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Synthesis of Structurally Diverse Molecular Scaffolds Enabled by Protected Oxyallyl Cations

Joshua Andrew Malone

Louisiana State University and Agricultural and Mechanical College

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SYNTHESIS OF STRUCTURALLY DIVERSE MOLECULAR SCAFFOLDS
ENABLED BY PROTECTED OXYALLYL 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
Joshua Andrew Malone
B.S., State University of New York, Oswego, 2014
May 2021

I dedicate this work to my parents, William A. Malone and Kimberlee J. Malone,

my little sister, Emily W. Malone, and my fiancé Delaney J. Darragh.

Thank you for always encouraging me and providing me with unconditional love and support

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List of Abbreviations

°C	degrees Celsius
α	alpha
β	beta
γ	gamma
μg	microgram
μL	microliter
^1H	proton NMR
^{13}C	carbon NMR
\AA	angstrom
AcOH	acetic acid
Alk	alkyl
Ar	aryl
AgBF ₄	silver tetrafluoroborate
AgOTf	silver triflate
b	broad
BEt ₃	triethylborane
BF ₃ •OEt ₂	boron trifluoride diethyl etherate
Bn	benzyl
Bu	butyl
Ca(NTf ₂) ₂	calcium(II) bis(trifluoromethanesulfonimide)
CCl ₄	carbon tetrachloride

CDCl_3	deuterated chloroform
cm^{-1}	per centimeter
CSA	camphorsulfonic acid
CH_2Cl_2	dichloromethane
conv	conversion
CsF	cesium fluoride
$\text{Cu}(\text{acac})_2$	copper (II) acetylacetonate
$\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$	copper (II) tetrafluoroborate hexahydrate
CuCl_2	copper (II) chloride
$\text{Cu}(\text{MeCN})_4\text{BF}_4$	copper (I) tetrakis acetonitrile tetrafluoroborate
$\text{Cu}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$	copper (II) nitrate hexahydrate
$\text{Cu}(\text{OAc})_2$	copper (II) acetate
$\text{Cu}(\text{OTf})_2$	copper (II) triflate
CuSO_4	copper (II) sulfate
cy	cyclohexyl
D	deuterium
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublet of doublets
ddt	doublet of doublet of triplets
DCE	dichloroethane
DFT	density functional theory

DIBAL.....	diisobutylaluminium hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
<i>E</i>	<i>Entgegen</i> (trans)
ee	enantiomeric excess
equiv	equivalent
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
Et ₃ N	triethylamine
Et ₂ O	diethyl ether
<i>f</i>	wavenumber
Fe(OTf) ₂	iron (II) triflate
FT-IR	Fourier-transform infrared
g	gram
GaMe ₃	trimethylgallium
h	hour/hours
H ₂	hydrogen gas
HCl.....	hydrochloric acid
H ₂ O.....	water

HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
<i>i</i> -Pr.....	isopropyl
J	coupling constant
kg	kilogram
K ₂ CO ₃	potassium carbonate
KH.....	potassium hydride
KOH.....	potassium hydroxide
LA	Lewis acid
LED.....	light-emitting diode
LDA	lithium diisopropylamide
Li	lithium metal
LiAlD ₄	lithium aluminum deuteride
LiAlH ₄	lithium aluminum hydride
LiHDMS	lithium bis(trimethylsilyl)amide
LiPF ₆	lithium hexafluorophosphate
M	molar
m	multiplet
<i>m</i>	meta
M ⁺	molecular ion
Me	methyl
MeCN	acetonitrile

MeI	methyl iodide
MeOH	methanol
mg	milligram
MgSO ₄	magnesium sulfate
mL	milliliter
mmol	millimol
MS	molecular sieves
<i>m/z</i>	mass-to-charge ratio
NaBF ₄	sodium tetrafluoroborate
NaCN	sodium cyanide
NaOMe	sodium methoxide
NaOtBu	sodium <i>tert</i> -butoxide
NBS	<i>N</i> -bromosuccinimide
<i>n</i> -BuLi.....	<i>n</i> -butyllithium
NiBF ₄ •6H ₂ O.....	nickel tetrafluoroborate hexahydrate
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
Nu.....	nucleophile
<i>o</i>	ortho
<i>p</i>	para
Ph	phenyl
PMB	para-methoxybenzyl
PNP	para-nitrophenyl

PPh ₃	triphenylphosphine
ppm	parts per million
PPTS	pyridinium para-toluenesulfonate
Pt/Cl	platinum on carbon
PtCl ₂	platinum dichloride
Py•TfOH	pyridinium triflate
R _f	retention factor
r.r.	regiometric ratio
rt	room temperature
s	singlet
SEM	2-(Trimethylsilyl)ethoxymethyl
S _N 2	bimolecular nucleophilic substitution
S _N 1	unimolecular nucleophilic substitution
t	triplet
TBAF	tetra- <i>N</i> -butylammonium fluoride
TBS	tert-butyl dimethylsilyl
<i>t</i> -Bu	tert-butyl
TES	triethylsilyl
TFE	trifluoroethanol
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TfOH	triflic acid
THF	tetrahydrofuran

Ti(OiPr) ₄	titanium isopropoxide
TMS	trimethylsilyl
TsOH	para-toluenesulfonic acid
TLC	thin layer chromatography
Ts	tosyl
UV	ultraviolet
Z	<i>Zusammen</i> (cis)

Abstract

This dissertation focuses on the synthesis of diverse molecular scaffolds through the use of protected oxyallyl cation intermediates. Chapter One provides background on the generation and applications of oxyallyl and silyloxyallyl cations, while focusing on the direct nucleophilic capture of these intermediates to generate functionalized ketones and silylenolates. Chapter Two depicts our approach to generate six-membered silyloxyallyl cations through the use of mild Brønsted acid activation. Regioselective nucleophilic capture of these intermediates successfully produced diverse α,α' -substituted silylenol ethers enabled by polar solvent and residual water.

Chapter three details strategies to generate 1,4-dicarbonyl compounds, focusing on the capture of cationic intermediates with enolate nucleophiles. Further implementation of previously observed solvent effects in the generation of silyloxyallyl cations allowed for a mild protocol for the regioselective synthesis of 1,4-monosilylated dicarbonyl compounds via silylenolate nucleophiles. Our synthesis of 1,4-monosilylated dicarbonyls was further applied in Chapter Four to generate tetrahydroindoles and tetrahydrocyclopenta[*b*]pyrroles in a one-pot, three-component approach utilizing silyloxyallyl cations, silylenolate nucleophiles, and primary amines. This Brønsted acid catalyzed formal [2+2+1] annulation reaction allowed for the assembly and functionalization of nitrogen containing heterocycles in a highly modular manner

Lastly, Chapter Five details a novel approach for the synthesis of α,α' -bis-quaternary ketones through an unprecedented copper catalyzed Claisen rearrangement. Regioselective nucleophilic capture of unsymmetrical disubstituted oxyallyl cations was enabled by a Lewis acidic, copper catalyst. A subsequent diastereoselective Claisen rearrangement resulted in highly functionalized α,α' -bis-quaternary ketones in moderate to excellent yields.

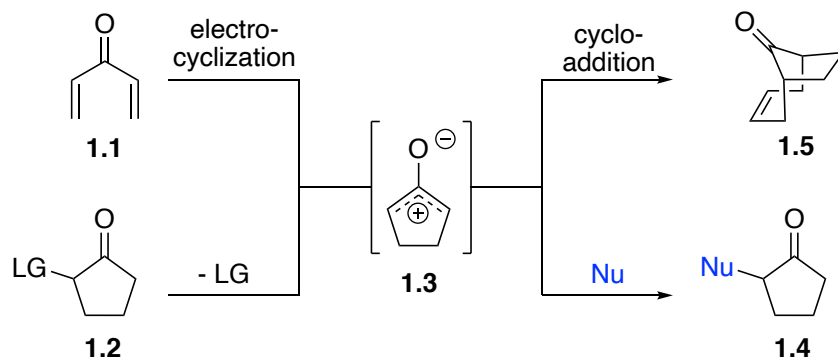
Chapter One: Generation and Nucleophilic Capture of Oxyallyl and Silyloxyallyl Cations

1.1 Purpose

The purpose of this chapter is to provide a brief review of the strategies developed to generate oxyallyl cations and showcase their synthetic utility to affording a variety of structural motifs. These electrophilic intermediates have been extensively explored in numerous synthetic applications including the Favoski rearrangement, Nazarov cyclization, and direct nucleophilic capture yielding highly functionalized ketones. Approaches to generate and intercept oxyallyl cations *via* ionization of α -haloketones and α -tosyl ketones will be discussed. Lastly a novel strategy to control regioselective nucleophilic capture of silyloxyallyl cations and the utility of these electrophilic intermediates to construct numerous molecular motifs will be presented.

1.2 Oxyallyl Cations

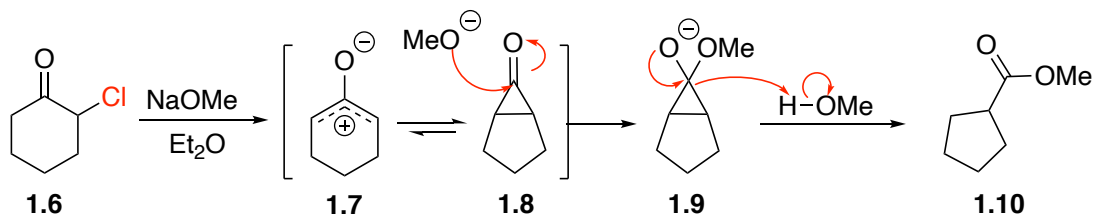
Oxyallyl cations are defined as a three-carbon centered zwitterionic species, in which the positive charge is delocalized across the three carbons with a negatively charged oxygen. There are two general approaches to generate these cationic species, one method being the activation of divinyl ketones **1.1** with either a Lewis or Brønsted acid to promote an electrocyclization, affording oxyallyl cation **1.3** (Scheme 1.1). The second approach to generate oxyallyl cations involves the ionization of ketones with a leaving group at the α -carbon **1.2** through either an E_{1cb} or S_N1 type mechanism. These highly reactive electrophilic intermediates have been proven to be powerful tools for numerous synthetic transformations, such as the Favorskii rearrangement,¹⁻⁵ [4+3], [3+3], and [3+2] cycloadditions,⁶⁻¹⁰ Nazarov cyclization's,¹¹⁻¹³ and direct nucleophilic capture of oxyallyl cations.^{5, 14-16}



Scheme 1.1 Oxyallyl Cation Generation and Utility

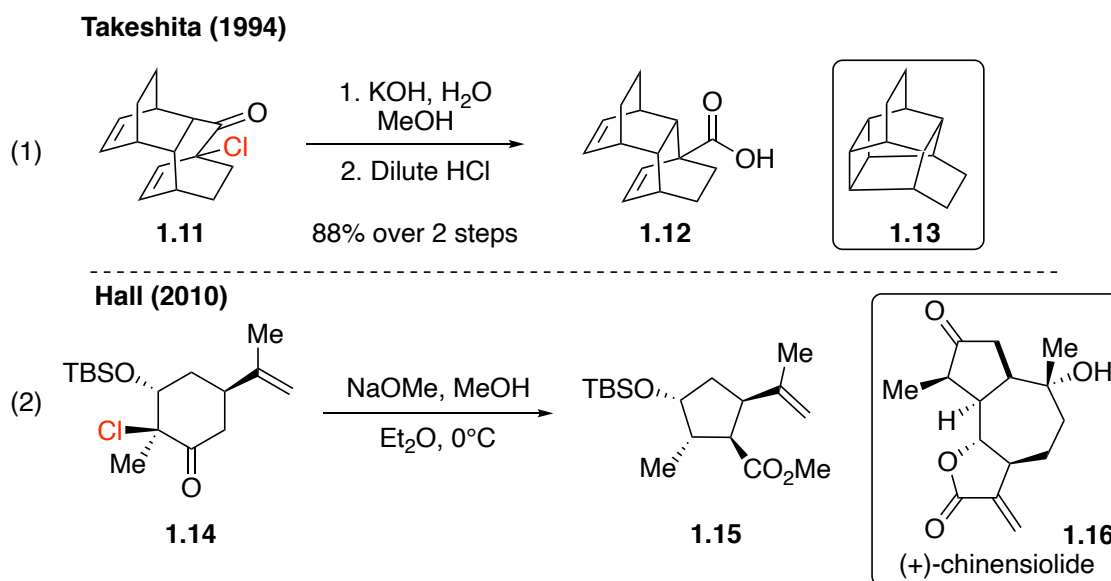
1.3 Oxyallyl Cations in the Favorskii Rearrangement

Organic chemists have extensively studied the generation and reactivity of the oxyallyl cation, specifically in the Favorskii rearrangement. First reported in 1894, Favorskii observed that generation of symmetrical oxyallyl cation **1.7** could be achieved through a base promoted dehalogenation of α -chloroketone **1.6** which is proposed to proceed through an E_{1cb} like mechanism (Scheme 1.2).² The punitive oxyallyl cation exists as the zwitterionic species **1.7** in equilibrium with the more stable cyclopropenone intermediate **1.8**.⁴ In the presence of a hard nucleophile such as a methoxide anion, 1,2-carbonyl addition occurs followed by subsequent ring contraction to readily afford ester **1.10**. The most common nucleophiles utilized in the Favorskii rearrangement are alkoxide or hydroxide sources, generating the corresponding ester or carbocyclic acid respectively.¹⁷⁻¹⁹



Scheme 1.2 The Favorskii Rearrangement

Following this seminal report, the Favorskii rearrangement has been utilized in the synthesis of complex systems as displayed in Scheme 1.3. For example, *en route* to the synthesis of hexacyclotetradecene **1.13**, Takeshita et al exploited the Favorskii rearrangement as their key transformation in the construction of their bicyclic scaffold.²⁰ Takeshita demonstrated that upon treatment of bridgehead α -chloroketone **1.11** with KOH in water, followed by addition of dilute HCl readily furnished carboxylic acid **1.12** in 88% over 2 steps. Another example of the Favorskii rearrangement was demonstrated by Hall in the total synthesis of (+)-chinensioidide **1.16**.²¹ Hall observed that the synthesis of tetrasubstituted cyclopentane **1.15** could readily be achieved by treatment of α -chloroketone **1.14** with sodium methoxide (NaOMe) to promote rearrangement.

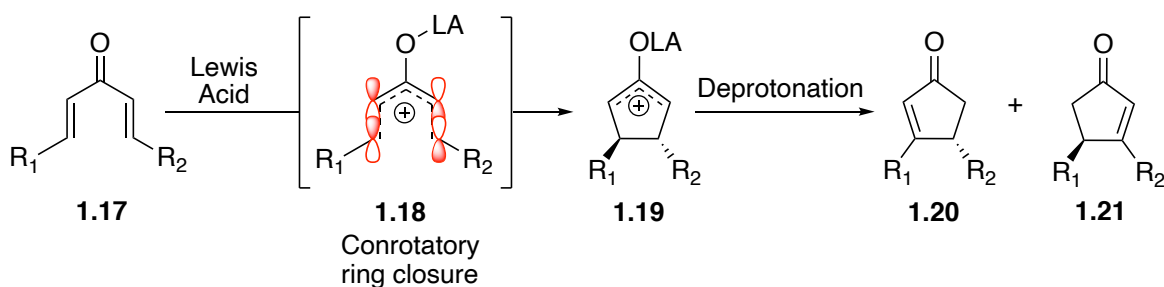


Scheme 1.3 Favorskii Rearrangements in Complex Molecule Synthesis

1.4 Oxyallyl Cations in Nazarov Cyclization's

An alternative approach to the generation of oxyallyl cations involves the activation of divinyl ketones with either a Lewis or Brønsted acid, better known as the Nazarov cyclization. The

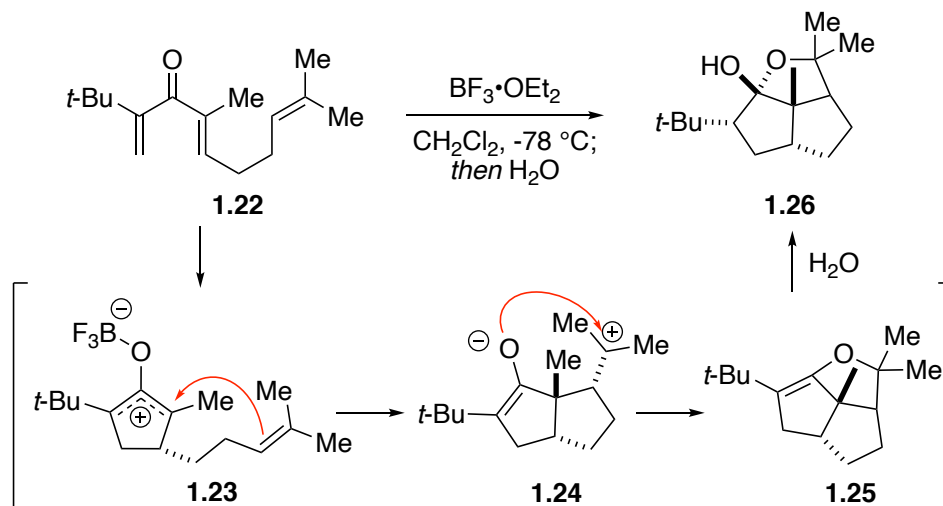
Nazarov cyclization is a widely utilized strategy to generate highly substituted and stereochemically rich cyclopentenones *via* oxyallyl cation intermediacy.^{11-13, 22-24} Initially reported by Nazarov in 1941, the electrocyclization involves Lewis or Brønsted acid activation of divinyl ketone **1.17** to generate pentadienyl cation **1.18** (Scheme 1.4). The use of an activator hypothetically decreases the HOMO-LUMO gap, allowing for the necessary orbital alignment of the vinyl groups. Furthermore, intermediate **1.18** undergoes conrotatory ring closure forming oxyallyl cation **1.19** with an observed trans-relationship between the substituents on the cyclopentanone. The generated oxyallyl cation intermediate **1.19** further undergoes nonselective deprotonation resulting in the generation of isomeric α - β -unsaturated ketones **1.20** and **1.21**.^{25, 26} Nonselective deprotonation of the β -hydrogens resulting in regioisomers remains a longstanding challenge in the Nazarov cyclization, but multiple methods to control this deprotonation step have been reported. Following the seminal report, many variations on the classic Nazarov transformation have been published including aza-Nazarov,²⁷⁻²⁹ the oxa-Nazarov,³⁰ and the imino-Nazarov reactions,³¹⁻³⁴ as well as the homo-Nazarov cyclization.³⁵⁻³⁷



Scheme 1.4 Lewis Acid Promoted Nazarov Cyclization

Recently, the “interrupted Nazarov” cyclization has gained popularity as a method to synthesize stereochemically enriched α -functionalized cyclopentenones.³⁸⁻⁴⁰ The interrupted

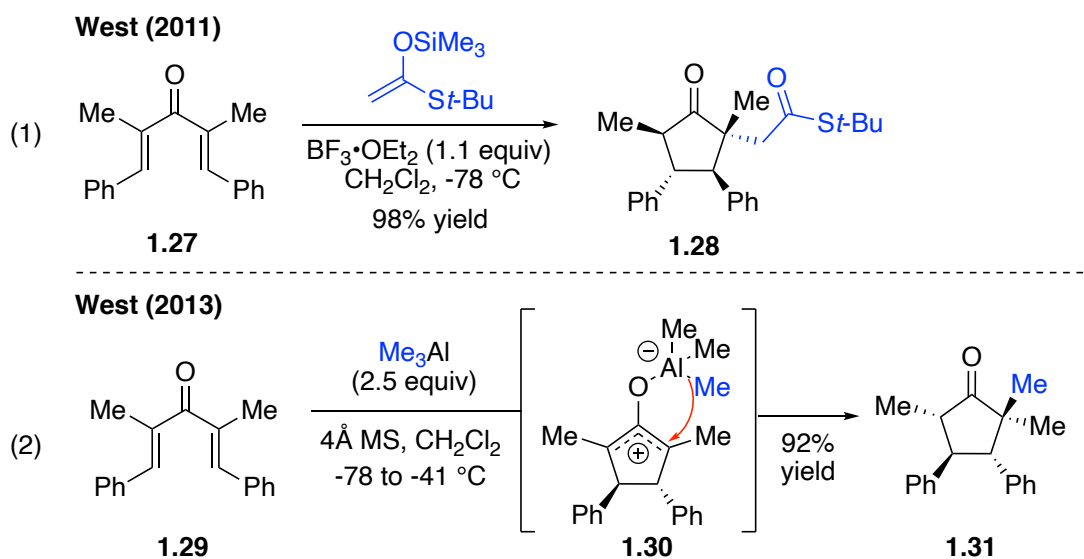
Nazarov cyclization is characterized by direct nucleophilic trapping of oxyallyl cation at the electrophilic α -carbon by heteroatom or carbon nucleophiles prior to deprotonation of the β -hydrogens. One of the first examples of trapping of the oxyallyl intermediate generated during a Nazarov cyclization was reported in 1998 by West et al in the generation of cyclic ether **1.26** (Scheme 1.5).⁴¹ By using $\text{BF}_3 \cdot \text{OEt}_2$ activation of divinyl ketone **2.23**, electrocyclic ring closure ensues forming cationic intermediate **1.23**. Simultaneous *5-exo* cyclization by the pendent olefin **1.24** followed by hemiacetal formation **1.25** and hydrolysis lead to the formation of diquinane **1.26**. This inspiring work reported by West has pioneered the field of interrupted Nazarov cyclization, expanding to intermolecular capture of oxyallyl cations utilizing various nucleophiles.^{38, 42-45}



Scheme 1.5 Mechanism of Intramolecular Interrupted Nazarov Cyclization

Following their initial report in interrupted Nazarov cyclization, West and co-workers reported an elegant synthesis of 1,4-dicarbonyl compounds **1.27** via homologous Mukaiyama addition of TBS-silylenolates to oxyallyl cations generated through $\text{BF}_3 \cdot \text{OEt}_2$ activation of ketone

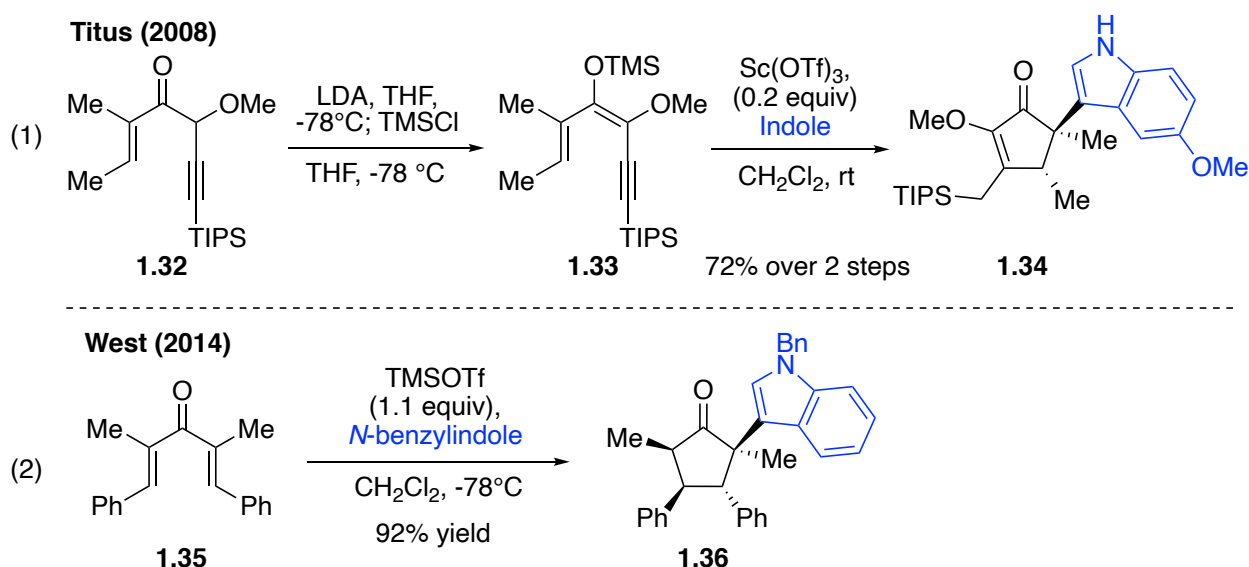
1.27 (Scheme 1.6, *eqn. 1*).⁴⁶ A variety of oxygenated π -nucleophiles were explored including silyl ketene acetals and silyl S,O-acetals. Another report by West detailed activation of divinyl ketone **1.29** with trimethylaluminum to promote Nazarov cyclization to generate oxyallyl cation **1.30**.⁴⁷ Further intramolecular delivery of a methyl group from trimethylaluminum afforded highly substituted cyclopentanone **1.31** in excellent diastereoselectivity (Scheme 1.6, *eqn. 2*). West also explored various organoaluminum catalysts allowing the preparation of alkyl-, phenyl-, cyano-, and azido-substituted cyclopentanones.



Scheme 1.6 Examples of Intermolecular Interrupted Nazarov Cyclization's

Meanwhile, the construction of α -indoyl ketones had been of interest to the synthetic community and both Titus and West reported an interrupted Nazarov cyclization method utilizing indole as their nucleophile source.^{48, 49} Titus demonstrated that treatment of allenyl vinyl ketone **1.32** with LDA and TMSCl could readily generate trimethylsilyl enol ether **1.33** (Scheme 1.7, *eqn 1*).⁴⁸ Furthermore, activation of vinyl-propargyl TMS silylenol ether **1.33** with $\text{Sc}(\text{OTf})_3$ induced Nazarov cyclization, which was then captured by 5-methoxyindole to form cyclopentanone **1.34**

in 72% yield in just two steps. Following their previous work, West showcased that activation of divinyl ketone **1.35** with stoichiometric TMSOTf to promote cyclization, followed by nucleophilic capture with *N*-benzylindole successfully afforded cyclopentanone **1.36** in high yield (Scheme 1.7, eqn. 2).⁴⁹ These reports of interrupted Nazarov cyclization with indoles has set the precedent for future work involving the synthesis of α -indoyl ketones through the use of oxyallyl cations.

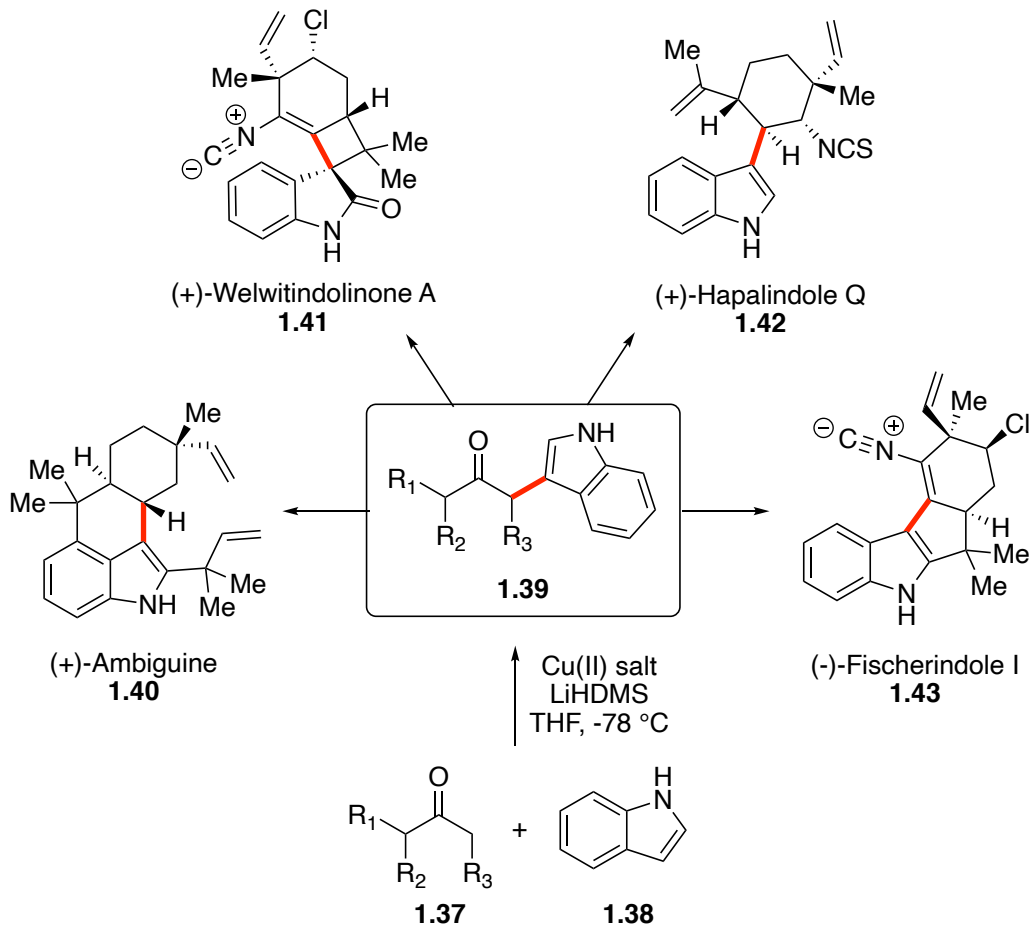


Scheme 1.7 Interrupting Nazarov Cyclization's with Indole Nucleophiles

1.5 Nucleophilic Addition at the α -Position of Ketones via Oxyallyl Cations

Synthesis of natural products and biologically active molecules is the shear driving force behind new reaction method development. Recently, the direct coupling of indoles to the α -position of ketones has gained recent interest due to their utilization in the total synthesis of various indole containing alkaloids (Scheme 1.8).⁵⁰⁻⁵² For example, Baran and co-workers were able to successfully synthesize Ambiguine H **1.40**, Welwitindolinone A **1.41**, Hapalindole Q **1.42** and Fischerindole I **1.43** via direct sp^2 - sp^3 coupling of indoles and ketones.⁵¹⁻⁵³ Baran's strategy to

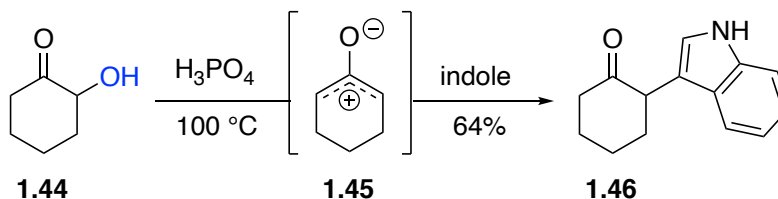
access α -indoyl ketones **1.39** was through the treatment of ketones **1.37** and indole **1.38** with LiHDMS and Cu(II) salts at -78°C in THF.⁵³ Their proposed mechanism suggests that LiHDMS deprotonates both the ketone and indole, and the copper species oxidizes both anions to form two radical species, forming α -indoyl ketone the upon termination.⁵²



Scheme 1.8 Baran's Approach to α -Indoyl Ketones and Applications in Total Synthesis

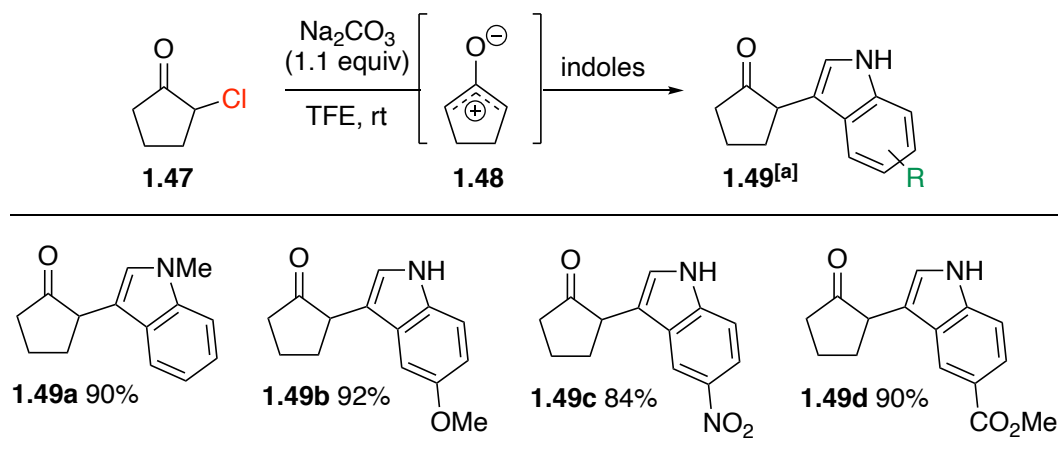
While Baran's strategy was well designed and robust, exploration for alternative methods to install indole at the α -position of carbonyls have been of recent interest. Due to its electrophilic nature, the oxyallyl cation intermediate serves as potential intermediate to generate α -indoyl

ketones.^{48, 49} The first report of direct trapping the punitive oxyallyl cation intermediate with indole was reported by Freter in 1978 (Scheme 1.9).⁵⁴ Freter detailed that treatment of α -hydroxy ketone **1.44** with phosphoric acid (H_3PO_4) at elevated temperature led to the formation of oxyallyl cation **1.45**, which upon subsequent trapping with indole furnished α -indoyl ketone **1.46** in 64% yield.



Scheme 1.9 Freter's Approach Towards α -Indoyl Ketones *via* Oxyallyl Cations

Further studies involving the direct trapping of oxyallyl cations with indoles were not revisited until 2012 by Chi (scheme 1.10).¹⁴ Chi and co-workers demonstrated that treatment of α -chloroketone **1.47** with Na_2CO_3 in trifluoroethanol (TFE) effortlessly generated oxyallyl cation **1.48** through an $\text{E}_{1\text{cb}}$ type mechanism. The electrophilic species further undergoes nucleophilic capture at the α -position with indole nucleophiles to afford α -indoyl ketones **1.49** in excellent yields. Chi importantly noted that the ionization power and low nucleophilicity of TFE attributed to the high yielding nature of their method. In fact, this method proceeded very cleanly, affording essentially pure products after simple filtration. A broad scope of electron rich and deficient indoles were tolerated under these basic conditions, leading to construction of α -indole ketone adducts **1.49a-1.49d** in excellent yields.



[a] Isolated yield after column chromatography.

Scheme 1.10 Chi's Approach to Oxyallyl Cation Generation

More interestingly, Chi further expanded the scope of α -haloketones to include acyclic and six-membered ketones as depicted in Table 1.1.¹⁴ To demonstrate their ability to employ other halogenated ketones, treatment of both acyclic α -bromo and α -chloro ketones **1.50a** under their optimized conditions led to corresponding α -indoyl ketones **1.52a** in identical yields. Similarly, treatment of regiomer α -chloro-ketones **1.50b** and **1.50c** led to the formation of **1.52b** and **1.52c** in 10:1 dr, with different rates of reaction observed. Chi proposed that this rate difference was attributed to the $\text{E}_{1\text{cb}}$ type mechanism in the generation of the unsymmetrical oxyallyl cation **1.51**, with the α -hydrogen of chloro-ketones **1.50b** more accessible for deprotonation. While their scope of α -halo ketones primarily focused on generating and capturing symmetrical oxyallyl cations, the nucleophilic capture of unsymmetrical oxyallyl cation proved problematic. As depicted in entry **3** base promoted dehalogenation of unsymmetrical ketone **1.50d** led to the formation of unsymmetrical oxyallyl cation and subsequent captured by indole produced **1.52d** as a mixture of regioisomers, favoring capture at the least substituted α -carbon.

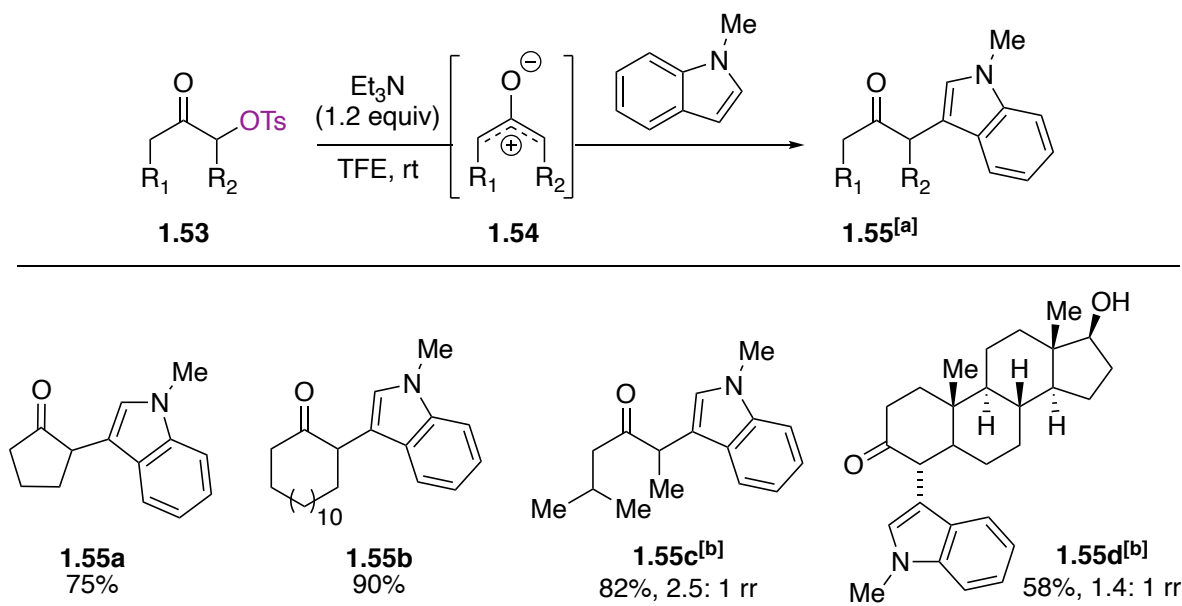
Table 1.1 Chi's Scope of α -Halo Ketones

Entry	Starting Material	Product	% Yield ^[a]
1	 X= Cl 1.50a X= Br 1.50a	 1.52a	1d, >95%
2	 1.50b R ₁ = H, R ₂ = Me 1.50c R ₁ = Me, R ₂ = H	 1.52b 1.52c	1.52b 1d, 88%, (10:1 dr) 1.52c 3d, 73% (10:1 dr)
3	 1.50d	 1.52d	15d, 56% 3:1 <i>rr</i>

^[a] No column chromatography required.

Following the work of Chi, MacMillan and co-workers reported similar approach to the direct nucleophilic capture of oxyallyl cations generated *via* base promoted elimination of α -tosyl ketones.⁵ MacMillan's work expanded the scope of nucleophiles to include substituted indoles, arenes and heteroatom nucleophiles. As depicted in Scheme 1.11, the formation of oxyallyl cation **1.54** was achieved by treatment of α -tosyloxy ketone **1.53** with triethylamine (Et₃N) in TFE. Subsequent interception of oxyallyl cation **1.54** with *N*-methyl indole successfully yielded α -indoyl ketone **1.55**. MacMillan proposed that TFE activation of the carbonyl through hydrogen bonding allowed for generation of the zwitterionic intermediate.⁵ MacMillan and co-workers

explored cyclic and acyclic α -tosyloxy ketones. For example, cyclic α -indoyl ketones **1.55a**-**1.55b** alongside acyclic α -indoyl ketones **1.55c** and **1.55d** were afforded in moderate to excellent yields. Similar to Chi's work, unsymmetrical ketones yielded regioisomeric products **1.55c** and **1.55d** respectively. The formation of regioisomers from unsymmetrical ketones provided plausible evidence of oxyallyl cation intermediacy, and furthermore that nucleophilic capture is sensitive to sterics causing addition to occur at the less hindered α -position.



^[a] Isolated yield after column chromatography over the average of two experiments.

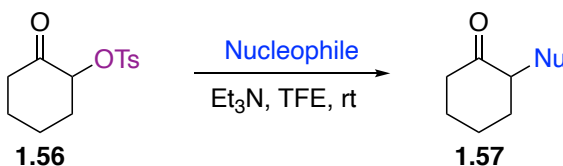
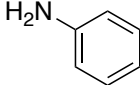
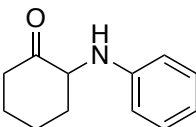
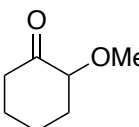
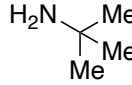
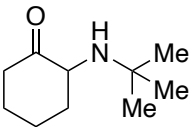
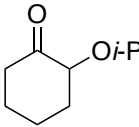
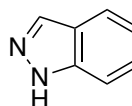
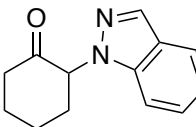
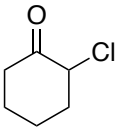
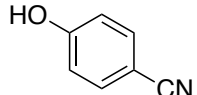
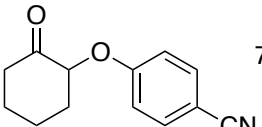
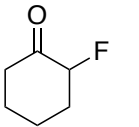
^[b] Regioisomeric ratio determined by ¹H NMR analysis.

Scheme 1.11 MacMillan's Approach to Oxyallyl Cation Generation

While α -indoyl ketones were the desired synthetic targets of their methodology, MacMillan further explored the viability of other nucleophiles to capture oxyallyl cations as demonstrated in Table 1.2. Employing aromatic, heteroaromatic and primary amines, they could effortlessly generate α -amino ketones **1.57a**-**1.57c** in moderate to excellent yields. Furthermore,

oxygen nucleophiles, such as 4-cyanophenol, methanol, and *iso*-propanol also trapped the oxyallyl cation intermediates to give α -ethers **1.57d-1.57f**. In addition to heteroatom nucleophiles, α -halo ketones **1.57g** and **1.57h** were successfully from their respective cesium salts.

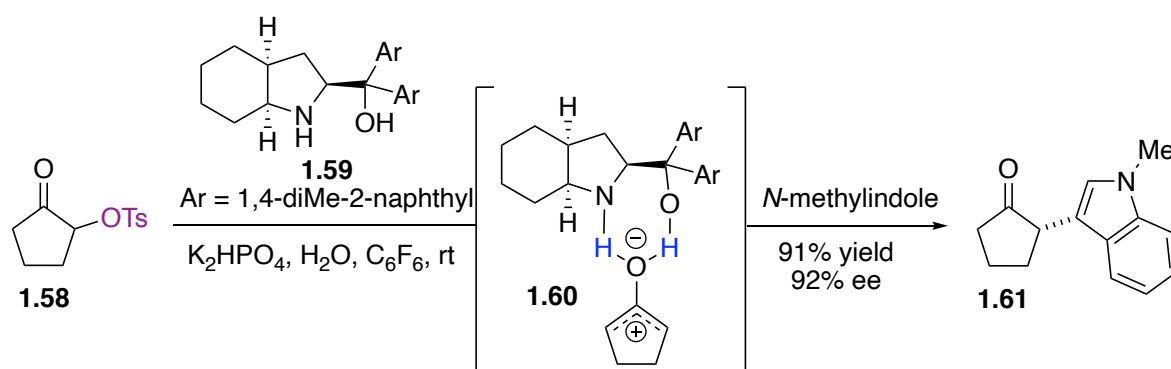
Table 1.2 MacMillan's Scope of Nucleophiles

							
Entry	Nucleophile	Product	Yield ^[a]	Entry	Nucleophile	Product	Yield ^[a]
1		 1.57a	71	5	MeOH	 1.57e	71
2		 1.57b	70	6	<i>i</i> -PrOH	 1.57f	82
3		 1.57c	62	7	CsCl	 1.57g	85
4		 1.57d	73	8	CsF	 1.57h	62

^[a] Isolated yield after column chromatography over the average of two experiments.

Following their seminal work in direct nucleophilic capture of oxyallyl cations, MacMillan reported an organocatalyzed enantioselective synthesis of α -indoyl ketones (Scheme 1.12).⁵⁵ MacMillan proposed that introduction of a chiral hydrogen bond-donating catalysts should coordinate with α -tosyloxy ketone **1.58** and undergo soft enolization to generate oxyallyl cation

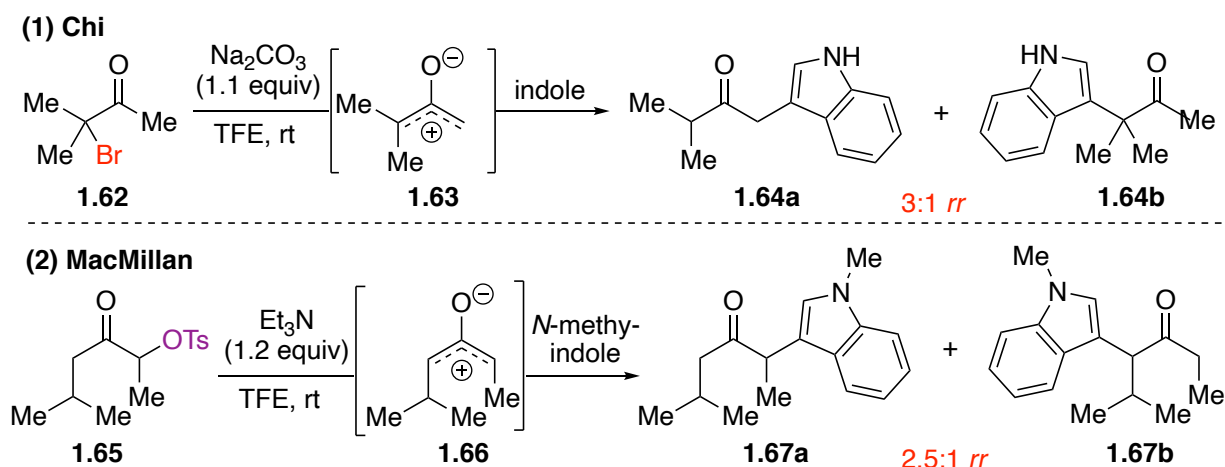
intermediate **1.60**. Combining racemic α -tosyloxy ketone **1.58** with pyrrolidine catalyst **1.59** and K_2HPO_4 in perfluorobenzene (C_6F_6) yielded enantioenriched ketone **1.61** in 91% yield and 92% ee *via* intermediate **1.60**. A wide scope of indoles and α -tosyloxy cyclopentanones were tolerated under these reaction conditions, yielding the enantioenriched α -indoyl ketones in excellent yields. Under these conditions, they observed α -tosyloxy cyclohexanones were unreactive, which was attributed to unfavorable ring strain that arises from unsaturation of the cyclohexanone ring.



Scheme 1.12 MacMillan's Approach to Enantioenriched α -Indoyl Ketones

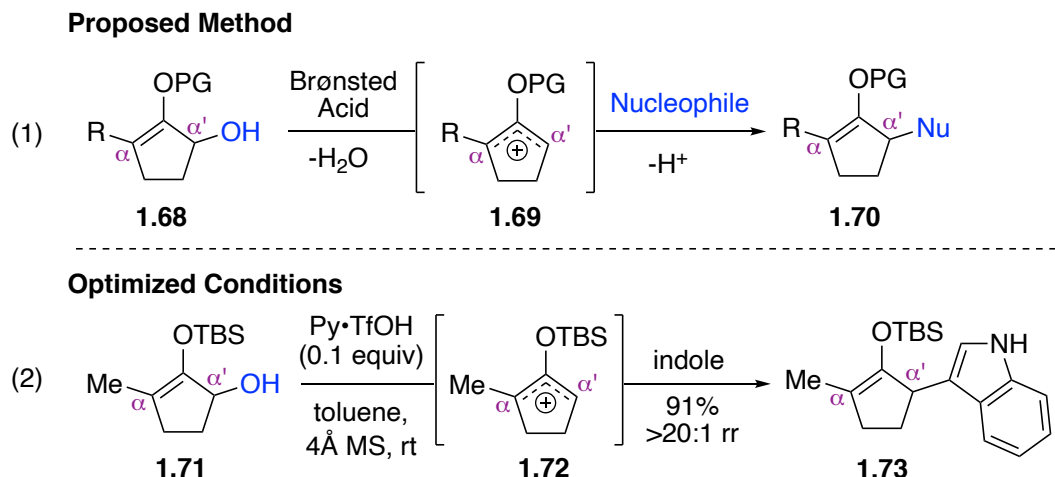
1.6 Nucleophilic Addition to Silyloxyallyl Cations

Freter, Chi, and MacMillan set the precedent for direct nucleophilic capture of oxyallyl cations with various nucleophiles for the generation of α -functionalized ketones, utilizing the umpolung characteristic of the oxyallyl cation.^{5, 14, 15, 54} Unfortunately, their strategies heavily relied on the exploitation of symmetrical oxyallyl cations, as utilization of unsymmetrical synthons led to mixtures of regioisomers as depicted in Scheme 1.13. Under their respective strategies, both Chi and MacMillan observed that nucleophilic capture of unsymmetrical oxyallyl cations **1.63** and **1.66** predominantly occurred at the less hindered carbon.^{5, 14}



Scheme 1.13 Problems with Regioselective Capture of Unsymmetrical Oxyallyl Cations

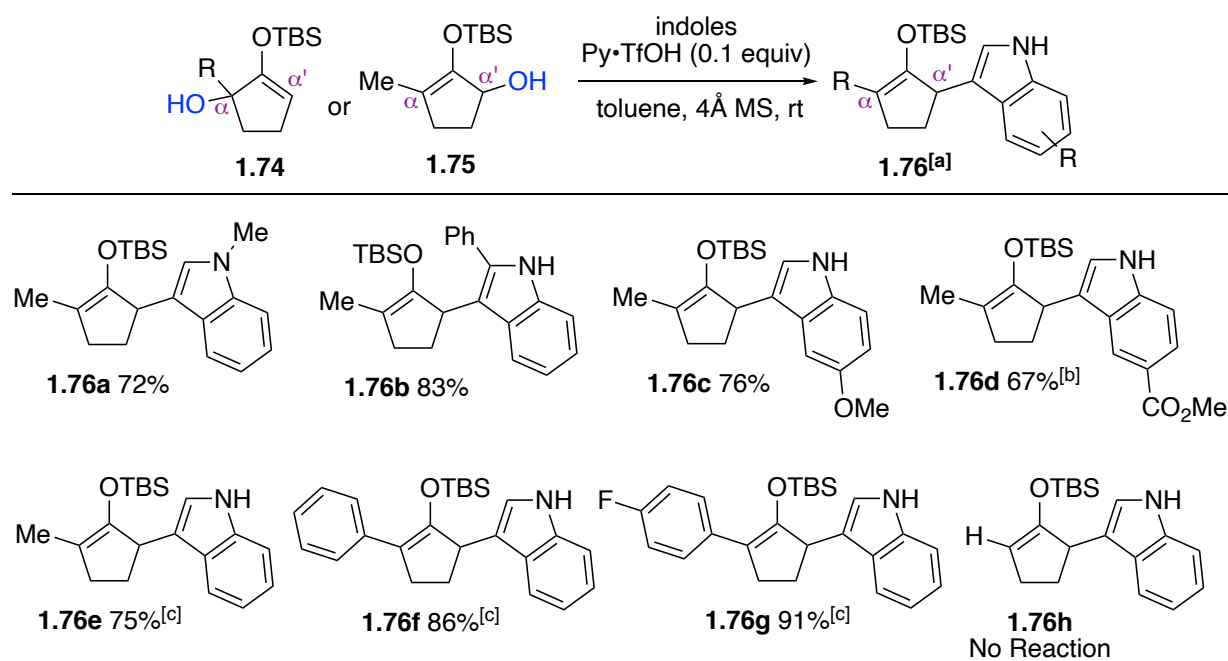
To address the important issue of regioselective nucleophilic capture of unsymmetrical oxyallyl cations, Kartika and co-workers developed a unique method utilizing a protected oxyallyl cation intermediate to control the regioselectivity of the ensuing nucleophilic capture.⁵⁶ Kartika and co-workers proposed that under mild acidic conditions ionization of protected α -hydroxy enol ether **1.68** could generate unsymmetrical protected oxyallyl cation **1.69** (Scheme 1.14 *eqn. 1*). They hypothesized that stabilization of oxyallyl cation **1.69** could be influenced through inductive effects and resonance provided by the oxygen protecting group and α -substituents. Furthermore, the electronics of the protected oxyallyl cation could potentially direct regioselective nucleophilic addition to occur at the sterically less hindered α' -position generating enol ether **1.70** in a regioselective manner. Ultimately, Kartika reported that TBS protected α -hydroxy enol ether **1.71** could be successfully ionized utilizing pyridinium triflate (Py•TfOH) in toluene, generating unsymmetrical silyloxyallyl cation **1.72**. As they proposed, subsequent nucleophilic capture of the silyloxyallyl cation occurred at the least hindered α' -carbon by indole successfully affording **1.73** in 91% yield as a single regioisomer. Addition of molecular sieves were employed to prevent ionization reversibility, and protodesilylation of **1.71** under acidic conditions.



Scheme 1.14 Kartika's Strategy to Control Regioselectivity

With their optimized conditions for the regioselective capture of silyloxyallyl cations, Kartika explored various indoles and substituent effects at the α -position **1.75** as displayed in Scheme 1.15.⁵⁶ Under their optimized conditions, *N*-Methyl and 2-phenyl indole were tolerated yielding **1.76a** and **1.76b** in 72% and 83% respectively as a single regioisomer. Electron rich 5-methoxyindole and electron deficient 5-carboxylateindole successfully yielded **1.76c** in **1.76d** in moderate yields. Furthermore, Kartika et al examined steric and electronic effects provided by the substituent at the α -position of tertiary α -hydroxy enol ether **1.74**. Unsurprisingly, Kartika detailed that treatment of methyl substituted tertiary α -hydroxy enol ether readily furnished indole adduct **1.76e** in 75% yield. This result supports their hypothesis that the reaction proceeds *via* a type S_N1 mechanism and silyloxyallyl cation intermediacy and just not an S_N2 mechanism. Aromatic substituents such as phenyl and para-fluorophenyl tertiary α -hydroxy enol ethers successfully generated α -phenyl- α' -indole silylenol ethers **1.76f** and **1.76g** without effecting regioselectivity. Surprisingly, it was observed that unsubstituted α -hydroxy silylenol ether failed to yield **1.76h** under their reaction conditions, suggesting that substituents at the α -position help generate and

stabilize the forming silyloxyallyl cation. This first example of direct regioselective nucleophilic addition to silyloxyallyl cations has served as a starting point for exploration into the synthetic utility of silyloxyallyl cations.

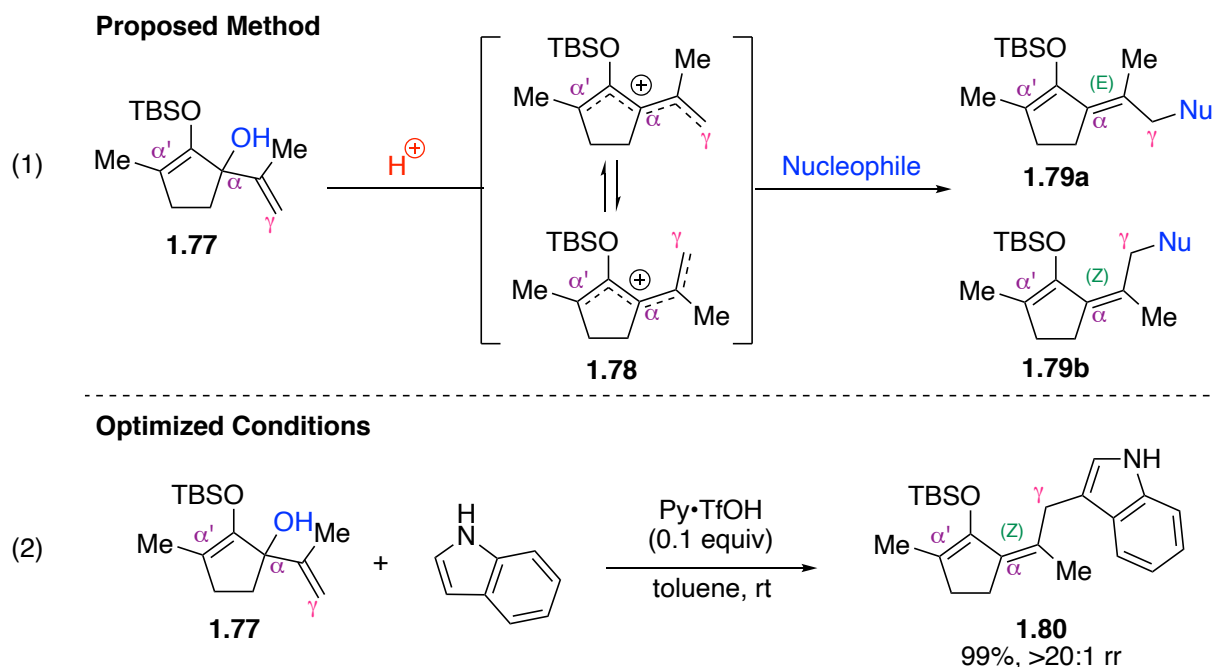


^[a] Isolated yield after column chromatography. ^[b] Starting material not fully consumed. ^[c] From **1.74** starting materials.

Scheme 1.15 Kartika's Scope of Indoles and α -Substituents

Kartika and co-workers then continued on the development of direct capture of silyloxyallyl cations extending it to the functionalization of silyldienol ethers at the γ -position through 2-silyloxypentadienyl cations.⁵⁷ They hypothesized that ionization of α -hydroxy silylenol ether **1.77** should readily generate the corresponding 2-silyloxypentadienyl cations **1.78** (Scheme 1.16). Similar to their previous methodology, nucleophilic capture should occur at the least substituted electrophilic γ -carbon producing either conjugated silyldienol ethers **1.79a** and **1.79b**. Kartika's conditions leading to γ -functionalized silyldienol ether **1.80** was detailed by treatment

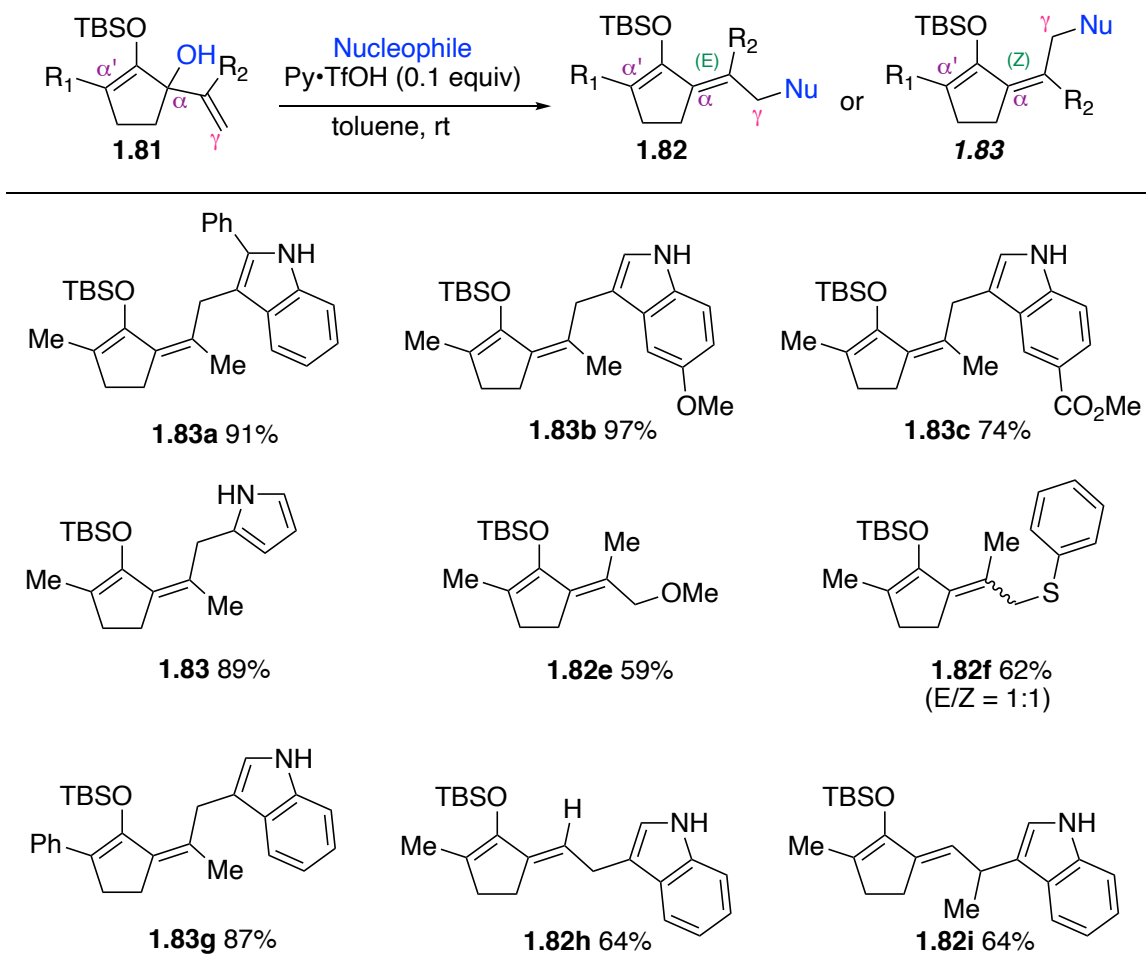
of divinyl alcohol **1.77** with catalytic Py•TfOH in toluene to generate 2-silyloxypentadienyl cation intermediate. They observed that in the presence of indole, addition occurred solely at the γ -position and the newly formed silyldienol ether **1.80** was produced the *Z*-isomer in 99% yield.



Scheme 1.16 γ -Functionalization of 2-Silyloxypentadienyl Cations

Following their initial γ -functionalization, Kartika and co-workers explored scope of carbon and heteroatom nucleophiles and α -hydroxy silylenol ethers **1.81** as shown in Scheme 1.17.⁵⁷ The use of sterically hindered, electron rich and deficient indole nucleophiles yielded exclusively *Z*-tetrasubstituted alkenes **1.83a-1.83c** in excellent yields. Furthermore, employment of pyrrole as a nucleophile successfully captured 2-silyloxypentadienyl cation exclusively at the γ -position yielding **1.83d** in 89% yield. Surprisingly, Kartika observed that utilization of methanol as a nucleophile afforded the corresponding silyldienol ether **1.82e** in 59% yield with complete reversal of selectivity exclusively generating the *E*-isomer, while thioether **1.83f** was generated as

a 1:1 mixture of isomers. With removal of the β -substituent, the reversed the olefin geometry was observed as demonstrated by the synthesis of **1.82h** and **1.82i** exclusively as the *E*-isomers.

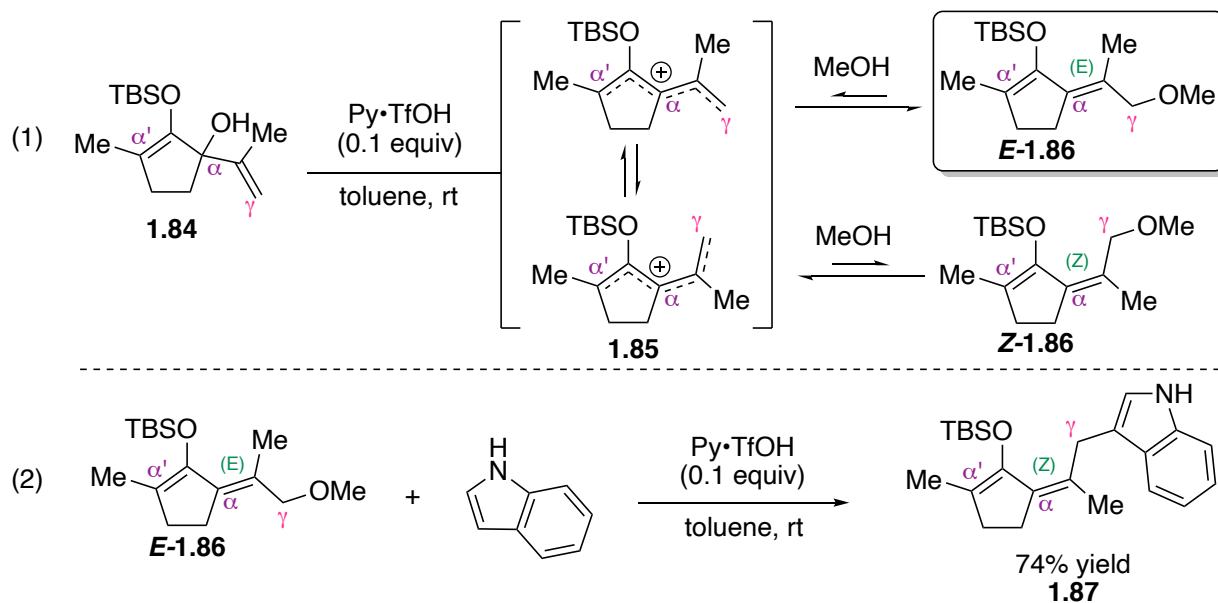


[a] Isolated yield after column chromatography. [b] Double bond geometry was determined by NOE

Scheme 1.17 Scope of Nucleophiles and Silyldienol Ethers

To support the formation of the *E*-isomer product observed with heteroatom nucleophiles, Kartika hypothesized that stereoselective formation of the *E*-alkene product **1.86** was ultimately driven by thermodynamics (Scheme 1.18, *eqn 1*).⁵⁷ It was proposed that under catalytic Brønsted acid, nucleophilic capture of 2-silyloxypentadienyl cations **1.85** with methanol is reversible after

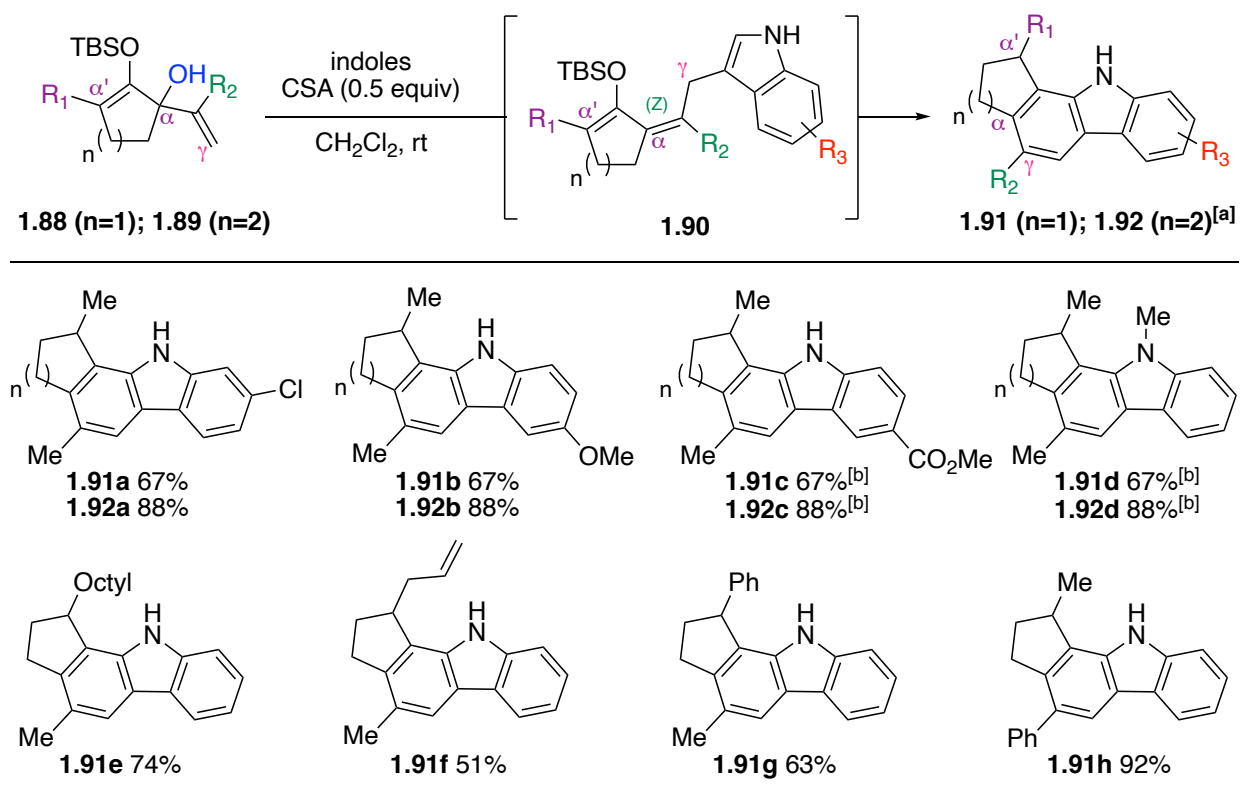
formation of **Z-1.86**. Further ionization of kinetic product **Z-1.86** with Py•TfOH regenerates cationic intermediates **1.85** driving the equilibrium to the more thermodynamically stable product **E-1.86**. This hypothesis was readily supported by activation of compound **E-1.86** with catalytic pyridinium triflate and indole, which generated γ -indole silyldienol ether **1.87** with a complete inversion of olefin geometry forming the *Z*-isomer as a single product (Scheme 1.18, eqn 2).



Scheme 1.18 Stereoselectivity of γ -Functionalization

While exploring the γ -functionalization of 2-silyloxypentadienyl cations generated from vinyl-substituted α -hydroxy silylenol ethers, Kartika et al expanded their methodology towards the synthesis of carbazoles (Scheme 1.19).⁵⁸ Preliminary investigations demonstrated that exchanging weak Brønsted acid Py•TfOH for, camphorsulfonic acid (CSA) in CH₂Cl₂ readily ionized vinyl-substituted α -hydroxy silylenol ether **1.88** and **1.89** readily generated γ -indolyl silylenol ethers **1.90** *in situ*. While in the presence strongly acidic CSA, further intramolecular annulation of **1.90** successfully afforded carbazoles **1.91** and **1.92**. Using the optimized conditions,

various substituted indoles and substituted five- and six-membered α -hydroxy silylenol ethers were explored. Kartika observed that halogenated, electron rich, electron poor and protected indoles were tolerated, successfully yielding carbazoles **1.91a-1.91d** and **1.91d-1.92d** in moderate to excellent yields. Through their studies, they observed that reactions involving six-membered α -hydroxy silylenol ethers **1.89** required elevated temperatures to promote cyclization to afford the desired carbazoles. Furthermore, octyl, allyl, phenyl and indole substituted five-membered α -hydroxy silylenol ethers **1.88** successfully afforded carbazoles **1.91e-1.91h** in moderate yields.

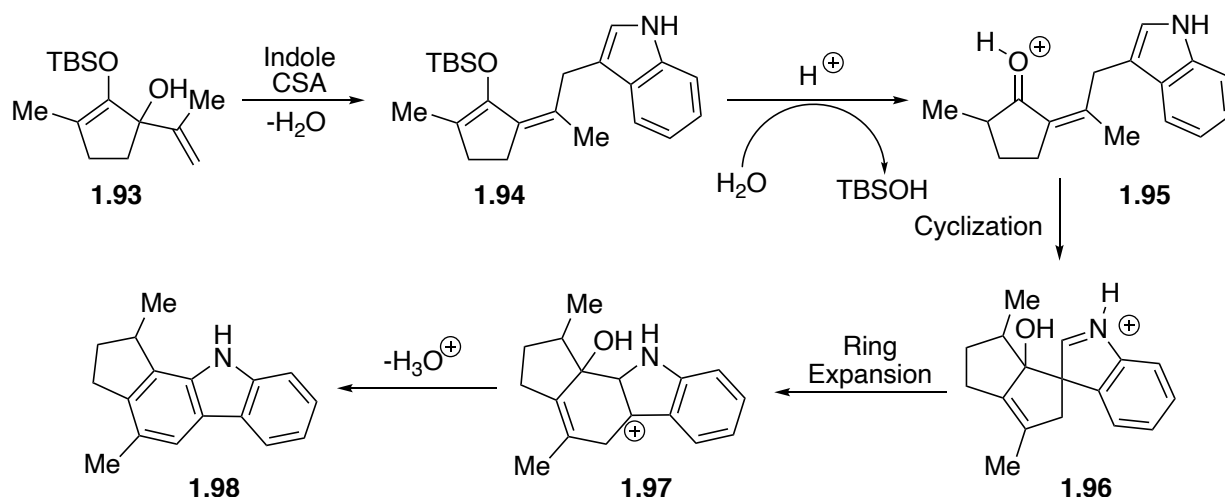


^[a] Isolated yield after column chromatography. ^[b] Reaction preformed at reflux.

Scheme 1.19 Carbazole Synthesis Through 2-Silyloxypentadienyl Cations

The proposed mechanism of this transformation is detailed in Scheme 1.20, in which γ -indolyl adduct **1.94** is generated via nucleophilic capture of 2-silyloxypentadienyl cation

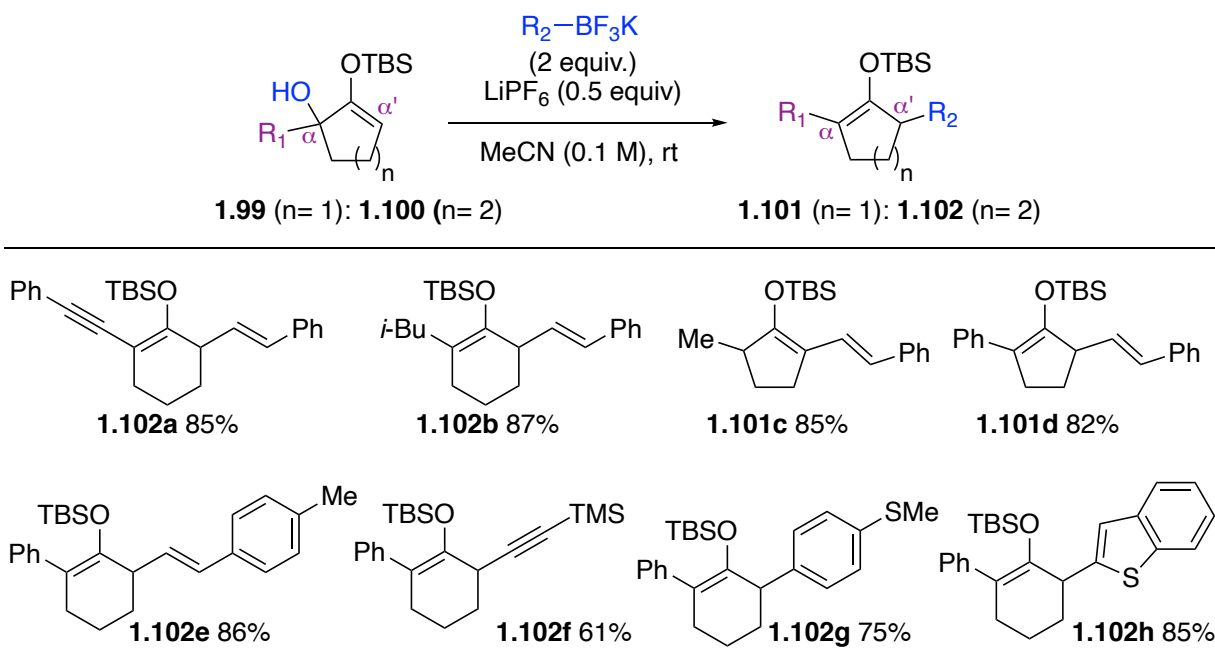
intermediate afforded by ionization of **1.93**.⁵⁸ Subsequent *in-situ* protodesilylation of **1.94** is believed to be promoted by catalytic CSA and water produced during ionization, forming α',β' -unsaturated ketone **1.95**. Under the acidic conditions ketone **1.95** most likely exists as the protonated species, allowing for intramolecular nucleophilic addition of the pendant indole resulting in formation of spirocyclic iminium ion **1.96**. Lastly, ring expansion of iminium ion **1.96** and regeneration of aromaticity furnished carbazole **1.98**.



Scheme 1.20 Proposed Mechanism of Carbazole Formation

Following the work of Kartika, May and co-workers reported a method to generate α,α' -substituted cyclic silylenolates through nucleophilic capture of silyloxyallyl cations with organoboronate nucleophiles (Scheme 1.21).⁵⁹ May observed that upon treatment of α -hydroxy silylenol ethers **1.99** and **1.100** with LiPF_6 in acetonitrile, generated unsymmetrical silyloxyallyl cation intermediates. Successive deborylation of organoboronate nucleophiles was promoted by LiPF_6 , regioselectively capturing the silyloxyallyl cations successfully producing α,α' -substituted ketones **1.101** and **1.102** with full regioselective control. Currently the mechanism in which

addition of organoboronates the oxyallyl cation species is unknown but is proposed to occur through a concerted intermolecular process.



Scheme 1.21 May's Strategy to Capture Silyloxyallyl Cations

May and co-workers explored the scope of their reaction using a variety of five and six-membered α -hydroxyl silyl enol ethers **1.99/1.20**, and trifluoroborates. Their conditions tolerated a wide array of α -substituents, such as *iso*-butyl, alkynyl, methyl, and phenyl successfully yielded adducts **1.102a-1.102b** and **1.101c-1.101d** excellent yields. Unexpectedly **1.101c** was yielded as a product of alkene isomerization. Following substituent effects, a wide array of alkenyl-, alkynyl-, and aryl/heteroaryl trifluoroborates were explored to generate diverse α, α' -substituted ketones. Though alkynyl boronates are sensitive in acidic medium, TMS-alkynyl α -substituted silyl enol ether **1.102f** was synthesized in 61% yield, while toluene styrenyl nucleophile successfully afforded

1.102e in 86% yield. Electron rich aromatic and heteroaromatic trifluoroborates, yielded methylthioether and thiophene adducts **1.102g** and **1.102h** in moderate yields.

1.7 Conclusion

Oxyallyl cations have been proven to be useful reactive synthetic intermediates in the generation of complex molecular scaffolds. Many reports of its synthetic utility have been exemplified through the Favorskii rearrangement, Nazarov cyclization and direct nucleophilic capture of the zwitterionic intermediate. The development of protected silyloxyallyl cations to control regioselective capture with various nucleophiles allowed for the development of vast complex molecular motifs.

Chapter Two: Effects of Solvent and Residual Water on Generating Six-Membered Silyloxyallyl Cations Towards Regioselective Capture^{1,2}

2.1 Purpose

This chapter depicts our approach to generate α' -indolyl silylenol ethers through regioselective nucleophilic capture of silyloxyallyl cations *via* ionization of six-membered α -hydroxy silylenol ethers through the use of solvent effects. It comprises of our efforts in the implementation of solvent effects to solve diminished reactivity of six-membered α -hydroxy silylenol ethers. The exploration of various compatible indole, heteroatom, and carbon nucleophiles are demonstrated in combination with various aliphatic and aromatic substituted α -hydroxy silylenol ethers. Furthermore, exploration into the role of catalytic water in rate enhancement of our reaction was observed through HPLC and ¹H-NMR studies.

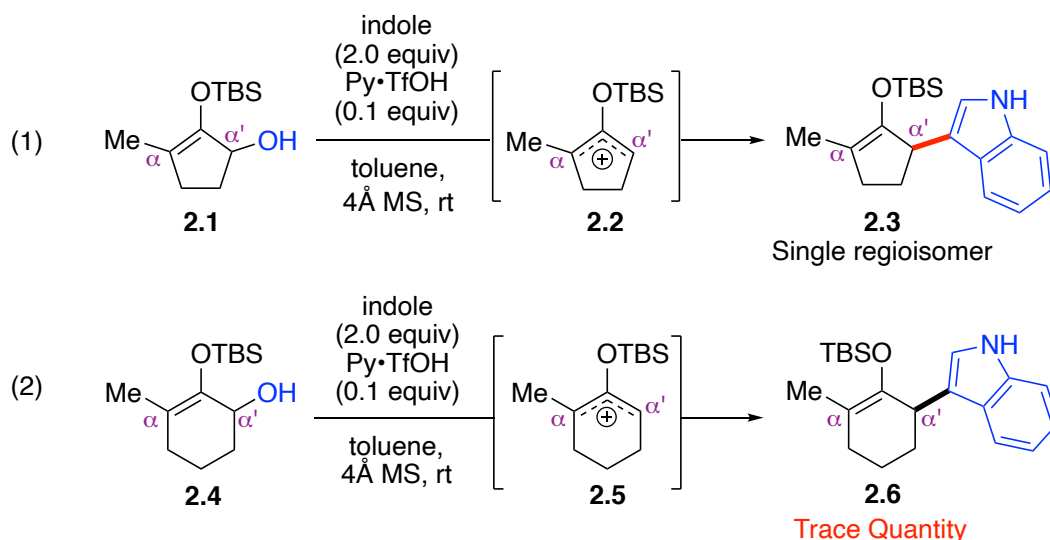
2.2 Proposed Activation of Six-Membered α -Hydroxy Silylenol Ethers

As detailed in Chapter One, the Kartika group has successfully developed several strategies revolving around the regioselective nucleophilic capture of silyloxyallyl cations generated from α -hydroxy silylenol ethers.^{56-58,60,61} In their seminal report, Kartika and coworkers initially proposed that treatment of α -hydroxy silylenol ether **2.1** with catalytic pyridinium triflate (Py•TfOH) in anhydrous toluene readily generated silyloxyallyl cation **2.2** (Scheme 2.1, *eqn. 1*).

¹ Reprinted (adapted) with permission from (Malone, J. A.; Cleveland, A. H.; Fronczek, F. R.; Kartika, R., Effects of Solvent and Residual Water on Enhancing the Reactivity of Six-Membered Silyloxyallyl Cations toward Nucleophilic Addition. *Org. Lett.* **2016**, *18*, 4408-4411.). Copyright (2016) American Chemical Society." – For sections 2.2 to 2.7.

² Reprinted (adapted) with permission from (Bresnahan, C. G.; Taylor-Edinbyrd, K. A.; Cleveland, A. H.; Malone, J. A.; Dange, N. S.; Milet, A.; Kumar, R.; Kartika, R., Mechanistic Perspectives in the Regioselective Indole Addition to Unsymmetrical Silyloxyallyl Cations. *J. Org. Chem.* **2019**, *84*, 7166-7174.) Copyright (2016) American Chemical Society." – For section 2.7.

Subsequent regioselective nucleophile capture with indole occurred at the least substituted α -carbon generating α -indoyl silyl enol ether **2.3** as a single regioisomer.⁵⁶ Under this mild method, five-membered cyclic substrate **2.1**, extending this method to the homologous six-membered α -hydroxy silylenol ether **2.4**, resulted in only trace quantities of α' -indoyl silylenol ether **2.6** (Scheme 2.1, *eqn. 2*).



Scheme 2.1 Observed Lack of Reactivity with Six-Membered α -Hydroxy Silylenol Ether

Kartika and co-workers hypothesized the diminished reactivity of the six-membered substrate **2.4** was attributed to destabilization of the emerging six-membered oxyallyl cation **2.5** as a result of more prominent allylic strain (Figure 2.1).⁶² To support their hypothesis, modeling studies of the ground state conformations of cations **2.2** and **2.5** were conducted using a 6-311g(d,p) DFT, B3LYP basis set.⁶² Present in the six-membered cation **2.5** there is decreased atomic distances between the methyl and silyloxy group compared to the analogous five-membered cation **2.2**. In addition, decreased bond angles present in the six-membered cyclic ring

forces the silyloxy and methyl group into close proximity therefore increasing the allylic strain. While not unique to the six-membered silyloxyallyl cation **2.5**, MacMillan reported similar lack in reactivity for the generation of oxyallyl cations from α -tosyl cyclohexanones under their enantioselective conditions.⁶³

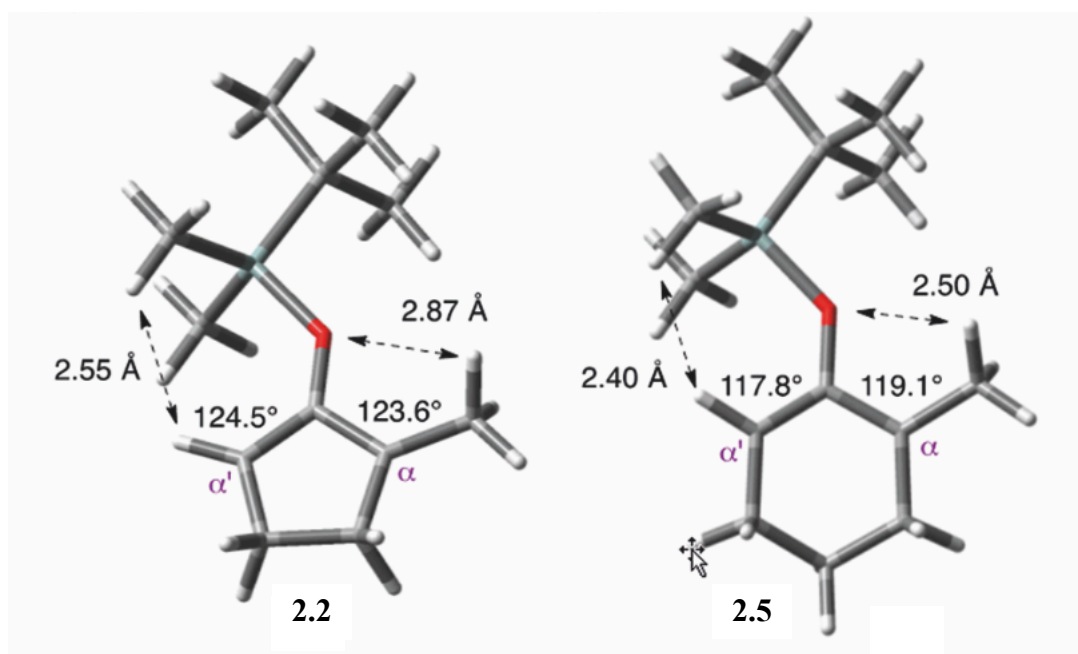


Figure 2.1 DFT Modeling of Ground State Conformations of **2.2** and **2.5**⁶²

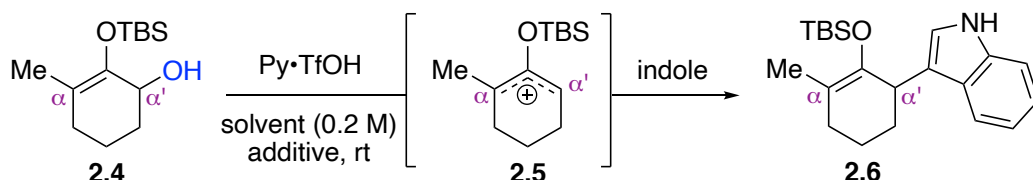
2.3 Reaction Optimization

Understanding that there is a thermodynamic barrier imposed by the emerging allylic strain *via* generation of silyloxyallyl cation **2.5**, we hypothesized that the barrier could be overcome by modifying the reaction conditions inspired by the Hughes-Ingold Rules. These rules outline the role of polar solvents involving the formation of charged intermediates in S_N1 type reactions.^{65, 66} The increase in solvent polarity would aid in polarization of the C-OH bond, enhancing the rate of ionization in which emerging oxyallyl cation is formed. Furthermore, the proposed rate enhancement would be a result of the polar solvent's ability assist in stabilization of the forming carbocation intermediate through solvation, ultimately lowering the energy required for **2.4** to

undergo Brønsted acid promoted ionization.^{65, 66} Similar approaches utilizing polar solvents in the generation of oxyallyl cations have been demonstrated by MacMillan, Chi and Tang groups, in which they all employed trifluoroethanol (TFE) as their reaction medium.^{5, 14, 15}

With our hypothesis in hand, we carried out reaction optimization for the six-membered substrate and the results are summarized in Table 2.1. We utilized α -hydroxy silylenol ether **2.4** as a model substrate as it is easily synthesized in two steps from commercially available materials.⁶⁷ As previously demonstrated by the Kartika group, Py•TfOH readily ionizes the five-membered α -hydroxy silylenol ethers to yield silyloxyallyl cations without observable decomposition of starting material, making it an ideal ionization source for our methodology.^{57, 60} As depicted in entry 1, our studies begin with treating **2.4** with 0.1 equivalent of Py•TfOH and 1.1 equivalents of indole in marginally polar solvent dichloromethane (CH₂Cl₂). In an attempt to prevent the reversible ionization and detrimental protodesilylation of **2.4** caused by residual water, 4Å molecular sieves were introduced into the reaction. Despite the prolonged reaction times, these conditions only produced trace amounts of the desired α' -indolyl silylenol ether **2.6**. Surprisingly, upon removal of 4Å molecular sieves we observed substantial rate enhancement with full consumption of **2.4** in just 48 hours, successfully affording the desired product **2.6** in 52% yield as a single regioisomer (Entry 2). This absence of molecular sieves suggests that water produced through ionization plays a crucial role in our reaction. Exemplifying the importance of a polar solvent, switching from dichloromethane to nonpolar toluene only resulted in **2.6** in 40% with incomplete consumption of **2.4** (entry 3). Furthermore, switching to a more polar solvent acetonitrile (MeCN) ultimately led to full consumption of compound **2.4** in just 26 hours, furnishing α' -indolyl silylenol ether **2.6** in 71% yield (entry 4). This increased reactivity observed by increasing solvent polarity follows the trend outlined by the Hughes-Ingold Rules.

Table 2.1 Solvent Screen and Reaction Optimization



entry	solvent	equiv of acid	additive	equiv of indole	time (h)	yield (%)
1	CH ₂ Cl ₂	0.1	4Å MS	1.1	>300	trace ^[b]
2	CH ₂ Cl ₂	0.1	--	1.1	48	52
3	toluene	0.1	--	1.1	>300	40 ^[b]
4	MeCN	0.1	--	1.1	26	71
5	MeCN	0.2	--	1.1	26	82
6	MeCN	0.5	--	1.1	7	80
7	MeCN	1.0	--	1.1	3	85
8	MeCN	0.2	--	1.0	24	76
9	MeCN	0.2	--	2.0	25	81
10	MeCN	0.2	4Å MS	1.1	>300	18 ^[b]
11	MeCN	0.2	H ₂ O ^[c]	1.1	13	60

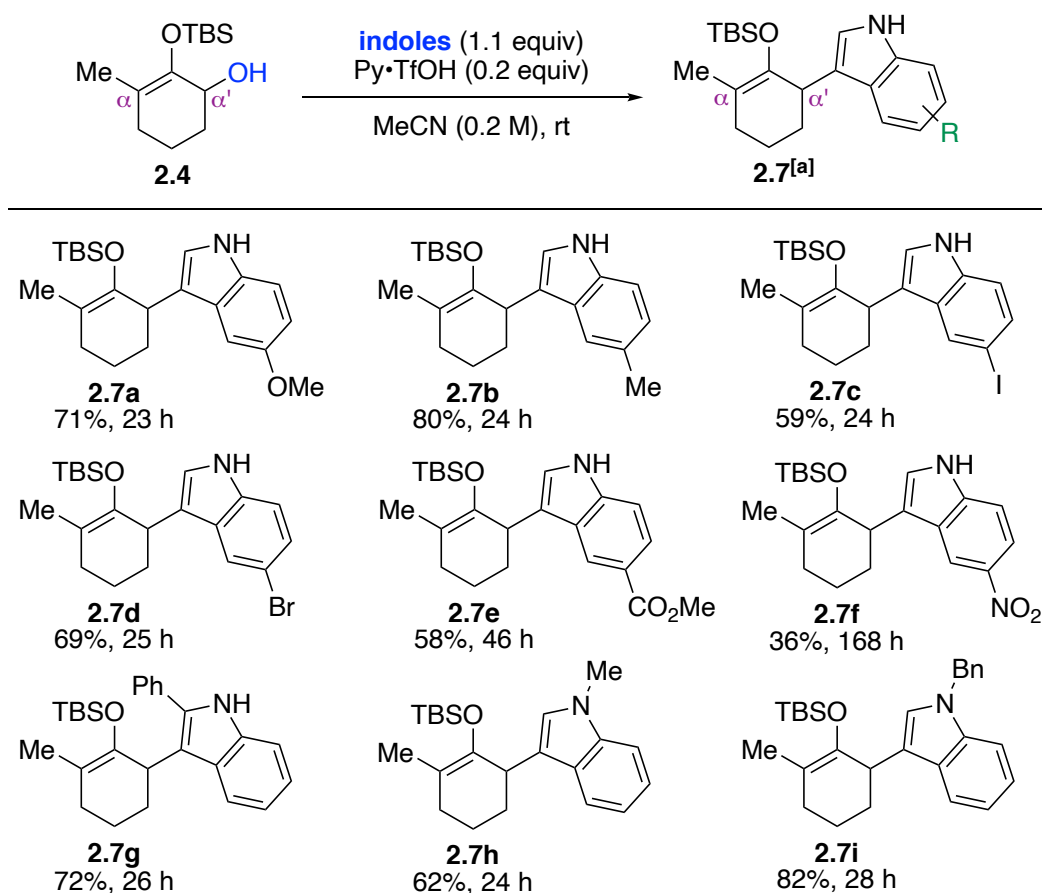
^[a] Isolated yields after flash column chromatography. ^[b] Starting material **2.4** was not fully consumed. ^[c] 0.1 equivalent of water was added.

Understanding that polar solvent dramatically accelerates the rate of ionization we continued our reaction optimization choosing MeCN as our solvent of choice. Furthermore, we systematically increased the equivalences of Py•TfOH to 1.0 equivalent (entries 5-7), only improved the yield of **2.6** to 85% (entry 7). With negligible differences in yields between the use of 1.0 and 0.2 equivalents Py•TfOH, we decided to continue reaction optimization with 0.2 equivalents of Py•TfOH (Entry 5). Moreover, we turned our attention to optimizing the equivalences of indole (entries 8 and 9), observing that the use of both 1.0 and 2.0 equivalents of indole did not affect the overall efficiency of the reaction. Lastly, we wanted to investigate the role of water in our reaction as depicted in entries 10 and 11. First, reimplementing 4Å molecular sieves into our reaction once again proved unfruitful as only 18% of **2.6** was obtained after greater than 300 hours. Moreover, addition of catalytic water (0.1 equiv) to the reaction appeared to accelerate

the rate of ionization, however a substantially lower yield of **2.6** was observed. Ultimately entry 5 was established as our optimized reaction conditions for the α' -functionalization of silylenol ether **2.4** with indole, utilizing 0.2 equiv of Py•TfOH in acetonitrile.

2.4 Scope of Indole Nucleophiles

Having the optimized conditions to perform our ionization and nucleophilic capture of α -hydroxy silylenol ether **2.4** in hand, we subsequently screened various substituted indole nucleophiles to demonstrate the scope of our reaction (Scheme 2.2). Expectedly, electron rich



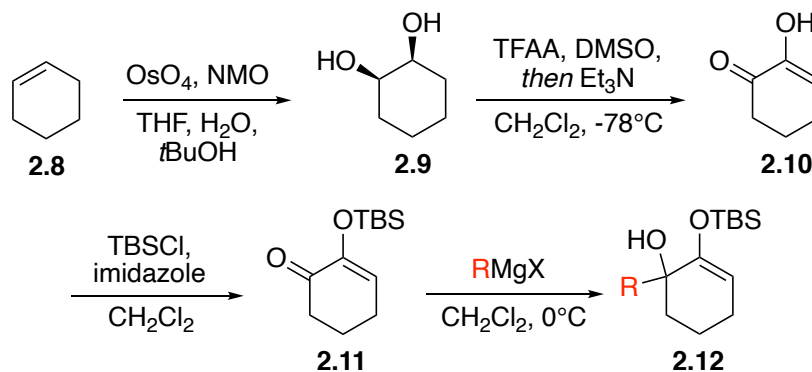
[a] Isolated yields after flash column chromatography. All products were isolated with >20:1 regioselectivity.

Scheme 2.2 Scope of Substituted Indole Nucleophiles

indoles such as 5-methoxyindole and 5-methylindole effortlessly afforded α -indoyl adducts **2.7a** and **2.7b** in 71% and 80% yields respectively. Halogen containing indoles readily produced brominated and iodinated silylenol ethers **2.7c** and **2.7d**, obtained in moderate yields. Our reaction α' -indoyl adducts **2.7e** and **2.7f**, albeit accompanied with lower yields and diminished rates of reaction. The use of sterically congested 2-phenyl indole readily delivered **2.7g** in 72% yield with complete regioselectivity. The use of *N*-protected indoles such as *N*-methylindole and *N*-benzylindole successfully produced the corresponding silylenol ethers **2.7h-2.7i** in 62% and 82% yield. All of the α -indoyl silylenol ethers were generated as a single regioisomer.

2.5 Evaluation of Substituent effects on Tertiary α -Hydroxy Silylenol Ethers

To continue our investigation into the tolerability and scope of our developed method, we set to explore aliphatic and arene substituent effects of α -hydroxy silylenol ethers. As previously reported by Kartika and co-workers, the use of five-membered tertiary α -hydroxy silylenol ethers have been shown to generate unsymmetrical silyloxyallyl cations, while still exhibiting regioselective nucleophilic capture.^{60, 62, 67} Adapting this strategy, we envisioned the synthesis of six-membered tertiary α -hydroxy silylenol ethers would allow for rapid functionalization at the α -position. As depicted in Scheme 2.3, the synthesis of six-membered tertiary α -hydroxy silylenol ethers **2.12** were achieved in four scalable steps from commercially available cyclohexane **2.8**. Initial Upjohn dihydroxylation of cyclohexane **2.8** readily afforded vicinal diol **2.9**. Subsequent oxidation of **2.9** with TFAA and DMSO readily yielded dione **2.10**, which upon TBS protection provided silylenol ether **2.11**. To generate our desired tertiary α -hydroxy silylenol ether starting materials, treatment of **2.11** with various aliphatic and aromatic Grignard reagents furnished **2.12** in moderate to excellent yields.

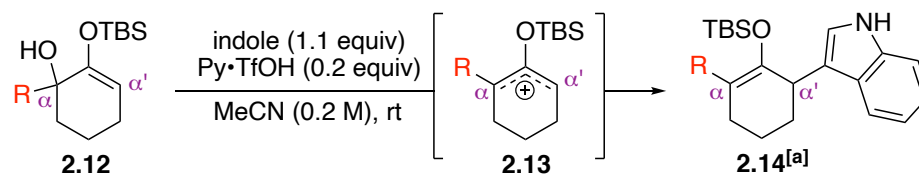


Scheme 2.3 Synthesis of Tertiary α -Hydroxy Silylenol Ethers

To demonstrate that the reaction proceeds through unsymmetrical oxyallyl cation intermediate **2.13**, we began with α -methyl silylenol ether **2.12a**. Under our optimized reaction conditions treatment of **2.12a** cleanly afforded α -methyl α' -indole adduct **2.14a** (entry 1) in a comparable yield and reaction time to that of secondary α -hydroxy silylenol ether **2.4**. Aliphatic substituents such as *n*-octyl **2.12b**, and allyl **2.12c**, were tolerated yielding α' -indolyl products **2.14b-2.14c** in 79% and 72% yield respectively. (entries 2-3). Surprisingly, introduction of sterically bulky groups such as *iso*-butyl **2.12d** and cyclohexyl **2.12e** afforded **2.14d** and **2.14e** in high yields and diminished reaction times. The substantial rate enhancement of substrates **2.12d** and **2.12e** were observed, suggesting that steric congestion at the α -carbon might influence the reversibility of ionization of the corresponding starting material. Entries 6-8 depict the utilization of aromatic substituents at the α -carbon. Employment of α -tolyl starting material **2.12f**, α' -diaryl silylenol ether **2.14f** was obtained in 82% yield, accompanied with an extensive decrease in rate of reaction.

We hypothesize the extended reaction time was likely attributed to formation of an unfavorable 1,3-allylic strain generated *via* the emerging silyloxyallyl cation as a consequence of

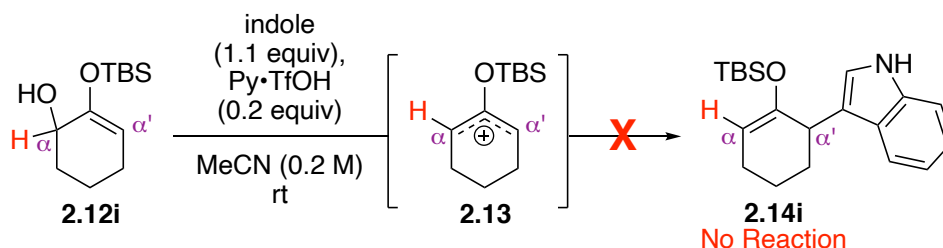
Table 3.2 Scope of α -Substituted α -Hydroxy Silylenol Ethers



entry	starting material	product	entry	starting material	product
1		 2.14a 73%, 24 h	5		 2.14e 76%, 6 h
2		 2.14b 79%, 16 h	6		 2.14f 82%, 168 h
3		 2.14c 72%, 24 h ^[b]	7		 2.14g 75%, 22 h
4		 2.14d 83%, 5 h	8		 2.14h 50%, >500 h ^[c]

[a] Isolated yields after flash column chromatography. All products were isolated with >20:1 regioselectivity. [b] A prolonged reaction time resulted in the decomposition of the product. [c] Starting material **2.12h** was not fully consumed.

planarization between the aromatic group and the oxyallyl cation moiety to enable delocalization of π -electrons. This barrier was readily overcome by introduction of electron rich *p*-methoxyphenyl substituted α -hydroxy silylenol ether **2.12g**, which afforded silylenol ether **2.14g** in 22 hours. Weakly deactivated *p*-chlorophenyl substituent **2.12h** further supports this hypothesis resulting in an unreactive species, allowing for minimal oxyallyl cation generation over 500 hours. Unsurprisingly, the unsubstituted α -hydroxy silylenol ether **2.12i** failed to react under our optimized conditions (Scheme 2.4). This result further supports our hypothesis that the reaction proceeds through a S_N1 mechanism and that α -substituents potentially assist in the stabilization of the silyloxyallyl cation intermediate through resonance and inductive effects.

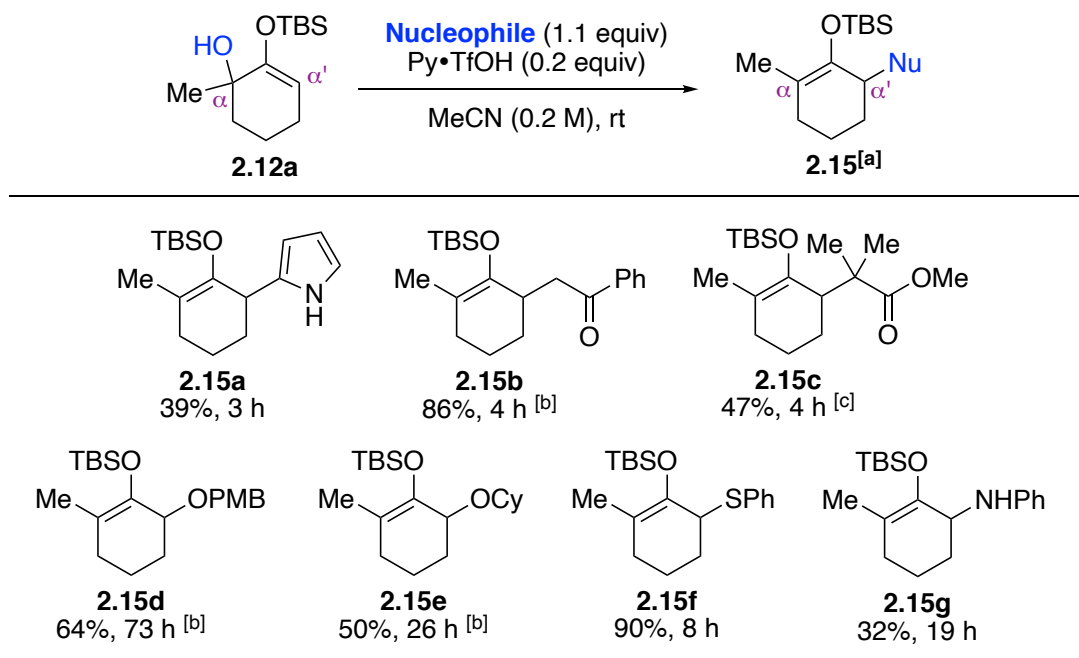


Scheme 2.4 Unsubstituted α -Hydroxy Silylenol Ether

2.6 Evaluation of Carbon and Heteroatom Nucleophiles

With the scope of substituted indoles, and substituted tertiary α -hydroxy silylenol ethers explored, we set to investigate the tolerance of various heteroatom and π -nucleophiles under our optimized conditions (Scheme 2.5). Tertiary α -hydroxy silylenol ether **2.12a** was employed as our model substrate for this study. Nitrogen containing heterocycle pyrrole yielded aryl silylenol ether **2.15a** in a modest 39% yield, while other heteroaromatics nucleophiles such as benzofuran and

benzothiophene failed to produce any α -functionalized products. We demonstrated that we could generate 1,4-monosilylated dicarbonyl compounds **2.15b** and **2.15c** in good yields *via* their respective silylenol ether and silylketene acetal π -nucleophiles. Through the use of oxygen centered heteroatom nucleophiles such as *p*-methoxybenzyl alcohol and cyclohexanol we successfully produced α' -alkoxy silylenol ethers **2.15d** and **2.15e** in 64% and 50% yields respectively. We observed reversibility of the nucleophilic capture of silyloxy allyl cations with alcohol nucleophiles, ultimately requiring higher equivalents of alcohol nucleophiles to obtain complete consumption of **2.12a**.⁵⁷ Additionally, heteroatom nucleophiles such as thiophenol and aniline yielded the corresponding thio silylenol ether **2.15f** in 90% yield and **2.15g** in 32% yield.

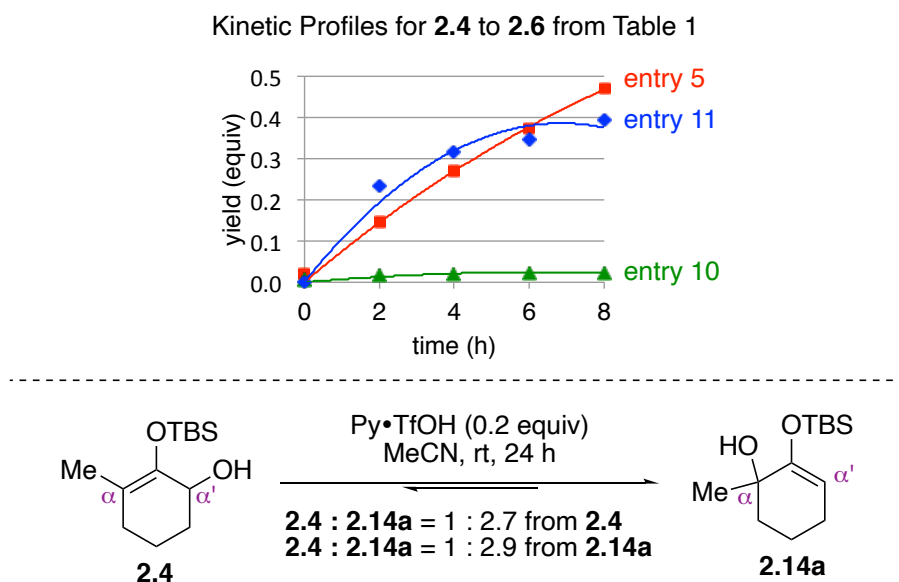


^[a] Isolated yields after flash column chromatography. All products were isolated with >20:1 regioselectivity. ^[b] 2.0 Equivalents of nucleophile was employed. ^[c] 3.0 Equivalents of nucleophile was employed.

Scheme 2.5 Scope of Carbon and Heteroatom Nucleophiles

2.7 Probing the Role of Water

During our reaction optimization studies (Table 2.1), we observed that catalytic water plays a crucial factor in the rate enhancement of ionization of **2.4**. To further understand the observed effect water on our reaction system we preformed HPLC kinetic measurements of entries 5, 10, and 11 from the reaction optimization table as depicted in Scheme 2.6. Under our optimized conditions (entry 5) we observed an almost linear increase in **2.6** generation, while introduction of 4Å molecular sieves (entry 10) produced trace product **2.6**. Addition of catalytic water (0.1 equiv) to the optimized conditions (entry 11) showed initial enhanced rate in the formation of **2.6**, followed by plateauing in product formation.

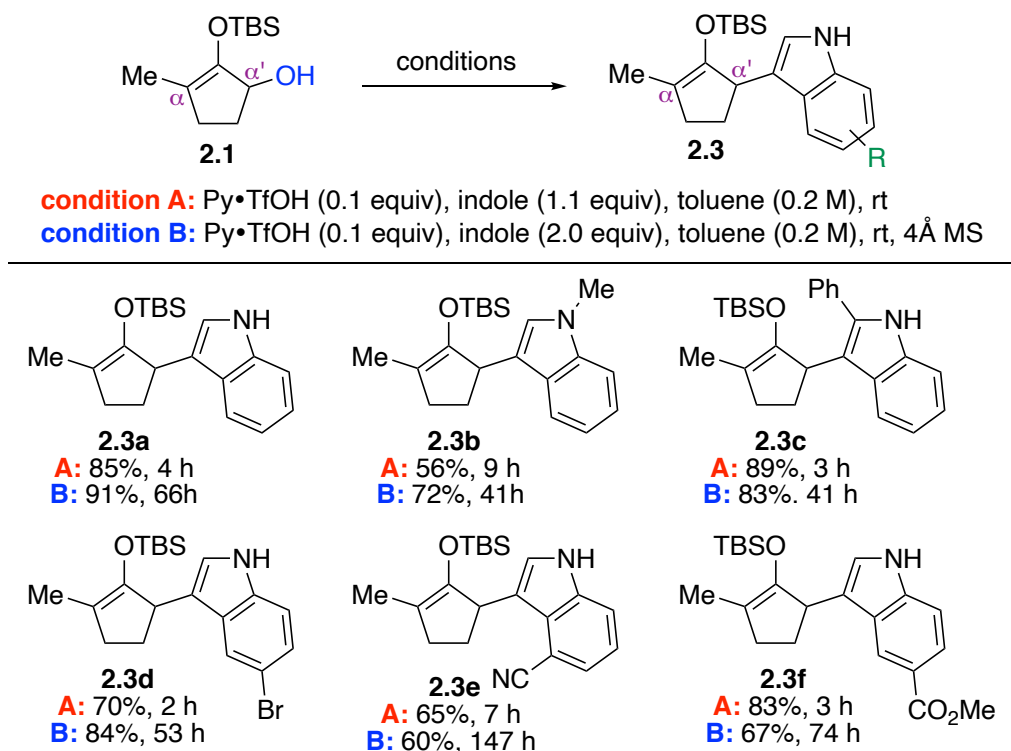


Scheme 2.6 Mechanistic Insight into the Role of Water

In conjunction with HPLC studies we individually subjected secondary and tertiary α' -hydroxy silylenol ethers **2.4** and **2.14a** to 0.2 equivalents of pyridinium triflate in acetonitrile to observe the migration of the hydroxyl group. To our surprise, upon equilibration for 24 hours each

sample was found to produce a mixture of both isomers **2.4** and **2.14a**, favoring the formation of tertiary alcohol **2.14a** in a roughly 3:1 ratio based on NMR analyses of the crude materials. From these NMR, and HPLC studies along with the solvation effect provided by the polarity in acetonitrile, we proposed that the silyloxyallyl cation intermediates are further stabilized by residual water through non-covalent interactions.

Further exploring the role of water in generation of silyloxyallyl cations, we subjected five-membered α -hydroxy silylenol ether **2.1** to the previously optimized conditions originally reported by Kartika and co-workers.^{60, 68} Two sets of reaction conditions were tested, conditions A where 4Å molecular sieves were excluded from the system and conditions B where the reaction included molecular sieves (Scheme 2.7). Evidence that water enhances the rate of ionization is supported



Scheme 2.7 Effect of Trace Water with the Five-Membered Silyloxyallyl Cation

by the synthesis of α' -indolyl silylenol ether **2.17a-2.17f** under conditions A.⁶⁸ We observed that generation of **2.17a-2.17f** in the absence of molecular sieves were obtained in a few hours with comparable yields, as opposed to days under the original reaction condition B.⁵⁶

2.8 Conclusion

Based on the studies explained in this chapter we were able to solve the problem with ionization of the six-membered α -hydroxy silylenol ethers by employing Hughes-Ingold rules to generate putative silyloxyallyl cations. Ionization utilizing catalytic pyridinium triflate in acetonitrile was relatively mild and tolerated numerous substituted indoles and heteroatom nucleophiles. Furthermore, we demonstrated that for silyloxyallyl cation formation substitution at the α' -position was crucial to stabilize the cationic intermediate. Proton NMR and HPLC studies demonstrated the role of catalytic water and its role in the stabilization of the silyloxyallyl cation intermediates through non-covalent interactions. With completion of this project, further demonstration on how solvent polarities enhance the rate of silyloxyallyl cation generation will be detailed in Chapters three and four.

Chapter Three: A Mild Approach to 1,4-Dicarbonyl Compounds Enabled by Regioselective Capture of Silyloxyallyl Cations with Silylenolates

3.1 Purpose

This chapter depicts our approach to develop a mild protocol for the synthesis of 1,4 and 1,6-dicarbonyl compounds through the regioselective nucleophilic capture of silyloxyallyl cation intermediates, by employing newly observed solvent effect. This third chapter comprises of a short background detailing the major synthetic strategies to generate 1,4-dicarbonyl compounds, while primarily focusing on the capture of oxyallyl cations with enolate nucleophiles. Our studies detail the initial exploration into various silyl protected enolate nucleophiles to capture silyloxyallyl cations promoted by pyridinium triflate ionization of α -hydroxy silylenolates in acetonitrile. A brief reaction optimization is detailed followed by exploration of reaction compatibility using various tertbutyldimethyl silylenolates and aliphatic and arene substituted α -hydroxy silylenol ethers. Moreover, our newly devised protocol is linearly compared to the previously developed method reported by Kartika to highlight differences in reactivity.

3.2 Background on the Synthesis of 1,4-Dicarbonyl Compounds

1,4-Dicarbonyl compounds are abundant structural components in various natural products such as maoecrystal V⁶⁹, herquiline A⁷⁰ and chamaejasmine⁷¹ as depicted in Figure 3.1. Outside their prevalence in natural products, 1,4-dicarbonyls are versatile building blocks for the synthesis of carbo/heterocyclic compounds such as cyclopentenones, furans, thiophenes, pyridazines, and pyrroles derivatives.⁷²⁻⁸⁰ Being important structural motifs within the synthetic community, many strategies have been developed to synthesize 1,4-dicarbonyls.^{63, 67, 81-88}

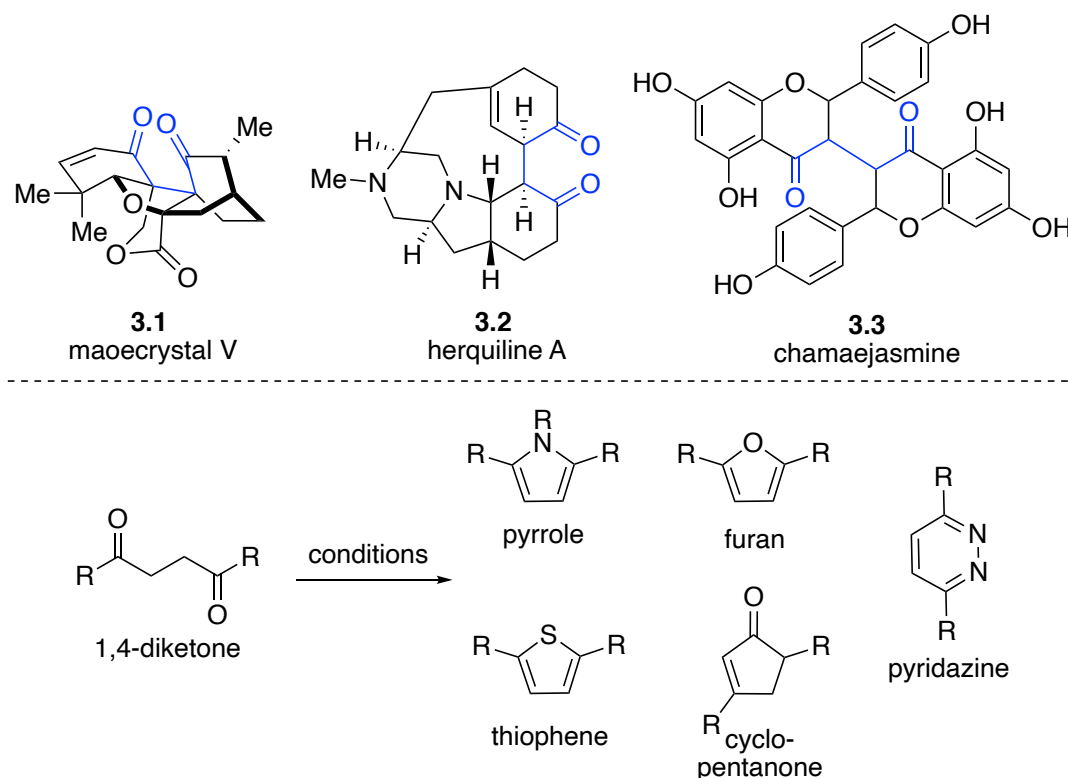
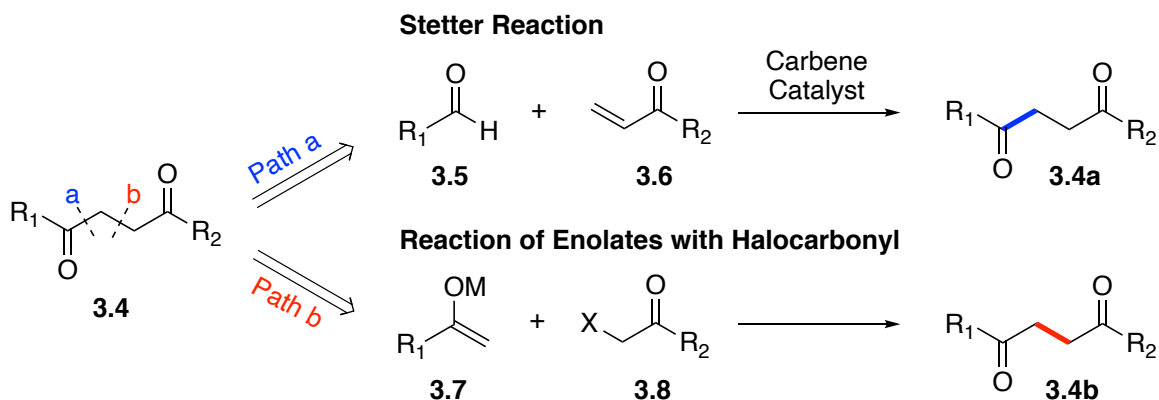


Figure 3.1 Synthetic Prevalence of 1,4-Diketones

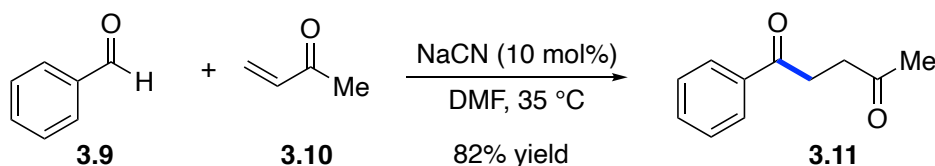
Two major retrosynthetic analyses of 1,4-dicarbonyl compounds are shown in Scheme 3.1, fragmenting dicarbonyl **3.4** into two distinct carbonyl units. One of the most well-known methods to generate 1,4-dicarbonyl compounds **3.4a** is through the Michael addition of an aldehyde **3.5** to α,β -unsaturated carbonyl **3.6** via carbene intermediates, this strategy is better known as the Stetter reaction (Path A).^{84, 89-92} Alternatively, the synthesis of 1,4-dicarbonyl compounds **3.4b** can be achieved is through the reaction of enolates **3.7** and α -halocarbonyl's **3.8** to generate the corresponding adducts (Path B). This reaction between enolates and α -halocarbonyl's have been reported to occur through both cationic and radical pathways.^{16, 67, 87, 93, 94} Although, there are other methods to access 1,4 dicarbonyl compounds such as oxidative homo- or heterocoupling of enolates, these strategies are among the most popular.^{88, 95}



Scheme 3.1 General Strategies to Access 1,4-Dicarbonyls

3.3 Synthesis of 1,4-Dicarbonyl Compounds via the Stetter Reaction

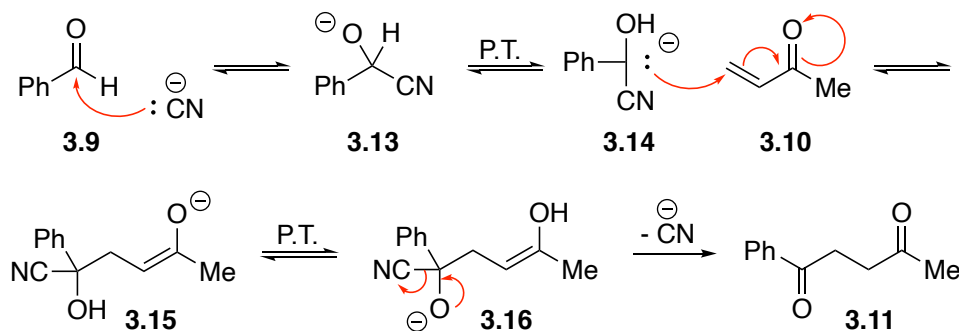
As discussed above, one of the most common strategies to access 1,4-dicarbonyl compounds is through the use of the Stetter reaction (Scheme 3.2). First reported in 1973, Stetter discovered that treatment of aldehyde **3.9** with catalytic sodium cyanide (NaCN) in the presence an α,β -unsaturated carbonyl **3.10** successfully generated 1,4-diketone **3.11** in 82% yield.^{84, 96} This seminal report tolerated a variety of aromatic aldehydes and Michael acceptors, affording a variety 1,4-diketones.



Scheme 3.2 The Stetter Reaction

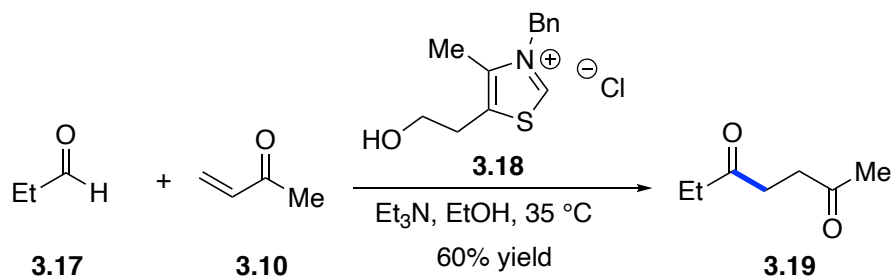
The proposed reaction mechanism for the Stetter reaction revolves around exploiting umpolung chemistry by transforming an electrophilic aldehyde into a nucleophilic species (Scheme 3.3). Stetter proposed that 1,2-nucleophilic addition of the cyanide anion to the

electrophilic aldehyde **3.9** generated charged tetrahedral intermediate **3.13**. Next, reversible proton transfer of **3.13** generated carbene **3.14** which forgoes nucleophilic attack to the Michael acceptor **3.10** forming cyanohydrin **3.15** intermediate. Subsequent proton transfer followed by collapse of the tetrahedral intermediate **3.16** successfully afforded 1,4-diketone **3.11**.



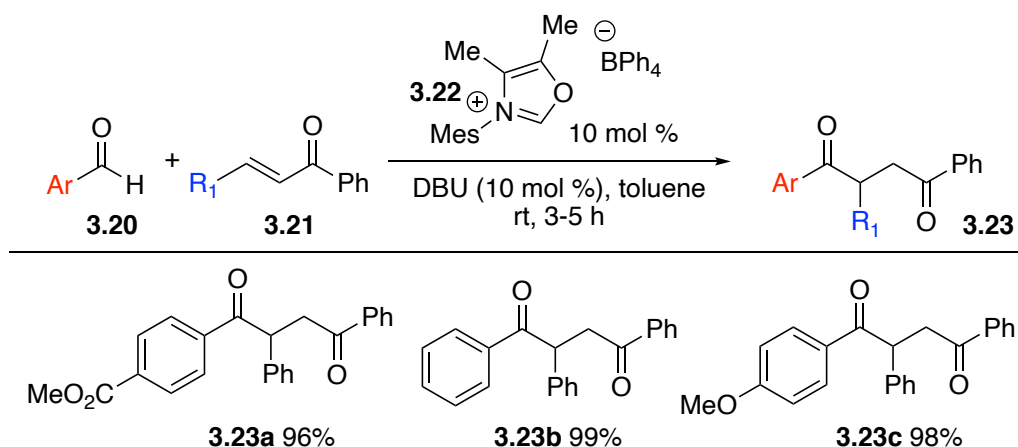
Scheme 3.3 Proposed Stetter Reaction Mechanism

Unfortunately, the use of NaCN as a catalyst limited the scope of aldehydes to aromatic substituents, as aliphatic aldehydes would readily undergo undesired aldol condensations.⁸⁴ To circumvent this undesired side reaction, Stetter observed that replacement of NaCN with catalyticthiazolium salt **3.18** prevented undesired aldol condensations (Scheme 3.4). He reported that treatment of aldehyde **3.17** with methyl vinyl ketone **3.10** and catalyst **3.18** successfully yielded 1,4-diketone **3.19** in 60% yield. The proposed reaction mechanism for the thiazolium catalyzed Stetter reaction proceeds *via* a similar mechanism to the cyanide variant but requires the addition of a base to deprotonate the thiazolium salt generating a nucleophilic carbene *in situ*. Since the initial report of the Stetter reaction, a variety of modifications have been developed, including the use of different NHC catalysts, and enantio- and diastereoselective variants to synthesize 1,4-dicarbonyl compounds. While there are countless examples of this reaction, only a few will be discussed and other examples will be cited in the reference section.^{83, 91, 97-100}



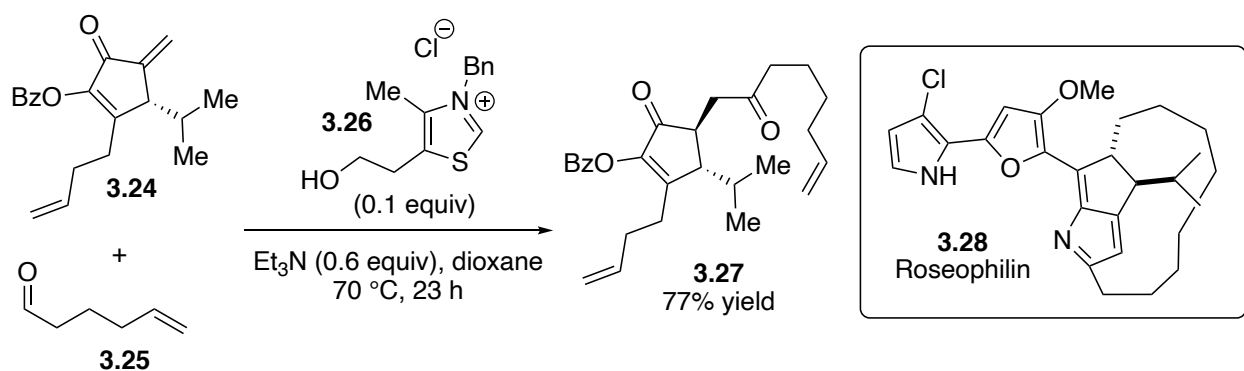
Scheme 3.4. NHC Catalyzed Stetter Reaction

A recent example of the Stetter reaction was reported by Gravel and co-workers, in which they achieved the synthesis of 1,4-diketones through a *N*-aryl oxazolium salt catalyzed Stetter reaction (Scheme 3.5).¹⁰¹ Gravel detailed that treatment of aromatic aldehydes **3.20** with oxazolium **3.22** successfully generated acyl anion *in situ*. Subsequent, conjugate addition to α,β -unsaturated ketones **3.21** successfully generated 1,4-diketones **3.23**. Electron rich and poor aldehydes were tolerated under the optimized conditions yielding adducts **3.23a-3.23c** in excellent yields. Unfortunate, under their reaction conditions employment of aliphatic aldehydes proved problematic, generating undesired homobenzoin products.



Scheme 3.5 Gravel's Oxazolium Catalyzed Stetter Reaction

Beyond methodology development, the Stetter reaction is widely utilized tool in the total synthesis of various natural products. For example, in the total synthesis of roseophilin **3.28** by Tius and co-workers they employed a thiazolium catalyzed Stetter reaction to construct their 1,4-diketone (Scheme 3.6).¹⁰² Treatment of 6-heptenal **3.25** with catalytic NHC **3.26** and triethylamine, readily generated an acyl carbanion which effortlessly added across α,β -unsaturated ketone **3.24**. Generation of 1,4-diketone **3.27** was achieved in 77% yield as the trans diastereomer, with a small amount of the cis compound formed. The installation of the 1,4-diketone served as a precursor to the pyrrole core present in roseophilin, which was achieved through a Paal-Knorr pyrrole reaction.

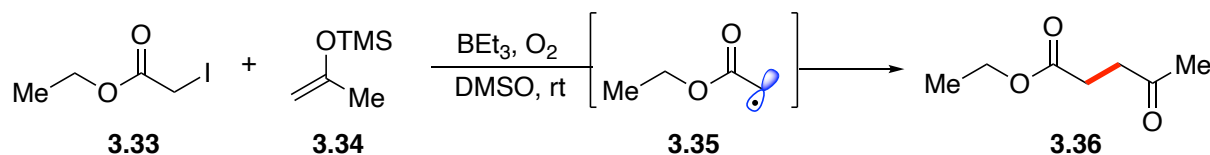


Scheme 3.6 Application of the Stetter Reaction in the Synthesis of Roseophilin

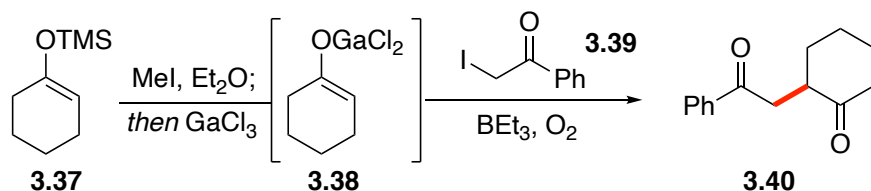
Another demonstration of the Stetter reaction in total synthesis was reported by Blechert and co-worker in the enantioselective synthesis of (+)-monomorine I **3.32** as detailed in Scheme 3.7.¹⁰³ Similar to the work by Tius, Blechert treated norborene carbaldehyde **3.29** with catalytic NHC **3.26** and Et_3N in the presence to *n*-butyl vinyl ketone **3.30**, easily generating 1,4-diketone **3.31** in 85% yield. The synthesis of 1,4-diketone **3.31** set up the required functionality to install the pyrroline core of **3.32**. These select examples showcased the overall synthetic power of the Stetter reaction to generate 1,4-diketones in the synthesis of complex molecular motifs.

diketone **3.40** in 49% yield. Under their reaction conditions, Oshima observed that α -iodoesters and α -iodoamides were tolerated, furnishing the corresponding ketoesters and ketoamides in moderate yields. These initial studies on radical pathways to generate 1,4-dicarbonyls from silyl enolates and α -halocarbonyl's have paved the way for recent advancements in the field.

(1) Muraglia (1994)



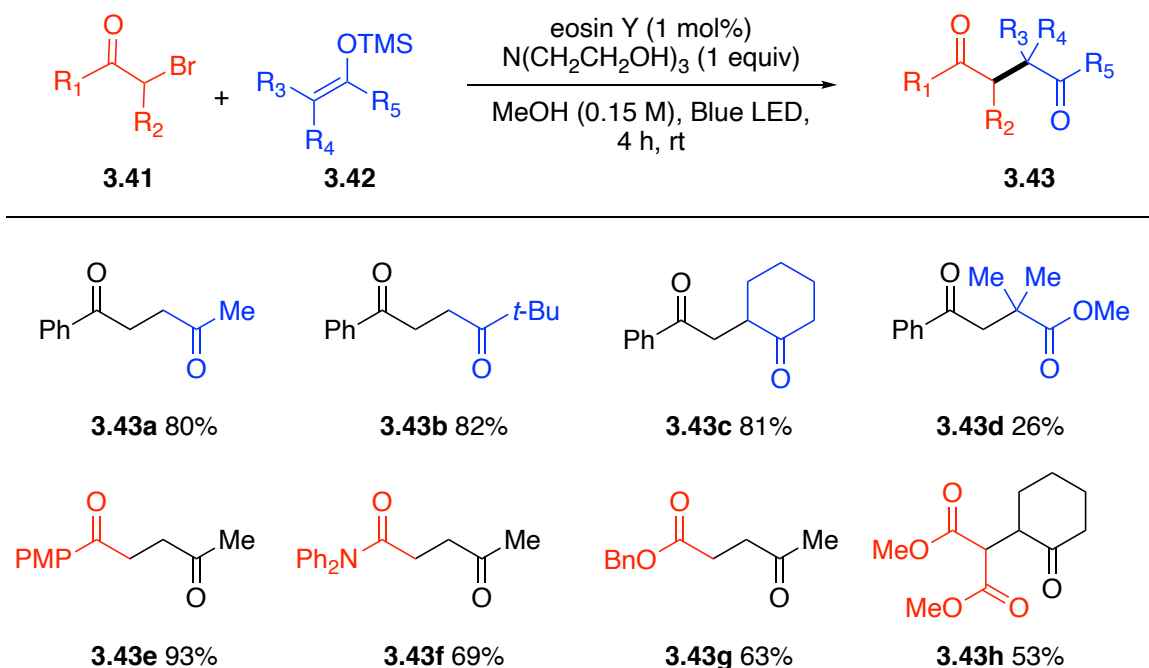
(2) Oshima (2002)



Scheme 3.8 Dicarboxyls *via* Enolates and α -Halocarbonyl's *via* a Radical Pathway

A more recent approach to the synthesis of 1,4-dicarbonyls through radical intermediacy was reported by Yasuda and co-workers in 2016.⁸⁶ Yasuda's report detailed the combination of silyl enol ethers **3.42** and α -haloketones **3.41** in the presence of photoredox catalyst eosin Y, and upon irradiation of the reaction mixtures with blue LEDs (468 nm), 1,4-diketones **3.43** could be successfully generated (Scheme 3.9). This method proved chemoselective, only generating the desired diketone with no observable carbonyl addition byproducts that readily occurs through radical processes. Through extensive reaction optimization, it was observed that triethanolamine as a reductive agent alongside irradiation was required for the reaction to proceed. Yasuda examined their reaction scope of by subjecting diverse silyl enol ethers **3.42** and α -bromoketones **3.41** to their optimized conditions. The observed that silyl enolates derived from aliphatic ketones

successfully produced 1,4-diketones **3.43a-3.43c** in excellent yields without formation of undesired carbonyl adducts. They also exemplified the use of a silyl ketene acetal nucleophile could be utilized, furnishing 1,4-ketoester **3.43d** albeit a diminished yield. Their use of assorted α -bromocarbonyl compounds proved advantageous, as they could readily generate diketone **3.43e**, ketoamide **3.43f**, and ketoesters **3.43g** and **3.43h** in moderate to excellent yields.

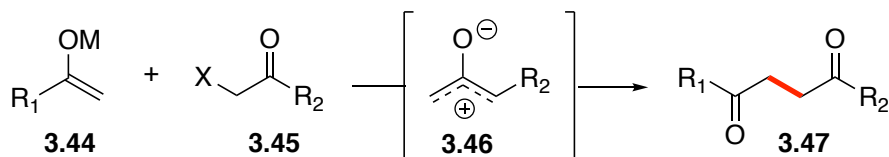


Scheme 3.9 Yasuda's Photocatalytic Approach to 1,4-Dicarbonyls

3.5 Synthesis of 1,4-Dicarbonyl Compounds via Oxyallyl Cations

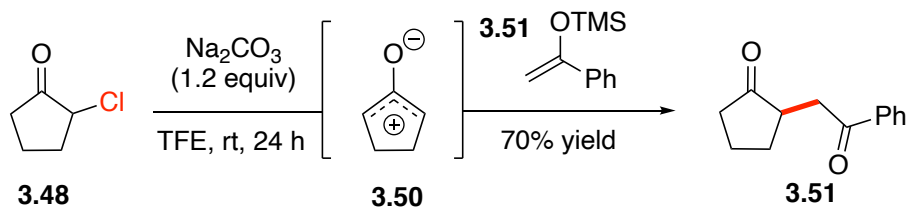
An alternative approach to the radical mediated synthesis of 1,4-dicarbonyl compounds with enolates and α -halocarbonyl's is through the use of cationic intermediates such as oxyallyl cations (Scheme 3.10). As previously described in Chapter one, oxyallyl cations are powerful electrophilic intermediates used for the synthesis of complex molecules. These zwitterionic intermediates **3.46** are typically generated *via* dehalogenation of α -haloketones **3.45** through an

E_{1cb} or S_N1 type mechanism and can be subsequently captured with enolate nucleophiles **3.44** to generate 1,4 dicarbonyl compounds **3.47**. To the best of our knowledge, few methods exploiting this zwitterionic intermediate exist for the construction of 1,4-dicarbonyls.



Scheme 3.10 Access 1,4-Dicarbonyls Through Oxyallyl Cations

In 2015, Tang and co-workers reported the use of oxyallyl cations and silyl enol ethers nucleophiles to readily furnish 1,4-diketones (Scheme 3.11).¹⁶ Following similar work of Chi, Tang and his team reported that treatment of α-chloroketone **3.48** with Na₂CO₃ in trifluoroethanol (TFE) readily generated oxyallyl cation **3.50** *in situ*. In the presence of TMS derived silyl enolate nucleophile **3.51**, nucleophilic capture of the zwitterionic intermediate afforded 1,4-diketone **3.52** in 70% yield. Through their reaction optimization they noted that excess silyl enolate nucleophile **3.51** was required for an efficient reaction as the nucleophile proved unstable in TFE.



Scheme 3.11 Tang's Oxyallyl Cation Strategy to 1,4-Diketones

Furthermore, Tang explored the applicability of their reaction by evaluating a series of silyl enolate nucleophiles (Table 3.1). Tang observed that a wide variety of aliphatic and cyclic TMS-

derived enolates **2.55** were tolerated under their reaction conditions. For example, acetophenone derived nucleophiles such as 4-methoxyacetophenone **2.55a** and 3-bromoacetophenone **2.55b** successfully generated 1,4-diketones **2.56a** and **2.56a** in moderate to excellent yields. Gratifyingly, steric effects introduced by the use of disubstituted silyl enol ethers did not affect the efficacy of

Table 3.1 Tang's Scope of Silylenolate Nucleophiles

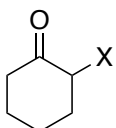
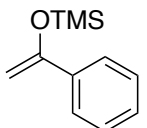
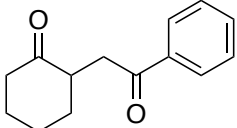
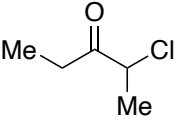
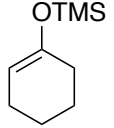
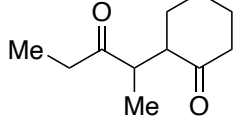
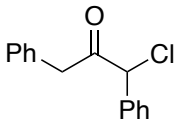
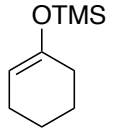
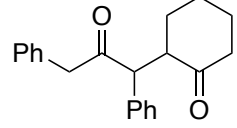
3.48	3.55	3.56	
entry	nucleophile	product	yield ^[a,b]
1			65%
	3.55a	3.56a	
2			78%
	3.55b	3.56b	
3			73% (1:1 dr)
	3.55c	3.56c	
5			67% (5:2 dr)
	3.55e	3.56e	

^[a] Isolated yield. ^[b] The diastereomer ratio was determined by ¹H NMR analysis of the crude reaction mixture

their reaction. For example, the use of silyl enolates **2.55c** and **2.55d** successfully furnished diketones **2.56c** and **2.56d** in 73% and 67% yields respectively, alas these substrates were accompanied with poor diastereoselectivities. Alas, Tang observed that electron deficient nucleophiles and enolates derived from aldehydes proved problematic, ultimately generating complex mixtures of products.

Continuing their investigation, further studies explored the scope of α -haloketones under their optimized conditions (Table 3.2). Exploring the tolerance of other halogen leaving, it was observed that the use of chloro, bromo or iodo α -haloketones **2.52a** ultimately lead to the formation

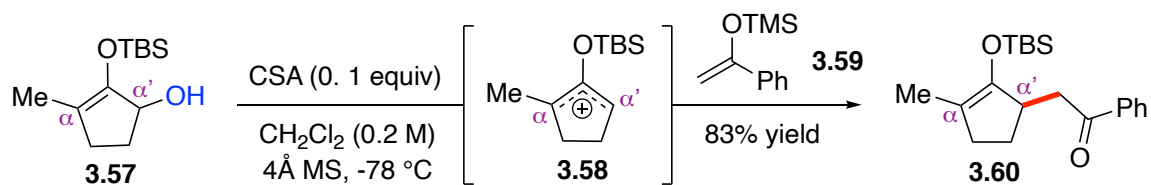
Table 3.2 Tang's Scope of α -Haloketones

$ \begin{array}{c} \text{R}_1\text{CH}_2\text{C}(=\text{O})\text{CH}(\text{X})\text{R}_2 \\ \textbf{3.52} \end{array} + \begin{array}{c} \text{OTMS} \\ \text{R}_3\text{CH}=\text{CH}\text{R}_4 \\ \textbf{3.53} \end{array} \xrightarrow[\text{TFE, rt, 24 h}]{\text{Na}_2\text{CO}_3 \text{ (1.2 equiv)}} \begin{array}{c} \text{R}_1\text{CH}_2\text{C}(=\text{O})\text{CH}(\text{R}_2)\text{CH}(\text{R}_3)\text{C}(=\text{O})\text{R}_4 \\ \textbf{3.54} \end{array} $				
entry	haloketone	nucleophile	product	yield ^[a,b]
1	 3.52a	 3.53a	 3.54a	62% (X = Cl) 60% (X = Br) 56% (X = I)
2	 3.52b	 3.53b	 3.54b	39% (5:1 dr)
3	 3.52c	 3.53c	 3.54c	73% (10:1 dr)

^[a] Isolated yield. ^[b] The diastereomer ratio was determined by ¹H NMR analysis of the crude reaction mixture

of diketone **2.54a** with similar efficiency for each of the α -haloketones. Outside the use of cyclic α -haloketones, the use of acyclic α -haloketones proved problematic. Under their reaction conditions α -chloroketones **2.52b** and **2.52c** readily furnished 1,4-diketones **2.54b** and **2.54c** respectively in moderate diastereoselectivities albeit diminished yields of the corresponding ketones. While Tang developed a robust method to generate 1,4-diketones *via* oxyallyl cations intermediates, this method relied on the use of symmetric α -haloketones to prevent regioisomers.

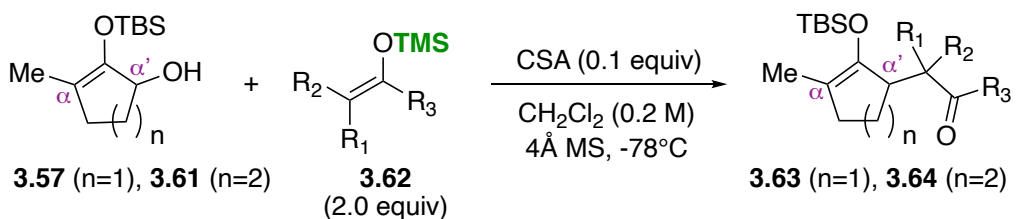
While Tang's novel approach to the synthesis of 1,4-diketone harnessed the reactivity of oxyallyl cations, ultimately their strategy relied on the use of symmetric oxyallyl cations.¹⁶ Inspired by this limitation, Kartika and co-workers developed an innovative strategy to access 1,4-monosilylated diketones via unsymmetrical silyloxyallyl cation intermediates (Scheme 3.12).⁶¹ Kartika discovered that ionization of α -hydroxy silylenol ether **3.57** through the use of catalytic camphorsulfonic acid (CSA) could generate unsymmetrical silyloxyallyl cation **3.58**. Furthermore, in the presence of a TMS-derived silyl enolate **3.59**, regioselective capture of **3.58** occurred at the least substituted α' -carbon readily furnished 1,4-monosilylated diketone **3.60**. Kartika observed that performing the reaction at cryogenic temperatures and the introduction of molecular sieves were necessary to preventing undesired protodesilylation of reactants under highly acidic conditions. In addition, the use of highly reactive TMS-silyl enolates were required for an efficient reaction as more stable TBS derived silyl enolates proved to be less reactive nucleophiles.



Scheme 3.12 Kartika's Regioselective Synthesis of 1,4-Monosilylated Diketones

Moreover, Kartika investigated the scope of their reaction through utilizing a variety of TMS-derived enolate nucleophiles (Table 3.3). For these studies both five and six-membered α -hydroxy silylenol ethers **3.57/3.61** were subjected to the optimized conditions. Acetophenone derived silyl enolate **3.62a** readily furnished adducts **3.63a/3.63b** albeit lower yields observed with

Table 3.3 Kartika's Scope of Silylenolate Nucleophiles



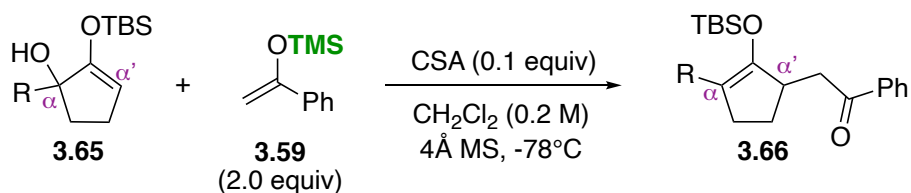
entry	nucleophile	product	yield, time [a]
1			3.63a : 83%, 7 h 3.64a : 61%, 42 h
2			3.63b : 89%, 36 h 3.64b : 67%, 48 h
3			3.63c : 75%, 5 h (2.5:1 dr) [b] 3.64c : 63%, 23 h (5:2 dr) [b]
4			3.63d : 50%, 20 h

[a] Isolated yield after column chromatography. [b] The diastereomer ratio was determined by ^1H NMR analysis of the crude reaction mixture

six-membered α -hydroxy silylenol ether **3.61**. Aliphatic silyl enolates were found to be tolerated, generating the desired products **3.63b/3.63c** and **3.64b/3.64c** *via* enolates **3.62b** and **3.62c** respectively. As demonstrated in entry 5, the use of silyldienol ether **3.62d** readily produce monosilylated 1,6-diketone **3.63e** in 50% yield. Throughout their studies it was observed that the yields of the six-membered 1,4-monosilylated diketones **3.64** were generally lower than that of five-membered analog, along with extended rates of reaction. They hypothesized that the decrease in yield and extended rates of reaction were attributed to the difficulty in generation of the six-membered silyloxyallyl cation.^{60, 62}

Further studies performed by Kartika and co-workers examined the substituent effects at the α -carbon of the α -hydroxy silylenol ether (Table 3.4). As previously demonstrated in their lab, tertiary α -hydroxy silylenol ethers **3.65** readily generated unsymmetrical silyloxyallyl cations under acidic conditions. Aliphatic substituents such as *n*-octyl **3.65a** and *iso*-butyl **3.65b** α -hydroxy silylenol ethers were tolerated successfully generating 1,4-monosilylated diketones **3.66a** and **3.66b** in moderate yields. The longer rate of reaction observed was hypothesized to be attributed to the steric congestion involving ionization the tertiary α -hydroxy silylenol ether **3.65**. Unsurprisingly, introduction of phenyl substituent **3.65a** rapidly gave access the corresponding adduct **3.66c** in an excellent yield. While the goal of this method was to generate 1,4-monosilylated diketones, it was also demonstrated that 1,4-diketones were accessible through these compounds through the use of tosic acid to induce protodesilylation.

Table 3.4 Kartika's Scope of α -Hydroxy Silylenol Ethers



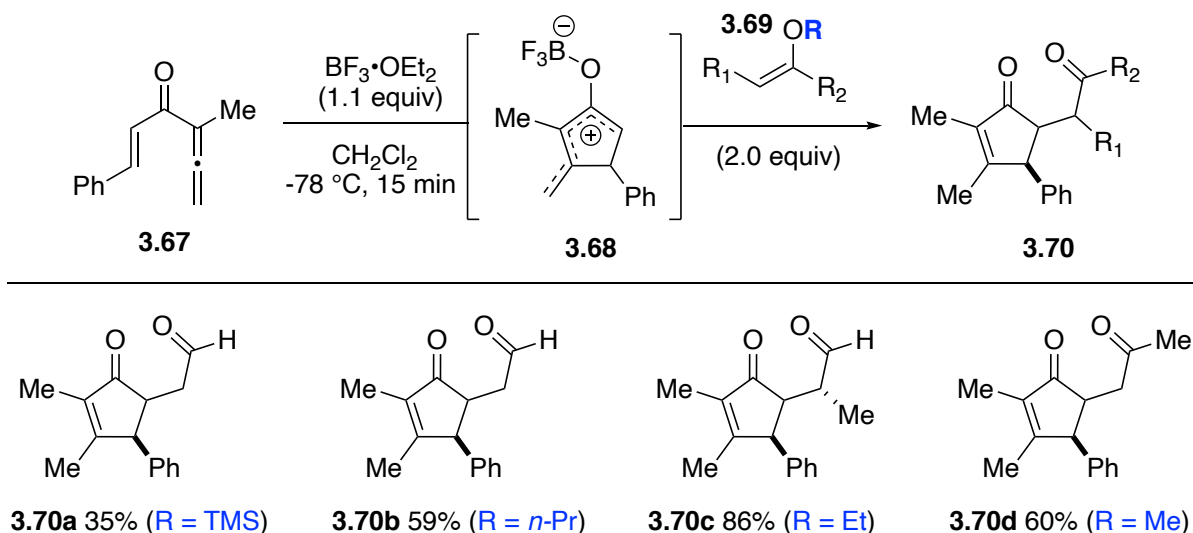
entry	starting material	product	yield, time [a]
1	 3.65a	 3.66a	49%, 49 h
2	 3.65b	 3.66b	59%, 18 h
3	 3.65c	 3.66c	83%, 10h

[a] Isolated yield after column chromatography.

3.5 1,4-Dicarbonyl Compounds via Interrupted Nazarov Cyclization's

Similar to the methods generating 1,4-dicarbonyl compounds through direct nucleophilic capture of oxyallyl and silyloxyallyl cations described above, the use of interrupted Nazarov cyclization has also proved itself a useful approach to generate 1,4-dicarbonyl compound.^{46, 106-108} As previously described in Chapter One, the interrupted Nazarov cyclization involves the formation of oxyallyl cations *via* Lewis or Brønsted acid promoted cyclization of divinyl ketones, followed by a nucleophilic capture of the oxyallyl cation generating functionalized cyclopentanones.

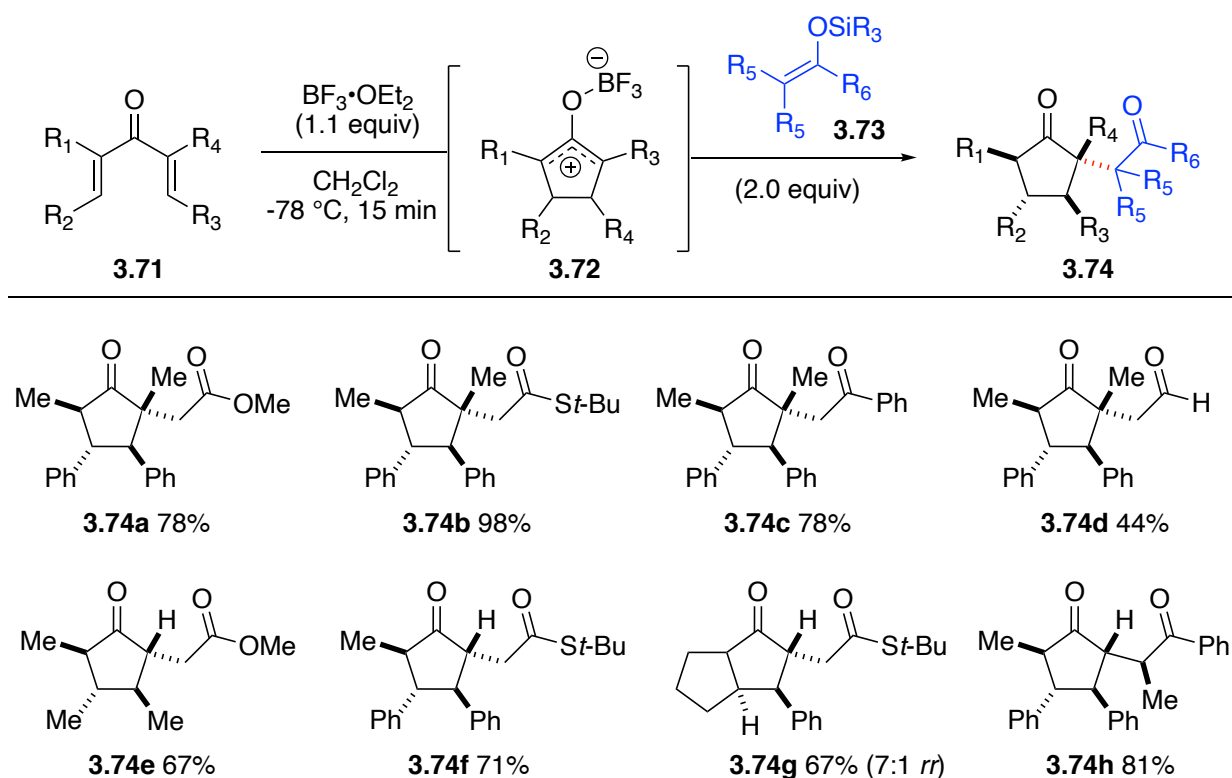
One of the earlier reports for generating 1,4-dicarbonyl compounds through an interrupted Nazarov cyclization was detailed by Burnell and co-workers in 2010 (Scheme 3.13).¹⁰⁶ Starting with allenyl vinyl ketone **3.67**, stoichiometric $\text{BF}_3 \cdot \text{OEt}_2$ effortlessly promoted Nazarov cyclization generating unsymmetrical oxyallyl cation **3.68**. In the presence of protected enol ethers **3.69** nucleophiles, regioselective capture of the oxyallyl cation **3.68** at the least hindered α -carbon produced the corresponding 1,4-dicarbonyls **3.70**. The scope of this reaction only tolerated select enolate nucleophiles. For example, silyl enol ether derived **3.69** inefficiently captured oxyallyl cation **3.68** yielding dicarbonyl in 35% yield. Burnell observed that switching to more electron rich nucleophiles such as *n*-propyl, ethyl or methyl protected enol ethers more efficiently generated the corresponding 1,4-dicarbonyl compounds **3.70b-3.70d** in moderate to excellent yields.



Scheme 3.13 Burnell's Interrupted Nazarov Cyclization with Enolate Nucleophiles

While Burnell only demonstrated a few examples of this unique reactivity, in 2011 West further expanded this chemistry to the synthesis of stereochemical rich 1,4-dicarbonyls (Scheme 3.14).⁴⁶ Similar to that of Burnell's work, West employed $\text{BF}_3 \cdot \text{OEt}_2$ to promote Nazarov

cyclization of divinyl ketones **3.71** generating oxyallyl cations **3.72**. Subsequent trapping of oxyallyl cation intermediates **3.72** with silyl enolates **3.73** afforded 1,4-dicarbonyls **3.74** moderate to excellent yields. West discovered that a wide variety of TBS protected enolates such as ketene acetals, , and silyl enol ethers were tolerated under their developed method. For example, the use of ketene acetals ketene and S,O-acetals silylenolates readily furnished 1,4-dicarbonyl compounds **3.74a** and **3.74b** in 78% and 98% yield respectively. Silyl enolates derived from acetophenone and acetaldehyde led to formation of adducts **3.74c** and **3.74d**, albeit diminished yields.

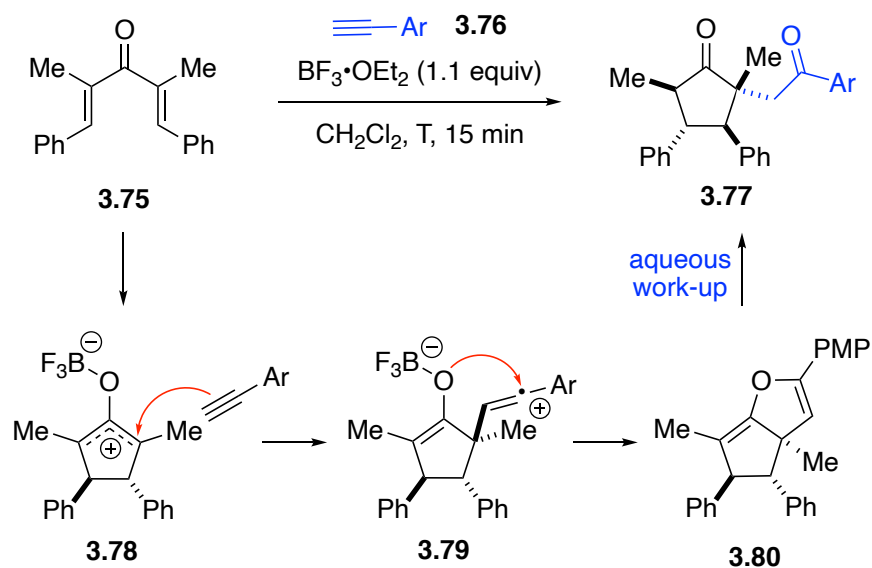


Scheme 3.14 West's Approach to Trapping Nazarov Intermediates with Silylenolates

West further demonstrated that they could employ unsymmetrical divinyl ketones to generate unsymmetrical oxyallyl cation **3.73**, which then could undergo regioselective nucleophilic capture. 1,4-Dicarbonyls **3.74e** and **3.74f** were provided as a single regioisomer in

moderate yields, and the observed regioselectivity was rationalized by the accessibility of the unsubstituted carbon alongside the formation of the more stable fully substituted enolate prior to decomplexation with $\text{BF}_3 \cdot \text{OEt}_2$. Alas, they observed the formation of **3.74g** as a mixture of regioisomers due to generation of unfavored ring strain in the bicyclic system, resulting in nucleophilic attack at the most substituted carbon. For the synthesis of stereochemical rich 1,4-diketone **3.74g**, the use of a Z-silyl enol ether resulted in the formation of the ketone adduct as single diastomer, ultimately generating five continuous stereocenters.

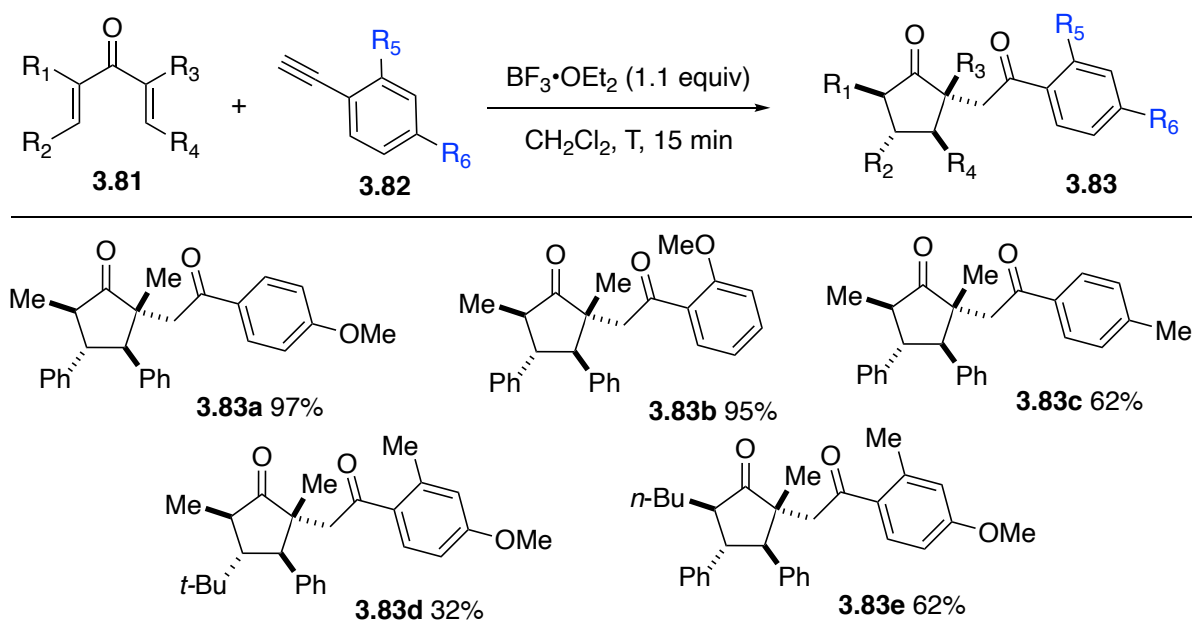
Succeeding their initial work generating 1,4-dicarbonyls *via* interrupting Nazarov cyclization's with nucleophilic silyl enolates, West and co-workers disclosed that they could access 1,4-diketones by trapping oxyallyl cations with electron rich alkynes (Scheme 3.15).¹⁰⁷ West observed that treatment of divinyl ketone **3.75** with $\text{BF}_3 \cdot \text{OEt}_2$ in the presence of an electron rich aromatic substituted alkyne **3.76** readily furnished 1,4-diketone **3.77**. This unique transformation was proposed to go through Lewis acid promoted Nazarov cyclization of **3.75** to



Scheme 3.15 Synthesis of 1,4-Diketones via Interrupted Nazarov with Alkynes

afford oxyallyl cation **3.78**, followed by nucleophilic capture of the cationic intermediate with alkyne **3.76** generating vinyl cation **3.79**. Furthermore, attack of the ensuing vinyl cation **3.79** by the enol ether oxygen produced dihydrofuran **3.80**, which upon aqueous workup is hydrolyzed generating 1,4-diketone **3.77**. Unfortunately, this alkyne was limited to the use of electron rich aromatic alkynes, as silyl, alkyl, or phenyl could not provide the required stabilization of **3.79**.

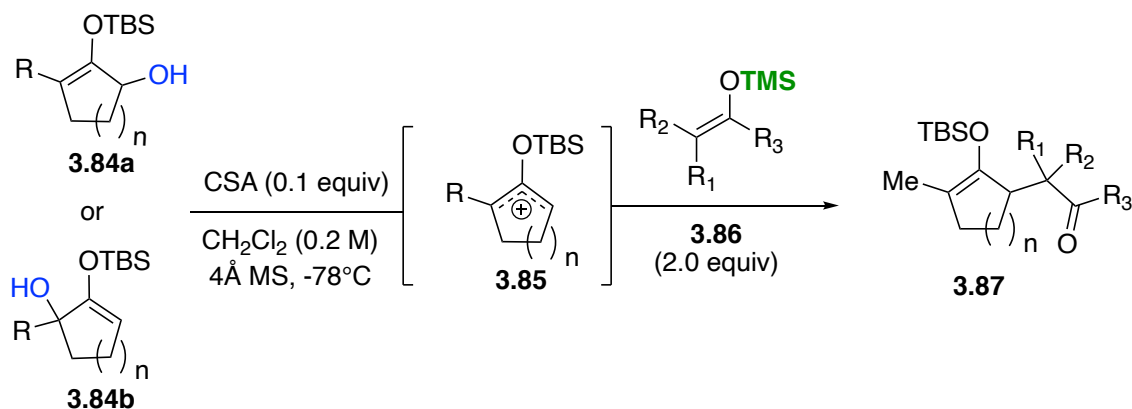
Probing the scope of their domino electrocyclization/carboalkoxylation reaction, they examined both divinyl ketones **3.81** and aromatic alkynes **3.82** in the formation of 1,4-diketones **3.83** (Scheme 3.16). Aromatic alkynes with ortho and para-methoxy substitution could successfully capture the oxyallyl cation, affording products **3.83a** and **3.83b** in excellent yields. Upon switching to less electron rich para-touylalkyne, adduct **3.83c** could be generated in 62% yield. While exhibiting a lower yield, this example demonstrated that para-alkyl substituents could provide the required stabilization to the vinyl cation intermediate. Furthermore, unsymmetrical divinyl ketones resulted in the formation of ketones **3.83d** and **3.83e** as single diastereomer.



Scheme 3.16 West's Scope of Divinyl Ketones and Alkynes

3.6 Revised Synthesis of 1,4-Diketones from Silyloxyallyl Cations

As previously described above Kartika and co-workers had developed an elegant approach to synthesize 1,4-monosilylated diketones **3.87** *via* regioselective nucleophilic capture of unsymmetrical silyloxyallyl cations **3.85** generated from either the five or six-membered α -hydroxy silyl enol ethers **3.84a** or **3.84b** (Scheme 3.17).⁶⁷ Alas, this approach was accompanied with several inherent drawbacks. First, they observed that the employment of relatively strong Brønsted acid CSA employed to promote ionization led to undesired protodesilylation of the TMS silylenolates **3.88**, preventing utilization of more acid sensitive nucleophiles. Secondly, to suppress undesired decomposition the reaction components was performed at cryogenic temperatures ultimately resulting in prolonged reaction times.



Scheme 3.17 Kartika's Previous Synthesis of 1,4-Monosilylated Diketones

To address the challenges associated with initial report to synthesize 1,4-monosilylated diketones by Kartika and co-worker's, we set to develop a more operationally practical strategy to access these highly useful molecules. As previously discussed in Chapter two, we observed that the use of polar solvents in cooperation with catalytic water generated through ionization assisted

in accelerating the rate of formation and stabilization of silyloxyallyl cations through Hughes-Ingold Rules.⁶⁴ Using this knowledge, we hypothesized that implementing a polar solvent alongside the use of weaker Brønsted acid we could develop a more practical protocol for the synthesis of 1,4- and 1,6-monosilylated dicarbonyls **3.87** from α -hydroxy enol ethers **3.84a** or **3.84b**, allowing for a room temperature reaction that would tolerate more acid sensitive nucleophiles.

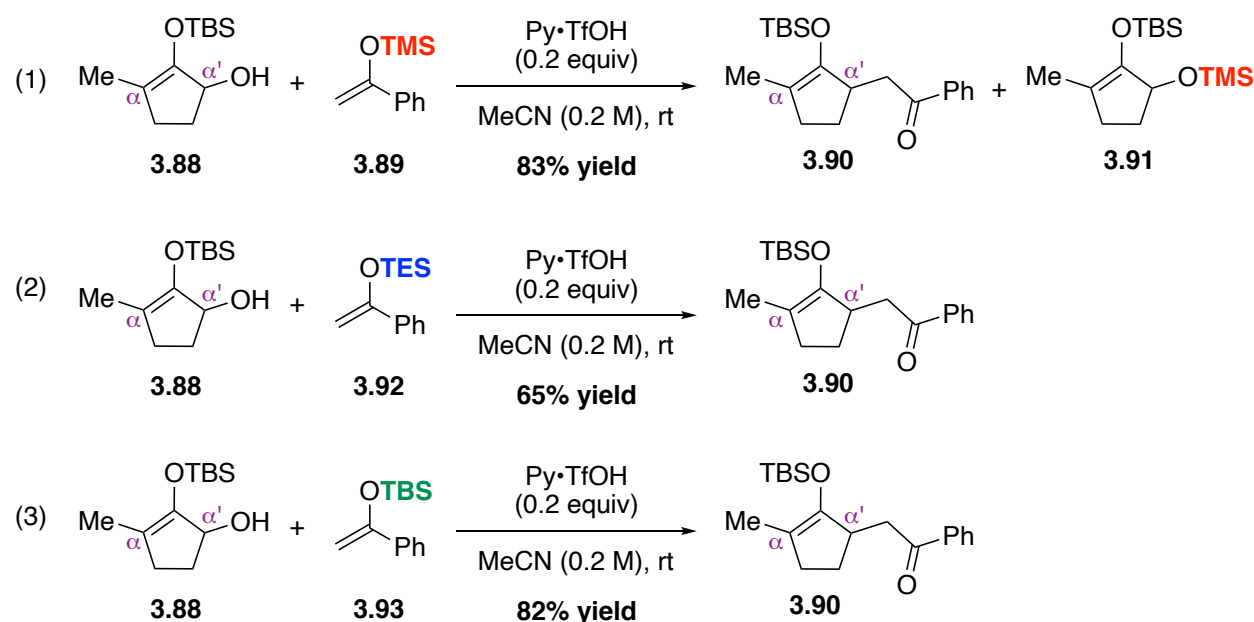
3.7 A Mild Reaction Optimization for the Synthesis of Monosilylated 1,4-Diketones³

Preliminary exploration into the feasibility of developing a milder methodology is depicted in Scheme 3.18. For our pilot experiments, we employed five-membered α -hydroxy silylenol ether **3.88** and acetophenone derived silylenolates in acetonitrile as our model system. We hypothesize that utilization of milder Brønsted acid, pyridinium triflate (Py•TfOH) would suppress decomposition of various silylenolates moieties at room temperature. Acetonitrile was chosen as our solvent based on previously observed rate enhancement in generation of six-membered silyloxyallyl cations as previously discussed in Chapter Two. Initially, we subjected TMS-protected acetophenone silylenolate **3.89** to our conditions at room temperature. To our surprise, under these polar-acidic conditions we were able to synthesize 1,4-monosilylated diketone **3.90** in 85%, in only 5 hours. While this initial result was exciting, the use of the TMS silylenolate **3.89** unfortunately yielded inconsistent results and reactivity. In addition, TMS-silylated enol ether **3.91** was observed as an inseparable byproduct.⁵

In an attempt to increase reproducibility and minimize undesired byproducts, we replaced the TMS protecting group with more acid stable TES and TBS protected silylenolates **3.92** and

³ Reprinted (adapted) with permission from (Malone, J. A.; Van Houten, J. P.; Ganiu, M. O.; Nepal, B.; Kartika, R., Brønsted Acid Catalyzed Synthesis of Functionalized 1,4- and 1,6-Dicarbonyl Monosilyl Enol Ethers under Operationally Practical Conditions. *J. Org. Chem.* **2017**, 82, 10659-10664.) Copyright (2017) American Chemical Society." – For sections 3.7 to 3.9.

3.93 respectively, with the knowledge that their nucleophilicity could potentially be reduced therefore negatively impacting the rate of reaction. While the TES protected enol ether **3.92** successfully yielded **3.90** in 65% yield, the TBS derived enol ether **3.93** unexpectedly furnished the desired product in 82% yield with no observable byproducts. This enhanced reactivity of the TBS silylenolate could be attributed to the stability of the TBS group in polar-acidic medium. Remarkably, under these polar conditions minimal protodesilylation of either α -hydroxy silylenol ether **3.88** or TBS silylenol ether **3.93** was observed at room temperature.



Scheme 3.18 Evaluation of Silylenolate Nucleophiles

With these preliminary results in hand we begin reaction optimization using five-membered α' -hydroxy silylenol ether **3.88**, TBS silylenolate **3.93**, and catalytic pyridiumn triflate as our model system. The results of our optimization studies are summarized in Table 3.5, initially we employed 0.2 equivalents of the $\text{Py}\cdot\text{TfOH}$ and 2.0 equivalents of silyl enolate nucleophile **3.93**. As illustrated in entries 1-3, we began optimization by varying the reaction concentration

performing the reaction in three different concentrations, 0.2, 0.5, and 1.0 M. Unexpectedly, under these conditions our desired product **3.90** was isolated in identical yields of 82%.

Table 3.5 Revised Optimization of 1,4-Monosilylated Diketones

entry	Py·TfOH (equiv)	3.93 (equiv)	conc. (M)	time (h)	yield (%) [a]
1	0.2	2.0	0.2	2	82
2	0.2	2.0	0.5	1	82
3	0.2	2.0	1.0	1	82
4	0.1	2.0	0.5	3	76
5	0.1	2.0	1.0	3	73
6	0.2	1.5	0.5	1	74
7	0.2	1.5	1.0	1	79
8	0.2	1.2	0.5	1	74
9	0.2	1.2	1.0	1	74

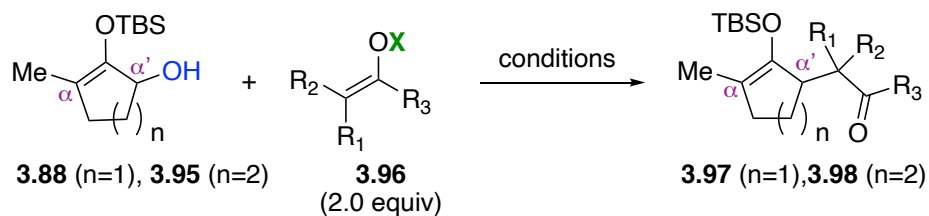
[a] Isolated yield after column chromatography.

Furthermore, we continued our studies with performing our reactions in both concentrations of 0.5 and 1.0 M as the reactions were completed within 1 hour. Our attempts to lower the catalyst loading to 0.1 equivalent are depicted in entries 4-5. Predictably, lowering the amount of catalyst resulted in diminished yields and extended reaction times for both 0.5 and 1.0 M reactions, furnishing **3.90** in 76 and 73% yield respectively. Similarly, reducing the molar equivalents of TBS silylenolate **3.93** to 1.2 or 1.5 equivalents resulted in diminished isolated yields as well (entries 6-9). From these brief studies we determined the optimized conditions for the synthesis of **3.90** are as indicated in entry 2.

