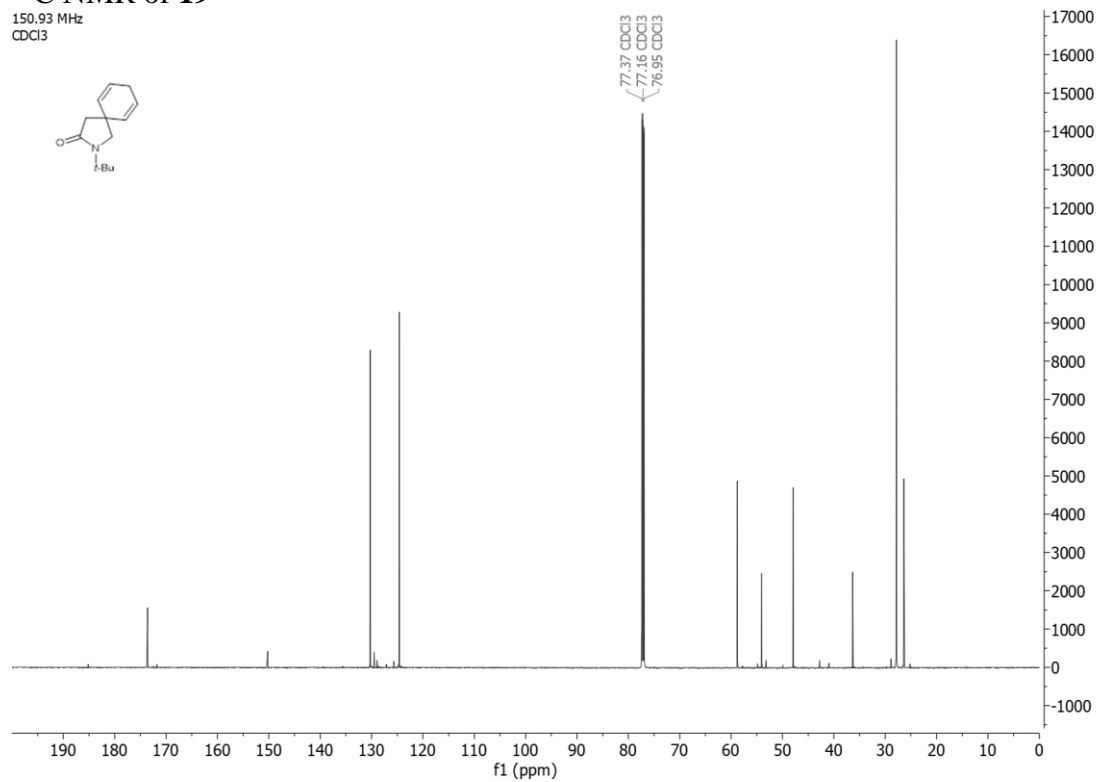
# <sup>1</sup>H NMR of **19**

600.18 MHz  
CDCl<sub>3</sub>



# <sup>13</sup>C NMR of **19**

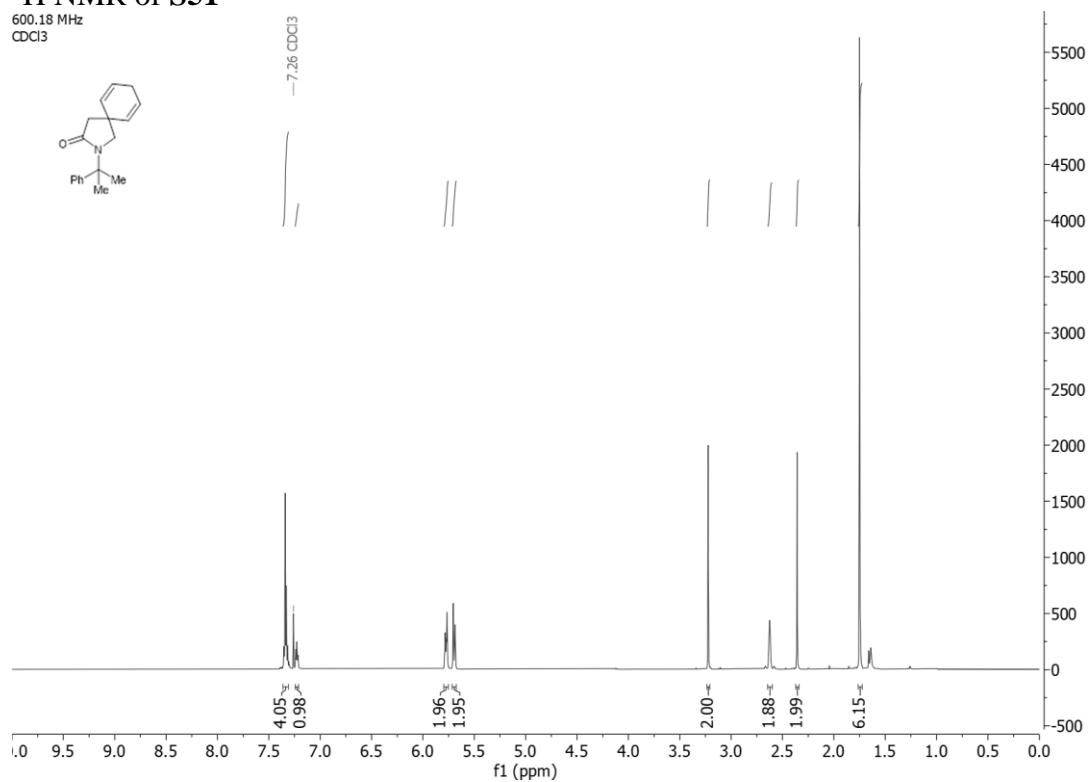
