

Electronic Supplementary Information for

**Copper(II)-mediated oxidative cyclization of enamides to oxazoles**

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## 1. General Considerations

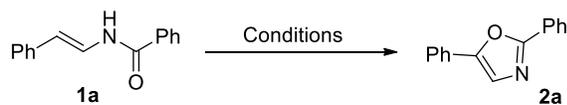
All commercially available compounds were purchased from Sigma-Aldrich, and used as received unless otherwise indicated. Solvents were dried over alumina columns prior to use; anhydrous 1,4-dioxane was used as received.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on Bruker AC-300 MHz or Varian Mercury-300 MHz spectrometers. Chemical shift values are given in parts per million relative to residual solvent peaks or TMS internal standard. Exact mass measurements were obtained by the mass spectrometry facility at the University of Wisconsin. Melting points were taken on a Mel-Temp II melting point apparatus. Gas Chromatography was done on a Shimadzu GC-17A using Shimadzu RTX-5MS (15m) column and referenced to an internal standard (trimethoxybenzene). Flash chromatography was performed using SilicaFlash® P60 (Silicycle, particle size 40-63  $\mu\text{m}$ , 230-400 mesh) from Sigma Aldrich.

## 2. Procedure for Reaction Screening

Reaction screening was carried out as follows. Under ambient air, a 1.5dr vial containing a flea stirbar was loaded with 10mg (0.045mmol) of *N*-[(*E*)-2-phenylethenyl]benzamide, **1**, followed by the addition of 12.1mg (0.09mmol) of anhydrous  $\text{CuCl}_2$ . Anhydrous 1,4-dioxane was added (0.5mL), followed by 7.2uL of *N*-methylimidazole. The vial was sealed firmly with a Teflon cap, and a dark blue coloration was observed. (If  $\text{N}_2$  or  $\text{O}_2$  atmosphere was desired the vial was equipped at this point with a septum, and flushed for 5-7minutes with dry  $\text{O}_2$  or  $\text{N}_2$  before being sealed with a Teflon cap. The vial(s) were then clamped in an oil bath already stabilized at 140  $^\circ\text{C}$ , and heated with gentle stirring for 20 h (although timecourse studies indicate that reaction is 90% complete after around 6hrs). Within 5 minutes of heating, the reaction had turned from dark blue to green. By the end of the reaction vials contained a clear to pale yellow solution with a black residue at the bottom. Vials were removed from heat and allowed to cool. Samples were diluted with 3mL EtOAc, and 1mL of internal standard stock solution (1,3,5-trimethoxybenzene in EtOAc) was added. Approximately 0.5 to 1.0 mL of saturated  $\text{Na}_2\text{S}$  solution was then added and the vial was shaken vigorously to precipitate out  $\text{CuS}$  salts. An aliquot of the organic phase was then filtered through celite and analyzed by Gas Chromatography. Yields were determined by comparison with internal standard, with retention factor corrections previously ascertained through calibration curves.

### 3. Additional screening Table, S1

Table S1. Additional Screening Data<sup>a</sup>

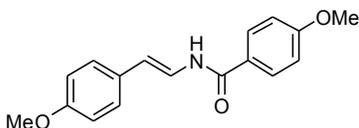


Entry	Cu Source	Solvent	Additive	Temp	% yield <sup>b</sup>
1.	15% Cu(OAc) <sub>2</sub>	DMSO	5eq AcOH	100C	<1 %
2.	20% Cu(OTf) <sub>2</sub>	<i>o</i> -xylene	-----	140C	<1 %
3.	20% Cu(OTf) <sub>2</sub>	toluene	-----	140C	<1 %
4.	20% Cu(OAc) <sub>2</sub>	toluene	-----	140C	1.7%
5.	20% Cu(OAc) <sub>2</sub>	toluene	2.0 eq pyridine	140C	<1 %
6.	20% Cu(OAc) <sub>2</sub>	toluene	2.0 eq NaOAc	140C	<1 %
7.	20% Cu(OAc) <sub>2</sub>	toluene	5.0 eq AcOH	140C	<1 %
8.	200% Cu(OAc) <sub>2</sub>	toluene	-----	140C	5.8 %
9.	200% CuCl <sub>2</sub>	toluene	-----	140C	7.9 %
10.	200% CuCl <sub>2</sub>	toluene	3.0 eq NaHCO <sub>3</sub>	140C	7.9%
11.	200% CuCl <sub>2</sub>	toluene	3.0 eq Na <sub>2</sub> CO <sub>3</sub>	140C	4.1%
12.	200% CuCl <sub>2</sub>	toluene	3.0 eq K <sub>2</sub> CO <sub>3</sub>	140C	5.1%
13.	200% CuCl <sub>2</sub>	toluene	3.0 eq Cs <sub>2</sub> CO <sub>3</sub>	140C	2.5%
14.	200% CuCl <sub>2</sub>	toluene	3.0 eq NaOAc	140C	9.4%
15.	200% CuCl <sub>2</sub>	toluene	0.8 eq pyridine	140C	14.4%
16.	200% CuCl <sub>2</sub>	toluene	0.8 eq imidazole	140C	19.2%
17.	200% CuCl <sub>2</sub>	toluene	0.8 eq DBU <sup>c</sup>	140C	17.8%
18.	200% CuCl <sub>2</sub>	toluene	0.8 eq DABCO <sup>d</sup>	140C	2.3%
19.	200% CuCl <sub>2</sub>	toluene	0.8 eq pyrrolidine	140C	18.6%
20.	200% CuCl <sub>2</sub>	toluene	0.8 eq bipy	140C	3.5%
21.	200% CuCl <sub>2</sub>	toluene	0.8 eq phen	140C	1.9%
22.	200% CuCl <sub>2</sub>	toluene	0.4 eq bipy	140C	3.9%
23.	200% CuCl <sub>2</sub>	toluene	0.4 eq phen	140C	5.0%
24.	200% CuCl <sub>2</sub>	toluene	0.3 eq DMAP	140C	16.3%
25.	200% CuCl <sub>2</sub>	toluene	0.5 eq DMAP	140C	19.1%
26.	200% CuCl <sub>2</sub>	toluene	0.8 eq DMAP	140C	15.4%
27.	200% CuCl <sub>2</sub>	toluene	1.0 eq DMAP	140C	13.9%
28.	200% CuCl <sub>2</sub>	toluene	2.0 eq DMAP	140C	6.4%
29.	200% CuCl <sub>2</sub>	1,4-dioxane	0.5 eq DMAP	140C	23.7%
30.	200% CuCl <sub>2</sub>	1,4-dioxane	0.5 eq imidazole	140C	31%
31.	200% CuCl <sub>2</sub>	1,4-dioxane	2 eq imidazole	140C	57.4%
32.	100% CuCl <sub>2</sub>	1,4-dioxane	2 eq imidazole	140C	1.7%
33.	100% CuCl <sub>2</sub>	1,4-dioxane	1 eq imidazole	140C	53.8%
34.	50% CuCl <sub>2</sub>	1,4-dioxane	2 eq imidazole	140C	2.3%
35.	50% CuCl <sub>2</sub>	1,4-dioxane	0.5 eq imidazole	140C	39.4%

<sup>a</sup> Reaction Conditions: reactions were run on 0.05mmol scale, at 0.1M in a sealed vessel at 140 C under air unless otherwise specified. <sup>b</sup> GC Yield. <sup>c</sup> 1,8-Diazabicyclo[5.4.0]undec-7-ene. <sup>d</sup> DABCO.

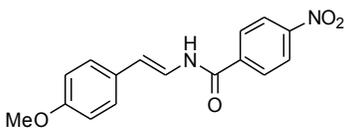
#### 4. Substrate Synthesis

All enamides substrates were prepared using the procedure developed by Gooßen et al<sup>1</sup>. Characterization data for substrates not reported therein are included below. Though not noted in their initial report, we found that trace carboxylic acid impurities in the amide substrates poisoned the catalyst; an additional base wash (10 % Na<sub>2</sub>CO<sub>3</sub>) was utilized on commercial amides containing these impurities. Ru(mta)<sub>2</sub>cod is commercially available, but was prepared from RuCl<sub>3</sub> according to the procedure of Genet et al.<sup>2</sup> An alternative, metal-free preparation of *N*-[(*E*)-2-phenylethenyl]benzamide, **1**, was adapted from Katritzky and coworkers.<sup>3</sup>



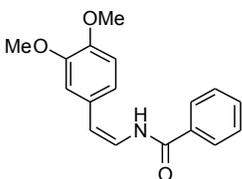
*4-methoxy-N-[(E)-2-(4-methoxyphenyl)ethenyl]benzamide*

Isolated as a cream-colored solid, mp = 200-203 °C. <sup>1</sup>H NMR (300MHz, DMSO-d<sup>6</sup>): δ 10.37 (d, NH, 9.9Hz), 7.95 (d, 2H, J = 8.7Hz), 7.49 (dd, 1H, J = 14.4, 9.6 Hz), 7.30 (d, 2H, J = 8.7Hz), 7.05 (d, 2H, J = 8.7Hz), 6.88 (d, 2H, J = 8.8Hz), 6.37 (d, 1H, J = 14.7Hz), 3.83 (s, 3H), 3.74 (s, 3H); <sup>13</sup>C NMR (300MHz, DMSO-d<sup>6</sup>): δ 163.93, 162.73, 158.58, 130.18, 129.87, 127.01, 126.25, 123.22, 114.91, 114.37, 112.81, 56.11, 55.75; EMM (ESI) *m/z* calcd for C<sub>17</sub>H<sub>17</sub>NO<sub>3</sub> [M+H]<sup>+</sup>: 284.1282, meas: 284.1288.



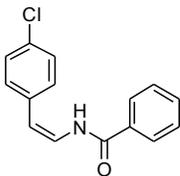
*N-[(E)-2-(4-methoxyphenyl)ethenyl]-4-nitrobenzamide*

Isolated as a yellow solid, decomposition to red oil at 217 °C. <sup>1</sup>H NMR (300MHz, DMSO-d<sup>6</sup>): δ 10.83 (d, NH, 9.3Hz), 8.37 (dt, 2H, J = 6.9, 2.1Hz), 8.20 (dt, 2H, J = 9.0, 2.1Hz), 7.50 (dd, 1H, 14.4, 9.3 Hz), 7.36 (d, 2H, J = 6.6Hz), 6.90 (d, 2H, J = 6.9Hz), 6.47 (d, 1H, J = 14.7 Hz); <sup>13</sup>C NMR (300MHz, DMSO-d<sup>6</sup>): δ 162.81, 158.89, 149.93, 139.74, 129.74, 129.35, 127.34, 124.31, 122.60, 114.94, 114.77, 55.77; EMM (ESI) *m/z* calcd for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub> [M]<sup>+</sup>: 298.0949, meas: 298.0953.



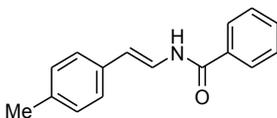
*N-[(Z)-2-(3,4-dimethoxyphenyl)ethenyl]benzamide*

Isolated as a white solid, mp 132-133 °C. <sup>1</sup>H NMR (300MHz, DMSO-d<sup>6</sup>): δ 9.94 (d, NH, J = 9.3Hz), 7.95 (m, 2H), 7.58 (t, 1H, J = 7.2Hz), 7.50 (t, 2H, J = 7.5Hz), 7.09 (d, 1H, J = 1.5Hz), 7.03 (dd, 1H, J = 8.4, 1.5Hz), 6.97 (d, 1H, J = 8.4Hz), 6.85 (t, 1H, J = 9.6Hz), 5.81 (d, 1H, J = 9.9Hz), 3.79 (s, 3H), 3.77 (s, 3H); <sup>13</sup>C NMR (300MHz, DMSO-d<sup>6</sup>): δ 165.81, 149.24, 148.38, 134.19, 132.44, 129.21, 129.04, 128.43, 122.05, 121.72, 113.72, 112.76, 112.62, 56.22, 55.99; EMM (ESI): *m/z* calcd for C<sub>17</sub>H<sub>17</sub>NO<sub>3</sub> [M]<sup>+</sup>: 283.1203, meas 283.1212.



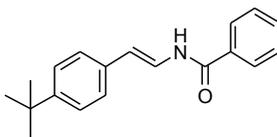
*N-[(Z)-2-(4-chlorophenyl)ethenyl]benzamide*

Isolated as a white solid, Mp = 131-133 °C; <sup>1</sup>H NMR (300MHz, DMSO-d<sup>6</sup>): δ 10.05 (d, NH, J = 9.3Hz), 7.91 (d, 2H, J = 6.9Hz), 7.38-7.59 (m, 6H), 6.94 (t, 1H, J = 9.6Hz), 5.75 (d, 1H, J = 9.6Hz); <sup>13</sup>C NMR (300MHz, DMSO-d<sup>6</sup>): δ 166.15, 135.42, 134.06, 132.55, 131.48, 130.85, 129.12, 129.02, 128.61, 124.29, 112.06; EMM (ESI) m/z calcd for C<sub>15</sub>H<sub>12</sub>ClNO[M+Na]:280.0500, meas: 280.0504.



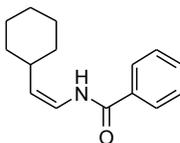
*N-[(E)-2-(4-methylphenyl)ethenyl]benzamide*

Isolated as a white solid, Mp = 178-179 °C. <sup>1</sup>H NMR (300MHz, DMSO-d<sup>6</sup>): δ 10.55 (d, NH, J = 9.9Hz), 7.94 (d, 2H, J = 6.9Hz), 7.47-7.61 (m, 4H), 7.27 (d, 2H, J = 8.1Hz), 7.10 (d, 2H, J = 7.8Hz), 6.42 (d, 1H, J = 15 Hz), 2.25 (s, 3H); <sup>13</sup>C NMR (300MHz, DMSO-d<sup>6</sup>): δ 164.63, 136.14, 134.38, 134.09, 132.51, 130.00, 129.14, 128.26, 125.86, 123.99, 113.64, 21.40. EMM (ESI) m/z calcd for C<sub>16</sub>H<sub>15</sub>NO [M+Na]<sup>+</sup>:260.1046, meas: 260.1053.