3.8 Scope of Silylenolate Nucleophiles


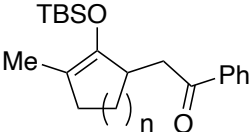
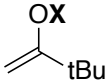
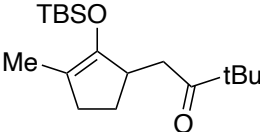
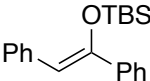
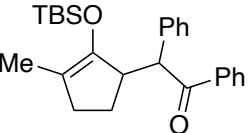
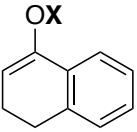
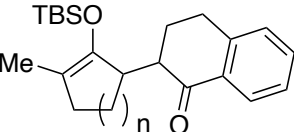
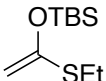
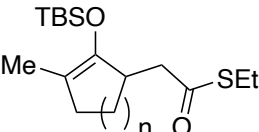
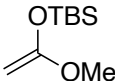
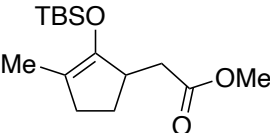
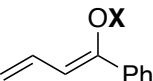
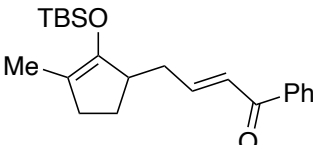
With the newly revised method to synthesize 1,4-monosilylated diketones in hand, we set to examination the applicability of various TBS silylenolates towards the nucleophilic capture of both five and six-membered α' -hydroxy silylenol ethers **3.88** and **3.95**. To determine if our newly devised protocol is an overall improvement direct comparison of the newly devised method (conditions A) and the previously developed method (conditions B) is depicted in Table 3.6. Nucleophilic capture of five and six membered α' -hydroxy silylenol ethers with acetophenone-derived TBS enolate **3.96a** readily furnished adducts **3.97a** and **3.98a** in 82% and 70% yield respectively. While these results are similar in yield to those obtained under conditions B, under conditions A we observed significant enhancement in the rate of reactions particularly with the six-membered starting material **3.97**. Unfortunately, we observed that TBS-derived *tert*-butyl ketone **3.96b** failed to react under our newly developed conditions, where **3.96b** was tolerated under conditions B, successful in furnishing adduct **3.97b** (entry 2). This lack of reactivity was most likely attributed to **3.96b** being insoluble in acetonitrile. Entry 3 depicts the use of sterically bulky α -phenyl ketone silylenolate **3.96c**, which effectively yielded monosilylated diketone **3.97c** in 57% yield as an inseparable 2:1 mixture of diastereomers. Moreover, subsection of α -tetralone derived silylenolate **3.96d** successfully generated monosilylated diketones **3.97d** and **3.98d** with comparable yields to conditions B. Surprisingly under conditions A, when α -tetralone **3.96d** was subjected to six-membered α' -hydroxy silylenol ether **3.95**, we observed a reversal of diastereoselectivity in the forming 1,4-diketone adduct **3.98d** in contrast to conditions B. As depicted in entries 5 and 6, acid sensitive silylketene thioacetal **3.96e** and silylketene acetal **3.96f** nucleophiles readily furnished 1,4-ketothioester and 1,4-ketoester adducts **3.97e**, **3.98e** and **3.97f** in 61% and 62% yield respectively. Through the use of TBS silyldienolate **3.96g**, we were able to

Table 3.6 Scope of Silylenolate Nucleophiles



conditions A: Py·TfOH (0.2 equiv), MeCN (0.5 M), rt, **X** = TBS

conditions B: CSA (0.1 equiv), CH₂Cl₂ (0.2 M), 4 Å MS, -78 °C, **X** = TMS

entry	nucleophile	product	conditions	yield, time [a]
1	 3.96a		A B A B	3.97a : 82%, 1 h 3.97a : 83%, 7 h 3.98a : 70%, 1.5 h 3.98a : 51%, 42 h
2	 3.96b		A B	3.97b : NR 3.97b : 89%, 36h
3	 3.96c		A	3.97c : 57%, 2 h (2:1 dr) ^[b]
4	 3.96d		A B A B	3.97d : 61%, 3.5 h (2:1 dr) ^[b] 3.97d : 75%, 5 h (5:2 dr) ^[b] 3.98d : 67%, 3.5 h (1:2 dr) ^[b] 3.98d : 63%, 23 h (2:1 dr) ^[b]
5	 3.96e		A A	3.97e : 62%, 1 h 3.98e : 70%, 1 h
6	 3.96f		A	3.97f : 61%, 1 h
7	 3.96g		A B	3.97g : 79%, 2 h 3.97g : 50%, 20 h

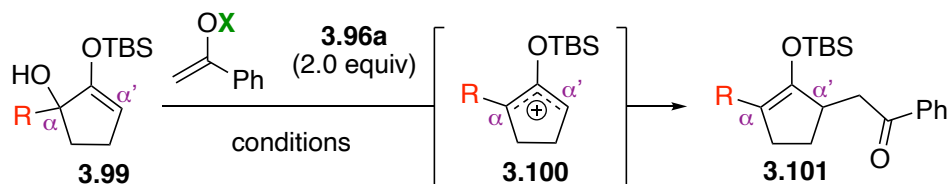
[a] Isolated yield after column chromatography. [b] Isolated yield as a mixture of inseparable diastereomers.

generate monosilylated 1,6-diketone **3.97g** in 68% yield within 3 hours. Similar to Kartika's previous report, we observed that the six-membered 1,4-monosilylated dicarbonyl adducts **3.98** were obtained in lower yields than that of the five-membered analogue **3.97**.

3.9 α -Substituent Effects in the Generation of Monosilylated 1,4-Diketones

Furthering our investigation, we evaluated the substituent effects at the α -carbon using five-membered tertiary α -hydroxy silylenol ether **3.99** as depicted in Table 3.7. We employed five-membered tertiary α -hydroxy silylenol ether **3.99**, as it has previously demonstrated to generate unsymmetrical silyloxyallyl cation **3.100**.^{60, 61} Similar to the scope of silylenolates, we compared our newly devised method (conditions A) to our previous method (conditions B). As hypothesized, introduction of a polar solvent accelerated in the rate of reaction dramatically in the presence of aliphatic substituents (entries 1-3). For example, under conditions A octyl-bearing substrate **3.99a** successfully furnished the corresponding silylenol ether adduct **3.101a** in 68% yield within just 5 hours, while conditions B furnished **3.101a** in an identical yield in 49 hours. Alas, the efficacy of our newly devised methodology declined significantly when introduction of sterically hindered *iso*-butyl **3.99b** and cyclohexyl **3.99c** α -hydroxy silylenol ethers (entries 2-3). While increased rates of ionization of **3.99b-3.99c** were observed, yields suffered furnishing **3.101b** and **3.101c** in only 30% and 22% yield respectably. Moreover, we noted that aromatic substituted α -hydroxy silylenol ethers **3.99d-3.99f** exhibited severely prolonged the rates of reaction under our revised protocol (entries 4-6). Tertiary α -hydroxy silylenol ethers decorated with phenyl **3.99d**, *p*-methoxyphenyl **3.99e** and *p*-fluorophenyl **3.99f** successfully furnished the corresponding monosilylated 1,4-diketones **3.101d-3.101f** in comparable yields to that of conditions B. Currently, the role of how the solvent effects the rate of reaction under both of these conditions is unknown.

Table 3.7 Evaluation of α -Substituted α -Hydroxy Silylenol Ethers



conditions A: Py·TfOH (0.2 equiv), MeCN (0.5 M), rt, **X** = TBS

conditions B: CSA (0.1 equiv), CH₂Cl₂ (0.2 M), 4Å MS, -78°C, **X** = TMS

entry	starting material	product	conditions	yield, time [a]
1	 3.99a	 3.101a	A B	68%, 5 h 68%, 49 h
2	 3.99b	 3.101b	A B	30%, 5 h 59%, 18 h
3	 3.99c	 3.101c	A B	22%, 6 h 25%, 20 h
4	 3.99d	 3.101d	A B	74%, 72 h 83%, 10 h
5	 3.99e	 3.101e	A B	60%, 120 h 79%, 10 h
6	 3.99f	 3.102f	A	71%, 72 h

[a] Isolated yield after column chromatography.

3.10 Conclusion

In conclusion this chapter provides a review of strategies to access 1,4-dicarbonyl compounds through the Stetter reaction and radical and cationic pathways. Furthermore, a revised protocol toward the regioselective synthesis of 1,4- and 1,6-dicarbonyl-derived monosilylenol ethers via silyloxyallyl cation technology was demonstrated. This newly developed protocol successfully expanded the synthetic scope of accessible dicarbonyl functionalities to include acid sensitive functionalities by replacement of CSA to weakly acidic pyridinium triflate. Furthermore, our revised method to access 1,4-monosilylated dicarbonyl compounds was compared against Kartika's previous method and we observed enhanced reaction rates, while maintain comparable yields. With the completion of this project, further applications of this method are showcased in Chapter Four, in which this technology is extended to the synthesis of tetrahydrocyclopenta[*b*]pyrroles and tetrahydroindoles.

Chapter Four: Synthesis of Tetrahydrocyclopenta[*b*]pyrroles and Tetrahydroindoles via a Brønsted Acid-Catalyzed Formal [2+2+1] Annulation⁴

4.1 Purpose

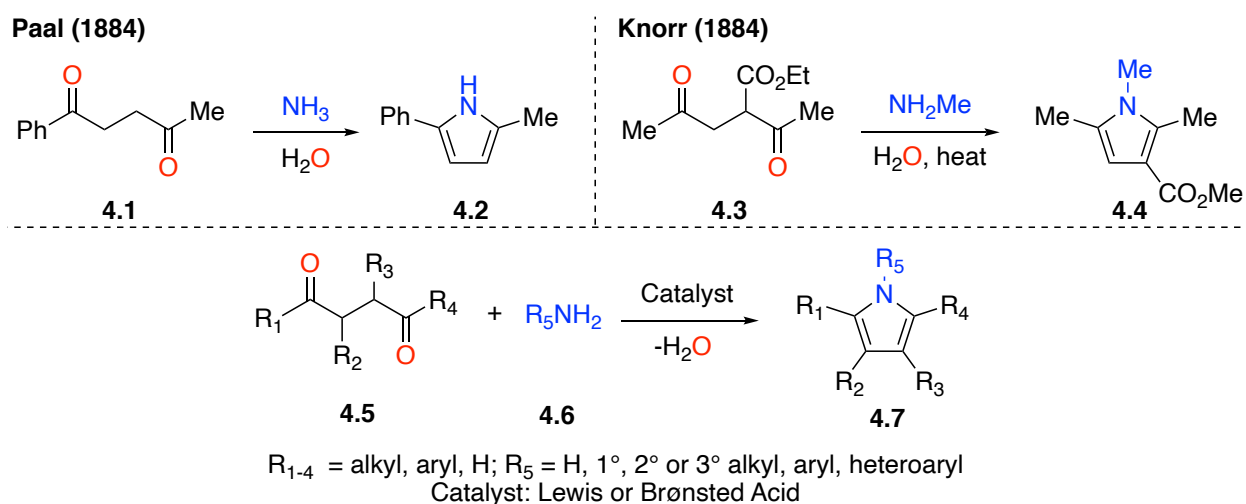
This chapter depicts our application of silyloxyallyl cation intermediates towards the synthesis of tetrahydroindoles and tetrahydrocyclopenta[*b*]pyrroles. A brief review of the Paal-Knorr pyrrole synthesis and known methods to synthesize tetrahydroindoles and tetrahydrocyclopenta[*b*]pyrroles will be presented. Our recent advancements in the synthesis of these molecular motifs *via* a Brønsted acid catalyzed 3-component, 1-pot reaction will be detailed, including brief optimization studies. The reaction compatibility of our 3-components: primary amines, silylenolate nucleophiles, and α -hydroxy silylenol ethers will be examined yielding a library of substituted tetrahydroindoles and tetrahydrocyclopenta[*b*]pyrroles. In addition, a few synthetic routes to access secondary α -hydroxy silylenol ethers will be presented.

4.2 The Paal-Knorr Pyrrole Synthesis

In the late 1800's, C. Paal and L. Knorr independently reported the treatment of 1,4-diketones **4.1** or **4.3** with an ammonia source or primary amine gave rise to substituted pyrroles **4.2** and **4.4** respectively (Scheme 4.1).^{109, 110} These set of reactions became better known as the Paal-Knorr pyrrole synthesis, an overview of the general reaction components are depicted in Scheme 4.1. While several 1,4-dicarbonyl compounds **4.5** can be employed for this transformation, 1,4-diketones are primarily utilized due to their stability and accessibility. Although the use of 1,4-dialdehydes or γ -keto aldehydes have been reported, these methods are not widely used due to the

⁴ Reprinted (adapted) with permission from (Malone, J. A.; Toussel, C. E.; Fronczek, F. R.; Kartika, R., Brønsted Acid-Catalyzed Formal 2+2+1 Annulation for the Modular Synthesis of Tetrahydroindoles and Tetrahydrocyclopenta[*b*]pyrroles. *Org. Lett.* **2019**, *21*, 3610-3614.) Copyright (2019) American Chemical Society." For sections 4.8 to 4.13.

instability or synthetic difficulty to generate these compounds.¹¹¹ The primary amine source **4.6** can range from aromatic, heterocyclic, and aliphatic amines, while catalysts to promote the reaction include both Lewis and Brønsted acids.¹¹²⁻¹¹⁴ The vast combinations of dicarbonyl compounds, amine sources, and catalysts provide the Paal-Knorr pyrrole synthesis a synthetically useful transformation. These seminal discoveries have led to similar methods for the synthesis of furans,^{76, 79, 115} thiophenes,^{77, 78,} and pyridazines¹¹⁶ from 1,4-dicarbonyl compounds.

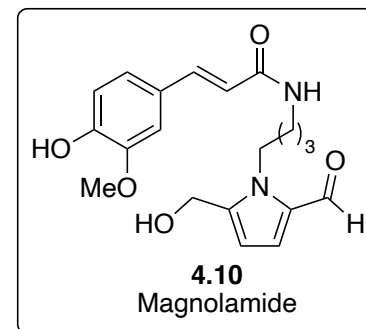
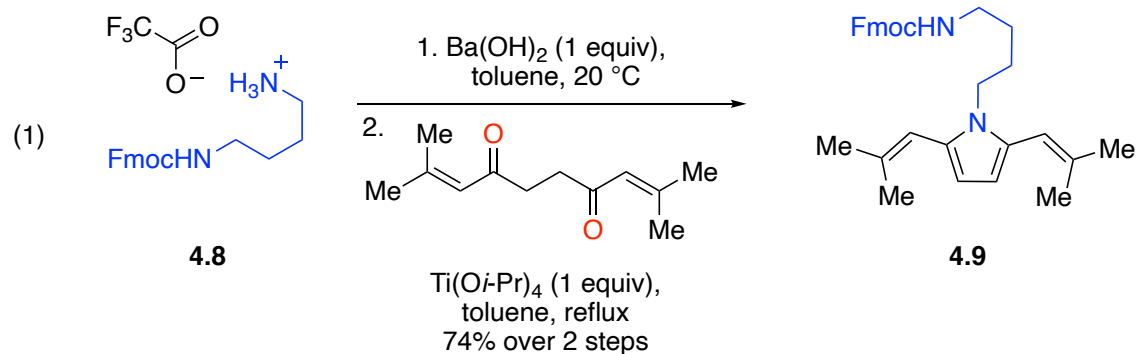


Scheme 4.1 The Paal-Knorr Pyrrole Synthesis

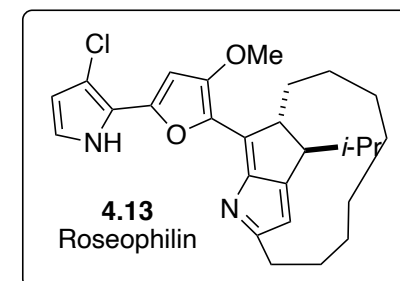
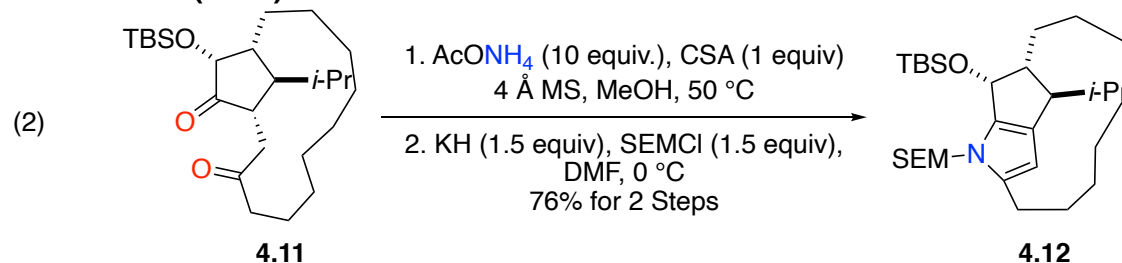
4.3 Applications of the Paal-Knorr Pyrrole Synthesis

Further demonstrations of the utility of Paal-Knorr pyrrole synthesis in recent years to generate complex pyrroles are depicted in Scheme 4.2. For example, in the first total synthesis of magnolamide reported by Quesne and co-workers, the Paal-Knorr pyrrole synthesis was utilized as their key transformation generating their trisubstituted pyrrole core (Scheme 4.2, *eqn. 1*).¹¹⁷ Quesne demonstrated that upon treatment of Fmoc-butanediamine trifluoroacetate **4.8** and their desired diketone with stoichiometric $\text{Ti}(\text{O}i\text{-Pr})_4$ at reflux, pyrrole **4.9** could successfully be

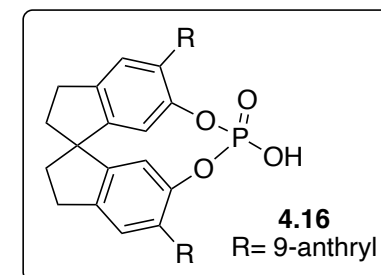
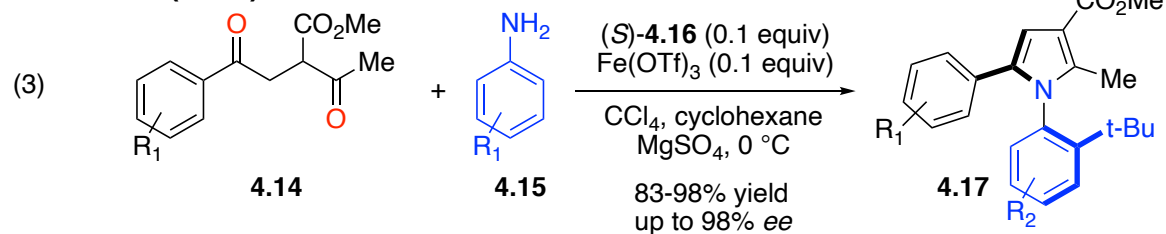
Quesne (2001)



Trost (2000)



Tan (2017)

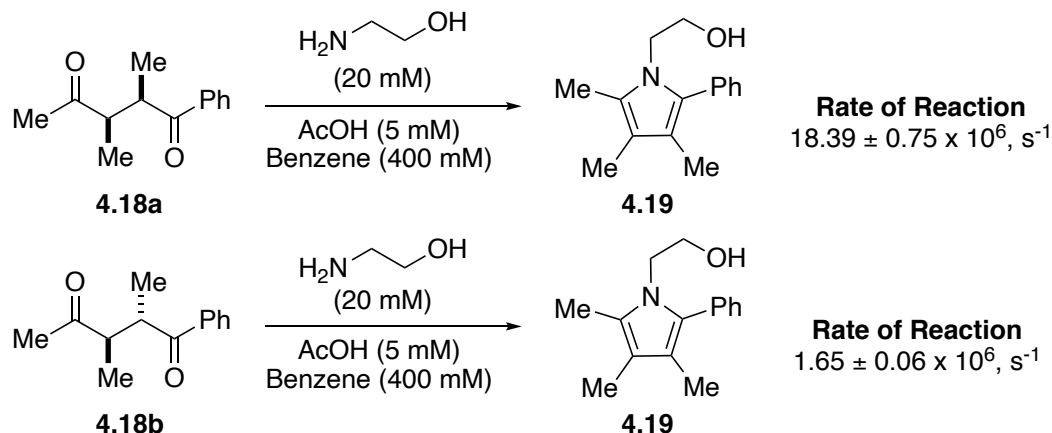


Scheme 4.2 Selected Applications of the Paal-Knorr Pyrrole Synthesis

generated in 74% yield. Moreover, the total synthesis of magnolamide **4.10** was completed in 8 total steps. Meanwhile, Trost demonstrated the usefulness of the Paal-Knorr condensation to install a trisubstituted pyrrole motif in their formal synthesis of roseophilin.⁷² Trost et al observed that treatment of 1,4-diketone **4.11** with excess of AcONH₄ in the presence of stoichiometric camphorsulfonic acid (CSA) in anhydrous methanol readily furnished their desired trisubstituted pyrrole (Scheme 4.2, *eqn.* 2). Unfortunately, their desired pyrrole was unstable requiring immediate SEM protection of crude pyrrole mixture to yield **4.12** in 76% over 2 steps. Stepping out of applications in total synthesis, in 2017 Tan developed an elegant atroposelective synthesis of arylpyrroles through the use of a catalytic asymmetric Paal–Knorr reaction (Scheme 4.2, *eqn.* 3).¹¹⁸ Tan discovered that treatment of diones **4.14** with aniline derivatives **4.15** in the presence of 9-anthryl spinol-derived phosphoric acid **4.16** and Fe(OTf)₃ yielded enantioenriched axially chiral arylpyrroles **4.17** in excellent yields and up to 98% ee. These select applications of the Paal-Knorr pyrrole synthesis demonstrate that after its initial discovery more than a hundred years later, this strategy to synthesize pyrroles is still widely used to construct valuable heterocycles motifs.

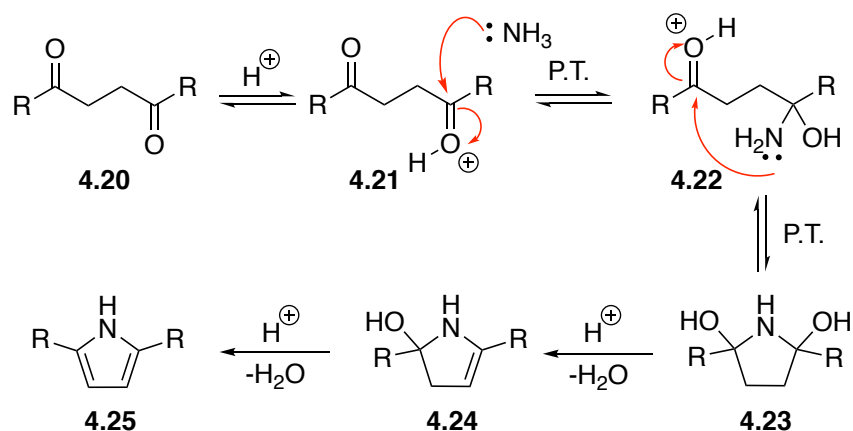
4.4 Paal-Knorr Pyrrole Mechanism

While the proposed reaction mechanism for the Paal-Knorr pyrrole synthesis has been heavily disputed amongst the community, Amarnath and co-workers reported a detailed investigation into the intermediates of the reaction and determined a probable mechanistic pathway.¹¹⁹ Amarnath explored the rates of cyclization of racemic diketone **4.18a** and *meso*-diketone **4.18b** under identical conditions as shown in Scheme 4.3. Under their conditions it was observed that cyclization between the racemic and meso diketones proceeded at unequal rates. In addition, the stereo-chemical identity of the unreacted diones **4.18a/4.18b** were preserved during the reaction. These observations suggested that enamine formation before cyclization is ruled out



Scheme 4.3 Rate of Paal-Knorr Cyclization

The mechanism proposed for the Paal-Knorr pyrrole synthesis by Amarnath and co-workers is detailed in Scheme 4.4. Under Brønsted acidic conditions, it is proposed that nonselective protonation of diketone **4.20** is followed by nucleophilic attack by a primary amine to the activated ketone **4.21** generates hemiaminal **4.22**. Subsequent cyclization of hemiaminal **4.22** to form pyrrolidine intermediate **4.23** was ultimately determined to be the rate-determining step. Ensuing elimination of water through iminium ion formation and deprotonation generates enamine **4.24**, followed by loss of water and deprotonation of **4.24** afforded pyrrole **4.25**.



Scheme 4.4 Proposed Mechanism of Paal-Knorr Pyrrole Synthesis

4.5 Tetrahydrocyclopenta[*b*]pyrroles and Tetrahydroindoles

Tetrahydrocyclopenta[*b*]pyrroles and tetrahydroindoles are a variation of the pyrrole heterocycle, in which there is a partially saturated five or six membered ring attached to the C2 and C3 position of the pyrrole core. These important classes of nitrogen-containing heterocycles have been found to exhibit a wide range of biological activities.¹²⁰⁻¹²⁶ As shown in Figure 4.1, tetrahydrocyclopenta[*b*]pyrroles have been shown to act as pharmacophores that exhibit protein tyrosine kinase inhibition, anti-inflammatory properties,¹²⁰ oxidase and cyclooxygenase inhibition. Meanwhile, tetrahydroindoles have been shown to demonstrate Src tyrosine kinase inhibition,¹²¹ dopaminergic and anti-cancer activity.¹²⁷ Due to their biological relevance, the development of synthetic methods to readily assemble tetrahydrocyclopenta[*b*]pyrroles and tetrahydroindoles remains important.

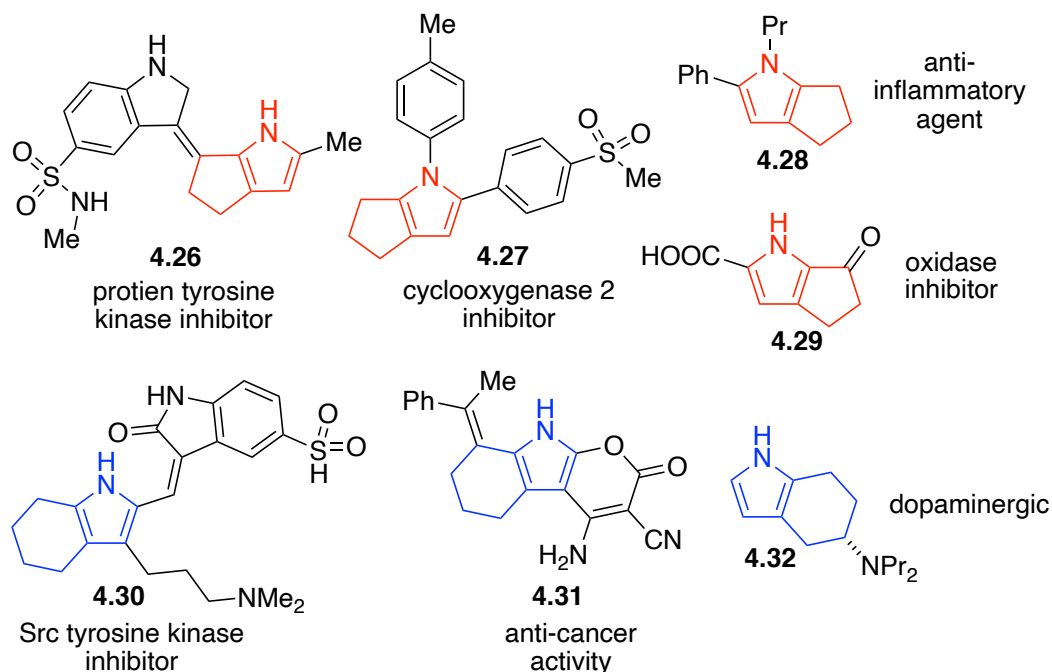
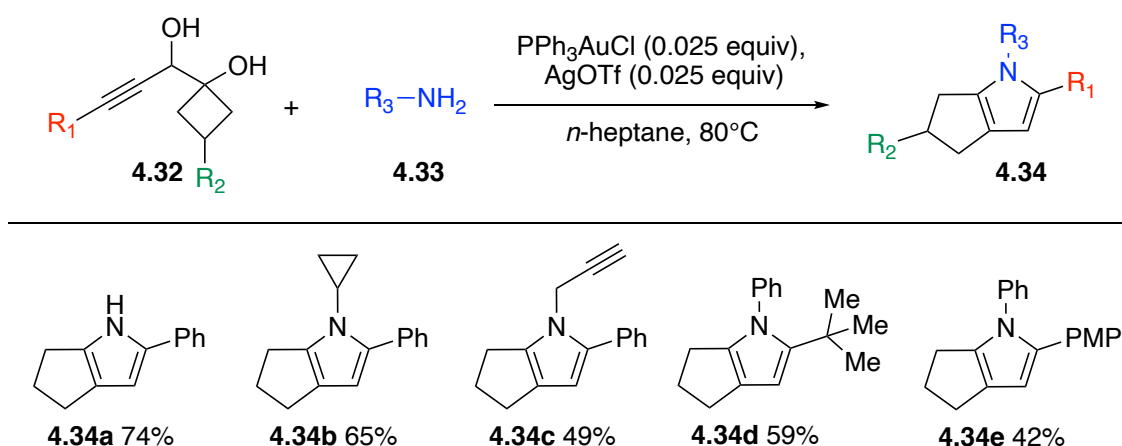


Figure 4.1 Biologically Relevant Heterocycles

4.6 Methods for the Synthesis of Tetrahydrocyclopenta[*b*]pyrroles

While tetrahydrocyclopenta[*b*]pyrroles have displayed a wide range of biological activity, methods to construct these valuable heterocycles are underdeveloped and underreported within recent literature. The most common approaches to construct these heterocycles rely on the use of dual Lewis acid catalyst. For example, in 2015 Zhang et al reported a unique gold and silver catalyzed rearrangement/cyclization cascade reaction towards the synthesis of poly-substituted tetrahydrocyclopenta[*b*]pyrroles as showcased in Scheme 4.5.¹²⁸ Zhang observed that upon activation of cyclobutanols **4.32** with PPh₃AuCl and AgOTf in the presence of primary amines **4.33**, readily afforded multi-substituted tetrahydrocyclopenta[*b*]pyrroles **4.34**.

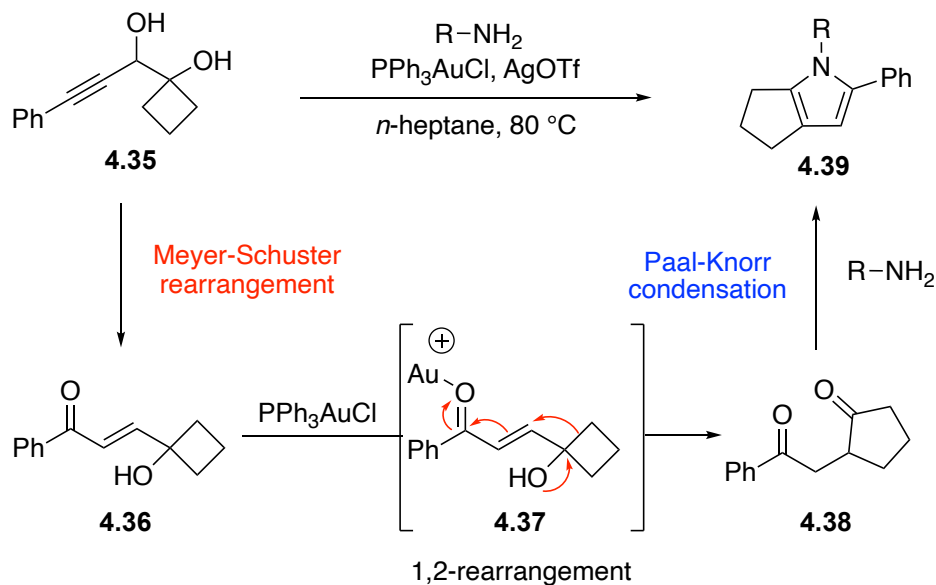


Scheme 4.5 Zhang's Strategy for the Synthesis of Tetrahydrocyclopenta[*b*]pyrroles

Furthermore, investigation into the scope of their method, explored the substituent effects on the alkyne, cyclobutane ring, and primary amine. Aliphatic amines such as cyclopropyl, and propargyl amines were well tolerated, usefully yielding heterocyclic compounds **4.34b–4.34c** in moderate yields. Demonstrating that aromatic substituted alkynes were not necessary for the

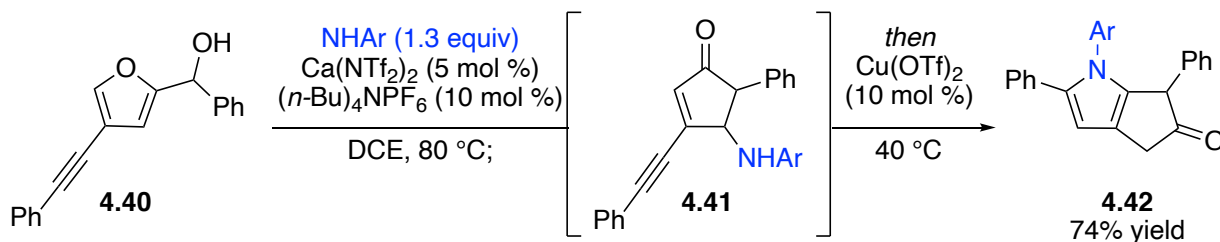
reaction to occur, sterically bulky *tert*-butyl substituted alkyne successfully yielded pyrrole **4.34d** in 59% yield, while *p*-methoxyphenyl substituted alkyne readily afforded **4.34e**.

Based upon previously reported work, Zhang and co-workers proposed a mechanism for their elegant atom economical cascade reaction as detailed in Scheme 4.6. In the presence of catalytic AgOTf, Zhang proposed that diol **4.35** would undergo a silver Lewis acid promoted Meyer–Schuster rearrangement to generate α,β -unsaturated ketone **4.36** *in situ*. Furthermore, PPh₃AuCl facilitates a 1,2-migration of α,β -unsaturated ketone **4.37** generating 1,4-diketone **4.38**, which further undergoes Paal-Knorr condensation with a primary amine to yield their desired tetrahydrocyclopenta[*b*]pyrroles **4.39**. Though their optimization studies it was observed that both PPh₃AuCl and AgOTf catalysts were required for their tandem reaction to occur.



Another dual Lewis acid approach to access tetrahydrocyclopenta[*b*]pyrroles cores was reported by Leboeuf in 2016, in which they reported an elegant one-pot procedure utilizing both calcium and copper Lewis acids (Scheme 4.7).¹²⁹ Their one-pot, two step reaction detailed the

treatment of 2-furylcarbinol **4.40** with $\text{Ca}(\text{NTf}_2)_2$ in the presence of aniline in dichloroethane (DCE) to facilitate an aza-Piancatelli type reaction generating α,β -unsaturated ketone **4.41**. Upon addition of catalytic $\text{Cu}(\text{OTf})_2$, proposed hydroamination and subsequent isomerization occurred providing tetrahydrocyclopenta[*b*]pyrrole **4.42** in 74% yield.

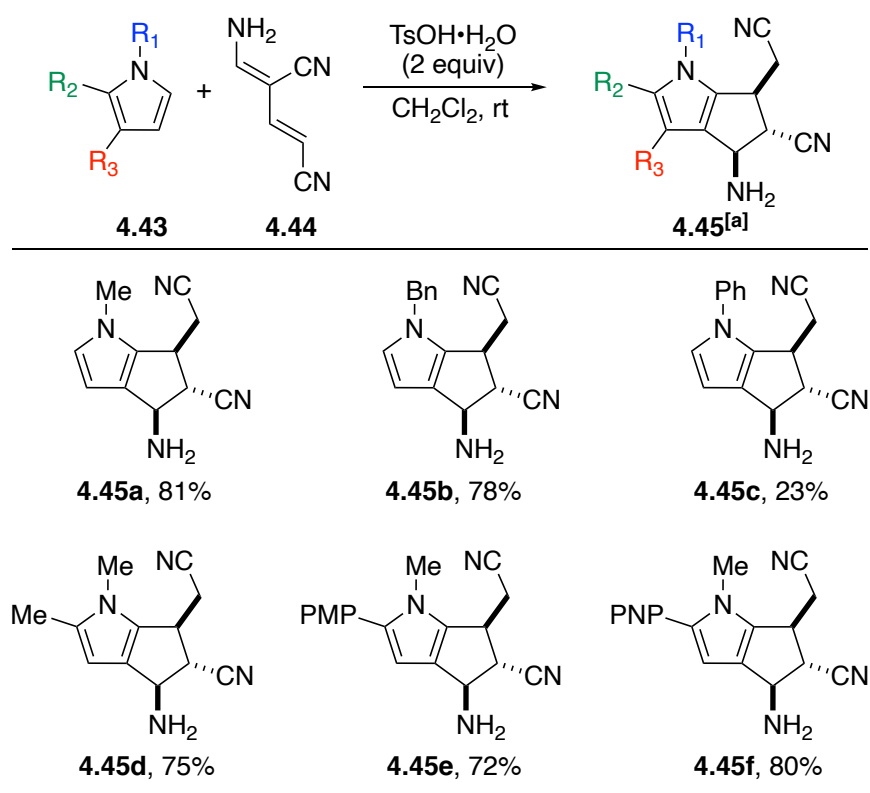


Scheme 4.7 Leboeuf's Synthesis of Cyclopenta[*b*]pyrroles

During the course of their reaction optimization, Leboeuf and his team determined that both $\text{Ca}(\text{NTf}_2)_2$ and $(n\text{-Bu})_4\text{NPF}_6$ were required for an efficient reaction, while $\text{Ca}(\text{NTf}_2)_2$ alone was not enough to promote hydroamination, requiring for the inclusion of $\text{Cu}(\text{OTf})_2$. The sequential addition of catalysts proved to be advantageous, as this prevented undesired Friedel–Crafts reaction between pyrrole **4.42** and 2-furylcarbinol **4.40**. With an efficient route to synthesized heavily substituted tetrahydrocyclopenta[*b*]pyrroles, an array of functionalized furylcarbinols and aniline derivatives were explored generating diverse motifs in moderate to excellent yields.

All of the previously discussed strategies to synthesis these compounds relied on the use of two catalysts to afford their desired heterocycle core. In a much simpler approach to synthesize tetrahydrocyclopenta[*b*]pyrroles, Yu and co-workers detailed a robust Brønsted acid catalyzed cascade alkylation/cyclization strategy (Scheme 4.8).¹³⁰ By combining *N*-protected pyrroles **4.43** with *N,N*-dimethylaminomethyleneglutaconic acid dinitrile **4.44** in the presence of excess tosic

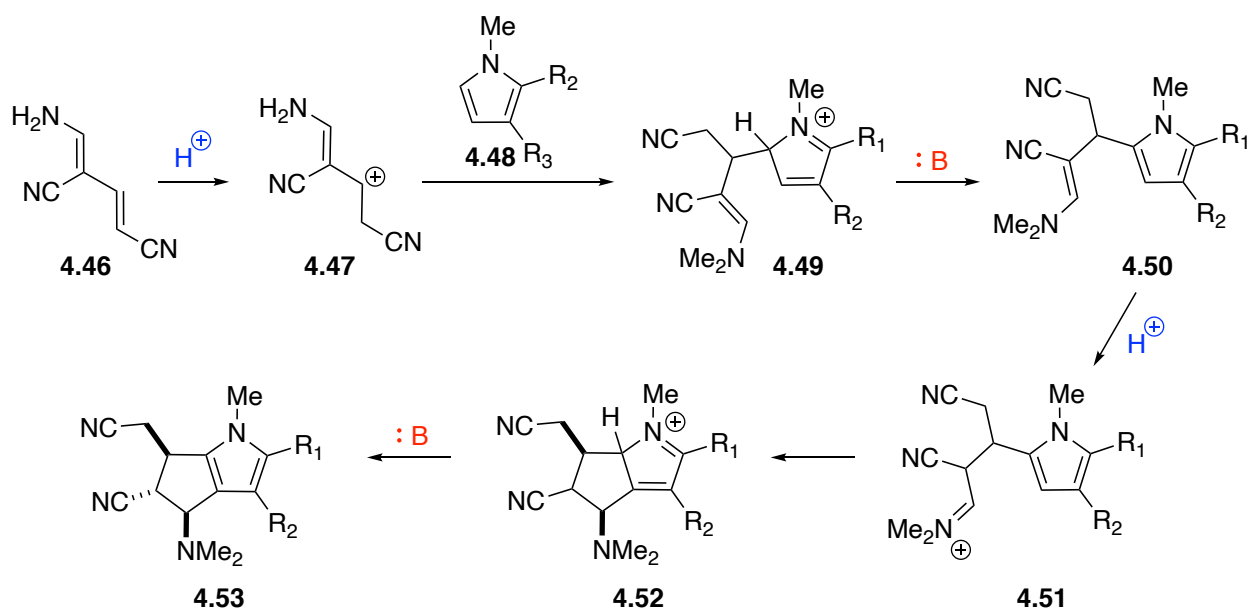
acid (TsOH•H₂O), the desired heterocycles **4.45** could be readily accessed as a single diastomer. Yu and his team explored a variety of protected pyrroles and observed that *N*-methyl and *N*-benzyl protected pyrroles successfully furnished adducts **4.45a** and **4.45b** in excellent yields, while increasing steric hinderance by introducing *N*-phenyl pyrrole resulted in formation of **4.45c** in a substantially lower yield. Furthermore, C2 substituted pyrroles were found to be tolerated under their optimized conditions, affording **4.45d-4.45f** in excellent yields. Unfortunately, Yu noted that use of unprotected pyrroles yielded unfruitful as the pyrroles **4.43** readily underwent decomposition and/or self-polymerization in the presence of TsOH.



[a] All products were obtained in >20:1 dr.

Scheme 4.8 Yu's Strategy to Access Tetrahydrocyclopenta[*b*]pyrroles

The mechanism proposed by Yu for the formation of tetrahydrocyclopenta[*b*]pyrrole **4.53** is outlined in Scheme 4.9. They suggested that initial protonation of the polarized alkene **4.46** by TsOH resulted in formation of carbocation **4.47**. Further electrophilic aromatic substitution at the C5 position of pyrrole **4.48** with carbocation **4.47** resulted in the formation of iminium ion **4.49**. Rearomatization of intermediate **4.49** further generates C5-alkylated pyrrole **4.50**. Furthermore, it was proposed that in the presence of TsOH, tautomerization of the enamine led to the formation of iminium ion **4.51**. Subsequent intramolecular Friedel–Crafts cyclization of **4.51** followed by a final deprotonation successfully provided tetrahydrocyclopenta[*b*]pyrrole **4.53**. The origin of diastereoselectivity in the formation of **4.53** was not discussed.



Scheme 4.9 Yu's Proposed Mechanism

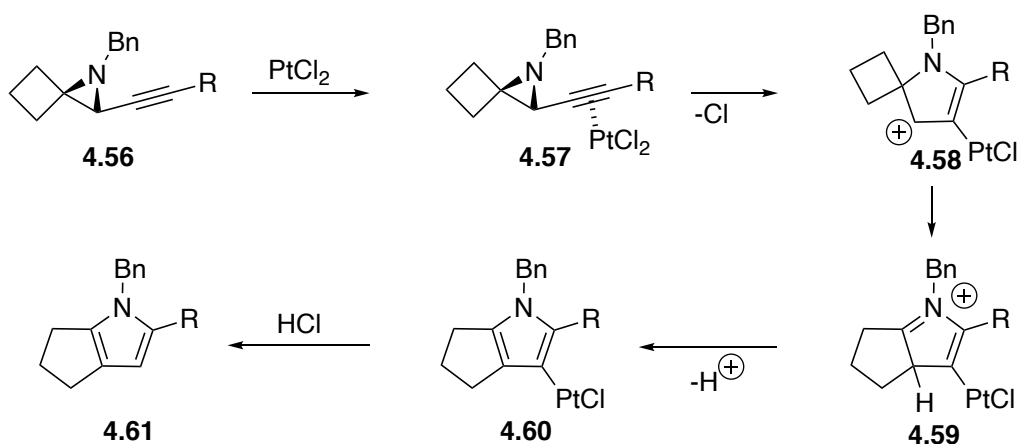
While reports of Lewis and Brønsted acid promoted synthesis of tetrahydrocyclopenta[*b*]pyrroles are more abundant, the use of transition metal catalysis is an underutilized approach. In 2011, Shishido and co-workers detailed a platinum chloride catalyzed approach to

tetrahydrocyclopenta[*b*]pyrroles **4.55** through a cyclization/ring expansion of 2-alkynyl-1-azaspiro[2.3]hexanes **4.54** (Table 4.1).¹³¹ Shishido and his team explored an appropriate scope of substrates using various substituted alkynes and cyclobutanes. Under their optimized conditions allyl and free hydroxyl substituted alkynes **4.51a** and **4.54b** were tolerated successfully affording tetrahydrocyclopenta[*b*]pyrroles **4.55a** and **4.55b** in 91% and 82% yield respectively. Moreover, Shishido demonstrated that they could construct tricyclic pyrroles **4.55c** and **4.55d** from aziridines **4.54c** and **4.54d** respectively.

Table 4.1 Shishido's Approach to Tetrahydrocyclopenta[*b*]pyrroles

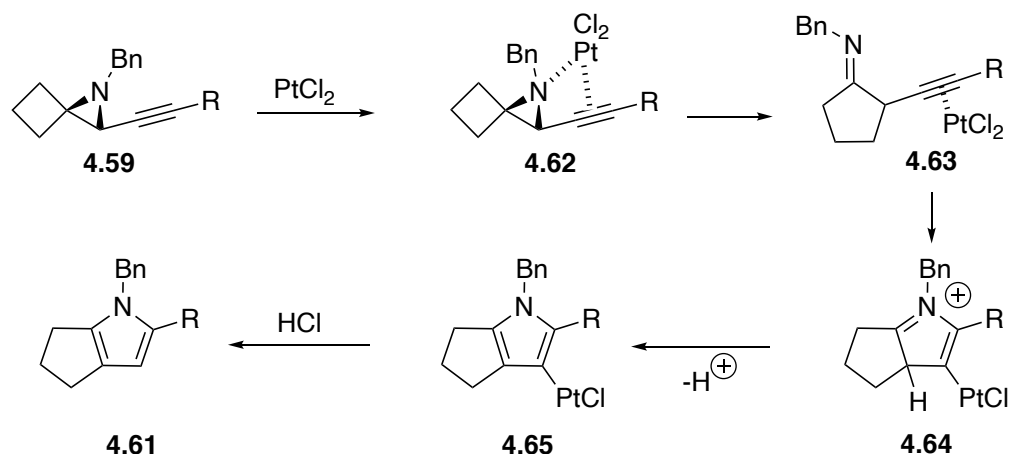
Entry	Substrate	Product	Yield (%)
1	 4.54a	 4.55a	91
2	 4.54b	 4.55b	82
3	 4.54c	 4.55c	50
4	 4.54d	 4.55d	80

For their platinum catalyzed synthesis of tetrahydrocyclopenta[*b*]pyrroles **4.55**, Shishido proposed two potential mechanistic routes, pathway A and B for their cascade reaction as depicted in Schemes 4.10 and 4.11.¹³¹ The first path, pathway A involved initial platinum coordination with the alkyne **4.57**, followed by nucleophilic addition of the aziridine to form spirocyclic cation **4.58**. Subsequent regioselective 1,2-migration/ring expansion of **4.58** generating pyrrolylplatinum species **4.59**. Furthermore, proto-demetalation of intermediate **4.59** ultimately affords the desired tetrahydrocyclopenta[*b*]pyrrole **4.61**.



Scheme 4.10 Pathway A: Mechanisms for Cascade Cyclization and Ring Expansion

While Shishido proposed that formation of the pyrrole could be generated by an initial cyclization reaction, an alternative mechanism details an initial ring expansion as depicted in Scheme 4.11. Under pathway B, they proposed that platinum coordination to the lone pair of the aziridine and the π -system of the alkyne **4.62** could promote ring expansion resulting in formation of imine **4.63**. Upon subsequent attack of the activated alkyne by the imine was proposed to generate cyclopentane iminium ion **4.64**. To access tetrahydrocyclopenta[*b*]pyrrole **4.61**, intermediate could forgo a cycloisomerization and subsequent proto-demetalation.

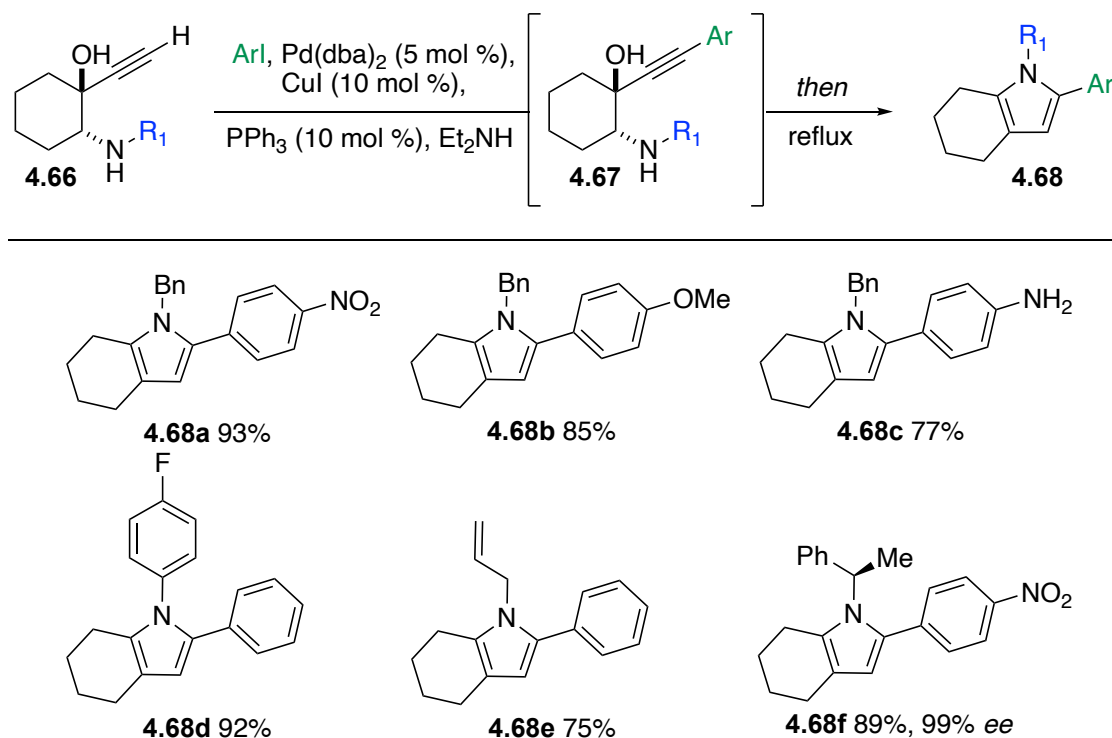


Scheme 4.11 Pathway B: Mechanisms for Cascade Cyclization and Ring Expansion

4.7 Methods for the Synthesis of Tetrahydroindoles

Unlike strategies to synthesize tetrahydrocyclopenta[*b*]pyrroles, general methods to access tetrahydroindoles are more abundant within literature. The use of metal catalyst such as palladium, iridium, and ruthenium have been used to construct tetrahydroindole cores. For example, in 2012 Kurkin and coworkers reported one-pot synthesis of tetrahydroindoles **4.68** from amino propargylic alcohols **4.66** through the use of palladium (Scheme 4.12).¹³² Their strategy relied on an initial Sonogashira coupling of a terminal alkyne **4.66** with an aryl iodide to generate amino propargylic alcohol **4.67** *in situ*. Furthermore, upon full consumption of **4.68** the reaction was warmed to reflux, facilitating a palladium-mediated *5-endo-dig* cyclization leading to the formation of tetrahydroindole **4.68**. An extensive substrate scope was performed with electron-rich, electron-deficient and heteroaromatic iodides yielding C2-substituted tetrahydroindoles **4.68a-4.68c** in excellent yields. Furthermore, Kurkin demonstrated the ability to diversify the nitrogen of the tetrahydroindole core with aromatic, aliphatic and chiral enriched fragments are exemplified via the formation of **4.68d-4.68f** in excellent yields and retention of *ee*. Following

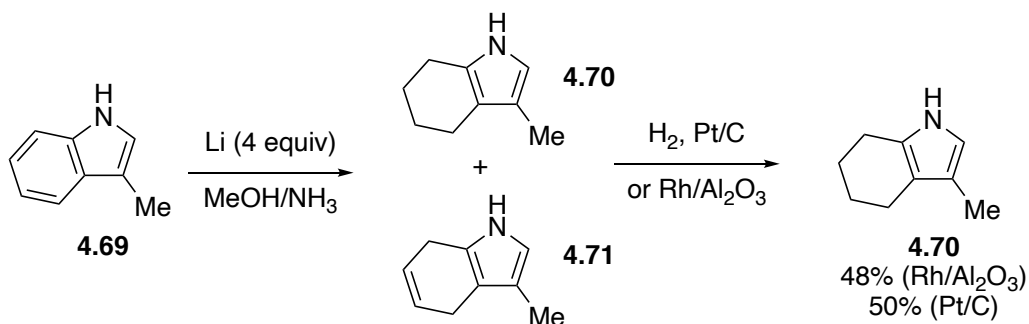
their seminal report, Kurkin also reported catalyst-free, thermal induced 5-*endo-dig* cyclization of amino propargylic alcohols **4.67** to afford tetrahydroindoles **4.68**.¹³³



Scheme 4.12 Kurkin's Method to Access Tetrahydroindoles

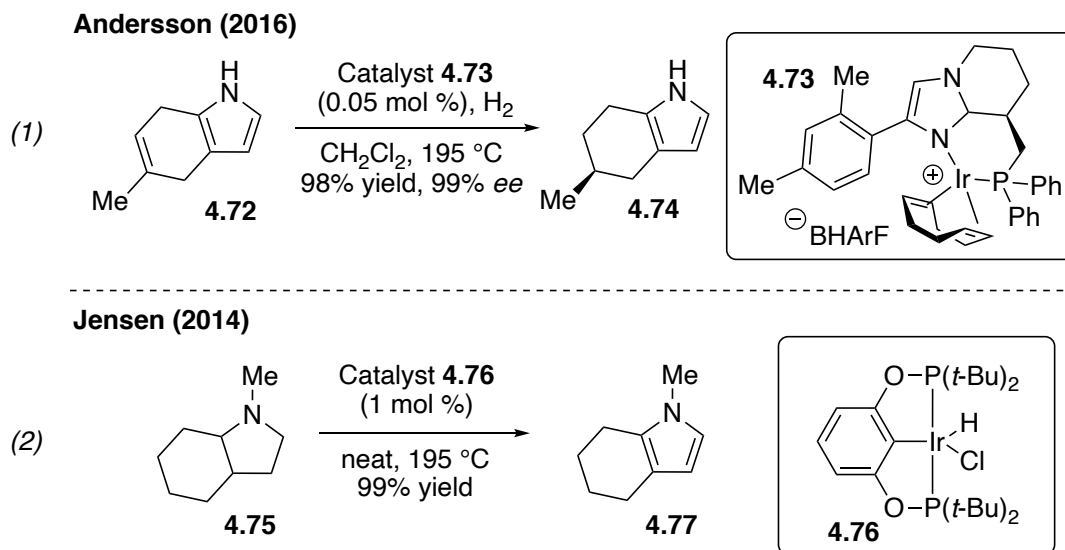
Hydrogenation and dehydrogenation of indoles and indolic compounds are commonly employed strategies for the synthesis of tetrahydroindoles. In 1999, Vraken and co-worker disclosed a two-step procedure for the reduction of indoles by a regioselective Birch reduction, followed by a catalytic hydrogenation (Scheme 4.13). Under treatment of indole **4.69** with lithium in ammonia and methanol resulted in a mixture of fully hydrogenated indole **4.70** alongside partially reduced indole **4.71**. In an attempt to fully reduce 4,7-dihydroindole **4.71**, treatment of the crude reaction mixture with either Pt/C or $\text{Rh/Al}_2\text{O}_3$ successfully afforded tetrahydroindole

4.70 in 48% and 50% yield respectively. Vraken explored reduction of various substituted indoles and carbazoles, generating the corresponding tetrahydroindoles in moderate yields.



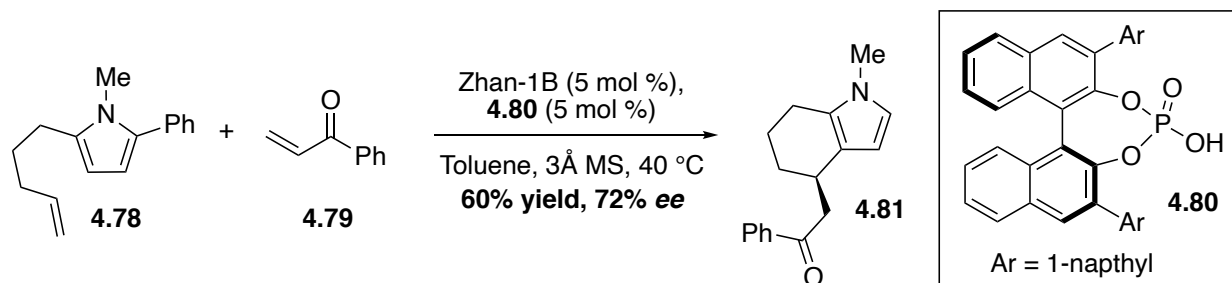
Scheme 4.13 Vraken's Reductive Strategy to Access Tetrahydroindoles

The use of iridium catalysts has gained much attention due to their ability to participate in both hydrogenation and dehydrogenation reactions to give access to tetrahydroindoles. An elegant enantio- and regioselective synthesis of tetrahydroindoles was reported by Anderson et al utilizing iridium catalysis (Scheme 4.14, *eqn. 1*). They detailed the treatment of 4,7-dihydroindole **4.72** with iridium catalyst **4.73** under 50 bar of hydrogen gas successfully affording enantioenriched tetrahydroindole **4.74** in 95% yield and 99% *ee*.¹³⁴ Under these highly pressurized conditions, no reduction of the pyrrole ring was observed. In contrast to the work reported by Anderson, Jensen demonstrated that they could selectively dehydrogenate indolic compounds using iridium catalysis (Scheme 4.14, *eqn. 2*).¹³⁵ Their report detailed dehydrogenation of **4.75** via an iridium pincer catalyst **4.76** under high temperatures successfully affording tetrahydroindole **4.77** in near quantitative yield. Jensen observed that the temperature window at which the reaction was performed was critical as to not induce over dehydrogenation, resulting in indole formation.



Scheme 4.14. Iridium Catalysts for the Synthesis of Tetrahydroindoles

Another useful strategy to access these valued heterocycles was reported by Yu and co-workers in which they developed an enantioselective synthesis of tetrahydroindoles (Scheme 4.15). Yu observed that treatment of pyrrole **4.78** and vinyl ketone **4.79** with Zhan-1B catalyst and chiral phosphoric acid **4.80** resulted in the formation of tetrahydroindole **4.81**, in 60% yield and 72% *ee*. This olefin cross-metathesis followed by intramolecular Friedel-Crafts alkylation approach provided access to chiral tetrahydroindoles in moderate yields and enantioselectivities.

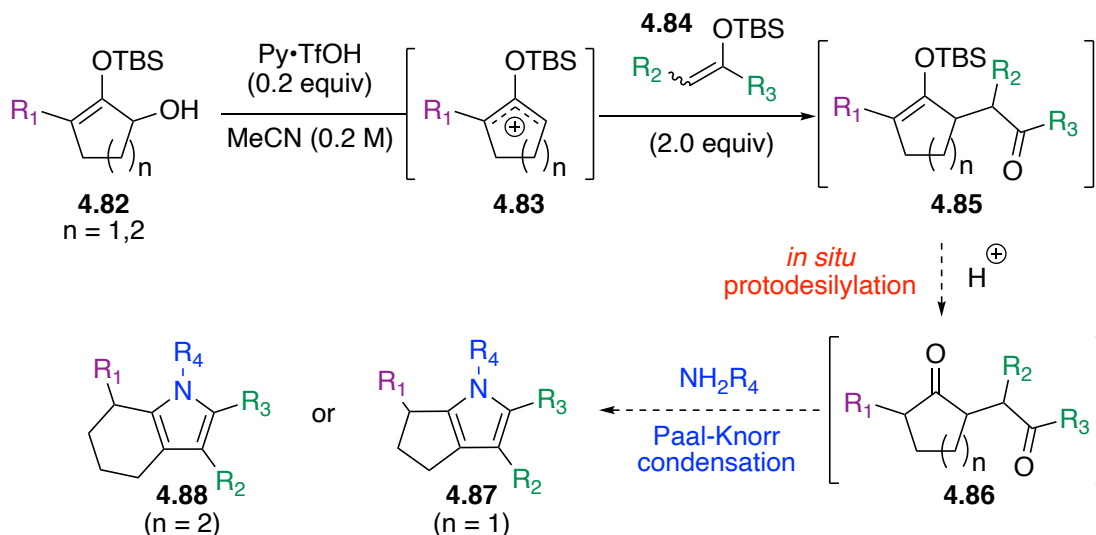


Scheme 4.15 Enantioselective Synthesis of Tetrahydroindoles

4.8 Multi-Component Strategy to Access Both Tetrahydrocyclopenta[*b*]pyrroles and Tetrahydroindoles

Despite these recent advancements in tetrahydroindoles and tetrahydrocyclopenta[*b*]pyrroles synthesis described above, many strategies to access both heterocycles rely on the use of metal catalysts and/or requiring linear preconstruction of the starting materials ultimately limiting the ability to easily synthesize and diversify the heterocycle core. With these limitations observed we sought to develop a multi-component strategy utilizing our silyloxyallyl cation intermediates, relying on the use of three simple components: α -hydroxy silylenol ethers, TBS-derived silylenolates, and primary amines.

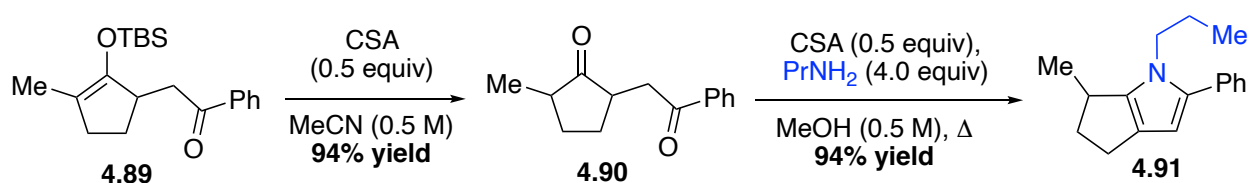
Our formal [2+2+1] annulation approach for the modular synthesis of highly substituted heterocycles is depicted in Scheme 4.16. We propose that the synthesis of tetrahydroindoles **4.88** and tetrahydrocyclopenta[*b*]pyrroles **4.87** could be achieved in single pot starting with α -hydroxy silylenol ethers **4.82**. As previously described in Chapter Three, we have successfully developed a mild approach to synthesize monosilylated diketones **4.85** through the use of silyloxyallyl cation intermediates **4.83** and TBS-derived silyl enolate nucleophiles **4.84** promoted by catalytic Py•TfOH.^{67, 85} From these monosilylated diketone **4.85**, we propose that through Brønsted acid promoted protodesilylation 1,4-diketone **4.86** could be generated *in situ*. Alas, in the presence of a primary amine, a Paal-Knorr condensation should occur yielding either tetrahydrocyclopenta[*b*]pyrrole **4.87** or tetrahydroindole **4.88** from the corresponding five- or six-membered α -hydroxy silylenol ethers. Overall, this multi-component strategy would allow for the rapid generation tetrahydrocyclopenta[*b*]pyrroles or tetrahydroindoles from easily synthesized and commercially available materials in a single synthetic operation.



Scheme 4.16 Our Approach to Tetrahydroindoles and Tetrahydrocyclopenta[*b*]pyrroles

4.9 Reaction Optimization Studies

Our initial studies explored the feasibility of synthesizing tetrahydrocyclopenta[*b*]pyrrole **4.92** from 1,4-monosilylated diketone **4.90** in a sequential fashion as depicted in Scheme 4.17. We observed that treatment of monosilylated diketone **4.90** with catalytic camphorsulfonic acid (CSA) in MeCN at room temperature cleanly generated diketone **4.91** in 94% yield, as a mixture of inseparable diastereomers. Moreover, treatment of **4.91** with excess propylamine and CSA in refluxing methanol, successfully afforded tetrahydrocyclopenta[*b*]pyrrole **4.92** in 94% yield. These sequential experiments provided necessary evidence that tetrahydrocyclopenta[*b*]pyrroles and tetrahydroindoles could be accessible *via* their respective monosilylated diketones.



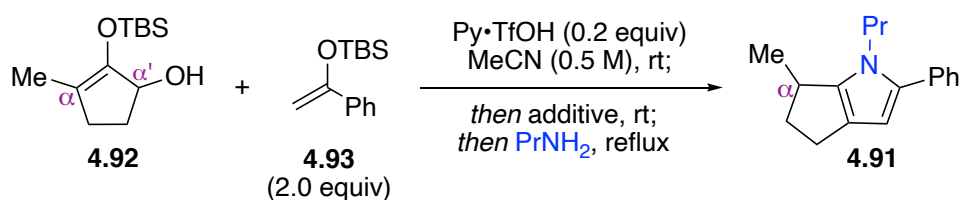
Scheme 4.17 Linear Synthesis of Tetrahydrocyclopenta[*b*]pyrrole **4.91**

Our efforts towards optimization of our multi-component reaction is depicted in Table 4.3. As previously detailed in Chapter Three, the synthesis of 1,4-monosilylated diketones from α -hydroxy silylenol ethers had previously been optimized, so further efforts for reaction optimization were focused on inducing protodesilylation and Paal-Knorr condensation.⁸⁵ For our studies, we employed five-membered α' -hydroxy silylenol ether **4.92**, acetophenone-derived TBS-silylenol ether **4.93**, and propylamine as our model substrates. As described in entry 1, we successfully coupled compounds **4.92** and **4.93** under catalytic Py•TfOH in acetonitrile, forming the monosilylated diketone *in situ*. Upon full consumption of **4.92** as monitored by TLC, we allowed for protodesilylation to occur at room temperature. When complete protodesilylation was observed, excess propylamine was added to the reaction mixture and was warmed to reflux, readily furnishing **4.91** in 77% yield. While this initial experiment furnished our desired product, the rate of reaction remained problematic. Independently, we observed that ionization of α' -hydroxy silylenol ether **4.93** and capture of silyloxyallyl cation concluded within 1 hour, while the Paal-Knorr condensation was complete within 3 hours. This indicated that the rate determining step in our three-step process was protodesilylation of the monosilylated 1,4-diketone intermediate.

In an attempt to increase the rate of protodesilylation, we hypothesized that introduction of a secondary Brønsted acid would accelerate protodesilylation as depicted in entries 2-5. We screened several Brønsted acids, such as pyridinium tosylate (PPTS), triflic acid (TfOH), camphor-sulfonic acid (CSA), and tosic acid (TsOH), introducing these additives the reaction mixture upon full consumption of **4.92**, but prior to addition of propylamine. Predictably, the addition of stronger Brønsted acids significantly enhanced the rate of protodesilylation, eventually leading us to employ TsOH as our additive of choice having successfully produced **4.91** in 83% yield in just 6 hours (entry 5). Further attempts to decrease the equivalences TsOH and amine are depicted in

entries 6-8. We observed that lowering the loadings of TsOH and propylamine did not have a significant effect on the efficiency on the protodesilylation or condensation, resulting in marginal decrease in the yield and lengthened reaction times. Lastly, entry 9 depicts our attempts to perform the condensation reaction in the absence of heat. While these conditions successfully generated our desired product, diminished yield and decreased rate of Paal-Knorr cyclization was observed in the absence of heat. From these brief studies our optimized reaction conditions for the synthesis of tetrahydrocyclopenta[*b*]pyrrole **4.91** are depicted in entry 6.

Table 4.2 Three-Component, One-Pot Reaction Optimization



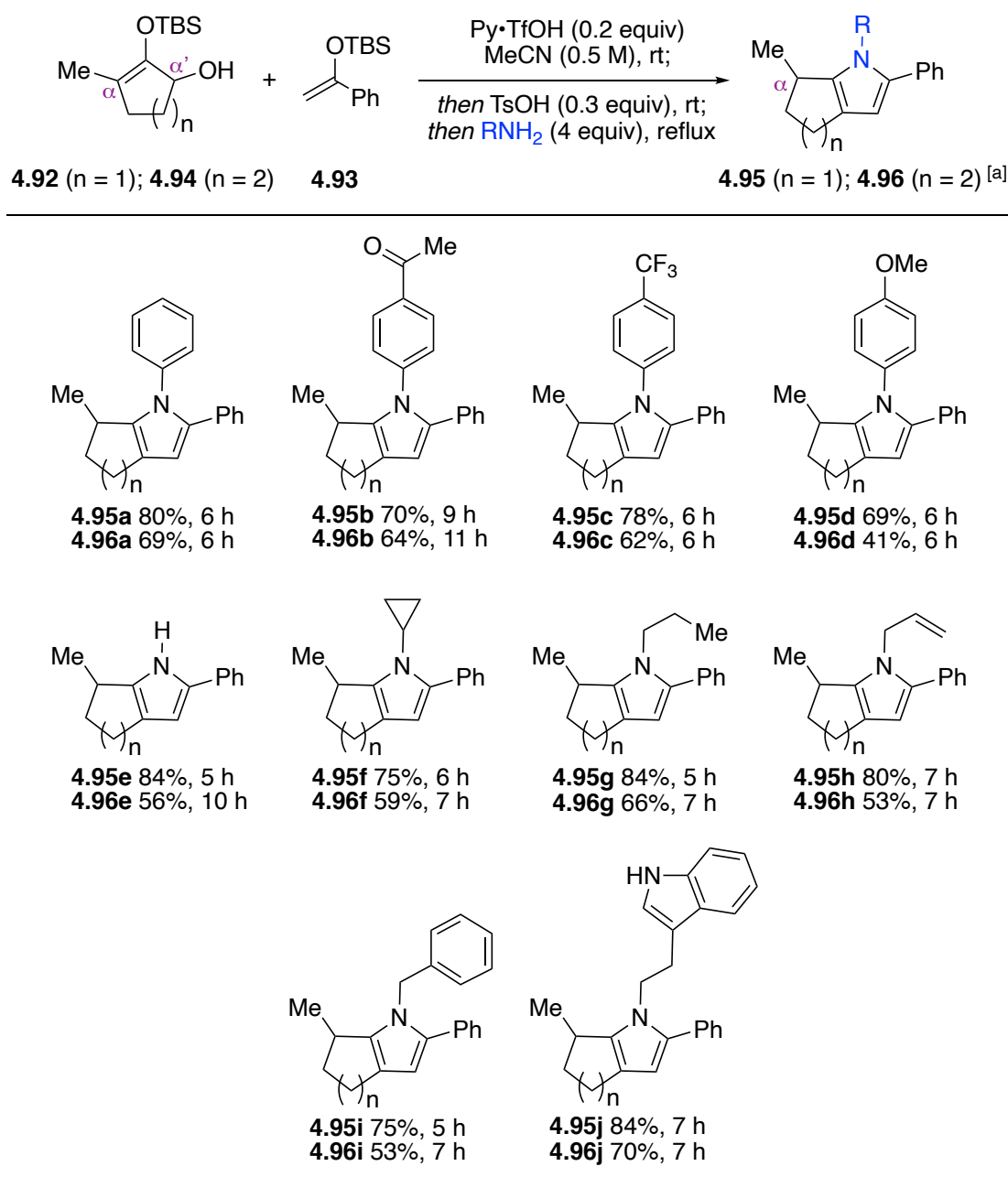
entry	additive	additive equiv.	PrNH ₂ equiv.	total reaction time (h)	yield (%) [a]
1	-	-	4.0	168	77
2	PPTS	0.5	4.0	96	74
3	TfOH	0.5	4.0	4	62
4	CSA	0.5	4.0	8	82
5	TsOH	0.5	4.0	6	83
6	TsOH	0.3	4.0	5	83
7	TsOH	0.2	4.0	8	77
8	TsOH	0.3	2.0	7	75
9	TsOH	0.3	4.0	192	56 [b]

[a] Isolated yield after column chromatography. [b] Reaction was performed at room temperature.

4.10 Scope of Primary Amines

With optimized reaction conditions in hand we set to explore the tolerance of our developed methodology to assorted aliphatic and aromatic primary amines as depicted in Scheme 4.18. To

generate a diverse library of *N*-substituted tetrahydrocyclopenta[*b*]pyrroles **4.95** and tetrahydroindoles **4.96**, both five- and six-membered α -hydroxy silylenol ethers **4.92** and **4.94** were exposed to the reaction conditions. In the synthesis of *N*-aryl substituted pyrroles, aniline and its derivatives



[a] Isolated yield after column chromatography.

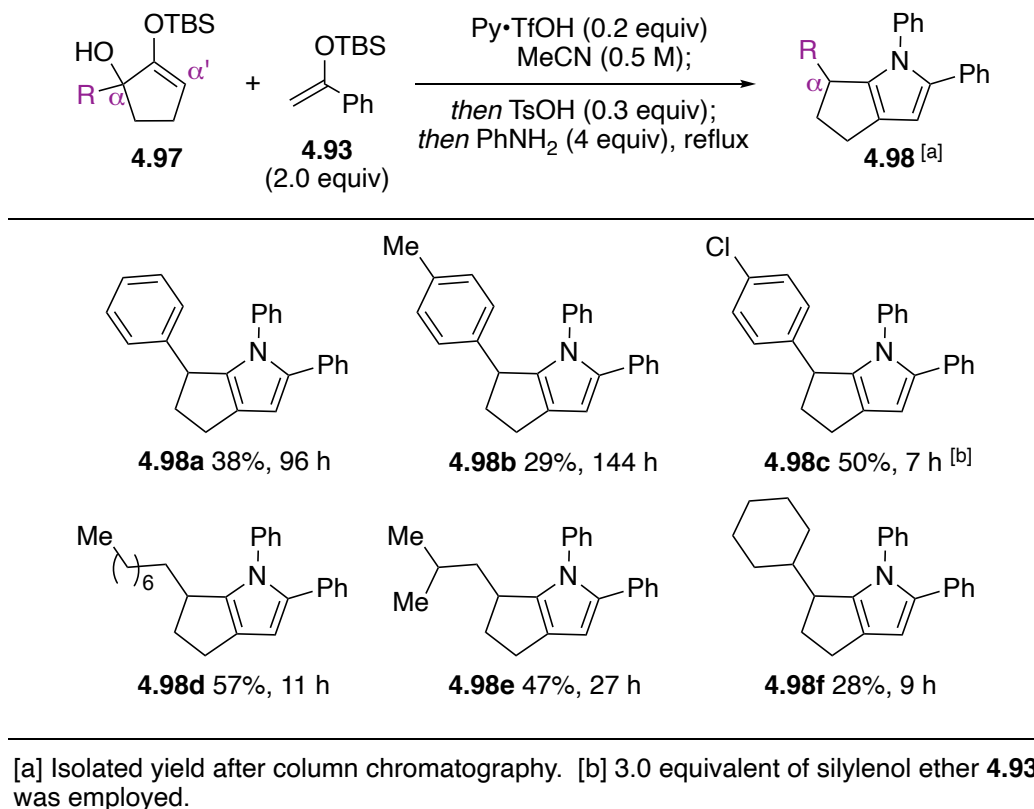
Scheme 4.18 Scope of Primary Amines

p-trifluoromethylaniline, *p*-aminoacetophenone, and *p*-methoxyaniline successfully furnished the desired *N*-aryl tetrahydrocyclopenta[*b*]pyrroles **4.95a-4.95d** and tetrahydroindoles **4.96a-4.96d** in moderate to excellent yields. Furthermore, we demonstrated that unsubstituted *N*-heterocyclic adducts **4.95e** and **4.96e** could be generated by employing 7*N* ammonia in methanol as our nitrogen source. Aliphatic primary amines such as cyclopropyl, propyl, allyl, and benzylamine were tolerated by our reaction conditions delivering adducts **4.95f-4.95i** and **4.96f-4.96i** in excellent yields. Lastly, the use of tryptamine yielded the corresponding adducts **4.95j** and **4.96j** in 84% and 70% yield respectively. Through these experiments, we observed that the formation of tetrahydroindoles **4.96** were typically lower yielding than that of the analogous tetrahydrocyclopenta[*b*]pyrrole **4.95**. The observed decrease in yields were most likely attributed to the generation and capture of six-membered silyloxyallyl cations as previously demonstrated in Chapter Three.

4.11 Scope of Tertiary α -Hydroxy Silylenol Ethers

In an attempt to further diversify the partially saturated five and six membered rings of the tetrahydrocyclopenta[*b*]pyrrole and tetrahydroindole cores, we studied the substituent effects at the α -carbon of the α -hydroxy silylenol ethers (Scheme 4.19). Initially, we subjected a series of aliphatic and aromatic substituted tertiary α' -hydroxy silylenol ethers **4.97**, silyl enolate **4.93** and aniline as to our optimized conditions. Unfortunately, we observed that aromatic bearing substrates proved problematic. While phenyl, tolyl, and *p*-chlorophenyl substituted α' -hydroxy silylenol ethers **4.97** successfully afforded the desired tetrahydrocyclopenta[*b*]pyrroles **4.98a-4.98c**, these substrates were accompanied with poor yields and extended rates of reaction. Furthermore, examination of aliphatic α' -hydroxy silylenol ethers substituted with octyl, *iso*-butyl, and cyclohexyl substituents also produced the desired adducts **4.98d-4.98f** but were plagued with severely diminished yields. We hypothesize that the poor reactivity of these substrates was

ultimately attributed to a steric barrier imposed by the tertiary alcohols **4.97**, therefore slowing the rate of ionization, leading to undesired decomposition. Moreover, implementing our optimized conditions to analogous six-membered tertiary α' -hydroxy silylenol ethers ultimately yielded unfruitful, as full consumption of the starting material was never achieved.

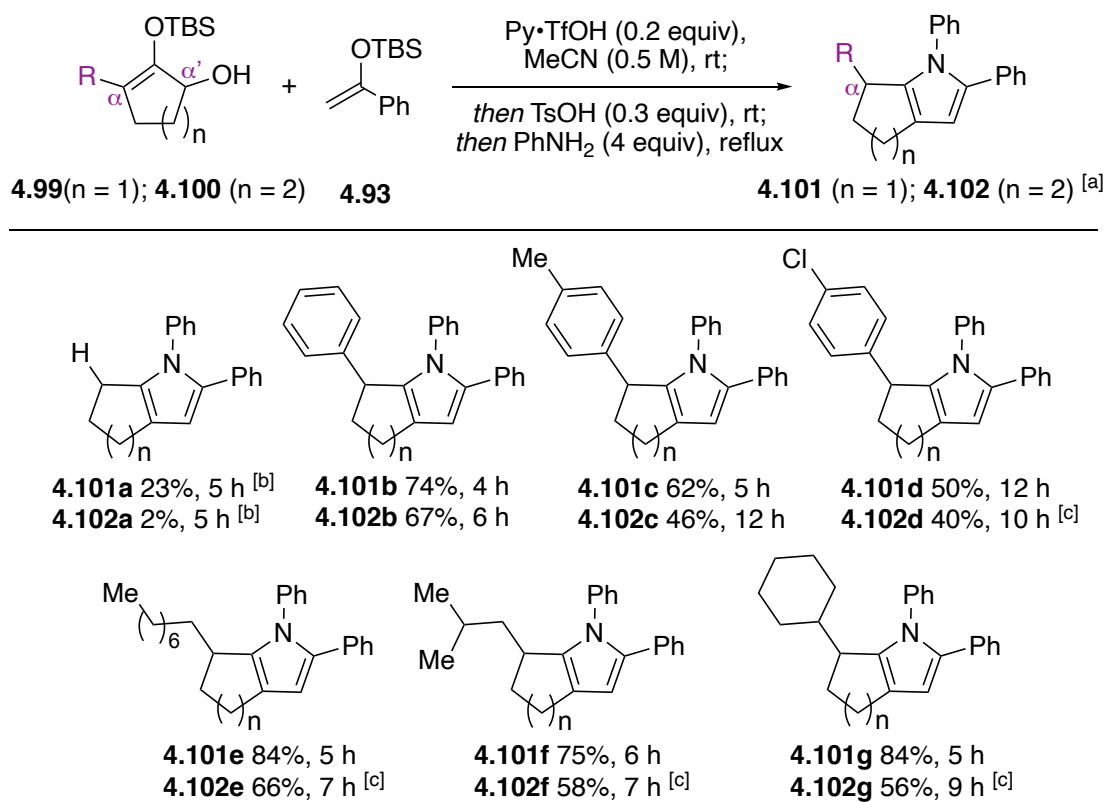


Scheme 4.19 Scope of Tertiary α -Hydroxy Silylenol Ethers

4.12 Scope of Secondary α -Hydroxy Silylenol Ethers

As described above, the utilization of five- and six-membered tertiary α' -hydroxy silylenol ethers yielded problematic in the synthesis of tetrahydrocyclopenta[*b*]pyrroles and tetrahydroindoles. To remove the proposed steric barrier imposed by the tertiary alcohols, we propose the utilization of analogous secondary α' -hydroxy silylenol ethers could circumvent the lack of

reactivity. To test our hypothesis, we subjected the analogous secondary α -hydroxy silylenol ethers **4.99** and **4.100** with identical aromatic and aliphatic substituents at the α -carbon to our optimized reaction conditions in Scheme 4.23 (See Chapter 6.3.2 for synthesis of **4.99** and **4.100**). Throughout initial experimentation, we observed coupling of silylenolate **4.93** and select six-membered substrates **4.100** required a higher loading of silylenol ether to achieve full consumption of **4.100**. Surprisingly, the use of unsubstituted α -hydroxy silylenol ethers furnished tetrahydrocyclopenta[*b*]pyrrole **4.101a** and tetrahydroindole **4.102a** respectively. The poor yields of these reactions are attributed to unidentifiable decomposition of starting material under our



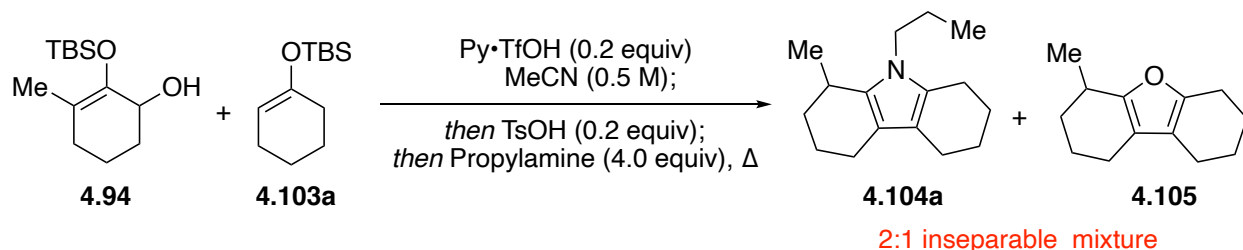
[a] Isolated yield after column chromatography. [b] The reaction was performed in 0.2 M concentration using 4.0 equivalents of silylenol ether **4.93**. [c] 3.0 equivalents of silylenol ether **4.93** was employed.

Scheme 4.23 Scope of Secondary α -Hydroxy Silylenol Ethers

reaction conditions. Improved yields and reactivity were observed by switching from the tertiary α -hydroxy silylenol ethers to the analogous secondary alcohol. For example, aromatic substituents such as phenyl, tolyl, and *p*-chlorophenyl successfully furnished tetrahydrocyclopenta[*b*]pyrroles **4.101b-4.101d** and tetrahydroindoles **4.102b-4.102d** in moderate to good yields, with enhanced rates of reaction and yields as compared to the tertiary α -hydroxy silylenol ethers analogues. With regards to aliphatic substituted α -hydroxy silylenol ethers, *n*-octyl substitution produced adducts **4.101e** and **4.101e** in 84% and 66% yield respectively. Strikingly, steric effects did not have significant influence in tetrahydrocyclopenta[*b*]pyrrole or tetrahydroindole formation, as both cyclohexyl and *iso*-butyl substituents produced **4.101f-4.101g** and **4.102f-4.102g** respectively, all in moderate to excellent yields. Ultimately, we observed that removal of the steric barrier imposed by the tertiary alcohol by switching to an analogous secondary alcohol successfully circumvented the poor reactivity and yields as previously observed.

4.13 Scope of Silylenolate Nucleophiles to Diversify the Pyrrole Core

Having established reactivity patterns for both primary amines and α -substituted secondary and tertiary α' -hydroxy silylenol ethers, lastly we examined the scope of TBS enolate nucleophiles to diversify the C2 and C3 positions of the pyrrole core. Beginning our exploration into our silylenolate studies, we observed within select six-membered α' -hydroxy silylenol ethers systems that undesired tetrahydrobenzofuran byproducts were formed (Scheme 4.24). For example, we

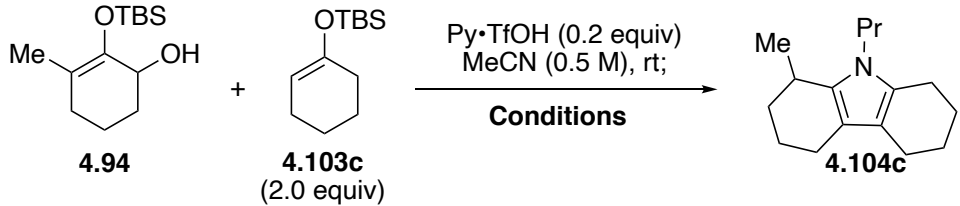


Scheme 4.24 Undesired Tetrahydrobenzofuran Formation

witnessed that subjecting α' -hydroxy silylenol ether **4.94** and cyclohexanone derived silylenolate **4.103** to our reaction protocol generated tetrahydroindole **4.104** and tetrahydrobenzofuran **4.105**. Ultimately, we determined that the undesired tetrahydrobenzofuran was a result of intramolecular cyclization of the 1,4-diketone intermediate at room temperature during protodesilylation γ -keto silylenol ether. This undesired annulation has been previously reported as in acidic mediums with pH under 3, furan formation is the major product in Paal-Knorr pyrrole synthesis.¹³⁷

To circumvent this undesired annulation, we devised alternative desilylation conditions as indicated in Table 4.3. We observed that replacement of protic desilylating agent TsOH with excess cesium fluoride (CsF) successfully led to protodesilylation with no observable tetrahydrobenzofuran formation.^{138, 139} Entry 1 depicts our attempt to induce desilylation with CsF at room temperature in which CsF was added after coupling of **4.94** and **4.103c** followed by addition of TsOH and propylamine, successfully yielding tetrahydroindole **4.104c** in 46% yield in 125 hours. To combat the extensive reaction times desilylation was performed at reflux alongside increasing tosic acid equivalents (entries 2 and 3), which furnished the desired adduct **4.104c** with entry 3 being our optimized revised conditions for the synthesis of tetrahydroindole **4.104c**.

Table 4.3 Revised Reaction Conditions

			
Entry	Conditions	total reaction time (h)	Yield (%) ^[a]
1	CsF (2.0 equiv), rt; TsOH (0.3 equiv), PrNH ₂ (4 equiv), reflux	125	46
2	CsF (2.0 equiv), reflux; TsOH (0.5 equiv), PrNH ₂ (4.0 equiv), reflux	30	47
3	CsF (2.0 equiv), reflux; TsOH (1.0 equiv), PrNH ₂ (4.0 equiv), reflux	8	51

[a] Isolated yield after column chromatography.

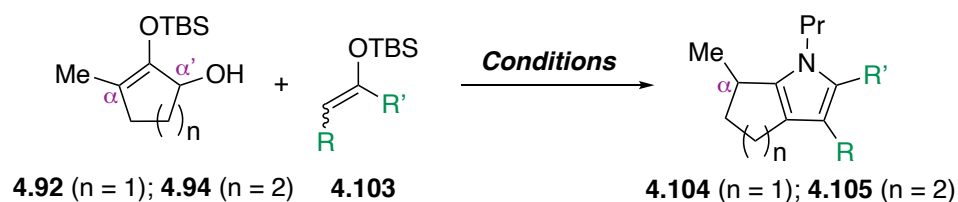
With the two equivalent sets of conditions in hand, we explored the tolerance of silylenolate nucleophiles as showcased in Table 4.4, in which conditions B were utilized when under conditions A furan formation was observed. Electron rich *p*-methoxy and electron deficient *p*-trifluoromethyl acetophenone-derived silylenol ethers **4.103a** and **4.103b** afforded the desired tetrahydrocyclopenta[*b*]pyrroles **4.104a/4.104b** and tetrahydroindoles **4.105a/4.105b** in poor to moderate yields. Interestingly in the synthesis of tetrahydroindoles **4.105a/4.105b**, only electron poor silylenolate **4.103b** required conditions B demonstrating that electronics of the diketone system play an important role in controlling reactivity. Furthermore, we demonstrated our ability to generate polycyclic heterocycles through the use of cyclohexanone and α -tetralone derived TBS enol ethers **4.103c** and **4.103d**, which effectively furnished **4.104c-4.104d** and **4.105c/4.105d** adducts in moderate yields. As previously demonstrated in Chapter Three, highly aliphatic silylenolates were insoluble in MeCN, consequently we were surprised that 3-pentanone derived enolate **4.103e** successfully afforded tetrahydrocyclopenta[*b*]pyrroles **4.04e** and tetrahydroindole **4.105e** in 50% and 54% respectively.⁸⁵ Moreover, tetrahydrocyclopenta[*b*]pyrrole **4.104f** and tetrahydroindole **4.105f** with phenyl incorporation at both C2 and C3 positions were isolated in good yields *via* silylenolate **4.103f**. Lastly, an attempt to introduce substitution exclusively at the C3 position using phenylacetaldehyde derived TBS enolate **4.103g** is shown in entry 7. While adduct **4.104g** was readily furnished from five-membered substrate **4.92** in 36% yield, utilization of **4.94** failed to produce the desired adduct under either set of conditions.

4.14 Conclusion

In conclusion, this chapter provides a short review of the Paal-Knorr pyrrole synthesis along with strategies to synthesize tetrahydroindoles and tetrahydrocyclopenta[*b*]pyrroles. This chapter also showcases our development of a robust 3-component, 1-pot method to construct

highly substituted tetrahydroindoles and tetrahydrocyclopenta[*b*]pyrroles under catalytic Brønsted acidic conditions. Our reaction involves three easily synthesized reaction partners, five- and six-membered silyloxyallyl cations, silylenolates, and primary amines. We explored an arrangement of primary amines and silylenolate nucleophiles, in combination with investigation into α -substituent effects on both secondary and tertiary hydroxy silylenol ethers. Different synthetic routes to secondary α -hydroxy silylenol ethers were developed in the course of reaction development to solve inherent reactivity problems. Further continuation of this work has been published by Fatimat Badmus, as she explored the synthesis of tetrahydrobenzofurans through the use of silyloxyallyl cations and silyl enolate nucleophiles.¹⁴⁰

Table 4.4 Scope of Silylenolate Nucleophiles



Conditions A: Py•TfOH (0.2 equiv), MeCN (0.5 M), rt; then TsOH (0.3 equiv), rt; then propylamine (4.0 equiv), reflux

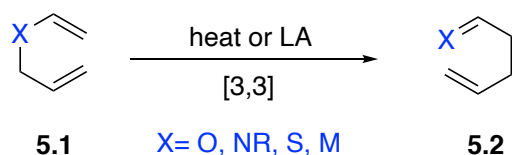
Conditions B: Py•TfOH (0.2 equiv), MeCN (0.5M), rt; then CsF (2.0 equiv), reflux; then TsOH (1.0 equiv), propylamine (4.0 equiv), reflux

entry	nucleophile	product	cond.	time (h)	yield [a]
1	<p>4.103a</p>	<p>4.104a</p>	A	5	66%
		<p>4.105a</p>	A	5	55%
2	<p>4.103b</p>	<p>4.104b</p>	A	27	52%
		<p>4.105b</p>	B	11	34%
3	<p>4.103c</p>	<p>4.104c</p>	A	6	64%
		<p>4.105c</p>	B	8	51%
4	<p>4.103d</p>	<p>4.104d</p>	A	31	50%
		<p>4.105d</p>	A	30	50%
5	<p>4.103e</p>	<p>4.104e</p>	A	5	50%
		<p>4.105e</p>	B	9	54%
6	<p>4.103f</p>	<p>4.104f</p>	A	19	62%
		<p>4.105f</p>	B	100 [b]	46%
7	<p>4.103g</p>	<p>4.104g</p>	A	6	36%
		<p>4.105g</p>	A / B	-	decomp

[a] Isolated yield after column chromatography. [b] Diketone was not fully consumed.

2 Introduction to the Claisen Rearrangement

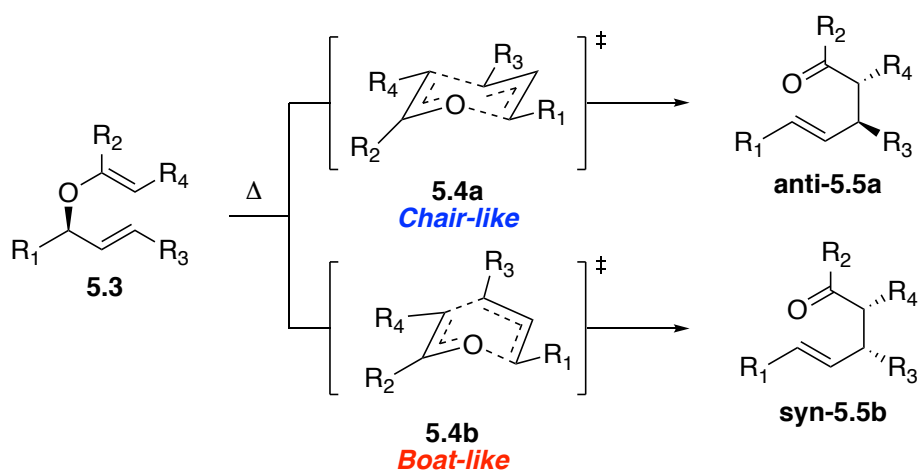
Since its initial discovery in 1912 by Ludwig Claisen, the Claisen rearrangement has been recognized as a powerful carbon-carbon bond forming tool within the synthetic community.^{141, 142} The Claisen rearrangement is defined as a thermal or Lewis-acid promoted [3,3]-sigmatropic rearrangement of allyl vinyl ethers **5.1** to the corresponding γ,δ -unsaturated carbonyl compounds **5.2** as depicted in Scheme 5.1. The exact mechanism of the rearrangement has been heavily disputed, multiple reports detail that the process could occur in three possible transition state; either an aromatic, radical/ion pair or zwitterionic transition state could be probable.¹⁴³⁻¹⁴⁷ Diverging from the traditional oxygen Claisen rearrangement in which $X = O$, there have been numerous developments in the aza-Claisen ($X = NR$),¹⁴⁷⁻¹⁴⁹ thio-Claisen ($X = S$)^{150, 151} and metallo-Claisen ($X = M$). In addition, other variants of these rearrangements have been developed such as the Eschenmoser,^{152, 153} Ireland,¹⁵⁴⁻¹⁵⁶ and Johnson Claisen^{157, 158} modifications which are used to synthesize a variety of γ,δ -unsaturated carbonyl compounds.



Scheme 5.1 The Claisen Rearrangement

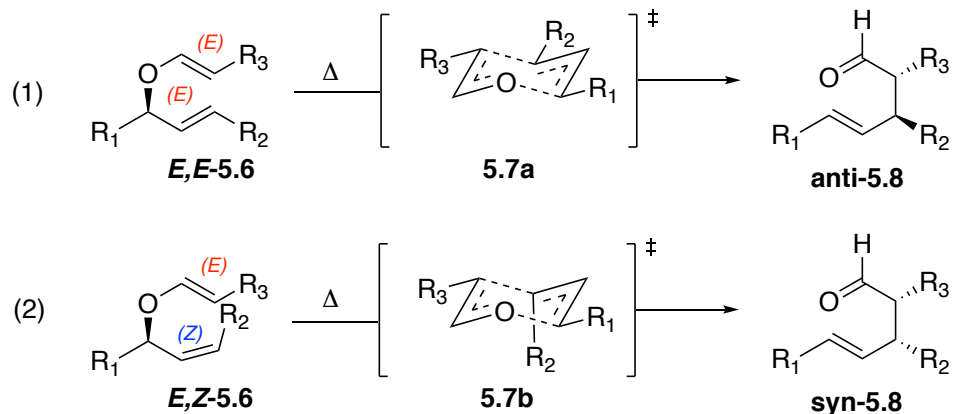
The simplicity of the Claisen rearrangement as a useful synthetic tool is exemplified by the ability to generate complex stereochemical motifs from relatively trivial precursors. The typical acyclic Claisen rearrangement typically proceeds via a highly ordered six-membered chair transition state.^{156, 160} For example, rearrangement of allyl vinyl ether **5.3** typically produces **anti-5.5** as the major product with an observable anti-relationship between the two substituents

(Scheme 5.2). While the chair transition state **5.4a** minimizes the torsional and transannular interactions, it is also possible for Claisen rearrangement to proceed through a boat-like transition state **5.4b** furnishing **syn-5.5** as a minor product. A boat transition state typically occurs when there are unfavorable steric interactions between the substituents on the two olefins. In addition, enantiomerically enriched allyl vinyl ethers result in the formation of γ,δ -unsaturated carbonyl compounds in high optical purities. Ultimately, the preferred transition state has been demonstrated to be substrate specific and can easily be controlled by alkene geometry.



Scheme 5.2 Possible Transition States of the Acyclic Claisen Rearrangement

Due to the highly ordered transition state, the stereochemical identity of the sigmatropic rearrangement products can be controlled by selecting the desired olefin geometries of both allyl and vinyl alkenes (Scheme 5.3). For instance, if both olefin geometries on the allyl vinyl ethers are *E,E*-**5.6** then the Claisen rearrangement will most likely proceed through a chair-like transition state **5.7a** to yield anti-configured product **anti-5.8**. Alternatively, utilizing mixed olefins *E,Z*-**5.6** results in syn-configured product **syn-5.8** resulting from a chair-like transition state. As previously discussed, these rearrangements could proceed via a boat-like transition state, if these transition

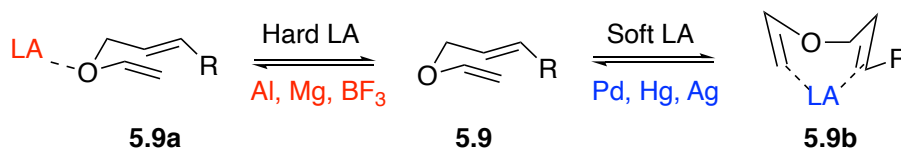


Scheme 5.3 Stereochemical Outcomes of the Claisen Rearrangement

states predominate the opposite stereochemical configuration is observed. The ability to predict the stereochemical outcome of the acyclic Claisen rearrangement by the careful choice of olefin geometries makes this reaction a powerful synthetic tool.

5.3 Copper Lewis Acid Catalyzed Claisen Rearrangements

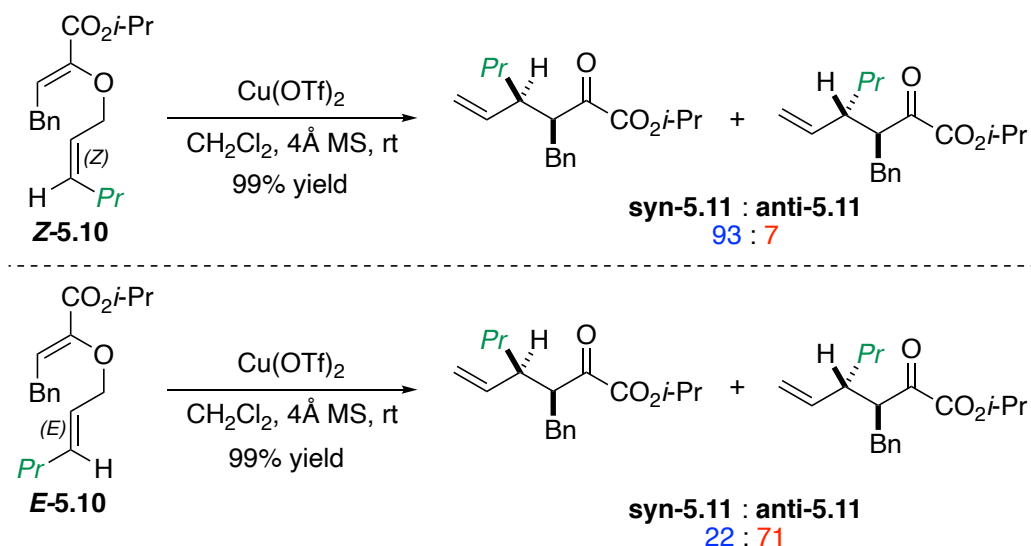
The utilization of Lewis acids to efficiently accelerate the rate of the Claisen rearrangements alongside their ability to act as stereochemical inductors is well preceded with recent literature.^{147, 161-166} The allylenol ether motif has three possible sites for Lewis acid activation, the oxygen of the enol ether and the two alkenes of the enol ether and allyl moiety (Scheme 5.3). Oxophilic activation of allylenol ether **5.9** relies on Lewis acid coordination to one of the lone electron pairs of the oxygen to facilitate the rearrangement **5.9a**. It has been demonstrated that hard Lewis acids such as aluminum, and magnesium prefer oxophilic coordination resulting in preferred chair-like transition states.^{161, 167, 168}



Scheme 5.4 Lewis Acid Modes of Activation

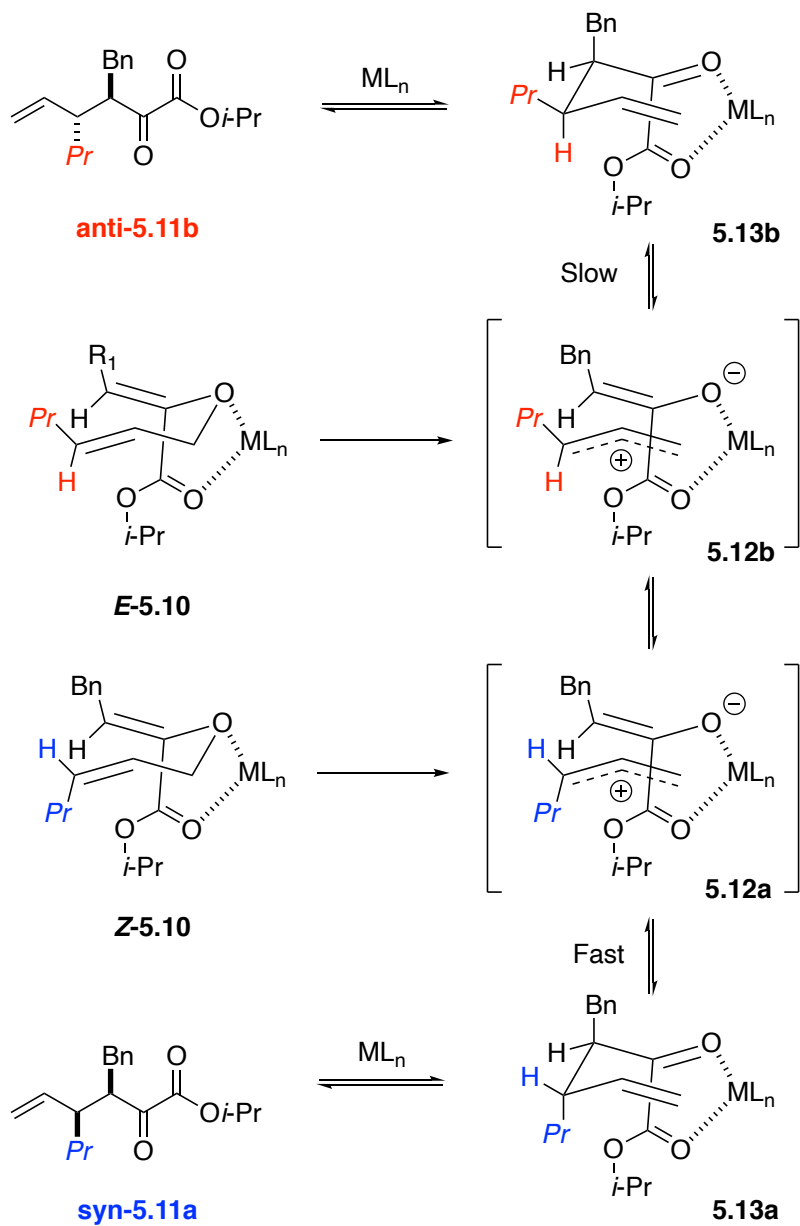
Contrary to oxophilic activation, soft Lewis acids such as palladium, mercury, and gold usually act as π -activators, coordinating to the olefins of allylenol ether **5.9b**.^{164, 169-172} This unique bidentate mode of activation results in a favorable boat-like transition state. While a wide array of Lewis acids such as aluminum, palladium, zinc and titanium have been reported to catalyze Claisen rearrangements, to the best of our knowledge the use of copper Lewis acids are under reported in literature. As copper can act as both a hard and soft Lewis acid depending on oxidation state, most reports detail copper participating in oxophilic activation.

One of the first reports of a copper catalyzed Claisen rearrangement was reported by Hiersemann and coworkers in 2000.¹⁷³ Their seminal reported detailed treatment of allyl vinyl ethers with catalytic Cu(OTf)₂ in anhydrous CH₂Cl₂, which successfully induced Claisen rearrangement readily affording α -keto esters at ambient temperature (Scheme 5.5). Under their reaction conditions, they discovered upon treatment of **Z-5.10** they could successfully afford α -keto esters **syn-5.11** as the major diastomer in a 93:7 dr. Alternately, upon rearrangement of allylenol ether **E-5.10** furnished **anti-5.11** in 22:71 dr, favoring formation of the anti-isomer. Alongside the use of Cu(OTf)₂ as a catalyst, it was also demonstrated that Yb(OTf)₃ could efficiently promote the Claisen rearrangements, exhibiting similar diastereoselective control.



Scheme 5.5 Hiersemann's Cu(OTf)_2 Catalyzed Claisen Rearrangement

While allylenol ether **Z-5.10** produced **syn-5.11** in excellent diastereoselectivity, diminished selectivities were noted with allylenol ether **E-5.10**, to explain this phenomena Hiersemann proposed a mechanism in order to explain the different diastereoselectivities (Scheme 5.6). For the synthesis of **syn-5.11**, they proposed that initial coordination of Cu(OTf)_2 to the ester carbonyl and ether oxygen of **Z-5.10** resulted in heterolytic cleavage of the ether bond to form ion pair **5.12a** in an antiperiplanar arrangement. From their observed outcome of **syn-5.11** being the

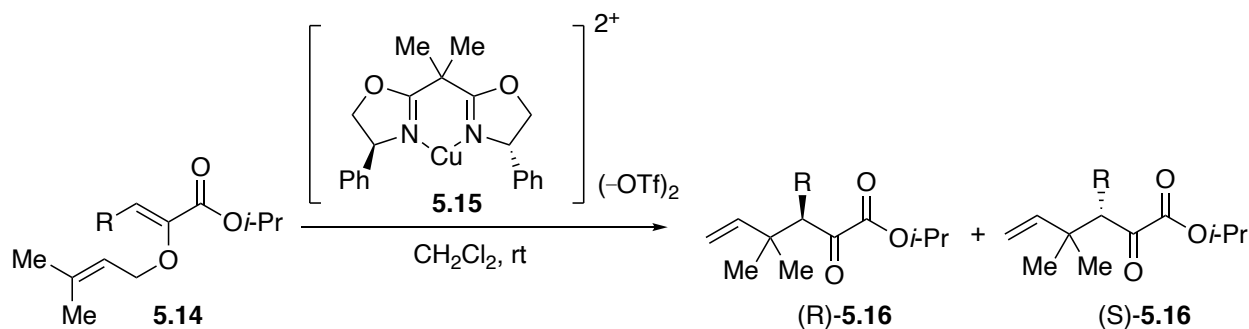


Scheme 5.6 Proposed Mechanism of the $\text{Cu}(\text{OTf})_2$ Claisen

major product, they proposed the rearrangement of intermediate **5.12a** proceeded relatively fast leading to the formation of **syn-5.11**. To account for the formation of the minor diastereomer **anti-5.11**, Hiersemann propositioned that equilibration existed between allylic cations **5.12a** and **5.12b** by a simple C-C bond rotation that could readily produce intermediate **5.13b**.

While this explained the observed outcome of the rearrangement of **Z-5.10**, they observed diminished selectivities with the **E-5.10**. To account for diminished selectivities, they hypothesized that upon generation of ion pair **5.12b**, the synclinal orientation was unfavorable due to steric interactions resulting in C-C bond rotation to form ion pair **5.12a**. Ultimately, the steric interactions reduced the rate of rearrangement, resulting in increased concentrations of intermediate **5.12a**. Moreover, Hiersemann concluded that reactivity and stereoselectivity was dependent on the substrate's olefin geometries in generation of the more favorable ion pair

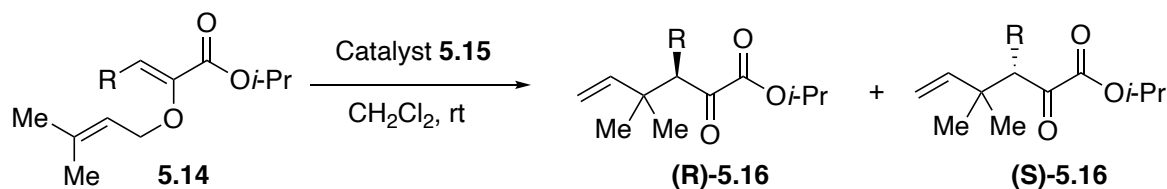
Further continuation of their work, Hiersemann and co-workers reported the first copper catalyzed enantioselective Claisen rearrangement of allyl vinyl ethers (Scheme 5.7).^{159, 174} They detailed that treatment of allyl vinyl ethers **5.14** with chiral [Cu^{II}(box)] complex **5.15**, effectively induced Claisen rearrangement furnishing α -keto esters **5.16** in high yields and enantiomeric excess. The capability to gain high enantioselectivity was attributed to the copper complexes



Scheme 5.7 Enantioselective Copper Promoted Claisen Rearrangement

ability to bidentate coordinate to the allyl vinyl ether and ester forming a tight transitions state. To determine the scope and limitations of their enantioselective Claisen rearrangement Hiersemann explored substitution of the vinyl group (Table 5.1). Both *E*- and *Z*-methyl substituted enol ethers **5.14a** and **5.14b** were tolerated yielding α -keto esters **(R)-5.16a** and **(S)-5.16b** in near quantitative

Table 5.1 Hierseman's Scope of Allyl Vinyl Ethers

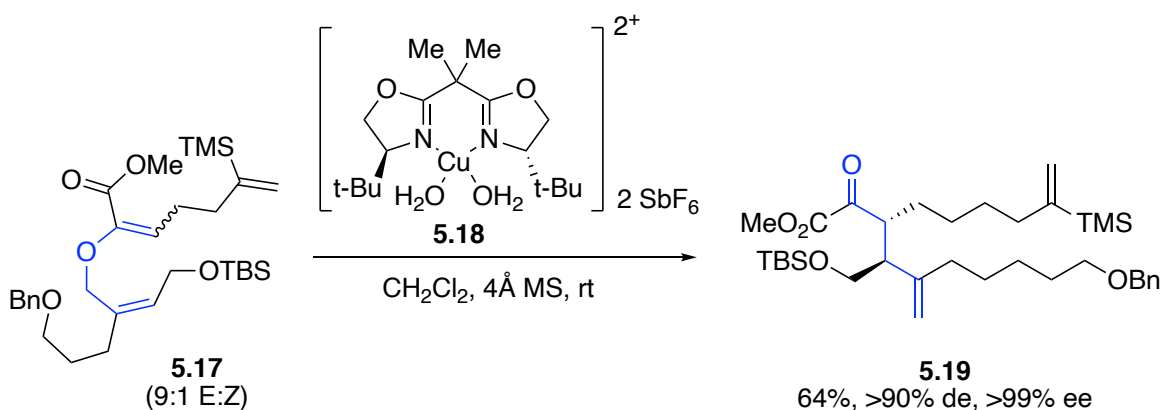


Entry	Starting material	Product	Yield
1	<p>5.14a</p>	<p>(R)-5.16a</p>	100% yield 91:9 (R:S)
2	<p>5.14b</p>	<p>(S)-5.16b</p>	99% yield 9:91 (R:S)
3	<p>5.14c</p>	<p>(R)-5.16c</p>	100% yield 93:7 (R:S)
4	<p>5.14d</p>	<p>(R)-5.16d</p>	99% yield 88:12 (R:S)

yields respectfully. It was observed that utilization of *Z*-alkene **5.14a** resulted in the formation of the (R)-isomer as the major enantiomer, while *E*-alkene **5.14b** yielded (S)-isomer as the major enantiomer. Both propenyl and benzyl substituted *Z*-alkenes were tolerated under their optimized

conditions furnishing (**R**)-**5.16c** and (**R**)-**5.16d** in excellent yields despite the diminished selectivity when employing bulky benzyl substituents.

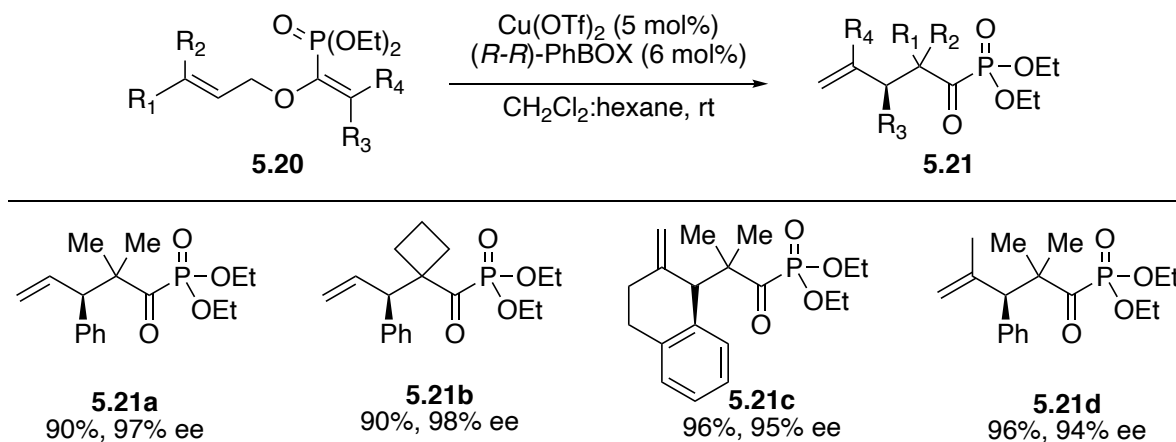
Furthermore, Hiersemann further showcased the power of their enantioselective Claisen rearrangement in the total synthesis of (-)-xeniolide F (Scheme 5.8).¹⁷⁵ Their key transformation in the formation of their enantioenriched ester relied on use of copper catalyst **5.18** to promote the rearrangement of allyl vinyl ether **5.17**, elegantly generating **5.19** as a single diastereomer and enantiomer. Similar to their previous studies, the stereochemical outcome was attributed to a chair-like transition state as well as the catalysts ability to coordinate in a bidentate fashion. While they started with a mixture of E/Z isomers, it was observed that the Z-isomer did not rearrange.



Scheme 5.8 Copper Catalyzed Claisen in the Synthesis of (-)-Xeniolide F

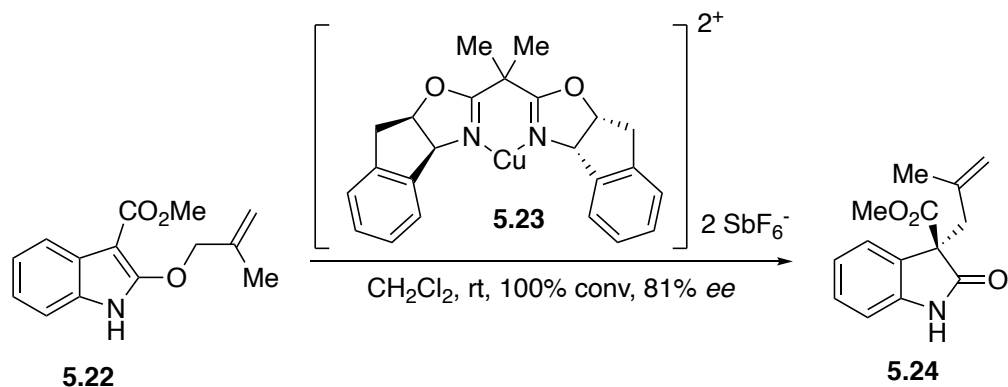
While Hiersemann pioneered the development of copper catalyzed Claisen rearrangements, in 2012 Yamamoto and co-workers reported a copper catalyzed asymmetric Claisen rearrangement of enolphosphonates as depicted in Scheme 5.9.¹⁷⁶ Yamamoto discovered that $\text{Cu}(\text{OTf})_2$ complexed with (R,R)-PhBOX ligand effortlessly promoted Claisen rearrangement of enolphosphonates **5.20** at room temperature, successfully affording a diverse library of enantioenriched α -ketophosphonates **5.21**. Enolphosphonates bearing dimethyl and cyclobutyl

groups readily generated α -ketophosphonates **5.21a** and **5.21b** in excellent enantiomeric excess. Sterically hindered substrates were tolerated successfully yielding **5.21c** and **5.21d** in 95% and 94% *ee* respectively. The exquisite enantiocontrol relied on bidentate chelation of [Cu(OTf)₂(box)] to both oxygens of the enol ether and phosphonate ester, locking the chair-like transition state.



Scheme 5.9 Enantioselective Synthesis of α -Ketophosphonates

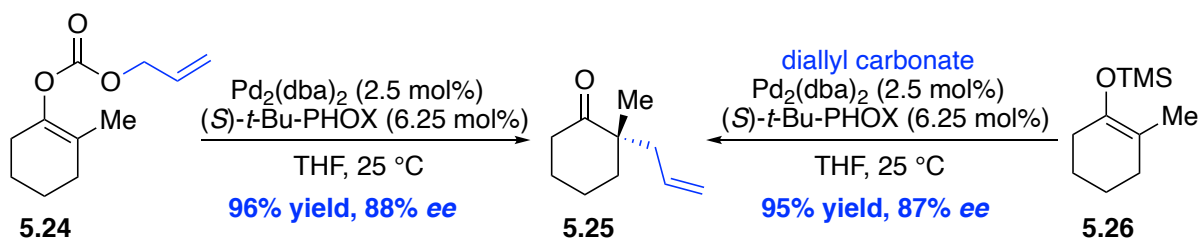
More recently, Kozłowski reported a copper catalyzed enantioselective Claisen rearrangement of allyloxy-indoles to furnish quaternary oxindoles (Scheme 5.10).¹⁷⁷ Kozłowski observed that treatment of indole **5.22** with stoichiometric Cu(SbF₆)₂ with indanol bisoxazoline complex **5.23** resulted in the formation of oxindole **5.24** in moderate enantiomeric excess. Further exploration into generating oxindoles it was discovered that catalytic palladium complexes promoted Claisen rearrangement of **5.22** more efficiently, ultimately generating **5.24** in higher enantioselectivity.



Scheme 5.10 Copper Claisen in the Synthesis of Oxindoles

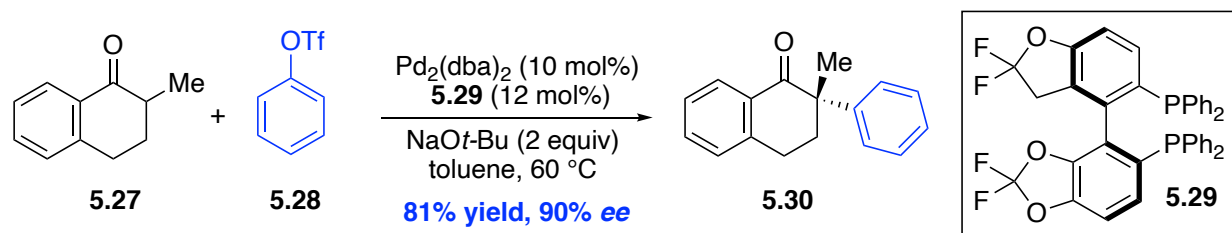
5.4 Synthesis of α -Quaternary Ketones

All carbon α -quaternary ketones are prominent features in many natural products and have been commissioned as key intermediates in many total syntheses. Apart from traditional enolate alkylation of ketones involving a base and an alkyl halide, there are countless modern strategies for the synthesis of α -quaternary ketones that can incorporate aryl and aliphatic groups in a regio- and stereoselective manner. For example, the Stoltz group has extensively studied the palladium catalyzed decarboxylative allylic alkylation of enol carbonates, and silyl enolates to furnish enantioenriched α -quaternary ketones (Scheme 5.11).¹⁷⁸ Stolz's seminal report on decarboxylative allylic alkylation detailed the treatment of enol carbonates **5.24** with catalytic $\text{Pd}_2(\text{dba})_2$ and *tert*-butylphosphinooxazoline ligand, successfully generating enantioenriched ketone **5.25** in 88% *ee*. Furthermore, they demonstrated that treatment of silylenolate **5.26** and electrophilic diallyl carbonate under the same conditions could afford ketone **5.25** in identical yield and *ee*. Since their seminal report, numerous advancements in decarboxylative allylic alkylation reactions have been developed for the synthesis of enantioenriched acyclic ketones, esters, amides, and have been displayed in a wide range of natural products synthesis.¹⁷⁹⁻¹⁸⁴



Scheme 5.11 Stoltz's Synthesis of α -Quaternary Ketones via Decarboxylative Allylic Alkylation

Another modern strategy for the synthesis of α -quaternary ketones is through α -arylation of ketones through transition metal catalysis. One example of this strategy was reported by Hartwig and co-workers, in which they were able to generate enantioenriched aryl ketones in excellent yields (Scheme 5.12).¹⁸⁵ Hartwig reported that treatment of ketone **3.27** and aryl triflate **3.28** with $\text{Pd}(\text{dba})_2$ and difluorophos ligand **5.29**, effortlessly furnished α -quaternary ketone **5.29** in 81% yield and 90% ee. Through extensive reaction optimization it was observed that the enantiomeric excess

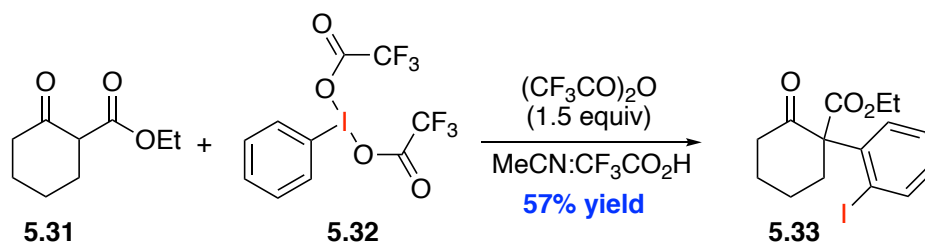


Scheme 5.12 α -Quaternary Ketones via Palladium Catalyzed α -Arylation

was attributed to the smaller dihedral angle within the difluorophos ligand **5.29** and the use of aryl triflates as their electrophile source. This conclusion was further supported by examination of the corresponding aryl halides which resulted in poor enantioselectivities under their reaction conditions. While Hartwig explored a wide array of cyclic ketones, and aryl triflates, their method was limited to blocking one α -carbon forcing the α -arylation to occur at the opposing α -carbon.

Other methods for the synthesis of α -quaternary ketones through α -arylation have been reported through the use of other catalysts such as nickel and copper.^{186, 187}

Alternative to the transition metal catalyzed approaches for generation α -quaternary aryl ketones, use of hyper-valent iodine reagents have proved an efficient route. One recent example of this interesting reactivity was reported by Shafir in 2014.¹⁸⁸ The detailed that treating β -ketoester **5.31** with PIFA **5.32** resulted in the formation of α -quaternary aryl ketone **5.33** in 57% yield, as a single regioisomer. Shafir observed that other iodine reagents such a PIDA did not afford the desired product and the reaction was depended on the careful choice of solvent using MeCN and CF₃CO₂H. Their reaction scope tolerated β -ketoesters, β -diketones, and α -cyanoketones successfully affording the corresponding quaternary ketones in moderate the excellent yields. Shafir proposed that introduction of the aryl group occurs through a [3,3] type rearrangement. Unfortunately, their strategy relies on the use of ketones with electron deficient groups at the α -carbon, influencing the formation of enolate generation.



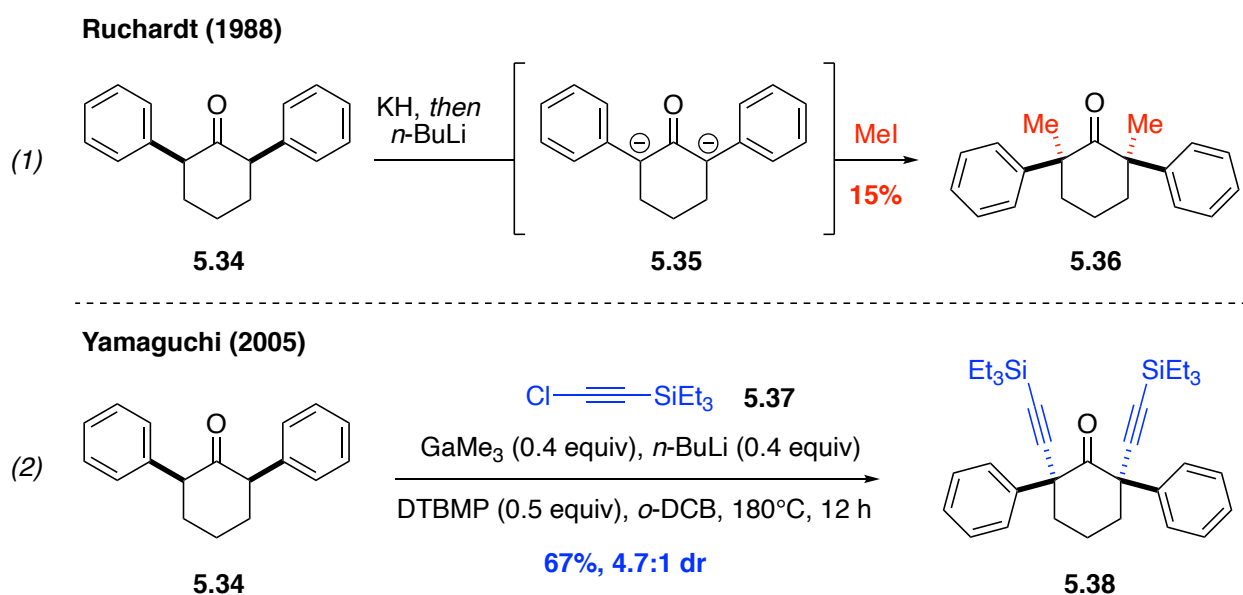
Scheme 5.13 α -Arylation Through Hyper-Valent Iodine Reagents

5.4 Synthesis of α,α' -Bis-Quaternary Ketones

Despite the substantial advancements in generation of a single quaternary center at the α -carbon of ketone, general methods to synthesize bis-quaternary ketones are limited. The classical

approach to synthesize bis-quaternary ketones through iterative α -functionalization of simple ketones are accompanied with fundamental drawbacks. Typically, several synthetic transformations are required to access these highly functionalized bis-quaternary ketones from mono-substituted ketones, and the inability to differentiate between chemically equivalent acidic protons results in the formation of multiple regioisomers. To the best of our knowledge, only a few methods have been reported to overcome these inherited drawbacks to synthesize bis-quaternary ketones within a single synthetic operation.

In 1988 Ruchardt reported the synthesis of a single bis-quaternary ketone from a disubstituted ketone as depicted in Scheme 5.15 *eqn 1*.¹⁸⁹ Ruchardt proposed that sequential treatment of bis-phenyl ketone **5.34** with potassium hydride (KH), followed by *n*-BuLi generated di-anionic intermediate **5.35** *in-situ*. Upon subsequent addition of excess iodomethane, bis-quaternary ketone **5.36** was produced in 15% yield. Their report failed to mention if ketone **5.36** was acquired as a single diastereomer, and only one example was provided of this reactivity.

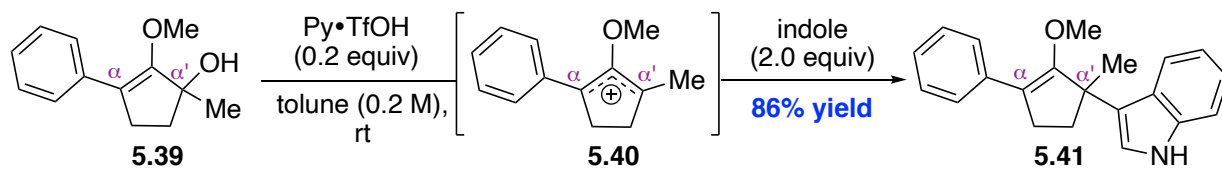


Scheme 5.15 Current Methods to Access bis-Quaternary Ketones

A more recent approach to the synthesis of bis-quaternary ketones was reported in 2006 by Yamaguchi and coworkers, in which they reported a base promoted α -ethynylation approach (Scheme 5.15, *eqn. 2*).¹⁹⁰ They observed that exposure of symmetrical ketone **5.34** to GaMe₃ and *n*-BuLi in the presence of chloroalkyne **5.37** successfully produced ketone **5.38** in 4.7:1 dr in a single synthetic step. Unfortunately, both methods developed by Ruchardt and Yamaguchi relied on the use of symmetrical ketone precursors, and the afforded symmetrical bis-quaternary ketones suffering from poor diastereoselective control.

5.5 Synthesis of Quaternary Centers via Protected Oxyallyl Cations

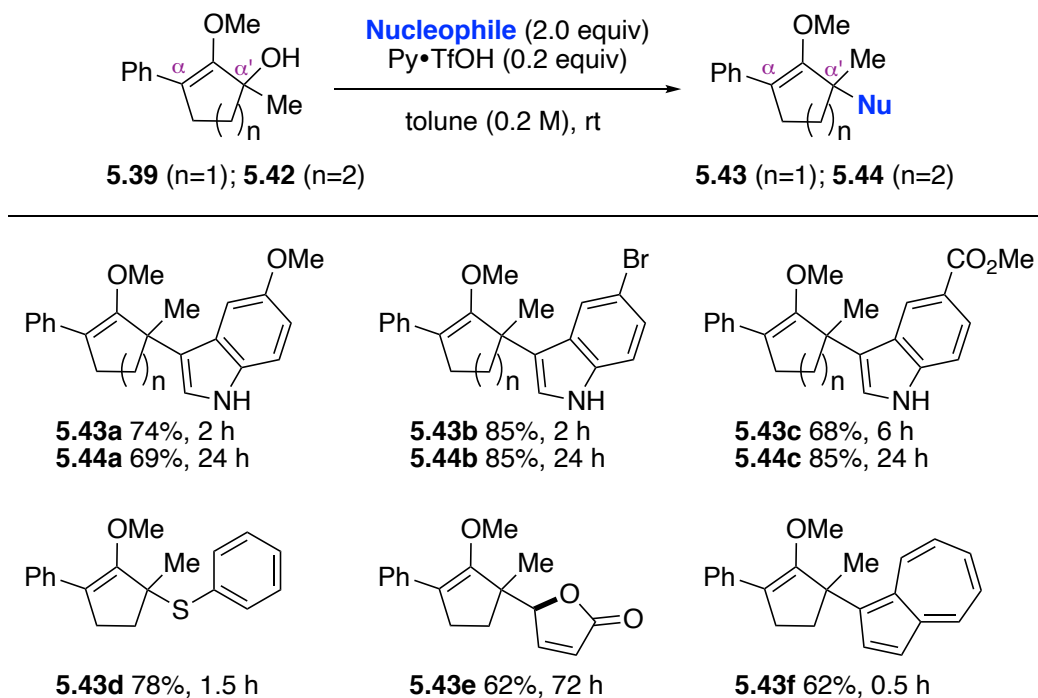
As previously described in the last few Chapters, oxyallyl cations are powerful electrophilic intermediates for the synthesis of a wide variety of molecular scaffolds. Previously work done by the Kartika lab focused the regioselective nucleophilic capture of mono-substituted silyloxyallyl cations. Further continuation of their work, Kartika and co-workers reported a unique strategy to generate a single quaternary center through the nucleophilic capture di-substituted unsymmetrical protected oxyallyl cations in a regioselective manner (Scheme 5.16).¹⁹¹ Their report detailed that treatment of methyl protected α -hydroxy enol ether **5.39** with catalytic Py•TfOH, readily facilitated the formation of unsymmetrical oxyallyl cation **5.40**. The strategic incorporation of phenyl and methyl substituents at the α and α' -positions resulted in the formation of electronically dissimilar electrophilic carbons. Ultimately, this electronical dissimilarity resulted in nucleophilic capture of the oxyallyl cation by indole to occur at the α' -carbon successfully



Scheme 5.16 Kartika's Synthesis of Quaternary Centers via Unsymmetrical Oxyallyl Cations

generating quaternary center **5.41** in 86% yield as a single regioisomer. Kartika hypothesized that the observed regioselectivity was a result of benzylic stabilization provided by the aromatic ring at the α -position, which further directed nucleophilic capture to occur at the α' -carbon. Furthermore, it was noted that an electron rich oxyallyl cations were required for the reaction to occur in an efficient manner, as the electron deficient silyloxyallyl cation analogue suffered from diminished reactivity.

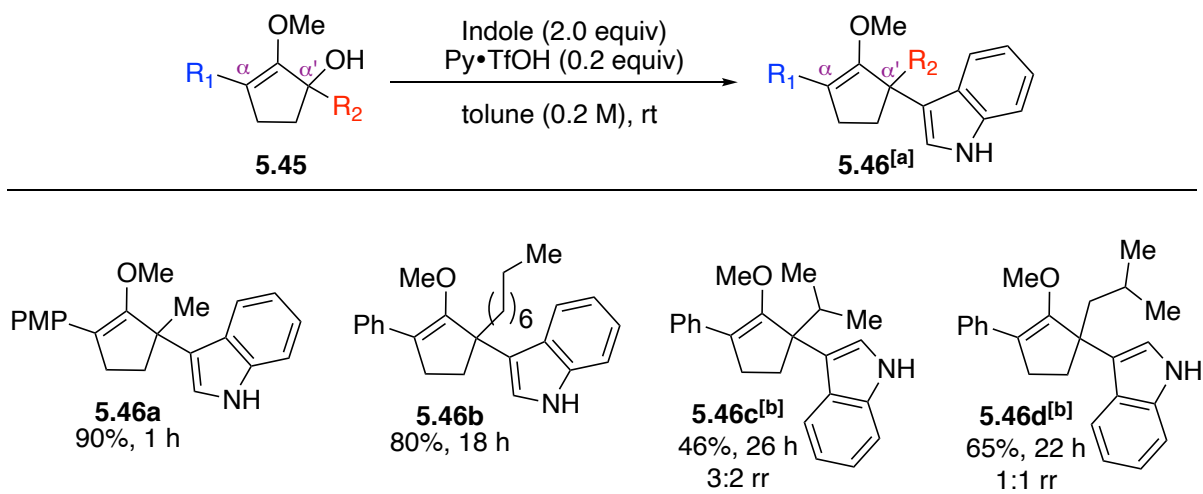
To further exemplify the synthetic utility of their chemistry, Kartika and co-workers explored the scope of indole, carbon and heteroatom nucleophiles with both five and six-membered α -hydroxy enol ethers **5.39** and **5.42** in the generation of α' -quaternary centers (Scheme 5.17). Electron-donating 5-methoxy indole readily furnished quaternary centers **5.43a** and **5.44a** in 74% and 69% yields, respectively. Furthermore, halogenated 5-bromo indole was found to be



Scheme 5.17 Kartika's Scope of Nucleophiles

tolerated under the optimized conditions affording indole adducts **5.43b** and **5.44b** in excellent yields. Quaternary adducts **5.43c** and **5.44c** were obtained *via* methyl-5-carboxylate indole accompanied with diminished yields and extended reaction times due the electron deficient nucleophile. Through the utilization of heteroatom and carbon nucleophiles such as thiophenol, 2-(trimethylsiloxy)furan and azulene the corresponding quaternary centers **5.43d-5.43f** in moderate yields as single regioisomers.

Furthermore, Kartika examined the role of aromatic and aliphatic substituents at the α and α' -positions of the α -hydroxy enol ethers **4.45**, and how they affect the regioselectivity of their reaction (Scheme 5.18). Under the optimized conditions they observed that electron donating *p*-methoxyphenyl enol ether **5.45a** successfully furnished indole adduct **5.46a** 90% yield, as single regioisomer. Furthermore, introduction of an aliphatic substituent such as octyl **5.45b** at the α' -position readily produced the corresponding quaternary center **5.46b** with full regioselectivity. Interesting, Kartika observed that introduction of bulky substituents at the α' -position of **5.45**



[a] Isolated yield after column chromatography. [b] Ratio of regioisomers determined by ^1H NMR analysis of the crude reaction mixture.

Scheme 5.18 Evaluation of Aromatic and Aliphatic Substituted α -Hydroxy Enol Ethers

resulted in significant erosion of regioselectivity. For example, incorporation of aliphatic substituents *iso*-propyl and *iso*-butyl α -hydroxy enol ethers **5.45c** and **5.45d** formed adducts **5.46c** in 3:2 *rr* and **5.46d** in 1:1 *rr* respectively. These results demonstrate that the regioselectivity of the ensuing nucleophilic capture of the proposed oxyallyl cation was sensitive to steric effects.

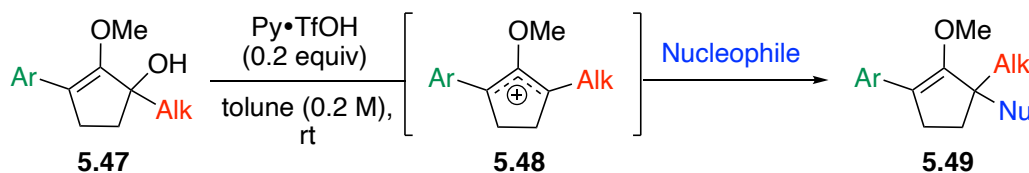
5.6 Our Approach to the Synthesis of α , α' -Bis-Quaternary Ketones

As described above, Kartika and co-workers had successfully developed a new protocol to generate quaternary centers *via* regioselective nucleophilic capture of unsymmetrical protected oxyallyl cations. In this approach, the protected α -hydroxy enol ether **4.57** undergoes ionization in presence of catalytic Py•TfOH to generate an unsymmetrical oxyallyl cation **5.28** (Scheme 5.19). Through benzylic stabilization provided by the α' -aromatic substituent, nucleophilic capture was selectively directed to the α -position generating quaternary stereocenter **5.49**.

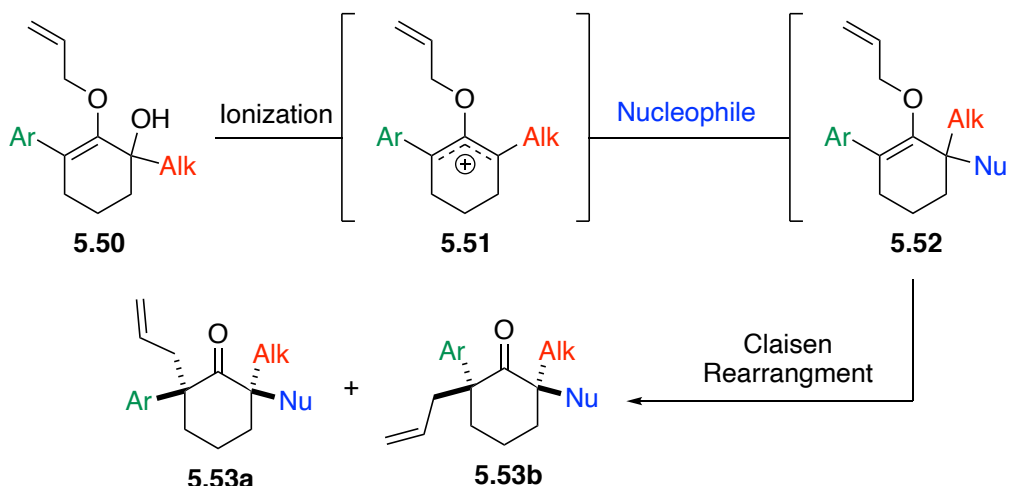
With the success in developing a regioselective synthesis of a single quaternary center, we aimed to extend this unique reactivity to synthesize bis-quaternary centers (Scheme 5.19). Our approach revolved around the regioselective nucleophilic capture of unsymmetrical allyl protected oxyallyl cations, followed by a subsequent Claisen rearrangement which could generate unprecedented α , α' -bis-quaternary ketones. We hypothesized that under Brønsted or Lewis acidic conditions, initial ionization of α -hydroxy allylenolate **5.50** could readily generate unsymmetrical oxyallyl cation **5.51**. Moreover, we propose that benzylic stabilization provided by the aromatic group would direct regioselective nucleophile addition to occur at the α -carbon adjacent to the alkyl substituent, generating our first α -quaternary center **5.52** *in situ*. We further envisioned that **5.52** could undergo a thermal or Lewis acid promoted Claisen type rearrangement generating the second quaternary center, affording bis-quaternary ketones **5.53a** and/or **5.53b**. This unique

strategy would allow for the synthesis of a diversely substituted ketones, due to the ability to readily vary the nucleophile source, alongside aromatic, aliphatic, and allyl substituents.

Previous Work



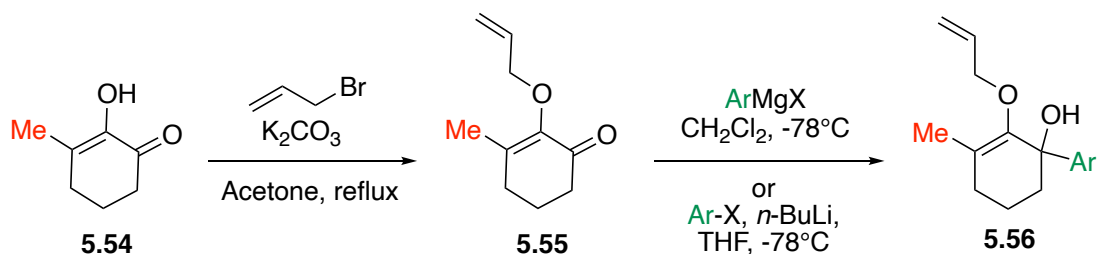
Proposed Synthesis of α,α' -Bisquaternary Ketones



Scheme 5.19 Our Proposed Synthesis of α,α' -Bis-Quaternary Ketones

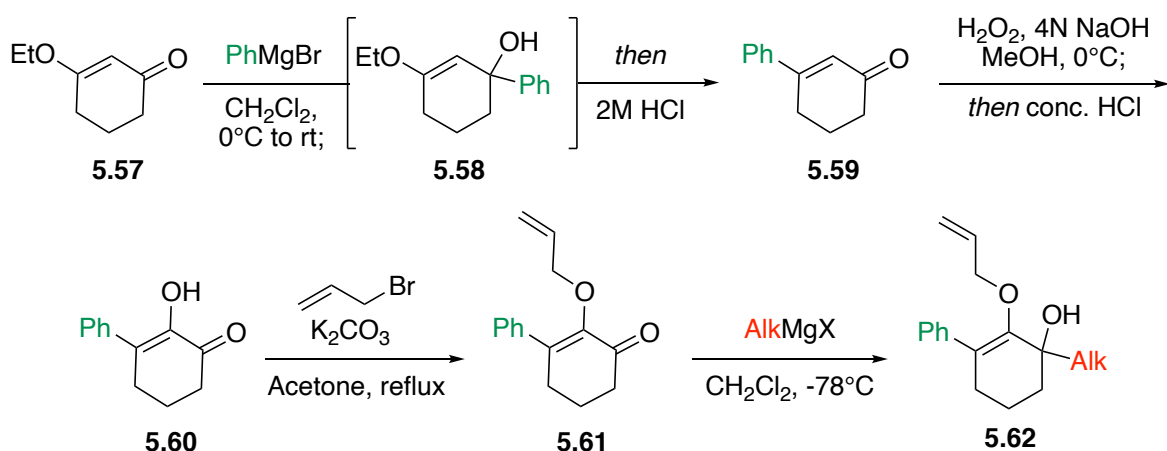
5.7 Synthesis of α -Hydroxy Allylenolates

In general, the preparation of our desired six-membered α -hydroxy allylenolate **5.56** can be achieved in just two steps from commercially available 1,2-cyclohexene dione **5.54** (Scheme 5.20). Initial allyl protection of 1,2-dione **5.54** readily furnished allyl protected enol ether **5.55**. Furthermore, introduction of aromatic substituents to afford our desired α -hydroxy allylenolates **5.56** could be generated through two different pathways, either by 1,2-nucleophilic addition using a Grignard reagent or through halogen-lithium exchange with an aryl halide and *n*-butyl lithium.



Scheme 5.20 Primary Route to the Synthesis of α -Hydroxy Allylenolates

While our initial route to the desired starting material allowed for introduction of a variety of aromatic and allyl substituents, it was limited to methyl as an aliphatic group. To overcome this limitation, we devised an alternative route to our desired starting material to accommodate other aliphatic substituents as depicted in Scheme 5.21. Starting with enol ether **5.57**, treatment with phenyl magnesium bromide resulted in the formation of alcohol **5.58** which upon quenching the reaction with 2M HCl, elimination and hydrolysis of intermediate **5.58** successfully generating α,β -unsaturated ketone **5.59**. Subsequent epoxidation of α,β -unsaturated ketone **5.59** with H_2O_2 and NaOH followed by treatment with concentrated HCl readily afforded dione **5.60**. Allyl protection of the crude dione **5.60** and subsequent incorporation of an aliphatic substituents with

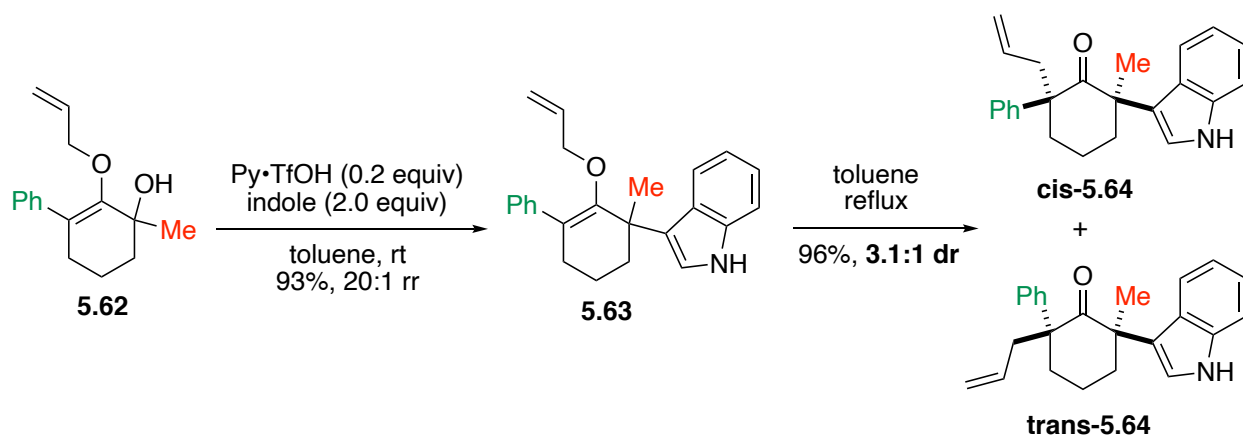


Scheme 5.21 Secondary Route to the Synthesis of α -Hydroxy Allylenolates

various Grignard reagents to ketone **5.61** effectively produced our desired α -hydroxy enol ether **5.62**. It is important to note that other aromatic Grignard reagents were compatible with this route.

5.8 Initial Investigations into the Synthesis of α, α' -Bis-Quaternary Ketones

As indicated in Scheme 5.22, our preliminary investigations into generating bis-quaternary ketones began with using α -hydroxy allylenolate **5.62** substituted with methyl and phenyl group as our model substrate. Following Kartika's previous conditions, we treated α -hydroxy allylenolate **5.62** with catalytic Py•TfOH in toluene; in the presence of indole, the first α -quaternary center **5.63** was successfully generated in 93% yield as a single regioisomer.¹⁹¹ To install the second α -quaternary center, indoyl allylvinyl ether **5.63** was subjected to thermal rearrangement in toluene at reflux. This presumed Claisen rearrangement successfully furnished out desired α, α' -bis-quaternary ketones **cis-5.64** and **trans-5.64** as a 3.1:1 mixture of separable diastereomers. The relative stereochemistry of the major diastereomer **cis-5.64** was unambiguously assigned using X-ray crystallography, in which the phenyl and indole groups are in a cis relationship. Furthermore, these aromatic substituents were both oriented in the axial positions of the cyclohexanone moiety.



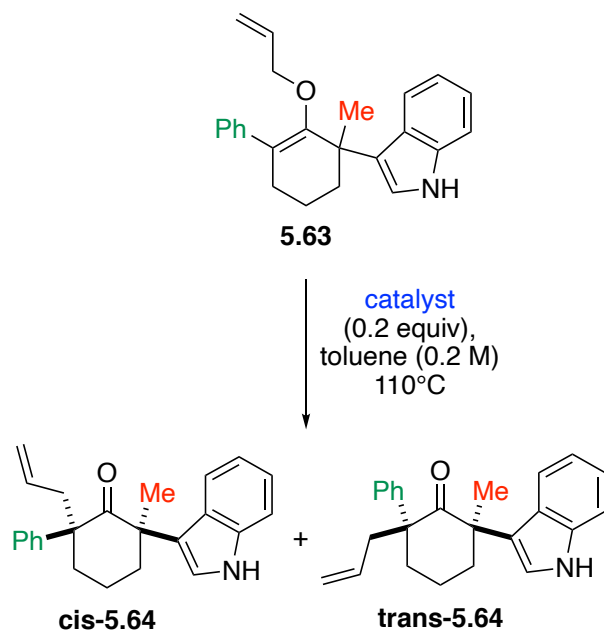
Scheme 5.22 Preliminary Studies in the Synthesis of α, α' -Bis-Quaternary Ketones

With these encouraging results, we questioned if we could control the diastereoselectivity of our rearrangement and focused our efforts towards improving the intrinsic diastereoselectivity observed. We hypothesized that the use of either an oxyphilic or a π -Lewis acidic additive could control the stereochemical outcome of the rearrangement. Our rationale is that complexation between the Lewis acid and allylvinyl ether **5.63** could hypothetically result in further differentiation in the activation energy of the two competing Claisen transition states, thus leading to the formation of a single diastereomer. As described in Section 5.3, there are precedents in which Lewis acid additives were employed to promote Claisen rearrangements.

Our efforts to control the diastereoselectivity of the Claisen rearrangement is summarized in Table 5.2, in which we subjected indoyl allylvinyl ether intermediate **5.63** to various catalytic Lewis acids in toluene at reflux. Subsequent analysis of the crude reaction mixture by ^1H NMR was preformed to determine the obtained diastereoselectivities. Beginning with $\text{BF}_3\cdot\text{OEt}_2$, AgOTf , and $\text{Cu}(\text{OTf})_2$ (entries 1-3), these relatively strong Lewis acids ultimately led to the rapid decomposition of **5.63** upon heating, resulting in unidentifiable mixtures. Furthermore, to evaluate the counter anion effects of coppers salts, we examined CuCl_2 , CuSO_4 , $\text{Cu}(\text{acac})_2$, and $\text{Cu}(\text{NO}_3)_2\cdot 6\text{H}_2\text{O}$ (entries 5-8) and we observed only minor improvements in diastereoselectivity compared to the uncatalyzed reaction. Surprisingly, we noticed significant improvement in diastereoselectivity when the rearrangement of indoyl allylvinyl ether **5.63** was performed in the presence of either $\text{Cu}(\text{BF}_4)_2\cdot 6\text{H}_2\text{O}$ or $\text{Cu}(\text{MeCN})_4\text{BF}_4$. ^1H NMR analysis of these crude reaction mixtures detected that α,α' -bis-quaternary ketone **cis-5.64** was produced cleanly as a single diastereomer (>20:1). To understand the significance of the copper tetrafluoroborate counter anion in the observed diastereoselectivity, we employed other tetrafluoroborate salts such as NaBF_4 ,

AgBF₄, and NiBF₄ which resulted in inferior diastereoselectivities compared to that of Cu(BF₄)₂•6H₂O and Cu(MeCN)₄BF₄.

Table 5.2 Screening of Lewis Acid Additives



entry	catalyst	crude dr ^[a] (cis : trans)
1	—	3.1 : 1
2	BF ₃ •OEt ₂	complex mixture
3	AgOTf	complex mixture
4	Cu(OTf) ₂	complex mixture
5	CuCl ₂	3.5 : 1
6	CuSO ₄	3.2 : 1
7	Cu(acac) ₂	3.6 : 1
8	Cu(NO ₃) ₂ •6H ₂ O	3.5 : 1
9	Cu(BF₄)₂•6H₂O	20 : 1
10	Cu(MeCN)₄BF₄	20 : 1
11	AgBF ₄	5.0 : 1
12	NaBF ₄	3.4 : 1
13	NiBF ₄ •6H ₂ O	5.1 : 1

^[a] Diastereomeric ratio was determined by ¹H NMR analyses of crude reaction mixture.

5.9 Reaction Optimization

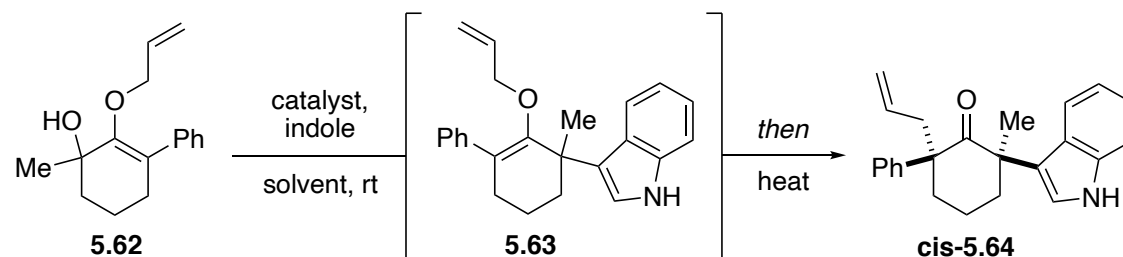
Our reaction optimization for the one-pot synthesis of α,α' -bis-quaternary ketone **cis-5.64** is detailed in Table 5.4. Observing that both Cu(BF₄)₂•6H₂O and Cu(MeCN)₄BF₄ catalysts exhibited diastereocontrol in the Claisen rearrangement, we proposed that either of these Lewis acid catalysts could promote ionization of α -hydroxy allylenolate **5.62**. As depicted in entries 1-2, we exposed α -hydroxy allylvinyl ether **5.62** to both Cu(BF₄)₂•6H₂O or Cu(MeCN)₄BF₄ catalysts in toluene (0.2 M) to presumably generate our unsymmetrical oxyallyl cation. Subsequent nucleophilic capture with indole at room temperature which afforded the first α -quaternary center

5.63 in a regioselective manner. Upon complete consumption of the **5.62** as monitored by TLC, the reaction mixtures were then heated to reflux to allow for the Claisen rearrangement to occur.

To our delight, we observed that using $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ resulted in formation of ketone **cis-5.64** as single diastereomer. The reaction with $\text{Cu}(\text{MeCN})_4\text{BF}_4$ surprisingly gave lower selectivities (13:1 dr) than $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$. In addition, under $\text{Cu}(\text{MeCN})_4\text{BF}_4$ activation we observed the formation of α -quaternary center intermediate **5.63** required a much longer reaction time compared to that of $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$. This prolonged reaction time in generation of **5.63** was attributed to the visible insolubility of the catalyst in toluene at room temperature. To circumvent the observed lack of reactivity, we exchanged the reaction solvent from toluene to dichloroethane (DCE), in an attempt to increase catalyst solubility. As demonstrated in entries 3-4, we observed that $\text{Cu}(\text{MeCN})_4\text{BF}_4$ noticeably outperformed $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ readily affording our desired ketone **cis-5.64** in 94% yield with improved diastereoselectivity of >20:1 in DCE.

As $\text{Cu}(\text{MeCN})_4\text{BF}_4$ demonstrated increased reactivity and selectivity in DCE, our studies continued with optimizing the molar equivalences of both $\text{Cu}(\text{MeCN})_4\text{BF}_4$ and indole (entries 5-7). Surprisingly, upon reducing the equivalences of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ to 0.1 and 0.05 we did not observe decreased yields, although extended rate of the Claisen rearrangement were noted. Unsurprising, decreasing the indole concentration proved detrimental, only yielding **cis-5.64** in 74% yield (entry 7). As previously reported, the residual water produced during ionization of α -hydroxy enol ether under catalytic Brønsted acidic conditions potentially assists in the stabilization of emerging silyloxy allyl cation intermediates.⁶⁴ To evaluate whether this phenomenon was relevant to this copper catalyzed reaction, we performed our experiment under anhydrous conditions in the presence of 4 Å molecular sieves (entry 8). As expected, the yield of this reaction

Table 5.3 Reaction Optimization Studies



entry	catalyst	catalyst equiv	solvent	indole equiv	heat temp (°C)	reaction time (h)		yield (%) ^[a]	dr ^[b]
						rt	heat		
1	Cu(BF ₄) ₂ •6H ₂ O	0.2	toluene	1.5	110	2	4	60	20 : 1
2	Cu(MeCN) ₄ BF ₄	0.2	toluene	1.5	110	184	6	92	13 : 1
3	Cu(BF ₄) ₂ •6H ₂ O	0.2	DCE	1.5	83	1	22	31	20 : 1
4	Cu(MeCN)₄BF₄	0.2	DCE	1.5	83	24	16	94	20 : 1
5	Cu(MeCN) ₄ BF ₄	0.1	DCE	1.5	83	28	20	86	20 : 1
6	Cu(MeCN) ₄ BF ₄	0.05	DCE	1.5	83	28	38	92	20 : 1
7	Cu(MeCN) ₄ BF ₄	0.2	DCE	1.1	83	24	21	74	20 : 1
8	Cu(MeCN) ₄ BF ₄	0.2	DCE	1.5	83	78	62	60 ^[c]	20 : 1
9	Cu(MeCN) ₄ OTf	0.2	DCE	1.5	83	0.5	2	complex mixture ^[d]	-
10	Cu(MeCN) ₄ PF ₆	0.2	DCE	1.5	83	16	48	complex mixture ^[d]	-

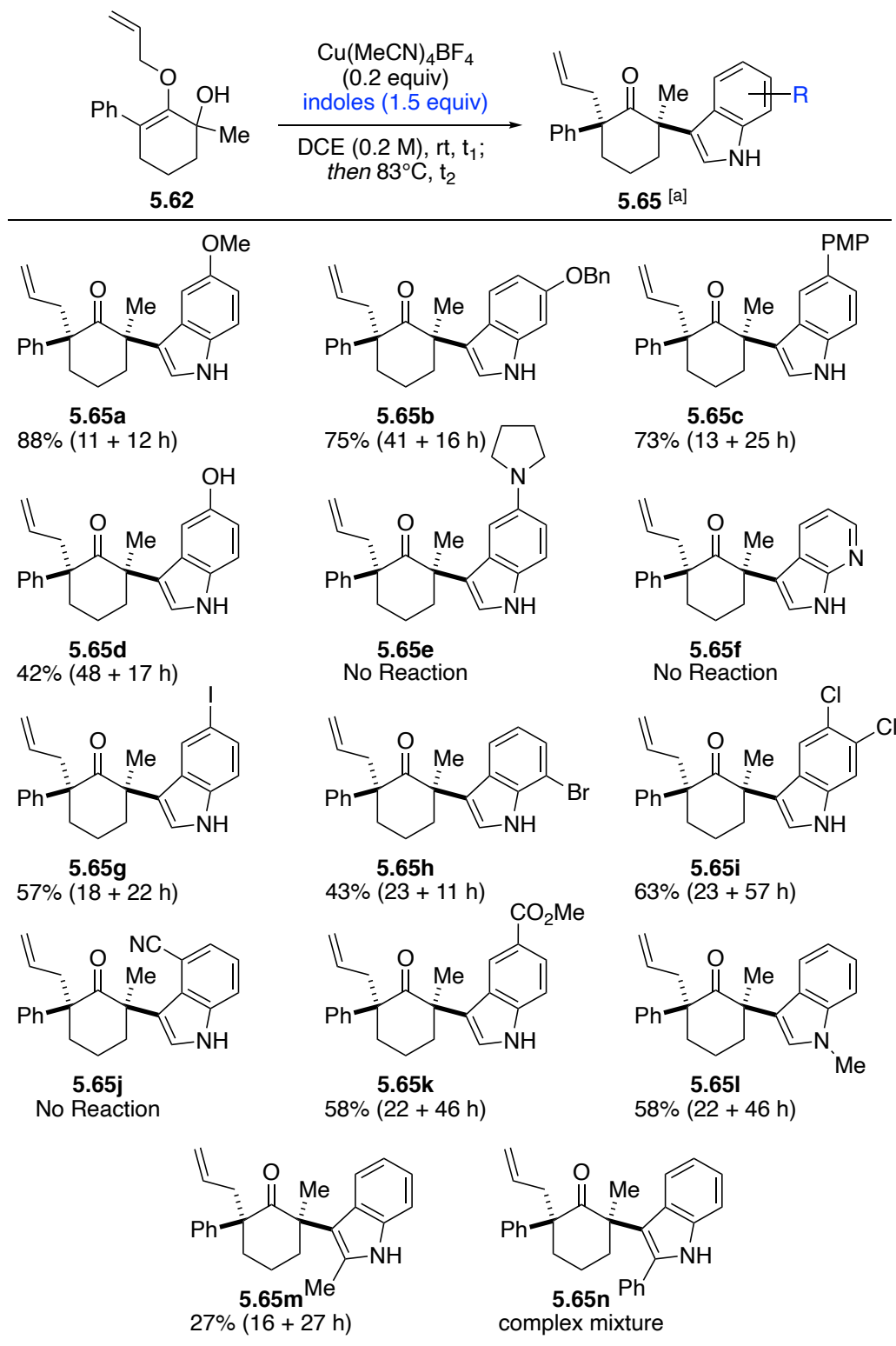
^[a] Isolated yield after column chromatography. ^[b] Diastereomeric ratio was determined by ¹H NMR analyses of the crude reaction mixture.

^[c] 4 Å Molecular sieves added to reaction mixture. ^[d] Upon heating to 83 °C an unidentifiable complex mixture was formed

substantially dropped to 60% yield, while extensive reaction times for both nucleophilic addition and the Claisen rearrangement were observed. Finally, to confirm the tetrafluoroborate counter anion is essential for reaction to proceed efficiently, we employed $\text{Cu}(\text{MeCN})_4\text{PF}_6$ and $\text{Cu}(\text{MeCN})_4\text{OTf}$ salts (entries 9-10). While both catalysts easily promoted ionization of α -hydroxy allylvinyl ether **5.62**, generating α -indolyl allylvinyl ether **5.63**; but upon heating to reflux the intermediates unexpectedly underwent decomposition. Ultimately, our reaction conditions are shown in entry 4, using 0.2 equiv of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ and 1.5 equiv of indole in DCE.

5.10 Evaluation of Indole Nucleophiles

With optimized conditions in hand for both ionization of α -hydroxy enol ether and the proposed Claisen rearrangement, we continued with investigating the scope of substituted indoles towards the synthesis of diverse α,α' -bis-quaternary ketones (Scheme 5.23). Beginning with electron-rich indoles, we exposed 5-methoxy, 6-benzyloxy, and 5-*p*-methoxyphenyl substituted indoles to our optimized conditions which successfully afforded ketones **5.65a-5.65c** as single cis-diastomers 88%, 75%, and 63% yields, respectively. While **5.65d** was readily synthesized in 42% yield from 5-hydroxyindole, the use of 5-pyrrolidine indole and azaindole failed to produce the desired ketones **5.65e** and **5.65f**. We observed that in the presence of these nucleophiles that ionization of **5.62** was unsuccessful, suggesting that this nucleophile might have interfered with the copper catalyst. Furthermore, halogen-containing indoles were also found to be compatible under our optimized conditions successfully generating adducts **5.65g-5.65i** in good yields. Electron-deficient indoles appeared to be problematic under our conditions as 4-cyanoindole yielded no reaction, while methyl-5-carboxylate indole produced the desired ketone **5.65k** in 58% yield. Moreover, protected *N*-methylindole could be employed which furnished **5.65l** in 73% yield. Alas, we observed a substantial decrease in yield when sterically congested 2-methylindole



[a] Isolated yield after column chromatography. Only one diastereomer (20:1 dr) was detected in the crude reaction mixture by ^1H NMR analyses. [b] Time broken down.

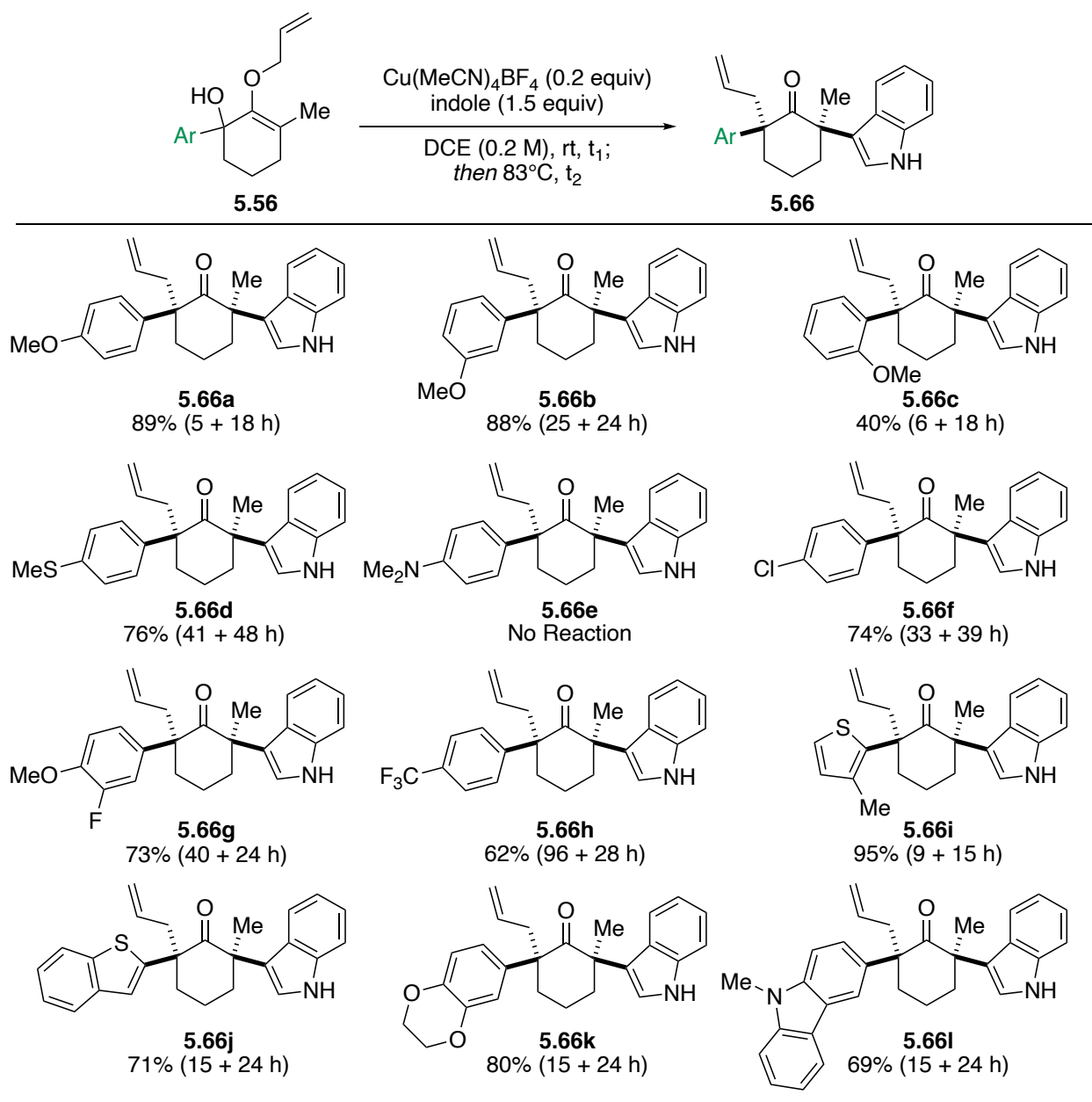
Scheme 5.23 Scope of Substituted Indole Nucleophiles

was employed, resulting in the formation of ketone **5.65m** in 27% yield, while 2-phenylindole resulted in formation of a complex mixture upon heating. Further Investigation into the suitability of other carbon and heteroatom nucleophiles yielded unfruitful, as capture of the proposed oxyallyl cationic intermediate was unsuccessful under our optimized conditions. Notably, we observed that all α,α' -bis-quaternary ketones **5.65a-5.65m** were isolated as single diastereomers and relative stereochemistry was unambiguously assigned from x-ray crystallography when the ketone adduct was a crystalline solid.

5.11 Scope of Aromatic α -Substituted α -Hydroxy Allylenolates

Continuing our investigation into the scope of our developed method, we next studied the effect of aromatic substituent at the α -carbon of the α -hydroxy allylenolates (Scheme 5.24). Initial studies focused on substitution patterns within the phenyl ring. We observed that *p*-methoxyphenyl and *m*-methoxyphenyl substituted α -hydroxy allylenolates **5.56** efficiently produced the corresponding ketones **5.66a** and **5.66b** in 89% and 88% yields. Unfortunately, we noted that *o*-methoxyphenyl resulted in a significant erosion in the yield of **5.66c**, while still maintaining diastereoselectivity. While electron-rich thioether substituted arene readily produced ketone **5.66d** in 76% yield, we observed that dimethylaminophenyl group failed to afford **5.66e**, resulting in only recovered starting material. Similar to that of 5-pyrrolidine and azaindole nucleophiles, the dimethylaminophenyl may have inadvertently interfered with the copper catalyst, prohibiting ionization of the α -hydroxy group. Further evaluation of *p*-chlorophenyl, *m*-fluoro-*p*-methoxyphenyl, and *p*-trifluoromethylphenyl aromatic groups led to the corresponding ketones **5.66f-5.66h** in good yields. Moreover, heteroaromatic substituents, such as 3-methyl thiophene, benzothiophene, benzodioxane, and *N*-methyl carbazole were well tolerated, readily producing ketone adducts **5.66i-5.66l** in 69-95% yields. Similar to our results in Scheme 5.23, all α,α' -bis-

quaternary ketone products **5.66a-5.66l** were generated as a single diastereomer, as determined by ^1H NMR analysis and the relative stereochemistry was unambiguously assigned from x-ray crystallography when the ketone was a crystalline solid.



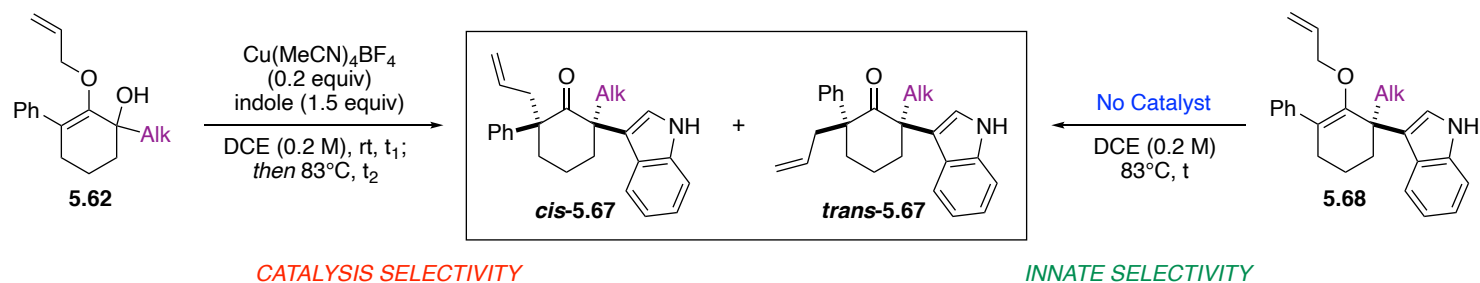
[a] Isolated yield after column chromatography. Only one diastereomer (20:1 dr) was detected in the crude reaction mixture by ^1H NMR analyses. [b] Time broken down.

Scheme 5.24 Evaluation of Aromatic Substituents

5.12 Exploration of Aliphatic α -Substituted α -Hydroxy Allylenolates

Furthermore, we examined the α -aliphatic substituent of the α -hydroxy allylenolate **5.62** and how it affects the stereoselectivity of the proposed Claisen rearrangement (Table 5.5). As depicted in entries 1-3, we systematically increased the aliphatic chain length from methyl to ethyl, and then to *n*-propyl, through the use of substrates **5.62a-5.62c**. To our surprise, the increase in chain length immediately resulted in decreased diastereoselectivities of the proposed rearrangement, resulting in the formation of both *cis*- and *trans*-diastereomers, with a slight bias favoring the formations of **trans-5.66b** and **trans-5.66c** as the major product. To determine if the copper catalyst was indeed influencing the diastereoselectivity, these results were then compared to the innate diastereoselectivities, which were obtained via thermal rearrangement of the respective α -indolyl allylvinyl ethers **5.67b** and **5.67c**. To our surprise, these uncatalyzed conditions also exhibited selectivity favoring the formation of **trans-5.66b** and **trans-5.66c**. Interestingly, we observed that upon treatment of allyl substituted α -hydroxy allylenolate **5.62d** to our catalyst conditions resulted in formation of the **cis-5.66c** as the major diastereomer, while the innate conditions favored the formation of **trans-5.66c** (entry 4). Moreover, as the steric size was further increased to the *n*-octyl group **5.62e** (entry 5), both the catalyzed and uncatalyzed reactions resulted in similar selectivities, favoring the formation of **trans-5.66d** diastereomer. Remarkably, introduction of a cyclopropyl group **5.62e** and **6.67e** under both catalyzed and innate rearrangement conditions resulted in formation of **cis-5.66e** as the major diastereomer. While our catalyst conditions did not exhibit exceptional diastereoselectivity in the rearrangements with other aliphatic groups, we observed a substantial rate enhancement of the rearrangements in the presence of Cu(MeCN)₄BF₄ in comparison to the innate rearrangements.

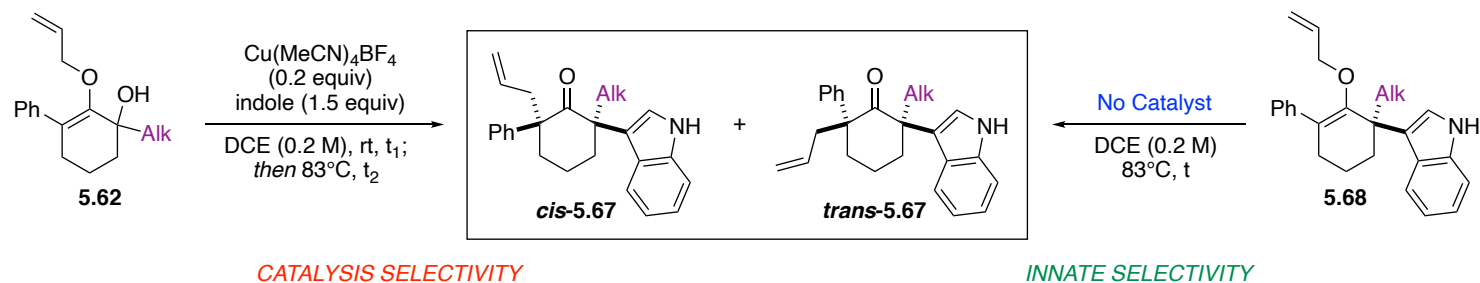
Table 5.5 Evaluation of Aliphatic Substituents



entry	substrate	time ($t_1 + t_2$ h)	<i>cis</i> : <i>trans</i> crude ratio ^[b] <i>cis</i> + <i>trans</i> yield ^[a]	products	<i>cis</i> : <i>trans</i> crude ratio ^[b] <i>cis</i> + <i>trans</i> yield ^[a]	time (t h)	substrate
1		24 + 16	20 : 1 94% + 0%		5.0 : 1 70% + 12%	112	
2		20 + 42	1 : 1.1 32% + 32%		1 : 1.7 37% + 62%	114	
3		16 + 48	1 : 1.2 38% + 41%		1 : 2.0 25% + 56%	114	

^[a] Isolated yield after column chromatography. ^[b] Diastereomeric ratio was determined by ^1H NMR analyses of crude reaction mixture.