150.93 MHz  
CDCl<sub>3</sub>





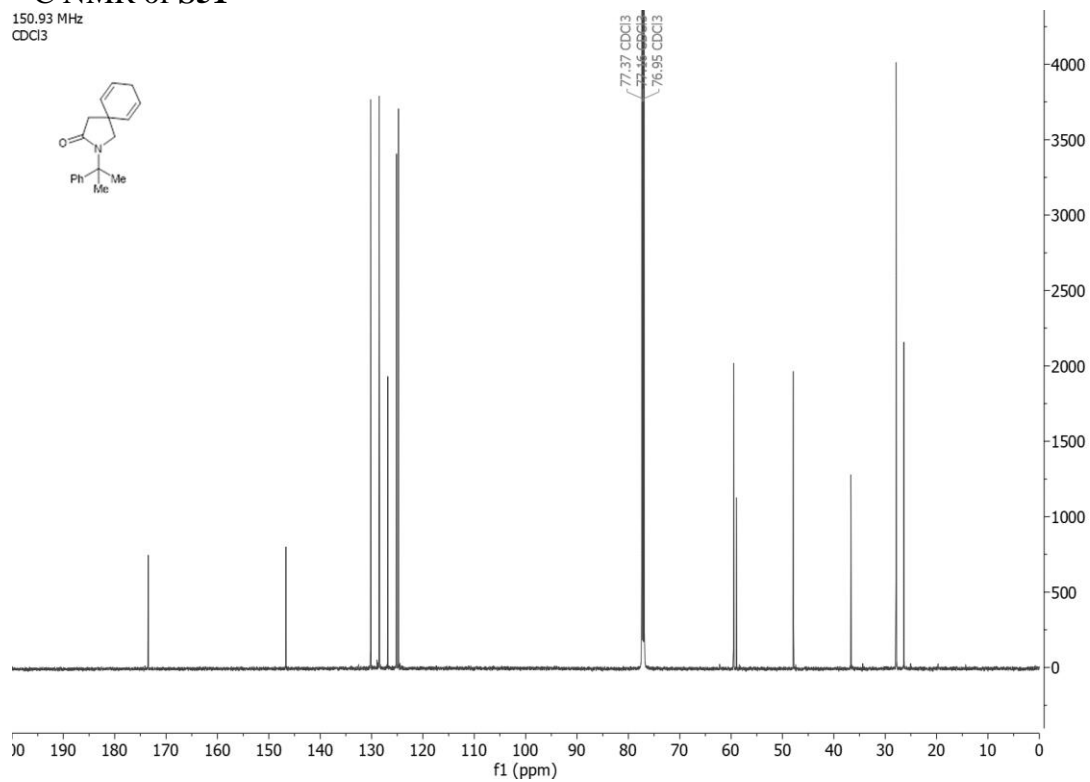
# <sup>1</sup>H NMR of S51

600.18 MHz  
CDCl<sub>3</sub>



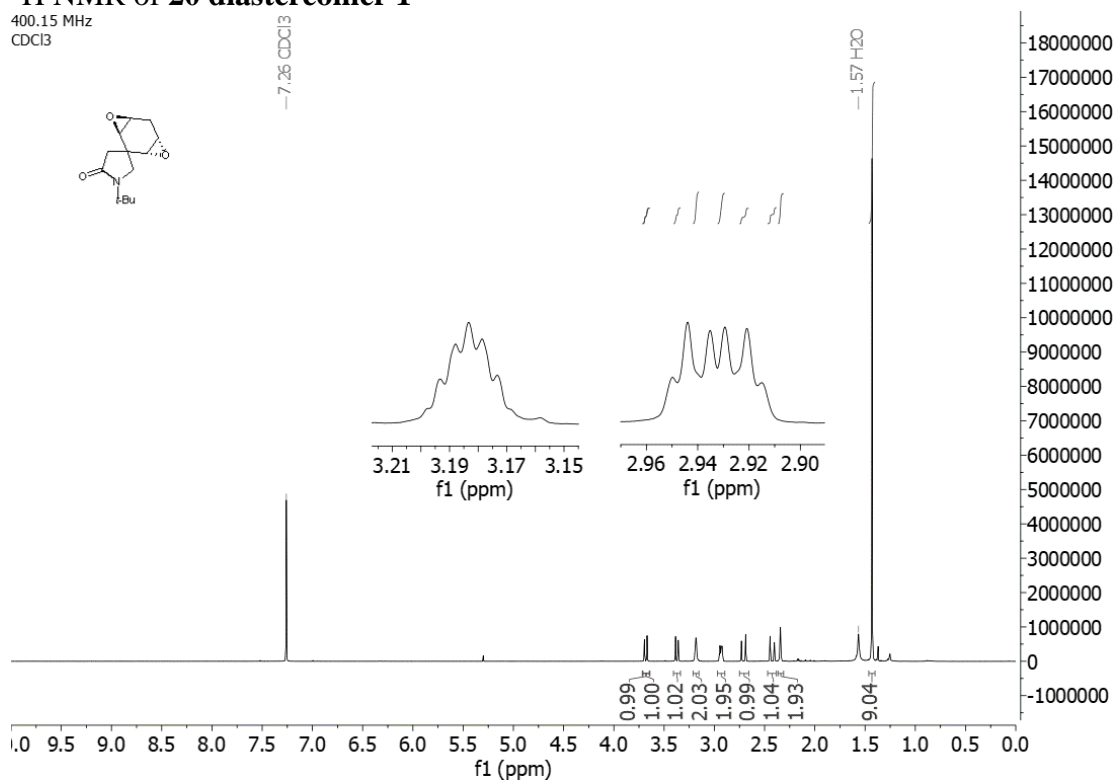