*N-[(E)-2-(4-tert-butylphenyl)ethenyl]benzamide*

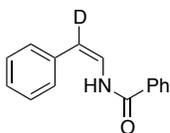
Isolated as a white solid, Mp = 196-199 °C. <sup>1</sup>H NMR (300MHz, DMSO-d<sup>6</sup>): δ 10.56 (d, NH, J = 9.9Hz), 7.95 (d, 2H, J = 6.6Hz), 7.47-7.63 (m, 4H), 7.30 (virtual s, 4H), 6.42 (d, 1H, J = 14.4Hz), 1.25 (s, 9H); <sup>13</sup>C NMR (300MHz, DMSO-d<sup>6</sup>): δ 164.64, 149.43, 134.38, 134.08, 132.52, 129.15, 128.26, 126.16, 125.67, 124.12, 113.49, 34.87, 31.77. EMM (ESI) m/z calcd for C<sub>19</sub>H<sub>21</sub>NO [M+H]<sup>+</sup>:280.1696, meas: 280.1697.



*N-[(Z)-2-cyclohexylethenyl]benzamide*

Isolated as an oil which solidified over time, mp: 90-93 °C. <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>): δ 7.79 (d, 2H, J = 6.9Hz), 7.67 (br d, 1H, J = 9.3Hz), 7.41-7.59 (m, 3H), 6.79 (t, 1H, J = 10.2 Hz), 4.75 (t, 1H, J = 9.3Hz), 2.20 (m, 1H), 1.69 (m, 5H), 1.14-1.34 (m, 5H); <sup>13</sup>C NMR (300MHz, CDCl<sub>3</sub>): δ 164.58, 134.31, 132.08, 128.96, 127.25, 119.63, 118.52, 35.80, 33.26, 26.10, 26.01. EMM(ESI) m/z calcd for C<sub>15</sub>H<sub>19</sub>NO [M+Na]<sup>+</sup>: 252.1359, Meas (M+Na): 252.1353.

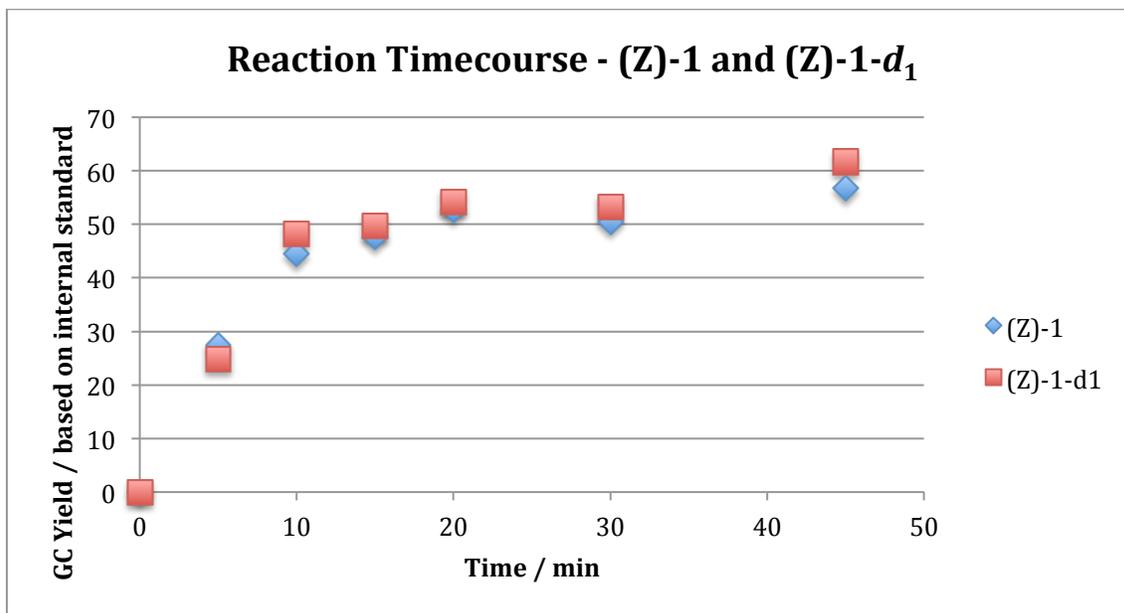
## 5. Kinetic Isotope Effect Determination



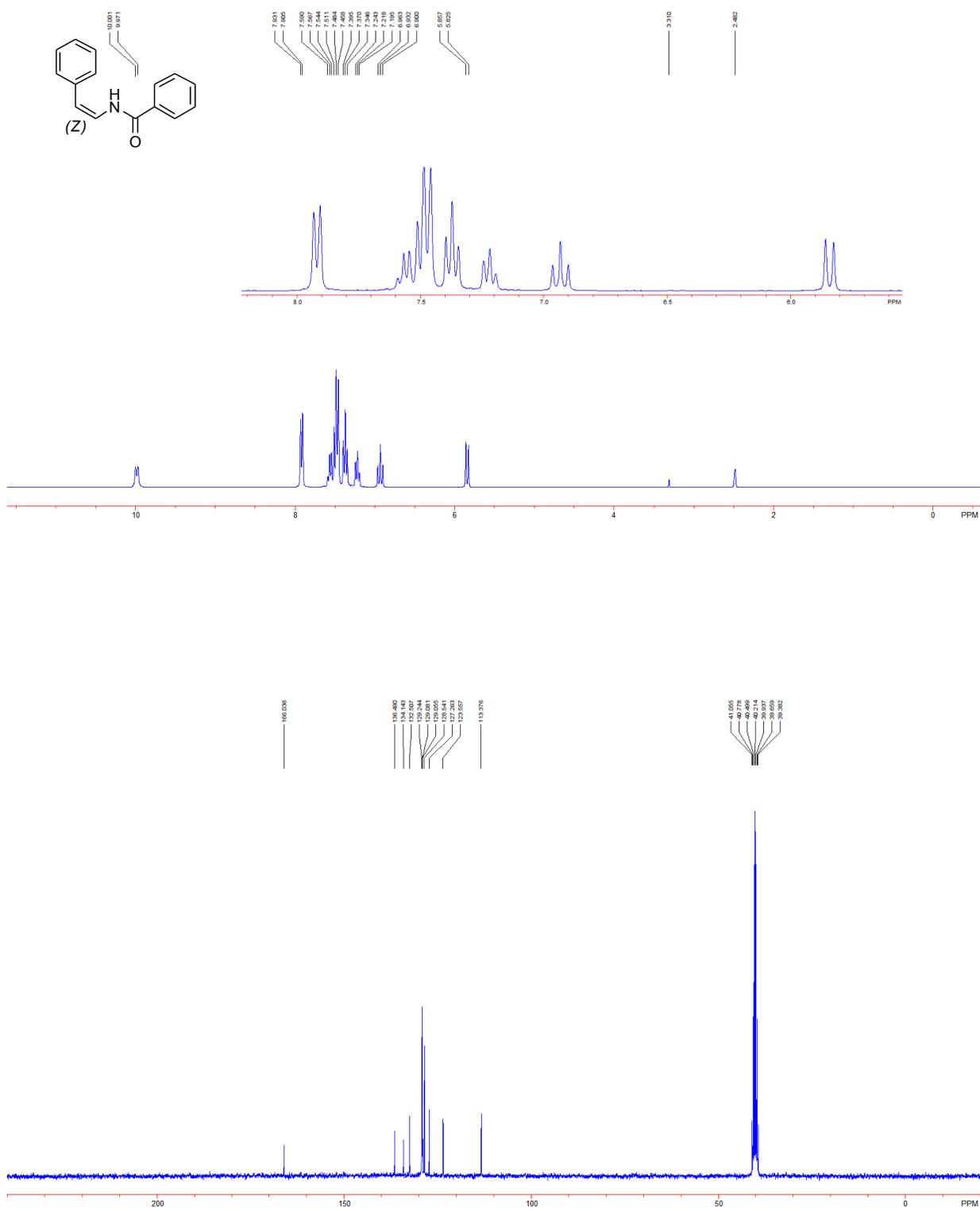
### *N*-[2'-Deutero-(*Z*)-2-phenylethenyl]benzamide, **1-d<sub>1</sub>**

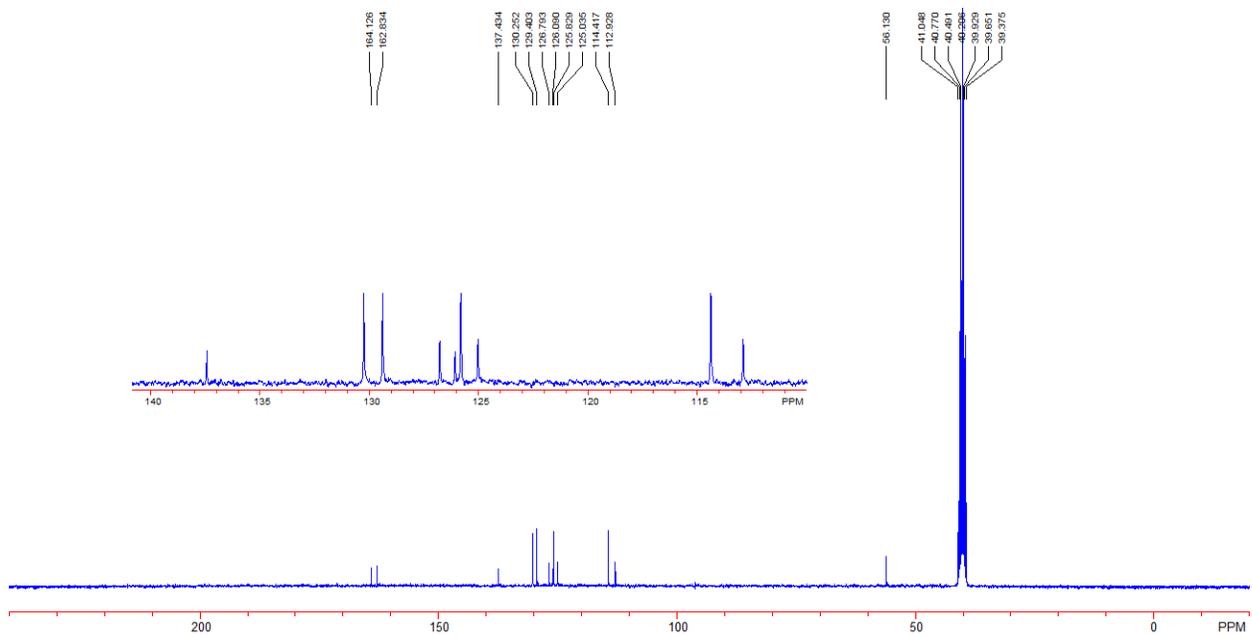
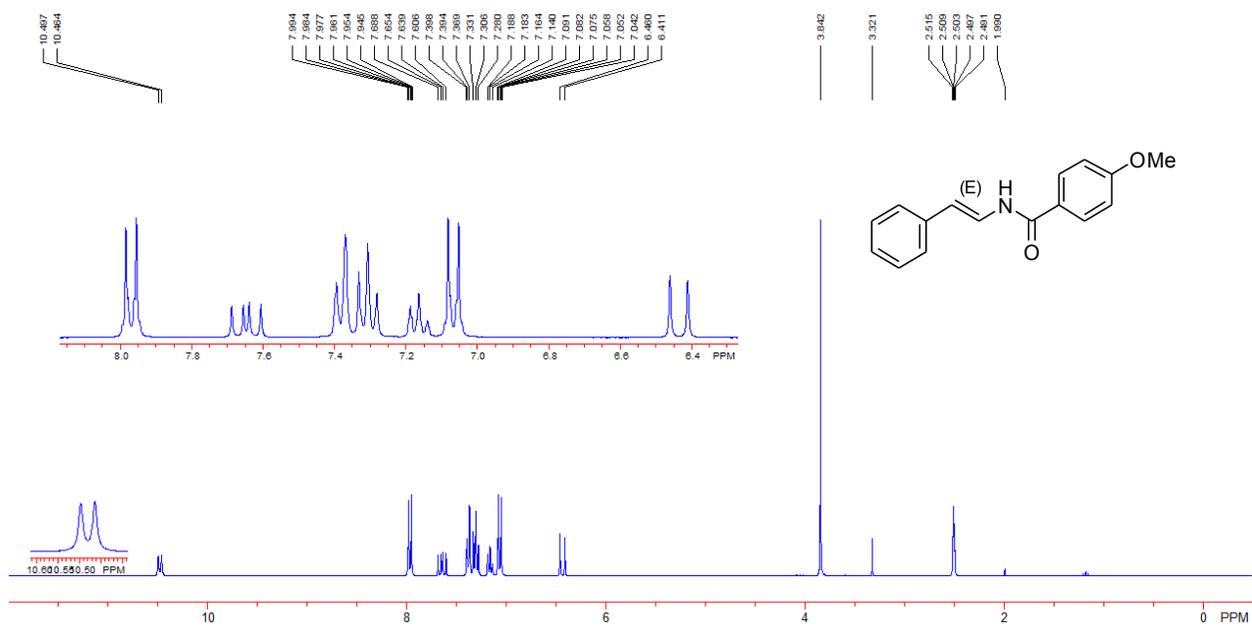
Deuterated enamide substrate **1-d<sub>1</sub>** was prepared from benzamide-*N-d<sub>2</sub>* according to the method of Goossen,<sup>4</sup> with slight modifications to the standard protocol. A Schlenk flask was washed three times with D<sub>2</sub>O (2-3 mL) acidified with a few drops of aqueous DCl (35 wt %), flame dried under vacuum, and transferred into an inert-atmosphere glovebox. The solid reaction components, benzamide-*d<sub>2</sub>* (0.49 g, 4.0 mmol), 1,4-bis(dicyclohexylphosphino)butane (0.108 g, 0.32 mmol), Ru(mta)<sub>2</sub>(COD) (0.064 g, 0.20 mmol), and ytterbium triflate (0.099 g, 0.16 mmol) were then added to the flask, followed by the addition of dry, degassed DMF (12 mL). After the sealed flask was removed from the glovebox, phenylacetylene (0.88 mL, 8.0 mmol) and degassed D<sub>2</sub>O (0.43 mL, 24 mmol) were added to the reaction flask. The reaction was subsequently carried out according to the literature procedures. Several flash column purifications were required to obtain pure product (column conditions: gradient 1:20-to-1:5 EtOAc:Hexanes, using a NEt<sub>3</sub>-washed silica column). The title compound was obtained with 93% deuterium incorporation, based on <sup>1</sup>H NMR spectroscopic analysis (220 mg, 25% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.36 (br s, 1H), 7.74 (d, 2H, J = 6.9 Hz), 7.1-7.5 (m, 9H); <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): δ 164.58, 135.95, 133.62, 132.38, 129.48, 129.07, 128.08, 127.30, 122.55, 110.83 (t, J = 24.9Hz); EMM (ESI) m/z calcd for C<sub>15</sub>H<sub>12</sub>DNO [M+H]: 225.1133, meas: 225.1138.