Table 5.5 Evaluation of Aliphatic Substituents (continued)

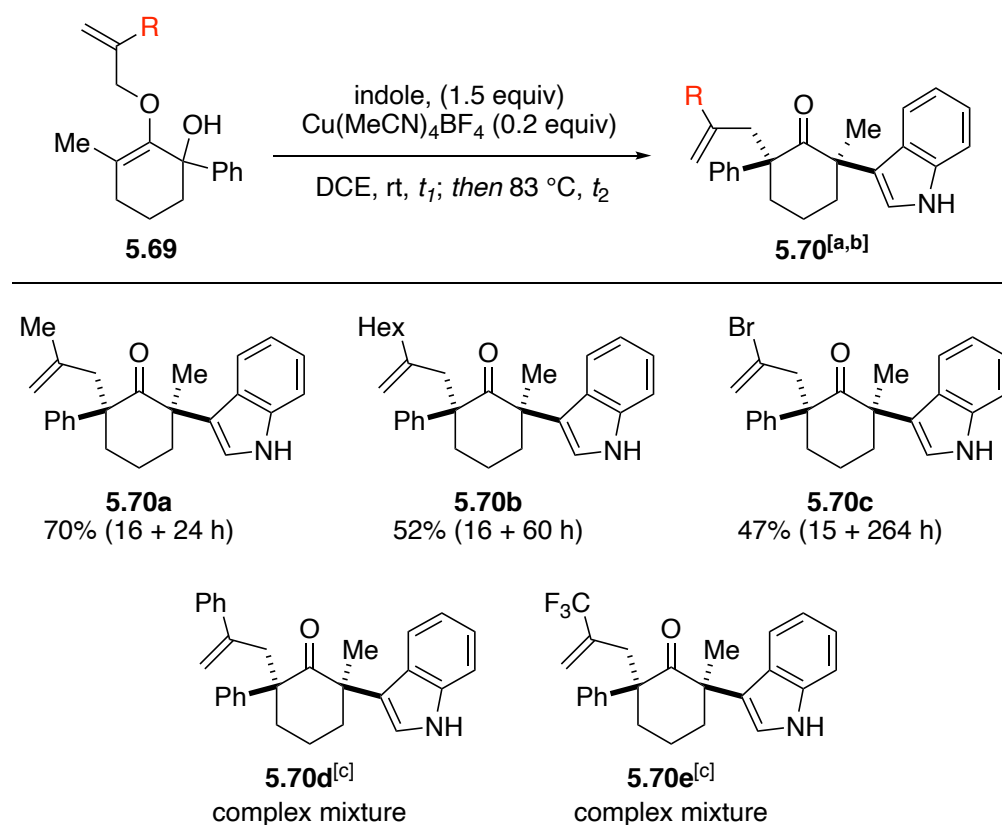


entry	substrate	time ($t_1 + t_2$ h)	<i>cis</i> : <i>trans</i> crude ratio ^[b] <i>cis</i> + <i>trans</i> yield ^[a]	products	<i>cis</i> : <i>trans</i> crude ratio ^[b] <i>cis</i> + <i>trans</i> yield ^[a]	time (t h)	substrate
4		40 + 72	2.6 : 1 49% + 23%	+	1 : 1.8 30% + 56%	136	
5		6 + 24	1 : 1.9 38% + 41%	+	1 : 1.7 28% + 57%	72	
6		2 + 24	1.9 : 1 45% : 25%	+	2.7 : 1 76% : 25%	136	

^[a] Isolated yield after column chromatography. ^[b] Diastereomeric ratio was determined by ^1H NMR analyses of crude reaction mixture.

5.13 Scope of Allyl Groups

Lastly, our studies toward understanding the scope of our reaction focused on examining substituent effects on the O-allyl moiety as depicted in Scheme 5.25. We began by introducing methyl and *n*-hexyl groups in the internal carbon of the allyl group. Exposure of these α -hydroxy allylenolates to our optimized conditions produced the corresponding ketones **5.70a** and **5.70b** in 70% and 52% yields respectively, each as a single diastereomer. To our surprise Bromoallyl-containing substrate **5.68** was also tolerated, furnishing ketone **5.70c** in 46 % yield with >20:1 dr despite the prolonged reaction time observed during the proposed Claisen rearrangement step.



^[a] Isolated yield after column chromatography. Only one diastereomer (20:1 dr) was detected in the crude reaction mixture by ^1H NMR analyses. ^[b] Time broken down.

^[c] Complex mixture was formed upon warming to reflux.

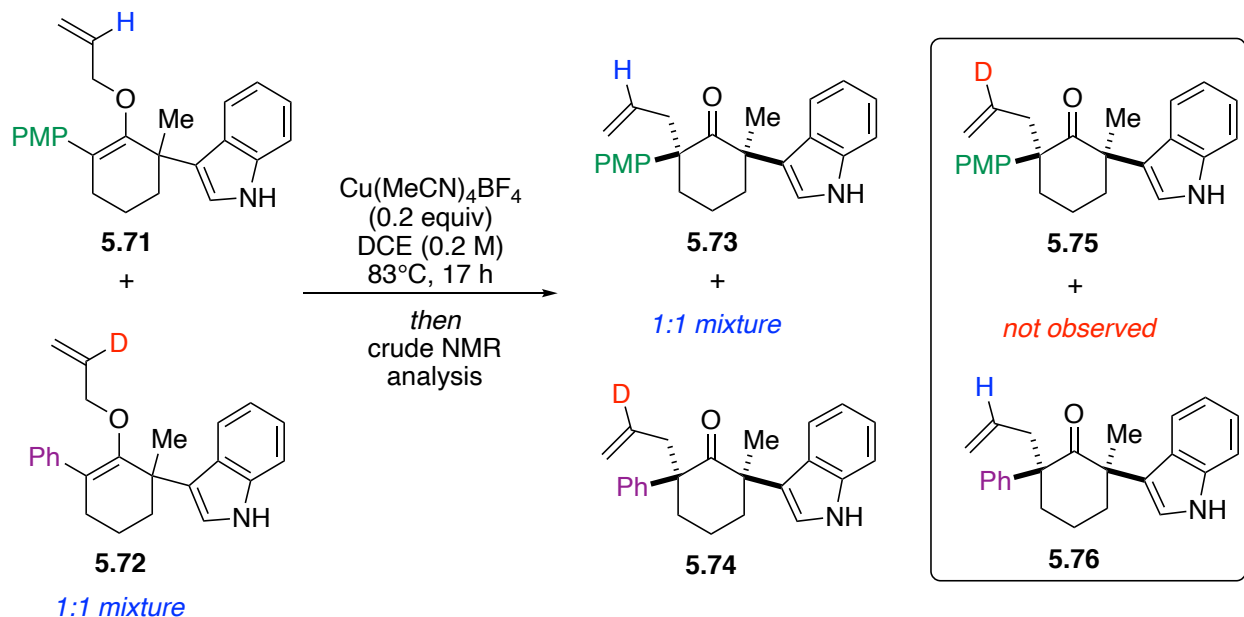
Scheme 5.25 Scope of O-Allyl Groups

Unfortunately, introduction of sterically congested phenyl-allyl and deactivating trifluoromethylallyl substrates **5.68** resulted in the formation of complex mixtures. While we observed that addition of indole to construct the first α -quaternary center readily occurred with these starting materials; decomposition rapidly occurred when the reaction mixture was heat.

5.14 Mechanistic Investigations

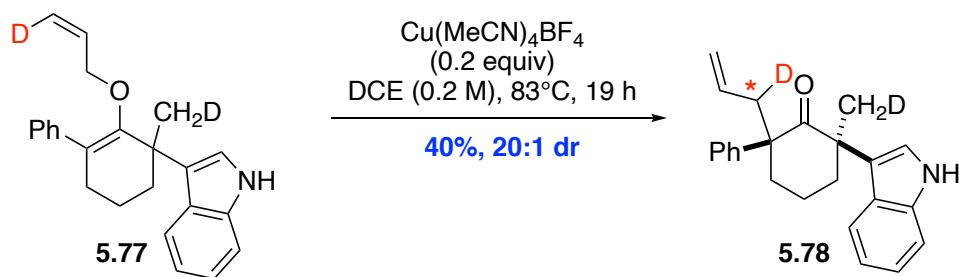
With an adequate scope of substrates in hand we turned our focus to investigate the mechanism of our unprecedented copper promoted rearrangement, we set to develop a series of experiments to determine if the reaction mechanism was indeed a Claisen rearrangement. Initially, to understand if our observed allyl migration occurs *via* an intra or intermolecular process, we set to develop a crossover experiment utilizing two substrates with distinctive substitution patterns on the allyl and aromatic fragments. We hypothesize that if the allyl fragment gets delivered through an intermolecular process four products should be observed via crossover processes. Alternatively, an intramolecular process would result in the formation of two products.

For this experiment, we propositioned that indole adducts **5.71** and **5.72** with incorporation of a deuterium into the allyl group with *p*-methoxyphenyl substituent will be useful starting materials for this experiment (Scheme 5.26). These two dissimilar intermediates would provide distinguishable chemical signals that could easily allow us to decipher if allyl-allyl crossover products **5.75** or **5.76** were generated through the use of ^1H NMR. To perform the crossover experiment, we subjected a 1:1 mixture of **5.71** and **5.72** to 0.2 equiv of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ in DCE at 83 °C (See Chapter 6.5 for synthesis of **5.71** and **5.72**). Upon completion of the reaction, the crude mixture was analyzed by ^1H NMR yielding a 1:1 mixture of ketones **5.73** and **5.74** with no crossover products **5.75** and **5.76** observed.



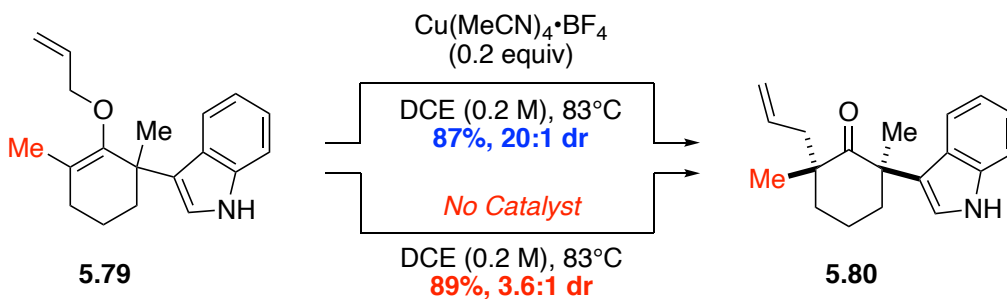
Scheme 5.26 Crossover Experiment

Additionally, to determine if the reaction does indeed proceed through a [3,3]-sigmatropic rearrangement and not a [1,3]-sigmatropic process, we designed a substrate with a terminal allyl substituent providing the necessary support for understanding the mode of rearrangement. We proposed that if rearrangement proceeds through a [3,3] process then the terminal substituent should be delivered to the internal methylene of the allyl group in a stereospecific manner, while under a [1,3]-rearrangement the substituent would remain at the terminal position of the allyl moiety. As depicted in Scheme 5.27, to test our hypothesis we subjected deuterated substrate **5.77** to our rearrangement conditions which successfully generated ketone **5.78** as a single diastereomer. Under these conditions we observed that the deuterium atom was transferred to the internal methylene carbon of the allyl substituent. As we know the olefin geometries for both allyl enol ether moiety **5.77**, the relative stereochemistry of the deuterium and phenyl could provide insight on the rearrangements possible transition state. Current efforts to deduce the resulting stereochemistry of the deuterium atom are underway.



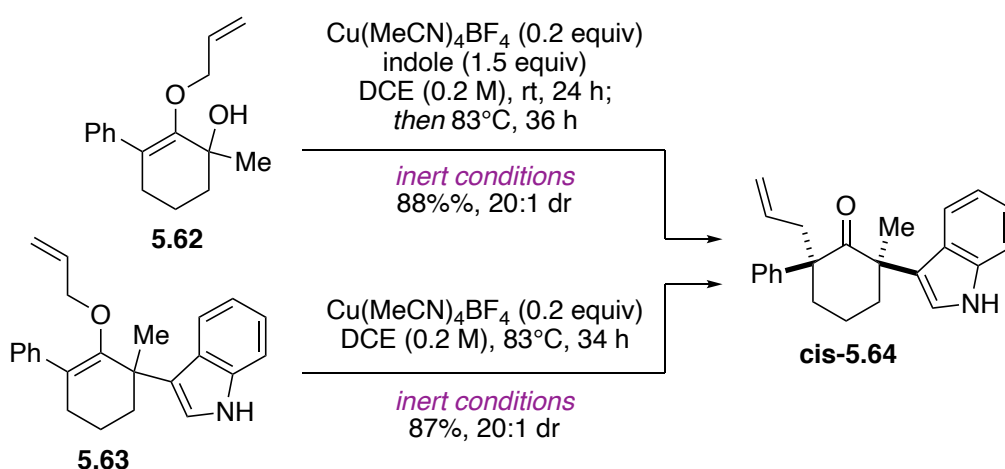
Scheme 5.27 Rearrangement of Terminally Substituted Allyl Group

Through the course of our studies we observed that the formation of the *cis* bis-quaternary ketones as major diastereomer. The conformation of the aromatic and indole substituents are located in axial positions of the *cis*-cyclohexanones as confirmed by X-ray crystallography. The axial orientation of these substituents suggests that π -stacking interaction may be the driving force for the observed *cis*-selectivity. To probe this hypothesis, we removed the aromatic substituent and replaced it with a methyl group as shown in Scheme 5.28. We observed that rearrangement of dimethyl indolyl adduct **5.79** with $\text{Cu}(\text{MeCN})_4\text{BF}_4$ resulted in the formation of ketone **5.80** as a single diastereomer; however, under in the absence of a catalyst **5.80** was isolated in a 3.6:1 mixture of diastereomers. This remove of the aromatic substituent, indicated that π -stacking interaction may not be the primary driving force for the formation of the *cis*-ketones.



Scheme 5.28 Removal of the Aromatic Substituent

As observed during the course of our optimization studies, both $\text{Cu}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ and $\text{Cu}(\text{MeCN})_4\text{BF}_4$ exhibited diastereoselective control during the proposed Claisen rearrangement. Ultimately, choosing $\text{Cu}(\text{MeCN})_4\text{BF}_4$ as our catalyst of choice, we set to rule out the possibility of our copper catalyst being oxidized to $\text{Cu}(\text{II})$ by atmospheric oxygen. While our reactions are usually performed under atmospheric conditions, we performed a series of reaction under inert conditions (Scheme 5.29). We executed our single pot reaction alongside the isolated rearrangement of **5.63** under inert conditions and observed the formation of *cis*-**5.64** as a single diastomer under both reactions. These set of reactions suggest that atmospheric oxygen does not further oxidize $\text{Cu}(\text{MeCN})_4\text{BF}_4$.



Scheme 5.29 Optimized Reactions Under Inert Conditions

As a result of our mechanistic investigations we propose that our allyl rearrangement proceed through a Claisen type rearrangement. This hypothesis is supported by the experiments depicted in Scheme 5.29 and 5.30. First, our crossover reaction (Scheme 5.29) resulted in the formation of only two bis-quaternary ketones, with no observed scrambling of allyl substituents. Suggesting that the rearrangement proceeds through an intramolecular process, which coincides

with proposed Claisen rearrangements mechanisms. Secondly, as depicted in Scheme 5.30 the rearrangement of the terminal deuterated substrate resulted in deuterium atom transfer to the internal methylene of the allyl group in a stereospecific manner which is in agreement with the known Claisen rearrangements. While our mechanistic studies suggest that our reaction proceeds through a Claisen rearrangement, the origin of diastereoselectivity is currently unknown. As copper can act as either an oxyphilic or a π -Lewis acid, there are three possible modes of activation under consideration as depicted in Figure 5.1, $\text{Cu}(\text{MeCN})_4\text{BF}_4$ activation of the oxygen of the enol ether **5.81**, or **5.82** and **5.83** in which the π -bonds are activated by the copper species. Most reports of copper catalyzed Claisen rearrangements detail copper (II) acting as oxyphilic Lewis acid to promote the rearrangement (See Section 5.3), and to the best of our knowledge there is no report of a copper (I) promoted reaction.¹³ The exact role of how $\text{Cu}(\text{MeCN})_4\text{BF}_4$ promotes and controls the diastereoselectivity of the Claisen rearrangement is currently unknown and further computational work is currently underway in collaboration with the Kumar group at Louisiana State University.

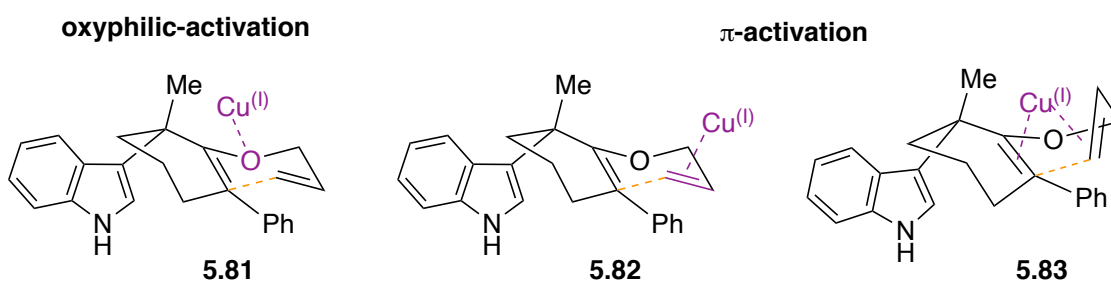


Figure 5.1 Possible Modes of Copper Activation

5.15 Conclusion

This chapter summarizes the Claisen rearrangement and the use of copper catalysts to promote and influence the diastereoselectivity and enantioselectivity of these sigmatropic

rearrangements for the synthesis of complex molecular scaffolds. Moreover, while there are numerous strategies to construct α -quaternary ketones, methods to access α,α' -bis-quaternary are limited. Current methods to access α,α' -bis-quaternary rely on the use of symmetrical ketone precursors and suffer for poor diastereoselectivities. Given this limitation we have successfully reported a diastereoselective synthesis of α,α' -bis-quaternary enabled by a $\text{Cu}(\text{MeCN})_4\text{BF}_4$ promoted regioselective nucleophilic capture of unsymmetrical di-substituted protected oxyallyl cations, followed by a novel diastereoselective Claisen rearrangement. This approach generated highly functionalized ketones in moderate to excellent yields, with most products generated in >20:1 dr, and relative stereochemistry assigned from x-ray crystallography. Several mechanistic studies were performed to determine the possible rearrangement mechanism. Further computational work to support the observed diastereoselectivity of our reaction is currently underway by the Kumar group at Louisiana State University. These results are currently unpublished, and the manuscript will be submitted for peer-review in due course.

Chapter Six: Experimental Procedures

6.1 General Information

Unless otherwise noted, all materials were used as received from commercial suppliers without further purification. All anhydrous reactions were performed using oven-dried or flame-dried glassware, which was then cooled under vacuum and purged with nitrogen gas. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), acetonitrile, toluene, and diethyl ether (Et_2O) were filtered through activated 3Å molecular sieves under nitrogen contained in an M-Braun Solvent Purification System. All reactions were monitored by EMD analytical thin layer chromatography (TLC Silica Gel 60 F₂₅₄, Glass Plates) and analyzed with 254 nm UV light and / or anisaldehyde – sulfuric acid or potassium permanganate treatment. Silica gel for column chromatography was purchased from Dynamic Adsorbents, Inc. or Sigma Aldrich (Flash Silica Gel 32-63µ).

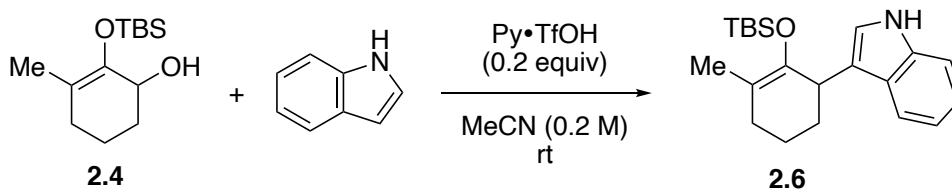
Unless otherwise noted, all ^1H and ^{13}C NMR spectra were recorded in CDCl_3 using a Bruker Ascend 400 spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C or Bruker Ascend 500 spectrometer operating at 500 MHz for ^1H and 125 MHz for ^{13}C . Chemical shifts (δ) are reported in ppm relative to residual CHCl_3 as an internal reference (^1H : 7.26 ppm, ^{13}C : 77.23 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), (septet), h (heptet), b (broad), and m (multiplet). FT-IR spectra were recorded on Bruker Tensor 27 spectrometer and OPUS 6.5 Data Collection Program, and absorption frequencies were reported in reciprocal centimeters (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.

6.2 Experimental Procedures for Chapter 2

6.2.1 Synthesis of α -Functionalized Silyl Enol Ethers

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1*H*-indole (2.6)



Procedure: Alcohol **2.4** (200 mg, 0.824 mmol) was dissolved in acetonitrile (4.0 mL). Indole (119 mg, 0.907 mmol) was then added, followed by pyridinium triflate (38 mg, 0.165 mmol). After stirring for 26 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 3% EtOAc in hexanes to give compound **2.6** in 82% yield (231 mg, 0.676 mmol) as a colorless oil.

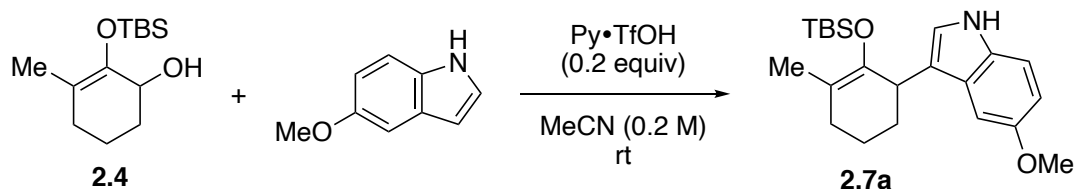
¹H NMR: (500 MHz, CDCl₃) δ = 7.91 (bs, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.95 (d, J = 2.2 Hz, 1H), 3.71 (s, 1H), 2.15 - 2.07 (m, 1H), 2.06 - 1.93 (m, 3H), 1.91 - 1.85 (m, 1H), 1.72 (s, 3H), 1.60 - 1.44 (m, 2H), 0.78 (s, 9H), -0.01 (s, 3H), -0.11 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 143.84, 136.49, 127.07, 123.06, 121.44, 118.93, 118.88, 118.75, 112.65, 110.95, 37.02, 31.14, 30.55, 25.77, 19.13, 18.25, 16.88, -3.86, -4.04.

IR: $\tilde{\nu}$ (cm⁻¹) = 3418, 3321, 2927, 1680, 1455, 1253, 1166, 1090, 1008, 939, 095, 828, 775, 735, 669, 582, 485.

HRMS (ESI-TOF) m/z : $(M+H)^+ = 342.2248$ calculated for $C_{21}H_{32}NOSi$; found 342.2257

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-5-methoxy-1*H*-indole (2.7a)



Procedure: Alcohol **2.4** (200 mg, 0.824 mmol) was dissolved in acetonitrile (4.0 mL). 5-Methoxyindole (134 mg, 0.907 mmol) was then added, followed by pyridinium triflate (38 mg, 0.165 mmol). After stirring for 23 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 2% EtOAc in hexanes to give compound **2.7a** in 71% yield (217 mg, 0.584 mmol) as a colorless oil.

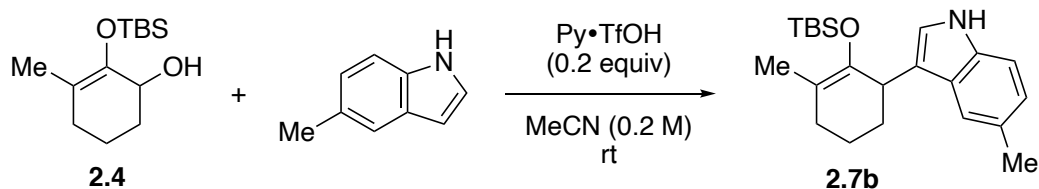
1H NMR: (400 MHz, $CDCl_3$) δ = 7.80 (bs, 1H), 7.22 (d, J = 8.7 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 6.92 (d, J = 2.1 Hz, 1H), 6.83 (dd, J = 8.7, 6.4 Hz, 1H), 3.86 (s, 3H), 3.63 (s, 1H), 2.15 - 1.81 (m, 4H), 1.71 (s, 3H), 1.61 - 1.43 (m, 2H), 0.77 (s, 9H), -0.03 (s, 3H), -0.12 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ = 153.65, 143.84, 131.72, 127.52, 123.93, 118.52, 112.58, 111.53, 111.36, 101.15, 55.96, 37.07, 31.11, 30.57, 25.77, 19.22, 18.25, 16.85, -3.86, -4.04.

IR: f (cm^{-1}) = 2928, 1680, 1483, 1251, 1196, 1041, 917, 830, 776.

HRMS (ESI-TOF) m/z : $(M+H)^+ = 372.2353$ calculated for $C_{22}H_{34}NO_2Si$; found 372.2363.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-5-methyl-1*H*-indole (2.7b)



Procedure: Alcohol **2.4** (200 mg, 0.824 mmol) was dissolved in acetonitrile (4.0 mL). 5-Methylindole (119 mg, 0.907 mmol) was then added, followed by pyridinium triflate (38 mg, 0.165 mmol). After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 1% EtOAc in hexanes to give compound **2.7b** in 80% yield (234 mg, 0.697 mmol) as a colorless oil.

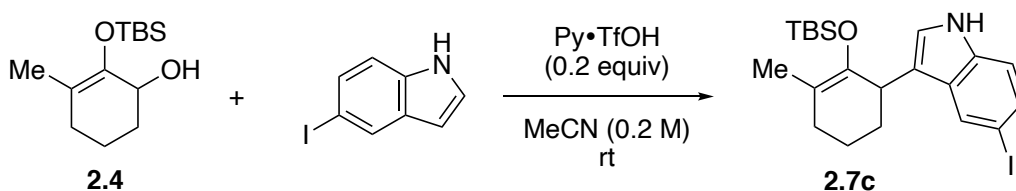
¹H NMR: (500 MHz, CDCl₃) δ = 7.81 (bs, 1H), 7.36 (s, 1H), 7.23 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 3.67 (s, 1H), 2.47 (s, 3H), 2.14 - 2.05 (m, 1H), 2.04 - 1.86 (m, 3H), 1.71 (s, 3H), 1.56 - 1.44 (m, 2H), 0.80 (s, 9H), -0.02 (s, 3H), -0.11 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 143.91, 134.84, 128.02, 127.29, 123.29, 123.02, 118.52, 118.17, 112.53, 110.59, 36.93, 30.95, 30.54, 25.80, 21.59, 19.00, 18.27, 16.86, -3.86, -4.00.

IR: f (cm⁻¹) = 3414, 2927, 2855, 1679, 1461, 1252, 1166, 942, 830, 776, 589.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 356.2404 calculated for C₂₂H₃₄NOSi; found 356.2405.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-5-iodo-1*H*-indole (**2.7c**)



Procedure: Alcohol **2.4** (224 mg, 0.924 mmol) was dissolved in acetonitrile (4.6 mL). 5-Iodoindole (248 mg, 1.02 mmol) was then added, followed by pyridinium triflate (42 mg, 0.185 mmol). After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then

directly purified with column chromatography using 100% hexanes to 5% EtOAc in hexanes to give compound **2.7c** in 59% yield (254 mg, 0.543 mmol) as a light pink solid.

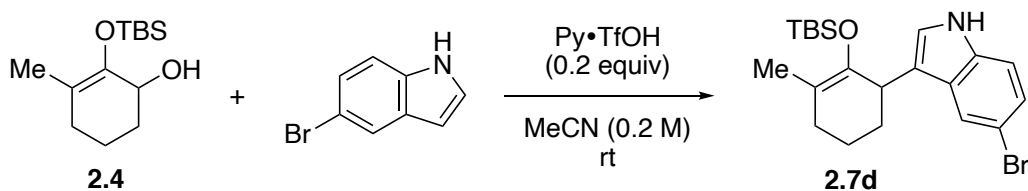
¹H NMR: (400 MHz, CDCl₃) δ = 7.98 (s, 1H), 7.92 (d, J = 1.8 Hz, 1H), 7.41 (dd, J = 8.4, 1.6 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.89 (dd, J = 2.4, 0.8 Hz, 1H), 2.16 - 1.89 (m, 2H), 11.88 - 1.78 (m, 1H), 1.73 (s, 3H), 1.56 - 1.42 (m, 1H), 0.79 (s, 9H), 0.01 (s, 3H), -0.09 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 143.60, 135.72, 129.97, 129.89, 127.99, 124.15, 118.45, 113.38, 113.24, 82.76, 37.14, 31.80, 31.40, 30.69, 25.98, 22.87, 19.31, 18.45, 17.12, 14.34, -3.77.

IR: $\tilde{\nu}$ (cm⁻¹) = 3426, 2927, 2854, 1680, 1454, 1349, 1319, 1253, 1165, 1090, 1005, 939, 906, 863, 828, 775, 731, 672, 653, 579, 492, 417.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 468.1214 calculated for C₂₁H₃₁INOSi; found 468.1222.

5-bromo-3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1*H*-indole (**2.7d**)



Procedure: Alcohol **2.4** (200 mg, 0.824 mmol) was dissolved in acetonitrile (4.0 mL). 5-Bromoindole (178 mg, 0.907 mmol) was then added, followed by pyridinium triflate (38 mg, 0.165 mmol). After stirring for 25 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 1% EtOAc in hexanes to give compound **2.4d** in 69% yield (239 mg, 0.568 mmol) as a light blue solid.

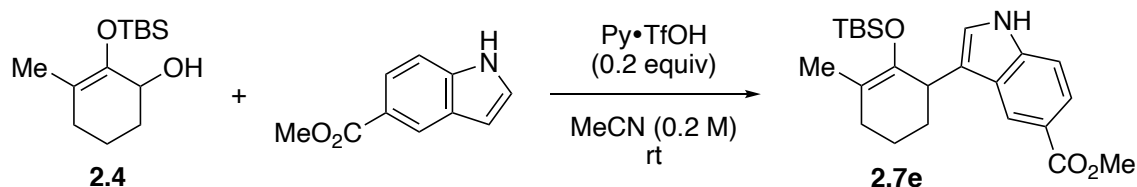
¹H NMR: (500 MHz, CDCl₃) δ = 7.95 (bs, 1H), 7.71 - 7.67 (m, 1H), 7.25 - 7.19 (m, 2H), 6.95 (s, 1H), 3.62 (s, 1H), 2.15 - 2.05 (m, 1H), 2.05 - 1.91 (m, 2H), 1.86 - 1.78 (m, 1H), 1.71 (s, 3H), 1.57 - 1.44 (m, 2H), 0.91 - 0.64 (m, 9H), -0.00 - -0.03 (m, 3H), -0.10 - -0.13 (m, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 143.36, 135.06, 128.83, 124.31, 121.48, 118.59, 113.12, 112.43, 112.34, 77.25, 77.00, 76.75, 36.98, 31.19, 30.49, 25.75, 19.15, 18.23, 16.89, -3.85, -4.00.

IR: $f(\text{cm}^{-1})$ = 3429, 2927, 2855, 1680, 1458, 1345, 1322, 1253, 1166, 1091, 1005, 939, 908, 884, 863, 227, 674, 582, 293.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 420.1353 calculated for C₂₁H₃₁BrNOSi; found 420.1360.

Methyl-3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1*H*-indole-5-carboxylate (2.7e)



Procedure: Alcohol **2.4** (180 mg, 0.742 mmol) was dissolved in acetonitrile (3.7 mL). Methyl indole-5-carboxylate (143 mg, 0.817 mmol) was then added, followed by pyridinium triflate (34 mg, 0.148 mmol). After stirring for 46 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 20% EtOAc in hexanes to give compound **2.7e** in 58% yield (173 mg, 0.584 mmol) as a white solid.

¹H NMR: (500 MHz, CDCl₃) δ = 8.36 – 8.34 (m, 1H), 8.11 (s, 1H), 7.88 (dd, J = 8.6, 1.6 Hz, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 2.2 Hz, 1H), 3.93 (s, 3H), 3.72 (bs, 1H), 2.15 - 2.06 (m, 1H),

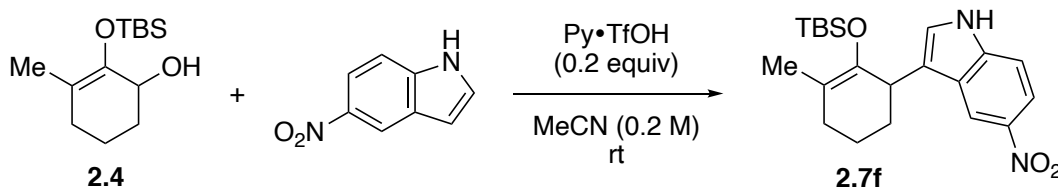
2.05 - 1.96 (m, 2H), 1.89 - 1.82 (m, 1H), 1.70 (s, 3H), 1.54 - 1.46 (m, 2H), 0.76 (s, 9H), -0.03 (s, 3H), -0.13 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 168.36, 143.37, 139.07, 126.69, 124.31, 122.99, 121.90, 121.12, 120.32, 113.17, 110.64, 77.25, 77.00, 76.75, 51.81, 36.92, 31.34, 30.48, 25.73, 25.31, 19.07, 18.21, 16.87, -3.88, -4.03.

IR: $\tilde{\nu}$ (cm⁻¹) = 2949, 2856, 1691, 1616, 1580, 1547, 1435, 1389, 1360, 1344, 1309, 1284, 1244, 1190, 1178, 1167, 1122, 1031, 1006, 985, 909, 864, 774, 731, 676, 627, 589, 526, 475.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 400.2302 calculated for C₂₃H₃₄NO₃Si; found 400.2308.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-5-nitro-1*H*-indole (2.7f)



Procedure: Alcohol **2.4** (200 mg, 0.824 mmol) was dissolved in acetonitrile (4.0 mL). 5-Nitroindole (147 mg, 0.907 mmol) was then added, followed by pyridinium triflate (38 mg, 0.165 mmol). After stirring for 168 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 4% EtOAc in hexanes to give compound **2.7f** in 36% yield (144 mg, 0.373 mmol) as a yellow solid.

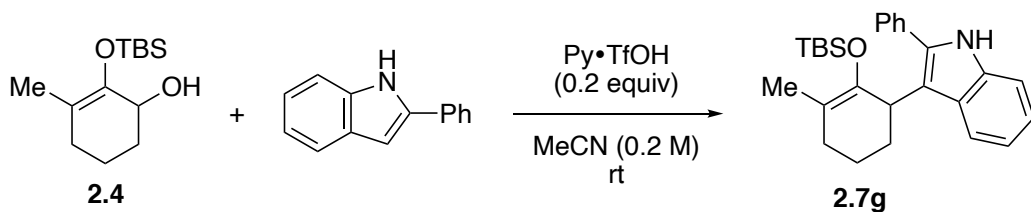
¹H NMR: (500 MHz, CDCl₃) δ = 8.57 (s, 1H), 8.29 (bs, 1H), 8.09 (dd, J = 6.8, 2.2 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.11 (d, J = 1.9 Hz, 1H), 3.71 (s, 1H), 2.16 - 2.08 (m, 1H), 2.08 - 1.99 (m, 2H), 1.86 - 1.80 (m, 1H), 1.72 (s, 3H), 1.55 - 1.48 (m, 2H), 0.74 (s, 9H), 0.00 (s, 3H), -0.11 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 142.79, 141.46, 139.37, 126.46, 125.92, 121.70, 117.43, 116.39, 113.83, 110.89, 37.09, 31.66, 30.44, 19.31, 18.16, 16.91, -3.88, -4.01.

IR: $\tilde{\nu}$ (cm⁻¹) = 3368, 2928, 2856, 1681, 1622, 1515, 1470, 1376, 1325, 1256, 1167, 1091, 941, 912, 777, 739, 588.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 387.2098 calculated for C₂₁H₃₁N₂O₃Si; found 387.2104.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-2-phenyl-1*H*-indole (2.7g)



Procedure: Alcohol **2.4** (200 mg, 0.824 mmol) was dissolved in acetonitrile (4.0 mL). 2-Phenylindole (144 mg, 0.907 mmol) was then added, followed by pyridinium triflate (38 mg, 0.165 mmol). After stirring for 26 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 1% EtOAc in hexanes to give compound **2.7g** in 72% yield (242 mg, 0.580 mmol) as a white solid.

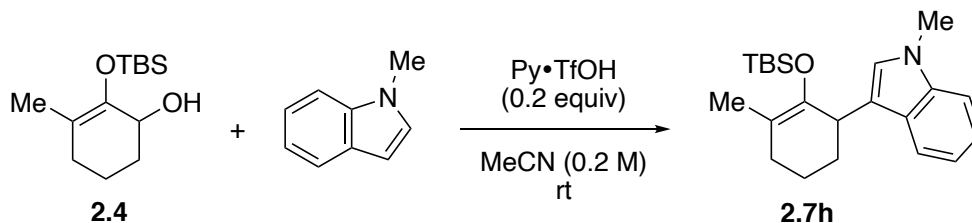
¹H NMR: (500 MHz, CDCl₃) δ = 7.90 (bs, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.34 (dd, J = 17.3, 8.8 Hz, 2H), 7.15 (t, J = 8.1 Hz, 1H), 7.05 (t, J = 7.9 Hz, 1H), 3.78 (s, 1H), 2.29 - 1.97 (m, 5H), 1.88 - 1.80 (m, 1H), 1.62 (s, 3H), 0.53 (s, 9H), -0.24 (s, 3H), -0.45 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 143.80, 135.92, 134.51, 133.73, 128.73, 128.48, 128.26, 127.40, 121.72, 120.86, 119.15, 116.01, 112.66, 110.32, 77.25, 77.00, 76.75, 37.47, 33.69, 31.11, 25.46, 22.21, 17.95, 17.11, -4.05, -4.51.

IR: $\tilde{\nu}$ (cm⁻¹) = 2926, 2854, 1671, 1603, 1486, 1456, 1342, 1311, 1256, 1176, 1071, 1011, 938, 907, 829, 775, 697, 670, 583, 563, 482.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 418.2561 calculated for C₂₇H₃₆NOSi; found 418.2576.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1-methyl-1*H*-indole (2.7h)



Procedure: Alcohol **2.4** (103 mg, 0.425 mmol) was dissolved in acetonitrile (2.1 mL). *N*-methyl indole (58 μ l, 0.468 mmol) was then added, followed by pyridinium triflate (19 mg, 0.0850 mmol). After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 12% DCM in hexanes to give compound **2.7h** in 65% yield (99 mg, 0.277 mmol) as a colorless oil.

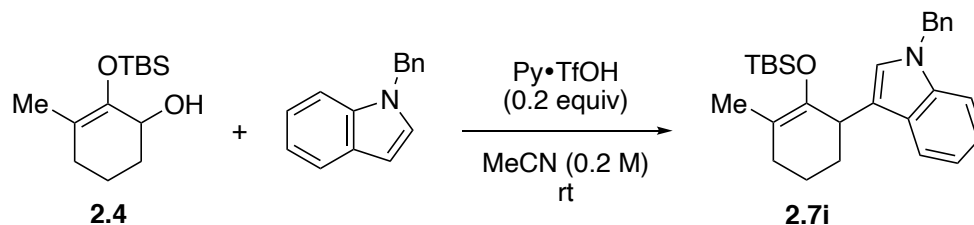
¹H NMR: (500 MHz, CDCl₃) δ = 7.56 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 7.0 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.80 (s, 1H), 3.74 (s, 3H), 3.68 (s, 1H), 2.14 - 1.89 (m, 3H), 1.87 - 1.80 (m, 1H), 1.71 (s, 3H), 1.61 - 1.52 (m, 1H), 1.51 - 1.41 (m, 1H), 0.77 (s, 9H), -0.03 (s, 3H), -0.12 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 144.00, 137.18, 127.89, 127.45, 120.94, 118.91, 118.30, 117.15, 77.31, 76.99, 76.67, 36.91, 32.55, 31.30, 30.54, 25.78, 19.06, 18.27, 16.87, -3.81, -4.04.

IR: $\tilde{\nu}$ (cm⁻¹) = 2924, 2854, 1680, 1462, 1250, 1178, 1163, 939, 914, 830, 776, 740.

HRMS (ESI-TOF) m/z : (M+H)⁺ 356.2404 calculated for C₂₂H₃₄NOSi; found 356.2408.

1-benzyl-3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1*H*-indole (2.7i)



Procedure: Alcohol **2.4** (100 mg, 0.412 mmol) was dissolved in acetonitrile (2.0 mL). *N*-benzylindole (94 mg, 0.454 mmol) was then added, followed by pyridinium triflate (20 mg, 0.0824 mmol). After stirring for 28 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 20% DCM in hexanes to give compound **2.7i** in 82% yield (146 mg, 0.338 mmol) as a colorless oil.

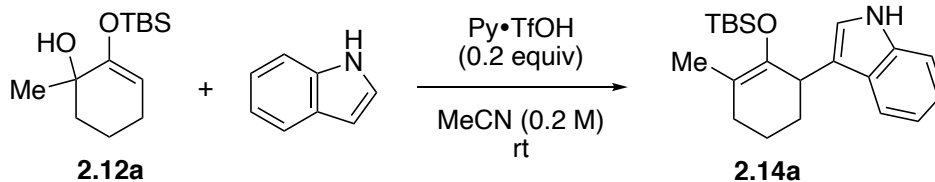
¹H NMR: (400 MHz, CDCl₃) δ = 7.76 (d, J = 7.9 Hz, 1H), 7.30 - 7.21 (m, 2H), 7.20 (d, J = 8.2 Hz, 2H), 7.13 - 7.08 (m, 3H), 7.04 - 6.99 (m, 1H), 6.90 (s, 1H), 5.25 (s, 2H), 4.83 (t, J = 4.1 Hz, 1H), 2.35 (ddd, J = 12.9, 9.4, 3.3 Hz, 1H), 2.25 - 2.07 (m, 2H), 1.73 - 1.65 (m, 1H), 1.62 - 1.49 (m, 5H), 0.62 (s, 9H), 0.09 (s, 3H), -0.09 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 155.19, 137.94, 137.19, 128.61, 127.32, 126.71, 126.51, 126.48, 122.51, 121.15, 120.95, 118.18, 109.46, 101.14, 77.25, 77.00, 76.75, 49.79, 39.85, 38.51, 25.48, 25.41, 24.71, 19.80, 17.90, -4.68.

IR: $\tilde{\nu}$ (cm⁻¹) = 2927, 2855, 1655, 1465, 1329, 1247, 954, 912, 836, 776, 736.

HRMS (ESI-TOF) m/z : (M+H)⁺ 432.2717 calculated for C₂₈H₃₈NOSi; found 432.2719.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1*H*-indole (2.14a)



Procedure: Alcohol **2.12a** (100 mg, 0.413 mmol) was dissolved in acetonitrile (2.0 mL). Indole (53 mg, 0.454 mmol) was then added, followed by pyridinium triflate (19 mg, 0.0825 mmol). After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 2% EtOAc in hexanes to give compound **2.14a** in 73% yield (104 mg, 0.304 mmol) as a colorless oil.

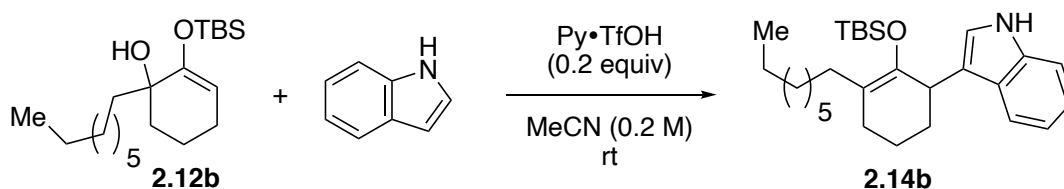
¹H NMR: (500 MHz, CDCl₃) δ = 7.91 (bs, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.95 (d, J = 2.2 Hz, 1H), 3.71 (s, 1H), 2.15 - 2.07 (m, 1H), 2.06 - 1.93 (m, 3H), 1.91 - 1.85 (m, 1H), 1.72 (s, 3H), 1.60 - 1.44 (m, 2H), 0.78 (s, 9H), -0.01 (s, 3H), -0.11 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 143.84, 136.49, 127.07, 123.06, 121.44, 118.93, 118.88, 118.75, 112.65, 110.95, 37.02, 31.14, 30.55, 25.77, 19.13, 18.25, 16.88, -3.86, -4.04.

IR: $\tilde{\nu}$ (cm⁻¹) = 3418, 3321, 2927, 1680, 1455, 1253, 1166, 1090, 1008, 939, 095, 828, 775, 735, 669, 582, 485.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 342.2248 calculated for C₂₁H₃₂NOSi; found 342.2257.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-octylcyclohex-2-en-1-yl)-1*H*-indole (**4.14b**)



Procedure: Alcohol **2.12b** (100 mg, 0.294 mmol) was dissolved in acetonitrile (1.5 mL). Indole (40 mg, 0.339 mmol) was then added, followed by pyridinium triflate (14.11 mg, 0.0616 mmol). After stirring for 16 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 2% EtOAc in hexanes to give compound **2.14b** in 79% yield (79 mg, 0.179 mmol) as a colorless oil.

3-(3-allyl-2-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)-1*H*-indole (2.14c)

Procedure: Alcohol **2.12c** (146 mg, 0.544 mmol) was dissolved in acetonitrile (2.70 mL). Indole (70 mg, 0.598 mmol) was then added, followed by pyridinium triflate (25 mg, 0.109 mmol). After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with

column chromatography using 100% hexanes to 5% EtOAc in hexanes to give compound **2.14c** in 72% yield (115 mg, 0.313 mmol) as a colorless oil.

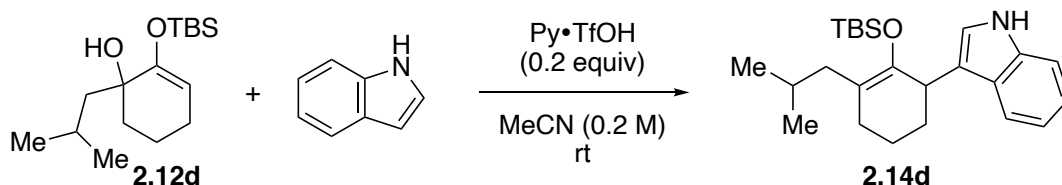
¹H NMR: (500 MHz, CDCl₃) δ = 7.91 (s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 7.1 Hz, 1H), 7.09 (t, J = 7.1 Hz, 1H), 6.94 (d, J = 1.7 Hz, 1H), 5.85 (ddt, J = 16.8, 10.0, 6.7 Hz, 1H), 5.04 (dd, J = 17.1, 10.1 Hz, 1H), 3.72 (s, 1H), 3.04 (dd, J = 14.2, 6.4 Hz, 1H), 2.79 (dd, J = 14.4, 7.0 Hz, 1H), 2.12 - 1.86 (m, 4H), 1.54 - 1.41 (m, 2H), 0.77 (s, 9H), -0.01 (s, 3H), -0.18 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 144.46, 137.20, 136.51, 126.97, 123.19, 121.51, 119.00, 118.83, 118.62, 114.55, 114.40, 110.99, 77.25, 77.20, 77.00, 76.75, 36.91, 35.10, 30.72, 27.78, 25.73, 18.79, 18.23, -3.91, -3.97.

IR: ν (cm⁻¹) = 2928, 2855, 1673, 1456, 1360, 1310, 1251, 1224, 1199, 1164, 942, 910, 888, 829, 776, 738, 671, 581.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 368.2404 calculated for C₂₃H₃₄NOSi; found 368.2407.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-isobutylcyclohex-2-en-1-yl)-1*H*-indole (2.14d)



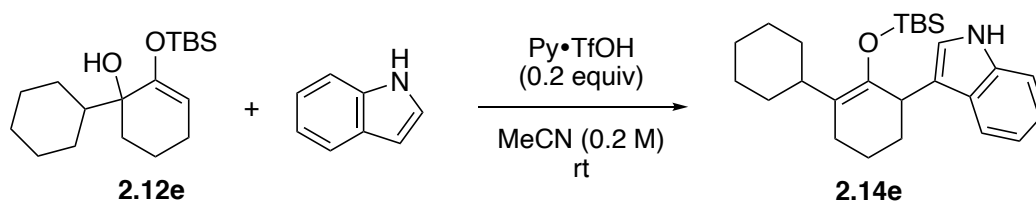
Procedure: Alcohol **2.12d** (50 mg, 0.176 mmol) was dissolved in acetonitrile (0.87 mL). Indole (23 mg, 0.193 mmol) was then added, followed by pyridinium triflate (8.1 mg, 0.0354 mmol). After stirring for 5 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 2% EtOAc in hexanes to give compound **2.14d** in 83% yield (56 mg, 0.146 mmol) as a colorless oil.

¹H NMR: (500 MHz, CDCl₃) δ = 7.89 (bs, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 8.1, 1H), 7.10 (t, J = 7.6 Hz, 1H), 6.96 (s, 1H), 3.73 (t, J = 4.4 Hz, 1H), 2.33 (dd, J = 13.0, 8.2 Hz, 1H), 2.08 - 2.02 (m, 2H), 1.99 - 1.80 (m, 3H), 1.76 (dd, J = 13.1, 6.9 Hz, 1H), 1.55 - 1.41 (m, 2H), 0.97 (d, J = 4.5 Hz, 6H), 0.79 (s, 9H), 0.01 (s, 3H), -0.20 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 144.40, 136.49, 127.01, 123.24, 121.46, 118.79, 116.11, 110.99, 77.25, 77.00, 76.75, 39.44, 36.99, 30.71, 28.53, 26.66, 25.81, 22.97, 18.92, 18.22, -3.92.

IR: ν (cm⁻¹) = 2952, 2928, 1710, 1671, 1456, 1361, 1252, 1225, 1161, 931, 907, 830, 775. **HRMS (ESI-TOF) m/z :** (M+H)⁺ = 384.2717 calculated for C₂₄H₃₈NOSi; found 384.2715.

3-(2-((*tert*-butyldimethylsilyl)oxy)-[1,1'-bi(cyclohexan)]-1-en-3-yl)-1*H*-indole (**2.14e**)



Procedure: Alcohol **2.12e** (50 mg, 0.161 mmol) was dissolved in acetonitrile (0.8 mL). Indole (20.74 mg, 0.1771 mmol) was then added, followed by pyridinium triflate (7.37 mg, 0.0322 mmol). After stirring for 6 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 2% EtOAc in hexanes to give compound **2.14e** in 76% yield (50 mg, 0.122 mmol) as a colorless oil.

¹H NMR: (500 MHz, CDCl₃) δ = 7.88 (bs, 1H), 7.58 (d, J = 7.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.16 (t, J = 8.1 Hz, 1H), 7.09 (t, J = 8.1 Hz, 1H), 6.91 (d, J = 1.7 Hz, 1H), 3.68 (t, J = 4.4 Hz, 1H), 2.87 (t, J = 11.9, Hz, 1H), 2.06 - 1.95 (m, 2H), 1.91 - 1.84 (m, 2H), 1.80 - 1.73 (m, 2H), 1.71 - 1.59

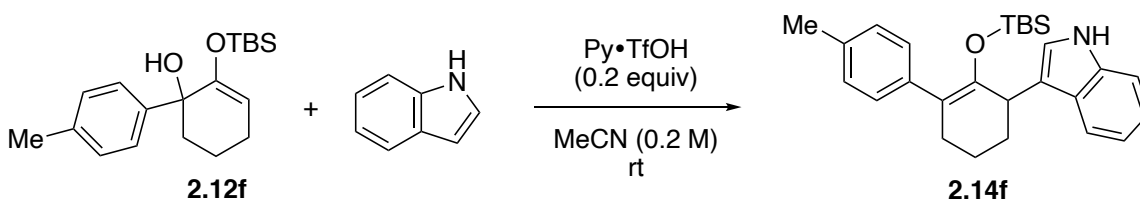
(m, 2H), 1.54 - 1.49 (m, 1H), 1.47 - 1.41 (m, 2H), 1.37 - 1.25 (m, 4H), 1.21 - 1.12 (m, 1H), 0.78 (s, 9H), -0.00 (s, 3H), -0.17 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 142.31, 136.51, 127.01, 123.21, 121.59, 121.41, 119.06, 118.91, 118.87, 110.95, 37.08, 36.92, 31.31, 30.40, 30.19, 26.95, 26.87, 26.45, 25.78, 23.31, 18.83, 18.26, -3.91, -4.15.

IR: $f(\text{cm}^{-1})$ = 3416, 3304, 2925, 2850, 1660, 1445, 1308, 1250, 1138, 1092, 938, 829, 776, 740.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 410.2874$ calculated for $\text{C}_{26}\text{H}_{40}\text{NOSi}$; found 410.2862.

3-(2-((*tert*-butyldimethylsilyl)oxy)-4'-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1H-indole (2.14f)



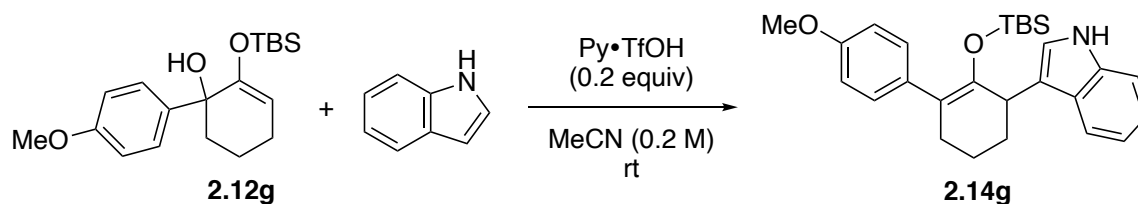
Procedure: Alcohol **2.12f** (50 mg, 0.157 mmol) was dissolved in acetonitrile (0.8 mL). Indole (20 mg, 0.173 mmol) was then added, followed by pyridinium triflate (7.2 mg, 0.0313 mmol). After stirring for 168 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 2% EtOAc in hexanes to give compound **2.14f** in 75% yield (49 mg, 0.118 mmol) as a colorless oil.

^1H NMR: (400 MHz, CDCl_3) δ = 7.94 (bs, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.20 (t, J = 7.1 Hz, 1H), 7.15 - 7.10 (m, 4H), 3.78 (t, J = 4.9 Hz, 1H), 2.67 - 2.57 (m, 1H), 2.35 (s, 3H), 2.31 - 2.22 (m, 1H), 2.14 - 1.95 (m, 2H), 1.76 - 1.58 (m, 2H), 0.55 (s, 9H), -0.17 (s, 3H), -0.42 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 145.98, 138.97, 136.51, 135.09, 128.75, 128.35, 126.99, 122.91, 121.54, 119.05, 119.02, 118.97, 117.85, 111.02, 77.32, 77.00, 76.68, 37.94, 31.18, 30.34, 25.47, 21.15, 19.81, 17.94, -4.33, -4.45.

IR: $\tilde{\nu}$ (cm⁻¹) = 3418, 2927, 2855, 1511, 1455, 1251, 1157, 909, 828, 777, 734, 579, 494. **HRMS** (ESI-TOF) m/z : (M+H)⁺ = 418.2561 calculated for C₂₇H₃₆NOSi; found 418.2562.

3-(2-((*tert*-butyldimethylsilyl)oxy)-4'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1*H*-indole (2.14g)



Procedure: Alcohol **2.12g** (67 mg, 0.201 mmol) was dissolved in acetonitrile (1.0 mL). Indole (26 mg, 0.222 mmol) was then added, followed by pyridinium triflate (9.2 mg, 0.0402 mmol). After stirring for 22 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 20% DCM in hexanes to give compound **2.14g** in 75% yield (66 mg, 0.151 mmol) as a colorless oil.

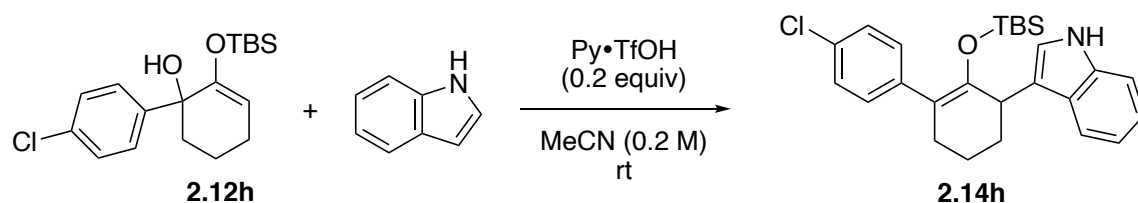
¹H NMR: (400 MHz, CDCl₃) δ = 7.94 (bs, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 8.3 Hz, 3H), 7.19 (t, J = 7.1 Hz, 1H), 7.14 - 7.07 (m, 2H), 6.86 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H), 3.77 (t, J = 5.0 Hz, 1H), 2.66 - 2.55 (m, 1H), 2.30 - 2.21 (m, 1H), 2.13 - 1.95 (m, 2H), 1.76 - 1.57 (m, 1H), 0.54 (s, 9H), -0.17 (s, 3H), -0.41 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 157.59, 145.87, 136.52, 134.46, 129.89, 126.99, 122.87, 121.55, 119.07, 119.02, 117.41, 113.13, 111.02, 77.32, 77.00, 76.68, 55.28, 37.98, 31.23, 30.39, 25.49, 19.89, 17.96, -4.31, -4.41.

IR: ν (cm⁻¹) = 3056, 2947, 2931, 2854, 1648, 1607, 1573, 1455, 1337, 1288, 1242, 1177, 1131, 1157, 1089, 988, 909, 860, 777, 732, 668.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 434.2510 calculated for C₂₇H₃₆NO₂Si; found 434.2503.

3-(2-((*tert*-butyldimethylsilyl)oxy)-4'-chloro-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1H-indole (2.14h)



Procedure: Alcohol **2.12h** (75 mg, 0.221 mmol) was dissolved in acetonitrile (1.1 mL). Indole (29 mg, 0.243 mmol) was then added, followed by pyridinium triflate (10.1 mg, 0.044 mmol). After stirring for >500 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 20% DCM in hexanes to give compound **2.14h** in 50% yield (46 mg, 0.105 mmol) as a colorless oil.

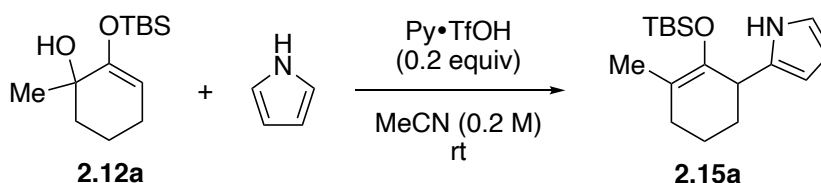
¹H NMR: (500 MHz, CDCl₃) δ = 7.95 (bs, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.37 (t, J = 7.9 Hz, 3H), 7.27 (d, J = 9.8 Hz, 2H), 7.20 (t, J = 7.1 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H), 7.08 (s, 1H), 3.78 (t, J = 4.8 Hz, 1H), 2.66 - 2.54 (m, 1H), 2.29 - 2.21 (m, 1H), 2.12 - 1.96 (m, 2H), 1.75 - 1.58 (m, 2H), 0.54 (s, 9H), -0.17 (s, 3H), -0.39 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 146.98, 140.36, 136.50, 131.11, 130.23, 127.78, 126.87, 122.82, 121.65, 119.11, 118.94, 118.67, 116.76, 111.07, 77.25, 77.00, 76.75, 37.85, 31.03, 30.06, 25.41, 19.65, 17.92, -4.23, -4.32.

IR: $\tilde{\nu}$ (cm^{-1}) = 2927, 2855, 1644, 1489.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 438.2014$ calculated for $\text{C}_{26}\text{H}_{33}\text{ClNOSi}$; found 438.2016.

2-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1*H*-pyrrole (2.15a)



Procedure: Alcohol **2.12a** (75 mg, 0.309 mmol) was dissolved in acetonitrile (1.5 mL). Pyrrole (24 μL , 0.340 mmol) was then added, followed by pyridinium triflate (14 mg, 0.0618 mmol). After stirring for 3 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 25% DCM in hexanes to give compound **2.15a** in 39% yield (35 mg, 0.119 mmol) as a brown oil.

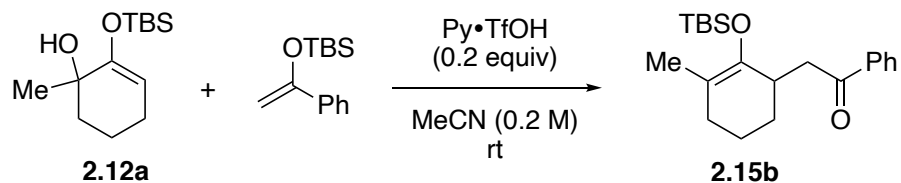
^1H NMR: (500 MHz, CDCl_3) δ = 8.42 (bs, 1H), 6.65 (dd, J = 3.0, 1.4 Hz, 1H), 6.24 - 6.11 (m, 1H), 5.94 (s, 1H), 3.44 (s, 1H), 2.18 - 2.01 (m, 1H), 2.05 - 1.89 (m, 2H), 1.67 (s, 3H), 1.59 - 1.50 (m, 2H), 0.93 (s, 6H), 0.10 (s, 3H), 0.04 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 143.11, 134.38, 115.45, 114.14, 107.92, 104.18, 38.51, 31.12, 30.54, 25.82, 19.45, 18.22, 16.94, -4.06, -4.09.

IR: $\tilde{\nu}$ (cm^{-1}) = 3460, 2928, 2856, 1679, 1470, 1341, 1314, 1252, 1164, 1119, 1090, 1026, 1005, 936, 911, 883, 776, 702, 667.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 292.2091$ calculated for $\text{C}_{17}\text{H}_{30}\text{NOSi}$; found 292.2085.

2-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1-phenylethan-1-one (2.15b)



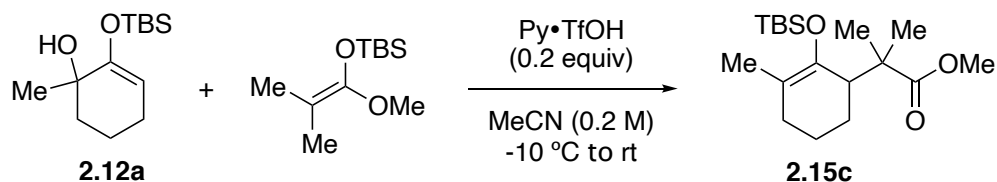
Procedure: Alcohol **2.12a** (118 mg, 0.487 mmol) was dissolved in acetonitrile (2.4 mL). Trimethyl((1-phenylvinyl)oxy)silane (200 μ L, 0.973 mmol) was then added, followed by pyridinium triflate (22 mg, 0.097 mmol). After stirring for 4 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 15% EtOAc in hexanes to give compound **2.15b** in 86% yield (144 mg, 0.417 mmol) as a colorless oil.

¹H NMR: (500 MHz, CDCl₃) δ = 7.98 (d, J = 7.65 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 3.32 (dd, J = 17.4, 2.3 Hz, 1H), 3.05 (dd, J = 17.5, 10.85 Hz, 1H), 2.87 (bs, 1H), 2.06 - 1.90 (m, 2H), 1.89 - 1.79 (m, 1H), 1.62 (s, 3H), 1.54 - 1.39 (m, 3H), 0.93 (s, 9H), 0.11 (d, J = 11.7 Hz, 6H).

¹³C NMR: (125 MHz, CDCl₃) δ = 199.84, 144.61, 137.51, 132.89, 128.53, 127.97, 113.77, 99.97, 77.25, 77.00, 76.75, 41.15, 34.88, 30.67, 28.99, 25.93, 19.67, 18.28, 17.12, -3.73, -4.32.

See: Stepherson J. R.; Fronczek. F. R.; Kartika R. *Chem. Commun.* **2016**, 52, 2300.

Methyl 2-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-2-methylpropanoate (2.15c)



Procedure: Alcohol **2.12a** (66 mg, 0.272 mmol) was dissolved in acetonitrile (1.4 mL). After cooling the solution to -10 °C, dimethylketene methyl trimethylsilyl acetal (166 µl, 0.817 mmol) was then added, followed by pyridinium triflate (12 mg, 0.054 mmol). After stirring for 4 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 10% EtOAc in hexanes to give compound **2.15c** in 47% yield (42 mg, 0.128 mmol) as a colorless oil.

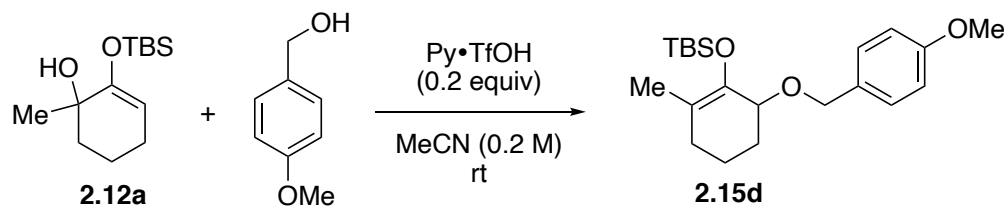
¹H NMR: (400 MHz, CDCl₃) δ = 3.65 (s, 3H), 2.56 (bs, 1H), 1.91 (bs, 2H), 1.69 - 1.60 (m, 2H), 1.46 (s, 3H), 1.35 – 1.33 (m, 2H), 1.30 (s, 3H), 1.09 (s, 3H), 0.95 (s, 9H), 0.14 (s, 3H), 0.01 (3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 178.57, 144.00, 116.55, 77.32, 77.00, 76.68, 51.55, 46.84, 44.92, 30.59, 27.38, 26.24, 26.01, 21.66, 21.07, 18.35, 17.85, -2.23, -4.35.

IR: $\tilde{\nu}$ (cm⁻¹) = 2929, 2858, 1732, 1672, 1471, 1388, 1361, 1250, 1157, 1128, 1085, 1007, 911, 830, 776, 676.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 327.2355 calculated for C₁₈H₃₅O₃Si; found 327.2359.

***tert*-butyl(((6-((4-methoxybenzyl)oxy)-2-methylcyclohex-1-en-1-yl)oxy)dimethylsilane
(**2.15d**)**



Procedure: Alcohol **2.12a** (75 mg, 0.309 mmol) was dissolved in acetonitrile (1.5 mL). 5-methoxybenzyl alcohol (76 µL, 0.619 mmol) was then added, followed by pyridinium triflate (14 mg, 0.0618 mmol). After stirring for 73 hours at room temperature, the reaction was quenched

with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 60% DCM in hexanes to give compound **2.15d** in 64% yield (72 mg, 0.199 mmol) as a colorless oil.

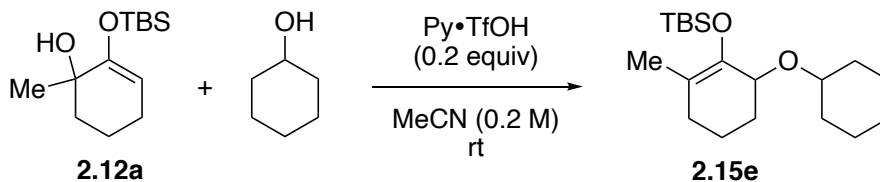
¹H NMR: (400 MHz, CDCl₃) δ = 7.28 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.52 (d, J = 11.1 Hz, 1H), 4.40 (d, J = 11.1 Hz, 1H), 3.79 (s, 3H), 2.08 - 1.91 (m, 3H), 1.84 - 1.69 (m, 1H), 1.61 (s, 3H), 1.58 - 1.44 (m, 2H), 0.95 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 158.87, 142.88, 131.36, 129.17, 116.93, 113.57, 77.25, 77.00, 76.75, 75.14, 70.04, 55.26, 30.68, 27.87, 25.99, 18.41, 17.75, 16.97, -3.83, -3.85.

IR: f (cm⁻¹) = 2929, 1613, 1513, 1462, 1245, 1172, 1076, 1076, 914, 828, 776, 672.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 362.2350 calculated for C₂₁H₃₄O₃Si; found 363.2359.

***tert*-butyl((6-(cyclohexyloxy)-2-methylcyclohex-1-en-1-yl)oxy)dimethylsilane (**2.15e**)**



Procedure: Alcohol **2.12a** (93 mg, 0.384 mmol) was dissolved in acetonitrile (2.0 mL). Cyclohexanol (80 μ L, 0.767 mmol) was then added, followed by pyridinium triflate (17 mg, 0.0767 mmol). After stirring for 26 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 5% EtOAc in hexanes to give compound **2.15e** in 50% yield (62 mg, 0.191 mmol).

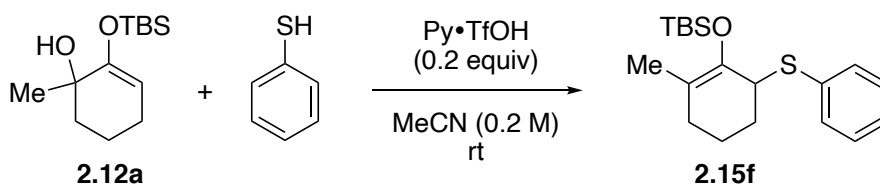
¹H NMR: (500 MHz, CDCl₃) δ = 3.77 (s, 1H), 3.35 - 3.29 (m, 1H), 2.01 - 1.84 (m, 6H), 1.79 - 1.70 (m, 3H), 1.61 - 1.42 (m, 7H), 1.35 - 1.09 (m, 6H), 0.96 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ =143.38, 116.62, 77.25, 77.00, 76.75, 75.89, 72.71, 34.23, 32.88, 30.76, 29.30, 25.95, 25.79, 24.92, 24.81, 18.31, 17.51, 17.33, -3.19, -3.73.

IR: $f(\text{cm}^{-1})$ = 2929, 2855, 1678, 1450, 1380, 1351, 1251, 1224, 1173, 1078, 1023, 986, 952, 920, 830, 776, 675.

HRMS (ESI-TOF) m/z : ($\text{M} + \text{H}$)⁺ 325.2557 calculated for $\text{C}_{19}\text{H}_{37}\text{O}_2\text{Si}$; found 325.2569.

***tert*-butyldimethyl((2-methyl-6-(phenylthio)cyclohex-1-en-1-yl)oxy)silane (**2.15f**)**



Procedure: Alcohol **2.12a** (75 mg, 0.309 mmol) was dissolved in acetonitrile (1.5 mL). Thiophenol (35 μL , 0.340 mmol) was then added, followed by pyridinium triflate (14 mg, 0.0618 mmol). After stirring for 8 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 20% DCM in hexanes to give compound **2.15f** in 90% yield (94 mg, 0.280 mmol) as a colorless oil.

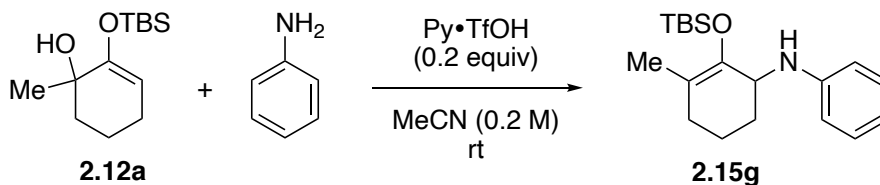
^1H NMR: (500 MHz, CDCl_3) δ = 7.43 - 7.36 (m, 2H), 7.32 - 7.25 (m, 2H), 7.22 - 7.17 (m, 1H), 3.71 (s, 1H), 2.15 - 1.76 (m, 5H), 1.64 (s, 3H), 1.58 - 1.51 (m, 1H), 0.99 (s, 9H), 0.17 (d, J = 7.5 Hz, 6H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 140.95, 136.65, 131.09, 128.73, 126.32, 116.74, 49.18, 30.30, 29.86, 25.95, 18.43, 18.17, 17.23, -3.68, -3.82.

IR: $f(\text{cm}^{-1})$ = 3073, 2856, 1672, 1462, 1438, 1313, 1251, 1207, 1121, 1088, 942, 856, 828, 755, 690 588.

HRMS (ESI-TOF) m/z : ($\text{M} + \text{H}$)⁺ 335.1859 calculated for $\text{C}_{19}\text{H}_{31}\text{OSSi}$; found 335.1866.

***N*-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)aniline (**2.15g**)**



Procedure: Alcohol **2.12a** (113 mg, 0.466 mmol) was dissolved in acetonitrile (2.3 mL). Aniline (50 μL , 0.513 mmol) was then added, followed by pyridinium triflate (21 mg, 0.0932 mmol). After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes to 5% EtOAc in hexanes to give compound **2.15g** in 32% yield (48 mg, 0.151 mmol).

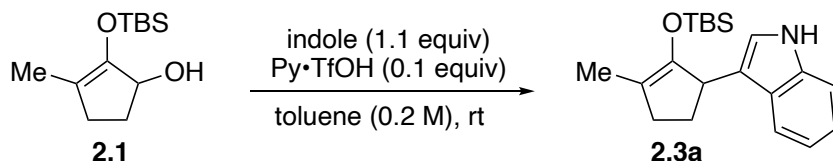
^1H NMR: (500 MHz, CDCl_3) δ = 7.16 (t, J = 8.5 Hz, 2H), 6.67 (t, J = 8.3 Hz, 1H), 6.57 (d, J = 8.5 Hz, 2H), 3.95 (s, 1H), 3.84 (s, 2H), 2.09 - 1.89 (m, 4H), 1.69 (s, 3H), 1.66 (s, 6H), 1.64 - 1.51 (m, 2H), 0.91 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 147.47, 142.56, 129.21, 116.79, 115.85, 112.78, 99.96, 77.25, 77.00, 76.75, 51.58, 30.44, 29.69, 28.75, 25.87, 18.35, 18.16, 16.83, -3.92, -4.00.

IR: $f(\text{cm}^{-1})$ = 2927, 2856, 1680, 1601, 1501, 1471, 1428, 1346, 1309, 1250, 1169, 1110, 1074, 1006, 934, 917, 828, 776, 745, 690, 672, 603, 506.

HRMS (ESI-TOF) m/z : ($\text{M}+\text{H}$) $^+$ = 318.2275 calculated for $\text{C}_{19}\text{H}_{31}\text{NOSi}$; found 318.2269.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1*H*-indole (2.3a**)**



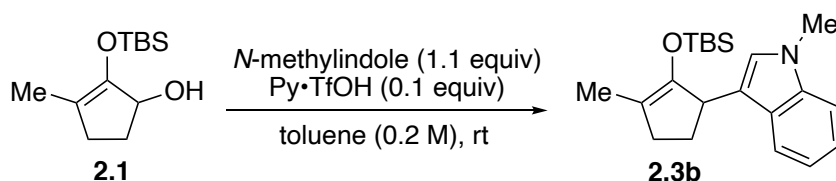
Procedure: Starting material **2.1** (145 mg, 0.635 mmol) was dissolved in toluene (3.2 mL). Indole (82 mg, 0.698 mmol) was then added, followed by pyridinium triflate (15 mg, 0.064 mmol). The reaction was stirred for 4 hours when it reached completion as monitored by TLC. The mixture was then concentrated in *vacuo* to obtain crude material, which was purified by flash column chromatography with 95: 5 hexanes: EtOAc to give product **2.3a** in 85% yield (177 mg, 0.540 mmol) as a clear oil.

Rf: 0.70 (70:30 hexanes : EtOAc)

¹H NMR: (500 MHz, CDCl₃) δ = 7.86 (s, 1H), 7.65 (d, J = 9.7 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.21 (t, J = 7.2 1H), 7.14 (t, J = 7.1 1H), 7.00 (s, 1H), 4.03 (m, 1H), 2.49 – 2.35 (m, 2H), 2.34 – 2.23 (m, 1H), 1.92 (m, 1H), 1.75 (s, 3H), 0.88 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H).

¹³C NMR: (126 MHz, CDCl₃) δ = 147.87, 136.51, 127.13, 121.54, 119.35, 119.27, 118.90, 113.54, 110.93, 76.75, 42.52, 32.27, 29.80, 25.64, 18.11, 12.46, -4.19, -4.26.

3-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1-methyl-1*H*-indole (**2.3b**)



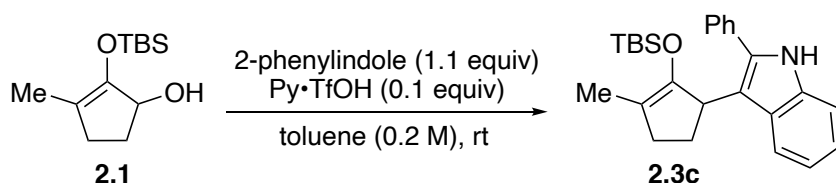
Procedure: Starting material **2.1** (175 mg, 0.327 mmol) was dissolved in toluene (1.6 mL). *N*-methylindole (45 μ L, 0.360 mmol) was then added, followed by pyridinium triflate (7 mg, 0.032 mmol). The reaction was stirred for 9 hours when it reached completion as monitored by TLC. The mixture was then concentrated in *vacuo* to obtain crude material, which was purified by flash column chromatography with 88: 12 hexanes: CH₂Cl₂ to give product **2.3b** in 56% yield (63 mg, 0.184 mmol) as a clear oil.

Rf: 0.60 (80:20, hexanes : EtOAc)

¹H NMR: (500 MHz, CDCl₃) δ = 7.58 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 7.20 (t, J = 7.1 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.85 (s, 1H), 3.99 – 3.94 (m, 1H), 3.73 (s, 3H), 2.42 – 2.30 (m, 2H), 2.28 – 2.21 (m, 1H), 1.88 – 1.80 (m, 1H), 1.69 (s, 3H), 0.82 (s, 9H), -0.05 (s, 3H), -0.11 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 148.01, 137.23, 127.57, 126.38, 121.08, 119.42, 118.30, 117.81, 113.43, 108.95, 42.39, 32.51, 32.23, 30.08, 25.65, 18.14, 12.45, -4.16, -4.23.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-2-phenyl-1*H*-indole (**2.3c**)



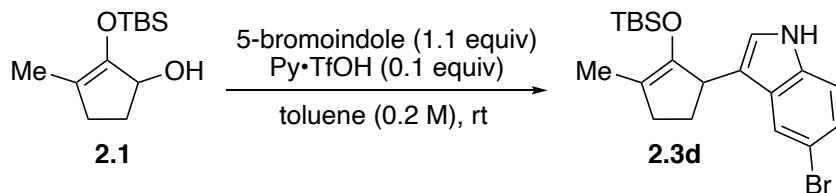
Procedure: Starting material **2.1** (111 mg, 0.489 mmol) was dissolved in toluene (2.4 mL). 2-Phenylindole (104 mg, 0.538 mmol) was then added, followed by pyridinium triflate (11 mg, 0.048 mmol). The reaction was stirred for 3 hours when it reached completion as monitored by TLC. The mixture was then concentrated in *vacuo* to obtain crude material, which was purified by flash column chromatography with 99:1 hexanes: EtOAc to give product **2.3c** in 89% yield (176 mg, 0.432 mmol) as a brown oil.

R_f: 0.68 (80:20, hexanes : EtOAc)

¹H NMR: (500 MHz, CDCl₃): δ = 7.92 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 7.0 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.37 (d, J = 7.4 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 8.1 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 4.18 4.21 – 4.15 (m, 1H), 2.53 – 2.44 (m, 1H), 2.43 – 2.33 (m, 2H), 2.21 – 2.11 (m, 1H), 1.68 (s, 3H), 0.64 (s, 9H), -0.35 (s, 3H), -0.45 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 147.98, 136.22, 135.15, 133.32, 128.60, 128.58, 128.09, 127.55, 121.91, 120.80, 119.24, 115.53, 112.44, 42.32, 32.84, 29.02, 25.46, 18.01, 12.71, -4.50, -4.68.

5-bromo-3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1*H*-indole (2.3d)



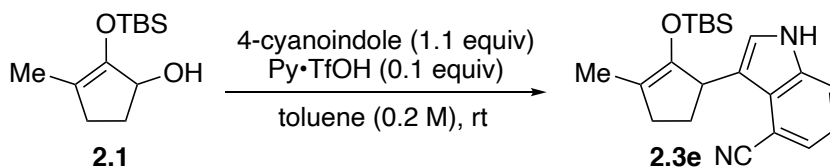
Procedure: Starting material **2.1** (112 mg, 0.490 mmol) was dissolved in toluene (2.5 mL). 5-Bromoindole (106 mg, 0.539 mmol) was then added, followed by pyridinium triflate (11 mg, 0.049 mmol). The reaction was stirred for 2 hours when it reached completion as monitored by TLC. The mixture was then concentrated in *vacuo* to obtain crude material, which was purified by flash column chromatography with 95:5 hexanes: EtOAc to give product **2.3d** in 70% yield (138 mg, 0.339 mmol) as a clear oil.

Rf: 0.79 (70:30, hexanes : EtOAc)

¹H NMR: (500 MHz, CDCl₃) δ = 7.92 (s, 1H), 7.71 (s, 1H), 7.26 – 7.23 (m, 1H), 7.19 (d, J = 8.6 Hz, 1H), 6.99 (d, J = 3.1 Hz, 1H), 3.95 – 3.88 (m, 1H), 2.42 – 2.23 (m, 3H), 1.87 – 1.77 (m, 1H), 1.69 (s, 3H), 0.82 (s, 9H), -0.03 (s, 3H), -0.09 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ = 147.39, 135.08, 128.91, 124.40, 122.73, 121.94, 119.16, 113.89, 112.34, 112.27, 42.35, 32.20, 29.73, 25.60, 25.34, 18.07, 12.43, -4.20, -4.25.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1*H*-indole-4-carbonitrile (2.3e)



Procedure: Starting material **2.1** (125 mg, 0.547 mmol) was dissolved in toluene (2.7 mL). 4-Cyanoindole (85 mg, 0.601 mmol) was then added, followed by pyridinium triflate (12 mg, 0.054

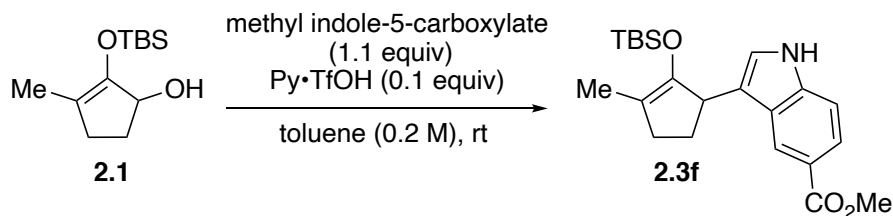
mmol). The reaction was stirred for 7 hours when it reached completion as monitored by TLC. The mixture was then concentrated in *vacuo* to obtain crude material, which was purified by flash column chromatography with 95:5 hexanes : EtOAc to give product **2.3e** in 65% yield (63 mg, 0.184 mmol) as a yellow solid.

Rf: 0.57 (80:20, hexanes : EtOAc)

¹H NMR: (400 MHz, CDCl₃) δ = 8.30 (s, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.47 (d, J = 7.4 Hz, 1H), 7.22 – 7.17 (m, 1H), 7.16 (d, J = 2.4 Hz, 1H), 4.46 – 4.34 (m, 1H), 2.68 – 2.50 (m, 1H), 2.24 (t, J = 7.0 Hz, 2H), 1.77 – 1.70 (m, 1H), 1.69 (s, 3H), 0.84 (s, 9H), 0.06 (s, 3H), -0.10 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 146.73, 136.58, 126.87, 126.14, 124.87, 121.10, 119.63, 119.33, 115.83, 114.91, 101.86, 41.61, 31.69, 31.41, 25.61, 18.08, 12.27, -4.26, -4.33.

Methyl 3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1*H*-indole-5-carboxylate (2.3f)



Procedure: Starting material **2.1** (112 mg, 0.490 mmol) was dissolved in toluene (2.4 mL). methyl indole-5-carboxylate (91 mg, 0.520 mmol) was then added, followed by pyridinium triflate (11 mg, 0.047 mmol). The reaction was stirred for 3 hours when it reached completion as monitored by TLC. The mixture was then concentrated in *vacuo* to obtain crude material, which was purified by flash column chromatography with 95:5 hexanes : EtOAc to give product **2.3f** in 83% yield (151 mg, 0.392 mmol) as a clear oil.

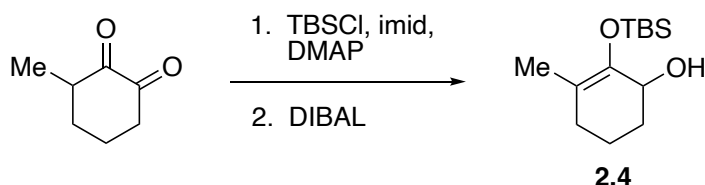
Rf: 0.69 (70:30, hexanes : EtOAc)

¹H NMR: (500 MHz, CDCl₃) δ = 8.36 (s, 1H), 8.12 (s, 1H), 7.88 (d, J = 6.2, 1.6 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.05 (s, 1H), 4.04 – 3.97 (m, 1H), 3.93 (s, 3H), 2.48 – 2.21 (m, 3H), 1.81 (m, 1H), 1.69 (s, 3H), 0.81 (s, 9H), -0.03 (s, 3H), -0.11 (s, 3H).

¹³C NMR: (126 MHz, CDCl₃) δ = 147.38, 139.08, 126.87, 123.12, 122.63, 122.37, 121.11, 121.01, 114.06, 110.56, 51.79, 42.26, 32.20, 29.99, 25.60, 18.09, 12.40, -4.20, -4.26.

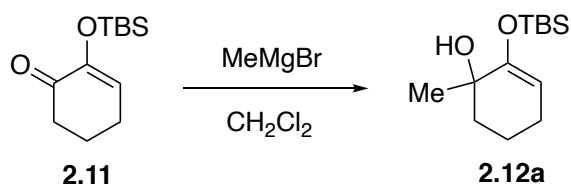
6.2.2 Synthesis of α -Hydroxy Silylenol Ethers

2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-ol (**2.4**)



See: Stepherson J. R.; Fronczek. F. R.; Kartika R. *Chem. Commun.* **2016**, 52, 2300.

2-((*tert*-butyldimethylsilyl)oxy)-1-methylcyclohex-2-en-1-ol (**2.12a**)



Procedure: Ketone **2.11** (3.64 g, 16.1 mmol) was dissolved in dichloromethane (80 mL), and the solution was cooled to 0 °C. Methylmagnesium bromide (10.7 mL, 3.0 M in Et₂O) was then added dropwise. After stirring for 2 hours at room temperature, the reaction was quenched with 1:1 DI water and saturated NH₄Cl solution (5 mL). The crude mixture was filtered through a celite plug and sequentially washed with DCM (500 mL) and DI H₂O (300 mL). The aqueous layer was then

extracted with DCM (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes to 10% EtOAc in hexanes to give product **2.12a** in 81% yield (3.15 g, 13.0 mmol) as a clear oil.

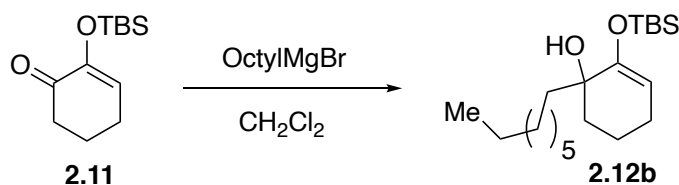
¹H NMR: (500 MHz, CDCl₃) δ = 4.76 (t, J = 4.0 Hz, 1H), 2.23 (s, 1H), 2.11 - 1.95 (m, 2H), 1.84 - 1.71 (m, 2H), 1.67 (dddt, J = 13.3, 10.1, 5.7, 2.8 Hz, 1H), 1.58 - 1.49 (m, 1H), 1.32 (s, 3H), 0.94 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 152.70, 102.89, 77.25, 77.20, 77.00, 76.75, 70.36, 37.65, 27.13, 26.06, 25.79, 24.41, 19.94, 18.16, -4.39, -4.71.

IR: $\tilde{\nu}$ (cm⁻¹) = 2959, 2931, 2858, 1661, 1462, 1363, 1258, 1192, 1173, 1090, 1014, 959, 900, 796, 685, 669, 604, 484.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 243.1775 calculated for C₁₃H₂₇O₂Si; found 243.1782.

2-((*tert*-butyldimethylsilyl)oxy)-1-octylcyclohex-2-en-1-ol (**2.12b**)



Procedure: Ketone **2.11** (300 mg, 1.32 mmol) was dissolved in dichloromethane (6.6 mL), and the solution was cooled to 0 °C. Octylmagnesium bromide (1.0 mL, 2.0 M in Et₂O) was then added dropwise. After stirring for 16 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH₄Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column

chromatography (buffered with 2% TEA) using 100% hexanes to 3% EtOAc in hexanes to give product **2.12b** in 86% yield (372 mg, 1.09 mmol) as a clear yellow oil.

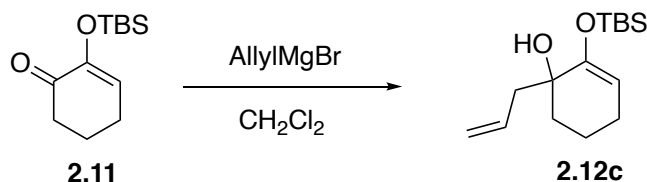
¹H NMR: (500 MHz, CDCl₃) δ = 4.80 (dd, J = 4.7, 3.3 Hz, 1H), 2.08 - 2.01 (m, 1H), 1.99 - 1.93 (m, 2H), 1.76 (ddd, J = 13.4, 10.0, 3.5 Hz, 1H), 1.71 - 1.51 (m, 5H), 1.30 - 1.23 (m, 12H), 0.94 (s, 9H), 0.88 (t, J = 7.1 Hz, 3H), 0.19 (s, 3H), 0.17 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 152.50, 103.71, 77.25, 77.00, 76.75, 72.52, 39.56, 34.25, 31.88, 30.25, 29.62, 29.28, 25.78, 24.40, 23.98, 22.66, 19.39, 18.15, 14.10, -4.54, -4.57.

IR: $f(\text{cm}^{-1})$ = 3600, 2926, 2855, 1657, 1462, 1251, 1176, 917, 836, 778, 673.

HRMS (ESI-TOF) m/z : (M+H)⁺ 341.2870 calculated for C₂₀H₄₁O₂Si; found 341.2868.

1-allyl-2-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-ol (2.12c)



Procedure: Ketone **2.11** (308 mg, 1.36 mmol) was dissolved in dichloromethane (7.0 mL), and the solution was cooled to 0 °C. Allylmagnesium bromide (2.0 mL, 1.0 M in Et₂O) was then added dropwise. After stirring for 18 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH₄Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes to 5% EtOAc in hexanes to give product **2.12c** in 77% yield (283 mg, 1.05 mmol) as a clear oil.

¹H NMR: (500 MHz, CDCl₃) δ = 5.81 (ddt, J = 16.2, 11.2, 7.4 Hz, 1H), 5.09 - 5.05 (m, 2H), 4.83 (t, J = 4.5, 3.4 Hz, 1H), 2.45 - 2.35 (m, 2H), 2.12 (s, 1H), 2.10 - 2.02 (m, 1H), 2.01 - 1.93 (m, 1H),

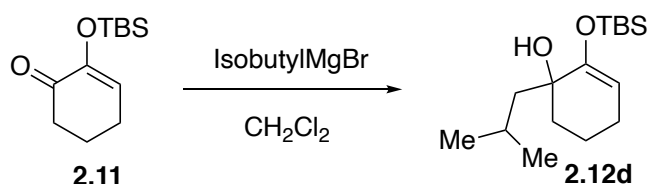
1.78 (ddd, $J = 13.2, 9.5, 3.5$ Hz, 1H), 1.71 - 1.65 (m, 1H), 1.64 - 1.60 (m, 1H), 1.57 - 1.51 (m, 1H), 0.94 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) $\delta = 151.95, 134.41, 117.70, 104.06, 77.25, 77.20, 77.00, 76.75, 71.90, 44.14, 34.42, 25.79, 25.73, 24.31, 19.21, 18.16, -4.52, -4.57$.

IR: ν (cm^{-1}) = 3475, 3075, 2857, 2375, 2189, 2171, 2158, 2068, 2006, 1939, 1703, 1640, 1554, 1471, 1435, 1389, 1337, 1283, 1240, 1168, 1086, 939, 912, 836, 778, 674, 573, 489, 424.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 251.1826$ calculated for $\text{C}_{15}\text{H}_{27}\text{OSi}$; found 251.1833.

2-((*tert*-butyldimethylsilyl)oxy)-1-isobutylcyclohex-2-en-1-ol (**2.12d**)



Procedure: Ketone **2.11** (300 mg, 1.32 mmol) was dissolved in dichloromethane (6.6 mL), and the solution was cooled to 0 °C. Isobutylmagnesium bromide (1.0 mL, 2.0 M in Et_2O) was then added dropwise. After stirring for 16 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH_4Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes to 2% EtOAc in hexanes to give product **2.12d** in 50% yield (200 mg, 0.703 mmol) as a clear oil.

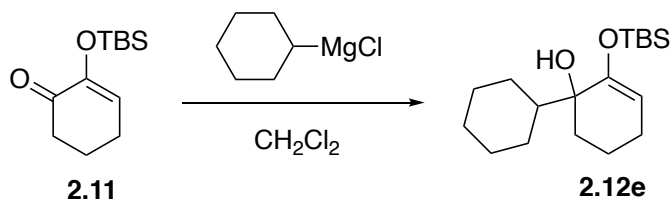
^1H NMR: (500 MHz, CDCl_3) $\delta = 4.77$ (dd, $J = 4.5, 3.5$ Hz, 1H), 2.10 - 2.03 (m, 1H), 2.01 - 1.94 (m, 1H), 1.87 - 1.68 (m, 3H), 1.67 - 1.59 (m, 1H), 1.59 - 1.49 (m, 3H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.95 (s, 9H), 0.92 (d, $J = 6.7$ Hz, 3H), 0.18 (s, 3H), 0.17 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 153.05, 103.27, 77.34, 77.29, 77.09, 76.84, 72.83, 47.60, 34.39, 25.91, 24.97, 24.48, 24.46, 24.08, 19.62, 18.27, -4.41, -4.54.

IR: $f(\text{cm}^{-1})$ = 3591, 2929, 1657, 1463, 1362, 1250, 1169, 919, 836, 778, 673.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 285.2244$ calculated for $\text{C}_{16}\text{H}_{33}\text{O}_2\text{Si}$; found 285.2239.

2-((*tert*-butyldimethylsilyl)oxy)-[1,1'-bi(cyclohexan)]-2-en-1-ol (10e)



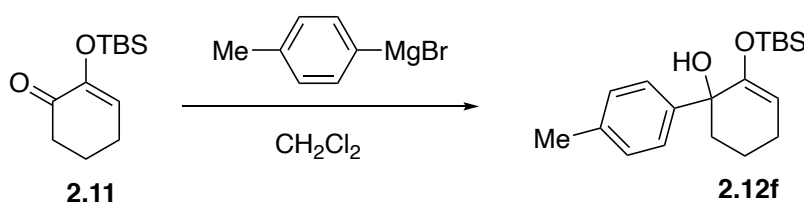
Procedure: Ketone **2.11** (200 mg, 0.883 mmol) was dissolved in dichloromethane (4.4 mL), and the solution was cooled to 0 °C. Cyclohexylmagnesium chloride (0.66 mL, 2.0 M in Et_2O) was then added dropwise. After stirring for 22 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH_4Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes to 2% EtOAc in hexanes to give product **2.12e** in 43% yield (119 mg, 0.384 mmol) as a clear oil.

^1H NMR: (500 MHz, CDCl_3) δ = 4.86 (dd, J = 6.0, 2.7 Hz, 1H), 2.04 - 1.96 (m, 1H), 1.95 - 1.87 (m, 2H), 1.83 - 1.77 (m, 1H), 1.75 - 1.64 (m, 4H), 1.61 - 1.48 (m, 4H), 1.27 - 0.95 (m, 5H), 0.94 (s, 9H), 0.92 - 0.87 (m, 1H), 0.18 (d, J = 7.2 Hz, 6H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 152.21, 104.91, 77.00, 74.97, 45.82, 30.84, 28.96, 27.21, 27.08, 27.04, 26.12, 25.99, 24.53, 19.36, 18.39, -4.28, -4.47.

IR: $\tilde{\nu}$ (cm⁻¹) = 3605, 2927, 1657, 1360, 1238, 1176, 963, 928, 912, 892, 827, 777, 732. **HRMS** (ESI-TOF) m/z : (M+H)⁺ = 333.2220 calculated for C₁₈H₃₄O₂Si; found 333.2221.

6-((*tert*-butyldimethylsilyl)oxy)-4'-methyl-3,4-dihydro-[1,1'-biphenyl]-1(2*H*)-ol (2.12f)



Procedure: Ketone **2.11** (200 mg, 0.883 mmol) was dissolved in dichloromethane (4.4 mL), and the solution was cooled to 0 °C. *p*-Tolyl magnesium bromide (1.33 mL, 1.0 M in THF) was then added dropwise. After stirring for 18 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH₄Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes to 3% EtOAc in hexanes to give product **2.12f** in 62% yield (174.5 mg, 0.5478 mmol) as a clear yellow oil.

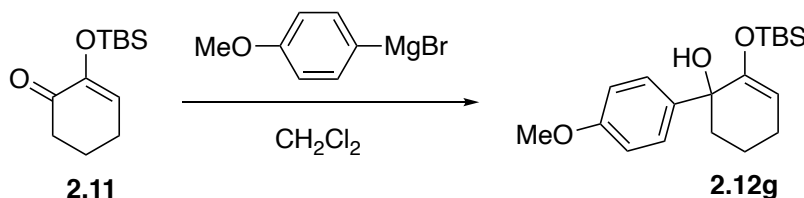
¹H NMR: (500 MHz, CDCl₃) δ = 7.36 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 7.5 Hz, 2H), 5.05 (t, J = 4.0 Hz, 1H), 2.73 (s, 1H), 2.33 (s, 3H), 2.23 - 2.09 (m, 2H), 2.06 - 1.99 (m, 1H), 1.94 - 1.88 (m, 1H), 1.66 - 1.58 (m, 1H), 1.49 - 1.40 (m, 1H), 0.72 (s, 9H), 0.18 (s, 3H), 0.06 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 150.66, 143.65, 136.21, 128.34, 126.04, 104.83, 78.62, 77.25, 77.00, 76.75, 75.25, 39.48, 25.47, 24.35, 21.00, 19.14, 17.90, -4.35, -5.00.

IR: $\tilde{\nu}$ (cm⁻¹) = 3581, 2929, 1662, 1461, 1361, 1241, 1175, 1050, 1006, 937, 916, 813, 776, 671, 536, 480.

HRMS (ESI-TOF) m/z : (M+Na)⁺ = 341.1907 calculated for C₁₉H₃₀O₂SiNa; found 341.1905.

6-((*tert*-butyldimethylsilyl)oxy)-4'-methoxy-3,4-dihydro-[1,1'-biphenyl]-1(2*H*)-ol (2.12g)



Procedure: Ketone **2.11** (196 mg, 0.864 mmol) was dissolved in dichloromethane (4.3 mL), and the solution was cooled to 0 °C. *p*-Methoxyphenyl magnesium bromide (2.6 mL, 0.5 M in THF) was then added dropwise. After stirring for 18 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH₄Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes to 4% EtOAc in hexanes to give product **2.12g** in 64 % yield (185 mg, 0.552 mmol) as a clear oil.

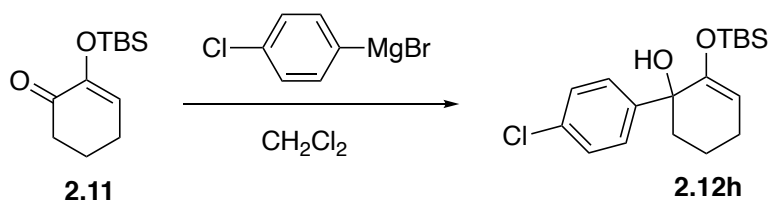
¹H NMR: (400 MHz, CDCl₃) δ = 7.39 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 5.04 (t, *J* = 4.0 Hz, 1H), 3.80 (s, 3H), 2.73 (s, 1H), 2.24 - 2.07 (m, 2H), 2.06 - 1.97 (m, 1H), 1.94 - 1.86 (m, 1H), 1.67 - 1.57 (m, 1H), 1.49 - 1.37 (m, 1H), 0.72 (s, 9H), 0.18 (s, 3H), 0.07 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 158.44, 150.61, 138.82, 127.31, 113.00, 104.80, 77.32, 77.00, 76.68, 75.06, 55.23, 39.51, 25.49, 24.35, 19.14, 17.90, -4.36, -4.96.

IR: *f* (cm⁻¹) = 3576, 2949, 2931, 2856, 1661, 1609, 1583, 1508, 1463, 1296, 1242, 1174, 1071, 916, 829, 778.

HRMS (ESI-TOF) *m/z*: (M+Na)⁺ = 357.1856 calculated for C₁₉H₃₀NaO₃Si; found 357.1858.

6-((*tert*-butyldimethylsilyl)oxy)-4'-chloro-3,4-dihydro-[1,1'-biphenyl]-1(2*H*)-ol (2.12h)



Procedure: Ketone **2.11** (300 mg, 1.33 mmol) was dissolved in dichloromethane (6.6 mL), and the solution was cooled to 0 °C. 4-Chlorophenylmagnesium bromide (1.98 mL, 1.0 M in THF) was then added dropwise. After stirring for 17 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH₄Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes to 2% EtOAc in hexanes to give product **2.12h** in 55% yield (248 mg, 0.731 mmol) as a colorless oil.

¹H NMR: (500 MHz, CDCl₃) δ = 7.43 - 7.40 (m, 2H), 7.29 - 7.26 (m, 2H), 5.07 (t, J = 3.7 Hz, 1H), 2.74 (s, 1H), 2.23 - 2.10 (m, 2H), 2.03 (ddd, J = 10.6, 10.4, 2.8 Hz, 1H), 1.86 (ddd, J = 13.1, 7.6, 3.0 Hz, 1H), 1.67 - 1.60 (m, 1H), 1.47 - 1.39 (m, 1H), 0.71 (s, 9H), 0.18 (s, 3H), 0.07 (s, 3H).

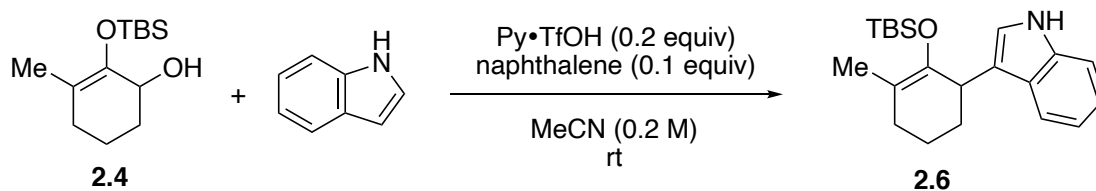
¹³C NMR: (125 MHz, CDCl₃) δ = 150.13, 145.34, 132.47, 127.78, 127.61, 105.21, 75.08, 39.46, 25.42, 24.28, 18.99, 17.87, -4.42, -4.97.

IR: f (cm⁻¹) = 3575, 2930, 2857, 1660, 1486 1471, 1400, 1361, 1337, 1241, 1208, 1175, 1140, 1090, 959, 915, 825, 809, 778, 672, 509.

HRMS (ESI-TOF) m/z : (M+Na)⁺ = 361.1361 calculated for C₁₈H₂₇ClO₂SiNa; found 361.1372.

2-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-ol (2.12i**)**

6.2.3 Kinetic and NMR Studies

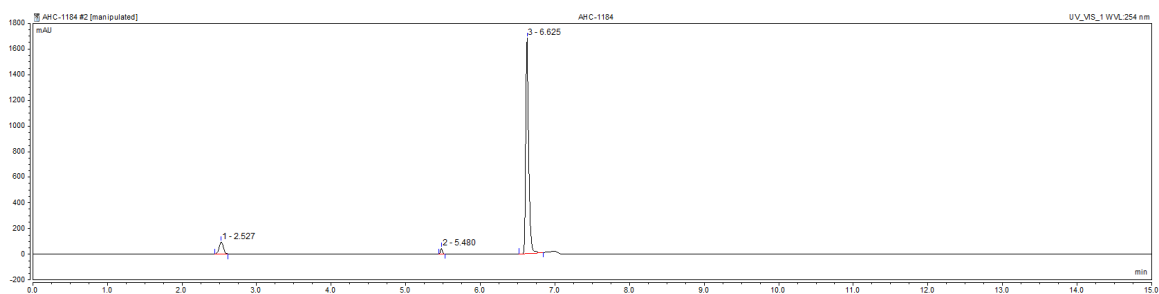


Procedure: Alcohol **2.4** (528 mg, 2.18 mmol) was dissolved in acetonitrile (10.9 mL). Indole (280 mg, 2.39 mmol) and naphthalene (28 mg, 0.218 mmol) were then added, followed by pyridinium triflate (100 mg, 0.435 mmol). The reaction progress was monitored by HPLC every two hours by diluting a 50 μL aliquot of the reaction mixture to 1 mL solution of 1% triethylamine in hexanes. This dilute sample was injected through a Hypersil GOLD Silica column (150 x 4.6 mm) using a linear gradient of 0-3% isopropanol in hexanes over 15 minutes at a flow rate of 1 mL/min. The UV detector was set at 254 nm.

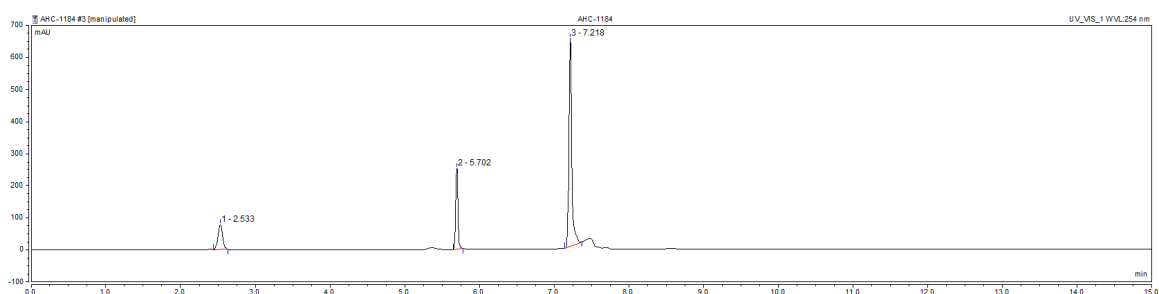
Table 6.1. Kinetic Profile of Table 2.1 (Entry 5)

Time (h)	Naphthalene		Silylenol Ether 2.6		2.6 / Napthlene
	Retention Time	Area	Retention time	Area	
	(min)		(min)		
0	2.53	6.58	5.48	1.37	0.02
2	2.53	5.67	5.70	8.33	0.15
4	2.43	6.40	5.28	17.33	0.27
6	2.40	5.84	5.28	21.83	0.37
8	2.43	4.97	6.14	23.32	0.47

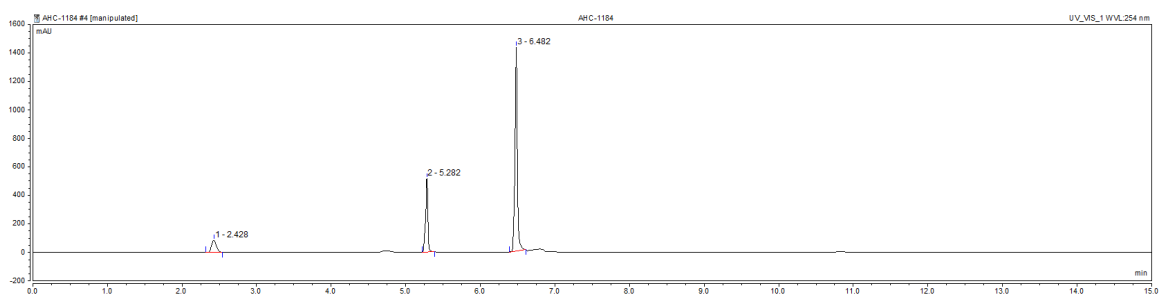
Time 0 h



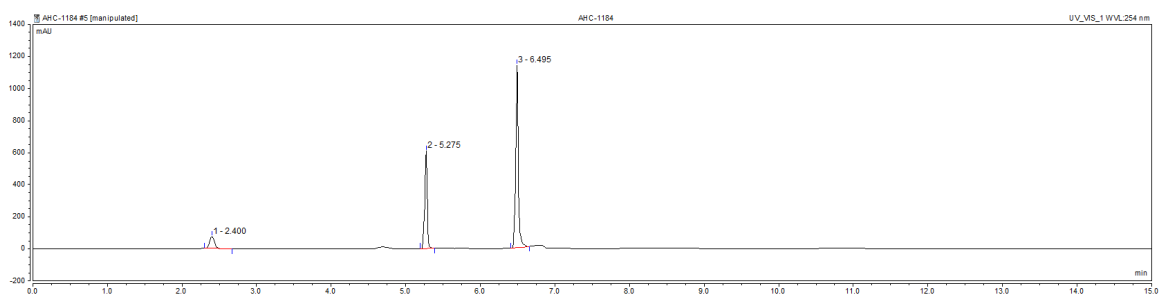
Time 2 h



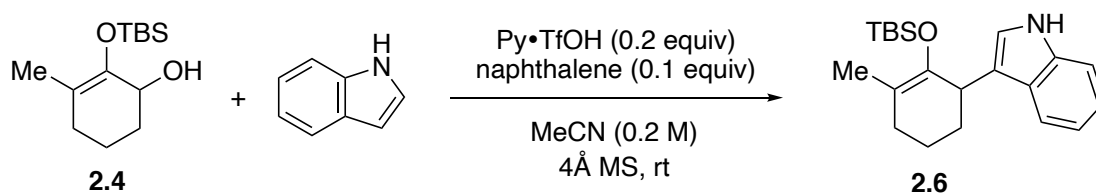
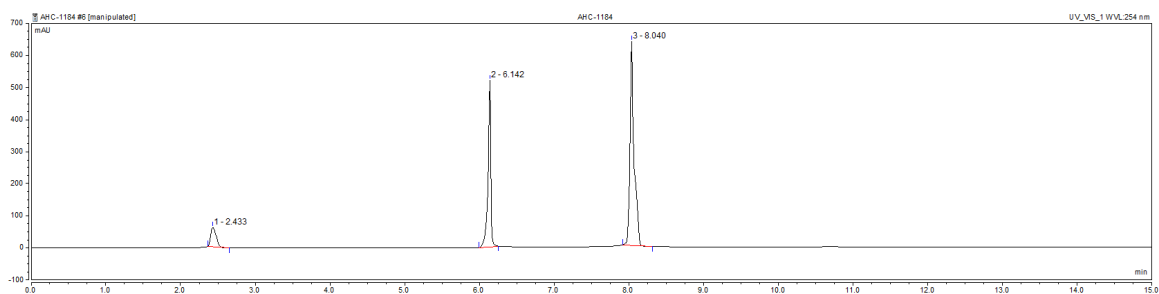
Time 4 h



Time 6 h



Time 8 h

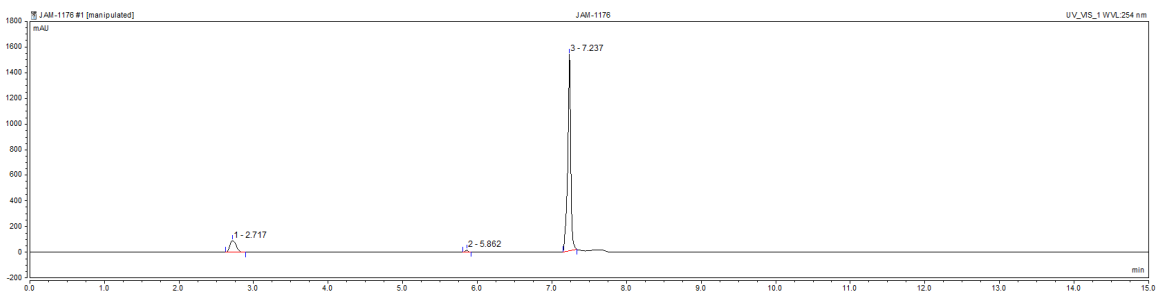


Procedure: Alcohol **2.4** (526 mg, 2.17 mmol) was dissolved in acetonitrile (10.8 mL). Indole (279 mg, 2.38 mmol), naphthalene (28 mg, 0.217 mmol), and 4Å molecular sieves (577 mg) were then added, followed by pyridinium triflate (99 mg, 0.434 mmol). The reaction progress was monitored by HPLC every two hours by diluting a 50 µL aliquot of the reaction mixture to 1 mL solution of 1% triethylamine in hexanes. This dilute sample was injected through a Hypersil GOLD Silica column (150 x 4.6 mm) using a linear gradient of 0-3% isopropanol in hexanes over 15 minutes at a flow rate of 1mL/min. The UV detector was set at 254 nm.

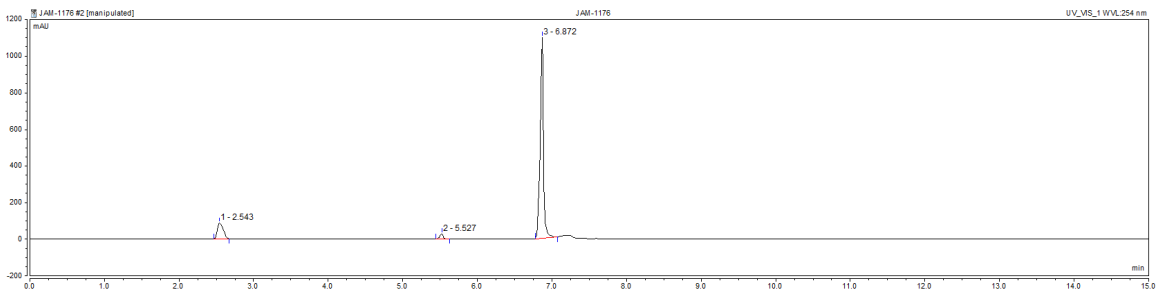
Table 6.2 Kinetic Profile of Table 2.1 (Entry 10)

Time (h)	Naphthalene		Silylenol Ether 2.6		2.6/ Naphthlene
	Retention Time	Area	Retention time	Area	
	(min)		(min)		
0	2.46	6.67	0.00	0.00	0.00
2	2.43	7.37	6.23	17.18	0.23
4	2.31	7.68	4.99	24.19	0.32
6	2.27	7.59	4.96	26.17	0.34
8	2.26	7.24	4.88	28.44	0.39

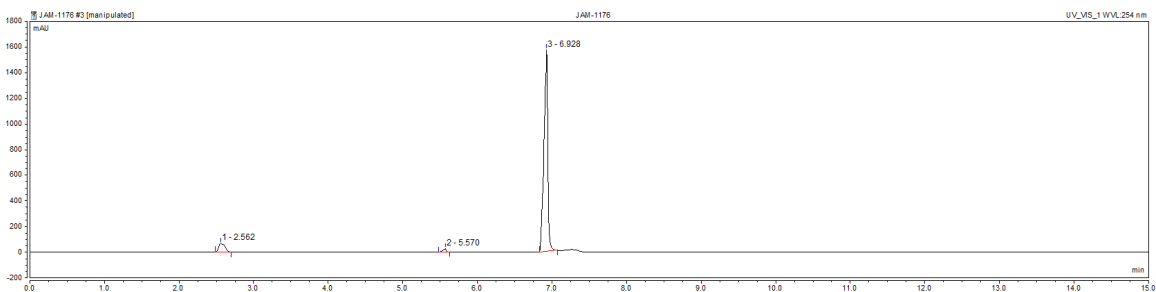
Time 0 h



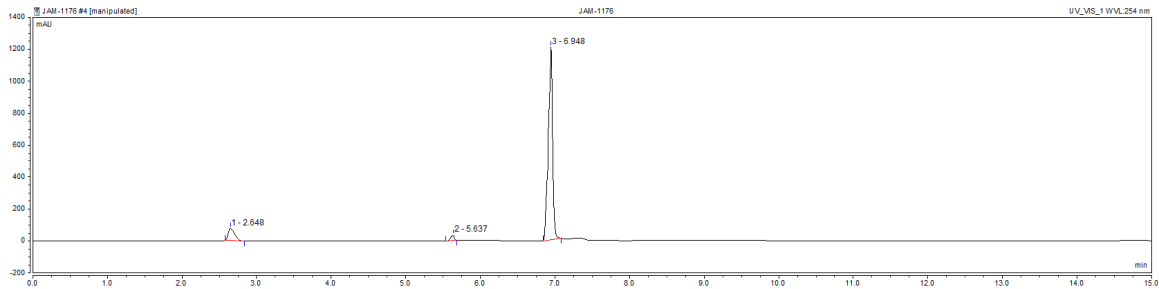
Time 2 h



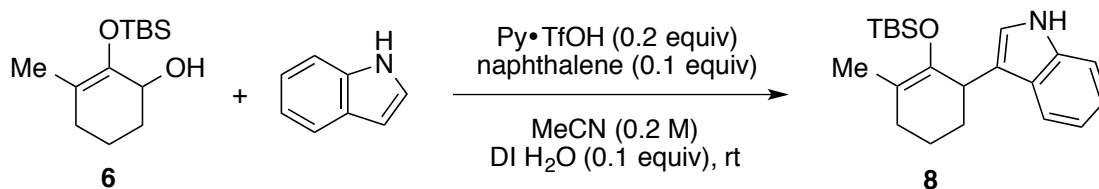
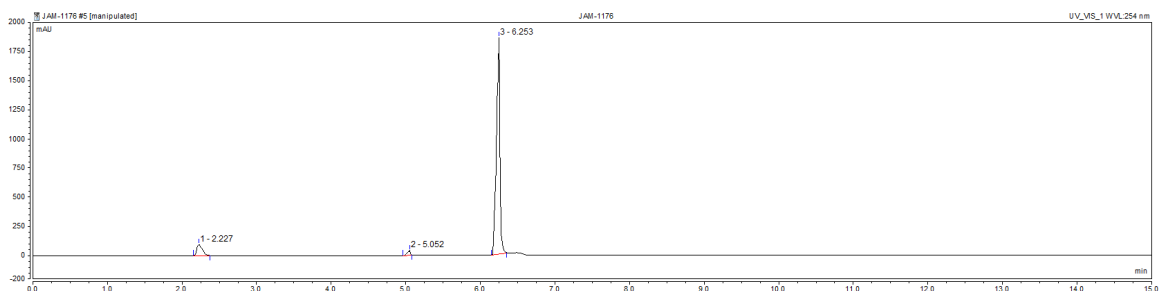
Time 4 h



Time 6 h



Time 8 h

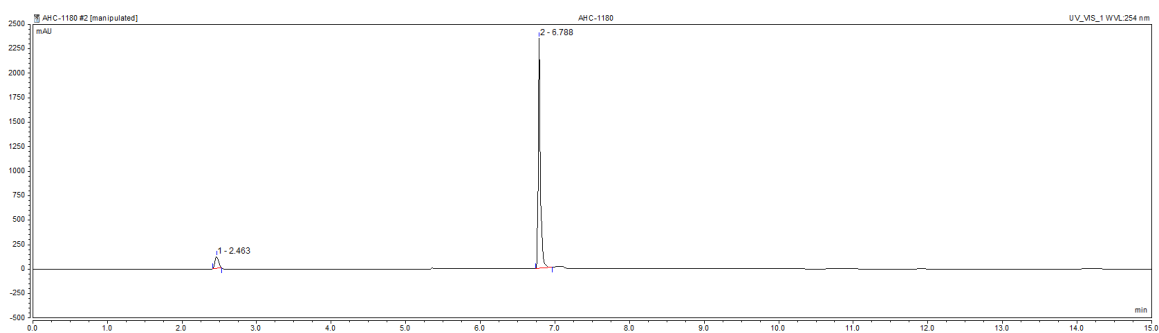


Procedure: Alcohol **6** (502 mg, 2.07 mmol) was dissolved in acetonitrile (10.4 mL). Indole (266 mg, 2.27 mmol), naphthalene (26 mg, 0.207 mmol), and DI water (4.0 μ L, 0.207 mmol) were then added, followed by pyridinium triflate (95 mg, 0.414 mmol). The reaction progress was monitored by HPLC every two hours by diluting a 50 μ L aliquot of the reaction mixture to 1 mL solution of 1% triethylamine in hexanes. This dilute sample was injected through a Hypersil GOLD Silica column (150 x 4.6 mm) using a linear gradient of 0-3% isopropanol in hexanes over 15 minutes at a flow rate of 1mL/min. The UV detector was set at 254 nm.

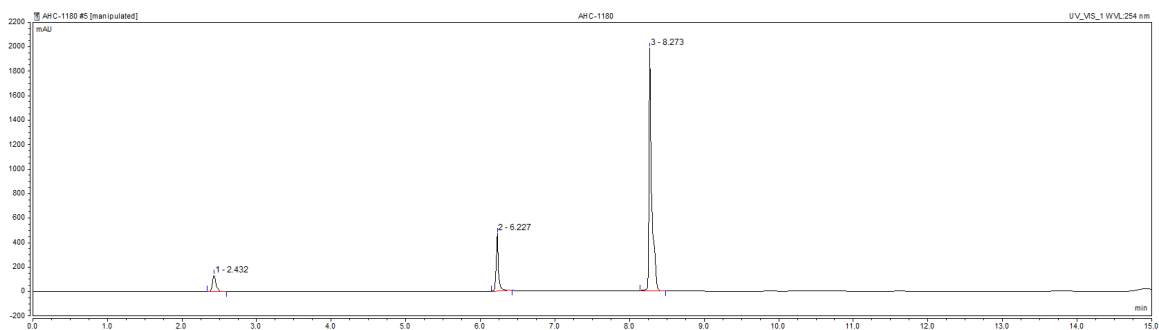
Table 6.3. Kinetic Profile of Table 2.1 (Entry 11)

Time (h)	Naphthalene		Silylenol Ether 2.6		2.6/ Napthlene
	Retention Time	Area	Retention time	Area	
	(min)		(min)		
0	2.46	6.67	0.00	0.00	0.00
2	2.43	7.37	6.23	17.18	0.23
4	2.31	7.68	4.99	24.19	0.32
6	2.27	7.59	4.96	26.17	0.34
8	2.26	7.24	4.88	28.44	0.39

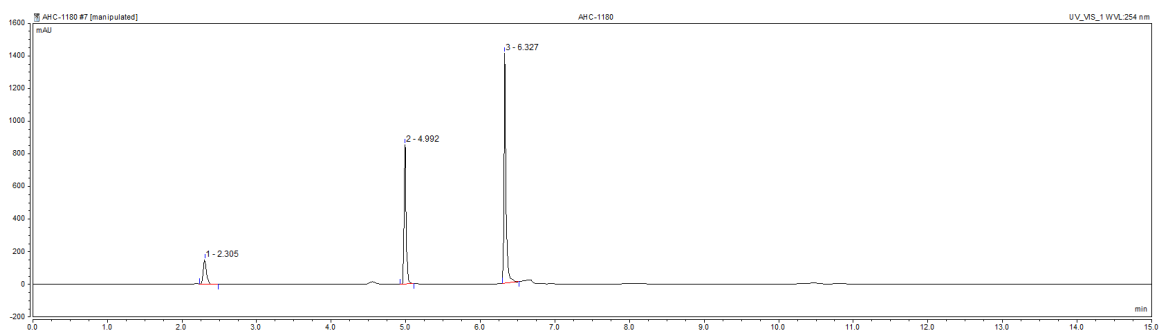
Time 0 h



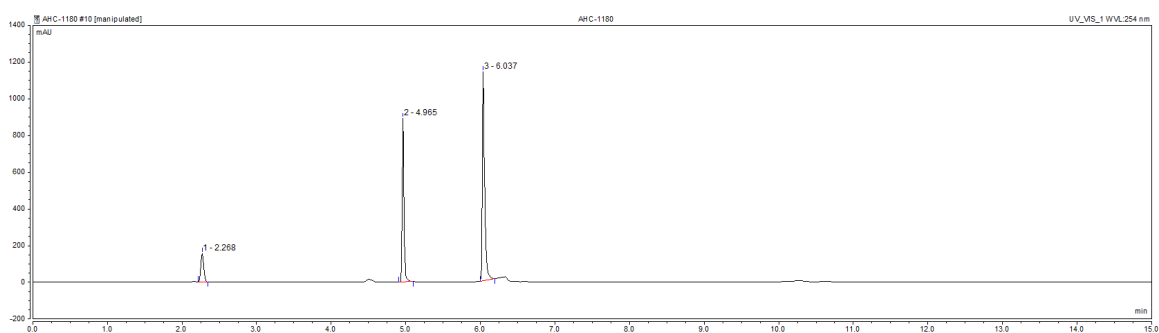
Time 2 h



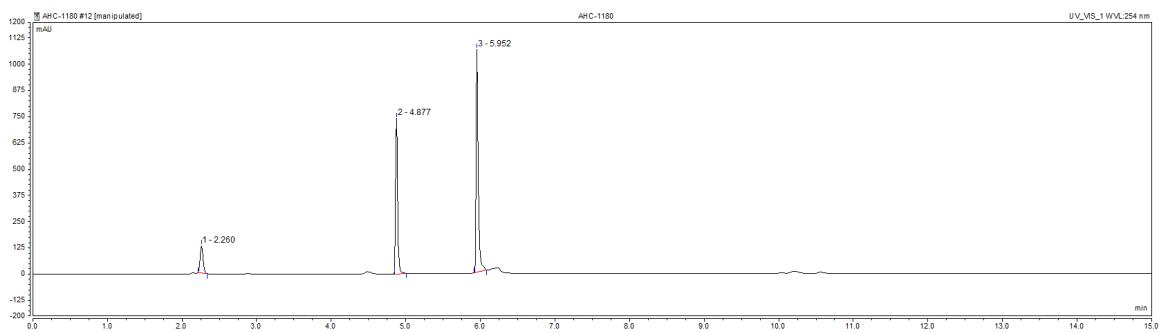
Time 4 h



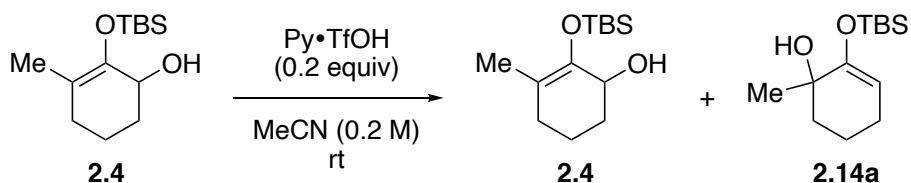
Time 6 h



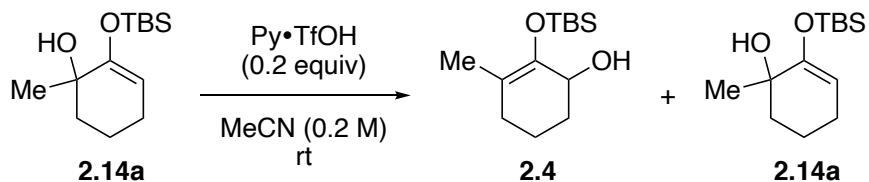
Time 8 h



NMR studies on the isomerization of starting materials **2.4** and **2.12a**



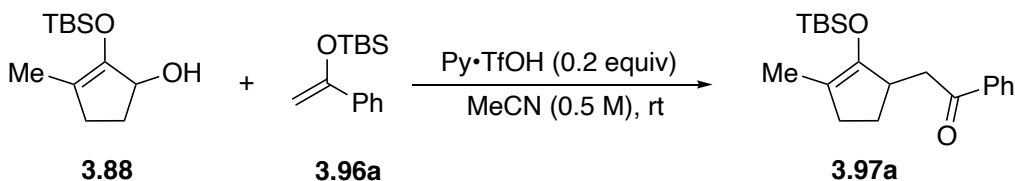
Alcohol **2.4** (65 mg, 0.268 mmol) was dissolved in acetonitrile (1.4 ml), and pyridinium triflate (12 mg, 0.054 mmol) was then added. After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and DI water (2 ml). The aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude mixture was then analysed by ^1H NMR.



Alcohol **12a** (66 mg, 0.272 mmol) was dissolved in acetonitrile (1.4 ml), and pyridinium triflate (12 mg, 0.054 mmol) was then added. After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and DI water (2 ml). The aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude mixture was then analysed by ^1H NMR.

6.3 Experimental Procedures for Chapter Three

2-(((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1-phenylethan-1-one(3.97a)

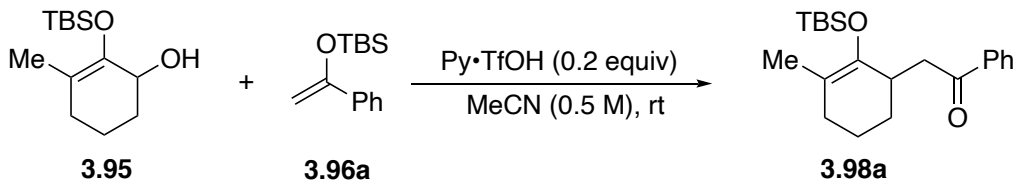


Starting material **3.88** (81 mg, 0.36 mmol) was dissolved in dry acetonitrile (0.7 mL). Silylenol ether **3.96a** (166 mg, 0.71 mmol) was then added, followed by $\text{Py}\cdot\text{TfOH}$ (0.3 mL, 0.14 mmol, 0.5 M solution in acetonitrile) to yield **3.97a** in 82% as a yellow oil (192 mg, 0.54 mmol). The purified product was eluted with hexanes to 98/2 hexanes/EtOAc.

^1H NMR: (400 MHz, CDCl_3) δ = 7.97 (d, J = 7.1 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 3.29 (dd, J = 16.8, 2.7 Hz, 1H), 3.09 (s, 1H), 2.90 (dd, J = 16.8, 10.7 Hz, 1H), 2.22 - 2.12 (m, 3H), 1.57 (s, 3H), 1.50 - 1.40 (m, 1H), 0.95 (s, 8H), 0.14 (s, 3H), 0.11 (s, 3H).

^{13}C NMR: (100 MHz, CDCl_3) δ = 199.8, 147.9, 137.2, 132.8, 128.4, 128.0, 113.7, 42.3, 41.3, 31.9, 26.9, 25.7, 18.0, 12.3, -4.0, -4.2.

2-(((tert-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1-phenylethan-1-one (3.98a)

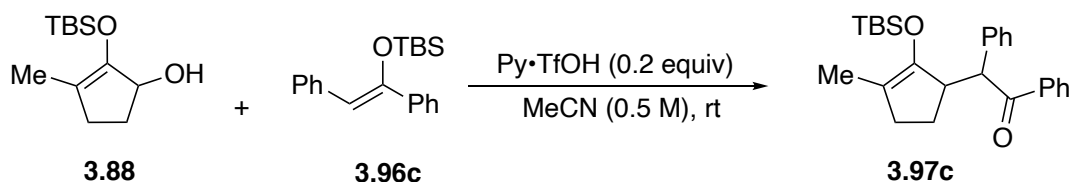


Starting material **3.95** (105 mg, 0.43 mmol) was dissolved in dry acetonitrile (0.9 mL). Silylenol ether **3.96a** (203 mg, 0.87 mmol) was then added, followed by $\text{Py}\cdot\text{TfOH}$ (0.2 mL, 0.09 mmol, 0.5 M solution in acetonitrile) to yield **3.98a** in 70% as a colorless oil (104 mg, 0.30 mmol). The purified product was eluted with 99/1 hexanes/EtOAc.

¹H NMR: (400 MHz, CDCl₃) δ = 7.98 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 6.5 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 3.33 (dd, *J* = 17.5, 2.0 Hz, 1H), 3.05 (dd, *J* = 17.4, 10.7 Hz, 1H), 2.88 (s, 1H), 2.06 - 1.93 (m, 2H), 1.90 - 1.81 (m, 1H), 1.62 (s, 3H), 1.57 - 1.39 (m, 3H), 0.94 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 199.8, 144.6, 137.5, 132.8, 128.5, 127.9, 113.7, 41.1, 34.9, 30.6, 29.0, 25.9, 19.6, 18.2, 17.1, -3.7, -4.3.

2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1,2-diphenylethan-1-one
(3.97c)



Starting material **3.88** (270 mg, 1.18 mmol) was dissolved in dry acetonitrile (2.4 mL). Silylenol ether **3.96c** (734 mg, 2.36 mmol) was then added, followed by Py·TfOH (0.5 mL, 0.24 mmol, 0.5 M solution in acetonitrile) to yield **3.97c** in 57% as a mixture of inseparable diastereomers, as a colorless oil (274 mg, 0.67 mmol). The purified product was eluted with hexanes to 60/40 hexanes/CH₂Cl₂.

¹H NMR: (400 MHz, CDCl₃) δ = 7.94 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 2H), 7.44 (dd, *J* = 8.5, 6.6 Hz, 1.5H), 7.35 (q, *J* = 7.7, 6.6 Hz, 4H), 7.29 - 7.15 (m, 8H), 4.87 - 4.79 (m, 1.5H), 3.27 (s, 1H), 3.16 (s, 0.5H), 2.25 - 2.14 (m, 0.5 H), 2.05 - 1.77 (m, 4H), 1.71 - 1.64 (m, 1H), 1.57 (d, *J* = 9.9 Hz, 0.5 H), 1.44 (s, 5H), 1.34 - 1.22 (m, 3H), 0.93 (s, 9H), 0.79 (s, 4.5H), 0.11 (s, 6H), -0.03 (s, 3H).

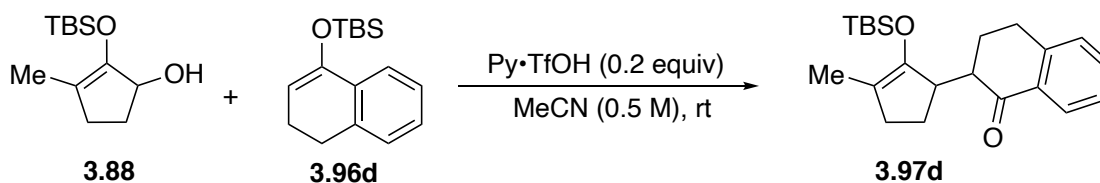
¹³C NMR: (100 MHz, CDCl₃) δ = 200.5, 200.4, 147.9, 146.5, 138.7, 137.8, 136.9, 136.9, 132.5, 132.4, 129.4, 128.9, 128.7, 128.4, 128.4, 128.3, 128.2, 127.9, 126.7, 126.6, 116.0, 115.3, 55.2,

54.1, 50.5, 47.8, 32.1, 31.8, 25.7, 25.7, 25.4, 23.0, 22.3, 18.0, 17.9, 14.0, 12.4, 12.2, -3.8, -3.9, -4.1, -4.5.

IR: $f(\text{cm}^{-1}) = 2928, 2855, 1681, 1597, 1580, 1495, 1446, 1379, 1329, 1078, 938, 861, 777$.

HRMS: (ESI-TOF) m/z : $(M+H)^+ = 407.2401$ calculated for $C_{26}H_{35}O_2Si$; Found 407.2402.

2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-3,4 dihydronaphthalen-1(2H)-one (3.97d).

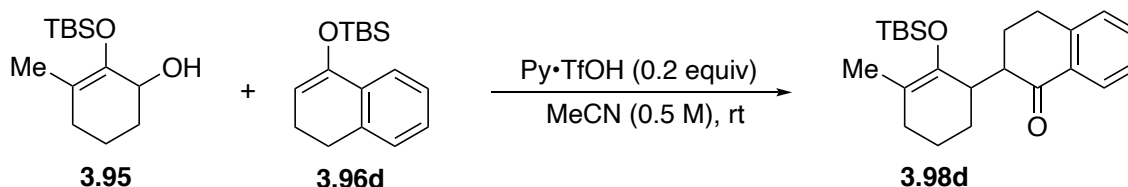


Starting material **3.88** (380 mg, 1.66 mmol) was dissolved in dry acetonitrile (3.3 mL). Silylenol ether **3.96d** (866 mg, 3.33 mmol) was then added, followed by Py•TfOH (0.7 mL, 0.33 mmol, 0.5 M solution in acetonitrile) to yield **3.97d** in 61% as mixture of inseparable diastereomers, as a colorless oil (359 mg, 1.01 mmol). The purified product was eluted hexanes to 80/20 hexanes/ CH_2Cl_2 .

1H NMR: (400 MHz, $CDCl_3$) δ = 8.04 (d, J = 7.8 Hz, 0.5H), 8.00 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.4 Hz, 0.5H), 7.41 (d, J = 7.4 Hz, 1H), 7.32 - 7.27 (m, 1H), 7.24 - 7.19 (m, 2H), 3.55 (s, 0.5H), 3.26 (s, 1H), 3.04 - 2.88 (m, 3.5H), 2.81 - 2.75 (m, 1H), 2.51 - 2.45 (m, 1H), 2.29 - 2.22 (m, 1H), 2.18 - 2.05 (m, 5H), 2.00 - 1.94 (m, 1H), 1.89 - 1.79 (m, 0.5H), 1.64 - 1.62 (m, 0.5H), 1.56 (s, 1.5H), 1.54 (s, 3H), 1.46 - 1.38 (m, 0.5H), 0.94 (s, 4.5H), 0.82 (s, 9H), 0.15 (s, 1.5H), 0.12 (s, 4.5H), 0.07 (s, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ = 200.0, 198.9, 147.6, 146.3, 144.5, 144.1, 133.1, 133.1, 133.0, 132.7, 128.6, 128.3, 127.5, 127.2, 126.4, 126.3, 114.8, 114.5, 51.7, 49.7, 45.3, 44.3, 32.8, 32.6, 29.6, 29.0, 26.2, 25.7, 25.5, 22.9, 22.3, 18.1, 17.9, 12.7, 12.3, -3.9, -4.0.

2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one (3.98d).

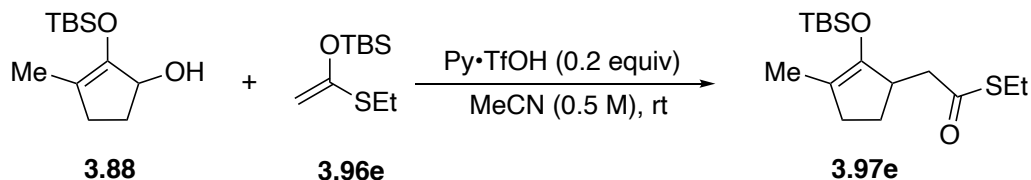


Starting material **3.95** (215 mg, 0.88 mmol) was dissolved in dry acetonitrile (1.8 mL). Silylenol ether **3.96d** (462 mg, 1.77 mmol) was then added, followed by Py•TfOH (0.4 mL, 0.18 mmol, 0.5 M solution in acetonitrile) to yield **3.98d** in 67% as a colorless oil (221 mg, 0.59 mmol). The purified product was eluted with hexanes to 60/40 hexanes/CH₂Cl₂.

¹H NMR: (400 MHz, CDCl₃) δ = 8.05 (d, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 0.1H), 7.47 - 7.40 (m, 1.5H), 7.32 - 7.27 (m, 1.5H), 7.22 (t, *J* = 7.7 Hz, 1.5H), 3.24 (s, 1H), 3.07 (dt, *J* = 13.4, 4.4, Hz, 1H), 3.00 – 2.94 (m, 3H), 2.88 (s, 1H), 2.60 (dt, *J* = 12.1, 4.9 Hz, 0.5H), 2.10 - 1.83 (m, 7.5H), 1.64 - 1.59 (m, 5.5H), 1.54 – 1.41 (m, 2H), 1.31 - 1.22 (m, 1H), 0.94 (s, 9H), 0.84 (s, 4.5H), 0.12 (s, 3H), 0.10 (s, 4.5H), 0.07 (s, 1.5H).

¹³C NMR: (100 MHz, CDCl₃) δ = 199.6, 198.9, 144.4, 144.1, 143.9, 143.1, 133.2, 133.1, 132.9, 132.7, 128.6, 128.4, 127.4, 127.2, 126.4, 126.3, 115.2, 113.8, 51.2, 49.2, 38.9, 38.5, 30.8, 30.8, 30.6, 30.0, 29.1, 27.2, 26.0, 25.9, 24.8, 23.9, 22.6, 22.0, 20.2, 18.2, 18.2, 17.2, -3.3, -3.8, -4.0, -4.4.

S-ethyl-2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)ethanethioate (3.99e).



Starting material **3.88** (177 mg, 0.66 mmol) was dissolved in dry acetonitrile (1.5 mL). Silylenol ether **3.96e** (331 mg, 1.51 mmol) was then added, followed by Py·TfOH (0.3 mL, 0.15 mmol, 0.5 M solution in acetonitrile) to yield **3.97e** in 62% as a colorless oil (148 mg, 0.57 mmol). The purified product was eluted with hexanes to 97/3 hexanes/EtOAc.

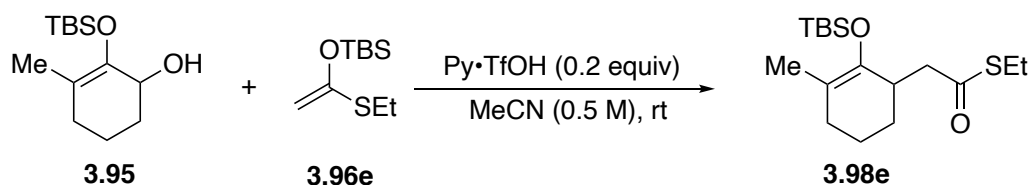
¹H NMR: (500 MHz, CDCl₃) δ = 2.94 - 2.84 (m, 4H), 2.39 - 2.33 (m, 1H), 2.23 - 2.12 (m, 2H), 2.22 - 2.12 (m, 1H), 1.60 - 1.53 (m, 4H), 1.25 (t, J = 7.4 Hz, 3H), 0.95 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 199.1, 147.3, 114.0, 47.7, 43.0, 34.3, 31.7, 26.0, 25.7, 23.2, 18.1, 14.7, 12.3, -4.0, -4.2.

IR: f (cm⁻¹) = 2929, 2856, 1686, 1462, 1380, 1380, 1252, 1212, 1155, 1074, 938.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 315.1809 calculated for C₁₆H₃₁O₂SSi; Found 315.1813.

S-ethyl-2-((tert-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)ethanethioate (3.98e).



Starting material **3.95** (529 mg, 2.18 mmol) was dissolved in dry acetonitrile (4.3 mL). Silylenol ether **3.96e** (953 mg, 4.36 mmol) was then added, followed by Py·TfOH (0.9 mL, 0.43 mmol, 0.5 M solution in acetonitrile) to yield **3.98e** in 70% as a colorless oil (500 mg, 1.52 mmol). The purified product was eluted with hexanes to 90/10 hexanes/CH₂Cl₂.

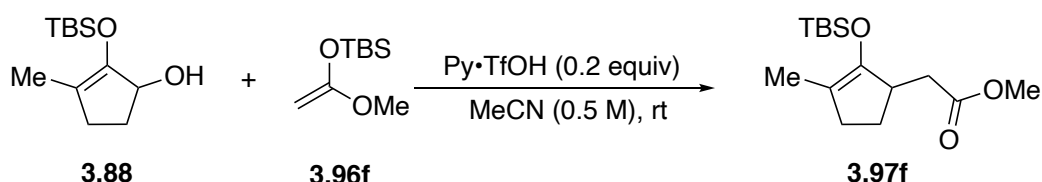
¹H NMR: (400 MHz, CDCl₃) δ = 3.00 (dd, J = 14.9, 2.7 Hz, 1H), 2.87 (q, J = 7.4 Hz, 2H), 2.60 (s, 1H), 2.45 (dd, J = 14.8, 11.2 Hz, 1H), 1.97 – 1.91 (m, 2H), 1.77 – 1.72 (m, 1H), 1.57 (s, 3H), 1.54 – 1.46 (m, 2H), 1.24 (t, J = 7.4 Hz, 3H), 0.96 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 199.2, 143.9, 113.8, 46.8, 36.8, 30.5, 28.2, 25.9, 23.2, 19.4, 18.2, 17.1, 14.7, -3.6, -4.2.

IR: f (cm⁻¹) = 2929, 2857, 1685, 1461, 1347, 1254, 1168, 1125, 1080, 1004, 917.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 329.1965 calculated for C₁₇H₃₃O₂SSi; Found 329.1967.

Methyl 2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)acetate (3.97f**)**



Starting material **3.88** (106 mg, 0.46 mmol) was dissolved in dry acetonitrile (0.9 mL). Silylenol ether **3.96f** (0.2 mL, 0.92 mmol) was then added, followed by Py•TfOH (0.2 mL, 0.09 mmol, 0.5 M solution in acetonitrile) to yield **3.97f** in 61% as a colorless oil (89 mg, 0.28 mmol). The purified product was eluted with hexanes to 98/2 hexanes/EtOAc.

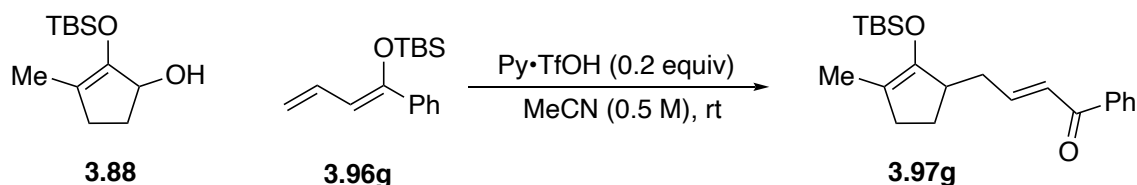
¹H NMR: (400 MHz, CDCl₃) δ = 3.67 (s, 3H), 2.87 (s, 1H), 2.68 (dd, J = 15.3, 3.2 Hz, 1H), 2.19 - 2.03 (m, 4H), 1.57 (dd, J = 4.5, 1.5 Hz, 1H), 1.54 (s, 3H), 1.51 - 1.43 (m, 1H), 0.95 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 173.7, 147.5, 113.7, 51.4, 42.3, 38.0, 26.5, 25.7, 18.1, 12.3, -4.0, -4.2.

IR: f (cm⁻¹) = 2930, 2857, 1740, 1687, 1472, 1435, 1281, 1328, 1211, 1066, 855, 835, 777.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 285.1880 calculated for C₁₅H₂₉O₃Si; Found 285.1883.

(E)-4-(2-(((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1-phenylbut-2-en-1-one (3.97g).

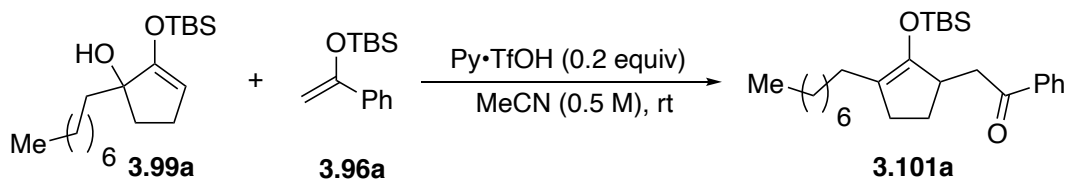


Starting material **3.88g** (155 mg, 0.67 mmol) was dissolved in dry acetonitrile (1.3 mL). Silylenol ether **3.96g** (353 mg, 1.35 mmol) was then added, followed by Py•TfOH (0.2 mL, 0.07 mmol, 0.5 M solution in acetonitrile) to yield **3.97g** in 82% as a colorless oil (97mg, 0.29 mmol). The purified product was eluted with hexanes to 98/2 hexanes/EtOAc.

¹H NMR: (400 MHz, CDCl₃) δ = 7.92 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.03 (p, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 15.4 Hz, 1H), 2.68 - 2.59 (m, 2H), 2.26 - 2.14 (m, 3H), 2.04 - 1.95 (m, 1H), 1.55 – 1.50 (m, 4H), 0.96 (s, 9H), 0.13 (s, 3H), 0.13 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 190.8, 148.5, 147.8, 138.0, 132.5, 128.5, 127.0, 113.7, 44.6, 36.7, 31.9, 25.7, 18.1, 12.3, -3.9, -4.1.

2-(2-(((tert-butyldimethylsilyl)oxy)-3-octylcyclopent-2-en-1-yl)-1-phenylethan-1-one (3.101a).⁵



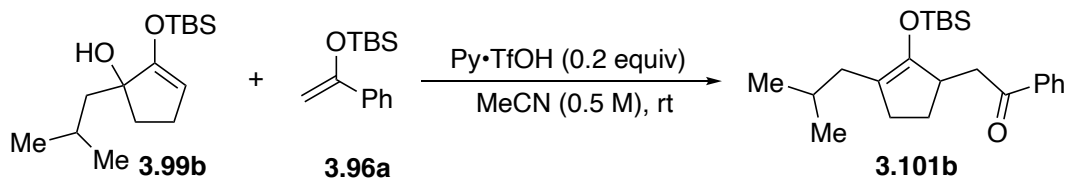
Starting material **3.99a** (150 mg, 0.46 mmol) was dissolved in dry acetonitrile (0.9 mL). Silylenol ether **3.96a** (216 mg, 0.92 mmol) was then added, followed by Py•TfOH (0.18 mL, 0.09 mmol,

0.5 M solution in acetonitrile) to yield **3.101a** in 68 % as a colorless oil (130 mg, 0.31 mmol). The purified product was eluted with hexanes to 50/50 hexanes/CH₂Cl₂.

¹H NMR: (400 MHz, CDCl₃) δ = 7.97 (d, J = 7.1 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 3.27 (dd, J = 16.8, 2.7 Hz, 1H), 3.12 - 3.05 (m, 1H), 2.90 (dd, J = 16.8, 10.6 Hz, 1H), 2.22 - 2.10 (m, 3H), 2.05 – 1.97 (m, J = 6.9 Hz, 2H), 1.48 – 1.41 (m, 1H), 1.28 (bs, 12H), 0.95 (s, 9H), 0.88 (t, J = 6.6 Hz, 3H), 0.13 (s, 3H), 0.11 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 200.1, 147.6, 137.3, 132.8, 128.5, 128.0, 118.4, 42.2, 41.4, 31.9, 29.7, 29.4, 29.3, 29.2, 27.6, 26.9, 26.6, 25.7, 22.6, 18.1, 14.1, -3.9, -4.3.

2-(2-(((tert-butyldimethylsilyl)oxy)-3-isobutylcyclopent-2-en-1-yl)-1-phenylethanone
(3.101b).⁵



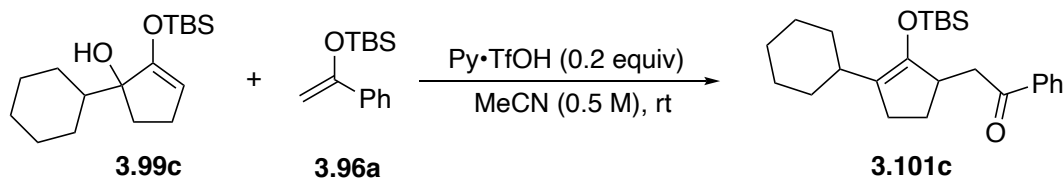
Starting material **3.99b** (150 mg, 0.55 mmol) was dissolved in dry acetonitrile (1.1 mL). Silylenol ether **3.96a** (260 mg, 1.11 mmol) was then added, followed by Py·TfOH (0.2 mL, 0.11 mmol, 0.5 M solution in acetonitrile) to yield **3.101b** in 30% as a colorless oil (63 mg, 0.17 mmol). The purified product was eluted with hexanes to 85/15 hexanes/CH₂Cl₂.

¹H NMR: (500 MHz, CDCl₃) δ = 7.98 (d, J = 7.7 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 3.27 (d, J = 16.9 Hz, 1H), 3.12 – 3.04 (m, 1H), 2.90 (dd, J = 16.9, 10.7 Hz, 1H), 2.27 – 2.07 (m, 3H), 1.95 (dd, J = 13.5, 8.3 Hz, 1H), 1.83 (dd, J = 13.5, 6.3 Hz, 1H), 1.71 (m, J = 13.6, 6.7 Hz, 1H), 0.94 (s, 9H), 0.88 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.12 (s, 3H), 0.11 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 200.2, 149.0, 137.5, 133.0, 128.7, 128.2, 117.6, 42.4, 41.6, 36.0, 29.8, 27.1, 26.9, 25.9, 23.2, 22.6, 18.3, -3.6, -4.0.

2-(2-((tert-butyldimethylsilyl)oxy)-3-cyclohexylcyclopent-2-en-1-yl)-1-phenylethanone

(3.101c).



Starting material **3.99c** (170 mg, 0.57 mmol) was dissolved in dry acetonitrile (1.1 mL). Silylenol ether **3.96a** (269 mg, 1.14 mmol) was then added, followed by Py•TfOH (0.2 mL, 0.11 mmol, 0.5 M solution in acetonitrile) to yield product **3.101c** in 22 % as a colorless oil (51 mg, 0.13 mmol). The purified product was eluted with hexanes to 80/20 hexanes/CH₂Cl₂.

¹H NMR (400 MHz, CDCl₃) δ = 7.97 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 3.26 (dd, J = 16.7, 2.7 Hz, 1H), 3.08 – 3.02 (m, 1H), 2.89 (dd, J = 16.7, 10.6 Hz, 1H), 2.39 (tt, J = 11.5, 3.4 Hz, 1H), 2.20 – 2.05 (m, 3H), 1.74 – 1.65 (m, 3H), 1.55 – 1.42 (m, 3H), 1.27 – 1.15 (m, 5H), 0.95 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H).

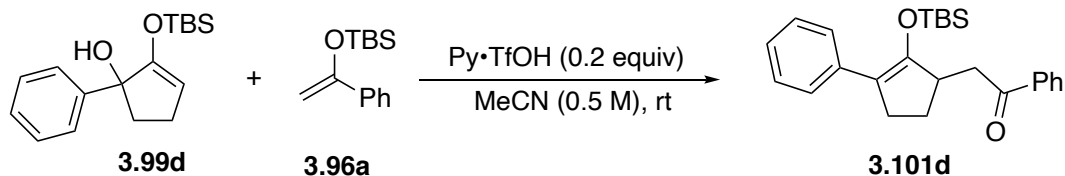
¹³C NMR: (125 MHz, CDCl₃) δ = 200.1, 146.2, 137.3, 132.8, 128.5, 128.0, 123.4, 42.2, 41.5, 35.5, 31.3, 31.1, 26.9, 26.5, 26.2, 25.9, 25.7, 18.1, -4.0, -4.4.

IR: $f(\text{cm}^{-1})$ = 2924, 2851, 1676, 1447, 1361, 1250, 1024, 835, 777, 688.

HRMS: (ESI-TOF) m/z : $(M+H)^+$ = 399.2714 calculated for C₂₅H₃₉O₂Si; Found 398.2718.

2-(2-((tert-butyldimethylsilyl)oxy)-3-phenylcyclopent-2-en-1-yl)-1-phenylethan-1-one

(3.101d).

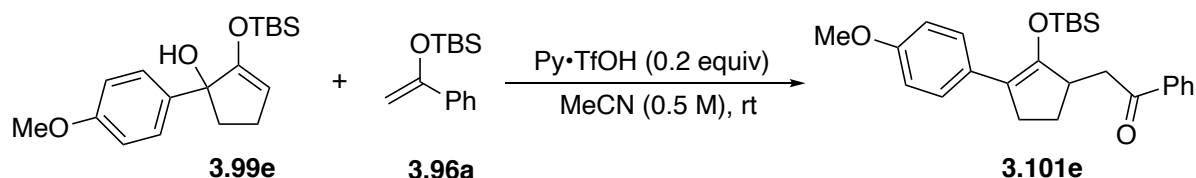


Starting material **3.99d** (150 mg, 0.52 mmol) was dissolved in dry acetonitrile (1.0 mL). Silyl another ether **3.96a** (244 mg, 1.0 mmol) was then added followed by Py•TfOH (0.2 mL, 0.10 mmol, 0.5 M solution in acetonitrile) to yield **3.101d** in 74% as a colorless oil (151 mg, 0.38 mmol). The purified product was eluted with hexanes to 50/50 hexanes/CH₂Cl₂.

¹H NMR: (400 MHz, CDCl₃) δ= 8.00 (d, *J* = 7.2 Hz, 2H), 7.57 (d, *J* = 7.2 Hz, 3H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 3.40 – 3.30 (m, 2H), 3.09 (dd, *J* = 17.6, 11.0 Hz, 1H), 2.82 – 2.73 (m, 1H), 2.59 – 2.51 (m, 1H), 2.35 – 2.26 (m, 1H), 1.59 – 1.52 (m, 1H), 0.94 (s, 9H), 0.11 (s, 3H), -0.02 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 199.5, 151.6, 137.3, 136.4, 133.1, 128.6, 128.1, 127.9, 127.0, 125.8, 42.9, 42.3, 29.8, 26.9, 25.9, 18.3, -3.7, -4.0.

2-(2-((tert-butyldimethylsilyl)oxy)-3-(4-methoxyphenyl)cyclopent-2-en-1-yl)-1-phenylethan-1-one (3.101e).⁵

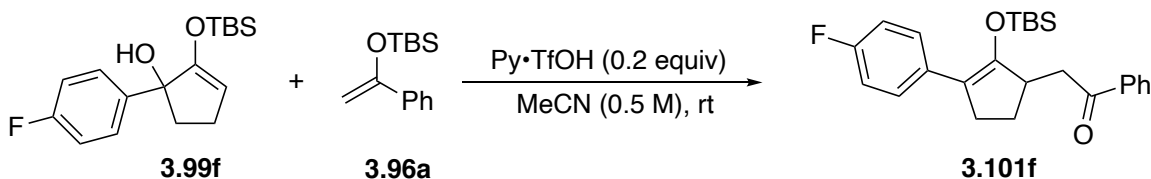


Starting material **3.99e** (150 mg, 0.47 mmol) was dissolved in dry acetonitrile (0.9 mL). Silyl another ether **3.96a** (220 mg, 0.94 mmol) was then added followed by Py•TfOH (0.2 mL, 0.10 mmol, 0.5 M solution in acetonitrile) to yield **3.101e** in 60 % as a colorless oil (119 mg, 0.28 mmol). The purified product was eluted with hexanes to 50/50 hexanes/CH₂Cl₂.

¹H NMR: (500 MHz, CDCl₃) δ = 8.00 (d, J = 8.0 Hz, 2H), 7.57 (t, J = 6.9 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.47 (t, J = 7.6 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 3.81 (s, 3H), 3.39 – 3.29 (m, 2H), 3.07 (dd, J = 17.0, 10.5 Hz, 1H), 2.76 – 2.70 (m, 1H), 2.54 – 2.48 (m, 1H), 2.32 – 2.24 (m, 1H), 1.60 -1.51 (m, 1H), 0.94 (s, 9H), 0.11 (s, 3H), -0.01 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 199.7, 157.6, 149.9, 137.3, 133.0, 129.2, 128.6, 128.1, 128.0, 55.2, 42.7, 42.3, 29.9, 26.8, 25.9, 18.2, -3.7, -4.1.

2-(2-((tert-butyldimethylsilyl)oxy)-3-(4-fluorophenyl)cyclopent-2-en-1-yl)-1-phenylethan-1-one (3.101f).



Starting material **3.99f** (150 mg, 0.49 mmol) was dissolved in dry acetonitrile (1.0 mL). Silyl another ether **3.961** (230 mg, 0.98 mmol) was then added followed by Py•TfOH (0.2mL, 0.10 mmol, 0.5 M solution in acetonitrile) to yield **3.101f** in 71 % as a colorless oil (142 mg, 0.35 mmol). The purified product was eluted with hexanes to 50/50 hexanes/CH₂Cl₂.

¹H NMR: (400 MHz, CDCl₃) δ = 8.00 (d, J = 7.1 Hz, 2H), 7.59 – 7.45 (m, 5H), 6.98 (t, J = 8.9 Hz, 2H), 3.39 – 3.29 (m, 2H), 3.07 (dd, J = 17.7, 11.1 Hz, 1H), 2.78 – 2.69 (m, 1H), 2.55 – 2.47 (m, 1H), 2.35 – 2.25 (m, 1H), 1.59 – 1.49 (m, 1H), 0.93 (s, 9H), 0.11 (s, 3H), -0.03 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 199.4, 161.9, 159.9, 151.3, 137.2, 133.1, 132.5, 128.6, 128.1, 115.1, 114.7, 42.7, 42.3, 29.9, 26.8, 25.8, 18.2, -3.7, -4.1.

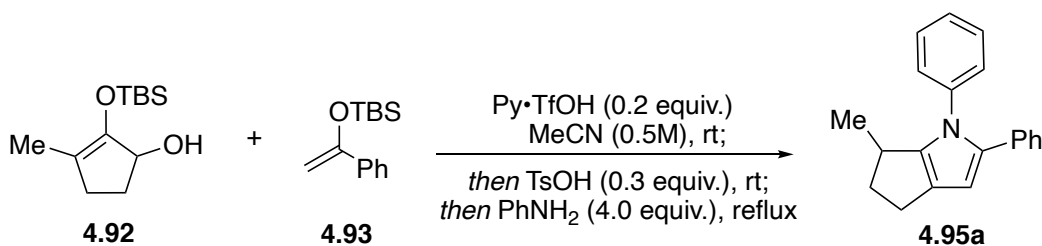
IR: $f(\text{cm}^{-1})$ = 2930, 2856, 1685, 1639, 1508, 1448, 1254, 1158, 1084, 1002, 831, 778, 582, 526.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 411.2150 calculated for C₂₅H₃₂FO₂Si: Found 411.2154.

6.4 Experimental Procedures for Chapter Four

6.4.1 Synthesis of Tetrahydrocyclopenta[b]pyrroles and Tetrahydroindoles

6-methyl-1,2-diphenyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole (4.95a)



Procedure: Alcohol **4.92** (217 mg, 0.950 mmol) was dissolved in dry acetonitrile (1.8 mL). Silylenol ether **4.93** (444 mg, 1.90 mmol) was added, followed by Py•TfOH (0.38 mL, 0.190 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (54 mg, 0.285 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, aniline (0.35 mL, 3.80 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.95a** in 80% yield (208 mg, 0.761 mmol) as a yellow solid.

Rf: 0.9 in 90:10 (hexanes : EtOAc)

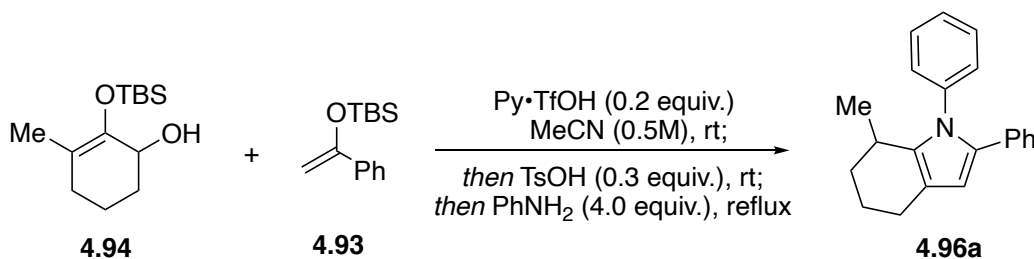
¹H NMR: (400 MHz, CDCl₃) δ = 7.32 (t, J = 5.6 Hz, 3H), 7.26 (t, J = 5.0 Hz, 1H), 7.17 – 7.13 (m, 4H), 7.10 – 7.07 (m, 3H), 6.22 (s, 1H), 3.30 – 3.26 (m, 1H), 2.78 – 2.63 (m, 3H), 2.02 – 1.93 (m, 1H), 0.81 (d, J = 6.7 Hz, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 144.74, 139.58, 136.99, 133.62, 128.86, 127.93, 127.89, 126.71, 126.59, 126.30, 125.60, 105.06, 38.29, 33.58, 24.24, 20.05.

IR: $f(\text{cm}^{-1}) = 2949, 2855, 1599, 1496, 1450, 1387, 1361, 1156, 1074, 909, 753, 695$.

HRMS (ESI-TOF) m/z : $(M+H)^+ = 274.1590$ calculated for $\text{C}_{20}\text{H}_{19}\text{N}$; found 274.1593.

7-methyl-1,2-diphenyl-4,5,6,7-tetrahydro-1H-indole (4.96a)



Procedure: Alcohol **4.94** (272 mg, 1.122 mmol) was dissolved in dry acetonitrile (2.2 mL). Silylenol ether **4.93** (525 mg, 2.243 mmol) was added, followed by Py•TfOH (0.45 mL, 0.224 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.94** as monitored by TLC, TsOH monohydrate (64 mg, 0.337 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, aniline (0.41 mL, 4.488 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH_2Cl_2 to yield **4.96a** in 69% yield (223 mg, 0.777 mmol) as a white solid.

Rf: 0.9 in 90:10 hexanes : EtOAc

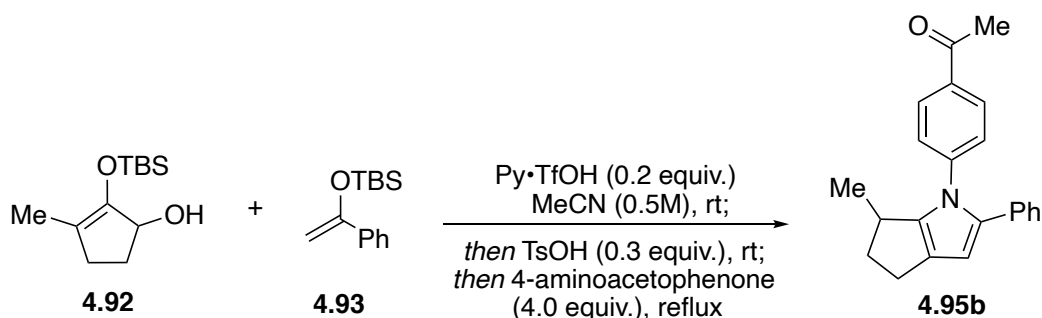
¹H NMR: (500 MHz, CDCl_3) $\delta = 7.32$ (t, $J = 7.4$ Hz, 2H), 7.27 (d, $J = 7.4$ Hz, 1H), 7.19 – 7.13 (m, 4H), 7.12 – 7.07 (m, 3H), 6.23 (s, 1H), 3.32 – 3.25 (m, 1H), 2.77 – 2.61 (m, 3H), 2.00 – 1.93 (m, 1H), 0.81 (d, $J = 6.8$ Hz, 3H).

^{13}C NMR: (100 MHz, CDCl_3) δ = 139.61, 135.35, 133.56, 133.43, 128.92, 127.99, 127.79, 127.13, 125.52, 117.85, 108.28, 31.88, 26.94, 23.41, 20.34, 19.79.

IR: $f(\text{cm}^{-1})$ = 2961, 2925, 2859, 1597, 1511, 1451, 1381, 1186, 1069, 911, 802, 759, 741, 695.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 288.1747$ calculated for $\text{C}_{21}\text{H}_{19}\text{N}$; Found 288.1748.

1-(4-(6-methyl-2-phenyl-5,6-dihydrocyclopenta[*b*]pyrrol-1(*4H*)-yl)phenyl)ethan-1-one
(4.95b)



Procedure: Alcohol **4.92** (225 mg, 0.985 mmol) was dissolved in dry acetonitrile (2.1 mL). Silylenol ether **4.93** (461 mg, 1.970 mmol) was added, followed by $\text{Py} \cdot \text{TfOH}$ (0.40 mL, 0.197 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.93** as monitored by TLC, TsOH monohydrate (56 mg, 0.296 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, 4-aminoacetophenone (532 mg, 3.940 mmol) was added, and the mixture was stirred at reflux for 7 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 hexanes : CH_2Cl_2 to yield **4.95b** in 70% yield (219 mg, 0.694 mmol) as a yellow solid.

Rf: 0.4 in 80:20 hexanes : EtOAc

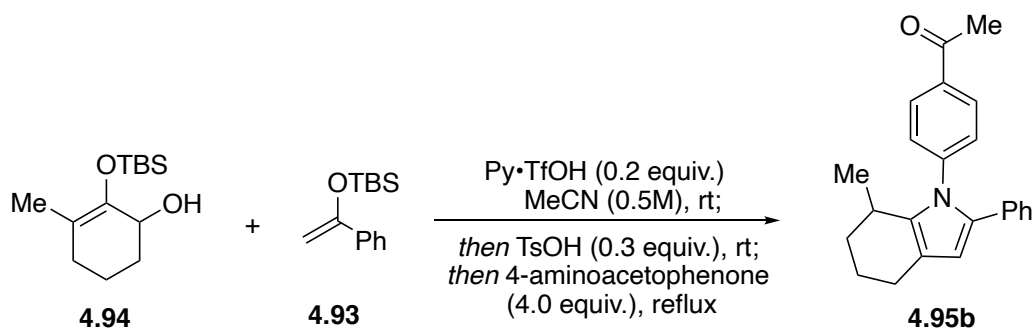
¹H NMR: (400 MHz, CDCl₃) δ = 7.92 (d, *J* = 8.3 Hz, 2H), 7.24 – 7.03 (m, 7H), 6.25 (s, 1H), 3.40 – 3.20 (m, 1H), 2.80 – 2.64 (m, 3H), 2.60 (s, 3H), 2.04 – 1.95 (m, 1H), 0.82 (d, *J* = 6.7 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 197.01, 144.40, 143.67, 137.04, 134.81, 133.29, 129.16, 128.13, 128.01, 127.35, 126.16, 125.99, 106.37, 38.14, 33.71, 26.51, 24.11, 20.03.

IR: *f* (cm⁻¹) = 2928, 2681, 1600, 1510, 1379, 1263, 1177, 956, 907, 848, 760, 727, 693.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 330.1852 calculated for C₂₃H₂₄NO; Found 330.1855.

1-(4-(7-methyl-2-phenyl-4,5,6,7-tetrahydro-1*H*-indol-1-yl)phenyl)ethan-1-one (4.96b)



Procedure: Alcohol **4.94** (229 mg, 0.945 mmol) was dissolved in dry acetonitrile (1.9 mL). Silylenol ether **4.93** (442 mg, 1.889 mmol) was added, followed by Py•TfOH (0.37 mL, 0.189 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.94** as monitored by TLC, TsOH monohydrate (54 mg, 0.283 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, 4-aminoacetophenone (510 mg, 3.778 mmol) was added, and the mixture was stirred at reflux for 8 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 40:60 hexanes : CH₂Cl₂ to yield **4.96b** in 64% yield (201 mg, 0.610 mmol) as a yellow solid.

Rf: 0.5 in 80:20 hexanes : EtOAc

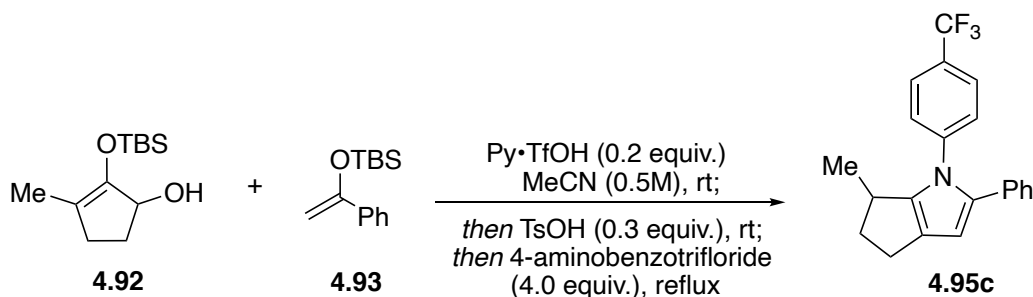
¹H NMR: (400 MHz, CDCl₃) δ = 7.94 (d, *J* = 8.0 Hz, 2H), 7.16 – 7.08 (m, 3H), 7.03 (d, *J* = 6.7 Hz, 2H), 6.23 (s, 1H), 3.02 (h, *J* = 6.6 Hz, 1H), 2.64 – 2.57 (m, 5H), 2.03 – 1.94 (m, 1H), 1.90 – 1.74 (m, 2H), 1.65 – 1.58 (m, Hz, 1H), 0.71 (d, *J* = 6.8 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 197.10, 143.98, 135.42, 135.20, 133.60, 133.06, 129.16, 128.17, 128.11, 127.98, 125.87, 118.71, 109.28, 31.76, 26.92, 26.57, 23.35, 20.38, 19.66.

IR: *f* (cm⁻¹) = 2955, 2863, 1679, 1598, 1510, 1453, 1408, 1381, 1262, 1354, 1175, 1070, 954, 907, 847.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 330.1852 calculated for C₂₃H₂₄NO; Found 330.1855.

**6-methyl-2-phenyl-1-(4-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole
(4.95c)**



Procedure: Alcohol **4.92** (245 mg, 1.073 mmol) was dissolved in dry acetonitrile (2.1 mL). Silylenol ether **4.93** (502 mg, 2.145 mmol) was added, followed by Py•TfOH (0.42 mL, 0.215 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (61 mg, 0.322 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, 4-aminobenzotrifluoride (0.54 mL, 4.290 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified

with column chromatography using 100% hexanes to 95:5 hexanes : CH₂Cl₂ to yield **4.95c** in 78% yield (285 mg, 0.834 mmol) as a brown solid.

Rf: 0.8 in 80:20 hexanes : EtOAc

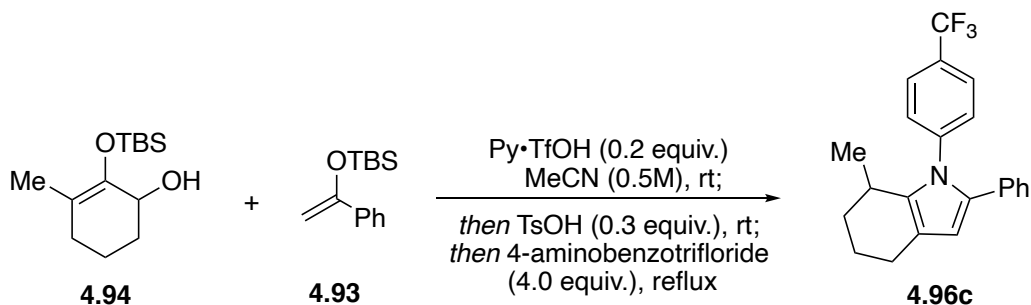
¹H NMR: (400 MHz, CDCl₃) δ = 7.59 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 6.4 Hz, 2H), 7.22 – 7.13 (m, 3H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.25 (s, 1H), 3.38 – 3.27 (m, 1H), 2.80 – 2.63 (m, 3H), 2.07 – 1.96 (m, 1H), 0.83 (d, *J* = 6.7 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 144.44, 137.11, 128.19, 128.05, 127.32, 126.50, 126.13, 126.09, 126.07, 126.02, 106.29, 99.96, 38.19, 33.68, 24.13, 20.09.

IR: ν (cm⁻¹) = 2956, 2863, 1611, 1513, 1453, 1380, 1318, 1160, 1115, 1015, 910, 842, 758, 696, 598.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 342.1464 calculated for C₂₁H₁₈F₃N; Found 342.1464.

7-methyl-2-phenyl-1-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1*H*-indole (**4.96c**)



Procedure: Alcohol **4.94** (225 mg, 0.928 mmol) was dissolved in dry acetonitrile (1.8 mL). Silylenol ether **4.93** (434 mg, 1.856 mmol) was added, followed by Py•TfOH (0.37 mL, 0.186 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.94** as monitored by TLC, TsOH monohydrate (53 mg, 0.278 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, 4-aminobenzotrifluoride (0.46 mL, 3.712 mmol) was added, and the mixture was stirred at

reflux for 5 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : CH₂Cl₂ to yield **4.96c** in 62% yield (205 mg, 0.577 mmol) as a brown solid.

Rf: 0.8 in 80:20 hexanes : EtOAc

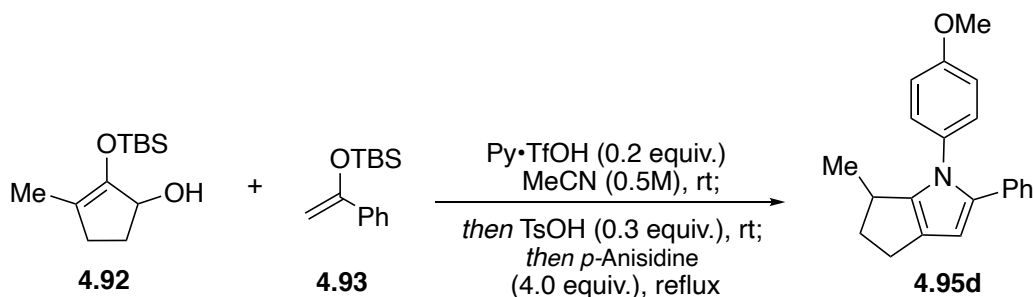
¹H NMR: (400 MHz, CDCl₃) δ = 7.62 (d, *J* = 7.8 Hz, 2H), 7.30 – 7.27 (m, 2H), 7.18 – 7.10 (m, 3H), 7.02 (d, *J* = 6.8 Hz, 2H), 6.24 (s, 1H), 3.04 – 2.95 (m, 1H), 2.66 – 2.57 (m, 2H), 2.05 – 1.93 (m, 1H), 1.88 – 1.74 (m, 2H), 1.68 – 1.59 (m, 1H), 0.73 (d, *J* = 6.8 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 142.89, 135.23, 133.70, 132.97, 128.15, 128.04, 126.15, 126.11, 125.95, 118.69, 109.26, 31.77, 26.90, 23.35, 20.42, 19.65.

