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Synthesis of heterocycles: Versatile aryne annulations via Michael addition, [3+2] cycloaddition, and palladium catalysis

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Synthesis of heterocycles: Versatile aryne annulations

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by

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LIST OF ABBREVATIONS

Ac	acetyl
aq	aqueous
Bn	benzyl
br s	broad singlet
Bu	butyl
t-Bu	*tert*-butyl
°C	degree Celsius
cat.	catalytic
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
dppf	1,1'-bis(diphenylphosphino)ferrocene
dt	doublet of triplets
eq	equation
equiv	equivalent
Et	ethyl
h	hour(s)
HRMS	high resolution mass spectroscopy
Hz	Hertz
m	multiple
Me	methyl
mg	milligram(s)

ml	milliliter(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
q	quartet
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

GENERAL INTRODUCTION

Introduction

Arynes are one of the most interesting species in organic synthesis because of their remarkably high reactivity. Although the structures of arynes were confirmed more than sixty years ago, the study of aryne chemistry was largely hindered by the harsh conditions needed to generate these reactive intermediates. Very recently, the discovery of *o*-silylaryl triflates, which can generate the corresponding arynes under very mild conditions, opened the way for a more thorough investigation into the remarkable chemistry of arynes. In the past several years in the Larock group, many aspects of the chemistry of arynes have been studied systematically and a variety of useful synthetic methodologies employing arynes have been discovered. The simple arylation of amines, phenols, carboxylic acids, carbamates, and sulfonamides by arynes was investigated first. It has also been discovered that the carbanion generated from nucleophilic attack on an aryne is able to further attack a neighboring electrophile to afford cyclization products. These tandem coupling-cyclization reactions have been employed to prepare various heterocycles exhibiting interesting biological activities. Furthermore, many heterocycles can be easily synthesized by the [3+2] cycloaddition of arynes by 1,3-dipoles. This dissertation reports in Chapters 1 and 2 one new methodology in each of the last two areas.

Palladium-catalyzed reactions have found numerous applications in organic synthesis, especially in processes involving C-C bond or C-X bond formation. The Larock research group has developed numerous palladium-mediated annulations, which generally involve multiple bond formation. These methodologies afford efficient and general protocols for the preparation of biologically active heterocycles. In the last several years, the Larock

group and other groups have been extending these metal-catalyzed annulation processes to arynes. By taken advantage of both the high reactivity of arynes and the high catalytic activity of palladium, polycyclic aromatic and heteroaromatic hydrocarbons can be synthesized from aryl halides. Chapters 3 and 4 describe two new palladium-catalyzed annulation reactions of arynes with aryl halides, in which C-C and C-N bonds can be formed simultaneously. The methods presented in this dissertation cover different areas of aryne chemistry and certainly underscore the synthetic versatility of arynes.

Dissertation Organization

This dissertation is divided into four chapters. Each chapter presented herein is written as a manuscript, which follows the guidelines for a full paper in the *Journal of Organic Chemistry*, and is composed of an abstract, introduction, results and discussion, conclusions, experimental section, acknowledgements and references.

Chapter 1 reports the synthesis of 9-substituted xanthenes from the coupling-cyclization of silylaryl triflates and *o*-hydroxychalcones in the presence of CsF. This chemistry presumably proceeds by a tandem intermolecular nucleophilic coupling of the phenoxide ion with an aryne and subsequent intramolecular Michael addition.

Chapter 2 describes the [3+2] cycloaddition of a variety of nitrones with arynes generated from *o*-silylaryl triflates in the presence of CsF. This process affords a wide variety of benzisoxazolines in good to excellent yields.

Chapter 3 reports a novel palladium-catalyzed annulation of arynes by *o*-halobenzamides, which involves simultaneous C-C and C-N bond formation to provide a novel way to synthesize a variety of phenanthridinones.

Chapter 4 describes a novel palladium-catalyzed annulation of arynes by *o*-haloacetanilides in the presence of CsF, which provides a novel route to a variety of *N*-acylcarbazoles.

Finally, all of the ^{1}H and ^{13}C NMR spectra for the new starting materials and reaction products have been compiled in appendices A-D, following the general conclusions for this dissertation.

CHAPTER 1. Synthesis of 9-Substituted Xanthenes by the Condensation of Arynes with *ortho*-Hydroxychalcones

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Abstract

The reaction of *o*-(trimethylsilyl)aryl triflates, CsF, and *o*-hydroxychalcones affords a general and efficient way to prepare biologically interesting 9-substituted xanthenes. This chemistry presumably proceeds by tandem intermolecular nucleophilic attack of the phenoxide of the chalcone on the aryne and subsequent intramolecular Michael addition. The introduction of an external base, Cs_2CO_3, has proven beneficial in this reaction.

Introduction

From some of the oldest known dyes[1] to newly developed agriculturally- and pharmaceutically-interesting intermediates,[2] xanthenes have attracted attention for decades and continue to be the focus of biological and material science studies today.

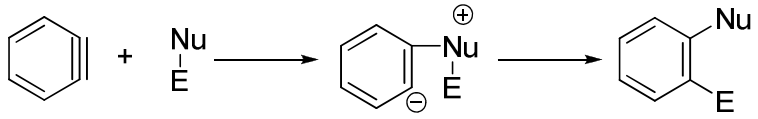
Many naturally-occurring and man-made xanthene derivatives have been reported to exhibit extraordinary biological activities, including anti-malarial,[3] anti-trypanosomal,[4] anti-leishmanial,[4] and anti-tumor[5] activities. More recently, the notable fluorescent properties of xanthenes have received attention. For example, xanthene derivatives have been prepared as fluorescent probes,[6] and electrostatic sensors.[7]

The synthesis of xanthene derivatives has also been widely studied. There are several well established approaches to xanthene derivatives,[8] which typically feature formation

of the central heterocyclic ring, often by combinations of Friedel-Crafts methodology and C-O bond formation. Xanthenes can also be obtained by reduction of the corresponding xanthones.[9] However, most of these synthetic approaches involve either multistep procedures or fairly harsh reaction conditions.

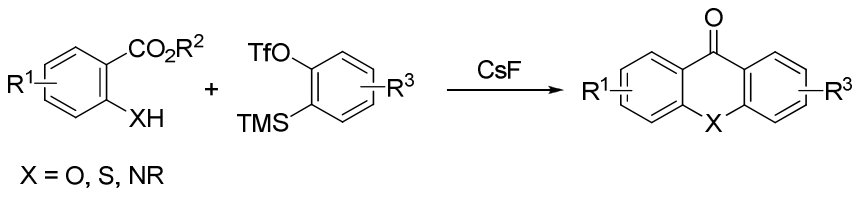
Since a convenient approach to aryne generation by the fluoride-induced 1,2-elimination of *o*-(trimethylsilyl)aryl triflates was first reported in 1983,[10] the reactivity of arynes, especially their electrophilicity, has been explored extensively. For example, in our group, *in situ* generated benzyne has been coupled with simple nucleophiles, such as amines, sulfonamides, phenols and arenecarboxylic acids,[11] to generate monosubstituted arenes. Besides those simple coupling reactions, insertion processes (Scheme 1) have

Scheme 1



been reported for nucleophiles bearing neighboring electrophiles, such as ureas,[12] keto esters,[13] amides,[14] sulfonamides,[14] and acid halides.[15] We have been particularly interested in annulation processes, which rapidly construct biologically-interesting ring systems by simple tandem processes. For example, we have reported that salicylates and *in situ* generated arynes readily react to form heteroatom ring systems, such as xanthones, thioxanthones and acridones (Scheme 2).[16]

Scheme 2



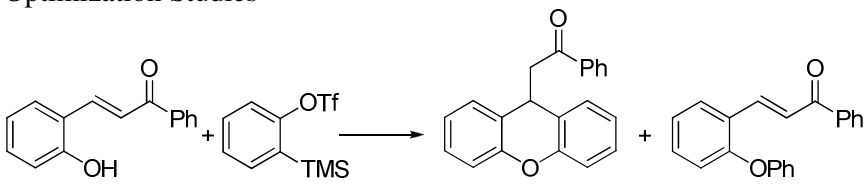
Herein, we present a novel coupling reaction between *o*-hydroxychalcones and *o*-(trimethylsilyl)aryl triflates, which provides a new method for the synthesis of 9-substituted xanthenes in a simple one step process under very mild reaction conditions.[17] During the course of our work, related chemistry has recently been reported.[18]

Results and Discussion

Optimization Studies

Our optimization work was carried out using commercially available *o*-hydroxychalcone **1a** and *o*-(trimethylsilyl)phenyl triflate (**2a**) under a variety of different reaction conditions (Table 1). We first examined some commonly used benzyne reaction

Table 1. Optimization Studies[a]



1a **2a** **3a** **4a**

entry	CsF (equiv)	solvent	temp (^oC)	additive (equiv)	% yield[b] **3a** (**4a**)
1	2.0	MeCN	rt	--------	32 (68)
2	2.0 TBAF[c]	THF	rt	--------	17 (65)
3	2.0	THF	rt	--------	trace[d]
4	2.0	THF	65	--------	60 (17)
5	3.0	THF	65	--------	67
6	5.0	THF	65	--------	74
7	3.0	THF	65	1.0 Cs_2CO_3	80

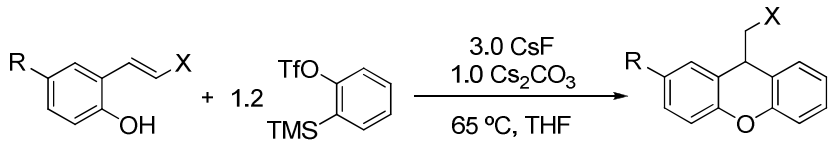
[a]Reactions were conducted on a 0.25 mmol scale with 1.2 equiv of **2a** in 10 ml of solvent for 24 h. [b]Yields of products isolated by column chromatography. [c]TBAF (1M in THF). [d] Very low conversion.

conditions, namely MeCN as the solvent with added CsF (entry 1), and THF solvent with TBAF[19] (entry 2). Not surprisingly,[11] our initial studies indicated that significant amounts of the corresponding phenyl ether **4a** were generated alongside **3a**, which was produced in only a low yield. When employing CsF in THF solvent (entry 3), although the reaction proceeded in very low conversion, the desired product **3a** was generated as the major product, which suggested that THF was able to suppress proton abstraction.[16] By raising the temperature to 65 ºC (entry 4), the reaction could be completed in 24 h and a 60% yield was produced. Interestingly, we observed that as the amount of the base CsF added to the system was increased (entries 5 and 6), the yield improved. Finally, with the addition of 1 equiv of Cs_2CO_3 (entry 7), the yield was improved to 80%. Other bases, such as Li_2CO_3 and K_2CO_3, were also tested, but none of them was as effective as Cs_2CO_3. Thus, the reaction conditions reported in entry 7 (3 equiv of CsF, 1 equiv of Cs_2CO_3 in THF solvent at 65 °C) were chosen as our optimal conditions for further study.

Synthesis of 9-Substituted Xanthenes

We next examined a wide range of *o*-hydroxychalcones bearing various functional groups (Table 2). Chalcones with electron-donating methoxy (entry 2) and methyl (entry 3) substituents provided decent yields, 74% and 64%, respectively. A fluoro-substituted chalcone (entry 4) also afforded good results. Substrates with other electron-withdrawing groups, such as I (entry 5), Br (entry 6), and NO_2 (entry 7) groups, resulted in much lower yields under our "optimal" conditions. However, by simply removing the Cs_2CO_3 base (1.2 equiv of **2a**, 3.0 equiv of CsF, THF, 65 ºC), the yields can be improved significantly. This is probably because phenoxide anions bearing electron-withdrawing groups can be generated in substantial amounts when Cs_2CO_3 is present, which favors the formation of the side products (see the mechanistic discussion).

Table 2. Reaction Scope with Different Chalcone Derivatives[a]



1a **2a** **3**

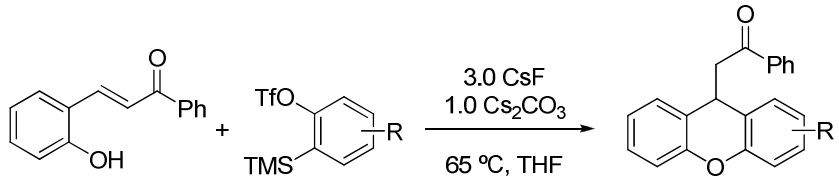
entry	chalcone	R	X	product / yield (%)[b]
1	**1a**	H	C(O)Ph	**3a** / 80
2	**1b**	OMe	C(O)Ph	**3b** / 74
3	**1c**	Me	C(O)Ph	**3c** / 64
4	**1d**	F	C(O)Ph	**3d** / 84
5	**1e**	I	C(O)Ph	**3e** / 60 (78)[c]
6	**1f**	Br	C(O)Ph	**3f** / 58 (75)[c]
7	**1g**	NO_2	C(O)Ph	**3g** / 41 (70)[c]
8	**1h**	H	$C(O)C_6H_4(OMe)$-*p*	**3h** / 61
9	**1i**	H	$C(O)C_6H_4I$-*p*	**3i** / 73
10	**1j**	H	C(O)Me	**3j** / 71
11	**1k**	H	C(O)*t*-Bu	**3k** / 65
12	**1l**	H	$C(O)C_6H_{11}$	**3l** / 64
13	**1m**	H	CHO	**3m** / 60
13	**1n**	H	CN	**3n** / 70
15	**1o**	H	CO_2*t*-Bu	**3o** / 60[d]
16	**1p**	H	SO_2Ph	**3p** / 15 (51)[e]

[a] Reactions were conducted on a 0.25 mmol scale for 24 h. [b] Yields of products isolated by column chromatography. [c] Reactions were conducted with 1.2 equiv of **2a**, 3.0 equiv of CsF and THF (10 ml) at 65 °C. [d] ^1H NMR spectroscopic yield. [e] This reaction was conducted with 2.0 equiv of **2a**, 3.0 equiv of CsF, THF (10 ml) at 45 °C for 30 h.

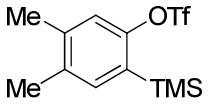
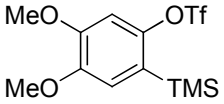
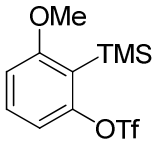
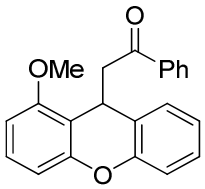
The effect of the group X on the carbon-carbon double bond has also been examined. Decent yields were provided by substrates with different acyl groups (entries 8-12). Aldehyde (entry 13) and cyano (entry 14) groups are also tolerated. For the substrate with an ester group (entry 15), an inseparable mixture of the desired product and arylation side product was generated. For reasons that are not obvious, a sulfonyl group does not activate the Michael acceptor sufficiently in this chemistry to produce a good yield. The use of additional benzyne precursor, a lower temperature and a longer reaction time were necessary to get a decent yield (entry 16).

The behavior of the aryne precursors **2b**, **2c**, and **2d** (Table 3) has also been examined

Table 3. Reaction with Different Benzyne Precursors[a]



1a **2** **3**

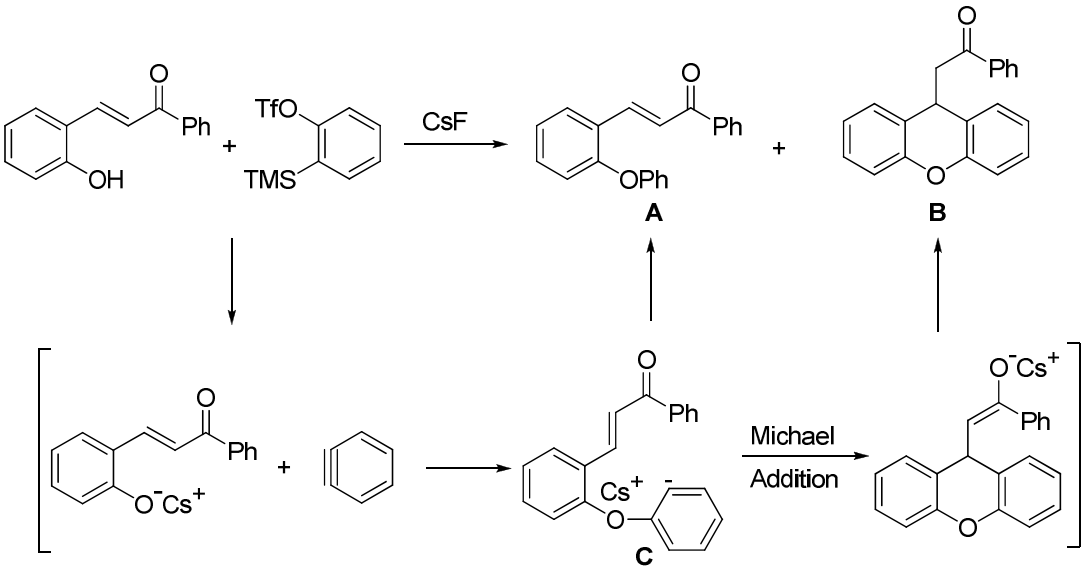
entry	aryne precursor		product / % yield[b]
1		**2b**	**3q** / 51
2		**2c**	**3r** / 46[c]
3		**2d**	 **3s** / 57

[a]Rections were conducted on a 0.25 mmol scale for 24 h in 10 ml of THF. [b]Yields of products isolated by column chromatography. [c]The reaction time was 48 h.

in this reaction. All of these substrates generated lower yields than benzyne itself, perhaps due to slower aryne generation. We have observed that aryne precursor **2d** affords a single isomeric product **3s**. This regioselectivity for 3-methoxybenzyne has been seen previously in our group and by others.[20]

Based on the experimental results and previous studies,[11,16] we postulate that this coupling reaction proceeds in the following manner (Scheme 3). The intermediate **C**

Scheme 3. Possible Mechanism



generated from nucleophilic coupling of the aryne and the aryl oxide undergoes intramolecular Michael addition to afford the desired xanthene **B** after protonation. However, well known H abstraction by **C** could lead to diaryl ether **A**, which has been observed by us as the major side product for most of the substrates examined in this reaction. Since the proton abstraction of **C** is quite fast, a competition is present between intramolecular cyclization and intermolecular proton abstraction. In order to supress this side reaction, dry reaction conditions and the addition of an extra base are necessary. This

helps to remove the acidic protons present before intermediate **C** is able to react with the proton and generate the side product **A**.

Conclusions

In conclusion, we have demonstrated that *o*-hydroxychalcones and related compounds undergo annulation reactions with *o*-(trimethylsilyl)aryl triflates through tandem nucleophilic coupling and subsequent Michael addition. This reaction affords a general one-pot approach to 9-substituted xanthenes from readily prepared starting materials. Mild reaction conditions allow a variety of functional groups to be tolerated in this reaction. With carbonyl and other functionalities in the products, further elaboration can easily be achieved.

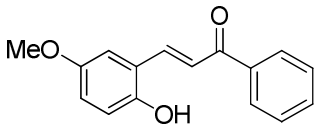
Experimental Section

General

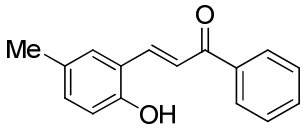
The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. High resolution mass spectra were recorded using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. All reactions were carried out in oven-dried glassware and monitored by thin layer chromatography (SiO_2, hexanes or hexanes/EtOAc). THF was distilled over Na. The silylaryl triflate **1a**, CsF, TBAF solution (1M in THF) and acetonitrile were purchased from Sigma-Aldrich Co. The 4,5-dimethyl-substituted silylaryl triflate **2b**, 4,5-dimethoxy-substituted silylaryl triflate **2c** and 3-methoxy-substituted silylaryl triflate **2d** were prepared according to a literature procedure.[21]

Non-commercial compounds

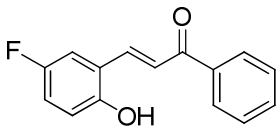
Non-commercially available starting materials were prepared according to literature procedures.[22]



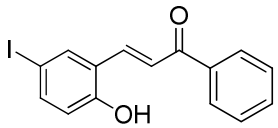
3-(2-Hydroxy-5-methoxyphenyl)-1-phenyl-2-propen-1-one (1b): yellow solid, mp 95-97 °C; ^{1}H NMR (400 MHz, d_6-acetone) δ 8.81 (s, 1H), 8.20 (d, J = 12.0 Hz, 1H), 8.16 (m, 2H), 7.90 (d, J = 16.0 Hz, 1H), 7.57 (m, 3H), 7.40 (s, 1H), 6.93 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (400 MHz, d_6-acetone) δ 189.75, 153.48, 151.45, 139.79, 138.76, 132.83, 128.85, 128.58, 122.50, 121.80, 118.85, 117.37, 112.29, 55.42; HRMS (EI) calcd for $C_{16}H_{14}O_3$: 254.0943, found 254.0947.



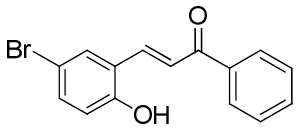
3-(2-Hydroxy-5-methyl)-1-phenyl-2-propen-1-one (1c): yellow solid, mp 143-145 °C; ^{1}H NMR (300 MHz, d_6-acetone) δ 8.99 (s, 1H), 8.19 (d, J = 15.0 Hz, 1H), 8.11 (m, 2H), 7.88 (d, J = 15.0 Hz, 1H), 7.58 (m, 4H), 7.10 (dd, J = 3.0, 9.0 Hz, 1H), 6.90 (d, J = 9.0 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (300 MHz, d_6-acetone) δ 189.68, 155.17, 139.99, 138.84, 132.75, 129.15, 128.84, 128.52, 121.90, 121.43, 116.35, 19.84; HRMS (EI) calcd for $C_{16}H_{14}O_2$: 238.0994, found 238.0996.



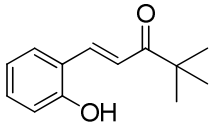
3-(5-Fluoro-2-hydroxy)-1-phenyl-2-propen-1-one (1d): yellow solid, mp 177-179 °C; ^{1}H NMR (300 MHz, d_6-acetone) δ 9.21 (s, 1H), 8.16 (m, 3H), 7.93 (d, J = 15.0 Hz, 1H), 7.62 (m, 4H), 7.05 (m, 2H); ^{13}C NMR (300 MHz, d_6-acetone) δ 189.36, 157.84, 153.42, 138.53, 138.27, 138.24, 132.96, 128.86, 128.62, 123.33, 123.25, 122.68, 118.49, 118.25, 117.53, 117.45, 114, 05, 113.83; HRMS (EI) calcd for $C_{15}H_{11}O_2F$: 242.0743, found 242.0747.



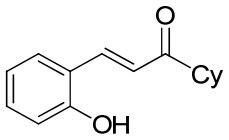
3-(2-Hydroxy-5-iodo)-1-phenyl-2-propen-1-one (1e): yellow solid, mp 164-165 °C; ^{1}H NMR (300 MHz, d_6-acetone) δ 9.51 (s, 1H), 8.16 (m, 3H), 8.08 (d, J = 15.0 Hz, 1H), 7.95 (d, J = 15.0 Hz, 1H), 7.60 (m, 4H), 6.86 (d, J = 6.0 Hz, 1H); ^{13}C NMR (300 MHz, d_6-acetone) δ 189.36, 156.96, 140.22, 138.51, 137.79, 137.05, 132.97, 128.87, 128.65, 125.15, 122.72, 118.87, 81.51. HRMS (EI) calcd for $C_{15}H_{11}O_2I$: 349.9804, found 349.9802.



3-(5-Bromo-2-hydroxy)-1-phenyl-2-propen-1-one (1f): yellow solid, mp 165-166 °C; ^{1}H NMR (300 MHz, d_6-acetone) δ 9.49 (s, 1H), 8.10 (m, 5H), 7.61 (m, 3H), 7.41 (d, J = 9.0 Hz, 1H), 6.98 (d, J = 9.0 Hz, 1H); ^{13}C NMR (300 MHz, d_6-acetone) δ 189.31, 156.27, 138.49, 137.78, 134.24, 132.98, 130.94, 128.87, 128.65, 124.57, 122.84, 118.40, 111.80. HRMS (EI) calcd for $C_{15}H_{11}O_2Br$: 302.9932, found 302.9933.



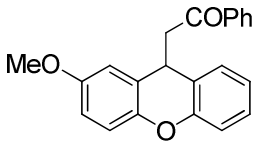
1-(2-Hydroxyphenyl)-4,4-dimethylpent-1-en-3-one (1k): white solid, mp 115-117 °C; ^{1}H NMR (400 MHz, d_6-acetone) δ 9.09 (s, 1H), 8.01 (d, J = 16.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 16.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.88 (t, J = 8.0 Hz, 1H), 1.20 (s, 9H); ^{13}C NMR (400 MHz, d_6-acetone) δ 203.35, 157.00, 137.77, 131.51, 128.94, 122.27, 121.03, 120.12, 116.34, 42.98, 25.94. HRMS (EI) calcd for $C_{13}H_{16}O_2$: 204.1150, found 204.1154.



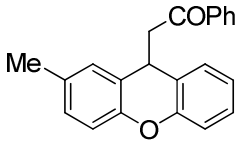
1-Cyclohexyl-3-(2-hydroxyphenyl)-2-propen-1-one (1l): white solid, mp 163-165 °C; ^{1}H NMR (300 MHz, d_6-acetone) δ 9.10 (s, 1H), 7.95 (d, J = 18.0 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.25 (t, J = 9.0 Hz, 1H), 7.03 (d, J = 18.0 Hz, 1H), 6.96 (d, J = 6.0 Hz, 1H), 6.89 (t, J = 9.0 Hz, 1H), 2.71 (m, 1H), 1.75 (m, 5H), 1.35 (m, 5H); ^{13}C NMR (300 MHz, d_6-acetone) δ 202.10, 156.89, 137.06, 131.51, 128.72, 124.88, 122.04, 120.17, 116.32, 49.07, 29.19, 26.08, 25.76. HRMS (EI) calcd for $C_{15}H_{18}O_2$: 230.1307, found 230.1312.

Representative procedure for the condensation of arynes with *o*-hydroxychalcones

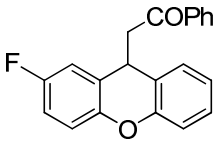
o-Hydroxychalcone (0.25 mmol), the silylaryl triflate (0.3 mmol), CsF (0.75 mmol) and Cs_2CO_3 (0.25 mmol) in 10 ml of anhydrous THF were stirred at 65 °C for about 24 h. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate and washed with brine. The aqueous layer was re-extracted with ethyl acetate. The organic layers were combined, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel.



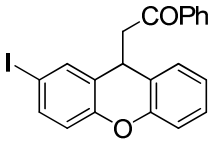
2-(2-Methoxy-9*H*-xanthen-9-yl)-1-phenylethanone (3b): white solid, mp 128-129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 7.5 Hz, 2H), 7.50 (t, J = 7.5 Hz, 1H), 7.35 (m, 3H), 7.20 (t, J = 6.0 Hz, 1H), 7.05 (m, 3H), 6.85 (d, J = 3.0 Hz, 1H), 6.77 (dd, J = 3.0, 9.0 Hz, 1H), 4.83 (t, J = 6.0 Hz, 1H), 3.74 (s, 3H), 3.36 (dd, J = 3.0, 6.0 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.16, 155.72, 152.78, 146.55, 137.14, 133.35, 128.96, 128.72, 128.29, 128.03, 126.35, 125.26, 123.44, 117.45, 116.67, 114.19, 113.05, 55.89, 49.79, 35.30; HRMS (EI) calcd for $C_{22}H_{18}O_3$: 330.1256, found 330.1253.



2-(2-Methyl-9*H*-xanthen-9-yl)-1-phenylethanone (3c): white solid, mp 82-83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.50 (t, J = 9.0 Hz, 1H), 7.35 (m, 3H), 7.20 (t, J = 8.0 Hz, 1H), 7.10 (m, 2H), 7.01 (m, 3H), 4.81 (t, J = 6.0 Hz, 1H), 3.35 (d, J = 6.0 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.16, 152.65, 150.38, 137.19, 133.28, 133.02, 129.21, 129.04, 128.68, 128.63, 128.27, 127.97, 125.71, 125.36, 123.45, 116.68, 116.41, 49.96, 34.85, 20.91; HRMS (EI) calcd for $C_{22}H_{18}O_2$: 314.1307, found 314.1307.

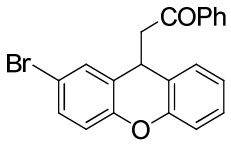


2-(2-Fluoro-9*H*-xanthen-9-yl)-1-phenylethanone (3d): white solid, mp 114-115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (m, 2H), 7.51 (t, J = 9.0 Hz, 1H), 7.31 (m, 4H), 7.08 (m, 4H), 6.91 (td, J = 3.0, 7.5 Hz, 1H), 4.84 (t, J = 6.0 Hz, 1H), 3.37 (dd, J = 3.0, 6.0 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 197.59, 160.34, 157.14, 152.49, 148.61, 136.93, 133.45, 128.85, 128.75, 128.24, 128.22, 127.13, 127.03, 124.84, 123.84, 117.85, 117.73, 116.71, 115.34, 115.03, 114.96, 114.65, 49.60, 34.78; HRMS (EI) calcd for $C_{21}H_{15}O_2F$: 318.1056, found 318.1055.

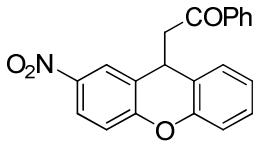


2-(2-Iodo-9*H*-xanthen-9-yl)-1-phenylethanone (3e): white solid, mp 133-134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.8 Hz, 2H), 7.63 (s, 1H), 7.53-7.18 (m, 6H), 7.06 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 4.78 (t, J = 6.0 Hz, 1H), 3.34 (d, J = 6.0 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 197.50, 152.45, 152.07, 137.58, 136.90, 133.45, 129.01,

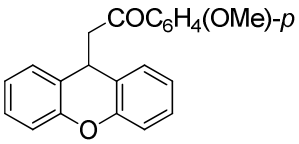
128.75, 128.25, 125.05, 123.96, 118.95, 116.76, 115.72, 49.78, 34.42; HRMS (EI) calcd for $C_{21}H_{15}O_2I$: 426.0117, found 426.0127.



2-(2-Bromo-9*H*-xanthen-9-yl)-1-phenylethanone (3f): white solid, mp 131-132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.48 (m, 2H), 7.39 (t, J = 7.2 Hz, 4H), 7.25 (m, 4H), 7.06 (m, 2H), 6.99 (d, J = 8.1 Hz, 1H), 4.81 (t, J = 6.6 Hz, 1H), 3.37 (d, J = 6.6 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 197.50, 152.16, 151.66, 136.94, 133.48, 131.66, 130.99, 130.26, 128.98, 128.84, 128.77, 128.27, 127.83, 124.99, 123.99, 118.53, 116.77, 115.72, 49.78, 34.42; HRMS (EI) calcd for $C_{21}H_{15}O_2Br$: 379.0244, found 379.0249.

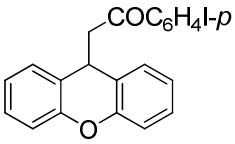


2-(2-Nitro-9*H*-xanthen-9-yl)-1-phenylethanone (3g): white solid, mp 133-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 2.4 Hz, 1H), 8.11 (dd, J = 9.0, 3.0 Hz, 1H), 7.83 (m, 2H), 7.52 (t, J = 7.5 Hz, 1H), 7.24 (m, 8H), 4.92 (t, J = 6.0 Hz, 1H), 3.44 (d, J = 6.0 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 196.92, 157.23, 151.37, 143.57, 136.68, 133.67, 128.89, 128.85, 128.67, 128.25, 126.29, 125.42, 124.92, 124.15, 124.09, 117.50, 116.95, 49.65, 34.17; HRMS (EI) calcd for $C_{21}H_{15}O_4N$: 345.1001, found 345.1002.

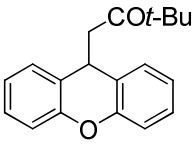


1-(4-Methoxyphenyl)-2-(9*H*-xanthen-9-yl)ethanone (3h): white solid, mp 111-112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.34 (d, J = 7.5 Hz, 2H), 7.22 (t, J = 6.0 Hz, 2H), 7.13 (d, J = 7.5 Hz, 1H), 7.03 (td, J = 7.5, 1.2 Hz, 2H), 6.84 (m, 2H), 4.86 (t, J = 6.0

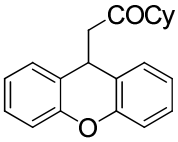
Hz, 1H), 3.83 (s, 3H), 3.31 (d, J = 6.0 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 196.56, 163.64, 152.47, 130.57, 130.28, 129.04, 127.97, 125.80, 123.62, 116.68, 113.80, 55.62, 49.55, 34.93; HRMS (EI) calcd for $C_{22}H_{18}O_3$: 330.1256, found 330.1256.



1-(4-Iodophenyl)-2-(9*H*-xanthen-9-yl)ethanone (3i): white solid, mp 129-131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.34 (d, J = 7.5 Hz, 2H), 7.22 (t, J = 6.0 Hz, 2H), 7.13 (d, J = 7.5 Hz, 1H), 7.03 (td, J = 7.5, 1.2 Hz, 2H), 6.84 (m, 2H), 4.86 (t, J = 6.0 Hz, 1H), 3.83 (s, 3H), 3.31 (d, J = 6.0 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 197.42, 152.49, 137.97, 136.34, 129.63, 128.93, 128.15, 125.46, 123.70, 116.79, 101.39, 49.63, 34.93; HRMS (EI) calcd for $C_{21}H_{15}O_2I$: 426.0117, found 426.0125.

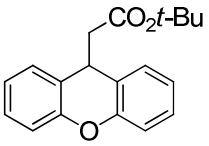


1-*tert*-Butyl-2-(9*H*-xanthen-9-yl)ethanone (3k): white solid, mp 86-87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 4H), 7.10 (m, 2H), 7.03 (td, J = 6.0, 1.5 Hz, 2H), 4.68 (t, J = 6.0 Hz, 1H), 2.81 (d, J = 6.0 Hz, 2H), 0.89 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 213.48, 152.52, 128.82, 127.96, 125.90, 123.59, 116.66, 48.04, 44.50, 34.86, 25.70; HRMS (EI) calcd for $C_{19}H_{20}O_2$: 280.1463, found 280.1463.

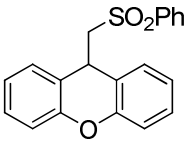


1-Cyclohexyl-2-(9*H*-xanthen-9-yl)ethanone (3l): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 4H), 7.04 (m, 4H), 4.64 (t, J = 6.0 Hz, 1H), 2.79 (d, J = 6.0 Hz, 2H), 2.04 (m, 1H), 1.63 (m, 5H), 1.11 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.91, 152.39,

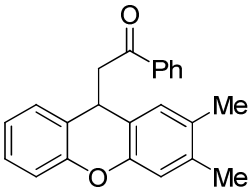
128.82, 127.97, 125.76, 123.60, 116.67, 51.90, 51.85, 34.59, 27.94, 25.95, 25.68; HRMS (EI) calcd for $C_{21}H_{22}O_2$: 306.1620, found 306.1623.



9*H*-Xanthene-9-acetic acid, *tert*-butyl ester (3o): colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 4H), 7.06 (m, 4H), 4.50 (t, J = 6.0 Hz, 1H), 2.60 (d, J = 6.0 Hz, 2H), 1.25 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.78, 152.28, 128.77, 128.13, 124.69, 123.46, 116.72, 80.99, 47.01, 35.92, 28.15; HRMS (EI) calcd for $C_{19}H_{20}O_3$: 296.1412, found 296.1402.

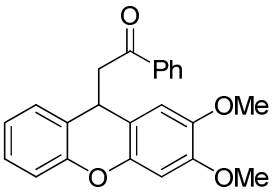


9-(Phenylsulfonyl)methyl-9*H*-xanthene (3p): white solid, mp 129-131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (m, 1H), 7.84 (m, 2H), 7.50 (m, 3H), 7.37 (d, J = 7.5 Hz, 2H), 7.23 (td, J = 7.5, 1.5 Hz, 2H) , 7.08 (d, J = 7.5 Hz, 3H), 4.86 (t, J = 5.7 Hz, 1H), 3.42 (d, J = 5.7 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 152.37, 140.18, 133.86, 133.36, 129.48, 129.30, 128.76, 127.93, 127.83, 123.95, 123.28, 116.88, 65.56, 33.77; HRMS (EI) calcd for $C_{20}H_{16}O_3S$: 336.0820, found 336.0810.

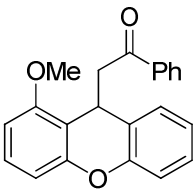


2-(2,3-Dimethyl-9*H*-xanthen-9-yl)-1-phenylethanone (3q): white solid, mp 95-97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.48 (t, J = 6.0 Hz, 1H), 7.31 (m, 3H), 7.17

(t, *J* = 6.0 Hz, 1H), 7.06 (m, 2H) , 6.98 (t, *J* = 6.0 Hz, 1H), 6.90 (s, 1H), 4.78 (t, *J* = 6.0 Hz, 1H), 3.33 (d, *J* = 6.0 Hz, 2H), 2.21 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.27, 166.55, 152.66, 150.38, 137.23, 136.50, 133.24, 131.75, 129.58, 129.07, 128.67, 128.28, 127.89, 125.81, 123.32, 122.62, 117.49, 116.68, 50.19, 34.37, 19.79, 19.21; HRMS (EI) calcd for $C_{23}H_{20}O_2$: 328.1126, found 328.1121.



2-(2,3-Dimethoxy-9*H*-xanthen-9-yl)-1-phenylethanone (3r): white solid, mp 138-140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 9.0 Hz, 2H), 7.50 (t, *J* = 9.0 Hz, 1H), 7.40-7.18 (m, 4H), 7.10-6.99 (m, 2H), 6.79 (s, 1H) , 6.68 (s, 1H), 4.80 (t, *J* = 6.0 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.33 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.61, 152.53, 148.73, 146.12, 145.28, 137.21, 133.37, 128.95, 128.72, 128.29, 127.94, 125.34, 123.53, 116.58, 115.92, 111.18, 100.77, 56.46, 56.19, 50.19, 34.62; HRMS (EI) calcd for $C_{23}H_{20}O_4$: 360.1218, found 360.1219.



2-(1-Methoxy-9*H*-xanthen-9-yl)-1-phenylethanone (3s): white solid, mp 125-127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.50 (t, *J* = 6.0 Hz, 1H), 7.33 (m, 3H), 7.20 (t, *J* = 6.0 Hz, 1H), 7.03 (m, 3H), 6.84 (d, *J* = 3.0 Hz, 1H) , 6.75 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.82 (t, *J* = 6.0 Hz, 1H), 3.73 (s, 3H), 3.35 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 198.16, 152.72, 152.78, 146.55, 137.15, 133.35, 128.96, 128.72, 128.29,

128.03, 126.35, 125.26, 123.44, 117.45, 116.67, 114.19, 113.05, 55.89, 49.79, 35.30; HRMS (EI) calcd for $C_{22}H_{18}O_3$: 330.1312, found 330.1318.

Acknowledgments

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CHAPTER 2. Synthesis of Benzisoxazolines by the Highly Efficient Coupling of Arynes with Nitrones

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Abstract

A variety of substituted benzisoxazolines have been synthesized by the [3+2] cycloaddition of nitrones and arynes. The reaction scope is broad, the reaction conditions are mild, and the process tolerates a variety of functional groups.

Introduction

Benzisoxazoline is a critical sub-unit in pharmaceuticals with important biological and pharmacological activities, including antimicrobial activity against *Salmonella paratyphi*, *Proteus vulgaris*, *Xanthomonas spp.*, *Fusarium solanii*, and *Botrytis cinerea*.[1] Benzisoxazolines can also be important synthetic intermediates for the preparation of more complex molecules.[2] Much effort has been devoted to the synthesis of this heterocyclic ring system.[3]

Since a convenient approach to aryne generation by the fluoride induced 1,2-elimination of *o*-(trimethylsilyl)aryl triflates was first reported,[4] highly electrophilic arynes have been employed extensively in recent years for the construction of many heteroaromatic structures.[5] Our group has recently reported that simple nucleophilic reactions,[6] annulation reactions of *ortho*-heteroatom (N, O, and S)-substituted benzoates[7]

and a variety of 1,3-dipolar cycloadditions[8] provide useful new synthetic routes to a variety of heterocycles, generally affording excellent yields under mild reaction conditions. In a continuation of our work on the reactions of arynes with dipoles, we have investigated the cycloaddition reactions of nitrones and arynes. During this project, related work was communicated by other groups,[9] although the reaction conditions are different. Herein, we wish to report our more detailed and extensive results of the 1,3-dipolar cycloaddition reaction of nitrones and arynes to afford substituted benzisoxazolines.[10]

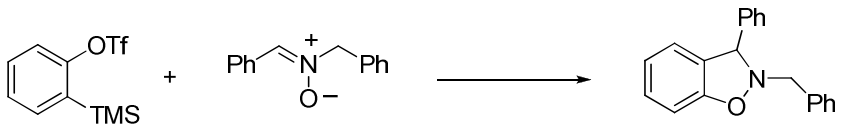
Results and Discussion

Optimization Studies

We optimized the reaction conditions for the reaction of the unsubstituted benzyne precursor *o*-(trimethylsilyl)phenyl triflate (**1a)** and *N*-benzylidenebenzylamine *N*-oxide (**2a)** (Table 1). Employing acetonitrile as the solvent and 3.0 equiv of CsF as the fluoride source, adding more CsF or more benzyne precursor failed to improve the yield significantly, presumably due to the fast generation of benzyne in acetonitrile (entries 1-3). Another fluoride ion source, TBAF,[11] was also examined (entries 4 and 5). By utilizing 2.0 equiv of **1a** and 4.0 equiv of TBAF in THF (entry 5), a high yield of the corresponding benzisoxazoline (92%) was obtained. These reaction conditions, however, turned out not to be suitable for other nitrones, probably again due to the relative rapid rate of benzyne generation. In order to better control the rate of benzyne generation, differing amounts of CsF in THF were examined, since CsF has limited solubility in THF, thus reducing the rate of benzyne generation (entries 6-9). Using 2.0 equiv of **1a** and 5.0 equiv of CsF at 65 ^{o}C in THF, a 93% yield of the desired cycloadduct was produced

(entry 7). Using reduced amounts of the benzyne precursor (1.6 equiv) and CsF (4.0 equiv) still afforded a high 91% yield (entry 8).

Table 1. Optimization studies of the reaction between *o*-(trimethylsilyl)phenyl triflate (**1a**) and *N*-benzylidenebenzylamine *N*-oxide (**2a**) [a]



1a **2a** **3a**

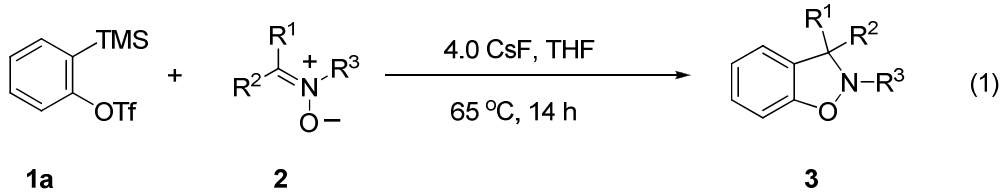
entry	benzyne (equiv)	CsF (equiv)	solvent	temp. (°C)	time (h)	% yield of **3a**[b]
1	1.2	3.0	MeCN	rt	24	60
2	1.2	4.0	MeCN	rt	24	65
3	2.0	3.0	MeCN	rt	24	56
4	1.2	2.0 TBAF[c]	THF	rt	24	45
5	2.0	4.0 TBAF[c]	THF	45	24	92
6	1.2	3.0	THF	65	24	68
7	2.0	5.0	THF	65	14	93
8	1.6	4.0	THF	65	14	91
9	1.6	3.0	THF	65	24	83

[a]All reactions were conducted on a 0.25 mmol scale in 5 ml of solvent for 24 h. [b]Yields of product isolated by column chromatography. [c]1M TBAF in THF solution.

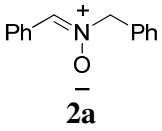
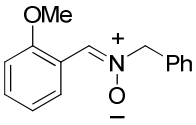
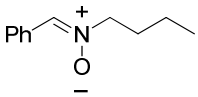
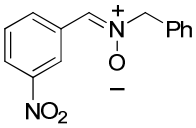
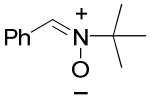
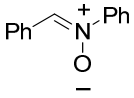
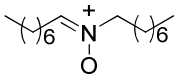
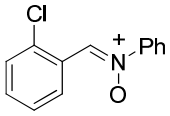
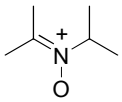
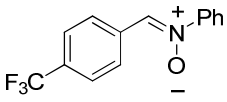
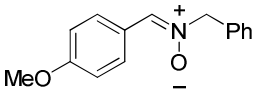
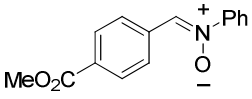
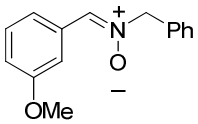
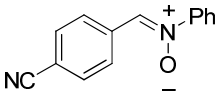
Reaction Scope and Limitations

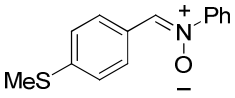
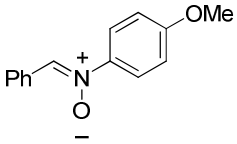
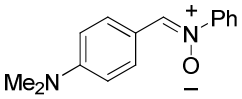
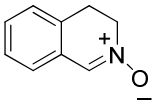
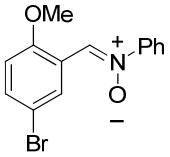
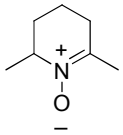
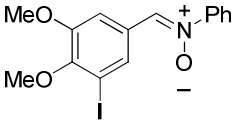
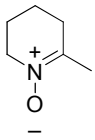
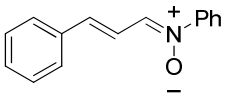
Using the optimal conditions shown in Table 1, entry 8, the scope and limitations of this methodology have been examined. Various substituted nitrones have been examined in this reaction (eq 1) and the results are summarized in Table 2.

Table 2. Cycloadditions of Benzyne with Nitrones [a]



1a **2** **3**

entry	nitrone	yield (%)[b]	entry	nitrone	yield (%)[b]
1	 **2a**	**3a**/91	8	 **2h**	**3h**/65
2	 **2b**	**3b**/88	9	 **2i**	**3i**/69
3	 **2c**	**3c**/95	10	 **2j**	**3j**/92
4	 **2d**	**3d**/90	11	 **2k**	**3k**/90
5	 **2e**	**3e**/79	12	 **2l**	**3l**/93
6	 **2f**	**3f**/90	13	 **2m**	**3m**/90
7	 **2g**	**3g**/79	14	 **2n**	**3n**/88

entry	nitrone	yield (%)[b]	entry	nitrone	yield (%)[b]
15	 **2o**	**3o**/77	20	 **2t**	**3t**/64
16	 **2p**	**3p**/74	21	 **2u**	**3u**/65
17	 **2q**	**3q**/57	22	 **2v**	**3v**/60
18	 **2r**	**3r**/70	23	 **2w**	**3w**/64
19	 **2s**	**3s**/56			

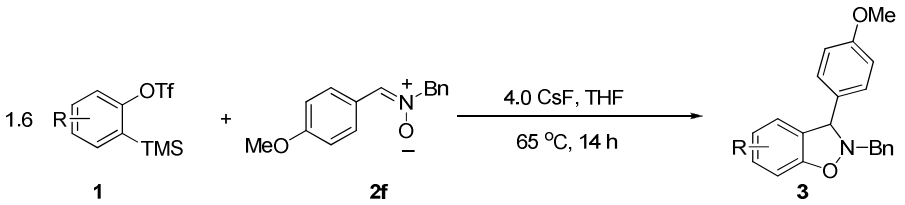
[a]Unless otherwise stated, all reactions have been carried out on a 0.25 mmol scale, with 1.6 equiv of benzyne precursor **1a** and 4.0 equiv of CsF in 5 ml of THF at 65 °C for 14 h.
[b] Yields of products isolated by column chromatography.

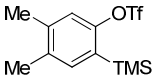
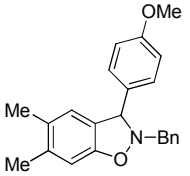
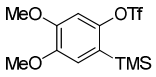
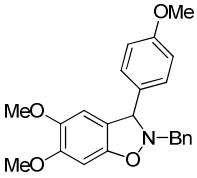
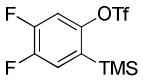
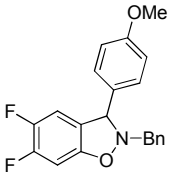
Excellent yields have been obtained from both *N*-alkyl (entries 2-5) and *N*-benzyl-substituted nitrones (entries 1, and 6-9). The results suggest that the steric effect of substituents on the carbon of the nitrone double bond are significant. Lower yields are observed for the substrates with more steric hindrance on the carbon of the C-N double bond. For example, **2e**, which has two methyls on the carbon of the C-N double bond (entry 5), and **2h,** which has an *ortho*-methoxy-substituted phenyl on that carbon (entries 8) both give lower yields. The process has also been applied to *N*-aryl-substituted nitrone **2j** (entry 10), which affords a high 92% yield of benzisoxazoline.

Nitrones with a variety of functionally-substituted phenyl groups on the nitrone carbon have been examined under our optimal conditions (entries 11-19). Many functional groups are well tolerated, including ester, cyano, amino, halogen and other groups. Nitrones with electron-donating groups tend to result in lower yields (entries 15 and 16) than nitrones with electron-withdrawing groups (entries 11-13), presumably due to the reduced electrophilicity of the carbon-nitrogen double bond due to the presence of such groups (see the later mechanistic discussion). Nitrone **2q** also afforded a relatively low yield of 57%, mainly due to the steric hindrance produced by the *ortho*-methoxy group (entry 17). Due to the presence of the additional carbon-carbon double bond in **2s**, the reaction was not as clean as that of other substrates, but still produced a good yield (entry 19).[12] Several cyclic nitrones have also been examined and moderate yields have been obtained (entries 21-23).

After a variety of substituted nitrones were examined, the behavior of various aryne precursors was examined in this reaction (Table 3). Dimethyl- (**1b**), dimethoxy- (**1c**) and difluoro-substituted (**1d**) benzyne precursors were employed under our optimal reaction conditions with nitrone **2f**. All of these substrates generated comparable, but lower yields than benzyne itself. Similar results have been observed before in other reaction systems.[6]

Table 3. Investigation of Different Arynes in the Coupling Reaction with Nitrone **2f** [a]



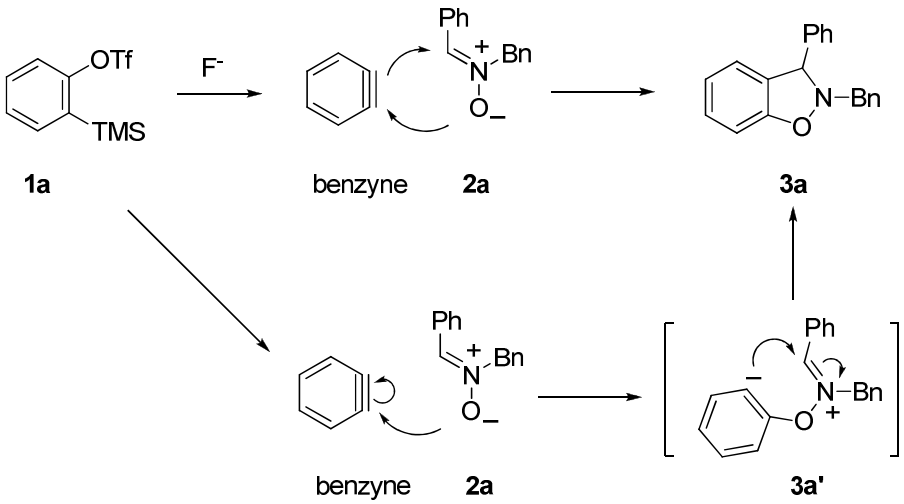
entry	aryne		product	yield (%)[b]
1		**1b**		(**3fb**) 72
2		**1c**		(**3fc**) 70
3		**1d**		(**3fd**) 41

[a] Unless otherwise stated, all reactions have been carried out on a 0.25 mmol scale with 1.6 equiv of aryne precursor and 4.0 equiv of CsF in 5 ml of THF at 65 °C for 14 h. [b] Yields of products isolated by column chromatography.

Two possible mechanisms for this process are proposed in Scheme 1 based on the experimental results and previous experience.[8] Following the formation of benzyne induced by fluoride from benzyne precursor **1a**, a [3+2] cycloaddition can occur. Nucleophilic attack of the oxygen anion of **2a** on benzyne, quickly followed by cyclization of **3a′**, can be envisioned as a mechanistic alternative. The significant steric and electronic effects of the substituents on the carbon-nitrogen double bond of the nitrone on the reaction results are consistent with both of these proposed mechanisms. The steric hindrance arising from the substituent on the carbon of the C-N double bond (see the results of entries 5, 8 and 17 in Table 2) are expected to disfavor the cycloaddition of **2a** to **3a** or the cycloaddition of **3a'** to **3a**. Furthermore, the presence of

electron-withdrawing substituents on the phenyl group present on the carbon of the C-N double bond (see the results of entries 12-16 in Table 2) would be expected to increase the electrophilicity of the C-N double bond in **3a'** producing higher yields.

Scheme 1. Possible Mechanisms



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Conclusions

In conclusion, we have developed a facile and general method for the synthesis of substituted benzisoxazolines by the 1,3-dipolar cycloaddition of arynes and nitrones under mild reaction conditions, which provides excellent yields. A variety of functional groups are well tolerated in this process, allowing further synthesis of more complicated molecules.

Experimental Section

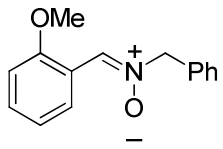
General

The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. High resolution mass spectra were recorded using EI at 70 eV. All reagents were used directly as obtained commercially

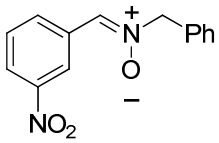
unless otherwise noted. All reactions were carried out in oven-dried glassware and monitored by thin layer chromatography (SiO_2, hexanes or hexanes/EtOAc). THF was distilled over Na. The silylaryl triflate **1a,** CsF, TBAF solution (1M in THF) and acetonitrile were purchased from Sigma-Aldrich Co. 4,5-Dimethyl-substituted silylaryl triflate **1b**, 4,5-dimethoxy-substituted silylaryl triflate **1c** and 4,5-difluoro-substituted silylaryl triflate **1d** were prepared according to a previous literature procedure.[13]

Non-commercially available compounds

Non-commercially available starting materials were prepared according to literature procedures.[14]

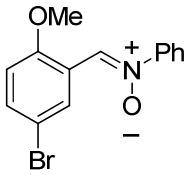


(2-Methoxyphenylmethylene)benzylamine-*N*-oxide (2h): light yellow solid, mp 78-79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (dd, J = 7.8, 1.5 Hz, 1H), 7.96 (s, 1H), 7.51-7.26 (m, 7H), 6.99 (t, J = 8.1 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 5.05 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.01, 133.87, 131.71, 129.10, 128.92, 128.83, 128.77, 120.82, 119.65, 109.83, 71.72, 55.64; HRMS (EI) calcd for $C_{15}H_{15}NO_2$: 241.1103, found 241.1101.

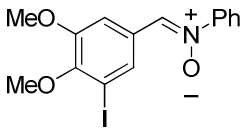


(3-Nitrophenylmethylene)benzylamine-*N*-oxide (2i): yellow solid, mp 142-144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.57 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.57-7.41 (m, 7H), 5.11 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 148.24, 133.78,

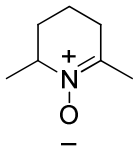
132.75, 132.11, 131.95, 129.64, 129.52, 129.45, 129.24, 124.65, 123.11, 71.85; HRMS (EI) calcd for $C_{14}H_{12}N_2O_3$: 256.0848, found 256.0843.



(5-Bromo-2-methoxyphenylmethylene)phenylamine-*N*-oxide (2q): yellow solid, mp 135-137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (d, J = 2.7 Hz, 1H), 8.33 (s, 1H), 7.78-7.74 (m, 2H), 7.51-7.46 (m, 4H), 6.79 (d, J = 9.0 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.54, 149.57, 134.61, 131.08, 130.11, 129.32, 128.15, 121.90, 121.65, 113.59, 111.65, 56.08; HRMS (EI) calcd for $C_{14}H_{12}NO_2Br$: 306.0041, found 306.0043.



(4,5-Dimethoxy-3-iodophenylmethylene)phenylamine-*N*-oxide (2r): yellow solid, mp 162-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 1.5 Hz, 1H), 7.94 (d, J = 1.8 Hz, 1H), 7.82 (s, 1H), 7.75-7.72 (m, 2H), 7.45 (m,, 3H), 3.92 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 152.21, 150.78, 148.86, 132.84, 132.30, 130.20, 129.33, 128.82, 121.67, 112.47, 92.01, 60.72, 56.13; HRMS (EI) calcd for $C_{15}H_{14}NO_3I$: 383.0018, found 383.0014.

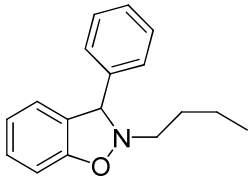


2,6-Dimethyl-2,3,4,5-tetrahydropyridine-*N*-oxide (2v): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (m, 1H), 2.25 (t, J = 6.0 Hz, 2H), 1.90-1.81 (m, 4H), 1.60-1.48 (m, 3H),

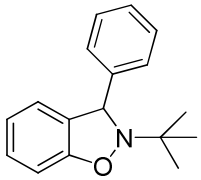
1.27 (dd, J = 9.0, 3.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.95, 61.85, 30.72, 29.40, 18.88, 18.72, 15.20; HRMS (EI) calcd for $C_7H_{13}ON$: 127.0997, found 127.0991.

Representative procedure for the cycloaddition of arynes and nitrones

An oven dried 6-dram vial equipped with a stir bar was charged with 0.25 mmol of the nitrone, 1.6 equiv of the aryne precursor and 4.0 equiv of CsF, followed by 5 ml of dry THF. The vial was sealed and placed in an oil bath at 65 °C for about 14 h. The resultant mixture was cooled and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel with ethyl acetate/hexanes or dichloromethane/hexane as the eluent.

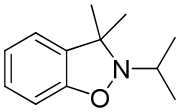


2-Butyl-3-phenyl-2,3-dihydrobenzo[*d*]isoxazole (3b): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.33 (m, 5H), 7.22 (t, J = 6.0 Hz, 1H), 7.00 (d, J = 6.0 Hz, 1H), 6.93-6.87 (m, 2H), 3.27 (m, 1H), 3.01 (m, 1H), 1.78-1.71 (m, 2H), 1.51-1.38 (m, 2H), 0.95 (t, J = 6.0 Hz, 3H),; ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.06, 140.82, 129.54, 128.94, 128.13, 127.99, 124.11, 121.33, 107.97, 74.47, 59.59, 29.95, 20.63, 14.11; HRMS (EI) calcd for $C_{17}H_{19}NO$: 253.1467, found 253.1463.

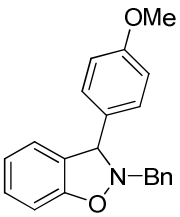


2-*tert*-Butyl-3-phenyl-2,3-dihydrobenzo[*d*]isoxazole (3c): white solid, mp 94-96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.26 (m, 5H), 7.14 (d, J = 9.0 Hz, 1H), 6.90 (d, J = 6.0 Hz, 1H), 6.83-6.79 (m, 2H), 5.61 (s, 1H), 1.20 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ

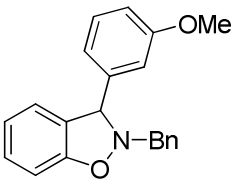
156.35, 144.09, 130.04, 128.79, 127.57, 127.54, 123.80, 120.86, 106.93, 67.18, 61.20, 29.92, 25.69; HRMS (EI) calcd for $C_{17}H_{19}NO$: 253.1467, found 253.1468.



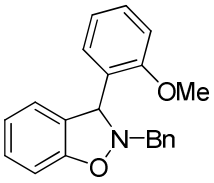
2-Isopropyl-3,3-dimethyl-2,3-dihydrobenzo[*d*]isoxazole (3e): light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21-7.15 (m, 2H), 6.92 (t, J = 6.0 Hz, 1H), 6.81 (d, J = 9.0 Hz, 1H), 4.05 (t, J = 6.0 Hz, 1H), 3.03 (m, 1H), 2.68 (m, 1H), 1.71 (m, 4H), 1.01 (td, J = 9.0, 6.0 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.25, 128.96, 128.65, 123.89, 121.09, 108.32, 71.22, 62.30, 29.47, 21.00, 11.95, 10.25; HRMS (EI) calcd for $C_{12}H_{17}NO$: 191.1310, found 191.1308.



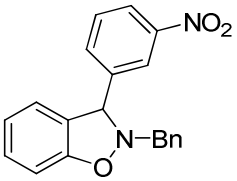
2-Benzyl-3-(4-methoxyphenyl)-2,3-dihydrobenzo[*d*]isoxazole (3f): white solid, mp 121-123 $^{\circ}$C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.31 (m, 5H), 7.26-7.20 (m, 3H), 7.02 (d, J = 6.0 Hz, 1H), 6.95-6.86 (m, 4H), 5.34 (s, 1H), 4.38 (d, J = 12.0 Hz, 1H), 4.18 (d, J = 12.0 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.55, 156.35, 136.64, 132.55, 129.45, 129.24, 129.22, 128.99, 128.61, 127.80, 124.33, 121.55, 114.17, 108.27, 72.48, 62.62, 55.45; HRMS (EI) calcd for $C_{21}H_{19}NO_2$: 317.1416, found 317.1420.



2-Benzyl-3-(3-methoxyphenyl)-2,3-dihydrobenzo[*d*]isoxazole (3g): white solid, mp 69-72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 6.0 Hz, 2H), 7.41-7.32 (m, 3H), 7.83 (m, 2H), 7.29-7.21 (m, 2H), 7.07 (d, J = 6.0 Hz, 1H), 6.96-6.83 (m, 5H), 5.36 (s, 3H), 4.42 (d, J = 12.0 Hz, 1H), 4.18 (d, J = 12.0 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.98, 156.25, 142.17, 136.49, 129.76, 129.50, 129.11, 128.75, 128.63, 127.86, 124.40, 121.60, 120.17, 113.75, 113.29, 108.33, 72.68, 62.91, 55.37; HRMS (EI) calcd for $C_{21}H_{19}NO_2$: 317.1416, found 317.1422.

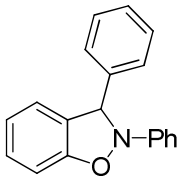


2-Benzyl-3-(2-methoxyphenyl)-2,3-dihydrobenzo[*d*]isoxazole (3h): white solid, mp 71-73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 6.0 Hz, 2H), 7.38-7.19 (m, 8H), 6.95-6.86 (m, 4H), 5.89 (s, 1H), 4.37 (d, J = 15.0 Hz, 1H), 4.18 (d, J = 15.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.69, 156.41, 137.09, 129.58, 129.44, 128.88, 128.85, 128.48, 127.61, 124.82, 121.60, 121.05, 110.40, 108.48, 66.35, 63.47, 55.49; HRMS (EI) calcd for $C_{21}H_{19}NO_2$: 317.1416, found 317.1419.

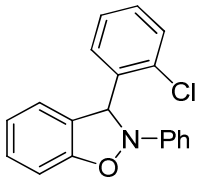


2-Benzyl-3-(3-nitrophenyl)-2,3-dihydrobenzo[*d*]isoxazole (3i): white solid, mp 118-120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, J = 6.0, 3.0 Hz, 2H), 7.62 (d, J = 6.0 Hz, 2H), 7.49-7.25 (m, 8H), 7.09 (d, J = 9.0 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 6.91 (d, J = 9.0 Hz, 1H), 5.44 (s, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.13 (d, J = 12.0 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.23, 148.08, 143.29, 135.67, 133.73, 129.82, 129.76, 129.56, 128.80,

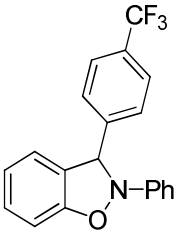
128.21, 127.28, 124.39, 123.00, 122.62, 122.08, 108.81, 71.46, 63.20; HRMS (EI) calcd for $C_{20}H_{16}N_2O_3$: 332.1161, found 332.1166.



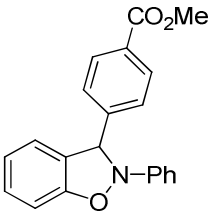
2,3-Diphenyl-2,3-dihydrobenzo[*d*]isoxazole (3j): light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.15 (m, 2H), 7.09-6.85 (m, 7H), 6.74 (d, J = 9.0 Hz, 2H), 6.62 (t, J = 6.0 Hz, 1H), 6.53-6.49 (m, 1H), 6.43 (dd, J = 6.0, 3.0 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 150.59, 138.58, 136.46, 131.45, 129.91, 129.54, 129.08, 127.67, 127.24, 122.82, 121.11, 118.32, 110.22, 108.89, 99.28; HRMS (EI) calcd for $C_{19}H_{15}NO$: 273.1154, found 273.1152.



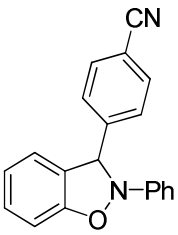
3-(2-Chlorophenyl)-2-phenyl-2,3-dihydrobenzo[*d*]isoxazole (3k): white solid, mp 74-76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 6.0 Hz, 1H), 7.44 (d, J = 9.0 Hz, 1H), 7.29-7.15 (m, 5H), 7.08 (dt, J = 9.0, 3.0 Hz, 2H), 6.99 (t, J = 9.0 Hz, 1H), 6.92-6.87 (m, 1H), 6.82-6.79 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 150.34, 142.32, 135.31, 134.38, 133.46, 130.98, 130.33, 129.63, 128.79, 127.61, 122.66, 121.41, 121.30, 117.47, 110.48, 109.23, 95.58; HRMS (EI) calcd for $C_{19}H_{14}NOCl$: 307.0764, found 307.0769.



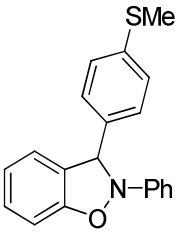
2-Phenyl-3-(4-trifluoromethylphenyl)-2,3-dihydrobenzo[*d*]isoxazole (3l): white solid, mp 86-88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (t, J = 9.6 Hz, 4H), 7.32-7.24 (m, 2H), 7.13-7.01 (m, 4H), 6.94-6.79 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 150.38, 142.61, 142.41, 134.60, 129.75, 127.68, 126.21, 126.15, 126.10, 126.06, 123.28, 121.57, 118.38, 110.81, 109.11, 98.38; HRMS (EI) calcd for $C_{20}H_{14}NOF_3$: 341.1027, found 341.1032.



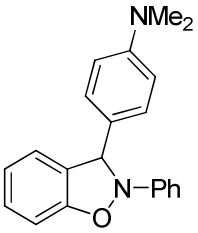
3-(4-Carbomethoxyphenyl)-2-phenyl-2,3-dihydrobenzo[*d*]isoxazole (3m): white solid, mp 118-120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.1 Hz, 2H), 7.27 (t, J = 7.5 Hz, 2H), 7.10 (m, 3H), 7.02 (t, J = 7.5 Hz, 1H) , 6.92-6.79 (m, 4H), 3.90 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.75, 150.46, 143.14, 142.49, 134.69, 131.54, 130.38, 129.66, 127.31, 123.17, 121.47, 121.37, 118.47, 110.54, 109.01, 98.62, 52.44; HRMS (EI) calcd for $C_{21}H_{17}NO_3$: 331.1208, found 331.1215.



3-(4-Cyanophenyl)-2-phenyl-2,3-dihydrobenzo[*d*]isoxazole (3n): white solid, mp 105-108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.65 (m, 4H), 7.30 (t, J = 7.5 Hz, 2H), 7.12-7.03 (m, 4H), 6.94-6.79 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 150.28, 143.47, 132.96, 129.81, 128.00, 123.49, 121.74, 121.71, 118.56, 118.46, 113.73, 111.01, 109.19, 98.17; HRMS (EI) calcd for $C_{20}H_{14}N_2O$: 298.1106, found 298.1106.

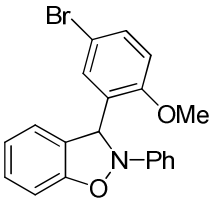


3-(4-Methylthiophenyl)-2-phenyl-2,3-dihydrobenzo[*d*]isoxazole (3o): white solid, mp 82-84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 9.0 Hz, 2H), 7.29-7.23 (m, 4H), 7.12-7.08 (m, 3H), 7.00 (t, J = 9.0 Hz, 1H), 6.90-6.83 (m, 1H) , 6.80-6.76 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 150.52, 142.45, 140.82, 135.18, 130.15, 129.57, 127.74, 126.65, 122.81, 121.24, 121.10, 118.44, 110.10, 108.88, 98.94, 15.65; HRMS (EI) calcd for $C_{20}H_{17}NOS$: 319.1031, found 319.1034.

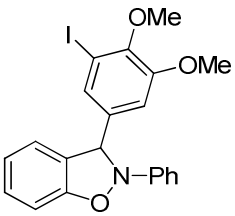


3-[4-(Dimethylamino)phenyl]-2-phenyl-2,3-dihydrobenzo[*d*]isoxazole (3p): light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.7 Hz, 2H), 7.29-7.20 (m, 3H), 7.16-7.08 (m, 3H), 6.98 (t, J = 7.2 Hz, 1H), 6.86 (td, J = 6.0, 3.0 Hz, 1H), 6.79-6.77 (m, 2H) , 6.70 (d, J = 9.0 Hz, 2H), 2.96 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 151.65, 150.67, 142.52, 129.63, 129.43, 128.35, 125.81, 122.51, 120.89, 120.72, 118.43, 112.42,

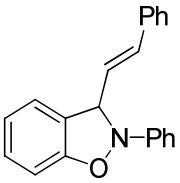
109.58, 108.72, 99.57, 40.59; HRMS (EI) calcd for $C_{21}H_{20}ON_2$: 316.1576, found 316.1583.



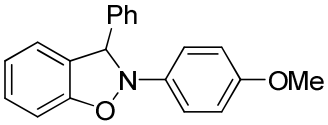
3-(5-Bromo-2-methoxyphenyl)-2-phenyl-2,3-dihydrobenzo[*d*]isoxazole (3q): white solid, mp 73-75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 3.0 Hz, 1H), 7.43 (dd, J = 6.0, 3.0 Hz, 1H), 7.27 (t, J = 6.0 Hz, 2H), 7.19-7.16 (m, 2H), 7.11-7.08 (dd, J = 9.0, 3.0 Hz, 2H), 7.00 (t, J = 9.0 Hz, 1H) , 6.90 (td, J = 6.0, 3.0 Hz, 1H), 6.85 (s, 1H), 6.80 (dd, J = 9.0, 3.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.66, 150.47, 142.79, 134.25, 133.74, 130.80, 129.56, 128.43, 122.59, 121.44, 121.22, 117.43, 113.54, 113.16, 110.99, 109.14, 93.43, 56.25; HRMS (EI) calcd for $C_{20}H_{16}NO_2Br$: 381.0364, found 381.0368.



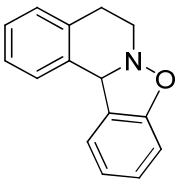
3-(4,5-Dimethoxy-3-iodophenyl)-2-phenyl-2,3-dihydrobenzo[*d*]isoxazole (3r): light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 3.0 Hz, 1H), 7.33 (d, J = 6.0 Hz, 2H), 7.16-7.05 (m, 6H), 6.93 (td, J = 9.0, 6.0 Hz, 1H), 6.83 (t, J = 6.0 Hz, 2H), 6.70 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 153.20, 150.29, 150.20, 142.60, 136.30, 134.78, 129.68, 129.46, 123.31, 121.40, 118.63, 111.36, 110.61, 109.00, 98.37, 92.87, 60.60, 56.24; HRMS (EI) calcd for $C_{21}H_{18}NO_3I$: 459.0331, found 459.0320.



2-Phenyl-3-(*E*-2-phenylethenyl)-2,3-dihydrobenzo[*d*]isoxazole (3s): light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$); δ 7.48-7.43 (m, 3H), 7.38-7.28 (m, 6H), 7.09-7.05 (m, 2H), 6.92-6.72 (m, 4H), 6.48-6.38 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 150.85, 142.79, 135.28, 131.49, 129.60, 129.31, 128.84, 128.70, 127.32, 125.38, 122.93, 121.18, 121.06, 118.49, 110.80, 108.91, 99.10; HRMS (EI) calcd for $C_{21}H_{17}ON$: 299.0383, found 299.1375.

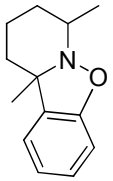


2-(4-Methoxyphenyl)-3-phenyl-2,3-dihydrobenzo[*d*]isoxazole (3t): white solid, mp 118-120 $^{\circ}$C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, J = 6.0, 3.0 Hz, 2H), 7.36 (t, J = 3.0 Hz, 1H), 7.03 (d, J = 9.0 Hz, 2H), 6.82-6.74 (m, 6H), 6.64 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.35, 150.43, 138.57, 136.91, 135.60, 129.89, 128.88, 127.59, 122.56, 121.34, 120.32, 114.83, 108.90, 108.42, 100.51, 55.56; HRMS (EI) calcd for $C_{20}H_{17}NO_2$: 303.1259, found 303.1255.

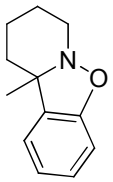


5,12-Dihydro-6*H*-[1,2]benzisoxazolo[3,2]isoquinoline (3u): white solid, mp 69-72 $^{\circ}$C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 9.0 Hz, 1H), 7.29 (t, J = 9.0 Hz, 1H), 7.22-7.09 (m, 4H), 6.90-6.83 (m, 2H), 5.80 (s, 1H), 3.36-3.30 (m, 2H), 3.00-2.77 (m, 2H); ^{13}C

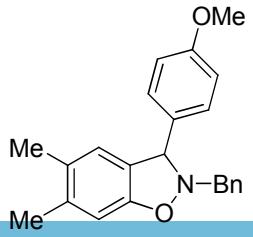
NMR (300 MHz, $CDCl_3$) δ 156.65, 134.11, 133.54, 129.09, 128.78, 128.62, 127.23, 127.04, 126.87, 123.63, 121.62, 108.71, 65.66, 49.92, 26.85; HRMS (EI) calcd for $C_{15}H_{13}NO$: 2233.0997, found 223.1003.



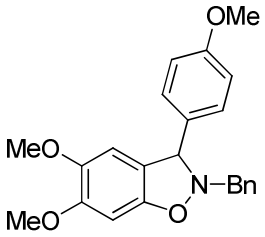
7,10a-Dimethylpyrido-8,9,10-trihydro[1,2]benzisoxazole (3v): colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (t, J = 6.0 Hz, 1H), 7.03 (d, J = 9.0 Hz, 1H), 6.87 (t, J = 6.0 Hz, 1H), 6.78 (d, J = 9.0 Hz, 1H), 3.22 (m, 1H), 1.63-1.51 (m, 9H), 1.41 (d, J = 9.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 155.52, 136.89, 128.00, 120.97, 120.75, 107.98, 65.55, 53.97, 33.34, 26.31, 22.81, 20.30, 19.34; HRMS (EI) calcd for $C_{13}H_{17}NO$: 203.1310, found 203.1306.



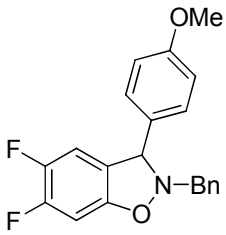
10a-Methyl-7,8,9,10-tetrahydropyrido[1,2]benzisoxazole (3w): colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, J = 9.0 Hz, 1H), 7.07 (d, J = 6.0 Hz, 1H), 6.97 (t, J = 6.0 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 3.39 (m, 1H), 2.64 (td, J = 9.0, 6.0 Hz, 1H), 2.29 (m, 1H), 1.86 (m, 1H), 1.65-1.51 (m, 3H), 1.35 (s, 3H), 1.35-1.23 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.22, 133.39, 128.21, 121.77, 121.70, 109.94, 67.00, 52.73, 32.81, 30.01, 23.48, 20.48; HRMS (EI) calcd for $C_{12}H_{15}NO$: 189.1154, found 189.1149.



2-Benzyl-3-(4-methoxyphenyl)-2,3-dihydro-5,6-dimethylbenzo[*d*]isoxazole (3fb): yellow solid, mp 121-123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.26 (m, 5H), 7.18 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 6.78 (s, 1H), 6.68 (s, 1H), 5.25 (s, 1H) , 4.35 (d, J = 13.0 Hz, 1H), 4.12 (d, J = 13.0 Hz, 1H), 3.79 (s, 3H), 2.25 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.46, 154.75, 137.50, 136.81, 133.17, 129.71, 129.57, 129.51, 129.14, 128.59, 127.74, 126.46, 125.10, 114.14, 109.33, 72.33, 62.75, 55.46, 20.46, 19.55; HRMS (EI) calcd for $C_{23}H_{23}NO_2$: 345.1729, found 345.1721.



2-Benzyl-5,6-dimethoxy-3-(4-methoxyphenyl)-2,3-dihydrobenzo[*d*]isoxazole (3fc): light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.27 (m, 5H), 7.16 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 6.53 (d, J = 9.0 Hz, 2H), 5.27 (s, 1H), 4.35 (d, J = 12.0 Hz, 1H), 4.14 (d, J = 15.0 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.61, 150.76, 150.25, 144.46, 136.77, 132.82, 129.48, 129.35, 128.62, 127.80, 118.67, 114.22, 107.91, 93.55, 73.01, 62.76, 56.98, 56.35, 55.50; HRMS (EI) calcd for $C_{23}H_{23}NO_4$: 377.1627, found 377.1620.



2-Benzyl-5,6-difluoro-3-(4-methoxyphenyl)-2,3-dihydrobenzo[*d*]isoxazole (3fd): light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.31 (m, 6H), 7.20 (d, J = 9.0 Hz, 2H),

6.89 (d, J = 9.0 Hz, 2H), 6.77 (t, J = 9.0 Hz, 1H), 6.66 (dd, J = 9.0, 6.0 Hz, 1H), 5.27 (s, 1H) , 4.34 (d, J = 12.0 Hz, 1H), 4.16 (d, J = 12.0 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.91, 136.17, 129.41, 129.34, 128.70, 128.02, 114.40, 112.70, 112.43, 98.29, 97.98, 72.48, 62.54, 55.52; HRMS (EI) calcd for $C_{21}H_{17}NO_2F_2$: 353.1227, found 353.1230.

Acknowledgments

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CHAPTER 3. Palladium-Catalyzed Annulation of Arynes by *ortho*-Halobenzamides: Synthesis of Phenanthridinones

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Abstract

The palladium-catalyzed annulation of arynes by substituted *o*-halobenzamides produces *N*-substituted phenanthridinones in good yields. This methodology provides this important heterocyclic ring system in a single step by simultaneous C-C and C-N bond formation, under relatively mild reaction conditions, and tolerates a variety of functional groups.

Introduction

Phenanthridinones are important sub-units found in many compounds possessing interesting biological and pharmaceutical activities. They have been used as PARP inhibitor anticancer drugs,[1] and as neurotrophin activity enhancers for the treatment of nerve diseases.[2] The most widely accepted approach for the synthesis of phenanthridinones is through the reductive cyclization of corresponding nitro-carbonyl-biphenyls.[3] However, traditional preparations of the starting nitro-carbonyl-biaryls, by Ullmann-coupling reactions or the nitration of biaryls,[4] require either harsh reaction conditions or exotic functionalized arenes, significantly limiting the broad application of this approach.

Transition metal-catalyzed annulation reactions are tremendously valuable in organic synthesis.[5] Among such processes, palladium-mediated reactions are by far the most powerful in constructing carbocycles and heterocycles,[6] due to the high efficiency with which they construct C-C and C-X (X = O, N) bonds[7] and their high compatibility with functional groups. For example, some phenanthridinone derivatives have been synthesized by palladium-catalyzed intramolecular or intermolecular cyclization processes of aryl halides and amides.[8]

Since a convenient approach to aryne generation by the fluoride-induced 1,2-elimination of *o*-(trimethylsilyl)aryl triflates was first reported,[9] arynes have attracted considerable attention.[10] The high electrophilicity of arynes has been used extensively in the construction of many heteroaromatic structures via either simple nucleophilic reactions[11] or annulation reactions.[12] To take further advantage of aryne chemistry, many metal-catalyzed coupling[13] and annulation reactions[14] of arynes have been explored. In our group, we are especially interested in the palladium-catalyzed annulation of arynes.[15]

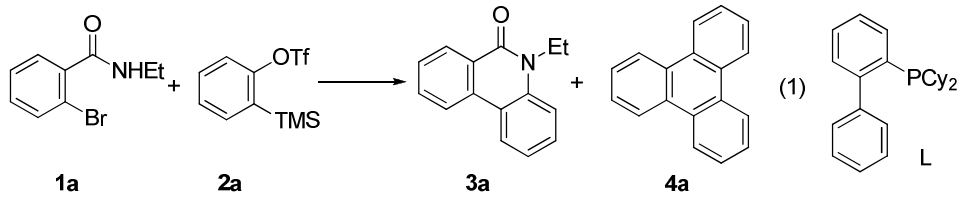
Herein, we report the palladium-catalyzed annulation of arynes by substituted *o*-halobenzamides to produce *N*-substituted phenanthridinones in good yields. In this reaction, C-C and C-N bonds are formed simultaneously to generate this important heterocyclic ring system.

Results and Discussion

Optimization Studies

We attempted to optimize the reaction of *N*-ethyl-2-bromobenzamide (**1a**) and the benzyne precursor *o*-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) in 4:1 toluene/acetonitrile with CsF as the fluoride source (Table 1). In all of the cases, there

Table 1. Optimization of the Pd-Catalyzed Annulation of Benzyne (eq 1)[a]



1a **2a** **3a** **4a**

entry	ligand (mol %)	additive (equiv)	solvent (toluene/MeCN)	% yield of **3a**[b]
1	--------	--------	4:1	10
2	PPh_3 (10)	--------	4:1	13
3	P(*o*-tolyl)$_3$ (10)	--------	4:1	50
4	dppm (10)	--------	4:1	66
5	dppe (10)	--------	4:1	30
6	dppf (10)	--------	4:1	25
7	L (10)[c]	--------	4:1	56
8	dppm (5)	--------	4:1	53
9	dppm (10)	Na_2CO_3 (1)	4:1	73
10	dppm (10)	K_2CO_3 (1)	4:1	70
11	dppm (10)	Cs_2CO_3 (1)	4:1	67
12	dppm (10)	Na_2CO_3 (2)	4:1	57
13	dppm (10)	Na_2CO_3 (1)	3:1	52
14	dppm (10)	Na_2CO_3 (1)	6:1	49
15	dppm (10)	Na_2CO_3 (1)	4:1	50[d]
16	dppm (10)	Na_2CO_3 (1)	4:1	60[e]

[a]All reactions were run using substrate **1a** (0.25 mmol), 5 mol % of $Pd(OAc)_2$, 2.0 equiv of **2a**, 5.0 equiv of CsF, 5 ml of solvent at 110 °C for 16-24 h, unless otherwise specified. [b] Isolated yield. [c] See L in equation 1. [d] The reaction was conducted at 90 °C for 12 h, at which time the Pd had precipitated out. [e] 1.6 Equiv of **2a** and 4.0 equiv of CsF were employed.

was side product **4a** produced by the cyclotrimerization of benzyne,[15] plus the desired benzyne annulation product **3a** (eq 1) .

Optimization work was conducted with respect to different palladium catalysts, ligands, solvents and temperatures and the results are shown in Table 1. Without any ligand, palladium black precipitated out very quickly with only a trace amount of the desired product formed and the aryl halide **1a** was left in large amounts (entry 1). Simple triphenylphosphine ligand did not improve the yield (entry 2). Both tri(*o*-tolyl)phosphine and the biarylphosphine ligand **L** (eq 1) increased the yield to around 50% (entries 3 and 7). Several bidentate ligands have also been examined (entries 4-6). Among them, dppm proved the most efficient, producing lactam **3a** in a 66% yield, although 10 mol % of ligand seemed necessary to maintain a decent yield (entry 8). Besides examining the effect on the yield of the ligand, several bases have also been tested in this reaction (entries 9-12). The results indicate that with 1.0 equiv of Na_2CO_3, a 73% yield of the desired product can be achieved (entry 9). Other bases gave lower yields. Based on our previous experience, the solvent can often prove critical for palladium-catalyzed benzyne reactions, mostly because the benzyne is generated at vastly different rates in different solvents.[14] With a toluene/acetonitrile mixed solvent and CsF as the fluoride source, benzyne is generated more slowly in mixtures with less acetonitrile, because CsF has a lower solubility in toluene. Thus, the solvent ratio was examined and 4:1 toluene/acetonitrile afforded the best result (compare entries 9, 13 and 14). With a 3:1 ratio, more side product, trimer **4a**, is formed; with a 6:1 ratio, the benzyne is generated too slowly, giving a lower yield.

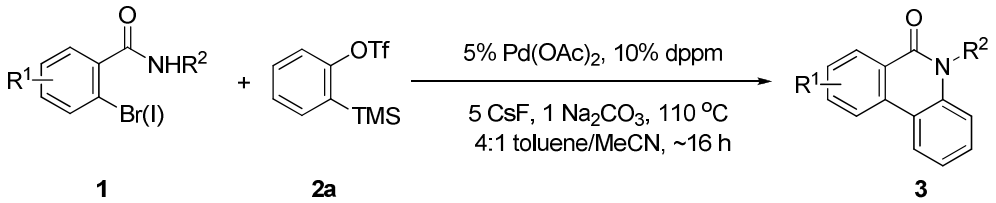
An effort was also made to lower the temperature and the benzyne precursor loading (entries 15 and 16), but it appears that 110 ^{o}C and 2 equiv of the benzyne precursor plus 5 equiv of CsF are necessary in order to obtain a high yield. Several other palladium

catalysts, including $PdCl_2(MeCN)_2$ (63%), $Pd(dba)_2$ (65%) and $Pd(PPh_3)_4$ (61%), have also been examined in this process; but none proved better than $Pd(OAc)_2$. In the end, we have chosen the reaction conditions reported in entry 9 of Table 1 as our optimal conditions.

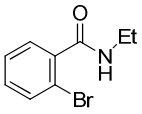
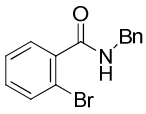
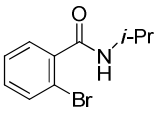
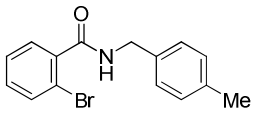
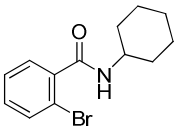
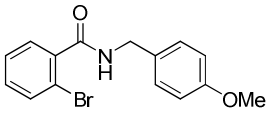
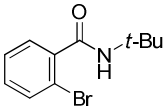
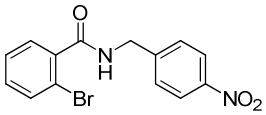
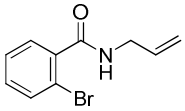
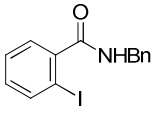
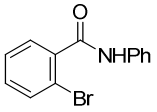
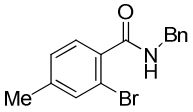
Reaction Scope and Limitations

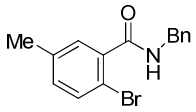
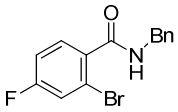
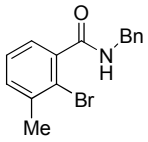
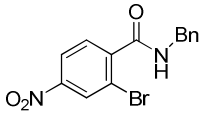
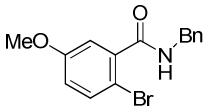
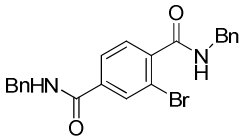
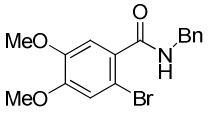
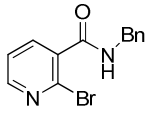
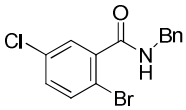
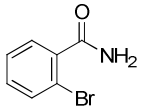
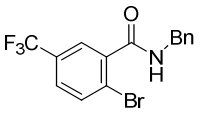
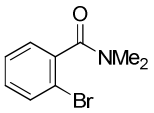
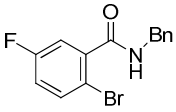
To further test the scope and limitations of this reaction, we have examined a variety of substituted 2- halobenzamides and the results are summarized in Table 2. Different amide nitrogen substituents, including alkyl (entries 1-4), allyl (entry 5), phenyl (entry 6) and benzyl groups (entries 7-10), have been examined. Among them, excellent yields were achieved for *N*-primary and secondary alkyl (entries 1-3) substituted amides, as well as *N*-benzyl substituted amides (entries 7-10). The analogous amide with an *N*-*t*-Bu (entry 4) afforded a lower yield presumably due to the steric hindrance of the *t*-Bu group. The presence of an *N*-allyl group (entry 5) also caused complications and the reaction looked messier on the TLC plate than the parent system (**1a**) with a resulting lower yield. Aryl-substituted amide **1f** produced some uncharacterized products which overlapped with the starting material amide left on the TLC plate (entry 6). The reaction was also performed using 2-iodobenzamide **1k** (entry 11) and a much lower yield was obtained than the corresponding bromobenzamide **1g**. Although for most palladium-catalyzed reactions of aryl halides, aryl iodides provide better results than the corresponding aryl bromides because the oxidative addition of Pd(0) to the aryl halide is easier and faster (see the later mechanistic discussion), there are several publications where the same halide effect as seen here has been reported and mechanistic studies on such reactions have been conducted.[17] The reason for this halogen effect is not clear. However, we have observed that palladium precipitates out more quickly with a lower conversion and more side products in the reaction of **1k** than in the reaction of **1g**.

Table 2. Pd-Catalyzed Annulation of Benzyne **2a**[a]



1 **2a** **3**

entry	substrate	% yield of **3**[b]	entry	substrate	% yield of **3**[b]
1	 (**1a**)	(**3a**) 73	7	 (**1g**)	(**3g**) 82
2	 (**1b**)	(**3b**) 70	8	 (**1h**)	(**3h**) 77
3	 (**1c**)	(**3c**) 87	9	 (**1i**)	(**3i**) 75
4	 (**1d**)	(**3d**) 64	10	 (**1j**)	(**3j**) 83
5	 (**1e**)	(**3e**) 65	11	 (**1k**)	(**3k**) 38
6	 (**1f**)	(**3f**) --[c]	12	 (**1l**)	(**3l**) 84

entry	substrate	% yield of **3**[b]	entry	substrate	% yield of **3**[b]
13	 (**1m**)	(**3m**) 79	20	 (**1t**)	(**3t**) 79
14	 (**1n**)	(**3n**) 74	21	 (**1u**)	(**3u**) 70
15	 (**1o**)	(**3o**) 74	22	 (**1v**)	(**3v**) 55
16	 (**1p**)	(**3p**) 70	23	 (**1w**)	(**3w**) 36
17	 (**1q**)	(**3q**) 67	24	 (**1x**)	(**3x**) 0
18	 (**1r**)	(**3r**) 52	25	 (**1y**)	(**3y**) 0
19	 (**1s**)	(**3s**) 65			

[a] Representative procedure: **1** (0.25 mmol), 2.0 equiv of **2**, 5.0 equiv of CsF, 5 mol % $Pd(OAc)_2$, 10 mol % dppm, 1.0 equiv of Na_2CO_3 in 5 ml of 4:1 toluene/MeCN at 110 ^oC for 16-24 h. [b] Isolated yield. [c] An unknown mixture were generated whose products overlapped with the starting material **1d** on the TLC plate.

To further test the scope and the limitations of the reaction, we examined a variety of 2-bromobenzamides with various functional groups (entries 12-22). Amides with slightly electron-donating methyl groups at the 3 (entry 14), 4 (entry 12), and 5 (entry 13) positions generally afforded excellent yields of above 70%, although **1n** provided a slightly lower yield than the others presumably due mainly to the steric hindrance of the methyl group during oxidative addition of the carbon-halogen bond to the palladium catalyst. Strong electron-donating methoxy groups also did not lower the yield significantly and yields above 70% were generated from **1o** and **1p**, which suggested that the oxidative addition of the aryl bromide to Pd(0) is not very difficult under these reaction conditions. Halogens, such as F (entries 19 and 20) and Cl (entry 17), were well tolerated in these reactions, providing good yields of the corresponding amides.

o-Bromobenzamides with electron-withdrawing groups, including CF_3, NO_2 and an amide group, were also tested and lower yields were obtained when compared to **1g.** The reason for this decrease can be explained as follows. Although the electron-withdrawing nature of these functional groups facilitates oxidative addition of the carbon-bromine bond in the amide to Pd(0), it at the same time decreases the nucleophilic nature of the nitrogen in the amide, which is critical for the cyclization step (see the later mechanistic discussion).

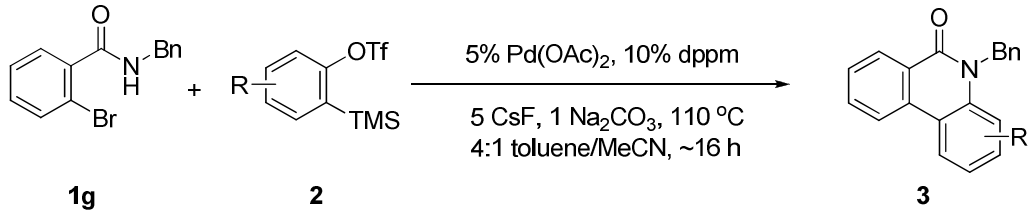
In addition to these *N*-benzyl-2-bromobenzamide derivatives, the pyridine-derived amide **1w** has also been examined, but only a 36% yield of the desired product was isolated, which may be caused by deactivation of the Pd catalyst through strong coordination of the nitrogen in the pyridine to Pd.

This reaction was also applied to 2-bromobenzamide (**1w**, entry 24) and *N,N*-dimethyl-2-bromobenzamide (**1y**, entry 25). Both **1w** and **1y** remained in the reaction system in very large amounts after the reaction and neither of the desired products was observed.

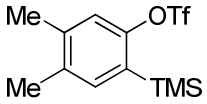
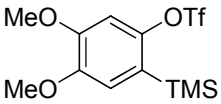
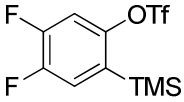
The reason for the failure of these two reactions may not, however, be the same. In the reaction of **1w**, strong coordination of the NH_2 group with the Pd in either complex **III** or **IV** (see Scheme 1) may inhibit the cyclization; while, in **1y**, two methyl groups on the nitrogen prohibit nucleophilic attack of the nitrogen on the Pd in complex **III** (see the step from **III** to **V** in Scheme 1).

In addition to phenyl triflate **2a**, other aryne precursors have also been examined in our methodology as an annulation partner (Table 3). 4,5-Dimethylbenzyne precursor **2b**, 4,5-dimethoxybenzyne precursor **2c** and 4,5-difluorobenzyne precursor **2d** have all been

Table 3. Investigation of Different Arynes in the Pd-Catalyzed Annulation of *o*-Halobenzamide **1g** [a]



1g **2** **3**

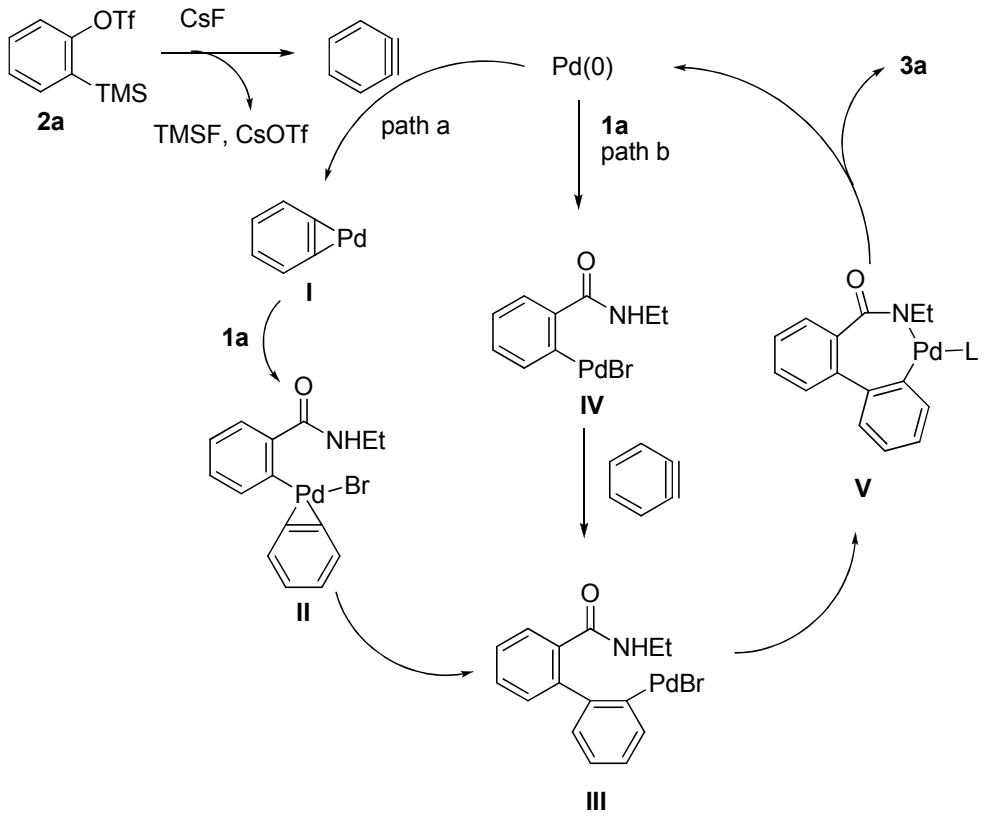
entry	aryne		% yield of **3**[b]
1		**2b**	(**3gb**) 50
2		**2c**	(**3gc**) 46
3		**2d**	(**3gd**) 43

[a] Representative procedure: **1g** (0.25 mmol), 2.0 equiv of **2,** 5.0 equiv of CsF, 5 mol % $Pd(OAc)_2$, 10 mol % dppm, 1.0 equiv of Na_2CO_3 in 5 ml of 4:1 toluene/MeCN at 110 °C for 16-24 h. [b] Isolated yield.

examined under our annulation conditions. They formed the expected annulation products **3gb**, **3gc** and **3gd** respectively, not surprisingly, with lower yields compared to benzyne precursor **2a** (Table 2, entries 1-3). This may be due to either the slower rate of generation of the arynes or the lack of stability of these arynes, as has been suggested by earlier work in our group.[18]

Based on our experimental results and previous experience with related processes,[15] we propose that this phenanthridinone synthesis proceeds through either of the possible pathways shown in Scheme 1.

Scheme 1. Tentative Mechanisms



One possible pathway proceeds by the oxidative cyclization of Pd(0) with the aryne generated from the silyl triflate to form palladacycle **I** (path a).[19] Oxidative addition of **1a** to this palladacycle forms Pd(IV) intermediate **II**. Reductive elimination gives rise to

arylpalladium(II) intermediate **III**. However, we cannot rule out the possibility that Pd(0) inserts directly into the C-Br bond of **1a** to form intermediate **IV**, which then undergoes carbopalladation of the aryne to give rise to intermediate **III**[20] (path b). Regardless of how intermediate **III** is formed, under the basic conditions, it is expected to cyclize to intermediate **V**. Finally, through reductive elimination the desired product can be generated, alongside Pd(0), which can reenter the catalytic cycle. However, there does not appear to be any particular evidence favoring either of these pathways.

Conclusions

In summary, we have developed a novel synthesis of phenanthridinones, which involves the palladium-catalyzed annulation of arynes by 2-halobenzamides. This method provides an efficient synthesis of substituted phenanthridinones from readily available starting materials. Our process has been shown to be tolerant of a wide variety of functional groups, which makes further elaboration possible.

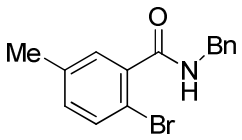
Experimental Section

General

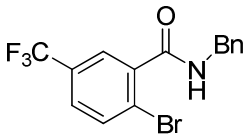
The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. High resolution mass spectra were recorded using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. All reactions were carried out in oven-dried glassware and monitored by thin layer chromatography (SiO_2, hexanes or hexanes/EtOAc). THF was distilled over Na. The silylaryl triflate **2a,** CsF, TBAF solution (1M in THF) and acetonitrile were purchased from Sigma-Aldrich Co. 4,5-Dimethyl-substituted silylaryl triflate **2b**, 4,5-dimethoxy-substituted silylaryl triflate **2c** and 4,5-difluoro-substituted silylaryl triflate **2d** were prepared according to a previous literature procedure.[21]

Non-commercially available compounds

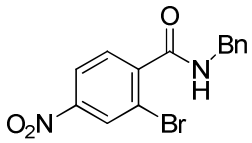
Non-commercially available starting materials were prepared according to literature procedures.[22]



***N*-Benzyl-2-bromo-5-methylbenzamide (1m):** white solid, mp 133-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.21 (m, 7H), 7.04 (dd, J = 9.0, 3.0 Hz, 1H), 6.47 (s, 1H), 4.59 (d, J = 3.0 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.78, 137.82, 137.74, 137.38, 133.16, 132.20, 130.33, 128.81, 128.08, 127.69, 115.94, 44.21, 20.89; HRMS (EI) calcd for $C_{15}H_{14}NOBr$: 304.0258, found 304.0255.

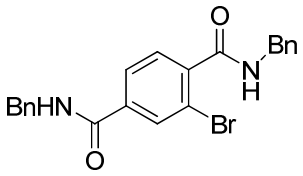


***N*-Benzyl-2-bromo-5-(trifluoromethyl)benzamide (1r):** white solid, mp 148-150 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 9.17 (t, J = 6.0 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.80 (s, 1H), 7.74 (dd, J = 9.0, 3.0 Hz, 1H), 7.42-7.25 (m, 5H), 4.50 (d, J = 6.0 Hz, 2H); ^{13}C NMR (300 MHz, d_6-DMSO) δ 166.04, 139.92, 138.73, 134.05, 128.35, 127.43, 127.39, 126.96, 125.48, 125.43, 123.87, 121.86, 42.66; HRMS (EI) calcd for $C_{15}H_{11}NOBrF_3$: 357.9966, found 357.9967.