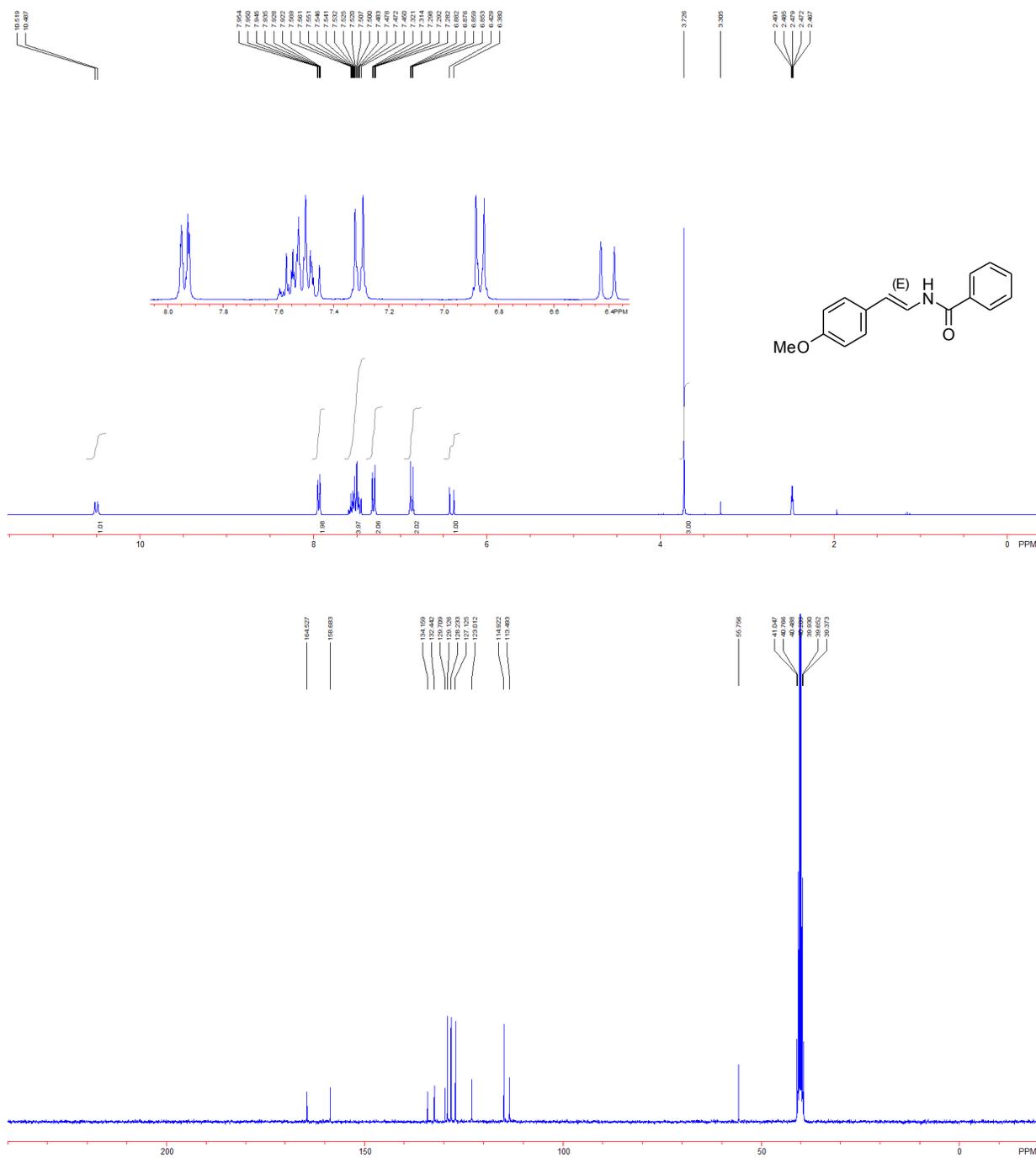
The kinetic isotope effect was determined by independent rate measurements of (*Z*)-**1** and (*Z*)-**1-d<sub>1</sub>**. A comparison of the initial linear region of the reaction timecourse (t=0 to t=10 min) results in a measured  $k_H/k_D$  of  $1.0 \pm 0.2$ .