# <sup>13</sup>C NMR of S51

150.93 MHz  
CDCl<sub>3</sub>



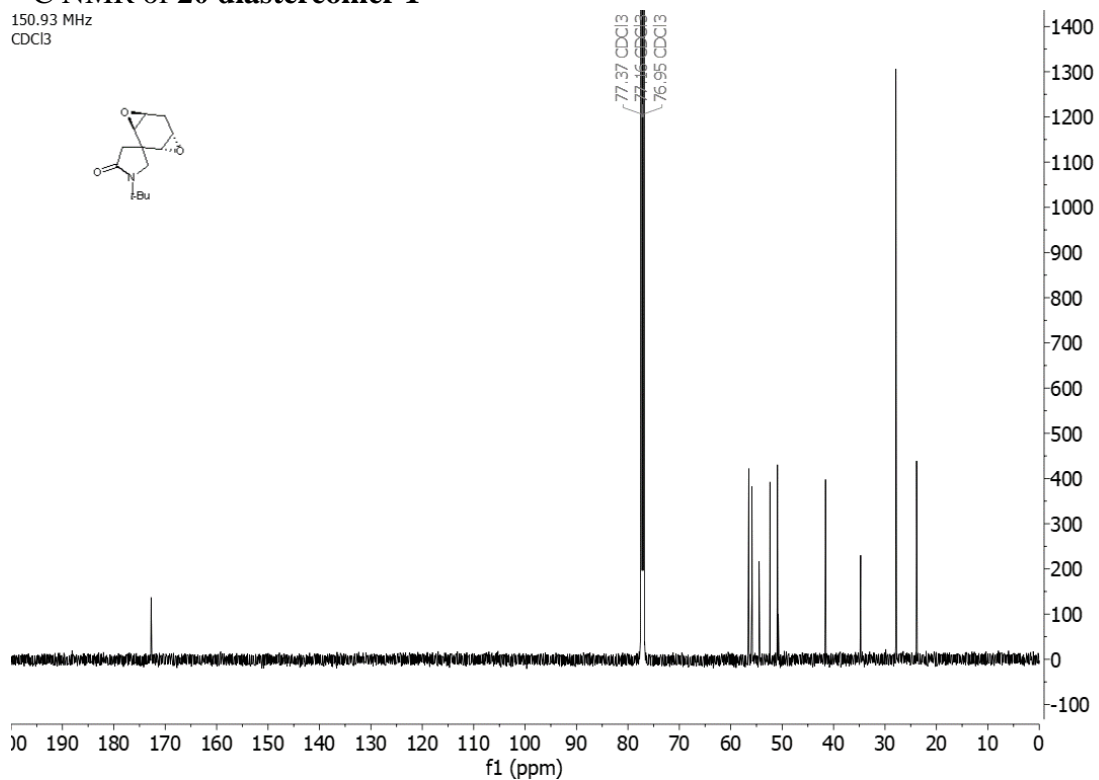
# <sup>1</sup>H NMR of **20** diastereomer **1**