***N*-Benzyl-2-bromo-4-nitrobenzamide (1u):** white solid, mp 148-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.17 (dd, J = 9.0, 3.0 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.37-7.26 (m, 5H), 6.39 (br s, 1H), 4.63 (d, J = 6.0 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$)

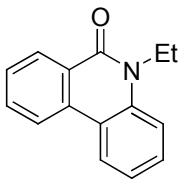
δ 165.90, 148.73, 143.53, 137.13, 130.33, 129.07, 128.60, 128.21, 128.16, 122.70, 120.20, 44.55; HRMS (EI) calcd for $C_{14}H_{11}N_2O_3Br$: 334.9933, found 334.9951.



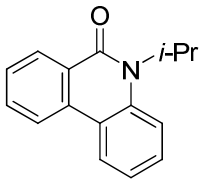
2-Bromo-*N,N'*-dibenzyl-1,4-benzenedicarboxamide (1v): white solid, mp 219-221 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 9.28 (t, J = 6.0 Hz, 1H), 9.09 (t, J = 6.0 Hz, 1H), 8.18 (s, 1H), 7.95 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.41-7.25 (m, 10H), 4.49 (d, J = 6.0 Hz, 2H;); ^{13}C NMR (300 MHz, d_6-DMSO) δ 168.86, 164.23, 141.36, 139.27, 138.95, 136.31, 131.35, 128.84, 128.36, 128.35, 127.32, 126.91, 126.89, 126.62, 118.99, 42.83, 42.49; HRMS (EI) calcd for $C_{22}H_{19}N_2O_2Br$: 422.0630, found 422.0625.

General Procedure for the Palladium-Catalyzed Synthesis of Phenanthridinones

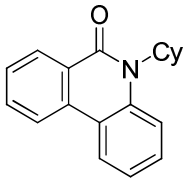
The 2-bromobenzamide (**1a**) (0.25 mmol), the 2-(trimethylsilyl)aryl triflate (2.0 equiv), CsF (5.0 equiv), Na_2CO_3 (1.0 equiv), $Pd(OAc)_2$ (5 mol %), dppm (10 mol %), 4 ml of toluene, and 1 ml of MeCN were placed in a 4 dram vial, and the vial was sealed. The reaction mixture was stirred first at room temperature for 1 min and then heated to 110 ºC for 16-24 h. The mixture was allowed to cool to room temperature, diluted with ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel using hexanes/EtOAc as the eluent.



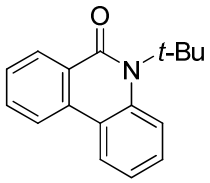
5-Ethylphenanthridin-6(5*H*)-one (3a): white solid, mp 98-99 °C; ^{1}H NMR (300 MHz, d_6-acetone) δ 8.48-8.44 (m, 4H), 7.82 (td, J = 9.0, 3.0 Hz, 1H), 7.65-7.59 (m, 3H), 7.35-7.30 (m, 1H), 4.46 (q, J = 6.0 Hz, 2H), 1.35 (t, J = 6.0 Hz, 3H); ^{13}C NMR (300 MHz, d_6-acetone) δ 160.39, 137.27, 133.83, 132.62, 130.00, 128.50, 128.01, 125.88, 123.85, 122.35, 122.17, 119.30, 115.65, 115.28, 37.29, 12.39; HRMS (EI) calcd for $C_{15}H_{13}NO$: 223.0997, found 223.0995.



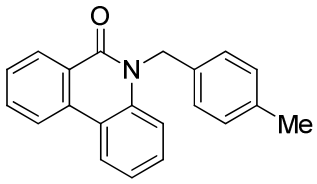
5-Isopropylphenanthridin-6(5*H*)-one (3b): white solid, mp 99-101 °C; ^{1}H NMR (300 MHz, d_6-acetone) δ 8.44 (dd, J = 9.0, 3.0 Hz, 3H), 7.84-7.76 (m, 2H), 7.64-7.54 (m, 2H), 7.32 (t, J = 9.0 Hz, 1H), 5.42 (m, 1H), 1.68 (d, J = 9.0 Hz, 9H); ^{13}C NMR (300 MHz, d_6-acetone) δ 162.49, 135.08, 133.79, 130.79, 129.60, 129.20, 128.03, 125.27, 123.48, 123.26, 121.11, 117.16, 49.12, 20.54; HRMS (EI) calcd for $C_{16}H_{15}NO$: 237.1154, found 237.1152.



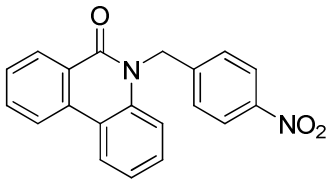
5-Cyclohexylphenanthridin-6(5*H*)-one (3c): white solid, mp 117-120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 7.8 Hz, 1H), 8.23 (dd, J = 10.0, 7.5 Hz, 2H), 7.74-7.45 (m, 5H), 7.26 (t, J = 7.2 Hz, 1H), 2.72 (m, 1H), 2.00-1.76 (m, 6H), 1.56-1.36 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.23, 138.05, 133.70, 132.34, 129.07, 128.71, 127.97, 126.79, 123.74, 122.22, 121.53, 120.26, 115.90, 57.88, 29.25, 26.89, 25.73; HRMS (EI) calcd for $C_{19}H_{19}NO$: 277.1467, found 277.1465.



5-*tert*-Butylphenanthridin-6(5*H*)-one (3d): white solid, mp 128-130 °C; ^{1}H NMR (300 MHz, d_6-acetone) δ 8.30-8.21 (m, 3H), 7.76-7.72 (m, 2H), 7.56 (t, J = 9.0 Hz, 1H), 7.42 (t, J = 9.0 Hz, 1H), 7.25 (td, J = 9.0, 3.0 Hz, 1H), 1.79 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.59, 138.09, 133.86, 132.13, 129.63, 127.89, 127.73, 126.76, 123.82, 122.68, 122.23, 121.53, 120.77, 60.72, 30.66; HRMS (EI) calcd for $C_{17}H_{17}NO$: 251.1310, found 251.1311.

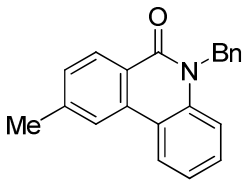


5-(4-Methlylbenzyl)phenanthridin-6(5*H*)-one (3h): white solid, mp 106-108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 8.1 Hz, 1H), 8.27 (t, J = 6.3 Hz, 1H), 7.77 (t, J = 7.2 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.36-7.07 (m, 8H), 5.61 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.06, 137.55, 136.97, 134.00, 133.73, 132.82, 129.71, 129.64, 129.34, 128.18, 126.70, 125.64, 123.42, 122.69, 121.85, 119.67, 116.22, 46.44, 21.26; HRMS (EI) calcd for $C_{21}H_{17}NO$: 299.1310, found 299.1307.

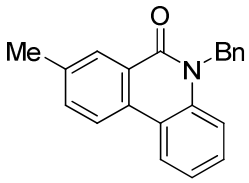


5-(4-Nitrobenzyl)phenanthridin-6(5*H*)-one (3j): white solid, mp 235-237 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 9.0 Hz, 1H), 8.36 (d, J = 9.0 Hz, 2H), 8.25 (dd, J = 6.0,

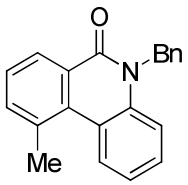
3.0 Hz, 1H), 7.85 (t, *J* = 9.0 Hz, 1H), 7.65 (t, *J* = 9.0 Hz, 1H), 7.42-7.27 (m, 4H), 7.09 (d, *J* = 9.0 Hz, 1H), 6.99 (dd, *J* = 6.0, 3.0 Hz, 1H), 6.05 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.60, 137.25, 134.40, 133.29, 132.56, 130.10, 129.41, 128.50, 128.36, 127.69, 125.91, 125.41, 123.82, 123.27, 122.05, 119.86, 115.74, 45.07; HRMS (EI) calcd for $C_{20}H_{14}N_2O_3$: 330.1004, found 330.1011.



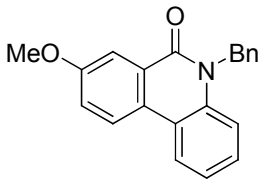
5-Benzyl-9-methylphenanthridin-6(5*H*)-one (3l): white solid, mp 173-175 °C; ^{1}H NMR (300 MHz, d_6-acetone) δ 8.47 (d, *J* = 6.0 Hz, 1H), 8.42 (d, *J* = 6.0 Hz, 1H), 8.35 (s, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.43 (dd, *J* = 6.0, 3.0 Hz, 2H), 7.31-7.23 (m, 6H), 5.70 (s, 2H), 2.59 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.10, 143.40, 137.65, 136.88, 133.99, 129.65, 129.59, 129.36, 128.96, 127.32, 126.69, 123.40, 122.61, 121.92, 119.68, 116.19, 46.57, 22.42; HRMS (EI) calcd for $C_{21}H_{17}NO$: 299.1310, found 299.1304.



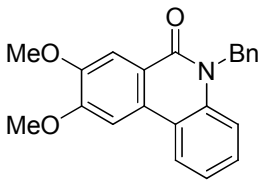
5-Benzyl-8-methylphenanthridin-6(5*H*)-one (3m): white solid, mp 173-175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.25 (d, *J* = 7.8 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.61 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.38-7.21 (m, 8H), 5.67 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.16, 138.40, 137.15, 136.87, 134.22, 131.56, 129.23, 129.09, 128.96, 127.33, 126.71, 125.45, 123.21, 122.68, 121.90, 119.84, 116.14, 46.63, 21.58; HRMS (EI) calcd for $C_{21}H_{17}NO$: 299.1310, found 299.1306.



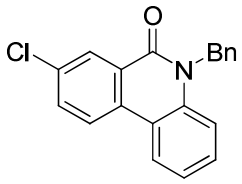
5-Benzyl-10-methoxyphenanthridin-6(5*H*)-one (3n): white solid, mp 122-123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 9.0 Hz, 1H), 8.46 (d, J = 6.0 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.52 (t, J = 9.0 Hz, 1H), 7.38-7.23 (m, 8H), 5.67 (s, 2H), 2.97 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.39, 137.70, 137.36, 136.78, 134.67, 133.50, 128.98, 128.82, 128.11, 127.82, 127.48, 127.32, 126.67, 121.87, 121.25, 116.01, 46.98, 26.31; HRMS (EI) calcd for $C_{21}H_{17}NO$: 299.1310, found 299.1303.



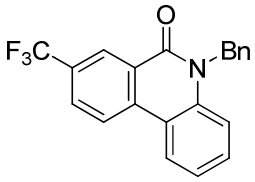
5-Benzyl-8-methoxyphenanthridin-6(5*H*)-one (3o): white solid, mp 133-135 °C; ^{1}H NMR (300 MHz, d_6-acetone) δ 8.42 (d, J = 9.0 Hz, 1H), 8.36 (d, J = 6.0 Hz, 1H), 7.96 (d, J = 3.0 Hz, 1H), 7.46-7.24 (m, 9H), 5.71 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (300 MHz, d_6-acetone) δ 162.30, 161.17, 138.77, 137.79, 130.05, 129.89, 128.71, 128.40, 128.26, 128.02, 125.48, 124.34, 123.92, 123.34, 120.78, 117.42, 110.94, 56.52, 47.12; HRMS (EI) calcd for $C_{21}H_{17}NO_2$: 315.1259, found 315.1259.



5-Benzyl-8,9-dimethoxyphenanthridin-6(5*H*)-one (3p): white solid, mp 210-212 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 7.8 Hz, 1H), 7.98 (s, 1H), 7.59 (s, 1H), 7.38-7.21 (m, 8H), 5.65 (s, 2H), 4.09 (s, 3H), 4.04 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 161.53, 153.60, 149.99, 137.00, 136.95, 128.93, 128.81, 128.75, 127.29, 126.68, 122.82, 122.49, 119.54, 119.51, 116.17, 109.41, 102.73, 56.36, 56.30, 46.60; HRMS (EI) calcd for $C_{22}H_{19}NO_3$: 345.1365, found 345.1370.

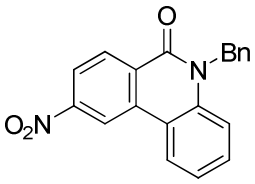


5-Benzyl-8-chlorophenanthridin-6(5*H*)-one (3q): white solid, mp 155-157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 2.1 Hz, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H), 7.73 (dd, J = 8.1, 2.4 Hz, 1H), 7.41 (m, 1H), 7.32-7.24 (m, 7H), 5.65 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 161.05, 137.39, 136.47, 134.47, 133.23, 132.48, 130.10, 129.06, 128.91, 127.51, 126.85, 126.70, 123.71, 123.49, 123.04, 119.00, 116.36, 46.83; HRMS (EI) calcd for $C_{20}H_{14}NOCl$: 319.0764, found 319.0756.

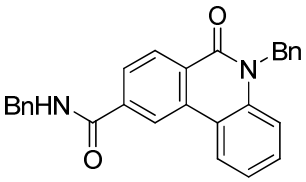


5-Benzyl-8-(trifluoromethyl)phenanthridin-6(*5H*)-one (3r): white solid, mp 186-188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.30 (dd, J = 8.1, 1.5 Hz, 1H), 7.99 (dd, J = 8.7, 1.8 Hz, 1H), 7.47 (m, 1H), 7.36-7.24 (m, 7H), 5.67 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 161.28, 138.14, 136.33, 131.05, 129.10, 129.04,

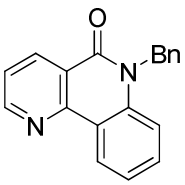
128.99, 127.60, 127.09, 126.98, 126.73, 125.68, 124.08, 123.19, 122.89, 118.61, 116.49, 46.86; HRMS (EI) calcd for $C_{21}H_{14}NOF_3$: 353.1027, found 353.1035.



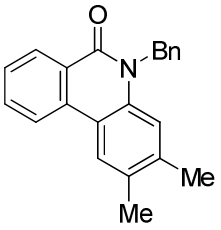
5-Benzyl-9-nitrophenanthridin-6(5*H*)-one (3u): yellow solid, decomposes above 300 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (d, J = 2.1 Hz, 1H), 8.80 (d, J = 8.7 Hz, 1H), 8.41-8.36 (m, 2H), 7.56-7.50 (m, 2H), 7.40-7.27 (m, 6H), 5.69 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.98, 160.74, 138.07, 136.03, 135.22, 131.54, 131.35, 131.10, 129.17, 129.01, 127.72, 126.69, 124.03, 123.55, 121.93, 118.50, 117.86, 116.61, 47.08; HRMS (EI) calcd for $C_{20}H_{14}N_2O_3$: 330.1004, found 330.1001.



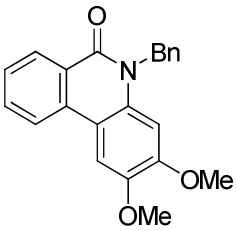
5-Benzyl-9-[(benzylamino)carbonyl]phenanthridin-6(5*H*)-one (3v): white solid, mp 197-200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.58 (d, J = 8.1 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H), 7.85 (dd, J = 8.4, 1.5 Hz, 1H), 7.33-7.22 (m, 3H), 6.88 (s, 1H), 5.61 (s, 2H), 4.72 (d, J = 5.7 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.84, 161.41, 138.14, 137.97, 136.35, 134.28, 130.27, 129.79, 129.01, 128.99, 128.19, 127.93, 127.44, 126.60, 125.33, 123.79, 123.01, 121.88, 119.16, 116.22, 46.74, 44.58; HRMS (EI) calcd for $C_{28}H_{22}N_2O_2$: 418.1681, found 418.1689.



6-Benzylbenzo-1,6-naphthyridin-5-one (3w): white solid, mp 129-131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (dd, J = 6.0, 3.0 Hz, 1H), 8.90 (d, J = 9.0 Hz, 1H), 8.83 (dd, J = 9.0, 3.0 Hz, 1H), 7.57-7.47 (m, 2H), 7.37-7.24 (m, 7H), 5.66 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.12, 154.20, 138.77, 137.24, 136.43, 131.53, 129.07, 127.56, 126.72, 125.53, 123.30, 123.21, 121.07, 115.71, 46.65; HRMS (EI) calcd for $C_{19}H_{14}N_2O$: 286.1106, found 286.1098.

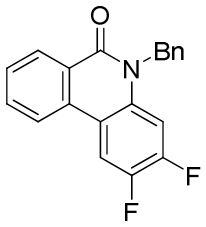


5-Benzyl-2,3-dimethylphenanthridin-6(5*H*)-one (3gb): white solid, mp 155-157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64-8.58 (m, 1H), 8.32-8.25 (m, 1H), 8.01 (s, 1H), 7.78-7.73 (m, 1H), 7.65-7.54 (m, 1H), 7.32-7.25 (m, 3H), 7.09 (s, 1H), 6.87 (d, J = 12.0 Hz, 2H), 5.64 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.07, 138.94, 137.07, 132.89, 132.70, 129.75, 129.38, 129.00, 128.96, 128.24, 127.27, 126.71, 123.48, 121.89, 116.23, 46.56, 20.68, 19.62; HRMS (EI) calcd for $C_{22}H_{19}NO$: 313.1467, found 313.1470.



5-Benzyl-2,3-dimethoxyphenanthridin-6(5*H*)-one (3gc): white solid, mp 153-155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (dd, J = 8.1, 1.5 Hz, 1H), 8.14 (d, J = 8.1, 1H), 7.76 (td, J = 8.1, 1.5 Hz, 1H), 7.64 (s, 1H), 7.56 (t, J = 8.1 Hz, 1H), 7.30-7.23 (m, 5H), 6.79 (s,

1H), 5.66 (s, 2H), 3.99 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.16, 150.77, 145.32, 137.08, 134.01, 132.75, 132.42, 129.53, 129.09, 127.53, 127.16, 126.81, 124.72, 121.32, 112.37, 105.37, 100.07, 56.50, 56.06, 47.07; HRMS (EI) calcd for $C_{22}H_{19}NO_3$: 345.1365, found 345.1370.



5-Benzyl-2,3-difluorophenanthridin-6(5*H*)-one (3gd): white solid, mp 187-189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 9.0 Hz, 1H), 8.05 (m, 1H), 7.82 (t, J = 9.0 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.35-7.08 (m, 7H), 5.60 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 161.90, 152.65, 148.07, 136.75, 135.88, 133.28, 129.63, 129.24, 129.01, 128.74, 128.27, 127.78, 127.39, 126.65, 116.26, 111.83, 105.60, 47.17; HRMS (EI) calcd for $C_{20}H_{13}NOF_2$: 321.0965, found 321.0973.

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CHAPTER 4. Palladium-Catalyzed Annulation of Arynes with *ortho*-Haloacetanilides: Synthesis of *N*-Acylcarbazoles

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Abstract

N-Acylcarbazoles have been synthesized in good yields by the annulation of *in situ* generated arynes with 2-haloacetanilides in the presence of a palladium catalyst and CsF. Both C-C and C-N bond can be formed simultaneously and a variety of functional groups are tolerated in this reaction.

Introduction

Carbazole alkaloids have been found to possess a variety of biological activities, including anti-bacterial, anti-fungal, anti-viral, anti-flammatory, and anti-tumor properties.[1] In addition to their use in the pharmaceutical field, some carbazole derivatives also find applications in material science, for example as photorefractive materials.[2]

Synthetic applications of aryne chemistry have attracted considerable attention[3] since a convenient approach to aryne generation by the fluoride induced 1,2-elimination of *o*-(trimethylsilyl)aryl triflates was first reported in 1983.[4] The high electrophilicity of arynes has been used extensively in our group in the construction of heteroaromatic structures via either simple nucleophilic reactions[5] or annulation reactions.[6] Palladium-mediated reactions are by far the most powerful metal-catalyzed processes for constructing

carbocycles and heterocycles,[7] due to the high efficiency with which they construct C-C and C-X (X = O, N) bonds[7] and their high compatibility with functional groups. To take advantage of the high reactivity and tremendous synthetic utility of arynes and the tremendous versatility of organopalladium chemistry, we[8] and several other groups[9] have been exploring the palladium-catalyzed annulation reactions of arynes.

Herein, we wish to report the palladium-catalyzed annulation of arynes by substituted 2-haloacetanilides to produce *N*-acylcarbazoles in decent yields. In this reaction, C-C and C-N bonds are formed simultaneously to generate this important heterocyclic ring system.

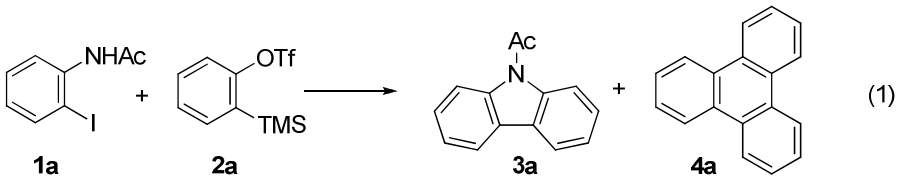
Results and discussion

Optimization studies

We attempted to optimize the reaction of 2-iodoacetanilide (**1a**) and the benzyne precursor *o*-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) in 4:1 toluene/acetonitrile with CsF as the fluoride source (Table 1). In all cases, there was always side product **4a** generated by the cyclotrimerization of benzyne,[10] plus the desired benzyne annulation product **3a** (eq 1). Optimization work was conducted with respect to different palladium catalysts, ligands, and solvents and the results are shown in Table 1.

Utilizing $Pd(dba)_2$ as the catalyst, several ligands were examined (entries 1-9) in a 4:1 toluene/acetonitrile mixed solvent. A low yield (23%) of the desired product was produced with the aryl halide **1a** left in large amounts, when employing tri(*o*-tolyl)phosphine as the ligand (entry 1). Bidentate ligands were also tested. Both dppm and dppb give low yields: 42% (entry 2) and 27% (entry 3) respectively. However, dppf improves the yield of the desired product dramatically to 69% (entry 4). Several different biarylphosphine ligands (L1-L5, Scheme 1) have also been examined in this process (entries 5-9), but the yield was only increased to around 50%.

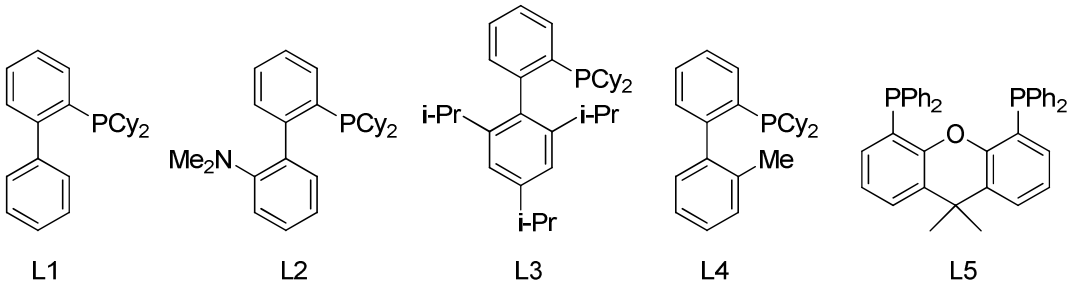
Table 1. Optimization of the Pd-Catalyzed Annulation of Benzyne (eq 1)[a]



entry	cat. (5 mol %)	ligand (mol %)	solvent (toluene/MeCN)	% yield [b] of **3a**
1	$Pd(dba)_2$	P(*o*-tolyl)$_3$ (10)	4:1	23
2	$Pd(dba)_2$	dppm (10)	4:1	42
3	$Pd(dba)_2$	dppb (10)	4:1	27
4	**$Pd(dba)_2$**	**dppf (10)**	**4:1**	**69**
5	$Pd(dba)_2$	L1 (10)[c]	4:1	45
6	$Pd(dba)_2$	L2 (10)[c]	4:1	54
7	$Pd(dba)_2$	L3 (10)[c]	4:1	56
8	$Pd(dba)_2$	L4 (10)[c]	4:1	51
9	$Pd(dba)_2$	L5 (10)[c]	4:1	17
10	$Pd(OAc)_2$	dppf (10)	4:1	54
11	$Pd(PPh_3)_4$	dppf (10)	4:1	60
12	$Pd(dba)_2$	dppf (5)	4:1	60
13	$Pd(dba)_2$	dppf (10)	3:1	54
14	$Pd(dba)_2$	dppf (10)	5:1	35
15	$Pd(dba)_2$	dppf (10)	C_3H_7CN	61
16	$Pd(dba)_2$	dppf (10)	DME[d]	45

[a]All reactions were run using substrate **1a** (0.25 mmol), 2.0 equiv of **2a**, 5.0 equiv of CsF, 10 ml of solvent at 110 °C for 24 h unless otherwise specified. [b]Isolated yield. [c]See L in Scheme 1. [d] The reaction was conducted at 90 °C for 36 h.

Scheme 1. Phosphine ligands examined



Besides examining the ligand, several commonly used Pd catalysts, including $Pd(OAc)_2$ and $Pd(PPh_3)_4$, were also tested in this reaction (entries 10 and 11). $Pd(dba)_2$ proved to be the most efficient. An effort to lower the ligand loading (entry 12) was made, but 10% dppf seemed necessary to maintain a decent yield. Based on our previous experience, the solvent can often prove critical for palladium-catalyzed benzyne reactions, mostly because the benzyne is generated at vastly different rates in different solvents.[8] With a toluene/acetonitrile mixed solvent and CsF as the fluoride source, benzyne is generated more slowly in mixtures with less acetonitrile, because CsF has a lower solubility in toluene. So the solvent ratio was tested and 4:1 toluene/acetonitrile afforded the best result (entries 13 and 14). With a 3:1 ratio, more side product, trimer **4a**, was formed. With a 5:1 ratio, the benzyne was generated too slowly, leading to a lower yield. Other solvents, including butyronitrile[11] (entry 15) and DME (entry 16), afforded only moderate yields. In the end, we have chosen the reaction conditions reported in entry 4 of Table 1 as our optimal conditions.

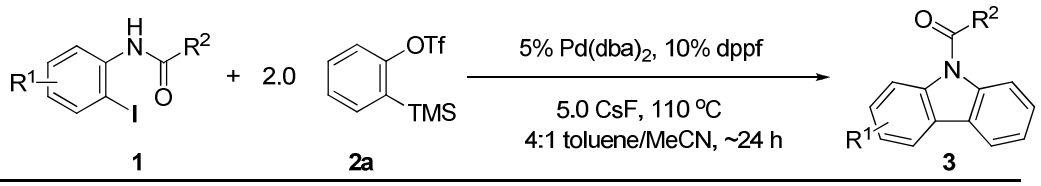
Synthesis of *N*-acylcarbazoles

In order to explore the scope and limitations of this chemistry, a number of *o*-haloacetanilide related amides were synthesized and were allowed to react with 2-

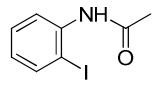
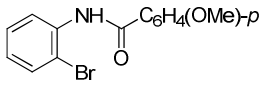
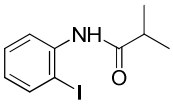
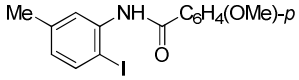
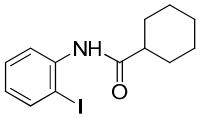
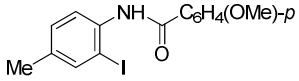
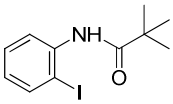
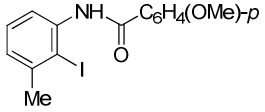
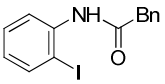
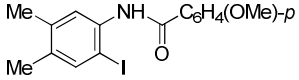
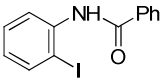
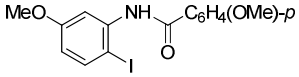
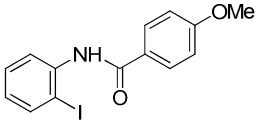
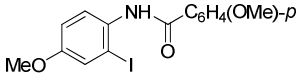
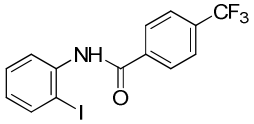
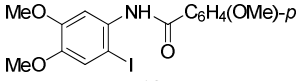
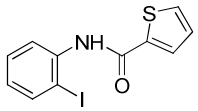
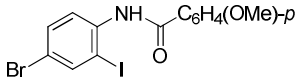
(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) under our optimized conditions. The results are summarized in Table 2.

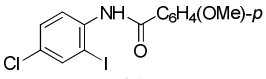
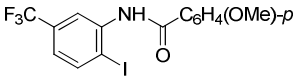
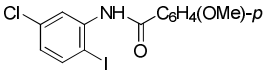
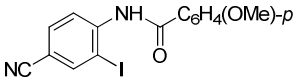
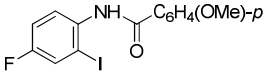
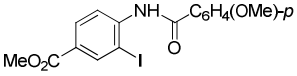
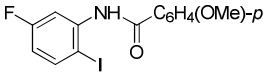
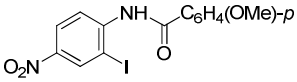
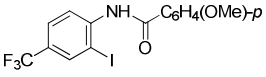
Different substituents in the acyl groups of the starting amides, including alkyl (entries 1-4), benzyl (entry 5), and phenyl (entries 6-8) groups, have been examined and decent yields have been produced, except for the reaction of amide **6**, which generated only trace amounts of the desired product along with a large amount of dehalogenated product and unidentified polymeric material. It is worth noting that the electronic nature of the phenyl group in the acyl substituent has a significant impact on the reaction yield (compare entries 6, 7, and 8). Thus, a substrate with a more electron-rich phenyl group (**9**) (entry 7) afforded a much higher yield than a similar substrate with a more electron-deficient phenyl group (**10**) (entry 8). This phenomena can be explained as follows. An electron-donating OMe group can increase the nucleophilicity of the nitrogen, which promotes nucleophilic attack of the nitrogen on Pd(II) in the cyclization step in going from complex **III** to complex **V** (see Scheme 2). On the other hand, an electron-withdrawing CF_3 group decreases the nucleophilicity, inhibiting the cyclization step. These experimental results suggest that the nucleophilicity of nitrogen, which is involved in the cyclization step from complex **III** to complex **V** (see Scheme 2), is critical for this reaction. An acetanilide with a thiophenyl substituent (**11**, entry 9) has also been tested and the reaction was observed to be messier than an analogous reaction of an alkyl-substituted substrate, producing a lower yield of 50%. A lower yield from bromo-aryl **12** (entry 10) was produced than when using the corresponding iodoacetanilide **9**. This is not suprising, since for most palladium-catalyzed reactions of aryl halides, iodine-containing substrates provide better results than bromine-containing substrates, because their oxidative addition to Pd(0) is easier and faster.

Table 2. Pd-Catalyzed Annulation of Benzyne **2a**[a]



1 **2a** **3**

entry	substrate	(product) % yield[b]	entry	substrate	(product) % yield[b]
1	 **(1)**	**(3)** 69	10	 **(12)**	**(35)** 60
2	 **(4)**	**(30)** 70	11	 **(13)**	**(38)**65
3	 **(5)**	**(31)** 73	12	 **(14)**	**(39)**74
4	 **(6)**	**(32)** trace	13	 **(15)**	**(40)** 44
5	 **(7)**	**(33)** 61	14	 **(16)**	**(41)** 77
6	 **(8)**	**(34)** 60	15	 **(17)**	**(42)** 55
7	 **(9)**	**(35)** 76	16	 **(18)**	**(43)** 34
8	 **(10)**	**(36)** 33	17	 **(19)**	**(44)** 40
9	 **(11)**	**(37)** 50	18	 **(20)**	**(45)** 60

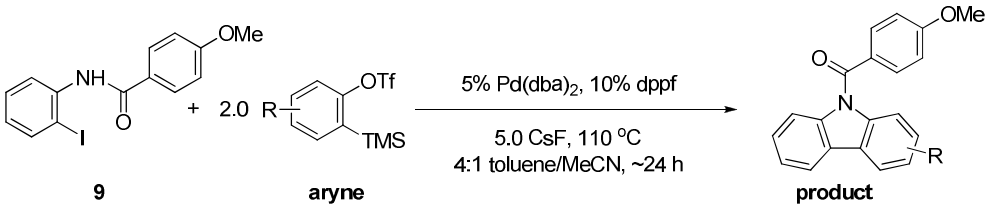
entry	substrate	(product) % yield[b]	entry	substrate	(product) % yield[b]
19	 (**21**)	(**46**) 55	24	 (**26**)	(**51**) 54
20	 (**22**)	(**47**) 63	25	 (**27**)	(**52**) 43
21	 (**23**)	(**48**) 65	26	 (**28**)	(**53**) 30
22	 (**24**)	(**49**) 53	27	 (**29**)	(**54**) 27 (50[c])
23	 (**25**)	(**50**) 40			

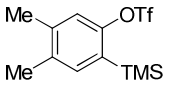
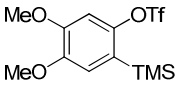
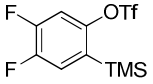
[a]Representative procedure: **1** (0.25 mmol), 2.0 equiv of **2**, 5.0 equiv of CsF, 5 mol % $Pd(dba)_2$, 10 mol % dppf in 10 ml of 4:1 toluene/MeCN at 110 °C for 24 h unless otherwise specified. [b]Isolated yield. [c]The reaction was conducted in 10 ml of 1:1 toluene/MeCN.

To further test the scope and the limitations of the reaction, we examined a variety of *N*-(2-iodophenyl)benzamides with various functional groups, including halogens (entries 18-22), electron-donating groups (entries 11-17), and electron-withdrawing groups (entries 23-27). Halogen atoms, including Br (entry 18), Cl (entries 19 and 20) and F (entries 21 and 22), are tolerated in this chemistry and decent yields are obtained for the corresponding amides, allowing further elaboration of these products via versatile metal-catalyzed reactions. Amides with a slightly electron-donating methyl group in the 4 (entry 12), and 5 (entry 11) positions and amides substituted with two methyl groups (entry 14) afford high yields of 74%, 65% and 77% respectively. An amide with a methyl group *ortho* to the iodine generates a much lower yield (44%) (entry 13), presumably because

the steric hindrance caused by the methyl group disfavors the oxidative addition step (see the later mechanistic discussion). Amides with strong electron-donating methoxy groups (entries 15-17) provide low yields of around 40%. Again this is presumably because electron-rich aryl halides undergo more sluggish oxidative addition in Pd chemistry. Strong electron-withdrawing CF_3, CN, ester, and NO_2 groups (**1l**, entry 12) lower the yield under our "optimal" conditions. We think the reason is that although these electron-withdrawing groups electronically benefit oxidative addition of the aryl halide to Pd(0), they strongly disfavor nucleophilic attack of the nitrogen on Pd(II) in complex **III** in the cyclization step to form complex **V** (see Scheme 2).

Table 3. Investigation of Different Arynes in the Pd-Catalyzed Annulation of *o*-Haloacetanilide **9** [a]



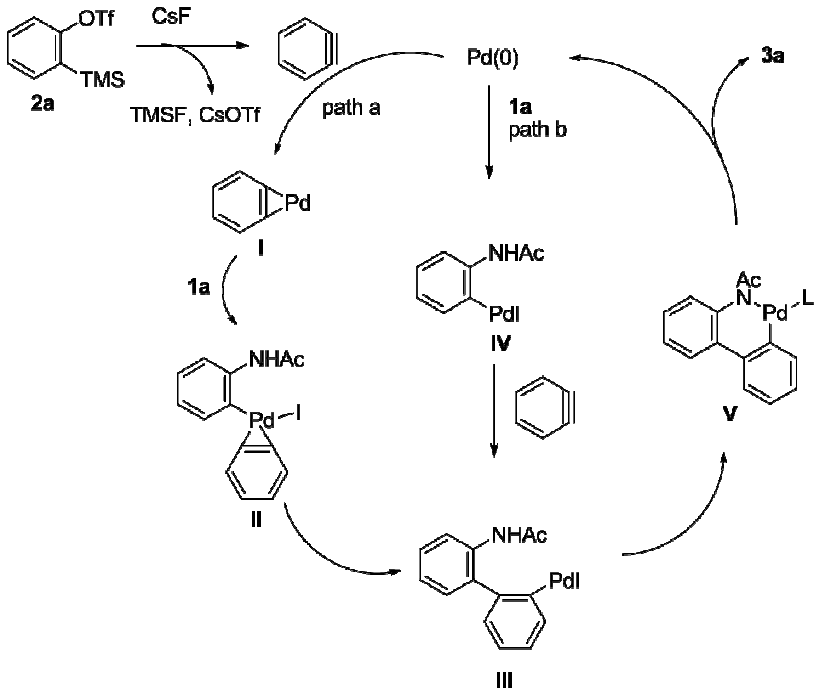
entry	aryne precursor		(product) % yield[b]
1		**2b**	**(16)** 62
2		**2c**	(**44**) 40[c]
3		**2d**	(**55**) 0

[a] Representative procedure: **9** (0.25 mmol), 2.0 equiv of the aryne precursor**,** 5.0 equiv of CsF, 5 mol % $Pd(dba)_2$, 10 mol % dppf in 10 ml of 4:1 toluene/MeCN at 110 °C for 24 h. [b] Isolated yield. [c] Reaction was conducted for 48 h.

In addition to the above reactions, which examined only the use of the benzyne precursor triflate **2a** as an annulation partner, other aryne precursors have been examined in our methodology (Table 3). When 4,5-dimethylbenzyne precursor **2b** was allowed to react with amide **9** under our optimized conditions, it provided the corresponding annulation product **16** in a decent yield. Dimethoxybenzyne precursor **2c** was also examined and a longer reaction time was necessary to get a 40% yield of the annulation product **44** (Table 3, entry 2). The low yield for **2c** may be attributed to the slower rate of generation of 4,5-dimethoxybenzyne compared with the generation of benzyne from **2a**, as has been suggested by earlier work in our group.[12] Difluorobenzyne precursor **2d** was also allowed to react with **1g** under the optimal conditions (Table 3, entry 3), but none of the desired product was observed and a large amount of **1g** was left, presumably due to the lack of stability of difluorobenzyne in the reaction system.

Based on our experimental results and previous experience with related processes,[13] we propose that this *N*-acylcarbazole synthesis proceeds through one of two possible pathways shown in Scheme 2. One possible pathway proceeds by the oxidative cyclization of Pd(0) with aryne generated from the silyl triflate to form palladacycle **I** (path a).[14] Oxidative addition of **1a** to this palladacycle forms Pd(IV) intermediate **II**. However, we cannot rule out the possibility that Pd(0) inserts directly into the C-I bond of **1a** to form intermediate **IV**, which then undergoes carbopalladation of the aryne to give rise to intermediate **III**[15] (path b). Then, under the basic conditions, intermediate **V** may be formed. Finally, through reductive elimination the desired product can be generated alongside Pd(0), which can reenter the catalytic cycle. However, there does not appear to does not appear to be any particular evidence favoring either of these pathways.

Scheme 2. Tentative Mechanisms



Conclusions

In summary, we have developed a novel method for the synthesis of *N*-acylcarbazoles, which involves the palladium-catalyzed annulation of arynes by 2-haloacetanilides. This method provides an efficient synthesis of carbazole derivatives from readily available starting materials. Our process has been shown to be tolerant of various functional groups, which makes further elaboration of these substrates possible.

Experimental Section

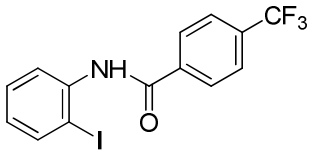
General

The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. High resolution mass spectra were recorded using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. CsF, acetonitrile and silyaryl triflate **2a** were purchased from

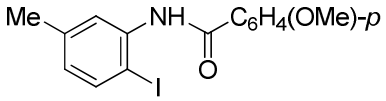
Sigma-Aldrich Co. 4,5-Dimethyl-substituted silylaryl triflate **2b**, 4,5-dimethoxy-substituted silylaryl triflate **2c** and 4,5-difluoro-substituted silylaryl triflate **2d** were prepared according to a previous literature procedure.[16]

Non-commercial compounds

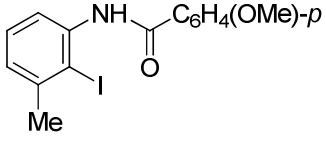
Non-commercially available starting materials were prepared according to literature procedures.[17]



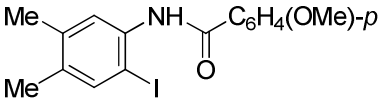
***N*-(2-Iodophenyl)-4-(trifluoromethyl)benzamide (10):** white solid, mp 173-175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 9.0 Hz, 1H), δ 7.82 (d, J = 9.0 Hz, 1H), 7.71-7.63 (m, 5H), 7.42 (t, J = 6.0 Hz, 1H), 6.92 (t, J = 9.0 Hz, 1H); ^{13}C NMR (300 MHz, d_6-DMSO) δ 165.80, 139.03, 135.83, 132.48, 130.20, 128.88, 128.50, 128.42, 128.14, 126.49, 126.43; HRMS (EI) calcd for $C_{14}H_9NOF_3Br$: 390.9681, found 390.9689.



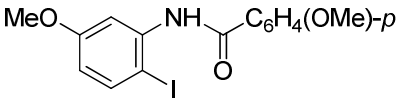
***N*-(2-Iodo-5-methylphenyl)-4-methoxybenzamide (13):** white solid, mp 95-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 1.8 Hz, 1H), 8.18 (s, 1H), 7.94 (d, J = 9.0 Hz, 2H), 7.66 (d, J = 8.1 Hz, 1H), 7.02 (d, J = 9.0 Hz, 2H), 6.71 (dd, J = 8.1, 2.1 Hz, 1H), 3.89 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 164.96, 162.92, 139.93, 138.47, 138.33, 129.25, 127.06, 126.99, 122.56, 114.33, 86.34, 55.69, 21.54; HRMS (EI) calcd for $C_{15}H_{14}NO_2I$: 367.0069, found 367.0077.



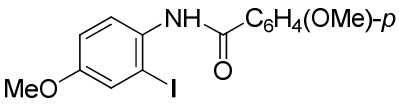
***N*-(2-Iodo-3-methylphenyl)-4-methoxybenzamide (15):** white solid, mp 148-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.24 (d, J = 6.0 Hz, 1H), 7.96 (d, J = 6.0 Hz, 2H), 7.27 (t, J = 9.0 Hz, 1H), 7.05-6.99 (d, J = 6.0 Hz, 3H), 3.88 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.01, 162.87, 142.43, 138.75, 129.29, 128.85, 127.14, 125.76, 119.16, 114.30, 98.02, 55.68, 29.88; HRMS (EI) calcd for $C_{15}H_{14}NO_2I$: 367.0069, found 367.0069.



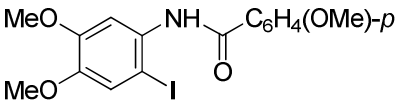
***N*-(4,5-Dimethyl-2-iodophenyl)-4-methoxybenzamide (16):** white solid, mp 125-127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.08 (s, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.55 (s, 1H), 7.00 (d, J = 6.0 Hz, 2H), 3.88 (s, 3H), 2.26 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 164.90, 162.82, 139.11, 138.33, 136.29, 135.01, 133.01, 129.21, 127.06, 123.10, 114.28, 86.76, 55.67, 20.03, 19.10; HRMS (EI) calcd for $C_{16}H_{16}NO_2I$: 381.0226, found 381.0227.



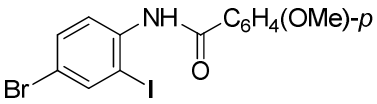
***N*-(2-Iodo-5-methoxyphenyl)-4-methoxybenzamide (17):** white solid, mp 107-110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23-8.22 (m, 2H), 7.93 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 6.49 (dd, J = 8.7, 3.0 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.04, 162.97, 160.89, 139.42, 138.71, 132.99, 129.22, 126.87, 114.35, 113.12, 106.75, 78.26, 55.69, 55.67; HRMS (EI) calcd for $C_{15}H_{14}NO_3I$: 383.0015, found 383.0023.



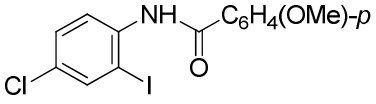
***N*-(2-Iodo-4-methoxyphenyl)-4-methoxybenzamide (18):** white solid, mp 134-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, J = 9.3 Hz, 1H), 8.16 (s, 1H), 7.88 (d, J = 6.9 Hz, 1H), 7.02-6.97 (m, 3H), 6.88 (dd, J = 9.0, 3.0 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 164.89, 162.81, 156.37, 129.12, 128.44, 127.10, 124.38, 123.12, 114.74, 114.27, 113.48, 55.91, 55.68; HRMS (EI) calcd for $C_{15}H_{14}NO_3I$: 383.0018, found 383.0028.



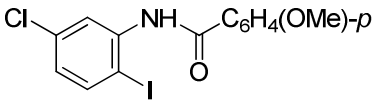
***N*-(4,5-Dimethoxy-2-iodophenyl)-4-methoxybenzamide (19):** white solid, mp 168-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.06 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.20 (s, 1H), 7.01 (d, J = 12.0 Hz, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.94, 162.83, 149.74, 146.40, 132.71, 129.10, 126.82, 120.40, 114.27, 105.85, 56.46, 56.16, 55.63; HRMS (EI) calcd for $C_{16}H_{16}NO_4I$: 413.0124, found 413.0121.



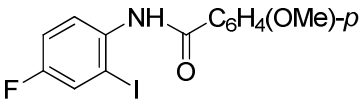
***N*-(4-Bromo-2-iodophenyl)-4-methoxybenzamide (20):** white solid, mp 151-152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 8.7 Hz, 1H), 8.19 (s, 1H), 7.93-7.90 (m, 3H), 7.50 (dd, J = 9.0, 2.1 Hz, 1H), 7.01 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H) ; ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.58, 163.12, 140.62, 137.94, 132.53, 129.68, 126.59, 122.54, 117.25, 114.42, 90.41, 55.73; HRMS (EI) calcd for $C_{14}H_{11}NO_2IBr$: 430.9018, found 430.9029.



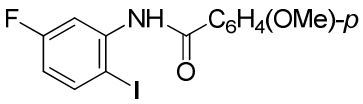
***N*-(4-Chloro-2-iodophenyl)-4-methoxybenzamide (21):** white solid, mp 148-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 9.0 Hz, 1H), 8.19 (s, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 2.4 Hz, 1H), 7.37 (dd, J = 9.0, 2.4 Hz, 1H), 7.01 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 164.96, 163.11, 137.99, 137.51, 129.84, 129.60, 129.30, 126.60, 122.16, 114.42, 90.01, 55.73; HRMS (EI) calcd for $C_{14}H_{11}NO_2ClI$: 386.9523, found 486.9524.



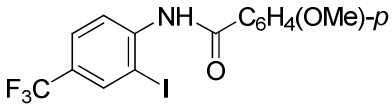
***N*-(5-Chloro-2-iodophenyl)-4-methoxybenzamide (22):** white solid, mp 123-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.22 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 12.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.94, 163.18, 139.59, 139.33, 135.80, 129.33, 126.50, 125.92, 121.53, 114.45, 86.86, 55.75; HRMS (EI) calcd for $C_{14}H_{11}NO_2ICl$: 386.9523, found 386.9524.



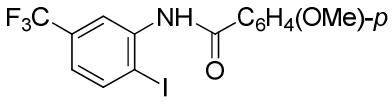
***N*-(4-Fluoro-2-iodophenyl)-4-methoxybenzamide (23):** white solid, mp 158-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, J = 12.0, 8.0 Hz, 1H), 8.09 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.54 (dd, J = 8.0, 4.0 Hz, 1H), 7.26 (s, 1H), 7.14 (td, J = 12.0, 4.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.01, 163.00, 157.06, 135.17, 129.25, 125.69, 125.36, 122.84, 116.19, 114.37, 89.89, 55.72; HRMS (EI) calcd for $C_{14}H_{11}NO_2FI$: 370.9818, found 370.9823.



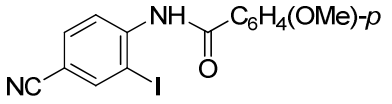
***N*-(5-Fluoro-2-iodophenyl)-4-methoxybenzamide (24):** white solid, mp 133-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (dd, J = 11.0, 2.7 Hz, 1H), 8.29 (s, 1H), 7.94 (d, J = 8.7 Hz, 2H), 7.74 (dd, J = 8.7, 6.0 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H), 6.70-6.63 (m, 1H), 3.90 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 164.91, 163.12, 161.85, 139.27, 139.15, 129.26, 126.44, 114.39, 113.09, 108.89, 82.50, 55.68; HRMS (EI) calcd for $C_{14}H_{11}NO_2FI$: 370.9818, found 370.9824.



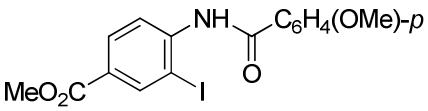
***N*-[2-Iodo-4-(trifluoromethyl)phenyl]-4-methoxybenzamide (25):** white solid, mp 148-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, J = 9.0 Hz, 1H), 8.38 (s, 1H), 8.04 (s, 1H), 7.94 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 6.0 Hz, 1H), 7.02 (d, J = 9.0 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.06, 163.29, 141.73, 135.89, 135.84, 129.39, 126.78, 126.29, 120.75, 114.38, 88.89, 82.25, 55.73; HRMS (EI) calcd for $C_{15}H_{11}NO_2F_3I$: 420.9782, found 420.9782.



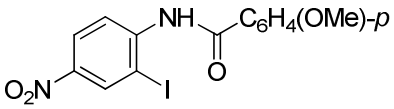
***N*-[2-Iodo-5-(trifluoromethyl)phenyl]-4-methoxybenzamide (26):** white solid, mp 146-148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, J = 2.1 Hz, 1H), 8.34 (s, 1H), 7.97-7.92 (m, 3H), 7.11 (dd, J = 8.1, 2.1 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.07, 163.29, 139.43, 139.39, 129.35, 126.34, 122.03, 118.09, 114.52, 93.74, 55.76; HRMS (EI) calcd for $C_{15}H_{11}NO_2F_3I$: 420.9787, found 420.9784.



***N*-(4-Cyano-2-iodophenyl)-4-methoxybenzamide (27):** white solid, mp 83-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, J = 6.0 Hz, 1H), 8.60 (s, 1H), 7.92-7.87 (d, J = 6.0 Hz, 2H; s, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.03 (d, J = 9.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.58, 163.50, 140.41, 132.87, 129.41, 126.02, 121.04, 117.66, 113.06, 108.02, 55.79; HRMS (EI) calcd for $C_{15}H_{11}N_2O_2I$: 377.9865, found 377.9860.



***N*-(4-Carbomethoxy-2-iodophenyl)-4-methoxybenzamide (28):** white solid, mp 165-167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 8.7 Hz, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.43 (s, 1H), 8.04 (dd, J = 8.7, 2.1 Hz, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.01 (d, J = 9.0 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.39, 164.96, 163.23, 142.49, 140.34, 131.12, 129.37, 126.94, 126.40, 120.04, 114.45, 88.88, 55.71, 52.45; HRMS (EI) calcd for $C_{16}H_{14}NO_4I$: 410.9968, found 410.9974.

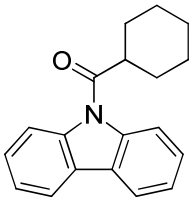


***N*-(2-Iodo-4-nitrophenyl)-4-methoxybenzamide (29):** white solid, mp 158-160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, J = 9.0 Hz, 1H), 8.69 (d, J = 3.0 Hz, 1H), 8.55 (s, 1H), 8.28 (dd, J = 9.0, 3.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.04, 163.60, 144.32, 134.42, 129.53, 126.15, 125.33, 119.66, 114.64, 87.90, 55.81; HRMS (EI) calcd for $C_{14}H_{11}N_2O_4I$: 397.9763, found 397.9833.

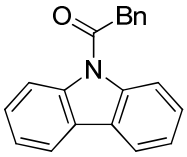
General Procedure for the Palladium-Catalyzed Synthesis of *N*-Acylcarbazoles

The 2-iodoacetanilide (**1**) (0.25 mmol), the 2-(trimethylsilyl)aryl triflate (2.0 equiv), CsF (5.0 equiv), $Pd(dba)_2$ (5 mol %), dppf (10 mol %), 8 ml of toluene, and 2 ml of MeCN

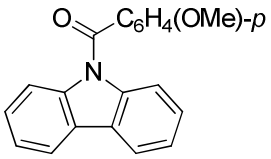
were placed in a 4 dram vial, and the vial was sealed. The reaction mixture was stirred first at room temperature for 1 min and then heated to 110 °C for 24 h. The mixture was allowed to cool to room temperature, diluted with ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel using hexanes/EtOAc as the eluent.



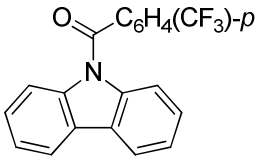
9-(Cyclohexylcarbonyl)carbazole (31): light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 9.0 Hz, 2H), 8.02 (d, J = 9.0 Hz, 2H), 7.51 (dd, J = 9.0, 6.0 Hz, 2H), 7.40 (dd, J = 9.0, 6.0 Hz, 2H), 3.38 (tt, J = 12.0, 3.0 Hz, 1H), 2.14 (d, J = 12.0 Hz, 2H), 1.96 (d, J = 12.0 Hz, 2H), 1.86-1.74 (m, 3H), 1.60-1.44 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 177.12, 138.80, 127.52, 126.58, 123.62, 123.62, 119.97, 116.39, 45.46, 29.68, 25.99, 25.85; HRMS (EI) calcd for $C_{19}H_{19}NO$: 277.1467, found 277.1466.



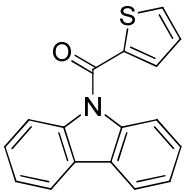
9-(Phenylacetyl)carbazole (33): white solid, mp 123-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.0 Hz, 2H), 8.04 (d, J = 8.0 Hz, 2H), 7.51-7.47 (t, J = 8.0 Hz, 2H), 7.43-7.40 (m, 4H), 7.38-7.34 (m, 3H), 4.53 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.55, 138.74, 133.71, 129.73, 129.02, 127.65, 126.75, 126.14, 124.04, 120.09, 116.71, 45.61; HRMS (EI) calcd for $C_{20}H_{15}NO$: 285.1154, found 285.1153.



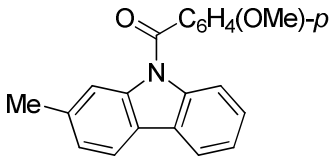
9-(4-Methoxybenzoyl)carbazole (35): white solid, mp 162-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02-7.99 (m, 2H), 7.72 (d, J = 8.7 Hz, 2H), 7.57-7.52 (m, 2H), 7.36-7.30 (m, 4H), 6.99 (d, J = 9.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.30, 163.40, 139.54, 131.99, 127.74, 126.79, 125.97, 123.23, 120.03, 115.73, 114.29, 55.73; HRMS (EI) calcd for $C_{20}H_{15}NO_2$: 301.1103, found 301.1104.



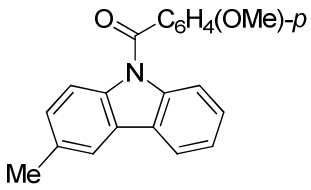
9-[4-(Trifluoromethyl)benzoyl]carbazole (36): white solid, mp 101-103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 9.0 Hz, 2H), 7.93 (d, J = 9.0 Hz, 1H), 7.79-7.70 (m, 2H), 7.53 (d, J = 6.0 Hz, 1H), 7.44-7.27 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.57, 138.86, 132.87, 131.00, 129.18, 128.60, 128.41, 127.46, 126.82, 124.41, 120.06, 116.25; HRMS (EI) calcd for $C_{20}H_{12}NOF_3$: 339.0871, found 339.0876.



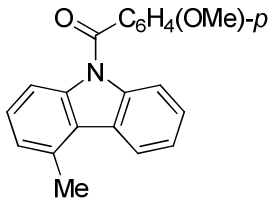
9-(Thiophenylcarbonyl)carbazole (37): light yellow solid, mp 95-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04-8.01 (m, 2H), 7.76-7.70 (m, 3H), 7.60 (d, J = 3.0 Hz, 1H), 7.39-7.36 (m, 4H), 7.16 (dd, J = 6.0, 3.0 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.98, 139.37, 137.98, 133.95, 133.38, 127.87, 126.82, 125.63, 123.45, 120.13, 115.46; HRMS (EI) calcd for $C_{17}H_{11}NOS$: 277.0561, found 277.0564.



2-Methyl-9-(4-methoxybenzoyl)carbazole (38): white solid, mp 129-131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 6.0 Hz, 1H), 7.90 (d, J = 9.0 Hz, 1H), 7.74 (d, J = 9.0 Hz, 2H), 7.54 (s, 1H), 7.40-7.24 (m, 3H), 7.19 (d, J = 9.0 Hz, 1H), 7.01 (d, J = 9.0 Hz, 2H), 3.93 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.34, 163.38, 139.98, 139.47, 137.16, 132.03, 127.79, 126.12, 124.62, 123.60, 123.10, 119.75, 119.63, 116.05, 115.62, 114.23; HRMS (EI) calcd for $C_{21}H_{17}NO_2$: 315.1259, found 315.1266.

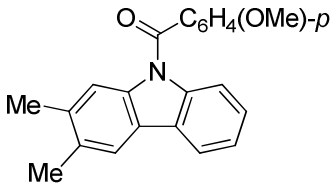


3-Methyl-9-(4-methoxybenzoyl)carbazole (39): light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, J = 6.0, 3.0 Hz, 1H), 7.82 (s, 1H), 7.73 (d, J = 9.0 Hz, 2H), 7.60 (dd, J = 6.0, 3.0 Hz, 1H), 7.42(d, J = 9.0 Hz, 1H), 7.37-7.33 (m, 2H), 7.16 (d, J = 9.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 3.92 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.22, 163.27, 139.76, 137.67, 132.89, 131.87, 129.16, 128.59, 127.96, 126.66, 126.00, 123.19, 120.05, 119.91, 115.81, 114.24, 55.71, 21.51; HRMS (EI) calcd for $C_{21}H_{17}NO_2$: 315.1257, found 315.1263.

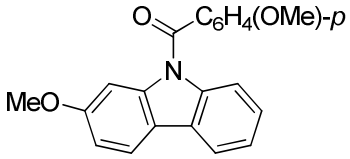


4-Methyl-9-(4-methoxybenzoyl)carbazole (40): light brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (m, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.65 (m, 1H),

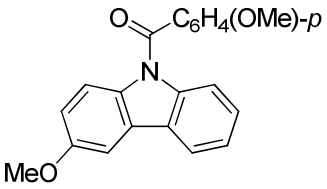
7.44 (d, J = 8.4 Hz, 1H), 7.34-7.23 (m, 2H), 7.18-7.13 (m, 1H), 7.00 (d, J = 8.8 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.34, 163.44, 140.54, 139.56, 133.05, 132.11, 129.75, 126.48, 126.30, 126.04, 124.85, 123.04, 122.59, 122.42, 115.31, 114.24, 113.08, 55.77, 21.18; HRMS (EI) m/z calcd for $C_{21}H_{17}NO_2$: 316.13321, found 316.13346.



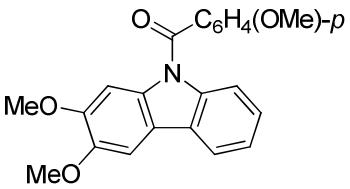
2,3-Dimethyl-9-(4-methoxybenzoyl)carbazole (41): white solid, mp 156-157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 9.0 Hz, 1H), 7.76 (s, 1H), 7.72 (d, J = 9.0 Hz, 2H), 7.47 (s, 1H), 7.38 (d, J = 9.0 Hz, 1H), 7.32-7.23 (m, 2H), 6.99 (d, J = 9.0 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.05, 163.26, 139.44, 138.30, 136.02, 131.92, 138.30, 136.02, 132.06, 131.92, 127.98, 126.23, 126.01, 123.99, 123.08, 120.39, 119.65, 116.51, 115.71, 114.20, 55.74, 21.06, 20.22; HRMS (EI) m/z calcd for $C_{20}H_{14}N_2O_3$: 330.14886, found 330.14919.



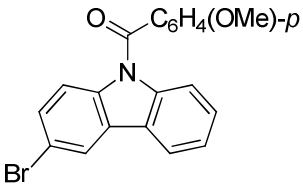
2-Methoxy-9-(4-methoxybenzoyl)carbazole (42): white solid, mp 109-111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.86 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 9.0 Hz, 2H), 7.37-7.22 (m, 4H), 7.01-6.94 (m, 3H), 3.91 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.38, 163.40, 159.43, 140.86, 139.43, 131.98, 127.66, 126.13, 125.32, 123.24, 120.57, 119.43, 119.24, 115.54, 114.27, 111.84, 100.32, 55.73; HRMS (EI) calcd for $C_{21}H_{17}NO_3$: 331.1208, found 331.1216.



3-Methoxy-9-(4-methoxybenzoyl)carbazole (43): light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 15.0 Hz, 1H), 7.63 (d, J = 6.0 Hz, 1H), 7.44-7.41 (m, 3H), 7.35-7.29 (m, 1H), 7.23-7.20 (m, 1H), 7.11 (d, J = 15.0 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 3.91 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.58, 161.91, 155.85, 138.55, 134.58, 129.84, 125.99, 122.45, 120.84, 120.44, 119.23, 118.10, 115.51, 115.26, 111.50, 110.95, 103.38, 56.30; HRMS (EI) calcd for $C_{21}H_{17}NO_3$: 331.1209, found 331.1215.

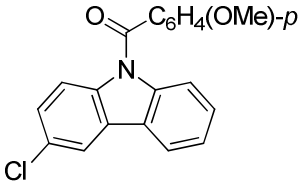


2,3-Dimethoxy-9-(4-methoxybenzoyl)carbazole (44): white solid, mp 114-116 $^{\circ}$C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 9.0 Hz, 2H), 7.43 (s, 1H), 7.42 (s, 1H), 7.32-7.17 (m, 4H), 7.01 (d, J = 9.0 Hz, 2H), 4.03 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.19, 163.26, 149.25, 146.82, 139.10, 134.03, 131.87, 127.88, 126.40, 125.12, 123.15, 119.04, 118.32, 115.69, 114.25, 101.66, 99.84, 56.54, 56.21, 55.75; HRMS (EI) calcd for $C_{22}H_{19}NO_4$: 361.1314, found 361.1318.

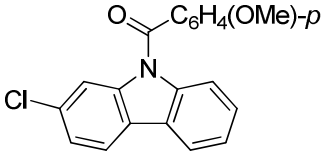


3-Bromo-9-(4-methoxybenzoyl)carbazole (45): white solid, mp 110-112 $^{\circ}$C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.99-7.96 (m, 1H), 7.72 (d, J = 9.0 Hz, 2H), 7.52-7.42

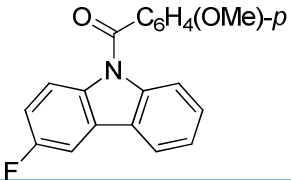
(m, 3H), 7.38-7.35 (m, 2H), 7.01 (d, J = 6.0 Hz, 2H), 3.93 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.58, 163.62, 139.81, 138.30, 132.05, 129.55, 127.80, 127.50, 127.31, 124.76, 123.51, 122.90, 120.25, 117.20, 116.38, 115.76, 114.40, 55.79; HRMS (EI) calcd for $C_{20}H_{14}NO_2Br$: 379.0208, found 379.0206.



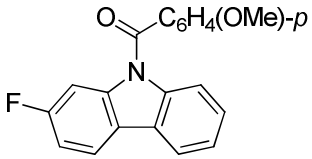
3-Chloro-9-(4-methoxybenzoyl)carbazole (46): light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.96 (m, 2H), 7.72 (d, J = 9.0 Hz, 2H), 7.56-7.49 (m, 1H), 7.37-7.29 (m, 3H), 7.01 (d, J = 9.0 Hz, 2H), 3.93 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.03, 163.59, 139.95, 137.90, 132.02, 129.18, 128.85, 127.46, 126.84, 124.90, 123.47, 120.66, 120.25, 119.85, 116.81, 115.79, 114.39, 55.78; HRMS (EI) calcd for $C_{20}H_{14}NO_2Cl$: 335.0713, found 335.0715.



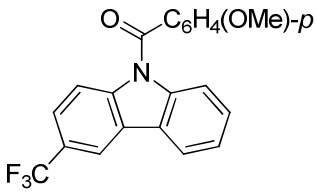
2-Chloro-9-(4-methoxybenzoyl)carbazole (47): white solid, mp 93-95 $^{\circ}$C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.77-7.72 (dd, J = 8.4, 1.8 Hz, 3H), 7.42 (d, J = 3.0 Hz, 1H), 7.35-7.32 (m, 3H), 7.02 (d, J = 9.0 Hz, 2H), 3.93 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.02, 163.68, 143.54, 139.07, 132.08, 130.71, 129.17, 128.60, 126.89, 124.43, 123.79, 123.42, 120.73, 120.06, 116.00, 115.65, 114.40, 55.79; HRMS (EI) m/z calcd for $C_{20}H_{14}NO_2Cl$: 336.07858, found 336.07904.



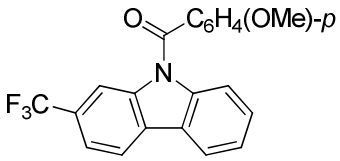
3-Fluoro-9-(4-methoxybenzoyl)carbazole (48): white solid, mp 90-93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.95 (m, 1H), 7.72 (d, J = 9.0 Hz, 2H), 7.69-7.60 (m, 2H), 7.48-7.45 (m, 1H), 7.36-7.33 (d, J = 6.0 Hz, 2H), 7.09 (td, J = 9.0, 2.7 Hz, 1H), 7.02 (d, J = 6.9 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.09, 163.48, 157.92, 140.21, 131.95, 127.55, 127.36, 123.30, 120.19, 116.95, 116.84, 115.88, 114.50, 114.37, 114.17, 106.17, 105.85, 55.77; HRMS (EI) m/z calcd for $C_{20}H_{14}NO_2F$: 320.10813, found 320.10895.



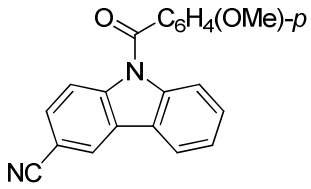
2-Fluoro-9-(4-methoxybenzoyl)carbazole (49): white solid, mp 115-117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.92 (m, 2H), 7.73 (d, J = 9.0 Hz, 2H), 7.44-7.41 (m, 2H), 7.32 (td, J = 9.0, 3.0 Hz, 2H), 7.11 (d, J = 6.0 Hz, 1H), 7.02 (d, J = 9.0 Hz, 2H), 3.93 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.13, 163.63, 160.51, 143.54, 140.24, 132.01, 129.17, 128.60, 126.30, 125.61, 123.45, 120.74, 119.75, 115.62, 114.41, 55.77; HRMS (EI) calcd for $C_{20}H_{14}NO_2F$: 319.1009, found 319.1010.



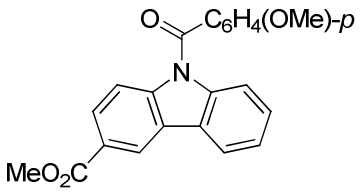
9-(4-Methoxybenzoyl)-3-(trifluoromethyl)carbazole (50): light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20-8.17 (m, 2H), 7.44-7.38 (m, 3H), 7.32 (dd, J = 5.1, 3.0 Hz, 1H), 7.30-7.21 (m, 3H), 7.10 (d, J = 8.7 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.09, 164.05, 148.23, 143.51, 132.46, 130.69, 130.46, 129.61, 129.15, 128.92, 128.58, 126.12, 125.89, 125.60, 122.04, 121.98, 120.62, 120.56, 118.25, 114.01, 55.70; HRMS (EI) calcd for $C_{21}H_{14}NO_2F_3$: 369.0975, found 369.0977.



9-(4-Methoxybenzoyl)-2-(trifluoromethyl)carbazole (51): white solid, mp 107-109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14-8.06 (m, 3H), 7.74 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 9.0 Hz, 1H), 7.44-7.38 (m, 3H), 7.03 (d, J = 9.0 Hz, 2H), 3.94 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.02, 163.82, 138.98, 138.36, 132.14, 130.49, 129.18, 128.61, 127.88, 126.97, 125.61, 123.54, 120.74, 120.67, 120.32, 115.74, 114.45, 55.83; HRMS (EI) calcd for $C_{21}H_{14}NO_2F_3$: 369.0977, found 369.0978.

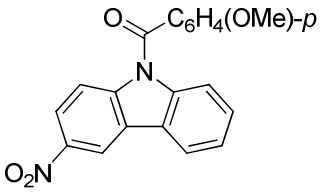


3-Cyano-9-(4-methoxybenzoyl)carbazole (52): white solid, mp 175-177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.08-8.05 (m, 1H), 7.76-7.70 (m, 3H), 7.63 (dd, J = 9.0, 3.0 Hz, 1H), 7.50-7.40 (m, 3H), 7.03 (d, J = 9.0 Hz, 2H), 3.94 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.88, 164.09, 141.60, 140.07, 132.35, 130.08, 128.13, 126.60, 126.21, 124.69, 124.24, 123.91, 120.52, 119.69, 116.25, 115.68, 114.57, 106.40, 55.86; HRMS (EI) calcd for $C_{21}H_{14}N_2O_2$: 326.3481, found 326.3468.



3-Carbomethoxy-9-(4-methoxybenzoyl)carbazole (53): white solid, mp 134-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.11-8.04 (m, 2H), 7.75 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 9.0 Hz, 1H), 7.54 (t, J = 3.6 Hz, 1H), 7.41-7.38 (m, 2H), 7.01 (d, J = 9.0 Hz,

2H), 3.99 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.13, 167.37, 163.82, 141.73, 140.10, 132.26, 129.01, 128.16, 127.42, 125.85, 125.44, 125.01, 123.66, 122.19, 120.42, 115.67, 115.22, 114.44, 55.82, 52.41; HRMS (EI) calcd m/z for $C_{22}H_{17}NO_4$: 360.12303, found 360.12378.



9-(4-Methoxybenzoyl)-3-nitrocarbazole (54): yellow solid, mp 170-172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (d, J = 2.1 Hz, 1H), 8.28 (dd, J = 9.0, 2.4 Hz, 1H), 8.14-8.11 (m, 1H), 7.78-7.71 (d, J = 9.0 Hz, 3H), 7.48-7.42 (m, 3H), 7.03 (d, J = 9.0 Hz, 2H), 3.95 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.81, 166.58, 164.21, 143.69, 142.89, 140.64, 132.43, 128.29, 126.39, 126.06, 124.67, 124.03, 122.19, 120.75, 116.38, 115.75, 115.48, 114.61, 55.87; HRMS (EI) m/z calcd for $C_{20}H_{14}N_2O_4$: 347.10263, found 337.10329.

Acknowledgments

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GENERAL CONCLUSIONS

In this dissertation, several novel aryne reactions have been investigated. The scope, limitations, and applications of these reactions are presented in detail. The reactions involve three major areas of aryne chemistry and show the versatility of arynes.

Chapter 1 reports the synthesis of a variety of biologically interesting 9-substituted xanthenes involving the reaction of arynes and *o*-hydroxychalcones. This chemistry presumably proceeds by intermolecular nucleophilic attack of the phenoxide of the chalcone on the aryne and subsequent intramolecular Michael addition. The introduction of an external base, Cs_2CO_3, has proven beneficial to this reaction.

Chapter 2 describes a 1,3-dipolar cycloaddition reaction of arynes and nitrones. Substituted benzisoxazolines were easily synthesized under mild reaction conditions. A variety of functional groups are well tolerated in this process, allowing for the facile synthesis of more complicated molecules.

Chapter 3 discusses a novel synthesis of phenanthridinones, which involves the palladium-catalyzed annulation of arynes by 2-halobenzamides. This method provides an efficient synthesis of substituted phenanthridinones from readily available starting materials. Both C-C and C-N bonds are formed simultaneously and a variety of functional groups are tolerated in this reaction, making further elaboration possible.

Chapter 4 reports a novel synthesis of *N*-acylcarbazoles, which involves the palladium-catalyzed annulation of arynes by 2-haloacetanilides. This methodology provides this important heterocyclic ring system in a single step by simultaneous C-C and C-N bond formation. This process has been shown to be tolerant of multiple functional groups, making further elaboration possible.

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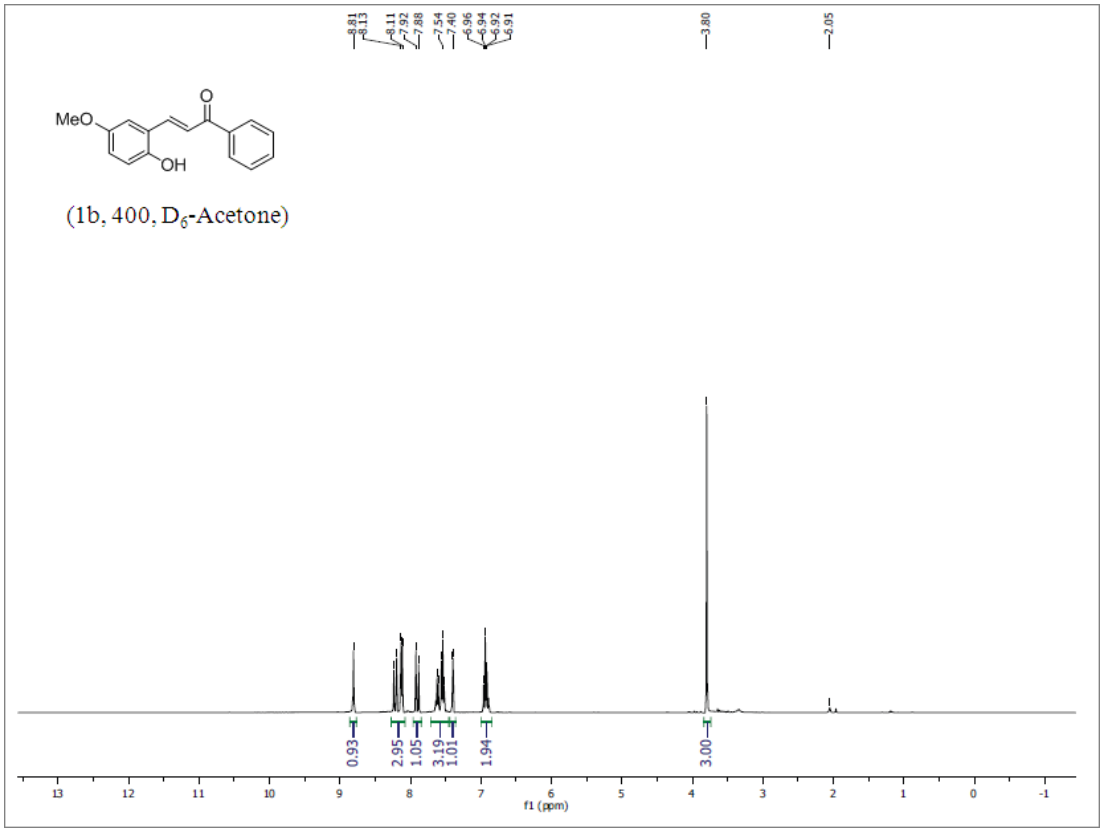
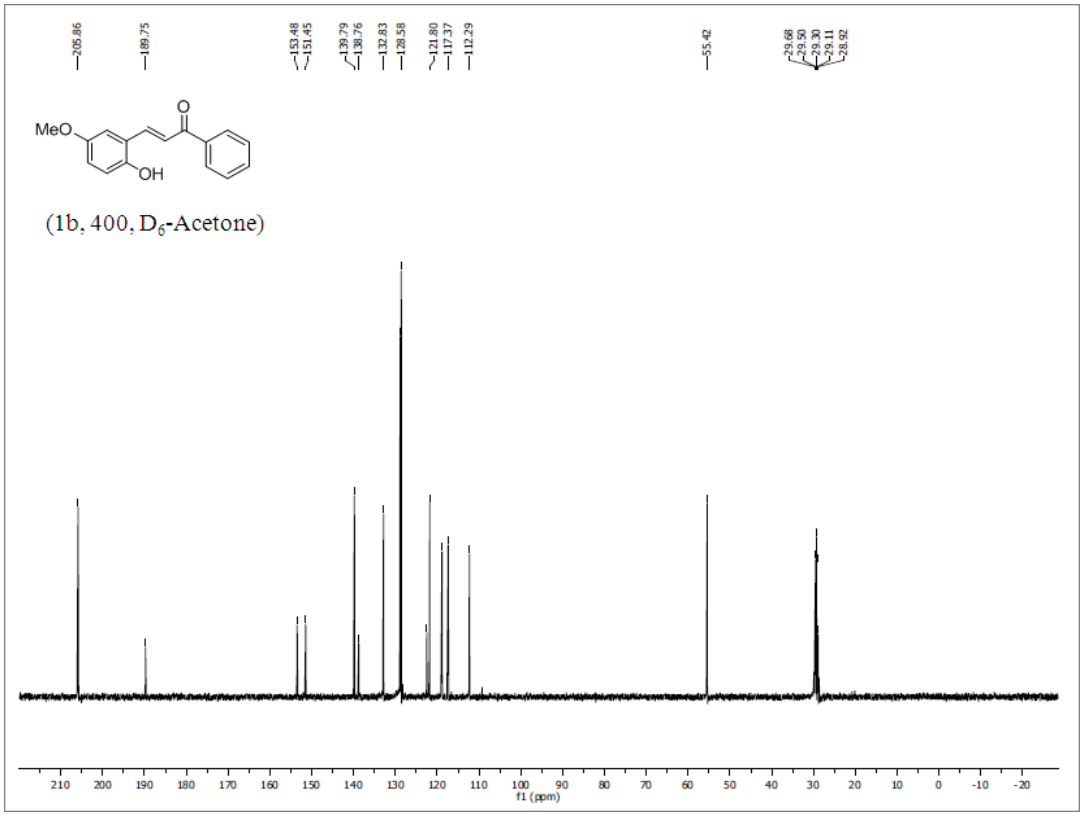
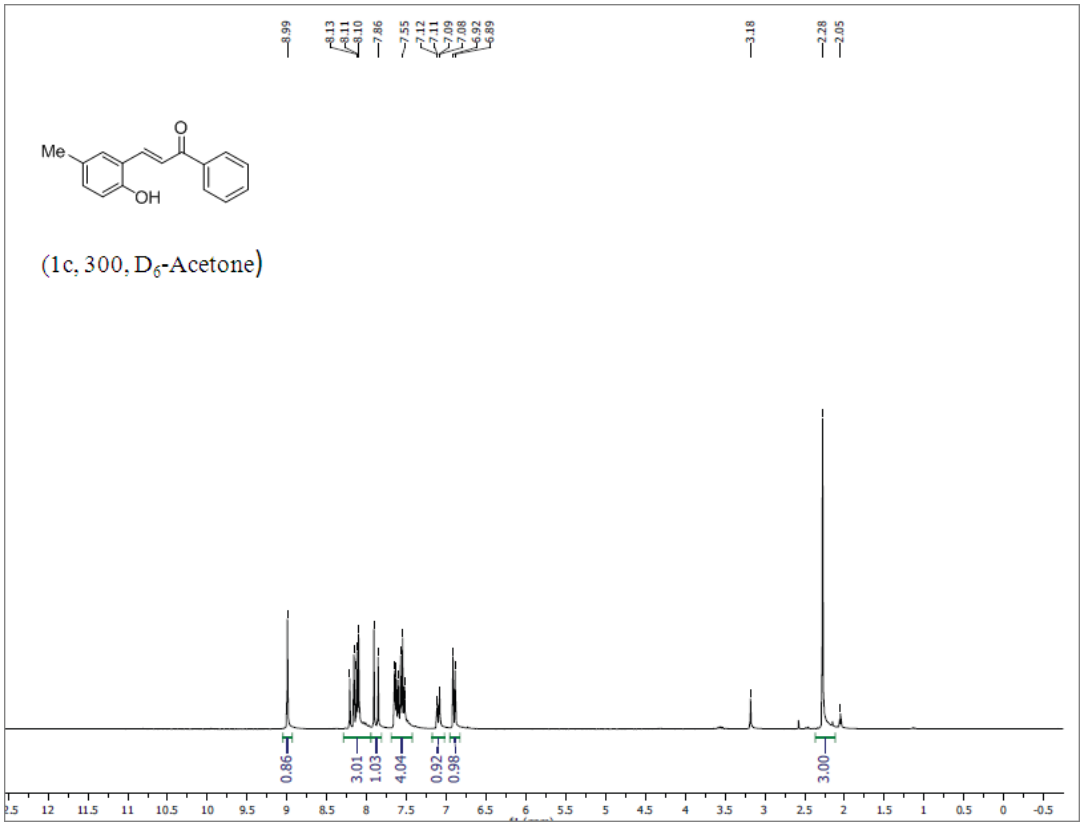
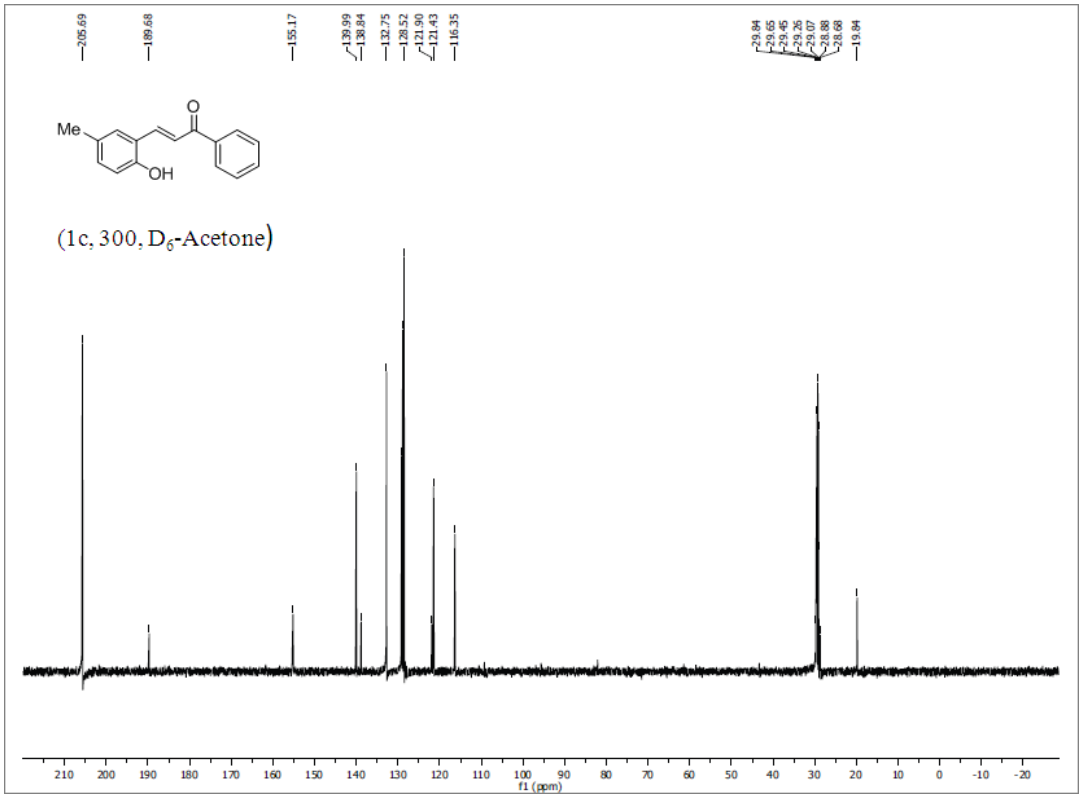
Finally, I want to thank my wonderful husband, Aoshuang, who made me all the better with his patience, encouragement, understanding and endless love.

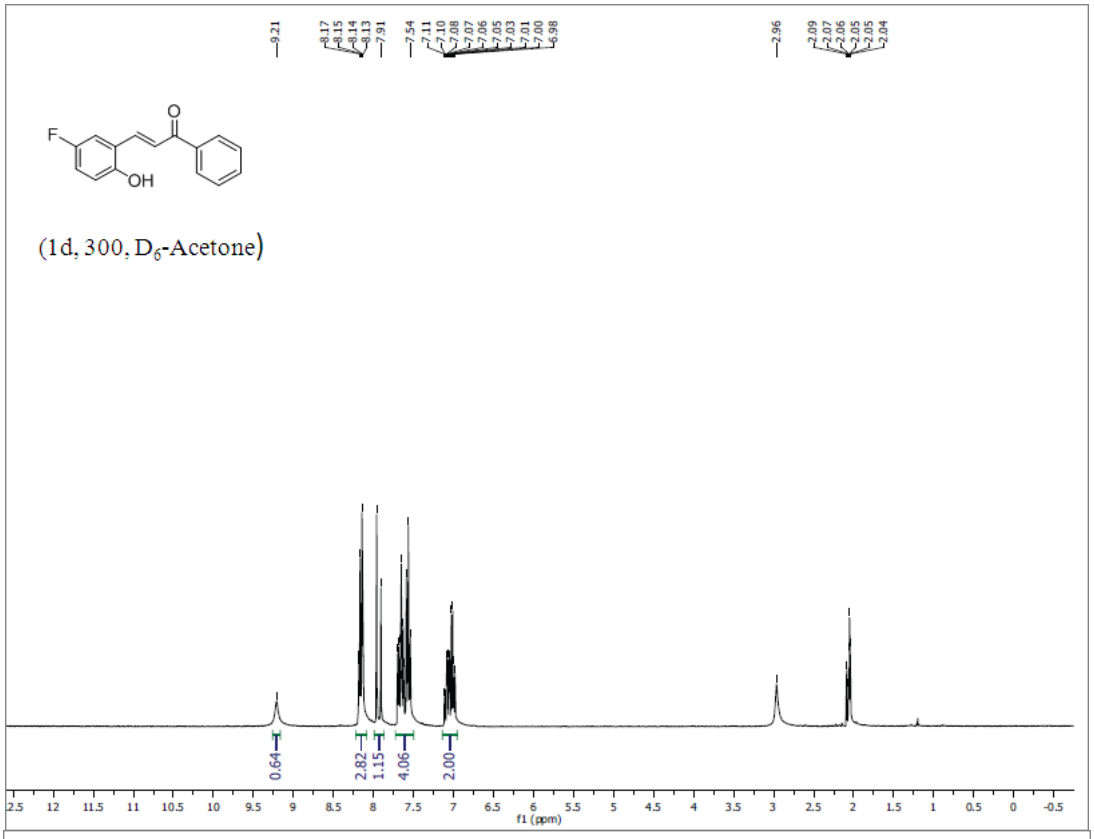
APPENDIX A. CHAPTER 1 ^{1}H AND ^{13}C NMR SPECTRA