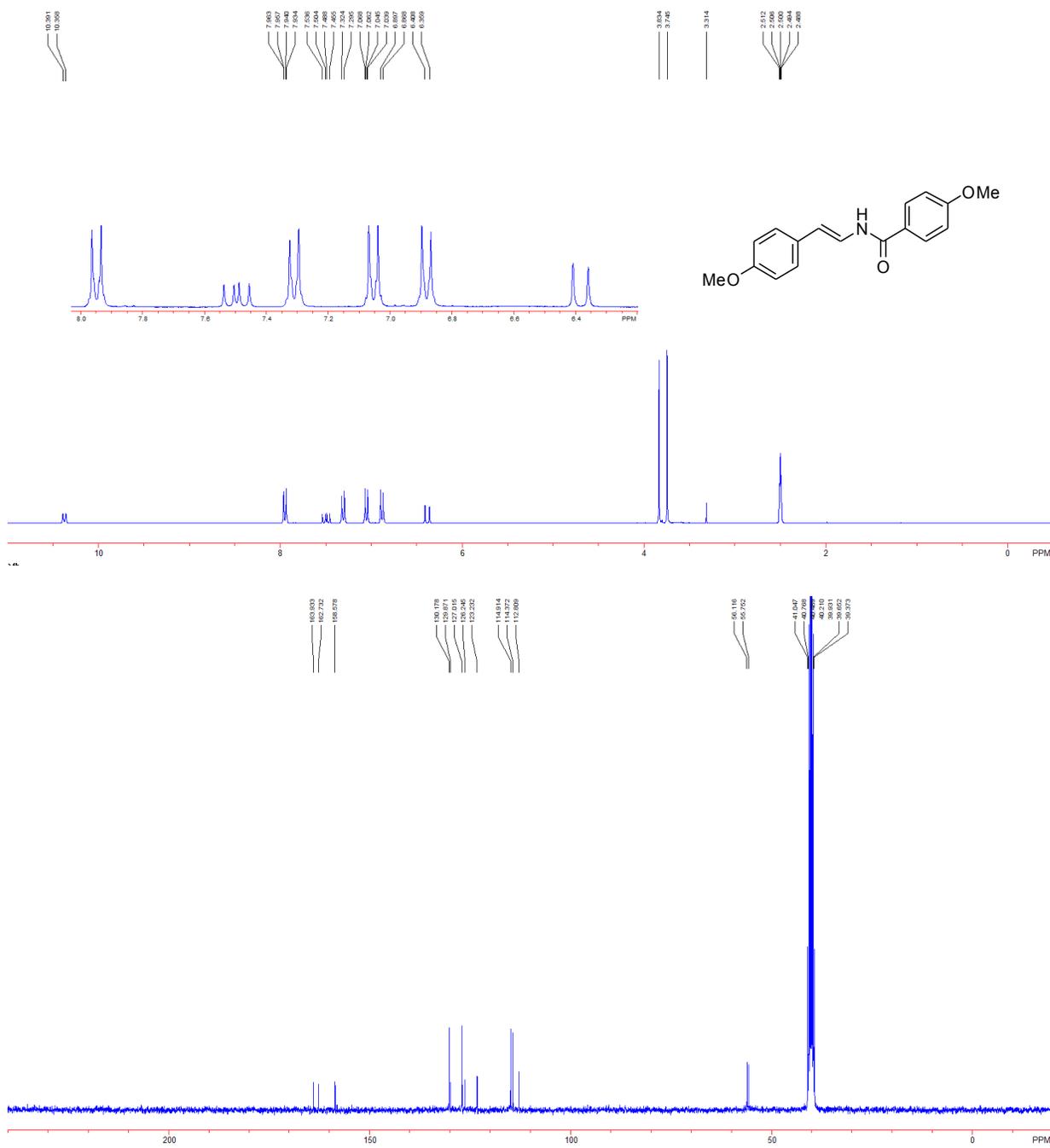


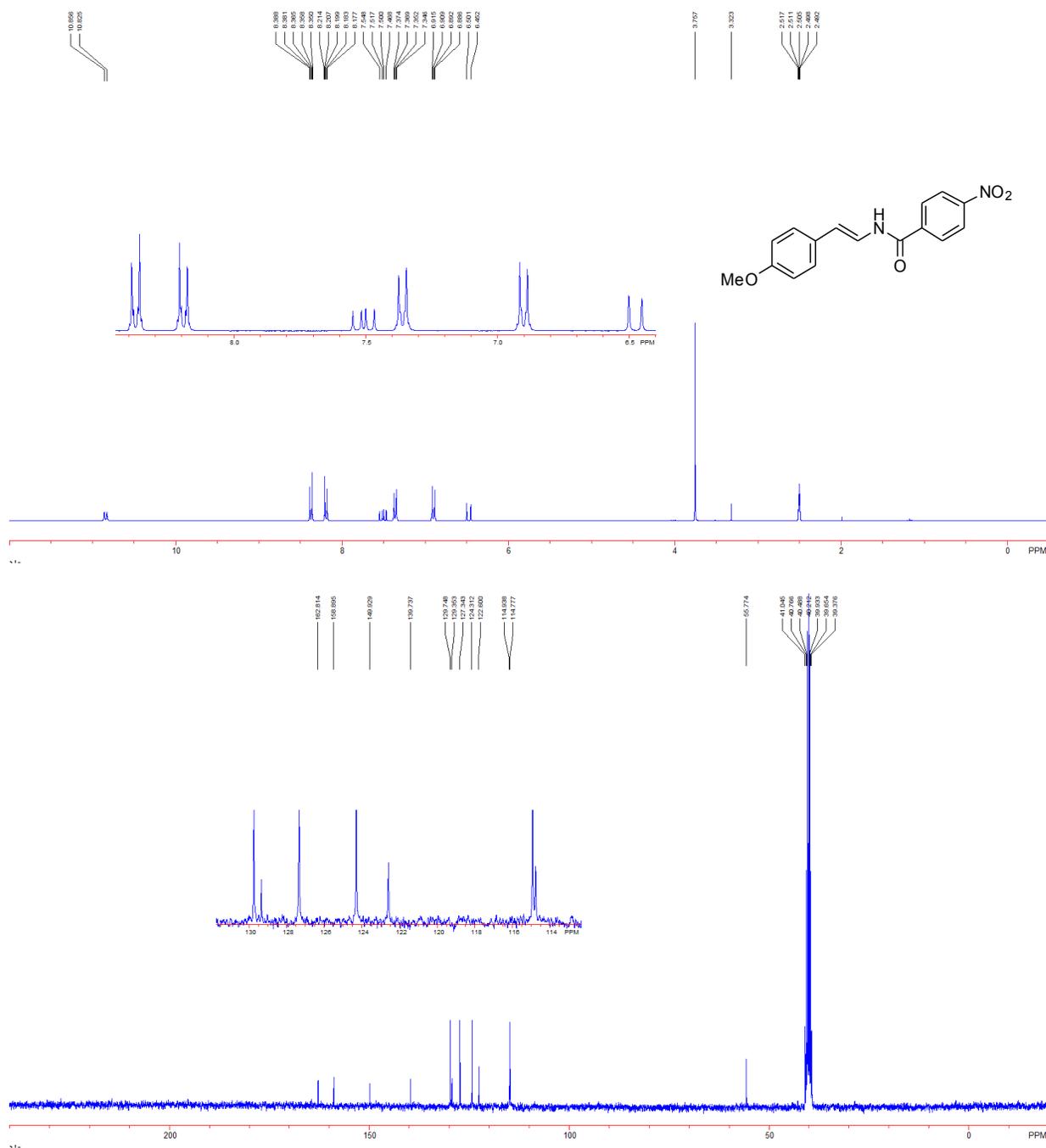


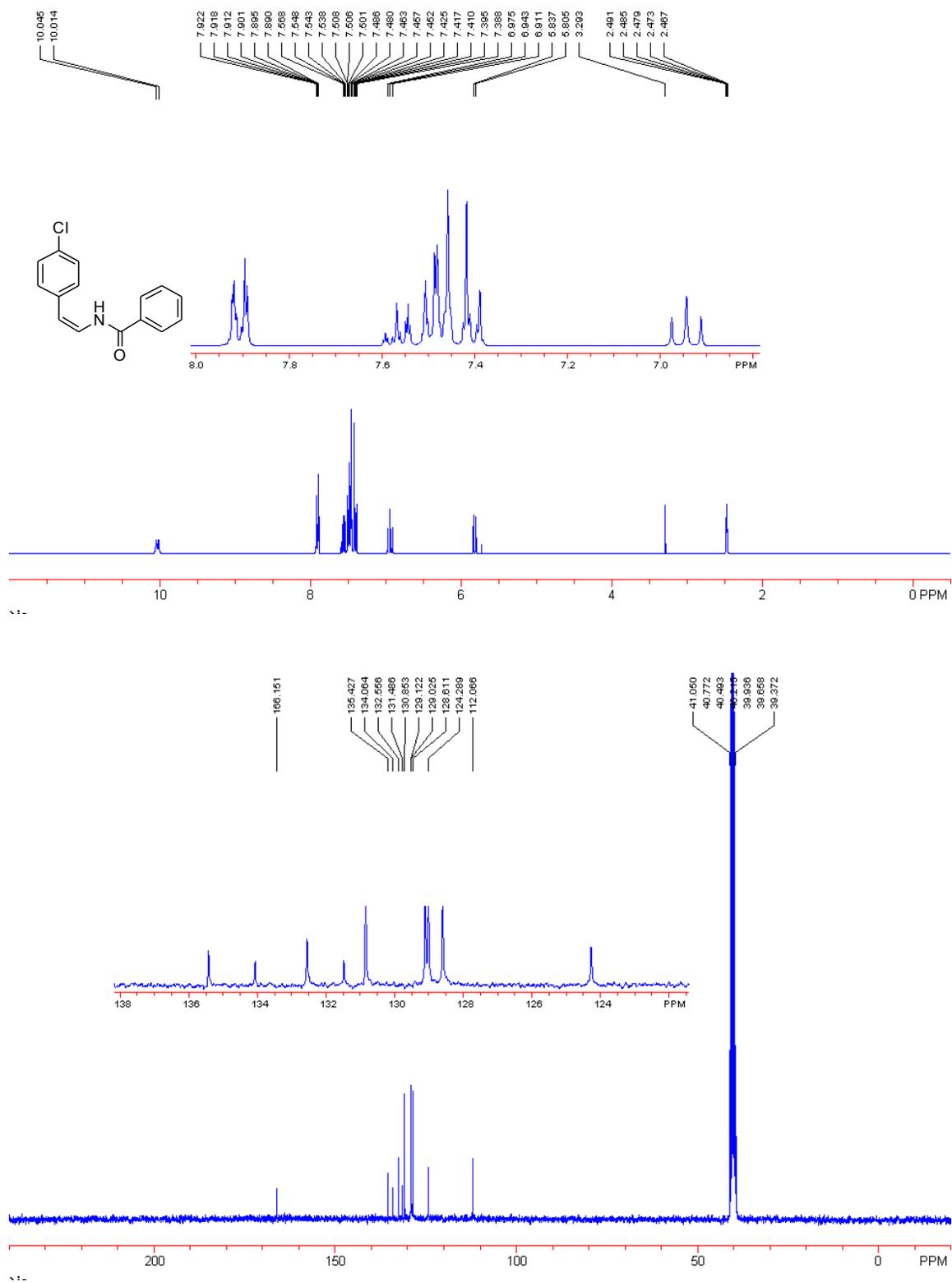


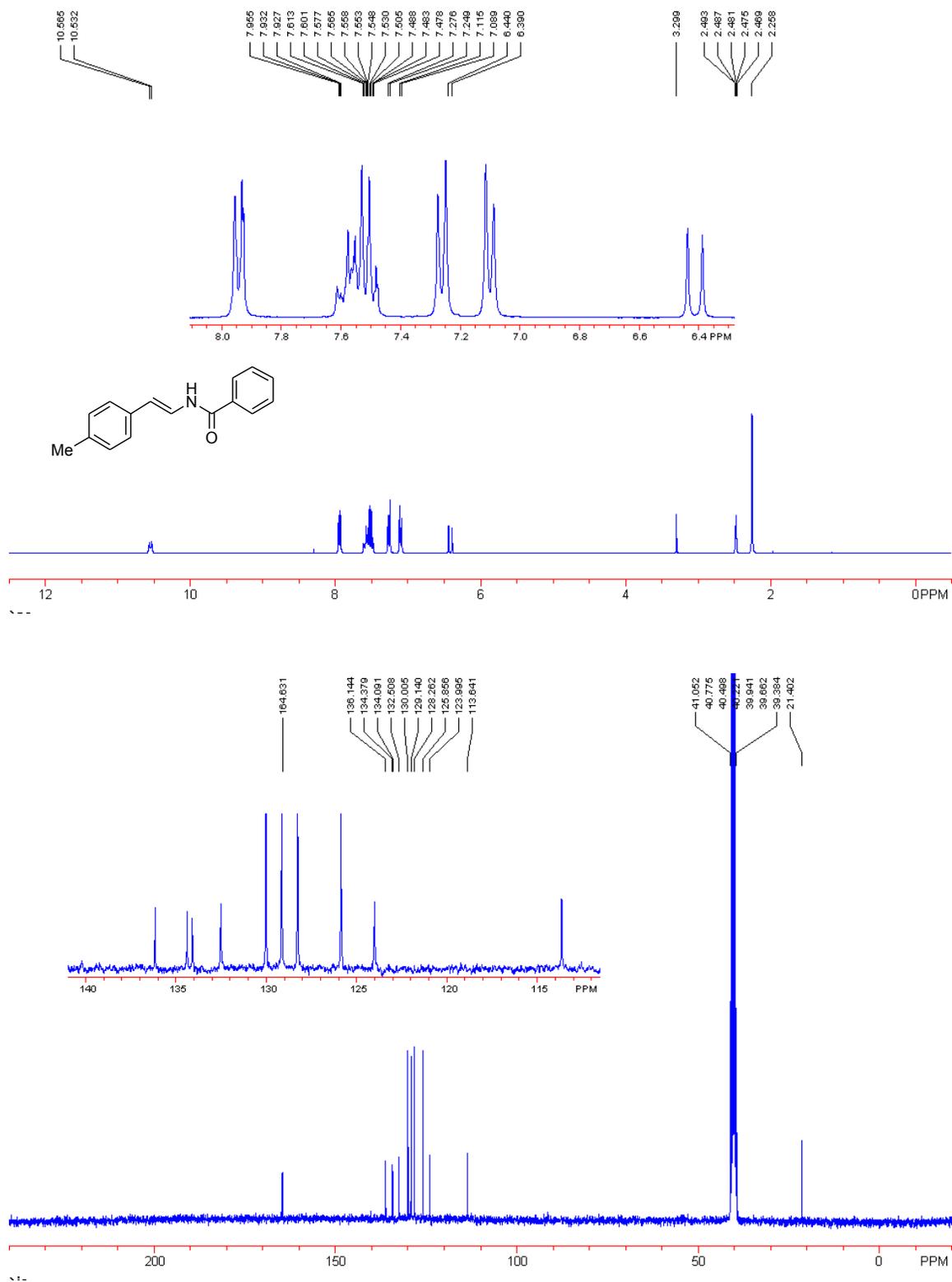


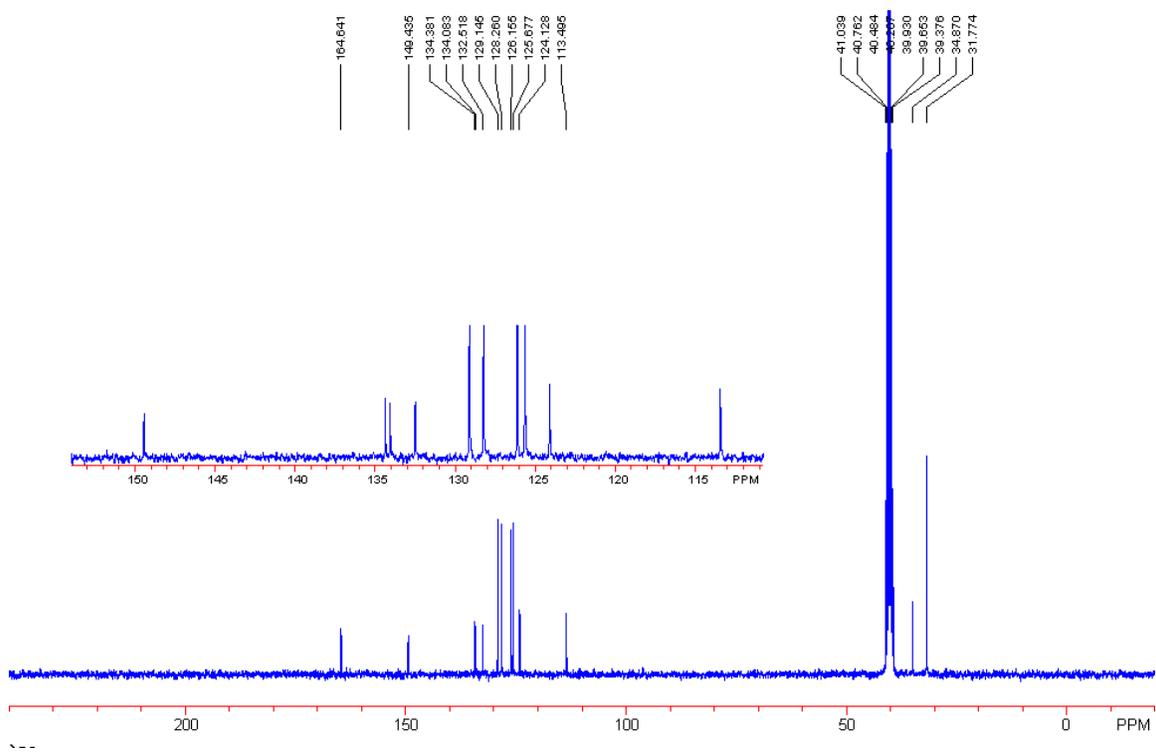
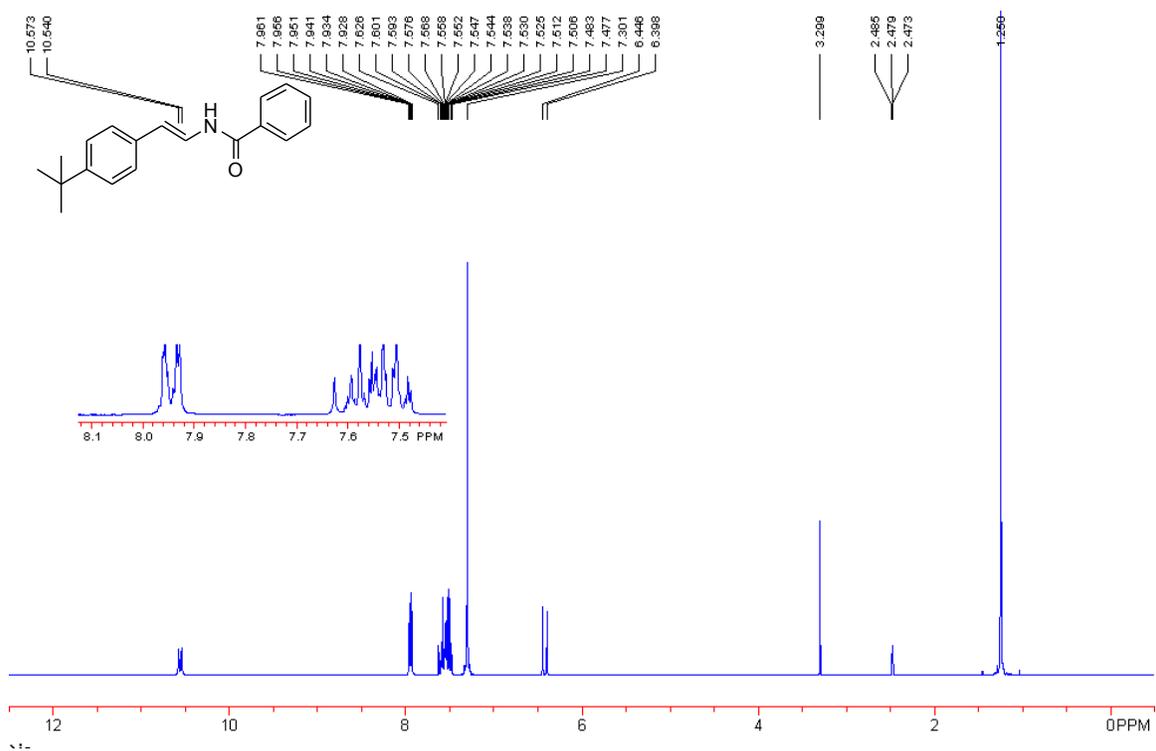