IR: $\tilde{\nu}$ (cm⁻¹) = 2919, 1612, 1518, 1453, 1381, 1319, 1162, 1062, 1016, 970, 845, 694, 616.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 356.1621 calculated for C₂₂H₂₀F₃N; Found 356.1622.

1-(4-methoxyphenyl)-6-methyl-2-phenyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (**4.95d**)



Procedure: Alcohol **4.92** (213 mg, 0.932 mmol) was dissolved in dry acetonitrile (1.9 mL). Silylenol ether **4.93** (436 mg, 1.865 mmol) was added, followed by Py•TfOH (0.37 mL, 0.186 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (53 mg, 0.280 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by

consumption of **4.94** as monitored by TLC, TsOH monohydrate (53 mg, 0.280 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, p-Anisidine (434 mg, 3.531 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 75:25 hexanes : CH₂Cl₂ to yield **4.96d** in 41% yield (116 mg, 0.365 mmol) as a white solid.

Rf: 0.8 in 80:20 hexanes : EtOAc

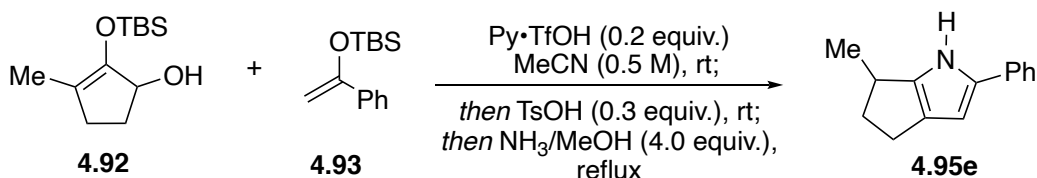
¹H NMR: (400 MHz, CDCl₃) δ = 7.16 – 7.11 (m, 2H), 7.09 – 7.03 (m, 3H), 6.87 (s, 2H), 6.22 – 6.19 (m, 1H), 3.82 (s, 3H), 2.97 – 2.87 (m, 1H), 2.60 (q, J = 8.1, 6.2 Hz, 2H), 1.97 – 1.73 (m, 3H), 1.63 – 1.57 (m, 1H), 0.77 (d, J = 6.8 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 158.48, 135.57, 133.65, 133.52, 132.43, 127.97, 127.81, 125.45, 117.57, 114.09, 107.89, 55.37, 31.91, 26.93, 23.41, 20.42, 19.81.

IR ν (cm⁻¹) = 2915, 2175, 2597, 1449, 1387, 1286, 1179, 1103, 909, 799, 692.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 318.1852 calculated for C₂₂H₂₄NO; Found 318.1853.

6-methyl-2-phenyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole (**4.95e**)



Procedure: Alcohol **4.92** (207 mg, 0.906 mmol) was dissolved in dry acetonitrile (1.8 mL). Silylenol ether **4.93** (424 mg, 1.813 mmol) was added, followed by Py•TfOH (0.36 mL, 0.181 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (52 mg, 0.272 mmol) was added,

and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, 7N $\text{NH}_3 \cdot \text{MeOH}$ (0.51 mL, 3.625 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH_2Cl_2 to yield **4.95e** in 84% yield (151 mg, 0.765 mmol) as a yellow oil.

Rf: 0.7 in 80:20 hexanes : EtOAc

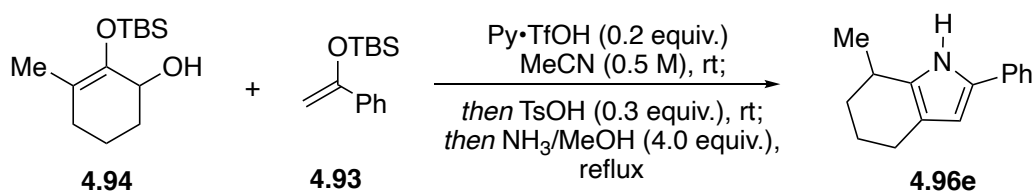
^1H NMR: (400 MHz, CDCl_3) δ = 8.02 (s, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.15 (t, J = 7.3 Hz, 1H), 6.28 (s, 1H), 3.19 (h, J = 6.9 Hz, 1H), 2.70 – 2.57 (m, 3H), 2.01 – 1.92 (m, 1H), 1.26 (d, J = 6.8 Hz, 3H).

^{13}C NMR: (100 MHz, CDCl_3) δ = 142.59, 135.07, 133.68, 128.78, 127.56, 125.51, 123.31, 101.69, 38.68, 33.15, 24.66, 20.47.

IR: $f(\text{cm}^{-1})$ = 3431, 2940, 2854, 1600, 1509, 1362, 1243, 1012, 803, 756, 690.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 198.1277$ calculated for $\text{C}_{14}\text{H}_{16}\text{N}$; Found 198.1276.

7-methyl-2-phenyl-4,5,6,7-tetrahydro-1H-indole (**4.96e**)



Procedure: Alcohol **4.94** (193 mg, 0.796 mmol) was dissolved in dry acetonitrile (1.6 mL). Silylenol ether **4.93** (372 mg, 1.592 mmol) was added, followed by $\text{Py} \cdot \text{TfOH}$ (0.32 mL, 0.159 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.94** as monitored by TLC, TsOH monohydrate (45 mg, 0.239 mmol) was added,

and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, 7N NH₃•MeOH (0.45 mL, 3.1844 mmol) was added, and the mixture was stirred at reflux for 6 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.96e** in 56% yield (95 mg, 0.450 mmol) as a colorless oil.

Rf: 0.7 in 80:20 hexanes : EtOAc

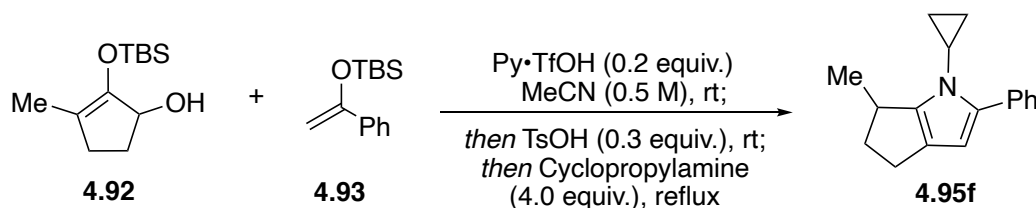
¹H NMR: (400 MHz, CDCl₃) δ = 7.97 (s, 1H), 7.44 (d, J = 7.7 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.17 (t, J = 7.3 Hz, 1H), 6.29 (s, 1H), 2.90 (q, J = 6.5 Hz, 1H), 2.55 (t, J = 5.7 Hz, 2H), 2.02 – 1.89 (m, 2H), 1.75 – 1.67 (m, 1H), 1.49 – 1.42 (m, 1H), 1.29 (d, J = 6.6 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 133.39, 133.20, 130.31, 128.73, 125.54, 123.42, 118.62, 105.10, 99.94, 32.50, 28.45, 23.15, 22.48, 20.51.

IR: $\tilde{\nu}$ (cm⁻¹) = 3367, 2924, 2848, 2009, 1696, 1517, 1450, 795, 756.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 211.1434 calculated for C₁₅H₁₈N; Found 212.1431.

1-cyclopropyl-6-methyl-2-phenyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole (**4.95f**)



Procedure: Alcohol **4.92** (218 mg, 0.954 mmol) was dissolved in dry acetonitrile (1.9 mL). Silylenol ether **4.93** (372 mg, 1.592 mmol) was added, followed by Py•TfOH (0.38 mL, 0.190 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (53 mg, 0.283 mmol) was added,

and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, cyclopropylamine (0.26 mL, 3.818 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.95f** in 75% yield (169 mg, 0.712 mmol) as a colorless oil.

Rf: 0.9 in 80:20 hexanes : EtOAc

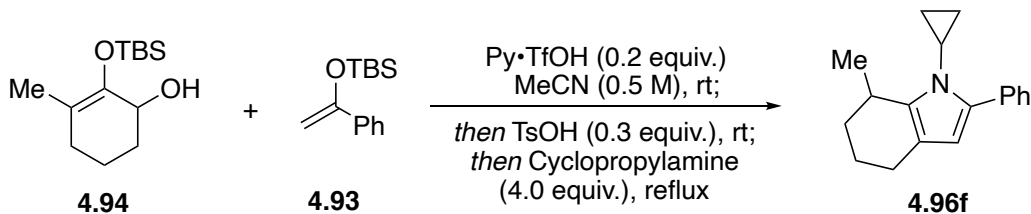
¹H NMR: (400 MHz, CDCl₃) δ = 7.49 (d, J = 7.1 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.23 (t, J = 7.4 Hz, 1H), 5.98 (s, 1H), 3.37 – 3.30 (m, 1H), 3.23 (q, J = 6.8 Hz, 1H), 2.70 – 2.61 (m, 2H), 2.57 – 2.50 (m, 1H), 2.00 – 1.94 (m, 1H), 1.39 (d, J = 6.7 Hz, 3H), 0.92 – 0.84 (m, 2H), 0.77 – 0.72 (m, 1H), 0.50 – 0.43 (m, 1H).

¹³C NMR: (100 MHz, CDCl₃) δ = 145.08, 138.00, 134.44, 127.98, 127.89, 125.75, 124.95, 103.19, 38.51, 33.96, 27.57, 24.32, 20.60, 9.58, 8.40.

IR: $\tilde{\nu}$ (cm⁻¹) = 2959, 2930, 2858, 1678, 1600, 1503, 1448, 1367, 1159, 1071, 1027, 908, 698.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 238.1594 calculated for C₁₇H₁₉N; Found 238.1598.

1-cyclopropyl-7-methyl-2-phenyl-4,5,6,7-tetrahydro-1*H*-indole (**4.96f**)



Procedure: Alcohol **4.94** (253 mg, 1.038 mmol) was dissolved in dry acetonitrile (2.1 mL). Silylenol ether **4.93** (486 mg, 2.079 mmol) was added, followed by Py•TfOH (0.42 mL, 0.208 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete

consumption of **4.94** as monitored by TLC, TsOH monohydrate (59 mg, 0.312 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, cyclopropylamine (0.29 mL, 4.154 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.96f** in 59% yield (151 mg, 0.601 mmol) as a colorless oil.

Rf: 0.9 in 80:20 hexanes : EtOAc

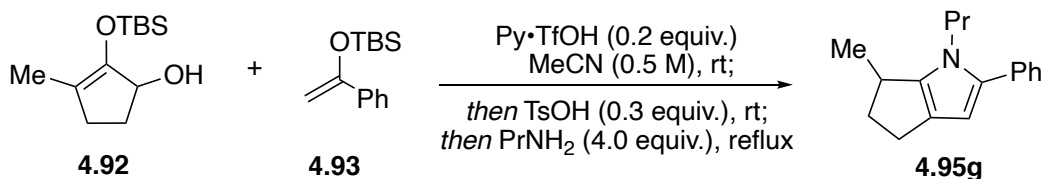
¹H NMR: (400 MHz, CDCl₃) δ = 7.47 (d, J = 8.1 Hz, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.23 (t, J = 6.9 Hz, 1H), 5.98 (s, 1H), 3.25 (tt, J = 7.3, 4.0 Hz, 1H), 3.14 – 3.05 (m, 1H), 2.57 – 2.44 (m, 2H), 2.01 – 1.92 (m, 1H), 1.88 – 1.78 (m, 1H), 1.74 – 1.60 (m, 2H), 1.40 (d, J = 6.8 Hz, 3H), 1.02 – 0.94 (m, 1H), 0.86 – 0.79 (m, 1H), 0.78 – 0.69 (m, 1H), 0.44 – 0.36 (m, 1H).

¹³C NMR: (100 MHz, CDCl₃) δ = 136.32, 134.41, 128.13, 127.83, 125.74, 117.08, 106.90, 32.35, 27.64, 27.48, 23.56, 20.80, 20.39, 9.91, 9.27.

IR: $f(\text{cm}^{-1})$ = 2924, 2846, 2255, 1600, 1515, 1452, 1388, 1030, 791, 697.

HRMS (ESI-TOF) m/z : ($M+H$)⁺ = 252.1747 calculated for C₁₈H₂₂N; Found 252.1749.

6-methyl-2-phenyl-1-propyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole (**4.95g**)



Procedure: Alcohol **4.92** (158 mg, 0.692 mmol) was dissolved in dry acetonitrile (1.4 mL). Silylenol ether **4.93** (323 mg, 1.383 mmol) was added, followed by Py•TfOH (0.28 mL, 0.138

mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (40 mg, 0.208 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, propylamine (0.23 mL, 2.767 mmol) was added, and the mixture was stirred at reflux for 3 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.95g** in 84% yield (139 mg, 0.581 mmol) as a colorless oil.

Rf: 0.90 in 90:10 (hexanes : EtOAc)

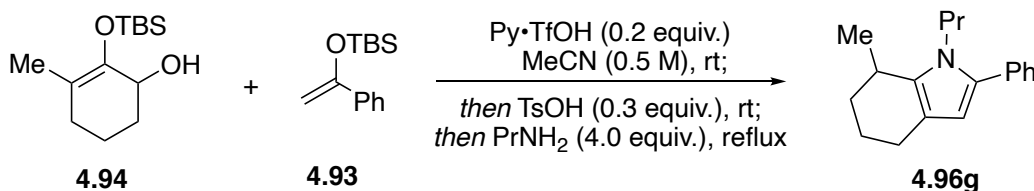
¹H NMR: (400 MHz, CDCl₃) δ = 7.38 (d, J = 4.2 Hz, 4H), 7.28 (dt, J = 7.6, 3.7 Hz, 1H), 5.97 (s, 1H), 3.85 (dq, J = 30.5, 6.7 Hz, 2H), 3.24 (h, J = 4.9, 3.7 Hz, 1H), 2.75 – 2.65 (m, 2H), 2.61 – 2.54 (m, 1H), 2.02 – 1.94 (m, 1H), 1.62 (q, J = 7.4 Hz, 2H), 1.31 (d, J = 6.7 Hz, 3H), 0.79 (t, J = 7.4 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 143.24, 137.24, 134.45, 128.69, 128.24, 126.31, 125.38, 103.56, 46.81, 38.88, 33.46, 24.56, 24.22, 20.45, 11.10.

IR: f (cm⁻¹) = 2941, 2885, 1624, 1493, 1417, 1391, 1190, 778, 719.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 240.1747 calculated for C₁₇H₂₂N; Found 240.1760.

7-methyl-2-phenyl-1-propyl-4,5,6,7-tetrahydro-1H-indole (**4.96g**)



Procedure: Alcohol **4.94** (158 mg, 0.692 mmol) was dissolved in dry acetonitrile (1.4 mL). Silylenol ether **4.93** (323 mg, 1.383 mmol) was added, followed by Py•TfOH (0.28 mL, 0.138

mmol, 0.5 M solution in acetonitrile) The mixture was stirred for 1 hour. Upon complete consumption of **4.94** as monitored by TLC, TsOH monohydrate (53 mg, 0.278 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, propylamine (0.30 mL, 3.712 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 85:15 hexanes : CH₂Cl₂ to yield **4.96g** in 69% yield (155 mg, 0.612 mmol) as a yellow oil.

Rf: 0.92 in 90:10 (hexanes : EtOAc)

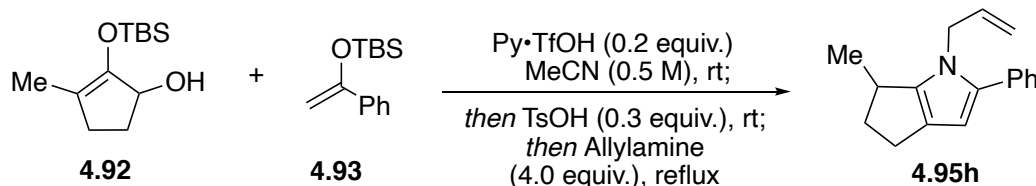
¹H NMR: (400 MHz, CDCl₃) δ = 7.42 – 7.35 (m, 4H), 7.29 (d, J = 6.8 Hz, 1H), 5.98 (s, 1H), 3.98 – 3.88 (m, 1H), 3.86 – 3.76 (m, 1H), 3.02 – 2.92 (m, 1H), 2.64 – 2.47 (m, 2H), 1.93 – 1.67 (m, 4H), 1.52 – 1.40 (m, 2H), 1.31 (d, J = 6.8 Hz, 3H), 0.73 (t, J = 7.4 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 134.59, 133.90, 133.32, 128.63, 128.23, 126.31, 116.71, 107.81, 45.61, 31.67, 26.62, 24.44, 23.28, 21.24, 19.21, 11.16.

IR: ν (cm⁻¹) = 2959, 2916, 1602, 1516, 1456, 1373, 1306, 1146, 1017, 789, 758, 699.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 254.1903 calculated for C₁₈H₂₃N; Found 254.1908.

1-allyl-6-methyl-2-phenyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (**4.95h**)



Procedure: Alcohol **4.92** (192 mg, 0.841 mmol) was dissolved in dry acetonitrile (1.6 mL). Silylenol ether **4.93** (393 mg, 1.681 mmol) was added, followed by Py•TfOH (0.33 mL, 0.168

mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (48 mg, 0.252 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, allylamine (0.25 mL, 3.362 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.95h** in 80% yield (160 mg, 0.674 mmol) as a yellow oil.

Rf: 0.8 in 80:20 hexanes : EtOAc

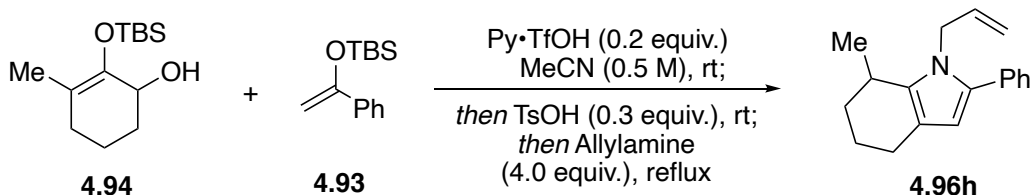
¹H NMR: (400 MHz, CDCl₃) δ = 7.40 – 7.33 (m, 5H), 6.02 (s, 1H), 5.92 (ddt, J = 15.3, 10.3, 4.4 Hz, 1H), 5.16 (dd, J = 10.4, 1.4 Hz, 1H), 4.98 (dd, J = 17.1, 1.4 Hz, 1H), 4.57 – 4.52 (m, 1H), 4.47 – 4.41 (m, 1H), 3.17 (q, J = 6.6 Hz, 1H), 2.76 – 2.55 (m, 4H), 2.01 – 1.93 (m, 1H), 1.25 (d, J = 6.8 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 143.66, 137.55, 135.13, 133.98, 128.54, 128.25, 126.41, 125.72, 116.08, 103.61, 47.39, 38.85, 33.32, 24.29, 20.47.

IR: f (cm⁻¹) = 2943, 2854, 1643, 1601, 1508, 1464, 1371, 1269, 1152, 990, 791, 757.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 238.1590 calculated for C₁₇H₂₀N; Found 238.1591.

1-allyl-7-methyl-2-phenyl-4,5,6,7-tetrahydro-1H-indole (**4.96h**)



Procedure: Alcohol **4.94** (225 mg, 0.928 mmol) was dissolved in dry acetonitrile (1.8 mL). Silylenol ether **4.93** (434 mg, 1.856 mmol) was added, followed by Py•TfOH (0.37 mL, 0.186

mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.94** as monitored by TLC, TsOH monohydrate (53 mg, 0.278 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, allylamine (0.28 mL, 3.712 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.96h** in 53% yield (124 mg, 0.494 mmol) as a yellow oil.

Rf: 0.9 in 80:20 hexanes : EtOAc

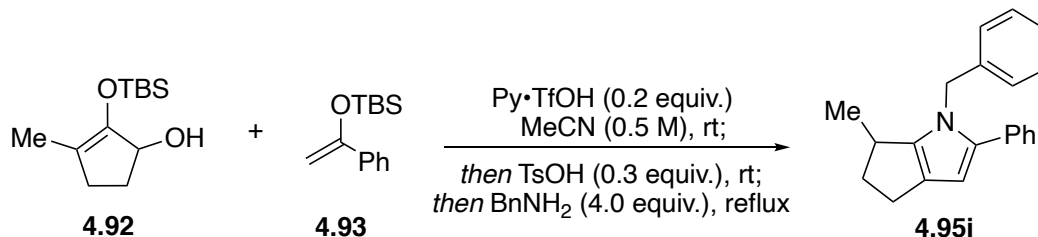
¹H NMR: (500 MHz, CDCl₃) δ = 7.39 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 7.3 Hz, 2H), 7.27 (m, 1H), 6.01 (s, 1H), 5.86 – 5.77 (m, 1H), 5.08 – 5.03 (m, 1H), 4.77 (d, J = 17.1 Hz, 1H), 4.60 – 4.54 (m, 1H), 4.49 – 4.43 (m, 1H), 1.89 – 1.82 (m, 2H), 1.79 – 1.73 (m, 1H), 1.71 – 1.66 (m, 1H), 1.26 (d, J = 6.9 Hz, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 135.40, 134.12, 134.04, 133.68, 128.78, 128.15, 126.44, 117.02, 115.68, 107.57, 46.17, 31.62, 26.35, 23.27, 21.14, 19.08.

IR: f (cm⁻¹) = 2926, 2846, 1602, 1516, 1453, 1375, 1306, 1071, 790, 756, 730.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 252.1747 calculated for C₁₈H₂₁N; Found 252.1739.

1-benzyl-6-methyl-2-phenyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole (**4.95i**)



Procedure: Alcohol **4.92** (216 mg, 0.945 mmol) was dissolved in dry acetonitrile (1.9 mL). Silylenol ether **4.93** (442 mg, 1.891 mmol) was added, followed by Py•TfOH (0.38 mL, 0.189

mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (53 mg, 0.283 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, benzylamine (0.40 mL, 3.783 mmol) was added, and the mixture was stirred at reflux for 3 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 85:15 hexanes : CH₂Cl₂ to yield **4.95i** in 75% yield (204 mg, 0.710 mmol) as a brown oil.

Rf: 0.8 in 80:20 hexanes : EtOAc

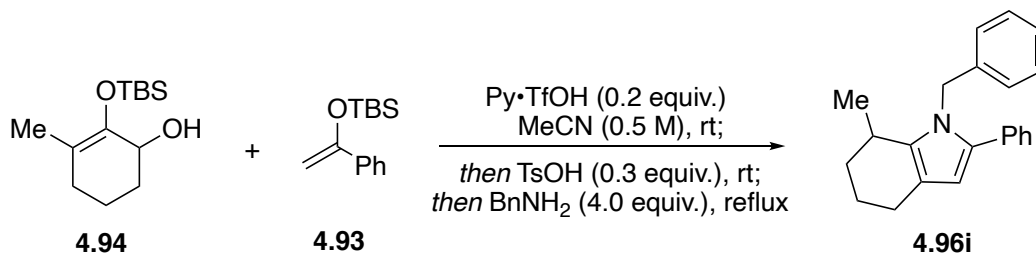
¹H NMR: (400 MHz, CDCl₃) δ = 7.36 – 7.28 (m, 6H), 7.26 – 7.21 (m, 2H), 7.01 (d, J = 7.5 Hz, 2H), 6.11 (s, 1H), 5.22 (d, J = 16.8 Hz, 1H), 5.08 (d, J = 16.8 Hz, 1H), 3.02 – 2.92 (m, 1H), 2.82 – 2.72 (m, 1H), 2.68 – 2.56 (m, 2H), 2.01 – 1.91 (m, 1H), 1.11 (d, J = 6.7 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 143.71, 139.22, 138.03, 133.88, 128.55, 128.52, 128.29, 126.96, 126.44, 126.07, 125.94, 103.83, 48.49, 38.85, 33.34, 24.38, 20.38.

IR: ν (cm⁻¹) = 3062, 2952, 2856, 1602, 1453, 1358, 1271, 1030, 759, 694.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 288.1747 calculated for C₂₁H₂₂N; Found 288.1744.

1-benzyl-7-methyl-2-phenyl-4,5,6,7-tetrahydro-1H-indole (**4.96i**)



Procedure: Alcohol **4.94** (143 mg, 0.590 mmol) was dissolved in dry acetonitrile (1.2 mL). Silylenol ether **4.93** (276 mg, 1.179 mmol) was added, followed by Py•TfOH (0.23 mL, 0.117

mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.94** as monitored by TLC, TsOH monohydrate (33 mg, 0.177 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, benzylamine (0.26 mL, 2.359 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.96i** in 53% yield (95 mg, 0.315 mmol) as a colorless oil.

Rf: 0.9 in 80:20 hexanes : EtOAc

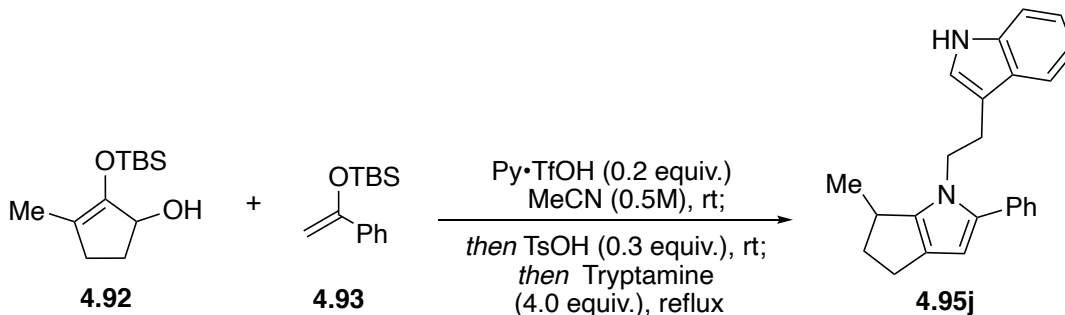
¹H NMR: (400 MHz, CDCl₃) δ = 7.37 – 7.19 (m, 8H), 6.88 (d, *J* = 7.3 Hz, 2H), 6.14 (s, 1H), 5.27 (d, *J* = 17.1 Hz, 1H), 5.12 (d, *J* = 17.1 Hz, 1H), 2.77 – 2.53 (m, 3H), 1.94 – 1.73 (m, 3H), 1.69 – 1.60 (m, 1H), 1.21 (d, *J* = 6.8 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 139.59, 134.24, 134.12, 133.83, 128.72, 128.47, 128.18, 126.75, 126.44, 125.56, 117.48, 107.75, 99.88, 47.30, 31.63, 26.44, 23.32, 21.04, 19.13.

IR: ν (cm⁻¹) = 2950, 2873, 1557, 1503, 1412, 1362, 1225, 1131, 1059, 865, 746, 710.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 302.1903 calculated for C₂₂H₂₃N; Found 302.1911.

3-(2-(6-methyl-2-phenyl-5,6-dihydrocyclopenta[b]pyrrol-1(4H)-yl)ethyl)-1H-indole (**4.95j**)



Procedure: Alcohol **4.92** (254 mg, 1.112 mmol) was dissolved in dry acetonitrile (2.2 mL). Silylenol ether **4.93** (520 mg, 2.224 mmol) was added, followed by Py•TfOH (0.44 mL, 0.222 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (63 mg, 0.333 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, tryptamine (712 mg, 4.448 mmol) was added, and the mixture was stirred at reflux for 5 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 80:20 hexanes : CH₂Cl₂ to yield **4.95j** in 84% yield (318 mg, 0.934 mmol) as an orange solid.

Rf: 0.7 in 80:20 hexanes : EtOAc

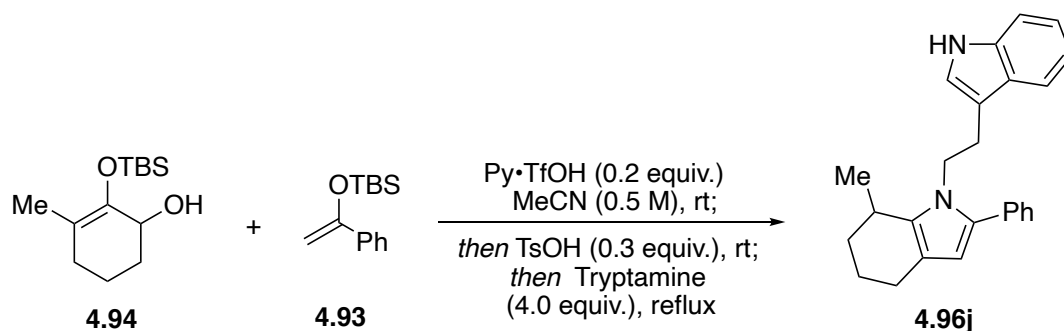
¹H NMR: (400 MHz, CDCl₃) δ = 7.90 (s, 1H), 7.45 – 7.39 (m, 4H), 7.33 (d, J = 8.1 Hz, 2H), 7.19 (q, J = 7.5 Hz, 2H), 7.05 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 2.1 Hz, 1H), 6.03 (s, 1H), 4.28 – 4.10 (m, 2H), 3.22 (q, J = 6.6 Hz, 1H), 3.02 – 2.95 (m, 2H), 2.78 – 2.58 (m, 3H), 2.06 – 1.96 (m, 1H), 1.34 (d, J = 6.7 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 143.23, 137.16, 136.10, 134.36, 128.93, 128.38, 127.18, 126.55, 125.47, 122.04, 121.69, 119.38, 118.53, 112.70, 111.02, 103.85, 46.01, 38.90, 33.37, 27.34, 24.28, 20.63.

IR: $\tilde{\nu}$ (cm⁻¹) = 3343, 2926, 2853, 1742, 1600, 1507, 1440, 1343, 1225, 1150, 1090, 1058, 919, 736, 590.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 341.2012 calculated for C₂₄H₂₅N₂; Found 341.2013.

3-(2-(7-methyl-2-phenyl-4,5,6,7-tetrahydro-1H-indol-1-yl)ethyl)-1H-indole (4.97j**)**



Procedure: Alcohol **4.94** (212 mg, 0.874 mmol) was dissolved in dry acetonitrile (1.7 mL). Silylenol ether **4.93** (409 mg, 1.749 mmol) was added, followed by Py•TfOH (35 mL, 0.175 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.94** as monitored by TLC, TsOH monohydrate (50 mg, 0.262 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, tryptamine (560 mg, 3.498 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 80:20 hexanes : CH₂Cl₂ to yield **4.96j** in 70% yield (216 mg, 0.609 mmol) as a red solid.

Rf: 0.7 in 80:20 hexanes : EtOAc

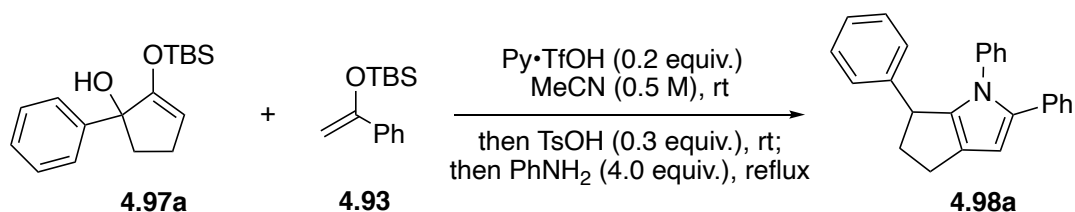
¹H NMR: (400 MHz, CDCl₃) δ = 7.84 (s, 1H), 7.63 – 7.39 (m, 5H), 7.34 (d, J = 7.3 Hz, 1H), 7.26 (s, 1H), 7.13 (s, 2H), 6.80 (s, 1H), 6.14 (s, 1H), 4.27 (d, J = 56.3 Hz, 2H), 2.96 (d, J = 45.5 Hz, 3H), 2.68 (s, 2H), 2.01 – 1.73 (m, 4H), 1.41 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 136.00, 134.47, 133.84, 133.21, 128.97, 128.41, 127.06, 126.58, 121.91, 121.66, 119.25, 118.50, 116.83, 112.69, 110.95, 108.02, 44.86, 31.55, 27.11, 26.55, 23.30, 21.33, 19.17.

IR: $\tilde{\nu}$ (cm⁻¹) = 2925, 2850, 1681, 1601, 1454, 1357, 1091, 907, 737, 700.

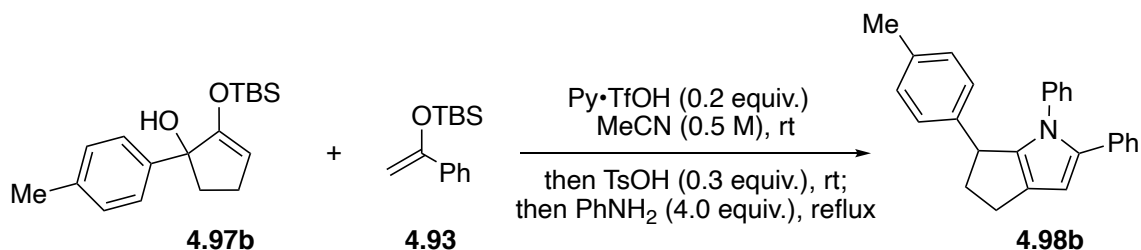
HRMS (ESI-TOF) m/z : $(M+H)^+ = 355.2169$ calculated for $C_{25}H_{26}N_2$; Found 355.2171.

1,2,6-triphenyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (4.98a)



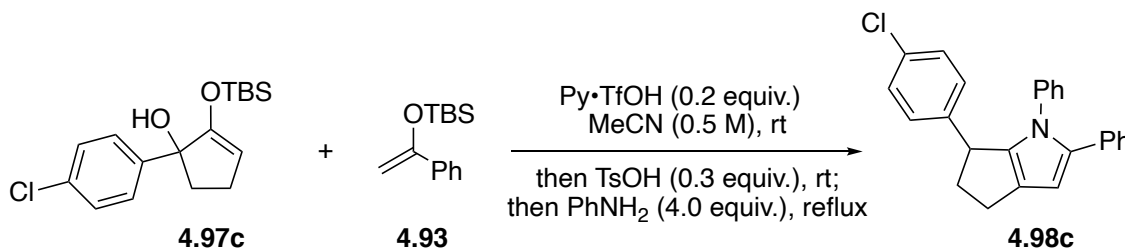
Procedure: Alcohol **4.97a** (123 mg, 0.423 mmol) was dissolved in dry acetonitrile (0.8 mL). Silylenol ether **4.93** (198 mg, 0.847 mmol) was added, followed by Py·TfOH (0.16 mL, 0.085 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 92 hours. Upon complete consumption of **4.97a** as monitored by TLC, TsOH monohydrate (24 mg, 0.127 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, aniline (0.15 mL, 1.694 mmol) was added, and the mixture was stirred at reflux for 2 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.98a** in 38% yield (54 mg, 0.161 mmol) as a white solid.

1,2-diphenyl-6-(*p*-tolyl)-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (4.98b)



Procedure: Alcohol **4.97b** (114 mg, 0.371 mmol) was dissolved in dry acetonitrile (0.8 mL). Silylenol ether **4.93** (175 mg, 0.749 mmol) was added, followed by Py•TfOH (0.15 mL, 0.075 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 142 hours. Upon complete consumption of **4.97b** as monitored by TLC, TsOH monohydrate (21 mg, 0.112 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, aniline (0.14 mL, 1.497 mmol) was added, and the mixture was stirred at reflux for 1 hour until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.98b** in 29% yield (39 mg, 0.107 mmol), as a white solid.

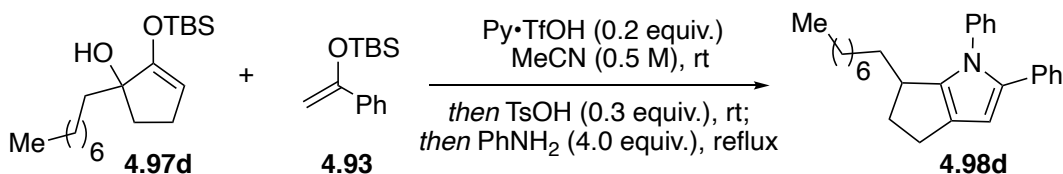
6-(4-chlorophenyl)-1,2-diphenyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (4.98c)



Procedure: Alcohol **4.97c** (134 mg, 0.412 mmol) was dissolved in dry acetonitrile (0.8 mL). Silylenol ether **4.93** (289 mg, 1.237 mmol) was added, followed by Py•TfOH (0.16 mL, 0.082 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 3 hours. Upon complete consumption of **4.97c** as monitored by TLC, TsOH monohydrate (23 mg, 0.123 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, aniline (0.14 mL, 1.649 mmol) was added, and the mixture was stirred at reflux for 2 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column

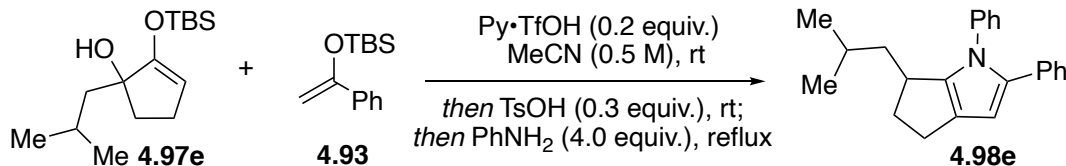
chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.98c** in 51% yield (78 mg, 0.211 mmol) as a yellow solid.

7-octyl-1,2-diphenyl-4,5,6,7-tetrahydro-1H-indole (4.98d)



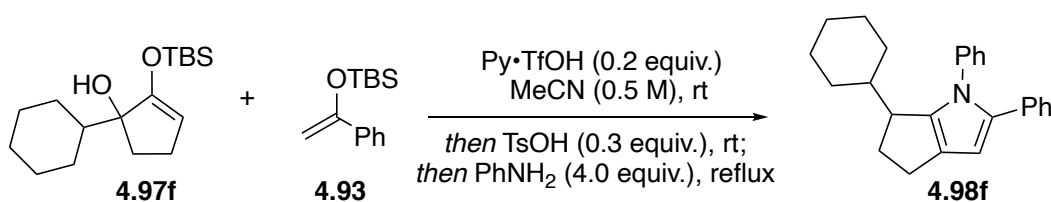
Procedure: Alcohol **4.97d** (91 mg, 0.278 mmol) was dissolved in dry acetonitrile (0.6 mL). Silylenol ether **4.93** (130 mg, 0.557 mmol) was added, followed by Py•TfOH (0.11 mL, 0.056 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 7 hours. Upon complete consumption of **4.97d** as monitored by TLC, TsOH monohydrate (16 mg, 0.083 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, aniline (0.15 mL, 1.730 mmol) was added, and the mixture was stirred at reflux for 3 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.98d** in 57% yield (58 mg, 0.156 mmol) as a colorless oil.

6-isobutyl-1,2-diphenyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole (4.98e)

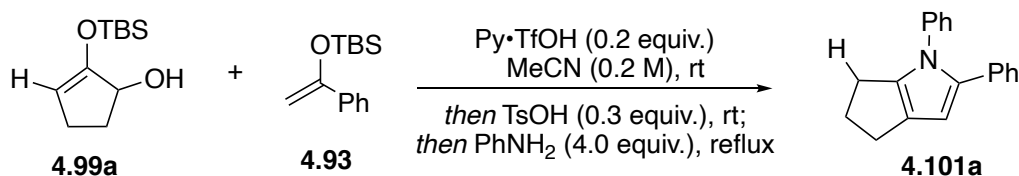


Procedure: Alcohol **4.97e** (117 mg, 0.432 mmol) was dissolved in dry acetonitrile (0.9 mL). Silylenol ether **4.93** (202 mg, 0.8651 mmol) was added, followed by Py•TfOH (0.17 mL, 0.087

mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 24 hours. Upon complete consumption of **4.97e** as monitored by TLC, TsOH monohydrate (25 mg, 0.130 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, aniline (0.15 mL, 1.730 mmol) was added, and the mixture was stirred at reflux for 2 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.98e** in 47% yield (64 mg, 0.203 mmol) as a white solid.



1,2-diphenyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (4.101a)



Procedure: Alcohol **4.99a** (156 mg, 0.727 mmol) was dissolved in dry acetonitrile (3.6 mL). Silylenol ether **4.93** (681 mg, 2.911 mmol) was added, followed by Py•TfOH (0.30 mL, 0.145 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.99a** as monitored by TLC, TsOH monohydrate (41 mg, 0.218 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, aniline (0.13 mL, 1.455 mmol) was added, and the mixture was stirred at reflux for 2 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.101a** in 23% yield (45 mg, 0.173 mmol) as a white solid.

Rf: 0.9 in 90:10 hexanes : EtOAc

¹H NMR: (400 MHz, CDCl₃) δ = 7.46 – 7.42 (m, 2H), 7.39 – 7.23 (m, 8H), 6.40 (s, 1H), 2.88 (q, *J* = 6.5 Hz, 4H), 2.62 – 2.52 (m, 2H).

¹³C NMR: (100 MHz, CDCl₃) δ = 141.13, 139.93, 136.79, 133.73, 128.86, 127.99, 127.85, 127.04, 126.16, 125.94, 125.67, 105.70, 28.47, 26.01, 25.65.

1,2-diphenyl-4,5,6,7-tetrahydro-1*H*-indole (4.102a)

Procedure: Alcohol **4.99b** (76 mg, 0.261 mmol) was dissolved in dry acetonitrile (0.5 mL). Silylenol ether **4.93** (122 mg, 0.523 mmol) was added, followed by Py•TfOH (0.10 mL, 0.052 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.99b** as monitored by TLC, TsOH monohydrate (15 mg, 0.078 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, aniline (0.10 mL, 1.046 mmol) was added, and the mixture was stirred at reflux for 1 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.101b** in 74% yield (64 mg, 0.190 mmol) as a white solid.

Rf: 0.8 in 90:10 hexanes : EtOAc

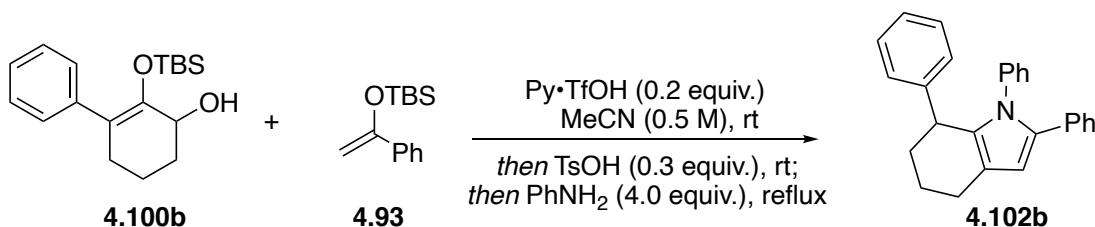
¹H NMR: (400 MHz, CDCl₃) δ = 7.16 – 7.05 (m, 11H), 6.91 (d, J = 7.1 Hz, 2H), 6.85 – 6.79 (m, 2H), 6.34 (s, 1H), 4.22 (d, J = 8.5 Hz, 1H), 3.03 – 2.89 (m, 2H), 2.80 – 2.71 (m, 1H), 2.36 – 2.28 (m, 1H).

¹³C NMR: (100 MHz, CDCl₃) δ = 145.42, 142.83, 139.47, 137.70, 133.61, 128.43, 128.15, 128.11, 127.96, 127.76, 127.13, 126.71, 126.27, 125.86, 125.69, 105.07, 45.14, 40.47, 24.72.

IR: ν (cm⁻¹) = 2988, 2877, 1554, 1475, 1369, 1213, 1046, 946, 883, 780, 717, 599.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 336.1747 calculated for C₂₅H₂₂N; Found 336.1751.

1,2,7-triphenyl-4,5,6,7-tetrahydro-1*H*-indole (**4.102b**)



Procedure: Alcohol **4.100b** (92 mg, 0.302 mmol) was dissolved in dry acetonitrile (0.6 mL). Silylenol ether **4.93** (141 mg, 0.604 mmol) was added, followed by Py•TfOH (0.12 mL, 0.060 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.100b** as monitored by TLC, TsOH monohydrate (17 mg, 0.090 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, aniline (0.10 mL, 1.208 mmol) was added, and the mixture was stirred at reflux for 3 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 85:15 hexanes : CH₂Cl₂ to yield **4.102b** in 67% yield (54 mg, 0.200 mmol) as a white solid.

Rf: 0.8 in 90:10 hexanes : EtOAc

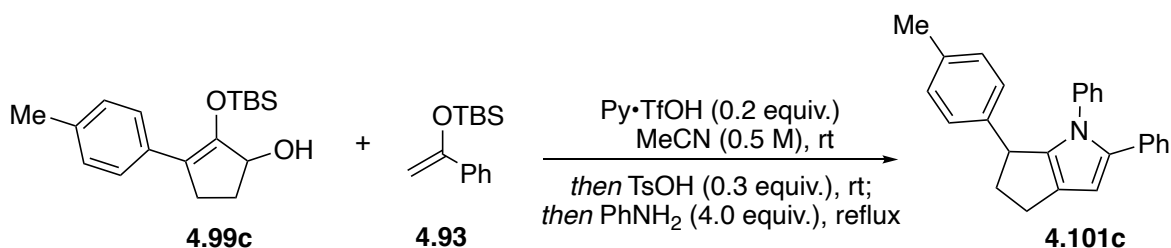
¹H NMR: (500 MHz, CDCl₃) δ = 7.14 – 6.99 (m, 10H), 6.87 (d, *J* = 6.9 Hz, 2H), 6.35 (s, 1H), 3.96 – 3.90 (m, 1H), 2.80 – 2.71 (m, 1H), 2.73 – 2.63 (m, 1H), 2.20 – 2.11 (m, 1H), 1.85 – 1.64 (m, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 145.79, 139.11, 134.11, 133.33, 132.13, 128.15, 127.84, 127.70, 127.66, 126.75, 125.54, 119.92, 39.19, 33.34, 23.05, 19.05.

IR: ν (cm⁻¹) = 3061, 3024, 2933, 2889, 2840, 1596, 1493, 1452, 1380, 1298, 1178, 1071, 1025, 966, 848, 806, 736, 692.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 350.1904 calculated for C₂₆H₂₄N; Found 350.1910.

1,2-diphenyl-6-(*p*-tolyl)-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (**4.101c**)



Procedure: Alcohol **4.99c** (69 mg, 0.227 mmol) was dissolved in dry acetonitrile (0.5 mL). Silylenol ether **4.93** (106 mg, 0.453 mmol) was added, followed by Py•TfOH (0.10 mL, 0.045 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 2 hours. Upon complete consumption of **4.99c** as monitored by TLC, TsOH monohydrate (13 mg, 0.067 mmol) was added, and the mixture was stirred for 1 hours. Once protodesilylation was completed as monitored by TLC, aniline (0.08 mL, 0.906 mmol) was added, and the mixture was stirred at reflux for 2 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.101c** in 62% yield (49 mg, 0.140 mmol) as a white solid.

Rf: 0.9 in 90:10 hexanes : EtOAc

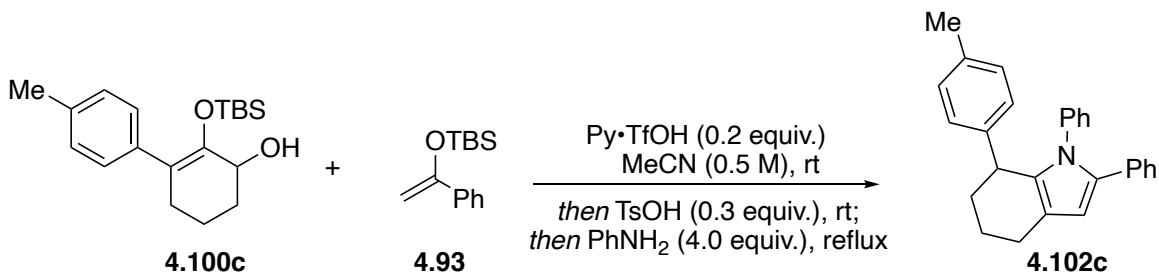
¹H NMR: (500 MHz, CDCl₃) δ = 7.17 – 7.07 (m, 8H), 6.94 (d, J = 7.4 Hz, 2H), 6.86 – 6.80 (m, 4H), 6.34 (s, 1H), 4.19 (d, J = 7.6 Hz, 1H), 3.01 – 2.89 (m, 2H), 2.78 – 2.70 (m, 1H), 2.32 – 2.25 (m, 4H).

¹³C NMR: (125 MHz, CDCl₃) δ = 142.99, 142.41, 139.48, 137.57, 135.26, 133.61, 128.82, 128.43, 128.06, 127.94, 127.75, 126.94, 126.66, 126.21, 125.65, 105.09, 4.64, 40.59, 24.63, 20.97.

IR: $\tilde{\nu}$ (cm⁻¹) = 2925, 2847, 1596, 1497, 1390, 1359, 1165, 1110, 1022, 912, 815, 692, 524.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 350.1903 calculated for C₂₆H₂₄N; Found 350.1904.

1,2-diphenyl-7-(*p*-tolyl)-4,5,6,7-tetrahydro-1*H*-indole (4.102c**)**



Procedure: Alcohol **4.100c** (81 mg, 0.254 mmol) was dissolved in dry acetonitrile (0.5 mL). Silylenol ether **4.93** (119 mg, 0.509 mmol) was added, followed by Py•TfOH (0.10 mL, 0.051 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 3 hours. Upon complete consumption of **4.100c** as monitored by TLC, TsOH monohydrate (15 mg, 0.076 mmol) was added, and the mixture was stirred for 5 hours. Once protodesilylation was completed as monitored by TLC, aniline (90 μ L, 1.016 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 85:15 hexanes : CH₂Cl₂ to yield **4.102c** in 46% yield (41 mg, 0.113 mmol) as a white solid.

Rf: 0.9 in 90:10 hexanes : EtOAc

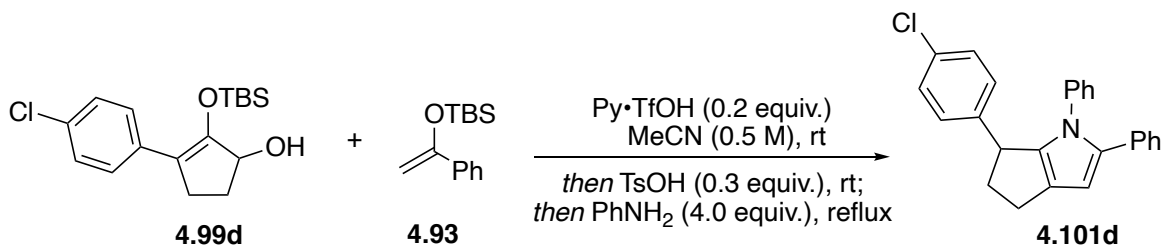
¹H NMR: (400 MHz, CDCl₃) δ = 7.19 – 6.99 (m, 9H), 6.94 (d, *J* = 7.7 Hz, 2H), 6.78 (d, *J* = 7.7 Hz, 2H), 6.35 (s, 1H), 3.89 (t, *J* = 4.4 Hz, 1H), 2.81 – 2.64 (m, 2H), 2.27 (s, 3H), 2.19 – 2.07 (m, 1H), 1.84 – 1.64 (m, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 142.84, 139.18, 134.93, 134.10, 133.40, 132.41, 128.51, 128.42, 128.22, 128.02, 127.83, 127.64, 126.72, 125.49, 119.78, 108.21, 38.71, 33.38, 23.03, 20.95, 18.92.

IR: $\tilde{\nu}$ (cm⁻¹) = 2927, 2848, 1598, 1498, 1450, 1379, 1024, 908, 755, 731, 695.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 364.2070 calculated for C₂₇H₂₅N; Found 364.2071

6-(4-chlorophenyl)-1,2-diphenyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole (4.101d)



Procedure: Alcohol **4.99d** (96 mg, 0.295 mmol) was dissolved in dry acetonitrile (0.5 mL). Silylenol ether **4.93** (138 mg, 0.591 mmol) was added, followed by Py•TfOH (0.11 mL, 0.059 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 7 hours. Upon complete consumption of **4.99d** as monitored by TLC, TsOH monohydrate (17 mg, 0.089 mmol) was added, and the mixture was stirred for 1 hours. Once protodesilylation was completed as monitored by TLC, aniline (0.10 mL, 1.181 mmol) was added, and the mixture was stirred at reflux for 14 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.101d** in 50% yield (54 mg, 0.146 mmol) as a yellow solid.

Rf: 0.7 in 90:10 hexanes : EtOAc

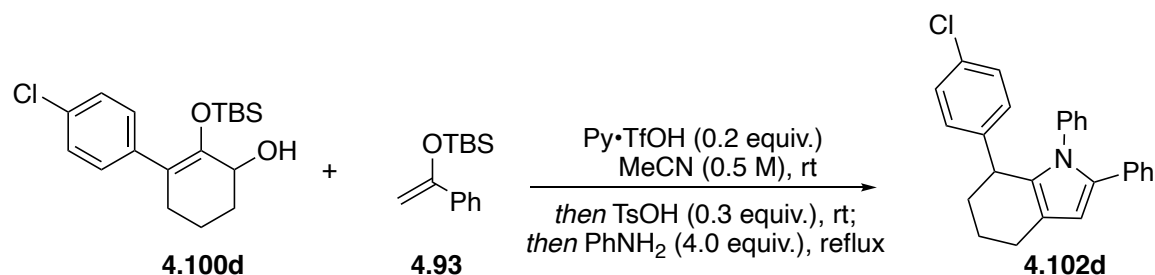
¹H NMR: (500 MHz, CDCl₃) δ = 7.17 – 7.03 (m, 10H), 6.82 (d, *J* = 8.2 Hz, 4H), 6.31 (s, 1H), 4.20 (d, *J* = 6.0 Hz, 1H), 3.02 – 2.92 (m, 1H), 2.92 – 2.82 (m, 1H), 2.78 – 2.69 (m, 1H), 2.28 – 2.20 (m, 1H).

¹³C NMR: (125 MHz, CDCl₃) δ = 143.91, 142.19, 133.41, 131.44, 128.57, 128.40, 128.21, 128.00, 127.76, 126.58, 126.46, 125.82, 105.04, 44.46, 40.39, 24.62.

IR: $\tilde{\nu}$ (cm⁻¹) = 2909, 2857, 1597, 1488, 1460, 1359, 1166, 1013, 912, 823, 793, 755, 694.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 370.1357 calculated for C₂₅H₂₀NCl; Found 370.1364

7-(4-chlorophenyl)-1,2-diphenyl-4,5,6,7-tetrahydro-1H-indole (4.102d)



Procedure: Alcohol **4.100d** (110 mg, 0.325 mmol) was dissolved in dry acetonitrile (0.7 mL). Silylenol ether **4.93** (228 mg, 0.973 mmol) was added, followed by Py•TfOH (0.13 mL, 0.065 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 4 hours. Upon complete consumption of **4.100d** as monitored by TLC, TsOH monohydrate (18 mg, 0.097 mmol) was added, and the mixture was stirred for 3 hours. Once protodesilylation was completed as monitored by TLC, aniline (0.11 mL, 1.298 mmol) was added, and the mixture was stirred at reflux for 3 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 85:15 hexanes : CH₂Cl₂ to yield **4.102d** in 40% yield (46 mg, 0.119 mmol) as a white solid.

Rf: 0.7 in 90:10 hexanes : EtOAc

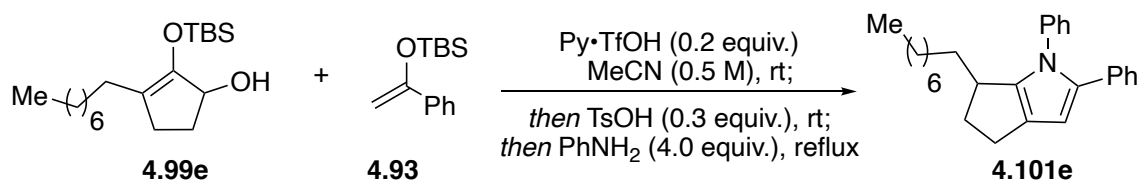
¹H NMR: (400 MHz, CDCl₃) δ = 7.14 – 7.01 (m, 9H), 6.79 (d, *J* = 8.3 Hz, 2H), 6.33 (s, 1H), 3.91 (t, *J* = 4.7 Hz, 1H), 2.80 – 2.60 (m, 2H), 2.20 – 2.11 (m, 1H), 1.79 – 1.65 (m, 3H).

¹³C NMR: (126 MHz, CDCl₃) δ = 144.33, 138.99, 134.32, 133.18, 131.52, 131.22, 129.39, 128.40, 127.88, 127.81, 127.74, 127.68, 126.94, 125.68, 120.06, 108.17, 38.65, 33.28, 22.97, 19.01.

IR: $f(\text{cm}^{-1})$ = 2925, 2847m 1596, 1493, 1448, 1382, 1089, 1015, 909, 790, 755, 546, 530.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 384.1514 calculated for C₂₆H₂₂NCl; Found 384.1522.

6-octyl-1,2-diphenyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (4.101e)



Procedure: Alcohol **4.99e** (62 mg, 0.189 mmol) was dissolved in dry acetonitrile (0.4 mL). Silylenol ether **4.93** (89 mg, 0.379 mmol) was added, followed by Py•TfOH (0.08 mL, 0.038 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 2 hours. Upon complete consumption of **4.99e** as monitored by TLC, TsOH monohydrate (11 mg, 0.057 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, aniline (0.06 mL, 0.759 mmol) was added, and the mixture was stirred at reflux for 1 hour until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.101e** in 70% yield (51 mg, 0.137 mmol) as a colorless oil.

Rf: 0.9 in 90:10 hexanes : EtOAc

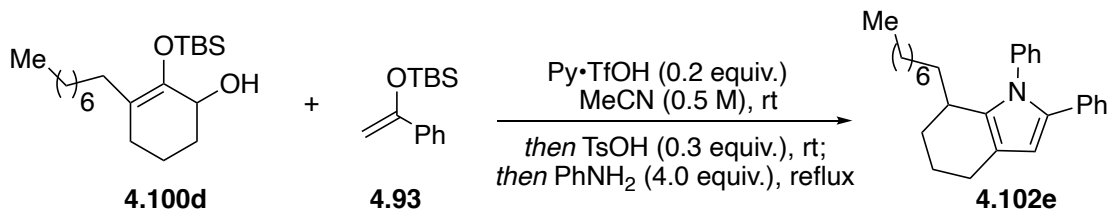
¹H NMR: (400 MHz, CDCl₃) δ = 7.34 (t, J = 7.4 Hz, 2H), 7.31 – 7.27 (m, 1H), 7.20 – 7.15 (m, 4H), 7.12 (d, J = 7.0 Hz, 3H), 6.25 (s, 1H), 3.28 – 3.21 (m, 1H), 2.78 – 2.63 (m, 3H), 2.16 – 2.07 (m, 1H), 1.30 – 1.05 (m, 14H), 0.89 (t, J = 7.1 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 143.61, 139.76, 136.92, 133.68, 128.82, 127.91, 127.90, 126.75, 126.63, 126.53, 125.55, 105.11, 38.80, 35.37, 33.92, 31.84, 29.43, 29.31, 29.17, 26.64, 24.47, 22.63, 14.09.

IR: f (cm⁻¹) = 2918, 2850, 1597, 1499, 1391, 1167, 1038, 911, 850, 755, 695.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 372.2686 calculated for C₂₇H₃₄N; Found 372.2691.

7-octyl-1,2-diphenyl-4,5,6,7-tetrahydro-1H-indole (4.102e)



Procedure: Alcohol **4.100e** (147 mg, 0.431 mmol) was dissolved in dry acetonitrile (0.8 mL). Silylenol ether **4.93** (304 mg, 1.295 mmol) was added, followed by Py•TfOH (0.17 mL, 0.086 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 2 hours. Upon complete consumption of **4.100e** as monitored by TLC, TsOH monohydrate (24 mg, 0.013 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, aniline (0.15 mL, 1.726 mmol) was added, and the mixture was stirred at reflux for 3 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.102e** in 55% yield (91 mg, 0.235 mmol) as a colorless oil.

Rf: 0.7 in 90:10 hexanes : EtOAc

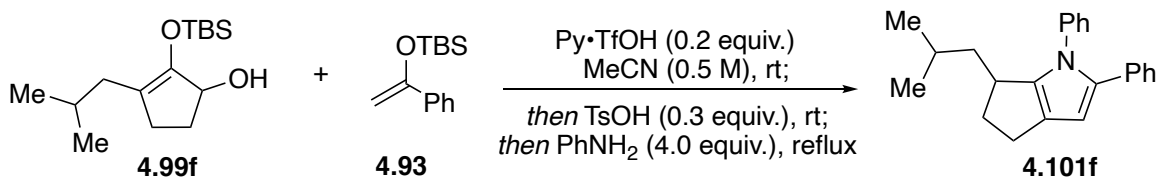
¹H NMR: (500 MHz, CDCl₃) δ = 7.37 – 7.26 (m, 3H), 7.12 (t, J = 7.2 Hz, 2H), 7.08 – 7.02 (m, 3H), 6.22 (s, 1H), 2.81 – 2.74 (m, 1H), 2.63 – 2.55 (m, 2H), 1.82 – 1.74 (m, 4H), 1.30 – 1.21 (m, 4H), 1.18 – 1.10 (m, 5H), 1.00 – 0.95 (m, 3H), 0.90 – 0.85 (m, 5H).

¹³C NMR: (125 MHz, CDCl₃) δ = 140.37, 133.62, 133.17, 132.49, 128.84, 128.26, 127.71, 127.02, 125.45, 120.04, 108.34, 40.27, 37.75, 31.13, 27.94, 27.12, 26.64, 26.55, 25.06, 23.55, 22.27.

IR: *f* (cm⁻¹) = 2922, 2852, 1599, 1496, 1453, 1382, 1300, 910, 793, 756, 697.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 386.2842 calculated for C₂₈H₃₃N; Found 386.2847

6-isobutyl-1,2-diphenyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (4.101f)



Procedure: Alcohol **4.99f** (43 mg, 0.158 mmol) was dissolved in dry acetonitrile (0.3 mL). Silylenol ether **4.93** (74 mg, 0.317 mmol) was added, followed by Py•TfOH (63 μ L, 0.032 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.99f** as monitored by TLC, TsOH monohydrate (9 mg, 0.047 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, aniline (88 μ L, 0.636 mmol) was added, and the mixture was stirred at reflux for 3 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.101f** in 53% yield (26 mg, 0.082 mmol) as a white solid.

Rf: 0.9 in 90:10 hexanes : EtOAc

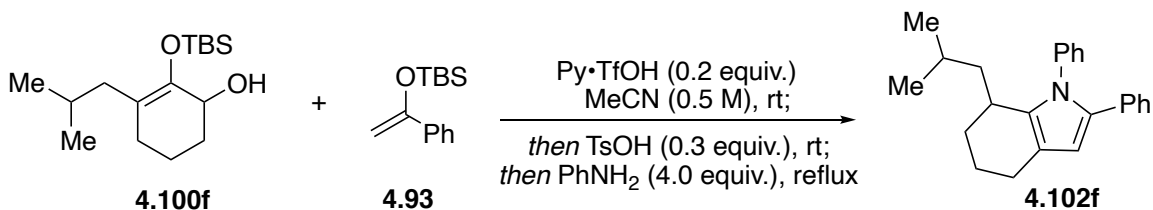
¹H NMR: (400 MHz, CDCl₃) δ = 7.30 (d, *J* = 7.7 Hz, 2H), 7.26 – 7.24 (m, 1H), 7.18 – 7.13 (m, 4H), 7.11 – 7.07 (m, 3H), 6.22 (s, 1H), 3.24 (t, *J* = 6.9 Hz, 1H), 2.78 – 2.61 (m, 3H), 2.12 – 2.04 (m, 1H), 1.50 – 1.41 (m, 1H), 1.07 (ddd, *J* = 13.6, 10.3, 4.3 Hz, 1H), 0.83 (ddd, *J* = 13.1, 9.4, 3.1 Hz, 1H), 0.68 (d, *J* = 6.6 Hz, 3H), 0.66 (d, *J* = 6.7 Hz, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 143.96, 139.60, 136.87, 133.66, 128.81, 127.93, 127.91, 126.59, 126.50, 126.38, 125.58, 105.17, 43.54, 36.93, 35.63, 26.18, 24.28, 23.68, 21.55.

IR: $\tilde{\nu}$ (cm⁻¹) = 2950, 2928, 1598, 1500, 1461, 1385, 1290, 1125, 1028, 755, 696.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 316.2060 calculated for C₂₃H₂₆N; Found 316.2059.

7-isobutyl-1,2-diphenyl-4,5,6,7-tetrahydro-1H-indole (4.102f)



Procedure: Alcohol **4.100f** (192 mg, 0.674 mmol) was dissolved in dry acetonitrile (1.3 mL). Silylenol ether **4.93** (474 mg, 2.024 mmol) was added, followed by Py•TfOH (0.27 mL, 0.135 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 2 hours. Upon complete consumption of **4.100f** as monitored by TLC, TsOH monohydrate (38 mg, 0.202 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, aniline (0.23 mL, 2.699 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:15 hexanes : CH₂Cl₂ to yield **4.102f** in 58% yield (129 mg, 0.392 mmol) as a white solid.

Rf: 0.9 in 90:10 hexanes : EtOAc

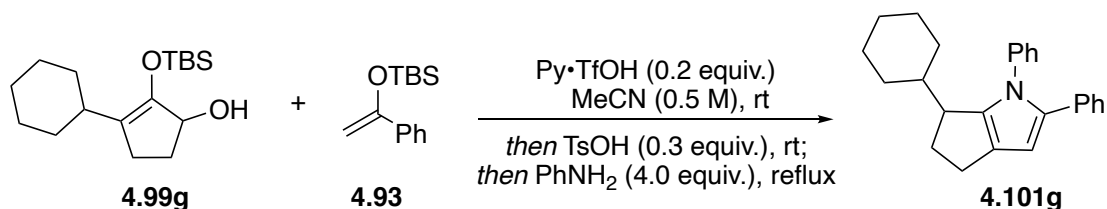
¹H NMR: (400 MHz, CDCl₃) δ = 7.26 (m, 4H), 7.15 – 7.01 (m, 6H), 6.21 (s, 1H), 2.88 – 2.78 (m, 1H), 2.67 – 2.53 (m, 2H), 1.84 – 1.73 (m, 4H), 1.44 – 1.34 (m, 1H), 1.32 – 1.21 (m, 2H), 0.70 (ddd, J = 13.3, 10.3, 2.3 Hz, 1H), 0.64 (d, J = 6.6 Hz, 3H), 0.35 (d, J = 6.5 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 139.31, 134.81, 133.47, 133.40, 128.90, 127.96, 127.77, 127.15, 125.47, 125.43, 117.89, 108.17, 42.57, 29.47, 26.75, 25.25, 23.93, 23.16, 20.76, 19.12.

IR: f (cm⁻¹) = 2950, 2925, 2850, 1668, 1514, 1450, 1311, 1181, 1045, 967, 779, 731, 596.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 330.2216 calculated for C₂₄H₂₇N; Found 330.2221

6-cyclohexyl-1,2-diphenyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (4.101g)



Procedure: Alcohol **4.99g** (93 mg, 0.313 mmol) was dissolved in dry acetonitrile (0.6 mL). Silylenol ether **4.93** (147 mg, 0.627 mmol) was added, followed by Py•TfOH (0.12 mL, 0.062 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 2 hours. Upon complete consumption of **4.99g** as monitored by TLC, TsOH monohydrate (18 mg, 0.094 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, aniline (0.10 mL, 1.254 mmol) was added, and the mixture was stirred at reflux for 2 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.101g** in 53% yield (57 mg, 0.167mmol) as a white solid.

Rf: 0.9 in 90:10 hexanes : EtOAc

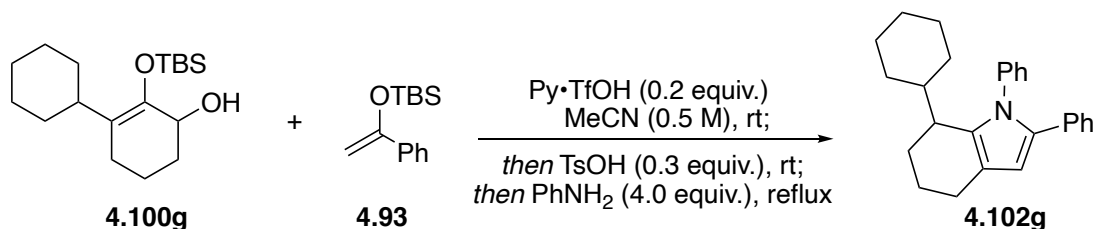
¹H NMR: (400 MHz, CDCl₃) δ = δ 7.33 – 7.27 (m, 3H), 7.16 – 7.12 (m, 4H), 7.09 – 7.06 (m, 3H), 6.21 (s, 1H), 3.20 – 3.15 (m, 1H), 2.67 – 2.61 (m, 2H), 2.50 – 2.40 (m, 1H), 2.27 – 2.19 (m, 1H), 1.59 – 1.44 (m, 4H), 1.34 (d, *J* = 7.2 Hz, 1H), 1.11 – 1.04 (m, 1H), 0.97 – 0.88 (m, 4H), 0.79 – 0.69 (m, 2H).

¹³C NMR: (100 MHz, CDCl₃) δ = 142.22, 140.02, 136.98, 133.72, 128.90, 128.83, 127.87, 127.55, 126.72, 126.58, 125.47, 104.91, 44.69, 40.74, 31.36, 31.03, 27.32, 26.69, 26.48, 26.29, 25.13.

IR: ν (cm⁻¹) = 2919, 2849, 1597, 1500, 1449, 1388, 1360, 1166, 1075, 1028, 908, 755.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 342.2216 calculated for C₂₅H₂₈N; Found 342.2215.

7-cyclohexyl-1,2-diphenyl-4,5,6,7-tetrahydro-1*H*-indole (4.102g)



Procedure: Alcohol **4.100g** (152 mg, 0.489 mmol) was dissolved in dry acetonitrile (1.0 mL). Silylenol ether **4.93** (344 mg, 1.468 mmol) was added, followed by Py•TfOH (0.2 mL, 0.098 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 2 hours. Upon complete consumption of **4.100g** as monitored by TLC, TsOH monohydrate (28 mg, 0.0147 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, aniline (0.17 mL, 1.959 mmol) was added, and the mixture was stirred at reflux for 5 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.102g** in 63% yield (109 mg, 0.306 mmol) as a white solid.

Rf: 0.9 in 90:10 hexanes : EtOAc

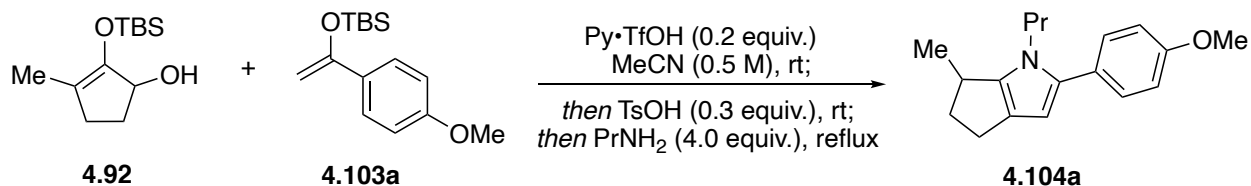
¹H NMR: (400 MHz, CDCl₃) δ = 7.46 – 7.26 (m, 4H), 7.16 – 7.03 (m, 6H), 6.23 (s, 1H), 2.94 (q, *J* = 5.2 Hz, 1H), 2.60 (q, *J* = 5.9, 5.5 Hz, 2H), 1.91 – 1.83 (m, 2H), 1.76 – 1.68 (m, 3H), 1.54 (d, *J* = 12.6 Hz, 2H), 1.46 (d, *J* = 13.2 Hz, 1H), 1.22 (s, 2H), 0.98 – 0.70 (m, 6H).

¹³C NMR: (100 MHz, CDCl₃) δ = 140.37, 133.63, 133.16, 132.46, 128.81, 128.24, 127.69, 126.99, 125.44, 120.04, 117.80, 108.36, 40.27, 37.74, 31.12, 27.95, 27.11, 26.63, 26.54, 25.06, 23.55, 22.26.

IR: ν (cm⁻¹) = 3061, 2921, 2848, 1597, 1496, 1447, 1381, 1300, 1171, 1071, 1027, 907, 840, 757.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 356.2373 calculated for C₂₆H₂₉N; Found 256.2376

2-(4-methoxyphenyl)-6-methyl-1-propyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (4.104a)



Procedure: Alcohol **4.92** (166 mg, 0.727 mmol) was dissolved in dry acetonitrile (1.4 mL). Silylenol ether **4.103a** (384 mg, 1.454 mmol) was added, followed by Py•TfOH (0.30 mL, 0.1453 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (41 mg, 0.218 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, propylamine (0.23 mL, 2.907 mmol) was added, and the mixture was stirred at reflux for 3 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : CH₂Cl₂ to yield **4.104a** in 66% yield (129 mg, 0.479 mmol) as a brown oil.

Rf: 0.7 in 90:10 hexanes : EtOAc

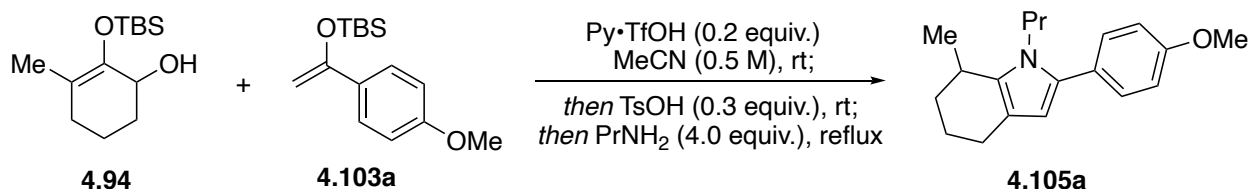
¹H NMR: (400 MHz, CDCl₃) δ = 7.30 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 5.90 (s, 1H), 3.85 (s, 3H), 3.84 – 3.72 (m, 2H), 3.23 (h, J = 6.6 Hz, 1H), 2.74 – 2.63 (m, 2H), 2.61 – 2.53 (m, 1H), 2.02 – 1.94 (m, 1H), 1.65 – 1.55 (m, 2H), 1.30 (d, J = 6.7 Hz, 3H), 0.79 (t, J = 7.4 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 158.38, 142.46, 136.92, 130.14, 127.09, 125.10, 113.66, 102.93, 55.23, 46.68, 38.87, 33.47, 24.58, 24.27, 20.48, 11.15.

IR: f (cm⁻¹) = 2955, 2856, 1610, 1521, 1464, 1366, 1284, 1174, 1105, 908, 833, 728, 645.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 270.1852 calculated for C₁₈H₂₄NO; Found 270.1856.

2-(4-methoxyphenyl)-7-methyl-1-propyl-4,5,6,7-tetrahydro-1*H*-indole (4.105b)



Procedure: Alcohol **4.94** (136 mg, 0.561 mmol) was dissolved in dry acetonitrile (1.1 mL). Silylenol ether **4.103a** (296 mg, 1.122 mmol) was added, followed by Py•TfOH (0.22 mL, 0.112 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.94** as monitored by TLC, TsOH monohydrate (32 mg, 0.168 mmol) was added, and the mixture was stirred for 3 hours. Once protodesilylation was completed as monitored by TLC, propylamine (0.18 mL, 2.144 mmol) was added, and the mixture was stirred at reflux for 3 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 85:15 hexanes : CH₂Cl₂ to yield **4.105a** in 55% yield (87 mg, 0.307 mmol) as a colorless oil.

Rf: 0.7 in 90:10 hexanes : EtOAc

¹H NMR: (400 MHz, CDCl₃) δ = 7.31 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.90 (s, 1H), 3.85 (s, 3H), 3.84 – 3.72 (m, 2H), 2.95 (p, J = 6.8, 5.7 Hz, 1H), 2.60 – 2.47 (m, 2H), 1.92 – 1.67 (m, 4H), 1.49 – 1.39 (m, 2H), 1.29 (d, J = 6.9 Hz, 3H), 0.73 (t, J = 7.4 Hz, 3H).

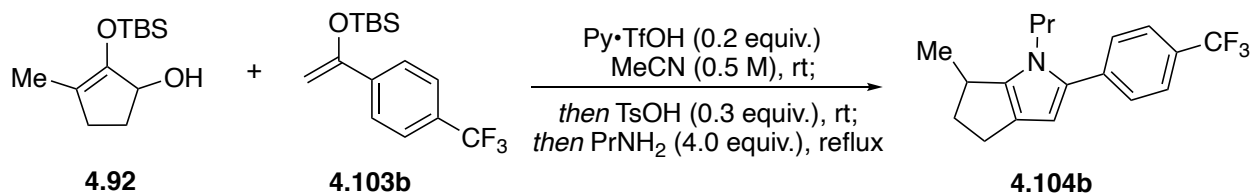
¹³C NMR: (100 MHz, CDCl₃) δ = 158.35, 133.18, 132.97, 130.03, 127.17, 116.42, 113.66, 107.13, 55.22, 45.55, 31.69, 26.60, 24.43, 23.29, 21.25, 19.23, 11.21.

IR: $f(\text{cm}^{-1})$ = 2959, 2927, 1611, 1526, 1460, 1372, 1280, 1242, 1173, 1105, 1043, 908, 832, 729, 646.

HRMS (ESI-TOF) m/z : $(M+H)^+ = 284.2009$ calculated for $C_{19}H_{26}NO$; Found 284.2009.

6-methyl-1-propyl-2-(4-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole

(4.104b)



Procedure: Alcohol **4.92** (154 mg, 0.6742 mmol) was dissolved in dry acetonitrile (1.3 mL). Silylenol ether **4.103b** (407 mg, 1.348 mmol) was added, followed by $Py \cdot TfOH$ (0.26 mL, 0.135 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, $TsOH$ monohydrate (38 mg, 0.202 mmol) was added, and the mixture was stirred for 24 hours. Once protodesilylation was completed as monitored by TLC, propylamine (0.22 mL, 2.697 mmol) was added, and the mixture was stirred at reflux for 2 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:15 hexanes : CH_2Cl_2 to yield **4.104b** in 52% yield (107 mg, 0.348 mmol) as a brown oil.

Rf: 0.8 in 90:10 hexanes : EtOAc

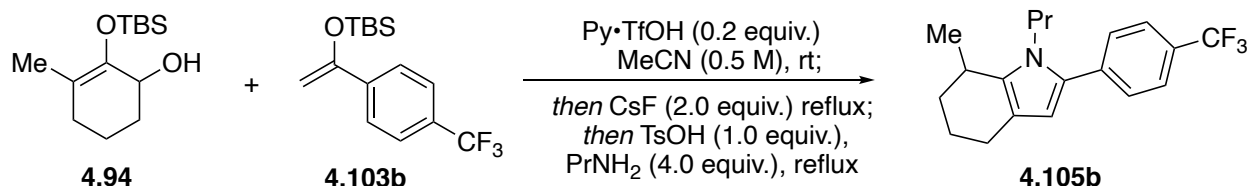
1H NMR: (400 MHz, $CDCl_3$) δ = 7.61 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 6.02 (s, 1H), 3.98 – 3.89 (m, 1H), 3.88 – 3.79 (m, 1H), 3.22 (h, J = 6.7 Hz, 1H), 2.74 – 2.62 (m, 2H), 2.59 – 2.51 (m, 1H), 2.04 – 1.94 (m, 1H), 1.63 – 1.54 (m, 2H), 1.29 (d, J = 6.8 Hz, 3H), 0.78 (t, J = 7.4 Hz, 3H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ = 144.85, 137.88, 135.65, 128.17, 125.95, 125.37, 125.34, 125.31, 125.28, 104.98, 47.03, 38.84, 33.44, 24.57, 24.10, 20.39, 11.08.

IR: $\tilde{\nu}$ (cm⁻¹) = 2958, 2935, 2860, 1614, 1462, 1321, 1161, 1086, 1014, 844, 794.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 308.1621 calculated for C₁₈H₂₁NF₃; Found 308.1624.

7-methyl-1-propyl-2-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1H-indole (4.105b)



Procedure: Alcohol **4.94** (198 mg, 0.817 mmol) was dissolved in dry acetonitrile (1.6 mL). Silylenol ether **4.103b** (493 mg, 1.633 mmol) was added, followed by Py•TfOH (0.32 mL, 0.163 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 6 hours. Upon complete consumption of **4.94** as monitored by TLC, CsF (238 mg, 1.633 mmol) was added, and the mixture was stirred at reflux for 1 hour. Once protodesilylation was completed as monitored by TLC, propylamine (0.26 mL, 3.266 mmol) and TsOH monohydrate (155 mg, 0.817 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to yield **4.105b** in 34% yield (89 mg, 0.277 mmol) as a brown oil.

Rf: 0.8 in 90:10 hexanes : EtOAc

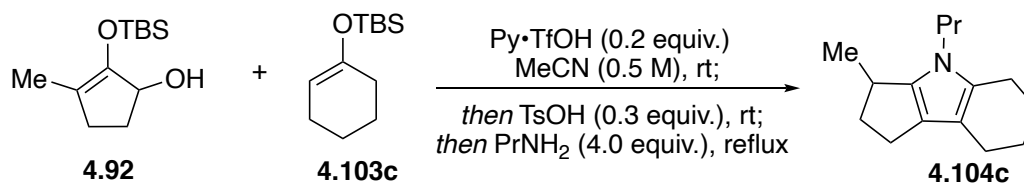
¹H NMR: (400 MHz, CDCl₃) δ = 7.62 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 6.04 (s, 1H), 3.94 (dt, J = 15.2, 7.4 Hz, 1H), 3.84 (dt, J = 14.5, 7.5 Hz, 1H), 3.02 – 2.91 (m, 1H), 2.60 – 2.44 (m, 2H), 1.95 – 1.68 (m, 4H), 1.48 – 1.36 (m, 2H), 1.30 (d, J = 6.8 Hz, 3H), 0.72 (t, J = 7.4 Hz, 3H).

^{13}C NMR: (100 MHz, CDCl_3) δ = 138.03, 135.47, 131.82, 128.14, 125.28, 125.24, 117.34, 109.27, 45.71, 31.49, 26.59, 24.49, 23.19, 21.20, 19.06, 11.12.

IR: $f(\text{cm}^{-1})$ = 2963, 2930, 2875, 1614, 1459, 1411, 1320, 1119, 1066, 10133, 844, 794, 734.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 322.1777$ calculated for $\text{C}_{19}\text{H}_{23}\text{F}_3\text{N}$; Found 322.1750.

3-methyl-4-propyl-1,2,3,4,5,6,7,8-octahydrocyclopenta[*b*]indole (**4.104c**)



Procedure: Alcohol **4.92** (216 mg, 0.946 mmol) was dissolved in dry acetonitrile (1.9 mL). Silylenol ether **4.103c** (401 mg, 1.891 mmol) was added, followed by $\text{Py}\cdot\text{TfOH}$ (0.37 mL, 0.189 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (54 mg, 0.283 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, propylamine (0.30 mL, 3.783 mmol) was added, and the mixture was stirred at reflux for 3 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : CH_2Cl_2 to yield **4.104c** in 64% yield (132 mg, 0.608 mmol) as a dark purple oil.

Rf: 0.9 in 80:20 hexanes : EtOAc

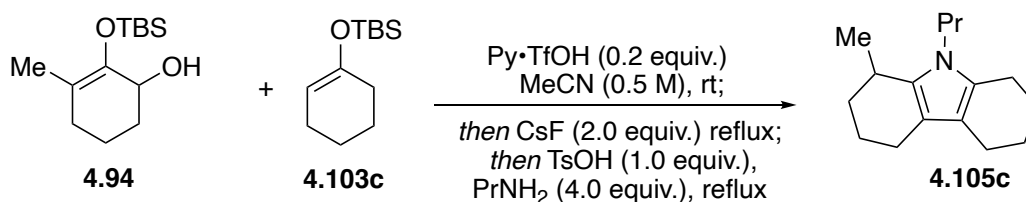
^1H NMR: (400 MHz, CDCl_3) δ = 3.63 (t, J = 7.8 Hz, 2H), 3.14 (h, J = 7.0 Hz, 1H), 2.66 – 2.50 (m, 5H), 2.49 – 2.42 (m, 3H), 1.95 – 1.89 (m, 1H), 1.85 – 1.79 (m, 2H), 1.76 – 1.66 (m, 4H), 1.24 (d, J = 6.7 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H).

^{13}C NMR: (100 MHz, CDCl_3) δ = 139.25, 130.00, 123.01, 111.75, 46.05, 38.92, 33.14, 24.88, 23.61, 23.42, 23.24, 22.50, 22.36, 20.83, 11.44.

IR: $\tilde{\nu}$ (cm^{-1}) = 2927, 2851, 1642, 1442, 1398, 1074, 908, 836, 728.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 218.1903$ calculated for $\text{C}_{15}\text{H}_{24}\text{N}$; Found 218.1916.

1-methyl-9-propyl-2,3,4,5,6,7,8,9-octahydro-1*H*-carbazole (4.105c)



Procedure: Alcohol **4.94** (202 mg, 0.833 mmol) was dissolved in dry acetonitrile (1.7 mL). Silylenol ether **4.103c** (354 mg, 1.666 mmol) was added, followed by $\text{Py}\cdot\text{TfOH}$ (0.33 mL, 0.166 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 3 hours. Upon complete consumption of **4.94** as monitored by TLC, CsF (253 mg, 1.666 mmol) was added, and the mixture was stirred at reflux for 2 hours. Once protodesilylation was completed as monitored by TLC, propylamine (0.27 mL, 3.333 mmol) and TsOH monohydrate (158 mg, 0.833 mmol) was added, and the mixture was stirred at reflux for 3 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH_2Cl_2 to yield **4.105c** in 51% yield (98 mg, 0.423 mmol) as a purple oil.

Rf: 0.9 in 80:20 hexanes : EtOAc

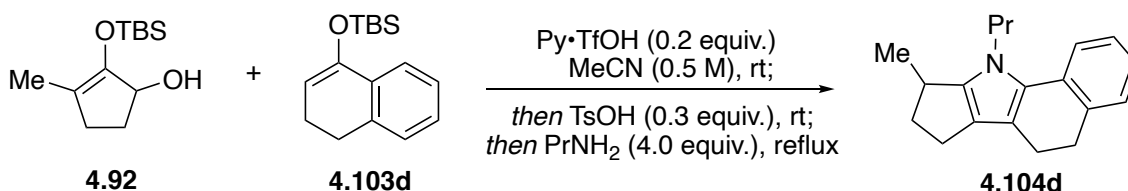
^1H NMR: (400 MHz, CDCl_3) δ = 3.65 (t, J = 7.5 Hz, 2H), 3.22 – 3.09 (m, 1H), 2.67 – 2.40 (m, 8H), 1.93 (q, J = 6.8, 6.1 Hz, 1H), 1.88 – 1.61 (m, 7H), 1.99 – 1.89 (m, 1H), 0.96 (t, J = 7.3 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 139.21, 129.96, 122.97, 111.70, 46.02, 38.89, 33.10, 24.85, 23.58, 23.38, 23.22, 22.46, 22.32, 20.80, 11.42.

IR: $\tilde{\nu}$ (cm⁻¹) = 2952, 2855, 1600, 1510, 1495, 1390, 1292, 1167, 908, 756, 695

HRMS (ESI-TOF) m/z : (M+H)⁺ = 232.2060 calculated for C₁₆H₂₆N; Found 232.2062.

9-methyl-10-propyl-5,6,7,8,9,10-hexahydrobenzo[*g*]cyclopenta[*b*]indole (4.104d)



Procedure: Alcohol **4.92** (208 mg, 0.910 mmol) was dissolved in dry acetonitrile (1.8 mL). Silylenol ether **4.103d** (474 mg, 1.821 mmol) was added, followed by Py•TfOH (0.36 mL, 0.182 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 2 hours. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (52 mg, 0.273 mmol) was added, and the mixture was stirred for 5 hours. Once protodesilylation was completed as monitored by TLC, propylamine (0.30 mL, 3.642 mmol) was added, and the mixture was stirred at reflux for 24 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.104d** in 50% yield (118 mg, 0.445 mmol) as a yellow oil.

Rf: 0.8 in 80:20 hexanes : EtOAc

¹H NMR: (400 MHz, CDCl₃) δ = 7.29 (d, J = 7.6 Hz, 1H), 7.20 (dt, J = 10.8, 5.3 Hz, 2H), 7.00 (t, J = 7.9 Hz, 1H), 4.19 – 4.09 (m, 1H), 4.02 – 3.93 (m, 1H), 3.22 (s, 1H), 2.86 – 2.81 (m, 2H), 2.71

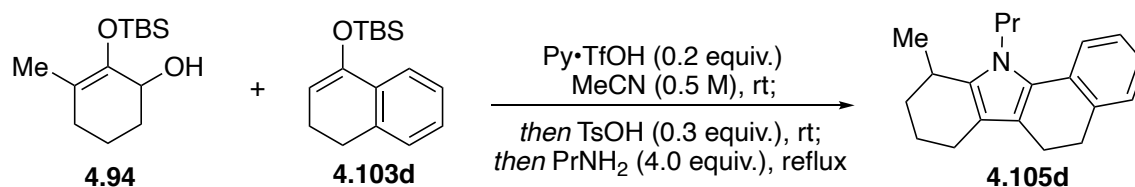
– 2.63 (m, 2H), 2.60 – 2.49 (m, 3H), 2.04 – 1.95 (m, 1H), 1.91 – 1.79 (m, 2H), 1.30 (d, $J = 6.8$ Hz, 3H), 0.97 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR: (100 MHz, CDCl_3) $\delta = 144.63, 135.68, 131.19, 130.27, 128.28, 126.40, 123.59, 122.83, 119.36, 117.51, 48.34, 38.59, 33.17, 31.19, 24.61, 22.89, 21.52, 20.75, 11.17$.

IR: ν (cm^{-1}) = 2951, 2926, 1599, 1489, 1489, 1364, 1282, 1036, 907, 752.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 266.1903$ calculated for $\text{C}_{19}\text{H}_{24}\text{N}$; Found 266.1906.

10-methyl-11-propyl-6,7,8,9,10,11-hexahydro-5H-benzo[*a*]carbazole (4.105d)



Procedure: Alcohol **4.94** (227 mg, 0.936 mmol) was dissolved in dry acetonitrile (1.9 mL). Silylenol ether **4.103d** (487 mg, 1.873 mmol) was added, followed by Py•TfOH (0.37 mL, 0.187 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 3 hours. Upon complete consumption of **4.94** as monitored by TLC, TsOH monohydrate (53 mg, 0.281 mmol) was added, and the mixture was stirred for 3 hours. Once protodesilylation was completed as monitored by TLC, propylamine (0.30 mL, 3.745 mmol) was added, and the mixture was stirred at reflux for 24 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH_2Cl_2 to yield **4.105d** in 50% yield (132 mg, 0.472 mmol) as a yellow oil.

Rf: 0.8 in 80:20 hexanes : EtOAc

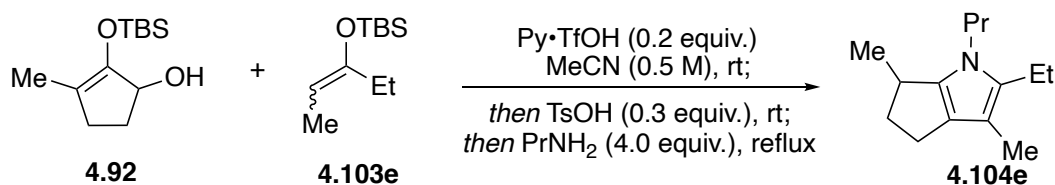
¹H NMR: (400 MHz, CDCl₃) δ = 7.37 (d, J = 7.8 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.02 – 6.97 (m, 1H), 4.15 (ddd, J = 14.9, 9.4, 5.7 Hz, 1H), 3.96 (ddd, J = 14.6, 9.6, 6.9 Hz, 1H), 2.96 (p, J = 6.8, 6.1 Hz, 1H), 2.84 (t, J = 7.4 Hz, 2H), 2.56 – 2.45 (m, 3H), 2.44 – 2.34 (m, 1H), 1.92 – 1.71 (m, 6H), 1.29 (d, J = 6.9 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 135.97, 130.87, 128.28, 126.40, 123.68, 120.76, 119.44, 113.86, 46.60, 31.61, 31.08, 24.39, 21.49, 21.40, 18.76, 11.17.

IR: f (cm⁻¹) = 2959, 2926, 1600, 1493, 1456, 1388, 1188, 1053, 754.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 280.2060 calculated for C₂₀H₂₆N; Found 280.2067.

2-ethyl-3,6-dimethyl-1-propyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (**4.104e**)



Procedure: Alcohol **4.92** (134 mg, 0.587 mmol) was dissolved in dry acetonitrile (1.1 mL). Silylenol ether **4.103e** (221 mg, 1.105 mmol) was added, followed by Py•TfOH (0.22 mL, 0.111 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (31 mg, 0.166 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, propylamine (0.18 mL, 2.211 mmol) was added, and the mixture was stirred at reflux for 2 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : CH₂Cl₂ to yield **4.104e** in 50% yield (60 mg, 0.292 mmol) as a purple oil.

Rf: 0.8 in 90:10 hexanes : EtOAc

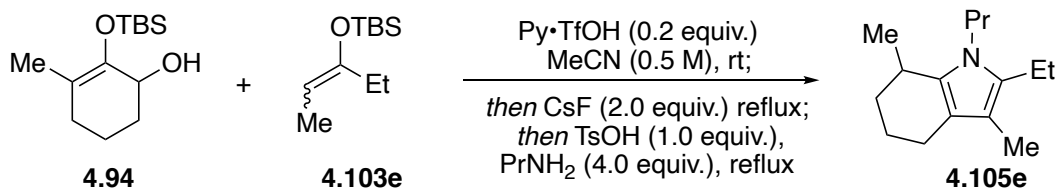
¹H NMR: (500 MHz, CDCl₃) δ = 3.66 (t, J = 8.4 Hz, 2H), 3.17 – 3.09 (m, 1H), 2.63 – 2.50 (m, 4H), 2.49 – 2.41 (m, 1H), 1.97 (s, 3H), 1.94 – 1.87 (m, 1H), 1.77 – 1.64 (m, 2H), 1.23 (d, J = 6.7 Hz, 3H), 1.13 (t, J = 7.5 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 138.59, 132.96, 124.81, 108.46, 46.32, 38.70, 33.46, 25.31, 23.24, 20.72, 17.92, 15.22, 11.43, 10.01.

IR: ν (cm⁻¹) = 2959, 2929, 1673, 1517, 1459, 1366, 1259, 1058, 795.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 206.1903 calculated for C₁₄H₂₄N; Found 206.1906.

2-ethyl-3,7-dimethyl-1-propyl-4,5,6,7-tetrahydro-1*H*-indole (4.105e)



Procedure: Alcohol **4.94** (148 mg, 0.610 mmol) was dissolved in dry acetonitrile (1.2 mL). Silylenol ether **4.103e** (244 mg, 1.221 mmol) was added, followed by Py•TfOH (0.24 mL, 0.120 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 3 hours. Upon complete consumption of **4.94** as monitored by TLC, CsF (185 mg, 0.122 mmol) was added, and the mixture was stirred at reflux for 2 hours. Once protodesilylation was completed as monitored by TLC, propylamine (0.20 mL, 2.442 mmol) and TsOH monohydrate (116 mg, 0.610 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.105e** in 50% yield (66 mg, 0.300 mmol) as a purple oil.

Rf: 0.8 in 90:10 hexanes : EtOAc

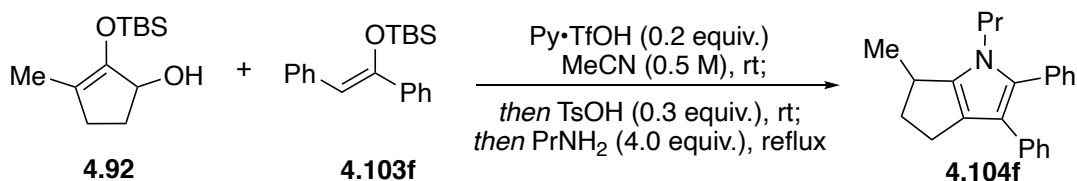
¹H NMR: (400 MHz, CDCl₃) δ = 3.67 (t, J = 5.1 Hz, 2H), 2.91 – 2.82 (m, 1H), 2.61 – 2.52 (m, 2H), 2.48 – 2.31 (m, 2H), 1.95 (s, 3H), 1.87 – 1.57 (m, 7H), 1.23 (d, J = 6.8 Hz, 3H), 1.16 (t, J = 7.5 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 129.80, 129.01, 115.09, 111.08, 45.11, 31.82, 26.30, 25.44, 21.72, 21.37, 19.14, 17.57, 15.16, 11.52, 8.91.

IR: ν (cm⁻¹) = 2959, 2925, 2870, 1457, 1388, 1317, 1251, 1057, 836, 780.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 220.2062 calculated for C₁₅H₂₆N; Found 220.2060.

6-methyl-2,3-diphenyl-1-propyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (4.104f)



Procedure: Alcohol **4.92** (208 mg, 0.911 mmol) was dissolved in dry acetonitrile (1.8 mL). Silylenol ether **4.103f** (565 mg, 1.821 mmol) was added, followed by Py•TfOH (0.36 mL, 0.182 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 2 hours. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (52 mg, 0.373 mmol) was added, and the mixture was stirred for 2 hours. Once protodesilylation was completed as monitored by TLC, propylamine (0.30 mL, 3.642 mmol) was added, and the mixture was stirred at reflux for 14 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : CH₂Cl₂ to yield **4.104f** in 62% yield (138 mg, 0.437 mmol) as a white solid.

Rf: 0.9 in 90:10 hexanes : EtOAc

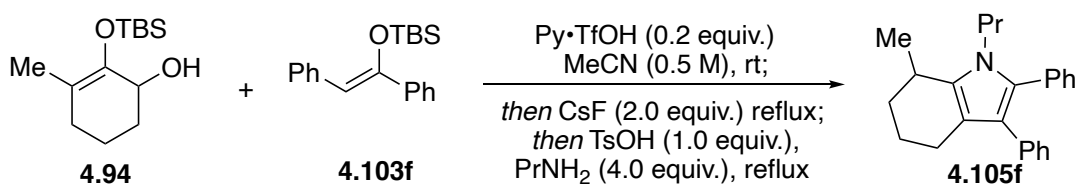
¹H NMR: (400 MHz, CDCl₃) δ = 7.40 – 7.29 (m, 5H), 7.13 (s, 4H), 7.03 (s, 1H), 3.77 – 3.67 (m, 2H), 3.28 (q, J = 6.6 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.83 – 2.70 (m, 2H), 2.11 – 2.00 (m, 1H), 1.56 (q, J = 7.5 Hz, 2H), 1.35 (d, J = 6.6 Hz, 3H), 0.77 (t, J = 7.3 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 141.73, 136.70, 133.84, 132.86, 131.30, 128.41, 127.86, 127.81, 127.19, 124.71, 124.36, 117.15, 46.61, 38.69, 33.41, 24.96, 24.59, 20.48, 11.17.

IR: $\tilde{\nu}$ (cm⁻¹) = 2961, 2873, 1676, 1600, 1501, 1445, 1403, 1318, 1289, 1159, 1028, 998.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 316.2060 calculated for C₂₃H₂₆N; Found 316.2063.

7-methyl-2,3-diphenyl-1-propyl-4,5,6,7-tetrahydro-1*H*-indole (4.105f)



Procedure: Alcohol **4.94** (199 mg, 0.821 mmol) was dissolved in dry acetonitrile (1.6 mL). Silylenol ether **4.103f** (509 mg, 1.647 mmol) was added, followed by Py•TfOH (0.30 mL, 0.164 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 24 hours. Upon complete consumption of **4.95** as monitored by TLC, CsF (250 mg, 1.647 mmol) was added, and the mixture was stirred at reflux for 2 hours. Once protodesilylation was completed as monitored by TLC, propylamine (0.4 mL, 4.924 mmol) and TsOH monohydrate (156 mg, 0.821 mmol) was added, and the mixture was stirred at reflux for 74 hours. Upon 100 hr the diketone was not fully consumed; the crude reaction mixture was concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.105f** in 46% yield (123 mg, 0.373 mmol) as a white solid.

R_f: 0.9 in 90:10 hexanes : EtOAc

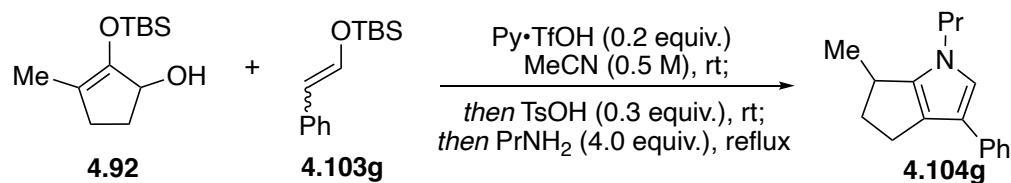
¹H NMR: (400 MHz, CDCl₃) δ = 7.32 – 7.27 (m, 2H), 7.26 – 7.22 (m, 3H), 7.14 (t, J = 7.5 Hz, 2H), 7.10 – 7.03 (m, 3H), 3.87 – 3.79 (m, 1H), 3.77 – 3.70 (m, 1H), 3.04 – 2.97 (m, 1H), 2.66 – 2.59 (m, 1H), 2.58 – 2.51 (m, 1H), 2.00 – 1.91 (m, 1H), 1.82 – 1.71 (m, 3H), 1.44 – 1.34 (m, 2H), 1.32 (d, J = 6.9 Hz, 3H), 0.67 (t, J = 7.4 Hz, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 136.35, 133.63, 132.92, 131.06, 129.97, 129.61, 128.18, 127.55, 126.71, 124.55, 120.69, 115.53, 45.51, 31.51, 26.61, 24.44, 23.35, 21.34, 19.36, 11.23.

IR: $\tilde{\nu}$ (cm⁻¹) = 2939, 2914, 2870, 2839, 1600, 1530, 1530, 1501, 1442, 1372, 1321, 1134, 1071, 906, 764, 696.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 330.2216 calculated for C₂₄H₂₈N; Found 330.2239

6-methyl-3-phenyl-1-propyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (4.104g)



Procedure: Alcohol **4.92** (217 mg, 0.950 mmol) was dissolved in dry acetonitrile (1.9 mL). Silylenol ether **4.103g** (445 mg, 1.900 mmol) was added, followed by Py•TfOH (0.38 mL, 0.190 mmol, 0.5 M solution in acetonitrile). The mixture was stirred for 1 hour. Upon complete consumption of **4.92** as monitored by TLC, TsOH monohydrate (54 mg, 0.285 mmol) was added, and the mixture was stirred for 1 hour. Once protodesilylation was completed as monitored by TLC, propylamine (0.30 mL, 3.785 mmol) was added, and the mixture was stirred at reflux for 4 hours until the full consumption of the 1,4-diketone intermediates as monitored by TLC. The reaction mixture was then concentrated under vacuum. The crude material was purified with

column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **4.104g** in 36% yield (82 mg, 0.343 mmol) as a yellow oil.

Rf: 0.8 in 90:10 hexanes : EtOAc

¹H NMR: (400 MHz, CDCl₃) δ = 7.47 (d, J = 7.3 Hz, 2H), 7.29 (t, J = 7.7 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 6.83 (s, 1H), 3.84 – 3.70 (m, 2H), 3.15 (h, J = 7.0 Hz, 1H), 2.95 – 2.87 (m, 1H), 2.80 – 2.68 (m, 2H), 2.05 – 1.98 (m, 1H), 1.83 – 1.77 (m, 2H), 1.26 (d, J = 6.8 Hz, 3H), 0.97 (s, 3H).

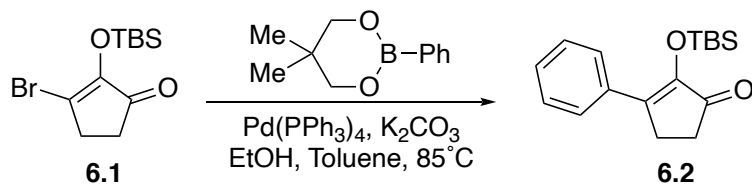
¹³C NMR: (400 MHz, CDCl₃) δ = 142.42, 136.51, 128.40, 124.82, 124.55, 123.44, 119.62, 118.74, 49.43, 38.93, 32.64, 31.56, 25.21, 24.71, 22.63, 20.53, 14.08, 11.33.

IR: f (cm⁻¹) = 2965, 2934, 1696, 1444, 1074, 907.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 240.1747 calculated for C₁₇H₂₁N; Found 240.1760.

6.4.2 Synthesis of Secondary α -Hydroxy Silylenol Ethers

2-((*tert*-butyldimethylsilyl)oxy)-3-phenylcyclopent-2-en-1-one (6.1)



Procedure: Ketone **6.1** (226 mg, 0.776 mmol) was dissolved in a mixture of 3:1 toluene and ethanol (7.8 mL). 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane (294 mg, 1.552 mmol) was then added, followed by K₂CO₃ (321 mg, 2.328 mmol) and Pd(PPh₃)₄ (18 mg, 0.038 mmol). The mixture was heated to 85 °C and stirred for 15 hours. Once the reaction was completed as monitored by TLC, the reaction was quenched with H₂O (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 10 mL) and washed with brine. The combined organic layers were dried over

sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **6.2** in 90% yield (223 mg, 0.773 mmol) as a yellow solid.

Rf: 0.7 in 80:20 hexanes : EtOAc

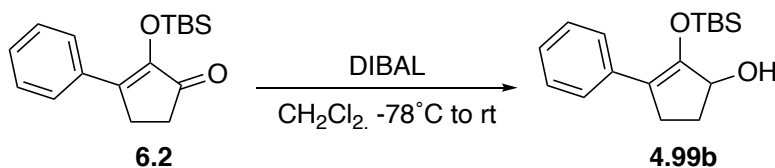
¹H NMR: (400 MHz, CDCl₃) δ = 7.92 (d, *J* = 7.0 Hz, 2H), 7.45 – 7.34 (m, 3H), 2.89 – 2.85 (m, 2H), 2.50 – 2.46 (m, 2H), 0.97 (s, 10H), 0.25 (s, 6H).

¹³C NMR: (100 MHz, CDCl₃) δ = 150.35, 135.81, 127.84, 127.13, 126.27, 117.35, 730.36, 27.97, 25.83, 18.29, -3.74, -3.79.

IR: f (cm⁻¹) = 2928, 2856, 1704, 1468, 1368, 1251, 1142, 1077, 895, 838, 782, 760, 691.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 289.1618 calculated for C₁₇H₂₄O₂Si; Found 289.1631.

2-((*tert*-butyldimethylsilyl)oxy)-3-phenylcyclopent-2-en-1-ol (**4.99b**)



Procedure: Ketone **6.2** (200mg, 0.693 mmol) was dissolved in CH₂Cl₂ and cooled to -78°C. Diisobutylaluminium hydride (1.0 mL, 1M in heptane) was added dropwise. Once addition was complete the reaction solution was warmed to room temperature. The mixture was stirred for 18 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0°C. The reaction mixture was quenched with 1:1 2M HCl (5 mL) and DI H₂O (5 mL). The mixture was then filtered through a celite plug. The aqueous layer was extracted with CH₂Cl₂ (4 x 10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **4.99b** in 68% yield (137 mg, 0.4716 mmol) as a colorless oil.

Rf: 0.7 in 80:20 hexanes : EtOAc

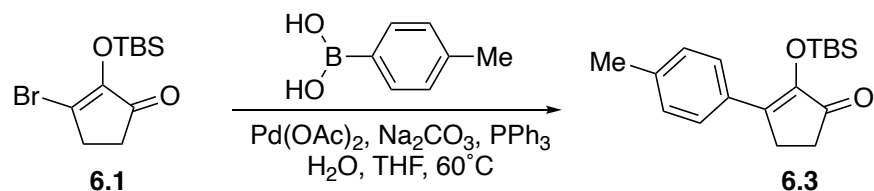
¹H NMR: (400 MHz, CDCl₃) δ = 7.62 (d, *J* = 7.1 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 4.71 – 4.64 (m, 1H), 2.74 – 2.59 (m, 2H), 2.41 – 2.32 (m, 1H), 1.83 – 1.74 (m, 1H), 0.97 (s, 10H), 0.19 (s, 4H), 0.13 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 150.35, 135.81, 127.84, 127.13, 126.27, 117.35, 730.36, 27.97, 25.83, 18.29, -3.74, -3.79.

IR: ν (cm⁻¹) = 3405, 2929, 2856, 1690, 1468, 1360, 1251, 1069, 835, 779, 692.

HRMS (ESI-TOF) *m/z*: (M-H₂O)⁺ = 273.1669 calculated for C₁₇H₂₄OSi; Found 273.1684

2-((*tert*-butyldimethylsilyl)oxy)-3-(*p*-tolyl)cyclopent-2-en-1-one (6.3)



Procedure: Ketone **6.1** (315 mg, 1.081 mmol) was dissolved in a mixture of 4:1 tetrahydrofuran and H₂O (10.8 mL). *p*-tolylboronic acid (220 mg, 1.622 mmol) was then added, followed by Na₂CO₃ (229 mg, 2.163 mmol). PPh₃ (28 mg, 0.108 mmol) was added followed by Pd(OAc)₂ (12 mg, 0.054 mmol). The mixture was then heated to 60 °C and stirred for 19 hours. Once the reaction was completed as monitored by TLC, the reaction was quenched with H₂O (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **6.3** in 42% yield (137 mg, 0.453 mmol) as a yellow solid.

Rf: 0.7 in 80:20 hexanes : EtOAc

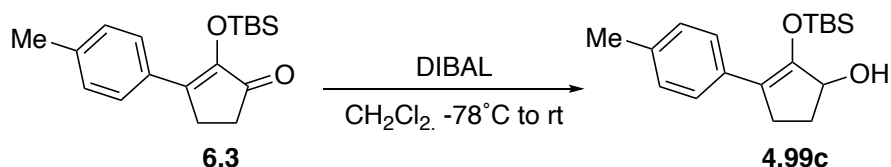
¹H NMR: (400 MHz, CDCl₃) δ = 7.83 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 2.86 – 2.82 (m, 2H), 2.48 – 2.45 (m, 2H), 2.39 (s, 3H), 0.98 (s, 9H), 0.25 (s, 6H).

¹³C NMR: (125 MHz, CDCl₃) δ = 203.08, 148.71, 144.98, 139.53, 131.67, 129.00, 127.30, 31.44, 25.92, 23.68, 21.46, 18.58, -3.54.

IR: *f* (cm⁻¹) = 2954, 2927, 2856, 1693, 1607, 1468, 1410, 1317, 1246, 1144, 1112, 898, 843.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 303.1775 calculated for C₁₈H₂₇O₂Si; Found 303.1780.

2-((*tert*-butyldimethylsilyl)oxy)-3-(*p*-tolyl)cyclopent-2-en-1-ol (4.99c)



Procedure: Ketone **6.3** (124mg, 0.409 mmol) was dissolved in CH₂Cl₂ (2.0 mL) and cooled to -78°C. Diisobutylaluminium hydride (0.6 mL, 1M in heptane) was added dropwise. Once addition was complete the reaction solution was warmed to room temperature. The mixture was stirred for 3 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0°C. The reaction mixture was quenched with 1:1 2M HCl (2.5 mL) and H₂O (2.5 mL). The mixture was then filtered through a celite plug. The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **4.99c** in 86% yield (107 mg, 0.351 mmol) as a white solid.

Rf: 0.5 in 90:10 hexanes : EtOAc

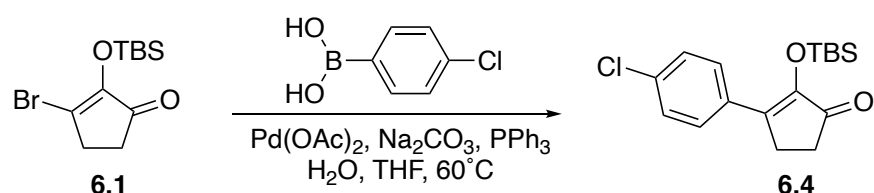
¹H NMR: (400 MHz, CDCl₃) δ = 7.52 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.70 – 4.64 (m, 1H), 2.70 – 2.58 (m, 2H), 2.34 (s, 3H), 1.81 – 1.73 (m, 1H), 1.67 (d, *J* = 6.9 Hz, 1H), 0.19 (s, 3H), 0.14 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 149.65, 135.90, 132.90, 129.10, 128.54, 127.01, 117.31, 99.97, 30.33, 28.00, 25.86, 21.19, 18.29, -3.72, -3.78.

IR: $\tilde{\nu}$ (cm⁻¹) = 3361, 2953, 2929, 2856, 1691, 1640, 1513, 1440, 1349, 1309, 1225, 1160, 1042, 1006, 939, 892, 837, 816.

HRMS (ESI-TOF) *m/z*: (M-H₂O)⁺ = 287.1462 calculated for C₁₈H₂₆OSi; Found 287.1483

2-((*tert*-butyldimethylsilyl)oxy)-3-(4-chlorophenyl)cyclopent-2-en-1-one (6.4)



Procedure: Ketone **6.1** (360 mg, 1.236 mmol) was dissolved in a mixture of 4:1 tetrahydrofuran and H₂O (12.4 mL). *p*-Chloroboronic acid (289 mg, 1.854 mmol) was then added, followed by Na₂CO₃ (261 mg, 2.472 mmol). PPh₃ (32 mg, 0.123 mmol) was added followed by Pd(OAc)₂ (14 mg, 0.061 mmol). The mixture was then heated to 60 °C and stirred for 15 hours. Once the reaction was completed as monitored by TLC, the reaction was quenched with H₂O (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 10 mL), and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **6.4** in 56% yield (399 mg, 0.697 mmol) as a white solid.

Rf: 0.5 in 90:10 hexanes : EtOAc

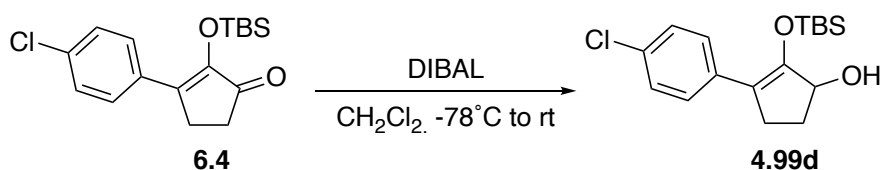
¹H NMR: (400 MHz, CDCl₃) δ = 7.86 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 2.89 – 2.78 (m, 2H), 2.53 – 2.41 (m, 2H), 0.97 (s, 9H), 0.26 (s, 6H).

¹³C NMR: (100 MHz, CDCl₃) δ = 202.87, 149.46, 143.05, 135.04, 132.95, 128.54, 128.53, 31.40, 25.88, 23.60, 18.56, -3.55.

IR: ν (cm⁻¹) = 2925, 2852, 1701, 1604, 1487, 1405, 1245, 1145, 1091, 1002, 895, 836, 810, 715, 665, 609, 575, 510.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 323.1239 calculated for C₁₇H₂₃O₂ClSi; Found 323.1249

2-((*tert*-butyldimethylsilyl)oxy)-3-(4-chlorophenyl)cyclopent-2-en-1-ol (4.99d)



Procedure: Ketone **6.4** (211mg, 0.653 mmol) was dissolved in CH₂Cl₂ (3.3 mL) and cooled to -78°C. Diisobutylaluminium hydride (1.0 mL, 1M in heptane) was added dropwise. Once addition was complete the reaction solution was warmed to room temperature. The reaction mixture was stirred for 2 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0°C. The reaction mixture was quenched with 1:1 2M HCl (2.5 mL) and H₂O (2.5 mL). The mixture was then filtered through a celite plug. The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL), and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **4.99d** in 88% yield (187 mg, 0.575 mmol) as a white solid.

R_f: 0.4 in 90:10 hexanes : EtOAc

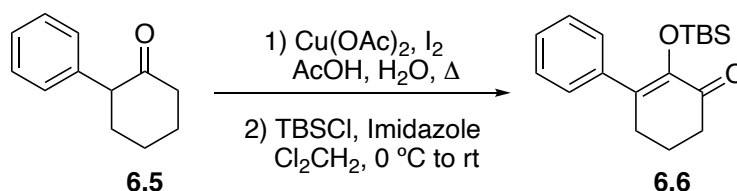
¹H NMR: (400 MHz, CDCl₃) δ = 7.56 (d, *J* = 8.7 Hz, 2H), 7.28 (s, 2H), 4.70 – 4.64 (m, 1H), 2.72 – 2.54 (m, 2H), 2.43 – 2.31 (m, 1H), 1.83 – 1.74 (m, 1H), 1.63 (d, *J* = 7.0 Hz, 1H), 0.96 (s, 9H), 0.21 (s, 3H), 0.15 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 150.99, 134.25, 131.69, 128.30, 127.98, 116.13, 76.56, 30.31, 27.82, 25.81, 18.28, -3.68.

IR: $\tilde{\nu}$ (cm⁻¹) = 3340, 2954, 2930, 2857, 1636, 1492, 1348, 1226, 1090, 1012, 970, 892, 782, 677.

HRMS (ESI-TOF) *m/z*: (M-H₂O)⁺ = 307.1279 calculated for C₁₇H₂₄OSiCl; Found 307.0920

2-((*tert*-butyldimethylsilyl)oxy)-5,6-dihydro-[1,1'-biphenyl]-3(4*H*)-one (6.6)



Procedure: Ketone **5.6** (1.58 g, 9.067 mmol), was dissolved in AcOH (15 mL) and DI H₂O (15 mL). Cu(OAc)₂ (2.1 g, 11.788 mmol) and I₂ (2.9 g, 11.788 mmol) was added to the solution. The mixture was heated to reflux and stirred for 22 hours. Once the reaction was completed as monitored by TLC, the reaction was diluted with DI H₂O (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 75:25 hexanes : EtOAc. The purified product was taken onto the next step.

The product from the previous step (1.14 g, 6.061 mmol) was dissolved in CH₂Cl₂ (12.1 mL) and cooled to 0°C. TBSCl (1.0 g, 6.975 mmol) was added to the reaction solution followed by imidazole (628 mg, 9.091 mmol). The reaction was warmed to room temperature and stirred

for 24 hours. After 24 hours the starting material was not fully consumed, the reaction was cooled to 0°C. The mixture was quenched with 2M HCl (10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **6.6** in 10% yield based on recovered starting material (259 mg, 0.856 mmol) as brown oil.

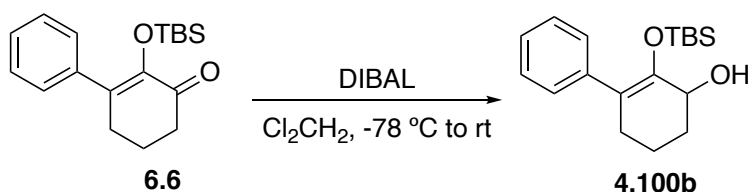
Rf: 0.7 in 80:20 hexanes : EtOAc

¹H NMR: (400 MHz, CDCl₃) δ = 7.44 (d, J = 7.0 Hz, 2H), 7.35 (t, J = 7.9 Hz, 2H), 7.29 (d, J = 8.7 Hz, 1H), 2.73 (t, J = 6.0 Hz, 2H), 2.58 – 2.53 (m, 2H), 2.11 – 2.05 (m, 2H), 0.66 (s, 9H), 0.00 (s, 6H).

¹³C NMR: (125 MHz, CDCl₃) δ = 195.69, 144.09, 138.42, 138.24, 134.09, 128.43, 127.90, 38.31, 31.05, 25.49, 22.76, 18.52, -4.27.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 303.1775 calculated for C₁₈H₂₆O₂Si; Found 303.1776

2-((*tert*-butyldimethylsilyl)oxy)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (**4.100b**)



Procedure: Ketone **6.6** (259 mg, 0.856 mmol) was dissolved in CH₂Cl₂ (2.8 mL) and cooled to -78°C. Diisobutylaluminium hydride (1.3 mL, 1M in heptane) was added dropwise. Once addition was complete the reaction solution was warmed to room temperature. The mixture was stirred for 24 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0°C. The reaction mixture was quenched with 1:1 2M HCl (5 mL) and H₂O (5 mL). The mixture was then filtered through a celite plug. The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and

washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **4.100b** in 62% yield (162 mg, 0.532 mmol) as a brown oil.

Rf: 0.6 in 80:20 hexanes : EtOAc

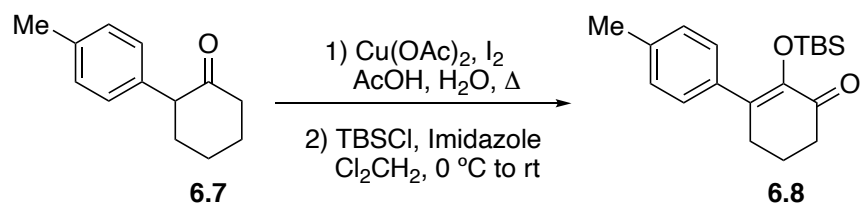
¹H NMR: (400 MHz, CDCl₃) δ = 7.30 – 7.27 (m, 4H), 7.21 – 7.16 (m, 1H), 4.17 – 4.11 (m, 1H), 2.50 – 2.41 (m, 1H), 2.32 – 2.23 (m, 1H), 2.21 (d, J = 3.5 Hz, 1H), 2.00 – 1.92 (m, 1H), 1.88 – 1.77 (m, 2H), 1.70 – 1.58 (m, 1H), 0.77 (s, 9H), -0.06 (s, 3H), -0.33 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 145.47, 140.40, 128.95, 127.85, 126.35, 120.10, 68.34, 31.66, 30.70, 25.64, 18.88, 18.08, -4.43, -4.69.

IR: $\tilde{\nu}$ (cm⁻¹) = 3281, 2929, 2856, 1658, 1465, 1251, 1210, 1184, 1127, 1062, 1008, 936, 876, 777, 754, 697.

HRMS (ESI-TOF) m/z : (M-H₂O)⁺ = 287.1822 calculated for C₁₈H₂₇OSi; Found 287.1849

2-((*tert*-butyldimethylsilyl)oxy)-4'-methyl-5,6-dihydro-[1,1'-biphenyl]-3(4*H*)-one (**6.8**)



Procedure: Ketone **6.7** (817 mg, 4.293 mmol), was dissolved in AcOH (10 mL) and DI H₂O (10 mL). Cu(OAc)₂ (1.0 g, 5.581 mmol) and I₂ (1.4 g, 5.581 mmol) was added to the solution. The mixture was heated to reflux and stirred for 23 hours. Once the reaction was completed as monitored by TLC, the crude solution was diluted with DI H₂O (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with

column chromatography using 100% hexanes to 80:20 hexanes : EtOAc. The purified product was taken onto the next step.

The product from the previous step (273 mg, 1.349 mmol) was dissolved in CH₂Cl₂ (6.7 mL) and cooled to 0°C. TBSCl (273 mg, 1.816 mmol) was added to the reaction solution followed by imidazole (137 mg, 2.024 mmol) and DMAP (68 mg, 0.558 mmol). The reaction was warmed to room temperature and stirred for 5 days. After 5 days the reaction was not complete, the reaction was cooled to 0°C. The mixture was quenched with 2M HCl (6 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **6.8** in 12% yield (167 mg, 0.527 mmol) as white solid.

Rf: 0.7 in 80:20 hexanes : EtOAc

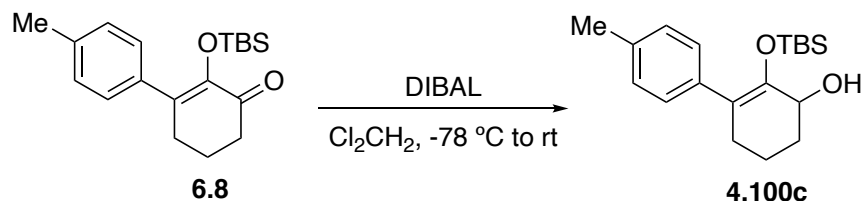
¹H NMR: (400 MHz, CDCl₃) δ = 7.37 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 2.71 (t, J = 6.0 Hz, 2H), 2.57 – 2.52 (m, 2H), 2.36 (s, 3H), 2.06 (p, J = 6.2 Hz, 2H), 0.69 (s, 9H), 0.00 (s, 6H).

¹³C NMR: (100 MHz, CDCl₃) δ = 195.55, 143.96, 138.16, 137.76, 135.37, 128.50, 128.38, 38.25, 30.98, 25.56, 22.67, 21.24, 18.53, -4.22.

IR: ν (cm⁻¹) = 2929, 2856, 1678, 1604, 1358, 1250, 1197, 1167, 935, 828, 781.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 317.1931 calculated for C₁₉H₂₈O₂Si; Found 317.1959

2-((*tert*-butyldimethylsilyl)oxy)-4'-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (4.100c)



Procedure: Ketone **6.8** (167 mg, 0.527 mmol) was dissolved in CH₂Cl₂ (2.6 mL) and cooled to -78°C. Diisobutylaluminium hydride (0.8 mL, 1M in heptane) was added dropwise. once addition was complete the reaction solution was warmed to room temperature. The mixture was stirred for 3 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0°C. The reaction mixture was quenched with 1:1 2M HCl (3mL) and H₂O (3 mL). The mixture was then filtered through a celite plug. The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 80:20 hexanes : EtOAc to yield **4.100c** in 65% yield (109 mg, 0.342 mmol) as a colorless oil.

Rf: 0.6 in 80:20 hexanes : EtOAc

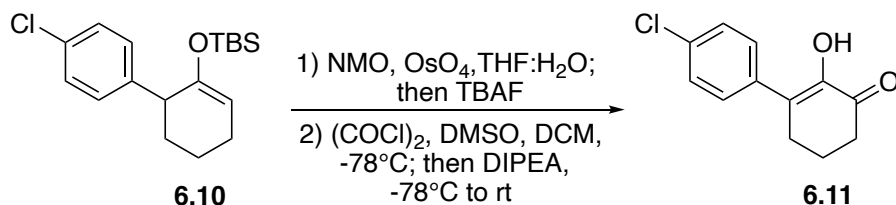
¹H NMR: (400 MHz, CDCl₃) δ = 7.19 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 4.18 – 4.10 (m, 1H), 2.49 – 2.39 (m, 1H), 2.32 (s, 3H), 2.22 (d, *J* = 3.4 Hz, 1H), 2.01 – 1.91 (m, 1H), 1.87 – 1.77 (m, 2H), 1.69 – 1.59 (m, 1H), 0.78 (s, 10H), -0.06 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 145.25, 137.35, 135.90, 128.80, 128.50, 119.92, 68.43, 31.65, 30.74, 25.69, 21.13, 18.92, 18.11, -4.44, -4.62.

IR: $f(\text{cm}^{-1})$ = 3483, 2928, 2856, 1657, 1512, 1462, 1389, 1252, 1128, 1072, 1004, 912, 864, 778.

HRMS (ESI-TOF) *m/z*: (M-H₂O)⁺ = 323.1230 calculated for C₁₉H₂₉OSi; Found 301.2205

4'-chloro-2-hydroxy-5,6-dihydro-[1,1'-biphenyl]-3(4*H*)-one (**6.11**)



Procedure: Silylenolate **6.10** (1.37 g, 4.256 mmol) was dissolved in a mixture of 3:1 THF : H₂O (4.0 mL). *N*-methylmorpholine *N*-oxide (997 mg, 8.513 mmol) was added to the solution followed by on crystal of OsO₄. The reaction was stirred for 4 hours when it reached completion as monitored by TLC. TBAF (10 mL, 1M solution in THF) was added, and the mixture was stirred for 3 hours. Once the reaction was completed as monitored by TLC, the solution was cooled to 0°C. The reaction mixture was quenched with aqueous NH₄Cl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 85/15 hexanes/EtOAc. The purified product was taken on without further purification.

Oxalyl chloride (0.6 mL, 7.008 mmol) was dissolved in CH₂Cl₂ (7.8 mL) and cooled to -78°C. DMSO (0.6 mL, 9.344 mmol) was added dropwise to the solution and stirred for 1 hour. The product from the previous step (525 mg, 2.336 mmol) was dissolved in CH₂Cl₂ (3 mL) and added dropwise to the solution. The reaction was stirred for 16 hours at -78°C. DIPEA (1.9 mL, 11.680 mmol) was added to the solution and warmed to room temperature. The reaction was stirred for 12 hours when it reached completion as monitored by TLC. The solution was cooled to 0°C and quenched with 2M HCl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude solution was concentrated under vacuum and purified with column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **6.11** in 60% yield as a white solid (310 mg, 1.392 mmol).

Rf: 0.5 in 80:20 hexanes : EtOAc

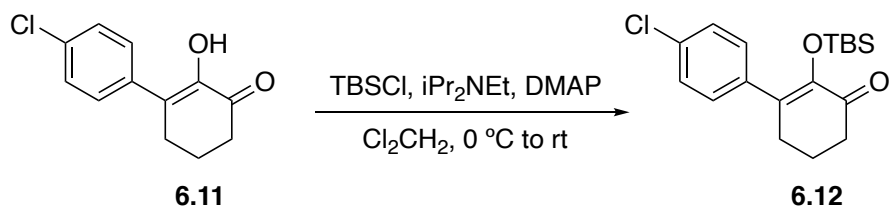
¹H NMR: (400 MHz, CDCl₃) δ = 7.69 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 6.82 (s, 1H), 2.76 (t, J = 5.9 Hz, 2H), 2.63 (t, J = 6.3 Hz, 2H), 2.12 (p, J = 6.5 Hz, 2H).

¹³C NMR: (100 MHz, CDCl₃) δ = 195.29, 143.66, 135.46, 134.04, 129.59, 128.32, 126.31, 35.67, 28.50, 22.49.

IR: *f* (cm⁻¹) = 3373, 2944, 1660, 1622, 1589, 1562, 1406, 1344, 1295, 1234, 1190, 1134, 1012.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 223.0520 calculated for C₁₂H₁₂O₂Cl; Found 223.0522

2-((*tert*-butyldimethylsilyl)oxy)-4'-chloro-5,6-dihydro-[1,1'-biphenyl]-3(4*H*)-one (6.12)



Procedure: Dione **6.11** (283 mg, 1.273 mmol) was dissolved in CH₂Cl₂ (6.3 mL) and the solution was cooled to 0 °C. TBSCl (574 mg, 3.820 mmol) was added to the solution, followed by iPr₂NEt (0.3 mL, 3.820 mmol) and DMAP (15 mg, 0.127 mmol). The reaction was warmed to room temperature and stirred for 72 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0 °C. The mixture was quenched with 2M HCl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 70:30 hexanes : CH₂Cl₂ to yield **6.12** in 82% yield (352 mg, 1.044 mmol) as a white solid.

Rf: 0.6 in 90:10 hexanes : EtOAc

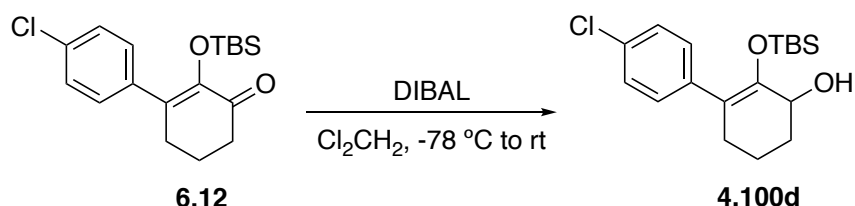
¹H NMR: (500 MHz, CDCl₃) δ = 7.41 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 2.70 (t, J = 6.0 Hz, 2H), 2.55 (t, J = 6.3 Hz, 2H), 2.07 (p, J = 6.6 Hz, 2H), 0.69 (s, 9H), 0.02 (s, 6H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 195.45, 144.35, 136.80, 136.37, 133.63, 129.88, 128.10, 38.24, 30.78, 25.54, 22.66, 18.54, -4.15.

IR: $f(\text{cm}^{-1})$ = 2929, 2885, 2856, 1680, 1605, 1470, 1397, 1315, 1198, 934, 828, 724.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 337.1385$ calculated for $\text{C}_{18}\text{H}_{25}\text{ClO}_2\text{Si}$; Found 337.1399.

2-((*tert*-butyldimethylsilyl)oxy)-4'-chloro-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (4.100d)



Procedure: Ketone **6.12** (327 mg, 0.972 mmol) was dissolved in CH_2Cl_2 (4.9.0 mL) and cooled to -78°C . Diisobutylaluminium hydride (1.5 mL, 1M in heptane, 1.458 mmol) was added dropwise. Once addition was complete the reaction solution was warmed to room temperature. The mixture was stirred for 2 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0°C . The reaction mixture was quenched with 1:1 2M HCl (5 mL) and H_2O (5 mL). The mixture was then filtered through a celite plug. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **4.100d** in 65% yield (213 mg, 0.628 mmol) as a white solid.

Rf: 0.5 in 90:10 hexanes : EtOAc

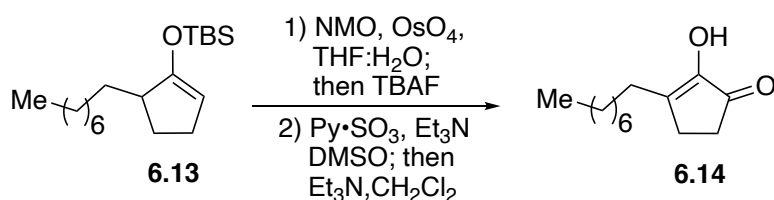
^1H NMR: (500 MHz, CDCl_3) δ = 7.27 – 7.26 (m, 4H), 4.18 – 4.11 (m, 1H), 2.47 – 2.37 (m, 1H), 2.28 – 2.20 (m, 1H), 2.16 (dd, J = 3.6, 1.3 Hz, 1H), 2.01 – 1.92 (m, 1H), 1.90 – 1.78 (m, 2H), 1.66 (t, J = 4.4 Hz, 1H), 0.79 (s, 9H), -0.02 (s, 3H), -0.28 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 146.10, 138.79, 131.95, 130.30, 127.98, 118.80, 68.21, 31.59, 30.45, 25.63, 18.74, 18.09, -4.29, -4.46.

IR: $f(\text{cm}^{-1})$ = 3303, 2929, 2857, 1646, 1490, 1392, 1344, 1252, 1204, 1089, 1004, 912, 865, 823, 777.

HRMS (ESI-TOF) m/z : $(\text{M}-\text{H}_2\text{O})^+ = 321.1454$ calculated for $\text{C}_{18}\text{H}_{25}\text{ClOSi}$; Found 321.1458

2-hydroxy-3-octylcyclopent-2-en-1-one (6.14)



Procedure: Silylenolate **6.13** (887 mg, 2.857 mmol) was dissolved in a mixture of 3:1 THF : H_2O (3.8 mL). *N*-methylmorpholine *N*-oxide (669 mg, 5.715 mmol) was added to the solution, followed by one crystal of OsO_4 . The reaction was stirred for 4 hours when it reached completion as monitored by TLC. TBAF (6 mL, 1M solution in THF) was then added, and the mixture was stirred for 18 hours. Once the reaction completed as monitored by TLC, the solution was cooled to 0°C . The reaction mixture was quenched with aqueous NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 85:15 hexanes : EtOAc. The purified product was taken onto the next step.

The product from the previous step (311 mg, 1.464 mmol) was dissolved in DMSO (2.9 mL). Et_3N (1.2 mL, 8.788) and $\text{Py}\cdot\text{SO}_3$ (923 mg, 5.868 mmol) was added to the solution. The reaction was stirred for 2 hours. Once the reaction was completed as monitored by TLC, the

solution was cooled to 0°C. The mixture was quenched with 2M HCl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was dissolved in CH₂Cl₂ (4.0 mL) and Et₃N (0.2 mL) and was stirred for 22 hr. The crude solution was concentrated under vacuum and purified with column chromatography using 100% hexanes to 94:4 hexanes : EtOAc to yield **6.14** in 17% yield (108 mg, 0.513 mmol) as brown oil.

Rf: 0.5 in 90:10 hexanes : EtOAc

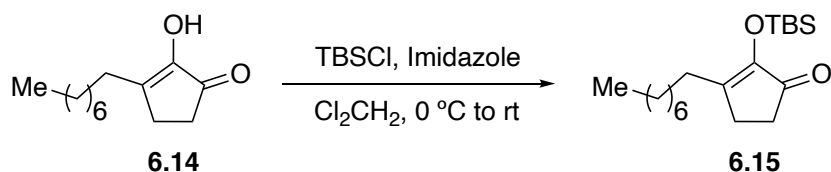
¹H NMR: (400 MHz, CDCl₃) δ = 6.03 (s, 1H), 2.45 – 2.36 (m, 5H), 1.60 – 1.48 (m, 2H), 1.36 – 1.15 (m, 10H), 0.87 (t, J = 6.7 Hz, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 203.20, 148.64, 148.27, 31.81, 29.58, 29.30, 29.17, 28.60, 26.81, 25.15, 22.61, 14.04.

IR: $f(\text{cm}^{-1})$ = 3334, 2922, 2853, 1695, 1651, 1456, 1360, 12332, 1112, 980, 719.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 211.1693 calculated for C₁₃H₂₂O₂; Found 211.1704

2-((*tert*-butyldimethylsilyl)oxy)-3-octylcyclopent-2-en-1-one (**6.15**)



Procedure: Dione **6.14** (98 mg, 0.466 mmol) was dissolved in CH₂Cl₂, the solution was cooled to 0 °C. TBSCl (81 mg, 0.5363 mmol) was added to the solution, followed by imidazole (47 mg, 0.700 mmol) and DMAP (6 mg, 0.047 mmol). The reaction was warmed to room temperature and stirred for 5 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0 °C. The mixture was quenched with 2M HCl (5 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium

sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 98:2 hexanes : EtOAc to yield **6.15** in 91% yield as a colorless oil (137 mg, 0.422 mmol).

Rf: 0.9 in 90:10 hexanes : EtOAc

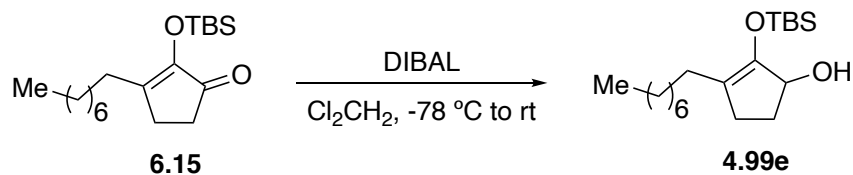
¹H NMR: (400 MHz, CDCl₃) δ = 2.40 – 2.27 (m, 5H), 1.54 – 1.43 (m, 2H), 1.34 – 1.22 (m, 11H), 0.94 (s, 9H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.18 (s, 6H).

¹³C NMR: (100 MHz, CDCl₃) δ = 203.02, 155.29, 149.17, 32.12, 31.80, 29.65, 29.33, 29.16, 28.70, 26.97, 25.74, 24.72, 22.61, 18.32, 14.05, -4.07.

IR: ν (cm⁻¹) = 2926, 2855, 1708, 1638, 1464, 1315, 1250, 1113, 1006, 840, 731.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 325.2557 calculated for C₁₉H₃₇O₂Si; Found 325.2563

2-((*tert*-butyldimethylsilyl)oxy)-3-octylcyclopent-2-en-1-ol (**4.99e**)



Procedure: Ketone **6.15** (140mg, 0.431mmol) was dissolved in CH₂Cl₂ (2.1 mL) and cooled to -78°C. Diisobutylaluminium hydride (0.7 mL, 1M in heptane) was added dropwise. Once addition was complete the reaction solution was warmed to room temperature. The mixture was stirred for 3 hours. Once the reaction was completed as monitored by TLC the reaction was cooled to 0°C. The reaction mixture was quenched with 1:1 2M HCl (2.5 mL) and H₂O (2.5 mL). The mixture was then filtered through a celite plug. The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using

100% hexanes to 95:5 hexanes : EtOAc to yield **4.99e** in 71% yield (99 mg, 0.303 mmol) as a colorless oil.

Rf: 0.8 in 90:10 hexanes : EtOAc

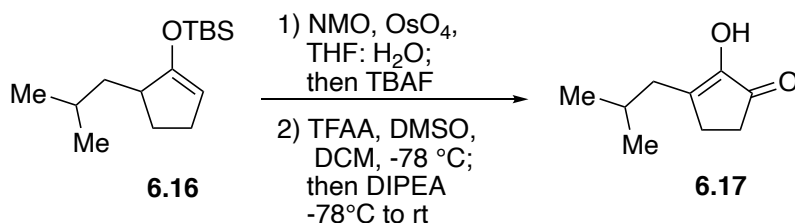
¹H NMR: (500 MHz, CDCl₃) δ = 4.53 – 4.46 (m, 1H), 2.34 – 2.26 (m, 1H), 2.25 – 2.16 (m, 1H), 2.13 – 2.07 (m, 1H), 2.06 – 2.01 (m, 2H), 1.69 – 1.61 (m, 1H), 1.52 (d, J = 6.2 Hz, 1H), 1.35 – 1.19 (m, 14H), 0.96 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃): δ = 147.53, 121.53, 76.12, 31.88, 30.50, 29.75, 29.48, 29.27, 27.94, 27.53, 26.57, 25.74, 22.67, 18.19, 14.11, -4.07, -4.12.

IR: f (cm⁻¹) = 3421, 2935, 2844, 1669, 1453, 1387, 1262, 1076, 989, 777.

HRMS (ESI-TOF) m/z : (M-H₂O)⁺ = 309.2608 calculated for C₁₉H₃₆OSi; Found 309.2611

2-hydroxy-3-isobutylcyclopent-2-en-1-one (**6.17**)



Procedure: Silylenolate **6.16** (524 mg, 2.058 mmol) was dissolved in a mixture of 3:1 THF : H₂O (4.1 mL). *N*-methylmorpholine *N*-oxide (289 mg, 2.469 mmol) was added to the solution followed by one crystal of OsO₄. The reaction was stirred for 3 hours when it reached completion as monitored by TLC. TBAF (5 mL, 1M solution in THF) was then added, and the mixture was stirred for 18 hours. Once the reaction was completed as monitored by TLC, the solution was cooled to 0°C. The mixture was quenched with aqueous NH₄Cl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column

chromatography using 100% hexanes to 75:25 hexanes : EtOAc. The purified product was taken onto the next step.

TFAA (0.15 mL, 1.123 mmol) was dissolved in CH₂Cl₂, and cooled to -78 °C. DMSO (0.16 mL, 2.246 mmol) was added dropwise to the solution, forming a white precipitate. The product from the previous step (117 mg, 0.748 mmol) was dissolved in 1 mL CH₂Cl₂ and was added dropwise to the chilled solution. The reaction was stirred for 2 hours at -78°C. DIPEA was added to the solution, and warmed to room temperature. . The reaction was stirred for 24 hours when it reached completion as monitored by TLC. The solution was cooled to 0°C and quenched with 2M HCl (5 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 60:40 hexanes : CH₂Cl₂ to yield **6.17** in 60% yield as a yellow solid (48 mg, 0.311 mmol).

Rf: 0.3 in 90:10 hexanes : EtOAc

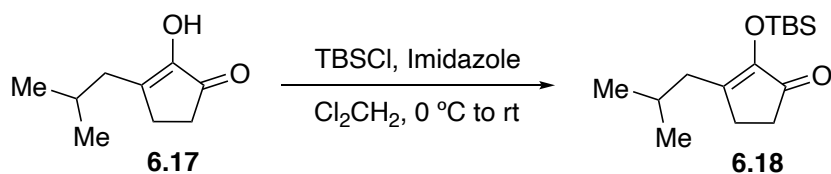
¹H NMR: (400 MHz, CDCl₃) δ = 5.37 (s, 1H), 2.46 – 2.38 (m, 4H), 2.29 (d, J = 7.4 Hz, 2H), 1.98 (h, J = 13.9, 6.8 Hz, 1H), 0.95 (d, J = 6.6 Hz, 6H).

¹³C NMR: (125 MHz, CDCl₃) δ = 203.02, 149.15, 146.94, 37.89, 31.82, 26.92, 25.67, 22.71.

IR: ν (cm⁻¹) = 3292, 2950, 2918, 2866, 1710, 1664, 1461, 1406, 1364, 1311, 1238, 1194, 1107, 676.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 155.1067 calculated for C₉H₁₄O₂; Found 155.10676

2-((*tert*-butyldimethylsilyl)oxy)-3-isobutylcyclopent-2-en-1-one (**6.18**)



Procedure: Dione **6.17** (79 mg, 0.504 mmol) was dissolved in CH₂Cl₂, the solution was cooled to 0 °C. TBSCl (87 mg, 0.580 mmol) was added to the solution, followed by imidazole (51 mg, 0.756 mmol). The reaction was warmed to room temperature and stirred for 15 hours. Once the reaction was completed as monitored by TLC, the solution was cooled to 0 °C. The reaction was quenched with 2M HCl (1 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 3 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 98:2 hexanes : EtOAc to yield **6.18** in 90% yield as a yellow oil (122 mg, 0.454 mmol).

Rf: 0.6 in 90:10 hexanes : EtOAc

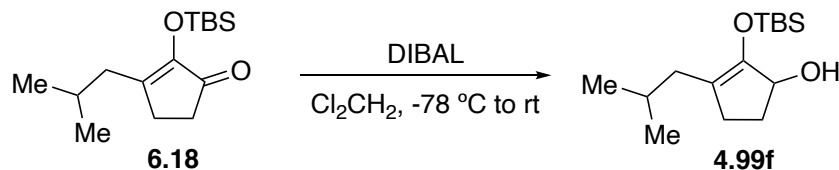
¹H NMR: (400 MHz, CDCl₃) δ = 2.43 – 2.38 (m, 2H), 2.35 – 2.30 (m, 2H), 2.25 (d, J = 7.4 Hz, 2H), 1.97 – 1.85 (m, 1H), 0.95 (s, 9H), 0.93 (d, J = 6.6 Hz, 6H), 0.20 (s, 6H).

¹³C NMR: (125 MHz, CDCl₃) δ = 203.15, 154.35, 149.92, 37.98, 32.21, 26.94, 25.81, 25.23, 22.78, 18.37, -3.96.

IR: $f(\text{cm}^{-1})$ = 2955, 2929, 2858, 1711, 1639, 1464, 1370, 1253, 1193, 1115, 1087, 869, 784, 688.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 269.1931 calculated for C₁₅H₂₉O₂Si; Found 269.1938.

2-((*tert*-butyldimethylsilyl)oxy)-3-isobutylcyclopent-2-en-1-ol (**4.99f**)



Procedure: Ketone **6.18** (115mg, 0.428 mmol) was dissolved in CH₂Cl₂ (2.1 mL) and cooled to -78°C. Diisobutylaluminium hydride (0.8 mL, 1M in heptane) was added dropwise. Once addition was complete the reaction solution was warmed to room temperature. The mixture was stirred for 20 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0°C.

The reaction mixture was quenched with 1:1 2M HCl (2.5 mL) and H₂O (2.5 mL). The reaction mixture was then filtered through a celite plug. The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **4.99f** in 56% yield (64 mg, 0.236 mmol) as a colorless oil.

Rf: 0.7 in 80:20 hexanes : EtOAc

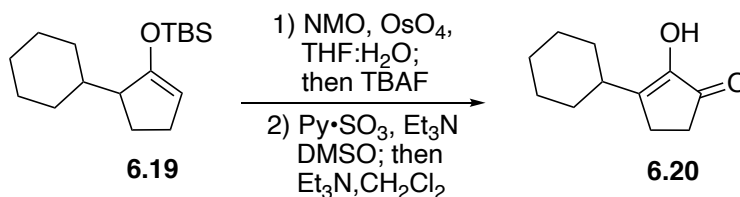
¹H NMR: (400 MHz, CDCl₃) δ = 5.37 (s, 1H), 2.46 – 2.38 (m, 4H), 2.29 (d, *J* = 7.4 Hz, 2H), 1.98 (h, *J* = 13.9, 6.8 Hz, 1H), 0.95 (d, *J* = 6.6 Hz, 6H).

¹³C NMR: (125 MHz, CDCl₃) δ = 148.62, 120.54, 76.05, 35.82, 30.63, 28.39, 26.70, 25.77, 22.71, 18.19, -4.01.

IR: ν (cm⁻¹) = 3390, 2954, 2930, 2894, 1679, 1463, 1352, 1252, 1044, 963, 838, 781.

HRMS (ESI-TOF) *m/z*: (M-H₂O)⁺ = 253.1985 calculated for C₁₅H₂₈OSi; Found 253.1985.

3-cyclohexyl-2-hydroxycyclopent-2-en-1-one (**6.20**)



Procedure: Silylenolate **6.19** (949 mg, 3.026 mmol) was dissolved in a mixture of 3:1 THF : H₂O (6.0 mL). *N*-methylmorpholine *N*-oxide (709 mg, 6.053 mmol) was added to the solution followed by one crystal of OsO₄. The reaction was stirred for 4 hours when it reached completion as monitored by TLC. TBAF (9 mL, 1M solution in THF) was added, and the mixture was stirred for 24 hours. Once the reaction was completed as monitored by TLC the solution was cooled to 0°C.

The reaction mixture was quenched with aqueous NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 85:15 hexanes : EtOAc. The purified product was taken onto the next step.

The product from the previous (167 mg, 0.916 mmol) was dissolved in DMSO (3.0 mL). Et_3N (0.6 mL, 4.581) and $\text{Py}\cdot\text{SO}_3$ (437 mg, 2.748 mmol) were added to the solution. . The reaction was stirred for 2 hours. Once the reaction was completed as monitored by TLC, the crude solution was cooled to 0° . The reaction was quenched with 2M HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was dissolved in CH_2Cl_2 (2.4 mL) and Et_3N (68 μL , 0.490 mmol) and was stirred for 6 hr. The solution was concentrated under vacuum and purified with column chromatography using 100% hexanes to 60:40 hexanes : CH_2Cl_2 to yield **6.20** in 17% yield as a white solid (93 mg, 0.515 mmol).

Rf: 0.5 in 80:20 hexanes : EtOAc

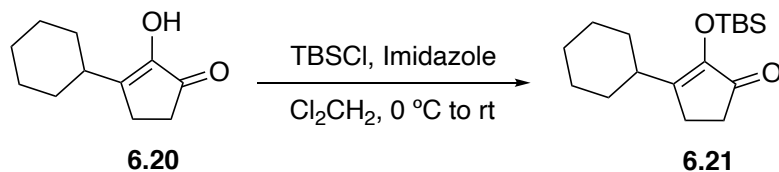
^1H NMR: (400 MHz, CDCl_3) δ = 5.25 (s, 1H), 3.15 – 3.06 (m, 1H), 2.70 – 2.60 (m, 1H), 2.45 – 2.41 (m, 2H), 2.40 – 2.35 (m, 2H), 1.81 – 1.71 (m, 4H), 1.44 – 1.34 (m, 5H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 203.25, 151.93, 147.39, 41.57, 37.94, 31.60, 30.06, 26.06, 22.64, 17.46.

IR f (cm^{-1}) = 3248, 2921, 2851, 1704, 1656, 1443, 1406, 1233, 1102.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 181.1223$ calculated for $\text{C}_{11}\text{H}_{16}\text{O}_2$; Found 181.1229.

2-((*tert*-butyldimethylsilyl)oxy)-3-cyclohexylcyclopent-2-en-1-one (6.21)



Procedure: Dione **6.20** (87 mg, 0.486 mmol) was dissolved in CH_2Cl_2 , the solution was cooled to $0\text{ }^\circ\text{C}$. TBSCl (83 mg, 0.558 mmol) was added to the solution, followed by imidazole (49 mg, 0.729 mmol). The reaction was warmed to room temperature and stirred for 15 hours. Once the reaction was completed as monitored by TLC, the solution was cooled to $0\text{ }^\circ\text{C}$. The mixture was quenched with 2M HCl (1 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 3 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **6.21** in 71% yield as a colorless oil (101 mg, 0.343 mmol).

Rf: 0.8 in 80:20 hexanes : EtOAc

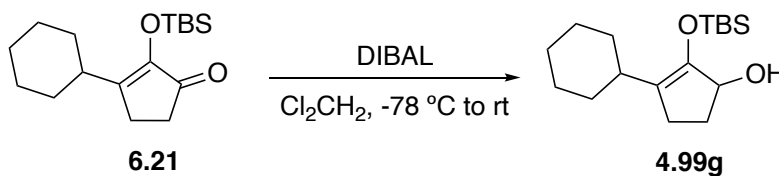
^1H NMR: (400 MHz, CDCl_3) δ = 2.79 – 2.68 (m, 1H), 2.42 – 2.36 (m, 2H), 2.32 – 2.26 (m, 2H), 1.82 – 1.64 (m, 5H), 1.35 – 1.16 (m, 5H), 0.96 (s, 9H), 0.19 (s, 6H).

^{13}C NMR: (100 MHz, CDCl_3) δ = 203.29, 159.57, 111.61, 37.53, 32.07, 30.18, 26.15, 25.76, 21.75, 18.39, -4.09.

IR: $f(\text{cm}^{-1})$ = 2926, 2854, 1707, 1632, 1448, 1379, 1343, 1249, 1200, 1106, 859, 840, 783, 732.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 295.2092$ calculated for $\text{C}_{17}\text{H}_{31}\text{O}_2\text{Si}$; Found 295.2092

2-((*tert*-butyldimethylsilyl)oxy)-3-cyclohexylcyclopent-2-en-1-ol (4.99g)



Procedure: Ketone **6.21** (115mg, 0.428 mmol) was dissolved in CH₂Cl₂ (2.1 mL) and cooled to -78°C. Diisobutylaluminium hydride (0.8 mL, 1M in heptane) was added dropwise. Once addition was complete the reaction solution was warmed to room temperature. The mixture was stirred for 20 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0°C. The reaction mixture was quenched with 1:1 2M HCl (2.5 mL) and H₂O (2.5 mL). The mixture was then filtered through a celite plug. The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **4.99g** in 56% yield (64 mg, 0.236 mmol) as a colorless oil.

Rf: 0.8 in 80:20 hexanes : EtOAc

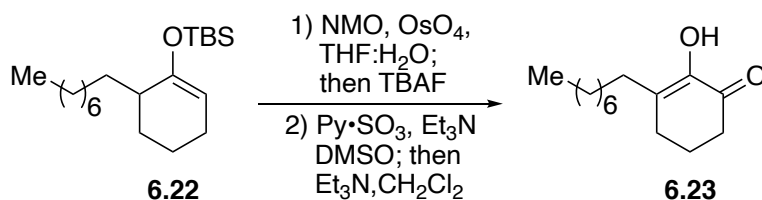
¹H NMR: (400 MHz, CDCl₃) δ = 4.51 – 4.45 (m, 1H), 2.44 – 2.36 (m, 1H), 2.33 – 2.23 (m, 1H), 2.20 – 2.14 (m, 1H), 2.12 – 2.02 (m, 1H), 1.76 – 1.55 (m, 5H), 1.51 – 1.48 (m, 1H), 1.32 – 1.13 (m, 5H), 0.97 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 146.17, 126.22, 76.20, 35.51, 31.24, 30.69, 30.47, 26.53, 26.17, 25.73, 24.75, 18.23, -4.16.

IR: $f(\text{cm}^{-1})$ = 3397, 2924, 2852, 1673, 1447, 1364, 1333, 1207, 1050, 867, 837, 779.

HRMS (ESI-TOF) m/z : (M-H₂O)⁺ = 279.2139 calculated for C₁₇H₃₀OSi; Found 279.2164

2-hydroxy-3-octylcyclohex-2-en-1-one (**6.23**)



Procedure: Silylenolate **6.22** (891 mg, 2.736 mmol) was dissolved in a mixture of 3:1 THF : H₂O (2.7 mL). *N*-methyldmorpholine *N*-oxide (641 mg, 5.472 mmol) was added to the solution followed by one crystal of OsO₄. The reaction was stirred for 4 hours when it reached completion as monitored by TLC. TBAF (6 mL, 1M solution in THF) was then added, and stirred for 18 hours. Once the reaction was completed as monitored by TLC, the crude solution was cooled to 0°C. The reaction mixture was quenched with aqueous NH₄Cl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 85:15 hexanes : EtOAc. The purified product was taken onto the next step.

The product from the previous step (446 mg, 1.970 mmol) was dissolved in DMSO (5.0 mL). Et₃N (1.5 mL, 10.836) and Py•SO₃ (1.1 g, 6.896 mmol) were added to the solution. The reaction was stirred for 4 hours. Once the reaction was completed as monitored by TLC, the solution was cooled to 0°C. The reaction was quenched with 2M HCl(10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was dissolved in CH₂Cl₂ (8.9 mL) and Et₃N (0.1 mL, 0.896 mmol) and was stirred for 26 hours. The solution was concentrated under vacuum and purified with column chromatography using 100% hexanes to 60:40 hexanes : CH₂Cl₂ to yield **6.23** in 20% yield (128 mg, 0.571 mmol) as colorless oil.

Rf: 0.4 in 90:10 hexanes : EtOAc

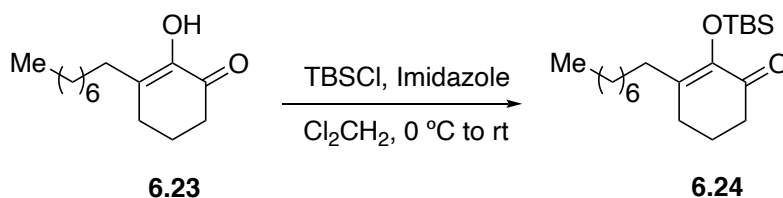
¹H NMR: (400 MHz, CDCl₃) δ = 6.05 (s, 1H), 2.47 (t, J = 6.4 Hz, 2H), 2.35 (t, J = 5.9 Hz, 2H), 2.32 – 2.25 (m, 2H), 1.95 (p, J = 6.2 Hz, 2H), 1.47 (q, J = 7.4 Hz, 2H), 1.34 – 1.24 (m, 11H), 0.89 – 0.85 (m, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 194.44, 143.52, 134.86, 35.84, 31.81, 30.78, 29.58, 29.38, 29.18, 28.42, 26.97, 22.60, 22.50, 14.03.

IR: $f(\text{cm}^{-1})$ = 3420, 2953, 2868, 1642, 1459, 1380, 1272, 1234, 2292, 1158, 1044, 885, 674, 540.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 225.1849 calculated for C₁₉H₂₈OSi; Found 225.1862

2-((*tert*-butyldimethylsilyl)oxy)-3-octylcyclohex-2-en-1-one (6.24)



Procedure: Dione **6.23** (112 mg, 0.498 mmol) was dissolved in CH₂Cl₂ (2.5 mL) and the solution was cooled to 0 °C. TBSCl (86 mg, 0.573 mmol) was added to the solution, followed by imidazole (50 mg, 0.748 mmol). The reaction was warmed to room temperature and stirred for 24 hours. Once the reaction was completed as monitored by TLC, the solution was cooled to 0 °C. The mixture was quenched with 2M HCl (5 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **6.24** in 50% yield (83 mg, 0.245 mmol) as a colorless oil.

Rf: 0.7 in 90:10 hexanes : EtOAc

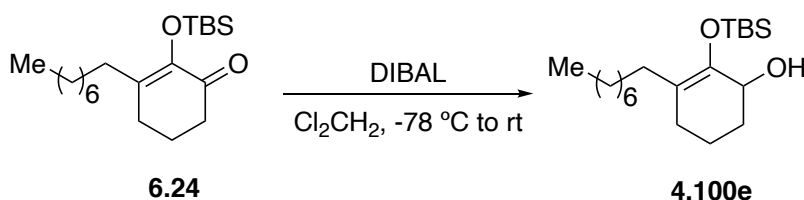
¹H NMR: (400 MHz, CDCl₃) δ = 2.44 – 2.39 (m, 2H), 2.35 (t, J = 6.0 Hz, 2H), 2.29 (t, J = 6.0 Hz, 2H), 1.94 – 1.87 (m, 2H), 1.47 – 1.37 (m, 2H), 1.32 – 1.24 (m, 10H), 0.94 (s, 9H), 0.91 – 0.86 (m, 3H), 0.17 (s, 6H).

^{13}C NMR: (100 MHz, CDCl_3) δ = 194.45, 144.11, 142.47, 38.16, 31.83, 31.60, 29.84, 29.49, 29.40, 29.20, 27.28, 26.10, 22.64, 22.50, 18.93, 14.08, -3.83.

IR: $\tilde{\nu}$ (cm^{-1}) = 2926, 2855, 1678, 1620, 1463, 1361, 1310, 1249, 1203, 1161, 1096, 1007, 932.

HRMS (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 339.2714$ calculated for $\text{C}_{20}\text{H}_{38}\text{O}_2\text{Si}$; Found 339.2719

2-((*tert*-butyldimethylsilyl)oxy)-3-octylcyclohex-2-en-1-ol (4.100e)



Procedure: Ketone **6.24** (733 mg, 2.165 mmol) was dissolved in CH_2Cl_2 (10.8 mL) and cooled to -78°C . Diisobutylaluminium hydride (3.2 mL, 1M in heptane) was added dropwise. Once addition was complete the reaction solution was warmed to room temperature. The mixture was stirred for 2 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0°C . The mixture was quenched with 1:1 2M HCl (5 mL) and H_2O (5 mL). The reaction mixture was then filtered through a celite plug. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **4.100e** in 64% yield (473 mg, 1.938 mmol) as a colorless oil.

Rf: 0.6 in 90:10 hexanes : EtOAc

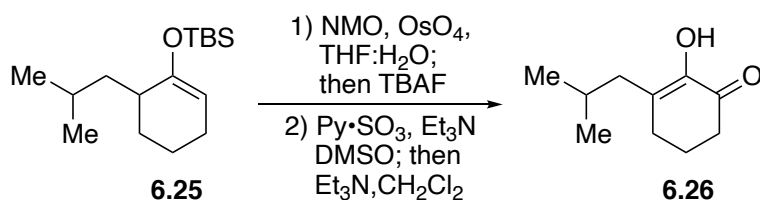
^1H NMR: (400 MHz, CDCl_3) δ = 4.01 (t, J = 4.4 Hz, 1H), 2.07 – 1.87 (m, 5H), 1.79 – 1.73 (m, 2H), 1.70 – 1.59 (m, 1H), 1.57 – 1.46 (m, 2H), 1.30 – 1.24 (m, 12H), 0.96 (s, 8H), 0.87 (d, J = 7.0 Hz, 3H), 0.16 (s, 3H), 0.15 (s, 3H).

^{13}C NMR: (100 MHz, CDCl_3) δ = 143.77, 119.95, 67.74, 32.11, 31.87, 30.26, 29.82, 29.58, 29.26, 28.31, 27.62, 25.87, 22.65, 18.32, 14.07, -3.95, -4.13.

IR: $f(\text{cm}^{-1})$ = 3437, 2925, 2945, 1669, 1462, 1387, 1252, 1176, 1076, 923, 831, 672.

HRMS (ESI-TOF) m/z : $(\text{M}-\text{H}_2\text{O})^+ = 323.2765$ calculated for $\text{C}_{19}\text{H}_{28}\text{OSi}$; Found 323.2792

2-hydroxy-3-isobutylcyclohex-2-en-1-one (6.26)



Procedure: Silylenolate **6.25** (1058 mg, 3.940 mmol) was dissolved in a mixture of 3:1 THF : H_2O (4.0 mL). *N*-methylmorpholine *N*-oxide (923 mg, 7.880 mmol) was added to the solution followed by one crystal of OsO_4 . The reaction was stirred for 5 hours when it reached completion as monitored by TLC. TBAF (6 mL, 1M solution in THF) was then added, and the mixture was stirred for 16 hours. Once the reaction was completed as monitored by TLC, the solution was cooled to 0°C . The reaction mixture was quenched with aqueous NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 85:15 hexanes : EtOAc. The purified product was taken onto the next step.

The product from the previous step (173 mg, 1.017 mmol) was dissolved in DMSO (2.0 mL). Et_3N (0.8 mL, 6.102 mmol) and $\text{Py}\cdot\text{SO}_3$ (643 mg, 4.068 mmol) were added to the solution. The reaction was stirred for 2 hours. Once the reaction was completed as monitored by TLC, the crude solution was cooled to 0°C . The reaction was quenched with 2M HCl (10 mL). The aqueous layer

was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was dissolved in CH₂Cl₂ (4.1 mL) and Et₃N (0.1 mL) and was stirred for 48 hours. The solution was concentrated under vacuum and purified with column chromatography using 100% hexanes to 94:4 hexanes : EtOAc to yield **6.26** in 16% yield (108 mg, 0.641 mmol) as yellow oil.

Rf: 0.5 in 90:10 hexanes : EtOAc

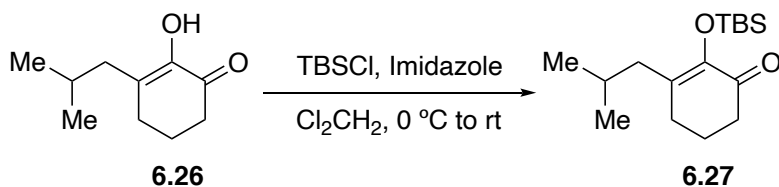
¹H NMR: (400 MHz, CDCl₃) δ = 6.06 (s, 1H), 2.47 (t, J = 6.0 Hz, 2H) 2.32 (t, J = 6.0 Hz, 2H), 2.17 (d, J = 7.5 Hz, 2H), 1.98 – 1.84 (m, 3H), 0.91 (d, J = 6.6 Hz, 6H).

¹³C NMR: (100 MHz, CDCl₃) δ = 194.52, 144.16, 133.97, 39.95, 35.92, 28.92, 26.84, 22.59.

IR: $\tilde{\nu}$ (cm⁻¹) = 3420, 2953, 2868, 1642, 1459, 1380, 1325, 1272, 1234, 1158, 1044, 849, 674.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 169.1223 calculated for C₁₀H₁₆O₂; Found 169.1223.

2-((*tert*-butyldimethylsilyl)oxy)-3-isobutylcyclohex-2-en-1-one (**6.27**)



Procedure: Dione **6.26** (108 mg, 0.642 mmol) was dissolved in CH₂Cl₂ (3.2 mL), the solution was cooled to 0 °C. TBSCl (144 mg, 0.963 mmol) was added to the solution, followed by imidazole (70 mg, 1.027 mmol). The reaction was warmed to room temperature and stirred for 24 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0 °C. The mixture was quenched with 2M HCl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using

100% hexanes to 60:40 hexanes : CH₂Cl₂ to yield **6.27** in 71% yield as a colorless oil (129 mg, 0.457 mmol).

Rf: 0.7 in 90:10 hexanes : EtOAc

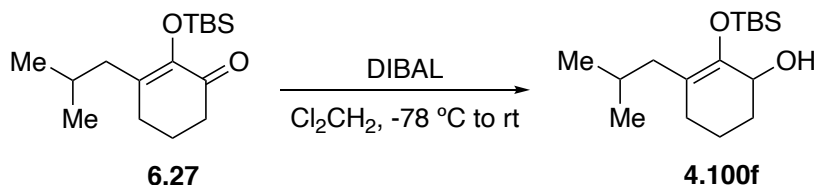
¹H NMR: (400 MHz, CDCl₃) δ = 2.41 (t, J = 6.6 Hz, 2H), 2.33 (t, J = 6.0 Hz, 2H), 2.20 (d, J = 7.6 Hz, 2H), 1.97 – 1.81 (m, 3H), 0.93 (s, 9H), 0.90 (d, J = 6.6 Hz, 6H), 0.16 (s, 6H).

¹³C NMR: (100 MHz, CDCl₃) δ = 194.41, 144.88, 141.28, 40.41, 38.21, 29.92, 26.84, 26.21, 26.18, 22.62, 22.52, -3.71.

IR: $f(\text{cm}^{-1})$ = 2954, 2858, 1675, 1617, 1361, 1249, 1197, 1088, 928, 907, 780, 731.

HRMS (ESI-TOF) m/z : (M+H)⁺ = 283.2088 calculated for C₁₆H₃₁O₂Si; Found 283.2090

2-((*tert*-butyldimethylsilyl)oxy)-3-isobutylcyclohex-2-en-1-ol (4.100f**)**



Procedure: Ketone **6.27** (114mg, 0.404 mmol) was dissolved in CH₂Cl₂ (2.0 mL) and cooled to -78°C. Diisobutylaluminium hydride (0.6 mL, 1M in heptane) was added dropwise. Once addition was complete the reaction solution was warmed to room temperature. The mixture was stirred for 2 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0°C. The mixture was quenched with 1:1 2M HCl (2.5 mL) and H₂O (2.5 mL). The reaction mixture was then filtered through a celite plug. The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL), and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using

100% hexanes to 90:10 hexanes : EtOAc to yield **4.100f** in quantitative yield (114 mg, 0.404 mmol) as a colorless oil.

Rf: 0.5 in 90:10 hexanes : EtOAc

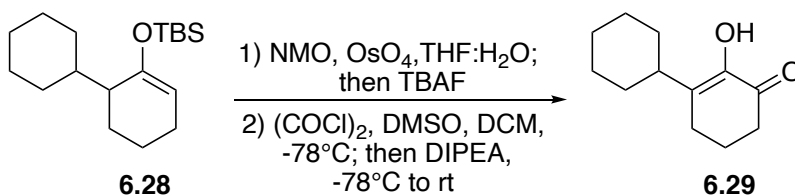
¹H NMR: (400 MHz, CDCl₃) δ = 4.03 (t, *J* = 4.4 Hz, 1H), 2.07 – 1.97 (m, 2H), 1.96 – 1.84 (m, 2H), 1.83 – 1.71 (m, 4H), 1.71 – 1.59 (m, 1H), 1.57 – 1.46 (m, 1H), 0.96 (s, 9H), 0.86 (t, *J* = 6.2 Hz, 6H), 0.16 (s, 6H).

¹³C NMR: (100 MHz, CDCl₃) δ = 144.81, 118.79, 67.78, 39.15, 32.13, 28.77, 26.38, 25.95, 22.71, 22.30, 18.34, -3.78, -3.98.

IR: ν (cm⁻¹) = 3453, 2930, 2860, 1668, 1463, 1253, 1173, 1173, 1077, 993, 925, 832, 778.

HRMS (ESI-TOF) *m/z*: (M-H₂O)⁺ = 267.2141 calculated for C₁₆H₃₀OSi; Found 267.2141

2-hydroxy-[1,1'-bi(cyclohexan)]-1-en-3-one (**6.29**)



Procedure: Silylenolate **6.28** (1.5 g, 5.093 mmol) was dissolved in a mixture of 3:1 THF : H₂O (5.0 mL). *N*-methylmorpholine *N*-oxide (1.2 g, 10.185 mmol) was added to the solution followed by one crystal of OsO₄. The reaction was stirred for 5 hours when it reached completion as monitored by TLC. TBAF (10 mL, 1M solution in THF) was added, and the mixture was stirred for 3 hours. Once the reaction was completed as monitored by TLC, the crude solution was cooled to 0°C. The reaction mixture was quenched with aqueous NH₄Cl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 10 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with

column chromatography using 100% hexanes to 85:15 hexanes : EtOAc. The purified product was taken onto the next step.

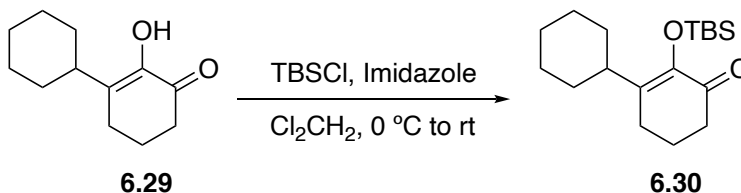
Oxalyl chloride (0.5 mL, 5.999 mmol) was dissolved in CH₂Cl₂ (20.0 mL) and cooled to -78°C. DMSO (0.8 mL, 10.798 mmol) was added dropwise to the solution and stirred for 1 hour. The product from the previous step (785 mg, 0.916 mmol) was dissolved in CH₂Cl₂ (2 mL) and added dropwise to the solution. The reaction was stirred for 3 hours at -78°C. DIPEA (2.3 mL, 13.197 mmol) was added to the solution and warmed to room temperature. The reaction was stirred for 24 hours when it reached completion as monitored by TLC. The solution was cooled to 0°C and quenched with 2M HCl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude solution was concentrated under vacuum and purified with column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **6.29** in 51% yield as a green solid (505 mg, 2.599 mmol).

Rf: 0.6 in 90:10 hexanes : EtOAc

¹H NMR: (400 MHz, CDCl₃) δ = 6.12 (s, 1H), 2.83 – 2.76 (m, 1H), 2.46 (t, J = 7.2 Hz, 2H), 2.32 (t, J = 6.0 Hz, 2H), 1.97 – 1.89 (m, 2H), 1.83 – 1.74 (m, 3H), 1.73 – 1.68 (m, 1H), 1.65 – 1.59 (m, 2H), 1.44 – 1.24 (m, 5H).

¹³C NMR: (125 MHz, CDCl₃) δ = 194.87, 142.45, 138.92, 38.60, 35.75, 29.66, 26.17, 24.46, 22.61.

2-((*tert*-butyldimethylsilyl)oxy)-[1,1'-bi(cyclohexan)]-1-en-3-one (6.30)



Procedure: Dione **6.29** (480 mg, 2.473 mmol) was dissolved in CH₂Cl₂ (12.0 mL), the solution was cooled to 0 °C. TBSCl (427 mg, 2.843 mmol) was added to the solution, followed by imidazole (252 mg, 3.709 mmol). The reaction was warmed to room temperature and stirred for 24 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0 °C. The mixture was quenched with 2M HCl (10 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 5 mL) and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 70:30 hexanes : CH₂Cl₂ to yield **6.30** in 85% yield as a colorless oil (645 mg, 2.091 mmol).

Rf: 0.7 in 90:10 hexanes : EtOAc

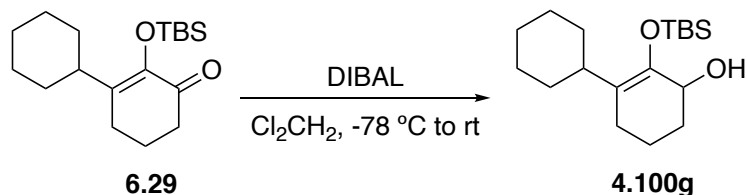
¹H NMR: (400 MHz, CDCl₃) δ = 3.04 – 2.96 (m, 1H), 2.39 (t, J = 7.2 Hz, 2H), 2.30 (t, J = 6.0 Hz, 2H), 1.92 – 1.84 (m, 2H), 1.78 – 1.72 (m, 2H), 1.59 – 1.53 (m, 2H), 1.32 – 1.23 (m, 5H), 0.95 (s, 9H), 0.17 (s, 6H).