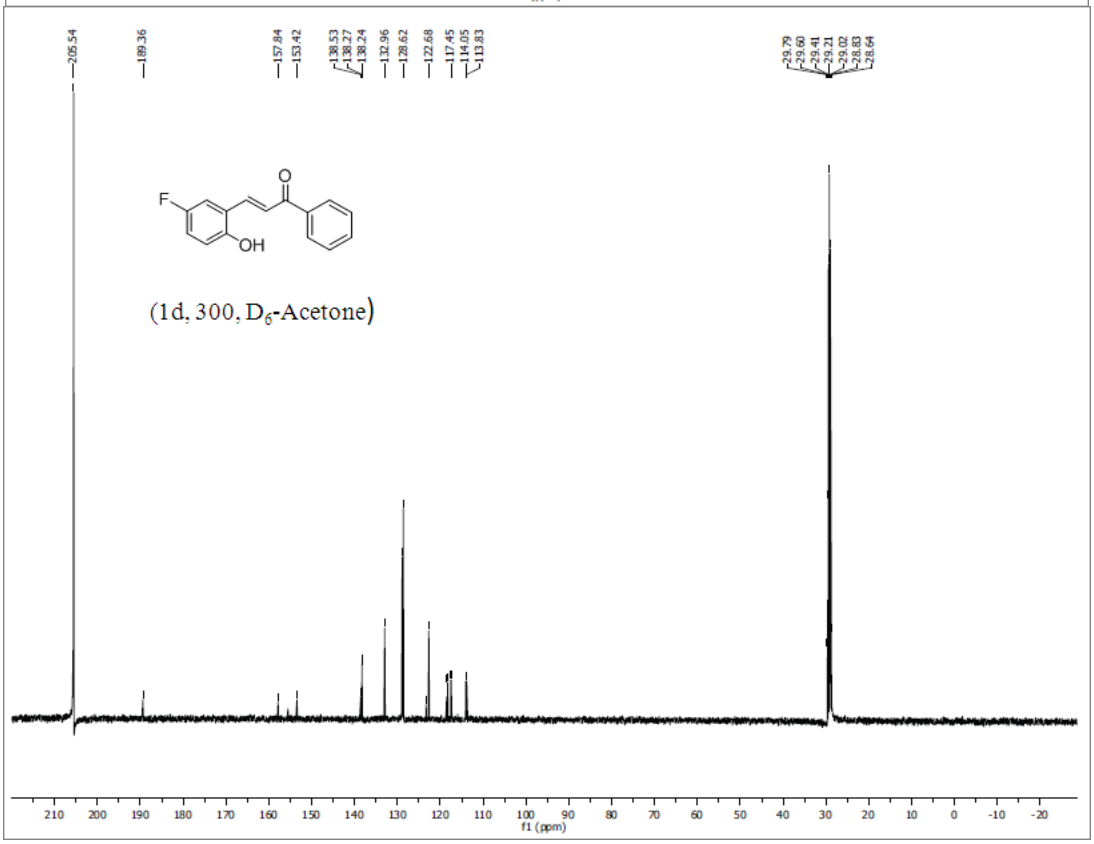


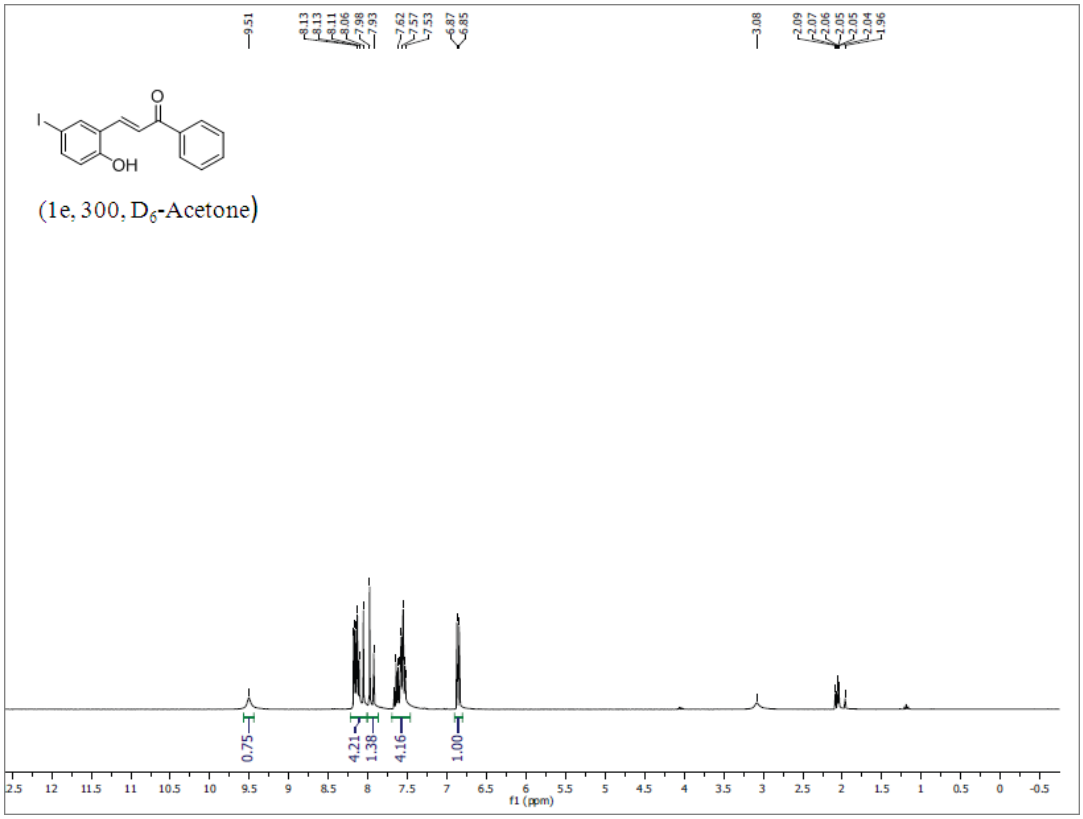


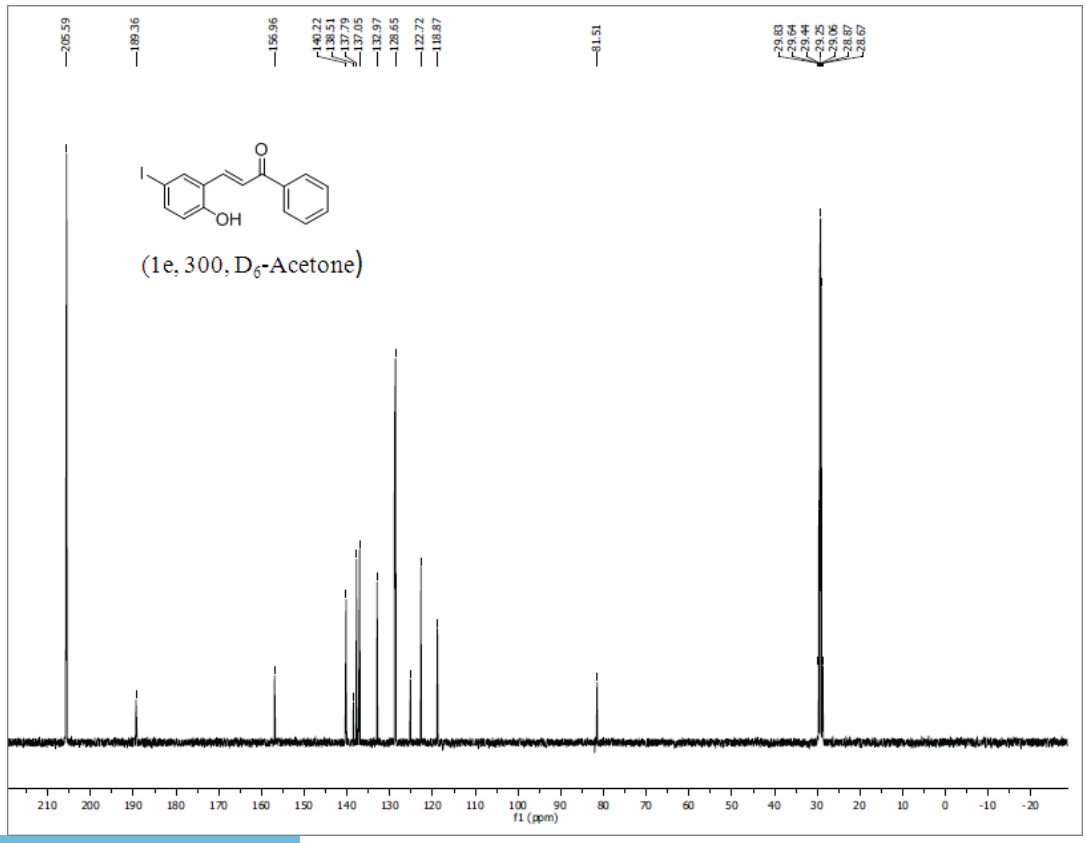


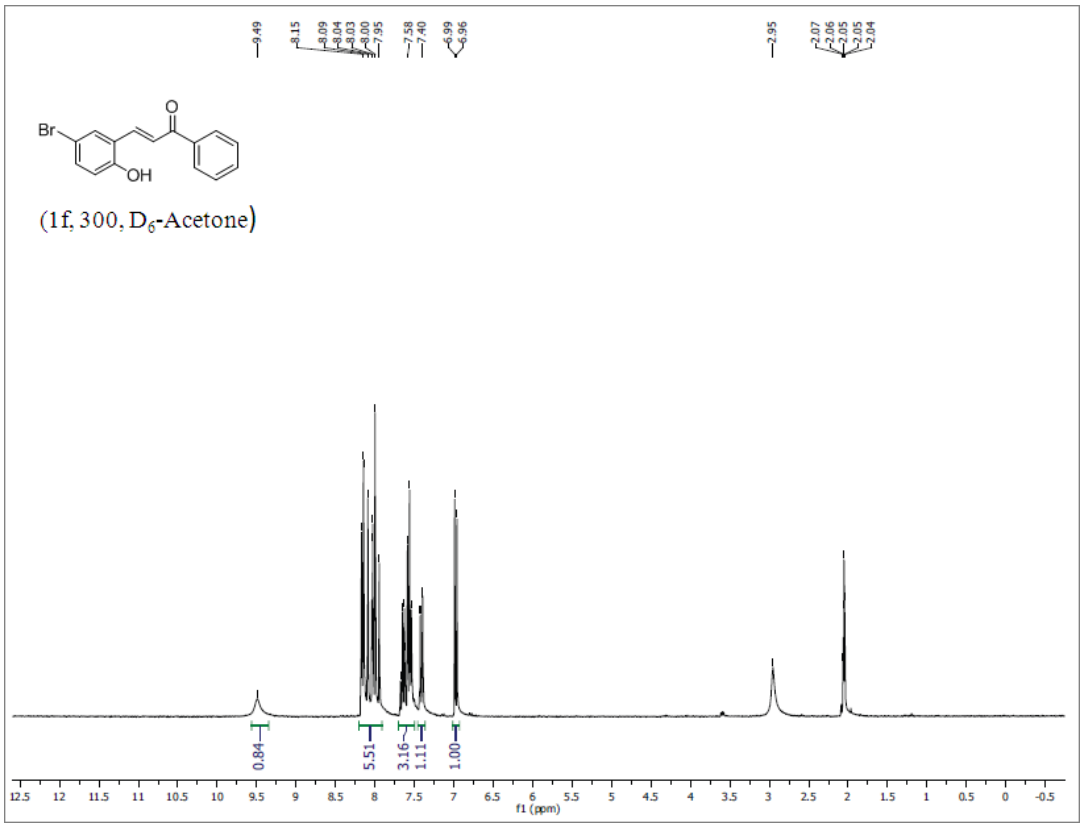


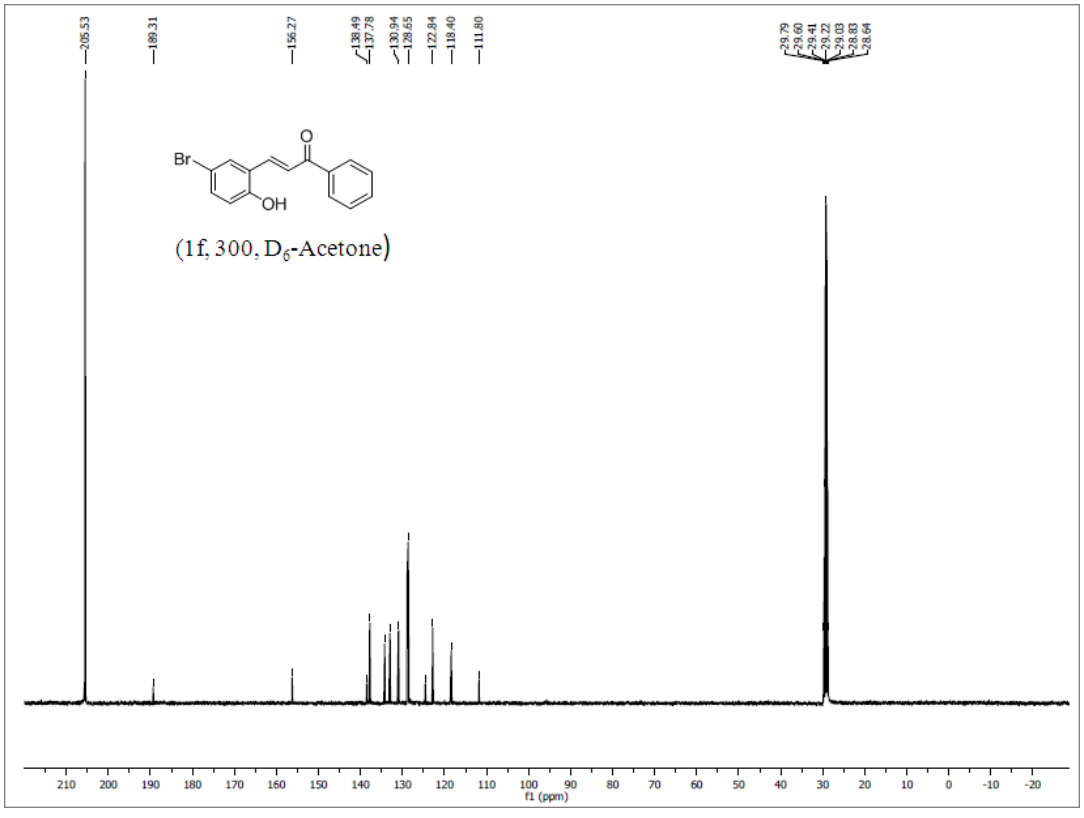


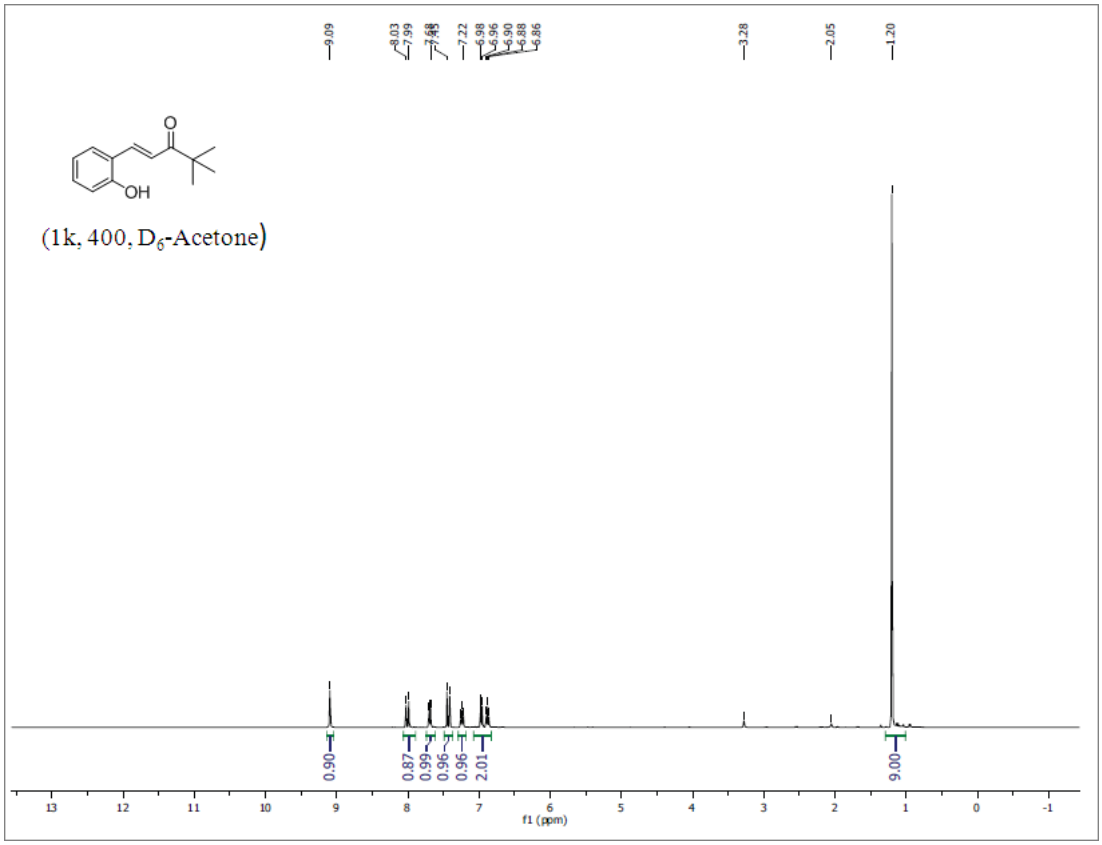


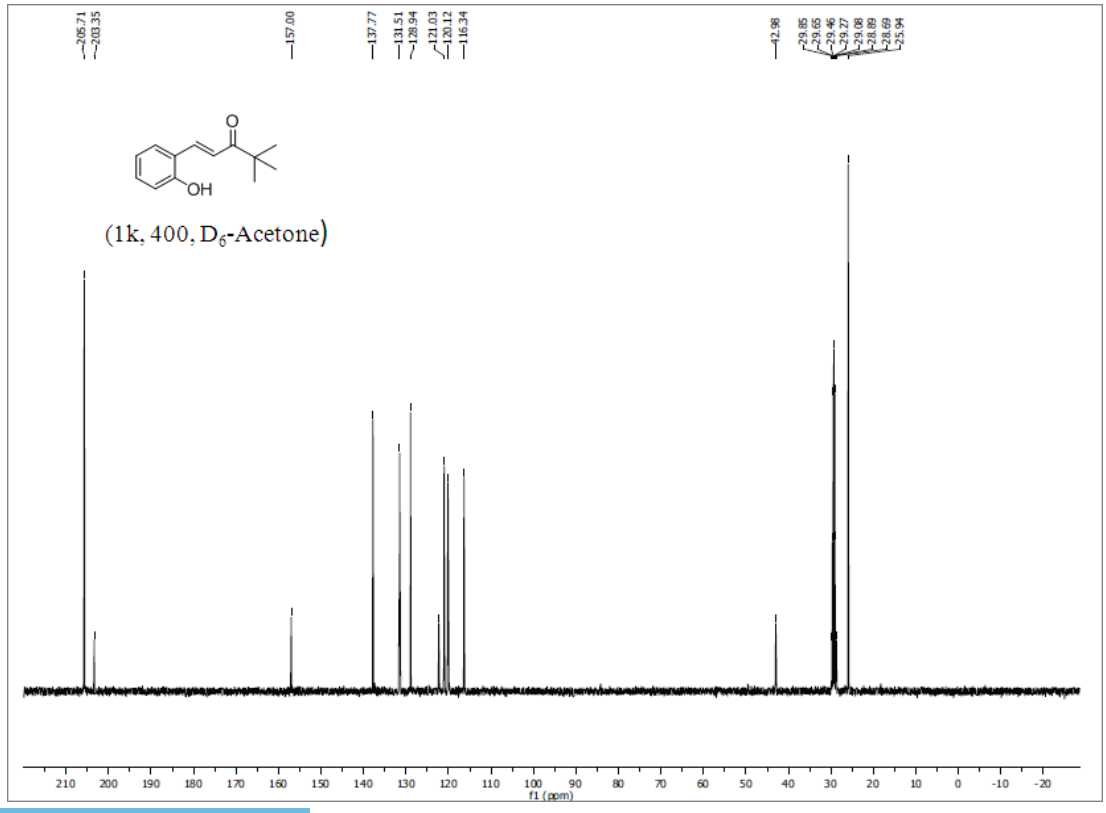


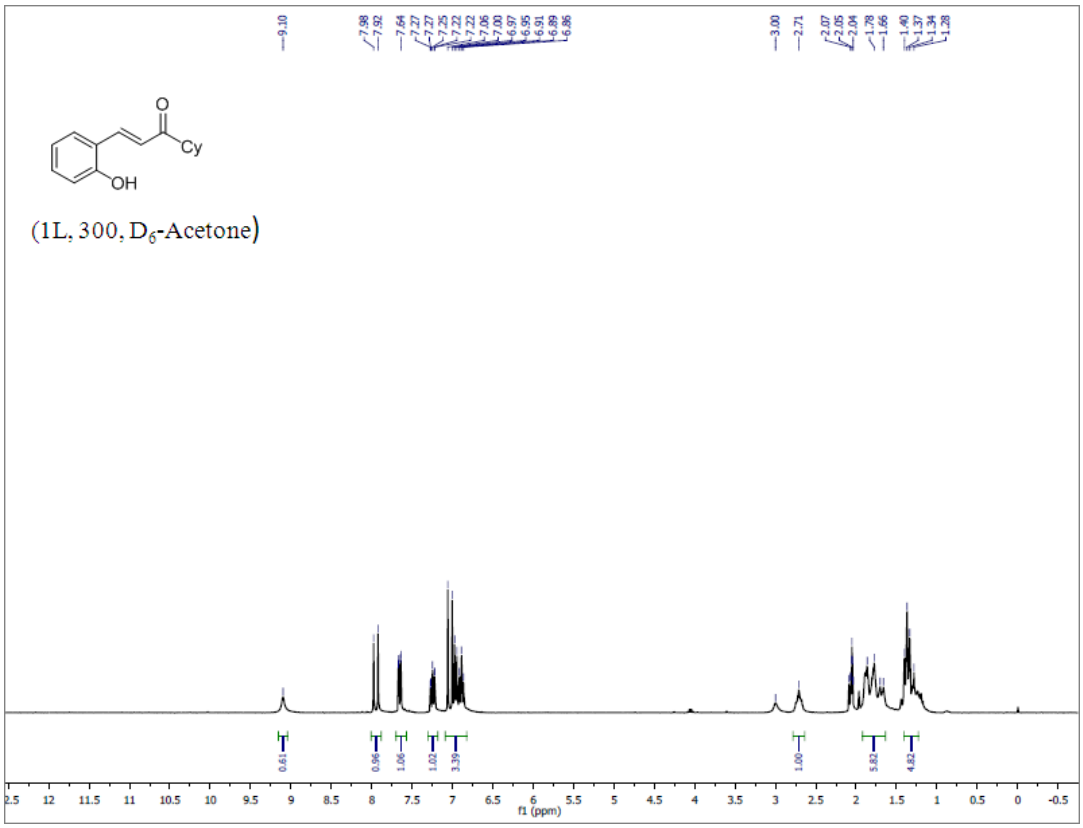


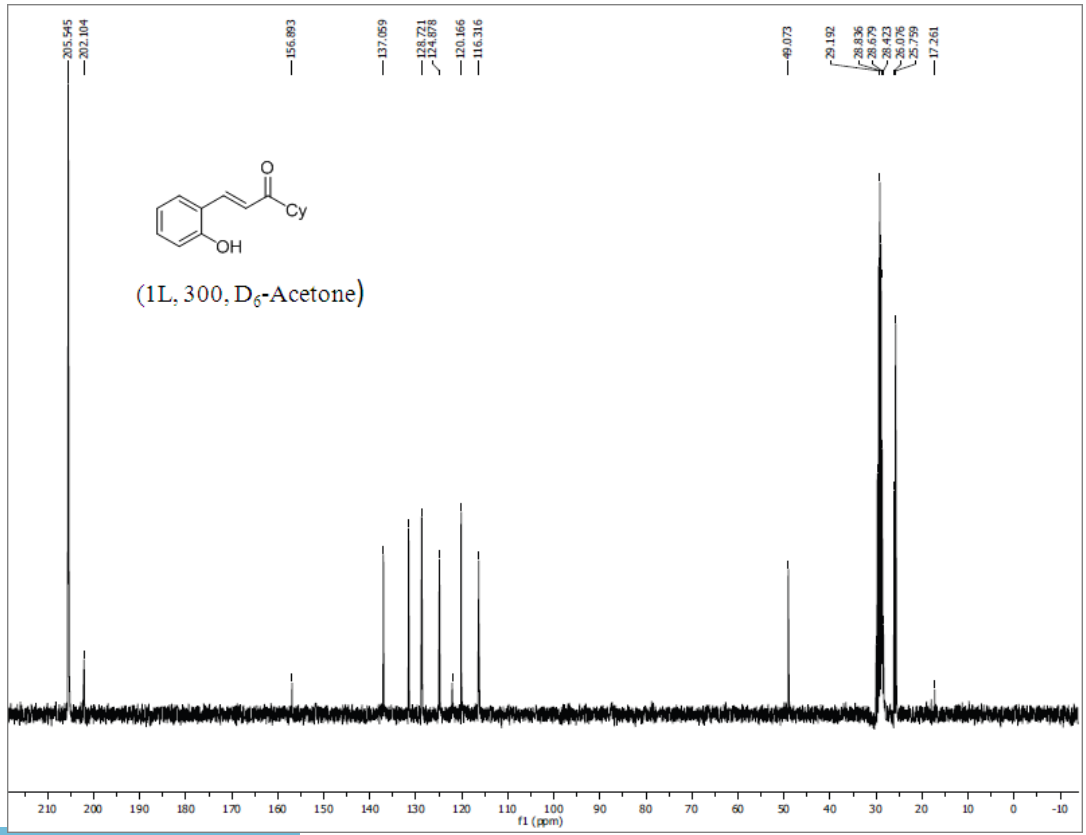


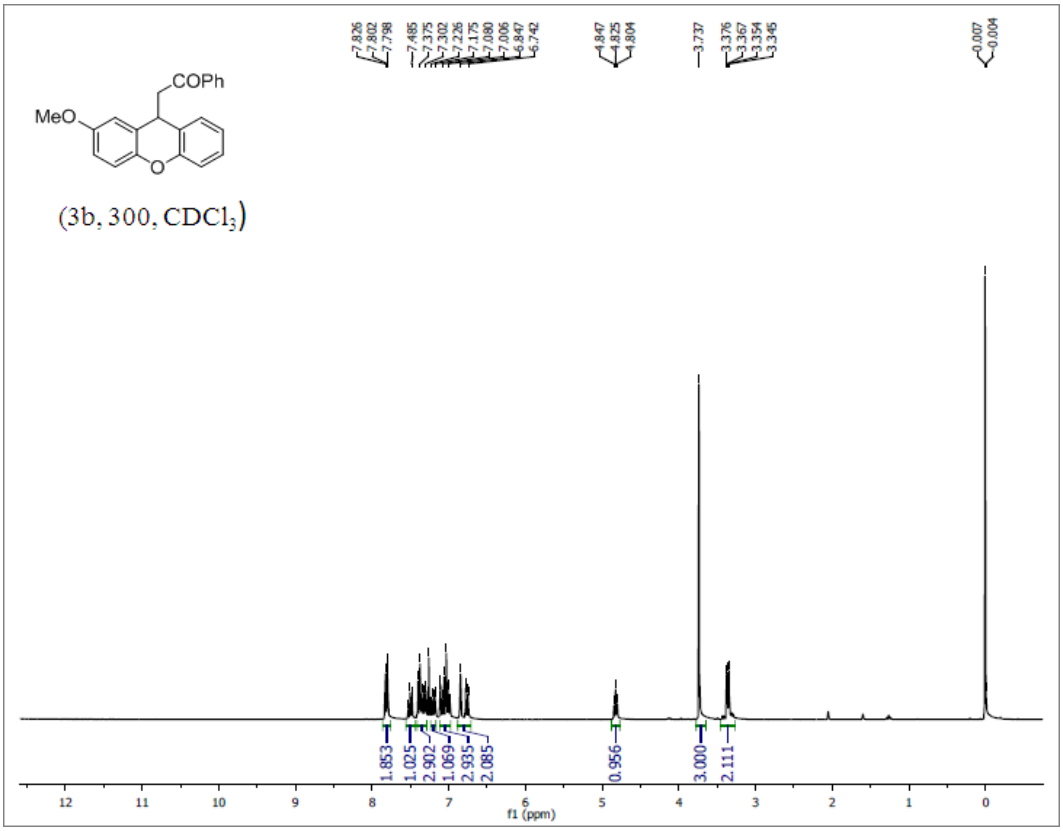


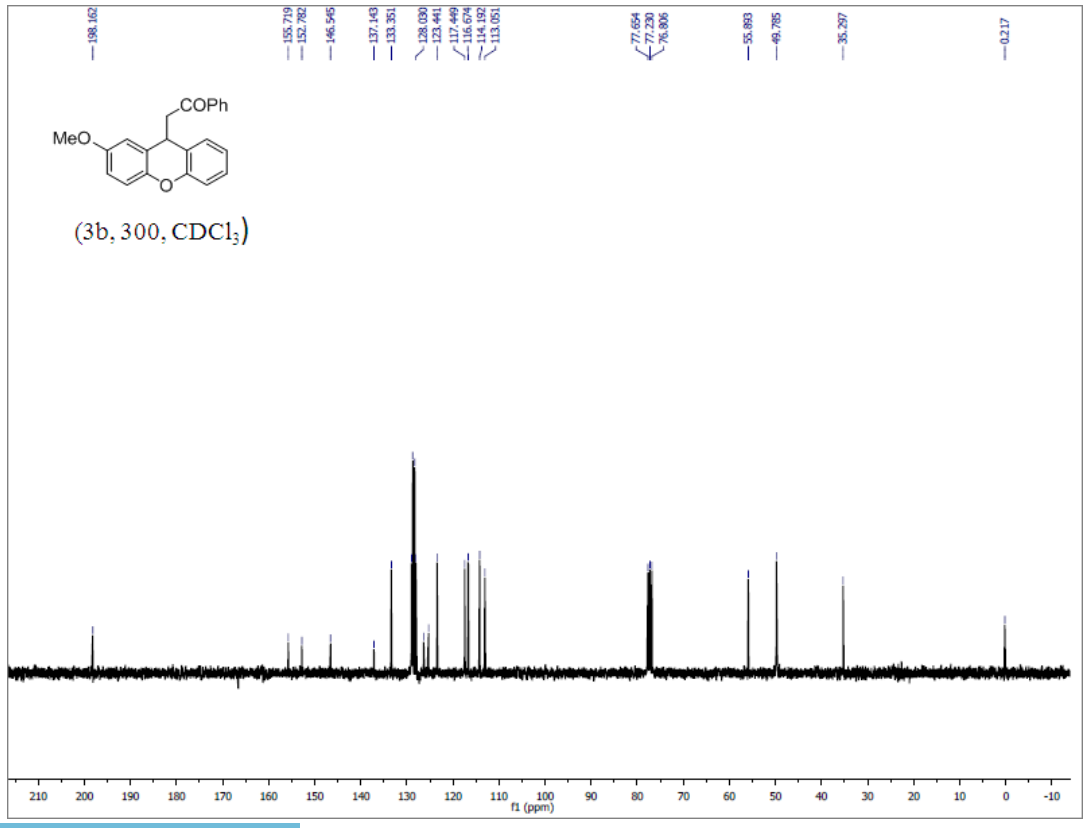


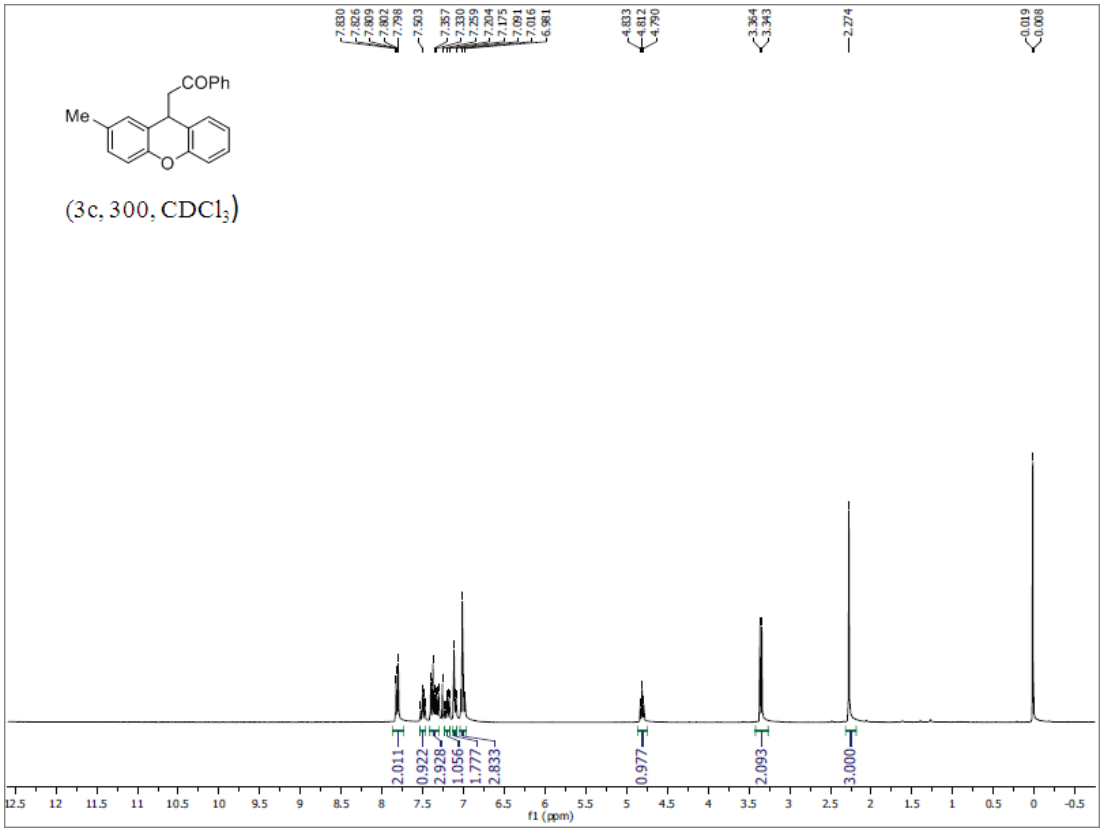


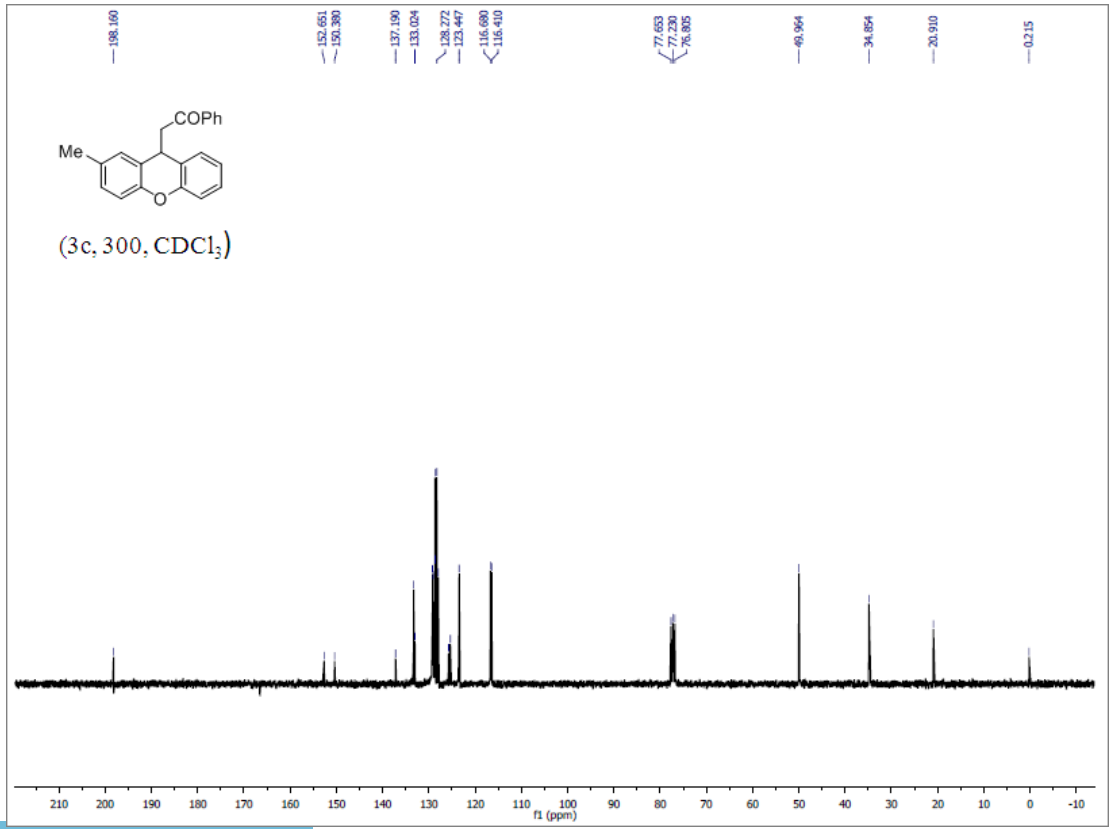


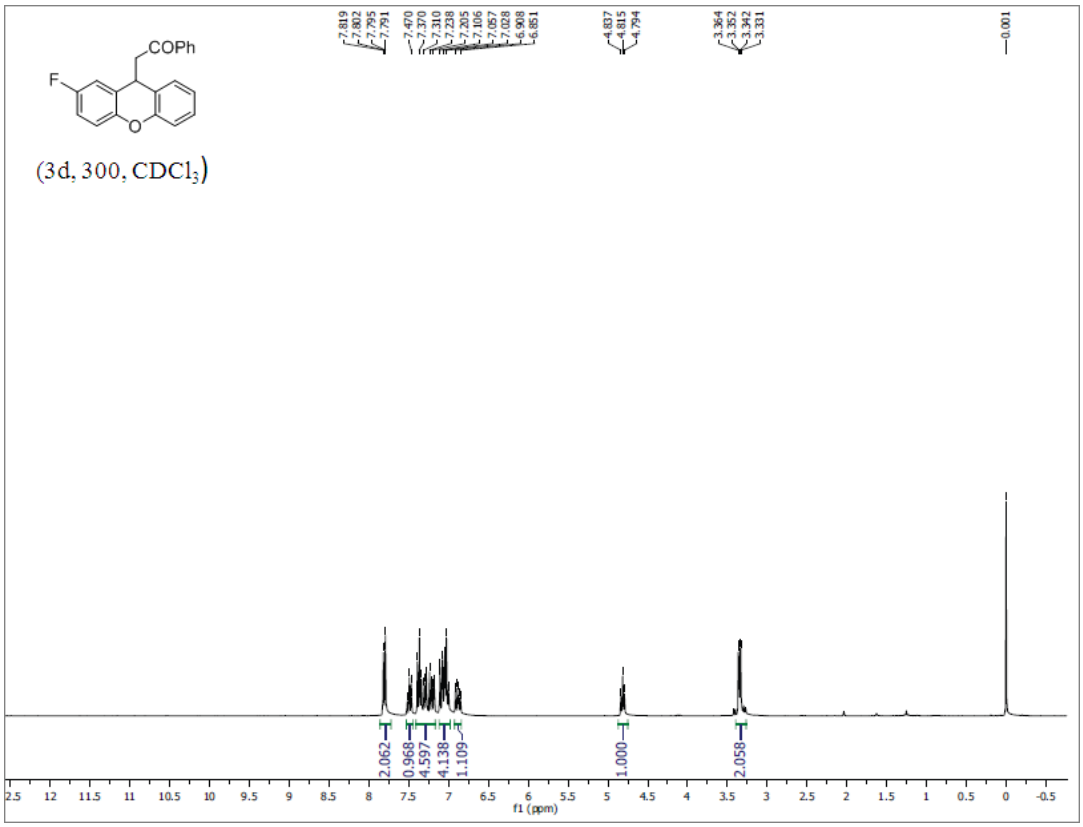


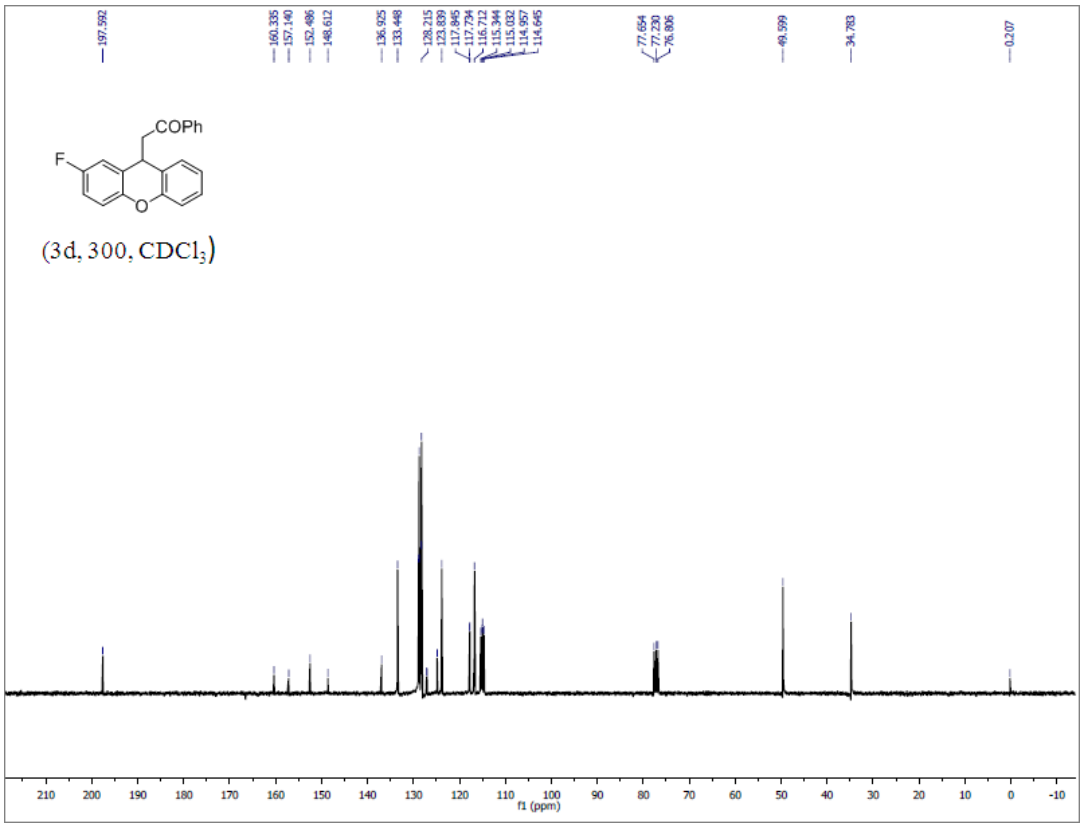


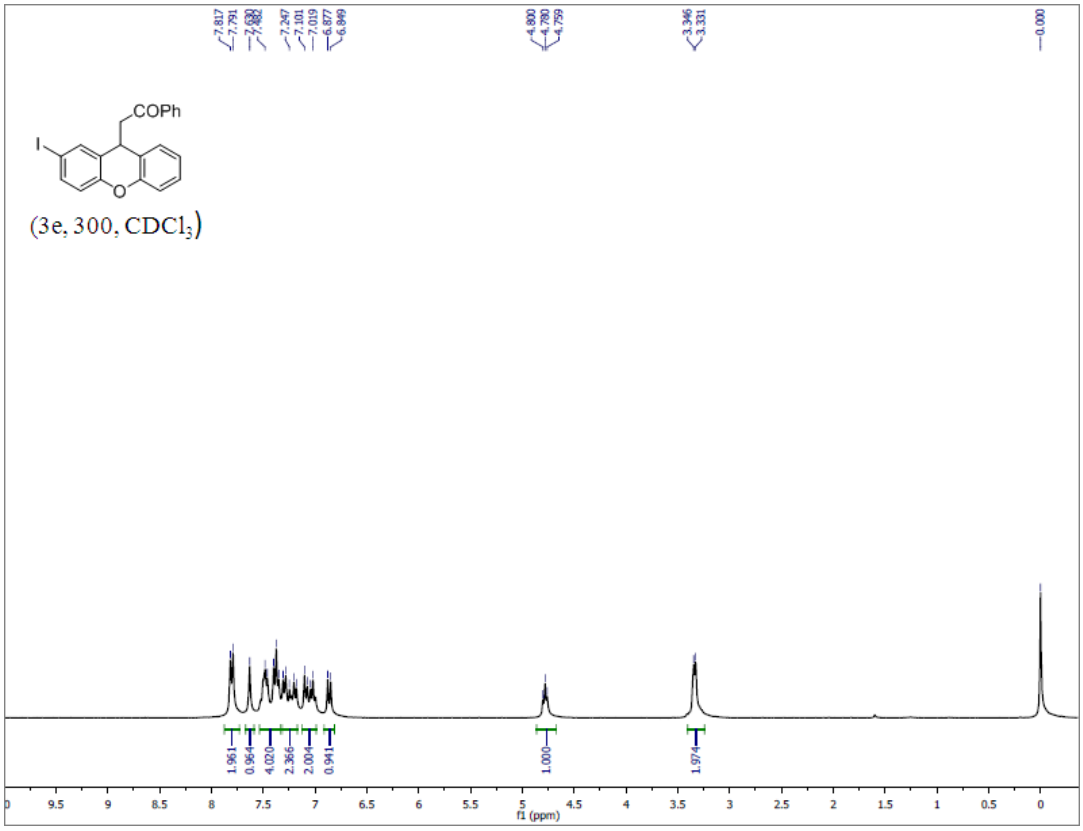


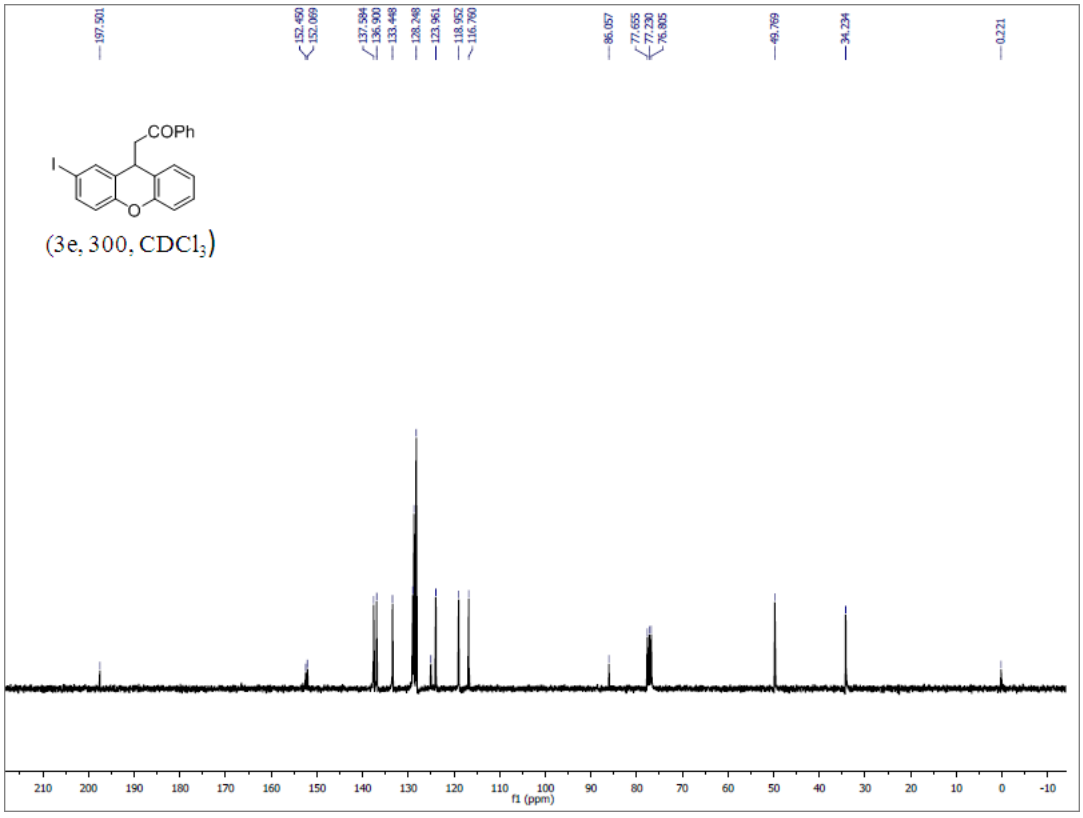


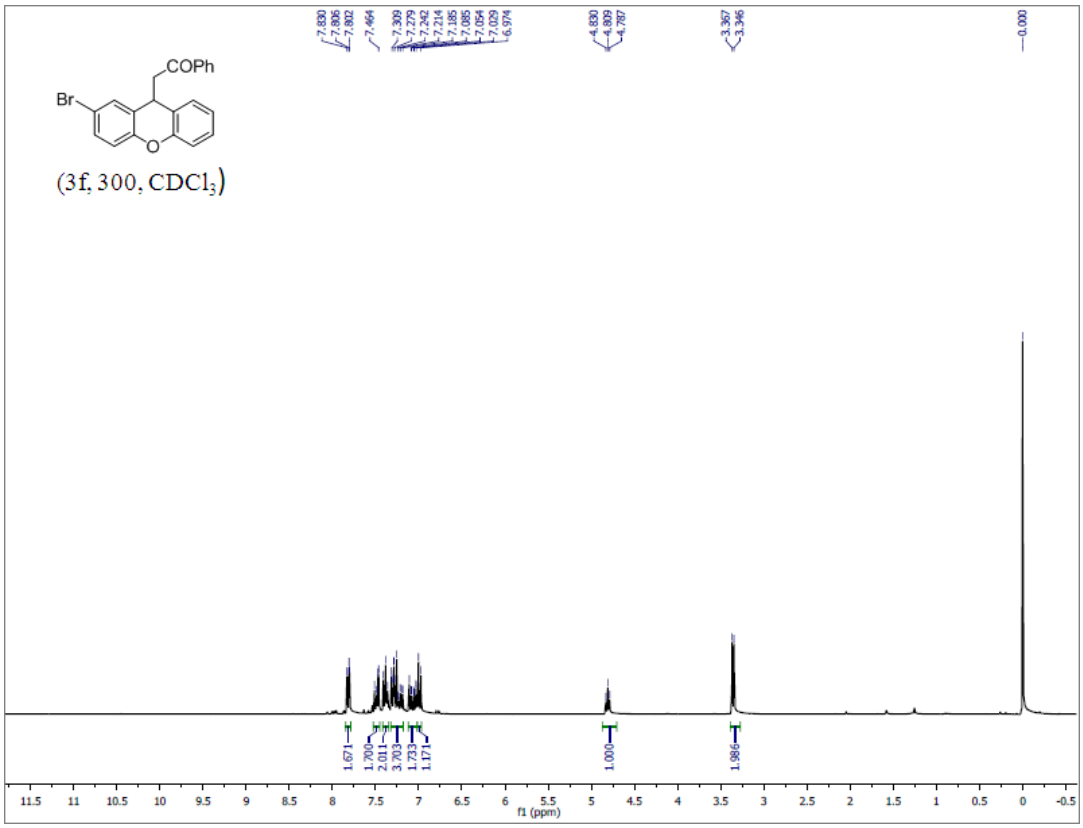


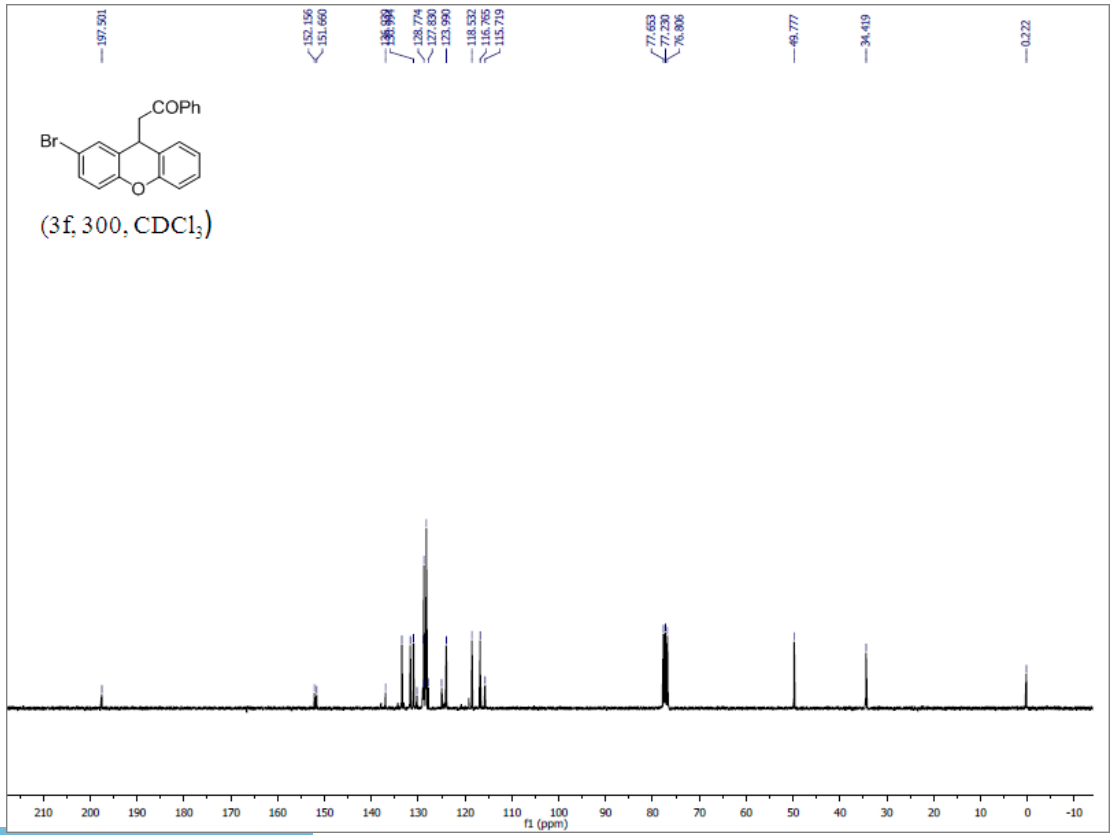


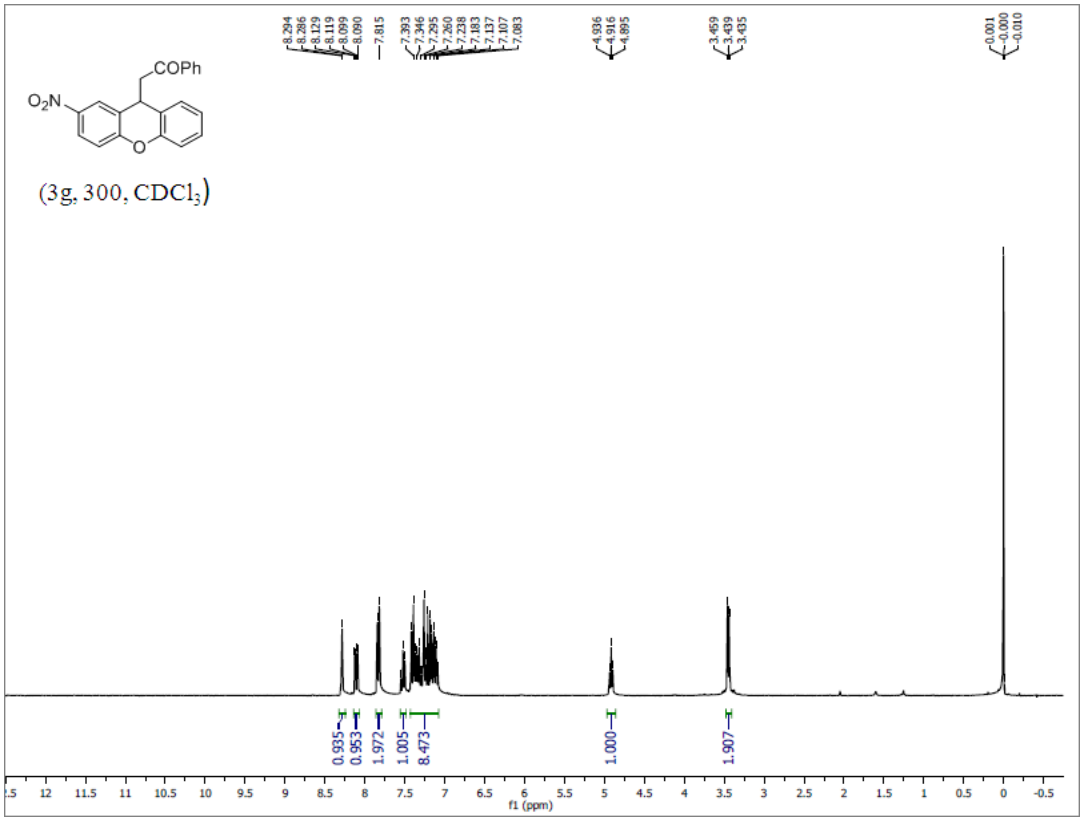


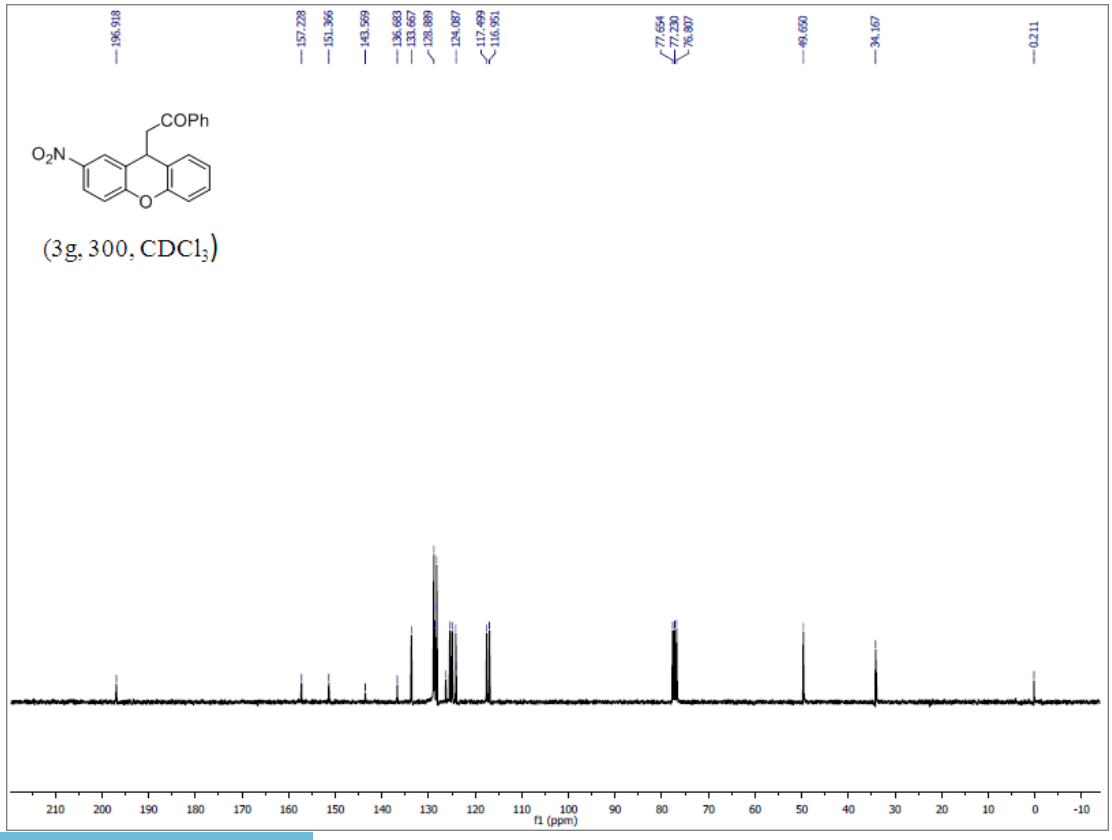


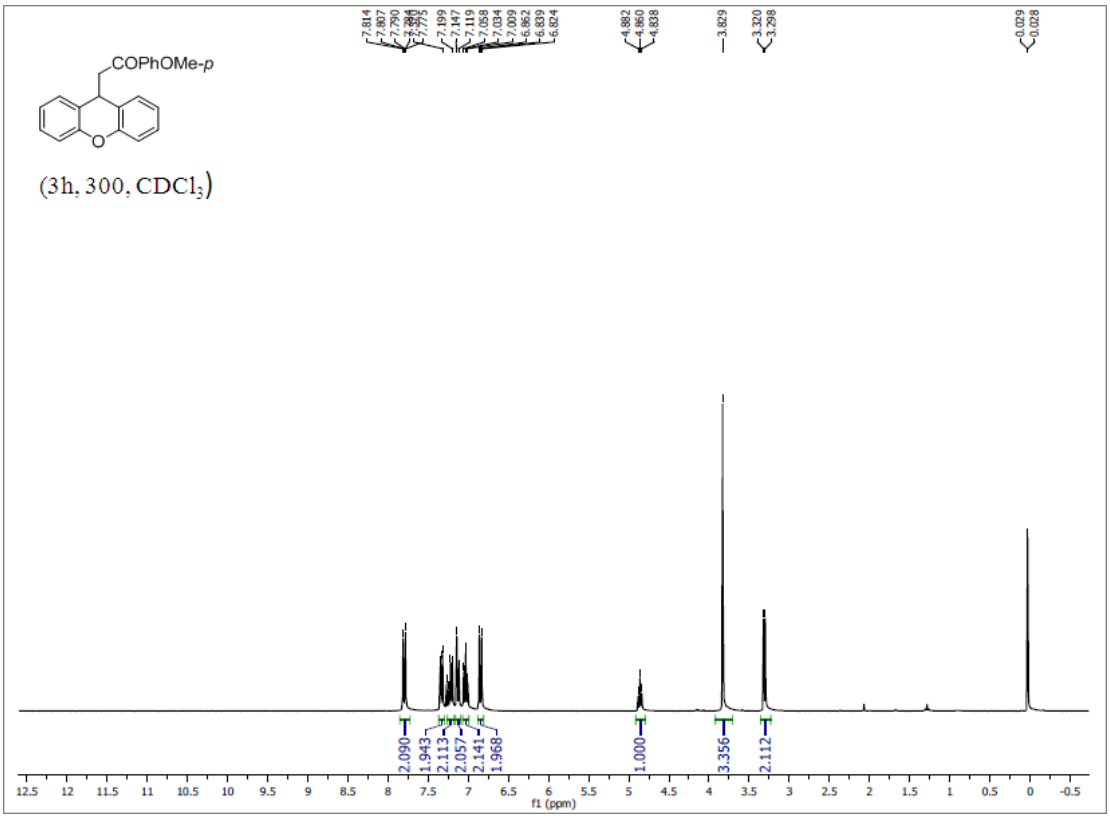


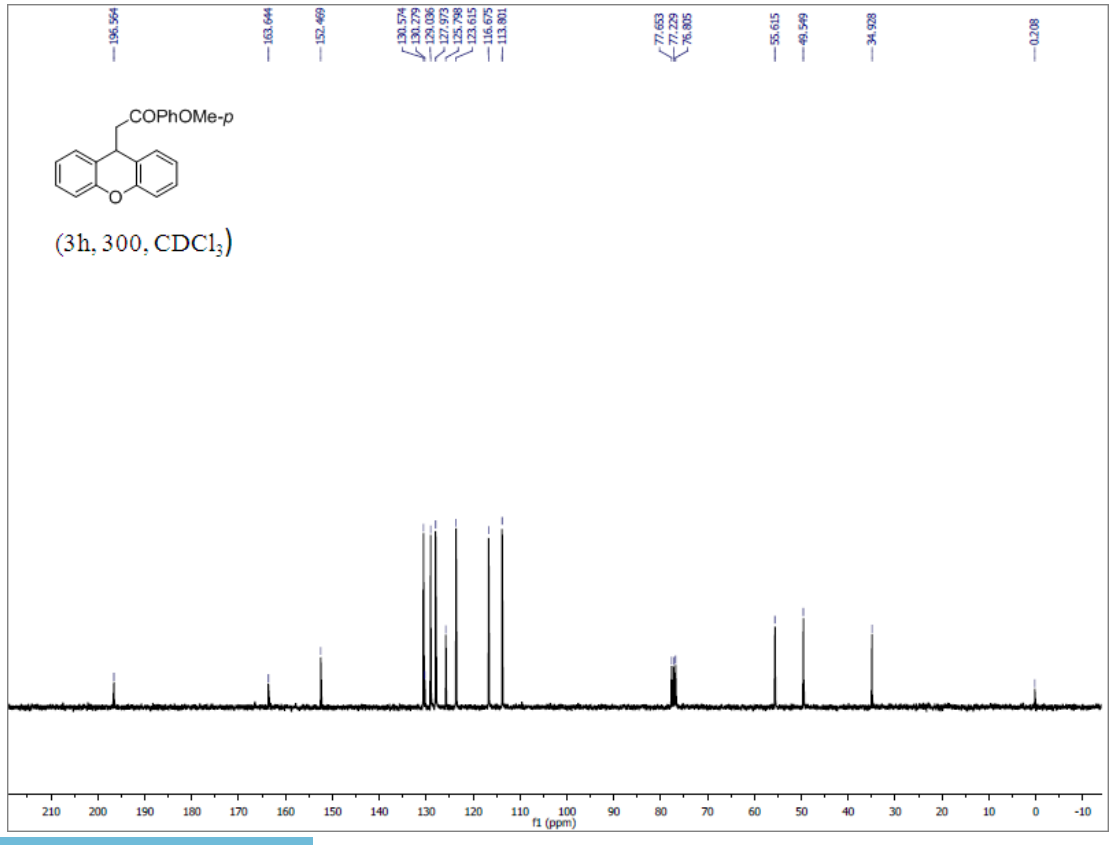


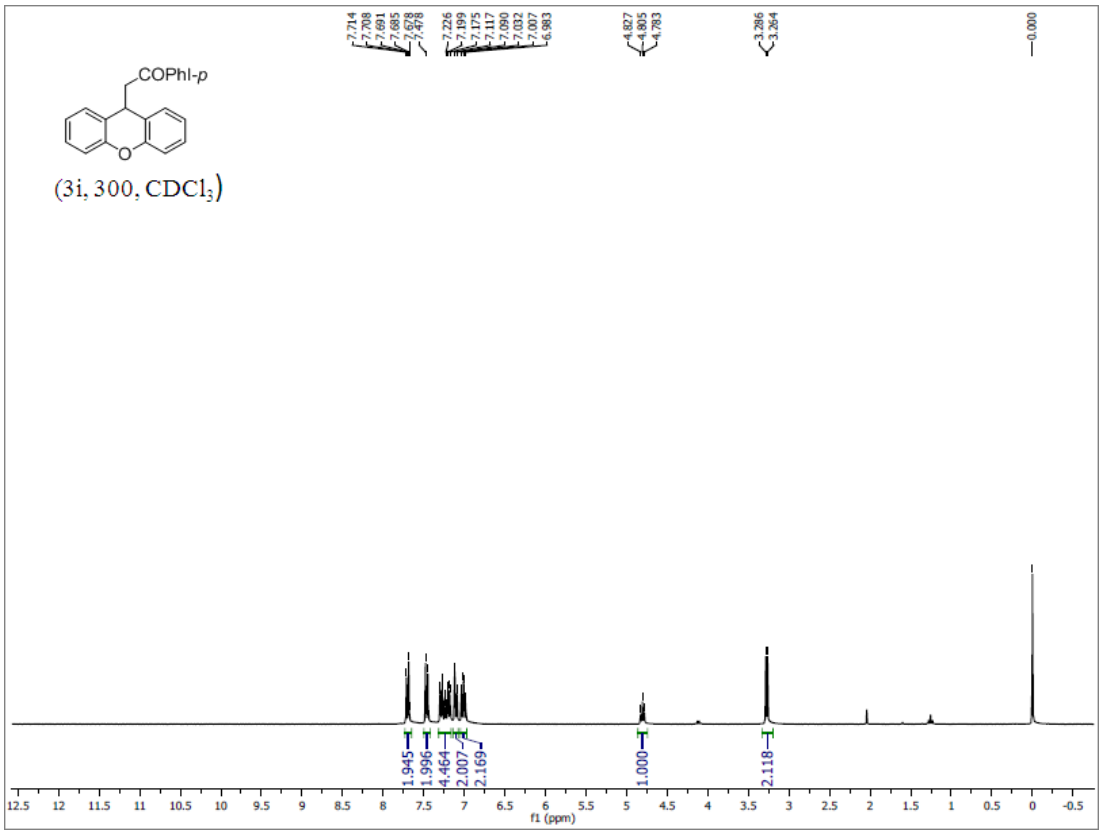


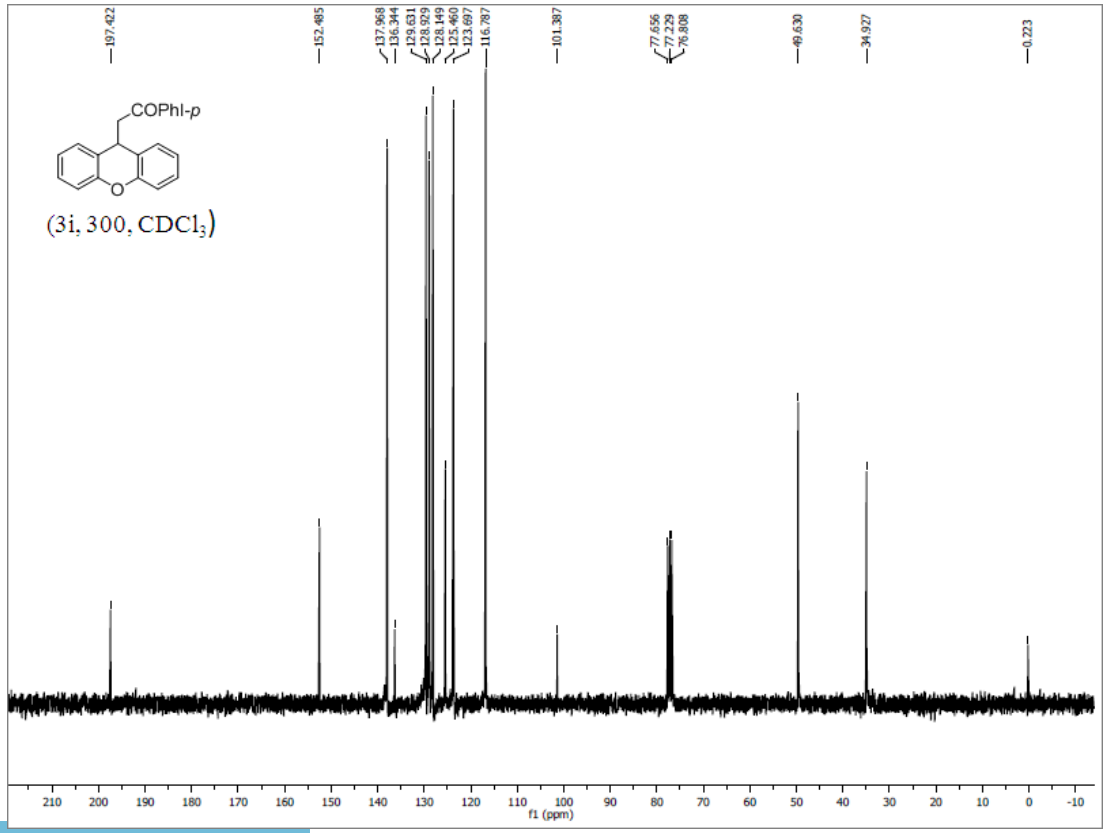


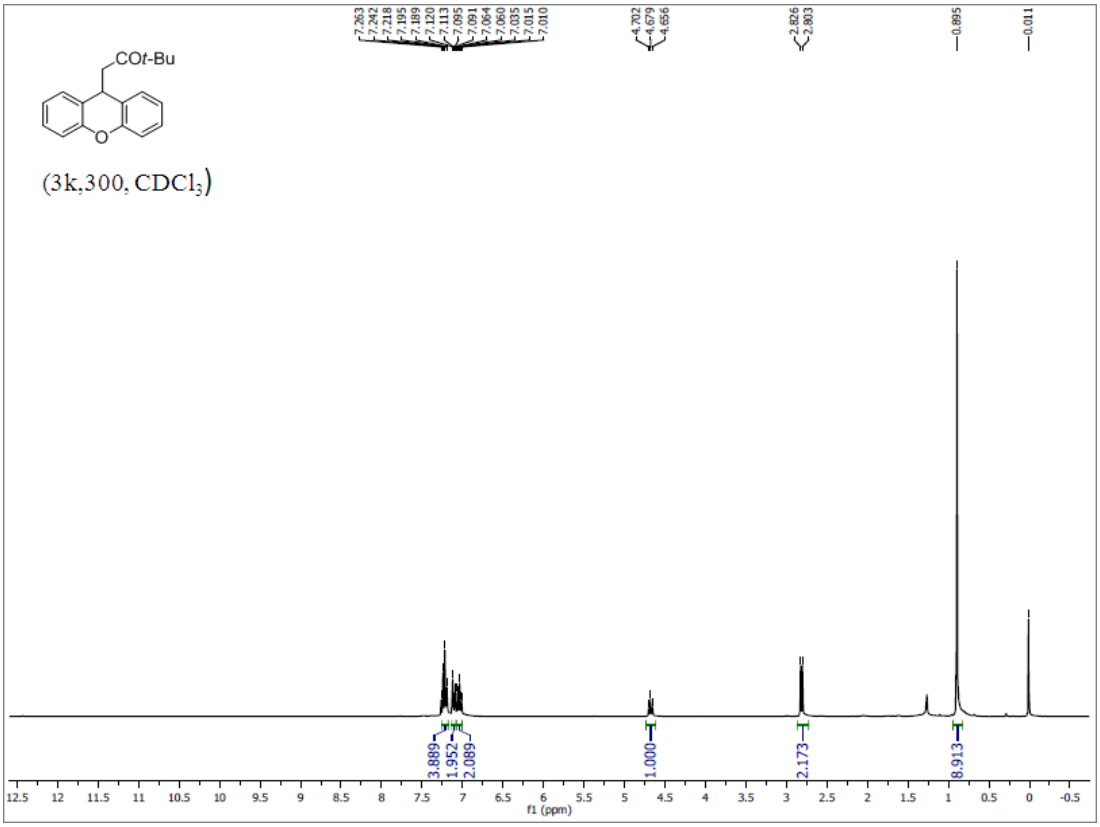


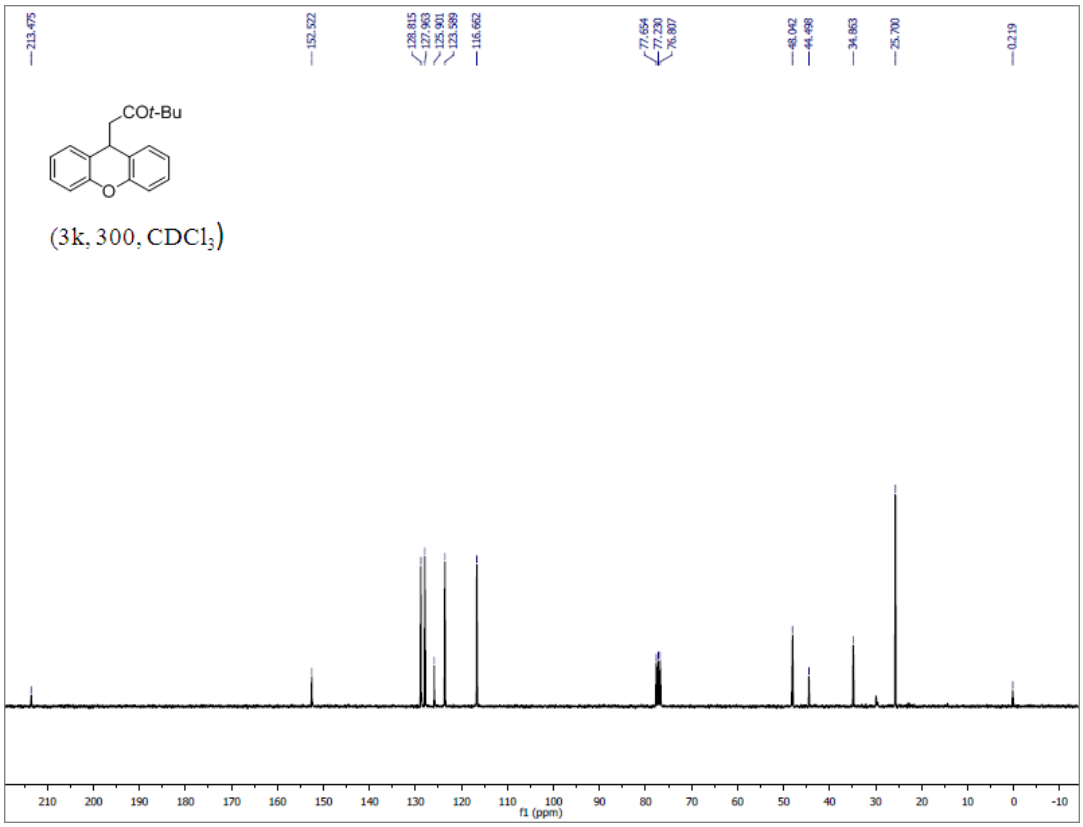


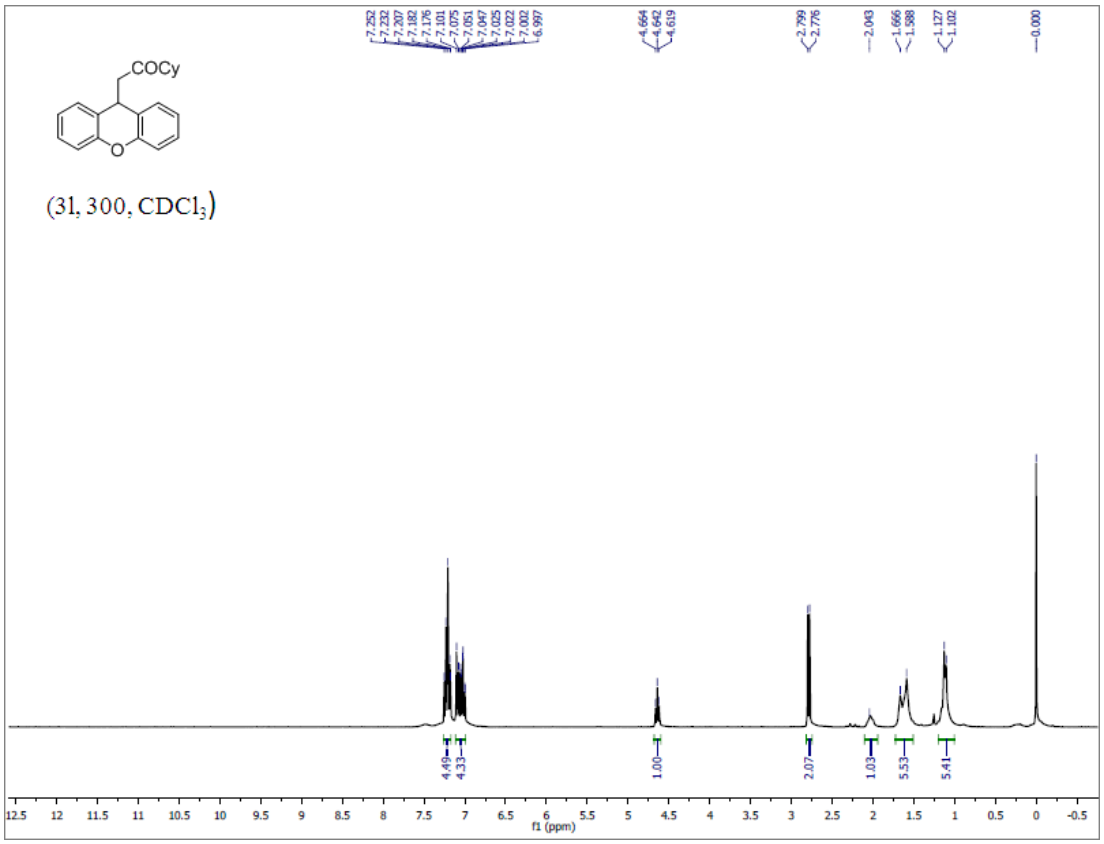


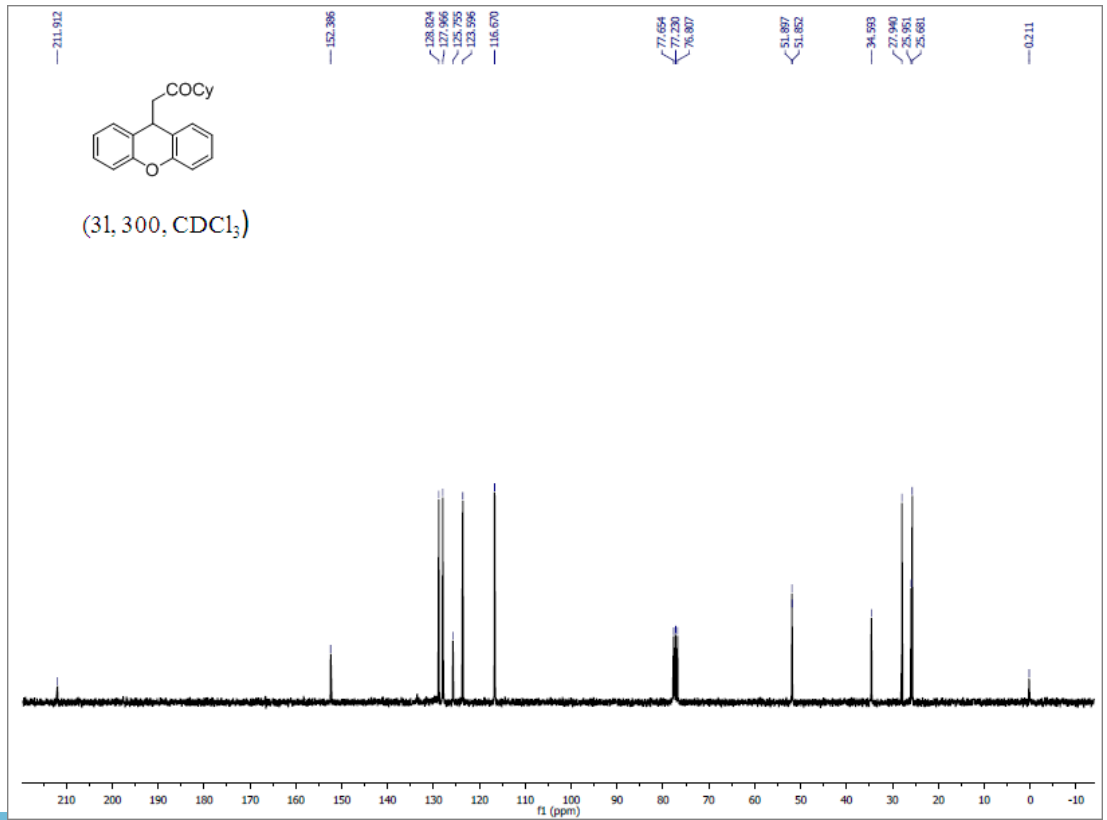


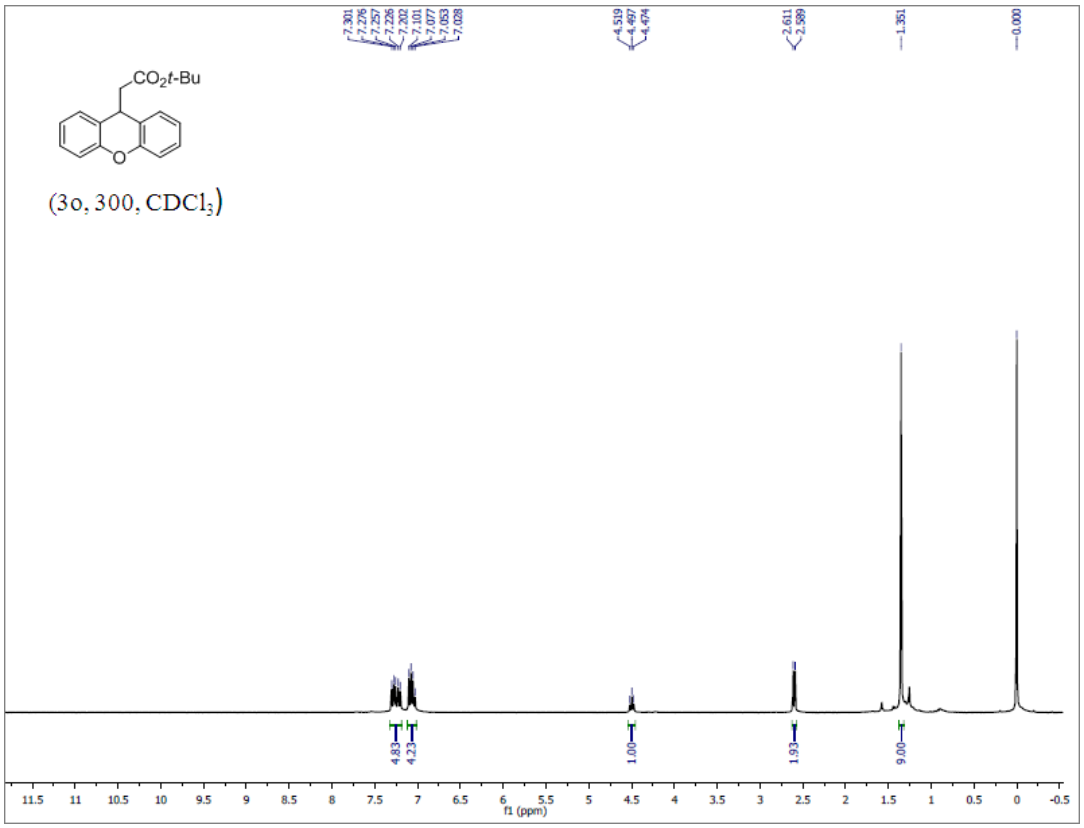


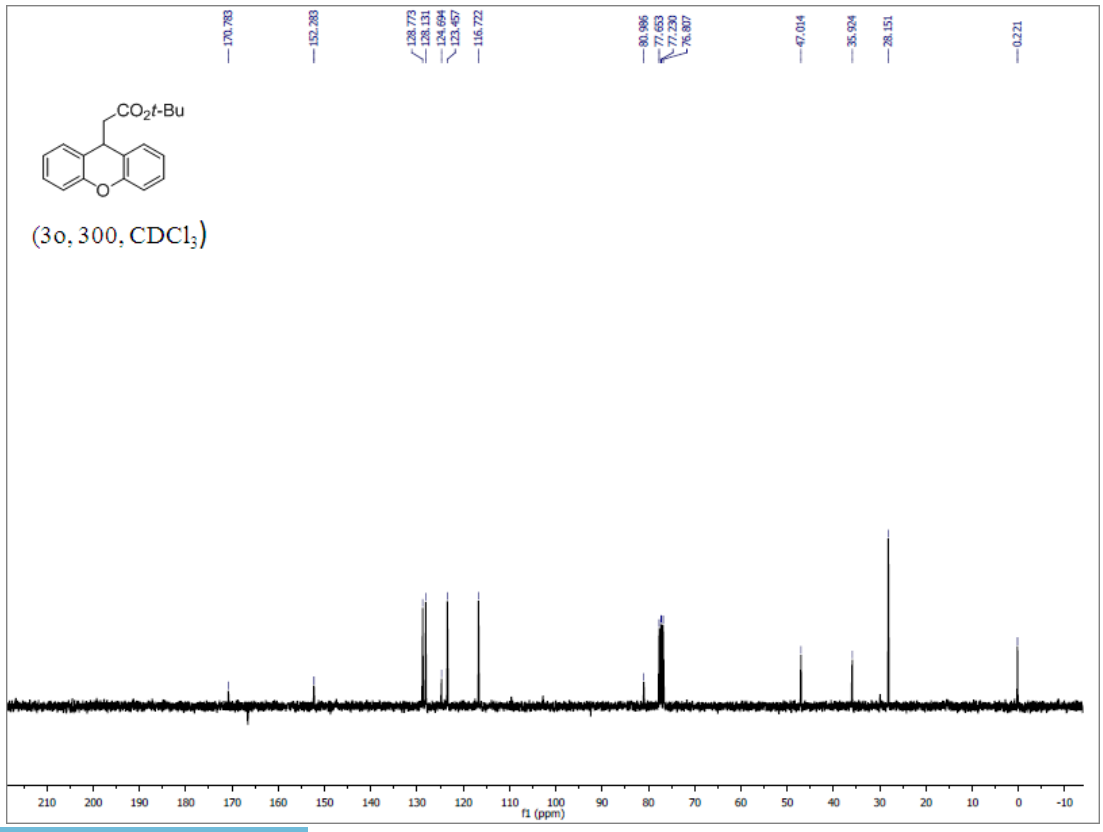


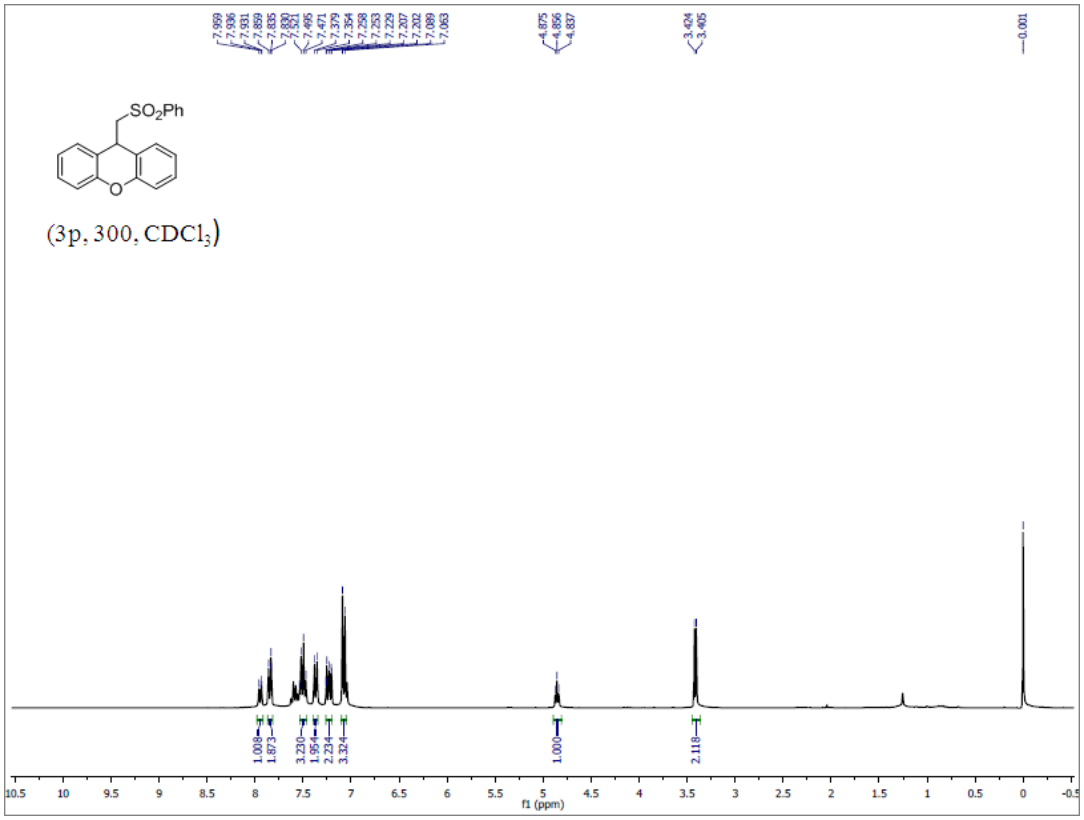


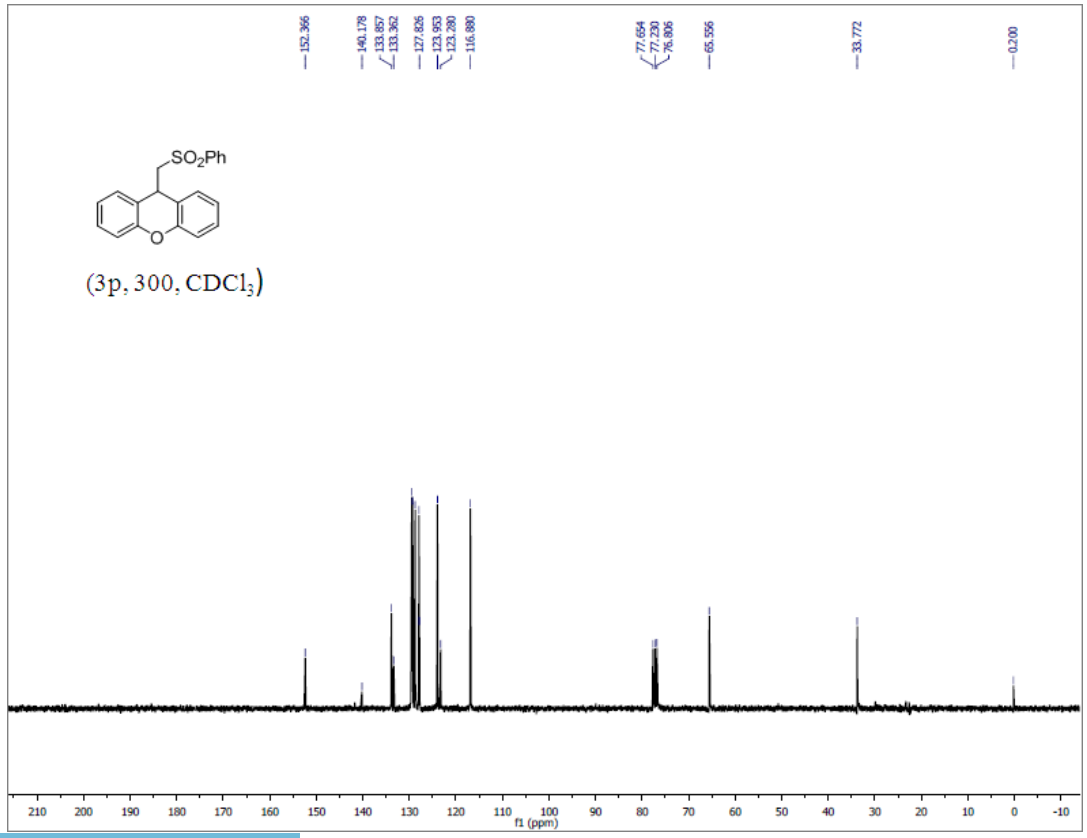


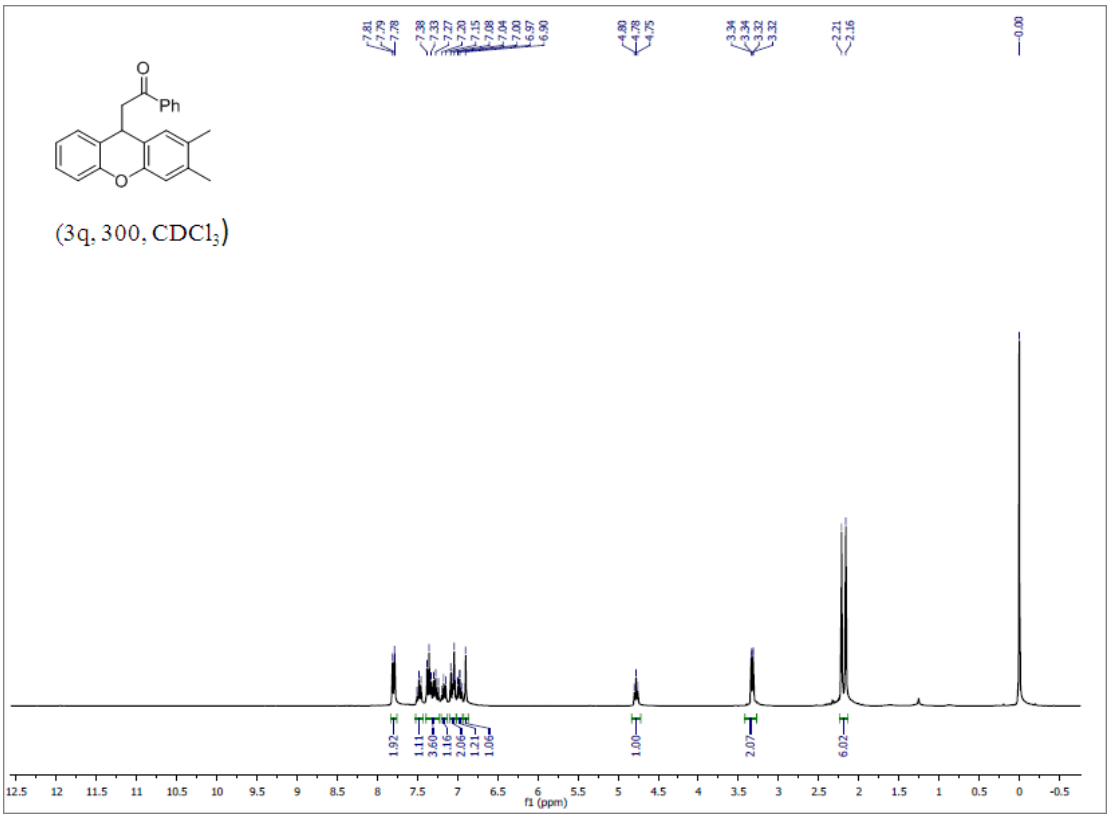


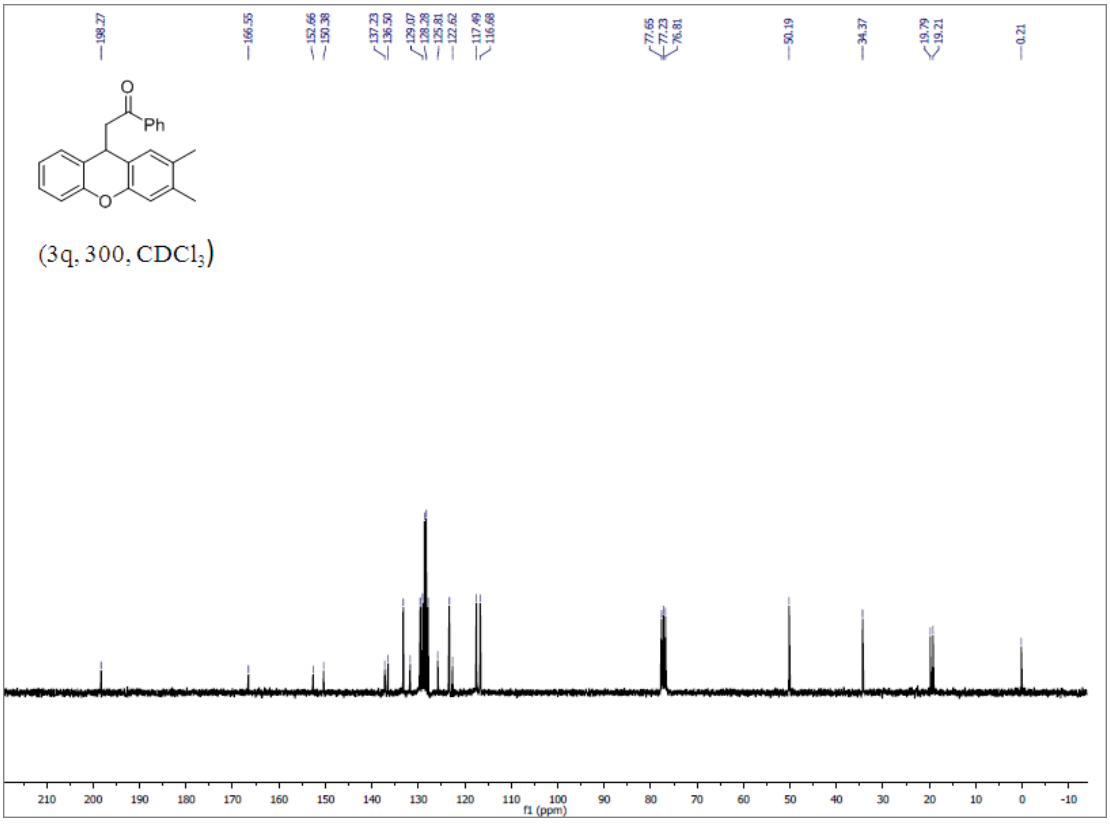


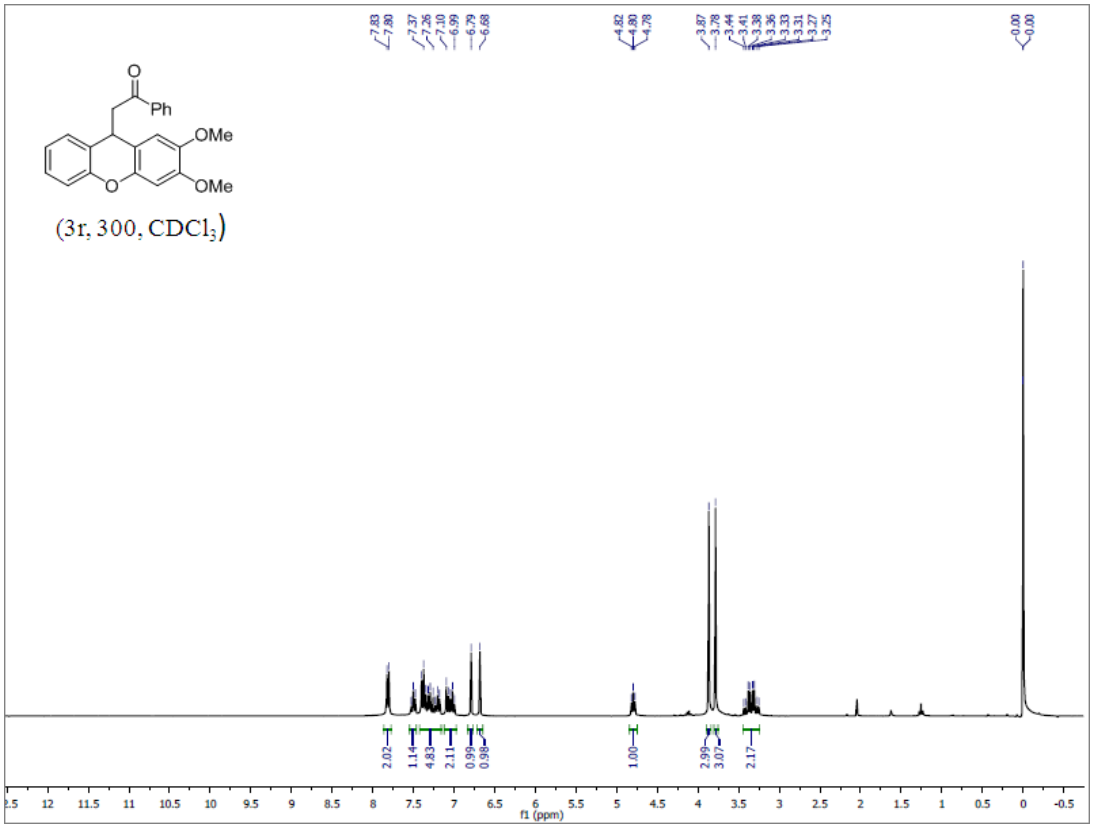


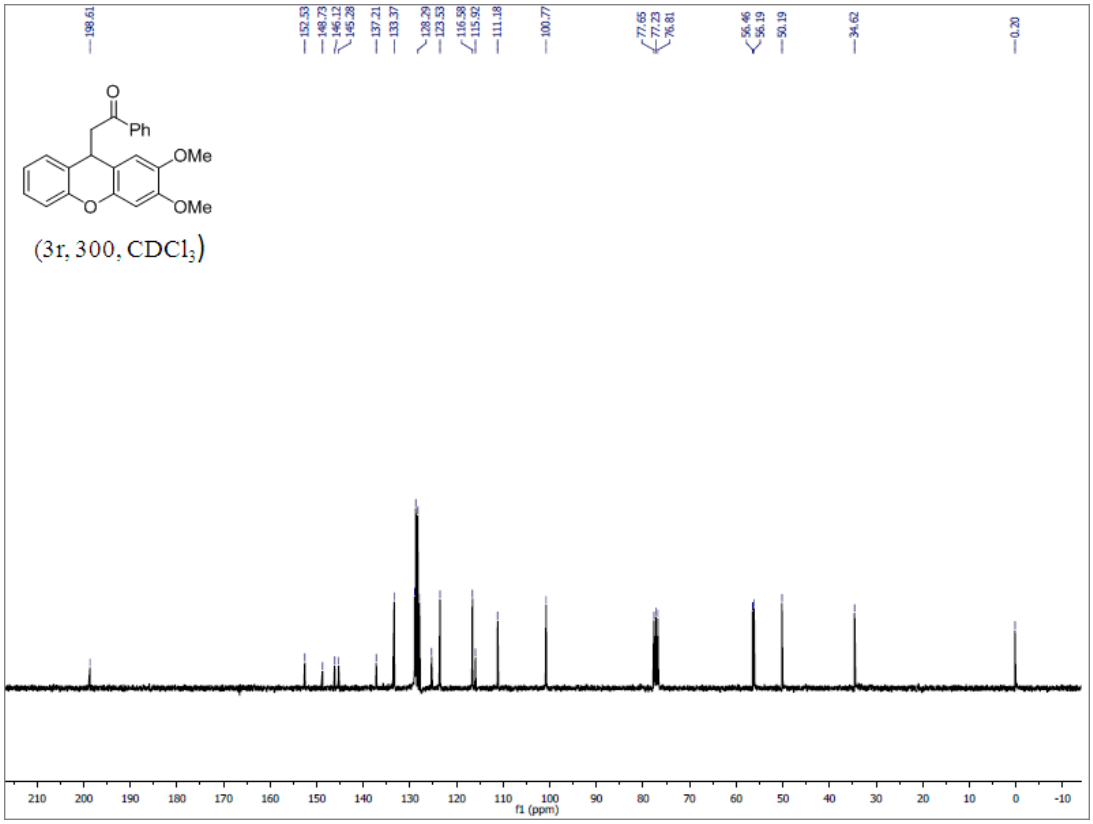


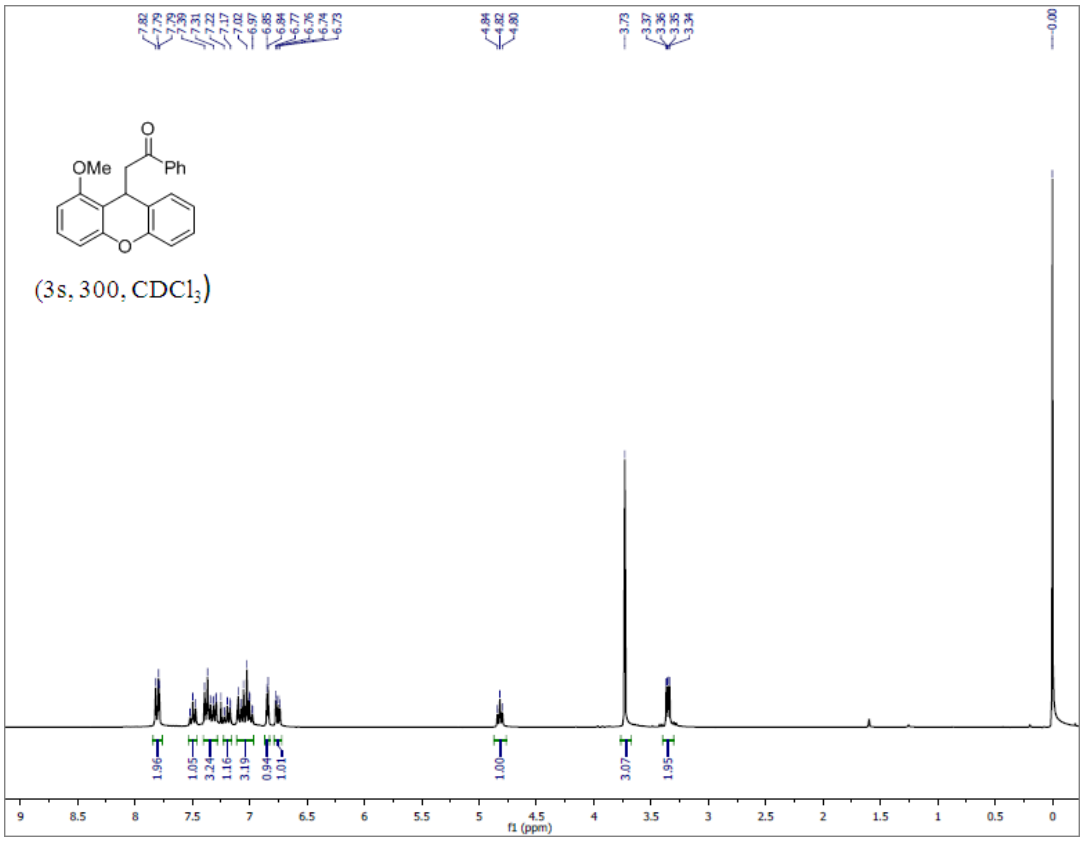


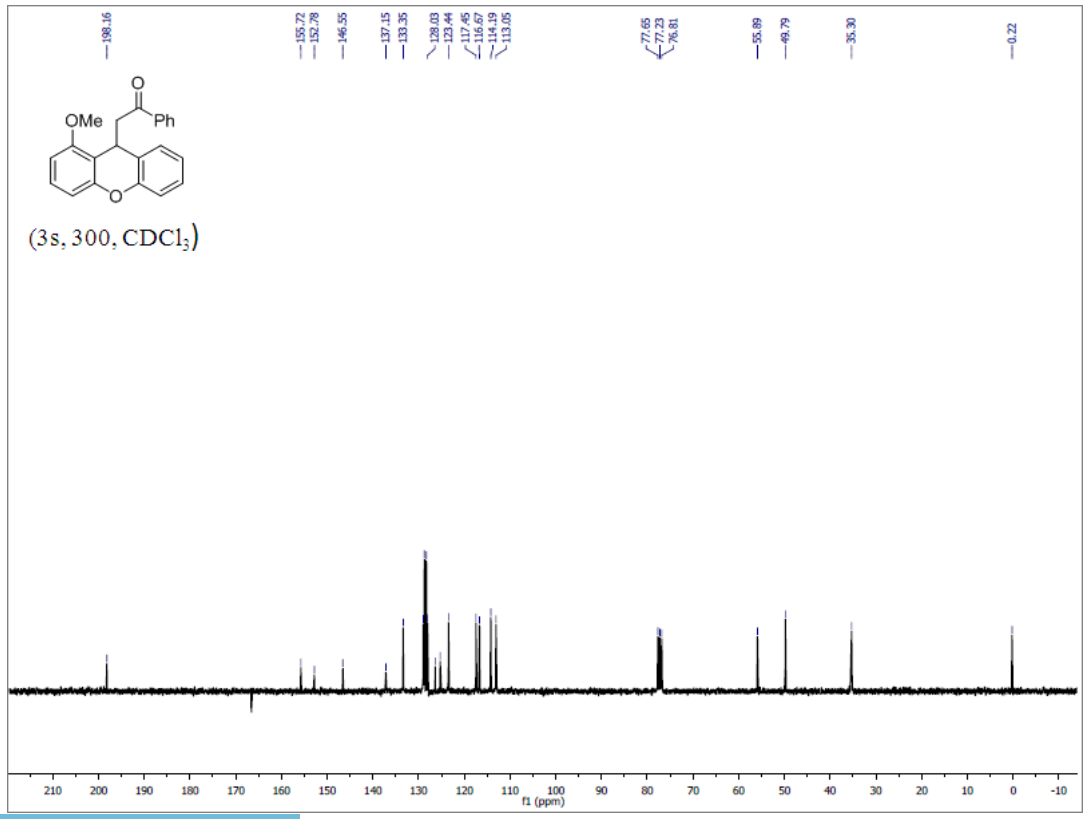




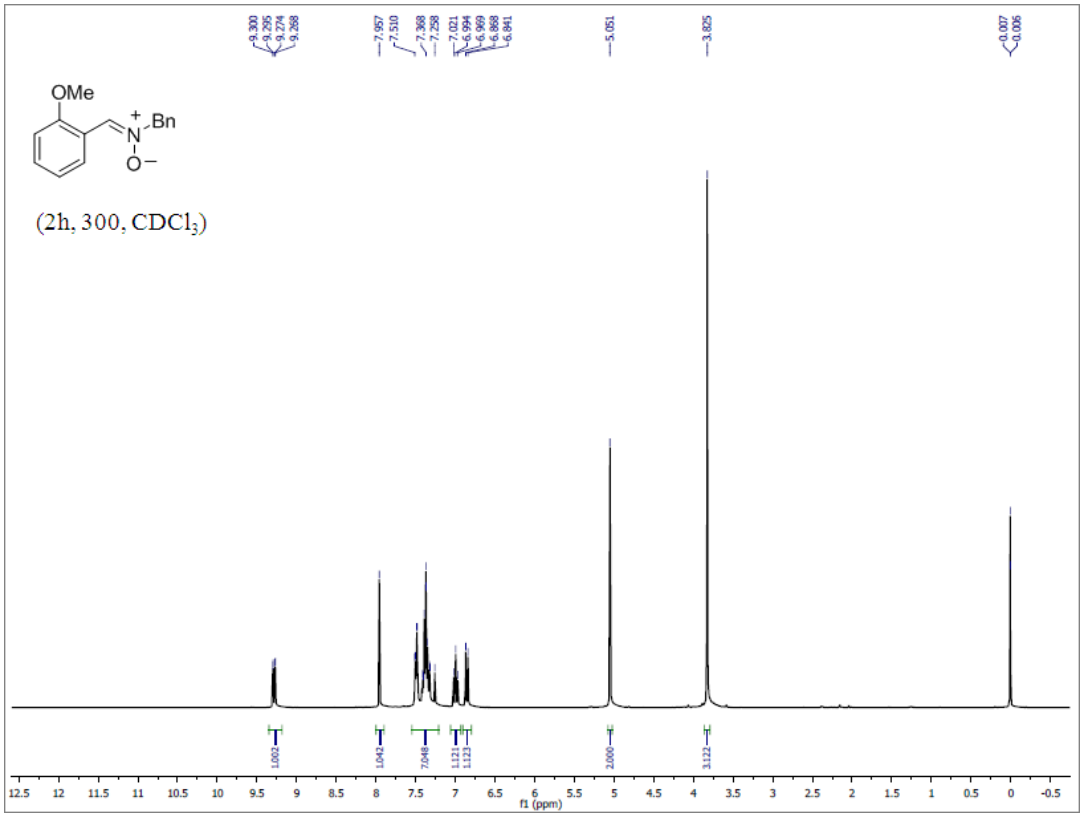


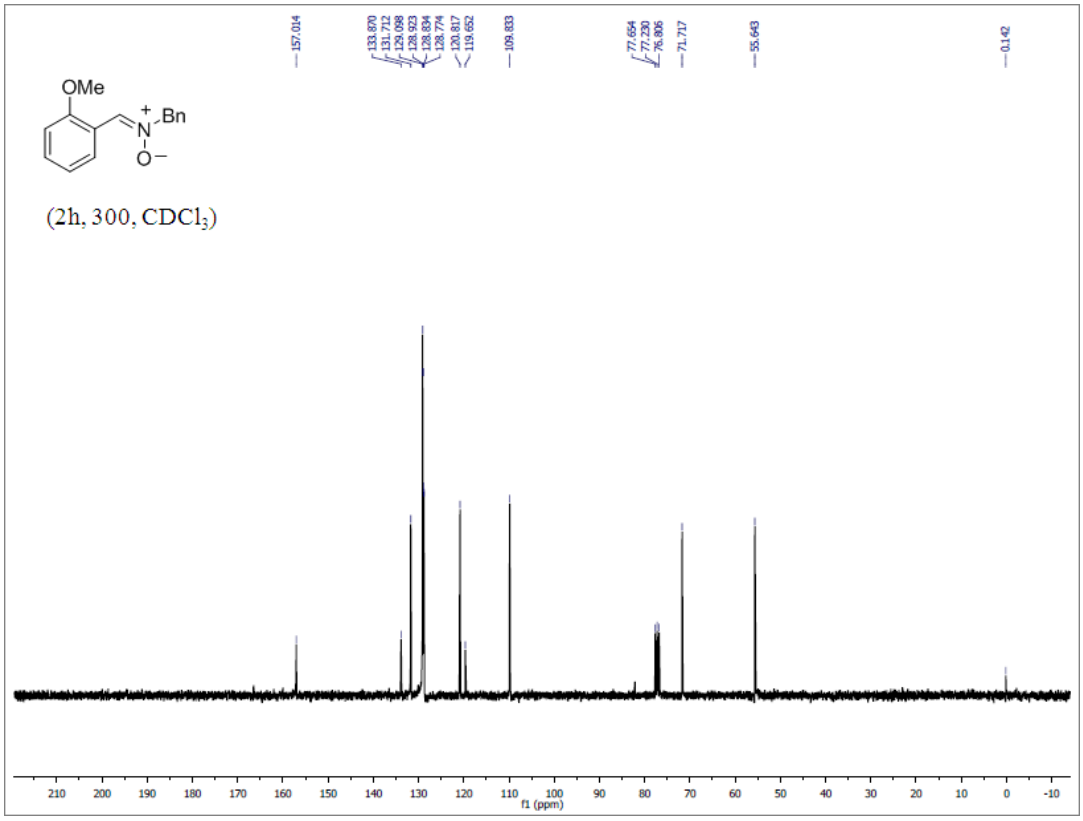


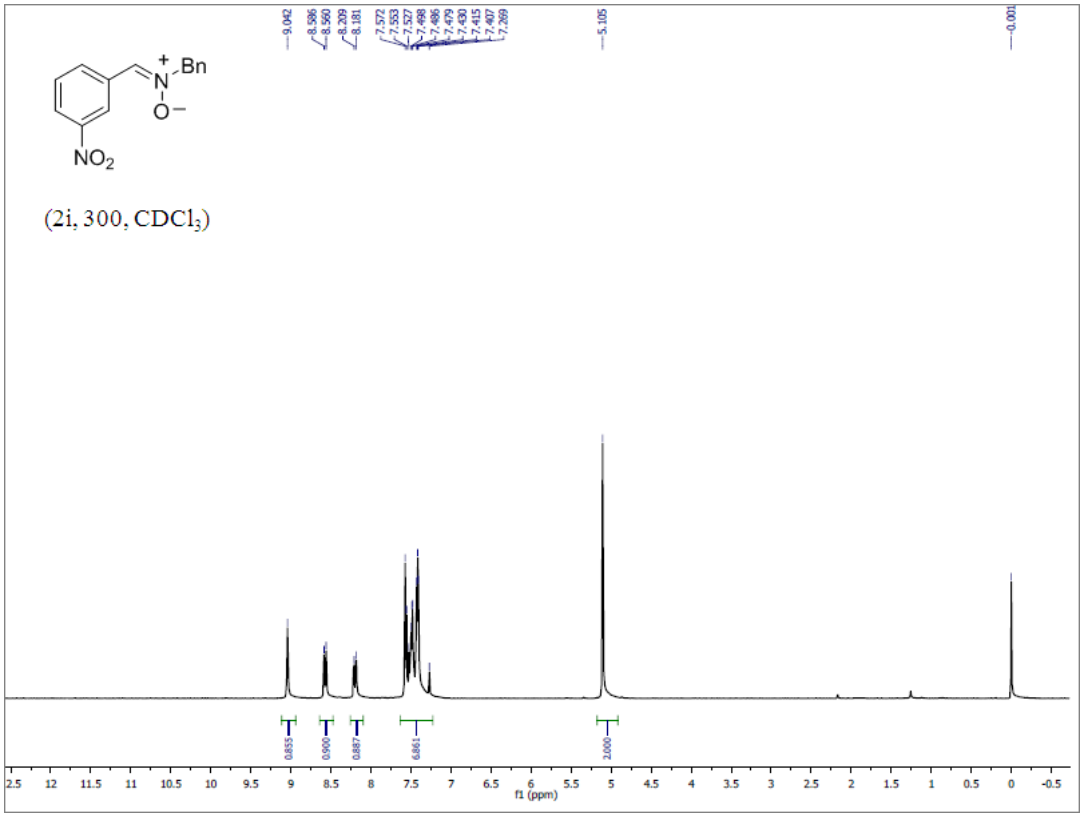


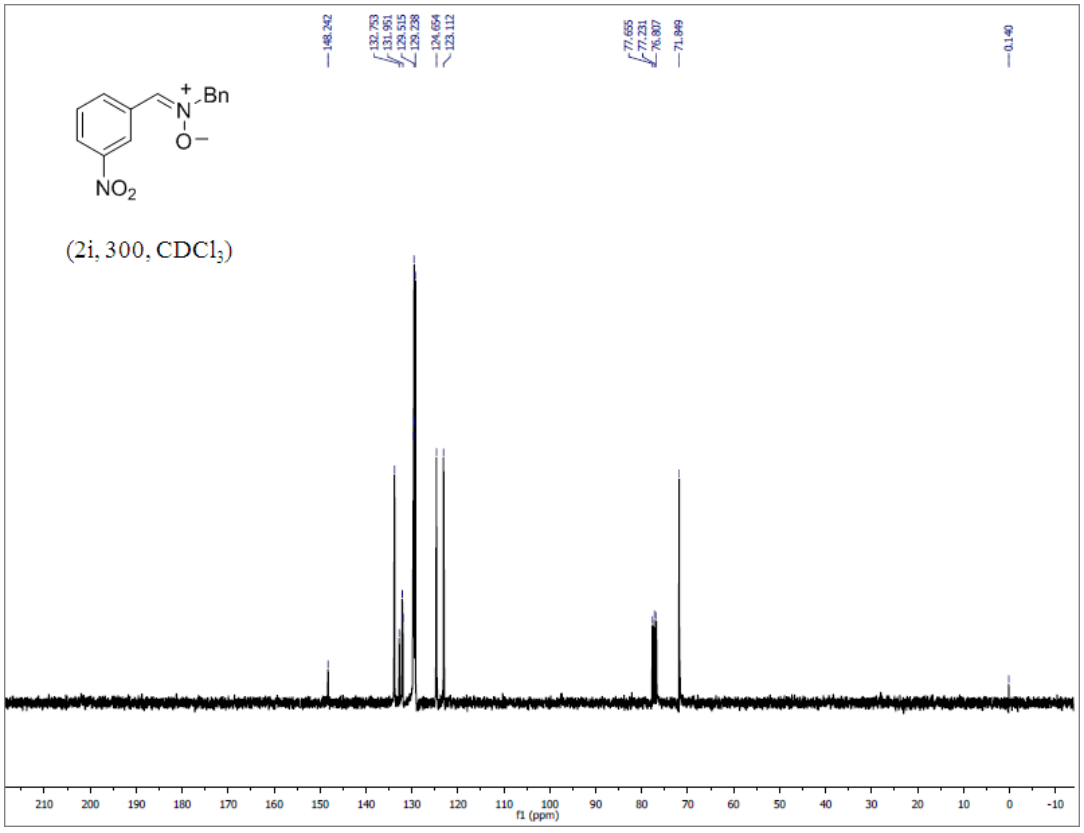


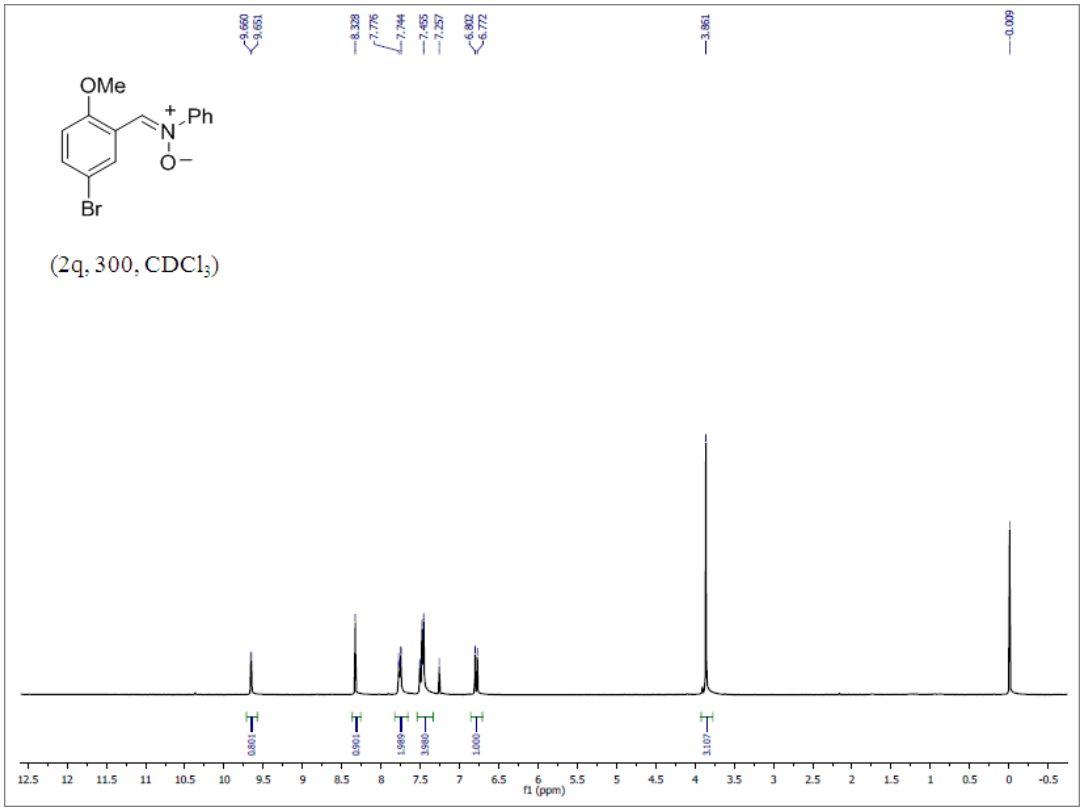
APPENDIX B. CHAPTER 2 ^{1}H AND ^{13}C NMR SPECTRA