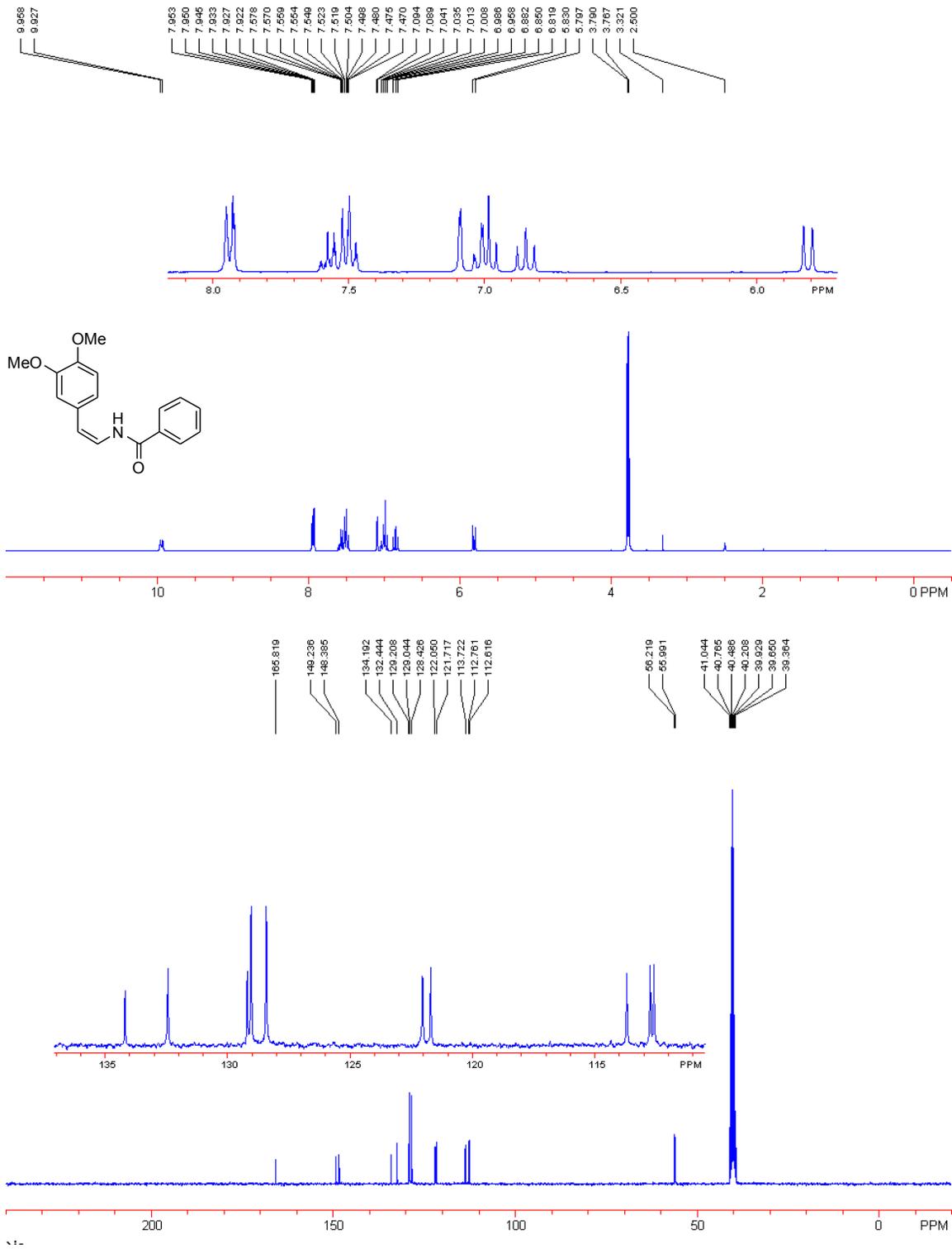


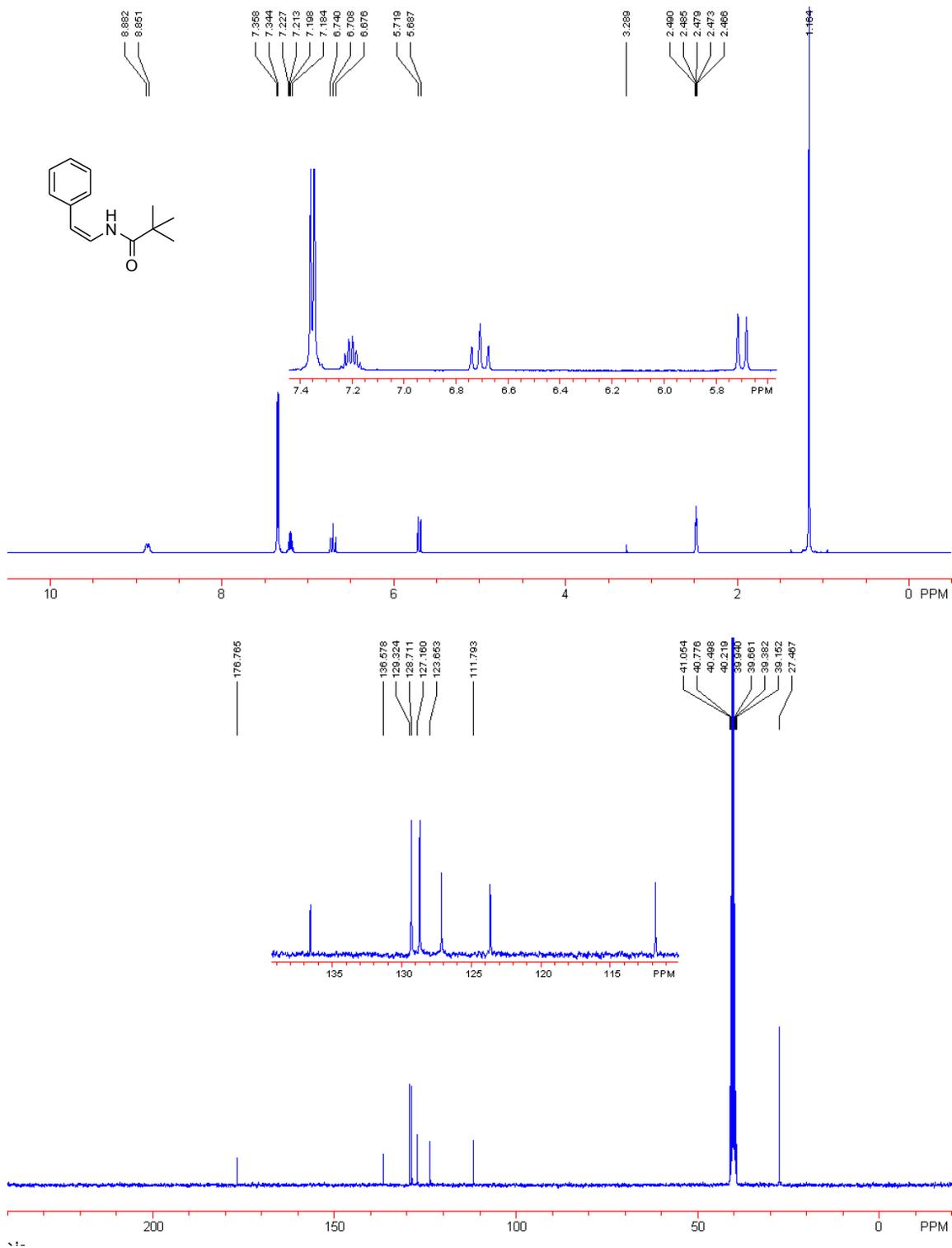


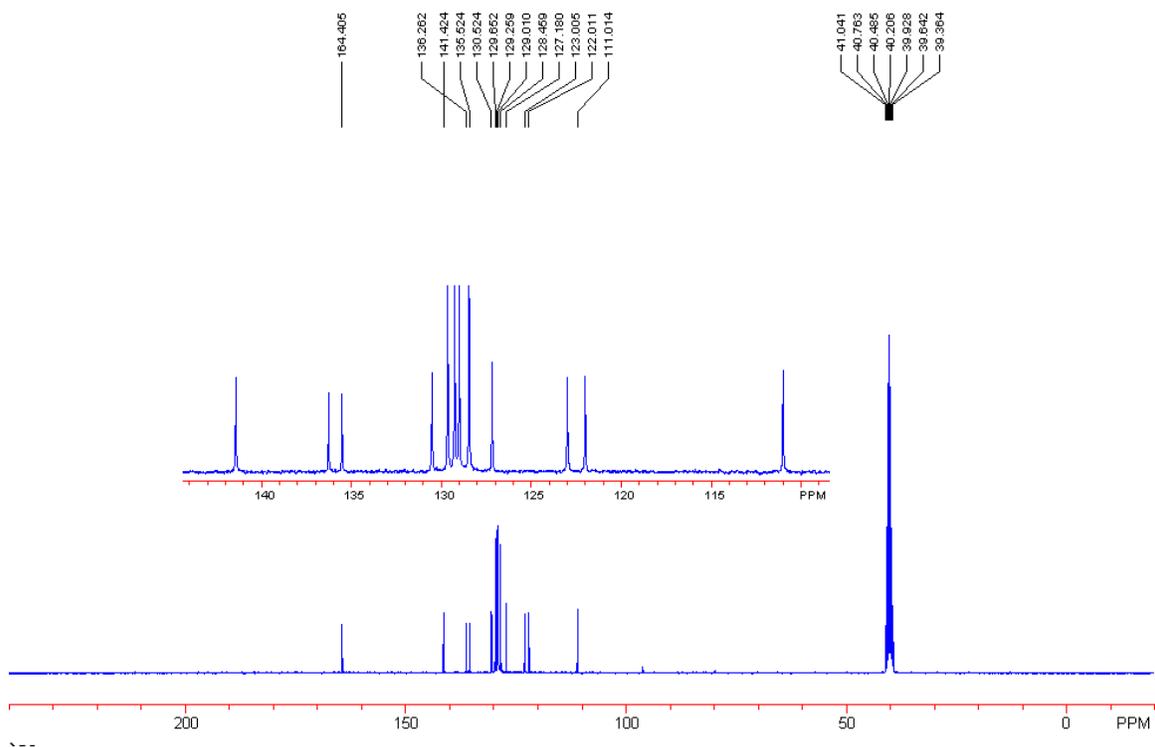
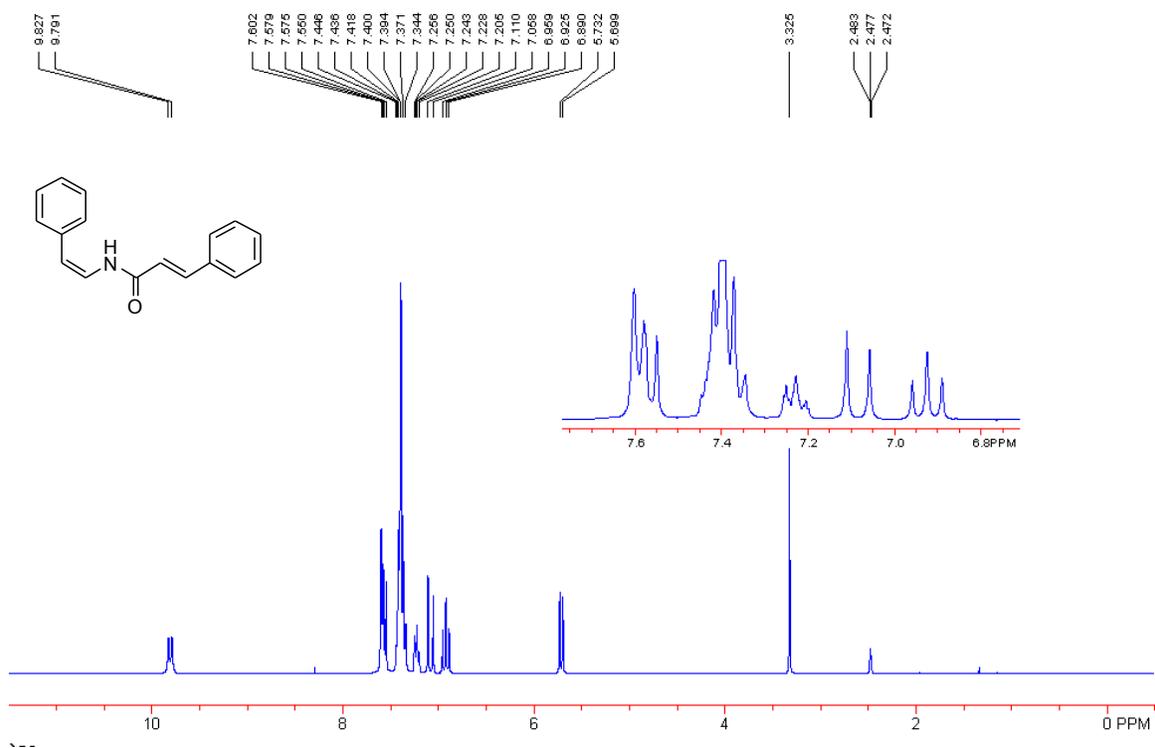




