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## New Synthetic Reactions Enabled by Protected Oxyallyl and Amidoallyl Cations

Binod Nepal

*Louisiana State University and Agricultural and Mechanical College*

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# NEW SYNTHETIC REACTIONS ENABLED BY PROTECTED OXYALLYL AND AMIDOALLYL CATIONS

A Dissertation

Submitted to the Graduate Faculty of the  
Louisiana State University and  
Agricultural and Mechanical College  
in partial fulfillment of the  
requirements for the degree of  
Doctor of Philosophy

in

The Department of Chemistry

by  
Binod Nepal  
M.Sc., Tribhuvan University, 2015  
May 2022

*I dedicate this work to my dear daughter Bibha Nepal, my wife Durga Dhakal and my parents Parashu Ram Nepal and Shanta Devi Nepal. Thank you all for providing the best environment and love and support throughout this journey.*

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## LIST OF ABBREVIATIONS

$\alpha$ .....	alpha
$[\alpha]^{20}_D$ .....	absolute optical rotation
$\beta$ .....	beta
$\gamma$ .....	gamma
$\delta$ .....	chemical shift
$\mu\text{L}$ .....	microliter
$\pi$ .....	pi
1D.....	one-dimension
$^1\text{H}$ .....	proton NMR
2D.....	two-dimension
$^{13}\text{C}$ .....	carbon-13 NMR
$\text{\AA}$ .....	angstrom
$^\circ\text{C}$ .....	degree Celsius
$\text{Ac}_2\text{O}$ .....	acetic anhydride
$\text{AlCl}_3$ .....	aluminium trichloride
$\text{AgBF}_4$ .....	silver tetrafluoroborate
$\text{AgNTf}_2$ .....	silver triflimide
$\text{AgOTf}$ .....	silver triflate
Bn.....	benzyl
Boc.....	tert-butoxycarbonyl
BINOL.....	1,1'-bi-2-naphthol
c.....	concentration $\text{cm}^{-1}$
CAS.....	chemical abstract services
CCDC.....	Cambridge crystallographic data center
$\text{CH}_2\text{Cl}_2$ .....	dichloromethane
CPA.....	chiral phosphoric acid
CSA.....	camphorsulfonic acid
$\text{C}_6\text{F}_6$ .....	hexafluorobenzene
$\text{Cu}(\text{OTf})_2$ .....	Copper triflate

d.....	doublet
dd.....	doublet of doublets
dr.....	diastereomeric ratio
DABCO.....	1,4-diazobicyclo[2.2.2]octane
DCE.....	dichloroethane
DDT.....	dichlorodiphenyltrichloroethane
DIPEA.....	<i>N,N</i> -diisopropylethylamine
DMAP .....	4-dimethylaminopyridine
DMF.....	dimethylformamide
DMP.....	Dess-Martin periodinane
DMSO.....	dimethylsulfoxide
ee.....	enantiomeric excess
er.....	enantiomeric ratio
eq.....	equation
equiv.....	equivalent
<i>E</i> .....	<i>Entgegen</i> (trans)
E2.....	bimolecular elimination reaction
E1CB.....	elimination unimolecular conjugate base
$E^+$ .....	electrophile
Et.....	ethyl
EtOAc.....	ethyl acetate
Et <sub>3</sub> N.....	Triethylamine
ESI.....	electrospray ionization
EWG.....	electron withdrawing group
<i>f</i> .....	wavenumber
FDA.....	the food and drug administration
FTIR.....	fourier transform infrared
g.....	gram
GC.....	gas chromatography
GCMS.....	gas chromatography mass spectrometry
h.....	heptet



h.....	hour
HCl.....	hydrochloric acid
HPLC.....	high performance liquid chromatography
H <sub>3</sub> PO <sub>4</sub> .....	phosphoric acid
HRMS.....	high resolution mass spectrometry
Hz.....	hertz
I <sub>2</sub> .....	iodine
IC <sub>50</sub> .....	half minimal inhibitory concentration
IR.....	infrared
<i>J</i> .....	coupling constant
KBr.....	potassium bromide
LA.....	Lewis acid
LAH.....	lithium aluminum hydride
LC <sub>50</sub> .....	half minimal lethal concentration
LDA.....	lithium diisopropylamide
LiPF <sub>6</sub> .....	lithium hexafluorophosphate
<i>m</i> .....	meta
m.....	multiplet
mg.....	milligram
min.....	minutes
mmol.....	millimol
mL.....	milliliter
<i>m/z</i> .....	mass to charge ion
<i>m</i> CPBA.....	<i>meta</i> -chloroperoxybenzoic acid
mM.....	millimolar
M.....	Molar
M <sup>+</sup> .....	molecular ion
Me.....	methyl
MeCN.....	acetonitrile
MeI.....	methyl iodate, iodomethane
MeOH.....	methanol

Me <sub>2</sub> Zn.....	dimethyl zinc
MHz.....	Megahertz
MOM.....	methoxymethyl ether
MOMCl.....	chloromethyl methyl ether
MS.....	molecular sieves
<i>n</i> -BuLi.....	normal butyllithium
nm.....	nanometer
NaHMDS.....	sodium hexamethyldisilazide
Na <sub>2</sub> CO <sub>3</sub> .....	sodium carbonate
NaIO <sub>4</sub> .....	sodium metaperiodate
Nuc.....	nucleophile
NBS.....	<i>N</i> -bromosuccinimide
NCS.....	<i>N</i> -chlorosuccinimide
NMO.....	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMR.....	nuclear magnetic resonance
NOE.....	nuclear Overhauser effect
<i>o</i> .....	ortho
<i>p</i> .....	para
<i>p</i> -Tol.....	<i>para</i> -toluoyl
p.....	pentet
Pd/C.....	palladium on carbon
Ph.....	phenyl
Piv.....	pivaloyl
Py•TfOH.....	pyridinium triflate
PCC.....	pyridinium chlorochromate
PMB.....	<i>para</i> -methoxybenzyl
PMP.....	<i>para</i> -methoxyphenyl
PPTS.....	pyridinium <i>para</i> -toluenesulfonate
PVC.....	polyvinyl chloride
rr.....	regiomer ratio
rt.....	room temperature

RuCl <sub>3</sub> .....	ruthenium trichloride
s.....	singlet
Sc(OTf) <sub>3</sub> .....	scandium triflate
SiO <sub>2</sub> .....	silica gel
S <sub>N</sub> 1.....	unimolecular nucleophilic substitution
S <sub>N</sub> 2.....	bimolecular nucleophilic substitution
SOCl <sub>2</sub> .....	thionyl chloride
SOCl <sub>3</sub> •py.....	sulphur trioxide pyridine complex
t.....	triplet
temp.....	temperature
<i>t</i> BuOH.....	<i>tert</i> -butanol
Tf <sub>2</sub> O.....	trifluoromethanesulfonic anhydride
TfOH.....	triflic acid
THF.....	tetrahydrofuran
TiCl <sub>2</sub> ( <i>Oi</i> Pr) <sub>2</sub> .....	titanium dichloride diisopropoxide
Ti( <i>Oi</i> Pr) <sub>4</sub> .....	titanium isopropoxide
TIPS.....	triisopropylsilyl
Ts.....	tosyl
TsNH <sub>2</sub> .....	<i>para</i> -toluene sulphonamide
TsOH.....	<i>para</i> -toluene sulfonic acid
TBAF.....	tetrabutylammonium fluoride
TBS.....	<i>tert</i> -butyldimethylsilyl
TBME.....	methyl <i>tert</i> -butyl ether
TBSCl.....	<i>tert</i> -butyldimethylsilyl chloride
TFA.....	trifluoroacetic acid
TFAA.....	trifluoro acetic anhydride
TFE.....	trifluoroethanol
THF.....	tetrahydrofuran
THP.....	tetrahydropyran
TIPS .....	triisopropylsilyl

TLC.....	thin layer chromatography
TMS.....	trimethylsilyl
TMSCl.....	trimethylsilyl chloride
TMSOTf .....	trimethylsilyl trifluoromethylsulfonate
TRIP.....	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
UV.....	ultraviolet
VAPOL.....	2,2'-diphenyl-(4-biphenanthrol)
Z.....	<i>Zusammen</i> (cis)
Zn(OTf) <sub>2</sub> .....	zinc trifluoromethanesulfonate

## ABSTRACT

This dissertation entails design and development of two new synthetic methodologies made possible through the generation of cationic species, namely oxyallyl and amidoallyl cations. Chapter 1 involves literature survey on generation and trapping of oxyallyl cations. Mostly known for cycloaddition reactions with these elusive species, the most recent approach of direct nucleophilic capture of oxyallyl cations are discussed. Apt design of substrates and reaction conditions by Kartika Group to access  $\alpha$ -electrophilic carbon towards the synthesis of a variety of value-added compounds, i.e., 1,4- and 1,6-dicarbonyls, carbazoles, densely substituted pyrroles and furans are elaborated.

Chapter 2 focuses on our discovery of a new type of reactivity of unsymmetrical oxyallyl cations generated by treating  $\alpha,\alpha$ -hydroxyalkynyl enol ethers with Py.TfOH. Our observation of the switch in regioselectivity when alkynes are substituted for their aliphatic counterpart to form  $\alpha$ -bis aryl quaternary centers is presented. Detailed reaction optimization and scope of reaction, as well as synthetic utility of product is also elaborated.

Chapter 3 describes the classical and most recent methods of generation of nitrogen analogue of oxyallyl cations *viz* amidoallyl cations. This chapter details how the chemistry of 2-amino and 2-amidoallyl cations is developed over time, and their interceptions made possible through cycloadditions and direct trapping with nucleophiles. Ionization of  $\alpha$ -hydroxy enamides with mild Brønsted acid and its capture at the  $\alpha$ -carbon is discussed, which set the stage for Chapter 4. Chapter 4 is focused on our work on enantioselective  $\beta$ -functionalization of cyclic enamides made possible through strategic tautomerization of 2-amidoallyl cations to 1-amidoallyl cations with the help of chiral phosphoric acid catalyst. Optimization and scope of the reaction followed by a proposed mode of activation is discussed, supported by computational data.

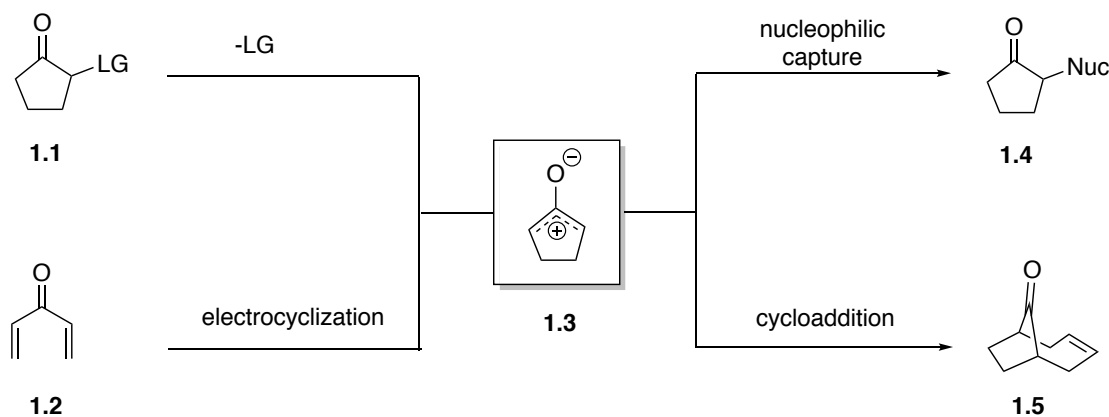
# CHAPTER ONE. INTRODUCTION TO OXYALLYL CATIONS, VARIATIONS AND DIRECT NUCLEOPHILIC CAPTURE

## 1.1 Purpose

The purpose of this chapter is to provide an insight into various methods of generation of oxyallyl cations, variations, and their subsequent capture *via* different strategies. Important approaches to capture of these unique electrophiles will be reviewed which mainly include classical Favorskii rearrangement, cycloadditions and direct nucleophilic capture. Functionalization of cyclic ketones at the  $\alpha$ -position via ionization of  $\alpha$ -halo and  $\alpha$ -tosyl ketones will be discussed. Finally, Kartika Lab's strategy toward regioselective capture of unsymmetrical oxyallyl cations and silyloxyallyl cations and their importance in construction of value-added structural motifs will be presented.

## 1.2 Introduction to Oxyallyl Cations

Oxyallyl cations are transient zwitterionic species (**1.3**) where the positive charge is delocalized over three carbon atoms and a negative charge in oxygen atom.<sup>1</sup> These species are typically generated from either a) activation of divinyl ketone species<sup>2</sup> or b) through ionization of ketones containing a leaving group at the  $\alpha$ -position.<sup>3</sup>

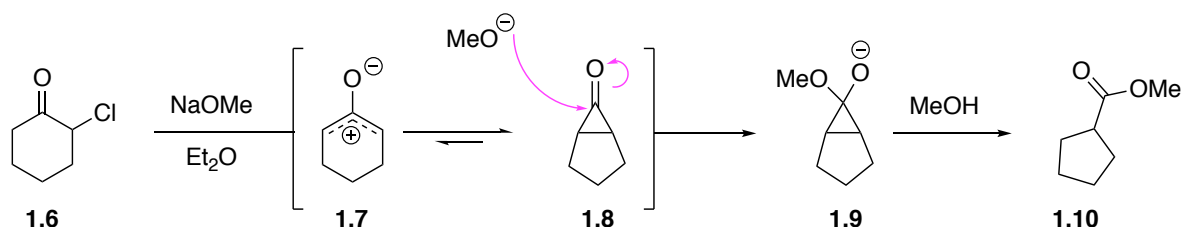


Scheme 1.1. Generation and trapping of oxyallyl cations

Owing to their reactivity, oxyallyl cations are employed in various synthetic transformations, i.e. Favorskii Rearrangements,<sup>4</sup> cycloadditions<sup>5</sup>, Nazarov cyclizations<sup>6</sup> and direct nucleophilic capture.<sup>3</sup> Scheme 1 reflects the overall summary of generation and typical usage of these species.

### 1.3 Favorskii Rearrangements with Oxyallyl Cations

Generation of oxyallyl cations in a rearrangement process was first reported by Favorskii in 1894, where a symmetrical oxyallyl cation **1.7** is formed by the dehalogenation of  $\alpha$ -chloro cyclohexanones **1.6**, upon treatment with sodium methoxide in ether.<sup>7</sup> These elusive species were observed to undergo a ring contraction to furnish the cyclopropenone intermediate **1.8** in equilibrium with the zwitterionic oxyallyl intermediate **1.7**. In presence of an alkoxide nucleophile, they were captured to produce cyclopentyl methyl esters **1.10**.

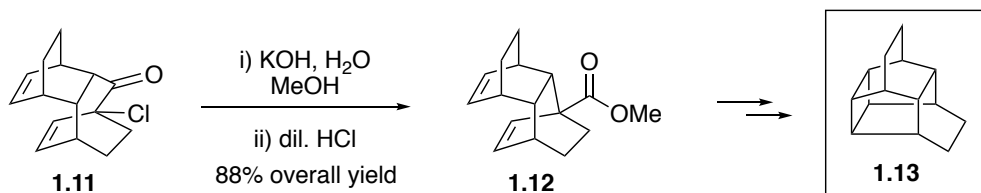


Scheme 1.2. Favorskii Rearrangement *via* Oxyallyl Cations

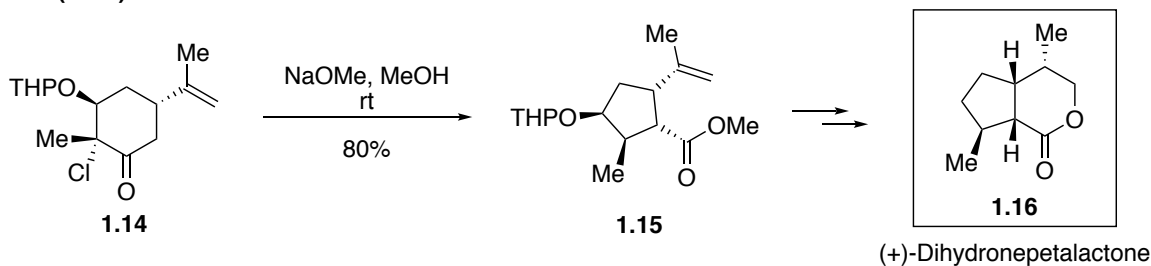
This observation has been utilized later by various synthetic chemists in their approach to synthesize complex molecular architectures. For instance, Takeshita (1994) employed this ring-contraction strategy in their synthesis of structurally complex bicyclic carboxylic acid ester **1.12** from the  $\alpha$ -chloro ketone **1.11**, i.e., towards the synthesis of hexacyclotetradecene **1.13**. The reaction was performed in water and KOH and subsequent treatment with dilute HCl.<sup>8</sup> The reaction yields *endo-syn*-tetracycloadducts **1.12** in a highly efficient manner after the sequence of dehalogenation and nucleophilic capture with hydroxide ion. Another example by Lee (1994) also utilized a similar strategy to access the tetrasubstituted chiral esters **1.15** from optically pure

carvone chlorohydrin **1.14** *en route* to the synthesis of (+)-Dihydronepetalactone **1.16**.<sup>4</sup> This reaction was carried out in presence of sodium methoxide in methanol, and the Favorskii rearrangement is observed to be stereoselective. Another example by Hall (2010) demonstrates the utility of the Favorskii rearrangement in a chiral pool synthetic approach of tetrasubstituted cyclopentane **1.18** from  $\alpha$ -chloro ketone **1.17** in sodium methoxide in methanol.<sup>9</sup> This key transformation led to the total synthesis of (+)-Chinensiolid B **1.19**.

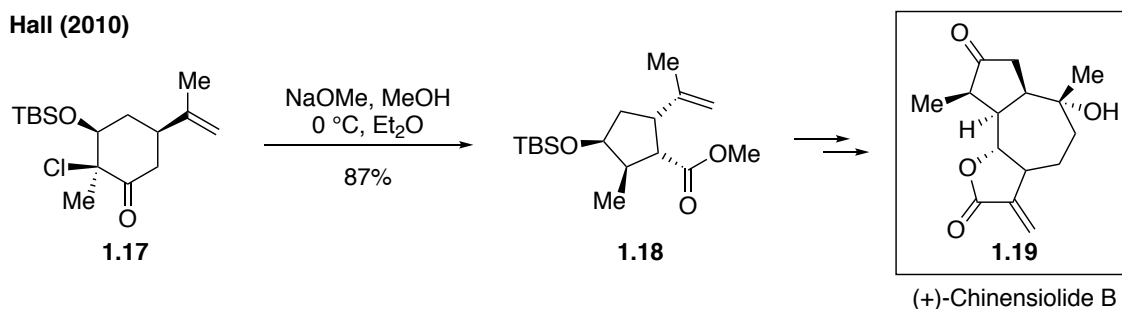
**Takeshita (1994)**



**Lee (1994)**



**Hall (2010)**

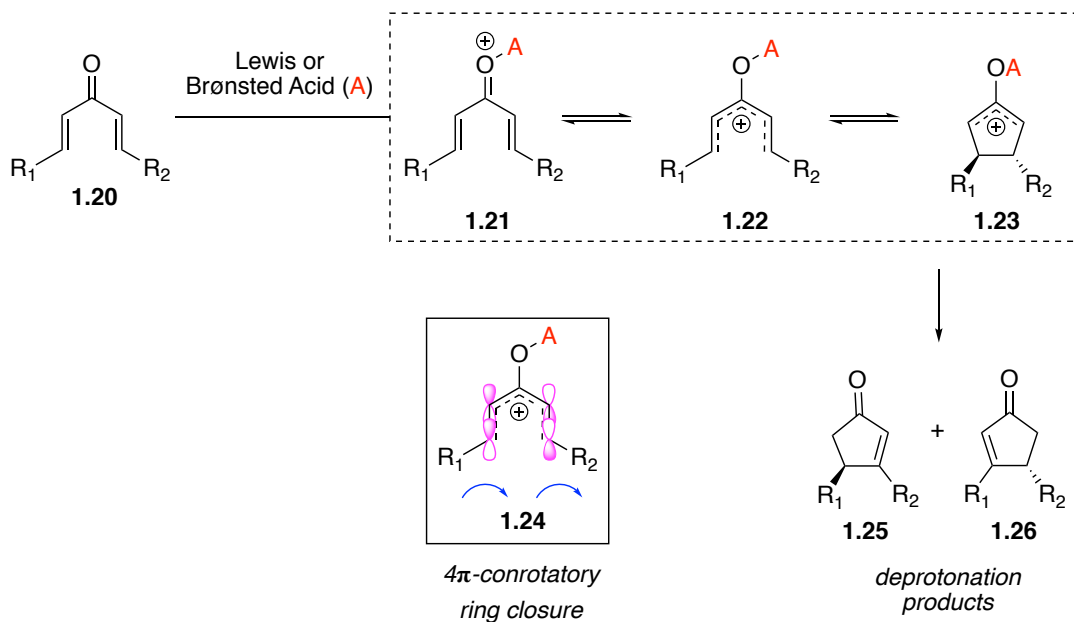


Scheme 1.3. Favorskii rearrangement reactions in complex architectures



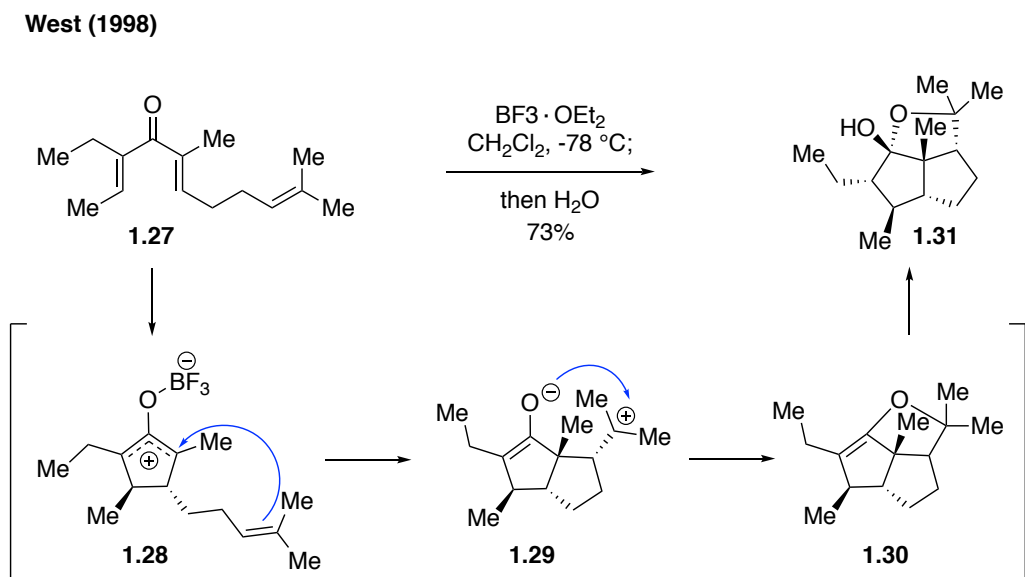
## 1.4 Nazarov Cyclization

An alternative approach to access the oxyallyl cations is through the activation of divinyl ketones. First reported by Nazarov in 1941,<sup>6</sup> divinyl ketone **1.20** can be activated by a Lewis or a Brønsted acid, which triggers the formation of pentadienyl cation **1.22** followed by a conrotatory  $4\pi$ -electrocyclic ring closure. The ring closure is stereospecific, and it furnishes a trans-relationship between two substituents in the five-membered ring through the orbital symmetry explanations in **1.24**. Thus generated cyclopentenyl cationic intermediate **1.23** undergoes deprotonation reactions to yield multiple products in the form of  $\alpha,\beta$ -unsaturated ketones **1.25** and **1.26**. Due to its stereospecificity, the Nazarov cyclization strategy has been employed in various synthetic endeavors toward the construction of substituted cyclopentenones with definite stereochemical integrity.<sup>10</sup> Furthermore, variations in Nazarov cyclizations i.e., imino-Nazarov, aza-Nazarov and homo-Nazarov reactions are also studied in the literature.<sup>11-13</sup>



Scheme 1.4. Nazarov cyclization promoted by Lewis acid

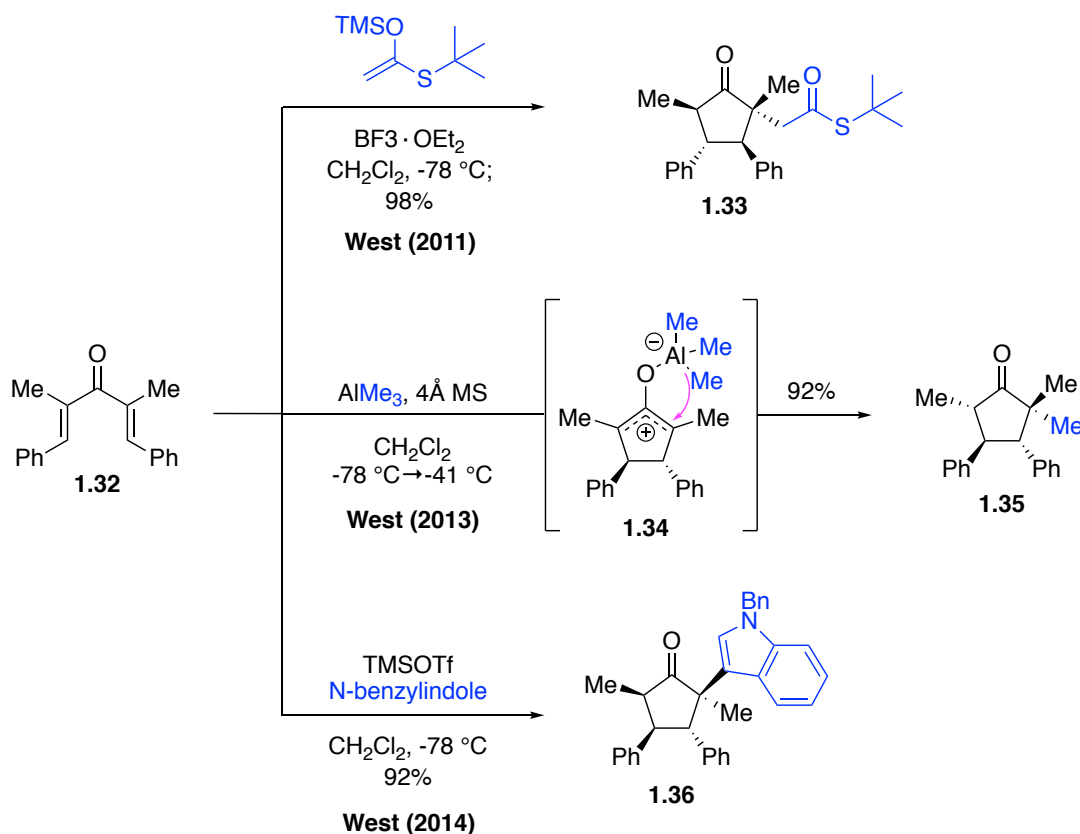
Due to the efficient generation of these electrophilic species, a novel strategy for trapping them with nucleophiles has emerged. This approach furnishes  $\alpha$ -functionalized cyclopentenones with an exquisite control of diastereoselectivity and offers a wide range of substitutions in five-membered rings. One of the pioneering works in this field is showcased by West et al. In one of their early works from 1998,<sup>14</sup> it is shown that the divinyl compounds, e.g., **1.27** can be activated with  $\text{BF}_3 \cdot \text{OEt}_2$  to generate the desired oxyallyl cation **1.28**, which can undergo a deliberate trapping by the pendant alkene nucleophile in a 5-exo cyclization, establishing a new C-C bond in **1.29**. Further cyclization sequence affords the cyclic ether **1.31**.



Scheme 1.5.  $\text{BF}_3 \cdot \text{OEt}_2$  promoted interrupted Nazarov cyclization

This work has inspired the West Group towards incorporation of silyl enolates as nucleophiles under similar activation conditions.<sup>15</sup> Substituted divinyl ketones **1.32** undergo Nazarov cyclization to produce oxyallyl cation upon activation by  $\text{BF}_3 \cdot \text{OEt}_2$ , which is intercepted by the silyl enol ether via homologous Mukaiyama addition to furnish stereo-enriched cyclopentanone **1.33**. In the same line of work, West et al showcased that instead of  $\text{BF}_3 \cdot \text{OEt}_2$ ,

trialkylaluminium can also be used as an activator.<sup>16</sup> Activation of identical substrate furnishes the oxyallyl cation **1.34**, where intramolecular delivery of an alkyl group from the Lewis acid provides the nucleophilic coupling partner in the formation of **1.35**. Similarly, TMSOTf was also successfully demonstrated as a Lewis acid activator for such transformations by the West Group in 2014,<sup>17</sup> where  $\pi$ -nucleophiles like indoles were very effective in intercepting the transient oxyallyl cations towards the formation of  $\alpha$ -indolyl cyclopentenones **1.36**.

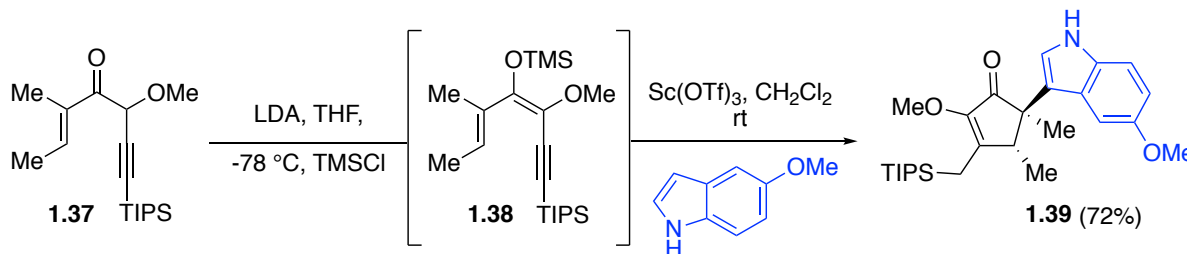


Scheme 1.6. Examples on interrupted Nazarov cyclizations with different Lewis acids

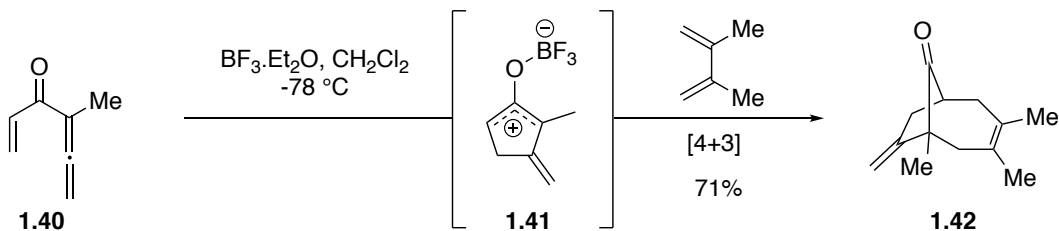
Not only the divinyl ketones, allenyl vinyl ketones are also used in the Nazarov cyclization towards generating oxyallyl cations. Tius (2008) used the propargyl vinyl ketone **1.37** as a starting material in their explorations on interrupted Nazarov cyclization.<sup>18</sup> Under basic conditions, the starting material is converted into TMS enol ether **1.38** followed by Lewis acid activation using  $\text{Sc}(\text{OTf})_3$ . The formation of allenyl vinyl ketone in the reaction induced a rapid cyclization, which

was captured by 5-methoxy indoles to afford  $\alpha$ -indolyl adduct **1.39**. Along this line of work, Burnell et al (2010) employed the allenyl vinyl ketones **1.40** directly with  $\text{BF}_3 \cdot \text{OEt}_2$  to induce cyclization intermediate **1.41**, which was captured in a [4+3] cycloaddition reaction with substituted butadiene to furnish bicyclic product **1.42**.<sup>19</sup>

**Tius (2008)**



**Barnell (2010)**

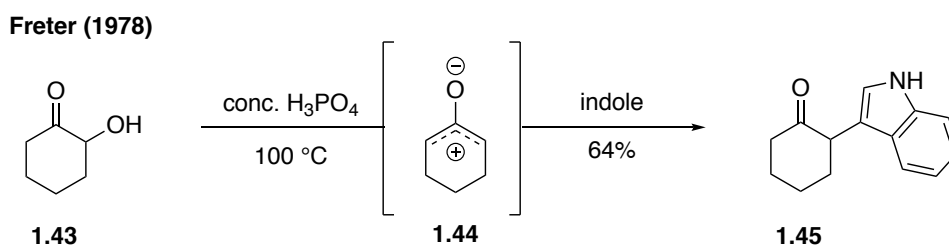


Scheme 1.7. Allenyl vinyl ketones as Nazarov cyclization precursors

## 1.5 Direct Nucleophilic Capture of Oxyallyl Cations

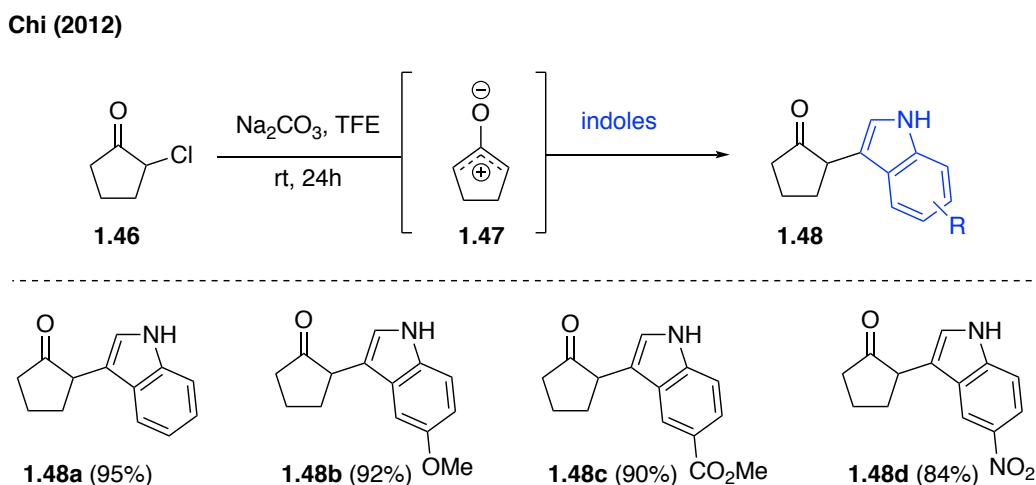
This section focuses on direct nucleophilic capture of oxyallyl cations generated from various methods. These putative species are electrophilic at the  $\alpha$ -position of ketone-derived compounds, this reversal of charge is known as umpolung approach.<sup>20</sup> This leads to unique reactivity and regioselectivity upon nucleophilic attack. Recent works from Phil S. Baran and coworkers on  $\text{sp}^2$ - $\text{sp}^3$  coupling between indole C3 and alpha-position of the ketone highlights the importance of synthetic methods to functionalize the  $\alpha$ -position of ketones.<sup>21</sup> Oxyallyl cation technology provides an alternate to the prevalent methods by providing an umpoled  $\alpha$ -carbon for

trapping by a nucleophile. First real example of direct nucleophilic capture was observed by Freter in 1978 when  $\alpha$ -hydroxy cyclohexanone **1.43** was treated with concentrated  $\text{H}_3\text{PO}_4$  at  $100\text{ }^\circ\text{C}$ .<sup>22</sup> Generation of symmetrical oxyallyl cation **1.44** and its subsequent capture by indole led to the formation of  $\alpha$ -indolyl cyclohexanone **1.45**.



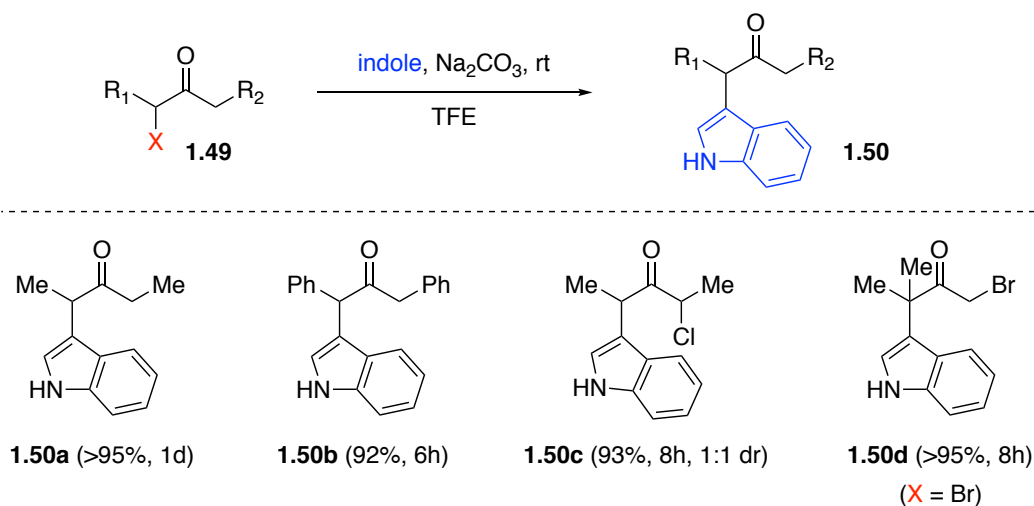
Scheme 1.8. Freter's work on direct nucleophilic capture of oxyallyl cation

Explorations into this mode of capture remained dormant until Chi and co-workers (2012) revitalized this strategy in their studies towards generation of symmetrical oxyallyl cation from  $\alpha$ -chlorocyclopentanone **1.46**.<sup>23</sup> In presence of sodium carbonate in trifluoroethanol, the  $\alpha$ -chlorocyclopentanone undergoes an  $\text{E}_1\text{CB}$  type reaction to furnish symmetrical oxyallyl cation **1.47** which is then captured by various indoles at the  $\alpha$ -position to afford  $\alpha$ -indolyl compounds **1.48**.



Scheme 1.9. Chi's strategy on generation and capture of oxyallyl cations

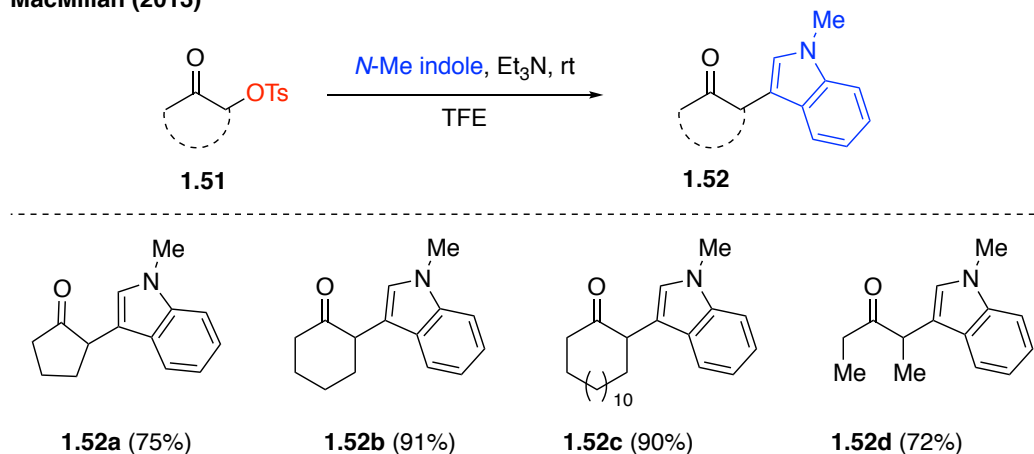
This method was robust and practical and also eliminated the need of column chromatography in many instances. In the same publication, Chi and co-workers also demonstrated that acyclic  $\alpha$ -haloketones **1.49** can also be used as a source of oxyallyl cations. When subjected to optimized conditions, these starting materials generate oxyallyl cations effectively and a smooth capture by the indoles were observed in the products **1.50**. The acyclic  $\alpha$ -haloketones reacted slowly albeit the product yields remained impressive.



Scheme 1.10. Chi's examples on acyclic  $\alpha$ -haloketones

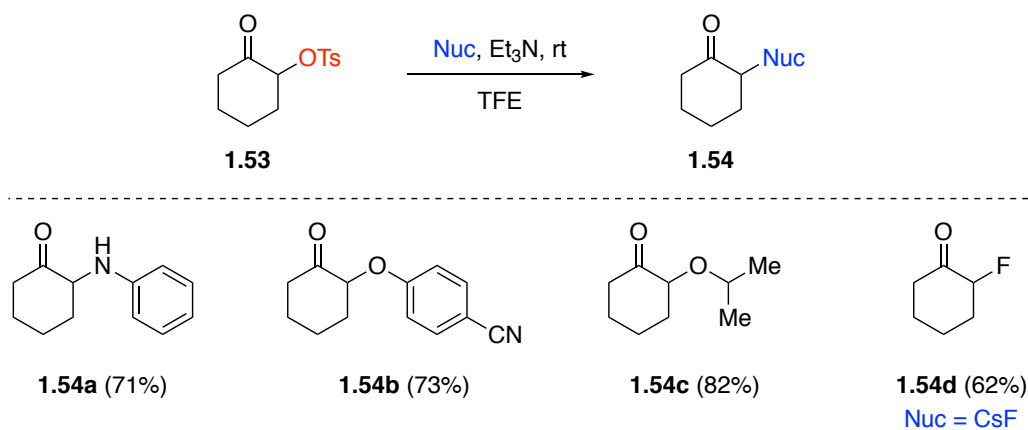
Following this work, MacMillan and co-workers (2013) pursued another mode of activation employing  $\alpha$ -tosyloxyketones **1.51** as their starting material to furnish oxyallyl cations and subsequent capture by *N*-Me protected indoles.<sup>3</sup> The optimized condition uses  $\text{Et}_3\text{N}$  as a base in trifluoroethanol as a solvent, which also serves as a source of carbonyl activation. Both five-membered and six-membered  $\alpha$ -tosyloxyketones **1.52a** and **1.52b** as well as macrocyclic ketones **1.52c** afforded the products in good yields.

MacMillan (2013)



Scheme 1.11. MacMillan's approach on oxyallyl cation capture by indoles

The method tolerated not only the indole nucleophiles, but also the aniline and phenol-based nucleophiles, aliphatic alcohols and cesium salts as showcased in products **1.54a**, **1.54b**, **1.54c** and **1.54d**.

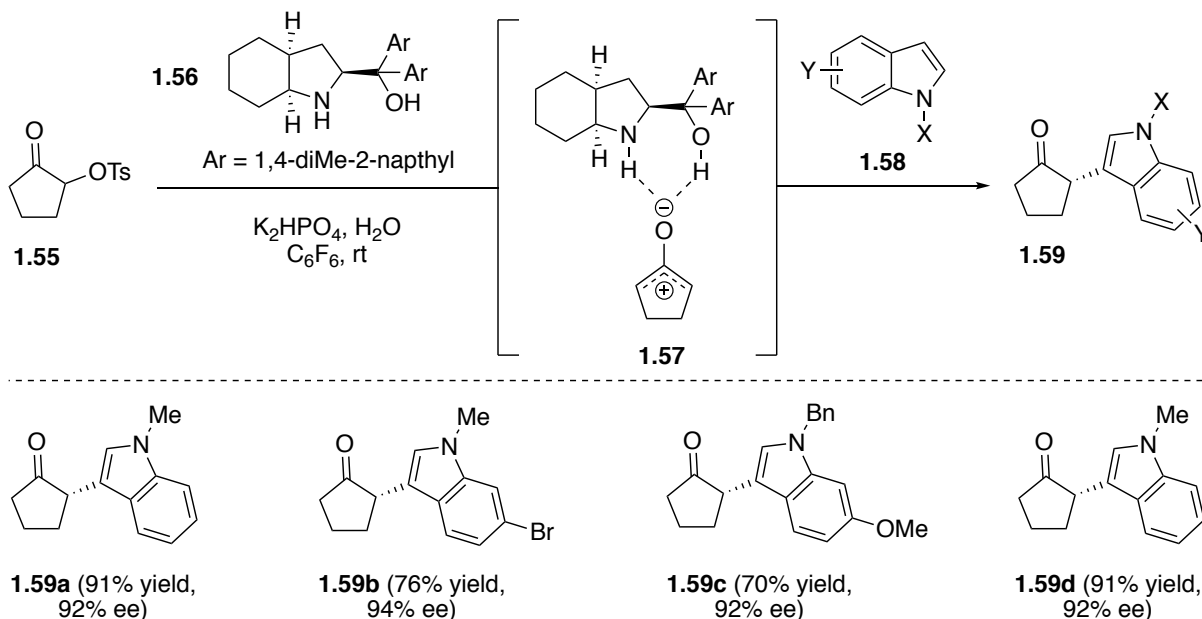


Scheme 1.12. Scope of nucleophiles in MacMillan's work

Inspired by this work, MacMillan and co-workers (2016) developed an enantioselective protocol towards the activation of  $\alpha$ -tosyloxycyclopentanones **1.55**.<sup>24</sup> This strategy employs chiral H-bond donating amino alcohol **1.56** derived from prolinol, which induces soft enolization of the starting material by activating the carbonyl group. This event produces an enantiodiscriminant oxyallyl cation **1.57**, which is captured by electron-rich indoles to install asymmetric center at the

$\alpha$ -carbon as demonstrated in structures **1.59a–d**. This method is limited to cyclic five-membered  $\alpha$ -tosylketones as the activation of six-membered analogs were futile.

**MacMillan (2016)**



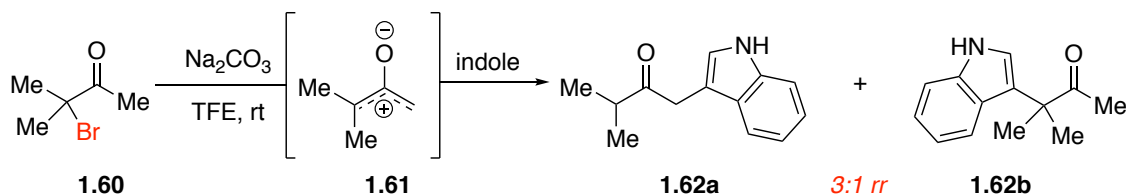
Scheme 1.13. MacMillan's work on enantioselective capture of oxyallyl cations

## 1.6 Protected Oxyallyl Cations

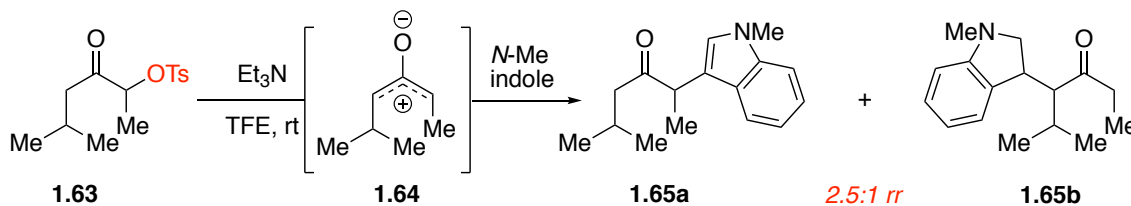
Seminal works from Chi and MacMillan elaborated the generation and trapping of various  $\sigma$ - and  $\pi$ -carbon nucleophiles as well as heteroatom nucleophiles as described in section 1.5.<sup>3, 23</sup> However, these methods are chiefly dependent on generation of symmetrical oxyallyl cations, leaving with regiomer mixtures of products for the unsymmetrical counterparts as showcased in scheme xxxx. When differently substituted corresponding starting materials **1.60** and **1.63** are ionized under standard conditions described by the approaches discussed above, mixture of regioisomers were observed in the concomitant step of nucleophilic capture. Steric effects are observed as the nucleophilic attack is preferred at the less-hindered  $\alpha$ -carbon, however they are highly competitive.



Chi (2012)



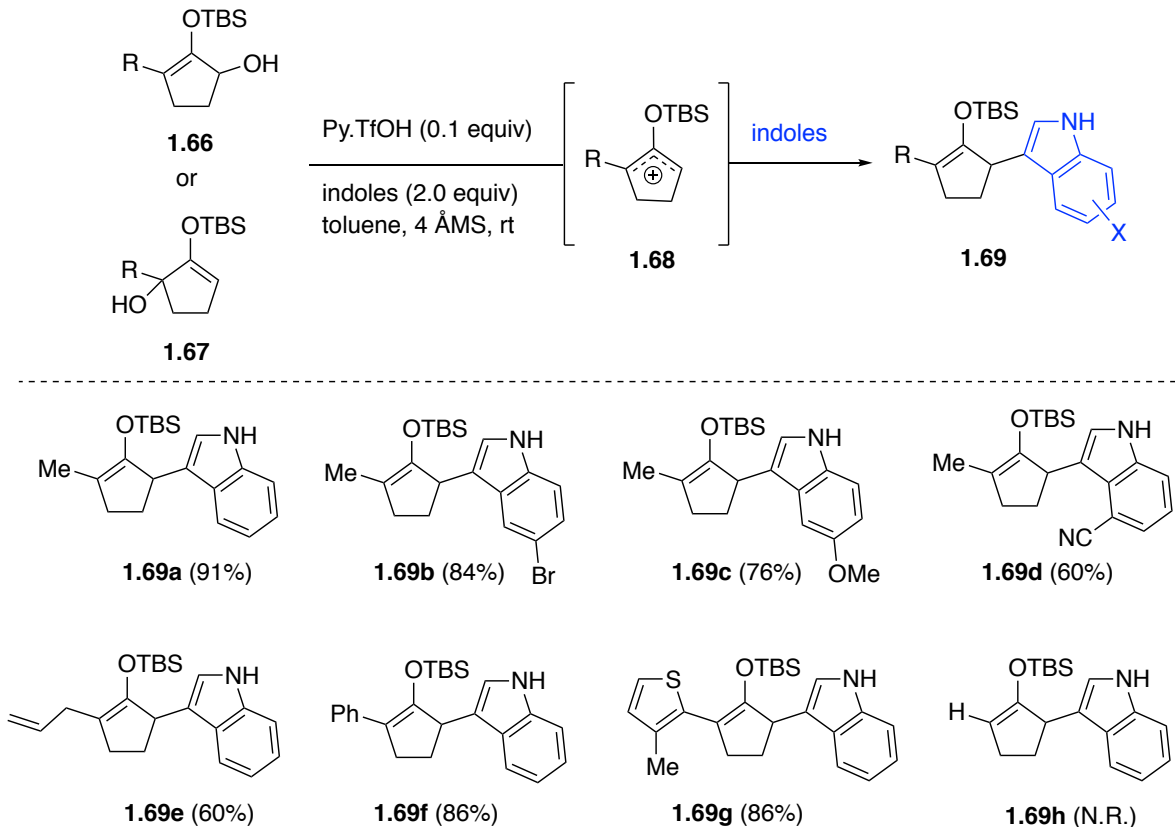
MacMillan (2013)



Scheme 1.14: Lack of regioselectivity in acyclic  $\alpha$ -leaving group containing ketones

In a quest to solve this problem, Kartika and co-workers invented a unique approach of protecting the oxygen atom of the oxyallyl cation as a silyl enol ether.<sup>20</sup> When  $\alpha$ -hydroxy silylenol ethers **1.66** or **1.67** were treated with  $\text{Py}\cdot\text{TfOH}$ , a mild Brønsted acid, unsymmetrical oxyallyl cation **1.68** was generated, which was captured by indole nucleophiles with an exquisite control of regioselectivity at the less substituted  $\alpha$ -position elaborated in structure **1.69**. Scope of the methodology was well explained by incorporation of various electronically different indoles in **1.69a-d** as well as different  $\alpha$ -substituents in **1.69e-g**. Most importantly, all the products shown in the scheme 1.15 were obtained as single regioisomers. Removal of the  $\alpha$ -substituent rendered the formation of oxyallyl cation disfavored as indicated in structure **1.69h**, signifying the role of these substituents in stabilizing the incipient cationic species.

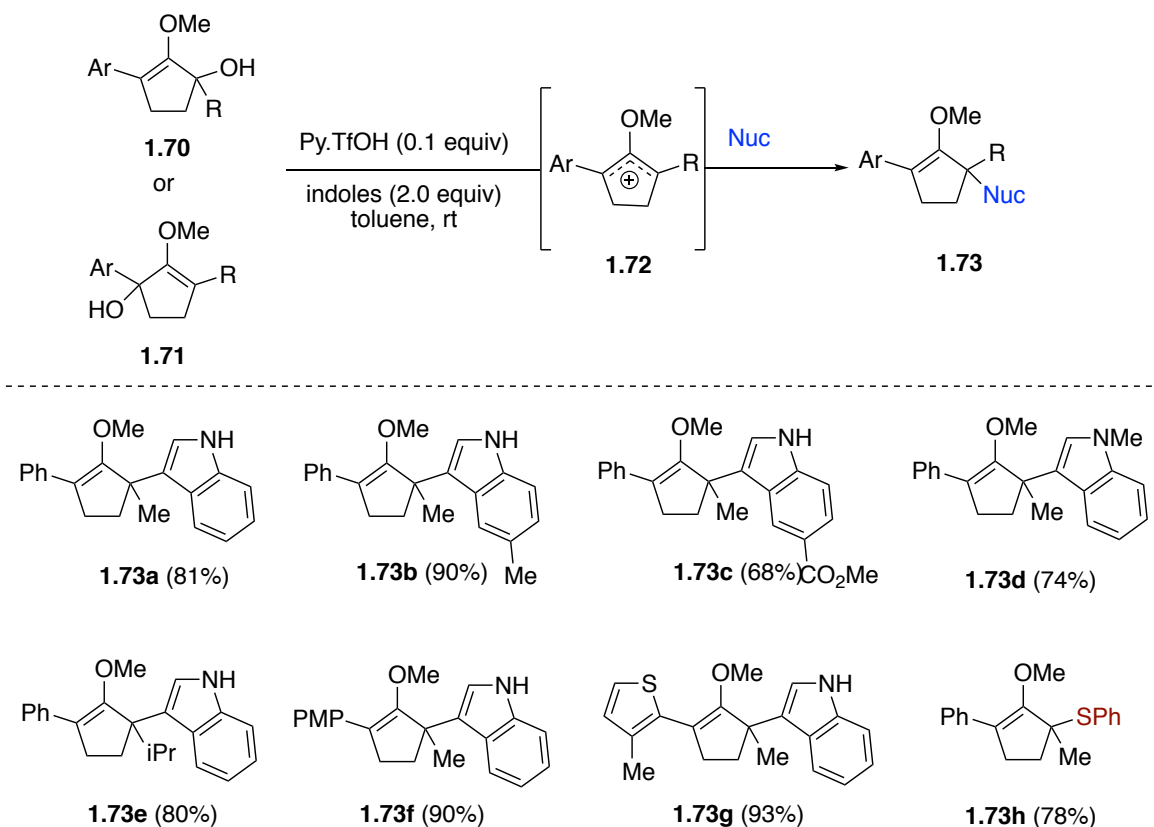
Kartika (2015)



Scheme 1.15. Kartika's work on controlling regioselectivity using silyloxyallyl cations

In another study, Kartika and co-workers successfully demonstrated the incorporation of methyl enol ethers as their protecting group for the oxyallyl cations **1.72**.<sup>25</sup> These species were generated from aryl substituted  $\alpha$ -hydroxy methyl enol ethers **1.70** or **1.71** ionized with the help of  $\text{Py.TfOH}$ , which furnishes the desired  $\alpha$ -functionalized products **1.73** in high yields and complete regiocontrol. Benzylic-oxyallylic stabilization from the  $\alpha$ -aryl substituents is believed to play a key role in controlling the regioselectivity. To add up, this methodology delivers quaternarization at the  $\alpha$ -carbon bearing an alkyl group as indicated in the compounds **1.73a-h**. Nucleophile scope includes indoles, pyrroles, and oxygen and sulfur nucleophiles.

**Kartika (2015)**

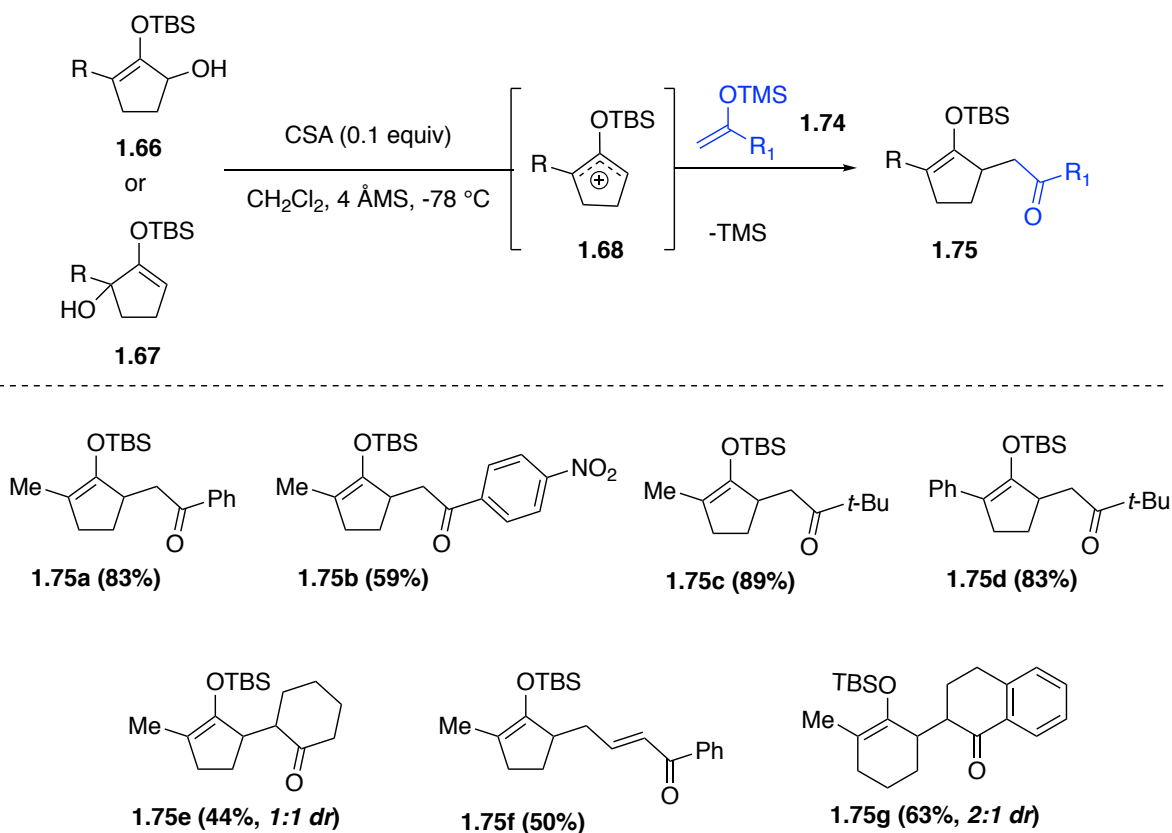


Scheme 1.16. Kartika's approach in capturing methyl enol ether protected oxyallyl cations

These encouraging findings led Kartika and co-workers to develop a different class of nucleophiles to capture unsymmetrical silyloxyallyl cations once they are generated from the corresponding  $\alpha$ -hydroxy silyl enol ethers **1.66** or **1.67**.<sup>26</sup> From relying heavily on indole nucleophiles, Kartika and co-workers demonstrated the utility of trimethylsilyl enolates **1.74** as nucleophiles towards the regioselective construction of 1,4-monosilyl dicarbonyl compounds **1.75** via  $\alpha$ -C-C bond formation. This work highlights the importance of non-trivial umpolung approach towards the synthesis of 1,4-diketone compounds as charge reversal at the  $\alpha$ -carbon is exploited for the nucleophile capture. Typical reaction condition included the ionization of secondary or tertiary  $\alpha$ -hydroxy silyl enol ethers by catalytic CSA at  $-78^\circ\text{C}$ , which furnished the unsymmetrical

silyloxyallyl cation **1.68**, that was captured by a TMS enolate **1.74** at the less substituted  $\alpha$ -carbon. This scope of this method is well elaborated in scheme 1.17 where various  $\alpha$ -substituents and TMS enolates furnished good to excellent results as showcased in structures **1.75a-e**. This methodology also served to access monosilyl protected 1,6-dicarbonyls **1.75f** when subjected to appropriate nucleophiles as well as six-membered silyl enol ethers e.g. **1.75g**. Although this method offers a new dimension of nucleophiles for capturing silyloxyallyl cations, the protocol suffered from necessity of cryogenic temperatures, strong Brønsted acid and longer reaction times.

Kartika (2016)

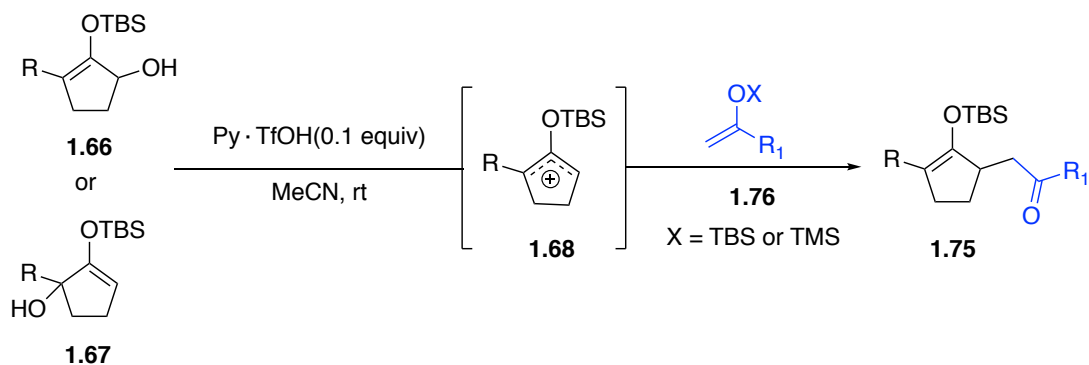


Scheme 1.17. Kartika's methodology towards monosilyl dicarbonyls synthesis

To circumvent this problem, Kartika and co-workers reinvented an improved reaction condition by utilizing either TBS or TMS enolates **1.76** as nucleophiles that trap the silyloxyallyl

cation **1.68**, which was generated from corresponding  $\alpha$ -hydroxy silylenol ethers **1.66** or **1.67** in presence of Py.TfOH in acetonitrile at room temperature.<sup>27</sup> This method was robust as reflected by reactions with less acid-labile TBS enolates proceeding smoothly without decomposition of the starting material. The practicality and faster reaction times made this method amenable in laboratory settings.

**Kartika (2017)**

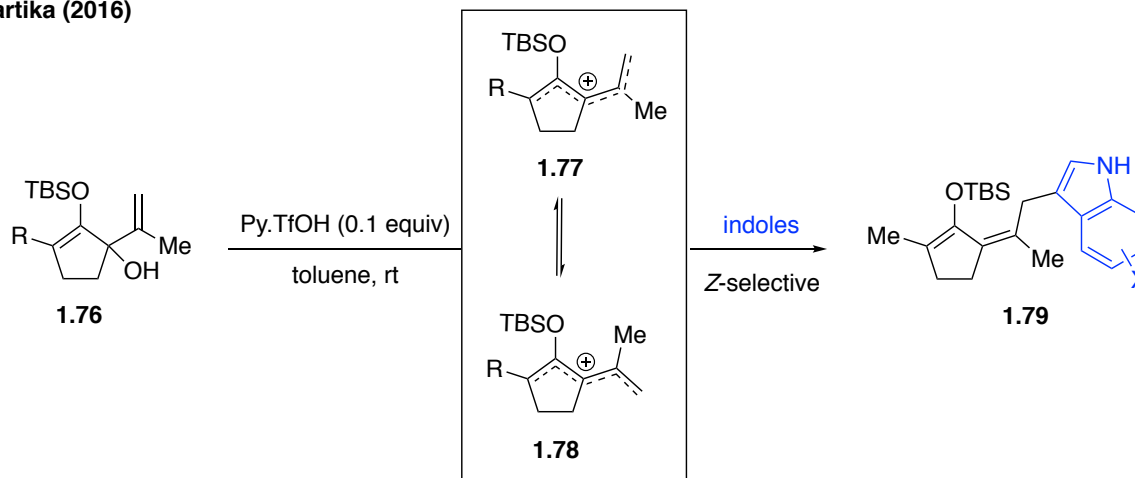


Scheme 1.18. Revised method for monosilyl carbonyls synthesis by Kartika and co-workers

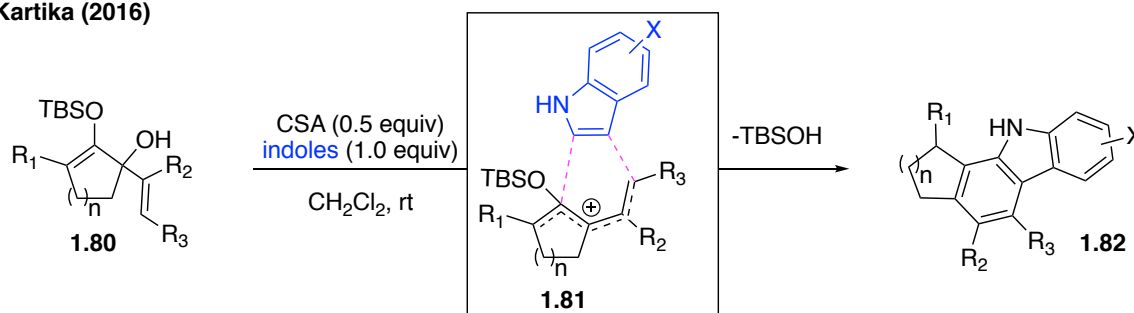
In an extension of the regular  $\alpha$ -capture of the oxyallyl cations by nucleophiles, two elegant methodologies have been developed by Kartika and co-workers in 2016, which is summarized in scheme 1.19. First work explains the  $\gamma$ -capture of  $\pi$ -extended oxyallyl cations, i.e. 2-silyloxypentadienyl cations **1.77/1.78** generated from silyldienol ethers **1.76** using  $\text{Py} \cdot \text{TfOH}$  as an ionization source.<sup>28</sup> The nucleophilic capture with indoles occurred exclusively at the  $\gamma$ -position with a *Z*-geometry in the exocyclic double presumably through thermodynamic control to furnish tetrasubstituted silyldienol ether product **1.79**. This *de novo* synthesis inspired Kartika and co-workers to explore the annulation reactions with 2-silyloxypentadienyl cations generated in presence of a much stronger Brønsted acid, CSA.<sup>29</sup> The regular capture by indoles at the  $\gamma$ -position sets the stage for a cascade reaction through a transition state **1.81**, with subsequent protodesilylation and dehydrative cyclization to afford substituted carbazole products **1.82**. The

process was facilitated by the usage of CSA, which helped in protodesilylation, as well as inherent water generation, which presumably helped in isomerization of the exocyclic C-C bond.

**Kartika (2016)**



**Kartika (2016)**

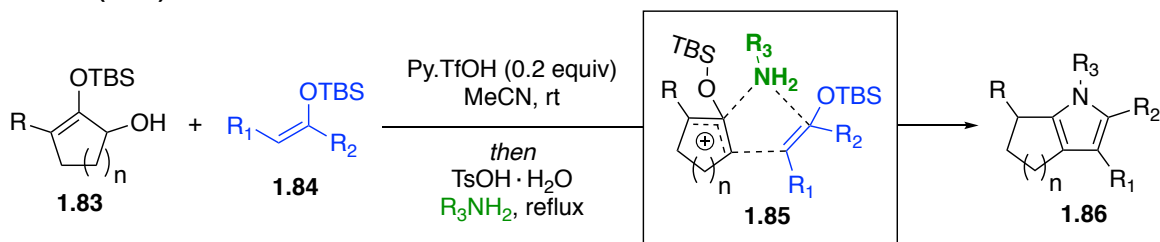


Scheme 1.19. Kartika's methodologies for  $\gamma$ -functionalization using oxyallyl cations

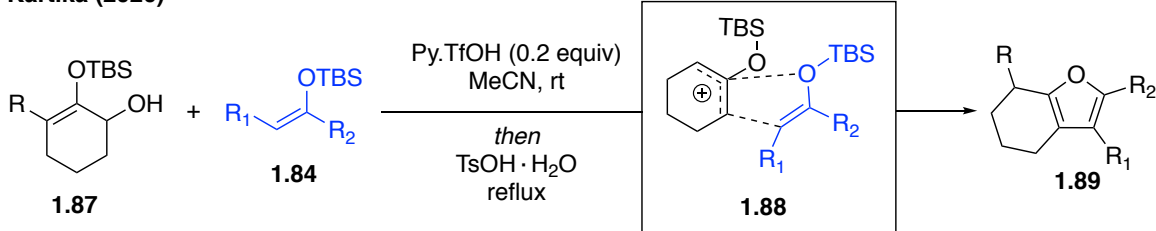
Silyloxyallyl cation strategy enables the synthesis of five-membered heterocycles i.e., pyrroles and furans. Kartika and co-workers (2019) have demonstrated that these cationic species can be directed to undergo [2+2+1] annulation reactions.<sup>30</sup> When silyloxyallyl cations generated from  $\alpha$ -hydroxy silyl enol ether **1.83** was reacted with a silyl enolate nucleophile **1.84** and a primary amine nucleophile in one-pot, differently substituted pyrroles **1.86** was obtained in high efficacy. Both five- and six-membered  $\alpha$ -hydroxy silylenol ethers produced the desired products in good yields. Similarly, tetrahydrobenzofurans **1.89** can be produced in a single synthetic operation via cascade cyclization process while omitting the primary amine component.<sup>31</sup> In both

these methodologies, TsOH.H<sub>2</sub>O was introduced into the reaction after the  $\alpha$ -C-C bond formation is complete, which induced protodesilylation before the Paal-Knorr condensation process.

**Kartika (2019)**



**Kartika (2020)**

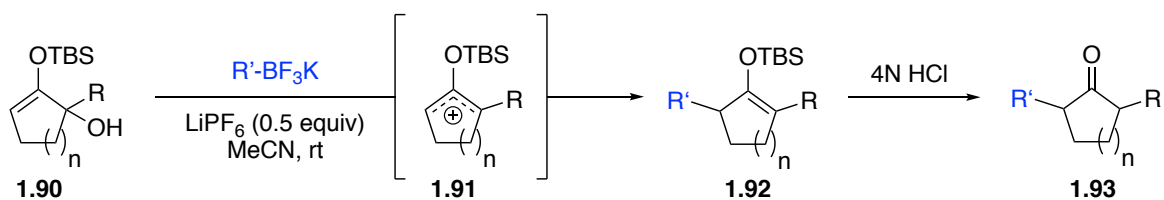


Scheme 1.20. Kartika's synthetic routes to heterocycles

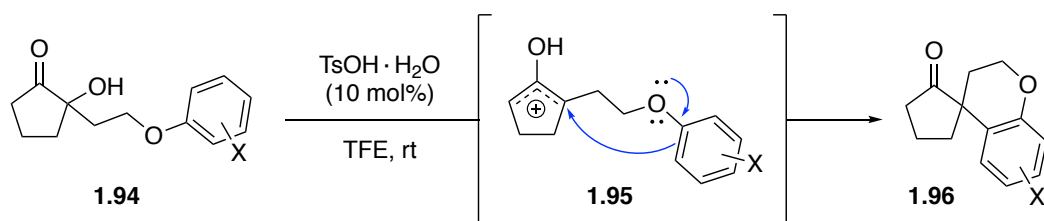
So far, oxyallyl and silyloxyallyl cations are centered around direct trapping with indoles and enolate nucleophiles, few examples on alternate nucleophiles are also reported. For example, May and co-workers (2019) demonstrated that oxyallyl cations can also be generated from the ionization of  $\alpha$ -hydroxy silylenol ether **1.90** by LiPF<sub>6</sub>. The emerging oxyallyl cation was then captured by unique sp<sup>2</sup>- and sp- organotrifluoroborate  $\pi$ -nucleophiles to afford  $\alpha$ -substituted silyl enol ethers **1.92** in high regioselectivity.<sup>32</sup> Another unorthodox example by Maruoka et al (2020) utilized the less reactive phenolic nucleophiles strategically placed at the  $\alpha$ -position as a tethered phenolic ether **1.94**.<sup>33</sup> These  $\alpha$ -hydroxy ketones were ionized by catalytic TsOH.H<sub>2</sub>O in trifluoroethanol which facilitated the formation and stabilization of oxyallyl cations **1.95** that is captured by the pendant phenolic ether moiety at the  $\alpha$ -position to afford spirocyclic ketones **1.96**.

This intramolecular mode of capture is less known, and it opens an avenue for addressing problems associated with nucleophilicity of relatively less-reactive phenols.

May (2019)



Maruoka (2020)



Scheme 1.21. Variations in nucleophilic capture on oxyallyl cations

## 1.7 Conclusions

Oxyallyl cations have proved to be an important synthetic toolbox to access various useful molecular scaffolds. Originally known for Favorskii rearrangements and cycloaddition reactions, these intermediates serve as an umpolung counterpart towards various nucleophiles at the electrophilic  $\alpha$ -carbon. From all carbon-quaternary centers to the asymmetric organocatalysis, these cationic species offer a wide range of  $\alpha$ -functionalizations via direct nucleophilic capture, albeit the enantioselective reactions with them is very less explored.



## CHAPTER TWO. SYNTHESIS OF GEMINAL BIS-ARYL QUATERNARY CENTERS IN FIVE-MEMBERED RINGS USING ALKYNES AS REGIODIRECTORS

### 2.1 Purpose

This chapter highlights our effort in generation of all-carbon  $\alpha$ -bis-aryl quaternary center in five-membered ring systems. An importance of bis-aryl quaternary centers and reported methods will be discussed especially focusing in installing such moiety in cyclopentane systems. Our unprecedented finding utilizing alkynes as regiodirecting group, and its significance will be discussed along with optimization and the scope of the reaction. Synthetic utility of the products will be showcased by their transformation into value-added structural motifs.

### 2.2 Significance of Bis-Aryl Compounds

Bis-aryl compounds are valuable class of organic compounds as they offer tremendous biological activities.<sup>34</sup> This includes antioxidants like phenolic compounds<sup>35</sup>, anticancer drugs, analgesics, antiviral and anti-hyperglycemic properties. In addition, they are prevalent in food and pesticide-related products, dyes, materials, and photochromic agents. Representative examples are listed in Fig 2.1.

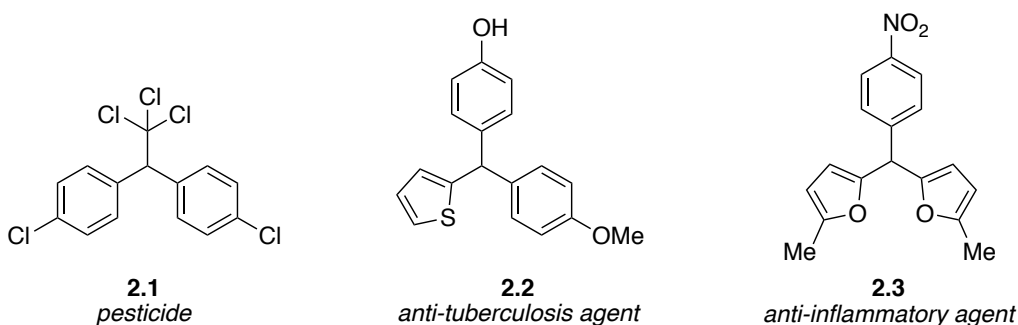


Figure 2.1. Important Bis-aryl compounds

One subclass of bis-aryl compounds is bis-indolyl compounds, also called BIMs.<sup>36</sup> Prevalence of indole in molecules offer various bioactivity, e.g., treatment of irritable bowel, and inhibition of

proliferation of cancer cells.<sup>37</sup> BIMs isolated from various marine bacteria has been studied for their pharmacological significance, few of them are shown in Fig 2.2. Not only the doubly added indole compounds, mono indolyl bis-aryl compounds are also ubiquitous in natural products, agrochemicals, pharmaceuticals, and others. Multitude of reports and FDA approved drugs has suggested the C3-substitution and functionalization of indoles provides a facile, yet powerful route to drug discovery and design.<sup>38</sup>

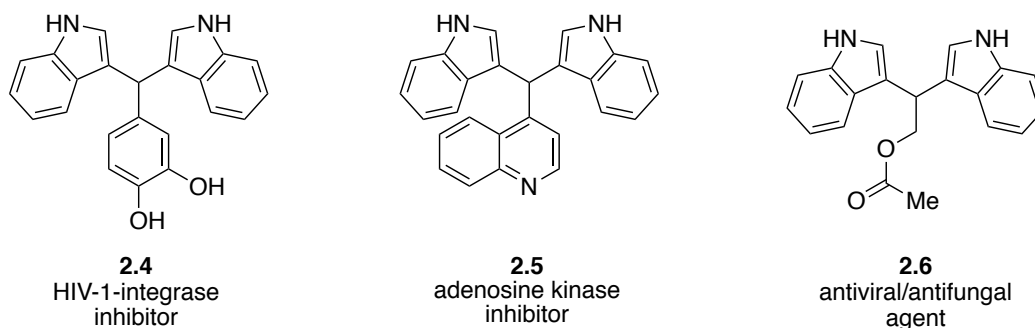
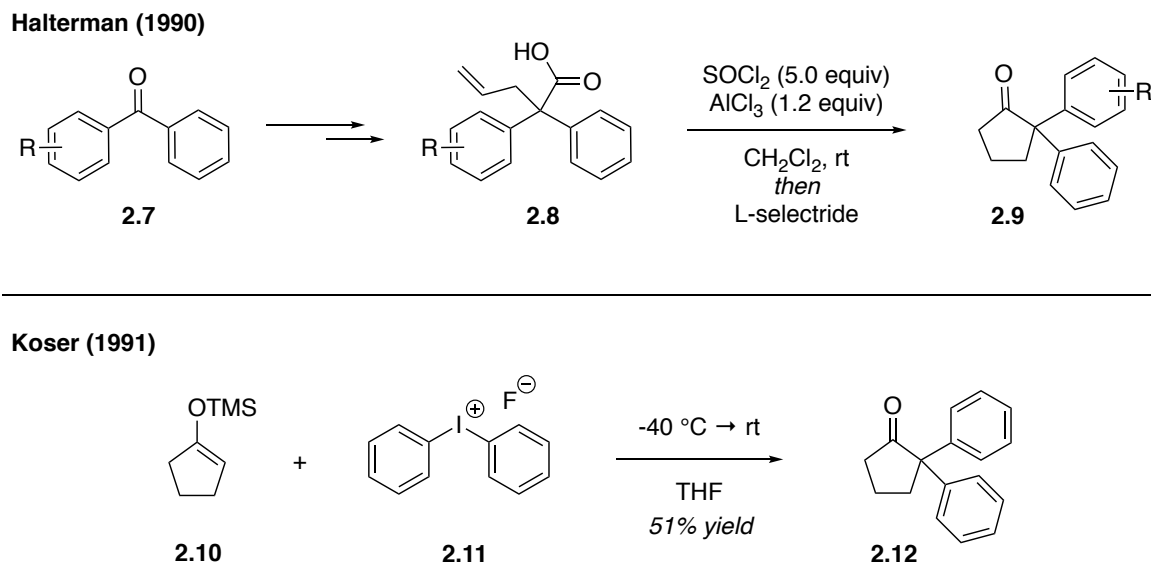


Figure 2.2. Representative examples of bis-indolyl compounds

### 2.3 $\alpha$ -Bis-Aryl Compounds in Five-Membered Rings

In the acyclic molecules, strategies on geminal bis-arylation has been studied in the past. Common approaches chiefly bank on incorporation of arenes as a Friedel-Craft partner or through transition-metal catalysis and related processes.<sup>39</sup> In the context of five-membered rings, very few literature reports are available, which highlights the challenges in installment of geminal bis-aryl moiety at the  $\alpha$ -position. Since our lab focuses on functionalizing five- and six-membered rings, we are intrigued by the rarity. One of the first reports in this field by Halterman and co-workers (1990) where they were able to isolate 2,2-bis-aryl cyclopentanones **2.9** *via* homologation from monosubstituted benzophenones **2.7**.<sup>40</sup> This was a multiple steps endeavor comprising of eight steps from the starting materials with feeble yields in each step. Final step involved the five-membered ring formation from allyl acid **2.8** followed by reduction with L-selectride. Despite the

fact the crude materials were used without purification mostly, this efficacy of this method succumbed lengthy workups, low yields and use of relatively stronger reagents. Another example from Koser et al. (1991) makes use of five-membered TMS enol ether **2.10**, where diphenyliodonium fluoride (DIF) **2.11** acts as a phenylating agent under cold conditions to produce the  $\alpha$ -bisphenyl adducts **2.12**.<sup>41</sup> Only few examples were reported.

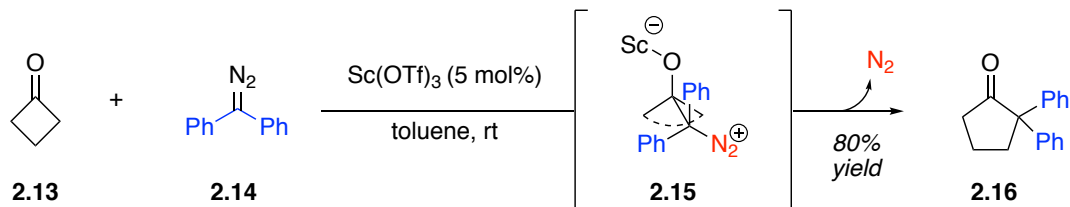


Scheme 2.1. Earlier examples on synthesis of geminal-bis aryl cyclopentanones

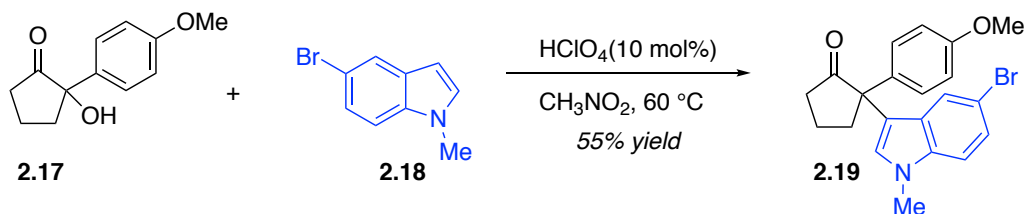
Recent examples on  $\alpha$ -bisarylation are shown in Scheme 2.2. Kingsbury and co-workers used a homologation approach on cyclobutanone **2.13** with diazophenyl **2.14** catalyzed by scandium triflate in toluene at room temperature.<sup>42</sup> The reaction occurred by nucleophilic attack by the diazophenyl on the carbonyl group forming a tetrahedral betaine intermediate **2.15**, followed by the expulsion of nitrogen gas to forge two new  $\alpha$ -C-C bonds producing geminal bis-aryl cyclopentanone **2.16** in one step. Another example by Zhou et. al. makes use of the classical Friedel-Craft arylation of the  $\alpha,\alpha$ -aryl,hydroxy cyclopentanone **2.17** with N-methyl protected bromoindole **2.18** catalyzed by perchloric acid *en route* to the  $\alpha$ -bis aryl product **2.19**.<sup>43</sup> In the same line of work, Schneider and co-workers used  $\alpha$ -hydroxy oxime ether **2.20** as a starting

material to afford  $\alpha$ -bis aryl quaternary centers in five-membered ring.<sup>44</sup> When **2.20** is ionized by  $\text{FeCl}_3$ , it was believed to form a putative azallyl cation *in situ*, which was trapped by indole in a Friedel-Craft process to furnish the  $\alpha$ -bis arylated adduct **2.21**. The oxime ether functionality was hydrolyzed to afford the corresponding cyclic ketone **2.22** in 80% yield.

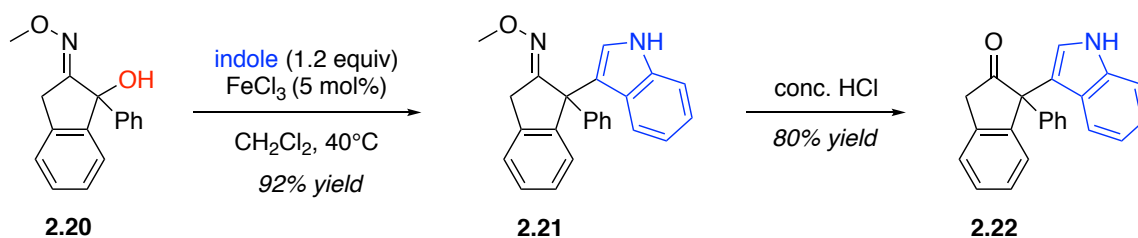
#### Kingsbury (2009)



#### Zhou (2012)



#### Schneider (2016)



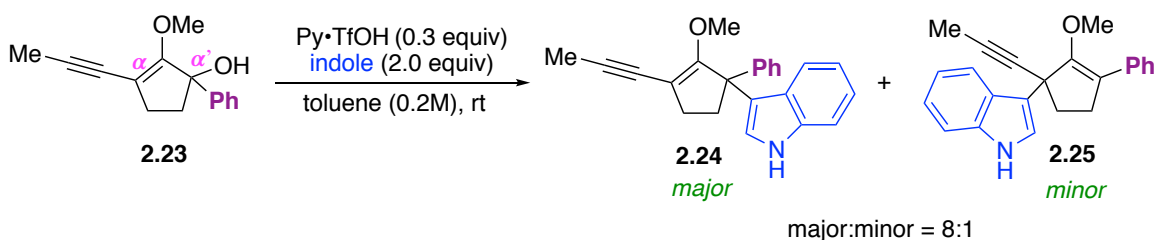
Scheme 2.2. Recent examples on installing  $\alpha$ -bis-aryl quaternary centers

## 2.4 Our Initial Studies and Optimization

While working with  $\alpha$ -hydroxy methyl enol ether **2.23**, we observed an interesting regioselectivity pattern. When **2.23** was ionized with  $\text{Py.TfOH}$  in toluene, we noticed that the emerging oxyallyl cation was captured by indole to afford two regioisomers **2.24** and **2.25**.

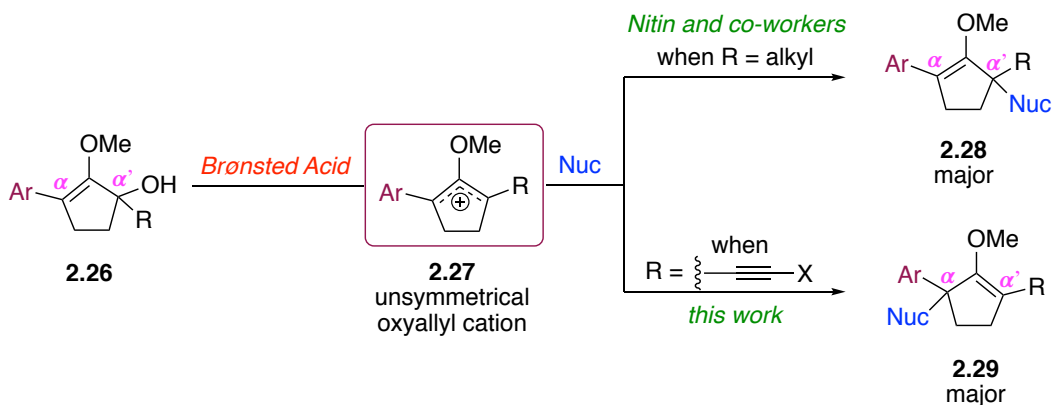
Interestingly, the  $\alpha$ -geminal bis aryl regioisomer **2.24** was found to be predominant at room temperature with a regiomer ratio of 8:1. This finding was significant since this outcome was favored by the presence of  $\alpha'$ -alkynyl substituent.

Scheme xxxx: Our serendipitous discovery



Scheme 2.3. Our serendipitous finding

In the past, Nitin and co-workers in our lab have reported the formation of all-carbon quaternary centers **2.28** with alkyl group as a substituent in substrates **2.26**, where the indole nucleophile was exclusively directed to the alkyl group bearing carbon.<sup>25</sup> This unprecedented switch of selectivity simply by replacing the alkyl chain with alkynyl chain (**2.28** vs **2.29**) enticed us to explore the reaction more. As detailed in the section 2.3, installing bis-aryl functionality at the  $\alpha$ -carbon in five-membered ring is non-trivial, our serendipitous finding appeared to provide an alternative to this rarity.



Scheme 2.4. Comparison of previous vs this finding

Our initial observation is listed in entry 1 of table 2.1. The formation of  $\alpha$ -bis-aryl adducts is favored by 8:1 ratio over the  $\alpha'$ -regioisomer at room temperature when the corresponding  $\alpha$ -hydroxy enol ether **2.23** was ionized with Py.TfOH in toluene at 0.2M concentration based on the starting material. Generation of oxyallyl cation was followed by a capture with indole nucleophile *in situ* affording 76% combined yield of two isomers in 1h. At this point, we opted to screen some solvents for improving the regiomic ratio. Changing to chlorinated solvent like CH<sub>2</sub>Cl<sub>2</sub> and DCE did not improve the outcome (entry 2 and 5), nor did THF and acetonitrile. In fact, reaction in acetonitrile improved the regiomic ratio to 9:1 but the yield suffered an erosion to 53% (entry 4). Additionally, decomposition of starting material was observed in acetonitrile contributing to the loss in yield. In addition, non-polar solvents like *o*-xylene afforded the product in similar yield and regiomic ratio (entry 6). Solvents like 1,4-dioxane afforded products in good yield up to 80% and modest regioselectivity of 7:1 over 1h (entry 7), explaining the less-pronounced role of solvent in this methodology. Adding molecular sieves to trap the water generated in the ionization process did not affect the reaction as detailed in entry 8 where similar yield and regioselectivity was observed. Next to the solvent screening, we briefly screened other Brønsted acids and Lewis-acid triflates, viz PPTS, Cu(OTf)<sub>2</sub>, Zn(OTf)<sub>2</sub> and AgOTf in toluene as shown in entry 9-12. At room temperature, all these catalysts afforded the products in modest yields with the regiomic ratio of up to 8:1 in similar reaction time of 1h. Based on these results, we decided to proceed with our entry 1 to further optimize the reaction, since the solvent effects were minimal, and Py.TfOH provided the most convincing results in form of yield and regioselectivity.

Table 2.1. Preliminary Screening of Solvents and Catalyst

entry	catalyst	solvent	conc. (M)	temp. (°C)	time (h)	r.r. <sup>a</sup> <b>2.25:2.24</b>	% yield <sup>b</sup>
1.	Py · TfOH	toluene	0.2	rt	1h	1:8	76
2.	Py · TfOH	CH <sub>2</sub> Cl <sub>2</sub>	0.2	rt	1h	1:7	77
3.	Py · TfOH	THF	0.2	rt	1h	1:7	66
4.	Py · TfOH	MeCN	0.2	rt	1h	1:9	53
5.	Py · TfOH	DCE	0.2	rt	1h	1:8	75
6.	Py · TfOH	o-xylene	0.2	rt	1h	1:8	78
7.	Py · TfOH	1,4-dioxane	0.2	rt	1h	1:7	80
8.	Py · TfOH	toluene <sup>c</sup>	0.2	rt	1h	1:8	74
9.	PPTS	toluene	0.2	rt	1h	1:8	75
10.	Cu(OTf) <sub>2</sub>	toluene	0.2	rt	1h	1:7	57
11.	Zn(OTf) <sub>2</sub>	toluene	0.2	rt	1h	1:8	68
12.	AgOTf	toluene	0.2	rt	1h	1:8	55

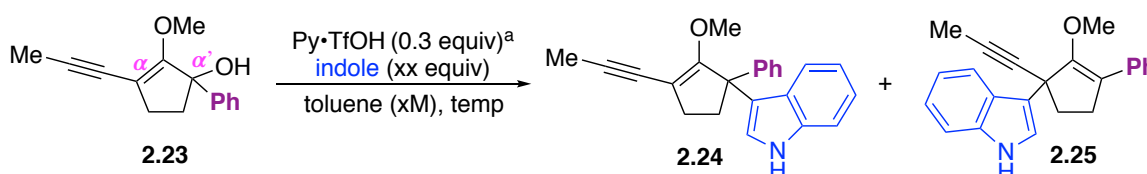
<sup>a</sup>Regiomer ratio was based on crude <sup>1</sup>H NMR analysis. <sup>b</sup>Combined isolated yield after column chromatography. <sup>c</sup>With 4Å MS

Next, we planned to modulate the temperature to see if the regioselectivity can be improved. Since Py.TfOH is a solid at room temperature, we decided to introduce it as a 0.5M solution in MeCN to make the addition practical under desired temperature setup. This also helped to maintain homogeneity of the reaction solution as solid Py.TfOH is insoluble in toluene. First, we cooled the reaction to 0 °C. We observed enhancement in both regioisomeric ratio as well as the yield, signaling the reaction to be kinetically driven. In fact, the reaction delivered the regiomer ratio of 10:1 and 92% yield favoring the bis-aryl regioisomer **2.24** in 3 hours. Excited by this result, we further cooled the reaction to -20 °C, which took 36 hours to complete, with similar yield of 92%, but the regiomer ratio improved further to 14:1. Cooling beyond -20 °C was not fruitful as the reaction was very slow with traces of product after a week (entry 4). At this point, we changed the reaction concentration to 0.5M and 0.05M (entry 5 and 6) at -20 °C. At concentration of 0.5M, the regiomer ratio increased slightly to 15:1 but the yield reduced to 74%. At a much dilute concentration of 0.05M, the regiomer ratio appeared to improve to 16:1 with 85% yield, but the reaction time increased significantly to 168h. This helped us to deduce the fact

that 0.2M concentration of the reaction mixture in toluene at -20 °C is the most suitable condition for this transformation. Reducing the equivalence of indole to 1.2 and 1.5 did not affect the reaction outcome significantly, leading us to our optimized condition as entry 7 which is as follows.

*Reaction carried out in toluene at the concentration of 0.2M with 0.3 equivalence of Py.TfOH and 1.2 equivalence of indole at -20 °C in 36h furnishing 97% combined yield of two regioisomers **2.24** and **2.25** in 16:1 regiomer ratio favoring **2.24**.*

Table 2.2. Final Optimization Table



entry	indole equiv	conc. (M)	temp. (°C)	time (h)	r.r. <sup>b</sup> 2.24:2.25	% yield <sup>c</sup>
1.	2.0	0.2	rt	1h	8:1	76
2.	2.0	0.2	0°C	3h	10:1	92
3.	2.0	0.2	-20°C	36h	14:1	92
4.	2.0	0.2	-40°C	~week	-	trace
5.	2.0	0.5	-20°C	36h	15:1	74
6.	2.0	0.05	-20°C	168h	16:1	85
7.	1.2	0.2	-20°C	36h	16:1	97
8.	1.5	0.2	-20°C	36h	14:1	92

<sup>a</sup>Added in 0.5M solution in MeCN. <sup>b</sup>Crude regiomer ratio was determined using <sup>1</sup>H NMR spectroscopy. <sup>c</sup>Isolated yield after flash column chromatography

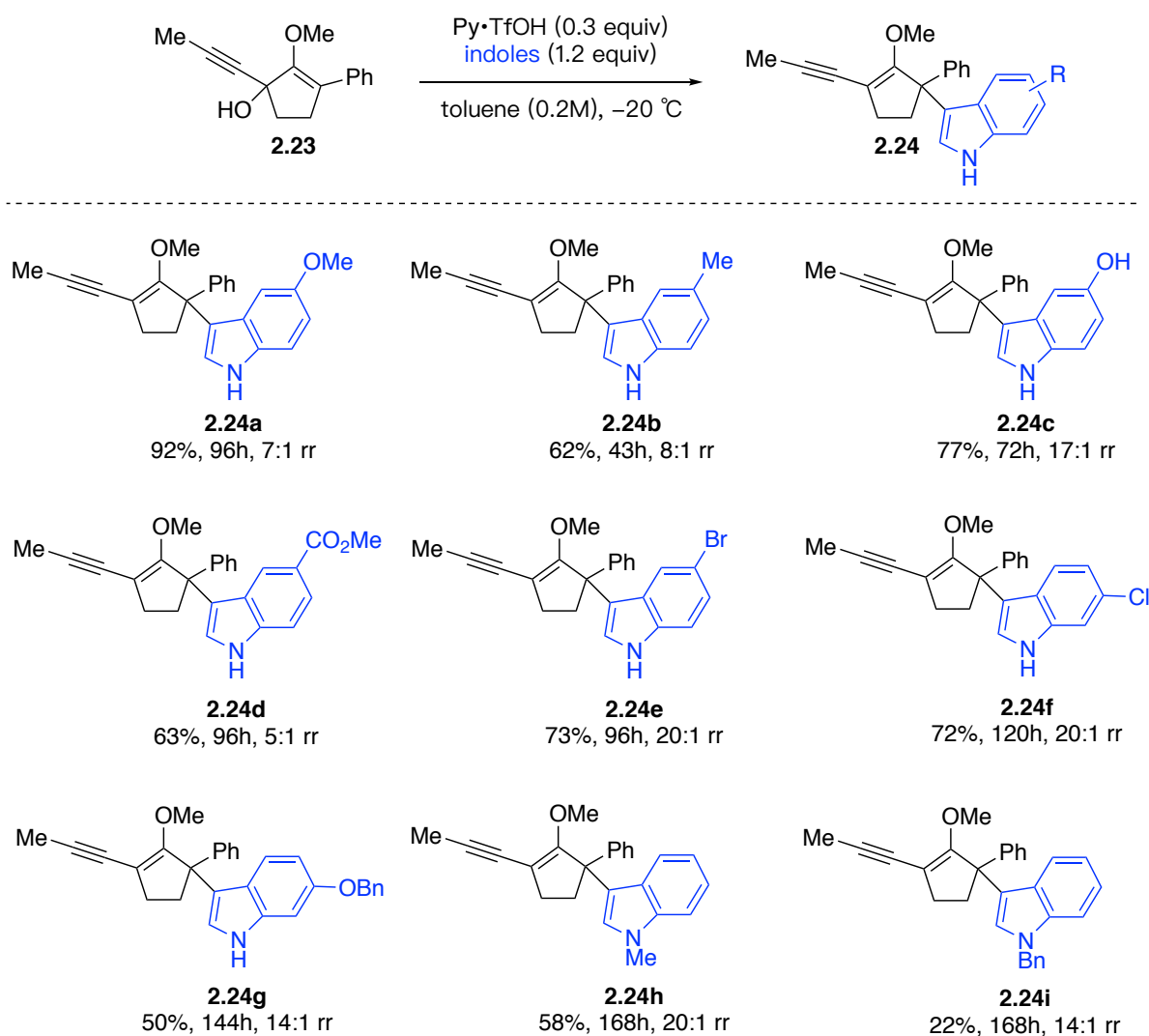
## 2.5 Scope of Indoles

With the optimized condition in hand, we began to explore the scope of nucleophiles. To start with, we subjected electron-rich indoles, i.e., 5-methoxyindole and 5-methylindole to the reaction conditions. The reactions afforded the indole adducts in good yields (**2.24a** and **2.24b**), but the regiomer ratio was surprising low in both cases. In contrary, 5-hydroxyindole afforded the bis-aryl adduct **2.24c** in 77% yield over 12h with regioselectivity of 17:1. Electron-withdrawing methyl-indole-5-carboxylate also tolerated the reaction condition producing the



indole adduct **2.24d** in 63% yield in 96h reaction time but the regioselectivity eroded to 5:1 rr. In the halogenated indole series, 5-Bromoindole and 5-chloroindole afforded the bis-aryl products **2.24e** and **2.24f** in 73% and 72% as single regioisomers in 96h and 120h reaction time respectively. We were able to crystallize the compound **2.24e**, which unambiguously deduced the regioisomer. We also tried 6-benzyloxyindole as a nucleophile, which furnished the desired bis-aryl indole adduct **2.24g** in 14:1 regioselectivity in modest 50% yield, but the reaction appeared to be very slow and took 144h to complete.

Table 2.3. Scope of Indoles



Further, *N*-protected indoles were examined. Both *N*-Me and *N*-Bn protected indole produced the desired bis-aryl adducts **2.24h** and **2.24i** in good regioselectivity of 20:1 and 14:1 respectively, but the yields depleted to 58% and 22% and, and a long reaction time. Overall, electronically different indoles tolerate this method, albeit the reactions are generally slow at -20 °C.

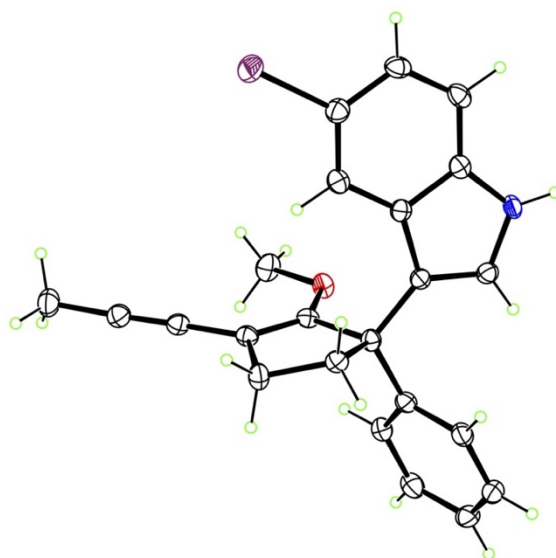


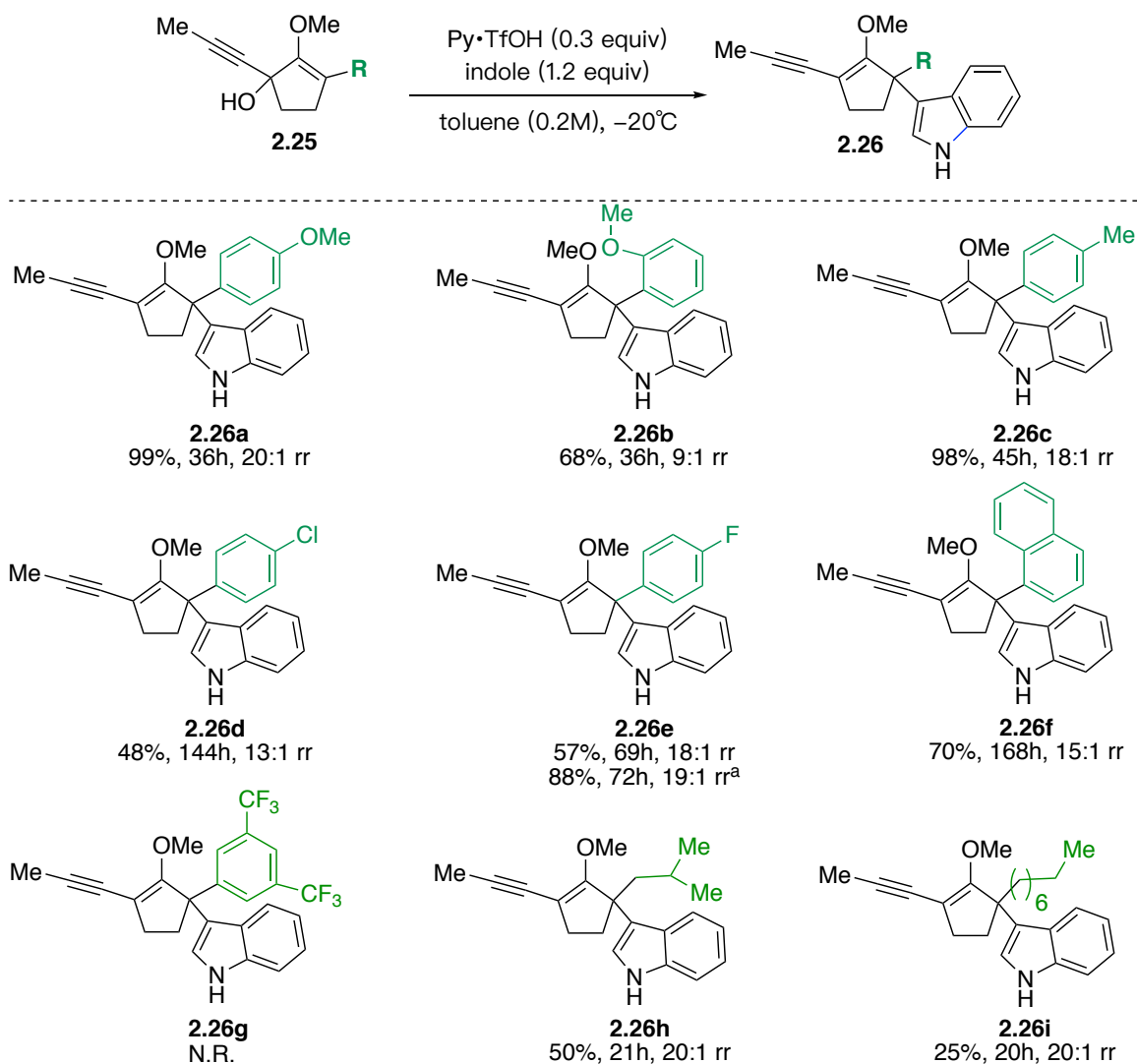
Fig 2.3. X-Ray Structure of Compound **2.24e**

## 2.6 Scope of $\alpha$ -Substituents

Next, we examined the substrates with different substitution at the  $\alpha'$ -position. First, electron rich 4-methoxyphenyl substituted substrate was tested, which afforded the desired bis-aryl adduct **2.26a** as a single regioisomer in almost quantitative yield over 36h. When the 2-methoxyphenyl substrate was used, the regioselectivity reduced to 9:1 rr in similar reaction time with 68% yield (**2.26b**), suggesting the steric factor to outcompete regiodirection imparted by the alkyne moiety. Another electron-rich  $\alpha$ -*p*-tolyl substrate furnished the product **2.26c** in 98% yield in 45h and 18:1 rr. In  $\alpha'$ -4-halophenyl substrates, the reactions afforded the desired bis-aryl products **2.26d** and **2.26e** in 13:1 and 18:1 rr for chloro- and fluoro-substituents respectively, but the yield suffered a significant erosion affording the respective products in 48% and 57% only.

When the reaction was performed in one gram scale, the 4-fluorophenyl substituted substrate afforded the product smoothly in 88% yield and 19:1 rr in 72h. This result indicates that the reaction can be scaled up without any loss of regioselectivity and even better yields. We also examined the bulky 2-anthracenyl substrate at the  $\alpha$ -position. Surprisingly, it produced the adduct **2.26f** in a good regioselectivity, i.e., 15:1 and 70% yield over relatively longer reaction time of 168h.

Table 2.4. Scope of  $\alpha$ -substrates



<sup>a</sup>Reaction performed in 1 gram scale.

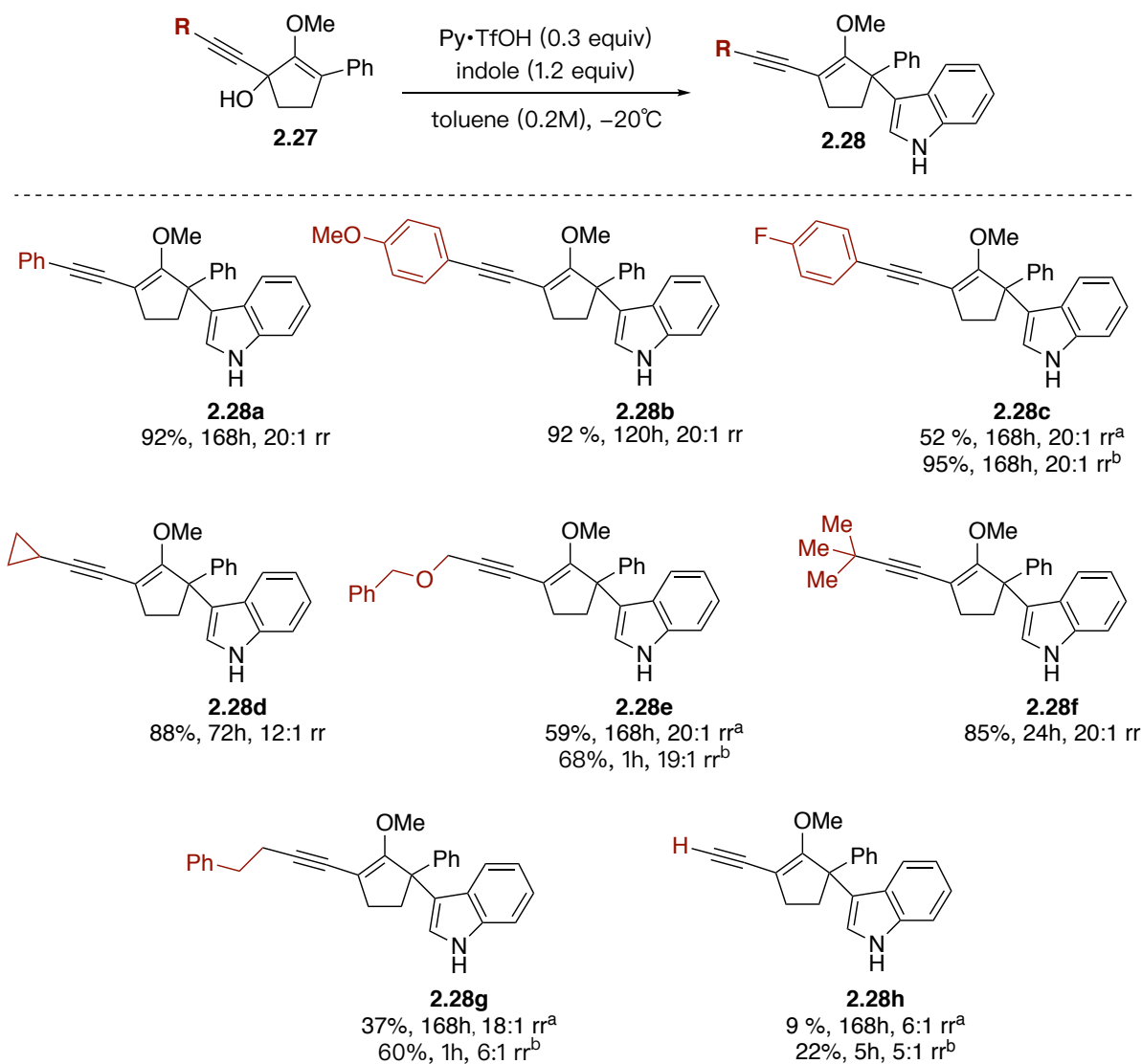
Highly electron-deficient 3,5-bis(trifluorophenyl) substituent did not allow the formation of incipient oxyallyl cation due to its highly deactivating effect. Only starting material was isolated after a week without any indole addition product. With the aliphatic  $\alpha$ -isobutyl and  $\alpha$ -octyl substrates, the regioselectivity was found to be exquisite over relatively quicker reaction times to afford products **2.26h** and **2.26i** with meager 50% and 25% yields respectively. The loss in yield is attributed to the decomposition of starting materials under reaction conditions.

## 2.7 Scope of Alkynes

We prepared a series of  $\alpha,\alpha$ -alkynylhydroxy alcohols **2.27** from the corresponding ketones via nucleophilic addition of the acetylides obtained from deprotonation of terminal alkynes (see supplementary information for the detail). When methyl group of the alkyne is replaced by phenyl and PMP groups, the substrates delivered the bis-aryl indole adducts **2.28a** and **2.28b** in 92% yield and as a single regioisomer. When a substrate contained 4-fluorophenyl group at the alkyne terminus, the reaction rate was found to be very slow at -20 °C with 52% isolated yield of bis-aryl regioisomer **2.28c**. The reaction did not go to completion even after a week. Interestingly, when the same reaction was performed at 0 °C, the reaction was still very slow, but it went to completion to furnish the product in 95% yield in 168h without affecting the regiomer ratio. Next, we examined aliphatic alkyne terminus. For the terminal cyclopropyl group-containing substrates, the transformation smoothly furnished the indole adduct **2.28d** in 88% yield and 12:1 rr over 72h. Similarly, benzyl methyl ether substituted alcohol was also examined. The reaction did not go to completion in a week, affording **2.28e** in 59% yield based on the starting material as a single bis-aryl isomer. When the reaction was performed at 0 °C, 68% yield was obtained in 19:1 rr in just 1h reaction time. Two other aliphatic alkynes were tested where t-butyl substituted starting material furnished the product **2.28f** as a single isomer in 85% yield. When phenethyl group was

used as a substituent, the rate of the reaction was slow and did not go to completion at -20 °C which afforded just 37% of the product **2.28g** at 18:1 rr. After running the reaction at 0 °C, we were able to isolate 60% of the **2.28g** in just 1h but the regiomer ratio took a significant drop to 6:1.

Table 2.5. Scope of alkynes



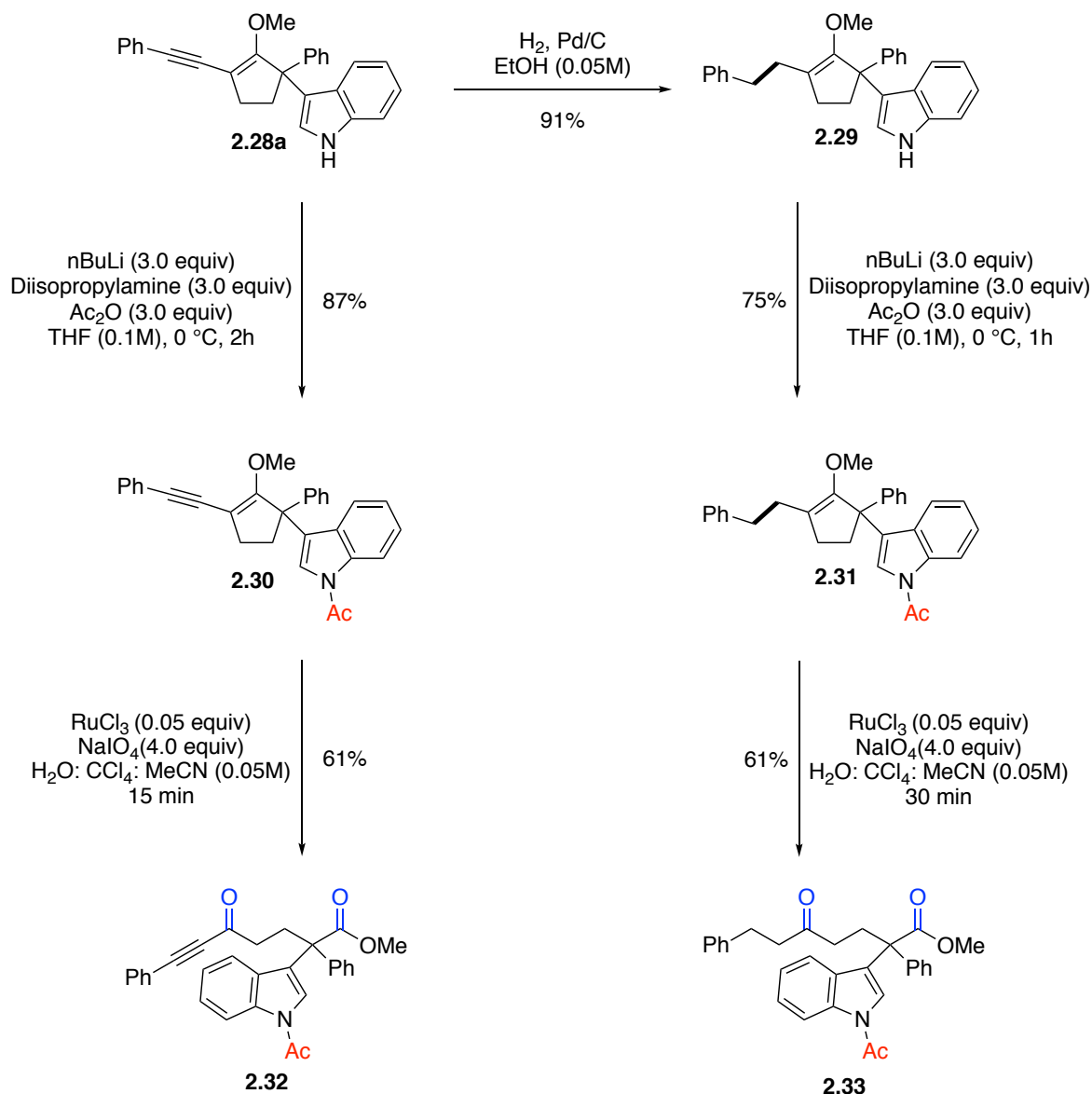
<sup>a</sup>Reaction did not go to completion after a week. <sup>b</sup>Reactions performed at 0 °C

Interestingly, when there is no substituent at the alkyne terminus, the reaction was not effective. In fact, only 9% of the product was isolated in a mere 6:1 rr over a week, and the reaction did not

go to completion. At 0 °C, the reaction took 5h to complete but it produced only 22% of the indole adduct in 5:1 rr. This highlights the role of substituent at the alkyne terminus, presumably to stabilize the emerging enyne functionality once the  $\alpha$ -bis aryl quaternary center is installed. The role of alkynyl groups in reaction rates appears to be more prominent than that of  $\alpha'$ -substituents.

## 2.8 Synthetic Utility of Products

This section includes few of the synthetic manipulations performed using  $\alpha$ -bis aryl adduct **2.28a**. Since the product contains a useful synthetic handle in form of an enyne, we planned to leverage this functionality to synthesize value-added intermediates. First, we were able to reduce the alkyne to alkane selectively to form an aliphatic side chain in **2.29**. Reaction of **2.28a** with H<sub>2</sub> gas in Pd-C in ethanol afforded the only compound **2.29** in 91% yield without reducing the double bond in the ring. These kinds of compounds were not possible to synthesize from our previous oxyallyl cation chemistry since direct nucleophilic capture of indole always preferred the  $\alpha$ -carbon with alkyl chain. Further, we were able to protect the indole nitrogen of each of the compounds **2.28a** and **2.29** with an acetyl group to furnish **2.30** and **2.31** respectively. The reaction condition involved a typical LDA assisted deprotonation of the indole -NH followed by a capture with acetic anhydride. These acetyl-protected compounds were successfully converted to the corresponding acyclic 1,5-diketones **2.32** and **2.33** *via* oxidative cleavage of the double bond of the enol ether moiety. The reaction yielded 61% of the desired product with all-carbon  $\alpha$ -bis-aryl quaternary centers, which was carried out in presence of catalytic RuCl<sub>3</sub> and NaIO<sub>4</sub>.<sup>25</sup>



Scheme 2.5. Synthetic manipulations of the bis-aryl product

## 2.9 Conclusions

In conclusion, we were able to utilize our spontaneous discovery of the synthesis of geminal bis-aryl quaternary centers towards solving a rarity in installing such stereocenters in five-membered rings. We were able to access the molecules that were not able to be made from our previous routes using oxyallyl cation chemistry. Coupled with the efficacy and a switch in

regioselectivity presumably imparted by the alkynyl group, we were able to showcase broad scope of this methodology in nucleophiles,  $\alpha$ -substrates and alkynyl group. Synthetic modifications of the products were also facile offering an alternate synthetic toolbox to access 1,5-diketones, adding value to this methodology.



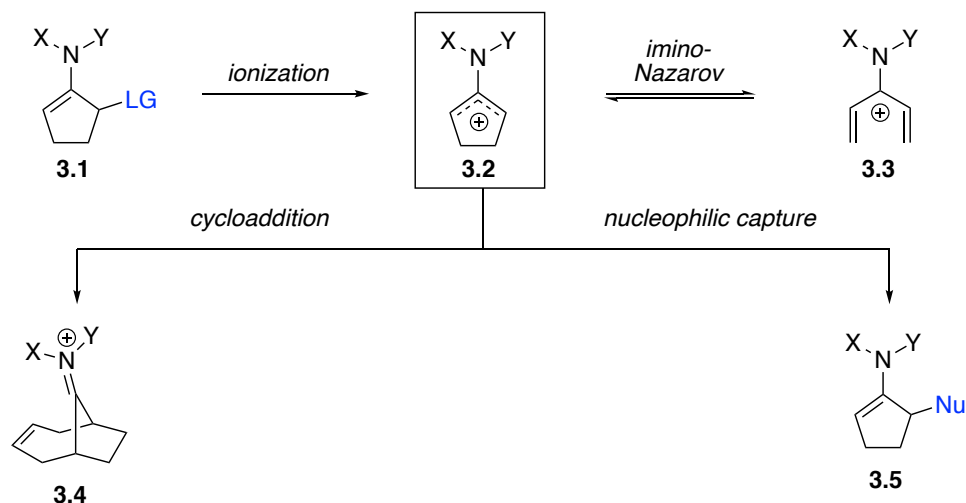
## CHAPTER THREE. STUDIES ON GENERATION AND CAPTURE OF 2-AMINOALLYL/AMIDOALLYL CATION INTERMEDIATES

### 3.1 Purpose

This purpose of this section is to discuss the development of aminoallyl and amidoallyl cations chemistry till date. The generation and reactivity these elusive species will be elaborated. Asymmetrical organocatalysis and its involvement in such cationic processes will be signified. Further, our efforts on unprecedented functionalization of the cyclic enamides at the  $\beta$ -carbon center will be presented, which is facilitated by chiral phosphoric acid catalysis. Detailed optimization studies as well as the scope of reaction will be presented followed by a proposed mode of activation.

### 3.2 Introduction to 2-Aminoallyl Cations

Not studied as much as the oxyallyl cations as discussed in Chapter 1, 2-aminoallyl cations are unique and has limited reports on functionalization studies. These three-carbon cationic species **3.3** which are stabilized by the lone pair in nitrogen atom, offer an umpolung alternative to the classical nucleophilic reactivity of enamines at the  $\alpha$ -position.<sup>45</sup> They are easily accessible from  $\alpha$ -leaving group containing enamines **3.1** via appropriate ionization conditions or from the imino-Nazarov cyclization reactions from divinyl cations **3.3**. Most of the studies in the past on utilizing these elusive species can be categorized into two divisions, 1) Cycloaddition reactions in a [4+3] of [3+2] fashion<sup>46</sup> or 2) direct nucleophilic capture at the  $\alpha$ -carbon.<sup>47</sup>

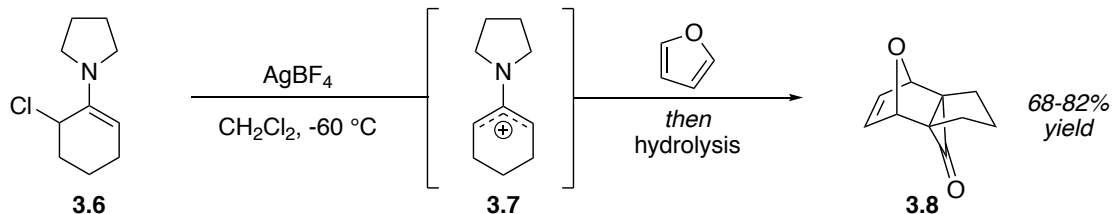


Scheme 3.1. General reactivity of 2-aminoallyl cations

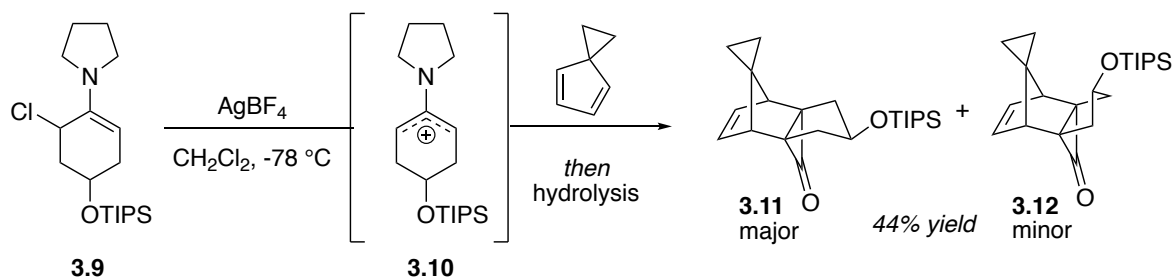
### 3.3 Ionization of $\alpha$ -chloroenamines/imines in cycloaddition reactions

In an early report from Schmid and co-workers in 1974,<sup>48</sup> 2-aminoallyl cations **3.7** were generated from the ionization of  $\alpha$ -chloroenamine **3.6** by using  $\text{AgBF}_4$  salt. Once generated in situ, these reactive intermediates were subsequently trapped by furan in a [4+3] cycloaddition process, followed by alkaline hydrolysis to afford a polycyclic ketone **3.8** in 68% yield. Similar approach was used by Cha and co-workers in 1995 in their effort towards synthesis of a marine natural product (+)-cis-lauthisan.<sup>49</sup> Another work by Cha and co-workers in 1994 utilized this strategy to afford complex polycyclic ketones **3.11** and **3.12** via ionization of TIPS-protected  $\alpha$ -chloroenamine **3.9**.<sup>50</sup> The formation of aminoallyl cation **3.10** was evident as these substrates successfully underwent [4+3] cyclization process with spiroheptadiene to afford cycloaddition products **3.11** and **3.12** in overall yield with a 4:1 diastereoselectivity.

Schmid (1974), Cha (1995)



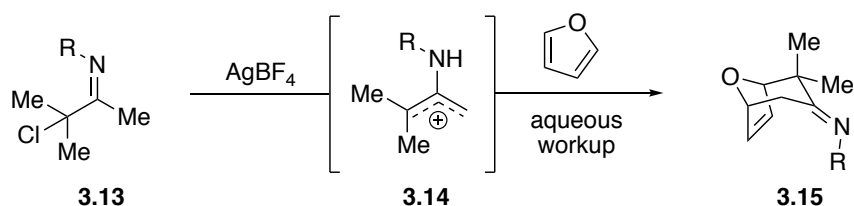
Cha (1994)



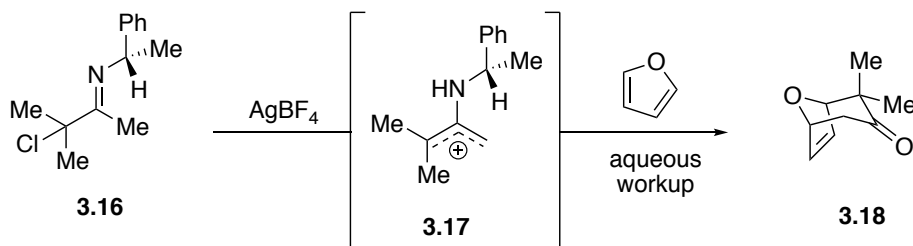
Scheme 3.2. Schmid and Cha's work on  $\alpha$ -chloroenamines

In the acyclic variants,  $\alpha$ -halogen containing compounds have similar fate to produce 2-aminoallyl cations **3.14** when silver salts are used. De Kimpe and co-workers (1986) used this strategy in their efforts towards the synthesis of imine-containing bicyclic compound **3.15** when  $\alpha$ -chloroimine **3.13** was reacted with  $\text{AgBF}_4$ .<sup>51</sup> This methodology also used furans as a cycloaddition diene component in a [4+3] fashion to construct complex imine **3.15** as a final product. In 1997, the first asymmetric [4+3] cycloaddition reaction of aminoallyl cations **3.17** was reported by Kende and Huang.<sup>46</sup> This work used  $\alpha$ -chloroimine **3.16** as a starting material where the nitrogen atom of imine is attached to a chiral auxillary. Subsequent ionization by  $\text{AgBF}_4$  and furan capture followed by hydrolysis afforded the bicyclic adduct **3.18** which had a 60% enantiomeric excess.

Di Kempe (1986)



Kende (1997)

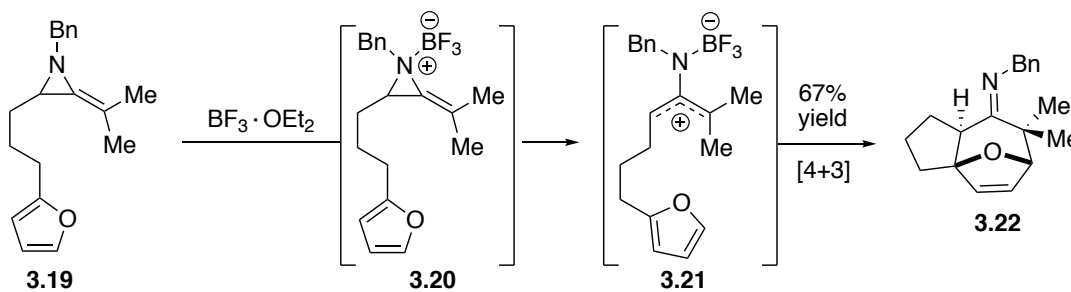


Scheme 3.3.  $\alpha$ -chloro imines as substrates for generation of 2-aminoallyl cations

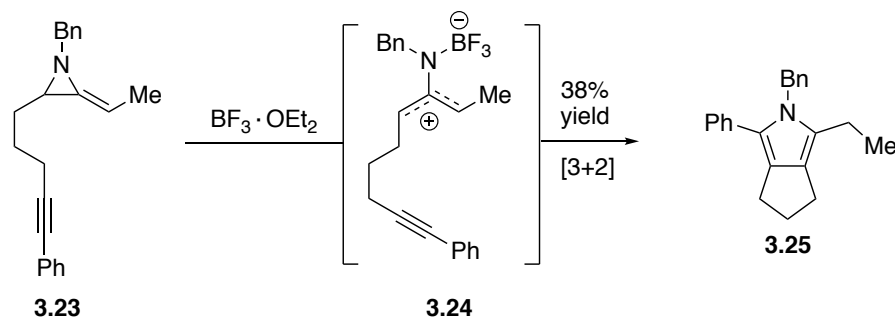
### 3.4 Aziridine Ring Opening Reactions

Generation of 2-aminoallyl cations from aziridine precursors has been studied by Shipman and co-workers in two independent studies. Inspired by the [4+3] cycloaddition reactions of these intermediates, Shipman and co-workers synthesized an aziridine precursor **3.19** with an exocyclic double bond. When ionized by  $\text{BF}_3 \cdot \text{OEt}_2$ , the highly strained aziridine ring opened to form an aminoallyl cation **3.21** *in situ* followed by a [4+3] cycloaddition with strategically placed furan tether in the molecule.<sup>52</sup> This process furnished tricyclic imine **3.22** as a single diastereomer in 67% yield. Similar approach in their studies from 2012 used analogous activation of aziridine ring, and the alkyne tether in aziridine precursor **3.23** captured the transient aminoallyl cation **3.24** to produce highly-substituted pyrrole **3.25** in 38% yield.<sup>53</sup>

Shipman (2004)



Shipman (2012)



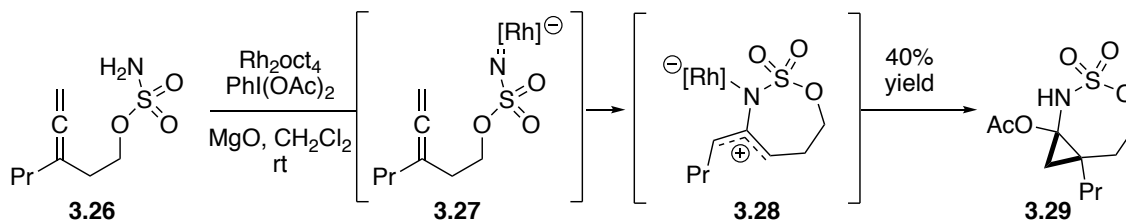
Scheme 3.4. Lewis-acid promoted aziridine ring opening

### 3.5 Allene Amidation Reactions

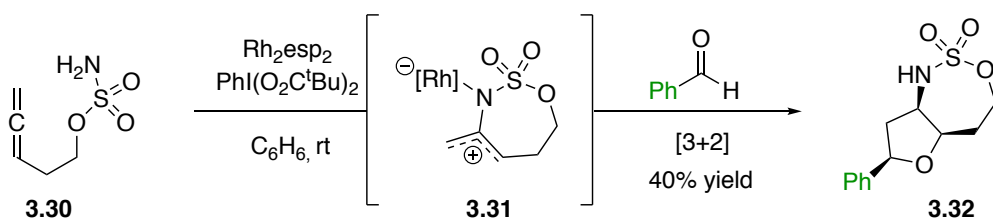
Three individual reports between 2010-2016 explain the new mode of generation of 2-amidoallyl cations from allene precursors. Robertson (2010)<sup>54</sup> and Blakey (2010)<sup>55</sup> employed allene sulfamates **3.26** and **3.30** respectively as starting materials which were activated with catalytic rhodium (II) and hypervalent iodine species to generate similar 2-amidoallyl cations **3.28** and **3.31**. Proposed reaction mechanism proceeds through the formation of metallonitrenes followed by an activation of the allene moiety in the molecule. This sequence led to the generation of 2-aminoallyl cations followed by an addition of acetate to afford bicyclic sulfonamides **3.29** or trapping by benzaldehyde to furnish [3+2] cycloaddition adduct **3.32**. Schomaker and co-workers utilized similar reaction conditions to furnish 2-aminoallyl cations **3.34** from homoallenic sulfonates **3.33** through rhodium (II) catalyzed aziridination-ring expansion cascade.<sup>56</sup> This led to the formation of 2-amidoallyl cation **3.34** followed by a formal [4+3] cycloaddition with furan to

afford complex aminated cycloheptene **3.35** bearing five consecutive stereocenters with modest diastereoselectivity.

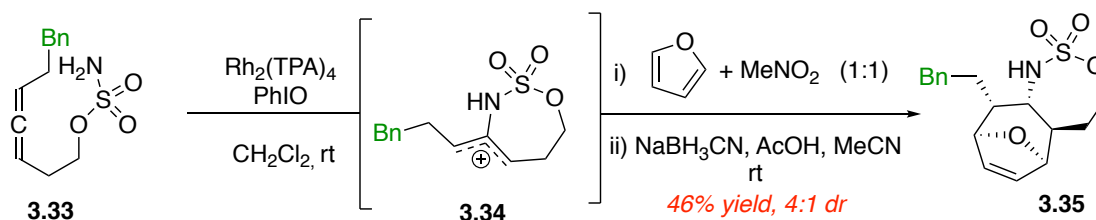
**Robertson (2010)**



**Blakey (2010)**



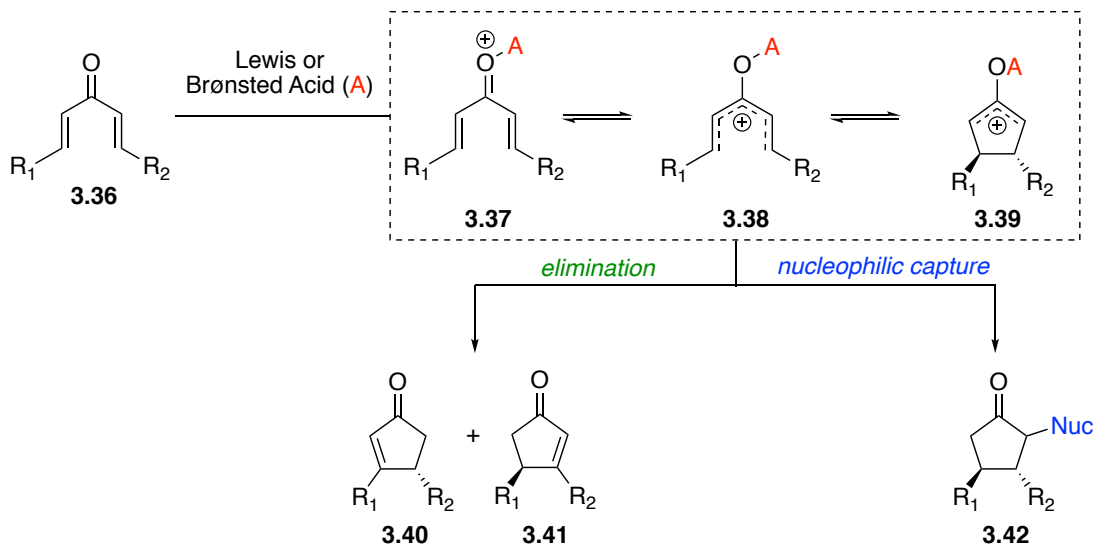
**Schomaker (2016)**



Scheme 3.5. Allene-amidation reactions to generate 2-amidoallyl cations

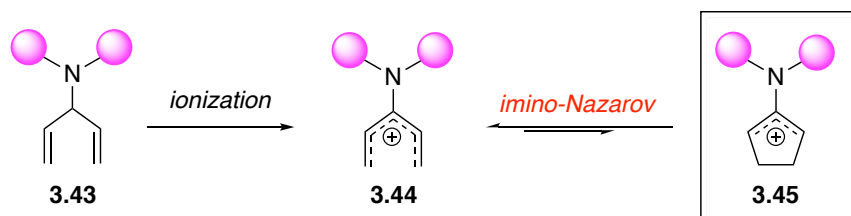
### 3.6 Imino-Nazarov Cyclizations

Nazarov cyclizations of divinyl ketones **3.36** are well known via activation of ketone by Lewis acids.<sup>10</sup> The conrotatory ring closure of such ketones leads to the ring structure with the generation of oxyallyl cations **3.39** which can undergo non-regioselective elimination to afford  $\alpha,\beta$ -unsaturated ketones **3.40** and **3.41**. Alternatively, these species can be captured by the nucleophiles to furnish sterically enriched adducts **3.42**. This field of study has been explored extensively in the past to construct various molecular scaffolds.



Scheme 3.6. Classical Nazarov-cyclization

Intriguingly, the nitrogen version of this chemistry, i.e., imino-Nazarov cyclization lacks enough reports due to the inherent instability around the cyclic 2-aminoallyl cations **3.45**.<sup>57</sup> This has been attributed to the increased participation of the lone pair of electrons from the nitrogen atom on to the pentadienyl cation **3.44** over the cyclic cation **3.45** which results in the equilibrium favoring the pentadienyl structure.

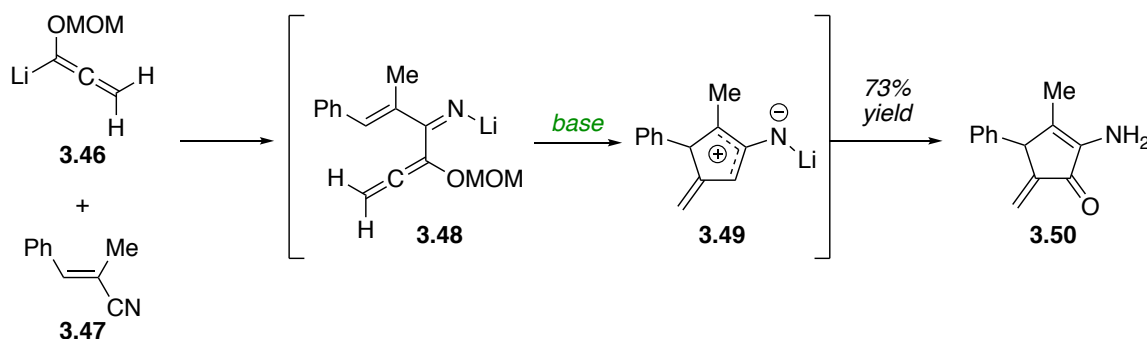


Scheme 3.7. Problems in Imino-Nazarov cyclization in aminoallyl cations

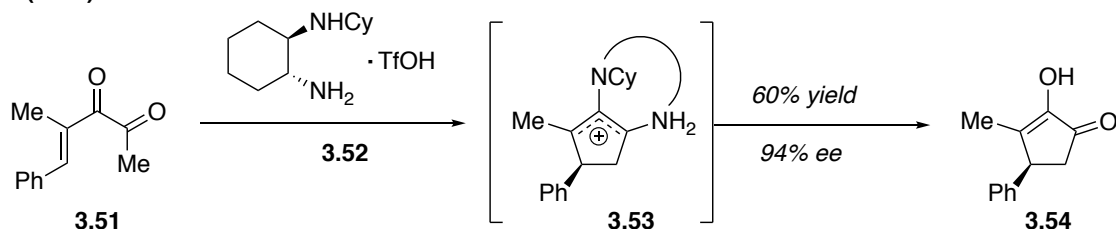
The first effort in undertaking this problem by Tius and co-workers (2001) makes use of divinyl imine **3.48** generated from lithiated allenic ether **3.46**.<sup>58</sup> The amine underwent imino-Nazarov cyclization to produce lithiated 2-aminoallyl cation **3.49**, which was transformed to an aminocyclopentanone **3.50** in 73% yield after basic workup with  $(\text{NH}_4)\text{H}_2\text{PO}_4$ . Tius and co-

workers later came up with an asymmetric variant of this methodology in 2010,<sup>59</sup> where  $\alpha,\beta$ -unsaturated ketone **3.51** furnished 2-aminoallyl cation **3.53** *in situ* when chiral diamine triflate salt **3.52** was used as an activator. Hydrolysis of the intermediate produced 3,4-substituted cyclopentadione **3.54** in 94% enantiomeric excess and 60% yield.

**Tius (2001)**



**Tius (2010)**



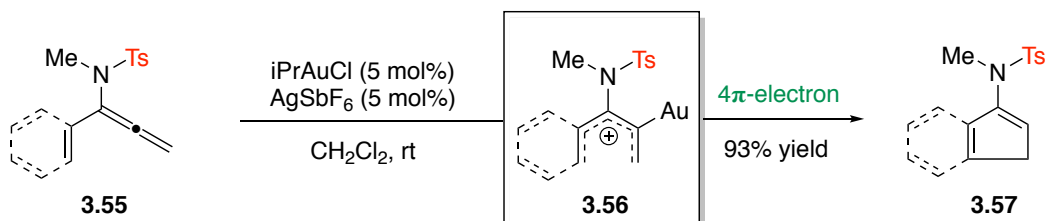
Scheme 3.8. Tius's Imino-Nazarov strategy towards 2-aminoallyl cations

However, common problem associated with 2-aminoallyl cations is the integrity of cyclic structure **3.45**, which tends to undergo imino-Nazarov ring fragmentation to the pentadienyl cation **3.44**. To circumvent this problem, deliberate incorporation of electron withdrawing groups in nitrogen atom has been used. One important example by Hsung and co-workers (2012) used  $\alpha$ -aryl allenamides **3.55** as a precursor for the 2-amidoallyl cations.<sup>57</sup> When  $i\text{PrAuCl}$  is used as a catalyst and  $\text{AgSbF}_6$  as an activator, cyclic enamides **3.57** with tosyl group at the nitrogen atom was observed as the only product. The process is explained to be driven by a  $4\pi$ -electrocyclization



of the corresponding divinyl cation **xxxx** to form 2-amidoallyl cation, which in turn furnished the cyclopentenamide product in high efficacy.

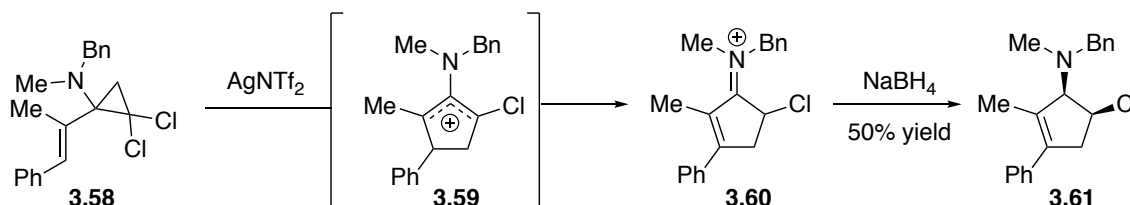
**Hsung (2012)**



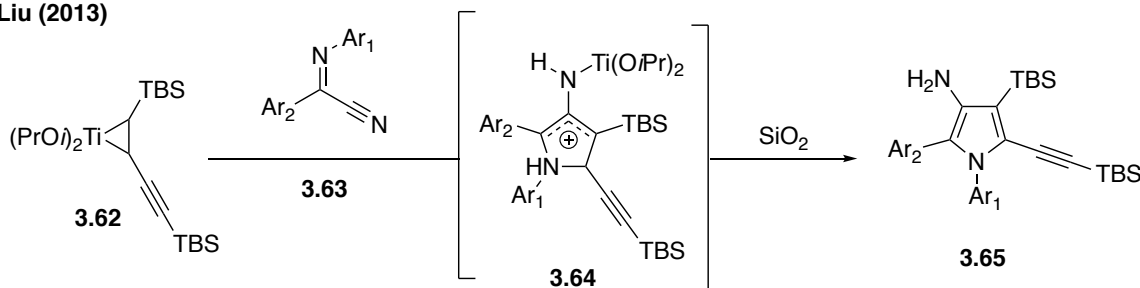
Scheme 3.9. Hsung's annulation strategy utilizing tosyl group at *N*-center

Few other metal-catalyzed methodologies involving imino-Nazarov cyclizations include works from West and co-workers (2013) and Liu and co-workers (2014). West reported an use of silver triflamide as a catalyst to catalyze the ring opening of aminocyclopropanes **3.58** to form 2-aminoallyl cations **3.59** *in situ* followed by a reduction to furnish asymmetric amines **3.61**.

**West (2013)**



**Liu (2013)**



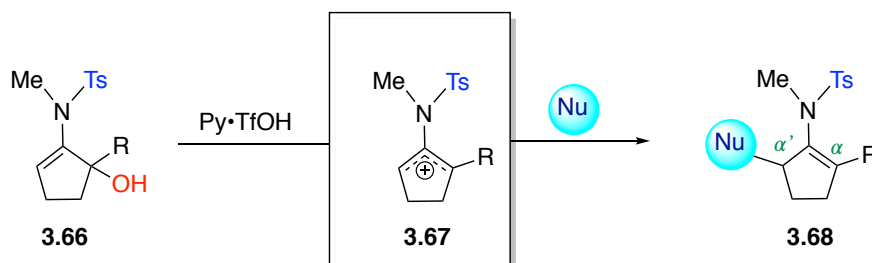
Scheme 3.10. Metal-catalyzed imino-Nazarov cyclizations

Another work by Liu involved the addition of  $\alpha$ -iminonitriles to the alkynyltitanacyclopropane **3.62** which was believed to proceed via 2-aminoallyl cation intermediates stabilized by the Ti(II)

on the nitrogen atom.<sup>60</sup> These intermediates furnished the 3-aminopyrroles **3.65** when subjected to column chromatography in silica.

### 3.7 Direct nucleophilic capture from $\alpha$ -Hydroxy Enamides

A new mode of generation and regioselective capture of unsymmetrical 2-amidoallyl cations **3.67** emerged in 2017. Kartika and co-workers devised a *de novo* generation of these elusive species from  $\alpha$ -hydroxy cyclopentenamides **3.66** by direct ionization using 0.3 equivalence of Py.TfOH in CH<sub>2</sub>Cl<sub>2</sub> at room temperature.<sup>47</sup> The integrity of the five-membered ring was enabled by strategic protection of nitrogen atom by a tosyl group, which rendered the problematic imino-Nazarov ring-fragmentation unfavorable. Once the cation was successfully generated, various  $\pi$ - and heteroatom nucleophiles were shown to be able to capture the unsymmetrical intermediate regioselectively at the less hindered  $\alpha$ -position to furnish synthetically useful enamine adducts **3.68**.

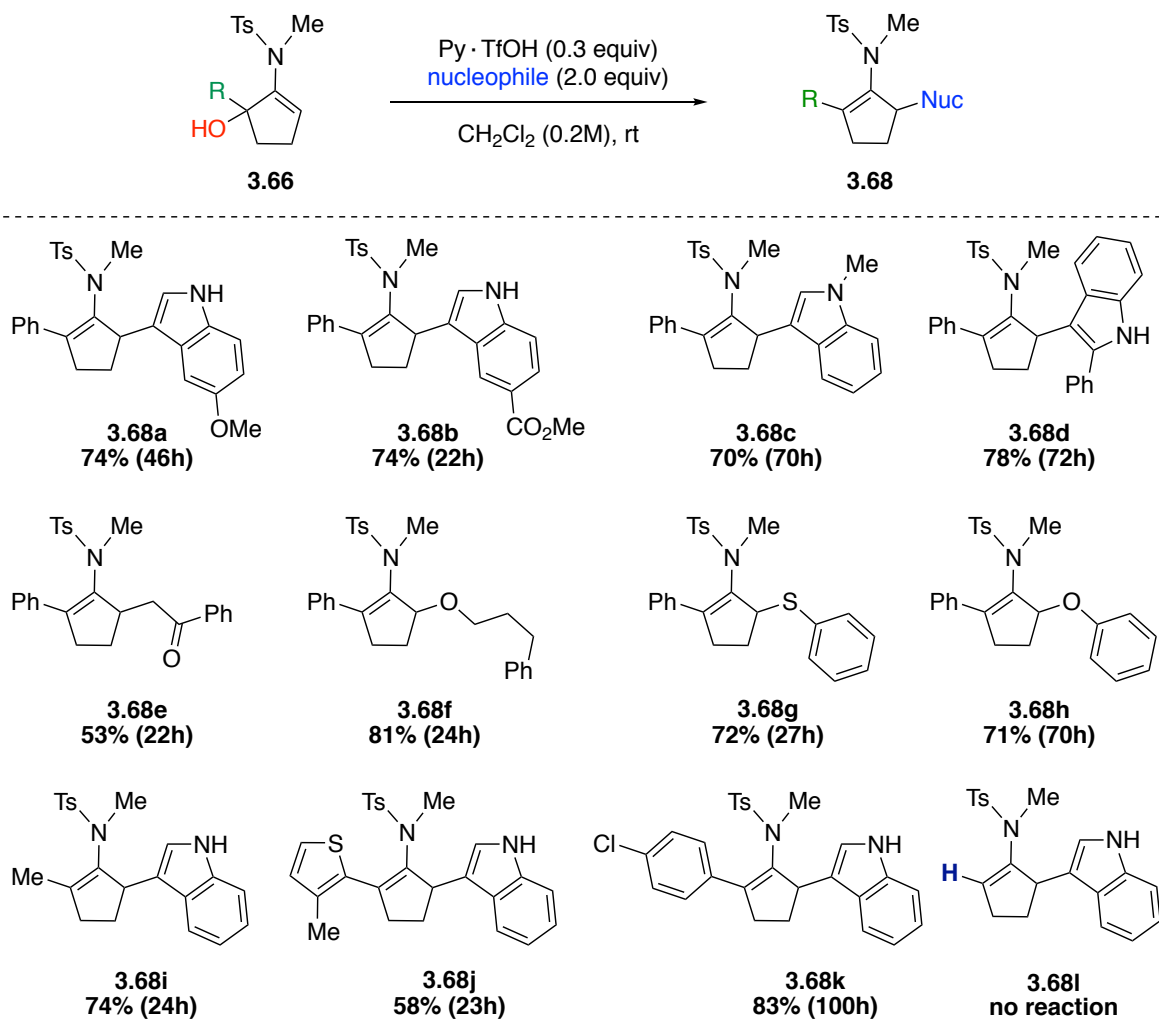


Scheme 3.11. Kartika's hypothesis on generation and trapping of 2-amidoallyl cations

Table 3.1 represents the scope of the methodology. Various electronically different indoles furnished the desired products with an exquisite control of regioselectivity as depicted in series **3.68a-d**. Not only the arene nucleophiles, TMS-enolate nucleophiles also furnished the ketone adduct **3.68e** in 53% yield as a single regioisomer. 3-phenyl propanol, phenol as well as thiophenol also trapped the 2-amidoallyl cation with high yields as illustrated in series **3.68f-h**. Various aromatic and aliphatic  $\alpha$ -substituents were also examined in this study which furnished the

products with the same regioselectivity to afford compounds represented by the series **3.68i-k**. Intriguingly, the reaction failed to proceed without the  $\alpha$ -substitution to produce **3.68l** which was attributed the role of the substituent in stabilizing the forming 2-amidoallyl cation either by resonance effect of the aryl group or through hyperconjugation and inductive effects of the aliphatic substituents. These unprecedented and robust generation of 2-amidoallyl cations under practical conditions laid foundations for the asymmetric  $\beta$ -functionalization studies on similar five-membered systems which will be discussed in Chapter 4.

Table 3.1. Scope of the Kartika's methodology on  $\alpha$ -functionalization of enamides



### 3.8 Conclusions

2-aminoallyl cations are extremely useful reactive intermediates towards different types of reactions that mainly involve cycloadditions, imino-Nazarov cyclization reactions and direct nucleophilic capture. These processes are facilitated by either Lewis acid or Brønsted acid catalysis of the corresponding starting materials. Most recent reports make use of the stability of 2-amidoallyl cations in ring systems that relies on deliberate incorporation of electron-withdrawing group in the nitrogen atom. These studies have offered a new dimension towards the development of unorthodox racemic and asymmetric methodologies.

## CHAPTER 4: ENANTIOSELECTIVE $\beta$ -FUNCTIONALIZATION OF ENAMIDES WITH INDOLES CATALYZED BY CHIRAL PHOSPHORIC ACID

### 4.1 Purpose

The purpose of this section is to discuss our work on  $\beta$ -functionalization of  $\alpha$ -hydroxy cyclopentenamides by indoles. The concept of asymmetric organocatalysis and a brief literature report on  $\beta$ -functionalization studies will be presented. This will be followed by our hypothesis and proof on concept studies, detailed reaction optimization studies and scope of the reaction. Our proposed mode of activation and experiments to support the activation model will also be discussed.

### 4.2 Introduction to Asymmetric Organocatalysis

Asymmetric catalysis refers to the stereoselective synthesis of chiral units in a molecule from the starting materials that has an equal opportunity of formation of two or more than two stereoisomers.<sup>61</sup> This refers to the installment of one or more asymmetric center in a molecule during the bond forming process. These types of transformations are generally achieved by introducing a suitable catalyst or a ligand that is chiral or through attachment of chiral auxiliaries in the molecule of interest. The transition states are generally biased towards a stereoisomer over other probable stereoisomers by being energetically more favored. The area of asymmetric synthesis is immensely important since different diastereomers or enantiomers of a compound can have different biological activity.