400.15 MHz  
CDCl<sub>3</sub>



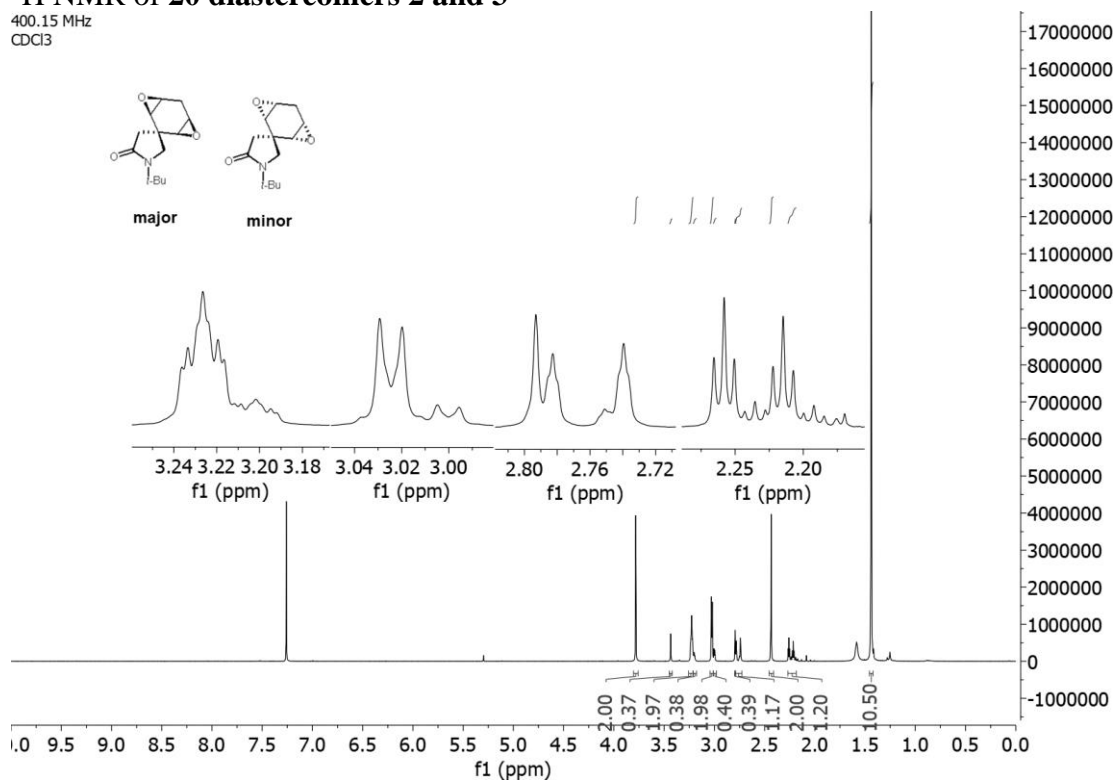
# <sup>13</sup>C NMR of **20** diastereomer **1**

150.93 MHz  
CDCl<sub>3</sub>



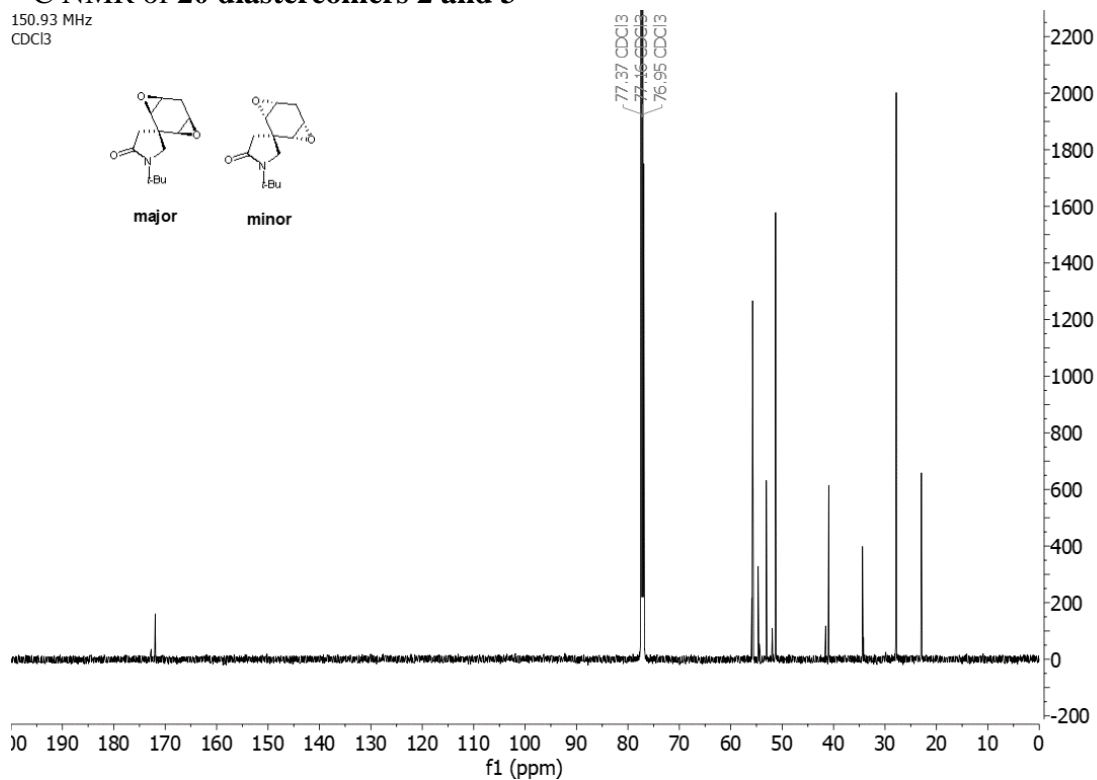
# <sup>1</sup>H NMR of **20** diastereomers **2** and **3**

