SUPPORTING INFORMATION

Palladium Catalyzed Cross-Coupling of Aziridinyl-Metal Species Generated by Sulfinyl-Magnesium Exchange with Aryl Bromides: Reaction Optimization, Scope, and Kinetic Investigations

Matthew Hughes, Tom Boultwood, Gianfranco Zeppetelli and James A Bull*

Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, UK

E-mail: j.bull@imperial.ac.uk

Table of Contents..... S1

General Experimental Conditions S2

Derivation of the Rate Law and Mechanistic Implications S3

Reaction Schemes for the Synthesis of Sulfinyl Aziridines **9**,**10**,**11** and their Cross-Coupling..... S4

Product Stereochemistry and nOe Data S6

^{1}H and ^{13}C NMR Spectra S7–S32

General Experimental Considerations

All non-aqueous reactions were run under an inert atmosphere (argon) with oven or flame dried glassware using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (THF, diethyl ether, CH_2Cl_2).

Flash column chromatography was performed using 230-400 mesh silica or 50-200 μm Brockmann I basic alumina, with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates or precoated, aluminium-backed alumina gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm), or aqueous potassium permanganate stain.

Infrared spectra (FTIR) were recorded in reciprocal centimeters (cm^{-1}).

Nuclear magnetic resonance spectra were recorded on 400 MHz spectrometers. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ = 7.27 ppm). Data were reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet and br = broad), coupling constant in Hz, integration]. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($^{13}CDCl_3$: 77.0 ppm).

Melting points are uncorrected.

Reagents: Commercial reagents were used as supplied or purified by standard techniques where necessary.

Palladium (II) acetate: 99.98% purity. $Pd_2(dba)_3 \cdot CHCl_3$ was prepared and recrystallized according to the method of Ananikov and coworkers.[i]

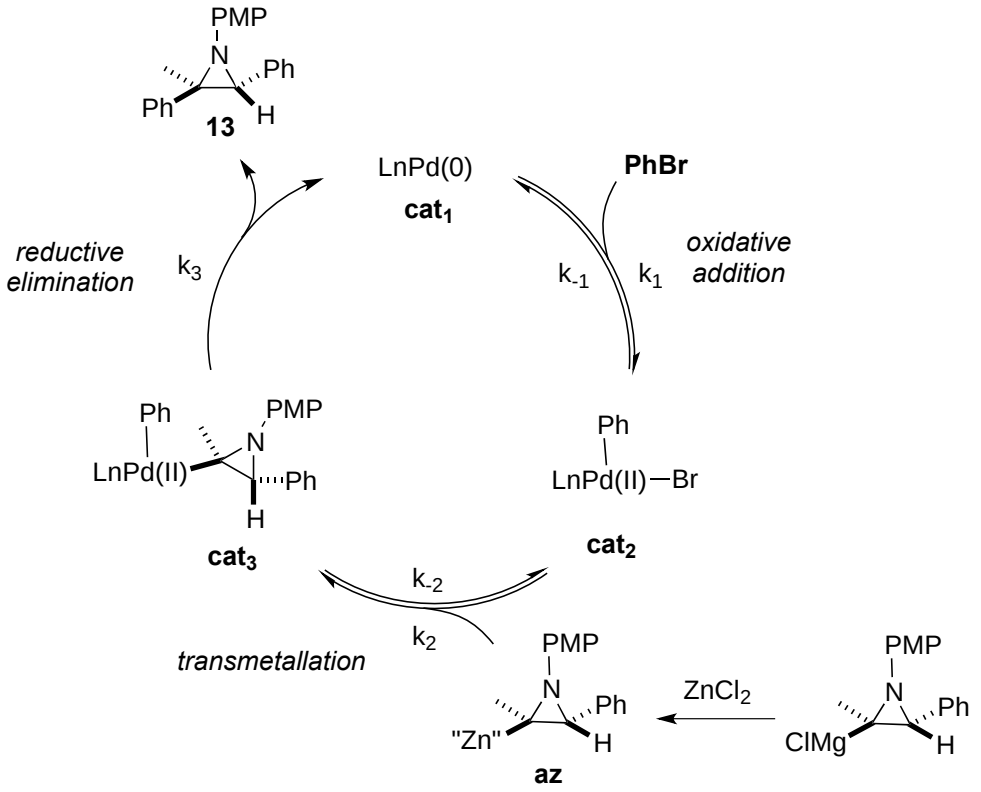
Zinc chloride: powder, anhydrous, ≥99.995 purity.

Note on purification of aziridines 13-23. Following the cross-coupling, the aziridines were unstable to silica gel chromatography, which afforded reduced yields. Chromatography using basic alumina afforded aziridines **13**-**23** in high purity and yield.

[i] Zalesskiy, S. S.; Ananikov, V. P. *Organometallics* **2012**, *31*, 2302.

Derivation of the Rate Law and Mechanistic Implications

Our proposed mechanism for the reaction is shown below, according to the widely accepted mechanism for Negishi cross coupling reaction. The aziridinyl (az) magnesium species is assumed to undergo transmetallation to the organozinc prior to entering the catalytic cycle.



$rate = k_3\,[\boldsymbol{cat_3}]$; $[\boldsymbol{cat}]_{tot} = [\boldsymbol{cat}_1] + [\boldsymbol{cat}_2] + [\boldsymbol{cat}_3]$

pre-equilibrium assumption $\Rightarrow K_1 = \frac{[\boldsymbol{cat_2}]}{[\boldsymbol{PhBr}][\boldsymbol{cat_1}]}$; $K_2 = \frac{[\boldsymbol{cat_3}][\boldsymbol{MBr}]}{[\boldsymbol{az}][\boldsymbol{cat_2}]}$; $k_3 \gg k_{-3}$

$$[\boldsymbol{cat}_2] = \frac{[\boldsymbol{cat}_3][\boldsymbol{MBr}]}{\boldsymbol{K_2}[\boldsymbol{az}]} \; ; \; [\boldsymbol{cat}_1] = \frac{[\boldsymbol{cat}_3][\boldsymbol{MBr}]}{\boldsymbol{K_1 K_2}[\boldsymbol{az}][\boldsymbol{PhBr}]}$$

$$[\boldsymbol{cat}]_{tot} = [\boldsymbol{cat}_3]\left(\frac{[\boldsymbol{MBr}]}{\boldsymbol{K_1 K_2}[\boldsymbol{az}][\boldsymbol{PhBr}]} + \frac{[\boldsymbol{MBr}]}{\boldsymbol{K_2}[\boldsymbol{az}]} + 1\right)$$

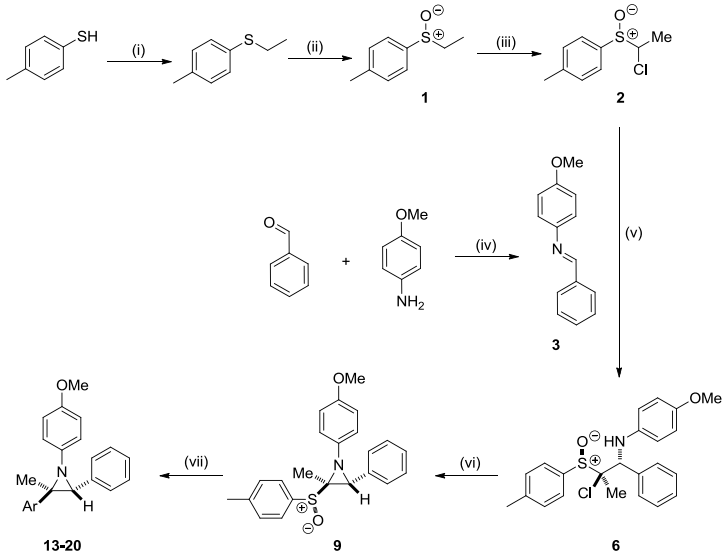
$$rate = \frac{k_3[\boldsymbol{cat}]_{tot}}{\left(\frac{[\boldsymbol{MBr}]}{\boldsymbol{K_1 K_2}[\boldsymbol{az}][\boldsymbol{PhBr}]} + \frac{[\boldsymbol{MBr}]}{\boldsymbol{K_2}[\boldsymbol{az}]} + 1\right)}$$

If the rate-determining step is reductive elimination, **cat₃** is the catalyst resting state and K_2 is large. Under these conditions, the rate equation simplifies to:
$rate = k_3\,[\boldsymbol{cat}]_{tot}$

If any of the other steps are rate-determining the reaction will have order in the substrates **PhBr** and/or **az**.

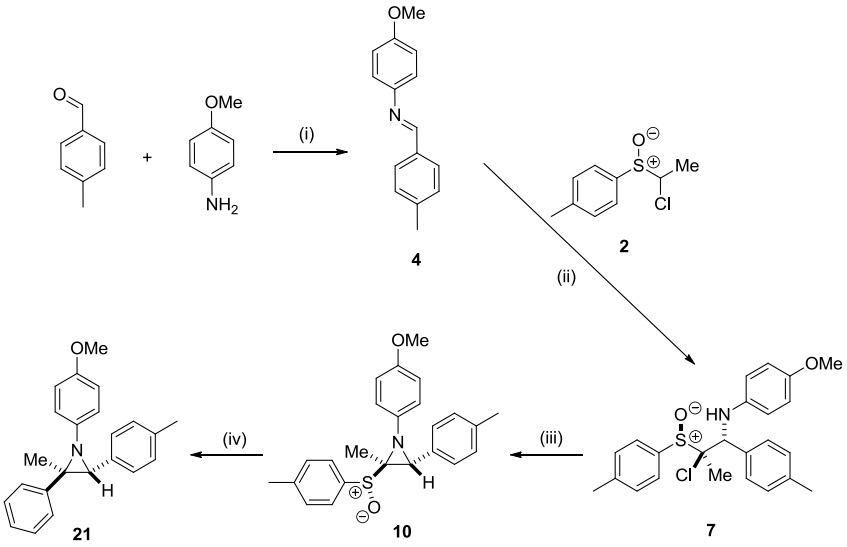
Reaction Schemes for the Synthesis of Sulfinyl Aziridines 9,10,11 and their Cross-Coupling

Synthesis of sulfinyl-aziridine **9** and palladium catalysed cross couplings to afford aziridines **13-20** (Scheme S1):



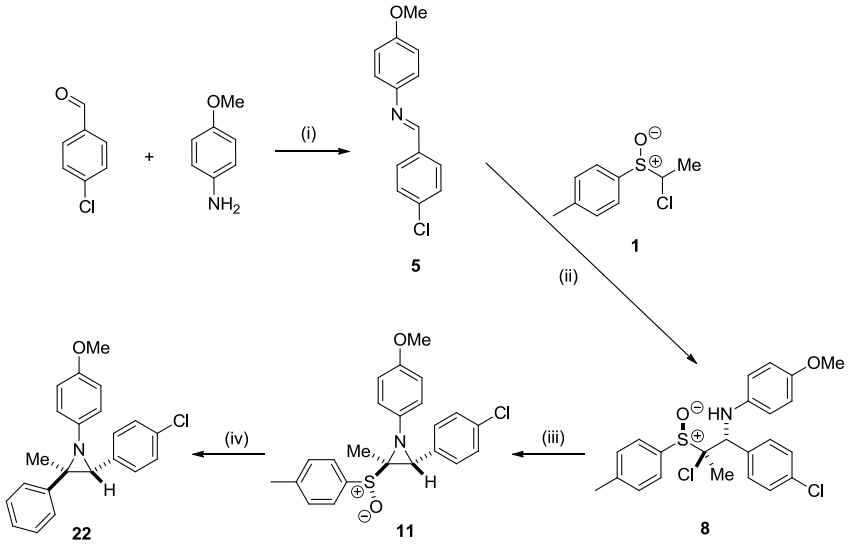
Scheme S1: i) EtBr, K_2CO_3, acetone, rt, 20 h. ii) mCPBA, CH_2Cl_2, –10 °C to rt, 2 h. iii) NCS, CH_2Cl_2, rt, 1 h. iv) $MgSO_4$, CH_2Cl_2, 48 h. v) LDA, THF, –78 °C. vi) KO*t*Bu, THF, reflux, 15 min. vii) *i*PrMgCl, THF, –78 to 0 °C, 10 min; $Pd_2(dba)_3{\cdot}CHCl_3$, P(*t*Bu)$_3$, $ZnCl_2$, ArBr, THF, rt, 15 h.

Synthesis of sulfinyl-aziridine **10** and palladium catalysed cross coupling (Scheme S2):



Scheme S2: i) $MgSO_4$, CH_2Cl_2, 48 h. ii) LDA, THF, –78 °C. iii) KO*t*Bu, THF, reflux, 15 min. iv) *i*PrMgCl, THF, –78 to 0 °C, 10 min; $Pd_2(dba)_3{\cdot}CHCl_3$, P(*t*Bu)$_3$, $ZnCl_2$, PhBr, THF, rt, 15 h.

Synthesis of sulfinyl-aziridine **11** and palladium catalysed cross coupling (Scheme S3):

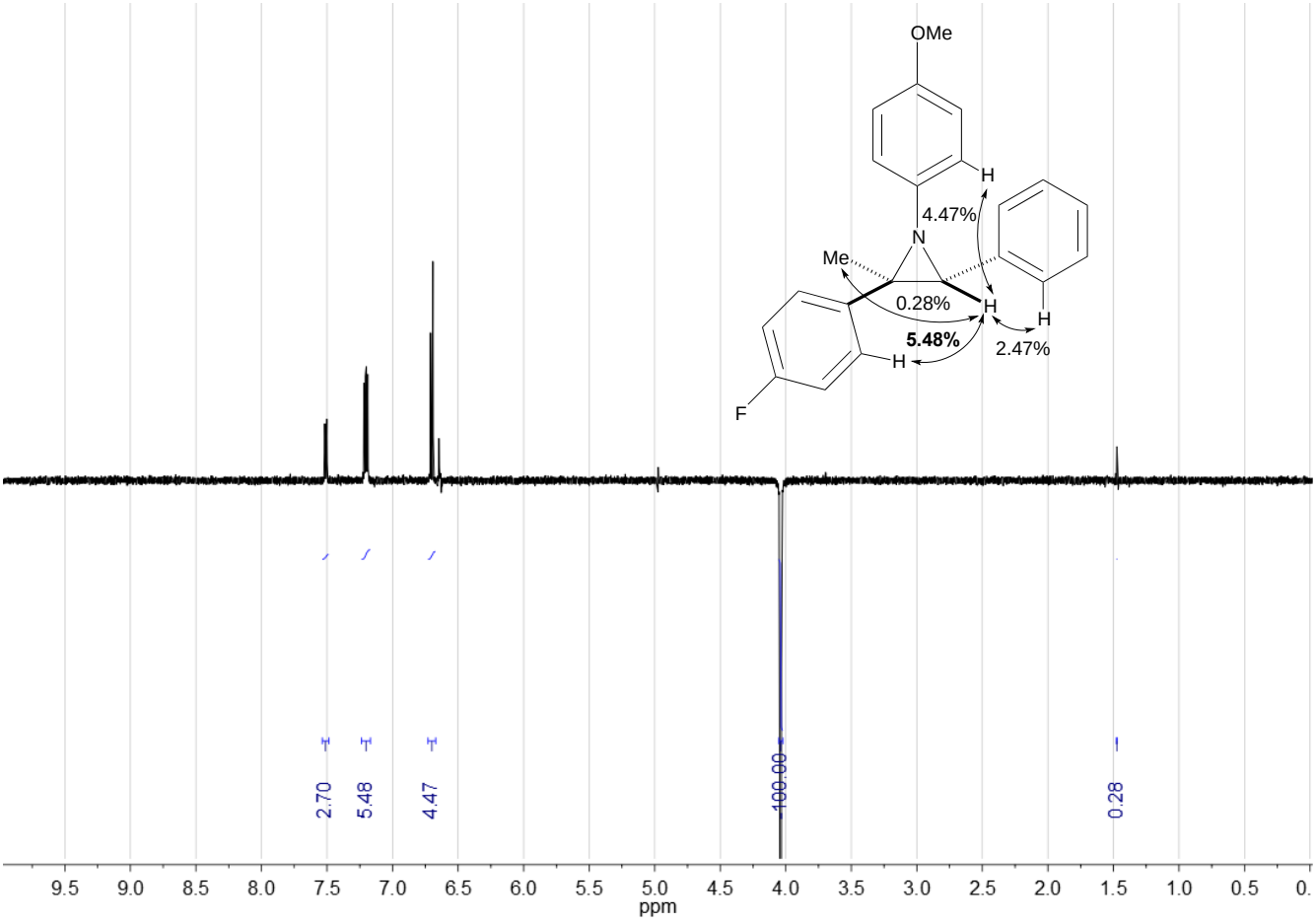


Scheme S3: i) $MgSO_4$, CH_2Cl_2, 48 h; ii) LDA, THF, –78 °C; iii) KO*t*Bu, THF, reflux, 15 min; iv) *i*PrMgCl, THF, –78 to 0 °C, 10 min; $Pd_2(dba)_3{\cdot}CHCl_3$, P(*t*Bu)$_3$, $ZnCl_2$, PhBr, THF, rt, 15 h.

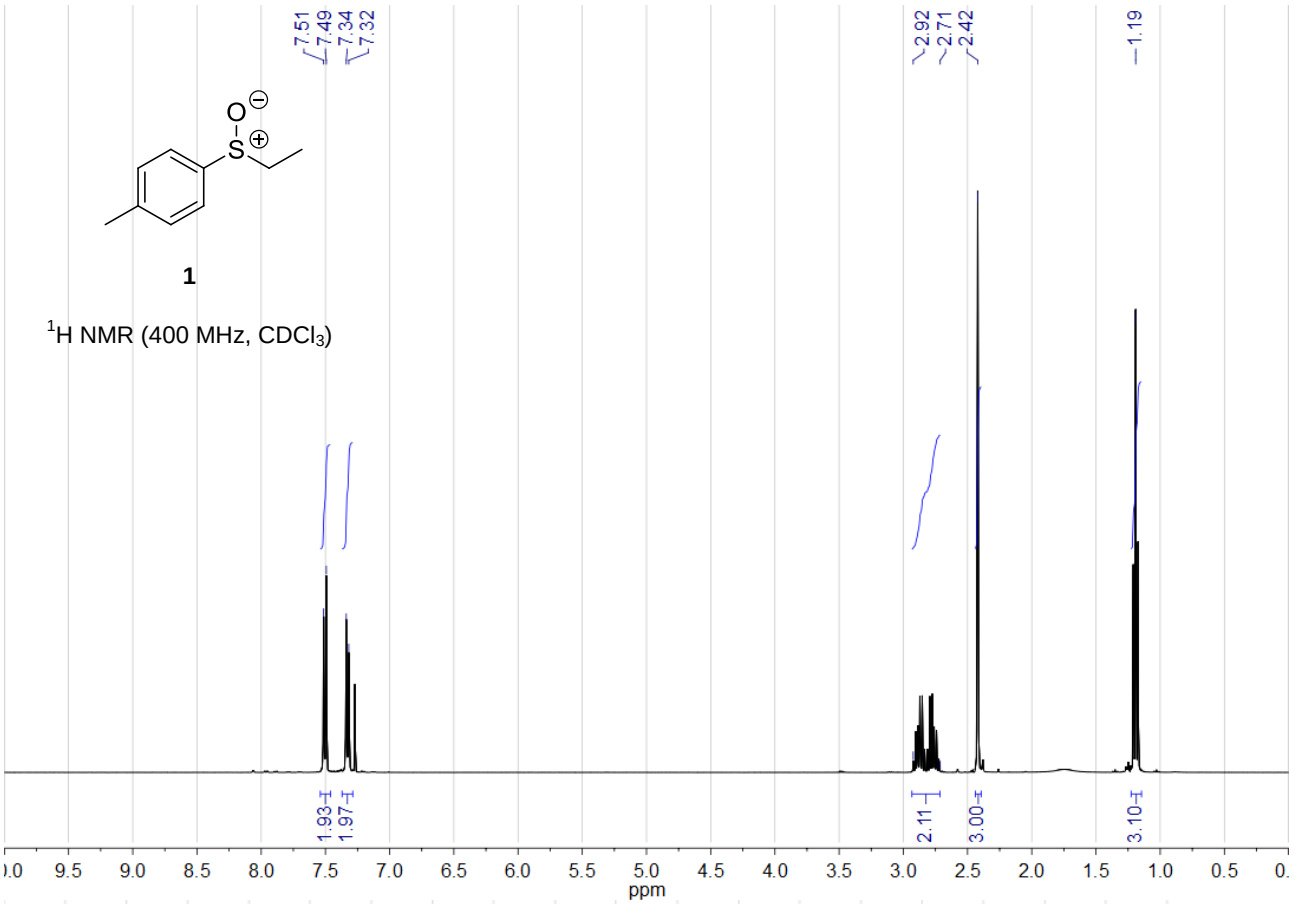
Product Stereochemistry and nOe Data

The stereochemistry of the product corresponds to retention of the stereochemistry at the cross coupled centre as defined in the sulfinyl-aziridine. This is consistent with the stereochemical outcomes of the quenching experiments to form **H-12** from both the aziridinyl magnesium and aziridinyl zinc intermediates (**H-12** has been shown to bear a *cis*-relationship as determined by the characteristic coupling constants, ^{3}J NCH-NCH = 6.5 Hz). In all cases the isolated products were found to be completely diastereomerically pure; during the course of the cross-coupling reaction, this structural information does not become scrambled and the process proceeds with overall retention of stereochemistry. This is also consistent with the stereochemical outcome observed by Vedejs (*see reference 6 in main text*).

In addition, the stereochemistry of the cross-coupling product **17** was examined by a selective nOe experiment (See Figure S4). On irradiation of the aziridinyl proton (NCH, δ = 4.05), a far stronger enhancement was observed for the signal of the fluorophenyl group (5.48%, δ = 7.24-7.19) than the signal of the methyl group (0.28%, δ = 1.49). This is consistent with the stereochemistry assigned. Indeed the fluorophenyl signal displays the largest enhancement. By analogy, the other products (**13**-**16**, **18**–**23**) are assumed to have the same stereochemistry.