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The data presented in section 4.5 - 4.8 have been previously published as Saputra, Mirza A.; Nepal, Binod; Dange, Nitin S.; Du, Pu; Fronczek, Frank R.; Kumar, Revati; Kartika, Rendy. "Enantioselective Functionalization of Enamides at the  $\beta$ - Carbon Center with Indoles". *Angew. Chem. Int. Ed.*, **2018**, 57, 15558-15562. Reprinted by permission of John Wiley and Sons.

Multitude of biocatalytic processes are based on substrate-specific enzymatic reactions, which has inspired the synthetic community in development of biomimetic synthetic routes towards complex natural products.<sup>62</sup> According to a report, more than 1500 research articles on asymmetric organocatalysis are being published each year in the last decade.<sup>63</sup> The impact of organocatalysis in establishing complex molecular architecture, drug discovery, design, and development has gained even bigger attention, thanks to the seminal works from Prof. David McMillan and Prof. Benjamin List, who shared the Nobel Prize in Chemistry in 2021 for their efforts in developing organocatalytic methodologies.<sup>64</sup>

### 4.3 Chiral Phosphoric Acids in Organocatalysis

For a long time, chiral phosphoric acids have been used in asymmetric transformations.<sup>65</sup> <sup>66</sup> The ability of these catalysts to perform in milder conditions and its ability to provide diverse mode of activation has played a key role in these transformations. The chiral phosphoric acids are Brønsted acids by nature, i.e., they furnish  $H^+$  ions in the reaction and activate the substrate. They can be easily converted to phosphoramides in one step which enhances the acidity of the catalyst. Not only this, dual activation or bifunctional catalysis with iminium or oxonium ions are also reported.<sup>67</sup> The H-bonding or ion-pair interactions of these catalysts is very effective in creating stereodifferentiation needed for the asymmetric synthesis. Tunability of the substituents and substrate recognition sites has made these acids more practical in developing new asymmetric methods.<sup>68</sup>

The development of chiral phosphoric acid catalysis has its roots to the phosphinic acid catalysts. In 1962, Sir John Cornforth developed phosphinic acid catalyst **4.1** which is conceptually very close to the modern day chiral phosphoric acid catalysis.<sup>69</sup> The idea of stereoselectivity arises from tunability of different substituents present in the molecule, small pocket of space for substrate

recognition mimicking enzymatic processes as well as useful backbone, that imparts axial chirality in the molecule.<sup>70</sup>

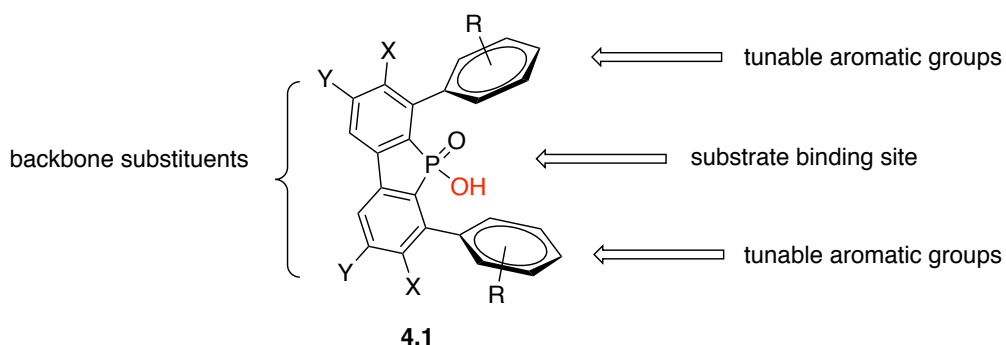
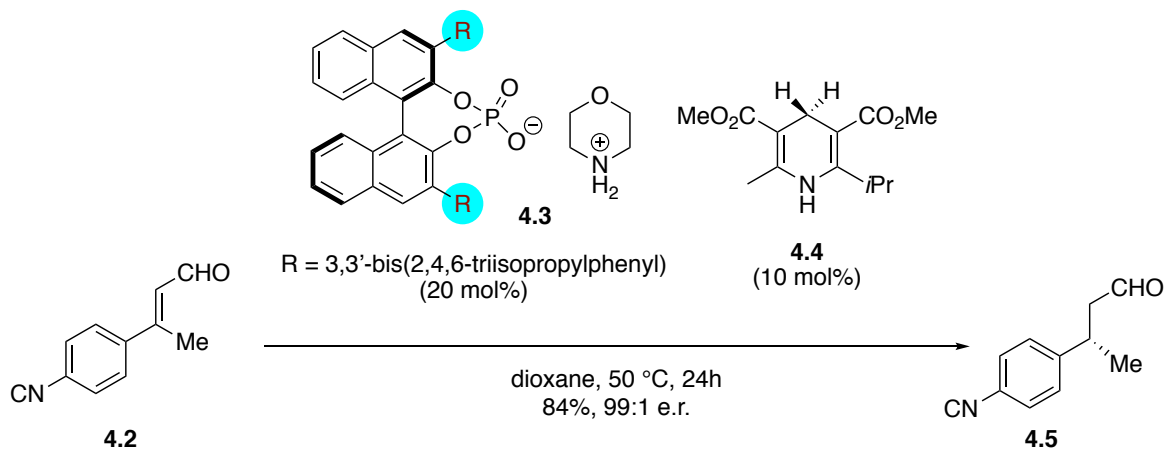


Figure 4.1. Cornforth's explanations of chiral phosphoric acids

The usage of chiral phosphoric acids has gained significant attention in the past 15 years, and numerous asymmetric synthesis has been reported.<sup>65</sup> A classic example from List and co-workers (2006) demonstrates that asymmetric transfer hydrogenation reactions can be catalyzed by chiral phosphate salt **4.3** which consists of achiral ammonium cation and a bulky chiral phosphate counter anion.<sup>71</sup> The reaction produces an iminium intermediate from  $\alpha,\beta$ -unsaturated aldehydes, e.g., **4.2** which gets reduced by Hantzsch dihydropyridine **4.4** under achiral environments.

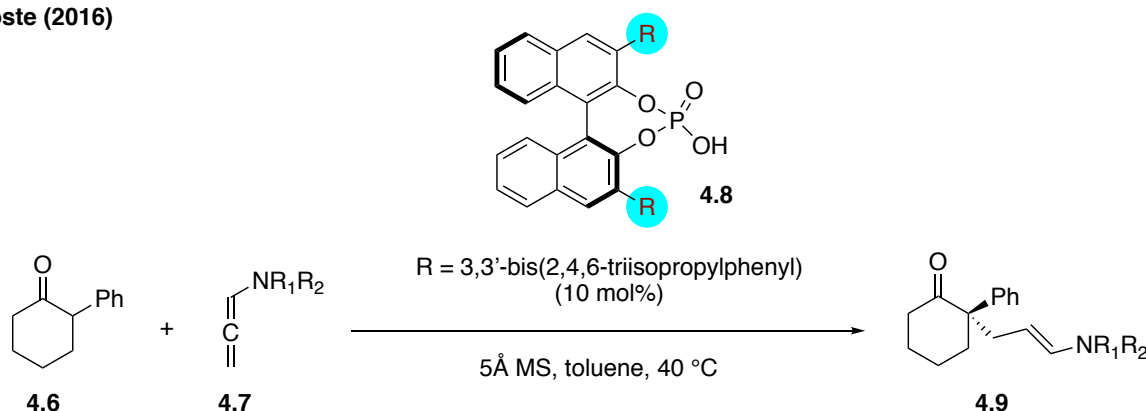
List (2006)



Scheme 4.1. List's CPA mediated enantioselective hydrogenation

Another representative work from Toste and co-workers (2016) on phosphate counter anion based asymmetric synthesis makes use of chiral phosphoric acid *S*-TRIP **4.8** that catalyzes the alkylation of  $\alpha$ -branched cyclic ketone **4.6** with allenamides **4.7**.<sup>72</sup> This methodology is effective in generating highly enantioenriched all-carbon quaternary centers **4.9** at 40 °C with only 10 mol% catalyst loading and is also believed to proceed via iminium intermediates.

Toste (2016)



Scheme 4.2. Toste's work on enantioselective  $\alpha$ -alkylation using CPA

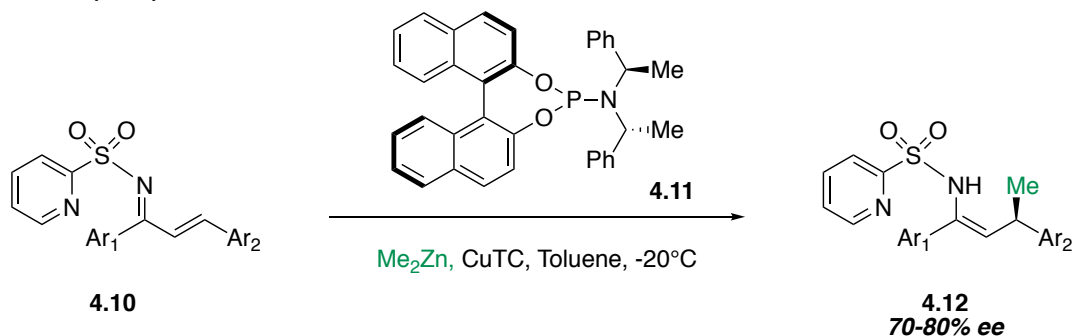
#### 4.4 Our hypothesis on $\beta$ -Functionalization and its Importance

$\beta$ -functionalization of imines and enamines in acyclic systems has been demonstrated by various research groups in the past. Although not as much explored as the regular Michael-addition type reaction for enones,<sup>73</sup> enamines/imines have been functionalized at the  $\beta$ -position through different catalysis approaches. A representative example from Carratero and co-workers makes use of metal catalysis, where 1,4 -addition of alkylzinc reagents to (2-pyridylsulfonyl) ketimines **4.10** was successfully carried out enantioselectively.<sup>74</sup> The process is catalyzed by copper thiophene-2-carboxylates and chiral phosphoramidite ligand **4.11**. In the same line of work, Smith and co-workers demonstrated a benzotetramisole **4.15** mediated asymmetric synthesis of dihydropyridines **4.17** from arylacetic acid **4.13** and N-tosyl- $\alpha,\beta$ -unsaturated ketimines **4.14** in

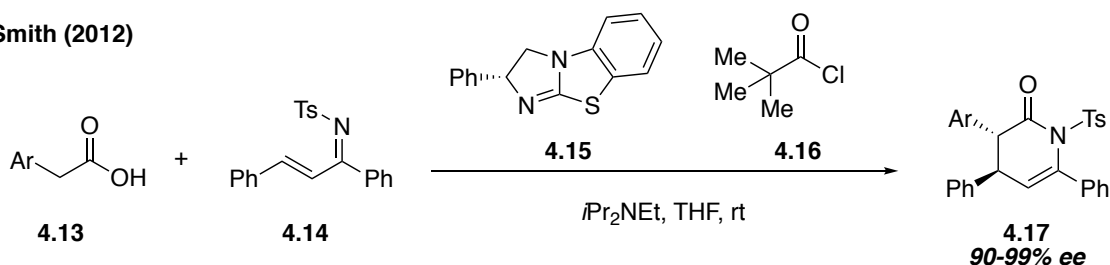


high yields and enantioselectivity.<sup>75</sup> This nucleophilic mode of addition/lactamization process involved the usage of pivaloyl chloride **4.16** to activate the arylacetic acid followed by enolization of the adduct and subsequent Michael addition. Another asymmetric  $\beta$ -functionalization study by Bandini et al. explains the dearomatization of indoles **4.18** via electrophilic activation of allenamides **4.19** by a chiral BINOL phosphoric acid **4.20**.<sup>76</sup>

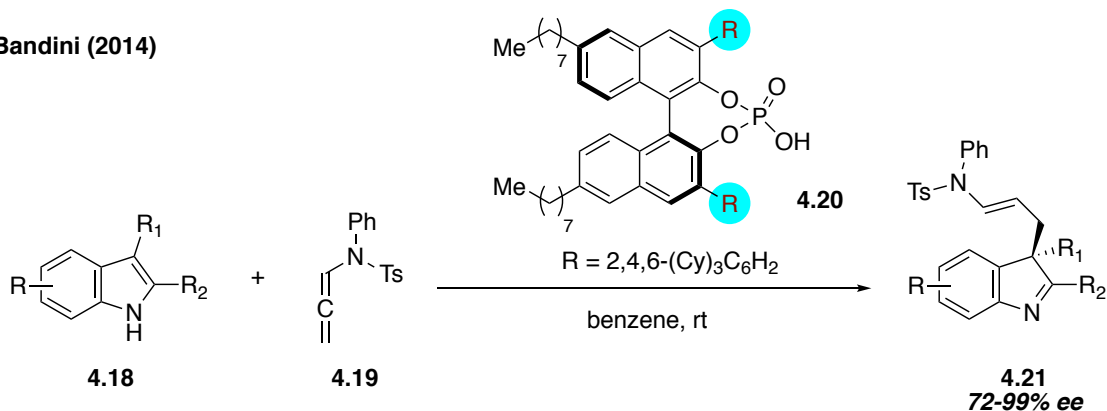
**Carratero (2005)**



**Smith (2012)**



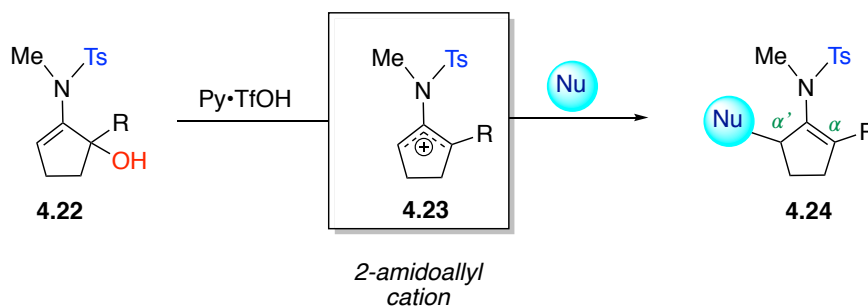
**Bandini (2014)**



Scheme 4.3. Select examples on  $\beta$ -functionalization of enamides

In the process, protonated allenamide i.e., the iminium intermediate is held together by chiral phosphate anion along with the indole by H-bonding through basic oxygen atoms in the phosphate group. This bifunctional catalysis was proposed to induce enantiodiscrimination in the final product **4.21**, albeit the chiral center is installed in the nucleophile.

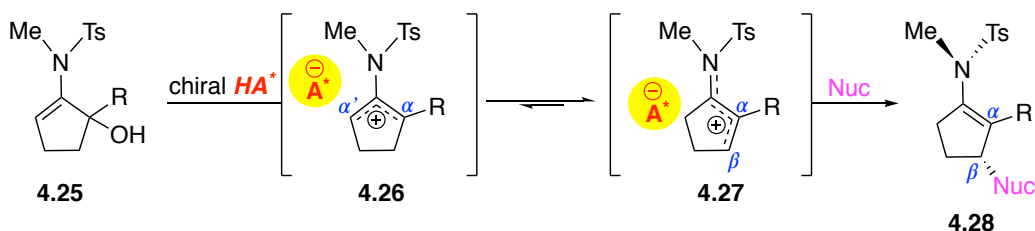
Majority of works on the  $\beta$ -functionalization of imines/enamines has been realized in acyclic systems with stereocenter lying in the nucleophilic partner. Furthermore, activation of a cyclic precursor towards chiral catalysis brings a huge synthetic challenge and instability of the starting materials under reaction conditions. To the best of our knowledge, direct addition of indoles to the  $\beta$ -position in five-membered enamides are unknown till date.<sup>77</sup> To solve this problem, we took an inspiration from our previous work on regioselective functionalization of  $\alpha$ -hydroxy cyclopentenamides **4.22** using Py.TfOH as a catalyst.<sup>47</sup> The robust generation of 2-amidoallyl cations **4.23** were able to be captured by indoles and other heteroatom nucleophiles exclusively at the less substituted  $\alpha$ -carbon to afford adducts **4.24**.



Scheme 4.4. Kartika's work on  $\alpha$ -functionalization using 2-amidoallyl cations

Our hypothesis is based on utilizing a suitable chiral Brønsted acid to ionize the racemic  $\alpha$ -hydroxy enamides **4.25**. We were cognizant of the role of the counter anion in such ionization process, so selection of catalytic system is very important. We envision that the ionization furnishes unsymmetrical 2-amidoallyl cation **4.26**. In presence of readily dissociated triflate anion, the 2-amidoallyl cation readily gets captured at the less substituted position as shown in Scheme

4.4. By changing the ionization source to chiral Brønsted acid, we sought to slow the kinetic process. This will be facilitated by a tight ion-pair interaction between forming 2-amidoallyl cation and the chiral counter anion at the  $\alpha$ -position. Consequently, proton transfer processes take place, which will lead to the formation of 1-amidoallyl cation **4.27** in equilibrium. These unique 1-amidoallyl cationic species will be captured at the less hindered  $\beta$ -position. With the bulky chiral counter anion associated with the ion-pair formation and tautomerization process, we expected the products **4.28** to be enantioenriched.



Scheme 4.5. Our hypothesis on  $\beta$ -functionalization

## 4.5 Proof-of-Concept Studies and Reaction Optimization

With the hypothesis in mind, senior graduate student Mirza A. Saputra and postdoctoral associate Nitin S. Dange started screening the reaction conditions for the desired transformation. The first task was to choose the catalytic system that will be able to ionize the  $\alpha$ -hydroxy enamides **4.25** and at the same time, should form a contact ion-pair in the solution. Based on the literature precedents on closest reactivity system *viz* iminium catalysis,<sup>65, 72</sup> ease of synthesis and manipulation, they decided to proceed with seven BINOL-derived **4.29a-f** and one VAPOL-derived chiral phosphoric acid **4.29g** for the initial screening. The catalysts were prepared according to the reported literature procedure.<sup>78</sup>

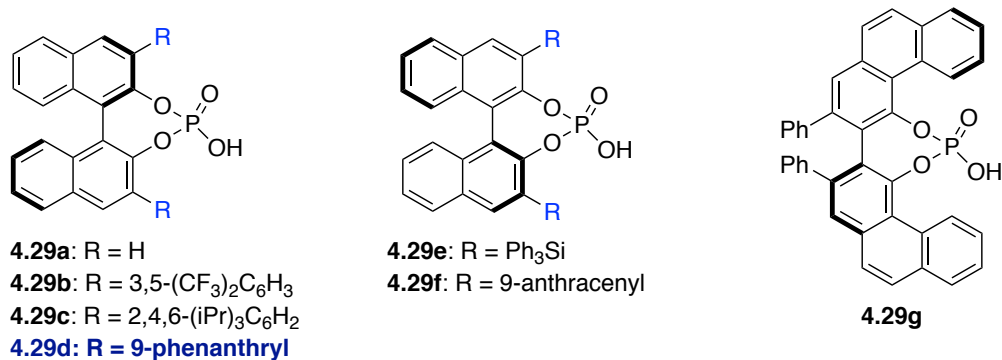
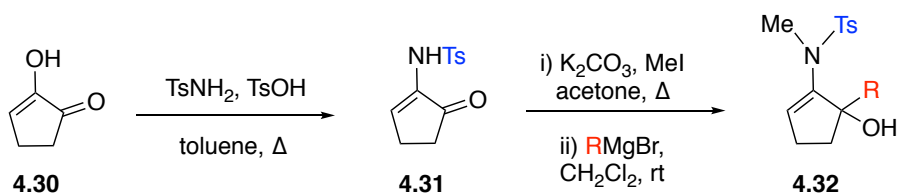


Figure 4.2. Chiral phosphoric acids chosen for optimization studies

The enamide starting material **4.32** was chosen as a model substrate and was prepared according to the previously developed method as showcased in Scheme 4.6.<sup>47</sup> Condensation of diketone **4.30** with *p*-toluenesulfonamide in catalytic tosic acid furnished the tosylamide **4.31**, which was *N*-methylated and Grignard reaction of the ketone afforded the  $\alpha$ -hydroxy enamide starting material **4.32**.

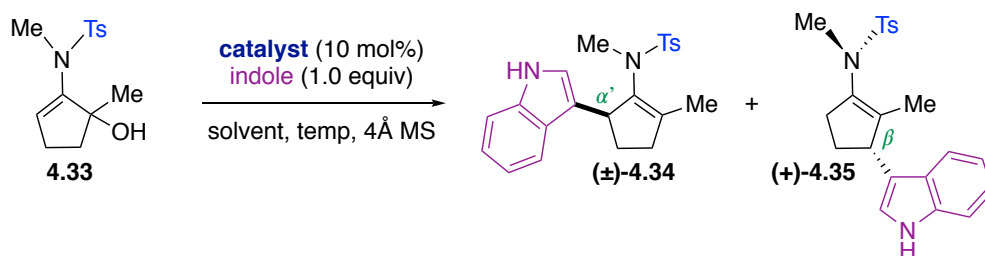


Scheme 4.6. Synthetic route to the starting material

Nitin started screening the reaction conditions by subjecting **4.33** to the 10 mol% catalyst and 2 equivalence of indole at 0.2M concentration of various solvents. He realized that the transformation yields a mixture of kinetically favored  $\alpha$ -indolyl adduct **4.34** and desired  $\beta$ -indolyl adduct **4.35**, with a slight regioselectivity in favor of  $\beta$ -adduct at room temperature. At the same time, he realized that use of non-polar solvents favored the formation of desired product in good yields and regioselectivity, albeit the enantiomeric ratio was found to be moderate. At this point, Mirza A. Saputra screened the reaction conditions by employing CH<sub>2</sub>Cl<sub>2</sub> as a solvent and it produced the product in much better regiomer ratio and good yields. The methodology showed

an improvement when 1 equivalence of indole is used instead of a slight excess of 2 equivalence of indole. Further, use of 4Å MS significantly helped to minimize the inherent hydrolysis of the products, as the reaction produces water which was trapped by the molecular sieves. These initial observations led to the new set of optimizations of the methodology which is depicted in table 4.1.

Table 4.1. Optimization Studies (Nitin S. Dange and Mirza.A. Saputra's work)



entry	catalyst	solvent	conc. (M)	temp. (°C)	time	r.r. <sup>a</sup>	e.r. <sup>b</sup>	% yield <sup>c</sup>
1.	<b>4.29a</b>	CH <sub>2</sub> Cl <sub>2</sub>	0.2	rt	40	1:3	52:48	76
2.	<b>4.29b</b>	CH <sub>2</sub> Cl <sub>2</sub>	0.2	rt	42	1:4.3	53:47	53
3.	<b>4.29c</b>	CH <sub>2</sub> Cl <sub>2</sub>	0.2	rt	24	1:4.3	58:42	74
4.	<b>4.29d</b>	<b>CH<sub>2</sub>Cl<sub>2</sub></b>	<b>0.2</b>	<b>rt</b>	<b>15</b>	<b>1:4.3</b>	<b>79:21</b>	<b>70</b>
5.	<b>4.29e</b>	CH <sub>2</sub> Cl <sub>2</sub>	0.2	rt	40	1:5.7	52:48	76
6.	<b>4.29f</b>	CH <sub>2</sub> Cl <sub>2</sub>	0.2	rt	40	1:5.7	56:44	63
7.	<b>4.29g</b>	CH <sub>2</sub> Cl <sub>2</sub>	0.2	rt	24	1:5.3	48:52	74
8.	<b>4.29d</b>	toluene	0.2	rt	15	1:6.1	72:28	44
9.	<b>4.29d</b>	Bu <sub>2</sub> O <sup>d</sup>	0.2	rt	38	1:7.3	68:32	49
10.	<b>4.29d</b>	CCl <sub>4</sub>	0.2	rt	16	1:2	64:36	46
11.	<b>4.29d</b>	CHCl <sub>3</sub>	0.2	rt	15	1:5.7	71:29	84
12.	<b>4.29d</b>	DCE	0.2	rt	15	1:4.3	88:12	76
13.	<b>4.29d</b>	DCE	0.2	4	14	1:6.7	92:9	74
14.	<b>4.29d</b>	DCE	0.2	-10	63	1:7.3	93:7	68
15.	<b>4.29d</b>	<b>DCE</b>	<b>0.1</b>	<b>-10</b>	<b>48</b>	<b>1:8</b>	<b>94:6</b>	<b>77</b>
16.	<b>4.29d</b>	DCE	0.05	-10	65	1:13.3	94:6	73
17.	<b>4.29d</b>	DCE	0.1	-10	60	1:13.3	94:6	66 <sup>e</sup>

<sup>a</sup>Regiomeric ratio was based on crude <sup>1</sup>H NMR analysis. <sup>b</sup>Enantiomeric ratio is determined by chiral HPLC analysis. <sup>c</sup>Combined yield after flash column chromatography. <sup>d</sup>catalyst not fully dissolved. <sup>e</sup>without 4Å MS, contaminated with inseparable byproducts

All the catalysts in the series **4.29a-g** were screened at 0.2M concentrations of CH<sub>2</sub>Cl<sub>2</sub>. The regiomeric ratios favored the β-regioisomer at reasonable reaction times. Out of eight catalysts, the *R*-BINOL catalyst with 9-phenanthryl substitution, i.e. **4.29d** afforded the best outcome with

CH<sub>2</sub>Cl<sub>2</sub> at room temperature. In fact, the desired regioisomer **4.35** is favored by 4.3:1 ratio over the  $\alpha$ -adduct **4.34** in 70% combined yield and 79:21 enantiomeric ratio in relatively fast 15 hours. This result inspired Mirza to screen some non-polar solvents in toluene and ether (entry 8 and 9). Although the regioselectivity is improved to upto 7.3:1, the product yields depleted to 44% and 49% respectively. This critical information led her to incorporate different chlorinated solvents. In CCl<sub>4</sub>, CHCl<sub>3</sub> and DCE (entry 10,11 and 12), the reactions were relatively faster. Reaction in CHCl<sub>3</sub> was very promising with 5.7:1 product ratio and 71:29 er in 84% yield over 15 hours. To her delight, DCE as a solvent gave the best results of all with an enantioenrichment of 88:12 and 76% combined yield and product ratio of 4.3:1. In further efforts to optimize the reaction, lowering temperature to -10 °C helped tremendously to achieve better regioselection of 7.3:1 and enantiomeric ratio of 93:7 in 63 hours and 68% combined yield (entry 14). Dilution of the reaction to 0.1M and 0.05M helped to improve the regioselectivity up to 13.3:1 and enantiomeric ratio up to 94:6 (entry 15 and 16), however the reaction time increased significantly to 65h for 0.05M concentration of reaction mixture. This led to the following condition as the optimized condition for this methodology.

*0.1M concentration of the reaction mixture in DCE as a solvent at -10 °C with 10 mol% of the catalyst **4.29d** and 1.0 equivalence of indole based on the starting material with 4Å MS additive (entry 15).*

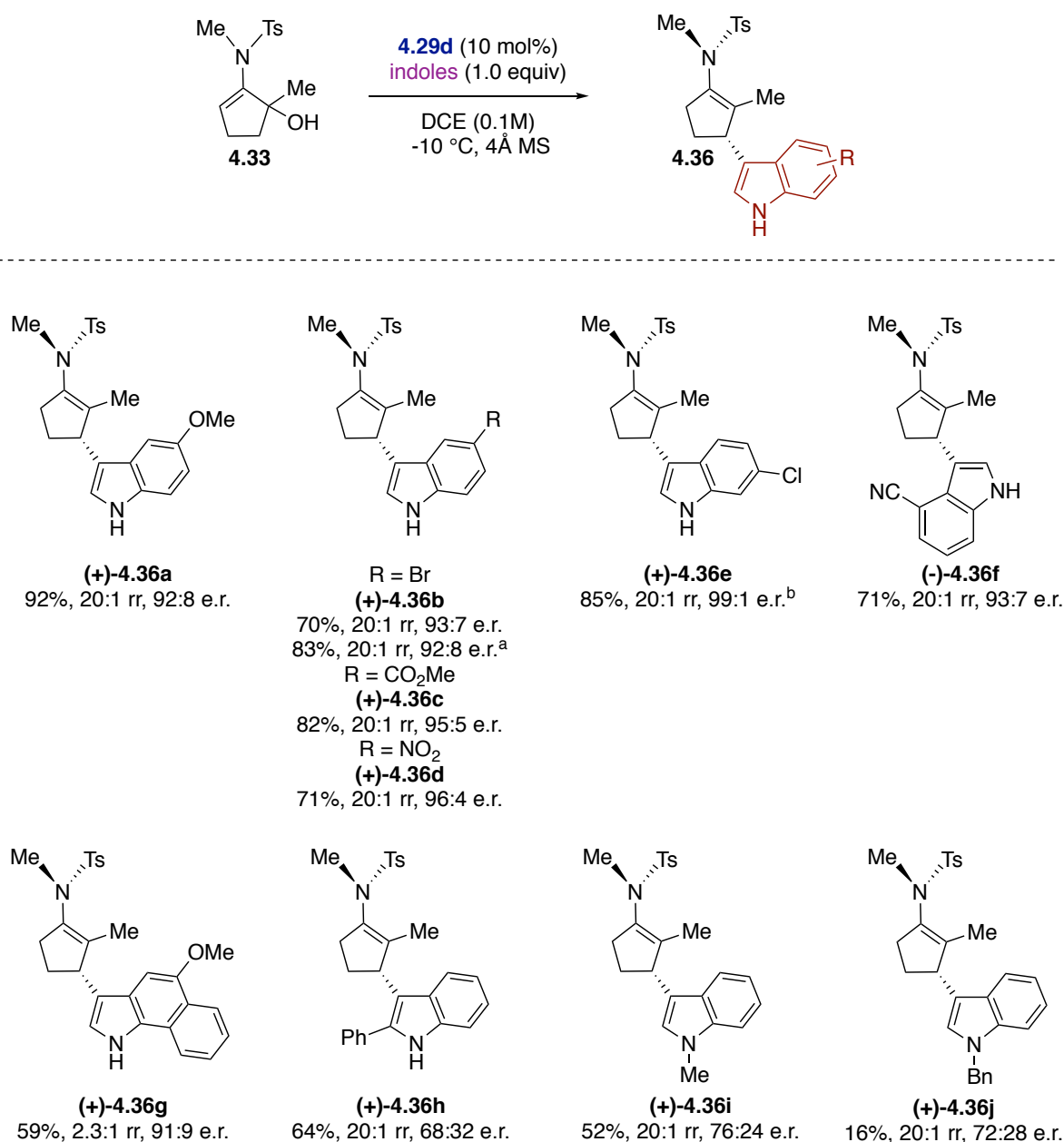
The role of molecular sieves is important in these reactions as the hydrolysis byproducts contaminated the desired product when reaction is performed without 4Å MS (entry 17).

## 4.6 Scope of Indole Nucleophiles

With the conditions optimized, I started exploring the scope of nucleophiles with senior graduate student Mirza A. Saputra. When subjected to reaction conditions, electron-rich 5-methoxyindoles furnished the desired  $\beta$ -isomer (+)-**4.36a** exclusively in 92% yield and 92:8 e.r. Halogenated indoles i.e., 5-bromoindole and 5-chloroindole also furnished the desired  $\beta$ -isomers (+)-**4.36b** and (+)-**4.36e** in 70% and 85% yields respectively as single regioisomers with excellent enantioenrichment. In fact, scaling up the reaction to one-gram scale with 5-bromoindole nucleophile resulted in higher yields and similar enantiomeric ratio of the product (+)-**4.36b**. In the series of electron-deficient indoles, methyl indole 5-carboxylate also furnished the indole adduct (+)-**4.36c** in 82% yield as a single regioisomer and 95:5 e.r. Similarly, 5-nitroindole and 4-cyanoindole also proved to be effective nucleophiles in this methodology affording the  $\beta$ -indolyl adducts (+)-**4.36d** and (+)-**4.36f** as single regioisomers and good control of enantioselectivity. With sterically demanding nucleophiles like 5-methoxy-1H-benzo[g]indole, competitive  $\alpha$ - and  $\beta$ - capture resulted in depleted regiomer ratio of 2.3:1 and product yield of 59% with slightly reduced enantiomeric ratio of 91:9 as indicated in adduct (+)-**4.36g**. Another sterically demanding 2-phenylindole nucleophile surprisingly produced only  $\beta$ -isomer (+)-**4.36h** in 64% yield although the enantiomeric ratio plummeted to 68:32 highlighting the role of sterics in the enantiodifferentiating step. Next, we examined the *N*-protected indoles. *N*-methylindoles and *N*-benzylindoles were able to produce the desired  $\beta$ -isomers (+)-**4.36i** and (+)-**4.36j** as single regioisomers but the yields and enantiomeric ratios were eroded significantly signalling that protected indoles are not suitable for this reaction. All the indole adducts were dextrorotatory when examined for optical rotation, except for the 4-CN indole adduct (-)-**4.36f** which was found to be levorotatory. Moreover, the stereochemical integrity in the solid state of compound (+)-**4.36e** was

evaluated by single crystal X-ray diffraction which helped us to determine the absolute stereochemistry of the compound in the solid state.

Table 4.2. Scope of indole nucleophiles



<sup>a</sup>Reaction was performed on one-gram scale. <sup>b</sup>Structure of the compound in the solid state is determined by single crystal X-ray analysis.



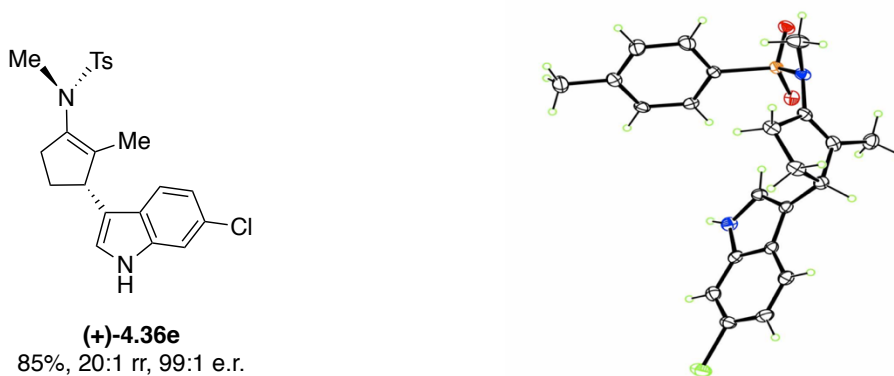


Fig 4.3. X-Ray structure of **(+) -4.36e**

#### 4.7 Scope of $\alpha$ -substituents

After encouraging results in the scope of indole nucleophiles, we started to examine the  $\alpha$ -substituents. Our first choice was the  $\alpha,\alpha$ -hydroxy phenyl cyclopentenamide **4.37**. When subjected to the optimized conditions, the substrate did not ionize even after 168h, creating a need of another round of screening reaction conditions for the desired transformation. Table **4.3** represents the revised optimization table for the  $\alpha$ -substituents. By warming the reaction to room temperature, we were able to ionize the starting material, although the reaction furnished 1:2 mixture of two regioisomers **( $\pm$ )-4.38** and **(+) -4.39** with 14:86 er and 49% yield (entry 2). By further modulation of reaction temperature and dilution of the reaction mixture, we were able to ionize and intercept the  $\alpha$ -hydroxyenamide **4.37** to afford the indole adduct in modest regioselectivity of 1:4.9 in favor of the  $\beta$ -isomer **(+) -4.39** with 5:95 er in 77% yield. This led to the optimized condition for the  $\alpha$ -substituted starting materials as follows.

*0.05M concentration of the reaction mixture in DCE as a solvent at -5 °C with 10 mol% of the catalyst **4.29d** and 1.0 equivalence of indole based on the starting material with 4Å MS additive (entry 5).*

Table 4.3. Re-optimization of the reaction for  $\alpha$ -substrates

entry	concentration	temperature	time (h)	ratio of (±)-4.38: (+)-4.39 [a]	enantiomeric ratio [b]	yield (%) [c]
1	0.1 M	10 °C	168	-	-	nr
2	0.1 M	room temp.	88	1 : 2	14 : 86	49
3	0.1 M	4 °C	88	1 : 2	8 : 92	63
4	0.1 M	-5 °C	138	1 : 4.3	7 : 93	66
<b>5</b>	<b>0.05 M</b>	<b>-5 °C</b>	<b>233</b>	<b>1 : 4.9</b>	<b>5 : 95</b>	<b>77</b>

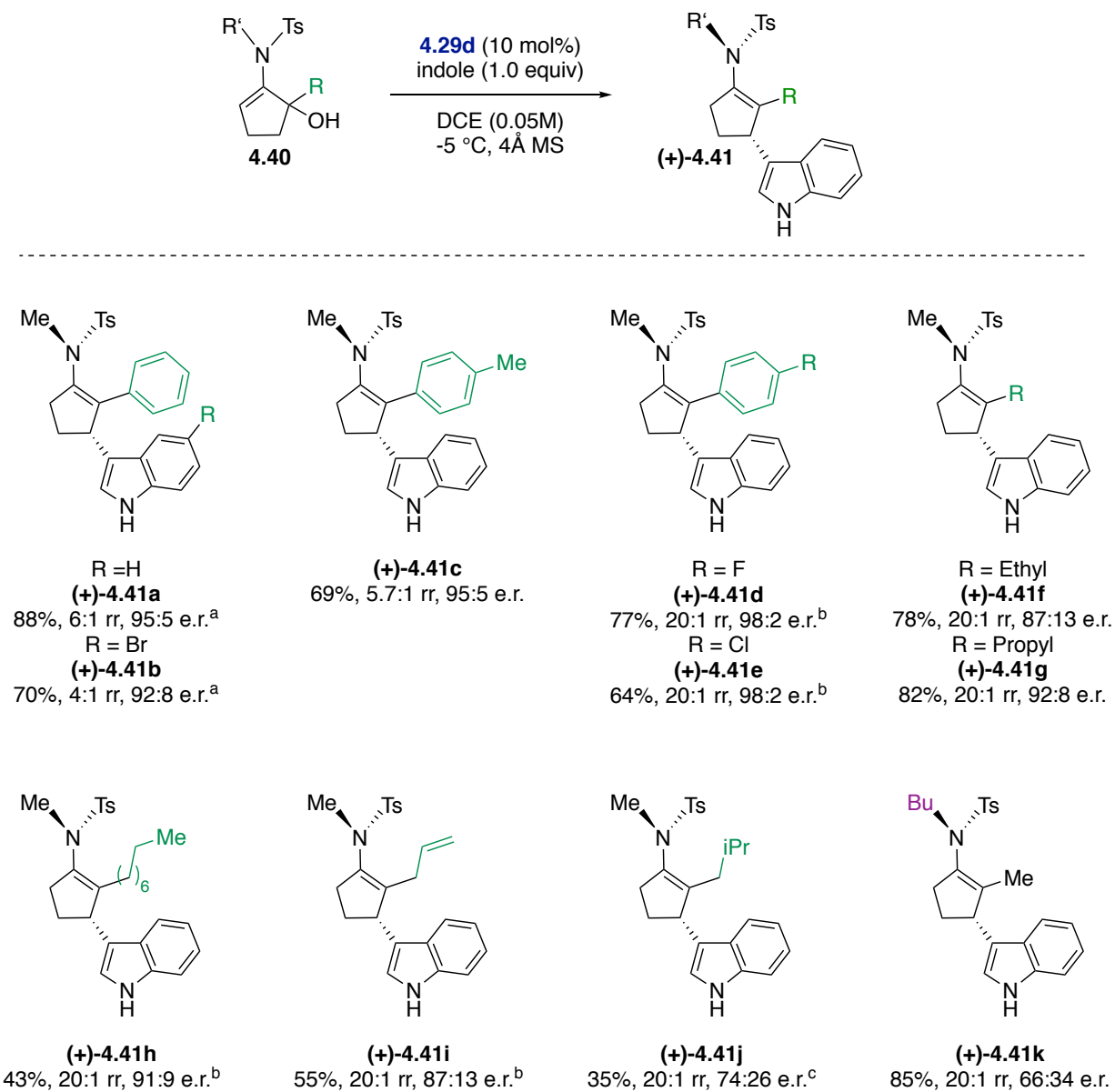
<sup>a</sup>Regiomer ratio of the products was determined by <sup>1</sup>H-NMR. <sup>b</sup>Enantiomeric ratio was determined by chiral HPLC analysis. <sup>c</sup>Combined yields of both regioisomers after flash column chromatography.

With the re-optimized conditions, we then examined the substrates with different  $\alpha$ -aryl groups.  $\alpha$ -phenyl substituent was tolerated under this methodology with the indole nucleophile and 5-bromoindole nucleophile to afford the desired  $\beta$ -isomers **(+)**4.41a and **(+)**4.41b in 88% and 70% yields with a modest regioselectivities of 6:1 and 4:1 and 95:5 and 92:8 er respectively. These both adducts were crystalline and the absolute stereochemistry of these products were assigned using X-ray crystallography.  $\alpha$ -Tolyl substituent also afforded the desired beta isomer **(+)**4.41c in good yields and enantioselectivity. When 4-fluoro and 4-chlorophenyl substituents are incorporated in the starting material, smooth conversion to the  $\beta$ -isomer was observed as a single regioisomers **(+)**4.41d and **(+)**4.41e in 77% and 64% yields respectively with 98:2 er. These substrates were not fully ionized at 10 mol% catalyst loading, so 30 mol% catalyst was used for these transformations.

In the aliphatic substituent series,  $\alpha$ -ethyl and  $\alpha$ -propyl substituents afforded the desired products **(+)**4.41f and **(+)**4.41g in good yields as a single regioisomer, but the enantiomeric ratio

depleted to 87:13 and 92:8 respectively. When decorated with an octyl substituent, the transformation was observed to be regioselective as the  $\beta$ -isomer **(+)-4.41h** was obtained as the only product, but the yield plummeted to 43% and 91:9 er.

Table 4.4. Scope of  $\alpha$ -substituents



<sup>a</sup>Structure determined by X-ray crystallography. <sup>b</sup>With 0.3 equivalence of catalyst. <sup>c</sup>Reaction performed at concentration of 0.1M

Similarly,  $\alpha$ -allyl and  $\alpha$ -isobutyl starting materials produced the desired beta-isomers **(+)**4.41i and **(+)**4.41j in meager 55% and 35% yields with significant erosion in enantioselectivities, viz 87:13 and 74:26 er. Lastly, when *N*-Me group was exchanged for *N*-Bn group in the starting material, the  $\beta$ -adduct **(+)**4.41k was obtained in 85% yield as a single regioisomer, with a drop in enantiomeric ratio to 66:34. These observations are critical as it signals the role of steric bulk around  $\alpha$ -carbon and nitrogen atom in the stereodefining step.

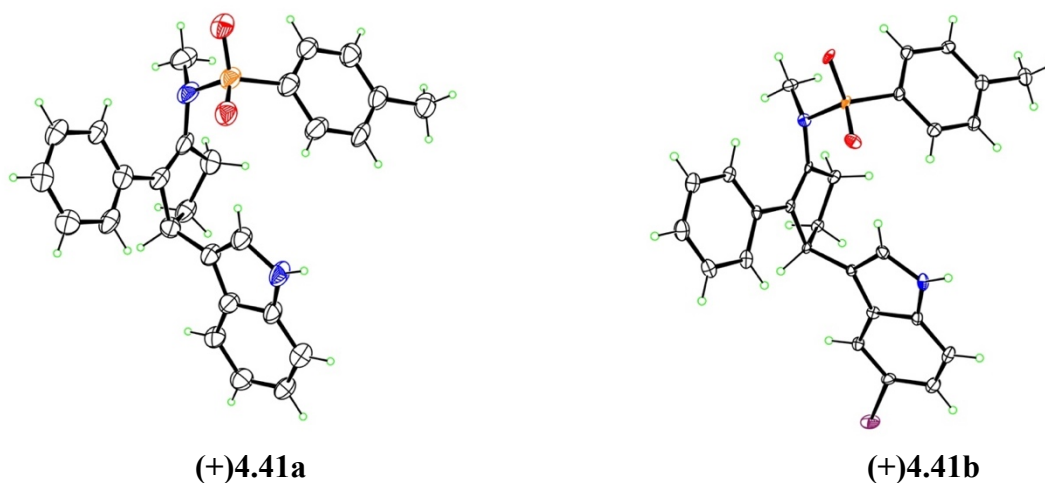
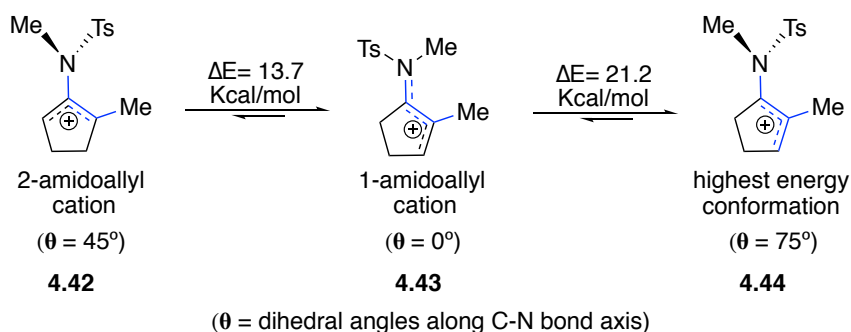


Figure 4.4. X-ray structures of enamide adducts **(+)**4.41a and **(+)**4.41b

#### 4.8 Proposed Mode of Activation

Based on the observations during the scope of the reaction, we noted down two main characteristics in this catalysis. 1) the indole -NH has a key role since protected indoles afforded products with depletion in er 2) steric bulk around the  $\alpha$ -substituent reduces the enantiomeric purity in the products. These two observations led us to propose a possible mode of activation which is based on the formation of contact ion-pair between the bulky conjugate base of chiral phosphoric acid and the incipient 1-amidoallyl cation.<sup>61</sup> The whole process starts with ionization of racemic  $\alpha$ -hydroxy cyclopentenamide **4.40** with chiral phosphoric acid **4.29d**. This leads to the

formation of 2-amidoallyl cation first and is closely associated with the bulky phosphate counter anion which renders the kinetic process unfavorable. We postulate that these 2-amidoallyl cations **4.42** are tautomerized to 1-amidoallyl cations **4.43** through proton transfer process. This assumption was supported by computational data in collaboration with Kumar Group at LSU. They found that the 1-amidoallyl cation **4.43** is energetically favored over the 2-amidoallyl cations by 13.2Kcal/mol and 21.2Kcal/mol lower in energy than the highest energy conformer **4.44**.



Scheme 4.7. Computational analysis on energy profile of amidoallyl cations

This stereoablative ionization and tautomerization sequence to 1-amidoallyl cation species resembles the electronics of iminium catalysis from the works of Bandini, Toste and List.<sup>71, 72, 76</sup> The allylic strain in the cationic species is relieved by the orientation of tosyl group perpendicular to the plane of the five-membered ring as depicted in figure **4.45**. Along with the contact ion-pair, the *H*-bonding ability of indole -*NH* and basic oxygen atom in the phosphate anion offers an asymmetric environment where indole can be delivered at the less hindered β-position of the cyclopentenamide ring. This is supported by the lack of enantioenrichment when *N*-protected indoles were used as nucleophiles to afford products **(+)-4.36i** and **(+)-4.36j**. Further, the transition state model also explains the sterically cumbersome α-substituents leading to less enantioenriched products as the space interference of these substituents in ion-pair interaction impede the ‘tightness’ of binding in the transition state **4.45**.

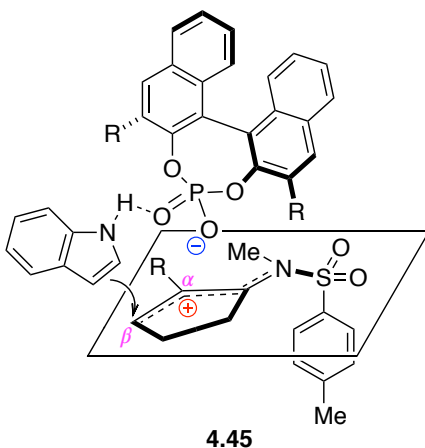


Figure 4.5. Proposed activation model

## 4.9 Conclusion

This work highlighted our effort in solving the longstanding problem in direct nucleophilic capture of amidoallyl cationic species in five-membered rings. Inspired from the bifunctional catalysis offered by chiral phosphoric acids, we were able to showcase a strategic tautomerization of 2-amidoallyl cations to 1-amidoallyl cations followed by an enantioselective capture by indole nucleophiles at the  $\beta$ -carbon. Good to excellent control of regioselectivity and enantioselectivity was observed. Although this method is currently limited to the indole nucleophiles, we are confident that tuning the reaction parameters will help expand the horizon of this chemistry beyond the  $\pi$ -nucleophiles.

## CHAPTER FIVE: EXPERIMENTALS

### 5.1 General Information

All materials, unless otherwise stated, were purchased from commercial sources, and utilized without further purification. Anhydrous reactions were conducted in oven-dried glassware, which was then cooled under vacuum and purged with nitrogen gas. Dichloromethane ( $\text{CH}_2\text{Cl}_2$ ), toluene, acetonitrile (MeCN), diethyl ether ( $\text{Et}_2\text{O}$ ), and tetrahydrofuran (THF) were filtered through activated 3Å molecular sieves under nitrogen in a solvent purification system. Reactions were monitored either by analytical thin-layer chromatography (TLC silica gel 60 F<sub>254</sub>, glass plates) and analyzed using 254 nm UV light and anisaldehyde - sulfuric acid stain.

All  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  using a Bruker Ascend 400 spectrometer operating at 400 MHz for  $^1\text{H}$  and 100 MHz for  $^{13}\text{C}$  or Bruker Ascend 500 spectrometer operating at 500 MHz for  $^1\text{H}$  and 125 MHz for  $^{13}\text{C}$ . Chemical shifts ( $\delta$ ) are reported in ppm relative to residual  $\text{CHCl}_3$  as an internal reference ( $^1\text{H}$ , 7.26 ppm;  $^{13}\text{C}$ , 77.00 ppm). Coupling constants ( $J$ ) are reported in hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), x (septet), h (heptet), b (broad), and m (multiplet). FT-IR spectra were recorded on Bruker Tensor 27 spectrometer and OPUS Data Collection Program, and absorption frequencies are reported in reciprocal centimeters ( $\text{cm}^{-1}$ ). High Resolution Mass Spectrometry – Electron Spray Ionization (HRMS-ESI) analyses were performed by the Louisiana State University Mass Spectrometry Facility using an Agilent 6210 Instrument. X-Ray structure analyses were performed by the Louisiana State University X-Ray Structure Facility using a Bruker APEX-II CCD diffractometer. HPLC analyses were carried out using Dionex Ultimate 3000 system on Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron) or Chiralpak IA-3 column (0.46 cm x 25 cm x 3 micron) using isopropanol ( $i\text{PrOH}$ ) in hexanes as the

eluent with a rate of 1 mL/min. Optical rotation was measured using JASCO-DIP-370 polarimeter.

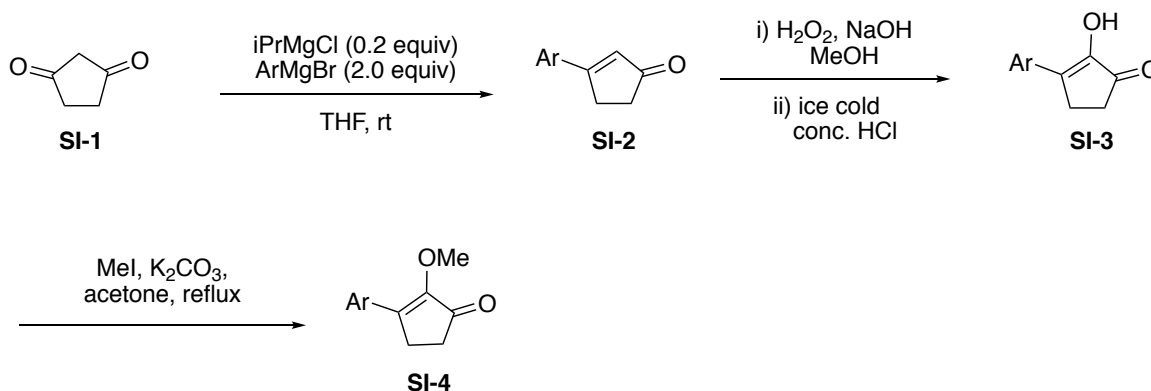
## 5.2 Experimental Procedures for Synthesis of Geminal Bis-Aryl Quaternary Center

### 5.2.1 Optimization Studies

Starting material **2.23** (50 mg, 0.219 mmol) was added to a vial equipped with a stir bar. Toluene (1.1 ml), 0.2 M was added followed by the addition of indole (51 mg, 0.438 mmol, 2 equiv). The solution was cooled to -20 °C and Py.TfOH (0.13 ml, 0.5M solution in MeCN, 0.3 equiv) was added dropwise. The reaction was stirred at -20 °C, monitored by TLC and once completed, quenched with 0.5 ml Et<sub>3</sub>N. The crude was directly loaded into a flash chromatography column and purified.

### 5.2.2 Synthesis of Starting Materials

The precursor ketones **SI-4** to the  $\alpha,\alpha$ -hydroxyalkynyl enol ethers were synthesized following the known route presented below.



**Typical Procedure:** To a solution of *i*-PrMgCl (0.2 eq.) was dropwise added the 1,3-diketone (1.0 eq.) in anhydrous THF at 0 °C. The mixture was stirred for 30 min at 0 °C and then the bromide Grignard reagent (2.5 eq.) was introduced. The mixture was warmed to 40 °C. After stirring for 4 h at 40 °C, the reaction was carefully quenched with 10% aqueous solution of acetic acid at 0 °C. The aqueous layer was extracted with ether and the combined organic layer was dried with

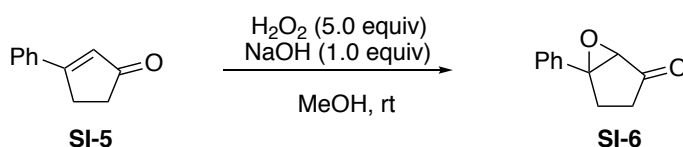


anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was then evaporated under the reduced pressure and the residue was purified by column chromatography to get known compounds **SI-2**.

**SI-2** was dissolved in MeOH, and the solution was cooled to 0 °C. Hydrogen peroxide (30% aqueous solution) was then added dropwise, followed by addition of aqueous NaOH (4M). After stirring at room temperature for 2 hours, the reaction mixture was then concentrated under vacuum to remove methanol. CH<sub>2</sub>Cl<sub>2</sub> and DI H<sub>2</sub>O were then added sequentially. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> three times. The combined organic layers were then washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to yield crude epoxide material. In a round bottom flask equipped with stir bar, crude epoxide material was cooled to 0 °C. Ice cold concentrated aqueous HCl (12 M) was then added dropwise. The mixture was stirred at room temperature for 12 hours. After cooling to 0 °C, the reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> followed by addition of DI H<sub>2</sub>O. The crude mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> three times. The combined organic layers were then washed with saturated NaHCO<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum to afford 1,2-diones **SI-3**, which was used without purification in the next step.

Dione **SI-3** was dissolved in Na<sub>2</sub>SO<sub>4</sub>-dried acetone (0.2 M). Iodomethane was added to the reaction mixture, followed by K<sub>2</sub>CO<sub>3</sub>. The solution was then warmed to reflux and stirred overnight. Upon completion, the reaction mixture was cooled to 0 °C and quenched with DI water. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> three times, and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum. The crude product **SI-4** was purified by flash column chromatography.

#### 5-phenyl-6-oxabicyclo[3.1.0]hexan-2-one (**SI-6**)

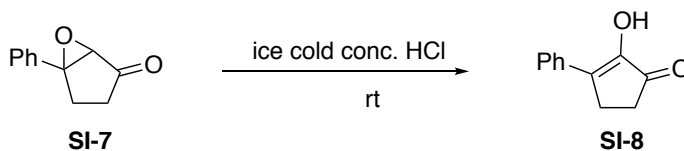


Compound **SI-5** (3.60 gm, 22.77 mmol) was dissolved in 36ml methanol in a round bottom flask equipped with a stir bar and the solution was cooled to 0°C. Hydrogen peroxide (13 ml, 113.87 mmol, 30% aqueous solution) was then added dropwise followed by addition of 4N aqueous NaOH (5.7ml, 22.77 mmol). The reaction mixture was stirred at rt for 2h and methanol was evaporated. DI H<sub>2</sub>O was added to the crude and extracted with CH<sub>2</sub>Cl<sub>2</sub> three times. The combined organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, and solvent was evaporated in a rotary evaporator to yield crude compound **SI-6** (2.81g, 71% yield).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.41 – 7.36 (m, 5H), 3.47 (s, 1H), 2.60 – 2.52 (m, 3H), 2.32 – 2.26 (m, 1H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 209.33, 135.15, 129.62, 128.66, 125.76, 120.67, 115.26, 67.80, 63.69, 32.54, 25.59.

### 2-hydroxy-3-phenylcyclopent-2-en-1-one (**SI-8**)



Compound **SI-7** (2.81 g, 16.14 mmol) was added to a dry round bottom flask equipped with stir bar and cooled to 0°C. Ice cold conc. HCl (12.5 ml) was then added dropwise to the flask. The reaction was stirred at 0°C for 3h and diluted with CH<sub>2</sub>Cl<sub>2</sub> followed by addition of DI H<sub>2</sub>O (15 ml) at 0°C. The crude was extracted with CH<sub>2</sub>Cl<sub>2</sub> three times followed by washing with saturated NaHCO<sub>3</sub> three times. The organic layers were combined, dried with Na<sub>2</sub>SO<sub>4</sub>, and evaporated using rotary evaporator to yield compound **SI-8** (2.35gm, 84% yield).

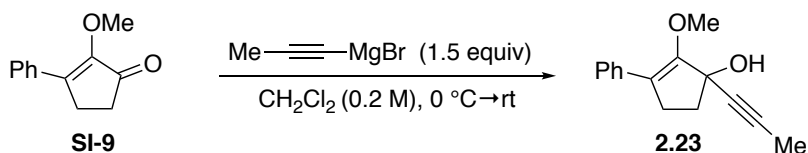
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 6.36 (s, 1H), 2.91 – 2.89 (m, 2H), 2.60 – 2.57 (m, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 202.92, 148.17, 137.98, 133.87, 129.46, 128.60, 127.68, 30.99, 23.33.

References for **SI-1** to **SI-4** transformation is as follows.

- 1) Yuan, R.; Zhao, D.; Zhang, L-Y.; Pan, X.; Yang, Y.; Wang, P.; Li, H-F.; Da, C-S. *Org. Biomol. Chem.*, **2016**, *14*, 724-728
- 2) Ashouri, M.A.; Arazi, O.; Alizadeh, H., *Asian J. Chem.*, **2010**, *22*(6), 4464-4468.
- 3) Dange, N. S.; Stepherson, J. R.; Ayala, C. E.; Fronczek, F. R.; Kartika, R., *Chem. Sci.*, **2015**, *6*, 6312-6319.

### 2-methoxy-3-phenyl-1-(prop-1-yn-yl)cyclopent-2-en-1-ol (**2.23**)



**Procedure:** An oven-dried round bottom flask was charged with compound **SI-9** (160 mg, 0.85 mmol) along with a stir bar. The flask was kept under nitrogen and dry  $\text{CH}_2\text{Cl}_2$  (4.3 ml) was added to the flask *via* syringe. The flask was cooled to  $0\text{ }^\circ\text{C}$  and propynyl magnesium bromide (2.6 ml, 1.28 mmol, 0.5M in THF) was added dropwise followed by warming to room temperature. The reaction was stirred at rt for 1h and quenched with DI  $\text{H}_2\text{O}$  at  $0\text{ }^\circ\text{C}$  and extracted with  $\text{CH}_2\text{Cl}_2$  (3x15ml). Thus, obtained crude material was further purified with flash column chromatography buffered with 1%  $\text{Et}_3\text{N}$  using 100% Hexanes  $\rightarrow$  10% EtOAc to afford compound **2.23** as a yellow oil (150 mg, 77 % yield).

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.59 (d, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 3.90 (s, 3H), 2.73 – 2.61 (m, 2H), 2.52 (ddd, *J* = 12.2, 8.0, 4.2 Hz, 1H), 2.45 (s, 1H), 2.20 (ddd, *J* = 13.7, 8.4, 5.6 Hz, 1H), 1.89 (s, 3H).

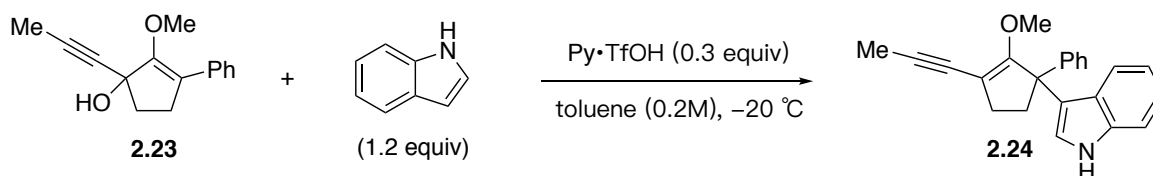
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 153.64, 135.37, 128.04, 127.26, 126.82, 118.76, 81.73, 80.52, 76.38, 59.07, 39.30, 27.71, 3.75.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3407, 3054, 2941, 2852, 2242, 1639, 1309, 1072, 763, 695.

**HRMS:** (ESI-TOF) *m/z*: [(M+H)]<sup>+</sup> 229.1223 calculated for C<sub>15</sub>H<sub>17</sub>O<sub>2</sub>; Found 229.1214.

### 5.2.3 Characterization of New Compounds

#### 3-(2-methoxy-1-phenyl-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1*H*-indole (2.24)



**Procedure:** Compound **2.23** (50 mg, 0.22 mmol) was added to a vial equipped with a stir bar. Toluene (1.1 ml) was added followed by the addition of indole (31 mg, 0.26 mmol). The solution was cooled to -20 °C and Py•TfOH (0.13 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 36 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub>, once completed. The crude reaction mixture was directly loaded into a column and purified using 100% Hexanes → 7.5% EtOAc to afford compound **2.24** as yellow fluffy solids (70 mg, 97 % yield, 16:1 rr).

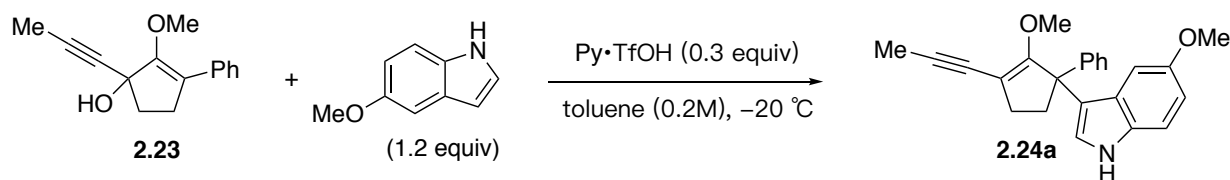
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.92 (s, 1H), 7.36 – 7.32 (m, 4H), 7.28 (t, *J* = 9 Hz, 2H), 7.24 – 7.20 (m, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.01 – 6.94 (m, 2H), 4.06 (s, 3H), 2.73 – 2.66 (m, 1H), 2.56 – 2.48 (m, 3H), 2.00 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 164.21, 145.48, 136.88, 127.89, 127.58, 126.54, 126.10, 122.48, 121.65, 121.58, 120.47, 119.00, 111.03, 92.88, 87.76, 58.66, 56.84, 38.44, 32.53, 4.62.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3477, 2941, 2853, 1635, 1457, 1378, 1203, 1014, 903, 723.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 328.1659 calculated for C<sub>23</sub>H<sub>22</sub>NO; Found 328.1690.

**5-methoxy-3-(2-methoxy-1-phenyl-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1*H*-indole (2.24a)**



**Procedure:** Compound **2.23** (50 mg, 0.22 mmol) was added to a vial equipped with a stir bar. Toluene (1.1 ml) was added followed by the addition of 5-methoxyindole (39 mg, 0.26 mmol). The solution was cooled to -20 °C and Py•TfOH (0.13 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 96 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub>. The crude was directly loaded into a column and purified using 100% Hexanes → 7.5% EtOAc to afford compound **2.24a** as yellow fluffy solids (72 mg, 92 % yield, 7:1 rr).

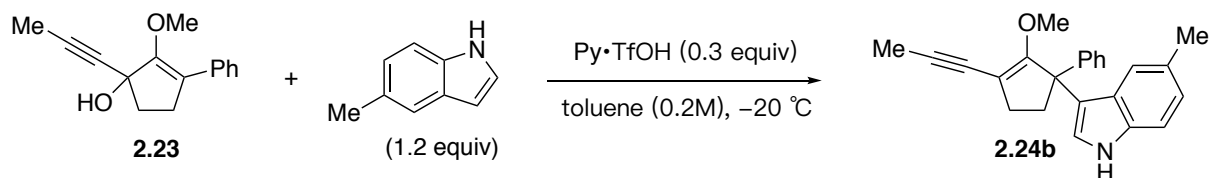
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.86 (s, 1H), 7.34 (d, *J* = 12.2 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.23 – 7.20 (m, 2H), 6.97 (d, *J* = 2.6 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.75 (d, *J* = 2.6 Hz, 1H), 4.06 (s, 3H), 3.68 (s, 3H), 2.68 – 2.62 (m, 1H), 2.55 – 2.47 (m, 3H), 1.99 (s, 3H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 164.18, 153.32, 145.36, 132.10, 127.88, 127.59, 127.04, 126.06, 123.22, 120.15, 111.63, 111.55, 103.85, 92.90, 87.72, 58.67, 56.77, 55.18, 37.73, 32.50, 5.44.

IR (cm<sup>-1</sup>):  $\nu$  = 3413, 2940, 2849, 2180, 1633, 1483, 1212, 995, 701.

HRMS: (ESI-TOF)  $m/z$  = [(M+H)]<sup>+</sup> = 358.1801 calculated for C<sub>24</sub>H<sub>24</sub>NO<sub>2</sub>; Found 358.1797.

### 3-(2-methoxy-1-phenyl-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-5-methyl-1H-indole (2.24b)



**Procedure:** Compound **2.23** (50 mg, 0.22 mmol) was added to a vial equipped with a stir bar. Toluene (1.1 ml) was added followed by the addition of 5-methylindole (34 mg, 0.26 mmol). The solution was cooled to -20 °C and Py•TfOH (0.13 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 43 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub>, once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 10% EtOAc to afford compound **2.24b** as yellow fluffy solids (46 mg, 62 % yield, 8:1 rr).

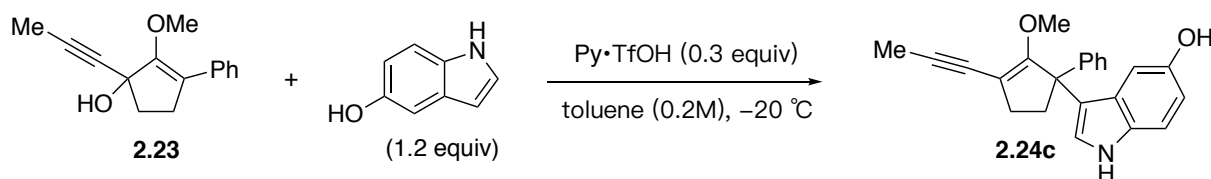
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.86 (s, 1H), 7.33 (d,  $J$  = 7.5 Hz, 2H), 7.27 – 7.18 (m, 3H), 7.10 (s, 1H), 6.97 (d,  $J$  = 8.4 Hz, 1H), 6.93 (d,  $J$  = 2.4 Hz, 1H), 4.04 (s, 4H), 2.71 – 2.64 (m, 1H), 2.55 – 2.46 (m, 3H), 2.34 (s, 3H), 1.98 (s, 3H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 164.44, 145.61, 135.23, 128.15, 128.05, 127.88, 127.62, 126.80, 126.04, 123.31, 122.77, 121.08, 119.82, 110.71, 92.88, 87.72, 58.70, 56.86, 38.44, 32.57, 21.58, 4.63.

IR (cm<sup>-1</sup>):  $\nu$  = 3406, 2939, 2259, 1634, 1491, 1274, 1093, 761.

**HRMS:** (ESI-TOF)  $m/z = [(M+H)]^+ = 342.1852$  calculated for  $C_{24}H_{24}NO$ ; Found 342.1848.

**3-(2-methoxy-1-phenyl-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1*H*-indol-5-ol (2.24c)**



**Procedure:** Compound **2.23** (50 mg, 0.22 mmol) was added to a vial equipped with a stir bar. Toluene (1.1 ml) was added followed by the addition of 5-hydroxyindole (35 mg, 0.26 mmol). The solution was cooled to  $-20\text{ }^{\circ}C$  and  $Py \cdot TfOH$  (0.13 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at  $-20\text{ }^{\circ}C$  for 72 h, monitored by TLC and quenched with 0.5 ml  $NEt_3$ , once completed. The crude was directly loaded into a column and purified using 100% Hexanes  $\rightarrow$  10% EtOAc to afford compound **2.24c** as yellow fluffy solids (58 mg, 77 % yield, 17:1 rr).

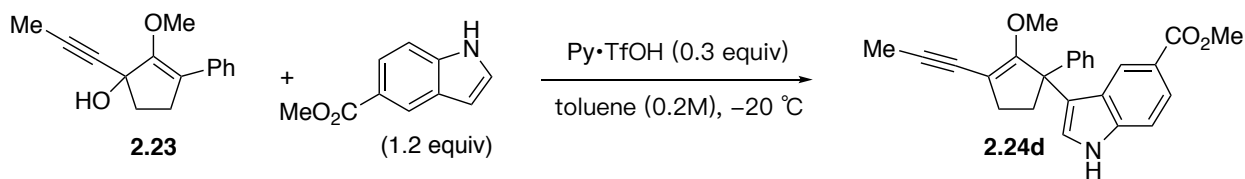
**$^1H$  NMR (400 MHz,  $CDCl_3$ )**  $\delta$  7.82 (s, 1H), 7.33 – 7.25 (m, 4H), 7.20 (t,  $J = 9.0$  Hz, 2H), 6.96 (d,  $J = 2.6$  Hz, 1H), 6.74 (d,  $J = 2.4$  Hz, 1H), 6.71 (d,  $J = 3.7$  Hz, 1H), 4.35 (s, 1H), 4.05 (s, 3H), 2.65z – 2.58 (m, 1H), 2.52 – 2.43 (m, 3H), 1.98 (s, 3H).

**$^{13}C$  NMR (125 MHz,  $CDCl_3$ )**  $\delta$  164.12, 148.72, 145.30, 132.17, 127.93, 127.58, 127.12, 126.12, 123.61, 119.67, 111.65, 111.44, 105.93, 92.86, 87.84, 58.66, 56.74, 38.27, 32.47, 4.59.

**IR ( $cm^{-1}$ ):**  $f = 3416, 2939, 2225, 1631, 1487, 1202, 1094, 908, 730$ .

**HRMS:** (ESI-TOF)  $m/z = [(M-(H_2O))]^+ = 325.1461$  calculated for  $C_{23}H_{19}NO$ ; Found 325.1594

**3-(2-methoxy-1-phenyl-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1*H*-indole-5-carboxylate (2.24d)**



**Procedure:** Compound **2.23** (50 mg, 0.22 mmol) was added to a vial equipped with a stir bar. Toluene (1.1 ml) was added followed by the addition of methyl indole-5-carboxylate (46 mg, 0.26 mmol). The solution was cooled to -20 °C and Py·TfOH (0.13 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 96 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub> once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 20% EtOAc to afford compound **2.24d** as yellow fluffy solids (53 mg, 63 % yield, 5:1 rr).

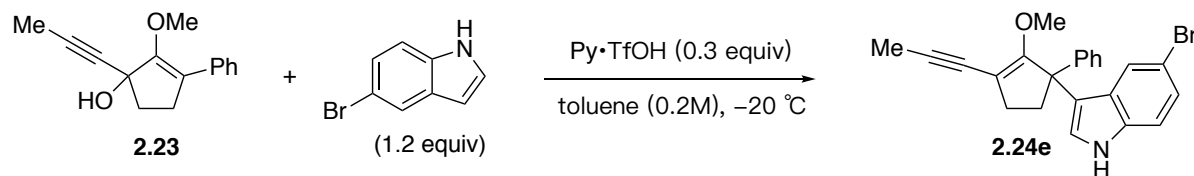
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 8.19 (s, 1H), 8.09 (s, 1H), 7.86 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.34 – 7.24 (m, 5H), 7.21 (d, *J* = 7.0 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 4.06 (s, 3H), 3.85 (s, 3H), 2.69 – 2.63 (m, 1H), 2.63 – 2.46 (m, 3H), 1.98 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 168.19, 163.81, 145.27, 139.48, 127.99, 127.44, 126.26, 126.20, 124.52, 123.72, 123.18, 121.97, 121.34, 110.74, 93.27, 87.99, 58.74, 56.75, 51.75, 38.56, 32.53, 4.62.

**IR (cm<sup>-1</sup>):** *f* = 3477, 2941, 2853, 2235, 1715, 1635, 1457, 1378, 1203, 1014, 903, 723.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 386.1750 calculated for C<sub>25</sub>H<sub>24</sub>NO<sub>3</sub>; Found 386.1754

#### 5-bromo-3-(2-methoxy-1-phenyl-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1*H*-indole (**2.24e**)





**Procedure:** Compound **2.23** (50 mg, 0.22 mmol) was added to a vial equipped with a stir bar. Toluene (1.1 ml) was added followed by the addition of 5-bromoindole (52 mg, 0.26 mmol). The solution was cooled to -20 °C and Py•TfOH (0.13 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 96 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub> once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 10% EtOAc to afford compound **2.24e** as yellow crystals (65 mg, 73 % yield, 20:1 rr).

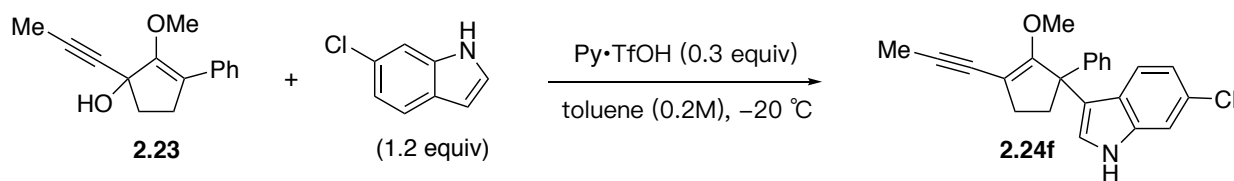
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.97 (s, 1H), 7.44 (s, 1H), 7.29 – 7.28 (m, 4H), 7.24 – 7.18 (m, 3H), 6.99 (d, *J* = 2.4 Hz, 1H), 4.06 (s, 3H), 2.66 – 2.58 (m, 1H), 2.54 – 2.47 (m, 3H), 1.99 (s, 3H).

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 163.76, 145.07, 135.50, 128.27, 128.02, 127.42, 126.29, 124.65, 123.97, 123.62, 120.24, 112.44, 112.42, 93.10, 87.98, 76.31, 58.70, 56.68, 38.44, 32.49, 4.62.

**IR (cm<sup>-1</sup>):** *f* = 3425, 2960, 2852, 2255, 1635, 1425, 1378, 1209, 1015, 903, 728.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 406.0801 calculated for C<sub>23</sub>H<sub>21</sub>BrNO; Found 406.0792.

#### 6-chloro-3-(2-methoxy-1-phenyl-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1*H*-indole (**2.24f**)



**Procedure:** Compound **2.23** (50 mg, 0.22 mmol) was added to a vial equipped with a stir bar. Toluene (1.1 ml) was added followed by the addition of 6-chloroindole (40 mg, 0.26 mmol). The solution was cooled to -20 °C and Py•TfOH (0.13 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 120 h, monitored by TLC and quenched with 0.5

ml NEt<sub>3</sub>, once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 10% EtOAc to afford compound **2.24f** as yellow fluffy solids (57 mg, 72 % yield, 20:1 rr).

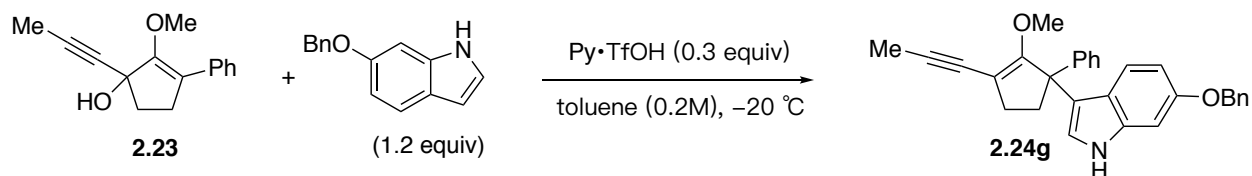
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.91 (s, 1H), 7.30 – 7.28 (m, 5H), 7.23 – 7.19 (m, 2H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.92 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.04 (s, 3H), 2.64 – 2.59 (m, 1H), 2.58 – 2.44 (m, 3H), 1.99 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 163.79, 145.22, 137.24, 127.97, 127.69, 127.45, 126.23, 125.16, 122.92, 122.54, 120.71, 119.79, 110.88, 93.05, 87.97, 76.33, 58.67, 56.71, 38.48, 32.48, 4.60.

**IR (cm<sup>-1</sup>):** *f* = 3422, 2950, 2851, 2245, 1635, 1457, 1375, 1205, 1014, 903, 720.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 362.1306 calculated for C<sub>23</sub>H<sub>21</sub>ClNO; Found 362.1294.

**6-(benzyloxy)-3-(2-methoxy-1-phenyl-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1*H*-indole (2.24g)**



**Procedure:** Compound **2.23** (50 mg, 0.22 mmol) was added to a vial equipped with a stir bar. Toluene (1.1 ml) was added followed by the addition of 6-benzyloxyindole (59 mg, 0.26 mmol). The solution was cooled to -20 °C and Py·TfOH (0.13 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 144 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub>, once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 15% EtOAc to afford compound **2.24g** as yellow oil (47 mg, 50 % yield, 14:1 rr).

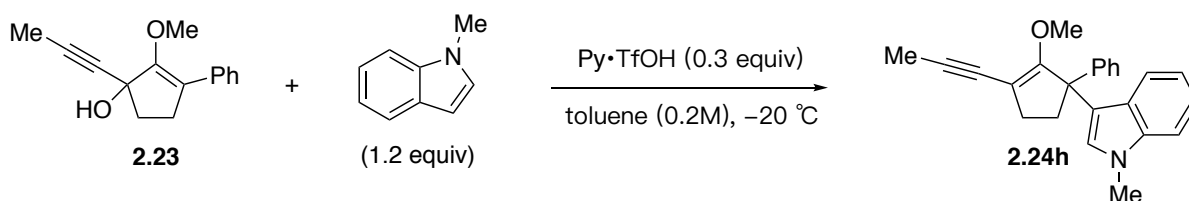
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.81 (s, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 3H), 7.30 – 7.26 (m, 2H), 7.21 (t, *J* = 8.2 Hz, 2H), 6.88 (dd, *J* = 8.2, 2.4 Hz, 2H), 6.73 (dd, *J* = 8.7, 2.3 Hz, 1H), 5.08 (s, 2H), 4.05 (s, 3H), 2.67 – 2.63 (m, 1H), 2.52 – 2.45 (m, 3H), 2.00 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 164.20, 155.36, 145.53, 137.55, 137.51, 128.52, 127.88, 127.79, 127.56, 127.46, 126.08, 122.25, 121.31, 121.19, 120.47, 109.70, 95.71, 92.83, 87.71, 76.52, 70.46, 58.67, 56.82, 38.52, 32.51, 29.69, 4.62.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3425, 3019, 2925, 2252, 1620, 1457, 1378, 1201, 1095, 903, 720.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 434.2114 calculated for C<sub>30</sub>H<sub>28</sub>NO<sub>2</sub>; Found 434.2103.

**3-(2-methoxy-1-phenyl-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1-methyl-1*H*-indole (2.24h)**



**Procedure:** Compound **2.23** (50 mg, 0.22 mmol) was added to a vial equipped with a stir bar. Toluene (1.1 ml) was added followed by the addition of *N*-methylindole (34 mg, 0.26 mmol). The solution was cooled to -20 °C and Py•TfOH (0.13 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 168 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub>, once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 15% EtOAc to afford compound **2.24h** as yellow oil (43 mg, 58 % yield, 20:1 rr).

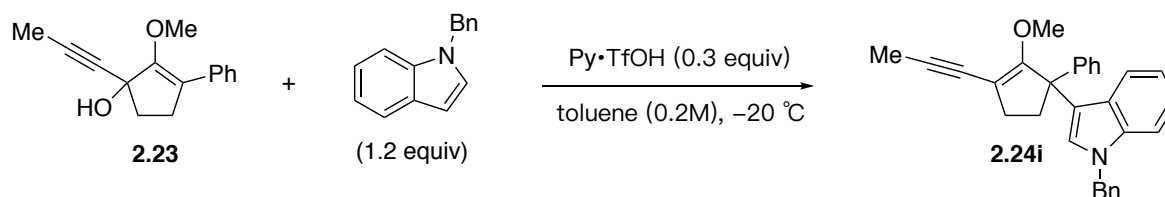
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.38 – 7.36 (m, 3H), 7.33 – 7.28 (m, 3H), 7.25 – 7.19 (m, 2H), 6.99 (t, *J* = 8.2 Hz, 1H), 6.84 (s, 1H), 4.09 (s, 3H), 3.75 (s, 3H), 2.74 – 2.68 (m, 1H), 2.66 – 2.51 (m, 3H), 2.01 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 164.30, 145.57, 137.59, 127.86, 127.57, 127.26, 126.93, 126.05, 121.59, 121.20, 118.86, 118.47, 109.08, 92.81, 87.70, 76.53, 58.69, 56.81, 38.62, 32.63, 32.50, 4.62.

**IR (cm<sup>-1</sup>):** *f* = 3425, 2920, 2850, 1618, 1425, 1315, 1205, 1014, 903, 736.

**HRMS:** (ESI-TOF) *m/z* = [(*M*+*H*)<sup>+</sup>] = 342.1852 calculated for C<sub>24</sub>H<sub>24</sub>NO; Found 342.1852.

### 3-(2-methoxy-1-phenyl-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1-benzyl-1*H*-indole (**2.24i**)



**Procedure:** Compound **2.23** (50 mg, 0.22 mmol) was added to a vial equipped with a stir bar. Toluene (1.1 ml) was added followed by the addition of *N*-benzylindole (54 mg, 0.26 mmol). The solution was cooled to -20 °C and Py•TfOH (0.13 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 168 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub>, once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 2% EtOAc to afford compound **2.24i** as yellow oil (20 mg, 22 % yield, 14:1 rr).

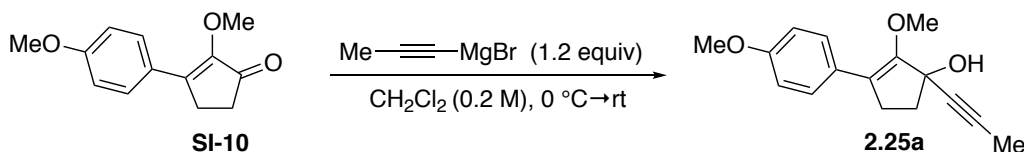
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.39 (t, *J* = 7.6 Hz, 3H), 7.36 – 7.29 (m, 5H), 7.24 (s, 1H), 7.15 (t, *J* = 8.7 Hz, 3H), 7.01 – 6.98 (m, 2H), 5.31 (s, 2H), 4.09 (s, 3H), 2.77 – 2.70 (m, 1H), 2.62 – 2.51 (m, 3H), 2.02 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 164.28, 145.63, 137.70, 137.21, 128.68, 127.88, 127.54, 127.41, 127.31, 126.75, 126.57, 126.06, 121.82, 121.38, 119.47, 118.73, 109.64, 92.86, 87.74, 76.53, 58.68, 56.83, 49.97, 38.64, 32.54, 4.60.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3435, 2940, 2852, 1618, 1420, 1325, 1265, 1018, 903, 735.

**HRMS:** (ESI-TOF)  $m/z$  = [(M+H)]<sup>+</sup> = 418.2165 calculated for C<sub>30</sub>H<sub>28</sub>NO; Found 418.2152.

**2-methoxy-3-(4-methoxyphenyl)-1-(prop-1-yn-1-yl)cyclopent-2-en-1-ol (2.25a)**



**Procedure:** An oven-dried round bottom flask was charged with compound **SI-10** (143 mg, 0.65 mmol) along with a stir bar. The flask was kept under nitrogen and dry CH<sub>2</sub>Cl<sub>2</sub> (3.3 ml) was added to the flask *via* syringe. The flask was cooled to 0 °C and propynyl magnesium bromide (1.6 ml, 0.78 mmol, 0.5M in THF) was added dropwise followed by warming to room temperature. The reaction was stirred at rt for 1h and quenched with DI H<sub>2</sub>O at 0 °C and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x15 ml). Thus, obtained crude material was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 20% EtOAc to afford compound **2.25a** as a yellow oil (144 mg, 85 % yield).

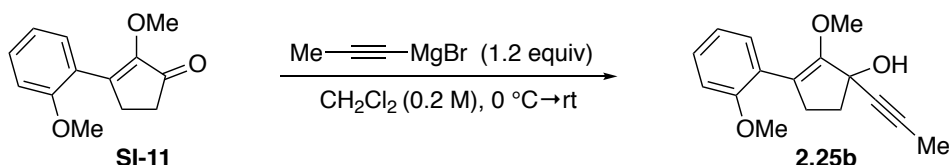
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 7.54 (d,  $J$  = 9.0 Hz, 2H), 6.88 (d,  $J$  = 9.0 Hz, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 2.72 – 2.57 (m, 2H), 2.53 – 2.47 (m, 1H), 2.33 (s, 1H), 2.21 – 2.14 (m, 1H), 1.88 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 158.46, 152.31, 128.50, 127.93, 119.01, 113.51, 81.59, 80.68, 76.43, 59.10, 55.22, 39.21, 27.71, 3.79.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3425, 2938, 2232, 1665, 1578, 1439, 1244, 1052, 753.

**HRMS:** (ESI-TOF)  $m/z$  =  $[(M+H)]^+ = 259.1328$  calculated for C<sub>16</sub>H<sub>19</sub>O<sub>3</sub>; Found 259.1319.

**2-methoxy-3-(2-methoxyphenyl)-1-(prop-1-yn-1-yl)cyclopent-2-en-1-ol (2.25a)**



**Procedure:** An oven-dried round bottom flask was charged with compound **SI-11** (168 mg, 0.77 mmol) along with a stir bar. The flask was kept under nitrogen and dry CH<sub>2</sub>Cl<sub>2</sub> (3.9 ml) was added to the flask *via* syringe. The flask was cooled to 0 °C and propynyl magnesium bromide (1.9 ml, 0.92 mmol, 0.5M in THF) was added dropwise followed by warming to room temperature. The reaction was stirred at rt for 1h and quenched with DI H<sub>2</sub>O at 0 °C and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x15ml). Thus, obtained crude material was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 10% EtOAc to afford compound **2.25b** as a yellow oil (158 mg, 79 % yield).

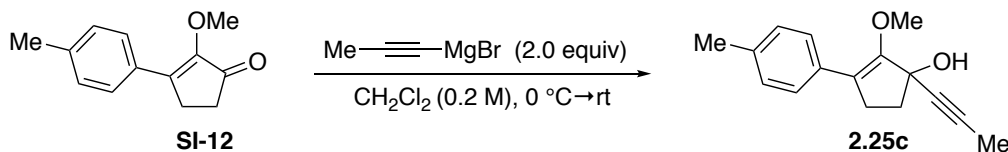
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta$  7.28 (d,  $J$  = 9.0 Hz, 1H), 7.23 (t,  $J$  = 7.8 Hz, 1H), 6.91 (t,  $J$  = 7.5 Hz, 1H), 6.86 (d,  $J$  = 8.2 Hz, 1H), 3.82 (s, 3H), 3.55 (s, 3H), 2.70- 2.65 (m, 1H), 2.59 – 2.54 (m, 2H), 2.48 - 2.43 (m, 1H), 2.20 – 2.17 (m, 1H), 1.90 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)**  $\delta$  157.21, 153.43, 130.71, 128.39, 125.68, 120.07, 113.75, 110.69, 80.84, 80.65, 76.48, 59.43, 55.39, 38.62, 30.44, 3.88.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3423, 2934, 2232, 1666, 1577, 1435, 1244, 1052, 753.

**HRMS:** (ESI-TOF)  $m/z$  =  $[(M+Na)]^+ = 281.1148$  calculated for C<sub>16</sub>H<sub>18</sub>O<sub>3</sub>; Found 281.1151.

### 2-methoxy-1-(prop-1-yn-1-yl)-3-(*p*-tolyl)cyclopent-2-en-1-ol (2.25c)



**Procedure:** An oven-dried round bottom flask was charged with compound **SI-12** (210 mg, 1.03 mmol) along with a stir bar. The flask was kept under nitrogen and dry CH<sub>2</sub>Cl<sub>2</sub> (5.2 ml) was added to the flask *via* syringe. The flask was cooled to 0 °C and propynyl magnesium bromide (4.2 ml, 2.08 mmol, 0.5M in THF) was added dropwise followed by warming to room temperature. The reaction was stirred at rt for 1h and quenched with DI H<sub>2</sub>O at 0 °C and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x15 ml). Thus, obtained crude material was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 10% EtOAc to afford compound **2.25c** as a yellow oil (144 mg, 57 % yield).

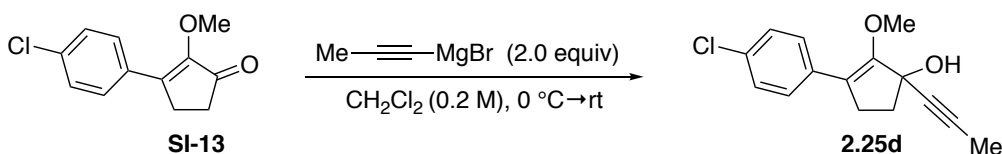
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.48 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 3.87 (s, 3H), 2.71 – 2.59 (m, 2H), 2.53 – 2.47 (m, 1H), 2.34 (s, 4H), 2.22 – 2.16 (m, 1H), 1.88 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 153.13, 136.65, 132.51, 128.80, 127.23, 119.13, 81.60, 80.69, 76.48, 59.17, 39.23, 27.83, 21.21, 3.77.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3425, 2938, 2232, 1665, 1578, 1439, 1244, 1052, 753.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 243.1379 calculated for C<sub>16</sub>H<sub>18</sub>O<sub>2</sub>; Found 243.1371.

### 3-(4-chlorophenyl)-2-methoxy-1-(prop-1-yn-1-yl)cyclopent-2-en-1-ol (2.25d)



**Procedure:** An oven-dried round bottom flask was charged with compound **SI-13** (128 mg, 0.58 mmol) along with a stir bar. The flask was kept under nitrogen and dry CH<sub>2</sub>Cl<sub>2</sub> (3 ml) was added to the flask *via* syringe. The flask was cooled to 0°C and propynyl magnesium bromide (2.3 ml, 1.15 mmol, 0.5M in THF) was added dropwise followed by warming to room temperature. The reaction was stirred at rt for 1h and quenched with DI H<sub>2</sub>O at 0 °C and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x15 ml). Thus, obtained crude material was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 10% EtOAc to afford compound **2.25d** as a yellow oil (66 mg, 44 % yield).

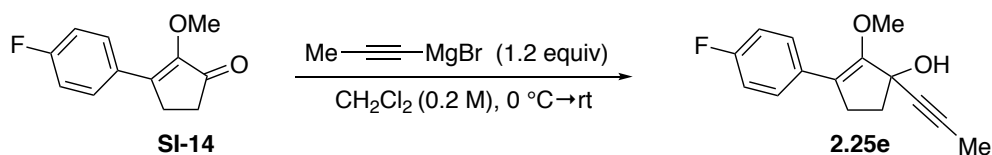
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.53 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 3.93 (s, 3H), 2.70 – 2.58 (m, 2H), 2.55 – 2.49 (m, 1H), 2.20 (ddd, *J* = 13.1, 8.4, 5.3 Hz, 1H), 1.89 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 154.12, 133.93, 132.39, 128.50, 128.24, 117.51, 82.12, 80.41, 76.31, 58.84, 39.62, 27.50, 3.73.

**IR (cm<sup>-1</sup>):** *f* = 3427, 2935, 2255, 1678, 1560, 1456, 1288, 1052, 753.

**HRMS:** (ESI-TOF) *m/z* = [(M-(H<sub>2</sub>O)+H)]<sup>+</sup> = 245.0727 calculated for C<sub>15</sub>H<sub>14</sub>ClO<sub>2</sub>; Found 245.0721.

### 3-(4-fluorophenyl)-2-methoxy-1-(prop-1-yn-1-yl)cyclopent-2-en-1-ol (**2.25e**)



**Procedure:** An oven-dried round bottom flask was charged with compound **SI-14** (79 mg, 0.38 mmol) along with a stir bar. The flask was kept under nitrogen and dry CH<sub>2</sub>Cl<sub>2</sub> (1.9 ml) was added to the flask *via* syringe. The flask was cooled to 0°C and propynyl magnesium bromide (0.9 ml,



0.46 mmol, 0.5M in THF) was added dropwise followed by warming to room temperature. The reaction was stirred at rt for 12h and quenched with DI H<sub>2</sub>O at 0 °C and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x15 ml). Thus, obtained crude material was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 15% EtOAc to afford compound **2.25e** as an yellow oil (60 mg, 64 % yield).

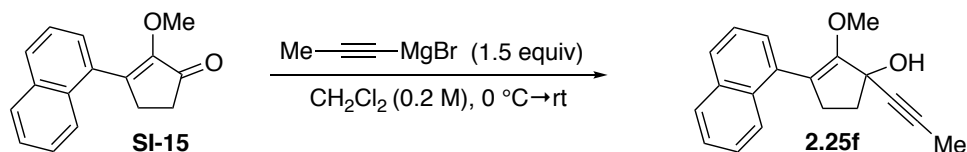
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.57 (dd, *J* = 9.0, 5.5 Hz, 2H), 7.02 (t, *J* = 8.8 Hz, 2H), 3.91 (s, 3H), 2.71 – 2.58p (m, 2H), 2.52 (ddd, *J* = 13.2, 8.0, 4.2 Hz, 1H), 2.28 (s, 1H), 2.20 (ddd, *J* = 13.1, 8.4, 5.4 Hz, 1H), 1.89 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 162.58, 160.62, 153.32, 131.48, 128.90, 117.82, 115.03, 114.86, 81.95, 80.48, 76.31, 58.88, 39.49, 27.69, 3.75.

**IR (cm<sup>-1</sup>):** *f* = 3414, 2944, 2854, 1509, 1227, 1161, 1092, 837, 568.

**HRMS:** (ESI-TOF) *m/z*: [(M+H)]<sup>+</sup> = 247.1128 calculated for C<sub>15</sub>H<sub>16</sub>FO<sub>2</sub>; found 247.1123.

### 2-methoxy-3-(naphthalen-1-yl)-1-(prop-1-yn-1-yl)cyclopent-2-en-1-ol (**2.25f**)



**Procedure:** An oven-dried round bottom flask was charged with compound **SI-15** (248 mg, 1.04 mmol) along with a stir bar. The flask was kept under nitrogen and dry CH<sub>2</sub>Cl<sub>2</sub> (5.2 ml) was added to the flask *via* syringe. The flask was cooled to 0°C and propynyl magnesium bromide (2.5 ml, 1.25 mmol, 0.5M in THF) was added dropwise followed by warming to room temperature. The reaction was stirred at rt for 1h and quenched with DI H<sub>2</sub>O at 0 °C and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x15 ml). Thus, obtained crude material was further purified with flash column chromatography

buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 15% EtOAc to afford compound **2.25f** as a yellow oil (268 mg, 93 % yield).

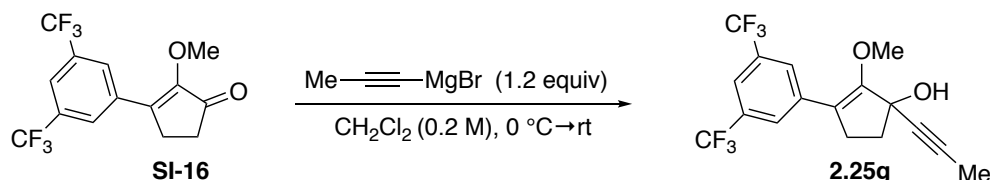
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.91 (s, 1H), 7.86 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.83 – 7.79 (m, 3H), 7.48 – 7.42 (m, 2H), 3.93 (s, 3H), 2.86 – 2.73 (m, 2H), 2.60 – 2.55p (m, 1H), 2.39 (s, 1H), 2.28 – 2.22 (m, 1H), 1.91 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 154.18, 133.26, 133.01, 132.37, 128.08, 127.50, 127.49, 126.00, 125.76, 125.64, 118.95, 81.86, 80.53, 76.51, 59.42, 39.31, 27.94, 3.81.

**IR (cm<sup>-1</sup>):** *f* = 3401, 2919, 2856, 1635, 1504, 1327, 1249, 1172, 819, 747, 475

**HRMS:** (ESI-TOF) *m/z* = [(M-H<sub>2</sub>O)+H]<sup>+</sup> = 261.1273 calculated for C<sub>19</sub>H<sub>16</sub>O; Found 261.1273.

**3-(3,5-bis(trifluoromethyl)phenyl)-2-methoxy-1-(prop-1-yn-1-yl)cyclopent-2-en-1-ol (2.25g)**



**Procedure:** An oven-dried round bottom flask was charged with compound **SI-16** (174 mg, 0.53 mmol) along with a stir bar. The flask was kept under nitrogen and dry CH<sub>2</sub>Cl<sub>2</sub> (2.7 ml) was added to the flask *via* syringe. The flask was cooled to 0 °C and propynyl magnesium bromide (1.3 ml, 0.64 mmol, 0.5M in THF) was added dropwise followed by warming to room temperature. The reaction was stirred at rt for 1h and quenched with DI H<sub>2</sub>O at 0 °C and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x15 ml). Thus, obtained crude material was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 15% EtOAc to afford compound **2.25g** as a yellow oil (149 mg, 76 % yield).

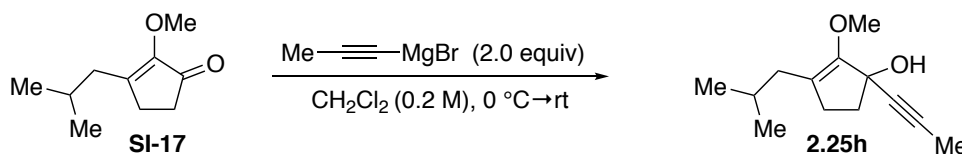
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 8.07 (s, 2H), 7.68 (s, 1H), 4.07 (s, 3H), 2.75 – 2.56 (m, 3H), 2.47 (s, 1H), 2.28 – 2.22 (m, 1H), 1.89 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 156.29, 136.79, 131.62, 131.36, 131.09, 130.83, 127.40, 126.70, 124.60, 122.44, 119.64, 115.95, 83.10, 79.71, 75.98, 58.28, 40.18, 26.79, 3.66.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3334, 2952, 2860, 2250, 1636, 1469. 1274, 1120, 892, 701.

**HRMS:** (ESI-TOF)  $m/z$  = [(M-H<sub>2</sub>O)]<sup>+</sup> = 346.0865 calculated for C<sub>17</sub>H<sub>12</sub>F<sub>6</sub>O; Found 347.0855.

### 3-isobutyl-2-methoxy-1-(prop-1-yn-1-yl)cyclopent-2-en-1-ol (**2.25h**)



**Procedure:** An oven-dried round bottom flask was charged with compound **SI-17** (200 mg, 1.19 mmol) along with a stir bar. The flask was kept under nitrogen and dry CH<sub>2</sub>Cl<sub>2</sub> (6 ml) was added to the flask *via* syringe. The flask was cooled to 0 °C and propynyl magnesium bromide (4.8 ml, 2.38 mmol, 0.5M in THF) was added dropwise followed by warming to room temperature. The reaction was stirred at rt for 1h and quenched with DI H<sub>2</sub>O at 0 °C and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x15 ml). Thus, obtained crude material was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 5% EtOAc to afford compound **2.25h** as a yellow oil (230 mg, 93 % yield).

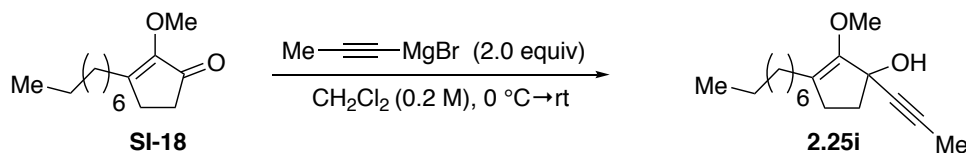
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 3.84 (s, 3H), 2.36 (ddd,  $J$  = 13.0, 8.3, 4.1 Hz, 1H), 2.28 – 2.22 (m, 2H), 2.21 – 2.14 (m, 1H), 2.07 (ddd,  $J$  = 13.4, 8.5, 5.0 Hz, 1H), 1.99 (d,  $J$  = 8.2 Hz, 2H), 1.86 (s, 3H), 1.75 (dt,  $J$  = 14.0, 7.1 Hz, 1H), 0.89 (dd,  $J$  = 6.6, 2.1 Hz, 6H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 152.83, 122.91, 81.13, 80.91, 75.81, 60.11, 39.51, 36.19, 27.89, 26.58, 22.63, 22.62, 3.76.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3455, 2938, 2232, 1635, 1578, 1439, 1248, 1052, 755.

**HRMS:** (ESI-TOF)  $m/z$  = [(M+H)]<sup>+</sup> = 209.1536 calculated for C<sub>13</sub>H<sub>22</sub>O<sub>2</sub>; Found 209.1517.

**2-methoxy-3-octyl-1-(prop-1-yn-1-yl)cyclopent-2-en-1-ol (2.25i)**



**Procedure:** An oven-dried round bottom flask was charged with compound **SI-18** (253 mg, 1.13 mmol) along with a stir bar. The flask was kept under nitrogen and dry CH<sub>2</sub>Cl<sub>2</sub> (5.6 ml) was added to the flask *via* syringe. The flask was cooled to 0 °C and propynyl magnesium bromide (4.5 ml, 2.26 mmol, 0.5M in THF) was added dropwise followed by warming to room temperature. The reaction was stirred at rt for 1h and quenched with DI H<sub>2</sub>O at 0 °C and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x15 ml). Thus, obtained crude material was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 5% EtOAc to afford compound **2.25i** as a yellow oil (103 mg, 35 % yield).

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 3.84 (s, 3H), 2.35 (ddd,  $J$  = 13.0, 8.5, 4.2 Hz, 1H), 2.29 (s, 1H), 2.29 – 2.23 (m, 1H), 2.20 – 2.14 (m, 1H), 2.14 – 2.03 (m, 3H), 1.85 (s, 3H), 1.42 – 1.37 (t,  $J$  = 7.6 Hz, 2H), 1.27 (m, 10H), 0.87 (t,  $J$  = 7.0 Hz, 3H).

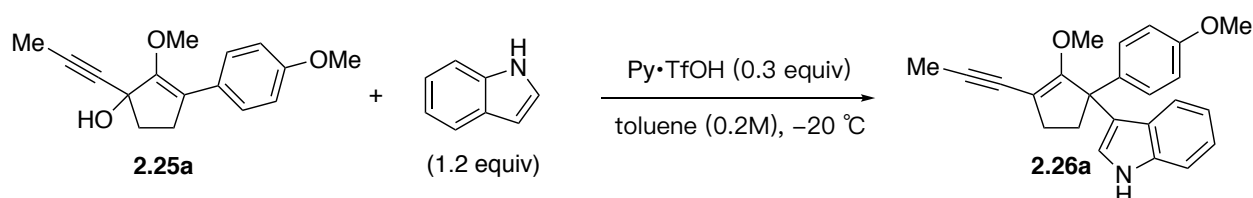
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 151.90, 123.62, 81.15, 80.81, 75.89, 60.27, 39.26, 31.84, 29.63, 29.42, 29.22, 27.64, 27.62, 27.04, 22.63, 14.06, 3.74.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3435, 2922, 2853, 2247, 1459, 1340, 1217, 1061, 878.

**HRMS:** (ESI-TOF)  $m/z = [(M+H)]^+ = 265.2162$  calculated for  $C_{17}H_{29}O_2$ ; Found 265.2143.

**3-(2-methoxy-1-(4-methoxyphenyl)-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1H-indole**

**(2.26a)**



**Procedure:** Compound **2.25a** (50 mg, 0.19 mmol) was added to a vial equipped with a stir bar. Toluene (1 ml) was added followed by the addition of indole (27 mg, 0.23 mmol). The solution was cooled to -20 °C and Py•TfOH (0.12 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 36 h, monitored by TLC and quenched with 0.5 ml  $NEt_3$ , once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 12% EtOAc to afford compound **2.25a** as yellow oil (74 mg, 99 % yield, 20:1 rr).

**$^1H$  NMR (500 MHz,  $CDCl_3$ )**  $\delta$  7.93 (s, 1H), 7.37 (d,  $J = 8.1$  Hz, 1H), 7.31 (d,  $J = 7.2$  Hz, 1H), 7.27 (d,  $J = 9.0$  Hz, 2H), 7.16 (t,  $J = 7.6$  Hz, 1H), 6.99 (t, 6.9 Hz, 1H), 6.92 (d,  $J = 2.6$  Hz, 1H), 6.83 (d,  $J = 6.7$  Hz, 2H), 4.06 (s, 3H), 3.79 (s, 3H), 2.68 – 2.63 (m, 1H), 2.57 – 2.47 (m, 3H), 2.00 (s, 3H).

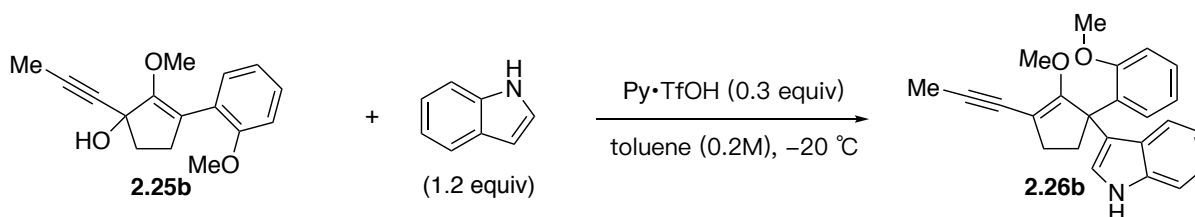
**$^{13}C$  NMR (125 MHz,  $CDCl_3$ )**  $\delta$  164.41, 157.80, 137.55, 136.88, 128.60, 126.48, 122.45, 121.59, 121.52, 120.65, 118.94, 113.19, 111.04, 92.60, 87.67, 76.57, 58.64, 56.12, 55.12, 38.40, 32.45, 4.60.

**IR ( $cm^{-1}$ ):**  $f = 3408, 3055, 2912, 2849, 2244, 1633, 1508, 1456, 1097, 795$ .

**HRMS:** (ESI-TOF)  $m/z = [(M+H)]^+ = 358.1801$  calculated for  $C_{24}H_{24}NO_2$ ; Found 358.1803.

### 3-(2-methoxy-1-(2-methoxyphenyl)-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1*H*-indole

(2.26b)



**Procedure:** Compound **2.25b** (87 mg, 0.33 mmol) was added to a vial equipped with a stir bar. Toluene (1.7 ml) was added followed by the addition of indole (47 mg, 0.23 mmol). The solution was cooled to -20 °C and Py•TfOH (0.20 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 36 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub>, once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 40% EtOAc to afford compound **2.26b** as yellow oil (82 mg, 68 % yield, 9:1 rr).

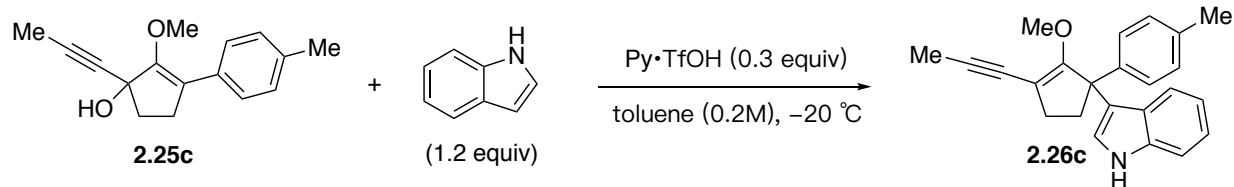
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.90 (s, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.23 (t, 7.23 Hz, 1H), 7.15 – 7.10 (m, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 2H), 6.81 (t, 6.25 Hz, 1H), 4.01 (s, 3H), 3.73 (s, 3H), 2.70 – 2.62 (m, 2H), 2.51 – 2.44 (m, 2H), 1.99 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 164.73, 157.92, 136.81, 133.15, 129.80, 127.74, 126.77, 122.28, 121.57, 121.32, 120.20, 119.91, 118.81, 111.62, 110.95, 92.15, 87.28, 58.56, 55.94, 55.29, 35.66, 32.75, 4.69.

**IR (cm<sup>-1</sup>):** *f* = 3408, 3055, 2912, 2849, 2244, 1633, 1508, 1456, 1097, 795.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 358.1801 calculated for C<sub>24</sub>H<sub>24</sub>NO<sub>2</sub>; Found 358.1804.

### 3-(2-methoxy-3-(prop-1-yn-1-yl)-1-(*p*-tolyl)cyclopent-2-en-1-yl)-1*H*-indole (2.26c)



**Procedure:** Compound **2.25c** (50 mg, 0.21 mmol) was added to a vial equipped with a stir bar. Toluene (1 ml) was added followed by the addition of indole (29 mg, 0.25 mmol). The solution was cooled to -20 °C and Py•TfOH (0.12 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 45 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub>, once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 10% EtOAc to afford compound **2.26c** as yellow oil (70 mg, 98 % yield, 18:1 rr).

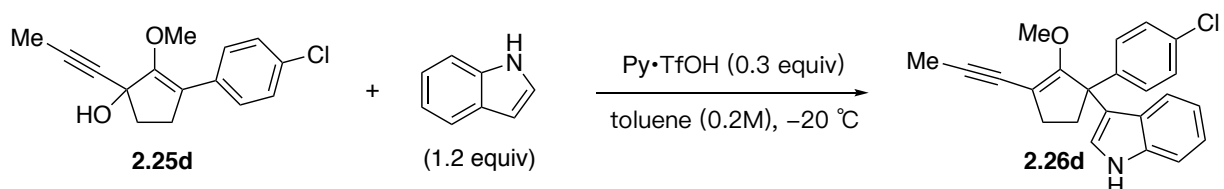
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.94 (s, 1H), 7.34 (d, *J* = 9.2 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.14 (t, 5.95 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.98 – 6.95 (m, 2H), 4.04 (s, 3H), 2.69 – 2.62 (m, 1H), 2.54 – 2.43 (m, 3H), 2.32 (s, 3H), 1.98 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 164.40, 142.44, 136.89, 135.52, 128.61, 127.47, 126.59, 122.43, 121.63, 120.63, 118.98, 111.00, 92.67, 87.63, 76.59, 58.66, 56.49, 38.47, 32.53, 20.98, 4.62.

**IR (cm<sup>-1</sup>):** *f* = 3411, 3053, 2939, 2851, 2245, 1511, 1377, 1097, 740.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 342.1852 calculated for C<sub>24</sub>H<sub>24</sub>NO; Found 342.1847.

### 3-(1-(4-chlorophenyl)-2-methoxy-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1H-indole (**2.26d**)



**Procedure:** Compound **2.25d** (50 mg, 0.19 mmol) was added to a vial equipped with a stir bar. Toluene (1 ml) was added followed by the addition of indole (27 mg, 0.23 mmol). The solution was cooled to -20 °C and Py•TfOH (0.11 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 144 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub>, once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 7.5% EtOAc to afford compound **2.26d** as yellow oil (33 mg, 48 % yield, 14:1 rr).

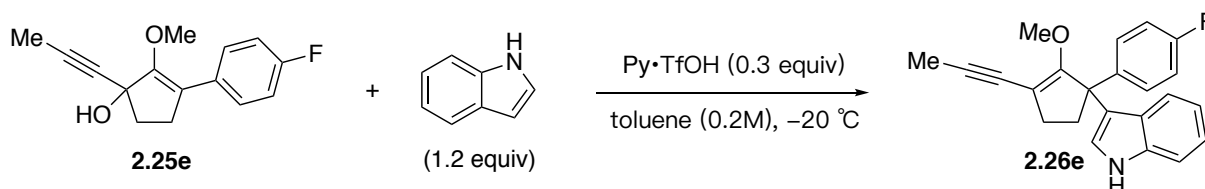
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.97 (s, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.28 (s, 1H), 7.23 (t, *J* = 8.5 Hz, 4H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.98 (dd, *J* = 14.0, 6.0 Hz, 2H), 4.04 (s, 3H), 2.67 – 2.62 (m, 1H), 2.51 – 2.46 (m, 3H), 1.98 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 163.67, 144.13, 136.91, 131.86, 129.05, 128.01, 126.34, 122.33, 121.84, 121.50, 120.06, 119.18, 116.57, 112.09, 111.08, 93.05, 87.21, 60.13, 56.45, 38.73, 33.14, 9.20.

**IR (cm<sup>-1</sup>):** *f* = 3565, 3169, 2254, 1472, 1381, 1095, 902, 722.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 362.1306 calculated for C<sub>23</sub>H<sub>21</sub>ClNO; Found 362.2510.

### 3-(1-(4-fluorophenyl)-2-methoxy-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1*H*-indole (**2.26e**)



**Procedure:** Compound **2.25e** (50 mg, 0.20 mmol) was added to a vial equipped with a stir bar. Toluene (1 ml) was added followed by the addition of indole (29 mg, 0.24 mmol). The solution was cooled to -20 °C and Py•TfOH (0.12 ml, 0.5M solution in MeCN) was added dropwise. The



reaction was stirred at -20 °C for 69 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub>, once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 10% EtOAc to afford compound **2.26e** as yellow oil (40 mg, 57 % yield, 18:1 rr).

*Gram-Scale Synthesis:*

Compound **2.25e** (1.01g, 4.10 mmol) was added to a vial equipped with a stir bar. Toluene (20.5 ml) was added followed by the addition of indole (577 mg, 4.92 mmol). The solution was cooled to -20 °C and Py•TfOH (2.46 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 65 h, monitored by TLC and quenched with 5 ml NEt<sub>3</sub>, once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 10% EtOAc to afford compound **2.26e** as yellow solids (1.24g, 88 % yield, 19:1 rr).

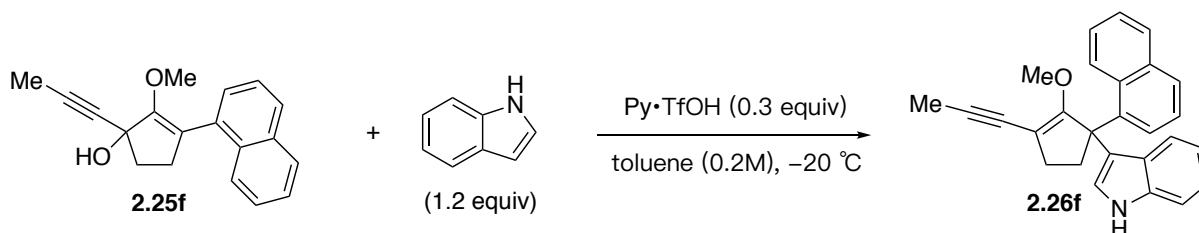
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.96 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.30 – 7.27 (m, 3H), 7.15 (t, *J* = 7.0 Hz, 1H), 6.99 – 6.97 (m, *J* = 2H), 6.94 (t, *J* = 8.8 Hz, 2H), 4.05 (s, 3H), 2.68 – 2.63 (m, 1H), 2.54 – 2.44 (m, 3H), 1.98 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 163.93, 162.31, 160.37, 141.20, 136.92, 129.16, 129.10, 126.39, 122.33, 121.79, 121.50, 120.40, 119.12, 114.66, 114.50, 111.07, 92.90, 87.93, 76.35, 58.71, 56.31, 38.43, 32.48, 4.61.

**IR (cm<sup>-1</sup>):** *f* = 3479, 2853, 1633, 1508, 1460, 1274, 1048, 9903, 835, 723.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 346.1601 calculated for C<sub>23</sub>H<sub>21</sub>FNO; Found 346.1599.

**3-(2-methoxy-1-(naphthalen-1-yl)-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1H-indole (2.26f)**



**Procedure:** Compound **2.25f** (109 mg, 0.39 mmol) was added to a vial equipped with a stir bar. Toluene (2 ml) was added followed by the addition of indole (55 mg, 0.47 mmol). The solution was cooled to -20 °C and Py•TfOH (0.24 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 168 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub>, once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 5% EtOAc to afford compound **2.26f** as yellow fluffy solids (103 mg, 70 % yield, 15:1 rr).

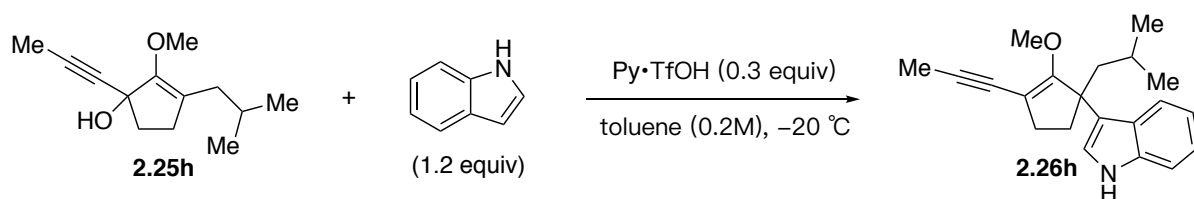
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.98 (s, 1H), 7.81 – 7.73 (m, 4H), 7.50 (d, *J* = 10.7 Hz, 1H), 7.43 – 7.42 (m, 2H), 7.37 – 7.33 (m, 2H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 4.07 (s, 3H), 2.76 – 2.71 (m, 1H), 2.66 – 2.62 (m, 1H), 2.60 – 2.50 (m, 2H), 2.00 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 164.15, 142.90, 136.93, 133.22, 132.15, 128.21, 127.45, 127.36, 126.67, 126.58, 125.68, 125.60, 125.40, 122.53, 121.73, 121.62, 120.51, 119.12, 111.03, 93.69, 88.80, 76.50, 59.53, 57.82, 39.99, 30.67, 7.33.

**IR** (cm<sup>-1</sup>): *f* = 3413, 3055, 2939, 2850, 1632, 1456, 906, 731.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 378.1852 calculated for C<sub>27</sub>H<sub>24</sub>NO; Found 390.1841.

### 3-(1-isobutyl)-2-methoxy-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1*H*-indole (**2.26h**)



**Procedure:** Compound **2.25h** (50 mg, 0.24 mmol) was added to a vial equipped with a stir bar. Toluene (1.2 ml) was added followed by the addition of indole (34 mg, 0.28 mmol). The solution was cooled to -20 °C and Py•TfOH (0.14 ml, 0.5M solution in MeCN) was added dropwise. The

reaction was stirred at -20 °C for 21 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub>, once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 10% EtOAc to afford compound **2.26h** as a yellow oil. (37 mg, 50 % yield, 20:1 rr).

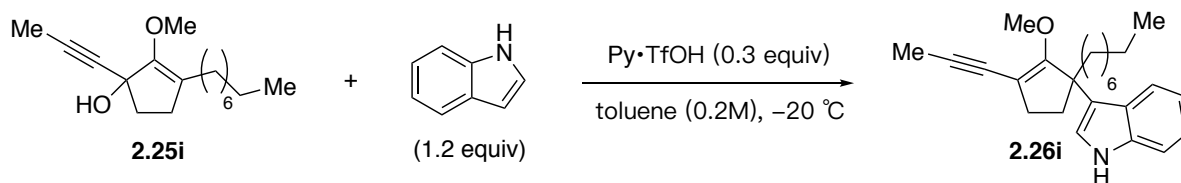
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.85 (s, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.16 (t, *J* = 6.9 Hz, 1H), 7.08 (t, *J* = 9.3 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 4.08 (s, 3H), 2.50 (t, *J* = 6.9 Hz, 2H), 2.36 – 2.30 (m, 1H), 2.13 – 2.03 (m, 2H), 1.98 (s, 3H), 1.82 – 1.75 (m, 2H), 0.94 (d, *J* = 6.6 Hz, 6H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 164.14, 136.89, 126.11, 122.38, 121.54, 120.83, 120.49, 118.96, 111.10, 91.21, 86.70, 76.89, 58.08, 51.83, 46.18, 34.22, 32.89, 25.43, 24.76, 24.14, 4.63.

**IR (cm<sup>-1</sup>):** *f* = 3404, 2950, 2851, 2235, 1635, 1456, 1203, 1102, 1075, 739.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 308.2008 calculated for C<sub>21</sub>H<sub>26</sub>NO; Found 308.2003.

### 3-(2-methoxy-1-octyl-3-(prop-1-yn-1-yl)cyclopent-2-en-1-yl)-1*H*-indole (**2.26i**)



**Procedure:** Compound **2.25i** (50 mg, 0.19 mmol) was added to a vial equipped with a stir bar. Toluene (0.9 ml) was added followed by the addition of indole (27 mg, 0.23 mmol). The solution was cooled to -20 °C and Py•TfOH (0.11 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 20 h, monitored by TLC and quenched with 0.5 ml NEt<sub>3</sub>, once completed. The crude was directly loaded into a column and purified using 100% Hexanes → 7.5% EtOAc to afford compound **2.26i** as a yellow oil. (17 mg, 25 % yield, 20:1 rr).



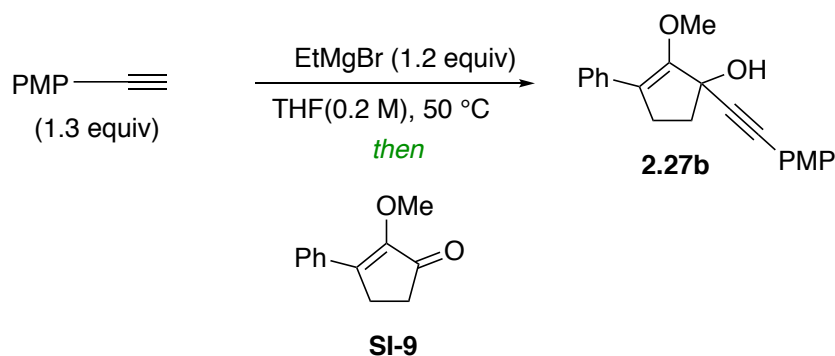
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.64 (d,  $J$  = 7.0 Hz, 2H), 7.47 – 7.45 (m, 2H), 7.37 (t,  $J$  = 7.8 Hz, 2H), 7.33 – 7.30 (m, 3H), 7.29 – 7.23 (m, 1H), 3.98 (s, 3H), 2.76 (t,  $J$  = 6.5 Hz, 2H), 2.69 (dt,  $J$  = 12.9, 6.7 Hz, 2H), 2.33 (dt,  $J$  = 13.1, 6.7 Hz, 1H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 153.32, 135.23, 131.60, 128.43, 128.24, 128.11, 127.29, 126.97, 122.53, 119.42, 90.16, 85.34, 76.53, 59.16, 39.24, 27.75.

**IR** (cm<sup>-1</sup>):  $\nu$  = 3400, 2939, 2851, 1638, 1490, 1345, 1232, 1069, 971, 755, 531

**HRMS**: (ESI-TOF)  $m/z$ : [(M-H<sub>2</sub>O)+H]<sup>+</sup> = 274.1352 calculated for C<sub>20</sub>H<sub>17</sub>O; Found 274.1304.

**2-methoxy-1-((4-methoxyphenyl)ethynyl)-3-phenylcyclopent-2-en-1-ol (2.27b)**



**Procedure:** 4-methoxyphenyl acetylene (281mg, 2.12 mmol) and THF (1.3 ml) were added into an oven-dried round bottom flask equipped with a stir bar and cooled to 0 °C. EtMgBr (0.77ml, 2.34 mmol, 3M in Et<sub>2</sub>O) was then added, and the mixture was stirred at 50 °C for 30 minutes. A solution of **SI-9** (200 mg, 1.06 mmol) in THF (4 ml) was added and the mixture was stirred at room temperature for 2h until the completion of reaction. The reaction was quenched with DI H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub> three times, organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and solvent was evaporated. Thus obtained crude material which was further purified with flash column

chromatography buffered with 1% Et<sub>3</sub>N using 5% Hexanes → 15% EtOAc in hexanes to afford compound **2.27b** as a colorless oil (267mg, 78% yield).

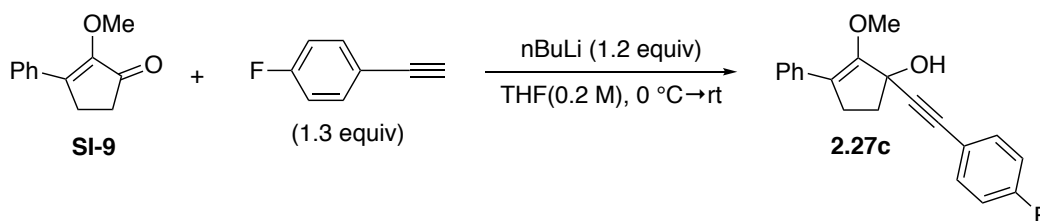
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.63 (d, *J* = 7.5 Hz, 2H), 7.36 (dd, *J* = 13.9, 8.4 Hz, 4H), 7.23 (d, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 3.97 (s, 3H), 3.81 (s, 3H), 2.76 – 2.71 (m, 2H), 2.70 – 2.63 (m, 2H), 2.34 – 2.27 (m, 1H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 159.68, 153.47, 135.29, 133.05, 128.09, 127.27, 126.90, 119.20, 114.62, 113.88, 88.77, 85.29, 76.57, 59.11, 55.24, 39.32, 27.71.

**IR** (cm<sup>-1</sup>): *f*=: 3407, 2937, 2838, 1639, 1569, 1442, 1243, 1031, 831, 695, 537

**HRMS**: (ESI-TOF) *m/z*: [(M-H<sub>2</sub>O)+H]<sup>+</sup> = 303.1379 calculated for C<sub>21</sub>H<sub>19</sub>O<sub>2</sub>; Found 303.1361.

#### 1-((4-fluorophenyl)ethynyl)-2-methoxy-3-phenylcyclopent-2-en-1-ol (**2.27c**)



**Procedure:** 4-fluorophenyl acetylene (161 mg, 1.33 mmol) and THF (4.0 ml) were added into an oven-dried round bottom flask equipped with a stir bar and cooled to 0 °C. nBuLi (0.5 ml, 1.23 mmol, 2.5M in hexanes) was then added, and the mixture was stirred at 0 °C for 30 minutes. A solution of **SI-9** (194 mg, 1.03 mmol) in THF (1.1 ml) was added and the mixture was warmed to rt stirred for 12h until the completion of reaction. The reaction was quenched with saturated NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub> three times, organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and solvent was evaporated. Thus, obtained crude material which was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 10% EtOAc to afford compound **2.27c** as a colorless oil (212 mg, 67% yield).

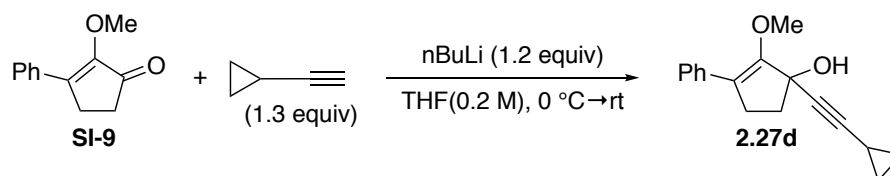
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.64 (d, *J* = 7.9 Hz, 2H), 7.45 (t, *J* = 8.55 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.03 (t, *J* = 8.7 Hz, 2H), 3.97 (s, 3H), 2.77 (t, *J* = 6.5 Hz, 2H), 2.68 (dt, *J* = 12.4, 6.0 Hz, 1H), 2.63 (s, 1H), 2.34 (dt, *J* = 13.5, 6.7 Hz, 1H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 163.57, 161.58, 153.24, 135.18, 133.56, 133.50, 128.14, 127.32, 127.04, 119.51, 118.64, 118.61, 115.65, 115.47, 89.87, 84.27, 76.58, 59.21, 39.19, 27.80.

**IR (cm<sup>-1</sup>):** *f* = 3420, 2940, 2253, 1640, 1495, 1346, 1073, 903, 698, 650.

**HRMS:** (ESI-TOF) *m/z*: [(M-H<sub>2</sub>O)+H]<sup>+</sup> = 291.1179 calculated for C<sub>20</sub>H<sub>16</sub>FO; Found 291.1176.

**1-(cyclopropylethynyl)-2-methoxy-3-phenylcyclopent-2-en-1-ol (2.27d)**



**Procedure:** Cyclopropyl acetylene (100 mg, 1.47 mmol) and THF (4.7 ml) were added into an oven-dried round bottom flask equipped with a stir bar and cooled to 0 °C. nBuLi (0.5 ml, 1.35 mmol, 2.5M in hexanes) was then added, and the mixture was stirred at 0 °C for 30 minutes. A solution of **SI-9** (213 mg, 1.13 mmol) in THF (1 ml) was added and the mixture was warmed to rt stirred for overnight until the completion of reaction. The reaction was quenched with saturated NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub> three times, organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and solvent was evaporated. Thus, obtained crude material which was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 10% EtOAc to afford compound **2.27d** as a colorless oil (195 mg, 68% yield).

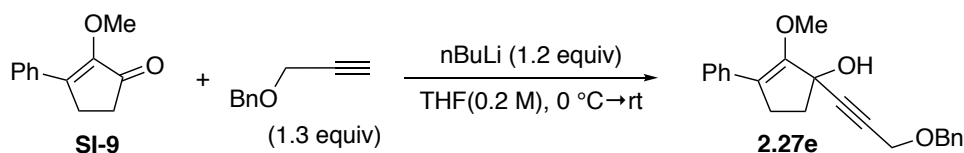
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.33 (t, *J* = 5.65 Hz, 2H), 7.22 (t, *J* = 8.7 Hz, 1H), 3.89 (s, 3H), 2.72 – 2.61 (m, 2H), 2.52 – 2.47 (m, 1H), 2.37 (s, 1H), 2.21 – 2.16 (m, 1H), 1.29 (tt, *J* = 8.2, 5.0 Hz, 1H), 0.80 – 0.76 (m, 2H), 0.71 – 0.68 (m, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 153.67, 135.38, 128.06, 127.24, 126.81, 118.77, 89.20, 76.48, 76.28, 58.99, 39.43, 27.64, 8.26, 8.24, -0.43.

**IR (cm<sup>-1</sup>):** *f* = 3592, 2941, 2263, 2150, 1958, 1275, 1034, 903, 581.

**HRMS:** (ESI-TOF) *m/z*: [(M-H)]<sup>+</sup> = 253.1223 calculated for C<sub>17</sub>H<sub>17</sub>O<sub>2</sub>; Found 253.1220.

**1-(3-benzyloxy)prop-1-yn-1-yl)- 2-methoxy-3-phenylcyclopent-2-en-1-ol (2.27e)**



**Procedure:** Benzyloxymethyl acetylene (167mg, 1.14 mmol) and THF (3.0 ml) were added into an oven-dried round bottom flask equipped with a stir bar and cooled to 0 °C. nBuLi (0.42ml, 1.05 mmol, 2.5M in hexanes) was then added, and the mixture was stirred at 0 °C for 30 minutes. A solution of **SI-9** (165 mg, 0.88 mmol) in THF (1.3 ml) was added and the mixture was warmed to rt and stirred for 12h until the completion of reaction. The reaction was quenched with saturated NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub> three times, organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and solvent was evaporated. Thus, obtained crude material which was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 10% EtOAc to afford compound **2.27e** as a colorless oil (220mg, 75% yield).



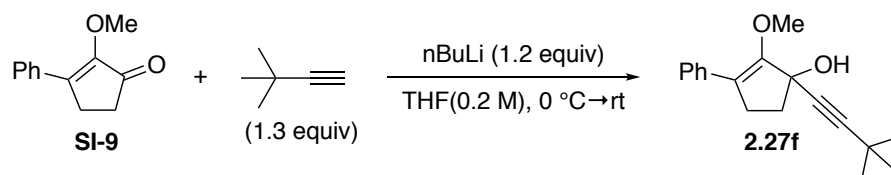
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.59 (d, *J* = 8.5 Hz, 2H), 7.36 – 7.33 (m, 6H), 7.31 – 7.29ff (m, 1H), 7.24 (d, *J* = 5.6 Hz, 1H), 4.61 (s, 2H), 4.26 (s, 2H), 3.89 (s, 3H), 2.76 – 2.65 (m, 2H), 2.57 (ddd, *J* = 12.1, 7.6, 4.3 Hz, 1H), 2.46 (s, 1H), 2.24 (ddd, *J* = 13.4, 8.2, 5.8 Hz, 1H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 153.10, 137.37, 135.20, 128.44, 128.12, 128.08, 127.89, 127.35, 127.03, 119.43, 87.69, 81.37, 71.68, 59.25, 57.52, 39.12, 27.87.

**IR (cm<sup>-1</sup>):** *f*=: 3405, 2939, 2853, 1640, 1351, 1171, 909, 738, 607.

**HRMS:** (ESI-TOF) *m/z*: [(M-H<sub>2</sub>O)+H]<sup>+</sup> = 317.1536 calculated for C<sub>22</sub>H<sub>21</sub>O<sub>2</sub>; Found 317.1533.

**1-(3,3-dimethylbut-1-yn-1-yl)- 2-methoxy-3-phenylcyclopent-2-en-1-ol (2.27f)**



**Procedure:** 2,2-dimethyl-1-propene (114 mg, 1.38 mmol) and THF (4.0 ml) were added into an oven-dried round bottom flask equipped with a stir bar and cooled to 0 °C. nBuLi (0.51 ml, 1.27 mmol, 2.5M in hexanes) was then added, and the mixture was stirred at 0 °C for 30 minutes. A solution of **SI-9** (200 mg, 1.06 mmol) in THF (1.3 ml) was added and the mixture was warmed to rt stirred for 12h until the completion of reaction. The reaction was quenched with saturated NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub> three times, organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and solvent was evaporated. Thus, obtained crude material which was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 10% EtOAc to afford compound **2.27f** as a colorless oil (206 mg, 72% yield).

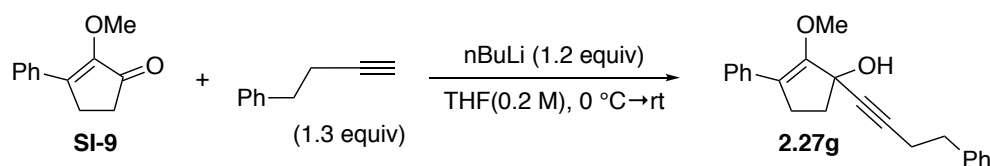
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.61 (d, *J* = 9.6 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 3.93 (s, 3H), 2.68 – 2.65 (*J* = 8.55, 2H), 2.52 – 2.47 (m, 1H), 2.33 (s, 1H), 2.25 – 2.17 (m, 1H), 1.23 (s, 9H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 153.89, 135.41, 128.08, 127.18, 126.77, 118.73, 94.27, 79.88, 76.06, 58.80, 39.62, 30.84, 27.45.

**IR (cm<sup>-1</sup>):** *f* = 3470, 2969, 2253, 1641, 1272, 1073, 904, 649.

**HRMS: (ESI-TOF)** *m/z*: [(M-H)]<sup>+</sup> = 269.1536 calculated for C<sub>18</sub>H<sub>21</sub>O<sub>2</sub>; Found 269.1533.

**2-methoxy-3-phenyl-1-(4-phenylbut-1-yn-1-yl)cyclopent-2-en-1-ol (2.27g)**



**Procedure:** Phenethyl acetylene (0.17 mL, 1.18 mmol) and THF (3.5 mL) were added into an oven-dried round bottom flask equipped with a stir bar and cooled to 0 °C. nBuLi (0.43 mL, 1.08 mmol, 2.5M in hexanes) was then added, and the mixture was stirred at 0 °C for 30 minutes. A solution of SI-9 (170 mg, 0.90 mmol) in THF (1 mL) was added and the mixture was warmed to rt stirred for 2h until the completion of reaction. The reaction was quenched with saturated NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub> three times, organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and solvent was evaporated. Thus, obtained crude material which was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 10% EtOAc to afford compound 2.27g as a colorless oil (201 mg, 70% yield).

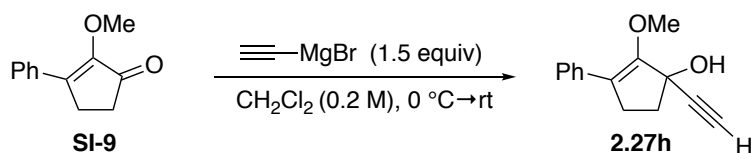
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.58 (d, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.24 – 7.18 (m, 5H), 3.81 (s, 3H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.71 – 2.59 (m, 3H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.51 – 2.46 (m, 1H), 2.29 (s, 1H), 2.20 – 2.15 (m, 1H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 153.58, 140.49, 135.38, 128.47, 128.32, 128.06, 127.25, 126.82, 126.28, 118.72, 85.39, 82.82, 76.24, 58.94, 39.45, 34.83, 27.63, 21.01.

**IR (cm<sup>-1</sup>):** *f*=: 3420, 2940, 2853, 1640, 1495, 1276, 1073, 903, 650.

**HRMS: (ESI-TOF)** *m/z*: [(M+K)]<sup>+</sup> = 357.1251 calculated for C<sub>22</sub>H<sub>22</sub>O<sub>2</sub>K; Found 357.1242.

### 1-ethynyl-2-methoxy-3-phenylcyclopent-2-en-1-ol



**Procedure:** An oven-dried round bottom flask was charged with compound **SI-9** (215mg, 1.14 mmol) along with a stir bar. The flask was kept under nitrogen and dry CH<sub>2</sub>Cl<sub>2</sub> (5.7ml) was added to the flask *via* syringe. The flask was cooled to 0°C and ethynyl magnesium bromide (3.4 ml, 1.71mmol, 0.5M in THF) was added dropwise followed by warming to room temperature. The reaction was stirred at rt for 12h and quenched with DI H<sub>2</sub>O at 0 °C and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3X). Thus, obtained crude material which was further purified with flash column chromatography buffered with 1% Et<sub>3</sub>N using 100% Hexanes → 10% EtOAc to afford compound **2.27h** as a colorless oil (180 mg, 74% yield).

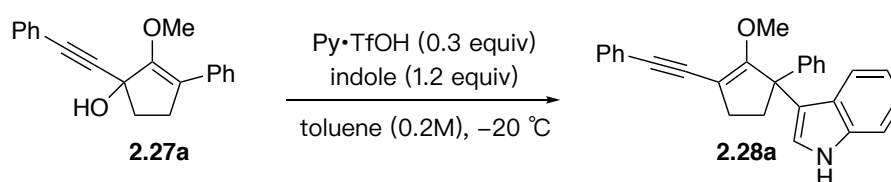
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 1H), 3.88 (s, 3H), 2.74 – 2.69 (m, 2H), 2.67 (s, 1H), 2.58 (ddd, *J* = 13.3, 7.6, 4.5 Hz, 1H), 2.49 (s, 1H), 2.26 – 2.20 (m, 1H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 152.90, 135.12, 128.13, 127.38, 127.10, 119.77, 85.09, 76.10, 73.48, 59.35, 38.92, 27.91.

**IR (cm<sup>-1</sup>):**  $\tilde{\nu}$  = 3415, 3289, 2944, 1641, 1329, 1071, 763, 668, 492.

**HRMS: (ESI-TOF)**  $m/z$ :  $[(M+H)]^+ = 215.1067$  calculated for C<sub>14</sub>H<sub>15</sub>O<sub>2</sub>; Found 215.1065.

### 3-(2-methoxy-1-phenyl-3-(phenylethynyl)cyclopent-2-en-1-yl)-1*H*-indole (**2.28a**)



**Procedure:** Compound **2.27a** (100 mg, 0.344 mmol) was added to a vial equipped with a stir bar. Toluene (1.7 ml) was added followed by the addition of indole (48 mg, 0.413 mmol). The solution was cooled to -20 °C and Py.TfOH (0.20 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 168 h, monitored by TLC and quenched with 0.5 ml Et<sub>3</sub>N. The crude was directly loaded into a flash chromatography column and purified using 100% Hexanes → 7.5% EtOAc to afford compound **2.28a** as green solids (123 mg, 92 % yield). <sup>1</sup>H NMR analysis of the crude reaction mixture indicated >20:1 rr.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.92 (s, 1H), 7.40 – 7.33 (m, 6H), 7.32 – 7.26 (m, 5H), 7.24 – 7.22 (t,  $J$  = 3.8Hz, 1H), 7.15 (t,  $J$  = 7.6 Hz, 1H), 7.00 – 6.96 (m, 2H), 4.19 (s, 3H), 2.78 – 2.70 (m, 1H), 2.68 – 2.53 (m, 3H).

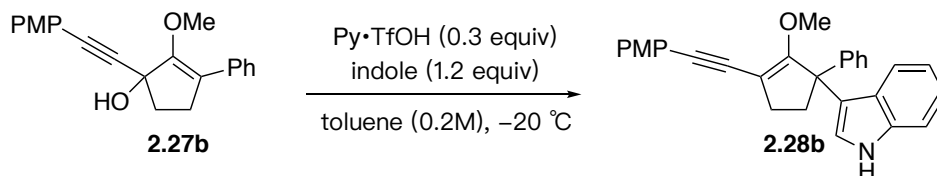
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 165.97, 145.16, 136.89, 130.76, 128.28, 127.96, 127.59, 127.55, 126.49, 126.23, 124.15, 122.50, 121.73, 121.57, 120.18, 119.09, 111.08, 92.03, 91.39, 87.09, 58.89, 57.15, 38.55, 32.37.

**IR (cm<sup>-1</sup>):**  $\tilde{\nu}$  = 3407, 3055, 2939, 2193, 1630, 1415, 1242, 906, 690.

**HRMS:** (ESI-TOF)  $m/z = [(M+H)]^+ = 390.1852$  calculated for  $C_{28}H_{23}NO$ ; Found 390.1847.

**3-(2-methoxy-3-((4-methoxyphenyl)ethynyl)-1-phenylcyclopent-2-en-1-yl)-1H-indole**

**(2.28b)**



**Procedure:** Compound **2.27b** (105 mg, 0.327 mmol) was added to a vial equipped with a stir bar. Toluene (1.6 ml) was added followed by the addition of indole (46 mg, 0.393 mmol). The solution was cooled to  $-20^\circ\text{C}$  and  $\text{Py} \cdot \text{TfOH}$  (0.20 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at  $-20^\circ\text{C}$  for 120 h, monitored by TLC and quenched with 0.5 ml  $\text{Et}_3\text{N}$ . The crude was directly loaded into a flash chromatography column and purified using 100% Hexanes  $\rightarrow$  10% EtOAc to afford compound **2.28b** as brown crystals (123 mg, 92 % yield).  $^1\text{H}$  NMR analysis of the crude reaction mixture indicated  $>20:1$  rr.

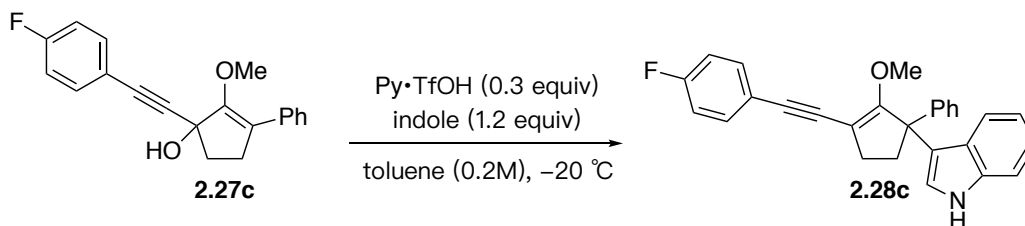
**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.95 (s, 1H), 7.40 – 7.34 (m, 6H), 7.31 (t,  $J = 8.0$  Hz, 2H), 7.24 (t,  $J = 7.3$  Hz, 1H), 7.17 (t,  $J = 7.1$  Hz, 1H), 7.02 – 6.99 (m, 2H), 6.85 (d,  $J = 9.0$  Hz, 2H), 4.19 (s, 3H), 3.82 (s, 3H), 2.78 – 2.73 (m, 1H), 2.70 – 2.56 (m, 3H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )**  $\delta$  165.32, 159.11, 145.27, 136.89, 132.20, 127.94, 127.60, 126.51, 126.19, 122.50, 121.71, 121.59, 120.29, 119.07, 116.34, 113.95, 111.06, 92.35, 91.25, 85.52, 58.85, 57.10, 55.25, 38.55, 32.43.

**IR ( $\text{cm}^{-1}$ ):**  $\nu = 3410, 2938, 2246, 1651, 1472, 1285, 903, 723$ .

**HRMS:** (ESI-TOF)  $m/z = [(M+H)]^+ = 420.1958$  calculated for  $C_{29}H_{25}NO_2$ ; Found 420.1948.

### 3-(3-((4-fluorophenyl)ethynyl)-2-methoxy-1-phenylcyclopent-2-en-1-yl)-1*H*-indole (2.28c)



**Procedure:** Compound **2.27c** (102 mg, 0.331 mmol) was added to a vial equipped with a stir bar. Toluene (1.7 ml) was added followed by the addition of indole (47 mg, 0.397 mmol). The solution was cooled to -20 °C and Py.TfOH (0.20 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 168 h, monitored by TLC and quenched with 0.5 ml Et<sub>3</sub>N. The crude was directly loaded into a flash chromatography column and purified using 100% Hexanes → 7.5% EtOAc to afford compound **2.28c** as yellow oil. (70 mg, 91% yield bsm, 52% overall). <sup>1</sup>H NMR analysis of the crude reaction mixture indicated >20:1 rr.

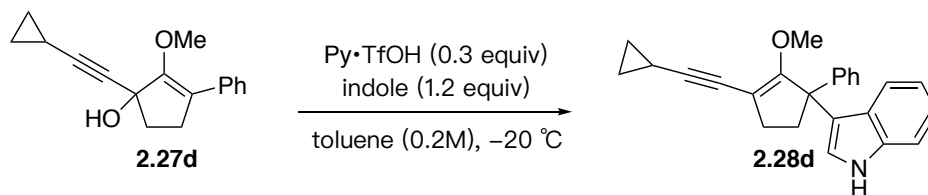
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.97 (s, 1H), 7.42 – 7.37 (m, 6H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 6.4 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.06 – 7.02 (m, 4H), 4.21 (s, 3H), 2.81 – 2.76 (m, 1H), 2.73 – 2.59 (m, 3H).

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 166.05, 163.04, 161.06, 145.11, 136.90, 132.60, 132.53, 127.98, 127.57, 126.48, 126.26, 122.49, 121.77, 121.56, 120.27, 120.24, 120.18, 119.12, 115.63, 115.46, 111.08, 91.86, 90.30, 86.69, 58.87, 57.15, 38.54, 32.35.

**IR (cm<sup>-1</sup>):** *f* = 3411, 2938, 2253, 1628, 1504, 1231, 1155, 903, 727.

**HRMS: (ESI-TOF)** *m/z* = [(*M*+*H*)<sup>+</sup>] = 408.1745 calculated for C<sub>28</sub>H<sub>22</sub>FNO; Found 408.1758.

### 3-(3-(cyclopropylethynyl)-2-methoxy-1-phenylcyclopent-2-en-1-yl)-1*H*-indole (2.28d)



**Procedure:** Compound **2.27d** (112 mg, 0.440 mmol) was added to a vial equipped with a stir bar. Toluene (2.2 ml) was added followed by the addition of indole (62 mg, 0.528 mmol). The solution was cooled to -20 °C and Py·TfOH (0.26 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 72 h, monitored by TLC and quenched with 0.5 ml Et<sub>3</sub>N. The crude was directly loaded into a flash chromatography column and purified using 100% Hexanes → 7.5% EtOAc to afford compound **2.28d** as yellow oil. (137 mg, 88% yield). <sup>1</sup>H NMR analysis of the crude reaction mixture indicated 12:1 rr.

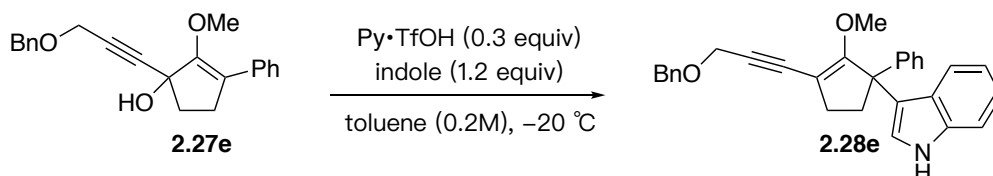
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.92 (s, 1H), 7.35 – 7.33 (m, 4H), 7.28 (d, *J* = 7.2 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.17 – 7.14 (m, 1H), 7.00 – 6.96 (m, 2H), 4.05 (s, 3H), 2.71 – 2.64 (m, 1H), 2.54 – 2.46 (m, 3H), 1.42 – 1.38 (m, 1H), 0.82 – 0.79 (m, 2H), 0.72 – 0.68 (m, 2H).

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ 164.56, 145.45, 136.87, 127.88, 127.57, 126.53, 126.09, 122.44, 121.65, 121.60, 120.45, 119.00, 111.01, 95.21, 92.72, 72.67, 58.66, 56.86, 38.44, 32.59, 8.25, 0.51.

**IR (cm<sup>-1</sup>):** *f* = 3411, 3026, 2852, 2249, 1632, 1453, 1097, 904, 728.

**HRMS: (ESI-TOF)** *m/z* = [(*M*+*H*)<sup>+</sup>] = 354.1852 calculated for C<sub>25</sub>H<sub>23</sub>NO; Found 354.1851.

### 3-(3-(3-benzyloxy)prop-1-yn-1-yl)-2-methoxy-1-phenylcyclopent-2-en-1-yl)-1*H*-indole (**2.28e**)



**Procedure:** Compound **2.27e** (110 mg, 0.329 mmol) was added to a vial equipped with a stir bar. Toluene (1.6 ml) was added followed by the addition of indole (46 mg, 0.394 mmol). The solution was cooled to -20 °C and Py.TfOH (0.19 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 168 h, monitored by TLC and quenched with 0.5 ml Et<sub>3</sub>N. The crude was directly loaded into a flash chromatography column and purified using 100% Hexanes → 7.5% EtOAc to afford compound **2.28e** as yellow oil. (84 mg, 95 % yield bsm, 59% overall).

*<sup>1</sup>H NMR analysis of the crude reaction mixture was inconclusive due to the overlapping peaks, assumed to be >20:1 rr based on isolation of only one regioisomer.*

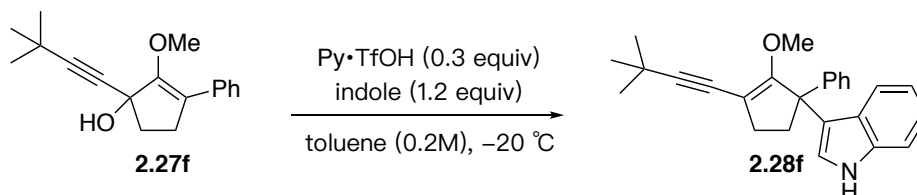
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.97 (s, 1H), 7.38 – 7.33 (m, 8H), 7.30 (t, *J* = 7.2 Hz, 3H), 7.23 (t, *J* = 7.1 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.0 – 6.97 (m, 2H), 4.63 (s, 2H), 4.35 (s, 2H), 4.11 (s, 3H), 2.76 – 2.67 (m, 1H), 2.63 – 2.52 (m, 3H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 166.05, 145.11, 137.57, 136.88, 128.41, 128.04, 127.94, 127.81, 127.55, 126.47, 126.22, 122.46, 121.73, 121.54, 120.14, 119.08, 111.06, 91.29, 87.23, 83.81, 71.59, 58.84, 58.34, 57.05, 38.48, 32.41.

**IR** (cm<sup>-1</sup>): *f* = 3479, 3070, 2946, 2254, 1631, 1320, 1094, 902, 722.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 434.2114 calculated for C<sub>30</sub>H<sub>27</sub>NO<sub>2</sub>; Found 434.2088.

### 3-(3-(3,3-dimethylbut-1-yn-1-yl)-2-methoxy-1-phenylcyclopent-2-en-1-yl)-1*H*-indole (**2.28f**)



**Procedure:** Compound **2.27f** (108 mg, 0.399 mmol) was added to a vial equipped with a stir bar. Toluene (2 ml) was added followed by the addition of indole (56 mg, 0.479 mmol). The solution



was cooled to -20 °C and Py.TfOH (0.24 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 24 h, monitored by TLC and quenched with 0.5 ml Et<sub>3</sub>N. The crude was directly loaded into a flash chromatography column and purified using 100% Hexanes → 7.5% EtOAc to afford compound **2.28f** as yellow oil. (125 mg, 85% yield). <sup>1</sup>H NMR analysis of the crude reaction mixture indicated >20:1 rr.