400.15 MHz  
CDCl<sub>3</sub>



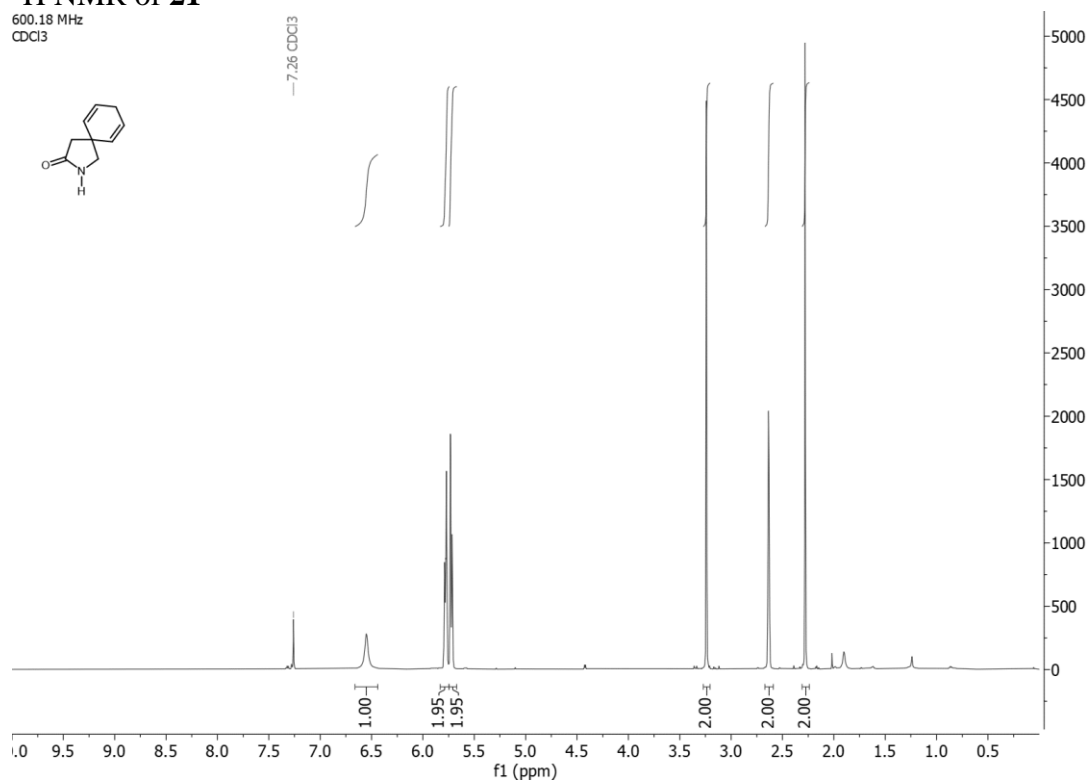
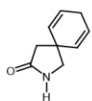
# <sup>13</sup>C NMR of **20** diastereomers **2** and **3**

150.93 MHz  
CDCl<sub>3</sub>



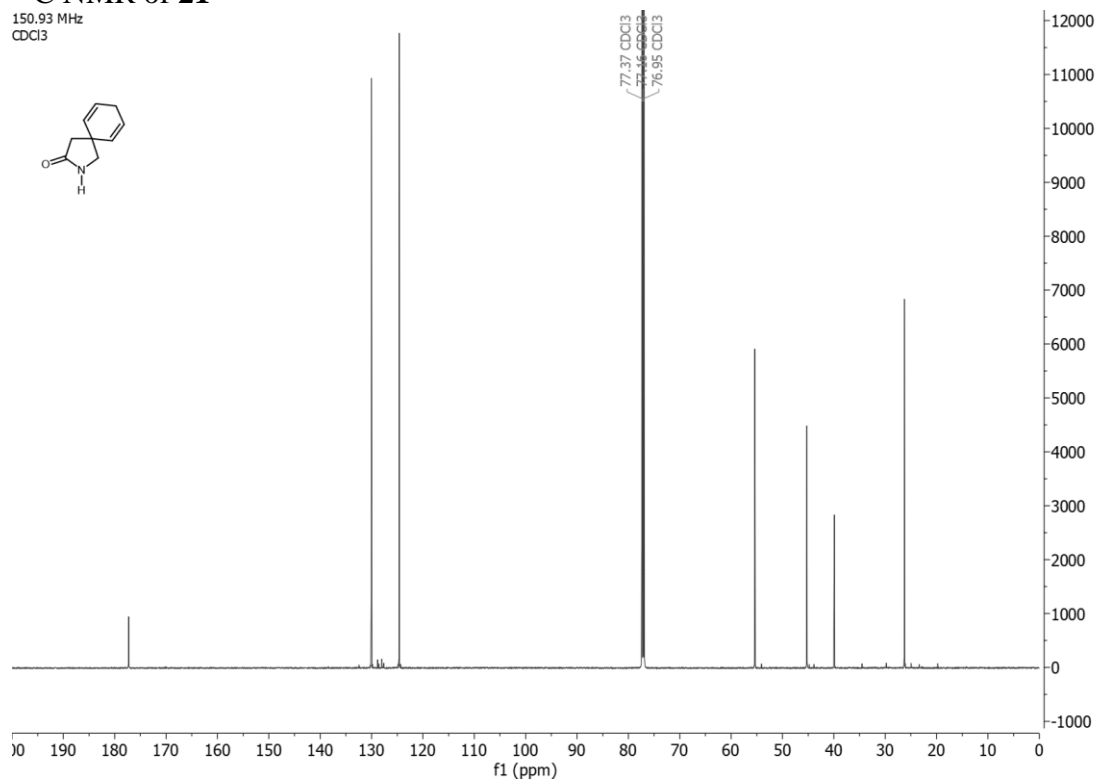
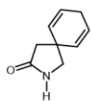
# <sup>1</sup>H NMR of **21**