¹³C NMR: (125 MHz, CDCl₃) δ = 194.74, 146.38, 143.00, 38.25, 38.02, 31.58, 29.86, 26.23, 26.09, 26.08, 24.87, 22.65, 22.59, 18.99, 14.11, -3.91.

IR: *f* (cm⁻¹) = 2926, 2852, 1676, 1608. 1448, 1367, 1335, 1313. 1247, 1200, 1159, 929, 829.

HRMS (ESI-TOF) *m/z*: (M+H)⁺ = 309.2244 calculated for C₁₈H₃₃O₂Si; Found 309.2247.

2-((*tert*-butyldimethylsilyl)oxy)-[1,1'-bi(cyclohexan)]-1-en-3-ol (4.100g)



Procedure: Ketone **6.29** (645 mg, 2.090 mmol) was dissolved in CH₂Cl₂ (7.0 mL) and cooled to -78°C. Diisobutylaluminium hydride (3.6 mL, 1M in heptane) was added dropwise. Once addition was complete the reaction solution was warmed to room temperature. The mixture was stirred for 2 hours. Once the reaction was completed as monitored by TLC, the reaction was cooled to 0°C. The mixture was quenched with 1:1 2M HCl (5 mL) and H₂O (5 mL). The reaction mixture was then filtered through a celite plug. The aqueous layer was extracted with CH₂Cl₂ (4 x 10 mL), and washed with brine. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **4.100g** in 94% yield (611 mg, 1.967 mmol) as a colorless oil.

Rf: 0.7 in 80:20 hexanes : EtOAc

¹H NMR: (400 MHz, CDCl₃) δ = 4.01 (t, J = 4.6 Hz, 1H), 2.72 – 2.63 (m, 1H), 1.90 – 1.87 (m, 1H), 1.75 – 1.71 (m, 4H), 1.66 – 1.58 (m, 2H), 1.26 (h, J = 5.6 Hz, 10H), 0.98 (s, 9H), 0.16 (s, 3H), 0.16 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 142.69, 124.43, 67.85, 36.83, 31.91, 31.61, 30.71, 30.15, 29.07, 26.67, 26.30, 25.93, 25.28, 23.71, 22.66, 18.37, 14.08, -3.91, -4.24.

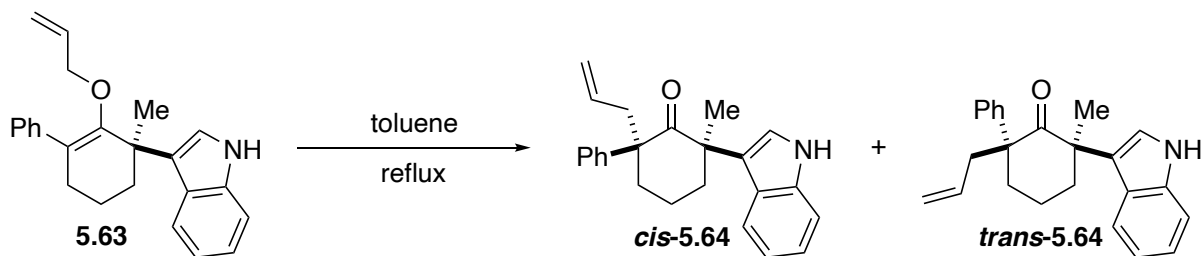
IR: *f* (cm⁻¹) = 3441, 2926, 2852, 1717, 1658, 1447, 1361, 1252, 1171, 1079, 833, 778.

HRMS (ESI-TOF) *m/z*: (M+Na)⁺ = 333.2220 calculated for C₁₈H₃₄O₂SiNa; Found 333.2205.

6.5 Experimental Procedures for Chapter Five

6.5.1 Synthesis of α - α' -Bis-Quaternary Ketones

(\pm)-(2*R*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-6-methyl-2-phenylcyclohexan-1-one (*cis*-5.64) and (\pm)-(2*S*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-6-methyl-2-phenylcyclohexan-1-one (*trans*-5.64)



Procedure: α -Indolyl allylvinyl ether **5.63** (55 mg, 0.149 mmol) was dissolved in DCE (0.7 mL, 0.2 M). The mixture was then heated to 110 °C in a preheated oil bath for 3 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield *cis*-**6.64** in 76% yield (42 mg, 0.114 mmol) as a white solid and *trans*-**6.64** in 25% yield (14 mg, 0.038) as a colorless oil. ¹H NMR analysis of the crude reaction mixture indicated 3.1:1 dr (*cis*-**6.64**: *trans*-**6.64**).

cis-**6.64**

Rf: 0.6 Rf in 50:50 (Hexanes : CH₂Cl₂)

¹H NMR: (500 MHz, CDCl₃) δ = 7.70 (d, *J* = 7.7 Hz, 1H), 7.47 (bs, 1H), 7.10 – 7.03 (m, 3H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.69 – 6.67 (m, 2H), 6.59 (t, *J* = 7.7 Hz, 2H), 5.34 – 5.26 (m, 1H), 4.89 (s, 1H), 4.88 – 4.85 (m, 1H), 2.67 – 2.56 (m, 3H), 2.54 – 2.43 (m, 2H), 1.96 – 1.89 (m, 1H), 1.88 – 1.79 (m, 2H), 1.55 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 212.63, 139.62, 136.41, 134.75, 126.71, 126.18, 125.72, 125.32, 121.58, 121.28, 120.75, 119.13, 118.33, 117.35, 110.56, 55.20, 49.03, 46.74, 39.22, 33.53, 27.43, 18.73.

IR: f (cm⁻¹) = 3373, 2955, 2861, 1681, 1460, 1421, 1343, 1245, 1105, 917.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 344.2009 calculated for C₂₄H₂₆NO; Found 344.2018.

***trans*-6.64**

Rf: 0.4 Rf in 50:50 (Hexanes : CH₂Cl₂)

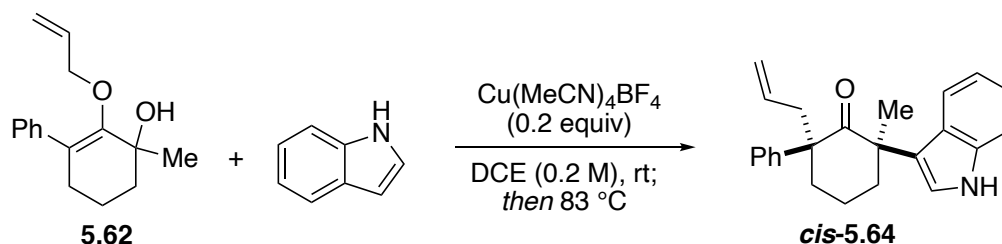
¹H NMR: (500 MHz, CDCl₃) δ = 8.01 (bs, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.40 – 7.34 (m, 5H), 7.29 – 7.25 (m, 2H), 7.19 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.94 (s, 1H), 5.51 – 5.41 (m, 1H), 4.95 – 4.93 (m, 1H), 4.93 – 4.90 (m, 1H), 2.62 – 2.56 (m, 3H), 2.54 – 2.48 (m, 1H), 2.07 – 2.00 (m, 2H), 1.76 – 1.66 (m, 1H), 1.25 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 213.63, 140.81, 137.08, 134.54, 128.56, 126.65, 126.23, 125.47, 121.82, 121.14, 121.10, 120.91, 119.24, 117.84, 111.42, 77.25, 77.00, 76.75, 55.13, 49.61, 46.96, 36.87, 30.33, 26.09, 17.71.

IR: f (cm⁻¹) = 3374, 2957, 2924, 2860, 1681, 1421, 1343, 1245, 1120, 1011, 917.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 344.2009 calculated for C₂₄H₂₆NO; Found 344.2018.

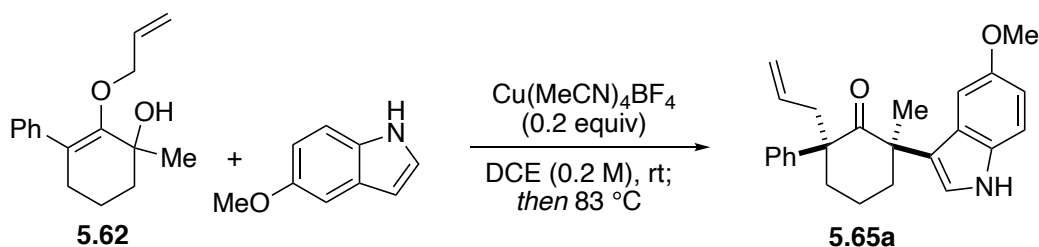
(±)-(2*R*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-6-methyl-2-phenylcyclohexanone (*cis*-6.64)



Procedure: α-Hydroxyl enol ether **5.62** (100 mg, 0.409 mmol) was dissolved in DCE (2 mL, 0.2 M). Indole (72 mg, 0.614 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (26 mg,

0.081 mmol). The mixture was stirred at room temperature for 24 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 16 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 90:10 hexanes : CH₂Cl₂ to yield **cis-6.64** in 94% yield (132 mg, 0.384 mmol) as a white solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

(±)-(2*R*,6*R*)-2-allyl-6-(5-methoxy-1*H*-indol-3-yl)-6-methyl-2-phenylcyclohexanone
(5.65a)



Procedure: α-Hydroxyl enol ether **5.62** (150 mg, 0.614 mmol) was dissolved in DCE (3.1, 0.2 M). 5-Methoxyindole (136 mg, 0.922 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (39 mg, 0.122). The mixture was stirred at room temperature for 11 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 12 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **5.65a** in 88% yield (201 mg, 0.538 mmol) as a white solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.6 in 2:4 (Hexanes : CH₂Cl₂)

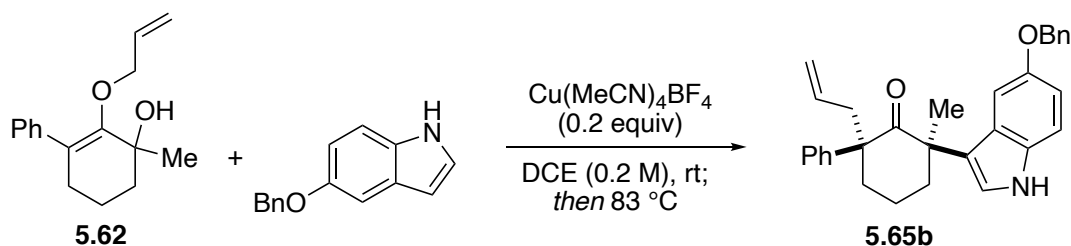
¹H NMR: (500 MHz, CDCl₃) δ = 7.44 (bs, 1H), 7.19 (d, *J* = 2.6 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 6.85 (d, *J* = 7.2 Hz, 2H), 6.76 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.71 – 6.66 (m, 2H), 6.62 (t, *J* = 7.8 Hz, 2H), 5.36 – 5.26 (m, 1H), 4.90 (s, 1H), 4.87 (d, *J* = 3.8 Hz, 1H), 3.91 (s, 3H), 2.67 – 2.54 (m, 3H), 2.52 – 2.43 (m, 2H), 1.97 – 1.88 (m, 1H), 1.87 – 1.79 (m, 2H) 1.53 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 212.45, 153.61, 139.60, 134.72, 131.60, 126.67, 126.48, 125.60, 125.34, 121.48, 117.84, 117.36, 111.92, 111.20, 111.19, 103.08, 56.05, 55.09, 48.87, 46.68, 39.27, 33.60, 27.10, 18.75.

IR: f (cm⁻¹) = 3381, 2926, 2858, 1691, 1484, 1449, 1216

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 374.2114 calculated for C₂₇H₂₈NO₂; Found 374.2105.

(±)-(2*R*,6*R*)-2-allyl-6-(5-(benzyloxy)-1*H*-indol-3-yl)-6-methyl-2-phenylcyclohexanone (5.65b)



Procedure: α-Hydroxyl enol ether **5.62** (150 mg, 0.614 mmol) was dissolved in DCE (3.1, 0.2 M). 6-Benzyloxyindole (205 mg, 0.922 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (39 mg, 0.122 mmol). The mixture was stirred at room temperature for 41 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 16 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column

chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **5.65b** in 75% yield (208 mg, 0.463 mmol) as a white solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.7 Rf in 50:50 hexanes : CH₂Cl₂

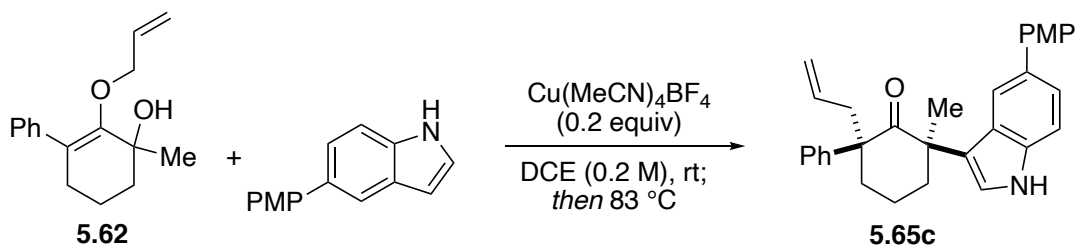
¹H NMR: (500 MHz, CDCl₃) δ = 7.57 (d, *J* = 8.9 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.38 (bs, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 3H), 6.69 (t, *J* = 7.2 Hz, 1H), 6.64 – 6.59 (m, 3H), 6.55 (d, *J* = 2.4 Hz, 1H), 5.37 – 5.27 (m, 1H), 5.09 (s, 2H), 4.91 (s, 1H), 4.88 (d, *J* = 4.4 Hz, 1H), 2.67 – 2.59 (m, 2H), 2.58 – 2.51 (m, 1H), 2.51 – 2.43 (m, 2H), 1.95 – 1.87 (m, 1H), 1.87 – 1.79 (m, 2H), 1.54 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ = 212.87, 155.10, 139.64, 137.59, 137.14, 134.79, 128.53, 127.79, 127.45, 126.77, 125.75, 125.39, 121.86, 120.96, 119.92, 118.27, 117.42, 109.76, 95.86, 70.53, 55.21, 49.00, 46.77, 39.12, 33.51, 27.56, 18.74.

IR: f (cm⁻¹) = 3392, 2924, 1692, 1626, 1496, 1453

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 450.2427 calculated for C₃₁H₃₂NO₂; Found 450.2426.

(±)-(2*R*,6*R*)-2-allyl-6-(5-(4-methoxyphenyl)-1*H*-indol-3-yl)-6-methyl-2-phenylcyclohexanone (5.65c)



Procedure: α -Hydroxyl enol ether **5.62** (163 mg, 0.668 mmol) was dissolved in DCE (3.3 mL, 0.2 M). 5-(4-methoxyphenyl)-1*H*-indole (223 mg, 1.002 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (42 mg, 0.134 mmol). The mixture was stirred at room temperature for 13

hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 25 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **5.65c** in 73% yield (219 mg, 0.487 mmol) as a white solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.7 in 50 : 50 (Hexanes : CH₂Cl₂)

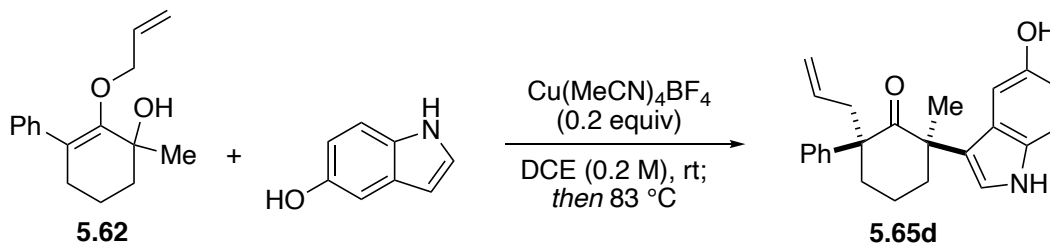
¹H NMR: (500 MHz, CDCl₃) δ = 7.84 (s, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.48 (bs, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 7.5 Hz, 2H), 6.72 (s, 1H), 6.66 (t, J = 6.8 Hz, 1H), 6.58 (t, J = 7.3 Hz, 2H), 5.32 – 5.24 (m, 1H), 4.88 (bs, 1H), 4.86 (bs, 1H), 3.89 (s, 3H), 2.68 – 2.56 (m, 3H), 2.55 – 2.43 (m, 2H), 1.98 – 1.89 (m, 1H), 1.89 – 1.80 (m, 2H), 1.56 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 212.48, 158.44, 139.42, 135.63, 135.43, 134.73, 132.27, 128.35, 126.68, 126.64, 125.80, 125.36, 121.33, 121.19, 119.18, 118.53, 117.36, 114.15, 110.72, 99.97, 55.41, 55.14, 49.04, 46.75, 39.18, 33.62, 27.52, 18.77.

IR: f (cm⁻¹) = 3443, 2996, 2925, 2867, 1686, 1604, 1447, 1336, 1177, 1090, 1013.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 450.2428 calculated for C₃₁H₃₂NO₂; Found 450.2445.

(±)-(2*R*,6*R*)-2-allyl-6-(5-hydroxy-1*H*-indol-3-yl)-6-methyl-2-phenylcyclohexanone
(5.65d)



Procedure: α -Hydroxyl enol ether **5.62** (147 mg, 0.602 mmol) was dissolved in DCE (3.0 mL, 0.2 M). 5-Hydroxyindole (120 mg, 0.902 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (38 mg, 0.120 mmol). The mixture was stirred at room temperature for 48 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 17 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 80:20 hexanes : EtOAc to yield **5.65d** in 42% yield (90 mg, 0.250 mmol) as a colorless solid. ^1H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.5 in 80 : 20 (Hexanes : EtOAc)

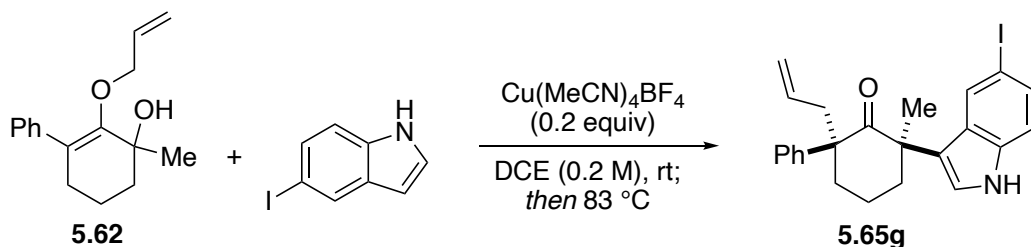
^1H NMR: (500MHz, CDCl_3) δ = 7.38 (bs, 1H), 7.02 (d, J = 2.5 Hz, 1H), 6.94 (d, J = 8.7 Hz, 1H), 6.88 – 6.86 (m, 2H), 6.75 – 6.71 (m, 1H), 6.70 – 6.65 (m, 4H), 5.34 – 5.26 (m, 1H), 4.89 (s, 1H), 4.88 – 4.85 (m, 1H), 4.57 (s, 1H), 2.65 – 2.58 (m, 2H), 2.58 – 2.52 (m, 1H), 2.48 – 2.42 (m, 2H), 1.93 – 1.88 (m, 1H), 1.87 – 1.81 (m, 2H), 1.51 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 212.75, 149.05, 139.73, 134.69, 131.72, 126.82, 126.64, 125.79, 125.41, 121.86, 117.66, 117.43, 111.28, 111.24, 105.55, 55.13, 48.83, 46.71, 38.92, 33.28, 26.92, 18.65.

IR: $f(\text{cm}^{-1})$ = 3403, 3071, 2962, 2866, 1682, 1582, 1466, 1372, 1208, 911, 858, 797.

HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 360.1959$ calculated for $\text{C}_{24}\text{H}_{26}\text{NO}_2$; Found 360.1975

(\pm)-(2*R*,6*R*)-2-allyl-6-(5-iodo-1*H*-indol-3-yl)-6-methyl-2-phenylcyclohexanone
(5.65g)



Procedure: α -Hydroxyl enol ether **5.62** (192 mg, 0.786 mmol) was dissolved in DCE (4.0 mL, 0.2 M). 5-Iodoindole (286 mg, 1.179 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (54 mg, 0.157 mmol). The mixture was stirred at room temperature for 18 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 $^{\circ}\text{C}$ in a preheated oil bath for 22 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH_2Cl_2 to yield **5.65g** in 57% yield (211 mg, 0.450 mmol) as a colorless solid. ^1H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.4 Rf in 50:50 (Hexanes : CH_2Cl_2)

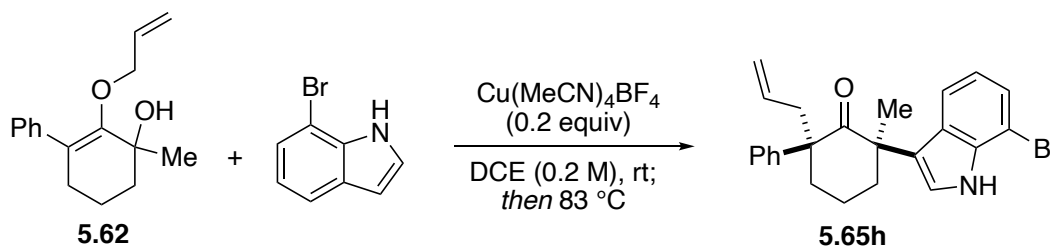
^1H NMR: (500 MHz, CDCl_3) δ = 7.97 (d, J = 2.0 Hz, 1H), 7.55 (bs, 1H), 7.33 (dd, J = 8.4, 1.7 Hz, 1H), 6.85 (t, J = 8.0 Hz, 3H), 6.71 – 6.63 (m, 4H), 5.33 – 5.24 (m, 1H), 4.89 (s, 1H), 4.87 (s, 1H), 2.69 – 2.59 (m, 2H), 2.57 – 2.50 (m, 1H), 2.50 – 2.41 (m, 2H), 1.95 – 1.80 (m, 3H), 1.49 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 212.31, 139.24, 135.39, 134.60, 130.06, 129.84, 128.65, 126.84, 125.84, 125.52, 121.49, 117.83, 117.48, 112.52, 82.75, 55.10, 48.80, 46.68, 38.84, 33.37, 27.43, 18.63.

IR: $f(\text{cm}^{-1})$ = 3366, 2924, 2855, 1685, 1494, 1110

HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 470.0975$ calculated for $\text{C}_{24}\text{H}_{25}\text{INO}$; Found 470.0976.

(±)-(2R,6R)-2-allyl-6-(7-bromo-1H-indol-3-yl)-6-methyl-2-phenylcyclohexanone (5.65h)



Procedure: α-Hydroxyl enol ether **5.62** (150 mg, 0.614 mmol) was dissolved in DCE (3.1 mL, 0.2 M). 7-Bromoindole (180 mg, 0.922 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (39 mg, 0.122 mmol). The mixture was stirred at room temperature for 23 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 11 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **5.65h** in 48% yield (124 mg, 0.293 mmol) as a white solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.8 Rf in 50:50 (Hexanes : CH₂Cl₂)

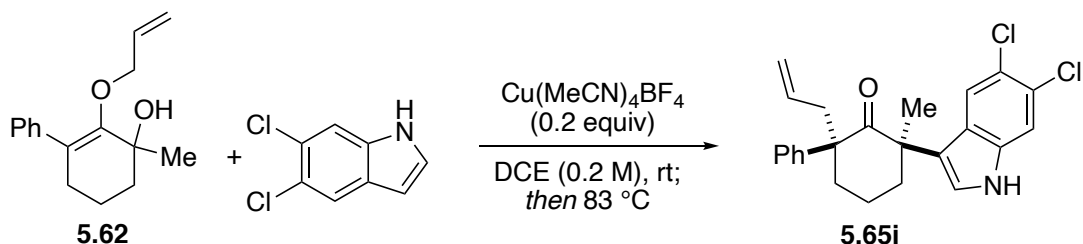
¹H NMR: (500 MHz, CDCl₃) δ = 7.67 (bs, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.27 – 7.23 (m, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 6.84 – 6.77 (m, 2H), 6.77 – 6.68 (m, 2H), 6.60 (t, *J* = 7.7 Hz, 2H), 5.34 – 5.24 (m, 1H), 4.90 (s, 1H), 4.87 (d, *J* = 4.9 Hz, 1H), 2.67 – 2.59 (m, 2H), 2.59 – 2.53 (m, 1H), 1.96 – 1.89 (m, 1H), 1.89 – 1.79 (m, 2H), 1.53 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 2212.39, 139.39, 134.93, 134.58, 127.44, 126.69, 125.67, 125.53, 123.89, 121.39, 120.59, 120.29, 119.66, 117.46, 104.20, 55.16, 49.05, 46.58, 39.05, 33.45, 27.30, 18.66.

IR: *f* (cm⁻¹) = 3412, 2925, 1689, 1433, 1374, 1208, 741, 701

HRMS: (ESI-TOF) *m/z*: (M+H)⁺ = 422.1114 calculated for C₂₄H₂₅BrNO; Found 422.1113.

(±)-(2*R*,6*R*)-2-allyl-6-(5,6-dichloro-1*H*-indol-3-yl)-6-methyl-2-phenylcyclohexanone (5.65i)



Procedure: α -Hydroxyl enol ether **5.62** (188 mg, 0.769 mmol) was dissolved in DCE (3.8 mL, 0.2 M). 5,6-dichloro-1*H*-indole (214 mg, 1.154 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (48 mg, 0.154 mmol). The mixture was stirred at room temperature for 23 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 57 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH_2Cl_2 to yield **5.65i** in 63% yield (199 mg, 0.483 mmol) as a white solid. ^1H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.7 in 50 : 50 (Hexanes : CH_2Cl_2)

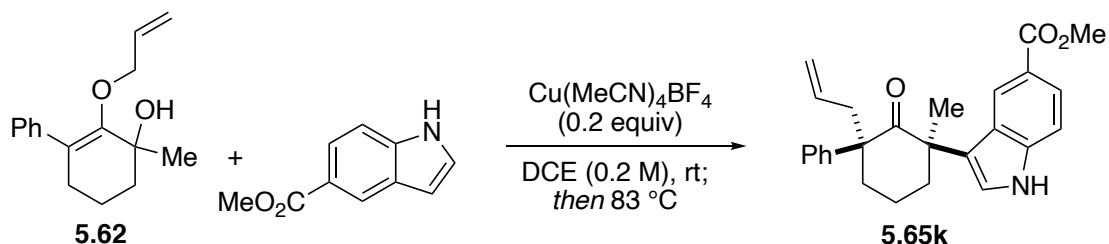
^1H NMR: (500 MHz, CDCl_3) δ = 7.73 (s, 1H), 7.52 (bs, 1H), 7.18 (s, 1H), 6.87 (d, J = 7.3 Hz, 2H), 6.76 – 6.72 (m, 2H), 6.69 (t, J = 7.0 Hz, 2H), 5.34 – 5.25 (m, 1H), 4.90 (bs, 1H), 4.88 – 4.85 (m, 1H), 2.67 – 2.60 (m, 2H), 2.54 – 2.41 (m, 3H), 1.93 – 1.82 (m, 3H), 1.49 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 212.19, 139.41, 135.21, 134.48, 127.02, 125.92, 125.89, 125.74, 125.62, 123.32, 122.68, 122.25, 118.53, 117.57, 111.94, 55.21, 48.71, 46.63, 38.64, 33.16, 27.31, 18.59.

IR: f (cm^{-1}) = 3374, 2978, 2926, 2824, 1734, 1695, 1545, 1448, 1329, 1141, 994, 925, 859, 735.

HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 412.1230$ calculated for $\text{C}_{24}\text{H}_{24}\text{Cl}_2\text{NO}$; Found 412.1235.

(±)-Methyl 3-((1*R*,3*R*)-3-allyl-1-methyl-2-oxo-3-phenylcyclohexyl)-1*H*-indole-5-carboxylate (5.65k**)**



Procedure: α-Hydroxyl enol ether **5.62** (150 mg, 0.614 mmol) was dissolved in DCE (3.0 mL, 0.2 M). Methyl 1*H*-indole-5-carboxylate (161 mg, 0.921 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (38 mg, 0.123 mmol). The mixture was stirred at room temperature for 22 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 46 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 80:20 hexanes : EtOAc to yield **5.65k** in 58% yield (142 mg, 0.354 mmol) as a white solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.6 in 70 : 30 (Hexanes : EtOAc)

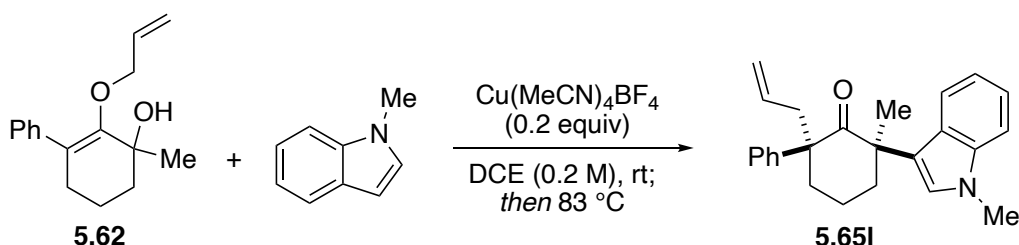
¹H NMR: (500 MHz, CDCl₃) δ = 8.46 (s, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.74 (bs, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.75 (s, 1H), 6.67 (t, *J* = 7.3 Hz, 1H), 6.58 (t, *J* = 7.7 Hz, 2H), 5.34 – 5.24 (m, 1H), 4.89 (bs, 1H), 4.86 – 4.85 (m, 1H), 3.98 (s, 3H), 2.66 – 2.54 (m, 3H), 2.49 – 2.45 (m, 2H), 1.97 – 1.91 (m, 1H), 1.87 – 1.81 (m, 2H), 1.57 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 212.24, 168.38, 139.47, 138.98, 134.60, 126.83, 125.83, 125.72, 125.45, 124.07, 123.24, 122.12, 121.32, 119.85, 117.47, 110.37, 55.22, 51.93, 48.97, 46.68, 39.05, 33.41, 27.73, 18.67.

IR: f (cm⁻¹) = 3382, 2917, 2866, 2848, 1698, 1683, 1434, 1242, 1179, 1100, 953.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 402.2064 calculated for C₂₆H₂₈NO₃; Found 402.2055.

(±)-(2*R*,6*R*)-2-allyl-6-methyl-6-(1-methyl-1*H*-indol-3-yl)-2-phenylcyclohexanone
(5.65I).



Procedure: α -Hydroxyl enol ether **5.62** (168 mg, 0.688 mmol) was dissolved in DCE (3.2 mL, 0.2 M). *N*-Methylindole (0.13 mL, 1.031 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (43 mg, 0.138 mmol). The mixture was stirred at room temperature for 16 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 48 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **5.65I** in 73% yield (178 mg, 0.498 mmol) as an orange solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.5 in 50 : 50 (Hexanes : CH₂Cl₂)

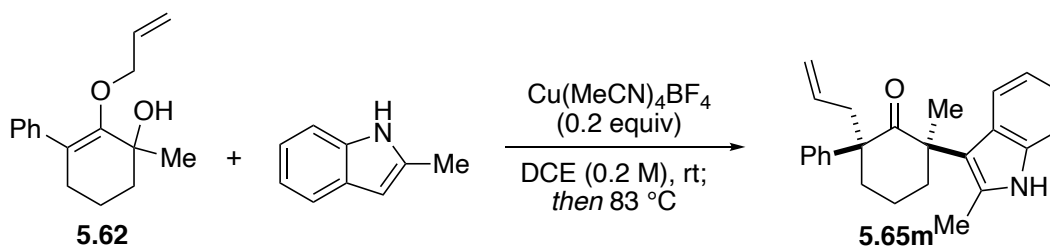
¹H NMR: (400 MHz, CDCl₃) δ = 7.68 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.0 Hz, 1H), 7.04 (t, *J* = 7.0 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.78 – 6.74 (m, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.56 (t, *J* = 8.0 Hz, 2H), 6.42 (s, 1H), 5.31 (dddd, *J* = 15.6, 9.2, 8.0, 6.6 Hz, 1H), 4.92 – 4.89 (m, 1H), 4.88 – 4.85 (m, 1H), 3.35 (s, 3H), 2.67 – 2.55 (m, 3H), 2.53 – 2.42 (m, 2H), 1.97 – 1.88 (m, 1H), 1.88 – 1.80 (m, 2H), 1.57 (s, 3H).

¹³C NMR: (100 MHz, CDCl₃) δ = 212.22, 137.08, 134.77, 126.66, 126.53, 125.83, 125.61, 124.83, 121.23, 121.10, 118.65, 117.32, 116.27, 108.64, 54.96, 48.98, 46.59, 39.31, 33.55, 32.21, 27.37, 18.88.

IR: f (cm⁻¹) = 3055, 2961, 2924, 1687, 1637, 1536, 1460, 1372, 1247, 1151, 1086, 1018, 1987.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 358.2170 calculated for C₂₅H₂₈NO; Found 358.2174.

(±)-(2*R*,6*R*)-2-allyl-6-methyl-6-(2-methyl-1*H*-indol-3-yl)-2-phenylcyclohexanone
(5.65m)



Procedure: α -Hydroxyl enol ether **5.62** (157 mg, 0.643 mmol) was dissolved in DCE (3.2 mL, 0.2 M). 2-Methylindole (236 mg, 0.963 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (40 mg, 0.129 mmol). The mixture was stirred at room temperature for 16 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 27 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column

chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **5.65m** in 27% yield (61 mg, 0.171 mmol) as a white solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.3 in 50 : 50 (Hexanes : CH₂Cl₂)

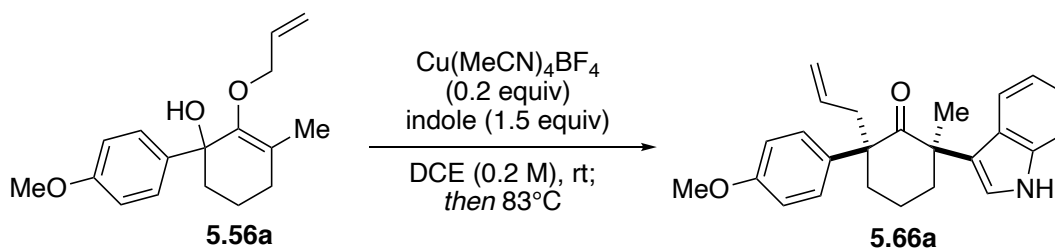
¹H NMR: (500 MHz, CDCl₃) δ = 7.68 (d, *J* = 7.7 Hz, 1H), 7.29 (bs, 1H), 7.07 – 6.98 (m, 5H), 6.88 – 6.80 (m, 3H), 5.29 – 5.20 (m, 1H), 4.93 (d, *J* = 17.0 Hz, 1H), 4.88 (d, *J* = 10.1 Hz, 1H), 3.03 – 2.97 (m, 1H), 2.93 (dd, *J* = 14.2, 5.8 Hz, 1H), 2.59 – 2.47 (m, 2H), 2.47 – 2.37 (m, 1H), 1.93 (s, 3H), 1.89 – 1.73 (m, 3H), 1.46 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 213.23, 140.07, 135.05, 134.62, 130.76, 127.64, 126.95, 126.19, 125.59, 120.68, 120.52, 119.01, 117.42, 111.65, 109.74, 54.77, 50.44, 45.45, 36.87, 31.21, 27.28, 18.70, 13.73.

IR: f (cm⁻¹) = 3388, 3055, 2925, 2866, 1688, 1492, 1460, 1373, 1300, 1069, 998, 910.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 358.2166 calculated for C₂₅H₂₈NO; Found 348.2166.

(±)-(2*R*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-2-(4-methoxyphenyl)-6-methylcyclohexanone
(5.66a)



Procedure: α-Hydroxyl enol ether **5.56a** (157 mg, 0.572 mmol) was dissolved in DCE (2.8 mL, 0.2 M). Indole (100 mg, 0.858 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (36 mg, 0.114 mmol). The mixture was stirred at room temperature for 5 hours, at which the starting

material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 18 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 30:70 hexanes : CH₂Cl₂ to yield **5.66a** in 89% yield (189 mg, 0.506 mmol) as an orange solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.8 in 50 : 50 (Hexanes : CH₂Cl₂)

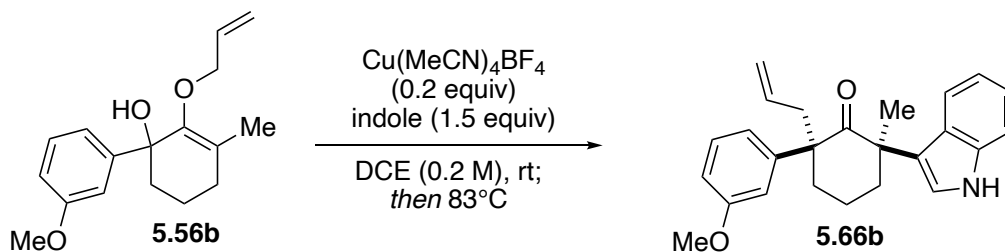
¹H NMR: (500 MHz, CDCl₃) δ = 7.67 (d, *J* = 7.9 Hz, 1H), 7.50 (bs, 1H), 7.08 (d, *J* = 3.6 Hz, 2H), 7.06 – 7.02 (m, 1H), 6.72 (d, *J* = 8.9 Hz, 2H), 6.70 (d, *J* = 2.6 Hz, 1H), 6.10 (d, *J* = 8.9 Hz, 2H), 5.35 – 5.26 (m, 1H), 4.89 – 4.88 (m, 1H), 4.87 – 4.85 (m, 1H), 3.50 (s, 3H), 2.63 – 2.56 (m, 3H), 2.50 – 2.46 (m, 1H), 1.94 – 1.86 (m, 1H), 1.85 – 1.76 (m, 2H), 1.53 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 212.89, 156.99, 136.44, 134.89, 131.67, 126.92, 126.22, 121.53, 121.29, 120.60, 119.04, 118.52, 117.26, 112.04, 110.51, 77.20, 54.91, 54.39, 48.86, 46.59, 39.18, 33.79, 27.39, 18.73.

IR: f (cm⁻¹) = 3402, 3064, 2929, 1964, 1690, 1608, 1511, 1417, 1248, 1183.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 374.2115 calculated for C₂₅H₂₈NO₂; Found 374.2114.

(±)-(2*R*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-2-(3-methoxyphenyl)-6-methylcyclohexanone
(5.66b)



Procedure: α -Hydroxyl enol ether **5.56b** (168 mg, 0.612 mmol) was dissolved in DCE (3.0 mL, 0.2 M). Indole (107 mg, 0.918 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (38 mg, 0.122 mmol). The mixture was stirred at room temperature for 25 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 24 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 30:70 hexanes : CH_2Cl_2 to yield **5.66b** in 88% yield (189 mg, 0.6105 mmol) as a white solid. ^1H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.8 in 50 : 50 (Hexanes : CH_2Cl_2)

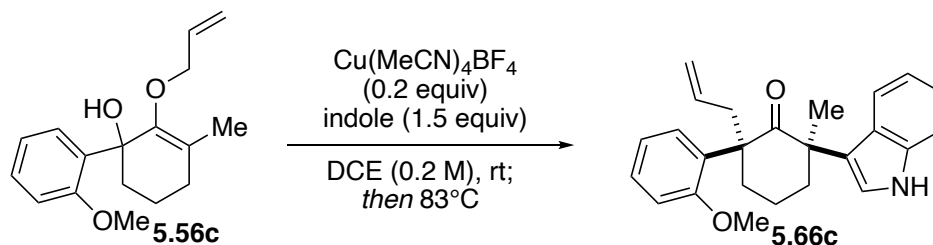
^1H NMR: (500 MHz, CDCl_3) δ = 7.74 (d, J = 7.8 Hz, 1H), 7.54 (bs, 1H), 7.13 – 7.02 (m, 3H), 6.72 (d, J = 2.5 Hz, 1H), 6.62 (t, J = 7.9 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 6.31 – 6.26 (m, 2H), 5.38 – 5.32 (dddd, J = 14.5, 9.2, 8.0, 6.7 Hz, 1H), 4.91 – 4.90 (m, 1H), 4.88 – 4.86 (m, 1H), 3.27 (s, 3H), 2.64 – 2.55 (m, 3H), 2.54 – 2.43 (m, 2H), 1.96 – 1.89 (m, 1H), 1.88 – 1.79 (m, 2H), 1.57 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 212.45, 158.56, 141.69, 136.42, 134.77, 127.74, 126.17, 121.57, 121.36, 120.99, 119.32, 118.43, 118.08, 117.35, 111.54, 111.44, 110.65, 55.28, 54.65, 49.02, 46.70, 39.18, 33.52, 27.39, 18.82.

IR: $f(\text{cm}^{-1})$ = 3405, 3070, 2961, 2927, 2865, 1691, 1598, 1489, 1338, 1244, 1105.

HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 374.2115$ calculated for $\text{C}_{25}\text{H}_{28}\text{NO}_2$; Found 374.2116.

(\pm)-(2*R*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-2-(2-methoxyphenyl)-6-methylcyclohexanone (5.66c)



Procedure: α -Hydroxyl enol ether **5.56c** (148 mg, 0.539 mmol) was dissolved in DCE (2.7 mL, 0.2 M). Indole (94 mg, 0.809 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (34 mg, 0.108 mmol). The mixture was stirred at room temperature for 6 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83°C in a preheated oil bath for 18 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH_2Cl_2 to yield **5.66c** in 40% yield (81 mg, 0.217 mmol) as a white solid. ^1H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.8 in 50 : 50 (Hexanes : CH_2Cl_2)

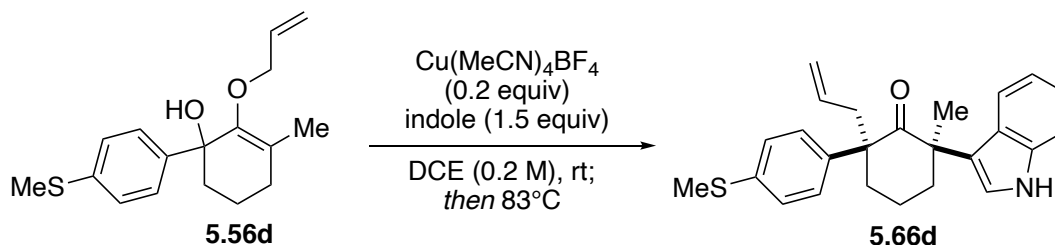
^1H NMR: (400 MHz, CDCl_3) δ = 7.93 (d, J = 7.3 Hz, 1H), 7.60 (s, 1H), 7.21 (dd, J = 7.7, 1.4 Hz, 1H), 7.17 (dd, J = 6.9, 1.6 Hz, 1H), 7.10 – 7.03 (m, 2H), 6.90 (td, J = 8.2, 1.5 Hz, 1H), 6.74 (td, J = 7.6, 1.0 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.06 (d, J = 7.8 Hz, 1H), 5.34 (dddd, J = 13.4, 8.1, 6.7, 6.3 Hz, 1H), 4.88 – 4.84 (m, 1H), 4.84 – 4.82 (m, 1H), 2.98 – 2.93 (m, 1H), 2.76 (s, 3H), 1.92 – 1.83 (m, 2H), 2.55 – 2.47 (m, 1H), 2.44 (dd, J = 14.4, 8.4 Hz, 1H), 2.36 – 2.27 (m, 1H), 1.92 – 1.83 (m, 2H), 1.70 – 1.64 (m, 1H), 1.62 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 212.83, 156.95, 136.36, 135.43, 129.55, 127.24, 126.79, 126.51, 122.63, 121.17, 120.44, 119.80, 119.10, 118.76, 116.60, 110.43, 109.65, 54.14, 53.62, 49.36, 41.04, 38.38, 34.56, 27.19, 17.96.

IR: $f(\text{cm}^{-1}) = 3363, 3064, 2966, 2869, 2833, 1696, 1582, 1490, 1459, 1338, 1244, 1108, 1027, 910$.

HRMS: (ESI-TOF) $m/z: (M+H)^+ = 374.2115$ calculated for $\text{C}_{25}\text{H}_{28}\text{NO}_2$; Found 374.2111.

(±)- (2*R*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-6-methyl-2-(4-(methylthio)phenyl)cyclohexanone (5.66d)



Procedure: α -Hydroxyl enol ether **5.56d** (191 mg, 0.658 mmol) was dissolved in DCE (3.2 mL, 0.2 M). Indole (115 mg, 0.986 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (41 mg, 0.132 mmol). The mixture was stirred at room temperature for 41 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83°C in a preheated oil bath for 48 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 40:60 hexanes : CH_2Cl_2 to yield **5.66d** in 76% yield (170 mg, 0.496 mmol) as a yellow solid. ^1H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.7 in 50 : 50 (Hexanes : CH_2Cl_2)

^1H NMR: (400 MHz, CDCl_3) $\delta = 7.66$ (d, $J = 7.8$ Hz, 1H), 7.52 (bs, 1H), 7.10 – 7.06 (m, 2H), 7.07 – 7.02 (m, 1H), 6.73 – 6.67 (m, 3H), 6.43 (d, $J = 8.5$ Hz, 2H), 5.35 – 5.23 (m, 1H), 4.89 (bs, 1H), 4.88 – 4.83 (m, 1H), 2.64 – 2.53 (m, 3H), 2.51 – 2.38 (m, 2H), 2.22 (s, 3H), 1.96 – 1.75 (m, 3H), 1.53 (s, 3H).

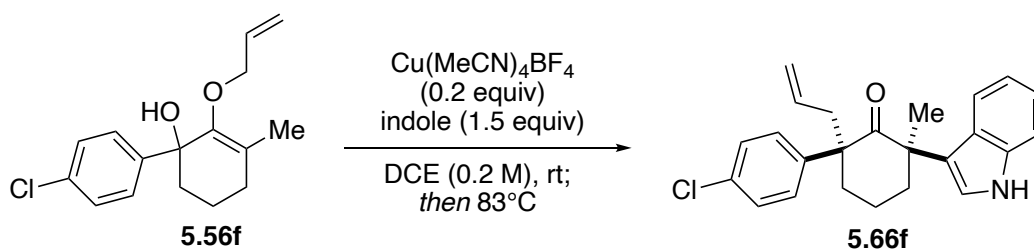
¹³C NMR: (125 MHz, CDCl₃) δ = 212.40, 136.50, 136.43, 134.78, 134.60, 126.26, 125.02, 121.64, 121.24, 120.71, 119.15, 118.20, 117.48, 110.60, 54.71, 48.98, 46.43, 39.35, 33.78, 27.36, 18.77, 15.73.

IR: f (cm⁻¹) = 3367, 3067, 2959, 2919, 1679, 1624, 1461, 1403, 1344, 1244, 1147, 1097, 1013, 993.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 390.1887 calculated for C₂₅H₂₈NO; Found 390.1890.

(±)-(2*R*,6*R*)-2-allyl-2-(4-chlorophenyl)-6-(1*H*-indol-3-yl)-6-methylcyclohexanone

(5.66f)



Procedure: α -Hydroxyl enol ether **5.56f** (157 mg, 0.563 mmol) was dissolved in DCE (2.8 mL, 0.2 M). Indole (99 mg, 0.845 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (35 mg, 0.113 mmol). The mixture was stirred at room temperature for 33 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 39 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH_2Cl_2 to yield **5.66f** in 74% yield (157 mg, 0.415 mmol) as a red/pink solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.5 in 50 : 50 (Hexanes : CH_2Cl_2)

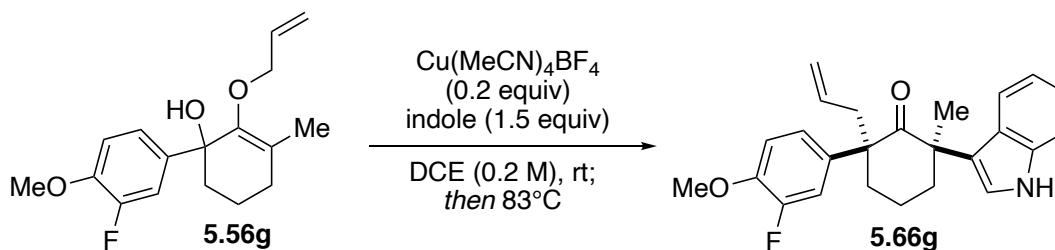
¹H NMR: (500 MHz, CDCl₃) δ = 7.65 (d, *J* = 8.1 Hz, 1H), 7.56 (bs, 1H), 7.12 (d, *J* = 4.3 Hz, 2H), 7.09 – 7.02 (m, 1H), 6.72 (d, *J* = 8.7 Hz, 2H), 6.70 (d, *J* = 2.6 Hz, 1H), 6.50 (d, *J* = 8.6 Hz, 2H), 5.33 – 5.23 (m, 1H), 4.91 – 4.83 (m, 2H), 2.63 – 2.55 (m, 3H), 2.49 – 2.40 (m, 2H), 1.96 – 1.89 (m, 1H), 1.87 – 1.78 (m, 2H), 1.55 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 211.99, 138.18, 136.54, 134.22, 131.06, 127.11, 126.64, 126.13, 121.89, 121.09, 120.72, 119.32, 118.01, 117.75, 110.81, 54.82, 49.09, 46.43, 39.32, 33.85, 27.34, 18.77.

IR: f (cm⁻¹) = 3404, 2927, 2860, 1692, 1491, 1460, 1246, 1095, 1013, 916, 824, 742.

HRMS: (ESI-TOF) m/z : (*M*+*H*)⁺ = 378.1620 calculated for C₂₄H₂₅ClNO; Found 378.1628.

(±)-(2*R*,6*R*)-2-allyl-2-(3-fluoro-4-methoxyphenyl)-6-(1*H*-indol-3-yl)-6-methylcyclohexanone
(5.66g)



Procedure: α -Hydroxyl enol ether **5.56g** (151 mg, 0.517 mmol) was dissolved in DCE (2.6 mL, 0.2 M). Indole (90 mg, 0.734 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (32 mg, 0.103 mmol). The mixture was stirred at room temperature for 40 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 24 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 30:70 hexanes : CH₂Cl₂ to yield **5.66g** in 73% yield (148

mg, 0.378 mmol) as a colorless oil. ^1H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.7 in 50 : 50 (Hexanes : CH_2Cl_2)

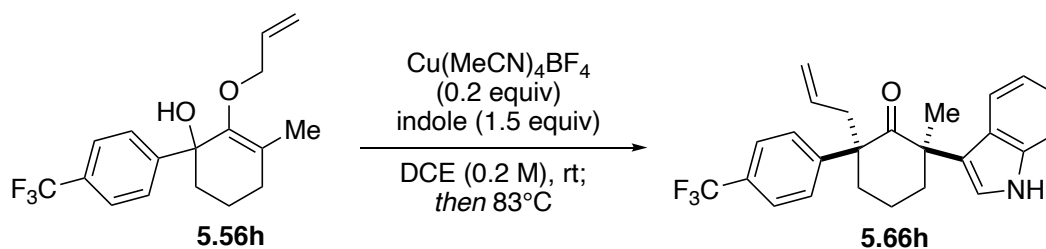
^1H NMR: (500 MHz, CDCl_3) δ = 7.64 (d, J = 8.4 Hz, 1H), 7.58 (bs, 1H), 7.09 (d, J = 3.6 Hz, 2H), 7.06 – 7.02 (m, 1H), 6.75 (s, 1H), 6.67 (dd, J = 13.4, 2.3 Hz, 1H), 6.39 (d, J = 8.6 Hz, 1H), 5.94 (t, J = 8.6 Hz, 1H), 5.29 (dddd, J = 16.8, 10.7, 7.9, 6.5 Hz, 1H), 4.89 (bs, 1H), 4.89 – 4.85 (m, 1H), 3.57 (s, 3H), 2.67 – 2.56 (m, 2H), 2.55 – 2.47 (m, 2H), 2.41 (dd, J = 14.0, 8.0 Hz, 1H), 1.94 – 1.88 (m, 1H), 1.86 – 1.78 (m, 2H), 1.52 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 212.05, 136.39, 134.39, 132.78, 132.74, 126.17, 122.67, 121.72, 121.13, 120.65, 119.24, 118.14, 117.63, 113.12, 112.96, 111.55, 110.51, 55.95, 54.24, 48.92, 46.44, 39.21, 34.08, 27.40, 18.74.

IR: $f(\text{cm}^{-1})$ = 3404, 3068, 2962, 2929, 2863, 1692, 1619, 1584, 1460, 1274, 1220, 1107, 11013.

HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 392.2021$ calculated for $\text{C}_{25}\text{H}_{27}\text{FNO}_2$; Found 392.2030.

(\pm)-(2*R*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-6-methyl-2-(4-(trifluoromethyl)phenyl)cyclohexanone (5.66h)



Procedure: α -Hydroxyl enol ether **5.56h** (202 mg, 0.647 mmol) was dissolved in DCE (3.2 mL, 0.2 M). Indole (151 mg, 1.293 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (101 mg, 0.3233 mmol). The mixture was stirred at room temperature for 96 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83°C in a

preheated oil bath for 28 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 30:70 hexanes : CH₂Cl₂ to yield **5.66h** in 62% yield (165 mg, 0.401 mmol) as a white solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.5 in 50 :50 (Hexanes : CH₂Cl₂)

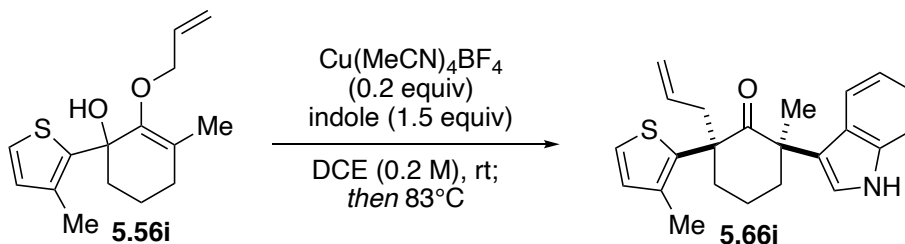
¹H NMR: (500 MHz, CDCl₃) δ = 7.63 (d, *J* = 7.9 Hz, 1H), 7.46 (bs, 1H), 7.14 – 7.07 (m, 1H), 7.08 – 7.03 (m, 2H), 6.87 (d, *J* = 8.2 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 2H), 6.69 (d, *J* = 2.6 Hz, 1H), 5.23 (dddd, *J* = 14.7, 10.4, 8.1, 6.7 Hz, 1H), 4.91 – 4.83 (m, 2H), 2.68 – 2.55 (m, 3H), 2.54 – 2.48 (m, 1H), 2.44 (dd, *J* = 14.1, 8.0 Hz, 1H), 1.95 (td, *J* = 13.5, 4.4 Hz, 1H), 1.89 – 1.79 (m, 2H), 1.54 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 211.48, 136.37, 133.88, 126.01, 125.92, 123.27, 123.24, 121.96, 120.90, 120.85, 119.38, 118.00, 117.43, 110.81, 55.14, 49.16, 46.37, 39.50, 33.97, 27.23, 18.79.

IR: ν (cm⁻¹) = 3361, 3051, 2963, 2928, 2861, 1680, 1636, 1458, 1374, 1243, 1194, 1113, 998.

HRMS: (ESI-TOF) *m/z*: (*M*+*H*)⁺ = 412.1883 calculated for C₂₅H₂₅F₃NO; Found 412.1886.

(±)-(2*S*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-6-methyl-2-(3-methylthiophen-2-yl)cyclohexanone (5.66i)



Procedure: α -Hydroxyl enol ether **5.56i** (166 mg, 0.628 mmol) was dissolved in DCE (3.1 mL, 0.2 M). Indole (110 mg, 0.942 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (40 mg, 0.126 mmol). The mixture was stirred at room temperature for 9 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 15 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH_2Cl_2 to yield **5.66i** in 95% yield (216 mg, 0.594 mmol) as a brown solid. ^1H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.7 in 50 :50 (Hexanes : CH_2Cl_2)

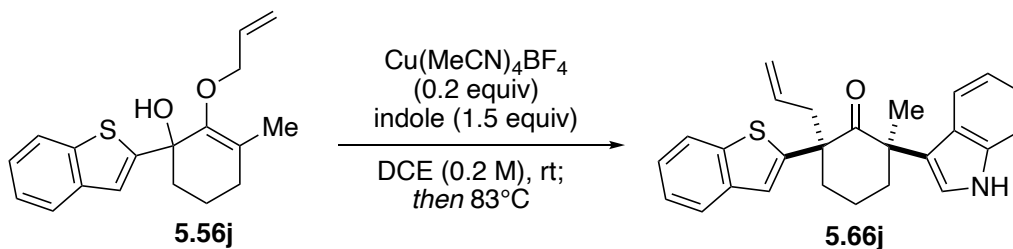
^1H NMR: (400 MHz, CDCl_3) δ = 7.71 (d, J = 8.1 Hz, 1H), 7.66 (bs, 1H), 7.17 (d, J = 8.1 Hz, 1H), 7.11 – 7.05 (m, 1H), 6.99 – 6.94 (m, 1H), 6.86 (d, J = 2.6 Hz, 1H), 6.72 (d, J = 5.1 Hz, 1H), 6.14 (d, J = 5.2 Hz, 1H), 5.38 (dddd, J = 16.8, 10.2 8.1, 6.5 Hz, 1H), 4.98 – 4.88 (m, 2H), 3.01 – 2.97 (m, 1H), 2.82 – 2.59 (m, 3H), 2.40 (dd, J = 14.2, 8.1 Hz, 1H), 1.95 – 1.83 (m, 3H), 1.60 (s, 3H), 1.57 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 211.27, 136.95, 136.45, 135.14, 134.43, 131.35, 126.03, 121.71, 121.60, 120.88, 120.36, 118.83, 118.81, 117.51, 110.49, 52.86, 49.02, 42.90, 37.79, 37.22, 27.15, 18.83, 15.14.

IR: $f(\text{cm}^{-1})$ = 3408, 3069, 2967, 2867, 1691, 1514, 1458, 1337, 1243, 178, 1106, 1012, 911.

HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 364.1730$ calculated for $\text{C}_{23}\text{H}_{27}\text{NOS}$; Found 364.1743.

(\pm)-(2*S*,6*R*)-2-allyl-2-(benzo[*b*]thiophen-2-yl)-6-(1*H*-indol-3-yl)-6-methylcyclohexanone (5.66j)



Procedure: α -Hydroxyl enol ether **5.56d** (188mg, 0.626 mmol) was dissolved in DCE (3.1 mL, 0.2 M). Indole (110 mg, 0.939 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (39 mg, 0.125 mmol). The mixture was stirred at room temperature for 15 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 24 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH_2Cl_2 to yield **5.66j** in 71% yield (178 mg, 0.446 mmol) as a yellow solid. ^1H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.7 in 50 :50 (Hexanes : CH_2Cl_2)

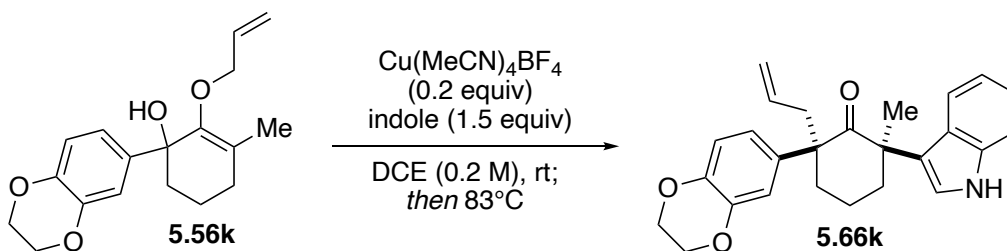
^1H NMR: (500 MHz, CDCl_3) δ = 7.80 – 7.74 (m, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.43 (bs, 1H), 7.12 – 7.08 (m, 1H), 7.08 – 7.04 (m, 3H), 7.00 – 6.97 (m, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 2.6 Hz, 1H), 6.32 (s, 1H), 5.55 (dddd, J = 17.0, 10.2, 7.8, 6.7 Hz, 1H), 4.97 – 4.96 (m, 1H), 2.78 – 2.73 (m, 1H), 2.72 – 2.66 (m, 1H), 2.65 – 2.52 (m, 2H), 2.52 – 2.46 (m, 1H), 2.07 – 2.00 (m, 1H), 1.99 – 1.86 (m, 2H), 1.59 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 210.90, 146.31, 139.31, 138.26, 136.49, 134.22, 125.92, 123.41, 123.28, 122.87, 121.84, 121.81, 121.28, 121.05, 120.93, 119.36, 118.46, 118.13, 110.82, 53.98, 48.97, 46.99, 37.99, 35.49, 27.33, 18.82.

IR: $f(\text{cm}^{-1})$ = 3414, 3055, 2961, 2927, 1695, 1458, 1246, 1105, 910.

HRMS: (ESI-TOF) m/z : $(M+H)^+ = 400.1730$ calculated for $C_{26}H_{25}NOS$; Found 400.1736.

(±)- (2*R*,6*R*)-2-allyl-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-(1*H*-indol-3-yl)-6-methylcyclohexanone (5.66k)



Procedure: α -Hydroxyl enol ether **5.56k** (151 mg, 0.499 mmol) was dissolved in DCE (2.5 mL, 0.2 M). Indole (88 mg, 0.749 mmol) was added, followed by addition of $Cu(MeCN)_4BF_4$ (31 mg, 0.100 mmol). The mixture was stirred at room temperature for 15 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 24 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 60:40 hexanes : CH_2Cl_2 to yield **5.66k** in 80% yield (160 mg, 0.399 mmol) as a colorless solid. 1H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.8 in 80:20 (Hexanes : EtOAc)

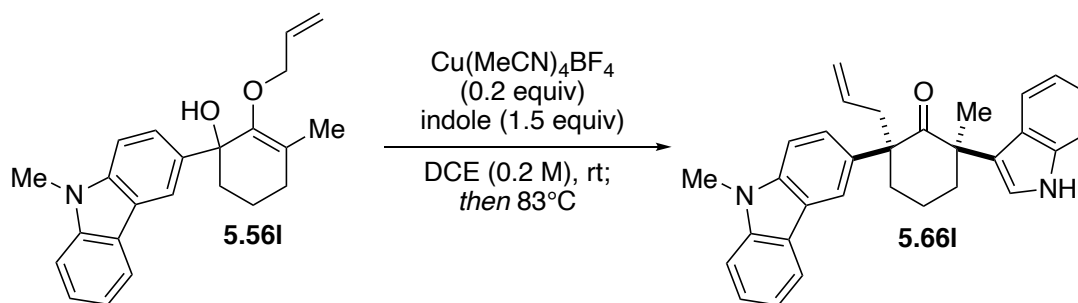
1H NMR: (500 MHz, $CDCl_3$) δ = 7.64 (s, 1H), 7.63 (bs, 1H), 7.13 – 7.11 (m, 1H), 7.10 – 7.02 (m, 2H), 6.76 (d, J = 2.5 Hz, 1H), 6.38 – 6.34 (m, 2H), 6.15 (d, J = 8.3 Hz, 1H), 5.33 (dddd, J = 16.7, 10.3, 8.0, 6.4 Hz, 1H), 4.94 – 4.89 (m, 1H), 4.89 – 4.87 (m, 1H), 4.02 – 3.94 (m, 3H), 3.84 – 3.78 (m, 1H), 2.64 (dd, J = 14.0, 6.4 Hz, 1H), 2.61 – 2.48 (m, 3H), 2.42 (dd, J = 14.0, 8.1 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.85 – 1.76 (m, 2H), 1.52 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 212.60, 142.02, 141.03, 136.28, 134.94, 132.98, 126.20, 121.47, 121.20, 120.60, 119.30, 118.79, 118.56, 117.22, 115.47, 115.21, 110.34, 63.95, 54.33, 48.85, 46.55, 39.03, 33.84, 27.44, 18.77.

IR: f (cm^{-1}) = 3401, 3067, 2967, 2927, 1688, 1638, 1587, 1458, 1372, 1285, 1207, 1051.

HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 402.2064$ calculated for $\text{C}_{26}\text{H}_{28}\text{NO}_3$; Found 402.2067.

(\pm)-(2*R*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-6-methyl-2-(9-methyl-9*H*-carbazol-3-yl)cyclohexanone (5.66I)



Procedure: α -Hydroxyl enol ether **5.56I** (172 mg, 0.495 mmol) was dissolved in DCE (2.5 mL, 0.2 M). Indole (86 mg, 0.743 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (31 mg, 0.990 mmol). The mixture was stirred at room temperature for 15 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83°C in a preheated oil bath for 24 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 40:60 hexanes : CH_2Cl_2 to yield **5.66I** in 69% yield (153 mg, 0.343 mmol) as a white solid. ^1H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf:

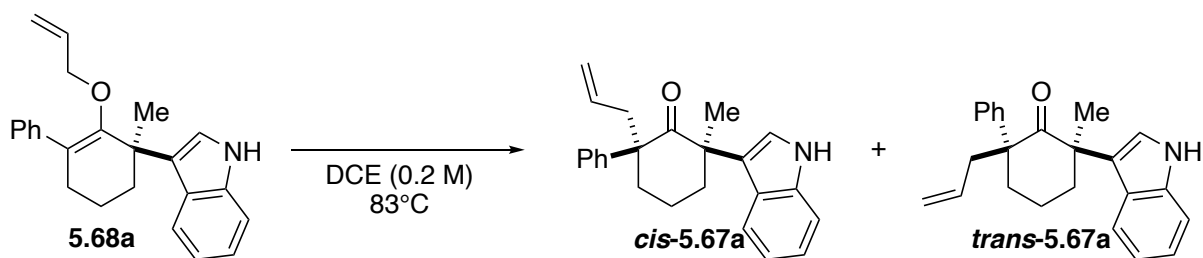
¹H NMR: (400 MHz, CDCl₃) δ = 7.81 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 1.7 Hz, 1H), 7.39 (t, *J* = 7.1, 1H), 7.27 (d, *J* = 8.0 1H), 7.16 – 7.10 (m, 2H), 7.09 – 7.04 (m, 1H), 6.96 (t, *J* = 8.0 Hz, 1H), 6.88 (dd, *J* = 8.6, 1.9 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 2.6 Hz, 1H), 6.49 (d, *J* = 8.6 Hz, 1H), 5.35 (dddd, *J* = 17.0, 10.1, 8.0, 6.4 Hz, 1H), 4.93 – 4.85 (m, 2H), 3.60 (s, 3H), 2.84 – 2.77 (m, 1H), 2.73 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.62 – 2.55 (m, 2H), 2.55 – 2.50 (m, 1H), 2.01 – 1.88 (m, 3H), 1.58 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 213.27, 140.91, 136.22, 135.17, 130.69, 126.24, 125.15, 124.62, 122.70, 121.49, 121.44, 120.46, 120.32, 119.14, 118.74, 118.29, 117.14, 117.05, 110.31, 107.98, 106.54, 55.32, 48.99, 47.04, 39.29, 34.05, 28.80, 27.48, 18.95.

IR: f (cm⁻¹) = 3415, 3052, 2925, 2864, 1688, 1601, 1482, 1482, 1333, 1248, 1011.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 447.2431 calculated for C₃₁H₃₁N₂O; Found 447.2433.

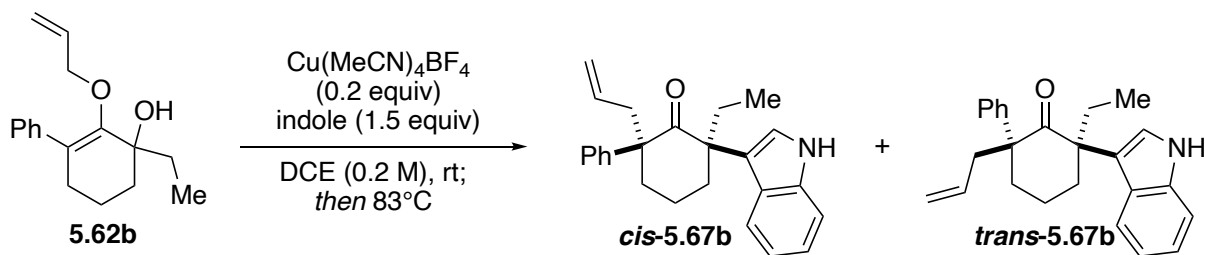
(±)-(2*R*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-6-methyl-2-phenylcyclohexan-1-one (*cis*-5.67a) and (±)-(2*S*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-6-methyl-2-phenylcyclohexan-1-one (*trans*-5.67a)



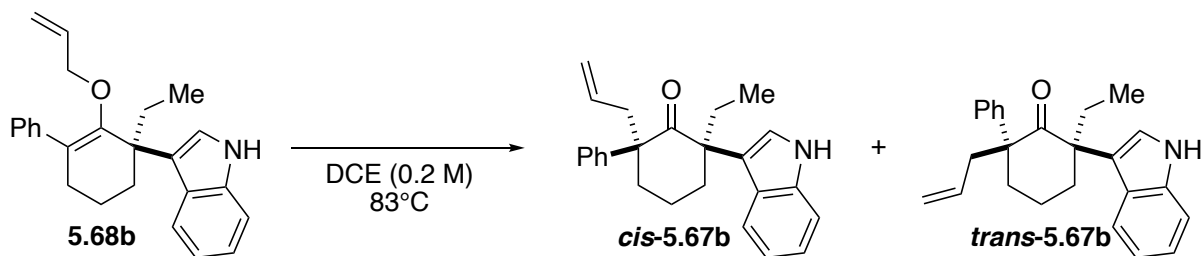
Procedure: α -Indolyl allylvinyl ether **5.68a** (140 mg, 0.408 mmol) was dissolved in DCE (2.0 mL, 0.2 M). The mixture was then heated to 83 °C in a preheated oil bath for 112 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to

50:50 hexanes : CH₂Cl₂ to yield **cis-5.67a** in 79% yield (111 mg, 0.323 mmol) as a white solid and **trans-5.67a** in 12% yield (17 mg, 0.049 mmol) as a colorless oil. ¹H NMR analysis of the crude reaction mixture indicated 5.0:1 dr (**cis-5.67a**: **trans-5.67a**).

(±)-(2*R*,6*R*)-2-allyl-6-ethyl-6-(1*H*-indol-3-yl)-2-phenylcyclohexanone (**cis-5.67b**) and (±)-(2*S*,6*R*)-2-allyl-6-ethyl-6-(1*H*-indol-3-yl)-2-phenylcyclohexanone (**trans-5.6b**)



Procedure: α-Hydroxyl enol ether **5.62b** (146 mg, 0.565 mmol) was dissolved in DCE (2.8 mL, 0.2 M). Indole (99 mg, 0.848 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (35 mg, 0.113 mmol). The mixture was stirred at room temperature for 20 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 42 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **cis-5.67b** in 32% yield (66 mg, 0.1846 mmol) as a white solid and **trans-5.67b** in 32% yield (64 mg, 0.1790) as a colorless oil. ¹H NMR analysis of the crude reaction mixture indicated 1:1.1 dr (**cis-5.67b**: **trans-5.67b**).



Procedure: α -Indolyl allylvinyl ether **5.68b** (78 mg, 0.219 mmol) was dissolved in DCE (1.1 mL, 0.2 M). The mixture was then heated to 83 °C in a preheated oil bath for 114 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **cis-5.67b** in 37% yield (29 mg, 0.081 mmol) as a white solid and **trans-5.67b** in 62% yield (49 mg, 0.137) as a colorless oil. ¹H NMR analysis of the crude reaction mixture indicated 1:1.7 dr (**cis-5.67b**: **trans-5.67b**).

cis-5.67b

Rf: 0.6 in 50 :50 (Hexanes : CH₂Cl₂)

¹H NMR: (500 MHz, CDCl₃) δ = 8.07 (bs, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.42 – 7.33 (m, 5H), 7.29 – 7.26 (m, 1H), 7.18 (t, J = 7.3 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 7.00 (d, J = 2.6 Hz, 1H), 5.38 – 5.28 (m, 1H), 4.83 (bs, 1H), 4.81 (bs, 1H), 2.61 (dd, J = 13.9, 6.9 Hz, 1H), 2.49 (dd, J = 14.0, 7.8 Hz, 1H), 2.38 – 2.30 (m, 2H), 2.03 – 1.91 (m, 2H), 1.90 – 1.81 (m, 2H), 1.77 – 1.68 (m, 2H), 0.56 (t, J = 7.4 Hz, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 212.27, 139.87, 136.52, 134.82, 126.64, 126.19, 125.64, 125.22, 122.37, 121.52, 121.43, 119.06, 117.31, 115.75, 110.50, 55.25, 52.52, 46.81, 34.82, 33.10, 30.58, 18.49, 7.89.

IR: f (cm⁻¹) = 3378, 2924, 2857, 1678, 1612, 1511, 1429, 1377, 1244, 1103, 1032, 912.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 358.2166 calculated for C₂₅H₂₈NO; Found 358.2169.

trans-5.67b

Rf: 0.8 in 50 :50 (Hexanes : CH₂Cl₂)

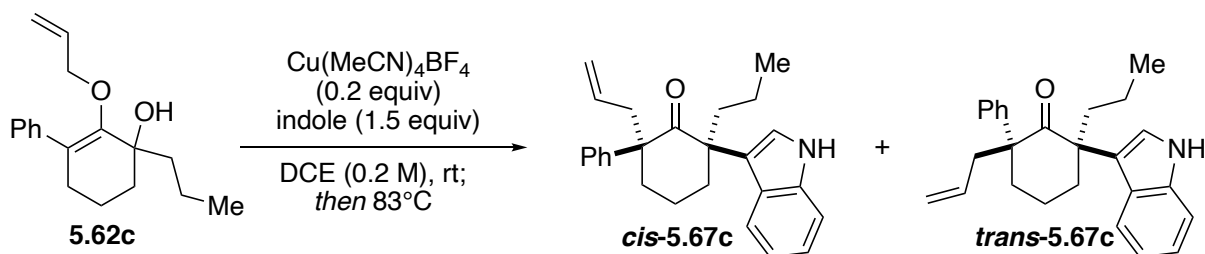
¹H NMR: (500 MHz, CDCl₃) δ = 8.08 (bs, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.42 – 7.35 (m, 5H), 7.28 (t, *J* = 7.0 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.11 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 2.5 Hz, 1H), 5.38 – 5.29 (m, 1H), 4.85 – 4.83 (m, 1H), 4.82 (s, 1H), 2.62 (dd, *J* = 13.9, 6.8 Hz, 1H), 2.49 (dd, *J* = 13.9, 7.8 Hz, 1H), 2.40 – 2.31 (m, 2H), 2.04 – 1.92 (m, 2H), 1.90 – 1.82 (m, 2H), 1.79 – 1.67 (m, 2H), 0.56 (t, *J* = 7.4 Hz, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 213.08, 140.34, 136.93, 134.52, 128.48, 126.62, 126.34, 126.05, 122.08, 121.81, 121.39, 119.43, 117.55, 117.34, 111.23, 54.84, 52.91, 46.56, 31.29, 29.06, 27.92, 16.86, 8.84.

IR: f (cm⁻¹) = 3407, 2937, 2874, 1689, 1457, 1378, 1104, 998, 907.

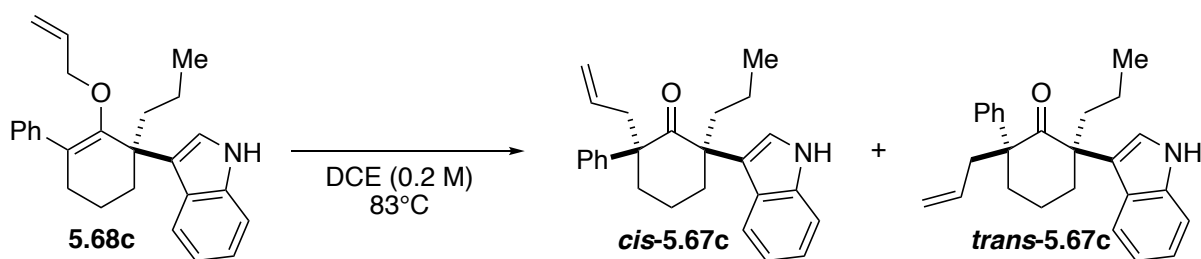
HRMS: (ESI-TOF) m/z : (*M*+*H*)⁺ = 358.2166 calculated for C₂₅H₂₈NO; Found 358.2169

(±)-(2*R*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-2-phenyl-6-propylcyclohexanone (*cis*-5.67c) and (±)-(2*S*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-2-phenyl-6-propylcyclohexanone (*trans*-5.67c)



Procedure: α -Hydroxyl enol ether **5.62c** (155 mg, 0.569 mmol) was dissolved in DCE (2.8 mL, 0.2 M). Indole (100 mg, 0.854 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (35 mg, 0.113 mmol). The mixture was stirred at room temperature for 16 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a

preheated oil bath for 48 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **cis-5.67c** in 38% yield (80 mg, 0.215 mmol) as a white solid and **trans-5.67c** in 41% yield (86 mg, 0.247 mmol) as a colorless oil. ¹H NMR analysis of the crude reaction mixture indicated 1:1.2 dr (**cis-5.67c**: **trans-5.67c**).



Procedure: α-Indolyl allylvinyl ether **5.68c** (104 mg, 0.280 mmol) was dissolved in DCE (1.4 mL, 0.2 M). The mixture was then heated to 83 °C in a preheated oil bath for 114 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **cis-5.67c** in 25% yield (26 mg, 0.070 mmol) as a white solid and **trans-5.67c** in 56% yield (59 mg, 0.159) as a colorless oil. ¹H NMR analysis of the crude reaction mixture indicated 1:1.7 dr (**cis-5.67c**: **trans-5.67c**).

cis-5.67c

Rf: 0.5 in 50 :50 (Hexanes : CH₂Cl₂)

¹H NMR: (500 MHz, CDCl₃) δ = 7.77 (d, J = 7.8 Hz, 1H), 7.47 (bs, 1H), 7.10 – 7.03 (m, 3H), 6.79 (d, J = 8.4 Hz, 2H), 6.68 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 2.9 Hz, 1H), 6.57 (t, J = 7.6 Hz, 2H),

5.35 – 5.27 (m, 1H), 4.89 (bs, 1H), 4.86 (d, $J = 6.0$ Hz, 1H), 2.63 – 2.53 (m, 3H), 2.49 – 2.39 (m, 3H), 1.89 – 1.82 (m, 2H), 1.81 – 1.70 (m, 2H), 1.13 – 1.07 (m, 1H), 0.81 – 0.71 (m, 4H).

^{13}C NMR: (125 MHz, CDCl_3) $\delta = 212.13, 139.94, 136.51, 134.85, 126.67, 126.25, 125.64, 125.23, 122.09, 121.54, 121.48, 119.12, 117.32, 116.27, 110.48, 55.22, 52.39, 46.86, 40.50, 35.49, 33.03, 18.56, 16.76, 14.69$.

IR: $f(\text{cm}^{-1}) = 3344, 2952, 2927, 2856, 1678, 1572, 1427, 1241, 1014, 995$.

HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 272.2322$ calculated for $\text{C}_{26}\text{H}_{29}\text{NO}$; Found 272.2321.

***trans*-5.67c**

Rf: 0.8 in 50 :50 (Hexanes : CH_2Cl_2)

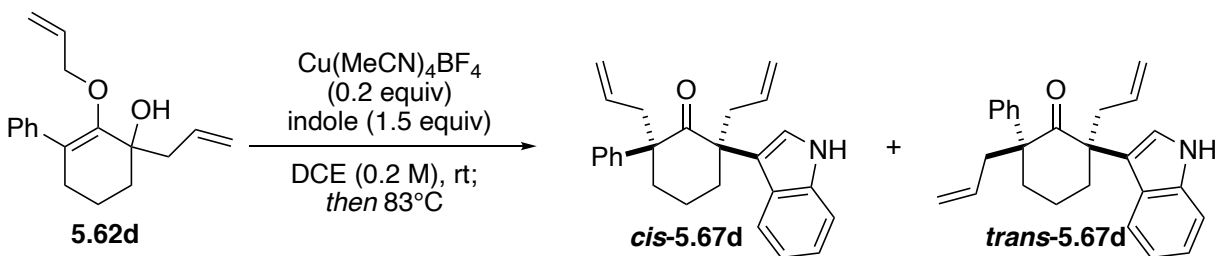
^1H NMR: (500 MHz, CDCl_3) $\delta = 8.04$ (bs, 1H), 7.78 (d, $J = 8.1$ Hz, 1H), 7.41 – 7.35 (m, 5H), 7.28 – 7.25 (m, 1H), 7.18 (t, $J = 7.6$ Hz, 1H), 7.10 (t, $J = 7.6$ Hz, 1H), 7.00 (d, $J = 2.8$ Hz, 1H), 5.39 – 5.27 (m, 1H), 4.84 – 4.83 (m, 1H), 4.81 (bs, 1H), 2.61 (dd, $J = 13.9, 6.9$ Hz, 1H), 2.48 (dd, $J = 13.9, 7.8$ Hz, 1H), 2.40 – 2.31 (m, 2H), 1.99 – 1.78 (m, 4H), 1.74 – 1.63 (m, 2H), 1.10 – 1.02 (m, 1H), 0.89 – 0.80 (m, 1H), 0.64 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR: (125 MHz, CDCl_3) $\delta = 212.98, 140.37, 136.90, 134.53, 128.47, 126.62, 126.30, 126.03, 121.94, 121.81, 121.33, 119.46, 117.65, 117.55, 111.23, 54.77, 52.70, 46.60, 41.31, 29.67, 27.70, 17.52, 16.92, 14.42$.

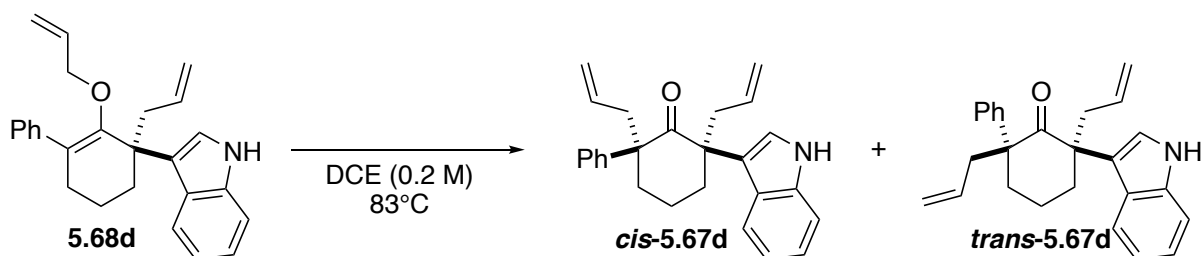
IR: $f(\text{cm}^{-1}) = 3322, 2959, 2920, 2857, 1681, 1572, 1430, 1244, 1032, 905$.

HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 272.2322$ calculated for $\text{C}_{26}\text{H}_{29}\text{NO}$; Found 272.2324.

(\pm)-(2*R*,6*S*)-2,6-diallyl-2-(1*H*-indol-3-yl)-6-phenylcyclohexanone (*cis*-5.67d) and (\pm)-(2*S*,6*S*)-2,6-diallyl-2-(1*H*-indol-3-yl)-6-phenylcyclohexanone (*trans*-5.67d)



Procedure: α -Hydroxyl enol ether **5.62d** (150 mg, 0.554 mmol) was dissolved in DCE (2.8 mL, 0.2 M). Indole (129 mg, 1.10 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (35 mg, 0.110 mmol). The mixture was stirred at room temperature for 40 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83°C in a preheated oil bath for 72 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 60:40 hexanes : CH_2Cl_2 to yield *cis*-**5.67d** in 49% yield (100 mg, 0.270 mmol) as a white solid and *trans*-**5.67d** in 23% yield (50 mg, 0.127 mmol) as a colorless oil. ^1H NMR analysis of the crude reaction mixture indicated 2.6:1 dr (*cis*-**5.67d**: *trans*-**5.67d**)



Procedure: α -Indolyl allylvinyl ether **5.68d** (50 mg, 0.135 mmol) was dissolved in DCE (0.7 mL, 0.2 M). The mixture was then heated to 83°C in a preheated oil bath for 144 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to

50:50 hexanes : CH₂Cl₂ to yield **cis-5.67d** in 30% yield (15 mg, 0.041 mmol) as a white solid and **trans-5.67d** in 56% yield (28 mg, 0.075 mmol) as a colorless oil. ¹H NMR analysis of the crude reaction mixture indicated 1:1.8 dr (**cis-5.67d**: **trans-5.67d**).

cis-5.67d

Rf: 0.7 in 4 : 2 (Hexanes : CH₂Cl₂)

¹H NMR: (500 MHz, CDCl₃) δ = 7.77 (dd, J = 7.0, 2.0 Hz, 1H), 7.49 (bs, 1H), 7.12 – 7.03 (m, 3H), 6.83 – 6.77 (m, 2H), 6.70 – 6.63 (m, 2H), 6.56 (t, J = 7.7 Hz, 2H), 5.44 – 5.26 (m, 2H), 4.95 – 4.84 (m, 4H), 3.16 (ddt, J = 14.0, 6.4, 1.5 Hz, 1H), 2.66 – 2.55 (m, 3H), 2.52 – 2.39 (m, 3H), 1.95 – 1.75 (m, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 211.47, 139.70, 136.50, 135.21, 134.71, 126.66, 126.08, 125.64, 125.28, 122.01, 121.63, 121.36, 119.25, 117.41, 116.99, 115.85, 110.56, 55.32, 51.75, 46.79, 43.00, 35.74, 33.34, 18.50.

IR: f (cm⁻¹) = 3411, 2924, 1690, 1459

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 370.2165 calculated for C₂₆H₂₈NO; Found 370.2166.

trans-5.67d

Rf: 0.3 in 4 : 2 (Hexanes : CH₂Cl₂)

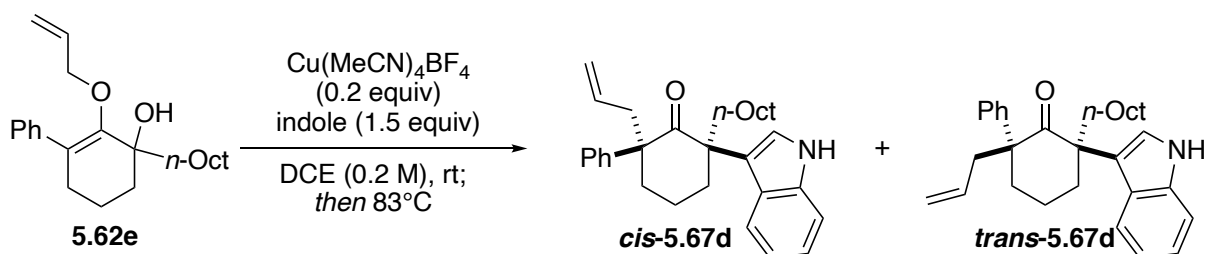
¹H NMR: (500 MHz, CDCl₃) δ = 8.08 (bs, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.43 – 7.33 (m, 5H), 7.30 – 7.24 (m, 2H), 7.22 – 7.15 (m, 1H), 7.15 – 7.09 (m, 1H), 7.01 (d, J = 2.5 Hz, 1H), 5.44 – 5.35 (m, 1H), 5.35 – 5.28 (m, 1H), 4.84 – 4.81 (m, 2H), 4.81 – 4.77 (m, 2H), 2.77 (ddt, J = 14.1, 6.5, 1.5 Hz, 1H), 2.57 (ddt, J = 14.0, 6.9, 1.3 Hz, 1H), 2.52 – 2.43 (m, 2H), 2.38 – 2.29 (m, 2H), 1.94 – 1.82 (m, 3H), 1.73 – 1.65 (m, 1H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 212.37, 140.24, 136.94, 134.81, 134.40, 128.50, 126.69, 126.36, 125.92, 122.10, 121.91, 121.39, 119.58, 117.63, 117.17, 116.86, 111.26, 54.92, 52.06, 46.36, 43.29, 29.21, 27.81, 16.76.

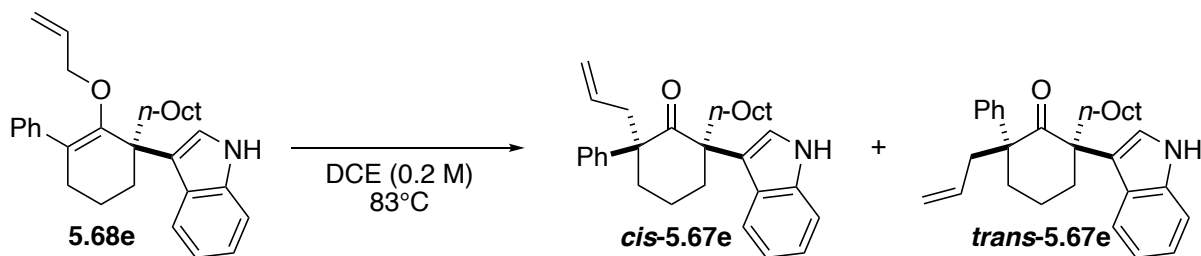
IR: $f(\text{cm}^{-1})$ = 3406, 2927, 1697, 1458

HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 370.2165$ calculated for $\text{C}_{26}\text{H}_{28}\text{NO}$; Found 370.2162.

(\pm)-(2*R*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-6-octyl-2-phenylcyclohexanone (*cis*-5.67e) and (\pm)-(2*R*,6*R*)-2-allyl-6-(1*H*-indol-3-yl)-6-octyl-2-phenylcyclohexanone (*trans*-5.67e)



Procedure: α -Hydroxyl enol ether **5.62d** (154 mg, 0.443 mmol) was dissolved in DCE (2.2 mL, 0.2 M). Indole (86 mg, 0.740 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (31 mg, 0.099 mmol). The mixture was stirred at room temperature for 6 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 24 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 60:40 hexanes : CH_2Cl_2 to yield **cis-5.67e** in 27% yield (55 mg, 0.125 mmol) as an off-white solid and **trans-5.67e** in 54% yield (105 mg, 0.238) as a yellow oil. ^1H NMR analysis of the crude reaction mixture indicated 1:1.9 dr (**cis-5.67e**: **trans-5.67e**).



Procedure: α -Indolyl allylvinyl ether **5.68e** (40 mg, 0.121 mmol) was dissolved in DCE (0.6 mL, 0.2 M). The mixture was then heated to 83 °C in a preheated oil bath for 90 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **cis-5.67e** in 28% yield (11 mg, 0.034 mmol) as a white solid and **trans-5.67e** in 57% yield (23 mg, 0.071 mmol) as pink solid. ¹H NMR analysis of the crude reaction mixture indicated 1:1.7 dr (**cis-5.67e**: **trans-5.67e**).

cis-5.67e

Rf: 0.6 in 4 : 2 (Hexanes : CH₂Cl₂)

¹H NMR: (400 MHz, CDCl₃) δ = 7.76 (d, J = 7.8 Hz, 1H), 7.47 (bs, 1H), 7.09 – 7.02 (m, 3H), 6.79 (d, J = 7.5 Hz, 2H), 6.68 (t, J = 7.2 Hz, 1H), 6.64 (d, J = 2.6 Hz, 1H), 6.57 (t, J = 7.8 Hz, 2H), 5.31 (ddt, J = 15.0, 11.2, 7.8 Hz, 1H), 4.89 (s, 1H), 4.86 (d, J = 5.0 Hz, 1H), 2.63 – 2.52 (m, 3H), 2.51 – 2.38 (m, 3H), 1.88 – 1.73 (m, 4H), 1.23 – 1.05 (m, 12H), 0.82 (t, J = 7.3 Hz, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 212.17, 139.94, 136.52, 134.86, 126.66, 126.24, 125.64, 125.22, 122.11, 121.50, 119.10, 117.31, 116.27, 110.46, 55.23, 52.34, 46.86, 38.11, 35.46, 33.03, 31.84, 30.19, 29.47, 29.25, 23.45, 22.61, 18.57, 14.06.

IR: f (cm⁻¹) = 2922, 1692, 1459, 1377, 1099.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 442.3104 calculated for C₃₁H₄₀NO; Found 442.3107.

trans-5.67e

Rf: 0.3 in 4 : 2 (Hexanes : CH₂Cl₂)

¹H NMR: (500 MHz, CDCl₃) δ = 8.06 (bs, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.42 – 7.34 (m, 5H), 7.28 (d, *J* = 6.8 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 2.6 Hz, 1H), 5.39 – 5.29 (m, 1H), 4.85 (d, *J* = 3.5 Hz, 1H), 4.82 (s, 1H), 2.64 (dd, *J* = 13.9, 6.9 Hz, 1H), 2.49 (dd, *J* = 14.0, 7.9 Hz, 1H), 2.40 – 2.31 (m, 2H), 2.00 – 1.79 (m, 5H), 1.77 – 1.60 (m, 3H), 1.27 – 1.00 (m, 12H), 0.83 (t, *J* = 7.2 Hz, 3H).

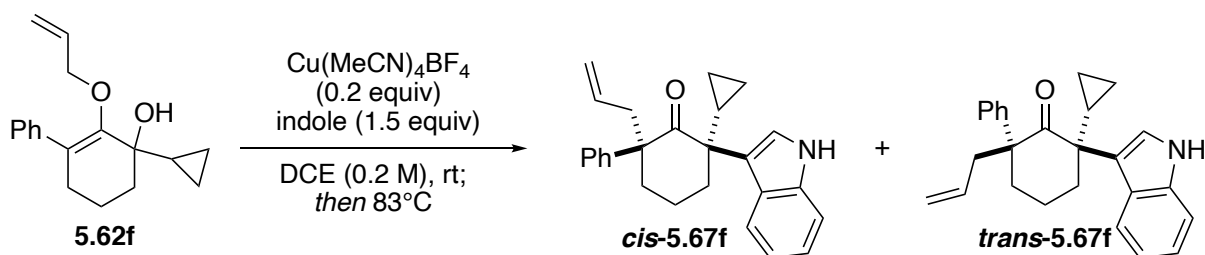
¹³C NMR: (125 MHz, CDCl₃) δ = 212.98, 140.31, 136.91, 134.53, 128.45, 126.62, 126.33, 125.98, 121.91, 121.76, 121.32, 119.39, 117.83, 117.56, 111.24, 54.78, 52.80, 46.66, 38.65, 31.79, 30.13, 29.93, 29.25, 29.15, 28.05, 24.12, 22.59, 16.97, 14.06.

IR: f (cm⁻¹) = 3384, 2925, 1694, 1459

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 442.3104 calculated for C₃₁H₄₀NO; Found 442.3104.

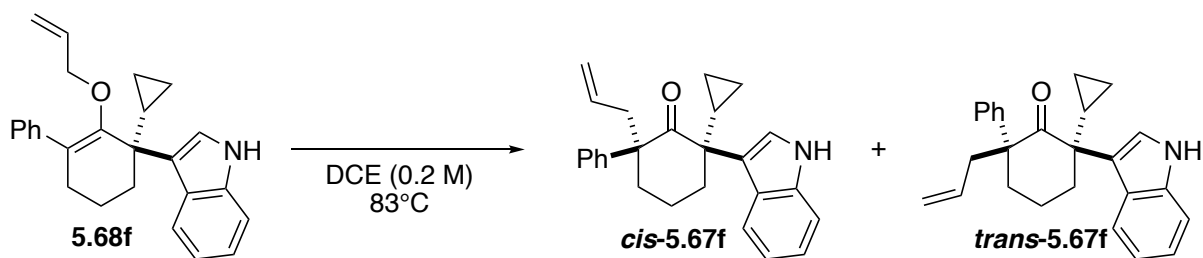
(±)-(2*R*,6*S*)-2-allyl-6-cyclopropyl-6-(1*H*-indol-3-yl)-2-phenylcyclohexanone (*cis*-5.67f) and

(±)-(2*S*,6*S*)-2-allyl-6-cyclopropyl-6-(1*H*-indol-3-yl)-2-phenylcyclohexan-1-one (*trans*-5.67f)



Procedure: α -Hydroxyl enol ether **5.62f** (150 mg, 0.5547 mmol) was dissolved in DCE (2.8 mL, 0.2 M). Indole (97 mg, 0.8320 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (38 mg, 0.1109 mmol). The mixture was stirred at room temperature for 2 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 22 hours. Once the Claisen rearrangement was complete as monitored by

TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 60:40 hexanes : CH₂Cl₂ to yield *cis*-**5.67f** in 49% yield (100 mg, 0.270 mmol) as a white solid and *trans*-**5.67d** in 23% yield (50 mg, 0.127 mmol) as a colorless oil. ¹H NMR analysis of the crude reaction mixture indicated 2.6:1 dr (*cis*-**5.67f**: *trans*-**5.67f**)



Procedure: α -Indolyl allylvinyl ether **5.68f** (55 mg, 0.1488 mmol) was dissolved in DCE (0.7 mL, 0.2 M). The mixture was then heated to 83 °C in a preheated oil bath for 136 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield *cis*-**5.67f** in 76% yield (42 mg, 0.1136 mmol) as a white solid and *trans*-**5.67f** in 25% yield (14 mg, 0.0379) as a colorless oil. ¹H NMR analysis of the crude reaction mixture indicated 1:1.7 dr (*cis*-**5.67f**: *trans*-**5.67f**).

cis-**5.67f**

¹H NMR: (400 MHz, CDCl₃) δ = 7.67 (d, *J* = 8.7 Hz, 1H), 7.54 (bs, 1H), 7.05 (d, *J* = 3.6 Hz, 2H), 7.03 – 6.98 (m, 1H), 6.93 – 6.90 (m, 2H), 6.72 – 6.68 (m, 1H), 6.66 – 6.62 (m, 2H), 6.60 (d, *J* = 2.6 Hz, 1H), 5.34 – 5.24 (m, 1H), 4.92 – 4.88 (m, 1H), 4.89 – 4.86 (m, 1H), 2.75 – 2.69 (m, 1H), 2.57 – 2.47 (m, 2H), 2.43 – 2.33 (m, 2H), 1.89 – 1.75 (m, 3H), 1.64 (m, 1H), 0.40 – 0.35 (m, 2H), 0.15 – 0.10 (m, 1H), 0.02 – -0.03 (m, 1H).

¹³C NMR: (125 MHz, CDCl₃) δ = 212.22, 139.62, 136.24, 134.82, 126.72, 126.55, 125.92, 125.29, 122.73, 121.95, 121.49, 119.10, 117.37, 113.91, 110.53, 55.10, 52.54, 46.75, 33.94, 32.91, 19.80, 18.50, 2.77, 0.53.

IR: f (cm⁻¹) = 3372, 2925, 2862, 1683, 1458, 1429, 1244, 1107, 964.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 370.2166 calculated for C₂₆H₂₇NO; Found 370.2163.

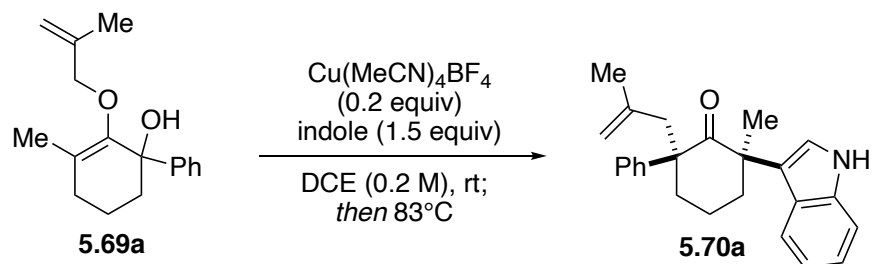
***trans*-5.67f**

¹H NMR: (500 MHz, CDCl₃) δ = 8.09 (bs, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.41 – 7.34 (m, 5H), 7.17 (t, J = 8.0 Hz, 1H), 7.09 (t, J = 8.1 Hz, 1H), 7.00 (d, J = 2.5 Hz, 1H), 5.44 – 5.35 (m, 1H), 4.88 – 4.81 (m, 2H), 2.57 (dd, J = 13.8, 6.9 Hz, 1H), 2.48 (dd, J = 13.9, 7.8 Hz, 1H), 2.34 – 2.21 (m, 2H), 1.90 – 1.77 (m, 1H), 1.78 – 1.70 (m, 2H), 1.54 – 1.45 (m, 1H), 1.18 (tt, J = 8.5, 5.6 Hz, 1H), 0.45 – 0.38 (m, 1H), 0.28 – 0.22 (m, 1H), 0.15 – 0.08 (m, 1H), -0.14 – -0.21 (m, 1H).

¹³C NMR: (125 MHz, CDCl₃) δ = 213.70, 140.39, 136.86, 134.56, 128.51, 126.63, 126.46, 126.27, 123.33, 121.82, 121.35, 119.66, 117.60, 114.35, 111.32, 54.84, 51.91, 46.33, 26.97, 26.15, 20.53, 16.53, 2.95, 0.55.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 370.2165 calculated for C₂₆H₂₇NO; Found 370.2162.

(±)-(2*R*,6*R*)-2-(1*H*-indol-3-yl)-2-methyl-6-(2-methylallyl)-6-phenylcyclohexanone (5.70a)



Procedure: α -Hydroxyl enol ether **5.69a** (176 mg, 0.6812 mmol) was dissolved in DCE (3.4 mL, 0.2 M). Indole (119 mg, 1.022 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (42 mg,

0.136 mmol). The mixture was stirred at room temperature for 16 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 24 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **5.70a** in 70% yield (171 mg, 0.252 mmol) as an orange solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.6 in 50 :50 (Hexanes : CH₂Cl₂)

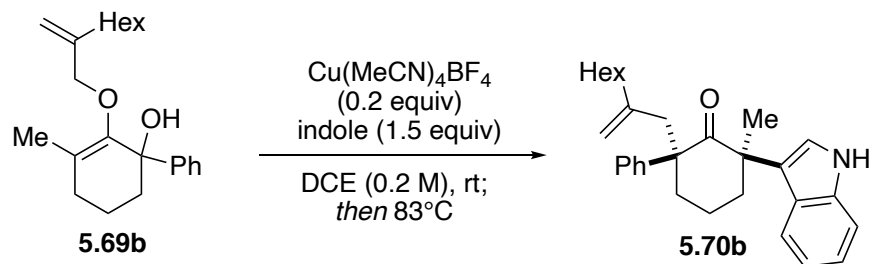
¹H NMR: (500 MHz, CDCl₃) δ = 7.70 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.09 – 7.01 (m, 3H), 6.88 – 6.84 (m, 2H), 6.70 – 6.65 (m, 2H), 6.58 (t, J = 7.6 Hz, 2H), 4.69 – 4.67 (m, 1H), 4.43 – 4.41 (m, 1H), 2.77 – 2.68 (m, 1H), 2.67 – 2.48 (m, 4H), 1.97 – 1.78 (m, 3H), 1.55 (s, 3H), 1.07 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 212.53, 142.90, 139.72, 136.40, 126.66, 126.16, 126.08, 125.33, 121.56, 121.33, 120.76, 119.10, 118.47, 114.72, 110.53, 54.88, 49.58, 49.07, 39.10, 33.47, 27.65, 24.23, 18.84.

IR: *f* (cm⁻¹) = 3433, 2962, 2927, 2854, 1685, 1639, 1334, 1245, 1188, 1082, 926.

HRMS: (ESI-TOF) *m/z*: (M+H)⁺ = 358.1166 calculated for C₂₅H₂₇NO; Found 358.2176.

(±)-(2*R*,6*R*)-2-(1*H*-indol-3-yl)-2-methyl-6-(2-methyleneoctyl)-6-phenylcyclohexan-1-one
(5.70b)



Procedure: α -Hydroxyl enol ether **5.69b** (89 mg, 0.2709 mmol) was dissolved in DCE (1.3 mL, 0.2 M). Indole (48 mg, 0.406 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (17 mg, 0.054 mmol). The mixture was stirred at room temperature for 16 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 60 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH_2Cl_2 to yield **5.70b** in 52% yield (60 mg, 0.140 mmol) as a purple oil. ^1H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.7 in 50 :50 (Hexanes : CH_2Cl_2)

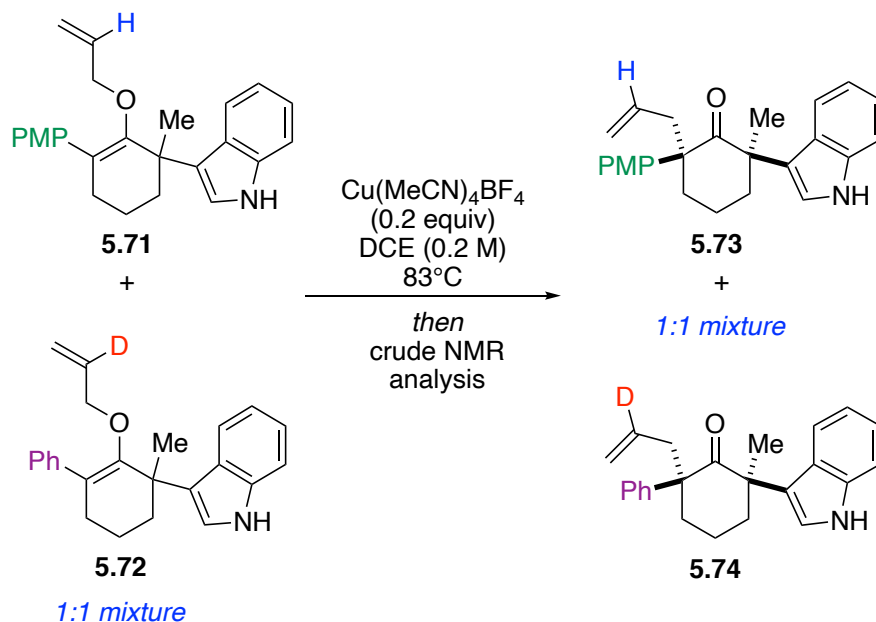
^1H NMR: (500 MHz, CDCl_3) δ = 7.72 (d, J = 7.5 Hz, 1H), 7.46 (bs, 1H), 7.09 – 7.03 (m, 3H), 6.84 (d, J = 7.2 Hz, 2H), 6.69 – 6.65 (m, 2H), 6.56 (t, J = 7.8 Hz, 2H), 4.67 (s, 1H), 4.42 (s, 1H), 2.75 – 2.68 (m, 2H), 2.60 – 2.55 (m, 1H), 2.52 – 2.44 (m, 2H), 1.97 – 1.77 (m, 3H), 1.56 (s, 3H), 1.32 – 1.26 (m, 1H), 1.20 – 1.13 (m, 2H), 1.11 – 1.02 (m, 5H), 1.00 – 0.87 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 212.75, 146.96, 139.62, 136.41, 126.61, 126.19, 126.10, 125.34, 121.54, 121.34, 120.76, 119.09, 118.54, 113.38, 110.54, 55.06, 49.08, 47.27, 39.10, 37.06, 33.51, 31.56, 28.84, 27.74, 27.63, 22.52, 18.82, 14.03.

IR: $f(\text{cm}^{-1})$ = 3401, 2955, 2924, 2856, 1691, 1636, 1459, 1373, 1245, 1106, 1083, 894.

HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 428.2948$ calculated for $\text{C}_{30}\text{H}_{37}\text{NO}$; Found 428.2945.

6.5.2 Experimental Procedures for Mechanistic Experiments



Procedure: α -Hydroxyl enol ether **5.72** (50 mg, 0.134 mmol) and α -Hydroxyl enol ether **5.72** (46 mg, 0.134 mmol) were dissolved in DCE (1.4 mL, 0.2 M), followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (17 mg, 0.054 mmol). The mixture was then heated to 83°C in a preheated oil bath for 16 hours. Once the both starting materials were consumed as monitored by TLC, the crude reaction mixture was concentrated under vacuum. The crude mixture was then purified by column chromatography using 100% hexanes to 20:80 hexanes : CH_2Cl_2 to **5.73** in 65% yield (30 mg, 0.087 mmol) as a pink solid and **5.74** in 50% yield (25 mg, 0.066 mmol) as a white solid. The ^1H NMR analysis of the crude reaction mixture indicated 1:1 mixture of desired products with no crossover of allyl groups during rearrangement.

(\pm)- (2*R*,6*R*)-2-(allyl-2-*d*)-6-(1*H*-indol-3-yl)-6-methyl-2-phenylcyclohexan-1-one (**5.74**)

Rf: 0.4 in 4:2 (Hexanes : CH_2Cl_2)

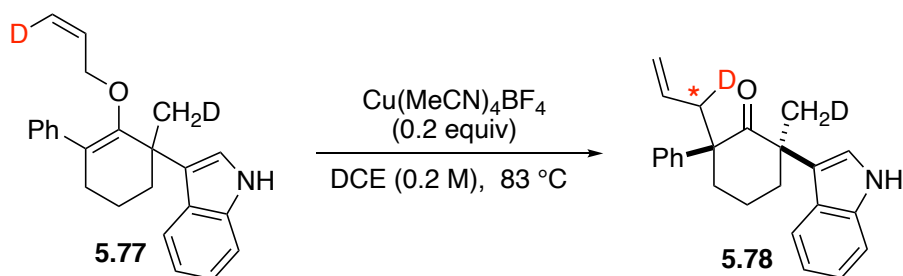
¹H NMR: (500 MHz, CDCl₃) δ = 7.70 (d, *J* = 7.8 Hz, 1H), 7.48 (s, 1H), 7.10 – 7.02 (m, 3H), 6.83 (d, *J* = 7.8 Hz, 2H), 6.71 – 6.66 (m, 2H), 6.59 (t, *J* = 7.7 Hz, 2H), 4.88 (s, 2H), 2.67 – 2.56 (m, 3H), 2.51 – 2.43 (m, 2H), 1.96 – 1.88 (m, 1H), 1.88 – 1.78 (m, 2H), 1.55 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 212.65, 139.63, 136.41, 126.71, 126.19, 125.72, 125.32, 121.58, 121.29, 120.76, 119.13, 118.33, 117.22, 110.57, 55.19, 49.03, 46.63, 39.21, 33.53, 27.42, 18.72.

IR: f (cm⁻¹) = 3405, 2926, 1692, 1510, 1460, 1248

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 374.2114 calculated for C₂₅H₂₈NO₂; Found 374.2115.

(±)-(2R,6R)-2-(allyl-1-d)-6-(1H-indol-3-yl)-6-(methyl-d)-2-phenylcyclohexan-1-one (5.78)



Procedure: α -Indolyl allylvinyl ether **5.77** (50 mg, 0.1451 mmol) was dissolved in DCE (0.7 mL, 0.2M). Cu(MeCN)₄•BF₄ (9 mg, 0.029 mmol) was added into the reaction solution followed heating to 83 °C in an oil bath and stirred for 19 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield 40% yield (20 mg, 0.058 mmol) as a white solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.4 in 50 :50 (Hexanes : CH₂Cl₂)

¹H NMR: (500 MHz, CDCl₃) δ = δ 7.70 (d, *J* = 8.7 Hz, 1H), 7.46 (bs, 1H), 7.10 – 7.01 (m, 3H), 6.82 (d, *J* = 8.2 Hz, 2H), 6.71 – 6.66 (m, 2H), 6.59 (t, *J* = 6.9 Hz, 2H), 5.34 – 5.25 (m, 1H), 4.89

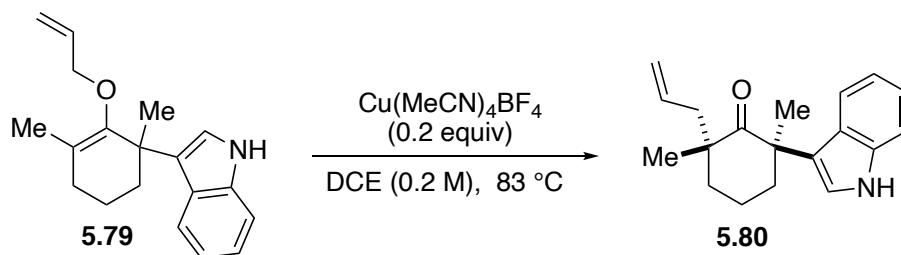
(s, 1H), 4.88 – 4.84 (m, 1H), 2.66 – 2.55 (m, 2H), 2.52 – 2.42 (m, 2H), 1.97 – 1.88 (m, 1H), 1.87 – 1.79 (m, 2H), 1.55 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 212.66, 139.62, 136.42, 134.73, 126.72, 126.20, 125.73, 125.32, 121.59, 121.30, 120.75, 119.15, 118.36, 117.39, 110.56, 55.13, 49.03, 39.22, 33.51, 27.42, 18.72, 18.62.

IR: f (cm⁻¹) = 2964, 2927, 1687, 1493, 1447, 1371.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 3.45.2072 calculated for C₁₉H₂₄DNO; Found 345.2074.

(±)-(2R,6R)-2-allyl-6-(1H-indol-3-yl)-2,6-dimethylcyclohexanone (5.80)



Procedure: α -Indolyl allylvinyl ether **5.79** (45 mg, 0.1599 mmol) was dissolved in DCE (0.8 mL, 0.2 M). $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (40 mg, 0.1255 mmol) was added into the reaction solution. The mixture was then heated to 83 °C in a preheated oil bath for 17 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **5.80** in 93% yield (42 mg, 0.1492 mmol) as a tan solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

Rf: 0.4 in 50 :50 (Hexanes : CH₂Cl₂)

¹H NMR: (500 MHz, CDCl₃) δ = 8.07 (bs, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.16 (t, J = 8.1 Hz, 1H), 7.11 (d, J = 2.5 Hz, 1H), 7.06 (t, J = 8.1 Hz, 1H), 5.83 – 5.73 (m, 1H),

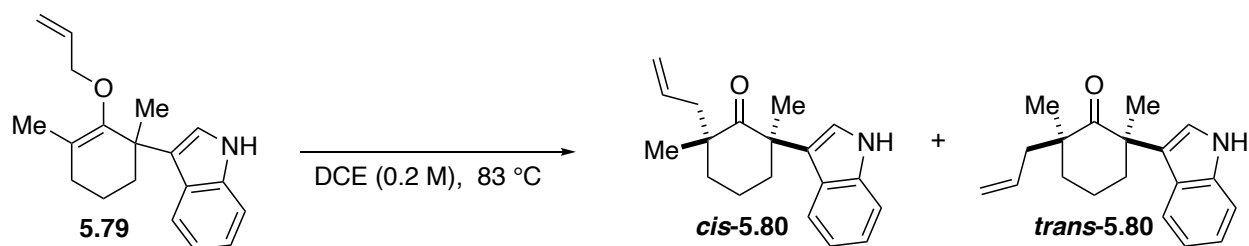
5.06 – 4.96 (m, 2H), 2.69 – 2.63 (m, 1H), 2.36 (dd, $J = 13.8, 6.9$ Hz, 1H), 2.26 – 2.16 (m, 2H), 1.86 – 1.73 (m, 3H), 1.69 – 1.62 (m, 1H), 1.47 (s, 3H), 0.68 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) $\delta = 216.40, 136.71, 135.14, 126.06, 121.95, 120.79, 120.11, 119.60, 119.44, 117.54, 111.00, 48.49, 48.44, 44.01, 38.62, 37.82, 27.98, 24.16, 18.29$.

IR: $f(\text{cm}^{-1}) = 3313, 2966, 2915, 2860, 1682, 1456, 1426, 1338, 1242, 1109, 991, 955, 913$.

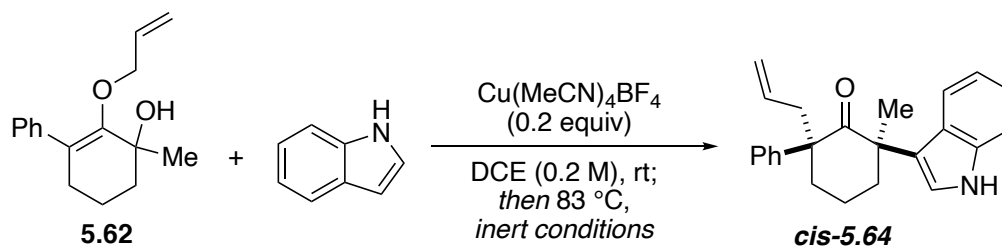
HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 282.1853$ calculated for $\text{C}_{19}\text{H}_{24}\text{NO}$; Found 282.1855.

(\pm)-(2R,6R)-2-allyl-6-(1H-indol-3-yl)-2,6-dimethylcyclohexanone (*cis*-5.80) and (\pm)-(2S,6R)-2-allyl-6-(1H-indol-3-yl)-2,6-dimethylcyclohexan-1-one (*trans*-5.80)

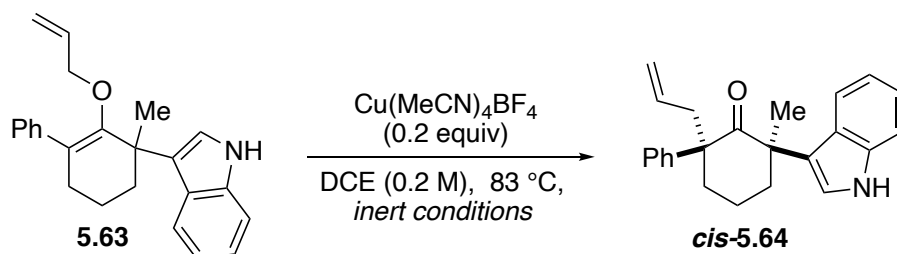


Procedure: α -Indolyl allylvinyl ether **5.79** (36 mg, 0.1279 mmol) was dissolved in DCE (0.1 mL, 0.2 M). The mixture was then heated to 83 °C in a preheated oil bath for 20 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH_2Cl_2 to yield an inseparable mixture of *cis*-5.80 and *trans*-5.80 in 89% yield (32 mg, 0.1137 mmol) as a brown solid ^1H NMR analysis of the crude reaction mixture indicated 3.6:1 dr (*cis*-5.80: *trans*-5.80).

Inert Conditions



Procedure: α -Hydroxyl enol ether **5.62** (111 mg, 0.454 mmol) was dissolved in DCE (2.2 mL, 0.2M). Indole (80 mg, 0.681 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (29 mg, 0.091 mmol). The solution removed from the glove box, and was stirred at room temperature for 24 hours, at which the starting material was fully consumed as monitored by TLC. The solution was then heated to 83 °C in a preheated oil bath for 24 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 90:10 hexanes : CH_2Cl_2 to yield **cis-5.64** in 87% yield (135 mg, 0.3930 mmol) as a white solid. ^1H NMR analysis of the crude reaction mixture indicated 20:1 dr.

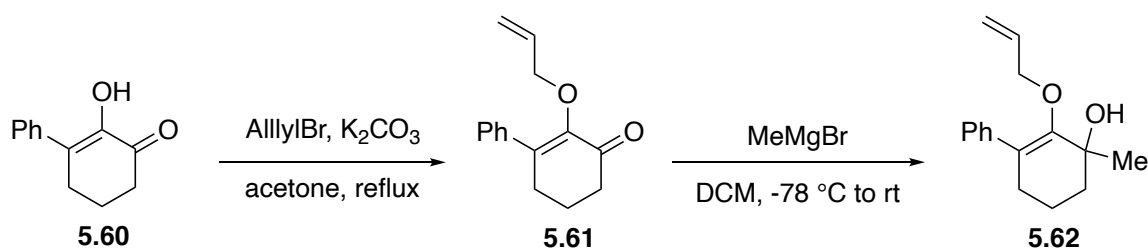


Procedure: In a glove box, α -Indolyl allylvinyl ether **5.79** (99 mg, 0.2883 mmol) was dissolved in degassed DCE (0.7 mL, 0.2 M). The solution removed from the glove box and the mixture was then heated to 83 °C in a preheated oil bath for 34 hours. Once the Claisen rearrangement was complete as monitored by TLC, the crude reaction mixture was concentrated under vacuum then

purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield ## in 88% yield (87 mg, 0.2532 mmol) as a white solid. ¹H NMR analysis of the crude reaction mixture indicated 20:1 dr.

6.5.3 Synthesis of α -Hydroxyl Enol Ethers and α -Indolyl Allylvinyl Ethers

2-(allyloxy)-3-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (5.62)



Procedure: Dione **5.60** (2.90 g, 15.494 mmol) was dissolved in acetone (70 mL, 0.2 M). Allylbromide (3.4 mL, 38.733 mmol) was added to the reaction mixture, followed by K₂CO₃ (9.0 g, 61.979 mmol). The solution was then warmed to reflux and stirred for 36 hours. Upon completion, the reaction mixture was cooled to 0 °C, and then quenched diluted with DI water (30 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude product **5.61** (1.54 g, 6.746 mmol) was taken onto the next step without further purification.

Procedure: Crude ketone **5.61** (1.54 g, 6.746 mmol) was dissolved in dry CH₂Cl₂ (33.0 mL, 0.2 M) and cooled to -78 °C. Methylmagnesium bromide (3.0 mL, 8.769 mmol, 3.0 M in THF) was then added dropwise. The solution was then warmed to room temperature and stirred for 30 minutes. The reaction was cooled to 0 °C, and then quenched with a saturated NH₄Cl solution (15mL) and further diluted with DI water (15 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, and

concentrated under vacuum. The crude material was purified by column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **5.61** in 81% yield (1.34 g, 5.484 mmol) as a yellow oil.

Rf: 0.5 in 80 : 20 (Hexanes : EtOAc)

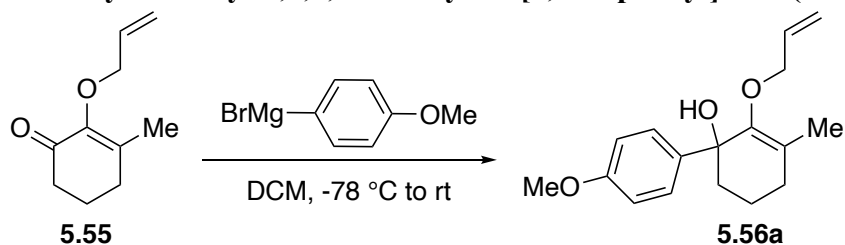
¹H NMR: (500 MHz, CDCl₃) δ = 7.37 – 7.31 (m, 5H), 7.24 – 7.20 (m, 1H), 5.73 (ddt, J = 16.0, 10.4, 5.7 Hz, 1H), 5.09 (dq, J = 17.1, 1.7 Hz, 1H), 5.05 (dq, J = 10.5, 1.4 Hz, 1H), 3.87 – 3.85 (m, 2H), 2.50 – 2.44 (m, 1H), 2.34 – 2.27 (m, 1H), 1.93 – 1.89 (m, 1H), 1.84 – 1.80 (m, 2H), 1.76 – 1.67 (m, 2H), 1.46 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 153.64, 140.10, 134.49, 128.32, 128.14, 126.70, 121.18, 116.64, 74.17, 71.29, 38.14, 31.30, 27.36, 19.91.

IR: f (cm⁻¹) = 3446, 2970, 2934, 1706, 1645, 1444, 1386, 1267, 1130, 1040, 985.

HRMS: (ESI-TOF) m/z : [(M-H₂O)+H]⁺ = 165.1273 calculated for C₁₁H₁₆O; Found 165.1273.

6-(allyloxy)-4'-methoxy-5-methyl-1,2,3,4-tetrahydro-[1,1'-biphenyl]-1-ol (5.56a)



Procedure: Ketone **5.55** (577 mg, 3.471 mmol) was dissolved in dry CH₂Cl₂ (17.0 mL, 0.2 M) and cooled to -78 °C. 4-Methoxyphenylmagnesium bromide (5.2 mL, 5.207 mmol, 1.0 M in THF) was then added dropwise. The solution was then warmed to room temperature and stirred for 1 hour. The reaction was cooled to 0 °C, and then quenched with a saturated NH₄Cl solution (8 mL) and further diluted with DI water (8 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, and

concentrated under vacuum. The crude material was purified by column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield 5.56a in 65% yield (621 mg, 2.264 mmol) as a colorless oil.

Rf: 0.4 in 80 : 20 (Hexanes : EtOAc)

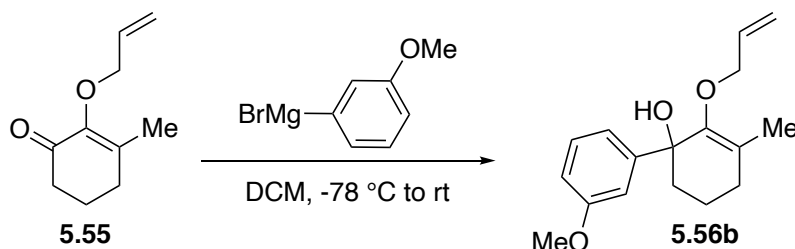
¹H NMR: (400 MHz, CDCl₃) δ = 7.41 (d, J = 8.9 Hz, 2H), 6.86 (d, J = 8.9 Hz, 2H), 5.80 (ddt, J = 15.8, 10.5, 5.4 Hz, 1H), 5.15 (dq, J = 17.2, 1.7 Hz, 1H), 5.07 (dq, J = 10.5, 1.4 Hz, 1H), 4.16 (t, J = 1.5 Hz, 1H), 4.14 (t, J = 1.5 Hz, 1H), 3.80 (s, 3H), 2.70 (bs, 1H), 2.24 – 2.07 (m, 2H), 2.02 – 1.94 (m, 1H), 1.92 – 1.84 (m, 1H), 1.78 (s, 3H), 1.68 – 1.60 (m, 1H), 1.54 – 1.42 (m, 1H).

¹³C NMR: (125 MHz, CDCl₃) δ = 158.41, 149.73, 138.84, 134.67, 127.29, 121.26, 116.33, 113.09, 75.41, 74.27, 55.16, 40.77, 31.02, 18.77, 16.77.

IR: f (cm⁻¹) = 3474.2933, 2865, 2834, 1608, 1507, 1244, 1162, 1034.

HRMS: (ESI-TOF) m/z : [(M-H₂O)+H]⁺ = 257.1537 calculated for C₁₇H₂₀O₂; Found 257.1529.

6-(allyloxy)-3'-methoxy-5-methyl-1,2,3,4-tetrahydro-[1,1'-biphenyl]-1-ol (5.56b)



Procedure: Ketone **5.55** (411 mg, 2.465 mmol) was dissolved in dry CH₂Cl₂ (12.0 mL, 0.2 M) and cooled to -78 °C. 3-Methoxyphenylmagnesium bromide (3.2 mL, 3.201 mmol, 1.0 M in THF) was then added dropwise. The solution was then warmed to room temperature and stirred for 1 hour. The reaction was cooled to 0 °C, and then quenched with a saturated NH₄Cl solution (8 mL) and further diluted with DI water (8 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, and

concentrated under vacuum. The crude material was purified by column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **5.56b** in 66% yield (447 mg, 1.629 mmol) as a colorless oil.

Rf: 0.4 in 80 : 20 (Hexanes : EtOAc)

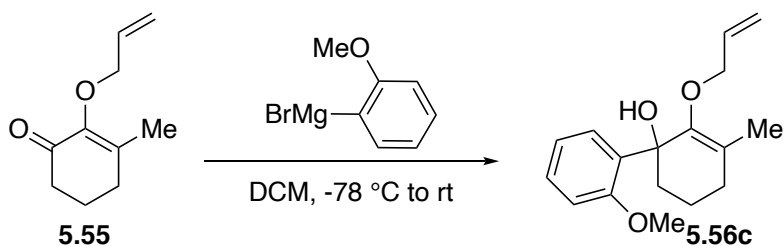
¹H NMR: (500 MHz, CDCl₃) δ = 7.24 (t, *J* = 7.9 Hz, 1H), 7.13 – 7.10 (m, 1H), 7.07 – 7.03 (m, 1H), 6.79 – 6.77 (m, 1H), 5.79 (ddt, *J* = 15.8, 10.6, 5.4 Hz, 1H), 5.15 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.07 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.15 (t, *J* = 1.5 Hz, 1H), 4.14 (t, *J* = 1.5 Hz, 1H), 3.82 (s, 3H), 2.76 (s, 1H), 2.22 – 2.10 (m, 2H), 2.02 – 1.96 (m, 1H), 1.93 – 1.87 (m, 1H), 1.78 (s, 3H), 1.68 – 1.62 (m, 1H), 1.56 – 1.52 (m, 2H).

¹³C NMR: (125 MHz, CDCl₃) δ = 159.35, 149.63, 148.68, 134.68, 128.70, 121.45, 118.75, 116.43, 112.16, 111.94, 75.66, 74.36, 55.21, 40.61, 31.05, 18.76, 16.83.

IR: f (cm⁻¹) = 3484, 2935, 2866, 2833, 1671, 1598, 1582, 1483, 1315, 1157, 1083.

HRMS: (ESI-TOF) m/z : [(M-H₂O)+H]⁺ = 257.1537 calculated for C₁₇H₂₀O₂; Found 257.1529.

6-(allyloxy)-2'-methoxy-5-methyl-1,2,3,4-tetrahydro-[1,1'-biphenyl]-1-ol (**5.56c**)



Procedure: Ketone **5.55** (576 mg, 3.455 mmol) was dissolved in dry CH₂Cl₂ (17.0 mL, 0.2 M) and cooled to -78 °C. 2-Methoxyphenylmagnesium bromide (5.2 mL, 5.182 mmol, 1.0 M in THF) was then added dropwise. The solution was then warmed to room temperature and stirred for 2 hours. The reaction was cooled to 0 °C, and then quenched with a saturated NH₄Cl solution (8 mL) and further diluted with DI water (8 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10

mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified by column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **5.56c** in 60% yield (568 mg, 2.070 mmol) as a colorless oil.

Rf: 0.4 in 80 : 20 (Hexanes : EtOAc)

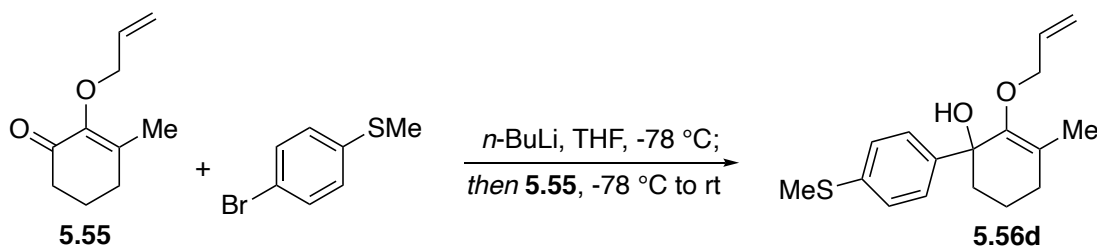
¹H NMR: (500 MHz, CDCl₃) δ = 7.35 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.22 (td, *J* = 8.1, 1.7 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 5.85 (ddt, *J* = 15.9, 10.7, 5.5 Hz, 1H), 5.15 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.03 (dd, *J* = 10.5, 1.7 Hz, 1H), 4.38 – 4.33 (m, 1H), 4.18 – 4.12 (m, 2H), 3.87 (s, 3H), 2.16 – 2.06 (m, 3H), 2.03 – 1.96 (m, 1H), 1.78 (s, 3H), 1.76 – 1.68 (m, 1H), 1.46 – 1.38 (m, 1H).

¹³C NMR: (125 MHz, CDCl₃) δ = 156.75, 148.92, 135.34, 133.32, 129.06, 127.94, 122.40, 120.60, 115.73, 111.33, 73.88, 55.40, 39.57, 31.06, 19.20, 16.90.

IR: f (cm⁻¹) = 3516, 2930, 2862, 2833, 1673, 1582, 1436, 1346, 1323, 1231, 1110, 1024.

HRMS: (ESI-TOF) m/z : [(M-H₂O)+H]⁺ = 257.1537 calculated for C₁₇H₂₀O₂; Found 257.1507.

6-(allyloxy)-5-methyl-4'-(methylthio)-1,2,3,4-tetrahydro-[1,1'-biphenyl]-1-ol (**5.56d**)



Procedure: 4-Bromophenyl methylsulfane (637 mg, 3.141 mmol) was dissolved in THF (12 mL) and cooled to -78°C. To the stirred solution, *n*-BuLi (1.3 mL, 2.5M in THF, 3.1405 mmol) was added dropwise and the reaction solution was stirred for 30 minutes. Ketone **5.55** (476 mg, 2.8550 mmol) dissolved in THF (4.0 mL) was added dropwise to the solution. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The mixture was cooled to 0°C and

quenched with a saturated NH_4Cl solution (8 mL). The mixture was further diluted with water (8 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **5.56d** in 52% yield (435 mg, 1.485 mmol) as a colorless oil.

Rf: 0.4 in 80 : 20 (Hexanes : EtOAc)

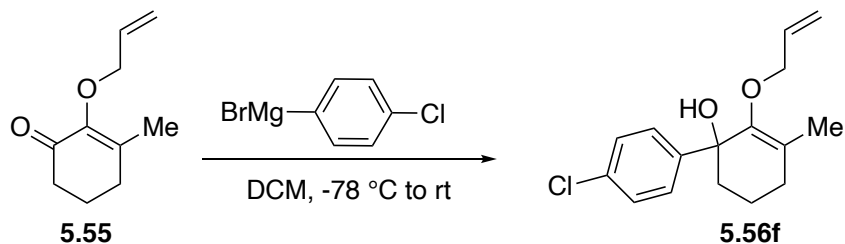
^1H NMR: (500 MHz, CDCl_3) δ = 7.42 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 5.79 (ddt, J = 15.9, 10.4, 5.3 Hz, 1H), 5.14 (dd, J = 17.4, 1.6 Hz, 1H), 5.06 (d, J = 10.5 Hz, 1H), 4.15 (t, J = 1.3 Hz, 1H), 4.14 (t, J = 1.3 Hz, 1H), 2.71 (bs, 1H), 2.47 (d, J = 1.4, 3H), 2.21 – 2.09 (m, 2H), 2.02 – 1.95 (m, 1H), 1.90 – 1.84 (m, 1H), 1.78 (s, 3H), 1.69 – 1.61 (m, 1H), 1.56 – 1.47 (m, 1H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 149.57, 143.91, 136.61, 134.64, 126.70, 126.25, 121.52, 116.38, 75.47, 74.20, 40.85, 31.06, 18.75, 16.78, 15.95.

IR: $f(\text{cm}^{-1})$ = 3477, 2982, 2921, 2863, 2831, 1671, 1595, 1489, 1438, 1396, 1245, 1160, 1040, 922.

HRMS: (ESI-TOF) m/z : $[(\text{M}-\text{H}_2\text{O})+\text{H}]^+ = 273.1308$ calculated for $\text{C}_{17}\text{H}_{20}\text{O}_2\text{S}$; Found 273.1306.

6-(allyloxy)-4'-chloro-5-methyl-1,2,3,4-tetrahydro-[1,1'-biphenyl]-1-ol (**5.56f**)



Procedure: Ketone **5.55** (586 mg, 3.525 mmol) was dissolved in dry CH_2Cl_2 (17.0 mL, 0.2 M) and cooled to $-78\text{ }^\circ\text{C}$. 4-Chlorophenyl magnesium bromide (5.3 mL, 1.0 M in THF, 5.288 mmol) was then added dropwise. The solution was then warmed to room temperature and stirred for 1

hour. The reaction was cooled to 0 °C, and then quenched with a saturated NH₄Cl solution (8 mL) and further diluted with DI water (8 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified by column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **5.56f** in 75% yield (739 mg, 2.651 mmol) as a yellow oil.

Rf: 0.3 in 80 : 20 (Hexanes : EtOAc)

¹H NMR: (500 MHz, CDCl₃) δ = 7.43 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 5.78 (ddt, J = 15.6, 10.6, 5.4 Hz, 1H), 5.14 (dd, J = 17.2, 1.6 Hz, 1H), 5.08 (dd, J = 10.5, 1.4 Hz, 1H), 4.15 (bs, 1H), 4.14 (bs, 1H), 2.76 (bs, 1H), 2.22 – 2.10 (m, 2H), 2.01 – 1.96 (m, 1H), 1.87 – 1.82 (m, 1H), 1.78 (s, 3H), 1.69 – 1.61 (m, 1H), 1.54 – 1.45 (m, 1H).

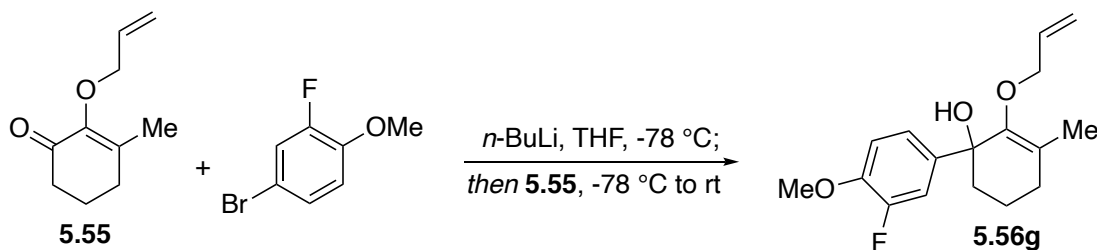
¹³C NMR: (125 MHz, CDCl₃) δ = 149.25, 145.31, 134.49, 132.55, 127.90, 127.63, 121.97, 116.59, 75.44, 74.30, 40.80, 30.99, 18.65, 16.82.

IR: f (cm⁻¹) = 3549, 2936, 2866, 2833, 1671, 1574, 1487, 1398, 1329, 1161, 1087, 1041, 1012.

HRMS: (ESI-TOF) m/z : [(M-H₂O)+H]⁺ = 262.1119 calculated for C₁₆H₁₇OCl; Found 262.1111.

6-(allyloxy)-3'-fluoro-4'-methoxy-5-methyl-1,2,3,4-tetrahydro-[1,1'-biphenyl]-1-ol

(**5.56g**)



Procedure: 4-Bromo-2-fluoro-1-methoxybenzene (0.51 mL, 3.044 mmol) was dissolved in THF (15 mL) and cooled to -78°C. To the stirred solution, *n*-BuLi (1.6 mL, 2.5M in THF, 3.044 mmol) was added dropwise and the reaction solution was stirred for 30 minutes. Ketone **5.55** (506 mg, 2.855 mmol) dissolved in THF (4.0 mL) was added dropwise to the solution. The reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. The mixture was cooled to 0°C and quenched with a saturated NH₄Cl solution (8 mL). The mixture was further diluted with water (8 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were then washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 80:20 hexanes : EtOAc to yield **5.56g** in 68% yield (602 mg, 1.941 mmol) as a yellow oil.

Rf: 0.6 in 80 : 20 (Hexanes : EtOAc)

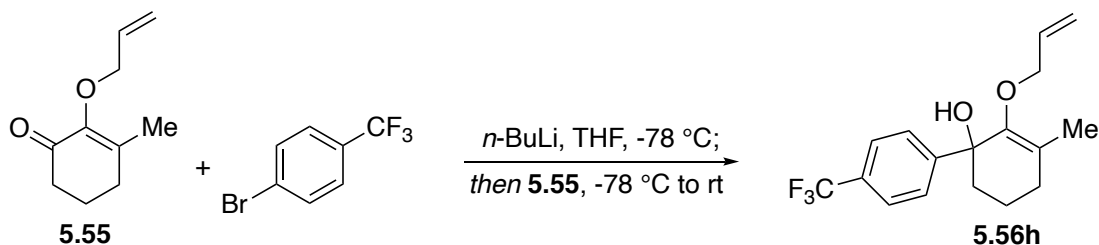
¹H NMR: (500 MHz, CDCl₃) δ = 7.24 (dd, *J* = 12.8, 2.2 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 6.90 (t, *J* = 8.6 Hz, 1H), 5.80 (ddt, *J* = 15.9, 10.6, 5.4 Hz, 1H), 5.15 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.08 (dd, *J* = 10.5, 1.3 Hz, 1H), 4.16 (s, 1H), 4.15 (s, 1H), 3.87 (s, 3H), 2.70 (s, 1H), 2.22 – 2.09 (m, 2H), 2.01 – 1.94 (m, 1H), 1.89 – 1.83 (m, 1H), 1.77 (s, 3H), 1.69 – 1.61 (m, 1H), 1.55 – 1.46 (m, 1H).

¹³C NMR: (125 MHz, CDCl₃) δ = 151.02, 149.41, 146.31, 140.24, 134.60, 121.71, 116.50, 114.40, 114.25, 112.85, 75.19, 74.32, 56.34, 40.76, 31.04, 18.75, 16.80.

IR: *f* (cm⁻¹) = 3471, 2935, 2866, 1837, 1620, 1584, 1509, 1307, 1271, 1159, 1087, 1027.

HRMS: (ESI-TOF) *m/z*: [(M-H₂O)+H]⁺ = 275.1442 calculated for C₁₇H₂₀O₂F; Found 275.1454.

**6-(allyloxy)-5-methyl-4'-(trifluoromethyl)-1,2,3,4-tetrahydro-[1,1'-biphenyl]-1-ol
(5.56h)**



Procedure: 1-Bromo-4-(trifluoromethyl)benzene (0.6 mL, 4.078 mmol) was dissolved in THF (11 mL) and cooled to -78°C . To the stirred solution, *n*-BuLi (1.7 mL, 2.5M in THF, 4.078 mmol) was added dropwise and the reaction solution was stirred for 45 minutes. Ketone **5.55** (523 mg, 2.855 mmol) dissolved in THF (4.0 mL) was added dropwise to the solution. The reaction mixture was allowed to warm to room temperature and stirred for 15 minutes. The mixture was cooled to 0°C and quenched with a saturated NH_4Cl solution (8 mL). The mixture was further diluted with water (8 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **5.56h** in 73% yield (716 mg, 2.292 mmol) as a yellow oil.

Rf: 0.5 in 80 : 20 (Hexanes : EtOAc)

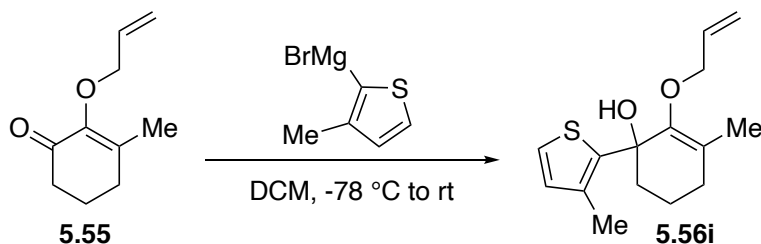
^1H NMR: (500 MHz, CDCl_3) δ = 7.62 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 5.78 (ddt, J = 15.9, 10.6, 5.4 Hz, 1H), 5.12 (dq, J = 17.2, 1.6 Hz, 1H), 5.08 (dq, J = 10.5, 1.4 Hz, 1H), 4.15 (s, 1H), 4.14 (s, 1H), 2.71 (s, 1H), 2.24 – 2.13 (m, 2H), 2.02 (ddd, J = 12.9, 9.4, 3.2 Hz, 1H), 1.90 – 1.84 (m, 1H), 1.80 (s, 3H), 1.73 – 1.65 (m, 1H), 1.58 – 1.49 (m, 1H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 150.96, 149.27, 134.50, 126.52, 124.83, 124.80, 122.31, 116.68, 75.67, 74.32, 40.99, 31.09, 18.70, 16.87.

IR: f (cm^{-1}) = 3458, 2937, 2868, 2836, 1617, 1409, 1322, 1160, 1119, 1087, 1016.

HRMS: (ESI-TOF) m/z : $[(\text{M}-\text{H}_2\text{O})+\text{H}]^+ = 295.1305$ calculated for $\text{C}_{17}\text{H}_{17}\text{OF}_3$; Found 295.1313.

2-(allyloxy)-3-methyl-1-(3-methylthiophen-2-yl)cyclohex-2-enol (**5.56i**)



Procedure: Ketone **5.55** (811 mg, 4.879 mmol) was dissolved in dry CH₂Cl₂ (24.0 mL, 0.2 M) and cooled to -78 °C. (3-Methylthiophen-2-yl)magnesium bromide (14.6 mL, 0.5M in THF, 7.319 mmol) was then added dropwise. The solution was then warmed to room temperature and stirred for 2 hours. The reaction was cooled to 0 °C, and then quenched with a saturated NH₄Cl solution (10 mL) and further diluted with DI water (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified by column chromatography using 100% hexanes to 70:30 hexanes : CH₂Cl₂ to yield **5.56i** in 61% yield (797 mg, 3.015 mmol) as a yellow oil.

Rf: 0.4 in 80 : 20 (Hexanes : EtOAc)

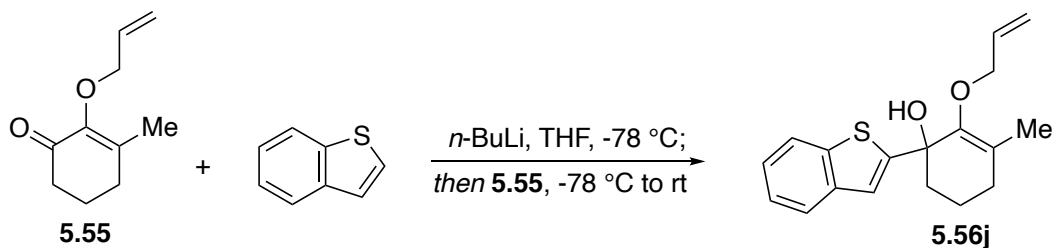
¹H NMR: (500 MHz, CDCl₃) δ = 7.04 (d, J = 5.1 Hz, 1H), 6.78 (d, J = 5.1 Hz, 1H), 5.84 (ddd, J = 15.85, 10.6, 5.4 Hz, 1H), 5.20 (dd, J = 17.3, 1.9 Hz, 1H), 5.11 (dd, J = 10.4, 1.5 Hz, 1H), 4.23 – 4.16 (m, 2H), 2.95 (bs, 1H), 2.20 (s, 3H), 2.15 – 2.13 (m, 2H), 2.10 – 1.98 (m, 2H), 1.75 (s, 3H), 1.75 – 1.68 (m, 1H), 1.66 – 1.59 (m, 2H).

¹³C NMR: (125 MHz, CDCl₃) δ = 149.33, 144.55, 134.84, 131.68, 131.39, 121.96, 121.46, 116.62, 74.32, 74.18, 39.17, 31.08, 19.10, 16.86, 14.57.

IR: *f* (cm⁻¹) = 3551, 2929, 2864, 1671, 1450, 1327, 1159, 1083, 1037, 923.

HRMS: (ESI-TOF) *m/z*: [(M-H₂O)+H]⁺ = 247.1151 calculated for C₁₅H₁₉OS; Found 247.1150.

2-(allyloxy)-1-(benzo[*b*]thiophen-2-yl)-3-methylcyclohex-2-enol (5.56j)



Procedure: Benzothiophene (396 mg, 2.951 mmol) was dissolved in THF (15 mL, 0.2 M) and cooled to -78°C . To the stirred solution, $n\text{-BuLi}$ (1.2 mL, 2.5 M in THF, 2.951 mmol) was added dropwise and the reaction solution was stirred for 1 hour. Ketone **5.55** (410 mg, 2.459 mmol) dissolved in THF (4.0 mL) was added dropwise to the solution. The reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. The mixture was cooled to 0°C and then quenched with a saturated NH_4Cl solution (8 mL). The mixture was further diluted with water (8 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **5.56j** in 76% yield (562 mg, 1.871 mmol) as an orange oil.

Rf: 0.4 in 80 : 20 (Hexanes : EtOAc)

^1H NMR: (500 MHz, CDCl_3) δ = 7.80 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.32 (t, J = 6.2 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.18 (s, 1H), 5.85 (ddt, J = 15.9, 10.6, 5.4 Hz, 1H), 5.21 (dd, J = 17.2, 1.6 Hz, 1H), 5.10 (dd, J = 10.5, 1.4 Hz, 1H), 4.24 (s, 1H), 4.23 (s, 1H), 3.35 (s, 1H), 2.27 – 2.19 (m, 1H), 2.18 – 2.04 (m, 3H), 1.81 (s, 3H), 1.76 – 1.68 (m, 2H).

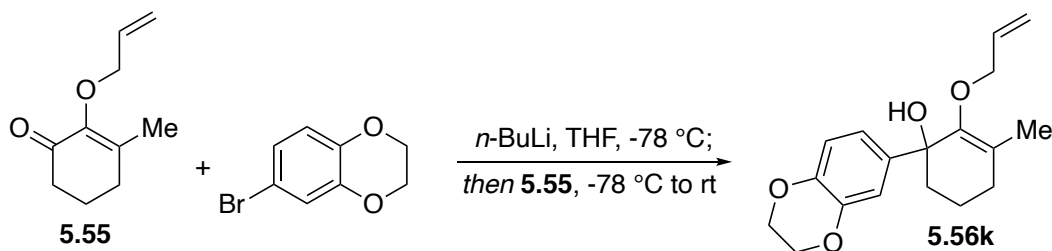
^{13}C NMR: (125 MHz, CDCl_3) δ = 153.26, 149.04, 139.68, 139.62, 134.36, 124.03, 123.78, 123.29, 122.27, 121.76, 120.65, 116.71, 74.93, 74.41, 39.72, 30.78, 18.84, 16.80.

IR: $f(\text{cm}^{-1})$ = 3434, 2911, 2865, 1673, 1456, 1434, 1331, 1246, 1156, 1039, 978.

HRMS: (ESI-TOF) m/z : $[(M-H_2O)+H]^+ = 283.1152$ calculated for $C_{18}H_{18}OS$; Found 283.1157.

2-(allyloxy)-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-methylcyclohex-2-enol

(5.56k)



Procedure: 6-Bromo-2,3-dihydrobenzo[*b*][1,4]dioxine (0.6 mL, 4.250 mmol) was dissolved in THF (10 mL, 0.2 M) and cooled to -78°C . To the stirred solution, $n\text{-BuLi}$ (1.7 mL, 2.5 M in THF, 4.250 mmol) was added dropwise and the reaction solution was stirred for 30 minutes. Ketone **5.55** (545 mg, 3.269 mmol) dissolved in THF (6.0 mL) was added dropwise to the solution. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was cooled to 0°C and quenched with a saturated NH_4Cl solution (8 mL). The mixture was further diluted with water (8 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 80:20 hexanes : EtOAc to yield **5.56k** in 39% yield (384 mg, 1.270 mmol) as a colorless oil.

Rf: 0.6 in 80 : 20 (Hexanes : EtOAc)

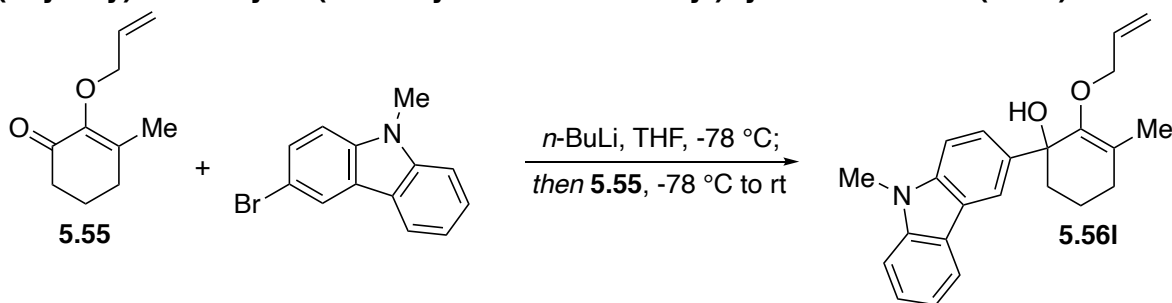
^1H NMR: (500 MHz, CDCl_3) δ = 7.02 (d, J = 2.1 Hz, 1H), 6.96 (dt, J = 8.4, 1.7 Hz, 1H), 6.80 (dd, J = 8.4, 1.7 Hz, 1H), 5.86 – 5.78 (m, 1H), 5.17 (dt, J = 17.2, 1.6 Hz, 1H), 5.08 (dt, J = 10.5, 1.5 Hz, 1H), 4.26 – 4.23 (m, 4H), 4.16 – 4.15 (m, 2H), 2.66 (d, J = 6.6 Hz, 1H), 2.20 – 2.06 (m, 2H), 1.99 – 1.93 (m, 1H), 1.89 – 1.84 (m, 1H), 1.76 (s, 3H), 1.67 – 1.59 (m, 1H), 1.56 – 1.46 (m, 1H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 149.75, 142.85, 142.40, 140.42, 134.80, 121.22, 121.21, 119.28, 116.49, 116.37, 115.34, 75.35, 74.35, 64.40, 64.38, 40.75, 31.10, 18.85, 16.81.

IR: $f(\text{cm}^{-1})$ = 3510, 2978, 2932, 2869, 1588, 1501, 1421, 1307, 1284, 1160, 1068, 990.

HRMS: (ESI-TOF) m/z : $[(\text{M}-\text{H}_2\text{O})+\text{H}]^+ = 285.1486$ calculated for $\text{C}_{18}\text{H}_{21}\text{O}_3$; Found 285.1485.

2-(allyloxy)-3-methyl-1-(9-methyl-9H-carbazol-3-yl)cyclohex-2-enol (5.56l)



Procedure: 3-Bromo-9-methyl-9H-carbazole (851 mg, 3.275 mmol) was dissolved in THF (10 mL, 0.2 M) and cooled to -78°C . To the stirred solution, $n\text{-BuLi}$ (1.3 mL, 2.5 M in THF, 3.275 mmol) was added dropwise and the reaction solution was stirred for 30 minutes. Ketone 5.55 (420 mg, 2.519 mmol) dissolved in THF (4.0 mL) was added dropwise to the solution. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The mixture was cooled to 0°C and quenched with a saturated NH_4Cl solution (8 mL). The mixture was further diluted with water (8 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 80:20 hexanes : EtOAc to yield 5.56l in 63% yield (549 mg, 1.580 mmol) as a colorless oil.

Rf: 0.7 in 80 : 20 (Hexanes : EtOAc)

^1H NMR: (500 MHz, CDCl_3) δ = 8.27 (d, J = 1.6 Hz, 1H), 8.13 (d, J = 7.7 Hz, 1H), 7.62 (dd, J = 8.5, 1.7 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.23 (d, J = 7.4 Hz, 1H), 5.81 – 5.73 (m, 1H), 5.12 (dd, J = 17.2, 1.6 Hz, 1H), 5.04 – 5.00 (m, 1H), 4.18

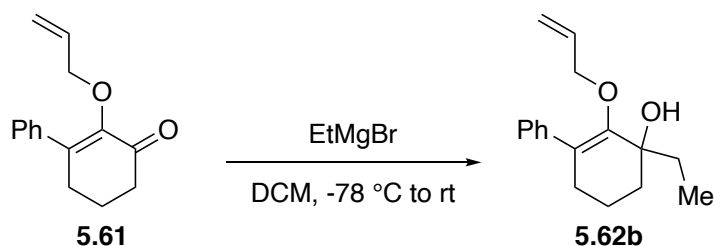
(d, $J = 6.5$ Hz, 2H), 3.85 (s, 3H), 2.90 (s, 1H), 2.23 (q, $J = 5.8$ Hz, 2H), 2.14 – 2.07 (m, 1H), 2.07 – 2.01 (m, 1H), 1.86 (s, 3H), 1.73 – 1.64 (m, 1H), 1.64 – 1.54 (m, 2H).

^{13}C NMR: (125 MHz, CDCl_3) $\delta = 150.07, 141.32, 140.16, 137.49, 134.74, 125.54, 124.35, 122.88, 122.32, 121.32, 120.34, 118.72, 117.88, 116.32, 108.37, 107.60, 76.07, 74.30, 41.38, 31.19, 29.11, 18.94, 16.92$.

IR: $f(\text{cm}^{-1}) = 3472, 2932, 2866, 2830, 1672, 1601, 1482, 1328, 1247, 1154, 990$.

HRMS: (ESI-TOF) m/z : $[(\text{M}-\text{H}_2\text{O})+\text{H}]^+ = 330.1853$ calculated for $\text{C}_{23}\text{H}_{24}\text{NO}$; Found 330.1867.

2-(allyloxy)-3-ethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (**5.62b**)



Procedure: Ketone **5.61** (503 mg, 2.203 mmol) was dissolved in dry CH_2Cl_2 (11.0 mL, 0.2 M) and cooled to -78°C . Ethylmagnesium bromide (1.1 mL, 3.0M in THF, 3.305 mmol) was then added dropwise. The solution was then warmed to room temperature and stirred for 1 hour. The reaction was cooled to 0°C , and then quenched with a saturated NH_4Cl solution (10 mL) and further diluted with DI water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The crude material was purified by column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **5.62b** in 87% yield (495 mg, 1.916 mmol) as a colorless oil.

Rf: 0.7 in 90 : 10 (Hexanes : EtOAc)

^1H NMR: (500 MHz, CDCl_3) $\delta = 7.36 - 7.29$ (m, 4H), 7.22 (tt, $J = 6.5, 1.6$ Hz, 1H), 5.77 – 5.68 (m, 1H), 5.09 (dq, $J = 17.2, 1.6$ Hz, 1H), 5.04 (dq, $J = 10.4, 1.2$ Hz, 1H), 3.86 (d, $J = 1.3$ Hz, 2H),

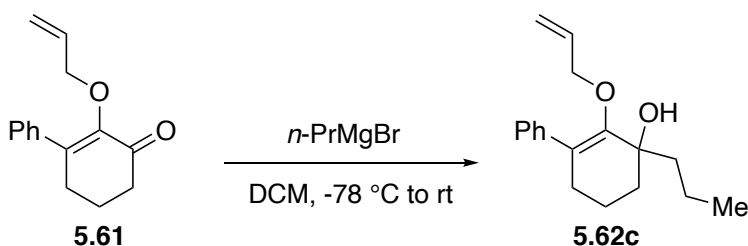
3.85 (d, $J = 1.4$ Hz, 1H), 2.53 – 2.47 (m, 1H), 2.29 – 2.22 (m, 1H), 1.88 – 1.67 (m, 7H), 0.97 (t, $J = 7.5$ Hz, 3H).

^{13}C NMR: (125 MHz, CDCl_3) $\delta = 153.56, 140.29, 134.65, 128.41, 128.15, 126.69, 122.13, 116.43, 74.14, 73.83, 33.92, 32.25, 31.37, 19.40, 8.53$.

IR: $f(\text{cm}^{-1}) = 3466, 2965, 2935, 1645, 1292, 1442, 1336, 1260, 1127, 978$.

HRMS: (ESI-TOF) m/z : $[(\text{M}-\text{H}_2\text{O})+\text{H}]^+ = 241.1587$ calculated for $\text{C}_{17}\text{H}_{21}\text{O}$; Found 241.1586.

2-(allyloxy)-3-propyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (**5.62c**)



Procedure: Ketone **5.61** (484 mg, 2.120 mmol) was dissolved in dry CH_2Cl_2 (10.0 mL, 0.2 M) and cooled to -78°C . Propylmagnesium bromide (1.5 mL, 2.0 M in THF, 2.756 mmol) was then added dropwise. The solution was then warmed to room temperature and stirred for 1 hour. The reaction was cooled to 0°C , and then quenched with a saturated NH_4Cl solution (10 mL) and further diluted with DI water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The crude material was purified by column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **5.62c** in 88% yield (509 mg, 1.869 mmol) as a colorless oil.

Rf: 0.4 in 80 : 20 (Hexanes : EtOAc)

^1H NMR: (500 MHz, CDCl_3) $\delta = 7.36 - 7.29$ (m, 4H), 7.23 – 7.20 (m, 1H), 5.73 (ddt, $J = 16.0, 10.7, 5.6$ Hz, 1H), 5.09 (dq, $J = 17.2, 1.6$ Hz, 1H), 5.04 (dq, $J = 10.4, 1.2$ Hz, 1H), 3.87 – 3.85 (m,

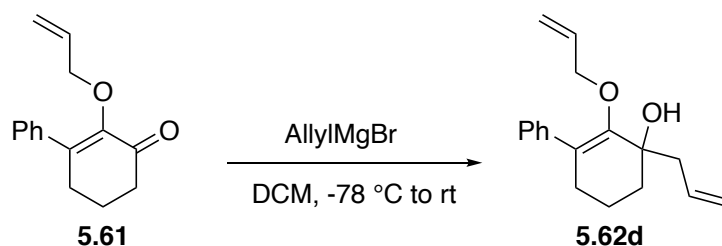
1H), 3.85 – 3.84 (m, 1H), 2.54 – 2.46 (m, 1H), 2.28 – 2.20 (m, 1H), 2.03 (s, 1H), 1.86 – 1.75 (m, 4H), 1.74 – 1.67 (m, 2H), 1.49 – 1.38 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 153.78, 140.32, 134.68, 128.42, 128.16, 126.68, 121.85, 116.43, 74.17, 73.51, 42.25, 34.68, 31.36, 19.50, 17.47, 14.71.

IR: $\tilde{\nu}$ (cm⁻¹) = 3470, 2934, 2870, 1734, 1647, 1492, 1443, 1331, 1132, 978, 923.

HRMS: (ESI-TOF) m/z : [(M-H₂O)+H]⁺ = 255.1744 calculated for C₁₈H₂₃O; Found 255.1730.

3-allyl-2-(allyloxy)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (**5.62d**)



Procedure: Ketone **5.61** (149 mg, 0.657 mmol) was dissolved in dry CH₂Cl₂ (3.3 mL, 0.2 M) and cooled to 0 °C. Allylmagnesium bromide (0.85 mL, 1 M in Et₂O, 7.011 mmol) was then added dropwise. The solution was then warmed to room temperature and stirred for 2 hours. The reaction was cooled to 0 °C, and then quenched with a saturated NH₄Cl solution (5 mL) and further diluted with DI water (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified by column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **5.62d** in 65% yield (114 mg, 0.421 mmol) as a yellow oil.

Rf: 0.4 in 80 : 20 (Hexanes : EtOAc)

¹H NMR: (500 MHz, CDCl₃) δ = 7.36 – 7.30 (m, 4H), 7.24 – 7.20 (m, 1H), 5.92 (ddt, J = 16.2, 10.8, 7.3 Hz, 1H), 5.73 (ddt, J = 16.0, 10.7, 5.5 Hz, 1H), 5.17 – 5.14 (m, 1H), 5.14 – 5.13 (m, 1H), 5.10 (dt, J = 17.2, 1.7 Hz, 2H), 5.05 (dt, J = 10.4, 1.5 Hz, 1H), 3.87 (t, J = 1.5 Hz, 1H), 3.86 (t, J =

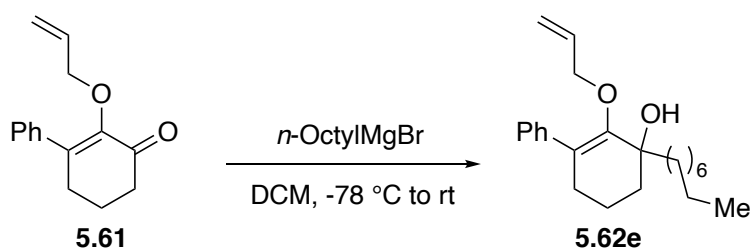
1.5 Hz, 1H), 2.55 (d, $J = 7.4$, Hz, 2H), 2.54 – 2.47 (m, 1H), 2.28 – 2.21 (m, 1H), 2.19 (bs, 1H), 1.90 – 1.75 (m, 3H), 1.75 – 1.68 (m, 1H).

^{13}C NMR: (125 MHz, CDCl_3) $\delta = 153.08, 140.14, 134.57, 134.23, 128.38, 128.17, 126.77, 122.34, 118.11, 116.50, 74.12, 72.89, 44.42, 34.85, 31.27, 19.29$.

IR: $f(\text{cm}^{-1}) = 2925, 1640, 1492, 1443, 1135, 980$

HRMS: (ESI-TOF) m/z : $[(\text{M}-\text{H}_2\text{O})+\text{H}]^+ = 253.1586$ calculated for $\text{C}_{18}\text{H}_{21}\text{O}$; Found 253.1583.

2-(allyloxy)-3-octyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (**5.62e**)



Procedure: Ketone **5.61** (1067 mg, 4.672 mmol) was dissolved in dry CH_2Cl_2 (23.0 mL, 0.2 M) and cooled to $-78\text{ }^\circ\text{C}$. Octylmagnesium bromide (3.5 mL, 2.0 M in THF, 7.011 mmol) was then added dropwise. The solution was then warmed to room temperature and stirred for 2 hours. The reaction was cooled to $0\text{ }^\circ\text{C}$, and then quenched with a saturated NH_4Cl solution (15 mL) and further diluted with DI water (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The crude material was purified by column chromatography using 100% hexanes to 90:10 hexanes : EtOAc to yield **5.62e** in 61% yield (1000 mg, 2.878 mmol) as a yellow oil.

Rf: 0.4 in 80 : 20 (Hexanes : EtOAc)

^1H NMR: (500 MHz, CDCl_3) $\delta = 7.36 - 7.29$ (m, 4H), 7.23 – 7.20 (m, 1H), 5.73 (ddt, $J = 15.9, 10.7, 5.5$ Hz, 1H), 5.10 (dq, $J = 17.2, 1.6$ Hz, 1H), 5.04 (dq, $J = 10.4, 1.3$ Hz, 1H), 3.87 – 3.86 (m,

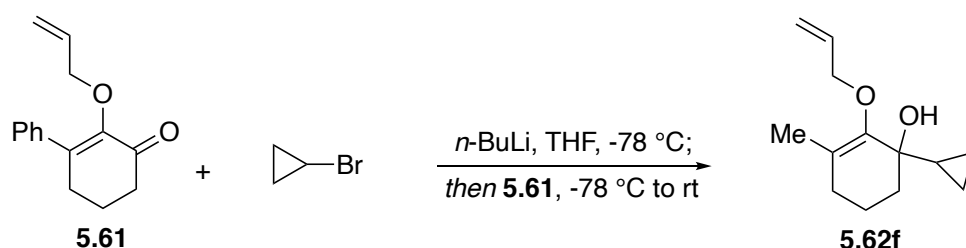
1H), 3.86 – 3.84 (m, 1H), 2.53 – 2.47 (m, 1H), 2.28 – 2.21 (m, 1H), 1.86 – 1.76 (m, 4H), 1.75 – 1.67 (m, 2H), 1.40 – 1.26 (m, 12H), 0.89 (t, *J* = 6.8 Hz, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 153.78, 140.30, 134.67, 128.40, 128.13, 126.66, 121.80, 116.34, 74.12, 73.53, 39.82, 34.62, 31.89, 31.34, 30.21, 29.60, 29.29, 24.10, 22.67, 19.48, 14.10.

IR: *f* (cm⁻¹) = 3483, 2925, 2853, 1645, 1467, 1442, 1378, 1264, 1160, 1130. 979.

HRMS: (ESI-TOF) *m/z*: (M-H₂O)⁺ = 325.2526 calculated for C₂₃H₃₃O; Found 325.2534.

2-(allyloxy)-3-cyclopropyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (**5.62f**)



Procedure: Bromocyclopropane (1.0 mL, 8.3181 mmol), was dissolved in THF (10 mL) and cooled to -78°C. To the stirred solution, *n*BuLi (3.3 mL, 2.5M in THF, 8.3181 mmol) was added dropwise and stirred for 30 minutes. Ketone **5.61** (633 mg, 2.7727 mmol) dissolved in THF (4.0 mL) was added dropwise to the solution. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was cooled to 0°C and quenched with a saturated NH₄Cl solution (8 mL). The mixture was further diluted with water (8 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were then washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 80:20 hexanes : EtOAc to yield **5.62f** in 88% yield (663 mg, 2.4521 mmol) as a colorless oil.

Rf:

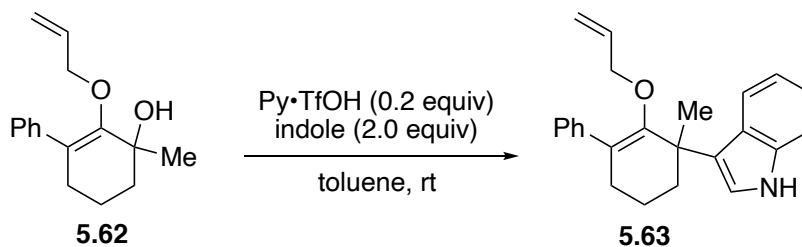
¹H NMR: (500 MHz, CDCl₃) δ = 7.38 (d, *J* = 7.3 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 5.72 (ddt, *J* = 16.1, 10.9, 5.6 Hz, 1H), 5.07 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.05 – 5.02 (m, 1H), 3.94 (dd, *J* = 12.3, 5.5 Hz, 1H), 3.80 (dd, *J* = 12.3, 5.7 Hz, 1H), 2.53 – 2.44 (m, 1H), 2.38 – 2.31 (m, 1H), 2.29 – 2.25 (m, 1H), 1.91 – 1.79 (m, 4H),

¹³C NMR: (125 MHz, CDCl₃) δ = 153.20, 140.02, 134.43, 128.24, 128.11, 126.68, 121.88, 116.55, 73.93, 71.15, 36.45, 31.09, 19.88, 19.53, 2.11, -0.43.

IR: f (cm⁻¹) = 3565, 3079, 3007, 2934, 1645, 1492, 1443, 1329, 1163, 1020, 973.

HRMS: (ESI-TOF) m/z : [(M-H₂O)+H]⁺ = 253.1587 calculated for C₁₈H₂₁O; Found 253.1582.

3-(2-(allyloxy)-3-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1*H*-indole (5.63)



Procedure: α -Hydroxyl enol ether **5.62** (96 mg, 0.393 mmol) was dissolved in toluene (2.0 mL, 0.2 M). Indole (92 mg, 0.786 mmol) was added, followed by addition of Py•TfOH (18 mg, 0.079 mmol). The mixture was stirred at room temperature for 24 hours, at which the starting material was fully consumed as monitored by TLC. The crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **5.63** in 93% yield (125 mg, 0. mmol) as an off-white solid.

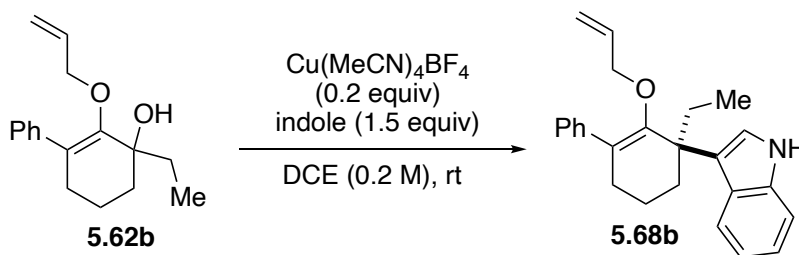
R_f: 0.6 in 50 : 50 (Hexanes : CH₂Cl₂)

¹H NMR: (500 MHz, CDCl₃) δ = 7.92 (bs, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 6.9 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.23 – 7.19 (m, 1H), 7.18 – 7.15 (m, 1H), 7.12 – 7.08 (m, 2H), 5.38 (ddt, *J* = 16.1, 10.7, 5.4 Hz, 1H), 4.79 – 4.77 (m, 1H), 4.77 – 4.74 (m, 1H), 3.66 (ddt, *J* = 8.7, 5.7, 1.6 Hz, 1H), 3.57 (ddt, *J* = 12.8, 5.2, 1.6 Hz, 1H), 2.59 (t, *J* = 6.2 Hz, 2H), 2.50 – 2.42 (m, 1H), 1.85 – 1.76 (m, 3H), 1.72 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 156.87, 141.57, 137.02, 134.73, 128.46, 128.11, 126.22, 125.95, 123.59, 122.10, 121.45, 120.80, 119.95, 118.90, 115.42, 111.29, 73.77, 40.47, 38.83, 31.73, 25.07, 20.22.

IR: f (cm⁻¹) = 3415, 2930, 2864, 2833, 1693, 1642, 1491, 1457, 1268, 1131, 990.

3-(2-(allyloxy)-3-ethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1*H*-indole (5.68b)



Procedure: α -Hydroxyl enol ether **5.62b** (130 mg, 0.503 mmol) was dissolved in DCE (2.5 mL, 0.2 M). Indole (88 mg, 0.755 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (31 mg, 0.101 mmol). The mixture was stirred at room temperature for 16 hours, at which the starting material was fully consumed as monitored by TLC. The crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 60:40 hexanes : CH₂Cl₂ to yield **5.68b** in 56% yield (101 mg, 0.282 mmol) as a purple oil.

Rf: 0.5 in 50 :50 (Hexanes : CH₂Cl₂)

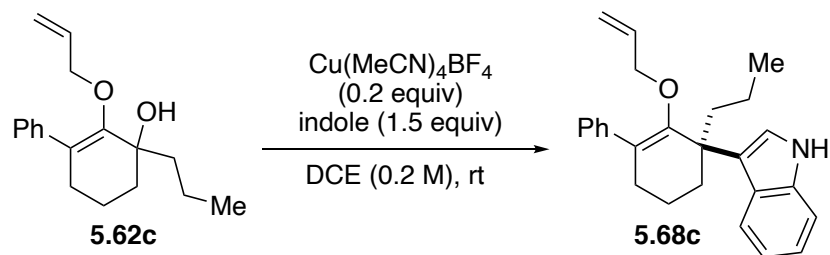
¹H NMR: (500 MHz, CDCl₃) δ = 8.07 (bs, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.41 – 7.34 (m, 5H), 7.28 (d, *J* = 6.8 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 2.6 Hz, 1H), 5.33 (ddt, *J* = 14.3, 9.5, 7.3 Hz, 1H), 4.84 (d, *J* = 3.1 Hz, 1H), 4.81 (s, 1H), 2.61 (dd, *J* = 13.9, 6.9 Hz, 1H), 2.49 (dd, *J* = 14.0, 7.8 Hz, 1H), 2.38 – 2.30 (m, 2H), 2.02 – 1.92 (m, 2H), 1.89 – 1.82 (m, 2H), 1.76 – 1.68 (m, 2H), 0.54 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 155.63, 141.95, 136.92, 134.82, 128.57, 128.10, 126.21, 123.27, 122.69, 121.33, 120.67, 118.83, 115.30, 111.22, 73.60, 44.55, 34.55, 31.82, 30.62, 20.09, 10.02.

IR: f (cm⁻¹) = 3414, 2931, 2869, 1643, 1456, 1336, 1129, 921.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 358.2165 calculated for C₂₅H₂₇NO; Found 358.2161.

3-(2-(allyloxy)-3-propyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1*H*-indole (5.68c)



Procedure: α -Hydroxyl enol ether **5.62c** (130 mg, 0.477 mmol) was dissolved in DCE (2.3 mL, 0.2 M). Indole (83 mg, 0.716 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (30 mg, 0.095 mmol). The mixture was stirred at room temperature for 17 hours, at which the starting material was fully consumed as monitored by TLC. The crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **5.68c** in 93% yield (166 mg, 0.447 mmol) as a purple oil.

Rf: 0.5 in 50 : 50 (Hexanes : CH₂Cl₂)

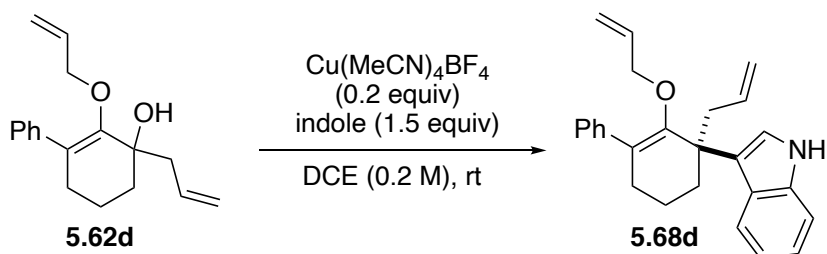
¹H NMR: (500 MHz, CDCl₃) δ = 7.94 (bs, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 2H), 7.36 – 7.31 (m, 3H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.11 – 7.06 (m, 2H), 5.38 (ddt, *J* = 16.3, 10.7, 5.4 Hz, 1H), 4.80 (d, *J* = 7.8 Hz, 1H), 4.77 (s, 1H), 3.69 (dd, *J* = 12.8, 5.7 Hz, 1H), 3.60 (dd, *J* = 12.8, 5.2 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.51 – 2.44 (m, 1H), 2.30 – 2.25 (m, 1H), 2.22 – 2.17 (m, 2H), 2.04 – 1.99 (m, 1H), 1.74 – 1.71 (m, 2H), 1.66 – 1.43 (m, 4H), 1.00 (t, *J* = 7.5 Hz, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 155.86, 141.95, 136.91, 134.80, 128.55, 128.09, 126.18, 126.15, 123.33, 122.62, 121.31, 121.28, 120.31, 118.81, 115.25, 111.23, 73.53, 44.33, 40.80, 35.23, 31.83, 20.18, 18.70, 15.07.