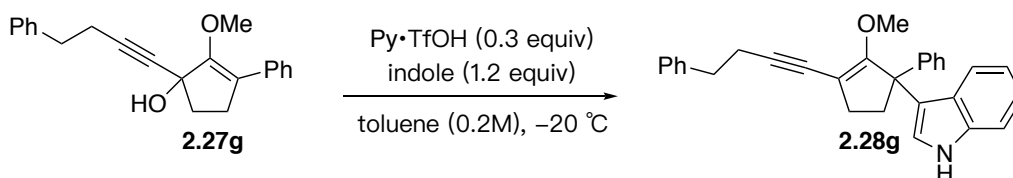
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.90 (s, 1H), 7.38 – 7.28 (m, 6H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.16 (t, *J* = 7.0 Hz, 1H), 7.01 – 6.98 (m, 2H), 4.10 (s, 3H), 2.71 – 2.65 (m, 1H), 2.58 – 2.47f (m, 3H), 1.28 (s, 9H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 163.99, 145.59, 136.86, 127.86, 127.59, 126.54, 126.05, 122.41, 121.68, 121.62, 120.45, 118.96, 111.00, 100.25, 92.86, 75.97, 58.59, 56.86, 38.49, 32.69, 30.91, 28.19.

**IR (cm<sup>-1</sup>):** *f* = 3418, 2967, 2242, 1632, 1456, 1255, 904, 727.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 370.2165 calculated for C<sub>26</sub>H<sub>27</sub>NO; Found 370.2156.

### 3-(2-methoxy-1-phenyl-3-(4-phenylbut-1-yn-1-yl)cyclopent-2-en-1-yl)-1H-indole (**2.28g**)



**Procedure:** Compound **2.27g** (102 mg, 0.320 mmol) was added to a vial equipped with a stir bar. Toluene (1.6 ml) was added followed by the addition of indole (45 mg, 0.384 mmol). The solution was cooled to -20 °C and Py.TfOH (0.19 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 168 h, monitored by TLC and quenched with 0.5 ml Et<sub>3</sub>N. The crude was directly loaded into a flash chromatography column and purified using 100% Hexanes

→ 7.5% EtOAc to afford compound **2.28g** as yellow oil. (50 mg, 47% yield bsm, 37% overall).

<sup>1</sup>H NMR analysis of the crude reaction mixture indicated 18:1 rr.

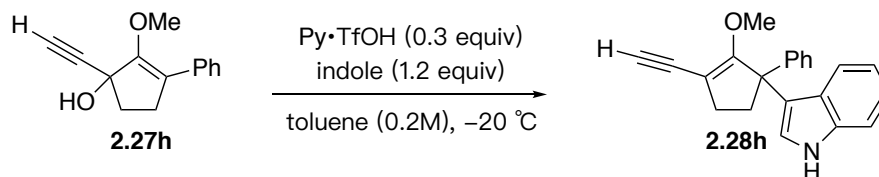
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.94 (s, 1H), 7.35 – 7.27 (m, 8H), 7.22 (m, 4H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.97 (m, 2H), 3.91 (s, 3H), 2.87 (t, *J* = 7.5 Hz, 2H), 2.67 (t, *J* = 7.5 Hz, 3H), 2.56 – 2.46 (m, 3H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 164.35, 145.44, 140.76, 136.89, 128.42, 128.32, 127.88, 127.57, 126.55, 126.21, 126.10, 122.43, 121.68, 121.62, 120.51, 119.02, 111.00, 92.44, 91.38, 78.20, 58.61, 56.87, 38.43, 35.11, 32.60, 21.83.

IR (cm<sup>-1</sup>):  $\nu$  = 3414, 2938, 2852, 2249, 1632, 1454, 1201, 1097, 904, 728.

HRMS: (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 418.2165 calculated for C<sub>30</sub>H<sub>27</sub>NO; Found 418.2161.

### 3-(3-ethynyl-2-methoxy-1-phenylcyclopent-2-en-1-yl)-1*H*-indole (**2.28h**)



Compound **2.27h** (107 mg, 0.499 mmol) was added to a vial equipped with a stir bar. Toluene (2.5 ml) was added followed by the addition of indole (70 mg, 0.599 mmol). The solution was cooled to -20 °C and Py·TfOH (0.30 ml, 0.5M solution in MeCN) was added dropwise. The reaction was stirred at -20 °C for 168 h, monitored by TLC and quenched with 0.5 ml Et<sub>3</sub>N. The crude was directly loaded into a flash chromatography column and purified using 100% Hexanes → 7.5% EtOAc to afford compound **2.28h** as yellow oil. (14 mg, 31% yield bsm, 9% overall). <sup>1</sup>H NMR analysis of the crude reaction mixture indicated 6:1 rr.

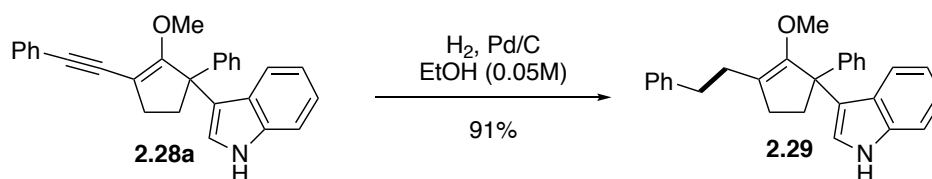
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.97 (s, 1H), 7.36 – 7.32 (m, 4H), 7.30 – 7.28 (m, 2H), 7.23 – 7.20 (m, 1H), 7.17 – 7.14 (m, 1H), 6.99 – 6.96 (m, 2H), 4.11 (s, 3H), 3.04 (s, 1H), 2.73 – 2.66 (m, 1H), 2.60 – 2.51 (m, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 166.94, 145.01, 136.91, 127.96, 127.56, 126.49, 126.26, 122.44, 121.79, 121.57, 120.14, 119.14, 111.06, 90.69, 81.36, 79.50, 58.87, 57.09, 38.50, 32.36.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3425, 2938, 2238, 1665, 1578, 1439, 1244, 1052, 755.

**HRMS:** (ESI-TOF)  $m/z$  = [(M+H)<sup>+</sup>] = 314.1539 calculated for C<sub>22</sub>H<sub>19</sub>NO; Found 314.1540.

### 3-(2-methoxy-3-phenethyl-1-phenylcyclopent-2-en-1-yl)-1H-indole (2.29)



**Procedure:** Compound 2.28a (100 mg, 0.26 mmol) was dissolved in EtOH (5.1 mL), and Pd/C (155 mg) was then added. The reaction mixture was stirred at room temperature under a hydrogen balloon for 24 hours until the completion of reaction, as monitored by TLC. The suspension was then filtered through a pad of celite and washed with EtOAc. After concentrating the filtrate in vacuo, the crude residue was further purified by flash column chromatography with 95:5 hexanes: EtOAc to afford product 2.29 as a colorless oil (92 mg, 91% yield).

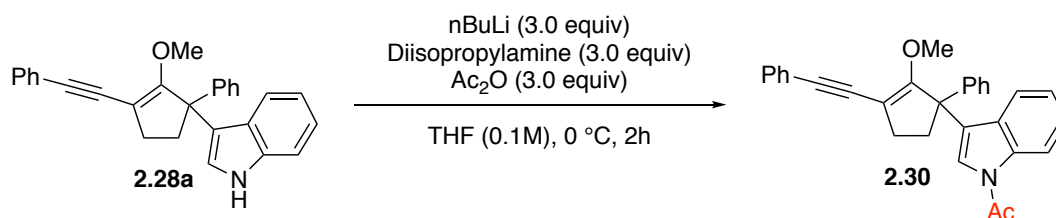
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 7.92 (s, 1H), 7.38 – 7.33 (m, 5H), 7.31 – 7.28 (m, 5H), 7.22 (t,  $J$  = 10 Hz, 2H), 7.18 (t,  $J$  = 8 Hz, 1H), 7.02 – 6.95 (m, 2H), 3.21 (s, 3H), 2.87 (t,  $J$  = 7.7 Hz, 2H), 2.74 – 2.61 (m, 4H), 2.51 – 2.36 (m, 2H)

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 157.04, 146.85, 142.08, 136.91, 128.52, 128.30, 127.76, 127.74, 126.66, 125.81, 125.77, 122.59, 121.65, 121.60, 121.51, 119.34, 118.88, 110.96, 60.38, 55.99, 38.29, 34.12, 29.59, 29.22.

IR (cm<sup>-1</sup>):  $\nu$  = 3415, 3057, 2941, 1601, 1456, 1098, 1014, 903, 724, 649.

HRMS: (ESI-TOF)  $m/z$  = [(M+H)]<sup>+</sup> = 394.2165 calculated for C<sub>28</sub>H<sub>28</sub>NO; Found 394.2170.

**1-(3-(2-methoxy-1-phenyl-3-(phenylethynyl)cyclopent-2-en-1-yl)-1*H*-indol-1-yl)ethan-1-one**  
**(2.30)**



**Procedure:** A solution of diisopropylamine (0.22 mL, 1.54 mmol) in THF (2.5 mL) was cooled to 0°C. n-BuLi (0.62 mL, 2.5M in hexane) was then added dropwise. After stirring for 30 minutes, a solution of compound **2.28a** (200 mg, 0.51 mmol) in THF (2.6 mL) was added dropwise. Upon further stirring for 60 minutes, acetic anhydride (0.15 mL, 1.54 mmol) was added. The reaction was continued for another 60 minutes until the completion of reaction, as monitored by TLC. The reaction was then quenched with saturated aqueous solution of NH<sub>4</sub>Cl (10 mL), and the mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O (50 mL, 1:1). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). The combined organic layers were then washed thoroughly with water, followed by brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The crude material was further purified by flash column chromatography with 92.5:7.5 hexanes: EtOAc to afford compound **2.30** (192 mg, 87%) as a colorless oil.

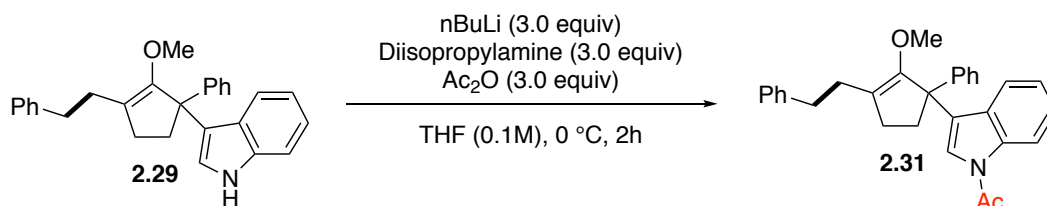
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 8.46 (d, *J* = 28.1 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 3H), 7.32-7.28 (m, 5H), 7.24 (s, 1H), 7.21 (s, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 4.18 (s, 3H), 2.73 – 2.61 (m, 4H), 2.59 (s, 3H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 168.45, 164.51, 143.76, 136.52, 130.81, 129.49, 128.32, 128.22, 127.77, 127.36, 126.72, 126.62, 124.89, 123.89, 123.13, 123.02, 121.70, 116.53, 92.93, 91.97, 86.40, 59.08, 56.89, 37.61, 32.37, 24.05.

**IR (cm<sup>-1</sup>):** *f* = 3052, 2930, 2865, 2245, 1699, 1601, 1385, 1229, 903, 722

**HRMS:** (ESI-TOF) *m/z* = [(*M*+*H*)]<sup>+</sup> = 432.1958 calculated for C<sub>30</sub>H<sub>26</sub>NO<sub>2</sub>; Found 432.1965.

**1-(3-(2-methoxy-3-phenylethyl-1-phenylcyclopent-2-en-1-yl)-1*H*-indol-1-yl)ethan-1-one**  
**(2.31)**



**Procedure:** A solution of diisopropylamine (0.20 mL, 1.41 mmol) in THF (2.5 mL) was cooled to 0°C. n-BuLi (0.56 mL, 2.5M in hexane) was then added dropwise. After stirring for 30 minutes, a solution of compound **2.29** (185 mg, 0.47 mmol) in THF (2.6 mL) was added dropwise. Upon further stirring for 60 minutes, acetic anhydride (0.13 mL, 1.41 mmol) was added. The reaction was continued for another 60 minutes until the completion of reaction, as monitored by TLC. The reaction was then quenched with saturated aqueous solution of NH<sub>4</sub>Cl (10 mL), and the mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O (50 mL, 1:1). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). The combined organic layers were then washed thoroughly with water, followed by brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The crude material was further purified by

flash column chromatography with 90:10 hexanes: EtOAc to afford compound **2.31** (153 mg, 75%) as a yellow oil.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 8.49 (d, *J* = 8.4 Hz, 1H), 7.34 – 7.28 (m, 10H), 7.24 – 7.22 (m, 2H), 7.13 (dt, *J* = 15.0, 7.2 Hz, 2H), 3.20 (s, 3H), 2.90 – 2.83 (m, 2H), 2.71 – 2.64 (m, 2H), 2.63 (s, 3H), 2.62 – 2.32 (m, 3H), 2.45 – 2.38 (m, 1H).

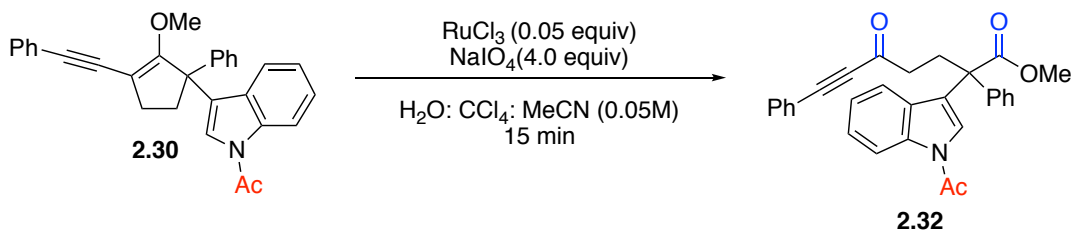
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 168.62, 156.28, 145.61, 141.82, 136.52, 129.71, 128.44, 128.33, 128.02, 127.97, 127.45, 126.24, 125.96, 124.73, 123.02, 122.96, 121.81, 120.03, 116.55, 60.71, 55.88, 37.41, 34.06, 29.80, 29.28, 24.09.

**<sup>13</sup>C NMR DEPT 135 (125 MHz, CDCl<sub>3</sub>)** δ 128.48, 128.41, 128.06, 127.48, 126.13, 125.52, 124.77, 123.66, 123.00, 122.38, 117.04, 60.75, 37.45, 33.66, 29.84, 29.31, 24.13.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3058, 2932, 2843, 1699, 1601, 1385, 1229, 903, 722

**HRMS:** (ESI-TOF) *m/z* = [(*M*+*H*)]<sup>+</sup> = 436.2271 calculated for C<sub>30</sub>H<sub>30</sub>NO<sub>2</sub>; Found 436.2275.

**methyl 2-(1-acetyl-1*H*-indol-3-yl)-5-oxo-2,7-diphenylhept-6-ynoate (**2.32**)**



**Procedure:** Compound **2.30** (103 mg, 0.24 mmol) was dissolved in a mixture of H<sub>2</sub>O/CCl<sub>4</sub>/CH<sub>3</sub>CN (1.3:1:1, 0.05 M). NaIO<sub>4</sub> (204 mg, 0.95 mmol) was then added, followed by RuCl<sub>3</sub> (2.5 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 15 min until the completion of reaction, as monitored by TLC. The reaction mixture was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5mL), stirred for 15 min, and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 15 mL).

The combined organic layers were then washed with water, followed by brine, and then concentrated in vacuo. The crude residue was further purified by flash column chromatography with 50:50 hexanes: CH<sub>2</sub>Cl<sub>2</sub> to afford product **2.32** (68 mg, 61% yield) as a yellow oil.

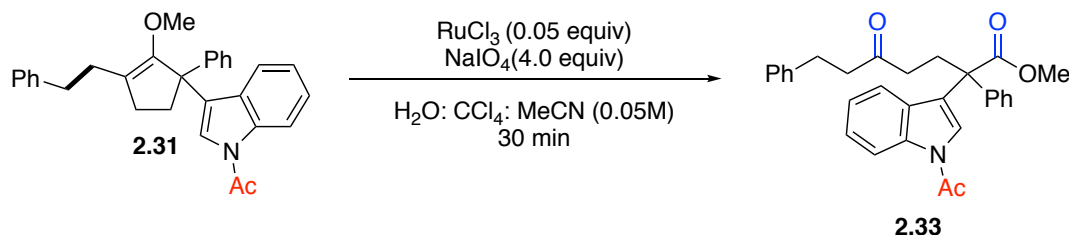
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ 8.45 (d, *J* = 8.2 Hz, 1H), 7.72 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.37 – 7.27 (m, 9H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 3.71 (s, 3H), 2.95 (t, *J* = 7.9 Hz, 2H), 2.69 (s, 3H), 2.66 – 2.51 (m, 2H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)** δ 186.62, 173.44, 168.57, 140.00, 136.28, 132.99, 130.74, 128.61, 128.58, 128.48, 127.93, 127.53, 125.11, 124.88, 123.29, 122.75, 121.68, 119.74, 116.49, 90.89, 87.65, 54.60, 52.62, 41.98, 30.84, 24.16.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3049, 2941, 2853, 2219, 1725, 1618, 1458, 1229, 906, 730.

**HRMS:** (ESI-TOF) *m/z* = [(M+H)]<sup>+</sup> = 464.1856 calculated for C<sub>30</sub>H<sub>26</sub>NO<sub>4</sub>; Found 464.1862.

#### methyl 2-(1-acetyl-1*H*-indol-3-yl)-5-oxo-2,7-diphenylheptanoate (**2.33**)



**Procedure:** Compound **2.31** (119 mg, 0.27 mmol) was dissolved in a mixture of H<sub>2</sub>O/CCl<sub>4</sub>/CH<sub>3</sub>CN (1.3:1:1, 0.05 M). NaIO<sub>4</sub> (234 mg, 1.09 mmol) was then added, followed by RuCl<sub>3</sub> (3 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 30 min until the completion of reaction, as monitored by TLC. The reaction mixture was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5mL), stirred for 15 min, and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 15 mL). The combined organic layers were then washed with water, followed by brine, and then

concentrated in vacuo. The crude residue was further purified by flash column chromatography with 95:5 hexanes: EtOAc to afford product **2.33** (78 mg, 61% yield) as a yellow oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta$  8.45 (d,  $J$  = 8.3 Hz, 1H), 7.67 (s, 1H), 7.31 – 7.27 (m, 6H), 7.22 (d,  $J$  = 7.5 Hz, 2H), 7.15 (t,  $J$  = 7.3 Hz, 1H), 7.09 (d,  $J$  = 6.7 Hz, 2H), 7.03 (t,  $J$  = 8.08 Hz, 1H), 6.91 (d,  $J$  = 7.9 Hz, 1H), 3.67 (s, 3H), 2.83 – 2.76 (m, 4H), 2.67 (s, 3H), 2.60 (t,  $J$  = 8.2 Hz, 2H), 2.37 – 2.20 (m, 2H)

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)**  $\delta$  209.06, 173.56, 168.52, 140.83, 140.18, 136.23, 128.65, 128.39, 128.34, 128.19, 127.92, 127.36, 126.04, 125.04, 124.66, 123.22, 123.06, 121.75, 116.42, 54.58, 52.48, 44.29, 39.14, 30.74, 29.69, 24.10.

**IR (cm<sup>-1</sup>):**  $\nu$  = 3425, 2938, 2232, 1722, 1698 1578, 1439, 1244, 1052, 721.

**HRMS:** (ESI-TOF)  $m/z$  = [(M+H)]<sup>+</sup> = 468.2169 calculated for C<sub>30</sub>H<sub>30</sub>NO<sub>4</sub>; Found 468.2172.

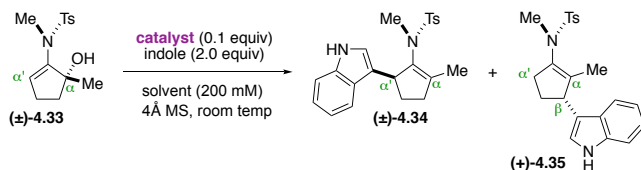
## 5.3 Experimental Procedures for Enantioselective $\beta$ -functionalization of Enamides

### 5.3.1 General Optimization Procedures

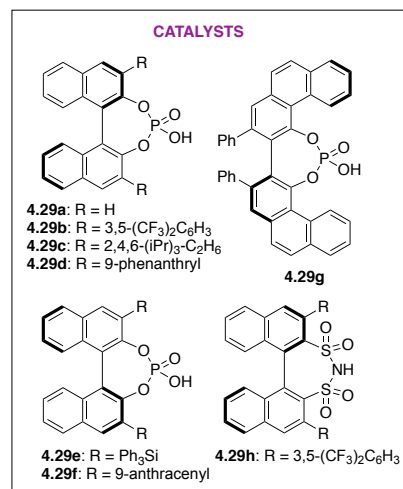
Unless otherwise noted, into an oven-dried 2.5 mL vial or 5 mL round bottom flask containing 4Å MS and magnetic stir bar, tertiary alcohol starting material (20 mg, 1.0 equiv) was dissolved in anhydrous solvent (0.2 M concentration based on starting material). Indole (2.0 equiv) was then added in one portion, followed by addition of chiral Brønsted acid (10 mol%), and the reaction mixture was let to stir in room temperature and monitored using TLC. After completion, the mixture was quenched with 0.5 mL of Et<sub>3</sub>N and loaded to flash column chromatography immediately, and eluted with hexanes:EtOAc.



### 5.3.1.1 Initial Optimization Studies



entry	catalyst	solvent	time (h)	ratio of (±)-9 : (+)-10 <sup>[a]</sup>	enantiomeric ratio <sup>[b]</sup>	yield (%) <sup>[c]</sup>
1	4.29a	toluene	48	1 : 1.9	53 : 47	44
2	4.29b	toluene	48	1 : 3.2	53 : 47	67
3	4.29c	toluene	48	1 : 5.7	52 : 48	51 <sup>[d]</sup>
4	4.29d	toluene	15	1 : 4.9	60 : 40	70
5	4.29e	toluene	48	1 : 2.5	50 : 50	52
6	4.29f	toluene	168	-	-	nr
7	4.29g	toluene	168	-	-	nr
8	4.29h	toluene	1	1 : 2.3	50 : 50	70
9	4.29c	<i>o</i> -xylene	48	1 : 4.9	59 : 41	74
10	4.29c	<i>m</i> -xylene	48	1 : 4.6	60 : 40	41
11	4.29c	<i>p</i> -xylene	48	1 : 6.1	58 : 42	56
12	4.29c	trifluorotoluene	48	1 : 5.3	56 : 44	44
13	4.29c	mesitylene	120	1 : 10	59 : 41	48
14	4.29c	benzene	48	1 : 7.3	60 : 40	63
15	4.29c	fluorobenzene	24	1 : 8.1	59 : 41	55
16	4.29c	chlorobenzene	17	1 : 3.5	59 : 41	25
17	4.29c	TBME	168	1 : 4	56 : 44	22
18	4.29c	toluene:Hx (1:3)	48	1 : 4.9	59 : 41	67
19	4.29c	IPA:tBuOH (1:1)	168	-	-	nr
20	4.29c	THF	168	-	-	nr
21	4.29c	EtOAc	168	-	-	nr
22	4.29c	MeCN	168	-	-	nr
23	4.29c	DCE	24	1 : 4.6	50 : 50	61
24	4.29c	CH <sub>2</sub> Cl <sub>2</sub>	24	1 : 9	50 : 50	62
25	4.29c	CH <sub>2</sub> Cl <sub>2</sub> <sup>[e]</sup>	24	1 : 10	58 : 42	74
26	4.29c	CH <sub>2</sub> Cl <sub>2</sub> (no 4Å MS) <sup>[e]</sup>	24	1 : 3	52 : 48	46 <sup>[f]</sup>
27	4.29c	CH <sub>2</sub> Cl <sub>2</sub> (0.5 M) <sup>[e]</sup>	20	1 : 9	50 : 50	61

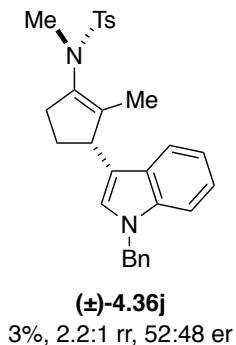
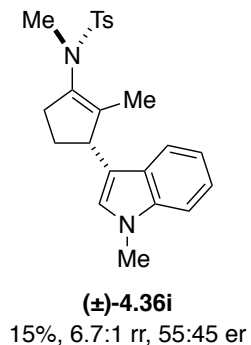
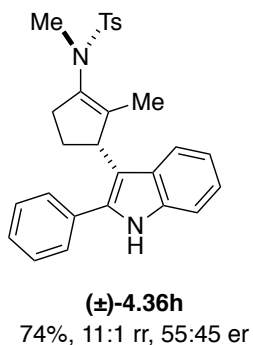
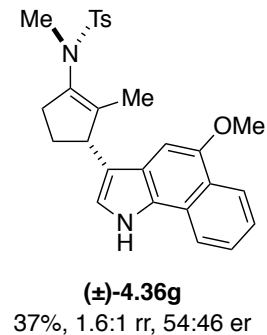
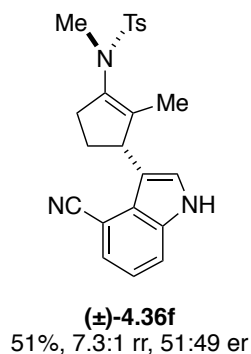
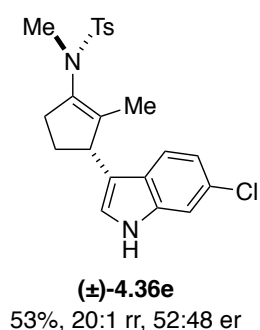
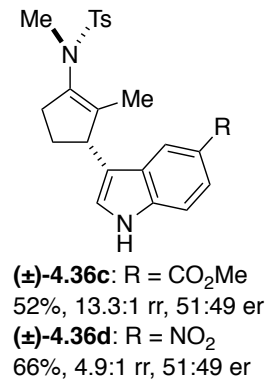
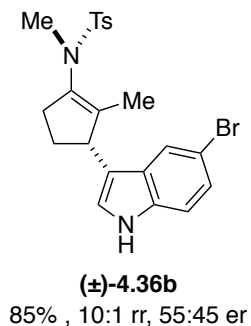
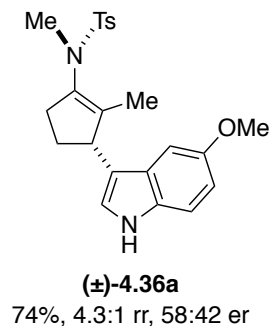
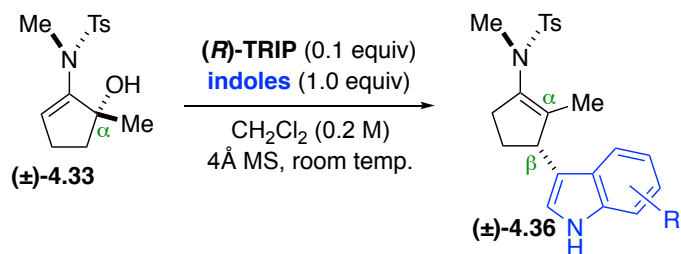


<sup>a</sup>Regiomer ratio of the products was determined by <sup>1</sup>H-NMR. <sup>b</sup>Enantiomeric ratio was determined by chiral HPLC analysis. <sup>c</sup>Combined yields of both regioisomers after flash column chromatography. <sup>d</sup>A trial with (*S*)-11c catalyst resulted the same products with similar rr, er, and % yield. <sup>e</sup>1.0 equivalent of indole was employed. <sup>f</sup>Contaminated with an inseparable byproduct.

### 5.3.2 General Procedure for Racemic Syntheses

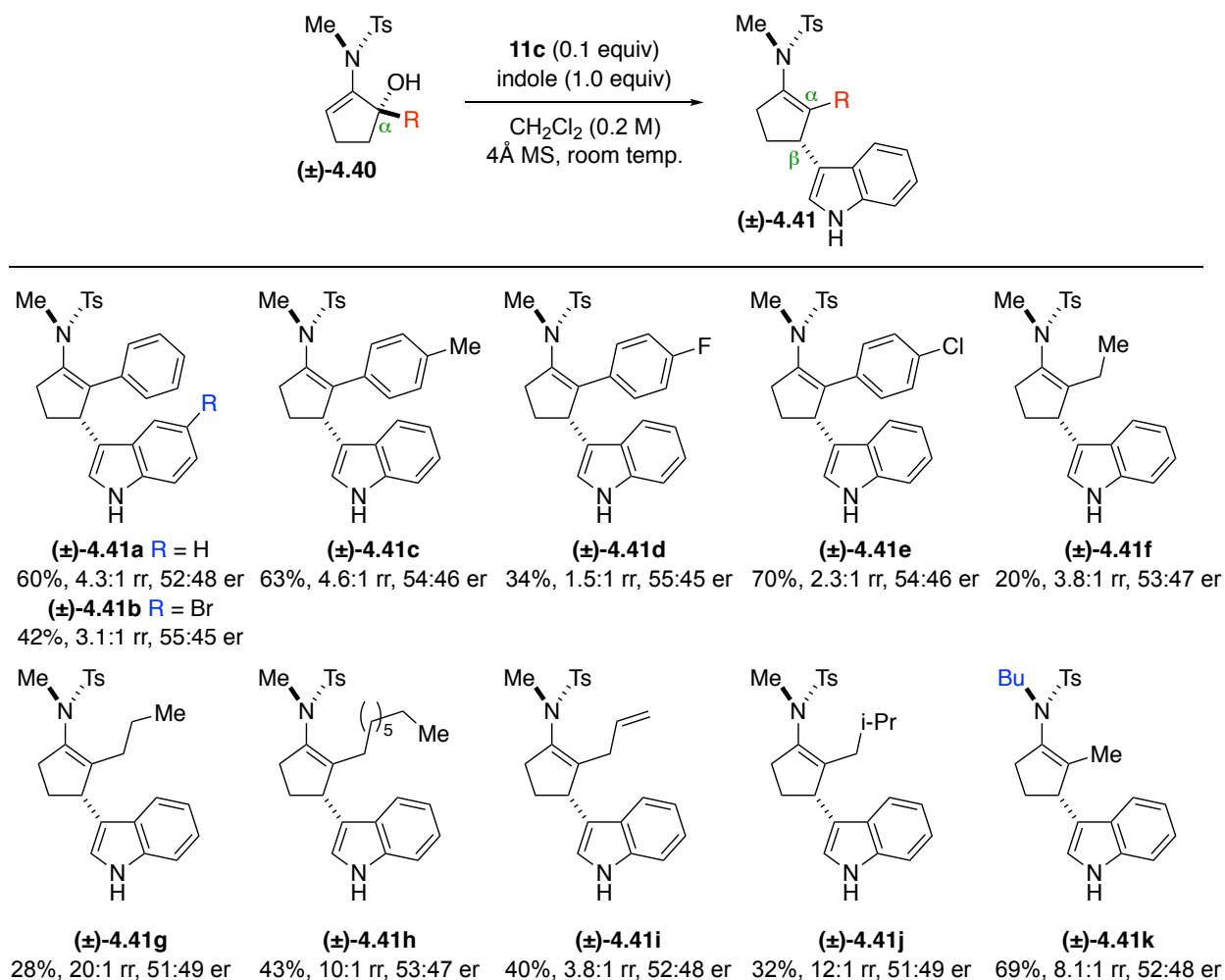
Tertiary alcohol starting material (30 mg, 1.0 equiv) and indole (1.0 equiv) were added into a pressure vessel containing 4Å MS. (*R*)-TRIP **4.29c** (0.1 equiv) was then added, and the mixture was dissolved in dry dichloromethane (0.2 M concentration based on starting material). The reaction mixture was let to stir in room temperature and monitored using TLC. After completion, the mixture was quenched with 0.5 mL of Et<sub>3</sub>N and loaded to flash column chromatography immediately, and eluted with hexanes:EtOAc.

### 5.3.2.1 Scope of Indoles Racemic Products Data <sup>[a] – [c]</sup>



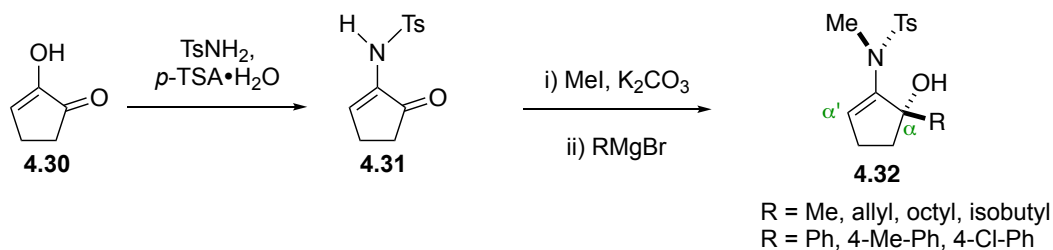
<sup>a</sup>Regiomer ratio of the products was determined by <sup>1</sup>H-NMR. <sup>b</sup>Enantiomeric ratio was determined by chiral HPLC analysis. <sup>c</sup>Combined yields of both regioisomers after flash column chromatography.

### 5.3.2.2. Scope of Substituents Racemic Products Data <sup>[a] – [c]</sup>

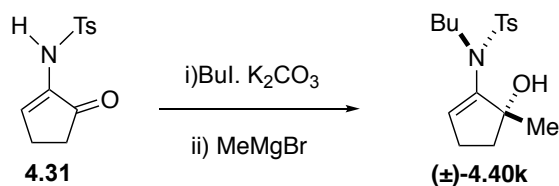


<sup>a</sup>Regiomer ratio of the products was determined by <sup>1</sup>H-NMR. <sup>b</sup>Enantiomeric ratio was determined by chiral HPLC analyses. <sup>c</sup>Combined yields of both regioisomers after flash column chromatography.

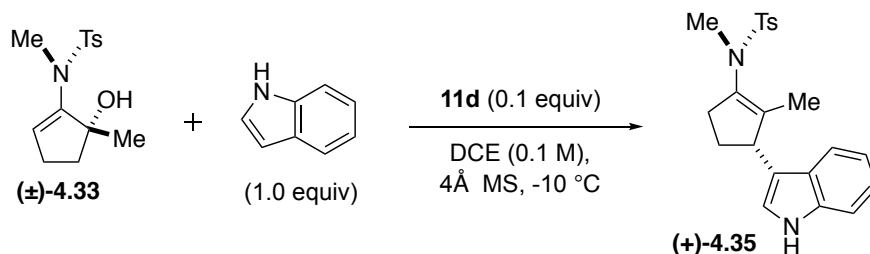
### $\alpha$ -Hydroxy- $\alpha$ -Substituent Starting Materials Synthesis:



Saputra, M. A.; Dange, N. S.; Cleveland, A. H.; Malone, J. A.; Kartika, R., *Org. Lett.* **2017**, *19*, 9, 2414-2417.



### (S)-N-(3-(1H-indol-3-yl)-2-methylcyclopent-1-en-1-yl)-N,4-dimethylbenzenesulfonamide ((+)-10)



**Procedure:** Compound **(±)-4.33** (44 mg, 0.16 mmol) and indole (18 mg, 0.16 mmol) were added into a pressure vessel containing 4Å MS (90 mg). (*R*)-catalyst **4.29d** (11 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (1.6 mL). Upon stirring at  $-10^\circ\text{C}$  for 48 hours, the reaction mixture was neutralized with 0.5 mL of  $\text{Et}_3\text{N}$ . The crude reaction mixture was then directly purified with flash column chromatography using 10%  $\rightarrow$  35% EtOAc in hexanes to give products **(+)-4.35** as yellow oil (46 mg, 77% yield, 8:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 8.11 (s, 1H), 7.80 (d,  $J$  = 8.0 Hz, 2H), 7.65 (d,  $J$  = 8.0 Hz, 1H), 7.40 (d,  $J$  = 8.0 Hz, 1H), 7.31 (d,  $J$  = 8.0 Hz, 2H), 7.24 – 7.17 (m, 1H), 7.15 (dd,  $J$  = 7.4, 7.4 Hz, 1H), 7.08 (s, 1H), 4.00 (dt,  $J$  = 6.9, 4.3, 4.3 Hz, 1H), 3.03 (s, 3H), 2.44 (s, 3H), 2.33 – 2.23 (m, 3H), 1.99 – 1.92 (m, 1H), 1.60 (s, 3H).

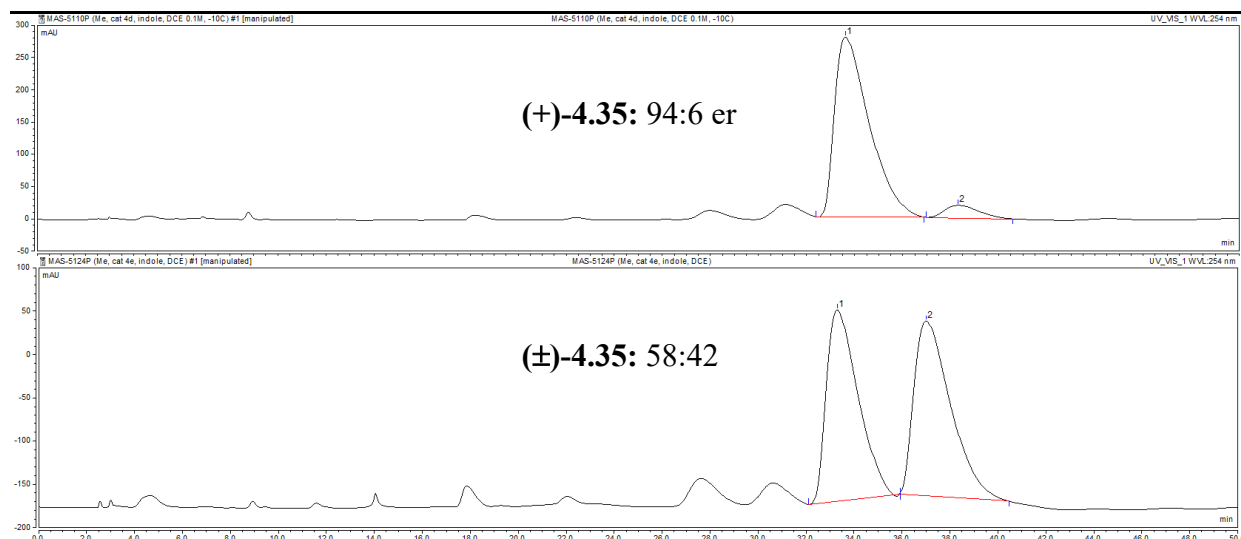
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 143.29, 140.91, 136.67, 136.29, 134.57, 129.53, 127.43, 126.66, 121.84, 121.47, 119.14, 119.01, 118.49, 111.23, 44.22, 36.11, 30.17, 29.34, 21.46, 13.18.

**IR** (cm<sup>-1</sup>):  $\nu$  = 3405, 2935, 1457, 1339, 1154, 1089, 814, 743.

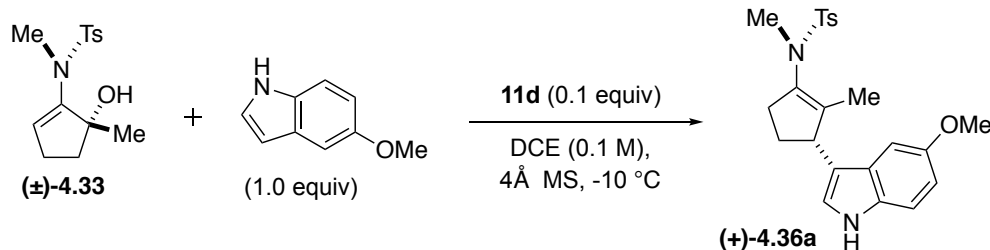
**HRMS**: (M+H)<sup>+</sup> = 381.1631 calculated for C<sub>22</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>S; experimental = 381.1625.

**Optical Rotation**:  $[\alpha]_{25}^D$  = +41.9 (c = 1.00 in CHCl<sub>3</sub>).

**HPLC**: 94:6 er using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 6.5% isopropanol in hexanes at 1 mL/min.



**(S)-N-(3-(5-methoxy-1H-indol-3-yl)-2-methylcyclopent-1-en-1-yl)-N,4-dimethylbenzenesulfonamide ((+)-4.36a)**



**Procedure:** Compound **(±)-4.33** (50 mg, 0.18 mmol) and 5-methoxyindole (26 mg, 0.18 mmol) were added into a pressure vessel containing 4Å MS (100 mg). (*R*)-catalyst **4.29d** (13 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (1.8 mL). Upon stirring at -10 °C for 112 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 20% EtOAc in hexanes to give product **(+)-4.36a** as yellow oil (67 mg, 92 % yield, 20:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.85 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.27 (dd, *J* = 8.2, 6.5 Hz, 3H), 7.09 (d, *J* = 2.3 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.91 (t, *J* = 7.0 Hz, 1H), 3.87 (s, 3H), 2.99 (s, 3H), 2.41 (s, 3H), 2.30 – 2.15 (m, 3H), 1.96 – 1.88 (m, 1H), 1.59 (s, 3H).

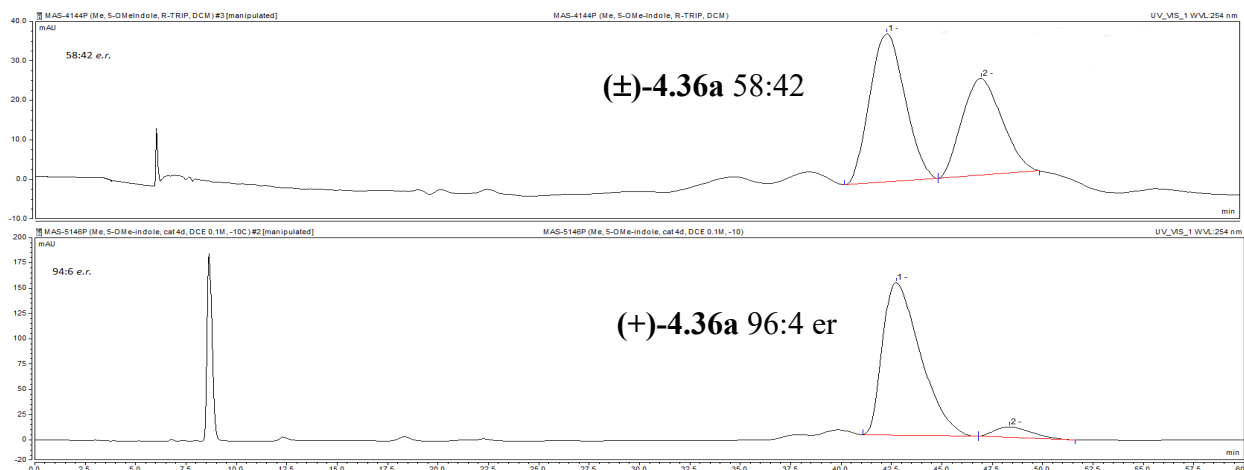
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 153.92, 143.28, 140.96, 136.39, 134.69, 131.87, 129.55, 127.49, 127.06, 122.33, 118.37, 112.12, 111.84, 101.14, 56.06, 44.32, 36.06, 30.15, 29.31, 21.51, 13.25.

**IR** (cm<sup>-1</sup>):  $\nu$  = 3403, 2935, 2854, 1583, 1484, 1455, 1341, 1303, 1219, 1154, 1089, 1033, 814, 730.

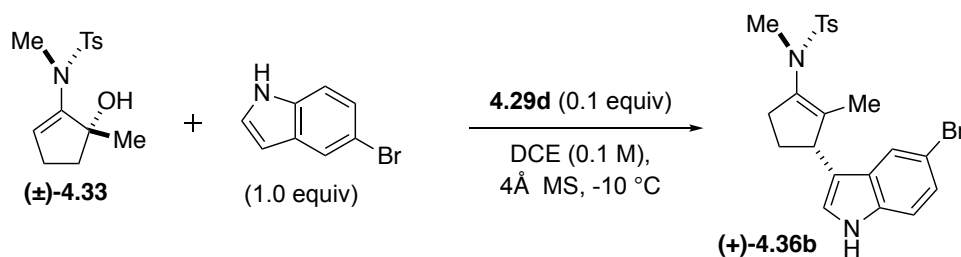
**HRMS** (M+H)<sup>+</sup> = 411.1737 calculated for C<sub>23</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub>S; experimental = 411.1742.

**Optical Rotation** [ $\alpha$ ]<sub>25</sub><sup>D</sup> = +54.6 (c = 1.00 in CHCl<sub>3</sub>).

**HPLC:** 96:4 er using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 6.5% isopropanol in hexanes at 1 mL/min.



**(S)-N-[3-(5-Bromo-1*H*-indol-3-yl)-2-methylcyclopent-1-en-1-yl]-N,4-dimethylbenzenesulfonamide ((+)-4.36b)**



**Procedure:** Compound (±)-4.33 (50 mg, 0.18 mmol) and 5-bromoindole (35mg, 0.18 mmol) were added into a pressure vessel containing 4Å MS (100 mg). (*R*)-catalyst **4.29d** (13 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (1.8 mL). Upon stirring at -10 °C for 42 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 30% EtOAc in hexanes to give product (+)-4.36b as yellow oil (57 mg, 70% yield, 20:1 rr).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ (ppm) = 8.02 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 1.9 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.25 (m, 2H), 7.09 (d, *J* = 2.3 Hz, 1H), 3.90 (t, *J* = 7.0 Hz, 1H), 3.00 (s, 3H), 2.41 (s, 3H), 2.29 – 2.15 (m, 3H), 1.89 – 1.82 (m, 1H), 1.54 (s, 3H).



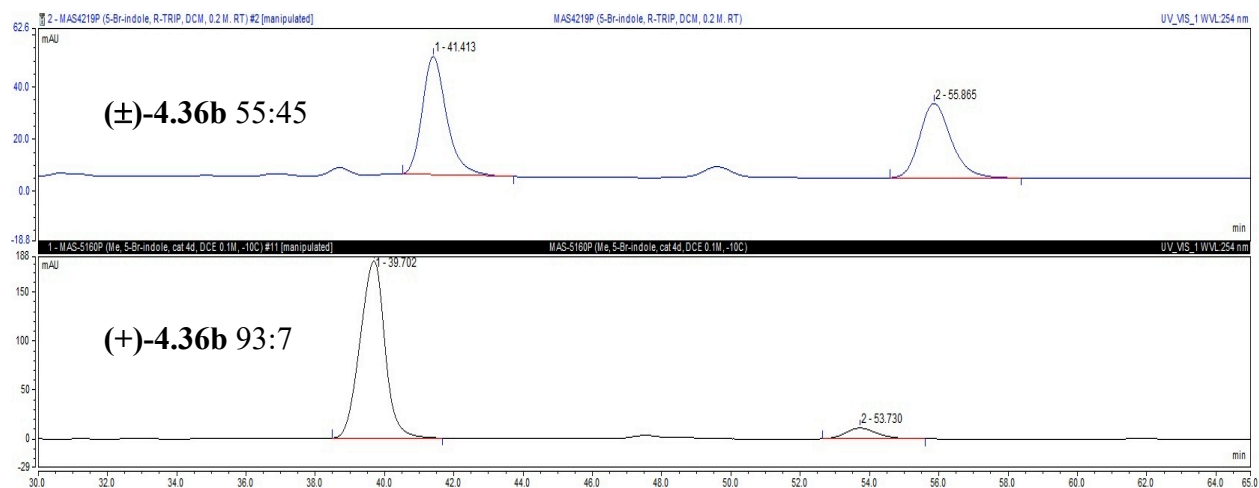
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 143.32, 140.51, 136.36, 135.31, 134.92, 129.59, 128.48, 127.46, 124.78, 122.71, 121.67, 118.47, 112.64, 112.57, 44.10, 36.06, 30.12, 29.25, 21.52, 13.20.

IR ( $\text{cm}^{-1}$ ):  $\nu$  = 3381, 2927, 2854, 1459, 1338, 1154, 1089, 911, 883, 814, 797.

HRMS ( $\text{M}+\text{H}^+$ ) = 459.0736 calculated for  $\text{C}_{22}\text{H}_{23}\text{BrN}_2\text{O}_2\text{S}$ ; experimental = 459.0736.

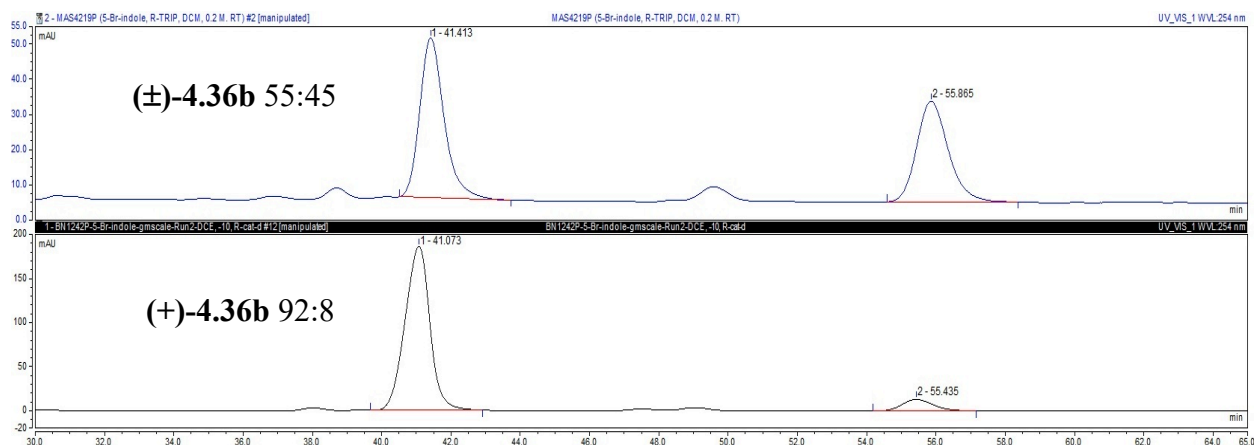
Optical Rotation  $[\alpha]_{25}^{\text{D}} = +35.7$  ( $c = 1.00$  in  $\text{CHCl}_3$ ).

HPLC: 93:7 using Chiralpak IA-3 column (0.46 cm x 25 cm x 3 micron), 5% isopropanol in hexanes at 1 mL/min.

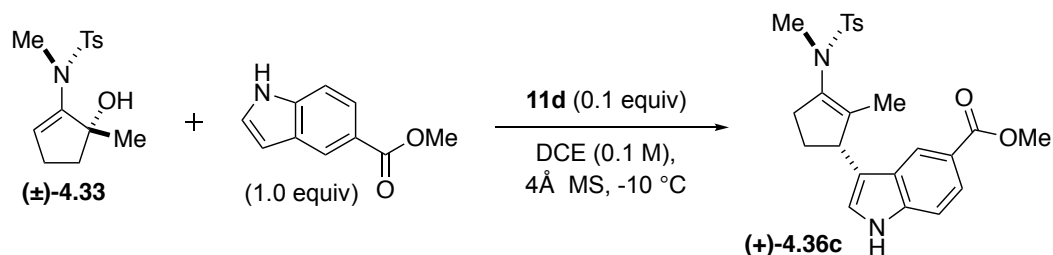


**Gram Scale Reaction:** Compound **(±)-4.33** (0.94 g, 3.34 mmol) and 5-bromo-indole (652 mg, 3.34 mmol) were added into a 100-mL round bottom flask containing 4Å MS (1.80 g). (*R*)-catalyst **4.29d** (235 mg, 0.33 mmol) was then added, and the mixture was dissolved in dry dichloroethane (33 mL). Upon stirring at -10 °C for 94 hours, the reaction mixture was neutralized with 18 mL of  $\text{Et}_3\text{N}$ , and the solvent was evaporated under vacuum. The crude reaction mixture was then purified with flash column chromatography using 10% → 30% EtOAc in hexanes to give products **(+)-4.36b** as yellow solids (1.27 g, 83% yield, 20:1 rr).

**HPLC:** 92:8 er using Chiralpak IA-3 column (0.46 cm x 25 cm x 3 micron), 5% isopropanol in hexanes at 1 mL/min.



**(S)-methyl 3-(3-(*N*,4-dimethylphenylsulfonamido)-2-methylcyclopent-2-en-1-yl)-1*H*-indole-5-carboxylate ((+)-4.36c)**



**Procedure:** Compound (±)-4.33 (70 mg, 0.25 mmol) and methyl-indole-5-carboxylate (44 mg, 0.25 mmol) were added into a pressure vessel containing 4Å MS (100 mg). (*R*)-catalyst **4.29d** (13 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (2.5 mL). Upon stirring at -10 °C for 168 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 20% EtOAc in hexanes to give product (+)-4.36c as yellow oil (90 mg, 82 % yield, 20:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ (ppm) = 8.37 (s, 1H), 8.23 (bs, 1H), 7.90 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 1.8 Hz, 1H), 3.99 (t, *J* = 6.0 Hz, 1H), 3.91 (s, 3H), 3.01 (s, 3H), 2.41 (s, 3H), 2.31 – 2.16 (m, 3H), 1.90 – 1.85 (m, 1H), 1.57 (s, 3H).

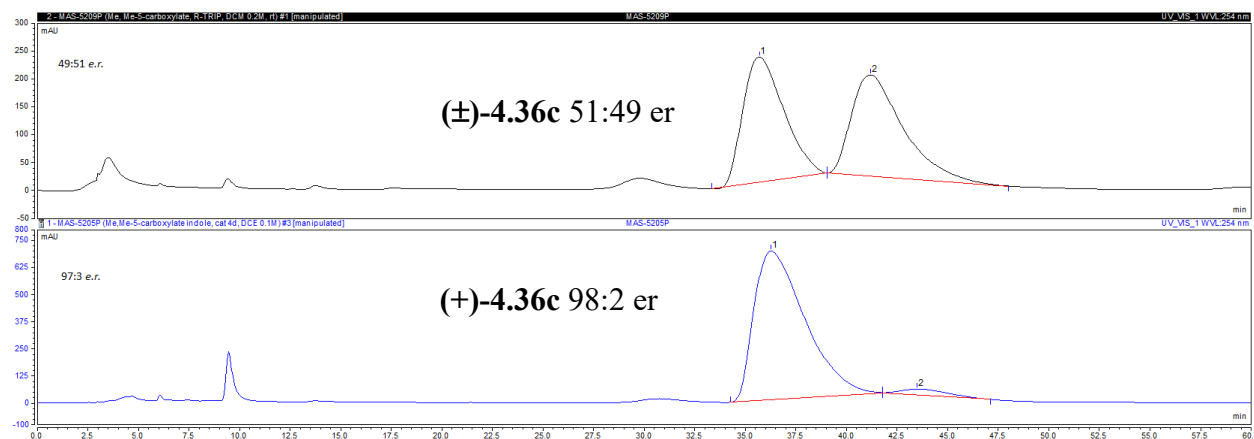
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>): δ (ppm) = 168.16, 143.33, 140.57, 139.29, 136.31, 134.99, 129.57, 127.48, 126.37, 123.43, 122.71, 122.06, 121.39, 120.25, 110.87, 51.81, 44.05, 35.98, 30.37, 29.14, 21.51, 13.22.

**IR (cm<sup>-1</sup>):** *f* = 3368, 2950, 2854, 1709, 1617, 1598, 1437, 1340, 1320, 1288, 1245, 1155, 1109, 1089, 909, 814, 773, 754, 733.

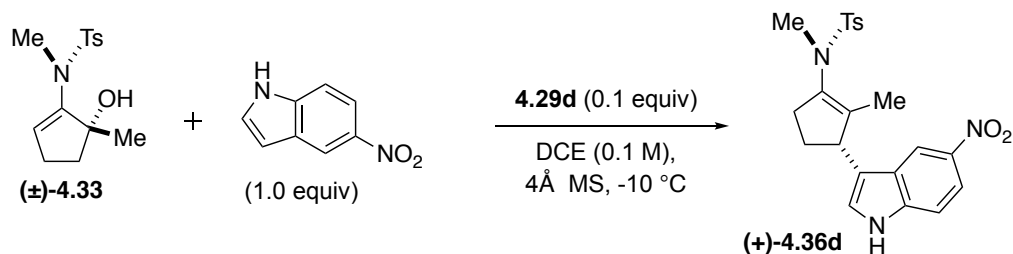
**HRMS** (M+H)<sup>+</sup> = 439.1686 calculated for C<sub>24</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>S; experimental = 439.1684.

**Optical Rotation**[α]<sub>25</sub><sup>D</sup> = +25.9 (c = 1.00 in CHCl<sub>3</sub>).

**HPLC:** 98:2 er using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 10% isopropanol in hexanes at 1 mL/min.



**(S)-N,4-dimethyl-N-(2-methyl-3-(5-nitro-1*H*-indol-3-yl)cyclopent-1-en-1-yl)benzenesulfonamide ((+)-4.36d)**



**Procedure:** Compound **(±)-4.33** (48 mg, 0.17 mmol) and 5-nitroindole (28 mg, 0.17 mmol) were added into a pressure vessel containing 4 Å MS (96 mg). (*R*)-catalyst **4.29d** (12 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (1.7 mL). Upon stirring at -10 °C for 42 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 40% EtOAc in hexanes to give product **(+)-4.36d** as yellow oil (52 mg, 71 % yield, 20:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 8.55 (d, *J* = 1.8 Hz, 1H), 8.52 (s, 1H), 8.09 (dt, *J* = 9.0, 0.9 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.39 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 2.8 Hz, 1H), 3.99 (t, *J* = 6.4 Hz, 1H), 3.02 (s, 3H), 2.42 (s, 3H), 2.32 (ddd, *J* = 12.2, 7.4, 2.4 Hz, 1H), 2.25 – 2.18 (m, 2H), 1.89 – 1.82 (m, 1H), 1.62 (s, 3H).

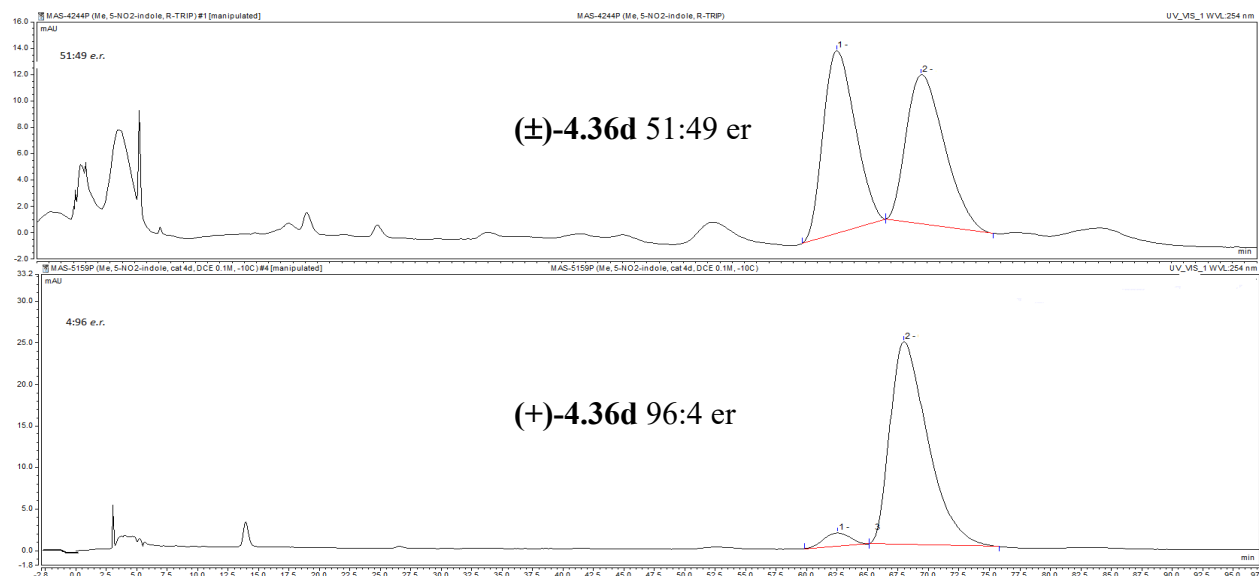
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 143.45, 141.53, 140.14, 139.66, 136.23, 135.32, 129.65, 127.49, 126.20, 124.51, 121.48, 117.77, 116.33, 111.14, 43.86, 35.95, 30.24, 28.91, 21.53, 13.28.

**IR** (cm<sup>-1</sup>):  $\nu$  = 3369, 2959, 2926, 2854, 1519, 1470, 1330, 1154, 1089, 909, 814, 738.

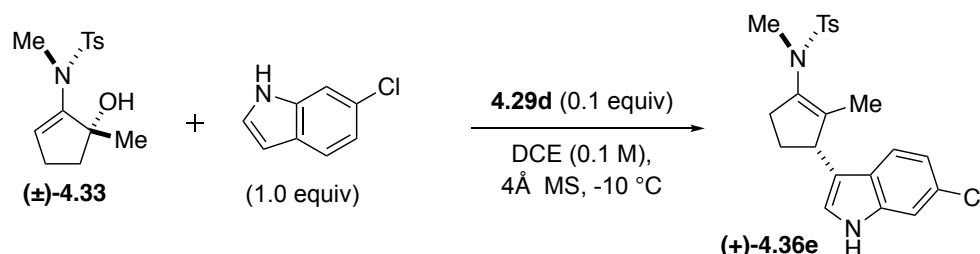
**HRMS** (M+H)<sup>+</sup> = 426.1482 calculated for C<sub>22</sub>H<sub>24</sub>N<sub>3</sub>O<sub>4</sub>S; experimental = 426.1495.

**Optical Rotation** [ $\alpha$ ]<sub>25</sub><sup>D</sup> = +27.1 (c = 1.00 in CHCl<sub>3</sub>).

**HPLC:** 96:4 er using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 5.5% isopropanol in hexanes at 1 mL/min.



**(S)-N-(3-(6-chloro-1*H*-indol-3-yl)-2-methylcyclopent-1-en-1-yl)-N,4-dimethylbenzenesulfonamide ((+)-4.36e)**



**Procedure:** Compound (±)-4.33 (45 mg, 0.16 mmol) and 6-chloroindole (24 mg, 0.16 mmol) were added into a pressure vessel containing 4 Å MS (90 mg). (*R*)-catalyst **4.29d** (11 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (1.6 mL). Upon stirring at -10 °C for 87 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 20% EtOAc in hexanes to give product (+)-4.36e as white crystals. (56 mg, 85 % yield, 20:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ (ppm) = 8.01 (s, 1H), 7.74 (d, *J* = 10.7 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 1.7 Hz, 1H), 7.28 (d, *J* = 8.25, 2H), 7.09 – 7.05 (m, 2H), 3.91 (t, *J* = 7.5 Hz, 1H), 2.99 (s, 3H), 2.41 (s, 3H), m (2.29 – 2.19, 3H), m (1.89 – 1.83, 1H), 1.54 (s, 3H).

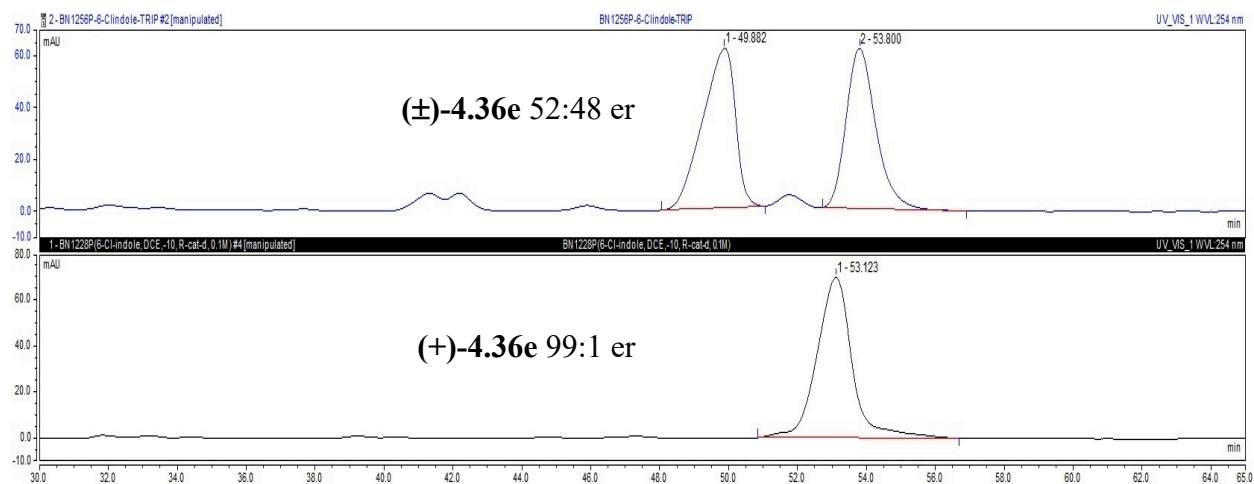
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 143.35, 140.61, 137.05, 136.36, 134.90, 129.57, 127.94, 127.48, 125.32, 122.08, 120.03, 119.96, 118.92, 111.13, 44.12, 36.08, 30.16, 29.31, 21.51, 13.17.

IR ( $\text{cm}^{-1}$ ):  $\nu$  = 3377, 2939, 1598, 1454, 1403, 1334, 1164, 1089, 907, 841, 812, 732, 662, 583, 548.

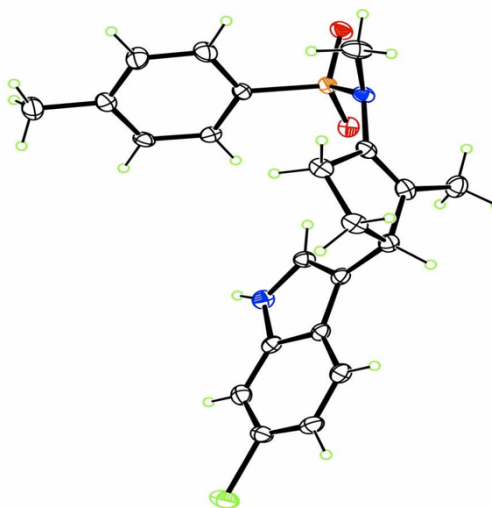
HRMS ( $\text{M}+\text{H}^+$ ) = 415.1242 calculated for  $\text{C}_{24}\text{H}_{24}\text{ClN}_2\text{O}_2\text{S}$ ; experimental = 415.1247.

Optical Rotation  $[\alpha]_{25}^{\text{D}} = +50.6$  ( $c = 1.00$  in  $\text{CHCl}_3$ ).

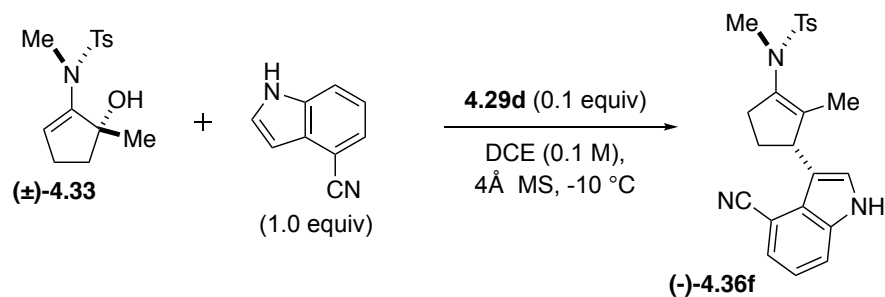
HPLC: 99:1 er using Chiralpak IA-3 column (0.46 cm x 25 cm x 3 micron), 5% isopropanol in hexanes at 1 mL/min.



X-RAY Structure (CCDC 1842375)



**(*S*)-*N*-(3-(4-cyano-1*H*-indol-3-yl)-2-methylcyclopent-1-en-1-yl)-*N*,4-benzenesulfonamide((-)-4.36f)**



**Procedure:** Compound (±)-4.33 (34 mg, 0.12 mmol) and 4-cyanoindole (17 mg, 0.12 mmol) were added into a pressure vessel containing 4Å MS (60 mg). (*R*)-catalyst **4.29d** (8 mg, 0.01 mmol) was then added, and the mixture was dissolved in dichloroethane (1.2 mL). Upon stirring at -10 °C for 122 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 40% EtOAc in hexanes to give product (-)-4.36f as yellow oil (35 mg, 71 % yield, 20:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ (ppm) = 8.41 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.61 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.48 (dd, *J* = 7.4, 0.7 Hz, 1H), 7.36 (d, *J* = 2.2 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 1H), 4.44 (d, *J* = 8.7 Hz, 1H), 2.97 (s, 3H), 2.42 - 2.39 (m, 4H), 2.12 – 2.04 (m, 2H), 1.82 – 1.80 (m, 4H).

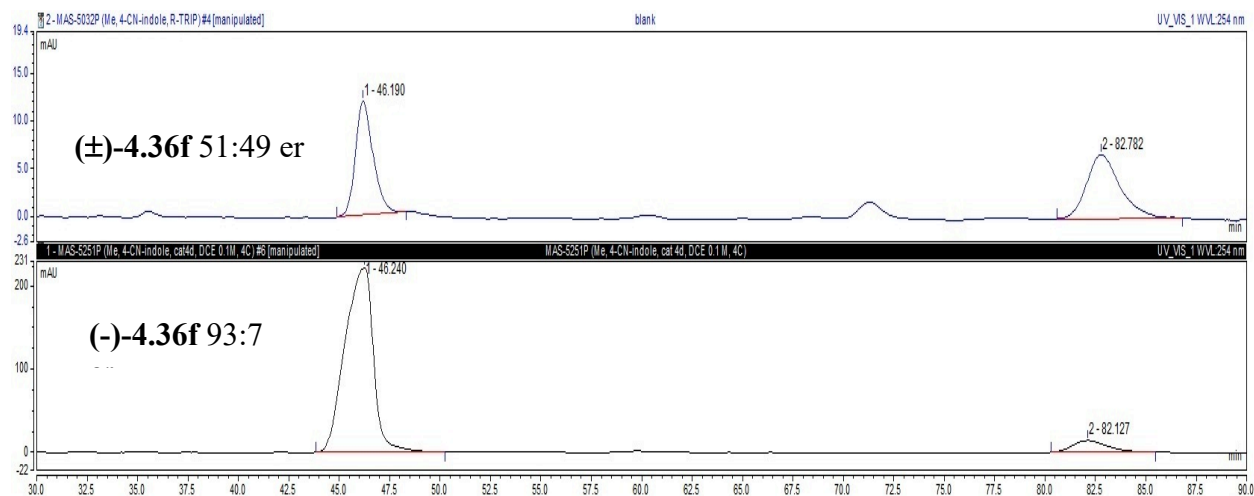
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>): δ (ppm) = 143.46, 140.48, 136.79, 136.12, 135.38, 129.61, 127.47, 126.63, 126.12, 124.55, 121.43, 119.32, 119.03, 116.09, 101.89, 42.98, 35.88, 31.45, 27.90, 21.51, 13.55.

**IR (cm<sup>-1</sup>):** *f* = 3364, 2925, 2855, 1598, 1494, 1453, 1344, 1263, 1155, 1088, 1050, 1018, 911, 814, 744, 667, 581, 549.

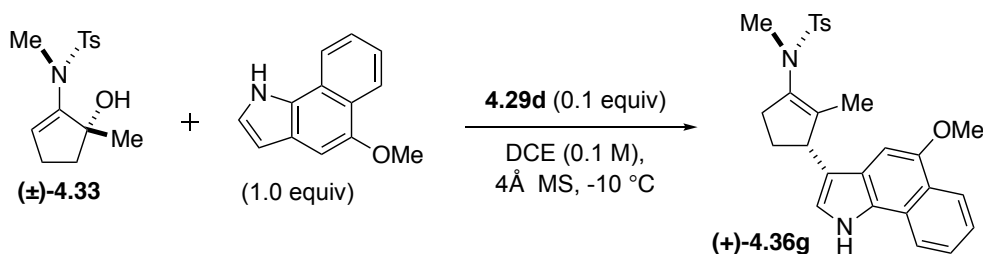
**HRMS** (M+H)<sup>+</sup> = 406.1584 calculated for C<sub>23</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub>S; experimental = 406.1592.

**Optical Rotation**  $[\alpha]_{25}^D = -41.6$  ( $c = 1.00$  in  $\text{CHCl}_3$ )

**HPLC:** 93:7 er using Chiralpak IA-3 column (0.46 cm x 25 cm x 3 micron), 5% isopropanol in hexanes at 1 mL/min.



**(S)-N-(3-(5-methoxy-1H-benzo[g]indol-3-yl)-2-methylcyclopent-1-en-1-yl)-N,4-dimethylbenzenesulfonamide ((+)-4.36g)**



**Procedure:** Compound (±)-4.33 (48 mg, 0.17 mmol) and 5-methoxy-1H-benzo[g]indole (34 mg, 0.17 mmol) was added into a pressure vessel containing 4 Å MS (96 mg). (R)-catalyst **4.29d** (12 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (2.1 mL). Upon stirring at -10 °C for 148 hours, the reaction mixture was neutralized with 0.5 mL of  $\text{Et}_3\text{N}$ . The



crude reaction mixture was then directly purified with flash column chromatography using 10% → 15% EtOAc in hexanes to give product **(+)-4.36g** as yellow oil (66 mg, 84% yield, 2.3:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 8.62 (s, 1H), 8.33 (d,  $J$  = 8.5 Hz, 1H), 7.93 (d,  $J$  = 8.1 Hz, 1H), 7.78 (d,  $J$  = 8.3 Hz, 2H), 7.55 (ddd,  $J$  = 8.1, 6.8, 1.1 Hz, 1H), 7.44 (ddd,  $J$  = 8.1, 7.0, 1.1 Hz, 1H), 7.28 (d,  $J$  = 8.1 Hz, 2H), 7.07 (s, 1H), 7.06 (s, 1H), 4.06 (s, 3H), 4.01 – 3.98 (m, 1H), 3.00 (s, 3H), 2.40 (s, 3H), 2.34 – 2.24 (m, 3H), 1.97 (ddt,  $J$  = 12.2, 8.3, 6.3 Hz, 1H), 1.60 (s, 3H).

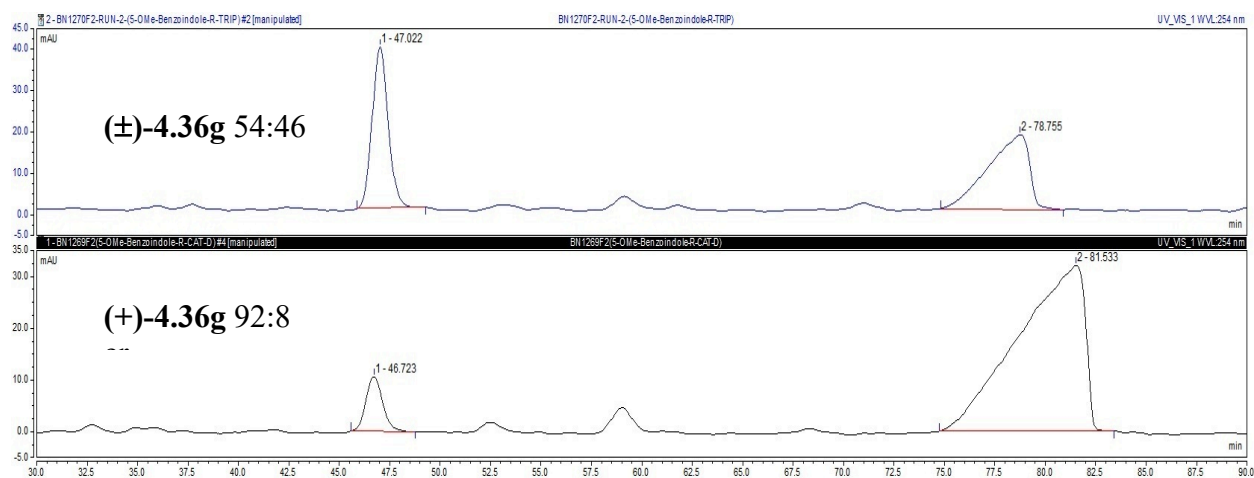
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 150.06, 143.31, 141.16, 136.36, 134.71, 129.56, 127.47, 126.35, 126.06, 123.55, 123.37, 122.32, 121.65, 120.08, 119.71, 119.15, 96.63, 56.04, 44.44, 36.06, 30.61, 29.44, 21.49, 13.25.

**IR** (cm<sup>-1</sup>):  $\nu$  = 3376, 2962, 2938, 1632, 1598, 1384, 1336, 1259, 1150, 1018, 909, 813, 763, 730.

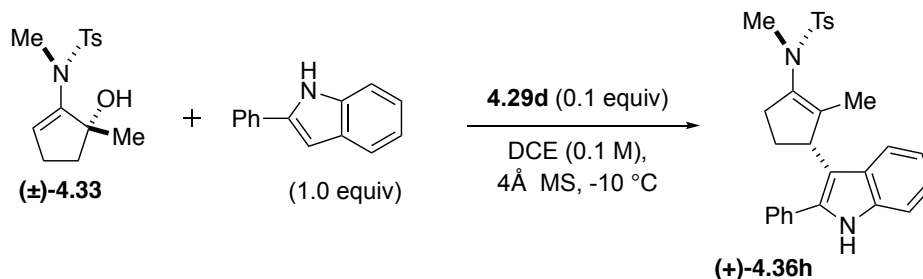
**HRMS** (M+H)<sup>+</sup> = 461.1893 calculated for C<sub>27</sub>H<sub>29</sub>N<sub>2</sub>O<sub>3</sub>S; experimental = 461.1899.

**Optical Rotation** [ $\alpha$ ]<sub>25</sub><sup>D</sup> = +104 (c = 1.00 in CHCl<sub>3</sub>).

**HPLC**: 92:8 er using Chiralpak IA-3 column (0.46 cm x 25 cm x 3 micron), 7% isopropanol in hexanes at 1 mL/min.



**(R)-N,4-dimethyl-N-(2-methyl-3-(2-phenyl-1*H*-indol-3-yl)cyclopent-1-en-1-yl)benzenesulfonamide ((+)-4.36h)**



**Procedure:** Compound **(±)-8** (50 mg, 0.18 mmol) and 2-phenylindole (34 mg, 0.18 mmol) were added into a pressure vessel containing 4Å MS (100 mg). (*R*)-catalyst **11d** (13 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (1.8 mL). Upon stirring at -10 °C for 50 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 30% EtOAc in hexanes to give product **(+)-12h** as yellow oil (52 mg, 64% yield, 20:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.99 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.49 (dt, *J* = 15.2, 7.4 Hz, 4H), 7.39 (dd, *J* = 13.0, 7.6 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 4H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 4.16 (t, *J* = 7.5 Hz, 1H), 3.03 (s, 3H), 2.46 – 2.25 (m, 6H), 2.13 (p, *J* = 9.9, 9.4 Hz, 1H), 1.37 (s, 3H).

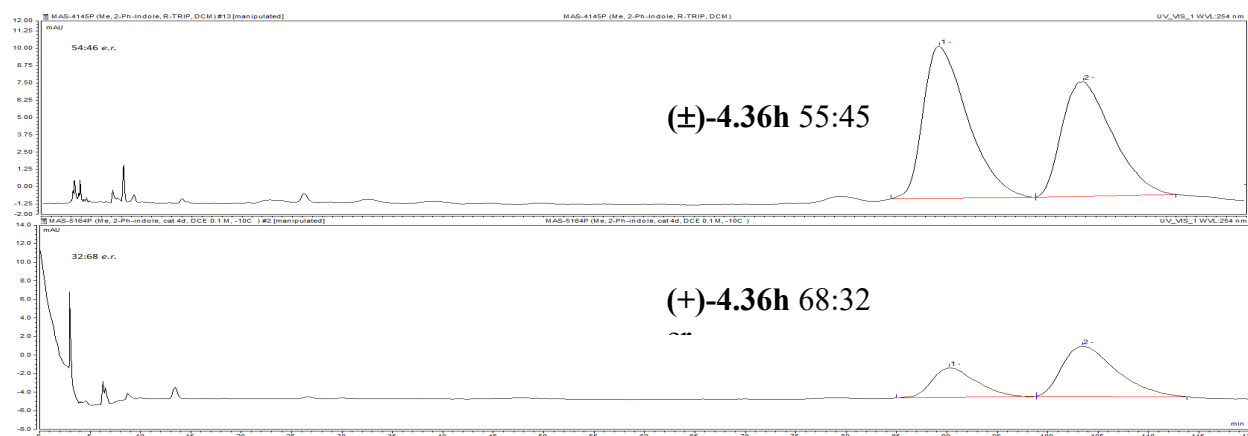
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 143.18, 140.96, 136.67, 136.14, 135.44, 134.49, 129.54, 129.02, 128.78, 128.63, 128.21, 127.88, 127.49, 125.28, 122.19, 119.66, 114.56, 110.87, 43.95, 36.13, 30.34, 29.74, 21.51, 13.02.

**IR** (cm<sup>-1</sup>):  $\nu$  = 3386, 2939, 2854, 1456, 1341, 1153, 1089, 910, 814, 744.

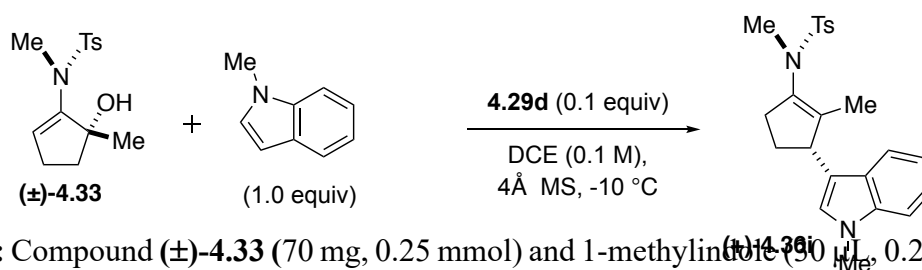
**HRMS** (M+H)<sup>+</sup> = 457.1944 calculated for C<sub>28</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>S; experimental = 457.1949.

**Optical Rotation** [ $\alpha$ ]<sub>25</sub><sup>D</sup> = +2.60 (c = 1.00 in CHCl<sub>3</sub>).

**HPLC:** 68:32 using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 2.8% isopropanol in hexanes at 1 mL/min.



**(S)-N,4-dimethyl-N-(2-methyl-3-(1-methyl-1*H*-indol-3-yl)cyclopent-1-en-1-yl)benzenesulfonamide ((+)-4.36i)**



**Procedure:** Compound (±)-4.33 (70 mg, 0.25 mmol) and 1-methylindole (90 mg, 0.25 mmol) were added into a pressure vessel containing 4 Å MS (140 mg). (*R*)-catalyst **4.29d** (18 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (2.5 mL). Upon stirring at -10 °C for 87 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 15% EtOAc in hexanes to give product (+)-4.36i as yellow oil (51 mg, 52% yield, 20:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ (ppm) = 7.76 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.29 (t, *J* = 9.0 Hz, 3H), 7.22 (td, *J* = 7.5, 0.9 Hz, 1H), 7.09 (td, *J* = 7.5, 0.9 Hz, 1H), 6.89 (s, 1H), 3.98 – 3.91 (m, 1H), 3.76 (s, 3H), 3.01 (s, 3H), 2.41 (s, 3H), 2.31 – 2.15 (m, 3H), 1.90 (tdt, *J* = 10.7, 7.1, 3.8 Hz, 1H), 1.54 (s, 3H).

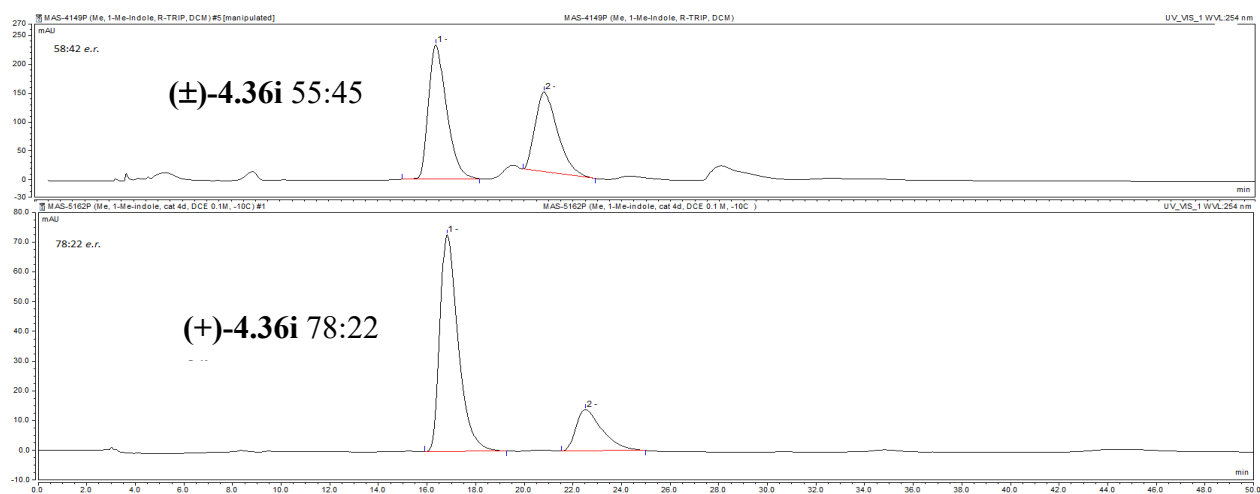
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 143.24, 140.95, 137.37, 136.42, 134.55, 129.52, 127.50, 127.09, 126.20, 121.50, 119.20, 118.68, 117.15, 109.24, 44.21, 36.14, 32.65, 30.51, 29.42, 21.52, 13.21.

IR ( $\text{cm}^{-1}$ ):  $\nu$  = 3050, 2934, 2878, 1469, 1344, 1155, 1089, 815, 741.

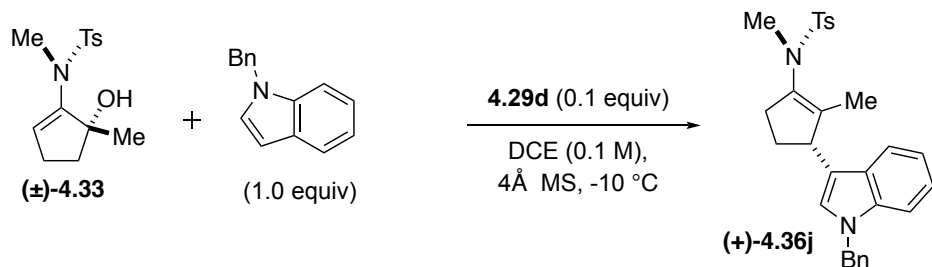
HRMS ( $\text{M}+\text{H}^+$ ) = 395.1788 calculated for  $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_2\text{S}$ ; experimental = 395.1787.

Optical Rotation  $[\alpha]_{25}^{\text{D}}$  = +14.9 ( $c$  = 1.00 in  $\text{CHCl}_3$ ).

HPLC: 78:22 using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 3.5% isopropanol in hexanes at 1 mL/min.



(*S*)-*N*-(3-(1-benzyl-1*H*-indol-3-yl)-2-methylcyclopent-1-en-1-yl)-*N*,4-dimethylbenzenesulfonamide ((+)-4.36j)



**Procedure:** Compound ( $\pm$ )-**4.33** (60 mg, 0.21 mmol) and 1-benzylindole (44mg, 0.21 mmol) were added into a pressure vessel containing 4Å MS (120 mg). (*R*)-catalyst **4.29d** (15 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (2.1 mL). Upon stirring at -10 °C for 117 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 15% EtOAc in hexanes to give product (+)-**4.36j** as yellow oil (16 mg, 16% yield, 20:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.71 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.14 – 7.09 (m, 3H), 6.98 (s, 1H), 5.29 (s, 2H), 3.96 (t, *J* = 6.7 Hz, 1H), 3.00 (s, 3H), 2.39 (s, 3H), 2.30 – 2.18 (m, 3H), 1.96 – 1.88 (m, 1H), 1.54 (s, 3H).

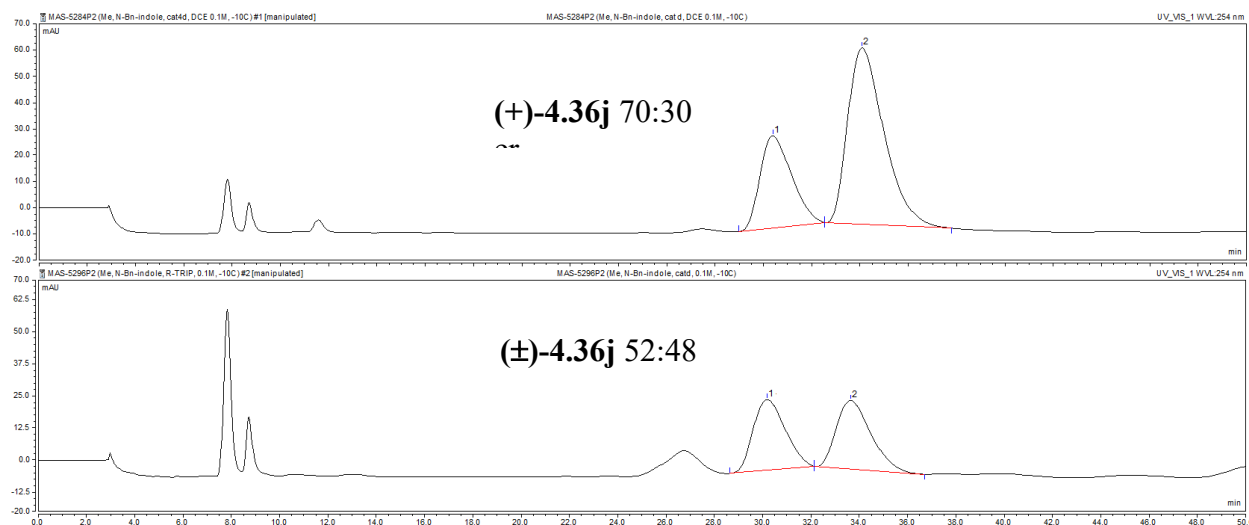
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 143.19, 140.88, 137.75, 137.05, 136.39, 134.60, 129.50, 128.72, 127.50, 127.47, 127.39, 126.76, 125.62, 121.71, 119.31, 118.96, 117.89, 109.75, 49.91, 44.26, 36.17, 30.36, 29.38, 21.51, 13.22.

**IR** (cm<sup>-1</sup>):  $\nu$  = 2925, 2853, 1466, 1346, 1154, 1089, 815, 741.

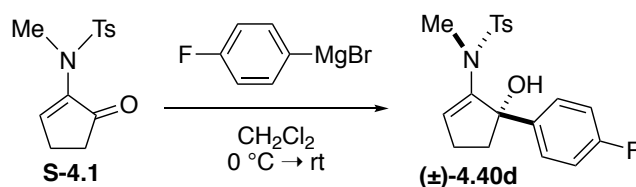
**HRMS** (M+Na)<sup>+</sup> = 493.1920 calculated for C<sub>29</sub>H<sub>30</sub>N<sub>2</sub>NaO<sub>2</sub>S; experimental = 493.1925.

**Optical Rotation** [ $\alpha$ ]<sub>25</sub><sup>D</sup> = +26.1 (c = 1.00 in CHCl<sub>3</sub>).

**HPLC:** 70:30 using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 3.5% isopropanol in hexanes at 1 mL/min.



**(S)-N-(5-(4-fluorophenyl)-5-hydroxycyclopent-1-en-1-yl)-N,4-dimethylbenzenesulfonamide**  
**(4.40d)**



**Procedure:** Compound **S-4.1** (96 mg, 0.36 mmol) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (1.8 mL) and cooled to  $0\text{ }^\circ\text{C}$ . 4-Fluoro-phenylmagnesium bromide (0.72 mL, 0.72 mmol, 1 M solution in THF) was then added dropwise at  $0\text{ }^\circ\text{C}$ . After stirring for 3 hours at room temperature, the reaction was cooled to  $0\text{ }^\circ\text{C}$ , and then quenched with  $\text{H}_2\text{O}$  (5 mL). Solid precipitate was filtered through celite, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 10 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. The crude material was purified with flash column chromatography (buffered with 1%  $\text{Et}_3\text{N}$ ) using 5%  $\rightarrow$  15%  $\text{EtOAc}$  in hexanes to give product **(±)-4.40d** (112 mg, 86% yield) as yellow solids.

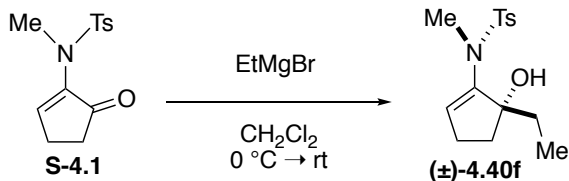
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.61 (d,  $J$  = 8.3 Hz, 2H), 7.40 (dd,  $J$  = 8.8, 5.4 Hz, 2H), 7.30 (d,  $J$  = 8.0 Hz, 2H), 7.02 (t,  $J$  = 8.8 Hz, 2H), 5.58 (t,  $J$  = 2.5 Hz, 1H), 4.59 (s, 1H), 2.73 (s, 3H), 2.66 – 2.57 (m, 1H), 2.44 (s, 3H), 2.42 – 2.29 (m, 3H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 147.42, 144.09, 133.16, 130.70, 129.48, 128.01, 127.09, 127.02, 114.87, 114.69, 84.16, 43.18, 39.86, 27.38, 21.58.

**IR** (cm<sup>-1</sup>):  $\nu$  = 3492, 3065, 2940, 1600, 1507, 1336, 1223, 1155, 1088, 837, 814.

**HRMS** (M-OH)<sup>+</sup> = 344.1115 calculated for C<sub>19</sub>H<sub>19</sub>FNO<sub>2</sub>S; experimental = 344.1136.

**(R)-N-(5-ethyl-5-hydroxycyclopent-1-en-1-yl)-N,4-dimethylbenzenesulfonamide (4.40f)**



**Procedure:** Compound **S-4.1** (125 mg, 0.47 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (2.4 mL) and cooled to 0 °C. Ethylmagnesium bromide (0.30 mL, 0.94 mmol, 3 M solution in Et<sub>2</sub>O) was then added dropwise at 0 °C. After stirring for 1 hour at room temperature, the reaction was cooled to 0 °C, and then quenched with H<sub>2</sub>O (5 mL). Solid precipitate was filtered through celite, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified with flash column chromatography (buffered with 1% Et<sub>3</sub>N) using 5% → 15% EtOAc in hexanes to give product **(±)-4.40f** (57 mg, 41% yield) as yellow oil.

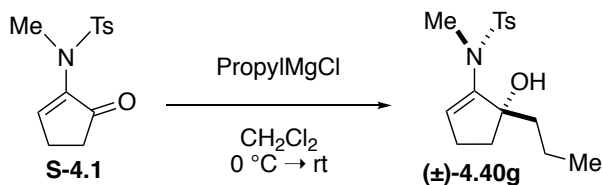
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.71 (d,  $J$  = 8.2 Hz, 2H), 7.32 (d,  $J$  = 8.2 Hz, 2H), 5.34 (t,  $J$  = 2.6 Hz, 1H), 3.85 (s, 1H), 2.93 (s, 3H), 2.44 (s, 3H), 2.16 – 2.09 (m, 1H), 2.05 - 1.95 (m, 3H), 1.92 - 1.84 (m, 1H), 1.72 - 1.64 (m, 1H), 0.94 (t,  $J$  = 7.5 Hz, 3H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ (ppm) = 147.60, 143.94, 132.37, 130.11, 129.34, 128.13, 83.39, 40.30, 36.17, 31.21, 26.74, 21.53, 8.43.

IR (cm<sup>-1</sup>):  $\nu$  = 3516, 2967, 1337, 1156, 1088, 960, 813.

HRMS (M-OH)<sup>+</sup> = 278.1215 calculated for C<sub>15</sub>H<sub>20</sub>NO<sub>2</sub>S; experimental = 278.1212.

**(R)-N-(5-hydroxy-5-propylcyclopent-1-en-1-yl)-N,4-dimethyl-benzenesulfonamide (4.40g)**



**Procedure:** Compound **S-4.1** (100 mg, 0.38 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (1.9 mL) and cooled to 0 °C. Propylmagnesium chloride (0.38 mL, 0.76 mmol, 2 M solution in Et<sub>2</sub>O) was then added dropwise at 0 °C. After stirring for 2 hours at room temperature, the reaction was cooled to 0 °C, and then quenched with H<sub>2</sub>O (5 mL). Solid precipitate was filtered through celite, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified with flash column chromatography (buffered with 1% Et<sub>3</sub>N) using 5% → 10% EtOAc in hexanes to give product **(±)-4.40g** (75 mg, 64% yield) as yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) = 7.70 (d,  $J$  = 8.3 Hz, 2H), 7.32 (d,  $J$  = 8.0 Hz, 2H), 5.33 – 5.30 (m, 1H), 3.88 (s, 1H), 2.93 (s, 3H), 2.44 (s, 3H), 2.15 – 2.07 (m, 1H), 2.00 (t,  $J$  = 6.6 Hz, 2H), 1.84 (td,  $J$  = 13.2 Hz, 4.3 Hz, 1H), 1.58 (td,  $J$  = 12.0, 4.1 Hz, 1H), 1.53 – 1.45 (m, 1H), 1.33 – 1.25 (m, 2H), 0.96 (t,  $J$  = 7.2 Hz, 3H).

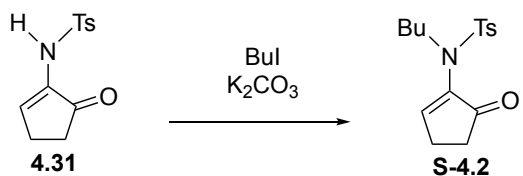
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) = 147.95, 143.94, 132.44, 129.95, 129.36, 128.23, 82.96, 41.06, 40.39, 36.88, 26.83, 21.57, 17.41, 14.68.

IR (cm<sup>-1</sup>):  $\nu$  = 3517, 2958, 1338, 1156, 813.



**HRMS** (M-OH)<sup>+</sup> = 292.1366 calculated for C<sub>16</sub>H<sub>22</sub>NO<sub>2</sub>S; experimental = 292.1369.

***N*-butyl-4-methyl-*N*-(5-oxocyclopent-1-en-1-yl)benzenesulfonamide (S-4.2)**



**Procedure:** Compound **4.31** (170 mg, 0.67 mmol) was dissolved in dry acetone (1.6 mL) in a pressure vessel. K<sub>2</sub>CO<sub>3</sub> (187 mg, 1.35 mmol) and iodobutane (120  $\mu$ L, 1.01 mmol) were then added subsequently. After stirring on reflux overnight, the reaction was quenched with H<sub>2</sub>O (3 mL) and the aqueous layer was extracted with EtOAc (3 x 8 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified with flash column chromatography using 10 %  $\rightarrow$  15% to give product **S-4.2** (78 mg, 38% yield) as yellow oil.

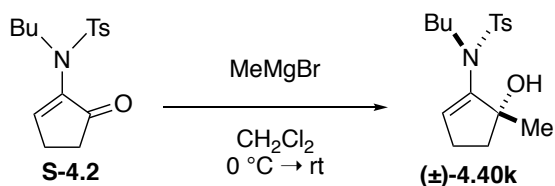
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.76 (t,  $J$  = 2.8 Hz, 1H), 7.65 (d,  $J$  = 8.3 Hz, 2H), 7.24 (s, 1H), 3.61 (t,  $J$  = 7.3 Hz, 2H), 2.69 – 2.63 (m, 2H), 2.43 – 2.35 (m, 5H), 1.43 (p,  $J$  = 8.1, 7.5 Hz, 2H), 1.30 (dt,  $J$  = 15.0, 7.2 Hz, 2H), 0.87 (t,  $J$  = 7.3 Hz, 3H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 204.04, 160.39, 143.52, 140.28, 136.57, 129.53, 127.24, 46.85, 33.88, 31.25, 24.73, 21.55, 19.56, 13.63.

**IR** (cm<sup>-1</sup>):  $\nu$  = 2959, 2255, 1713, 1347, 1165, 1091, 1041, 815, 665, 547, 480, 410.

**HRMS** (M+H)<sup>+</sup> = 308.1315 calculated for C<sub>16</sub>H<sub>22</sub>NO<sub>3</sub>S; experimental = 308.1320.

***N*-butyl-4-methyl-*N*-(5-oxocyclopent-1-en-1-yl)benzenesulfonamide (4.40k)**



**Procedure:** Compound **S-4.2** (117 mg, 0.38 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (1.9 mL) and cooled to 0 °C. Methylmagnesium chloride (0.25 mL, 0.76 mmol, 3 M solution in Et<sub>2</sub>O) was then added dropwise at 0 °C. After stirring for 5 minutes at room temperature, the reaction was cooled to 0 °C, and then quenched with H<sub>2</sub>O (5 mL). Solid precipitate was filtered through celite, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude material was purified with flash column chromatography (buffered with 1% Et<sub>3</sub>N) using 5% → 10% EtOAc in hexanes to give product (±)-**4.40k** (101 mg, 82% yield) as yellow oil.

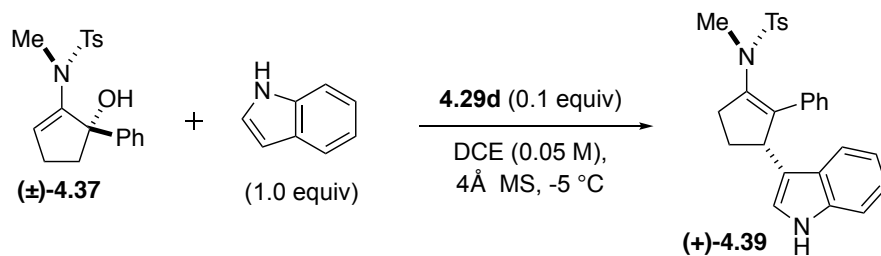
**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.70 (d,  $J$  = 8.1 Hz, 2H), 7.29 (d,  $J$  = 8.0 Hz, 2H), 5.38 (d,  $J$  = 2.8 Hz, 1H), 4.03 (s, 1H), 3.60 – 3.52 (m, 1H), 2.95 (ddd,  $J$  = 16.9, 9.0, 4.5 Hz, 1H), 2.43 (s, 3H), 2.18 – 2.12 (m, 2H), 1.94 (dt,  $J$  = 13.6, 8.1 Hz, 1H), 1.52 – 1.43 (m, 2H), 1.40 (s, 3H), 1.36 – 1.26 (m, 2H), 0.88 (t,  $J$  = 7.3 Hz, 3H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 146.20, 143.71, 134.12, 131.46, 129.34, 127.96, 80.11, 52.07, 40.43, 30.26, 26.81, 25.76, 21.56, 19.79, 13.66.

**IR** (cm<sup>-1</sup>):  $\nu$  = 3518, 2961, 1452, 1336, 1158, 1090, 1038, 814, 667, 591, 553.

**HRMS** (M-H<sub>2</sub>O)<sup>+</sup> = 306.1522 calculated for C<sub>17</sub>H<sub>24</sub>NO<sub>2</sub>S; experimental = 306.1536.

**(S)-N-(3-(1*H*-indol-3-yl)-2-phenylcyclopent-1-en-1-yl)-N,4-dimethylbenzenesulfonamide**  
**((+)-4.39)**



**Procedure:** Compound ( $\pm$ )-**4.37** (62 mg, 0.18 mmol) and indole (21mg, 0.18 mmol) were added into a pressure vessel containing 4Å MS (1125 mg). (*R*)-catalyst **4.29d** (13 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (3.6 mL). Upon stirring at -5 °C for 223 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 15% EtOAc in hexanes to give product (+)-**4.39** as yellow oil (70 mg, 88% yield, 6:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.89 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 9.3 Hz, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.15 – 7.09 (m, 4H), 7.04 (d, *J* = 2.2 Hz, 1H), 4.50 (dt, *J* = 5.8, 3.1, 3.0, Hz, 1H), 2.97 (s, 3H), 2.76 – 2.66 (m, 1H), 2.42 (s, 3H), 2.41 – 2.36 (m, 2H), 2.00 (dt, *J* = 11.1, 6.0, 2.3 Hz, 1H).

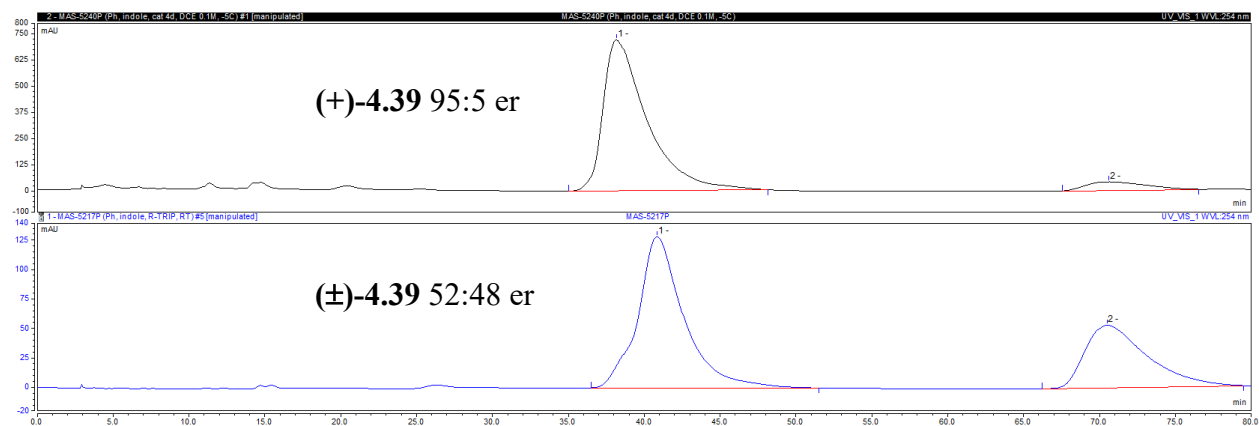
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 143.39, 139.49, 137.12, 136.60, 136.33, 135.01, 129.51, 127.93, 127.90, 127.59, 127.20, 126.73, 122.10, 121.84, 119.17, 118.92, 118.43, 111.15, 43.12, 36.31, 31.09, 30.51, 21.51.

**IR** (cm<sup>-1</sup>):  $\nu$  = 2935, 1736, 1470, 1345, 1155, 1089, 1013, 815, 742.

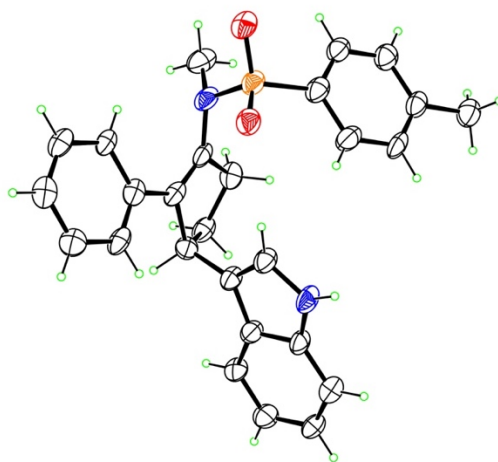
**HRMS** (M+H)<sup>+</sup> = 443.1788 calculated for C<sub>27</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>S; experimental = 443.1794.

**Optical Rotation** [ $\alpha$ ]<sub>25</sub><sup>D</sup> = +70.6 (c = 1.00 in CHCl<sub>3</sub>).

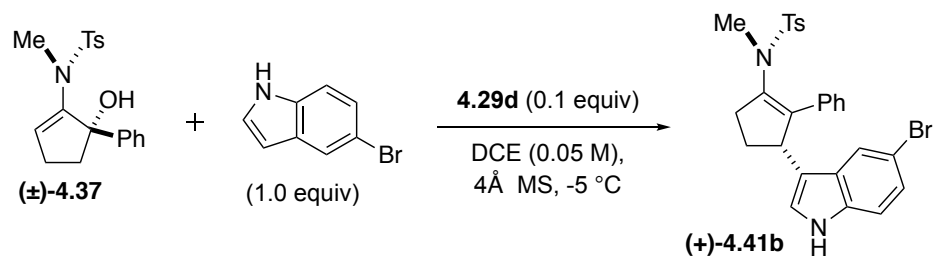
**HPLC:** 95:5 using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 7.5% isopropanol in hexanes at 1 mL/min.



X-ray structure (CCDC 1589611):



**(*S*)-*N*-(3-(5-bromo-1*H*-indol-3-yl)-2-phenylcyclopent-1-en-1-yl)-*N*,4-dimethylbenzenesulfonamide ((+)-4.41b)**



**Procedure:** Compound ( $\pm$ )-**4.37** (63 mg, 0.18 mmol) and 5-bromoindole (36mg, 0.18 mmol) were added into a pressure vessel containing 4Å MS (125 mg). (*R*)-catalyst **4.29d** (13 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (3.6 mL). Upon stirring at -5 °C for 65 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 30% EtOAc in hexanes to give product (+)-**4.41b** as white crystals (67 mg, 70% yield, 4:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.95 (s, 1H), 7.77 (d, *J* = 1.7 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.32 (dd, *J* = 6.5, 3.3 Hz, 2H), 7.28 – 7.23 (m, 3H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.13 – 7.10 (m, 3H), 7.05 (d, *J* = 2.3 Hz, 1H), 4.43 (d, *J* = 7.4 Hz, 1H), 2.96 (s, 3H), 2.76 – 2.67 (m, 1H), 2.44 – 2.36 (m, 5H), 1.97 – 1.92 (m, 1H).

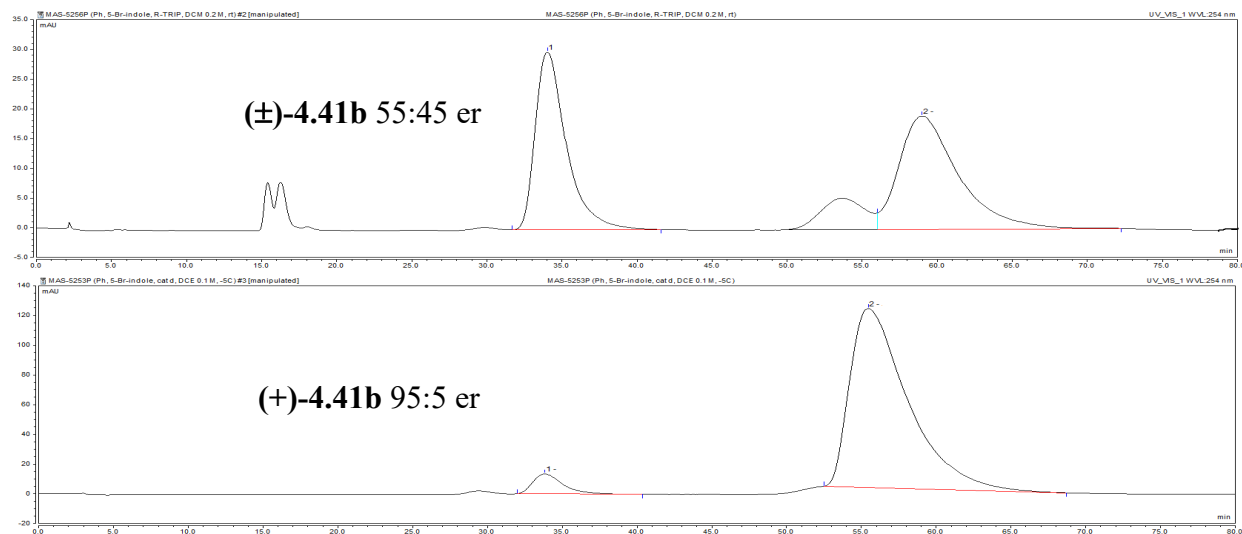
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 143.47, 139.22, 137.30, 136.19, 135.19, 134.80, 129.56, 128.46, 127.96, 127.85, 127.57, 127.31, 124.64, 123.38, 121.45, 118.17, 112.64, 112.47, 42.93, 36.27, 31.09, 30.47, 21.52.

**IR** (cm<sup>-1</sup>):  $\nu$  = 3420, 2934, 2859, 1598, 1458, 1341, 1153, 1088, 944, 884, 839, 732.

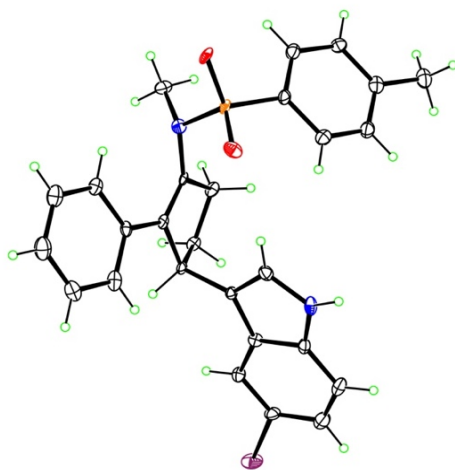
**HRMS** (M+H)<sup>+</sup> = 521.0893 calculated for C<sub>27</sub>H<sub>26</sub>BrN<sub>2</sub>O<sub>2</sub>S; experimental = 521.0898.

**Optical Rotation** [ $\alpha$ ]<sub>25</sub><sup>D</sup> = +73.8 (c = 1.00 in CHCl<sub>3</sub>).

**HPLC:** 95:5 using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 6.5% isopropanol in hexanes at 1 mL/min.

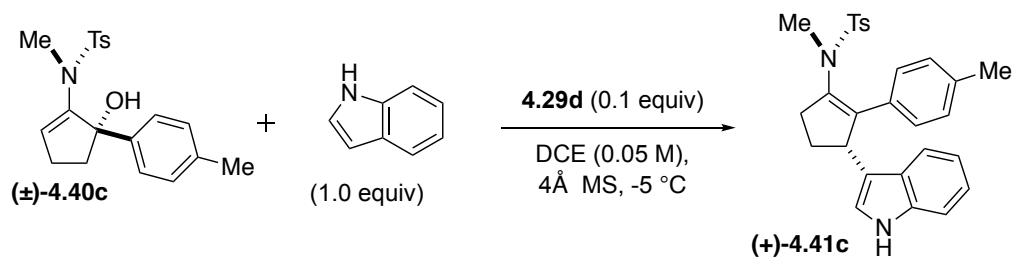


X-ray structure (CCDC 1589612):



**(S)-N-(3-(1*H*-indol-3-yl)-2-(p-tolyl)cyclopent-1-en-1-yl)-N,4-dimethylbenzenesulfonamide**

**((+)-4.41c)**



**Procedure:** Compound ( $\pm$ )-**4.40c** (50 mg, 0.14 mmol) and indole (17 mg, 0.14 mmol) were added into a pressure vessel containing 4Å MS (100 mg). (*R*)-catalyst **4.29d** (10 mg, 0.01 mmol) was then added, and the mixture was dissolved in dichloroethane (2.9 mL). Upon stirring at -5 °C for 89 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 30% EtOAc in hexanes to give product (+)-**4.41c** as yellow oil (45 mg, 69% yield, 5.7:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.87 (s, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.18 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H), 7.12 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.04 (d, *J* = 2.2 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 2H), 4.4.8 (d, *J* = 6.9 Hz, 1H), 2.97 (s, 3H), 2.69 – 2.63 (m, 1H), 2.42 (s, 3H), 2.39 – 2.33 (m, 2H), 2.24 (s, 3H), 1.98 (dt, *J* = 9.0, 6.6, 3.1 Hz, 1H).

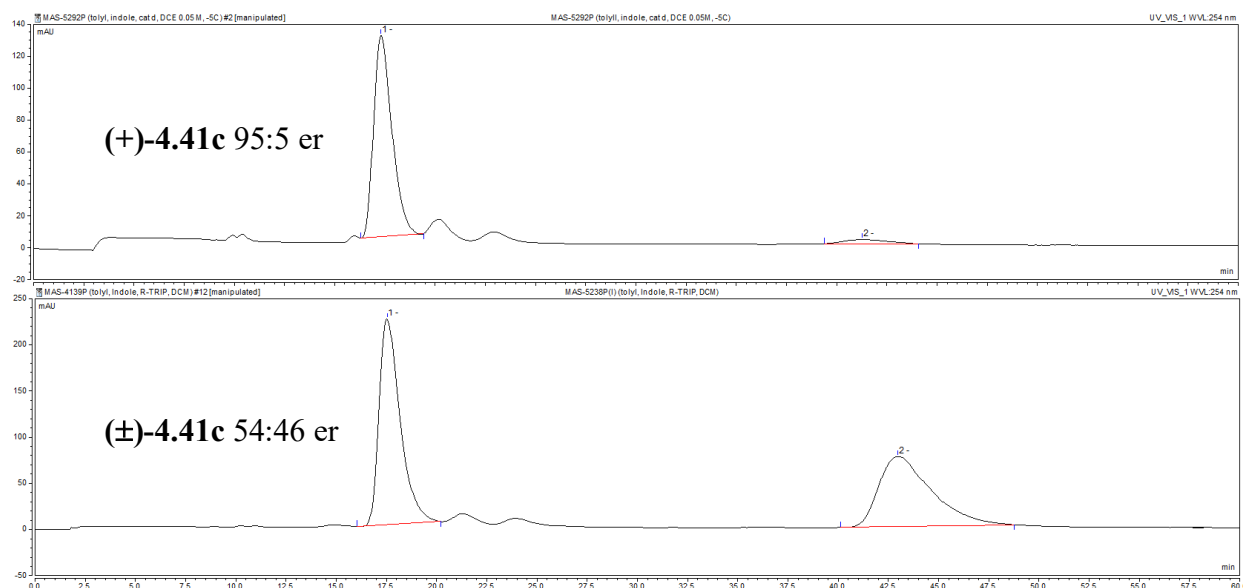
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 143.32, 139.35, 136.98, 136.61, 136.47, 136.40, 132.03, 129.49, 128.65, 127.82, 127.60, 126.80, 122.12, 121.83, 119.18, 118.96, 118.61, 111.12, 42.99, 36.25, 30.96, 30.48, 21.53, 21.19.

**IR** (cm<sup>-1</sup>):  $\nu$  = 3416, 2924, 2854, 1456, 1337, 1154, 1087, 911, 815, 740.

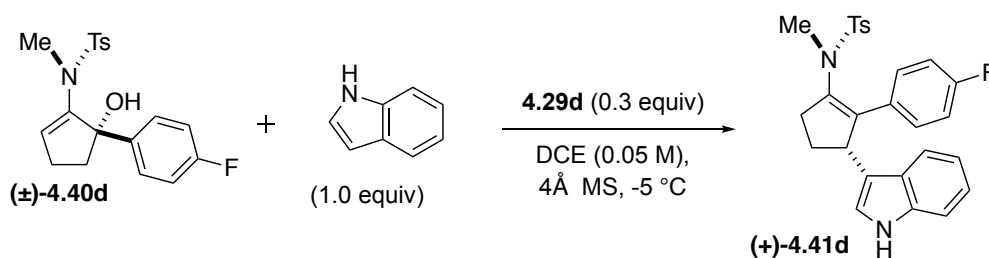
**HRMS** (M+H)<sup>+</sup> = 457.1950 calculated for C<sub>28</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>S; experimental = 457.1956.

**Optical Rotation** [ $\alpha$ ]<sub>25</sub><sup>D</sup> = +87.8 (c = 1.00 in CHCl<sub>3</sub>).

**HPLC:** 95:5 using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 10% isopropanol in hexanes at 1 mL/min.



**(*S*)-*N*-(2-(4-fluorophenyl)-3-(1*H*-indol-3-yl)cyclopent-1-en-1-yl)-*N*,4-dimethylbenzenesulfonamide ((+)-4.41d)**



**Procedure:** Compound (±)-4.40d (86 mg, 0.24 mmol) and indole (28 mg, 0.24 mmol) were added into a pressure vessel containing 4 Å MS (170 mg). (*R*)-catalyst 4.29d (50 mg, 0.07 mmol) was then added, and the mixture was dissolved in dichloroethane (4.8 mL). Upon stirring at -5 °C for 98 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 15% EtOAc in hexanes to give product (+)-4.41d as yellow oil (84 mg, 77% yield, 20:1 rr).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ (ppm) = 7.93 (s, 1H), 7.67 (dd, *J* = 12.2, 8.1 Hz, 3H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 10.5 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.13 (t,



$J = 7.5$  Hz, 1H), 7.07 (d,  $J = 8.5$  Hz, 2H), 7.05 – 7.02 (m, 1H), 4.46 (d,  $J = 7.6$  Hz, 1H), 2.99 (s, 3H), 2.71 – 2.62 (m, 1H), 2.45 – 2.34 (m, 5H), 2.00 (td,  $J = 9.1, 3.6$  Hz, 1H).

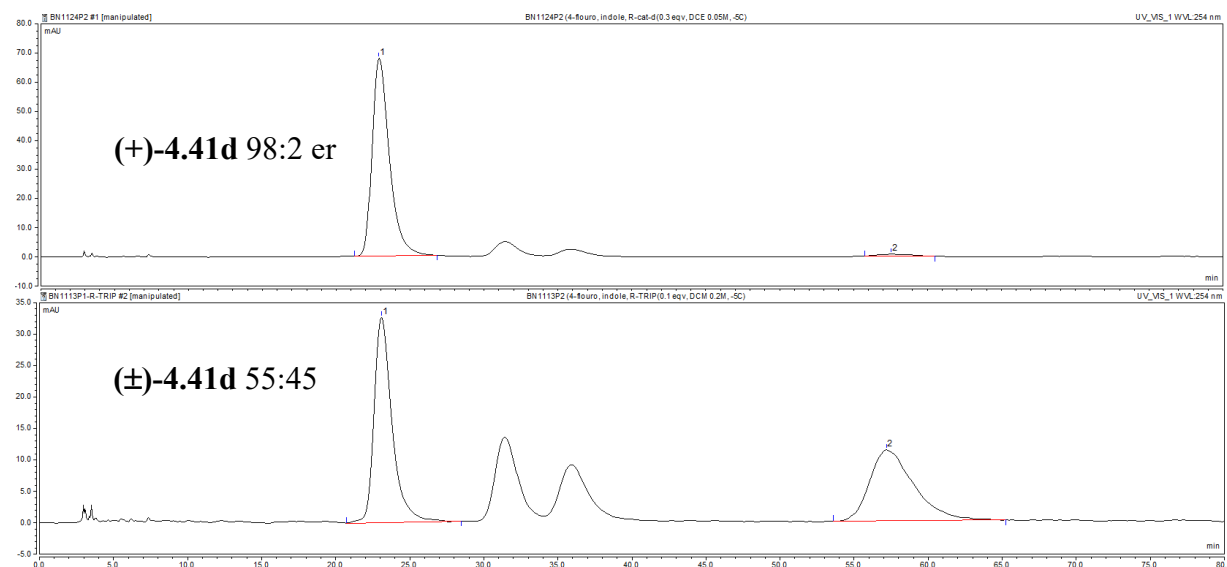
$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 162.75, 160.78, 143.53, 138.75, 136.89, 136.63, 136.24, 129.71, 129.65, 129.54, 127.55, 126.61, 122.09, 121.93, 119.25, 118.86, 114.88, 114.71, 111.22, 43.18, 36.20, 30.70, 30.40, 21.49.

IR ( $\text{cm}^{-1}$ ):  $f = 3409, 2924, 1598, 1508, 1456, 1337, 1228, 1156, 1087, 910, 835, 807, 742$ . HRMS

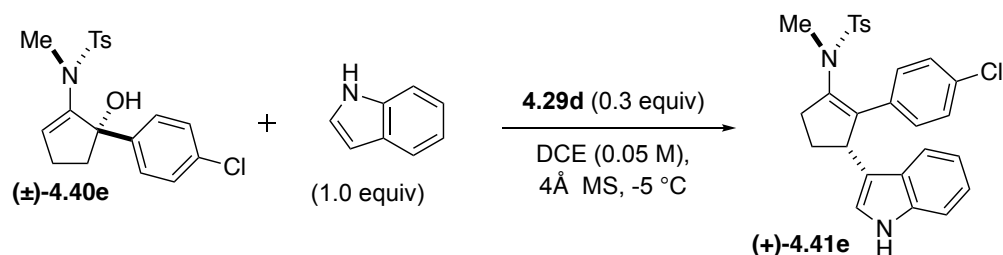
HRMS ( $\text{M}+\text{H}^+$ ) = 461.1694 calculated for  $\text{C}_{27}\text{H}_{26}\text{FN}_2\text{O}_2\text{S}$ ; experimental = 461.1695.

Optical Rotation  $[\alpha]_{25}^{\text{D}} = +88.5$  ( $c = 1.00$  in  $\text{CHCl}_3$ ).

HPLC: 98:2 er using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 7.5% isopropanol in hexanes at 1 mL/min.



**(*S*)-*N*-(2-(4-chlorophenyl)-3-(1*H*-indol-3-yl)cyclopent-1-en-1-yl)-*N*,4-dimethylbenzenesulfonamide((+)-4.41e)**



**Procedure:** Compound ( $\pm$ )-4.40e (66 mg, 0.17 mmol) and indole (21 mg, 0.17 mmol) were added into a pressure vessel containing 4 Å MS (130 mg). (*R*)-catalyst 4.29d (37 mg, 0.05 mmol) was then added, and the mixture was dissolved in dichloroethane (3.5 mL). Upon stirring at -5 °C for 91 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 30% EtOAc in hexanes to give product (+)-4.41e as yellow oil (52 mg, 64% yield, 20:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.93 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.65 (dd, *J* = 8.3, 3.3 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.32 – 7.22 (m, 4H), 7.20 (td, *J* = 8.1, 1.2 Hz, 1H), 7.13 (td, *J* = 7.9, 0.9 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 2.2 Hz, 1H), 4.46 (dd, *J* = 7.0, 1.5 Hz, 1H), 2.98 (s, 3H), 2.71 – 2.61 (m, 1H), 2.44 – 2.34 (m, 5H), 2.00 (td, *J* = 8.7, 3.5 Hz, 1H).

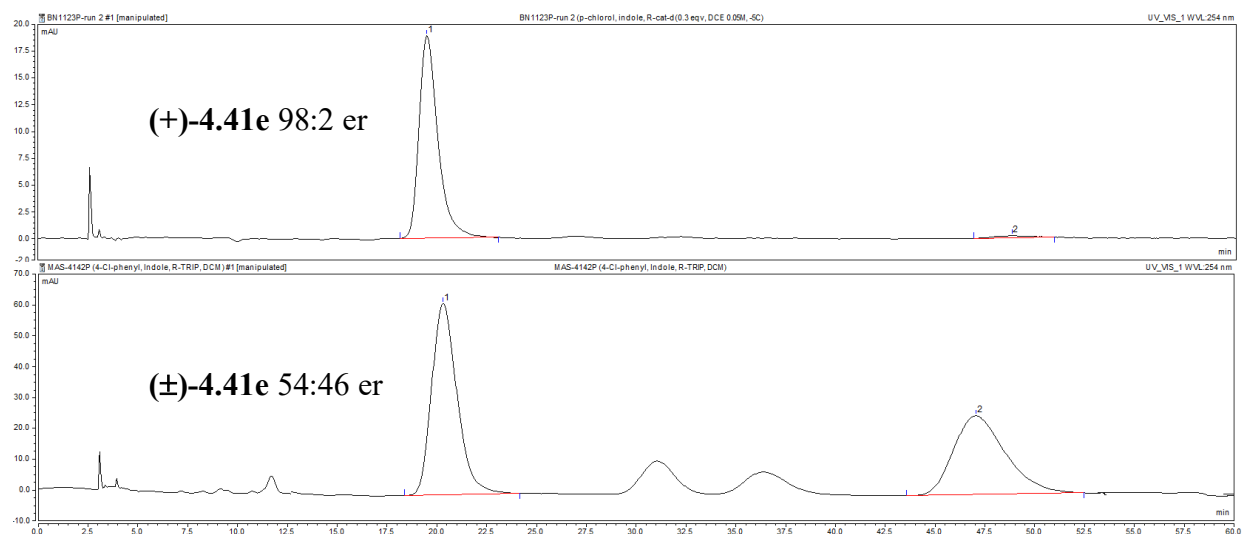
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 143.58, 138.63, 137.75, 136.63, 136.27, 133.47, 132.90, 129.55, 129.26, 128.10, 127.54, 126.60, 122.07, 122.01, 119.32, 118.90, 118.20, 111.22, 43.09, 36.26, 30.92, 30.41, 21.54.

**IR** (cm<sup>-1</sup>):  $\nu$  = 3404, 2925, 2854, 1491, 1457, 1339, 1155, 1089, 1037, 1012, 830, 813, 741.

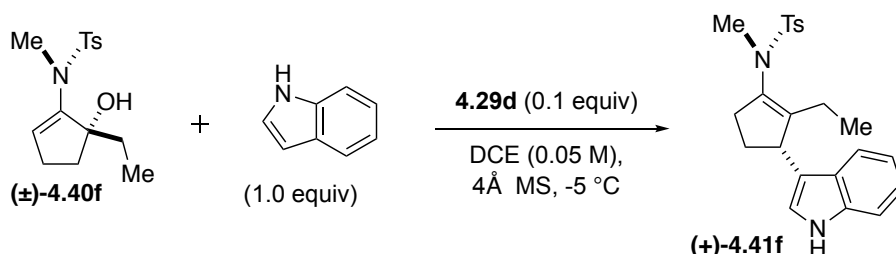
**HRMS** (M+H)<sup>+</sup> = 477.1398 calculated for C<sub>27</sub>H<sub>26</sub>ClN<sub>2</sub>O<sub>2</sub>S; experimental = 477.1392.

**Optical Rotation** [ $\alpha$ ]<sub>25</sub><sup>D</sup> = +111 (*c* = 1.00 in CHCl<sub>3</sub>).

**HPLC:** 98:2 er using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 7.5% isopropanol in hexanes at 1 mL/min



**(S)-N-(2-ethyl-3-(1*H*-indol-3-yl)cyclopent-1-en-1-yl)-N,4-dimethylbenzenesulfonamide ((+)-4.41f)**



**Procedure:** Compound (±)-4.40f (68 mg, 0.23 mmol) and indole (27 mg, 0.23 mmol) were added into a pressure vessel containing 4 Å MS (136 mg). (*R*)-catalyst **4.29d** (16 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (2.3 mL). Upon stirring at -5 °C for 89 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 15% EtOAc in hexanes to give product (+)-4.41f as yellow oil (71 mg, 78% yield, 20:1 rr).

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 7.98 (s, 1H), 7.77 (d,  $J$  = 8.3 Hz, 2H), 7.63 (d,  $J$  = 7.9 Hz, 1H), 7.38 (d,  $J$  = 8.1 Hz, 1H), 7.28 (d,  $J$  = 2H), 7.20 (t,  $J$  = 7.5 Hz, 1H), 7.14 – 7.08 (m, 2H), 4.13 (t,  $J$  = 5.7 Hz, 1H), 3.01 (s, 3H), 2.41 (s, 3H), 2.38 - 2.34 (m, 1H), 2.29 - 2.19 (m, 3H), 1.94 – 1.86 (m, 1H), 1.86 – 1.76 (m, 1H), 0.86 (t,  $J$  = 7.6 Hz, 3H).

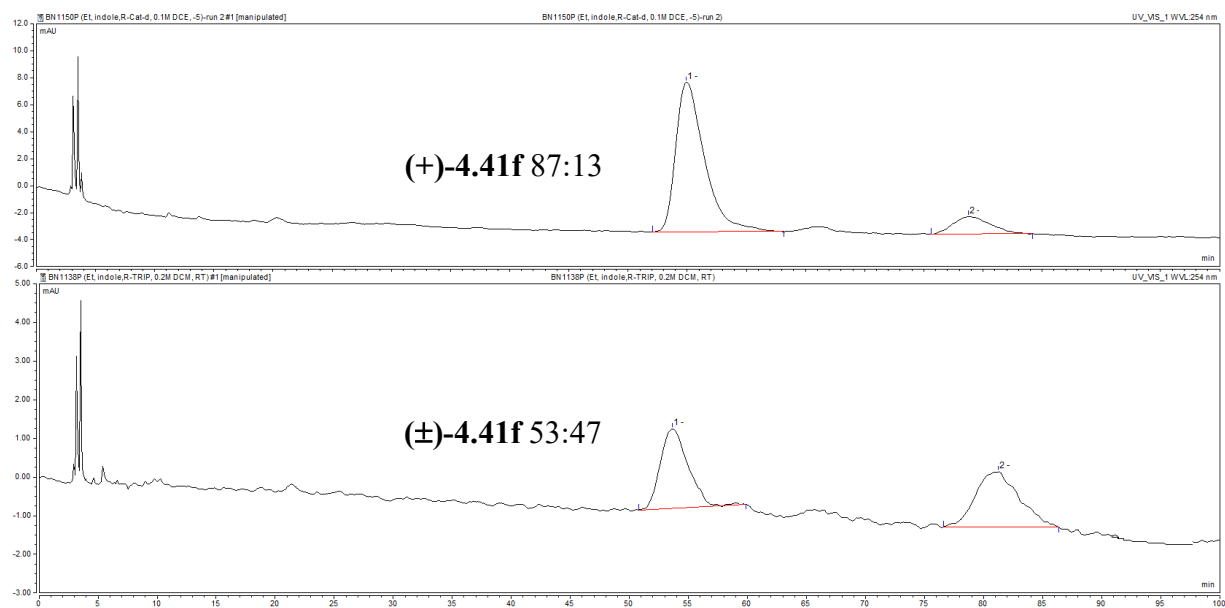
**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 146.38, 143.25, 136.66, 136.45, 134.01, 126.76, 121.91, 121.56, 119.23, 119.09, 118.61, 111.17, 40.97, 36.43, 30.37, 29.13, 21.50, 20.13, 11.88.

**IR** ( $\text{cm}^{-1}$ ):  $\nu$  = 3406, 2964, 1597, 1456, 1336, 1151, 1088, 1017, 907, 813, 727.

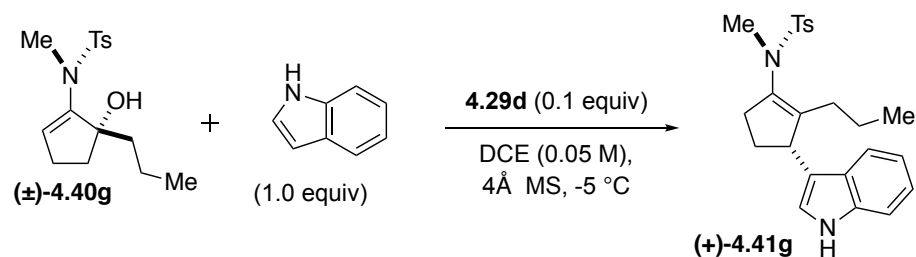
**HRMS** ( $\text{M}+\text{H}$ ) $^+$  = 395.1788 calculated for  $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_2\text{S}$ ; experimental = 395.1796.

**Optical Rotation**  $[\alpha]_{25}^{\text{D}}$  = +62.5 ( $c$  = 1.00 in  $\text{CHCl}_3$ ).

**HPLC**: 87:13 er using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 3% isopropanol in hexanes at 1 mL/min



**(*S*)-*N*-(3-(1*H*-indol-3-yl)-2-propylcyclopent-1-en-1-yl)-*N*,4-dimethylbenzenesulfonamide**  
**(+)-4.41g**



**Procedure:** Compound (±)-4.40g (75 mg, 0.24 mmol) and indole (28 mg, 0.24 mmol) were added into a pressure vessel containing 4 Å MS (150 mg). (*R*)-catalyst **4.29d** (17 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (2.4 mL). Upon stirring at -5 °C for 165 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 15% EtOAc in hexanes to give product (+)-4.41g as yellow oil (81 mg, 82% yield, 20:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ (ppm) = 7.99 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.28 (s, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 2H), 4.09 (t, *J* = 5.3, 1H), 3.00 (s, 3H), 2.40 (s, 3H), 2.38 – 2.32 (m, 1H), 2.24 – 2.18 (m, 1H), 1.91 – 1.82 (m, 2H), 1.42-1.36 (m, 2H), 1.28 – 1.20 (m, 2H), 0.77 (t, *J* = 7.3 Hz, 3H).

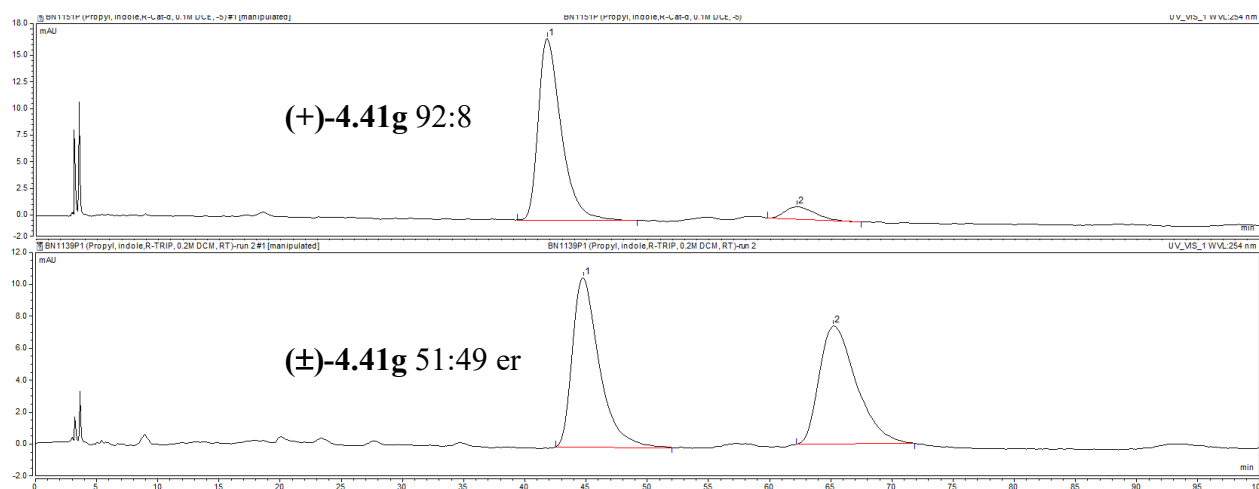
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>): δ (ppm) = 145.20, 143.27, 136.66, 136.50, 134.77, 129.54, 127.53, 121.91, 121.58, 119.24, 119.07, 118.68, 111.16, 41.15, 36.42, 30.45, 28.98, 28.83, 21.49, 20.37, 14.10.

**IR** (cm<sup>-1</sup>): *f* = 3407, 2957, 2869, 1597, 1456, 1339, 1154, 1089, 814, 742.

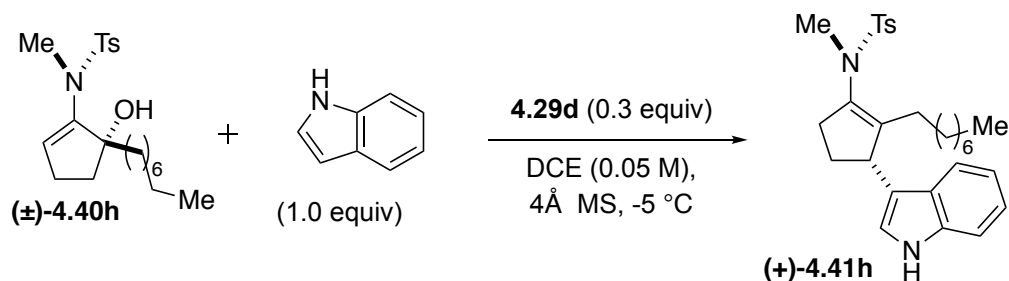
**HRMS** (M+H)<sup>+</sup> = 409.1944 calculated for C<sub>23</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>S; experimental = 409.1940.

**Optical Rotation** [α]<sub>25</sub><sup>D</sup> = +15.2 (c = 1.00 in CHCl<sub>3</sub>).

**HPLC:** 92:8 er using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 3% isopropanol in hexanes at 1 mL/min



**(S)-N-(3-(1*H*-indol-3-yl)-2-octylcyclopent-1-en-1-yl)-N,4-dimethylbenzenesulfonamide ((+)-4.41h)**



**Procedure:** Compound **(±)-4.40h** (50 mg, 0.13 mmol) and indole (15 mg, 0.13 mmol) were added into a pressure vessel containing 4 Å MS (100 mg). (*R*)-catalyst **4.29d** (28 mg, 0.04 mmol) was then added, and the mixture was dissolved in dichloroethane (2.6 mL). Upon stirring at -5 °C for 211 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 60% EtOAc in hexanes to give product **(+)-4.40h** as yellow oil (27 mg, 43% yield, 20:1 rr).

**$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 8.01 (s, 1H), 7.76 (d,  $J$  = 8.3 Hz, 2H), 7.63 (d,  $J$  = 7.9 Hz, 1H), 7.38 (d,  $J$  = 8.1 Hz, 1H), 7.26 (d,  $J$  = 8.3 Hz, 4H), 7.20 (ddd,  $J$  = 8.3, 6.9, 1.1 Hz, 1H), 7.15 – 7.10 (m, 2H), 4.08 (dd,  $J$  = 9.2, 3.1 Hz, 1H), 3.00 (s, 3H), 2.40 (s, 3H), 2.39 – 2.30 (m, 1H), 2.26 – 2.15 (m, 3H), 1.93 – 1.85 (m, 1H), 1.81 (dddd,  $J$  = 11.7, 8.9, 4.9, 2.2 Hz, 1H), 1.38 – 1.05 (m, 12H), 0.86 (t,  $J$  = 7.1 Hz, 3H).

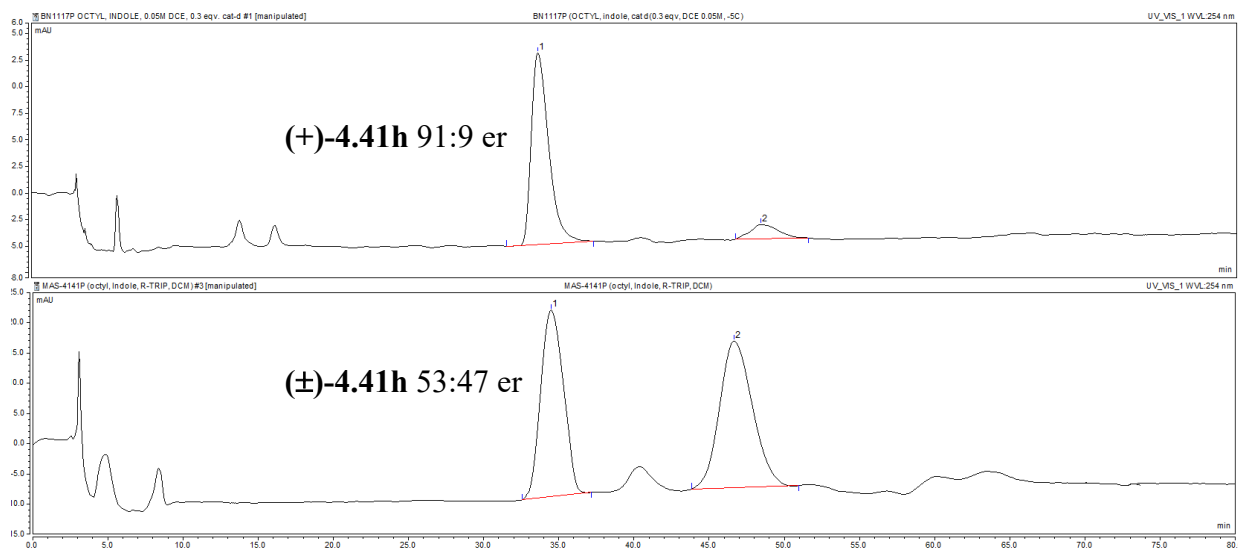
**$^{13}\text{C}$  NMR** (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 145.35, 143.23, 136.68, 136.54, 134.57, 129.53, 127.54, 126.83, 121.92, 121.57, 119.25, 119.10, 118.72, 111.14, 41.20, 36.43, 31.86, 30.41, 29.63, 29.35, 29.22, 28.95, 27.14, 26.92, 22.64, 21.50, 14.09.

**IR** ( $\text{cm}^{-1}$ ):  $f$  = 3409, 2925, 2854, 1457, 1155, 1088, 1012, 813, 741, 664, 585, 549.

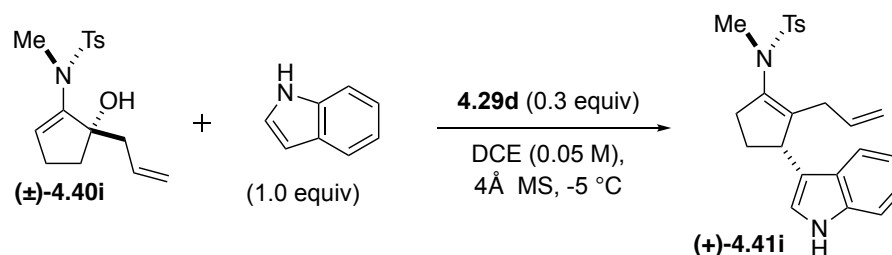
**HRMS** ( $\text{M}+\text{H}$ ) $^+$  = 479.2727 calculated for  $\text{C}_{29}\text{H}_{39}\text{N}_2\text{O}_2\text{S}$ ; experimental = 479.2727.

**Optical Rotation**  $[\alpha]_{25}^{\text{D}}$  = +50.2 ( $c$  = 1.00 in  $\text{CHCl}_3$ ).

**HPLC**: 91:9 er using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 3-4% isopropanol in hexanes at 1 mL/min



**(*S*)-*N*-(2-allyl-3-(1*H*-indol-3-yl)cyclopent-1-en-1-yl)-*N*,4-dimethylbenzenesulfonamide ((+)-4.41i)**



**Procedure:** Compound (±)-4.40i (52 mg, 0.17 mmol) and indole (20 mg, 0.17 mmol) were added into a pressure vessel containing 4 Å MS (100 mg). (*R*)-catalyst 4.29d (12 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (3.4 mL). Upon stirring at -5 °C for 258 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 30% EtOAc in hexanes to give product (+)-4.41h as yellow oil (38 mg, 55% yield, 20:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ (ppm) = 7.98 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.13 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.10 (d, *J* = 2.3 Hz, 1H), 5.74 – 5.64 (m, 1H), 4.93 – 4.83 (m, 2H), 4.12 – 4.07 (m, 1H), 3.16 (dd, *J* = 15.0, 5.8 Hz, 1H), 3.00 (s, 3H), 2.53 (dd, *J* = 14.9, 7.3 Hz, 1H), 2.41 (s, 3H), 2.29 – 2.15 (m, 3H), 1.92 (dt, *J* = 11.4, 7.6, 3.8 Hz, 1H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>): δ (ppm) = 143.37, 142.75, 136.70, 136.36, 135.36, 135.07, 129.58, 127.53, 126.75, 121.94, 121.67, 119.25, 119.12, 118.42, 115.85, 111.16, 41.37, 36.45, 31.51, 30.17, 29.06, 21.52.

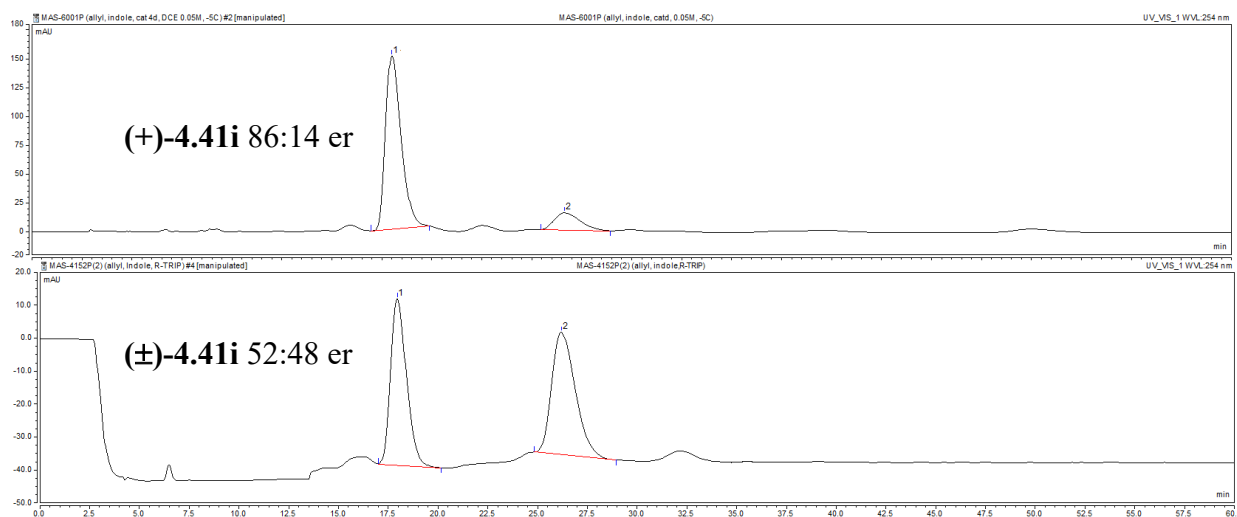
**IR (cm<sup>-1</sup>):** *f* = 3409, 2926, 2855, 1457, 1424, 1339, 1154, 1088, 994, 912, 814, 742, 664, 586, 548.

**HRMS** (M+H)<sup>+</sup> = 407.1788 calculated for C<sub>24</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>S; experimental = 407.1814.

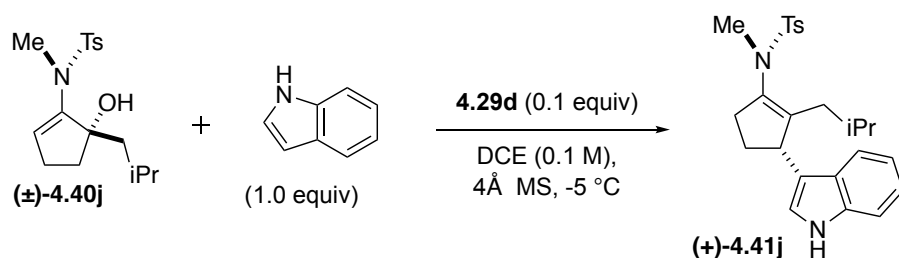
**Optical Rotation** [α]<sub>25</sub><sup>D</sup> = +76.3 (c = 1.00 in CHCl<sub>3</sub>).



**HPLC:** 86:14 er using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 7% isopropanol in hexanes at 1 mL/min



**(S)-N-(3-(1*H*-indol-3-yl)-2-isobutylcyclopent-1-en-1-yl)-N,4-dimethylbenzenesulfonamide**  
**((+)-4.41j)**



**Procedure:** Compound **(±)-4.40j** (69 mg, 0.21 mmol) and indole (25 mg, 0.21 mmol) were added into a pressure vessel containing 4Å MS (140 mg). (*R*)-catalyst **4.29d** (15 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (2.1 mL). Upon stirring at -5 °C for 140 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 15% EtOAc in hexanes to give product **(+)-4.41j** as yellow oil (38 mg, 35% yield, 20:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.98 (s, 1H), 7.75 (d,  $J$  = 7.0 Hz, 2H), 7.66 (d,  $J$  = 7.8 Hz, 1H), 7.39 (d,  $J$  = 8.1 Hz, 1H), 7.27 (d,  $J$  = 7.8 Hz, 2H), 7.22 – 7.18 (m, 2H), 7.13 (t,  $J$  = 7.5 Hz, 1H), 4.07 (t,  $J$  = 5.4 Hz, 1H), 2.98 (s, 3H), 2.40 (s, 3H), 2.33 (t,  $J$  = 12.2 Hz, 1H), 2.22 – 2.12 (m, 2H), 2.07 – 2.01 (m, 1H), 1.90 – 1.85 (m, 2H), 1.77 – 1.68 (m, 1H), 0.80 (dd,  $J$  = 6.2, 5.3 Hz, 6H).

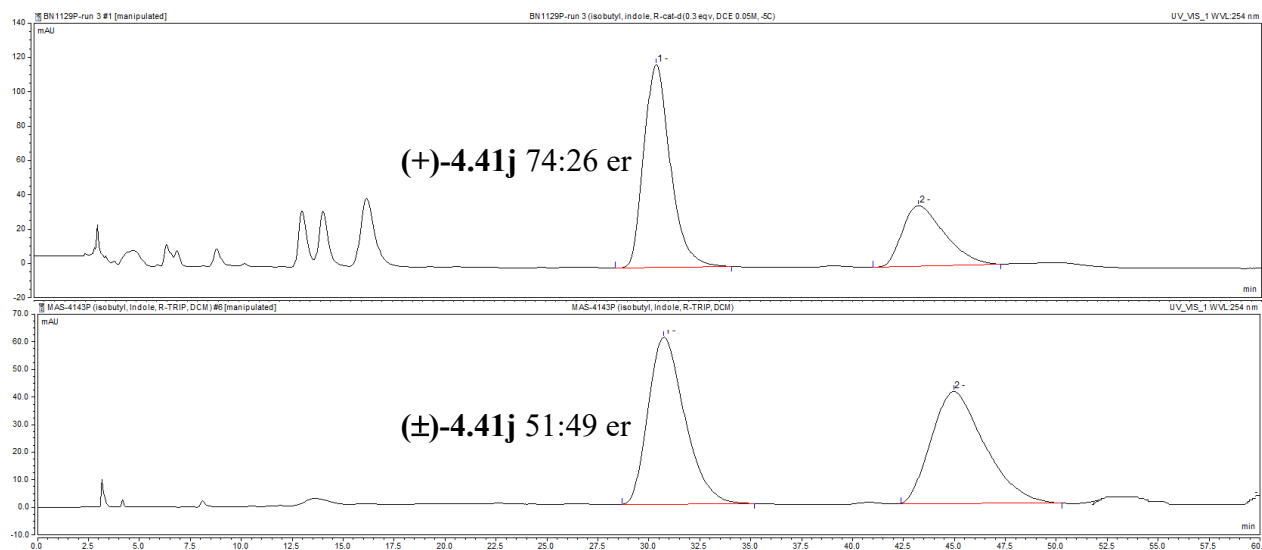
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 144.97, 143.29, 136.67, 136.47, 135.47, 129.55, 127.56, 126.92, 121.91, 121.70, 119.24, 119.02, 118.62, 111.14, 41.15, 36.25, 36.00, 30.54, 28.15, 26.04, 23.50, 21.75, 21.50.