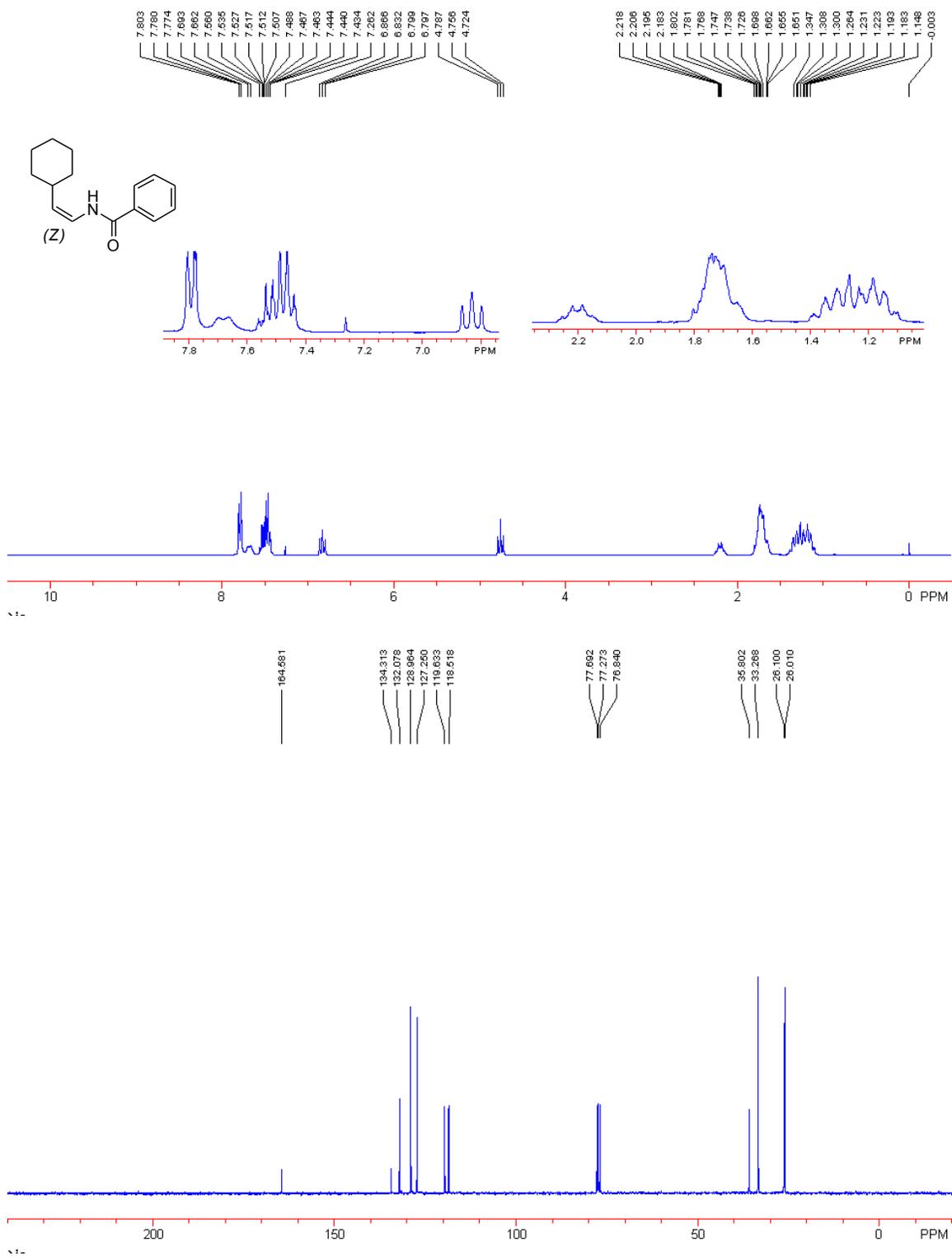


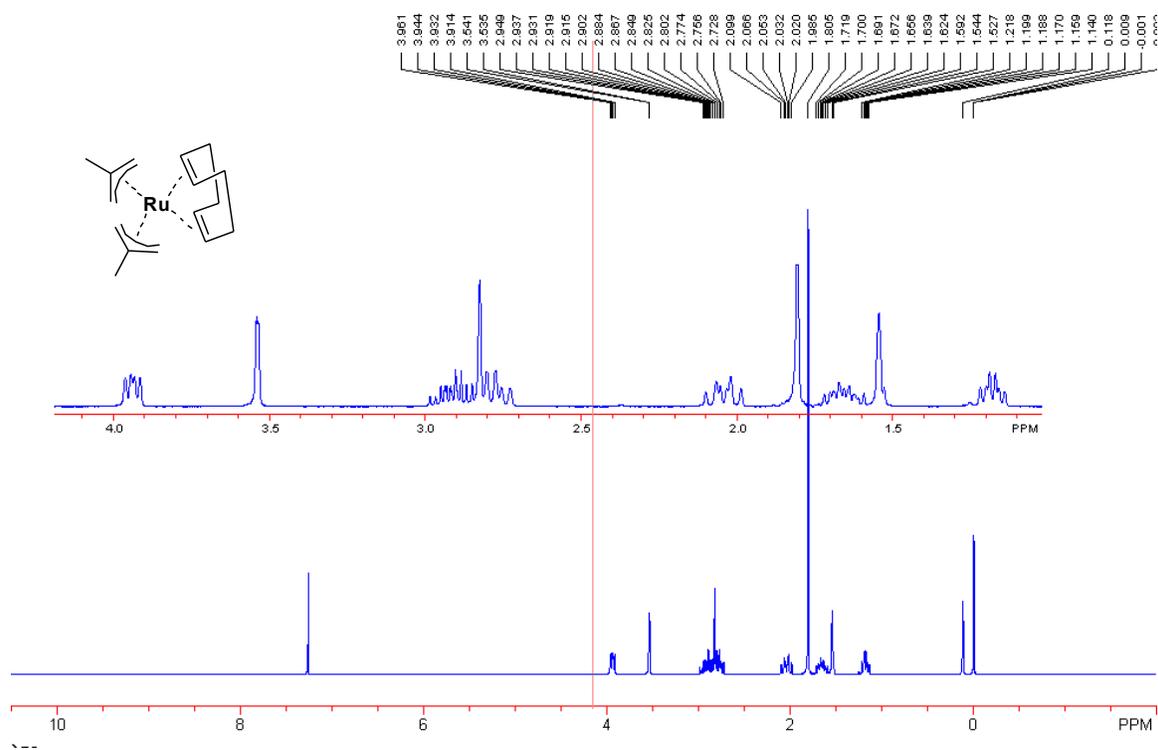




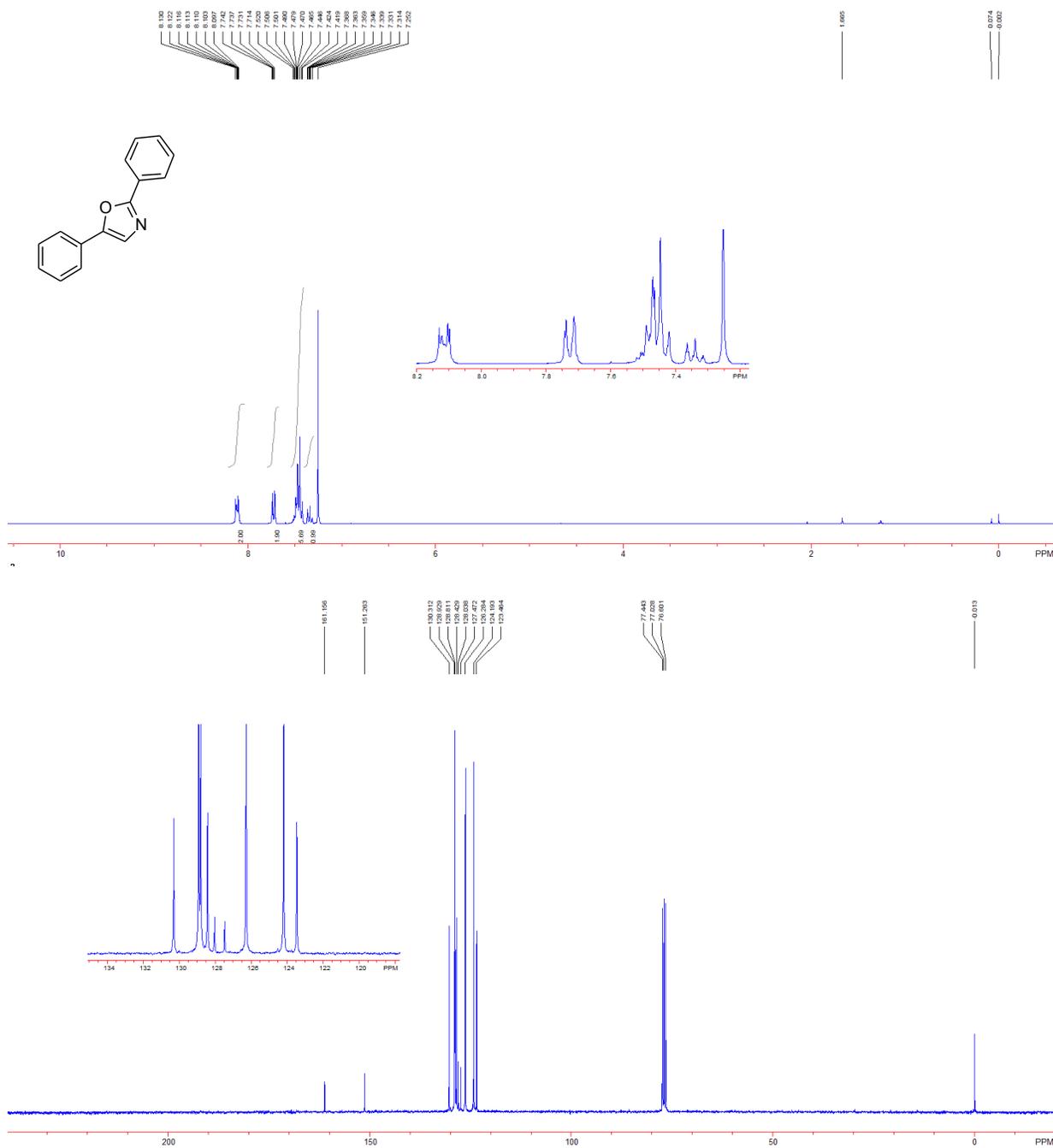


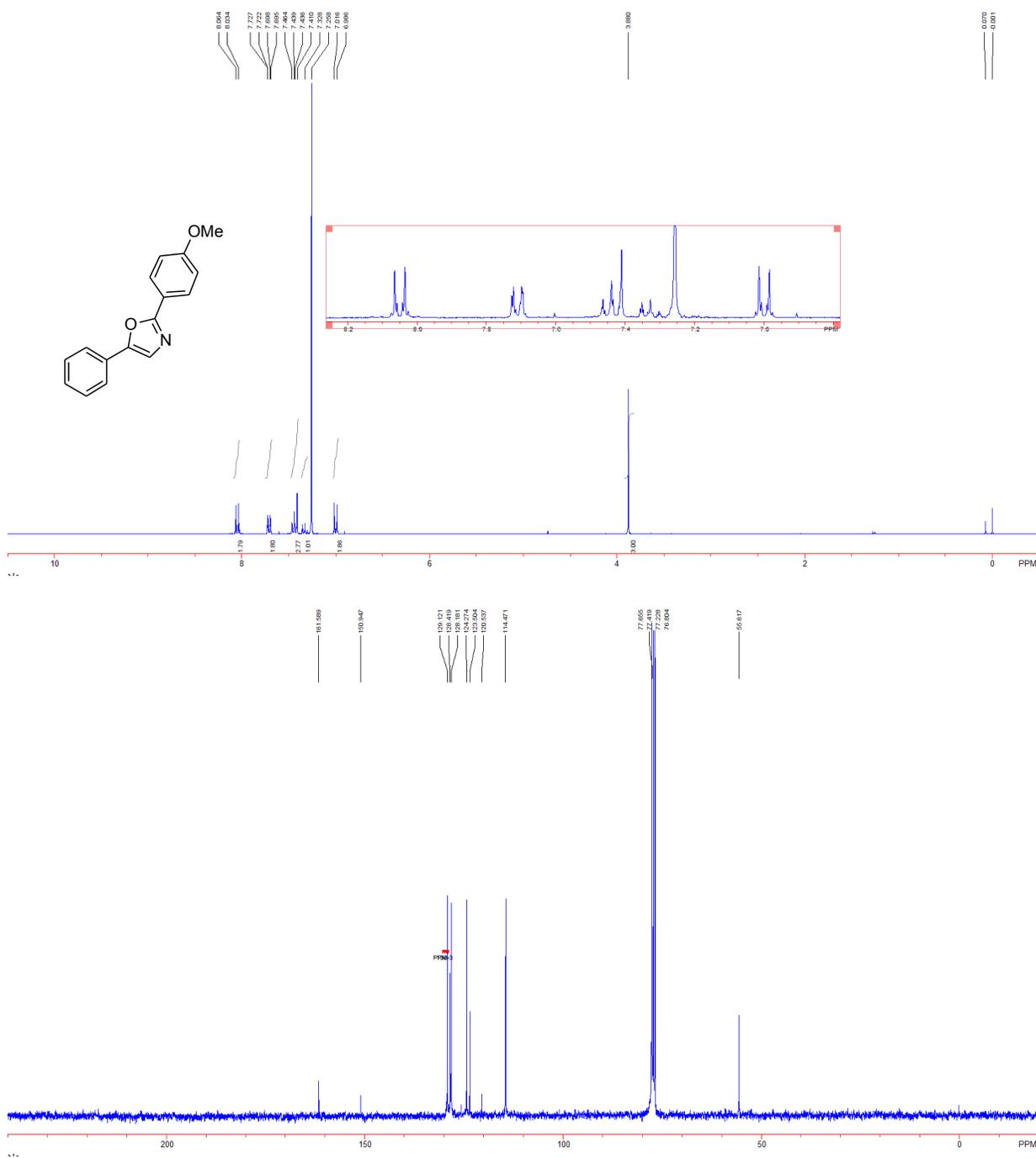