600.18 MHz  
CDCl<sub>3</sub>



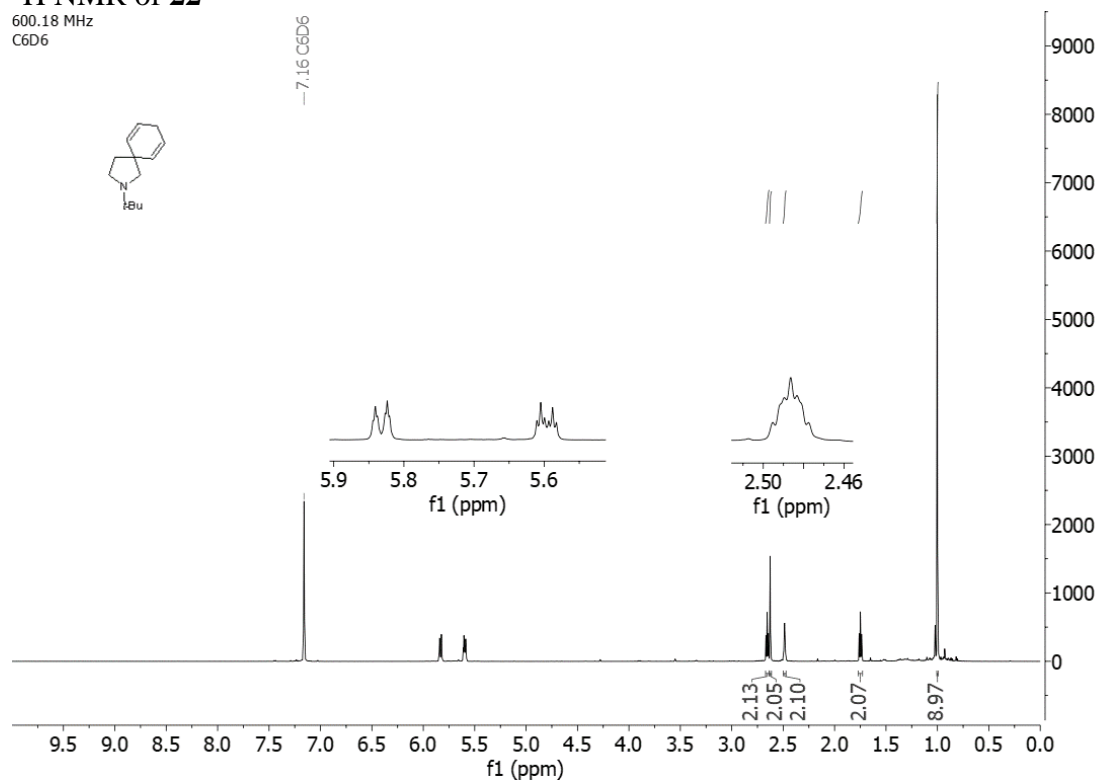
# <sup>13</sup>C NMR of **21**

150.93 MHz  
CDCl<sub>3</sub>



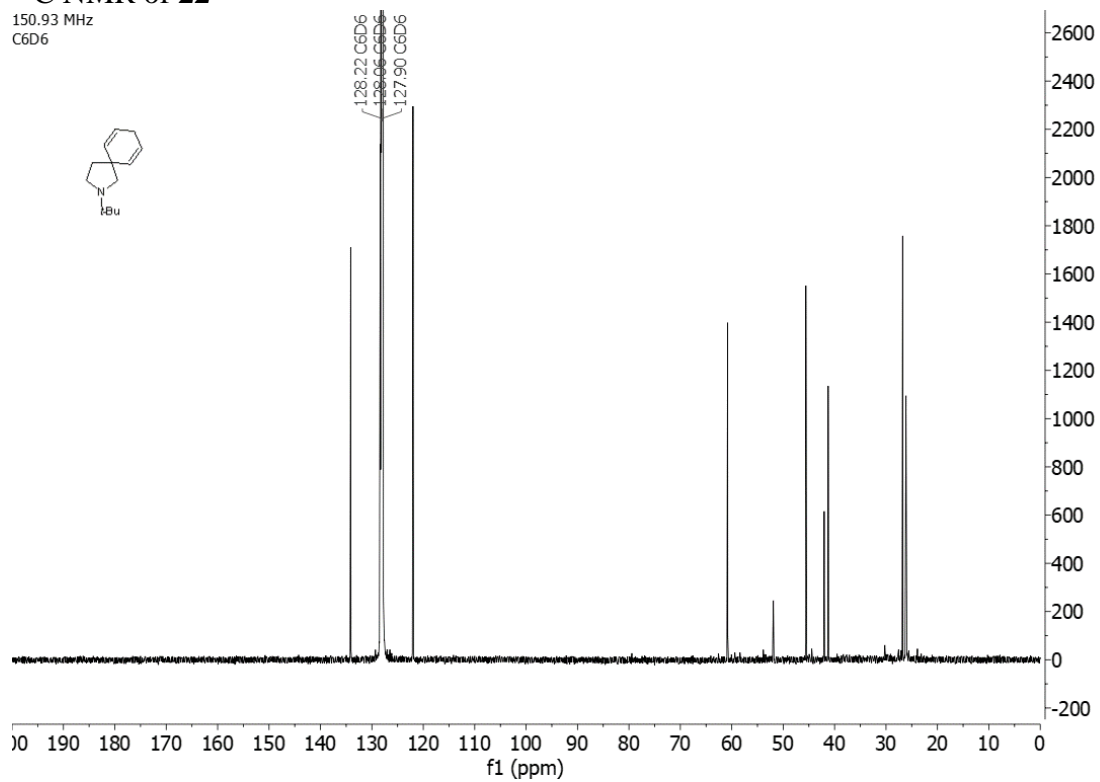
# <sup>1</sup>H NMR of **22**

600.18 MHz  