**IR** (cm<sup>-1</sup>):  $\nu$  = 3409, 2954, 2927, 2866, 1457, 1339, 1259, 1153, 1087, 1012, 908, 797, 732.

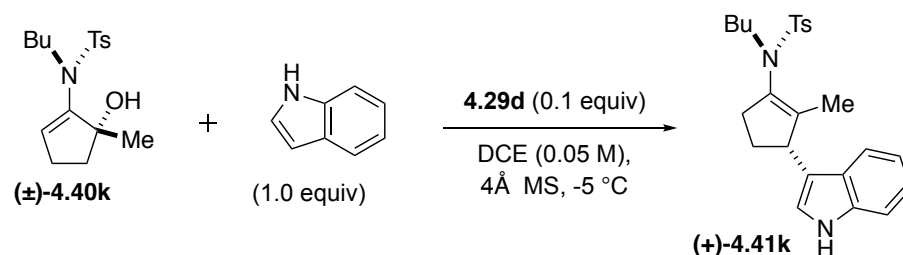
**HRMS** (M+H)<sup>+</sup> = 423.2101 calculated for C<sub>25</sub>H<sub>31</sub>N<sub>2</sub>O<sub>2</sub>S; experimental = 423.2109.

**Optical Rotation** [ $\alpha$ ]<sub>25</sub><sup>D</sup> = +56.4 (c = 1.00 in CHCl<sub>3</sub>).

**HPLC**: 74:26 er using Chiralcel OD-H column (0.46 cm x 25 cm x 5 micron), 3% isopropanol in hexanes at 1 mL/min



**(S)-N-(3-(1*H*-indol-3-yl)-2-methylcyclopent-1-en-1-yl)-*N*-butyl-4-methylbenzenesulfonamide ((+)-4.41k)**



**Procedure:** Compound (±)-4.40k (69 mg, 0.21 mmol) and indole (25 mg, 0.21 mmol) were added into a pressure vessel containing 4 Å MS (140 mg). (*R*)-catalyst **4.29d** (15 mg, 0.02 mmol) was then added, and the mixture was dissolved in dichloroethane (2.1 mL). Upon stirring at -5 °C for 140 hours, the reaction mixture was neutralized with 0.5 mL of Et<sub>3</sub>N. The crude reaction mixture was then directly purified with flash column chromatography using 10% → 15% EtOAc in hexanes to give product (+)-4.41k as yellow oil (38 mg, 35% yield, 20:1 rr).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ (ppm) = 8.00 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.25 (s, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.13–7.09 (m, 2H), 4.00 (t, *J* = 7.9 Hz, 1H), 3.38 – 3.35 (m, 1H), 3.25 – 3.20 (m, 1H), 2.42 – 2.40 (m, 4H), 2.27–2.24 (m, 1H), 2.17 – 2.14 (m, 1H), 1.95 – 1.89 (m, 1H), 1.60 (s, 3H), 1.56 – 1.49 (m, 2H), 1.43 – 1.40 (q, *J* = 7.2 Hz, 2H), 0.94 (t, *J* = 7.2 Hz, 3H).

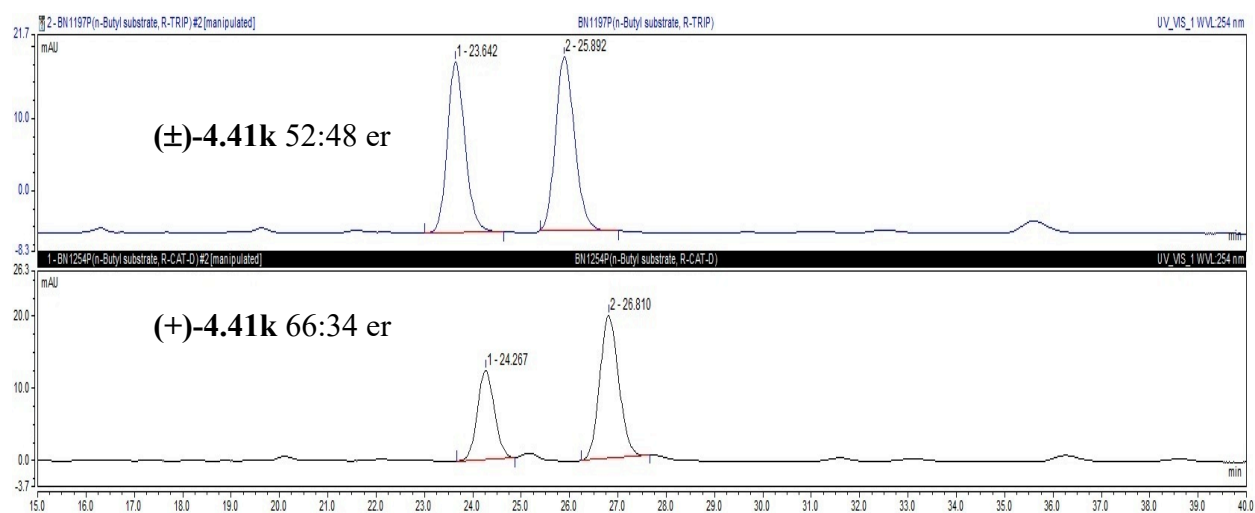
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>): δ (ppm) = 143.37, 143.07, 137.75, 136.68, 132.15, 129.48, 127.27, 126.66, 121.80, 121.55, 119.06, 118.98, 118.38, 111.24, 47.66, 44.33, 30.77, 30.24, 29.16, 21.42, 19.76, 13.74, 13.43.

**IR** (cm<sup>-1</sup>): *f* = 3405, 2929, 1598, 1457, 1337, 1100, 1090, 813, 741, 662, 585, 547, 426.

**HRMS** (M+H)<sup>+</sup> = 423.2101 calculated for C<sub>25</sub>H<sub>31</sub>N<sub>2</sub>O<sub>2</sub>S; experimental = 423.2113.

**Optical Rotation** [α]<sub>25</sub><sup>D</sup> = +35.0 (c = 1.00 in CHCl<sub>3</sub>).

**HPLC:** 66:34 er using Chiralpak IA-3 column (0.46 cm x 25 cm x 3 micron), 3% isopropanol in hexanes at 1 mL/min.



## APPENDIX A. COPYRIGHT RELEASE FOR CHAPTER FOUR

3/7/22, 9:14 PM

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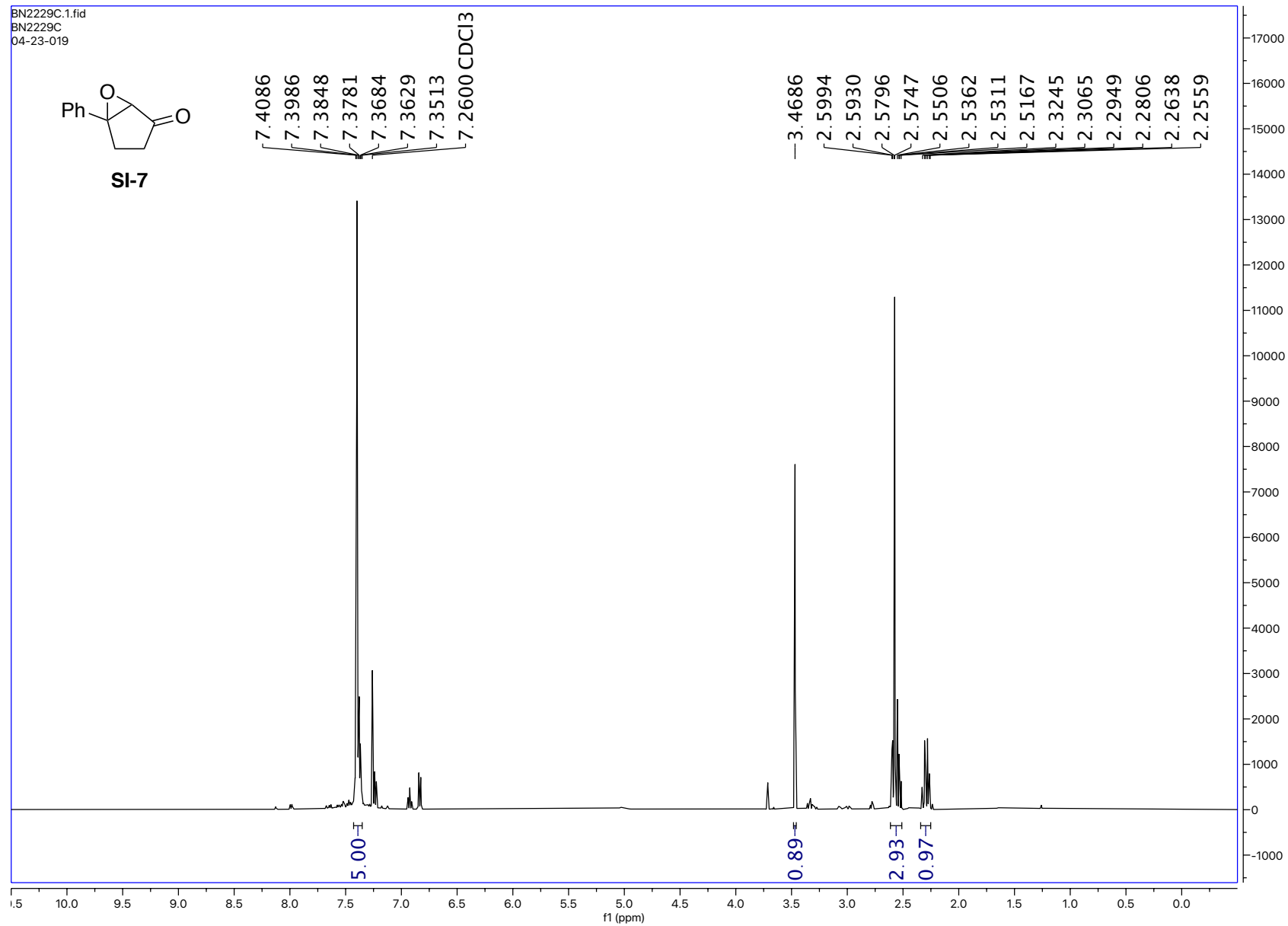
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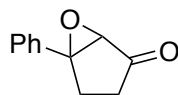
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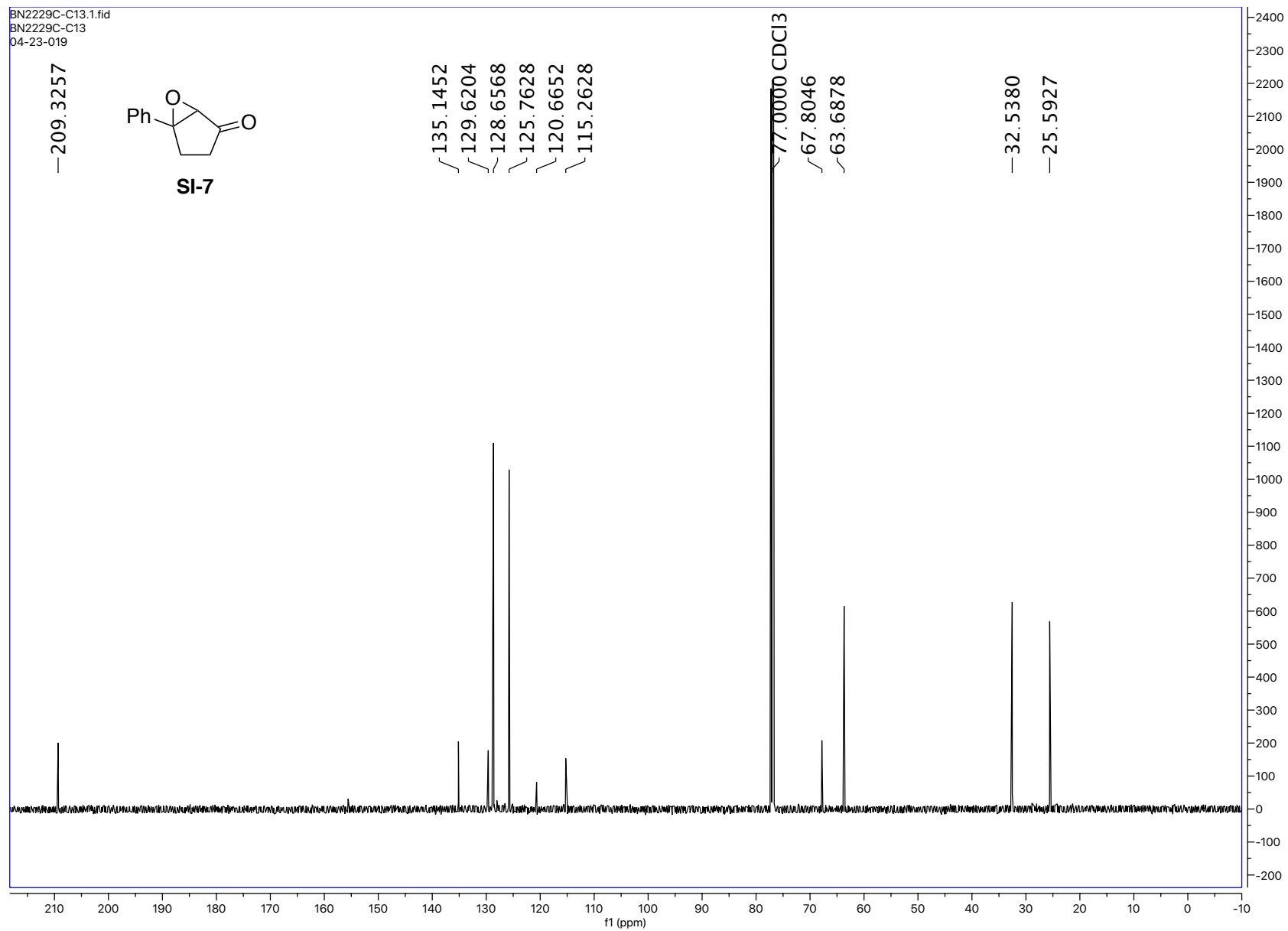
## **APPENDIX B. CHARACTERIZATION SPECTRA**



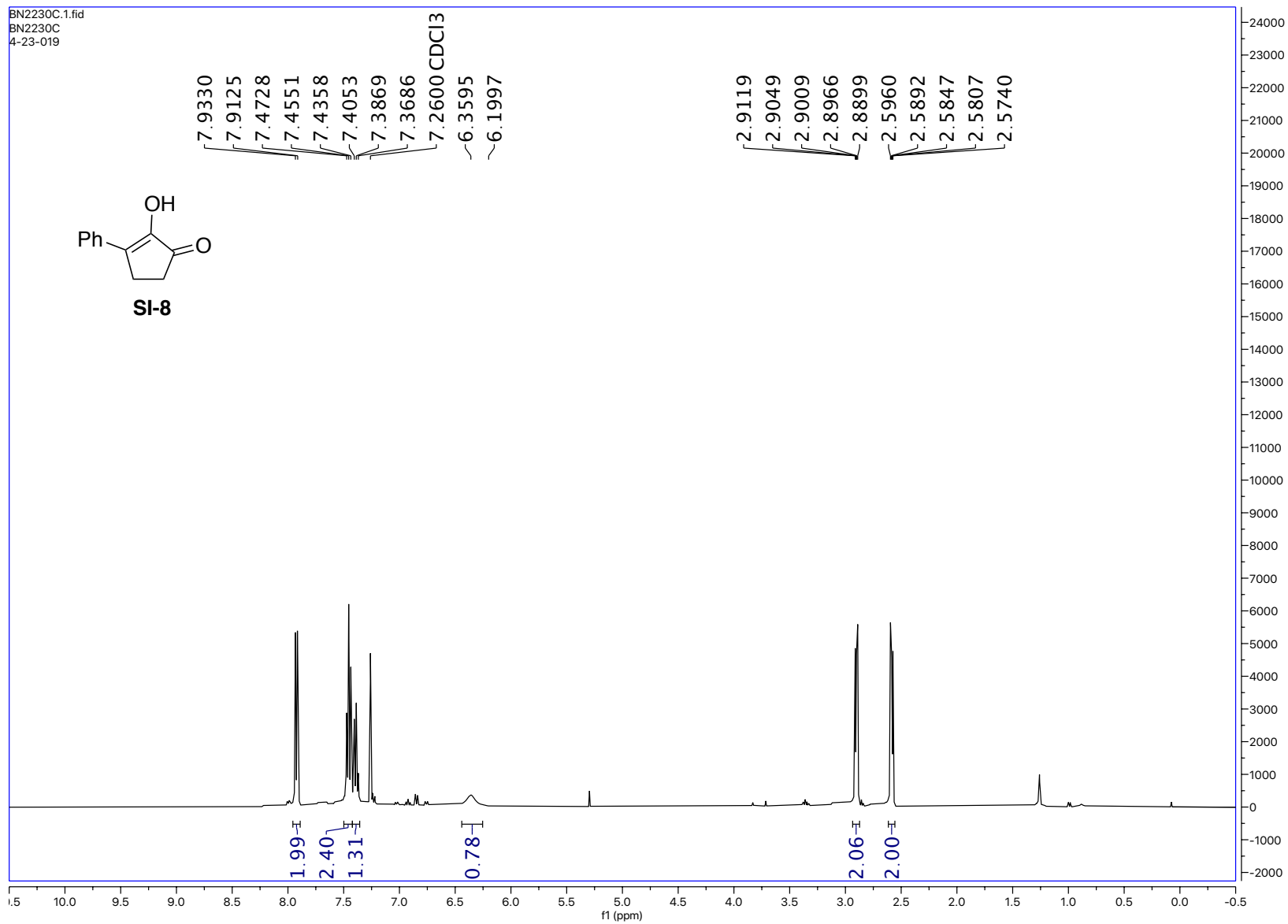
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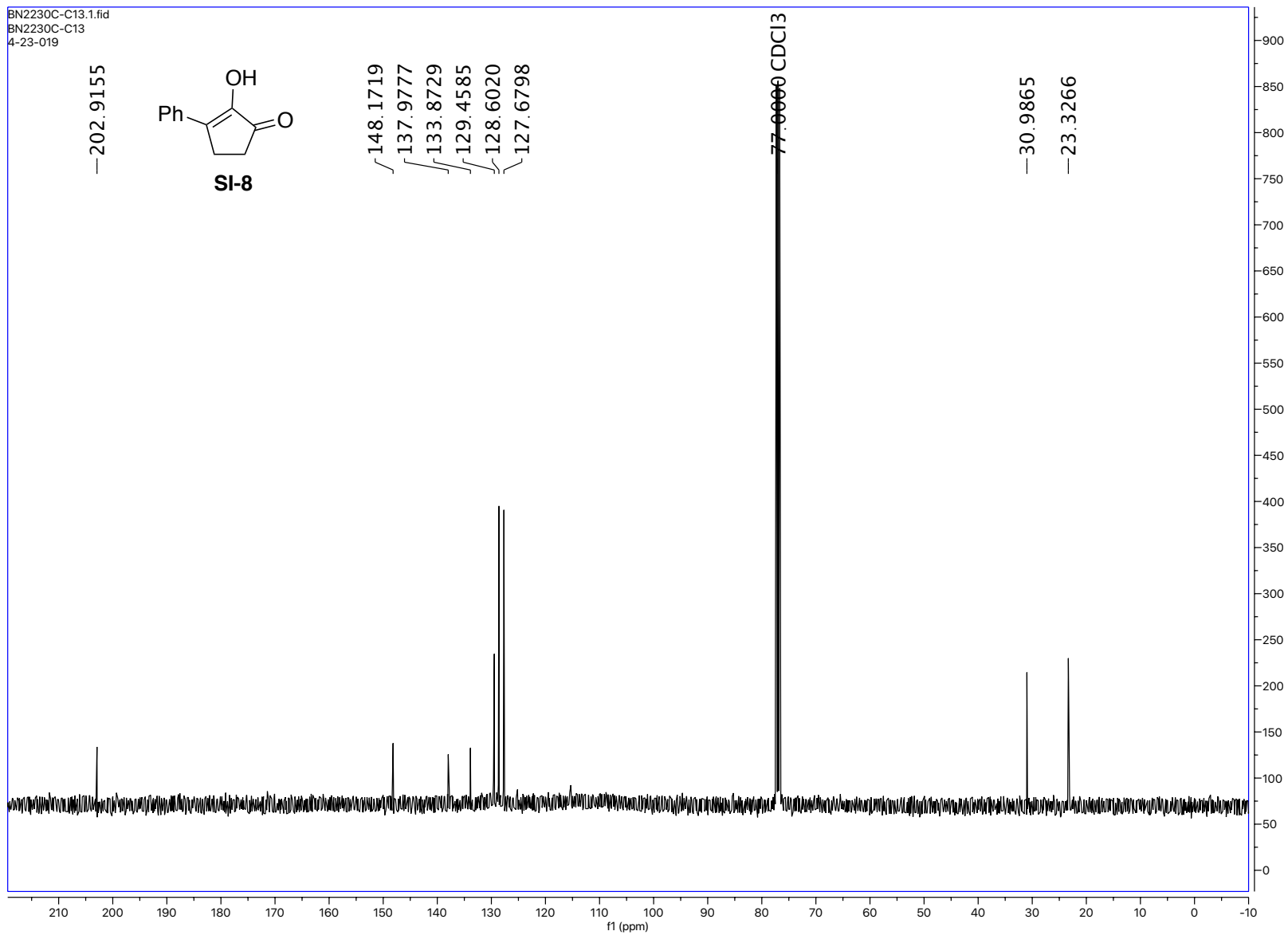


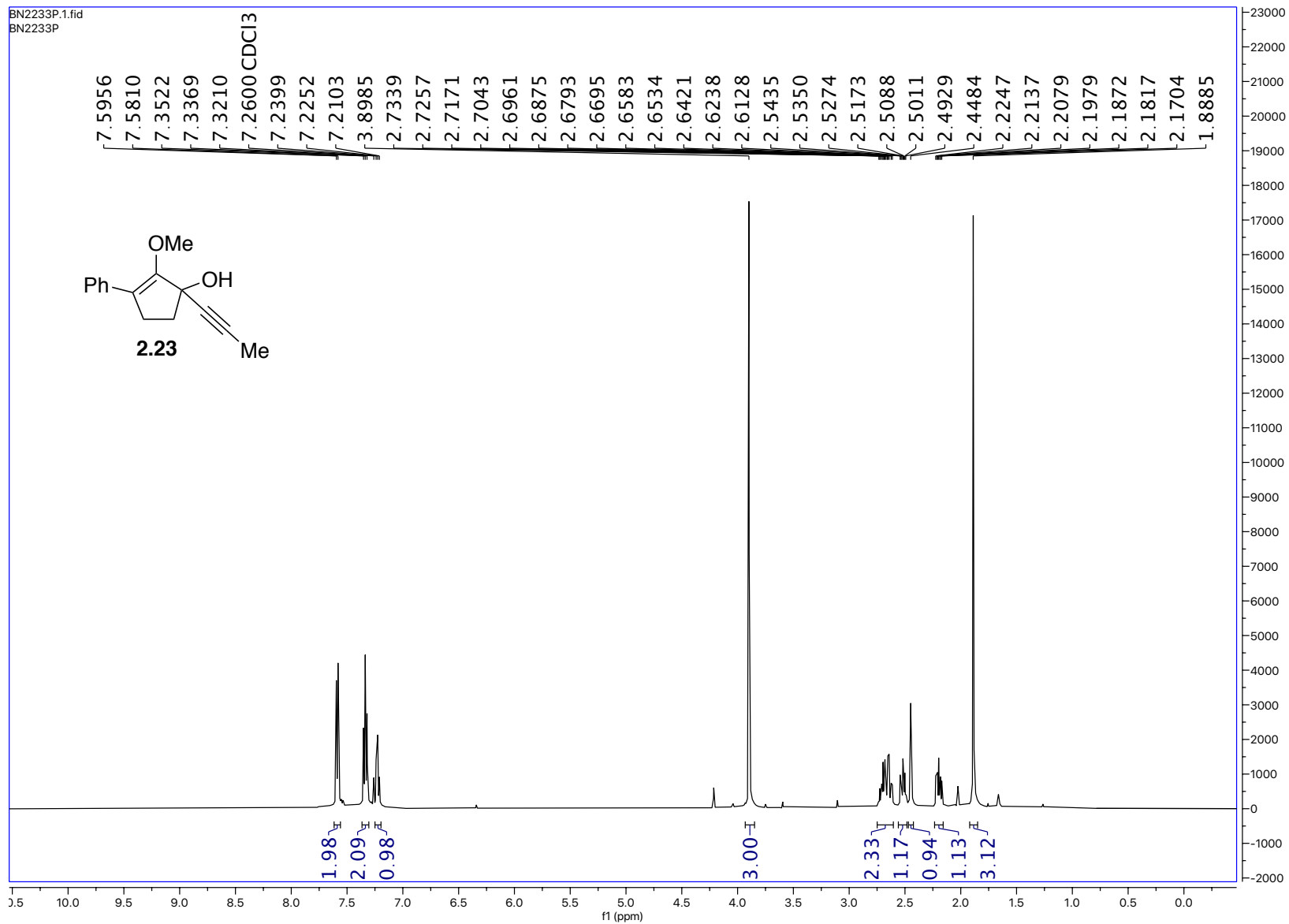
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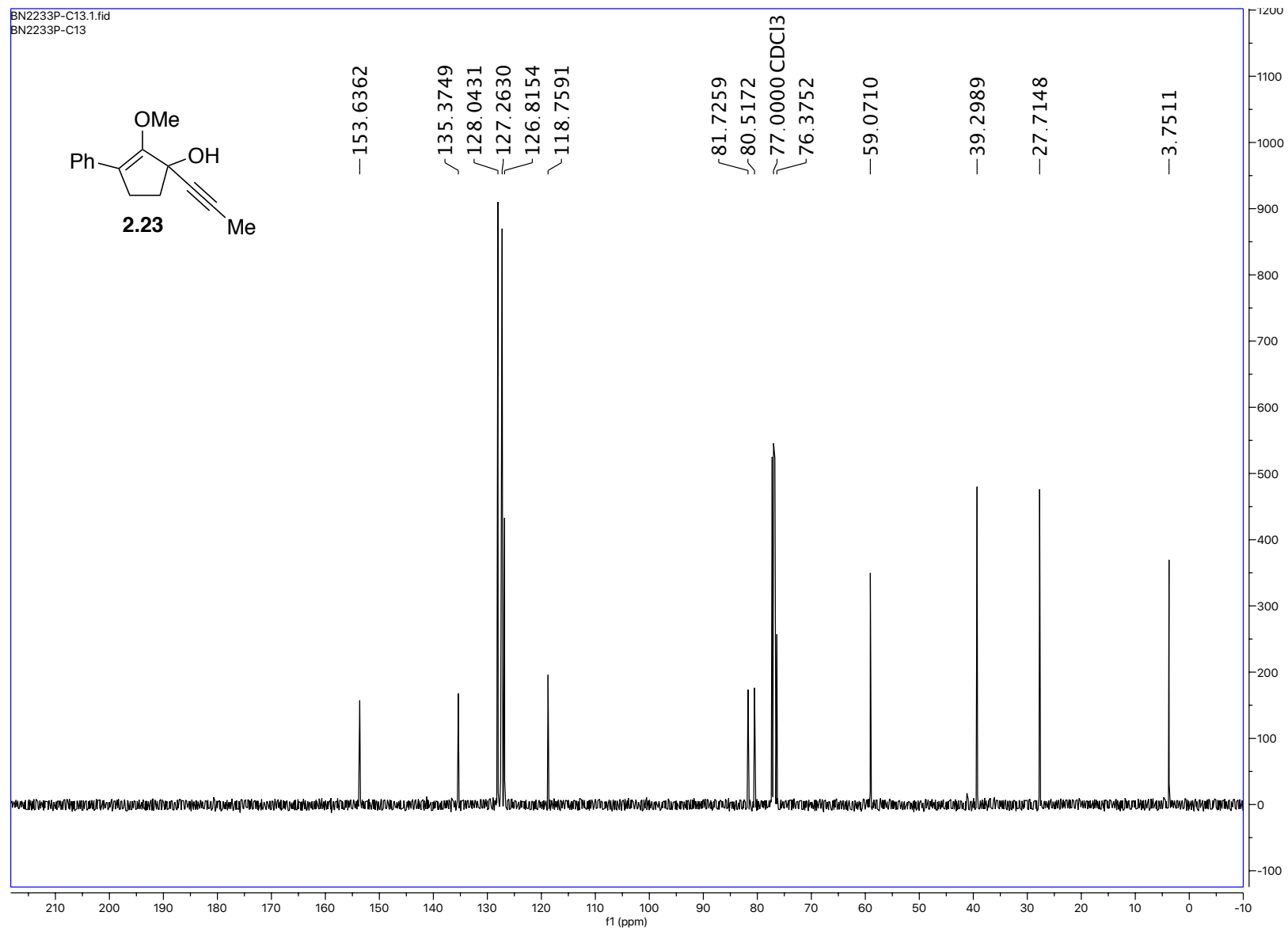


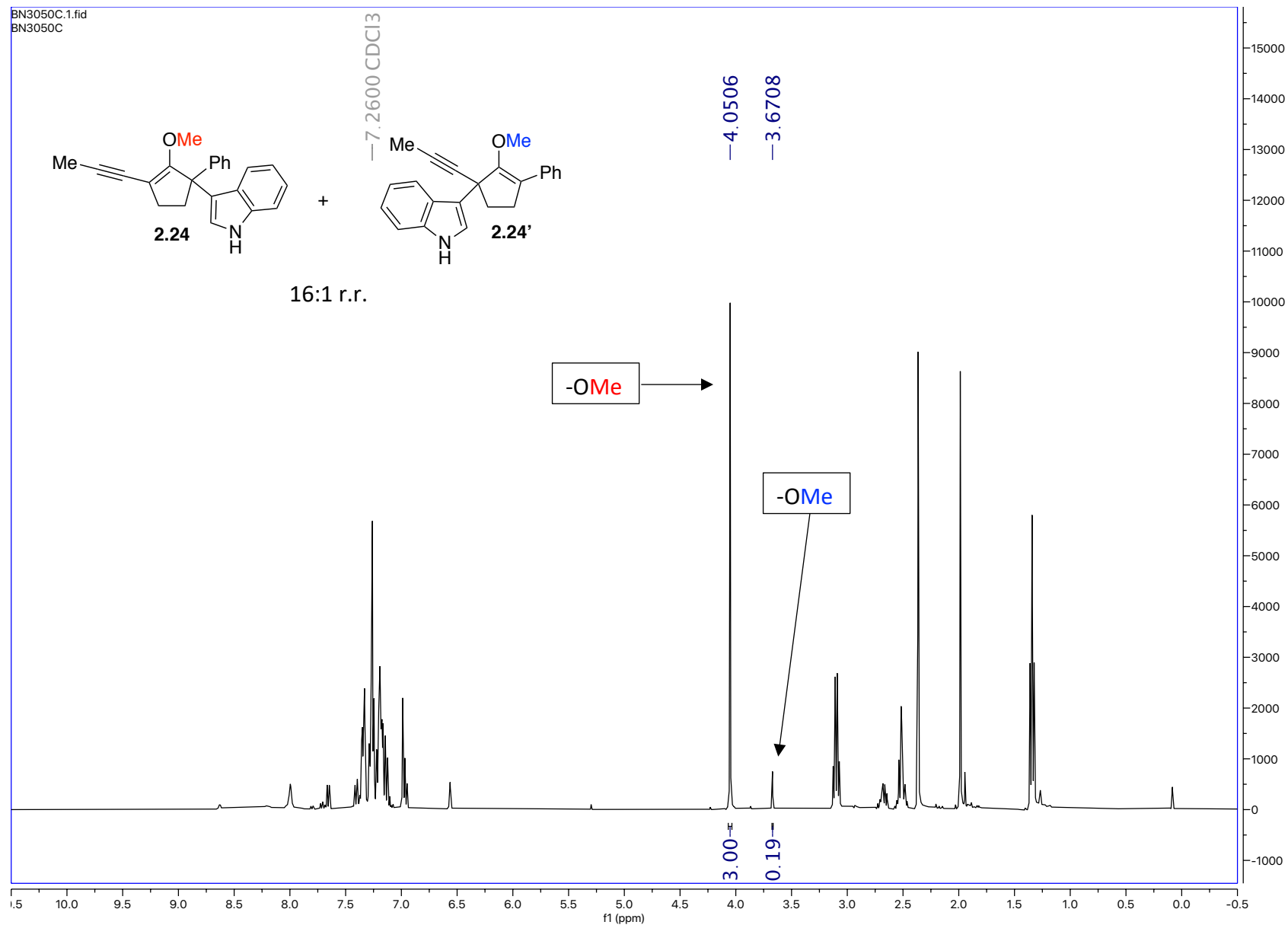


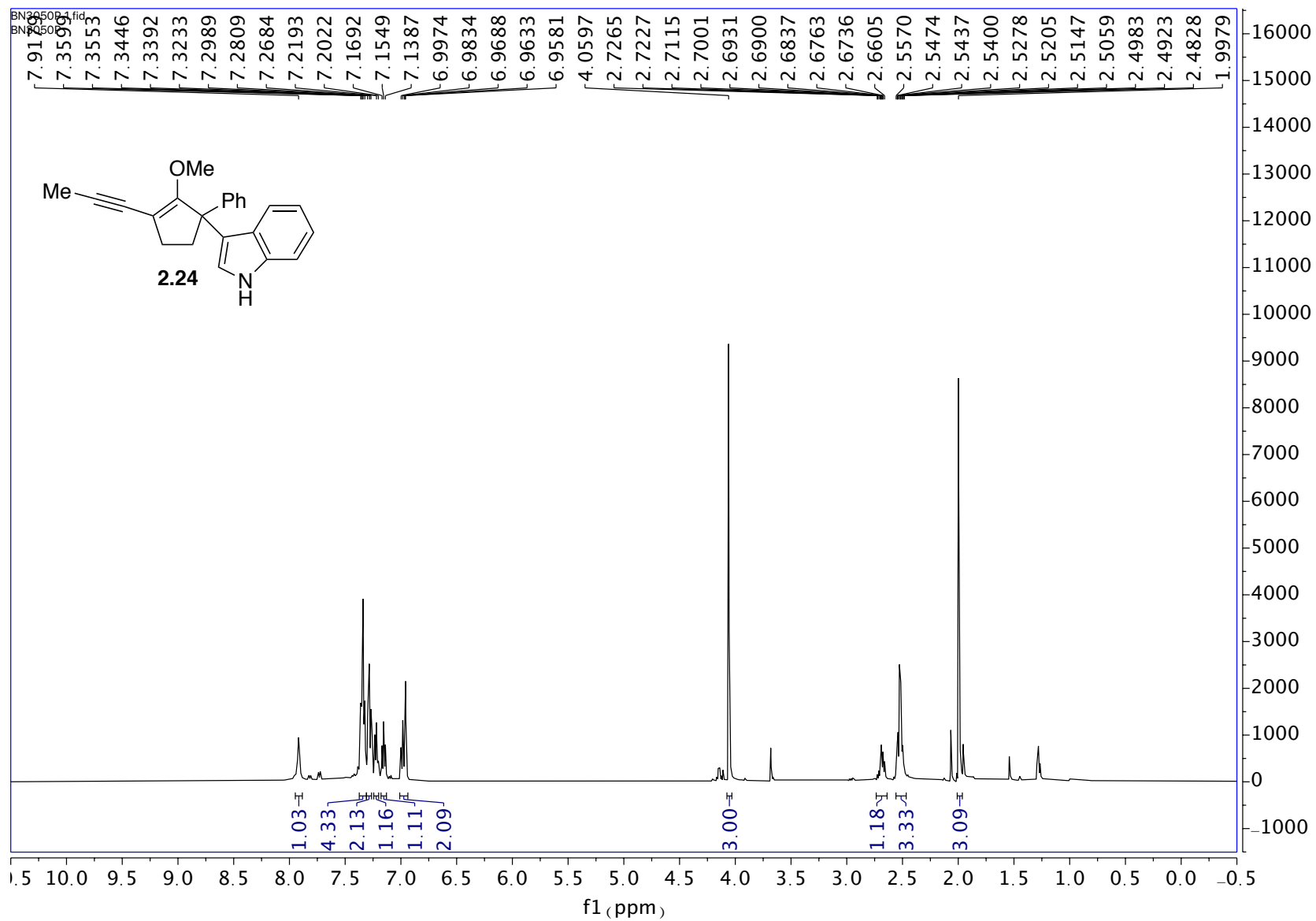


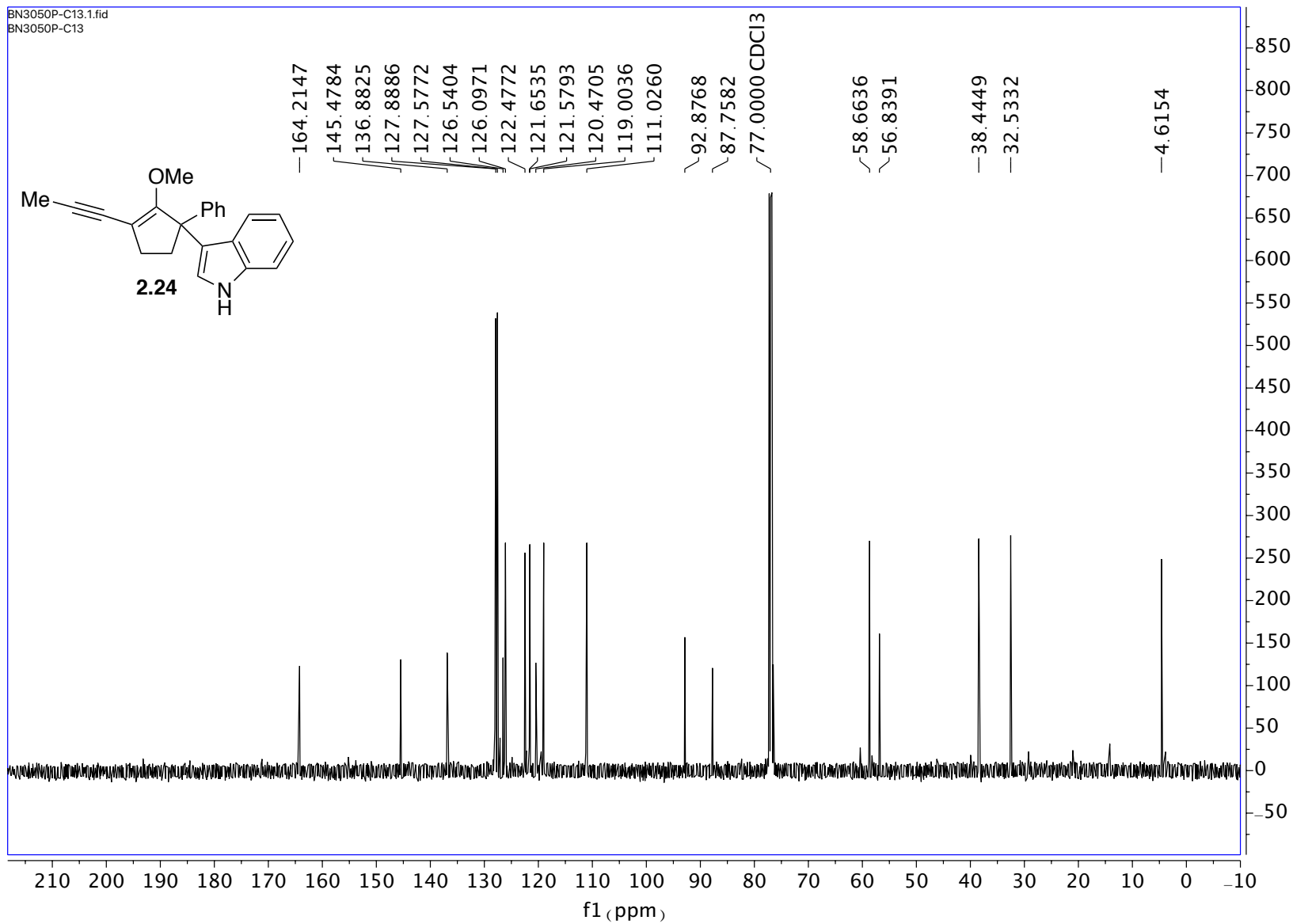




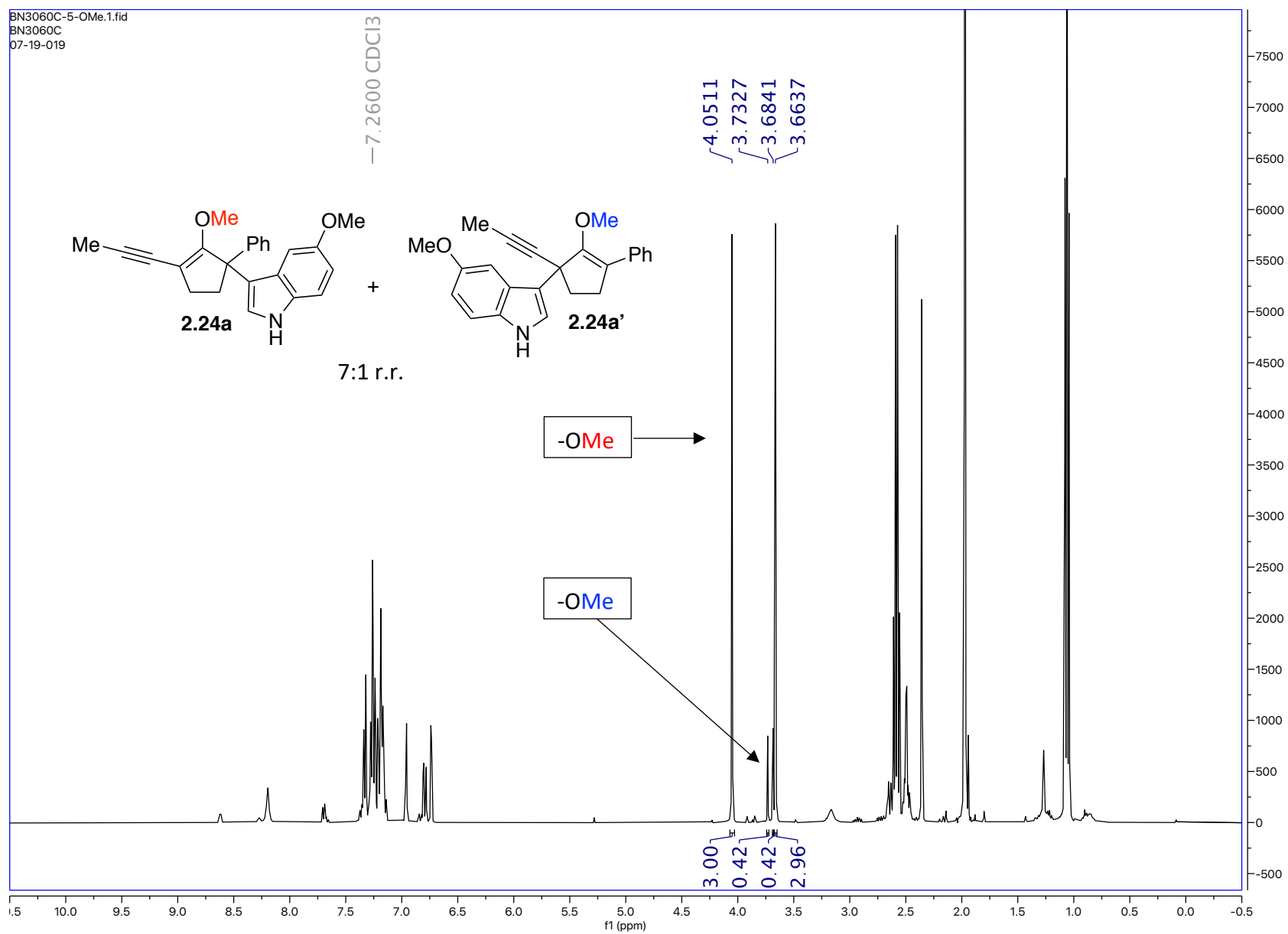




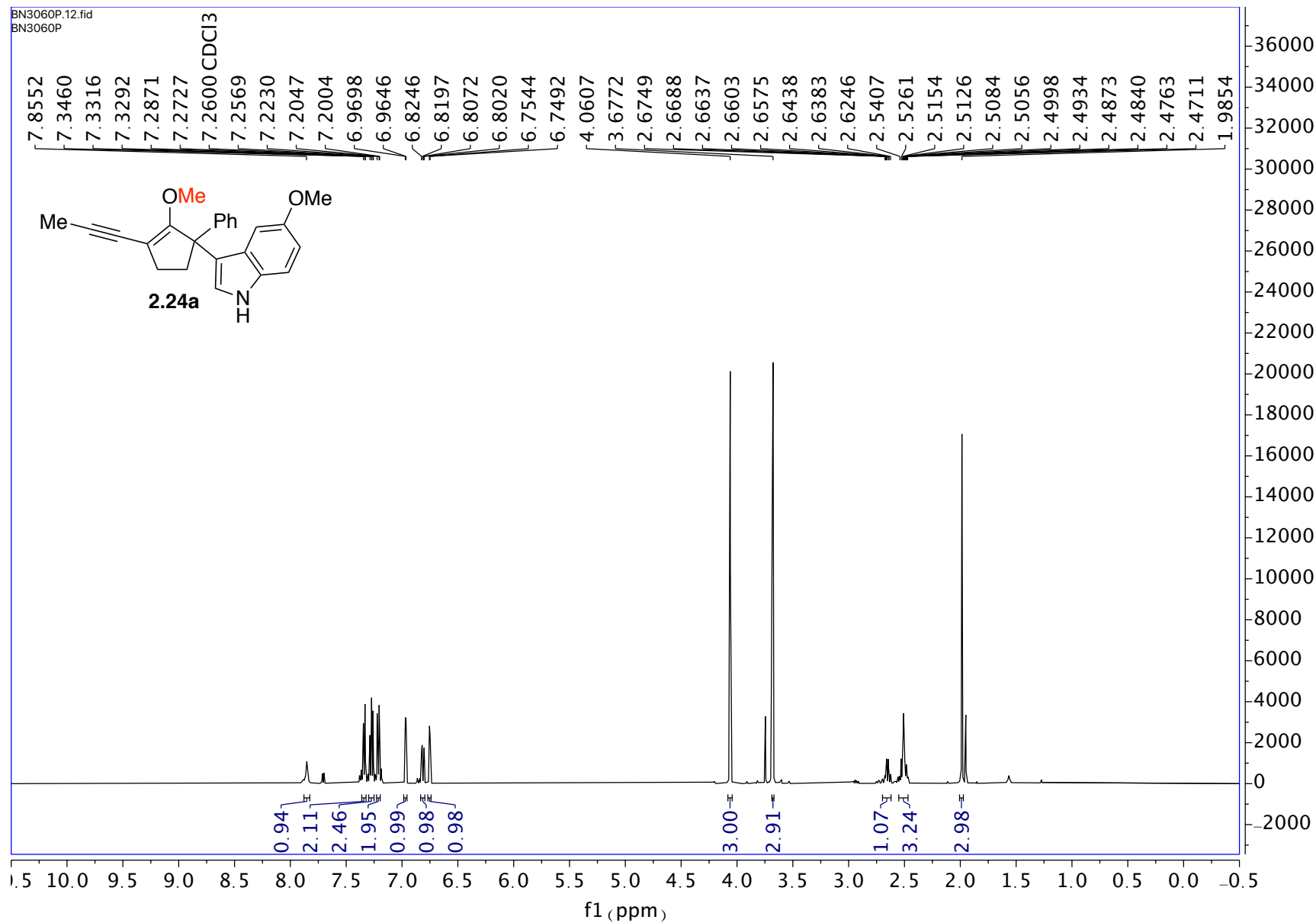




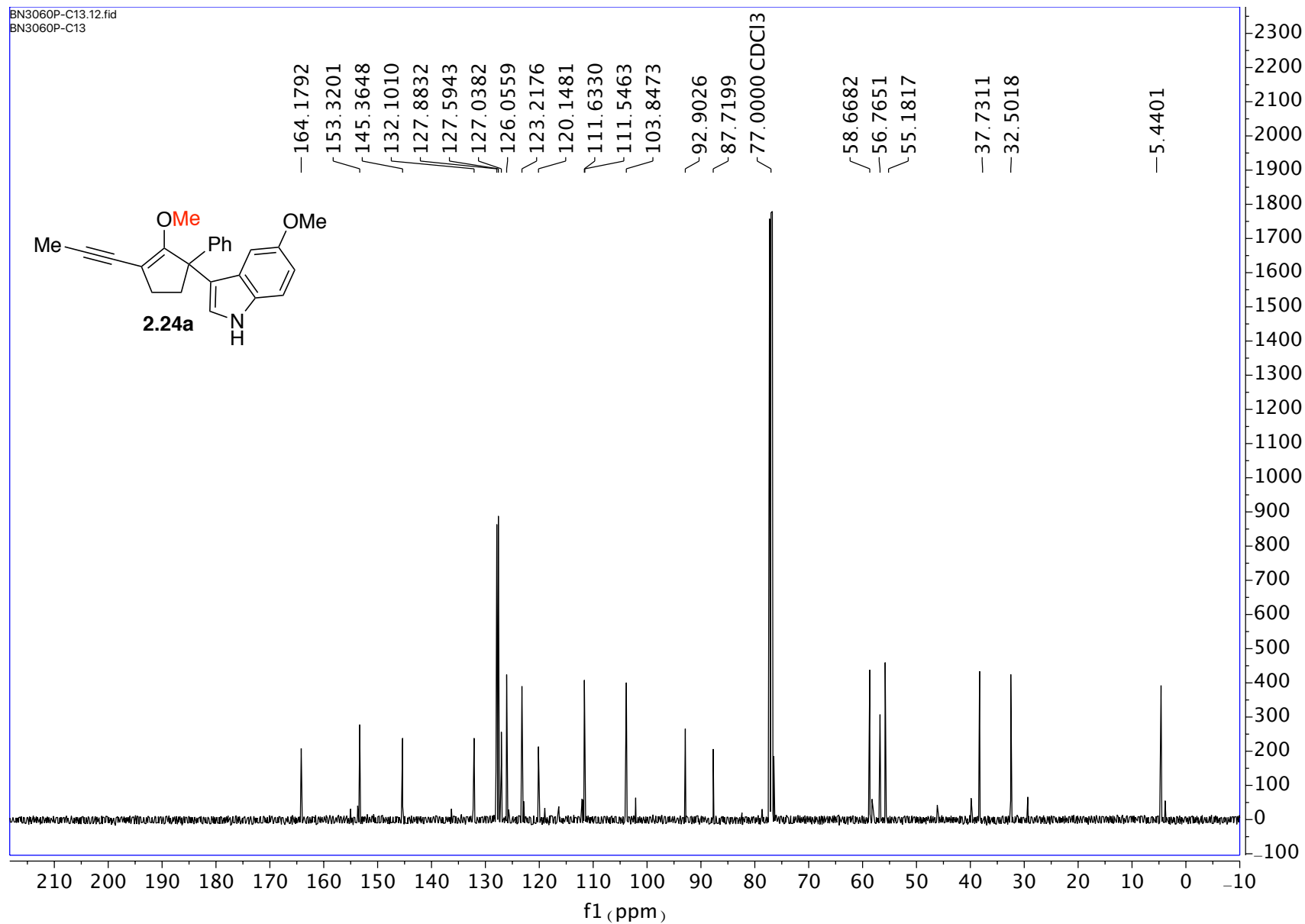
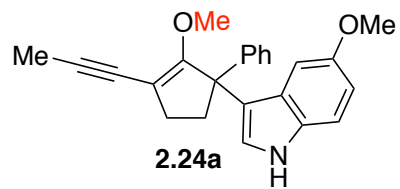
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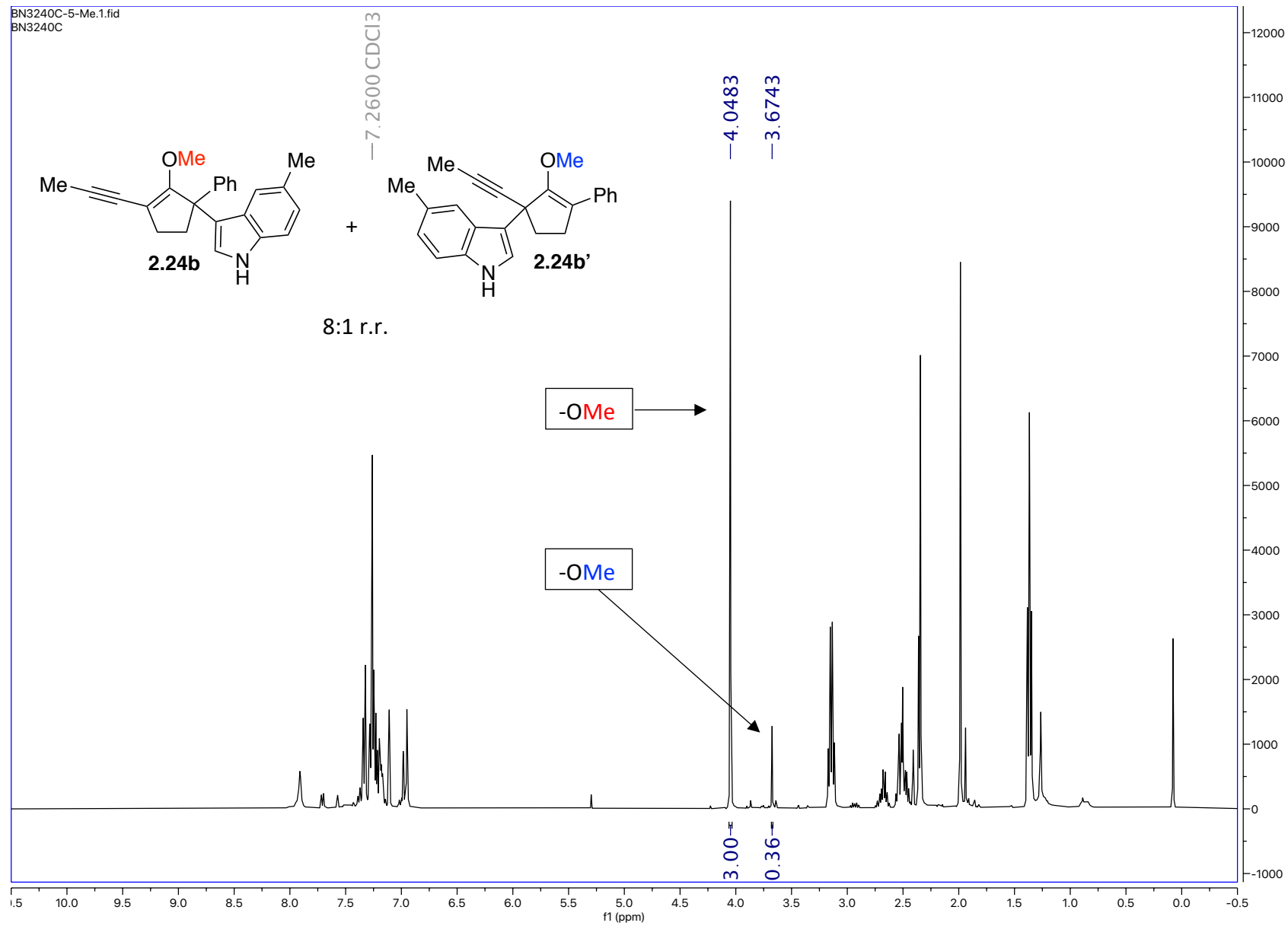




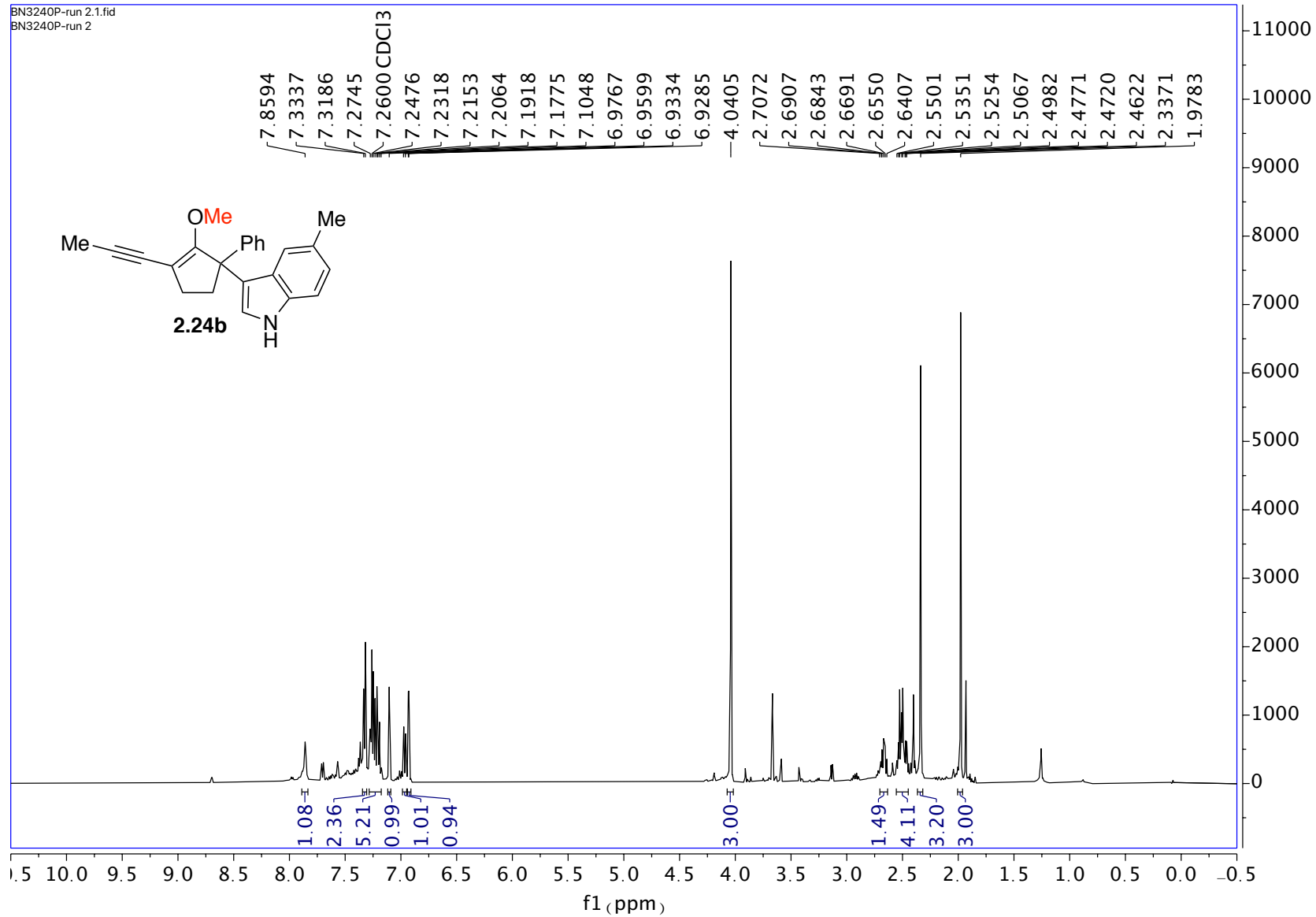
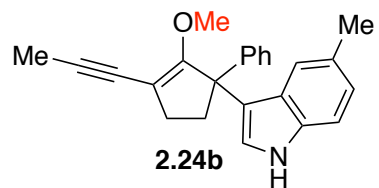


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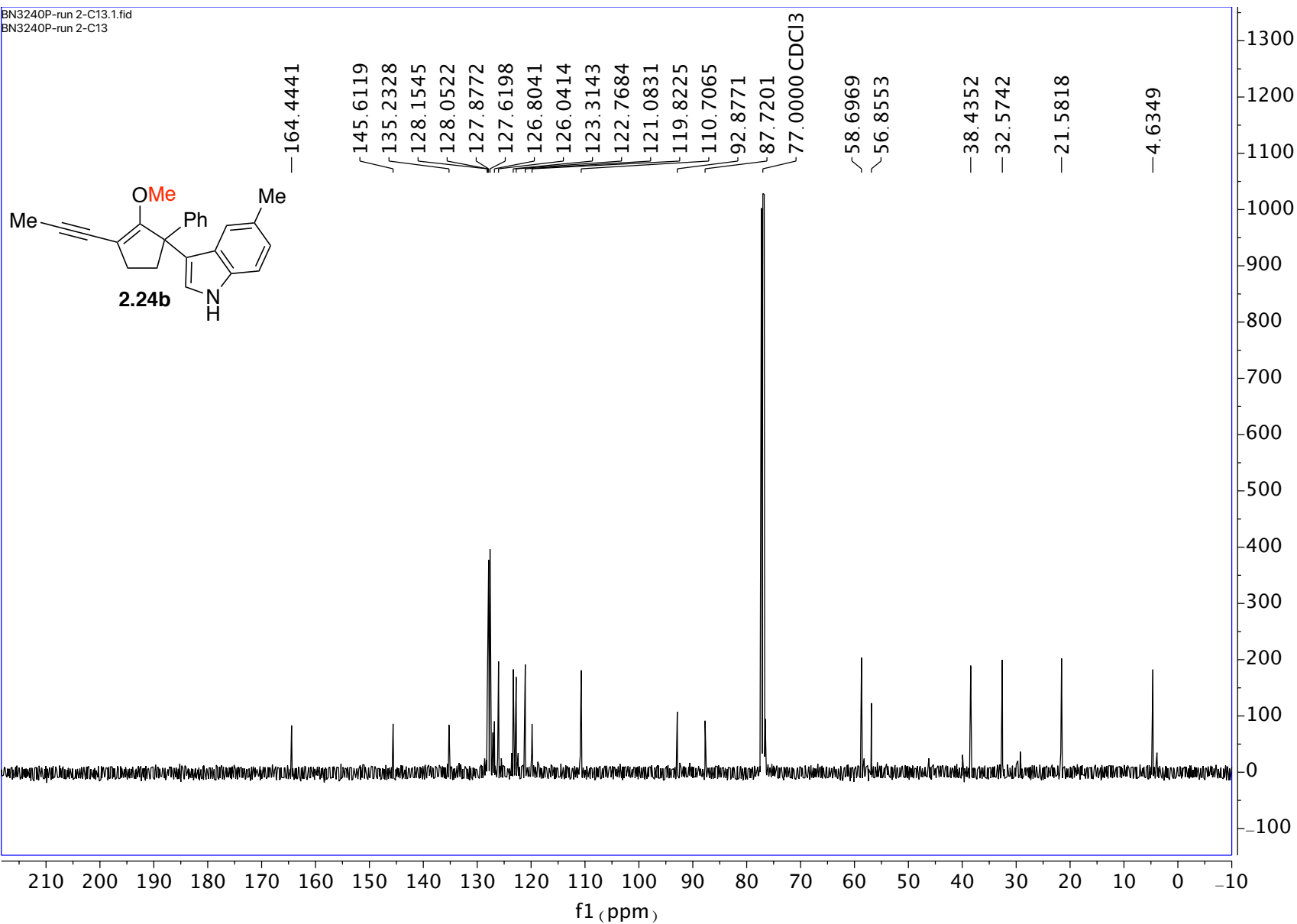


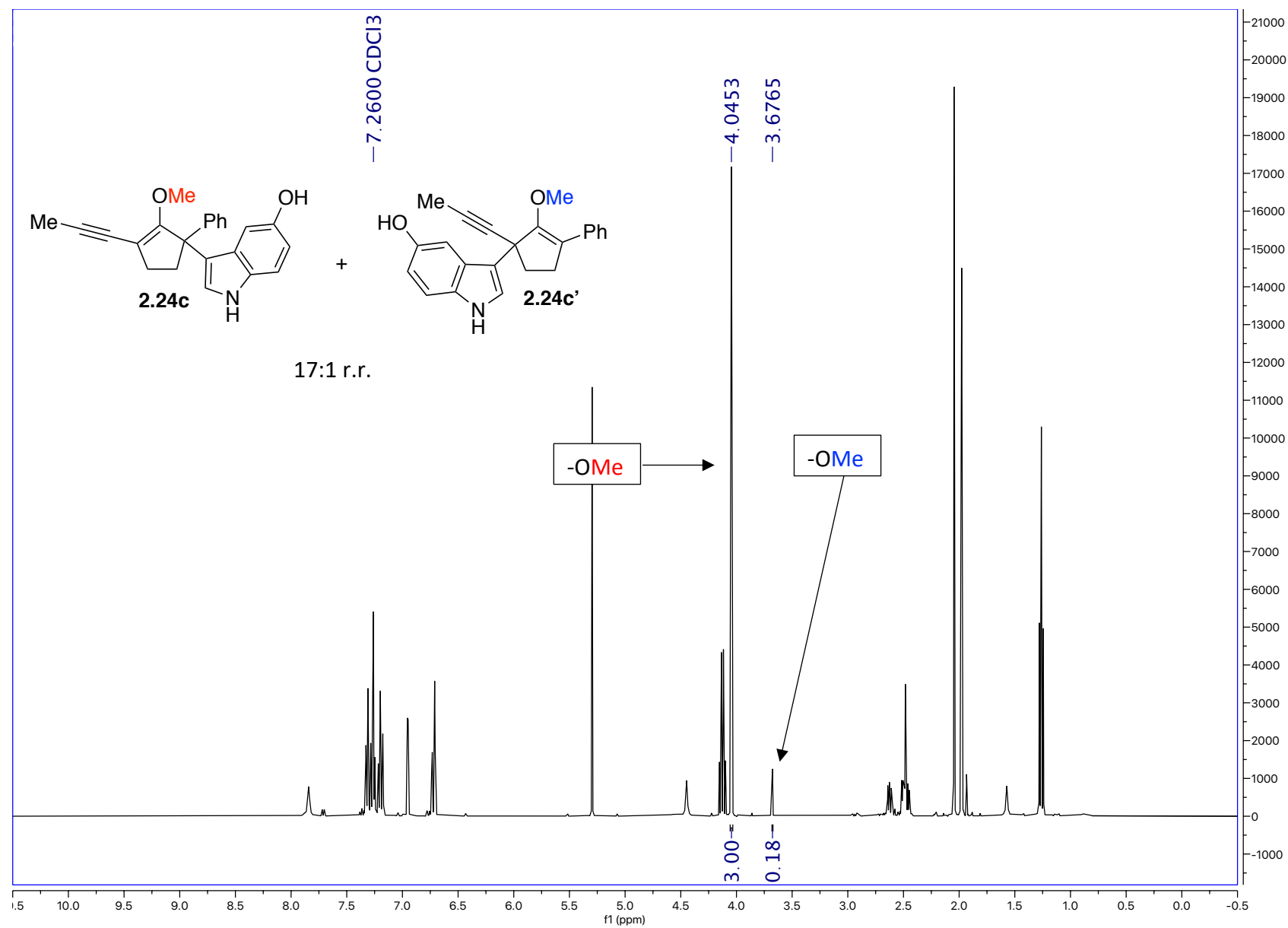


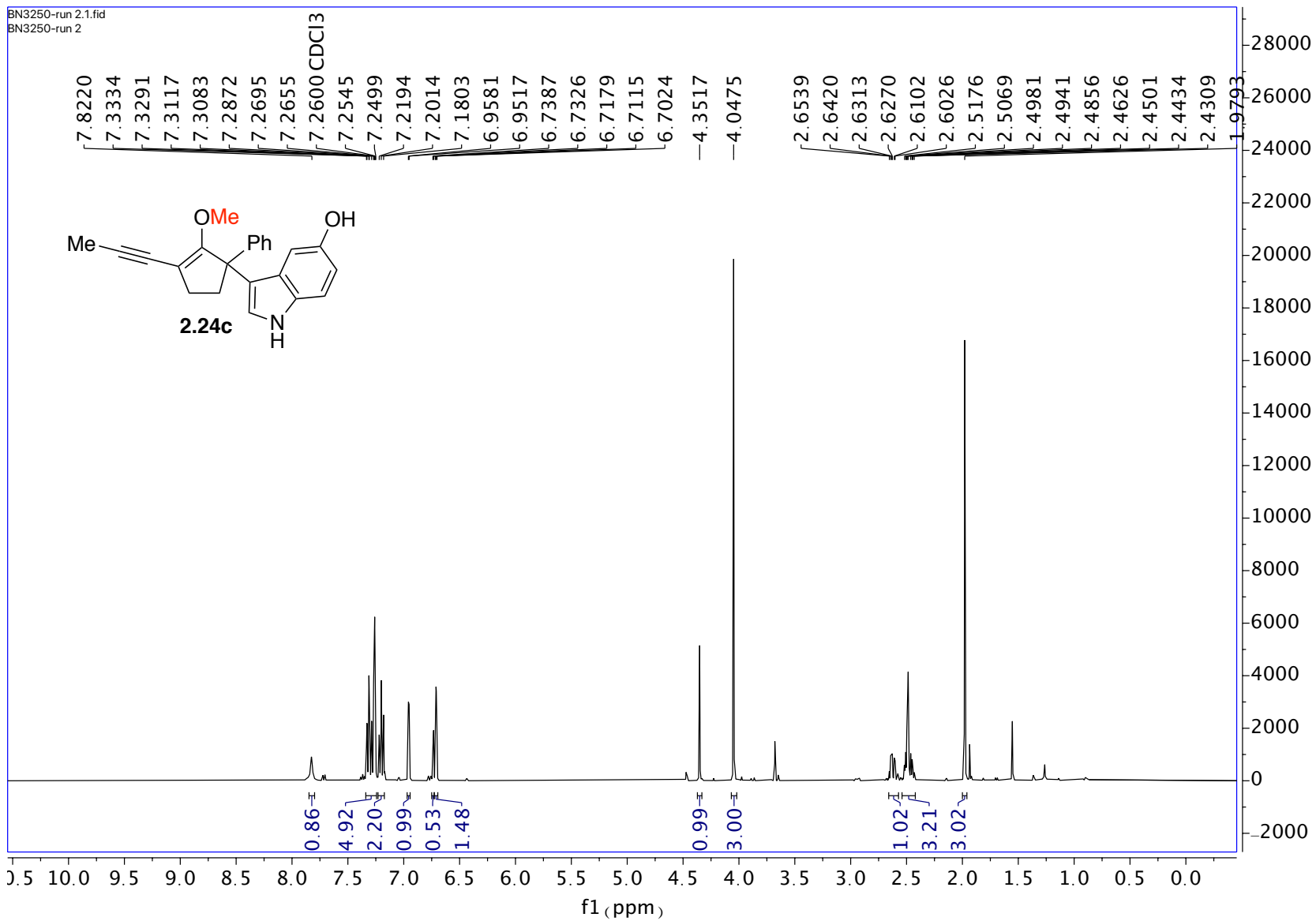
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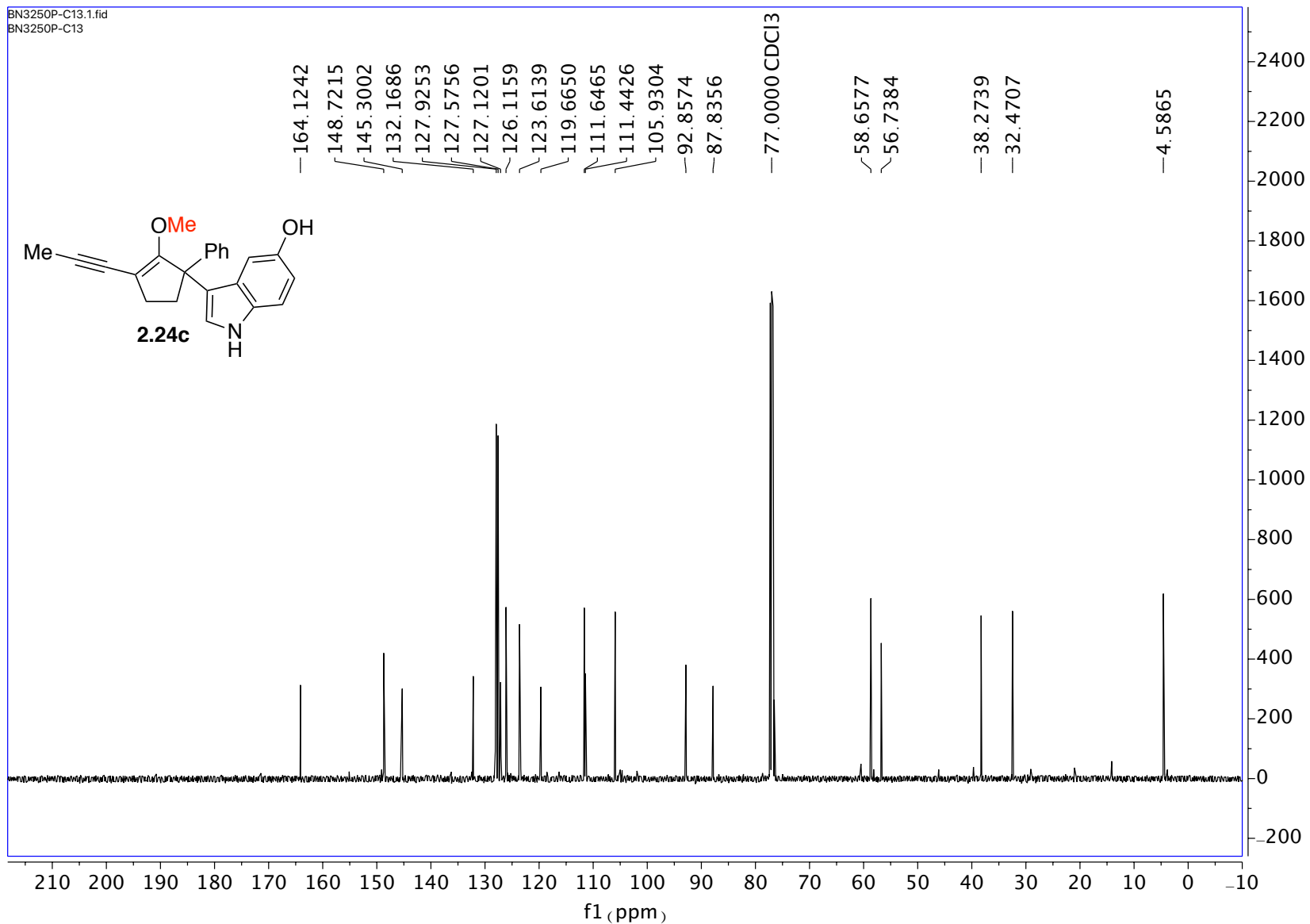
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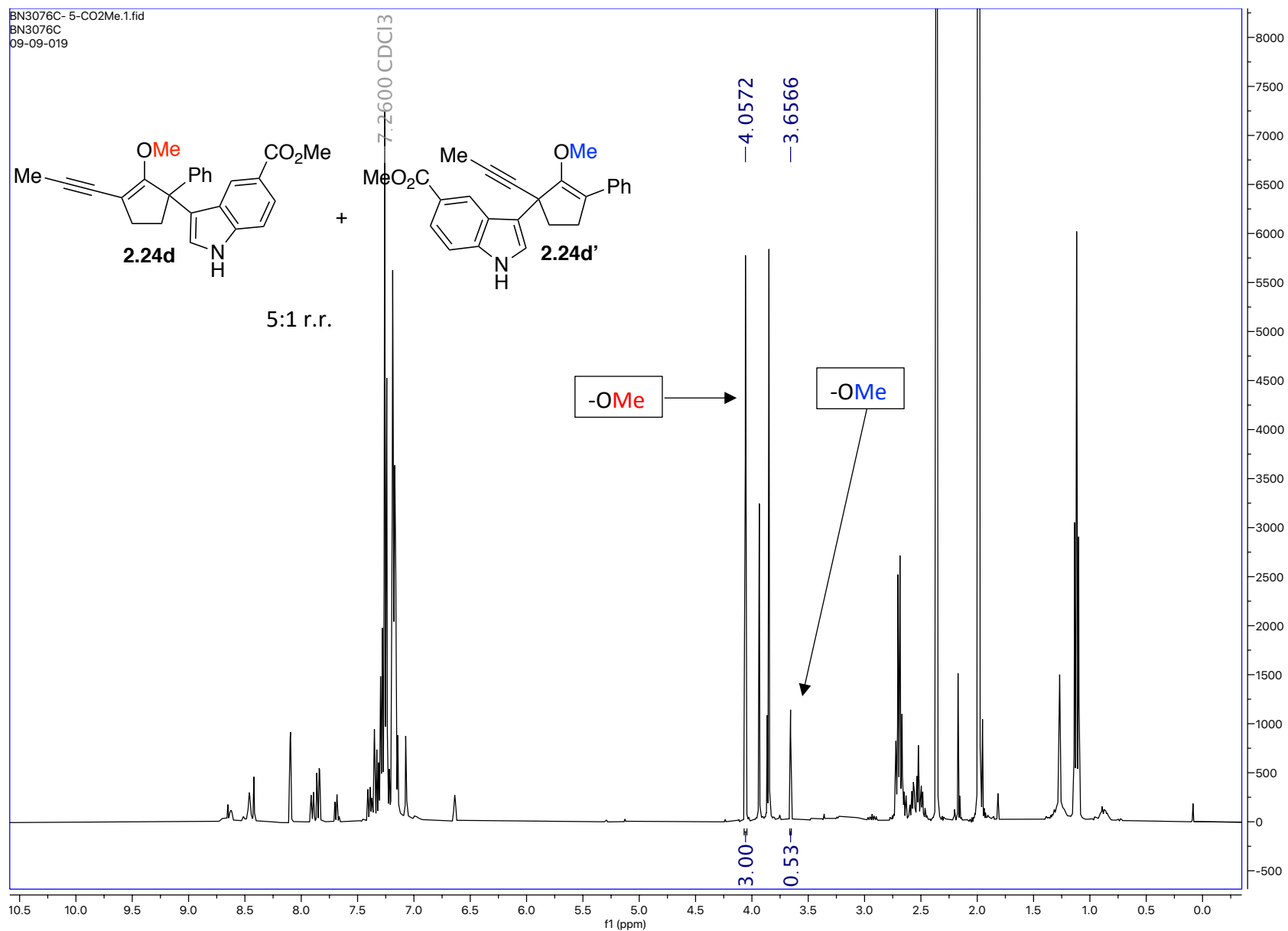


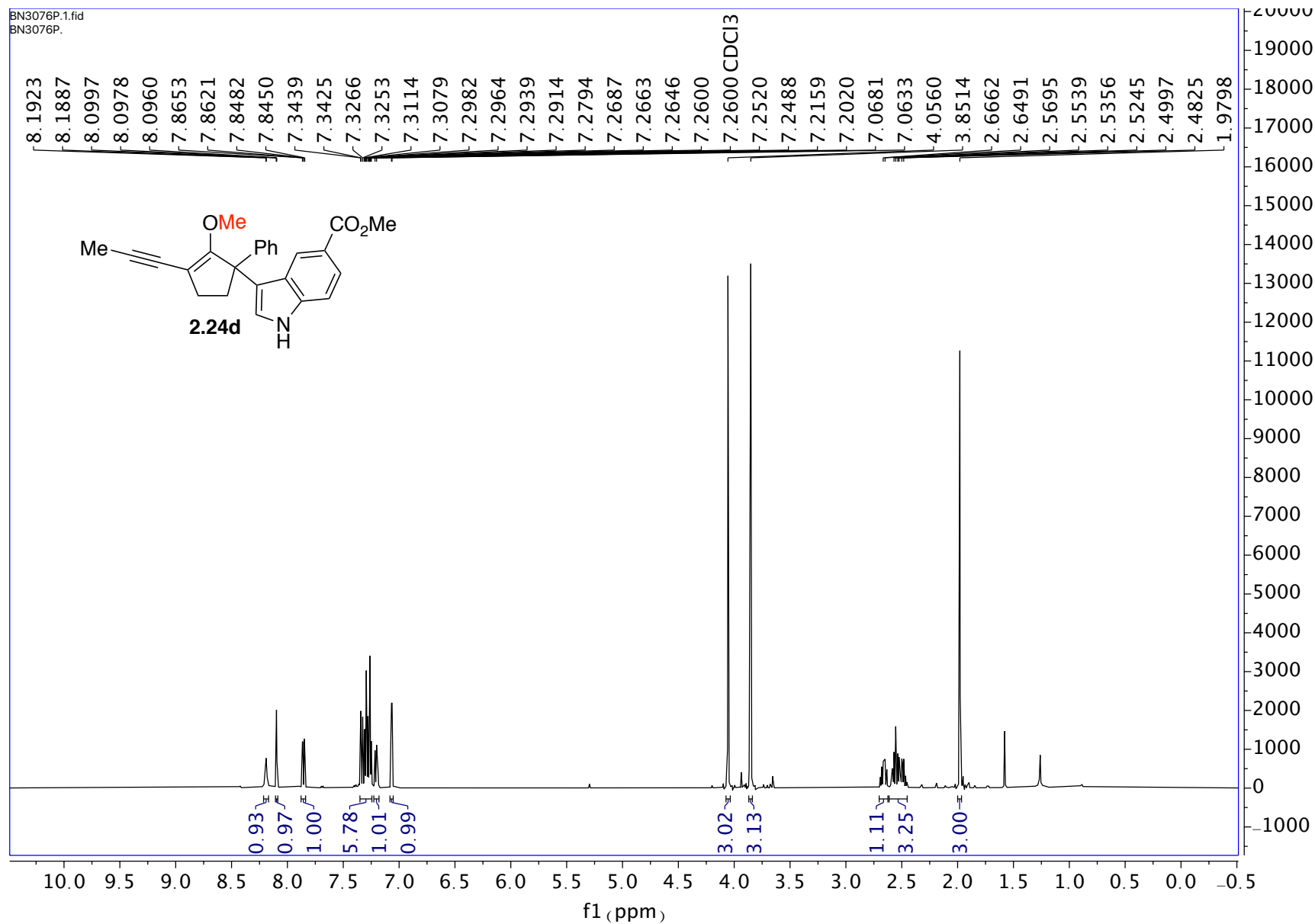
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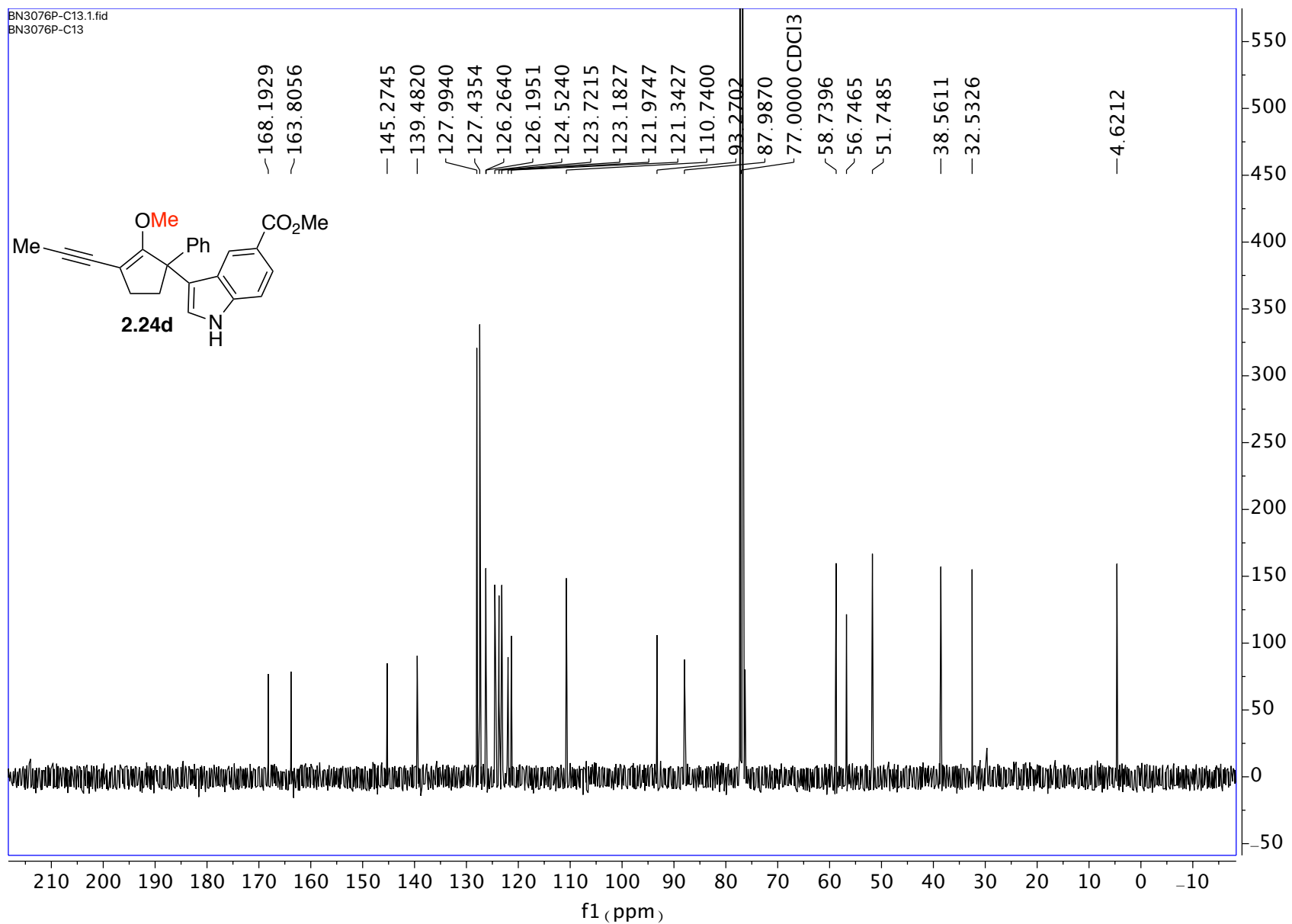


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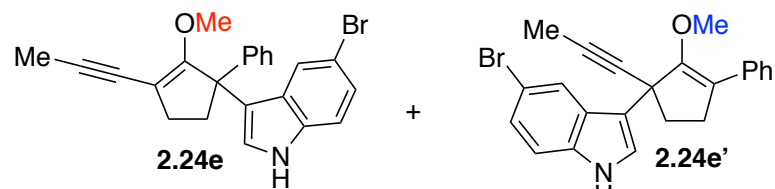




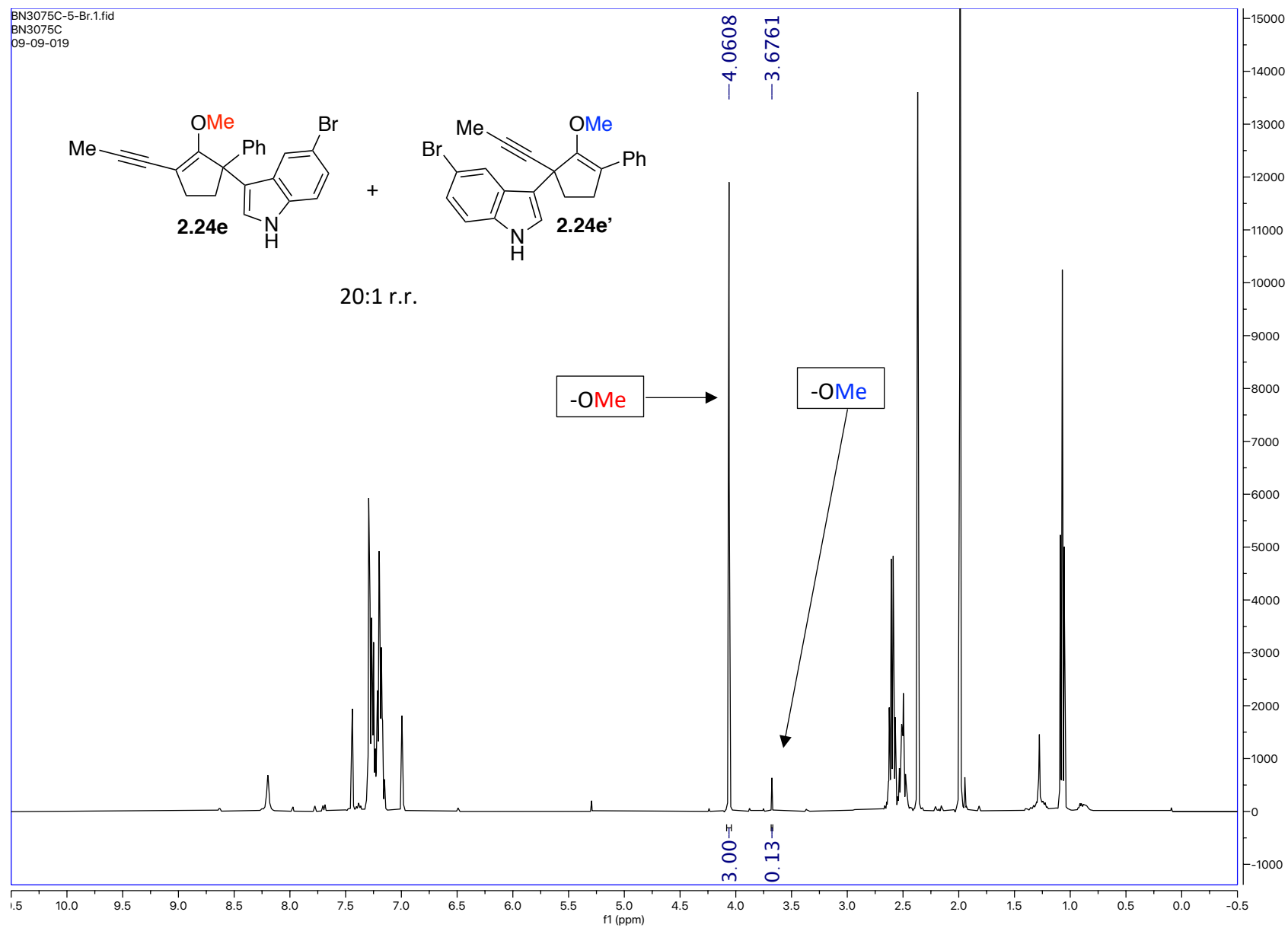
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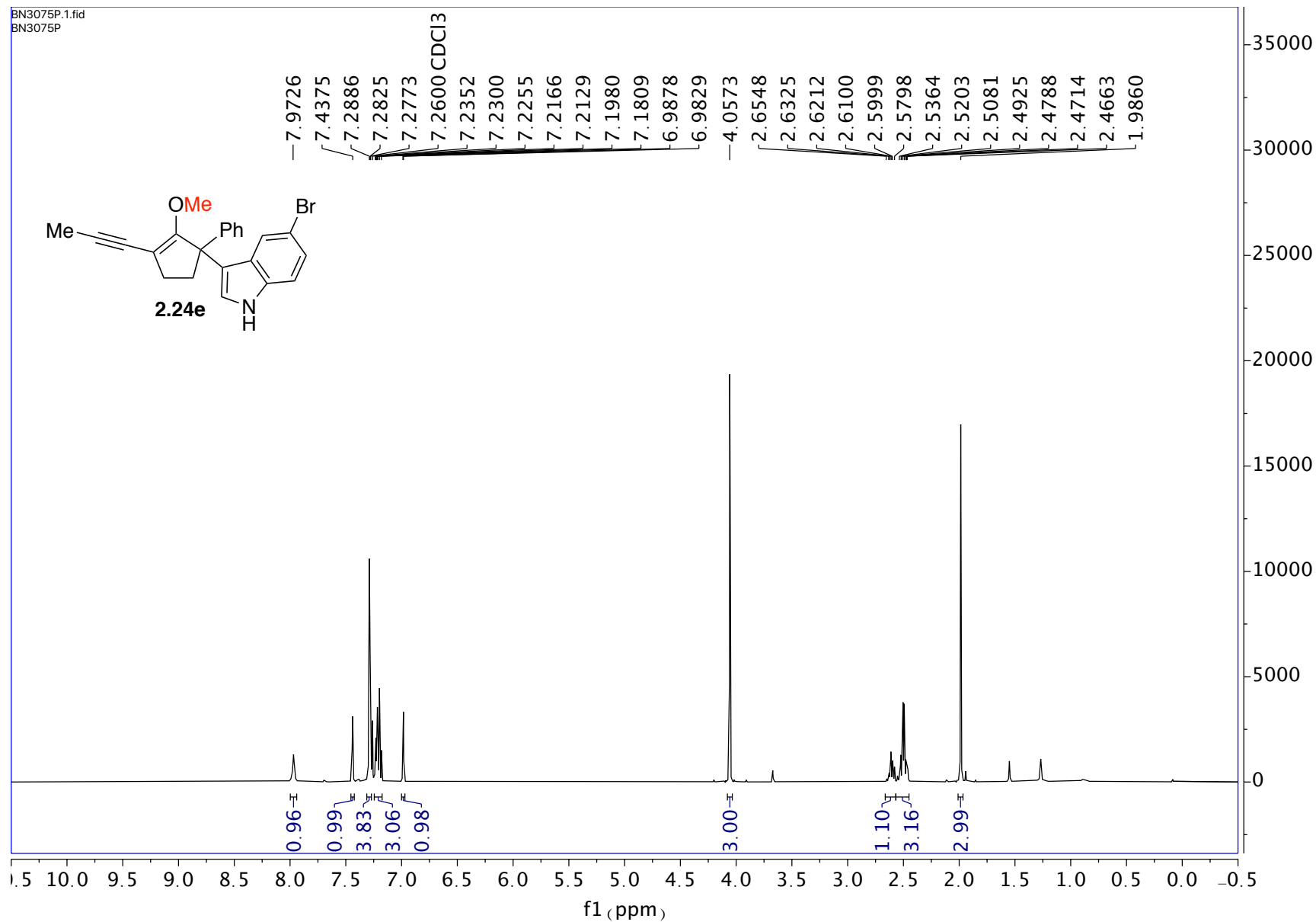
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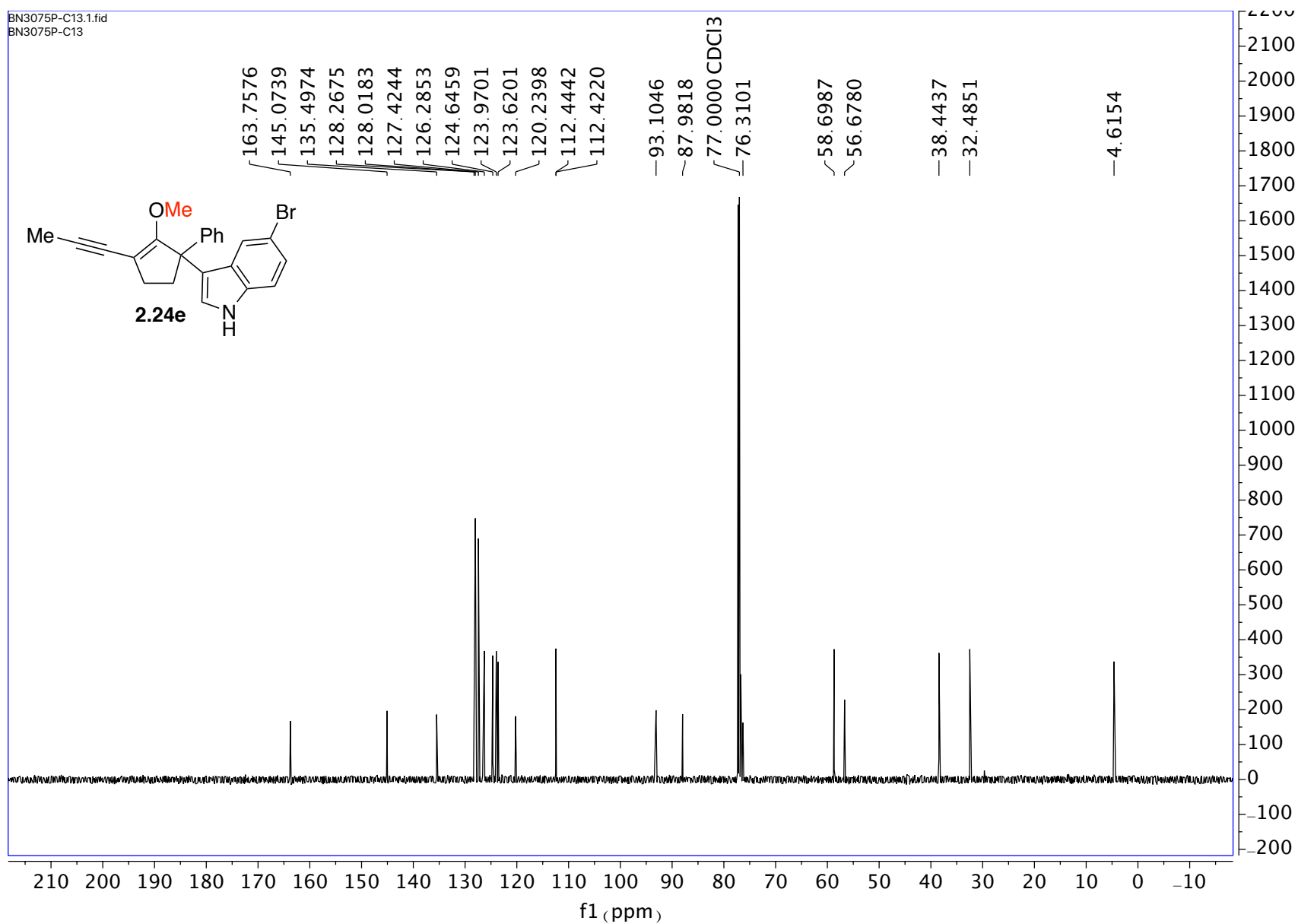
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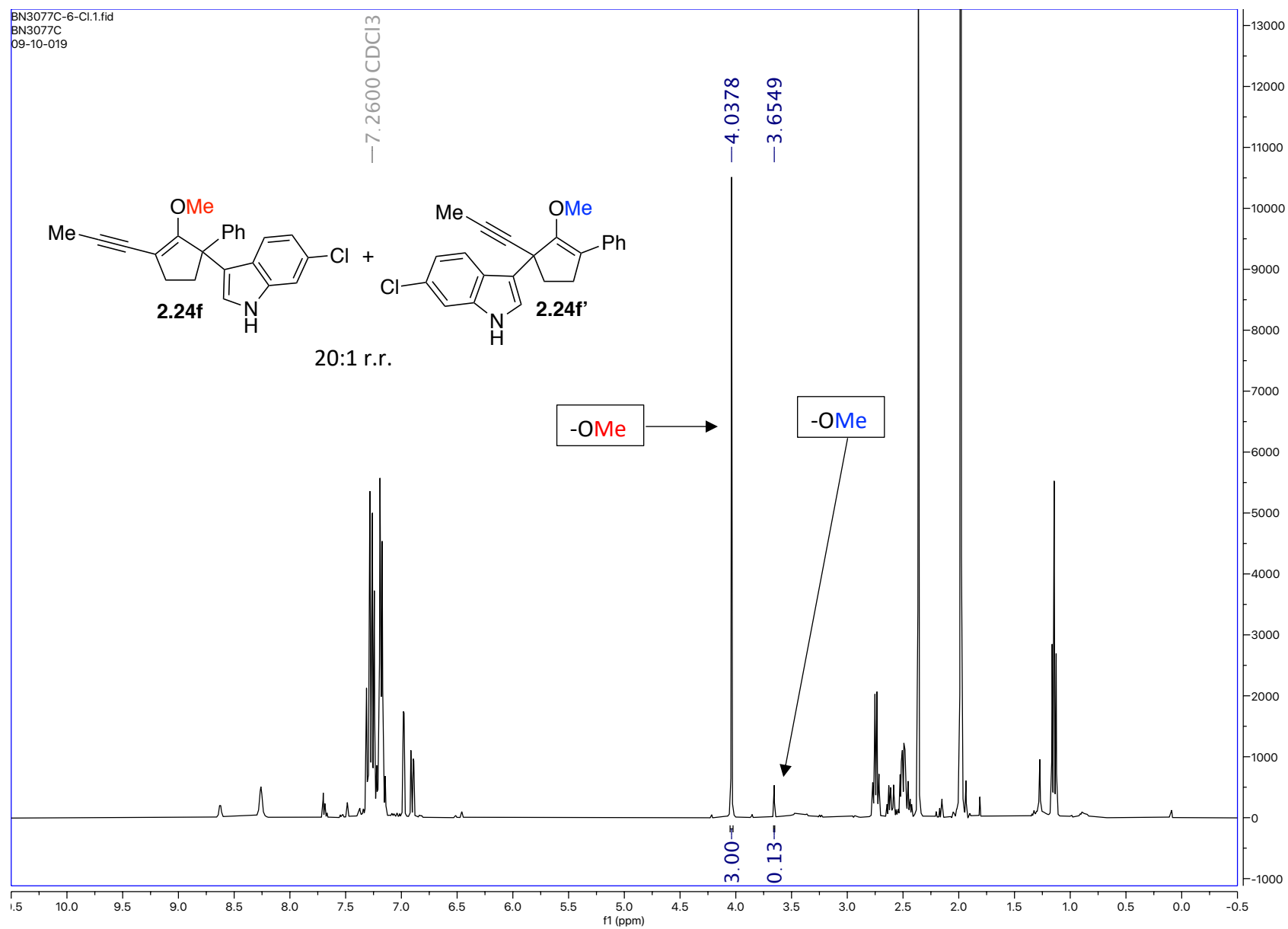
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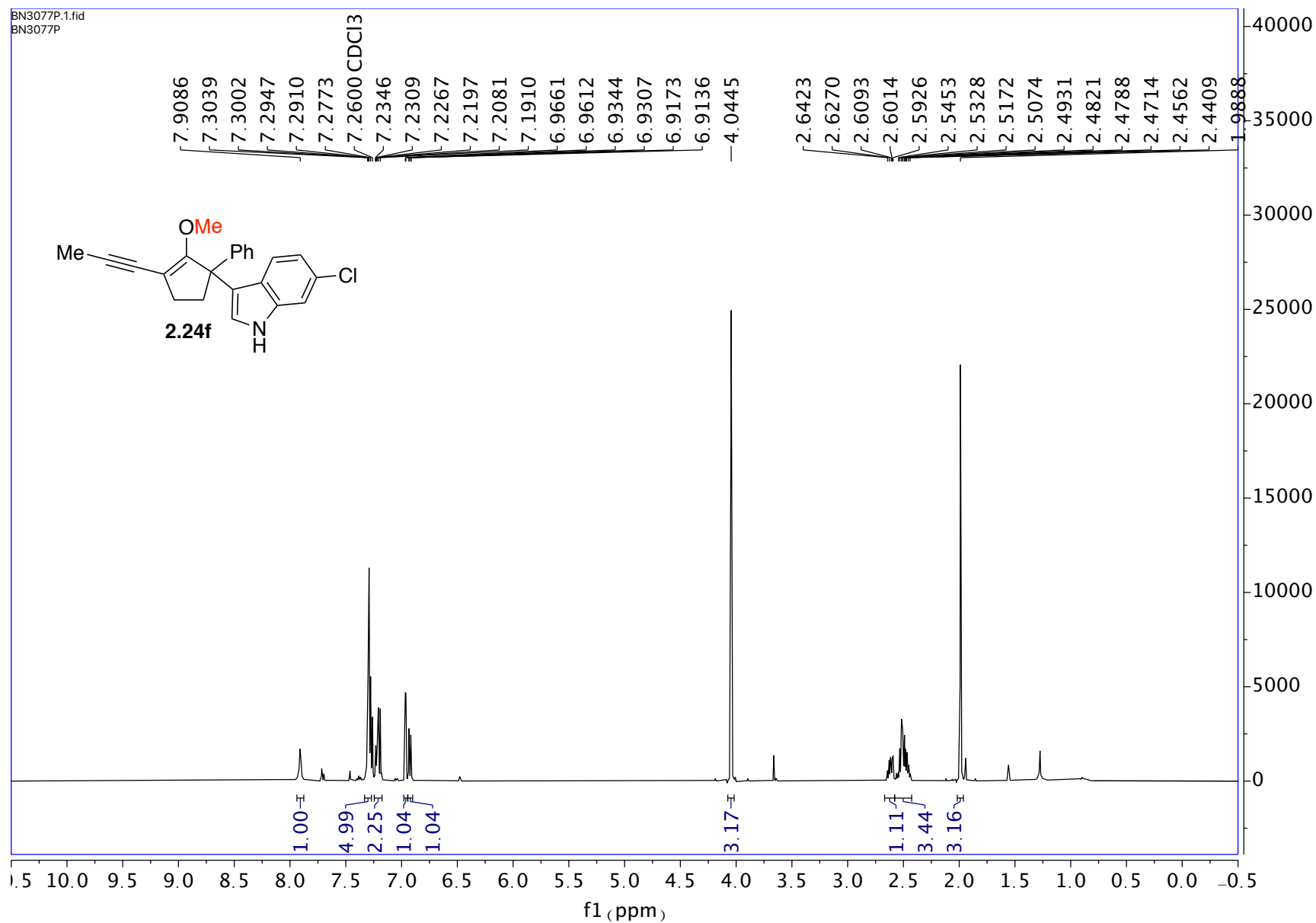


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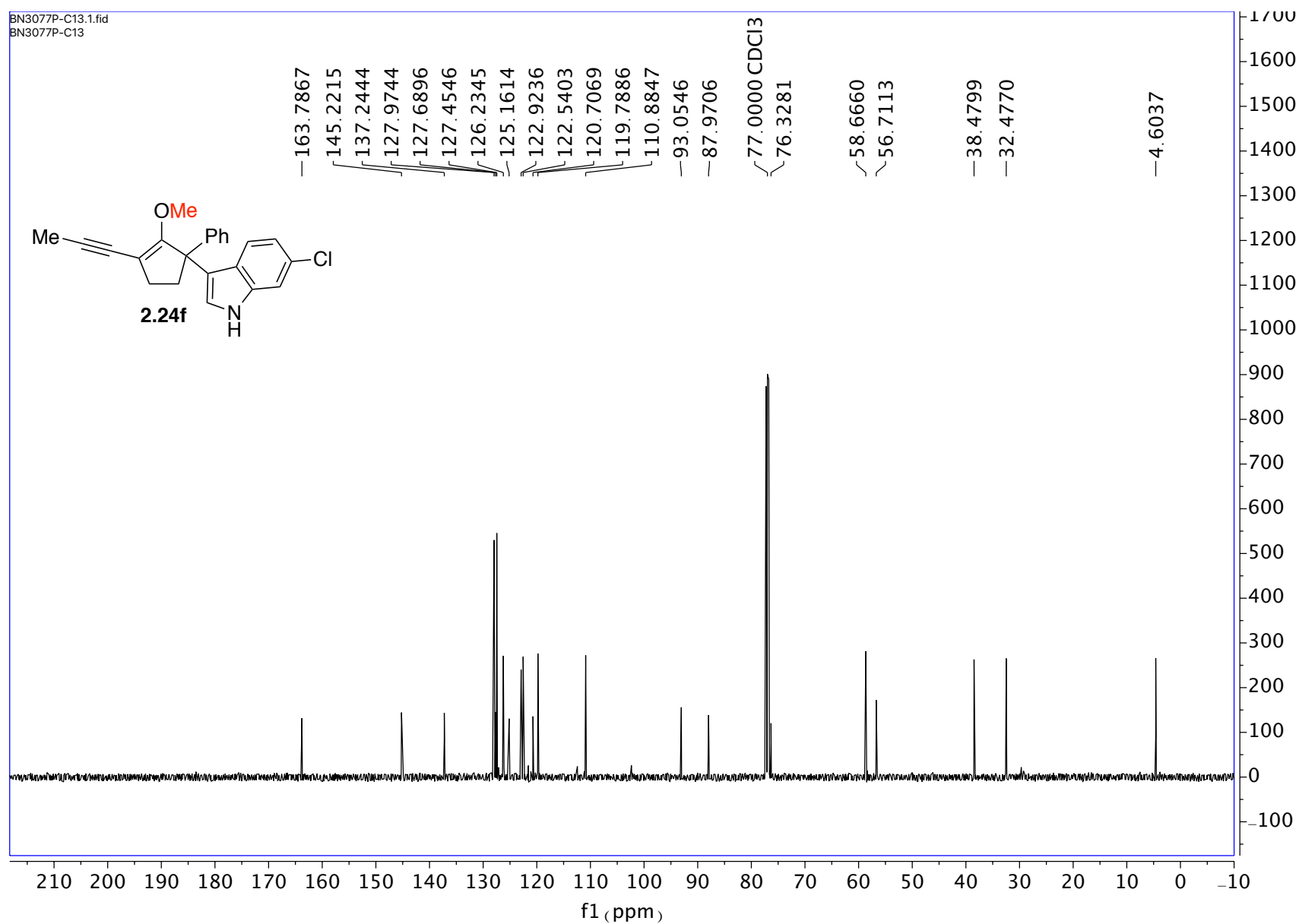
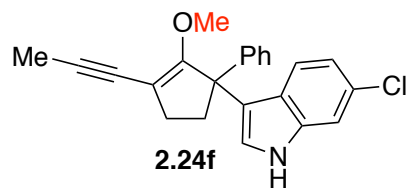
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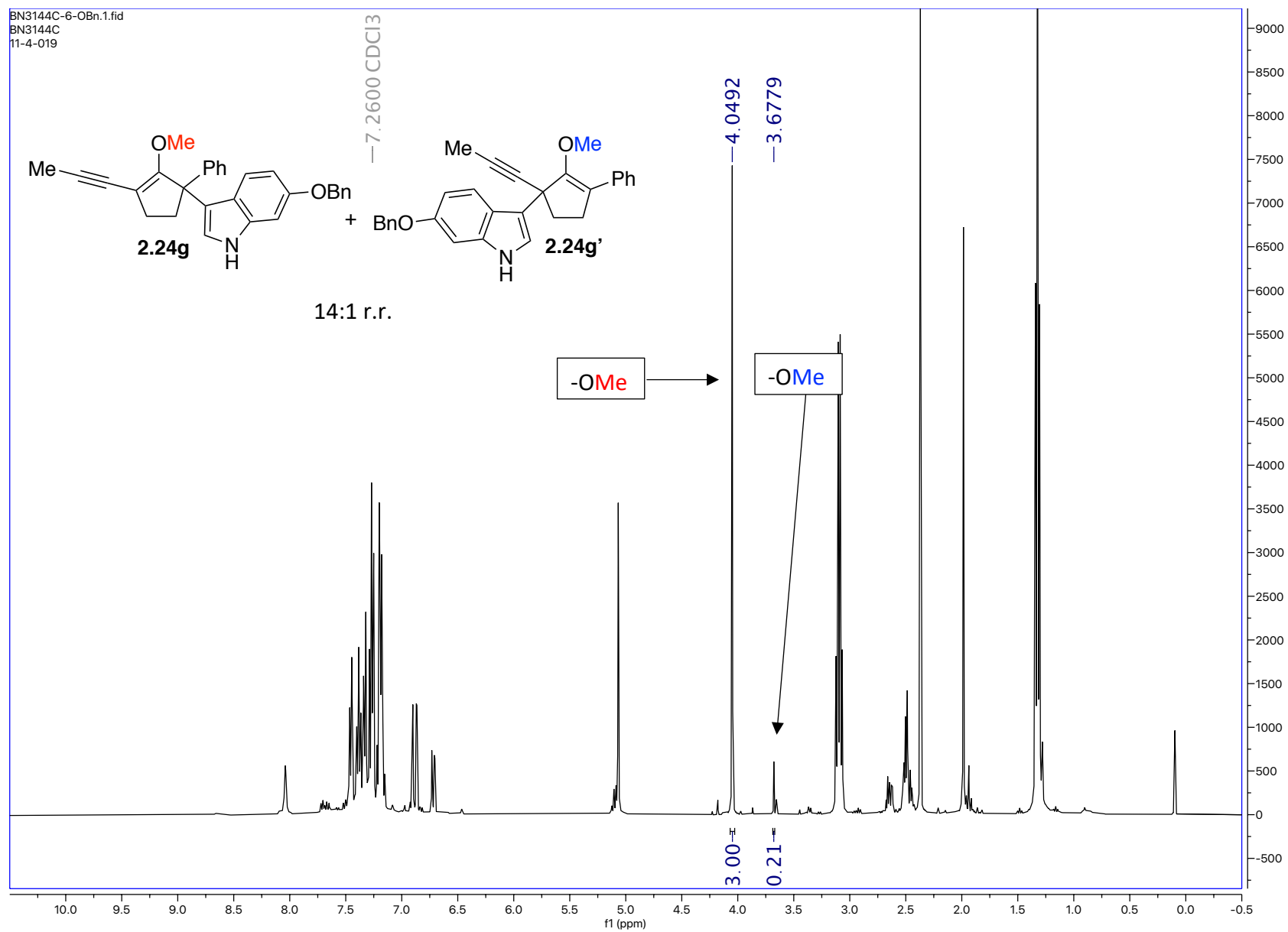




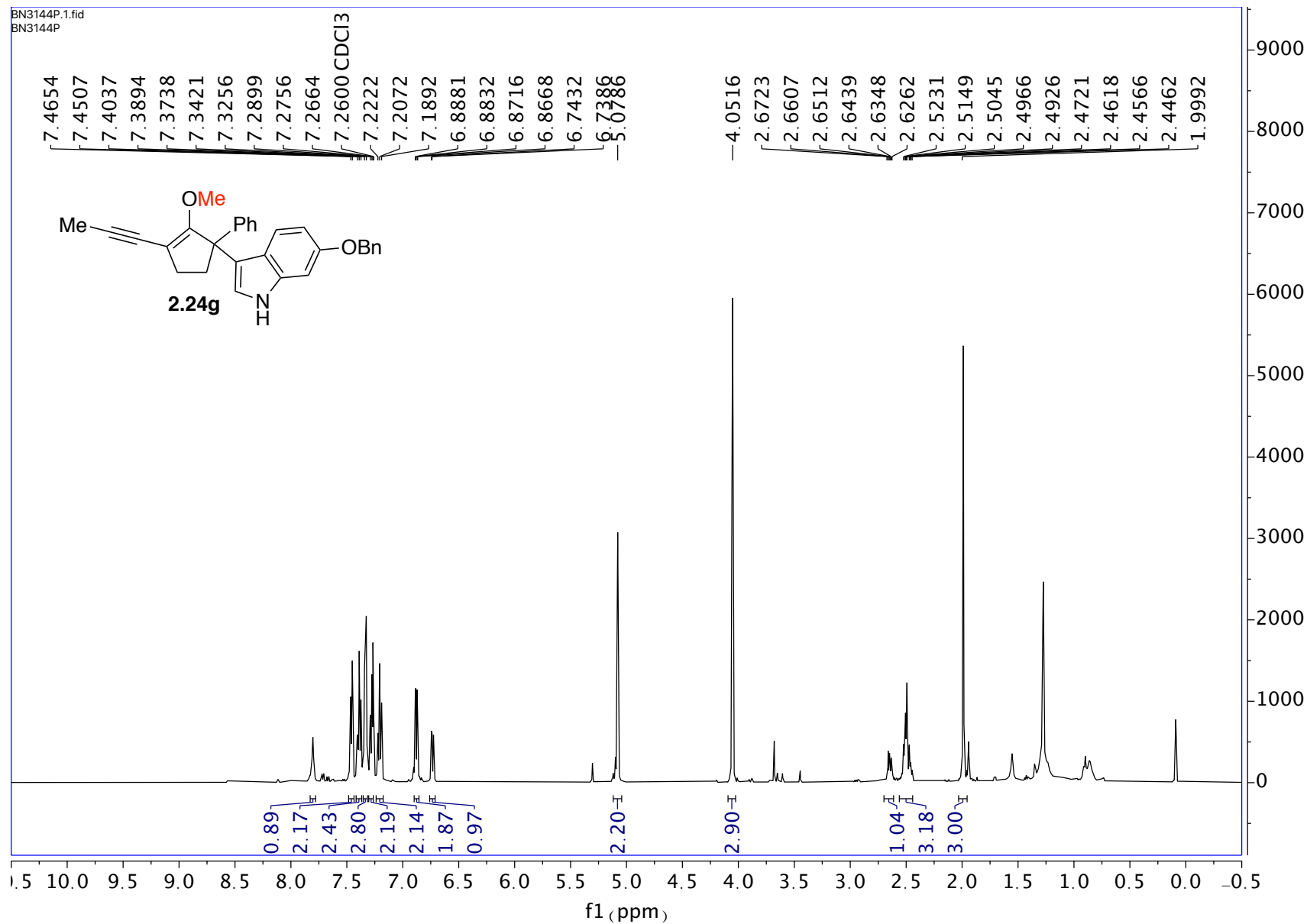
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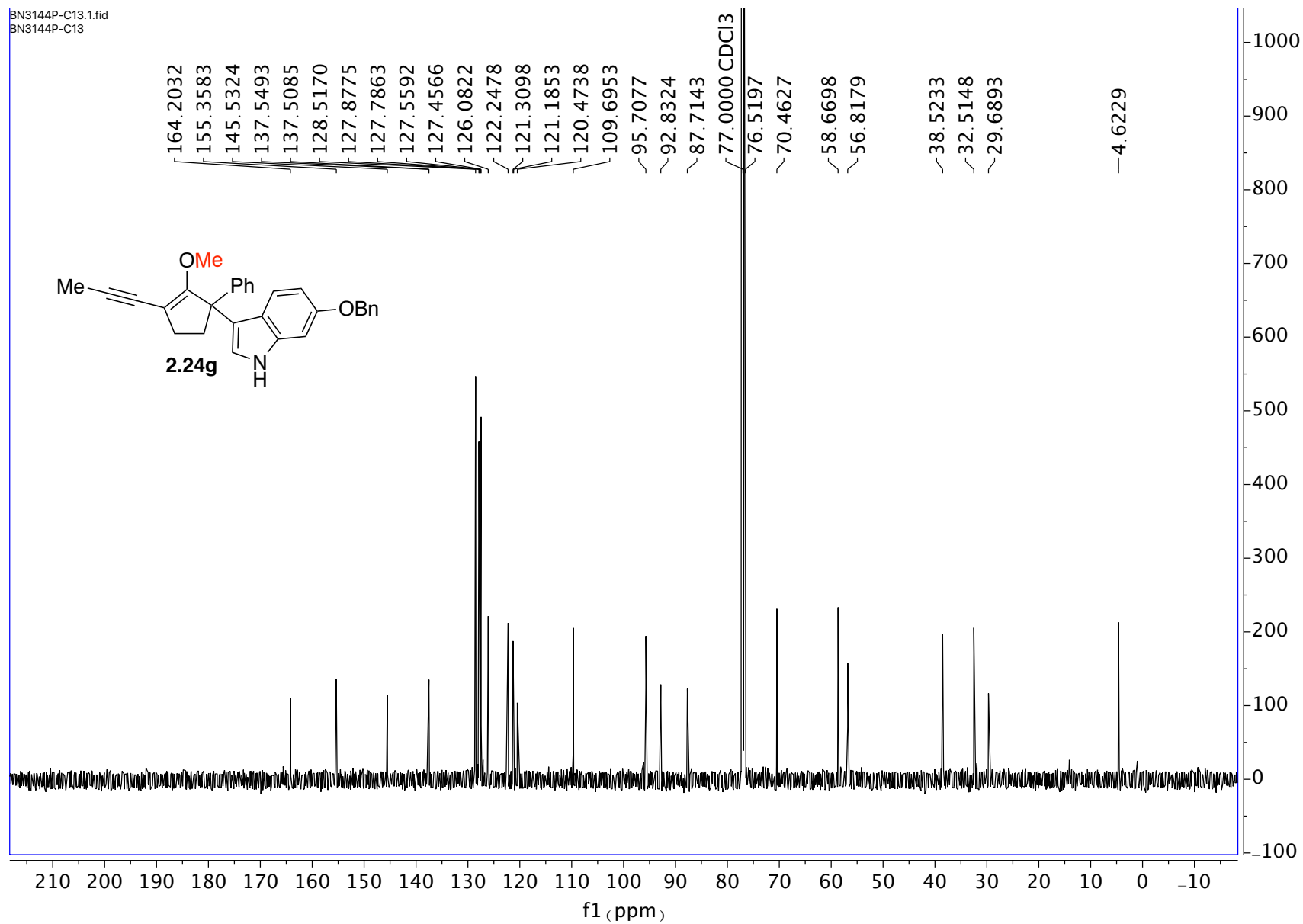
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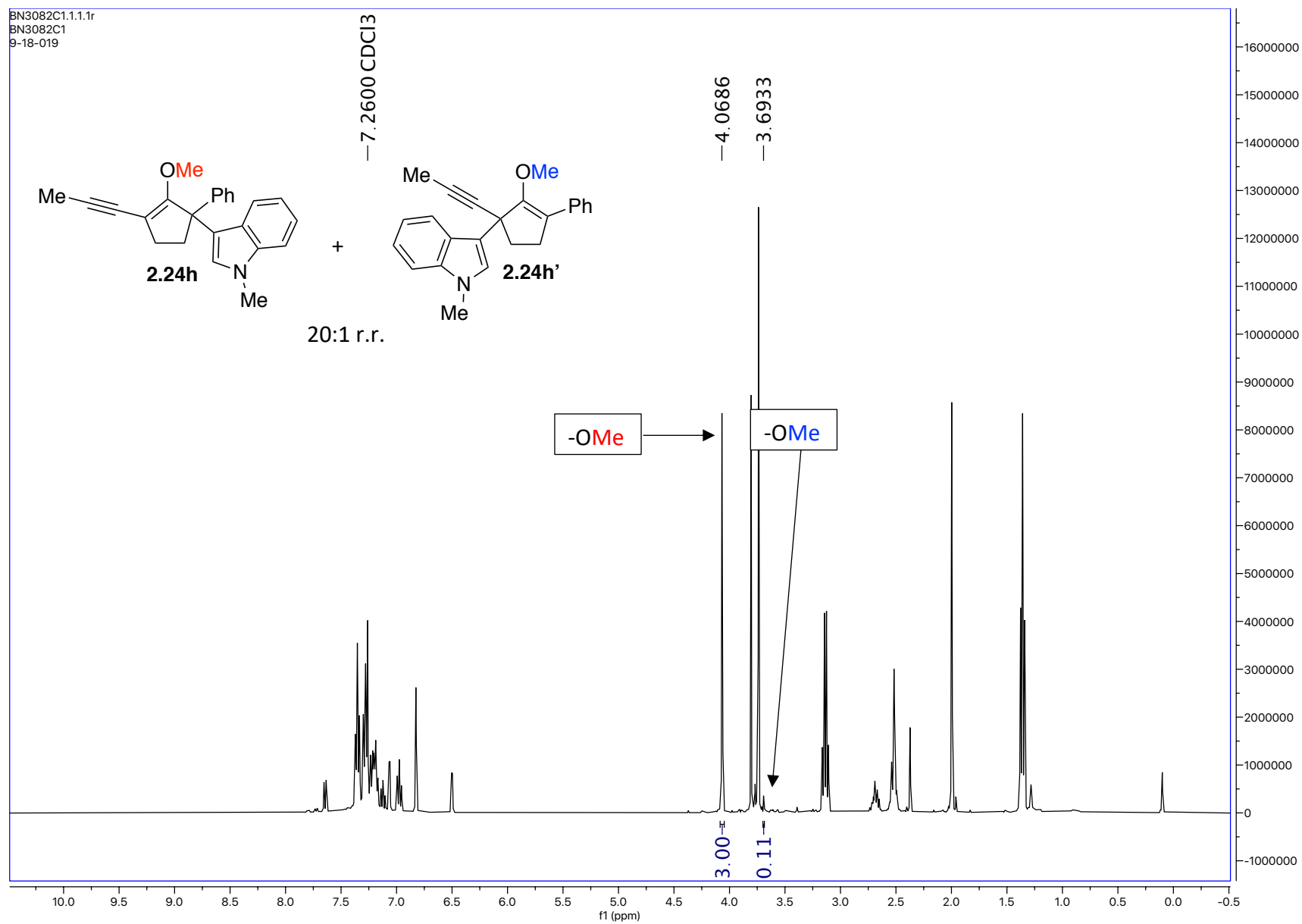
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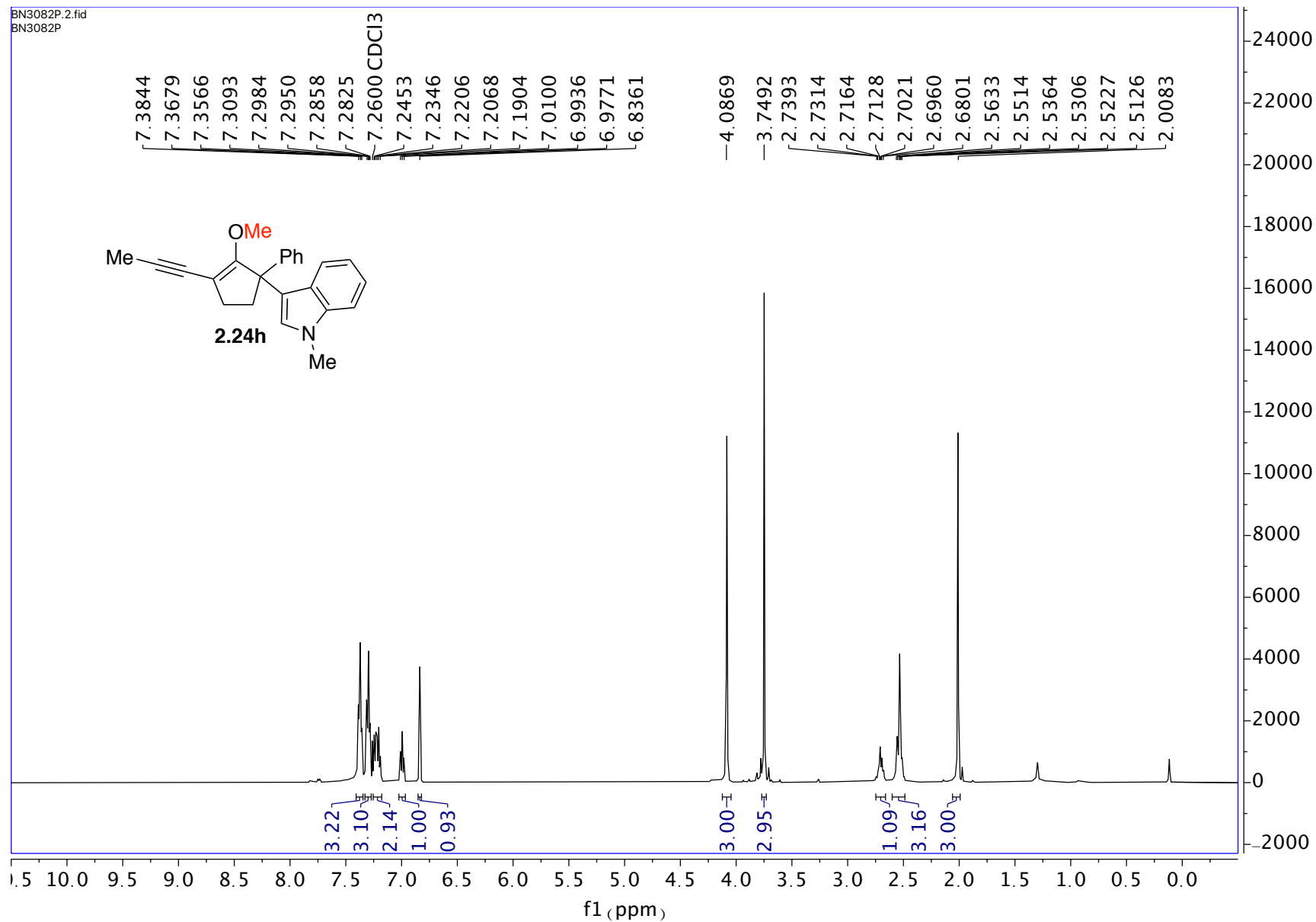
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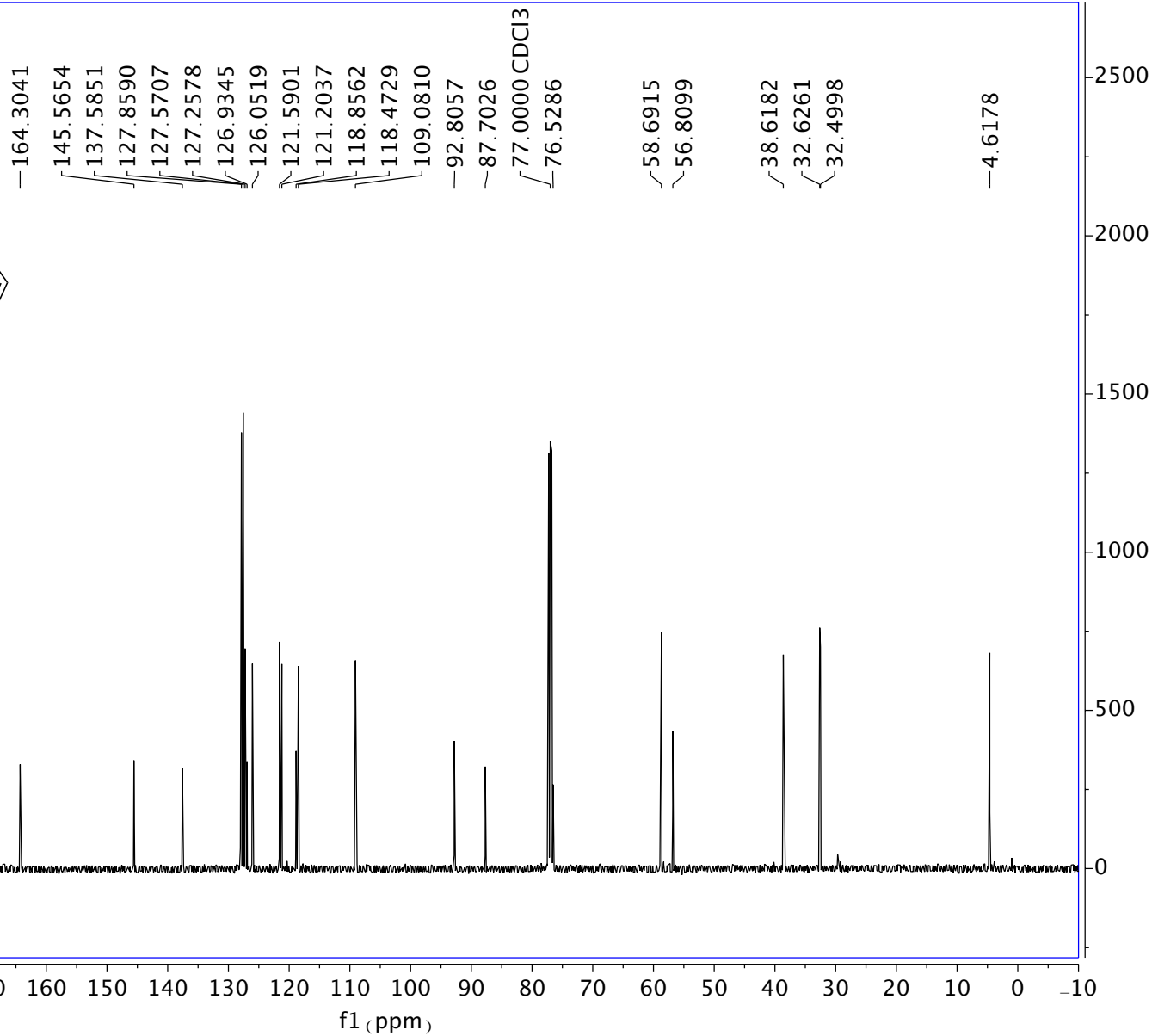
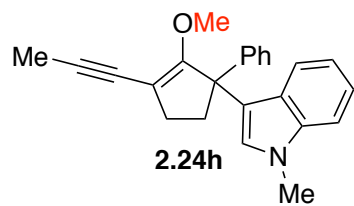
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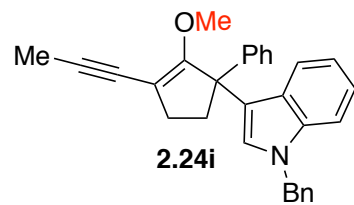
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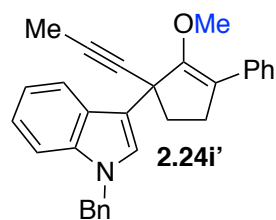
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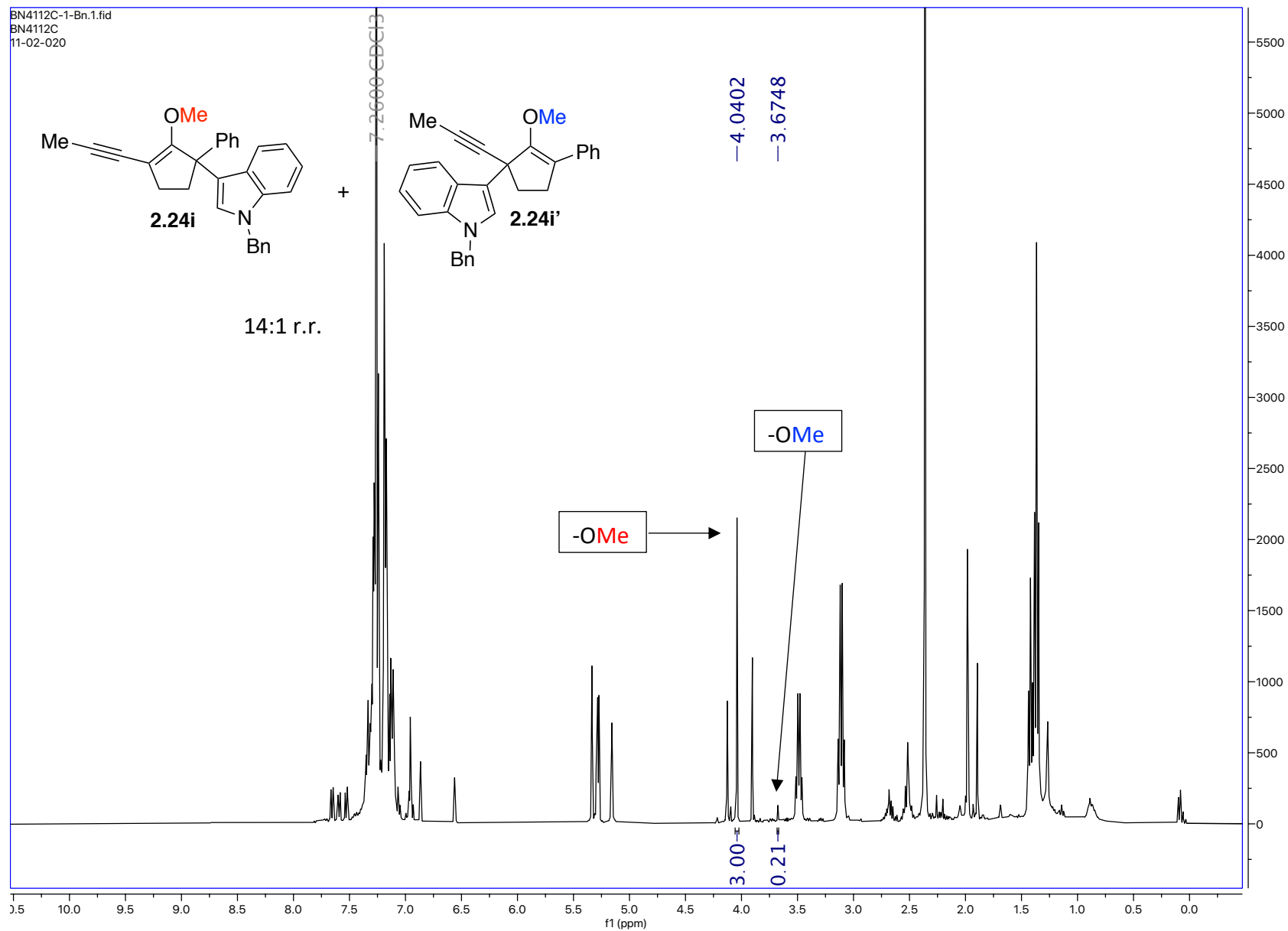
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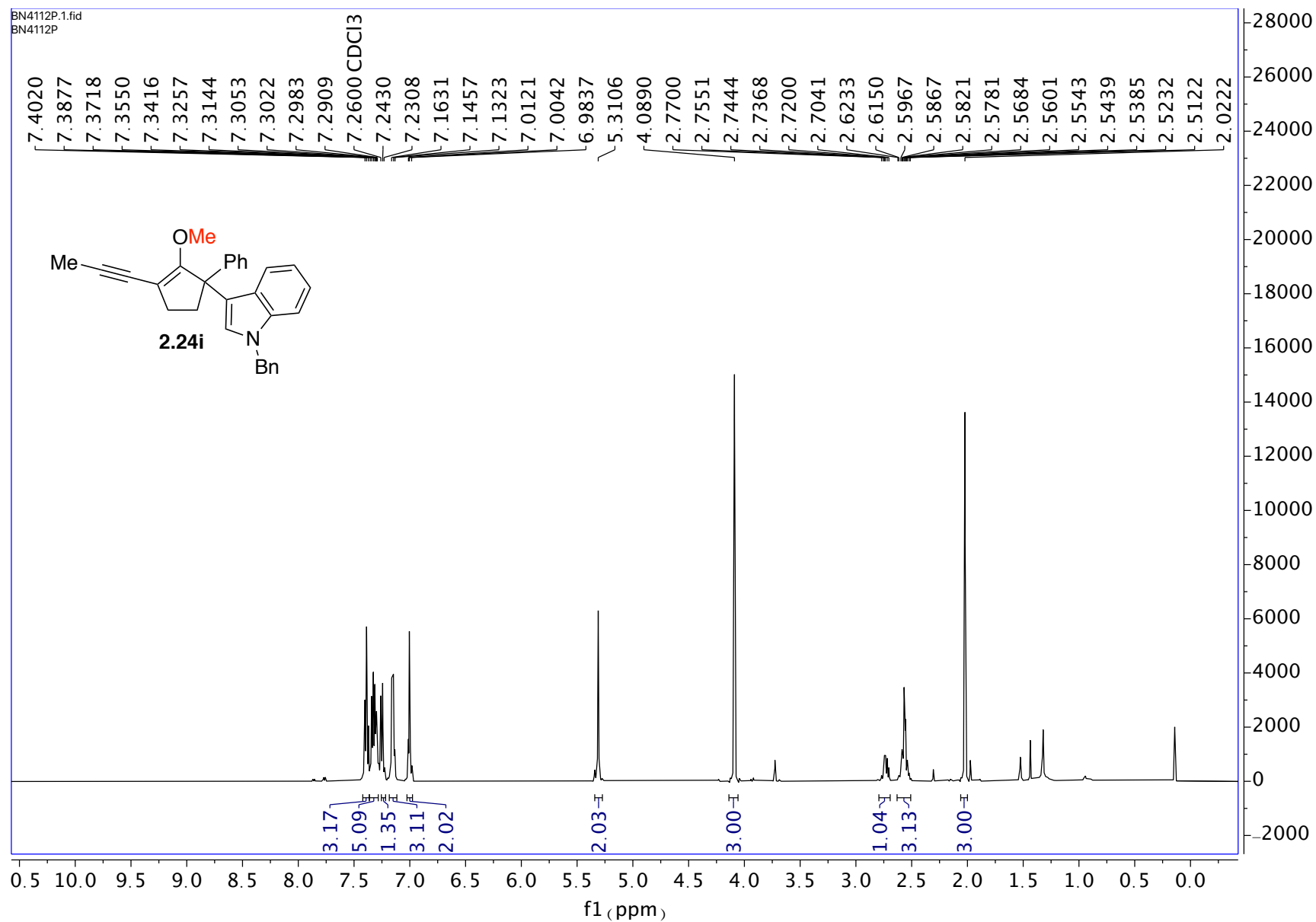
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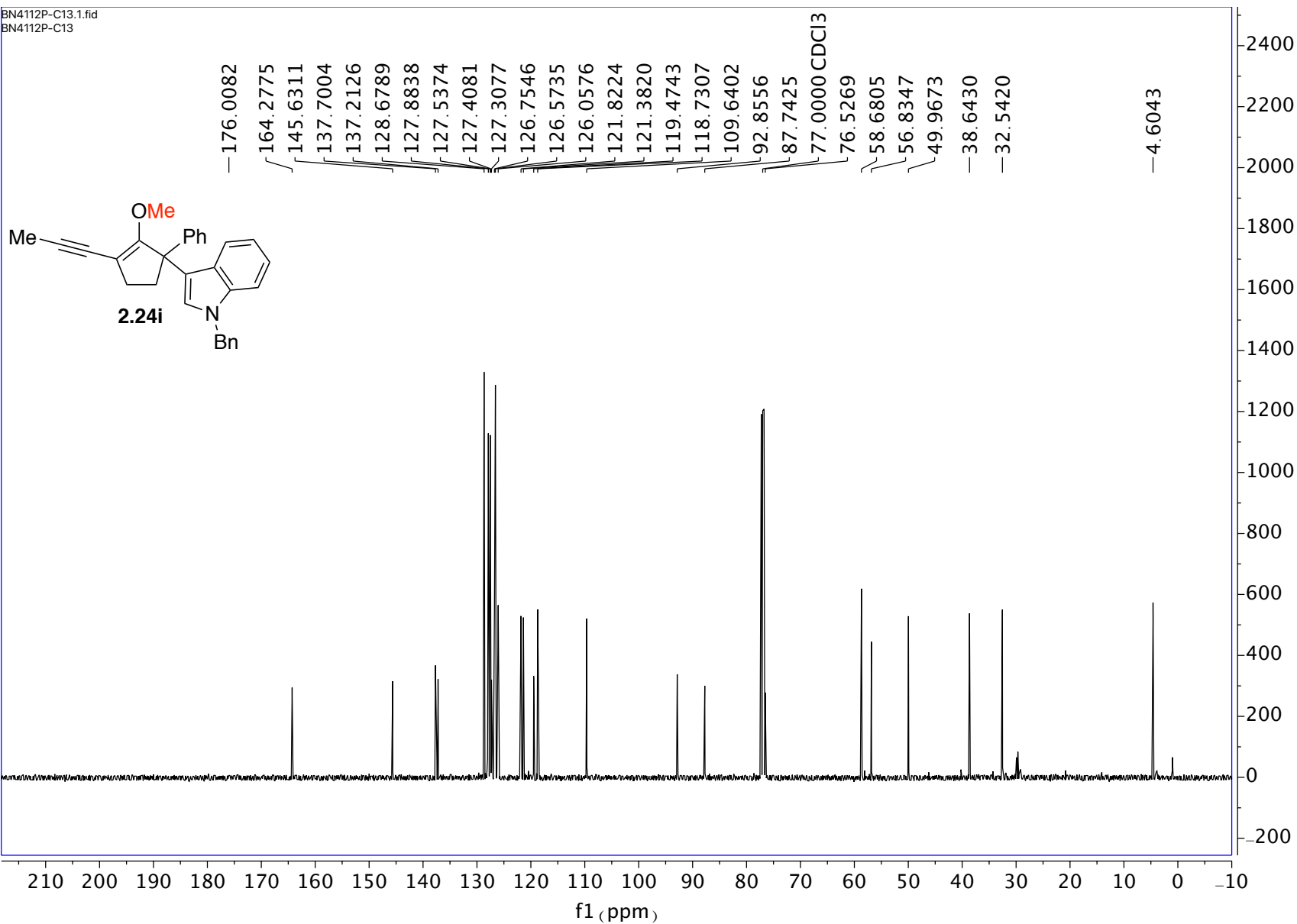
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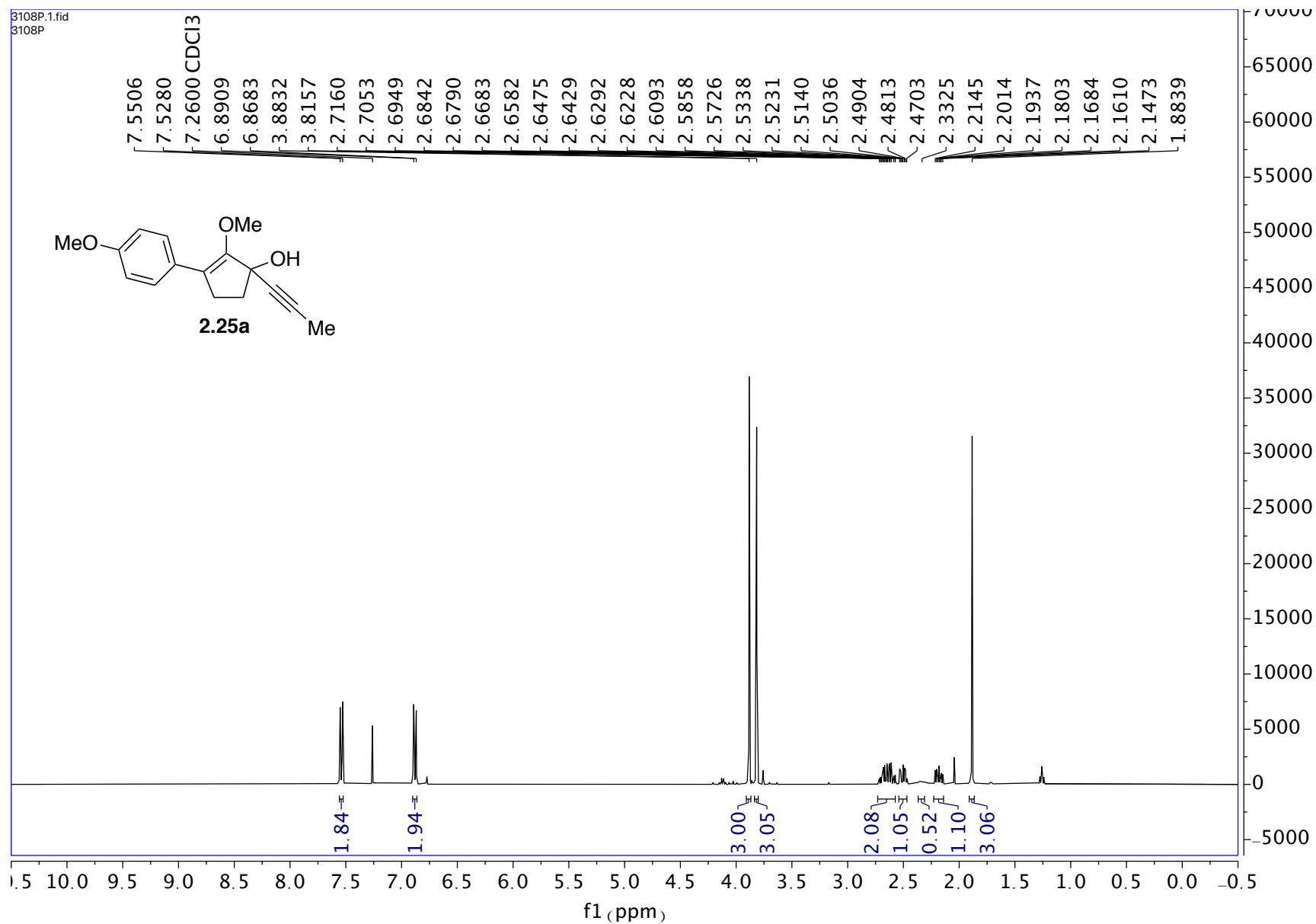




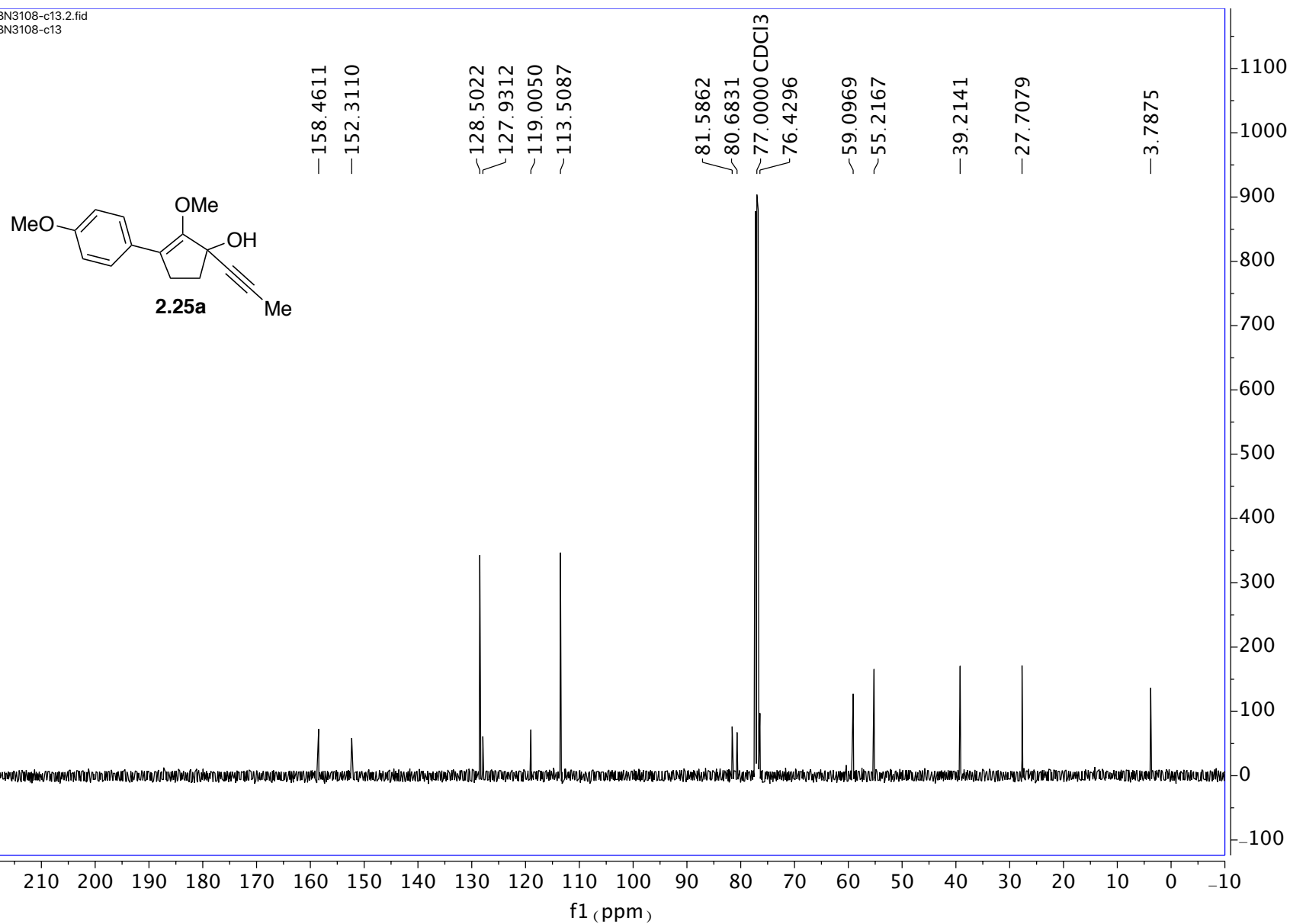


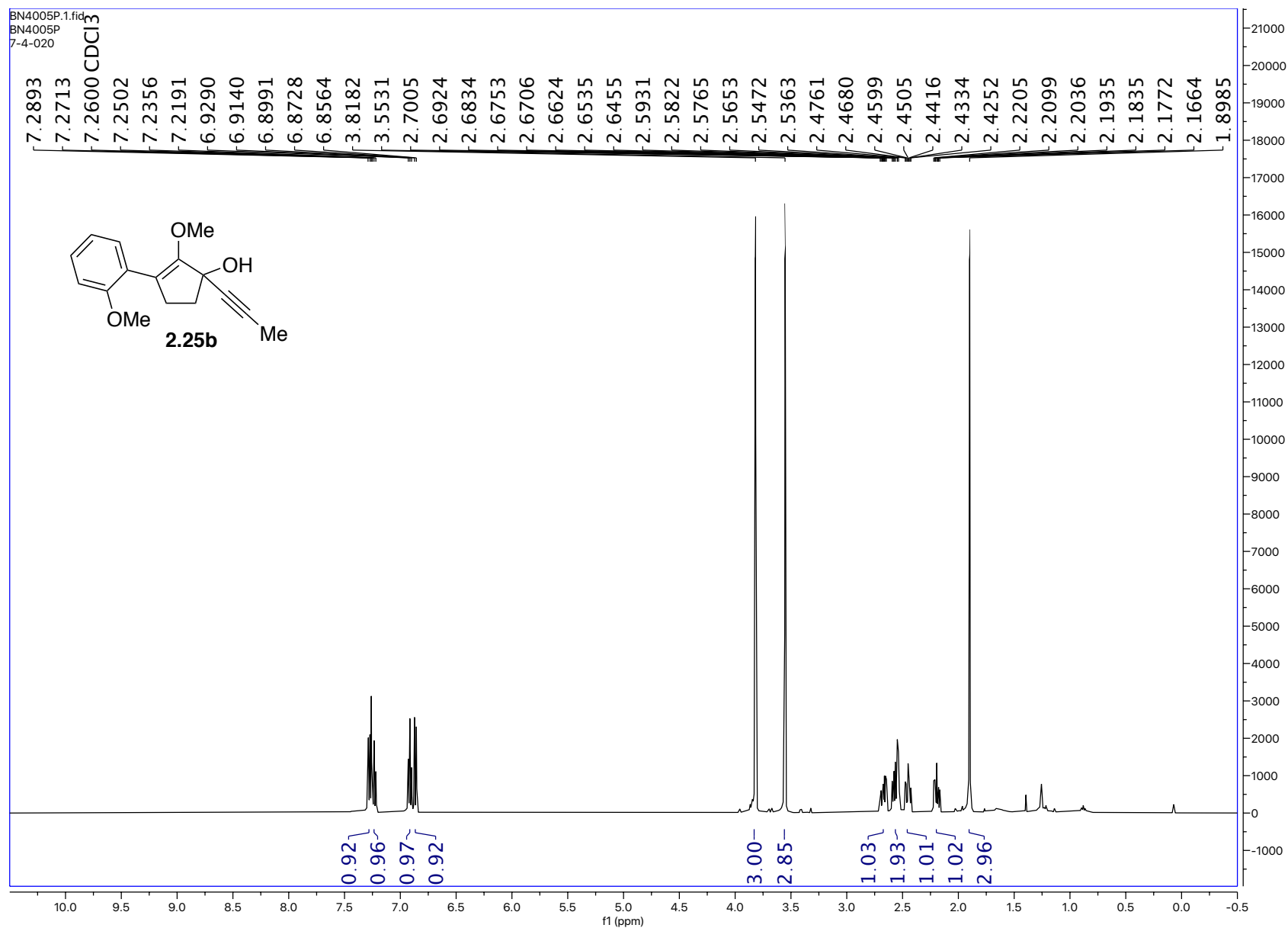
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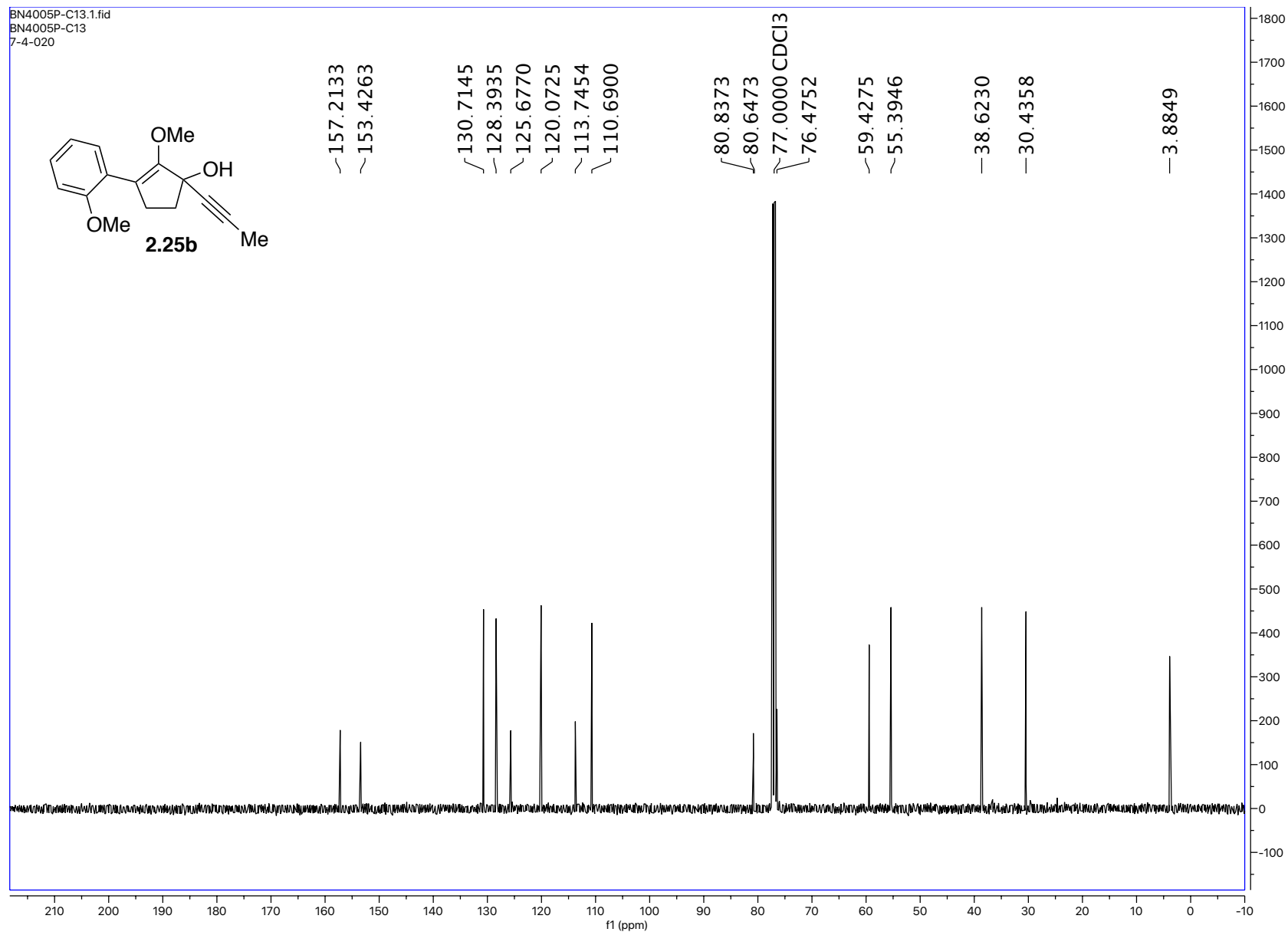
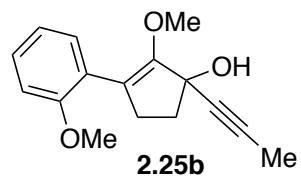