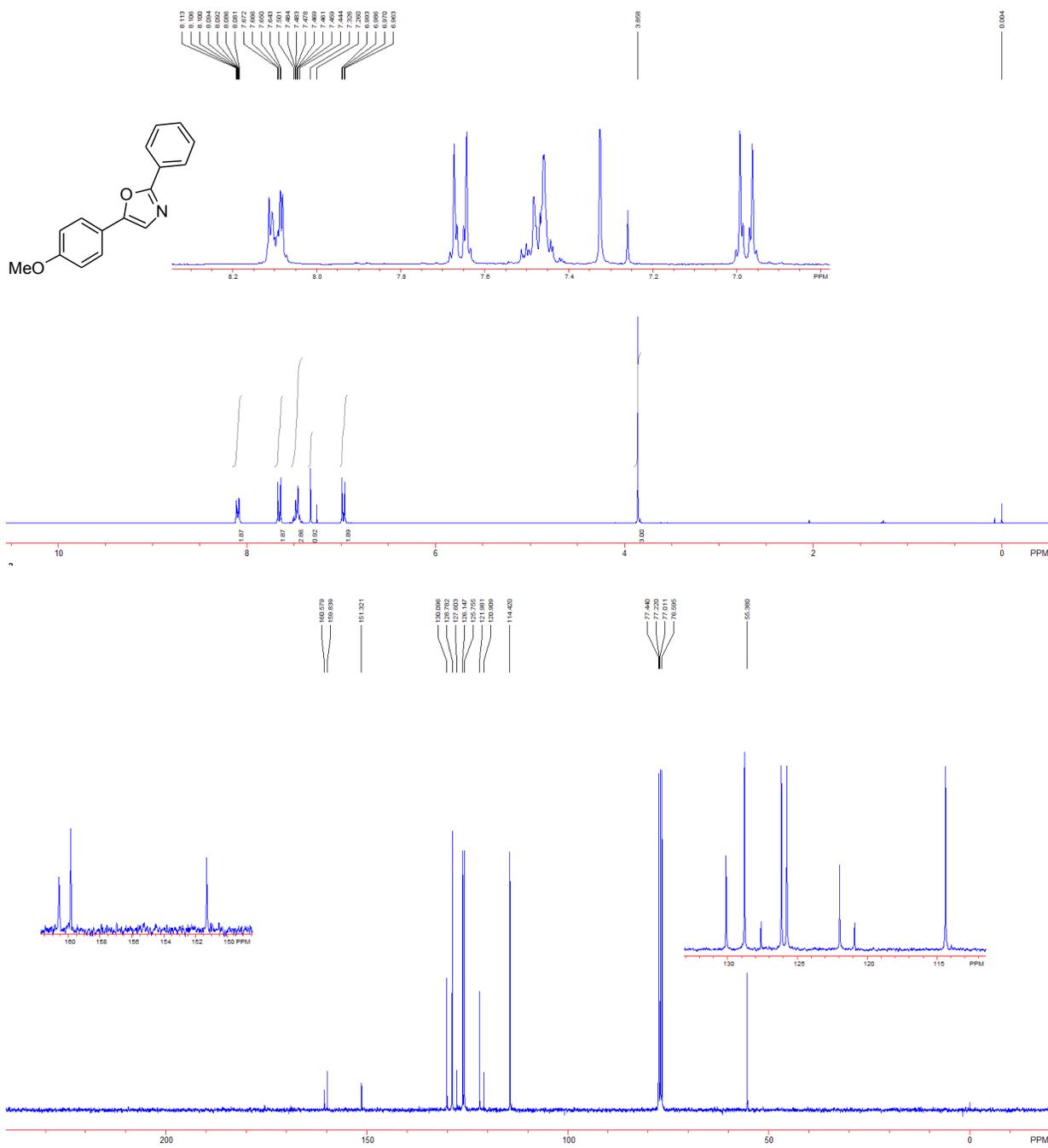


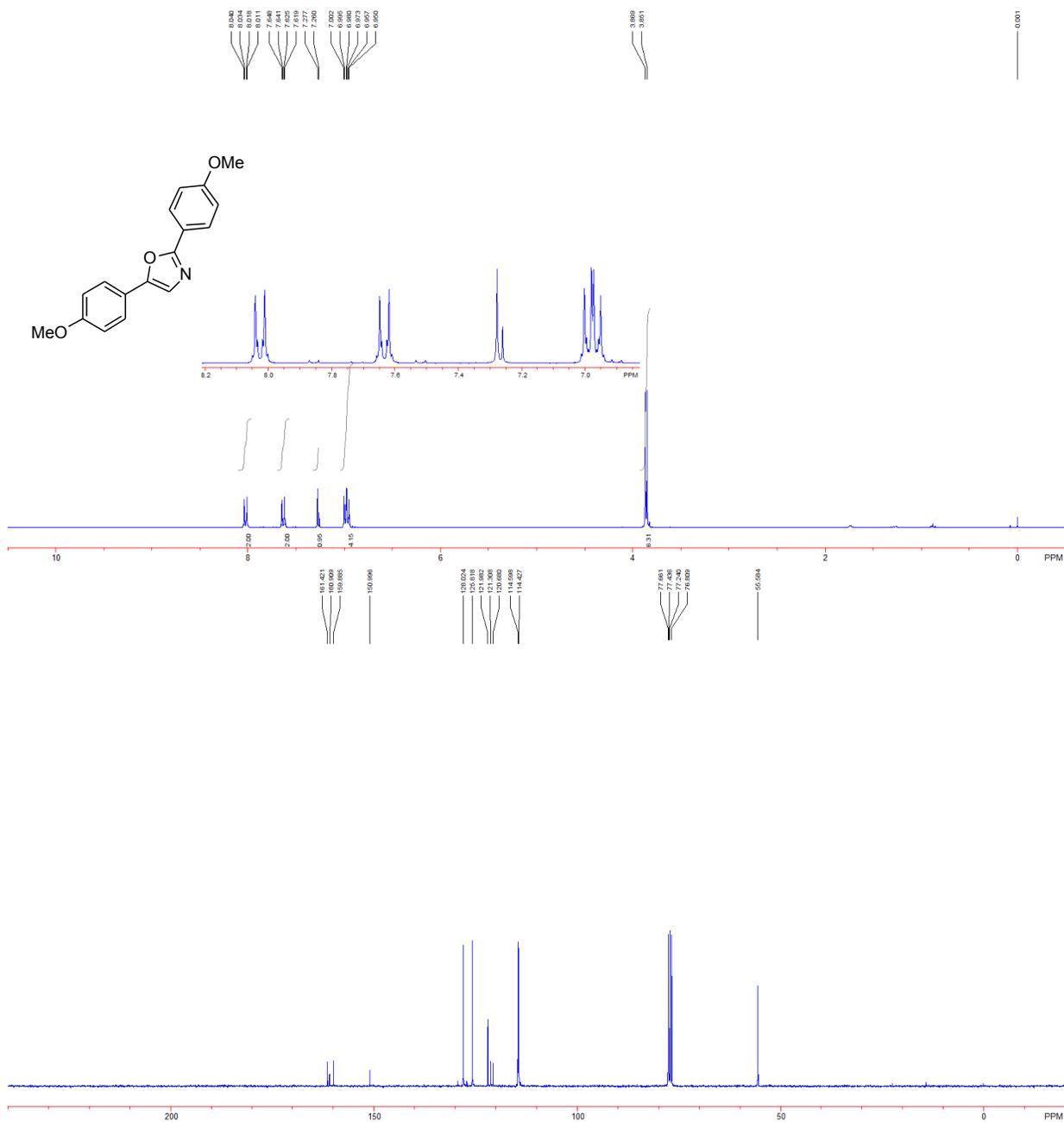


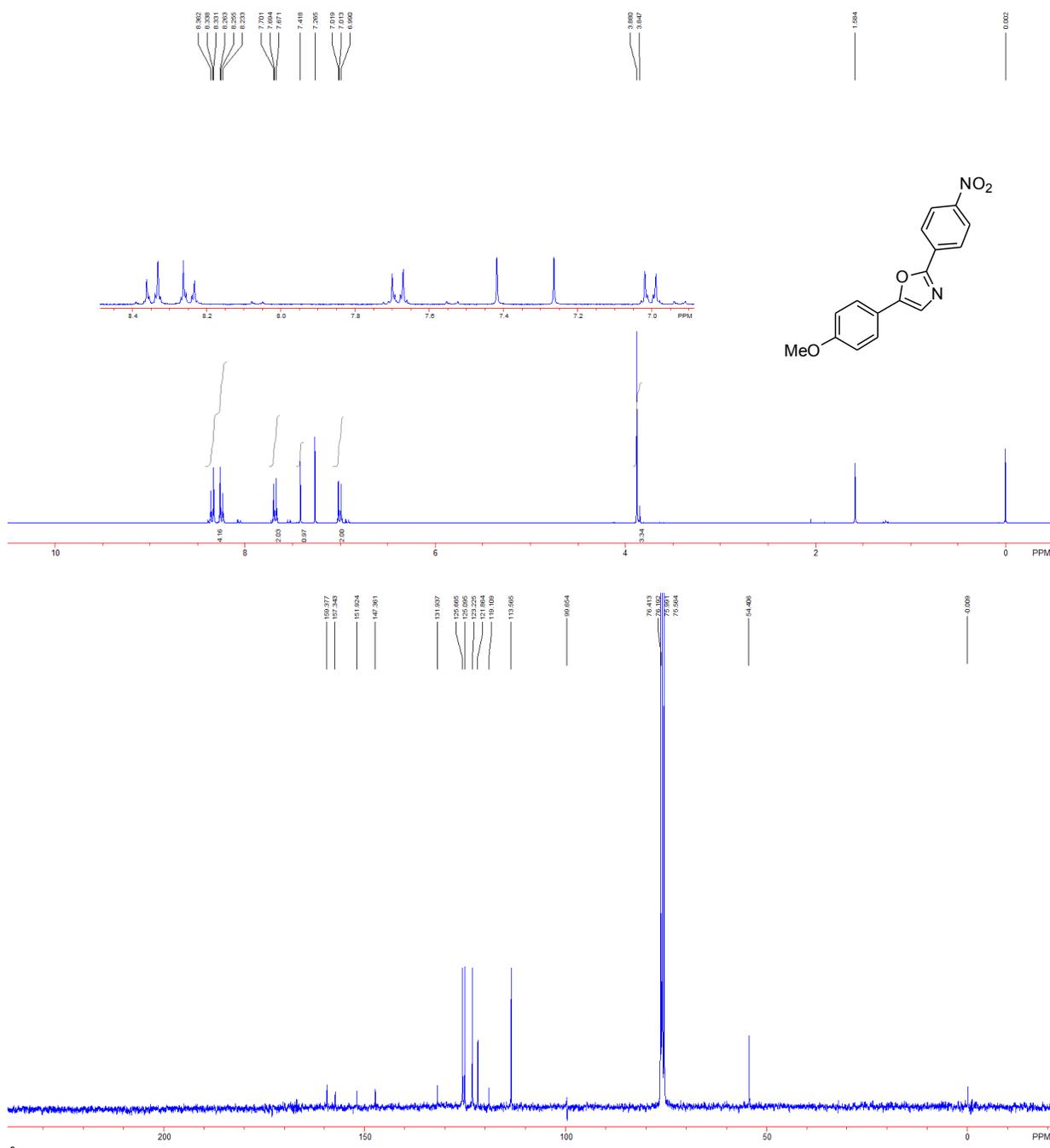
## 7. $^1\text{H}$ and $^{13}\text{C}$ NMR Spectra of Products