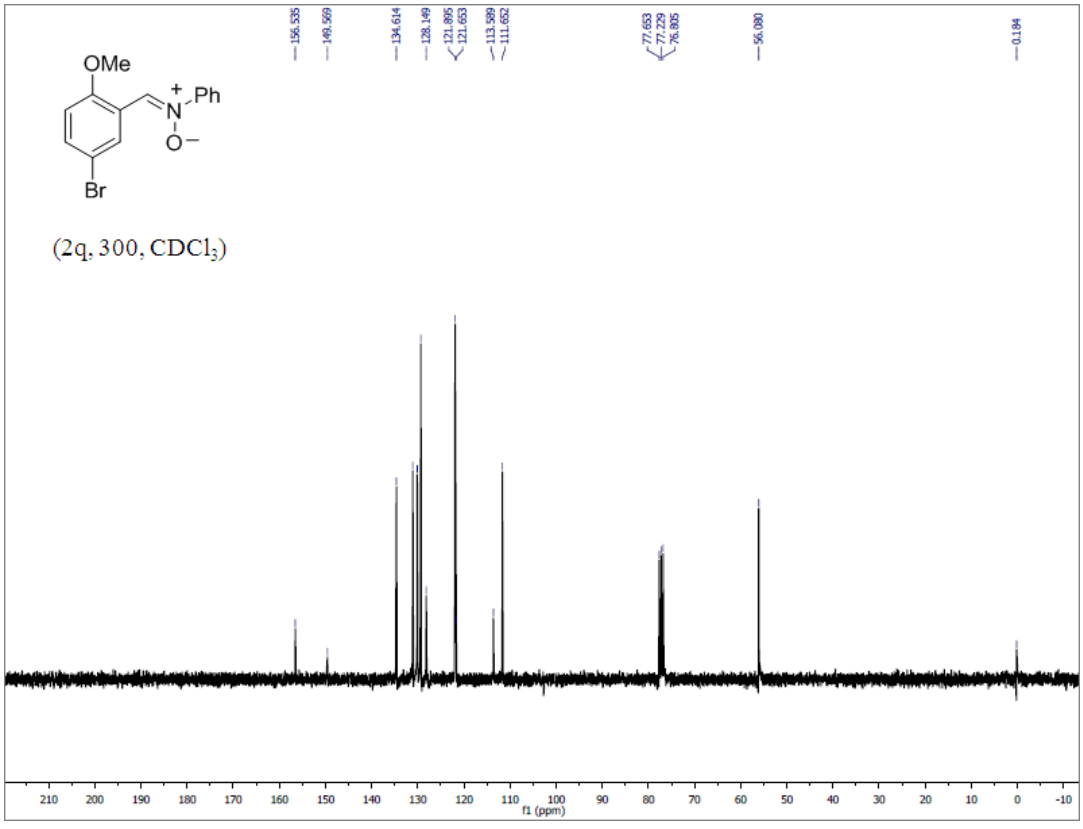


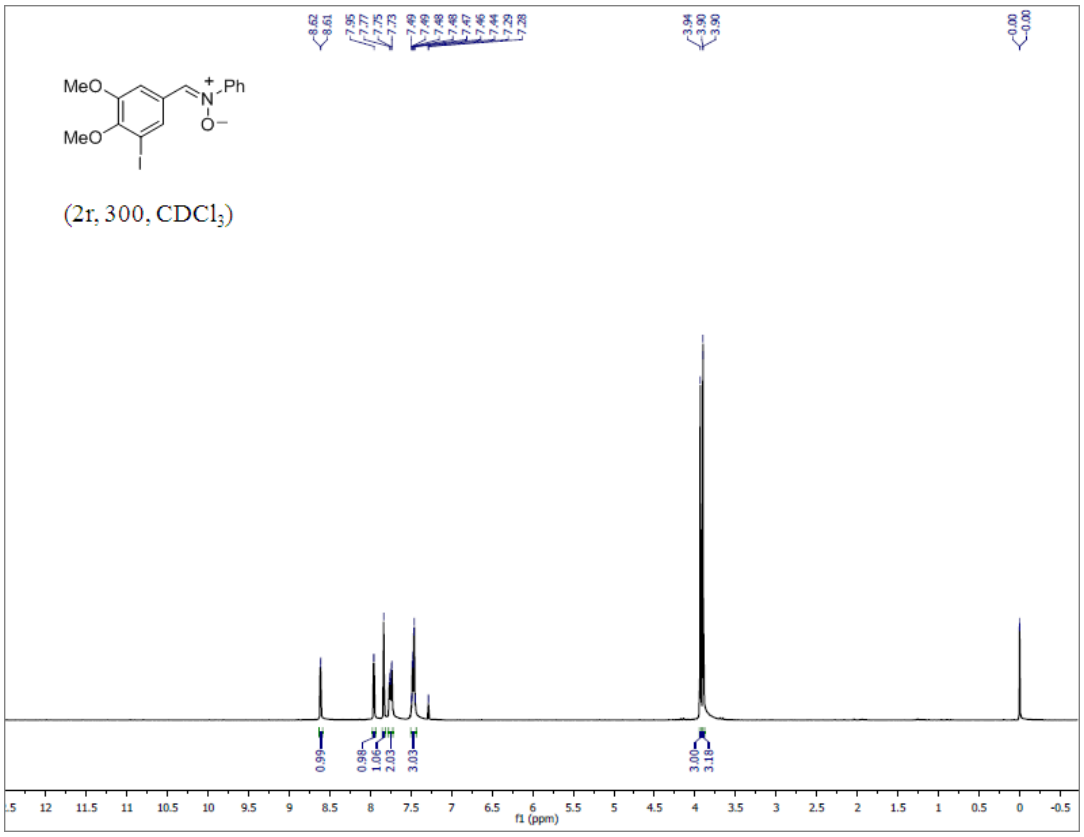


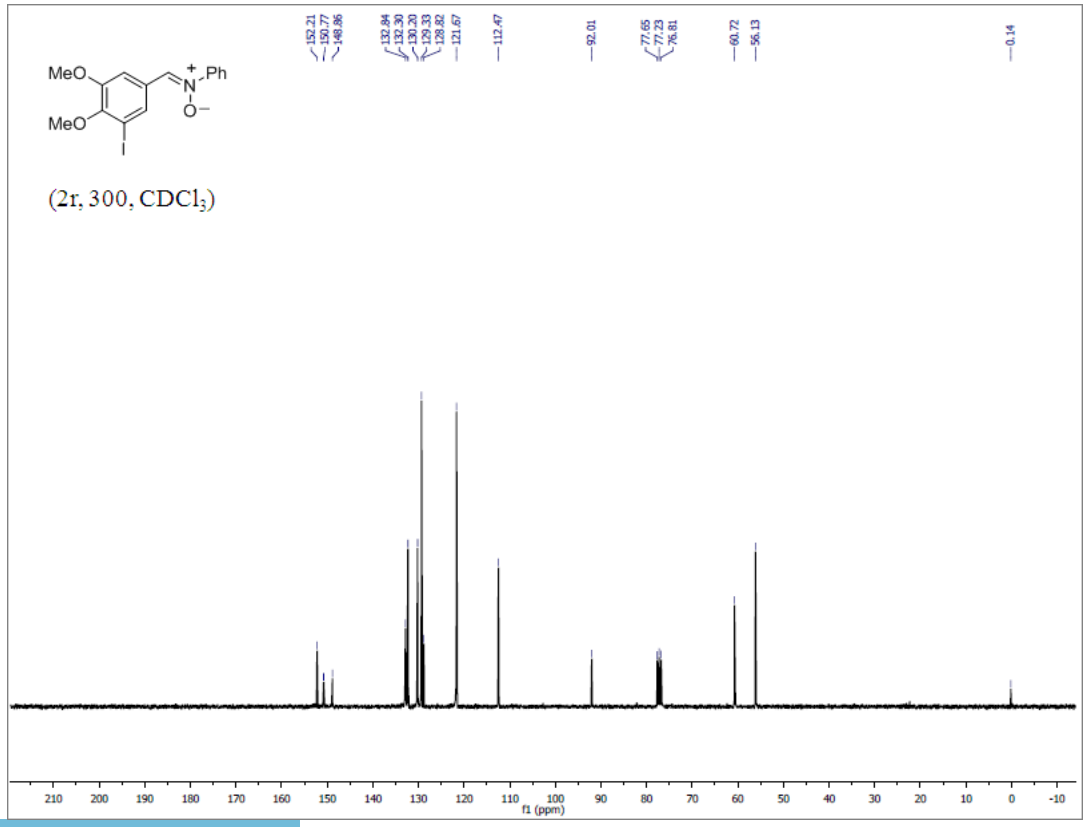


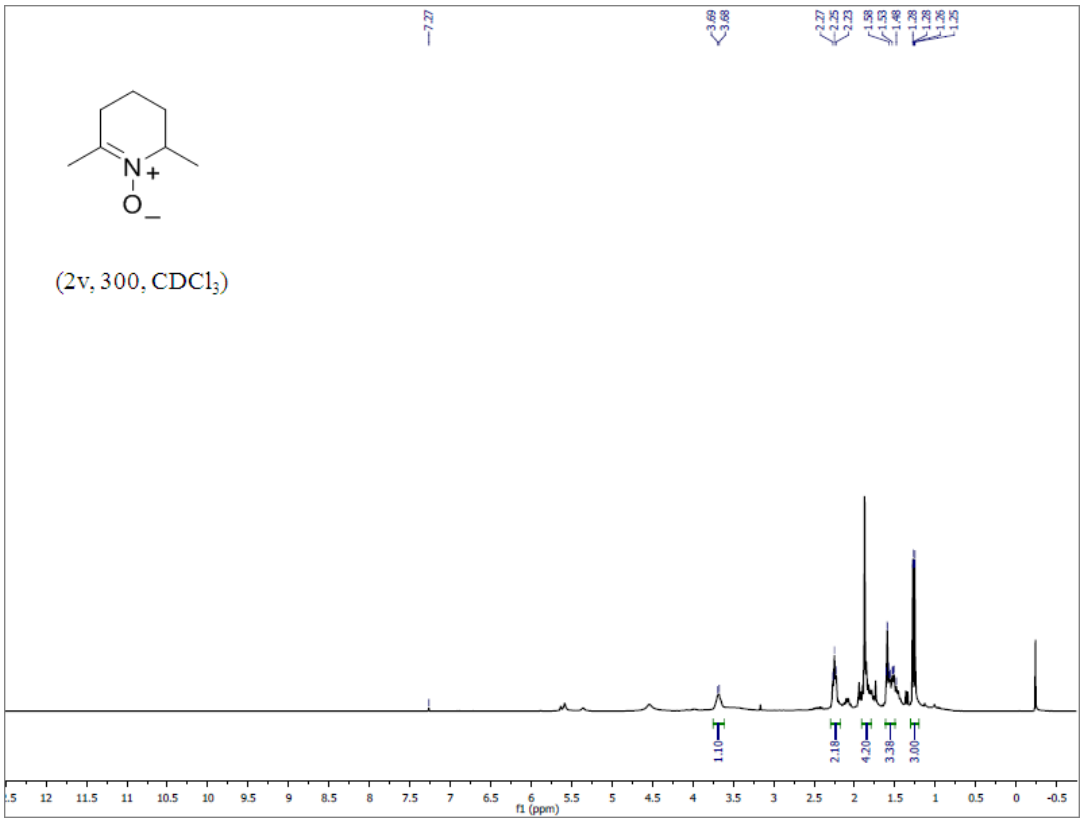












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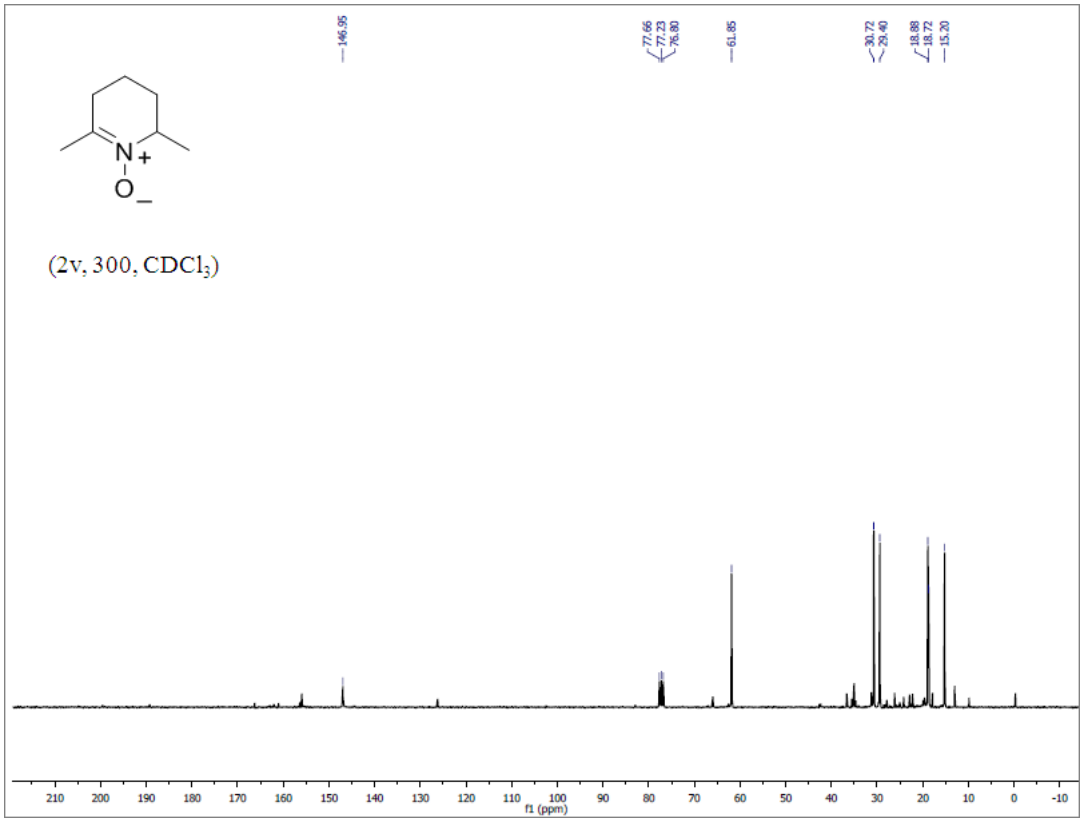

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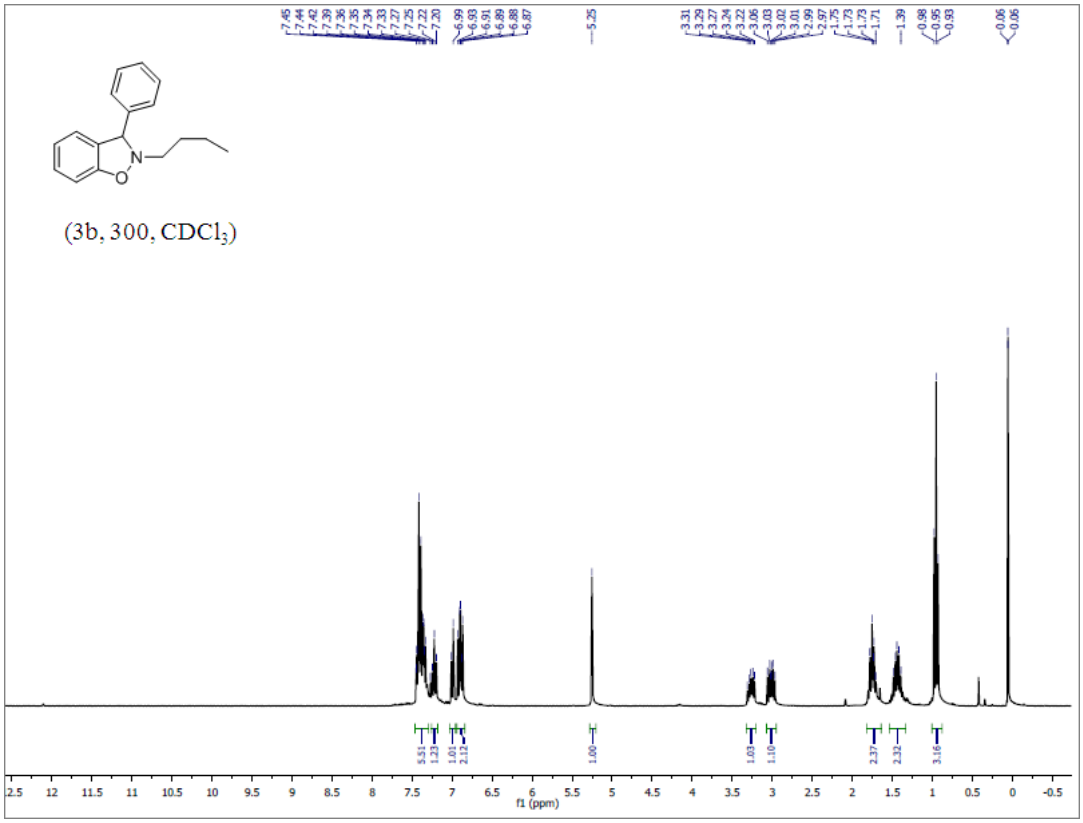

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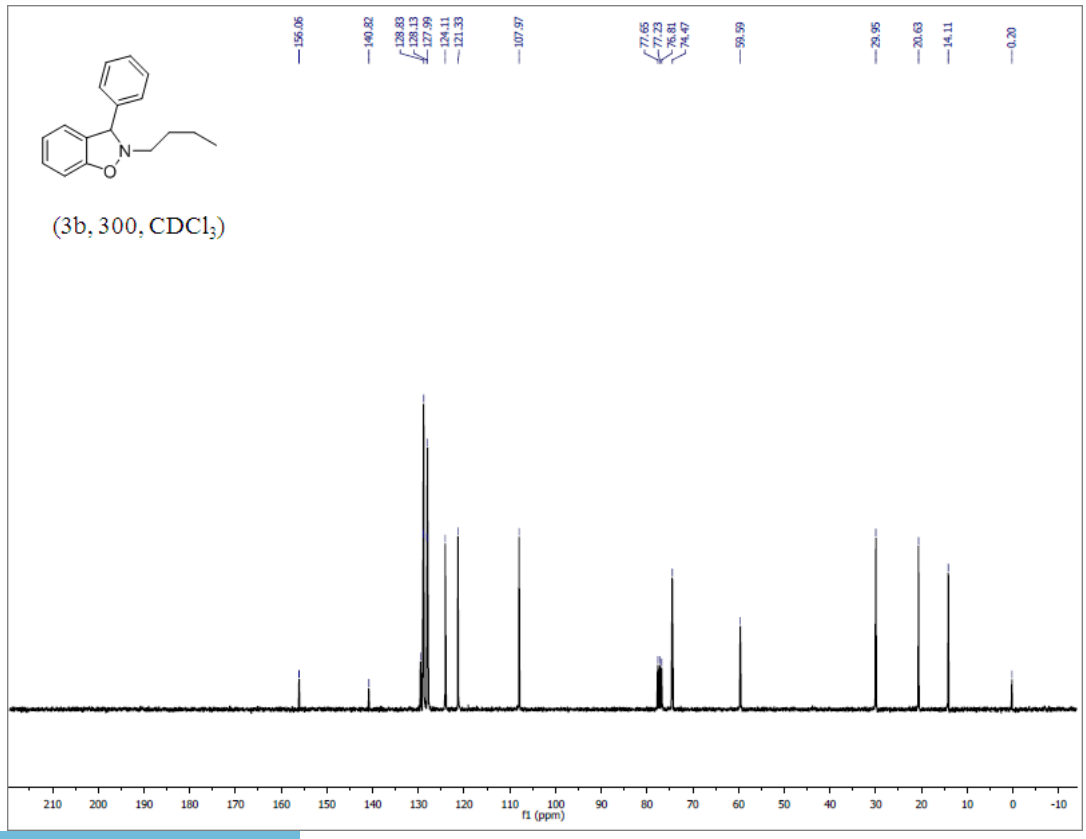

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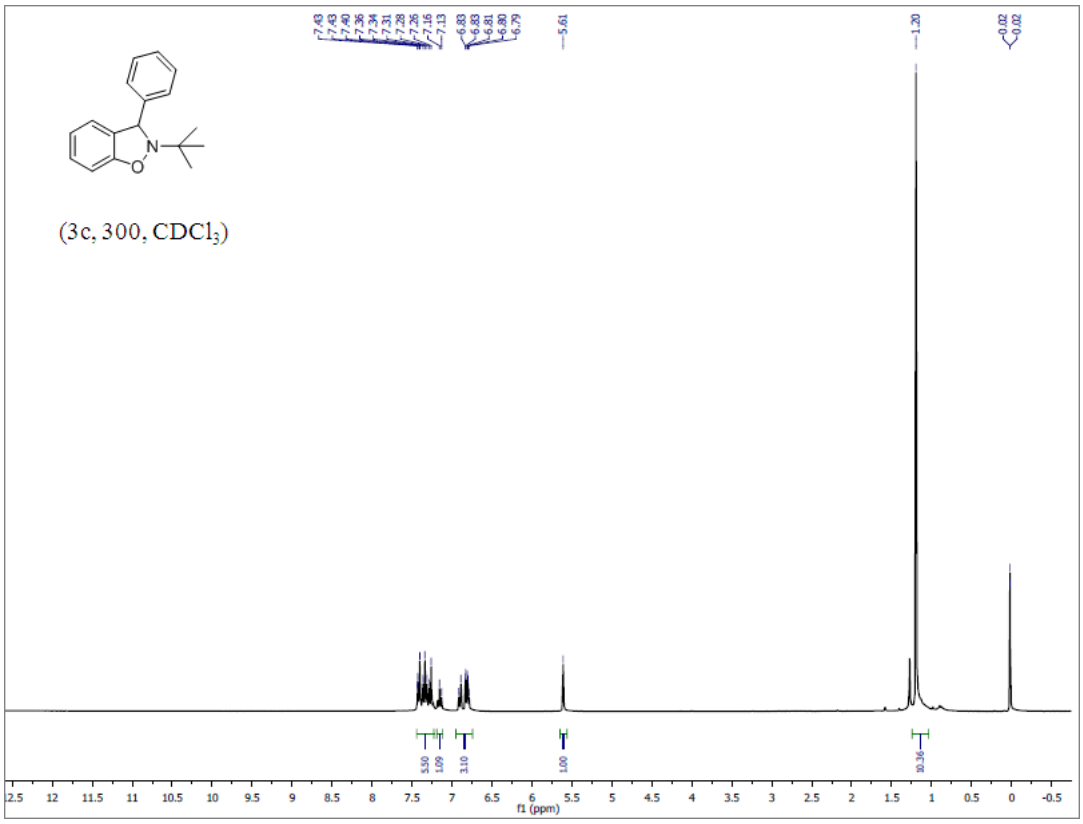

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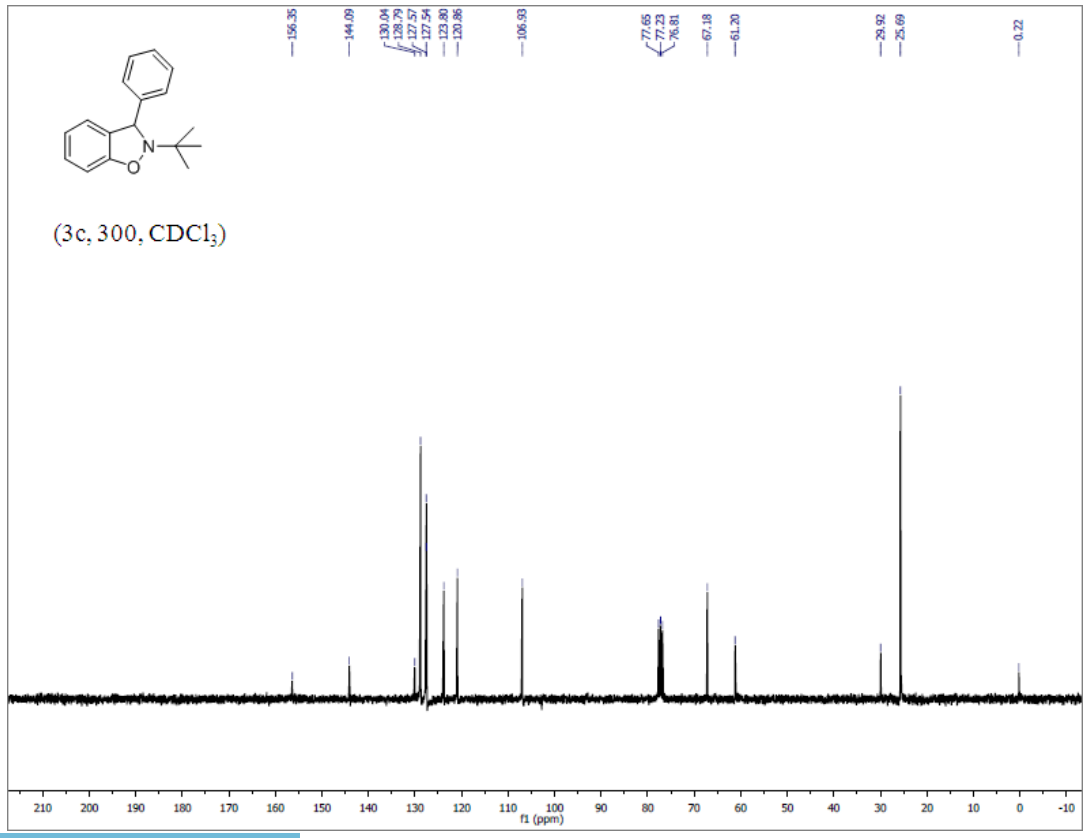

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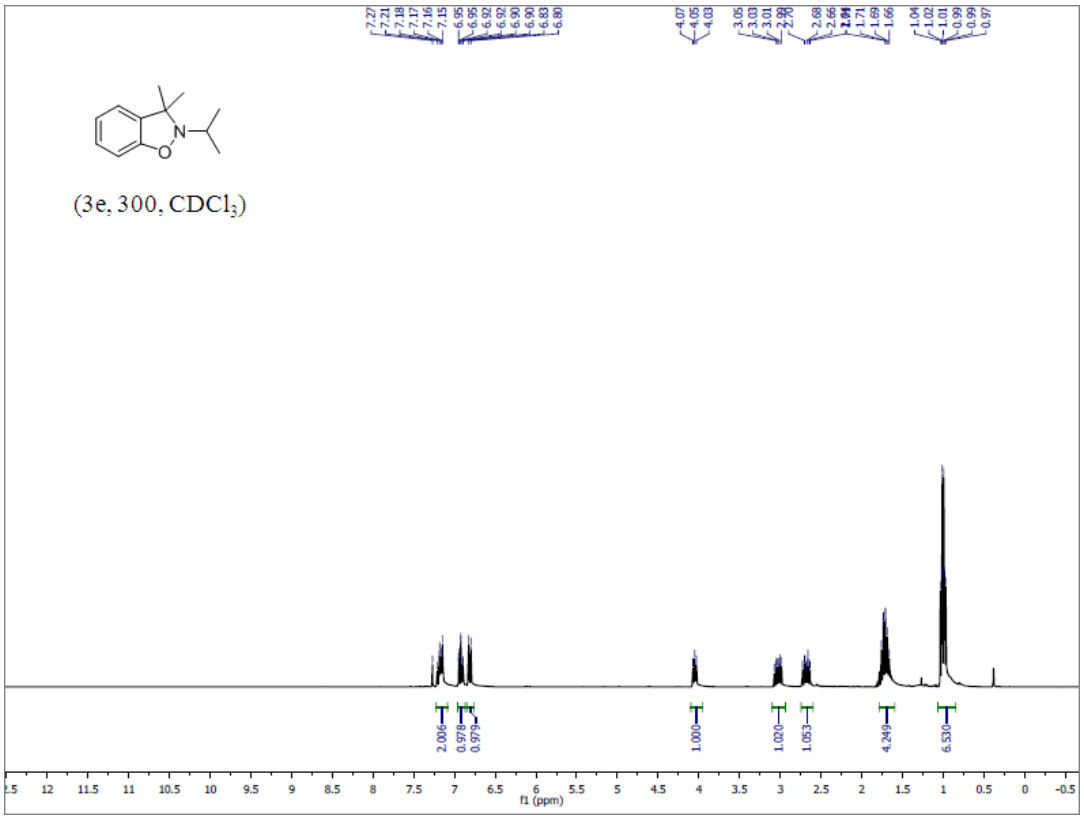

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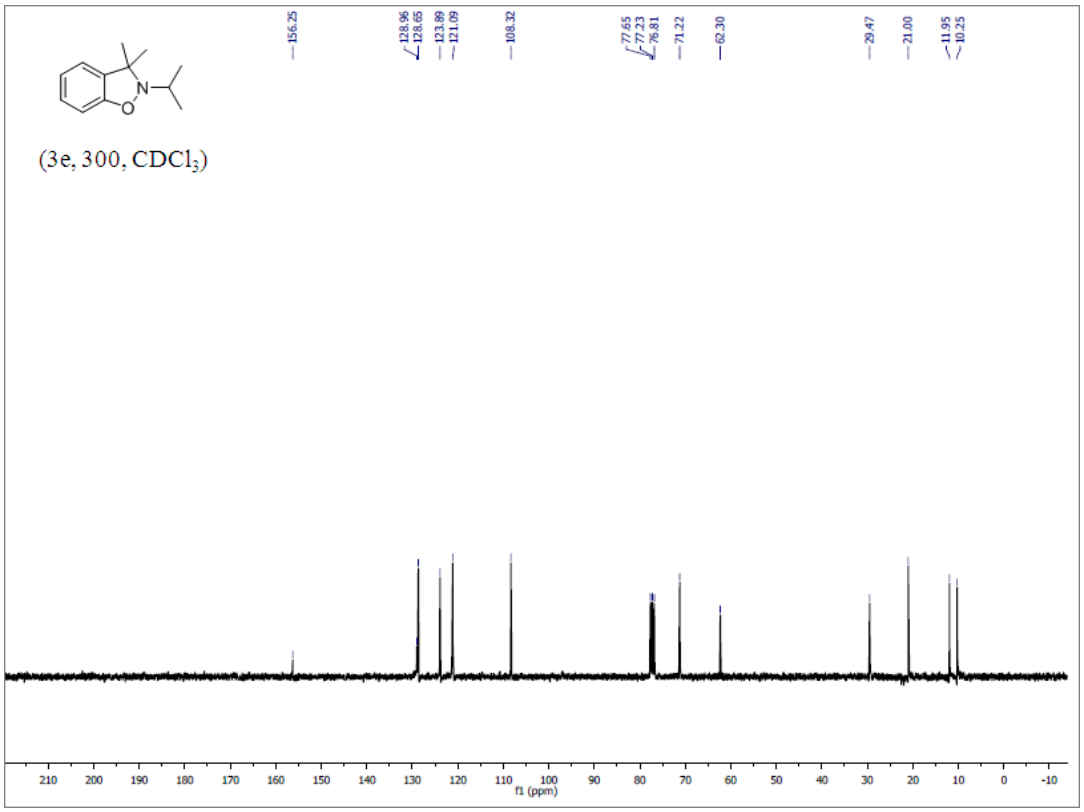

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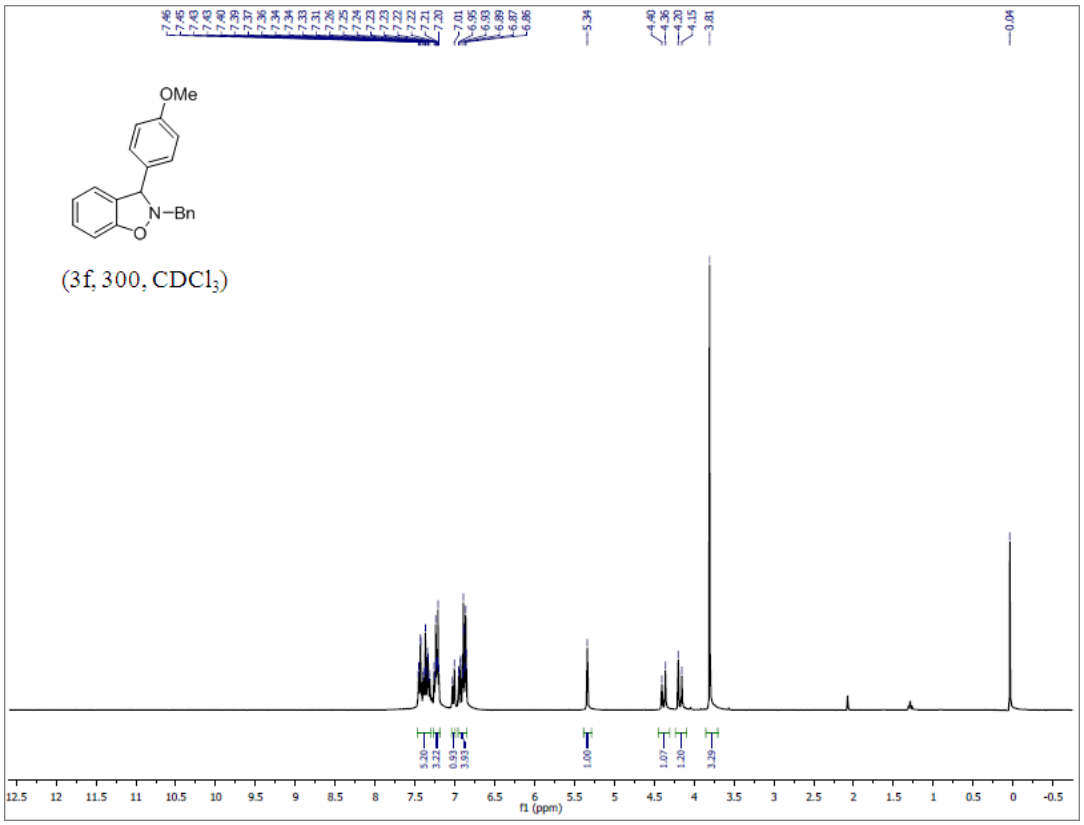

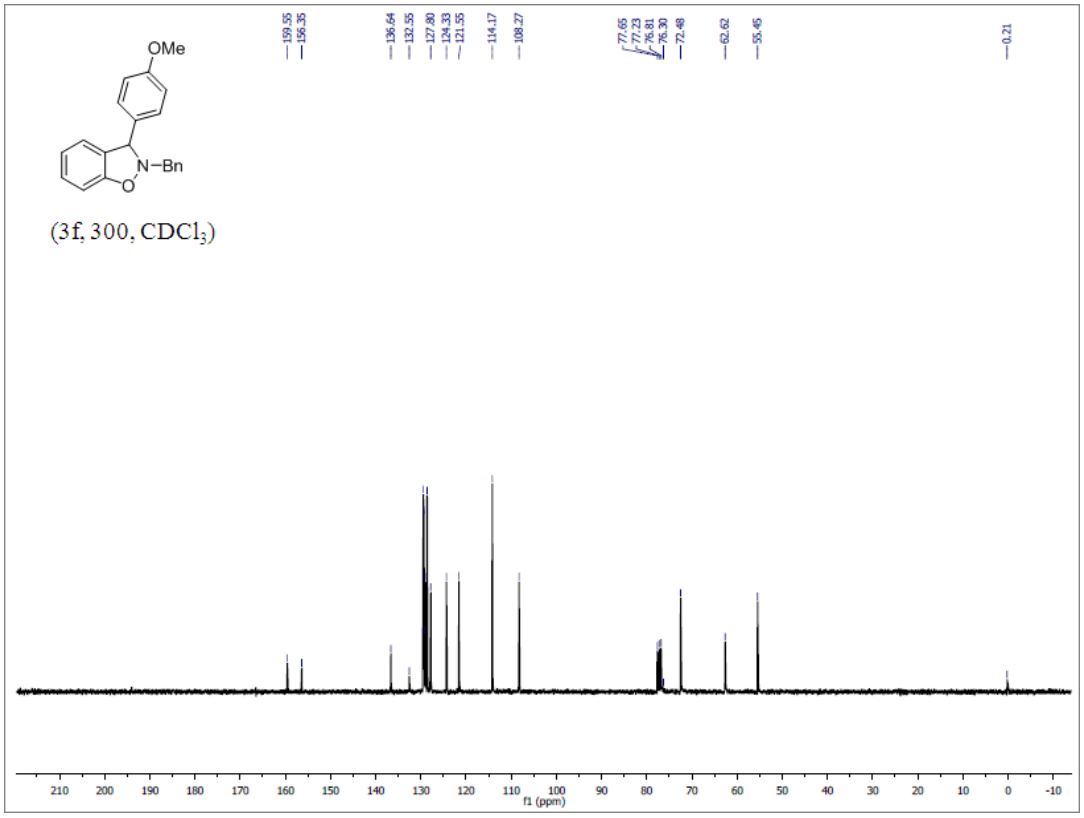

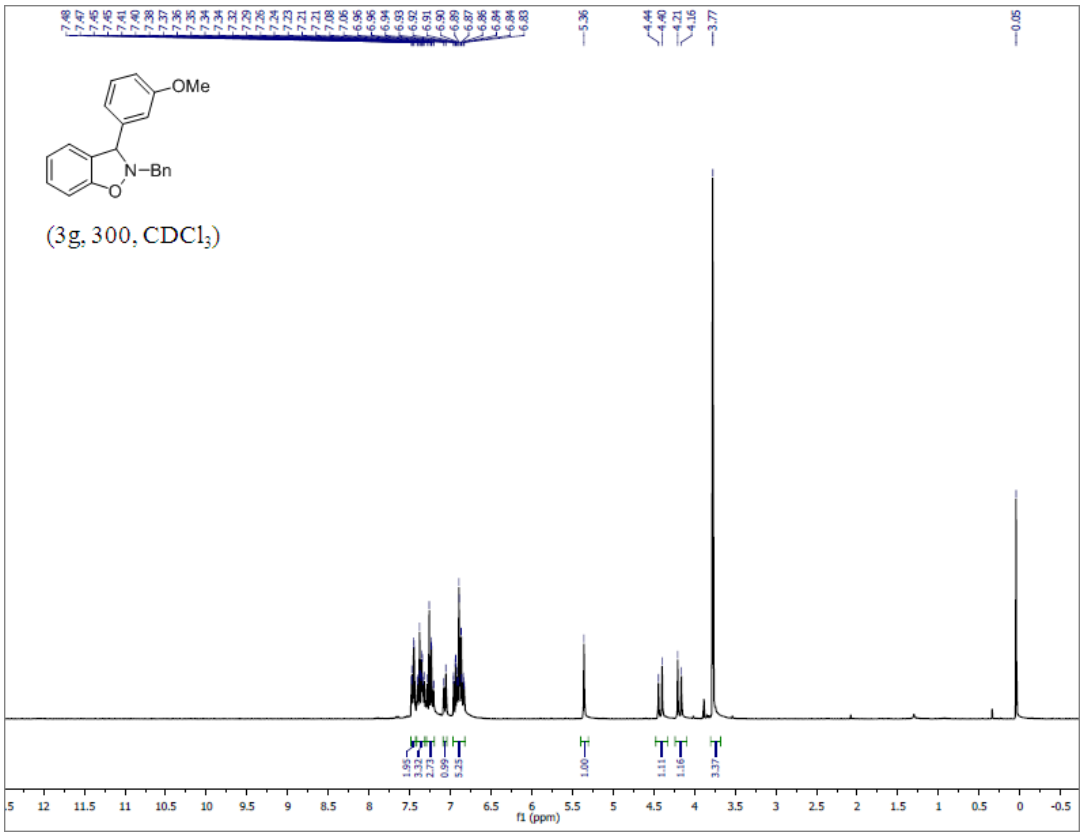

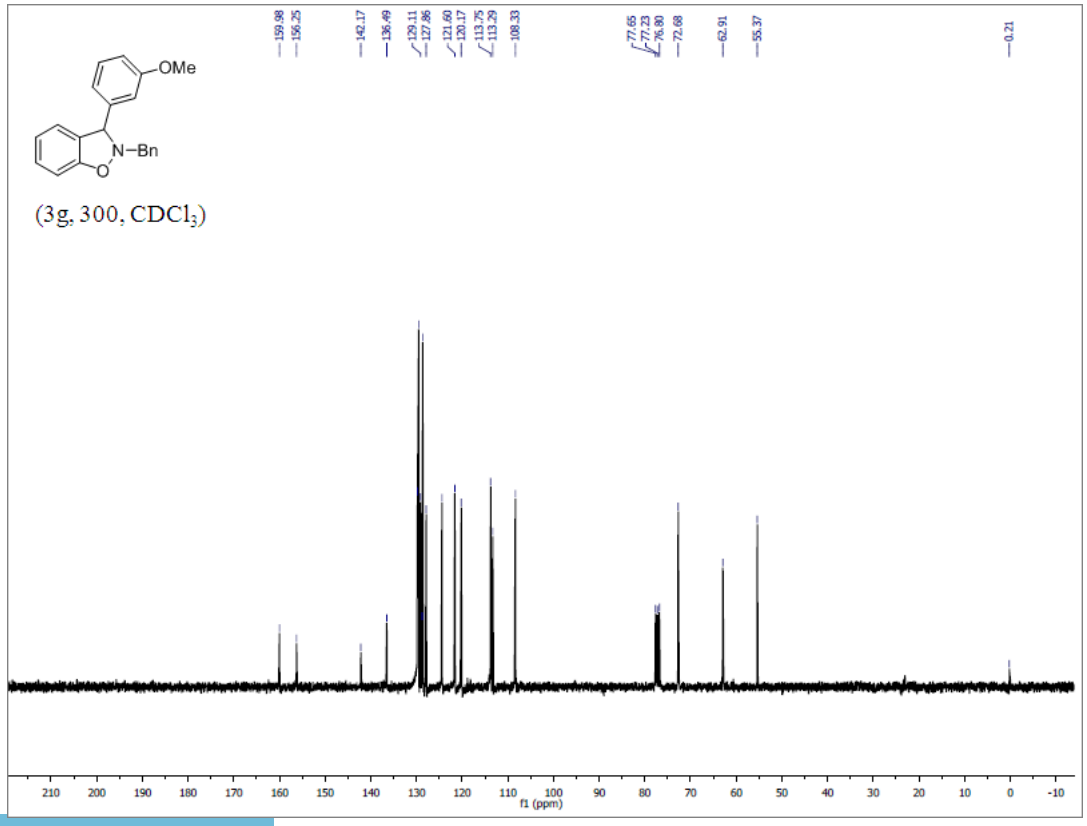

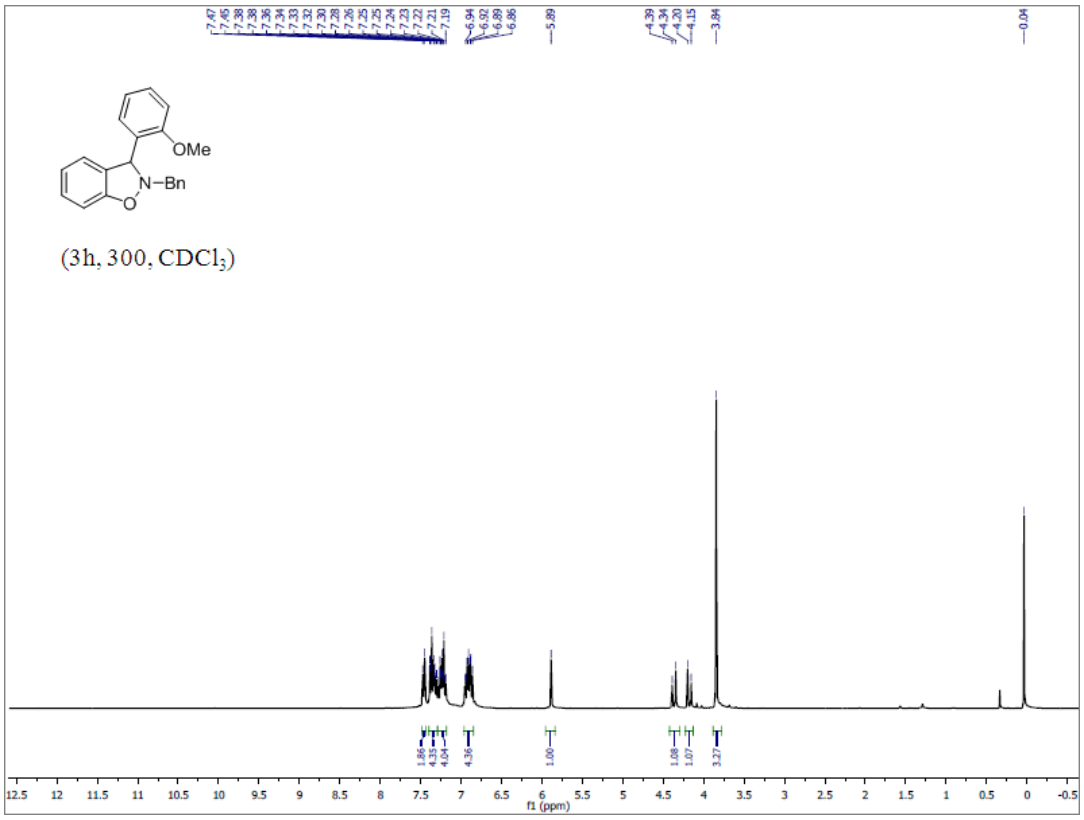

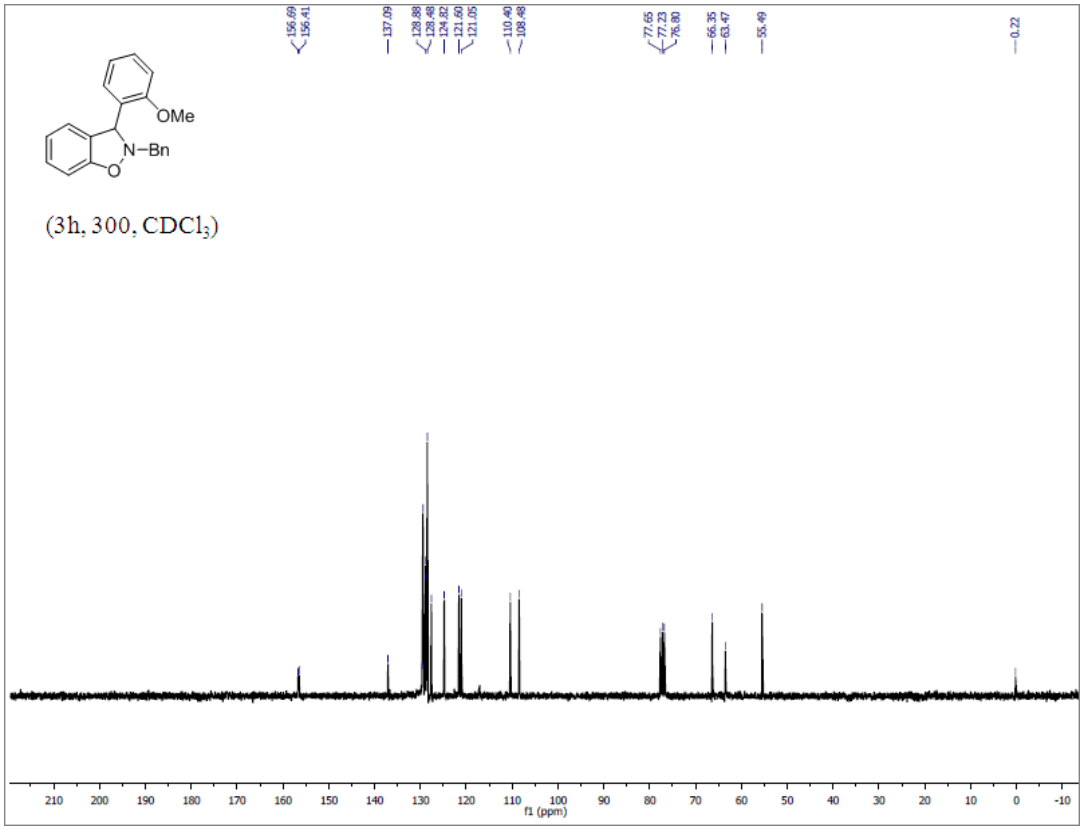

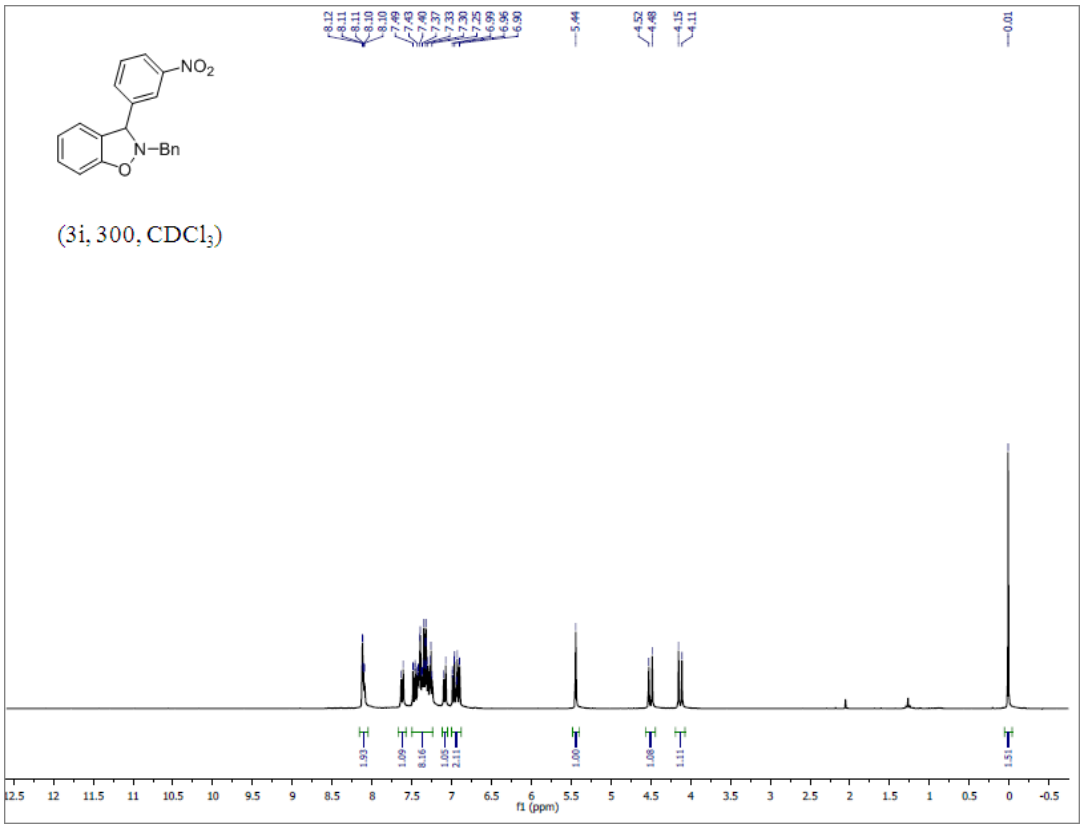

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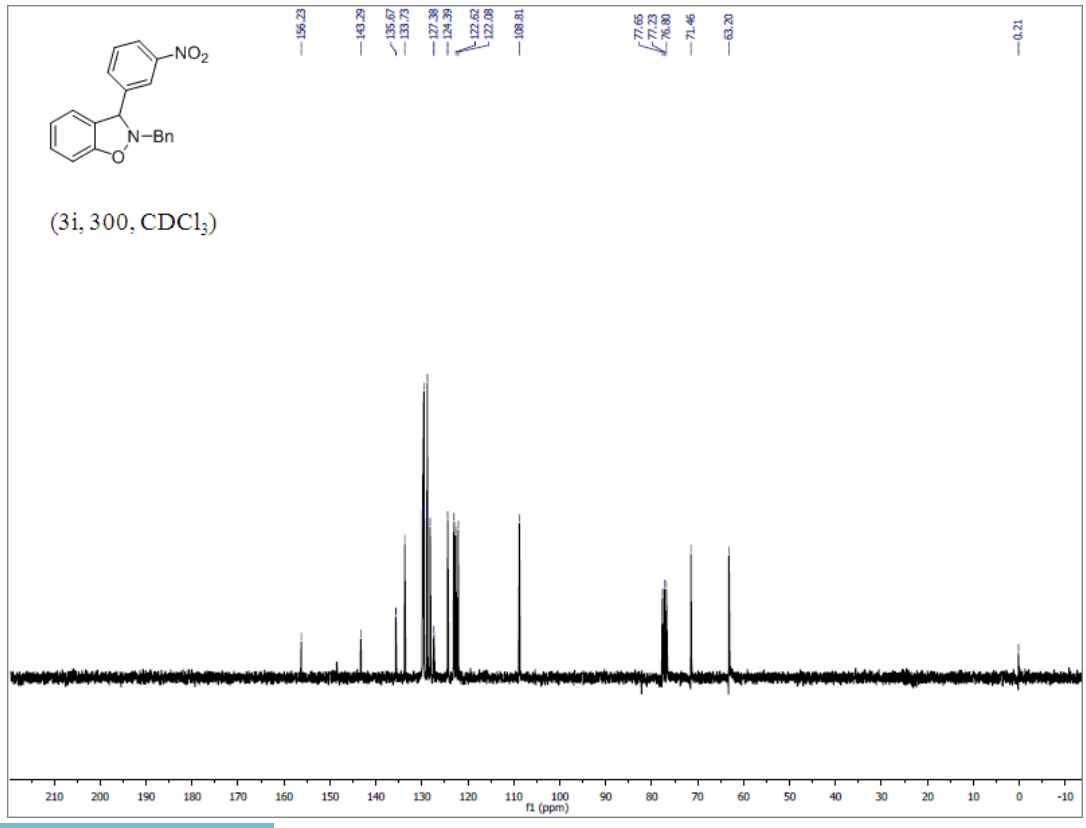

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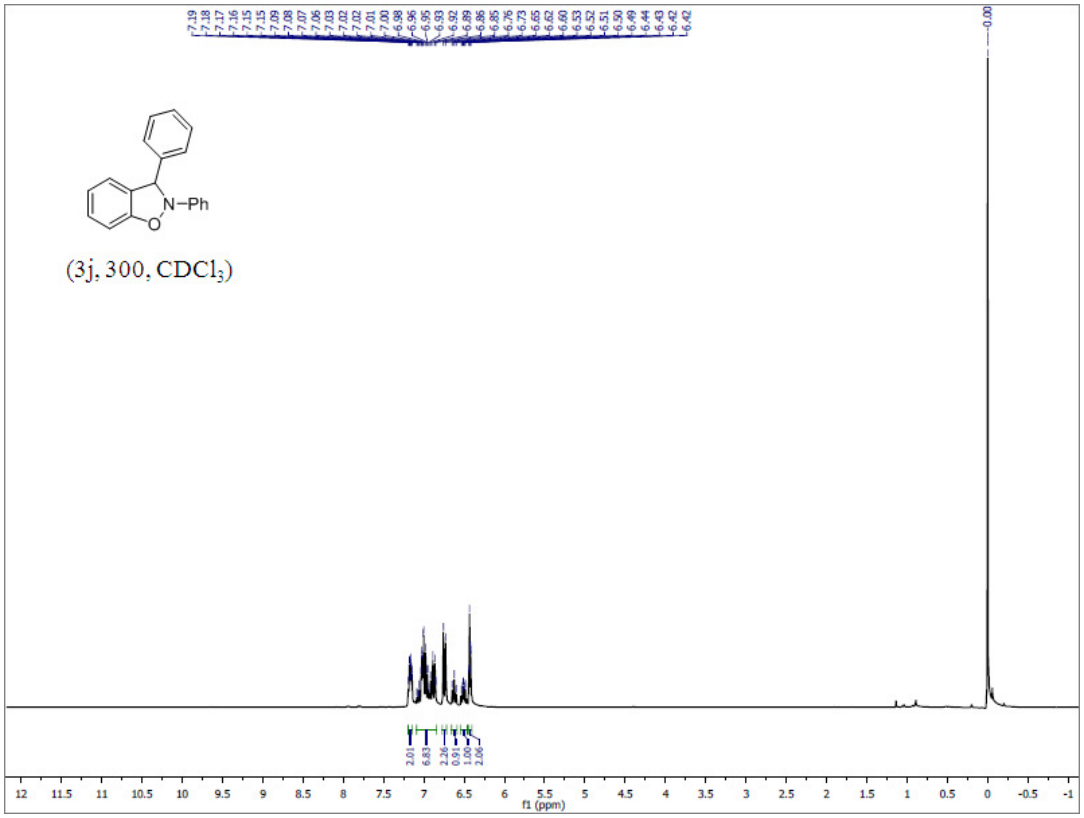

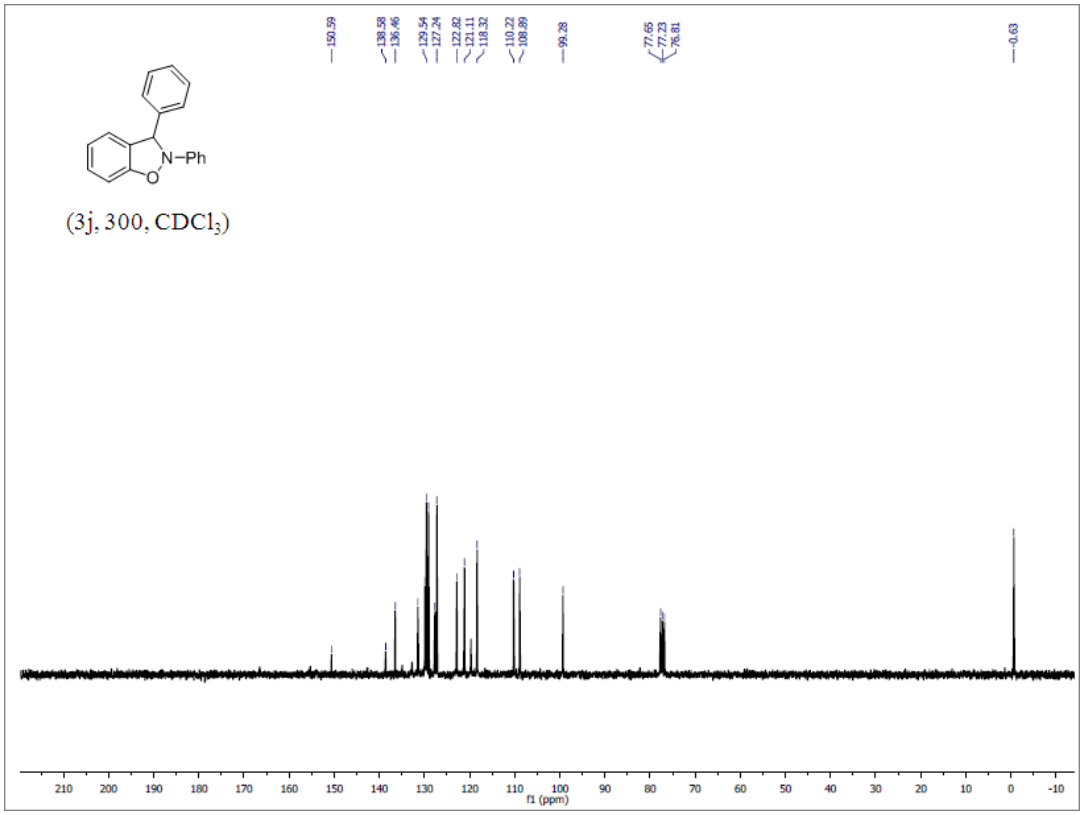

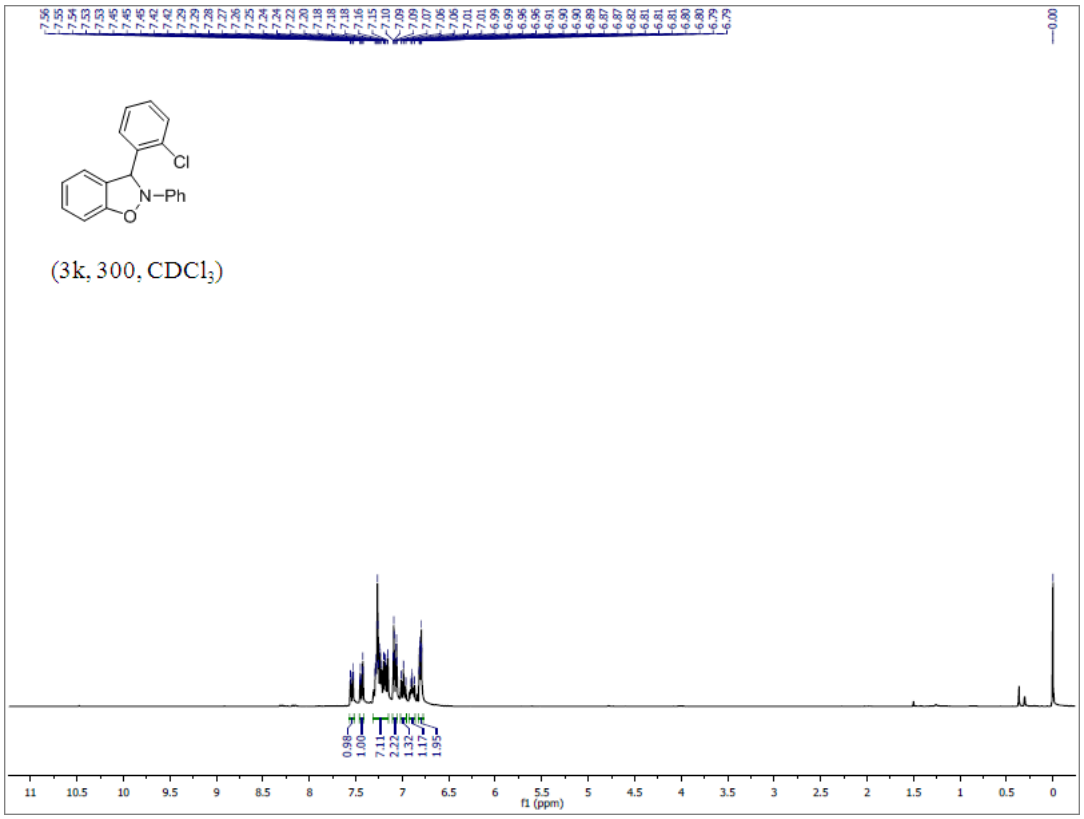

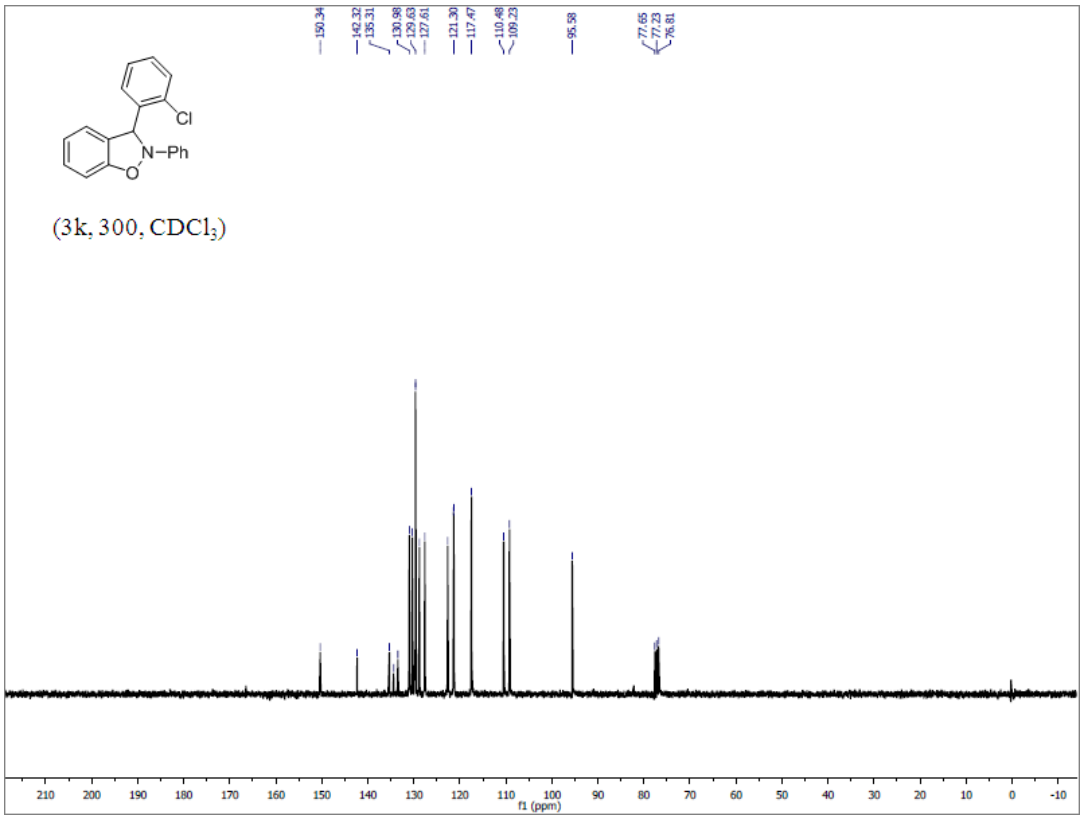

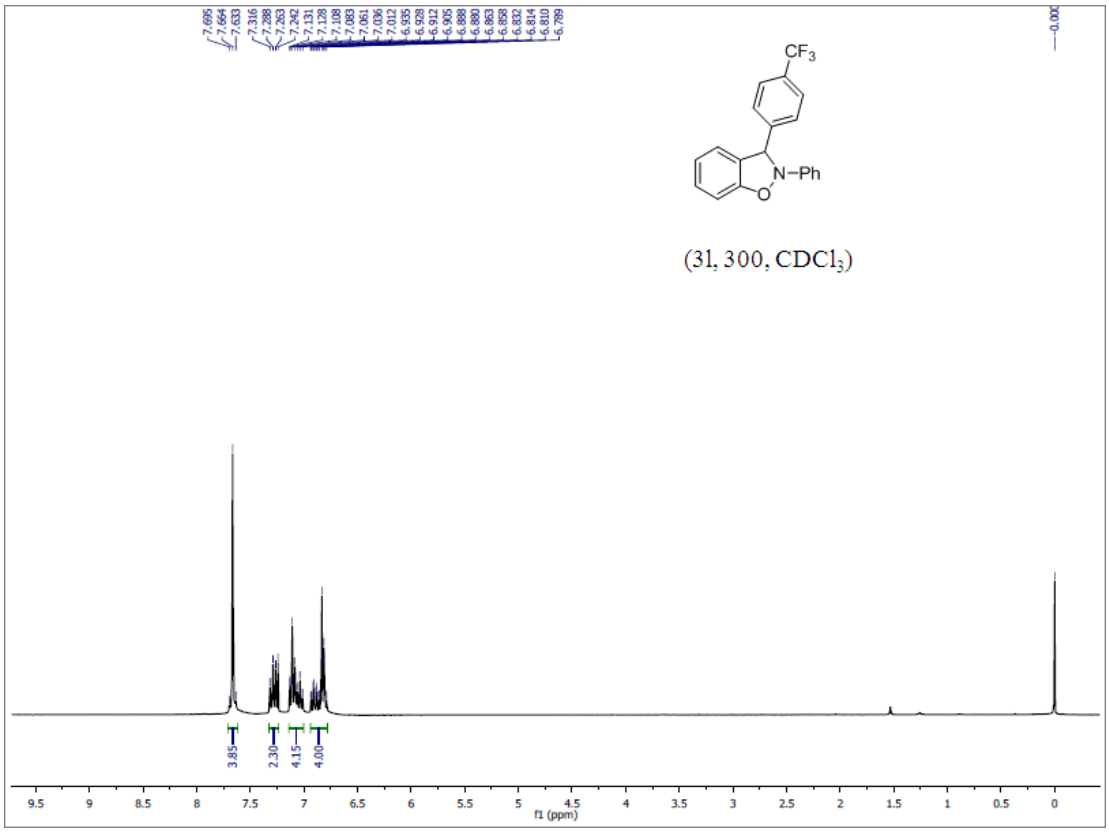

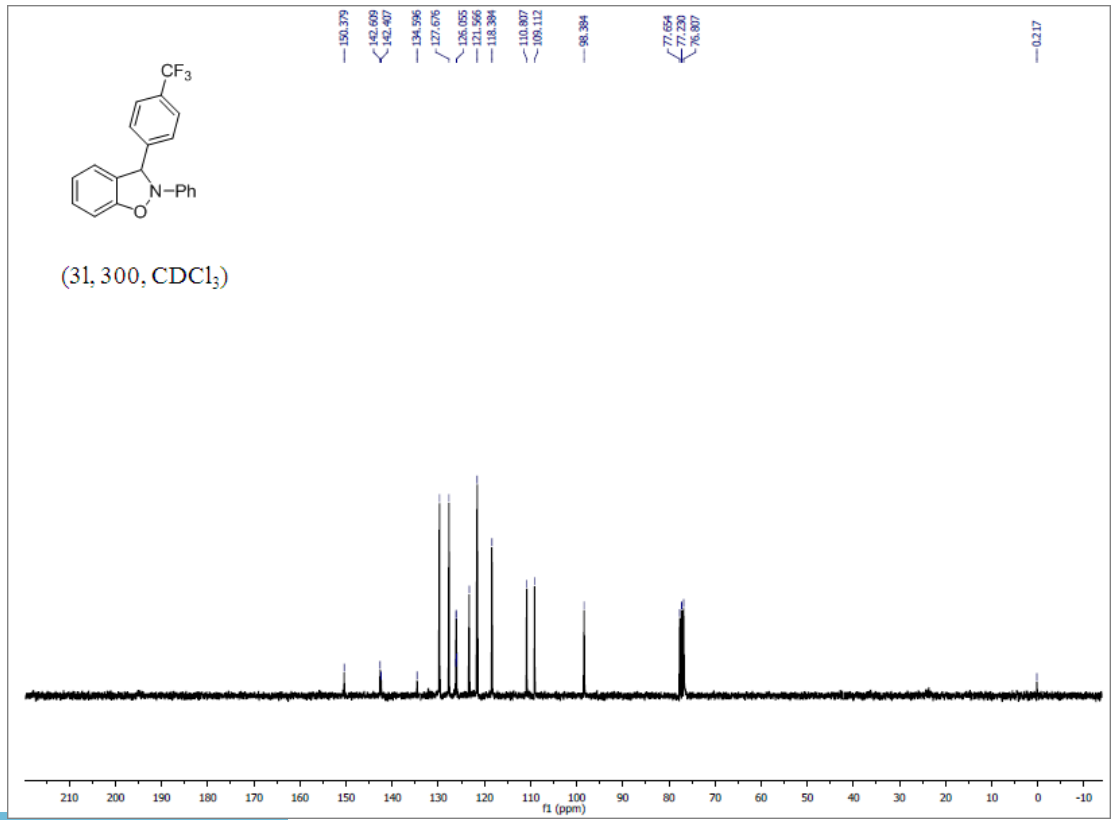

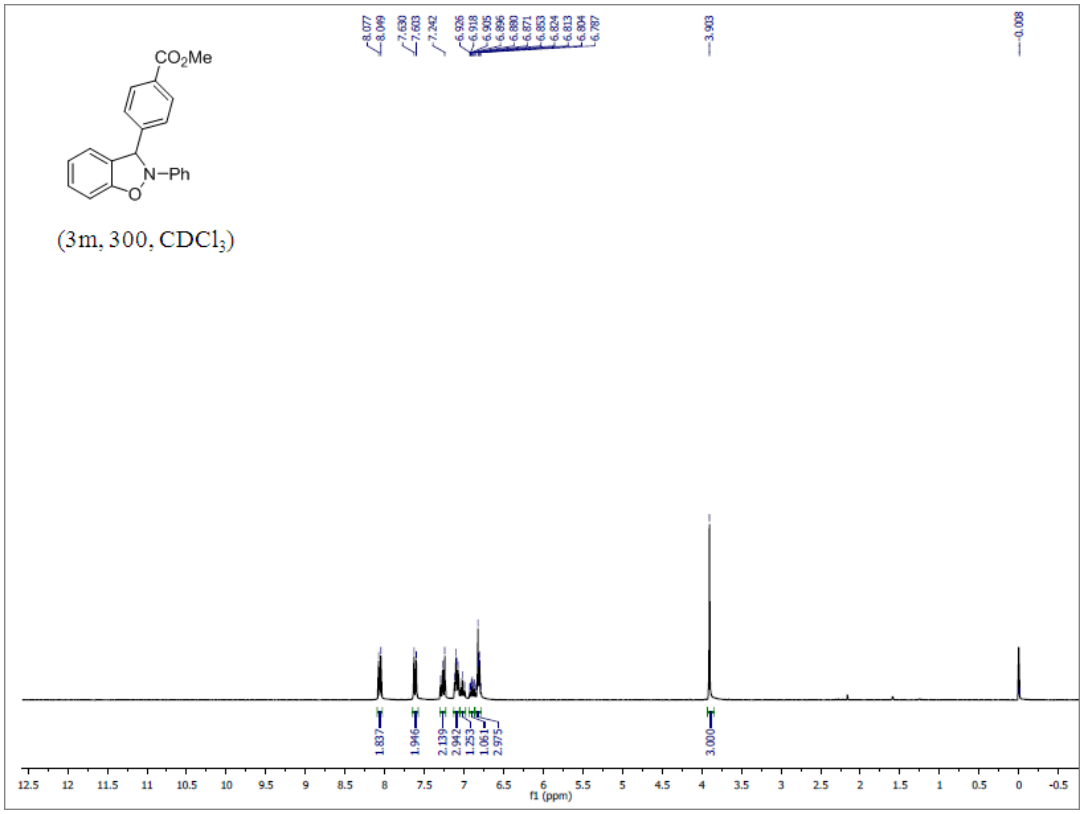

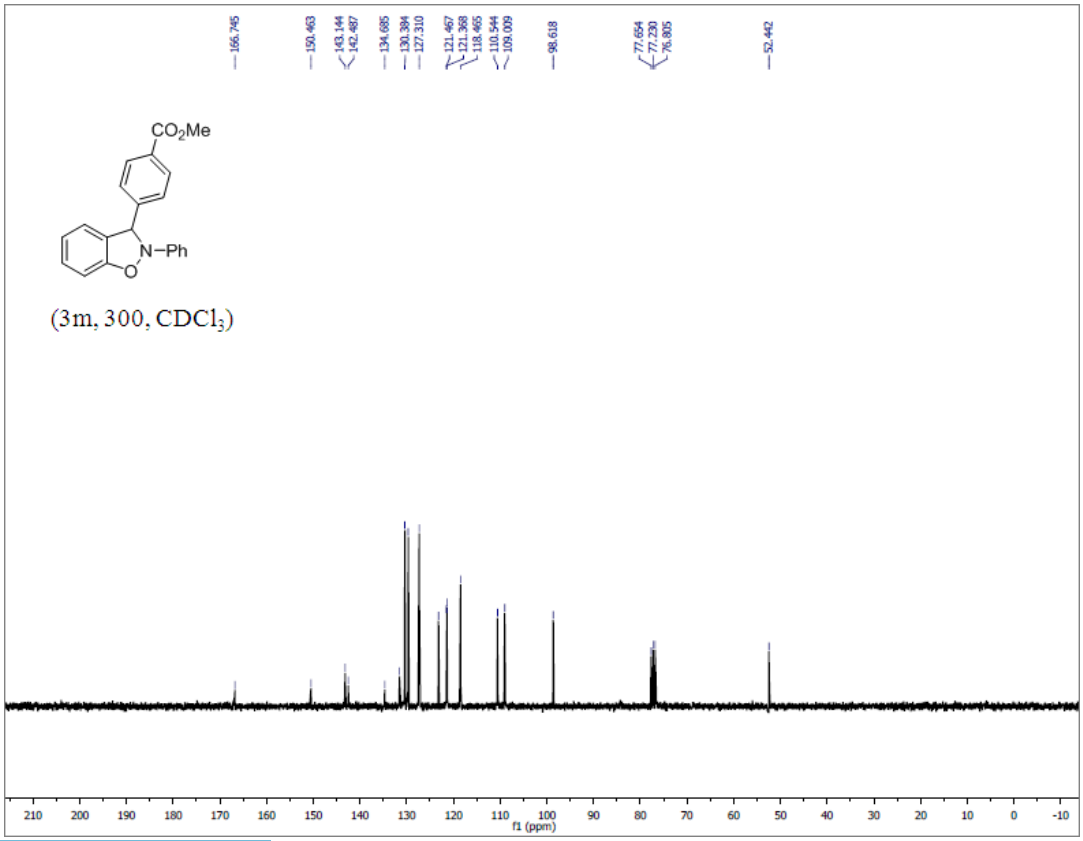

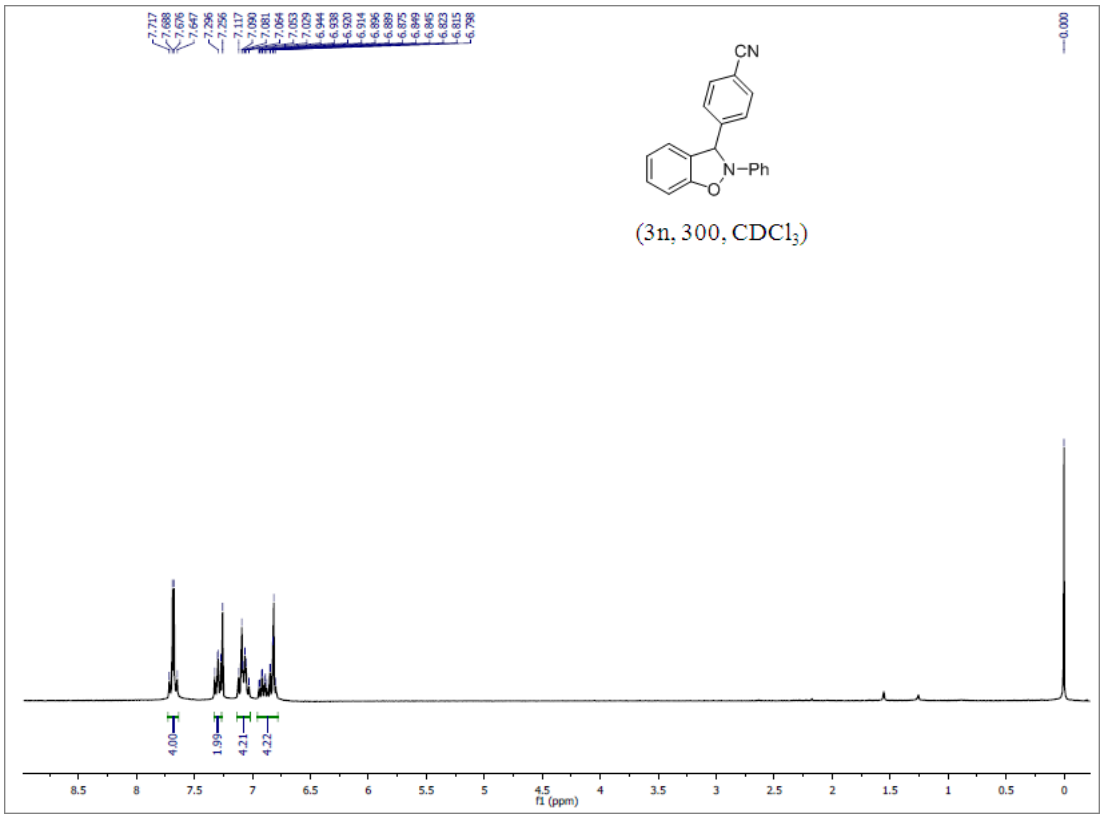

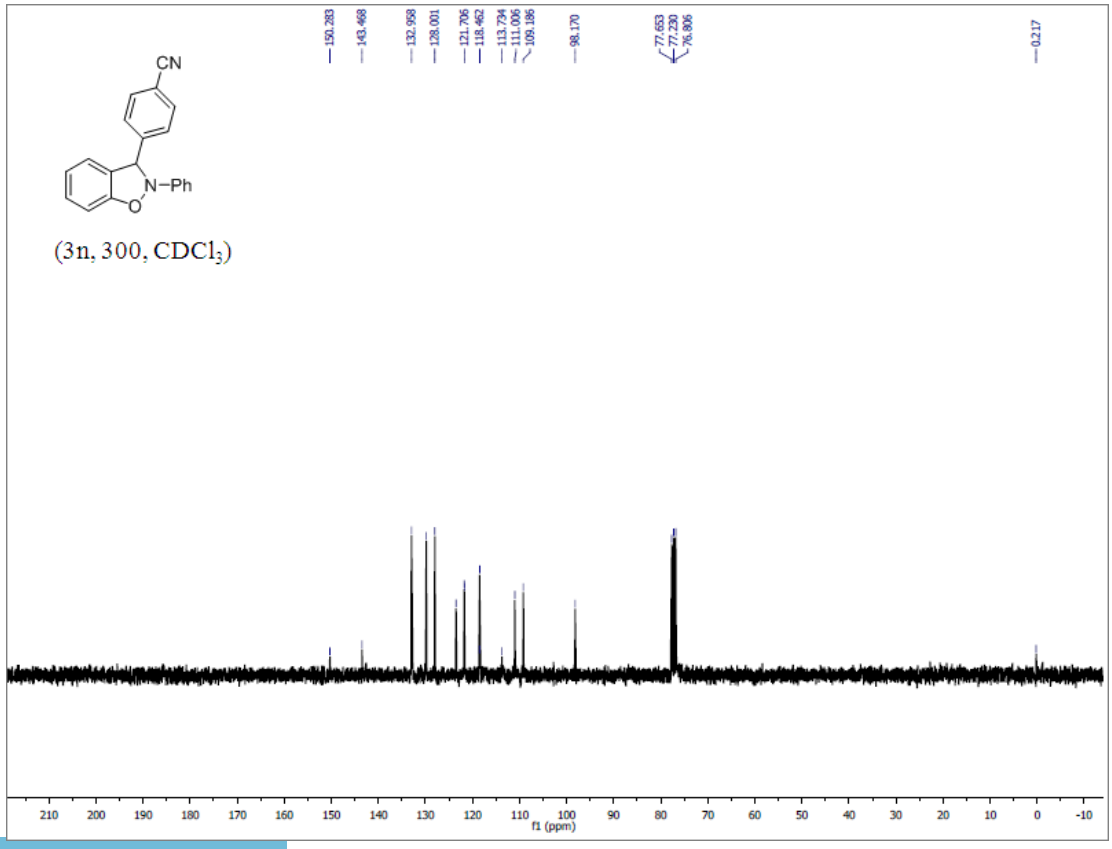

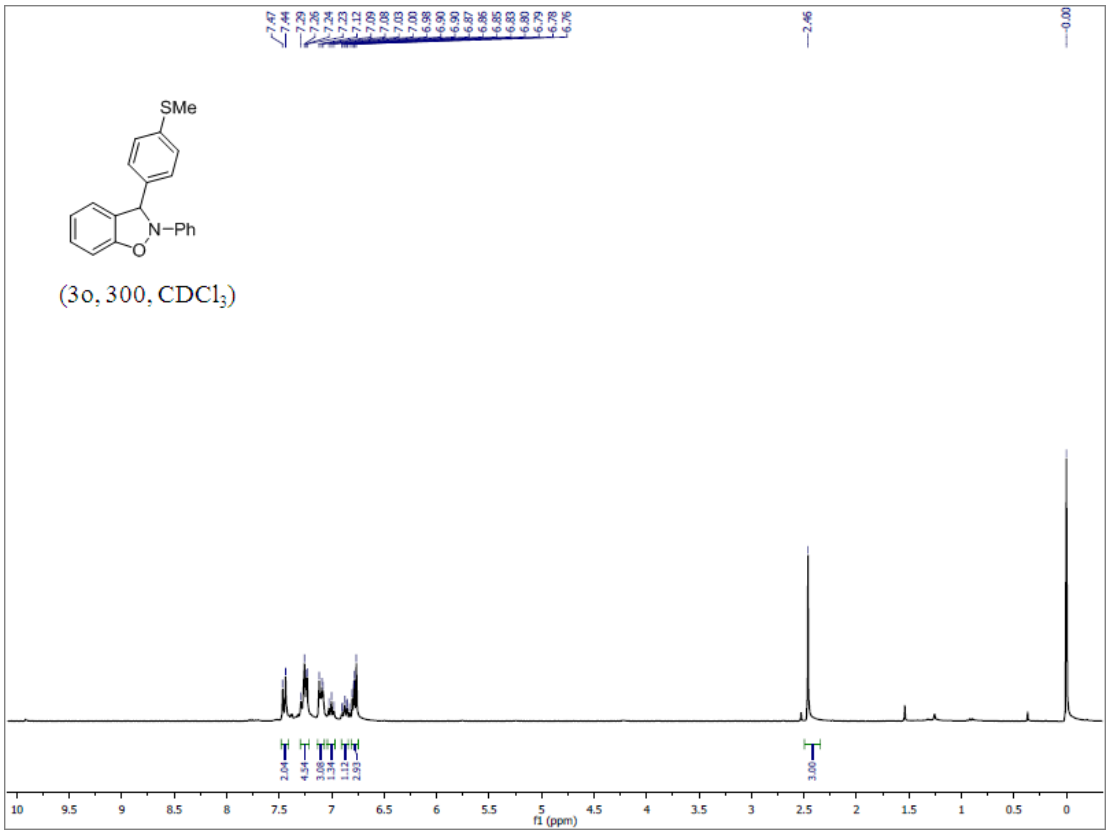

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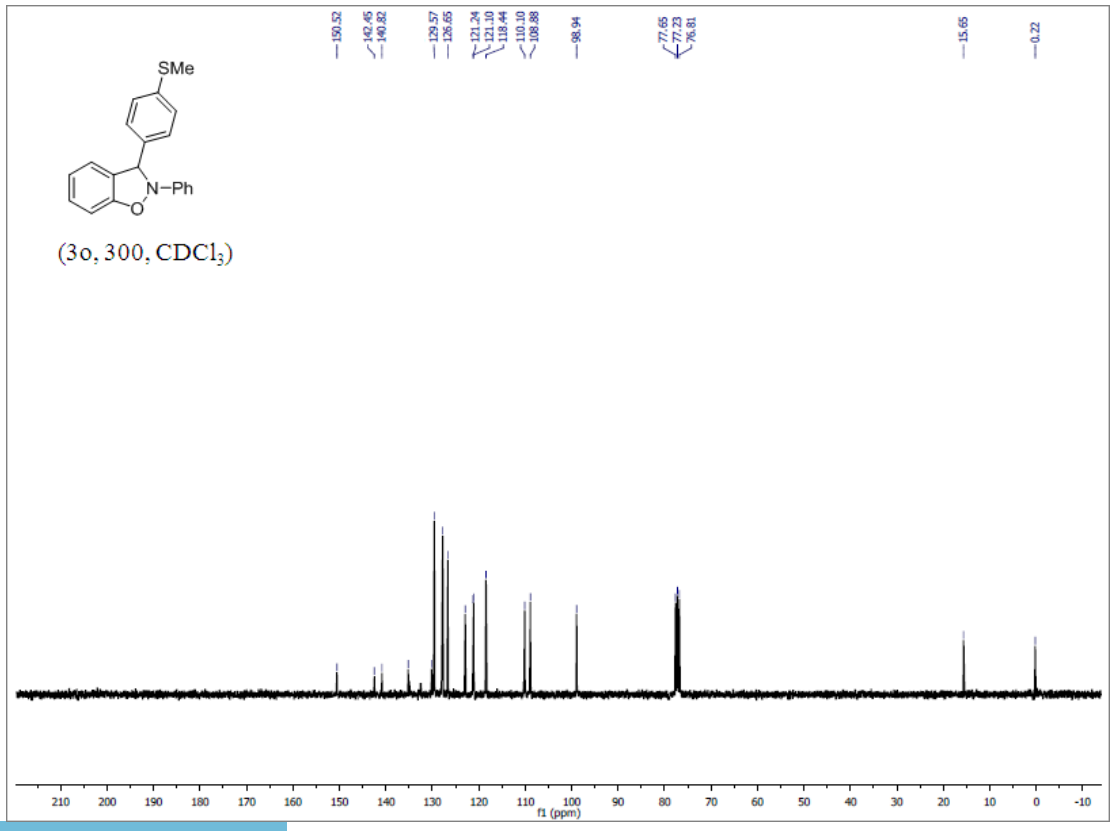

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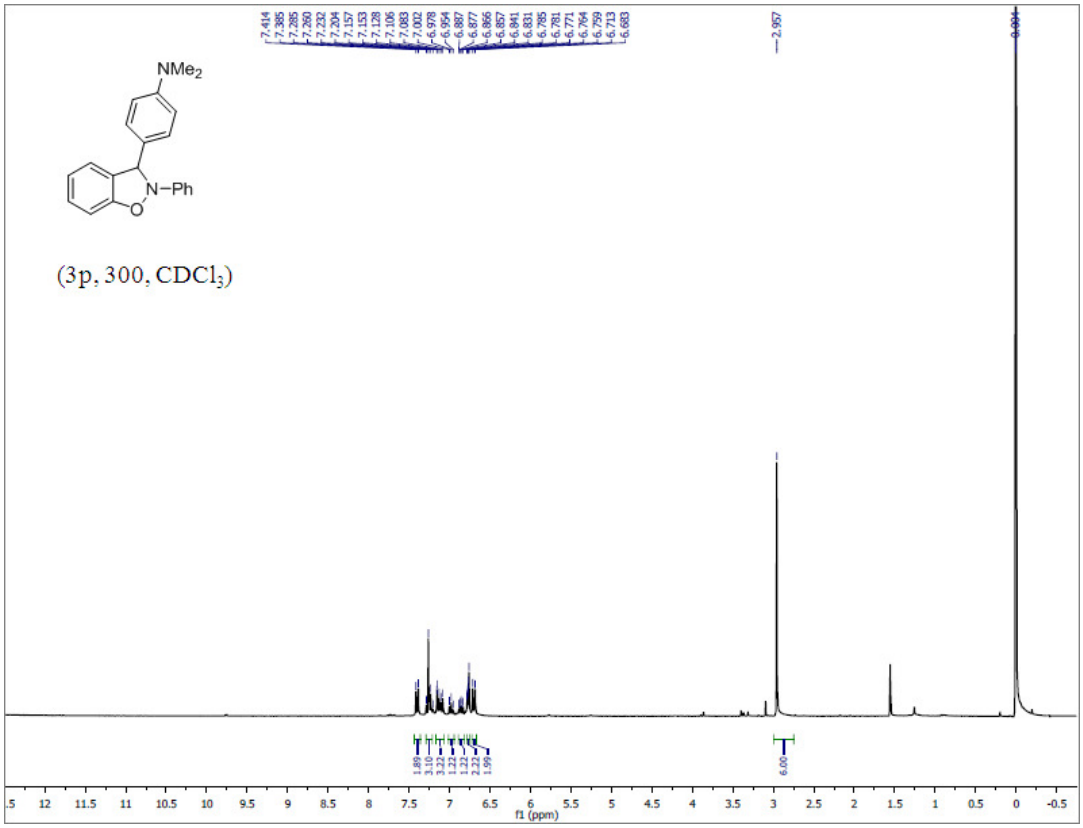