IR: f (cm⁻¹) = 3414, 2929, 2868, 1643, 1489, 1417, 1243, 1130, 908.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 372.2322 calculated for C₂₆H₂₉NO; Found 372.2318.

3-(3-allyl-2-(allyloxy)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1*H*-indole (**5.68d**)



Procedure: α -Hydroxyl enol ether **5.62d** (148 mg, 0.548 mmol) was dissolved in DCE (2.8 mL, 0.2 M). Indole (129 mg, 1.096 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (35 mg, 0.109 mmol). The mixture was stirred at room temperature for 15 hours, at which the starting material was fully consumed as monitored by TLC. The crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 75:25 hexanes : CH₂Cl₂ to yield **5.68d** in 47% yield (95 mg, 0.257 mmol) as a white solid.

Rf: 0.6 in 50:50 hexanes: CH₂Cl₂

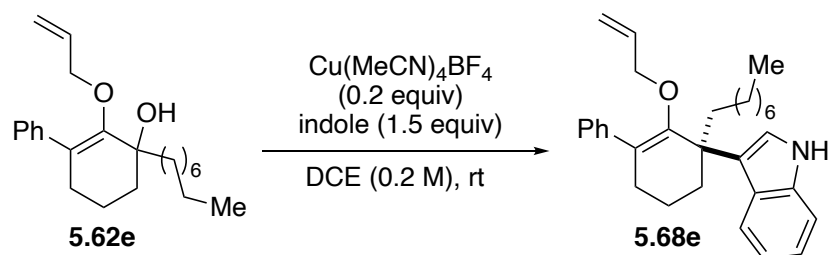
¹H NMR: (500 MHz, CDCl₃) δ = 7.96 (bs, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.37 – 7.31 (m, 3H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.13 – 7.07 (m, 2H), 6.14 – 6.04 (m, 1H), 5.38 (ddt, *J* = 16.3, 10.7, 5. Hz, 1H), 5.22 (d, *J* = 15.3 Hz, 1H), 5.13 (d, *J* = 10.2 Hz, 1H), .78 (s, 1H), 3.72 (dd, *J* = 12.8, 5.5 Hz, 1H), 3.59 (dd, *J* = 12.8, 5.2 Hz, 1H), 3.09 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.97 (dd, *J* = 14.0, 8.1 Hz, 1H), 2.61 – 2.54 (m, 1H), 2.51 – 2.44 (m, 1H), 2.31 – 2.24 (m, 1H), 2.09 – 2.03 (m, 1H), 1.81 – 1.66 (m, 2H)

¹³C NMR: (125 MHz, CDCl₃) δ = 155.15, 141.74, 136.89, 136.68, 134.70, 128.52, 128.11, 126.29, 126.05, 122.71, 122.64, 121.44, 121.20, 120.67, 118.93, 116.62, 115.33, 111.28, 73.52, 44.00, 42.62, 35.00, 31.73, 19.90.

IR: f (cm⁻¹) = 3411, 2925, 1719, 1617, 1458, 1132

HRMS: (ESI-TOF) m/z : ($M+H$)⁺ = 370.2165 calculated for C₂₆H₂₈NO; Found 370.2174.

3-(2-(allyloxy)-3-octyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1*H*-indole (5.68e)



Procedure: α -Hydroxyl enol ether **5.62e** (164 mg, 0.479 mmol) was dissolved in DCE (2.3 mL, 0.2 M). Indole (84 mg, 0.719 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (35 mg, 0.095 mmol). The mixture was stirred at room temperature for 13 hours, at which the starting material was fully consumed as monitored by TLC. The crude reaction mixture was concentrated

under vacuum then purified by column chromatography using 100% hexanes to 60:40 hexanes : CH₂Cl₂ to yield **5.68e** in 95% yield (200 mg, 0.438 mmol) as a brown oil.

Rf: 0.6 in in 50 : 50 (Hexanes : CH₂Cl₂)

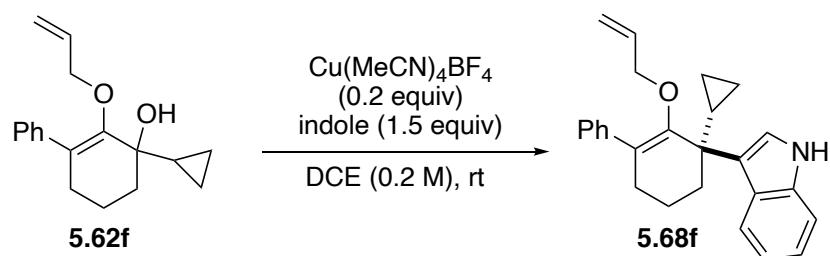
¹H NMR: (500 MHz, CDCl₃) δ = 7.98 – 7.92 (m, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.34 (t, *J* = 7.9 Hz, 3H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.12 – 7.05 (m, 2H), 5.39 (ddt, *J* = 16.2, 10.6, 5.3 Hz, 1H), 4.87 – 4.75 (m, 2H), 3.75 – 3.67 (m, 1H), 3.65 – 3.57 (m, 1H), 2.61 – 2.45 (m, 2H), 2.34 – 2.15 (m, 4H), 2.07 – 2.00 (m, 1H), 1.73 (m, 2H), 1.67 – 1.49 (m, 3H), 1.44 – 1.18 (m, 14H), 0.90 (t, *J* = 7.2 Hz, 3H)

¹³C NMR: (125 MHz, CDCl₃) δ = 155.88, 141.95, 136.91, 134.80, 128.54, 128.08, 126.17, 126.15, 123.32, 122.63, 121.29, 120.23, 118.79, 115.20, 111.23, 73.48, 44.29, 38.35, 35.10, 31.92, 31.83, 30.70, 29.72, 29.42, 25.40, 22.70, 20.17, 14.13.

IR: ν (cm⁻¹) = 3414, 2924, 1699, 1457

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 442.3104 calculated for C₃₁H₄₀NO; Found 442.3100.

(S)-3-(2-(allyloxy)-3-cyclopropyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1H-indole (5.68f**)**



Procedure: α -Hydroxyl enol ether **5.62f** (120 mg, 0.481 mmol) was dissolved in DCE (2.4 mL, 0.2 M). Indole (84 mg, 0.721 mmol) was added, followed by addition of Cu(MeCN)₄BF₄ (30 mg, 0.096 mmol). The mixture was stirred at room temperature for 3 hours, at which the starting material was fully consumed as monitored by TLC. The crude reaction mixture was concentrated

under vacuum then purified by column chromatography using 100% hexanes to 60:40 hexanes : CH₂Cl₂ to yield **5.68f** in 80% yield (142 mg, 0.384 mmol) as a white solid.

Rf: 0.6 in in 50 : 50 (Hexanes : CH₂Cl₂)

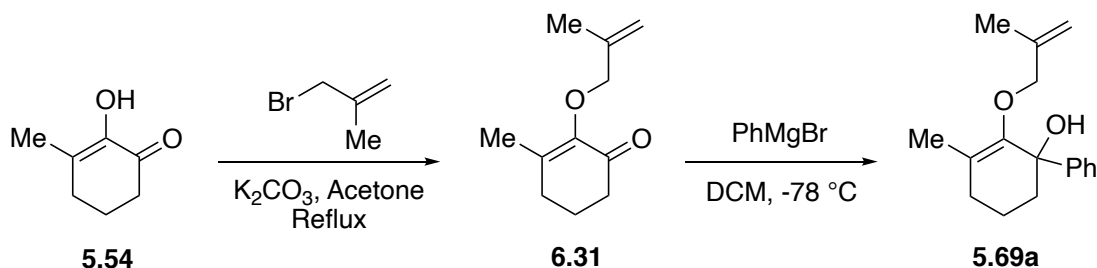
¹H NMR: (500 MHz, CDCl₃) δ = 7.97 (d, *J* = 8.1 Hz, 1H), 7.96 (bs, 1H), 7.51 – 7.46 (m, 2H), 7.40 – 7.34 (m, 3H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.18 (t, *J* = 6.9 Hz, 1H), 7.12 (t, *J* = 6.9 Hz, 1H), 5.36 (ddt, *J* = 16.3, 10.7, 5.4 Hz, 1H), 4.80 – 4.76 (m, 1H), 4.76 – 4.74 (m, 1H), 3.80 (ddt, *J* = 12.7, 5.5, 1.5 Hz, 1H), 3.62 (ddt, *J* = 12.7, 5.2, 1.6 Hz, 1H), 2.53 – 2.48 (m, 2H), 2.20 – 2.13 (m, 1H), 1.85 – 1.76 (m, 1H), 1.76 – 1.66 (m, 1H), 1.60 – 1.53 (m, 1H), 1.53 – 1.46 (m, 1H), 0.95 – 0.88 (m, 1H), 0.83 – 0.76 (m, 1H), 0.68 – 0.62 (m, 1H), 0.60 – 0.52 (m, 1H).

¹³C NMR: (125 MHz, CDCl₃) δ = 155.36, 141.92, 136.94, 134.82, 128.27, 128.10, 126.18, 126.17, 123.58, 123.46, 121.28, 121.18, 121.03, 118.81, 115.17, 111.21, 73.62, 43.07, 32.90, 31.46, 19.57, 18.81, 3.78, 1.81.

IR: f (cm⁻¹) = 2865, 2865, 1643, 1490, 1417, 1335, 1265, 1123.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 370.2165 calculated for C₂₆H₂₇NO; Found 370.2162.

5-methyl-6-((2-methylallyl)oxy)-1,2,3,4-tetrahydro-[1,1'-biphenyl]-1-ol (**5.69a**)



Procedure: Dione **5.54** (756 mg, 5.9762 mmol) was dissolved in Acetone (20 mL). To the stirred solution 3-bromo-2-methylprop-1-ene (1.5 mL, 14.9405 mmol) was added followed by K₂CO₃ (3.3 g, 23.9048 mmol). The reaction mixture was heated to reflux and stirred overnight. Upon

consumption of ## as monitored by TLC, the reaction mixture was cooled to 0°C. The mixture was diluted with water (10 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were then washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **6.31** in 64% yield (688 mg, 3.8171 mmol) as a colorless oil.

Rf: 0.7 in 80 : 20 (Hexanes : EtOAc)

¹H NMR: (500 MHz, CDCl₃) δ = 5.02 (s, 1H), 4.90 (s, 1H), 4.22 (s, 2H), 2.44 (t, J = 6.5 Hz, 2H), 2.38 (t, J = 5.9 Hz, 2H), 1.95 – 1.91 (m, 5H), 1.82 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 194.73, 148.09, 145.87, 141.86, 112.66, 75.60, 38.76, 31.53, 22.15, 19.70, 17.76.

IR: $f(\text{cm}^{-1})$ = 3434, 2941, 2875, 1729, 1672, 1377, 1193, 1153, 1046, 992.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 118.1223 calculated for C₁₁H₁₇O₂; Found 118.1213.

Procedure: Ketone **6.31** (600 mg, 3.3288 mmol) was dissolved in CH₂Cl₂ (17.0 mL). After cooling to -78°C, phenyl magnesium bromide (1.5mL, 3.0 M in THF, 4.3274 mmol) was added drop wise. The reaction mixture was then stirred at room temperature for 3 hours until the completion of reaction, as monitored by TLC. After cooling to 0°C, the reaction mixture was then quenched with a saturated NH₄Cl solution (8 mL). The mixture was further diluted with water (8 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were then washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 97:3 hexanes : EtOAc to yield **5.69a** in 73% yield (631 mg, 2.4423 mmol) as a colorless oil.

Rf: 0.7 in 80 : 20 (Hexanes : EtOAc)

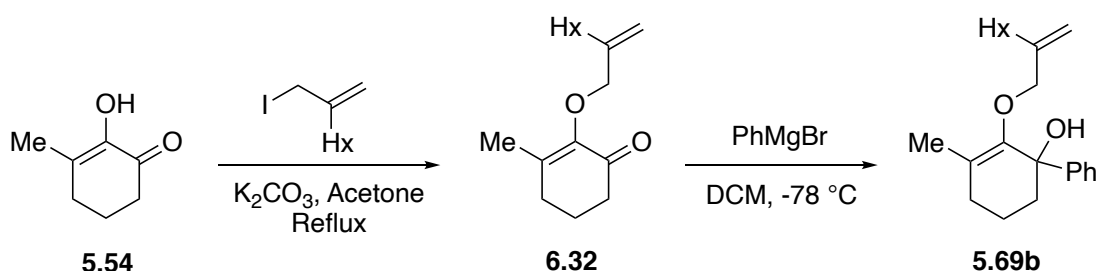
¹H NMR: (500 MHz, CDCl₃) δ = 7.51 (d, *J* = 8.3 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 4.82 (s, 1H), 4.77 (s, 1H), 4.05 (q, *J* = 12.7 Hz, 2H), 2.78 (s, 1H), 2.20 – 2.14 (m, 2H), 2.01 (ddd, *J* = 13.0, 9.9, 3.2 Hz, 1H), 1.92 – 1.87 (m, 1H), 1.80 (s, 3H), 1.72 – 1.63 (m, 1H), 1.57 (s, 3H), 1.56 – 1.48 (m, 1H).

¹³C NMR: (125 MHz, CDCl₃) δ = 149.82, 146.81, 142.53, 127.75, 126.70, 126.07, 121.57, 111.19, 75.79, 40.90, 31.11, 19.26, 18.78, 16.74.

IR: ν (cm⁻¹) = 3466, 2934, 2963, 1656, 1446, 1158, 1090, 992, 899.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 259.1693 calculated for C₁₇H₂₂O₂; Found 259.1682.

5-methyl-6-((2-methyleneoctyl)oxy)-1,2,3,4-tetrahydro-[1,1'-biphenyl]-1-ol (5.69b)



Procedure: Dione **5.54** (286 mg, 2.2738 mmol) was dissolved in Acetone (12 mL). To the stirred solution 2-(iodomethyl)oct-1-ene (860 mg, 3.4108 mmol) was added followed by K₂CO₃ (942 mg, 6.8214 mmol). The reaction mixture was heated to reflux and stirred overnight. Upon consumption of **5.54** as monitored by TLC, the reaction mixture was cooled to 0°C. The mixture was diluted with water (10 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were then washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 70:30 hexanes : CH₂Cl₂ to yield **6.32** in 70% yield (403 mg, 1.6096mmol) as a yellow oil and used immediately.

Procedure: Ketone **6.32** (303 mg, 1.210 mmol) was dissolved in CH₂Cl₂ (8 mL). After cooling to -78°C, phenyl magnesium bromide (0.7 mL, 3.0 M in THF, 2.0923 mmol) was added drop wise. The reaction mixture was then stirred at room temperature for 2 hours until the completion of reaction, as monitored by TLC. After cooling to 0°C, the reaction mixture was then quenched with a saturated NH₄Cl solution (5 mL). The mixture was further diluted with water (8 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were then washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 98:2 hexanes : EtOAc to yield **5.69b** in 61% yield (242 mg, 0.7367 mmol) as a yellow oil.

Rf: 0.3 in 80 : 20 (Hexanes : EtOAc)

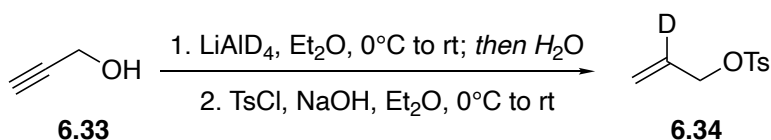
¹H NMR: (400 MHz, CDCl₃) δ = 7.51 – 7.47 (m, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.25 – 7.20 (m, 1H), 4.84 (s, 1H), 4.76 (s, 1H), 4.06 (q, J = 12.8 Hz, 2H), 2.77 (s, 1H), 2.16 (q, J = 5.7 Hz, 2H), 2.00 (ddd, J = 13.0, 9.8, 3.3 Hz, 1H), 1.92 – 1.81 (m, 3H), 1.79 (s, 3H), 1.71 – 1.61 (m, 1H), 1.55 – 1.48 (m, 1H), 1.31 – 1.14 (m, 9H), 0.86 (t, J = 7.1 Hz, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 149.88, 146.87, 127.77, 126.72, 126.09, 121.61, 110.24, 75.95, 75.79, 40.91, 32.97, 31.63, 31.15, 28.96, 27.51, 22.57, 18.81, 16.79, 14.06.

IR: $f(\text{cm}^{-1})$ = 3531, 2926, 2856, 1650, 1490, 1447, 1330, 1159, 1090, 988, 900.

HRMS: (ESI-TOF) m/z : [(M-H₂O)+H]⁺ = 311.2370 calculated for C₂₂H₃₀O; Found 311.2336.

Allyl-2-*d* 4-methylbenzenesulfonate (**6.34**)



Procedure: Propargyl alcohol **6.33** (250mg, 4.460 mmol) was dissolved in dry Et₂O (3 mL) and added dropwise to a suspension of LiAlD₄ in dry Et₂O (10 mL) at 0 °C under N₂ atmosphere. The resulting reaction mixture was allowed to warm to room temperature and stirred overnight (17h). The reaction mixture was again cooled to 0 °C and quenched water (1 mL) slowly. The reaction was further stirred for 3 hours and warmed to room temperature. The crude mixture was filtered through celite and washed with Et₂O (15 mL) and the resultant filtrate was dried over 3Å molecular sieves. The deuterated allyl alcohol obtained here is expected to be low boiling, hence it is used as such for next tosylation step after drying over molecular sieves.

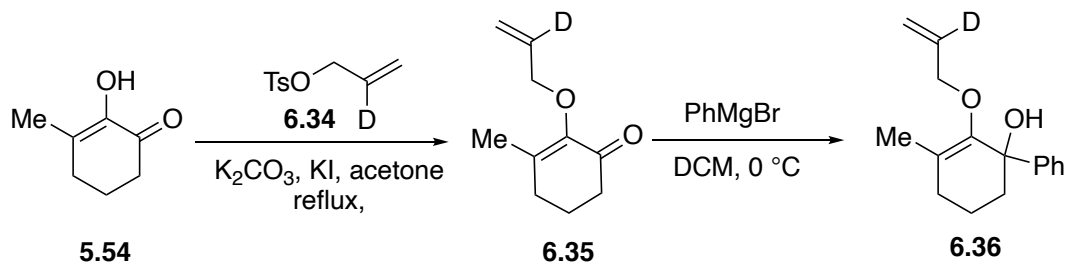
In a separate round bottom flask, NaH (102 mg, 4.460 mmol) was weighed under N₂ (g), and suspended in Et₂O (1 mL). The previously obtained crude reaction mixture was dissolved in Et₂O (25mL) and then added to this suspension at 0 °C. The reaction was stirred for 15 minutes, followed by addition of solution of Tosyl chloride (760 mg, 4.04 mmol) in dry Et₂O (10 mL). The resulting reaction mixture was stirred at room temperature for another 18 hours and quenched with saturated NH₄Cl solution (20 mL). The mixture was further diluted with water (10 mL), and the aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic layers were then washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 96:4 hexanes : EtOAc to yield **6.34** in 38% yield over 2 steps (353 mg, 1.660 mmol) as a colorless oil.

Rf: 0.5 in 80 : 20 (Hexanes : EtOAc)

¹H NMR: (500 MHz, CDCl₃) δ = 7.80 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 5.32 – 5.29 (m, 1H), 5.26 – 5.24 (m, 1H), 4.53 (s, 2H), 2.45 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 144.79, 133.25, 129.82, 127.90, 120.15, 70.67, 21.62.

6-((Allyl-2-*d*)oxy)-5-methyl-3,4-dihydro-[1,1'-biphenyl]-1(2*H*)-ol (6.36)



Procedure: Dione **5.54** (209 mg, 1.657 mmol) was dissolved in Acetone (15 mL) in sealed tube under N₂ atmosphere. To this stirred solution **6.34** (353 mg, 1.657 mmol) was added followed by addition of KI (275 mg, 1.657 mmol) and K₂CO₃ (457 mg, 3.314 mmol). The reaction mixture was heated to reflux and stirred overnight (24h). Upon completion as monitored by TLC, the reaction mixture was cooled and concentrated to remove acetone. The reaction mixture was re-dissolved in EtOAc and diluted with water (10 mL), and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were then washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **6.35** in 41% yield (111 mg, 0.663 mmol) as a yellow oil.

Rf: 0.3 in 80 : 20 (Hexanes : EtOAc)

¹H NMR: (500 MHz, CDCl₃) δ = 5.28 – 5.26 (m, 1H), 5.19 – 5.16 (m, 1H), 4.33 (s, 2H), 2.44 (t, J = 6.1 2H), 2.38 (t, J = 5.5 Hz, 2H), 1.96 – 1.90 (m, 5H).

¹³C NMR: (125 MHz, CDCl₃) δ = 194.91, 147.72, 146.50, 117.58, 72.79, 38.67, 31.48, 22.12, 17.92.

IR: $f(\text{cm}^{-1}) = 2930, 1672, 1630, 1378, 1150$.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 168.1129 calculated for C₁₀H₁₄DO₂; Found 168.1124.

Procedure: Ketone **6.36** (100 mg, 0.598 mmol) was dissolved in CH₂Cl₂ (5 mL). After cooling to 0 °C, phenyl magnesium bromide (0.3 mL, 3.0 M in Et₂O, 0.778 mmol) was added drop wise. The reaction mixture was then stirred for 3 hours at 0 °C until the completion of reaction, as monitored by TLC. The reaction mixture was then quenched with a saturated NH₄Cl solution (5 mL). The mixture was further diluted with water (8 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were then washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 98:2 hexanes : EtOAc to yield **6.36** in 84% yield (125mg, 0.509 mmol) as a colorless oil.

Rf: 0.5 in 80 : 20 (Hexanes : EtOAc)

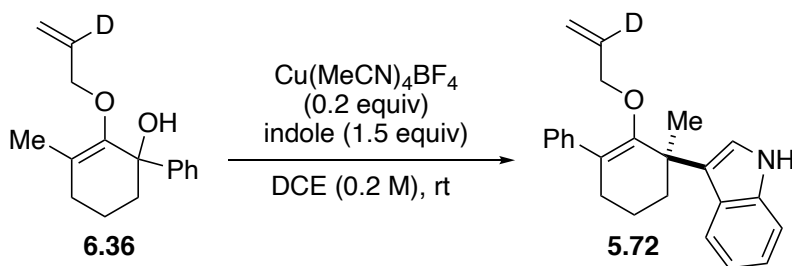
¹H NMR: (500 MHz, CDCl₃) δ = 7.52 – 7.48 (m, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.26 – 7.22 (m, 1H), 5.13 – 5.10 (m, 1H), 5.07 – 5.04 (m, 1H), 4.14 (s, 2H), 2.73 (s, 1H), 2.23 – 2.13 (m, 2H), 2.04 – 1.98 (m, 1H), 1.93 – 1.87 (m, 1H), 1.79 (s, 3H), 1.70 – 1.62 (m, 1H), 1.57 – 1.48 (m, 1H).

¹³C NMR: (125 MHz, CDCl₃) δ = 149.70, 146.77, 127.82, 126.81, 126.13, 121.54, 116.30, 75.74, 74.22, 40.81, 31.08, 18.76, 16.83.

IR: f (cm⁻¹) = 3476, 2934, 1697, 1448, 1161

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 228.1493 calculated for C₁₆H₁₈DO; Found 228.1492.

3-(2-((allyl-2-d)oxy)-3-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1H-indole(5.72)



Procedure: α -Hydroxyl enol ether **6.36** (112 mg, 0.457 mmol) was dissolved in DCE (2.5 mL, 0.2 M). Indole (81 mg, 0.685 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (29 mg, 0.091 mmol). The mixture was stirred at room temperature for 24 hours, at which the starting material was fully consumed as monitored by TLC. The crude reaction mixture was concentrated under vacuum and then purified by column chromatography using 100% hexanes to 60:40 hexanes : CH_2Cl_2 to yield **5.72** in 79% yield (123 mg, 0.357 mmol) as a white solid.

Rf: 0.5 in 50 :50 (Hexanes : CH_2Cl_2)

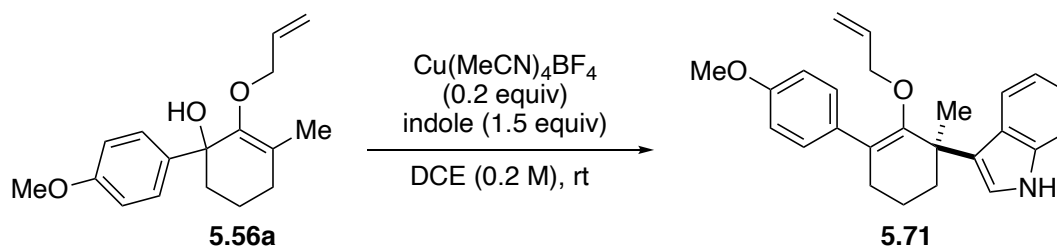
^1H NMR: (500 MHz, CDCl_3) δ = 7.92 (bs, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.44 (dd, J = 8.2, 1.4 Hz, 2H), 7.37 – 7.30 (m, 3H), 7.22 – 7.19 (m, 1H), 7.19 – 7.15 (m, 1H), 7.11 – 7.07 (m, 2H), 4.78 – 4.76 (m, 1H), 4.76 – 4.74 (m, 1H), 3.65 (d, J = 12.8 Hz, 1H), 3.57 (d, J = 12.8 Hz, 1H), 2.58 (t, J = 6.2 Hz, 2H), 2.49 – 2.42 (m, 1H), 1.83 – 1.75 (m, 3H), 1.71 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 156.88, 141.57, 137.03, 128.47, 128.12, 126.22, 125.96, 123.61, 122.10, 121.46, 120.82, 119.96, 118.91, 115.30, 111.30, 73.70, 40.48, 38.84, 31.74, 25.07, 20.23.

IR: $f(\text{cm}^{-1})$ = 3413, 2926, 1696, 1597, 1491, 1132

HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+ = 345.2071$ calculated for $\text{C}_{24}\text{H}_{25}\text{DNO}$; Found 345.2075.

(R)-3-(2-(allyloxy)-4'-methoxy-3-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1H-indole(5.71)



Procedure: α -Hydroxyl enol ether **5.56a** (171 mg, 0.624 mmol) was dissolved in DCE (3 mL, 0.2 M). Indole (110 mg, 0.936 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (39 mg,

0.124 mmol). The mixture was stirred at room temperature for 17 hours, at which the starting material was fully consumed as monitored by TLC. The crude reaction mixture was concentrated under vacuum and then purified by column chromatography using 100% hexanes to 55:45 hexanes : CH₂Cl₂ to yield **5.71** in 80% yield (186 mg, 0.498 mmol) as a white solid.

Rf: 0.6 in 50 :50 (Hexanes : CH₂Cl₂)

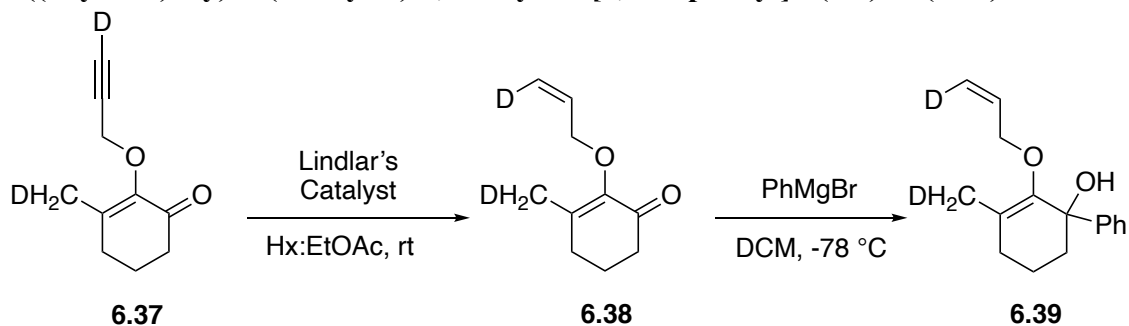
¹H NMR: (500 MHz, CDCl₃) δ = 7.94 (bs, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 6.9 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.47 – 5.39 (m, 1H), 4.84 – 4.81 (m, 1H), 4.81 – 4.78 (m, 1H), 3.82 (s, 3H), 3.71 – 3.61 (m, 2H), 2.57 (t, *J* = 6.3 Hz, 2H), 2.49 – 2.41 (m, 1H), 1.85 – 1.74 (m, 3H), 1.71 (s, 3H).

¹³C NMR: (125 MHz, CDCl₃) δ = 157.91, 156.43, 137.02, 134.85, 133.78, 129.49, 125.95, 123.67, 122.06, 121.40, 120.80, 119.29, 118.86, 115.38, 113.50, 111.28, 73.57, 55.20, 40.47, 38.87, 31.78, 25.01, 20.23.

IR: f (cm⁻¹) = 3413, 2925, 1509, 1243, 1099, 1012

HRMS: (ESI-TOF) m/z : (*M*+*H*)⁺ = 374.2114 calculated for C₂₅H₂₈NO₂; Found 374.2110.

(Z)-6-((allyl-3-d)oxy)-5-(methyl-d)-3,4-dihydro-[1,1'-biphenyl]-1(2H)-ol (6.39)



Procedure: Ketone **6.37** (1.66 g, 10.061 mmol) was dissolved in a 1:1 mixture of hexanes:EtOAc (0.1 M). Lindlar's catalyst (167 mg, 0.503 mmol) was added to the reaction mixture, and purged 3 times with hydrogen gas. The reaction was stirred for 3 days, at which the starting material was

fully consumed as monitored by TLC. The reaction mixture was filtered through a celite plug, and concentrated under vacuum and **6.38** (1.66 g, 10.061 mmol) was used without further purification.

Procedure: Ketone **6.38** (1.66 g, 10.061 mmol) was dissolved in CH₂Cl₂ (50mL). After cooling to -78°C, phenyl magnesium bromide (4.0 mL, 3.0 M in THF, 11.917 mmol) was added drop wise. The reaction mixture was then stirred at room temperature for 30 minutes until the completion of reaction, as monitored by TLC. After cooling to 0°C, the reaction mixture was then quenched with a saturated NH₄Cl solution (20mL). The mixture was further diluted with water (25 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were then washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The crude material was purified with column chromatography using 100% hexanes to 95:5 hexanes : EtOAc to yield **6.39** in 89% yield (2.02g, 8.849 mmol) as a colorless oil.

Rf: 0.5 in 80 :20 (Hexanes : EtOAc)

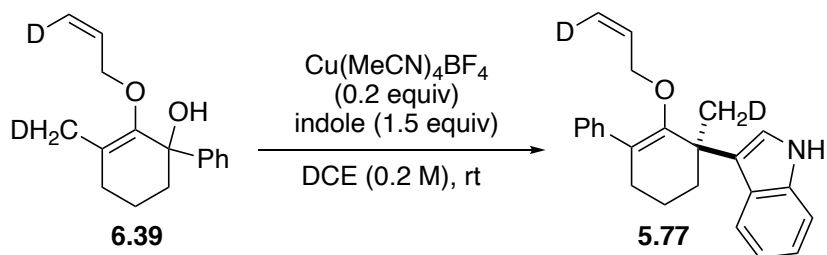
¹H NMR: (500 MHz, CDCl₃) δ = 7.50 (dd, J = 8.2, 1.3 Hz, 2H), 7.35 – 7.30 (m, 3H), 7.26 – 7.22 (m, 1H), 5.79 – 5.73 (m, 1H), 5.04 (dt, J = 10.5, 1.4 Hz, 1H), 4.15 (s, 1H), 4.14 (s, 1H), 2.72 (s, 1H), 2.22 – 2.11 (m, 2H), 2.04 – 1.97 (m, 1H), 1.93 – 1.87 (m, 1H), 1.79 (s, 3H), 1.69 – 1.62 (m, 1H), 1.55 – 1.47 (m, 1H).

¹³C NMR: (125 MHz, CDCl₃) δ = 146.77, 134.58, 127.82, 126.82, 126.14, 125.81, 121.56, 115.99, 75.75, 74.28, 40.81, 31.06, 18.67, 16.84.

IR: f (cm⁻¹) = 3488, 2930, 2862, 1674, 1491, 1447, 1071.

HRMS: (ESI-TOF) m/z : [(M-H₂O)+H]⁺ = 228.1493 calculated for C₁₆H₁₈DO; Found 228.1490

(±)-(R,Z)-3-(2-((allyl-3-d)oxy)-3-(methyl-d)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1H-indole (5.77)



Procedure: α -Hydroxyl enol ether **6.39** (2.02 g, 8.233 mmol) was dissolved in DCE (29 mL, 0.2 M). Indole (1.4 g, 12.350 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (367 mg, 1.169 mmol). The mixture was stirred at room temperature for 18 hours, at which the starting material was fully consumed as monitored by TLC. The crude reaction mixture was concentrated under vacuum and then purified by column chromatography using 100% hexanes to 55:45 hexanes : CH_2Cl_2 to yield **5.77** in 86% yield (2.44 g, 7.083 mmol) as a white solid.

Rf: 0.6 in 50 :50 (Hexanes : CH_2Cl_2)

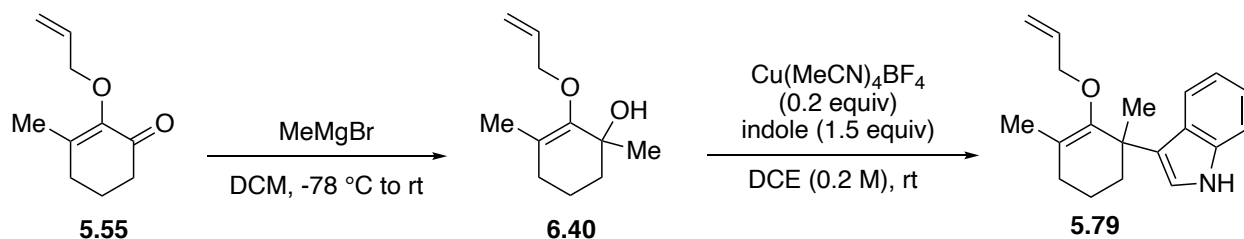
^1H NMR: (500 MHz, CDCl_3) δ = 7.93 (bs, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.37 – 7.30 (m, 3H), 7.22 – 7.18 (m, 1H), 7.18 – 7.14 (m, 1H), 7.12 – 7.06 (m, 2H), 5.40 – 5.32 (m, 1H), 4.76 (d, J = 10.5 Hz, 1H), 3.67 – 3.62 (m, 1H), 3.59 – 3.54 (m, 1H), 2.58 (t, J = 6.3 Hz, 1H), 2.49 – 2.41 (m, 1H), 1.83 – 1.75 (m, 3H), 1.71 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 139.62, 136.42, 134.73, 126.72, 126.20, 125.73, 125.32, 121.59, 121.30, 120.75, 119.15, 118.36, 117.39, 117.36, 110.56, 55.13, 49.03, 39.22, 33.51, 27.42, 18.72.

IR: $f(\text{cm}^{-1})$ = 2932, 2862, 1642, 1490, 1416, 1132, 1102.

HRMS: (ESI-TOF) m/z : $(\text{M}+\text{H})^+$ = 345.2071 calculated for $\text{C}_{24}\text{H}_{24}\text{DNO}$; Found 345.2095.

3-(2-(allyloxy)-1,3-dimethylcyclohex-2-en-1-yl)-1H-indole (5.79)



Procedure: Ketone **5.55** (485 mg, 2.918 mmol) was dissolved in dry CH_2Cl_2 (15.0 mL, 0.2 M) and cooled to $-78\text{ }^\circ\text{C}$. Methylmagnesium bromide (1.1 mL, 3.0 M in THF, 3.501 mmol) was then added dropwise. The solution was then warmed to room temperature and stirred for 1 hour. The reaction was cooled to $0\text{ }^\circ\text{C}$, and then quenched with a saturated NH_4Cl solution (10 mL) and further diluted with DI water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The crude material was purified by column chromatography using 100% hexanes to 97:3 hexanes : EtOAc to yield **6.40** in 68% yield (360 mg, 1.975 mmol) as a colorless oil.

Rf: 0.4 in 90 :10 (Hexanes : EtOAc)

^1H NMR: (500 MHz, CDCl_3) δ = 6.03 (ddt, J = 15.9, 10.7, 5.3 Hz, 1H), 5.37 – 5.33 (m, 1H), 5.22 – 5.18 (m, 1H), 4.41 – 4.35 (m, 1H), 4.31 – 4.26 (m, 1H), 2.06 – 1.98 (m, 2H), 1.95 – 1.92 (m, 1H), 1.81 – 1.74 (m, 1H), 1.72 – 1.66 (m, 2H), 1.65 (s, 3H), 1.58 – 2.56 (m, 1H), 1.36 (s, 3H).

^{13}C NMR: (125 MHz, CDCl_3) δ = 151.60, 134.85, 120.18, 116.45, 74.71, 71.16, 39.18, 31.23, 27.04, 19.29, 16.68.

IR: $f(\text{cm}^{-1})$ = 3448, 3932, 2885, 1671, 1450, 1367, 1256, 1143, 1106, 986.

HRMS: (ESI-TOF) m/z : $(\text{M}-\text{H}_2\text{O})^+ = 165.1307$ calculated for $\text{C}_{11}\text{H}_{17}\text{O}$; Found 165.1273.

Procedure: α -Hydroxyl enol ether **6.40** (153 mg, 0.840 mmol) was dissolved in DCE (4.2 mL, 0.2 M). Indole (147 mg, 1.259 mmol) was added, followed by addition of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (52 mg, 0.168 mmol). The mixture was stirred at room temperature for 15 hours, at which the starting

material was fully consumed as monitored by TLC. The crude reaction mixture was concentrated under vacuum then purified by column chromatography using 100% hexanes to 50:50 hexanes : CH₂Cl₂ to yield **5.79** in 97% yield (228 mg, 0.810 mmol) as a white solid.

Rf: 0.6 in 50 :50 (Hexanes : CH₂Cl₂)

¹H NMR: (500 MHz, CDCl₃) δ = 7.90 (bs, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.15 (t, J = 7.2 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 7.03 (s, 1H), 5.67 (ddt, J = 15.7, 10.5, 5.3 Hz, 1H), 5.02 (d, J = 17.3 Hz, 1H), 4.95 (d, J = 10.4 Hz, 1H), 4.00 (dd, J = 12.8, 5.3 Hz, 1H), 3.85 (dd, J = 12.8, 5.3 Hz, 1H), 2.36 – 2.21 (m, 2H), 2.13 – 2.08 (m, 1H), 1.76 (s, 3H), 1.71 – 1.67 (m, 1H), 1.64 (s, 3H), 1.64 – 1.57 (m, 2H).


¹³C NMR: (125 MHz, CDCl₃) δ = 153.85, 136.98, 135.07, 126.14, 123.73, 122.20, 121.37, 121.03, 118.83, 117.97, 115.43, 111.19, 73.84, 39.84, 39.54, 31.65, 25.40, 19.84, 17.32.

IR: f (cm⁻¹) = 3412, 2929, 2863, 1669, 1456, 1244, 1192, 1167, 1128, 1013.

HRMS: (ESI-TOF) m/z : (M+H)⁺ = 282.1852 calculated for C₁₉H₂₃NO; Found 282.1850.

Appendix A: Copyright Release

A1. Release for Chapter Two



Effects of Solvent and Residual Water on Enhancing the Reactivity of Six-Membered Silyloxyallyl Cations toward Nucleophilic Addition

Author: Joshua A. Malone, Alexander H. Cleveland, Frank R. Fronczek, et al
Publication: Organic Letters
Publisher: American Chemical Society
Date: Sep 1, 2016

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A1. Release for Chapter Two



Mechanistic Perspectives in the Regioselective Indole Addition to Unsymmetrical Silyloxyallyl Cations

Author: Caitlin G. Bresnahan, Kiara A. Taylor-Edinbyrd, Alexander H. Cleveland, et al
Publication: The Journal of Organic Chemistry
Publisher: American Chemical Society
Date: Jun 1, 2019

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A3. Release for Chapter Three



Brønsted Acid Catalyzed Synthesis of Functionalized 1,4- and 1,6-Dicarbonyl Monosilyl Enol Ethers under Operationally Practical Conditions

Author: Joshua A. Malone, Joshua P. Van Houten, Moshood O. Ganiu, et al

Publication: The Journal of Organic Chemistry

Publisher: American Chemical Society

Date: Oct 1, 2017

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A3. Release for Chapter Four



Brønsted Acid-Catalyzed Formal [2 2 1] Annulation for the Modular Synthesis of Tetrahydroindoles and Tetrahydrocyclopenta[b]pyrroles

Author: Joshua A. Malone, Courtney E. Toussel, Frank R. Fronczek, et al

Publication: Organic Letters

Publisher: American Chemical Society

Date: May 1, 2019

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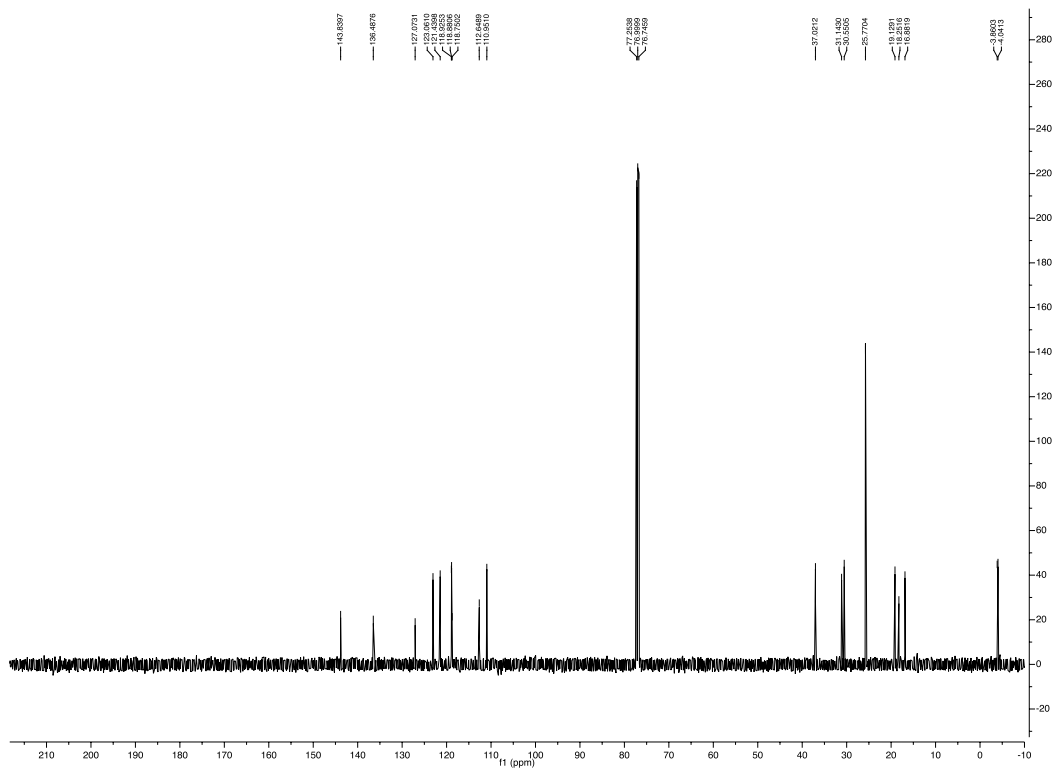
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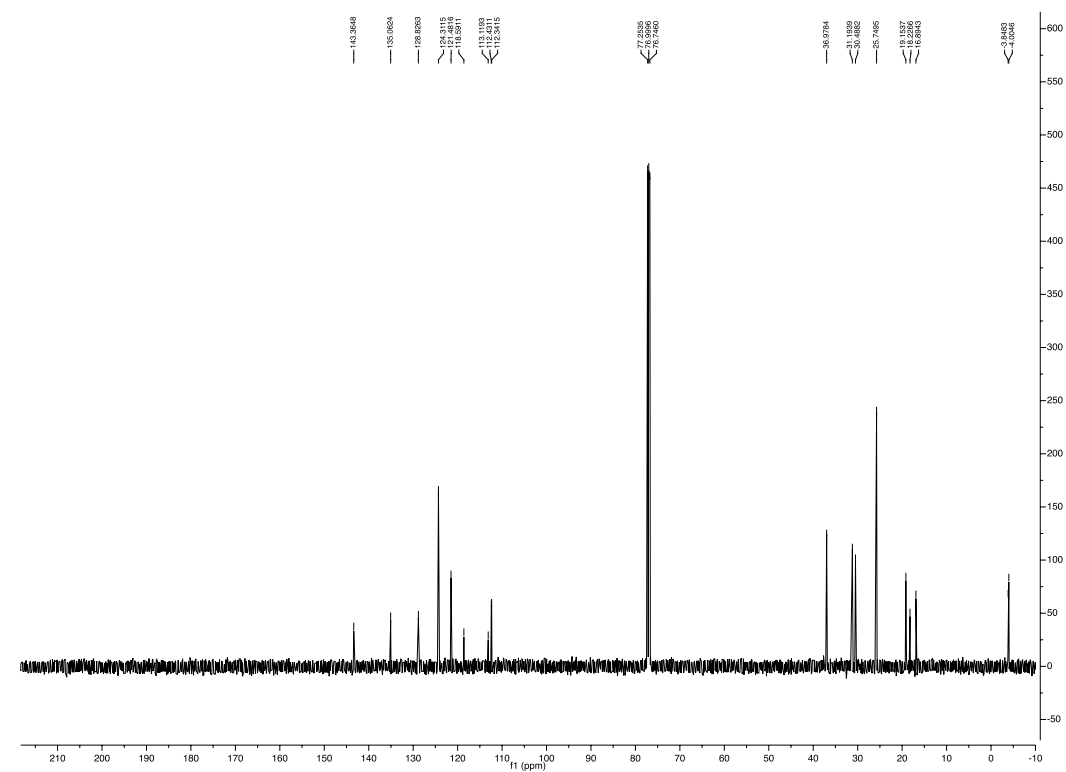
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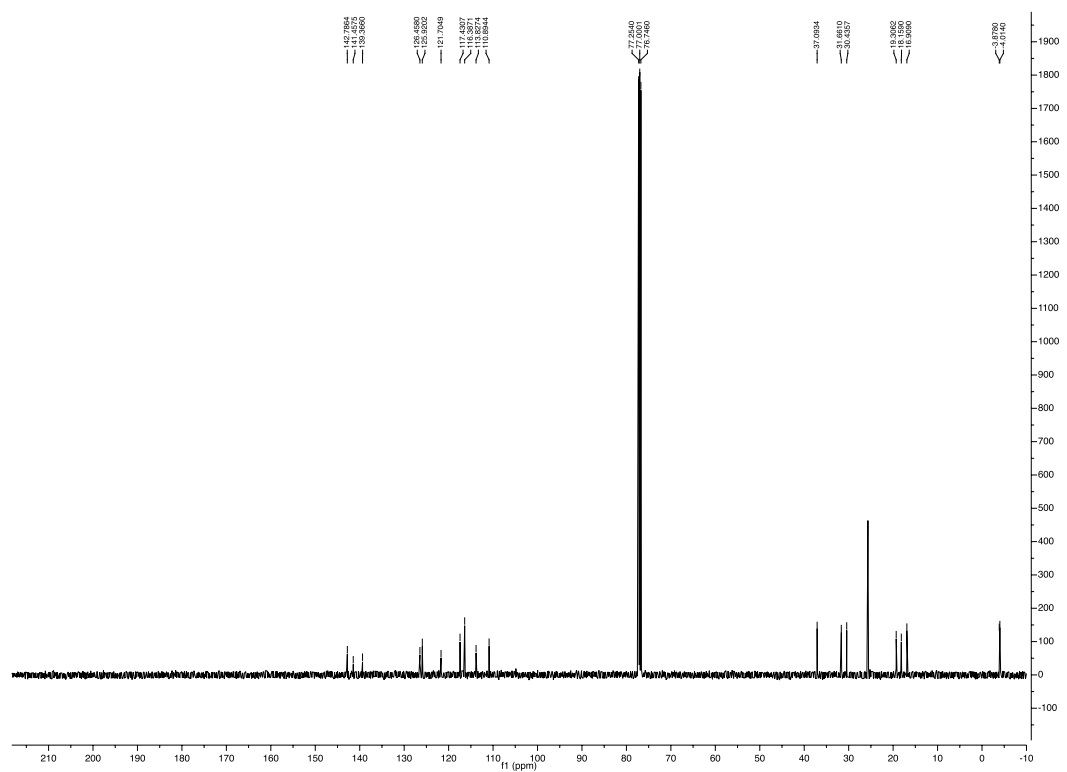
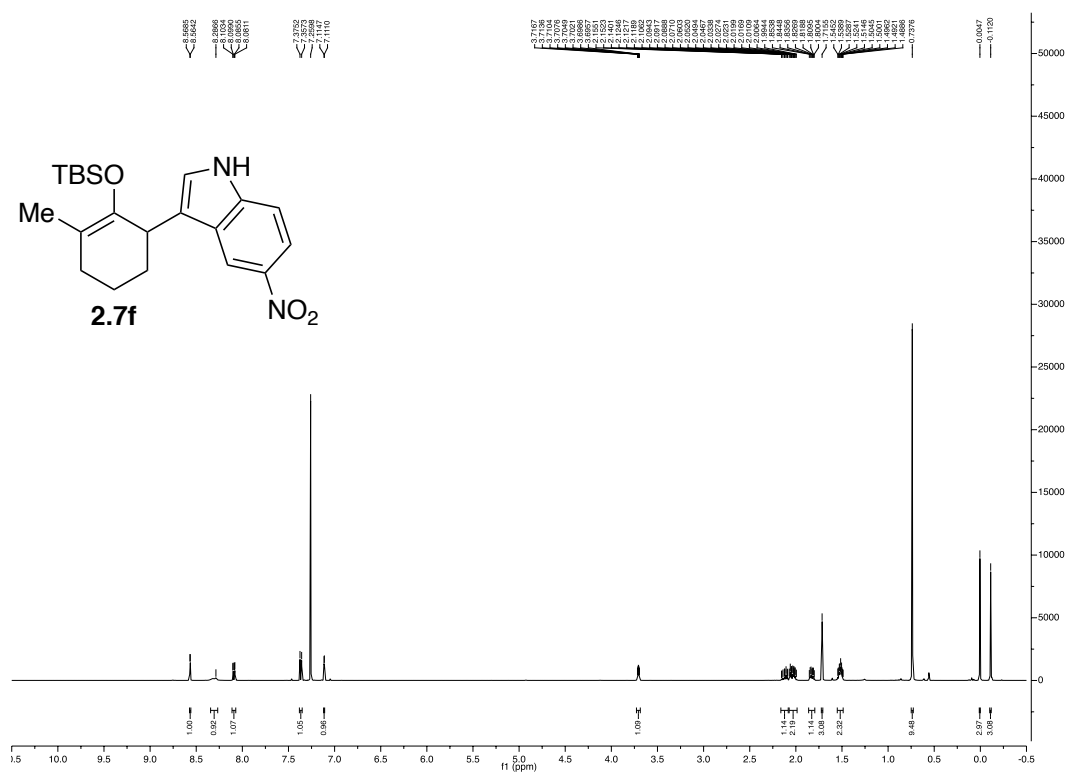
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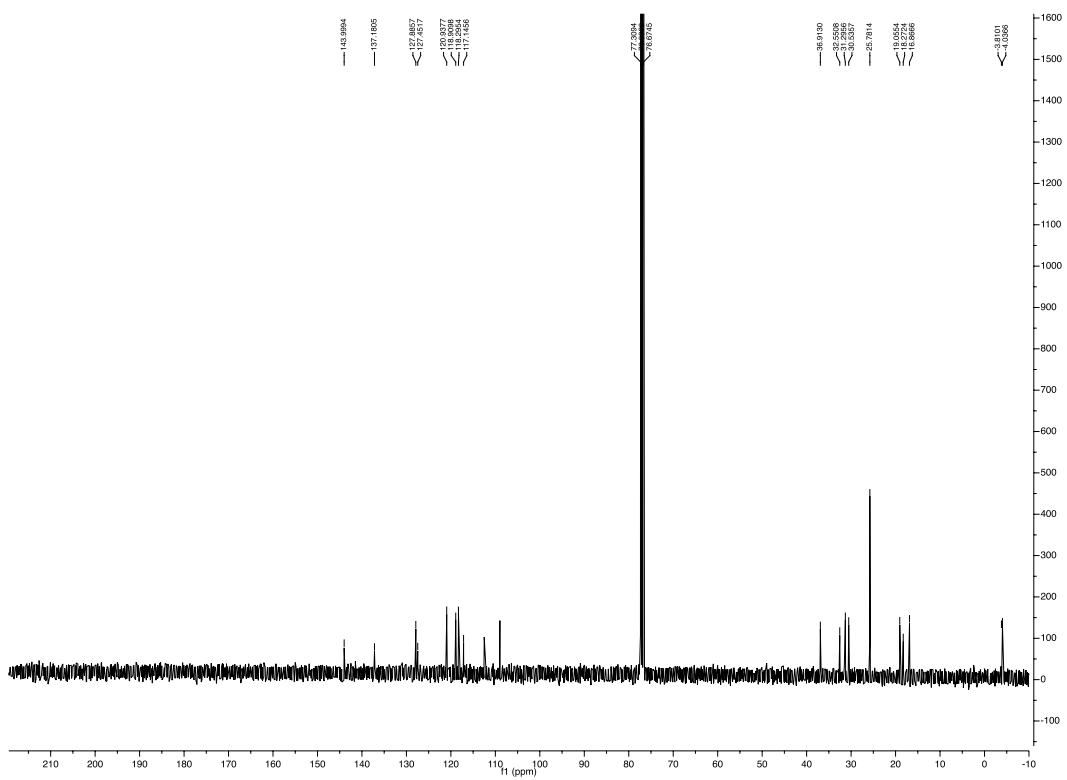


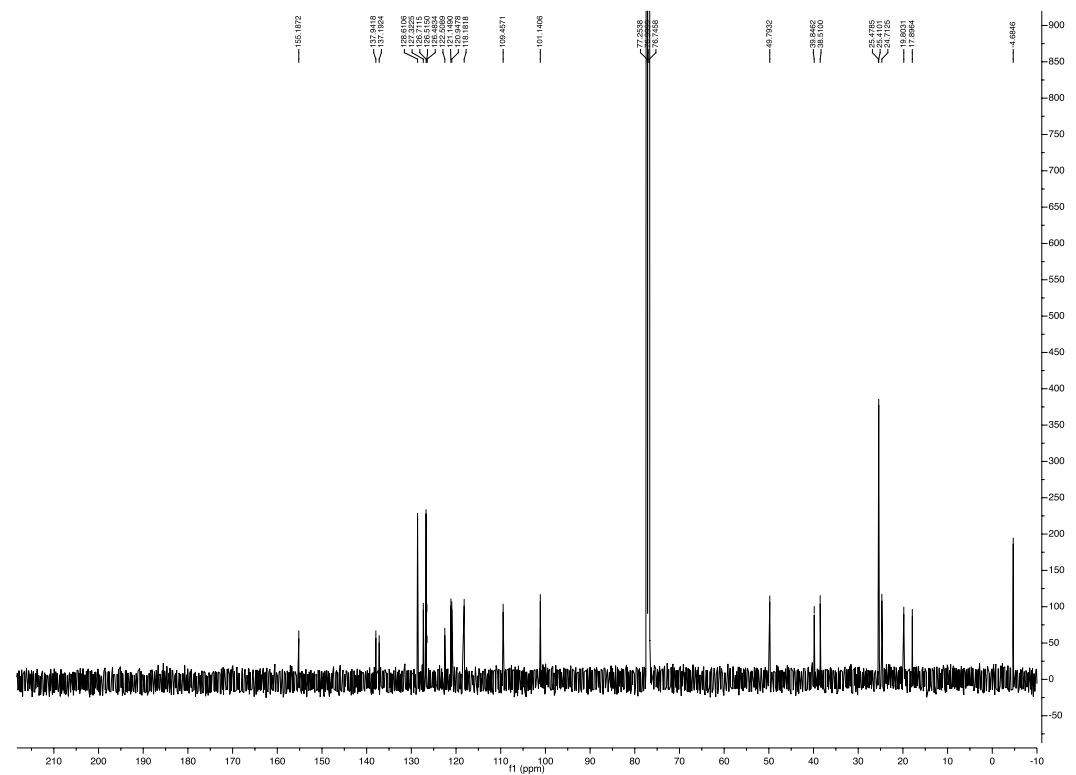






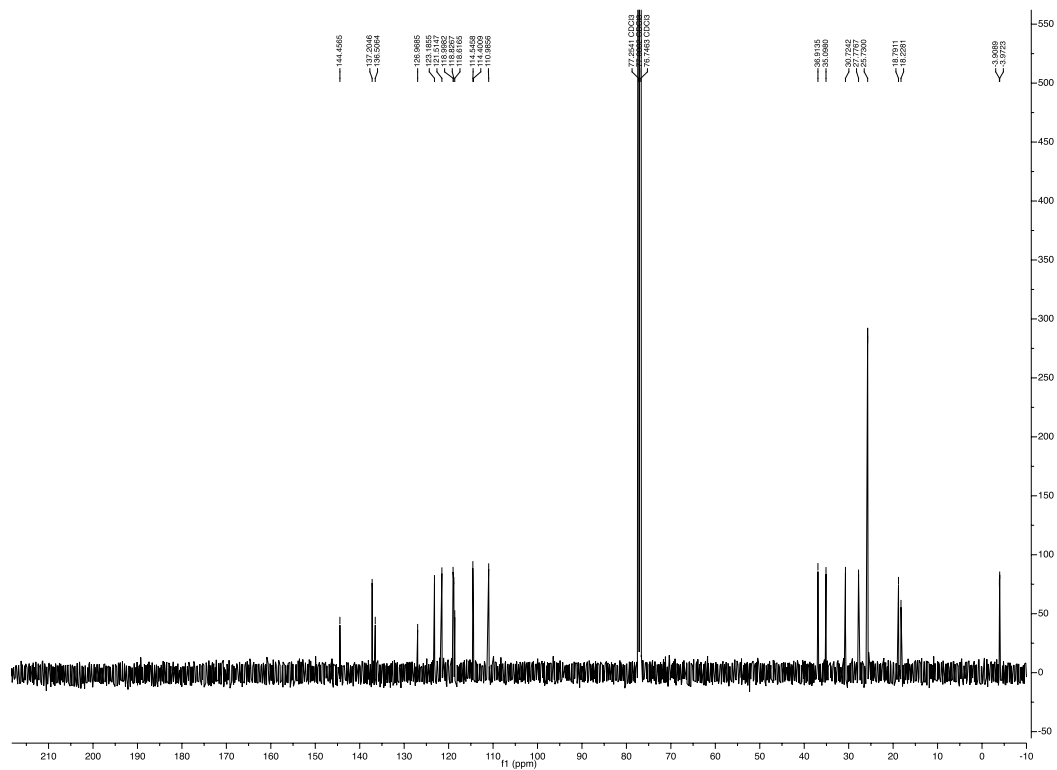
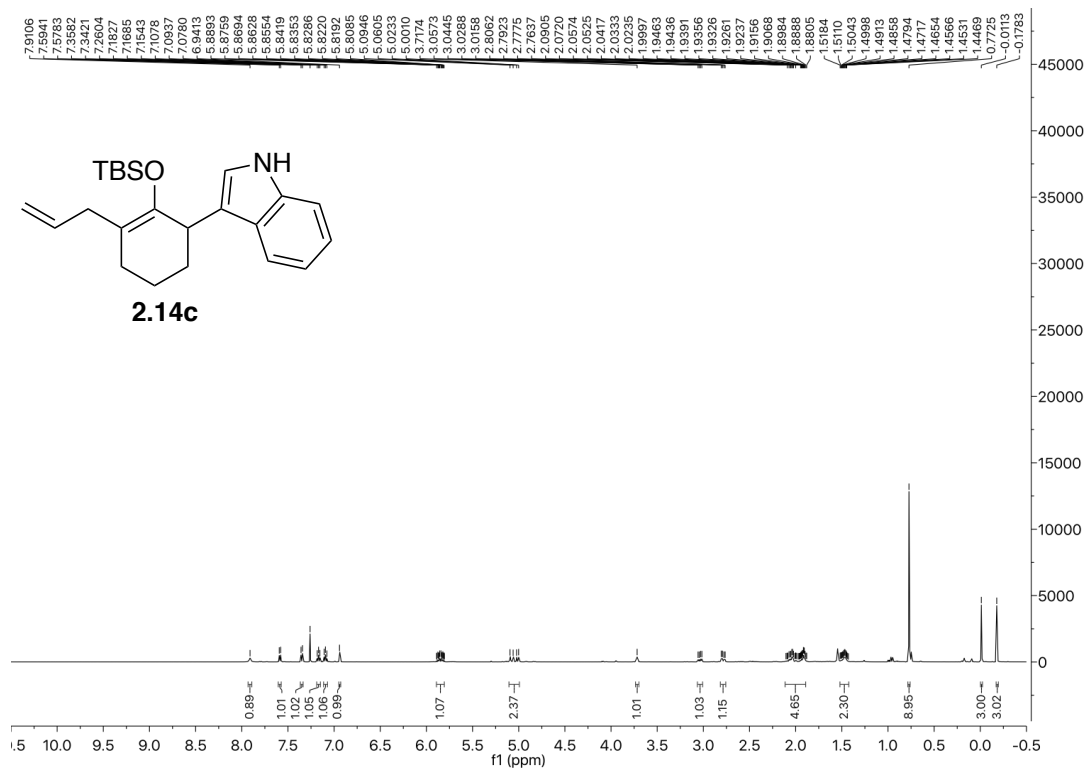


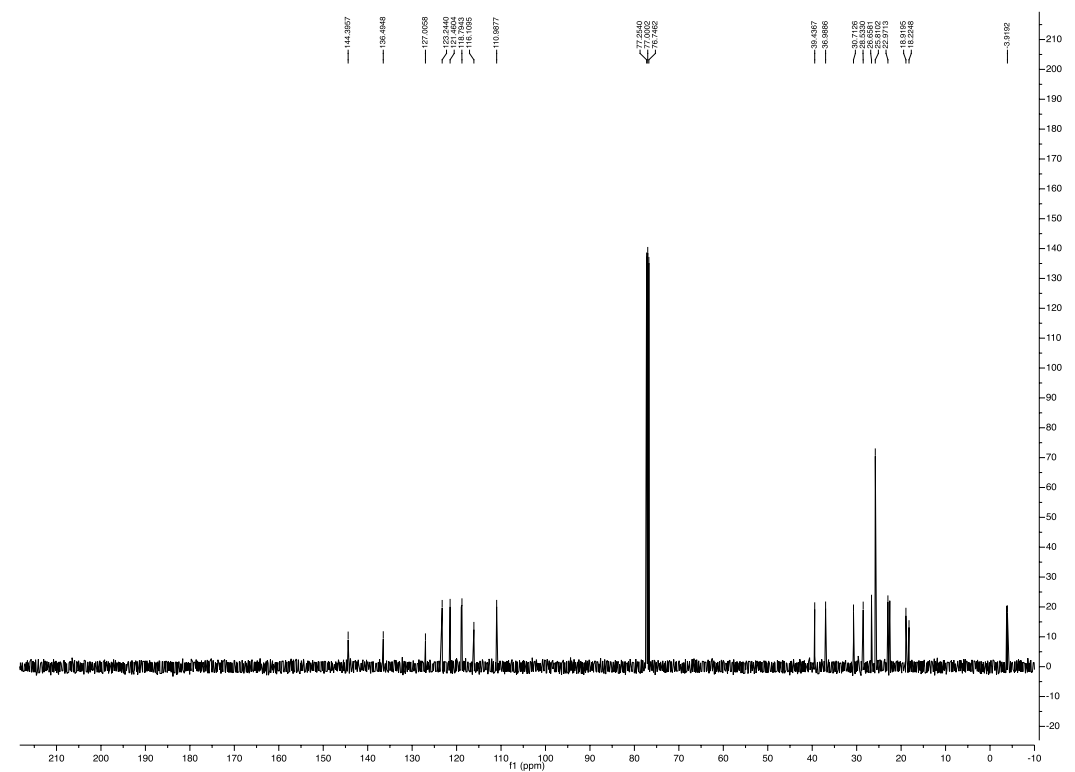


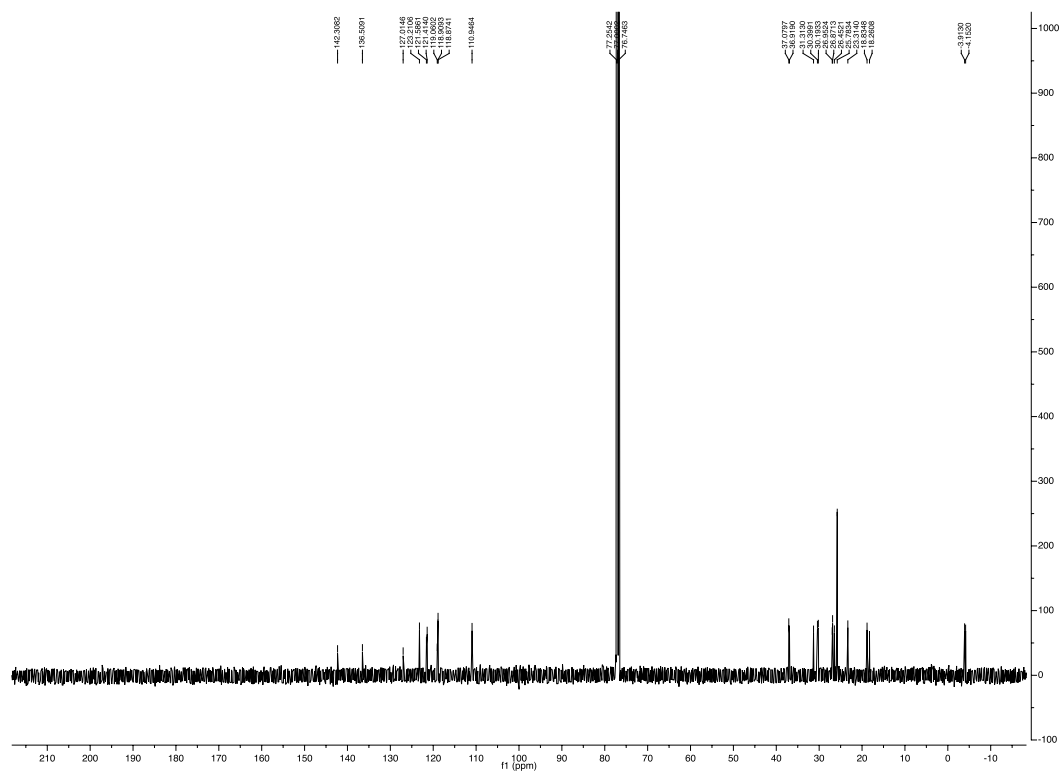
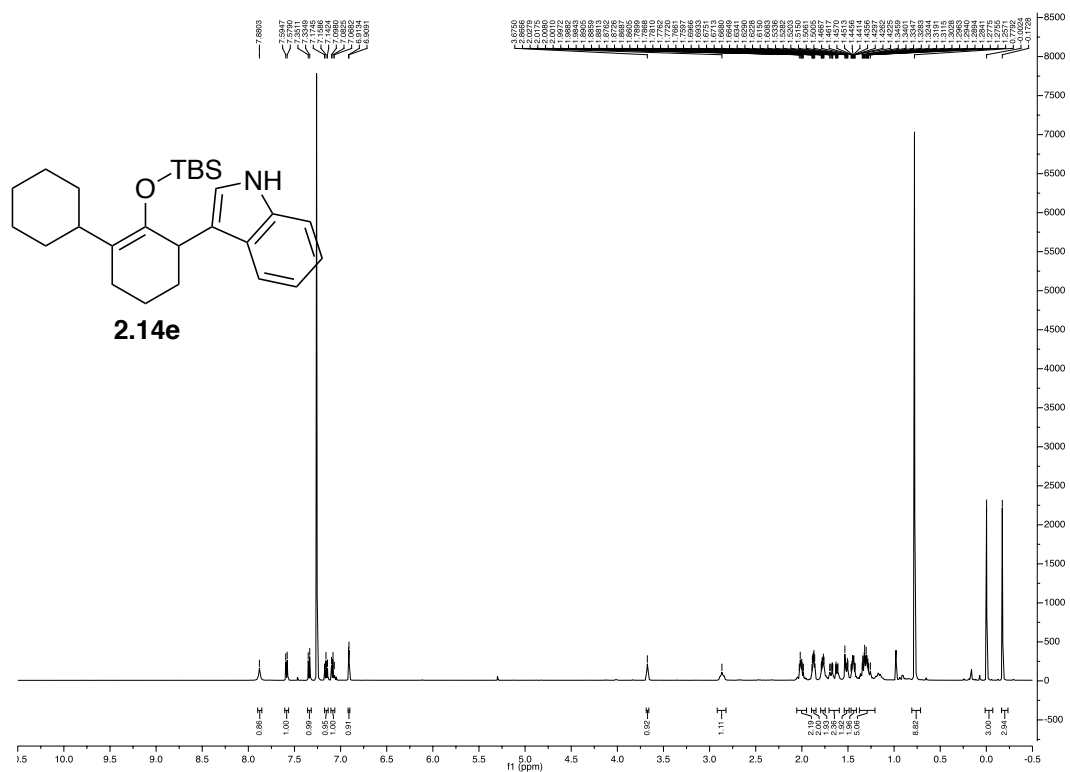


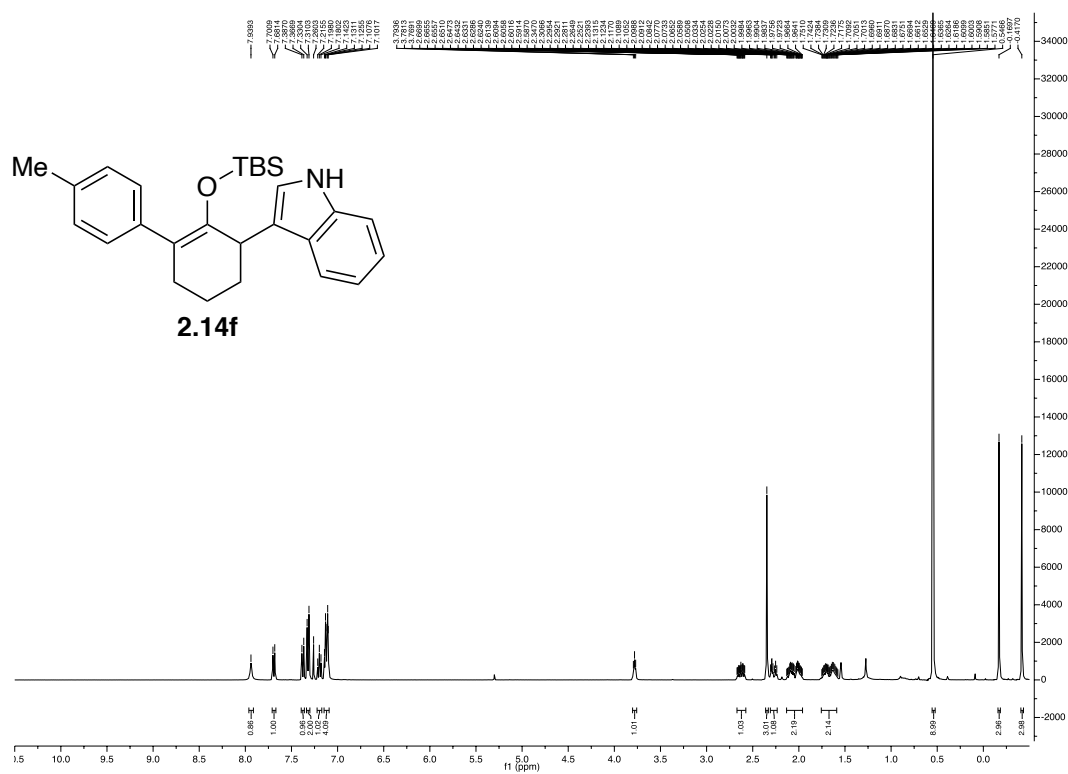


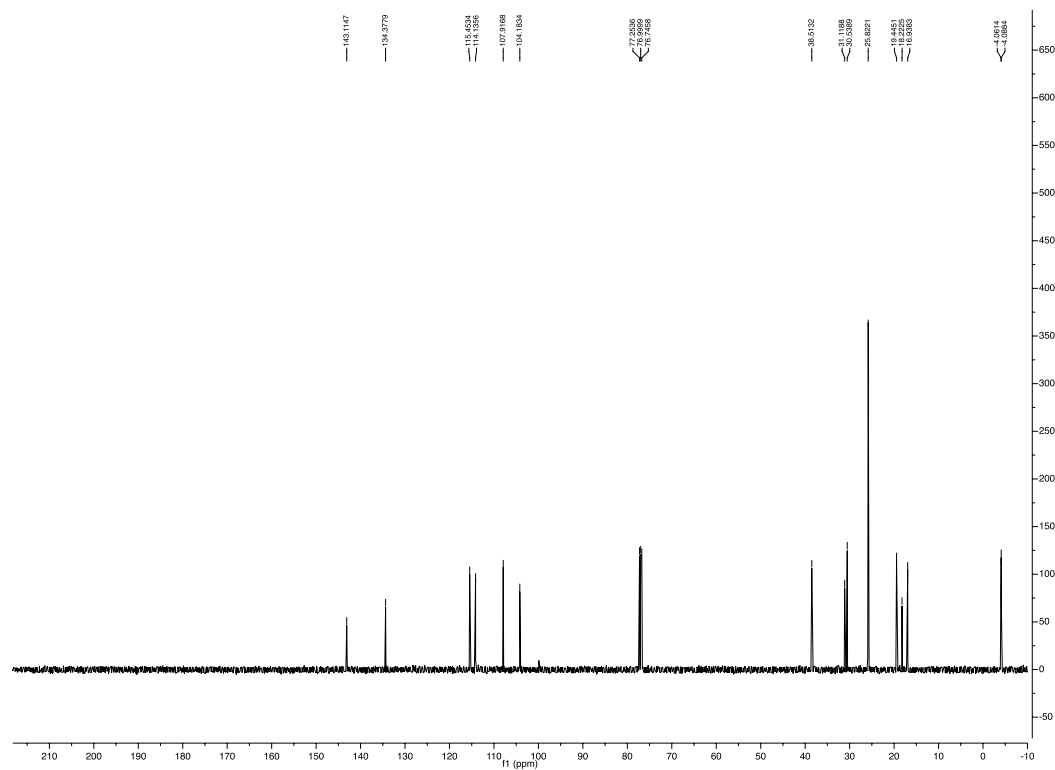
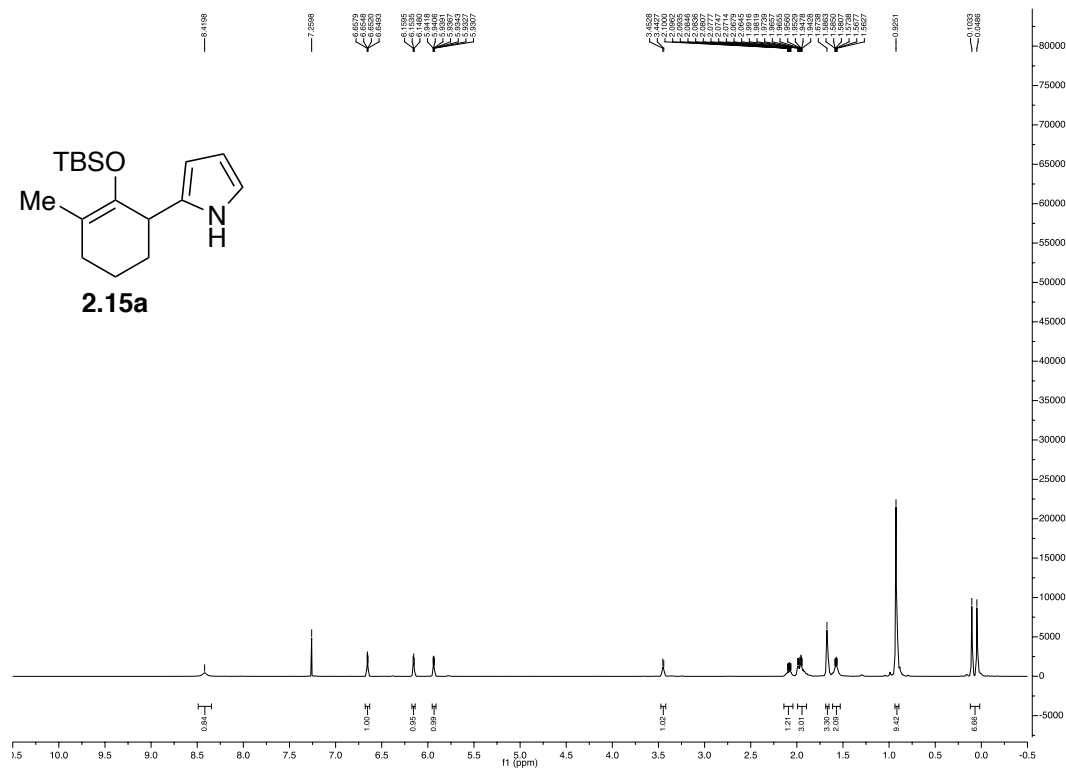


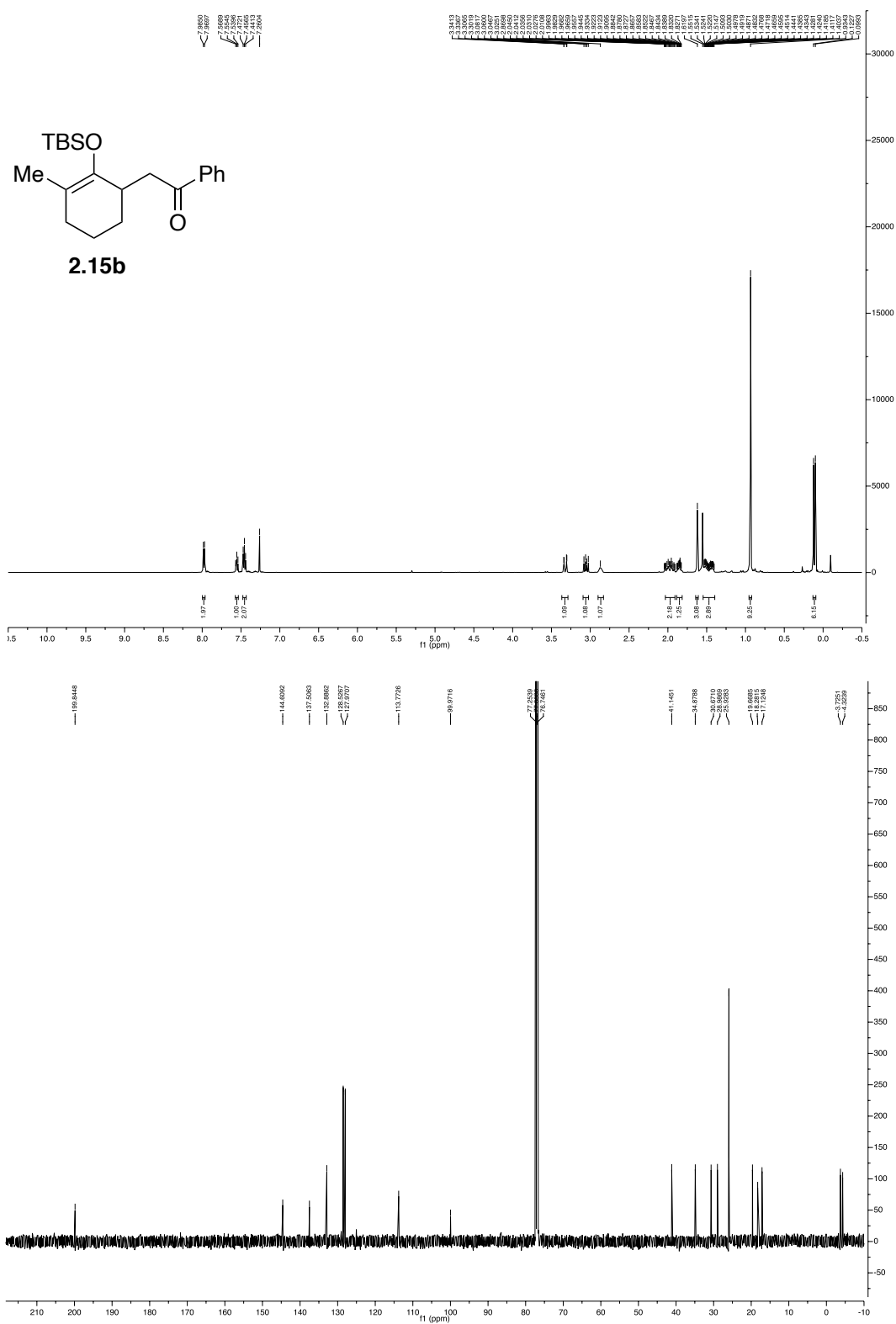


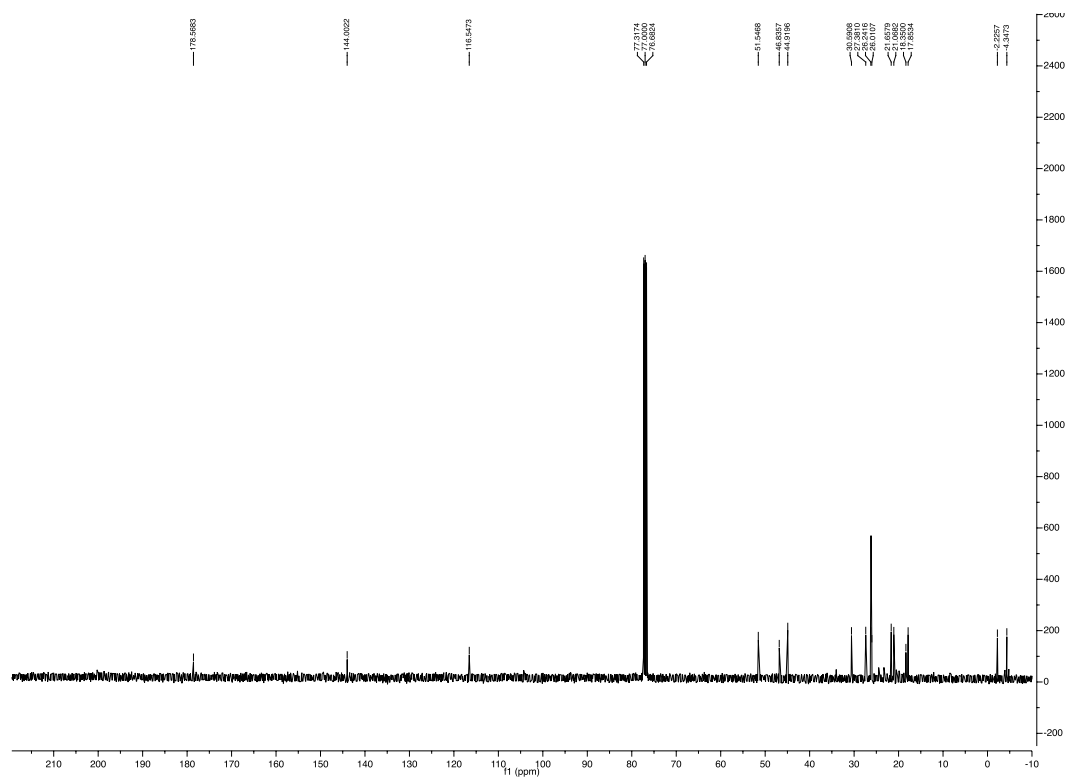
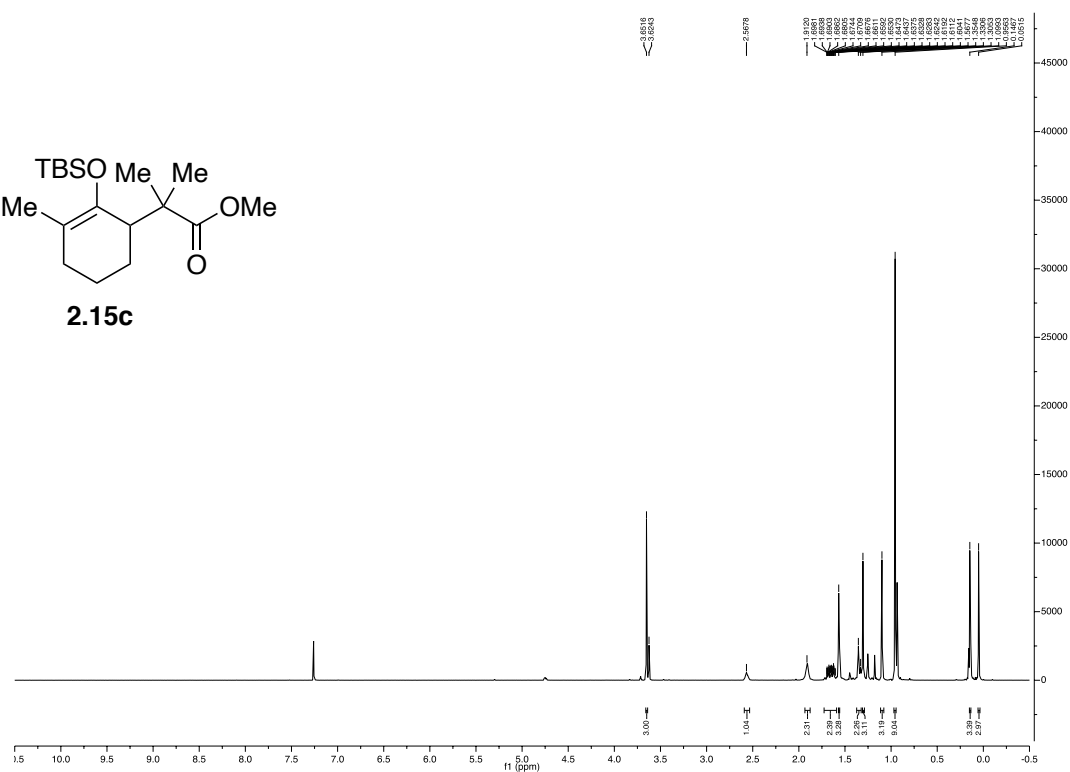


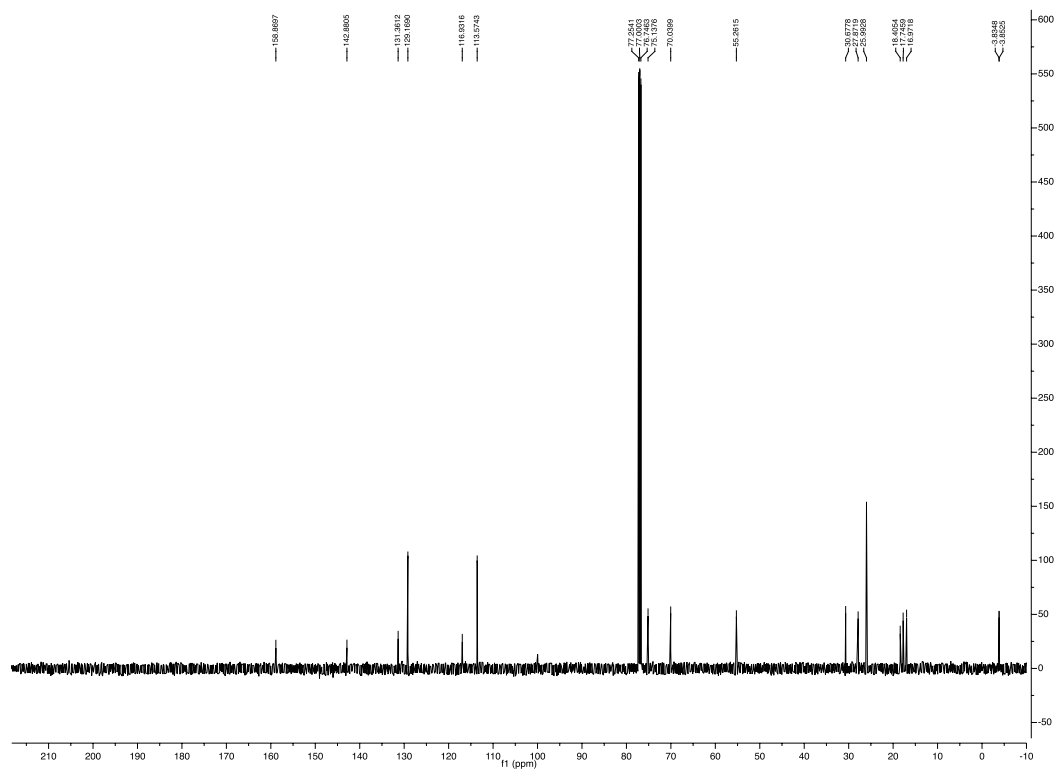
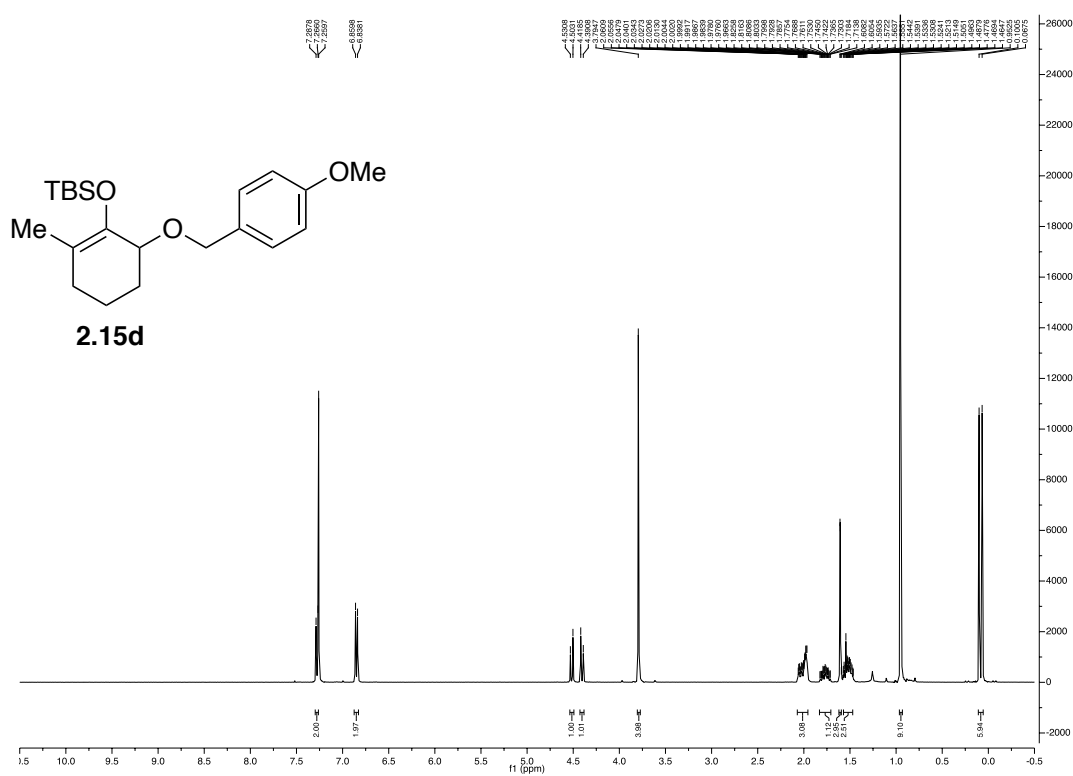


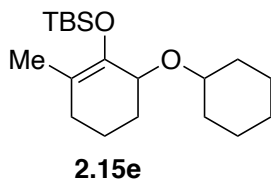


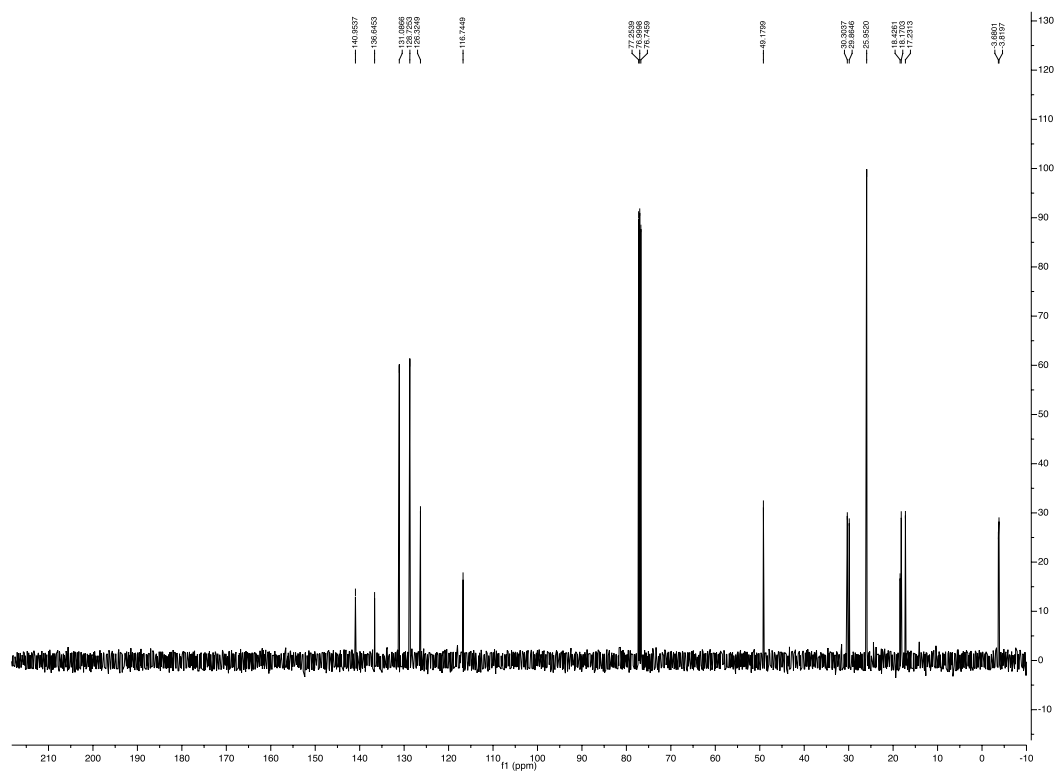
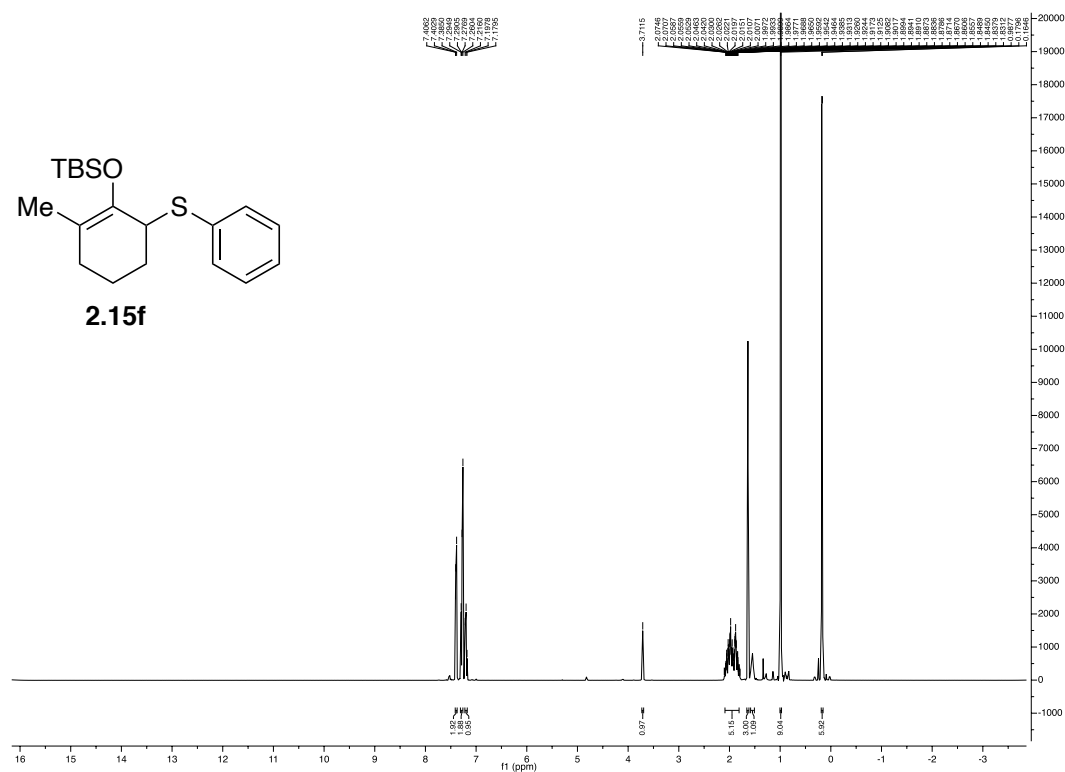


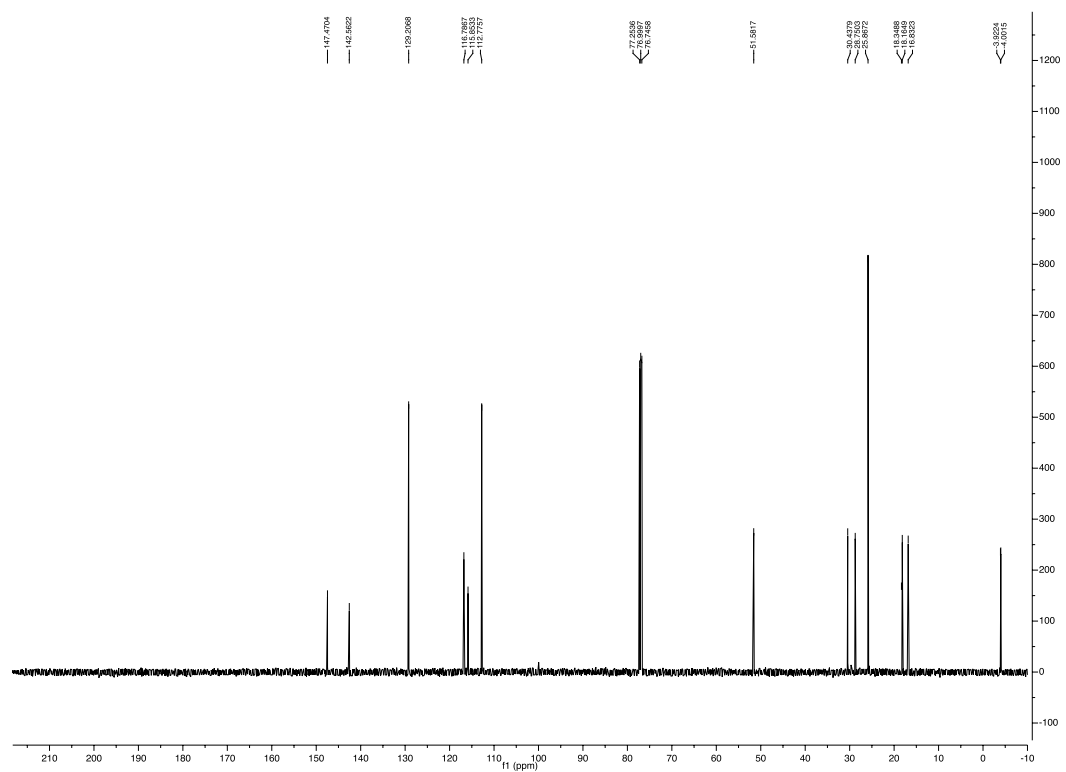
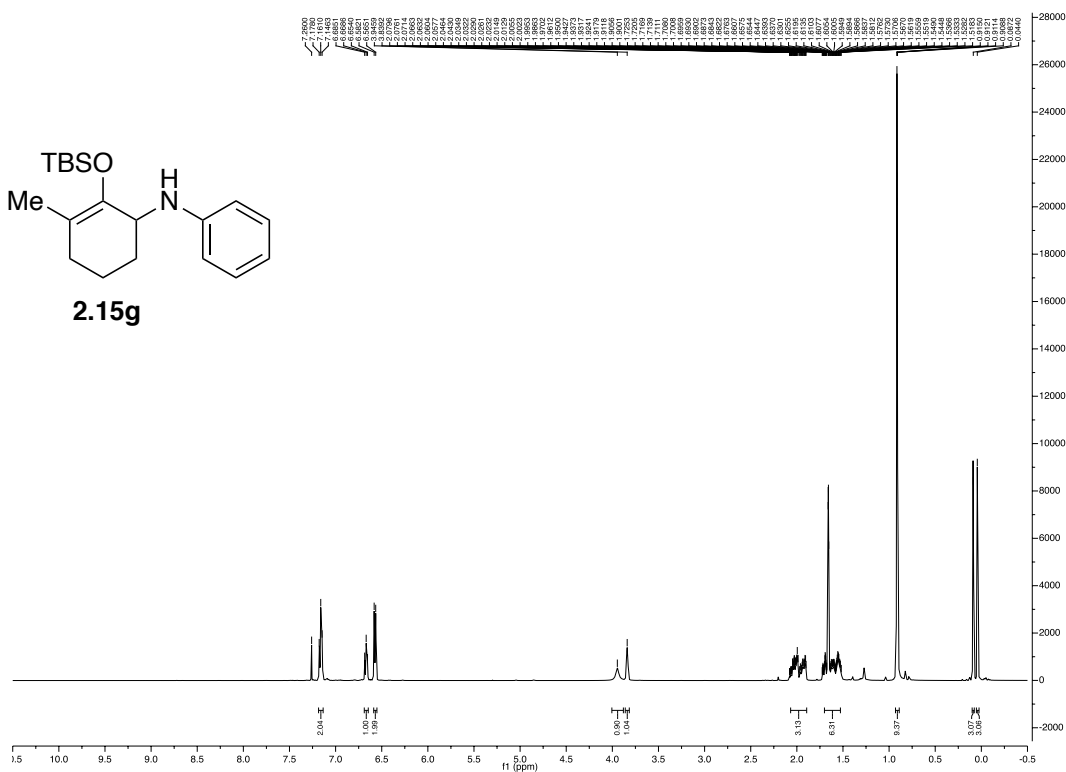


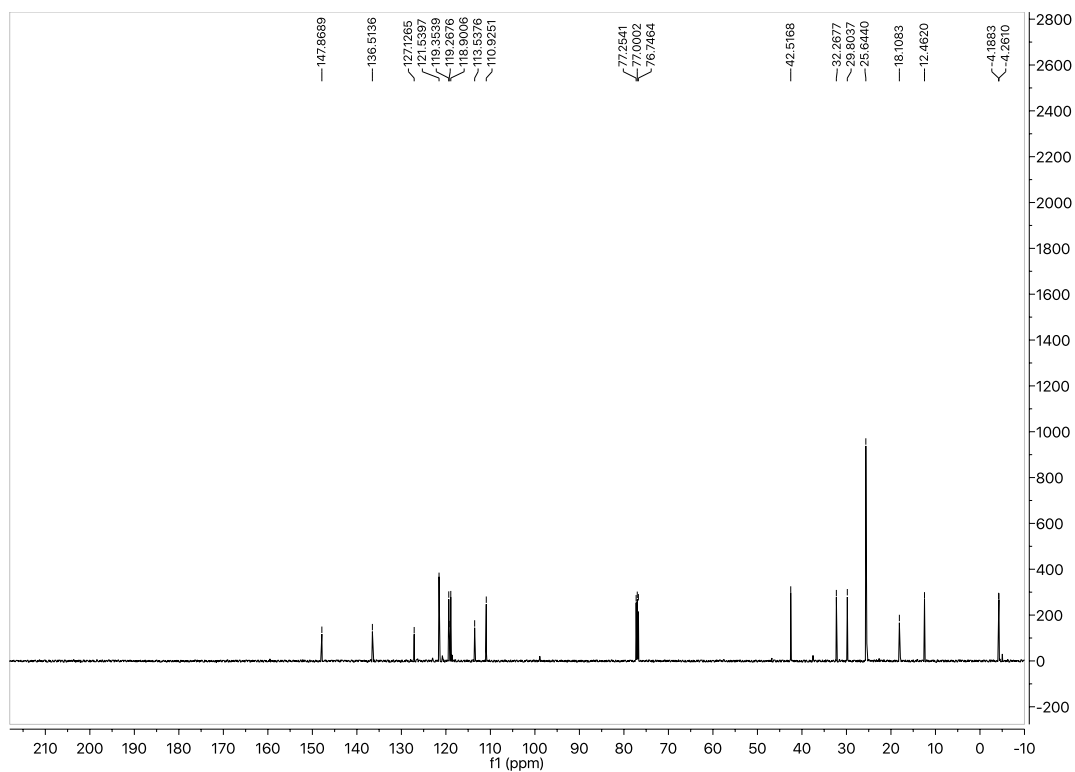
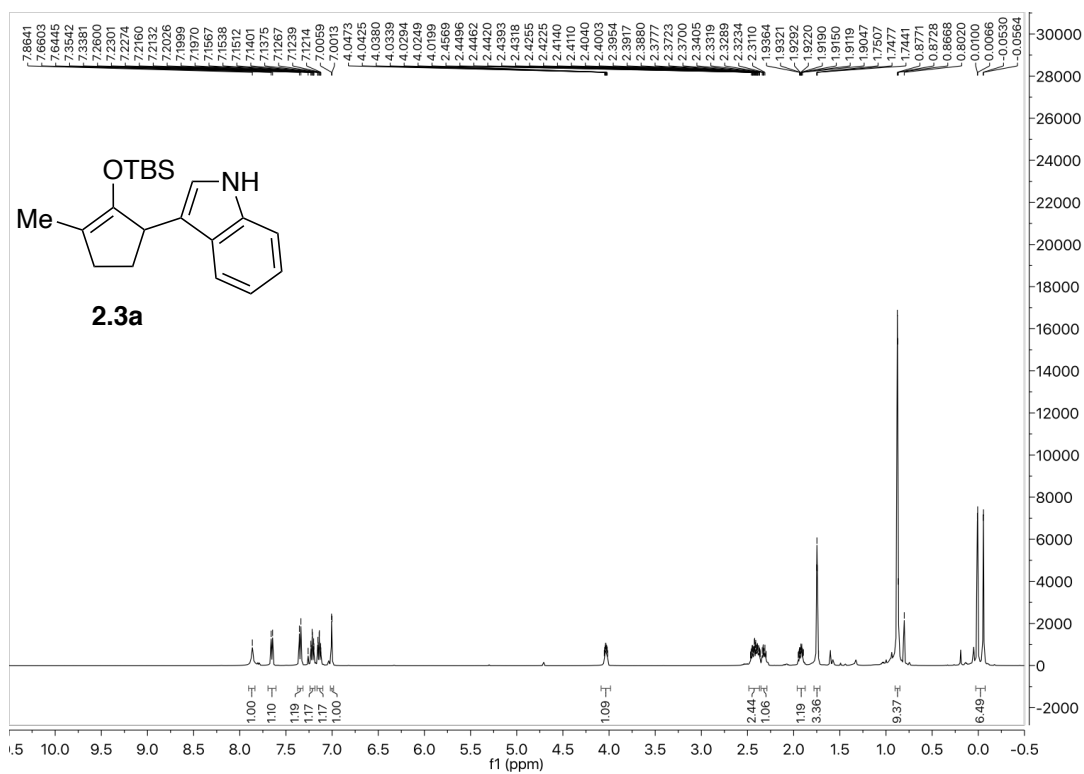


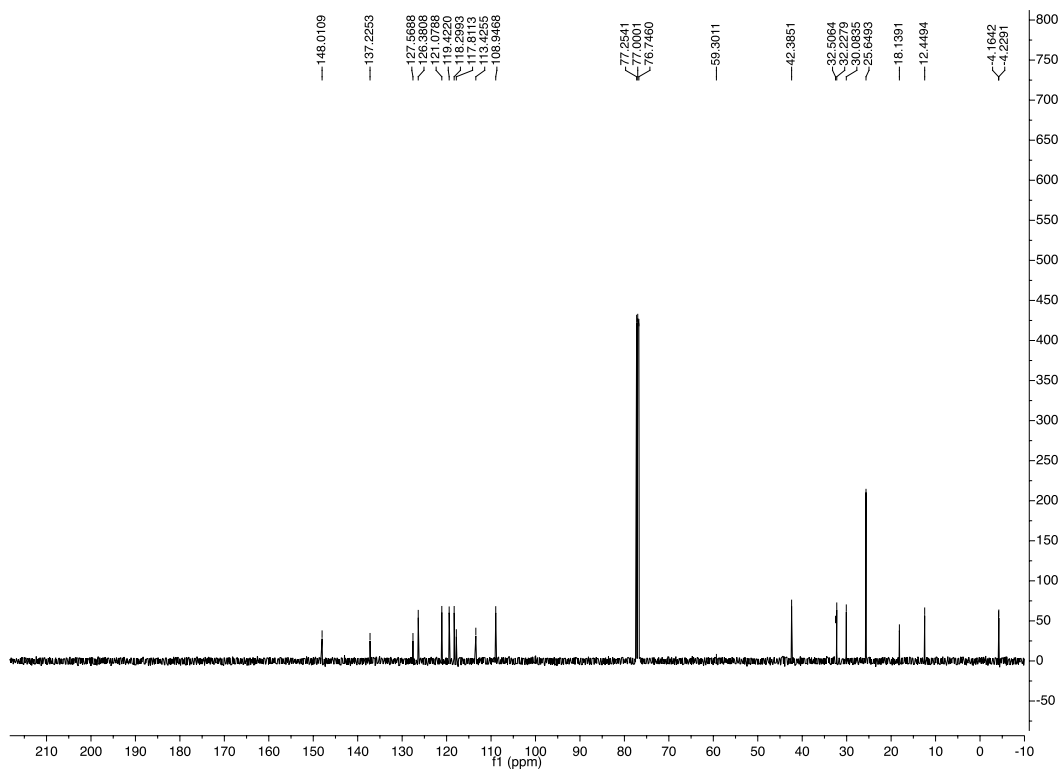
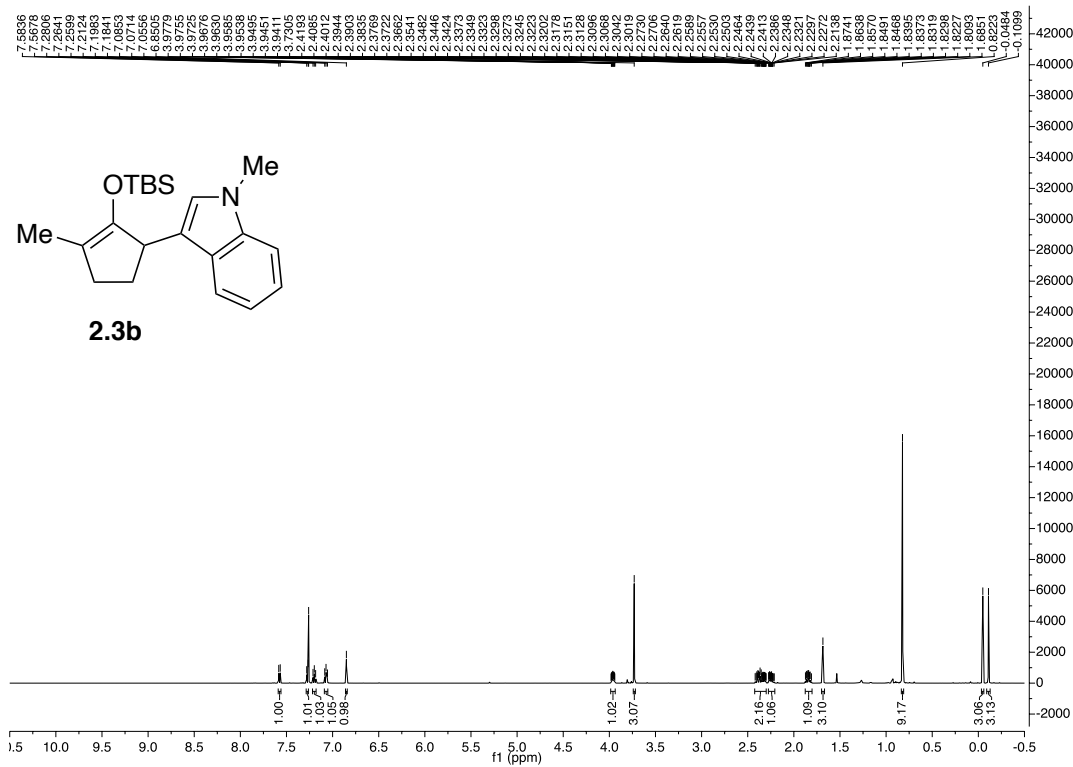


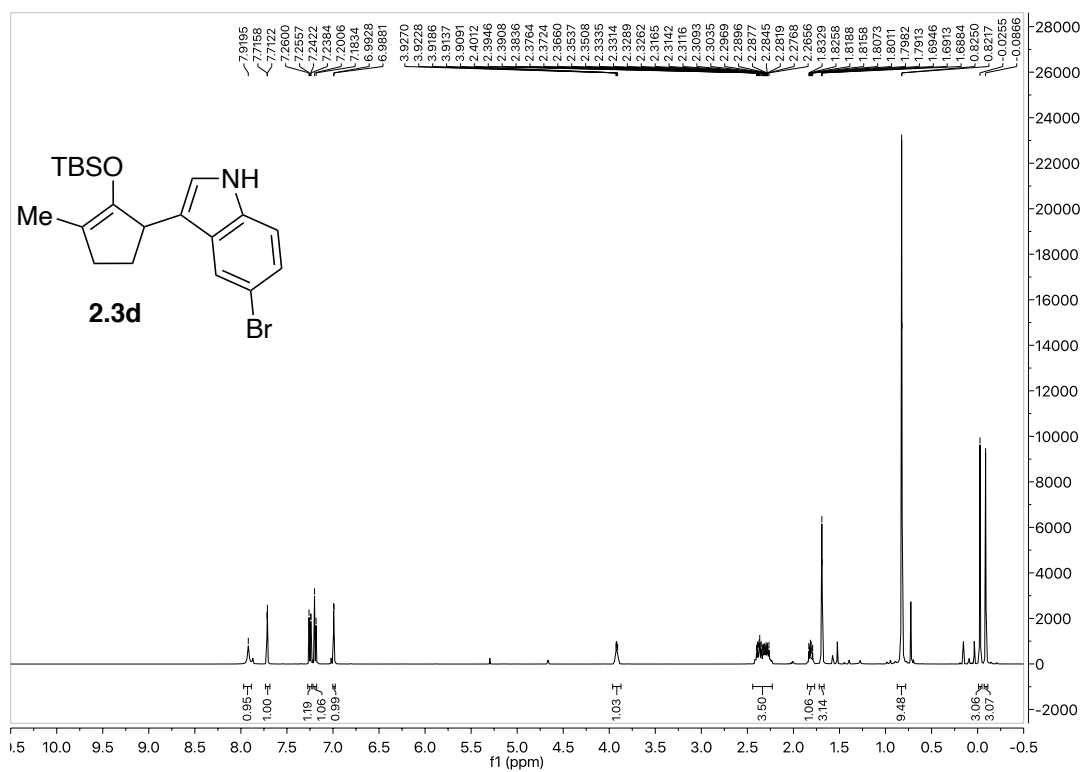


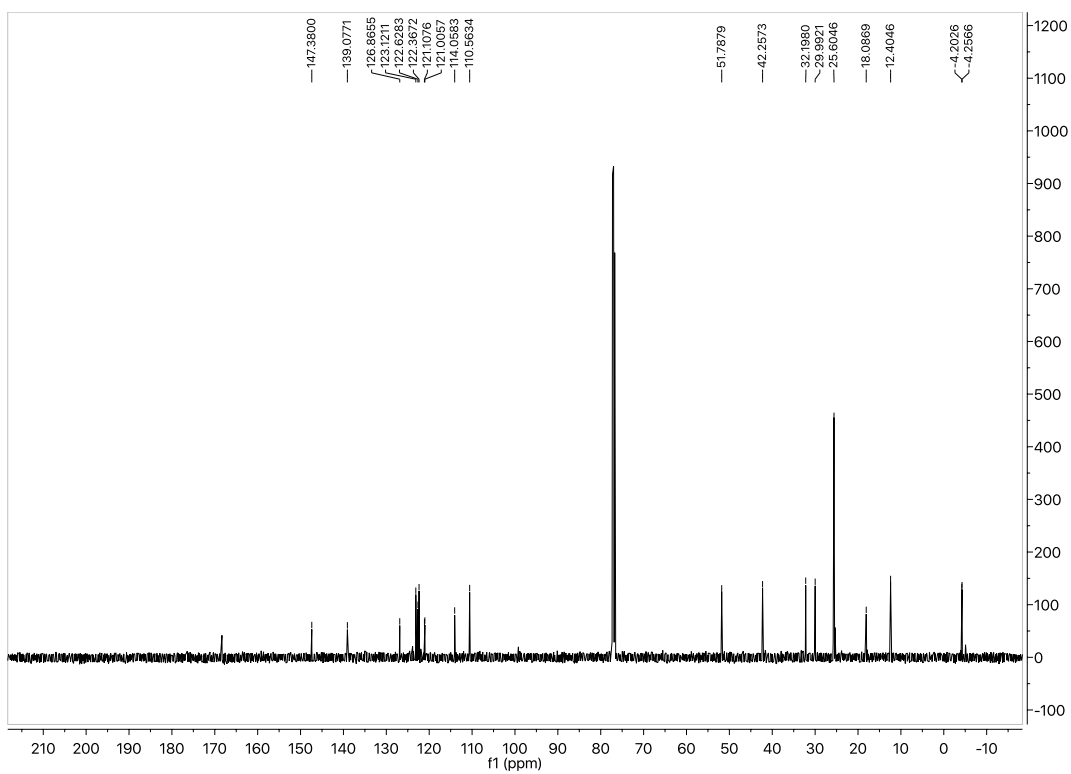
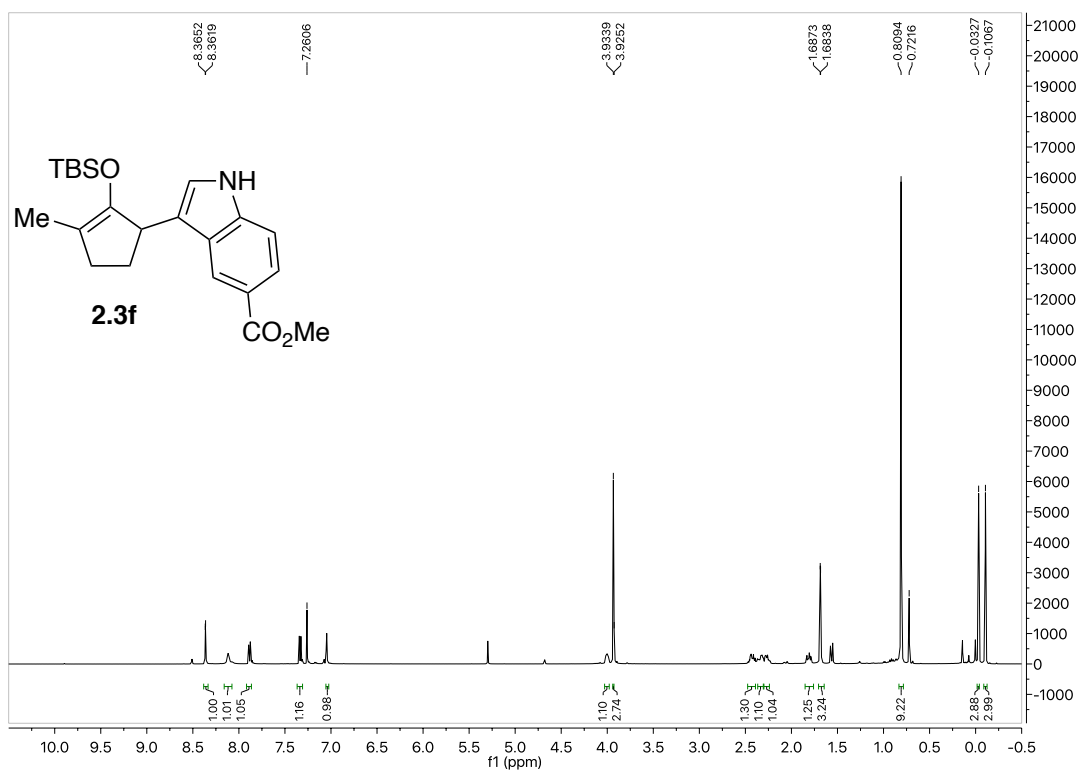


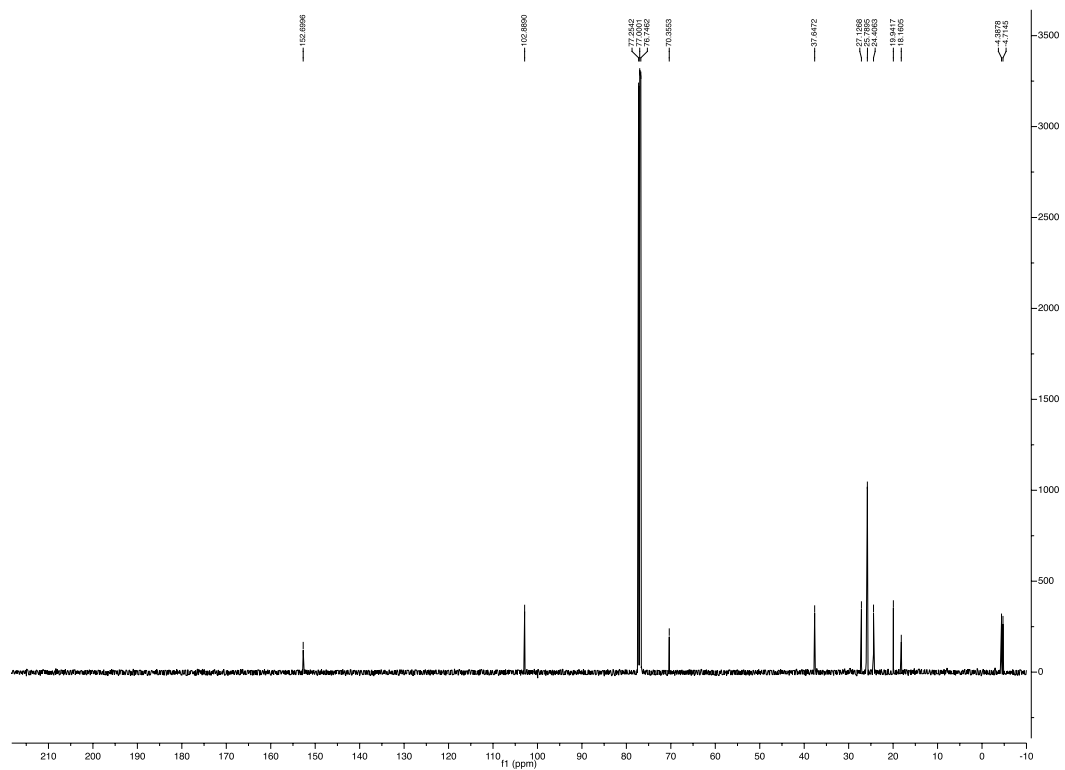
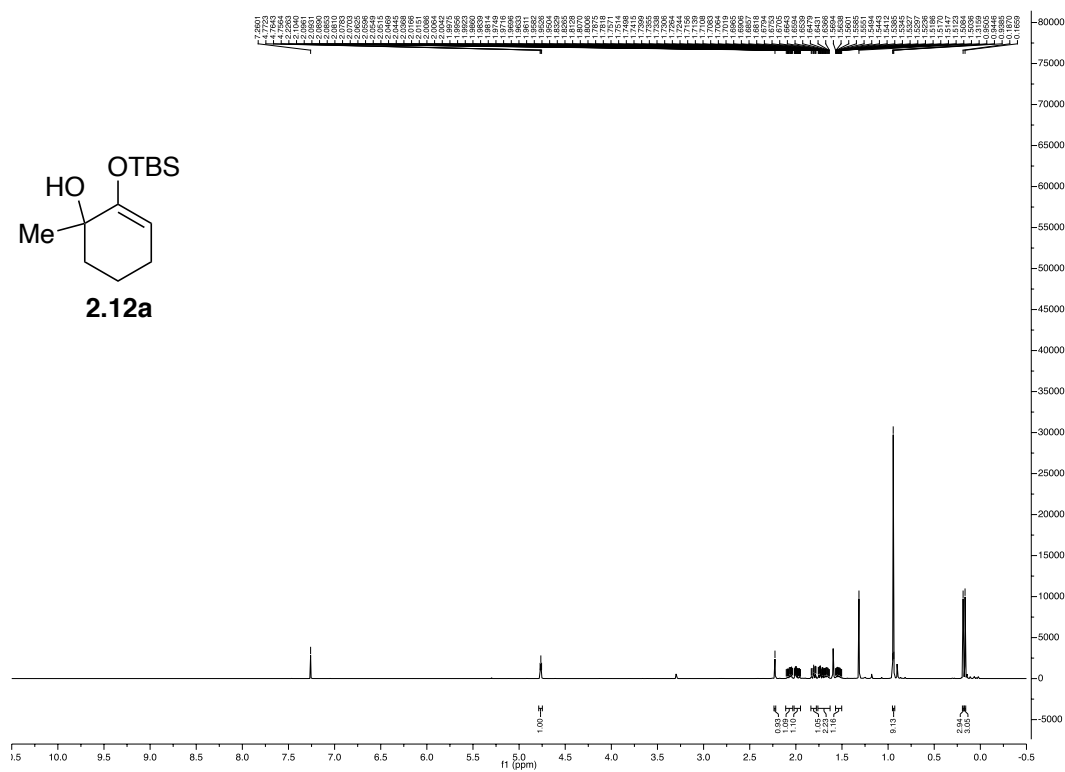
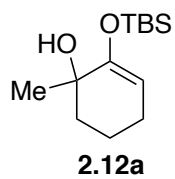


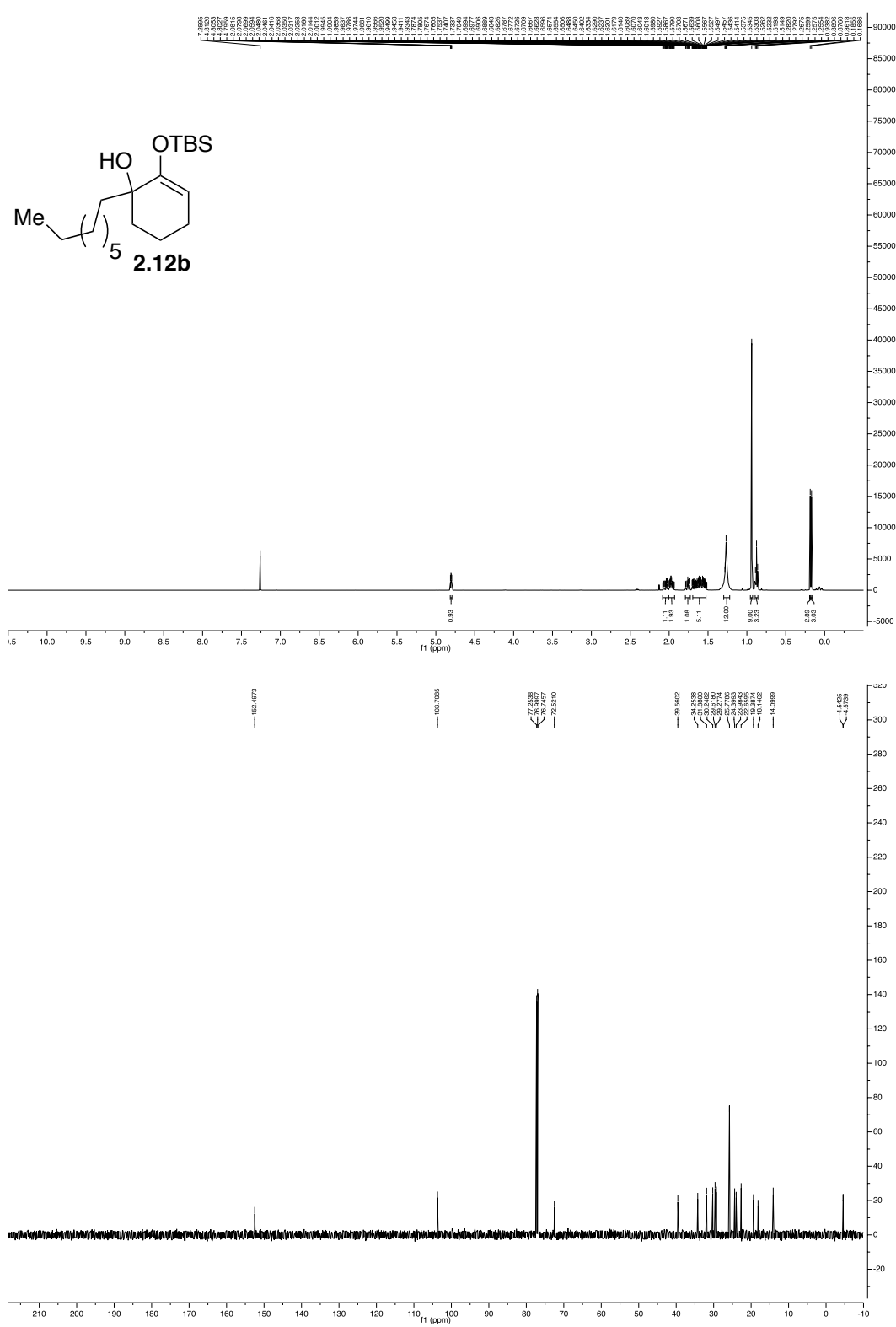


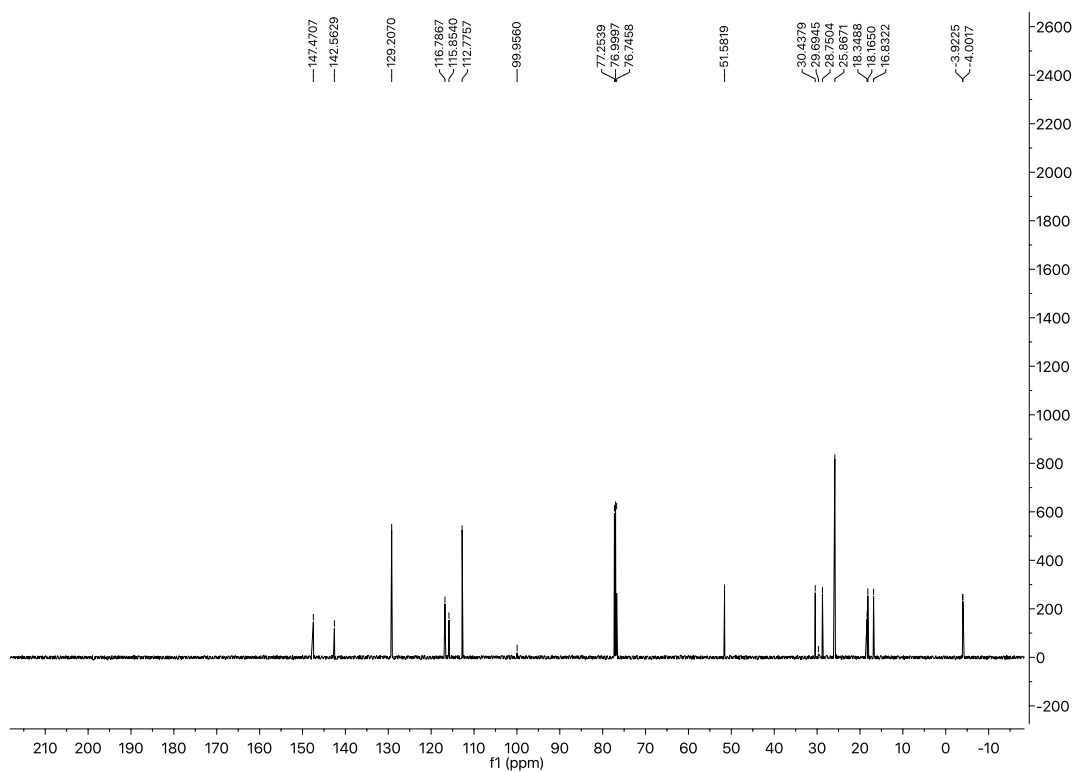
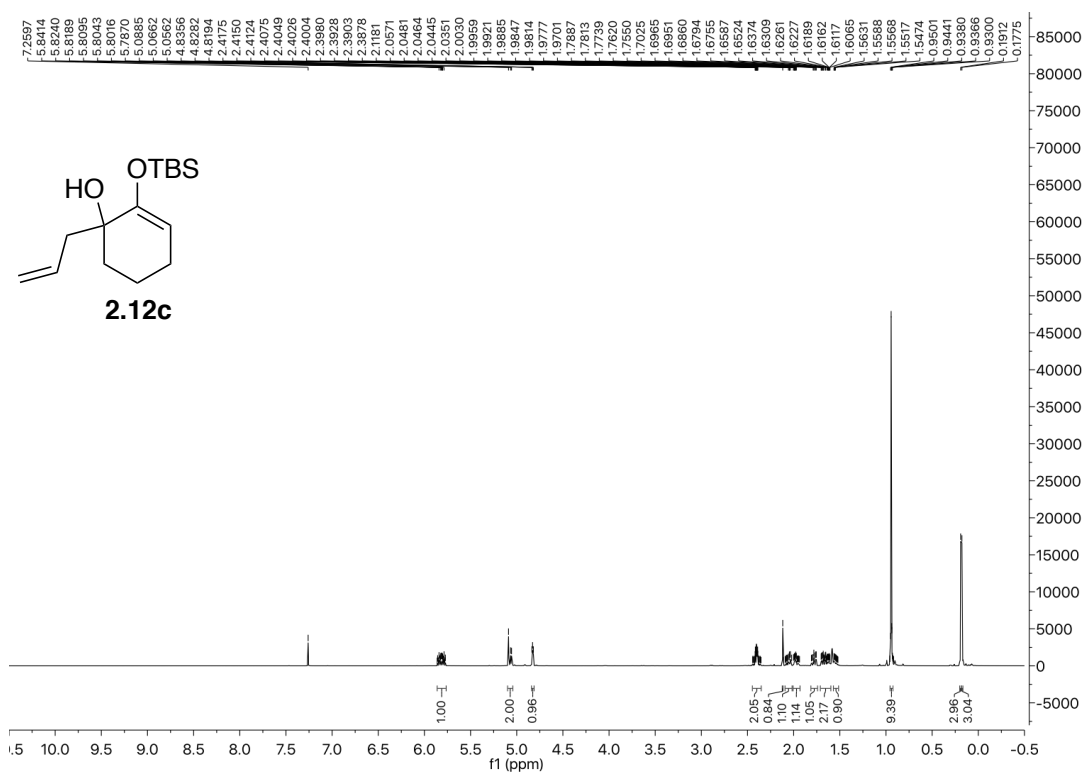


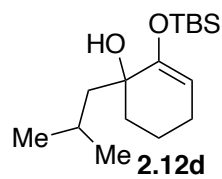


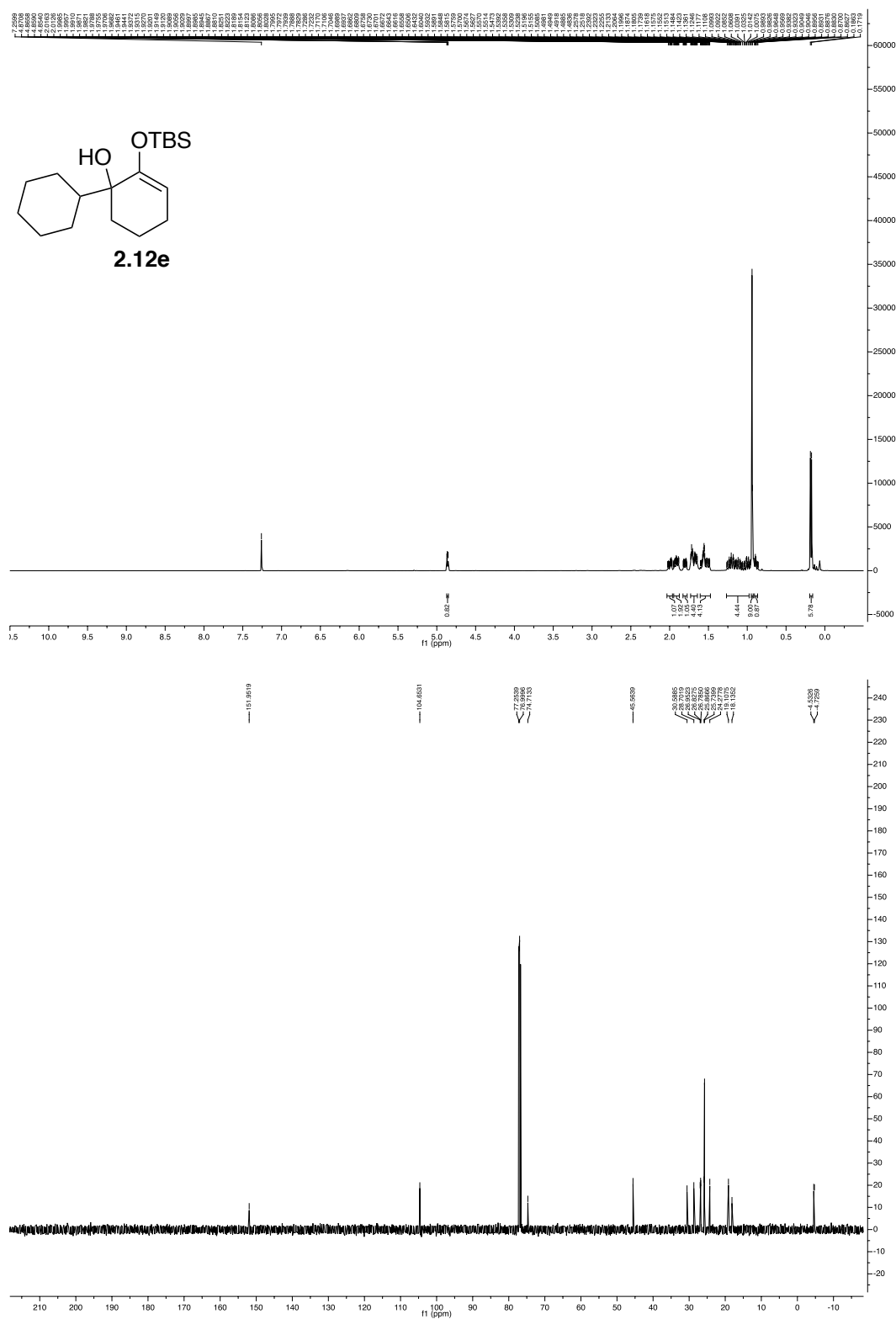


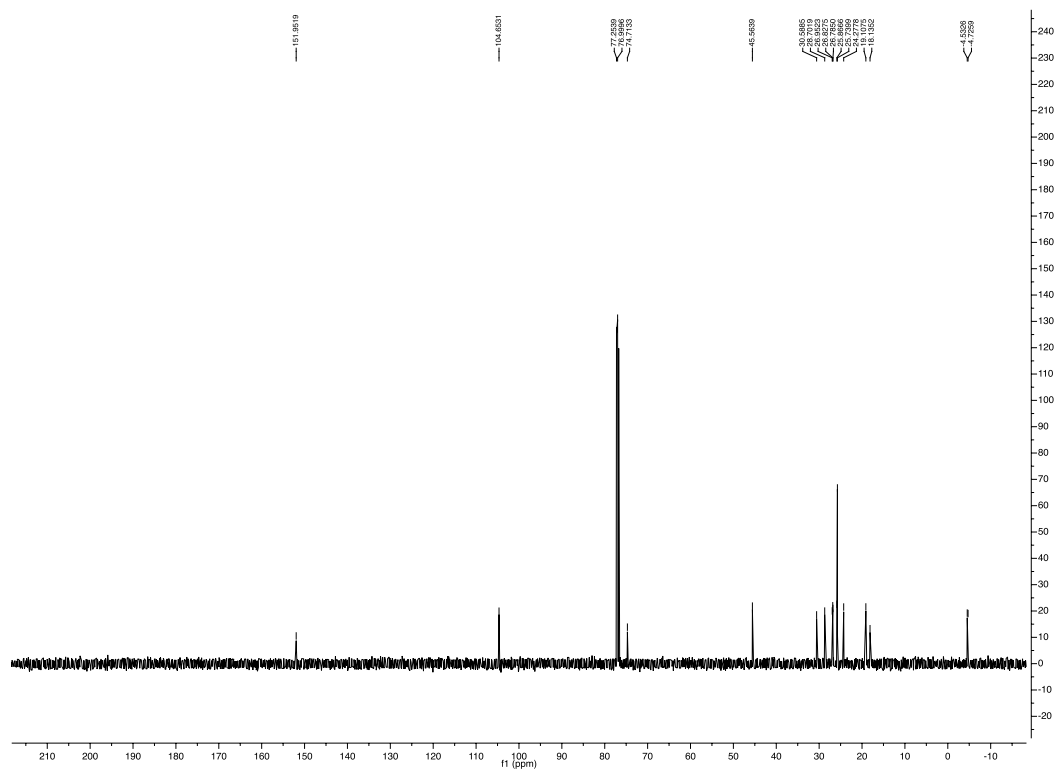
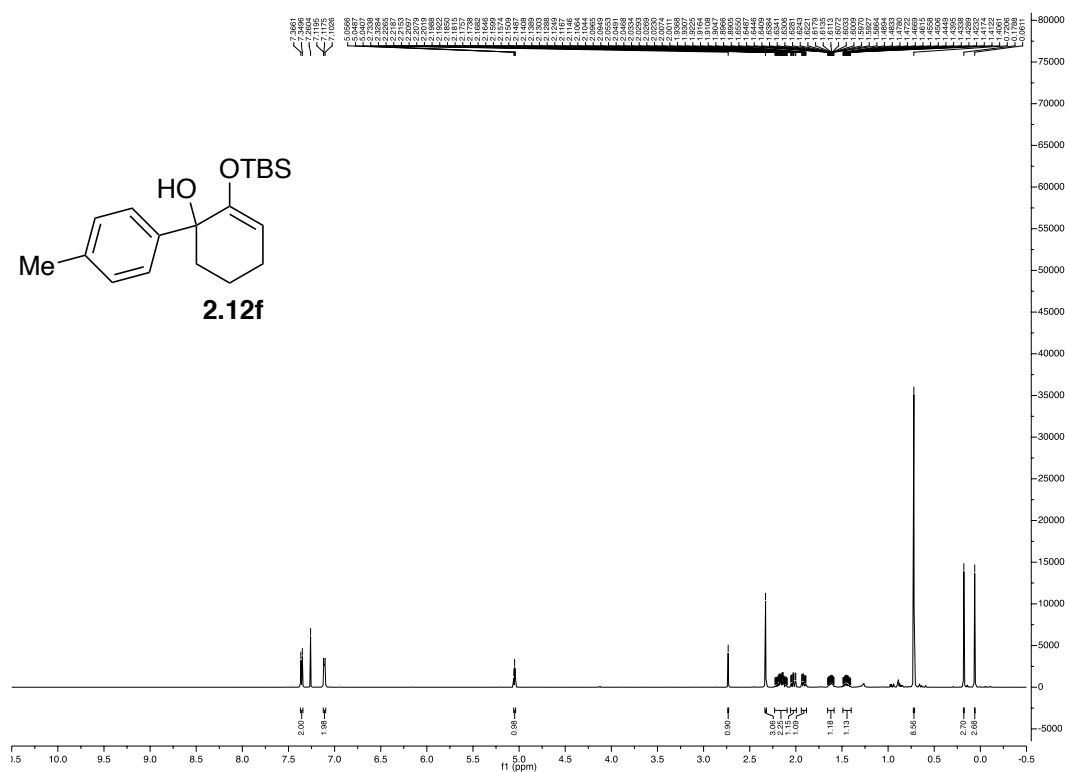


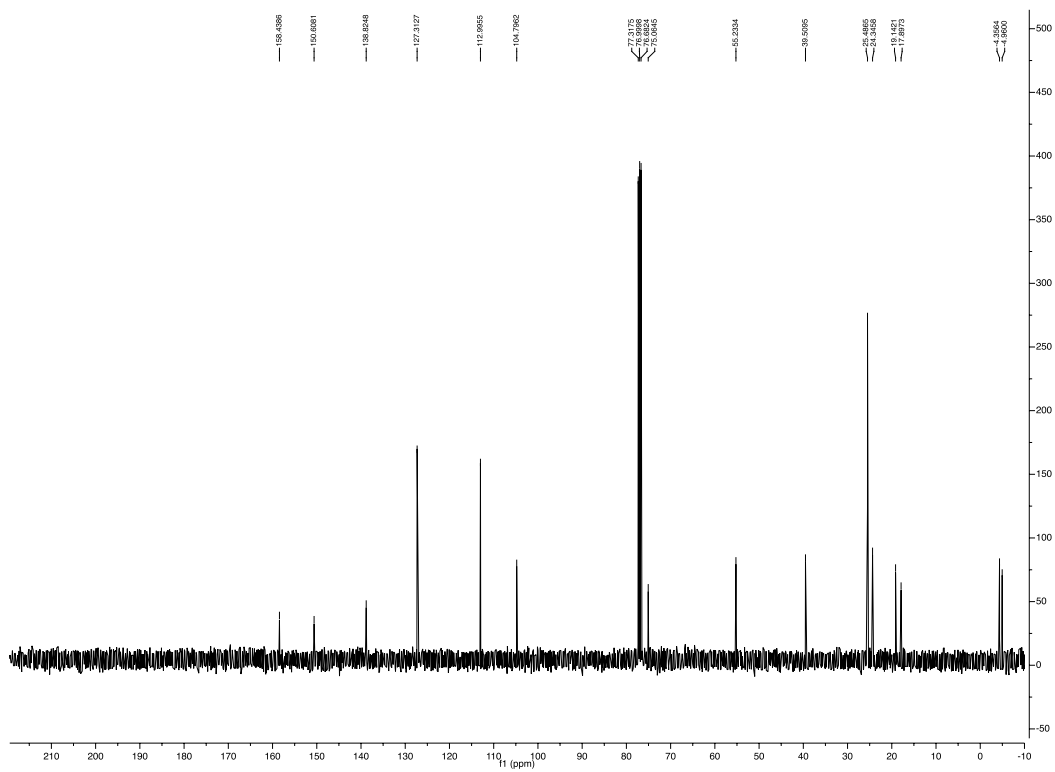
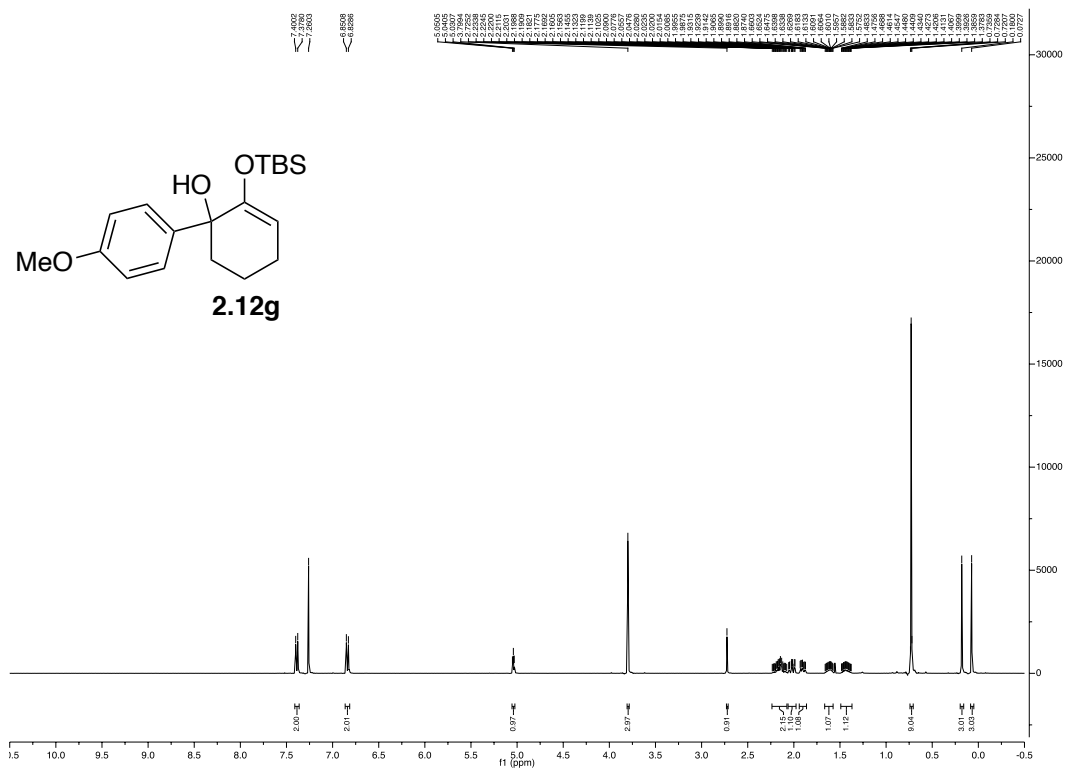


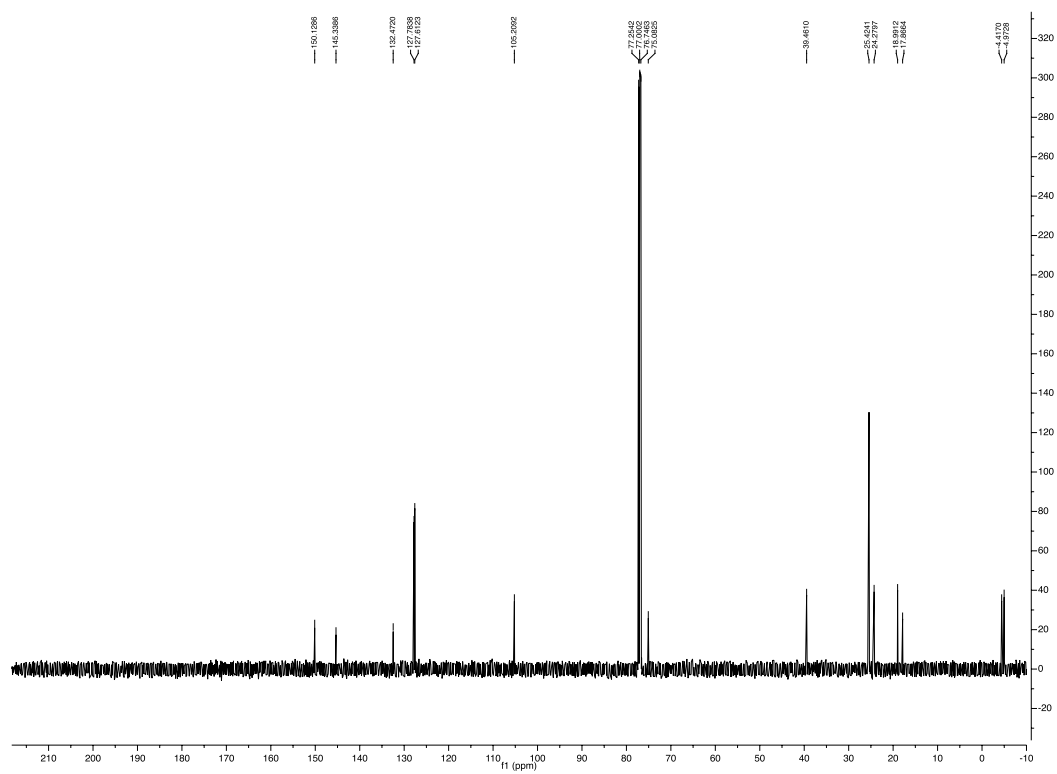
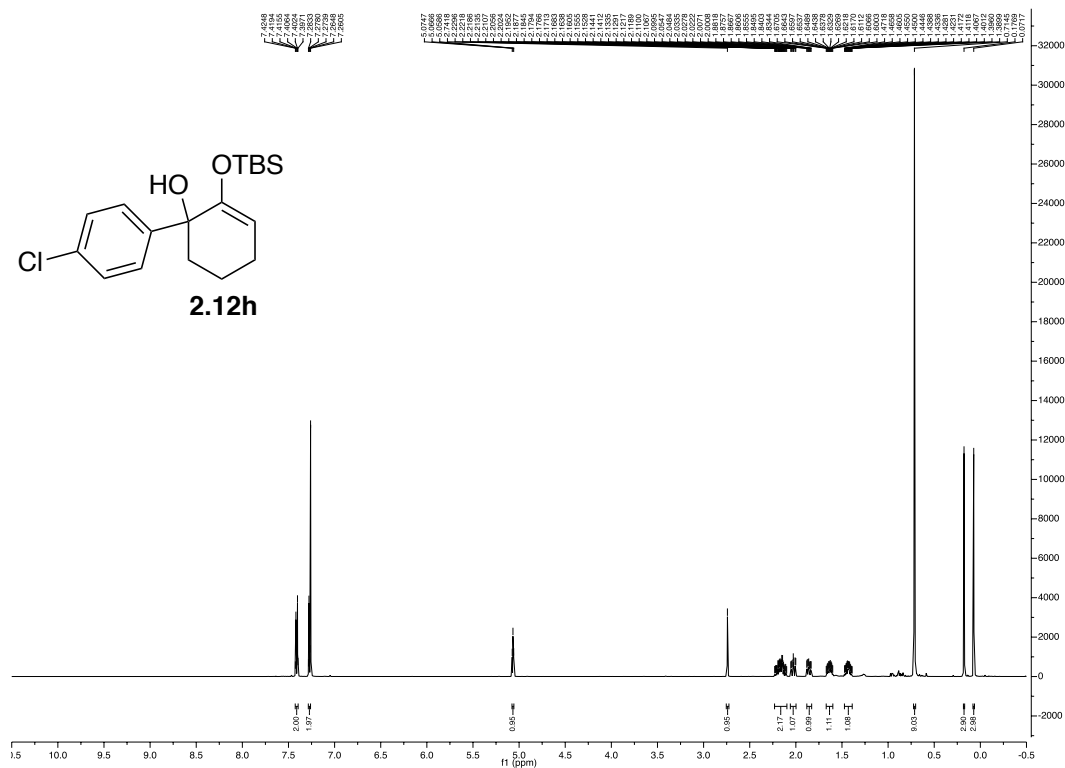


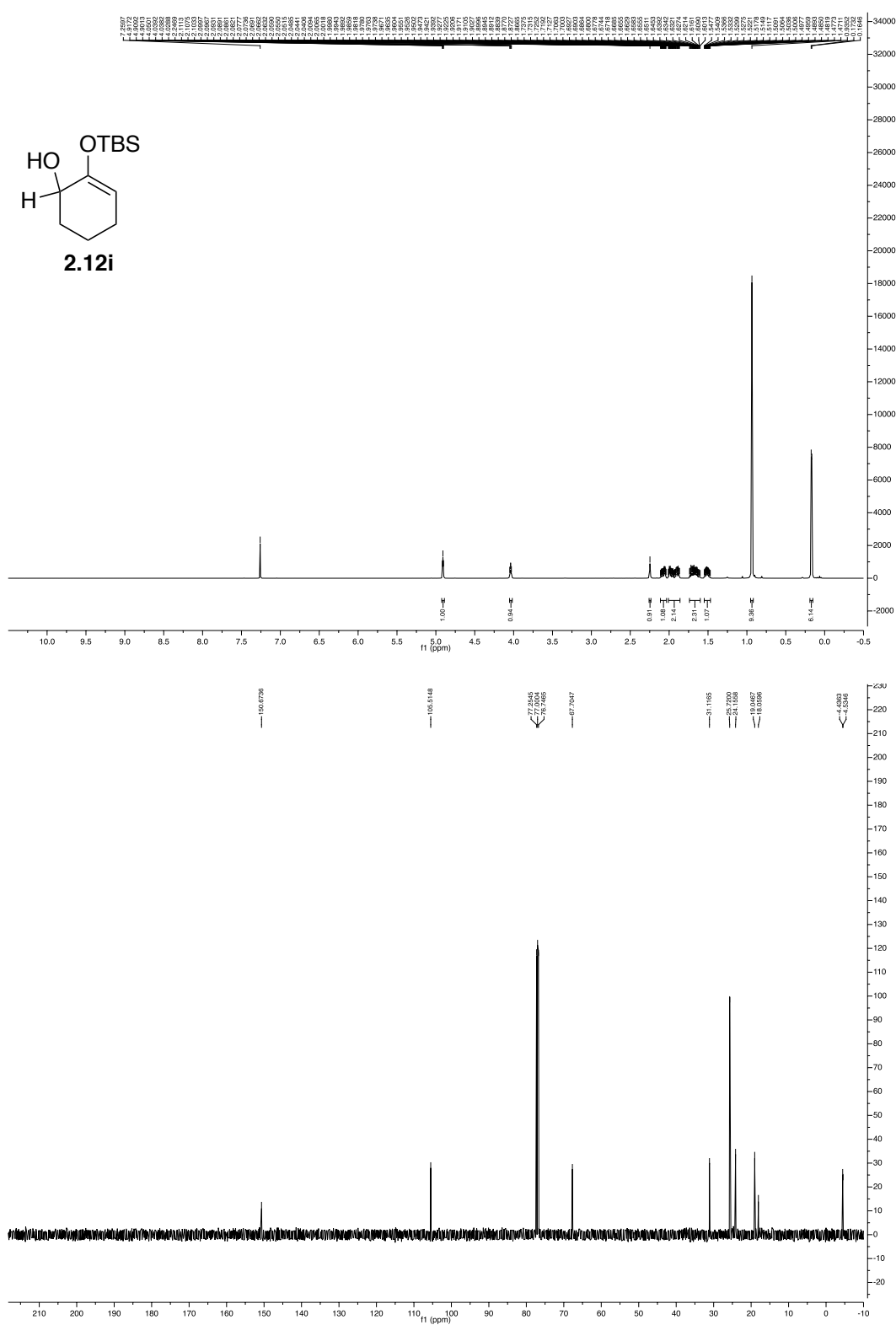


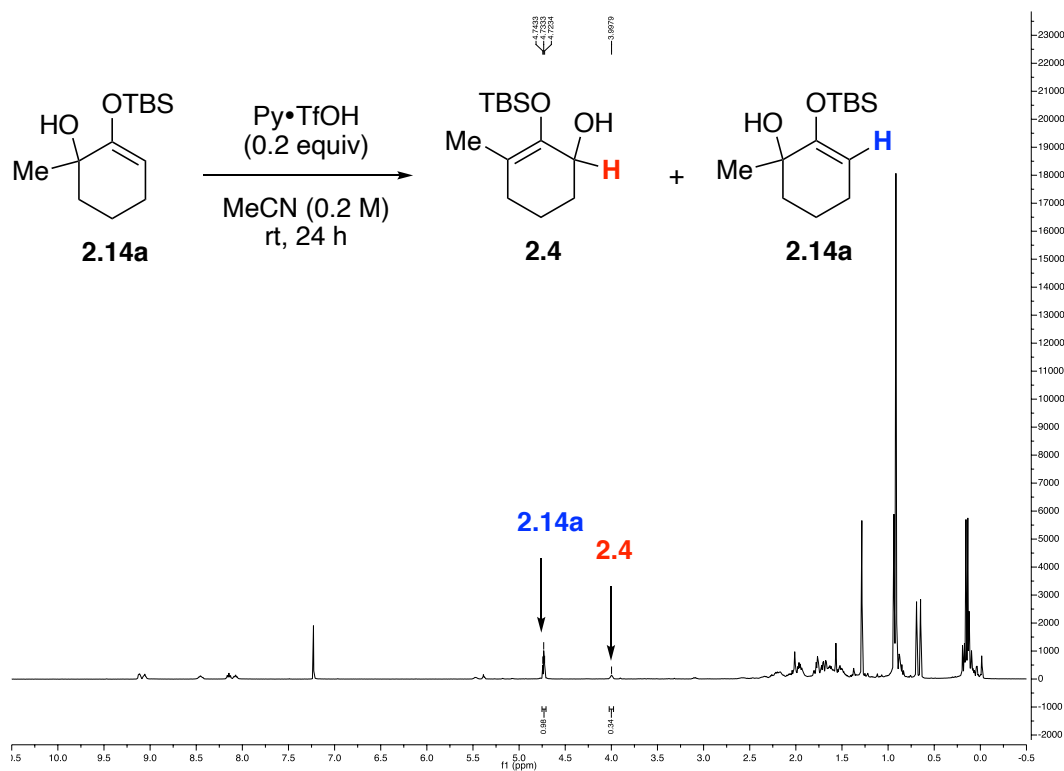
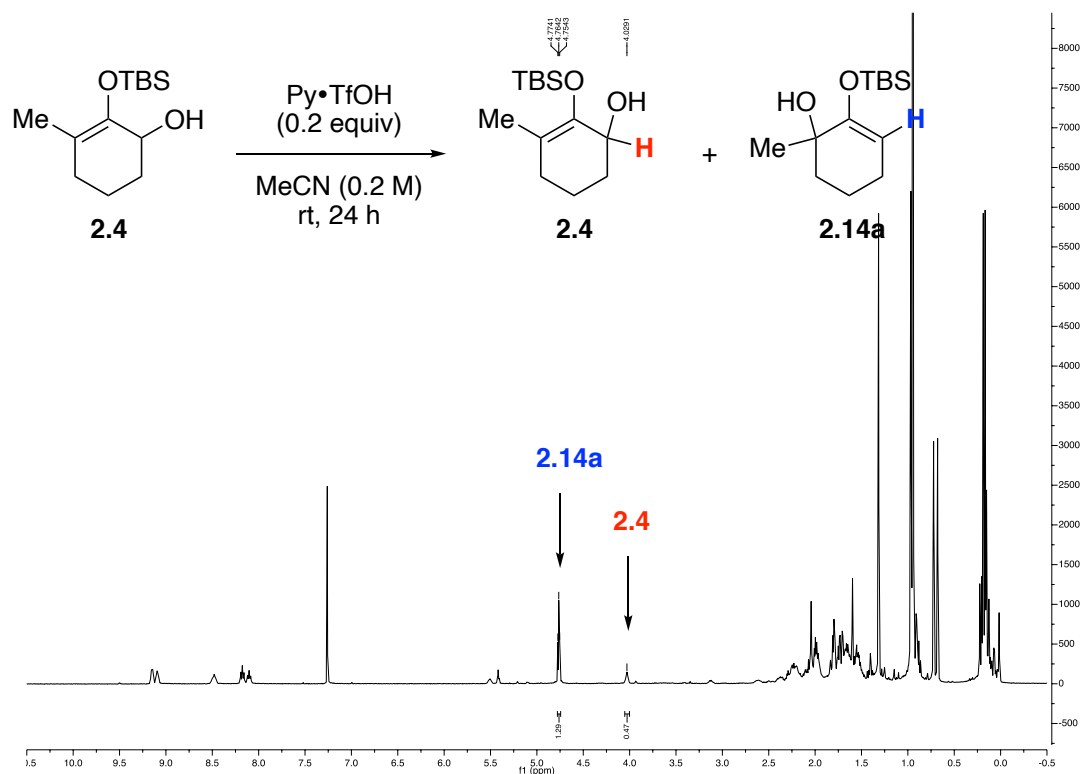