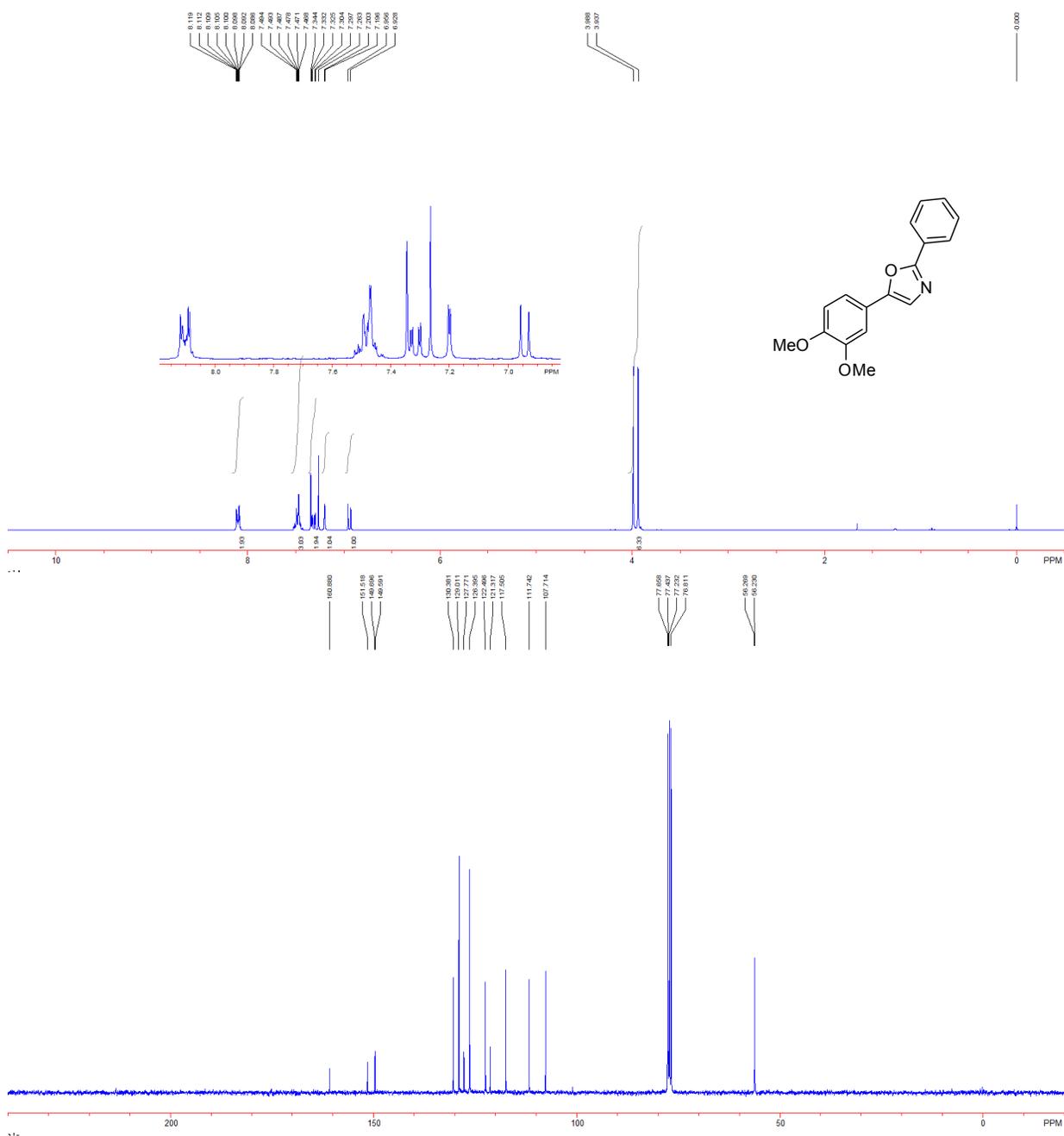


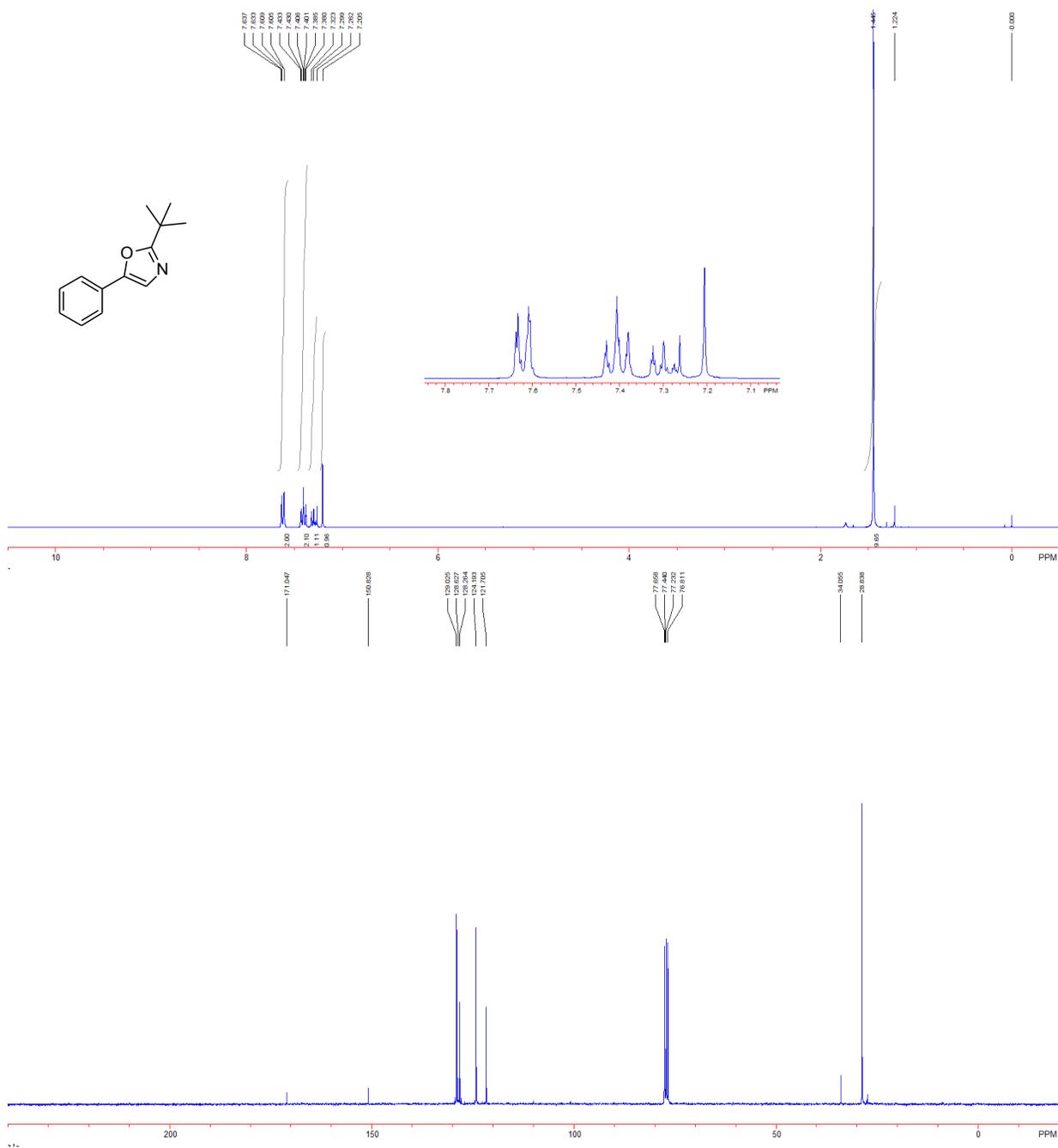




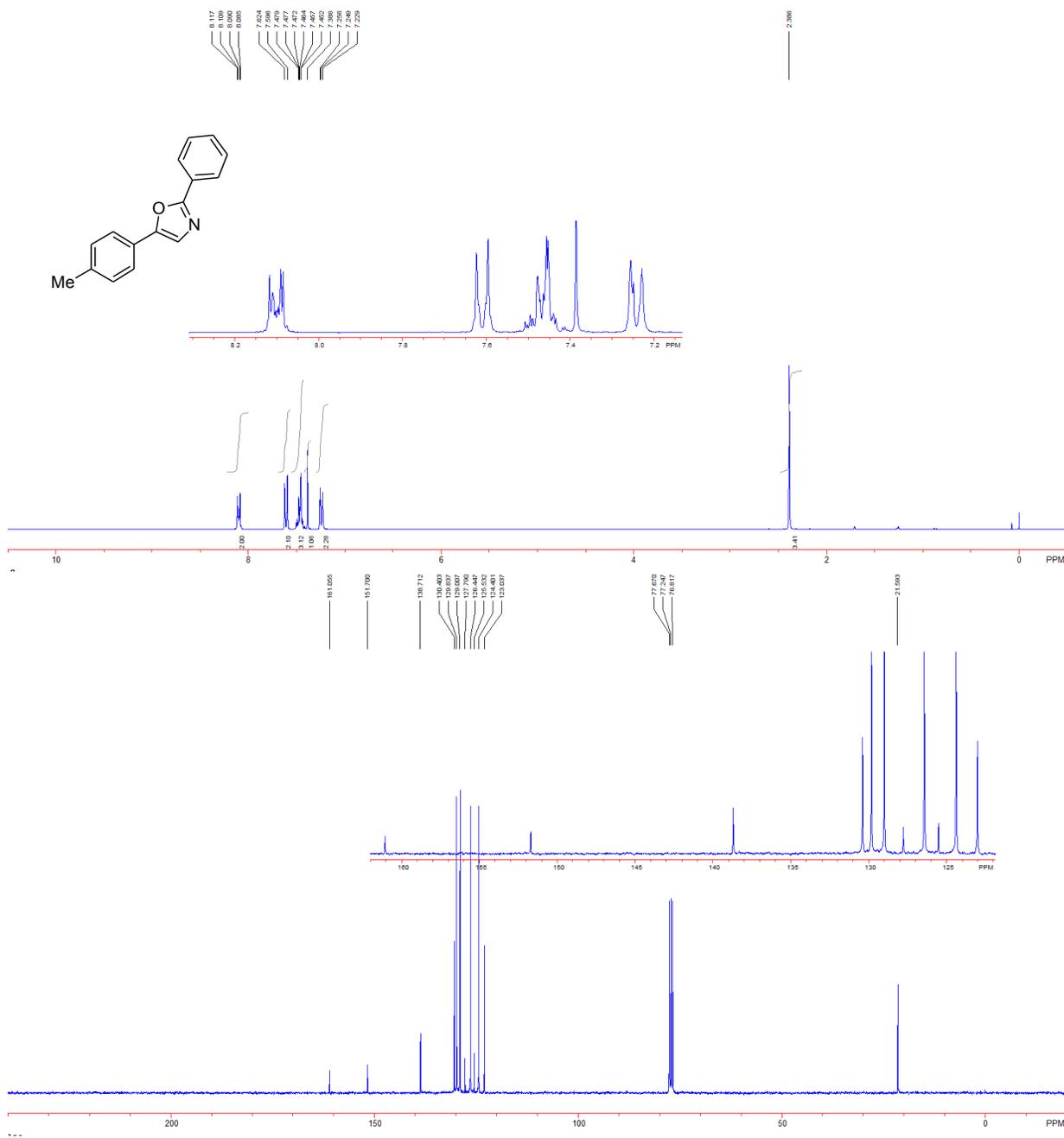






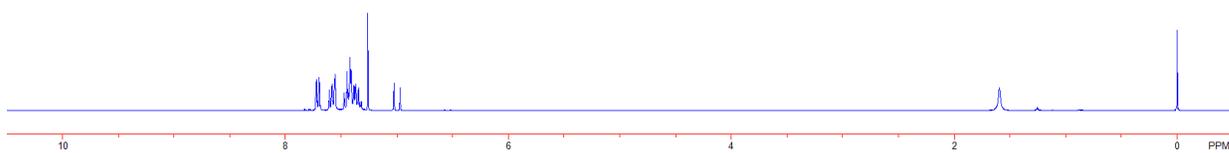
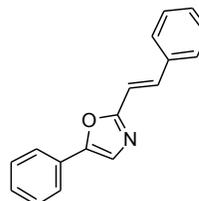
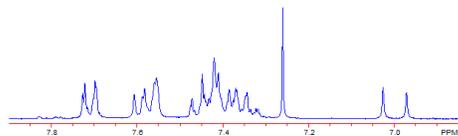
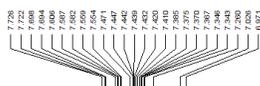




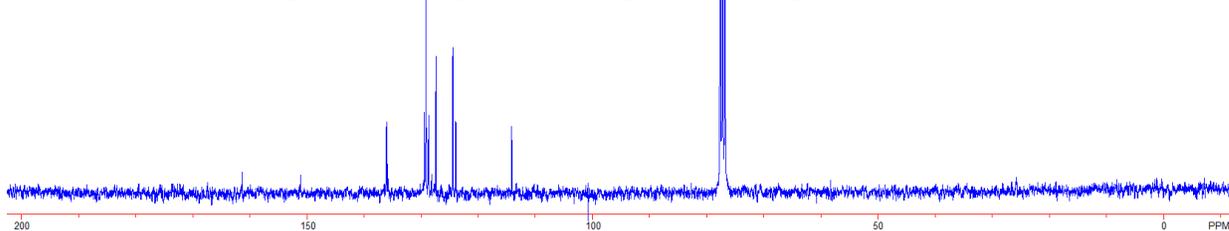
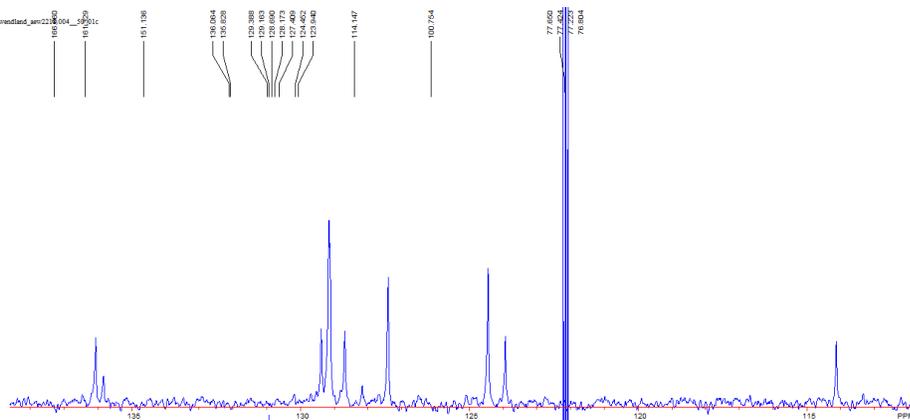


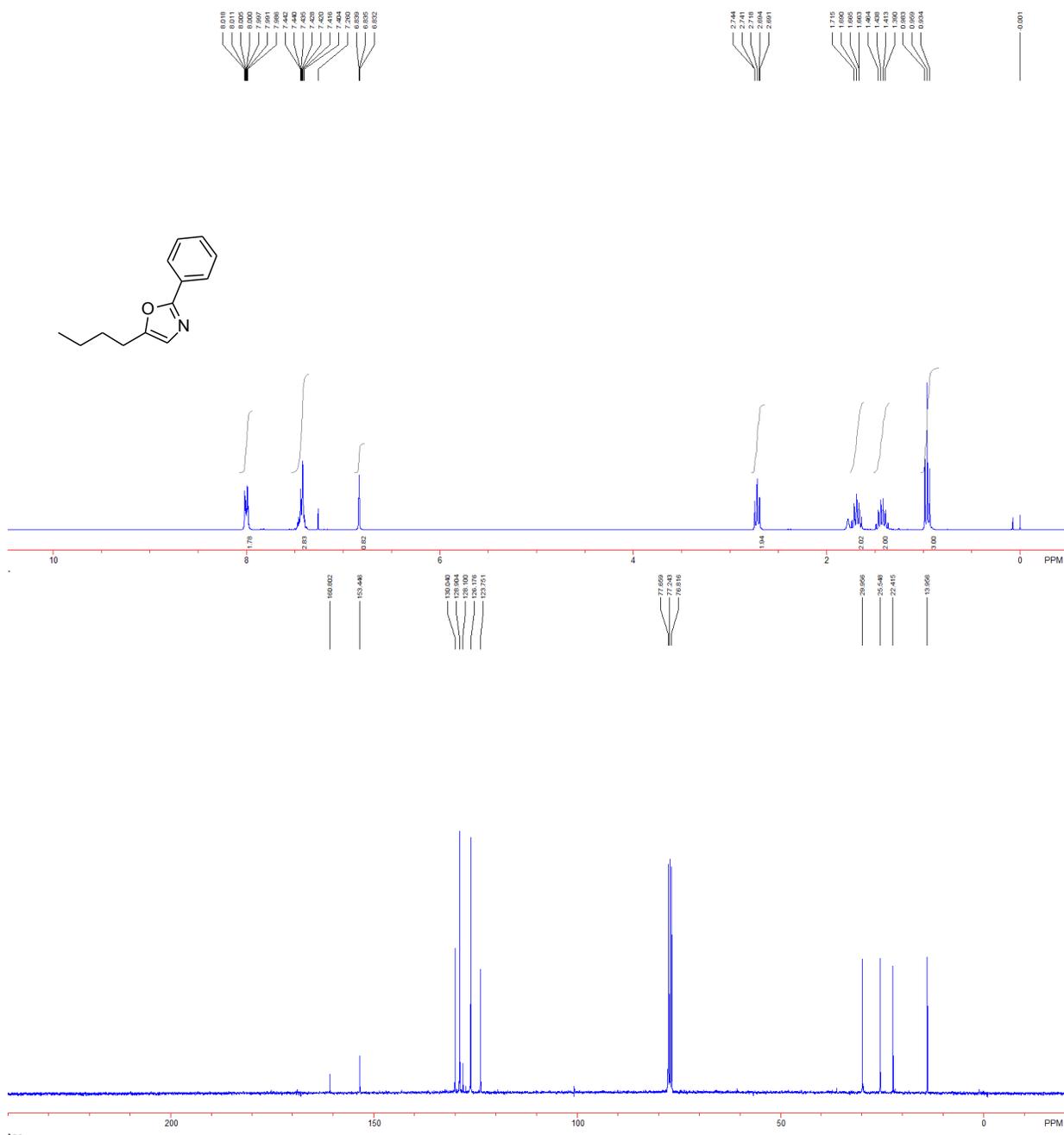


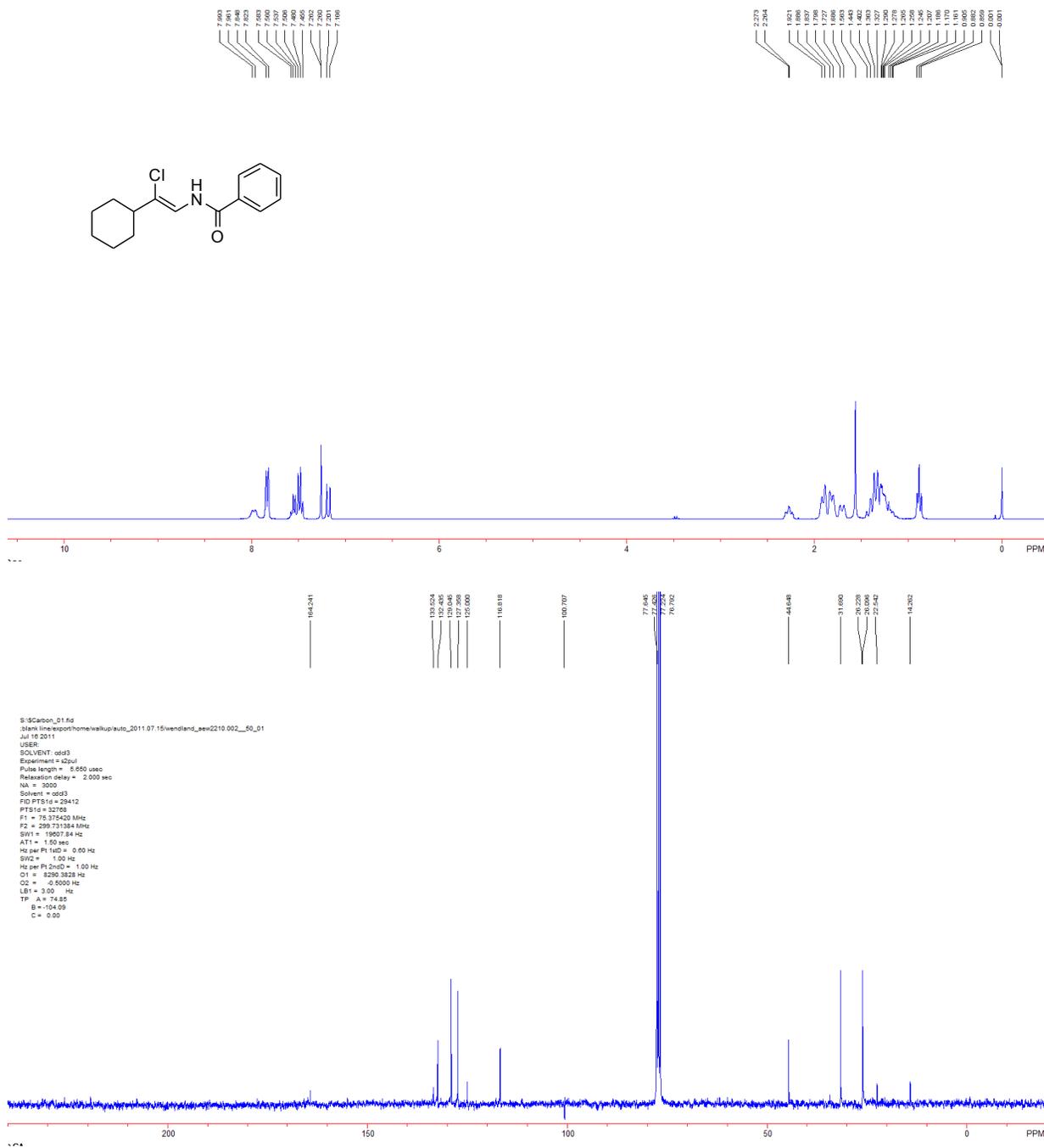
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 SOLVENT:  
 NA = 12  
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 PFS16 = 32750  
 F1 = 300.135101 MHz  
 F2 = 1.000000 MHz  
 SW1 = 6024.10 Hz  
 AT1 = 2.72 sec  
 Hz per Pt 140 = 0.18 Hz  
 SW2 = 1.00 Hz  
 Hz per Pt 200 = 1.00 Hz  
 O1 = 1732.1458 Hz  
 O2 = -1.0000 Hz  
 LB1 = 0.20 Hz  
 TP A = 80.23  
 B = -10.50  
 C = 0.00



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 Jul 22 2011  
 USER:  
 SOLVENT: cdcl3  
 Experiment = 30p1  
 Pulse length = 5.630 usec  
 Relaxation delay = 2.000 sec  
 NA = 1000  
 Solvent = cdcl3  
 FID PFS16 = 28412  
 PFS16 = 32748  
 F1 = 75.17420 100Hz  
 F2 = 299.13184 300Hz  
 SW1 = 16907.94 Hz  
 AT1 = 1.50 sec  
 Hz per Pt 140 = 0.60 Hz  
 SW2 = 1.00 Hz  
 Hz per Pt 200 = 1.00 Hz  
 O1 = 6200.3833 Hz  
 O2 = -0.5000 Hz  
 LB1 = 1.00 Hz  
 TP A = 84.56  
 B = -18.75  
 C = 0.00







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## 8. References

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