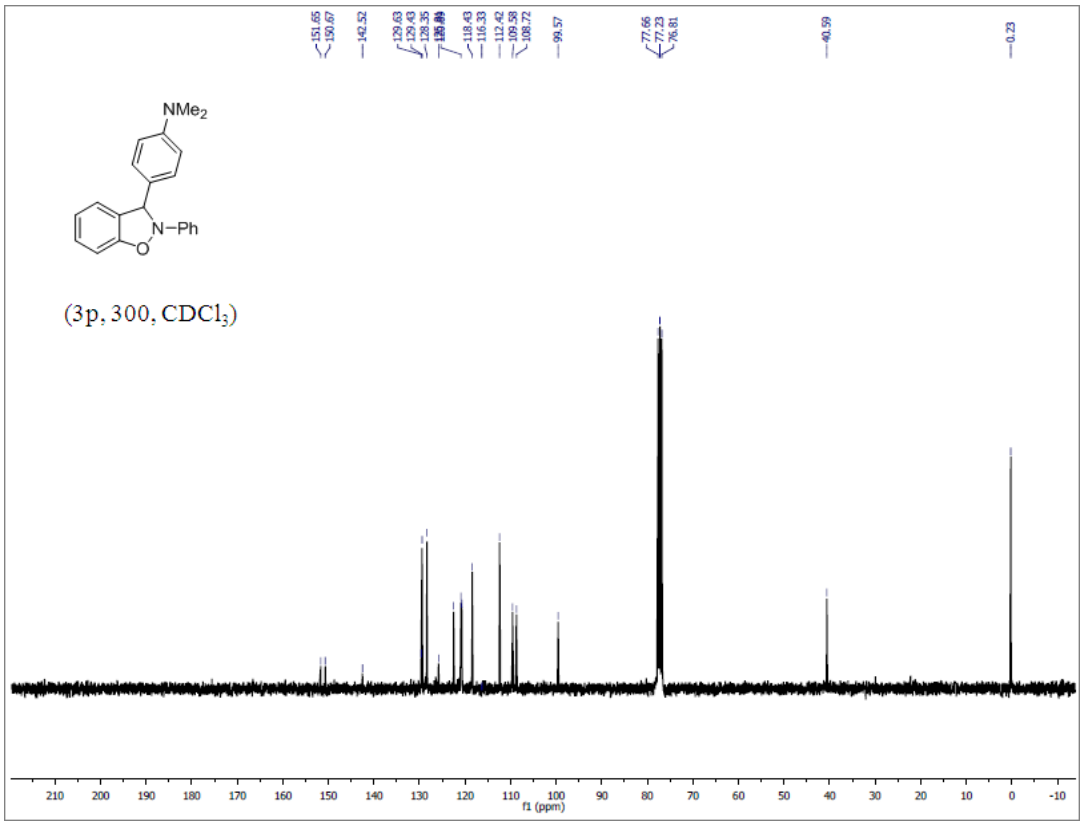

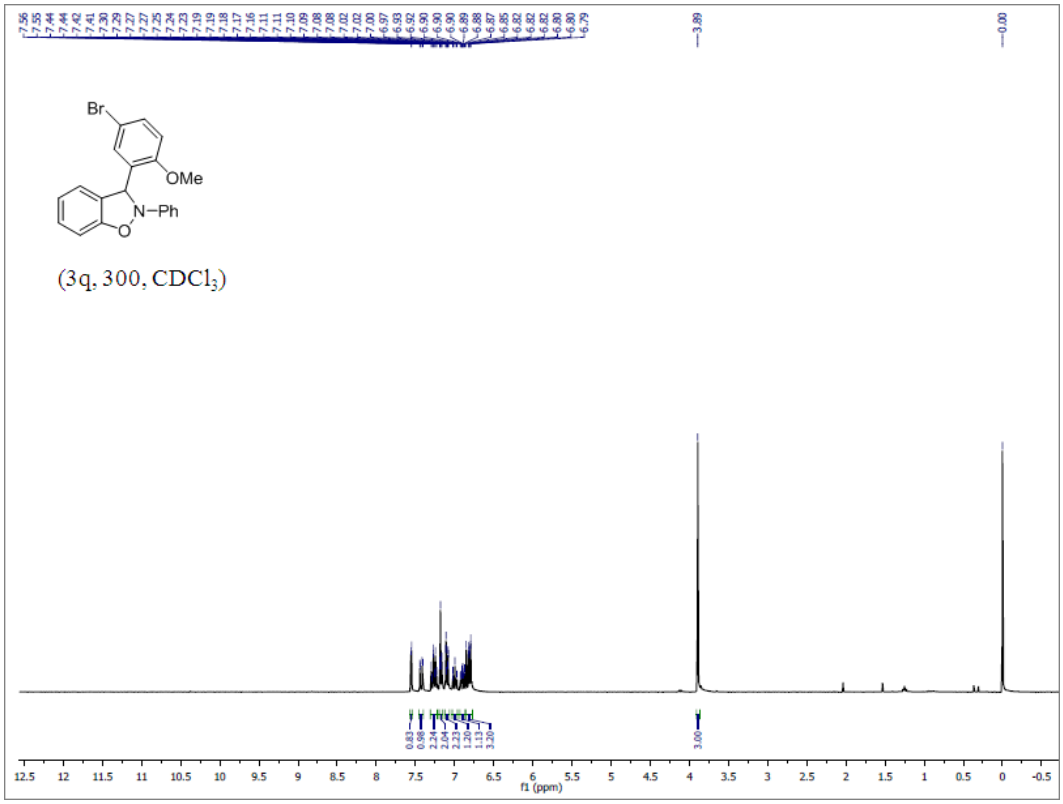

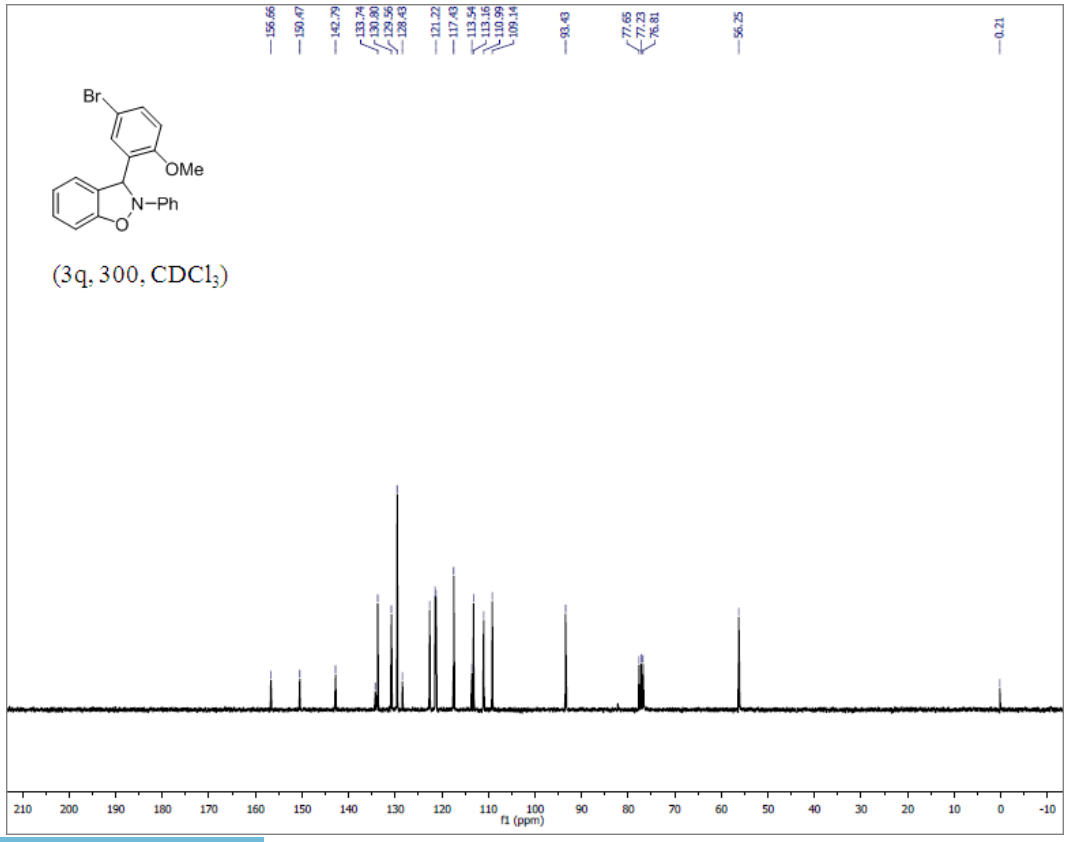

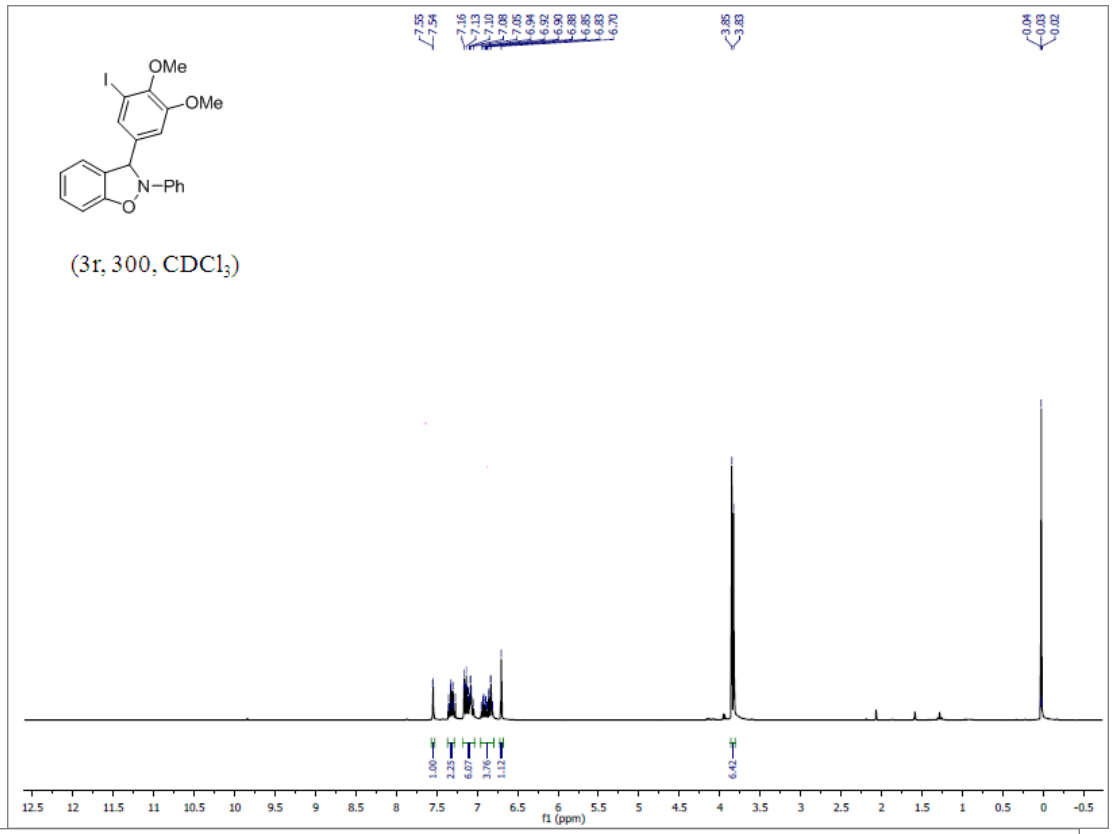

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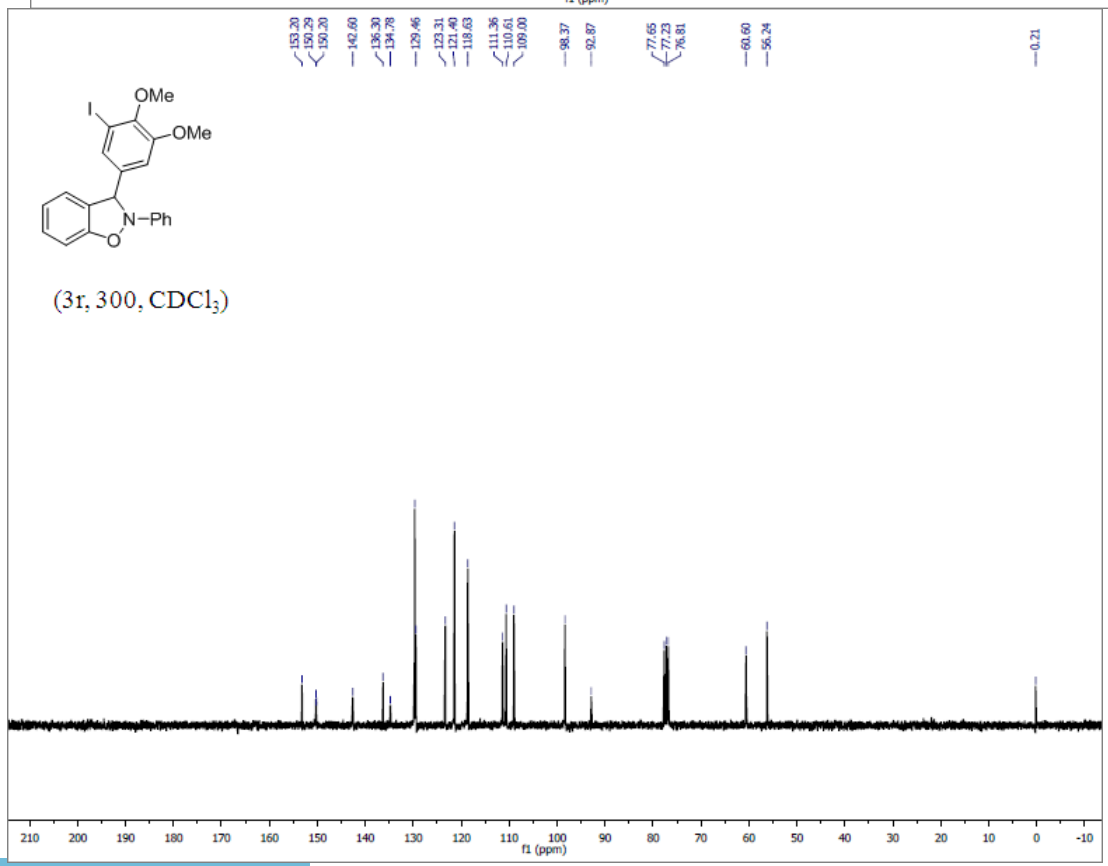

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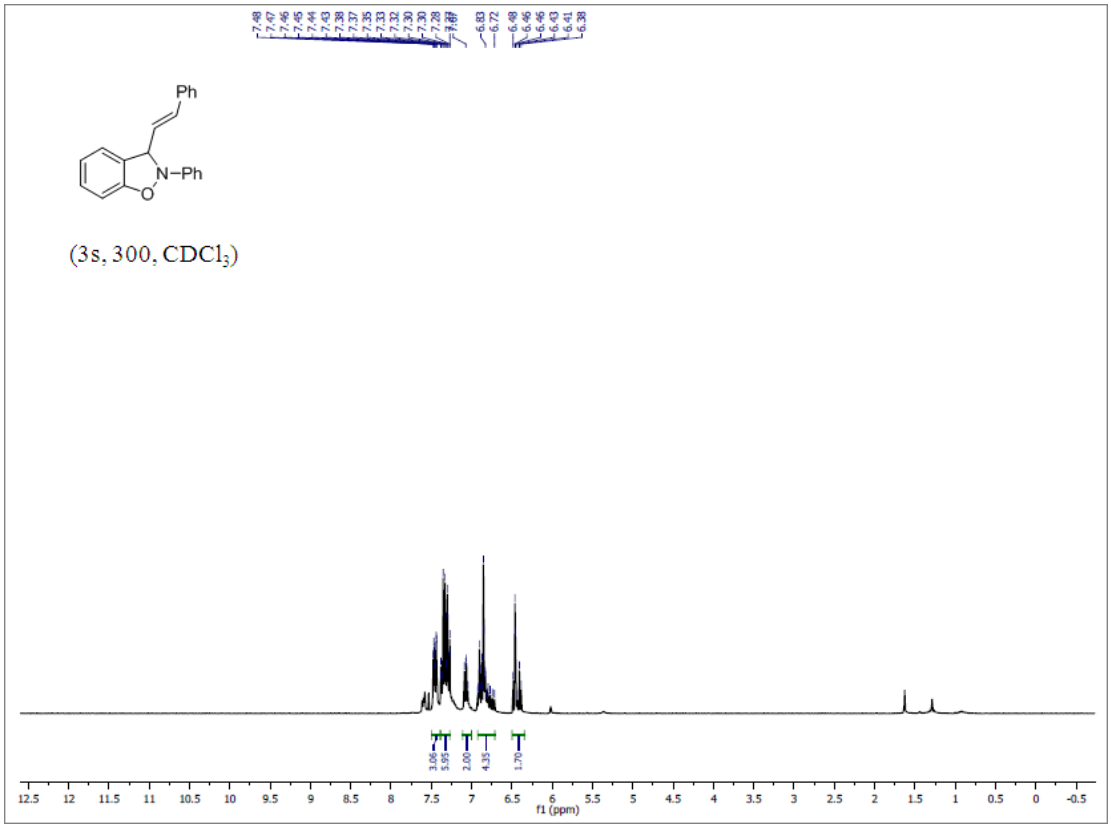
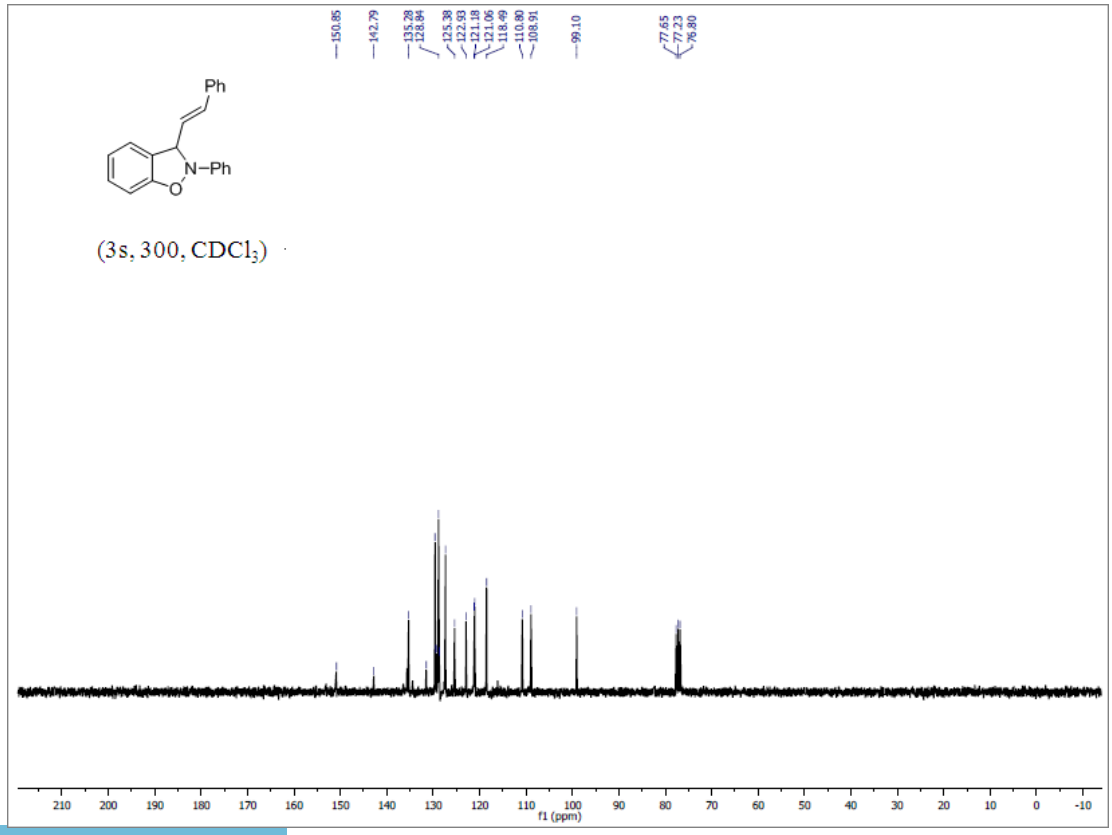
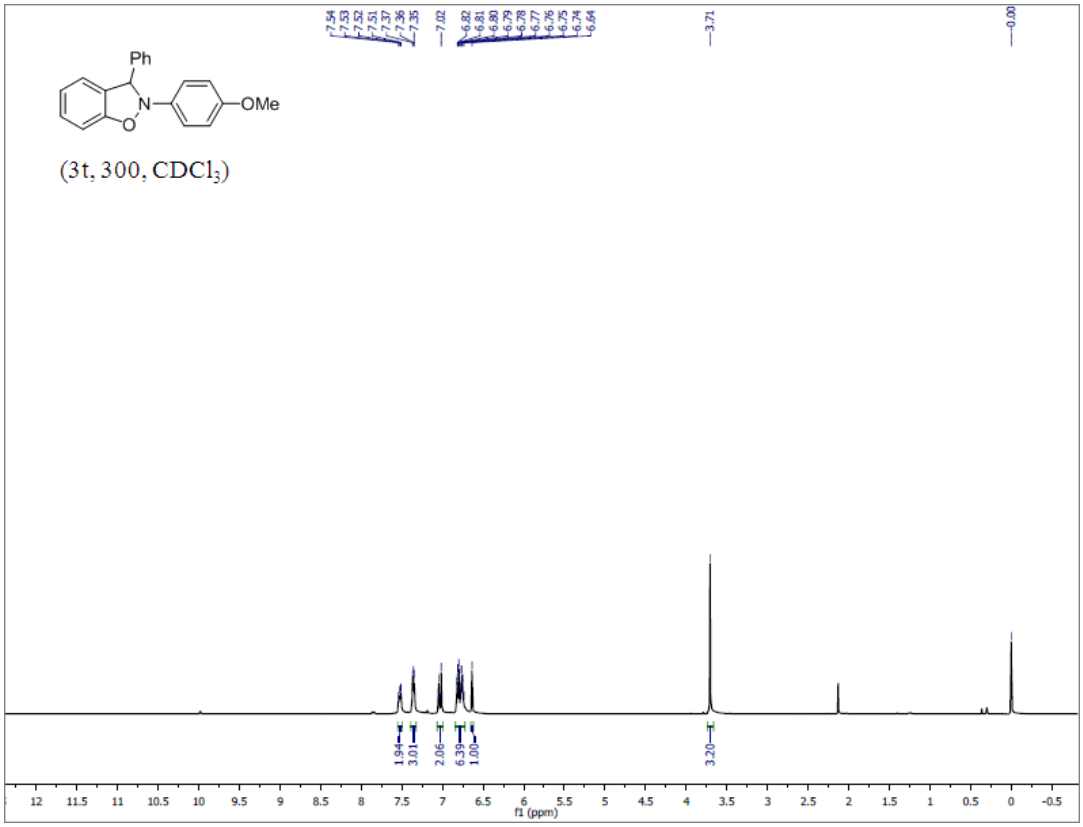
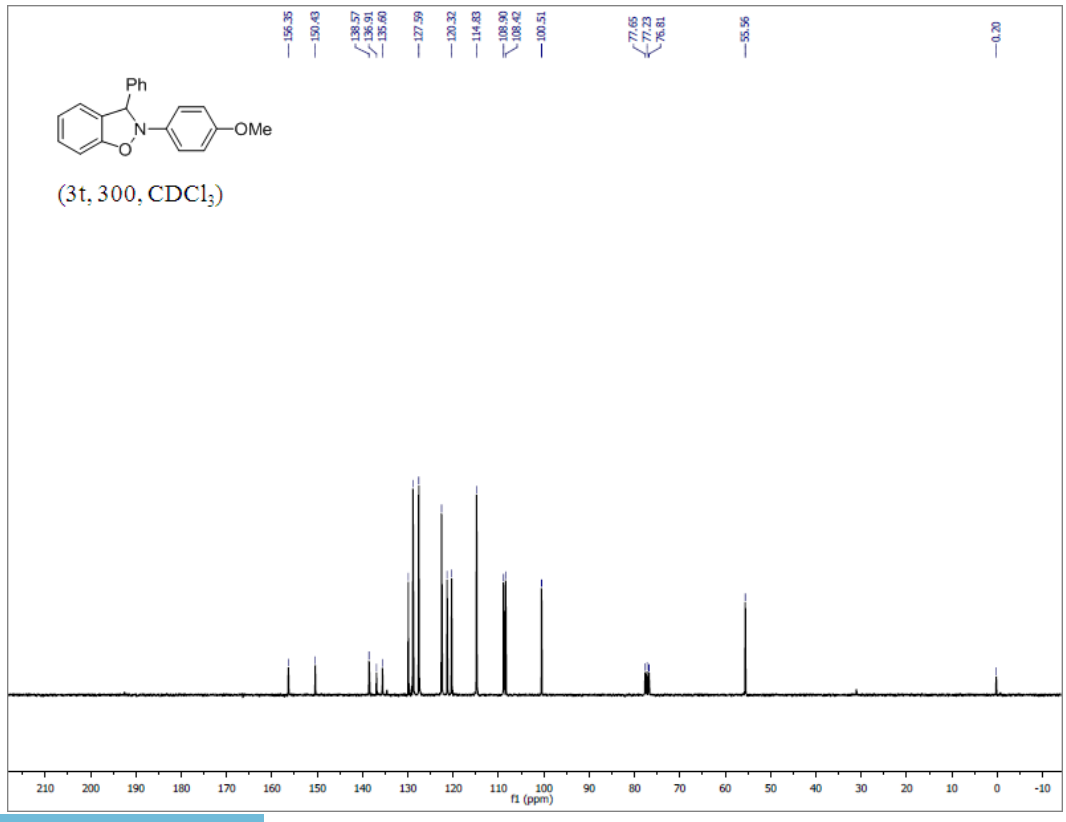
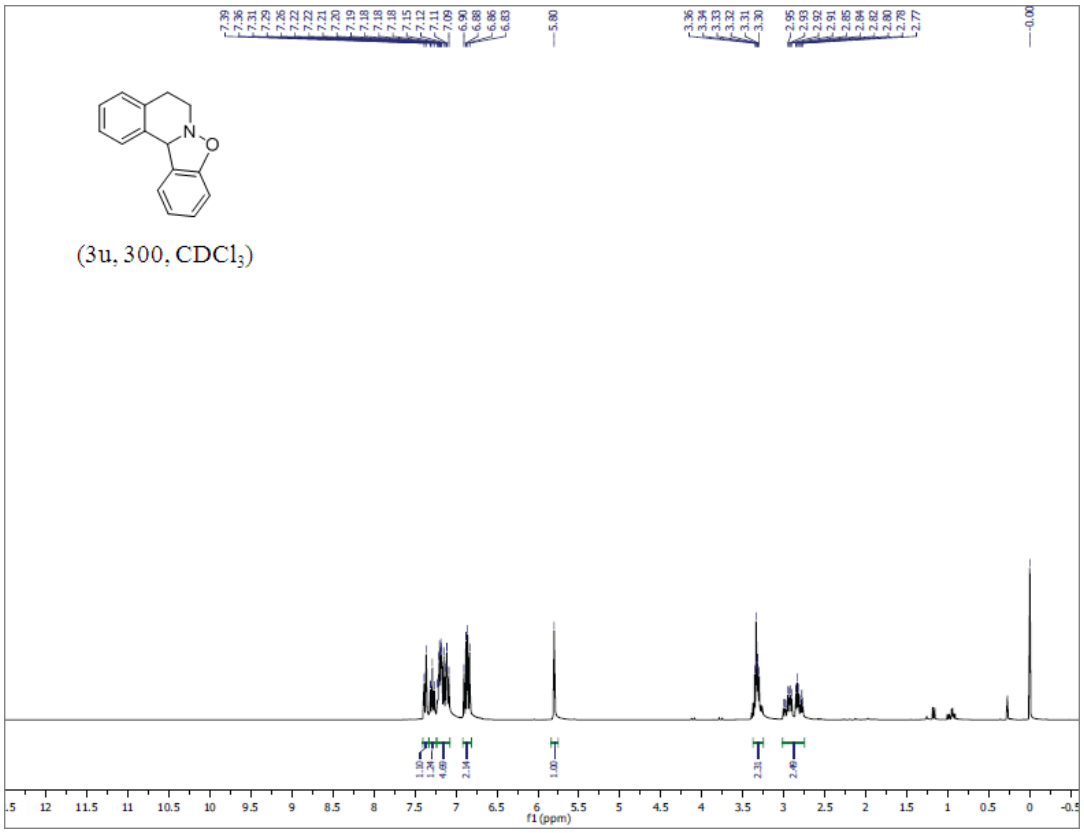


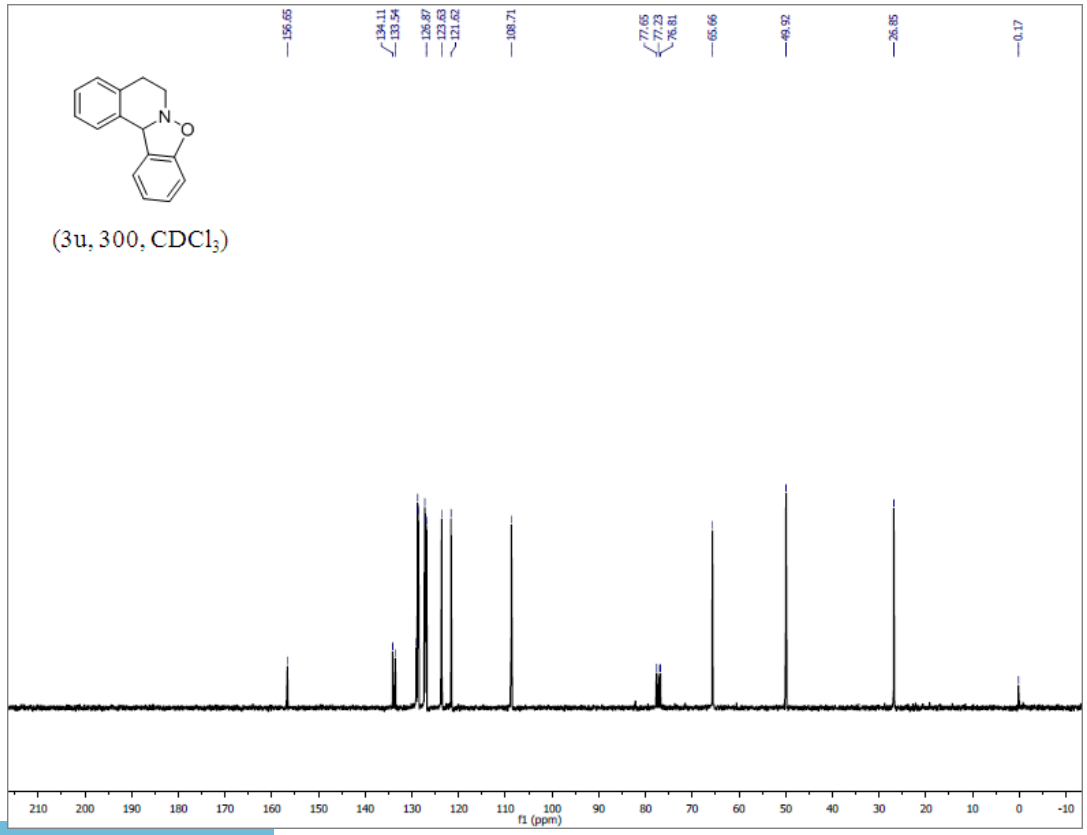




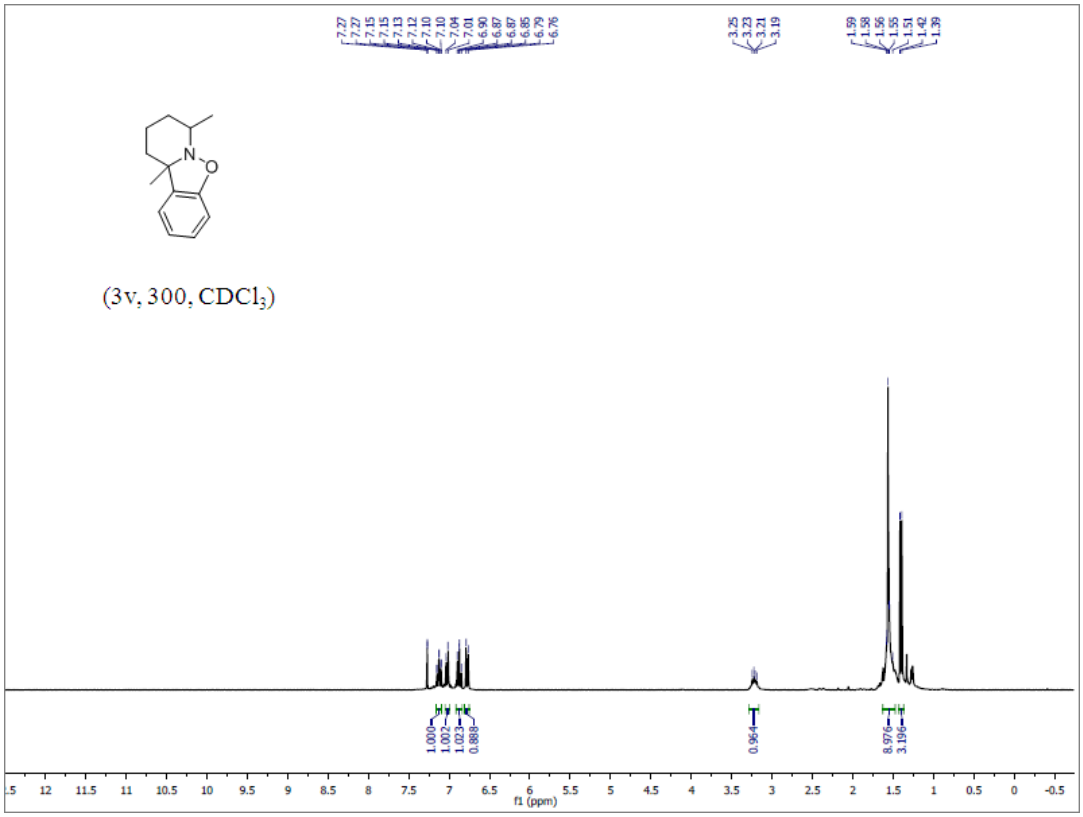




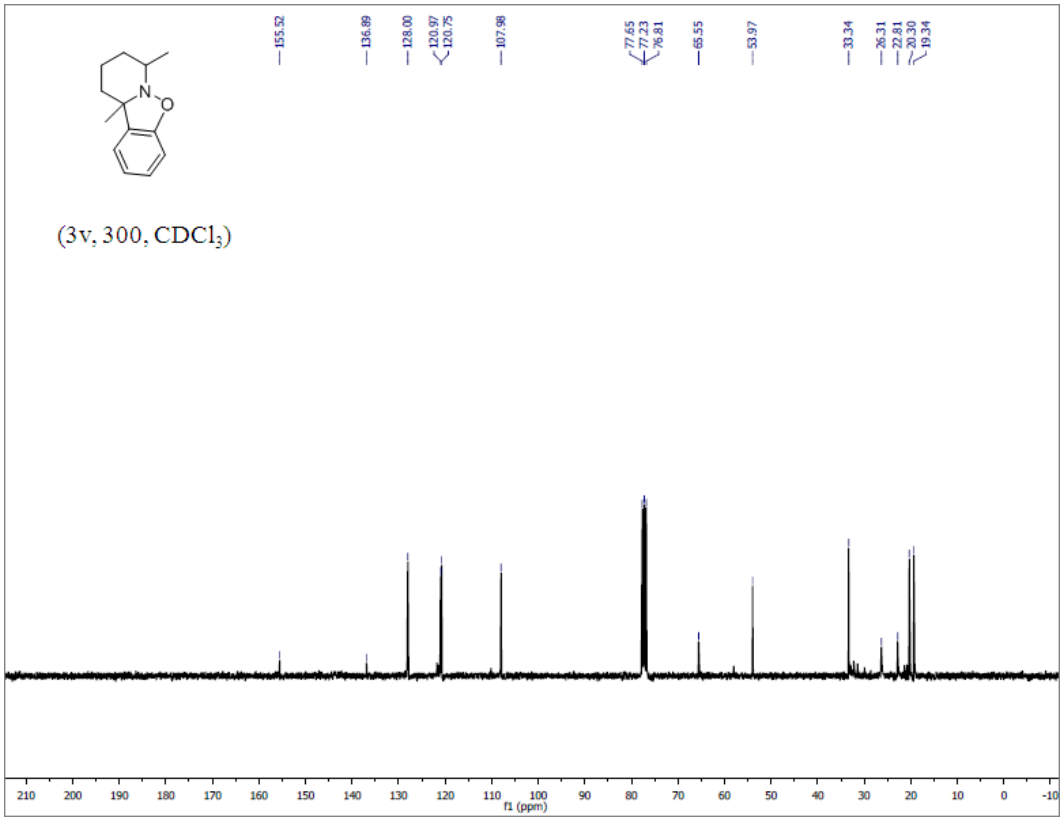
(3u, 300, $CDCl_3$)



(3u, 300, $CDCl_3$)



(3v, 300, $CDCl_3$)



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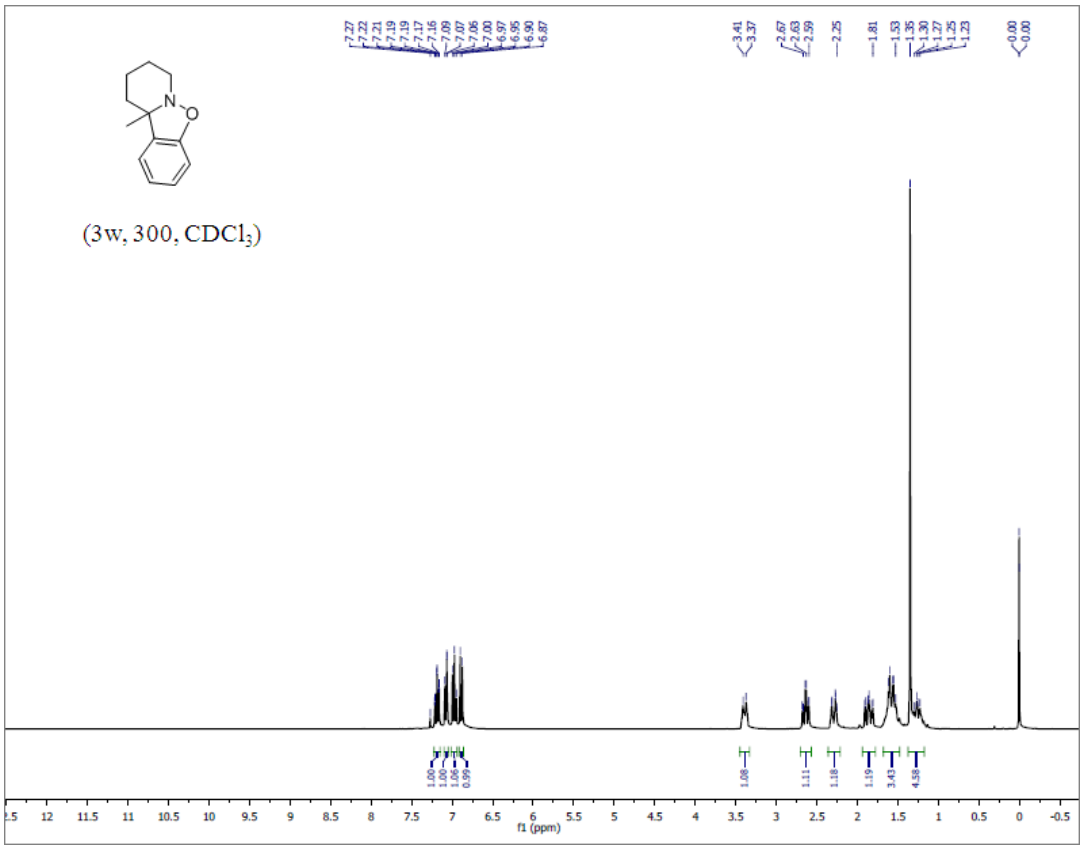
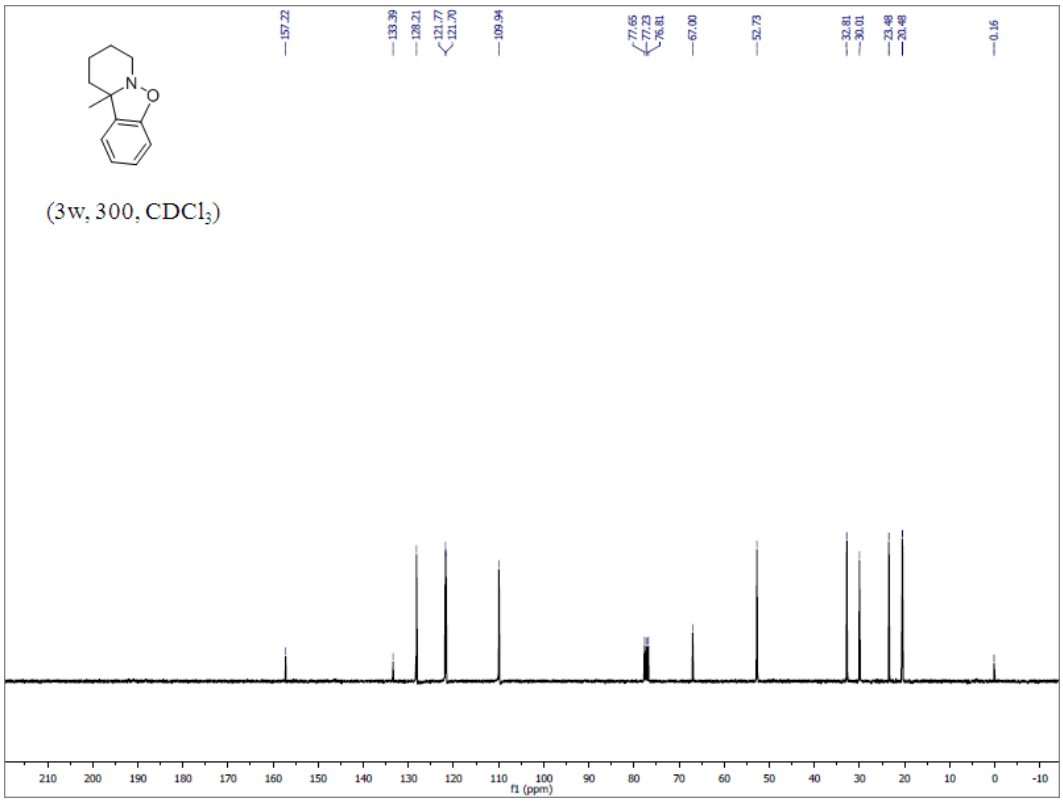
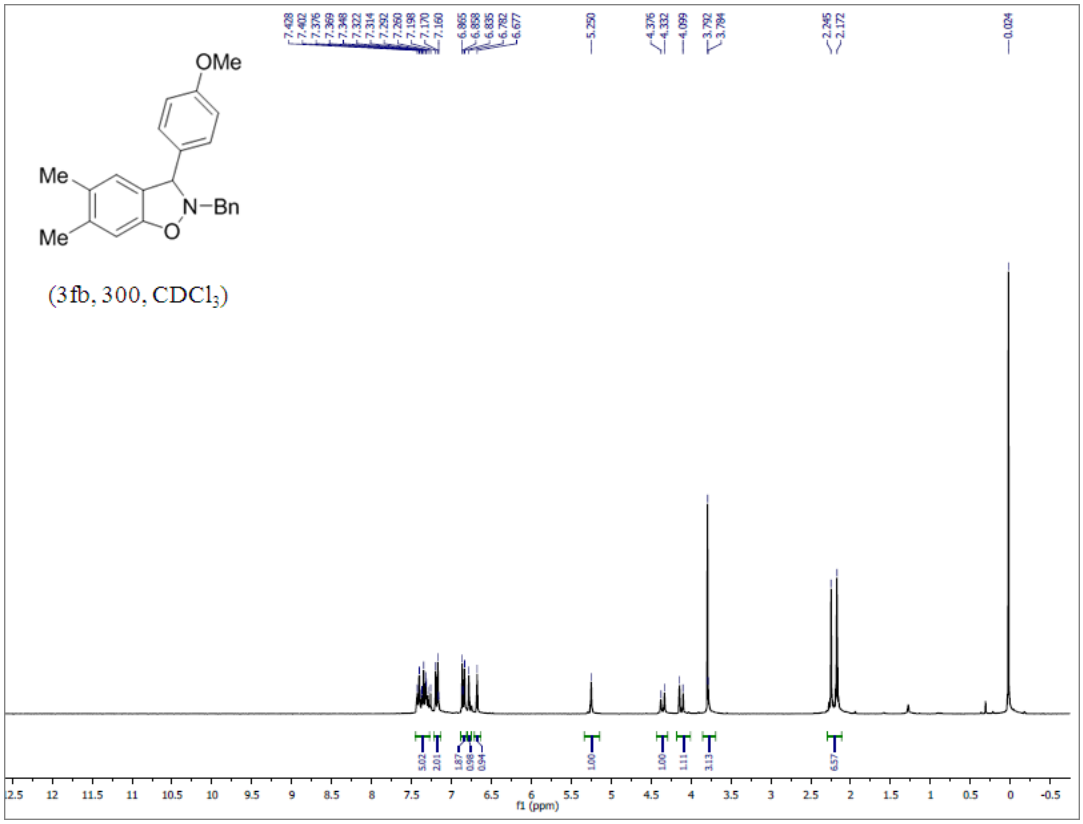
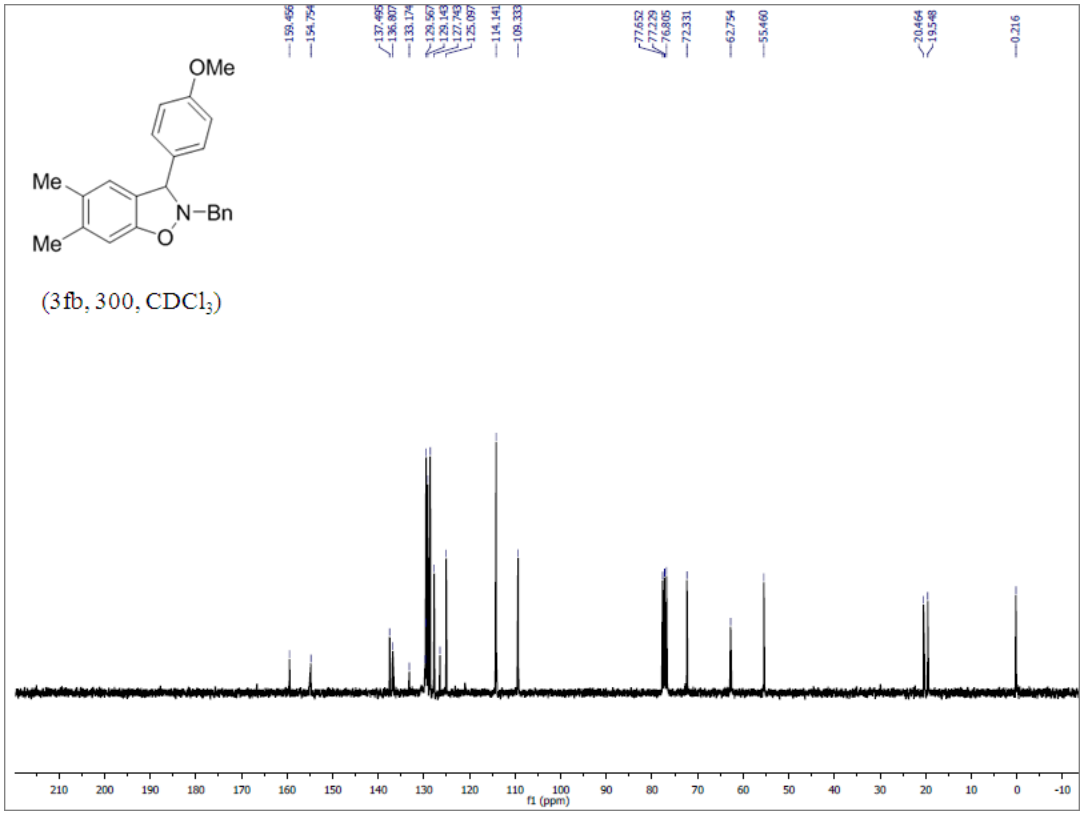
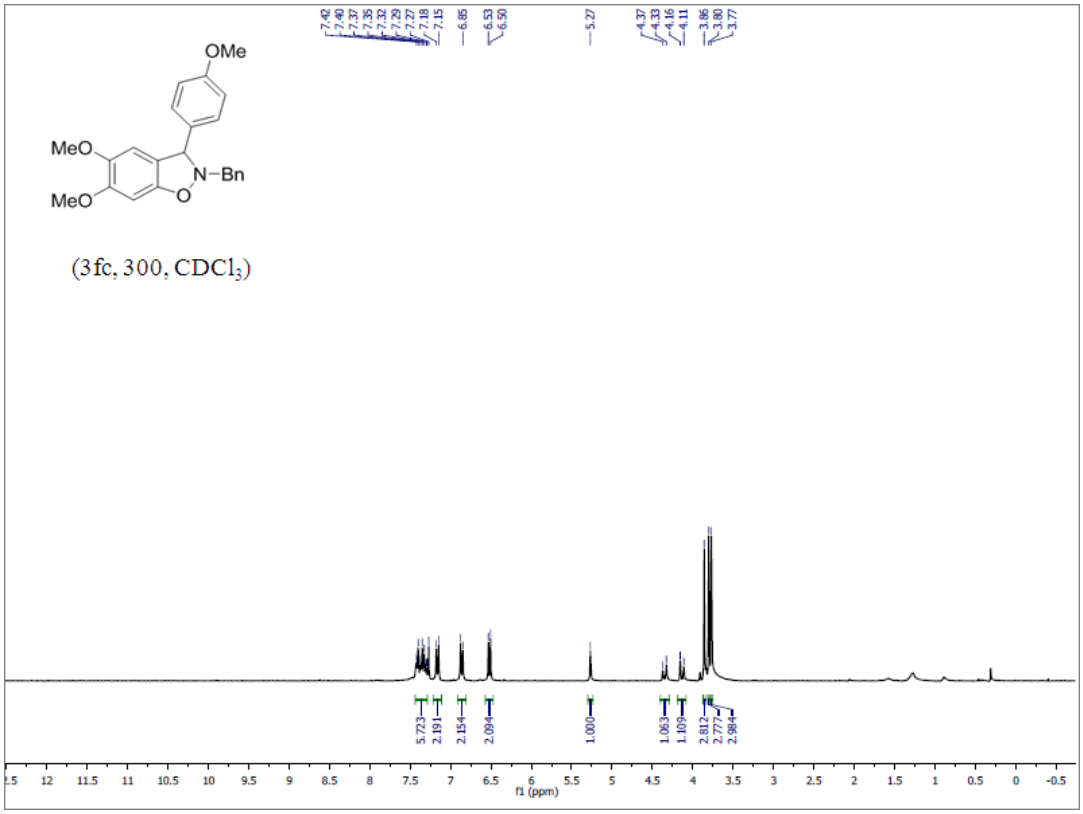
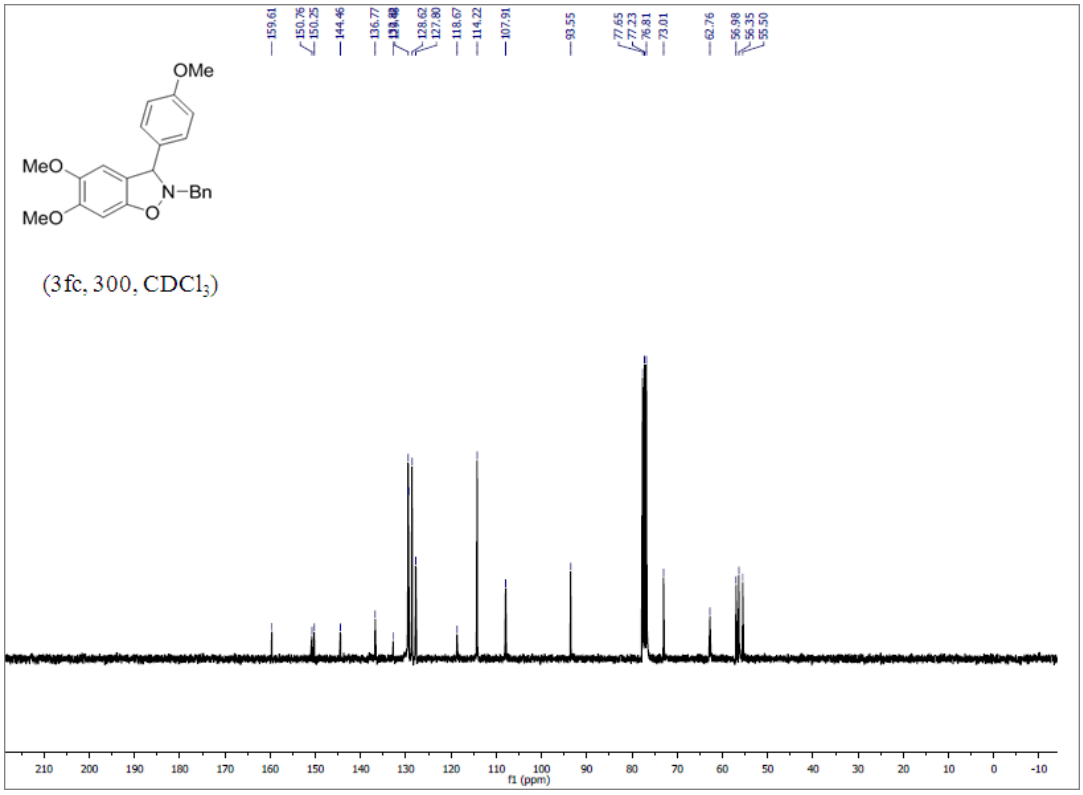


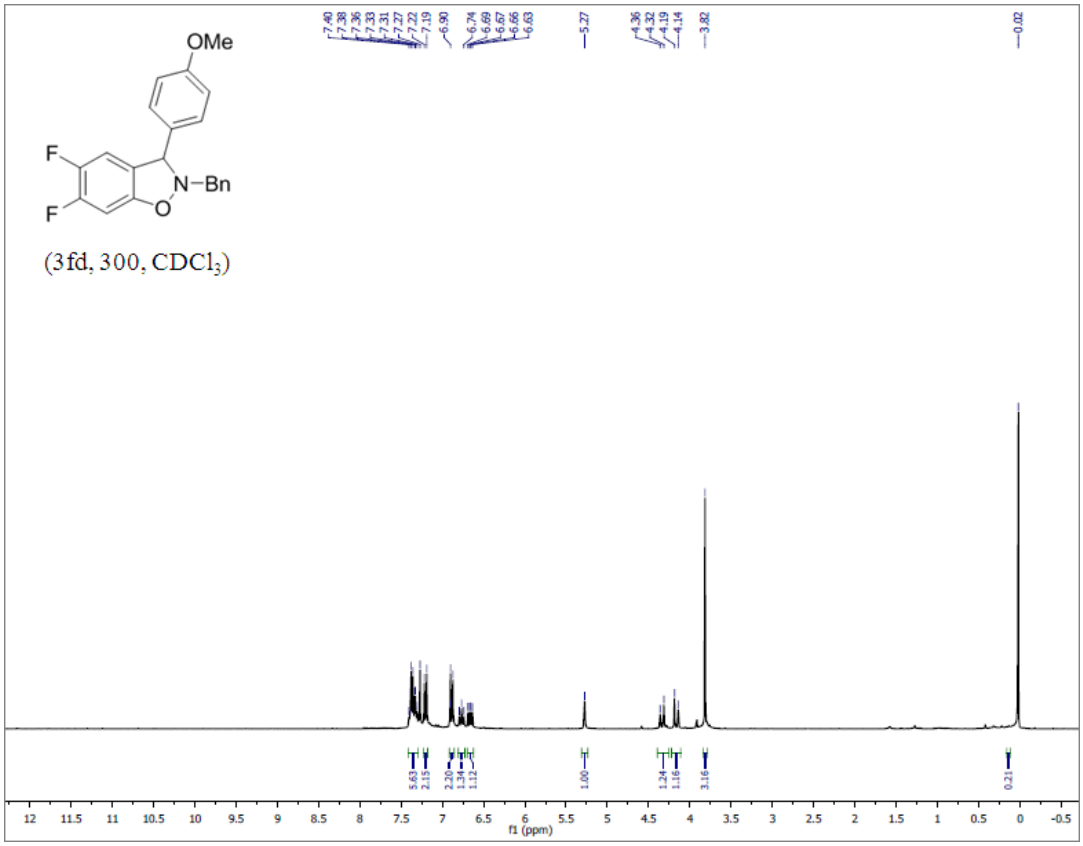




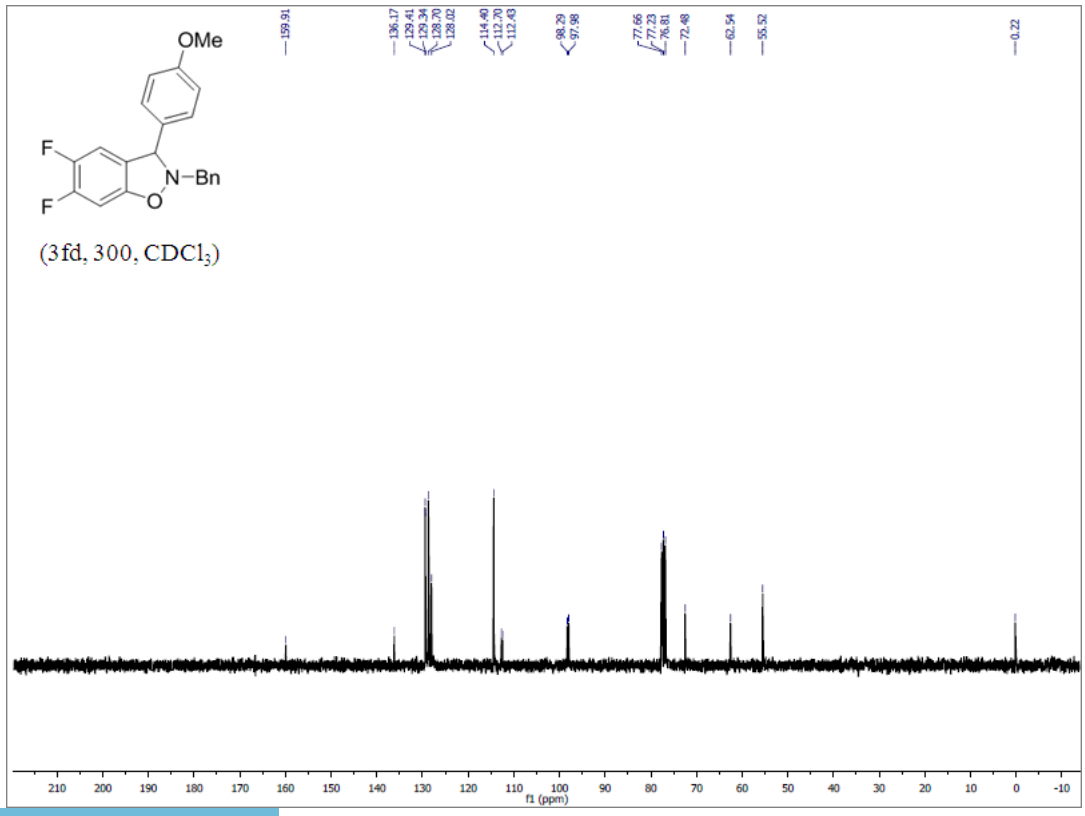






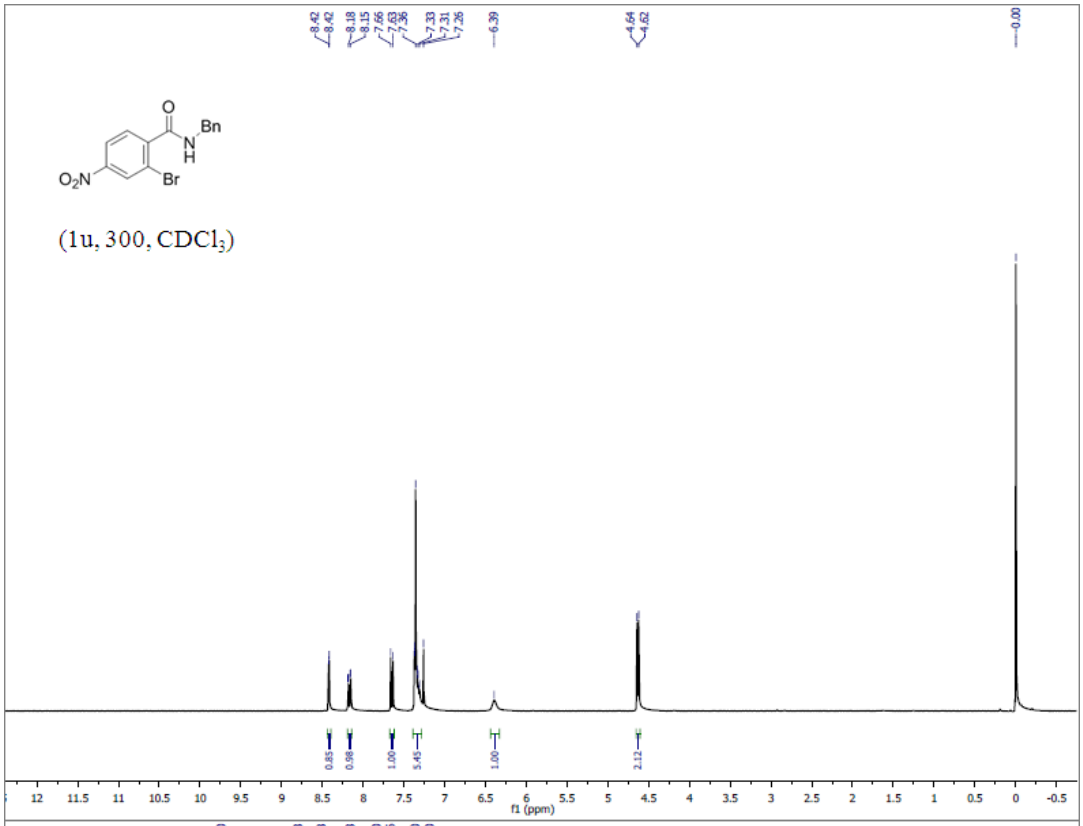


(3fd, 300, $CDCl_3$)

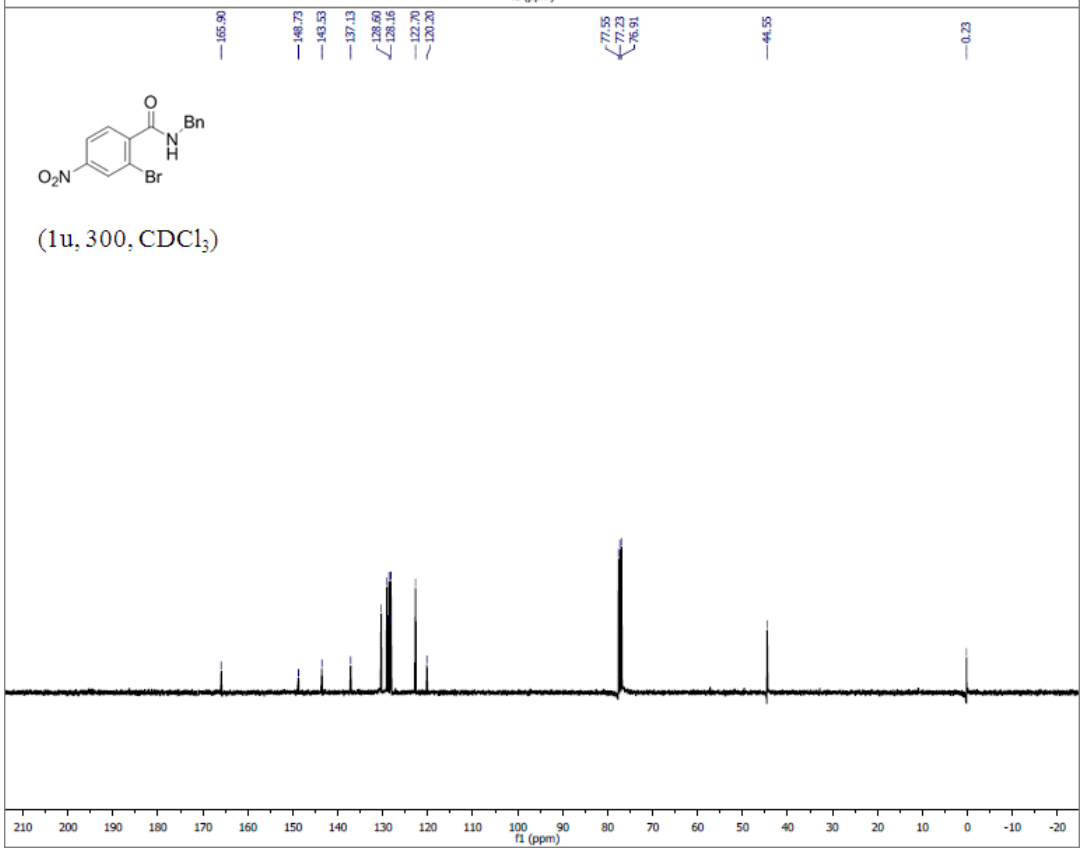


(3fd, 300, $CDCl_3$)

APPENDIX C. CHAPTER 3 ^{1}H AND ^{13}C NMR SPECTRA



(1u, 300, $CDCl_3$)



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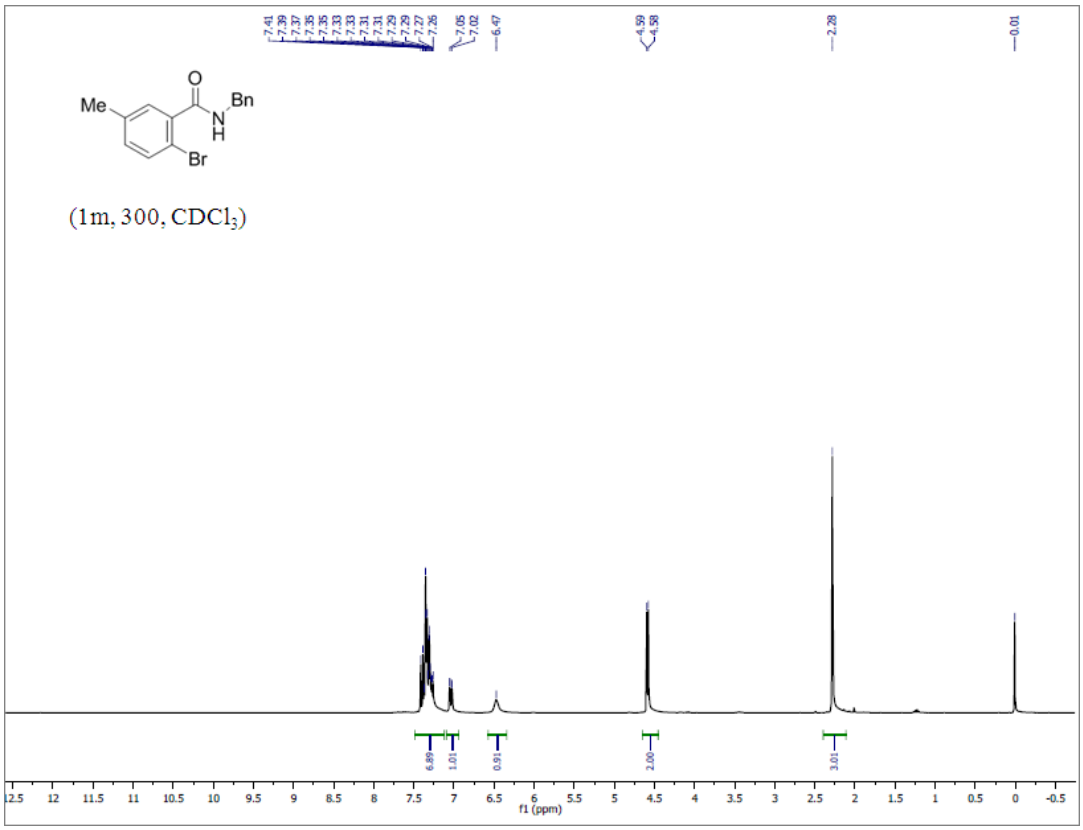
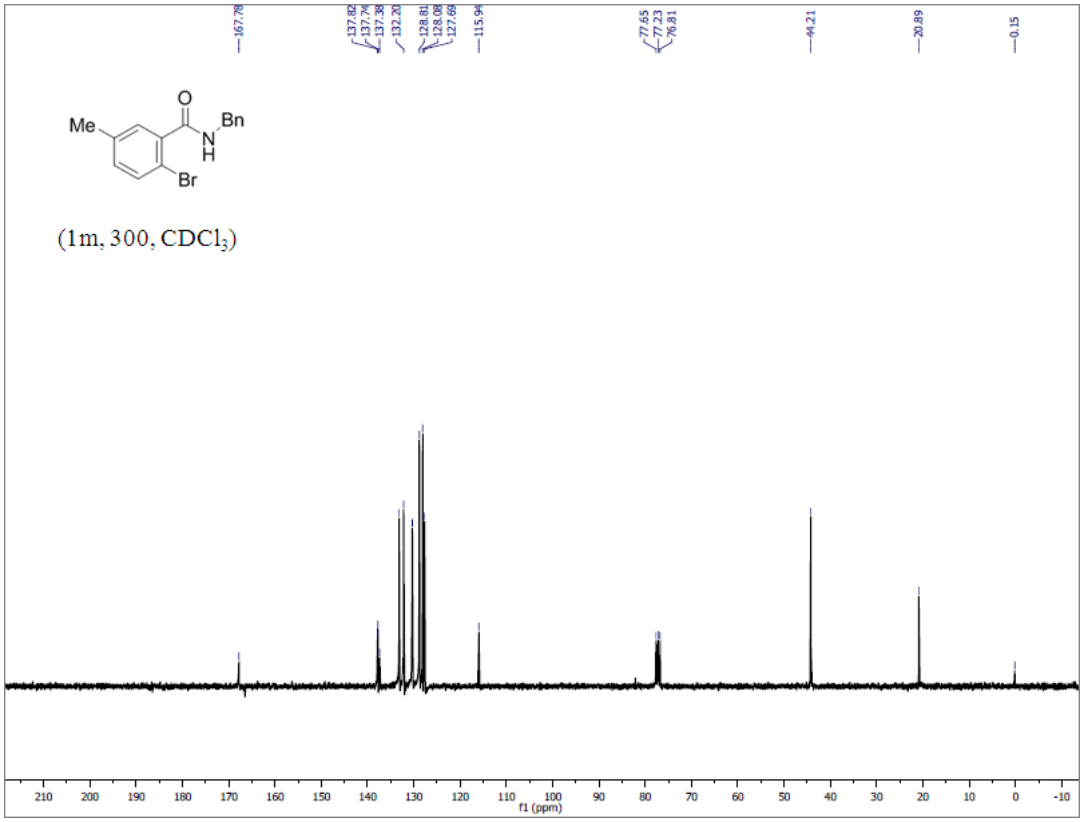
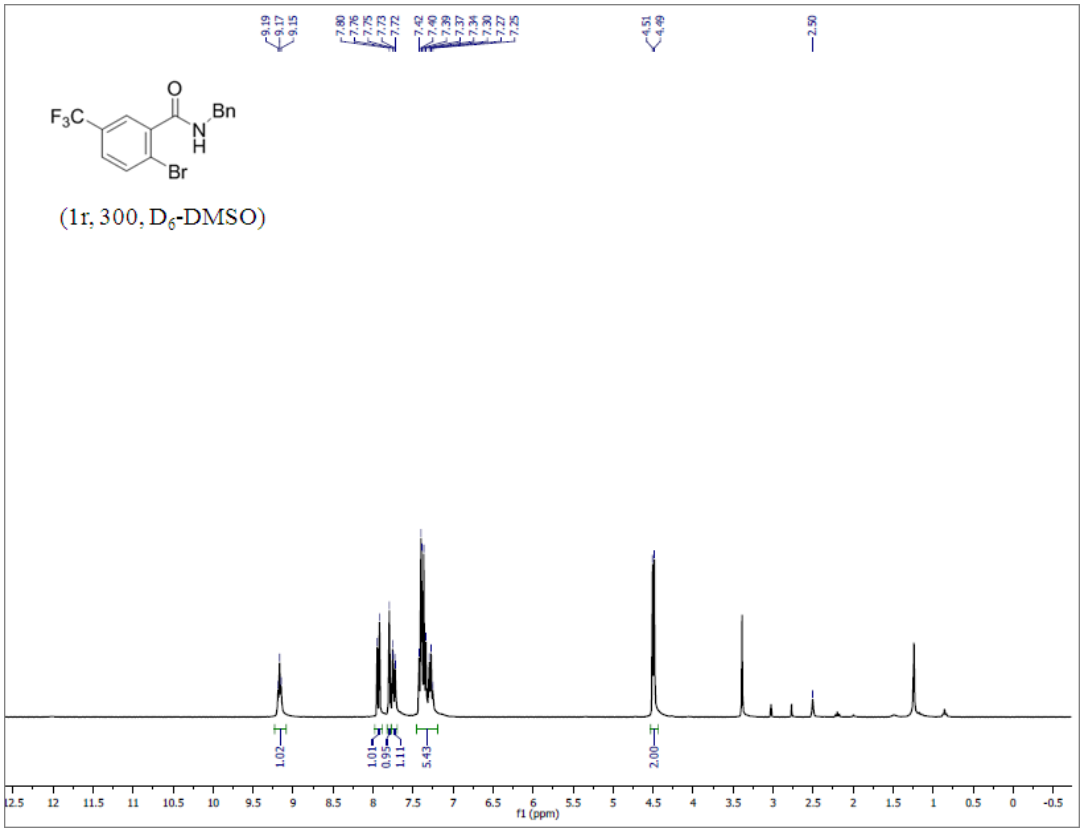
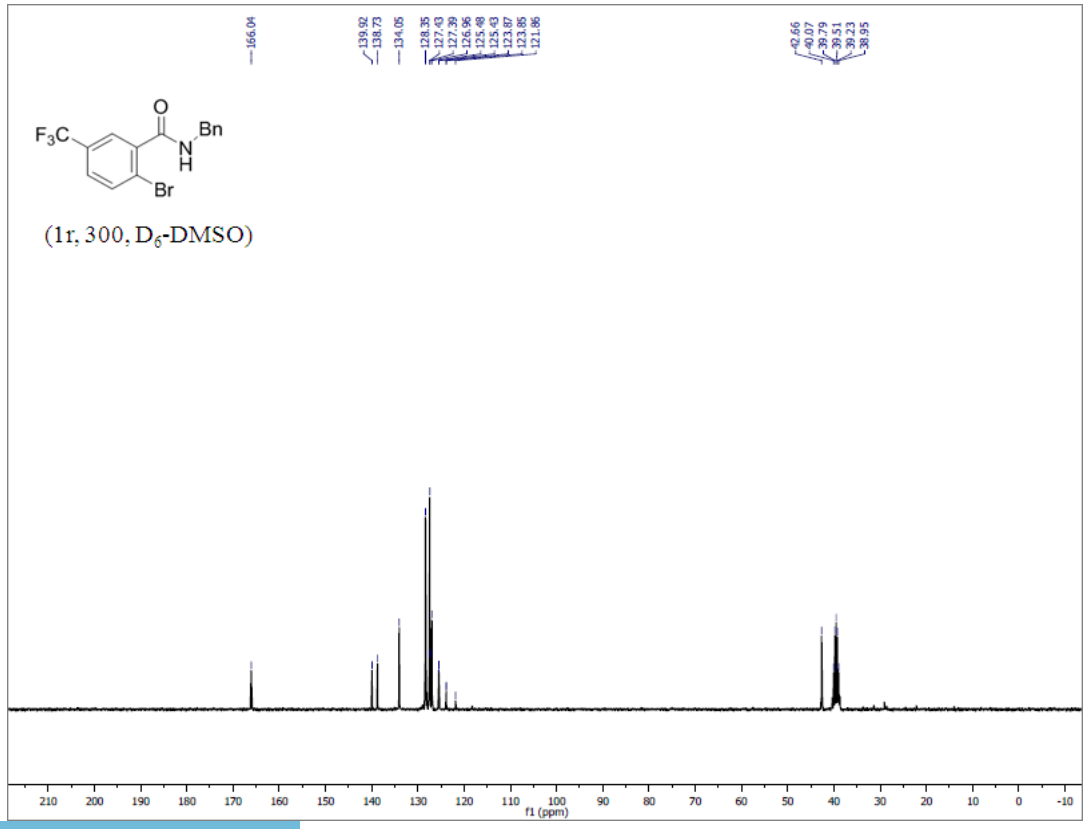






(1r, 300, D_6-DMSO)



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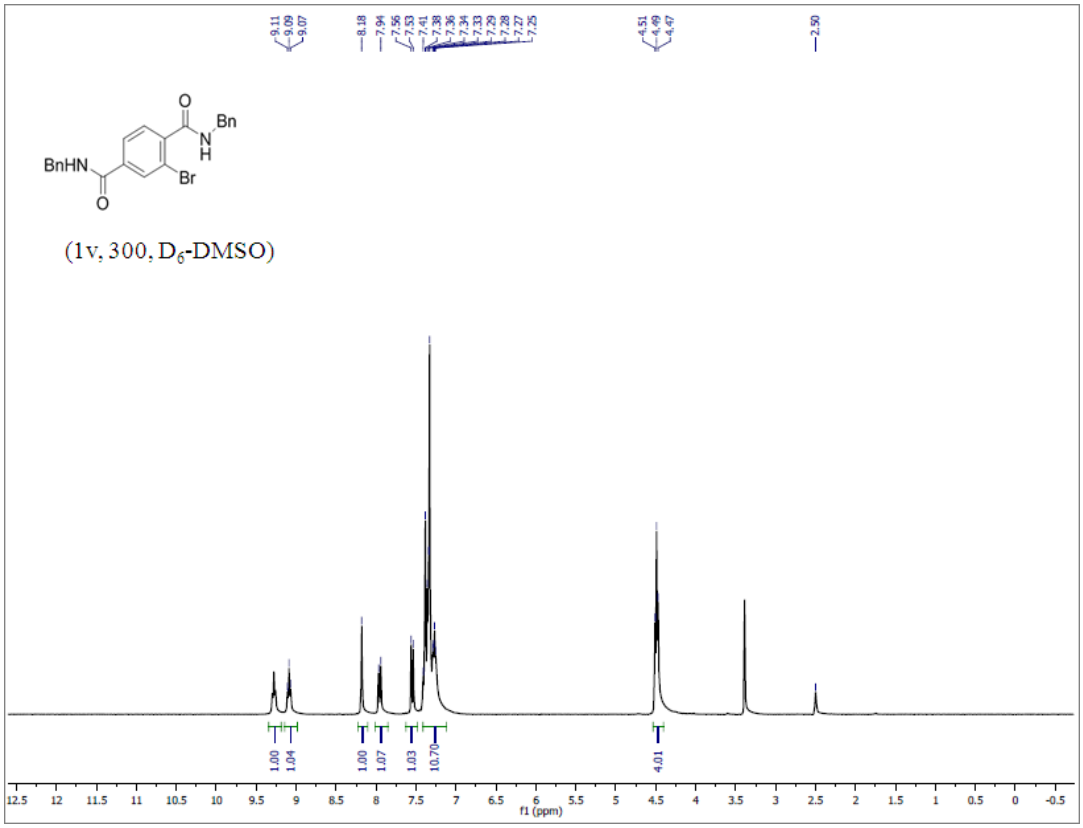
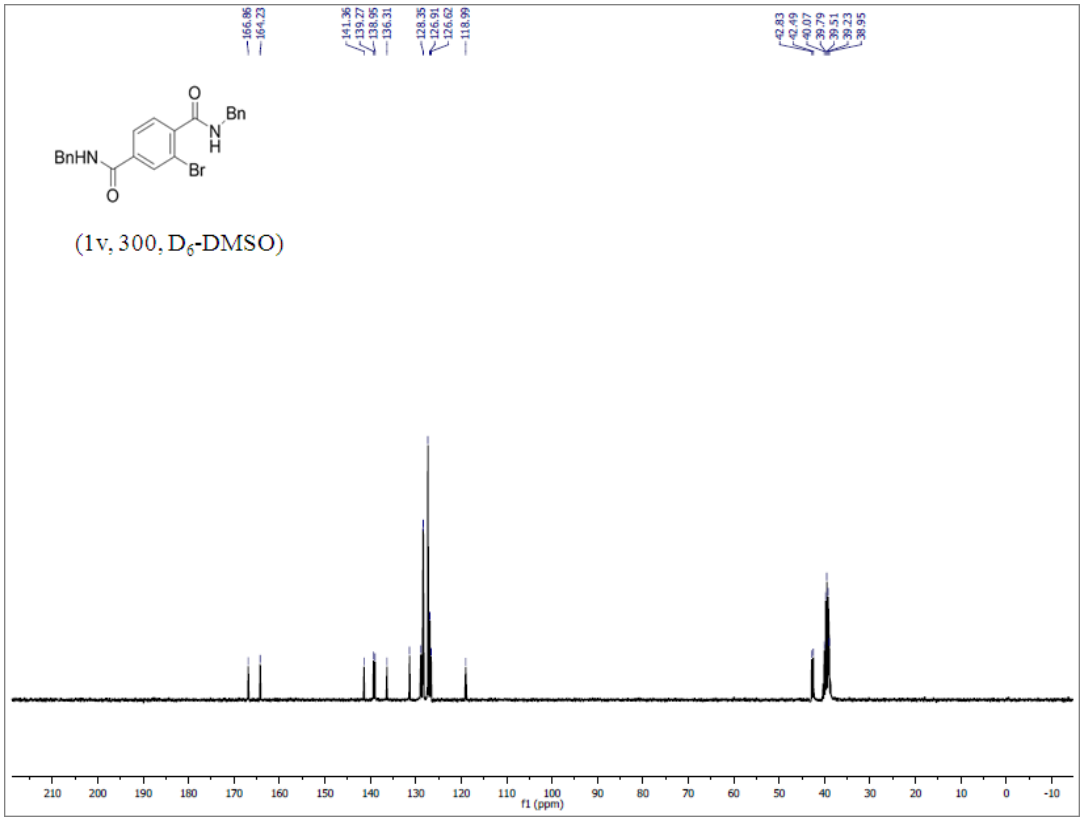
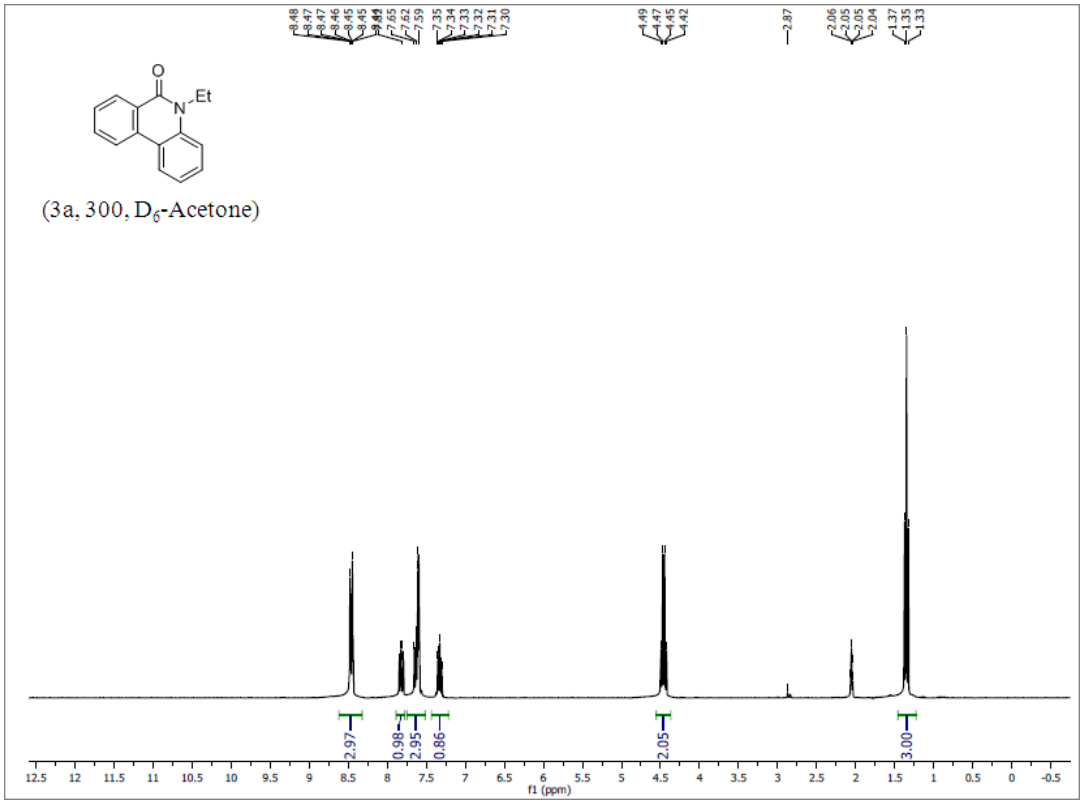
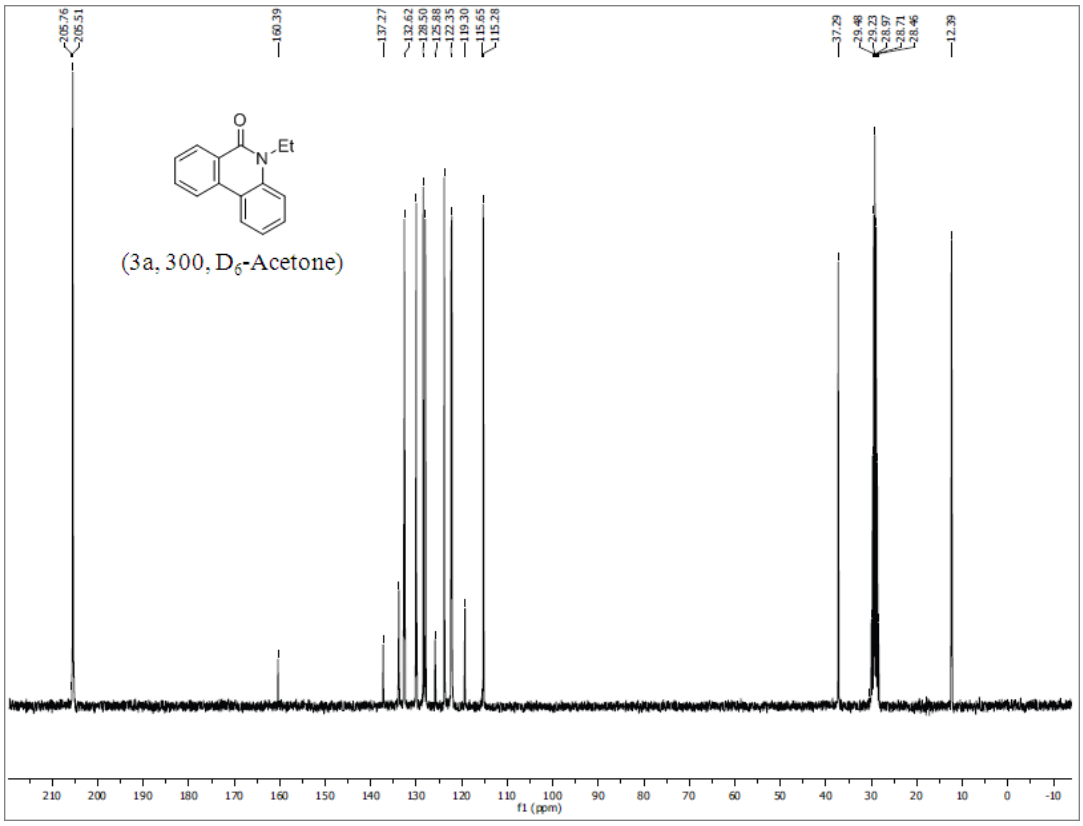
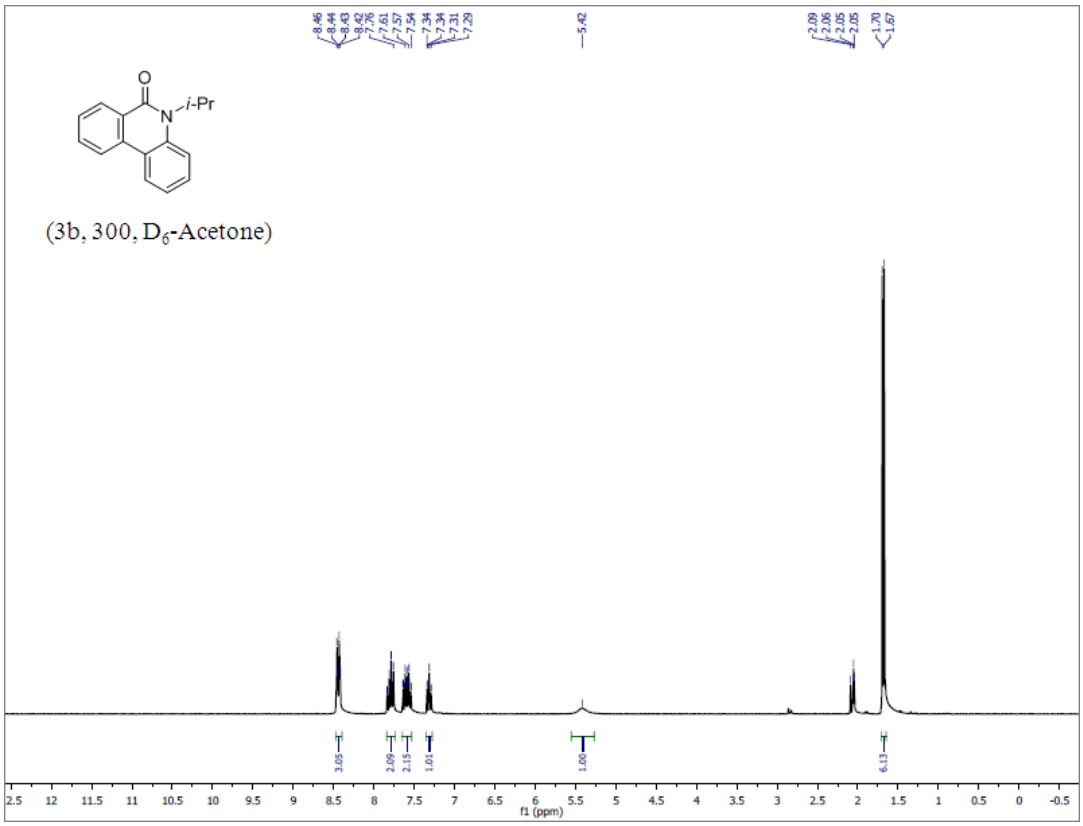
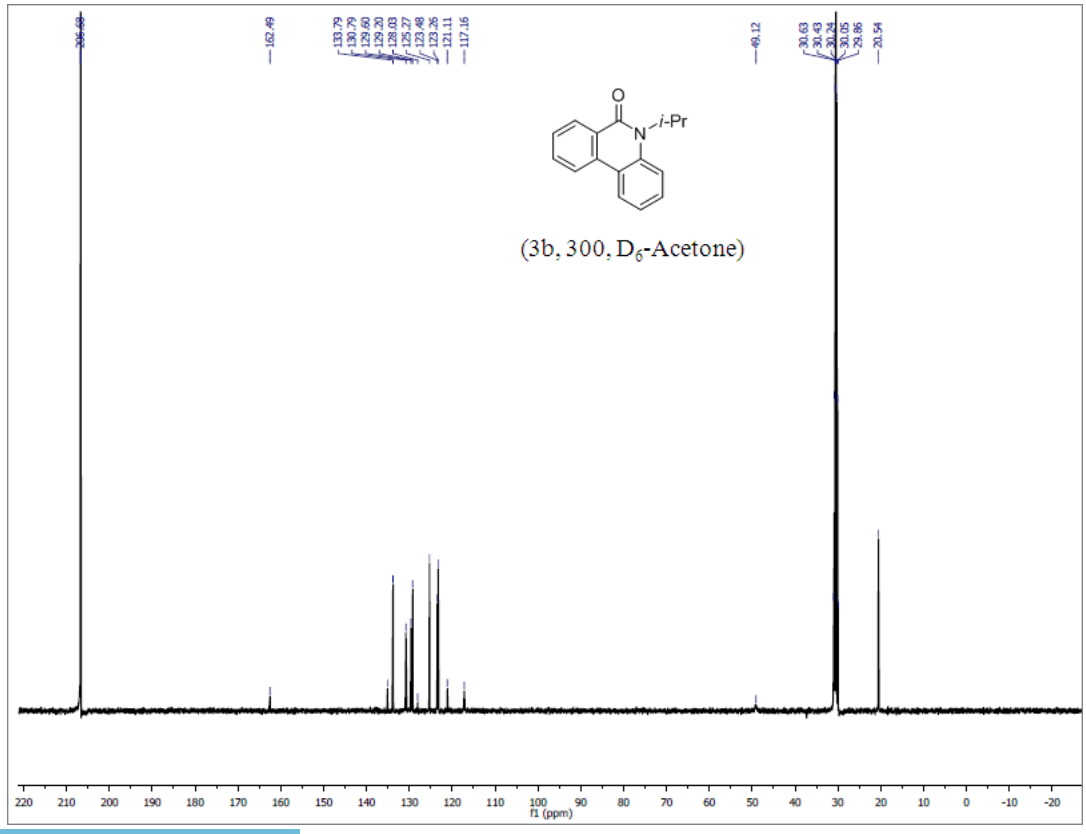