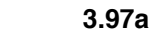


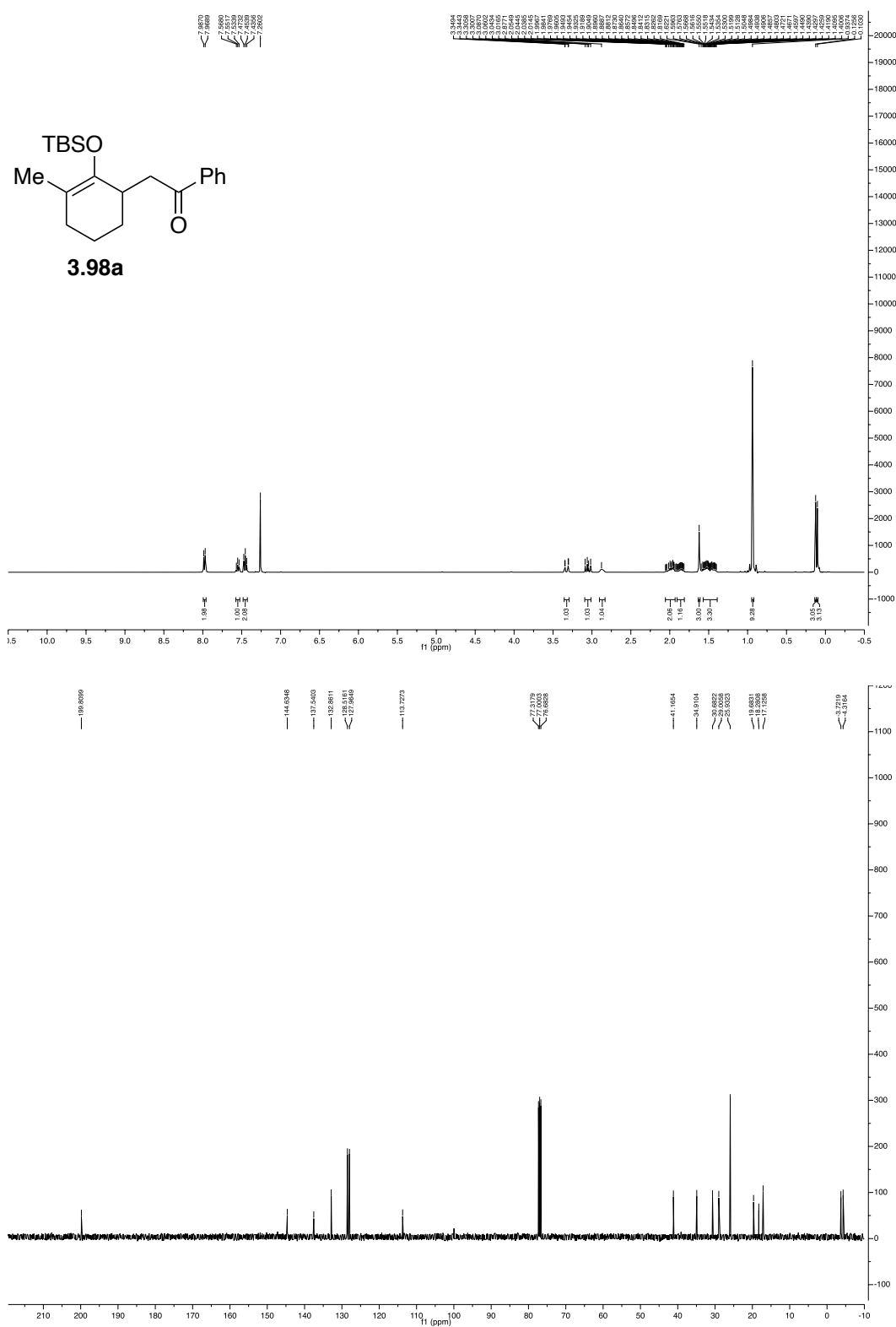


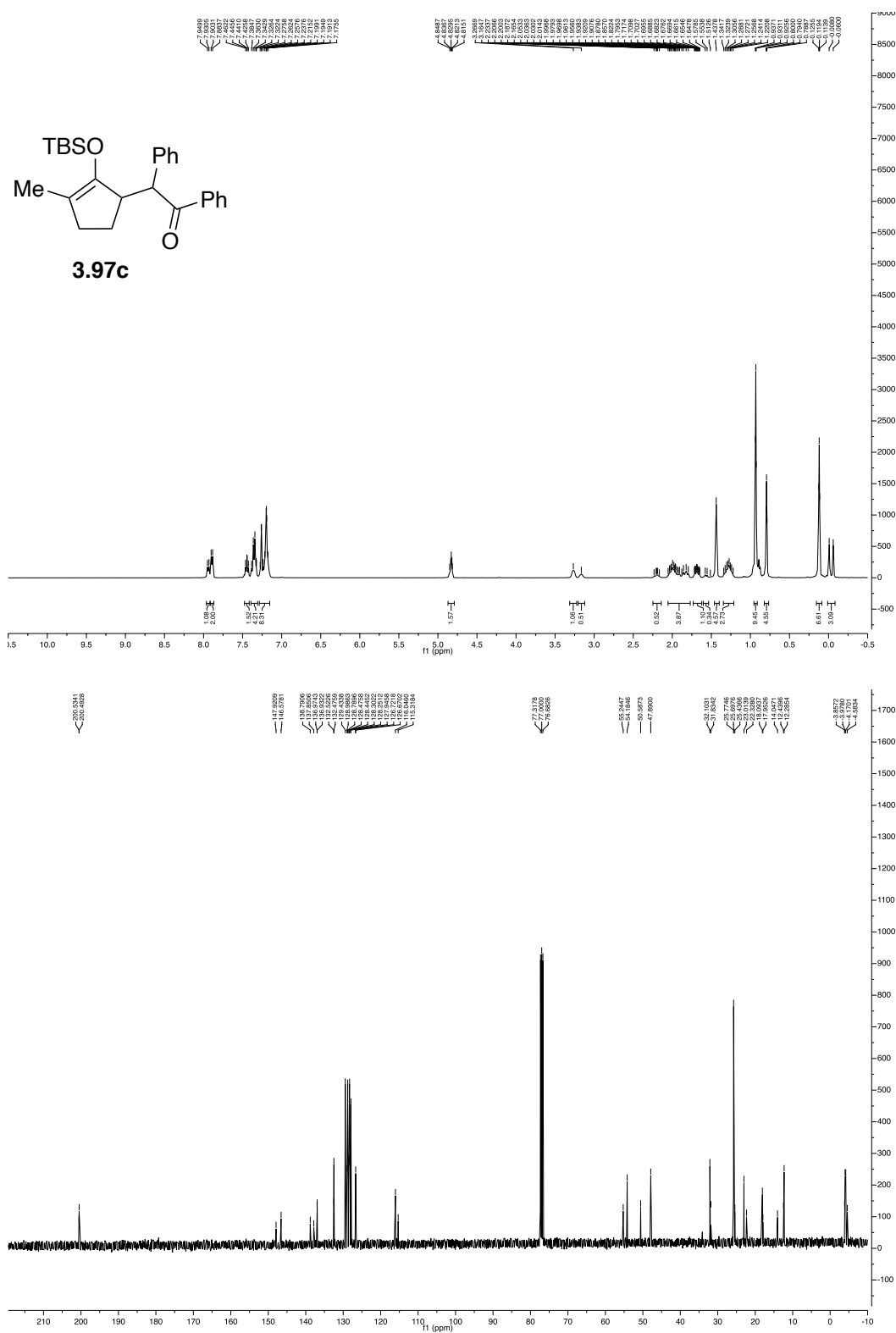


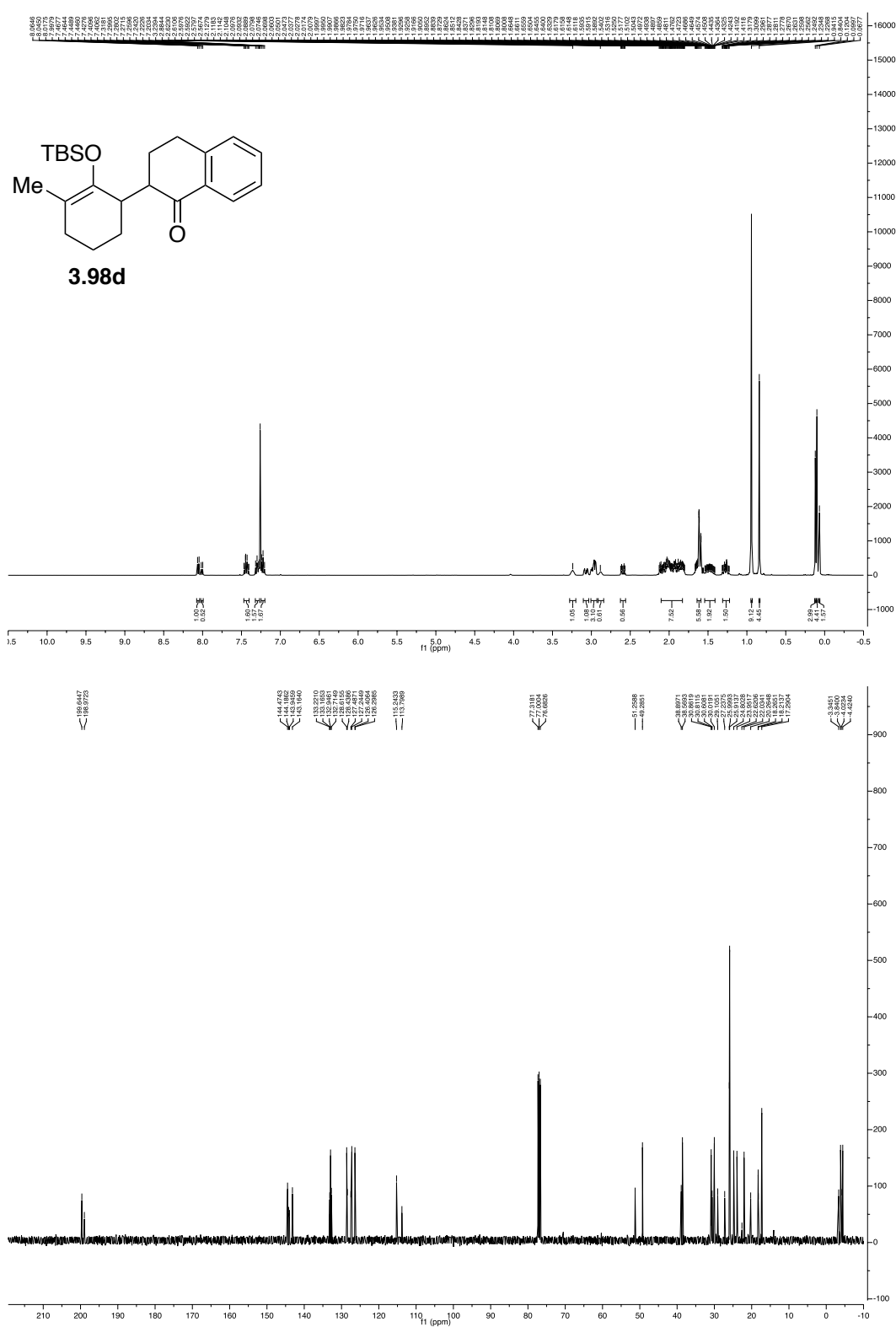


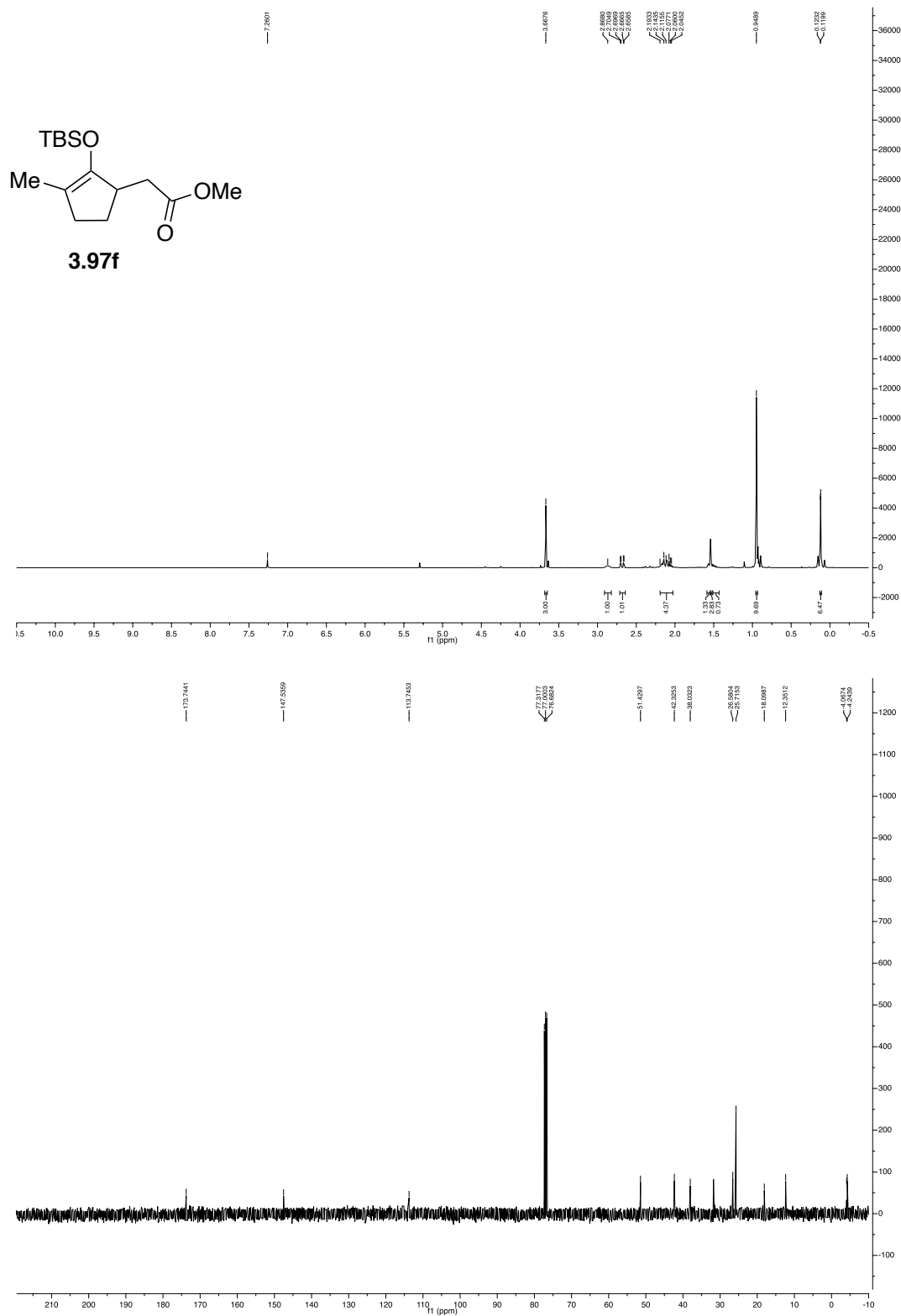




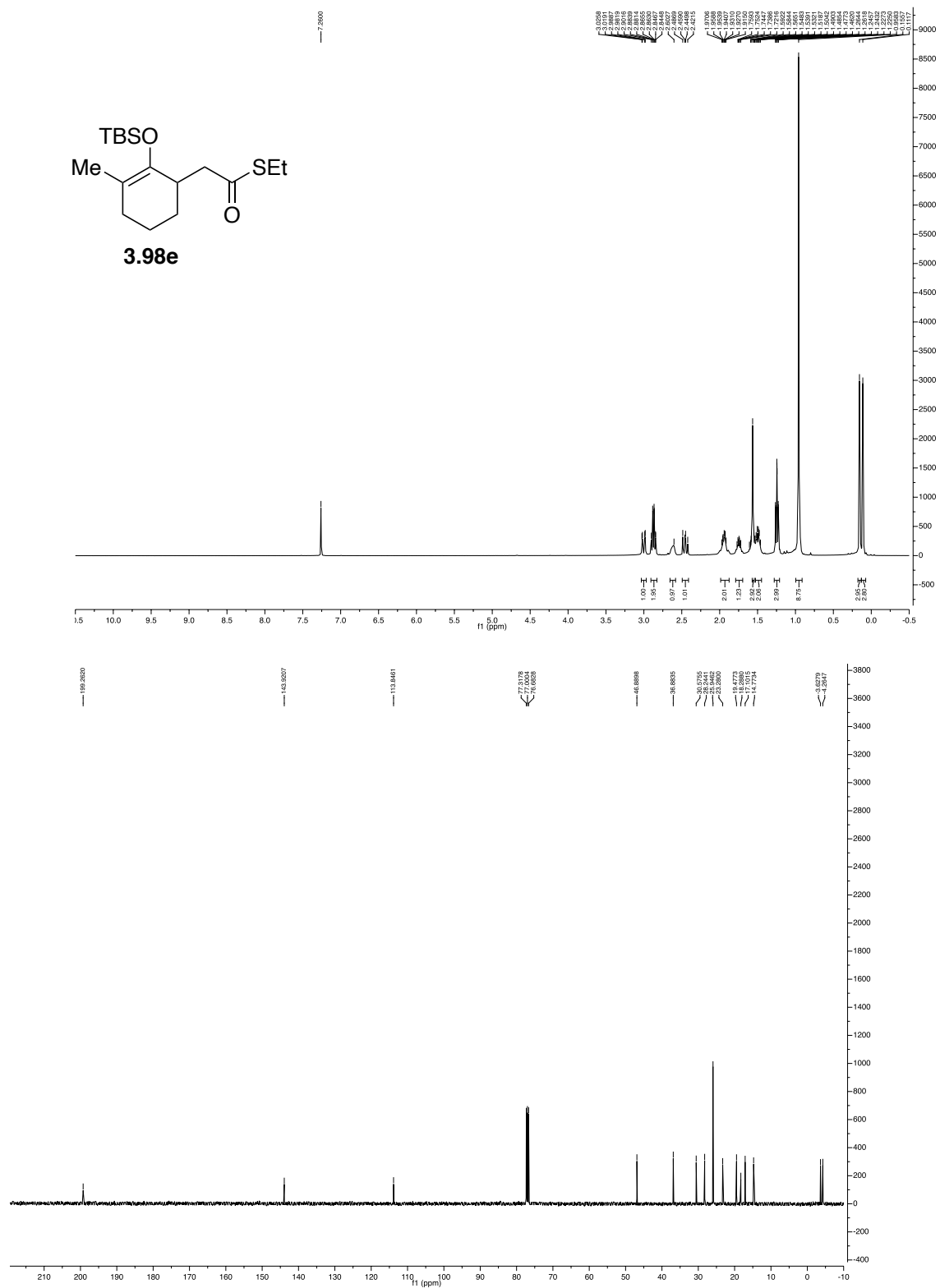




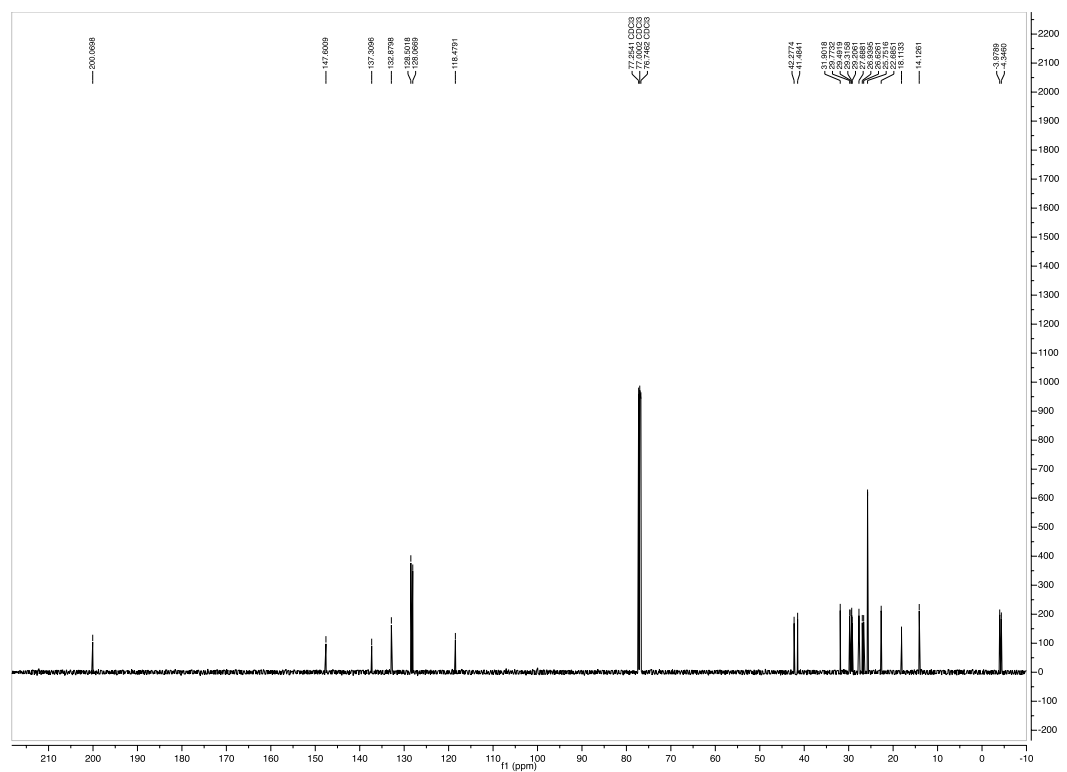


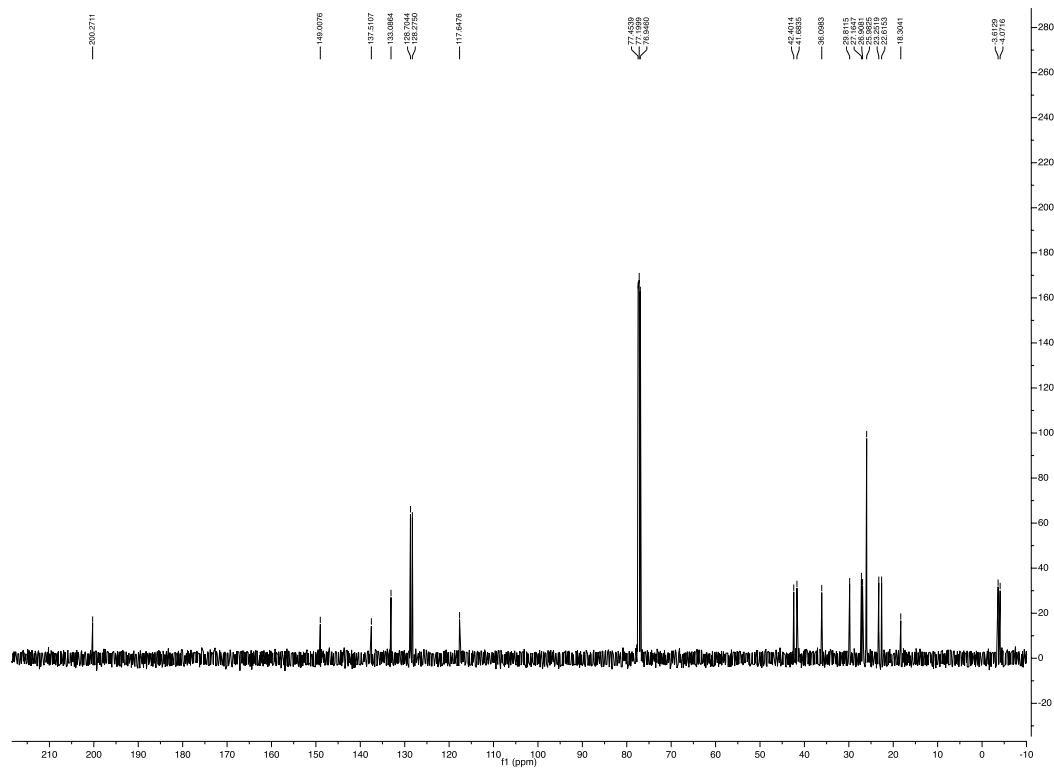


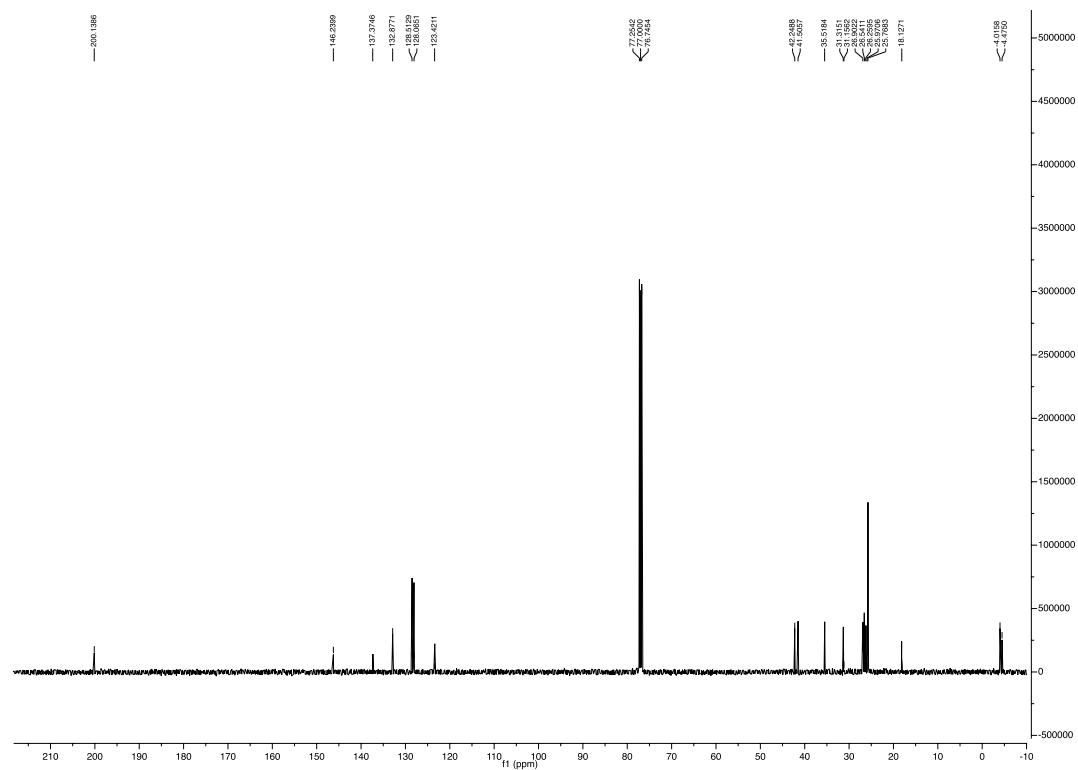
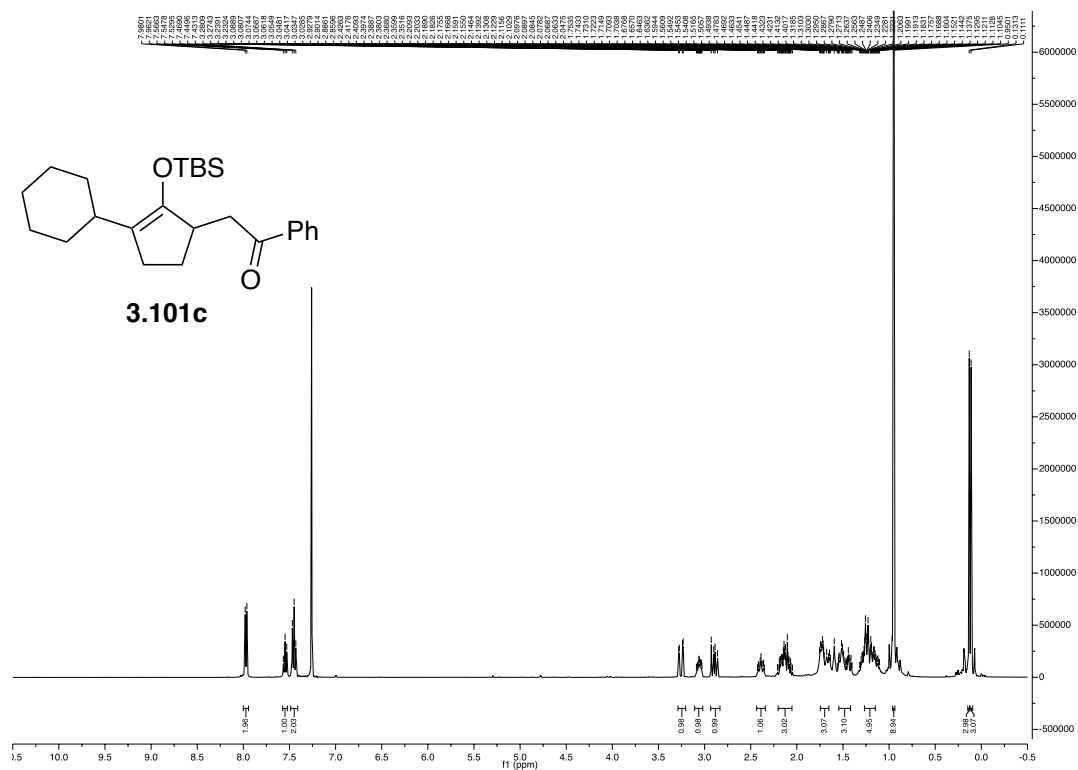


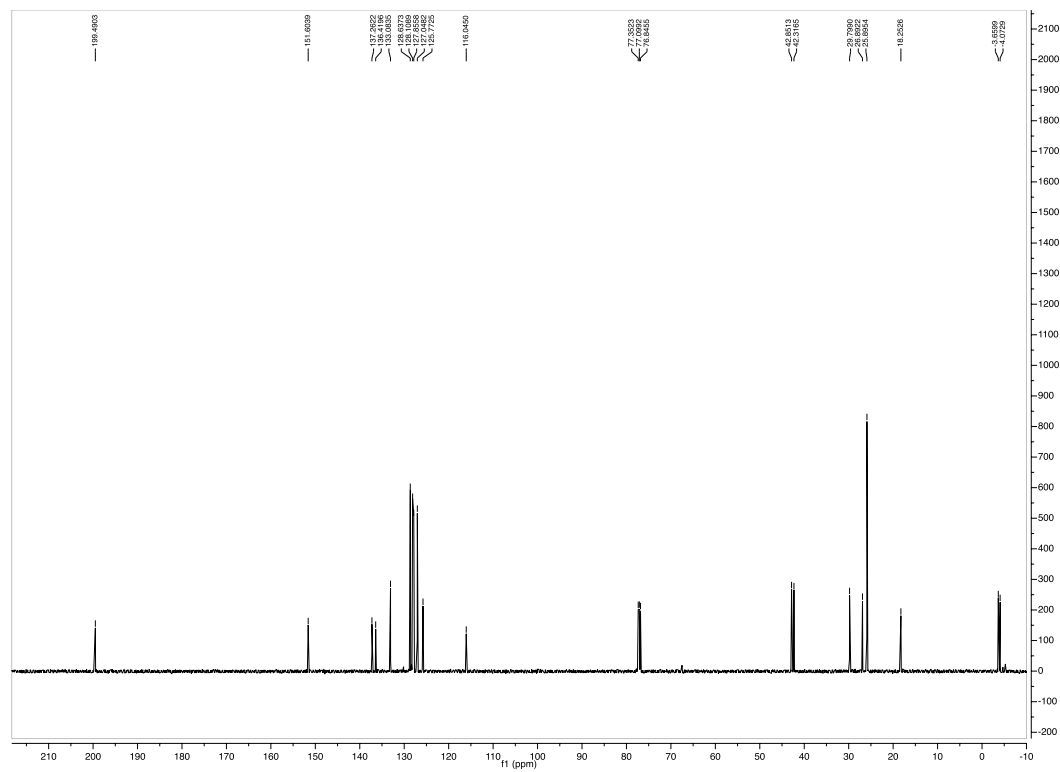
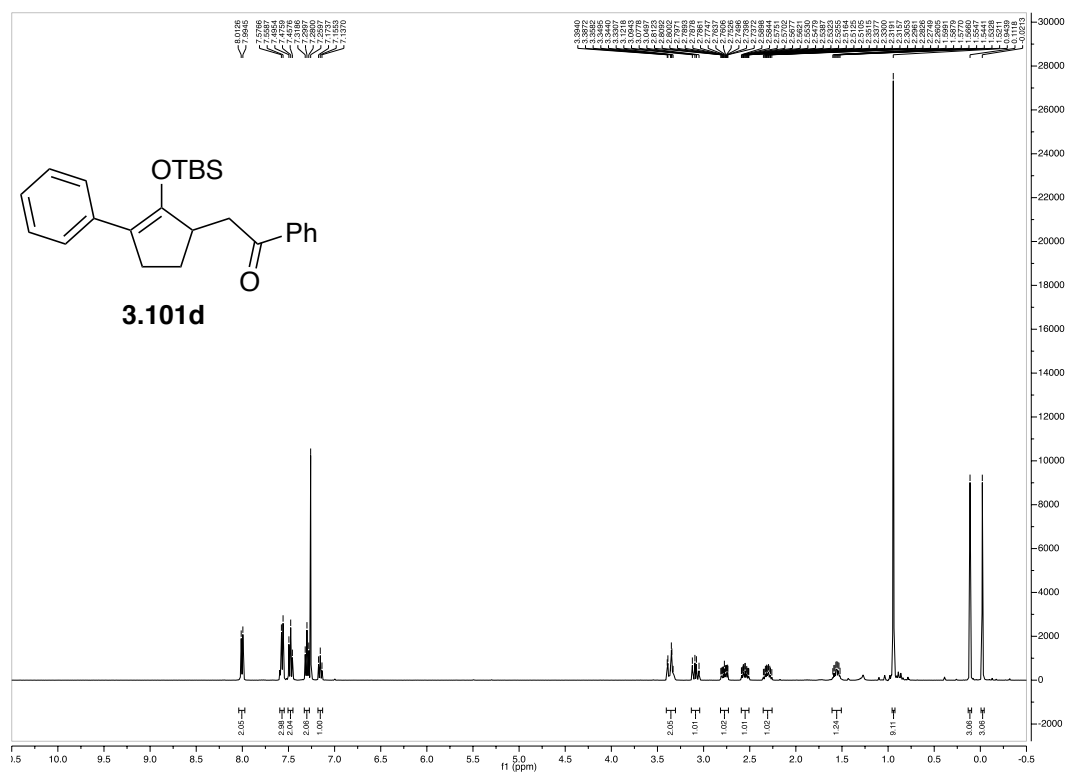


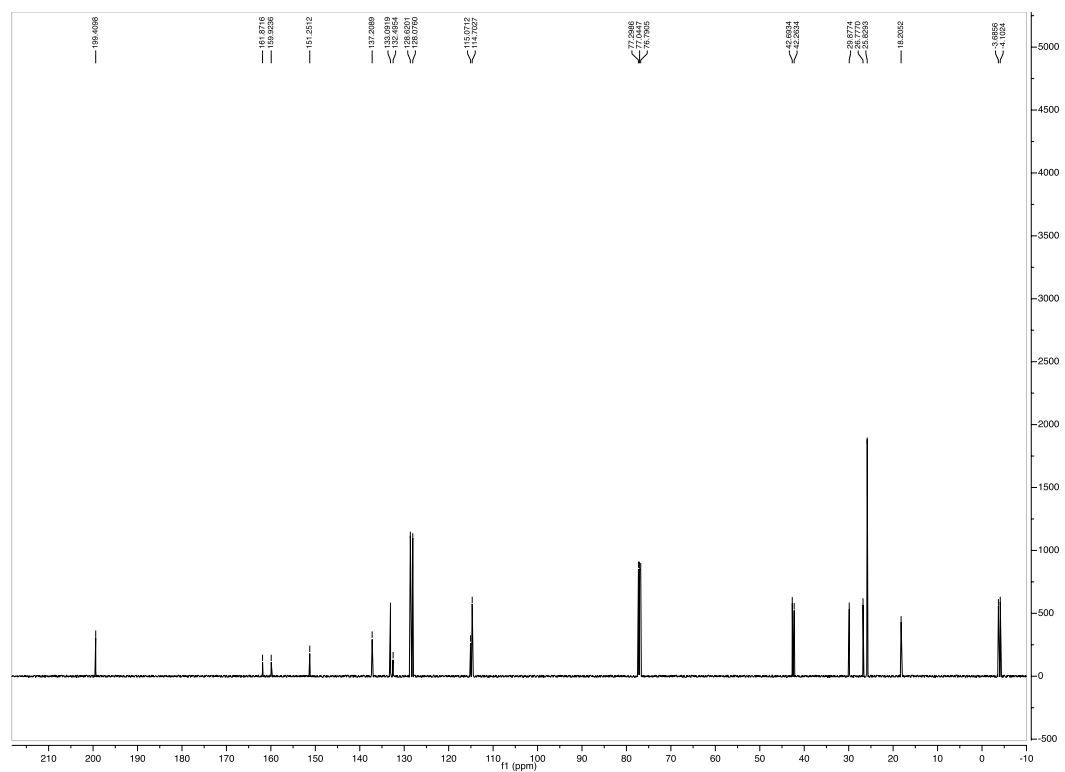
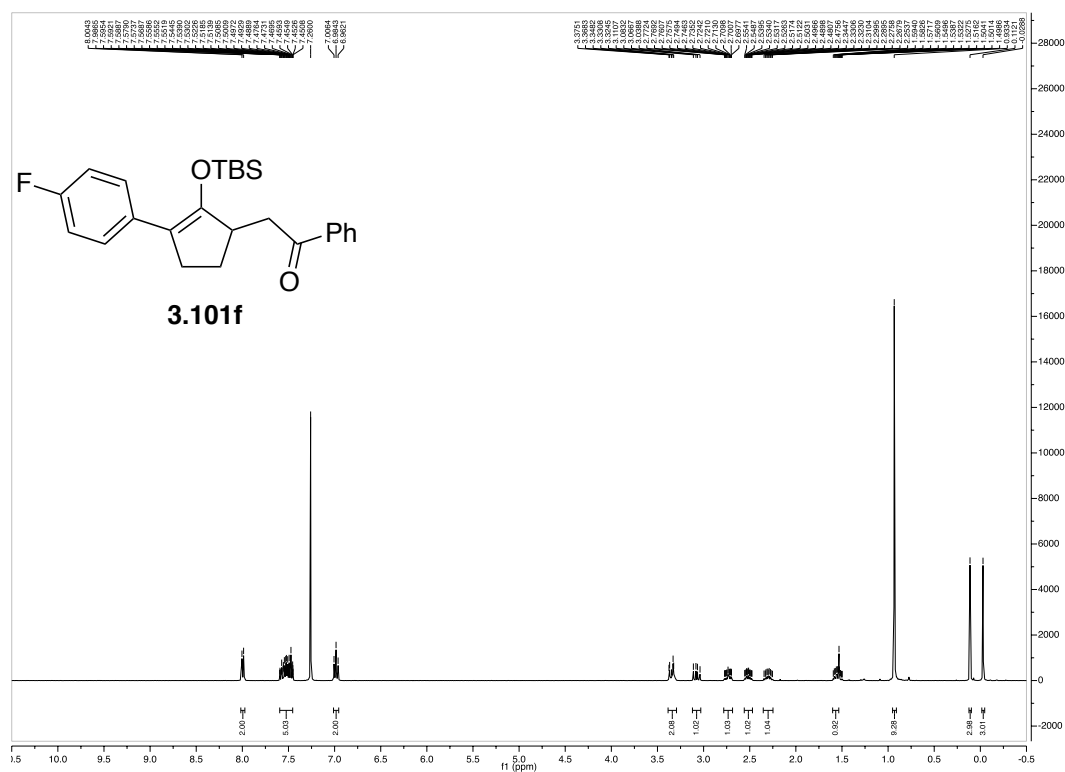


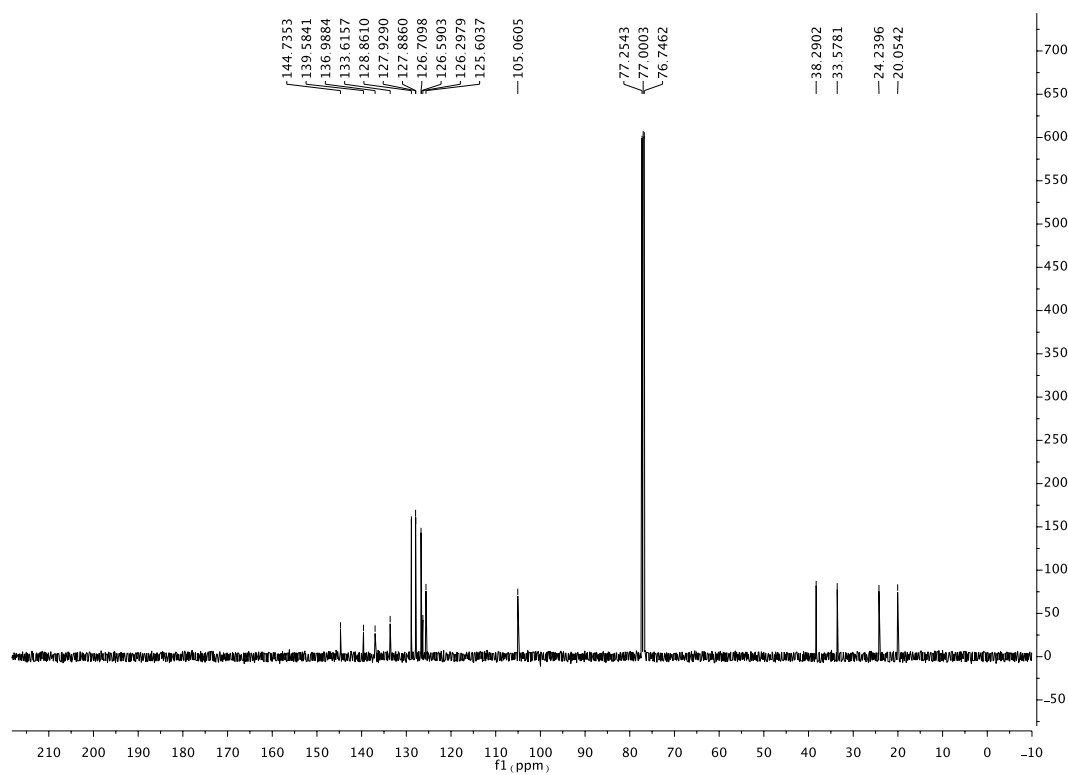
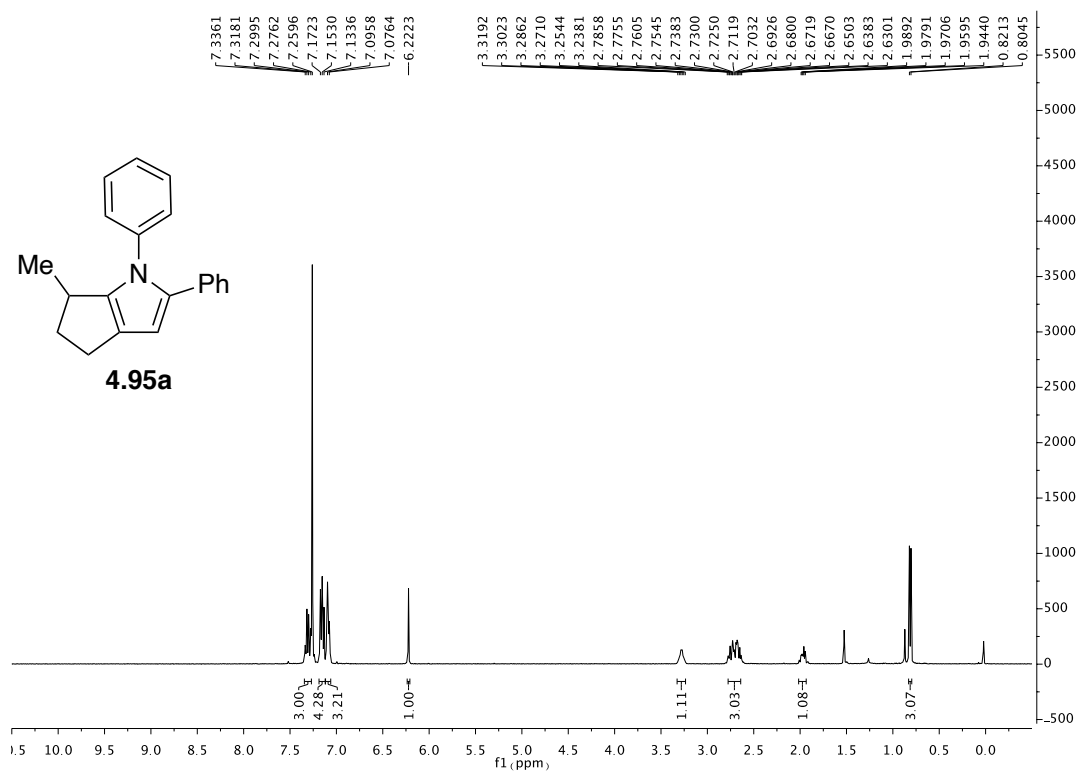


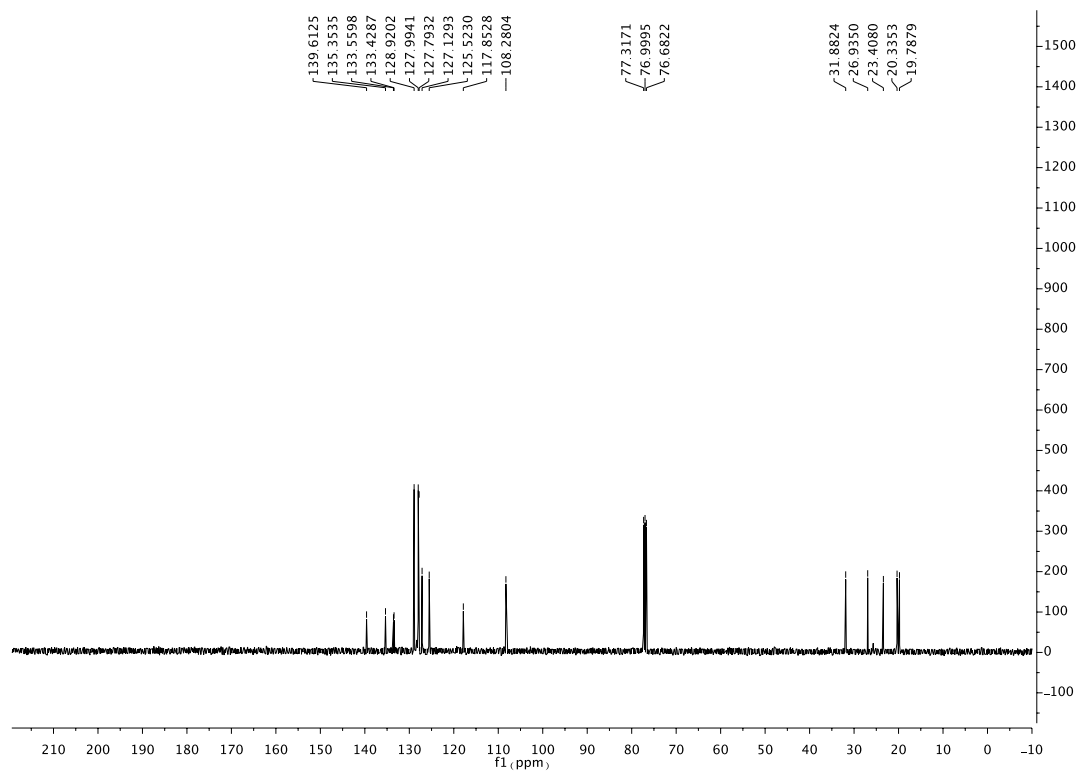
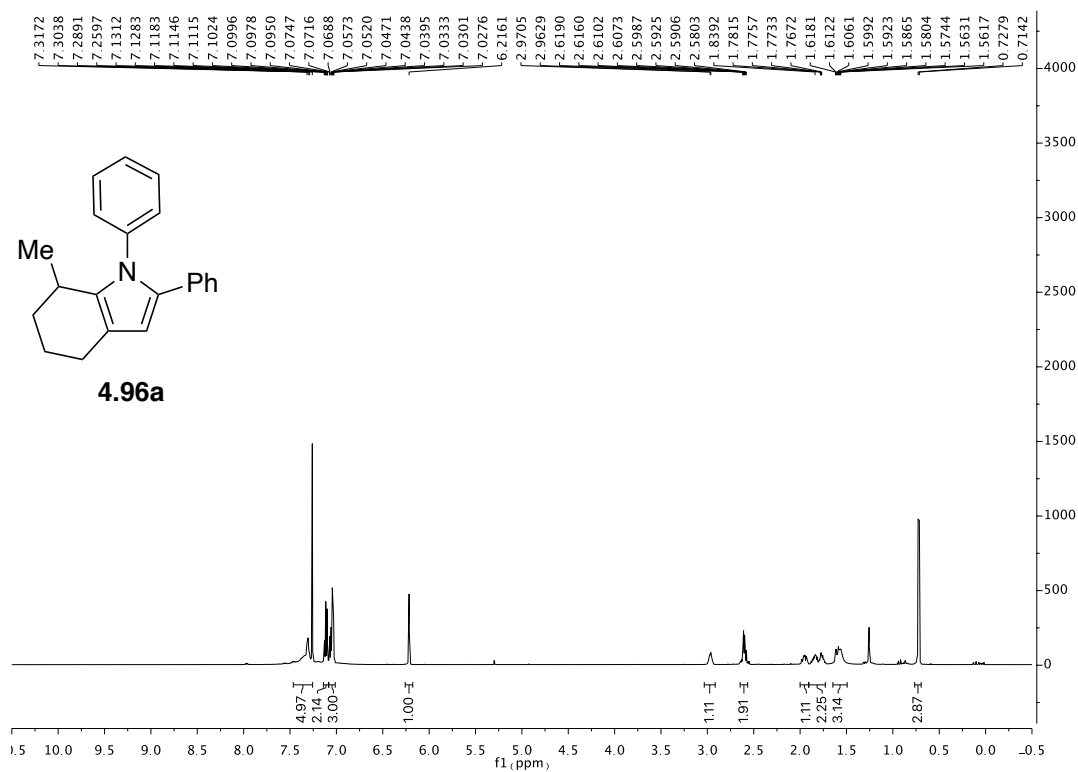


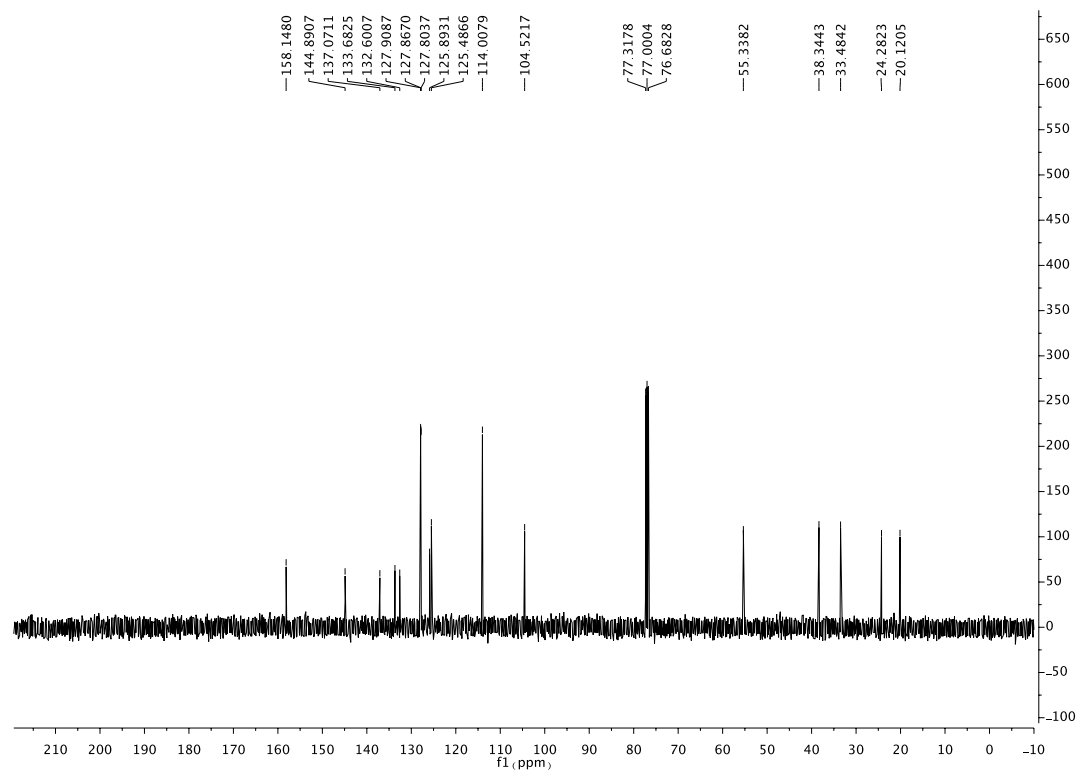
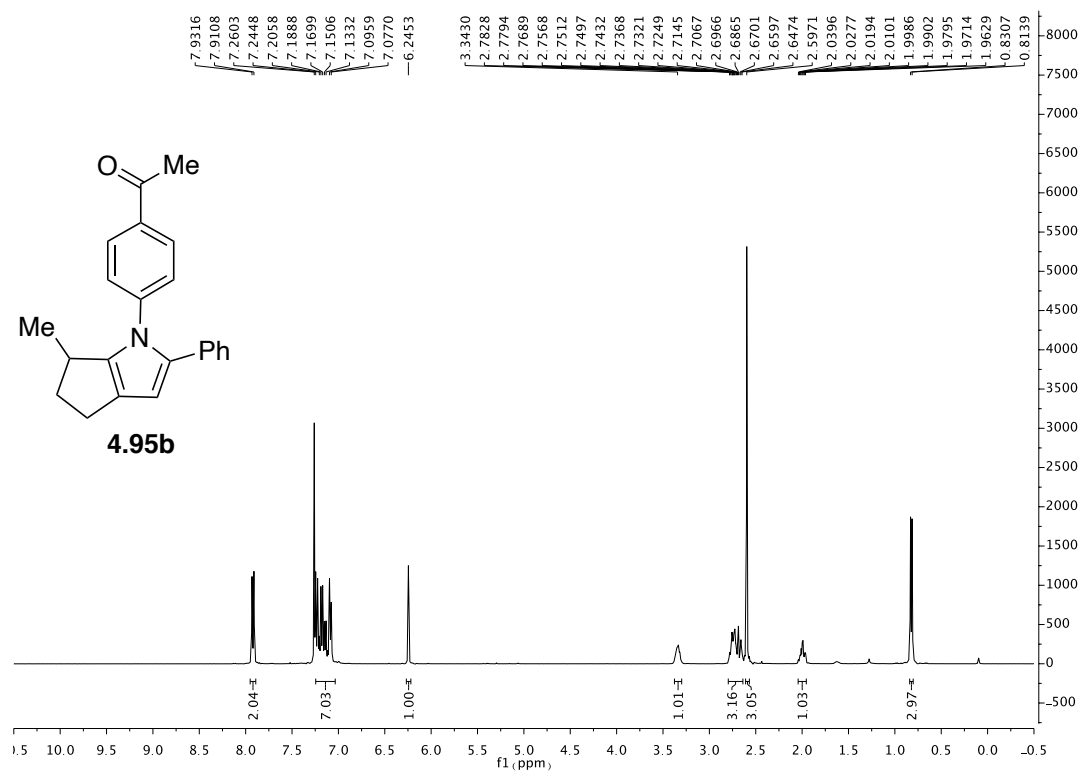


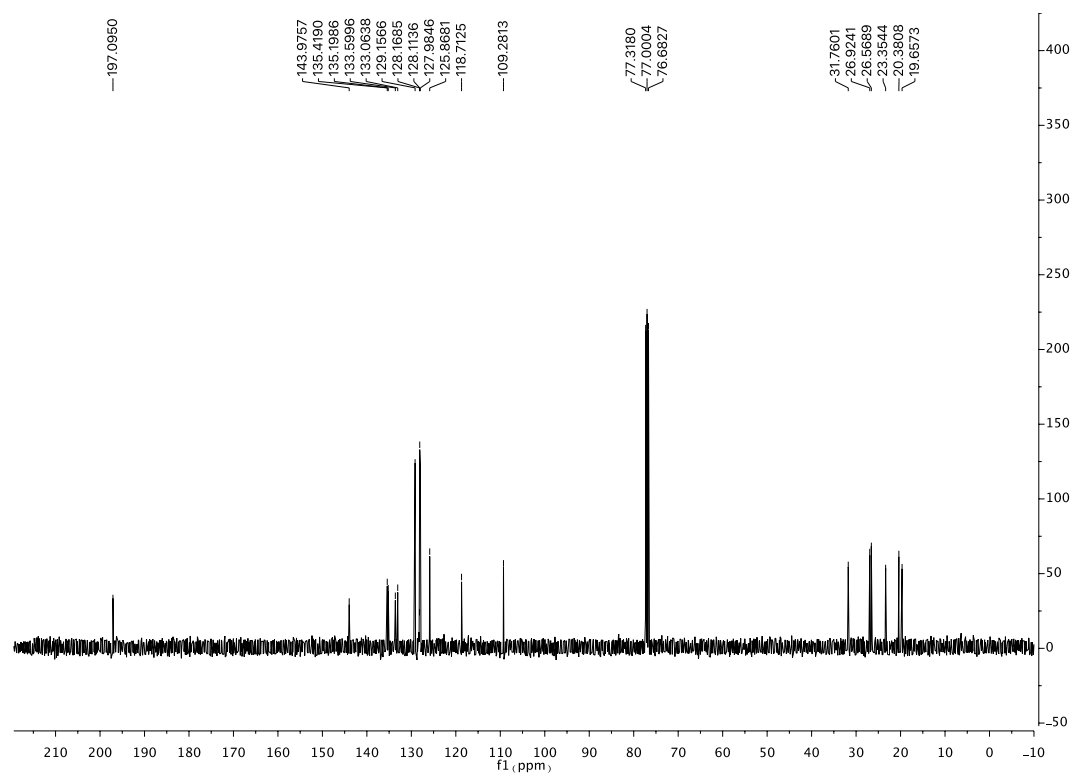
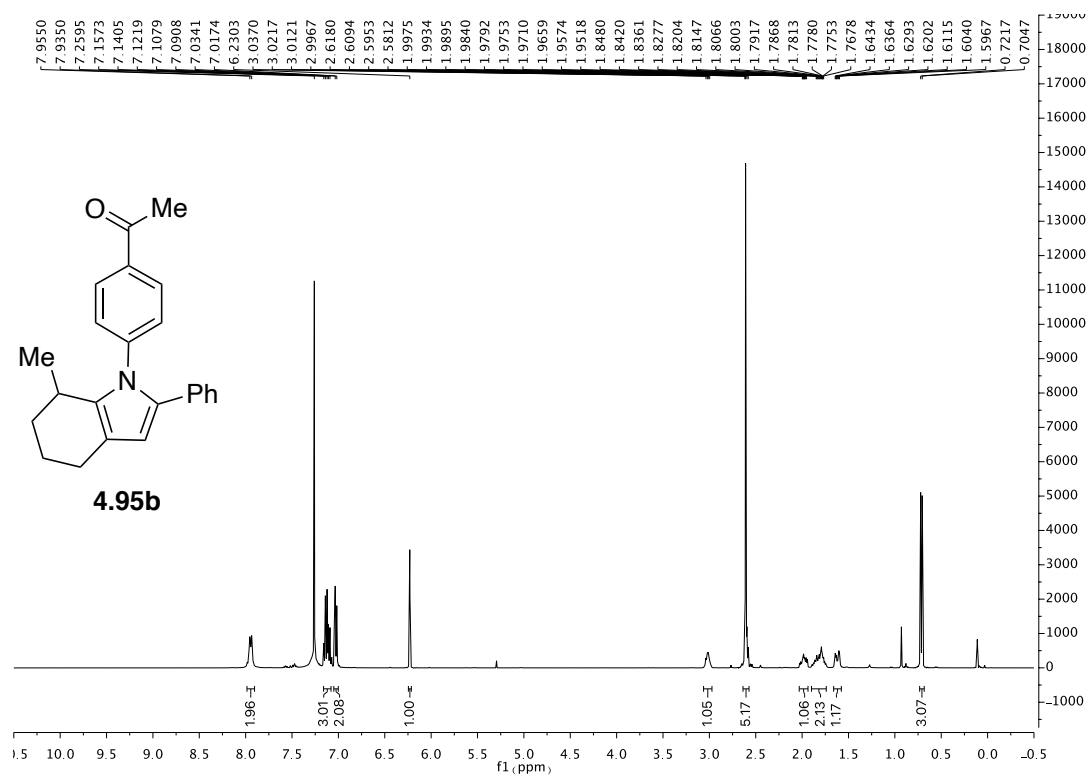


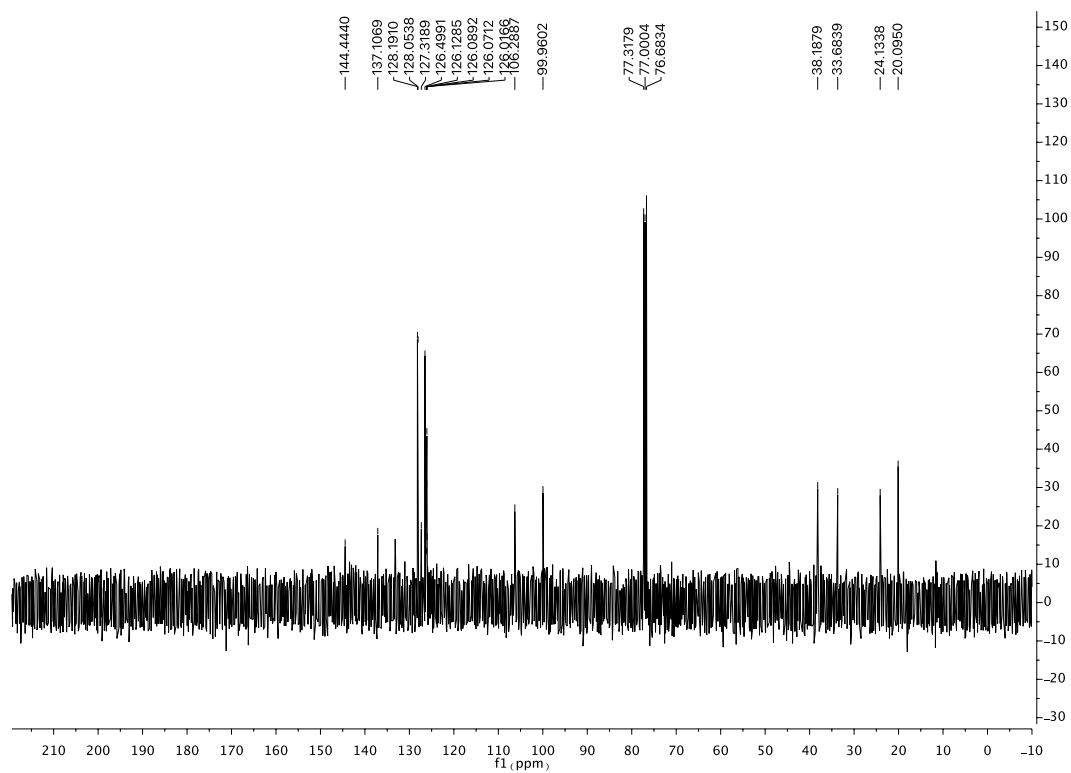
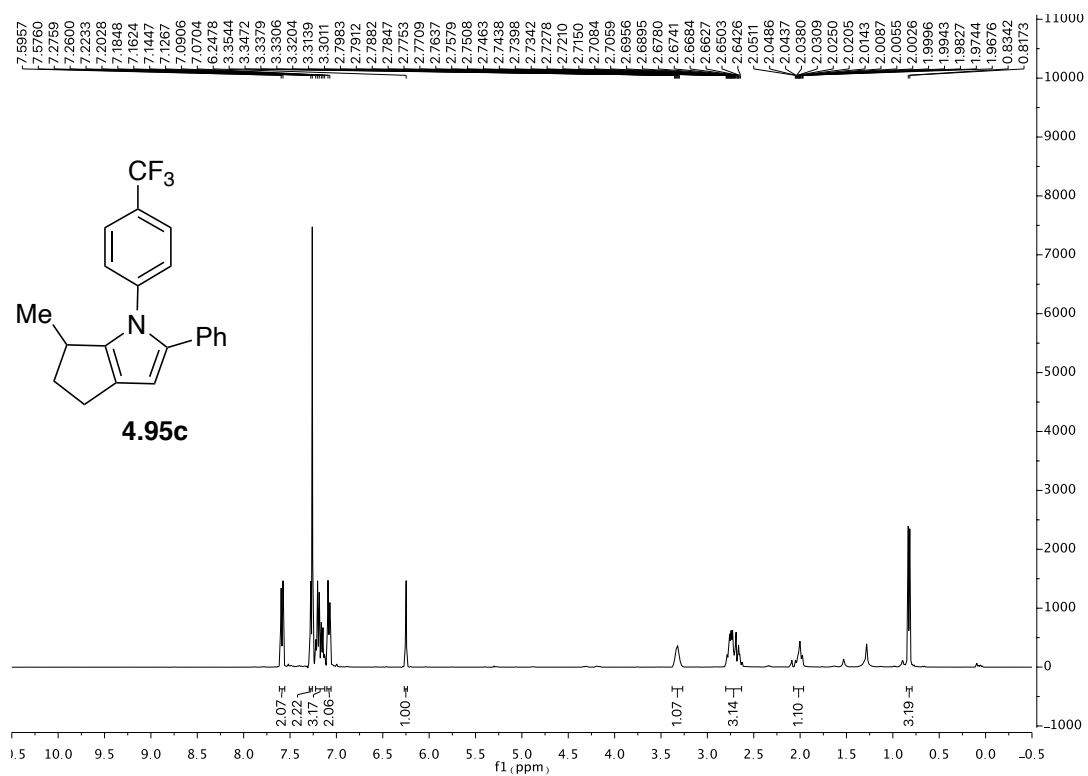


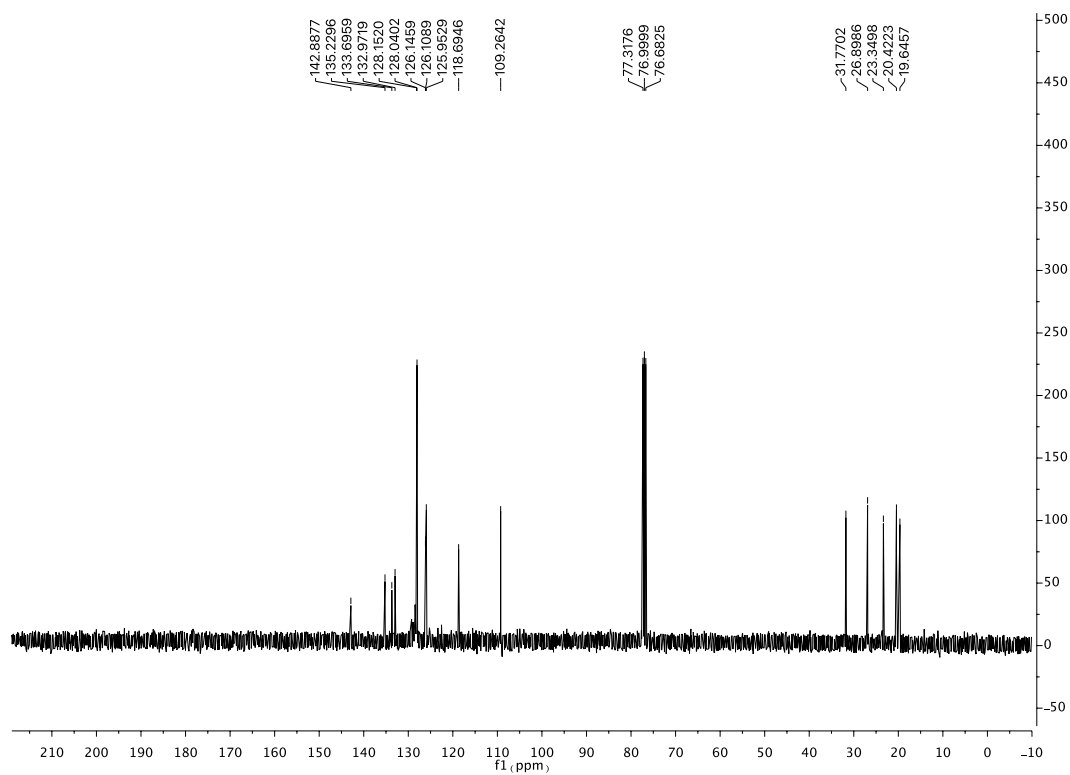
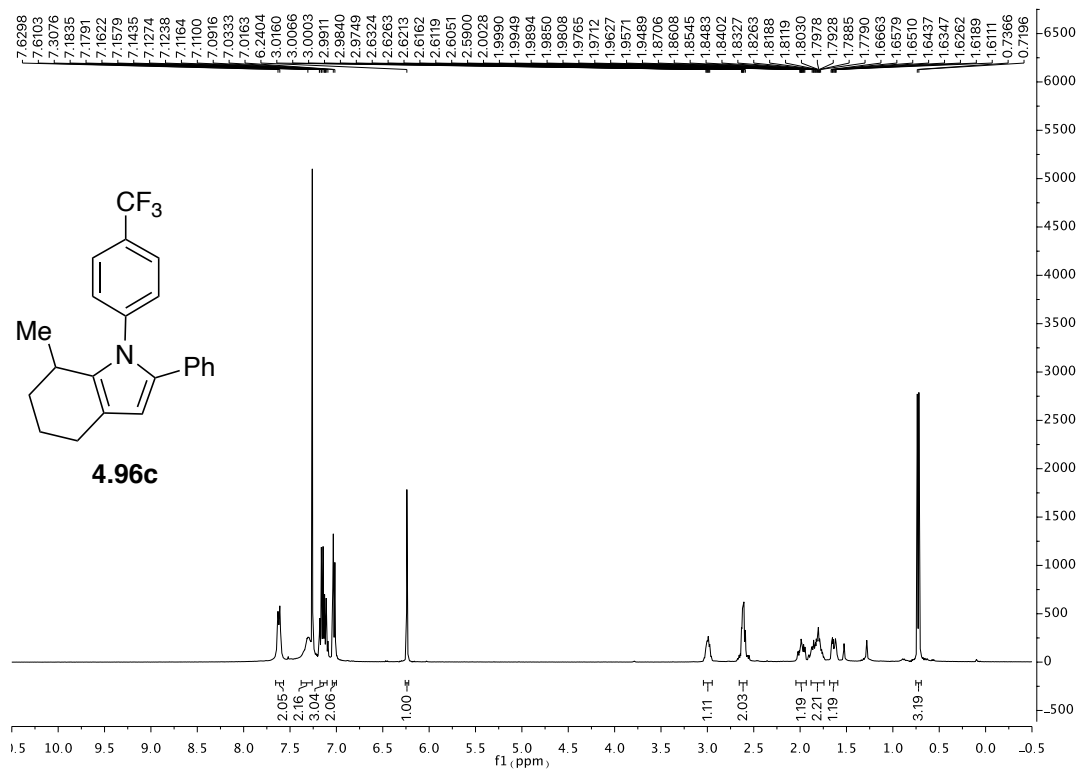


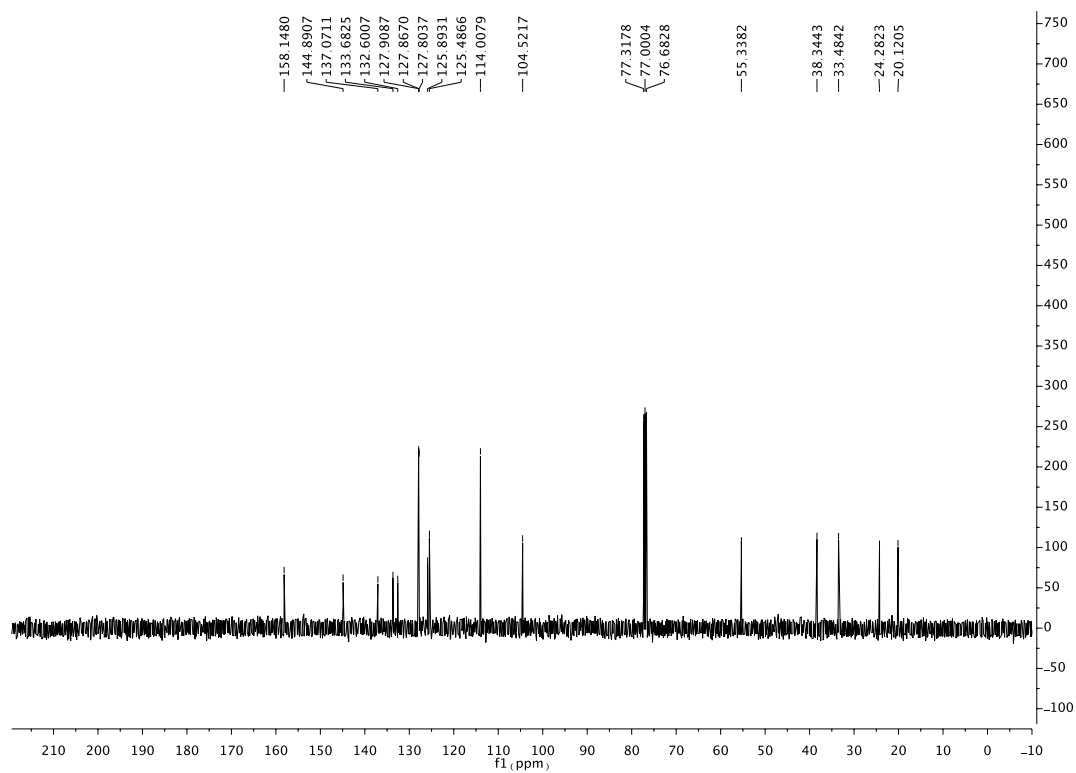
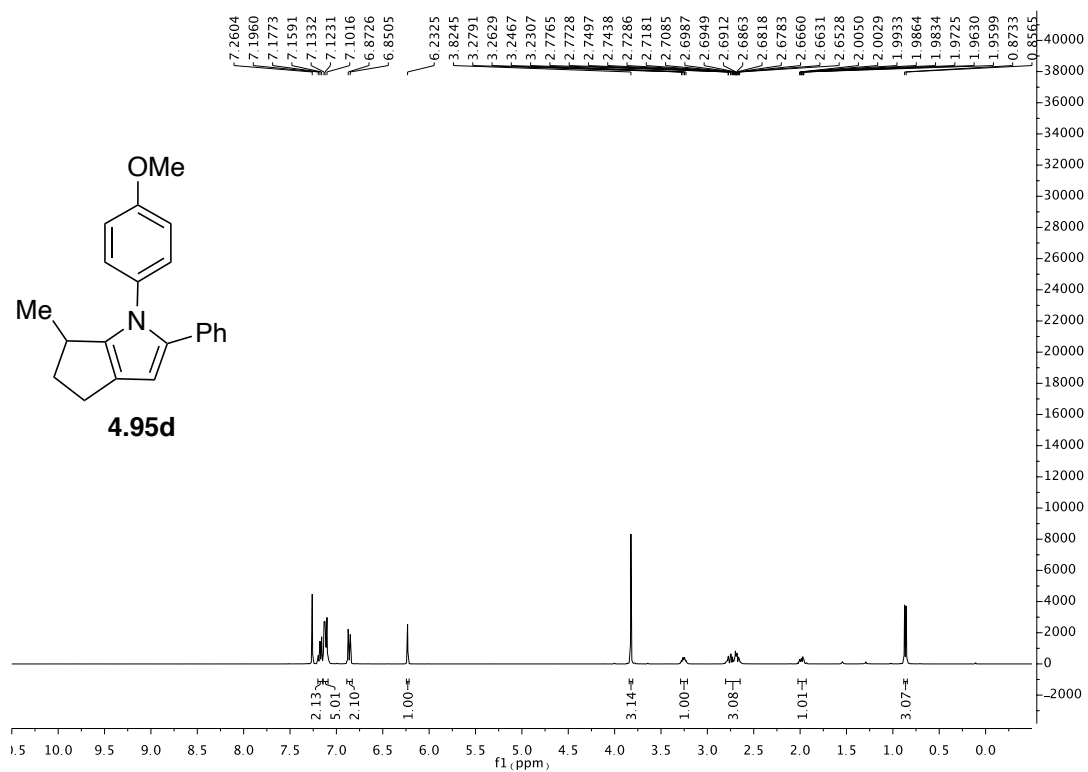


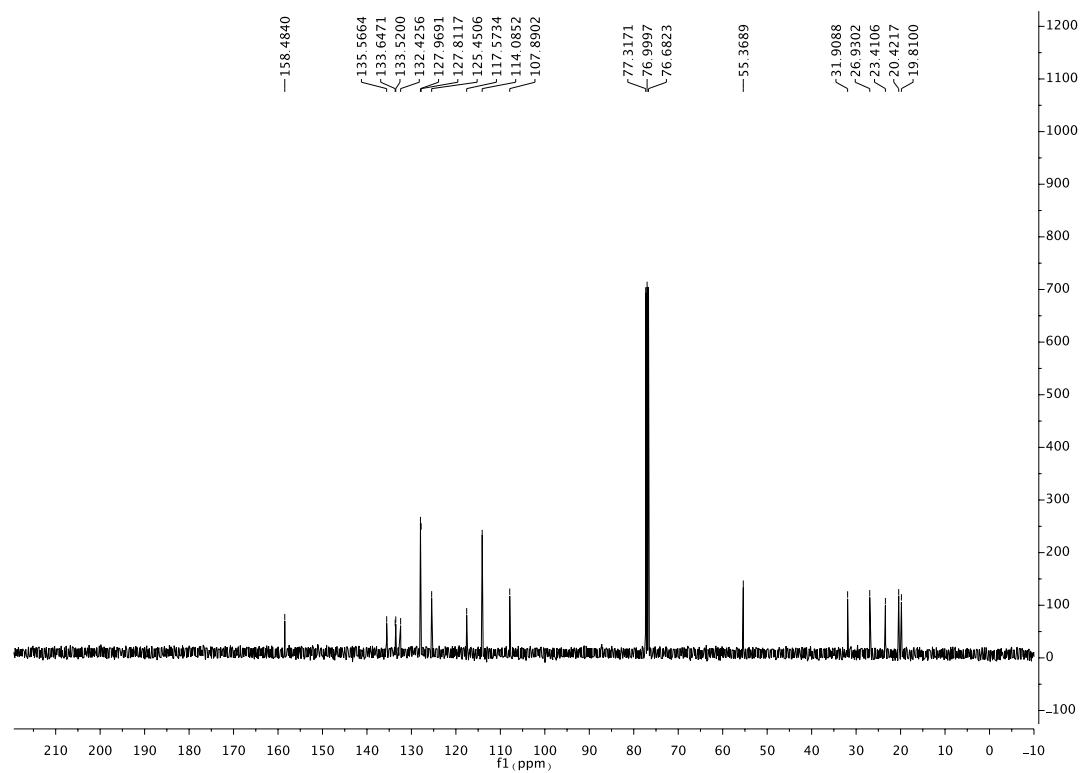
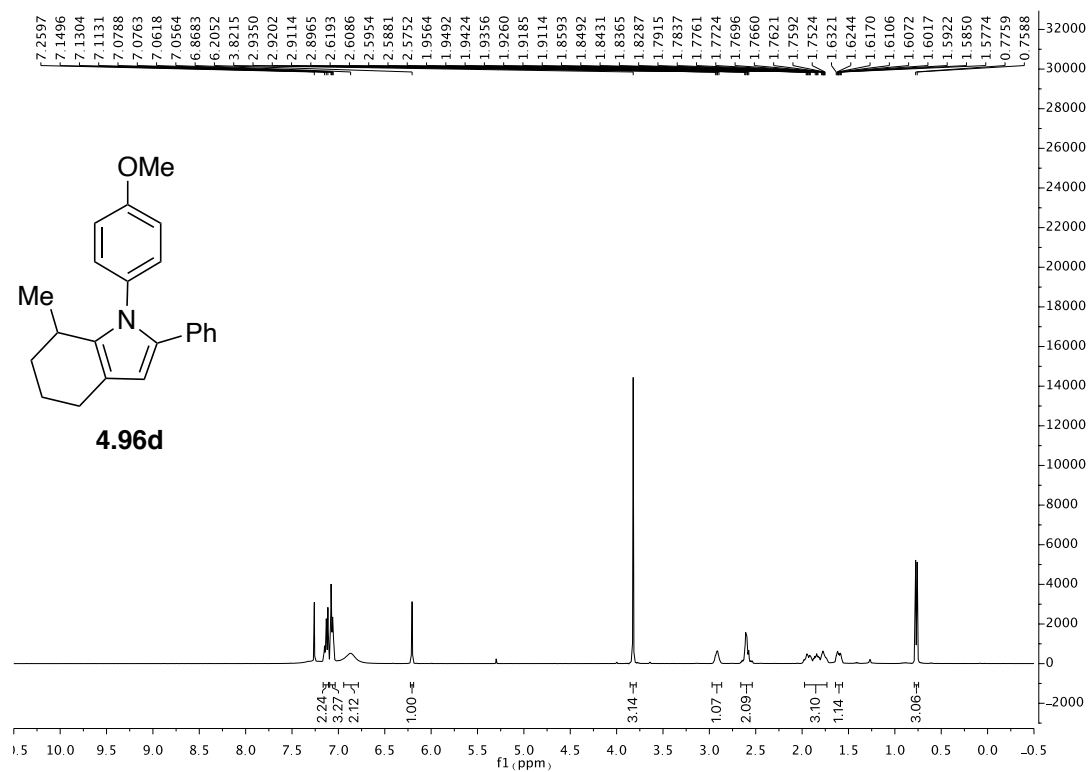


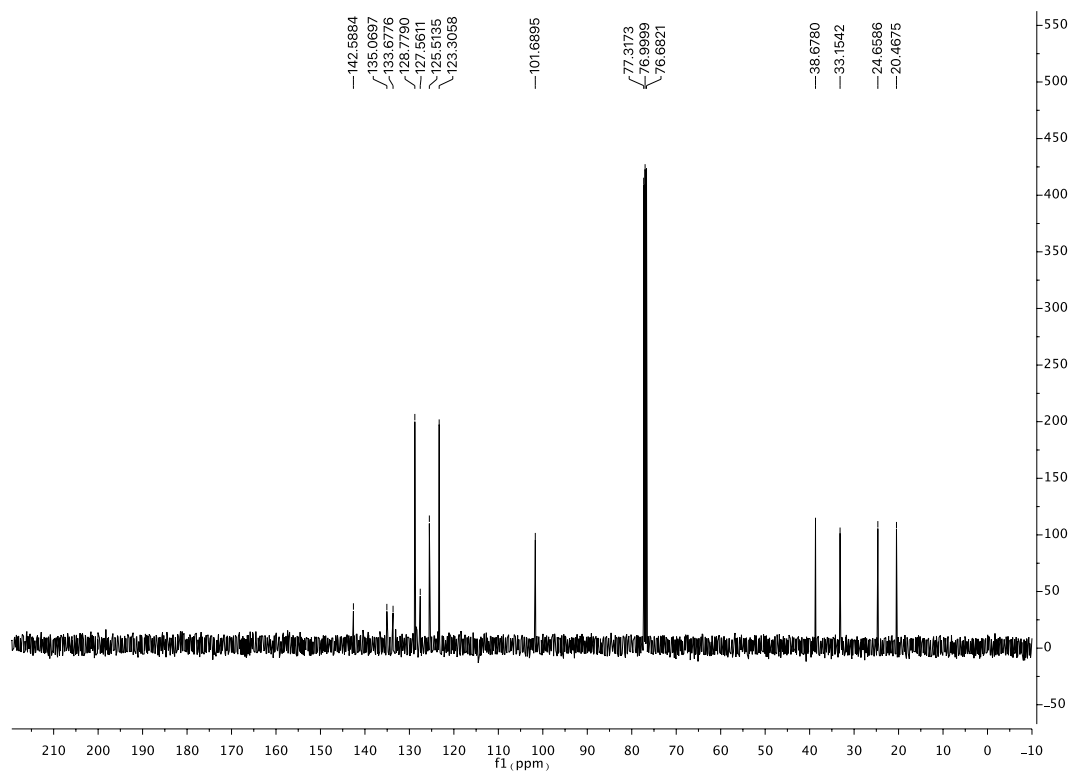
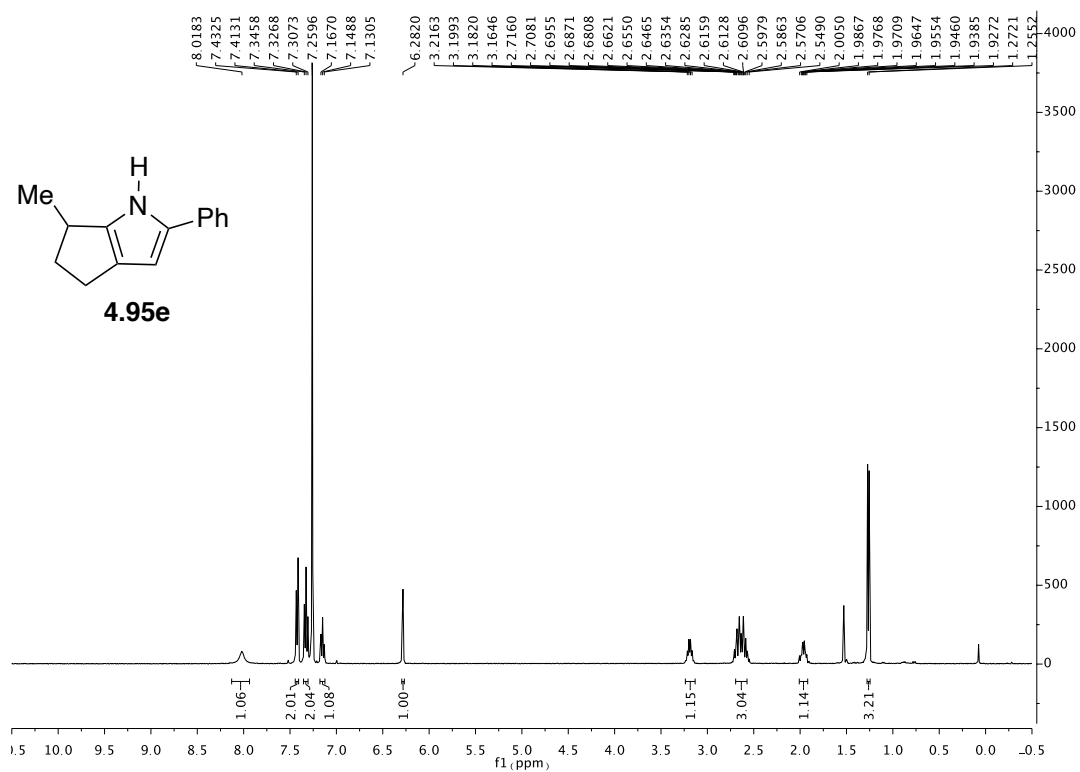


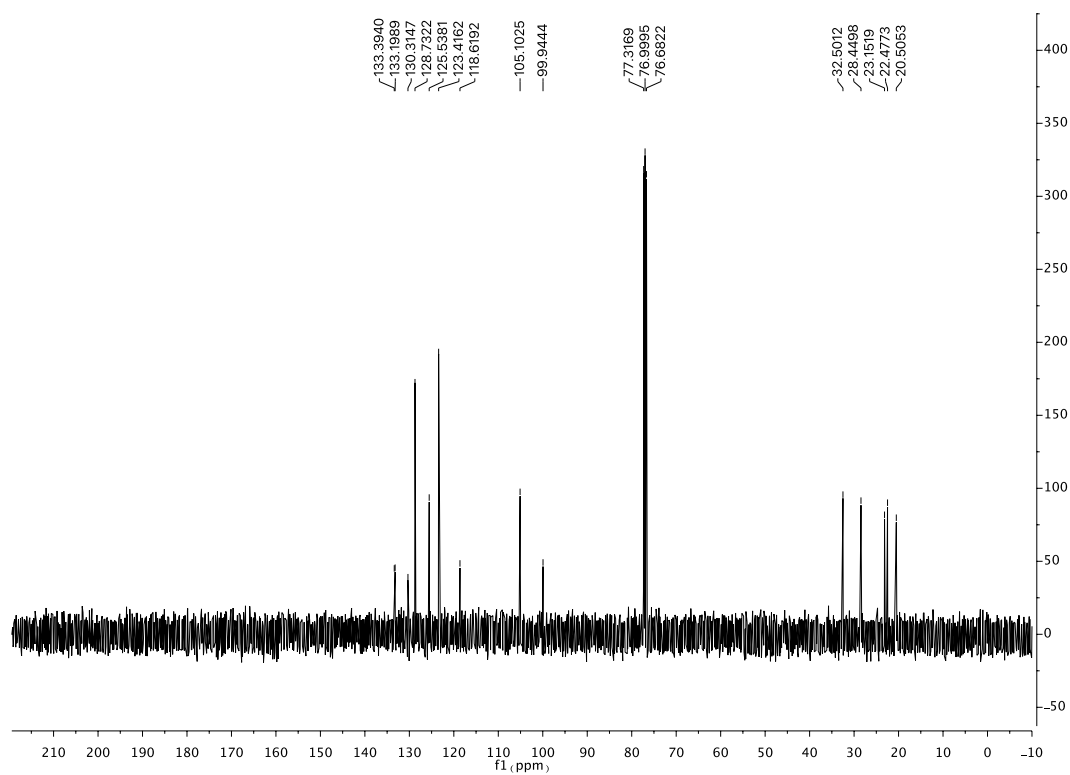
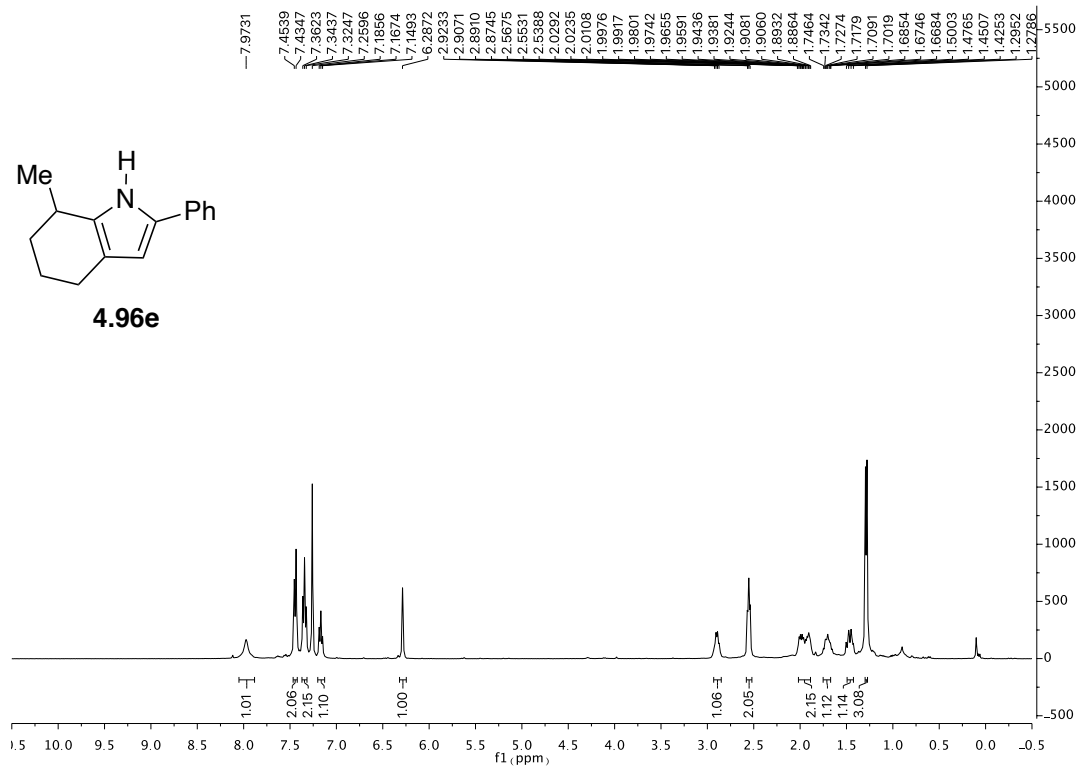


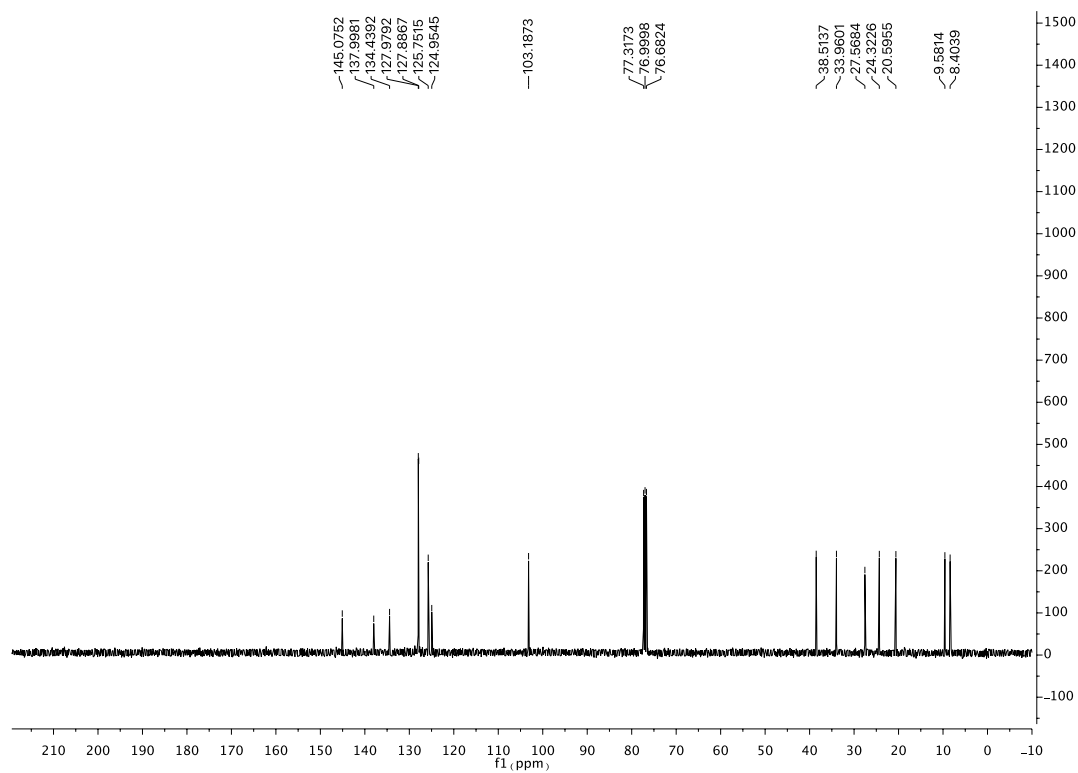
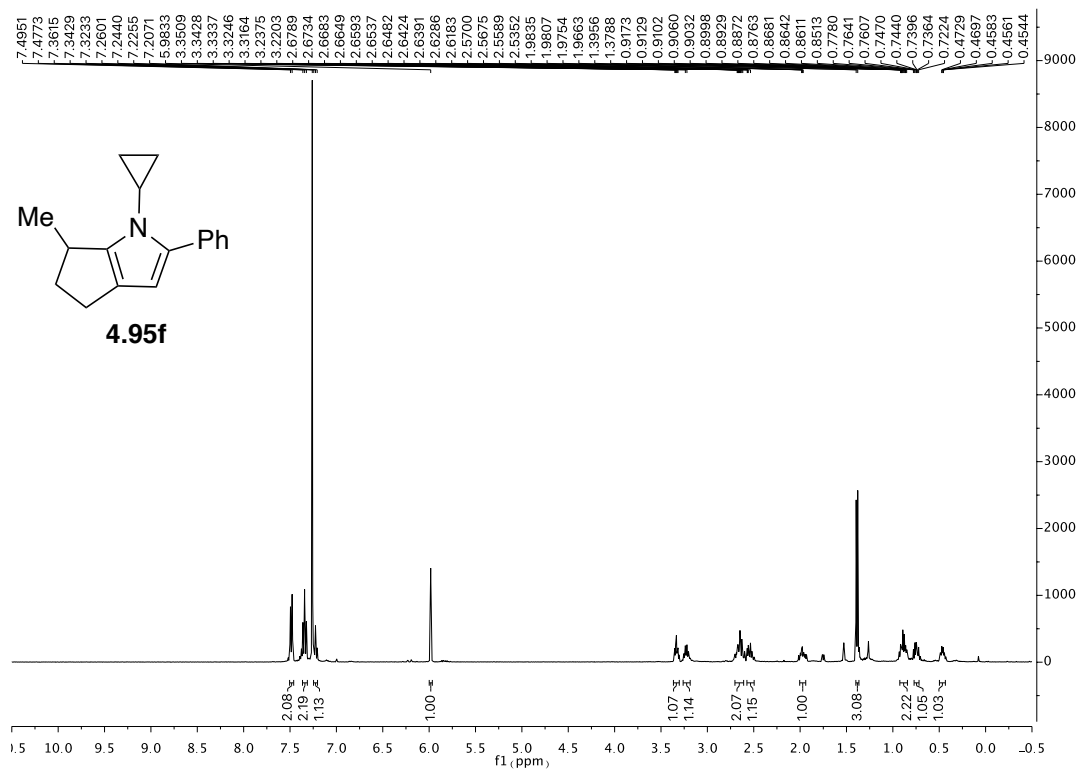


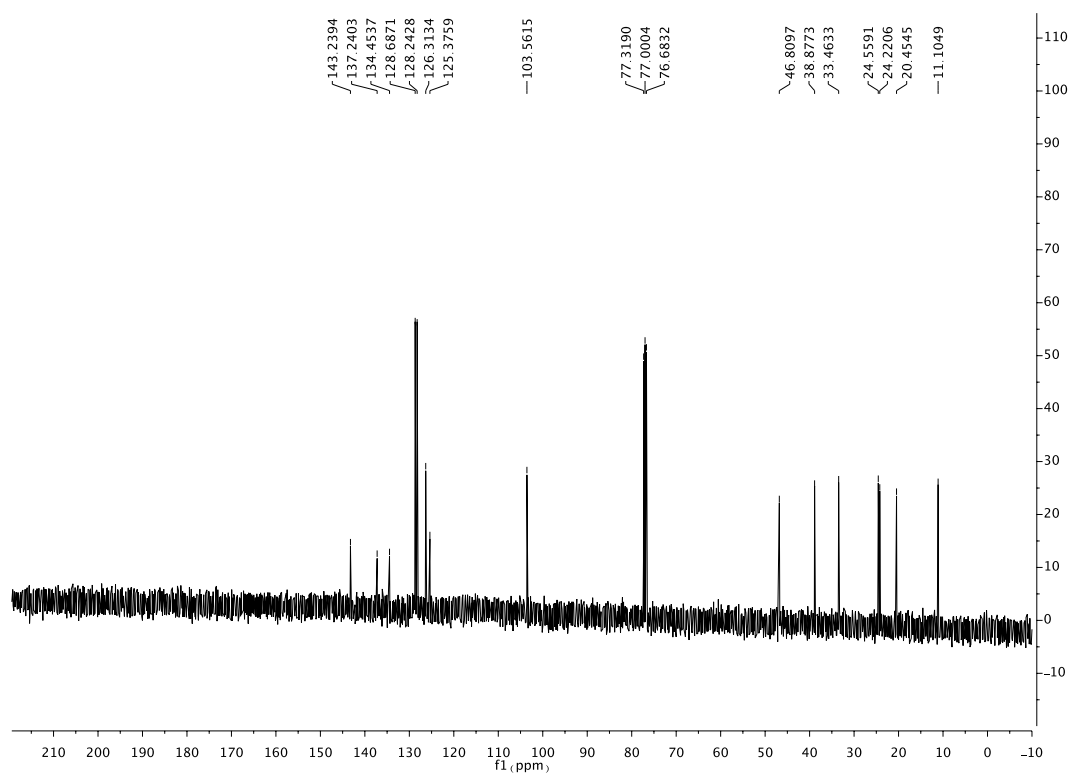
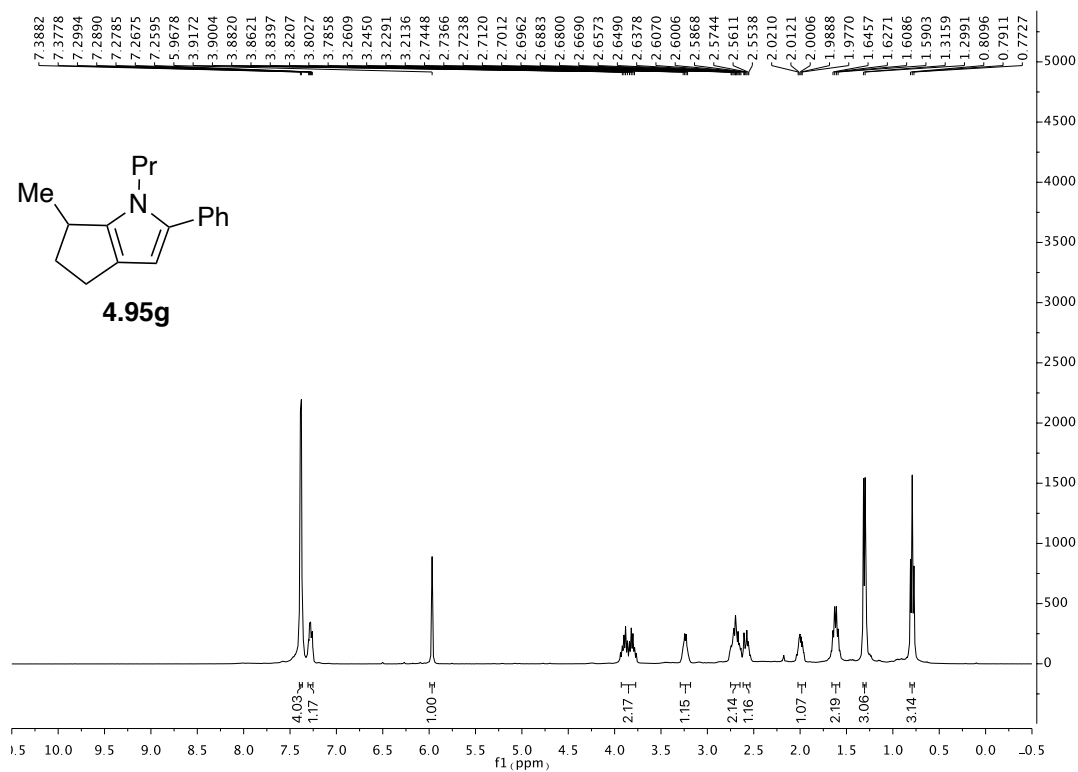


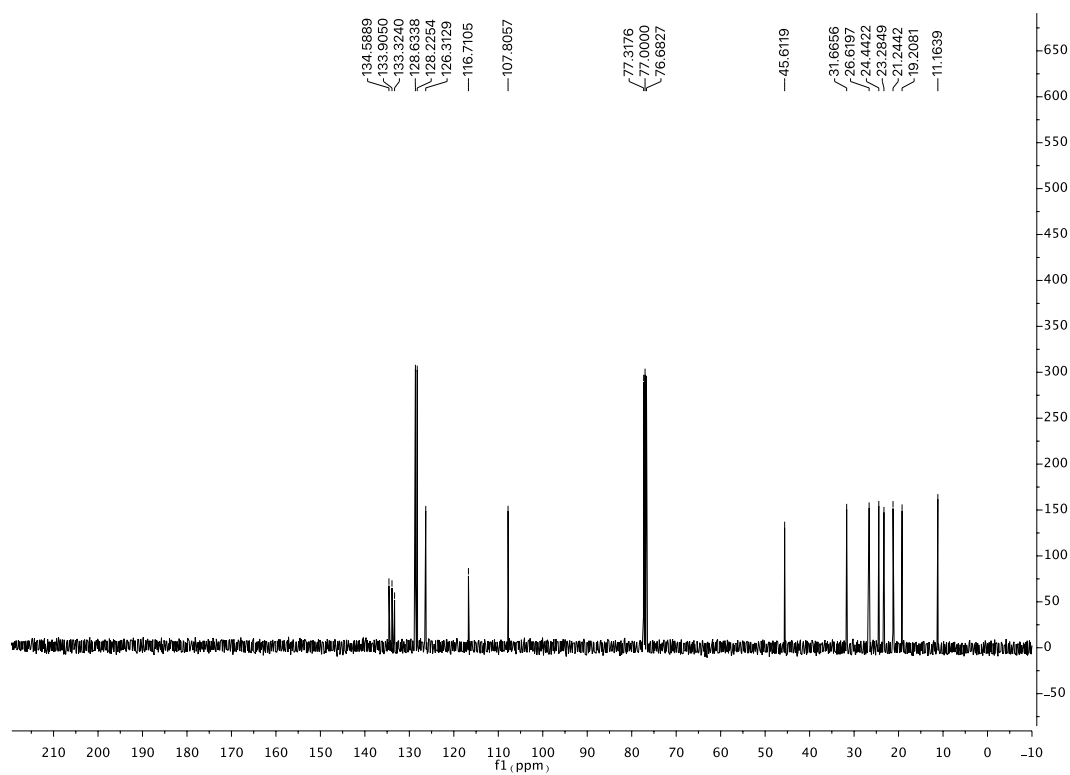
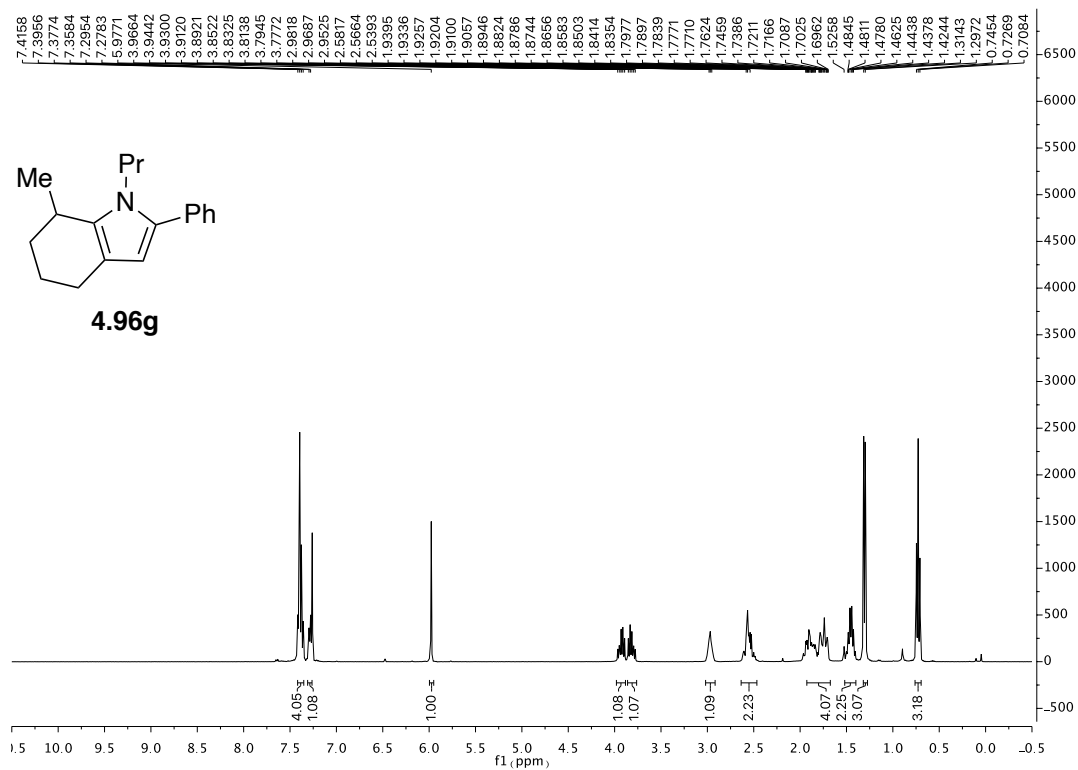


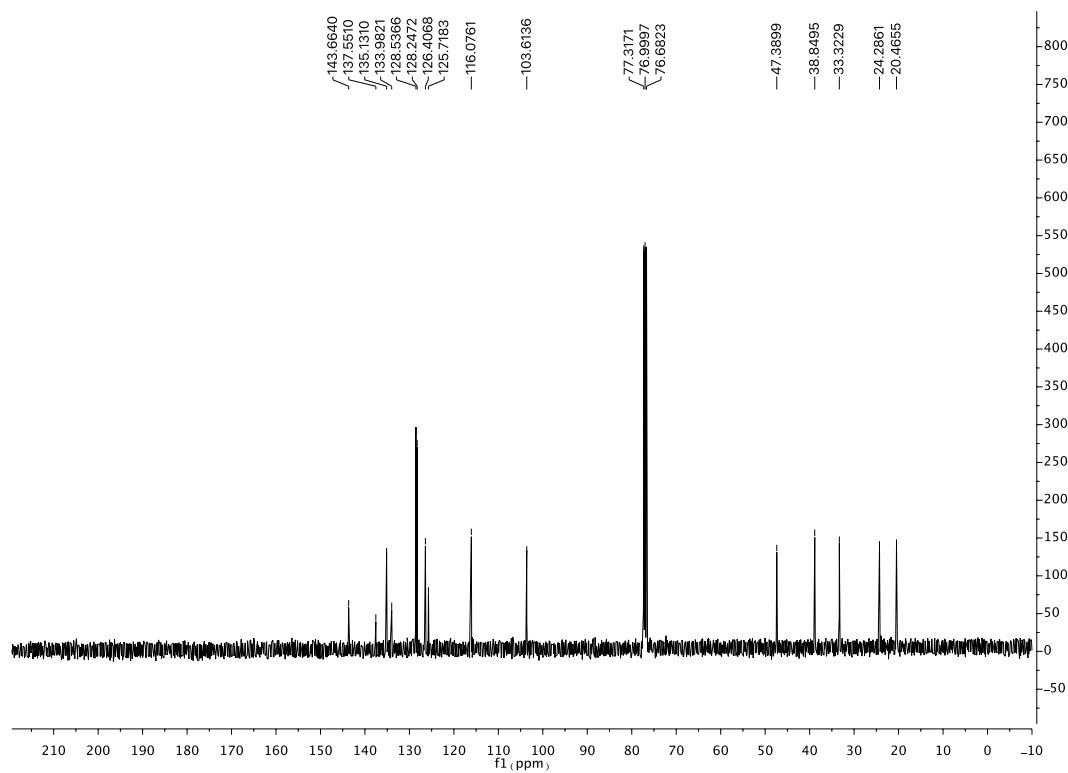
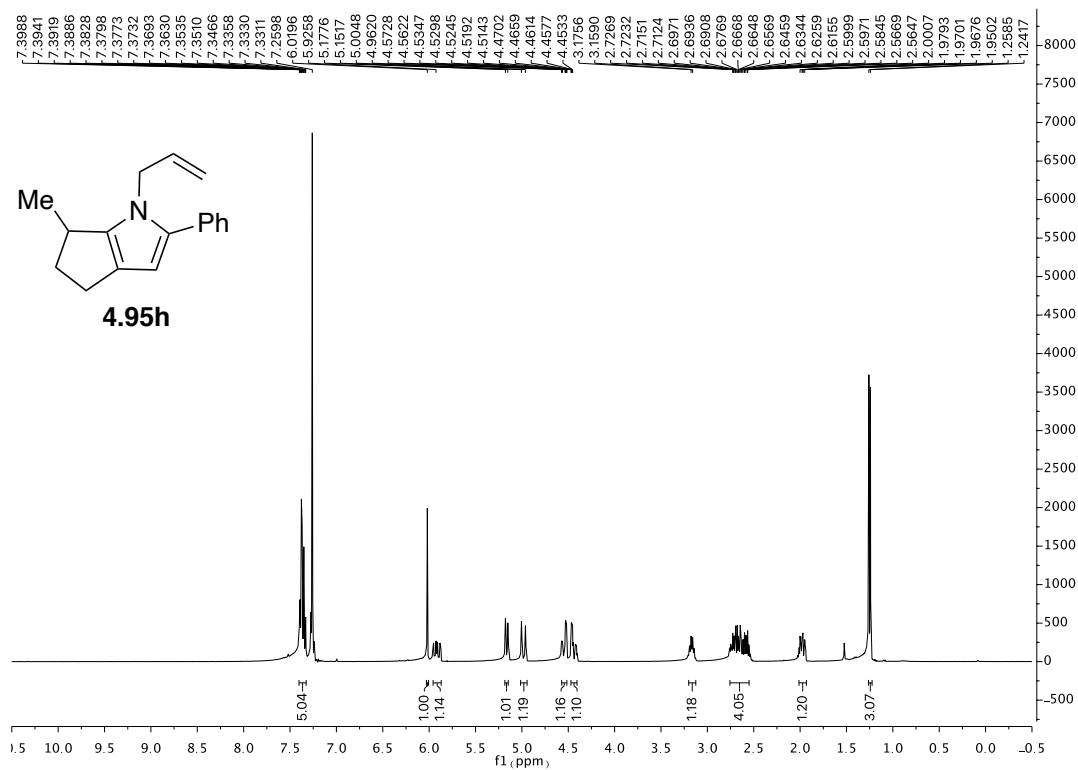


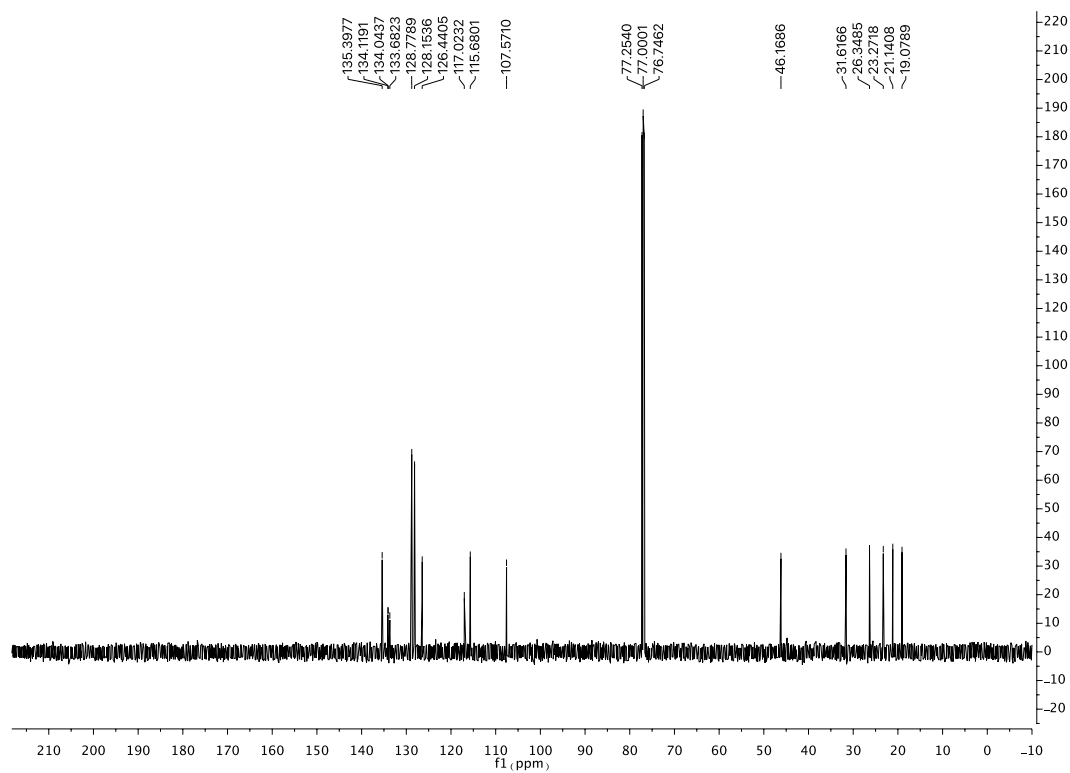
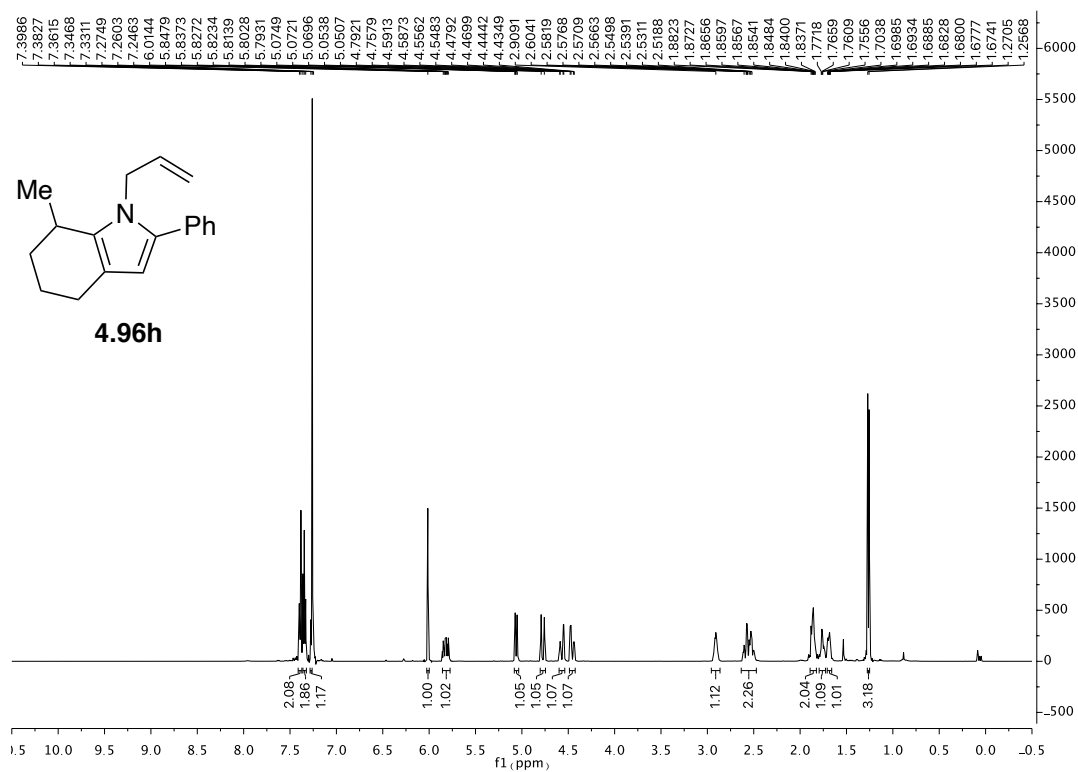


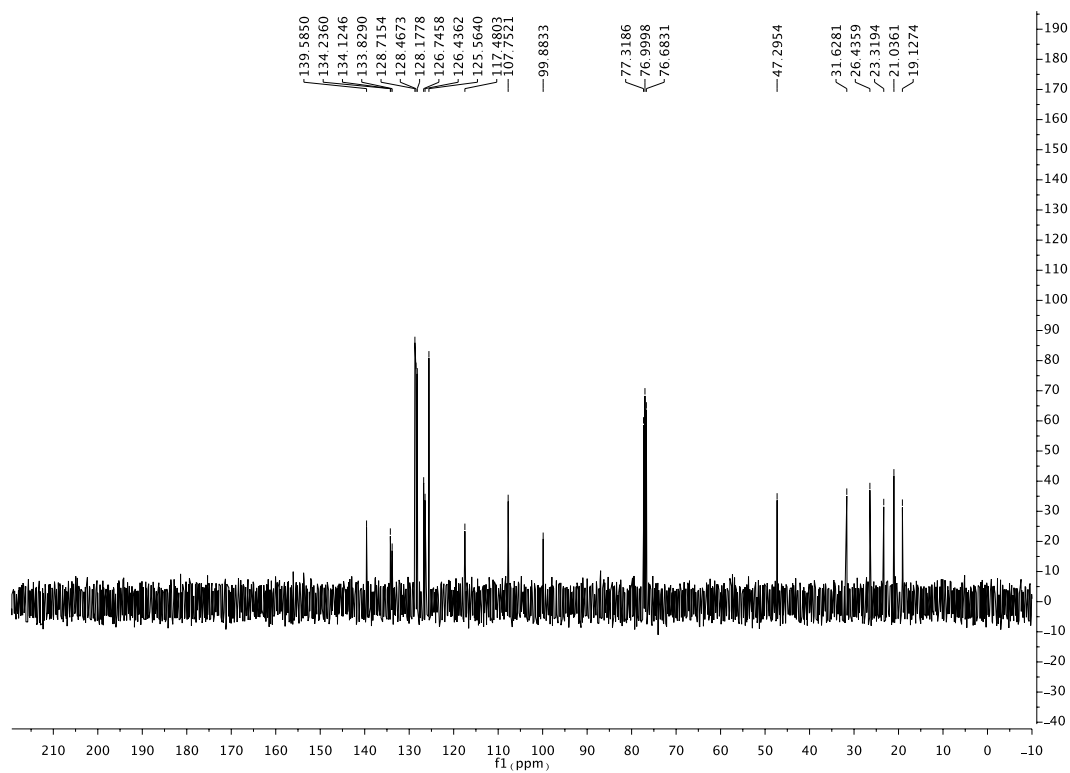
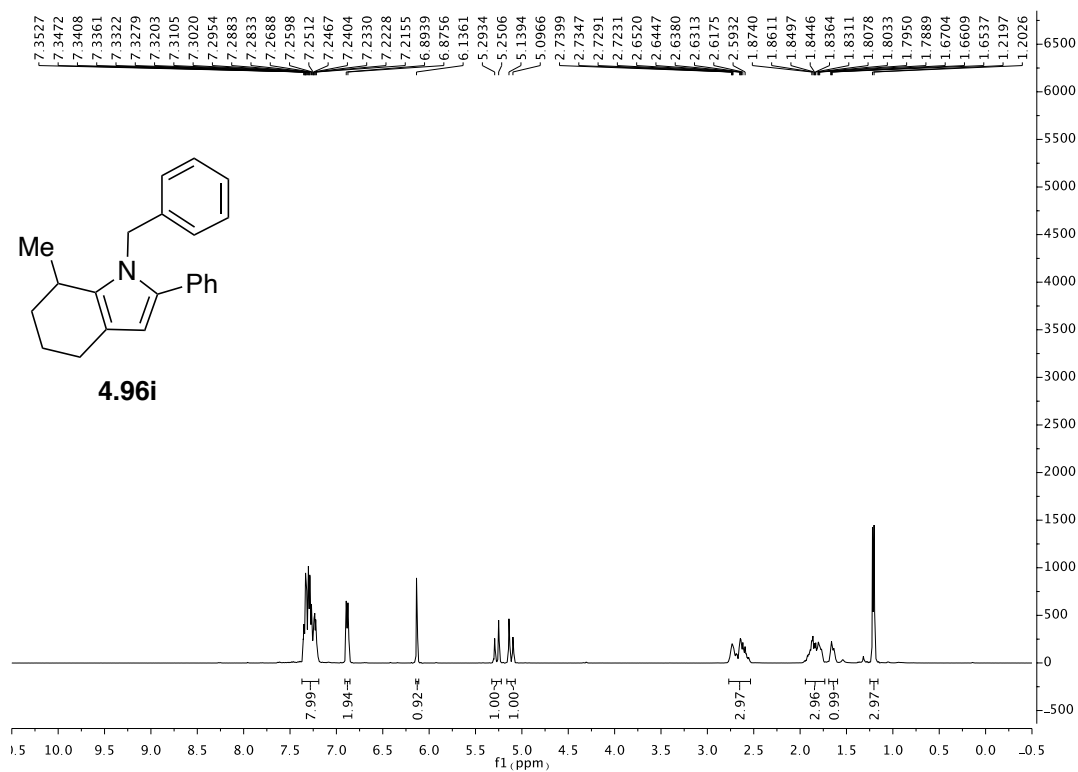


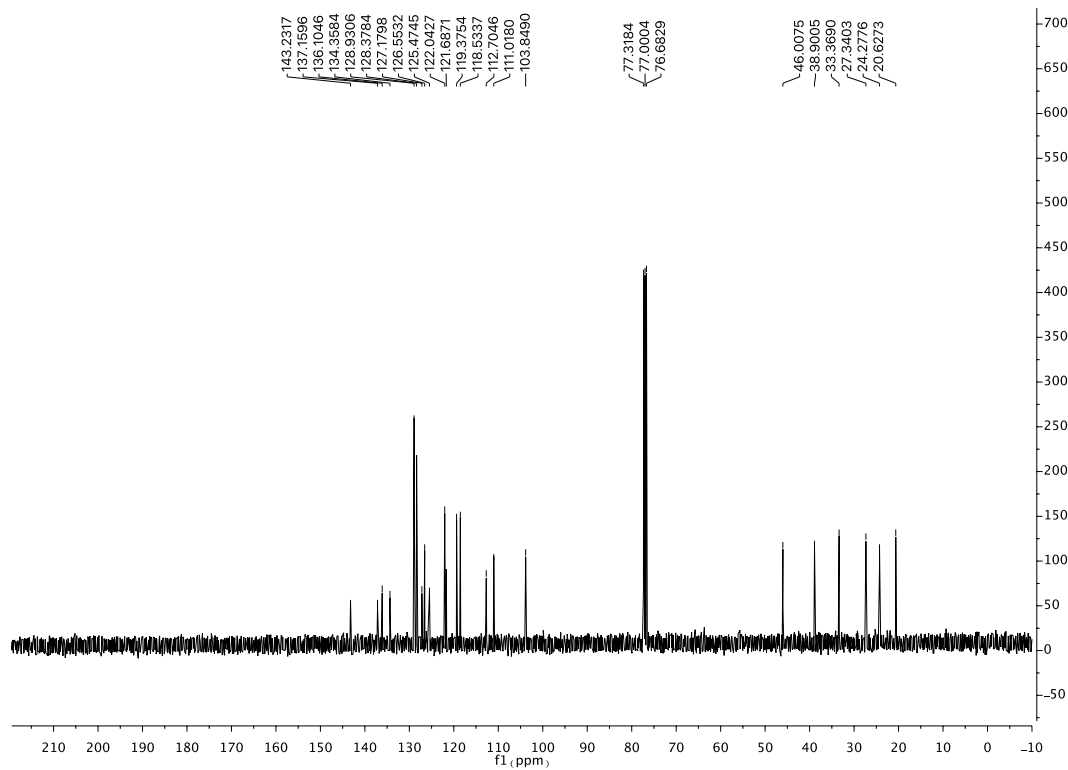
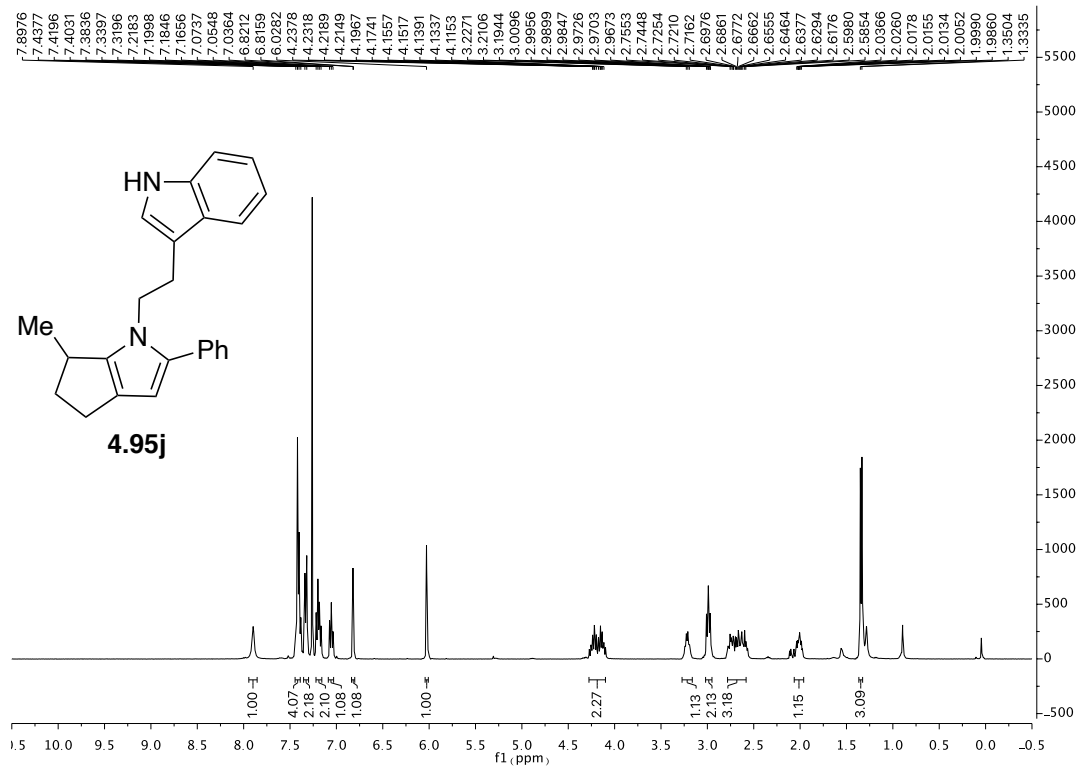


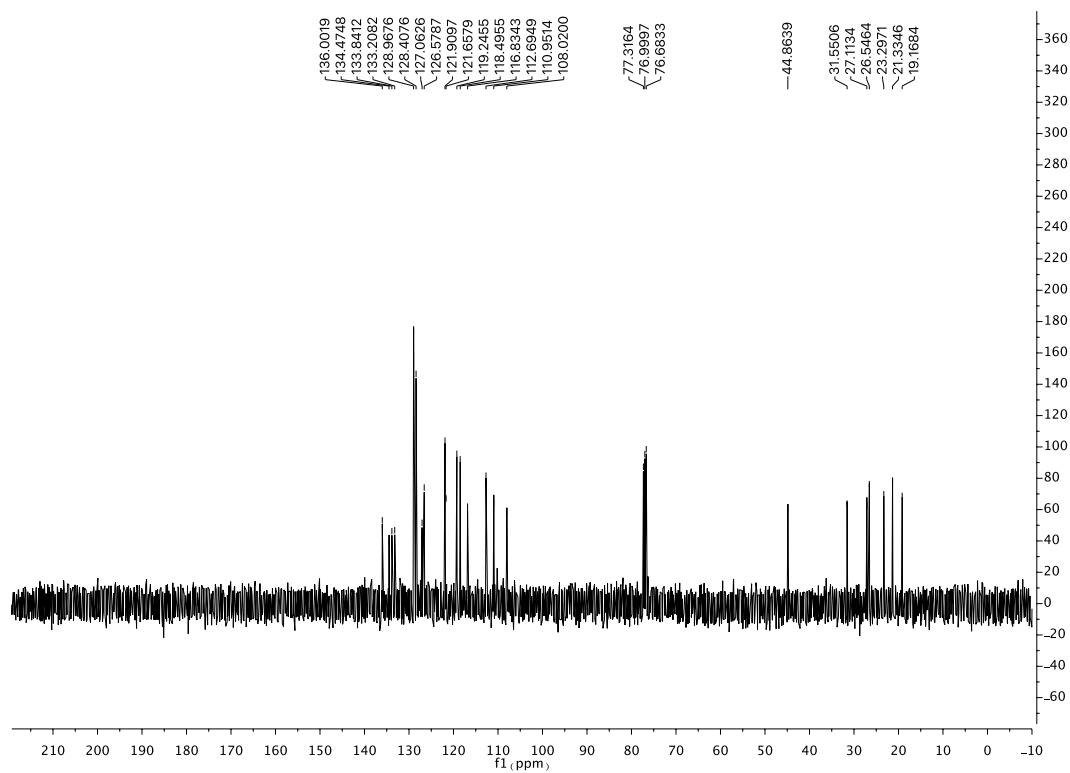
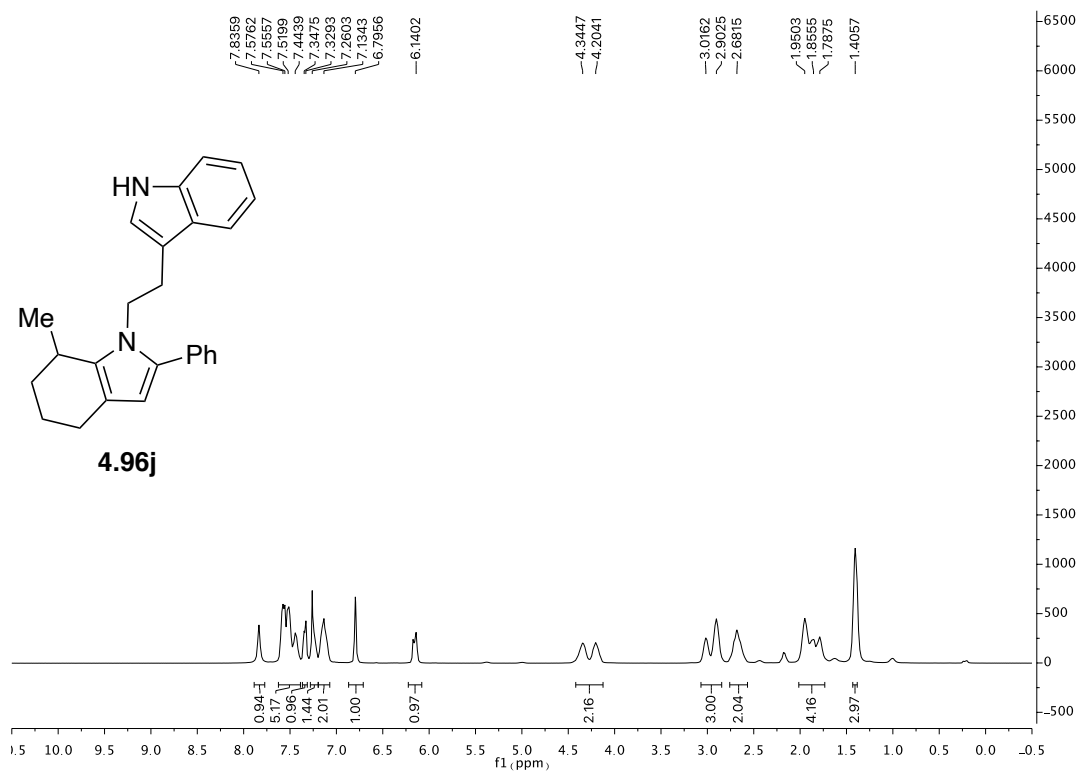


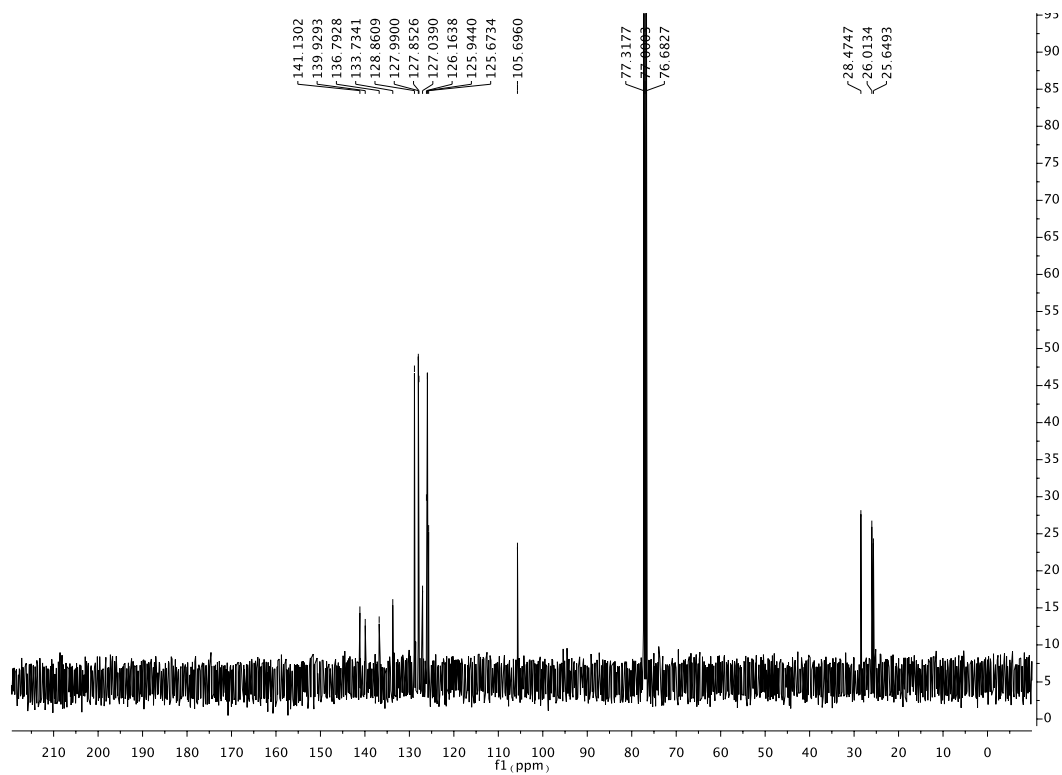
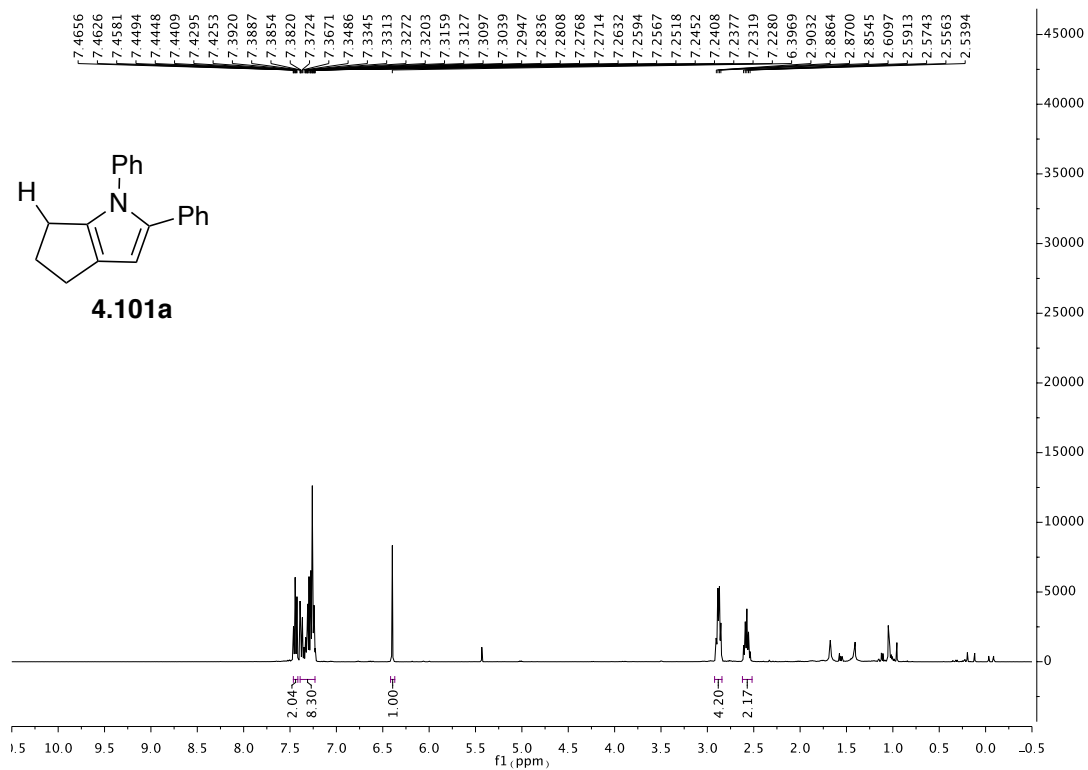


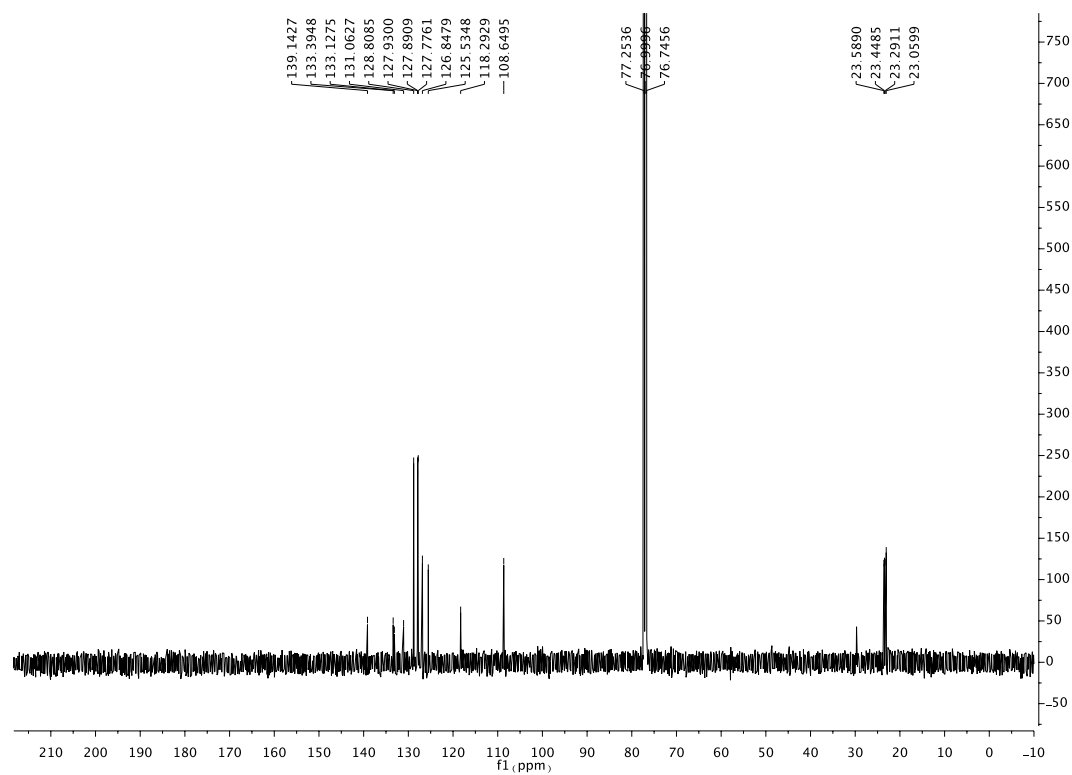
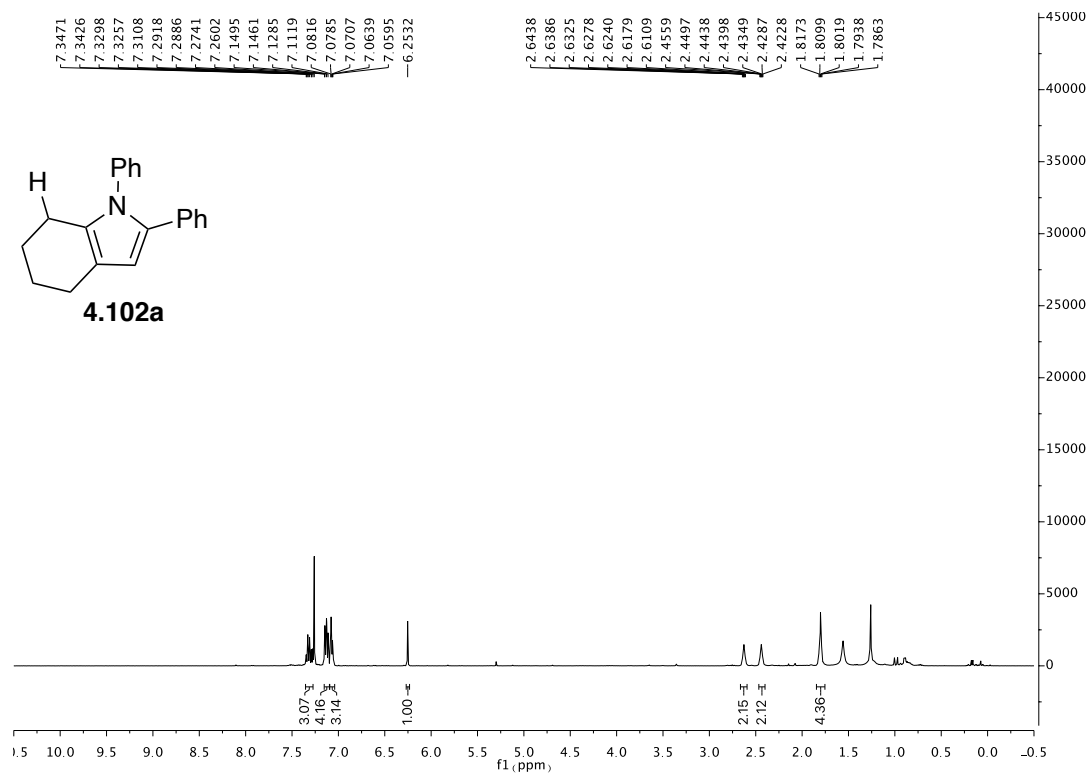


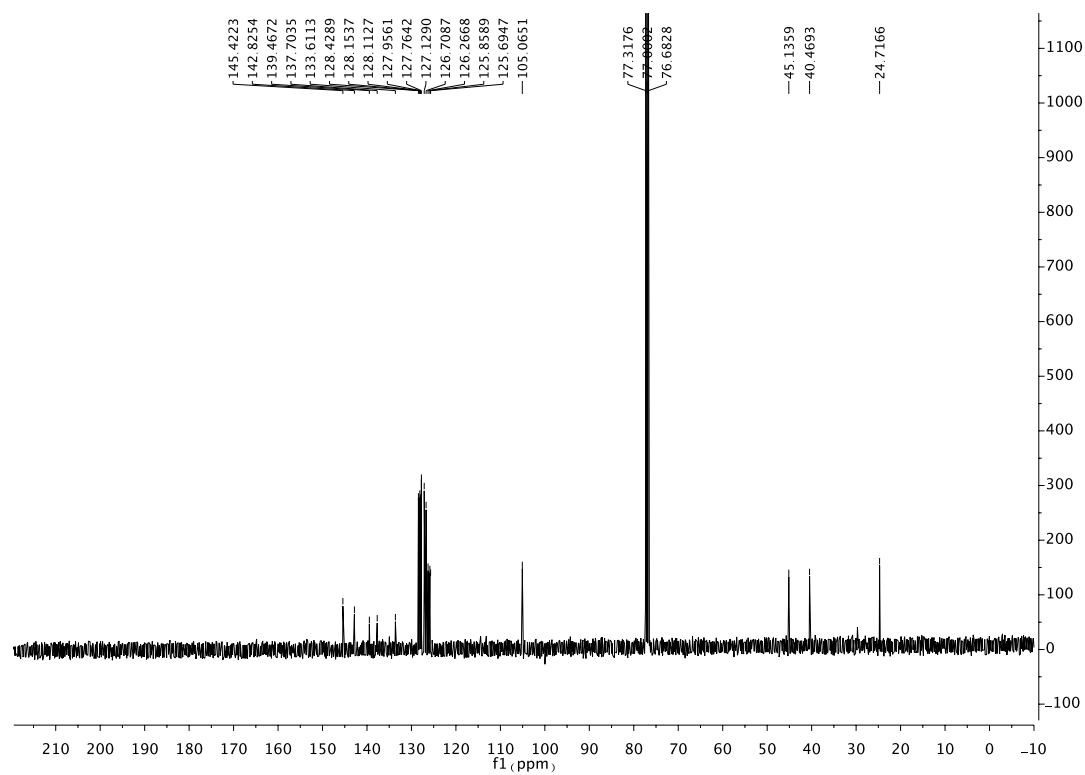
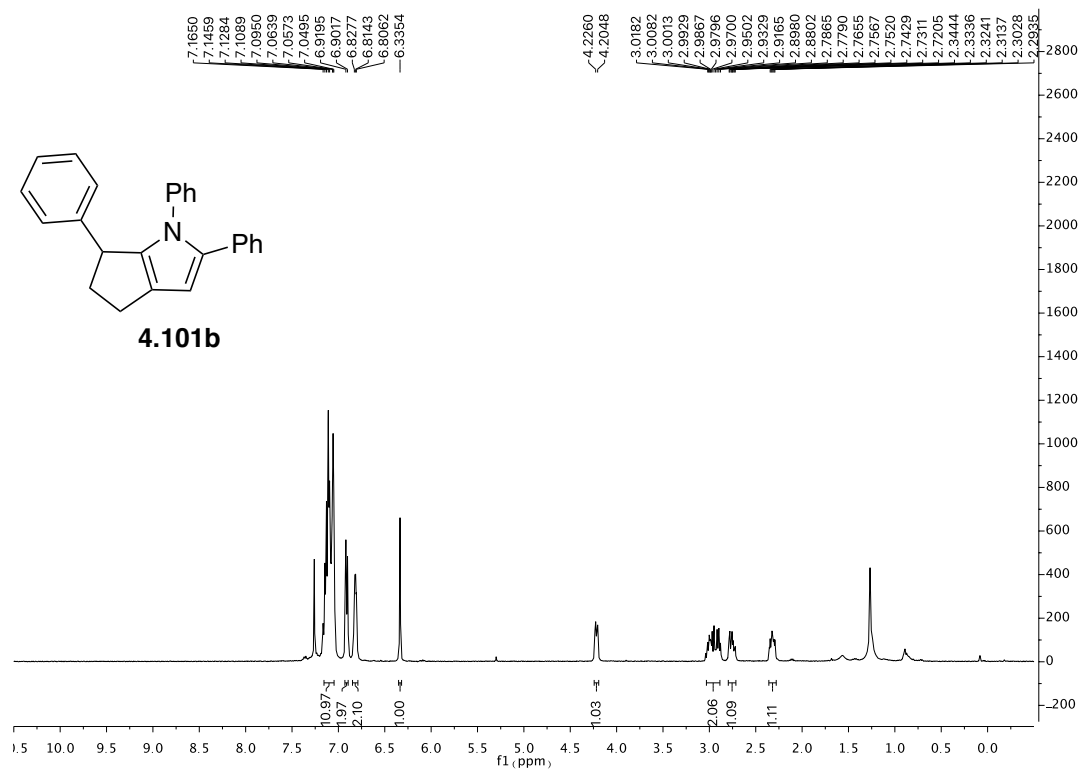


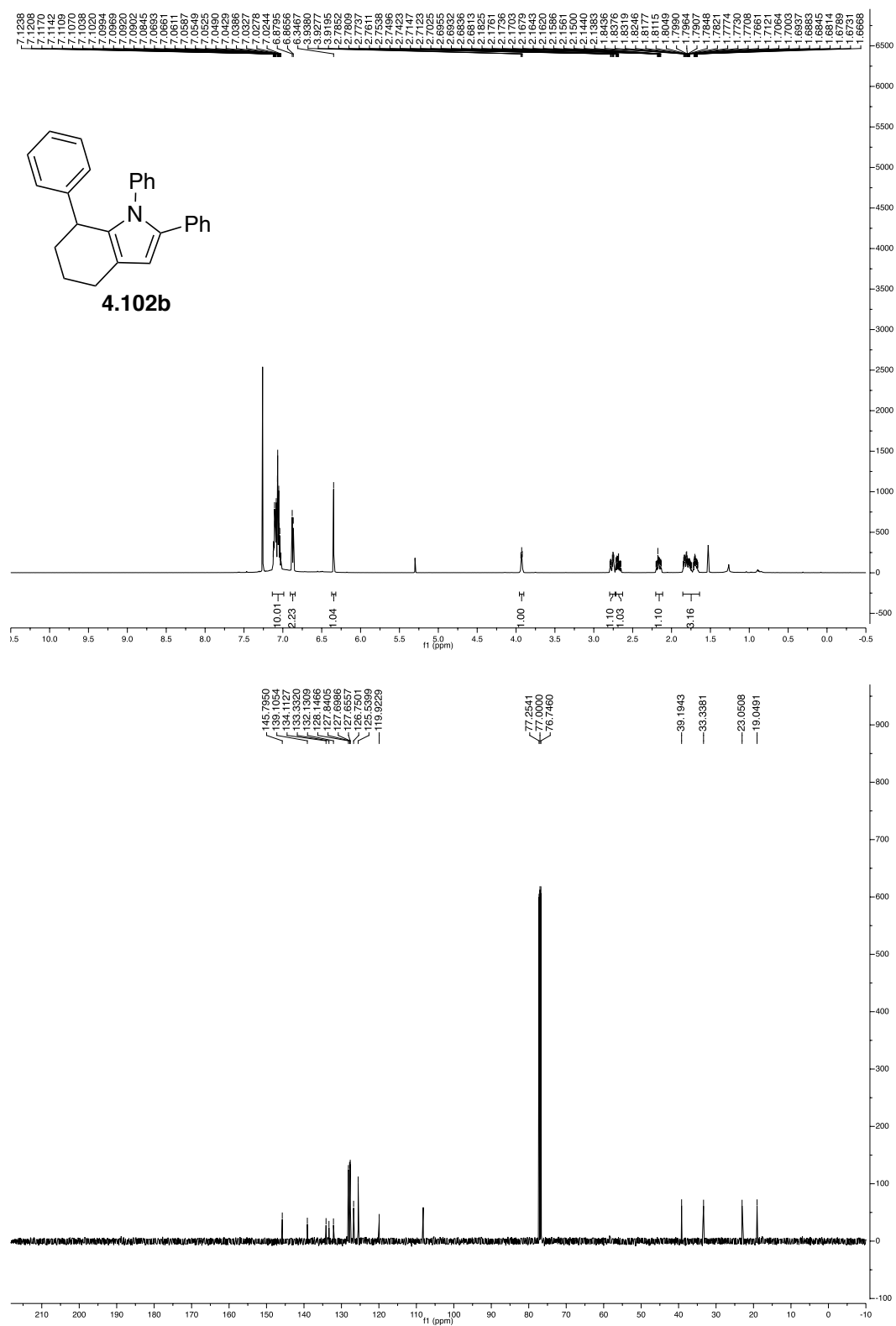


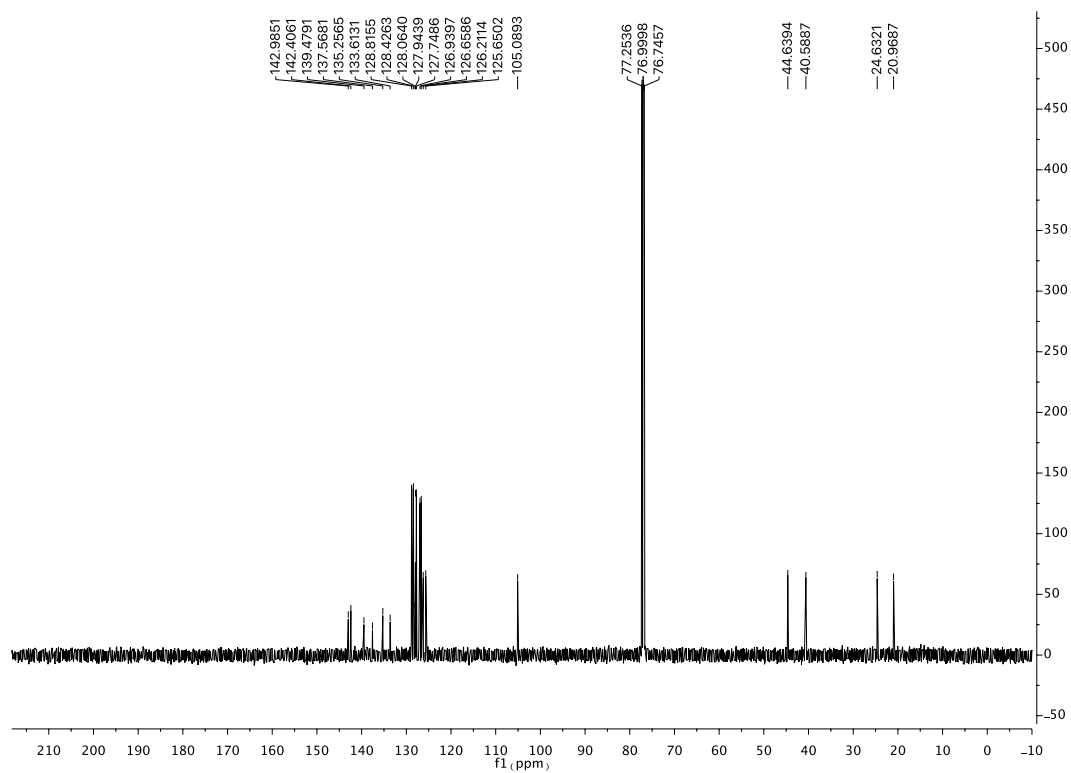
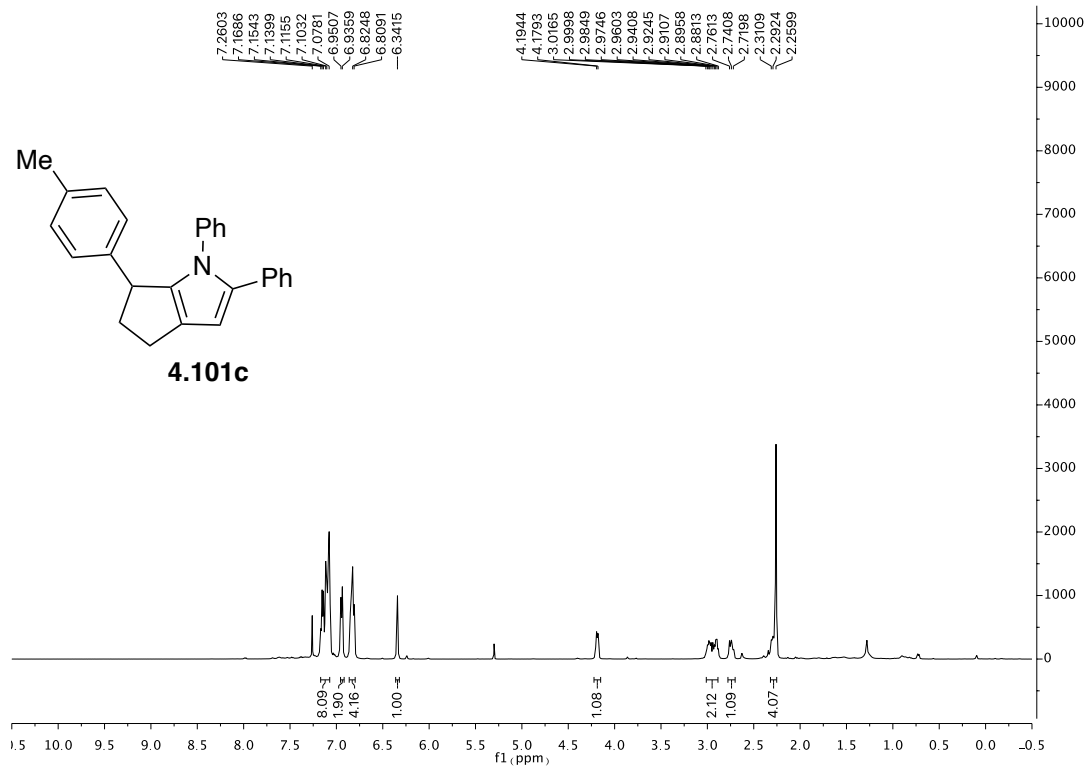


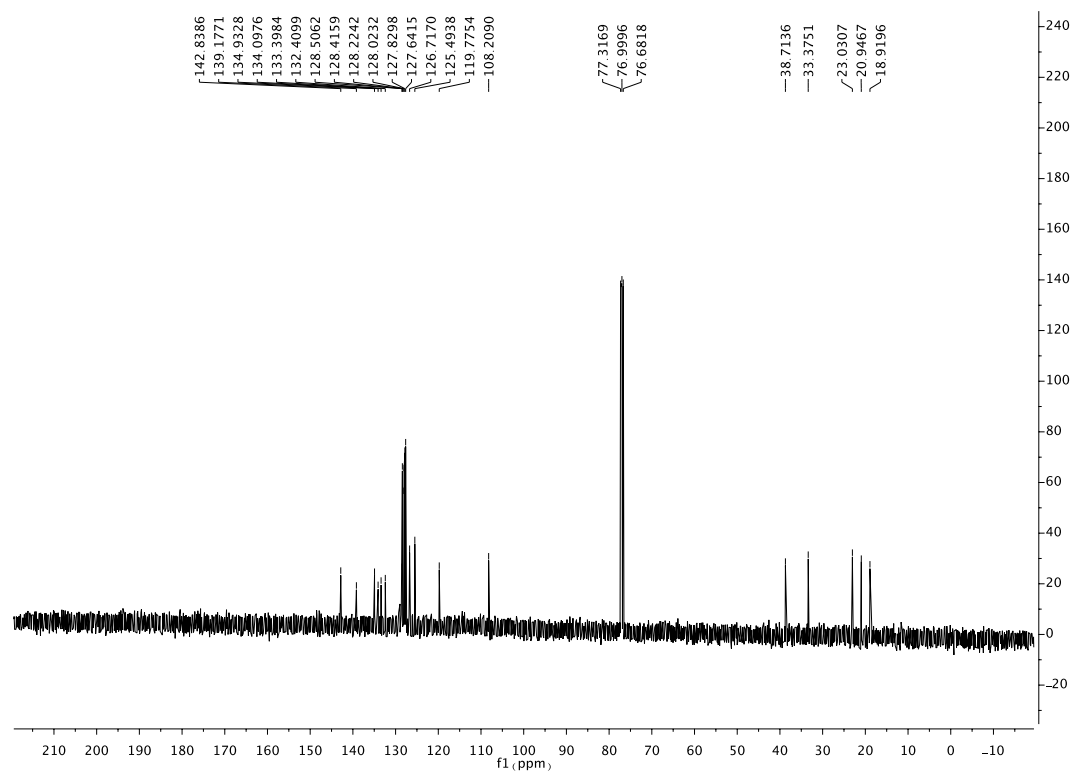
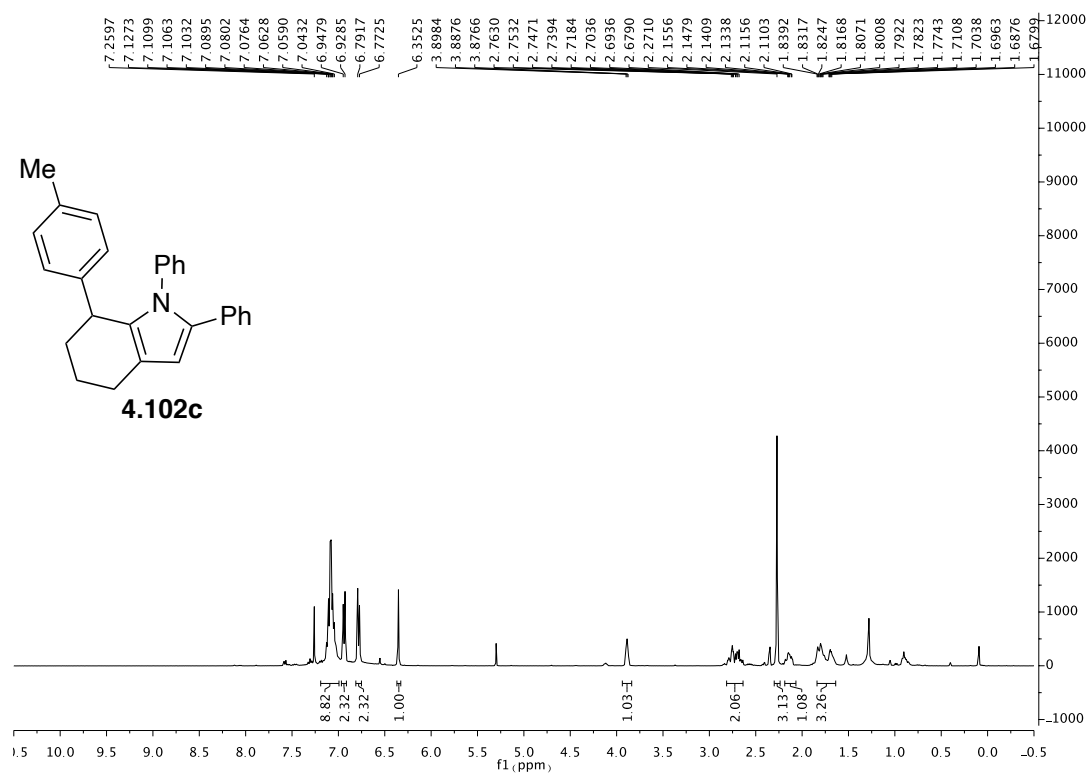


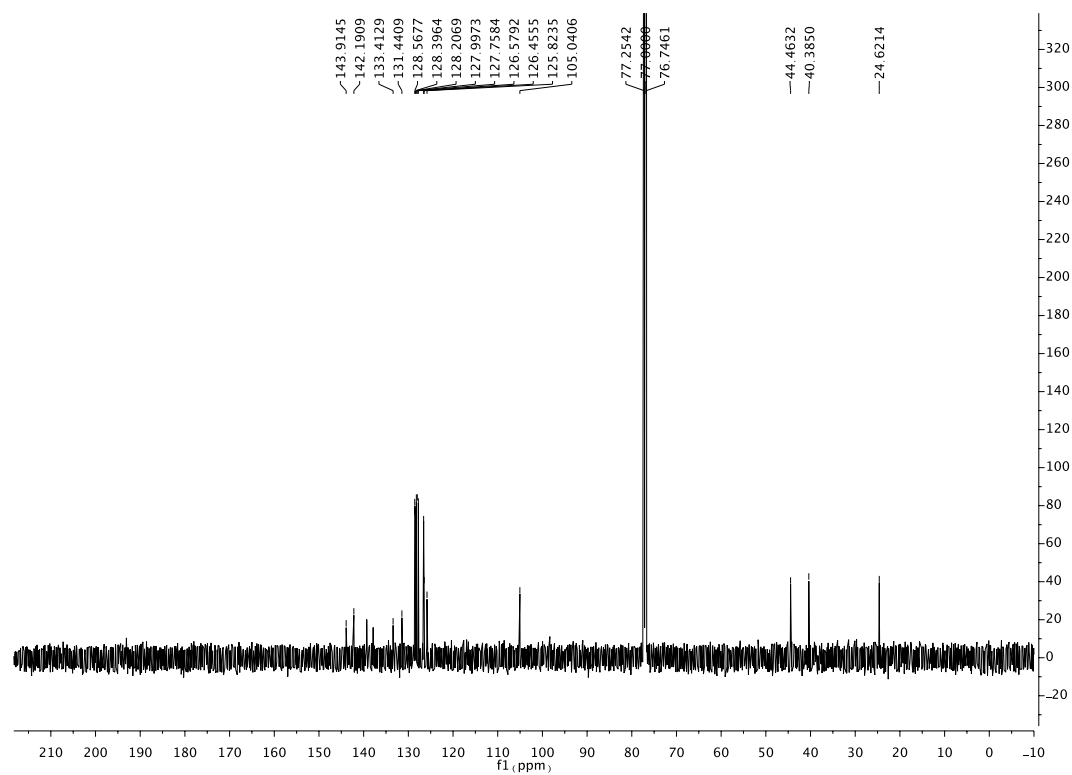
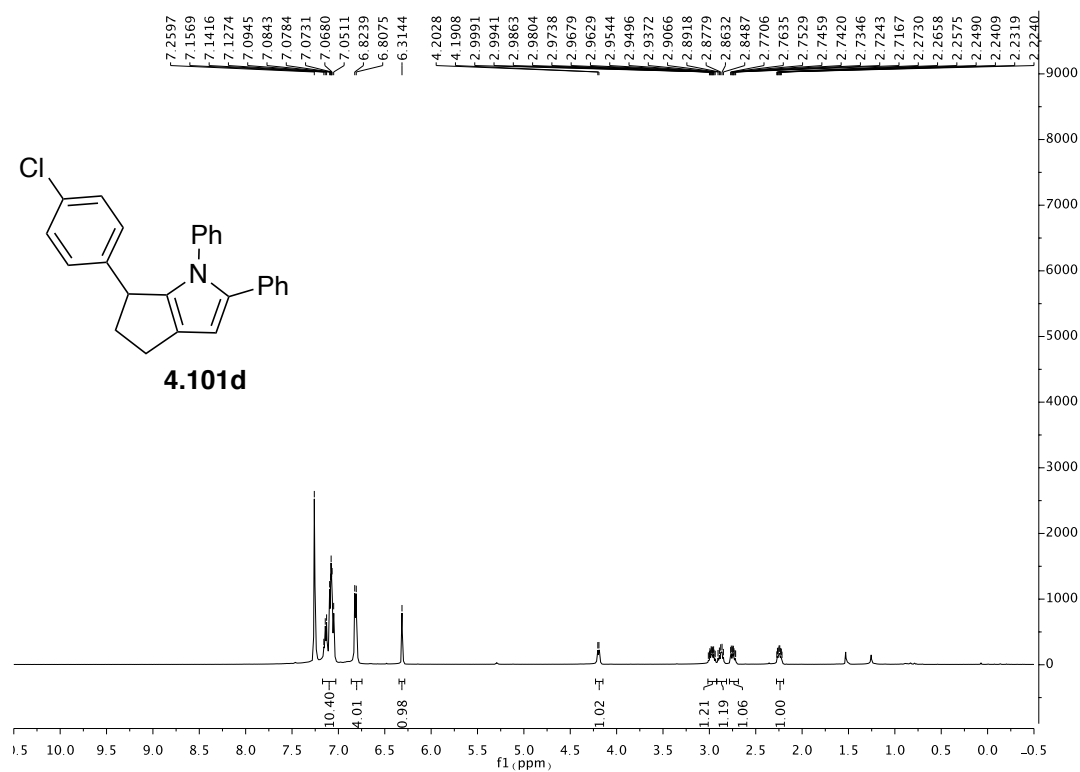


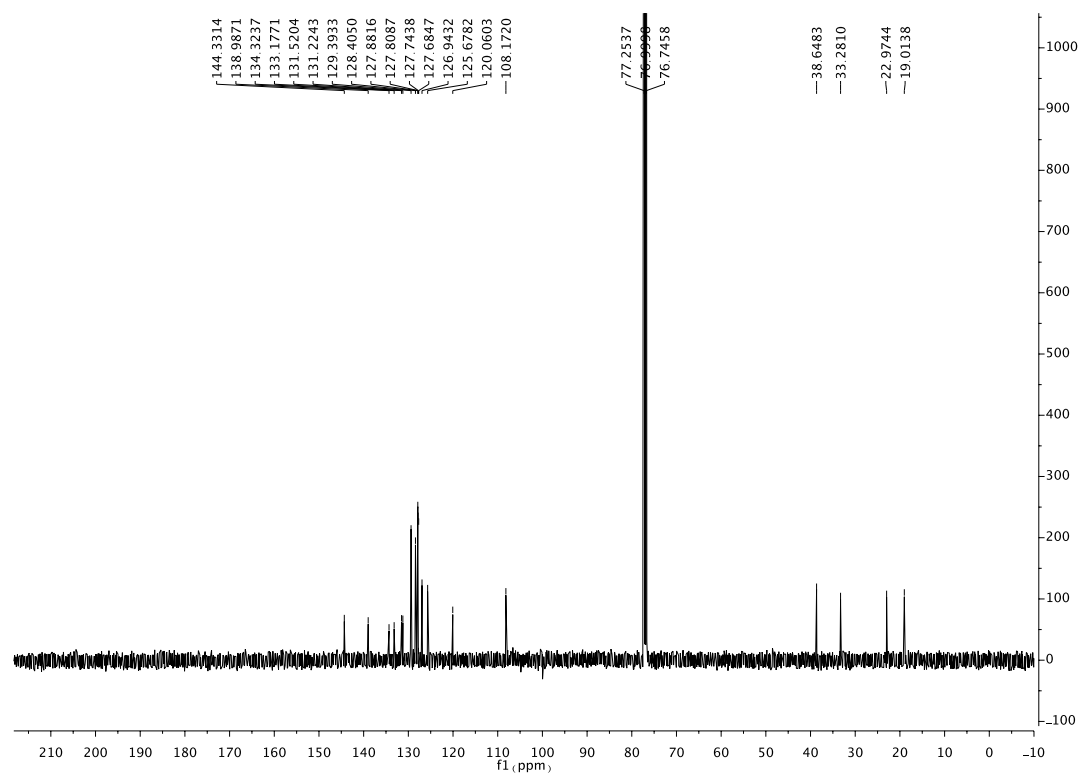
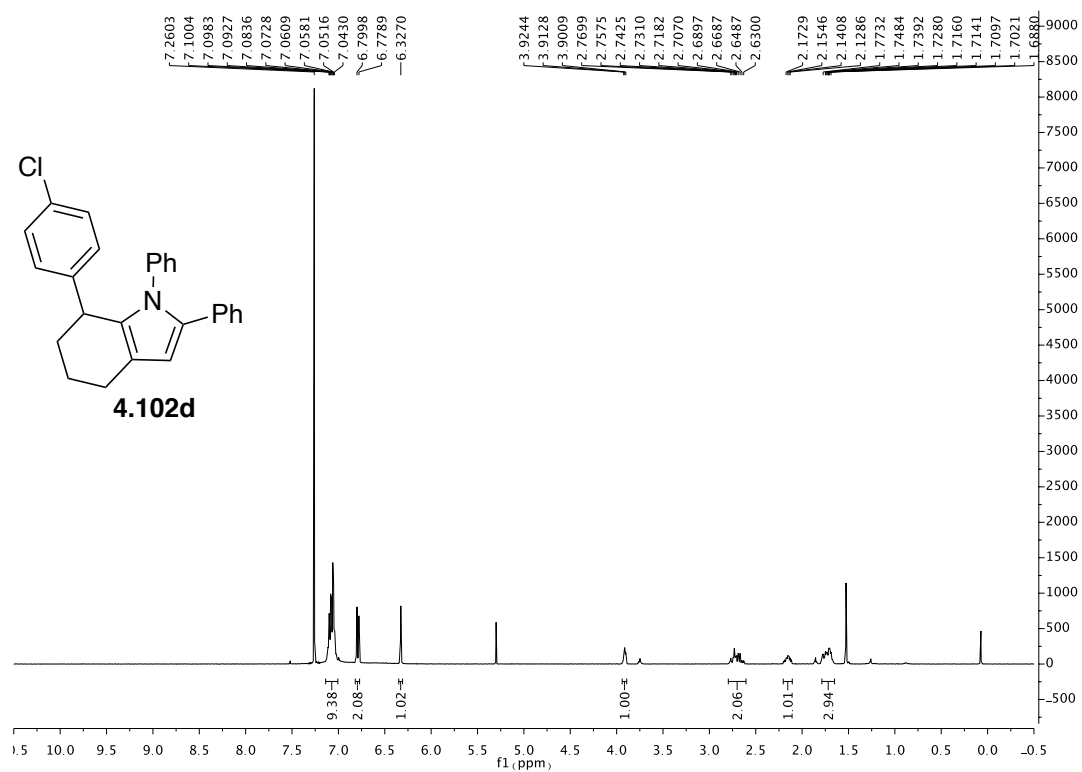


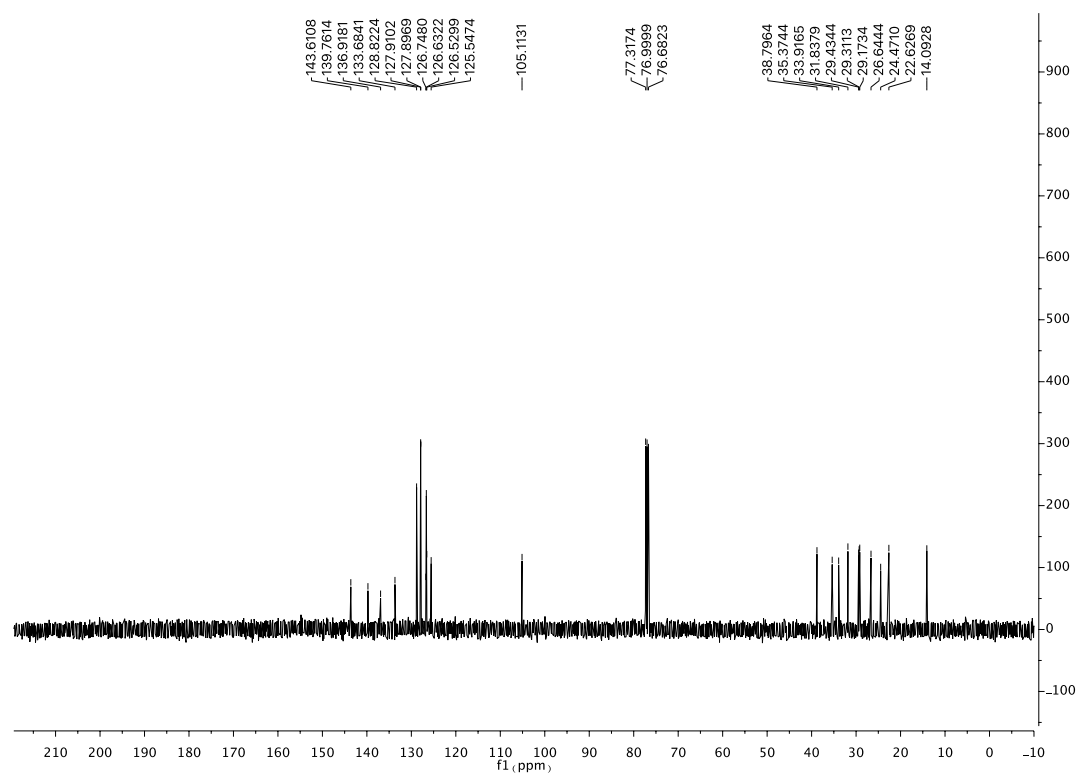
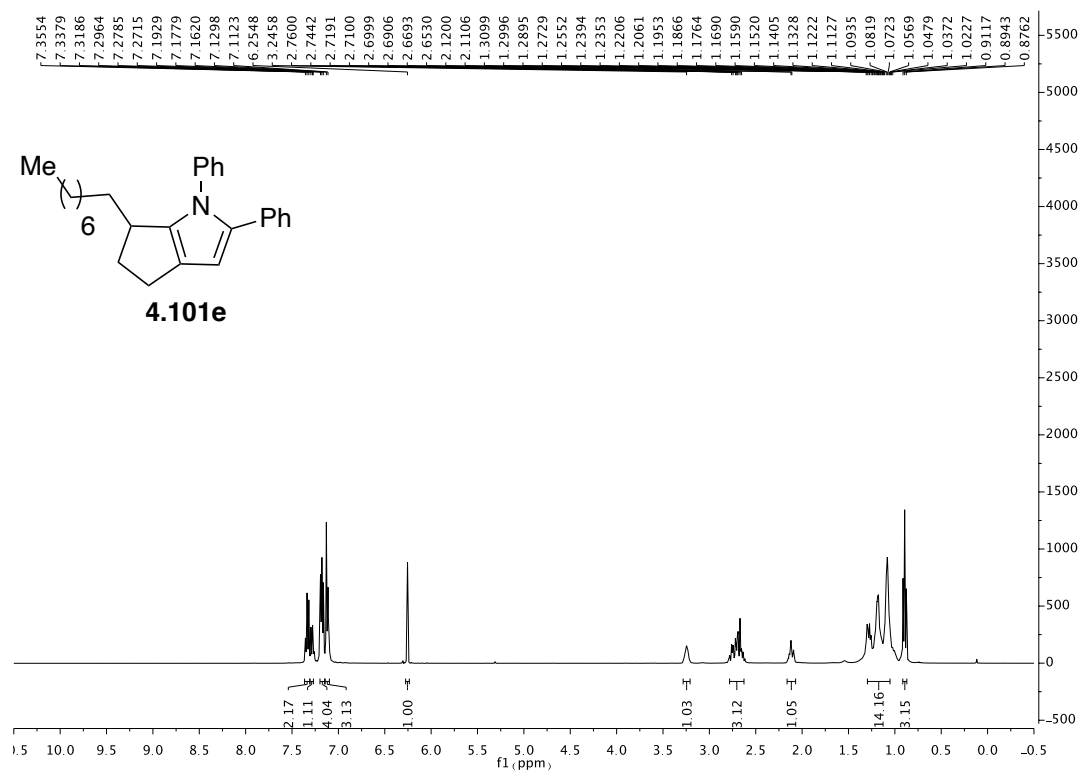


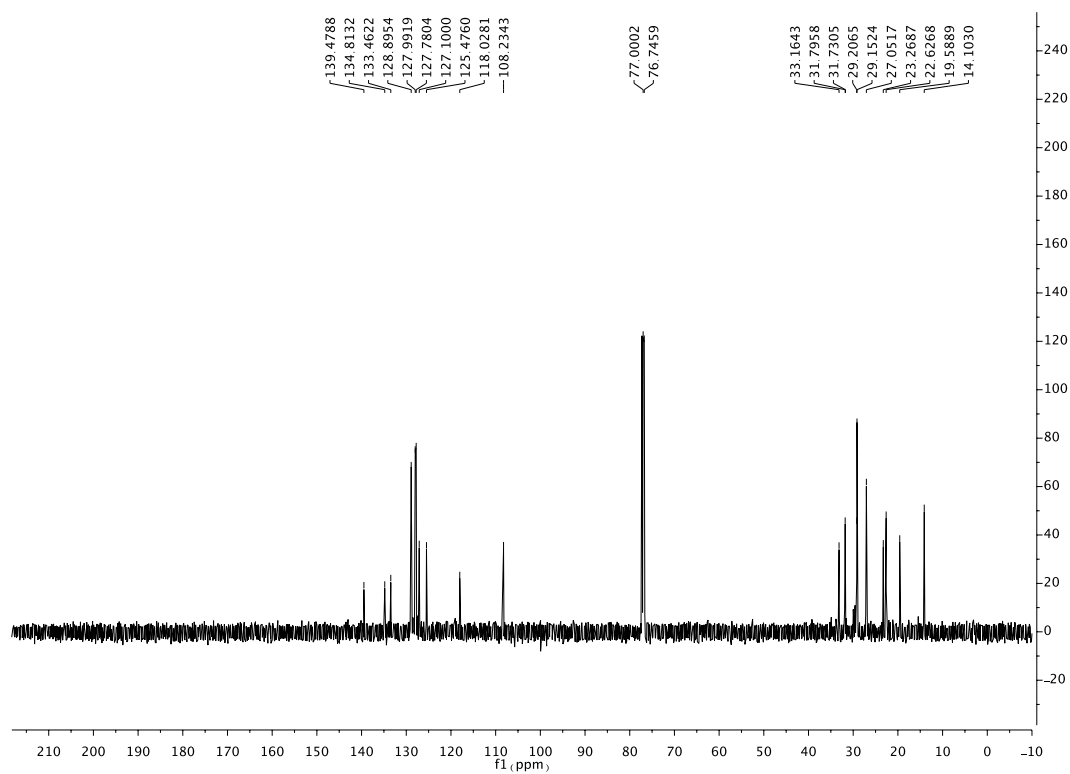
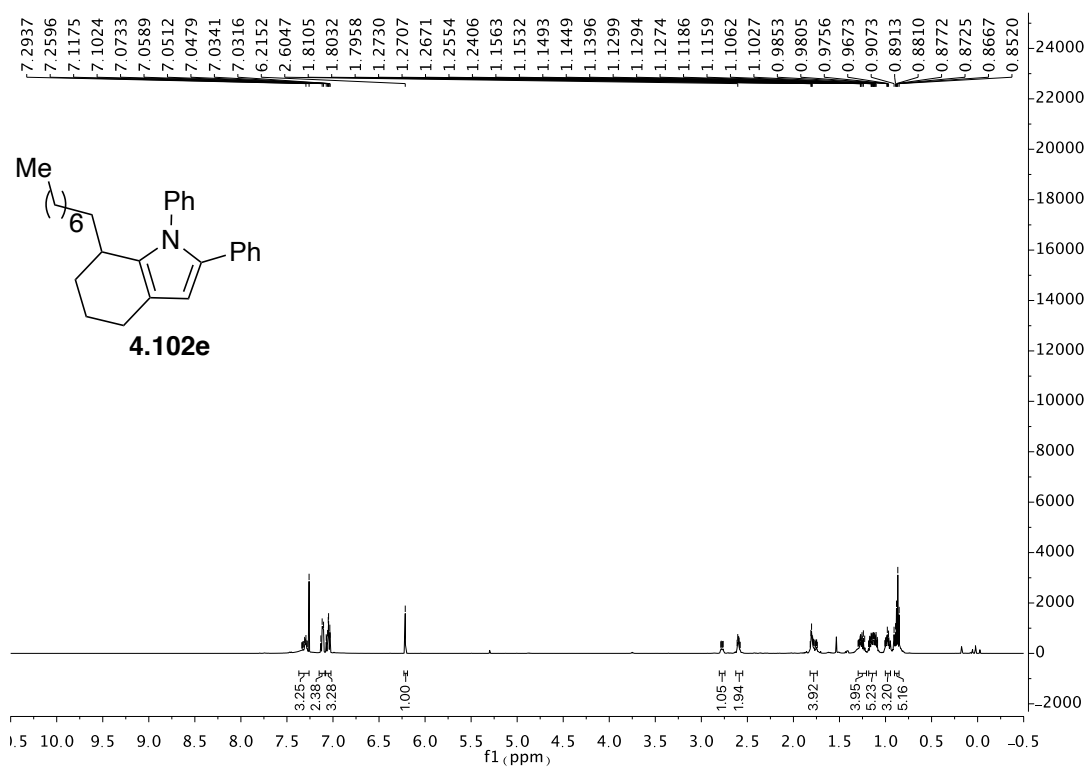