C6D6



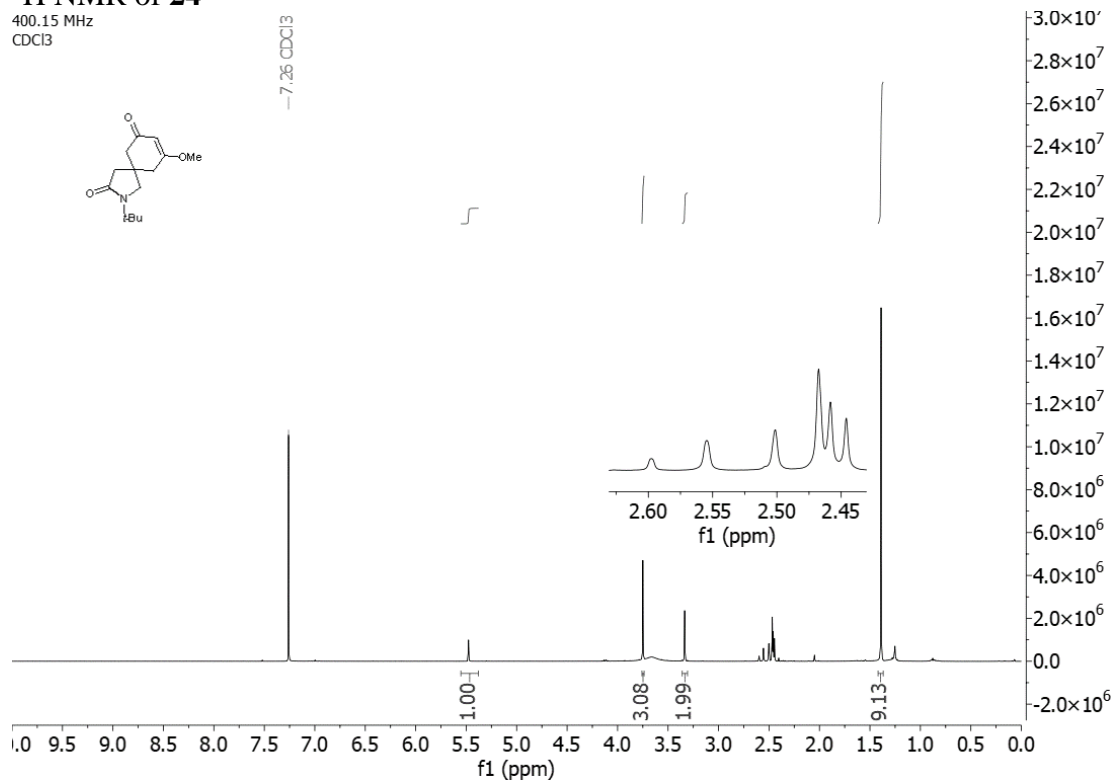
# <sup>13</sup>C NMR of **22**

150.93 MHz  
C6D6



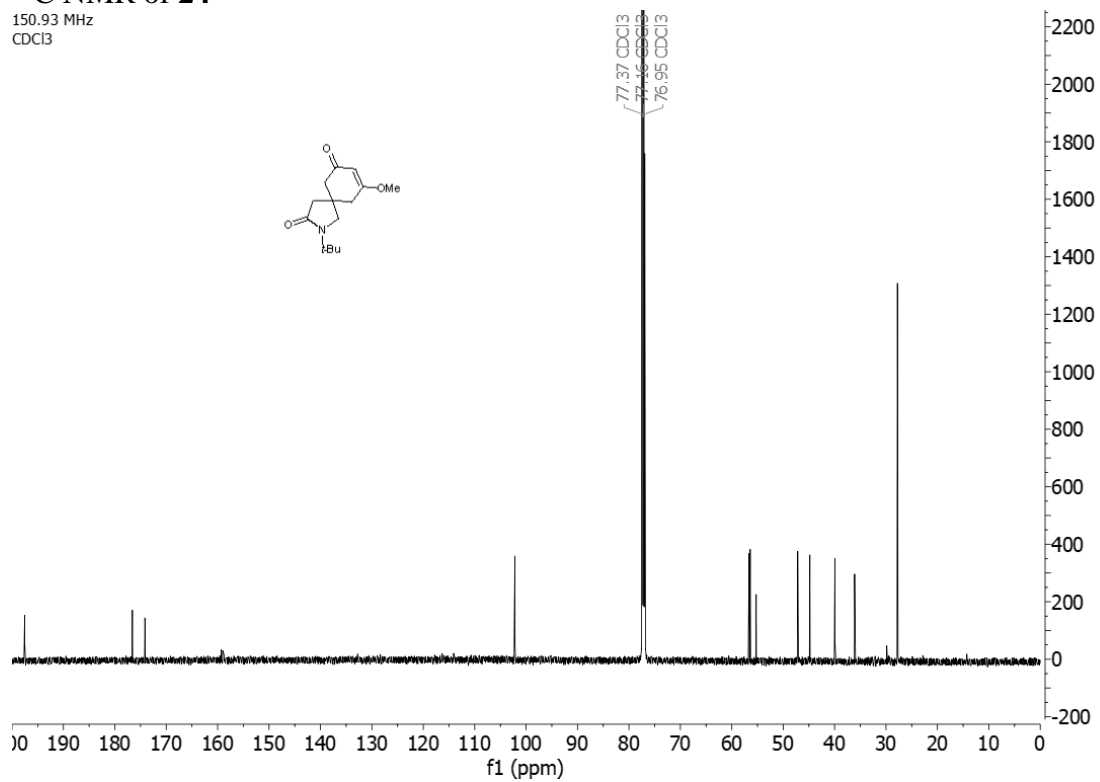
# <sup>1</sup>H NMR of **24**

400.15 MHz  
CDCl<sub>3</sub>