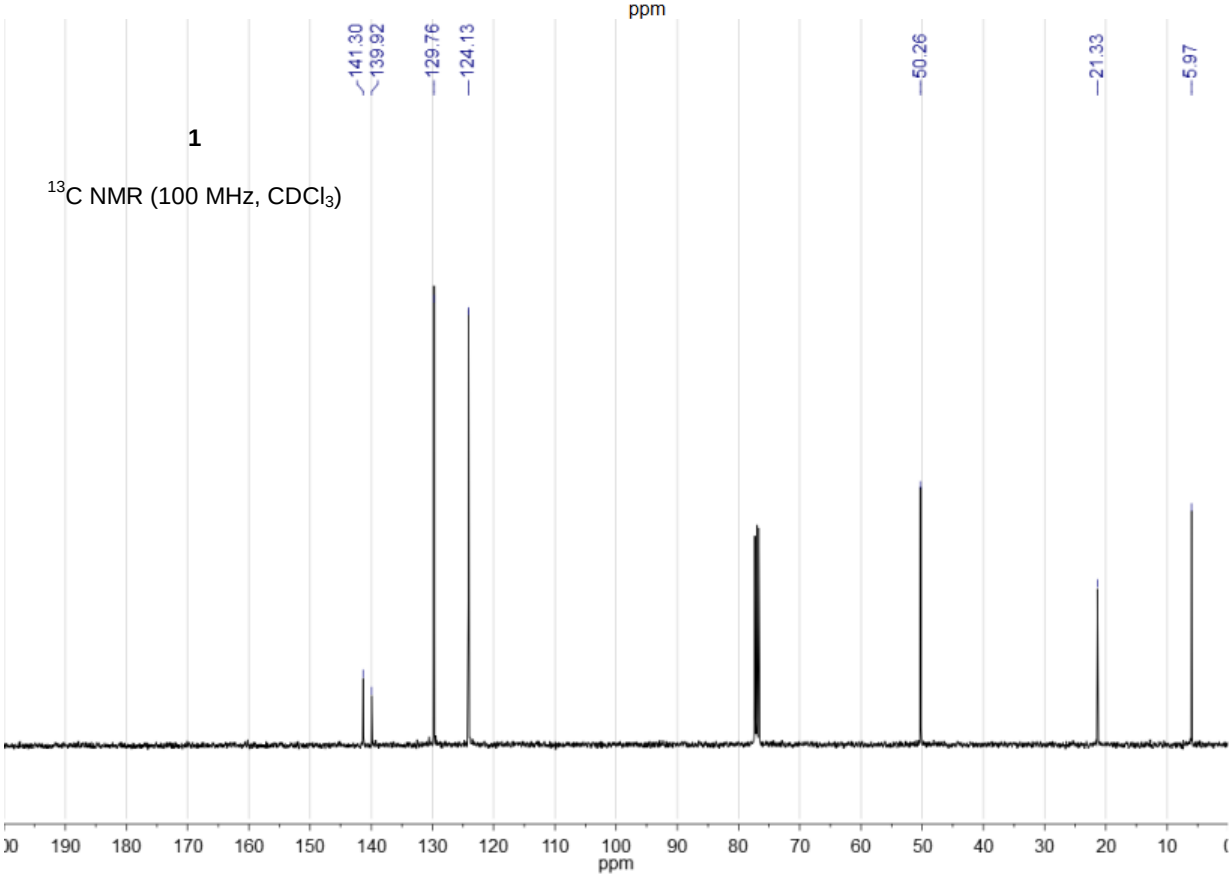


^{1}H and ^{13}C NMR spectra of selected compounds



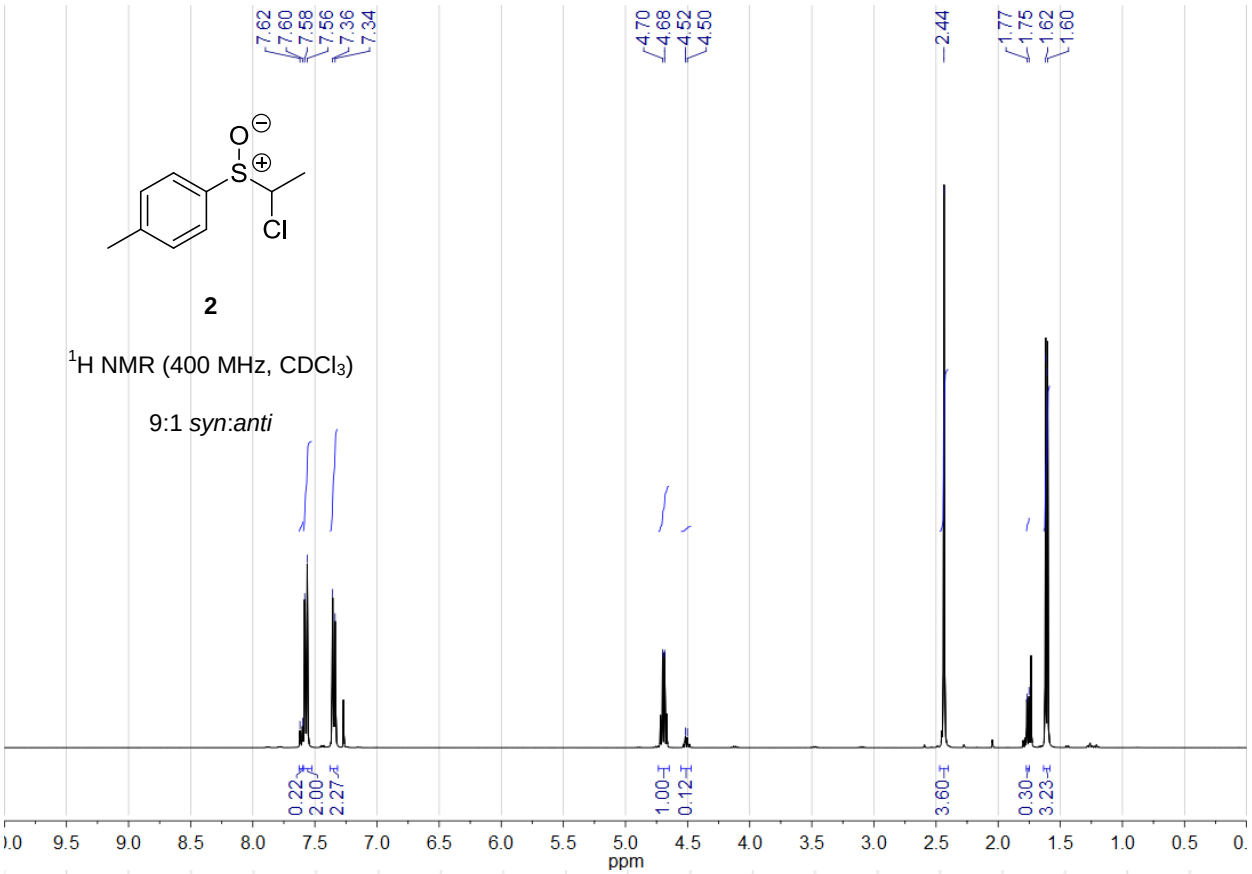
1

^{1}H NMR (400 MHz, $CDCl_3$)



1

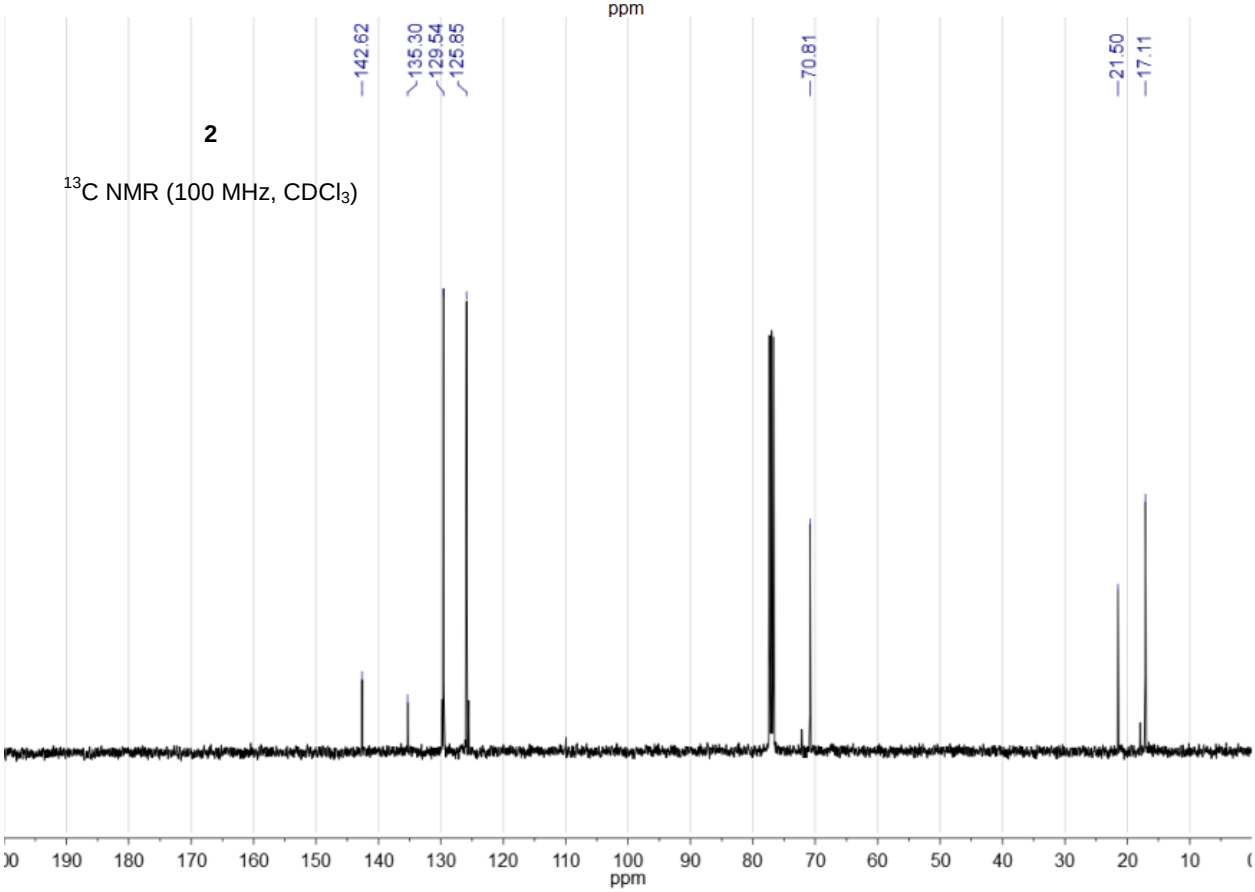
^{13}C NMR (100 MHz, $CDCl_3$)



2

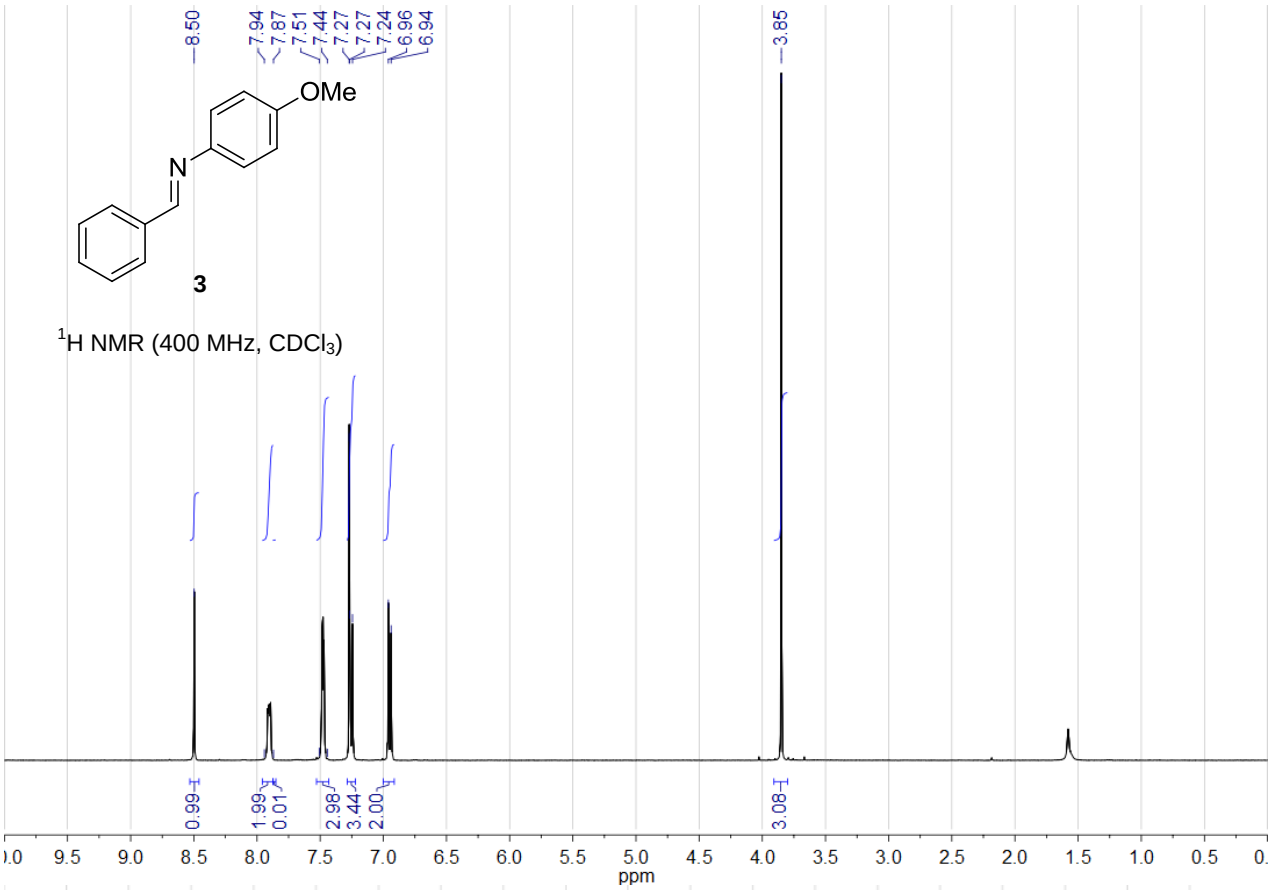
^{1}H NMR (400 MHz, $CDCl_3$)

9:1 *syn*:*anti*



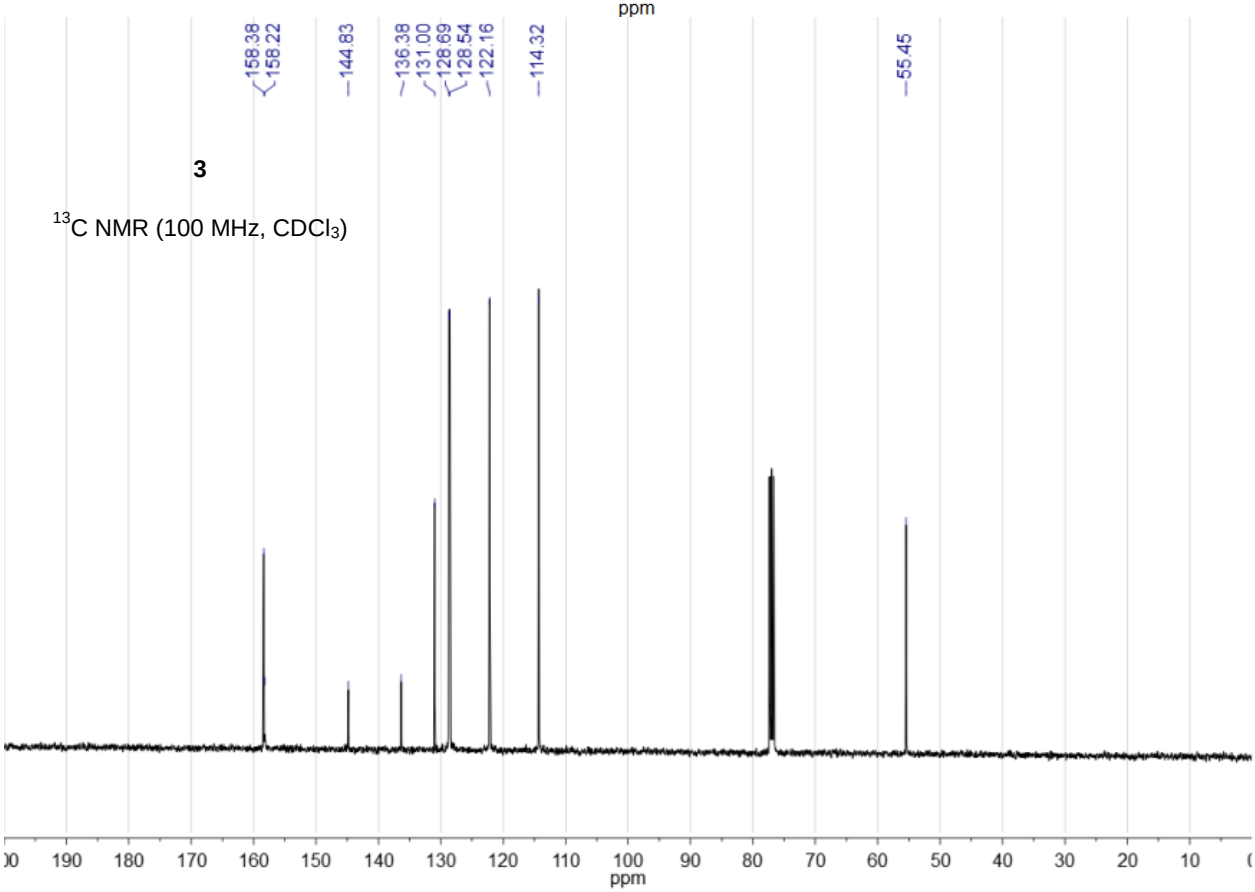
2

^{13}C NMR (100 MHz, $CDCl_3$)



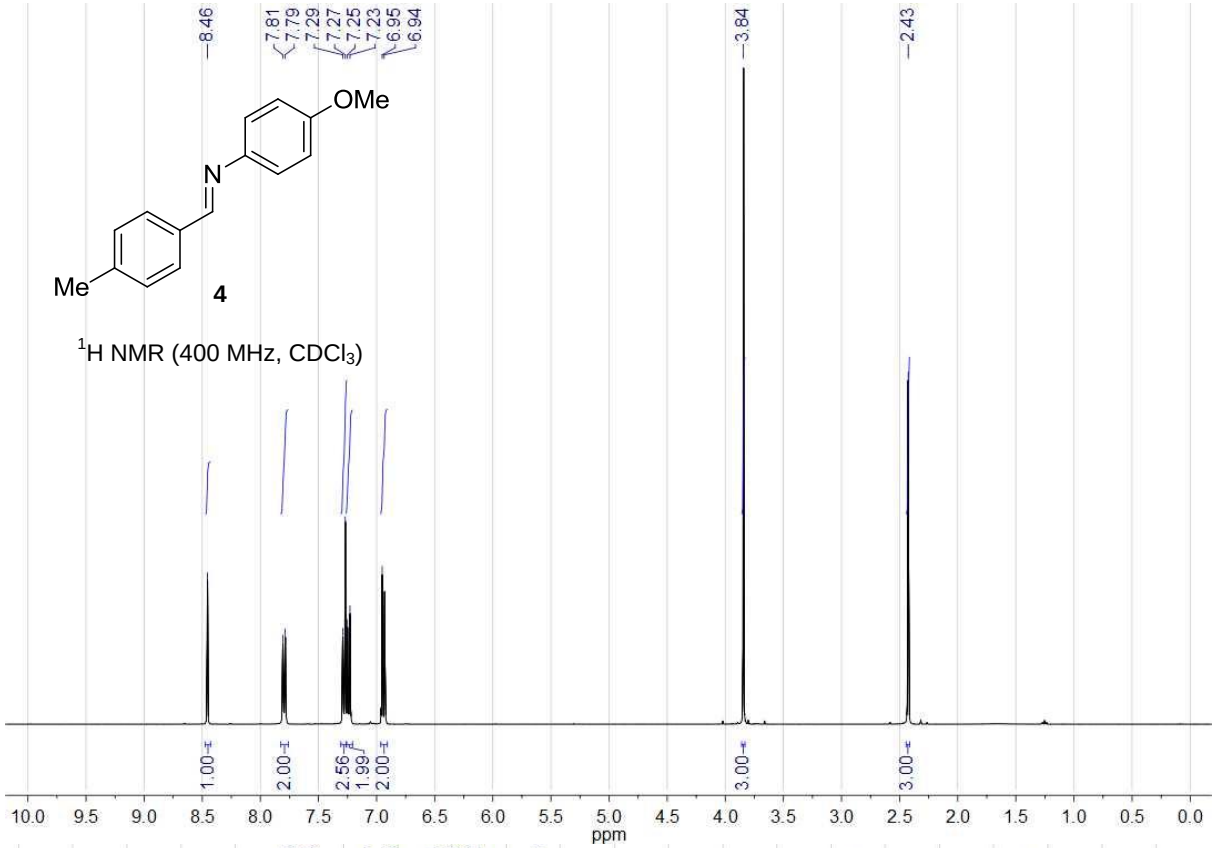
3

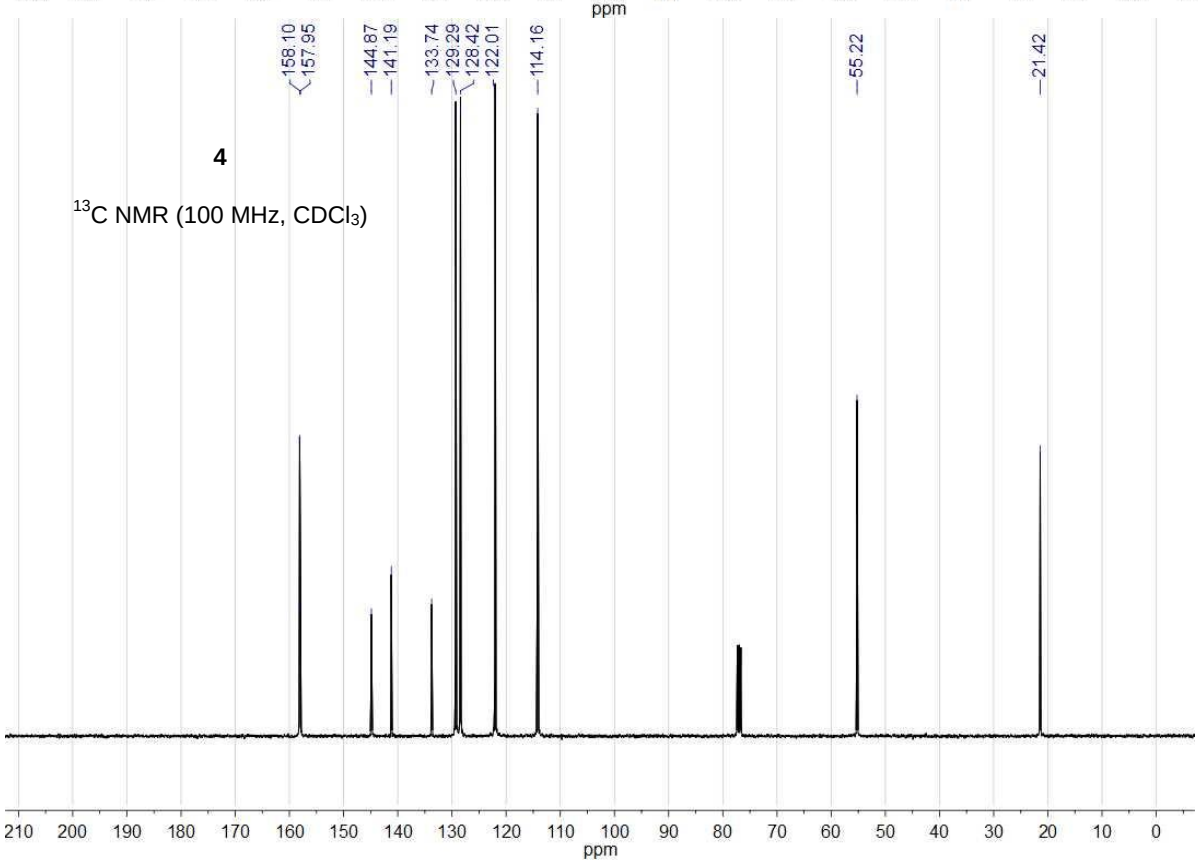
^{1}H NMR (400 MHz, $CDCl_3$)