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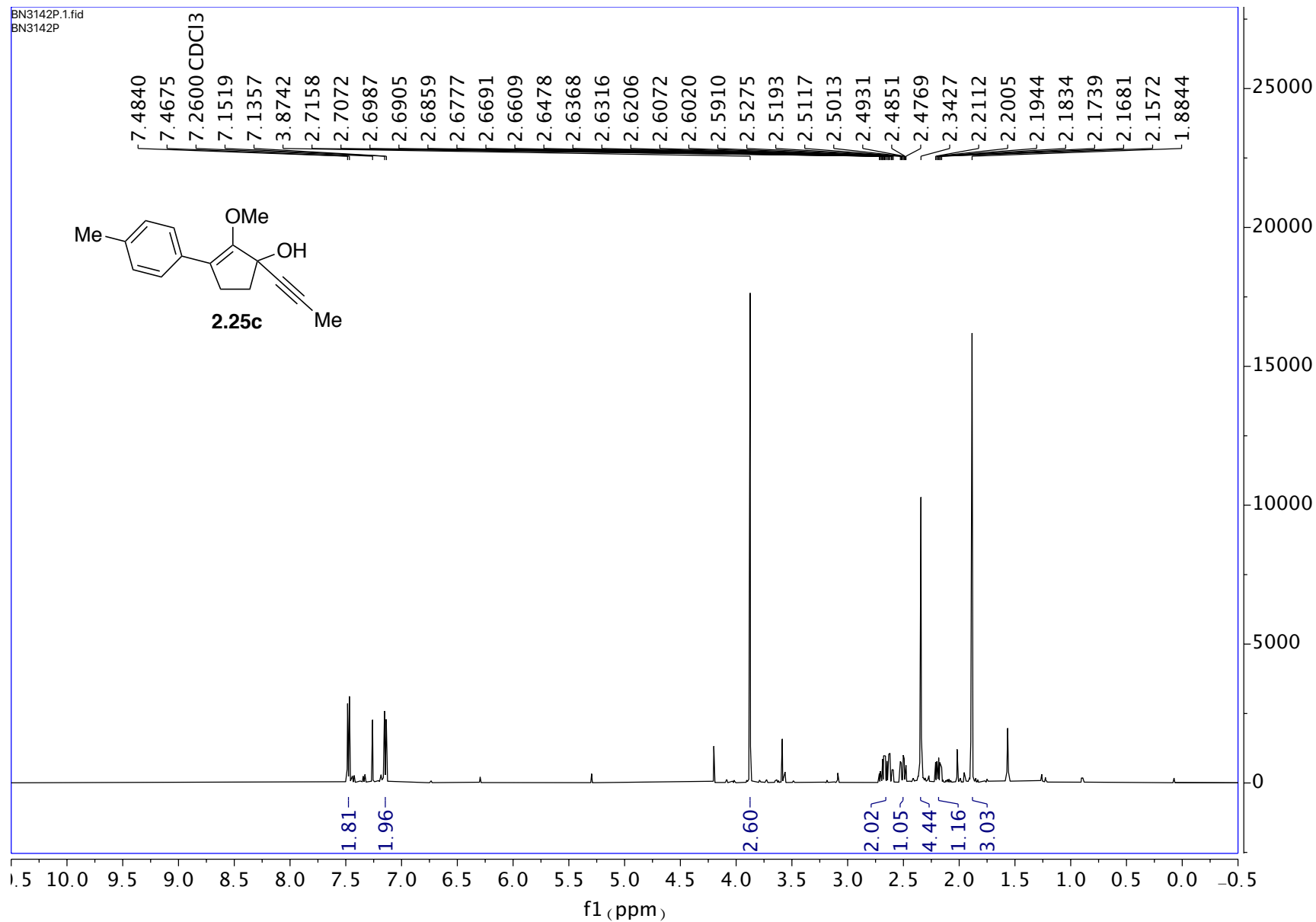




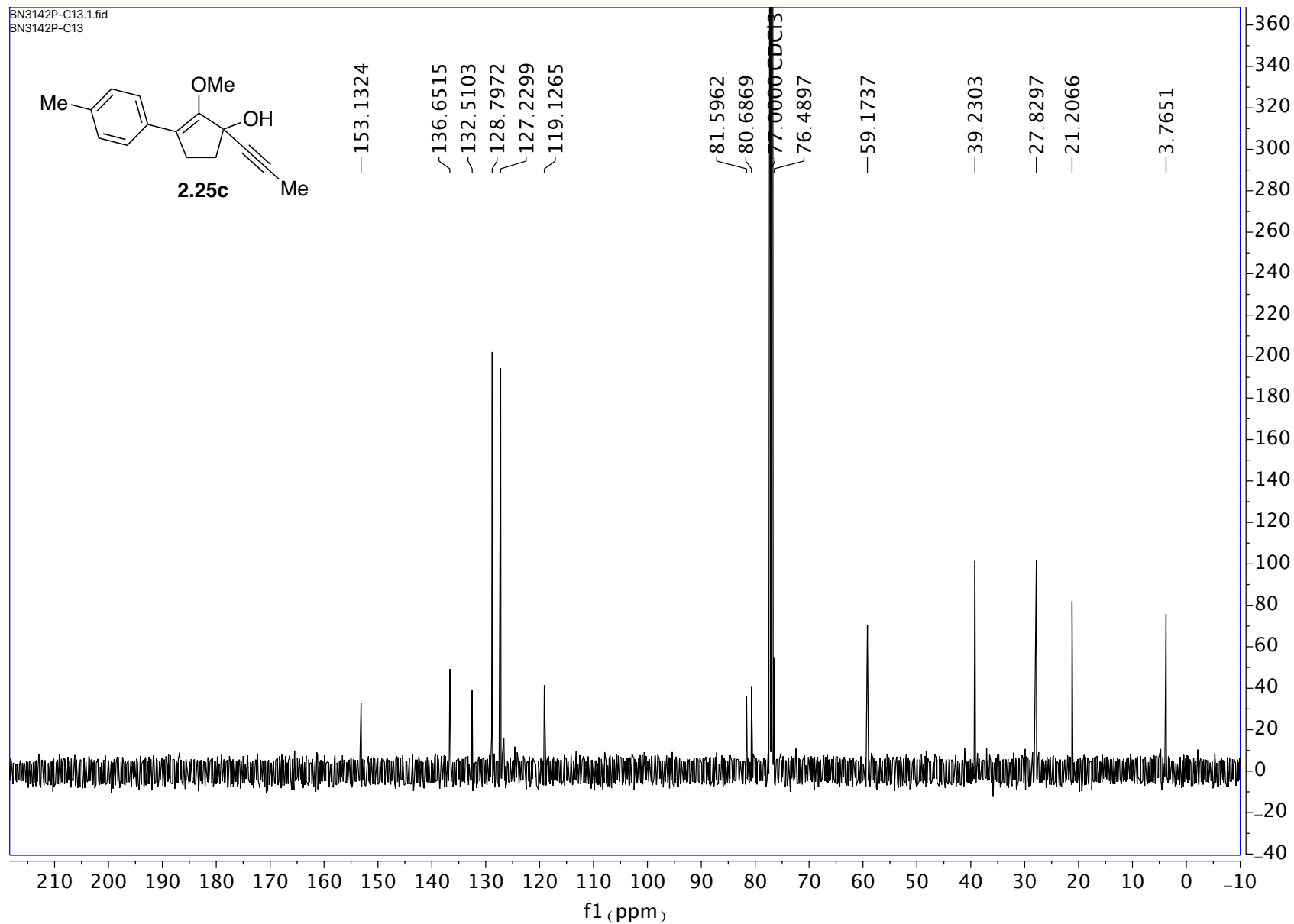
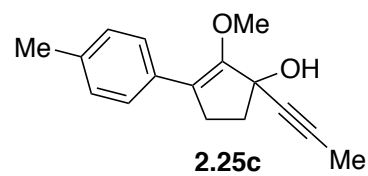
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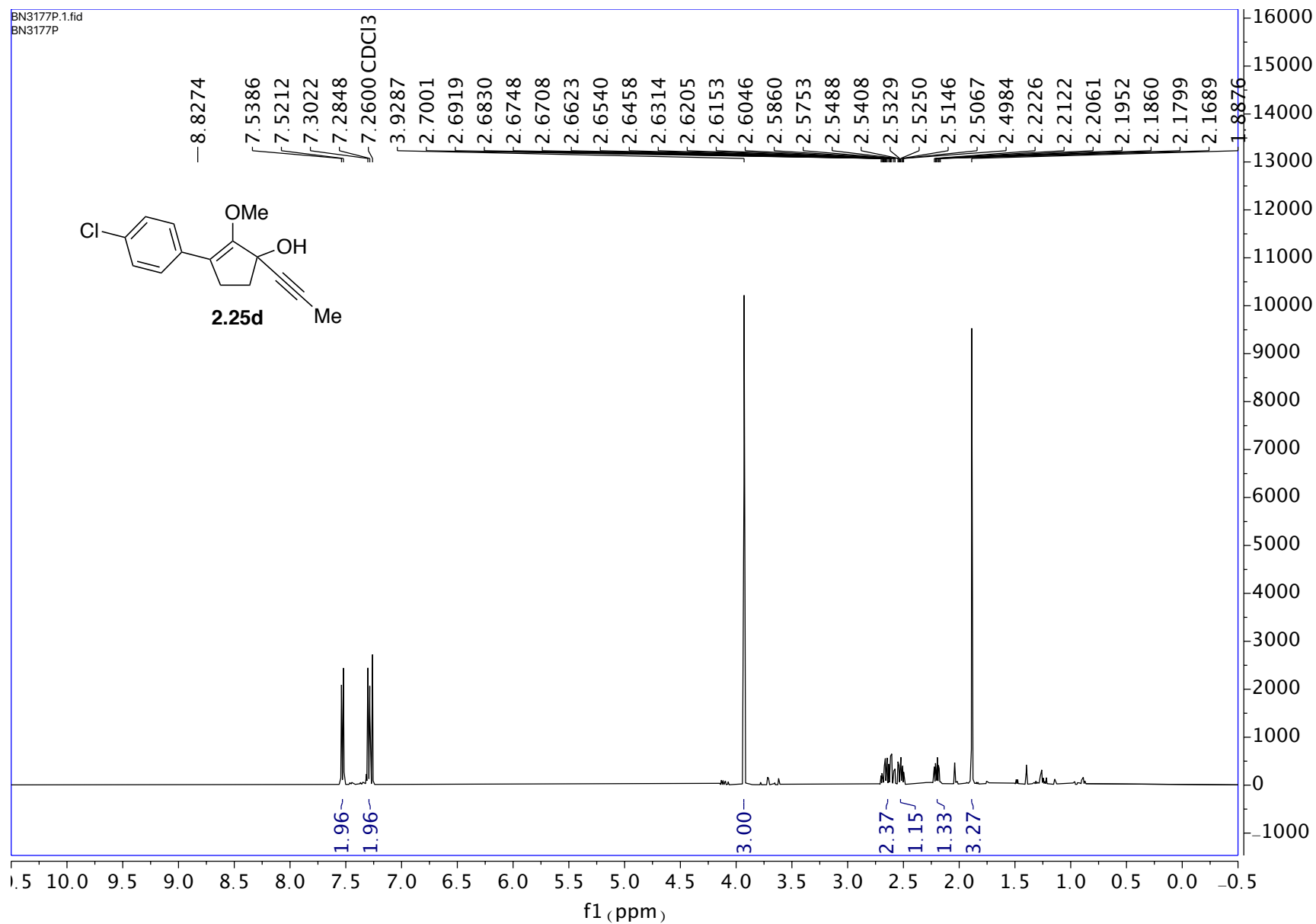
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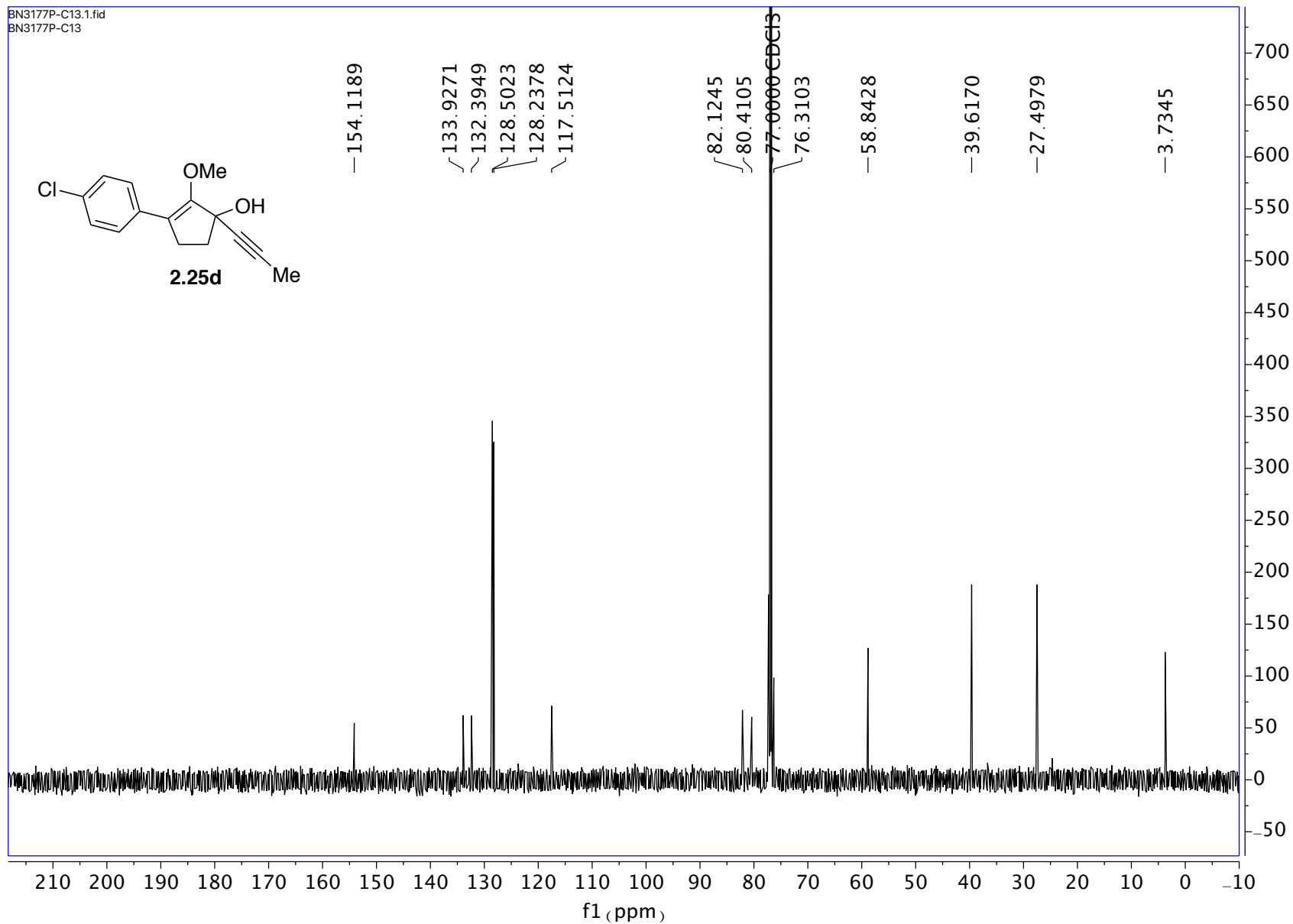
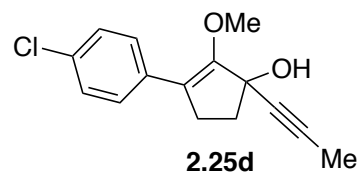
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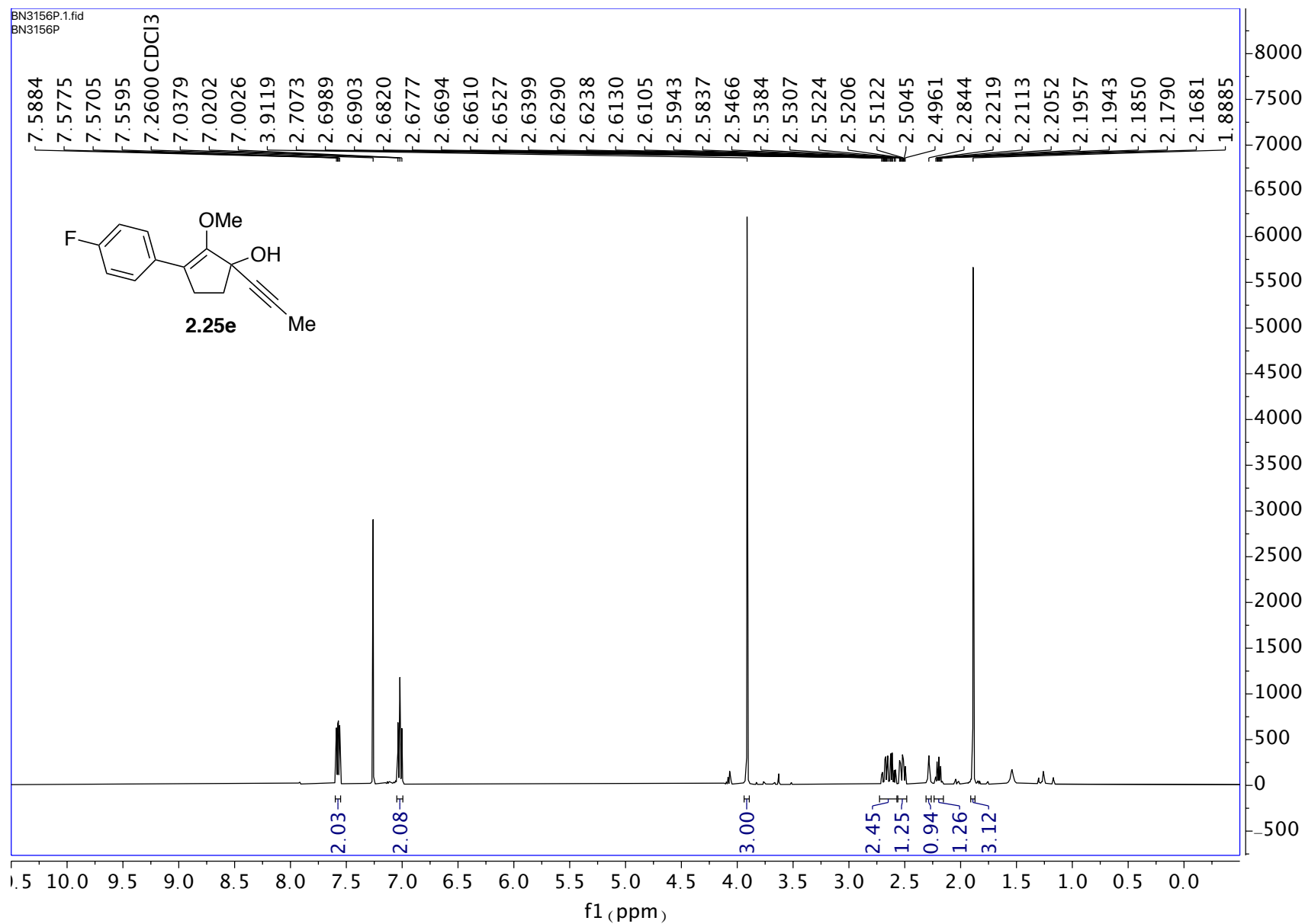




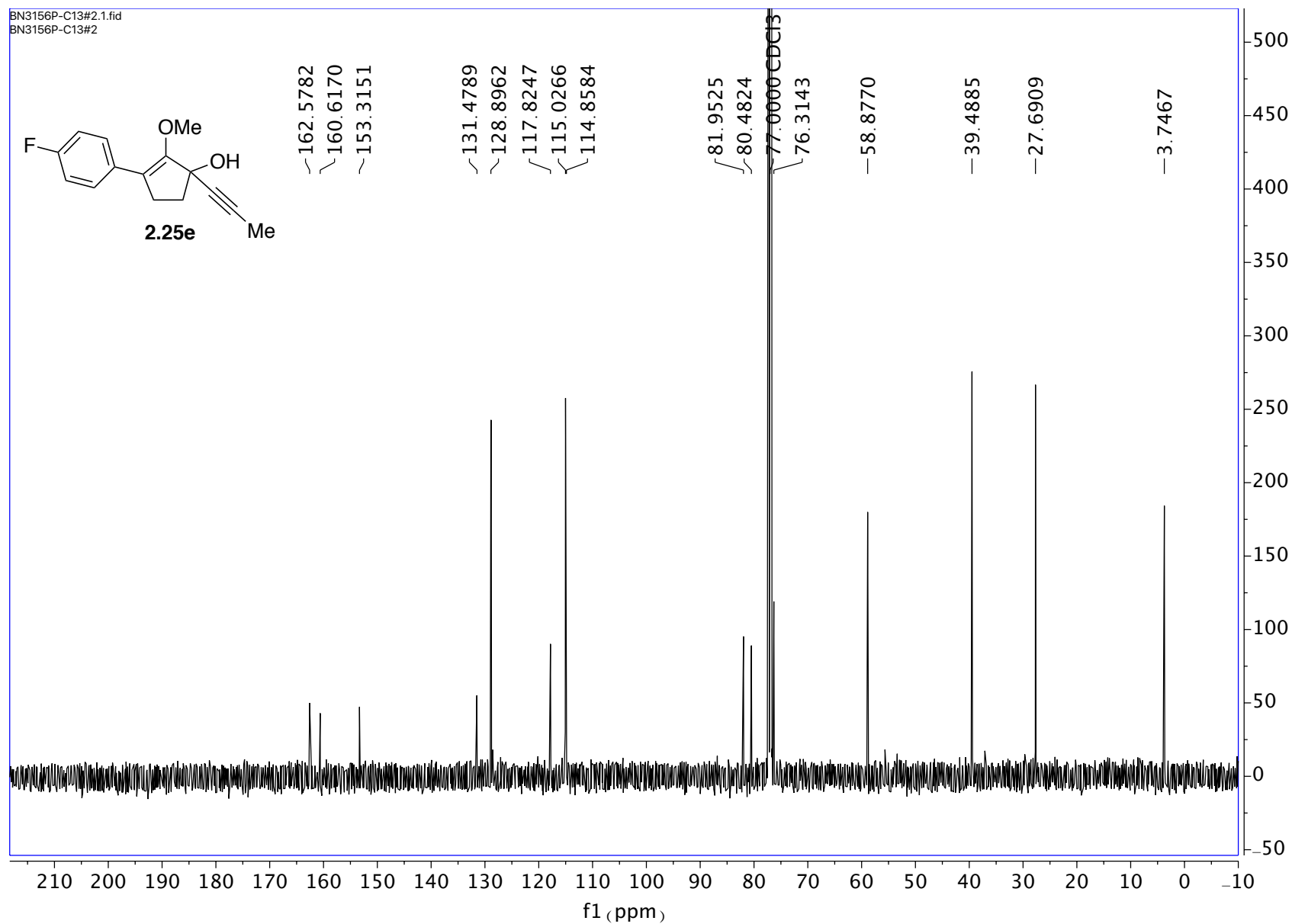


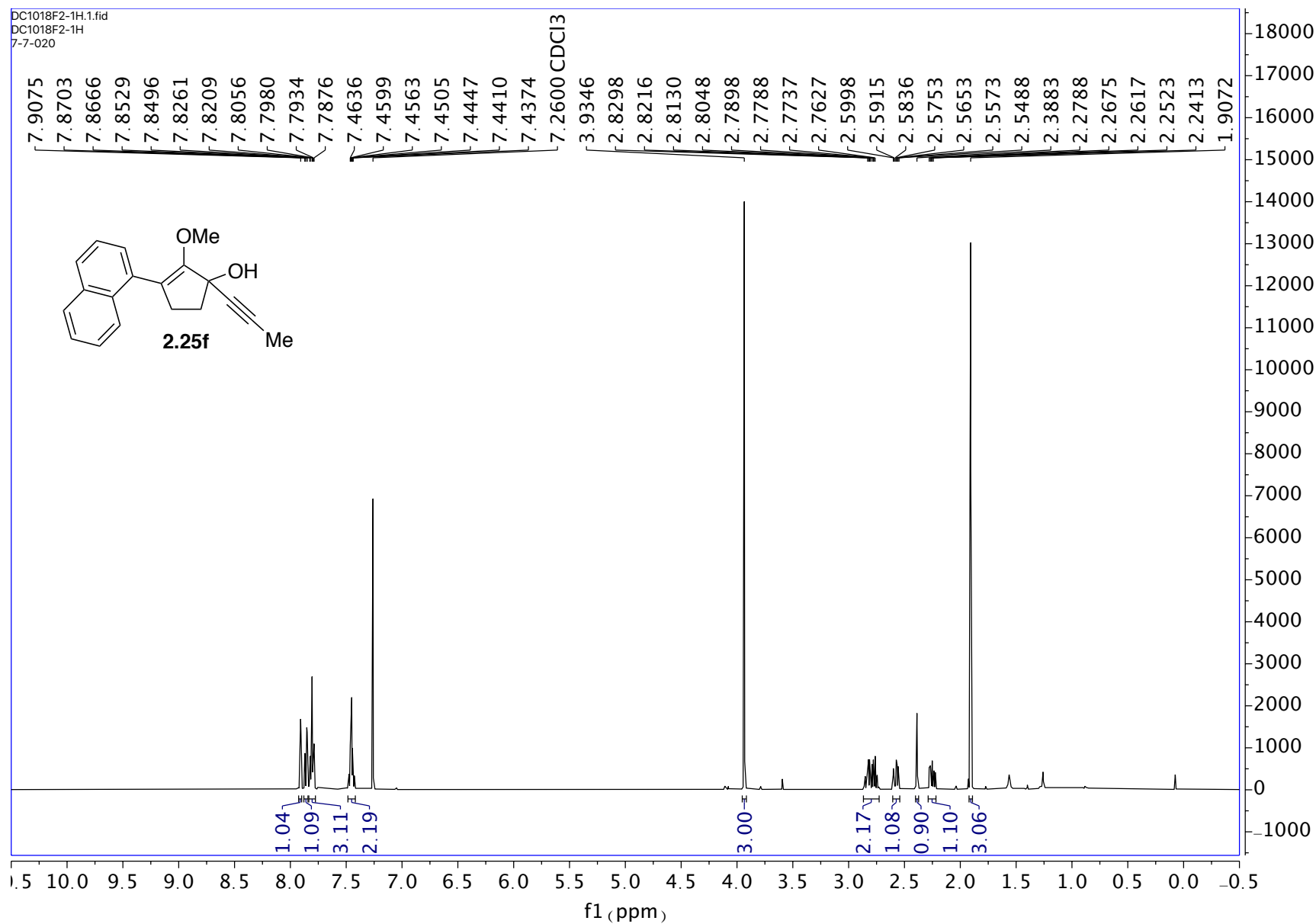
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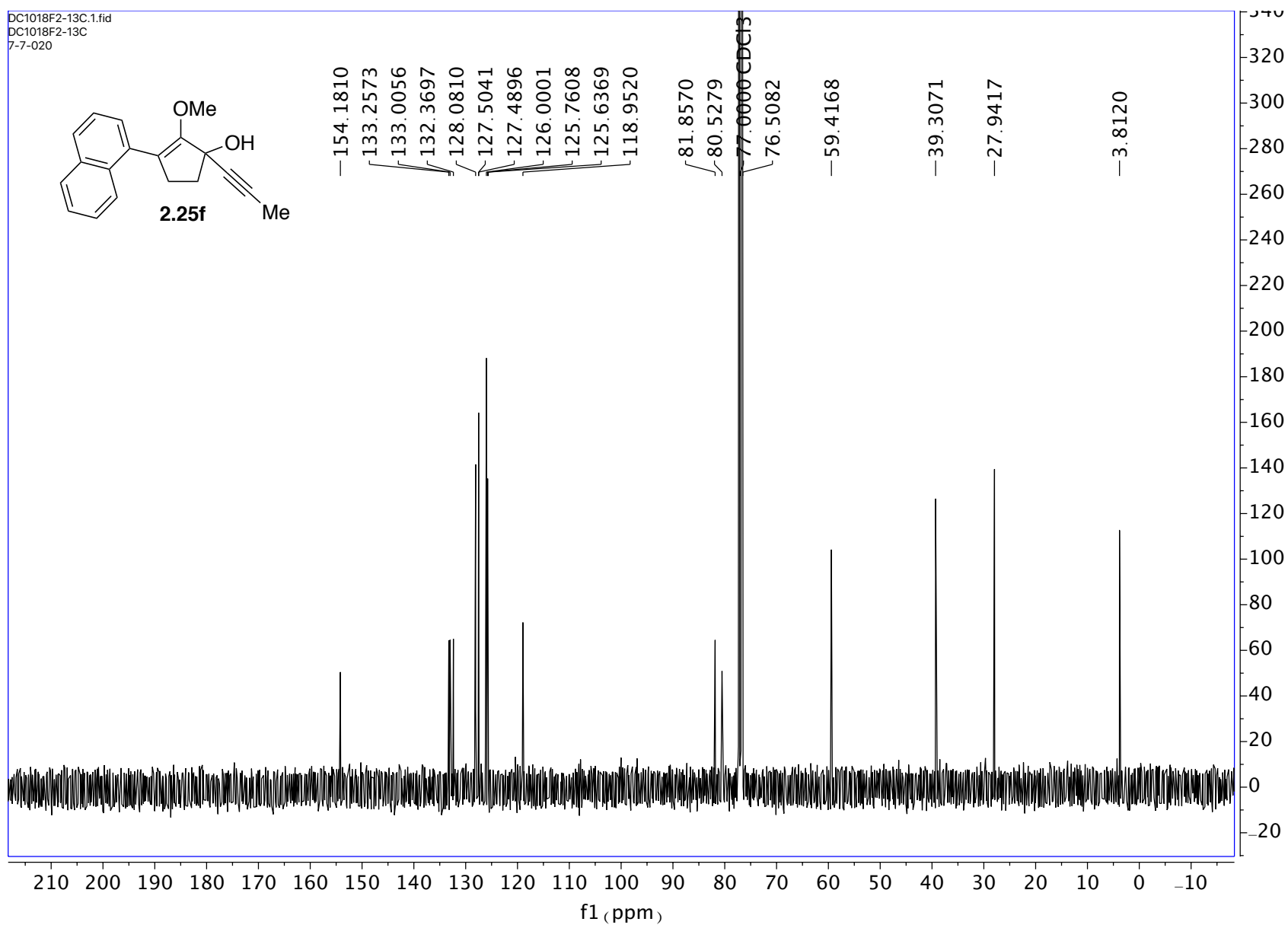
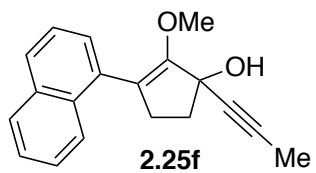


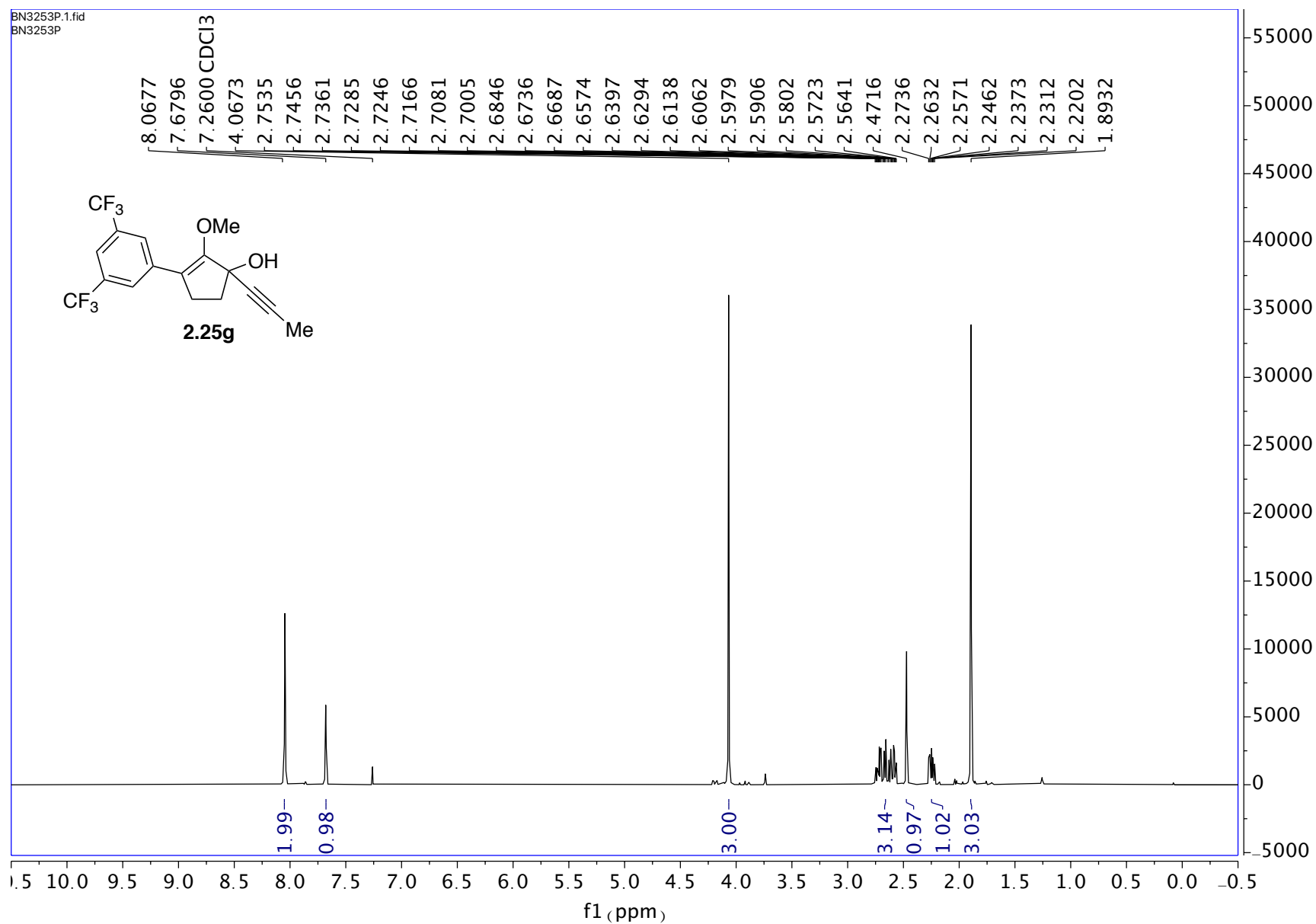
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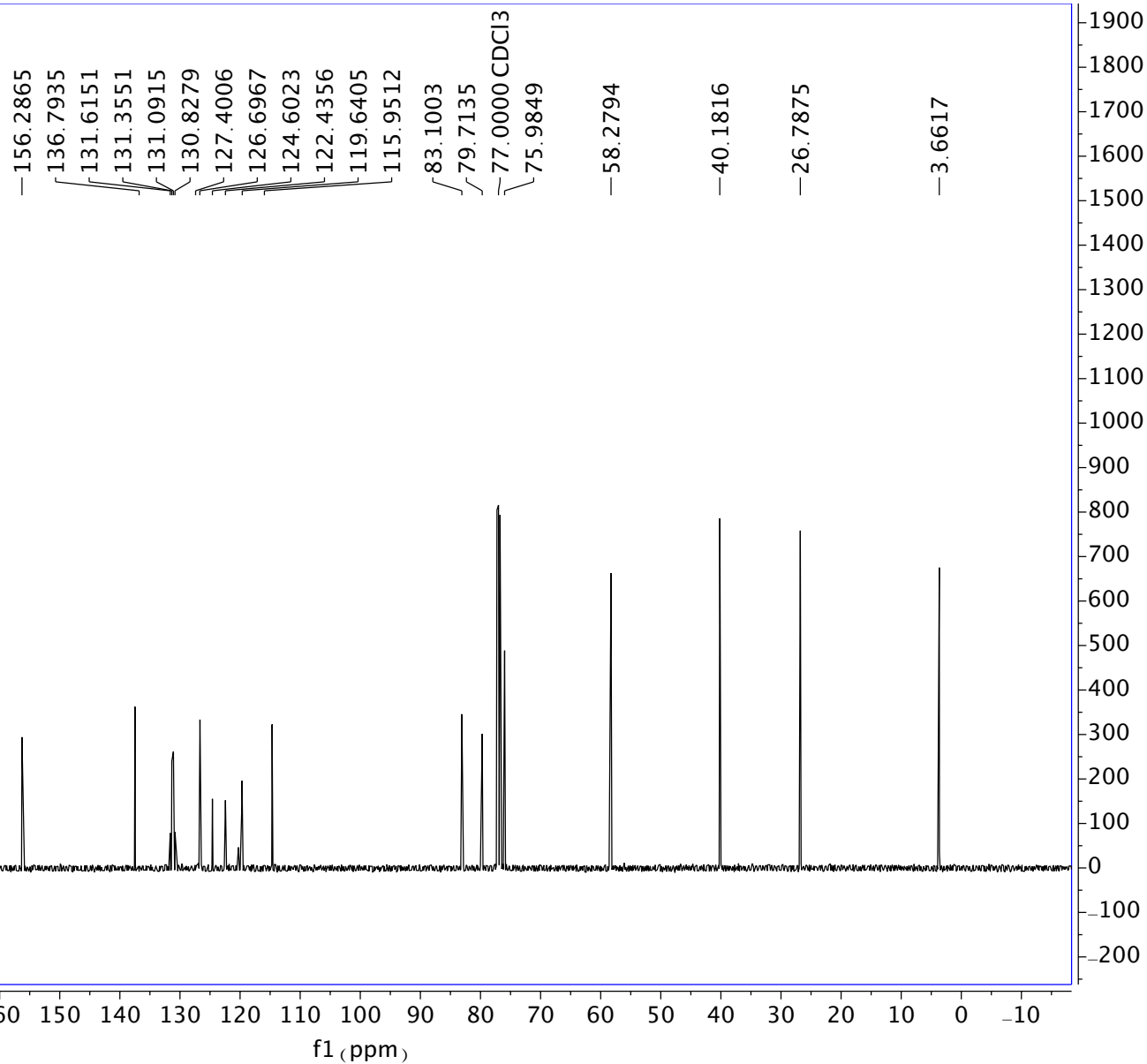
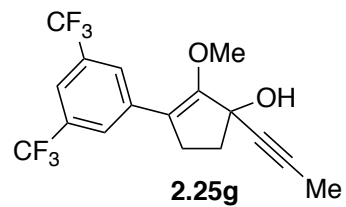


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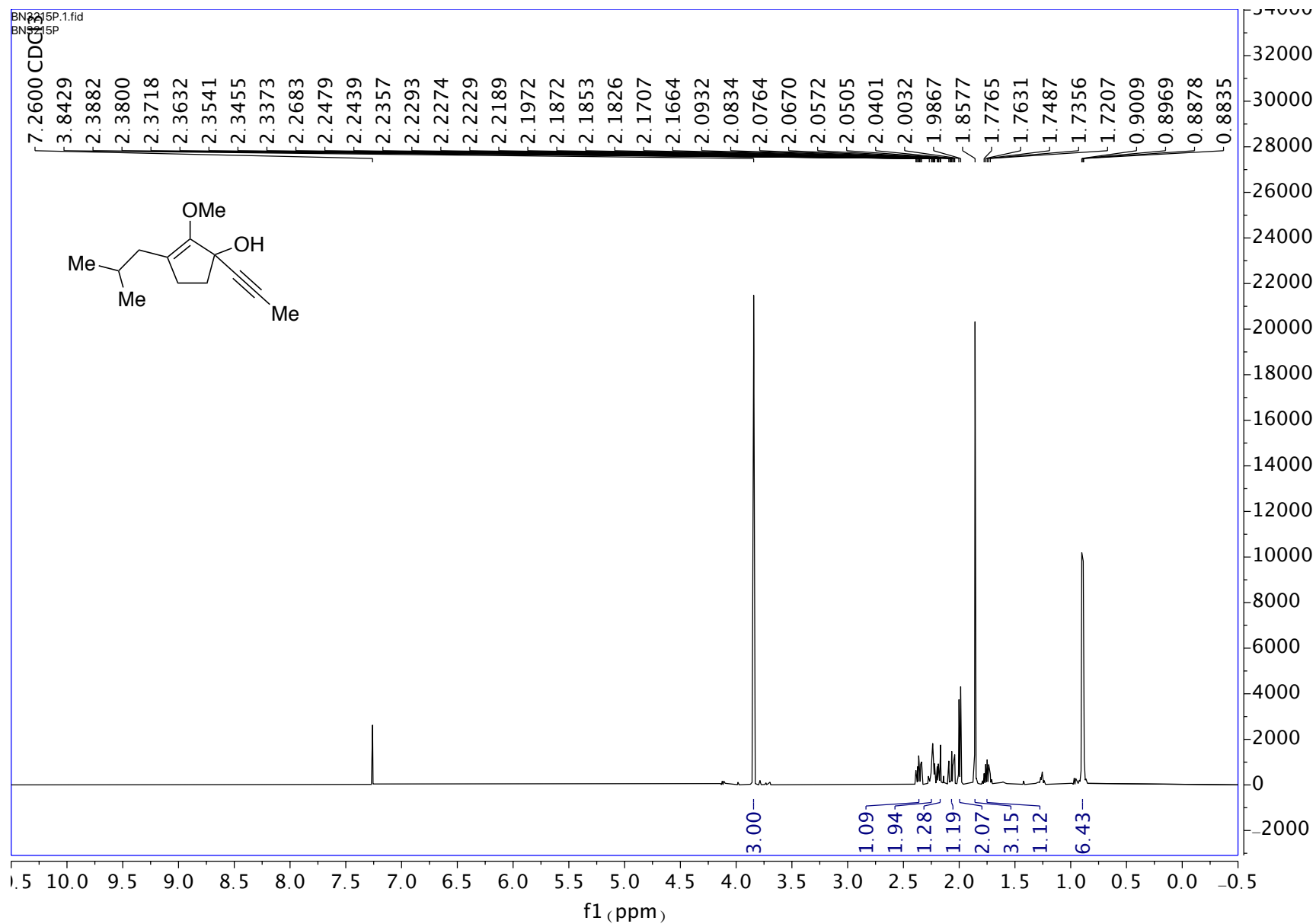




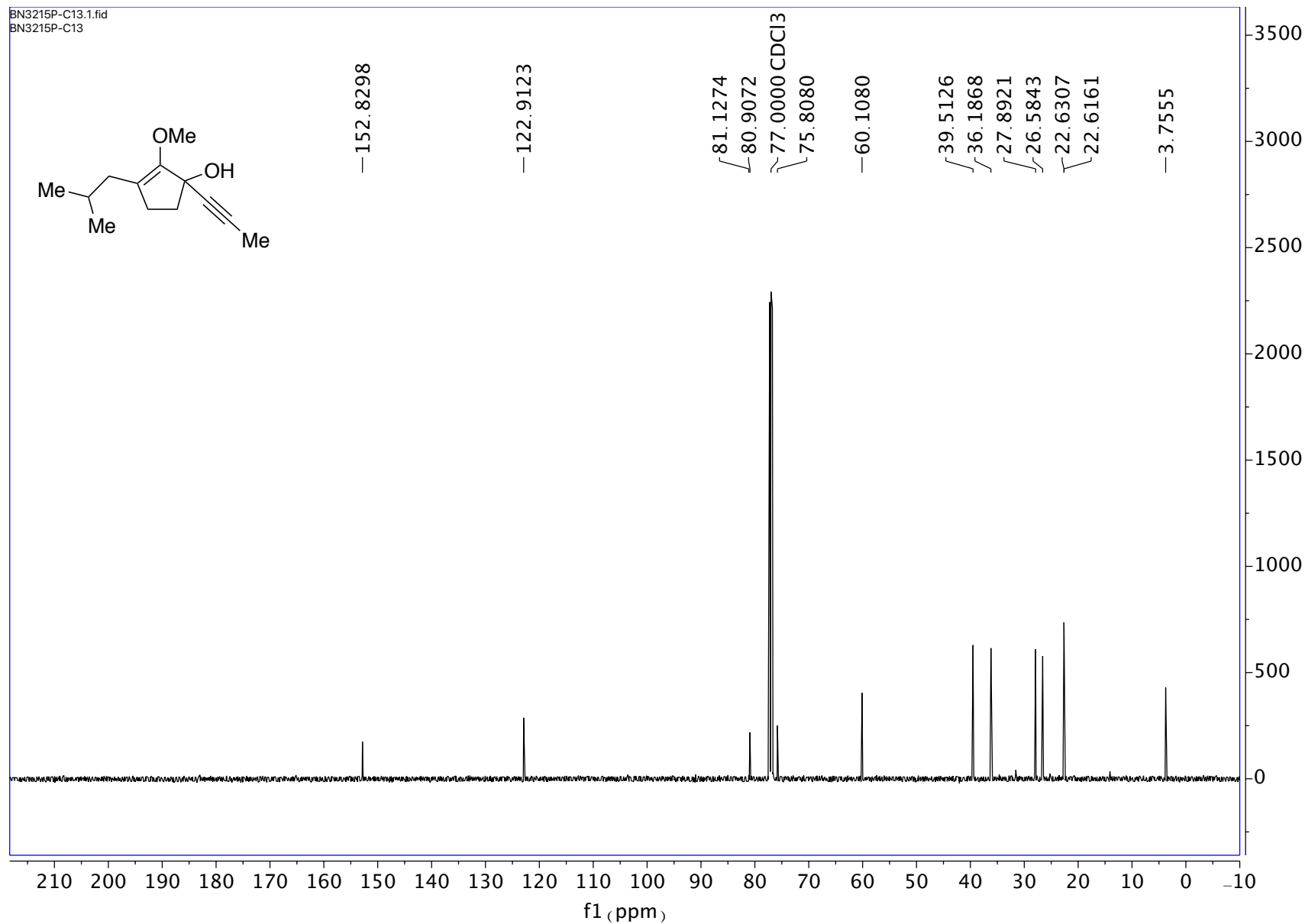
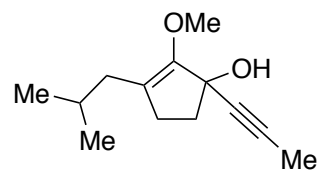
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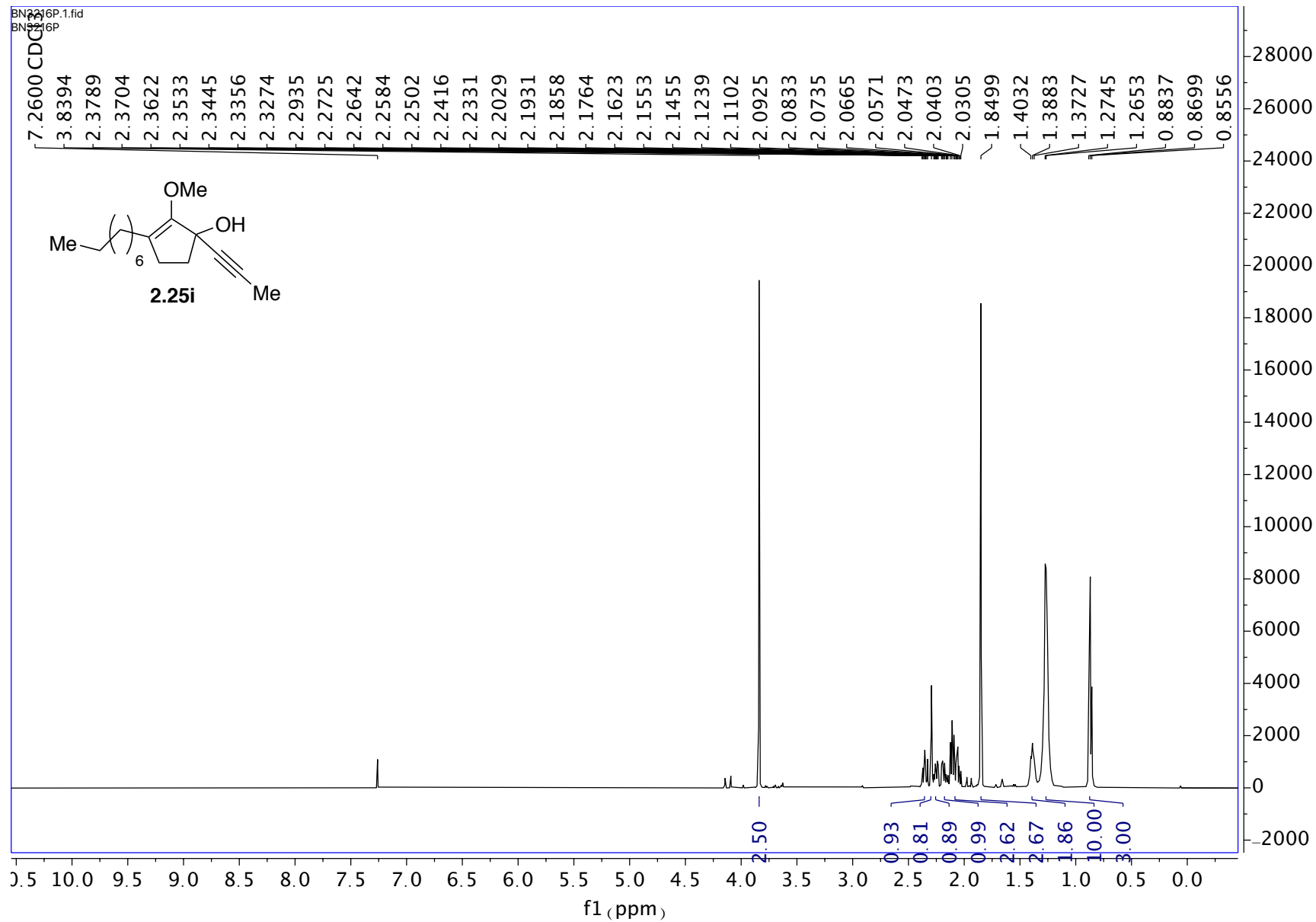




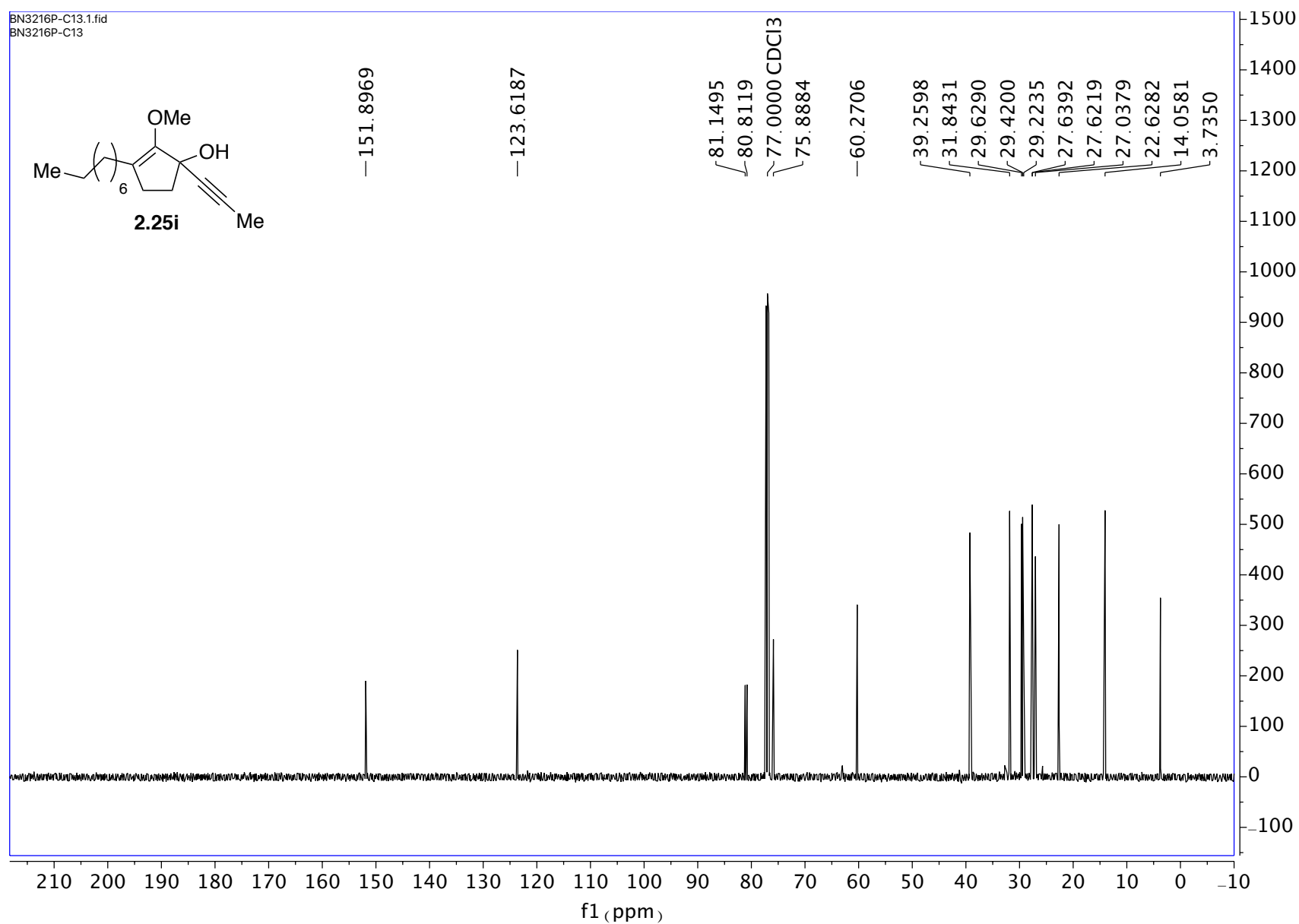
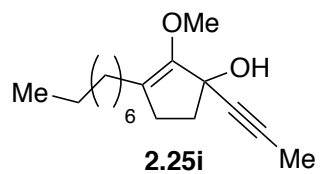


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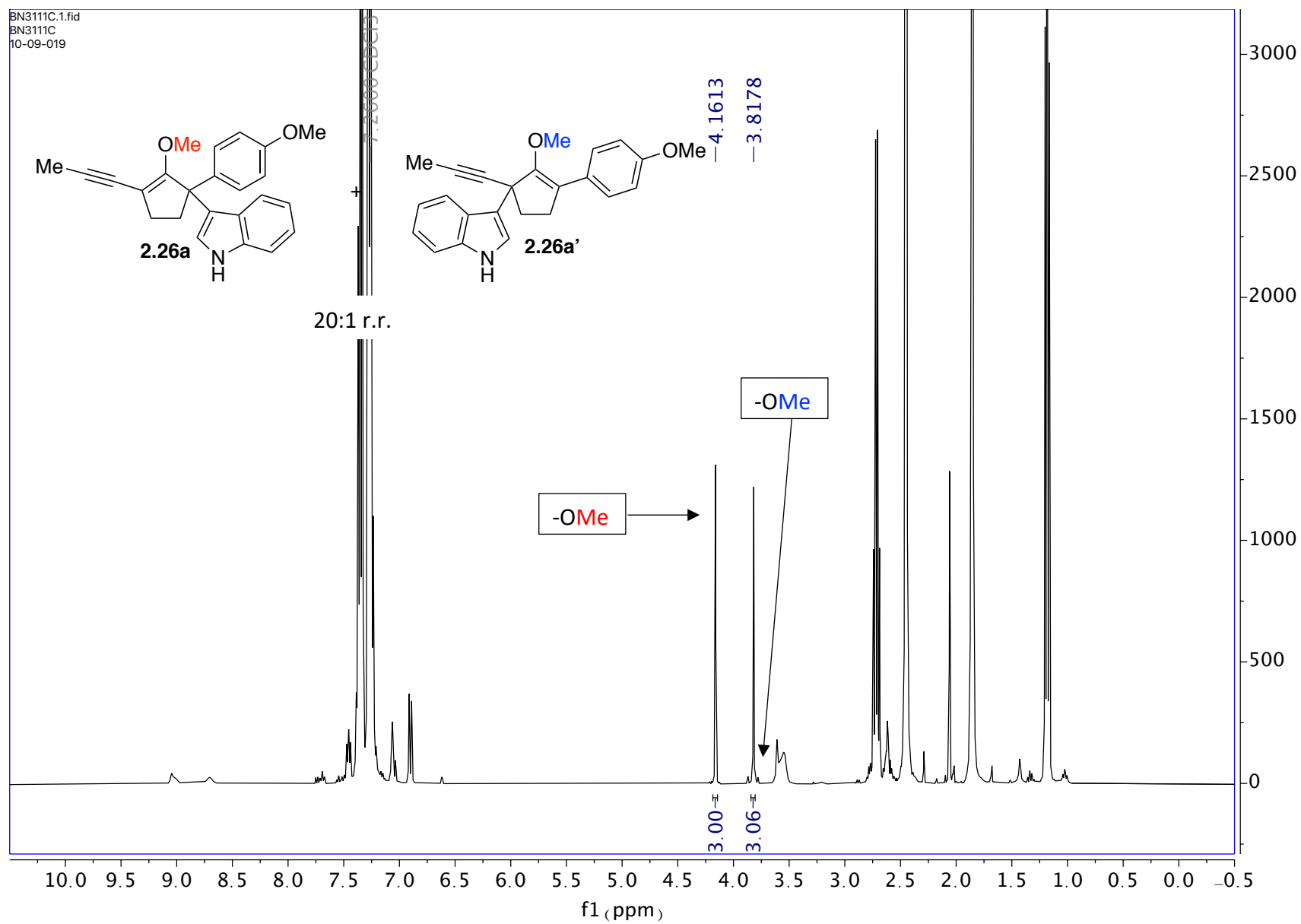


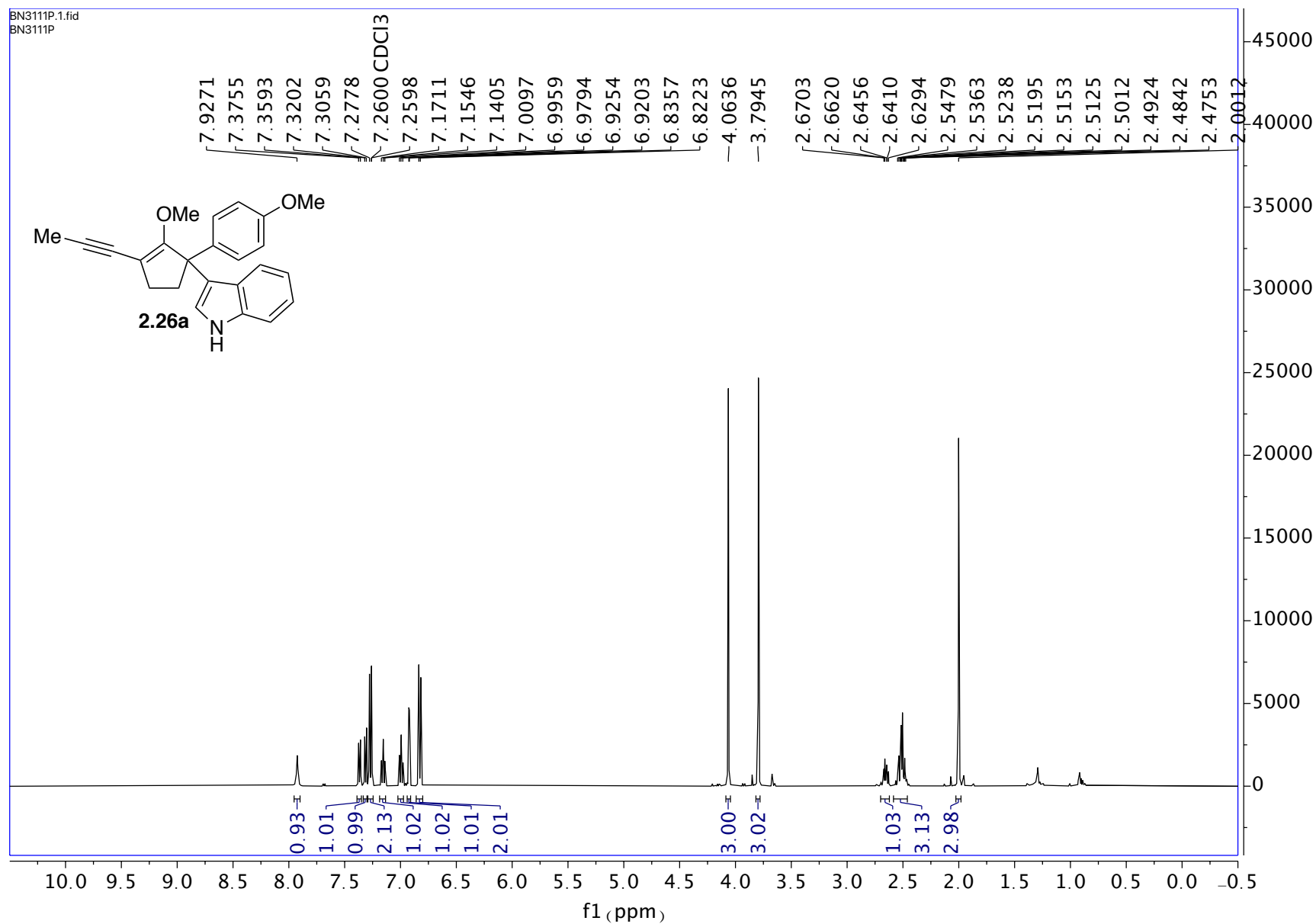


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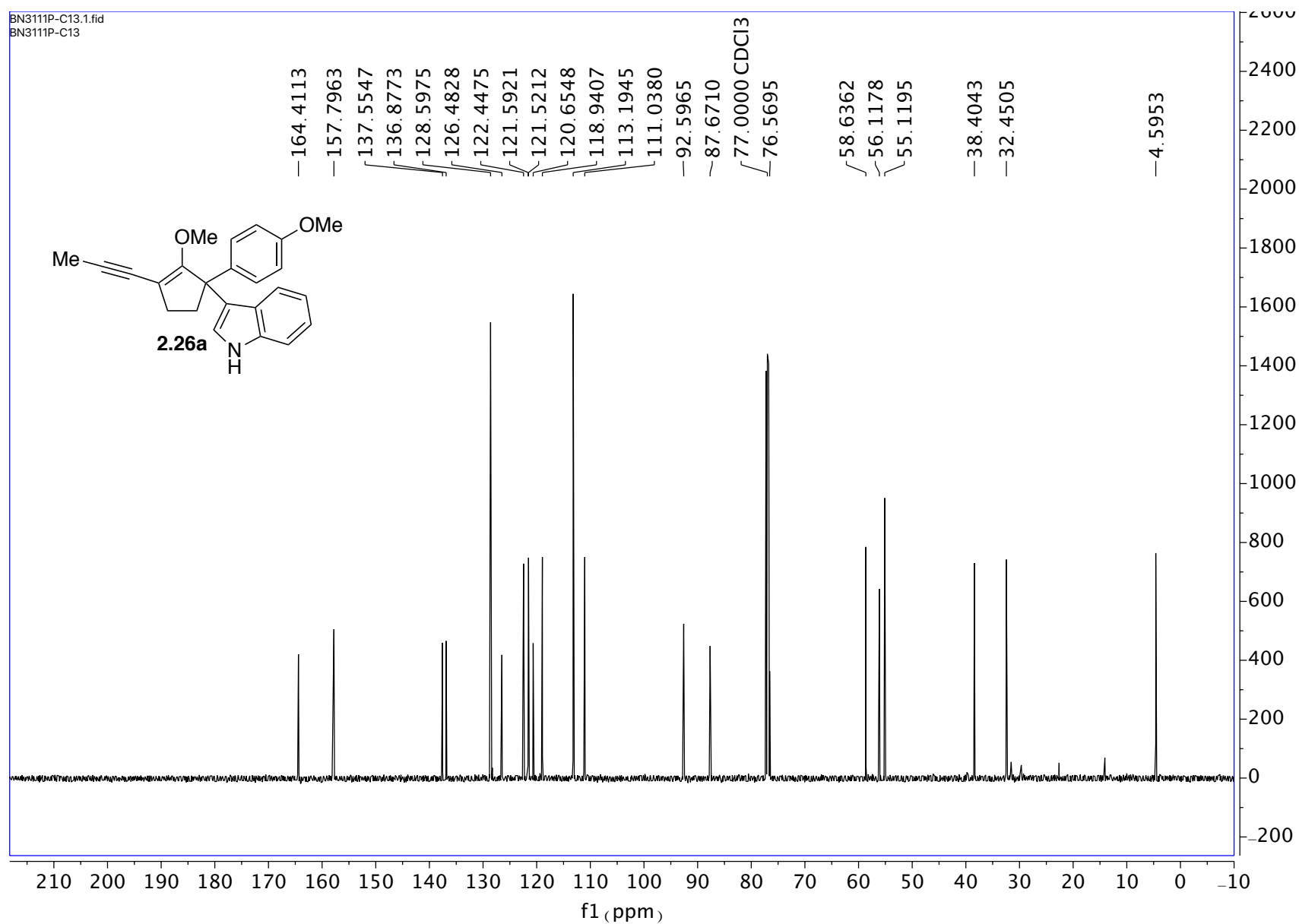
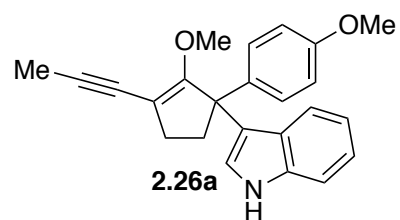


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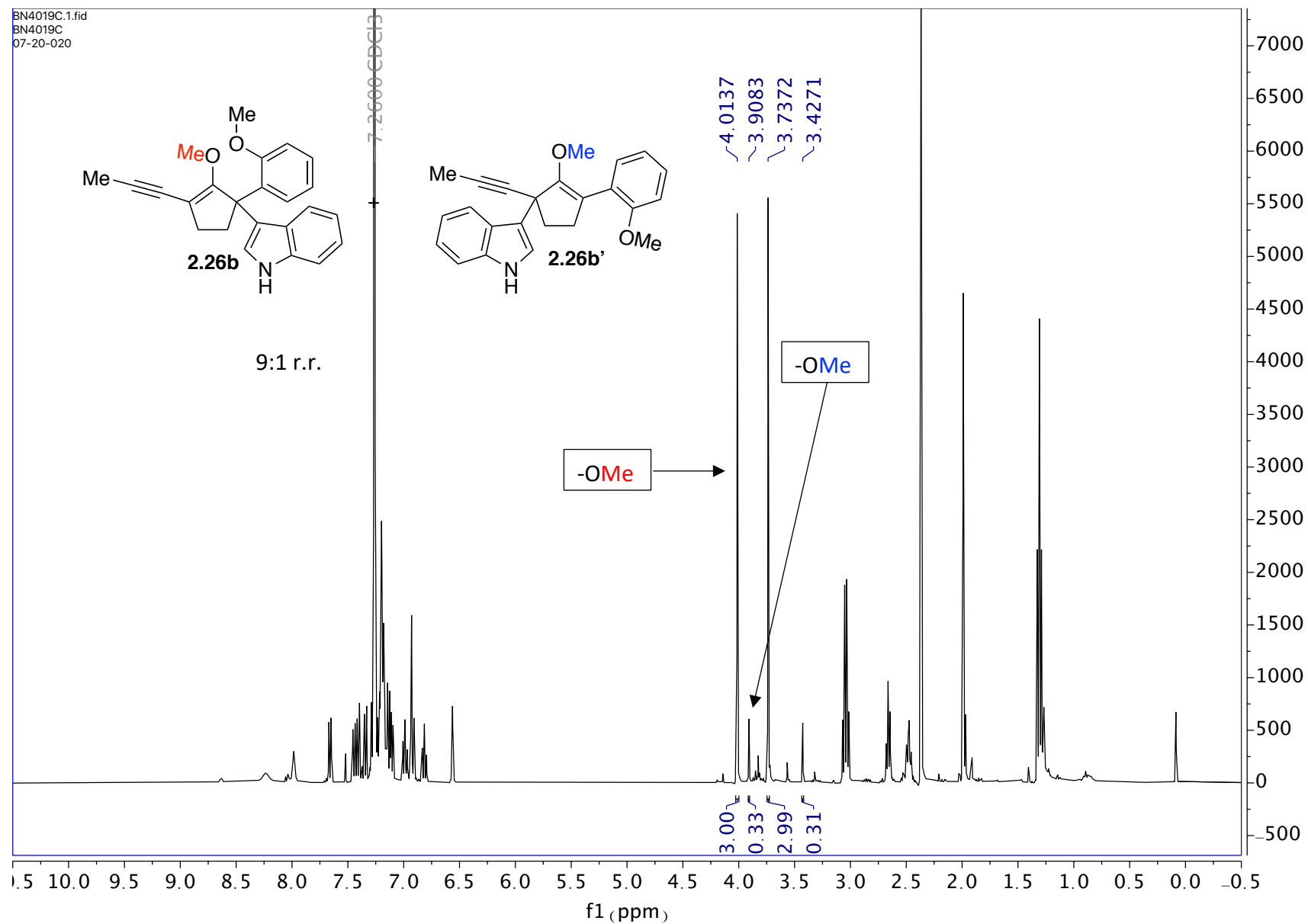




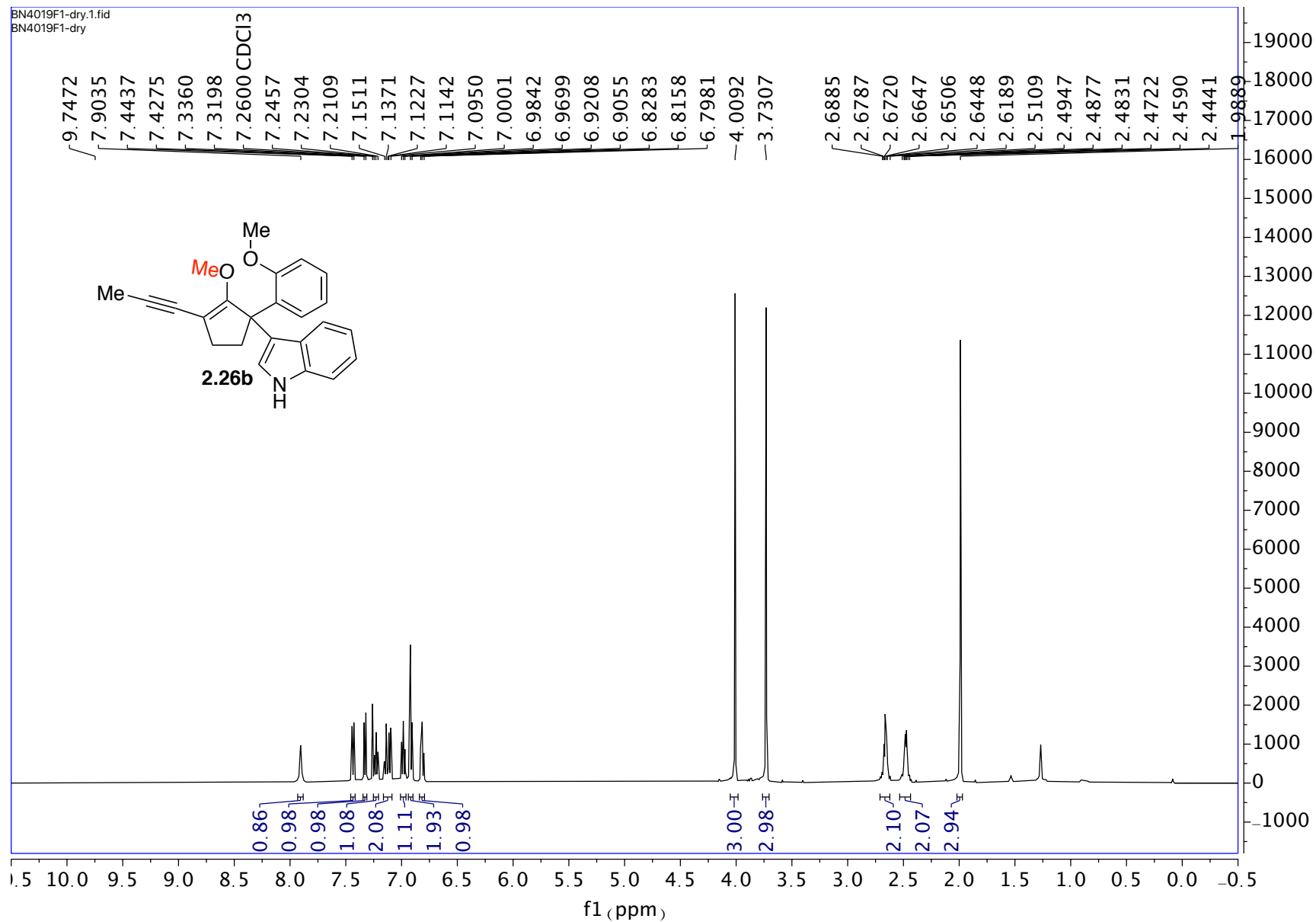
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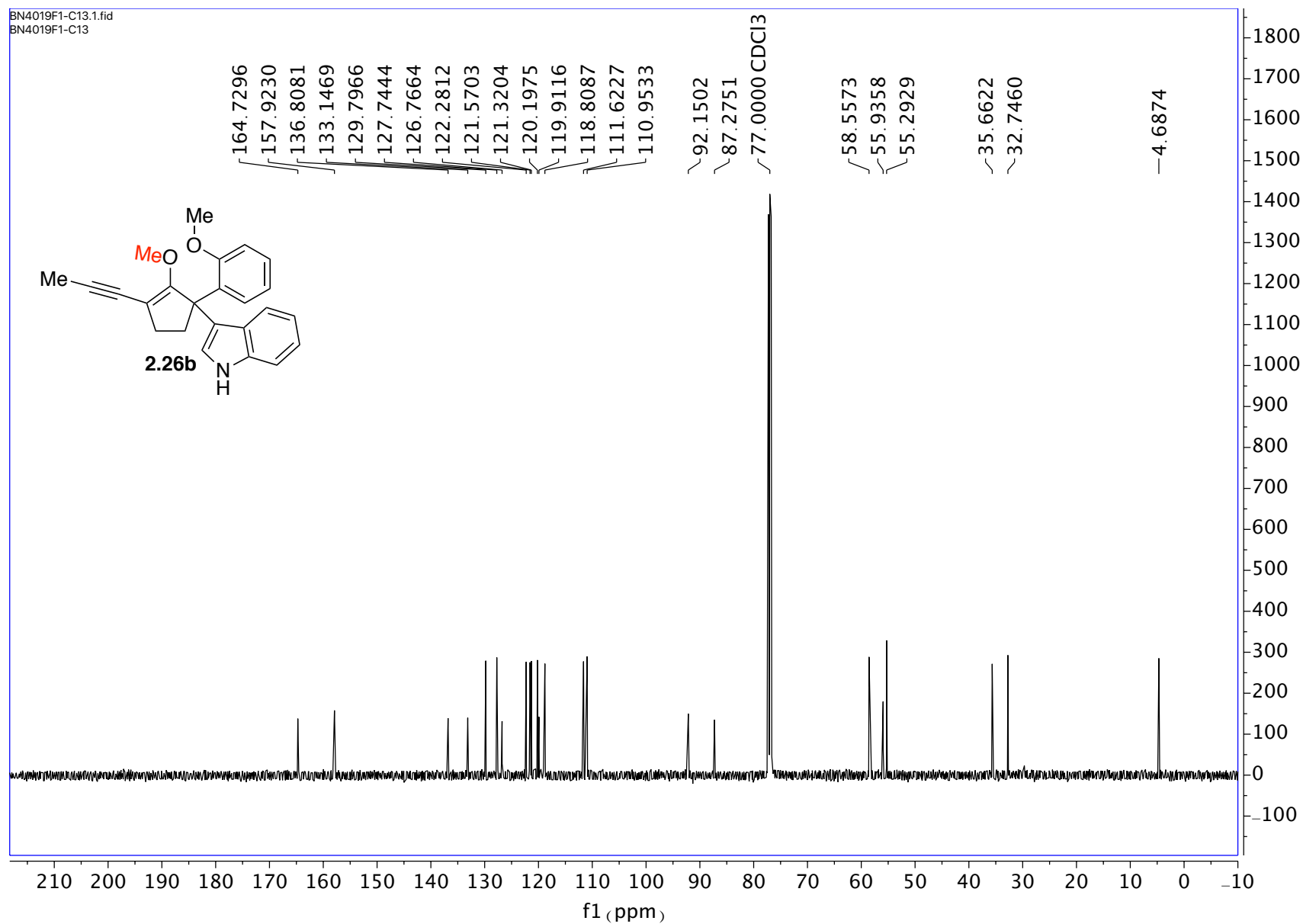
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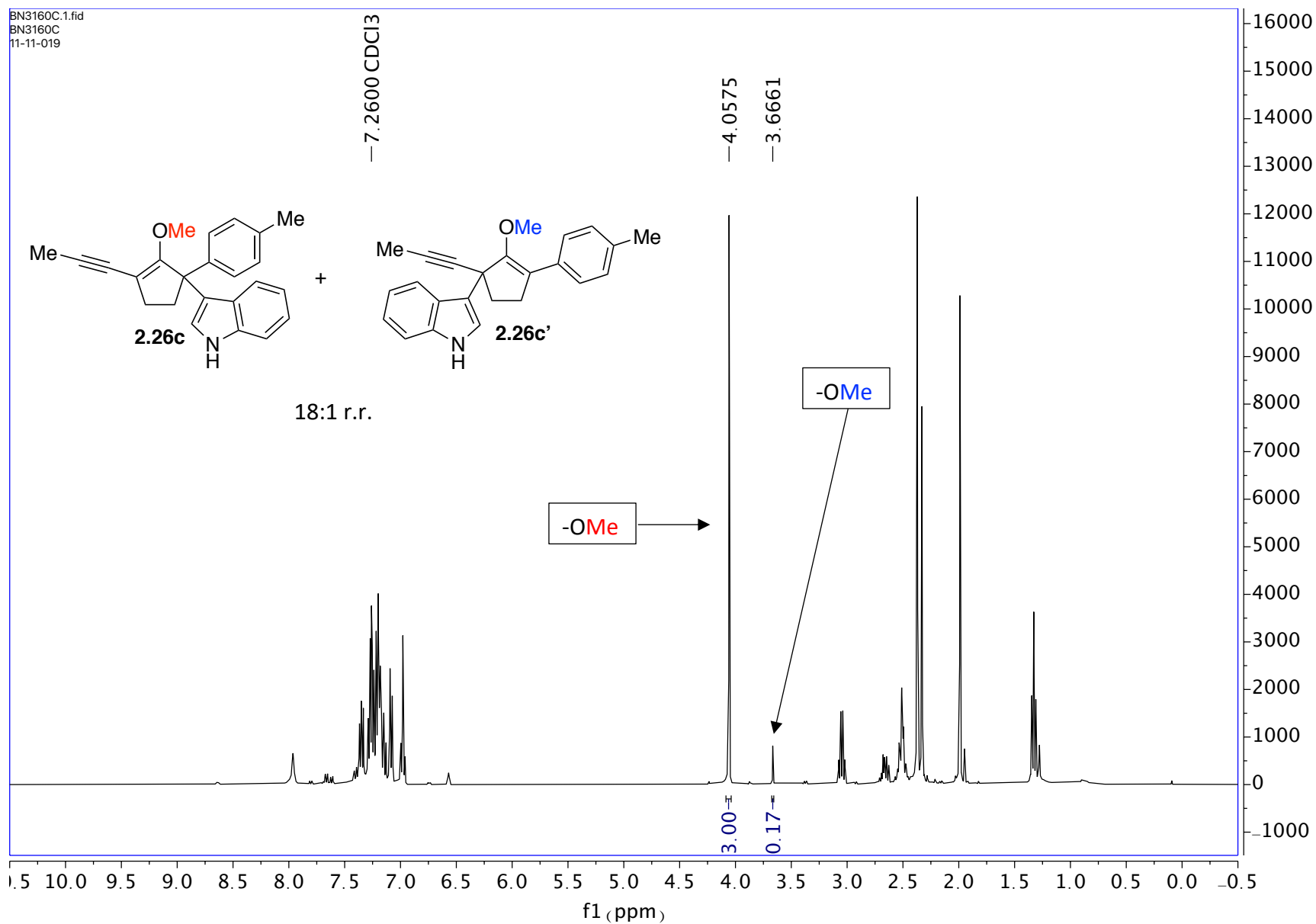




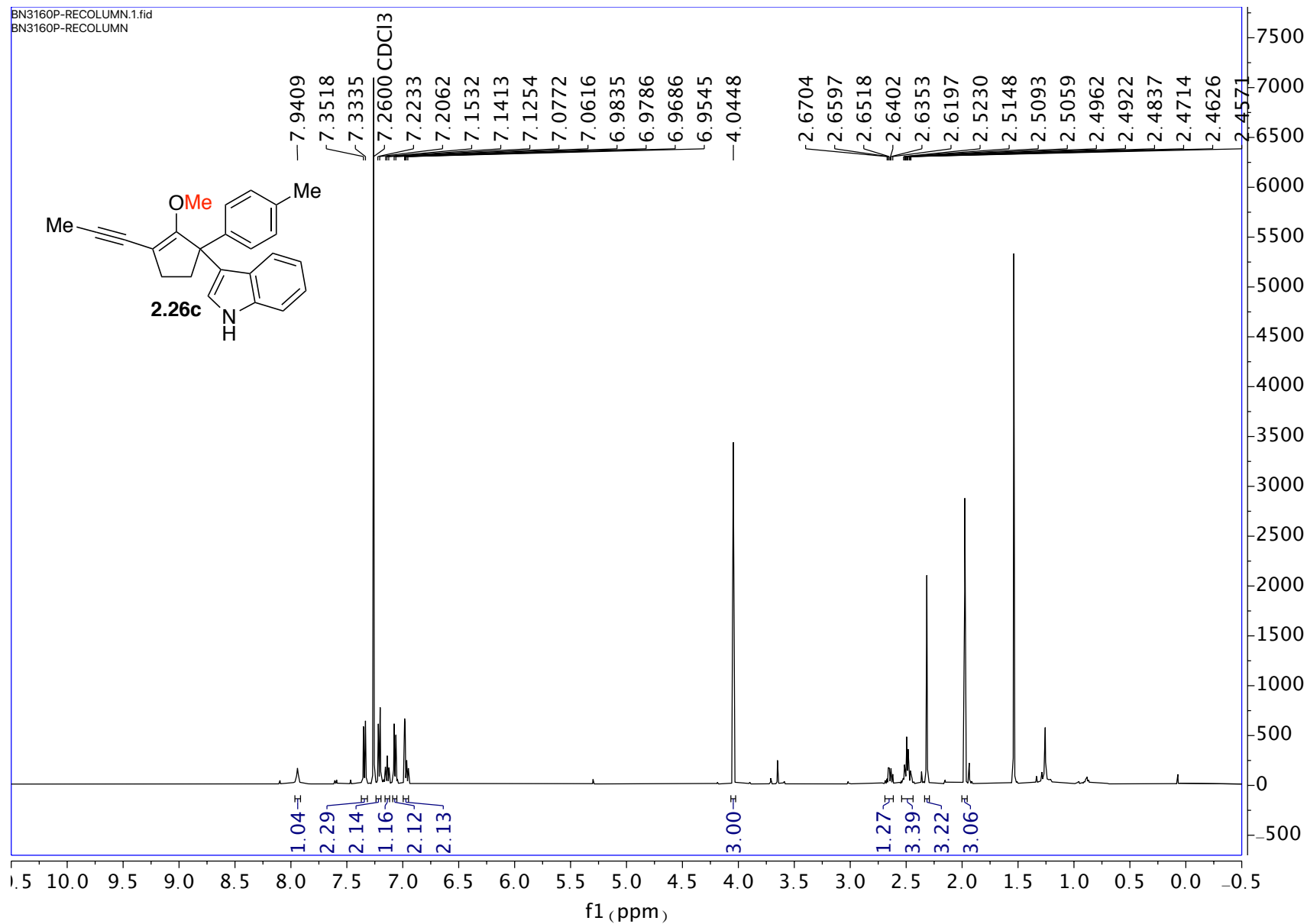
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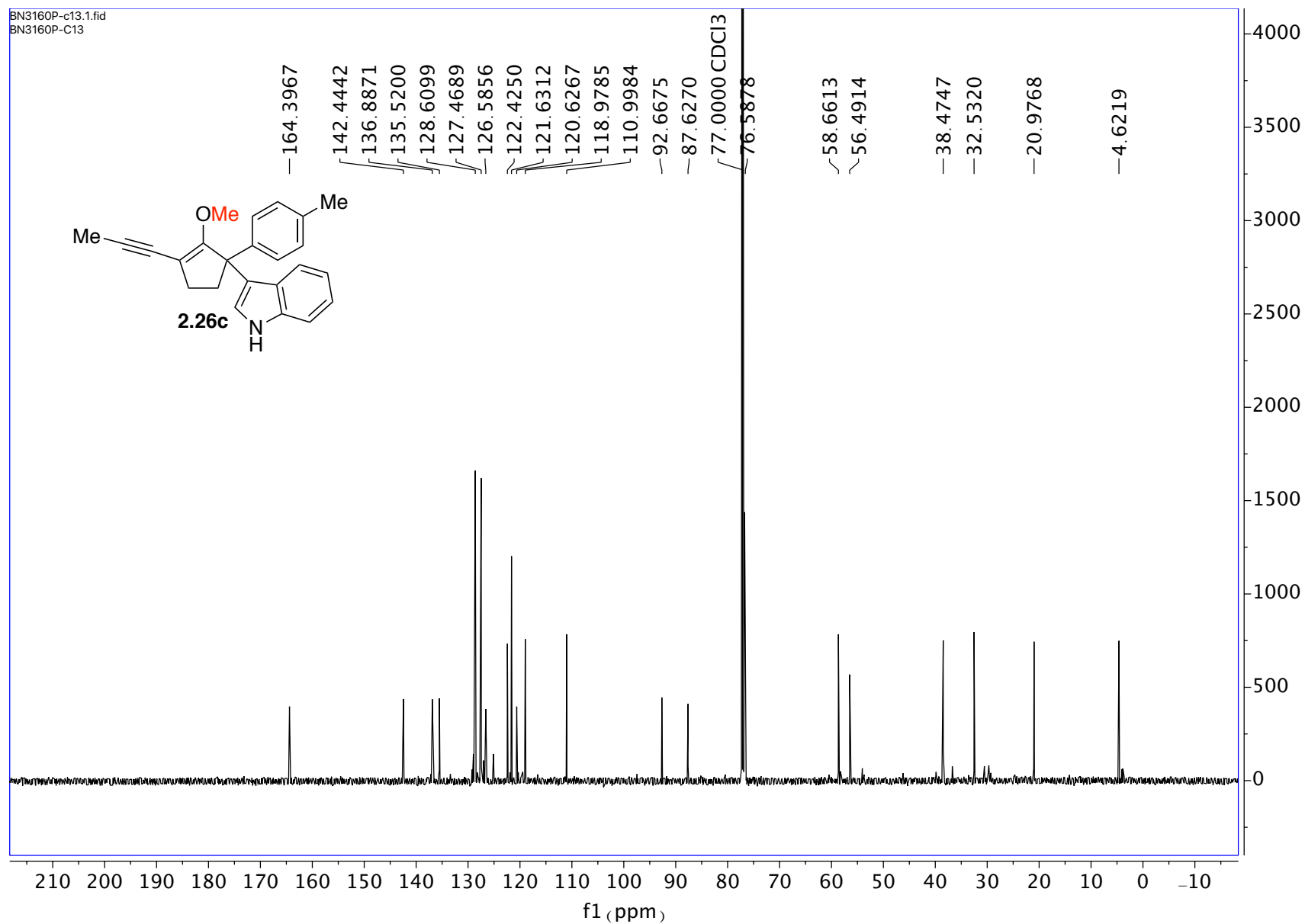
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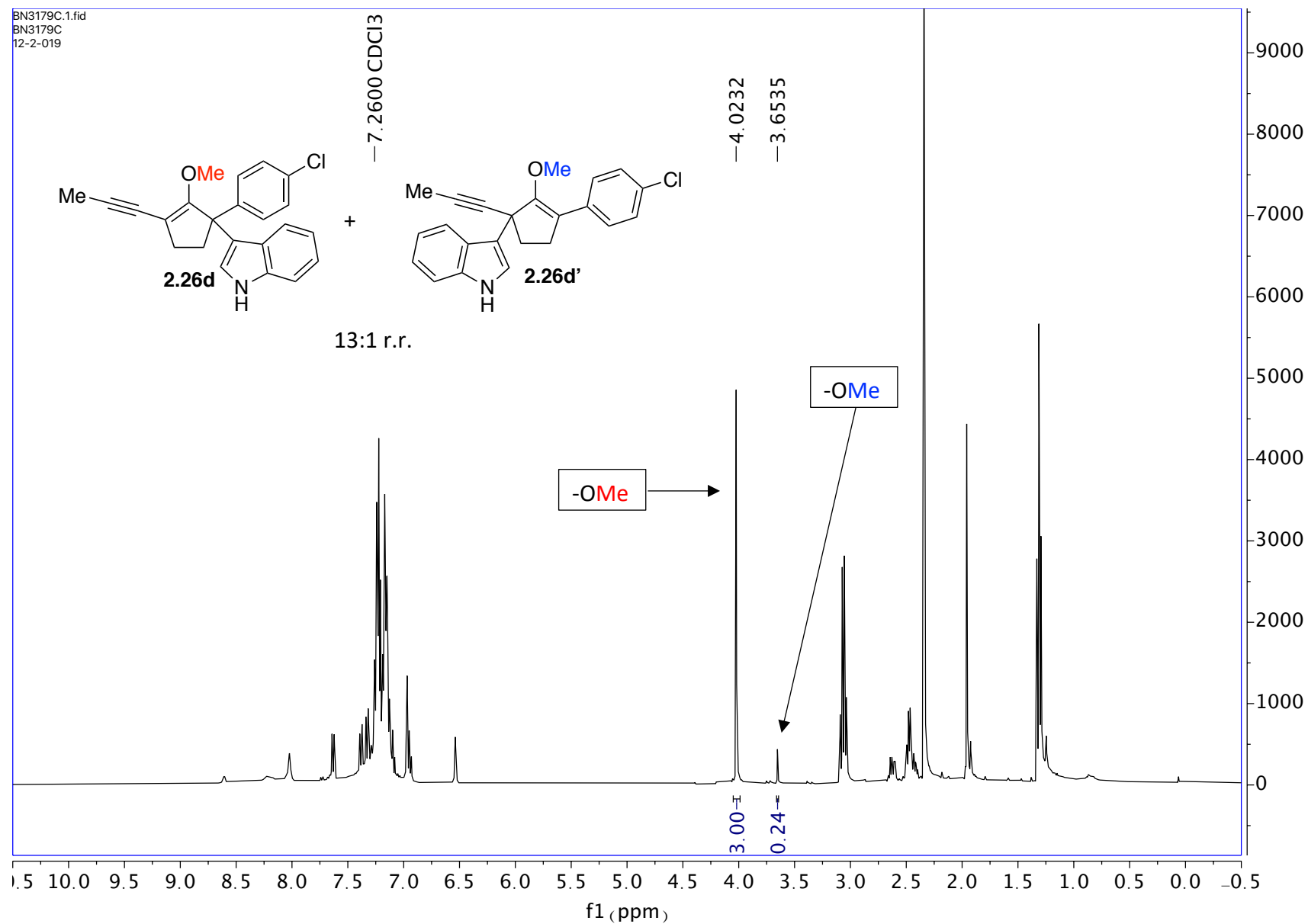
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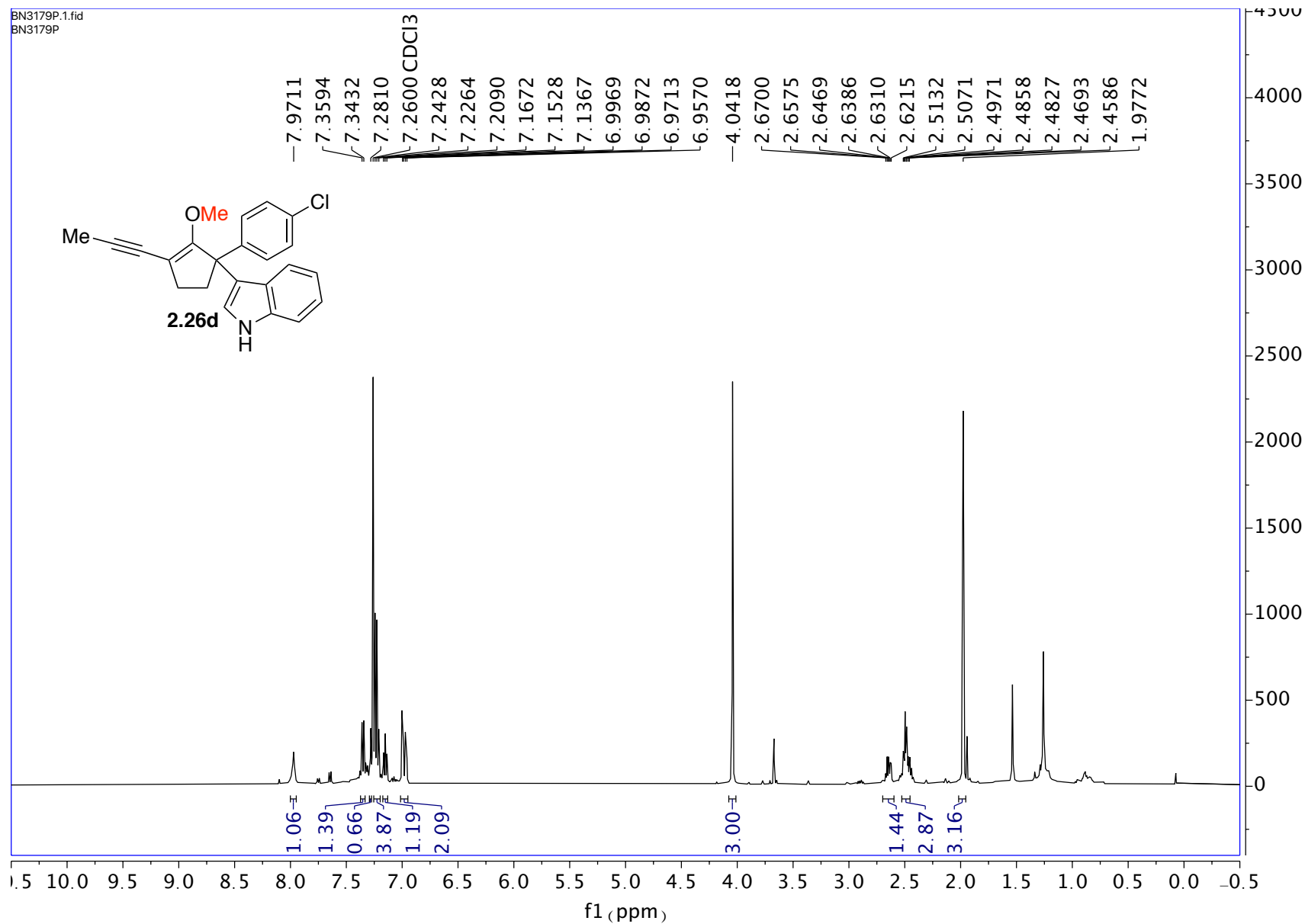
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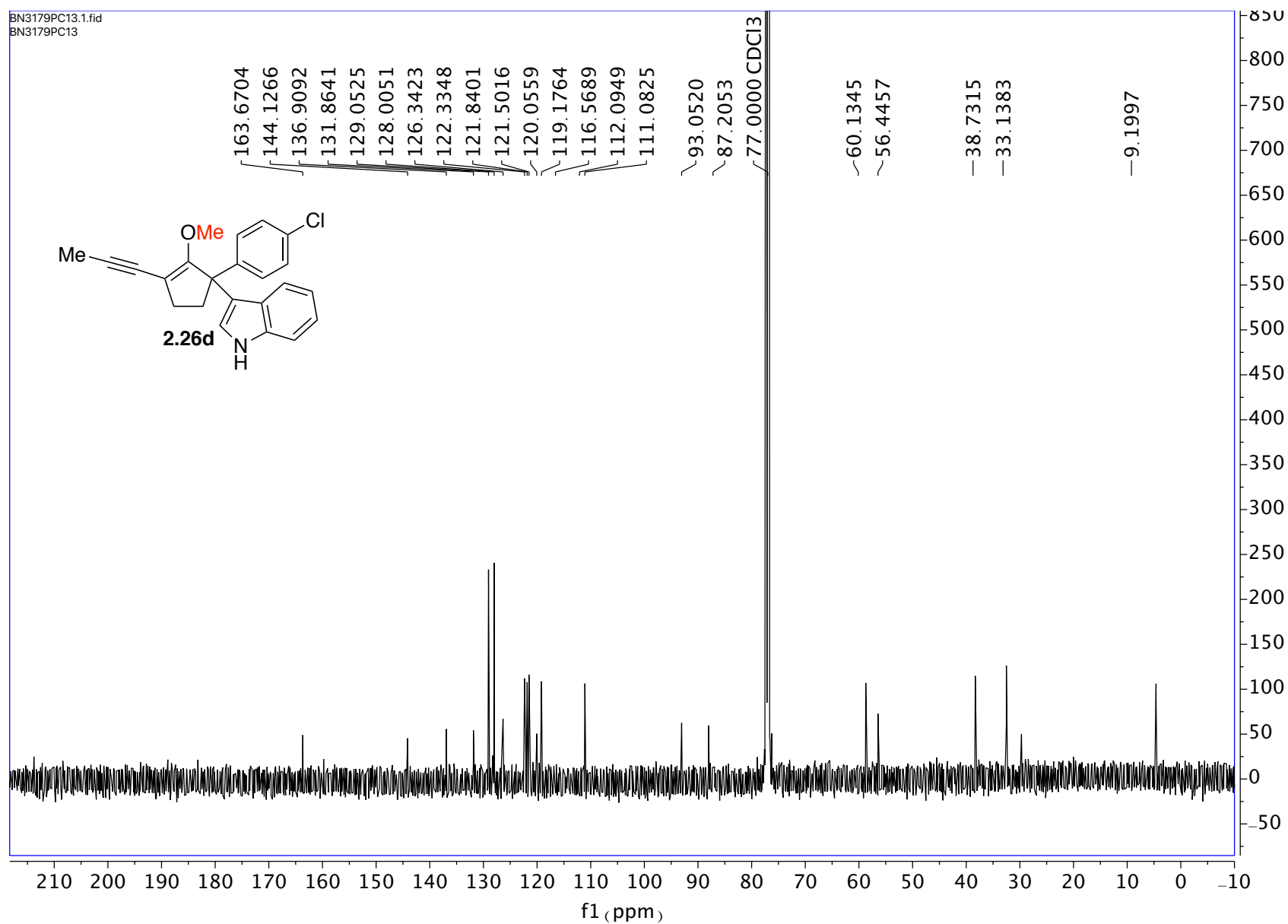
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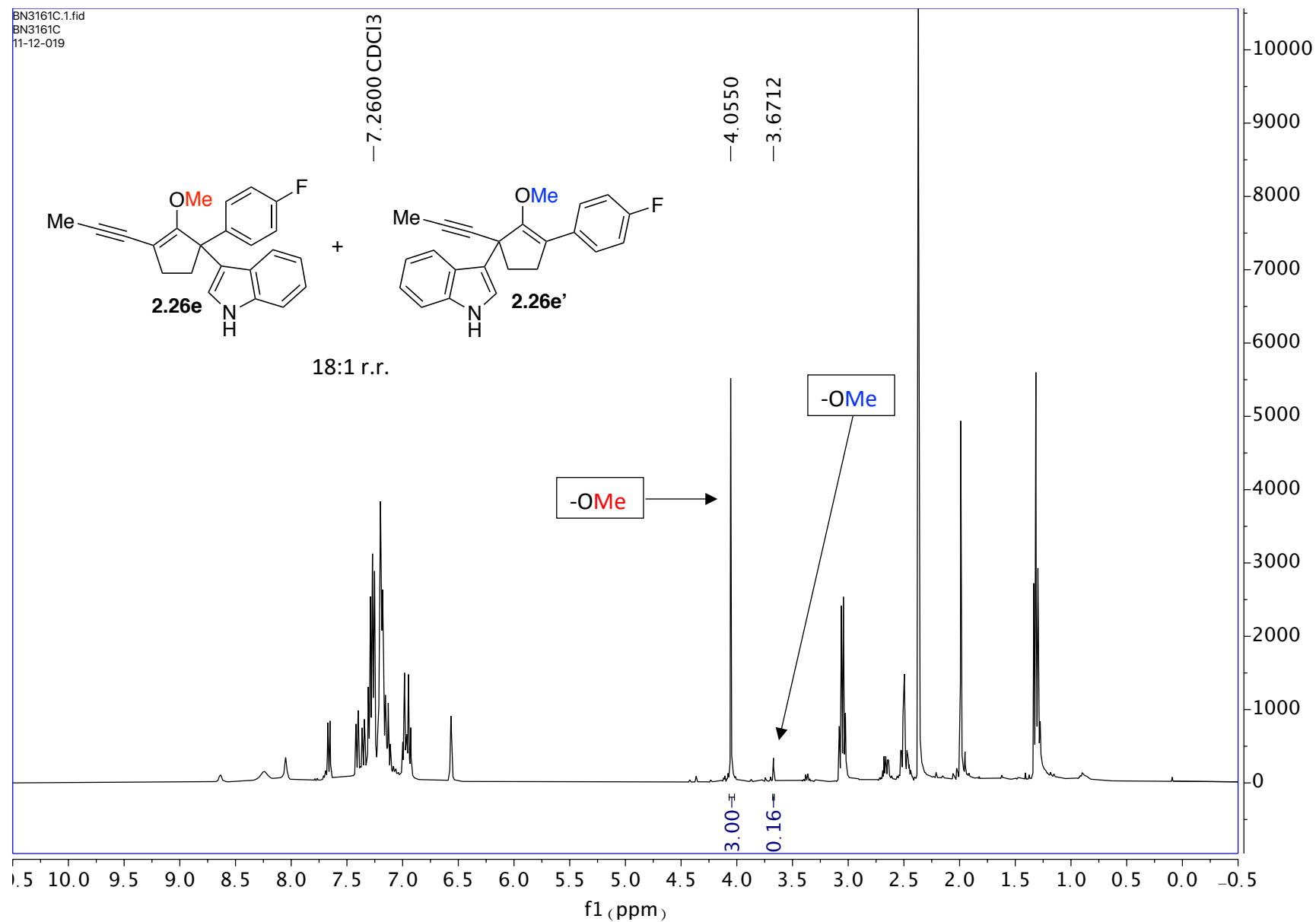


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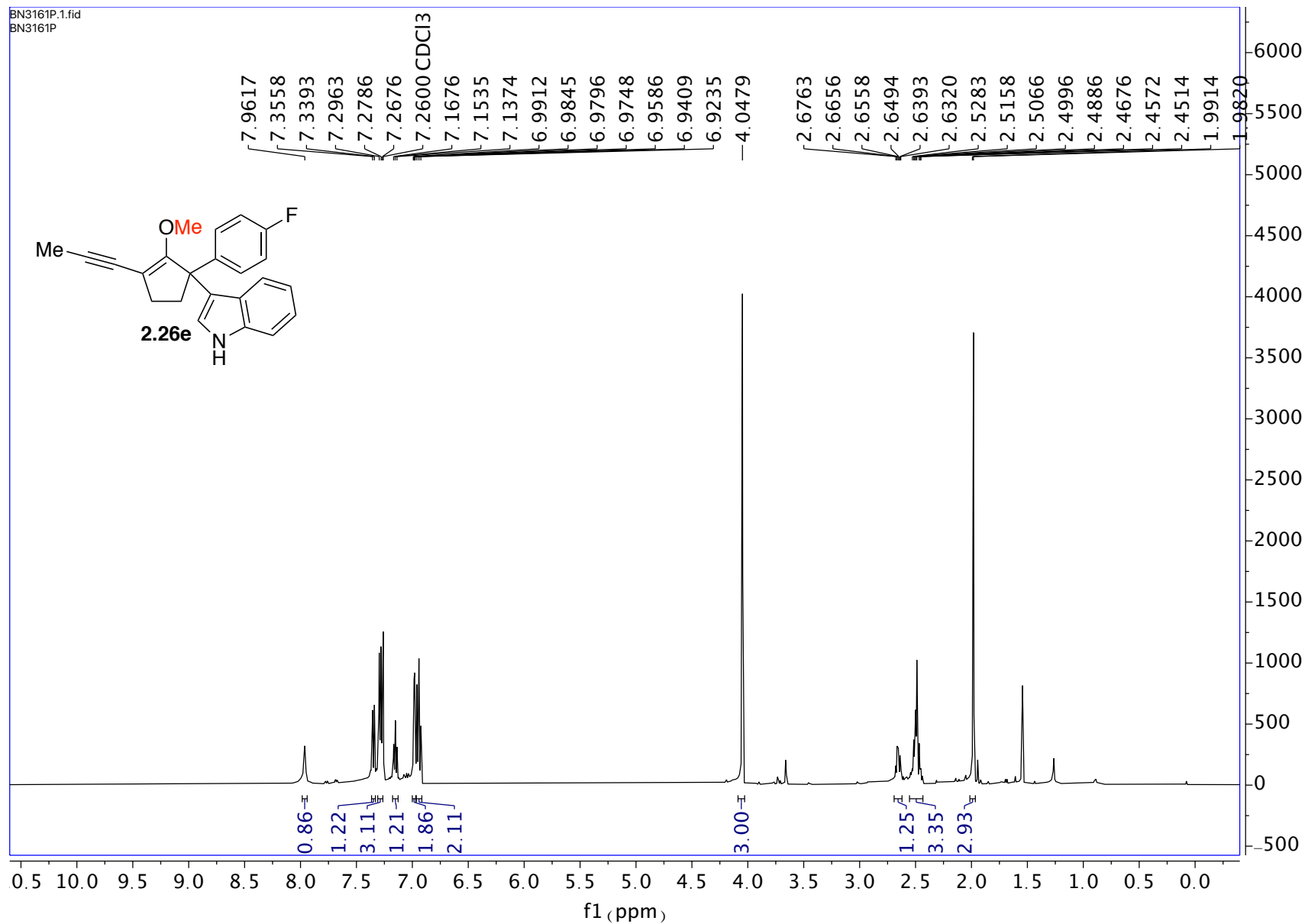




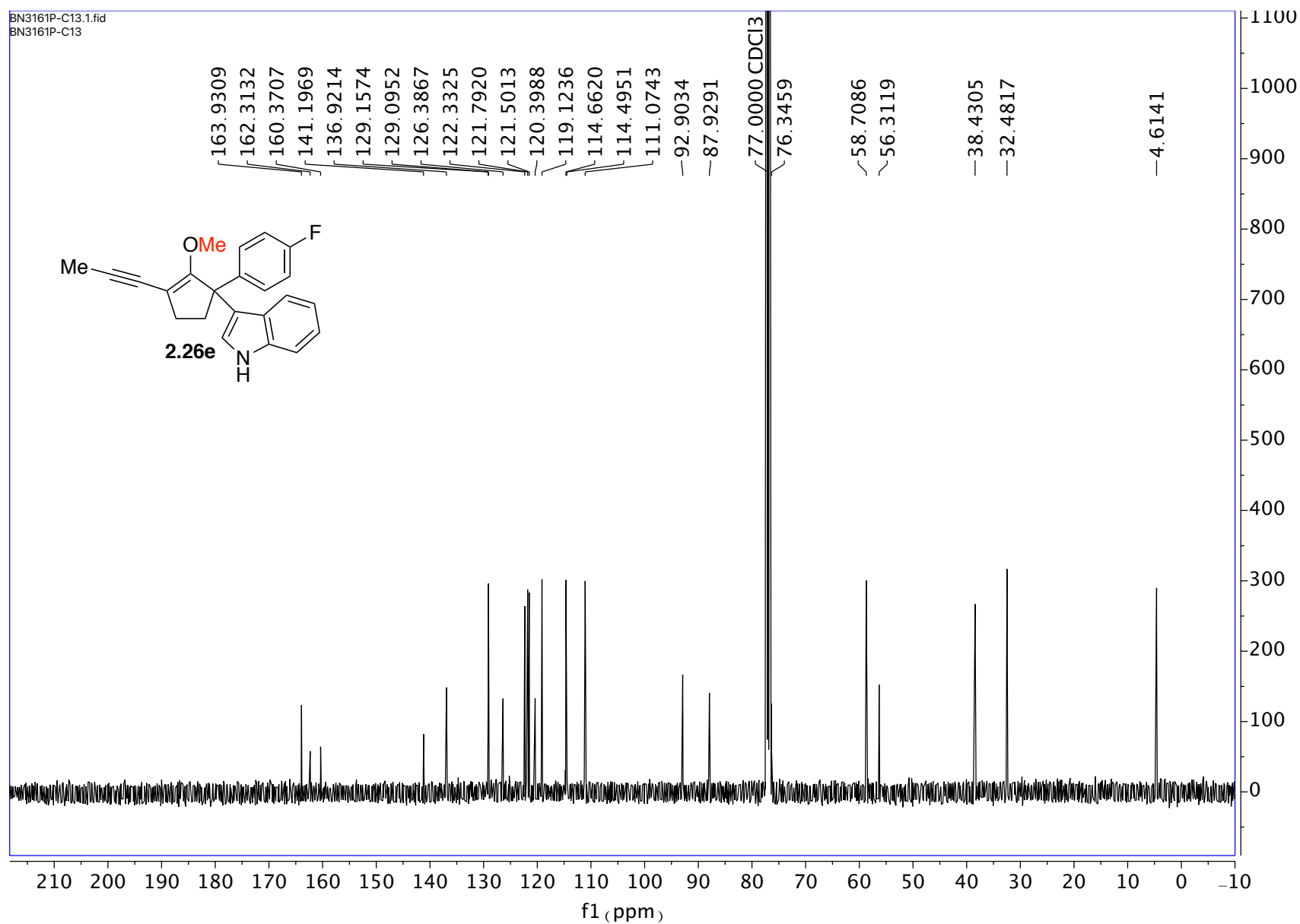
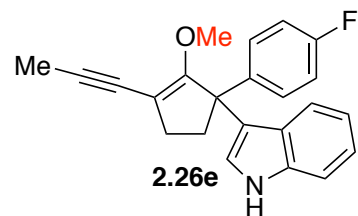
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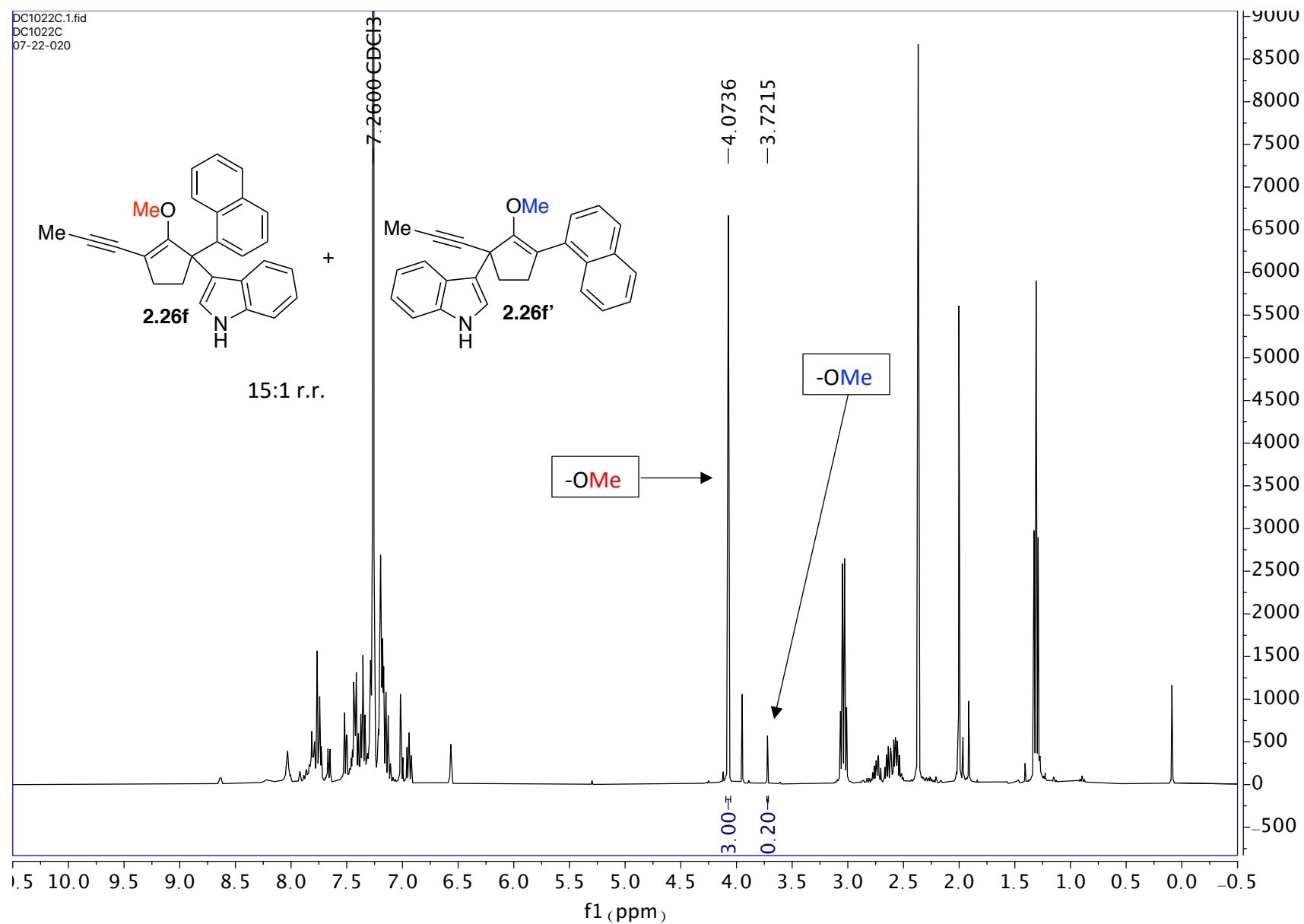
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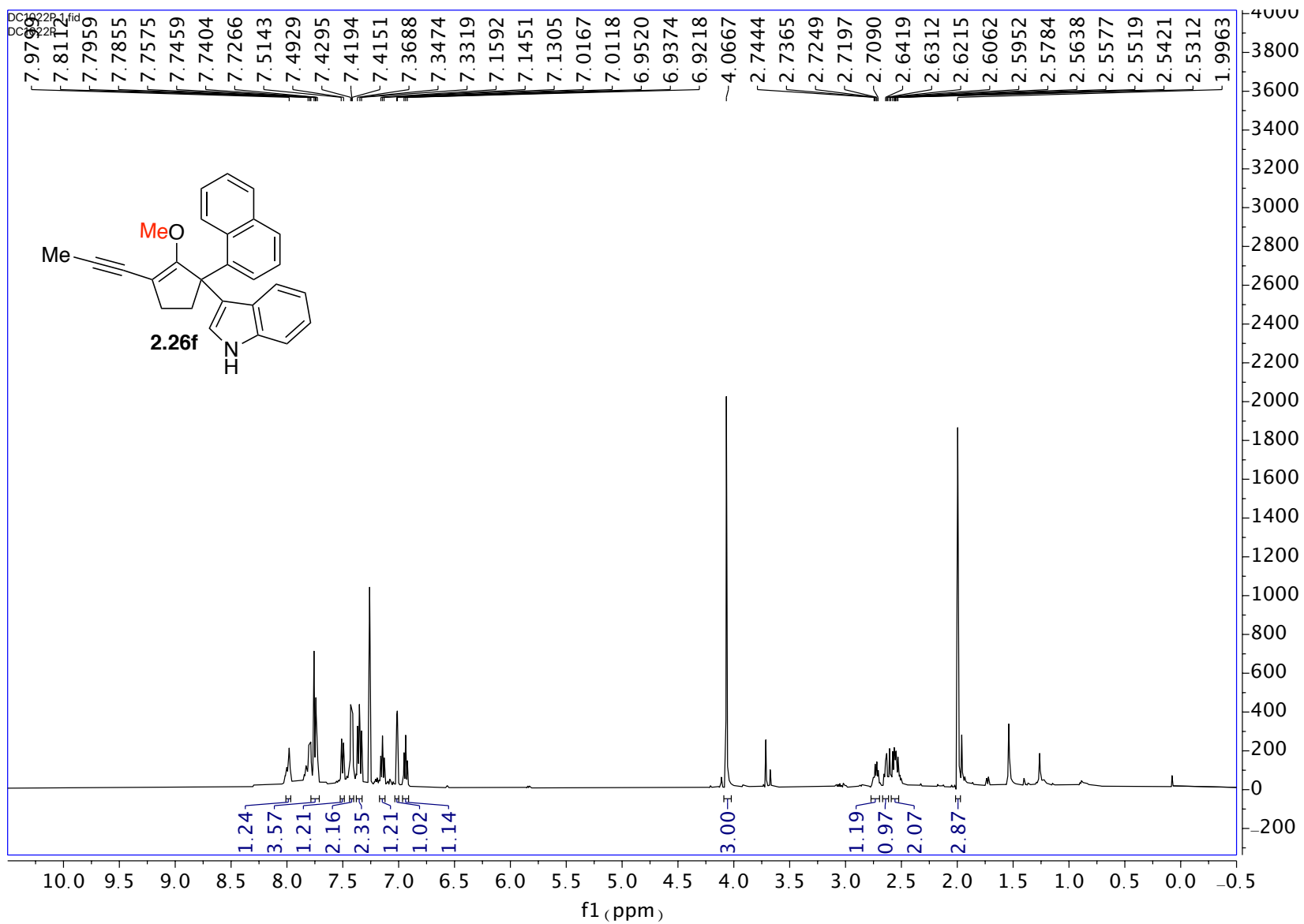


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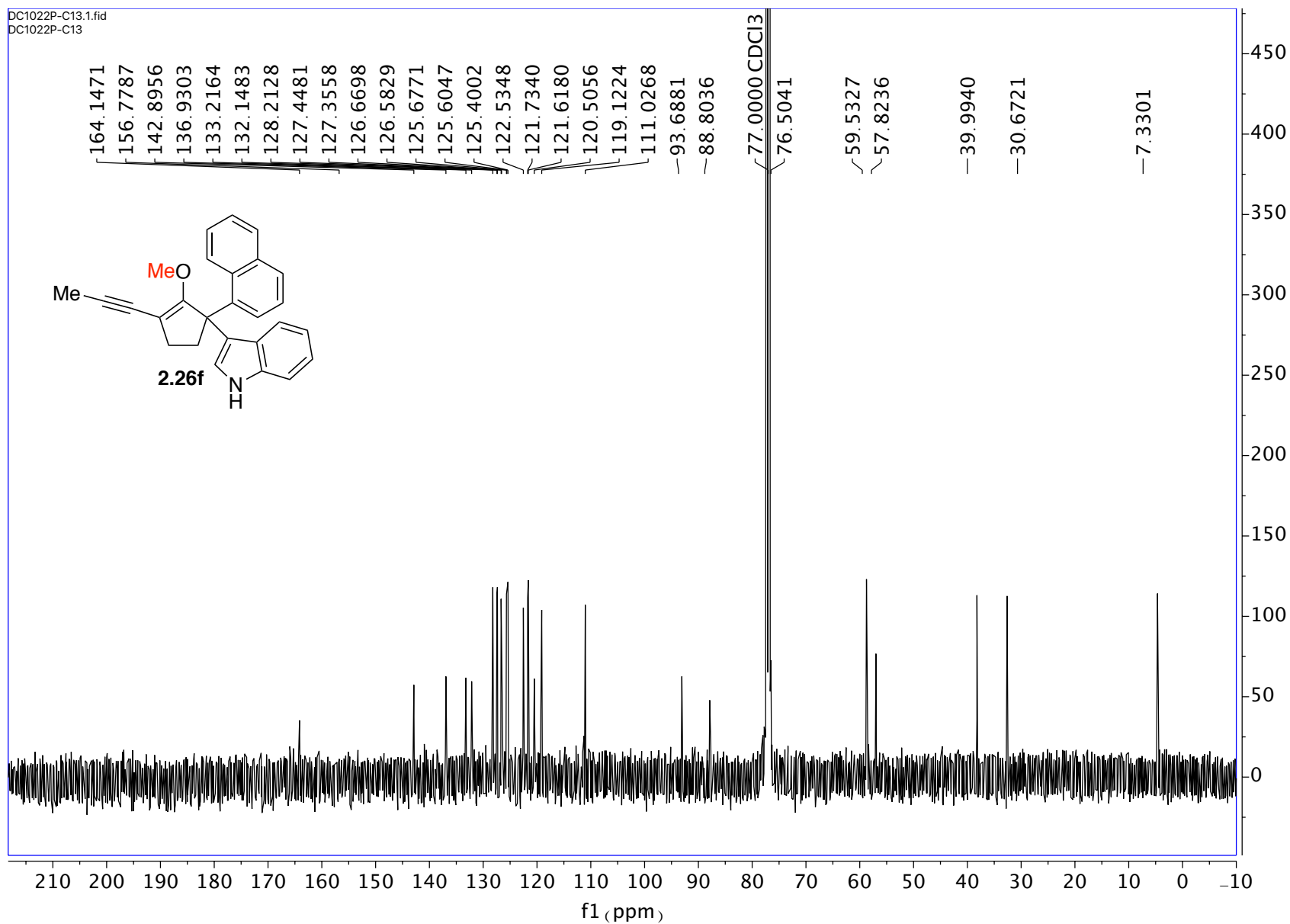


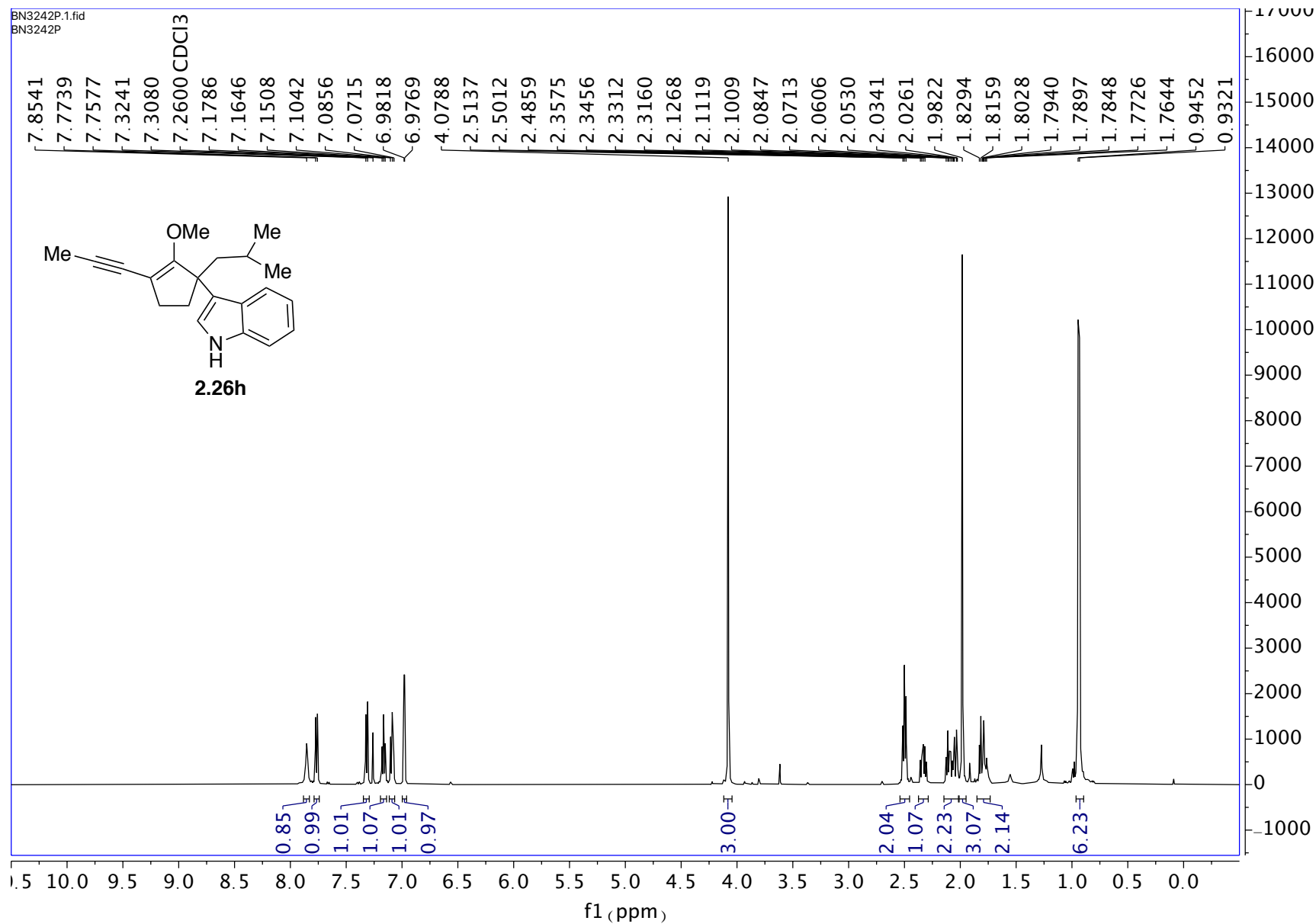
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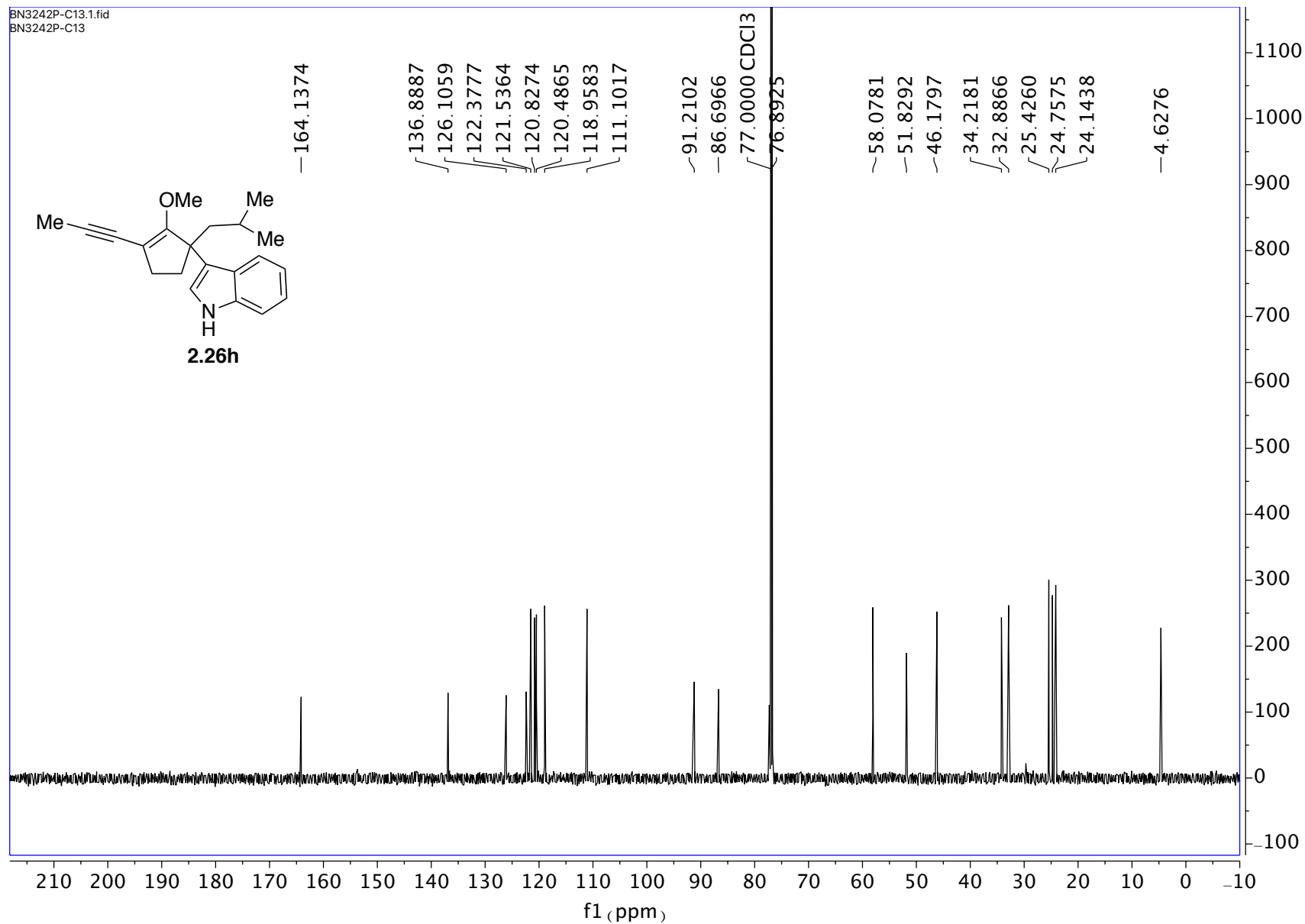
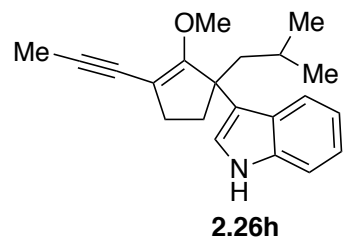


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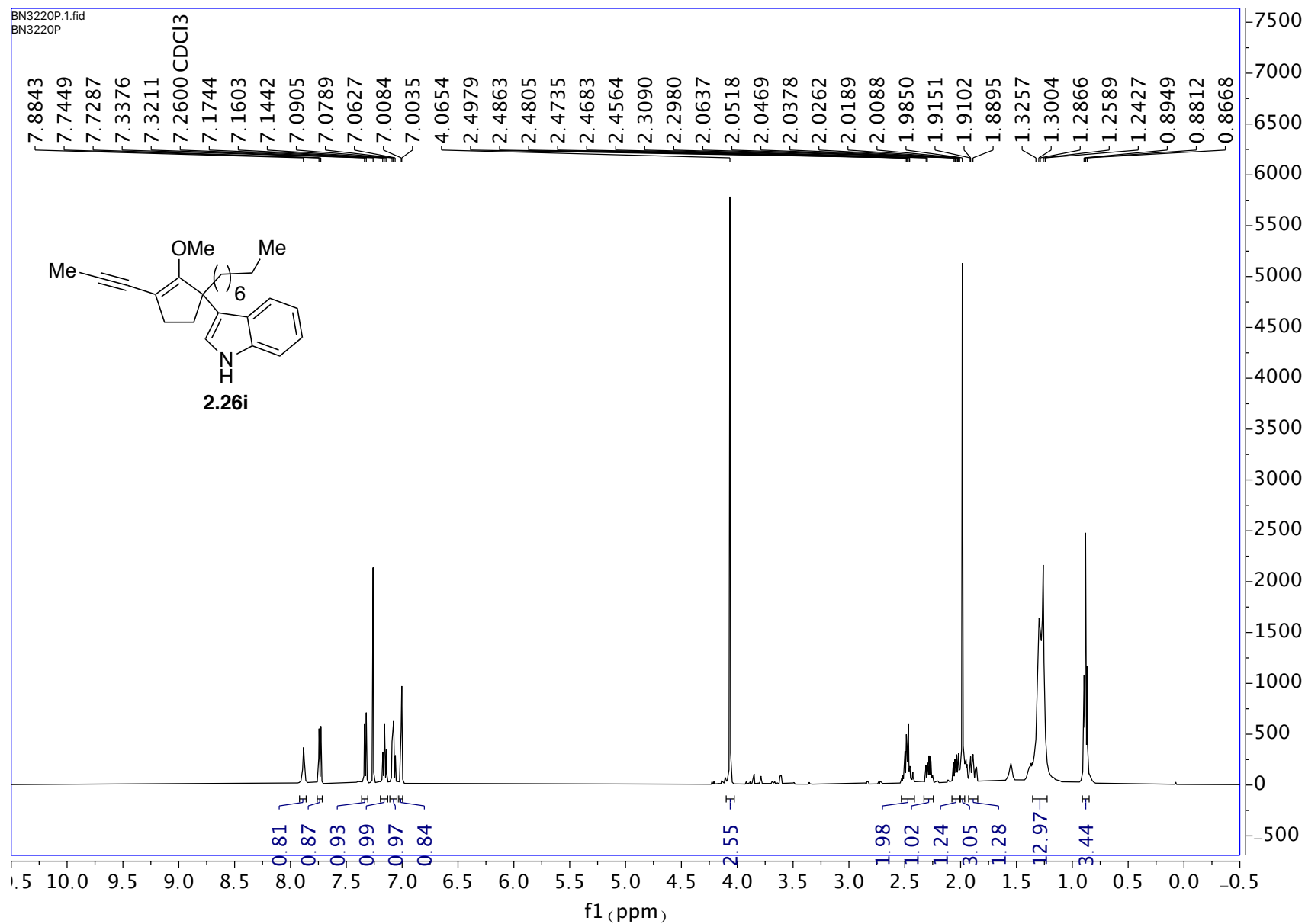




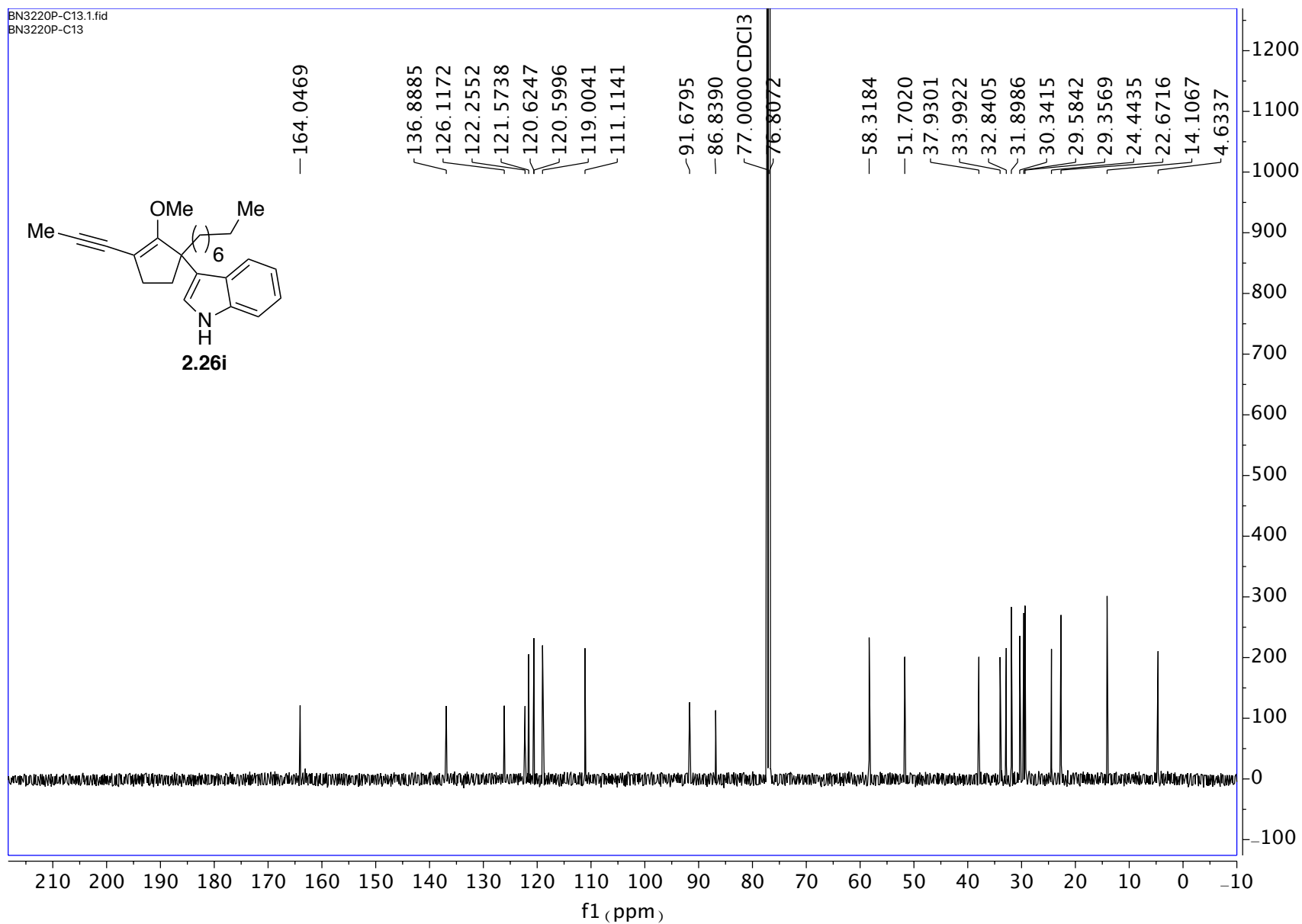
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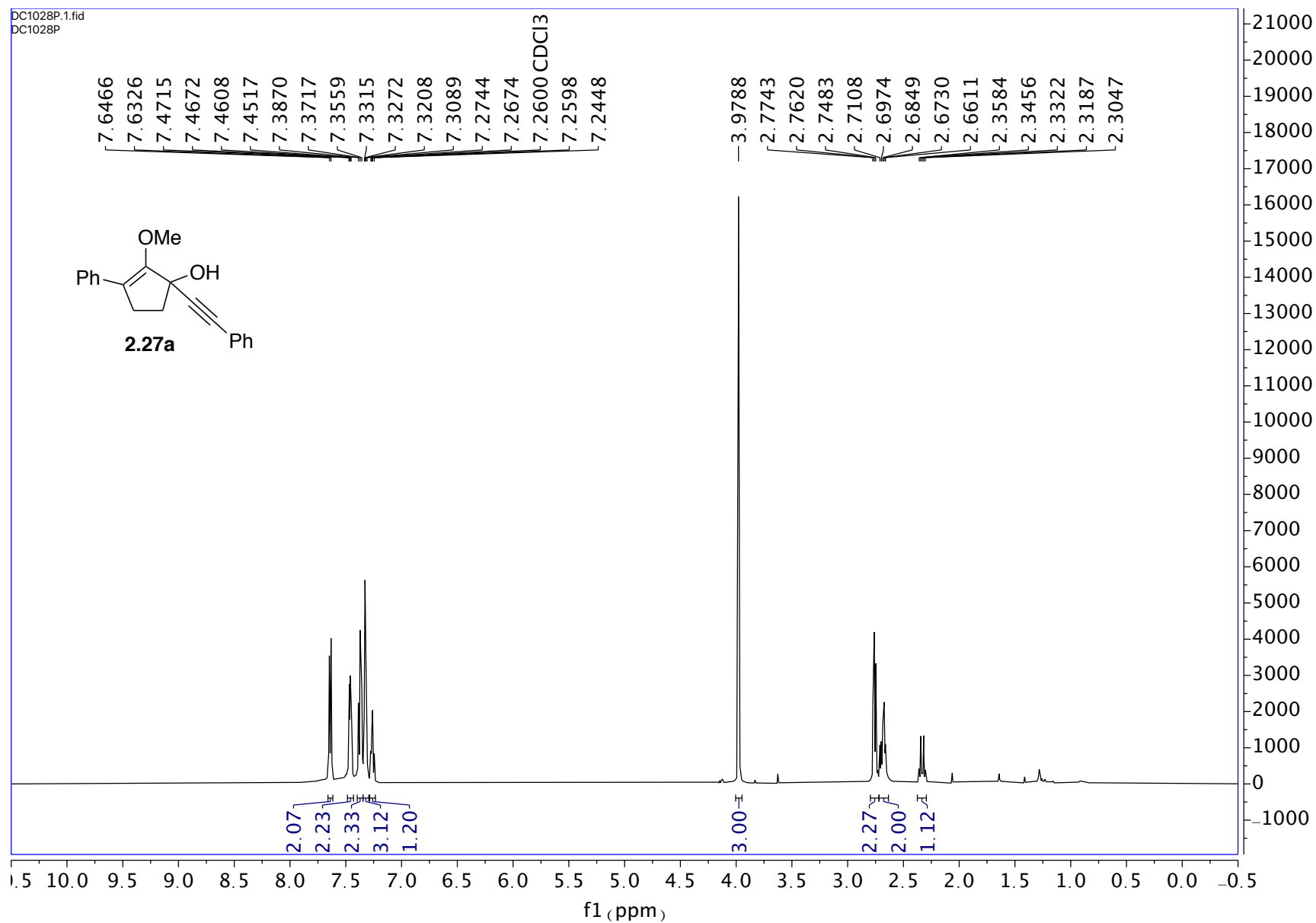


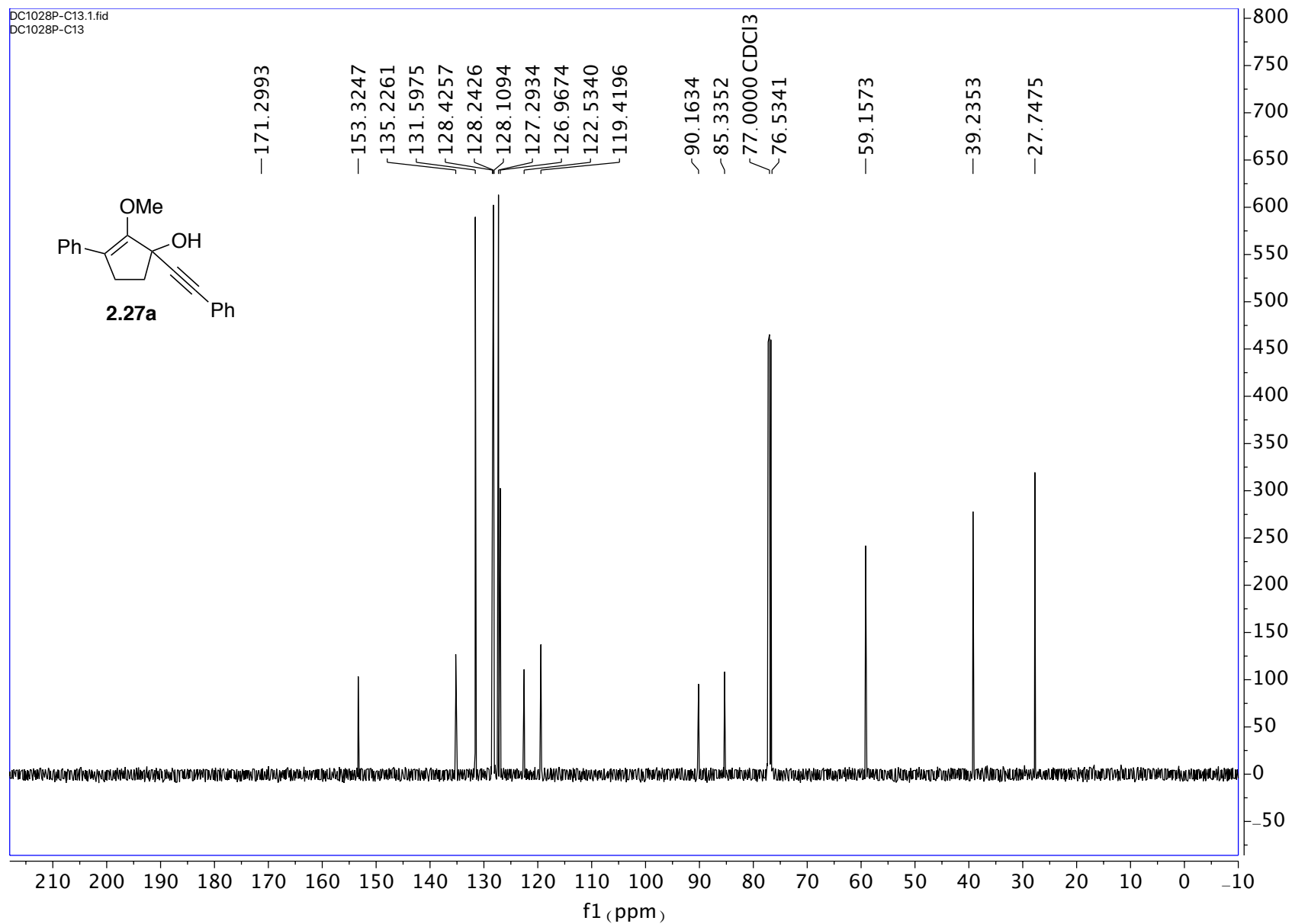




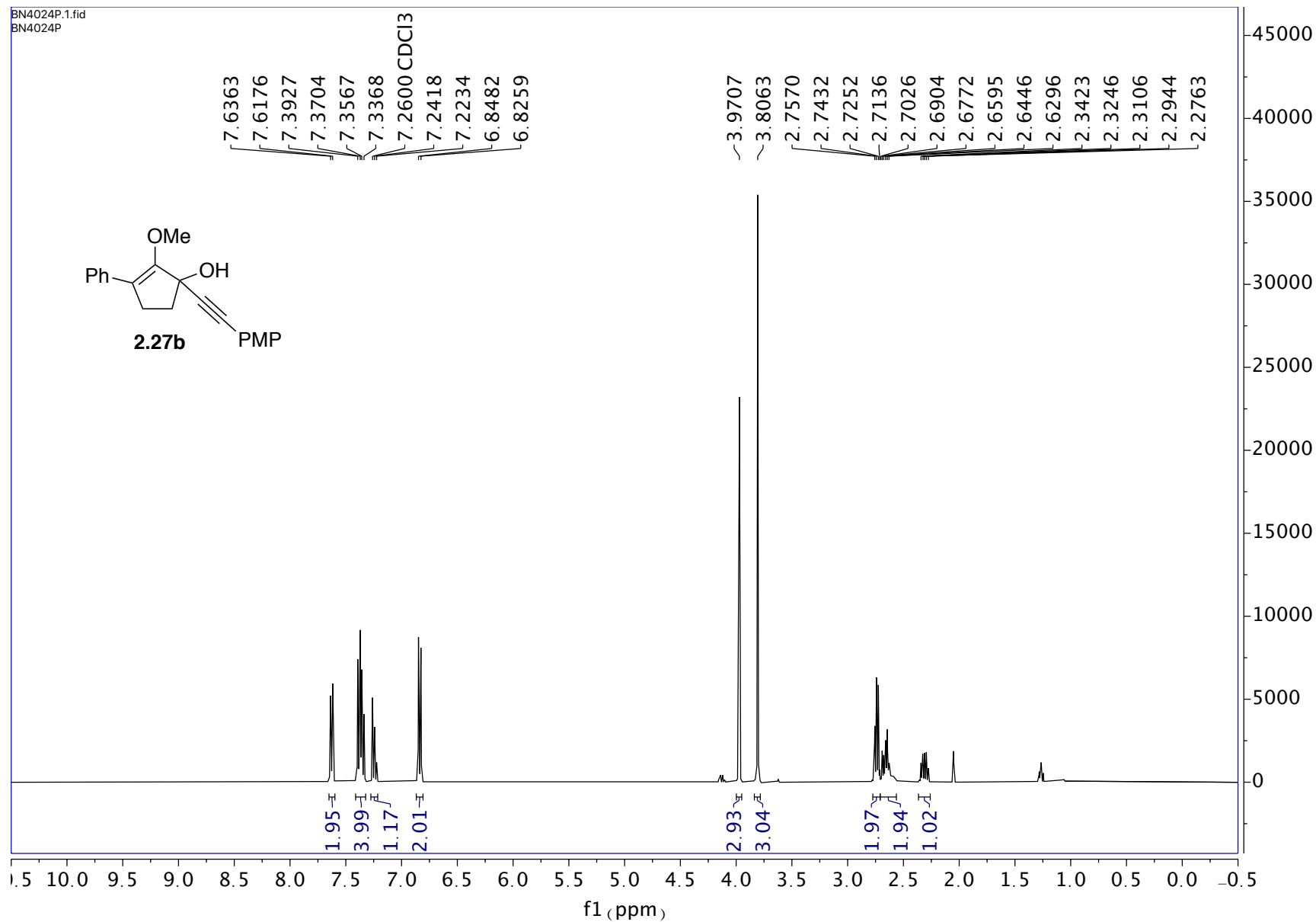
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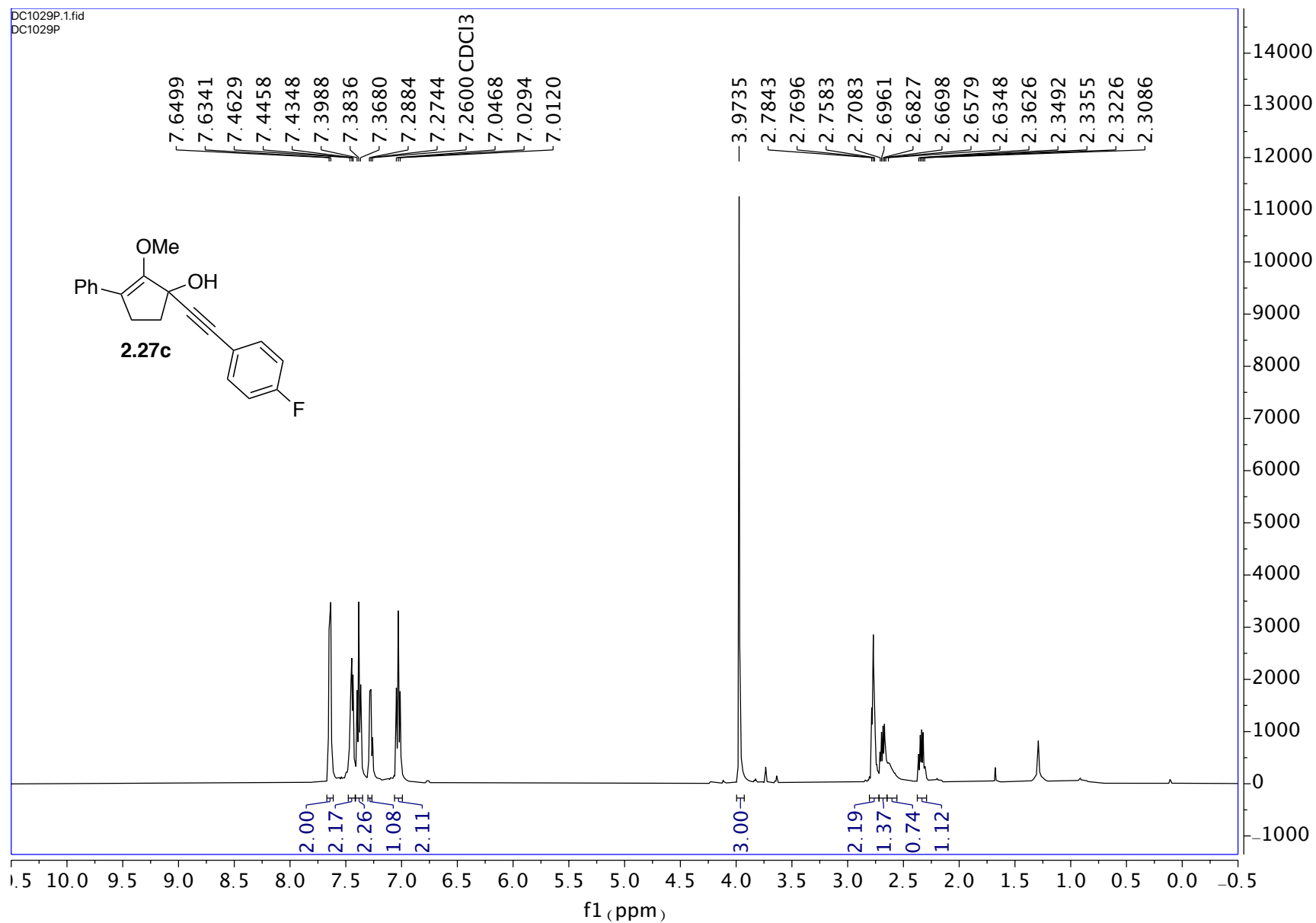