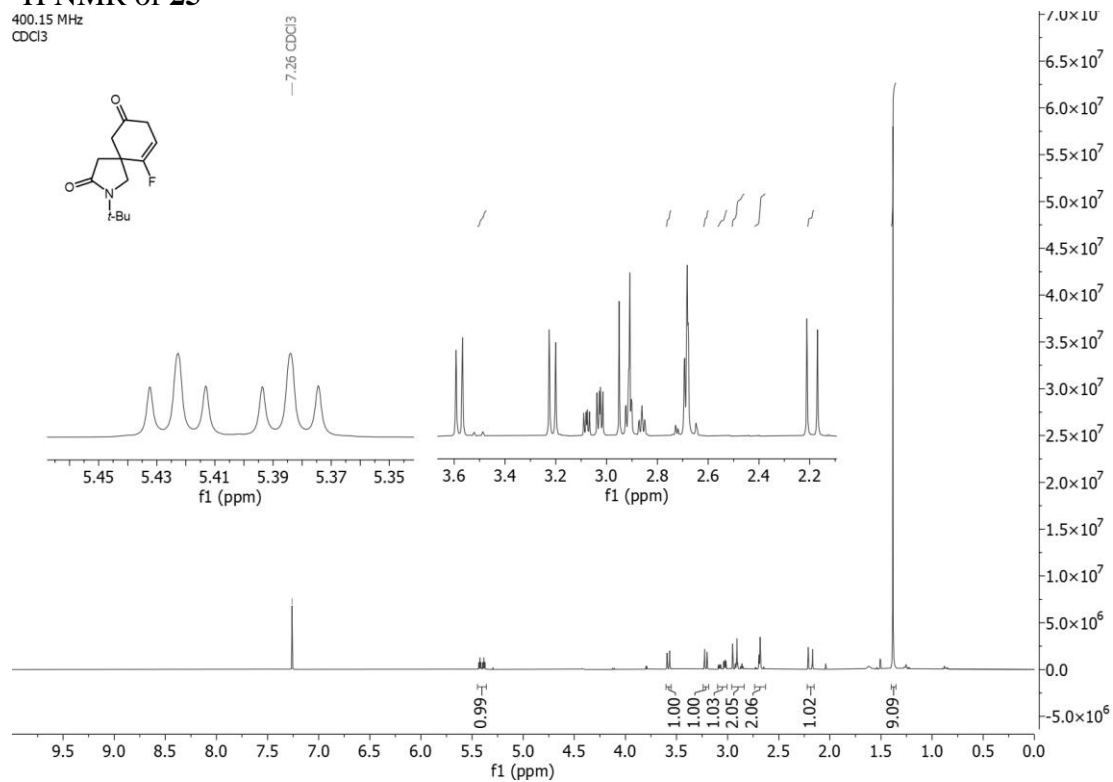
# <sup>13</sup>C NMR of **24**

150.93 MHz  
CDCl<sub>3</sub>



# <sup>1</sup>H NMR of **25**

400.15 MHz  
CDCl<sub>3</sub>



# <sup>13</sup>C NMR of **25**

100.63 MHz  
CDCl<sub>3</sub>