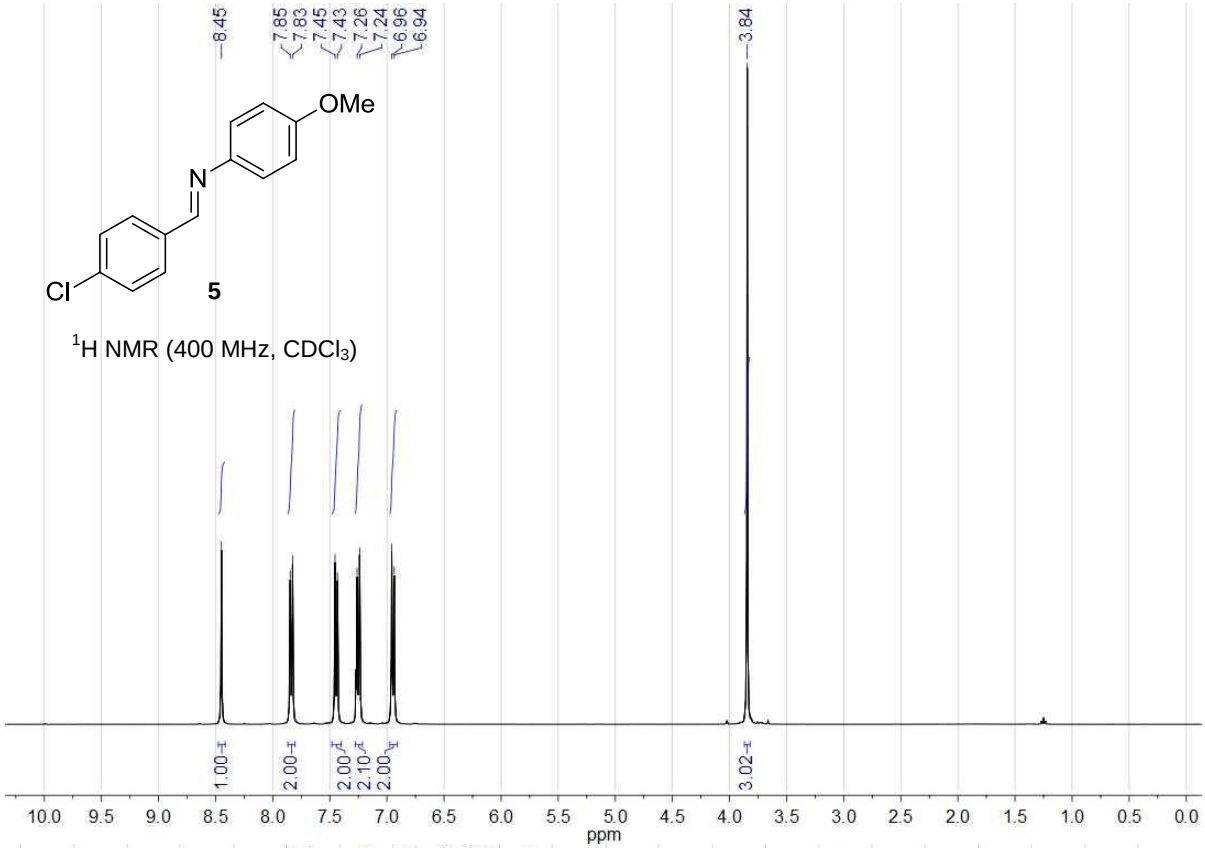


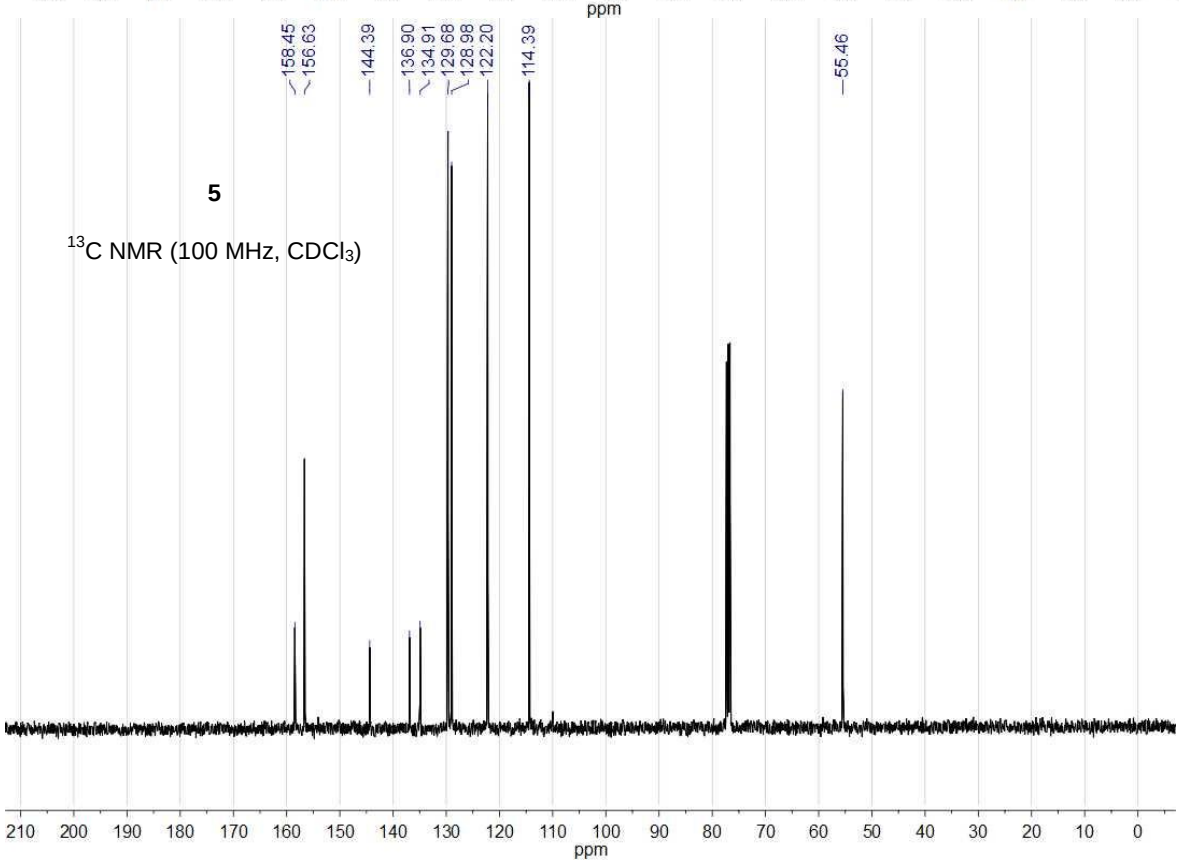
3

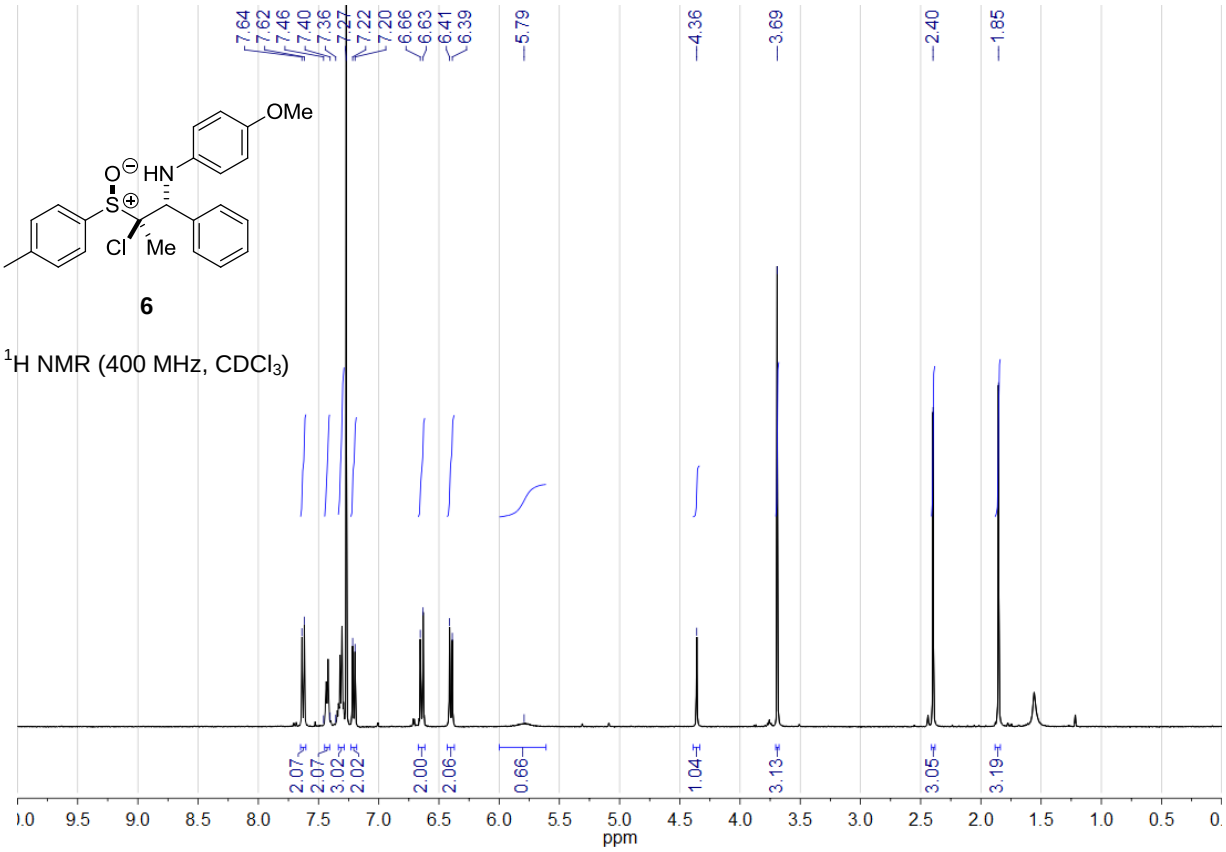
^{13}C NMR (100 MHz, $CDCl_3$)


8.46
7.81
7.79
7.29
7.27
7.25
7.23
6.95
6.94
3.84
2.43
OMe
N
Me
4
1H NMR (400 MHz, CDCl3)
1.00
2.00
2.56
1.99
2.00
3.00
3.00
ppm


158.10
157.95
144.87
141.19
133.74
129.29
128.42
122.01
114.16
55.22
21.42
4
13C NMR (100 MHz, CDCl3)
ppm

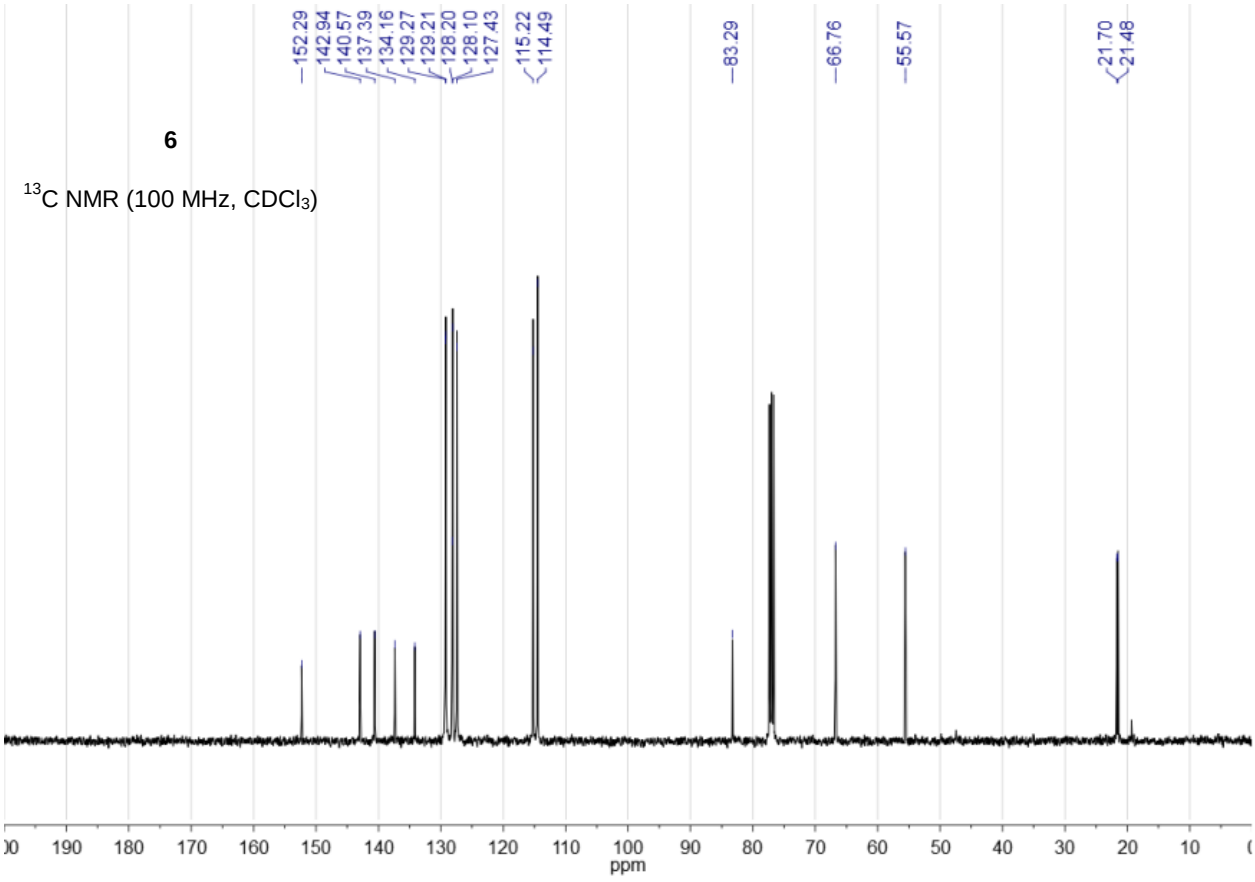

8.45
7.85
7.83
7.45
7.43
7.26
7.24
6.96
6.94
3.84
OMe
N
Cl
5
1H NMR (400 MHz, CDCl3)
1.00
2.00
2.00
2.10
2.00
3.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


158.45
156.63
144.39
136.90
134.91
129.68
128.98
122.20
114.39
55.46
5
13C NMR (100 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm



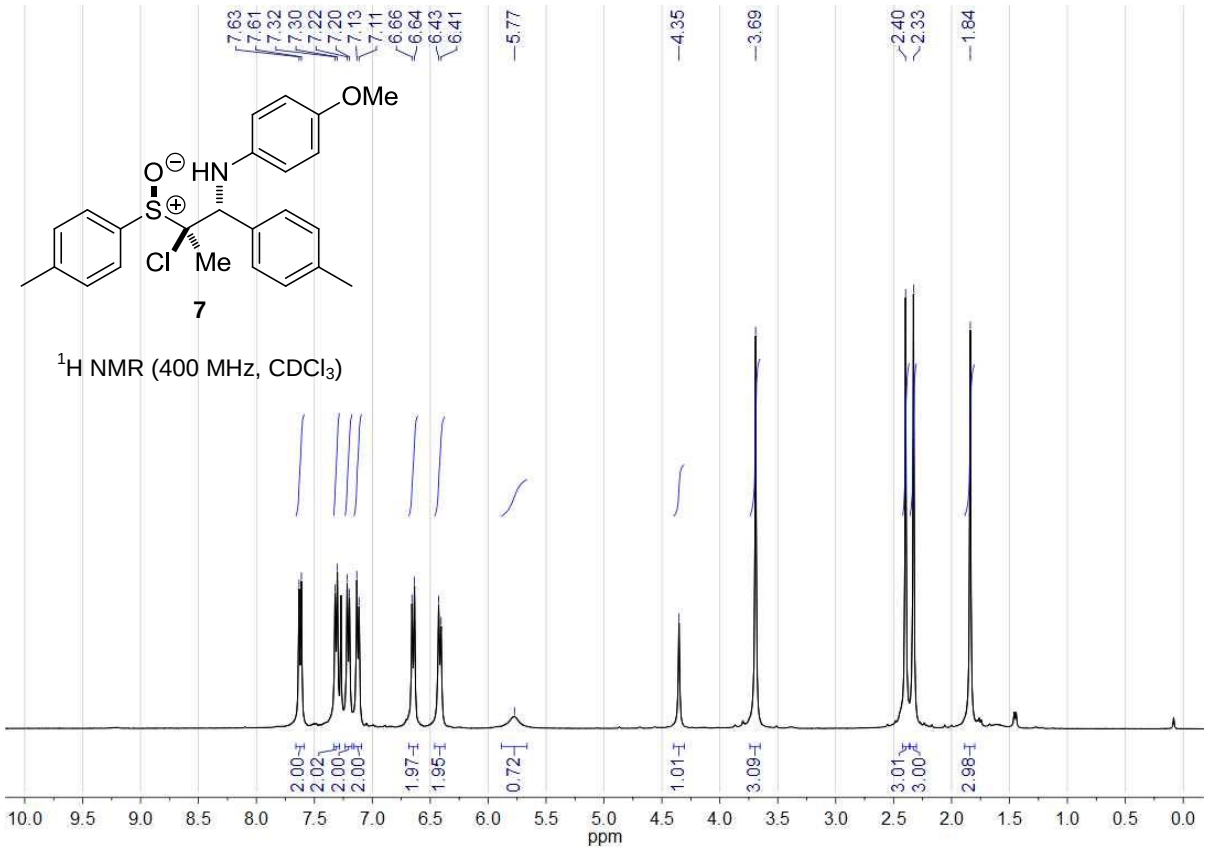
6

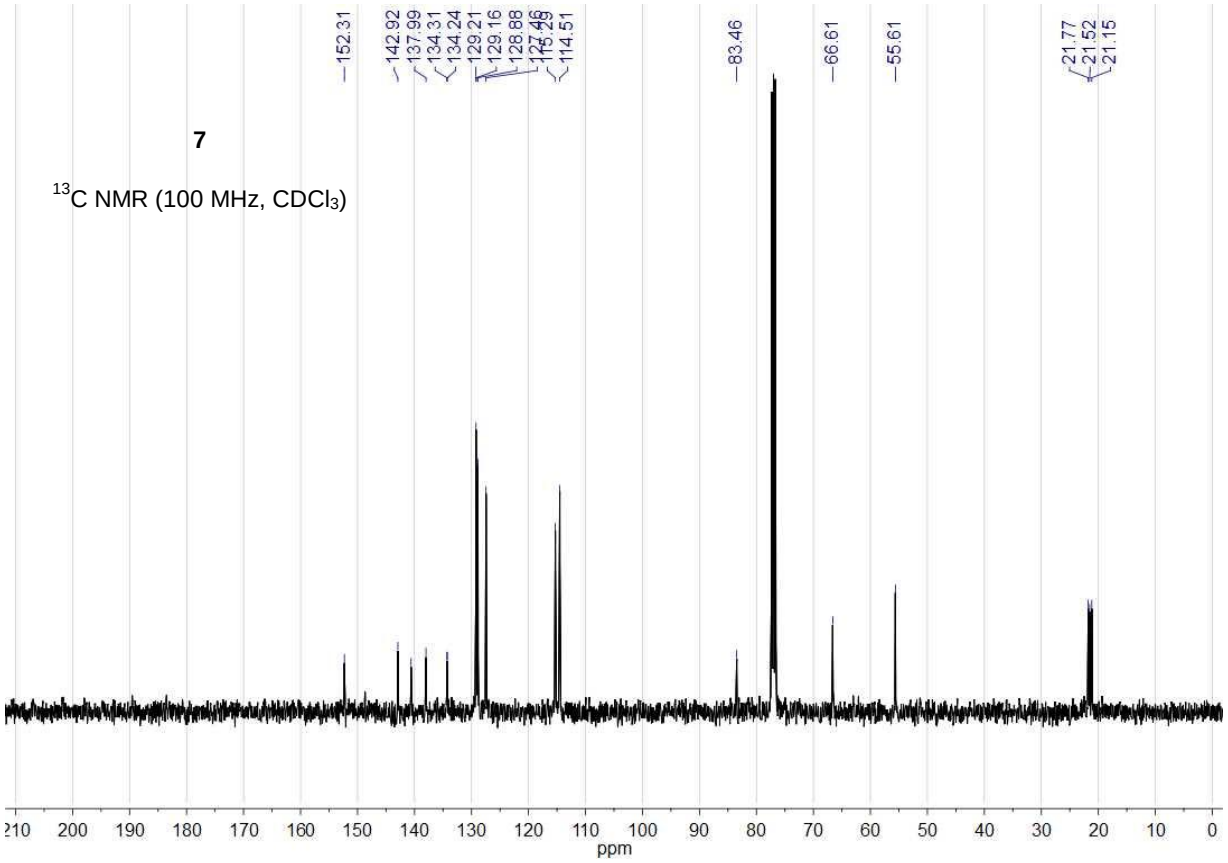
^{1}H NMR (400 MHz, $CDCl_3$)

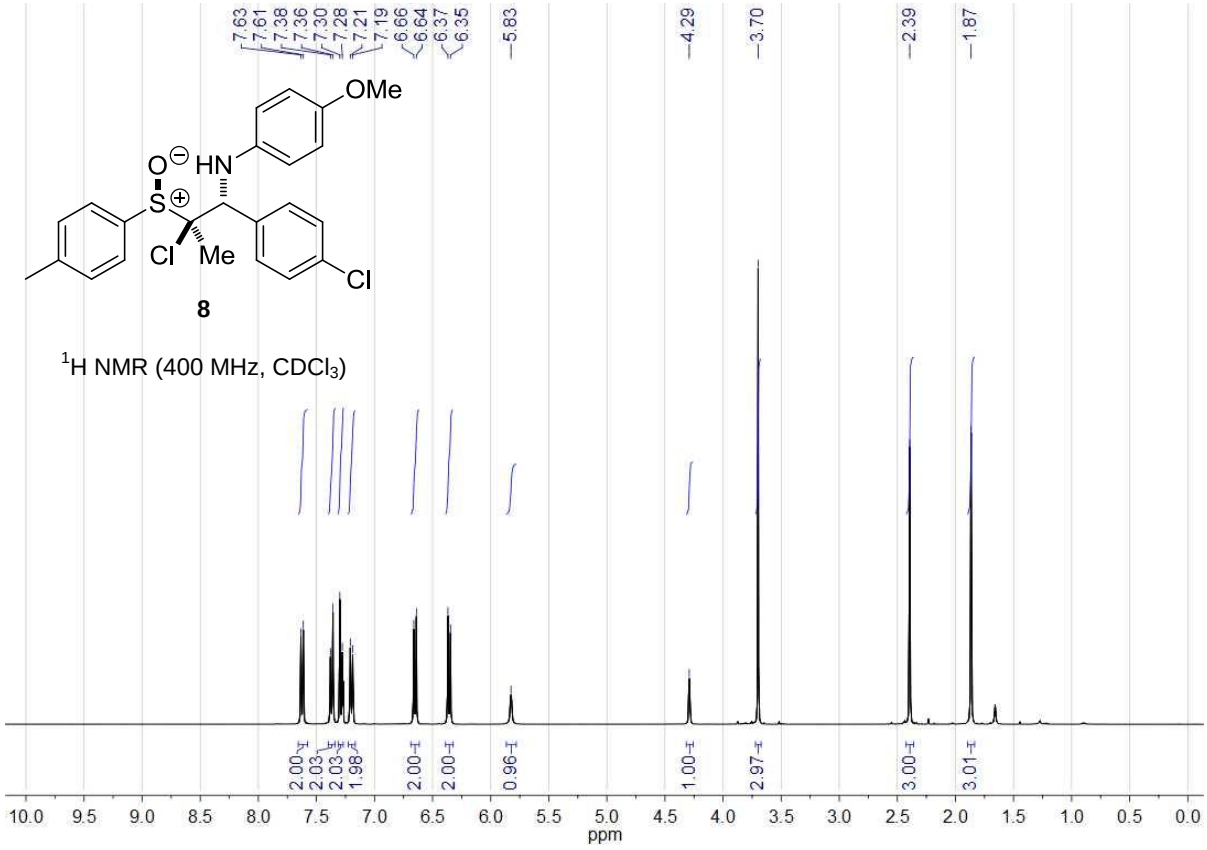


6

^{13}C NMR (100 MHz, $CDCl_3$)