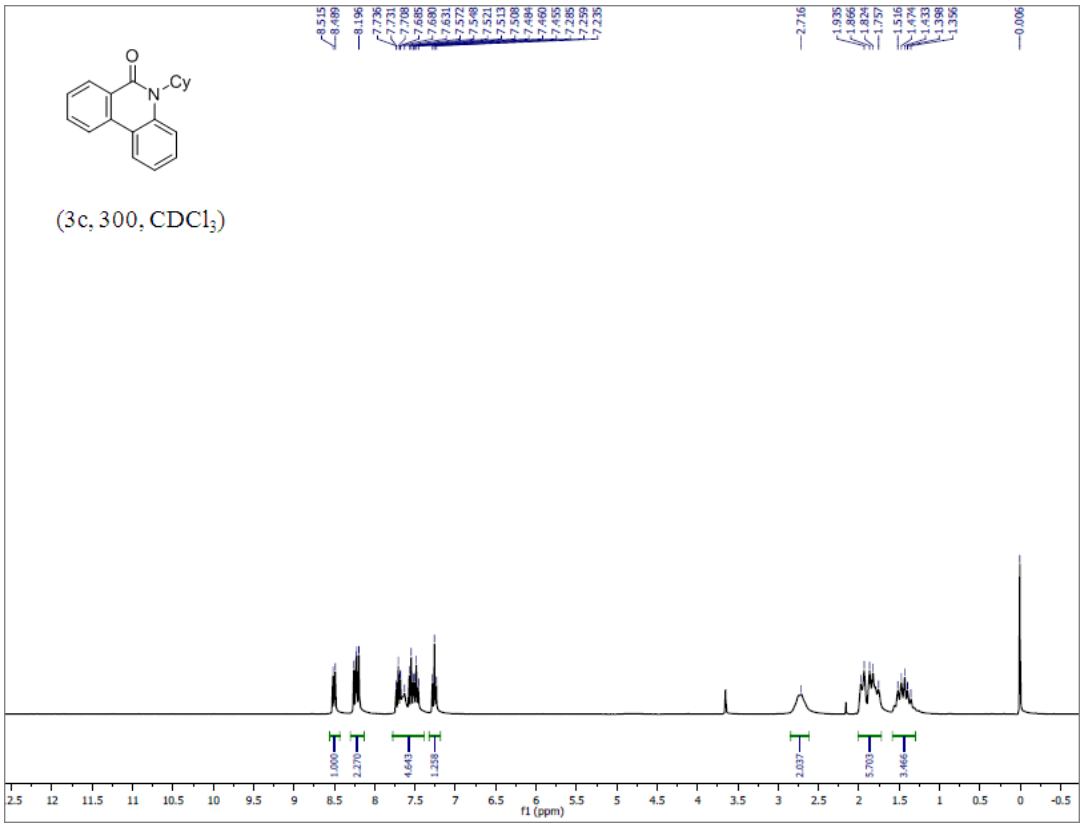


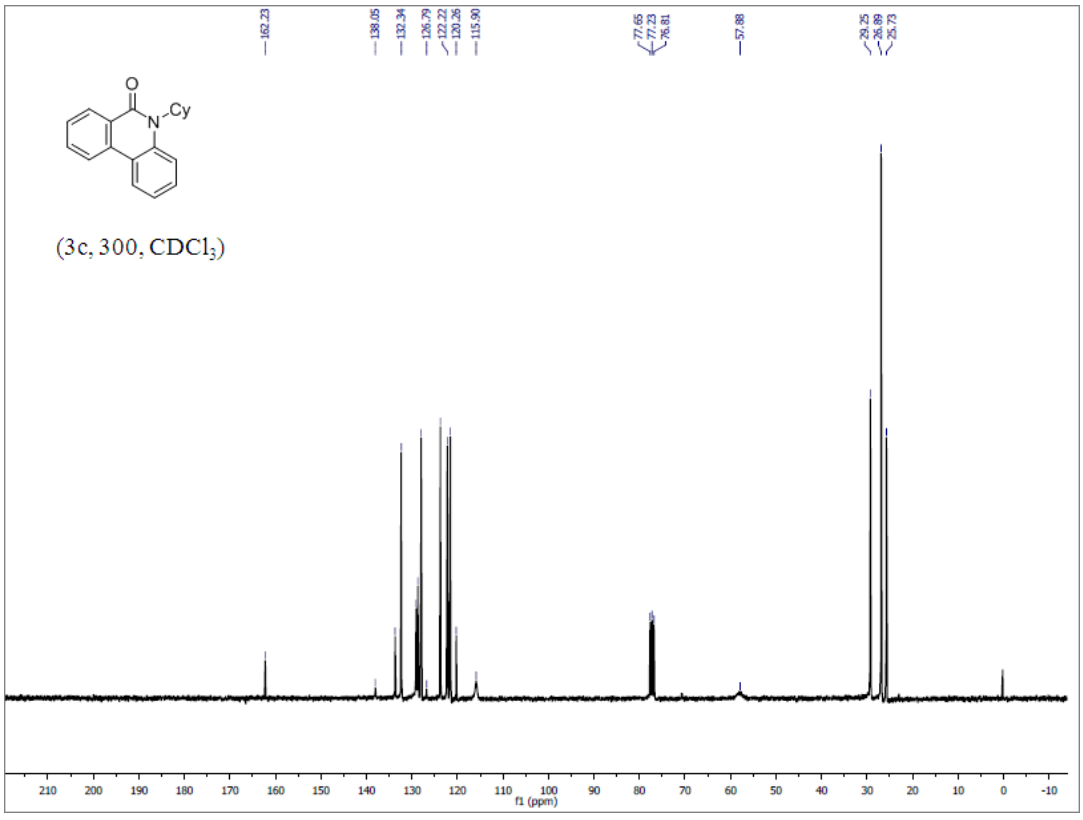


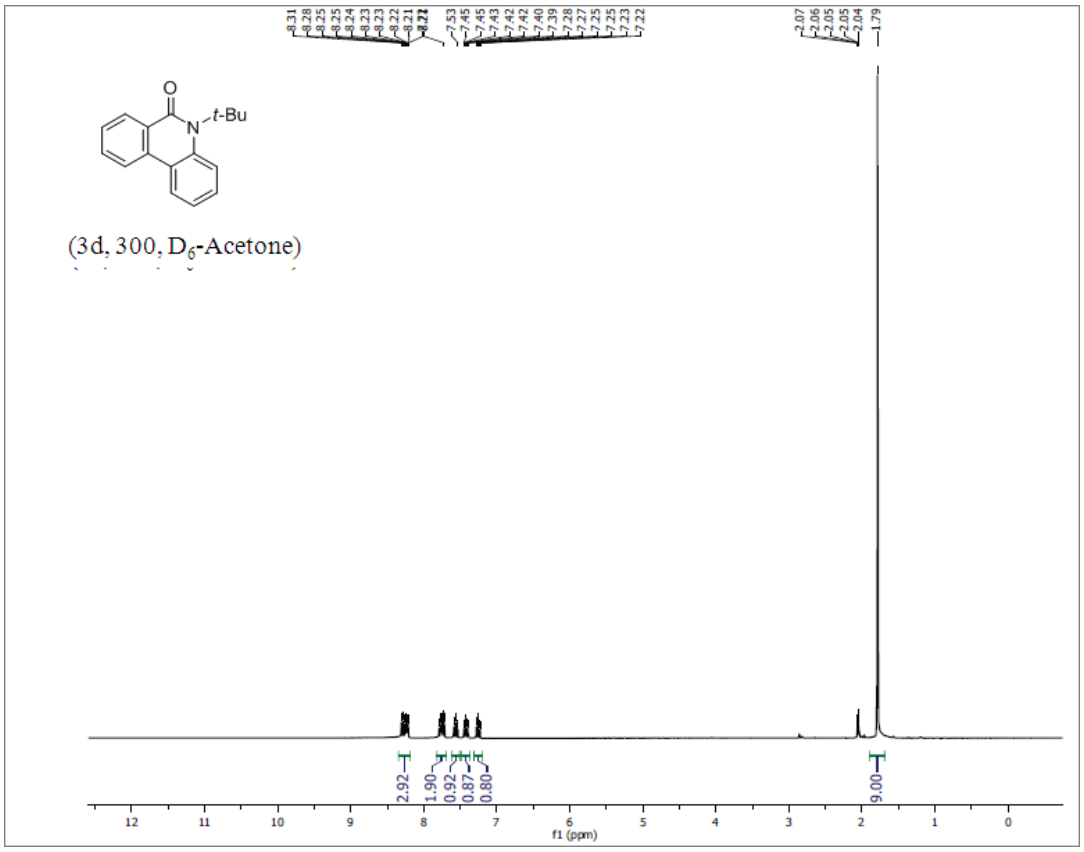


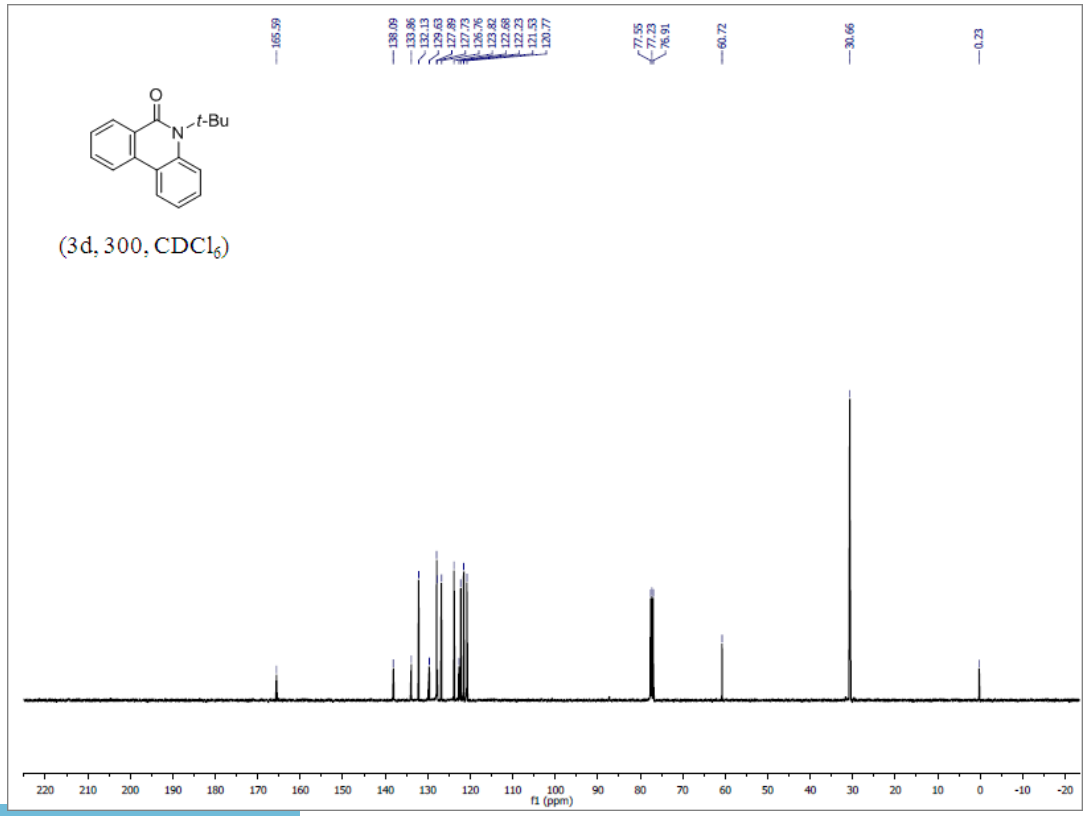


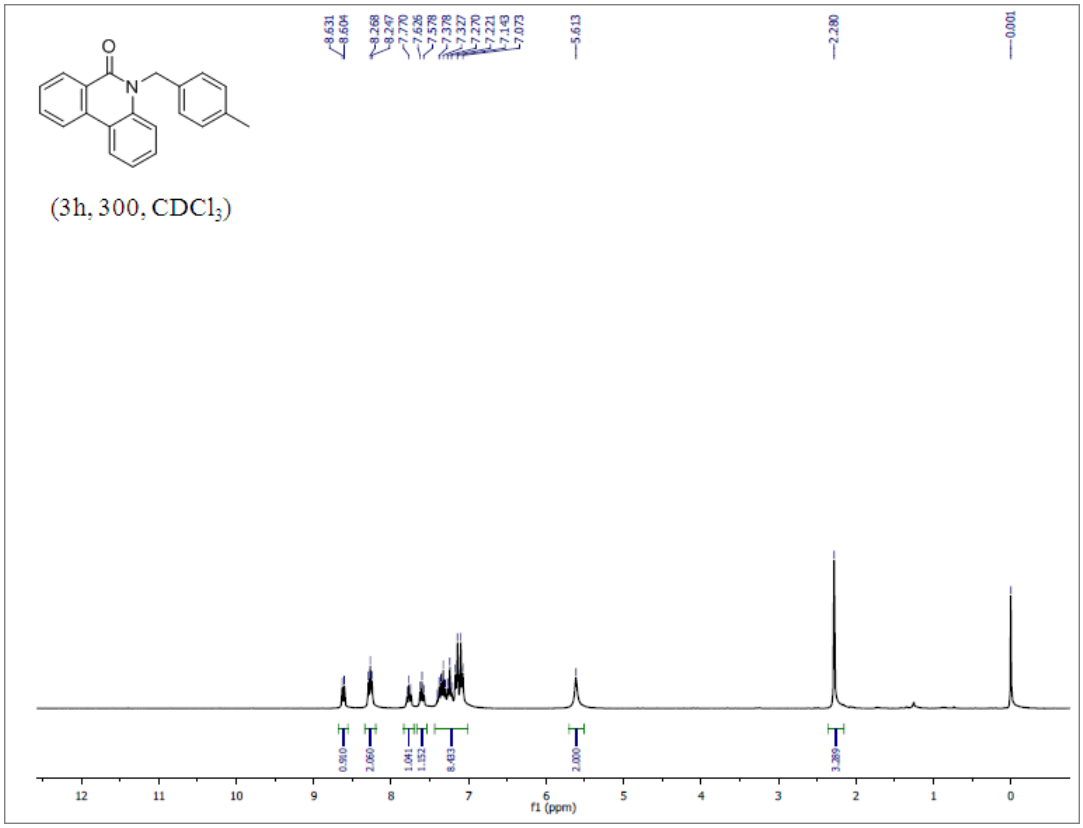


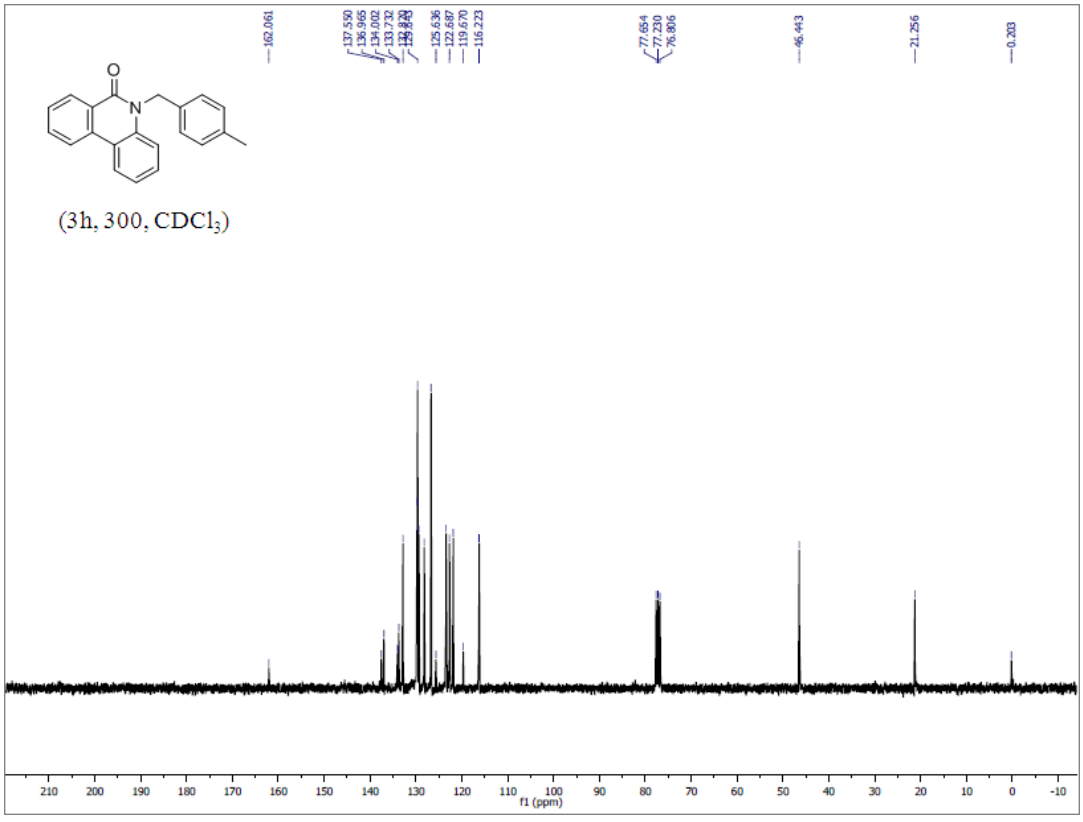


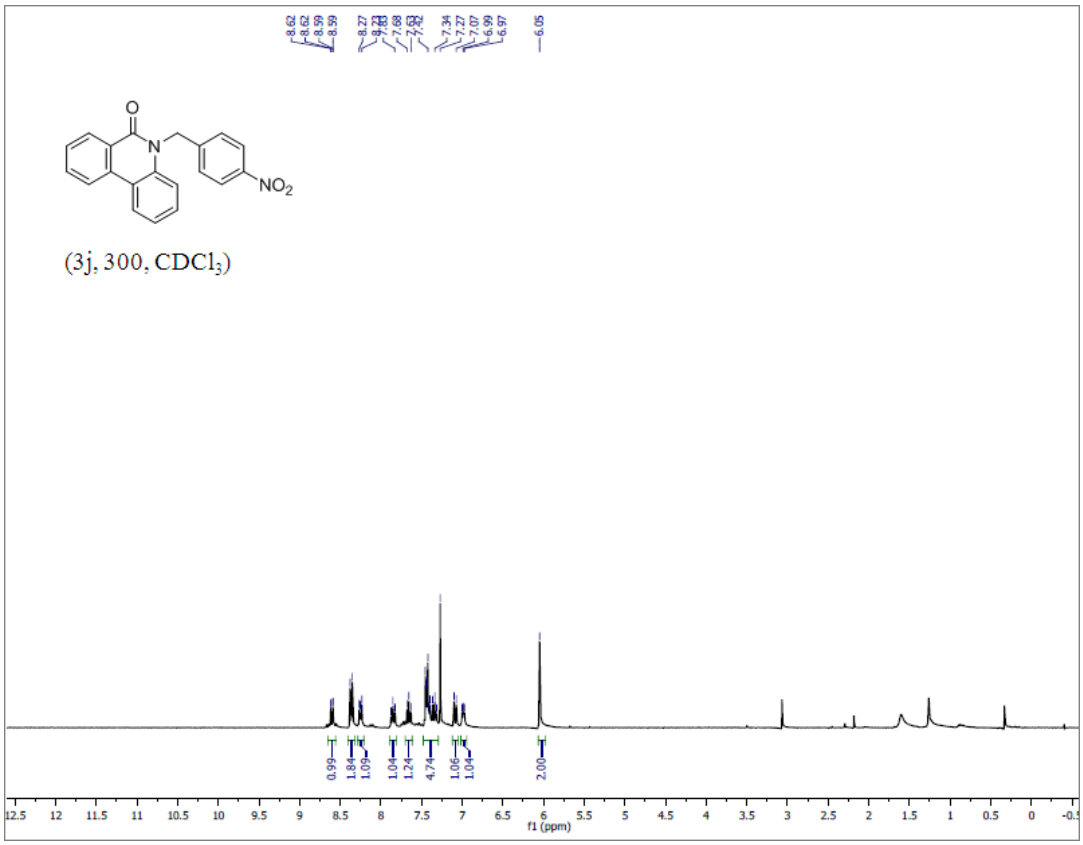




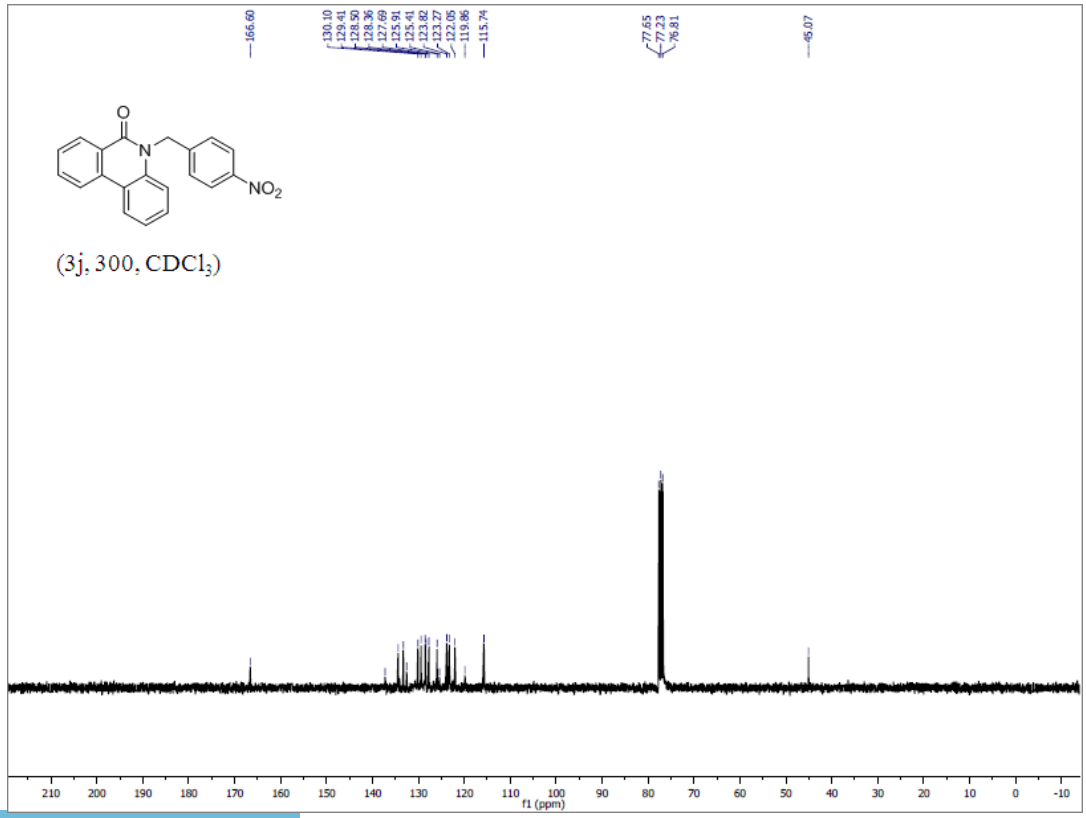








(3j, 300, $CDCl_3$)



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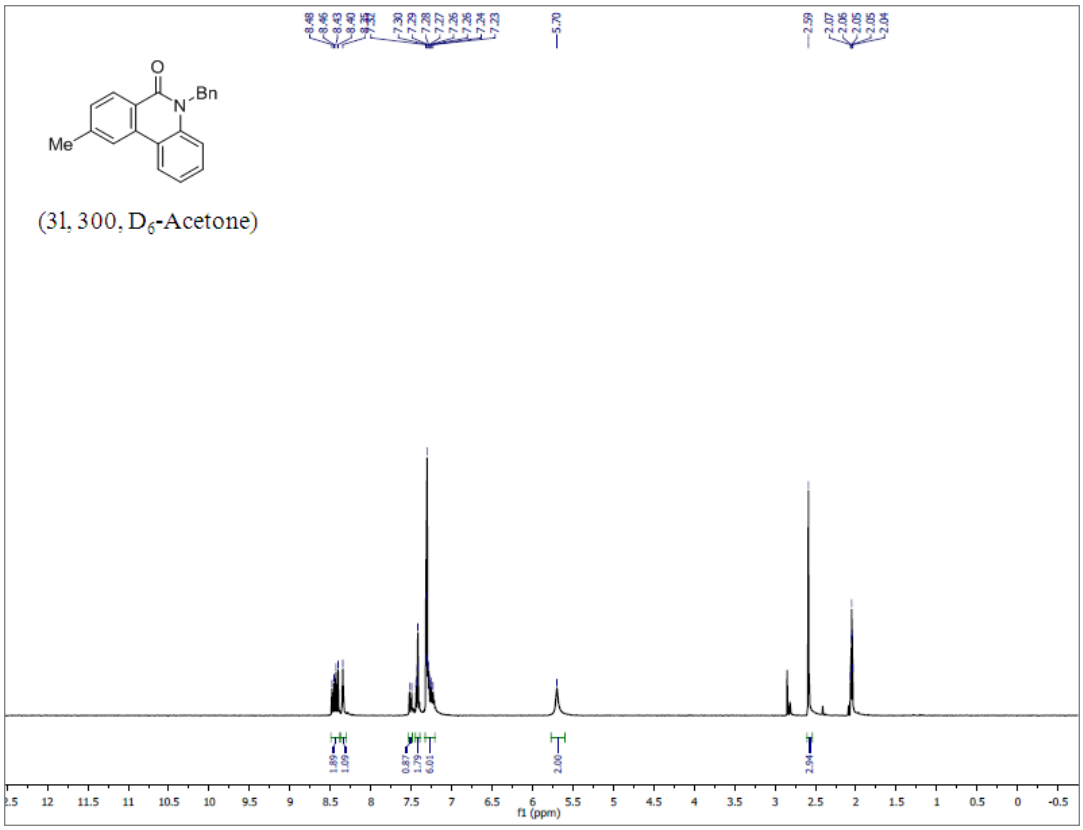

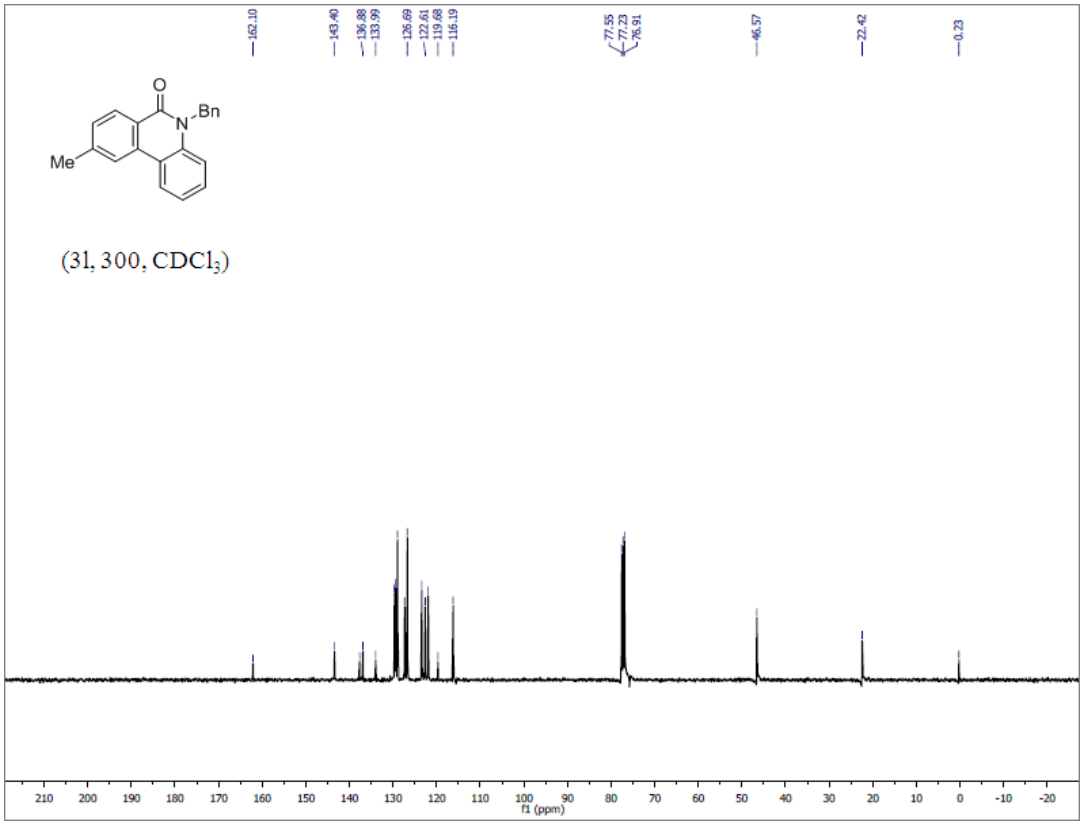

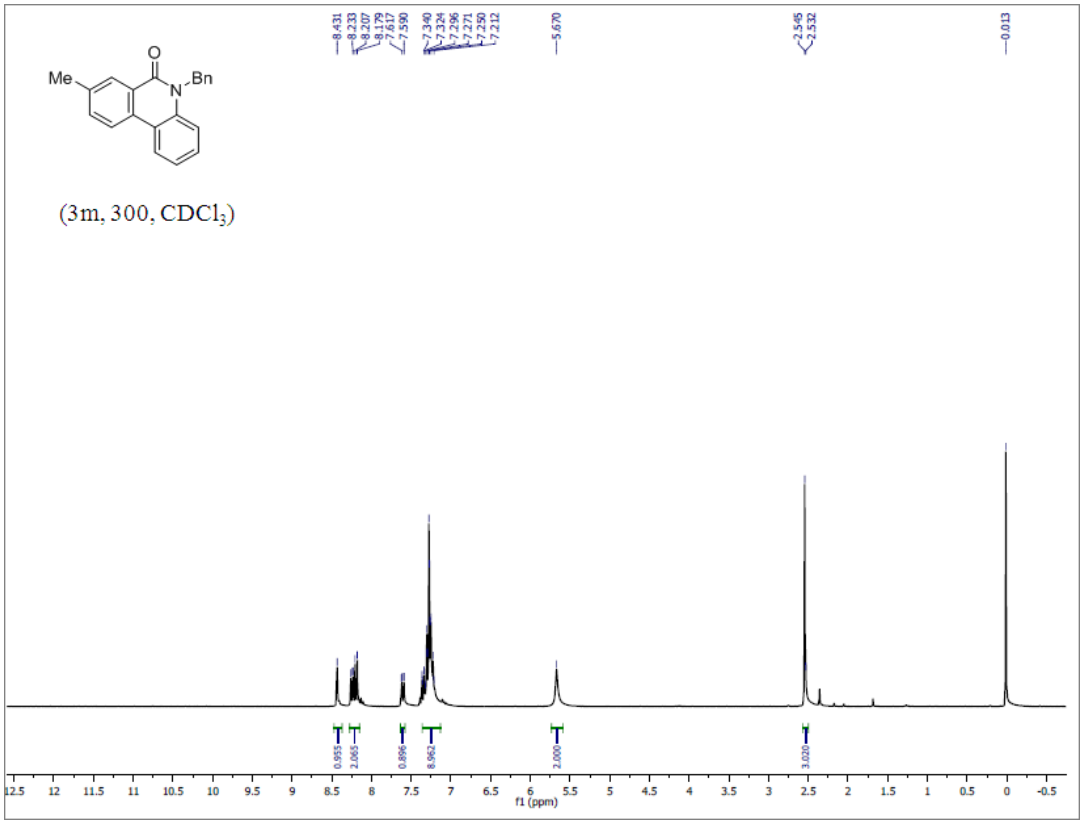

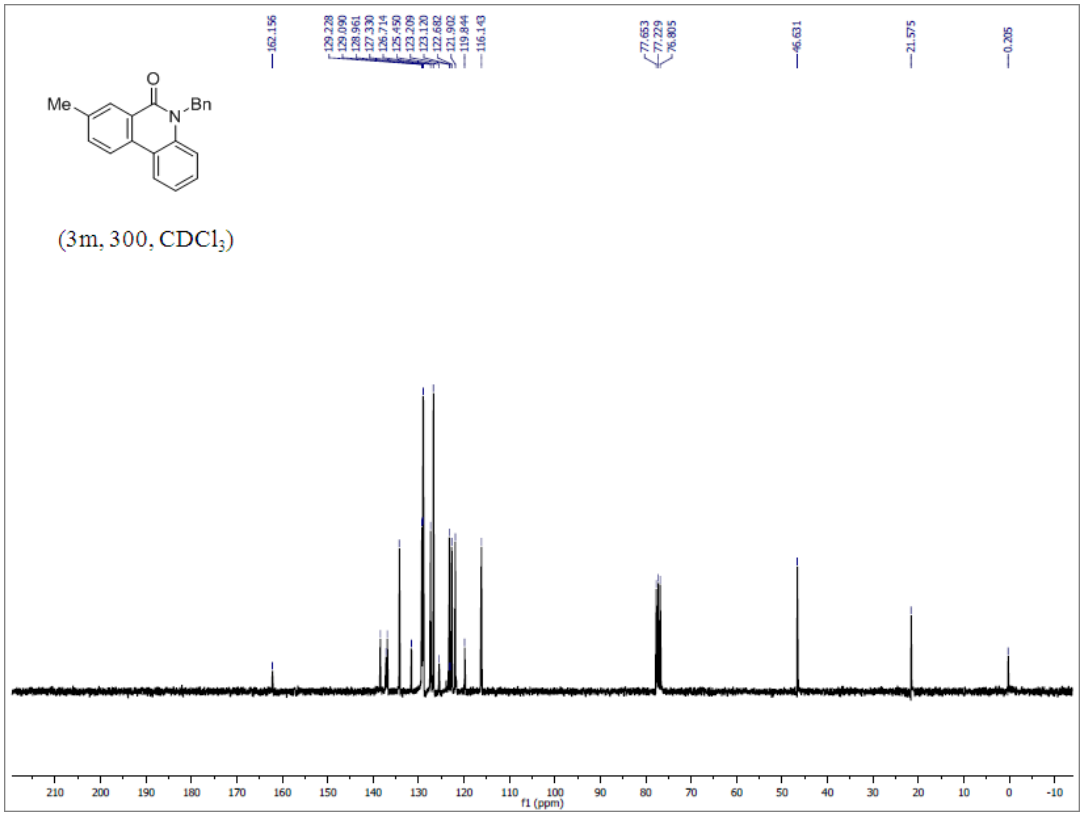

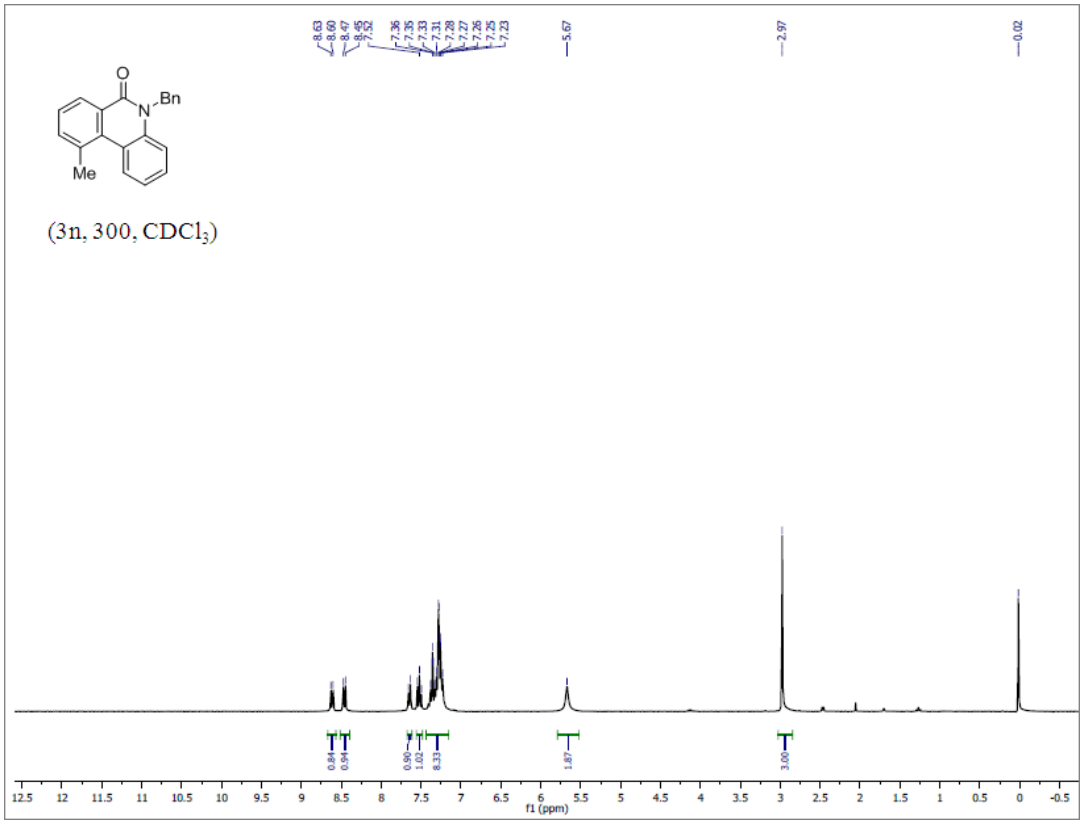

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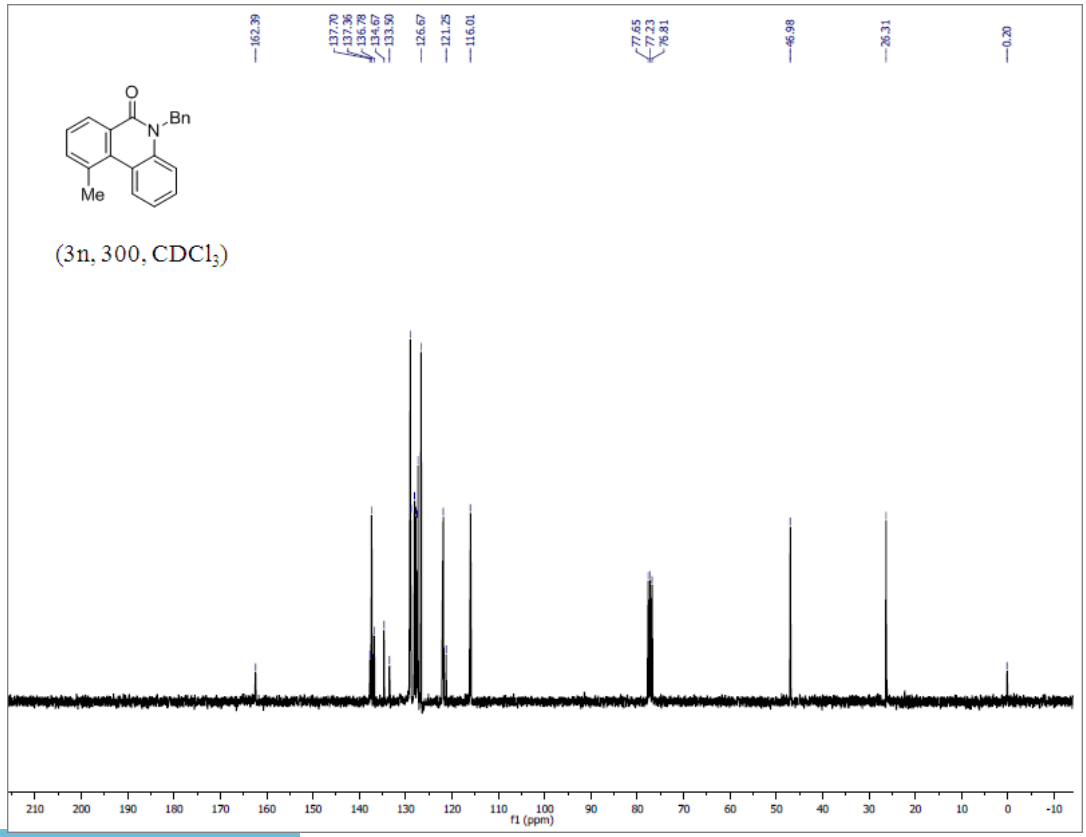

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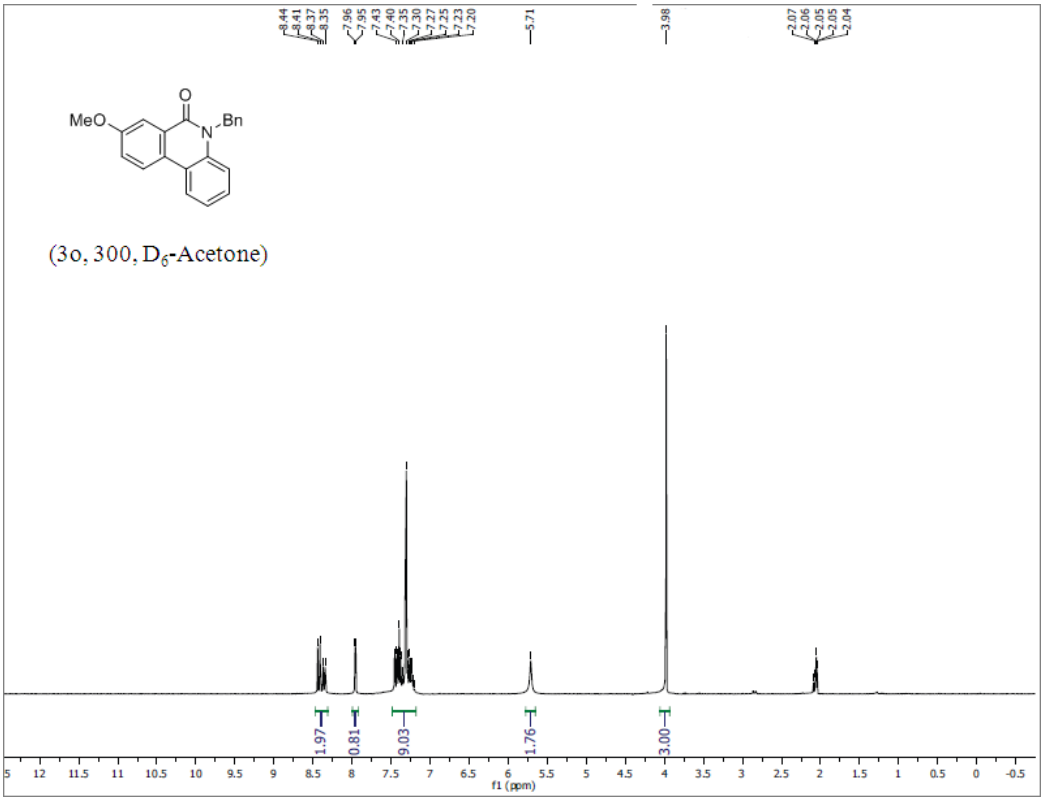
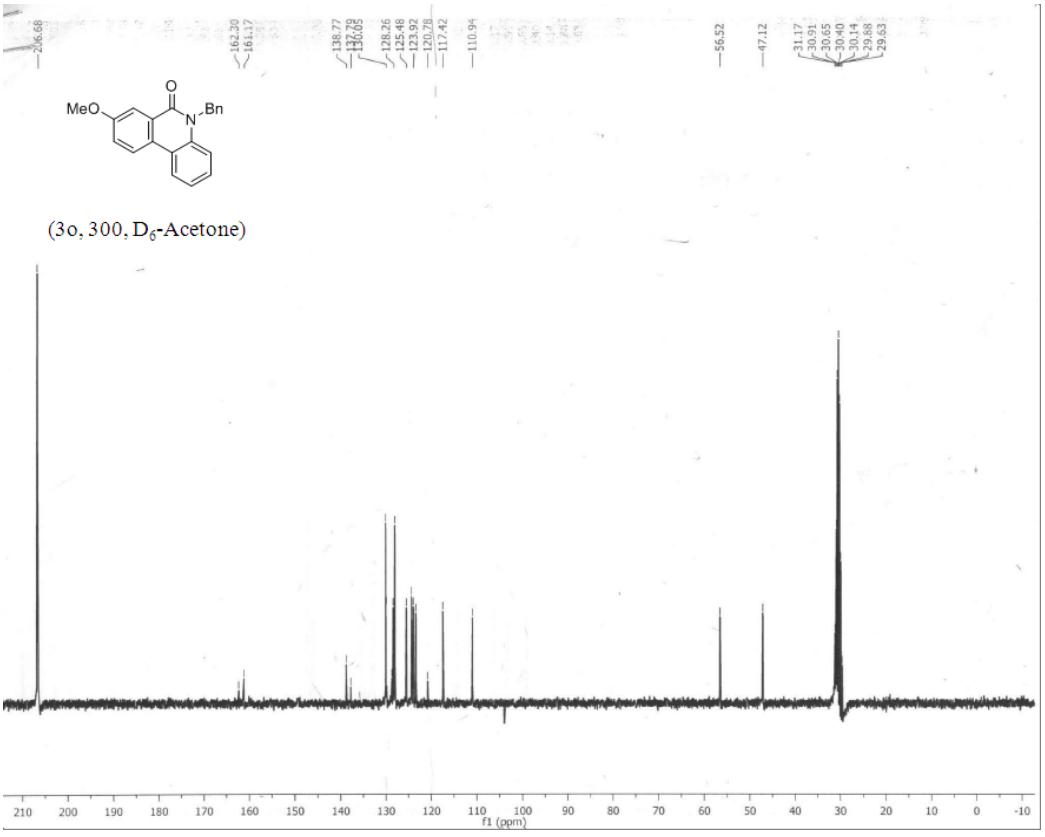
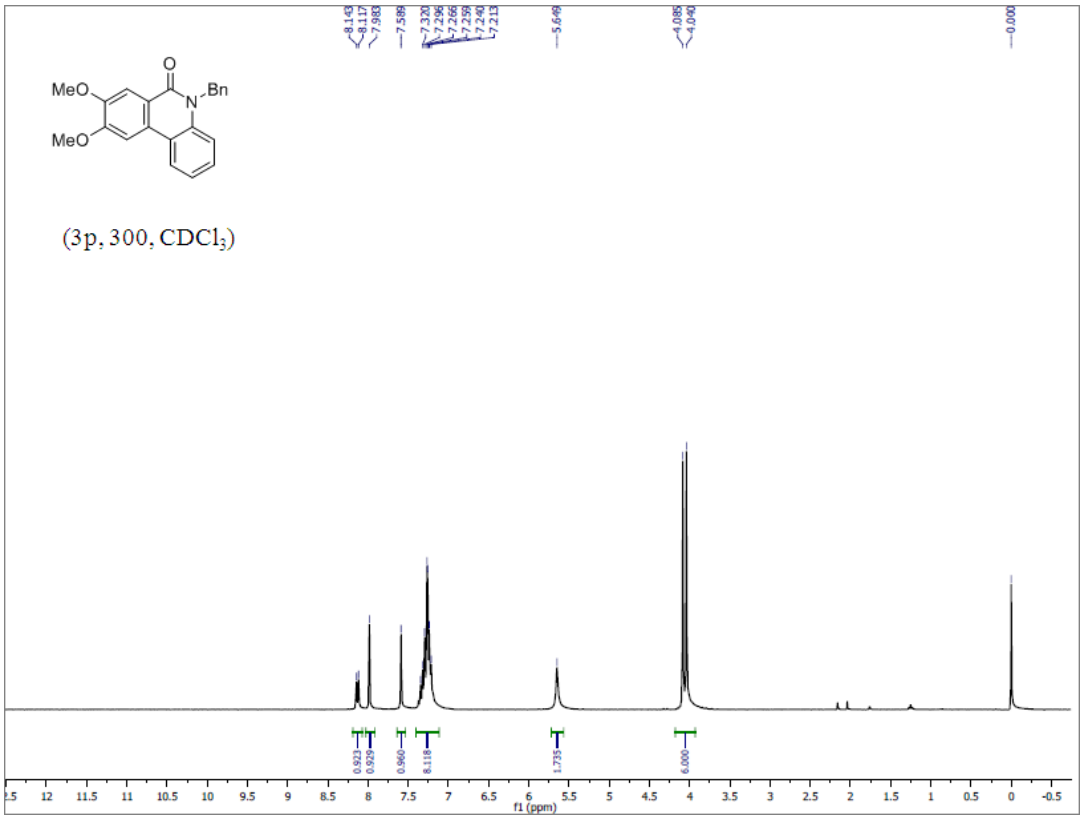
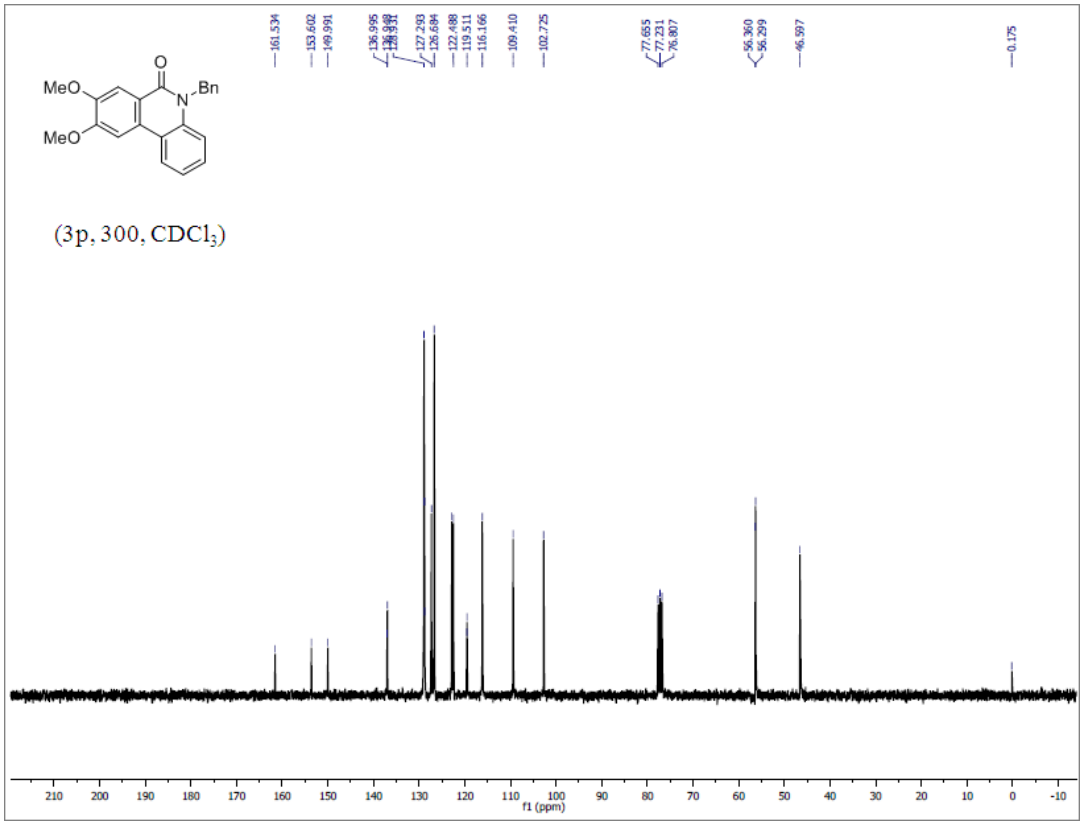
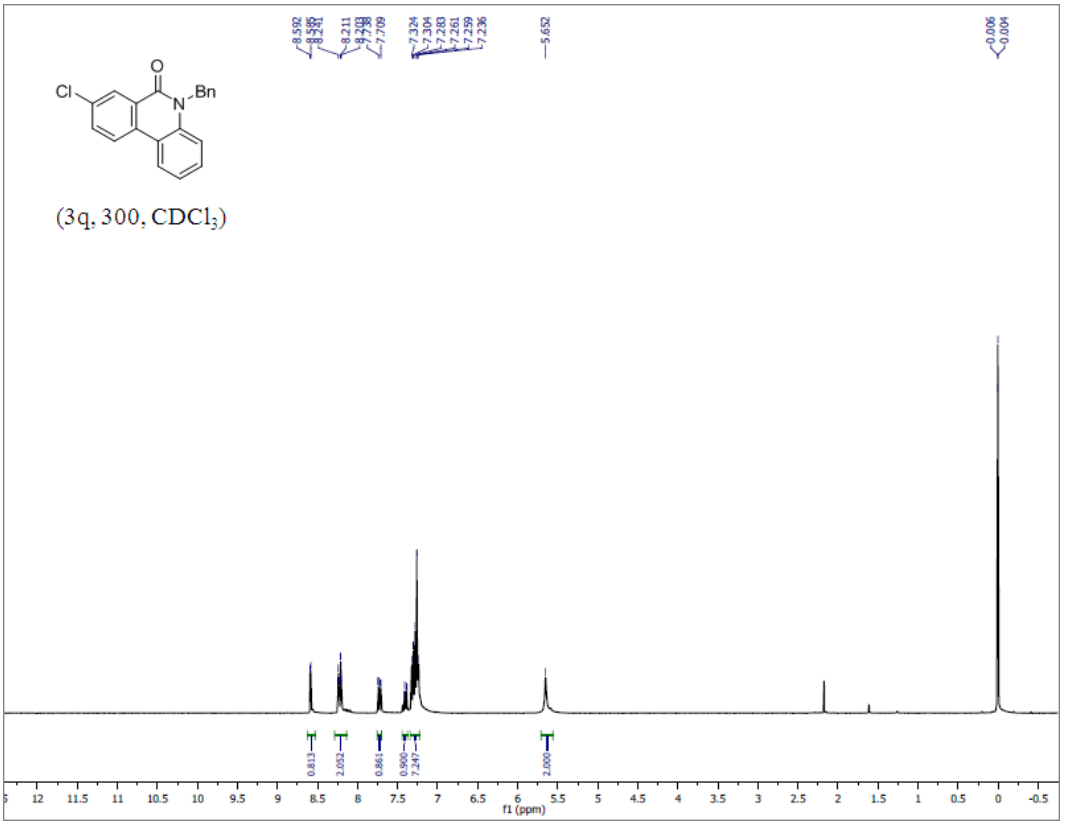
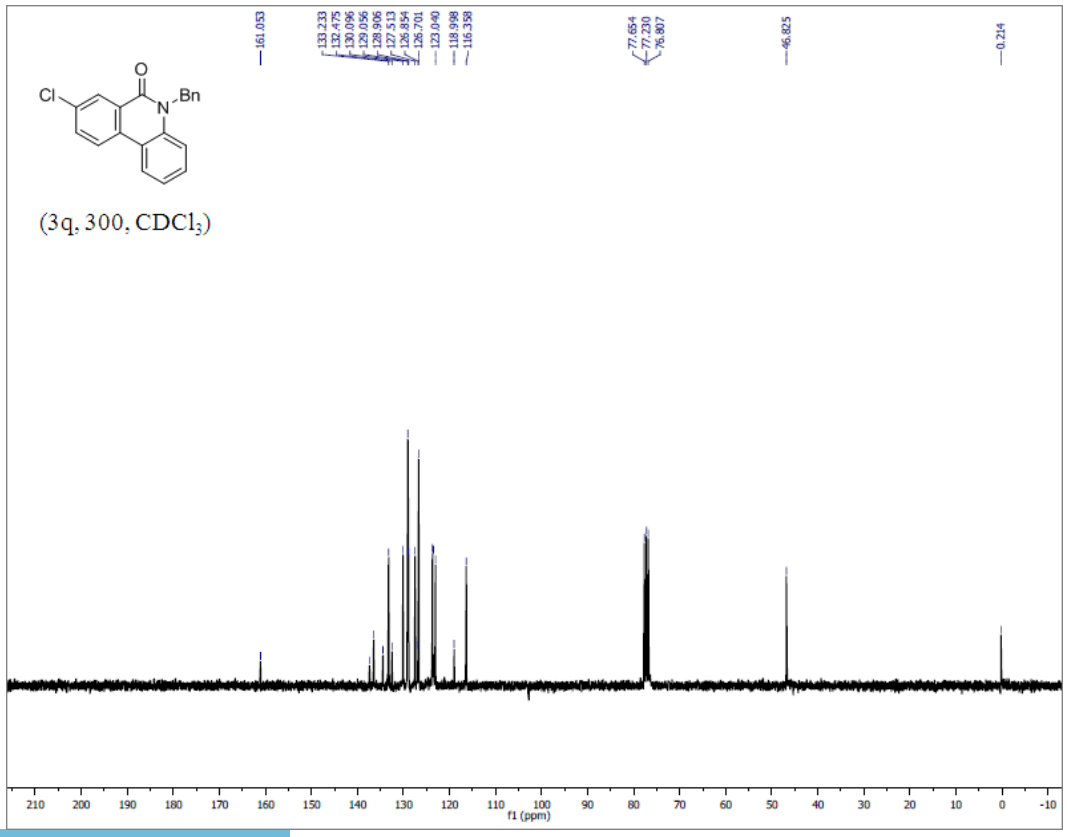


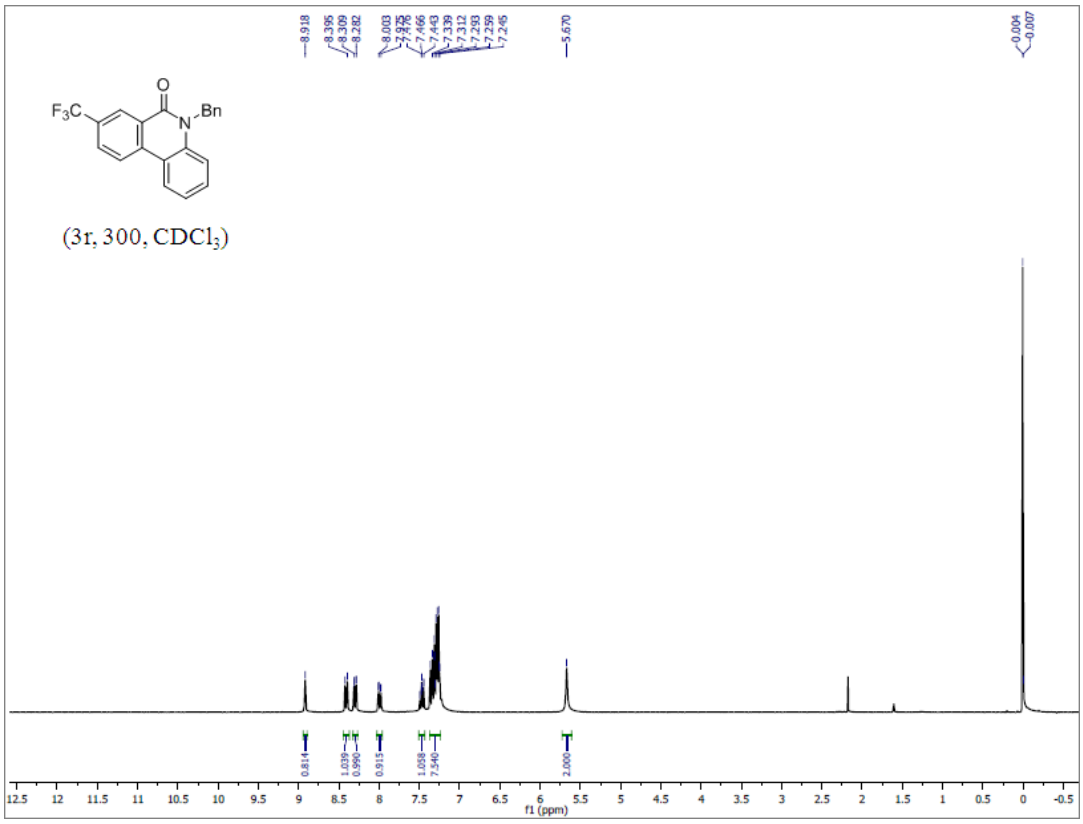


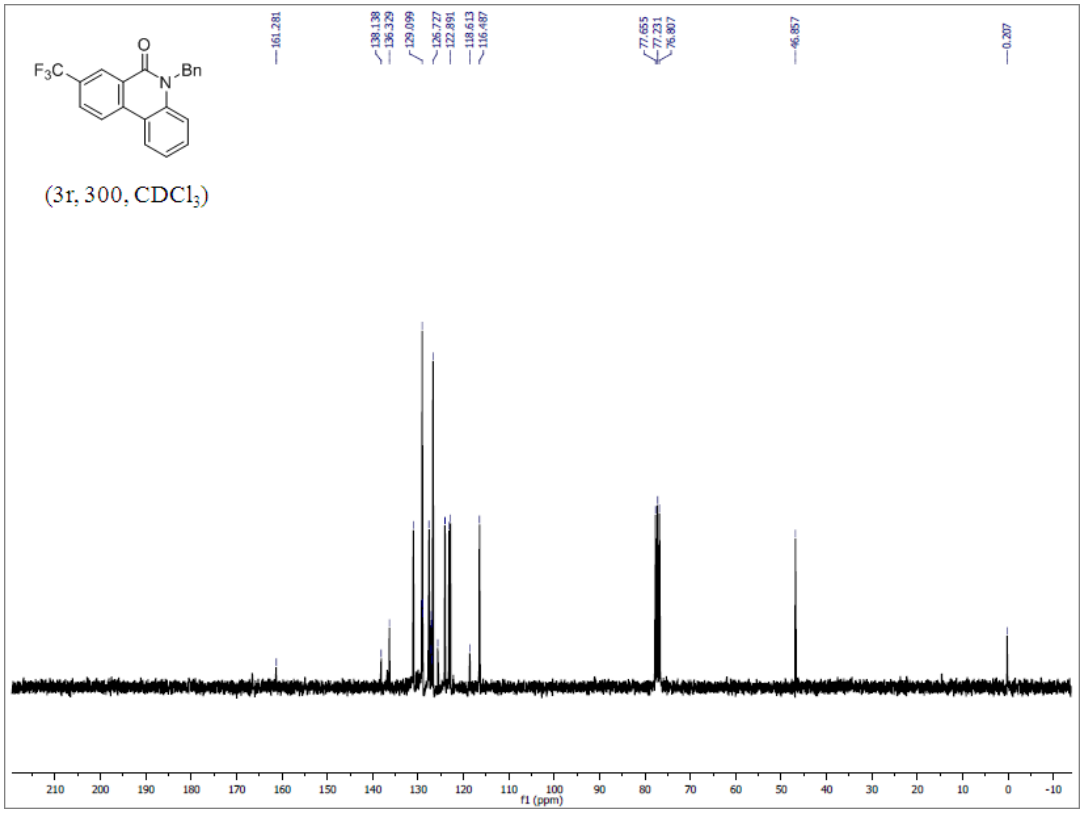


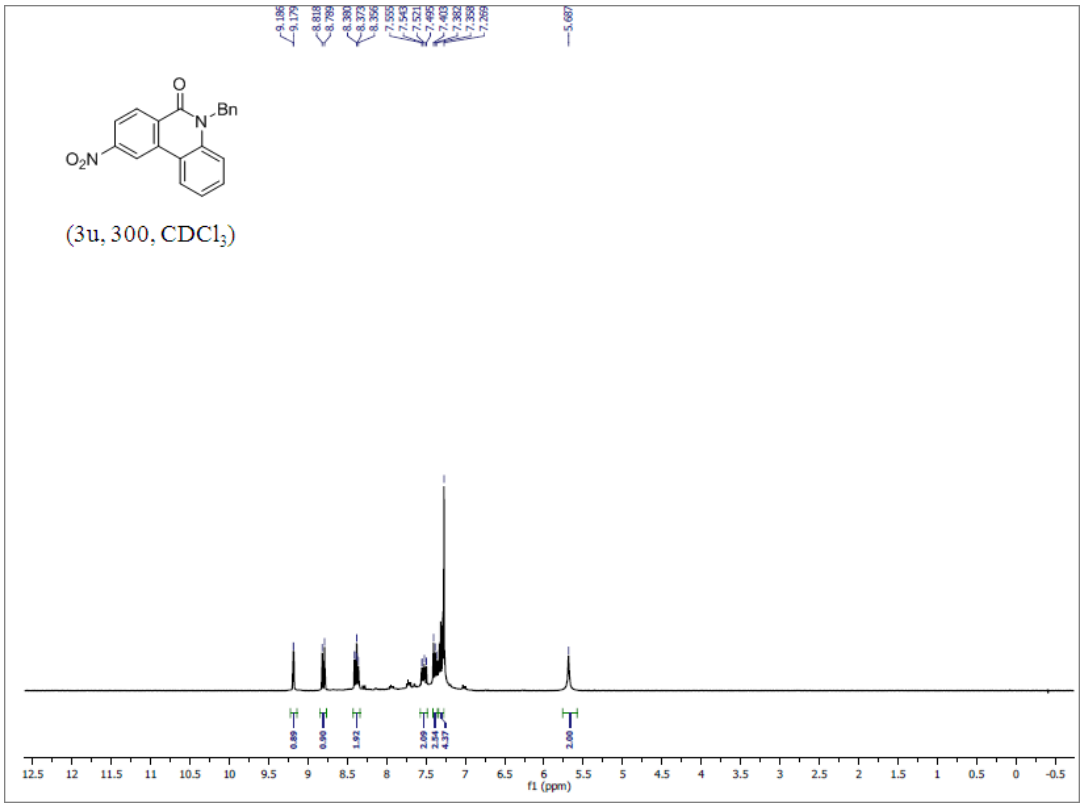


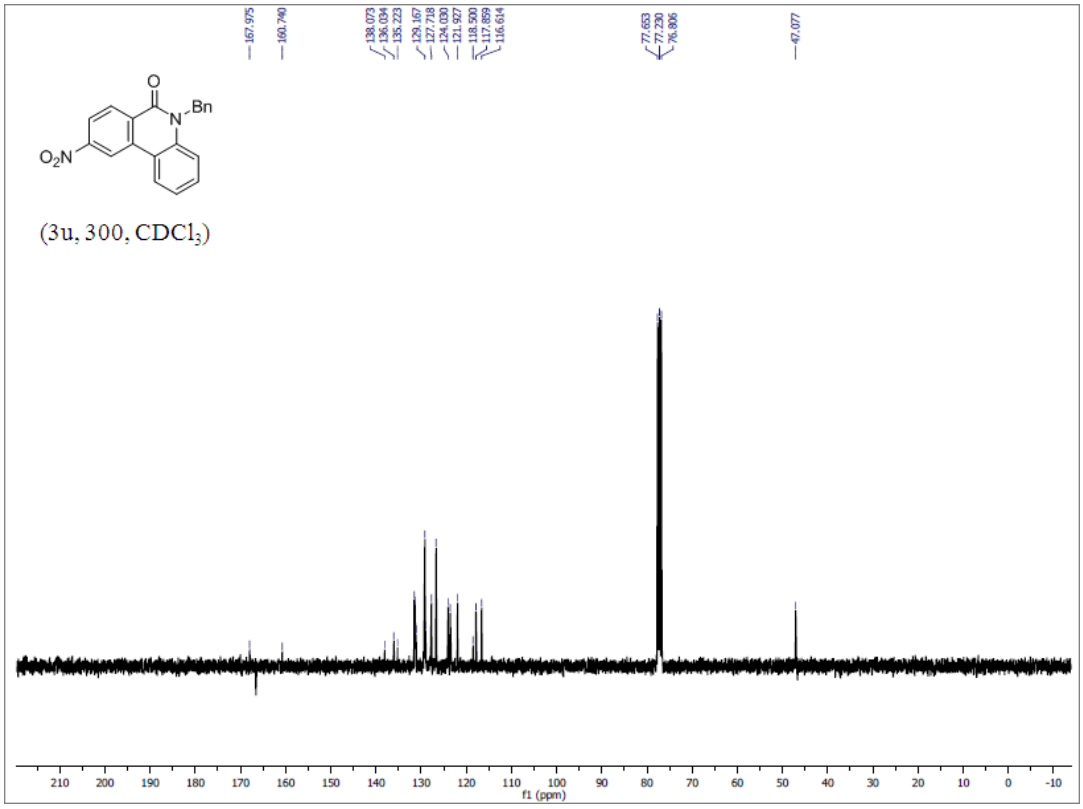


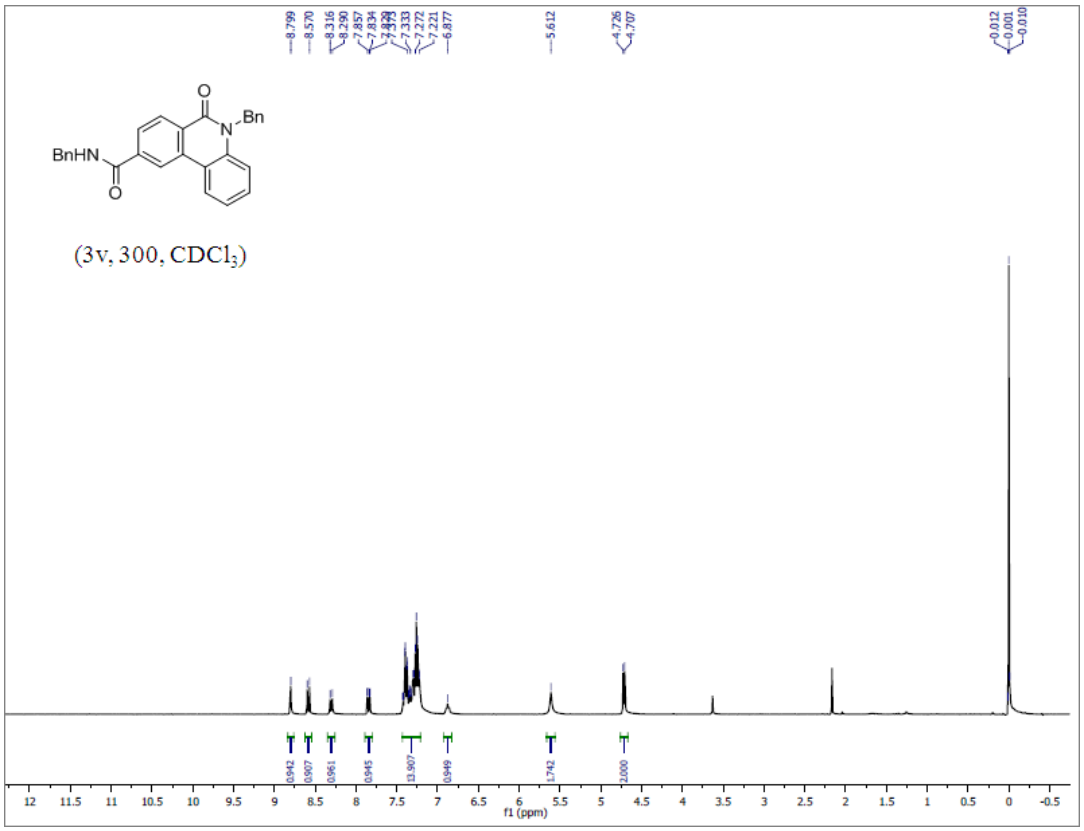


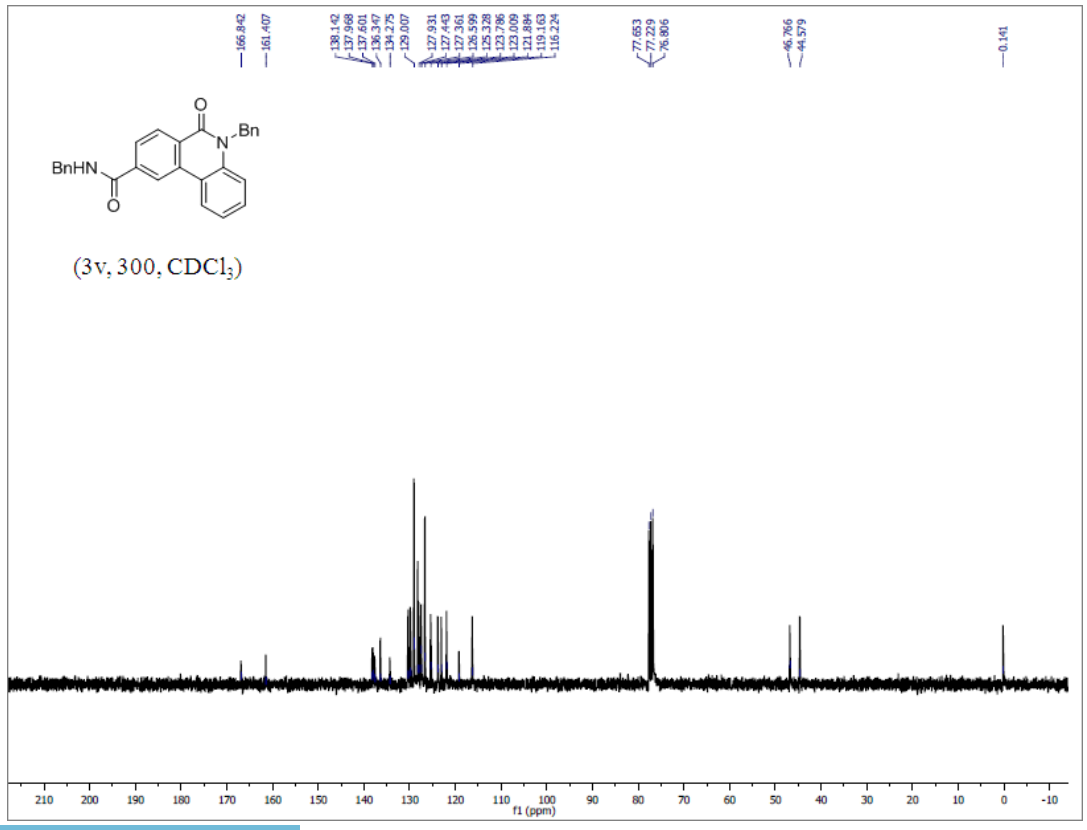


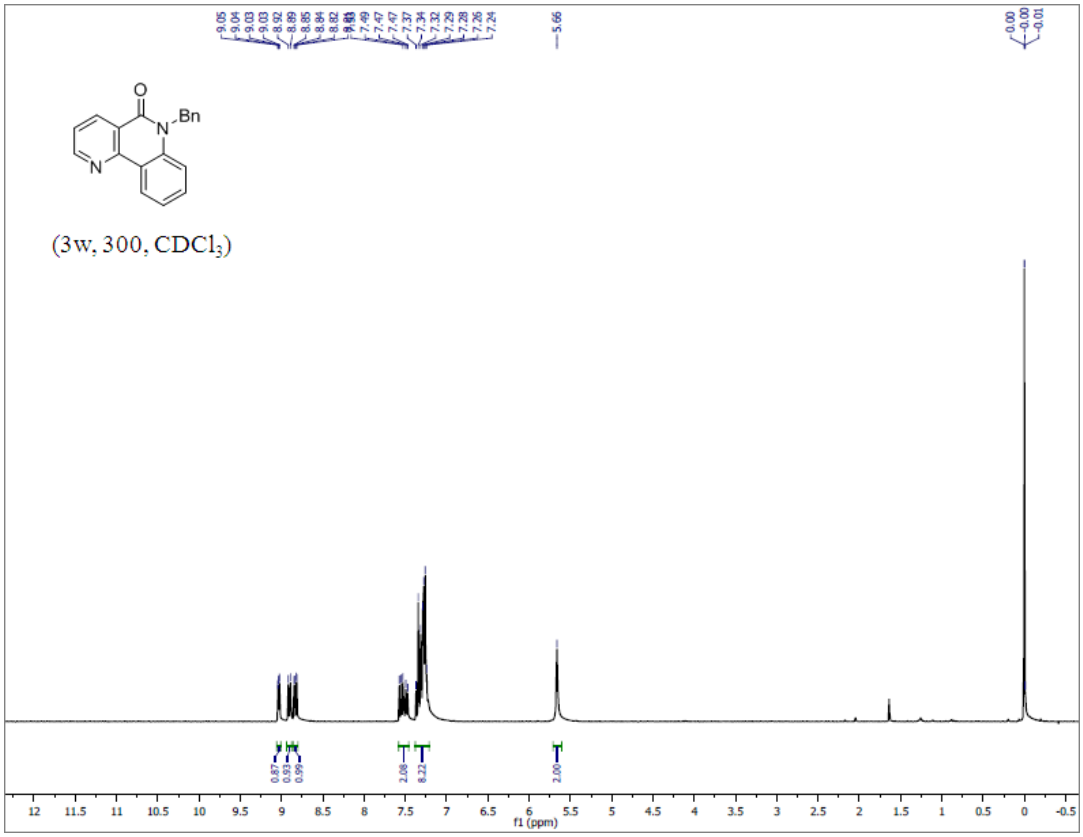


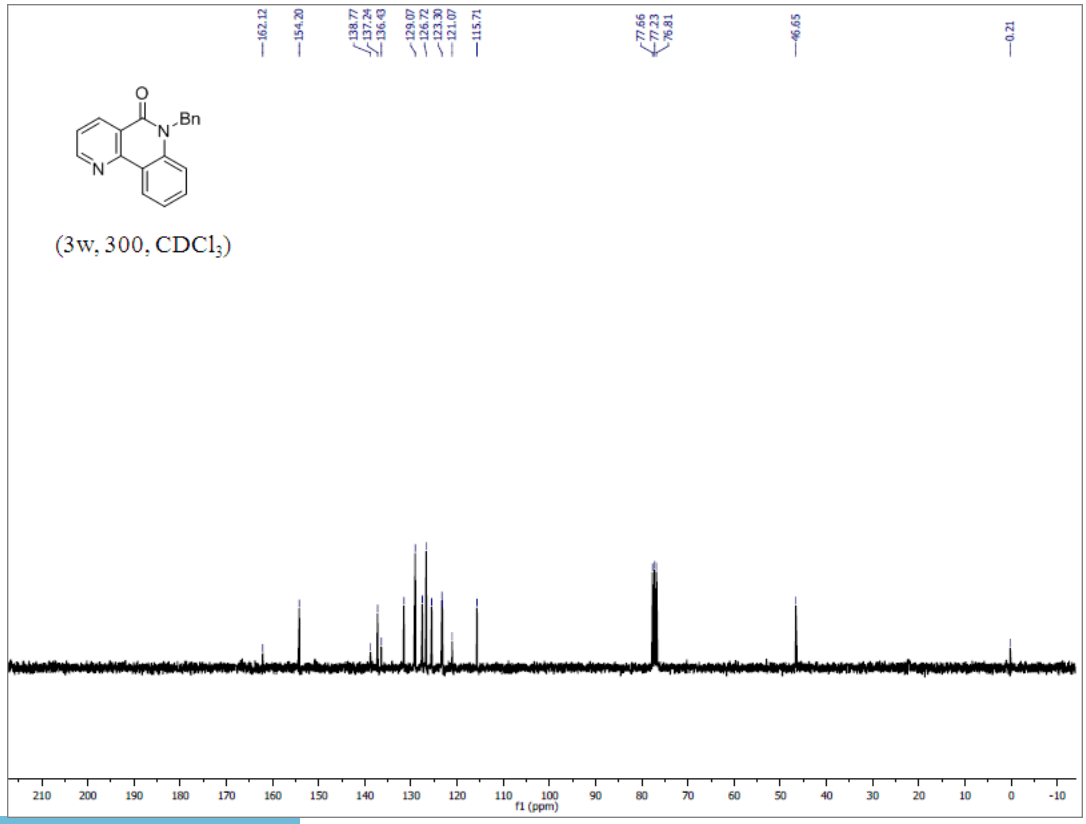


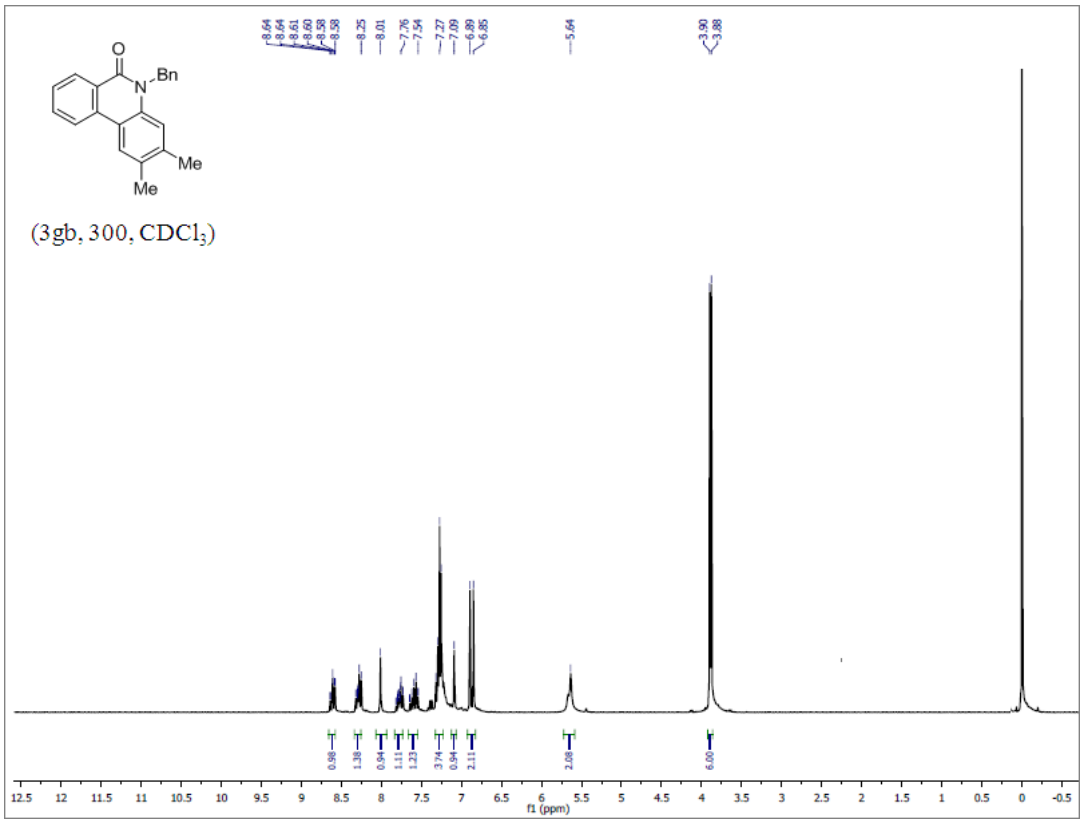


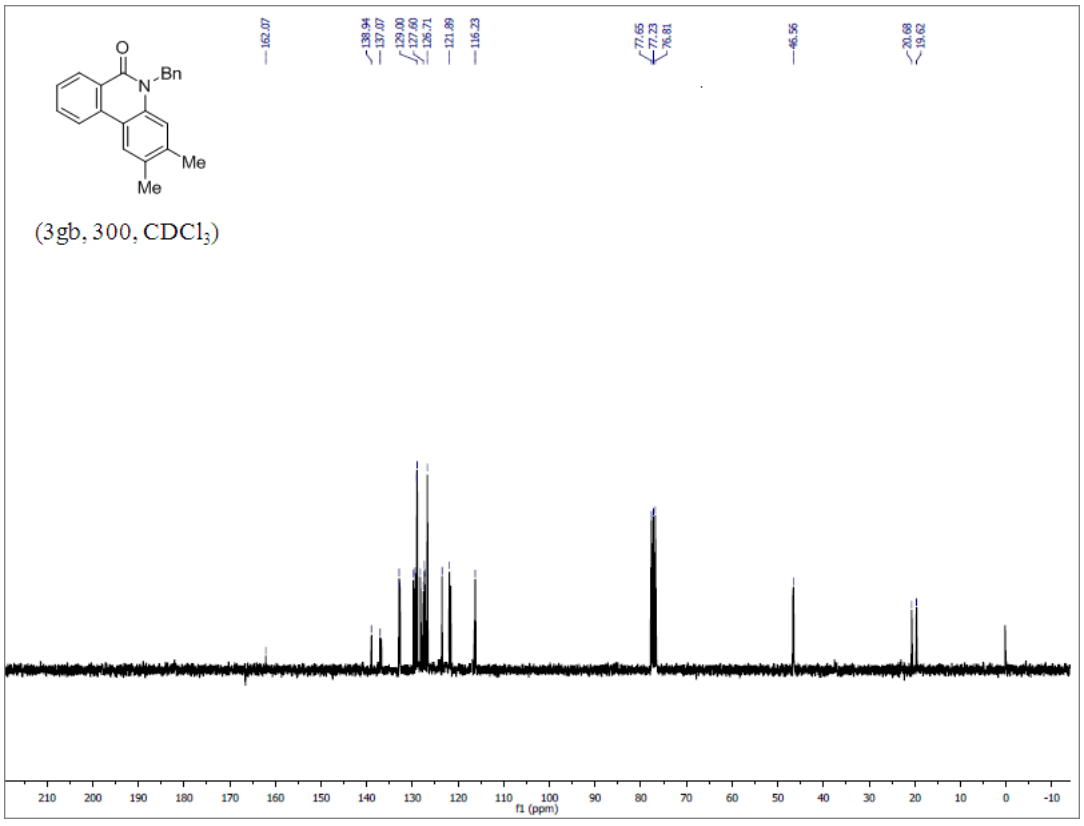


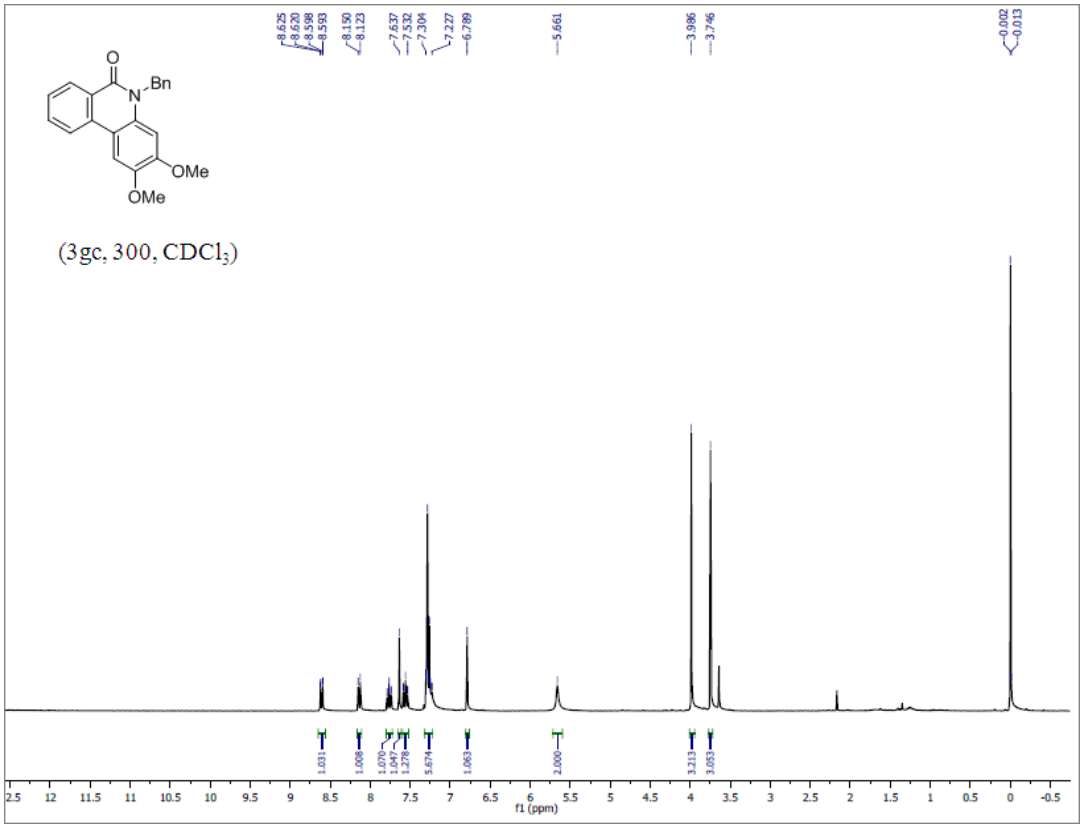


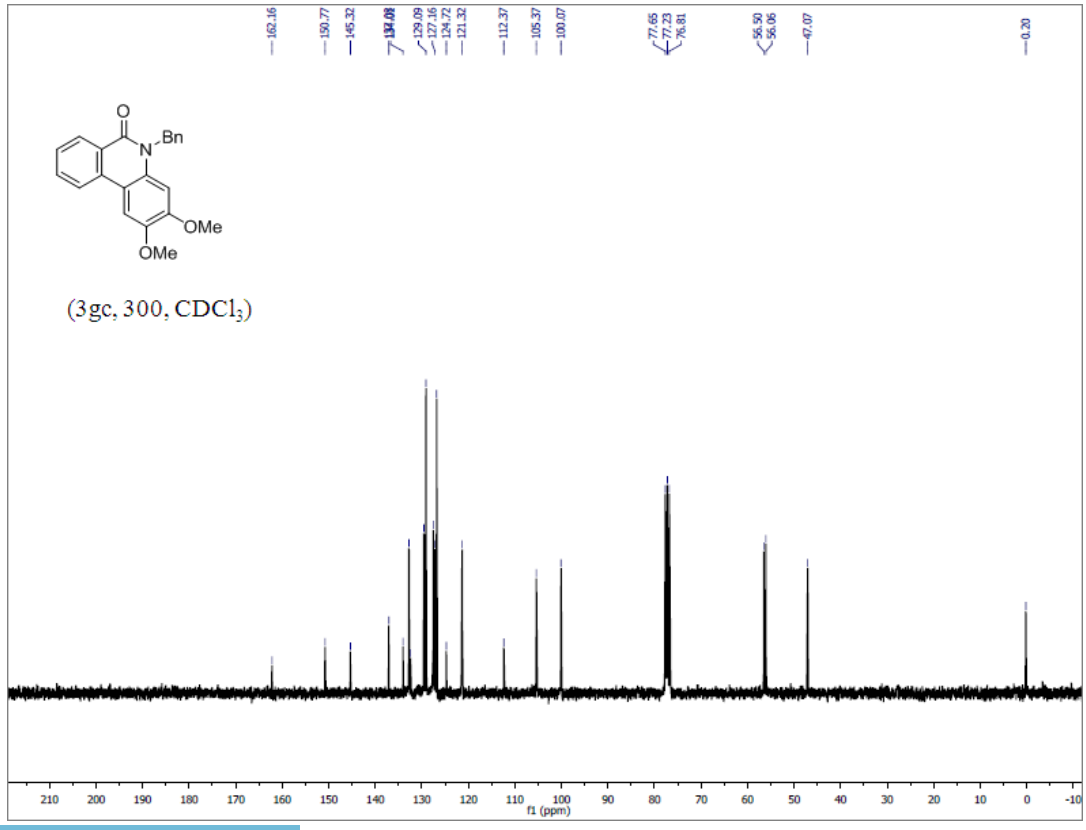


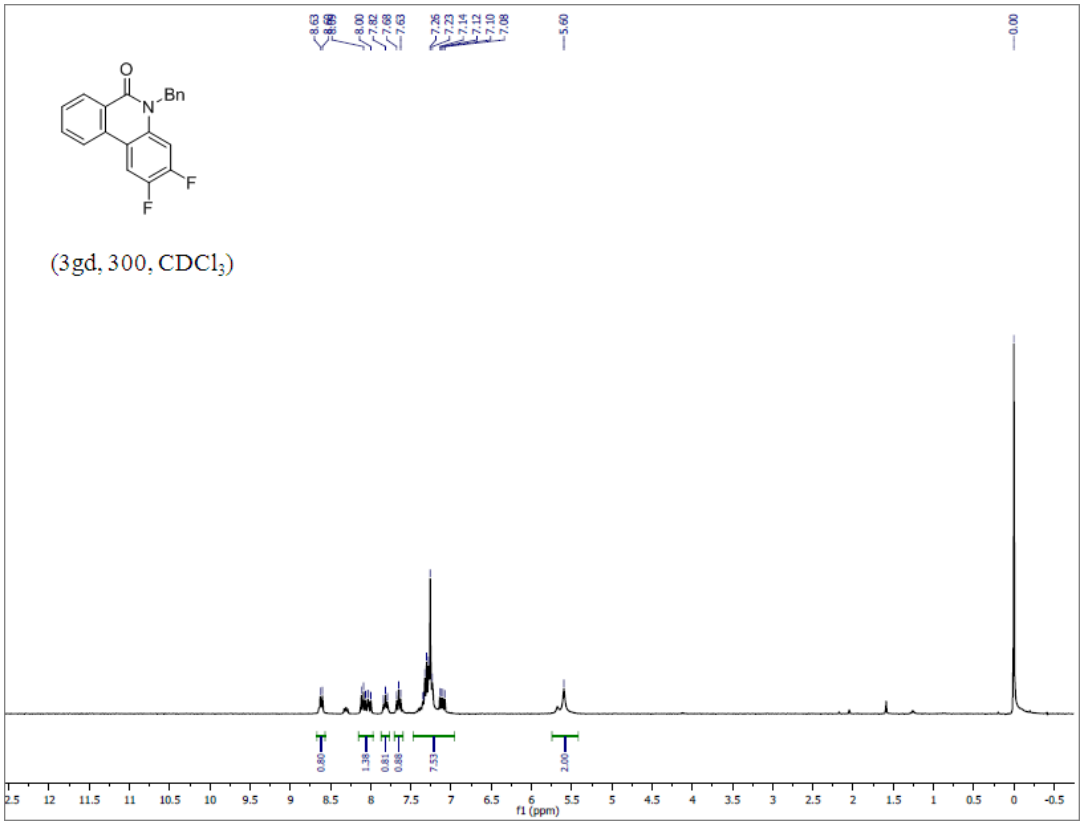


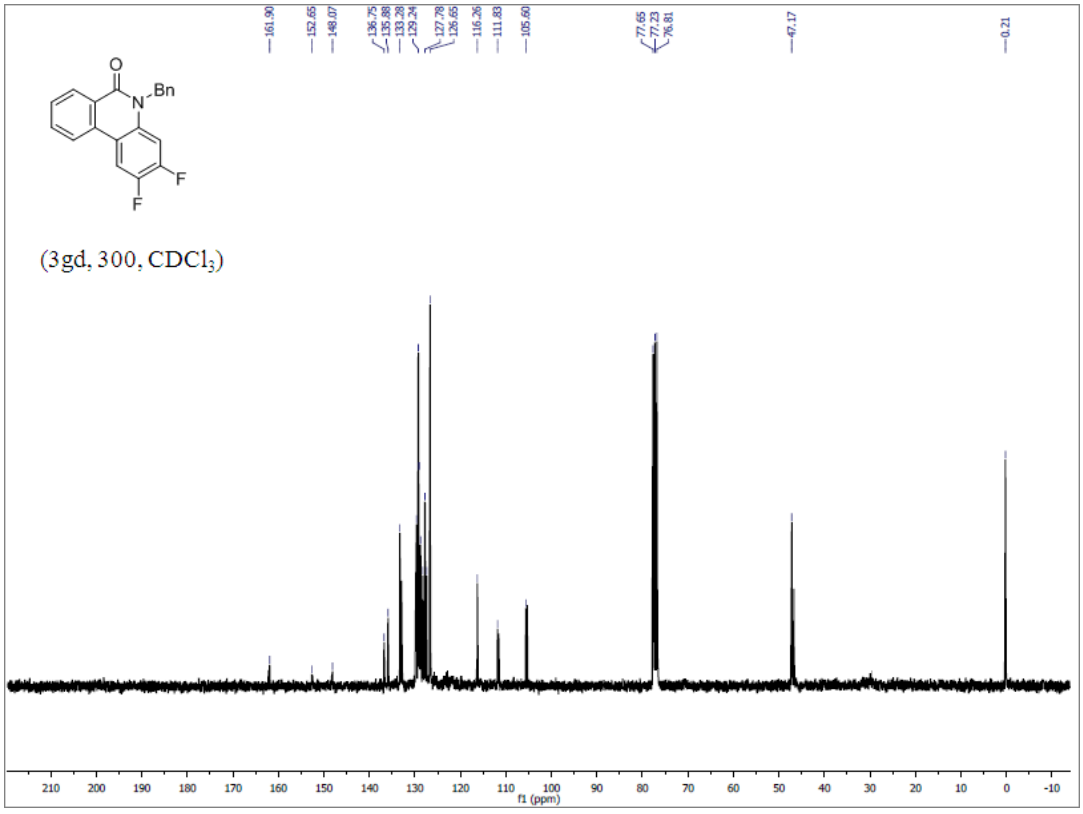




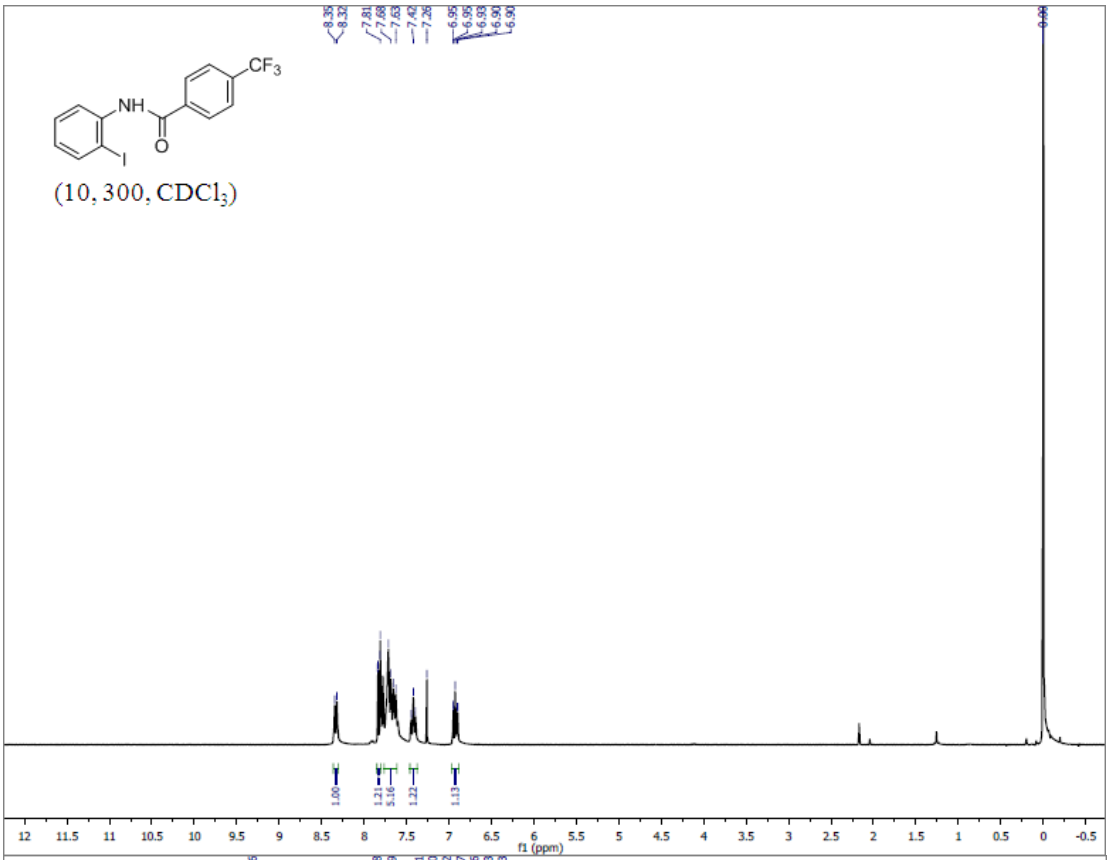


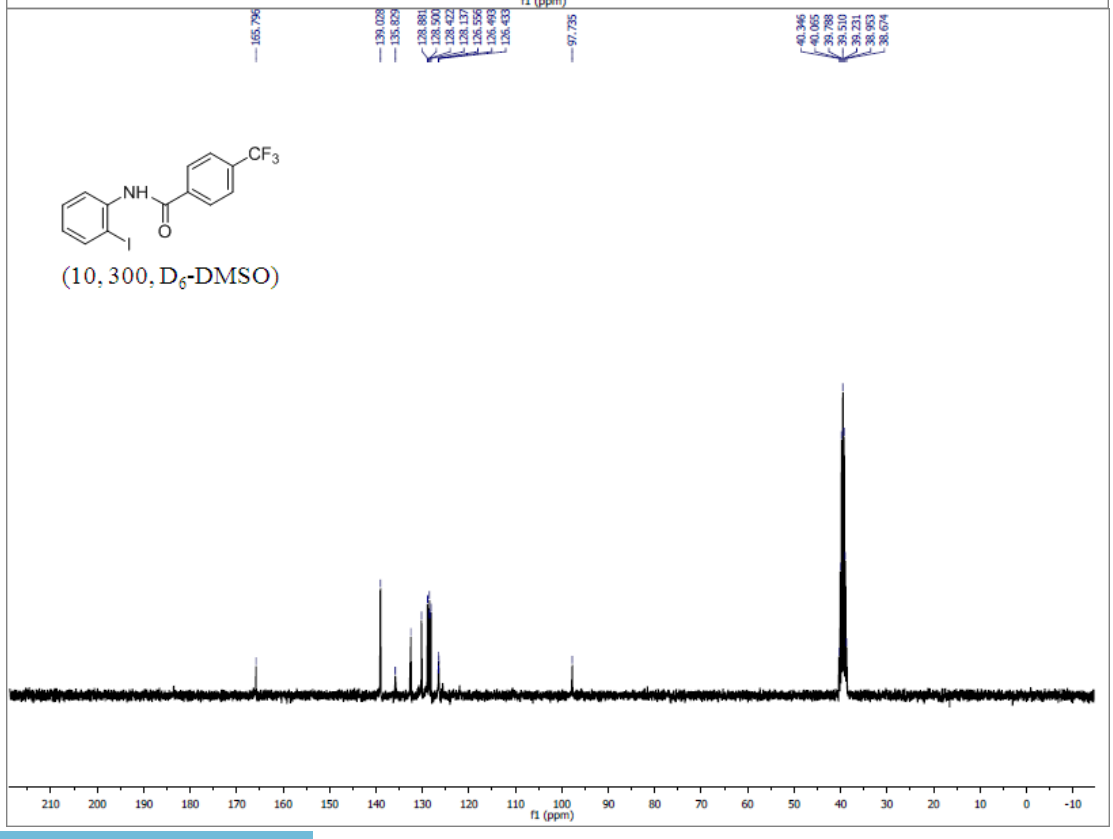


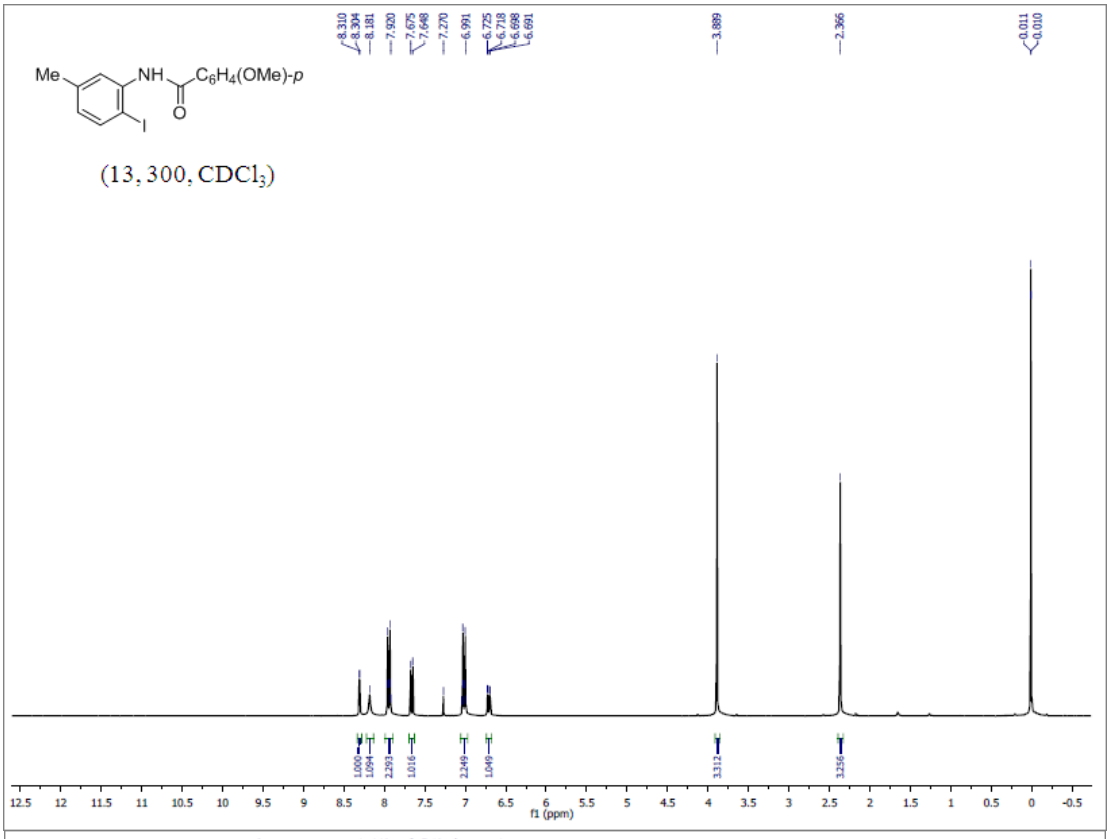


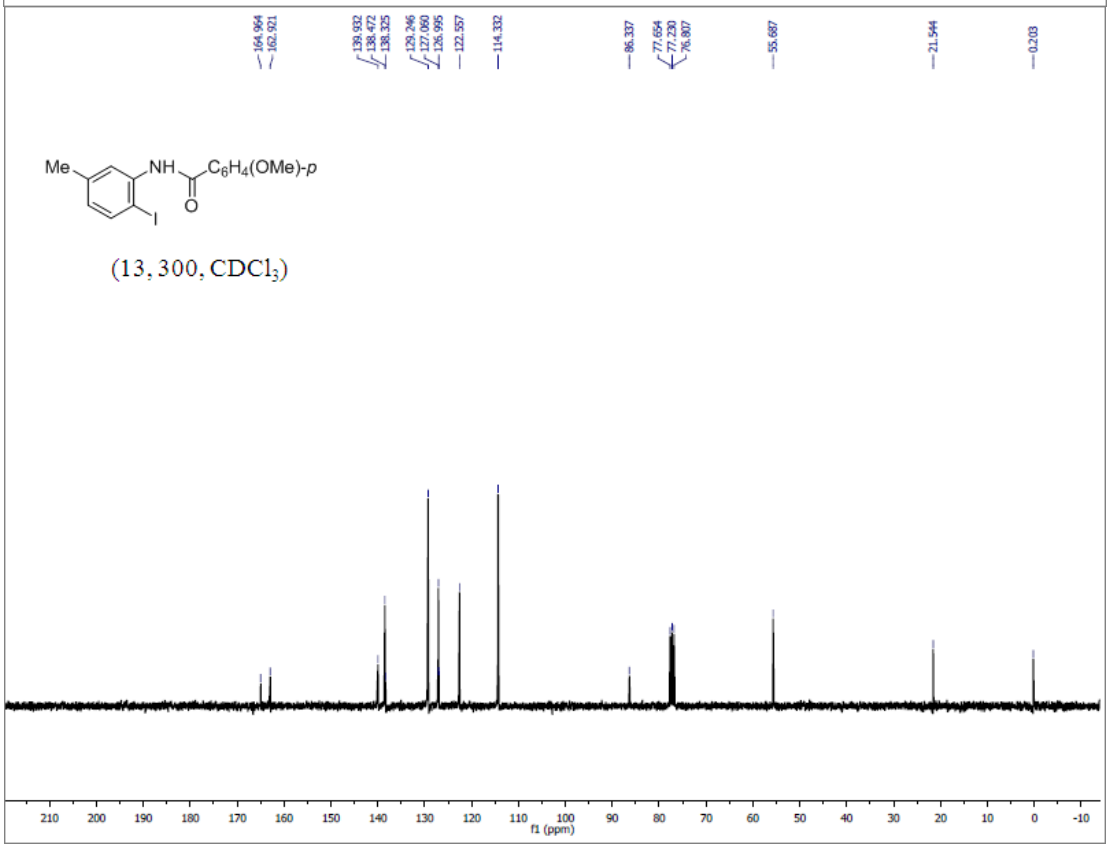


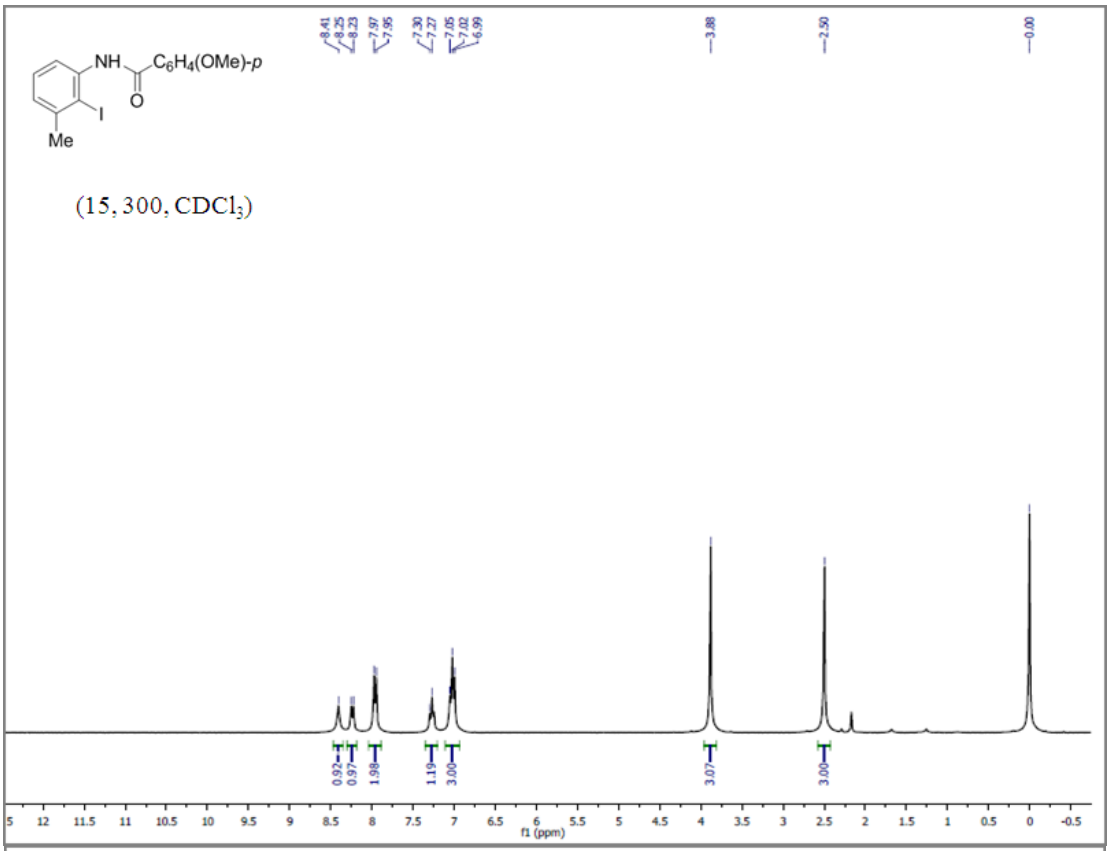
APPENDIX D. CHAPTER 4 ^{1}H AND ^{13}C NMR SPECTRA