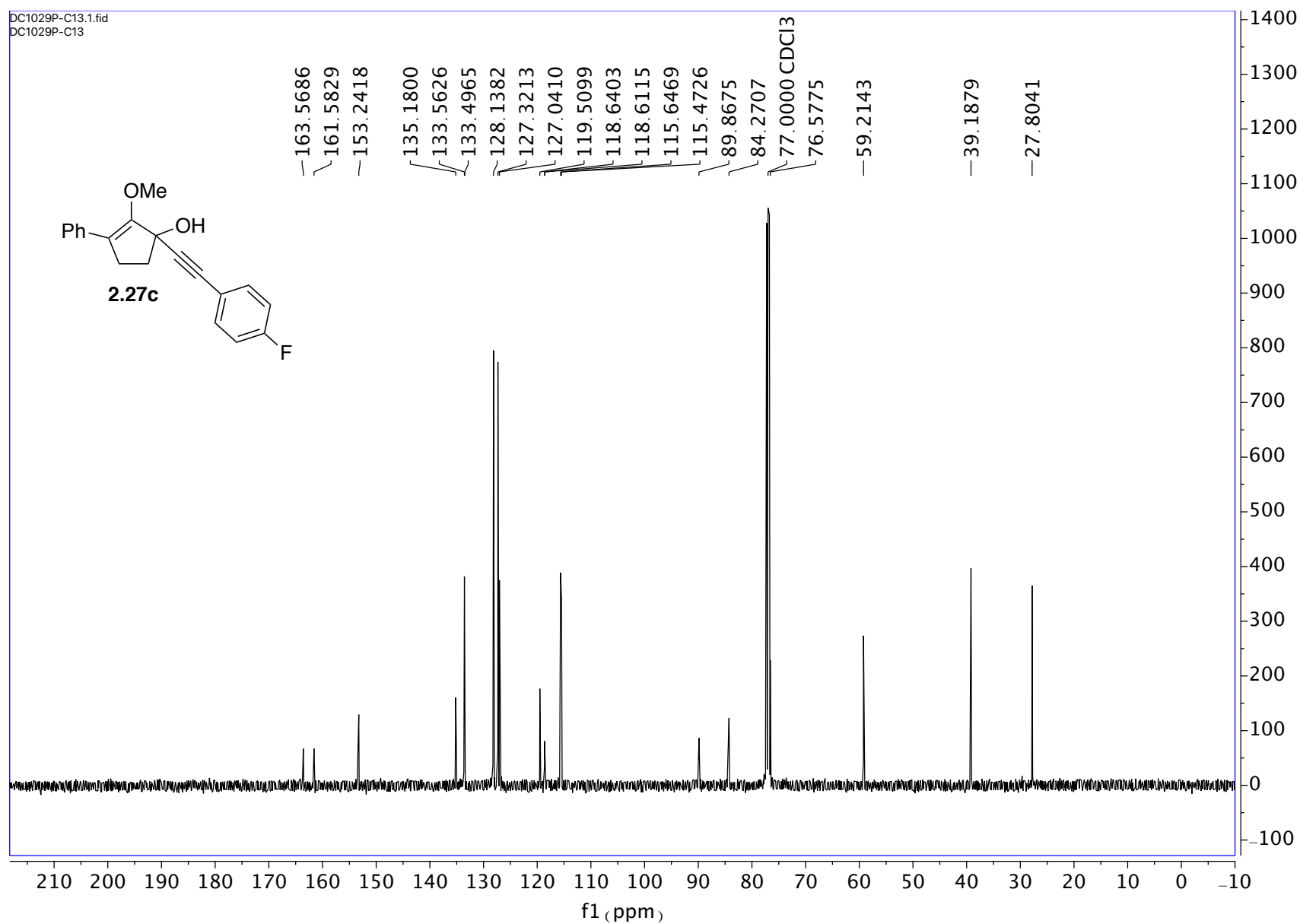
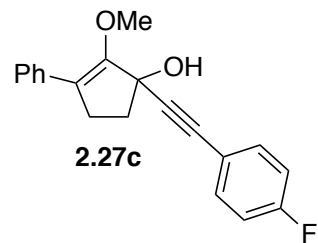
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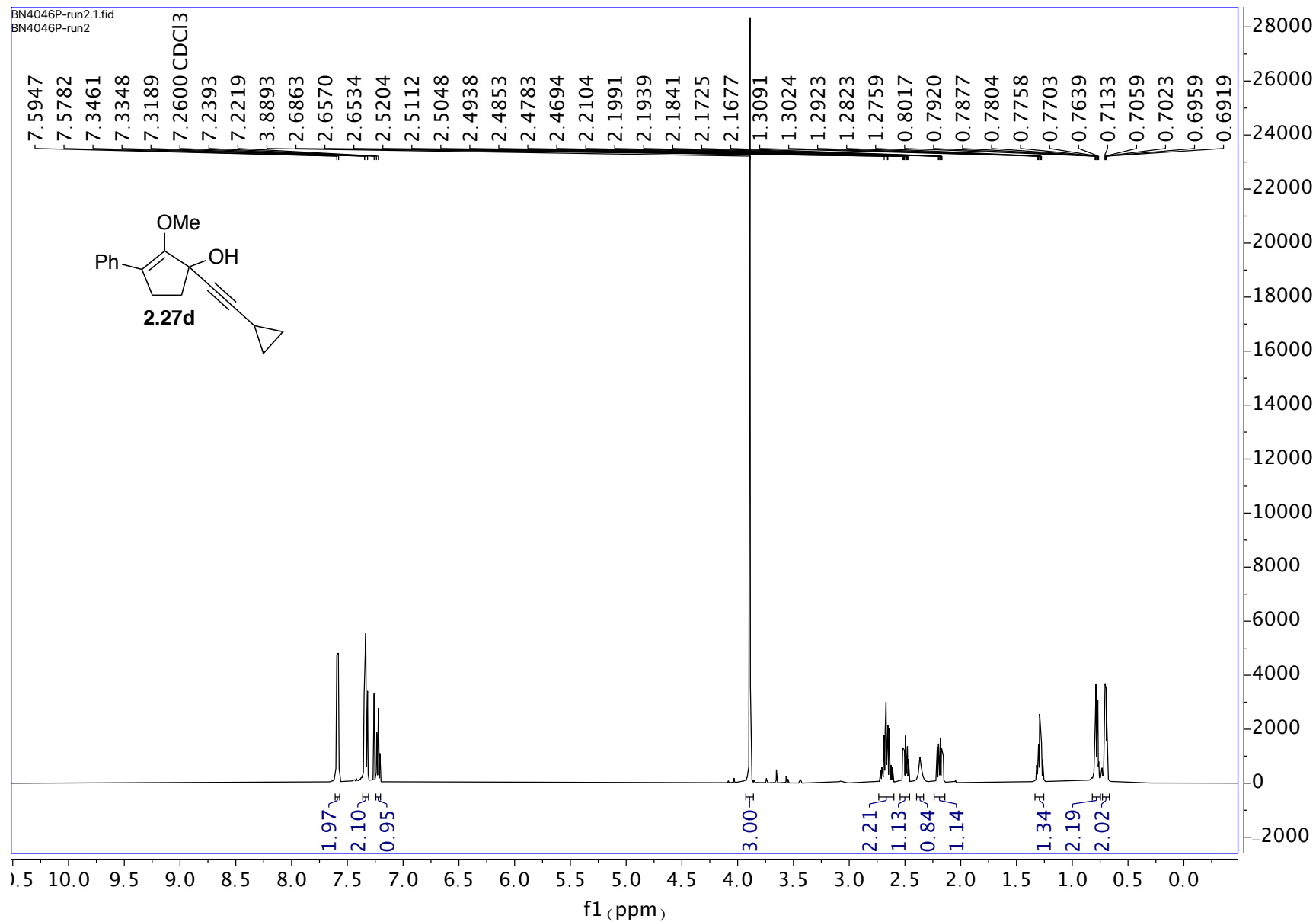


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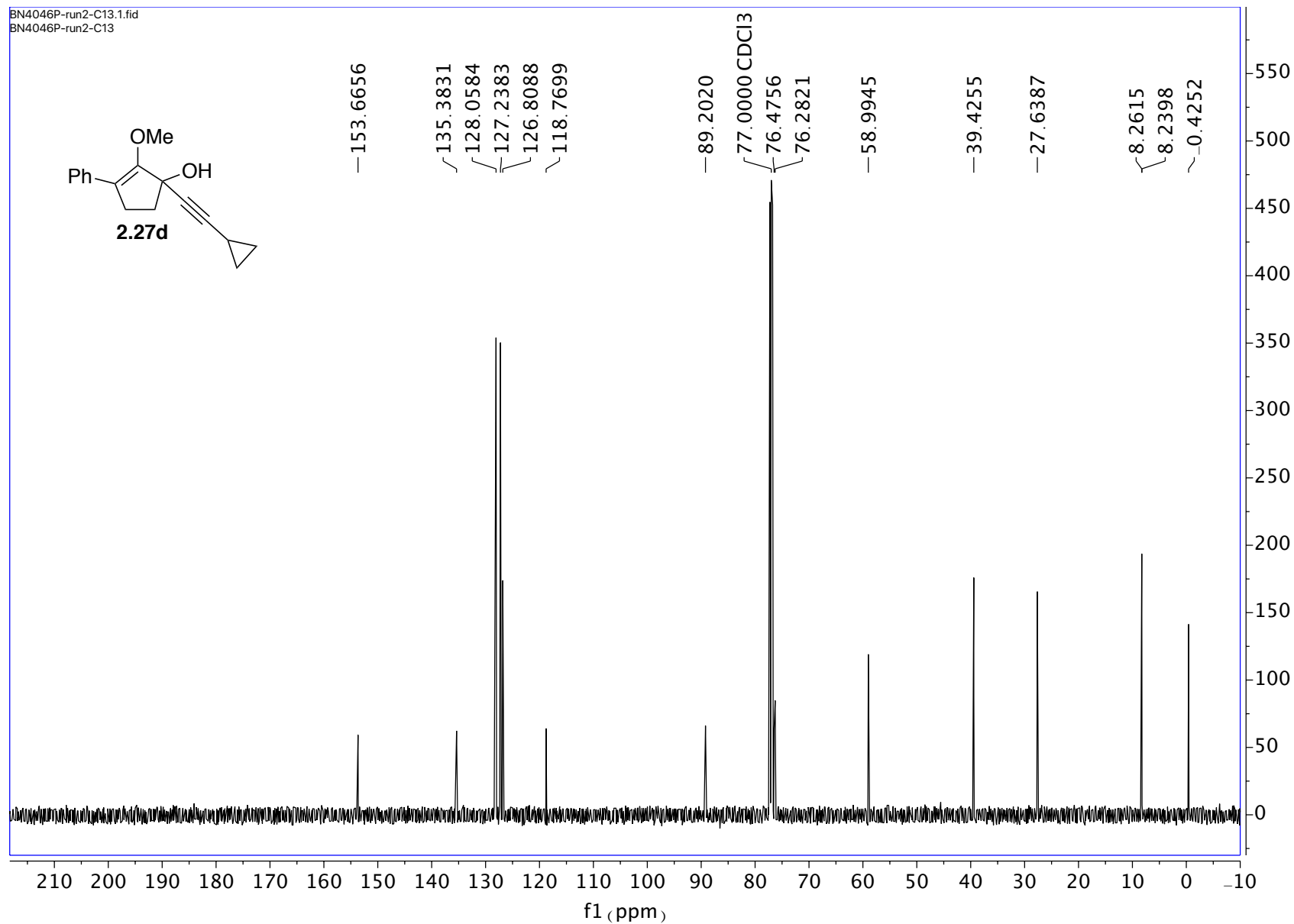
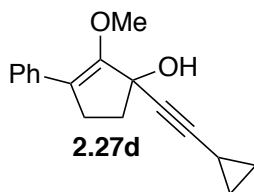




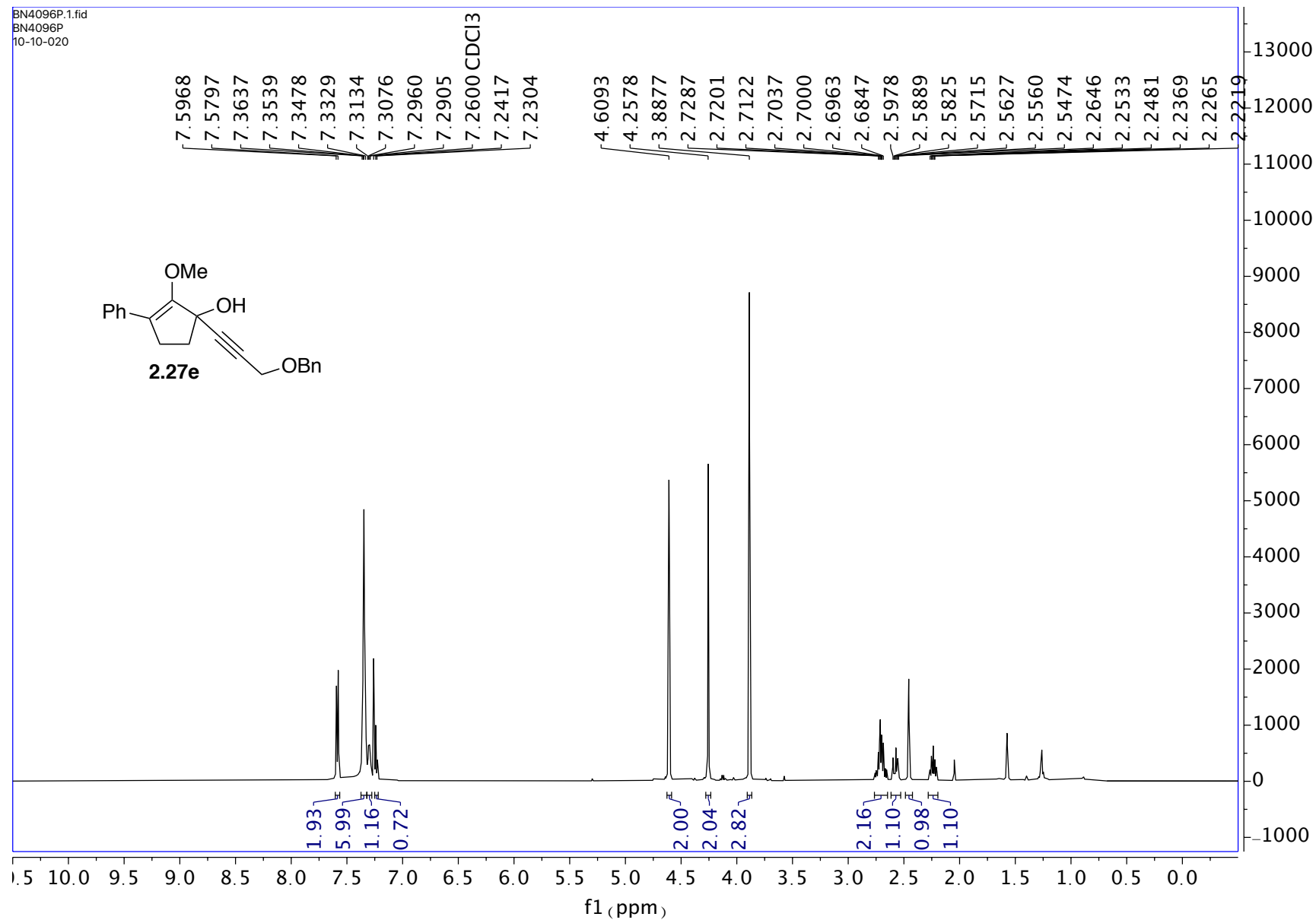
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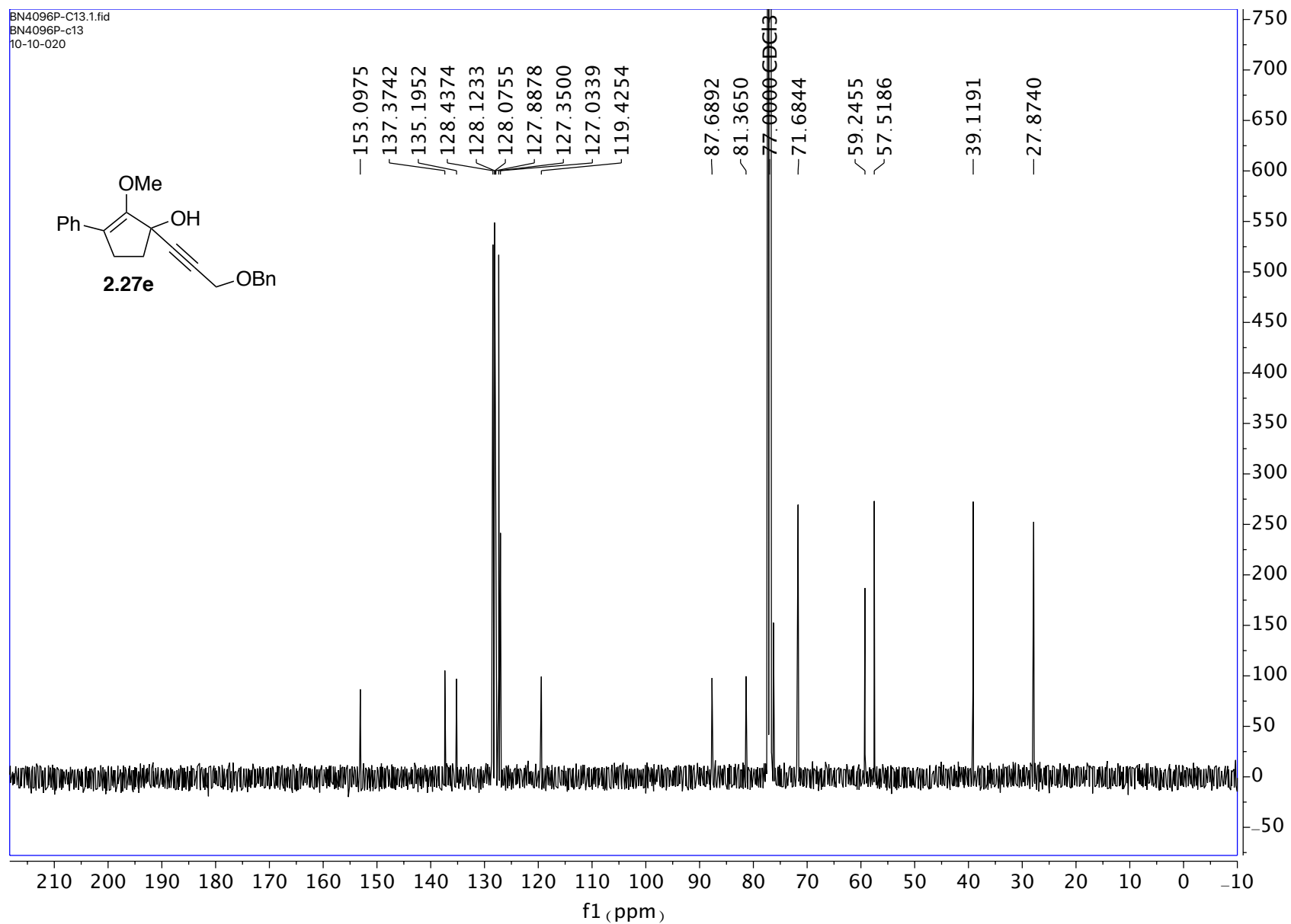
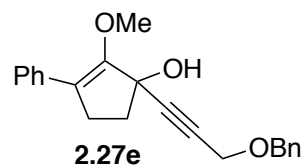
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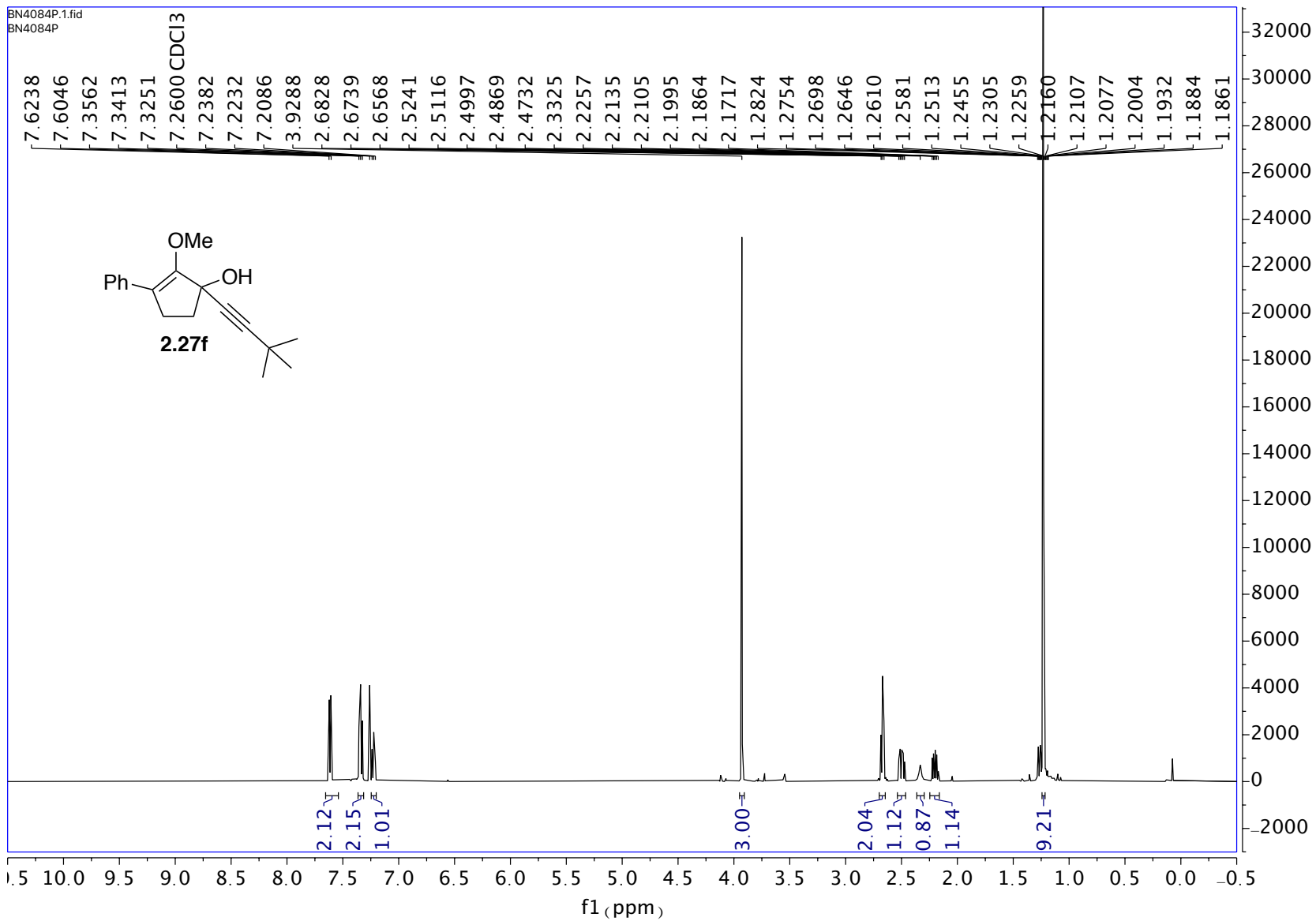


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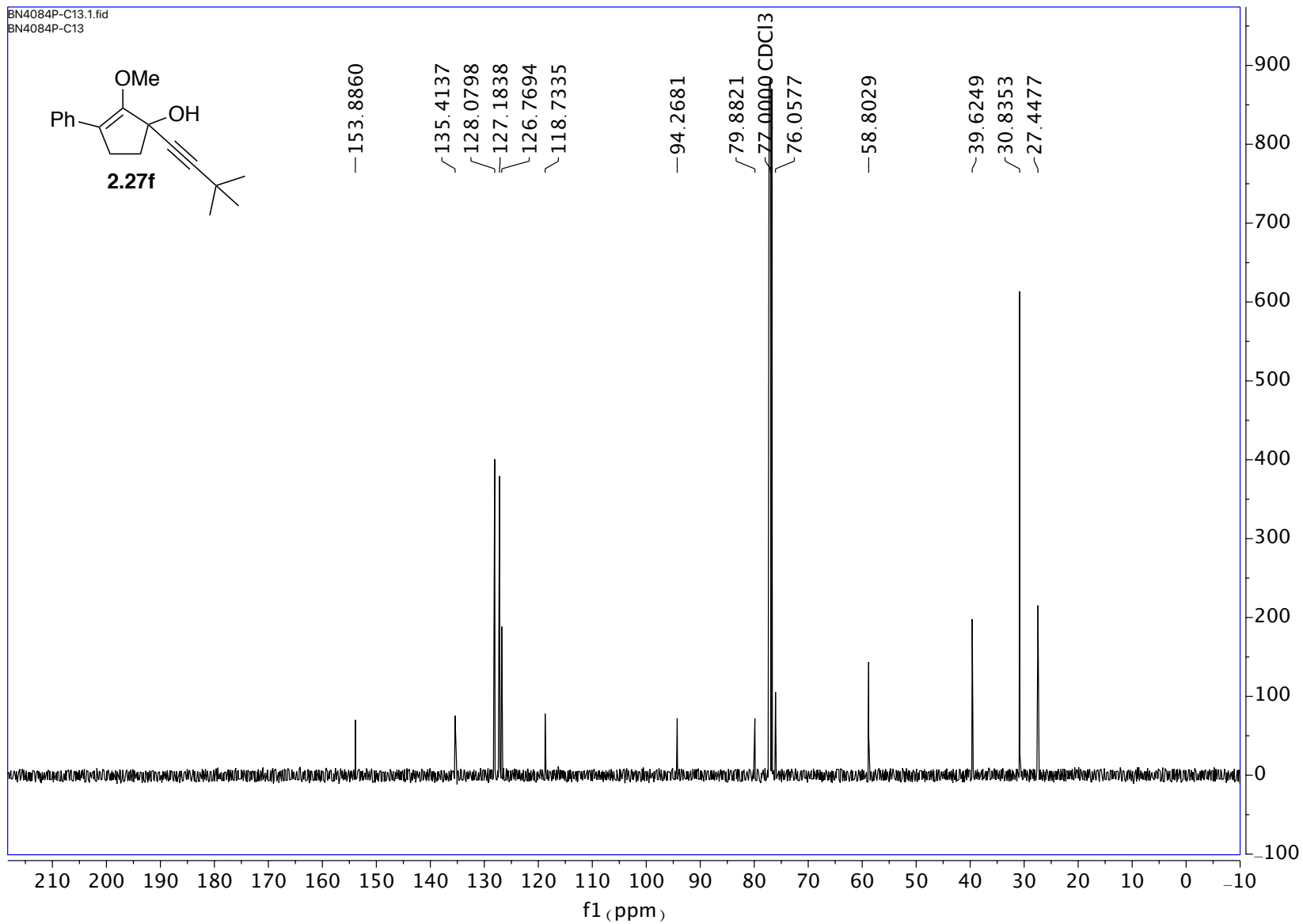
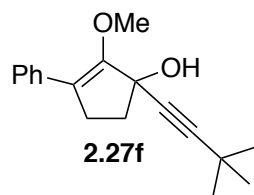


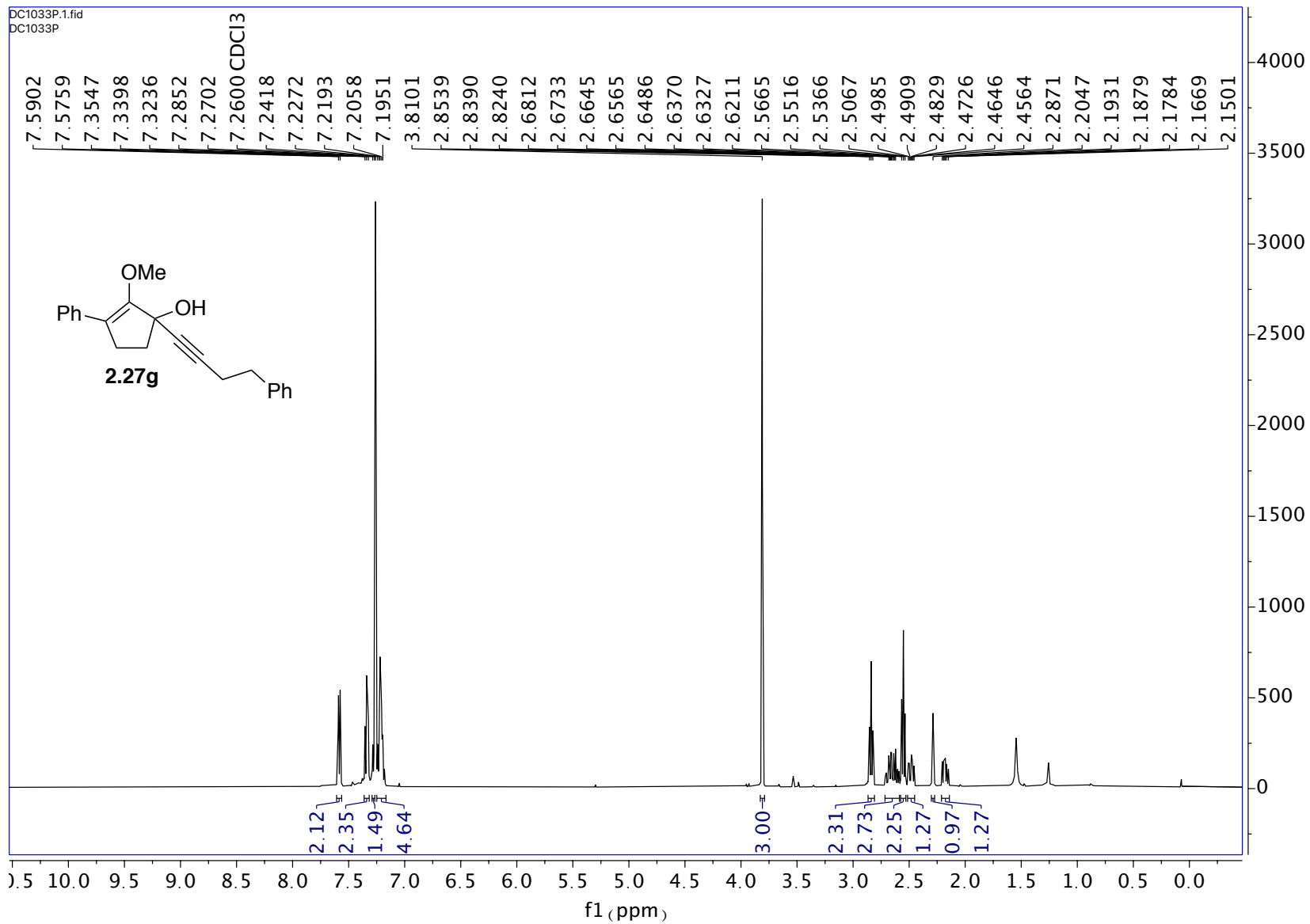
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10-10-020



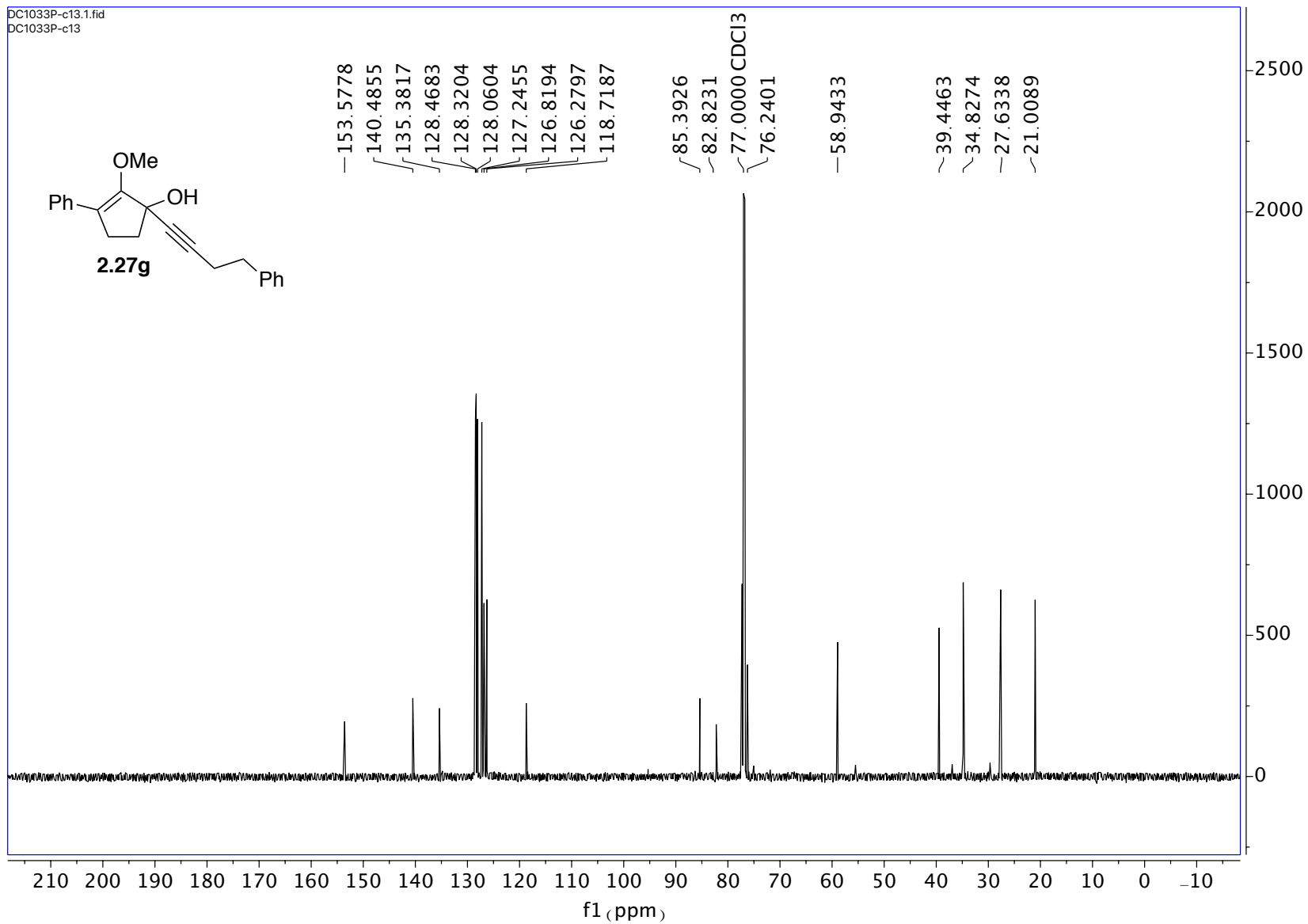
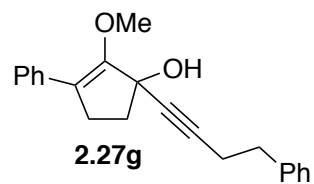


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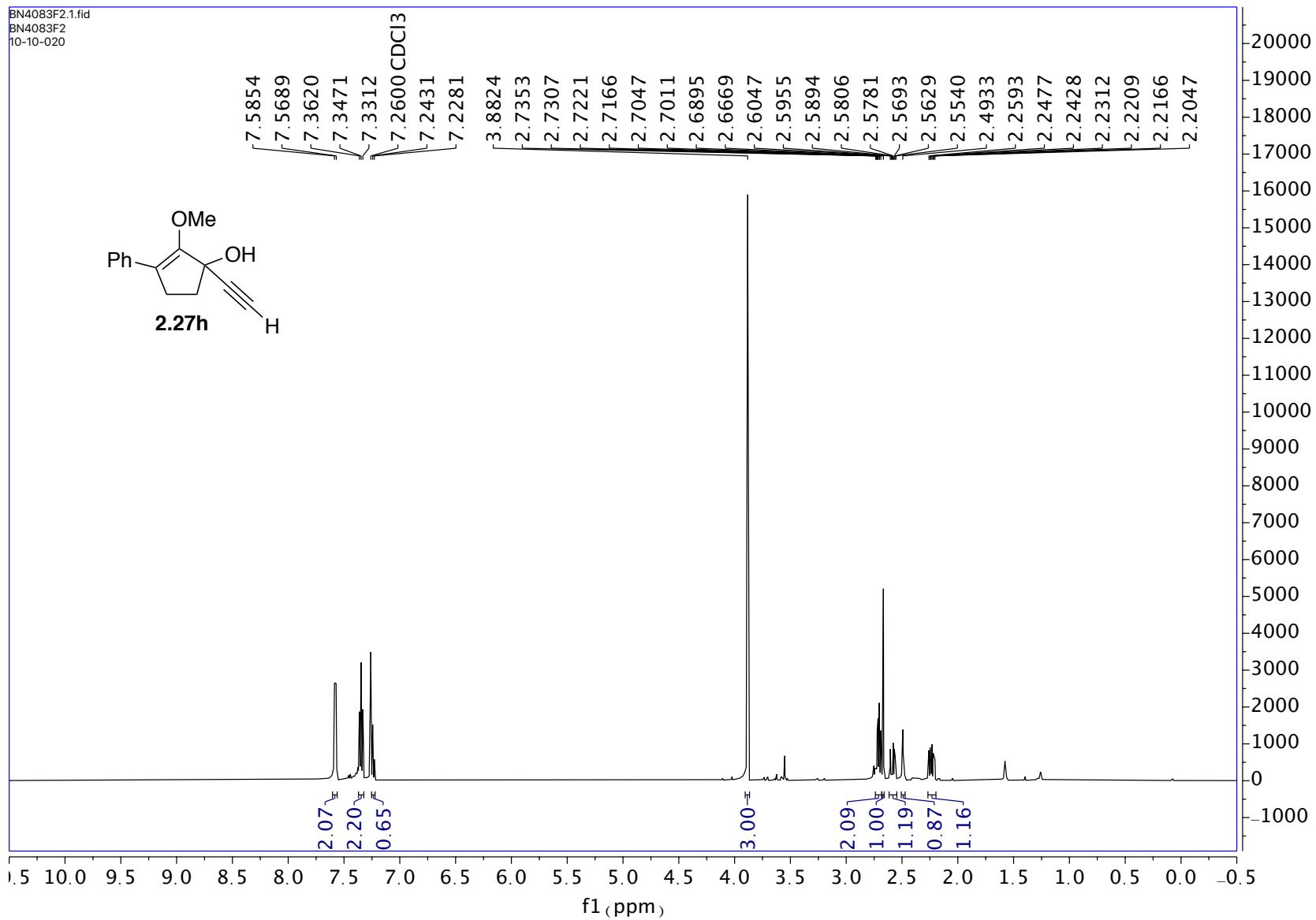
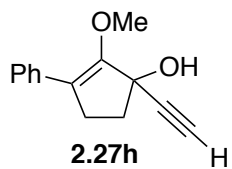


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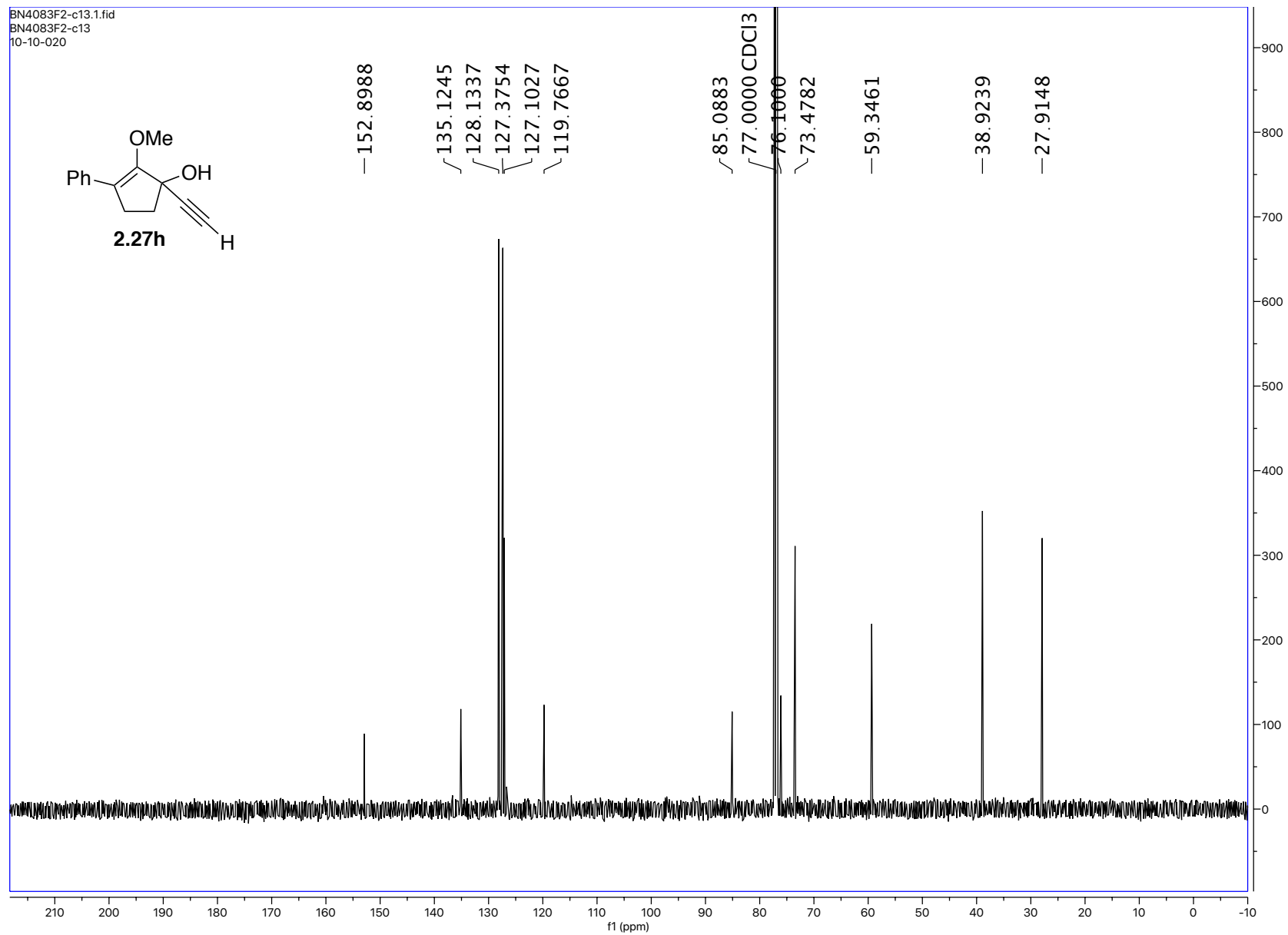
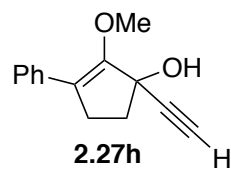




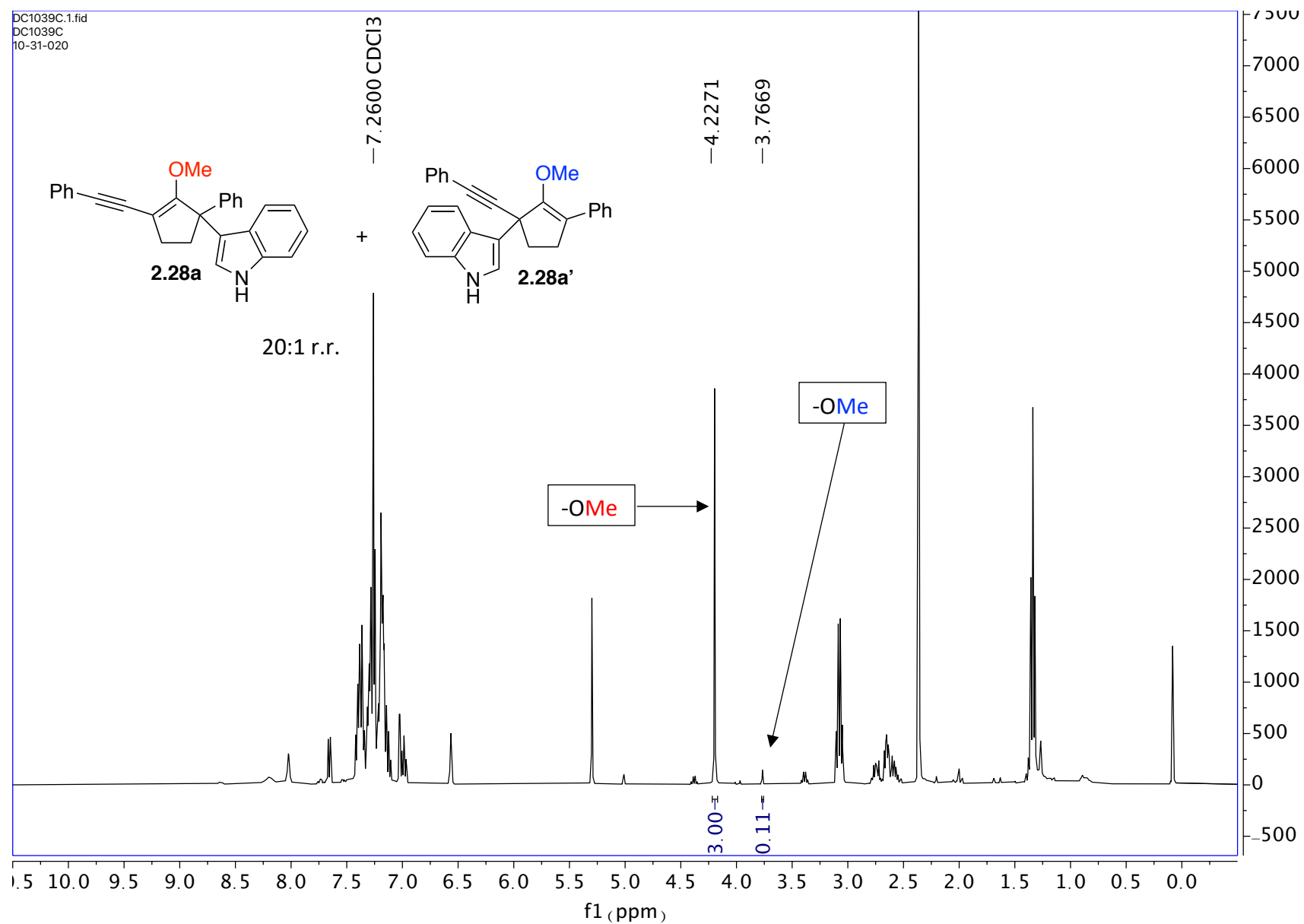
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10-10-020



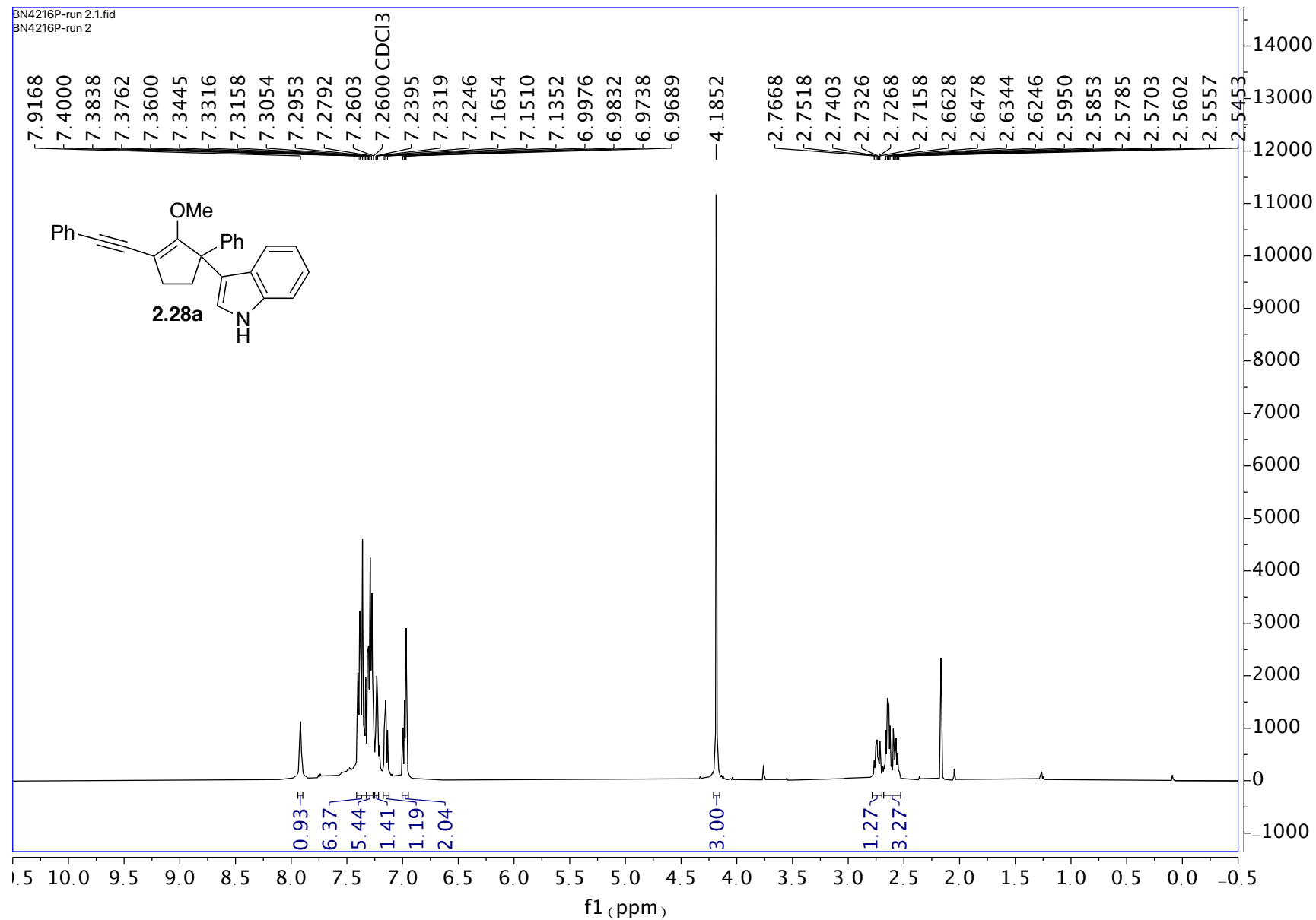
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10-10-020



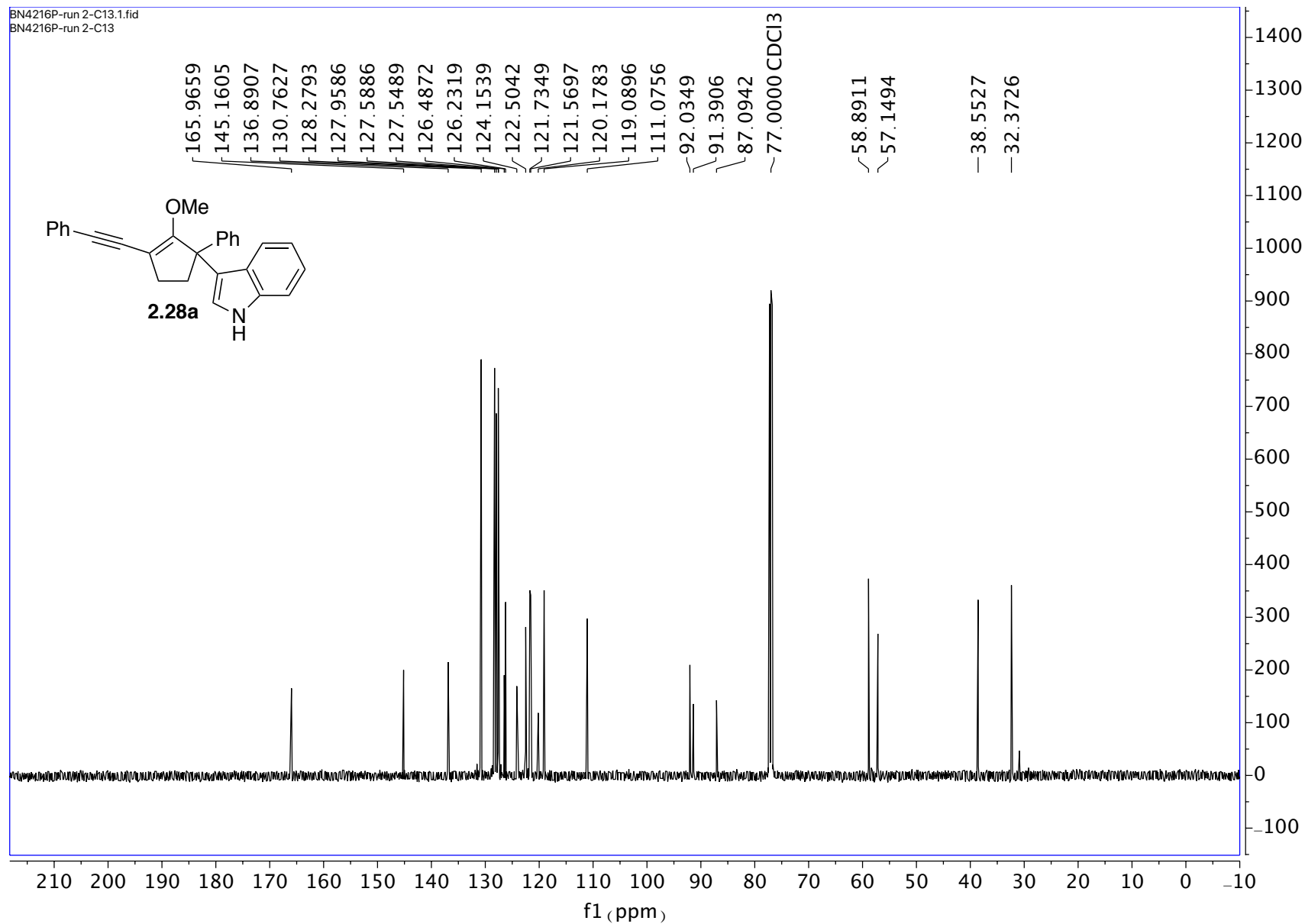
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10-31-020



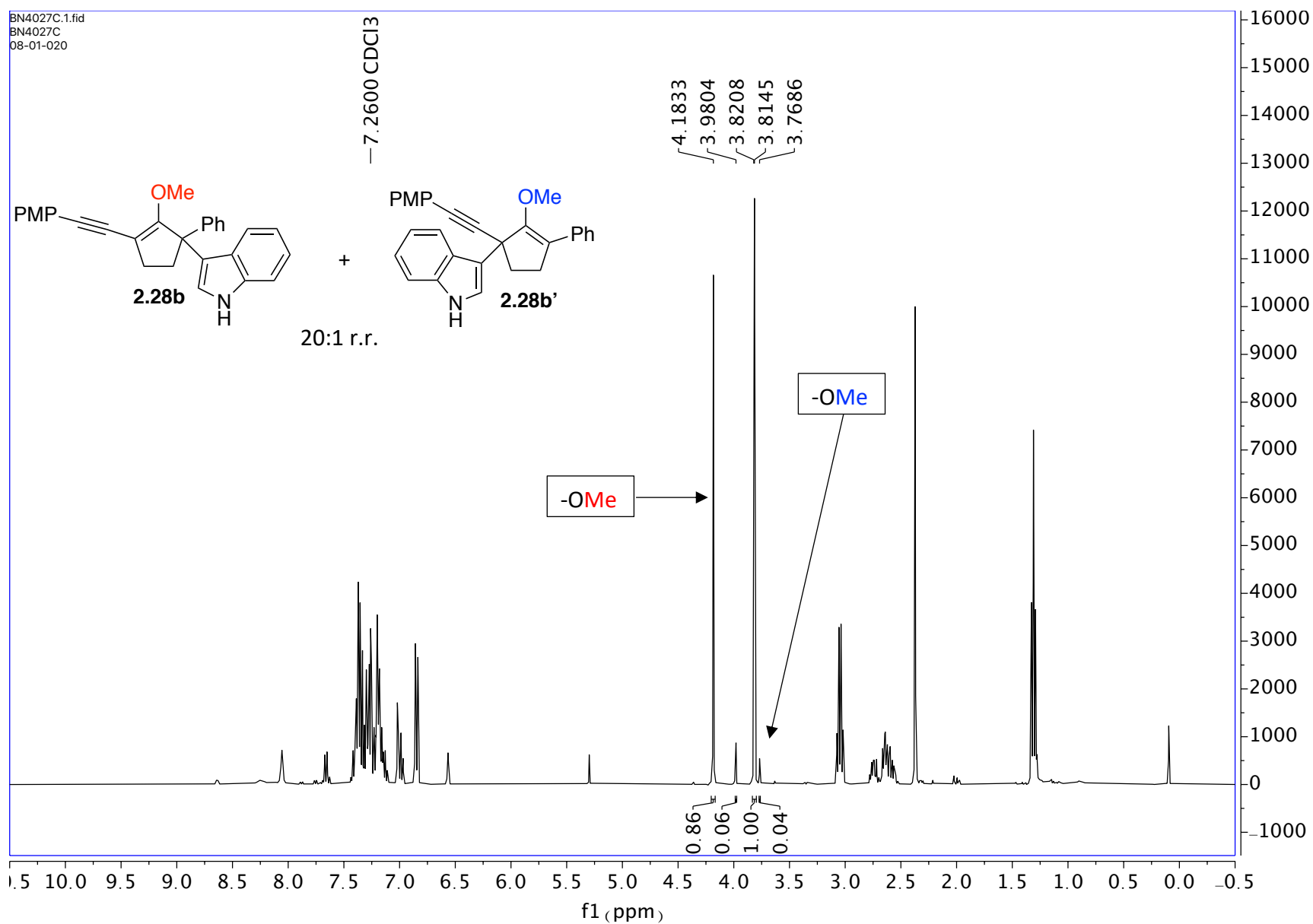
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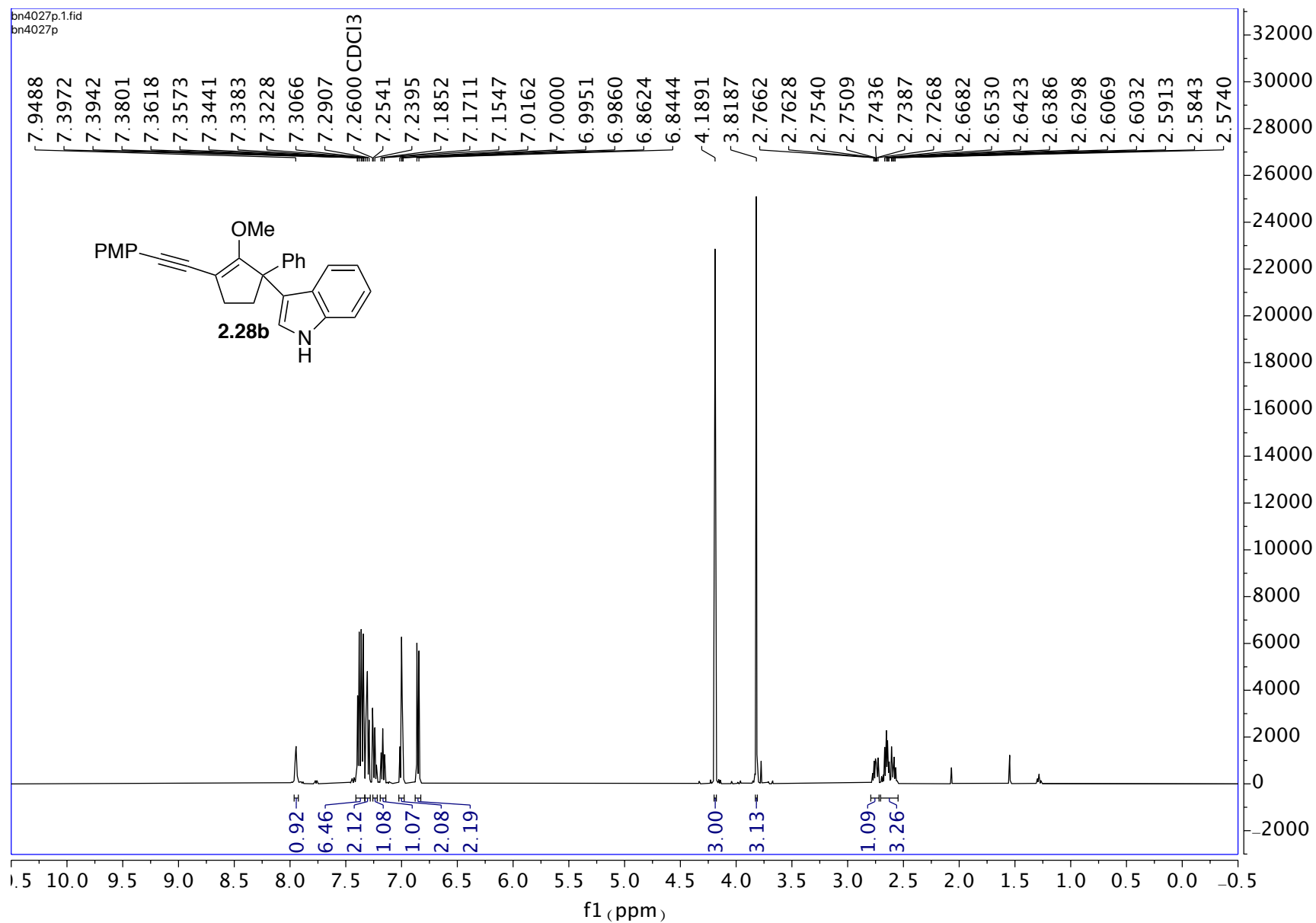


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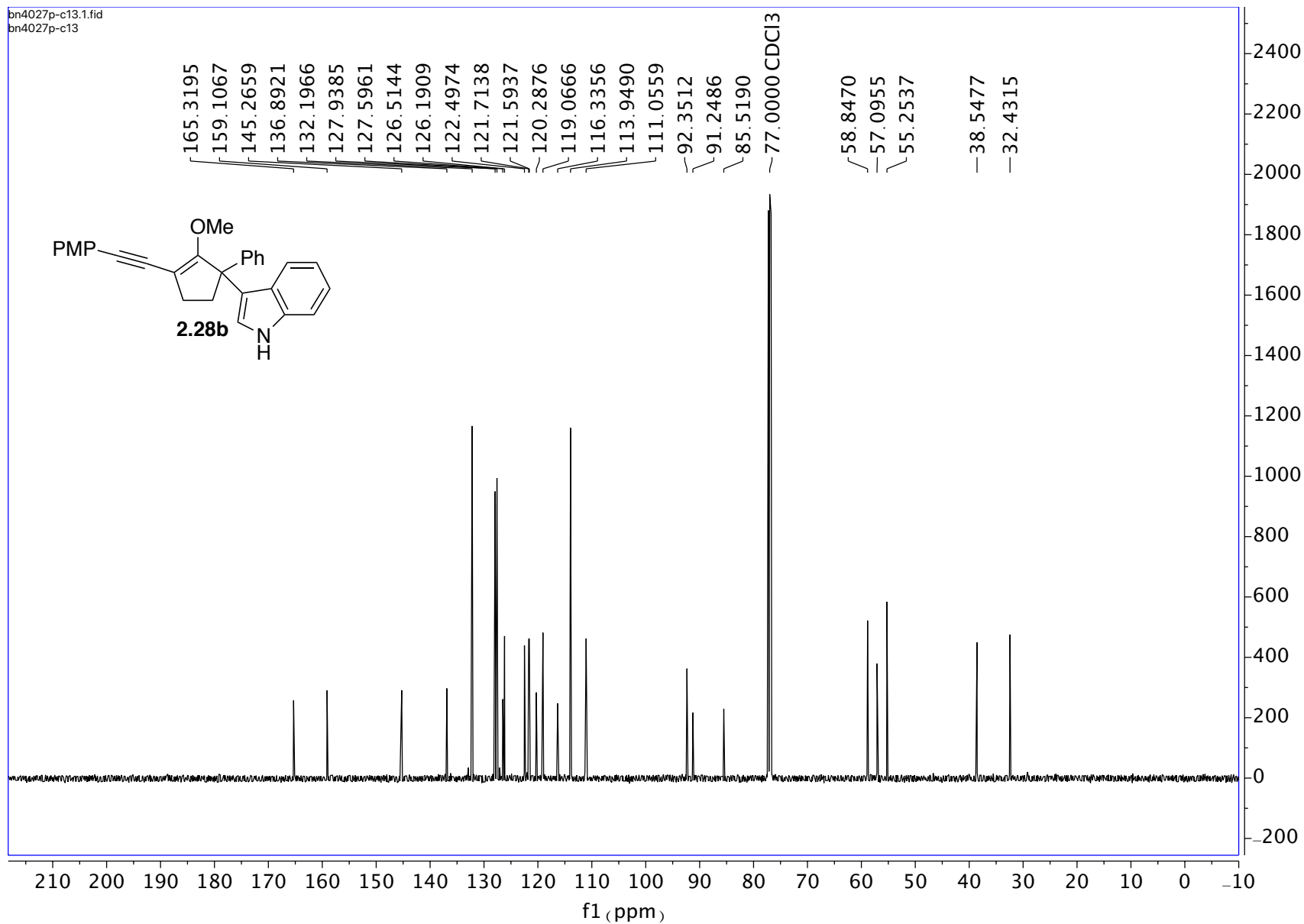
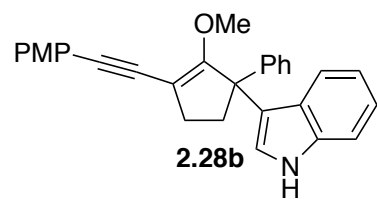


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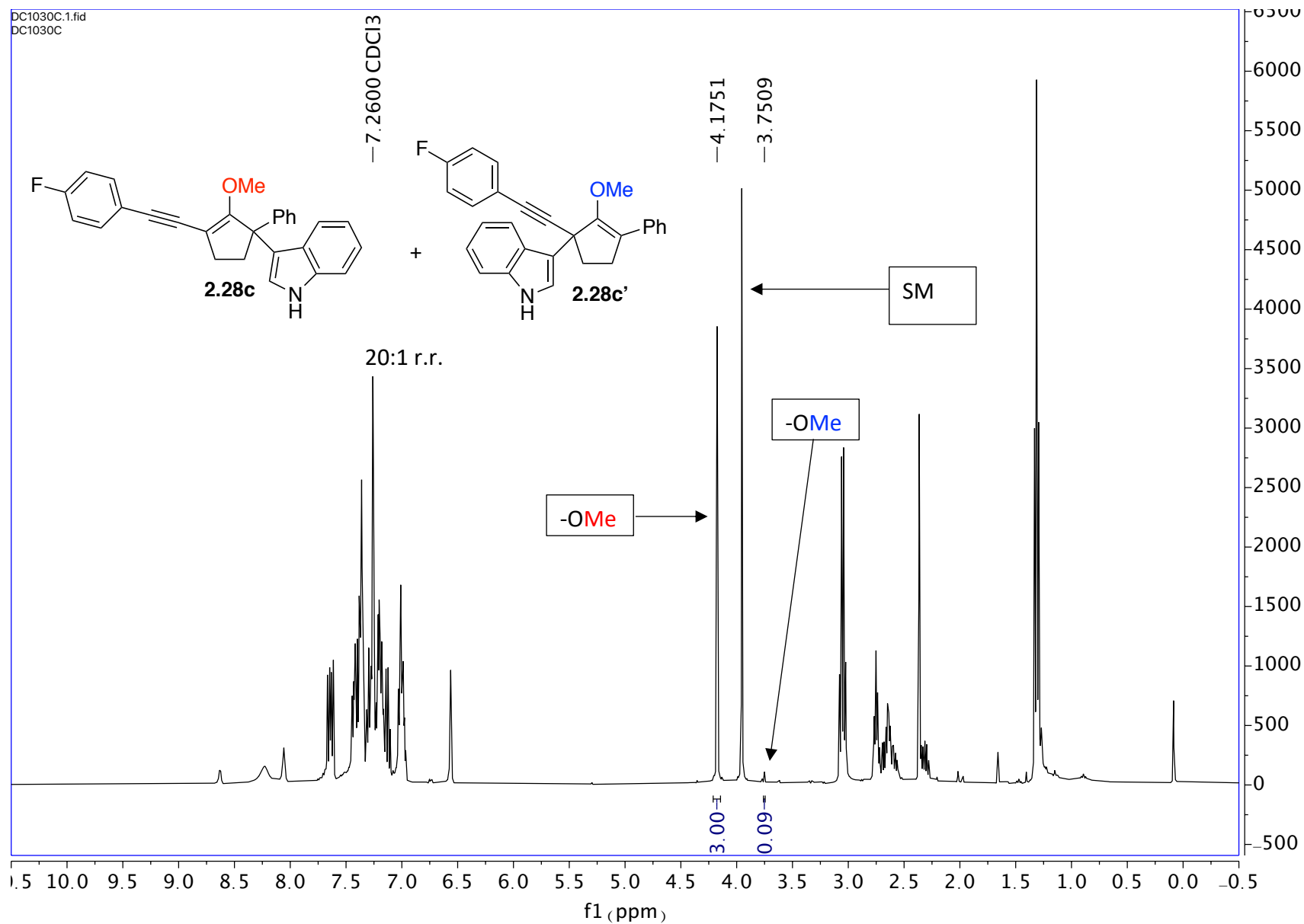


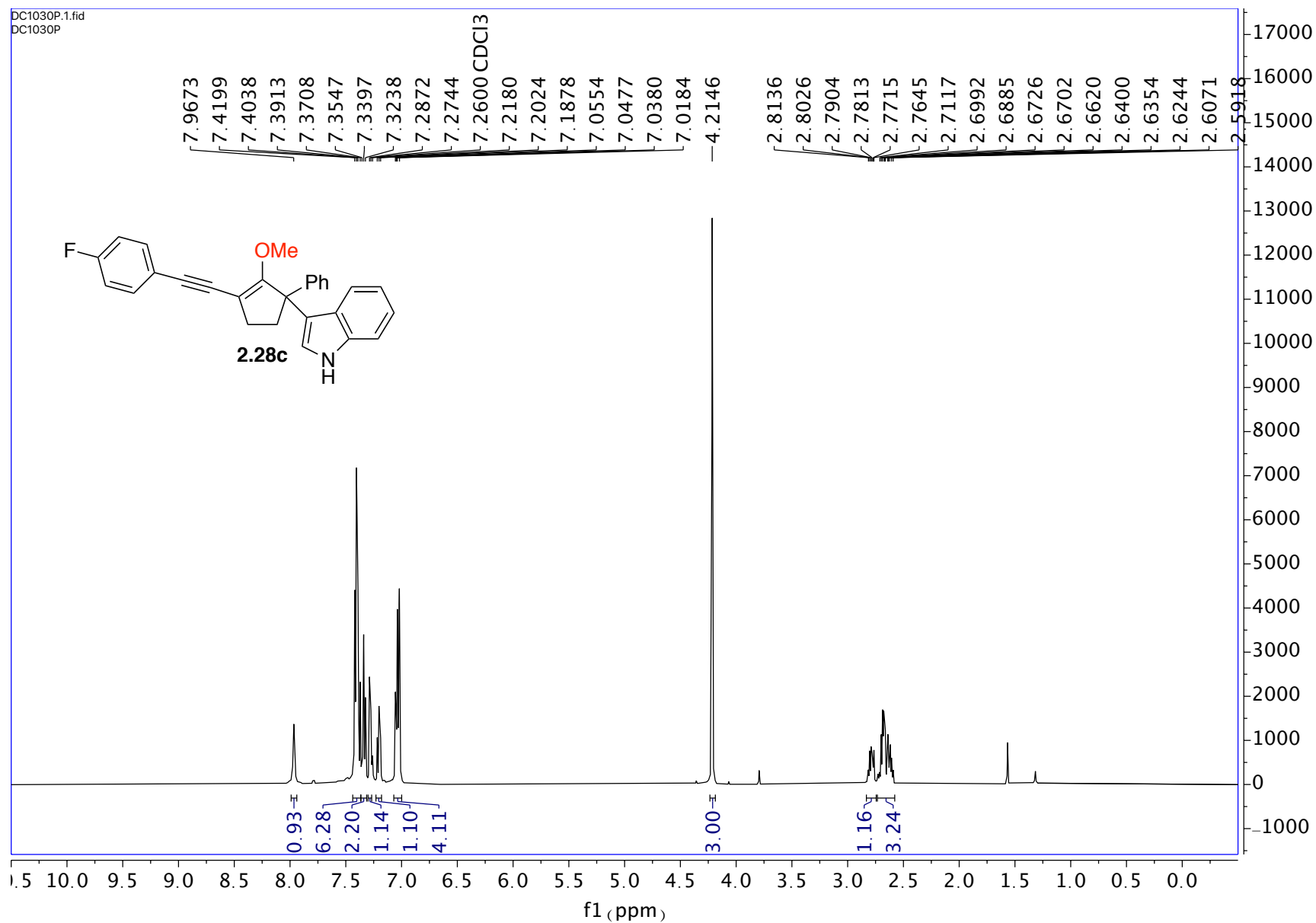


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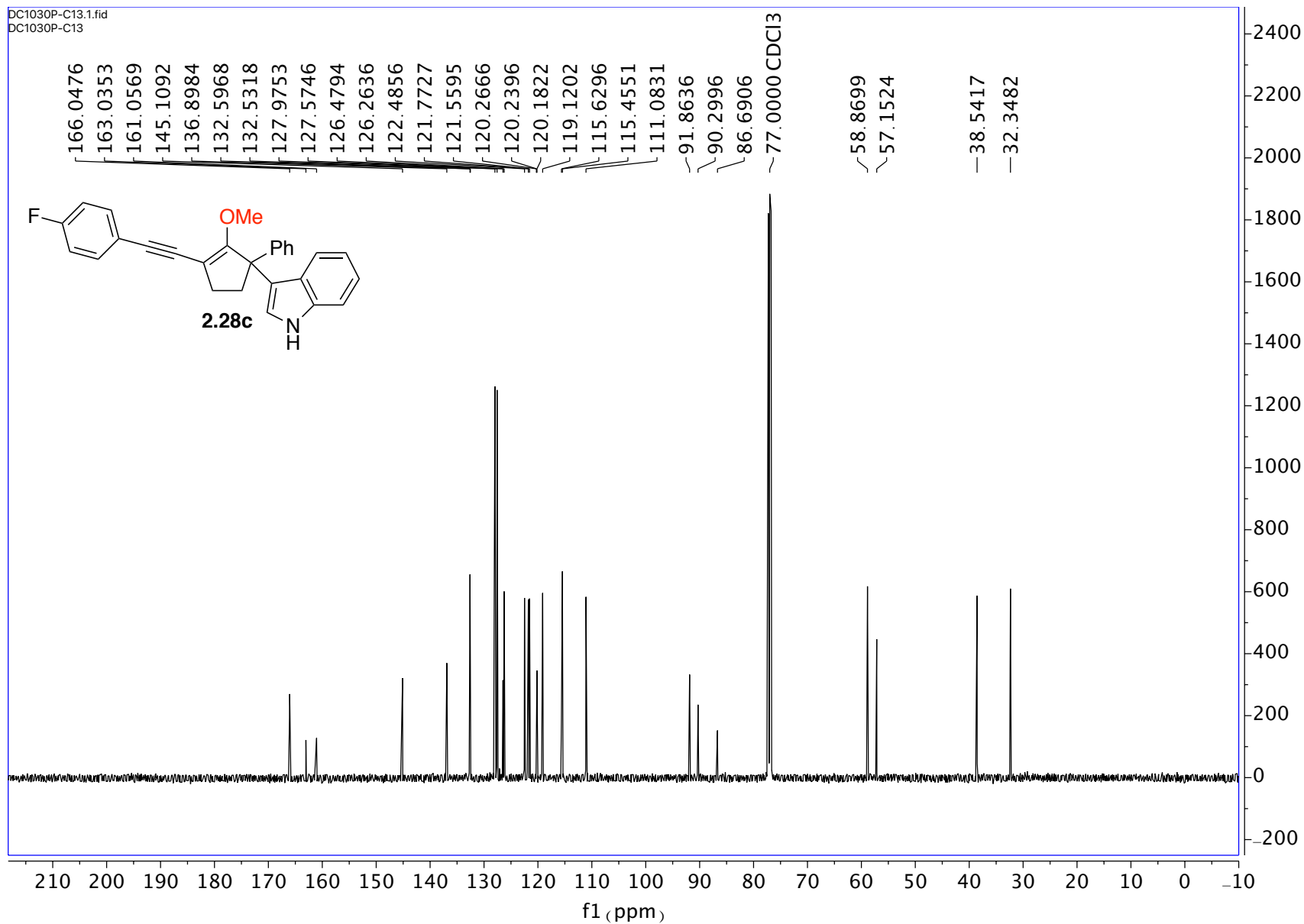




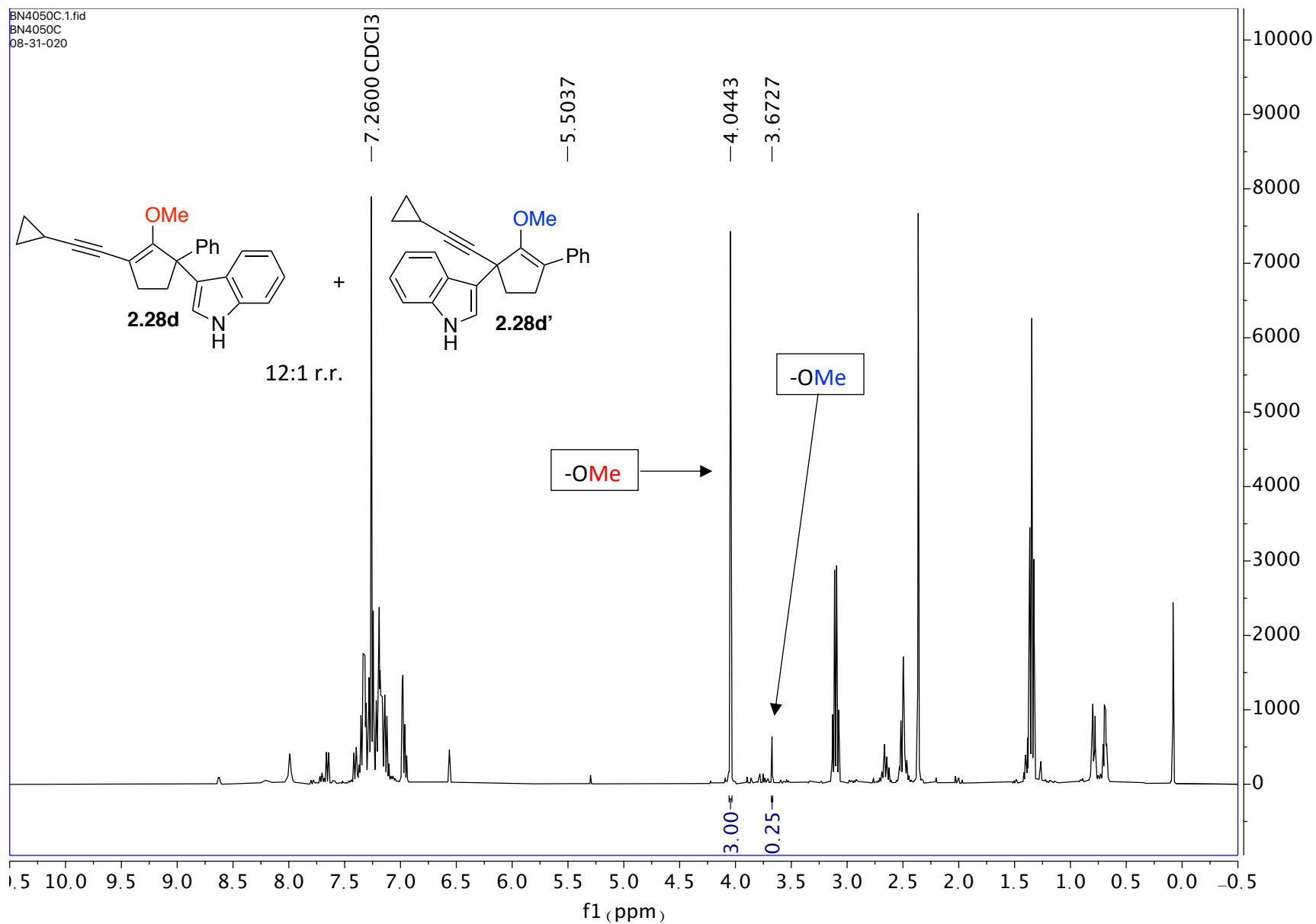


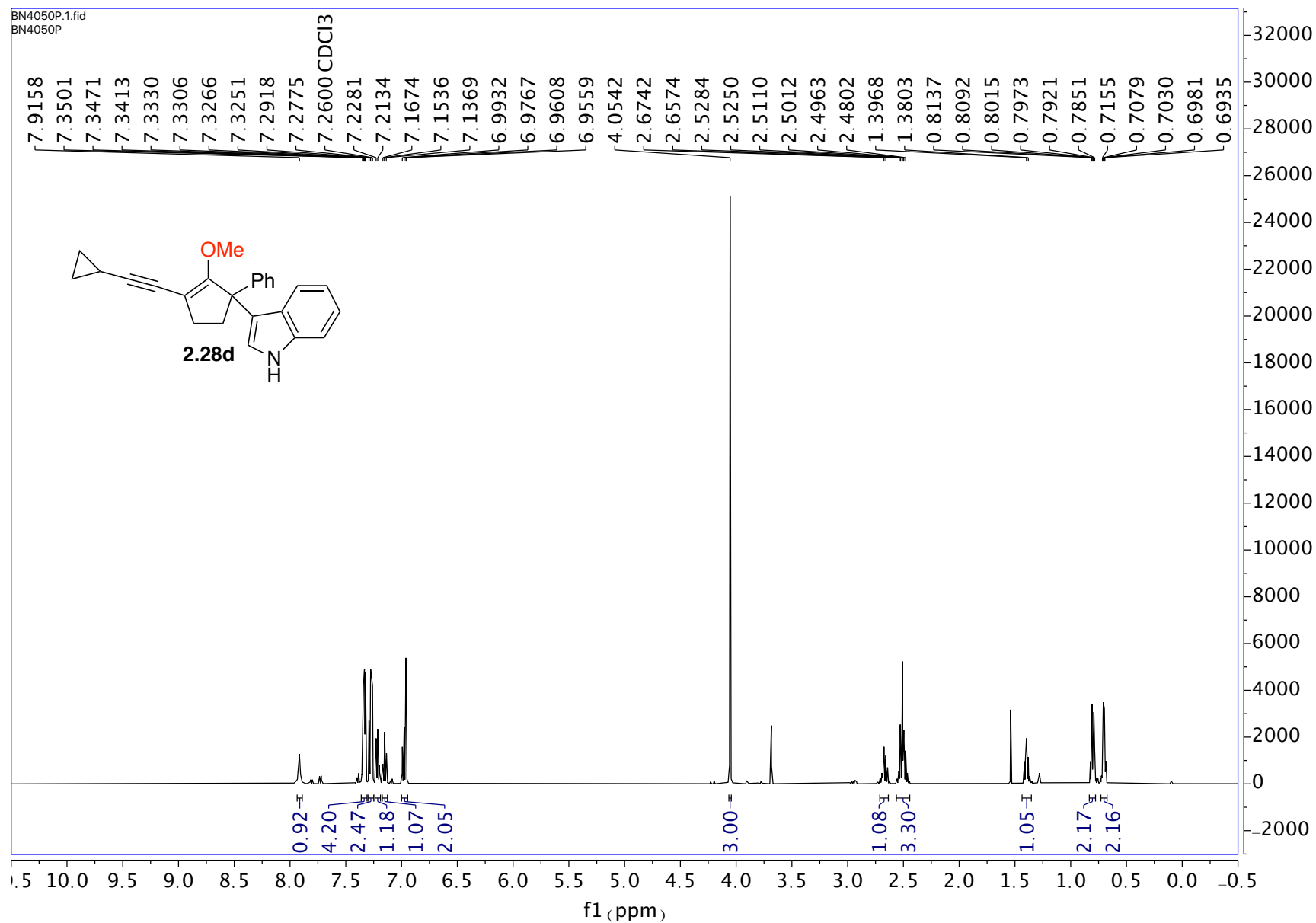


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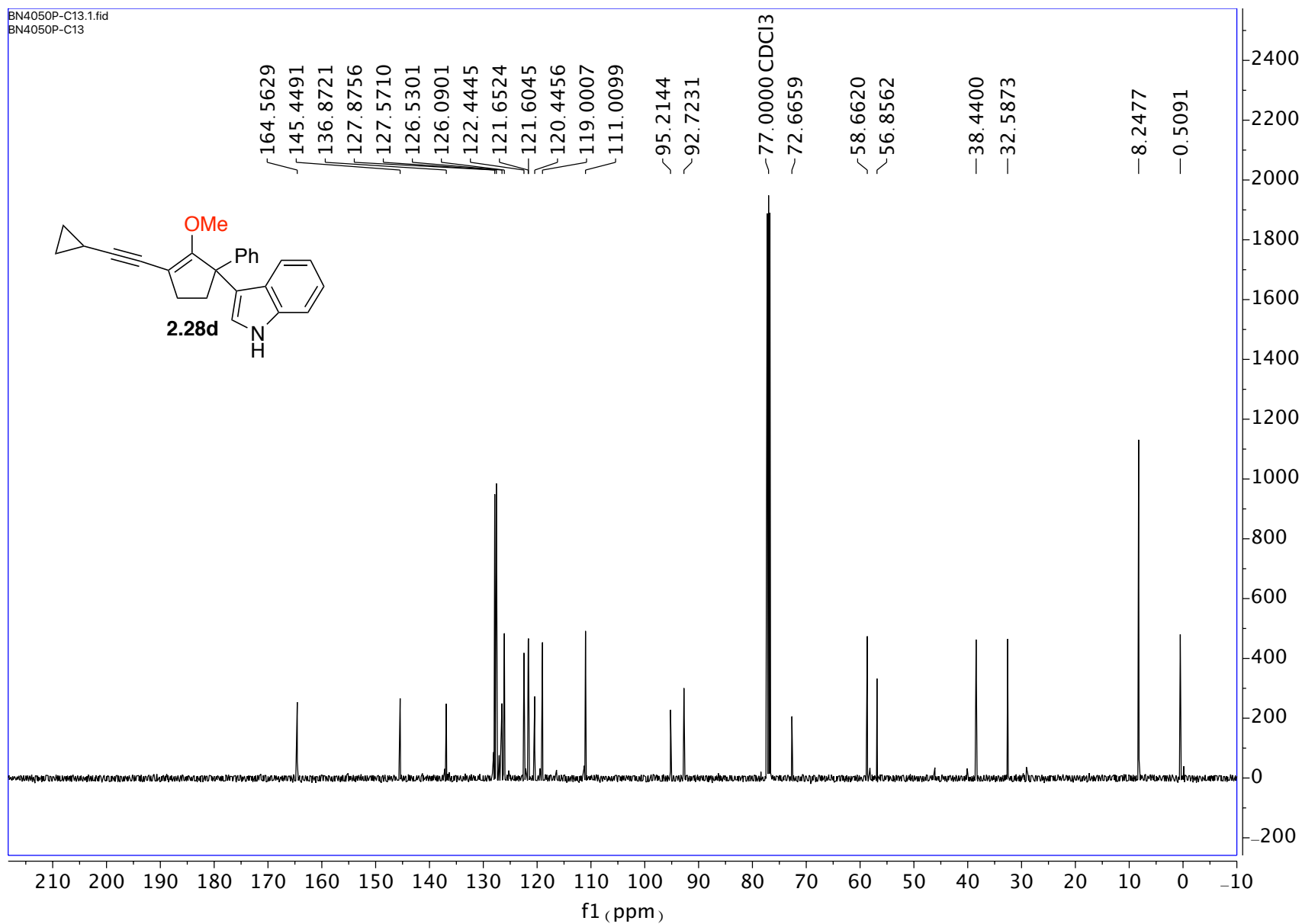


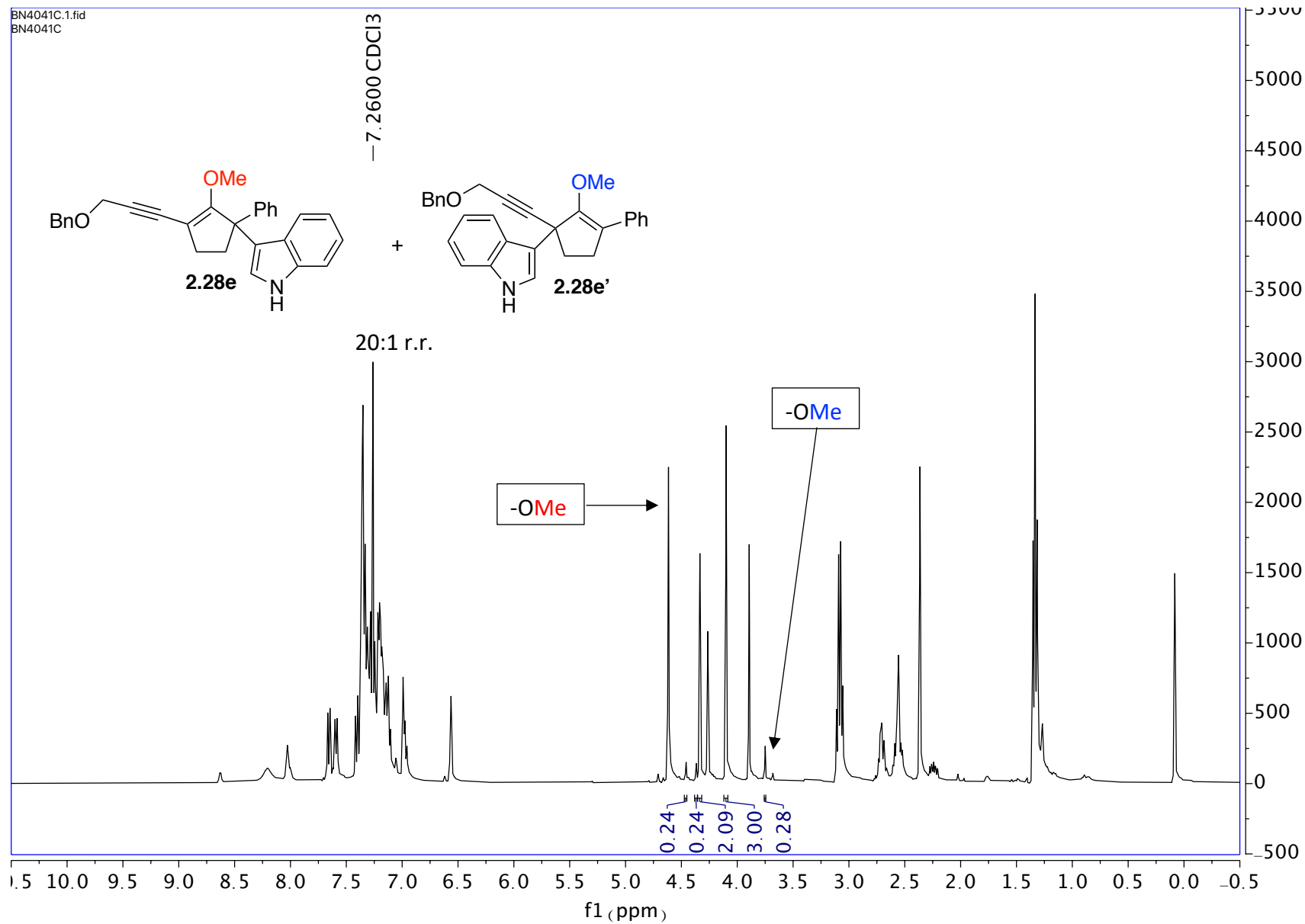
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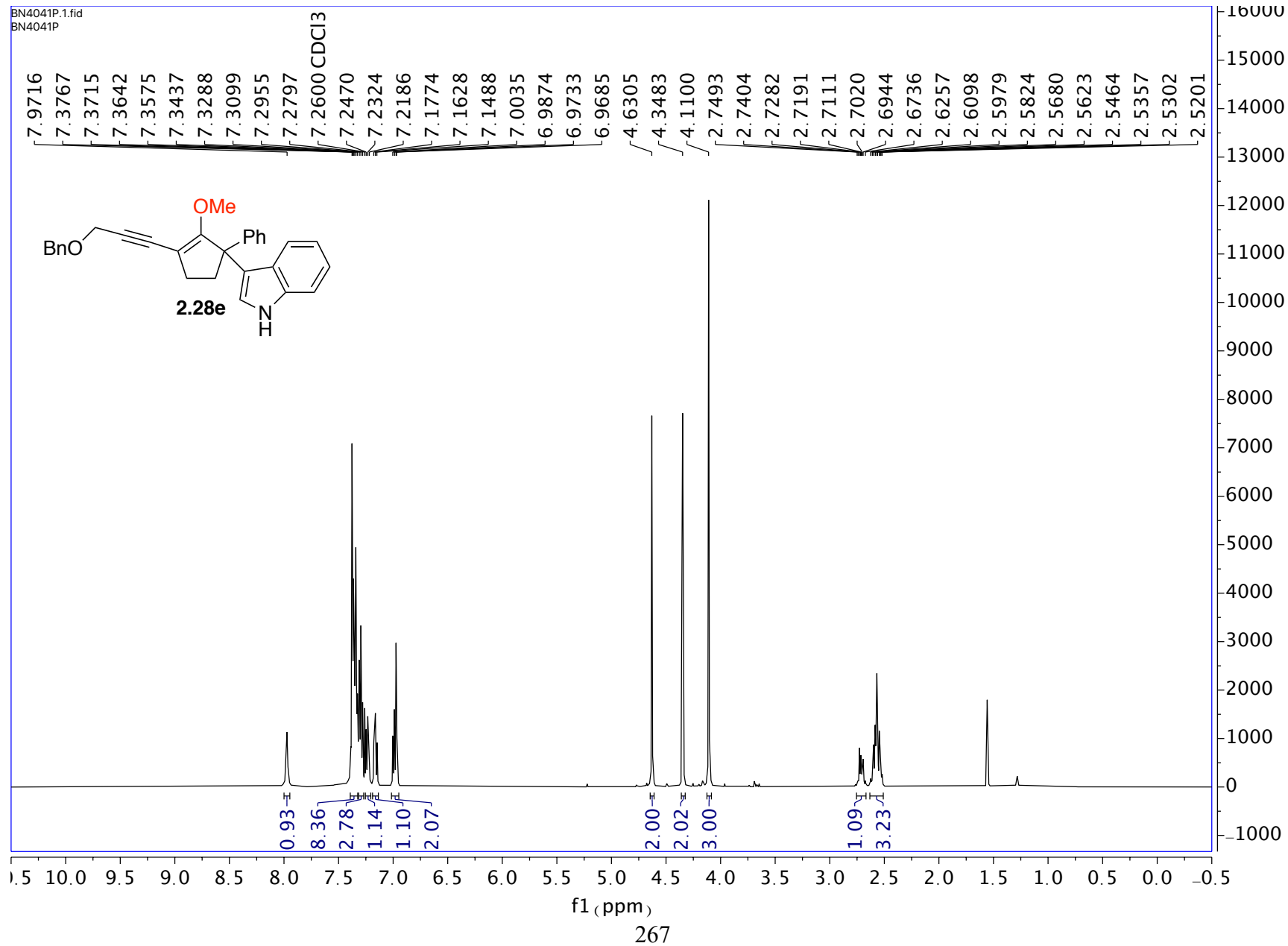




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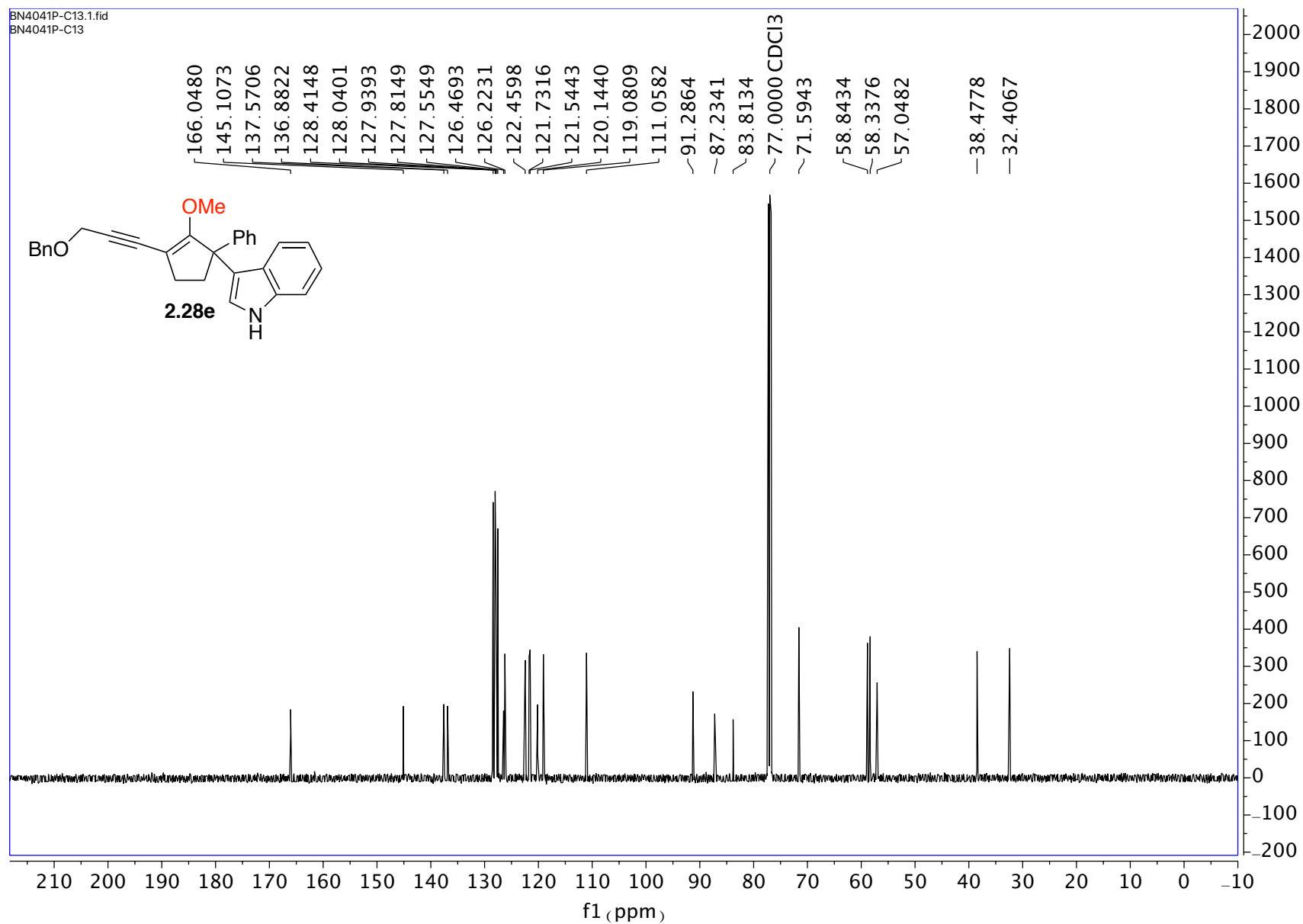




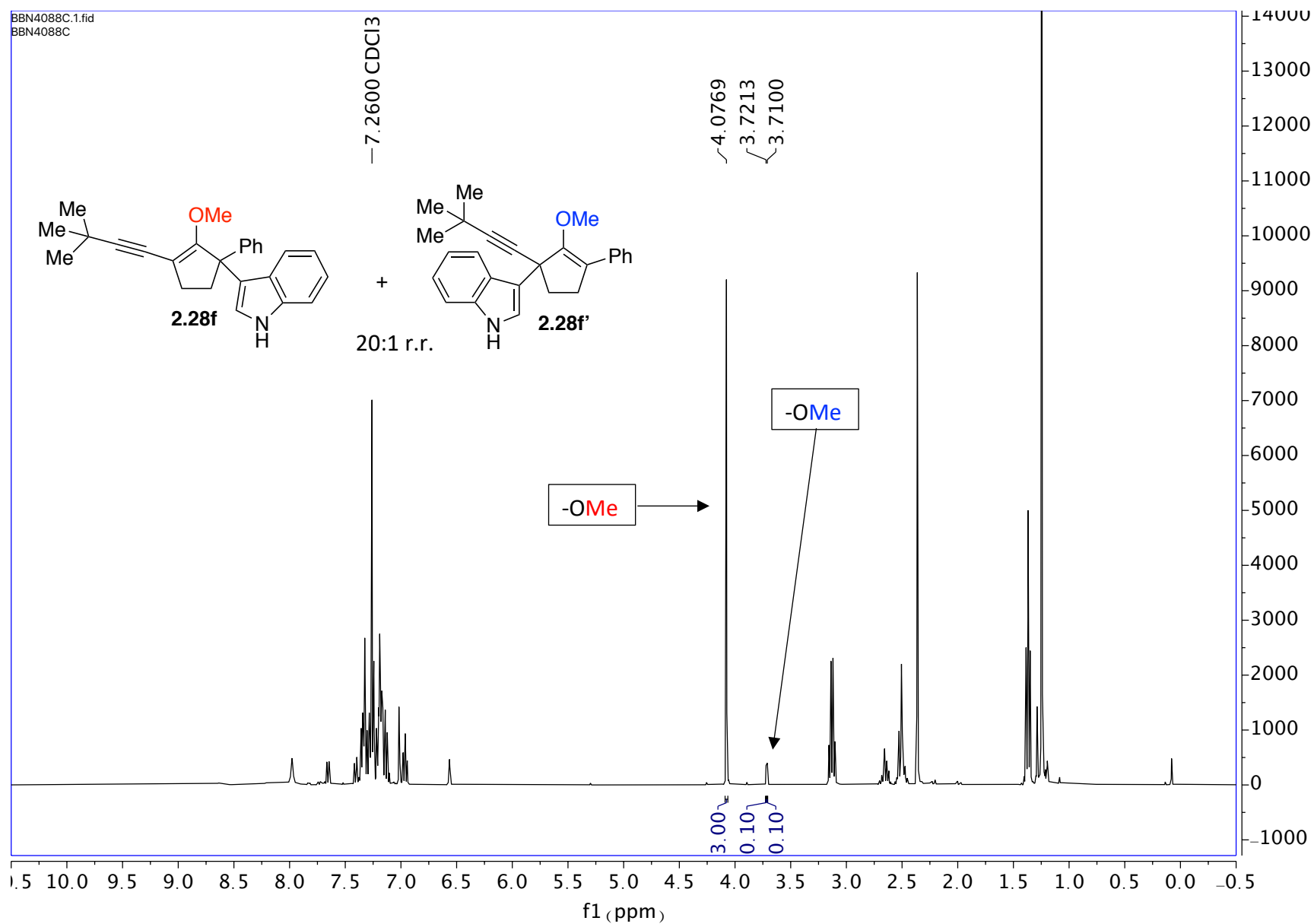


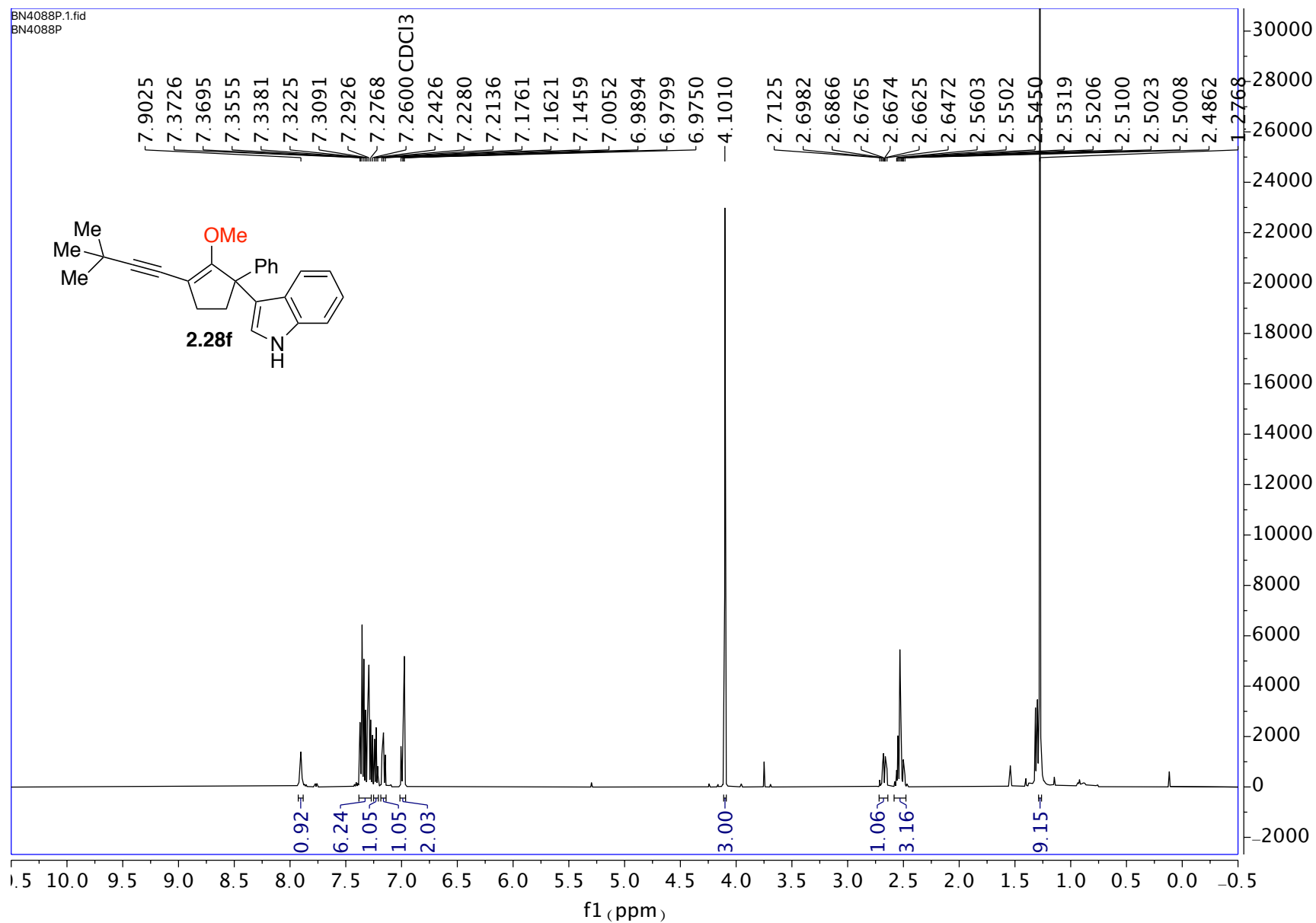


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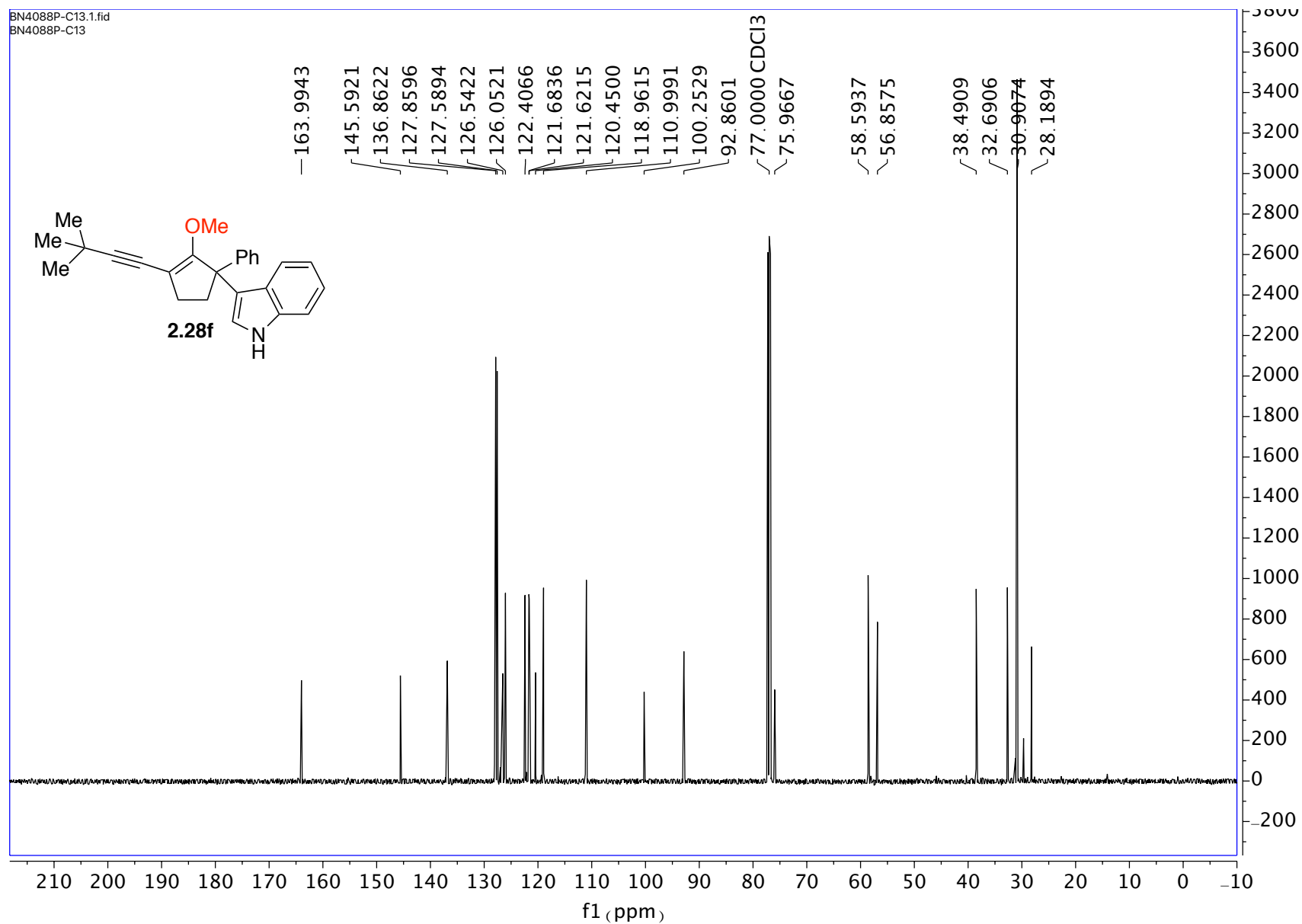


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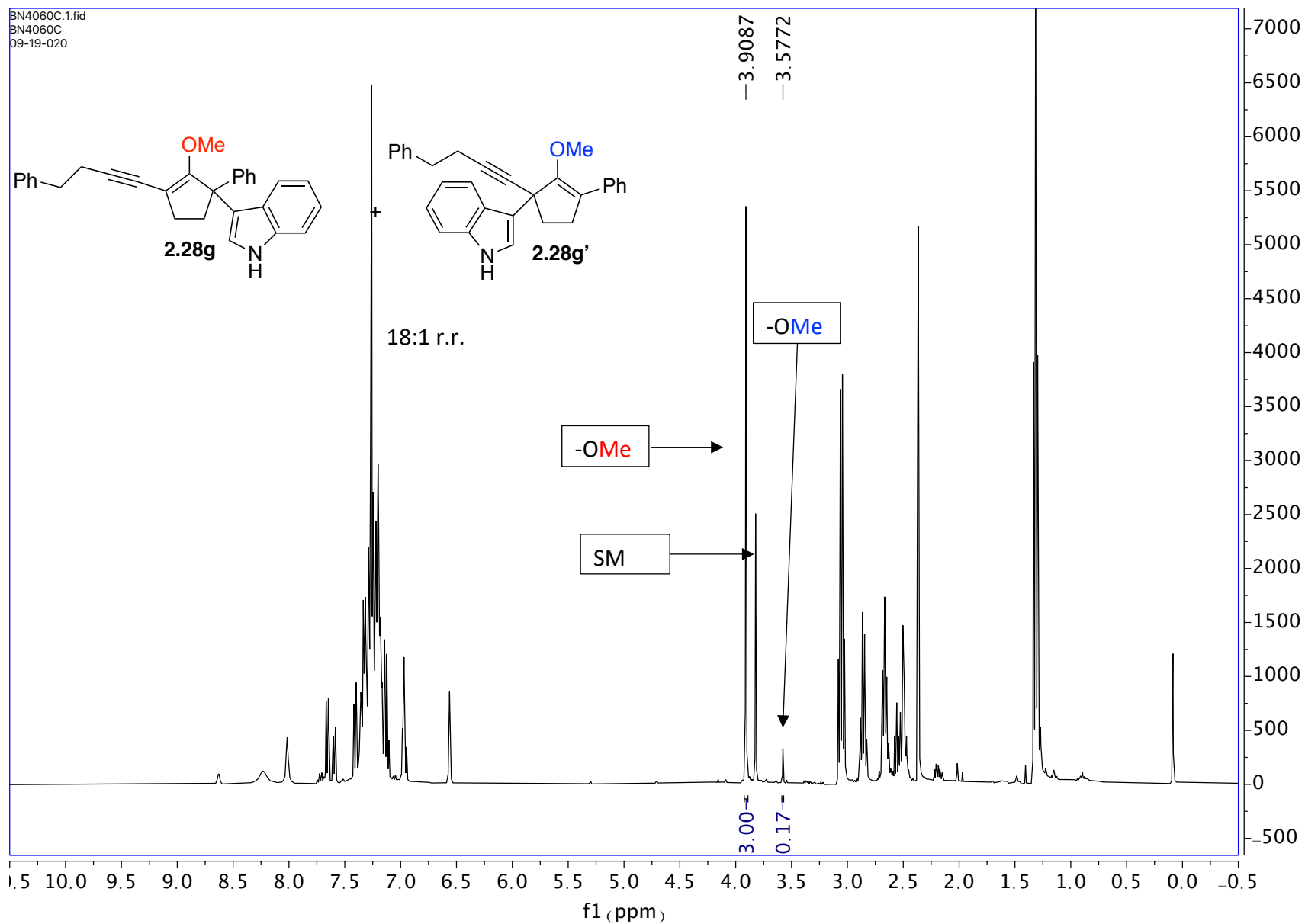




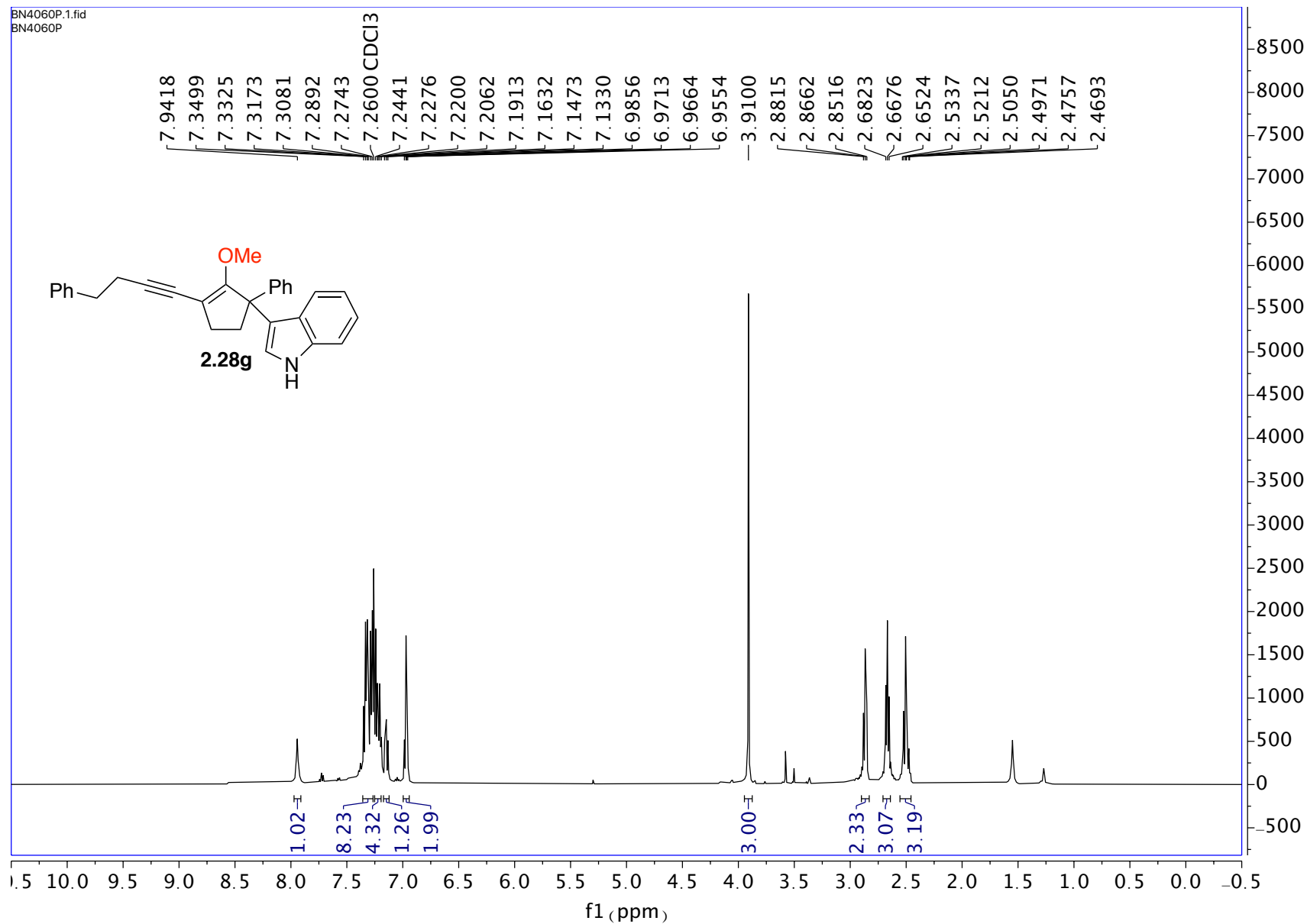
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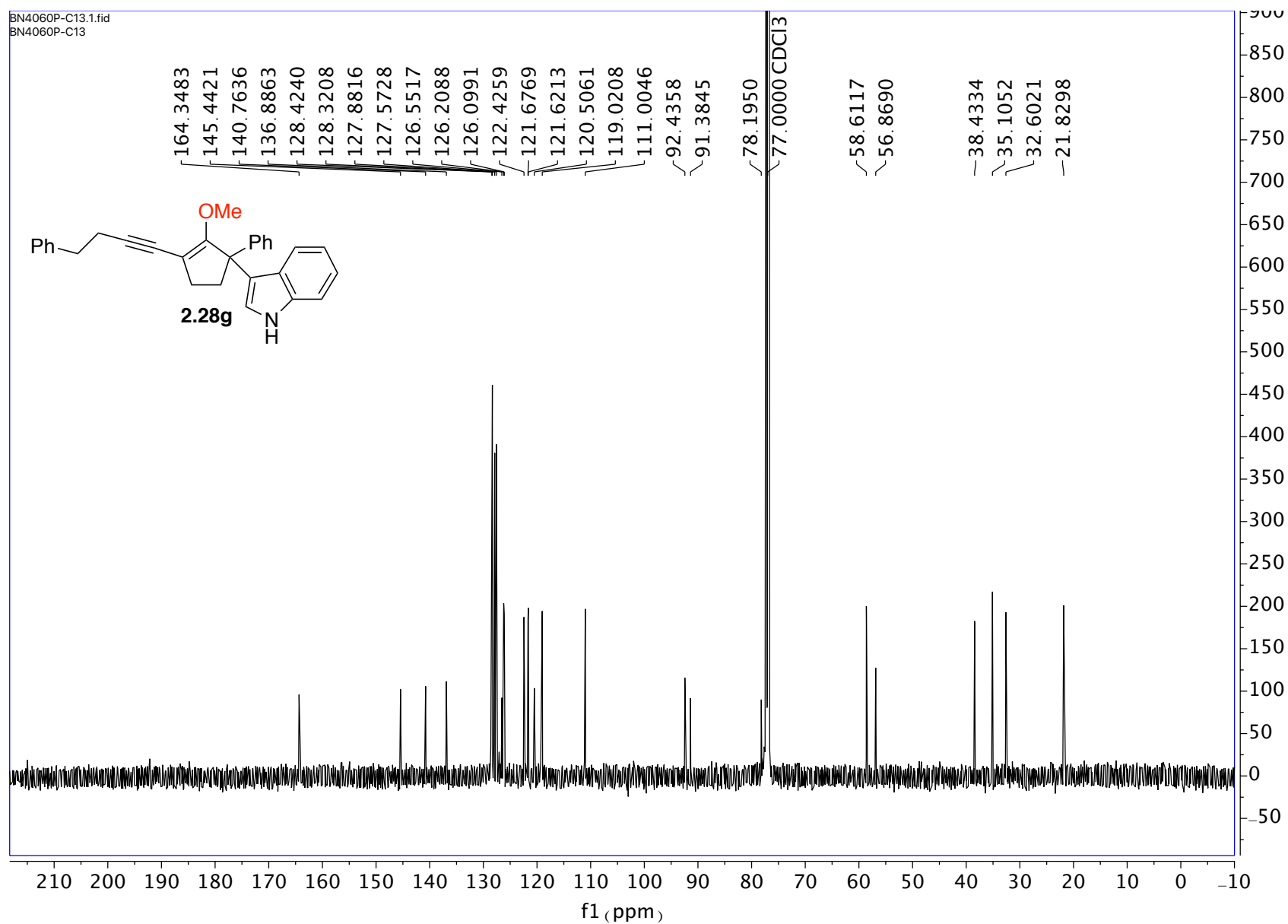
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09-19-020



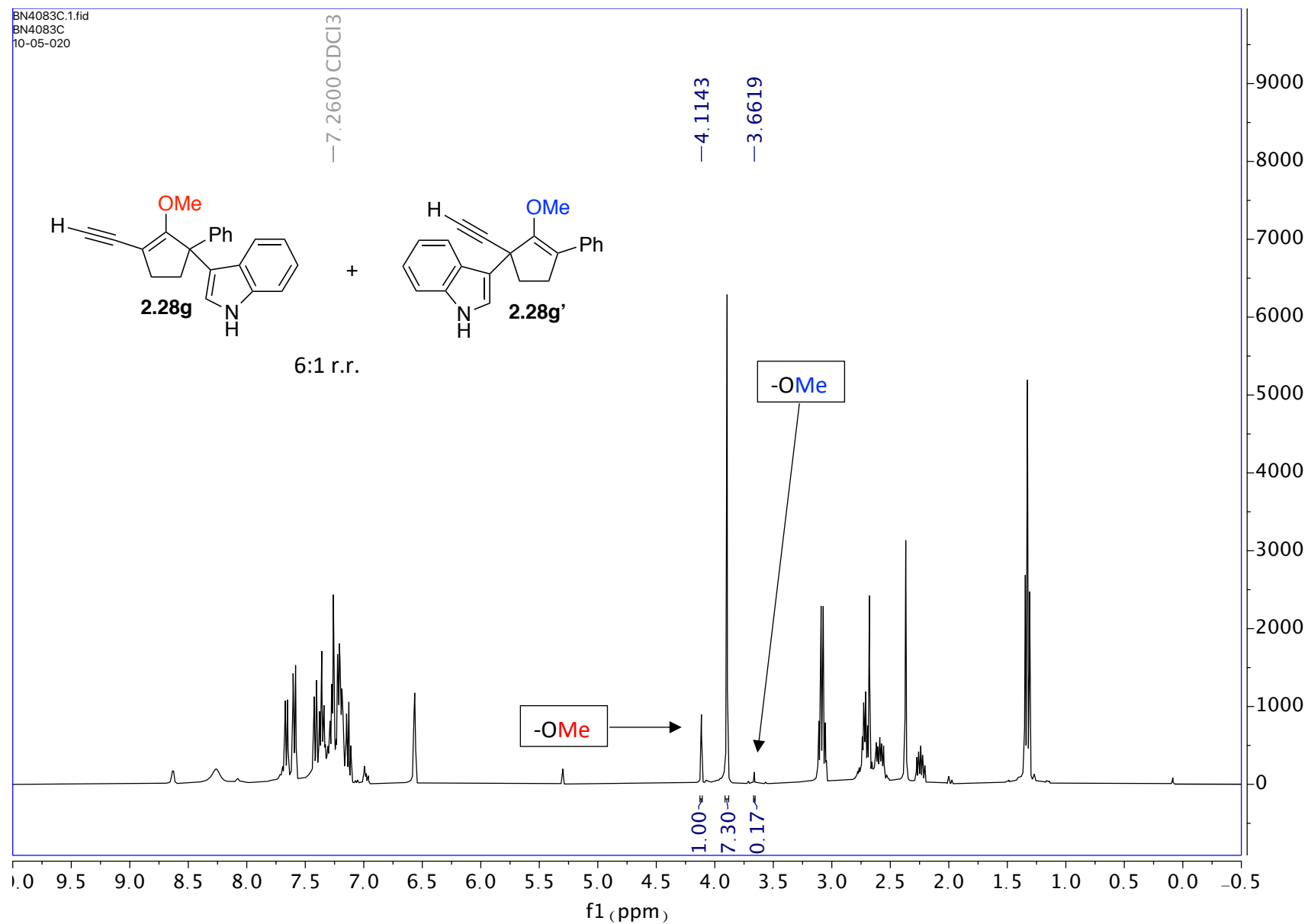
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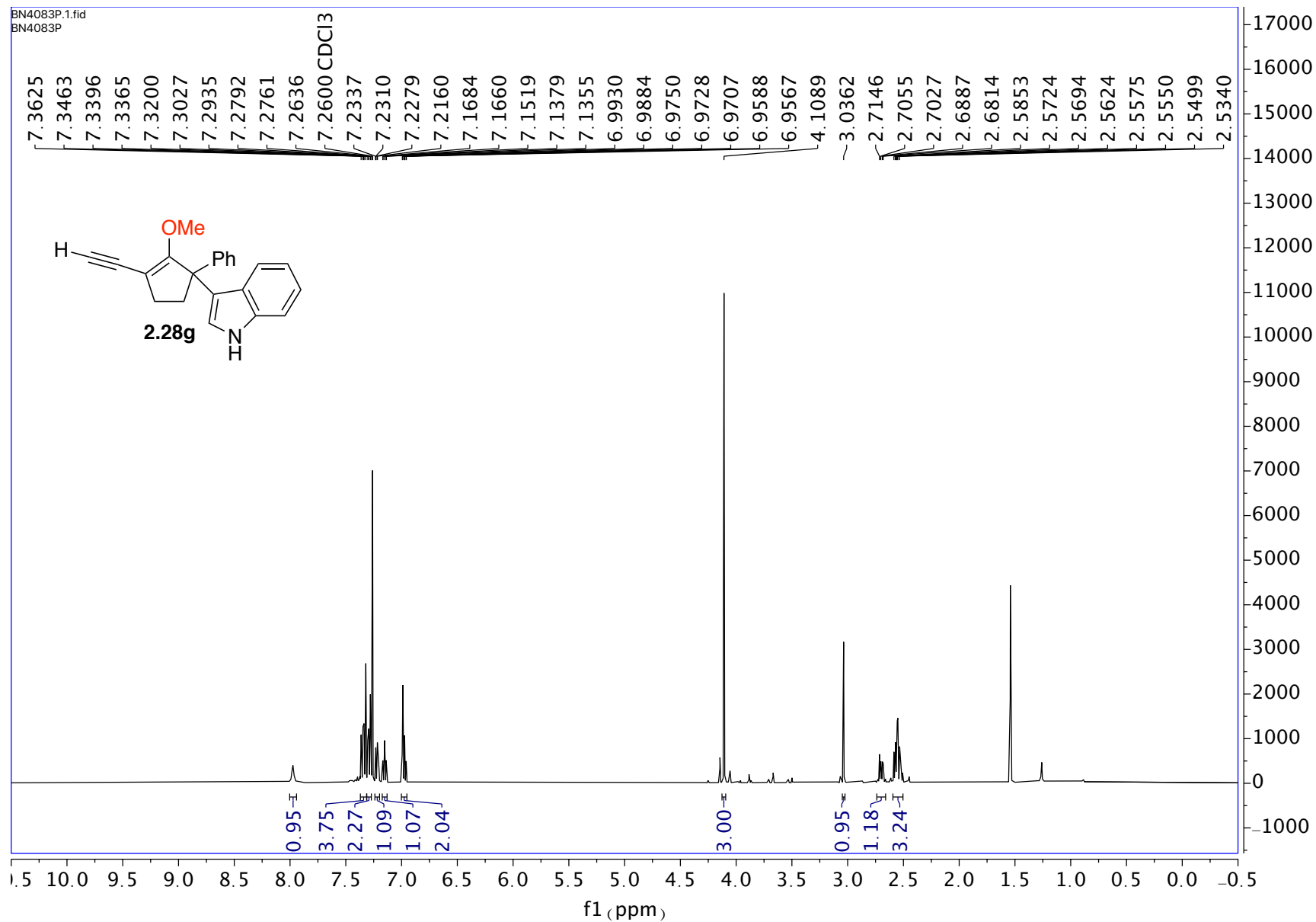
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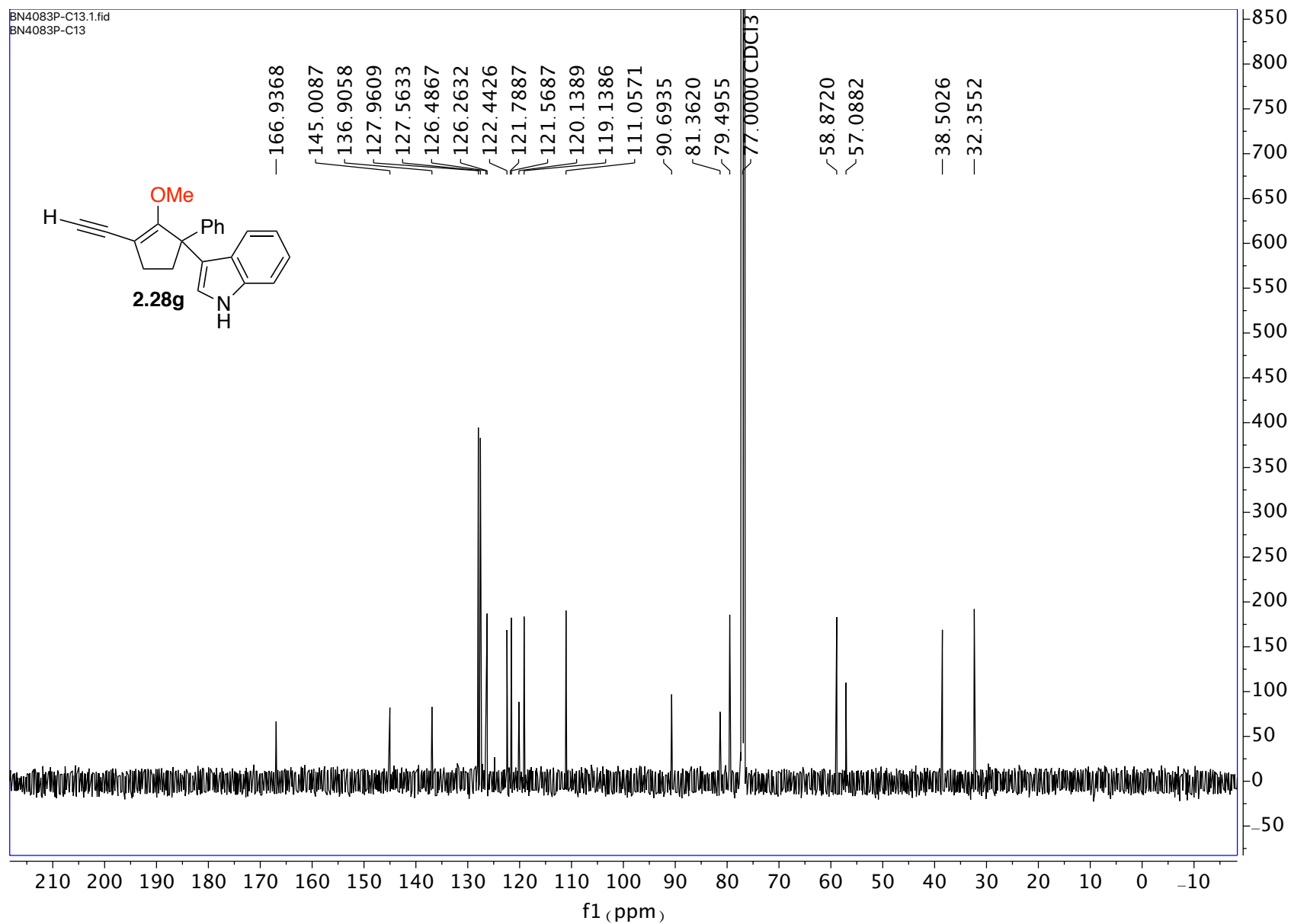
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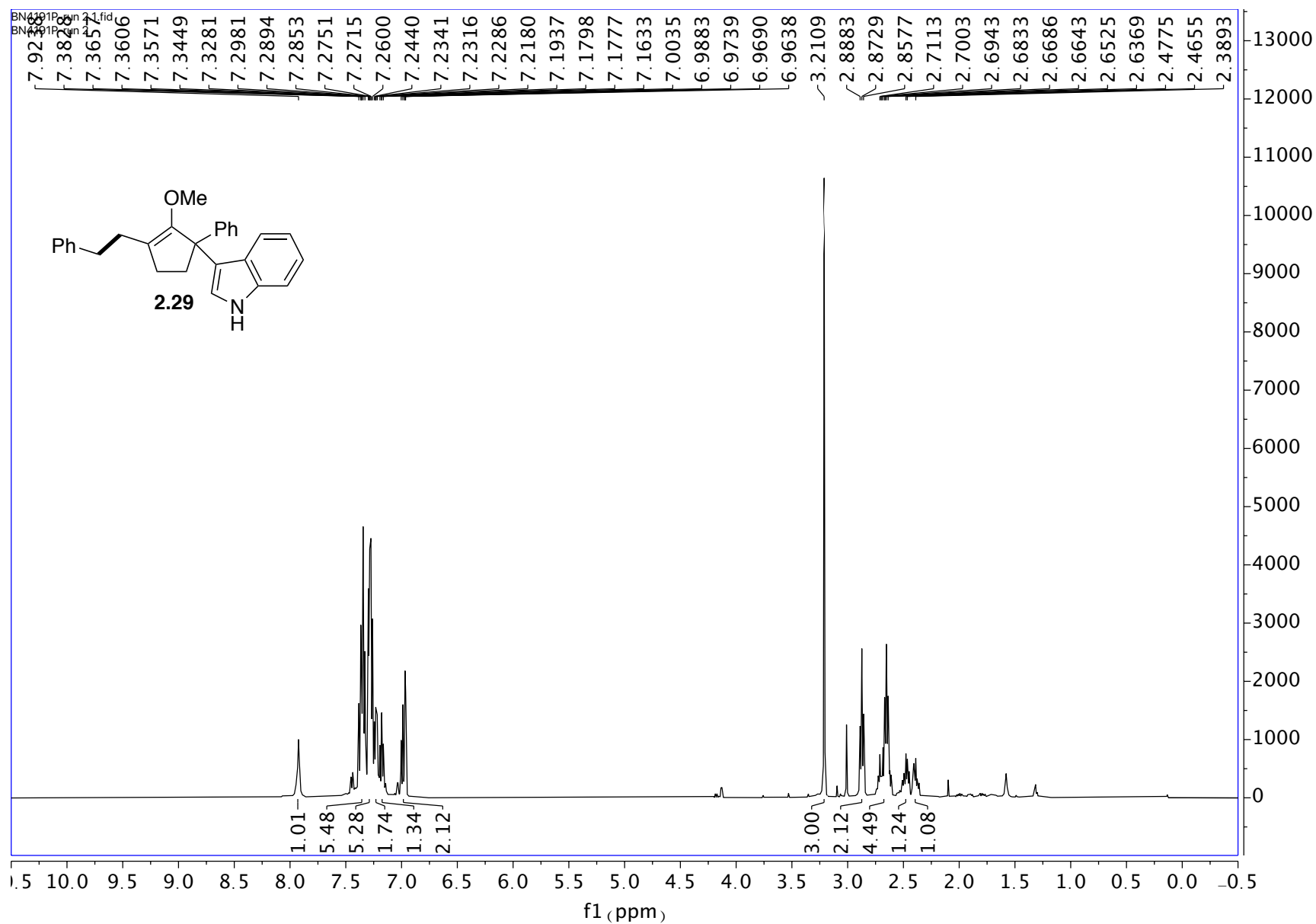




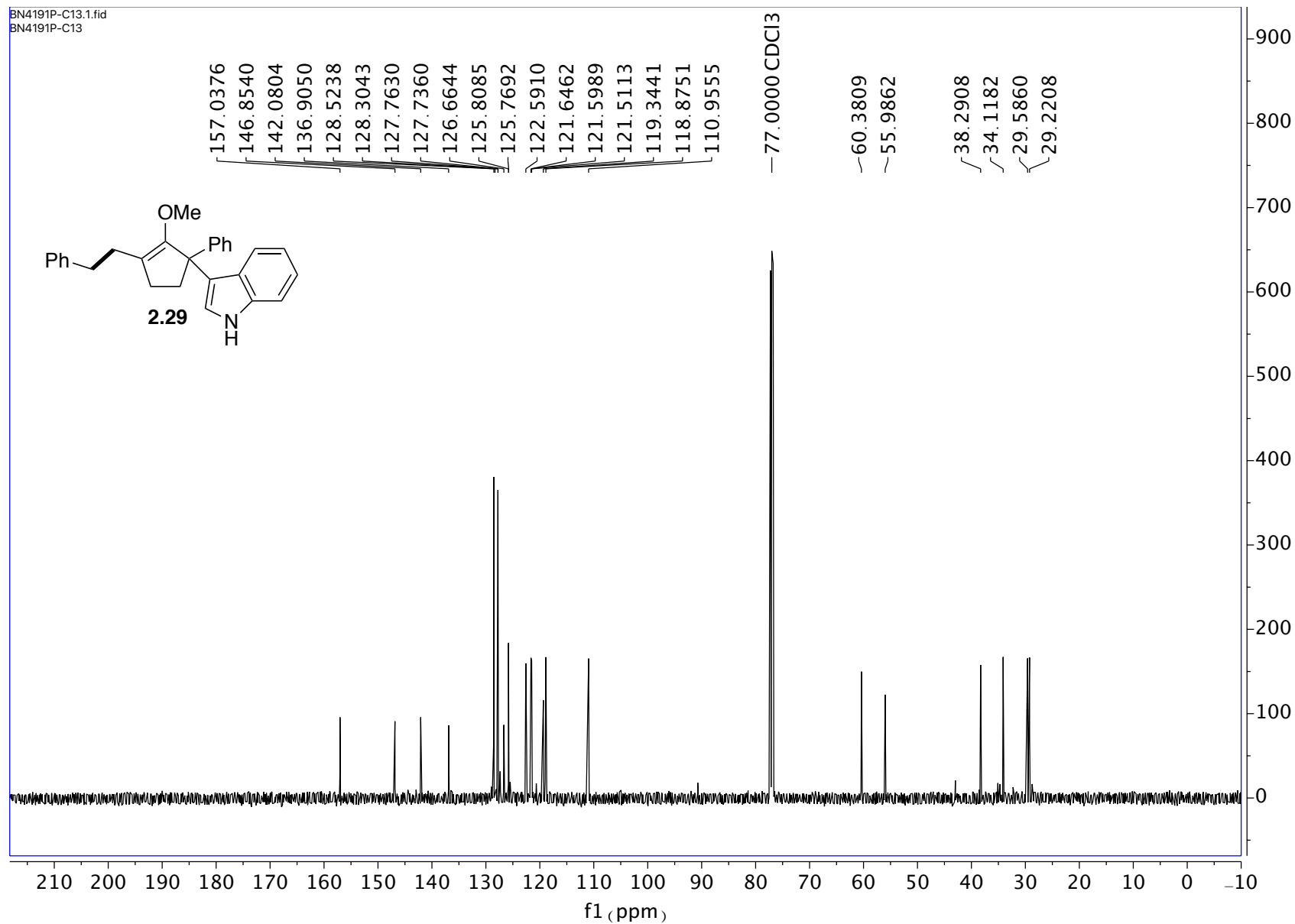
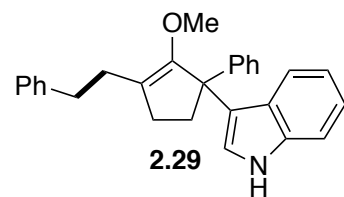


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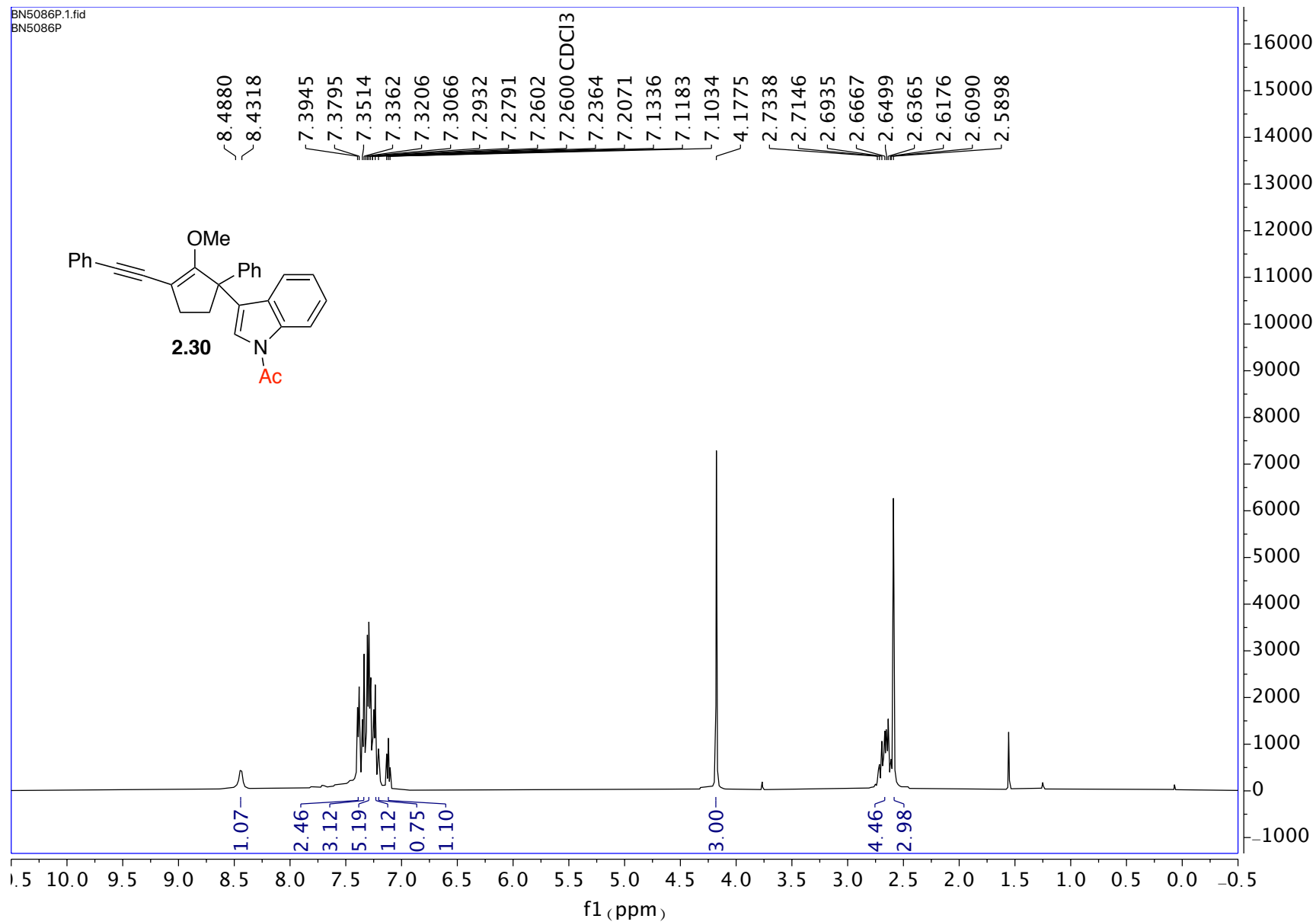