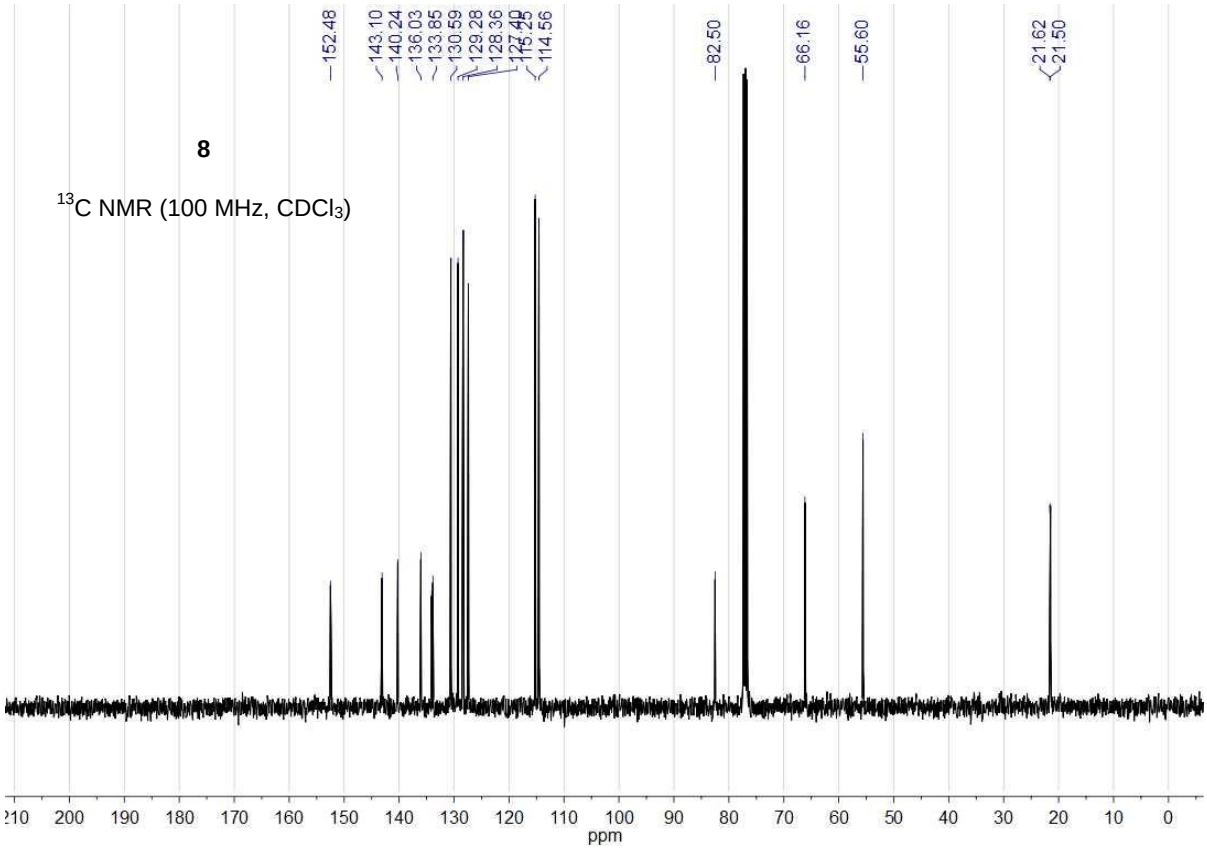

7.63
7.61
7.32
7.30
7.22
7.20
7.13
7.11
6.66
6.64
6.43
6.41
5.77
4.35
3.69
2.40
2.33
1.84
OMe
HN
O
S
Cl
Me
7
1H NMR (400 MHz, CDCl3)
2.00
2.02
2.00
2.00
1.97
1.95
0.72
1.01
3.09
3.01
3.00
2.98
ppm


152.31
142.92
137.99
134.31
134.24
129.21
129.16
128.88
114.51
83.46
66.61
55.61
21.77
21.52
21.15
7
13C NMR (100 MHz, CDCl3)
ppm



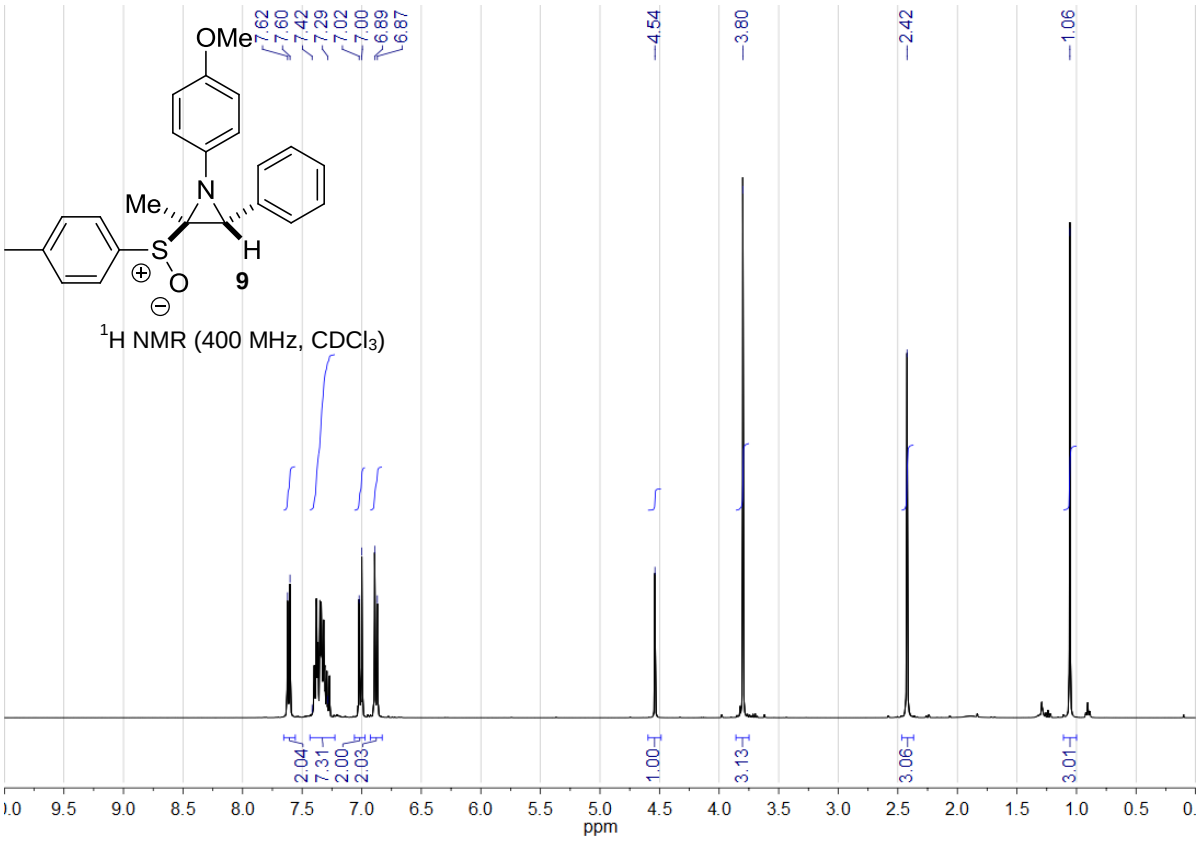
8

^{1}H NMR (400 MHz, $CDCl_3$)

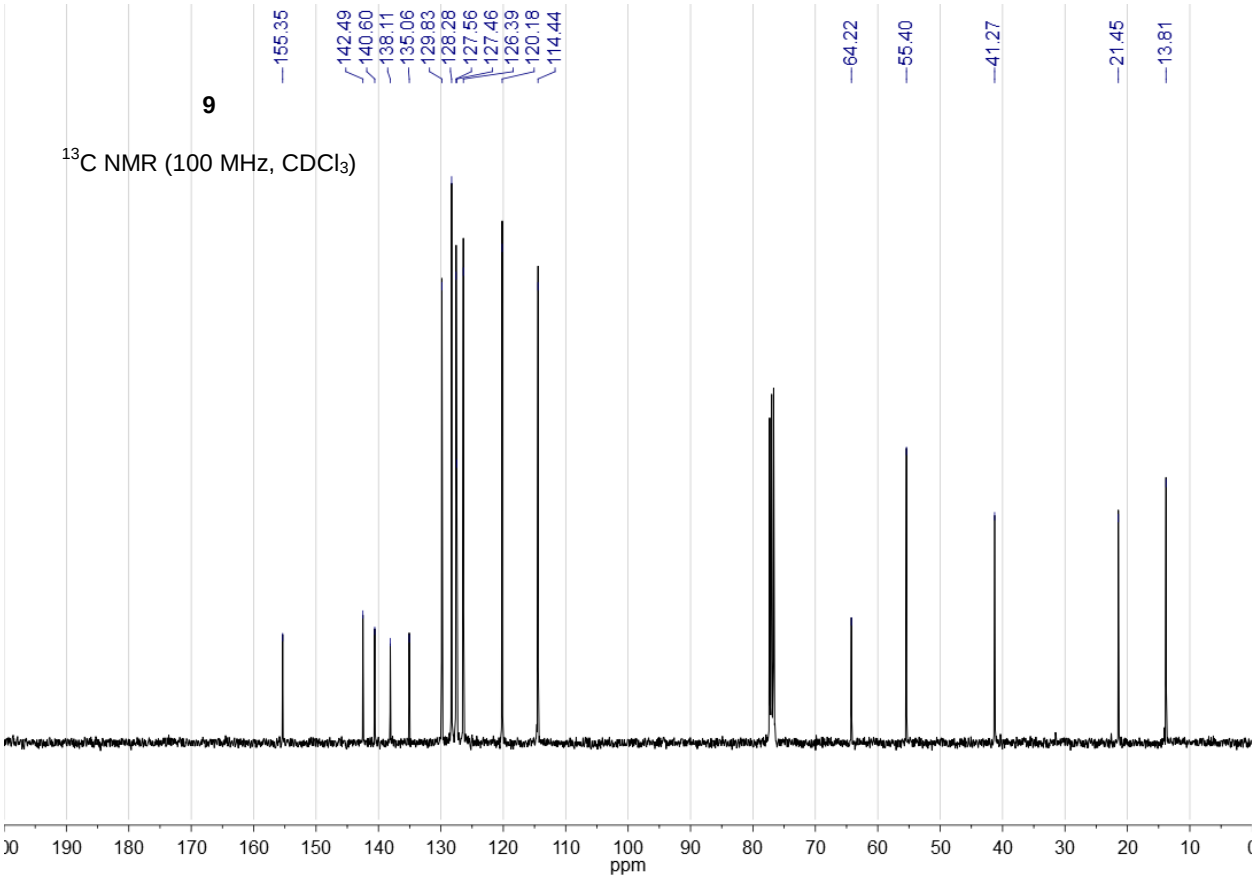


8

^{13}C NMR (100 MHz, $CDCl_3$)

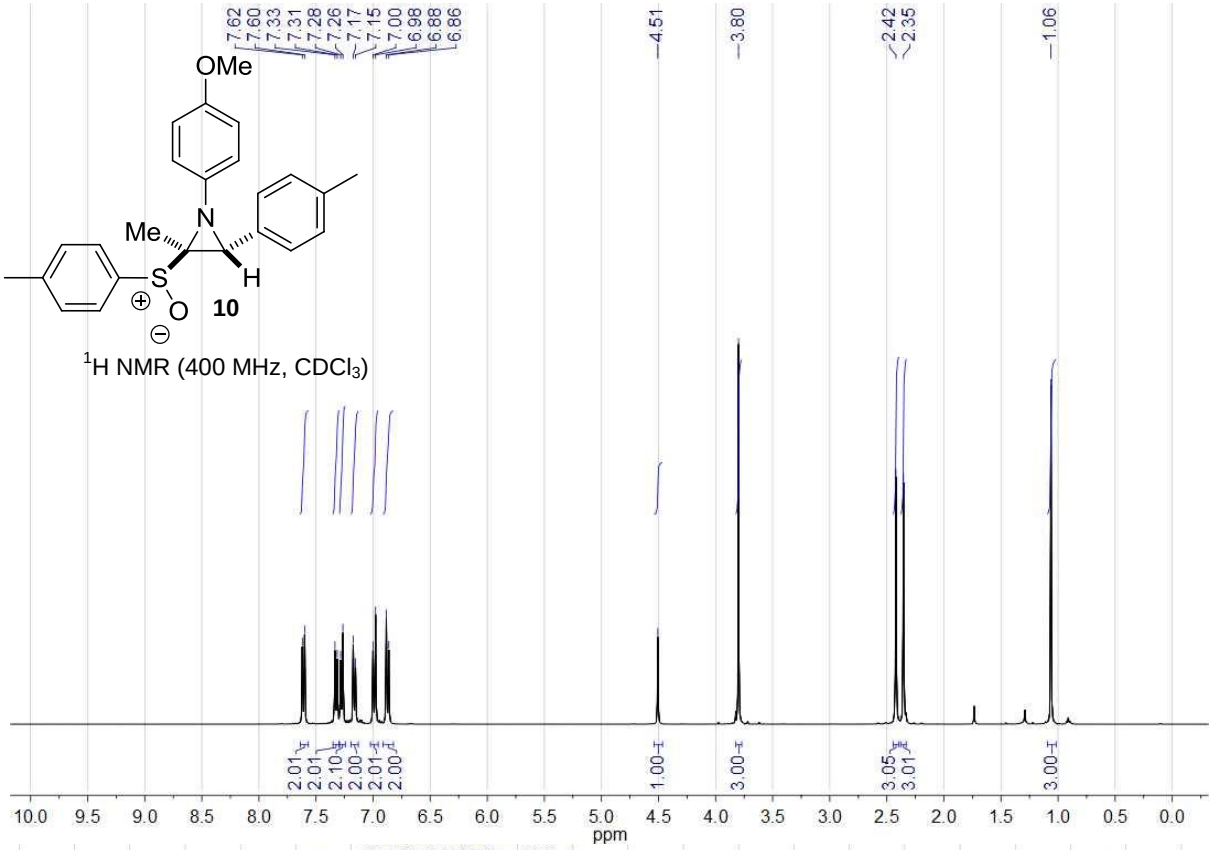


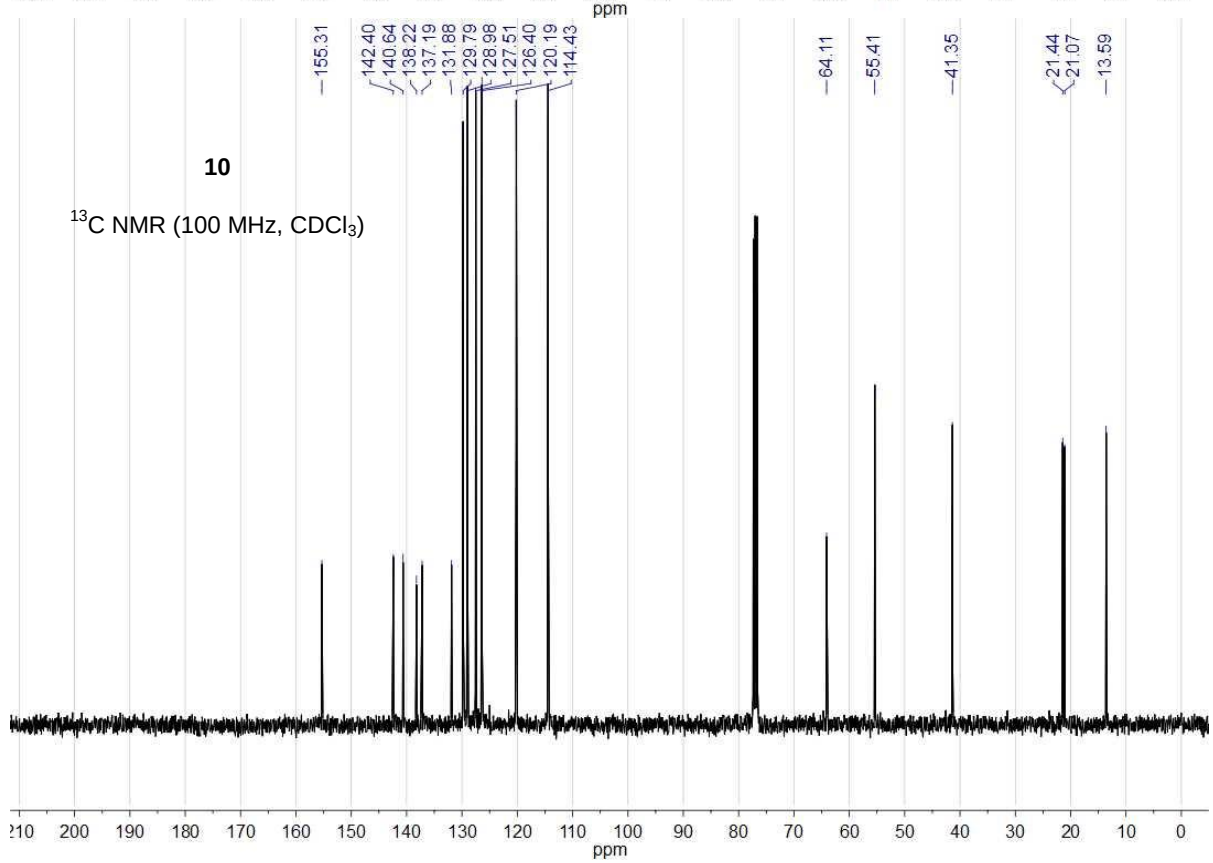
^{1}H NMR (400 MHz, $CDCl_3$)

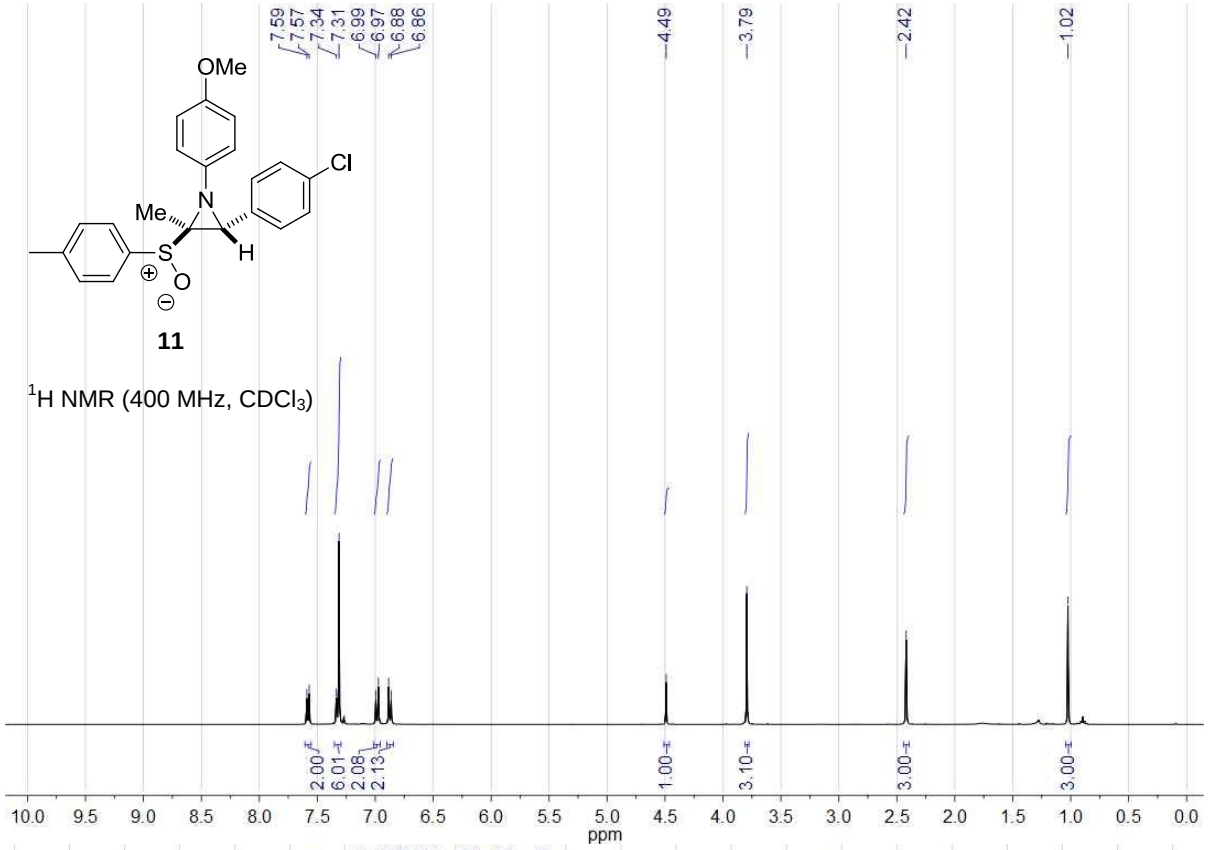


9

^{13}C NMR (100 MHz, $CDCl_3$)

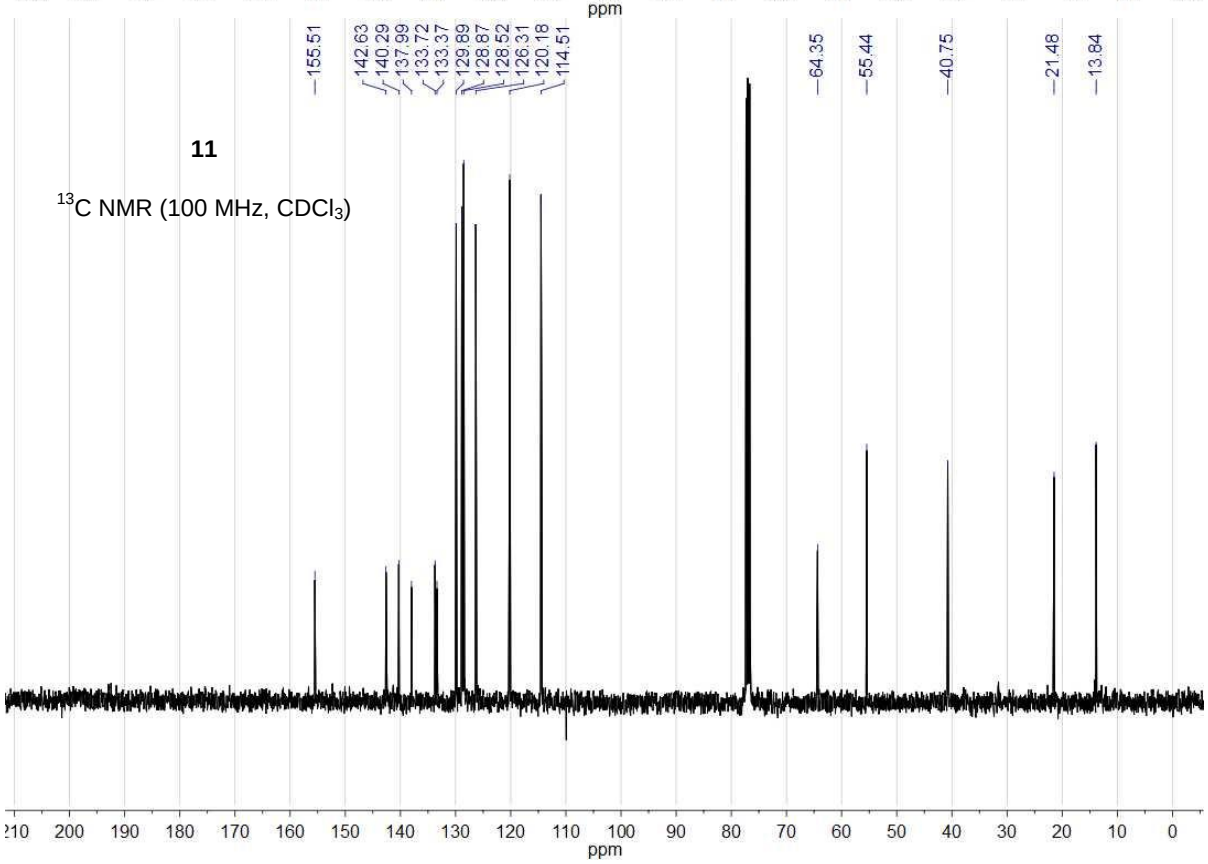

7.62
7.60
7.33
7.31
7.28
7.26
7.17
7.15
7.00
6.98
6.88
6.86
4.51
3.80
2.42
2.35
1.06
OMe
N
Me
S
O
H
10
1H NMR (400 MHz, CDCl3)
2.01
2.01
2.10
2.00
2.01
2.00
1.00
3.00
3.05
3.01
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


155.31
142.40
140.64
138.22
137.19
131.88
129.79
128.98
127.51
126.40
120.19
114.43
64.11
55.41
41.35
21.44
21.07
13.59
10
13C NMR (100 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm