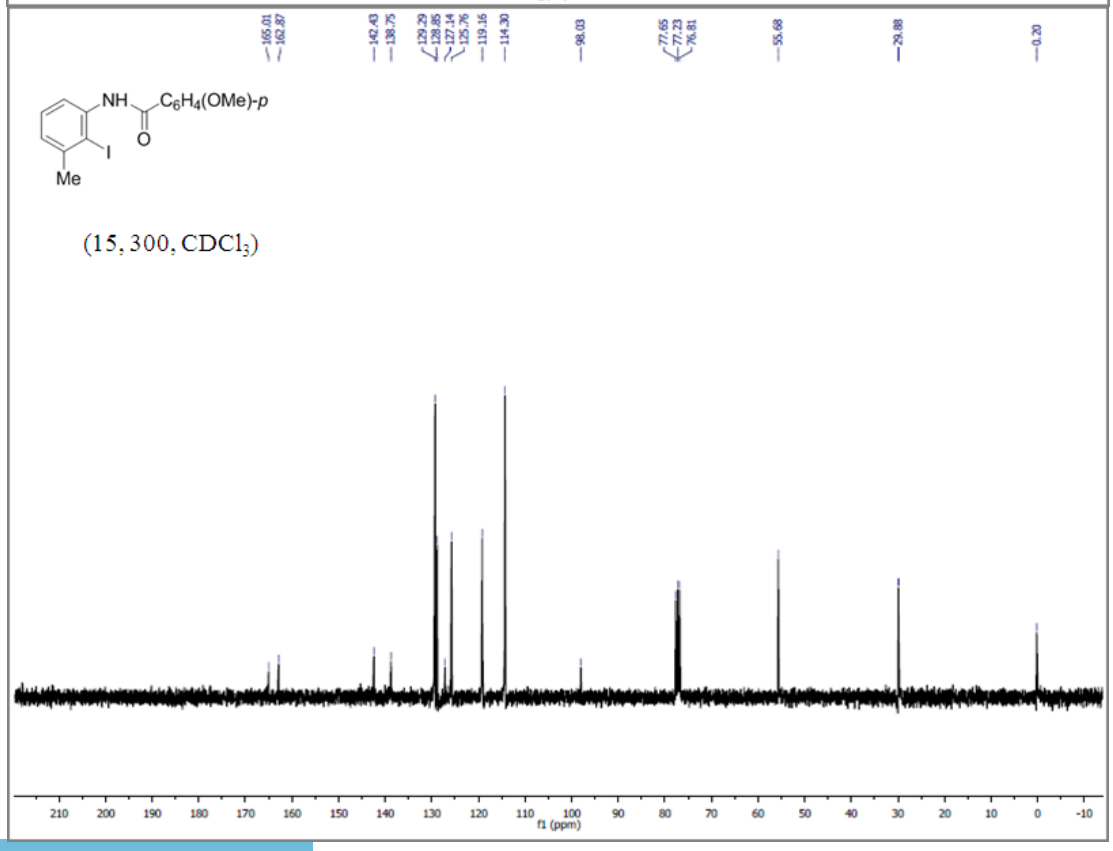


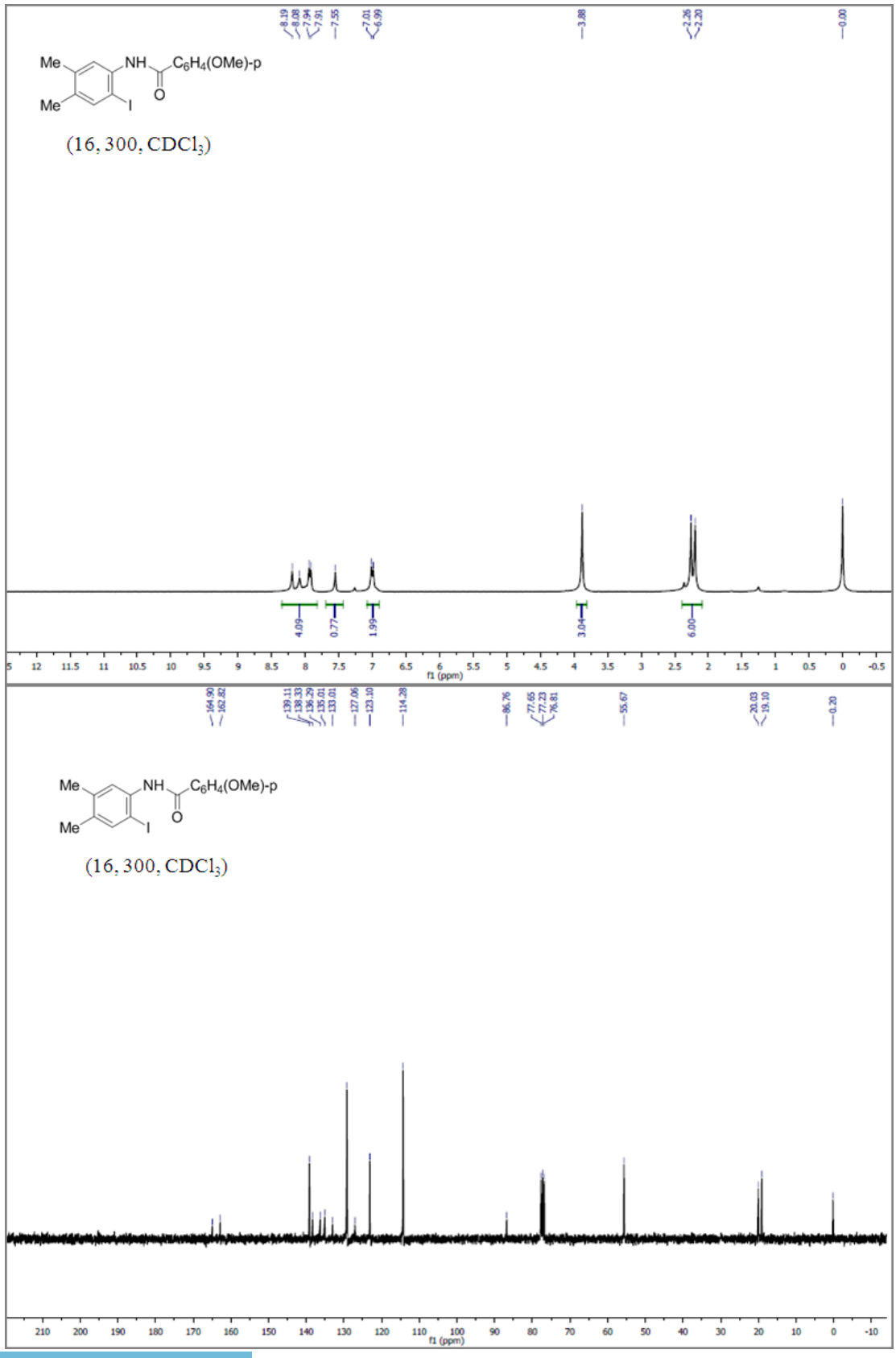


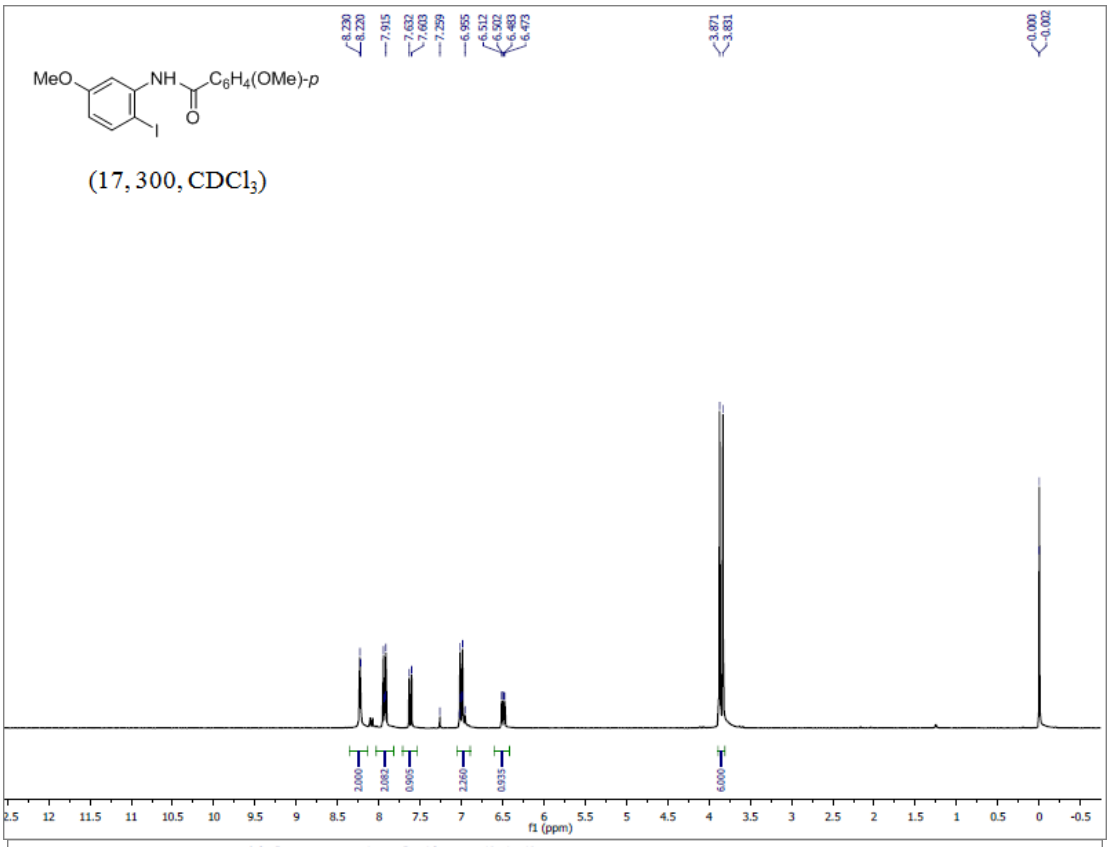




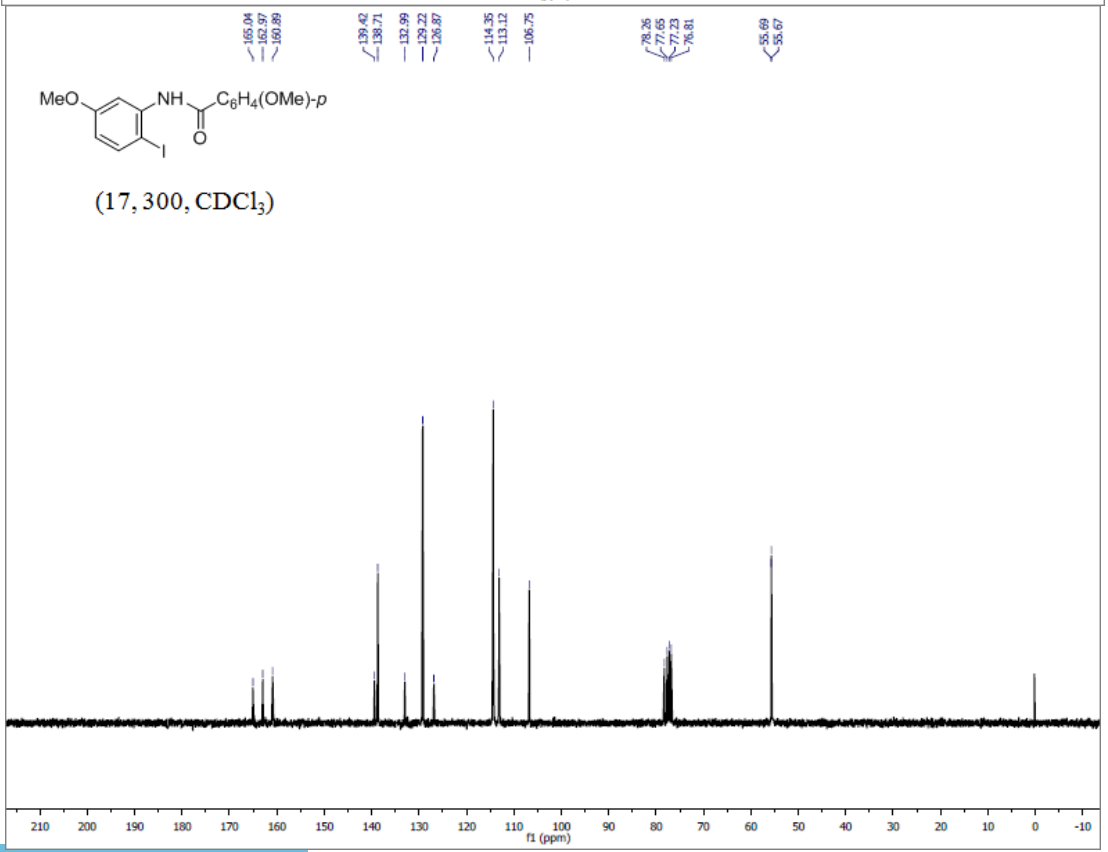








(17, 300, $CDCl_3$)



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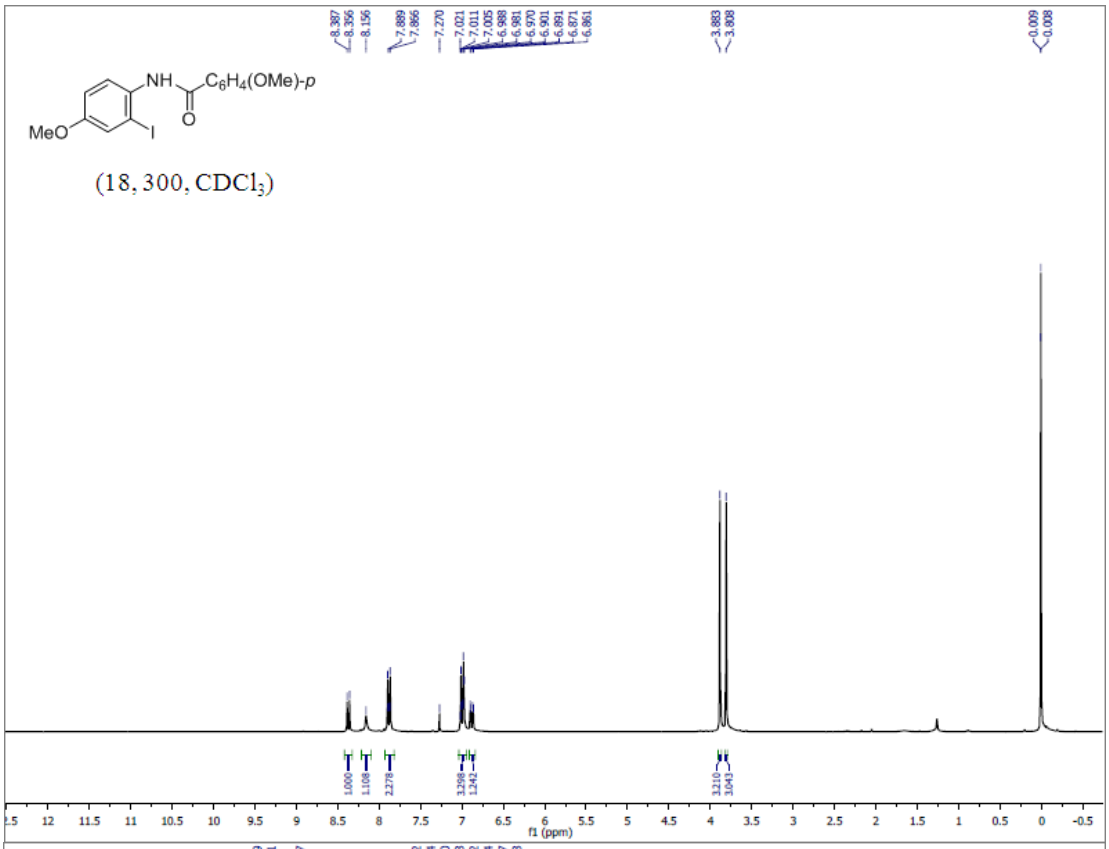

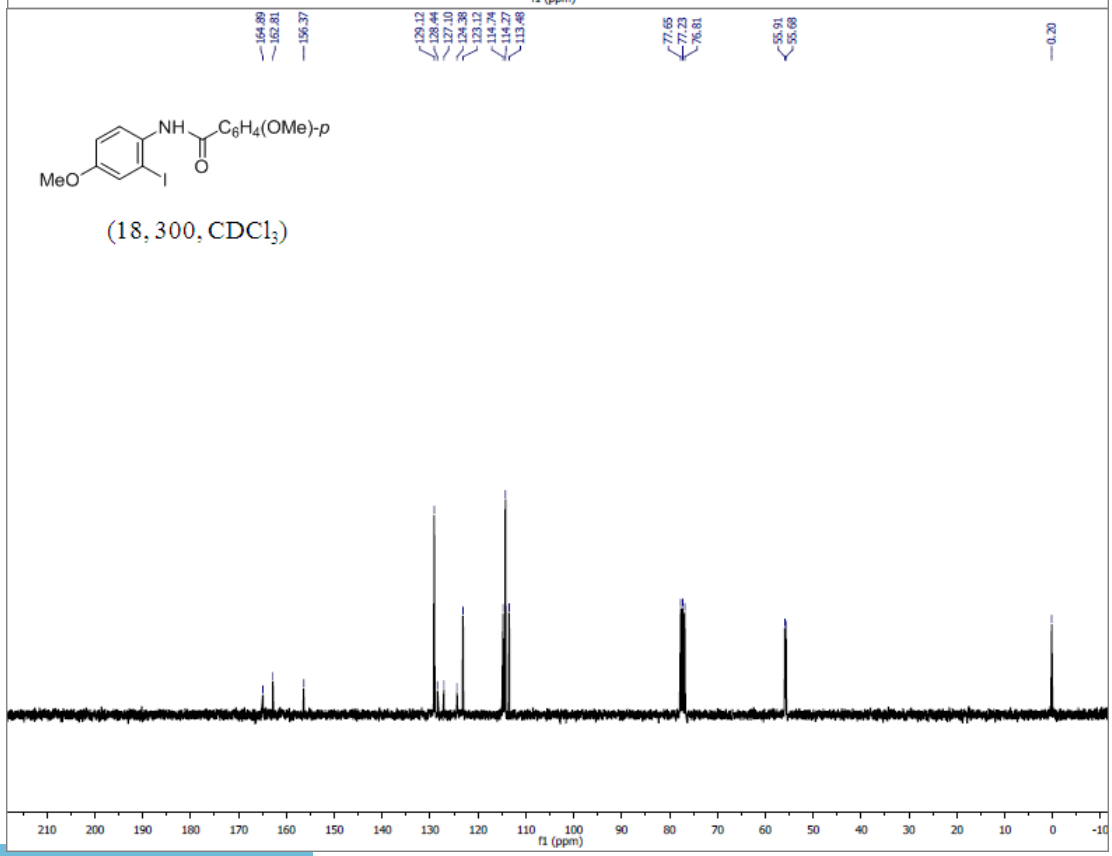

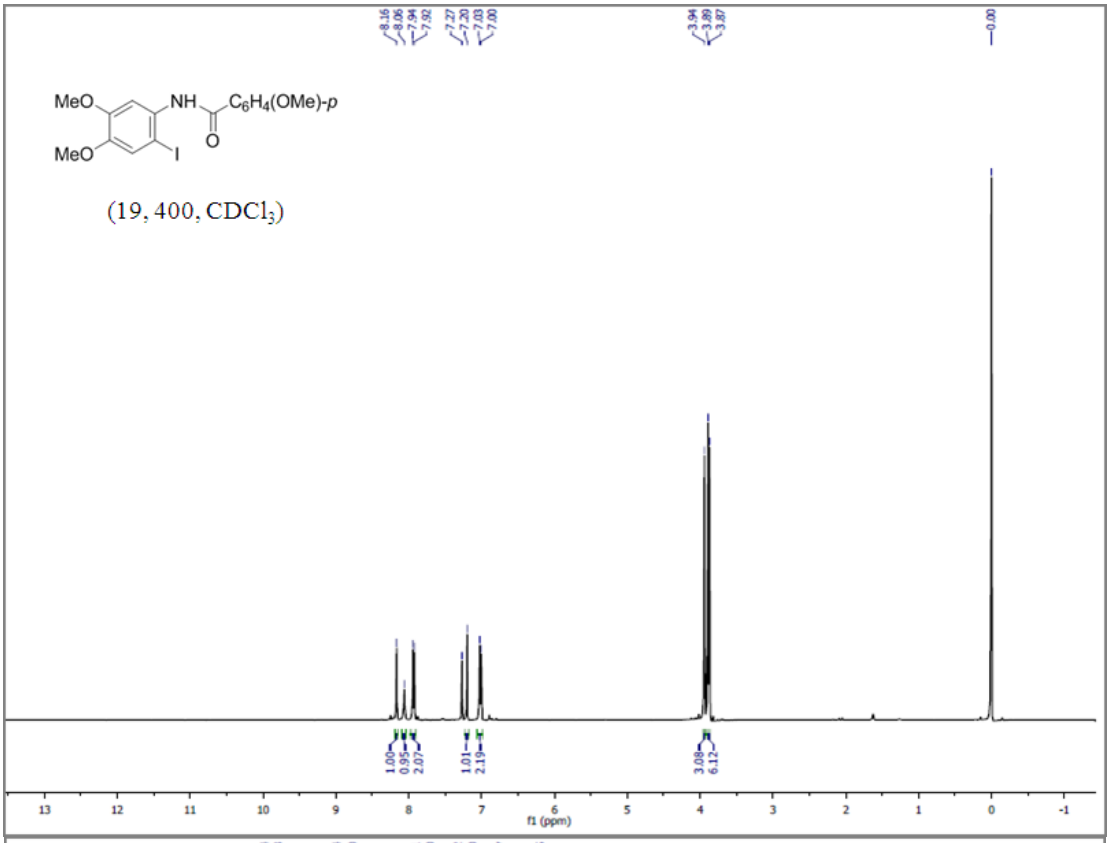

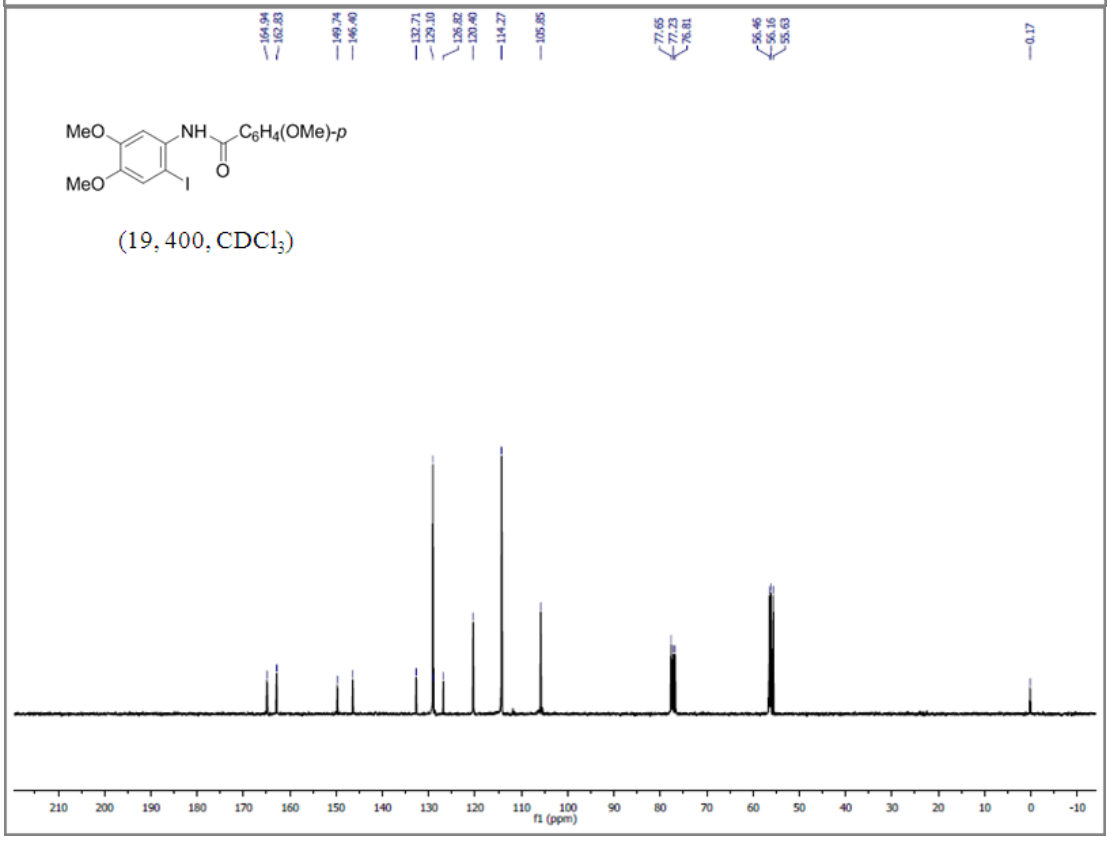

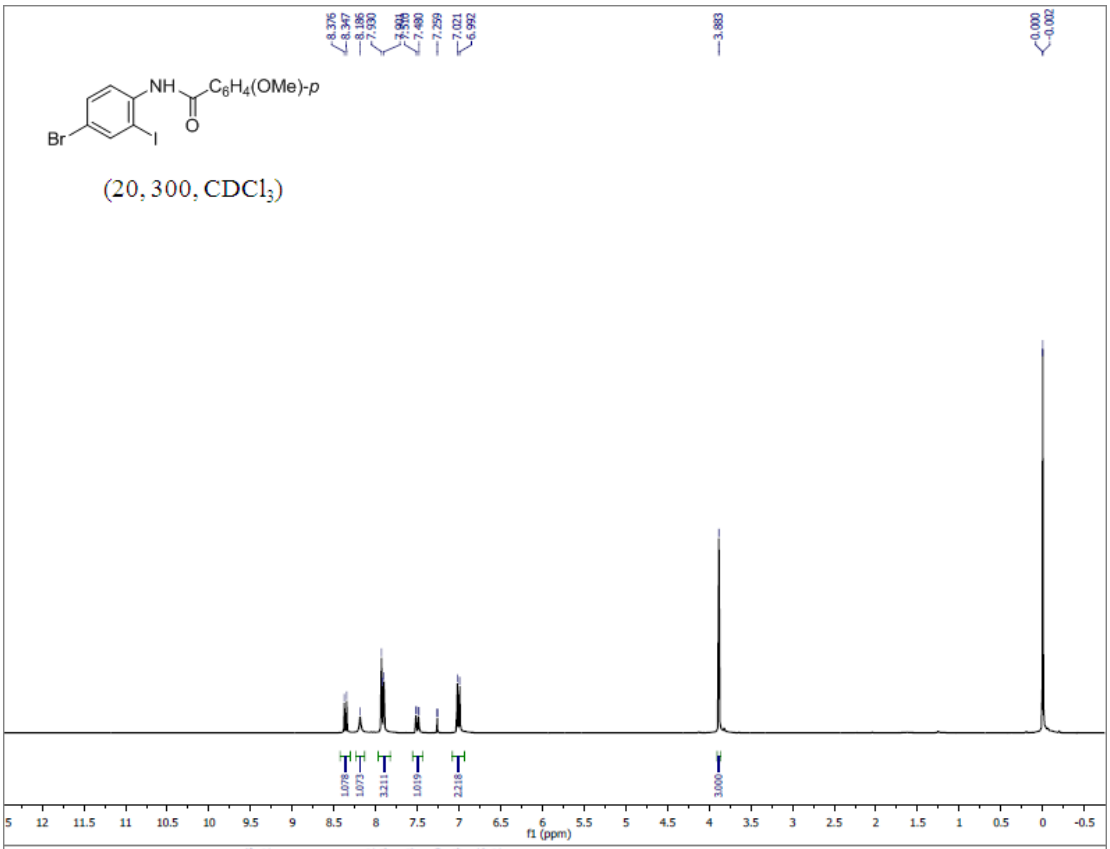

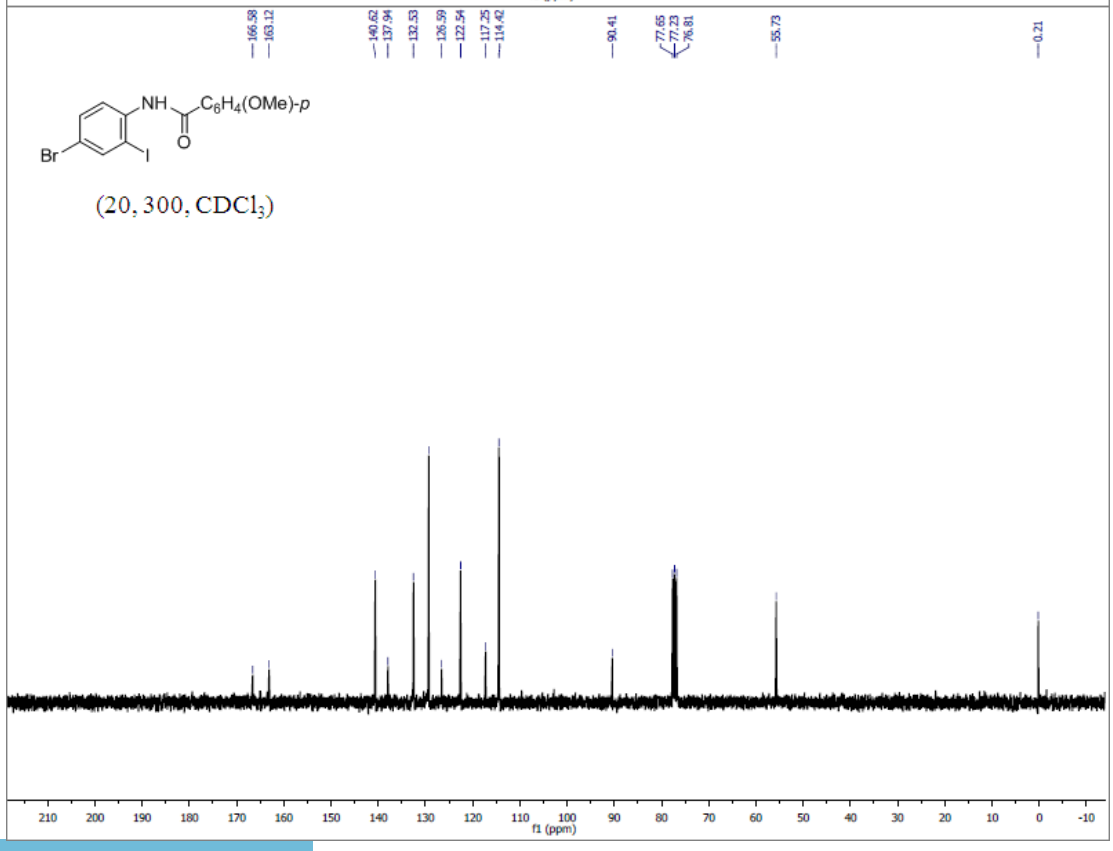

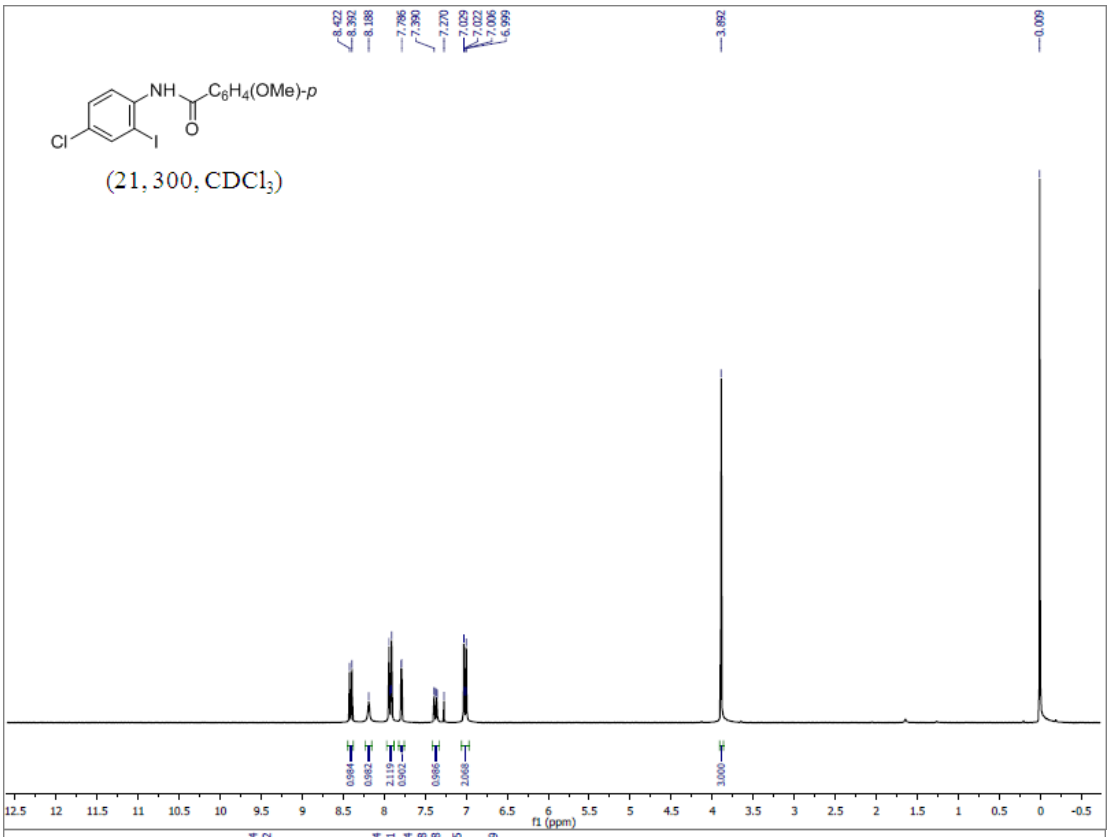

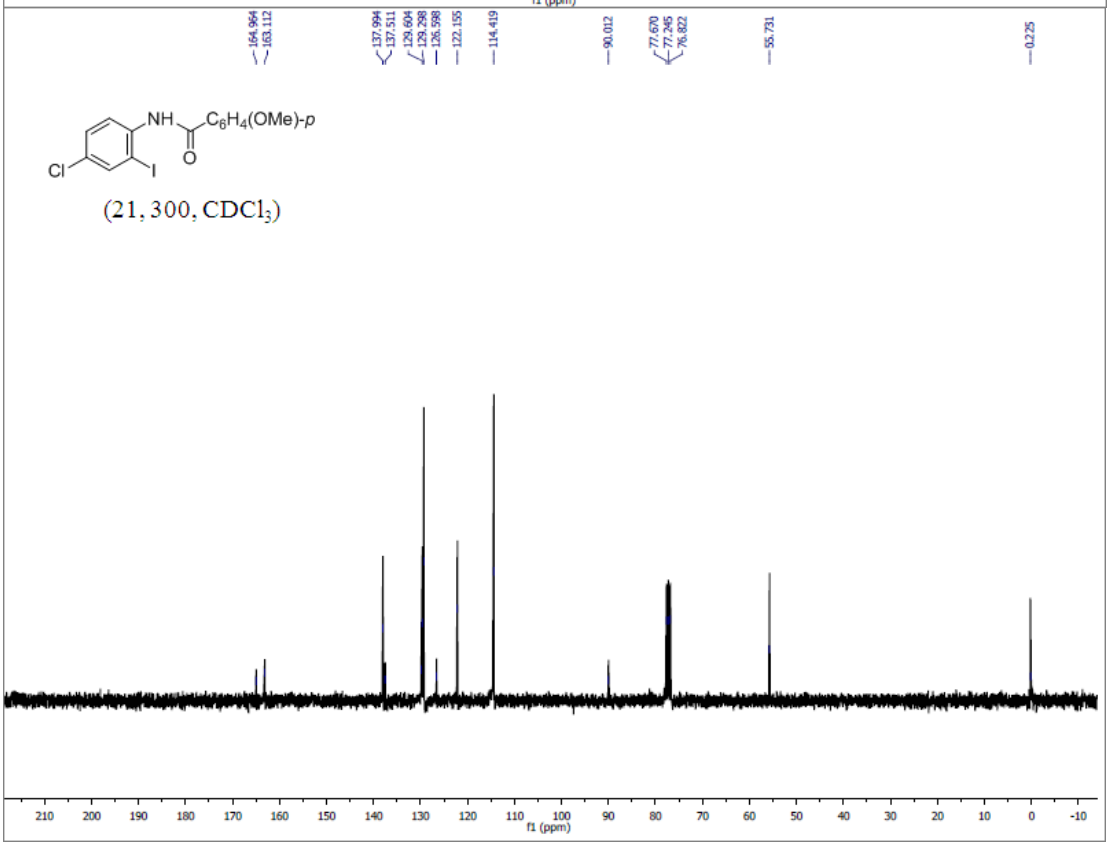

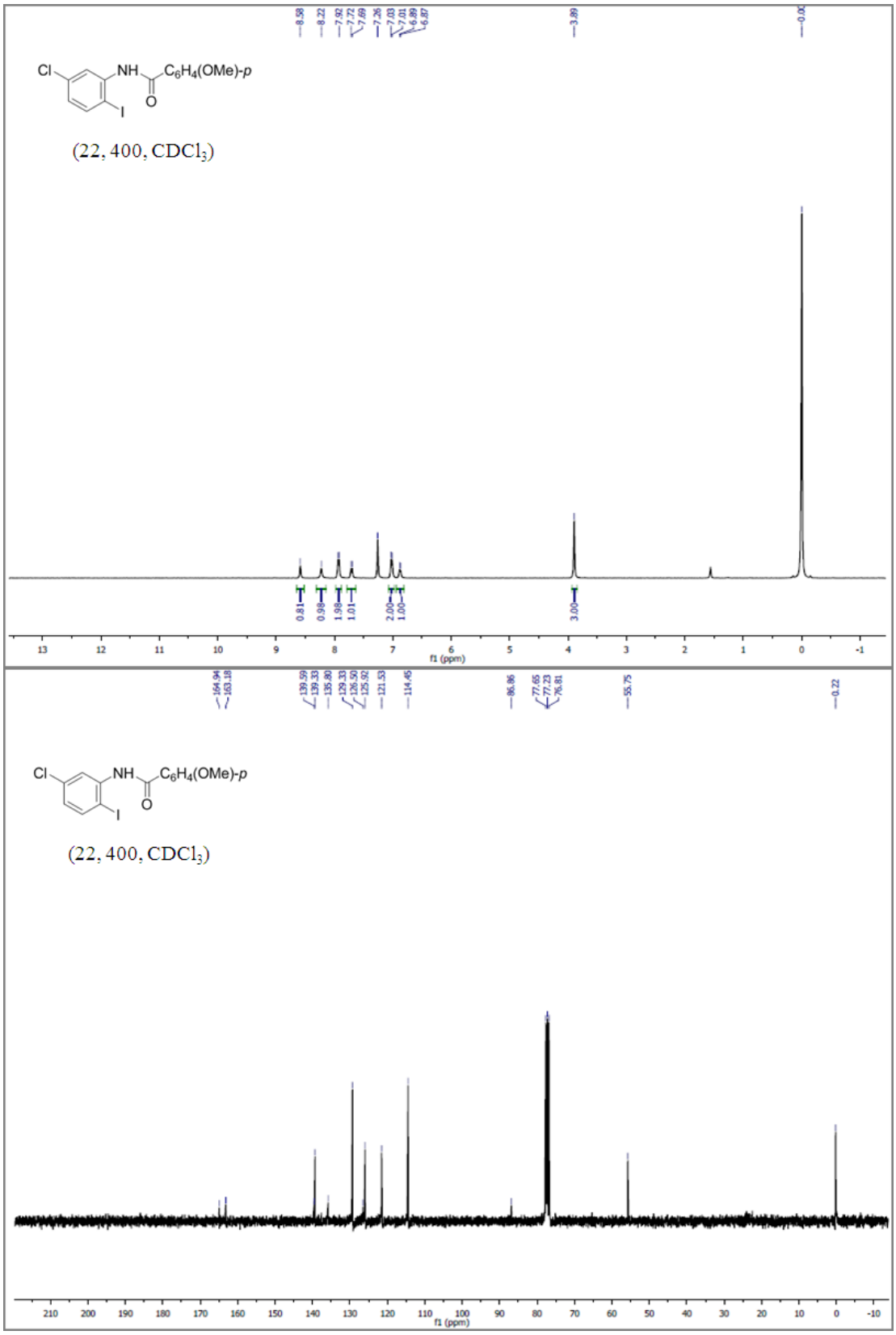

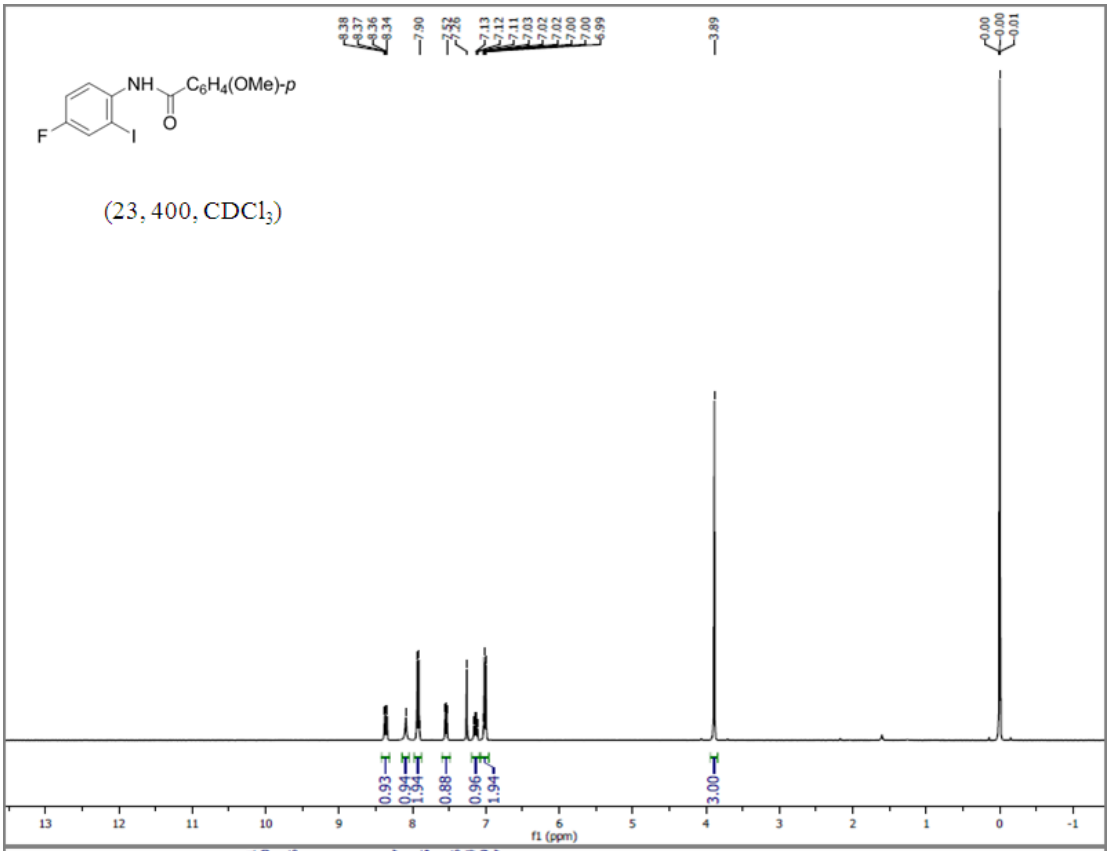

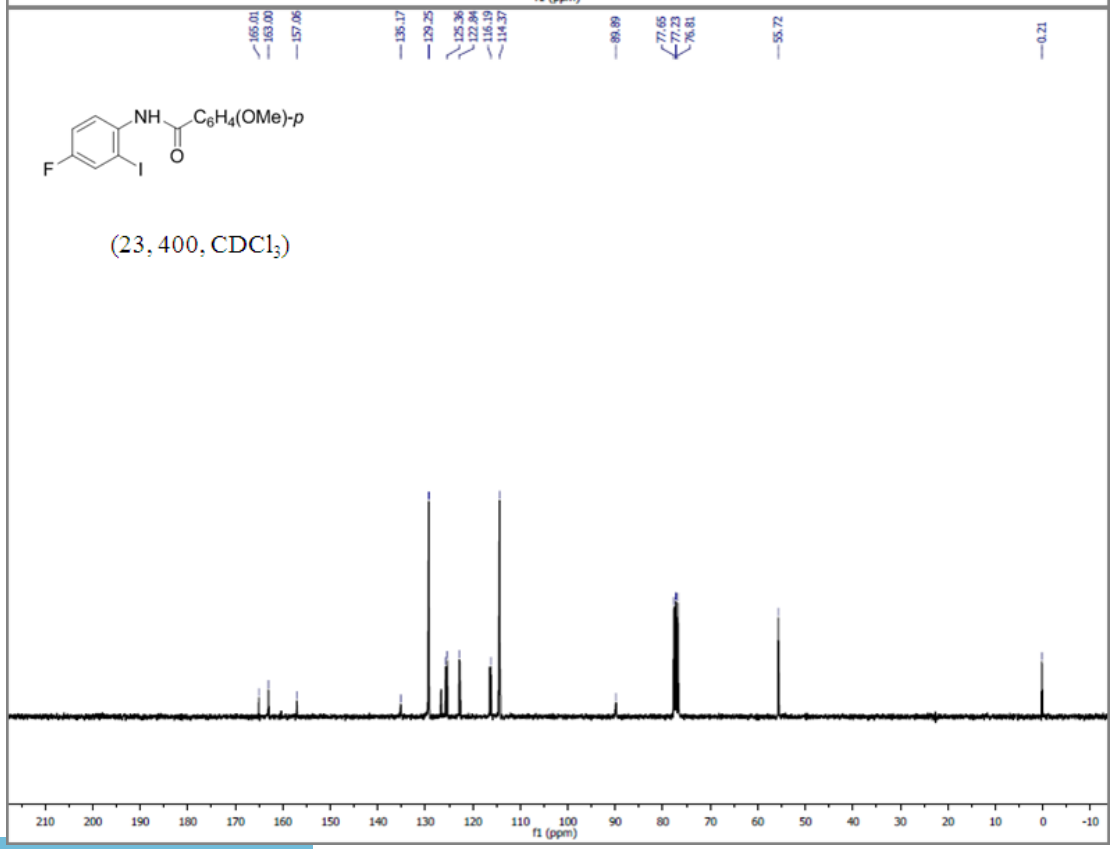

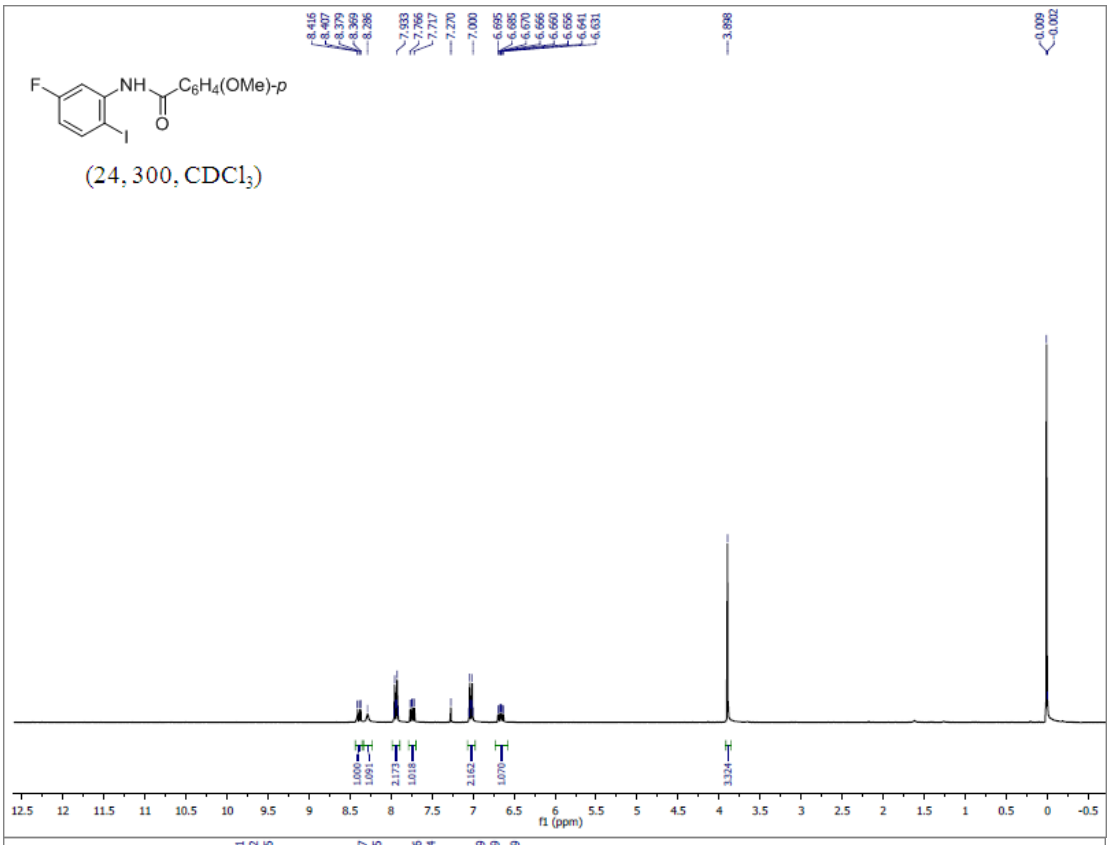

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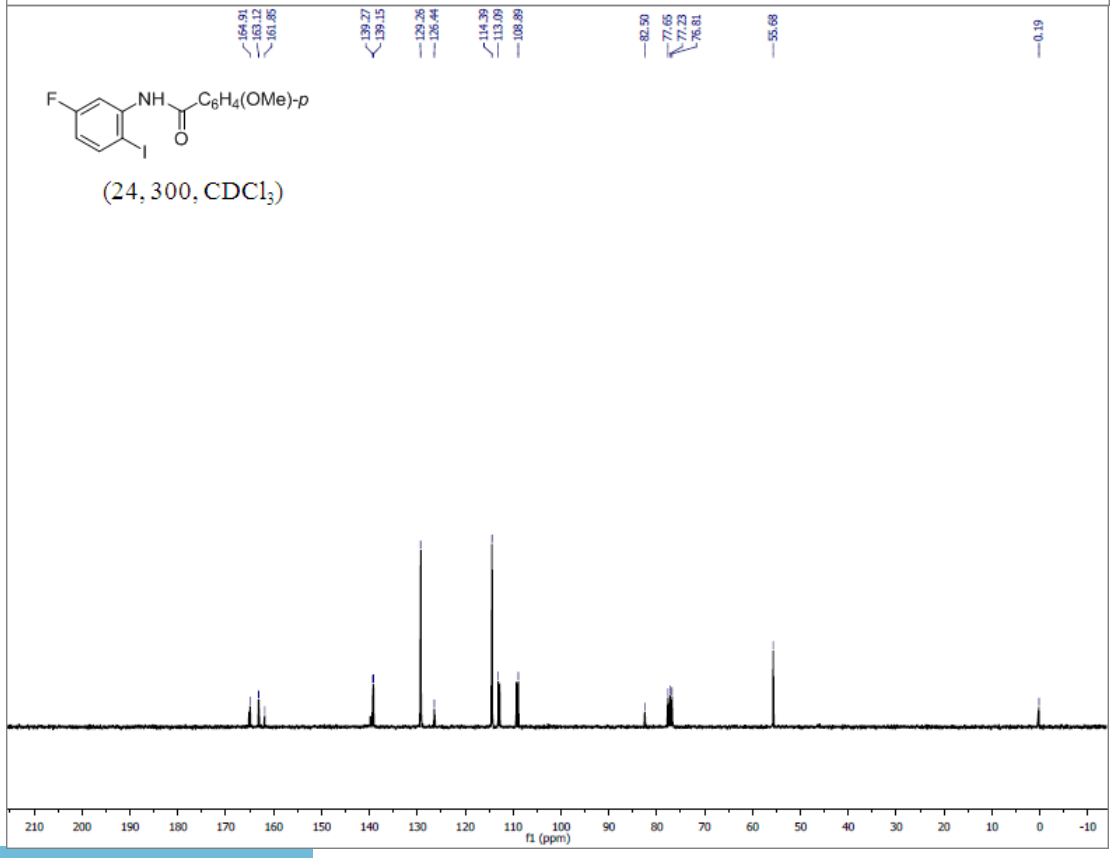

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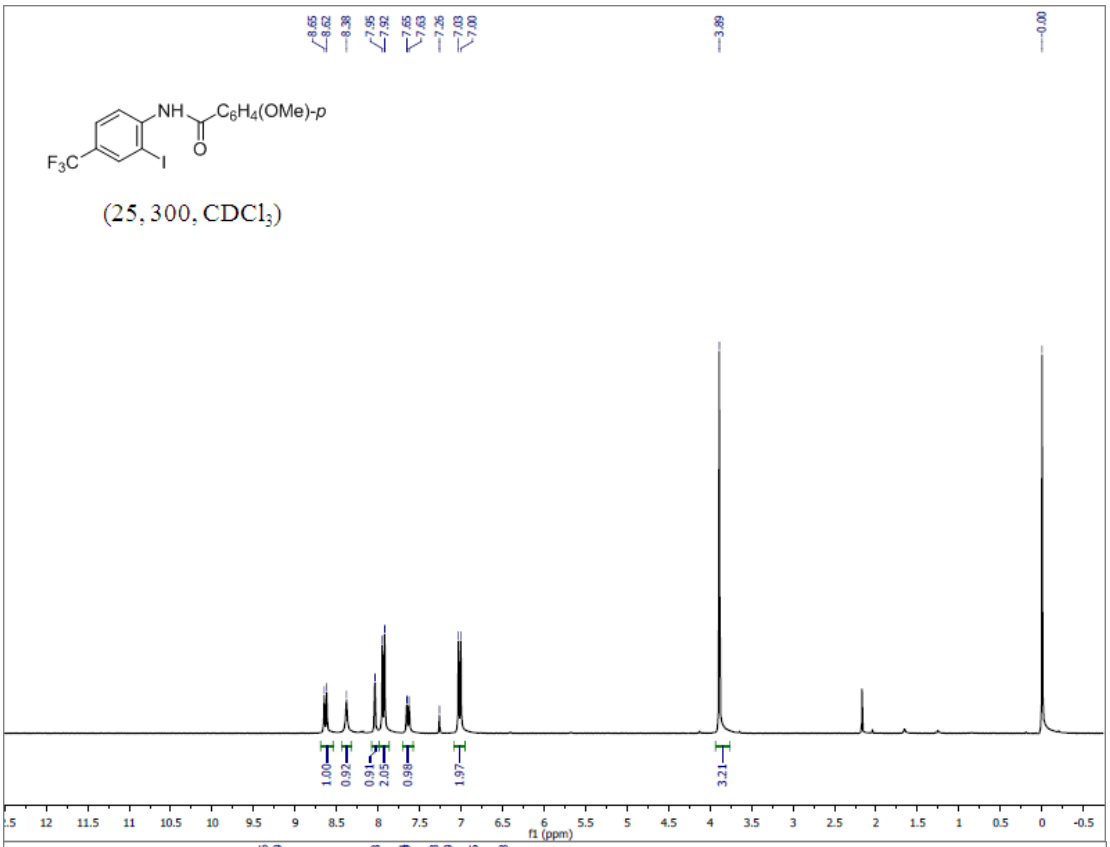

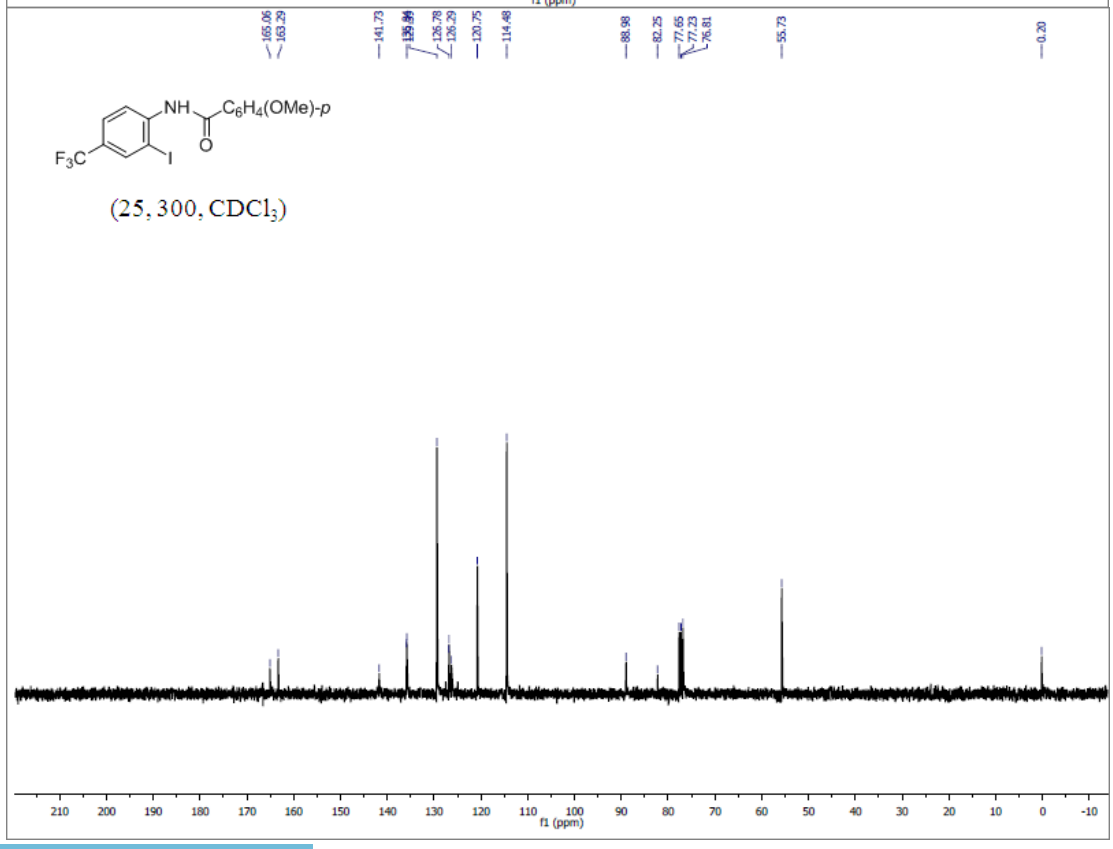

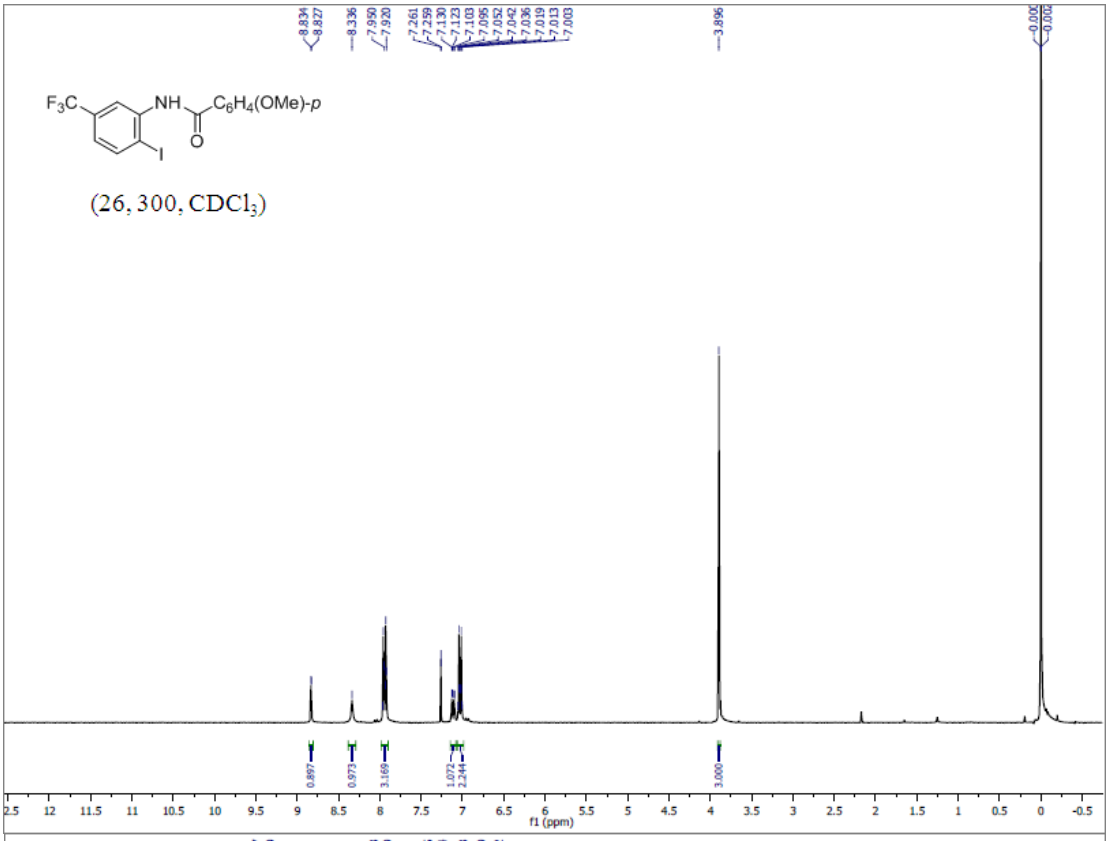

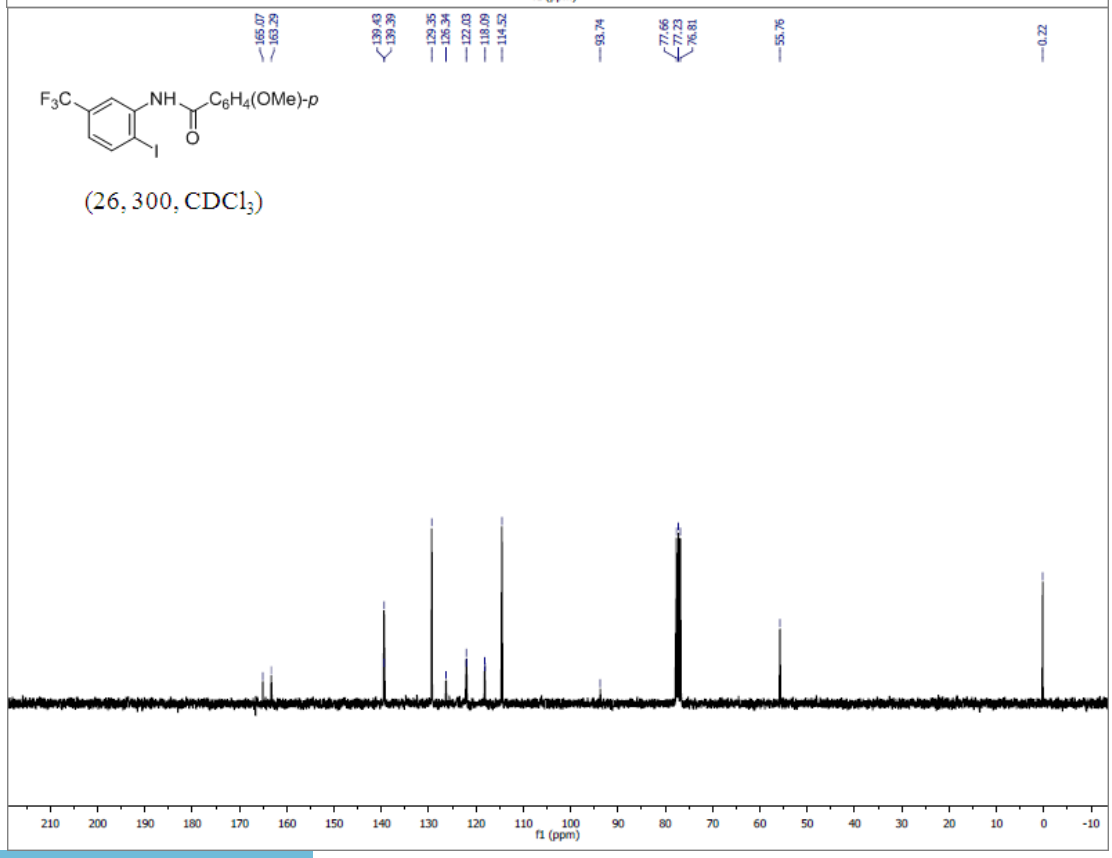

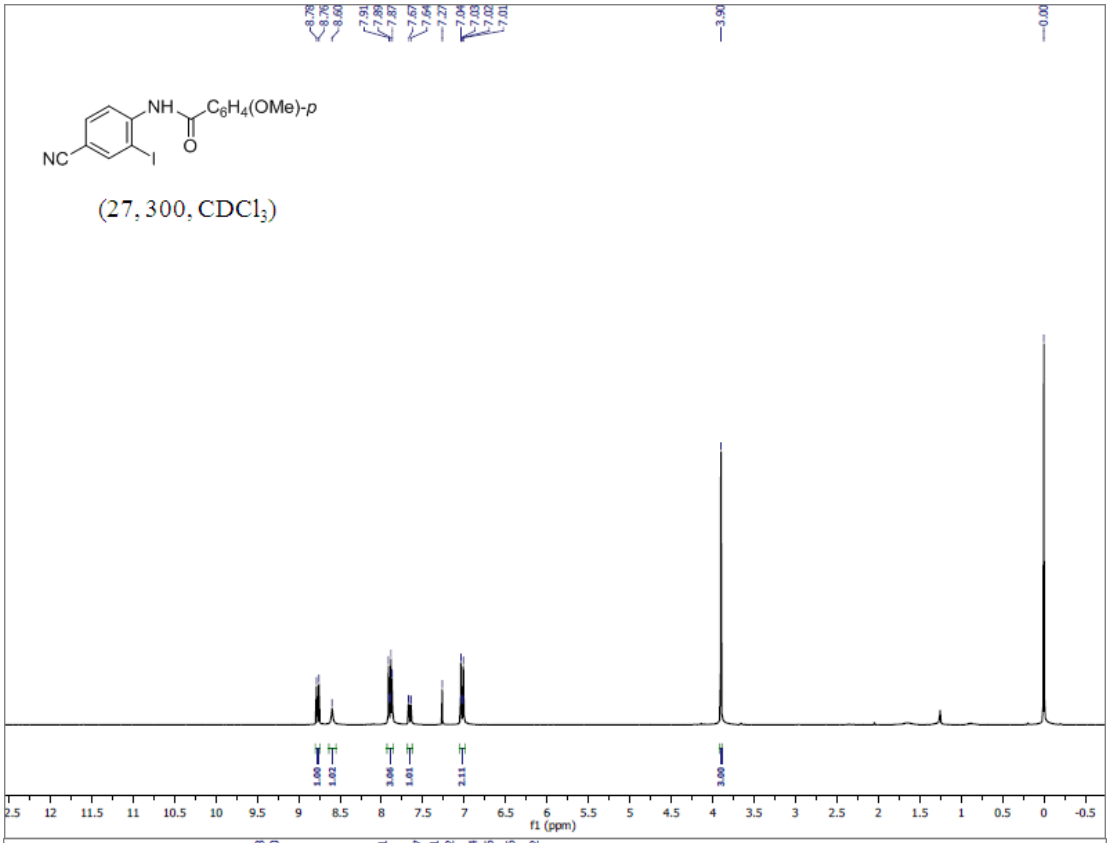

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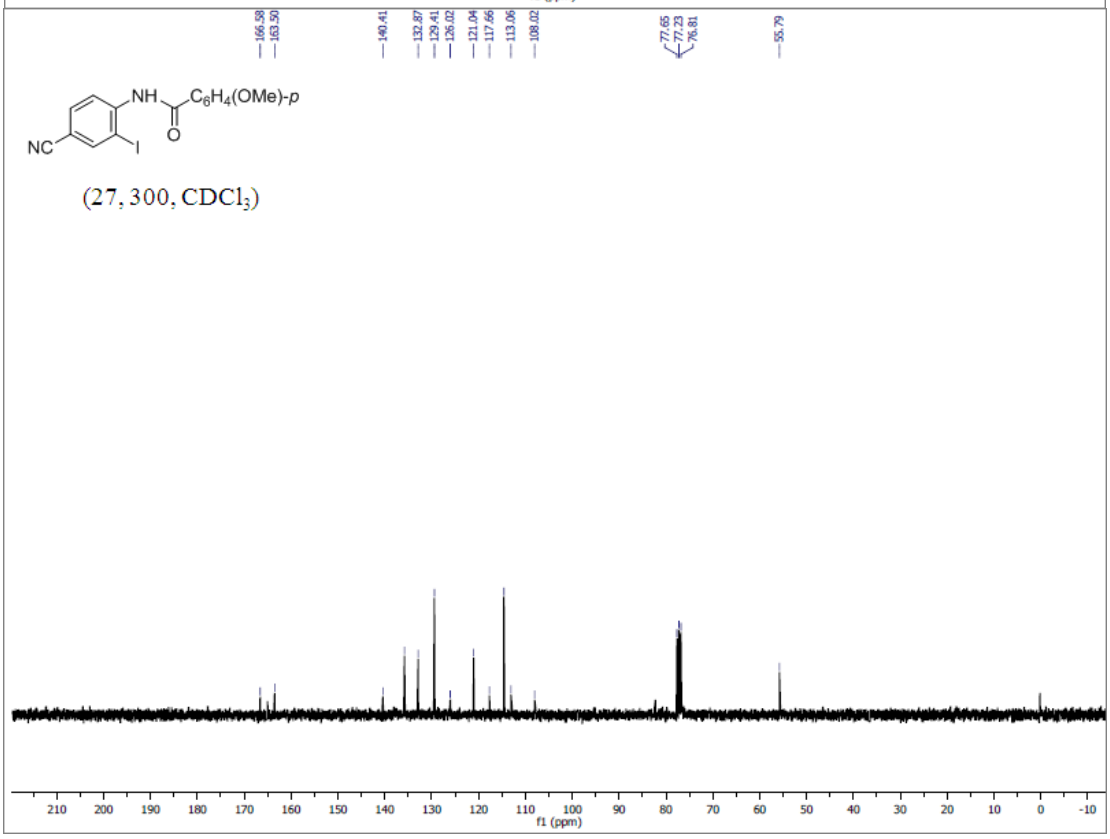

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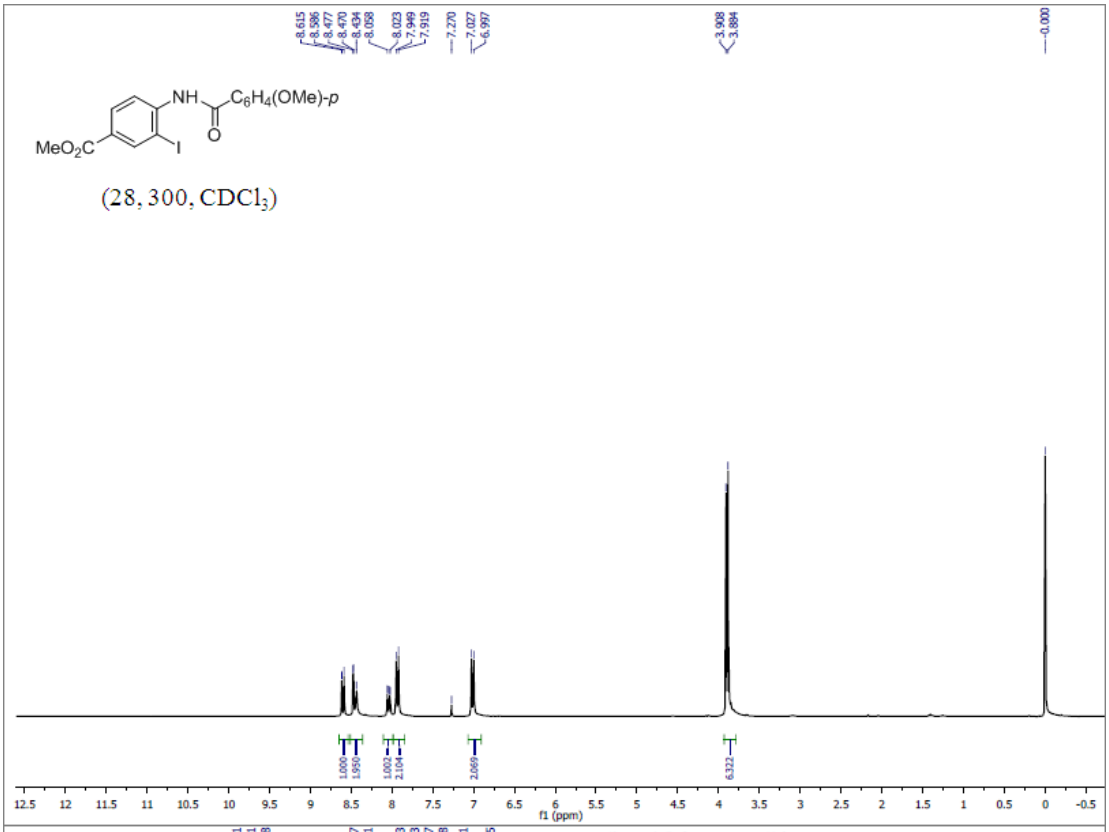

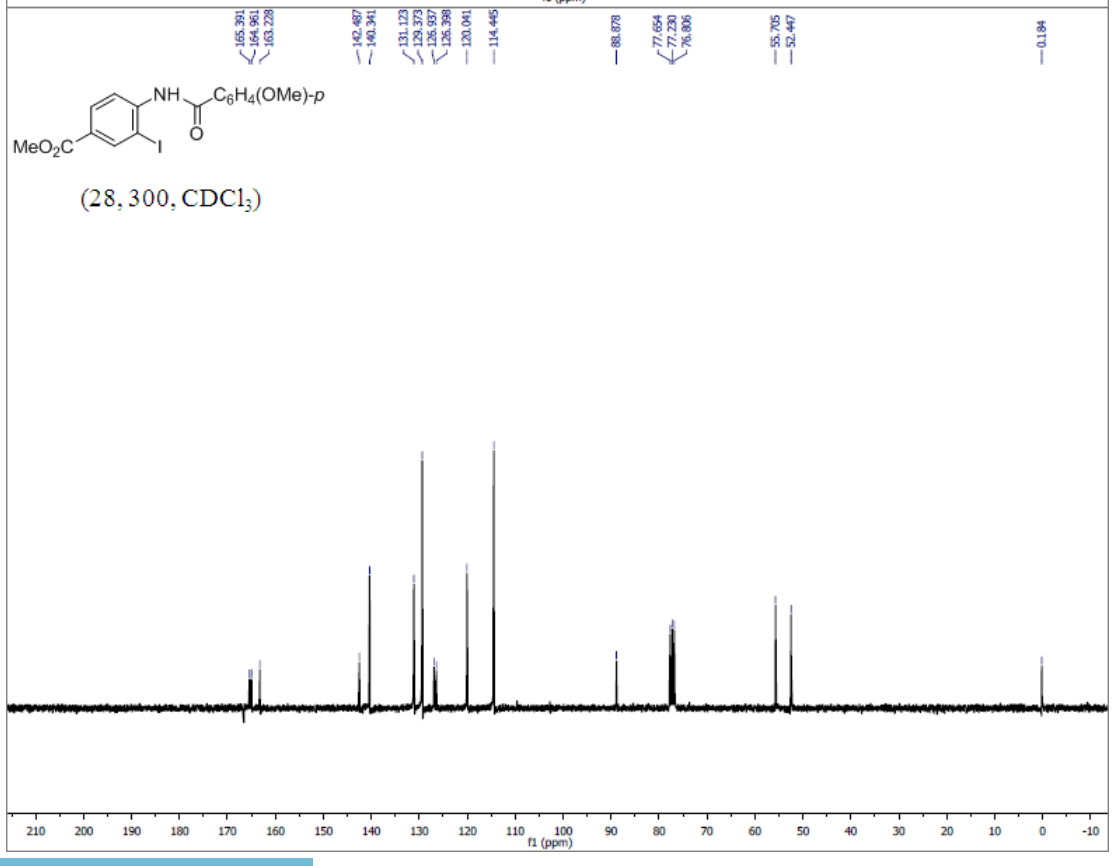

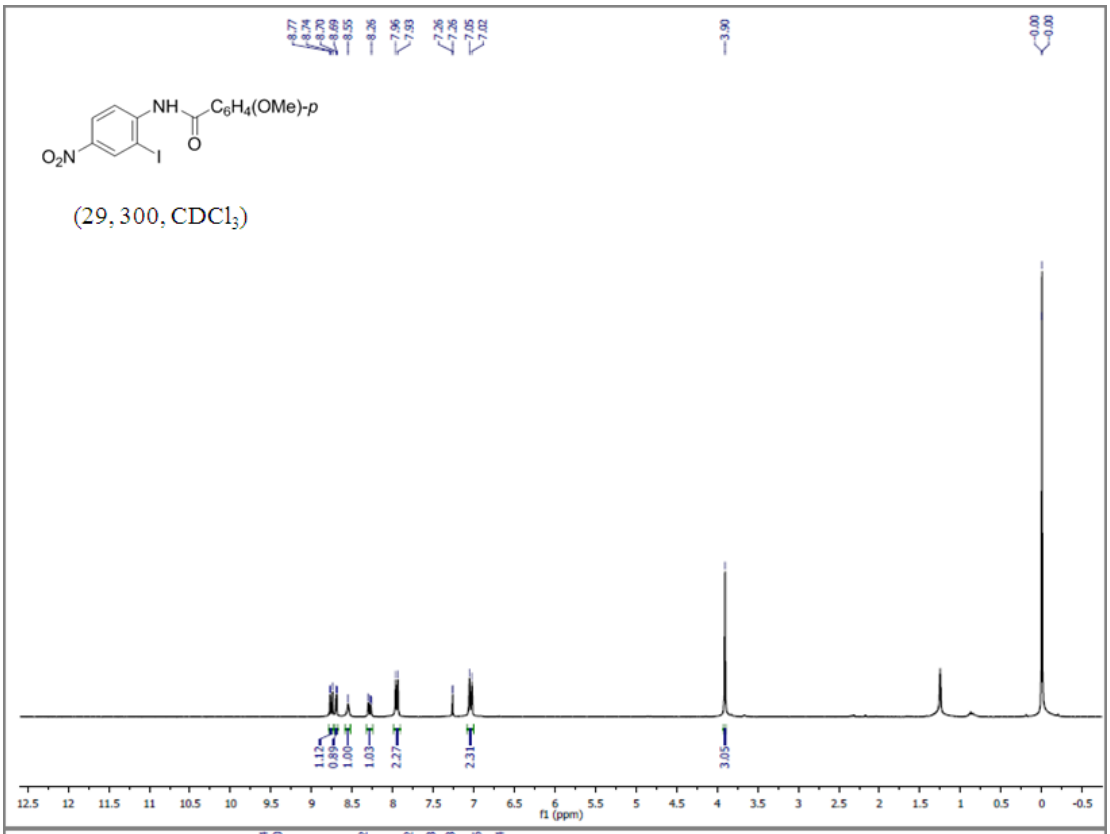

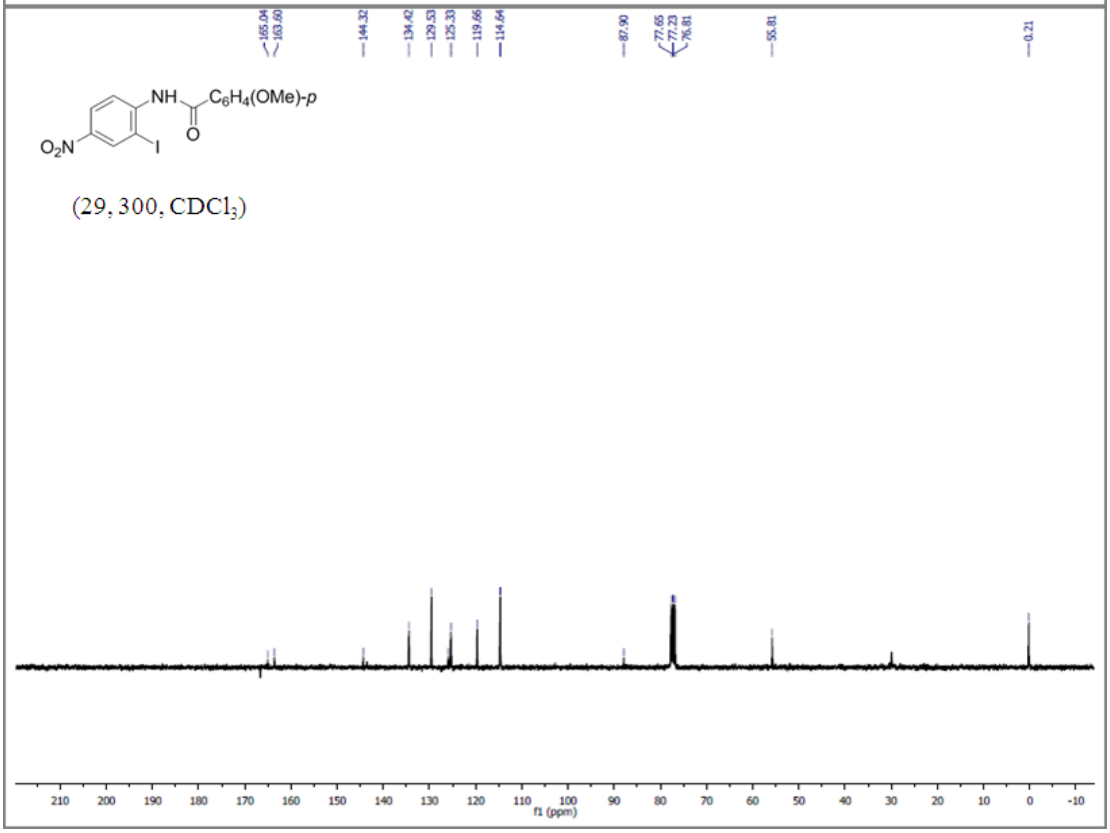

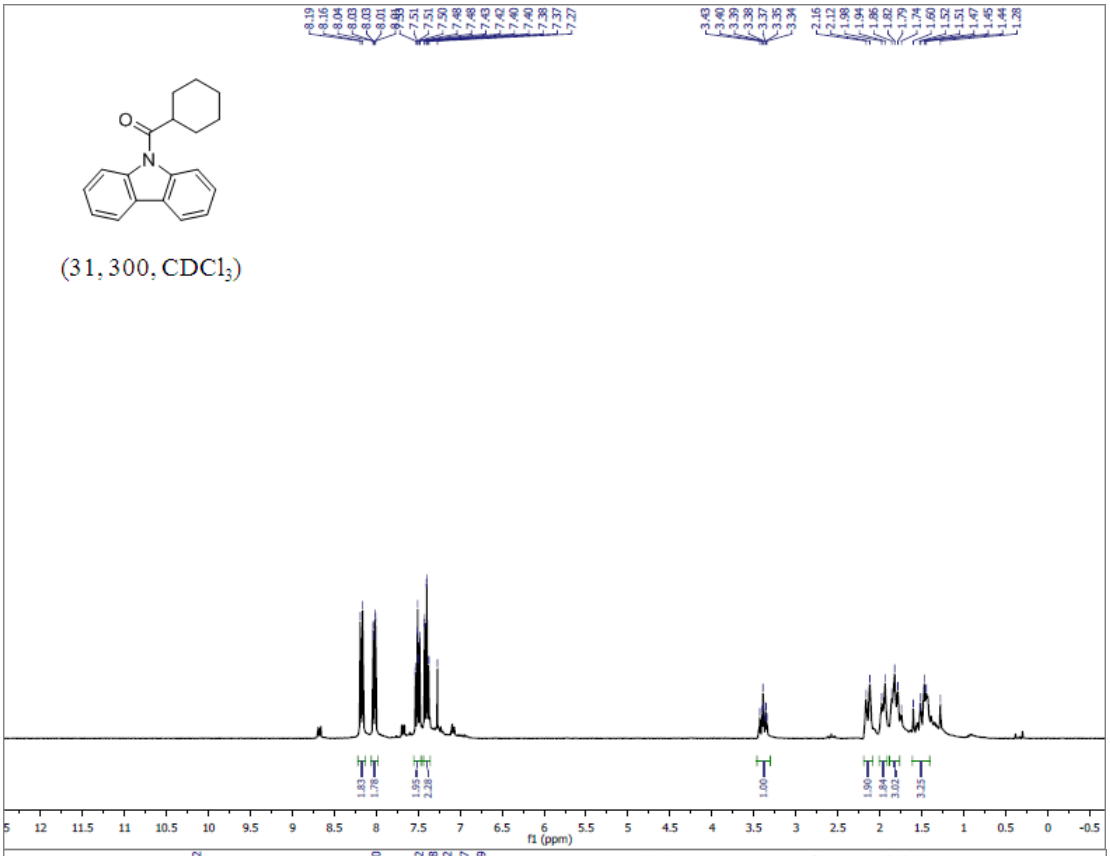

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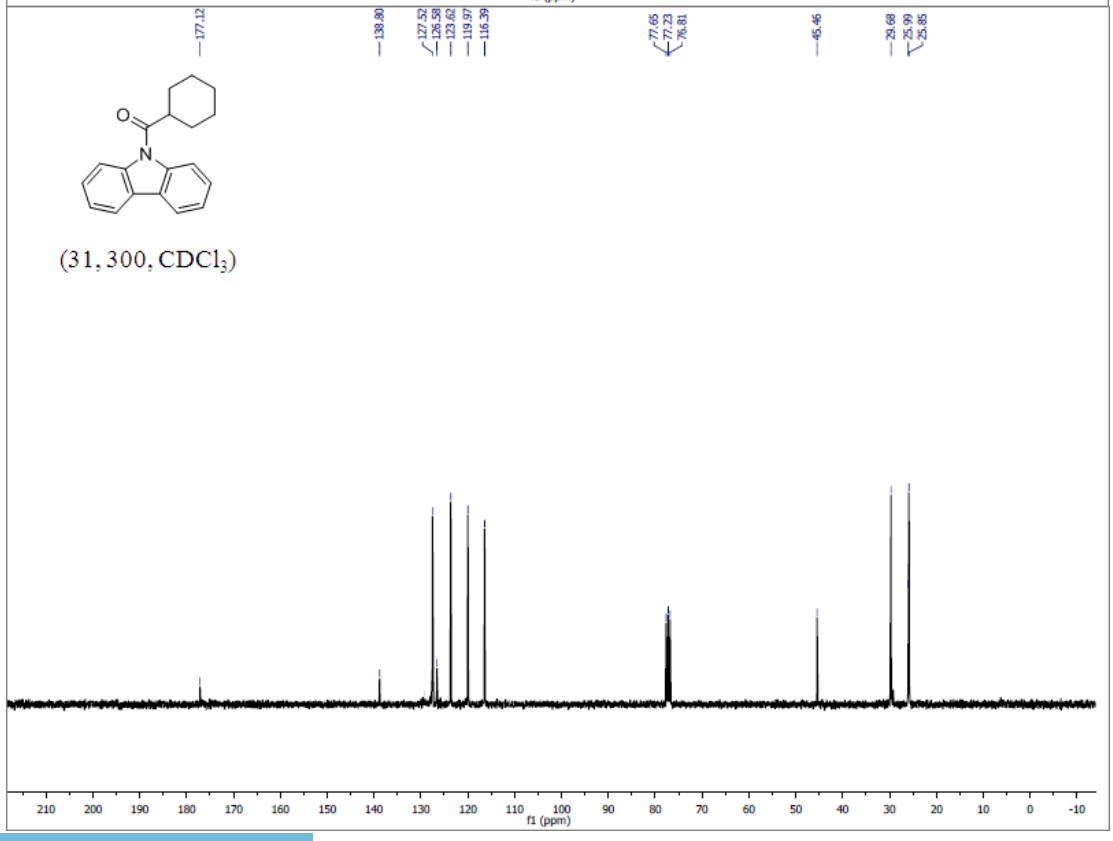

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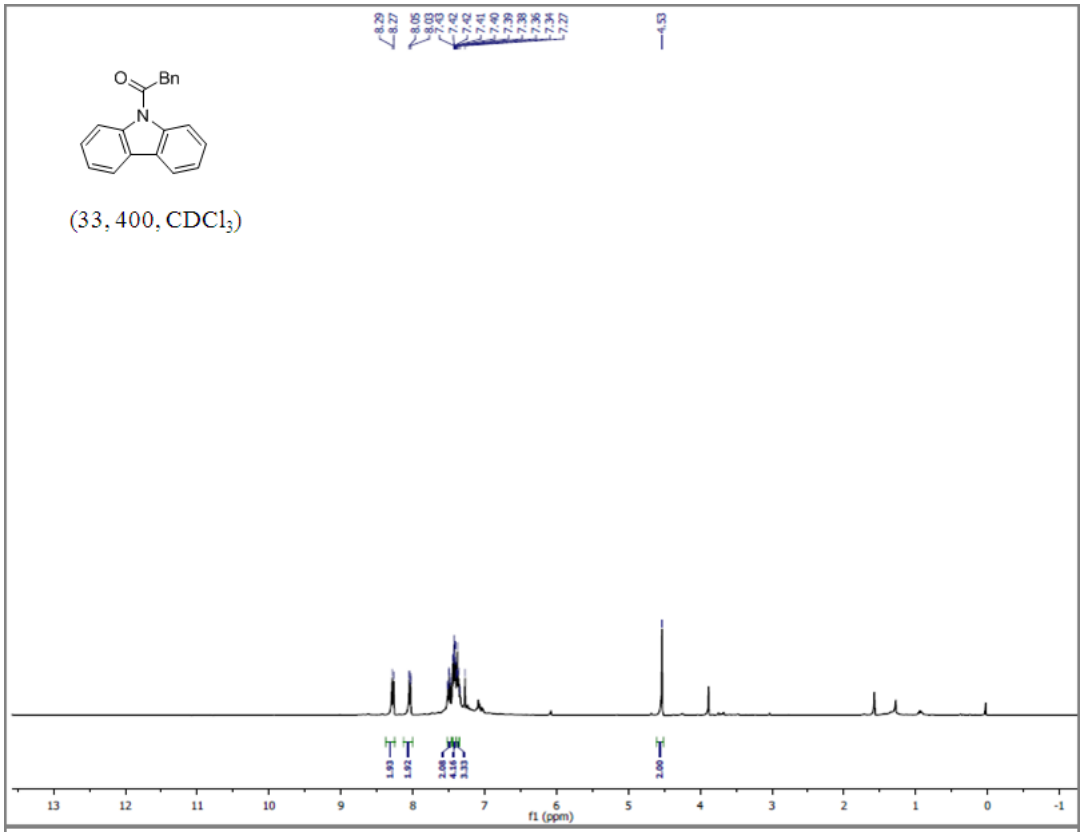

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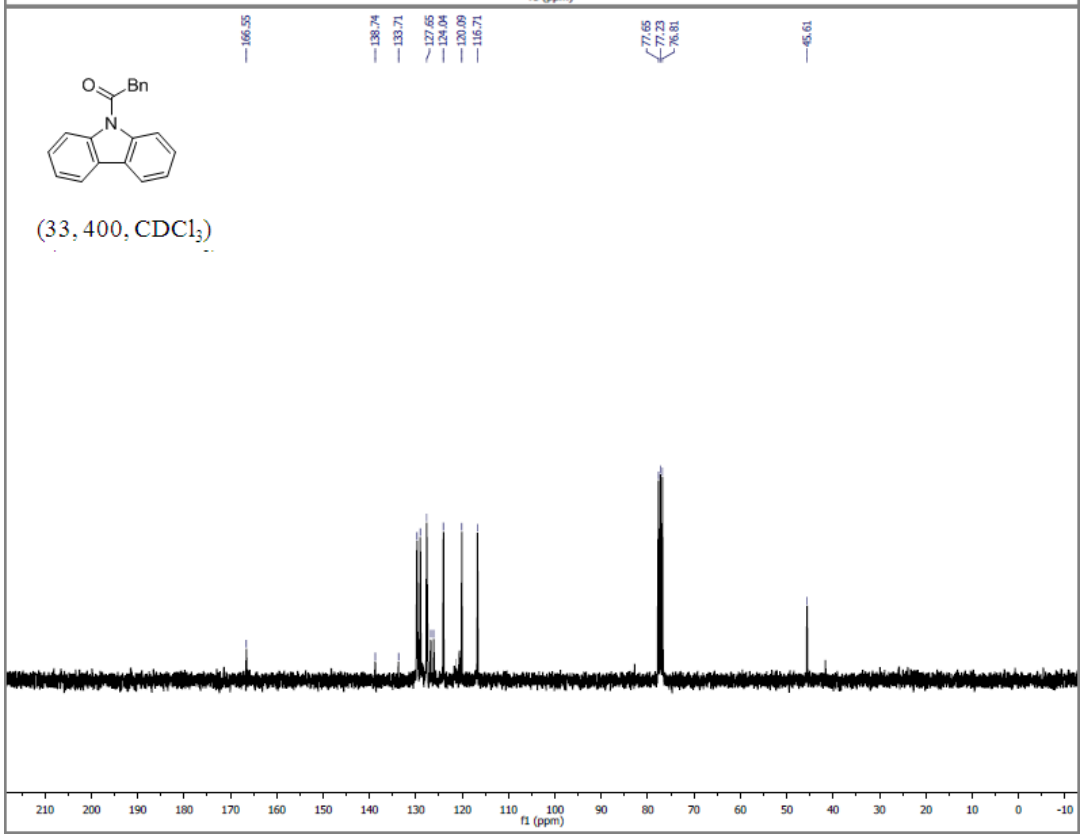

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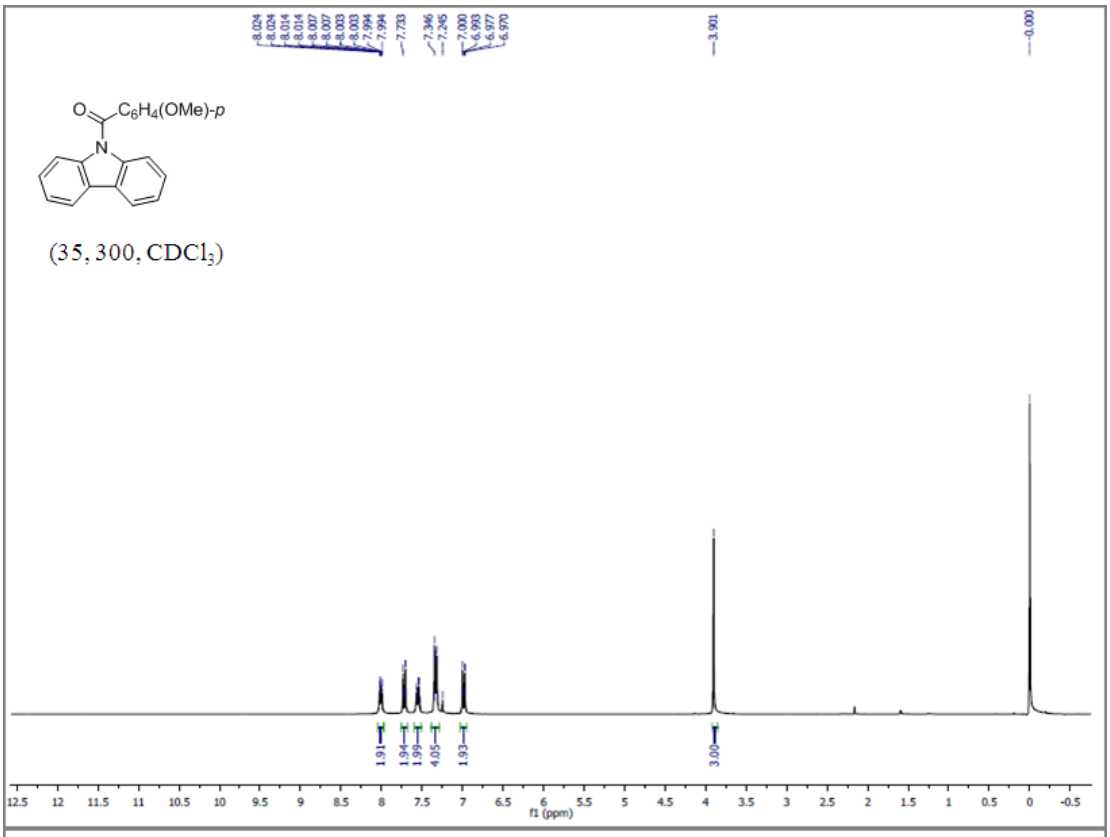

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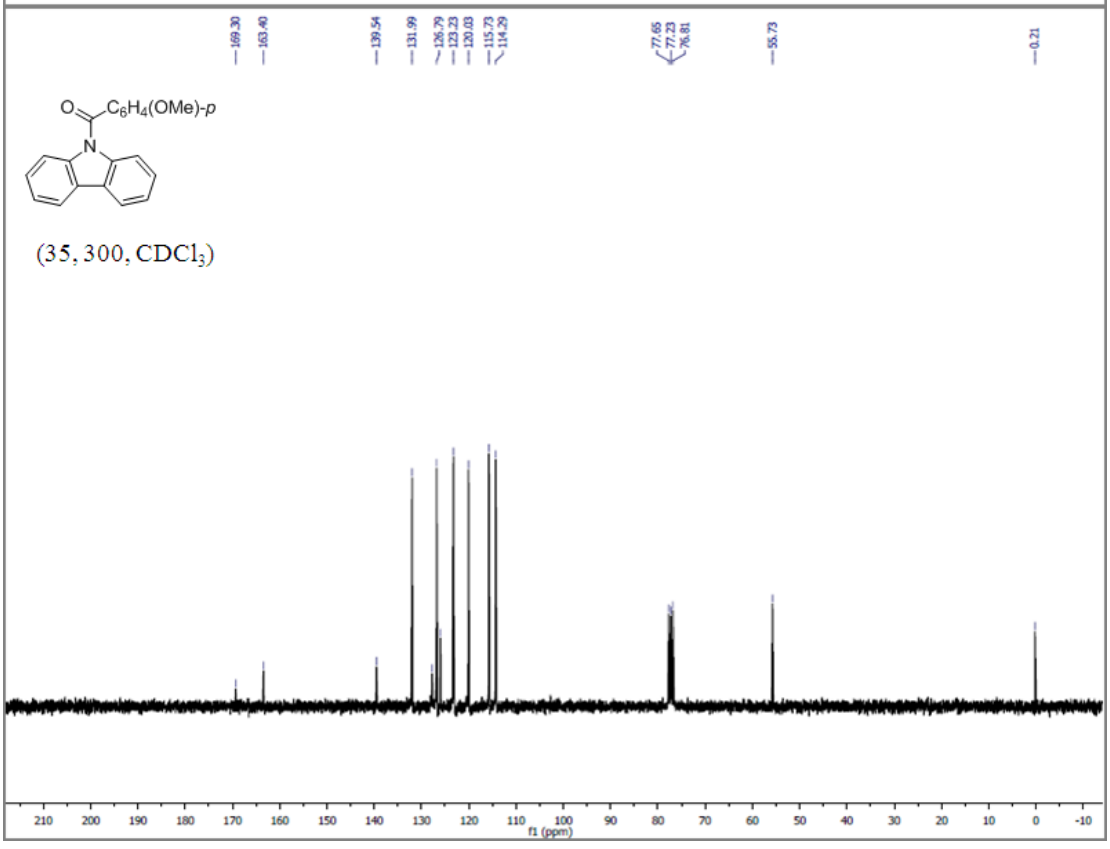

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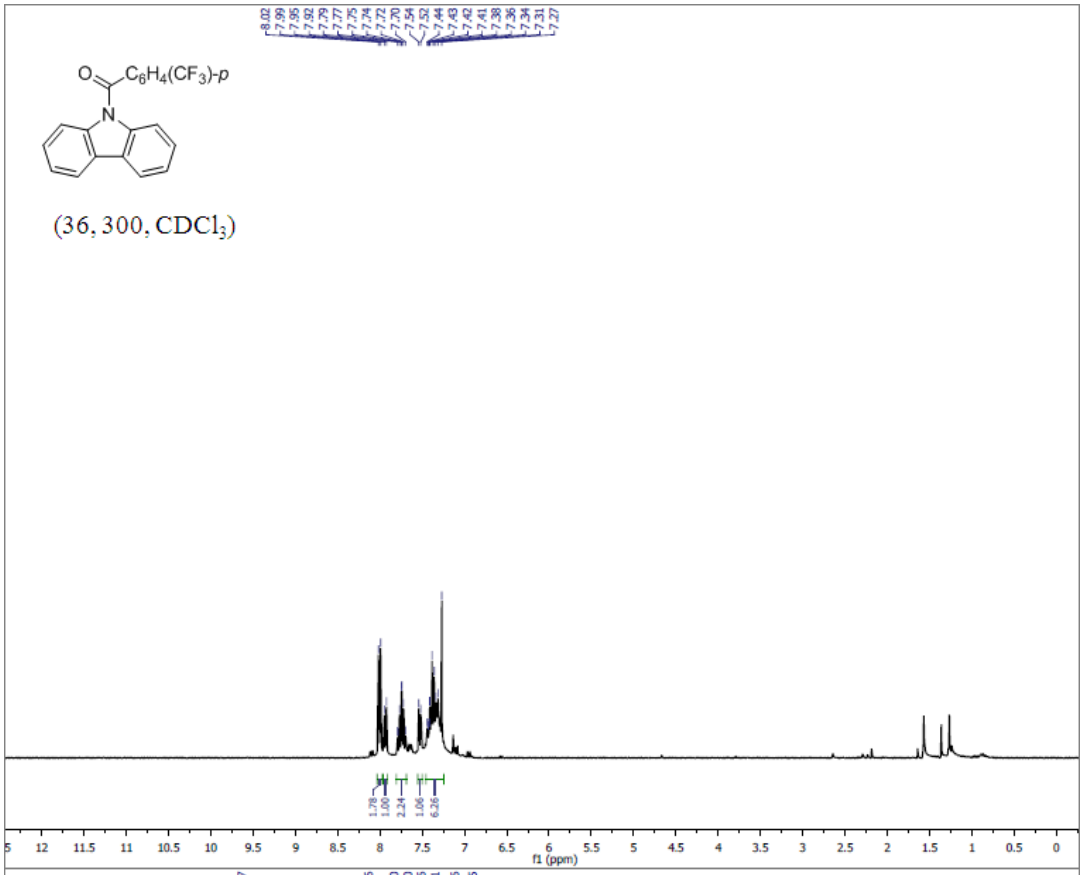

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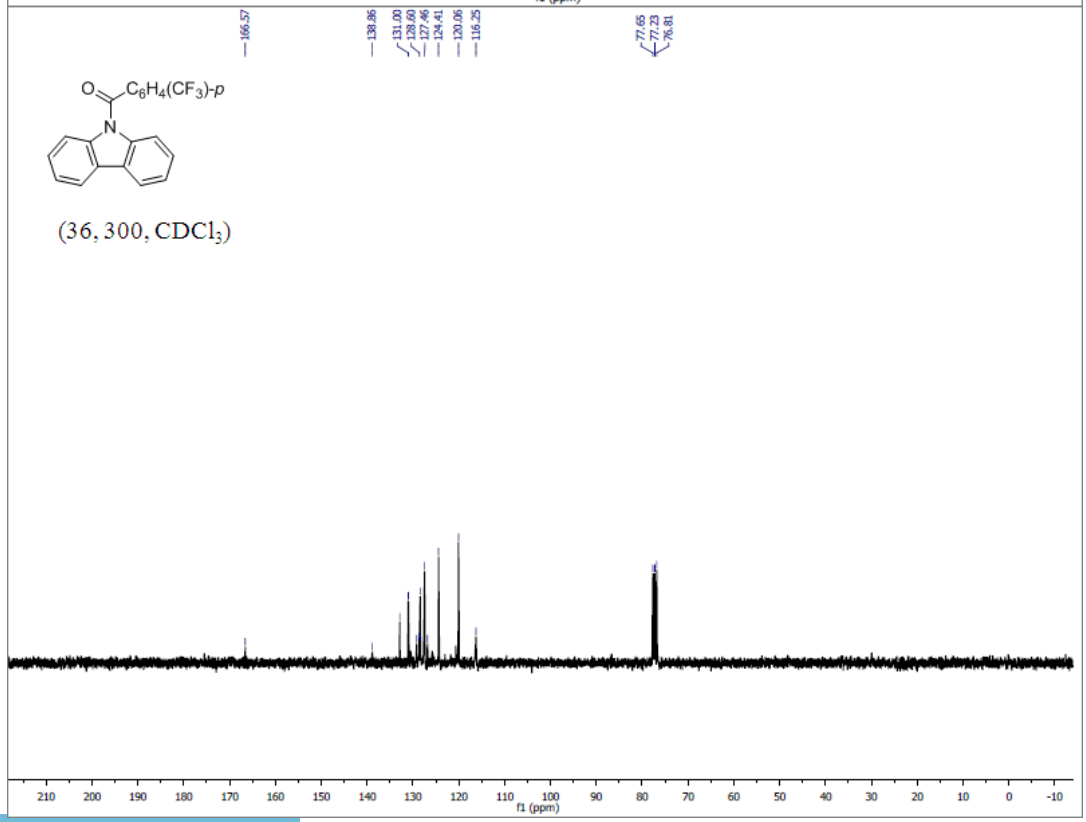