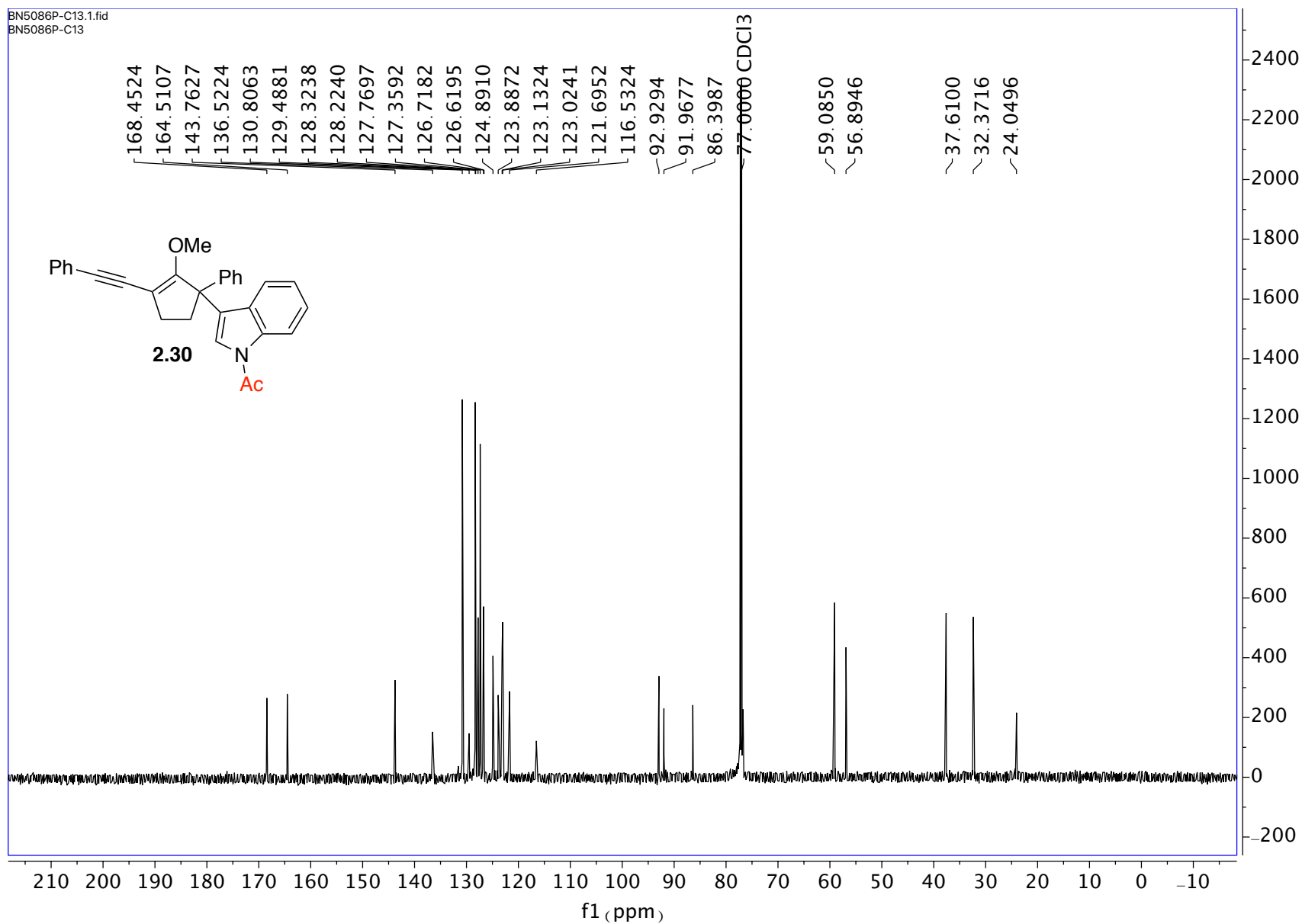
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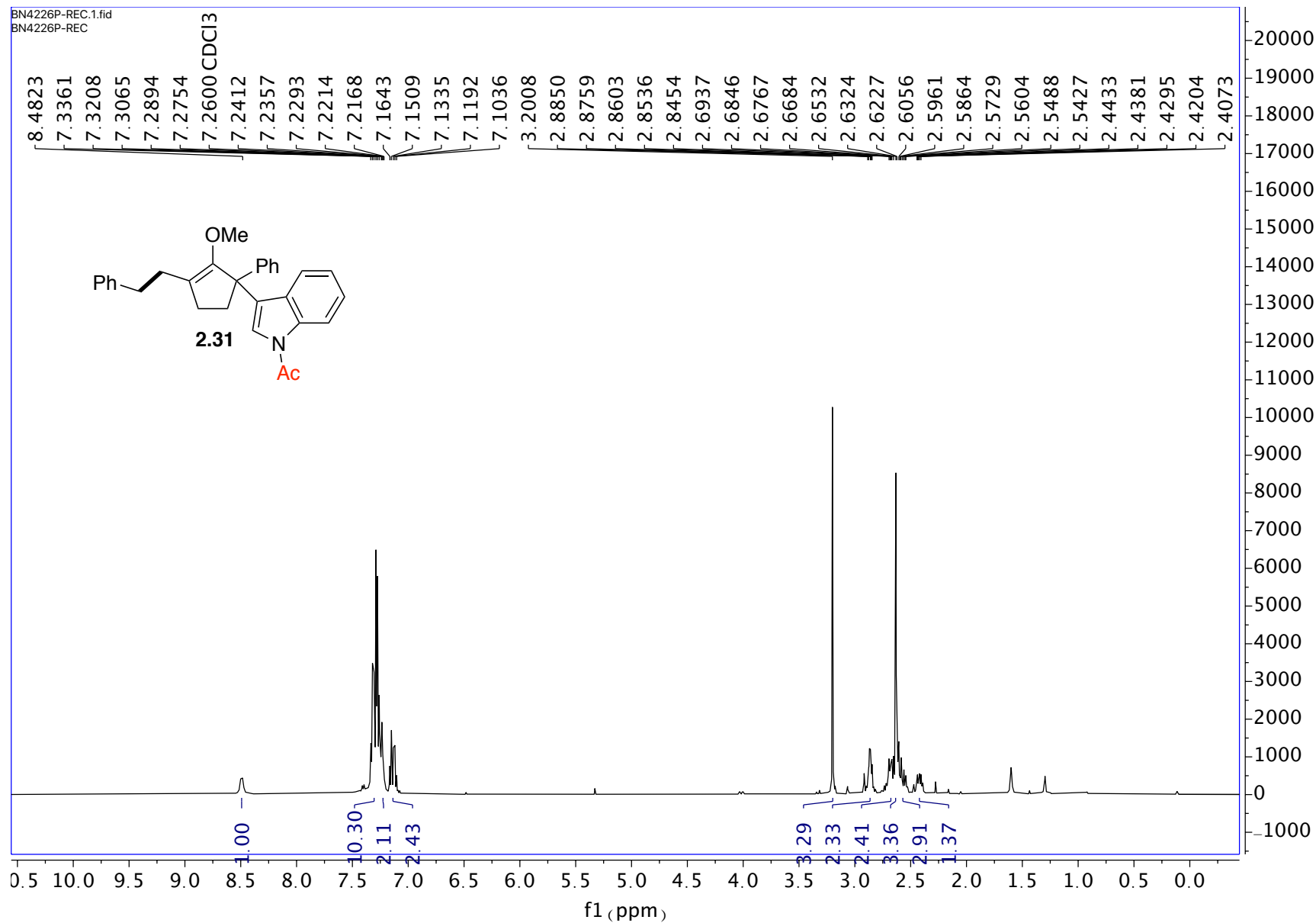
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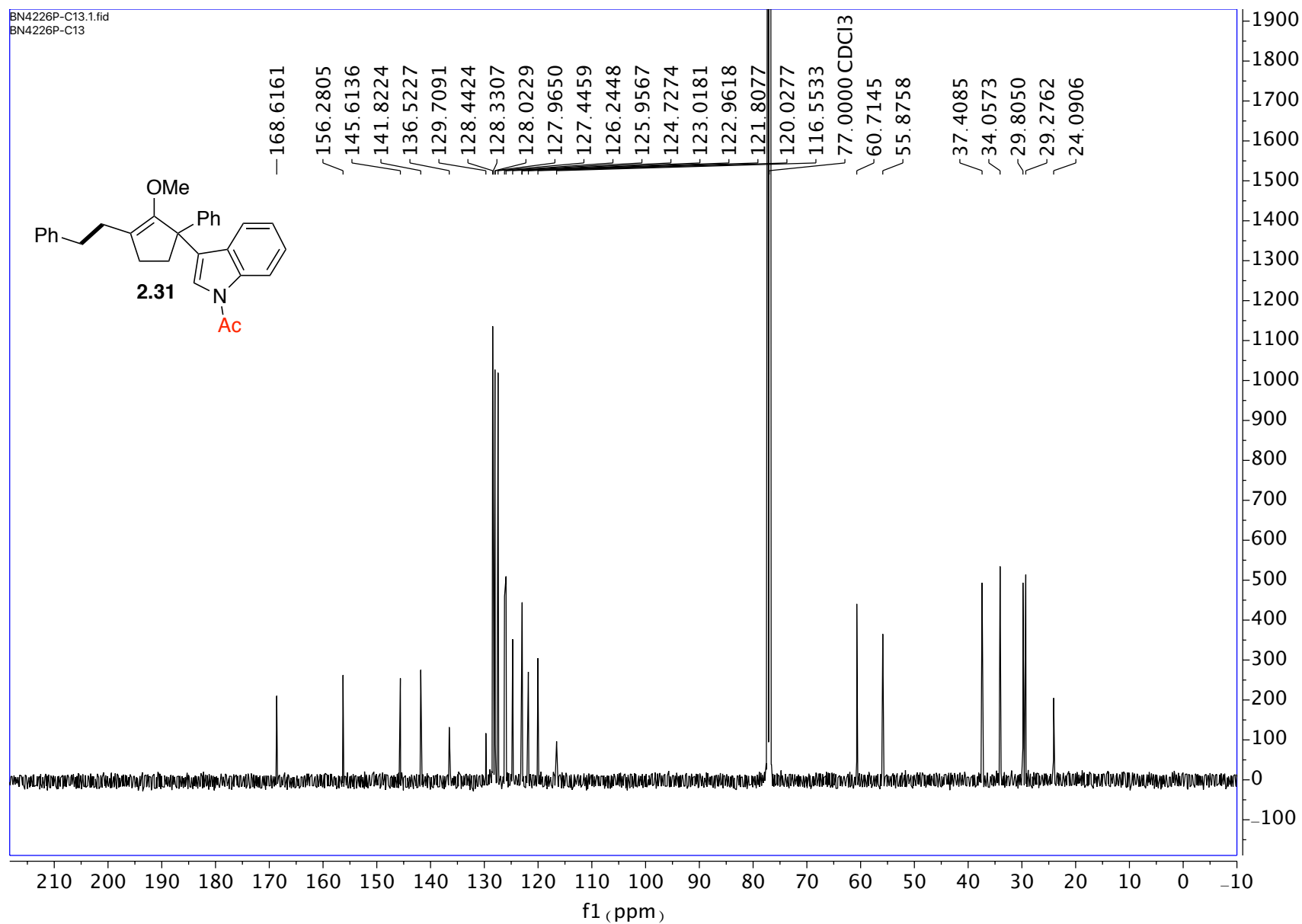
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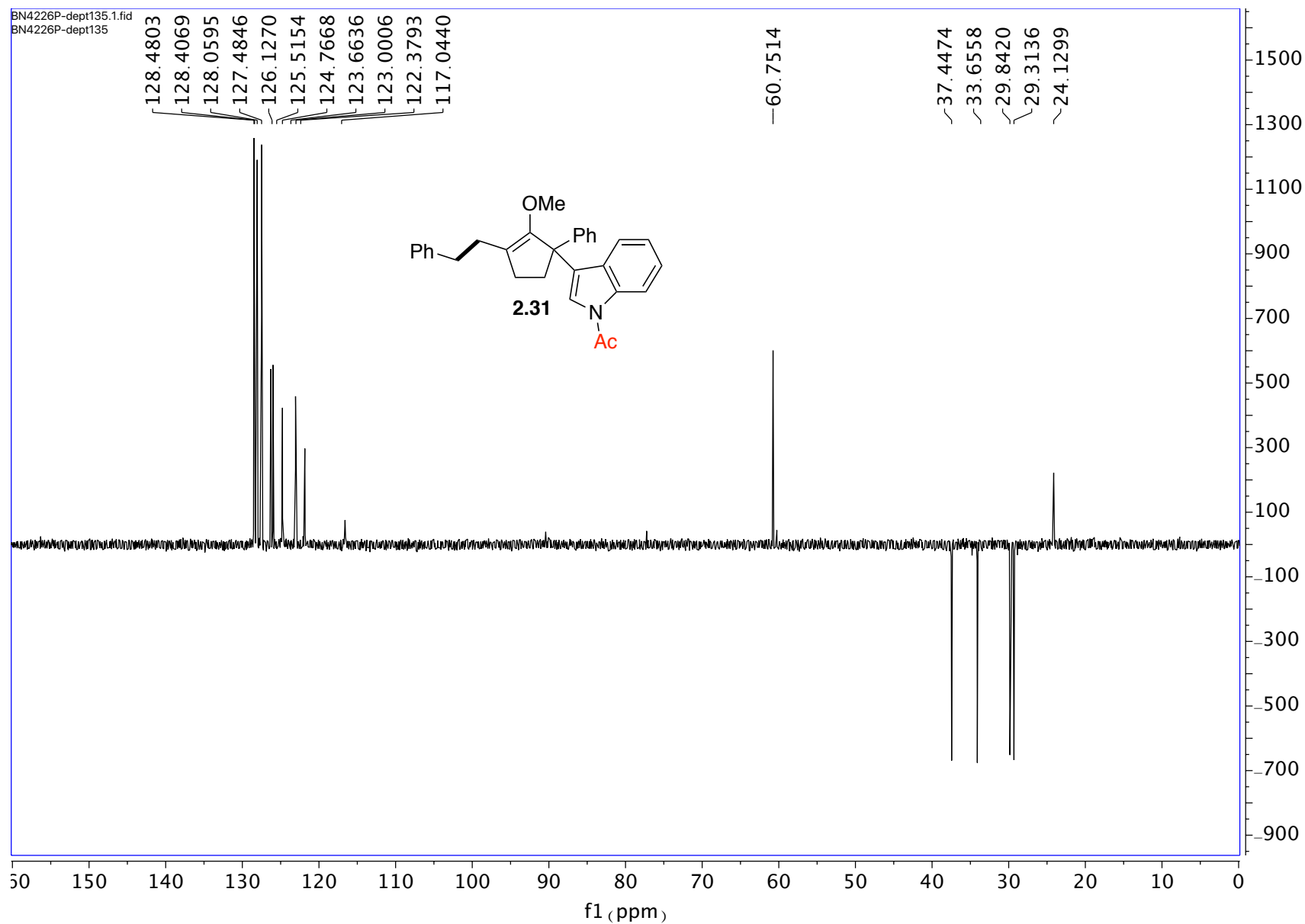
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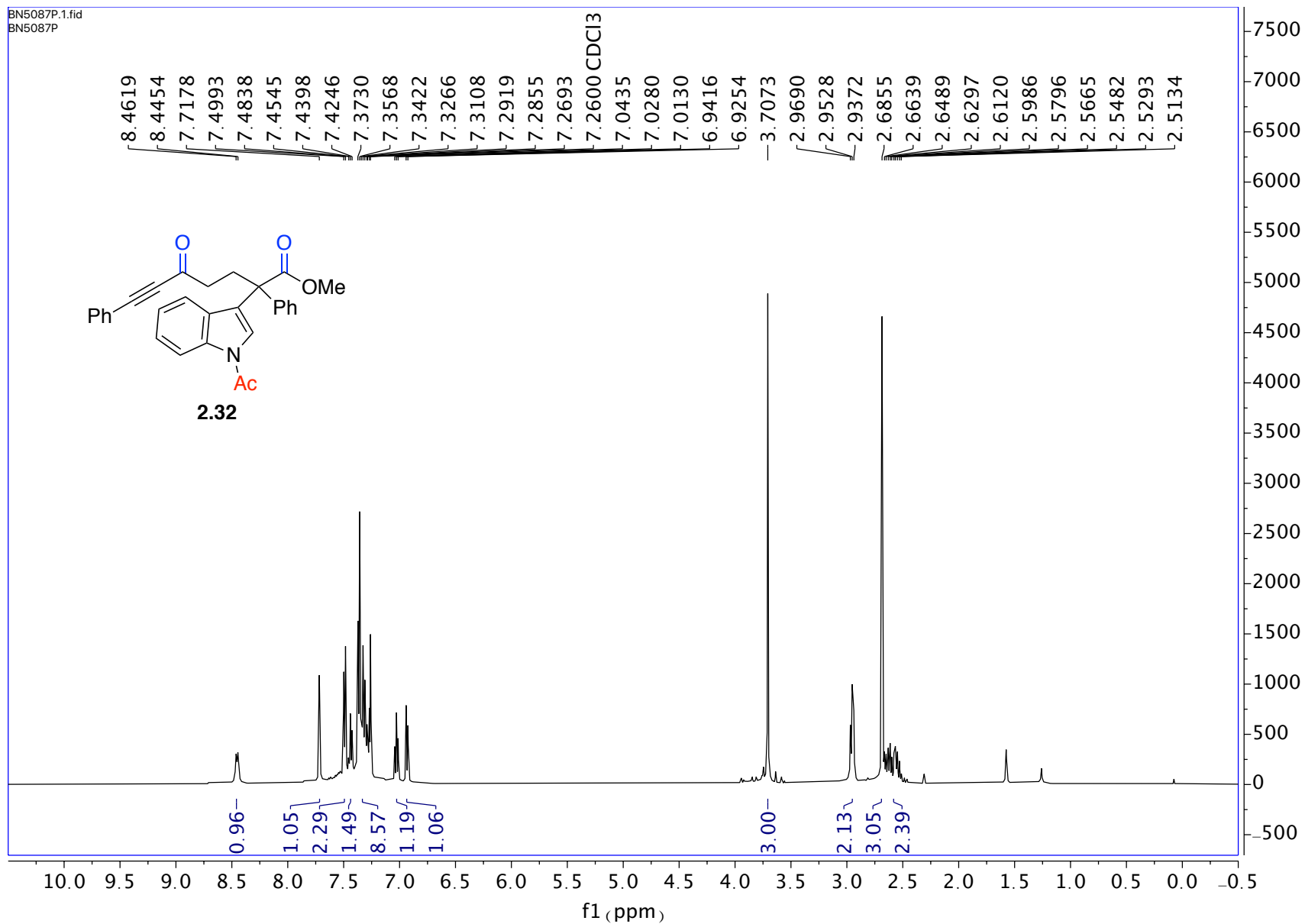
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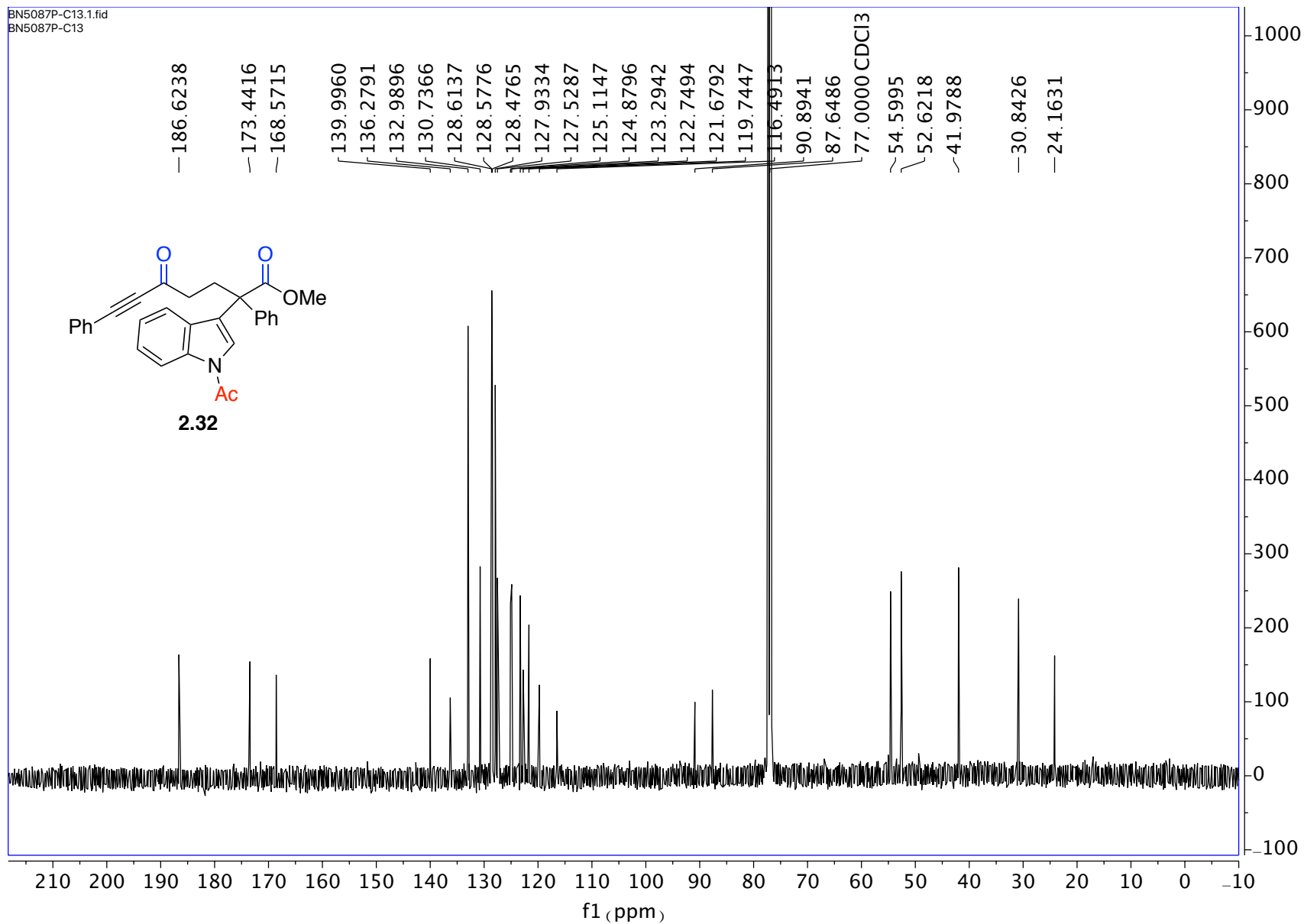
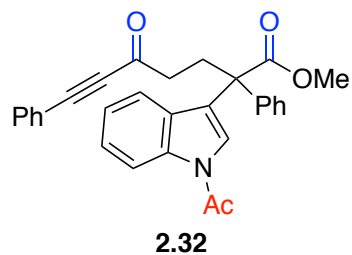


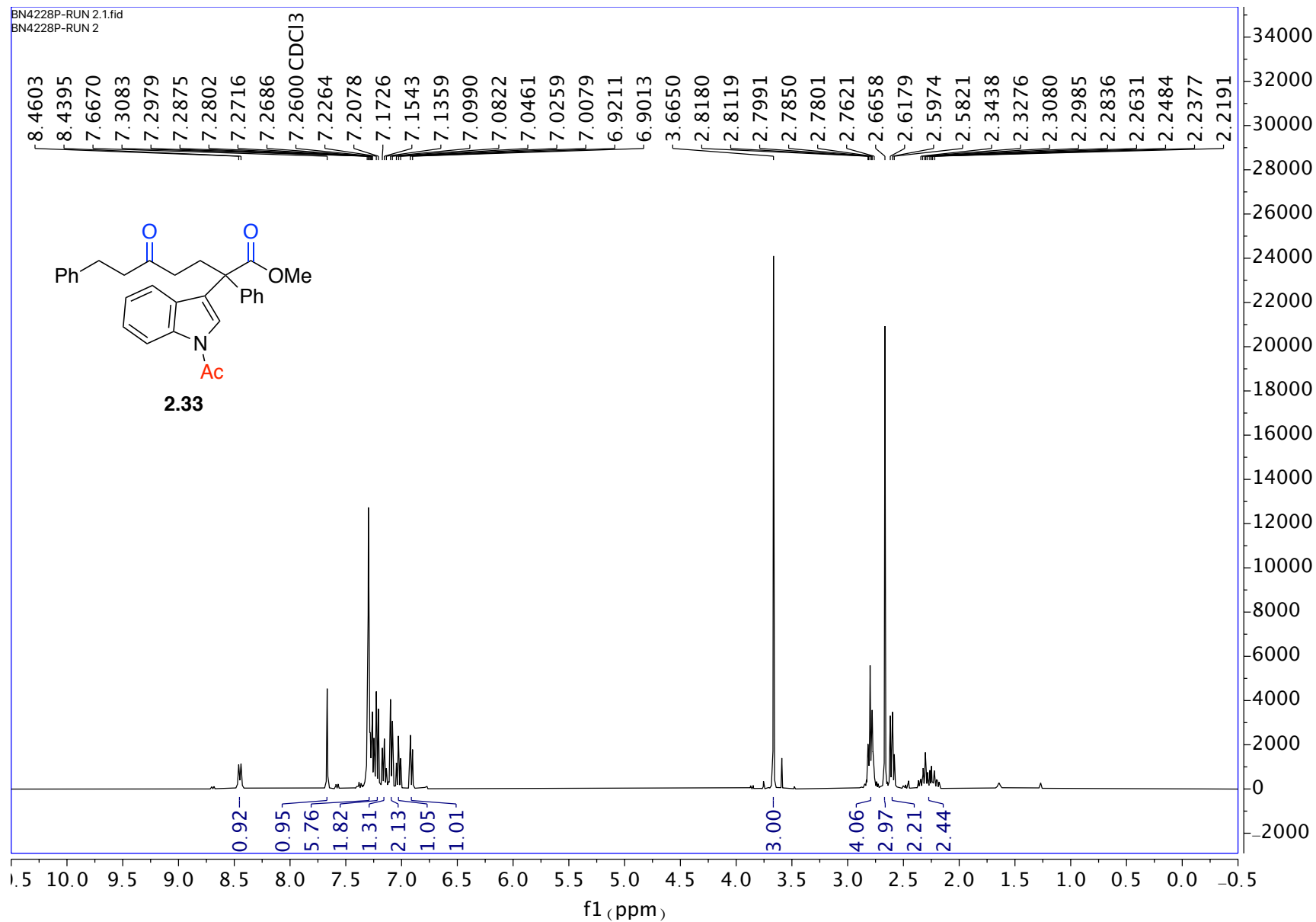


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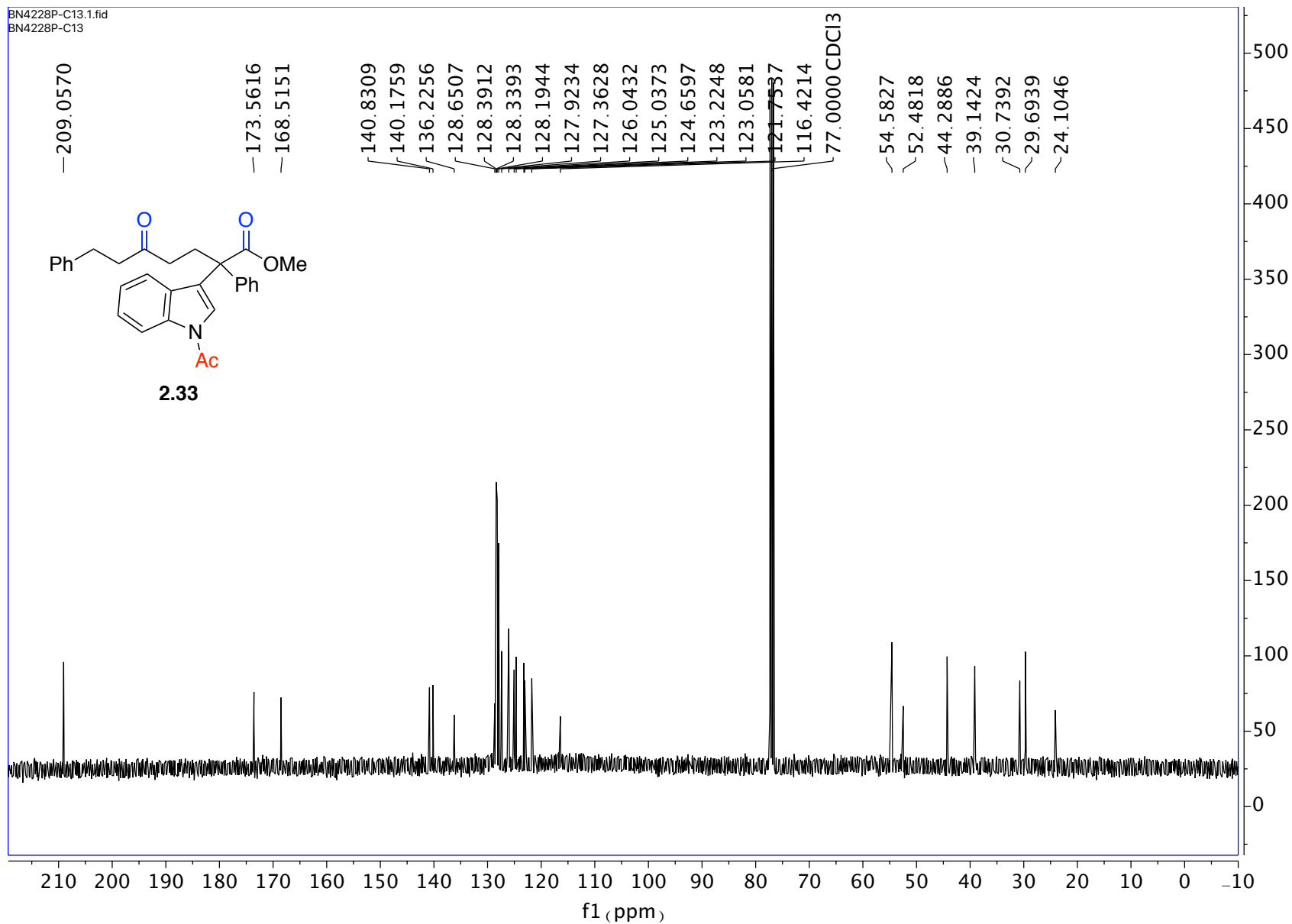


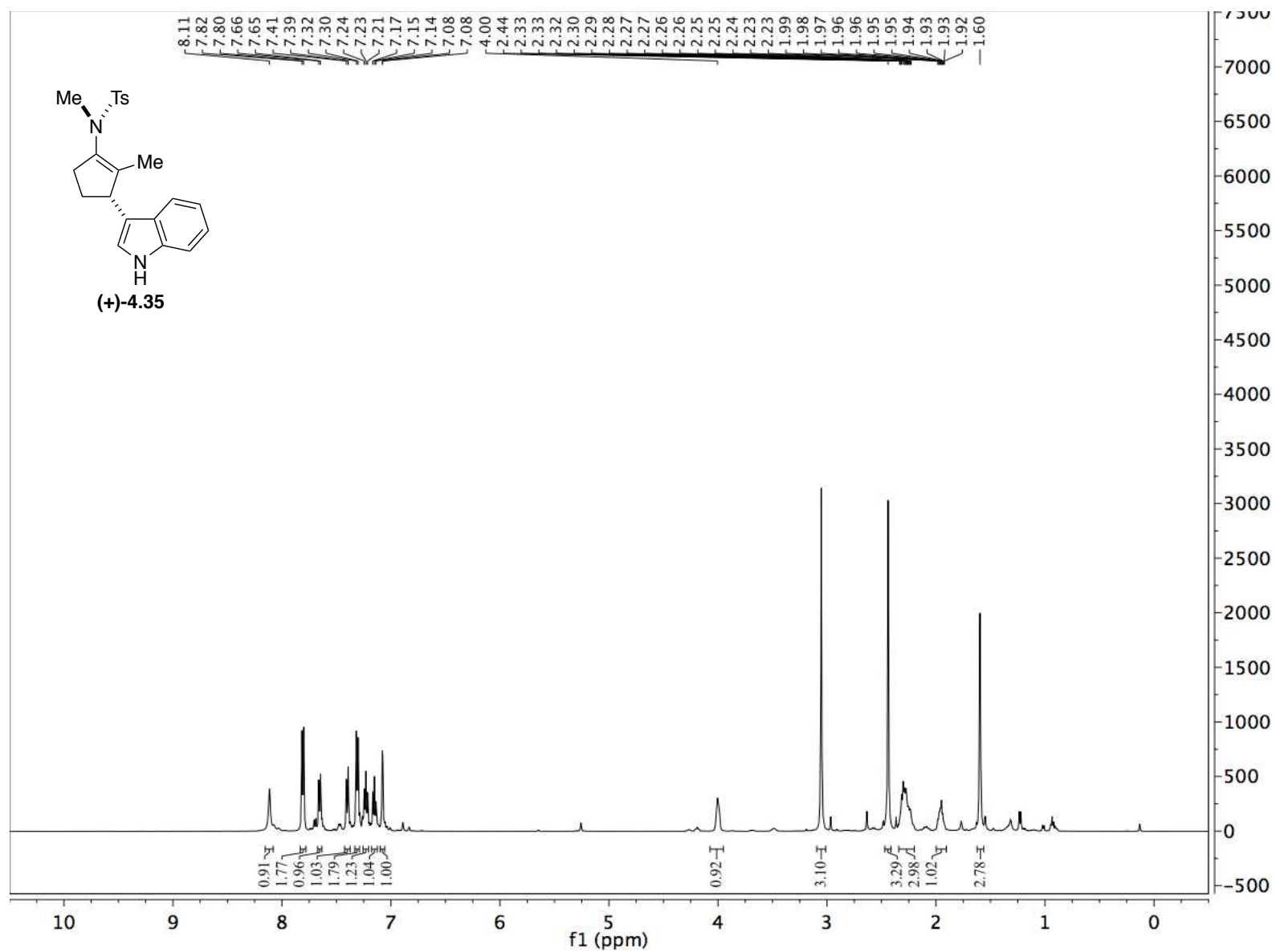
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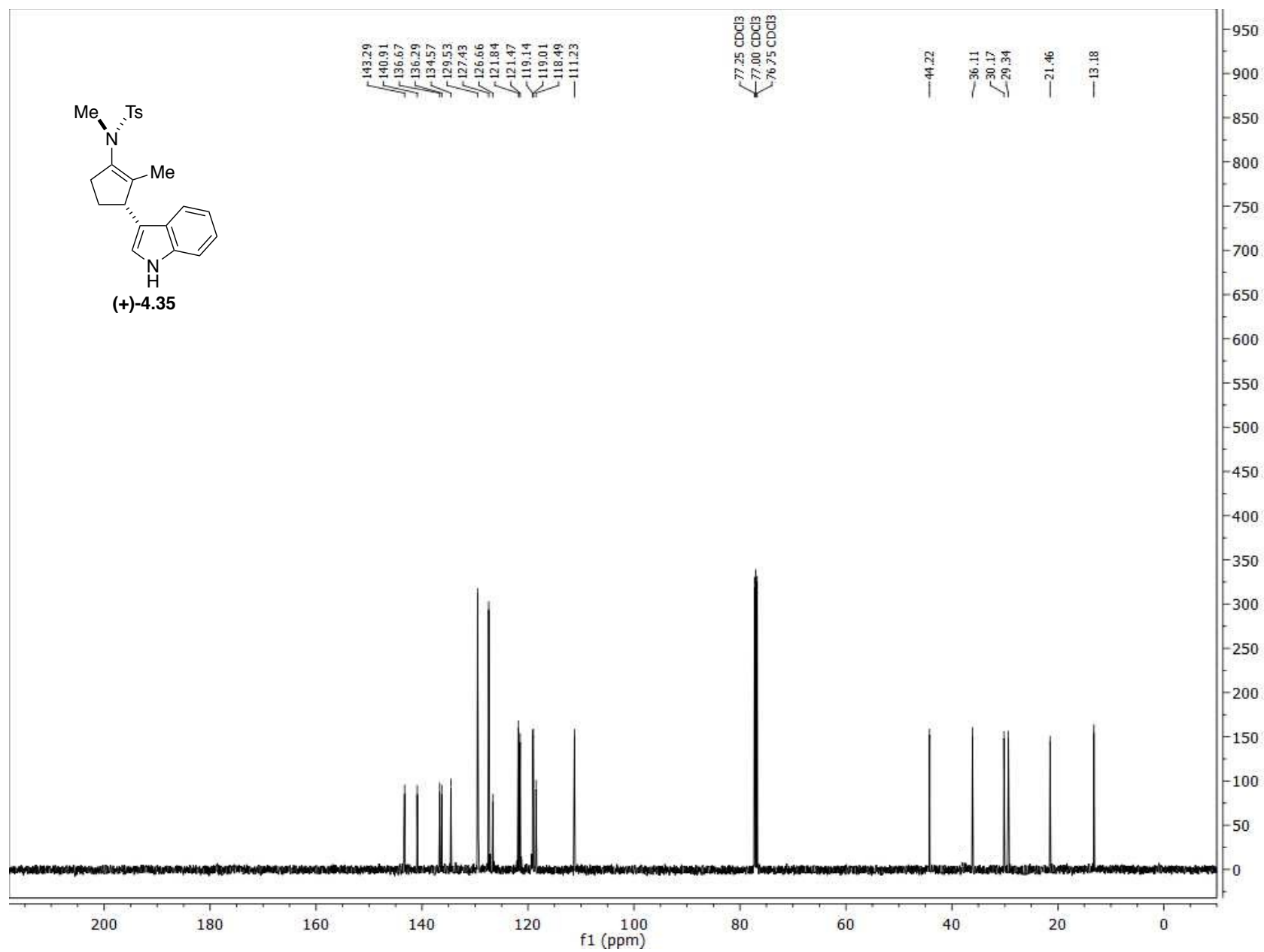


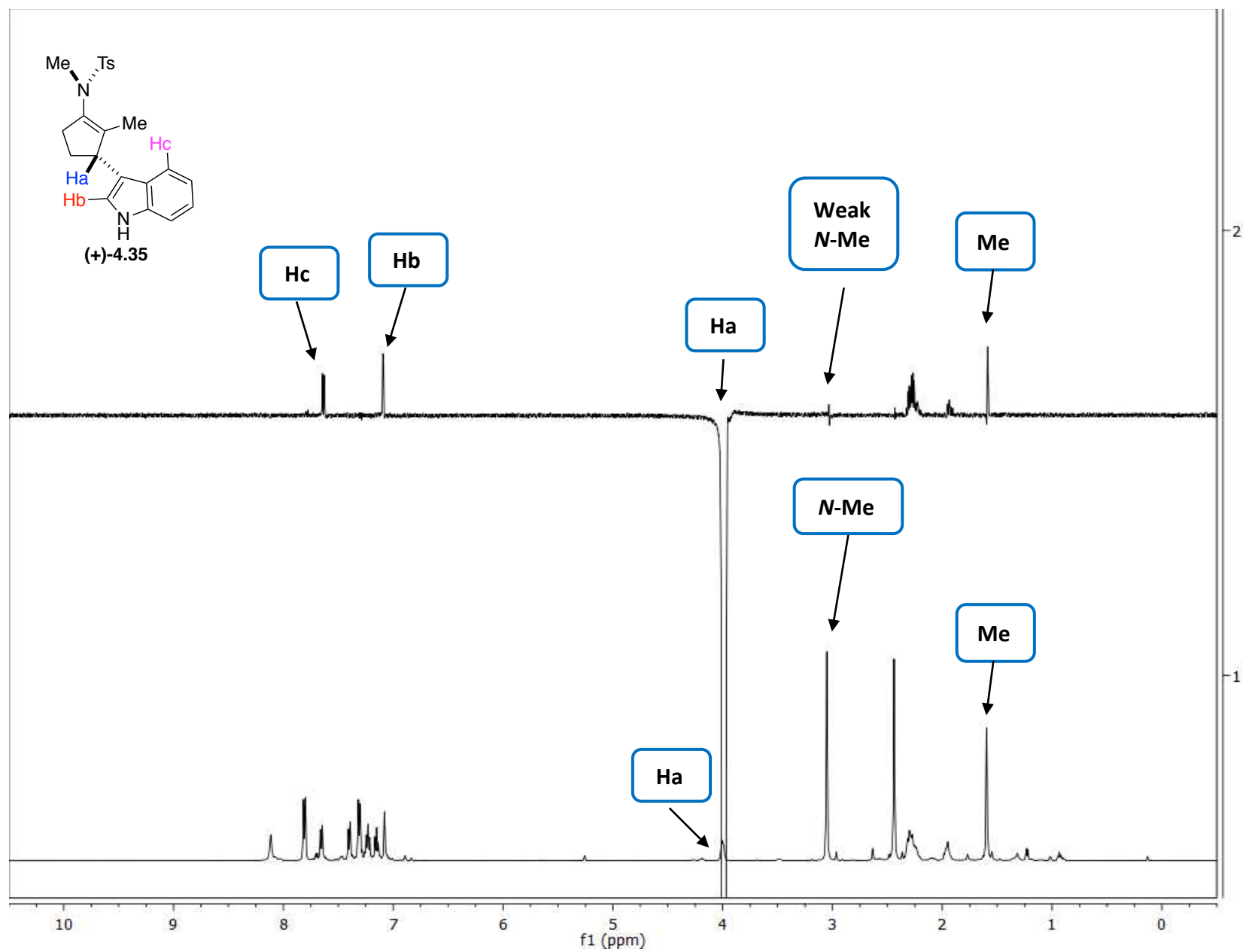


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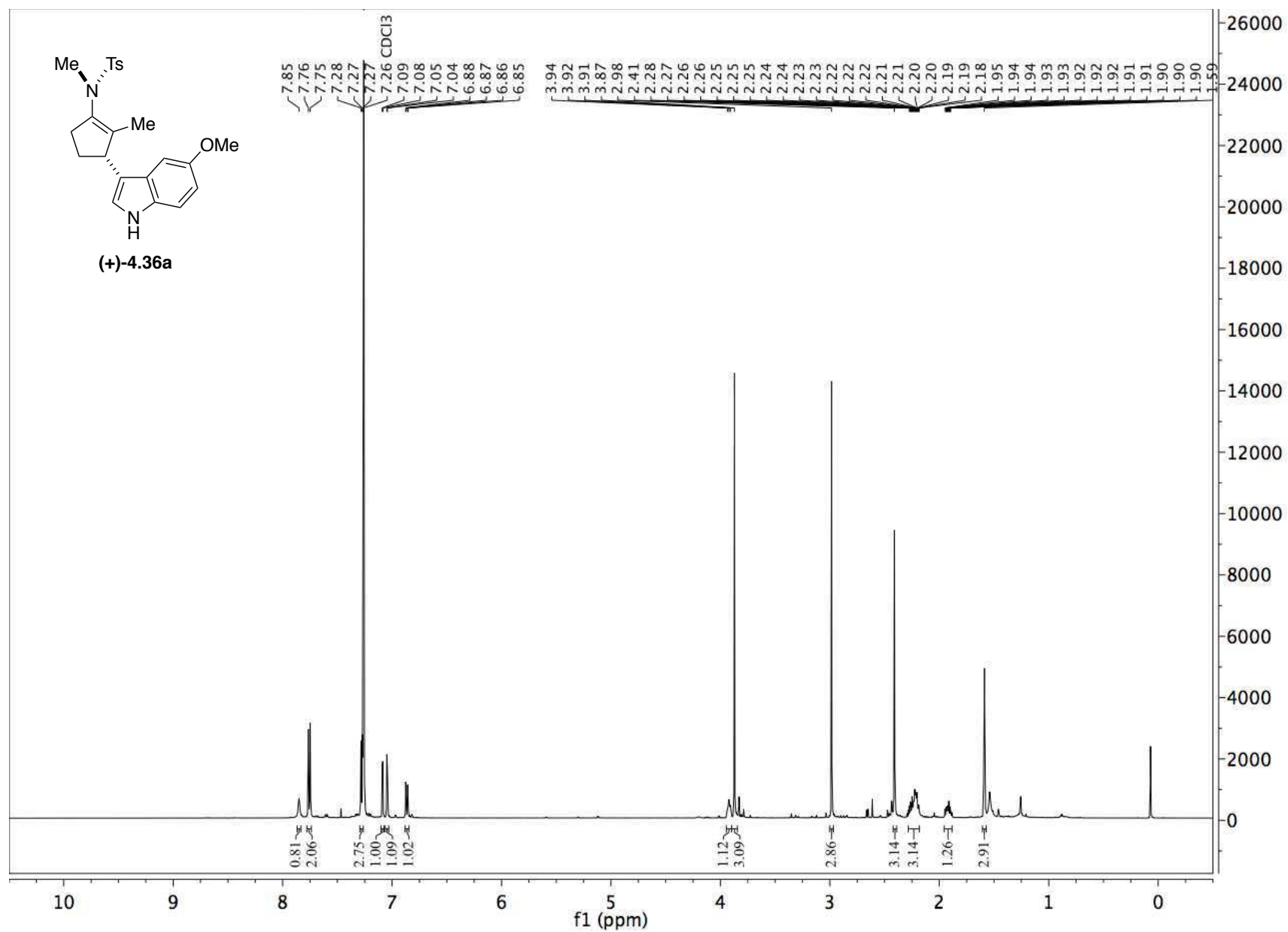