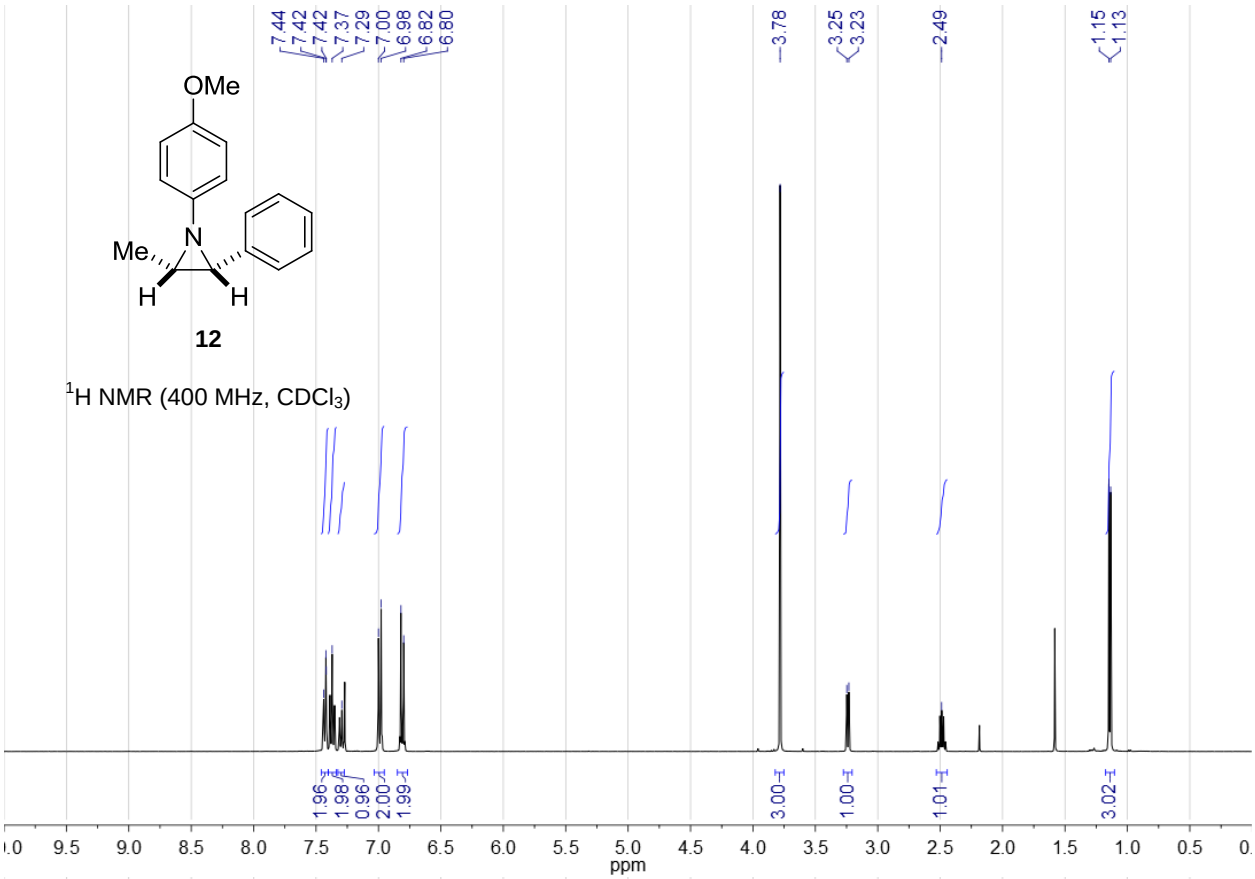
11

^{1}H NMR (400 MHz, $CDCl_3$)



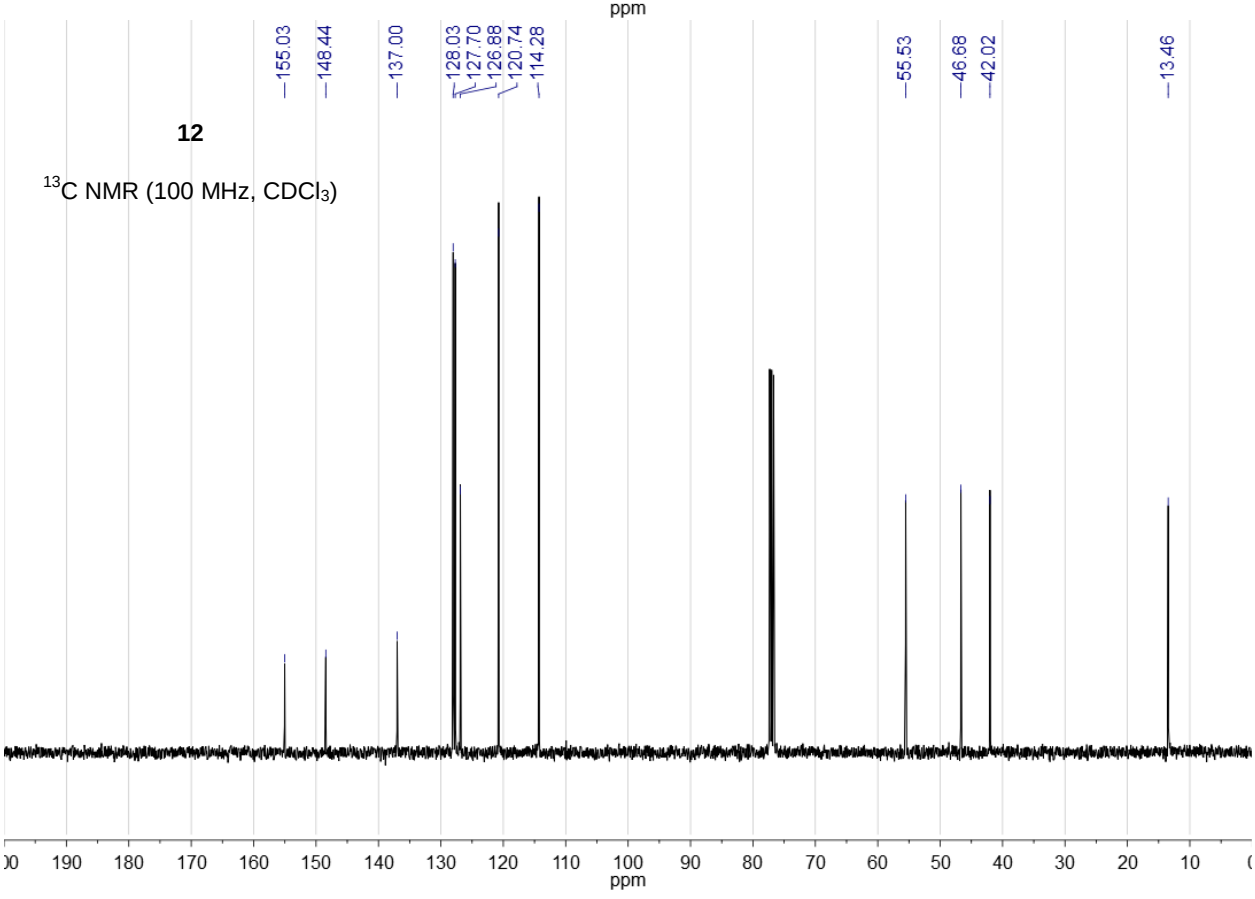
11

^{13}C NMR (100 MHz, $CDCl_3$)



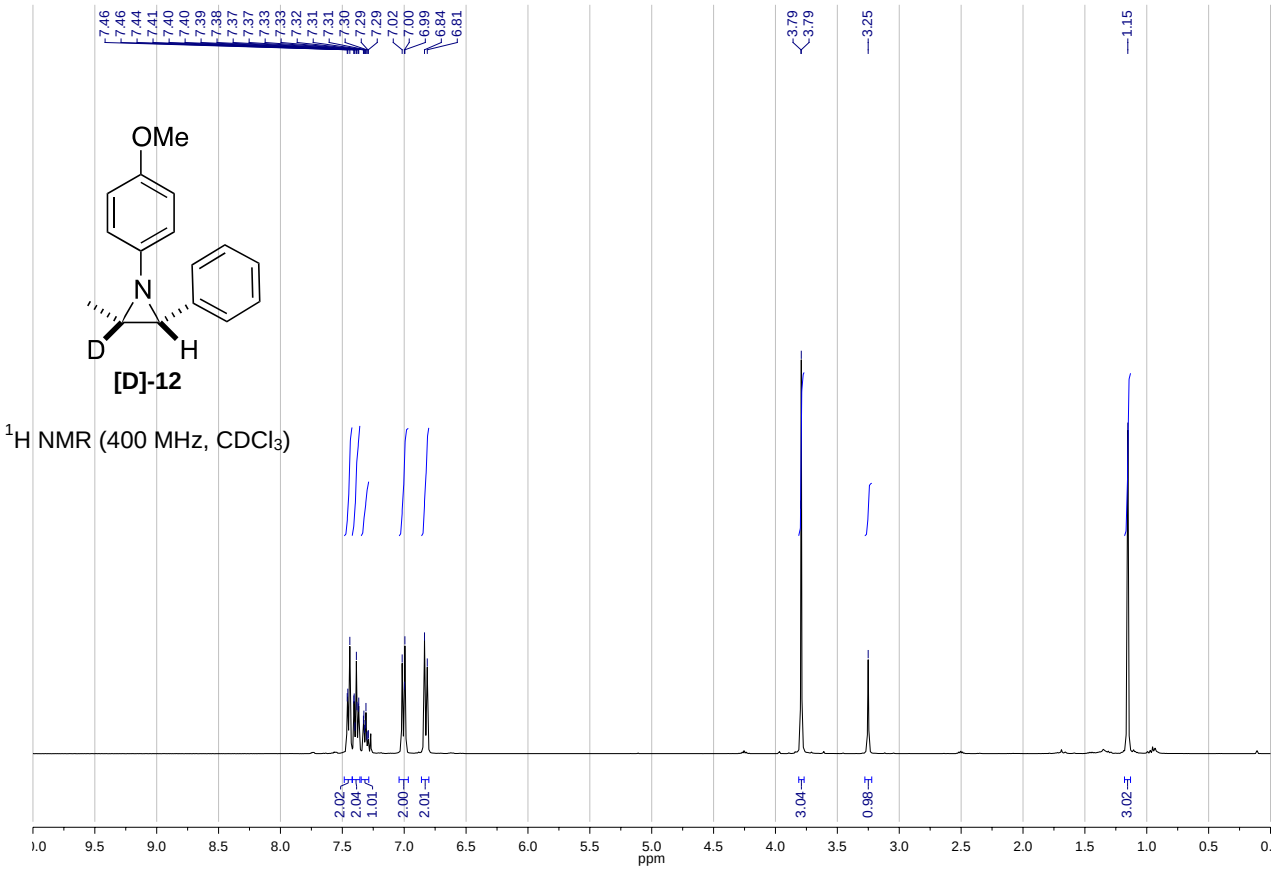
12

^{1}H NMR (400 MHz, $CDCl_3$)



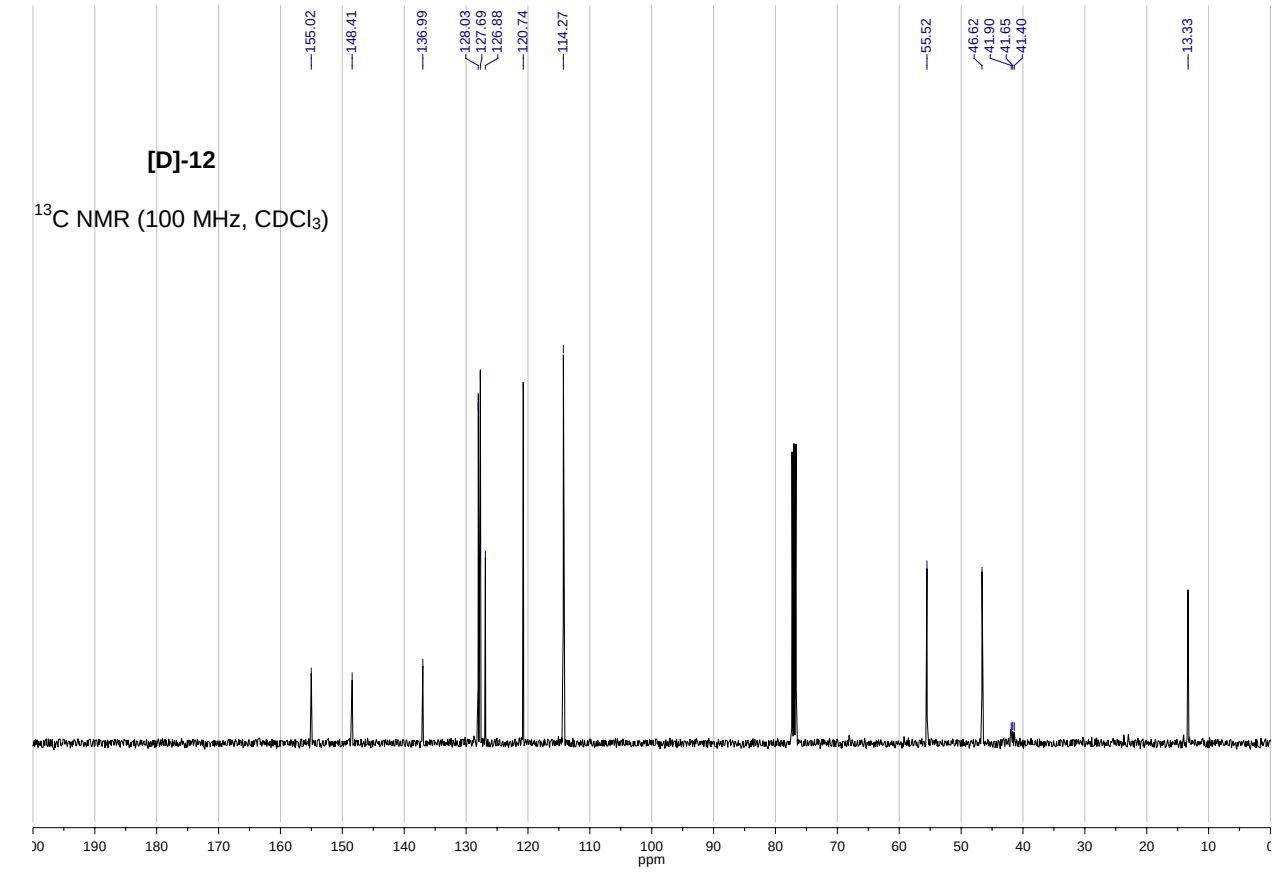
12

^{13}C NMR (100 MHz, $CDCl_3$)



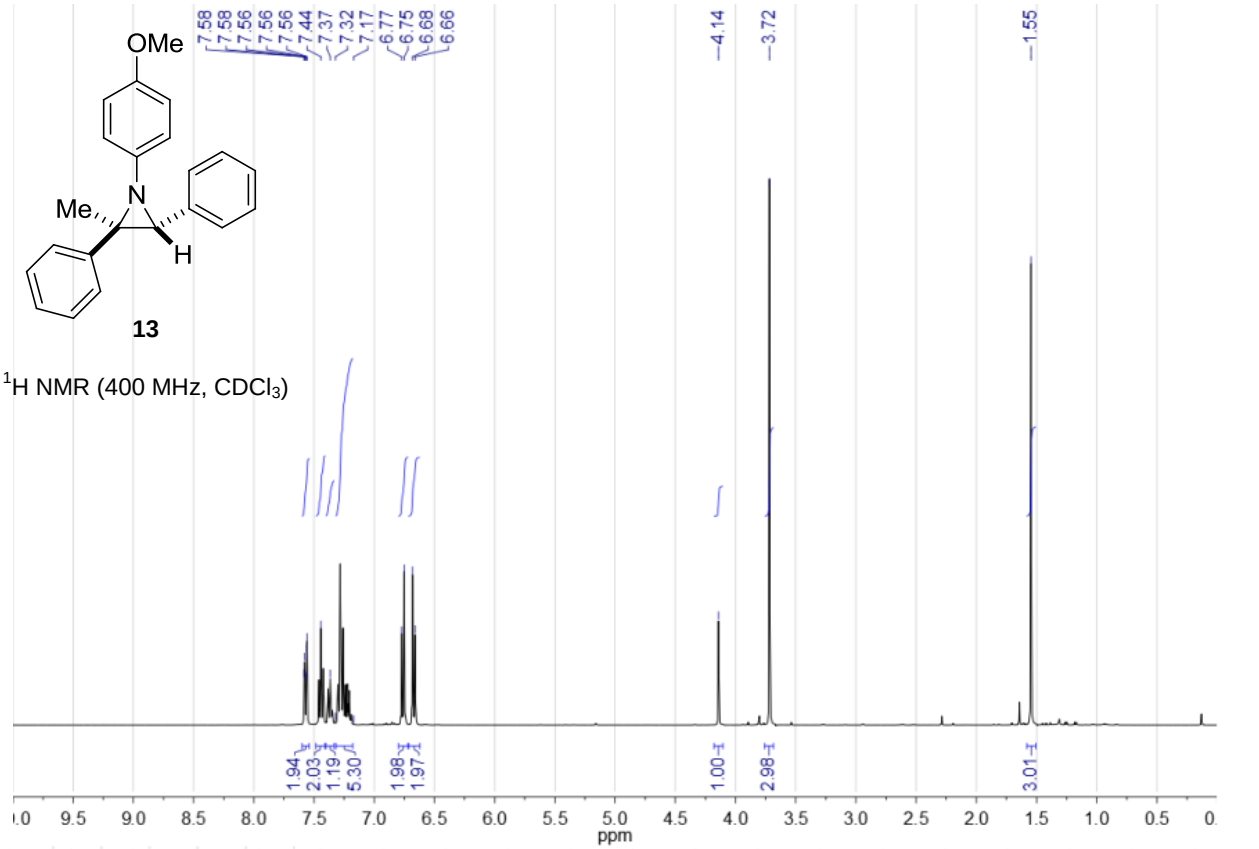
[D]-12

^{1}H NMR (400 MHz, $CDCl_3$)



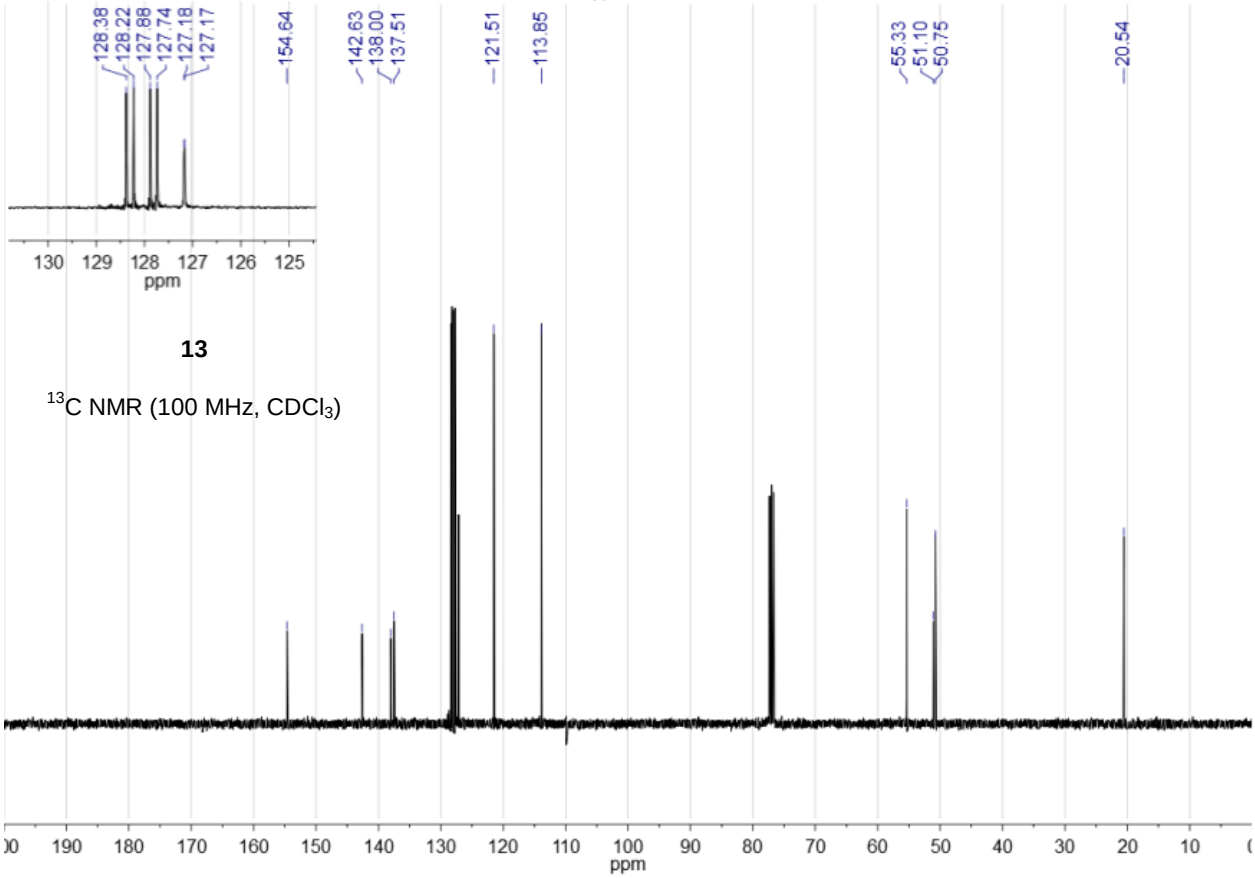
[D]-12

^{13}C NMR (100 MHz, $CDCl_3$)



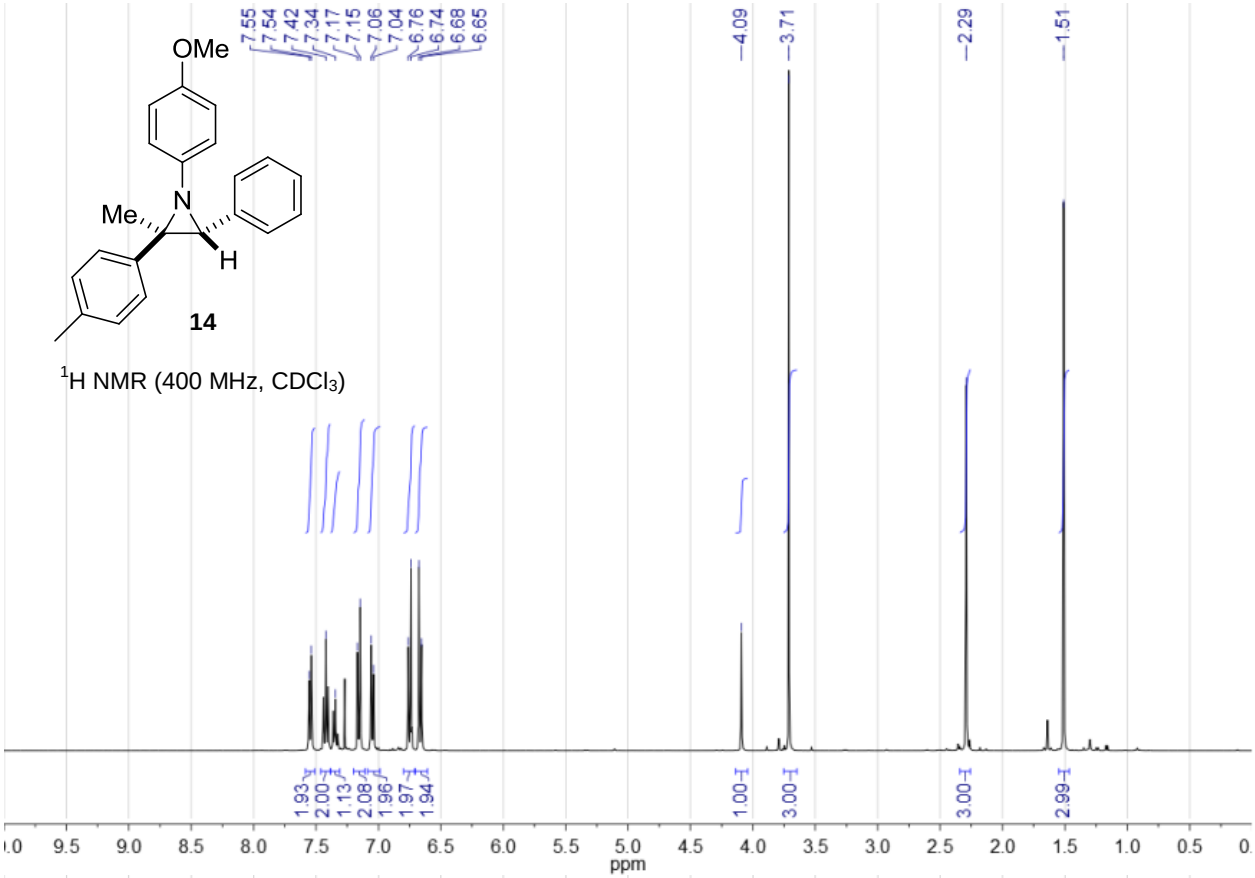
13

^{1}H NMR (400 MHz, $CDCl_3$)