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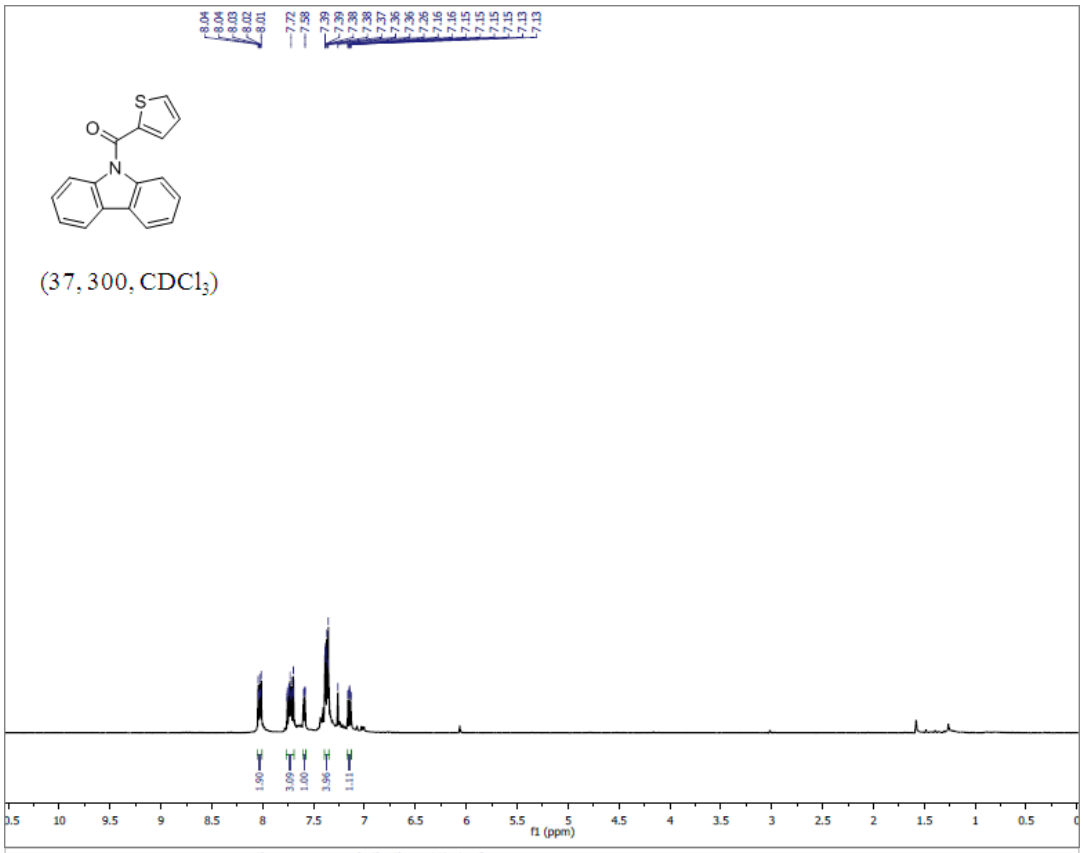

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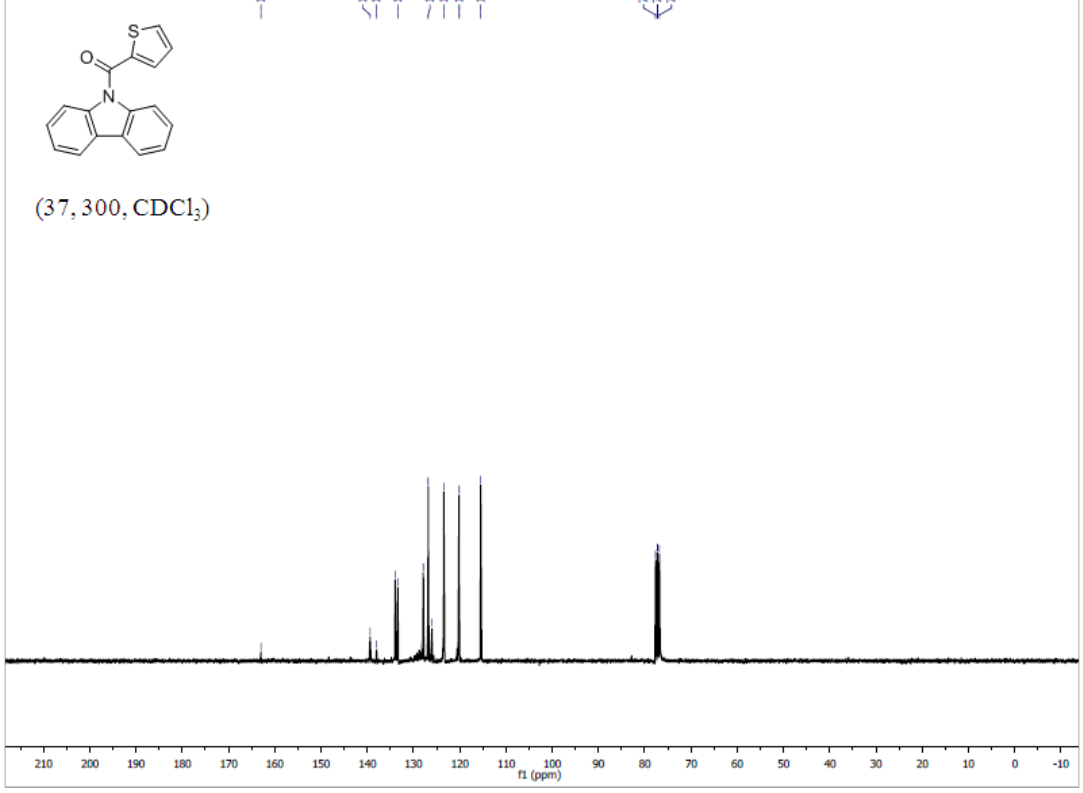

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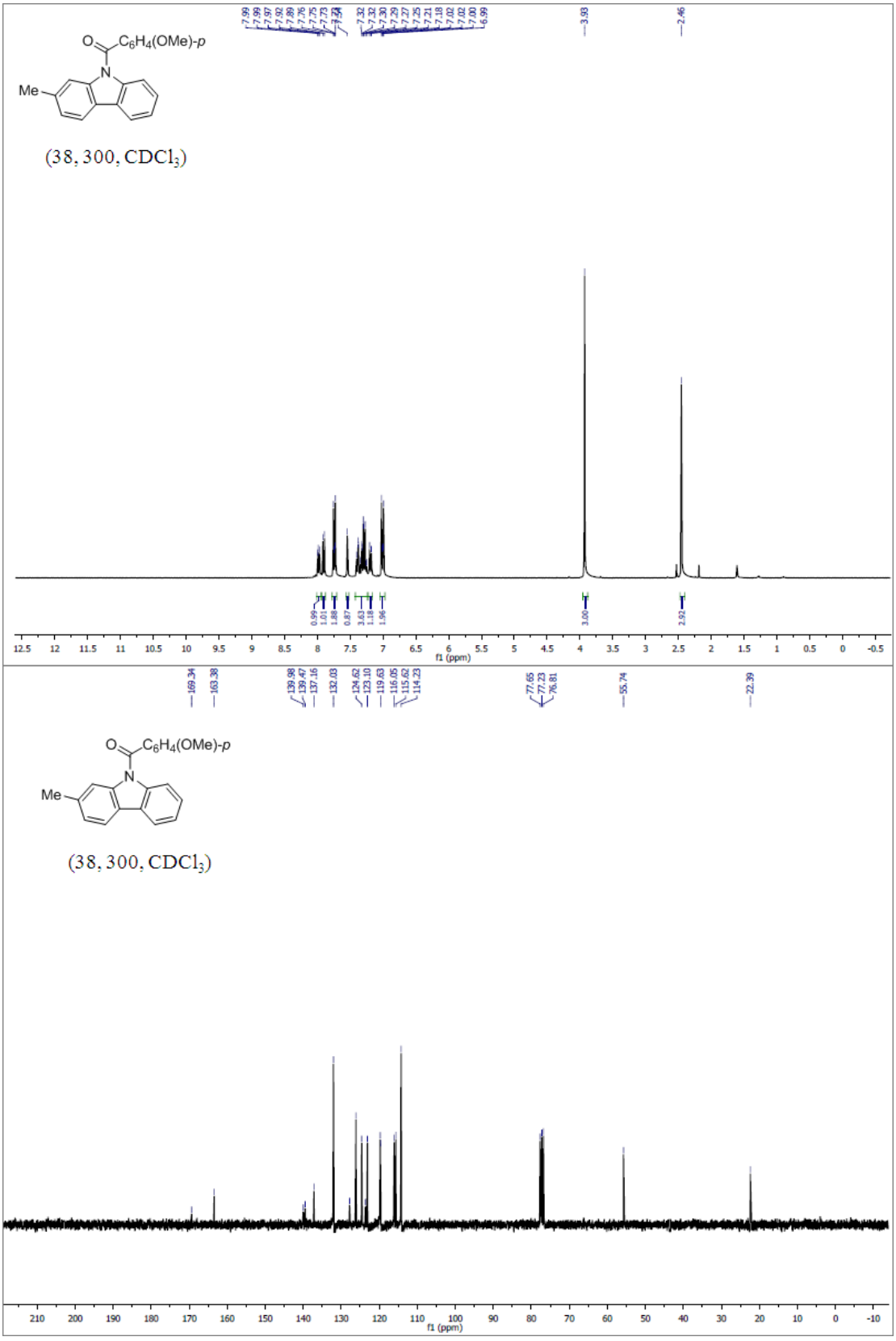

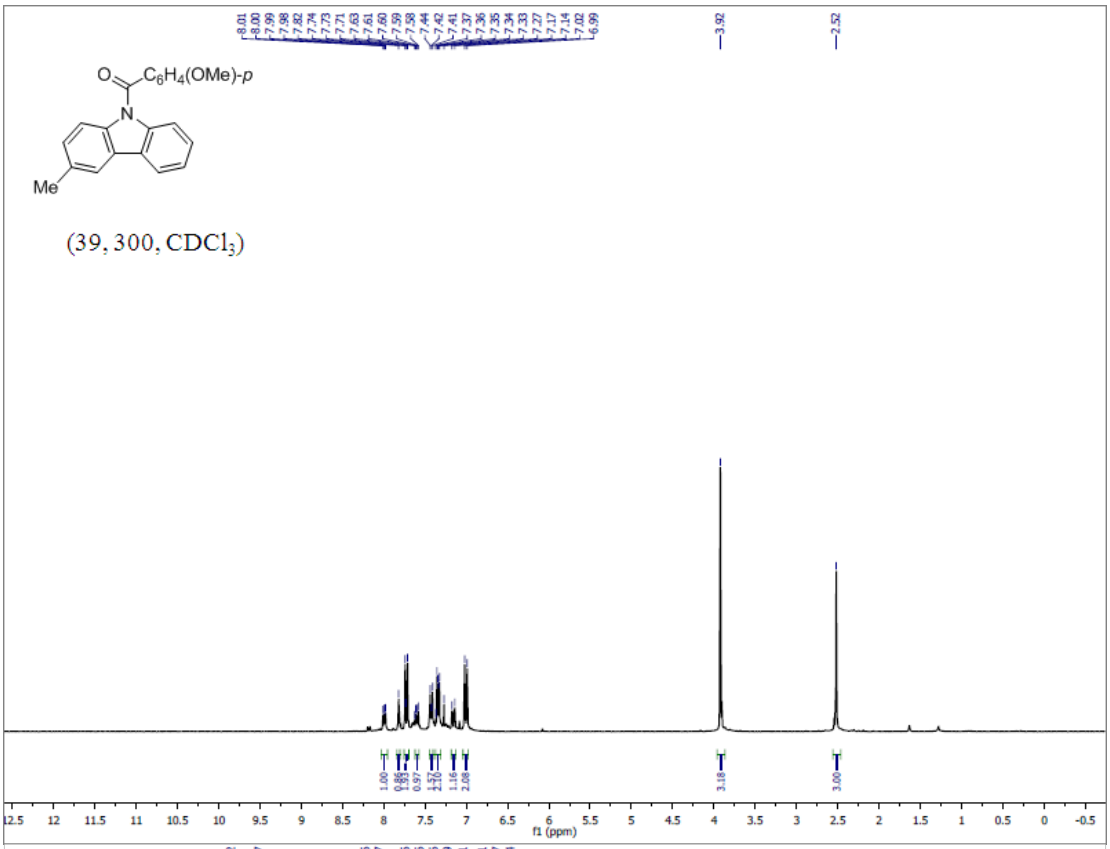

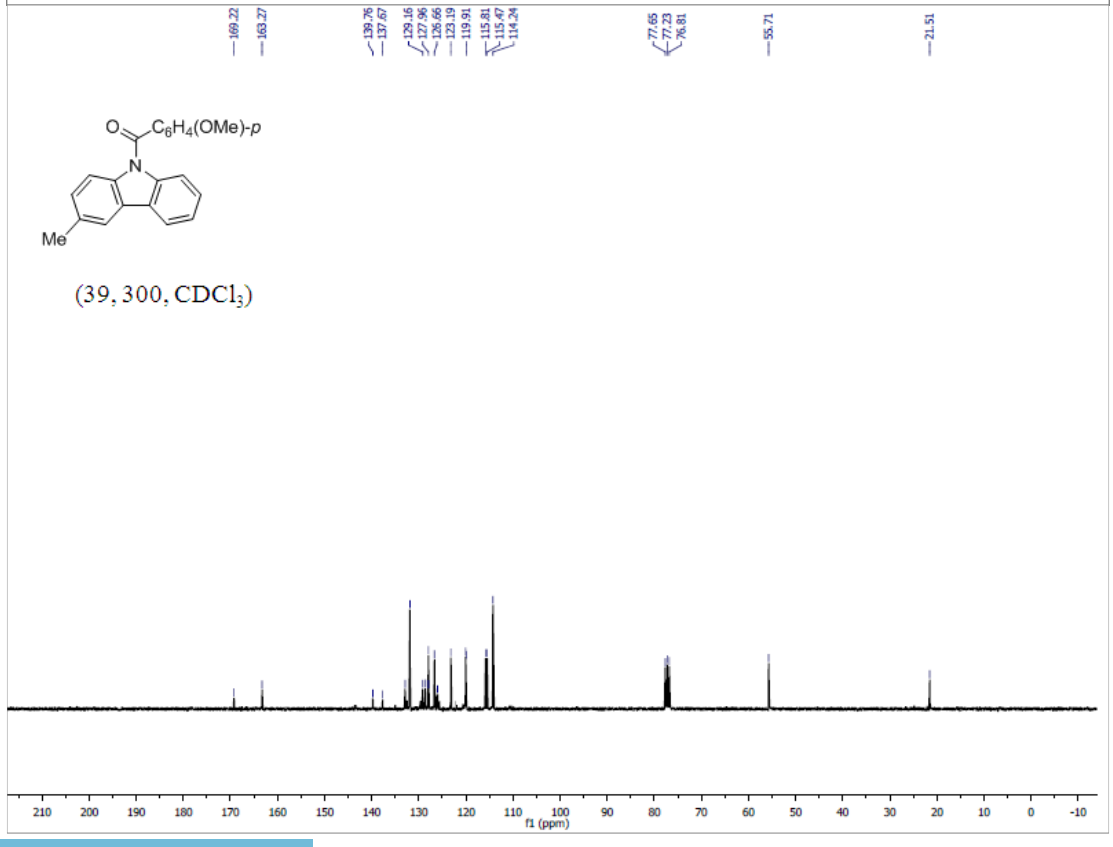

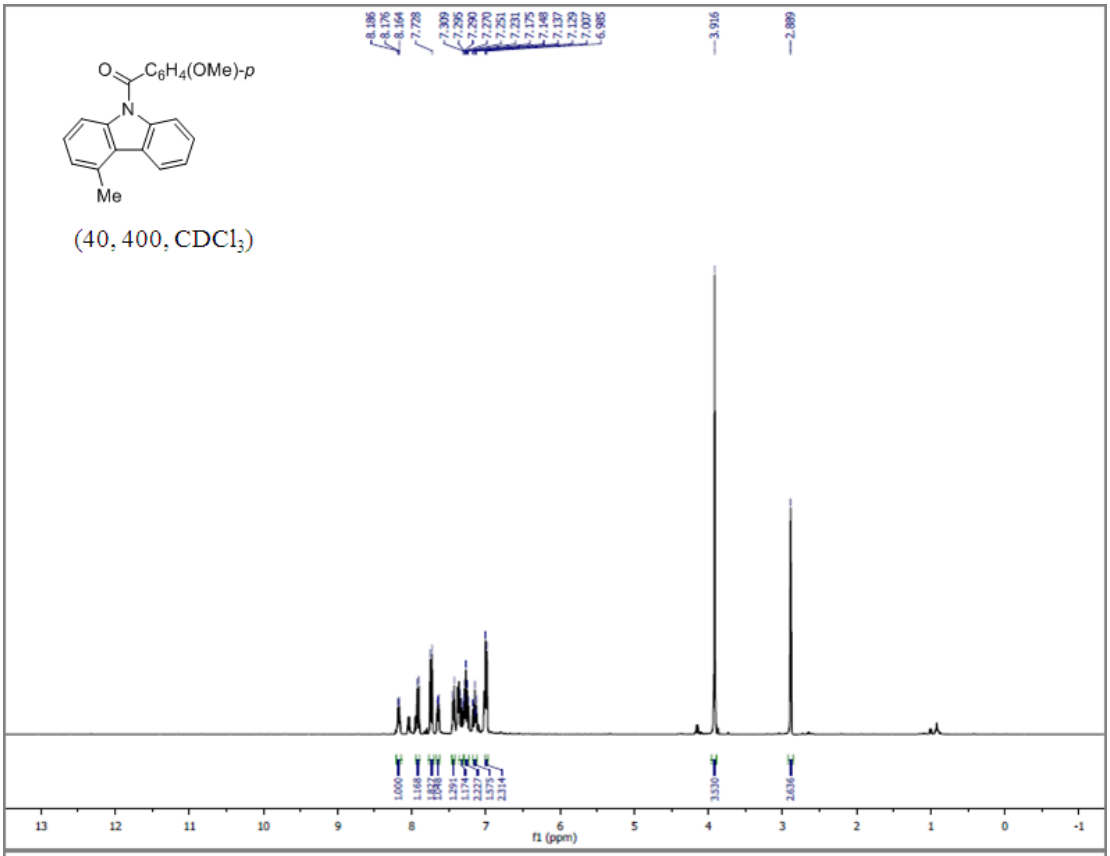

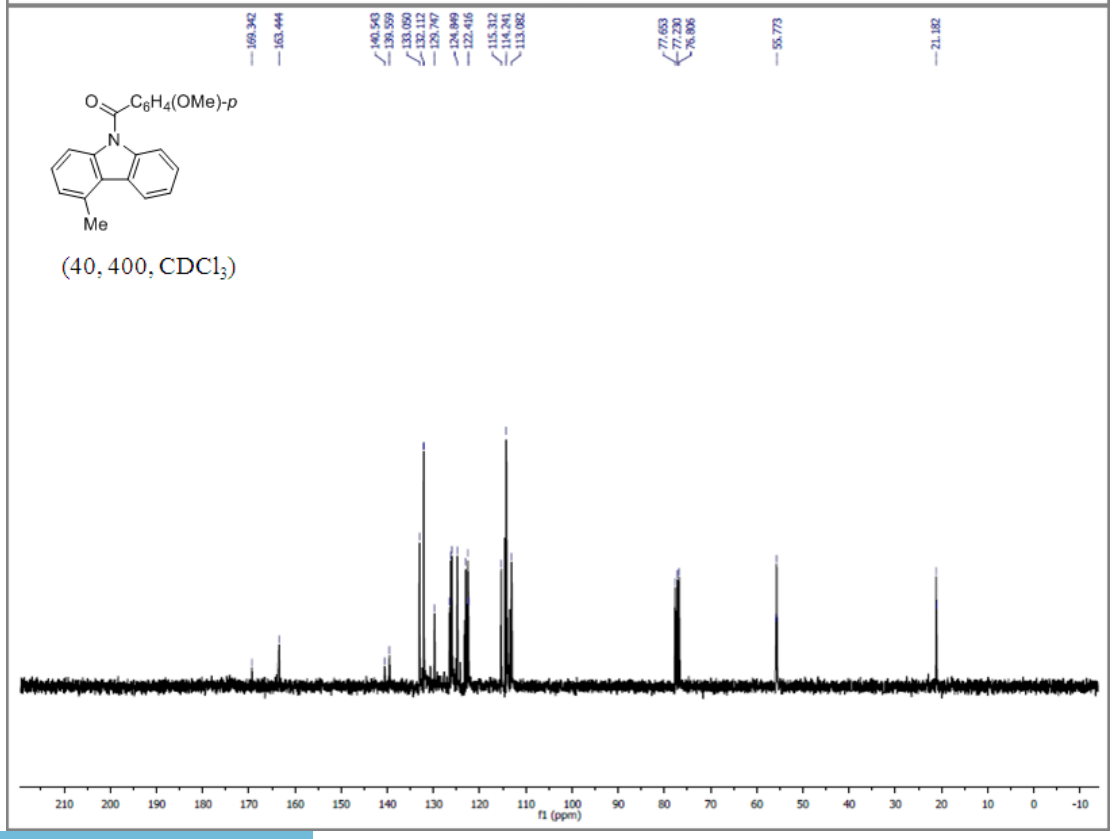

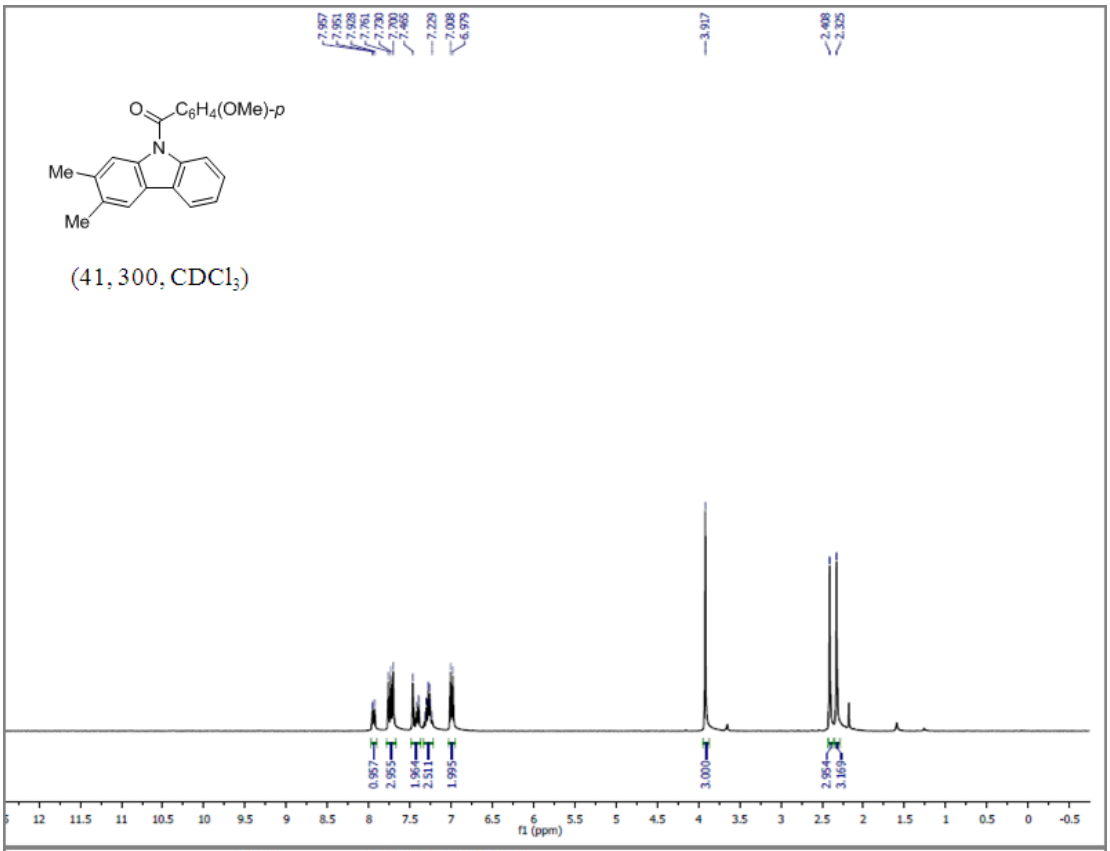

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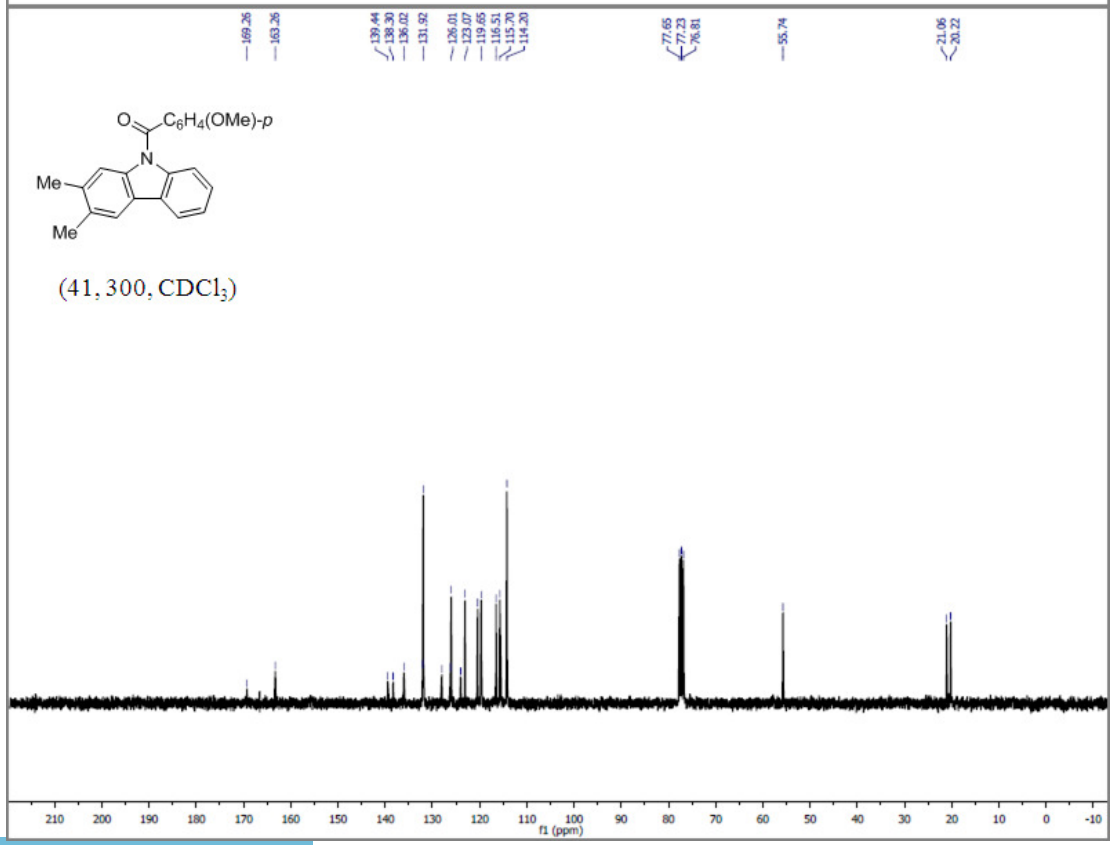

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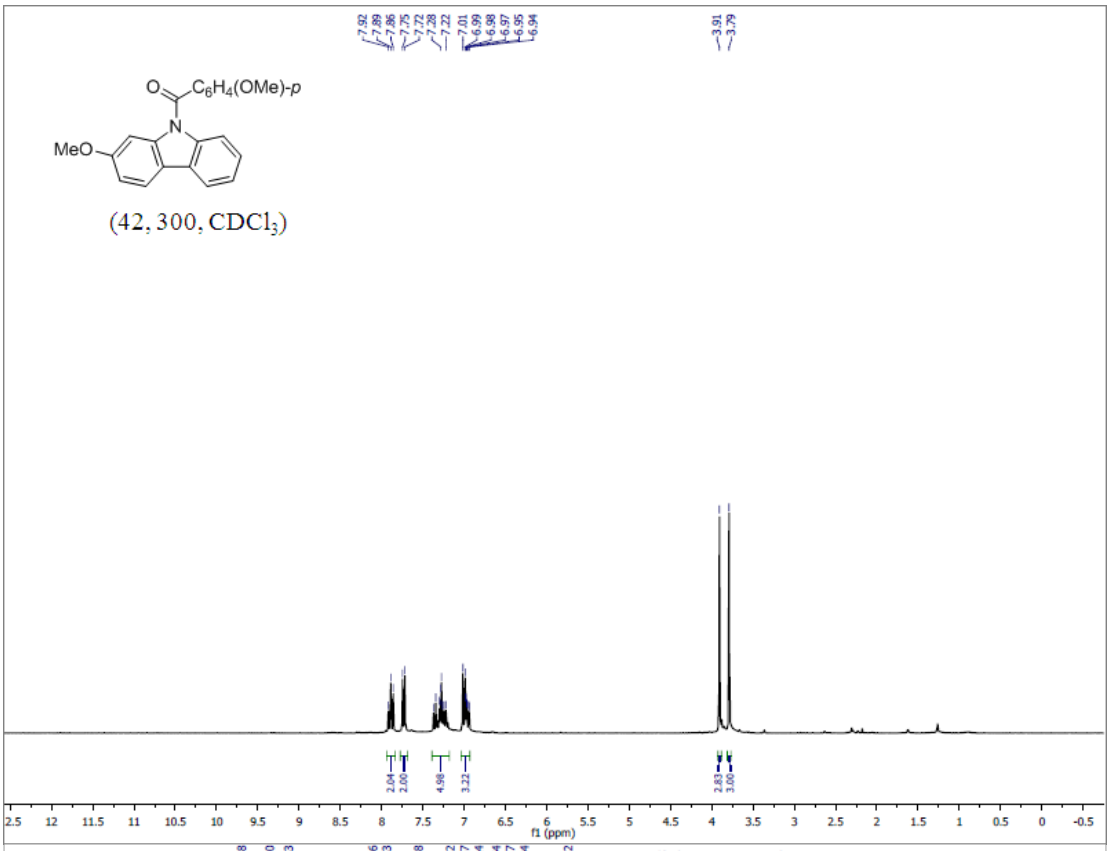

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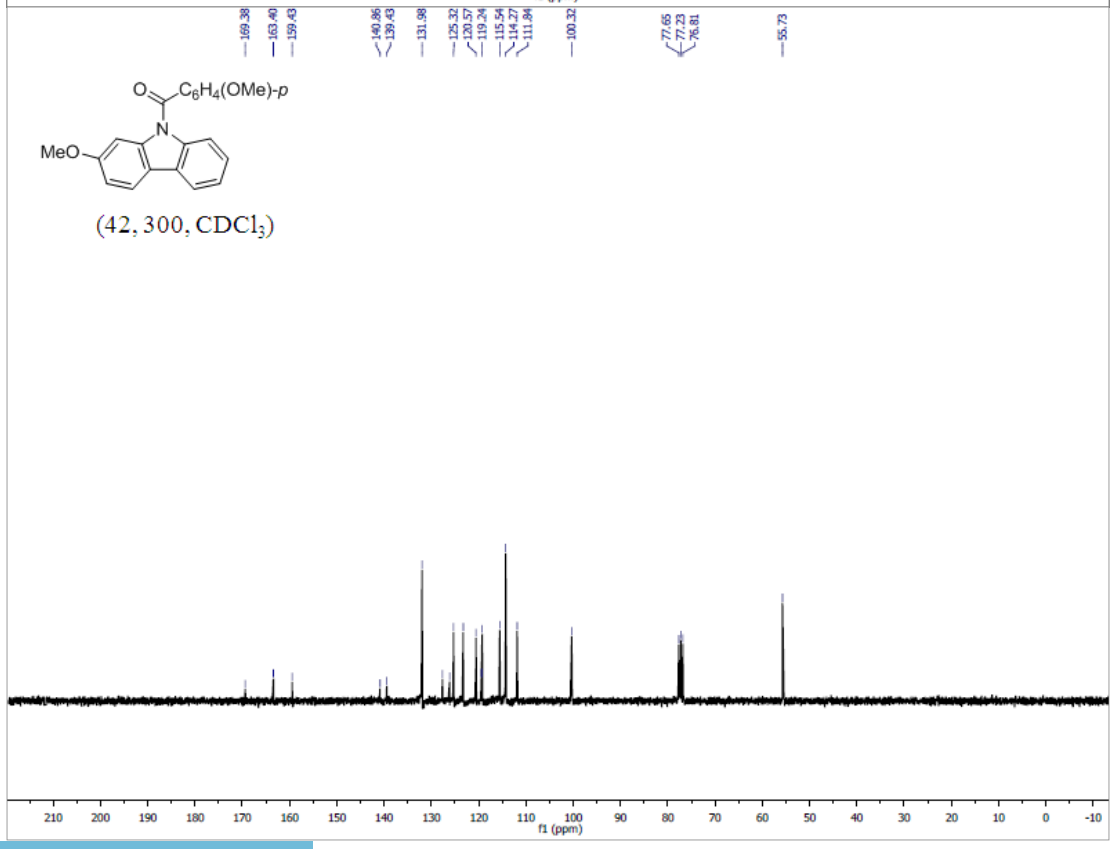

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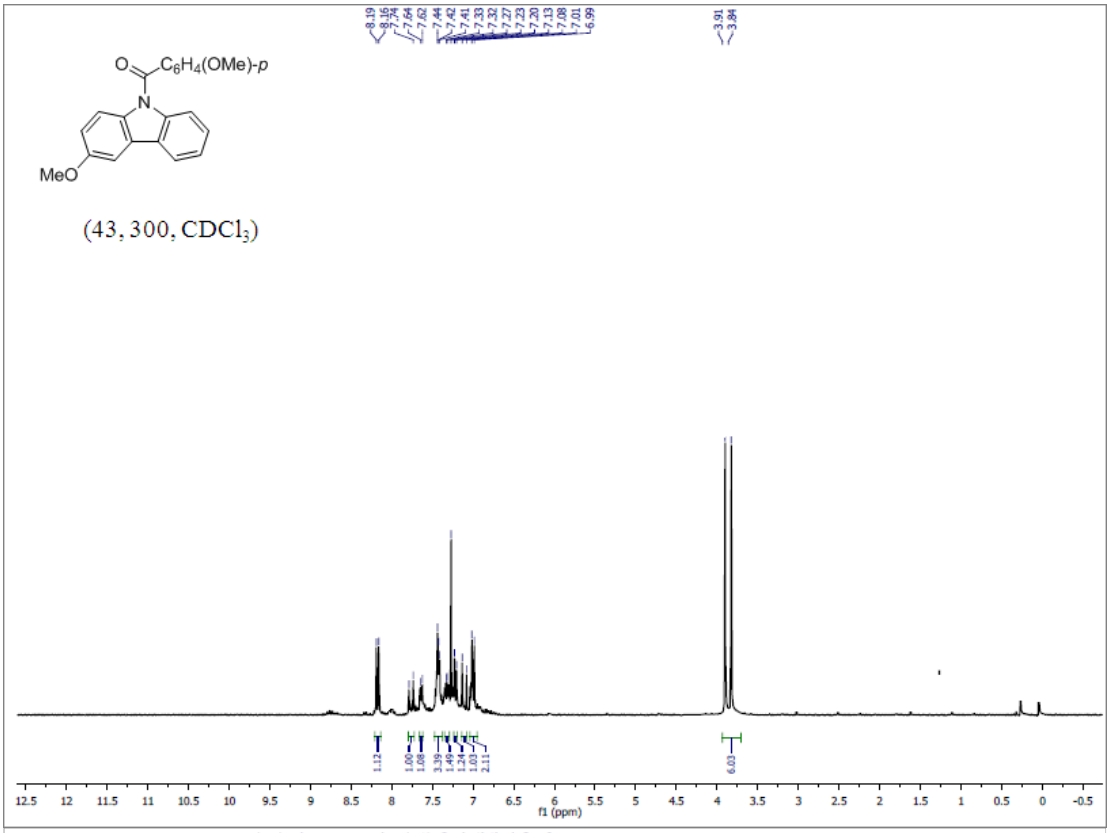

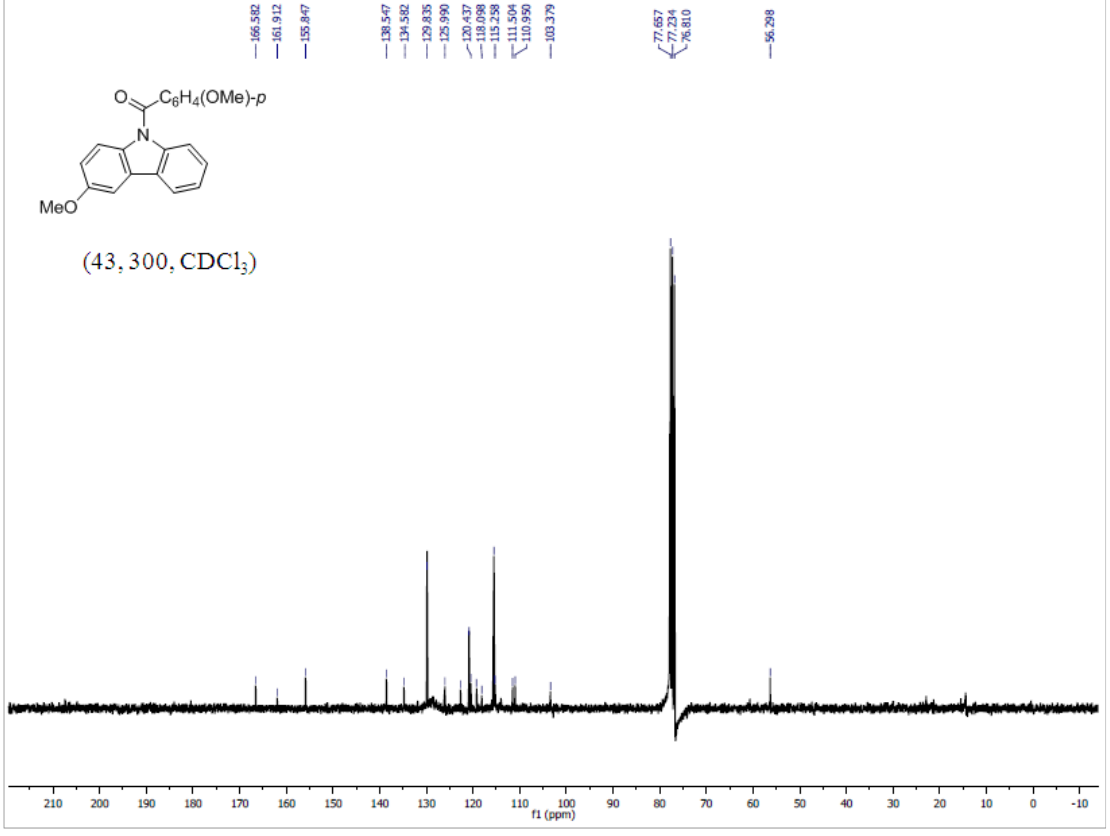

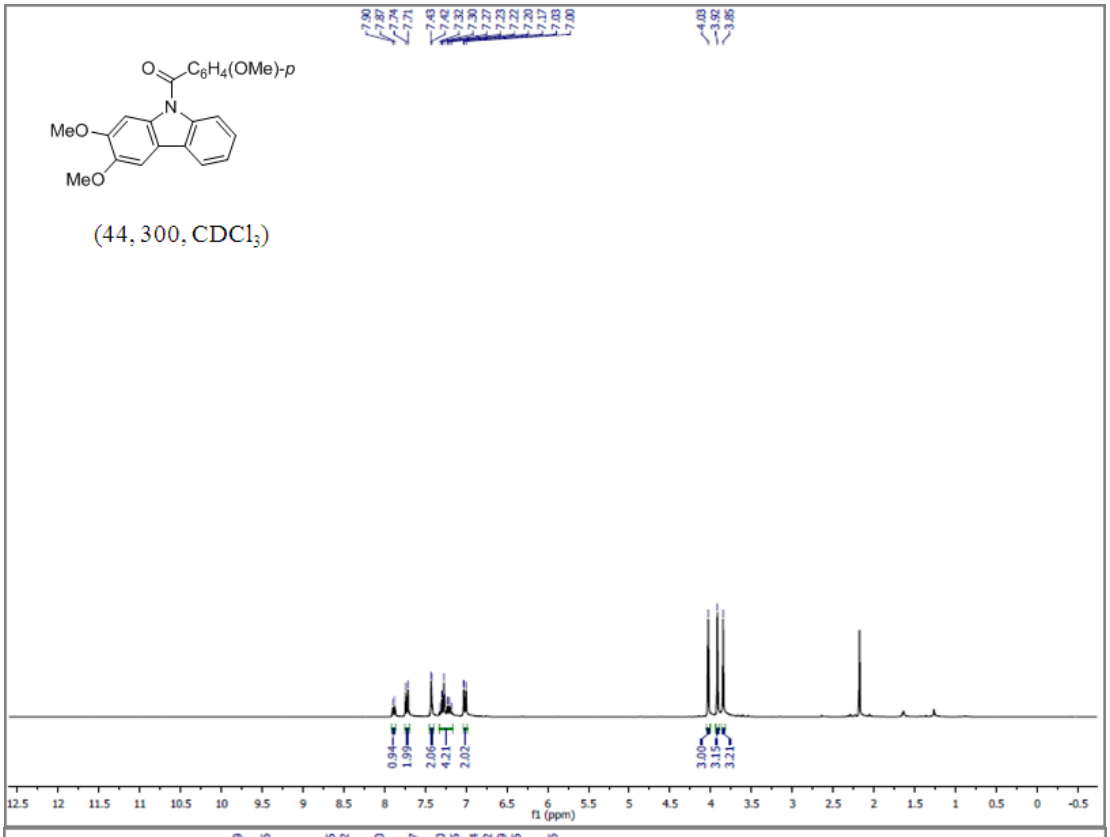

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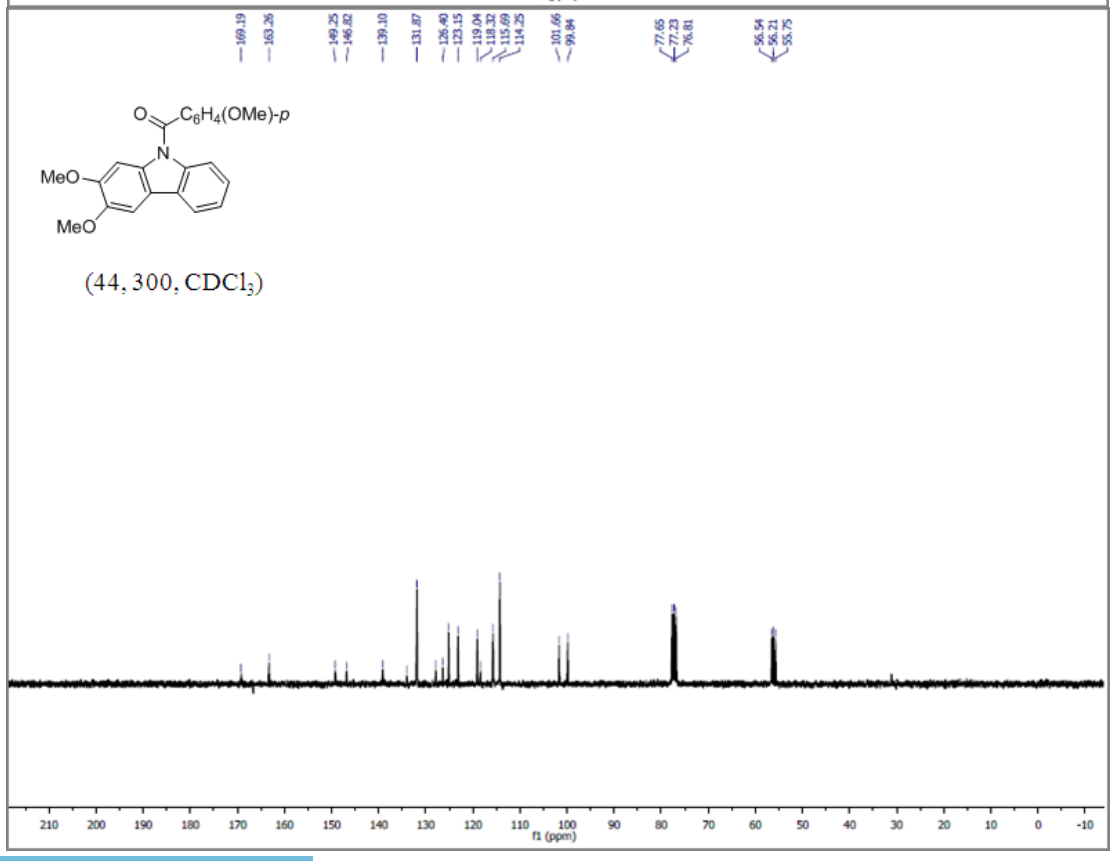

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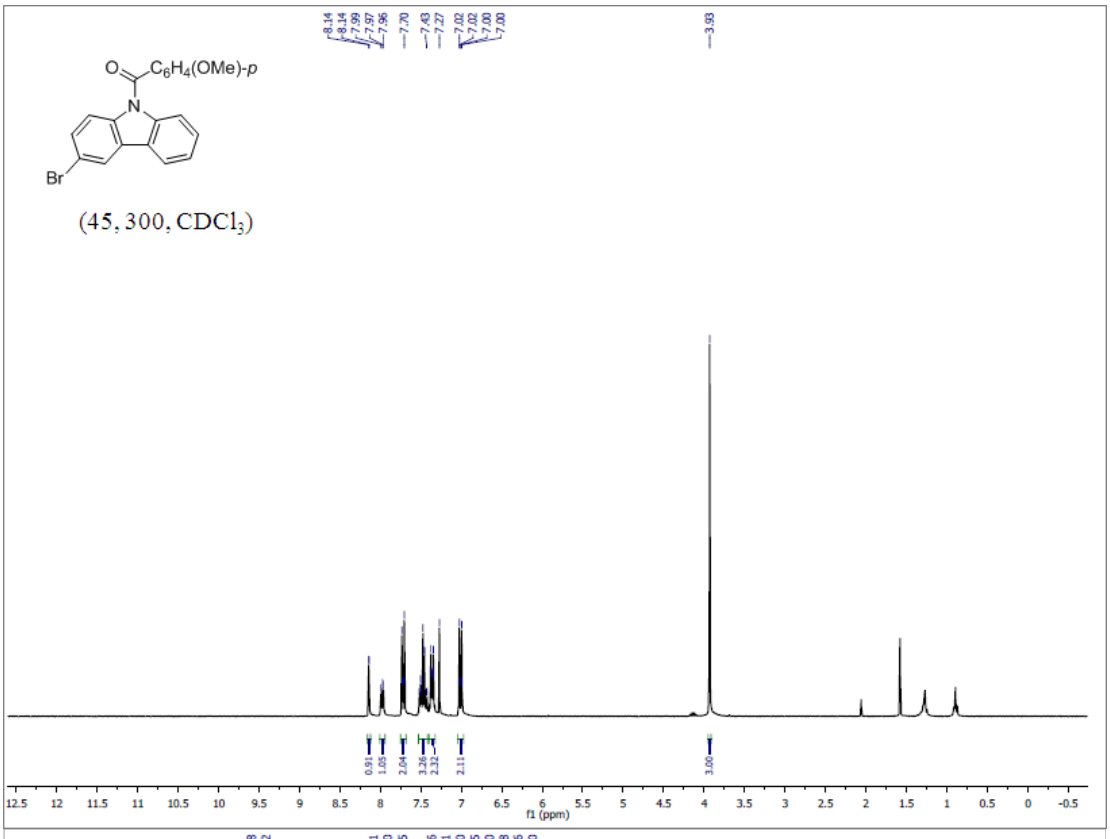

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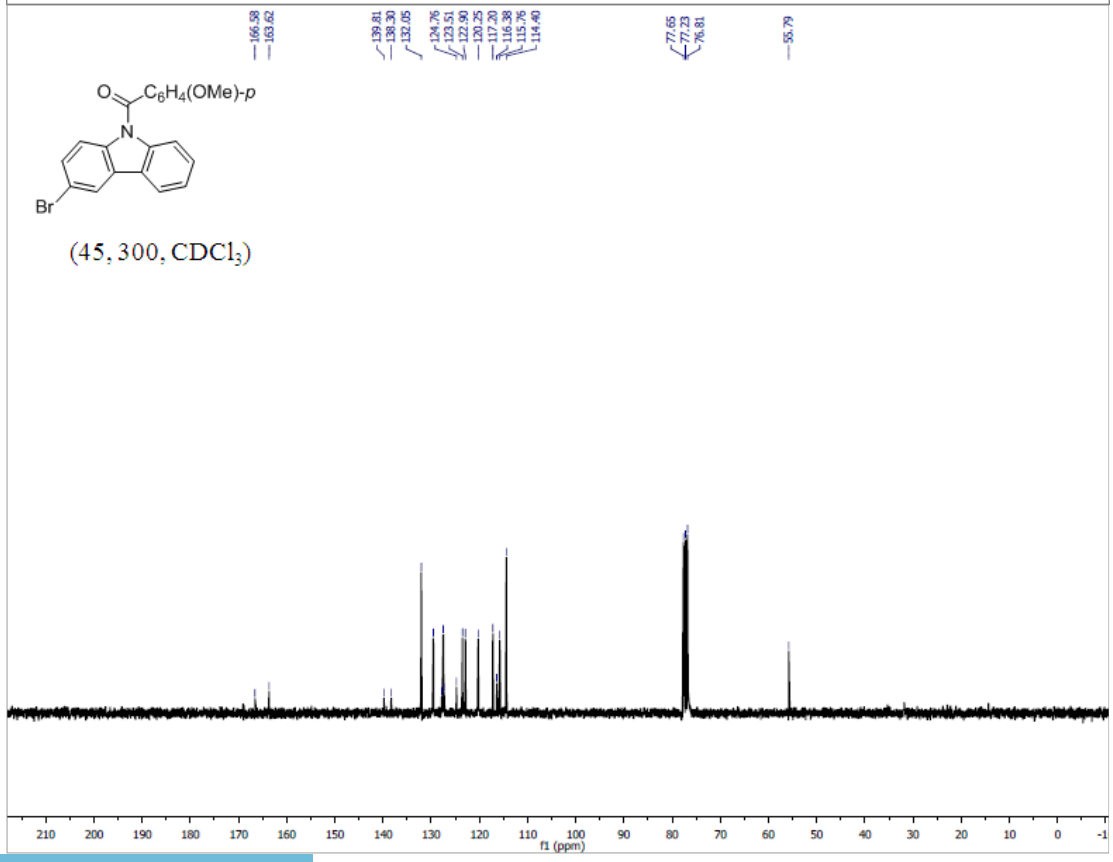

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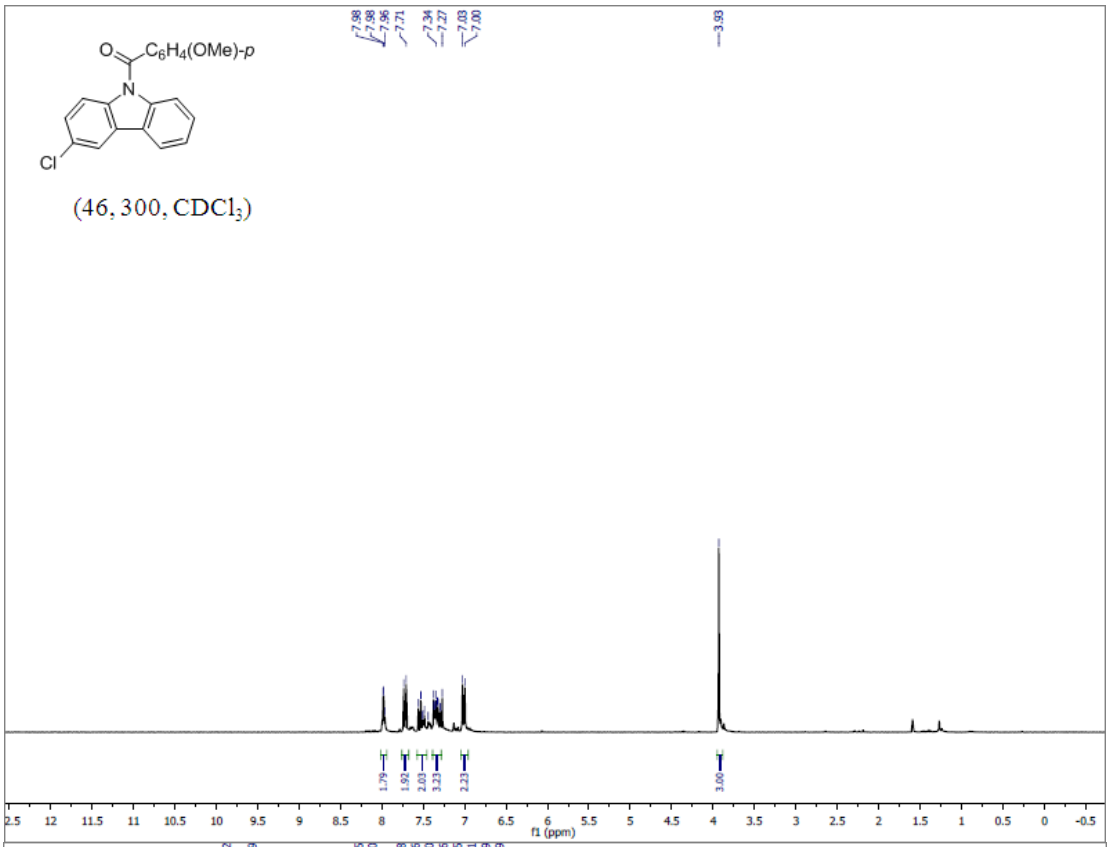

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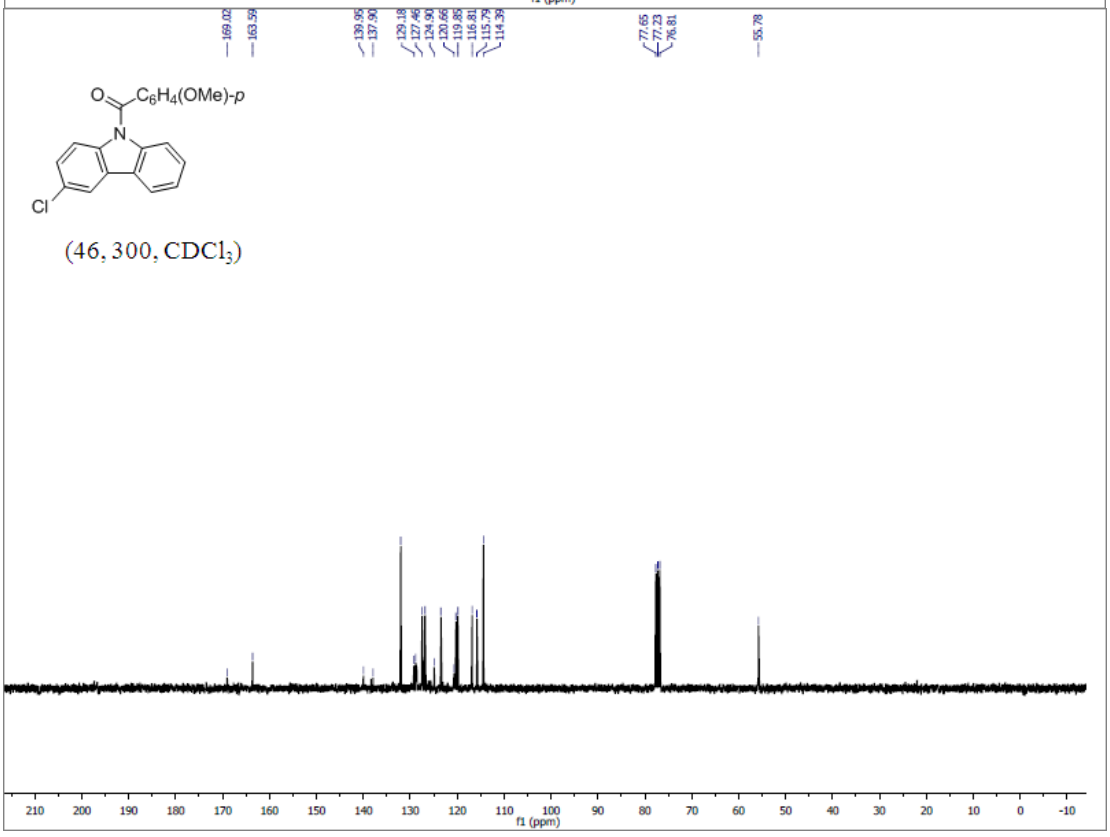

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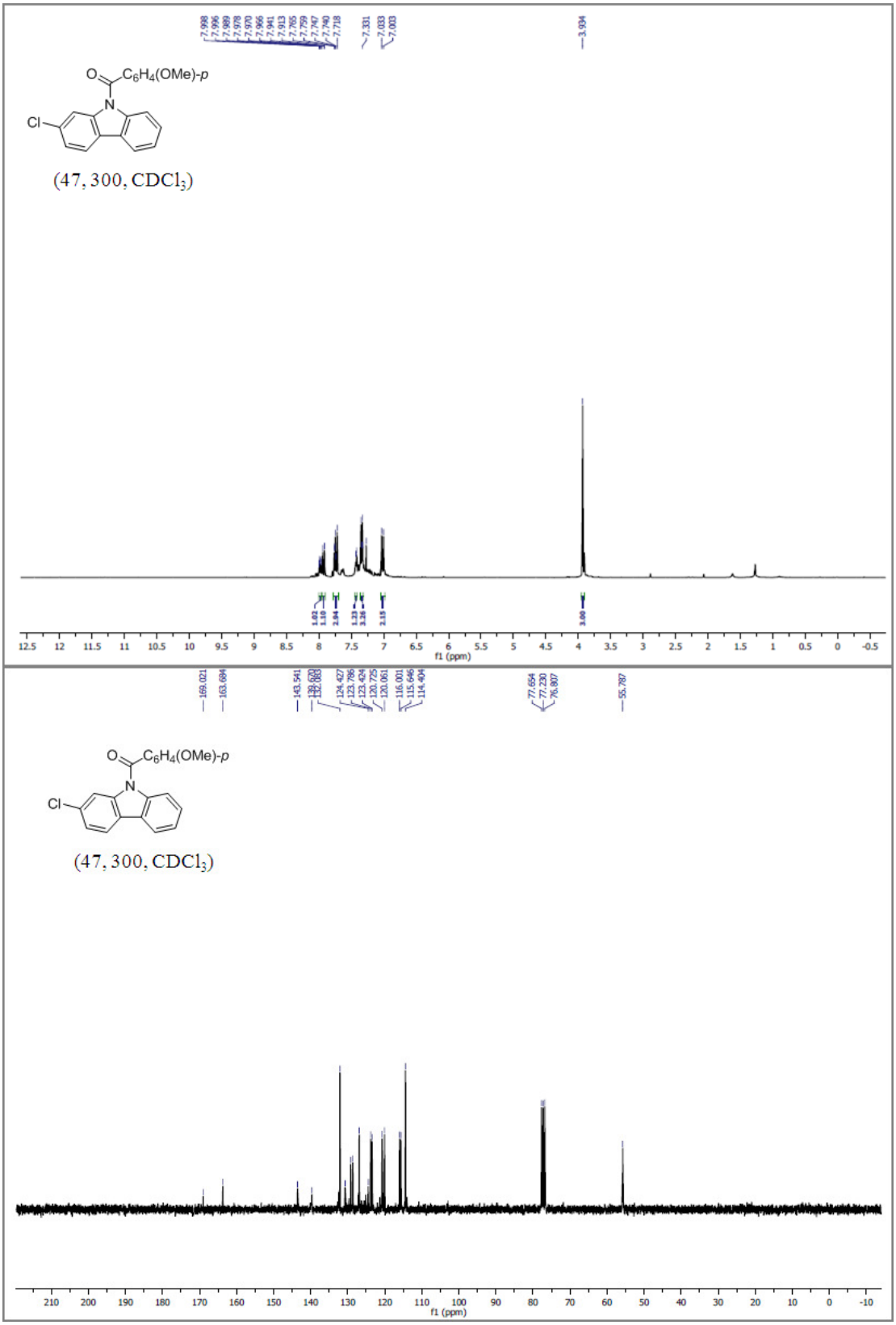

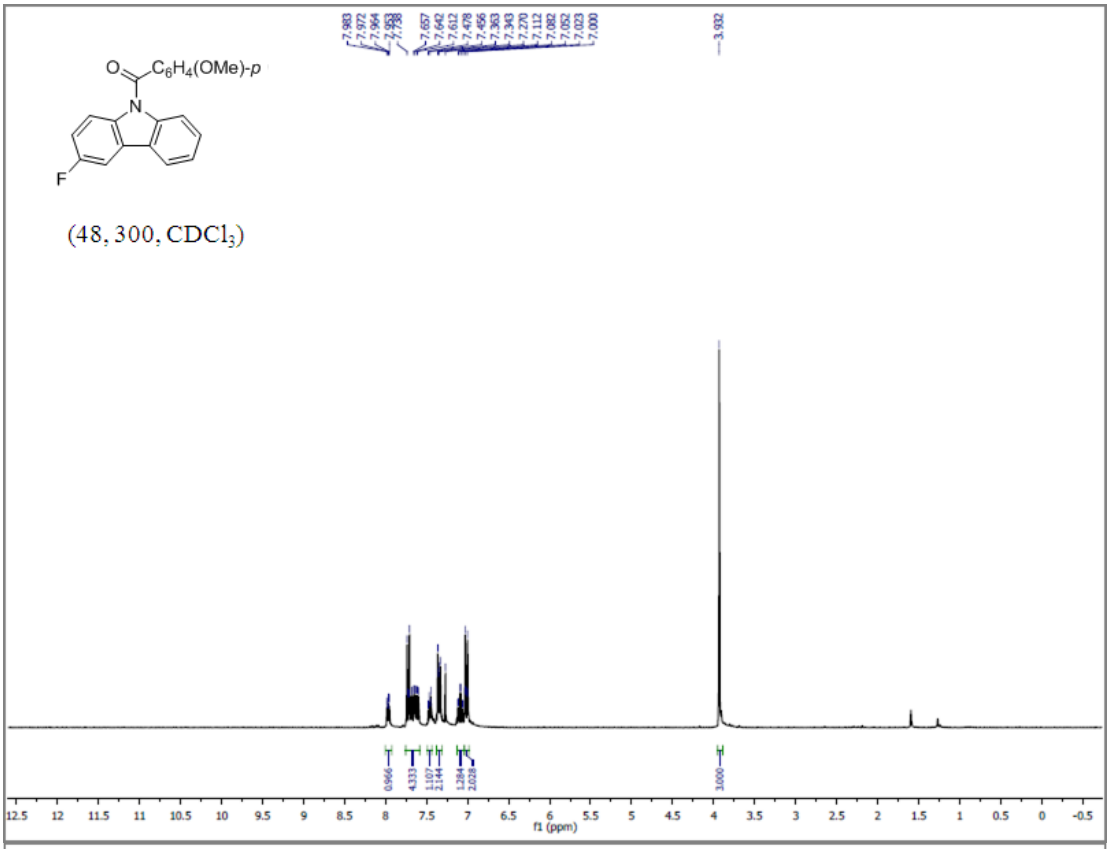

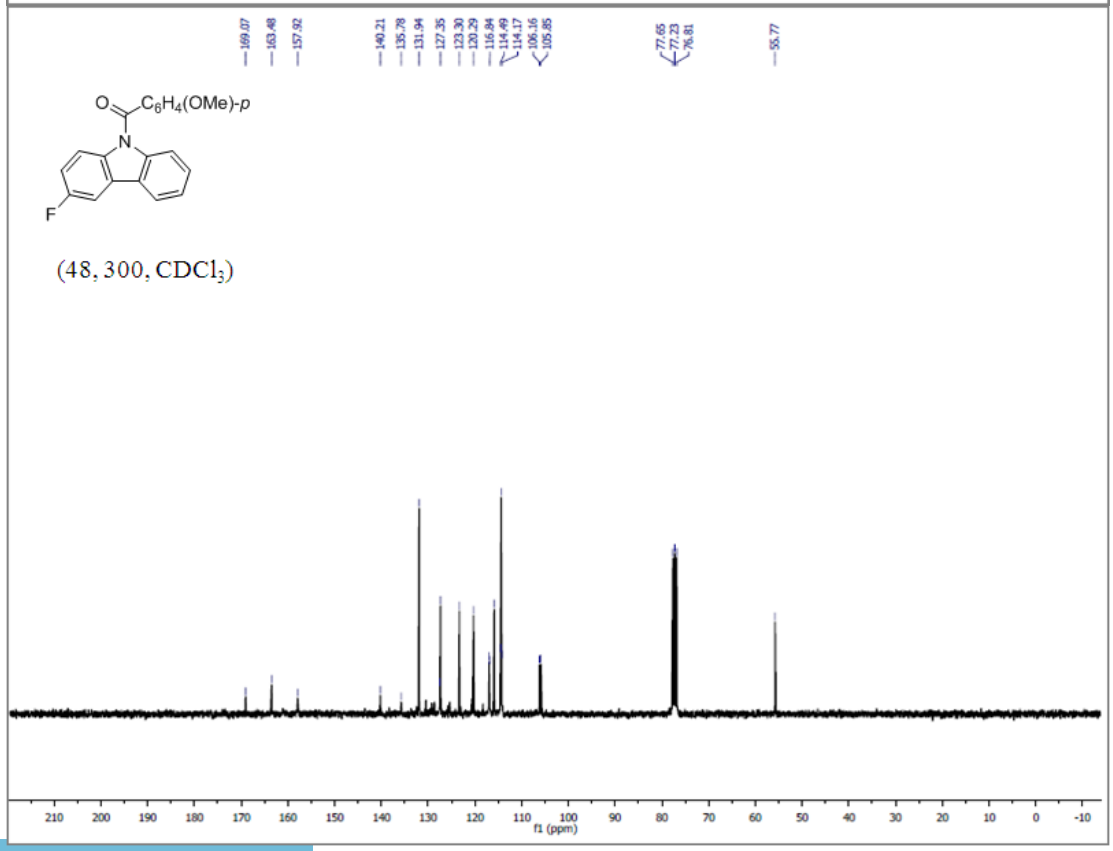

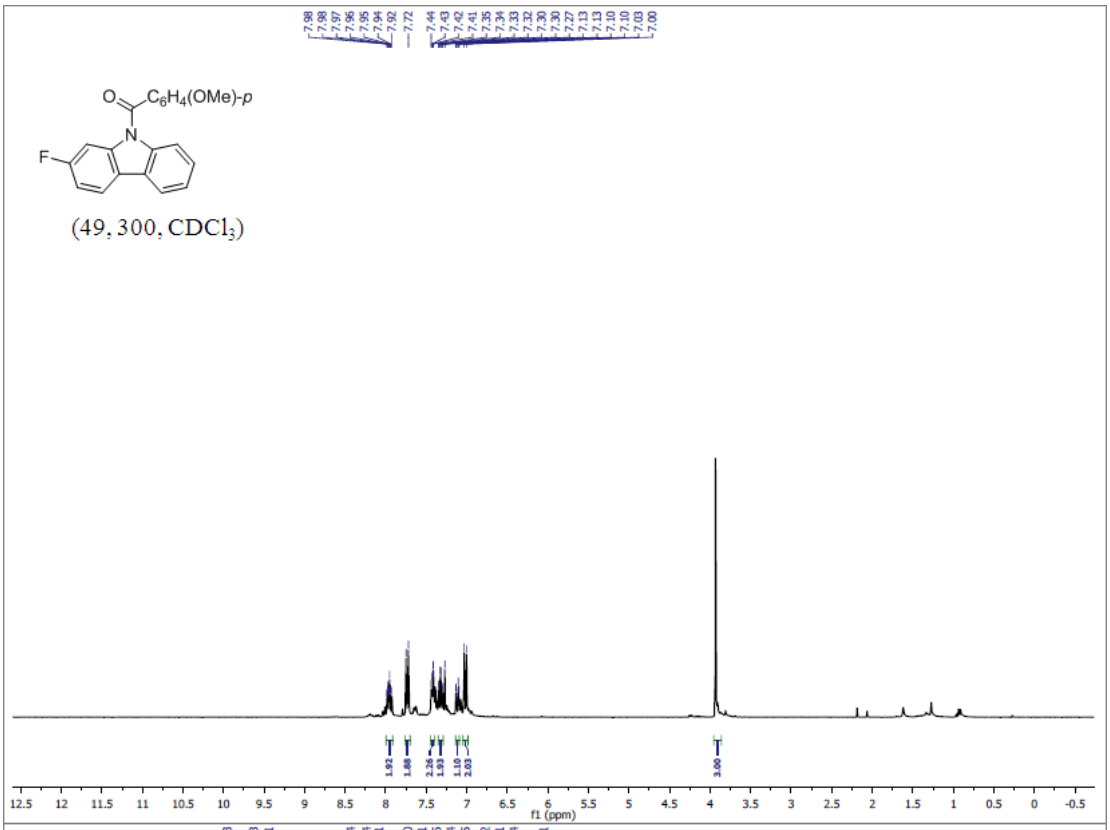

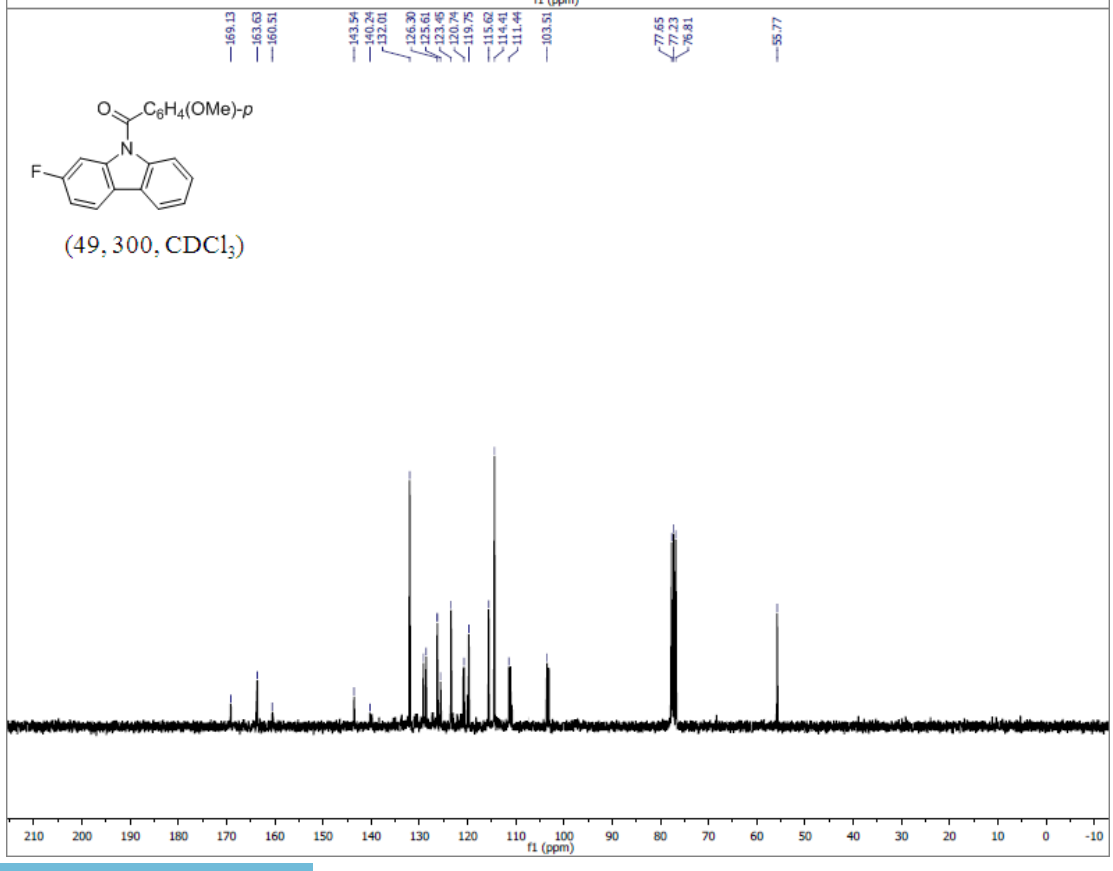

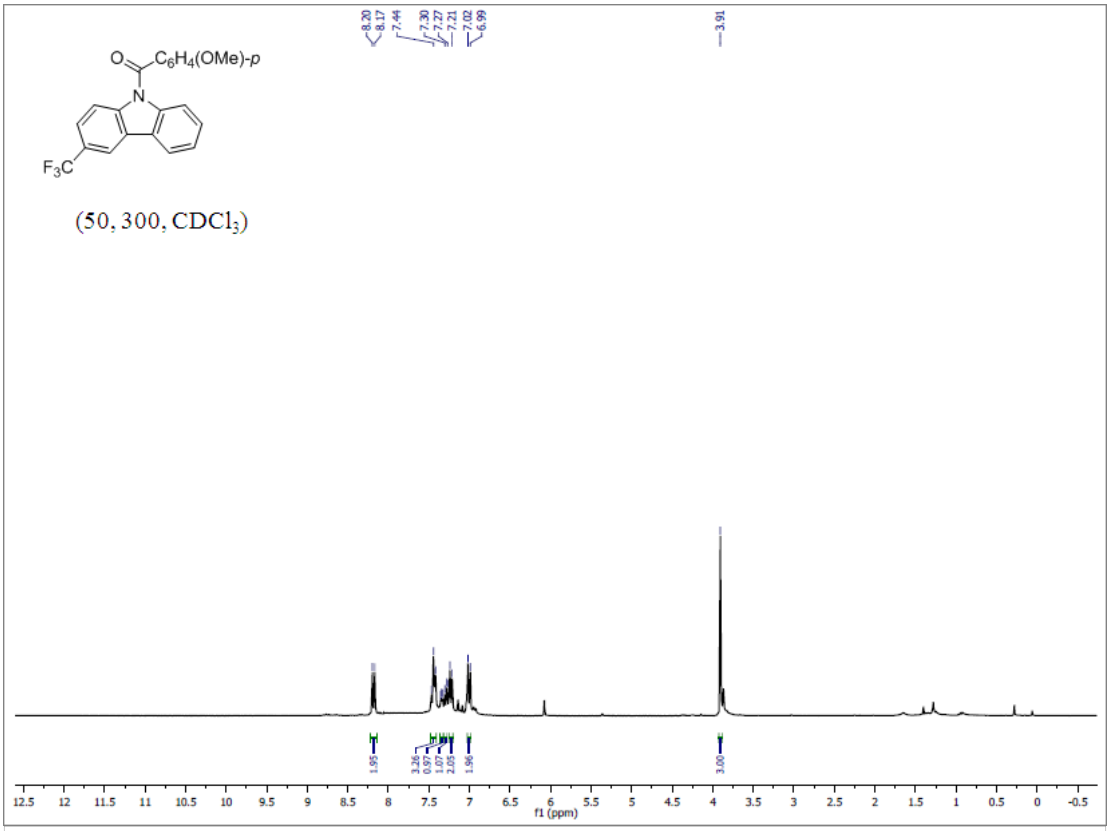

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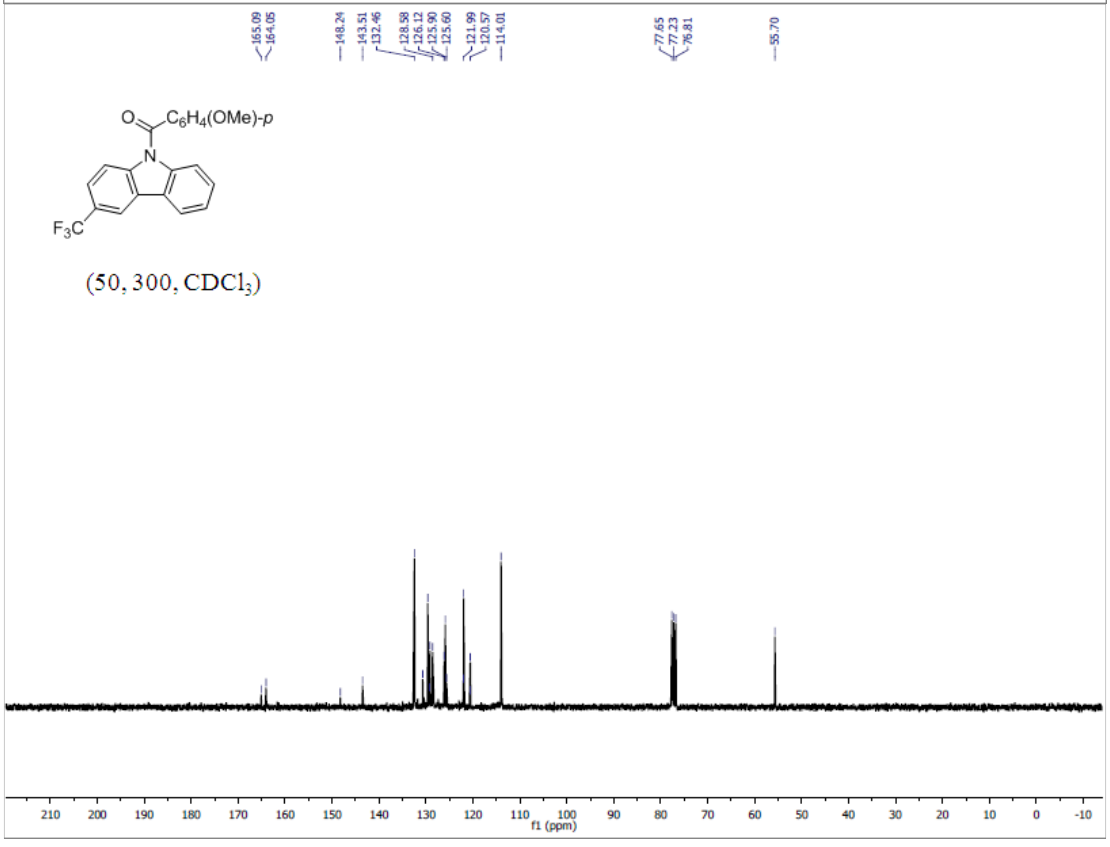

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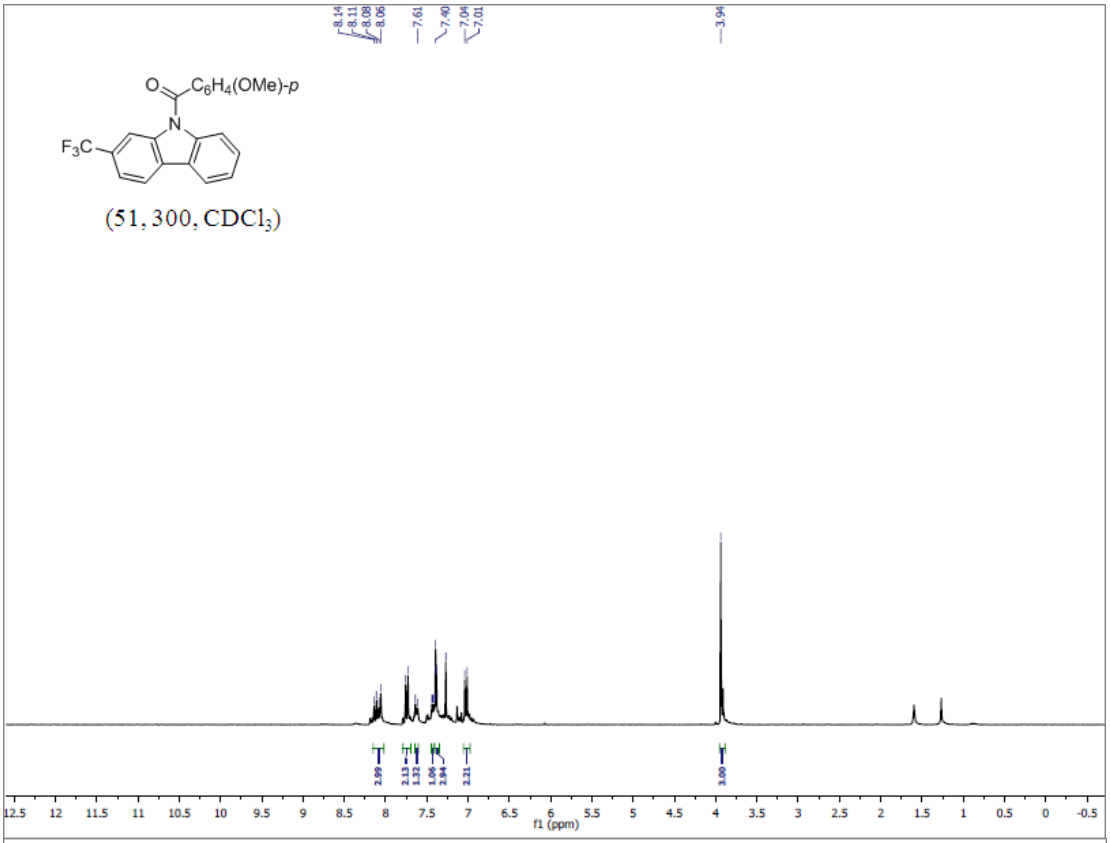
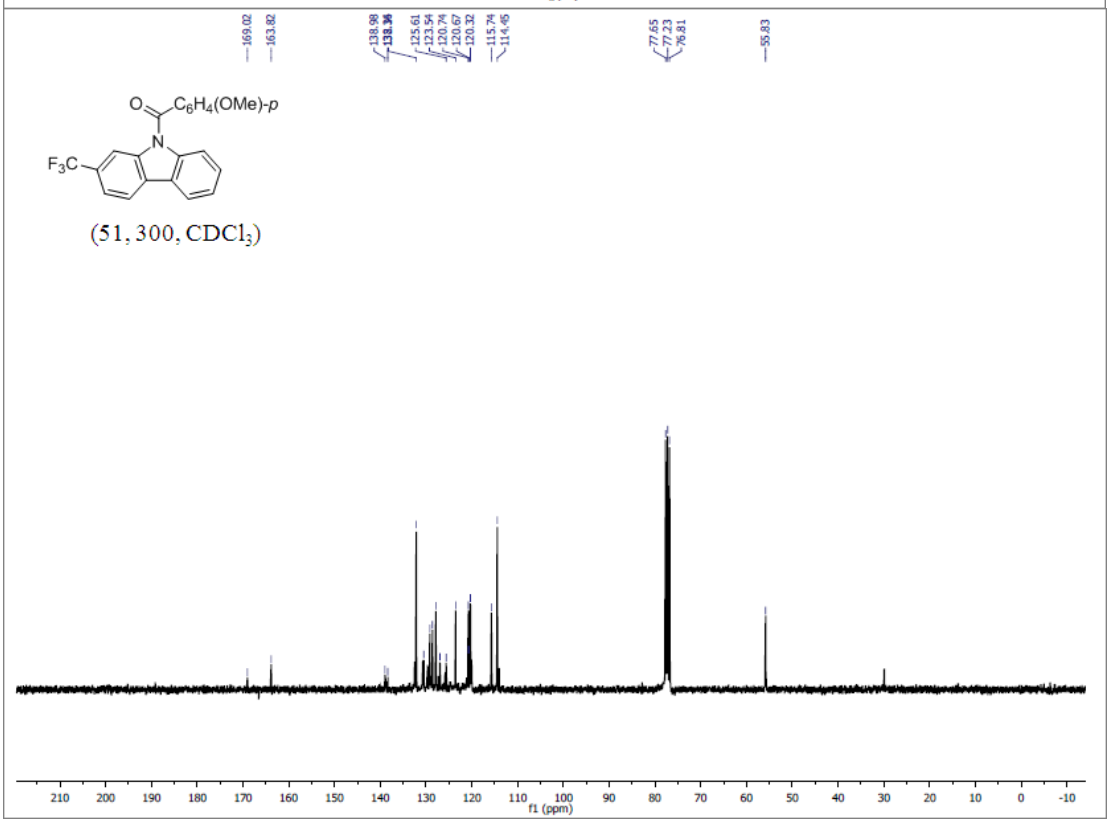


(51, 300, $CDCl_3$)



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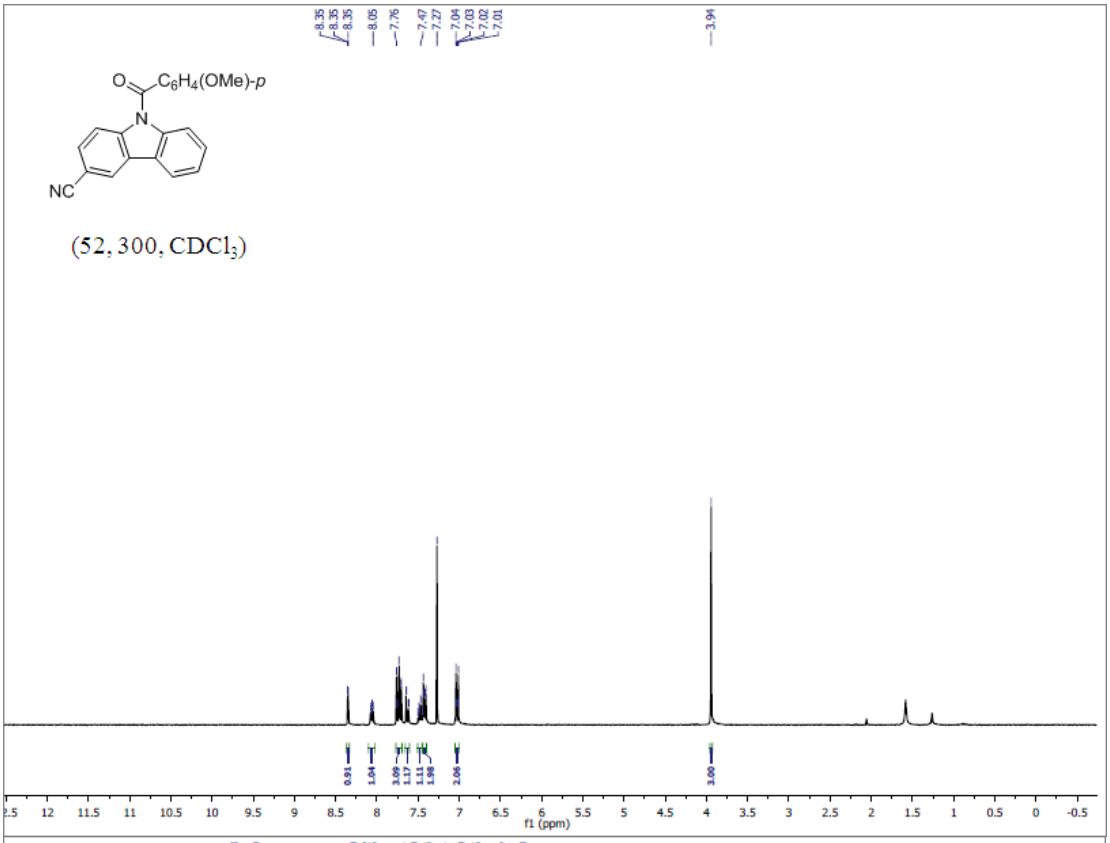

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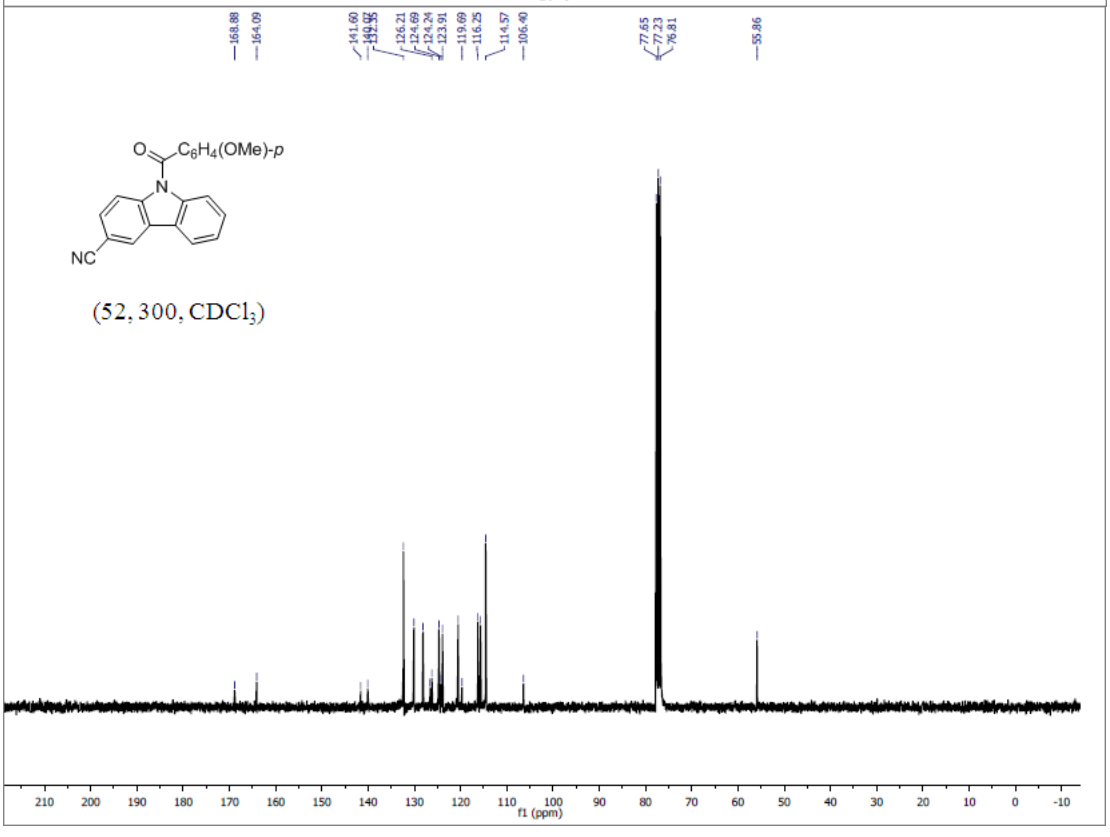

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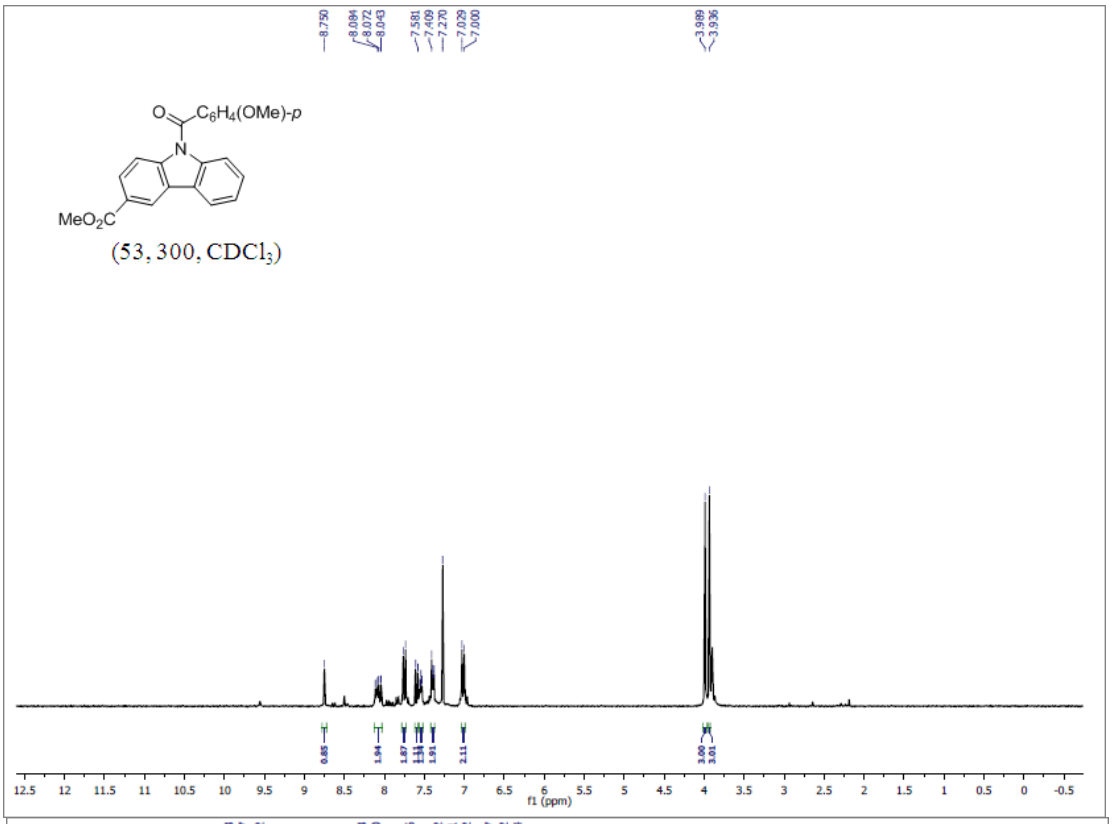

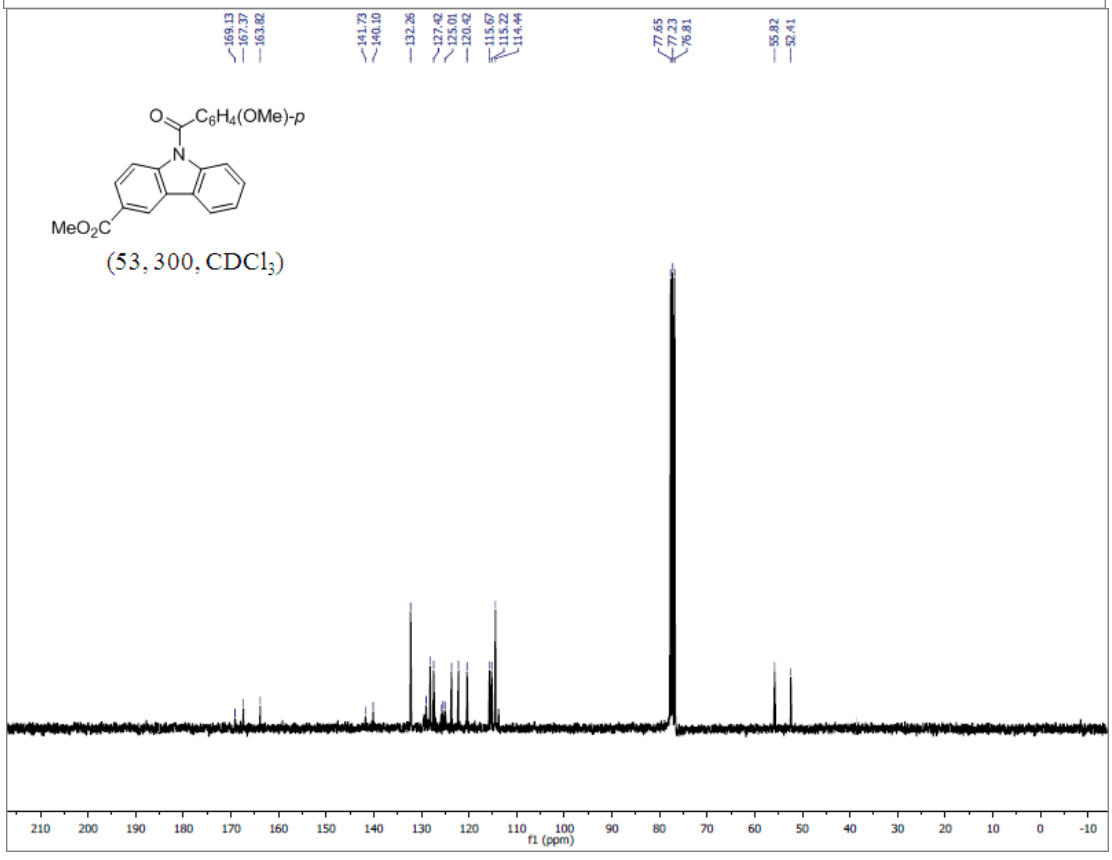

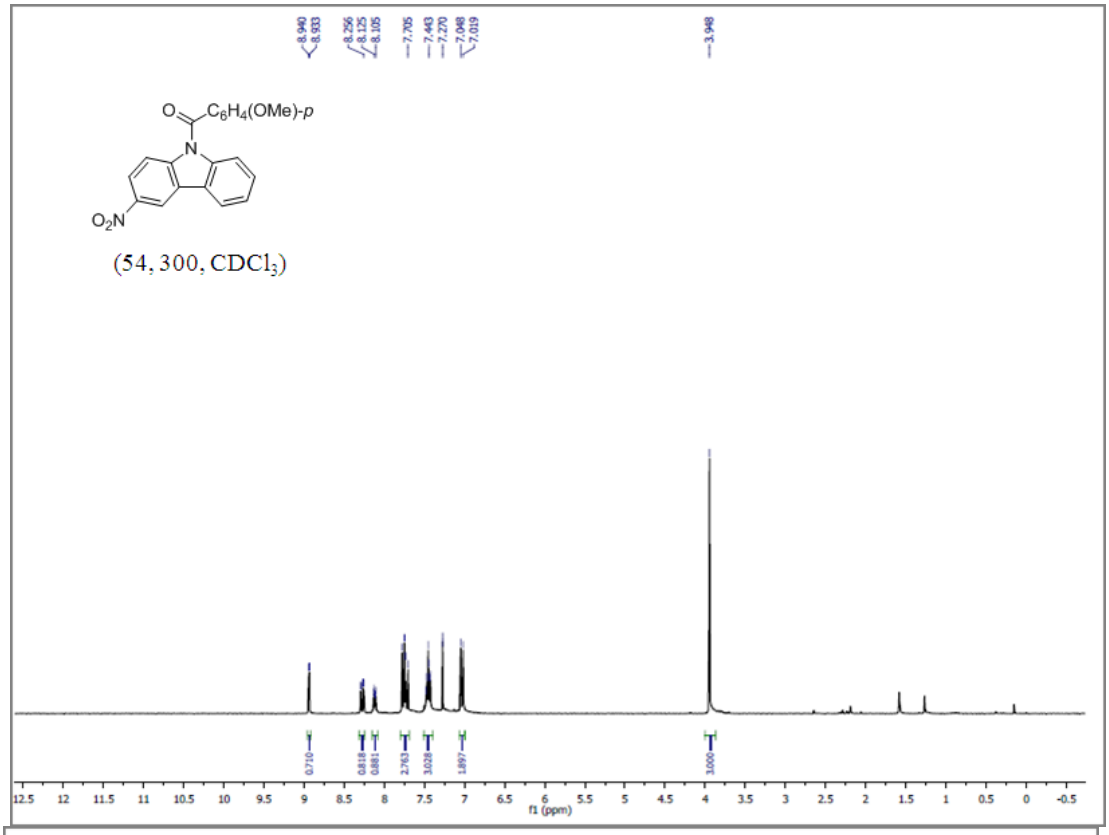

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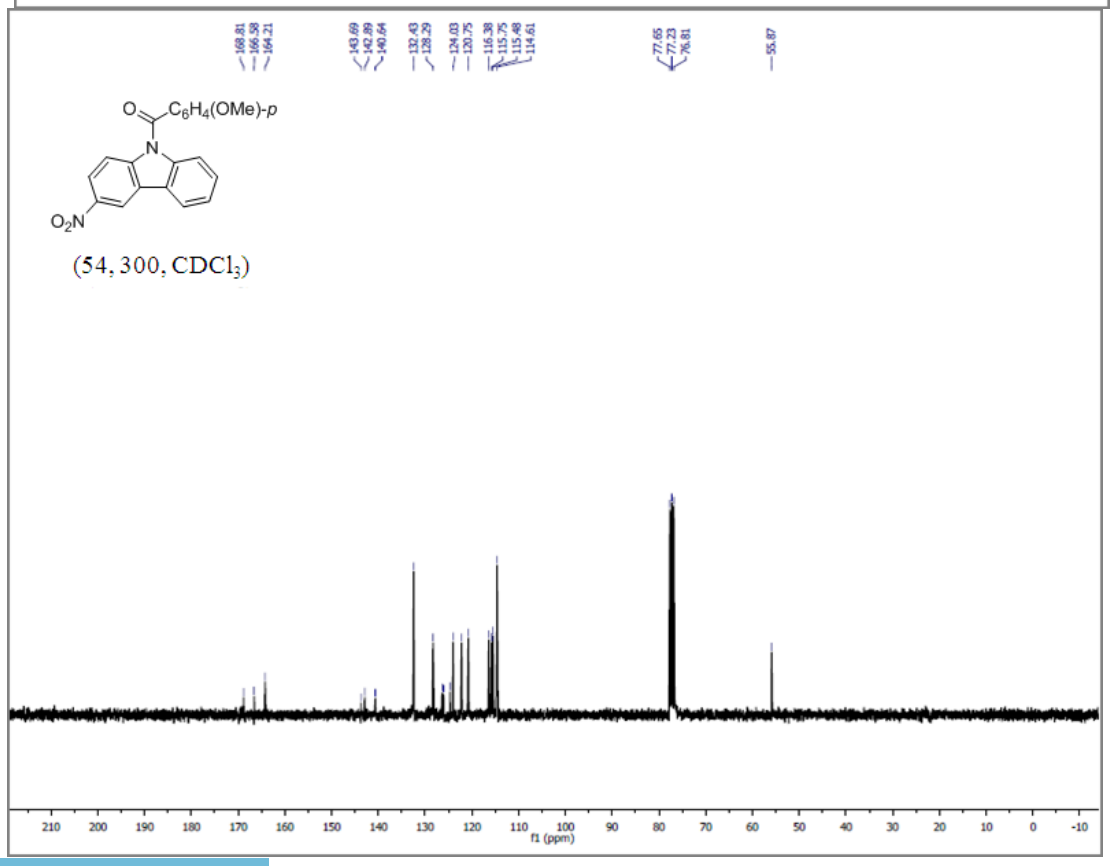

(54, 300, $CDCl_3$)