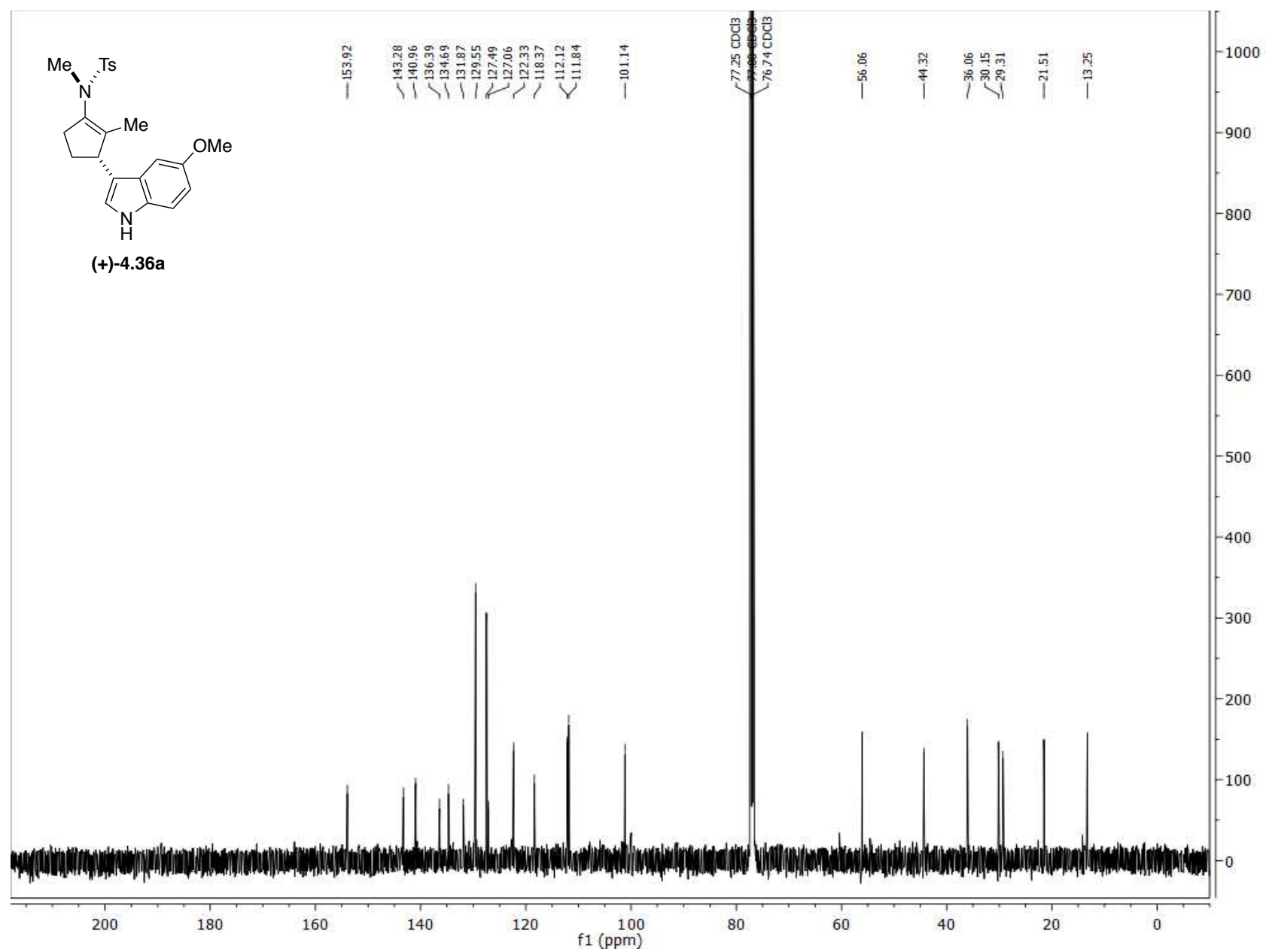


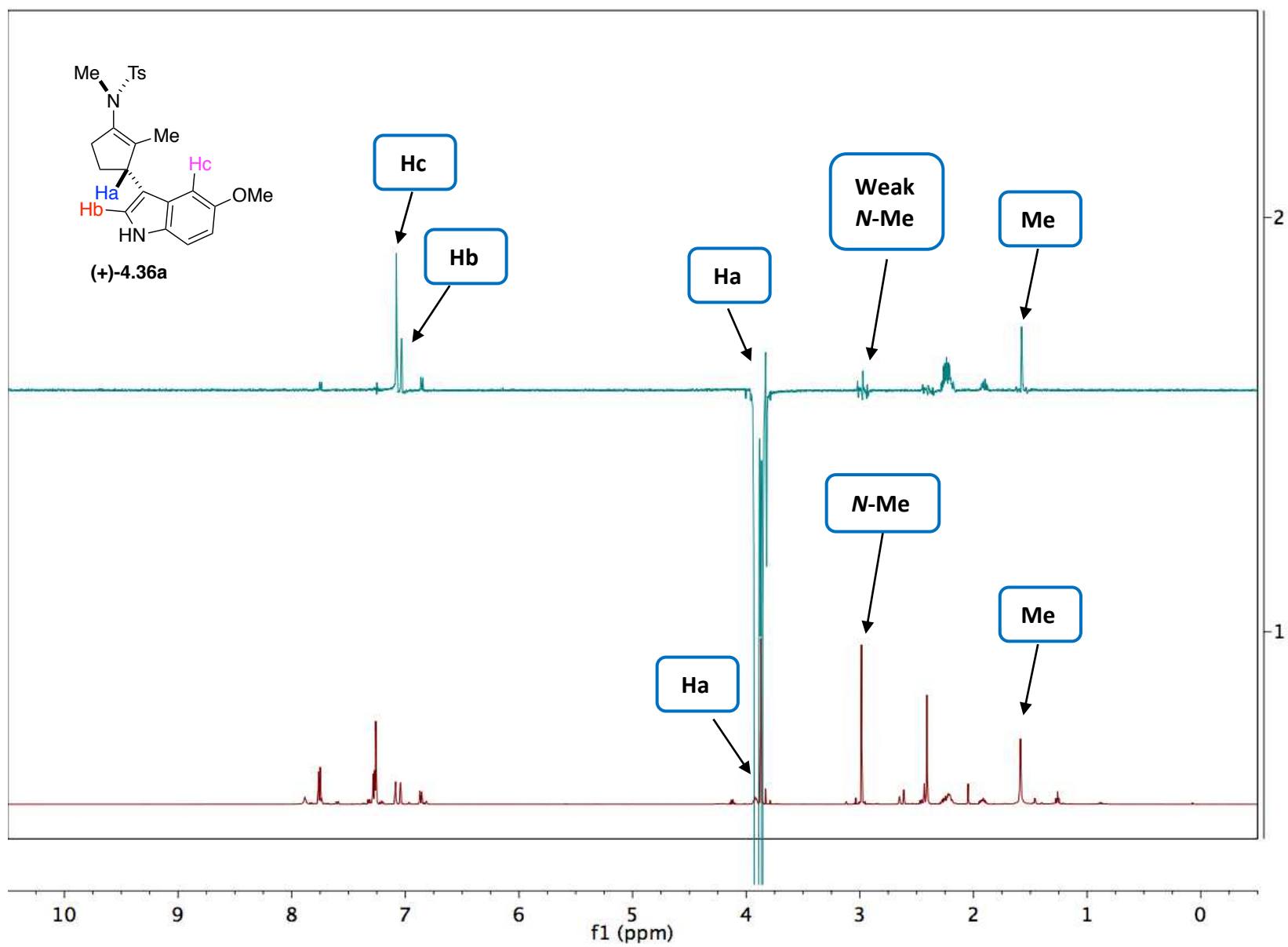


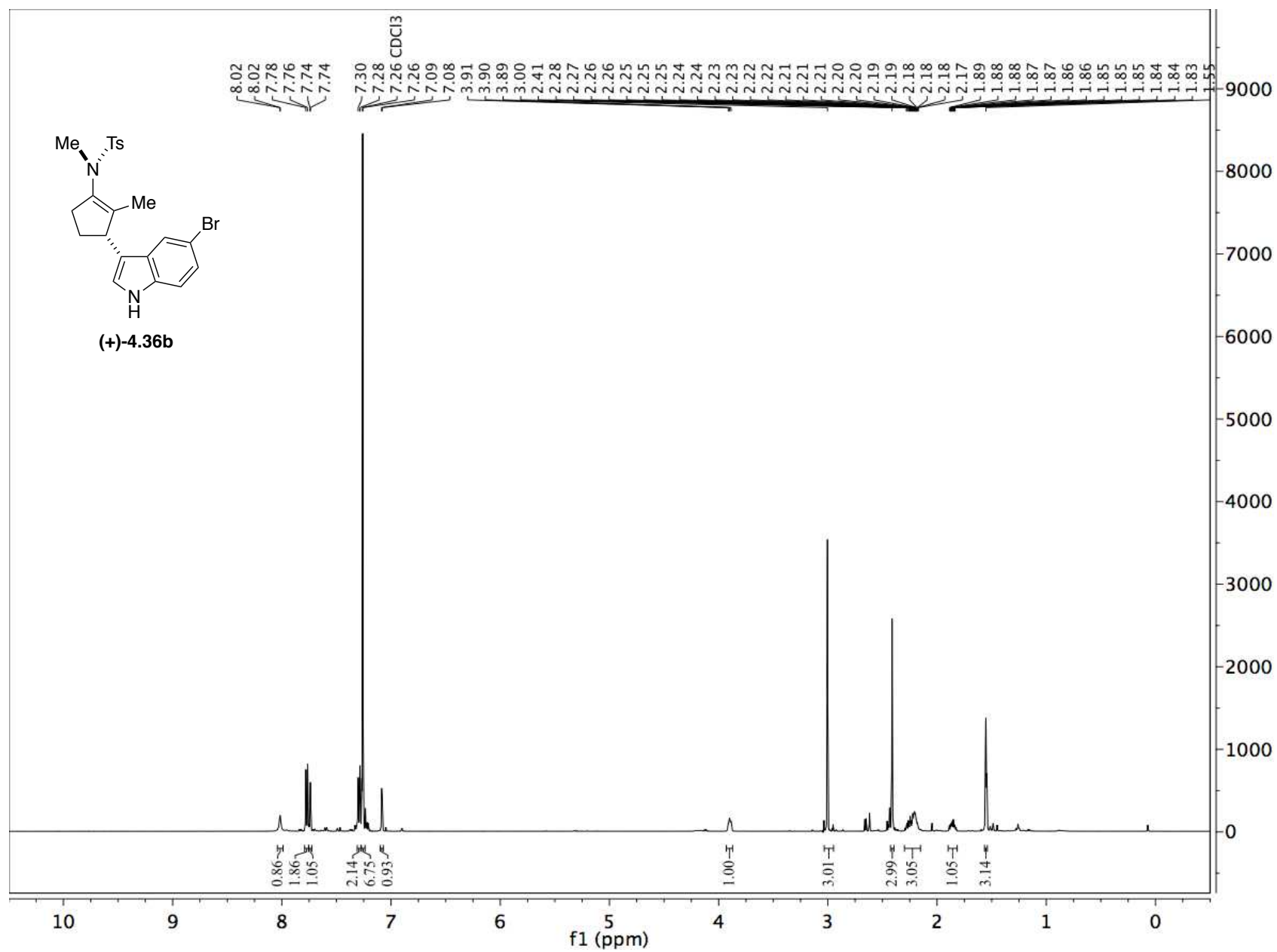


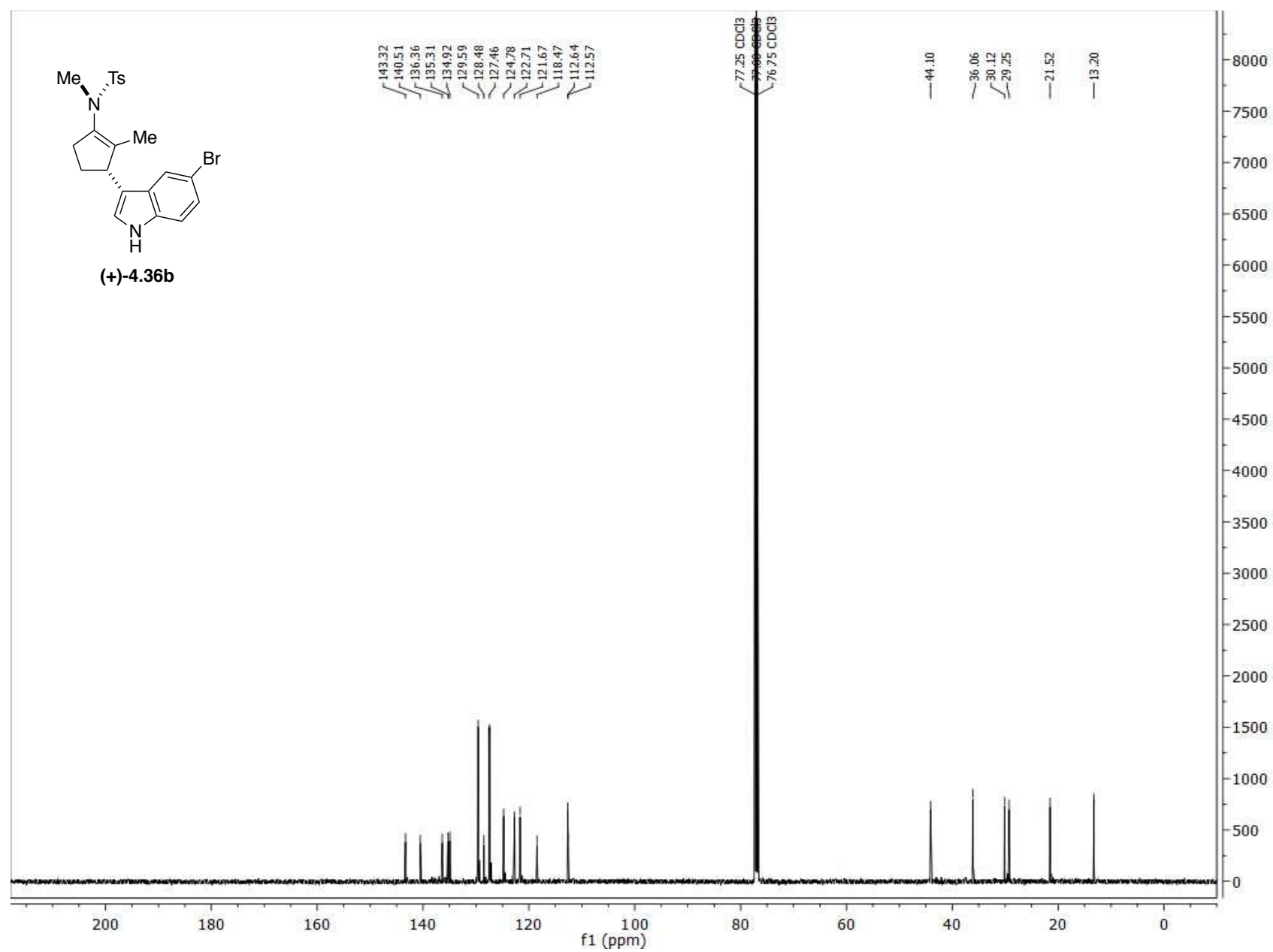


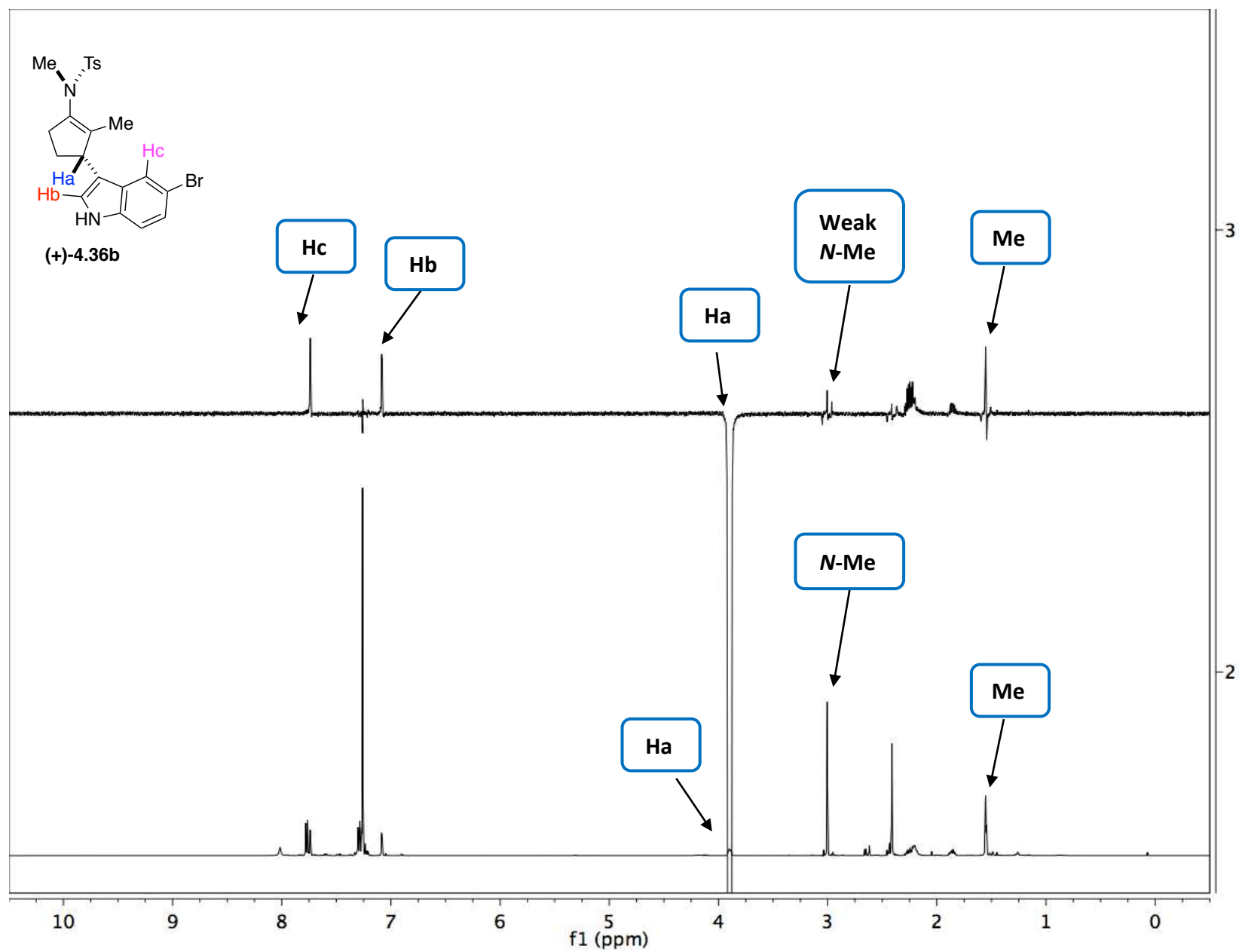


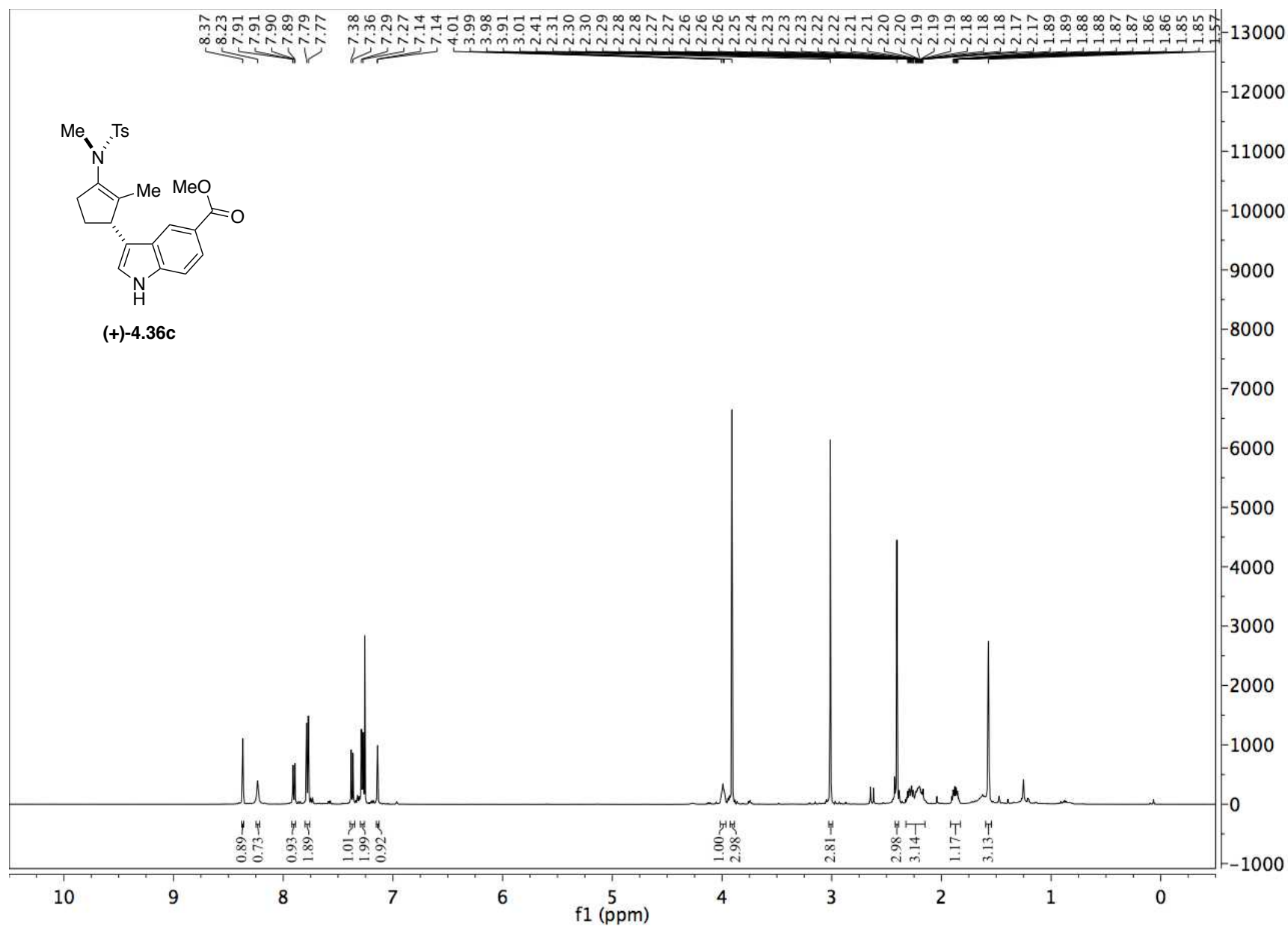


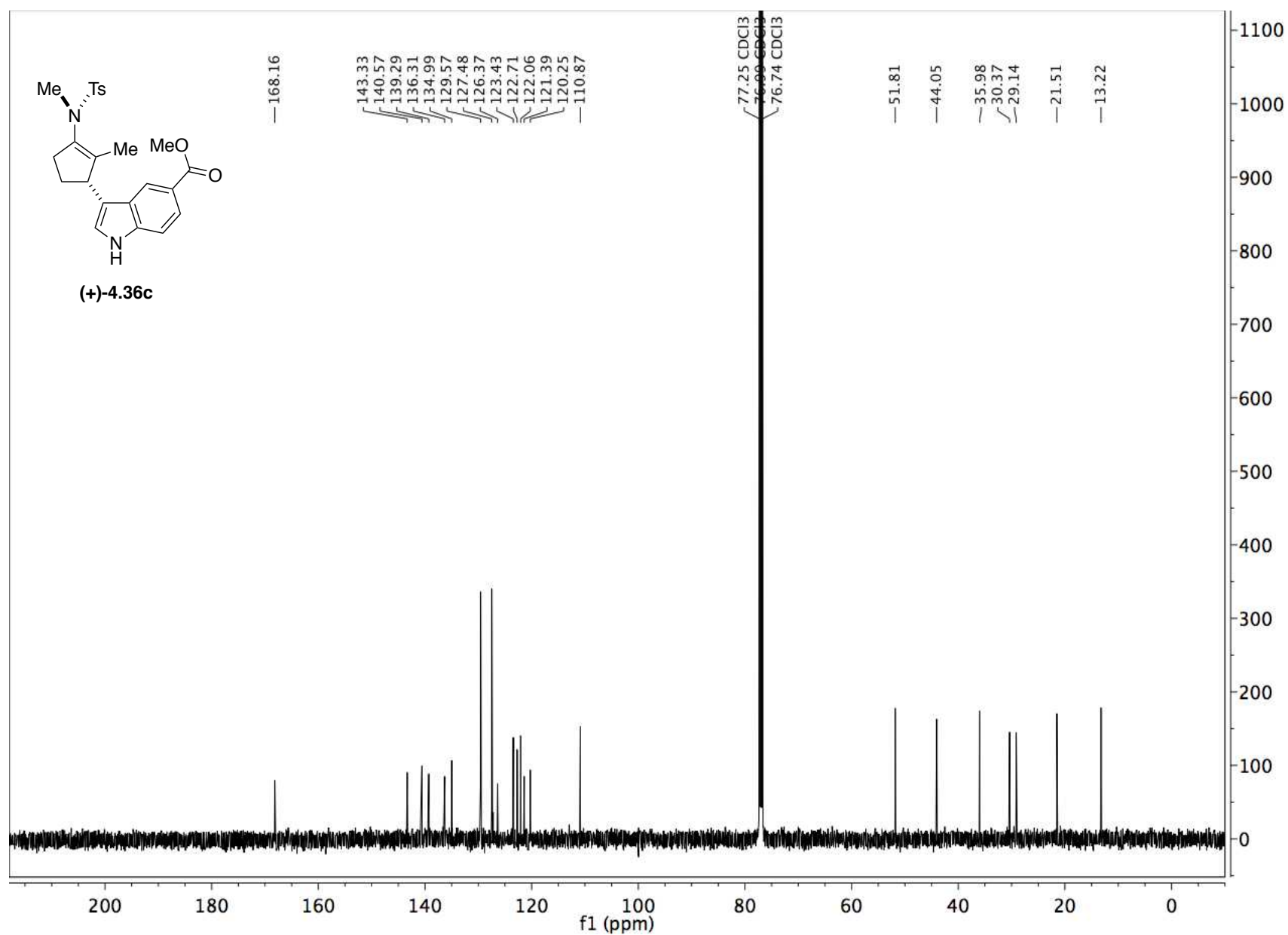




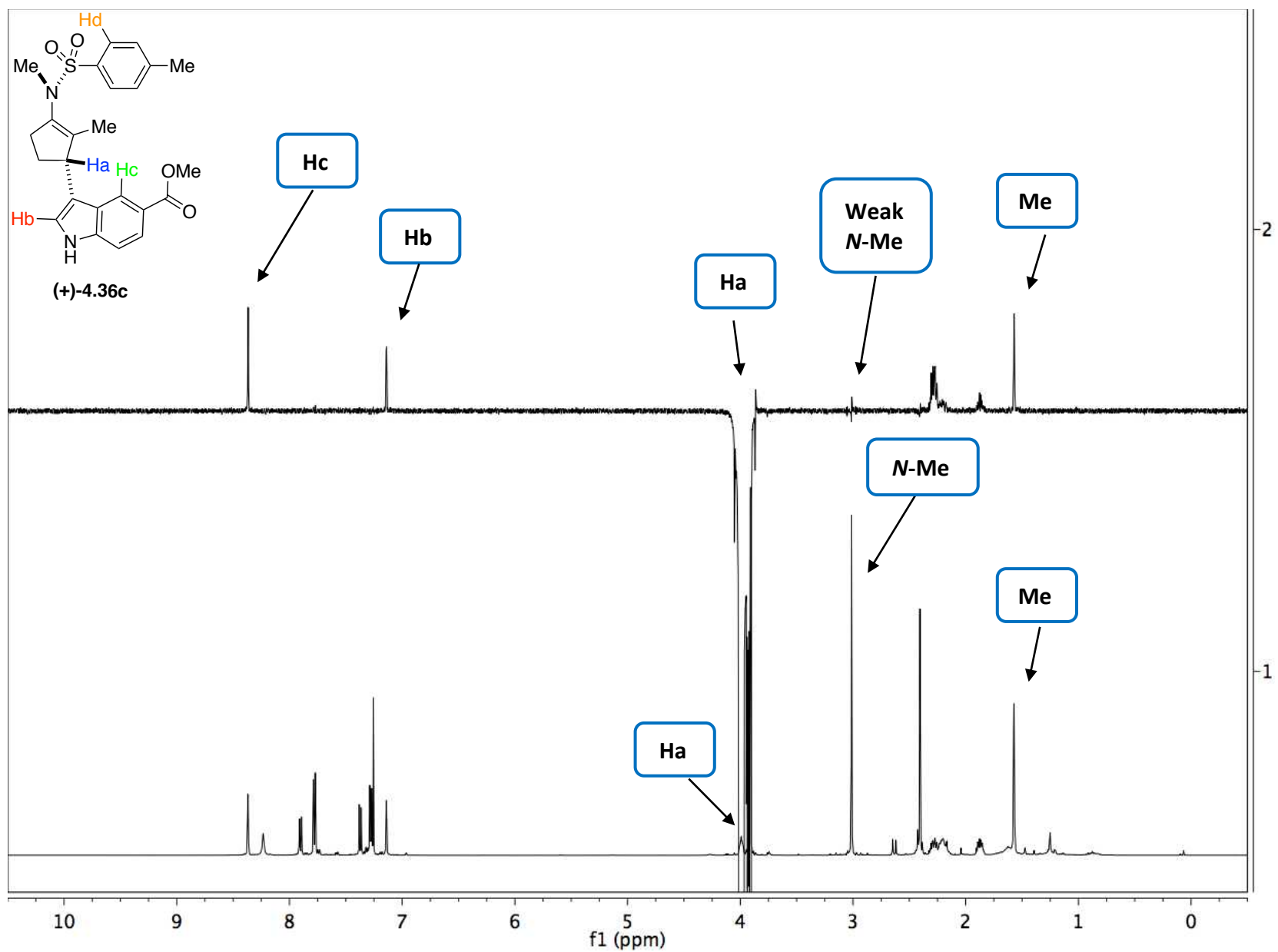


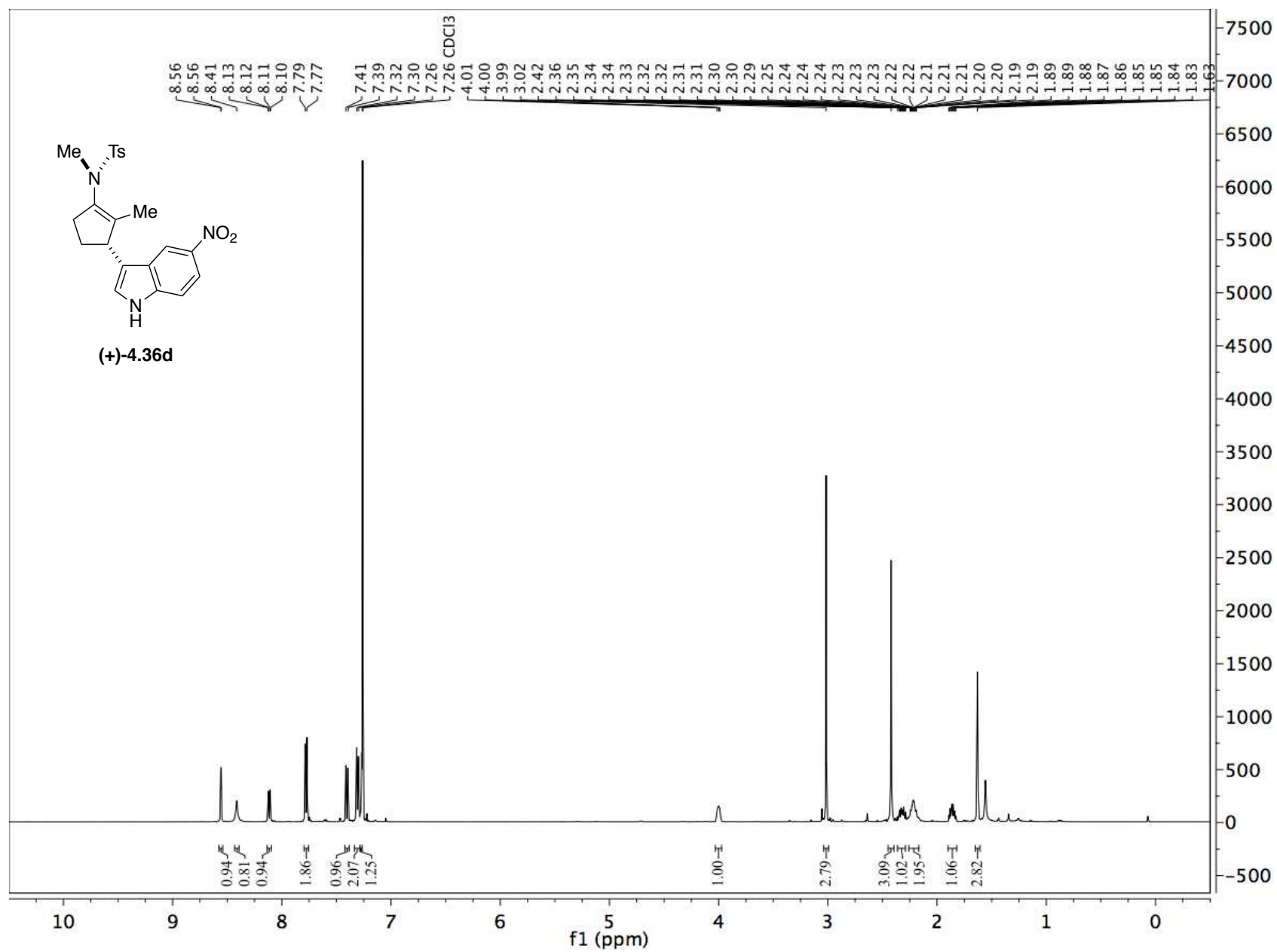


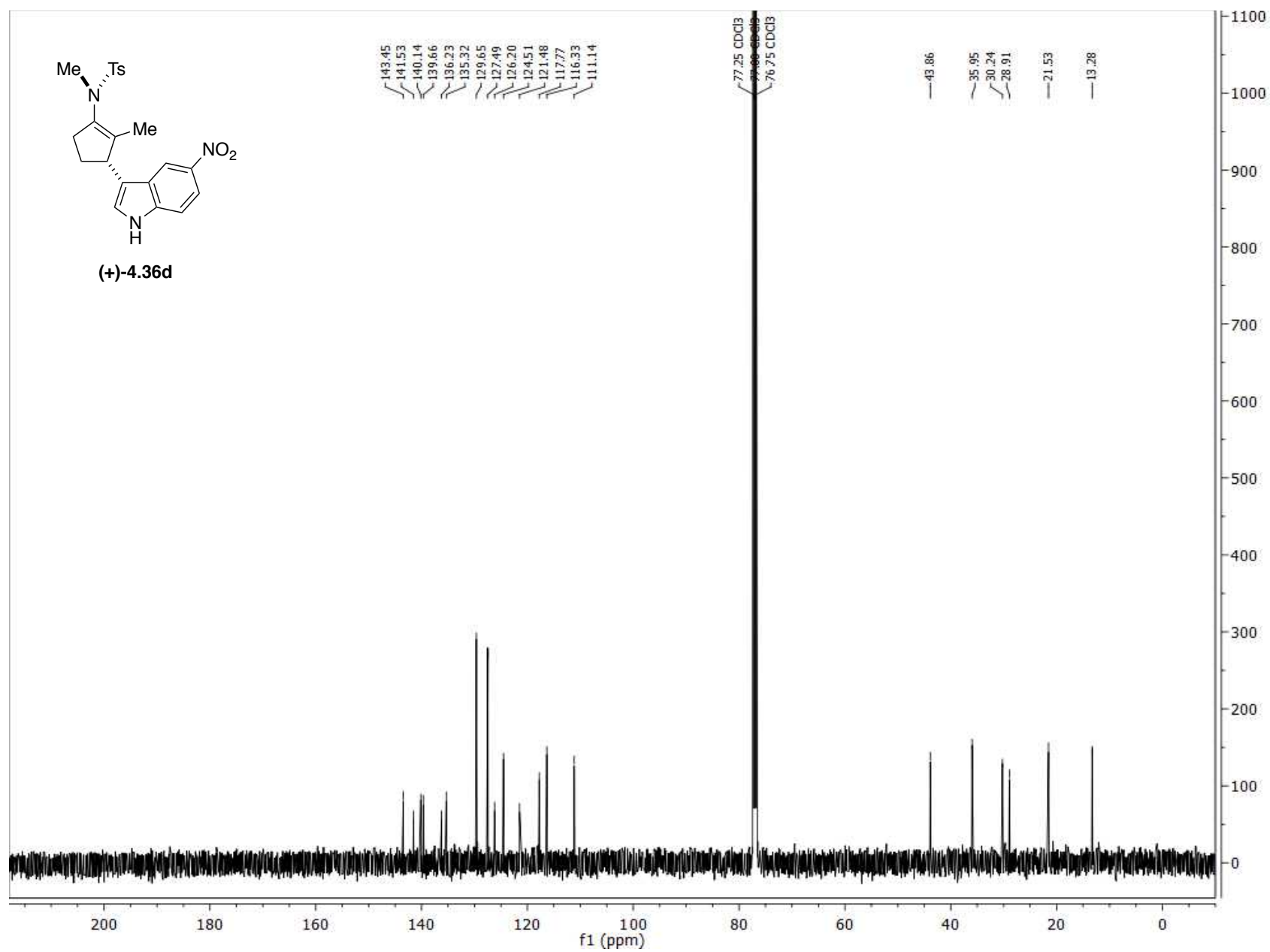


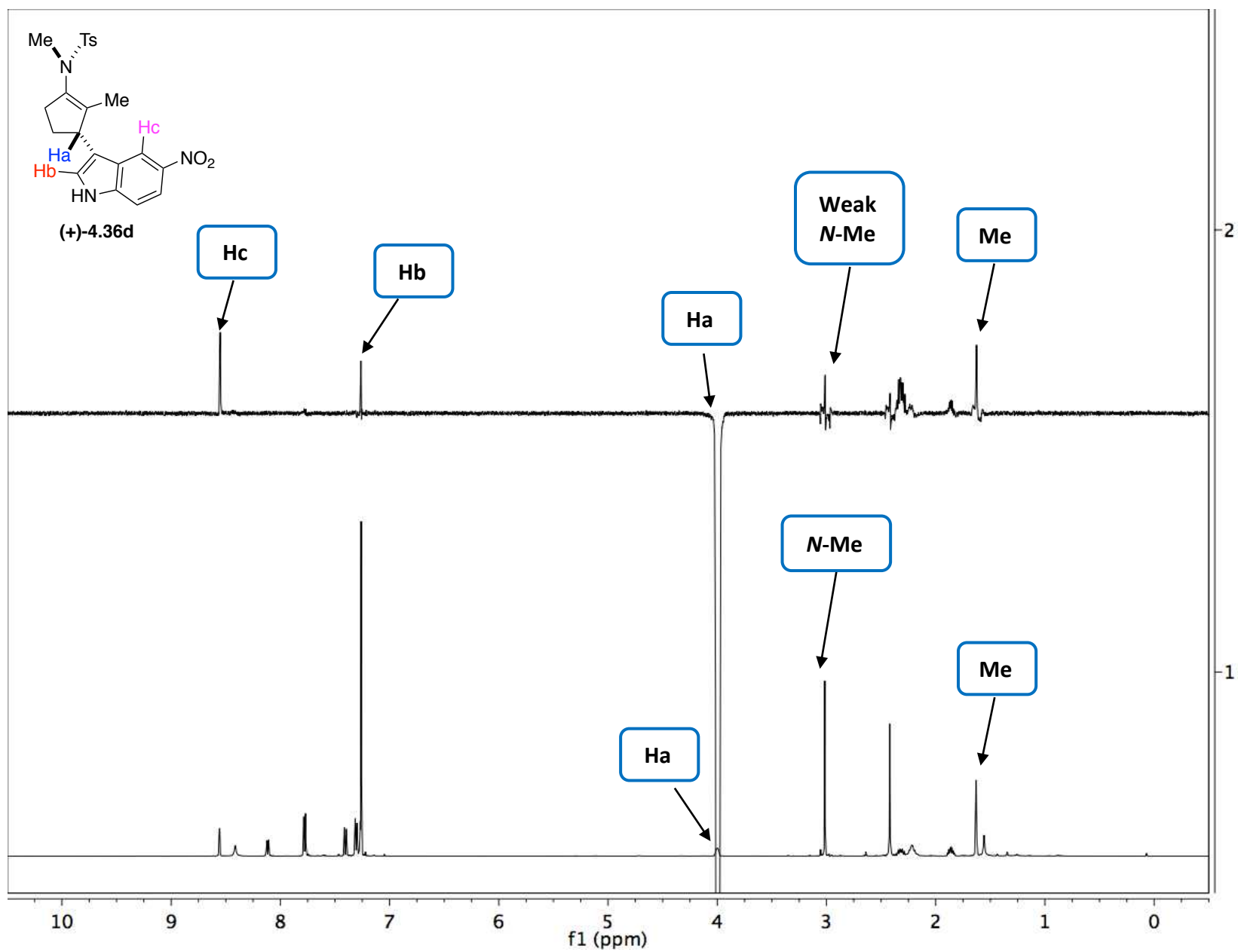


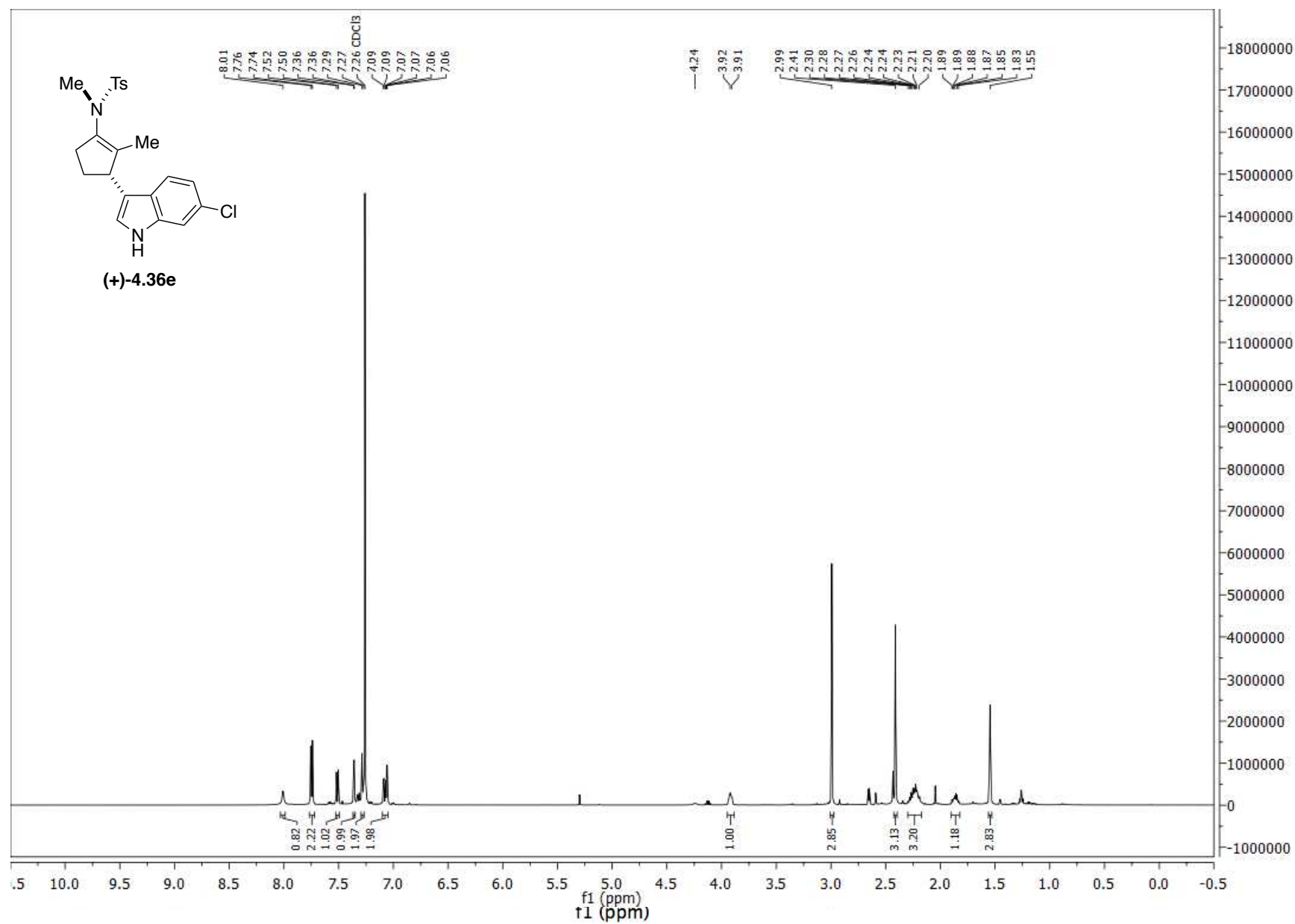


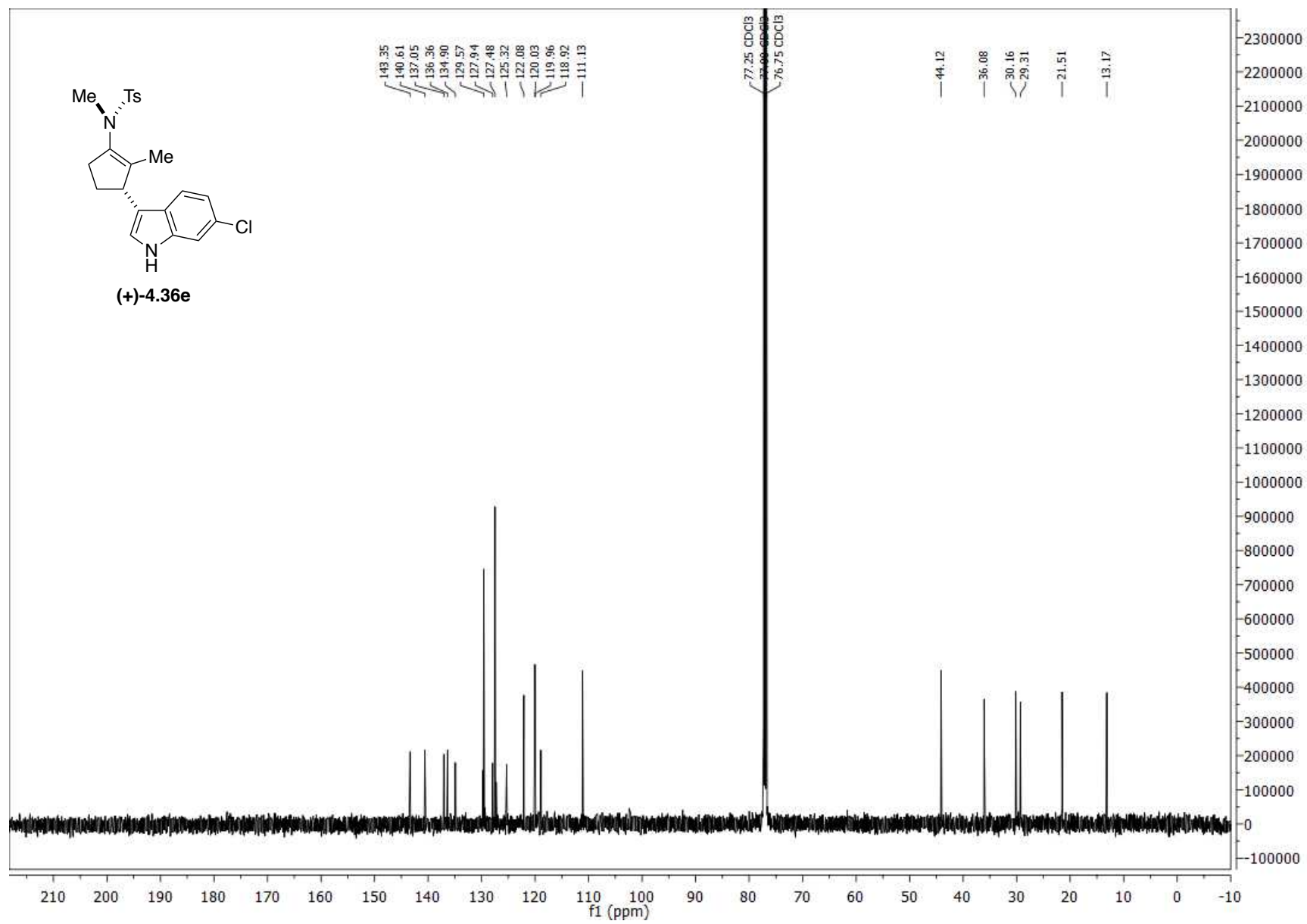


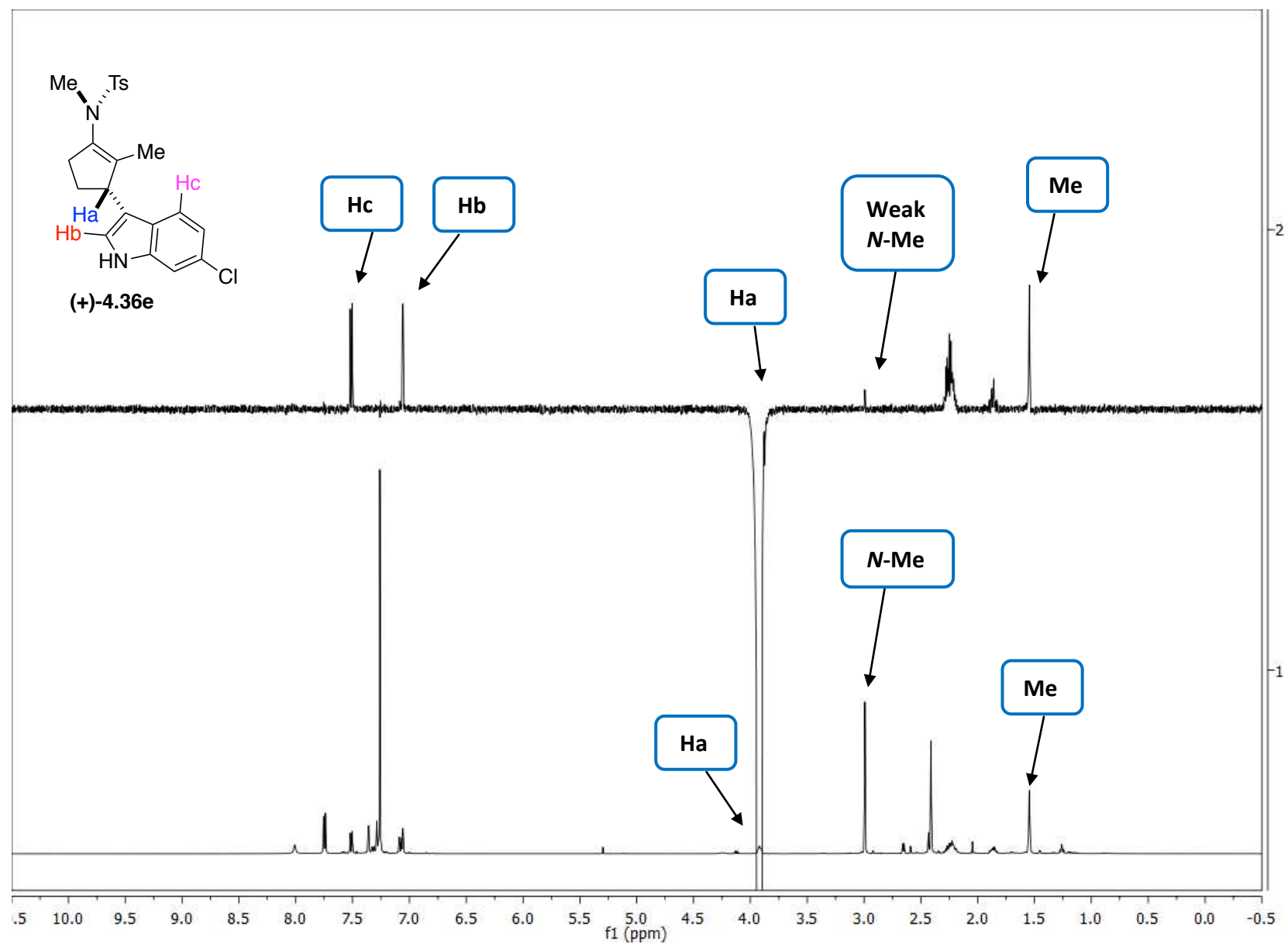


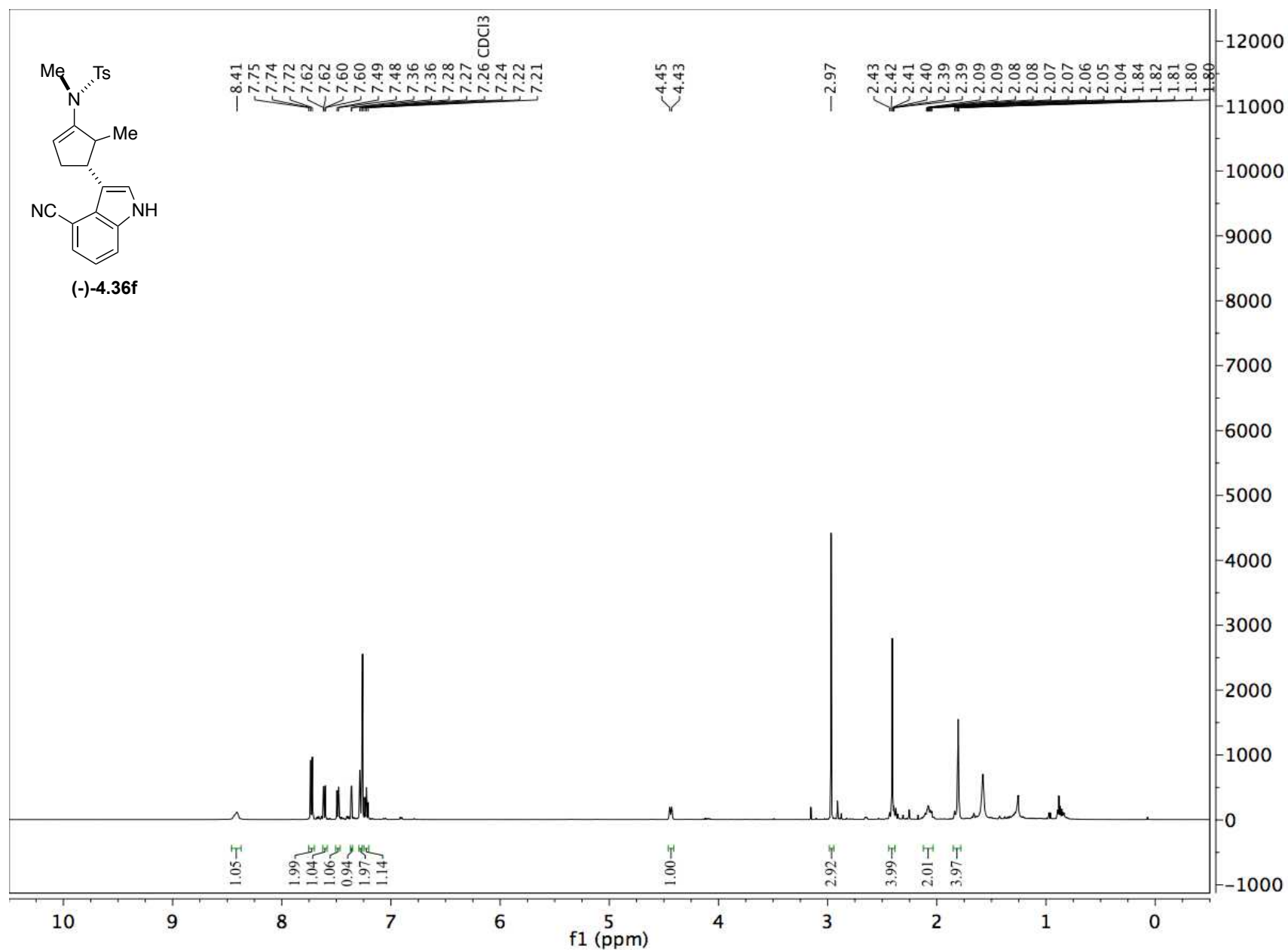




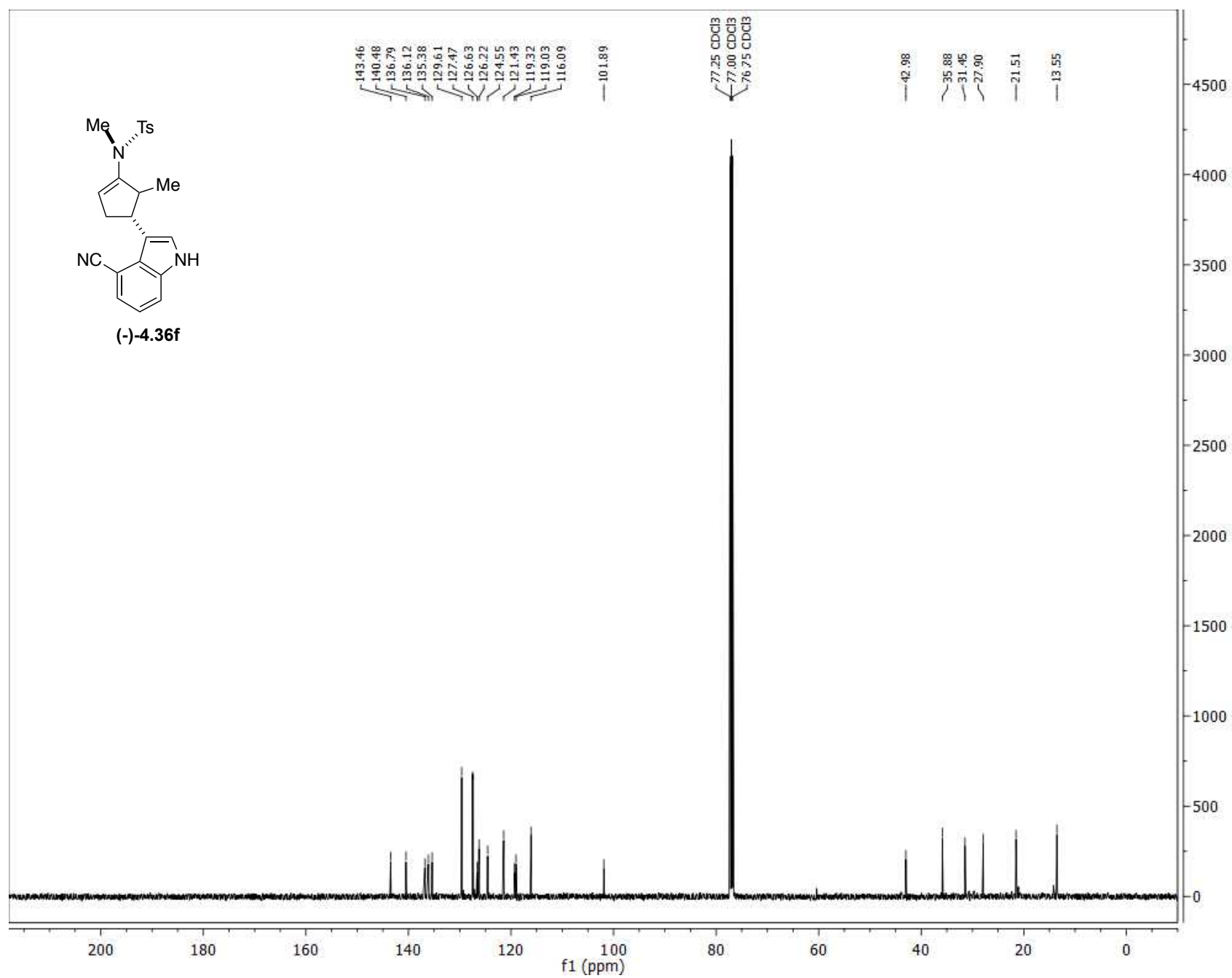


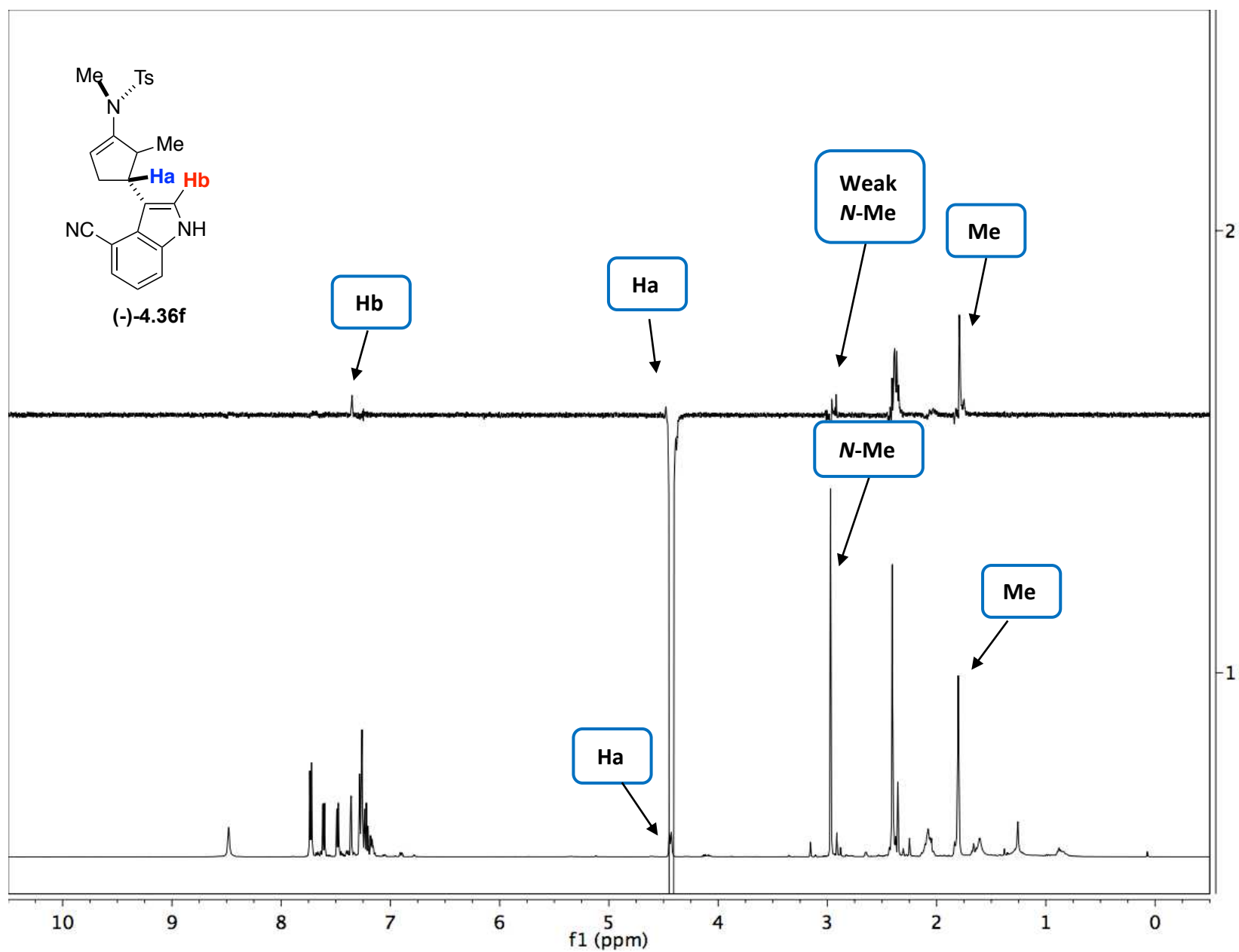


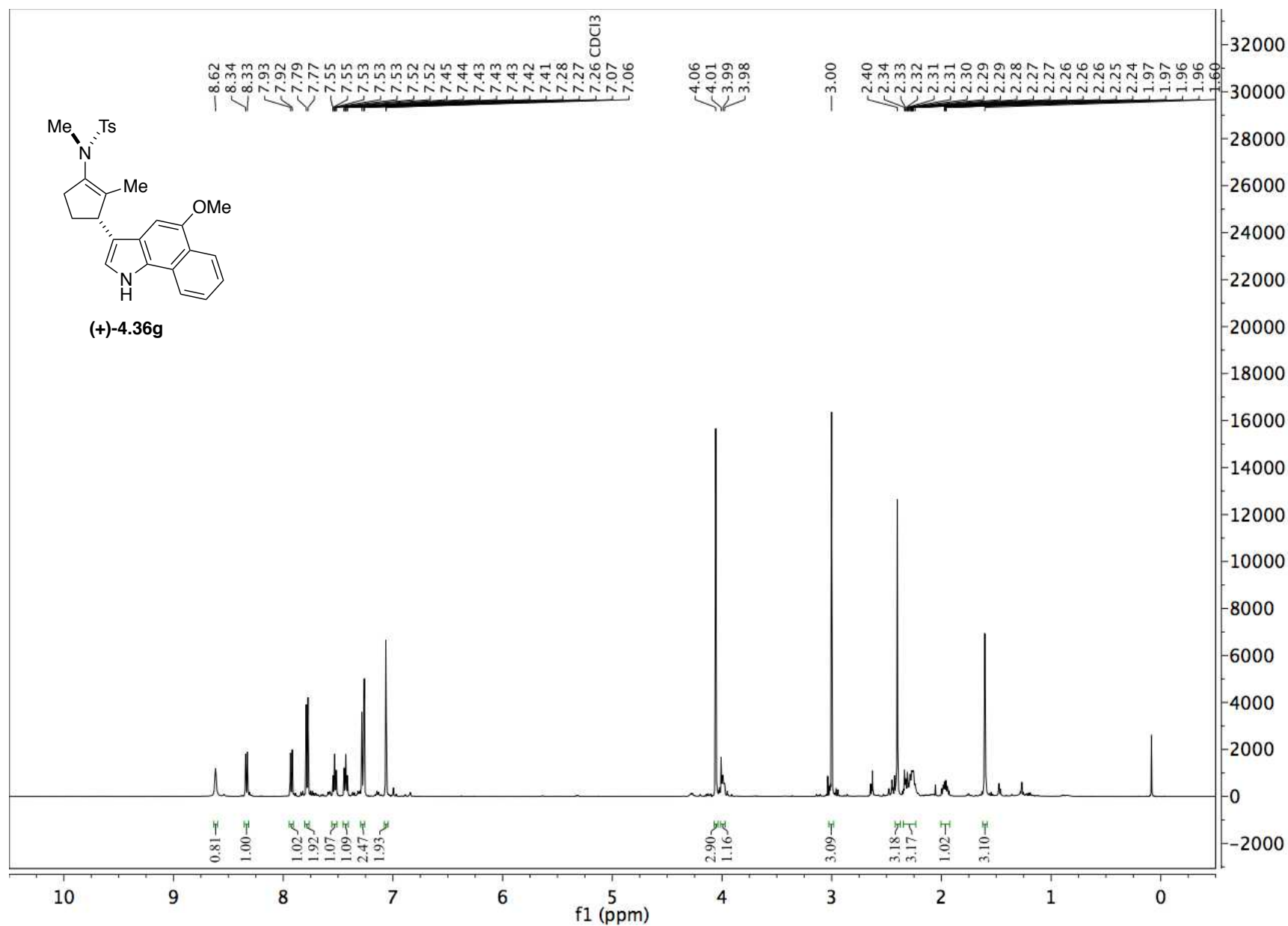


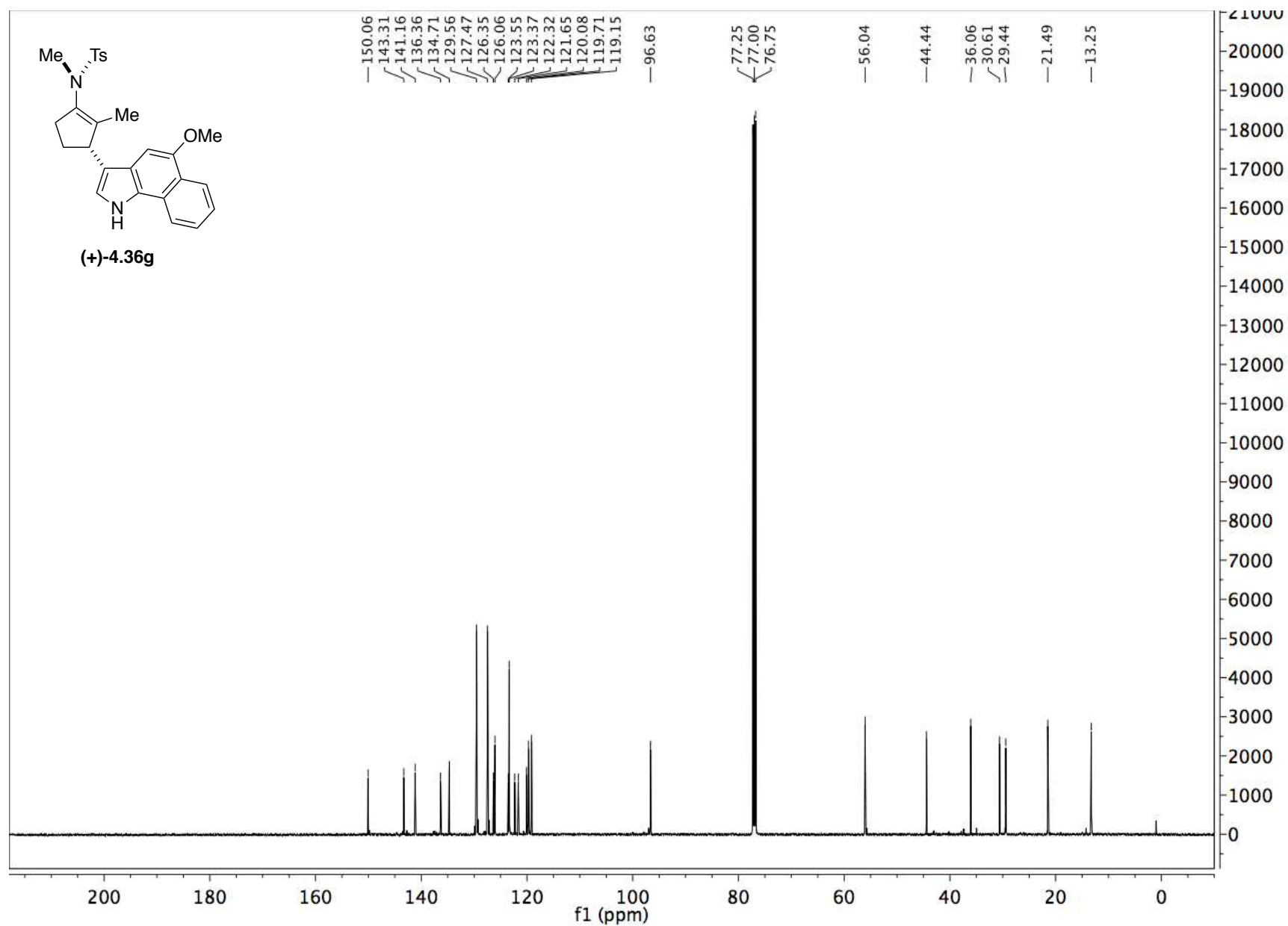


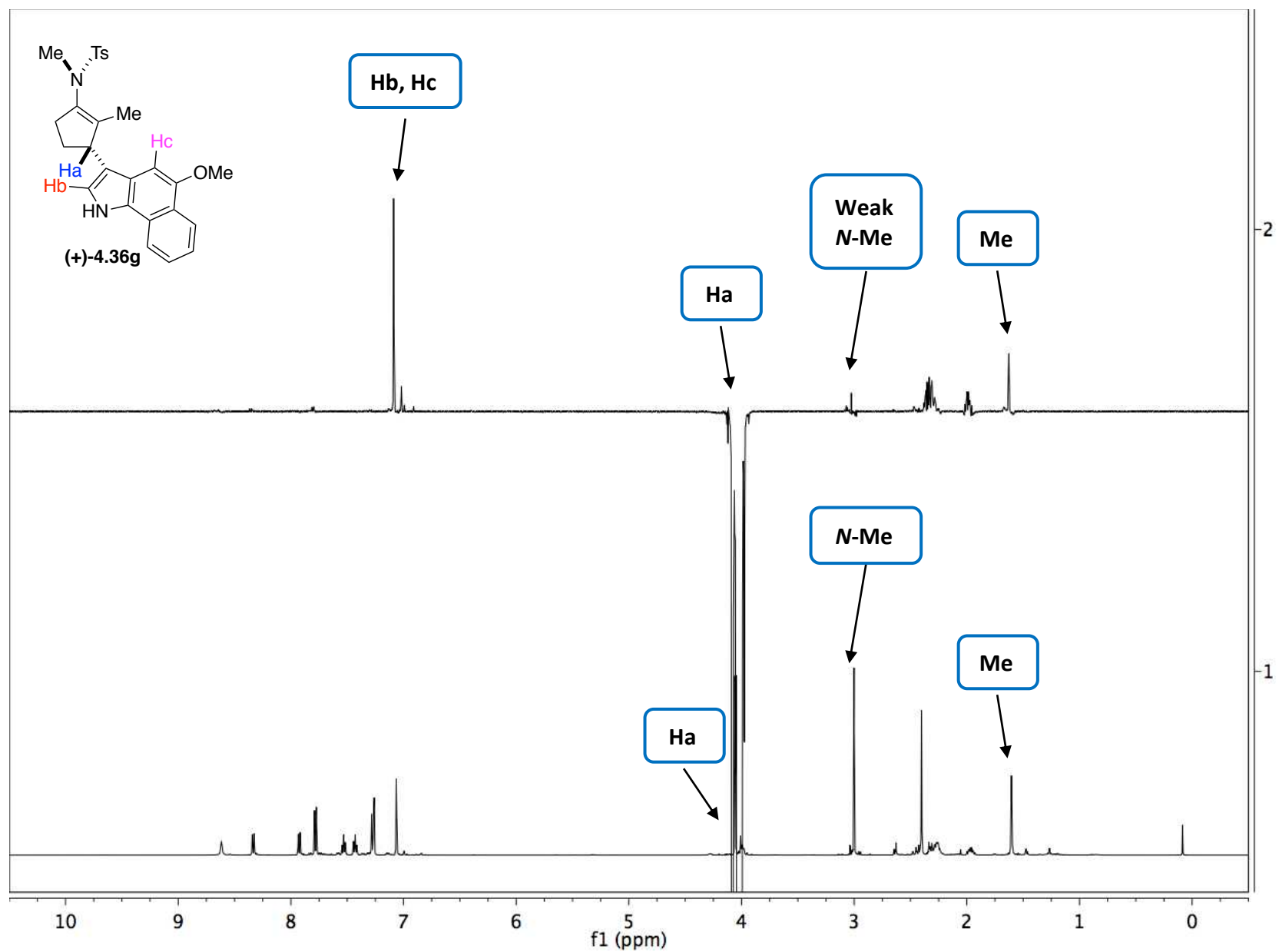


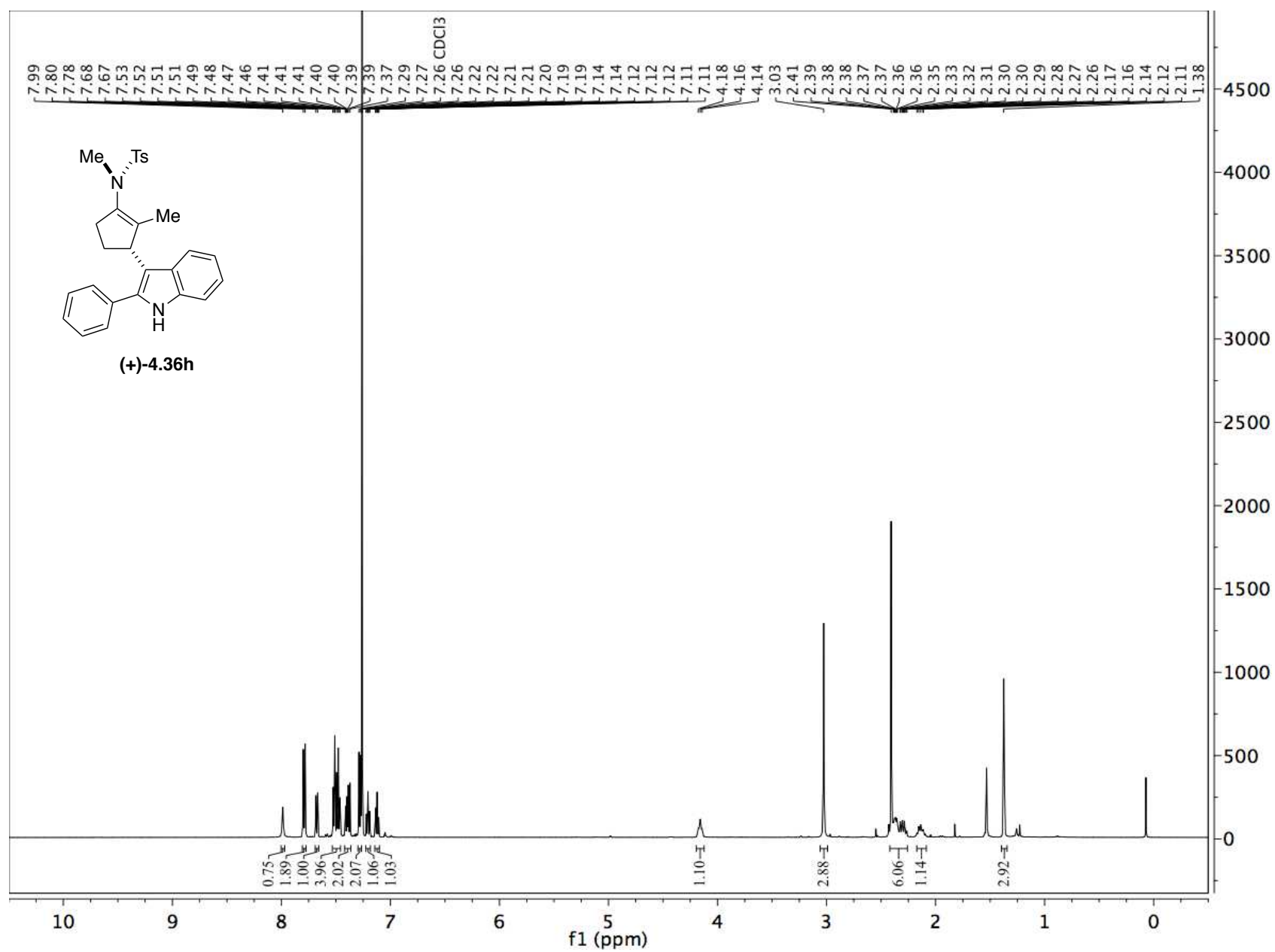


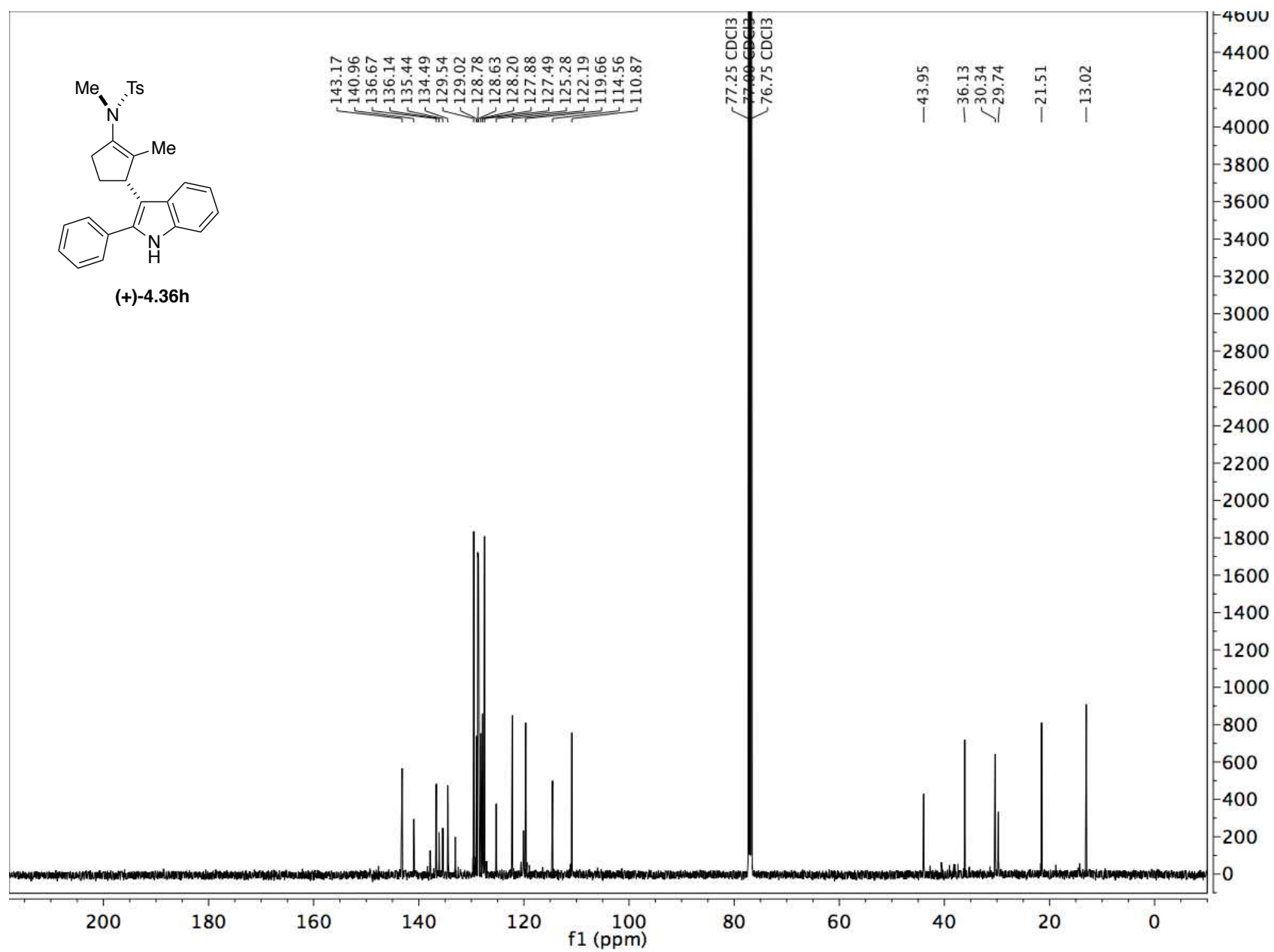


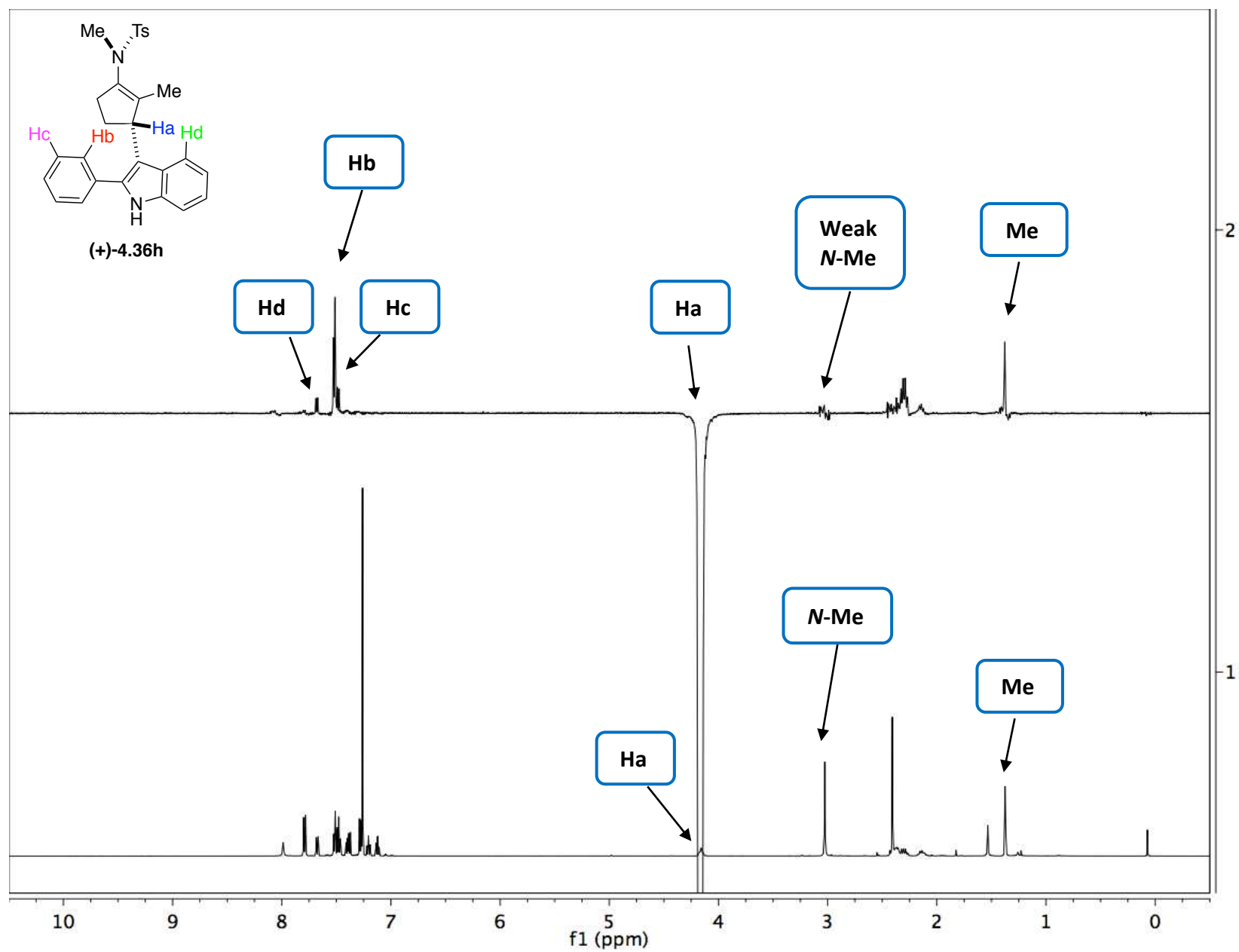




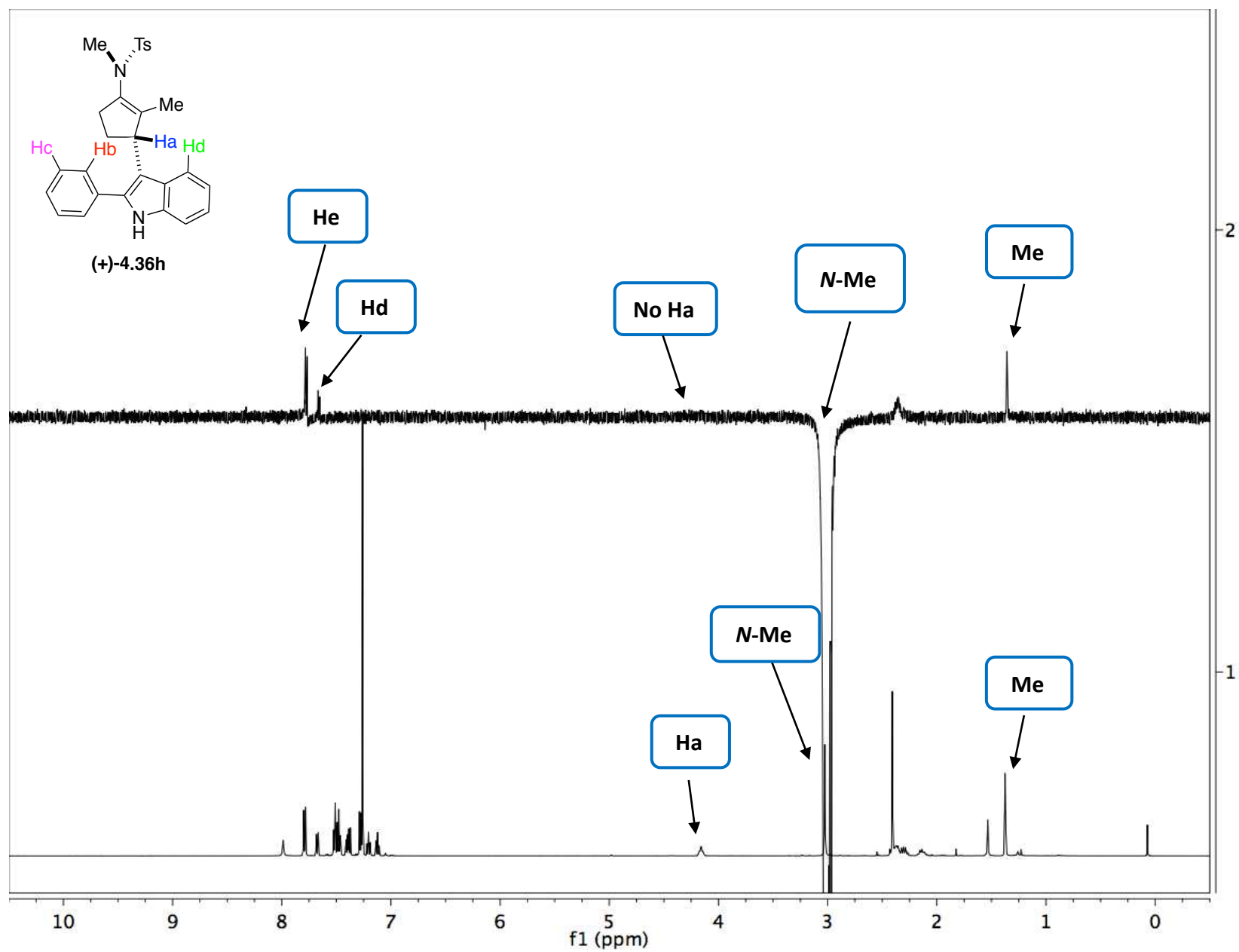


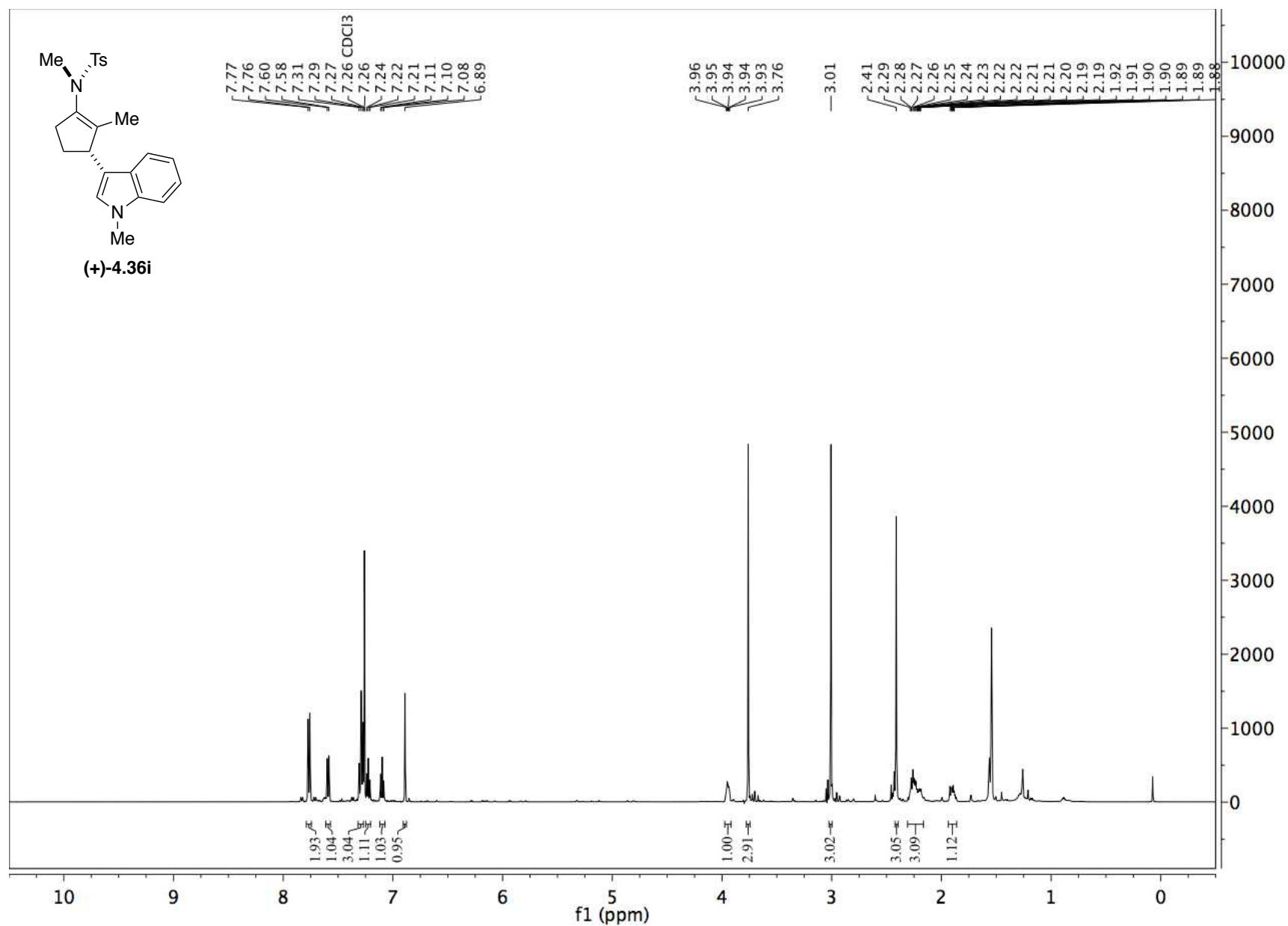


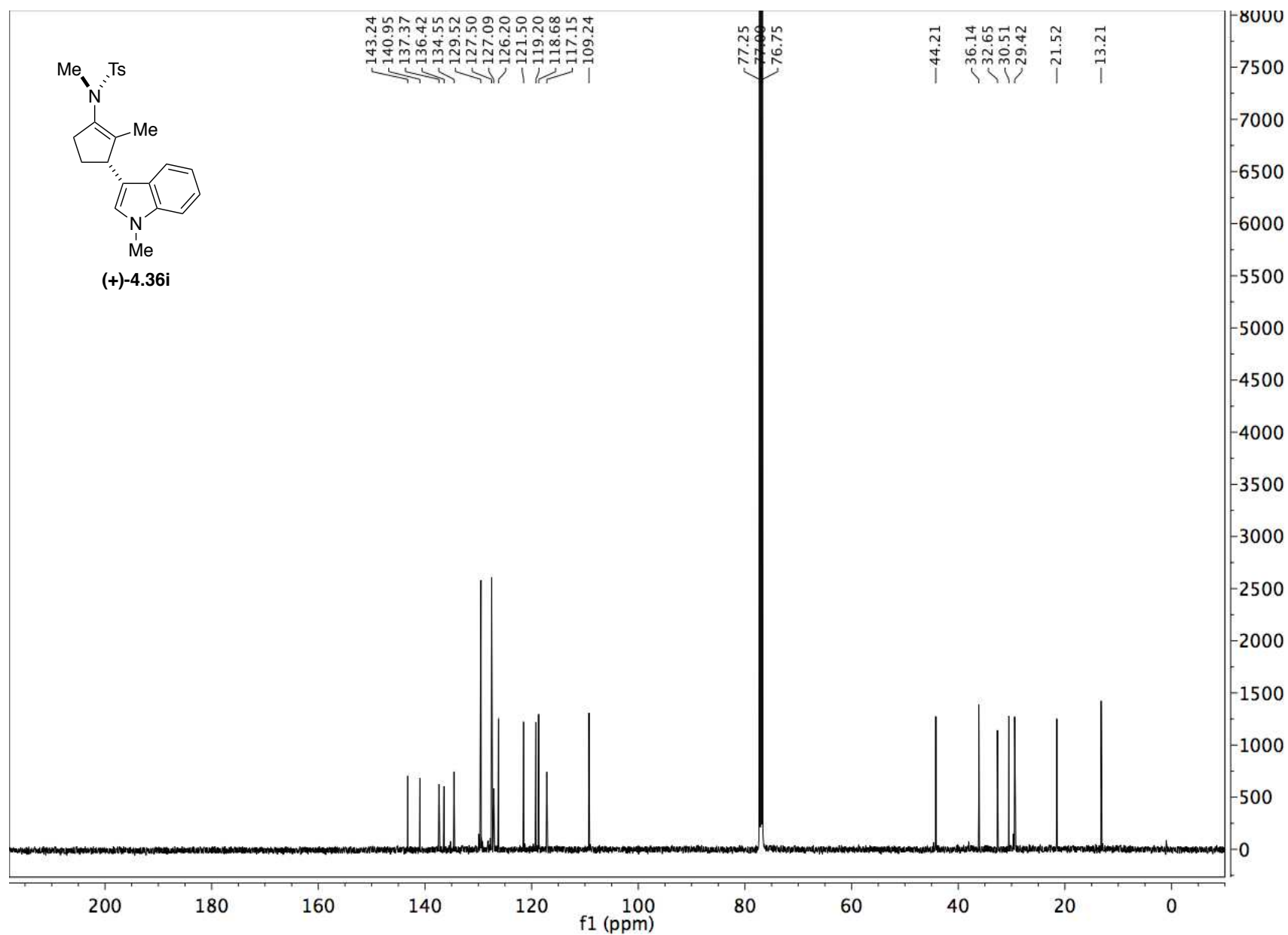


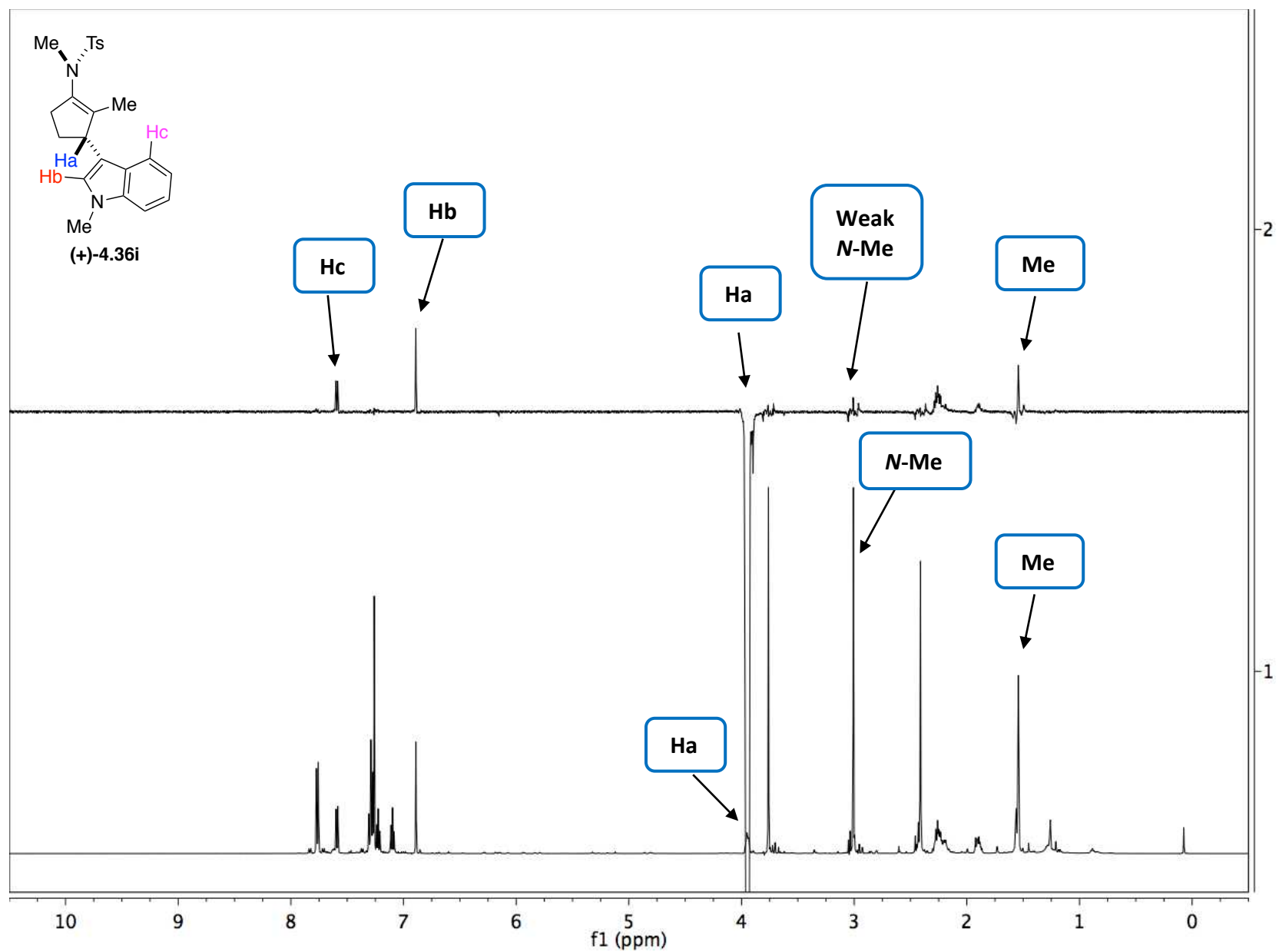


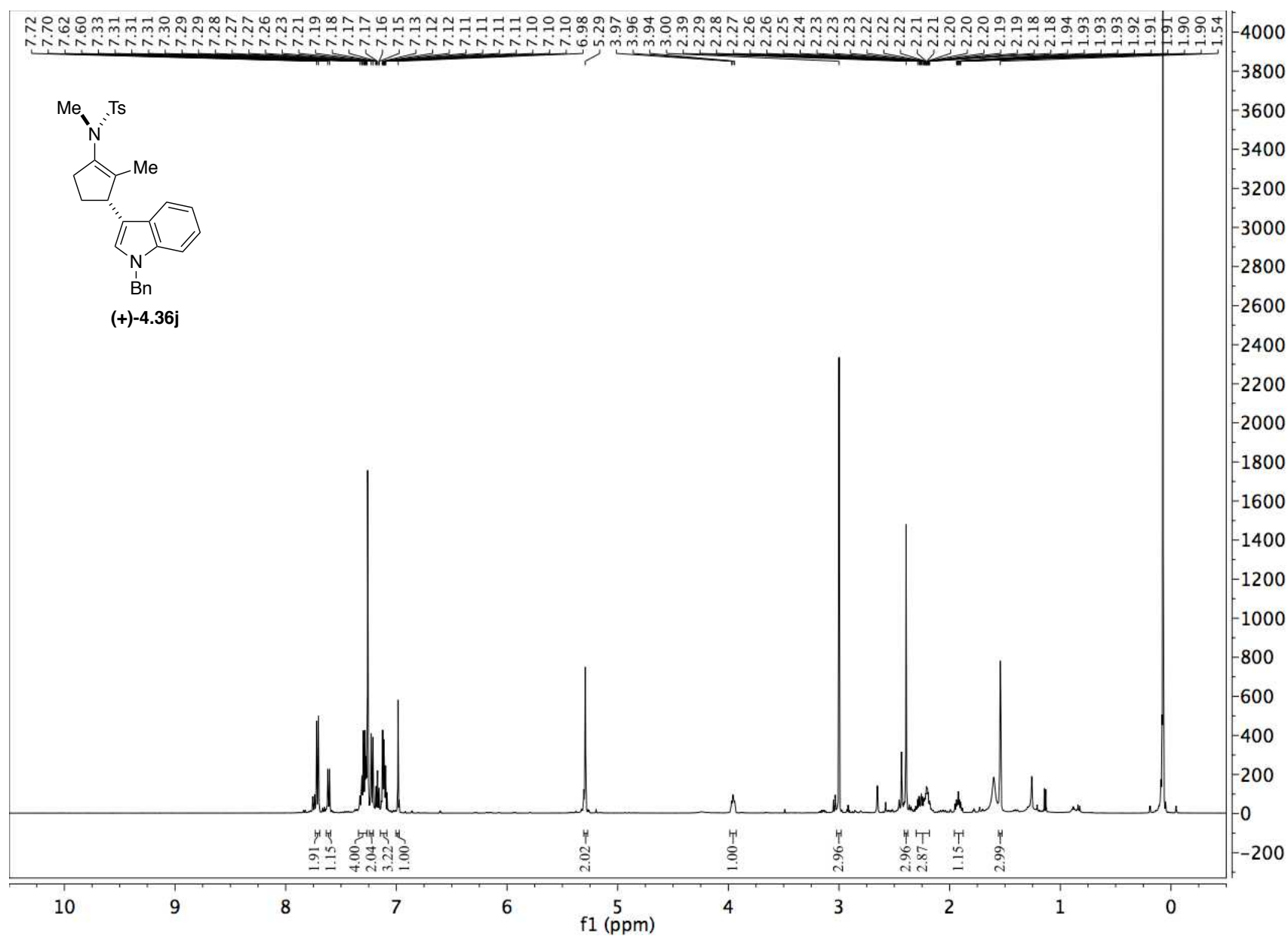


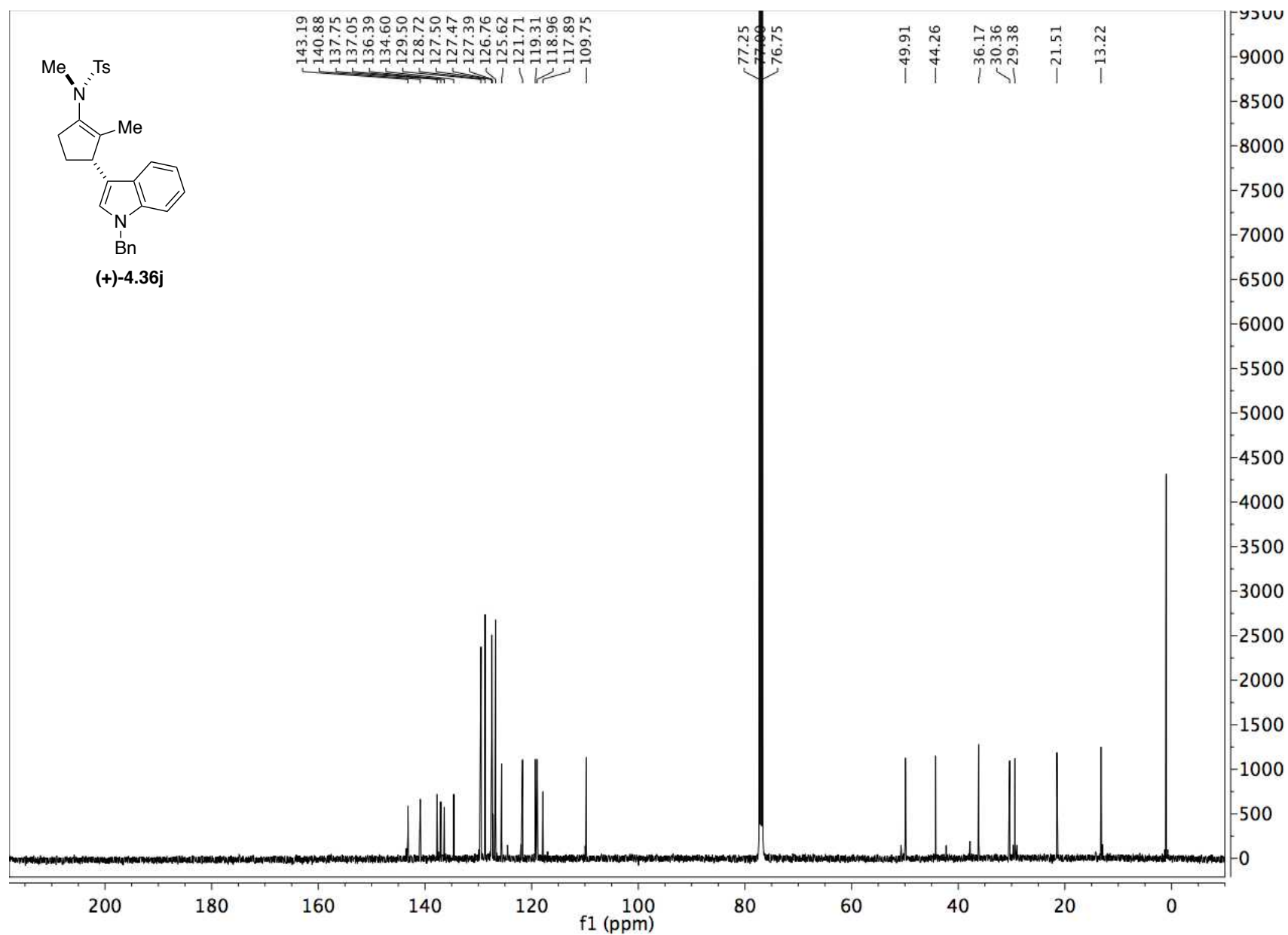


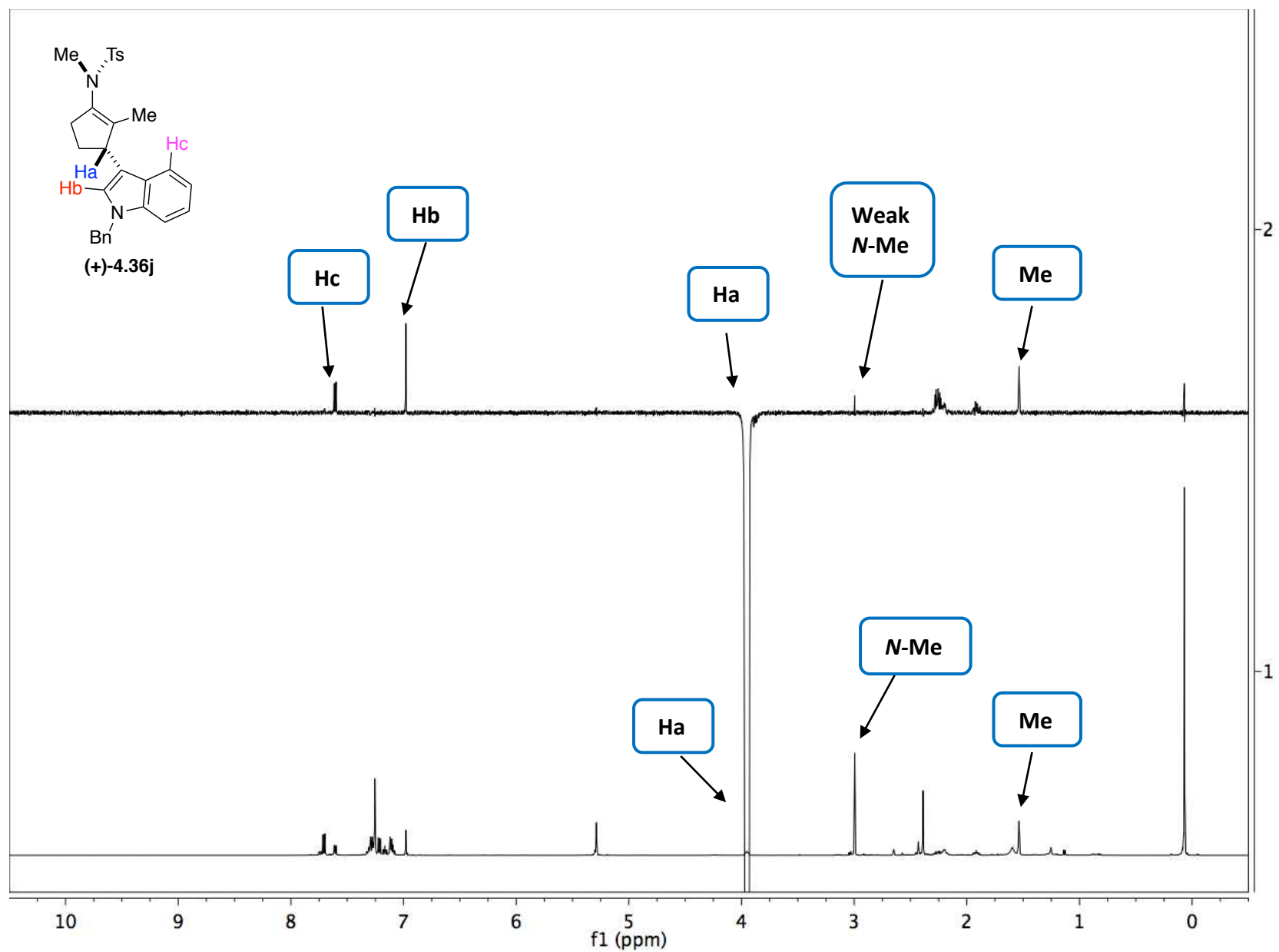


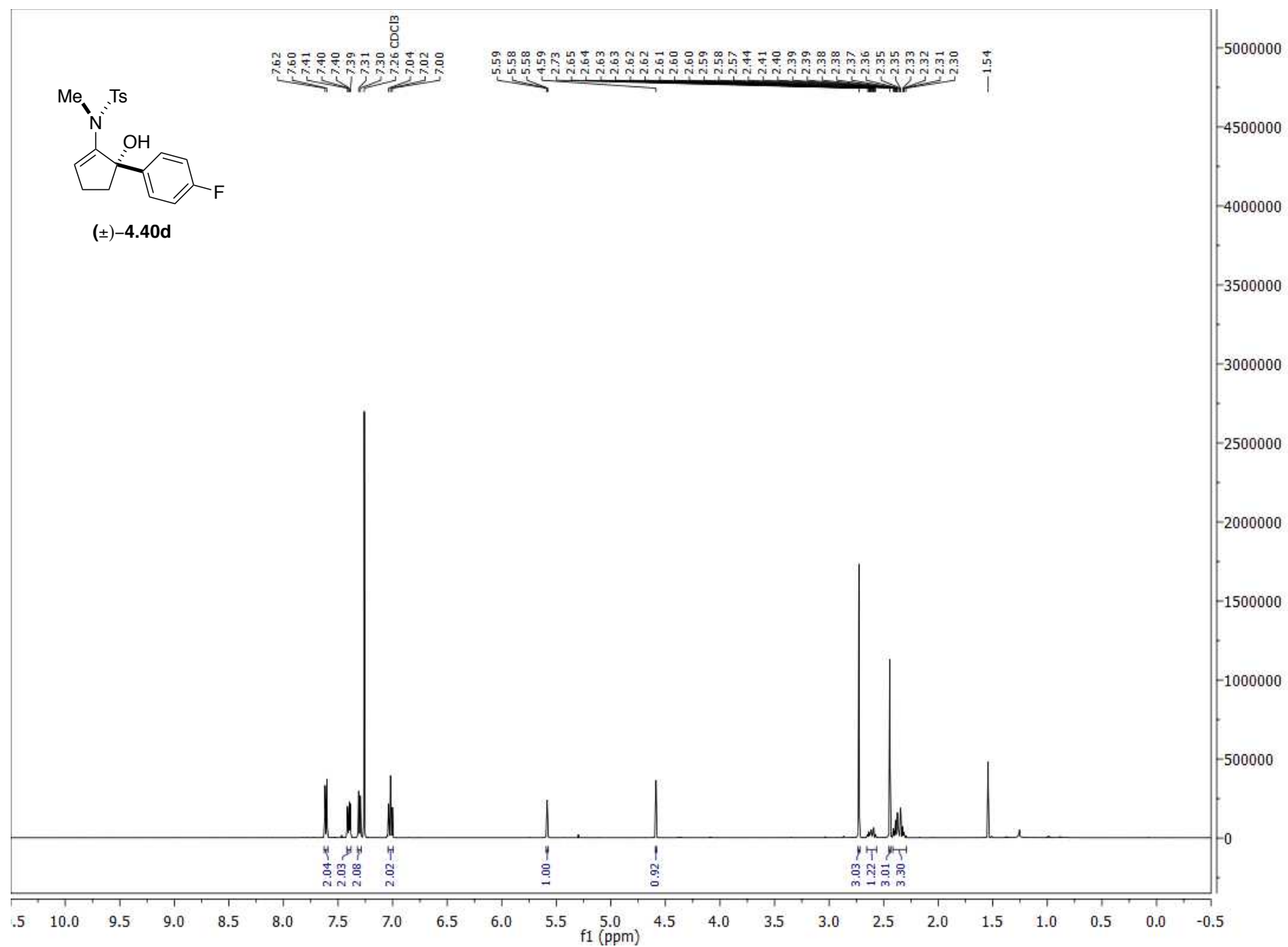




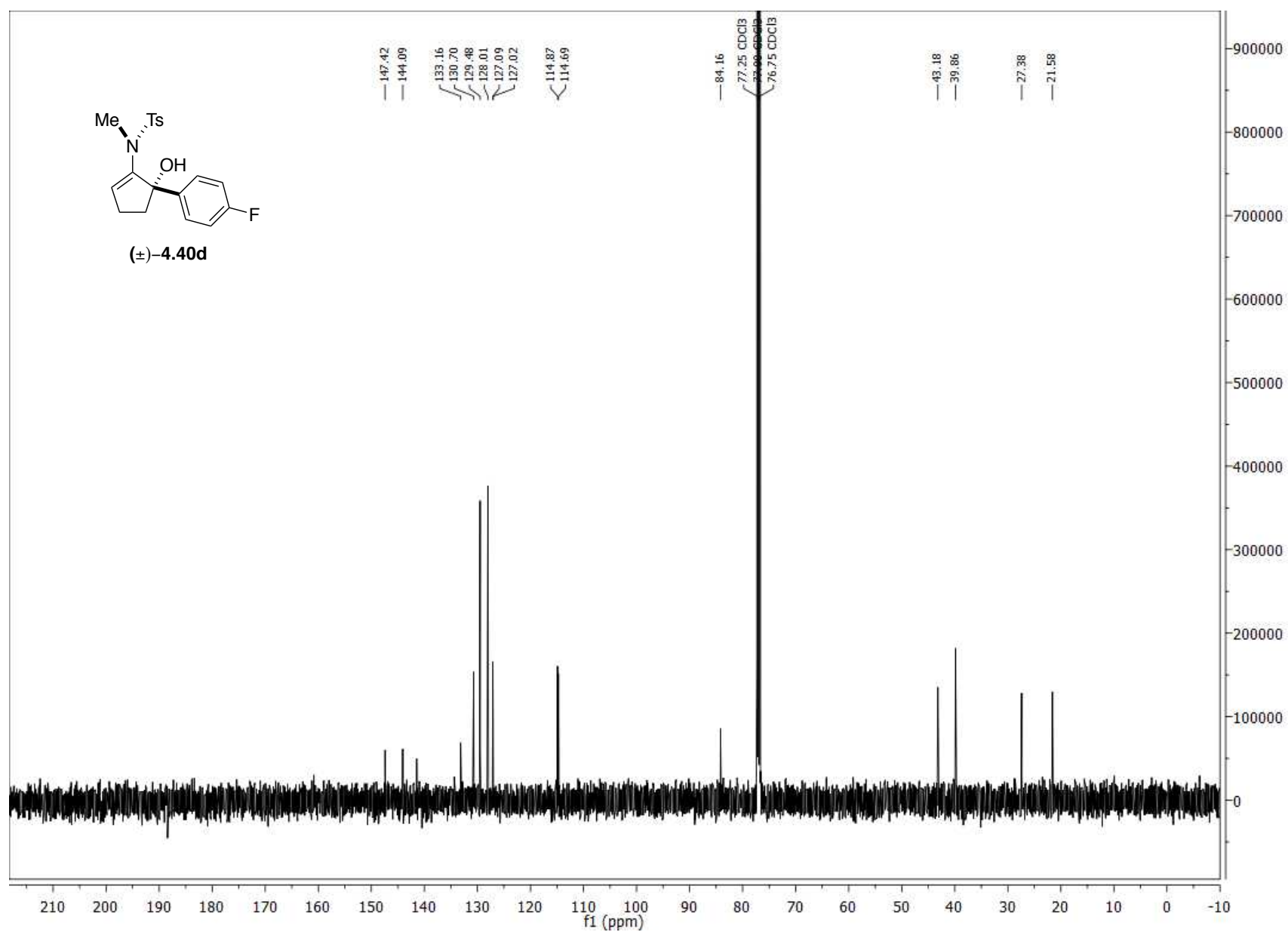


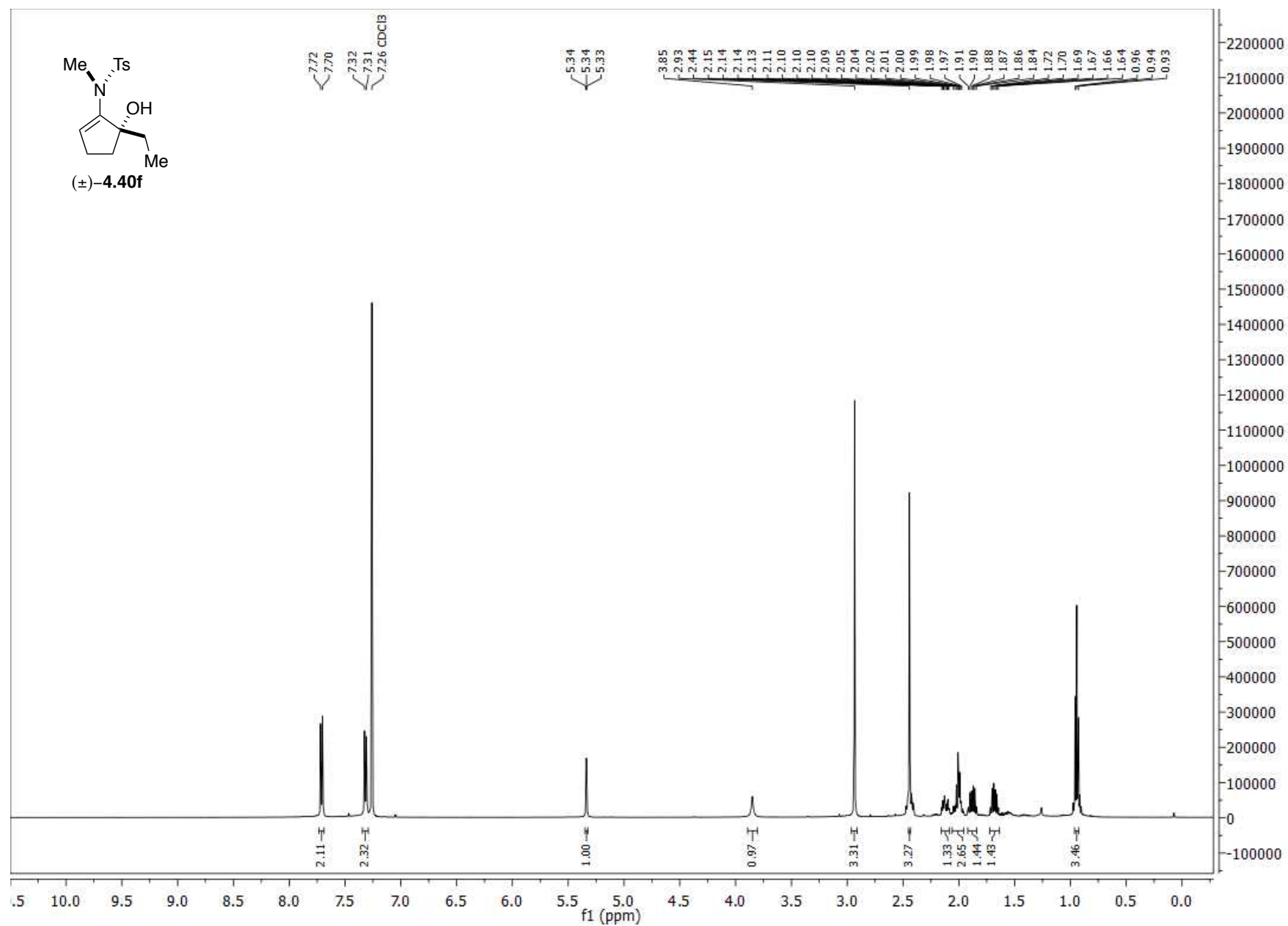


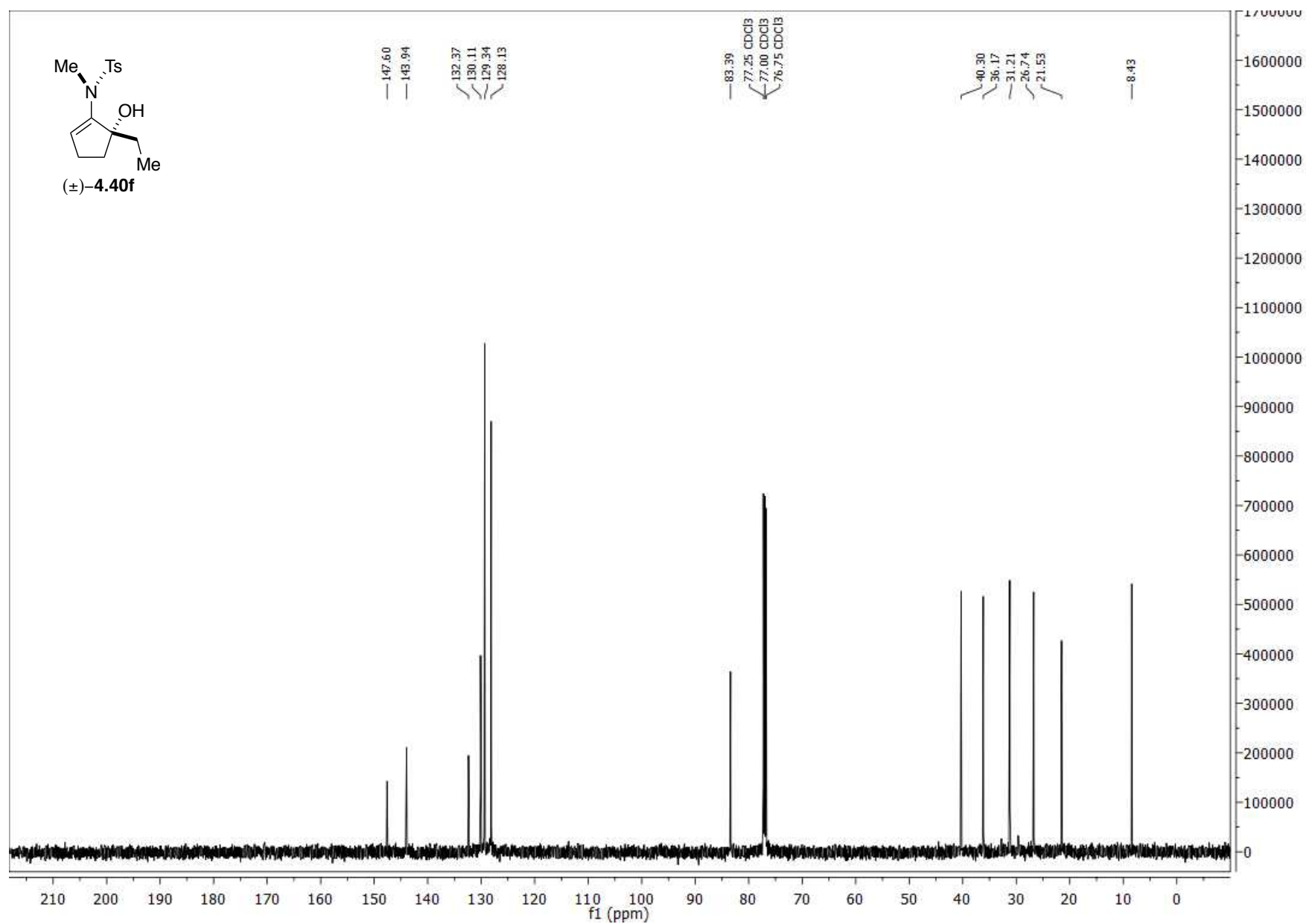


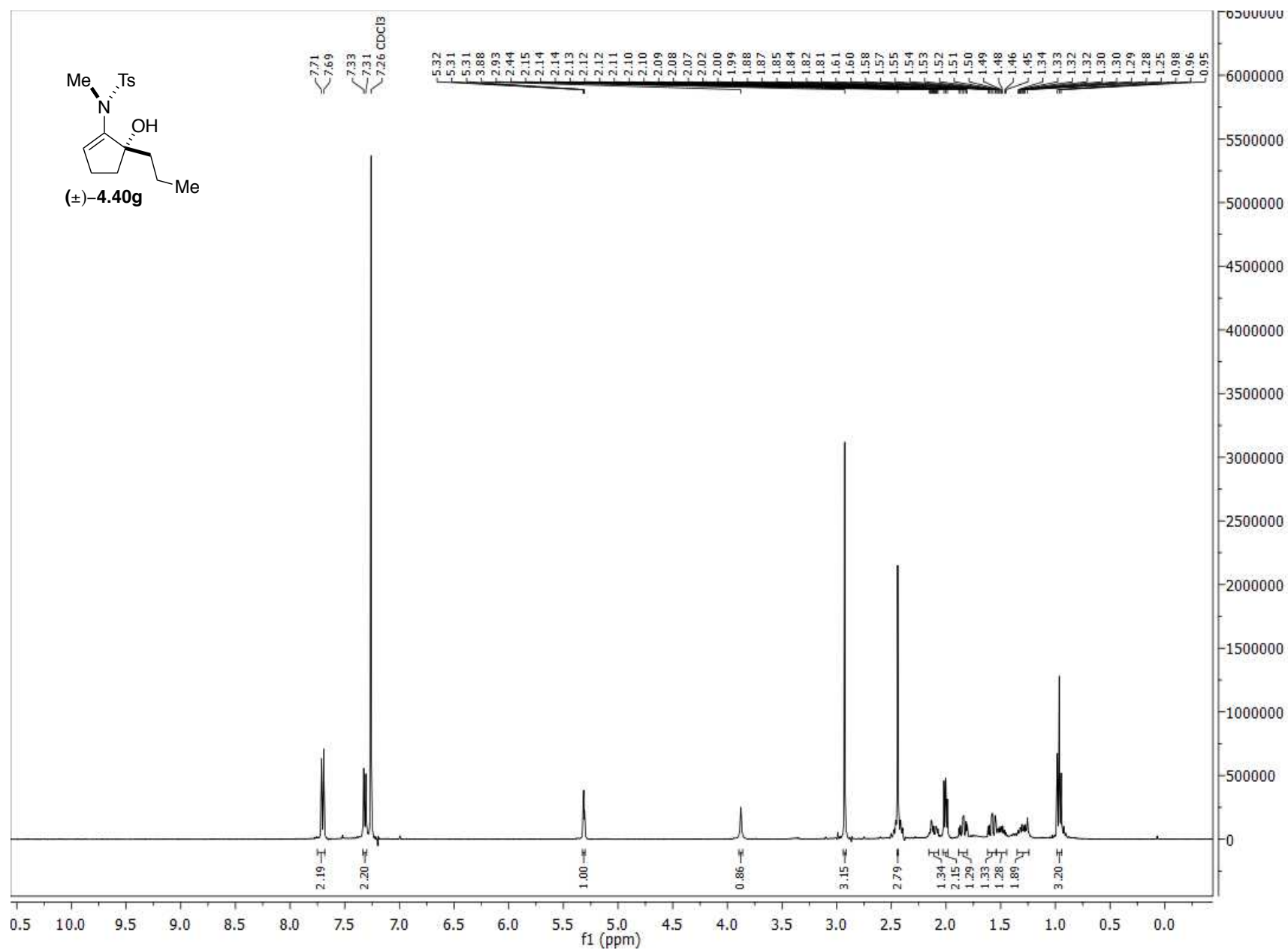


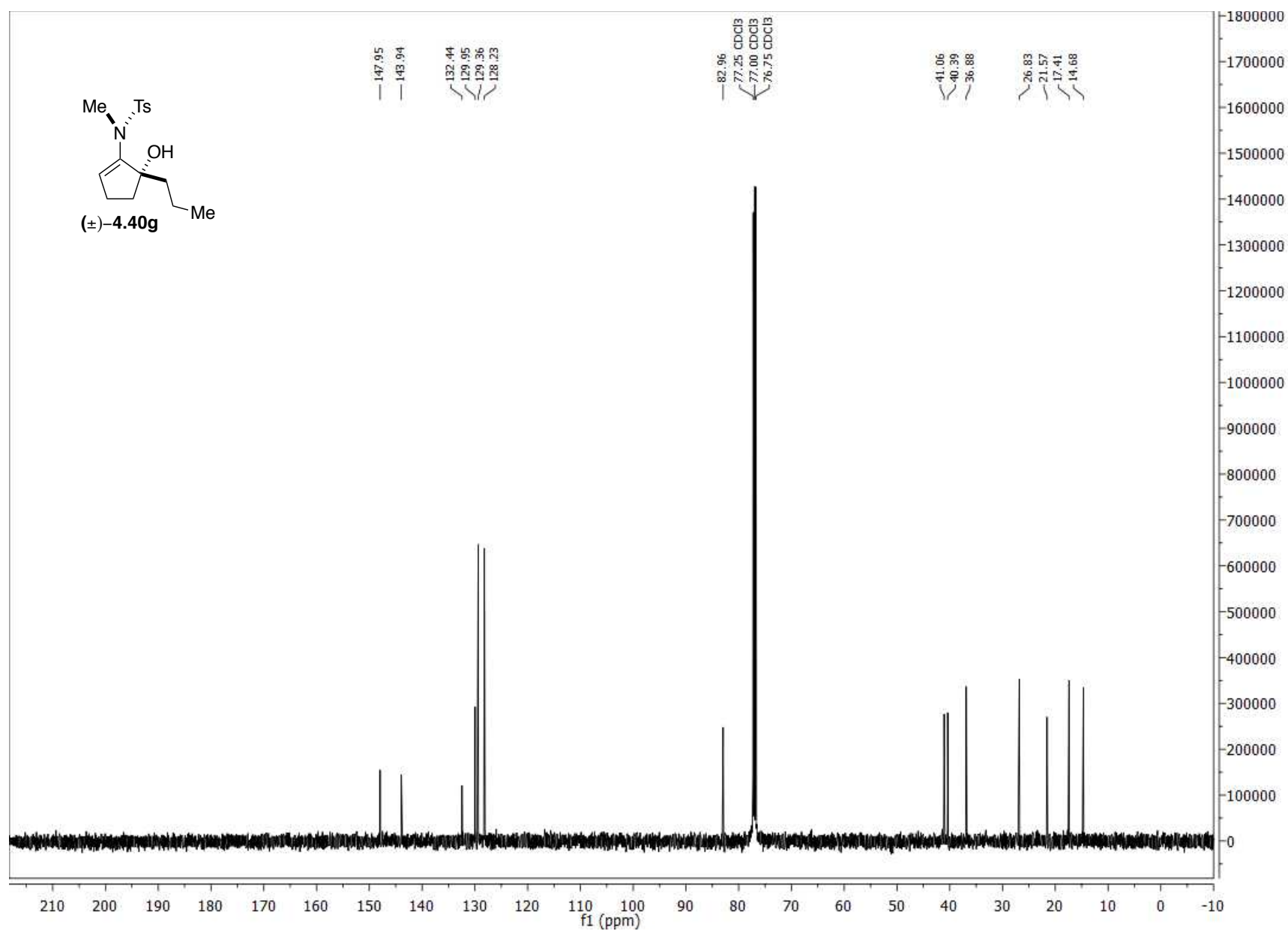


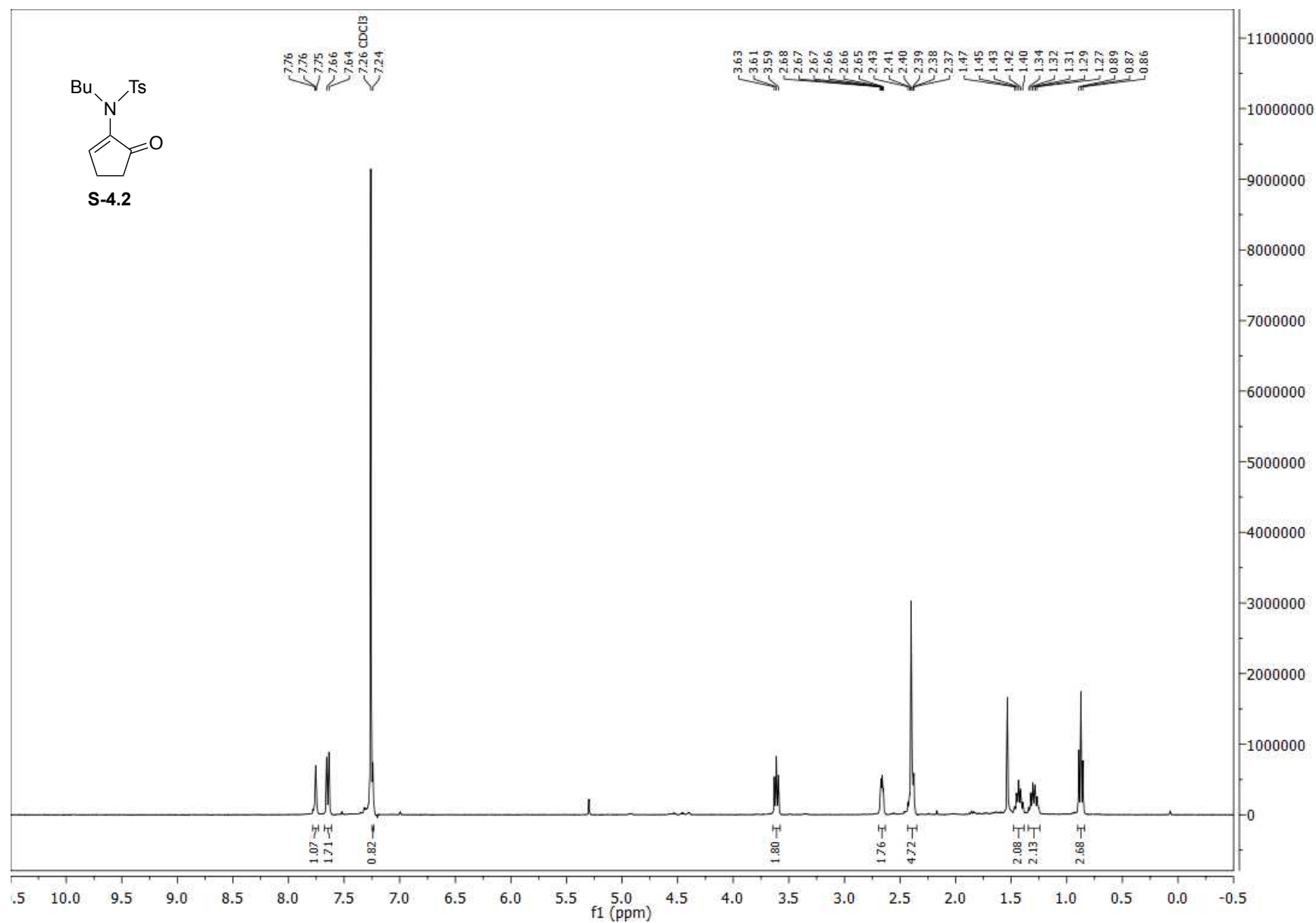


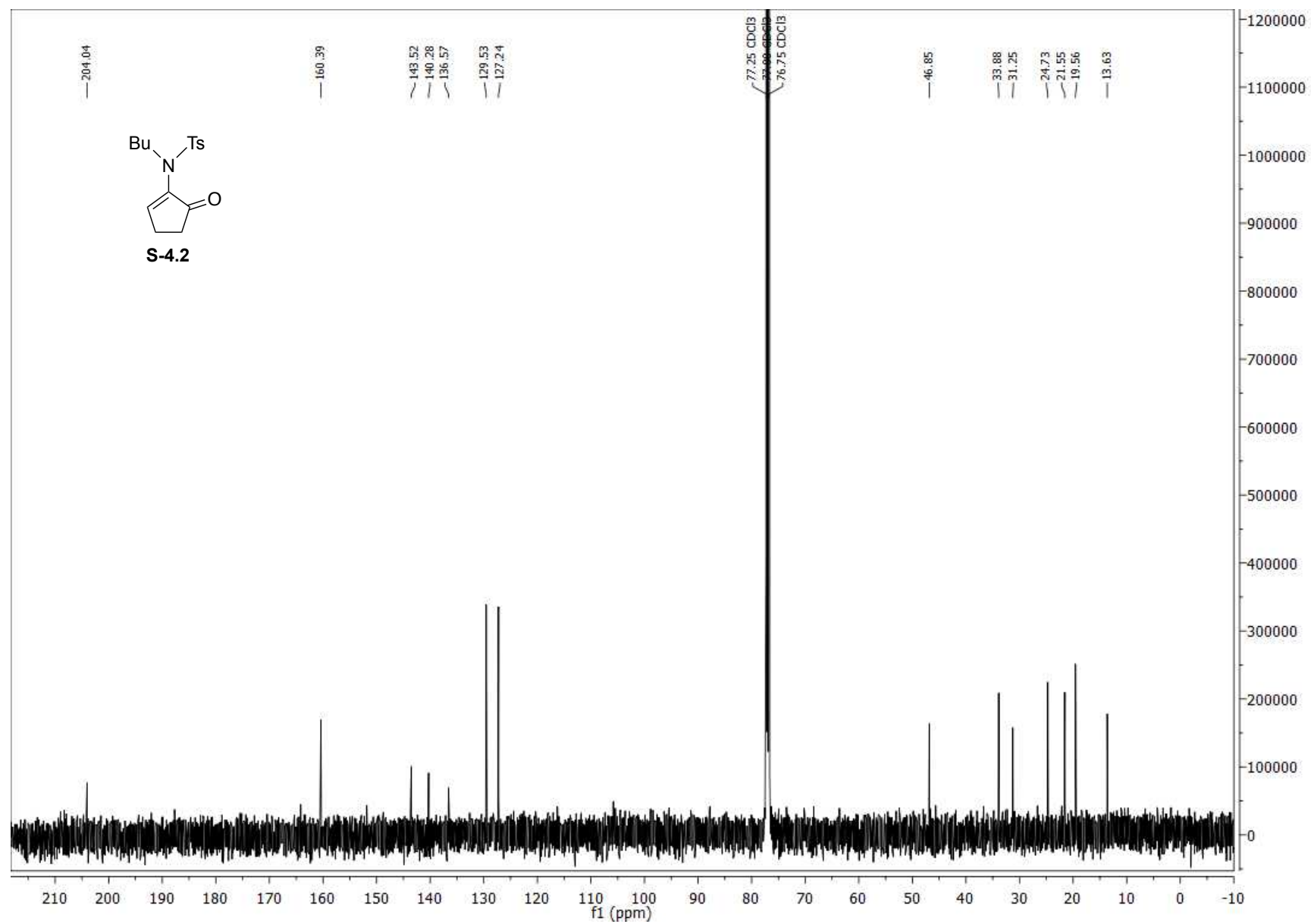


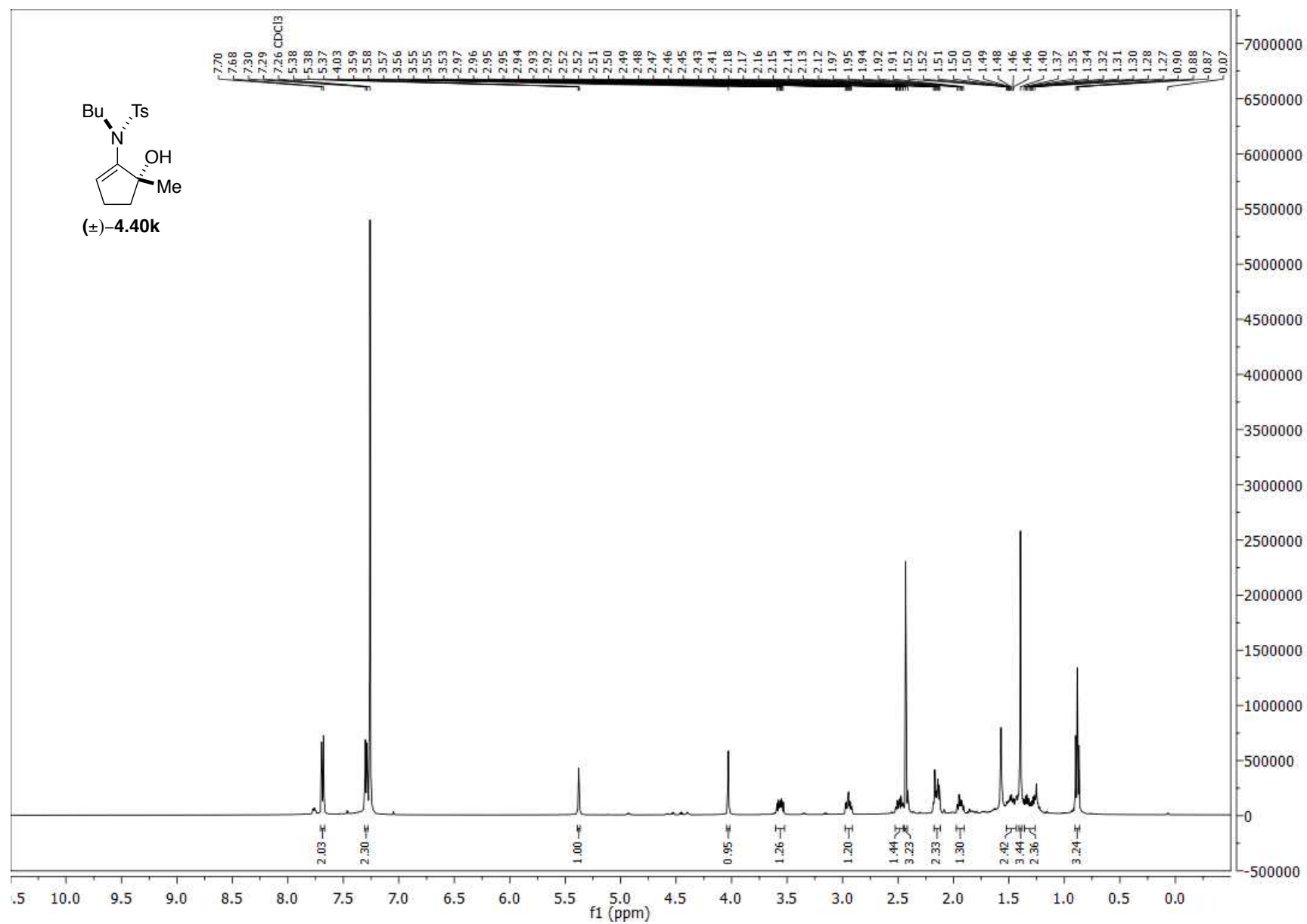




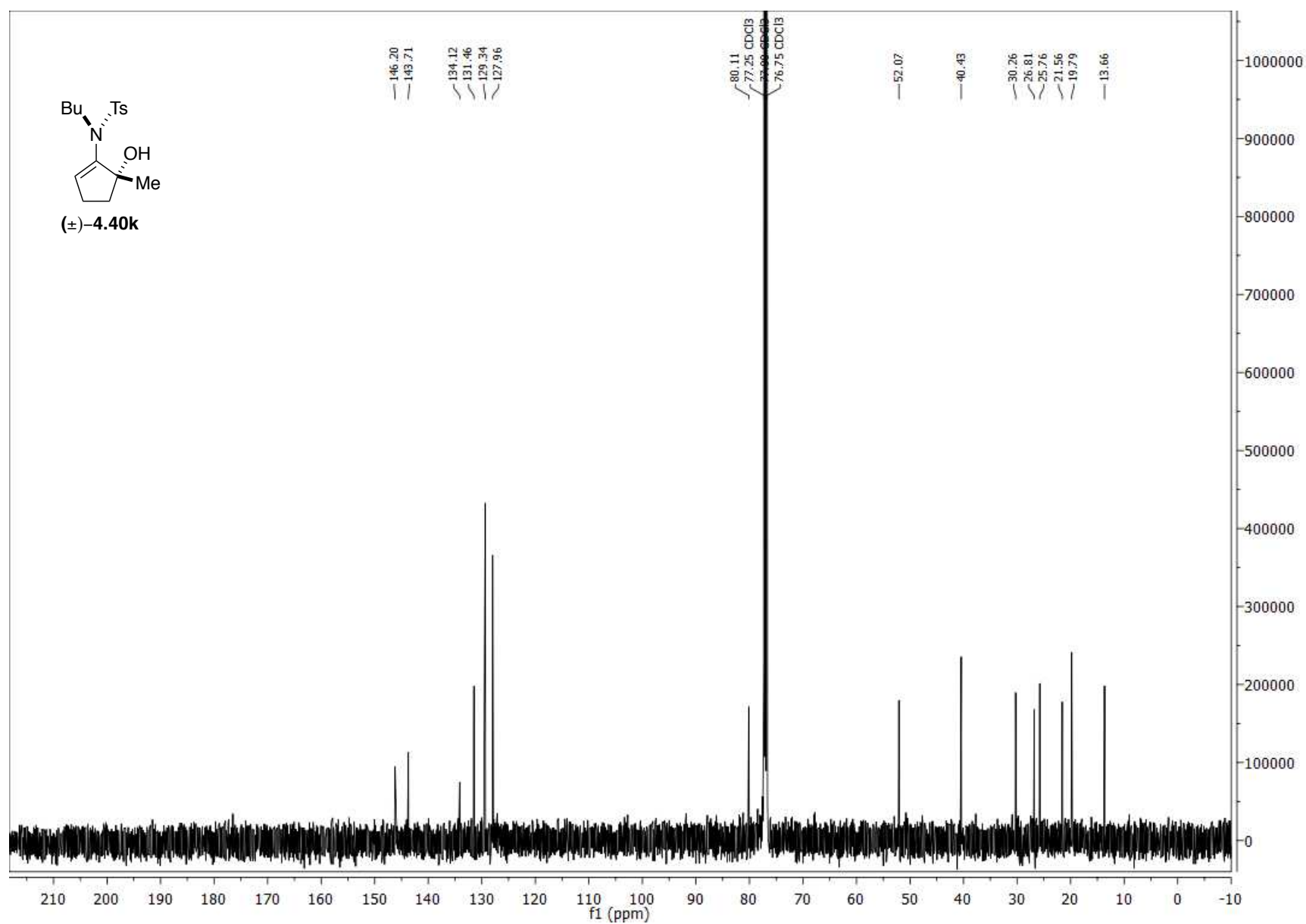


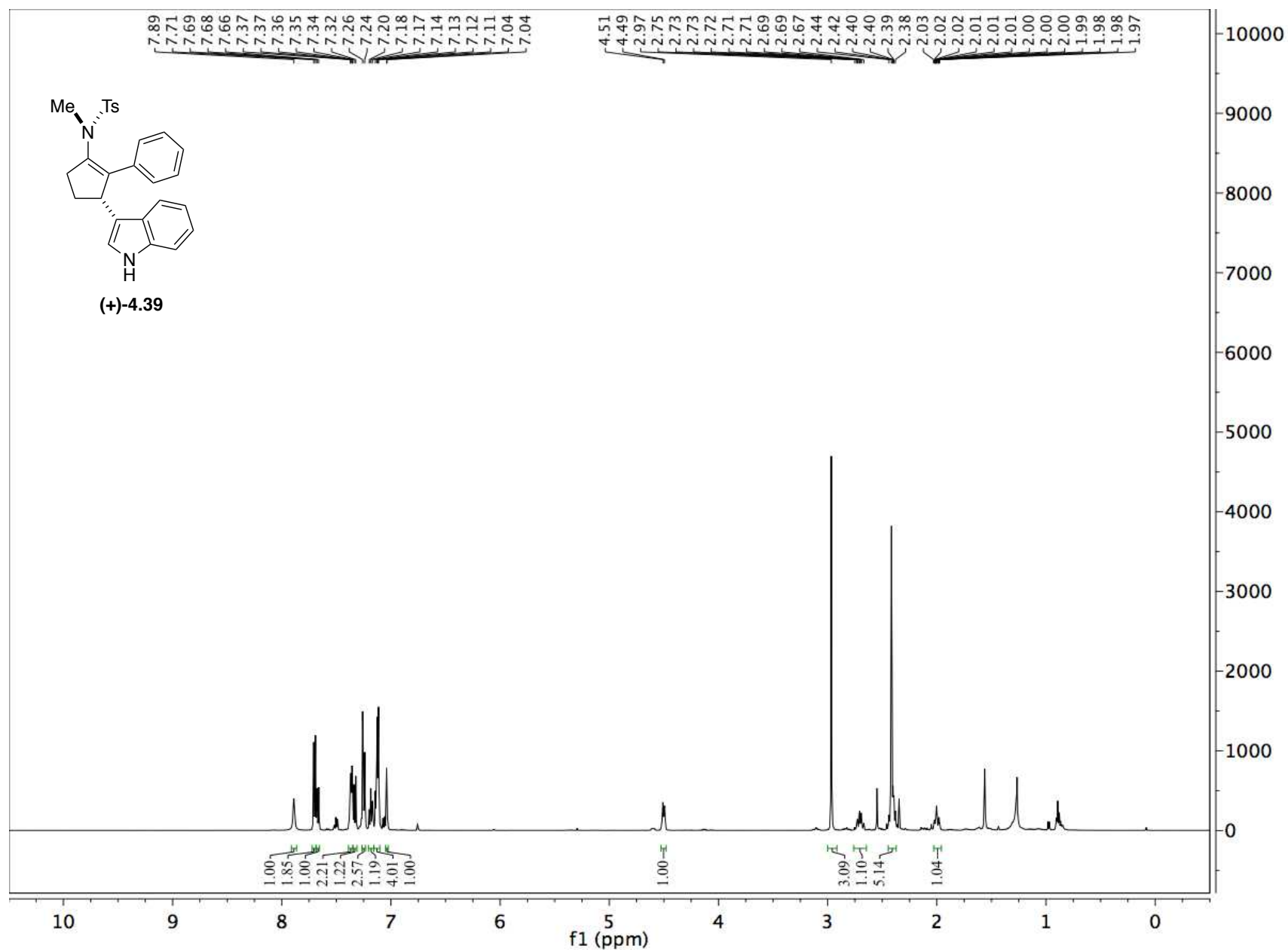


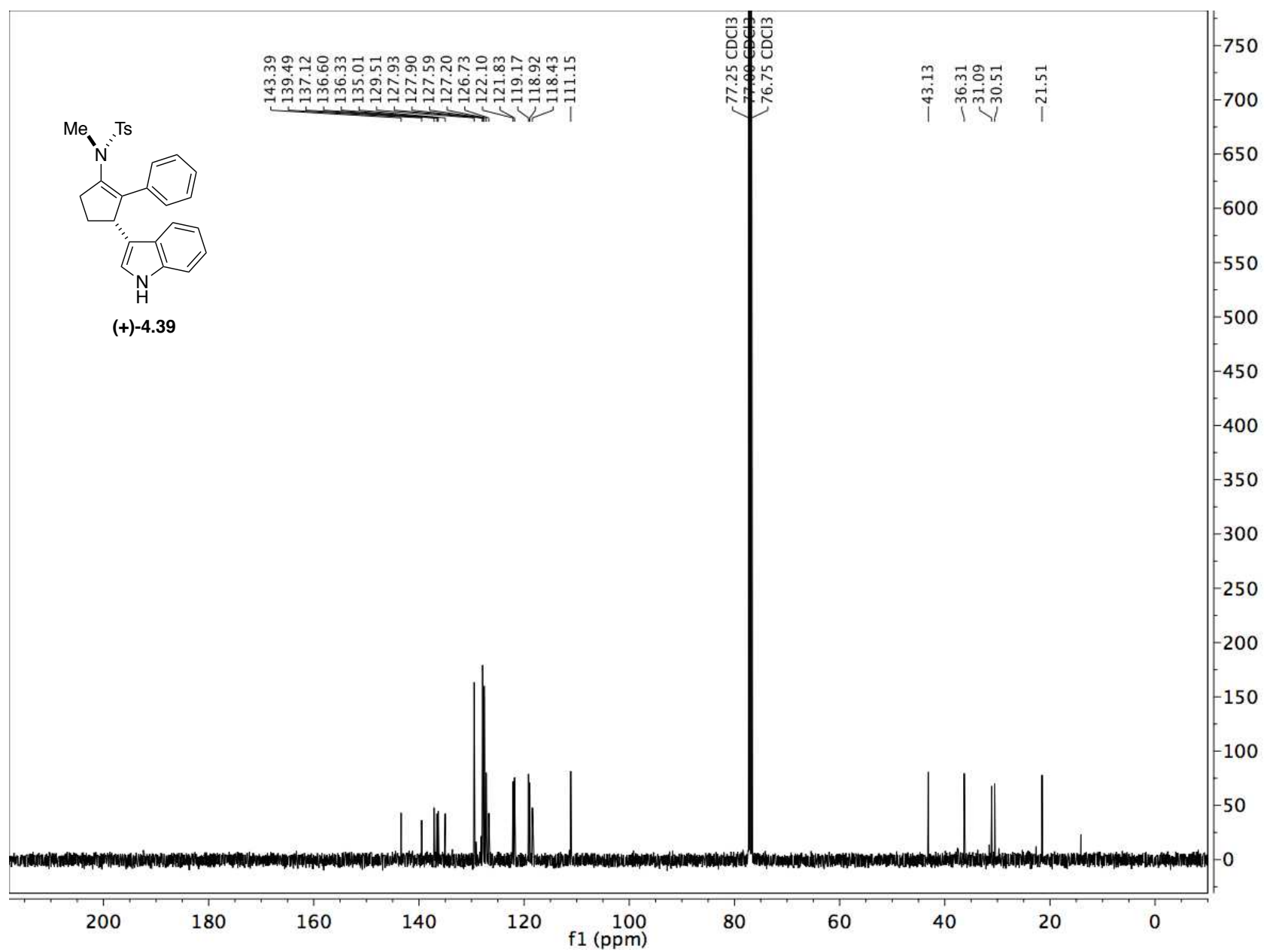


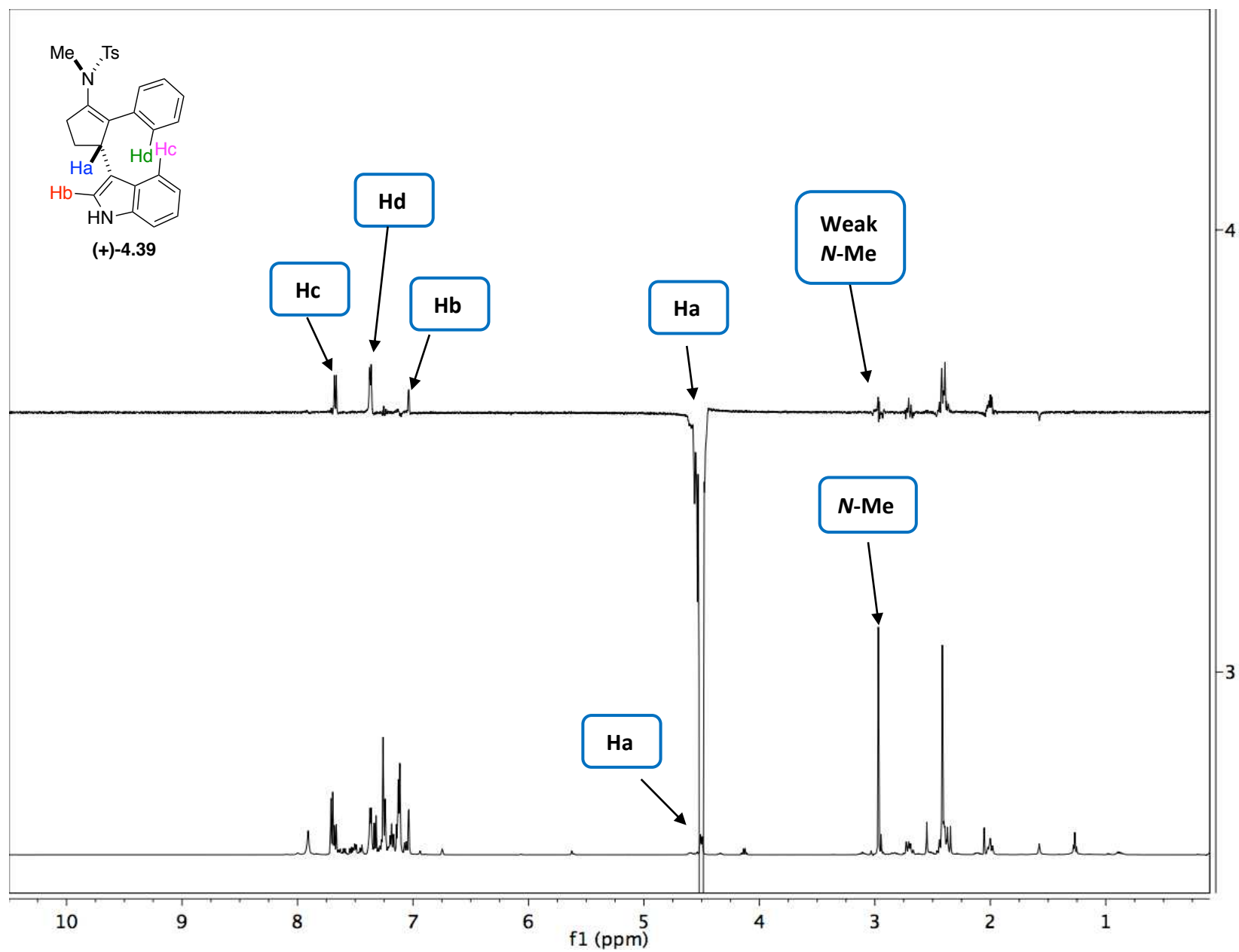


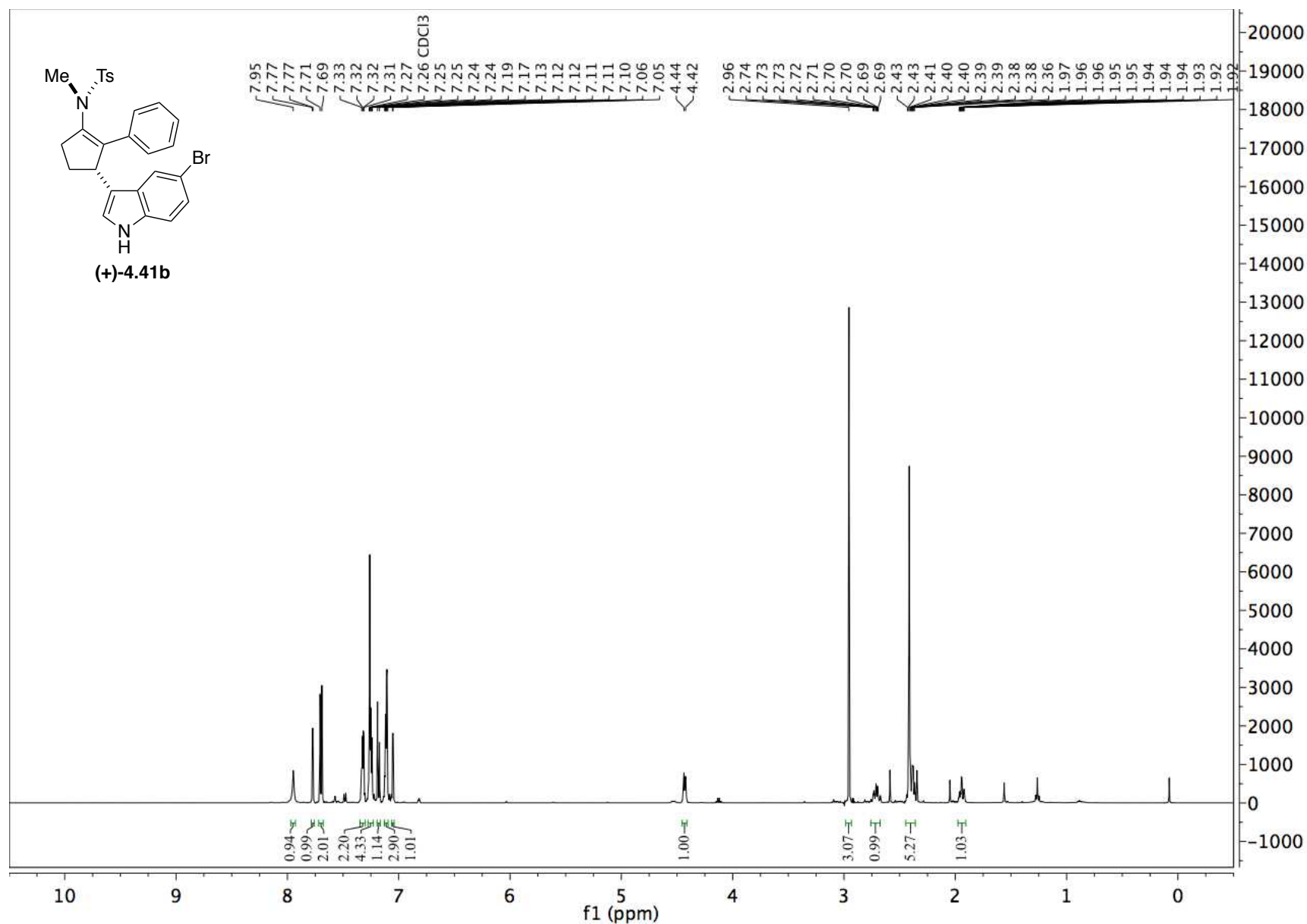


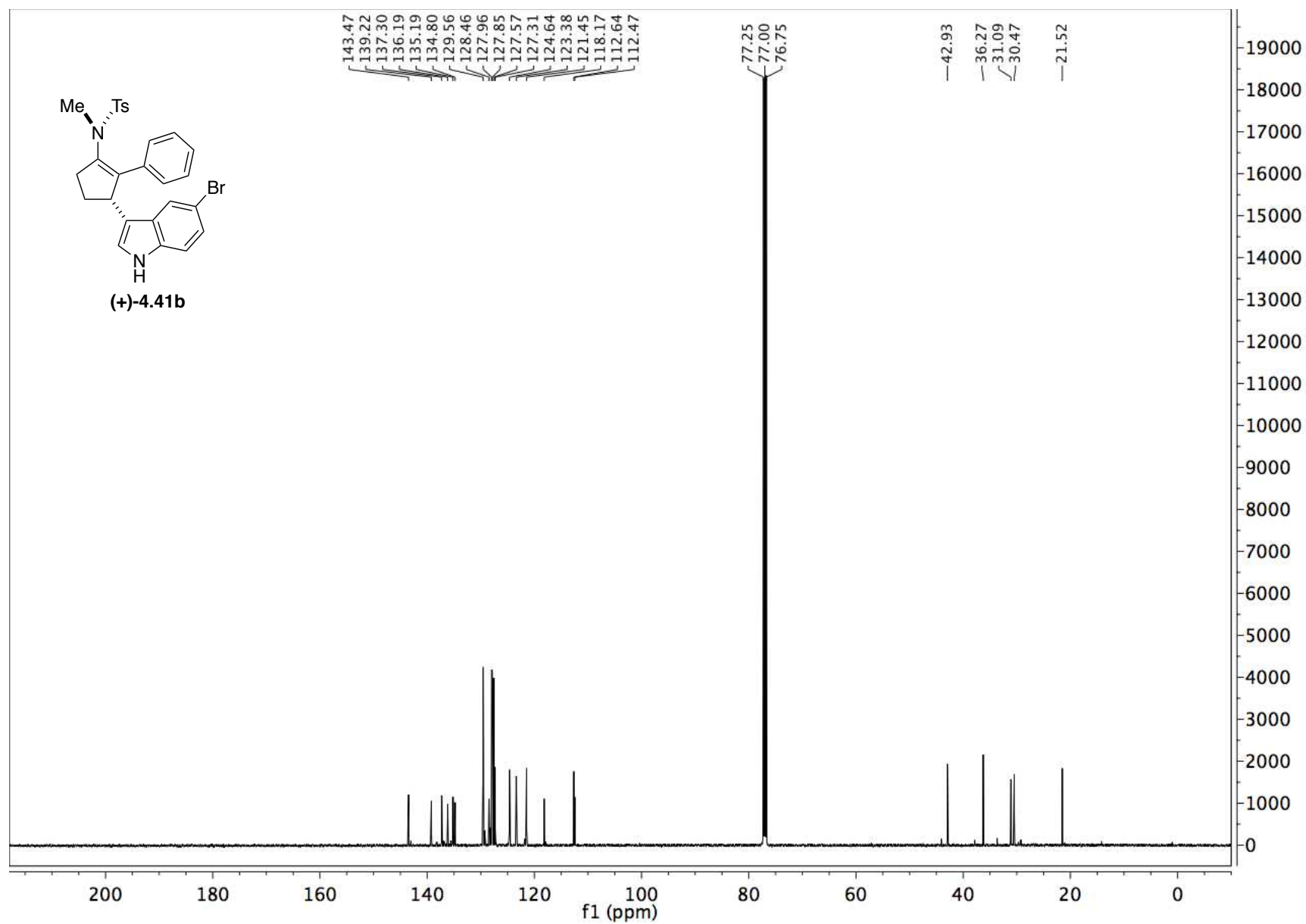


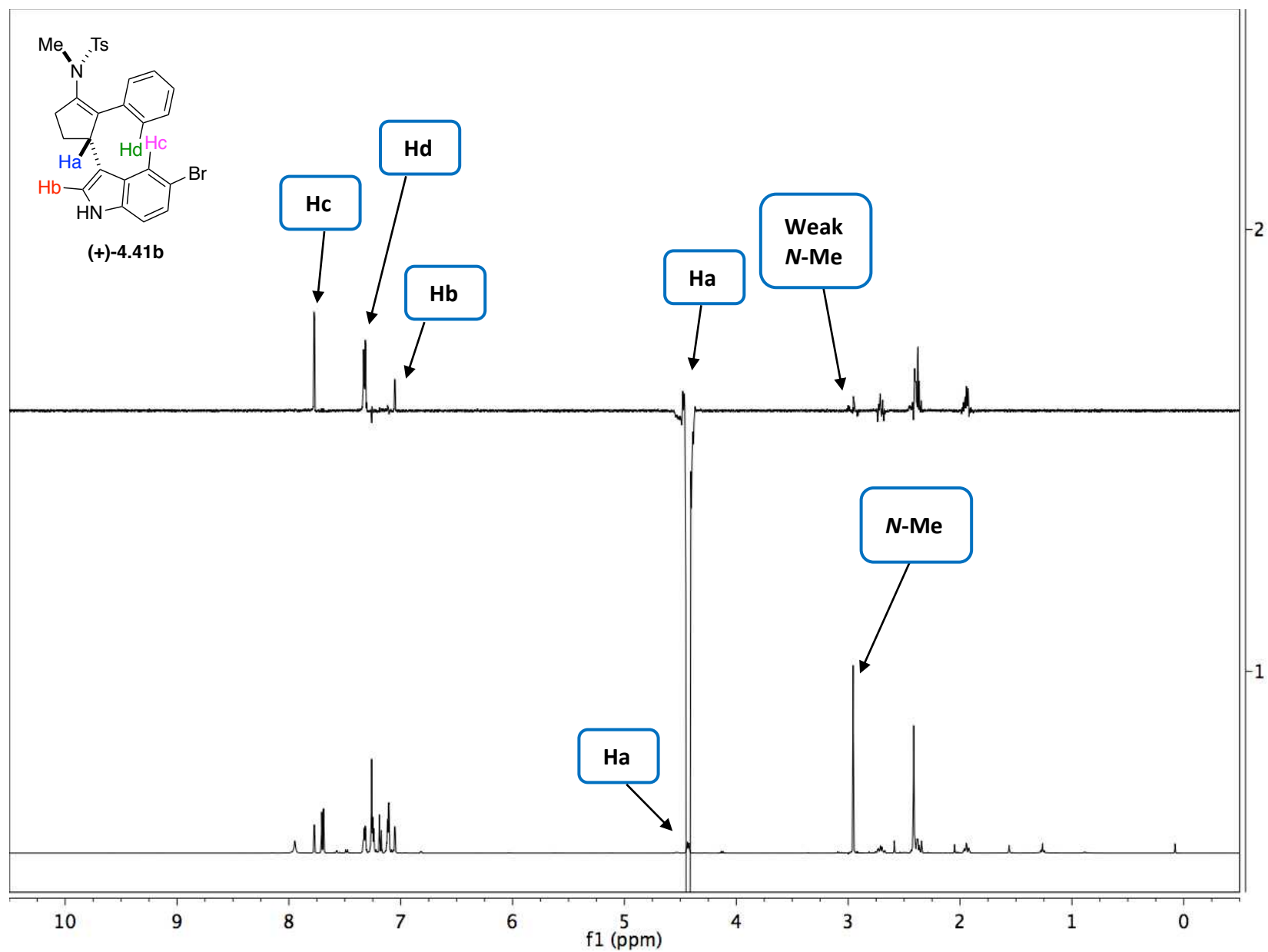


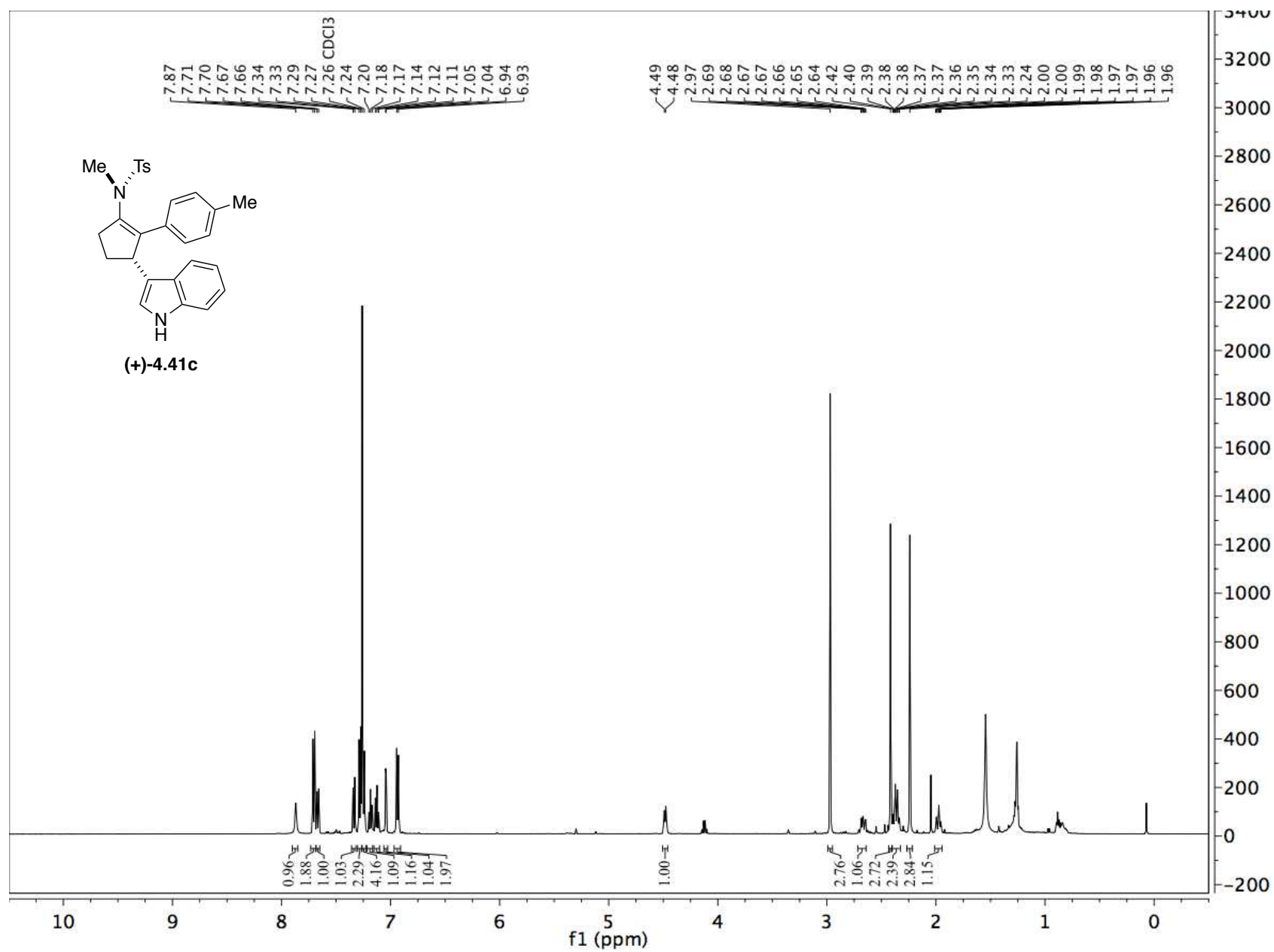




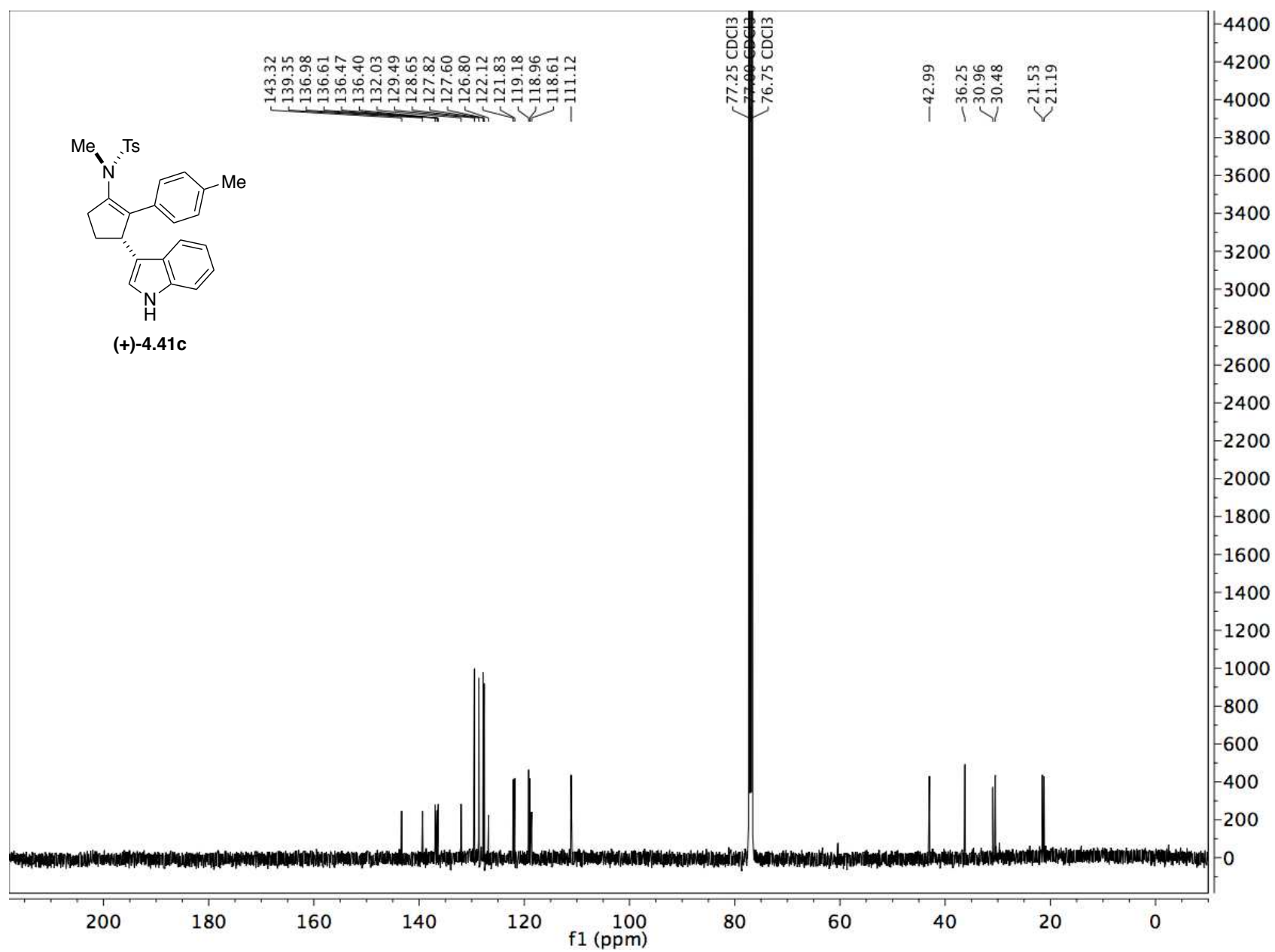


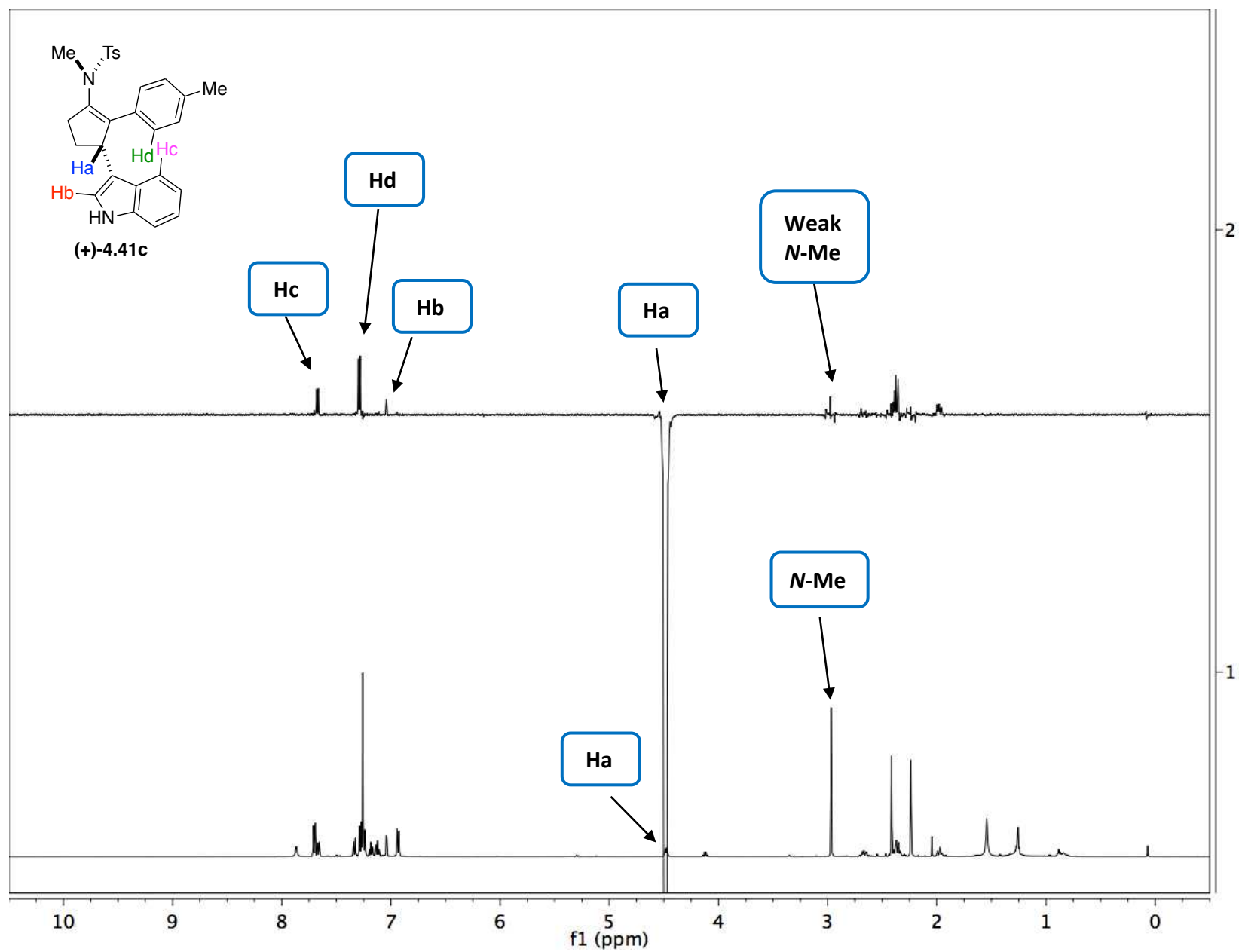


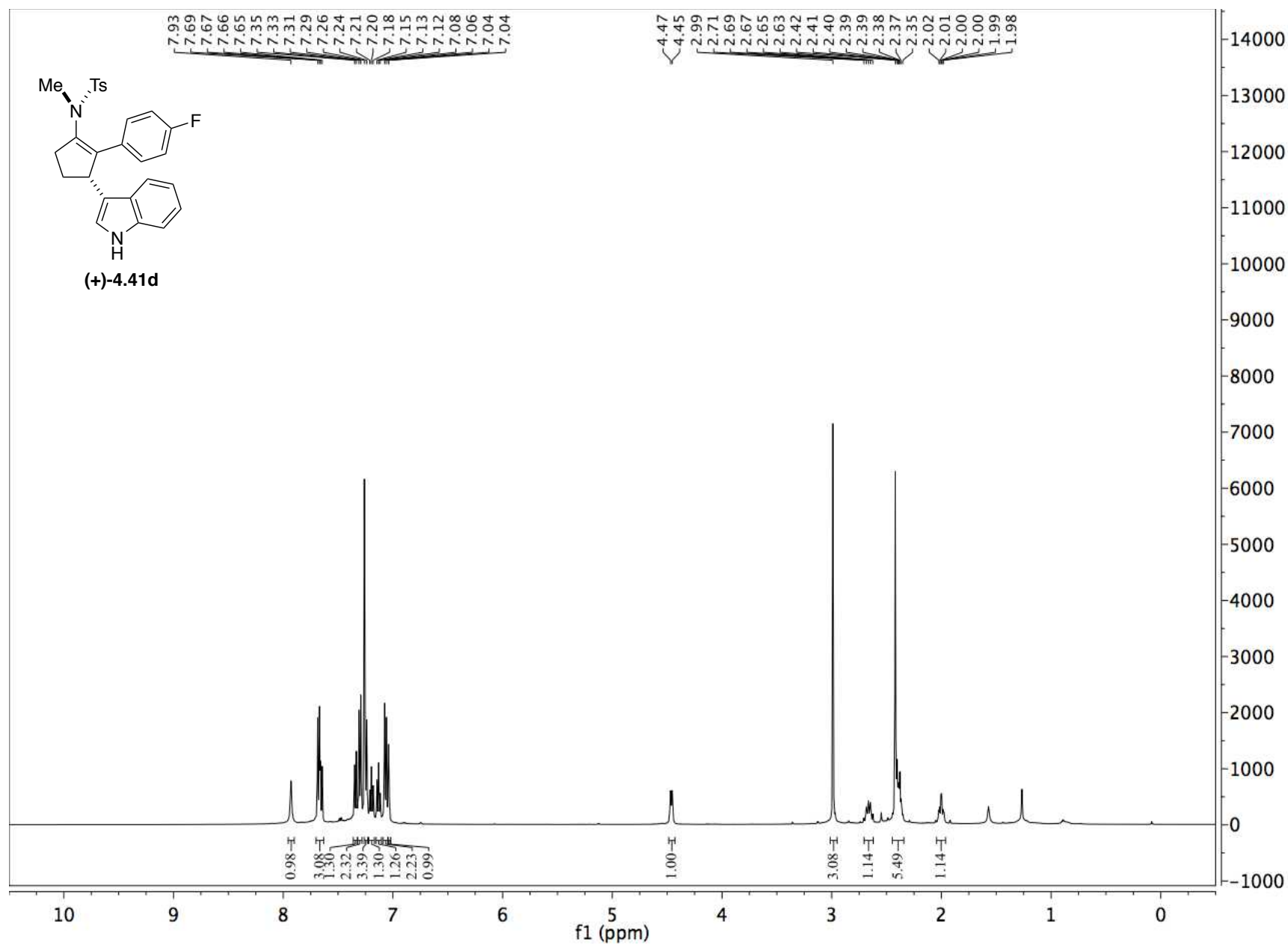


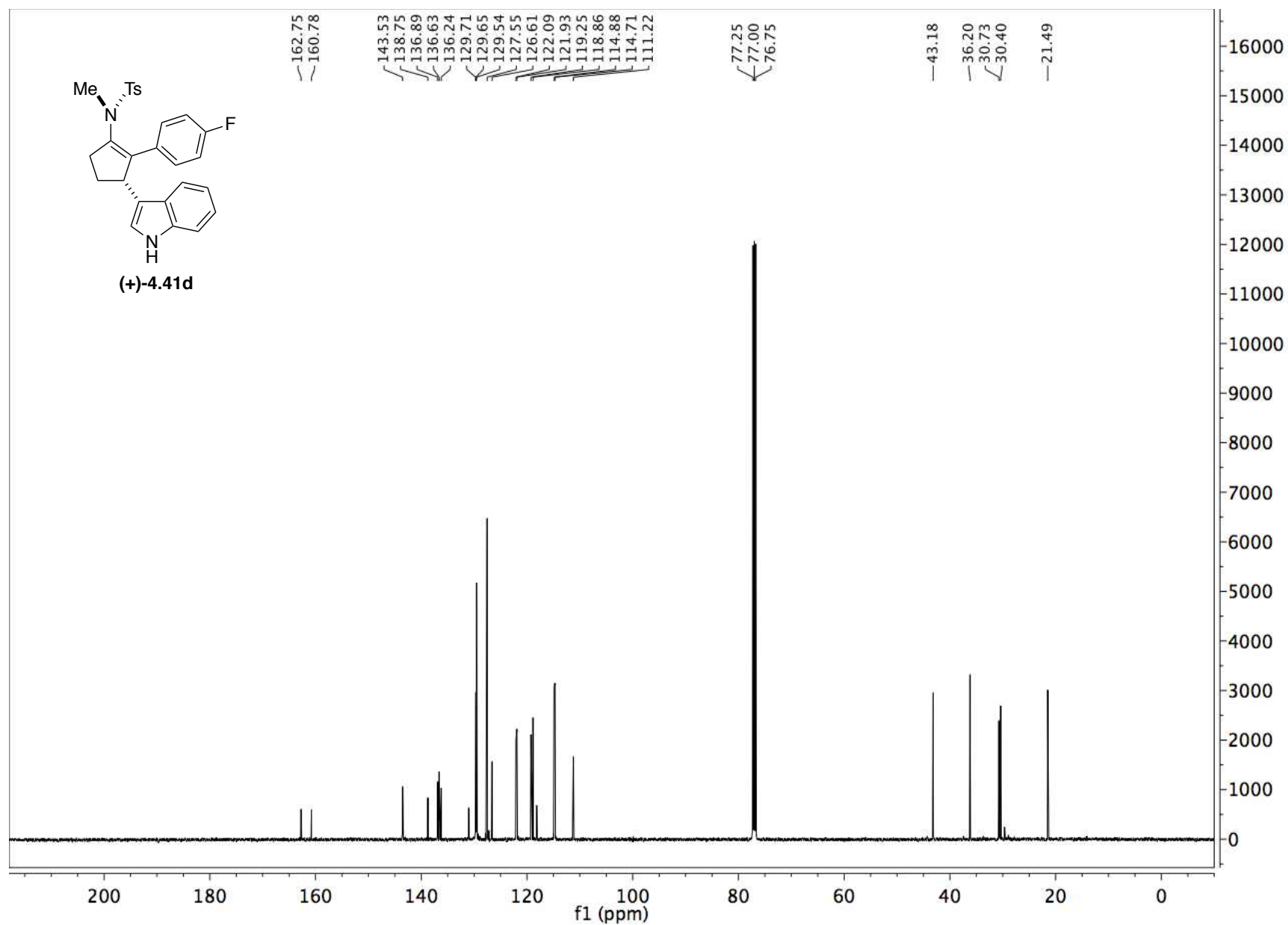




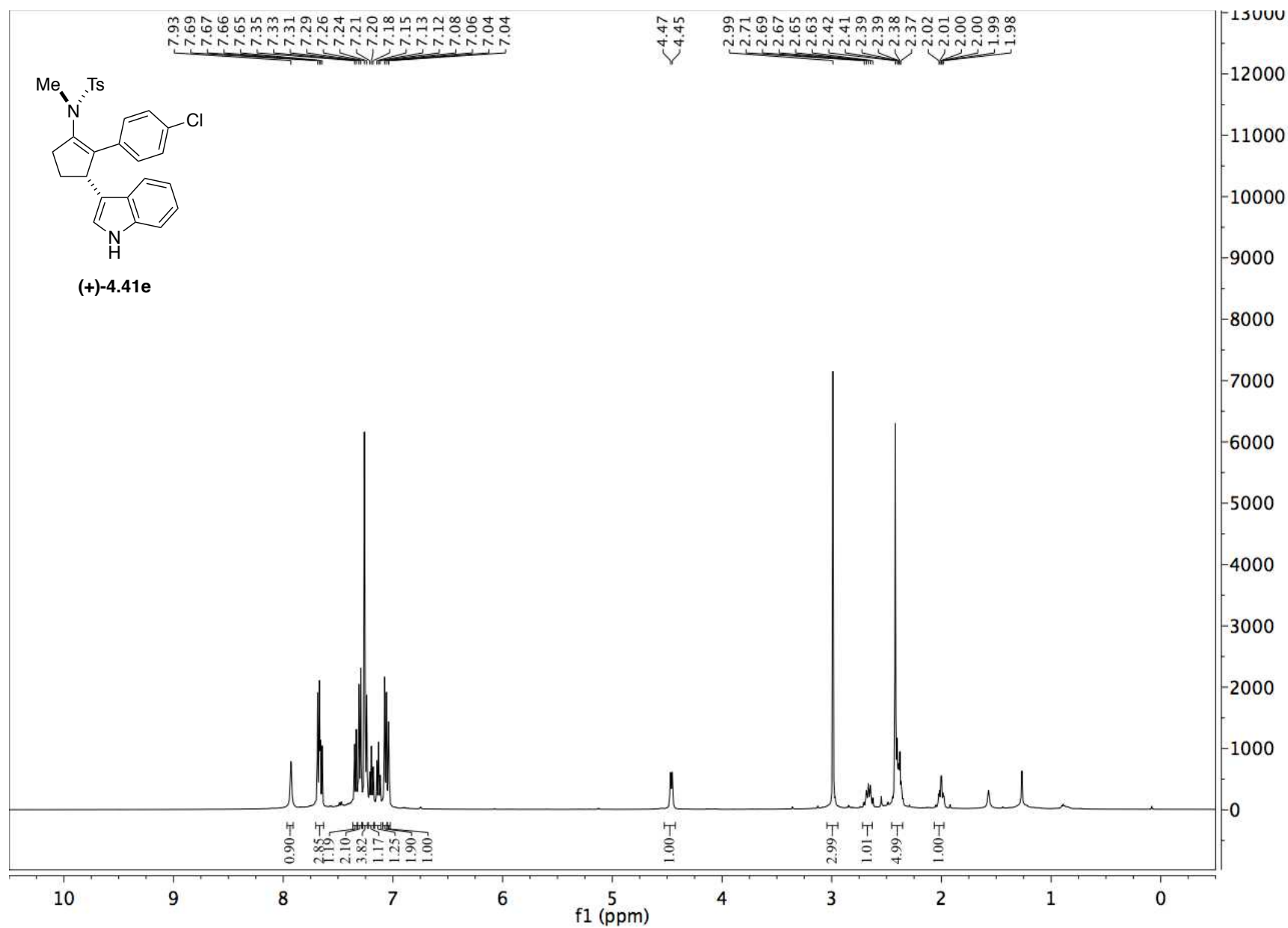


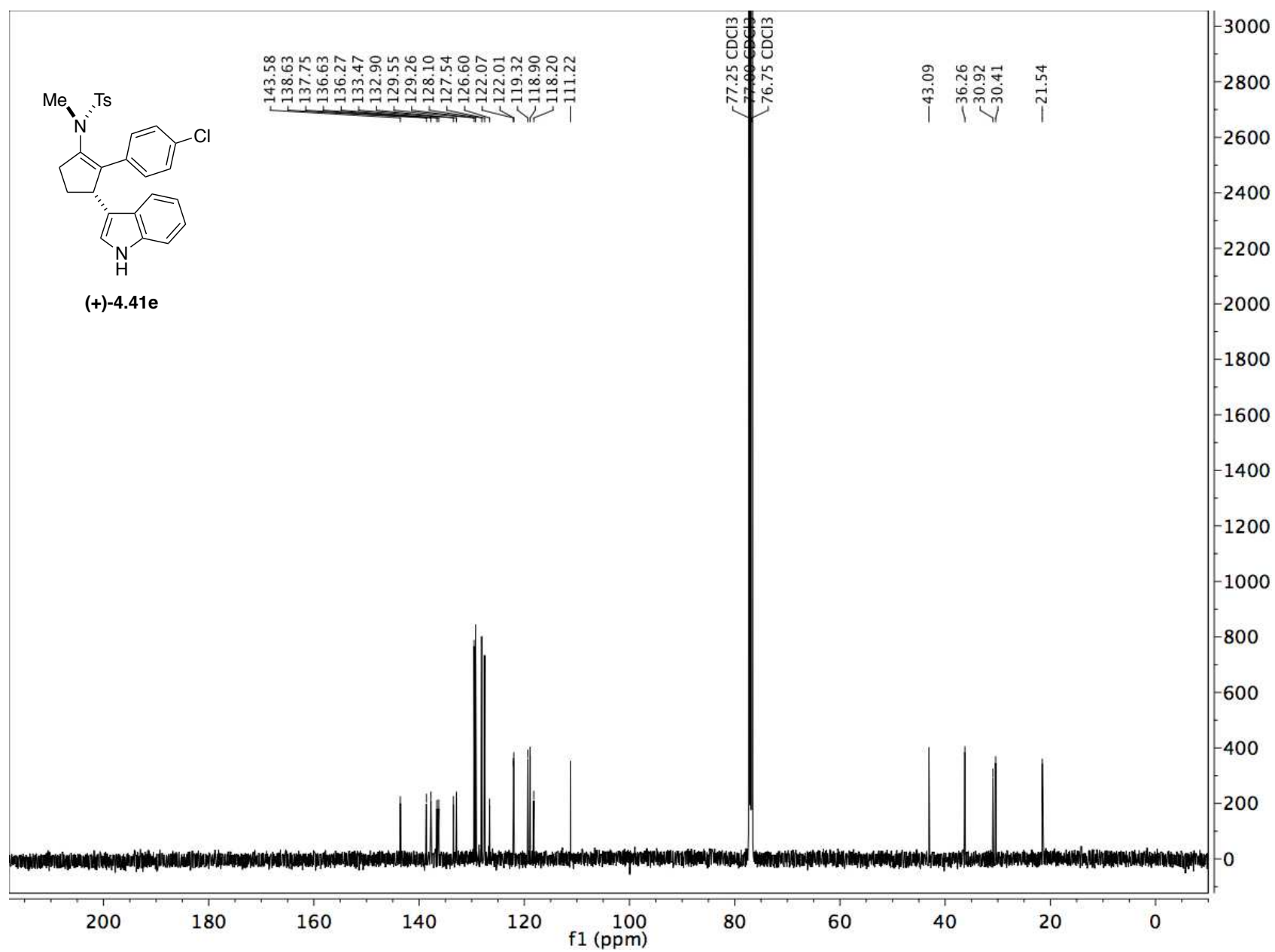


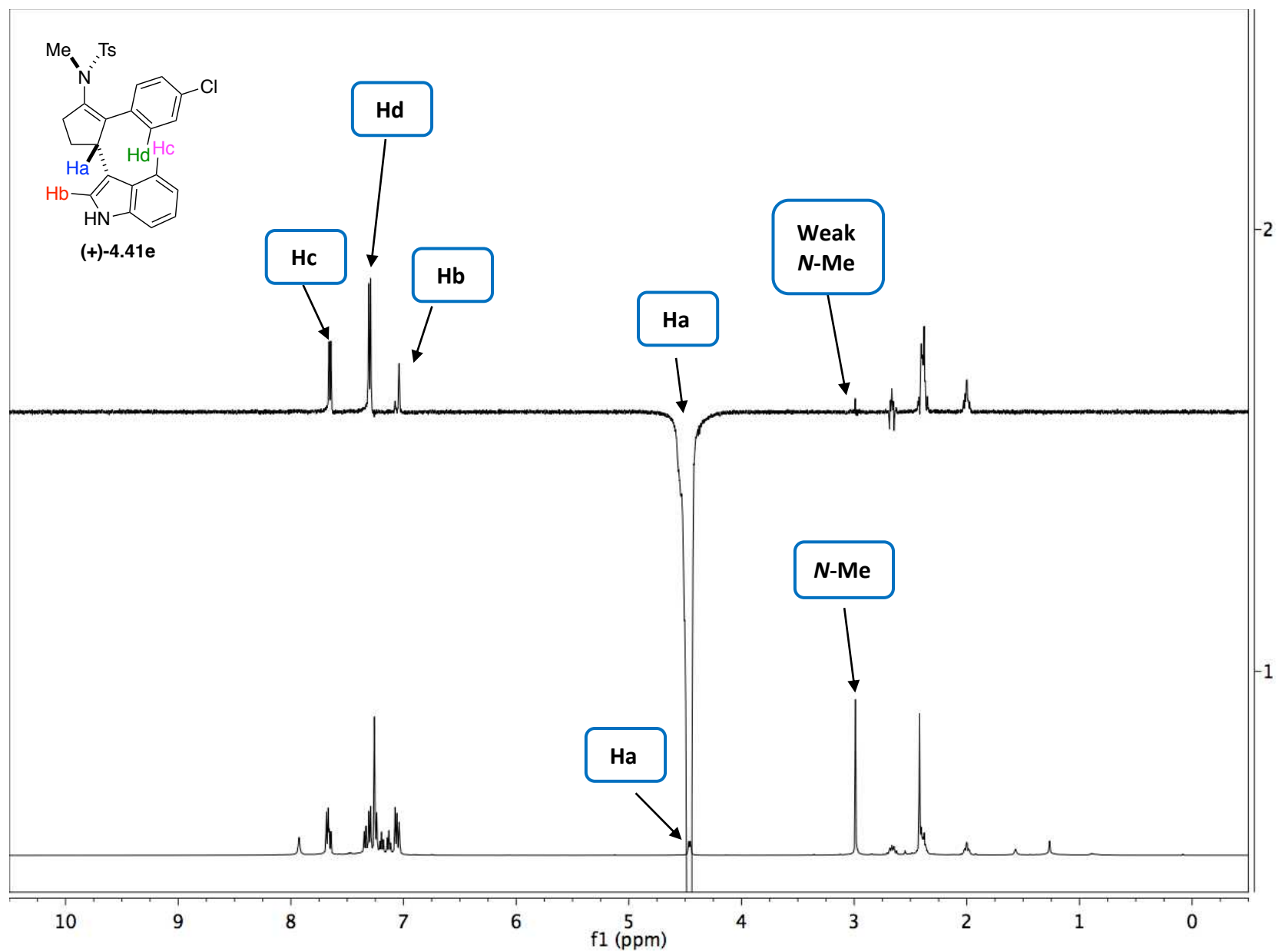




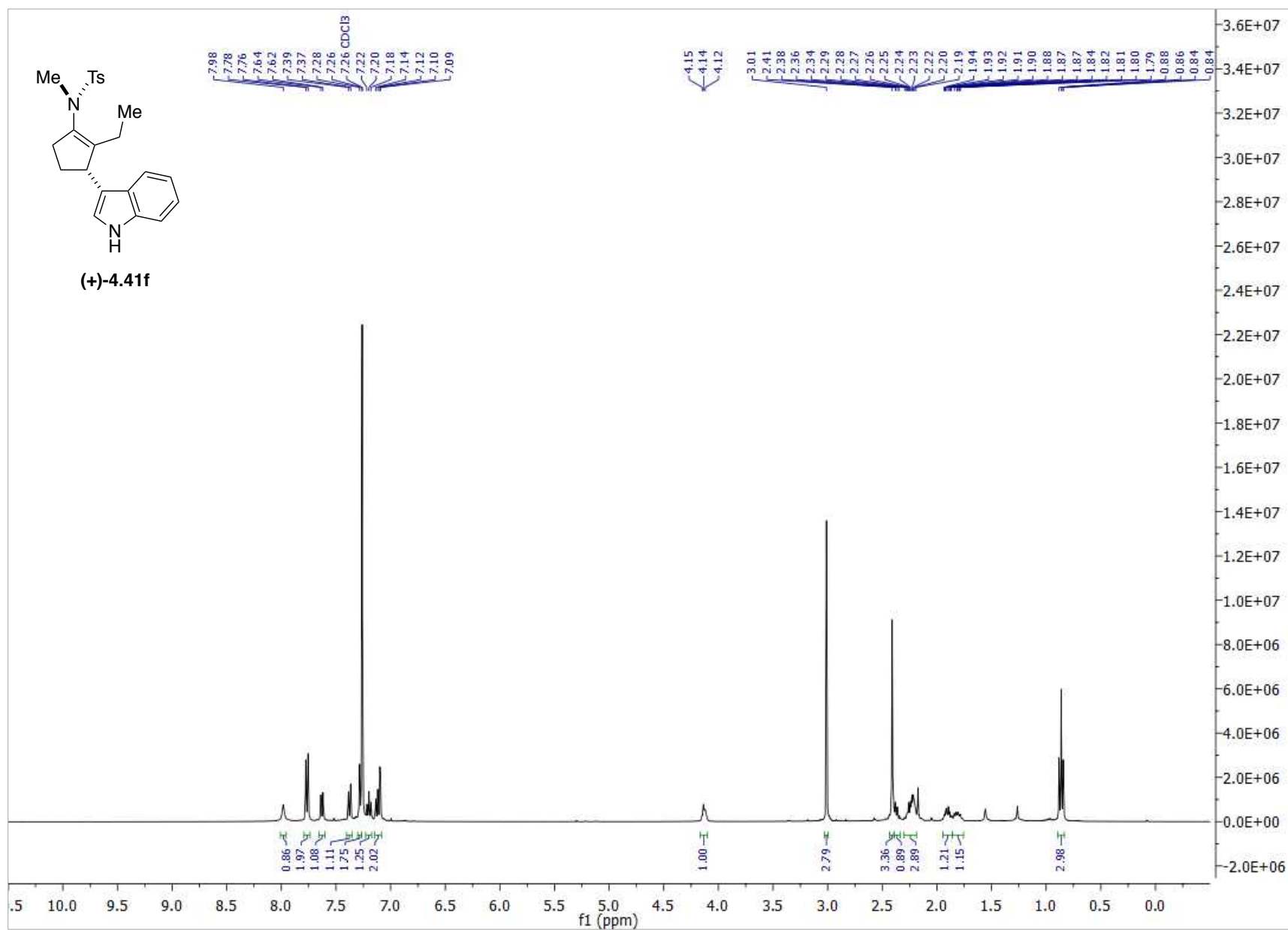


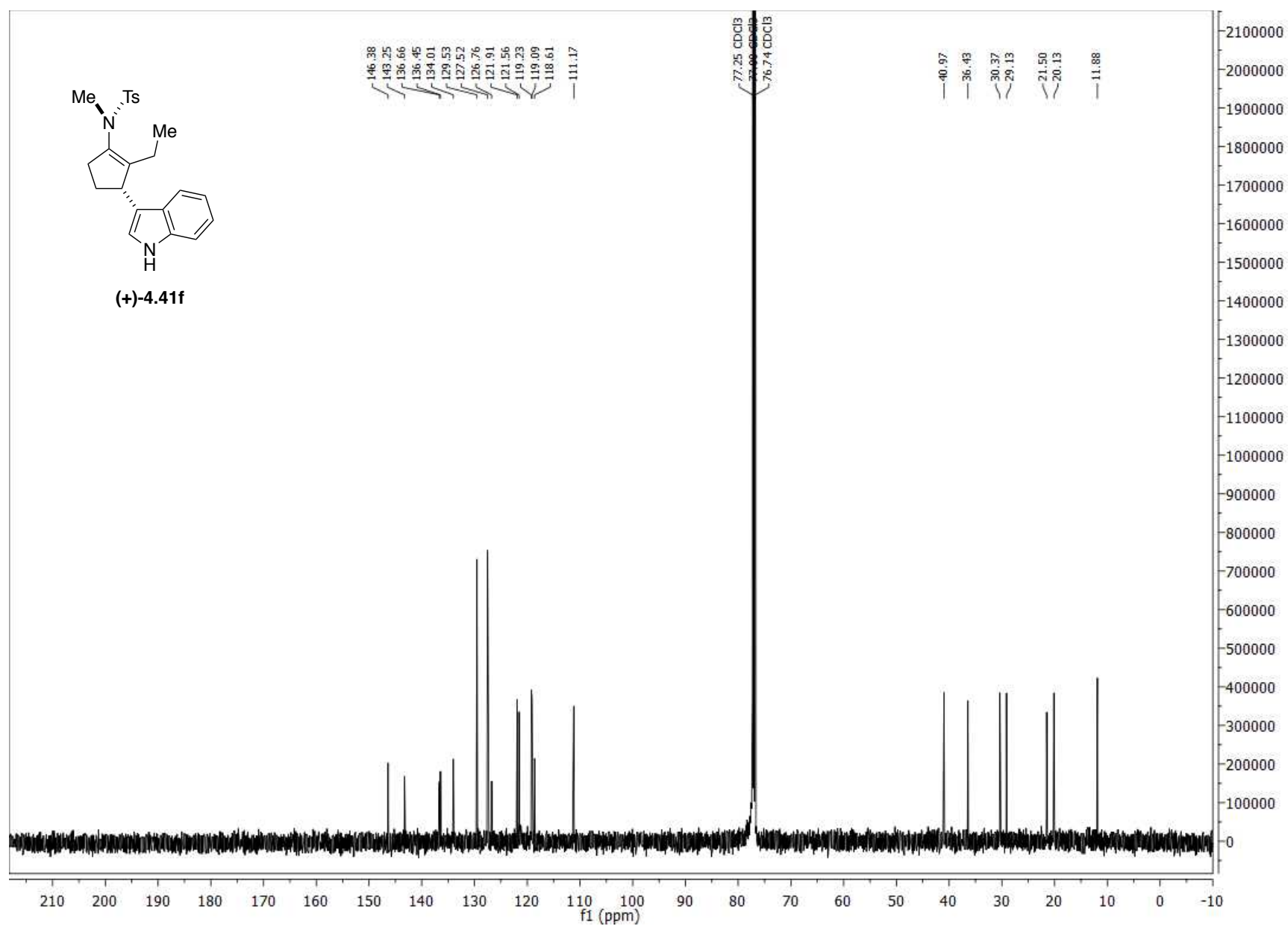


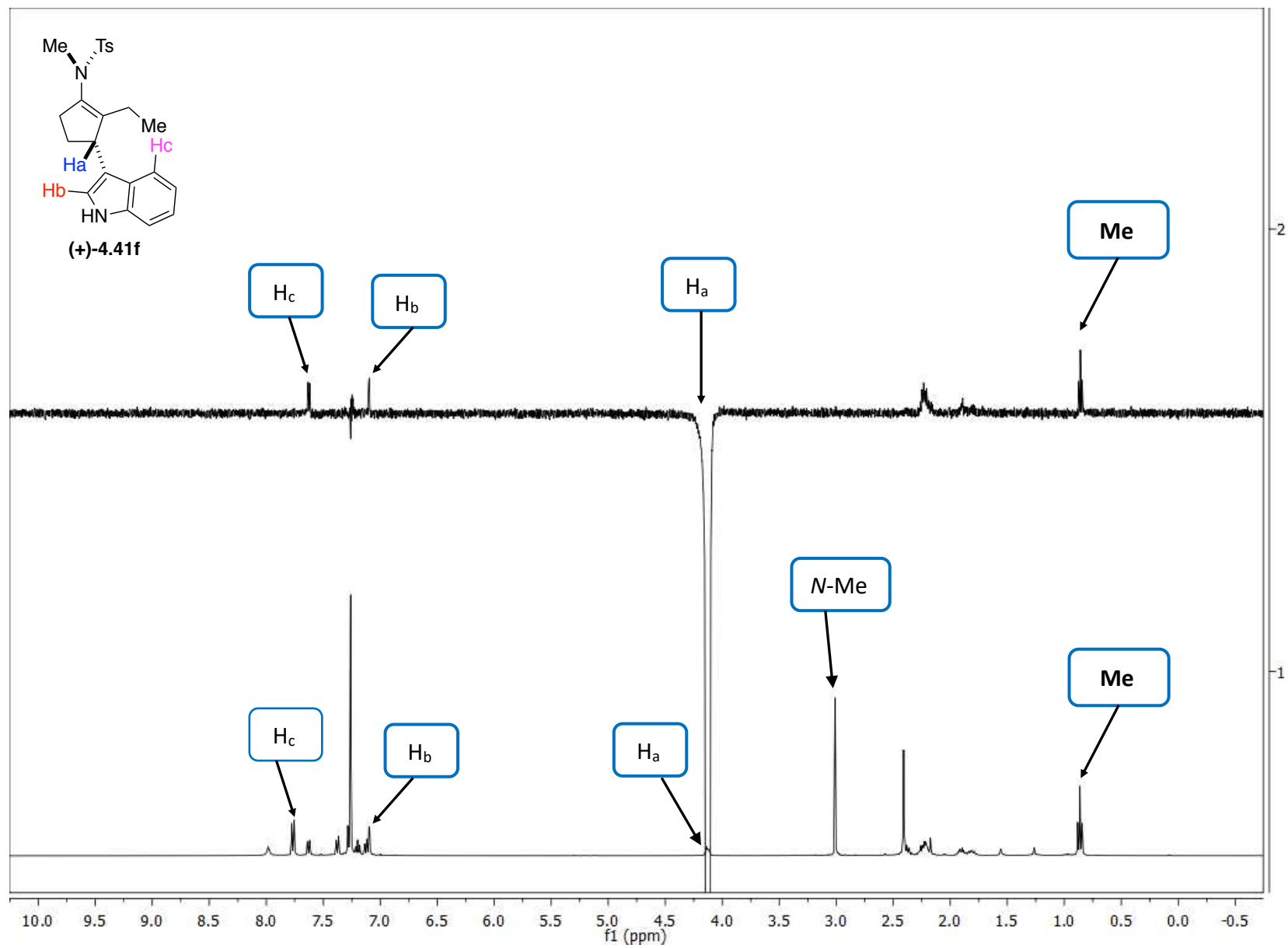


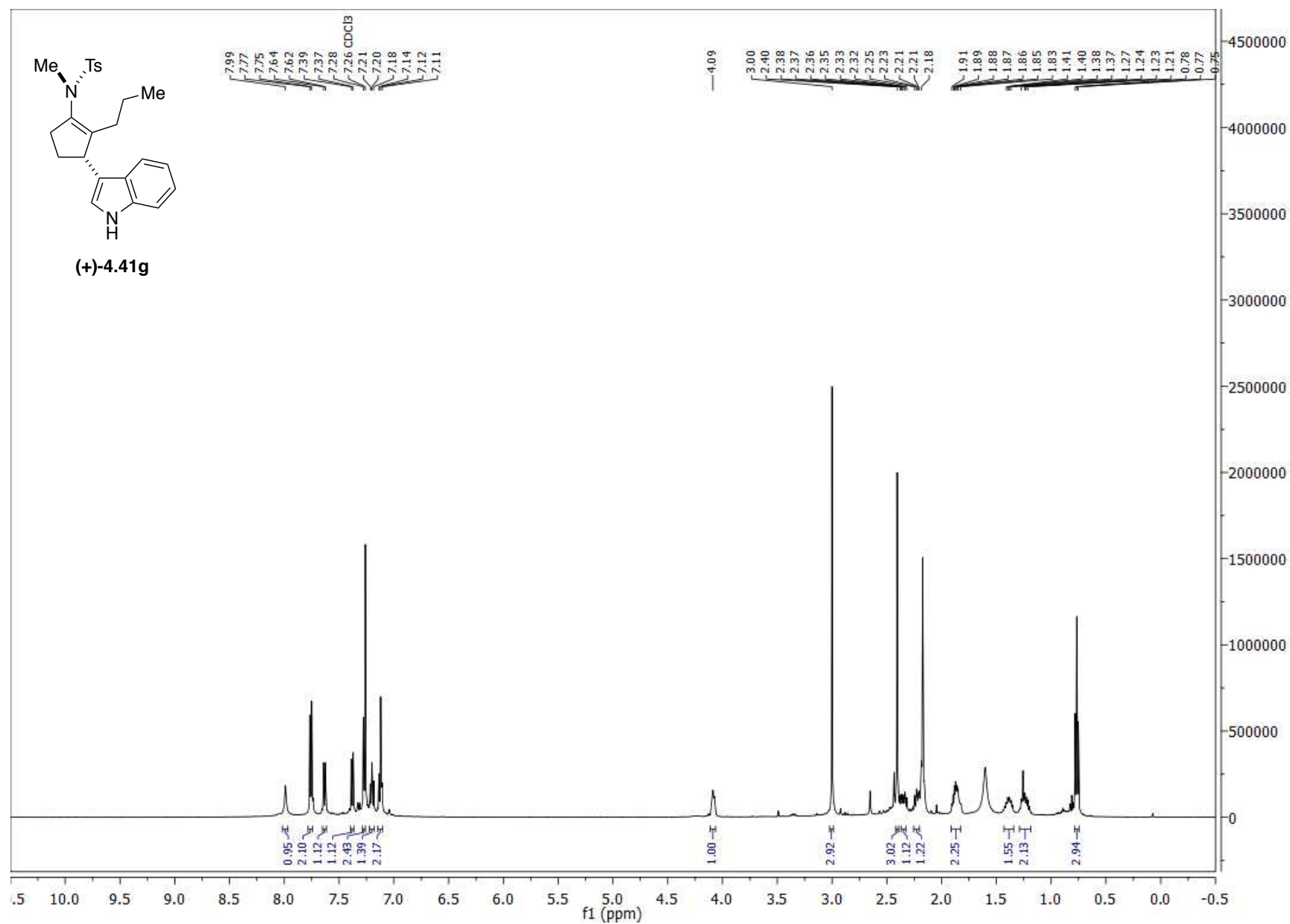


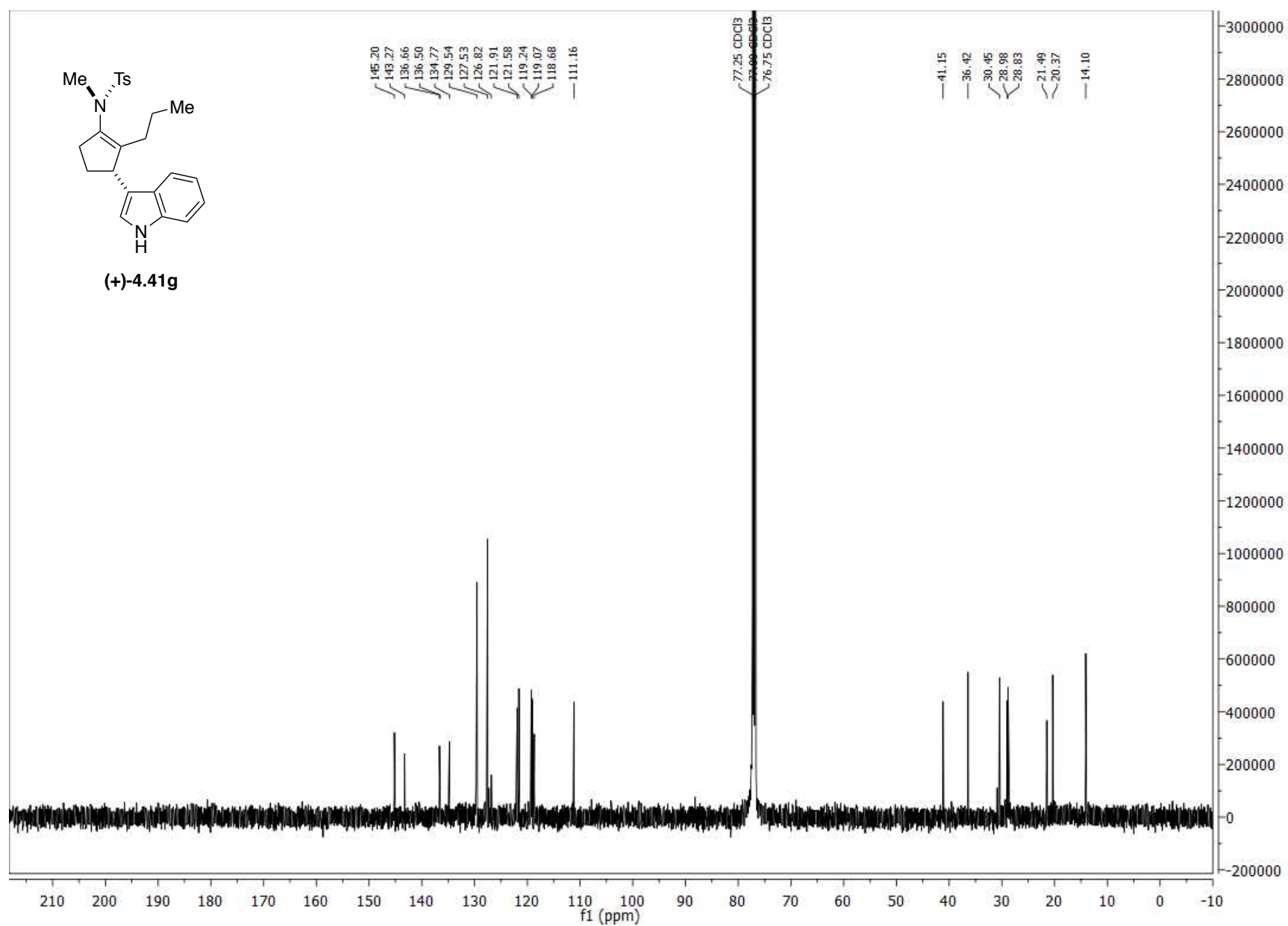


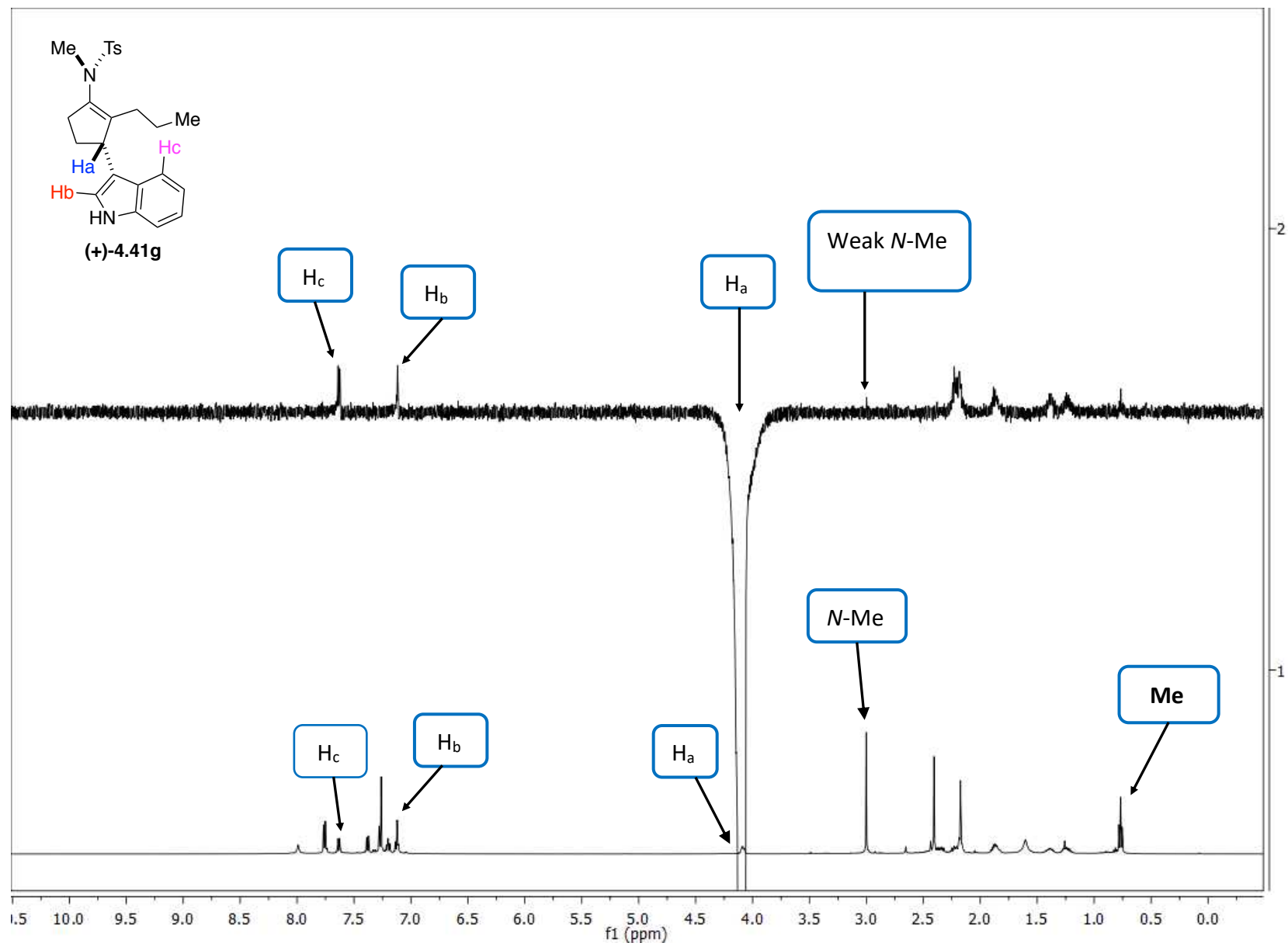


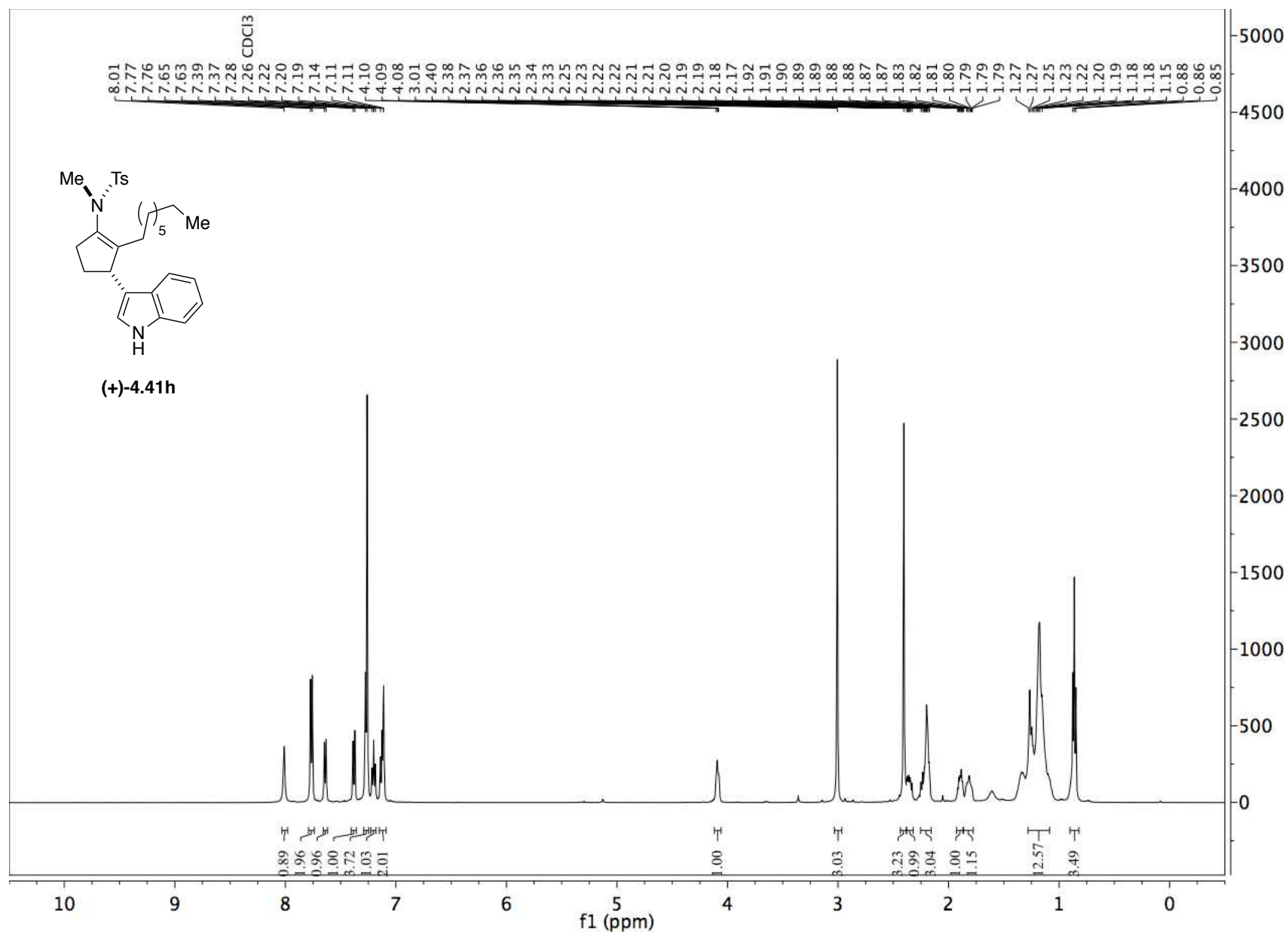


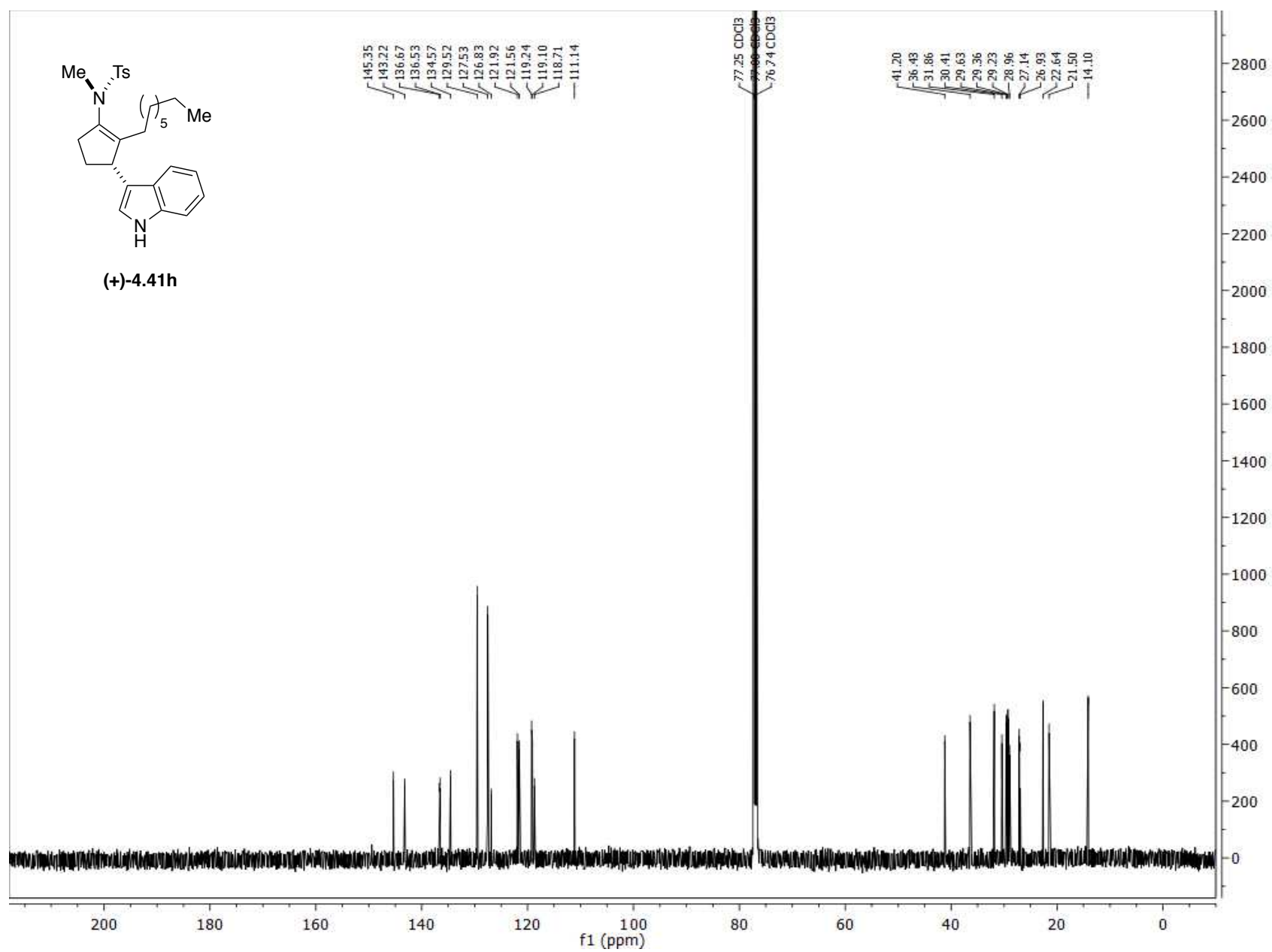




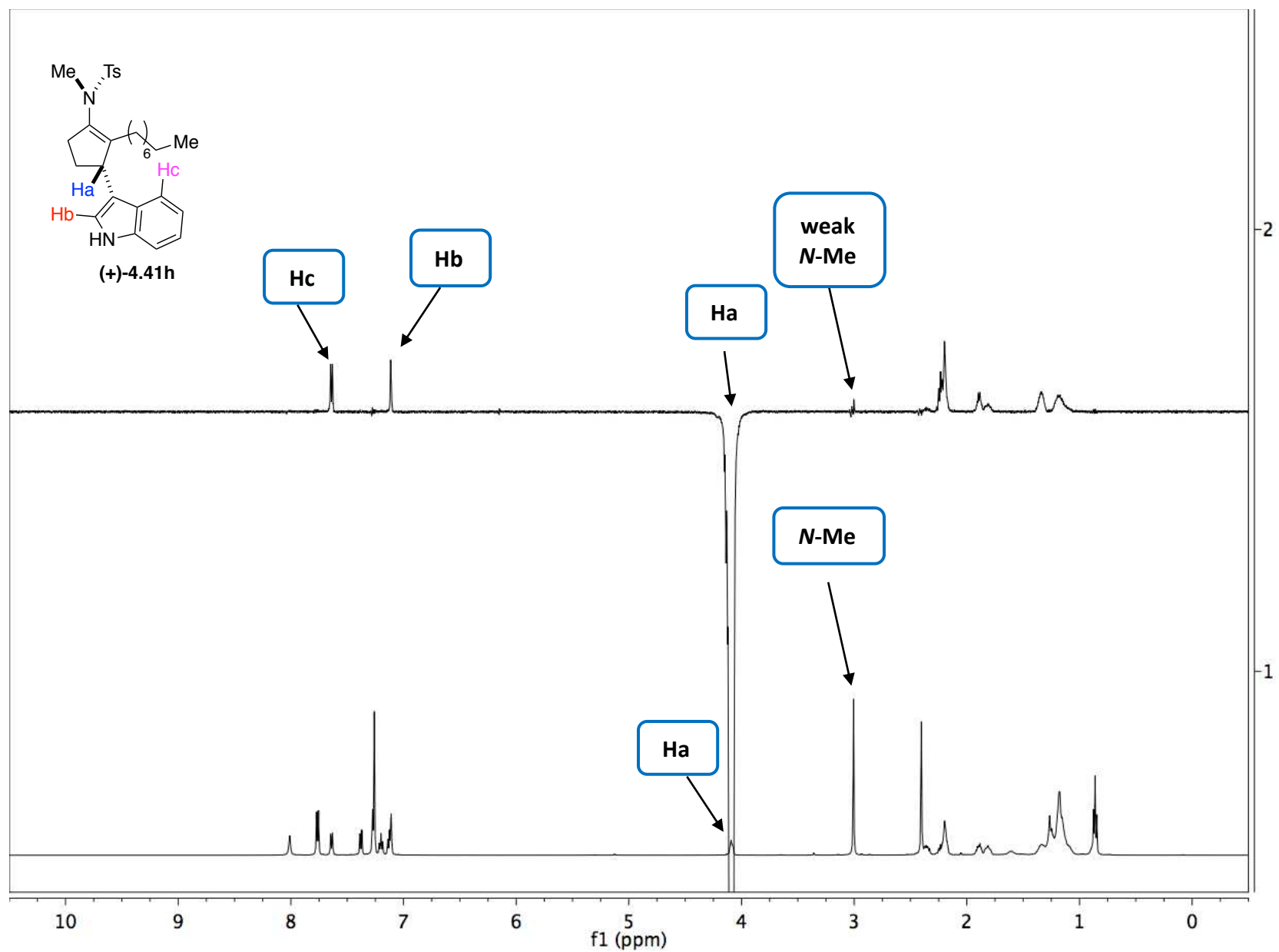


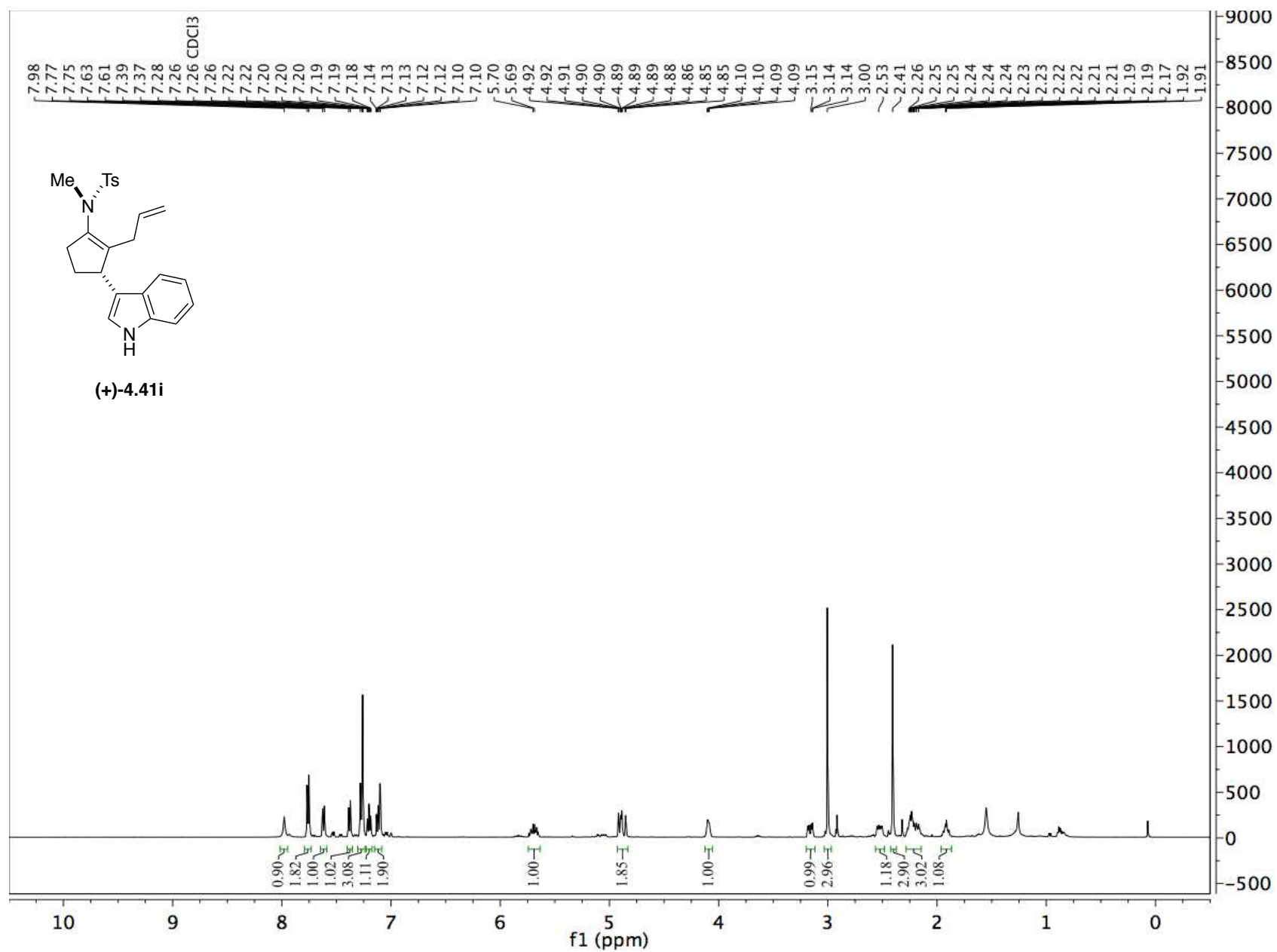


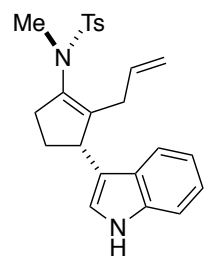




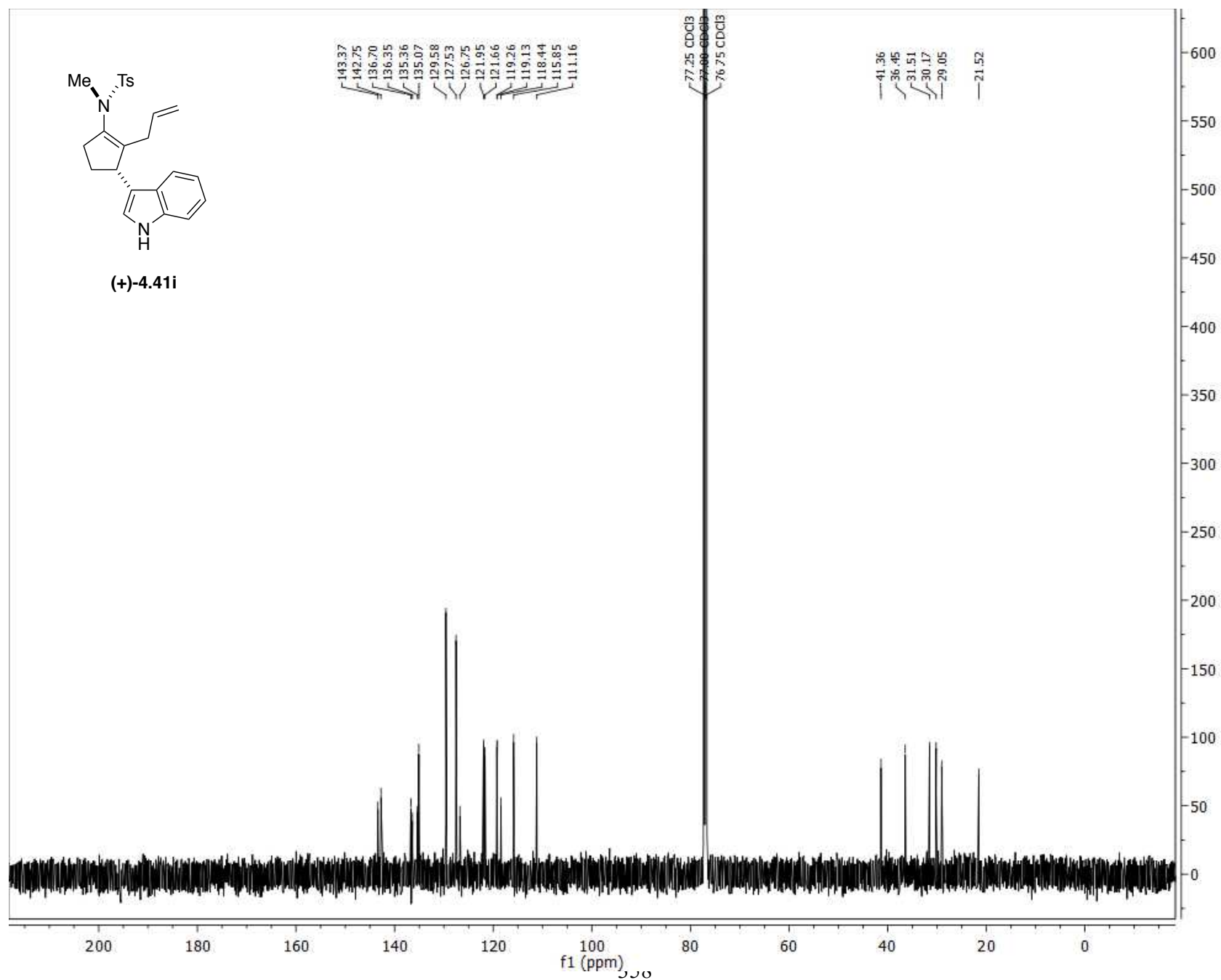


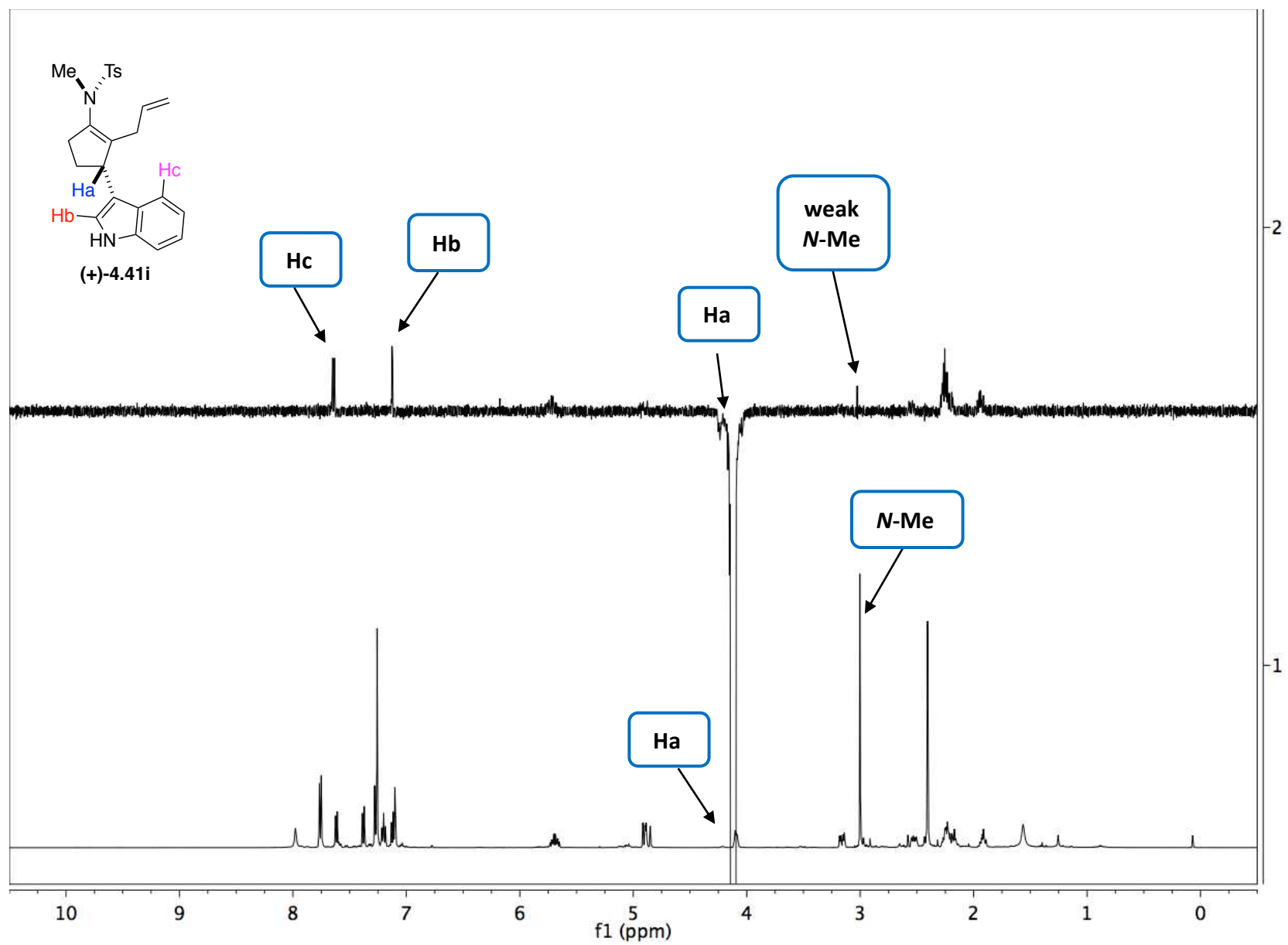




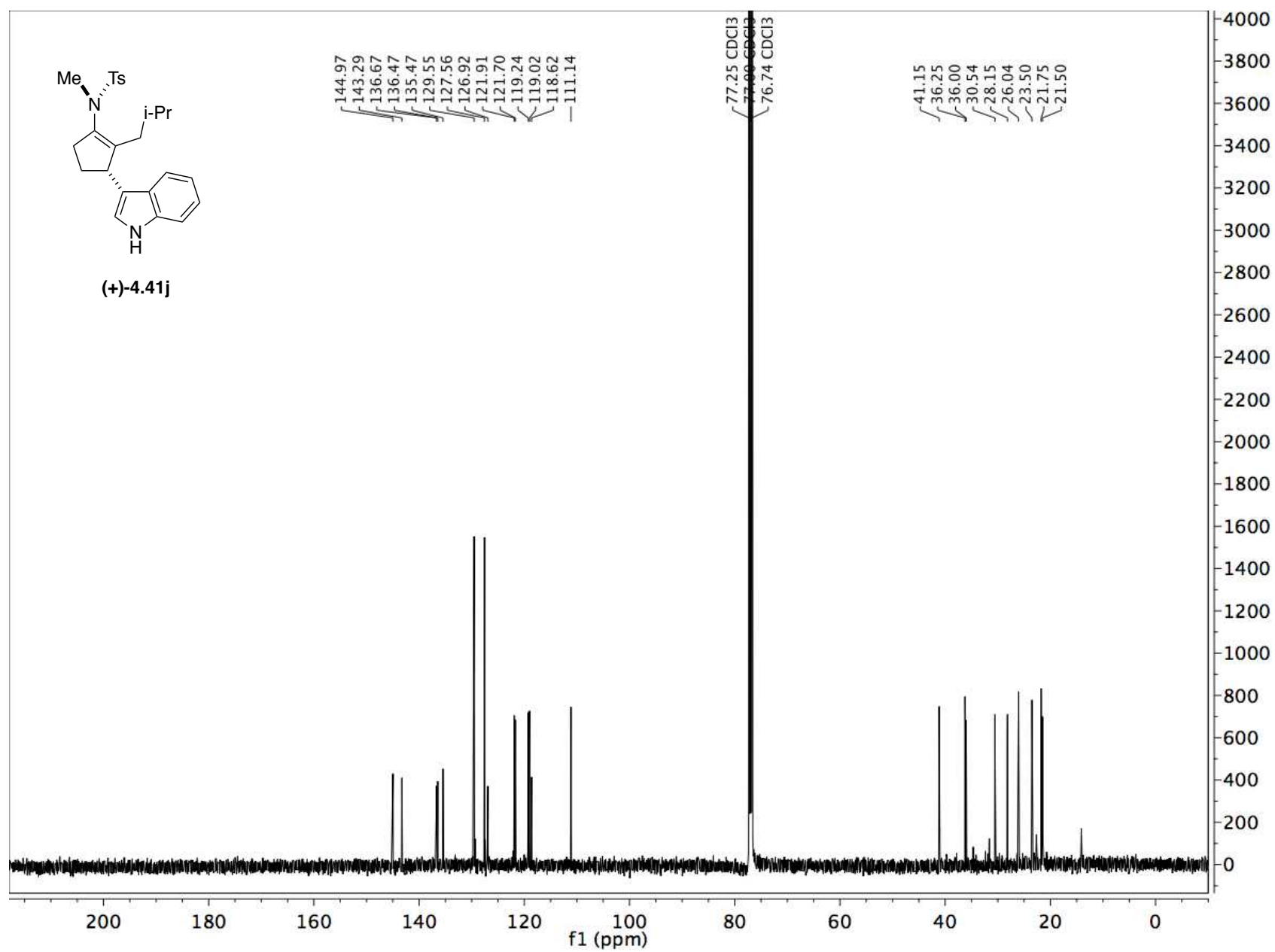


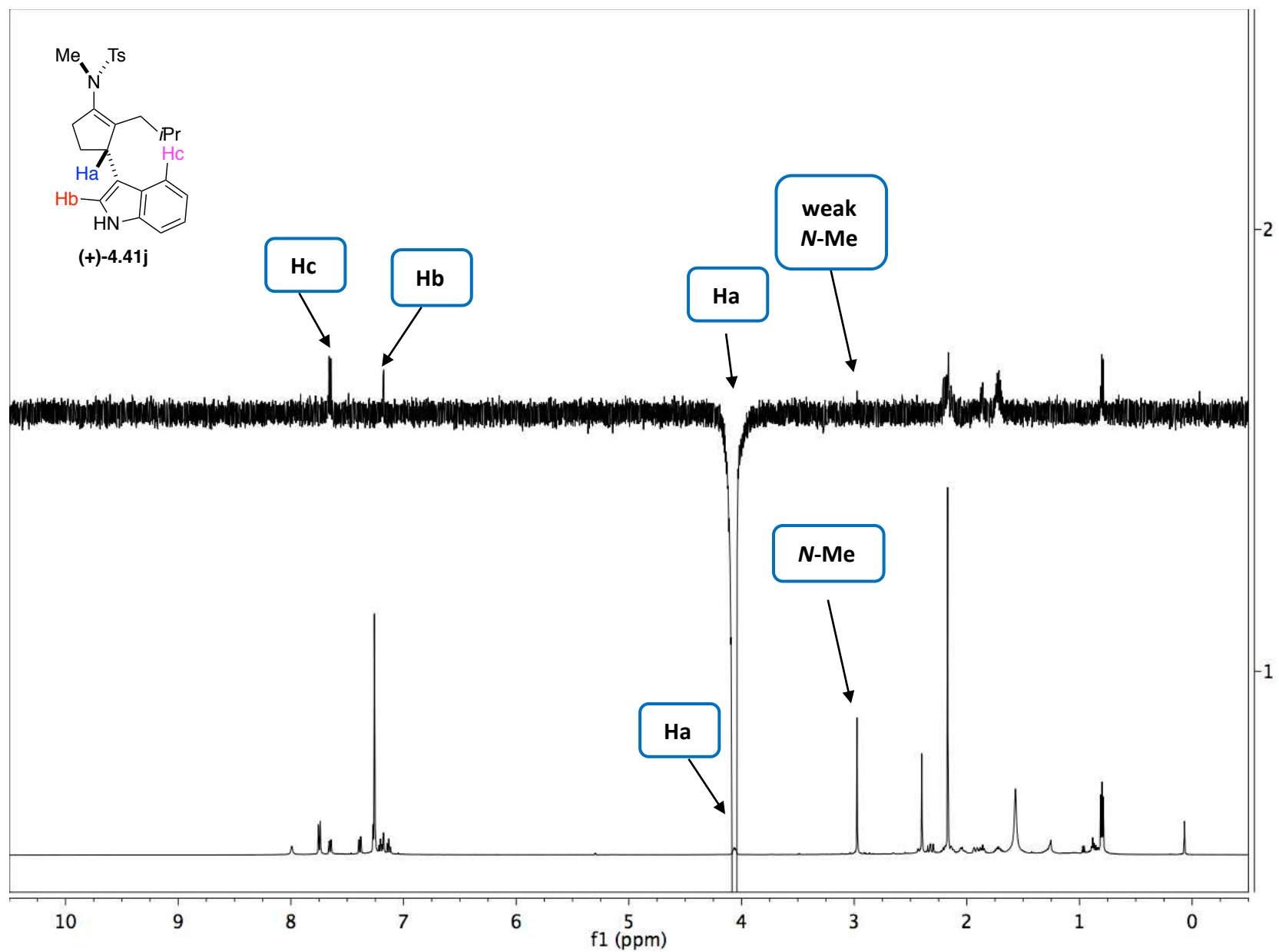
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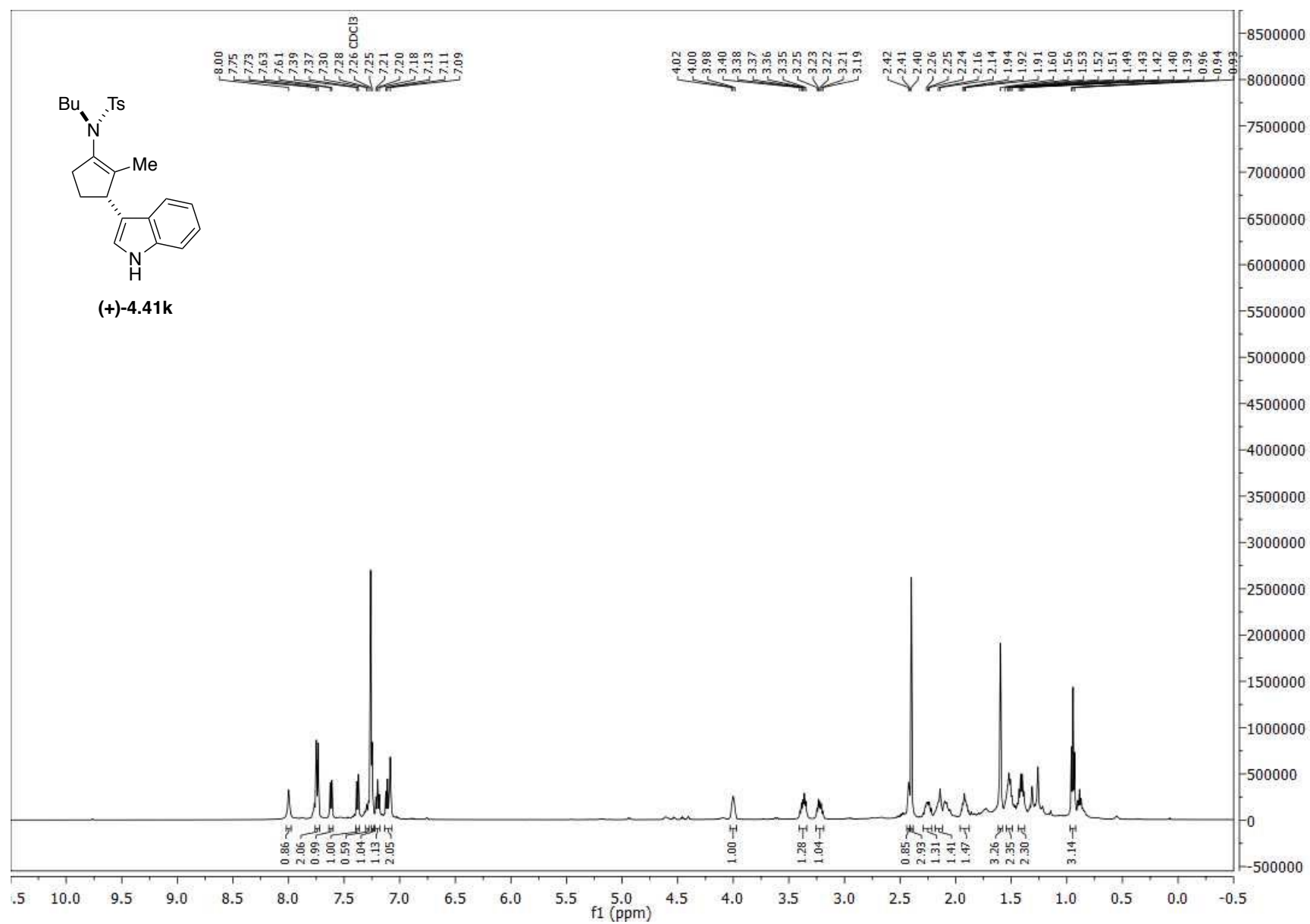




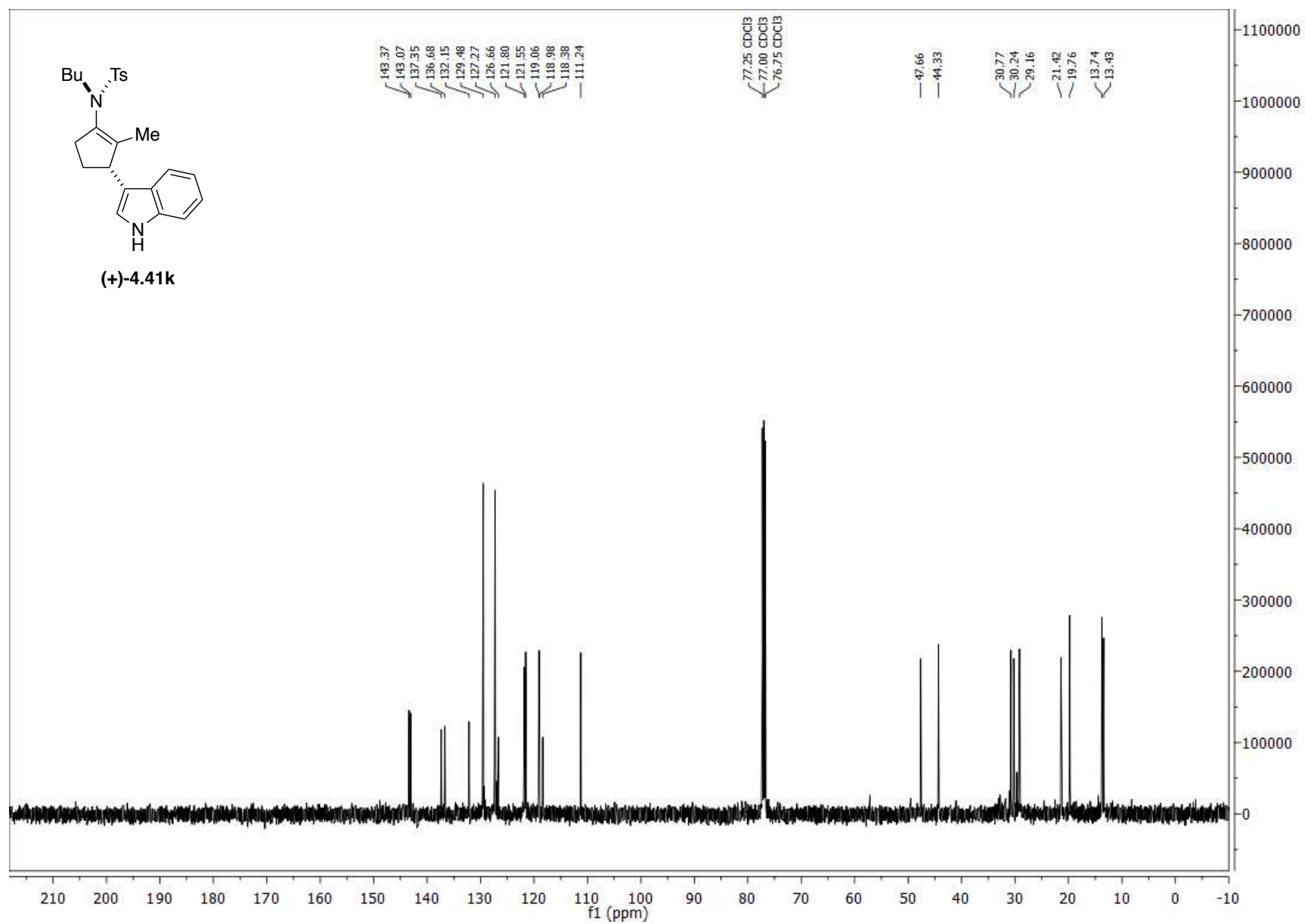


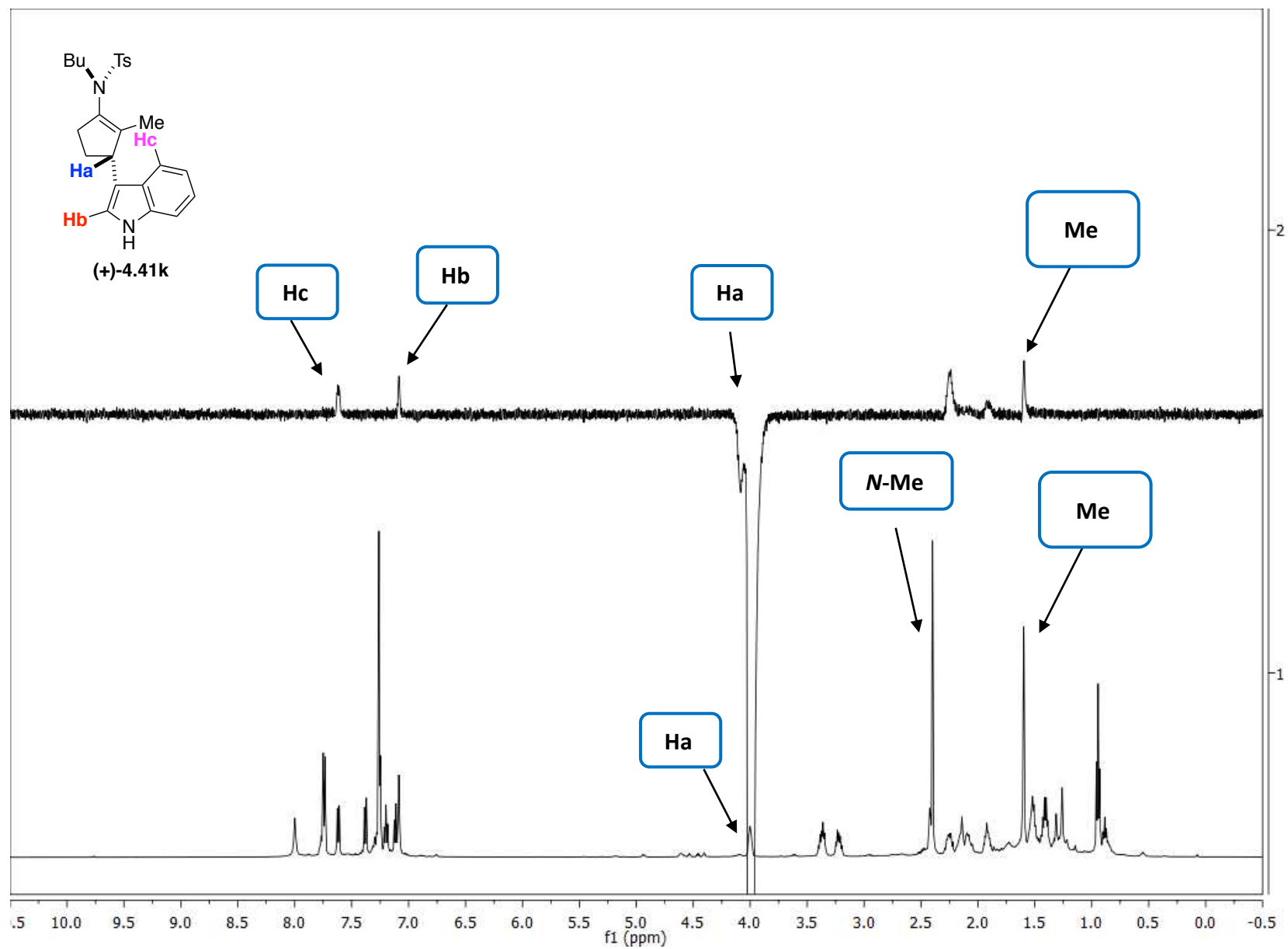












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## VITA

Binod Nepal was born in a small town called Baireni, in Dhading district of Nepal. He attended the then Shree Bageshwaree Secondary School for the high-school level education. He then moved to the capital city of Nepal, Kathmandu for the undergraduate studies in the Amrit Campus, where he discovered his love for organic chemistry. He then went on to earn his master's degree in Organic Chemistry from the Central Department of Chemistry, Tribhuvan University in 2015. His master's thesis under the supervision of Prof. Susan Joshi involved extraction of essential oil and phytosterols from medicinal plants and evaluating their antibacterial and antioxidant properties. Binod then moved to the United States in Fall 2016, where he is a PhD candidate under the supervision of Prof. Rendy Kartika at Louisiana State University. During his PhD research, Binod has worked on multiple projects involving regioselective and enantioselective trapping of oxyallyl and amidoallyl cationic species. Binod plans to graduate in Spring 2022 with a PhD degree.