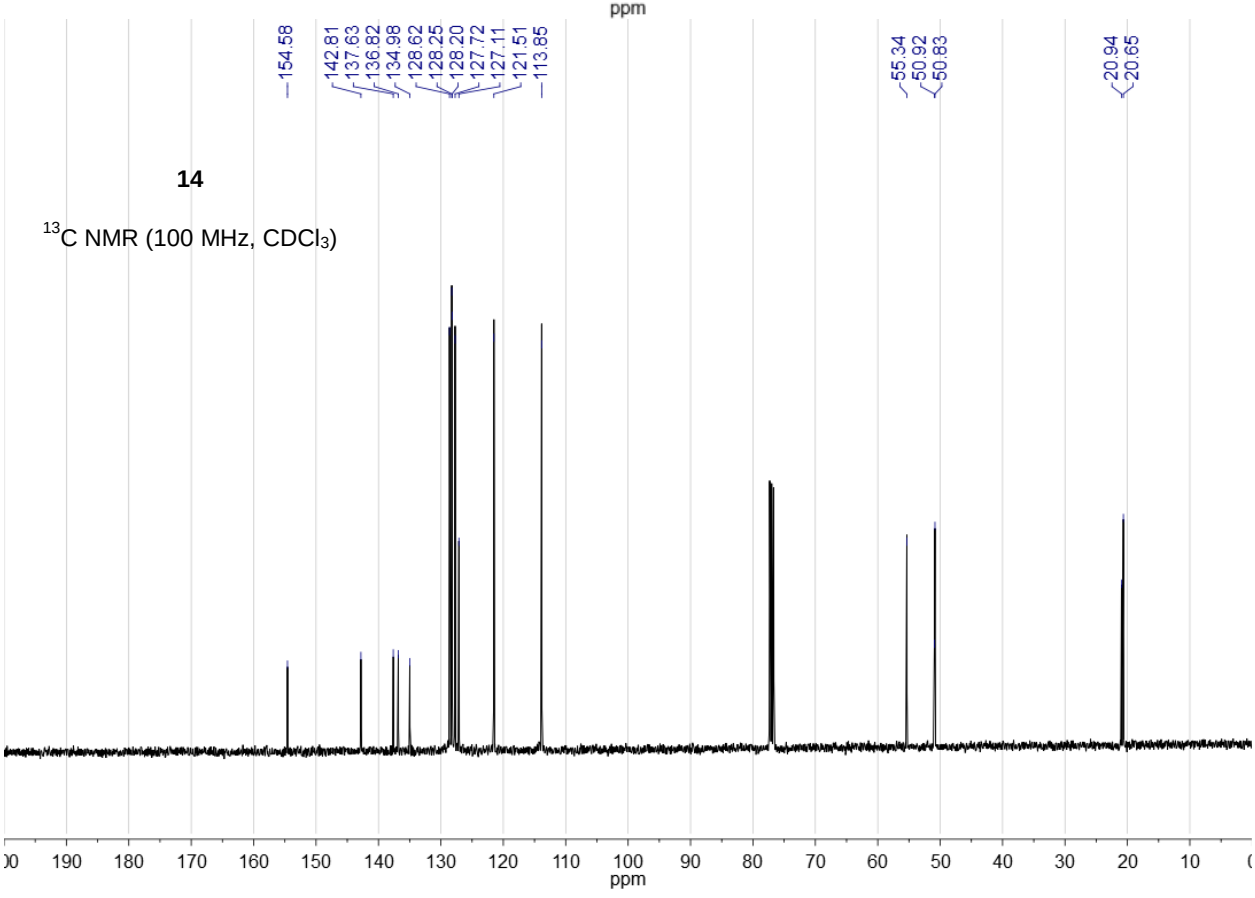
13

^{13}C NMR (100 MHz, $CDCl_3$)



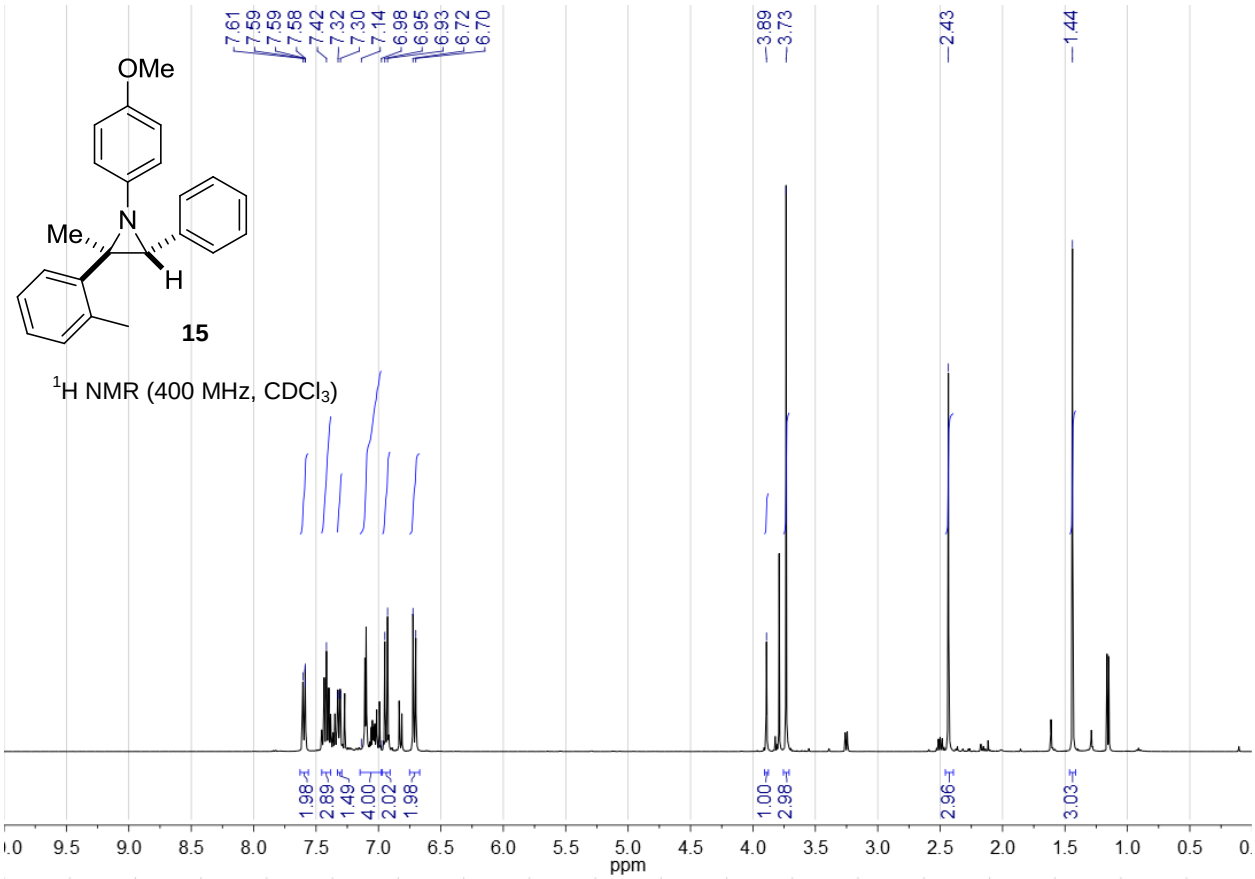
14

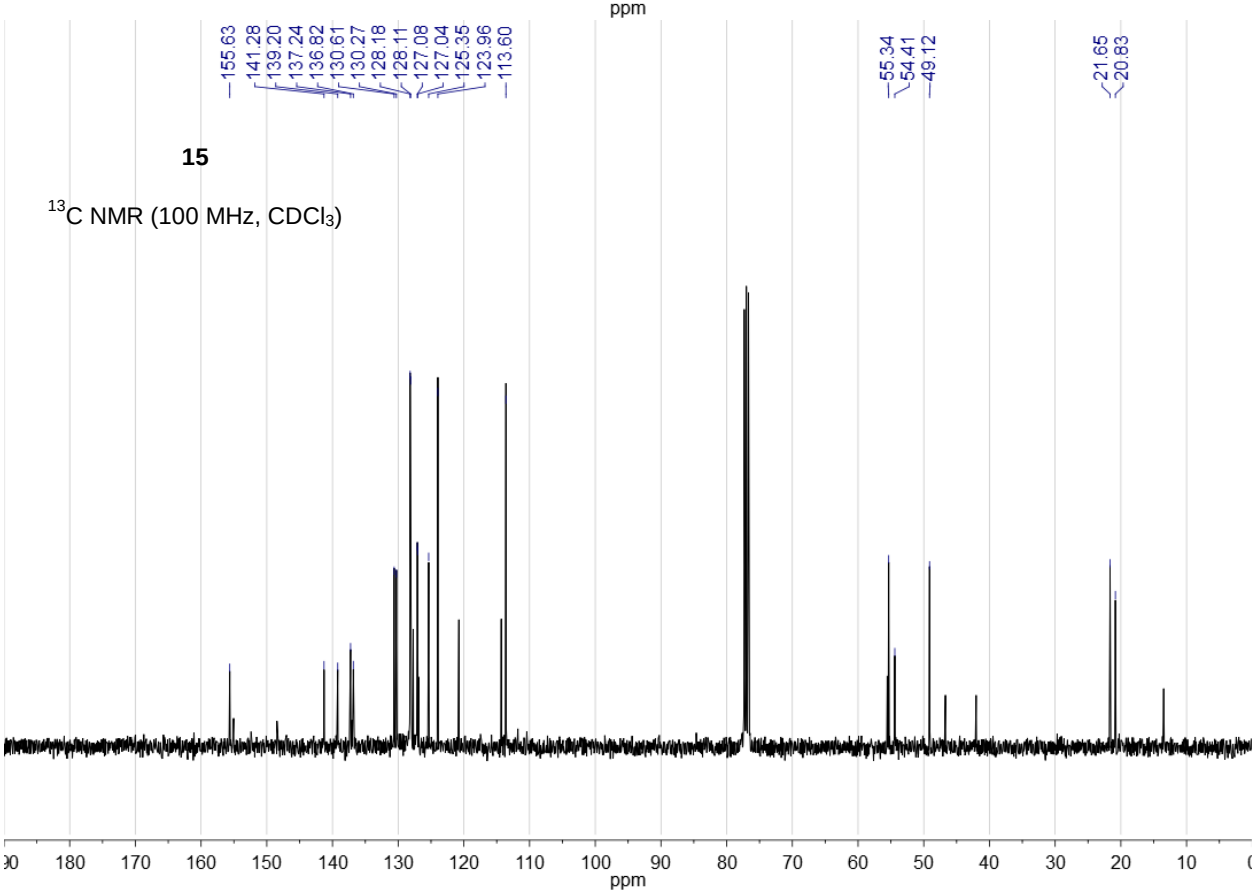
^{1}H NMR (400 MHz, $CDCl_3$)



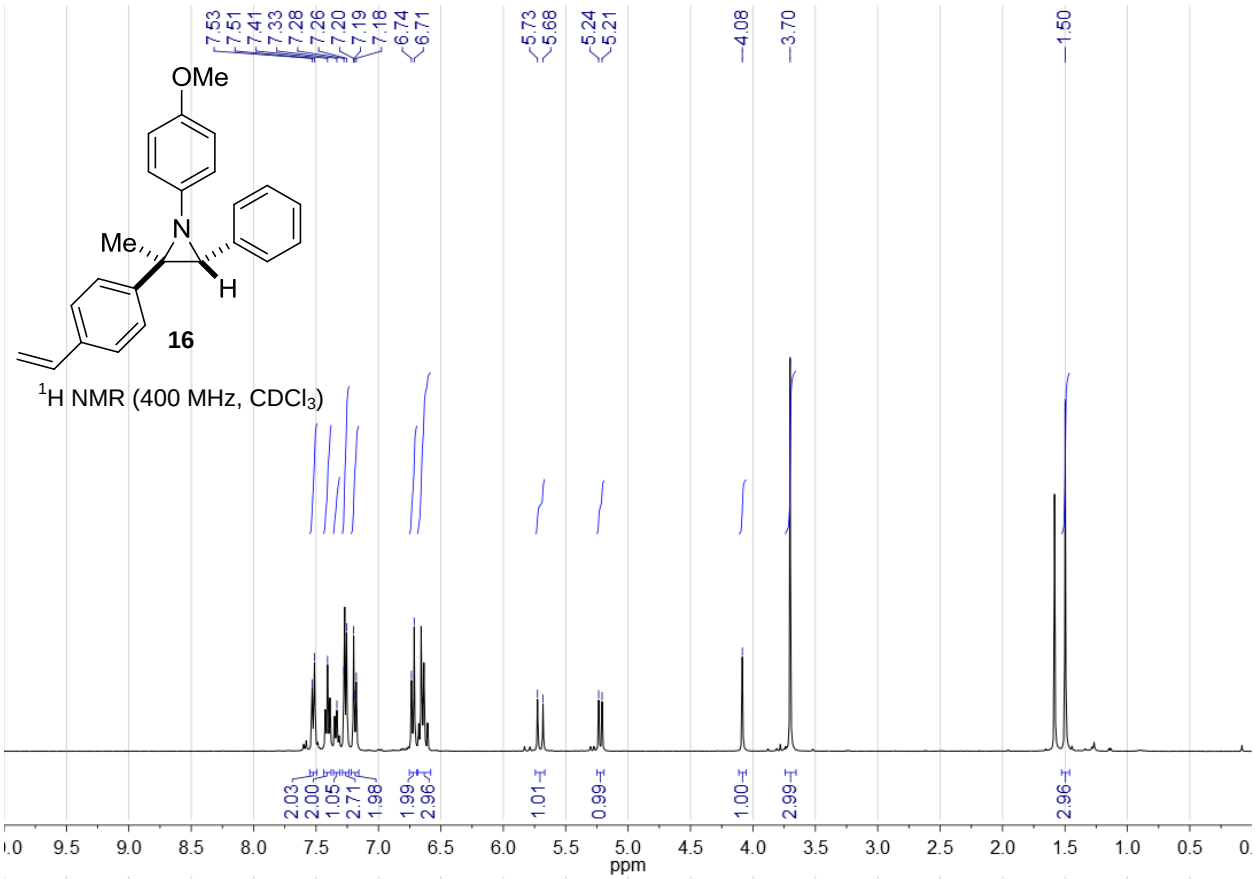
14

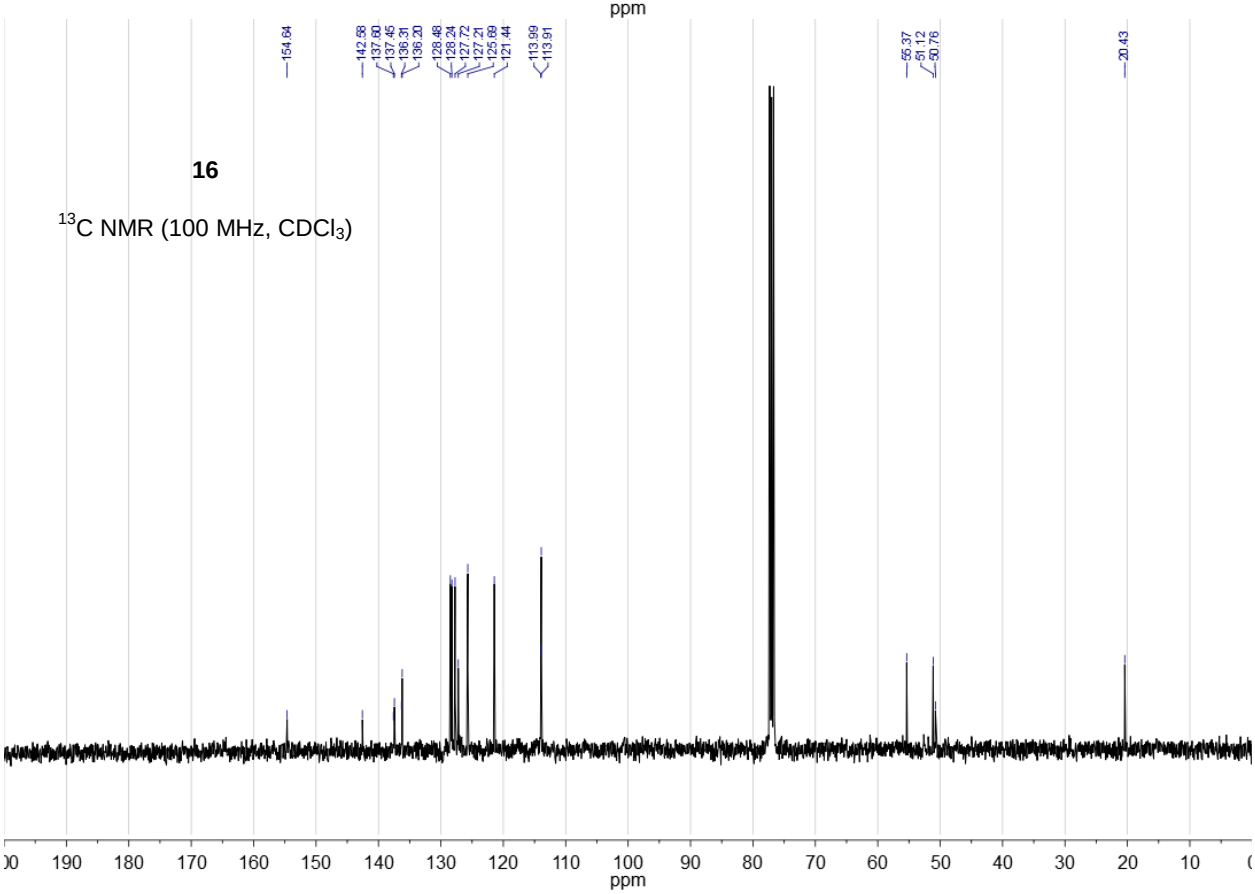
^{13}C NMR (100 MHz, $CDCl_3$)



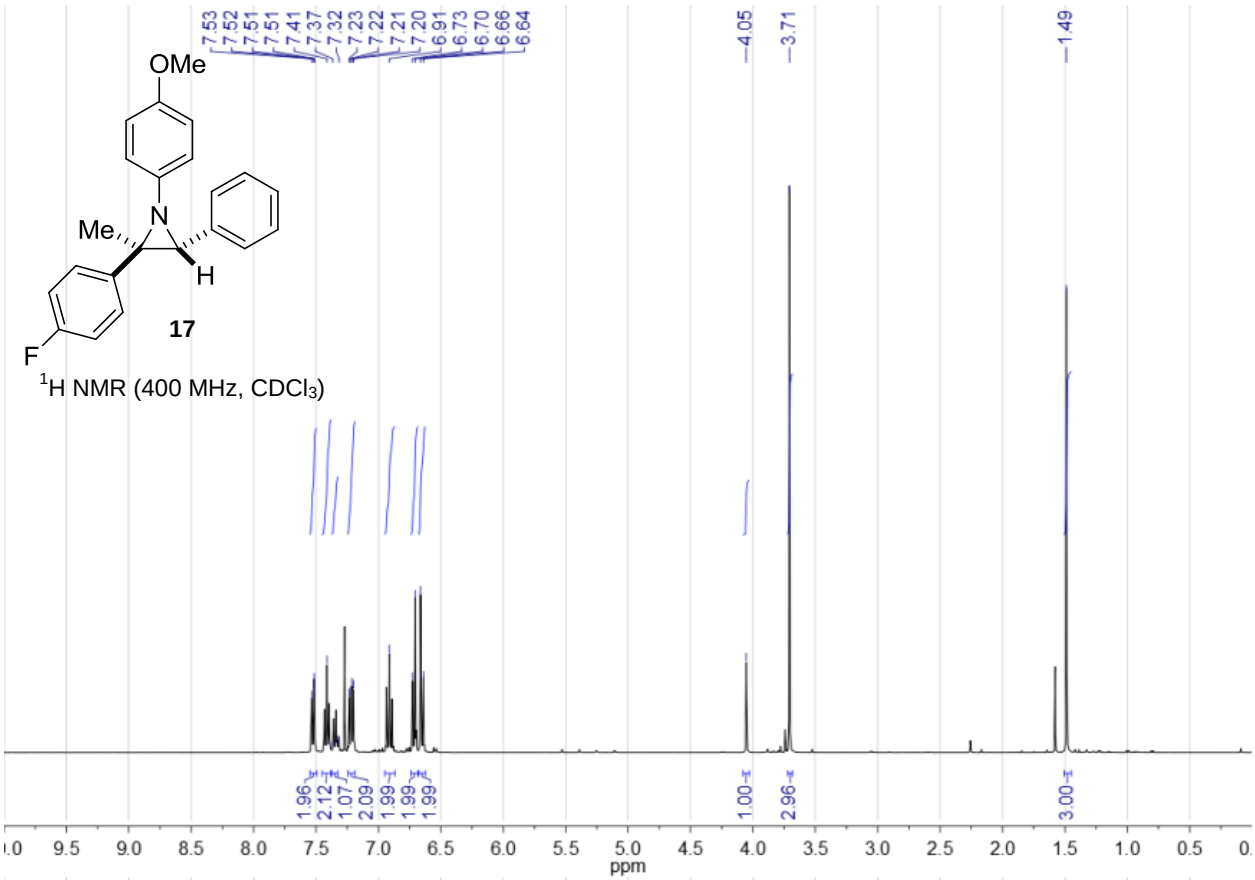


Note: Compound **15** was isolated as an inseparable mixture with aziridine **H-13** (28% **15**; 6% **H-13**).



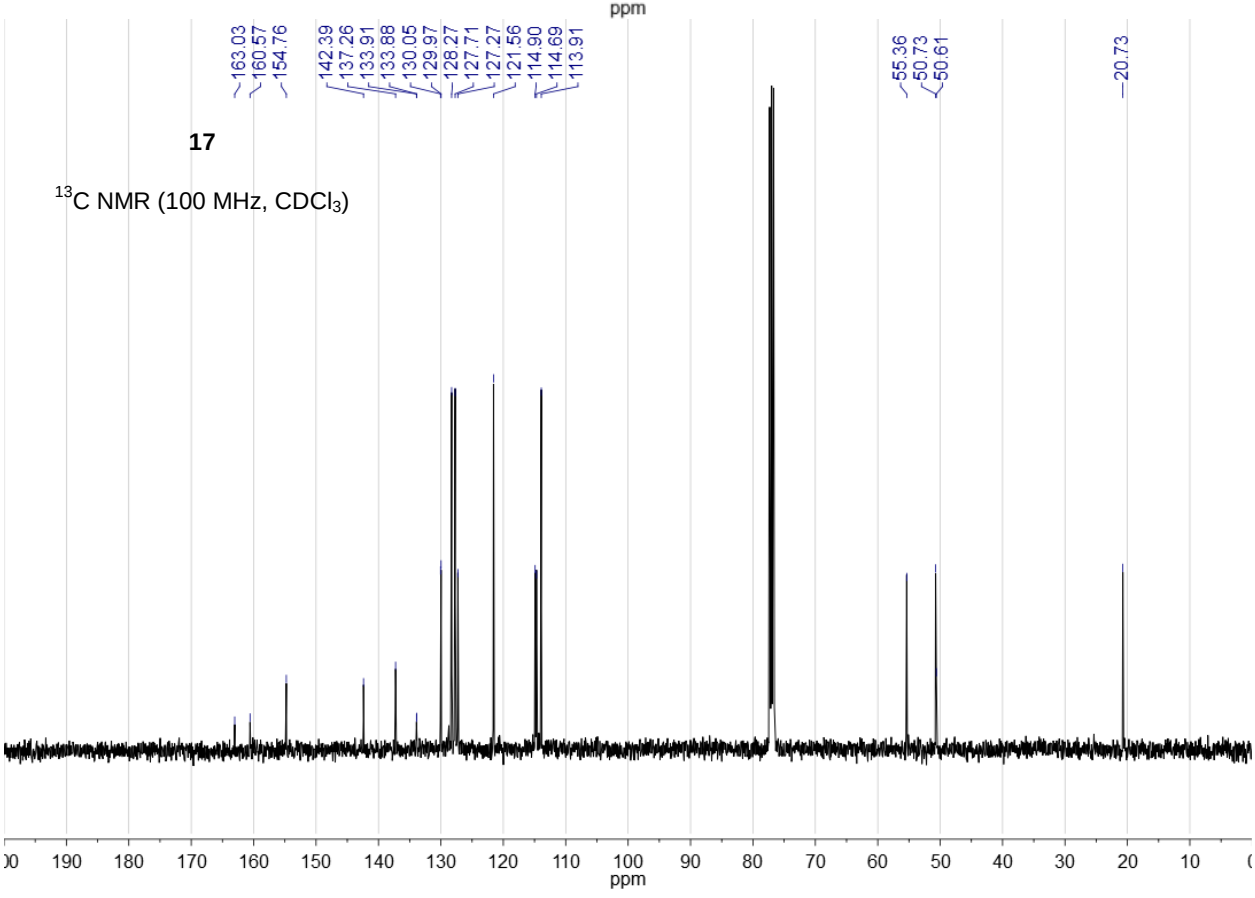


Note: Compound **16** was isolated as an inseparable mixture with Ar-Ar dimer (>9:1).



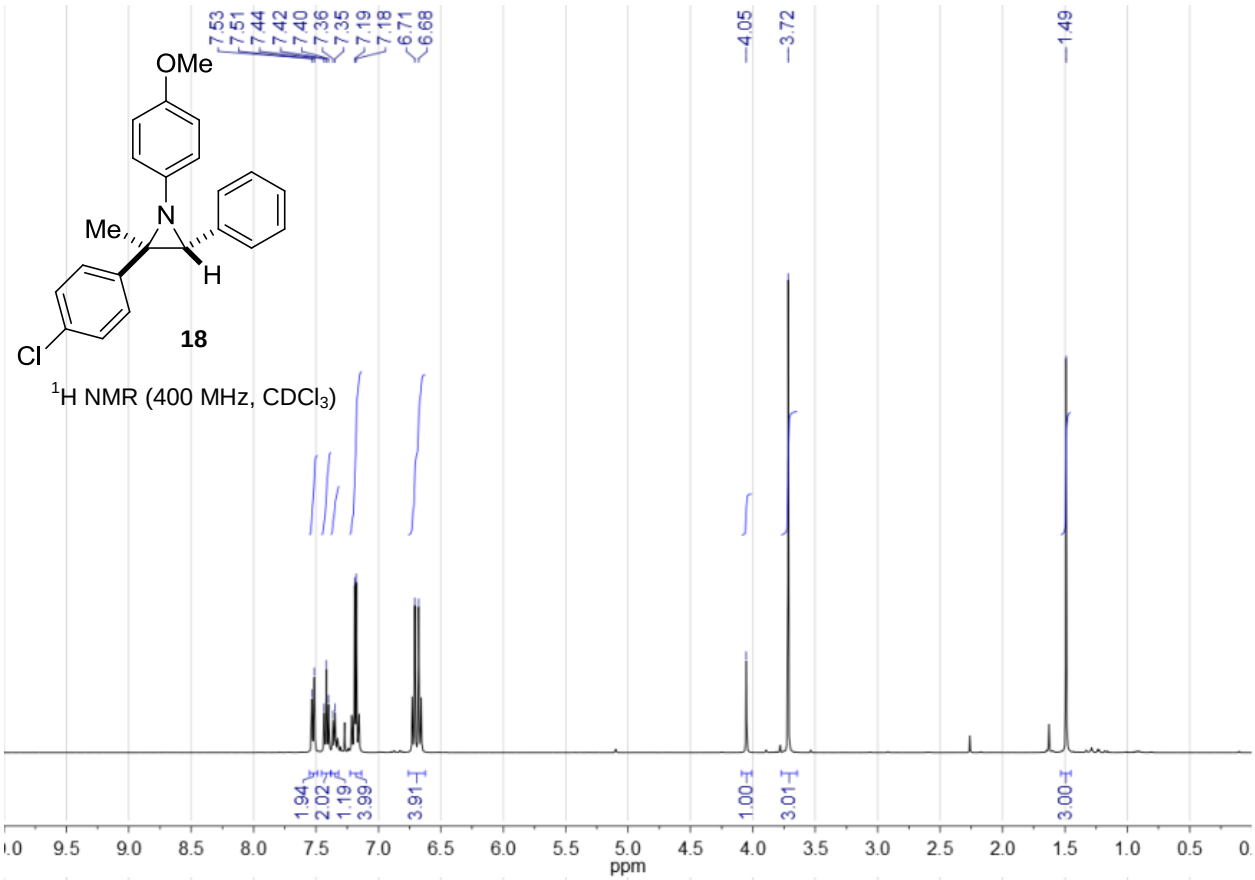
17

^{1}H NMR (400 MHz, $CDCl_3$)



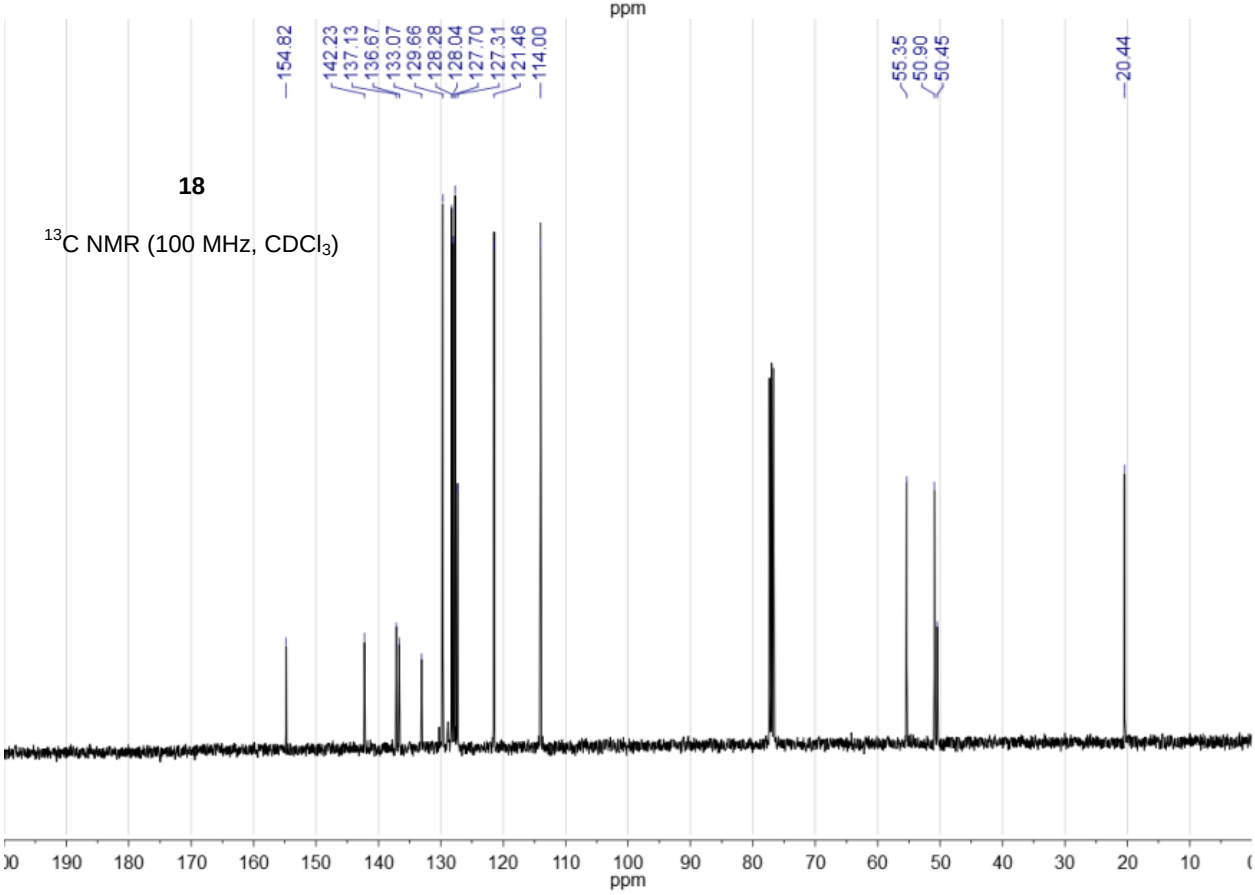
17

^{13}C NMR (100 MHz, $CDCl_3$)



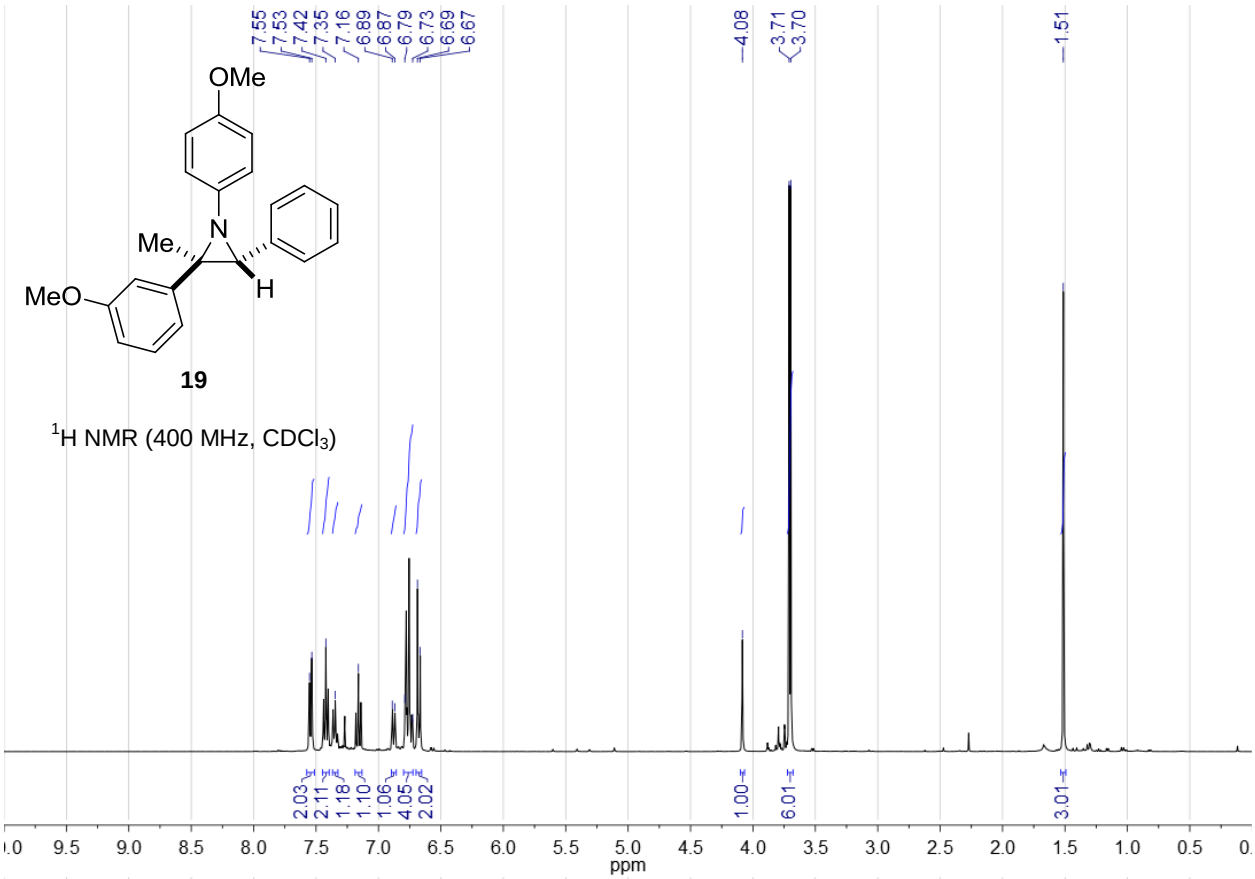
18

^{1}H NMR (400 MHz, $CDCl_3$)



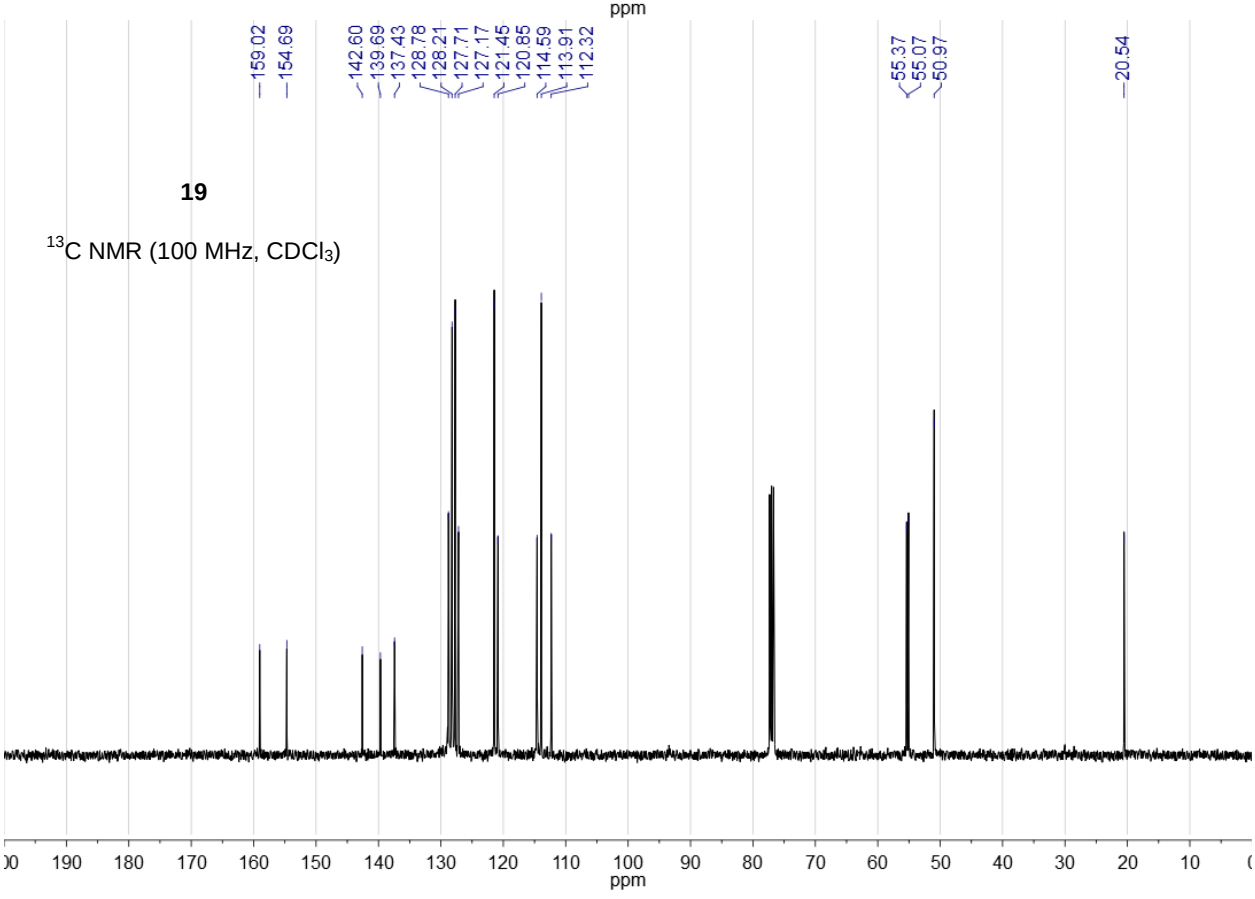
18

^{13}C NMR (100 MHz, $CDCl_3$)



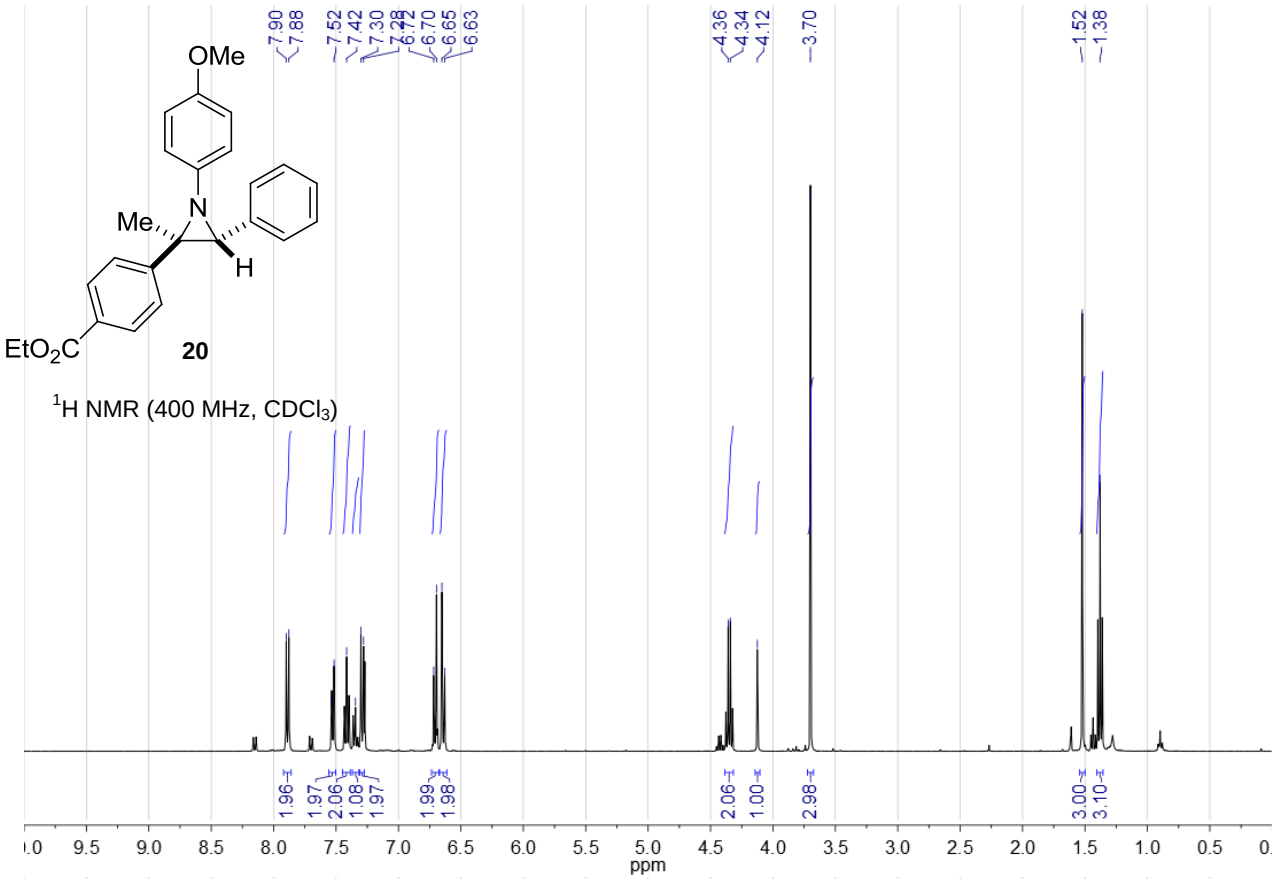
19

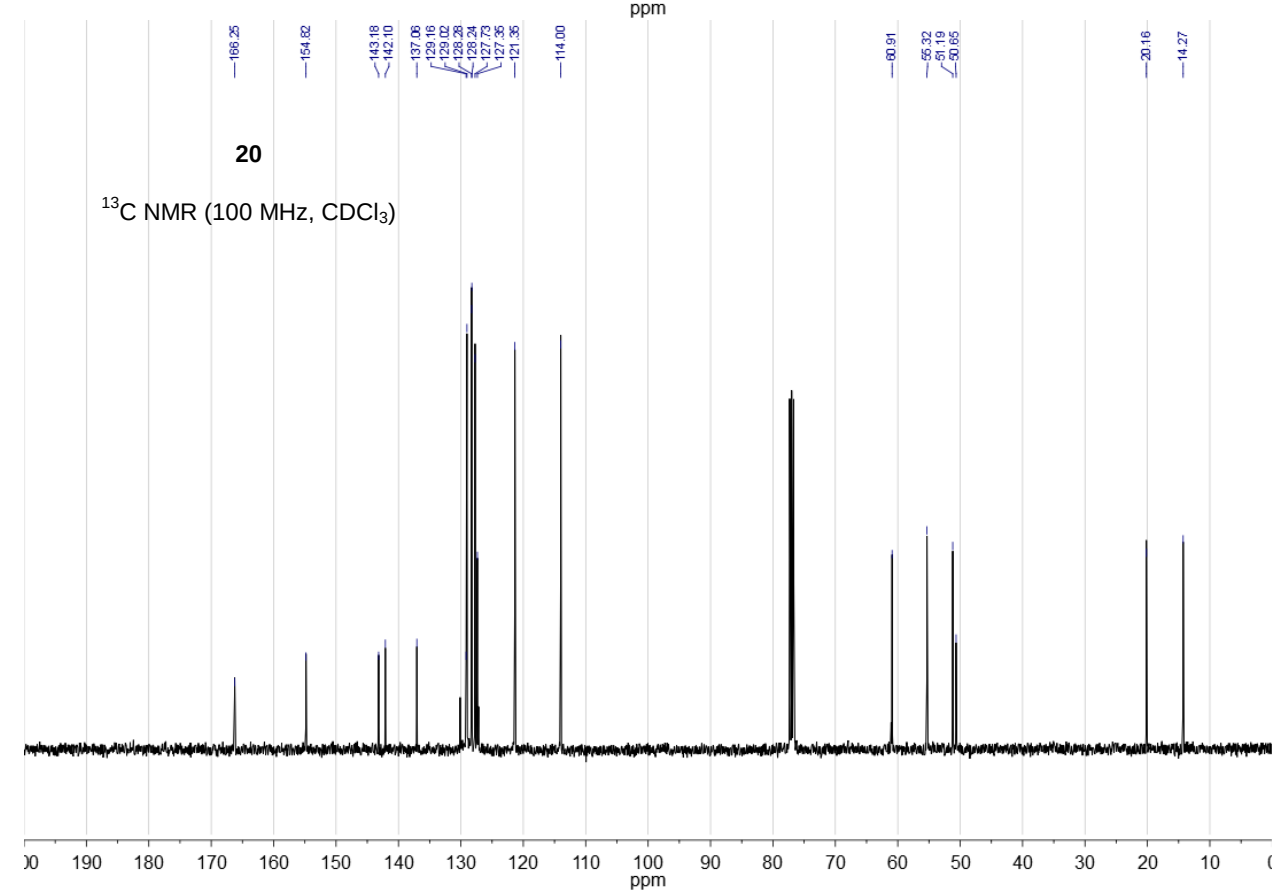
^{1}H NMR (400 MHz, $CDCl_3$)



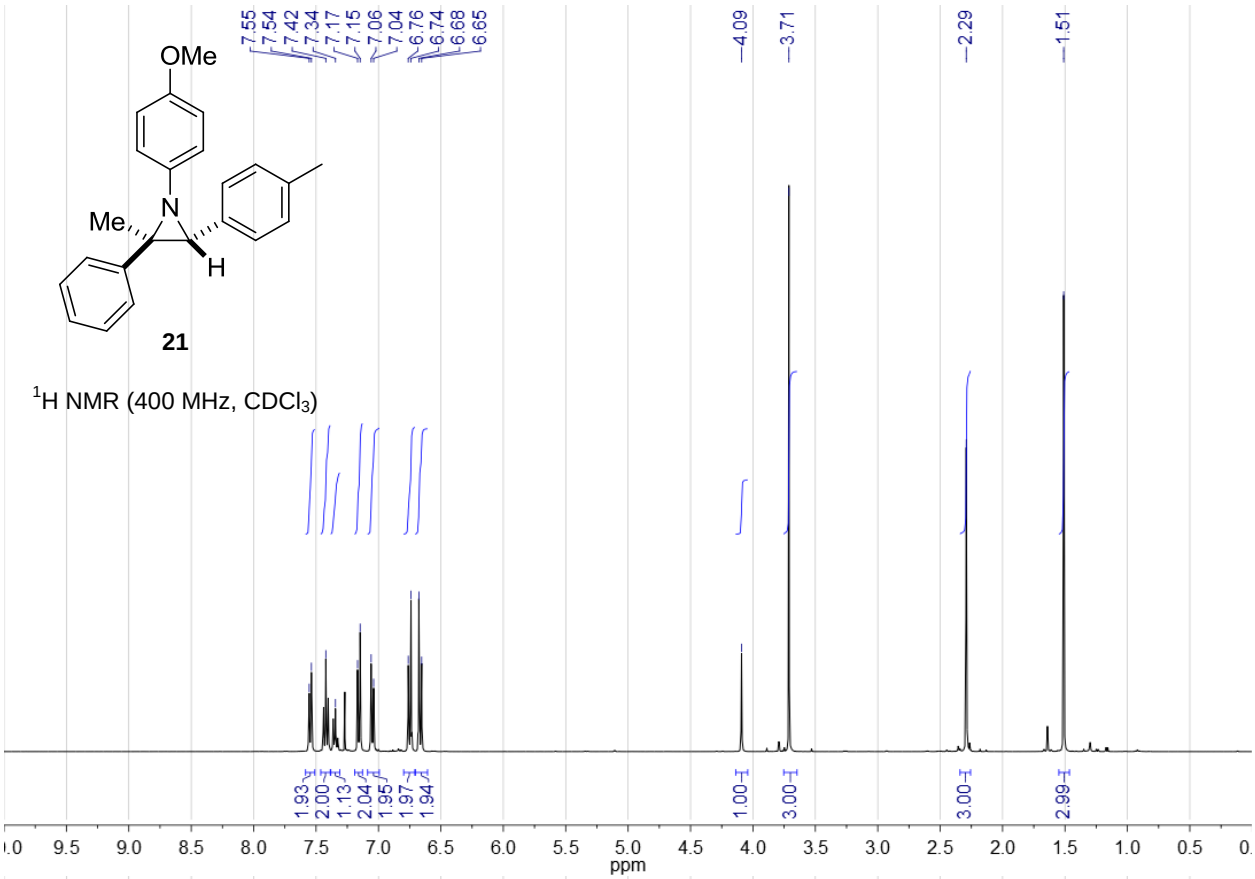
19

^{13}C NMR (100 MHz, $CDCl_3$)



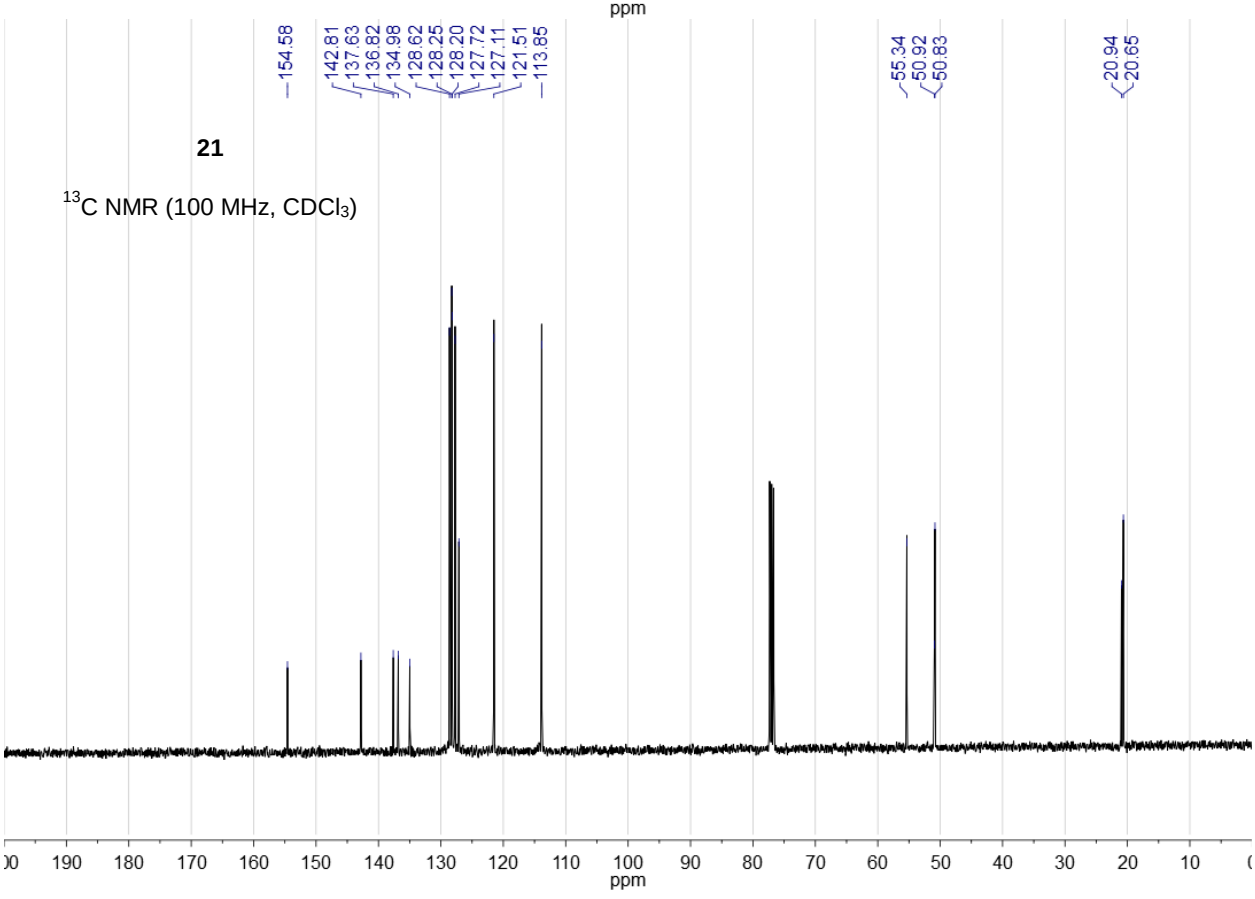


Note: Compound **20** was isolated as an inseparable mixture with Ar-Ar dimer (>9:1).



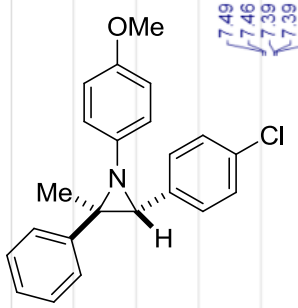
21

^{1}H NMR (400 MHz, $CDCl_3$)



21

^{13}C NMR (100 MHz, $CDCl_3$)

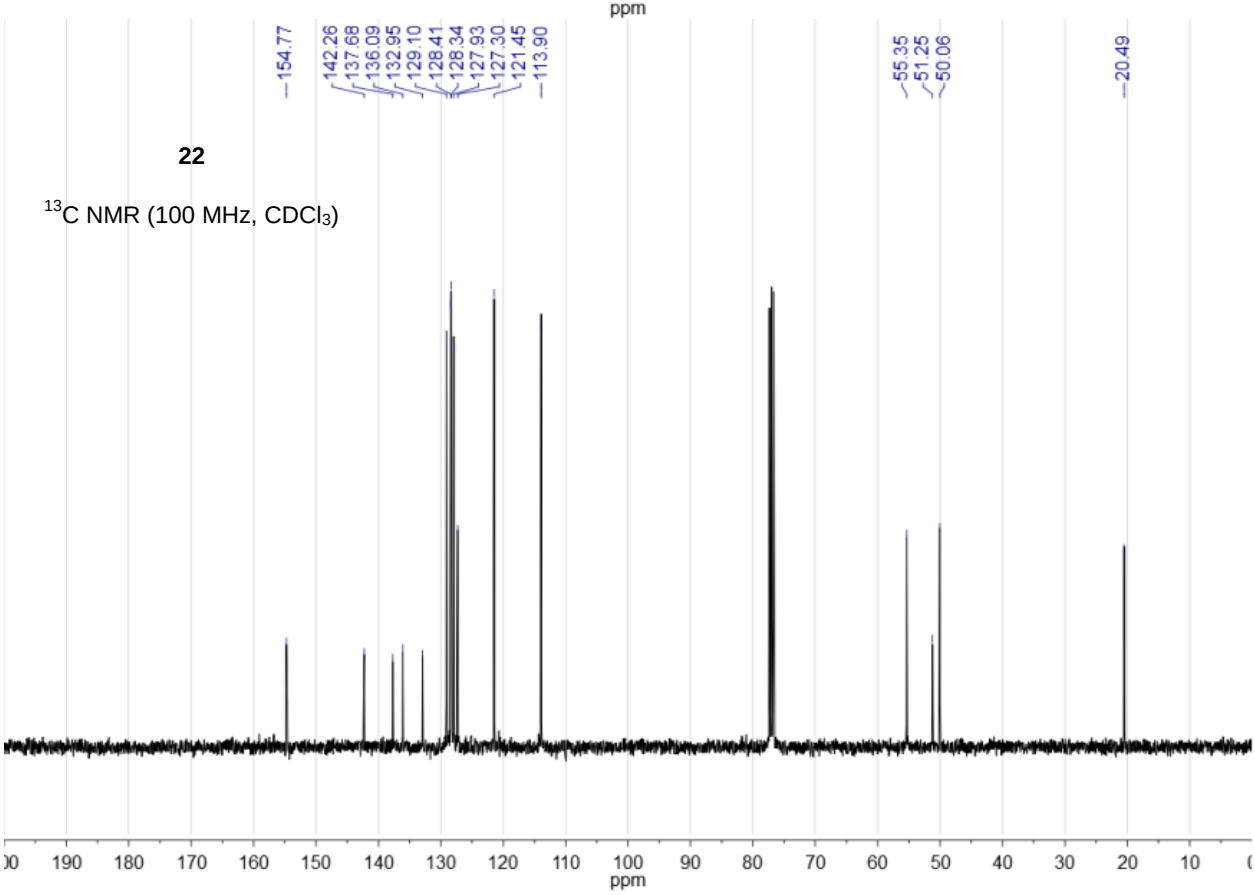


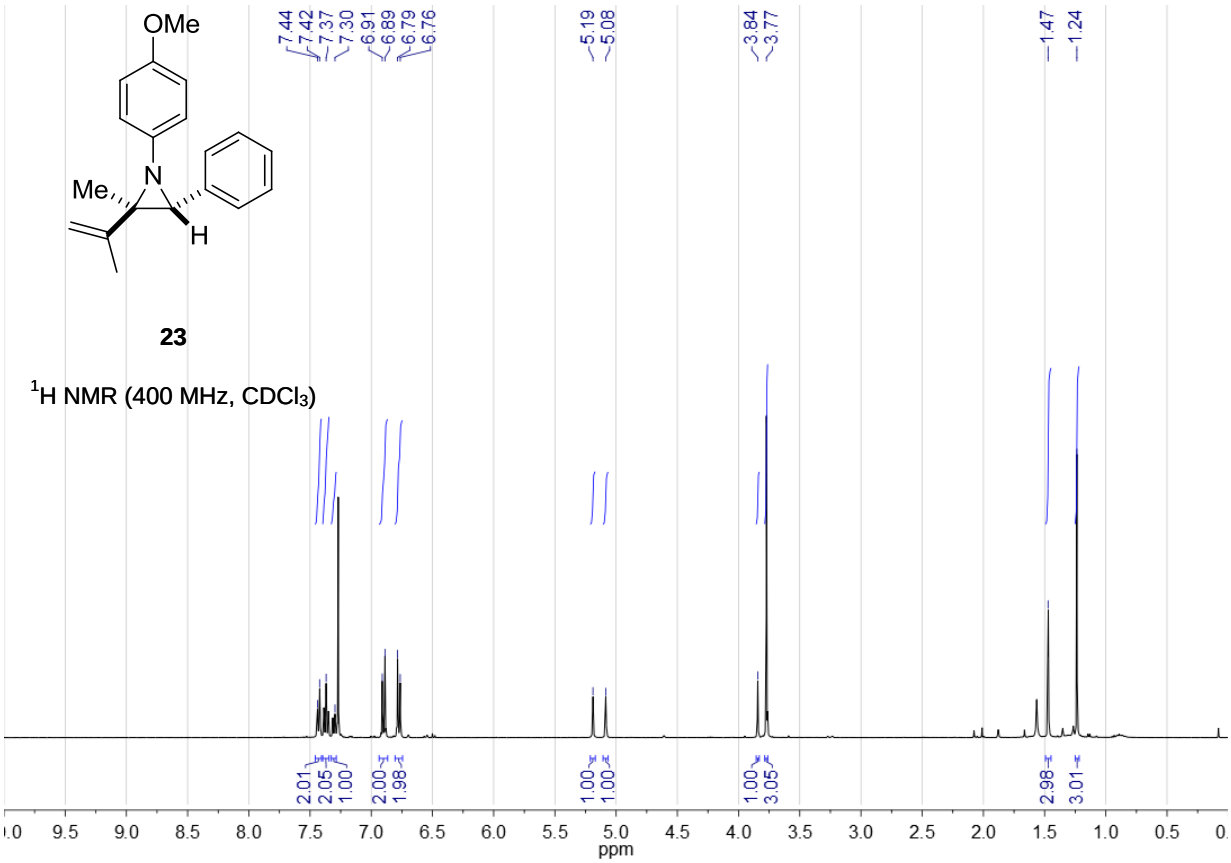
22

^{1}H NMR (400 MHz, $CDCl_3$)

22

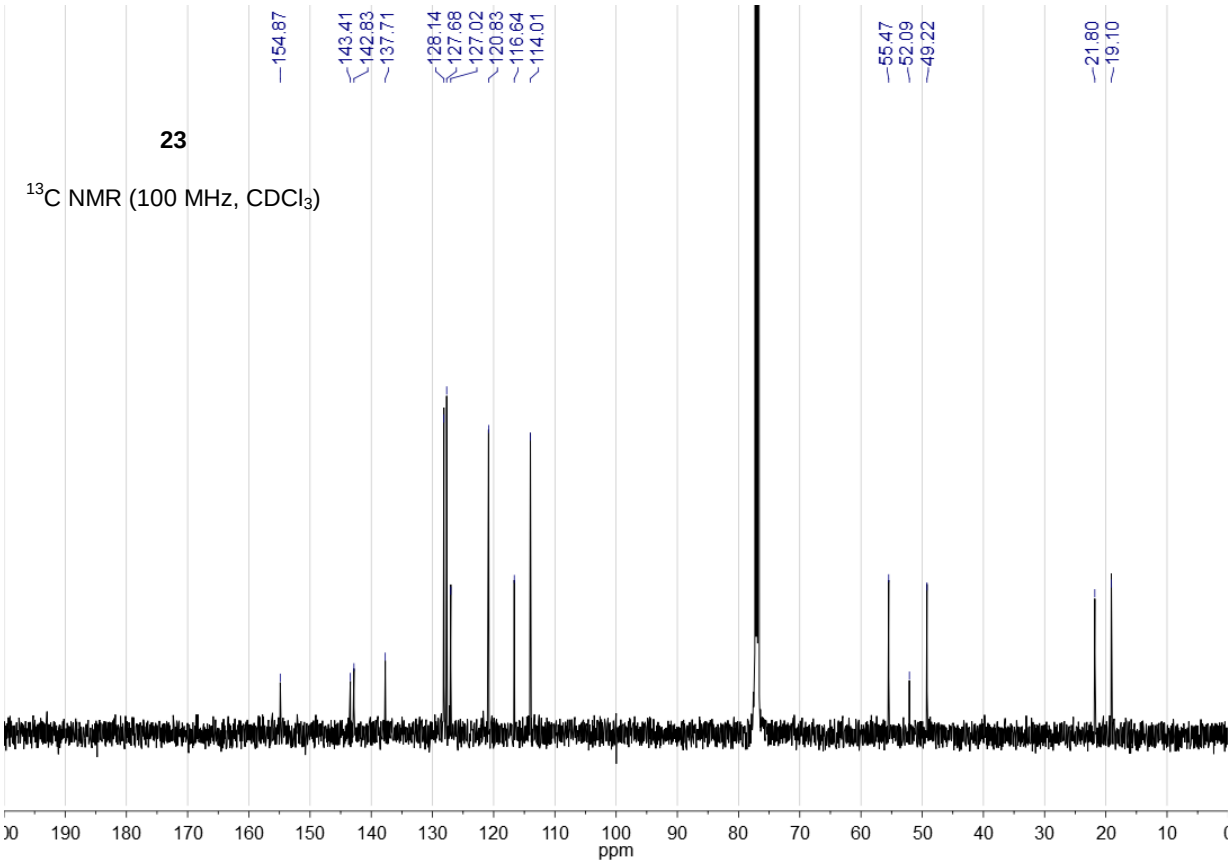
^{13}C NMR (100 MHz, $CDCl_3$)





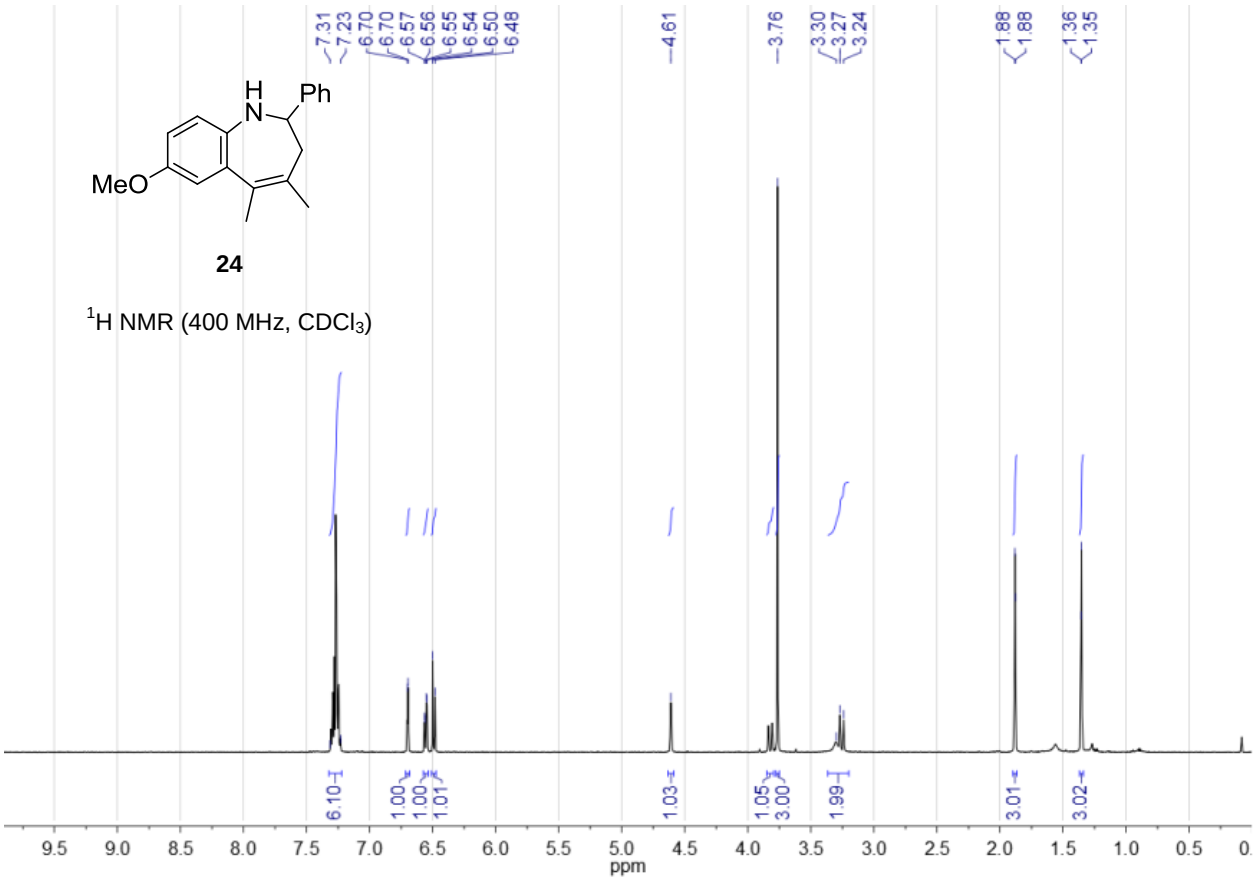
23

^{1}H NMR (400 MHz, $CDCl_3$)



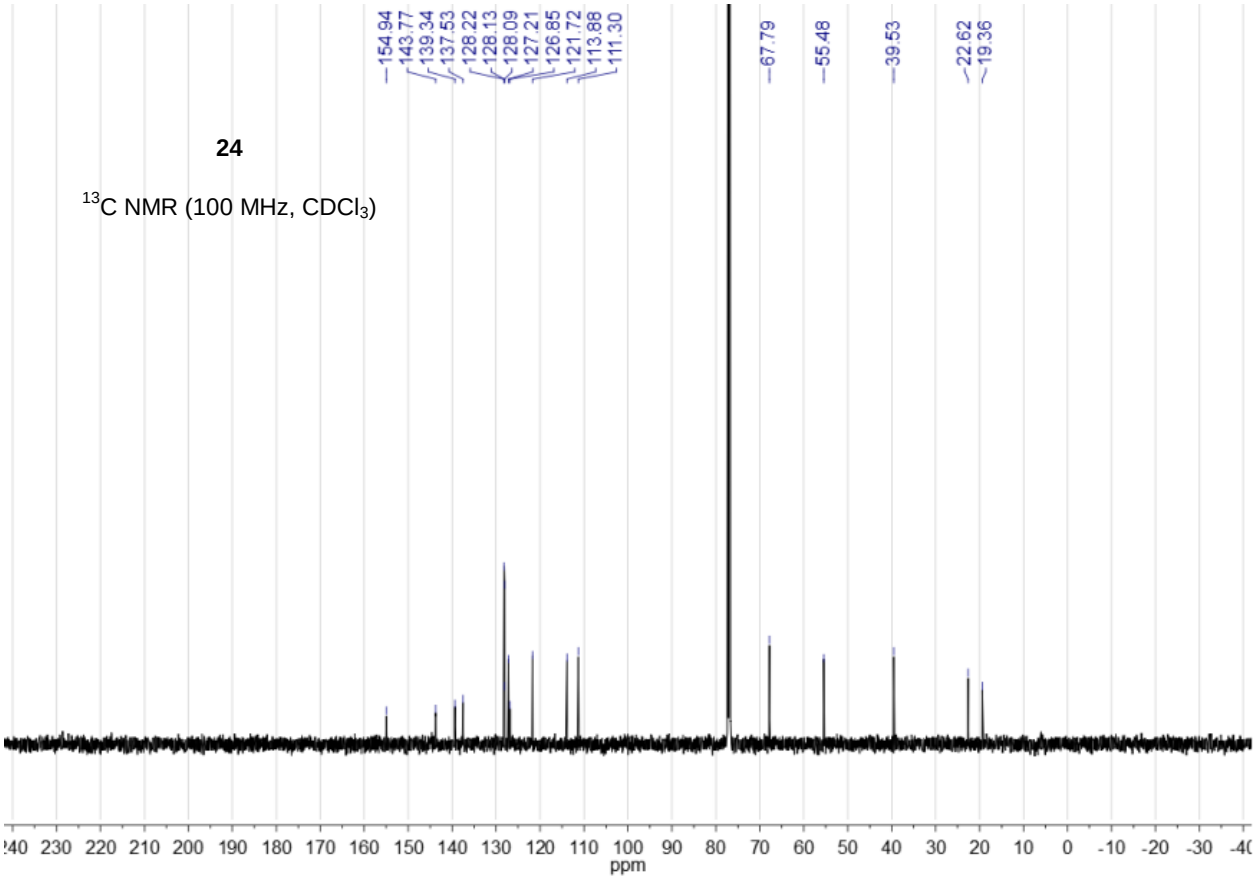
23

^{13}C NMR (100 MHz, $CDCl_3$)



24

^{1}H NMR (400 MHz, $CDCl_3$)



24

^{13}C NMR (100 MHz, $CDCl_3$)