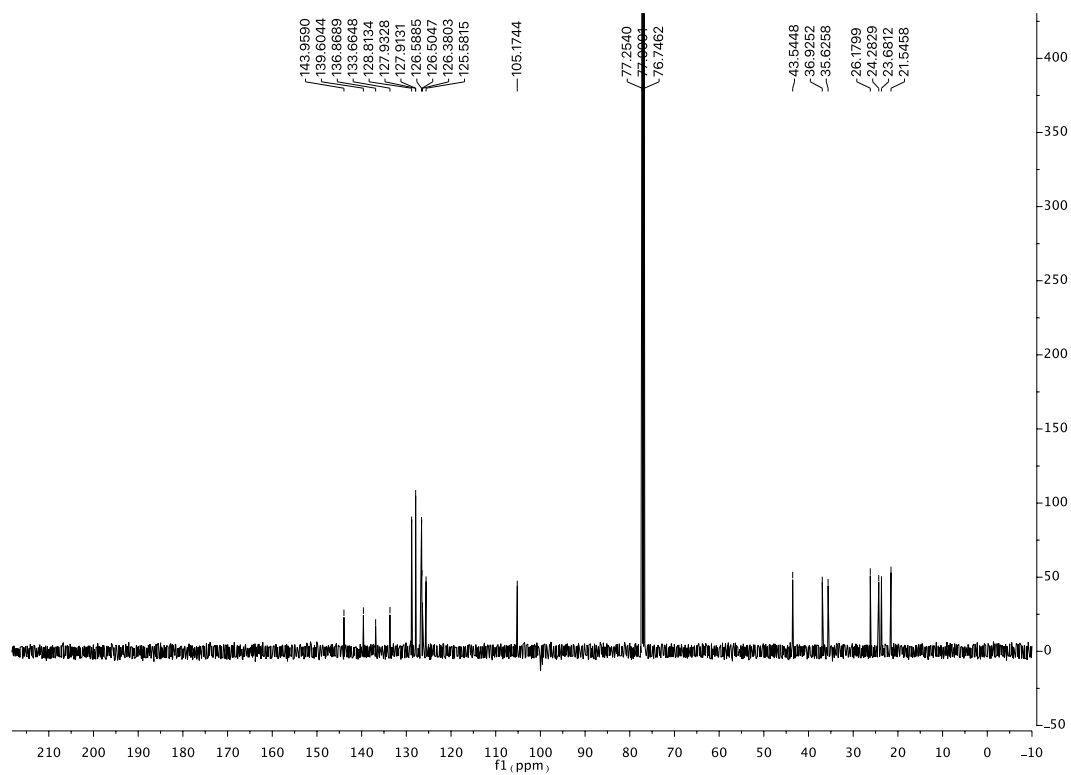
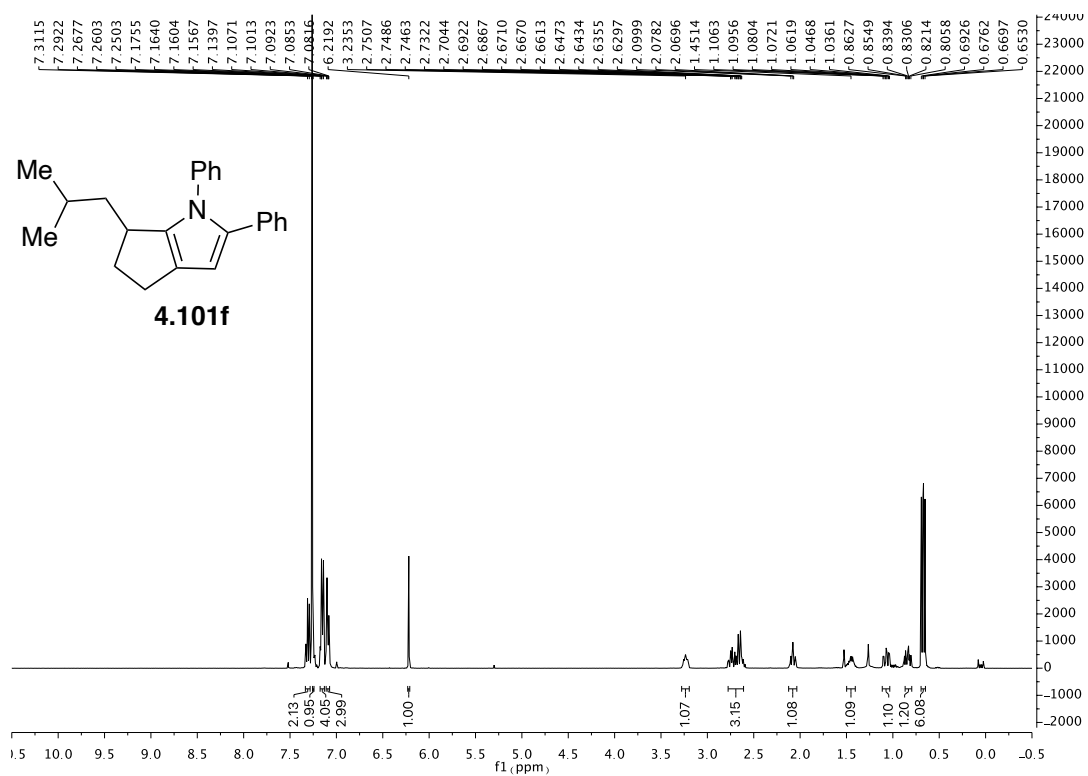


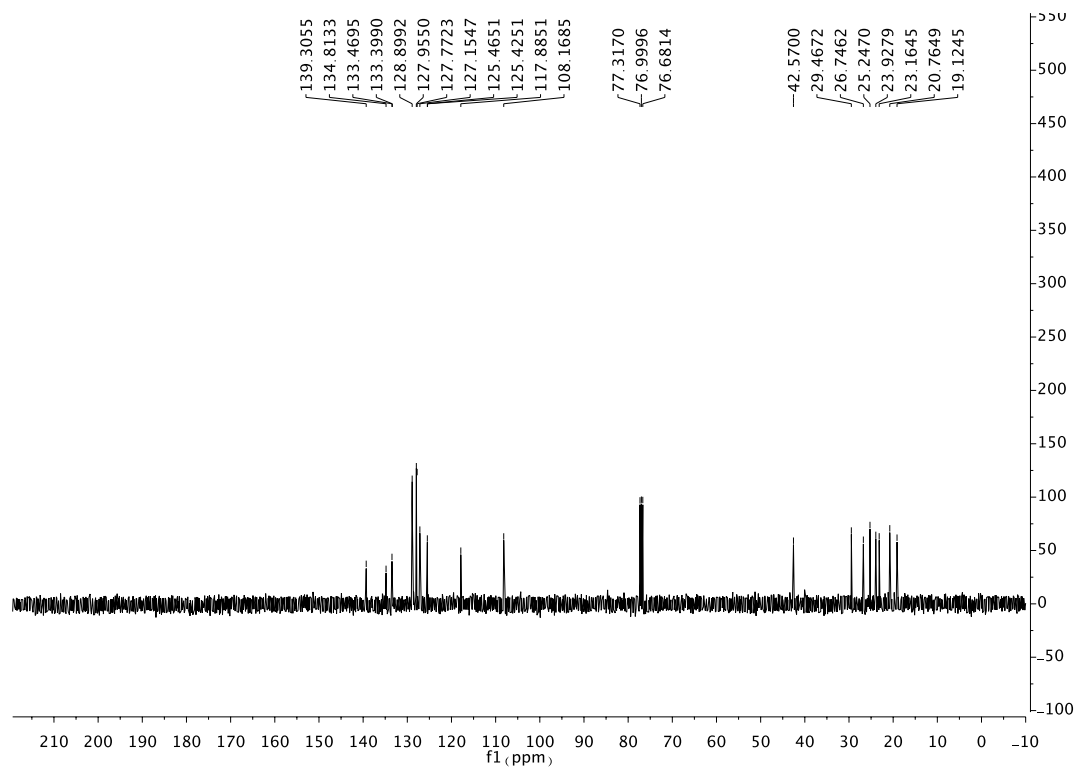
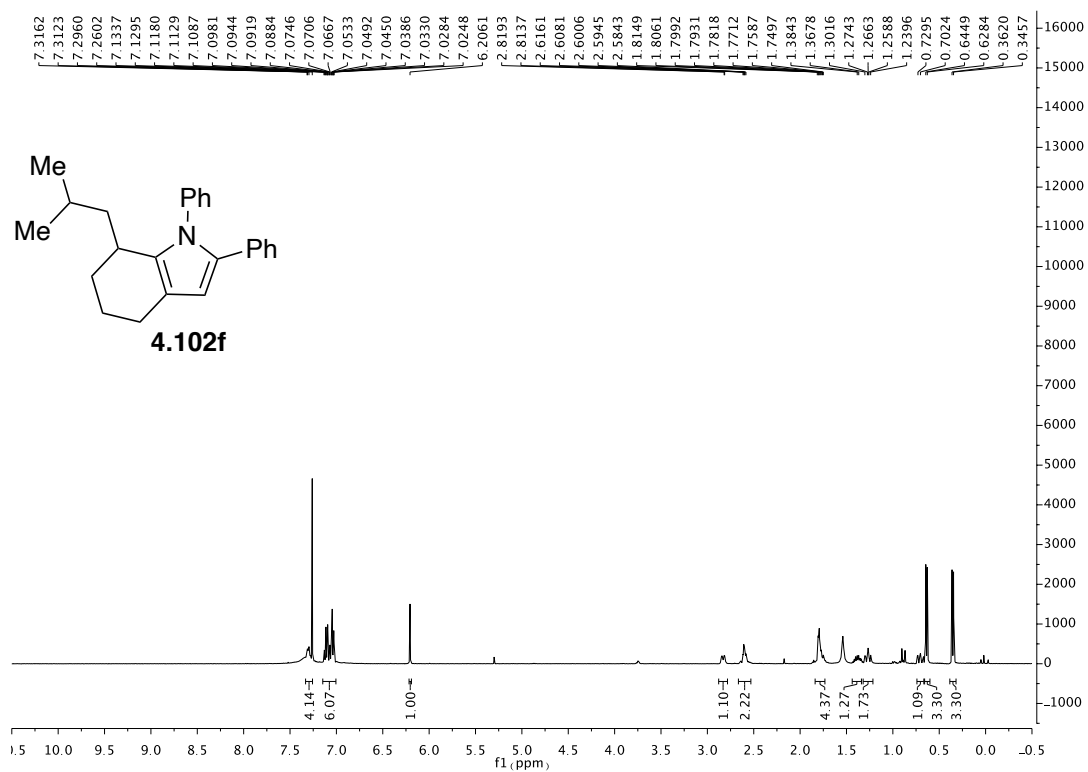


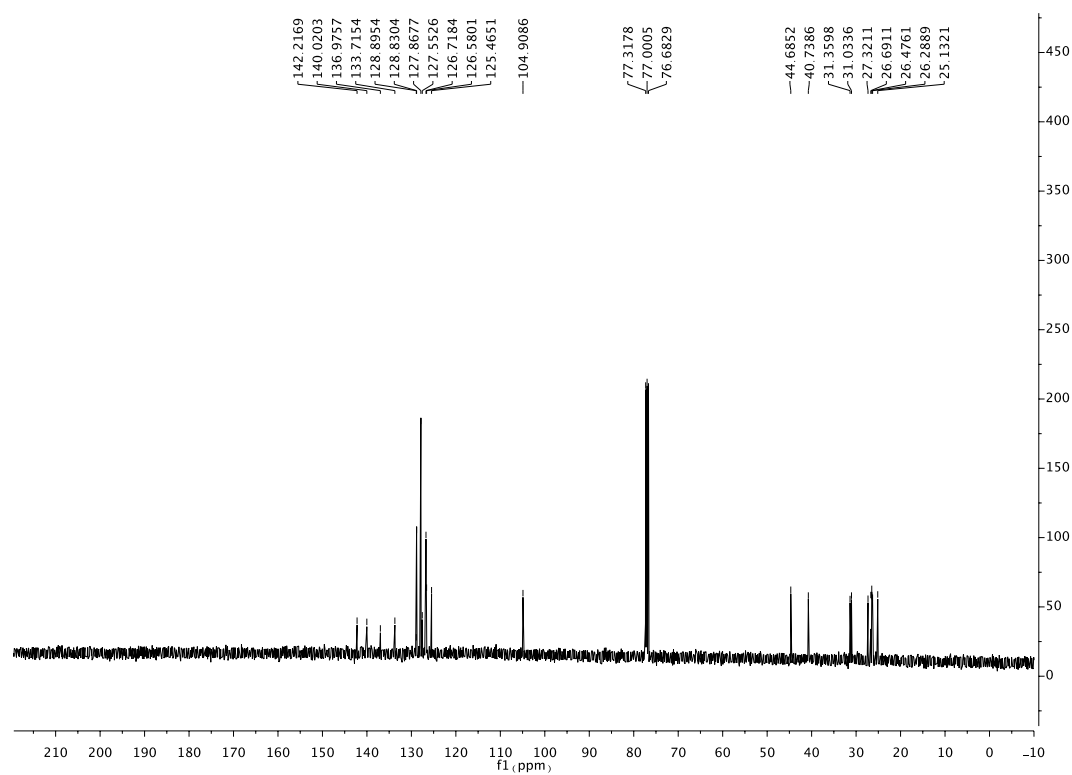
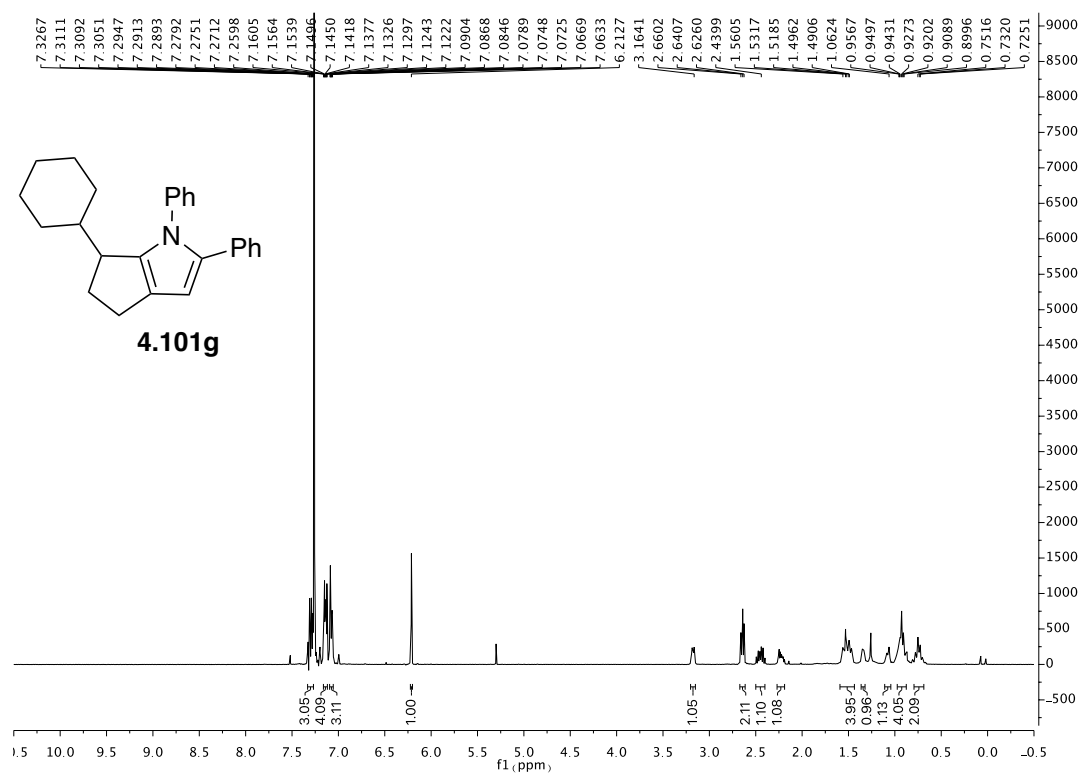


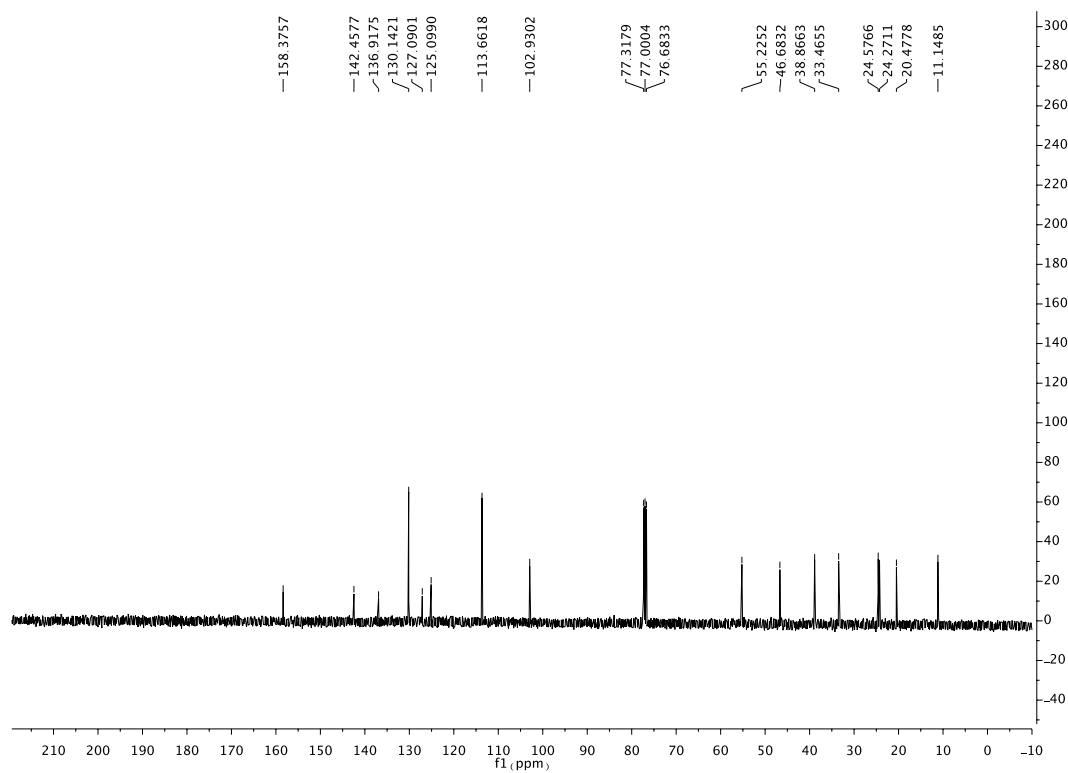
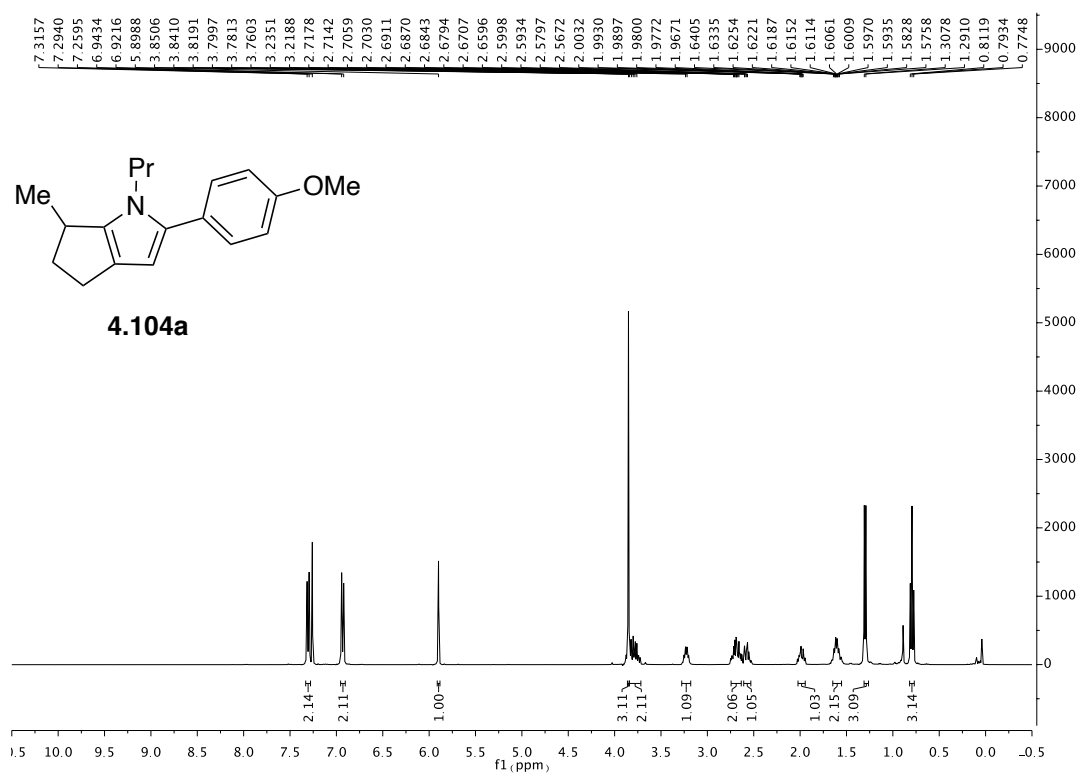


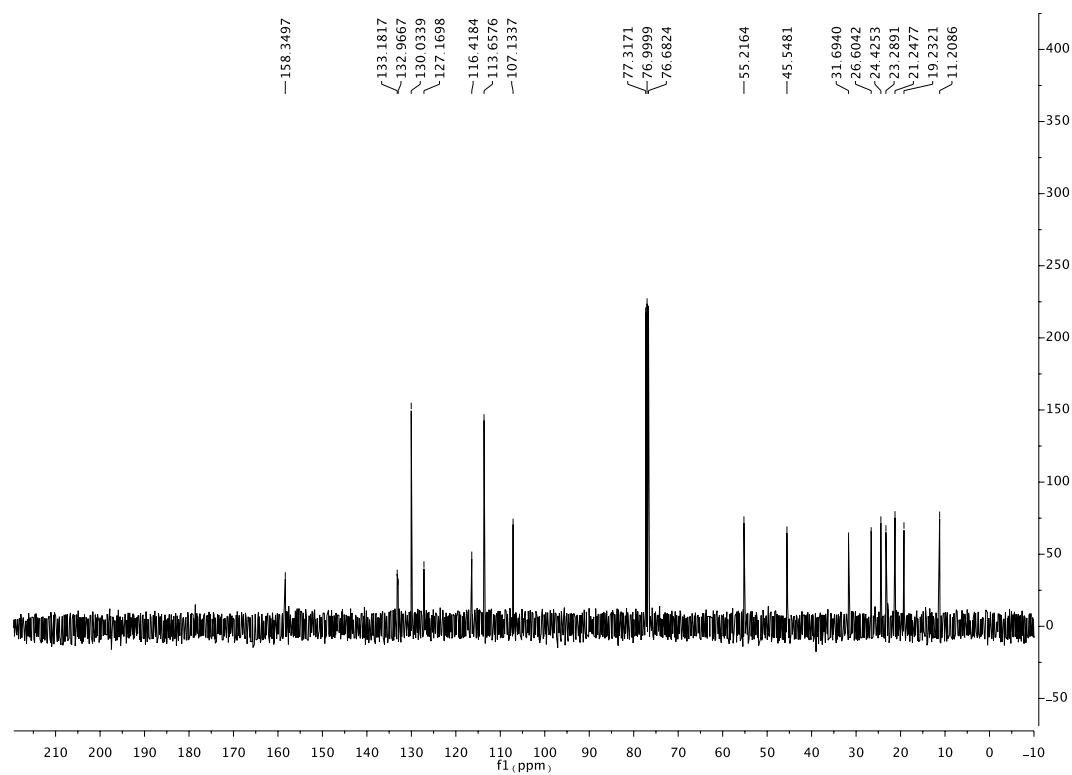
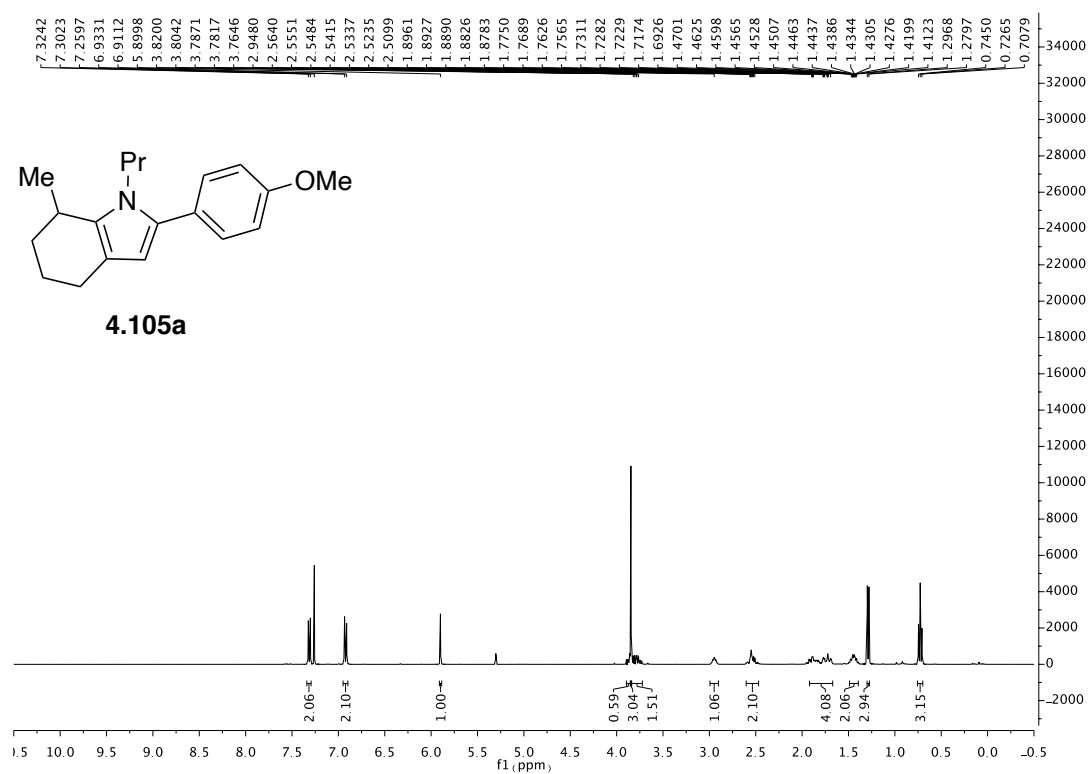


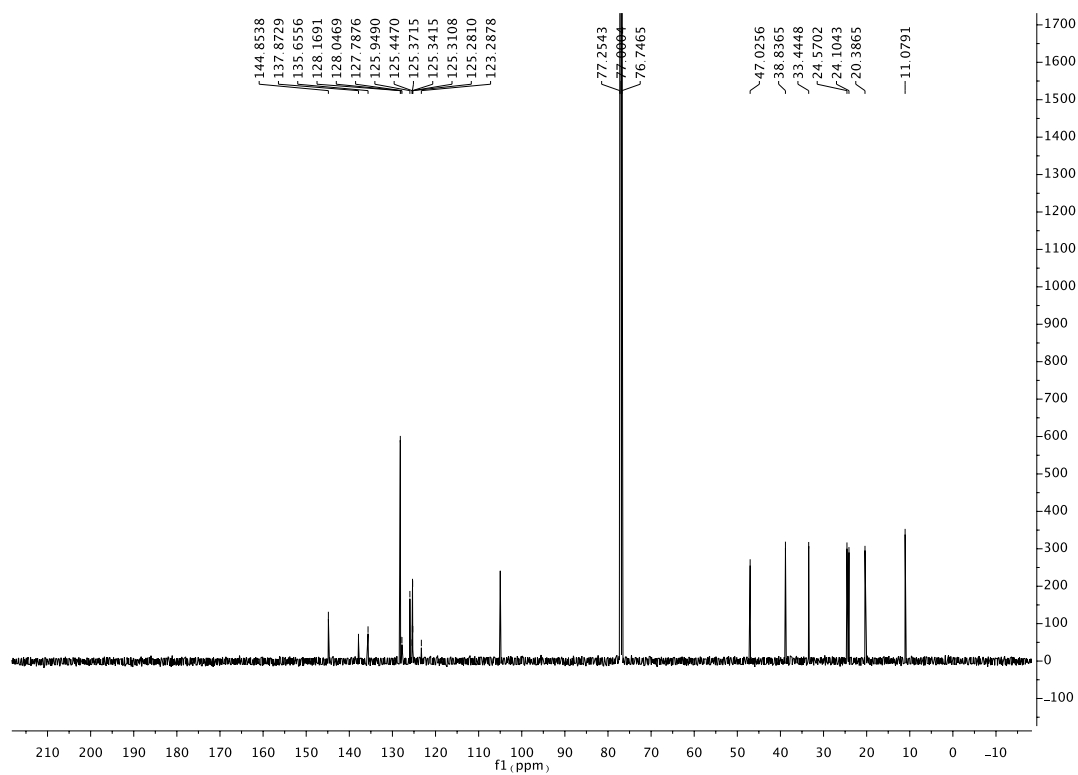
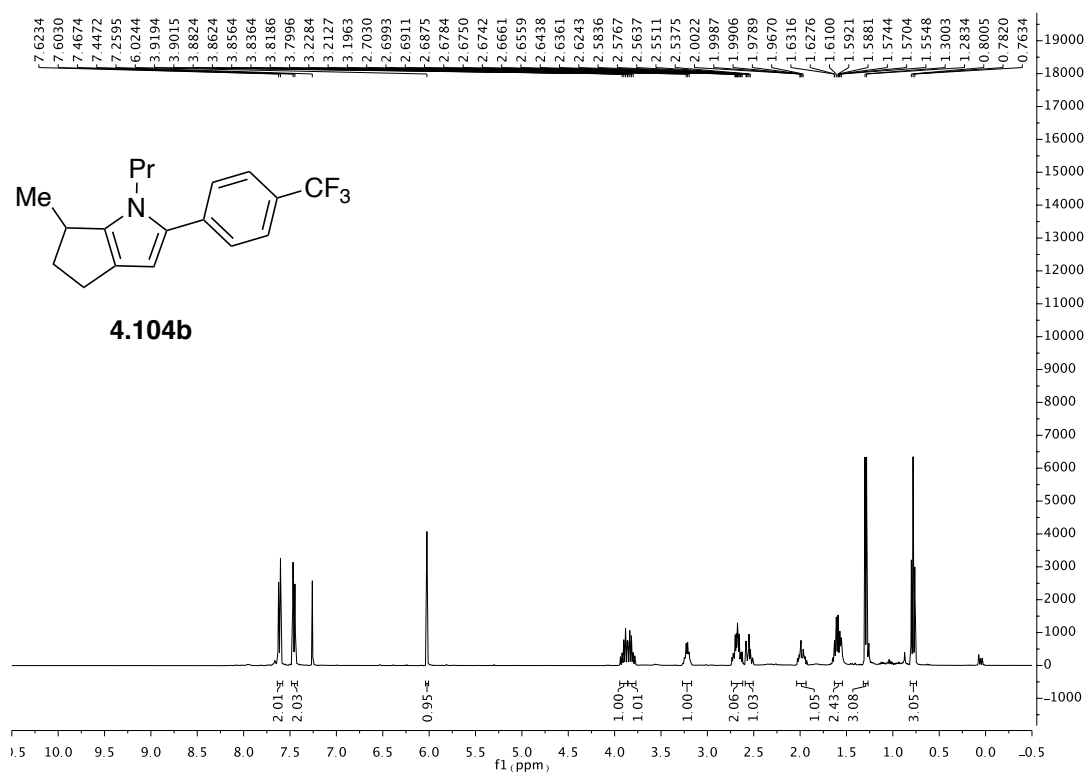


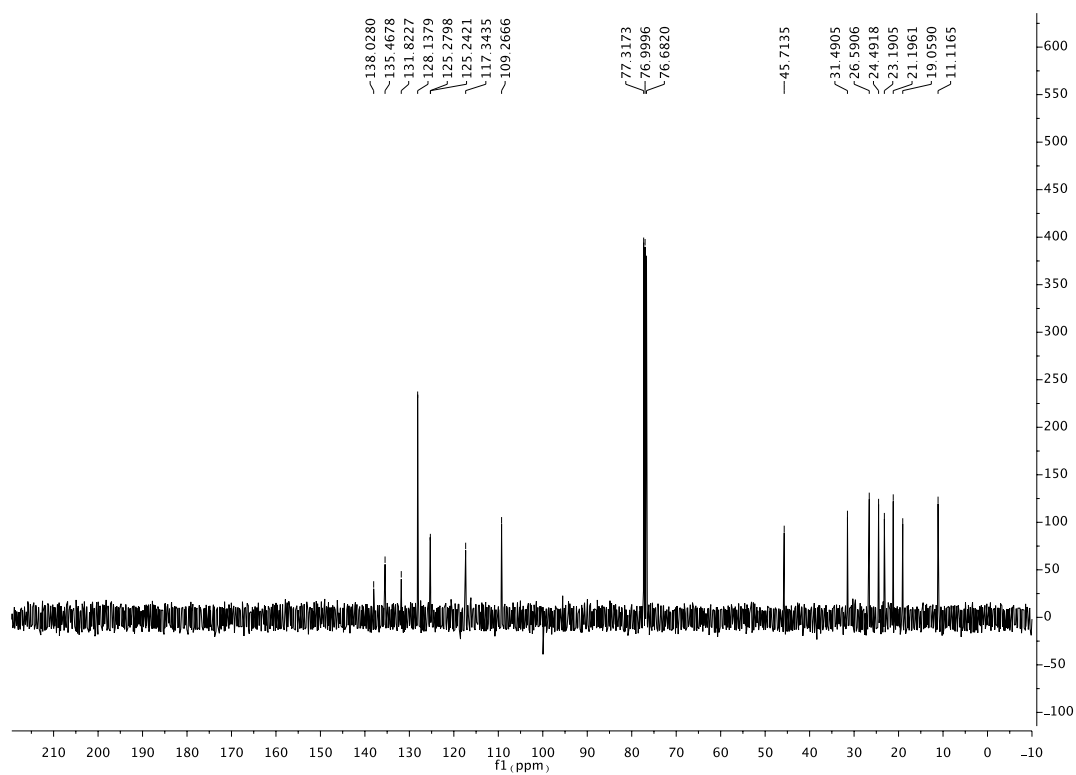
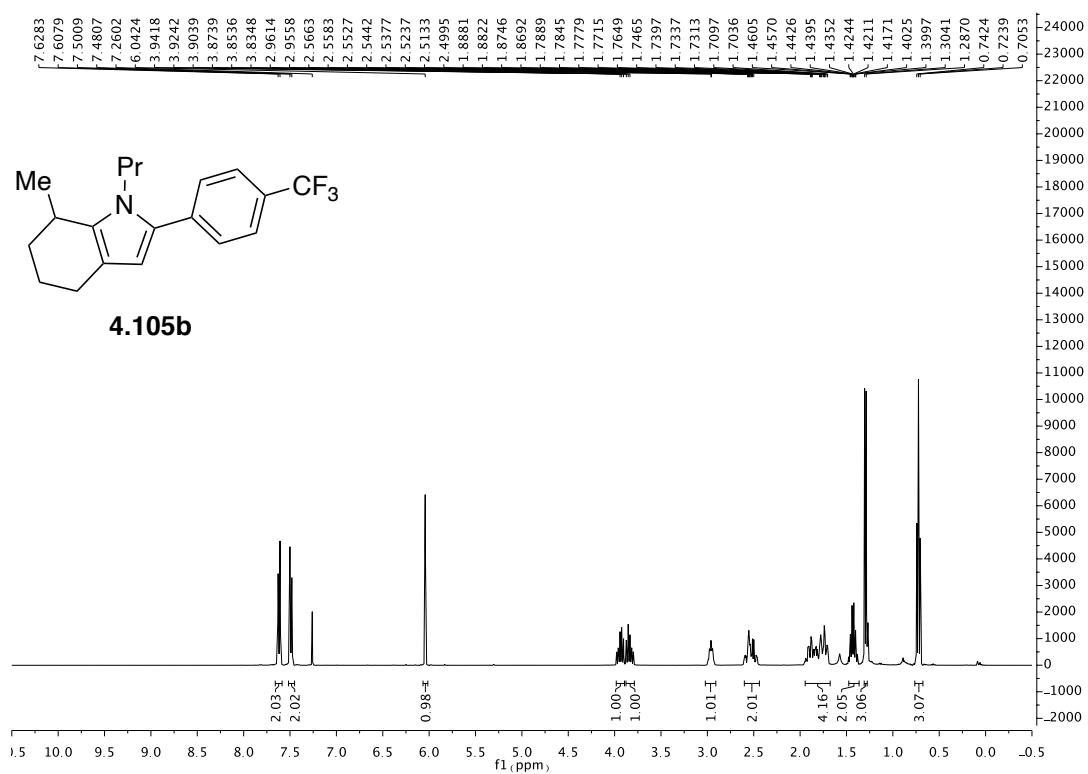


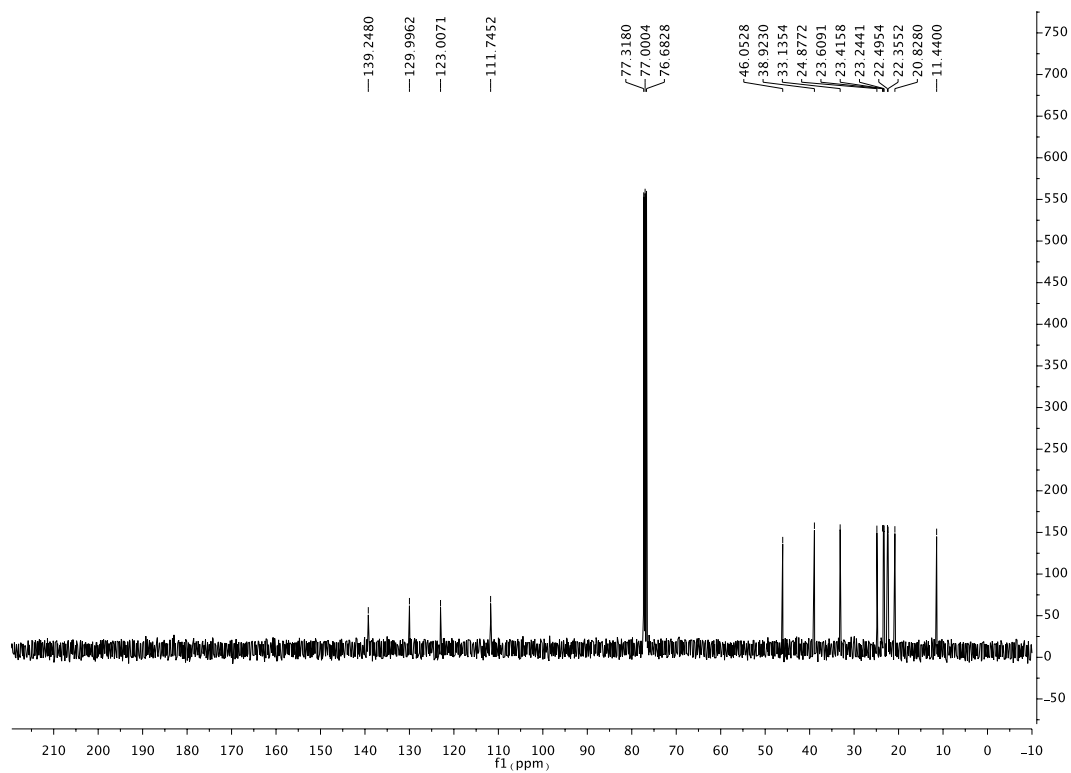
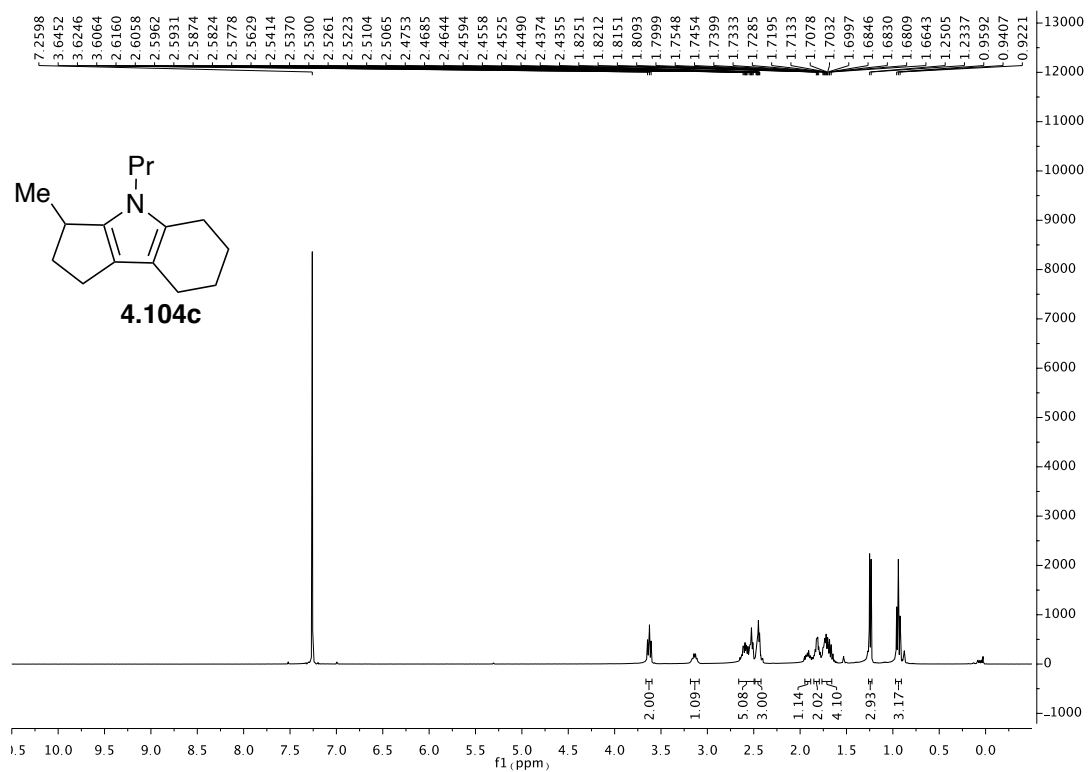


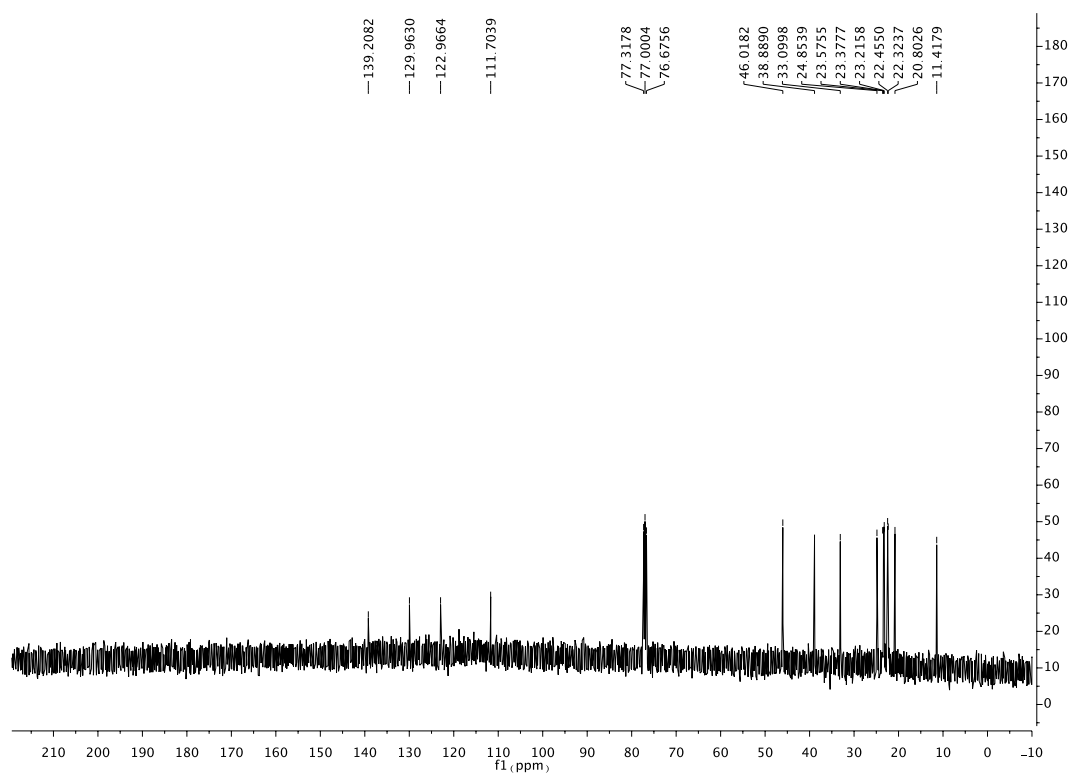
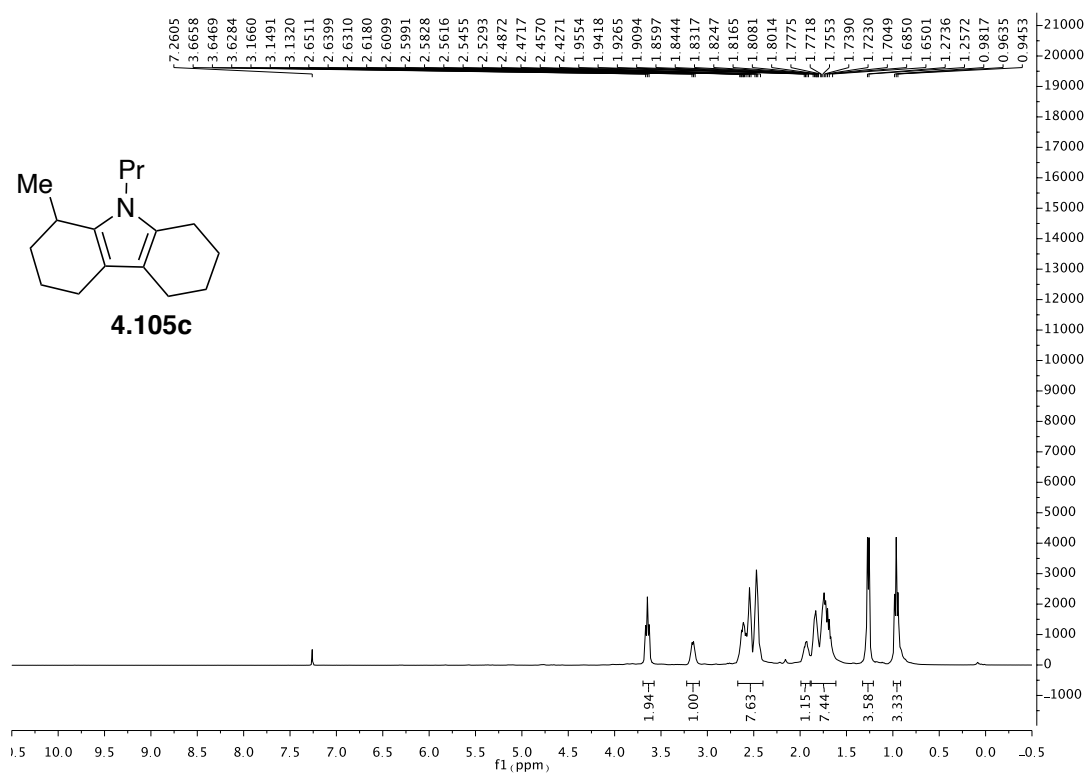


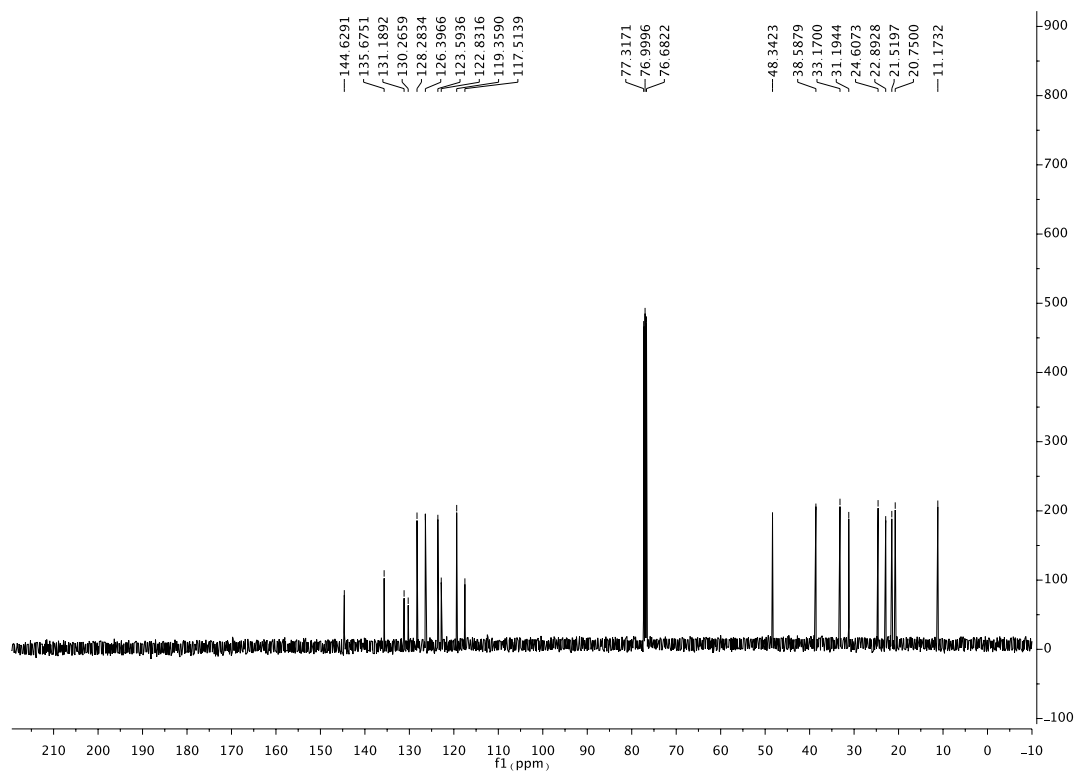
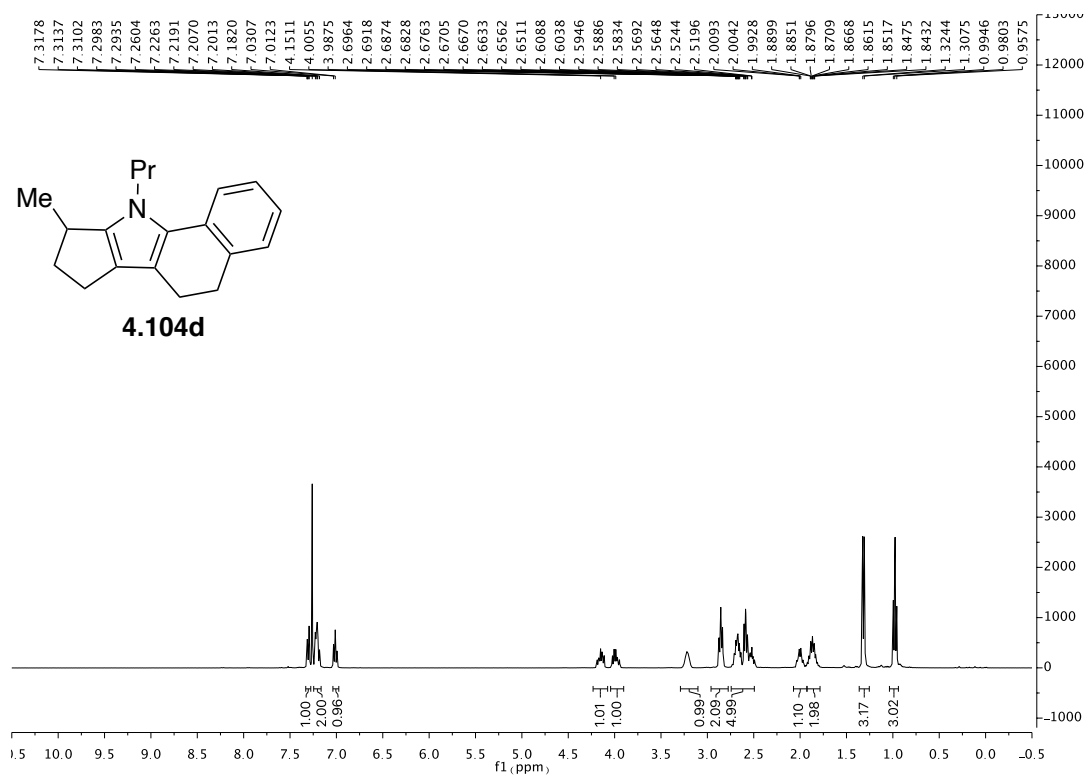


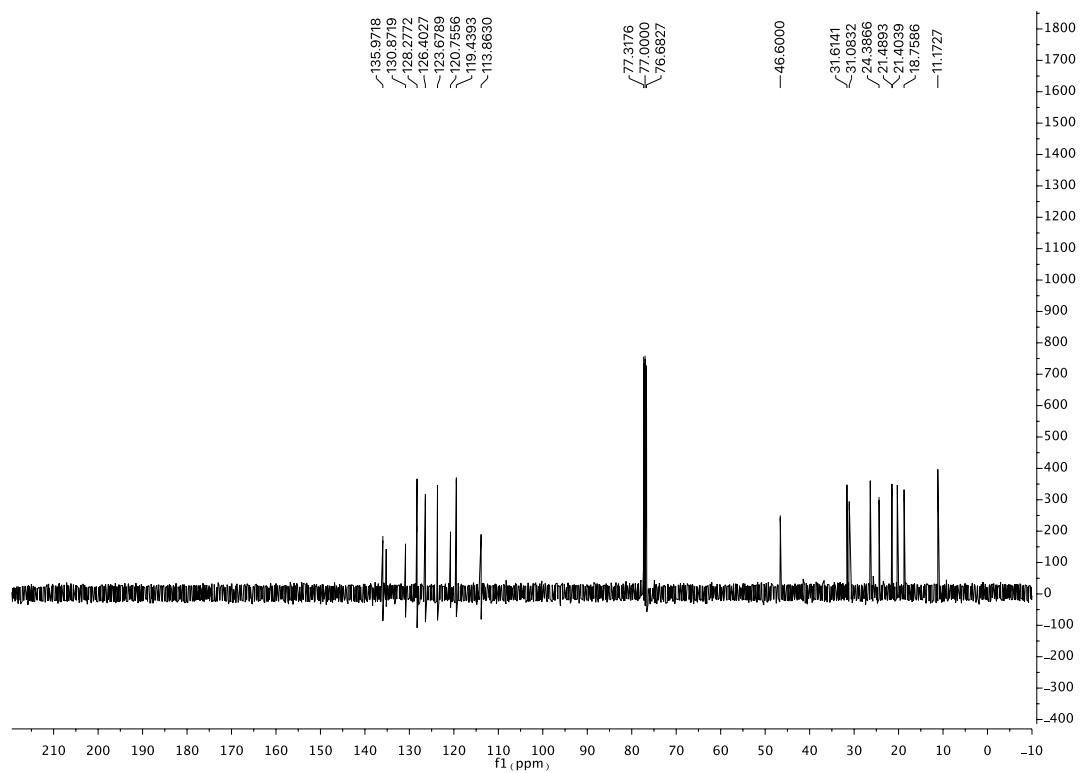
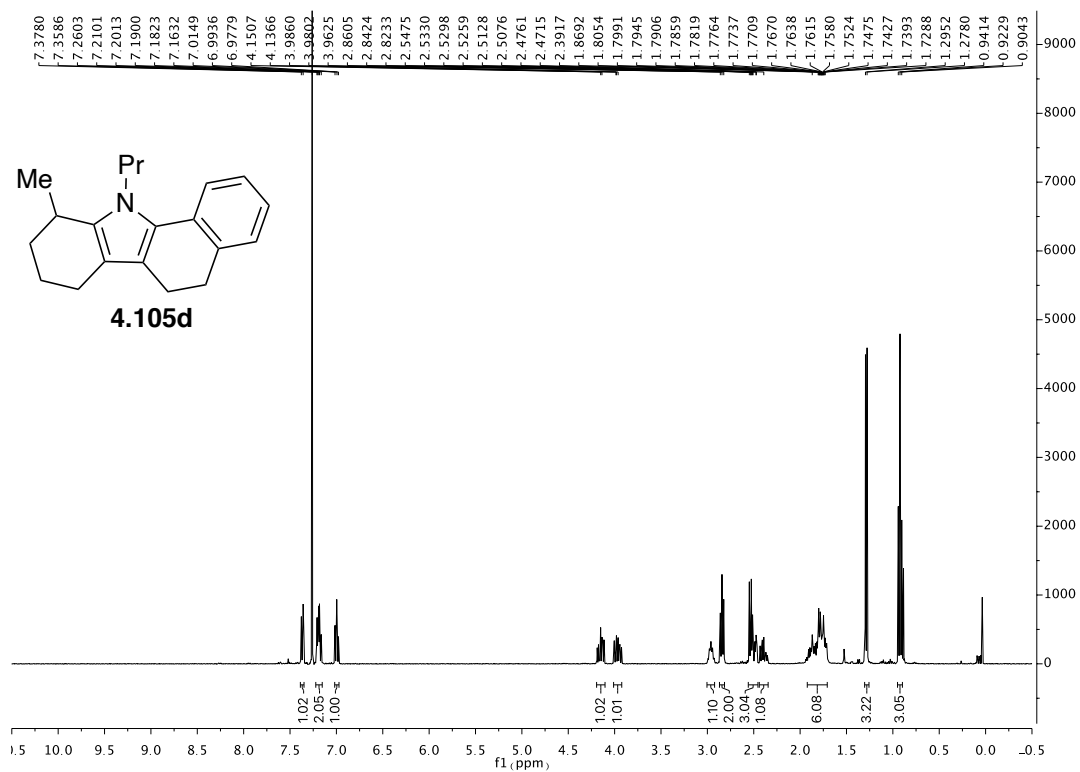


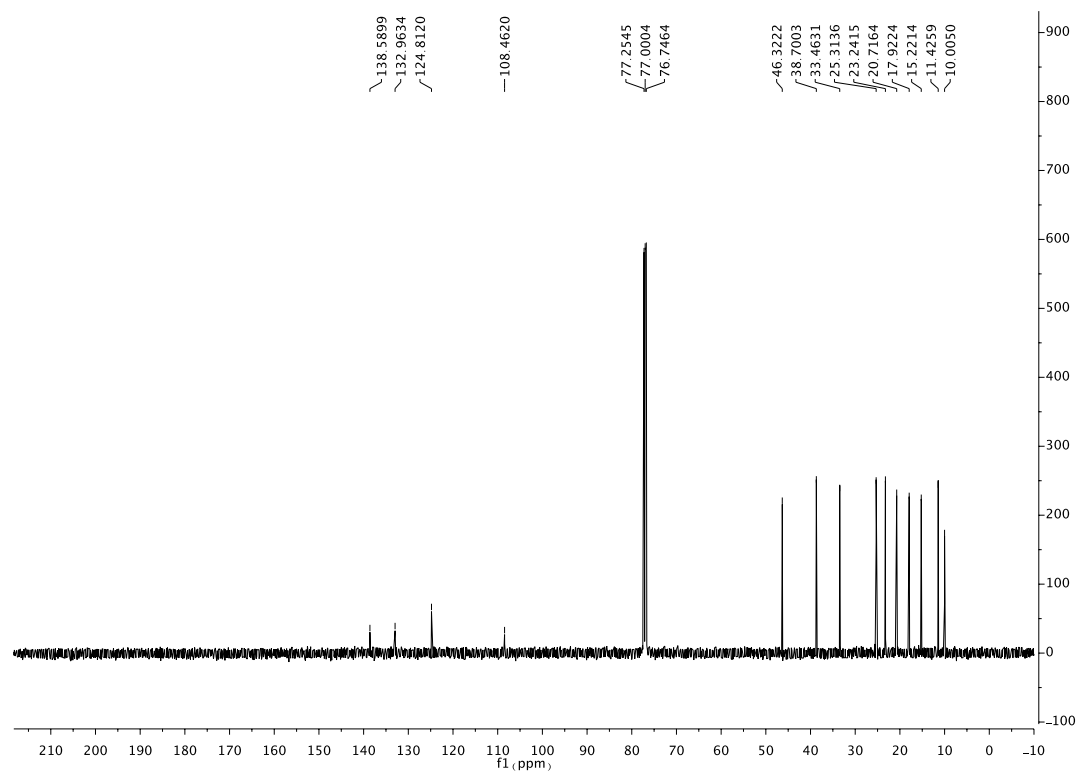
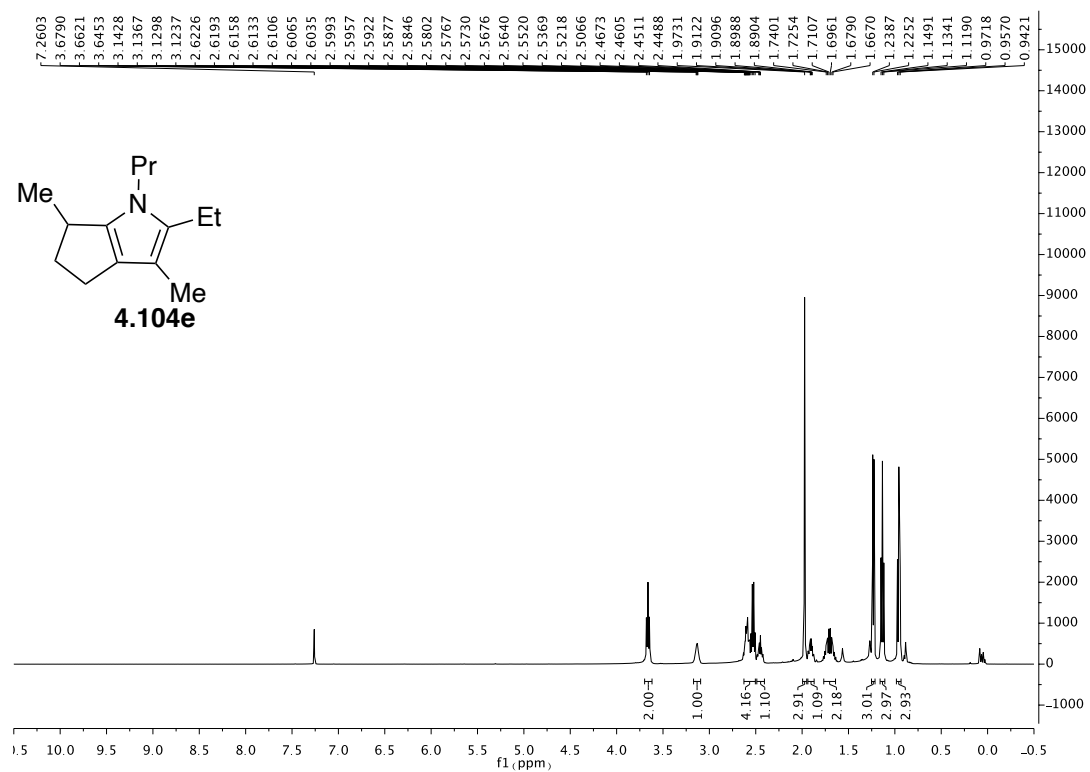


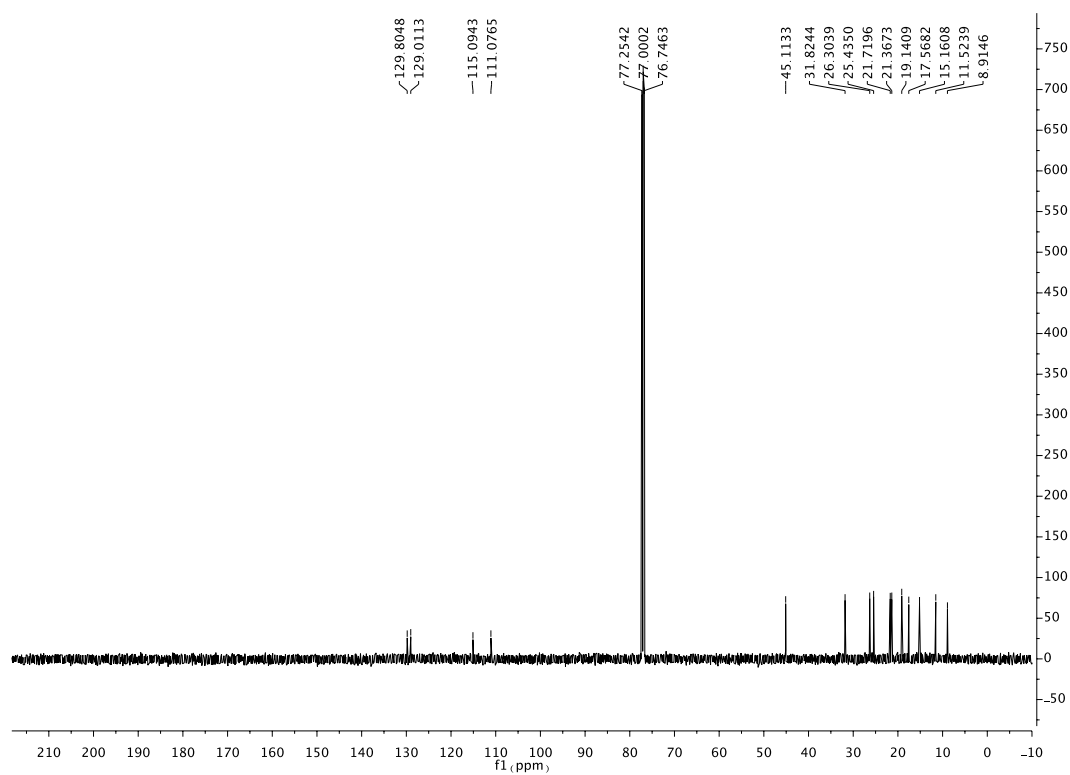
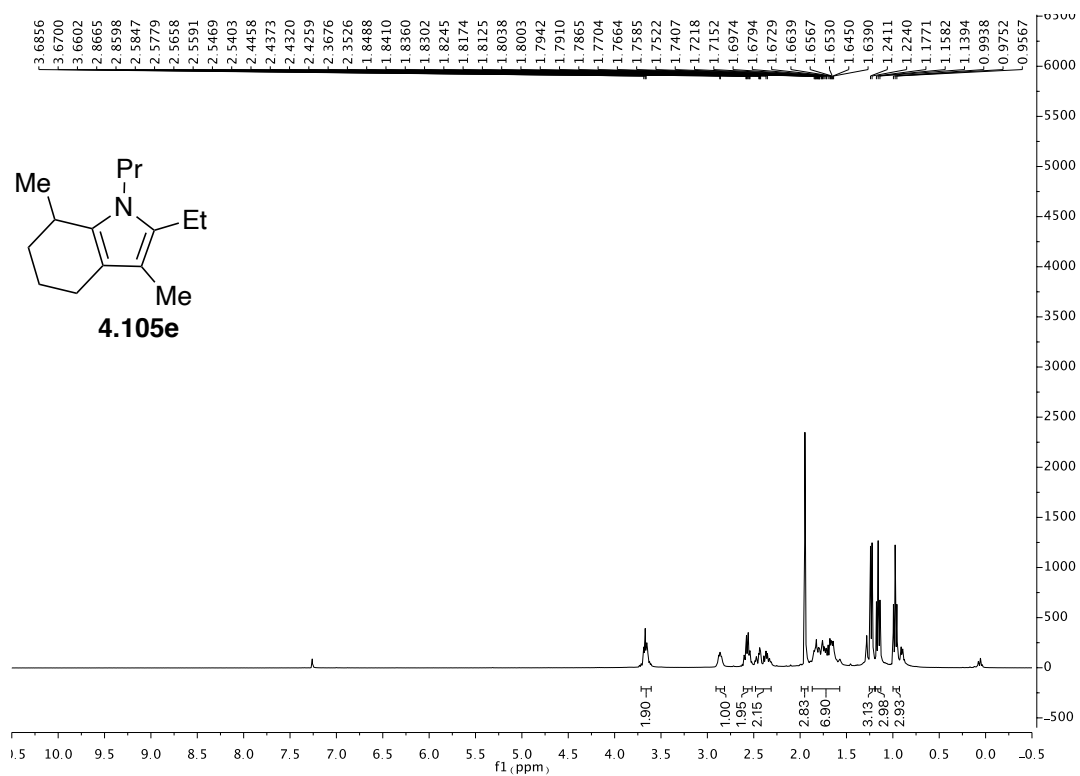


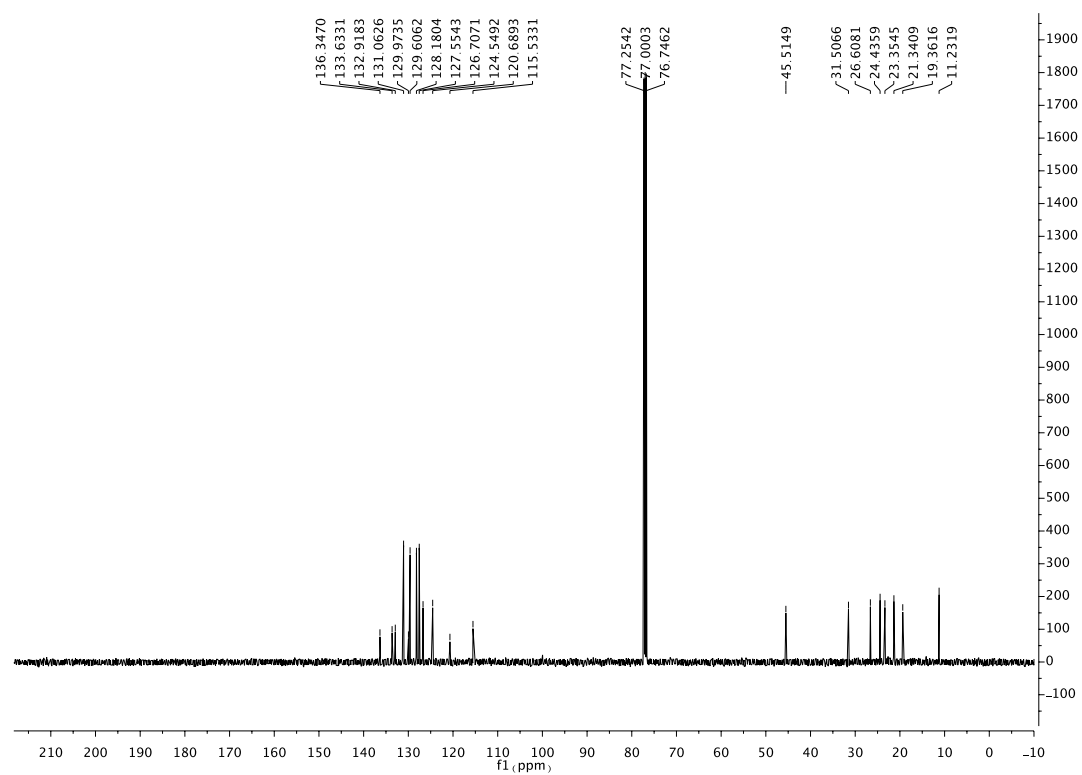
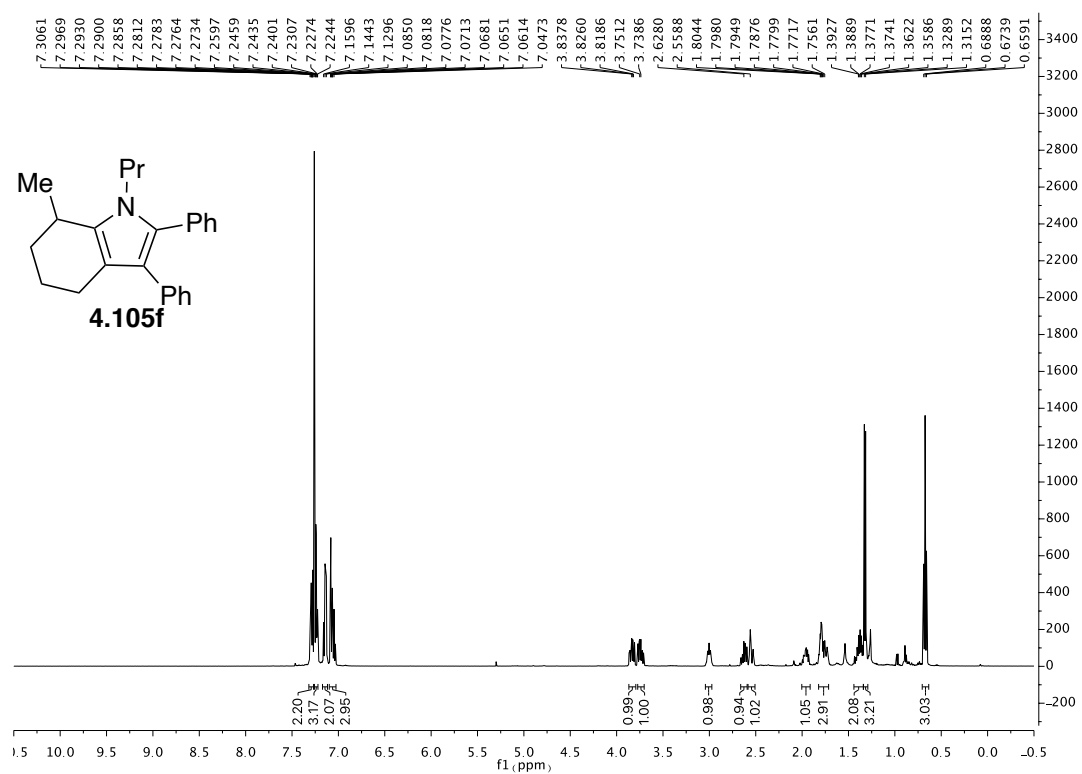


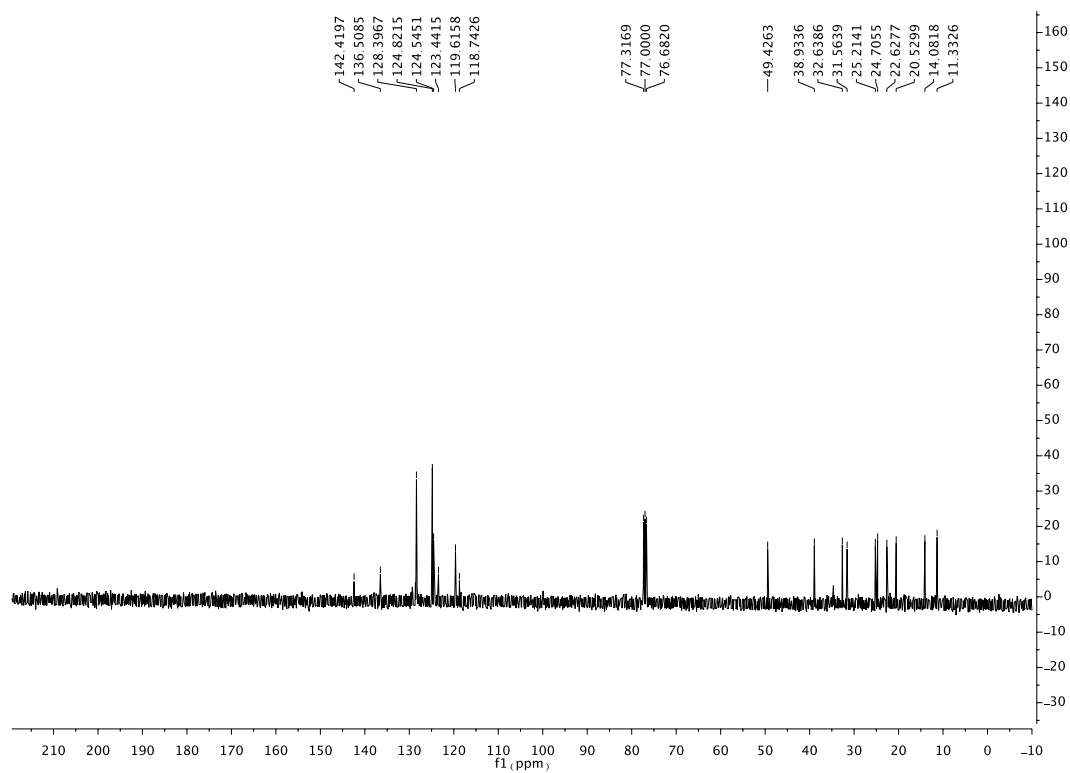
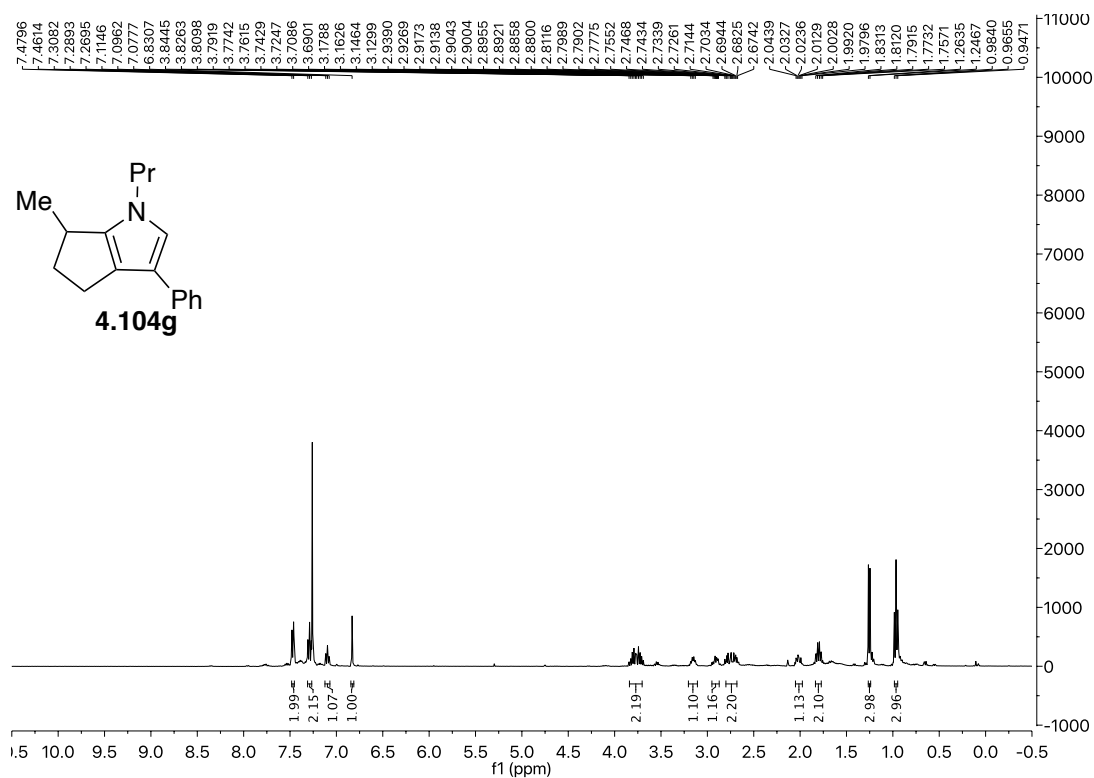


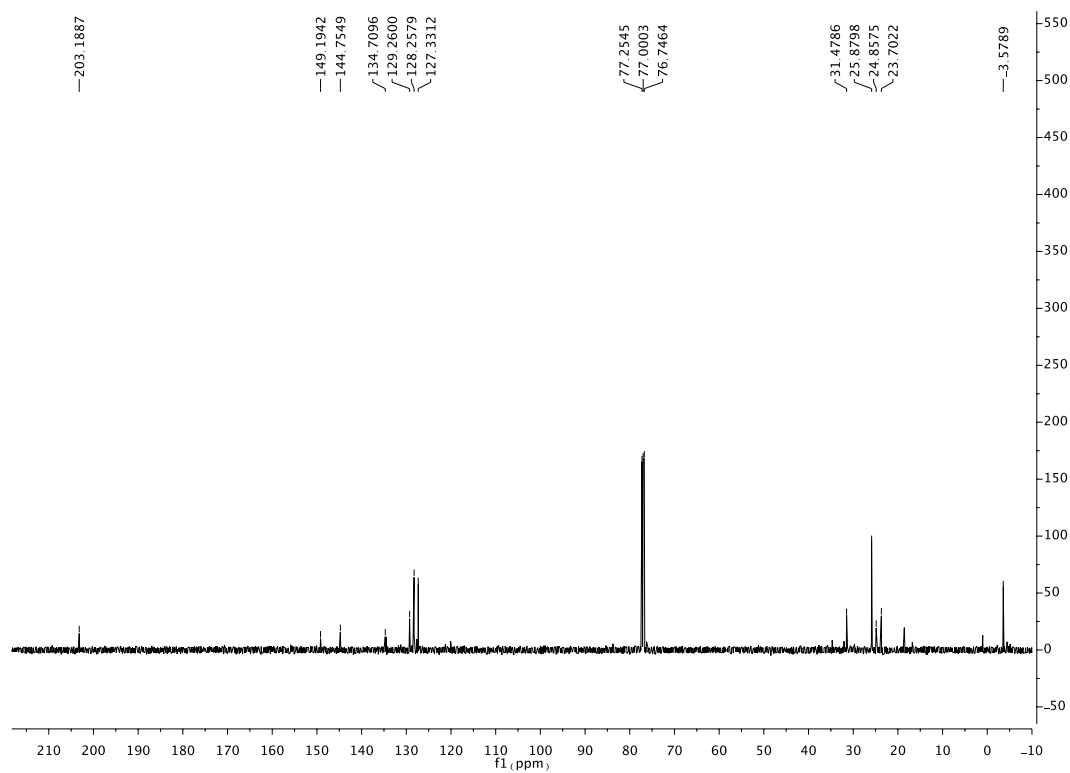
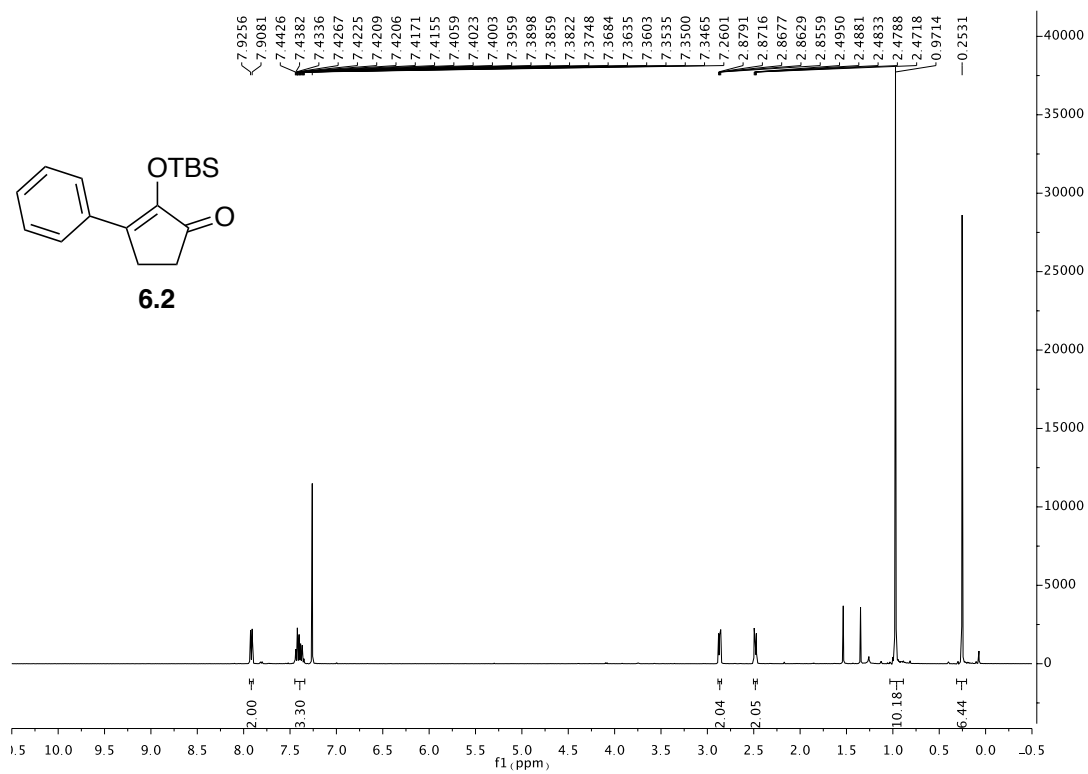


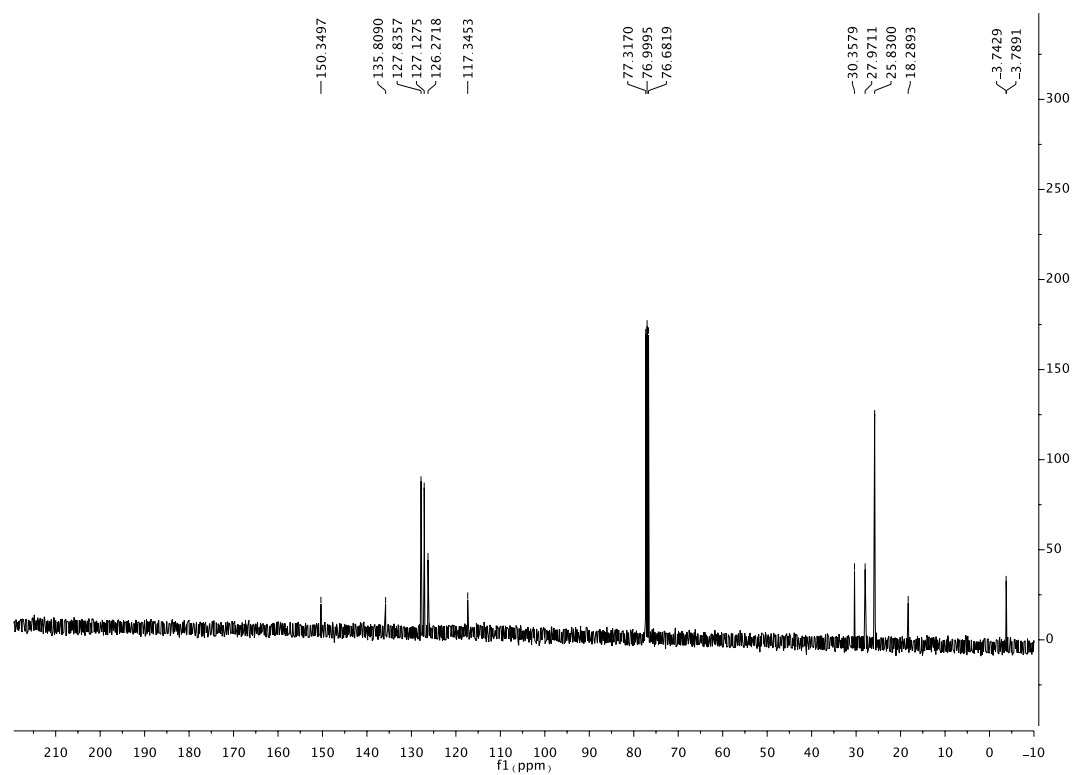
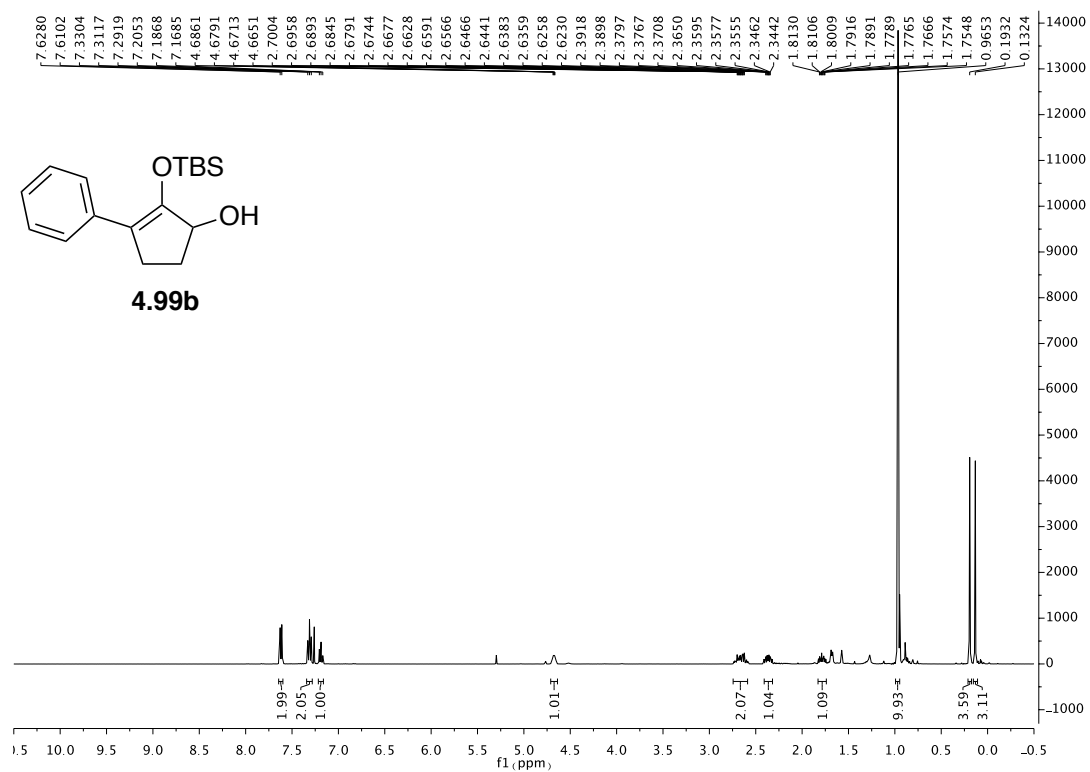


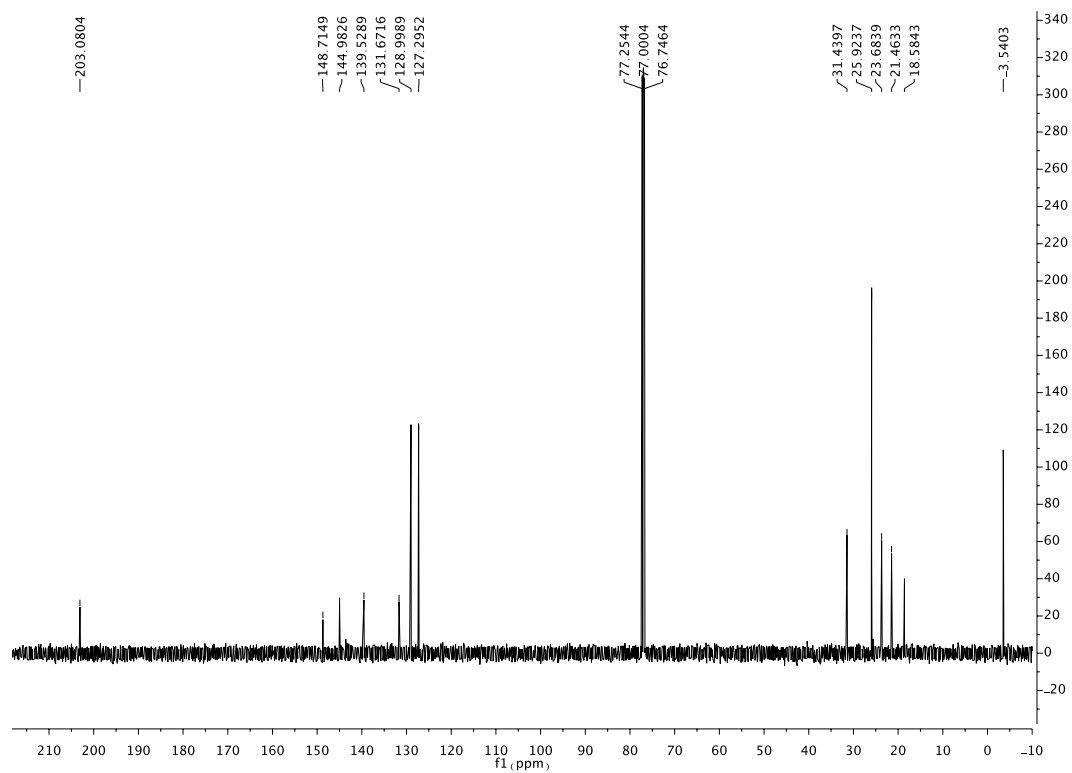
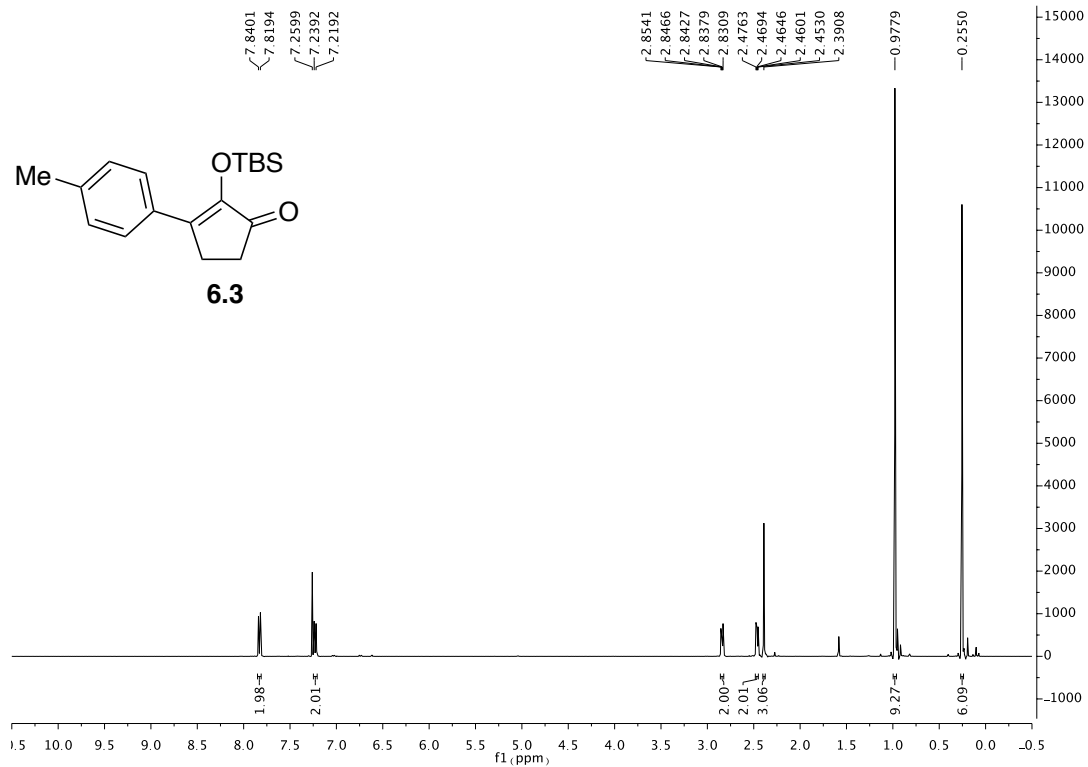


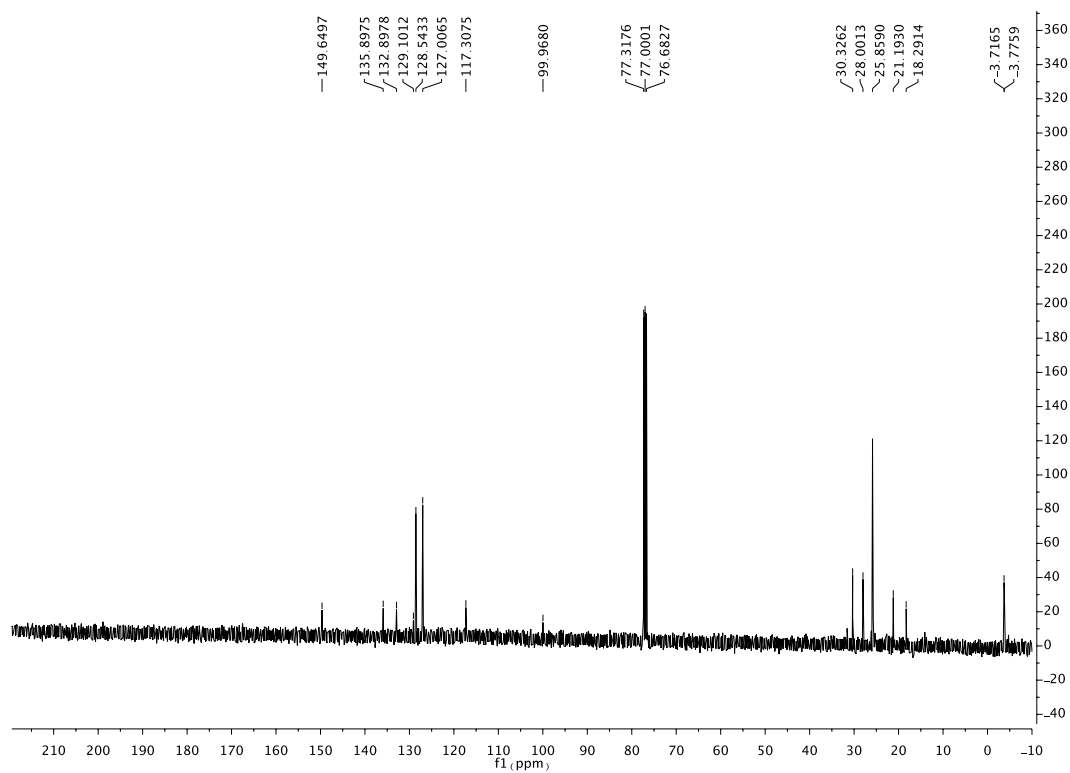
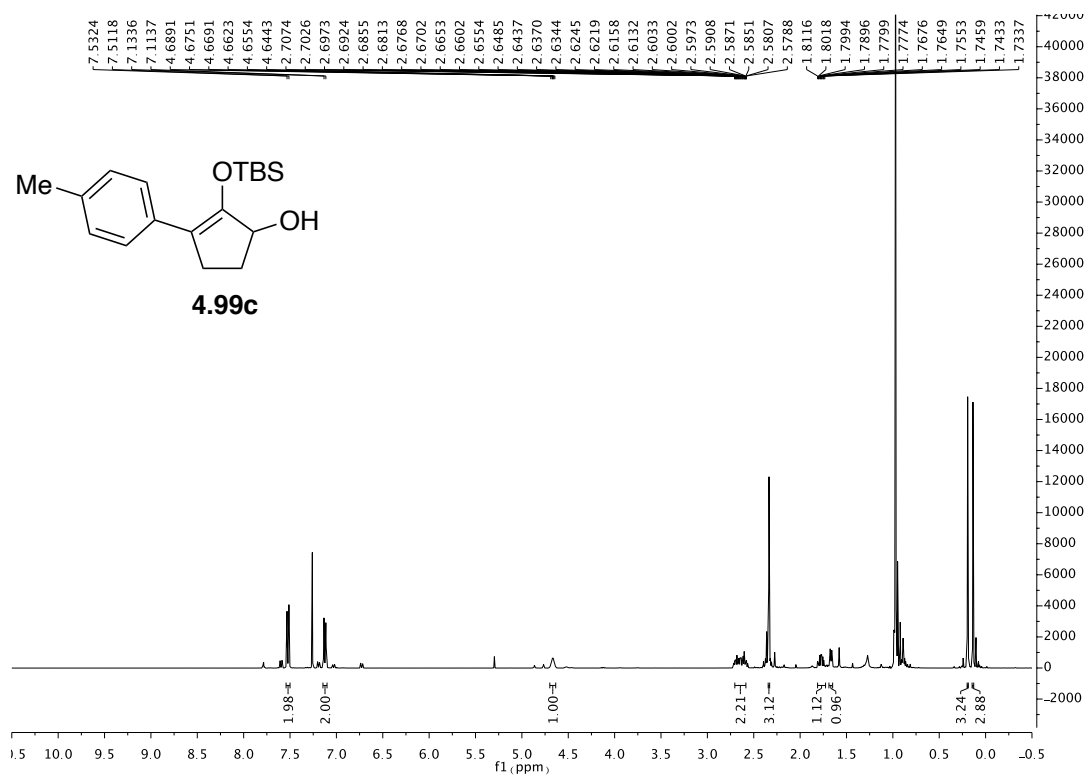


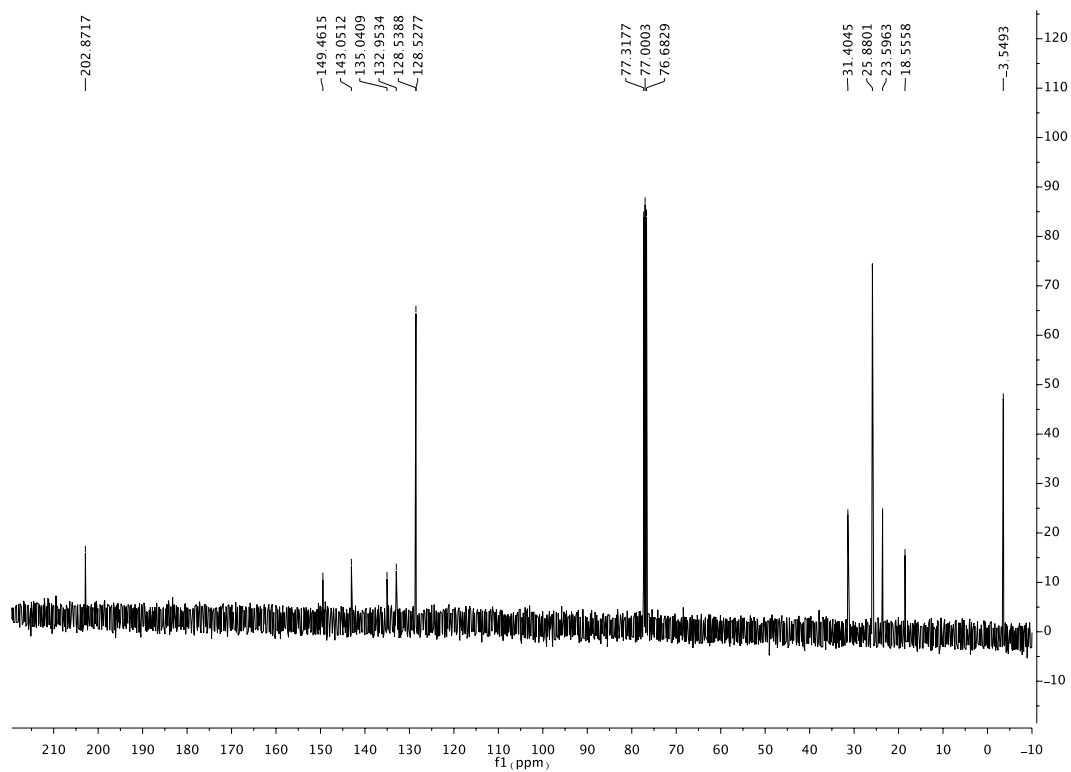
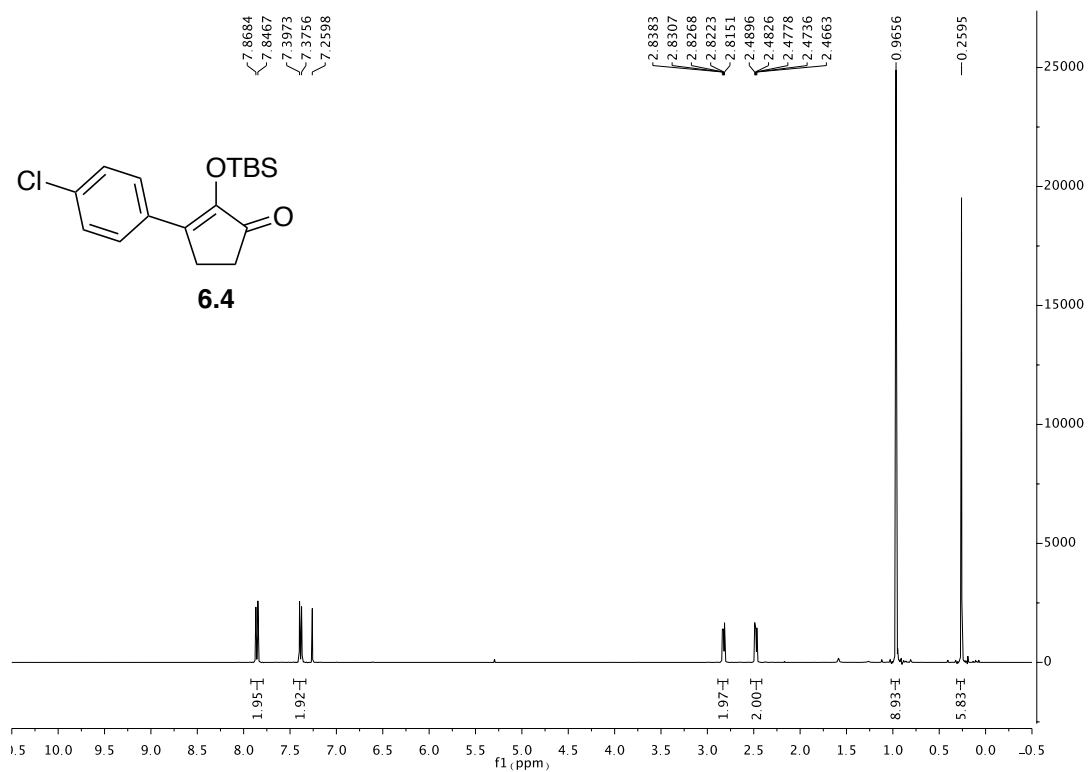


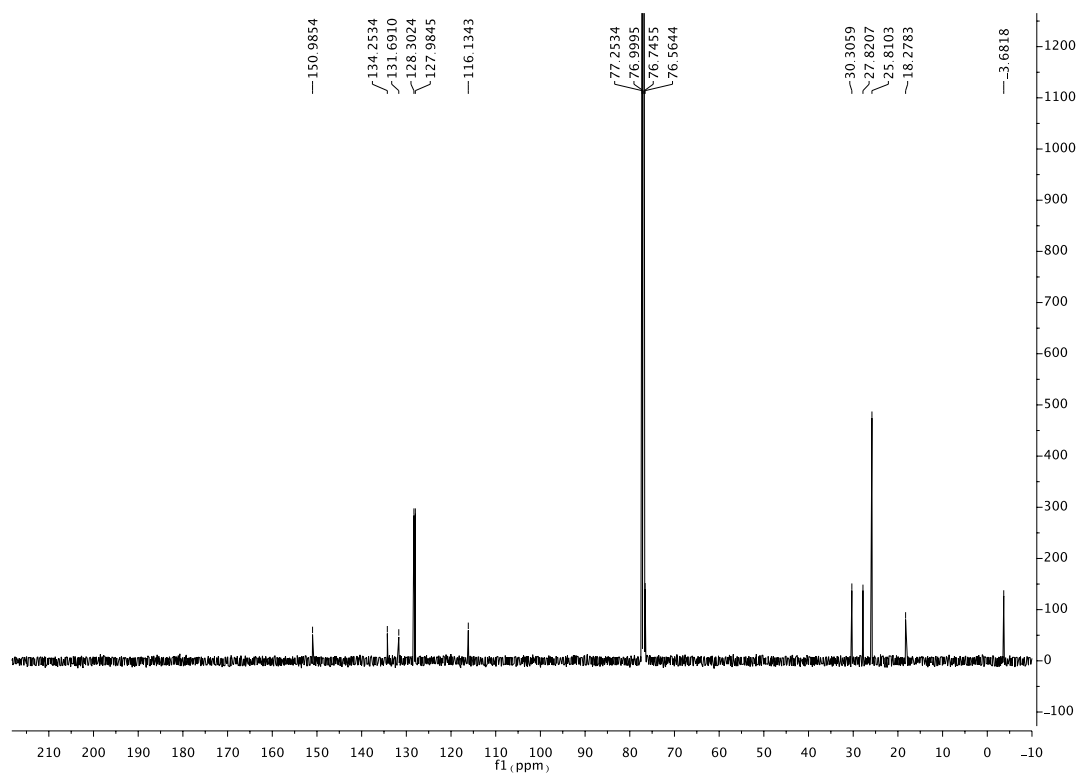
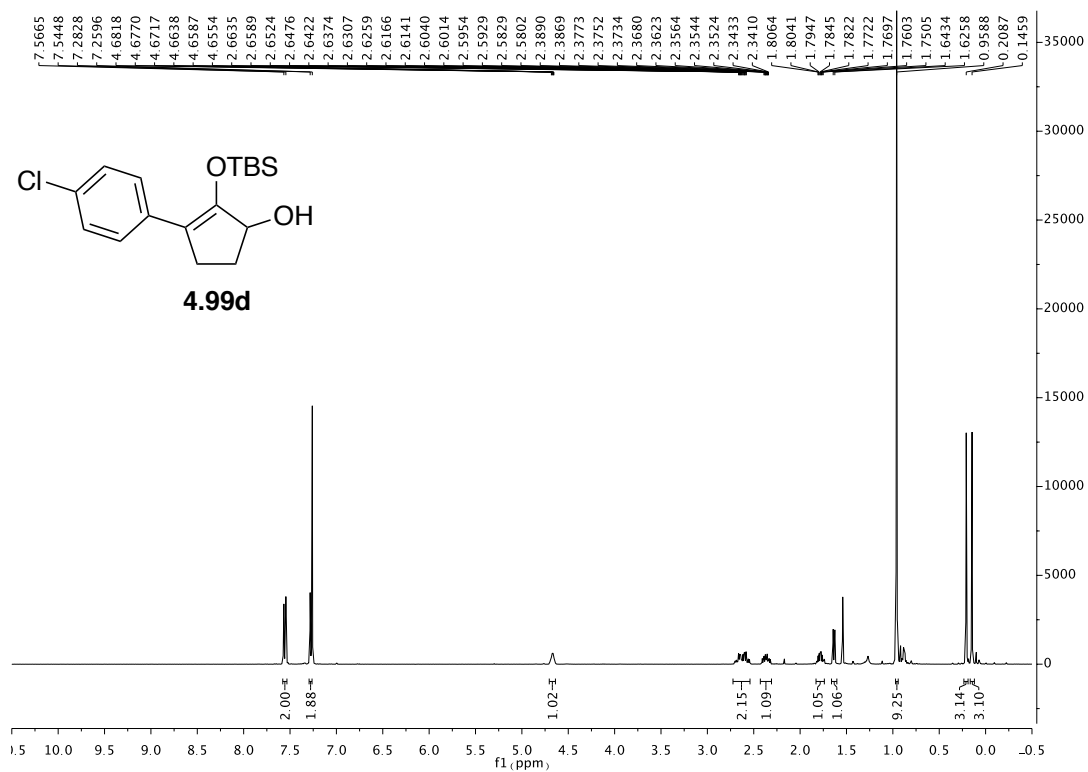


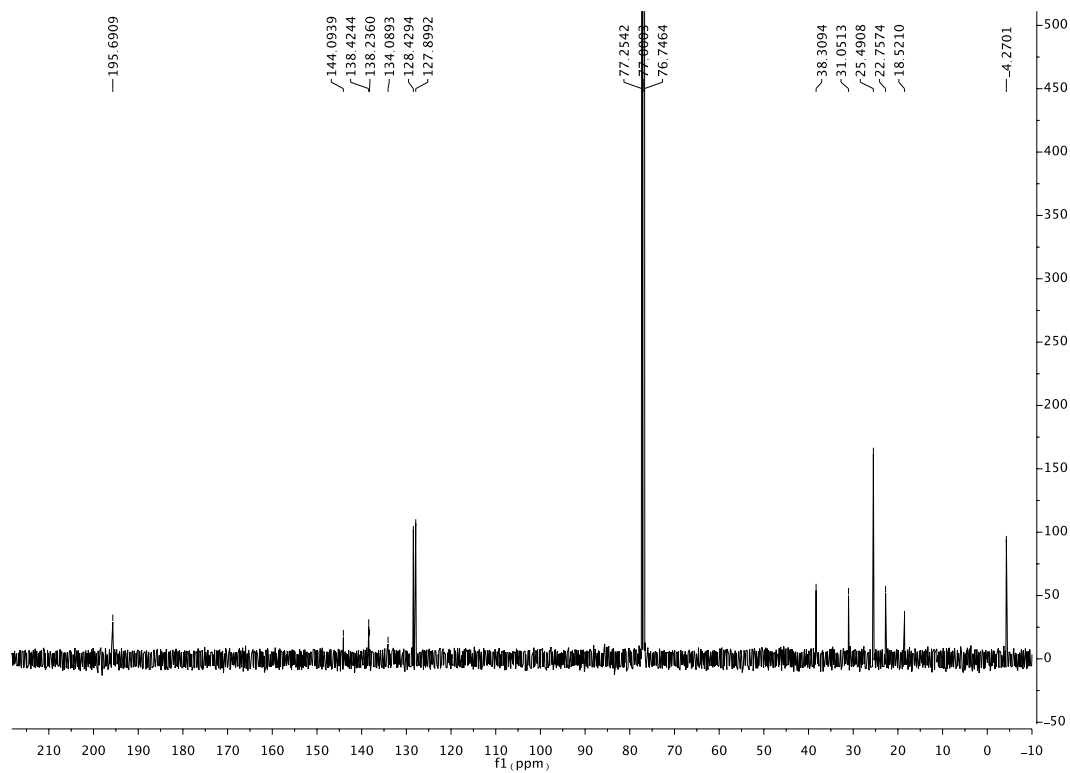
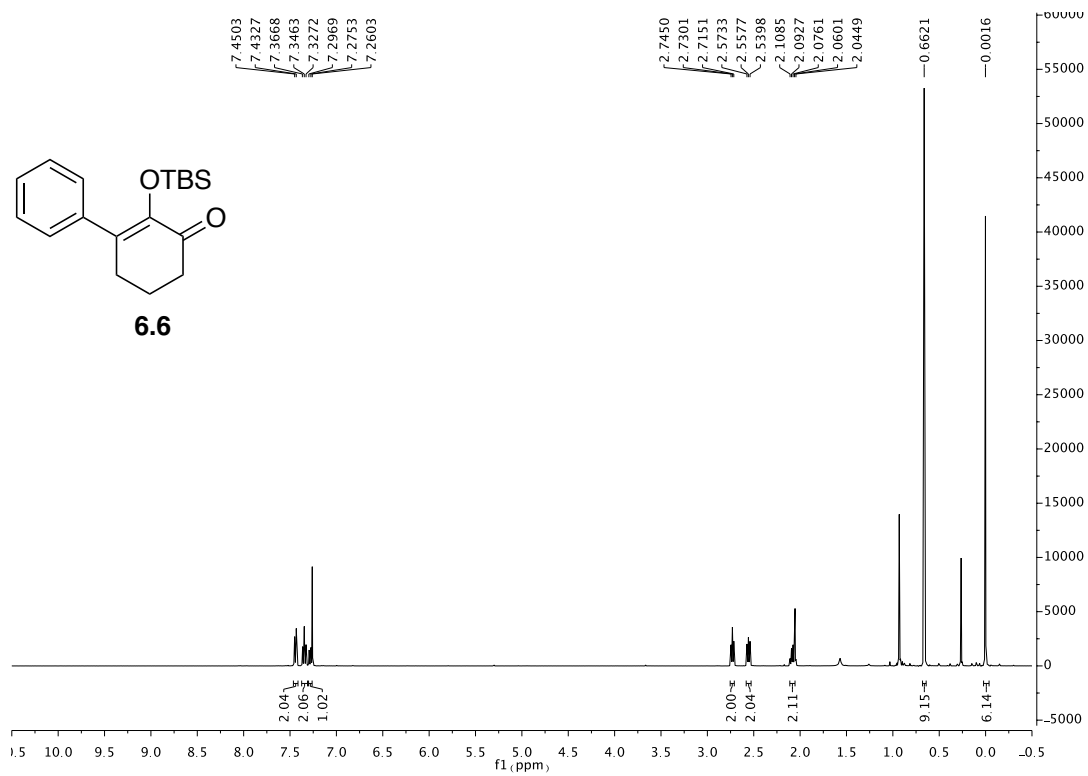


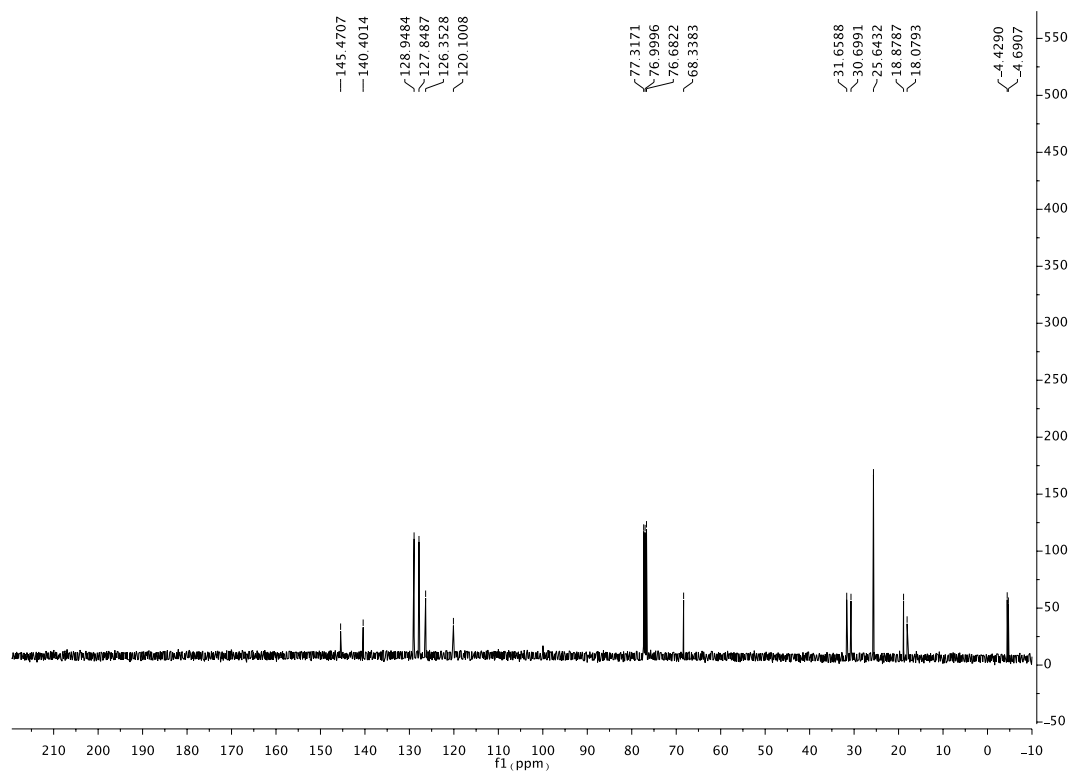
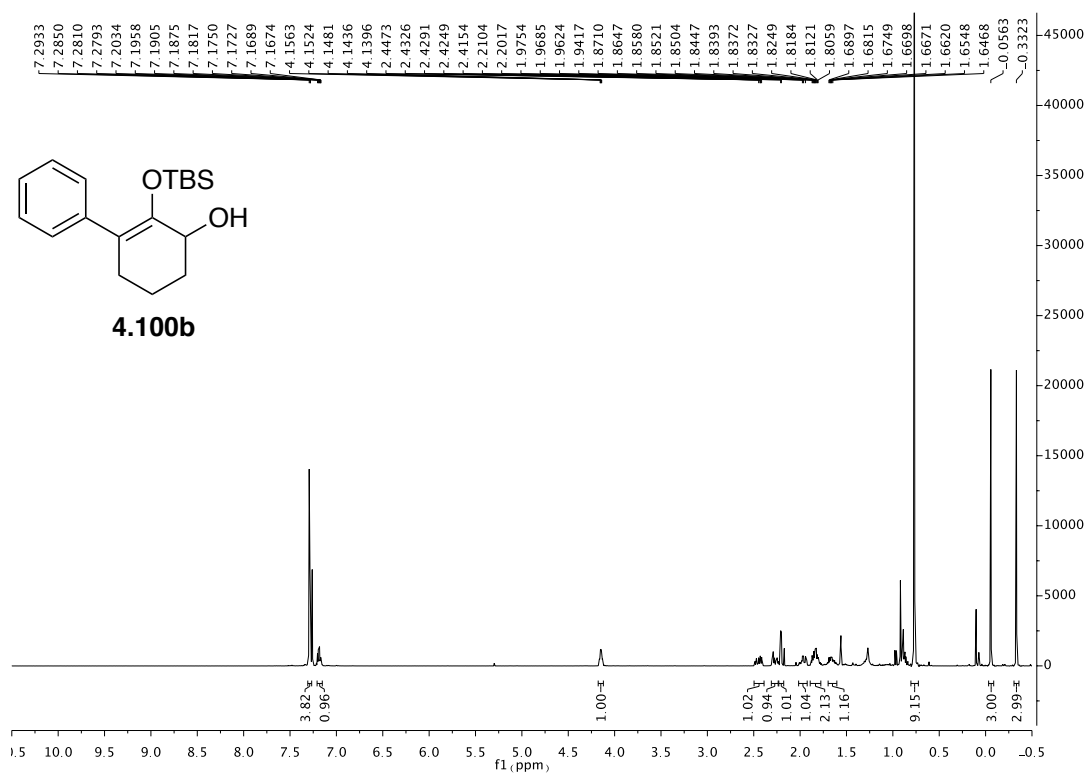


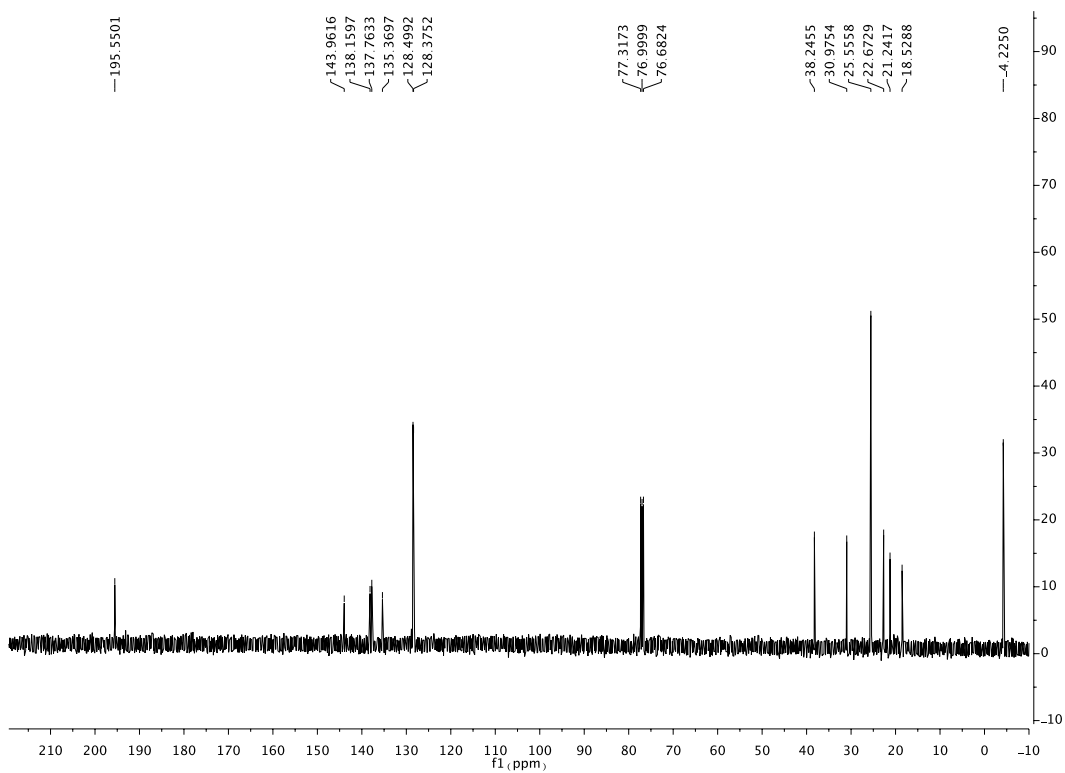


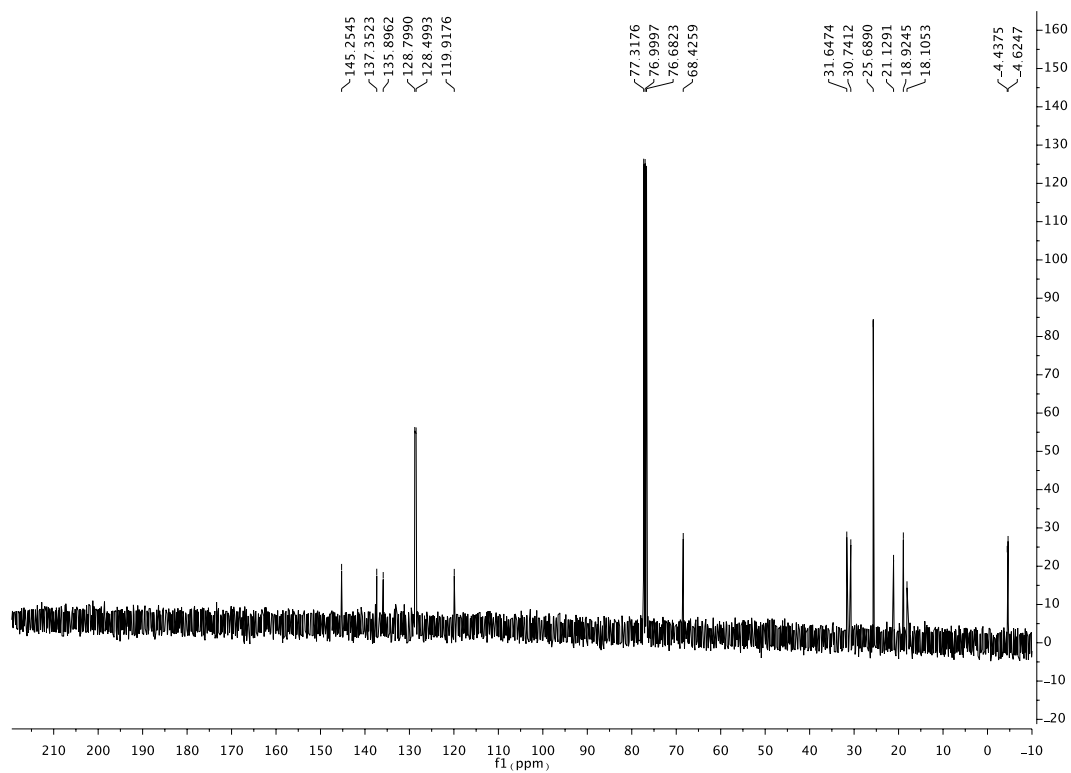
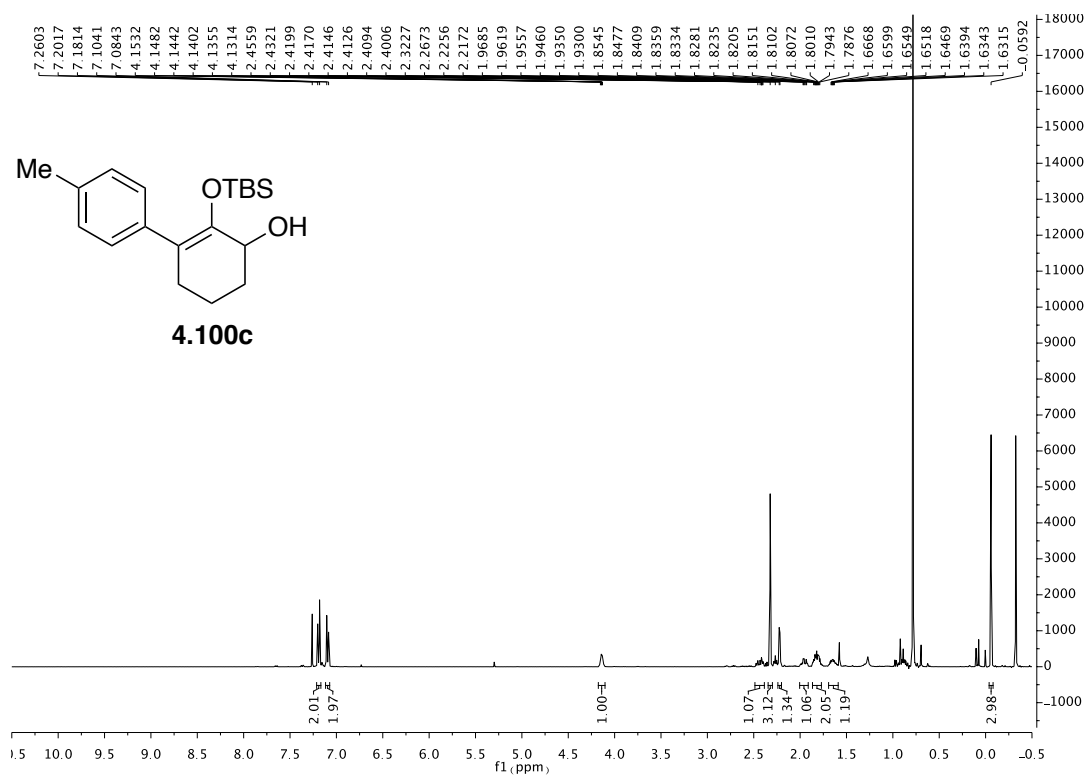


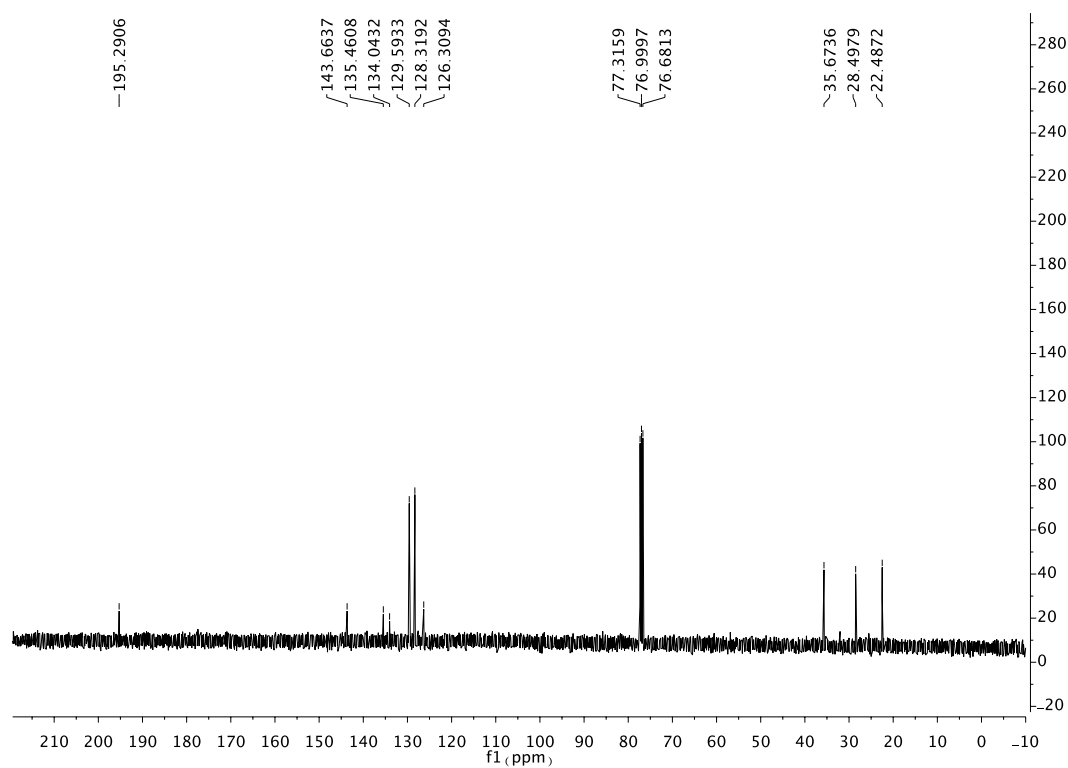
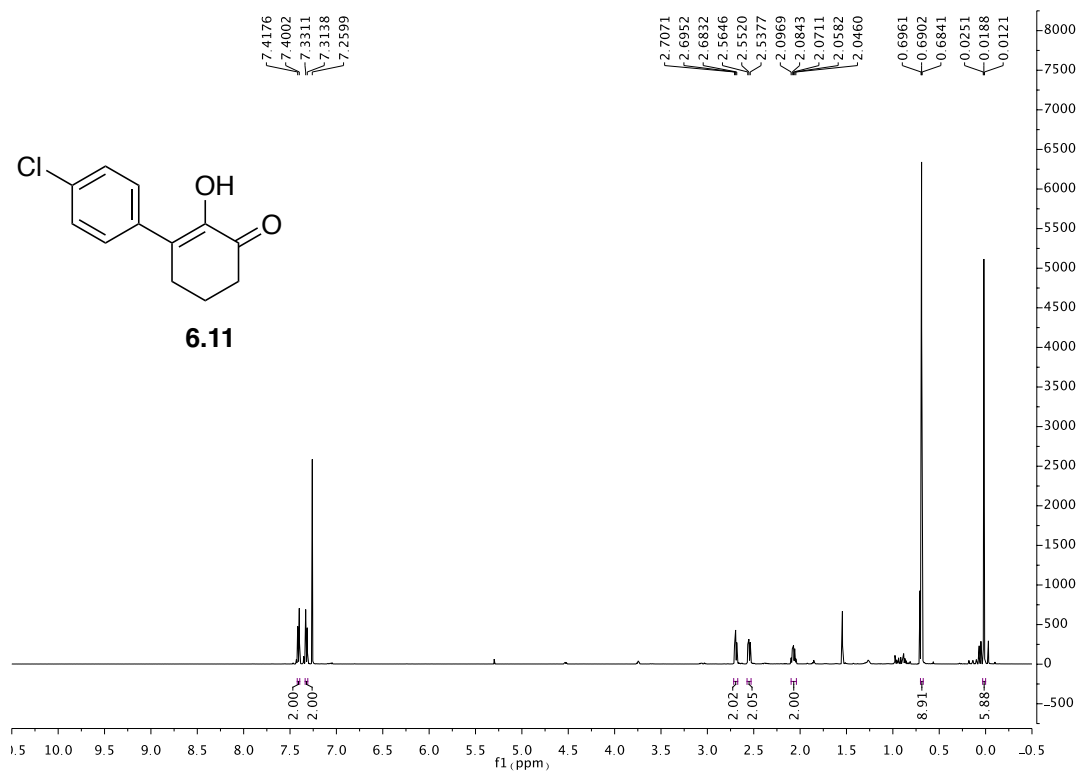


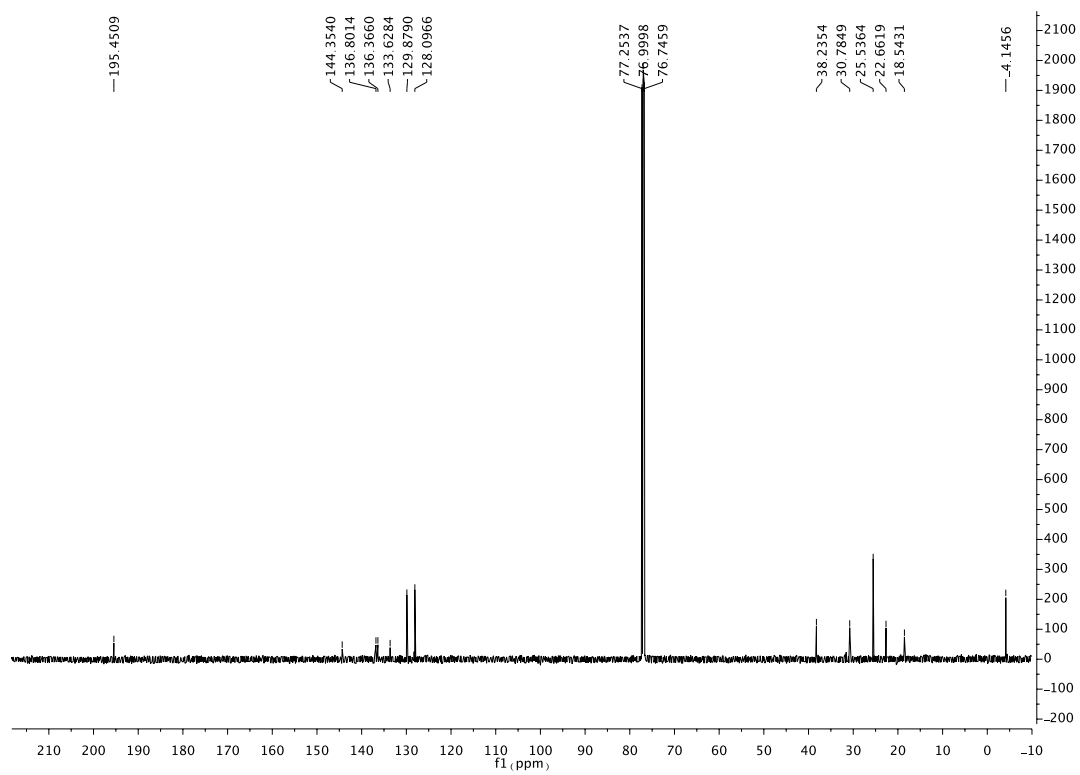
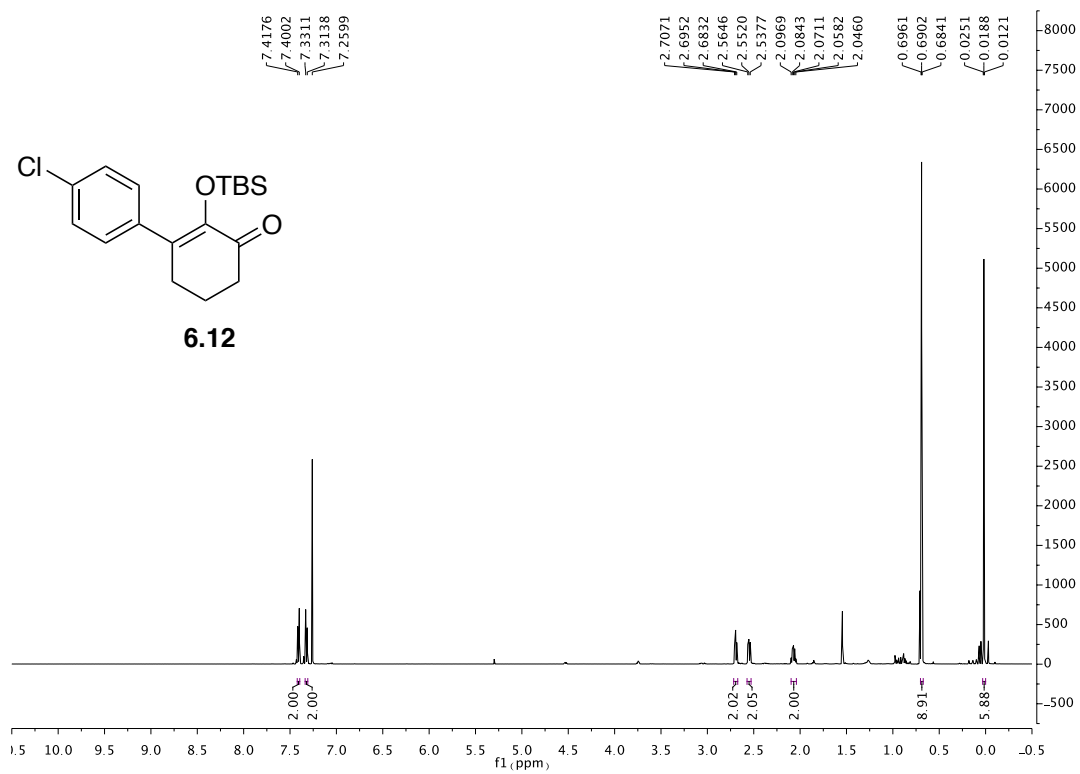


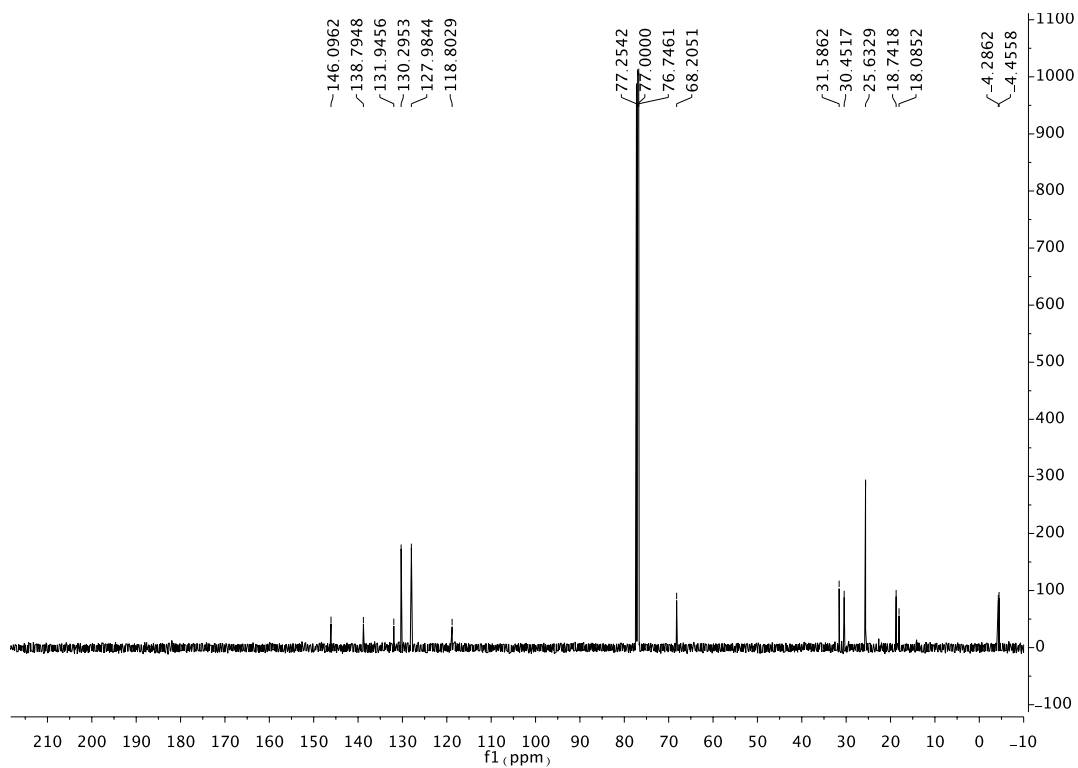
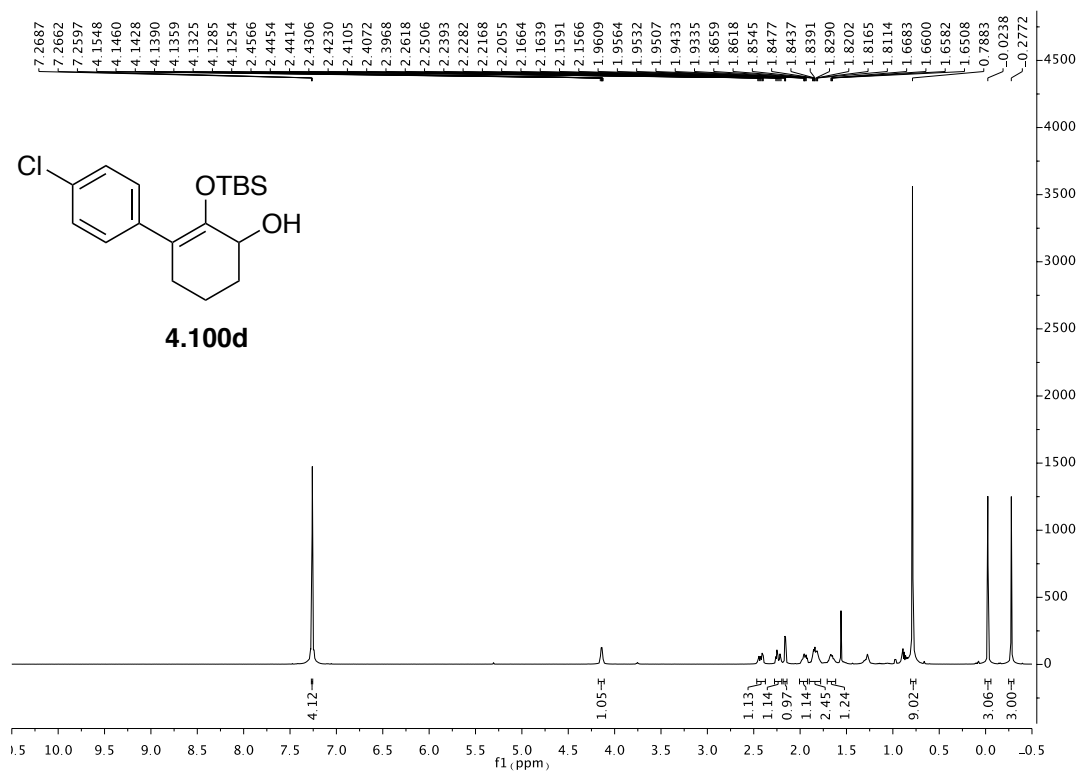


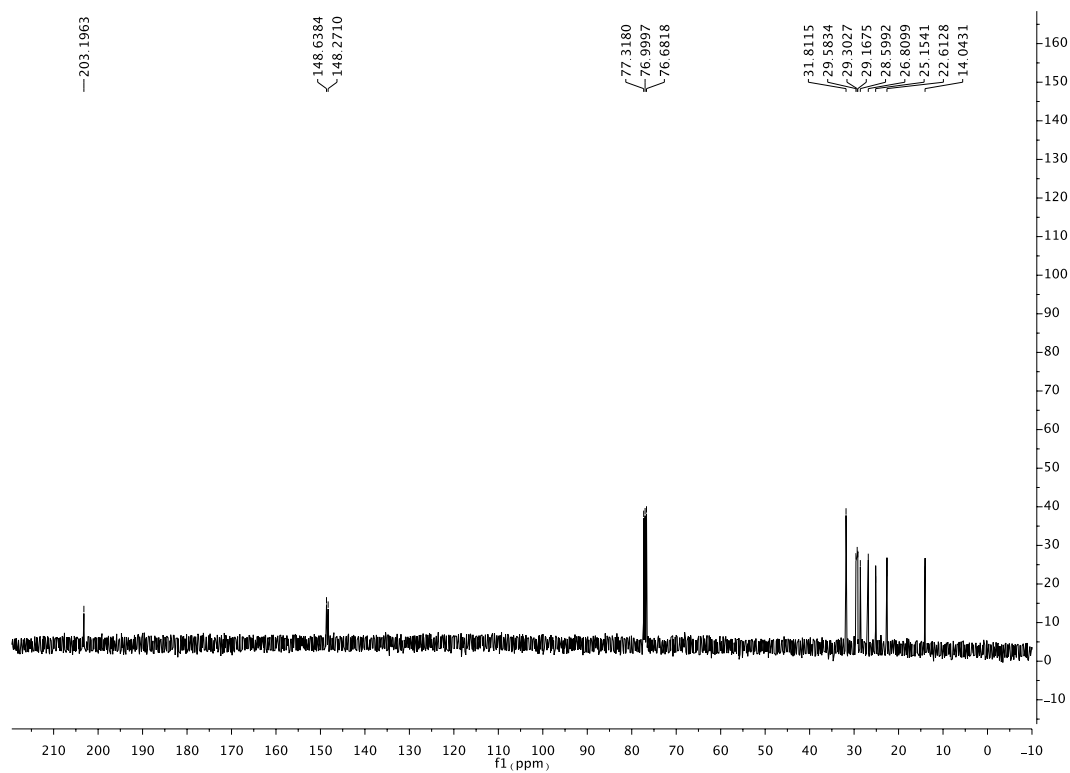
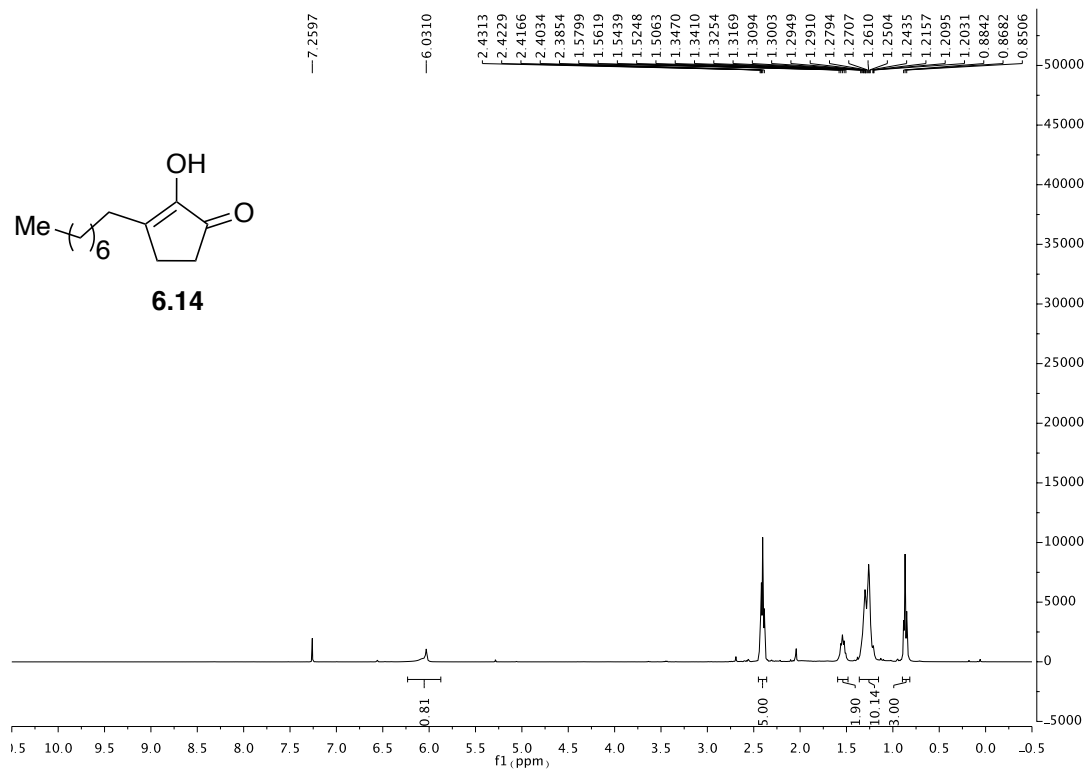


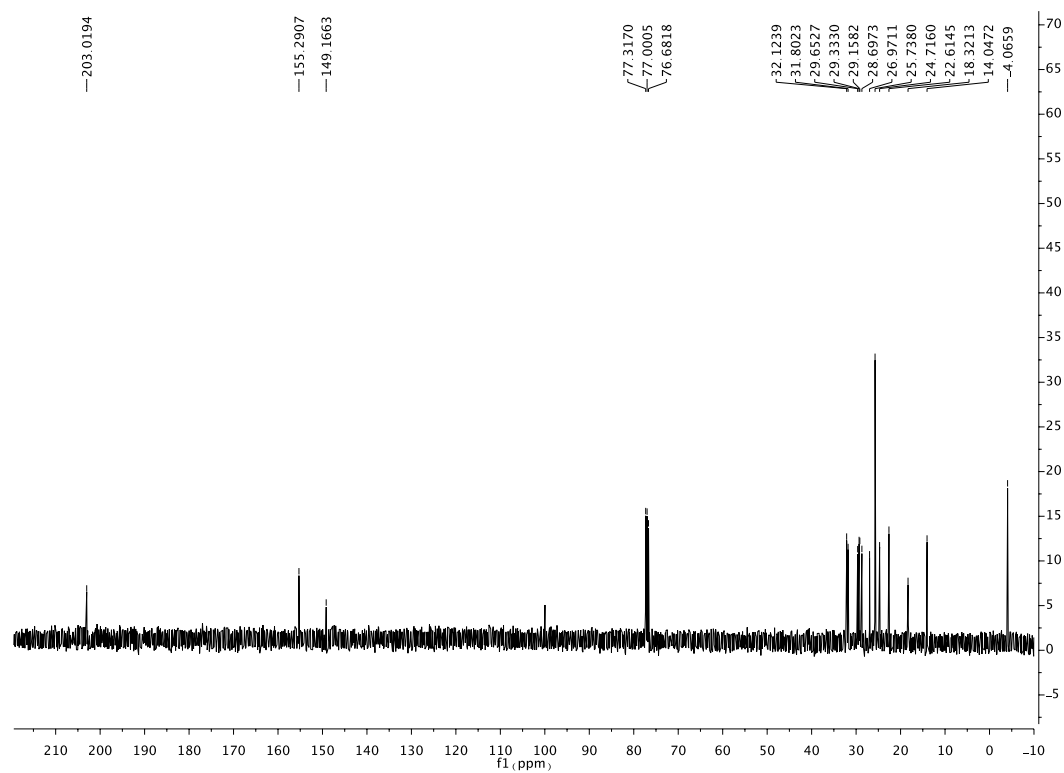
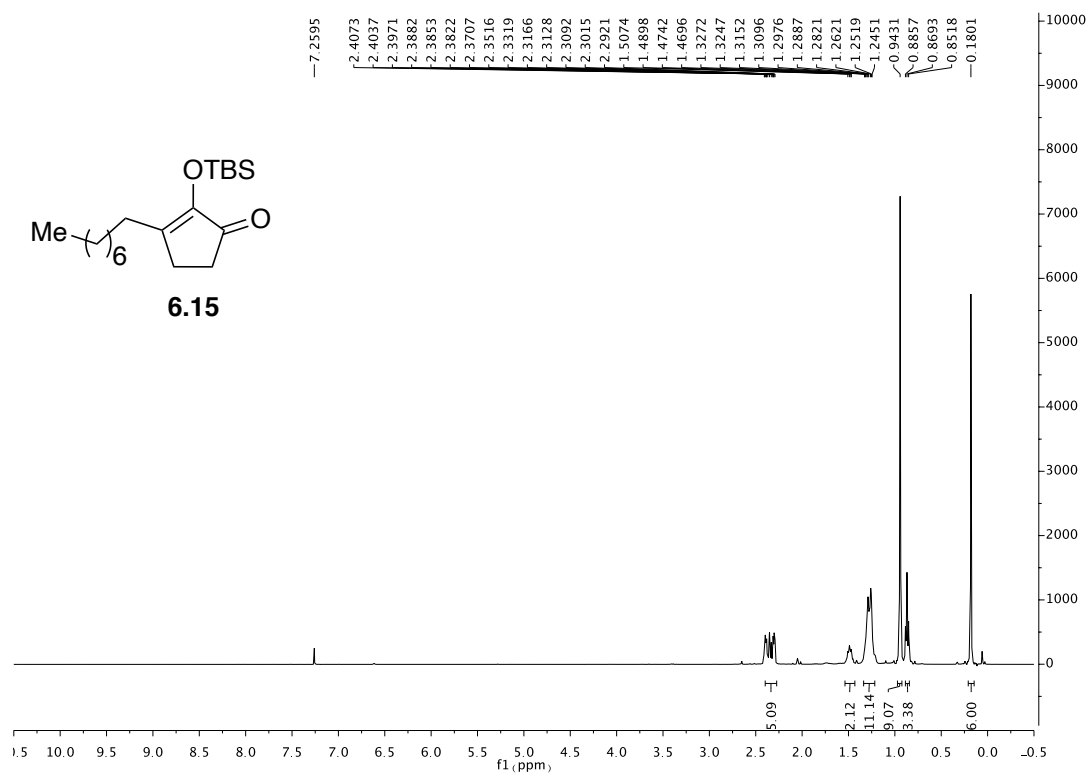


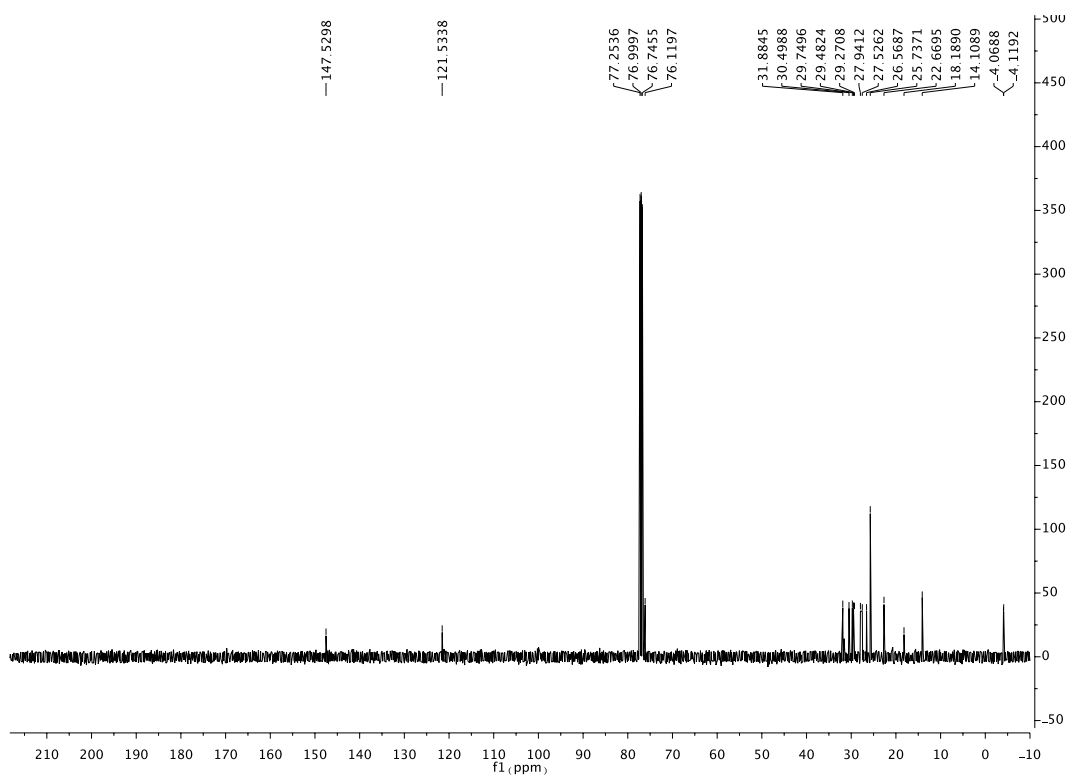
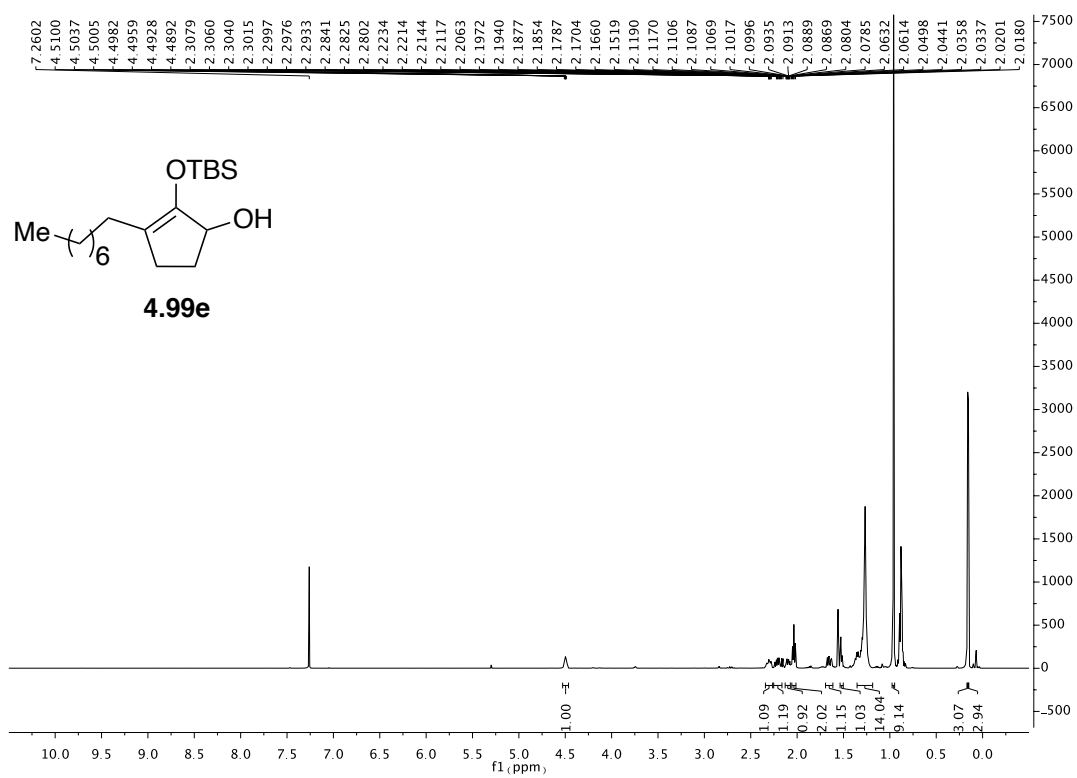


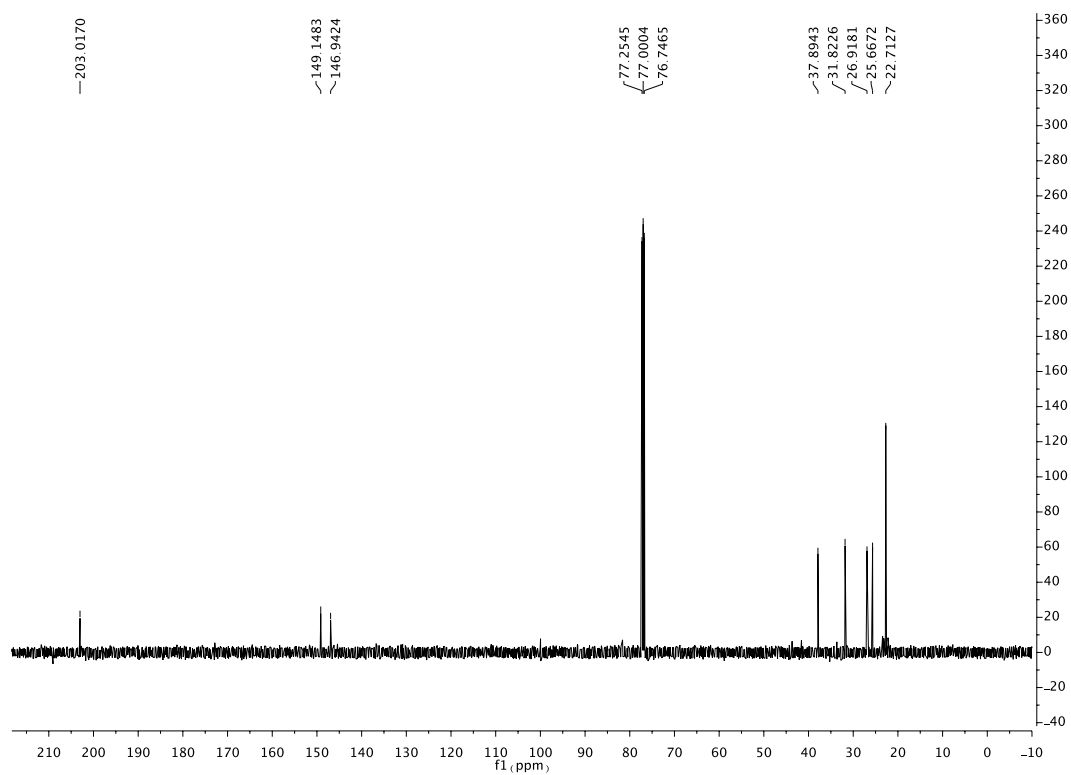
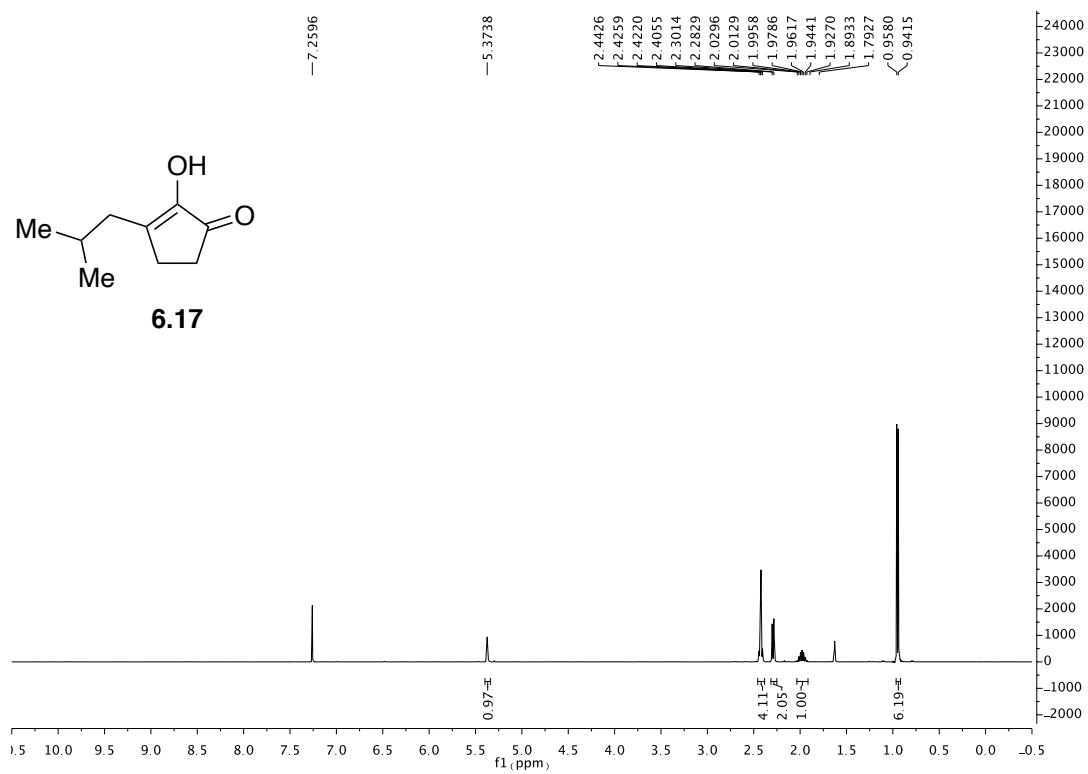


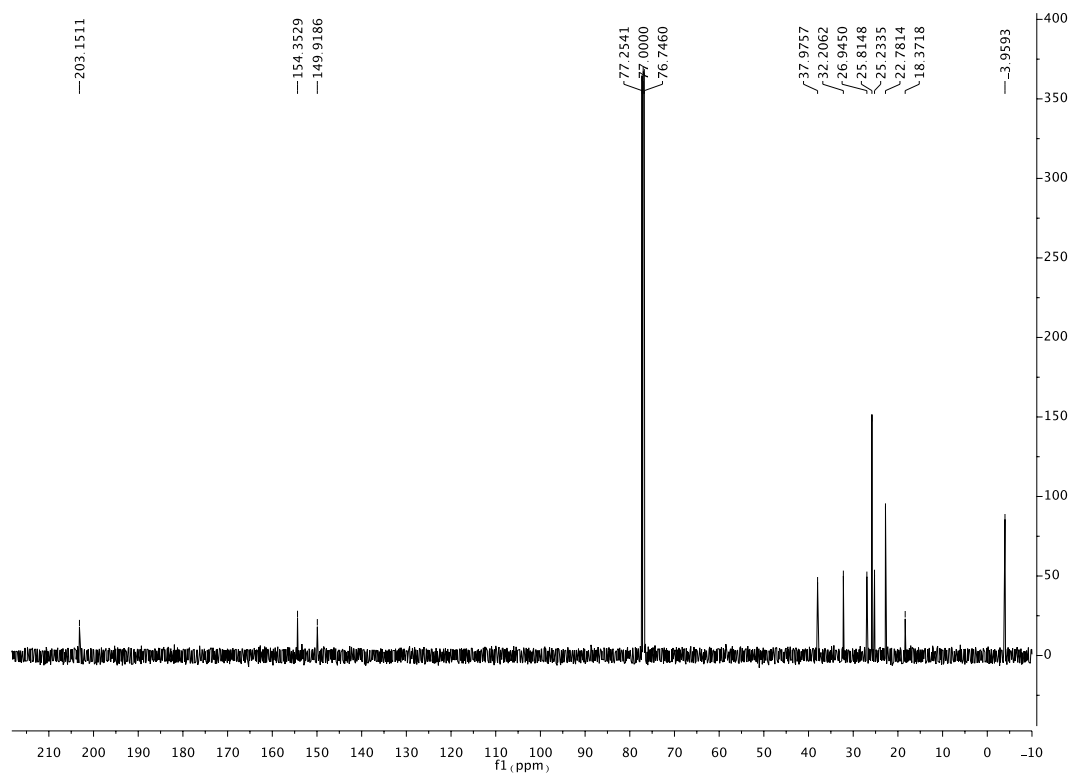
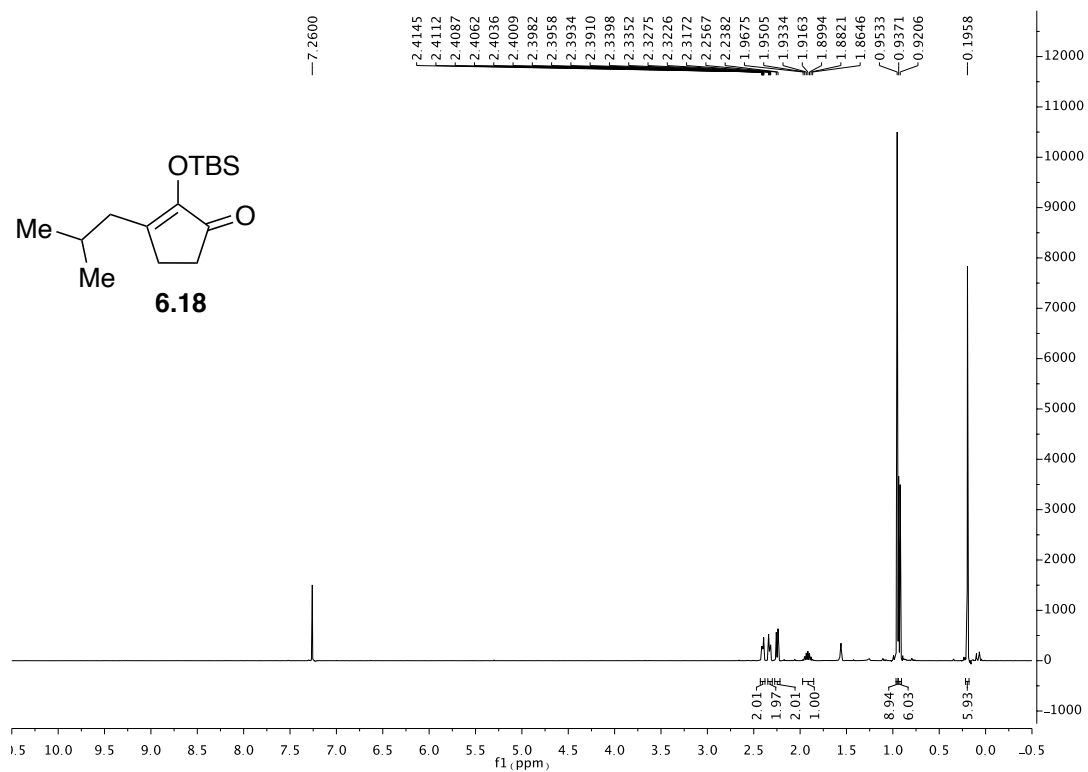


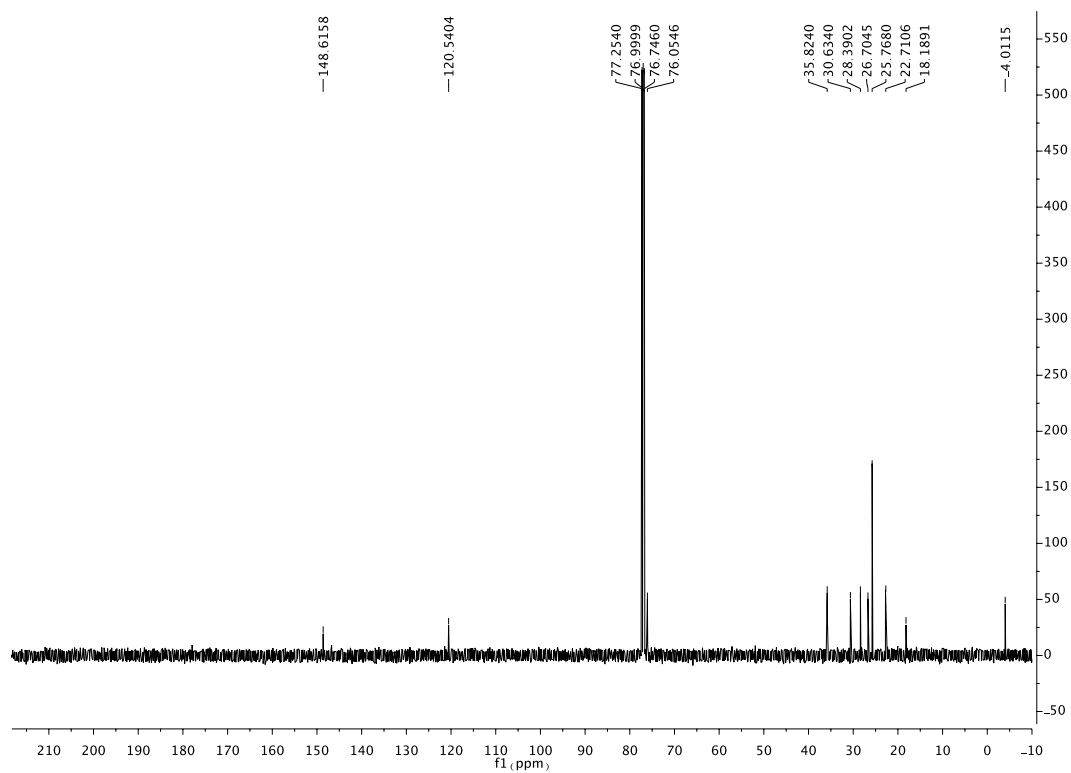
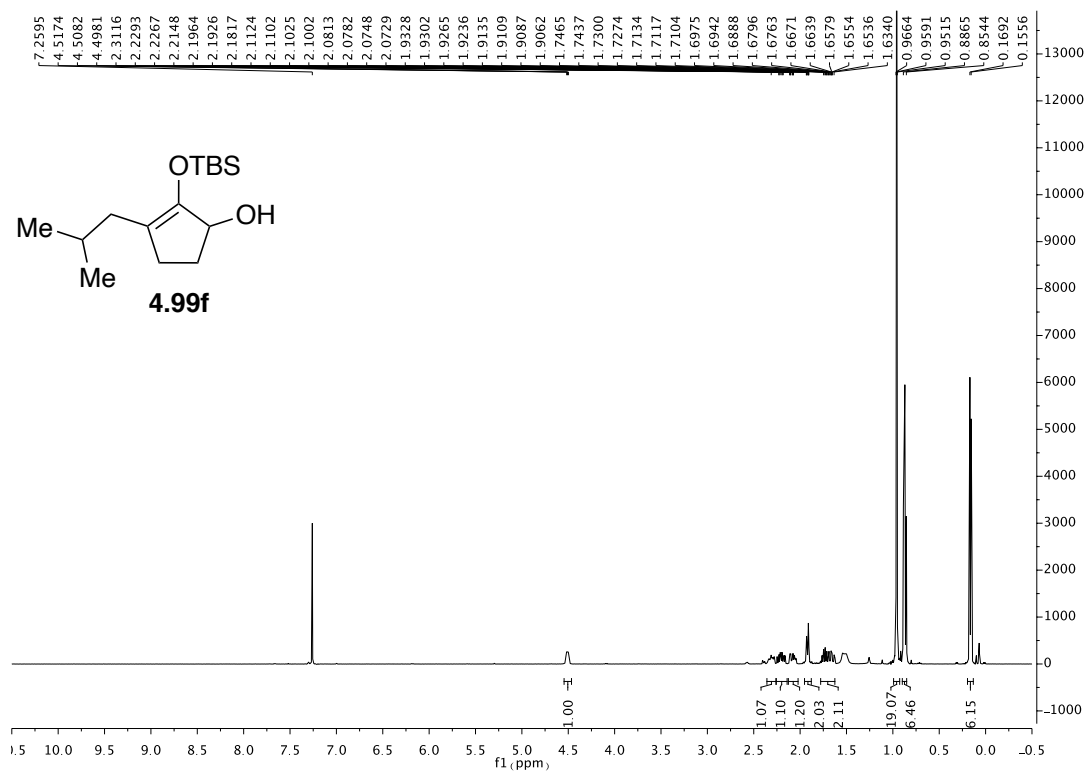


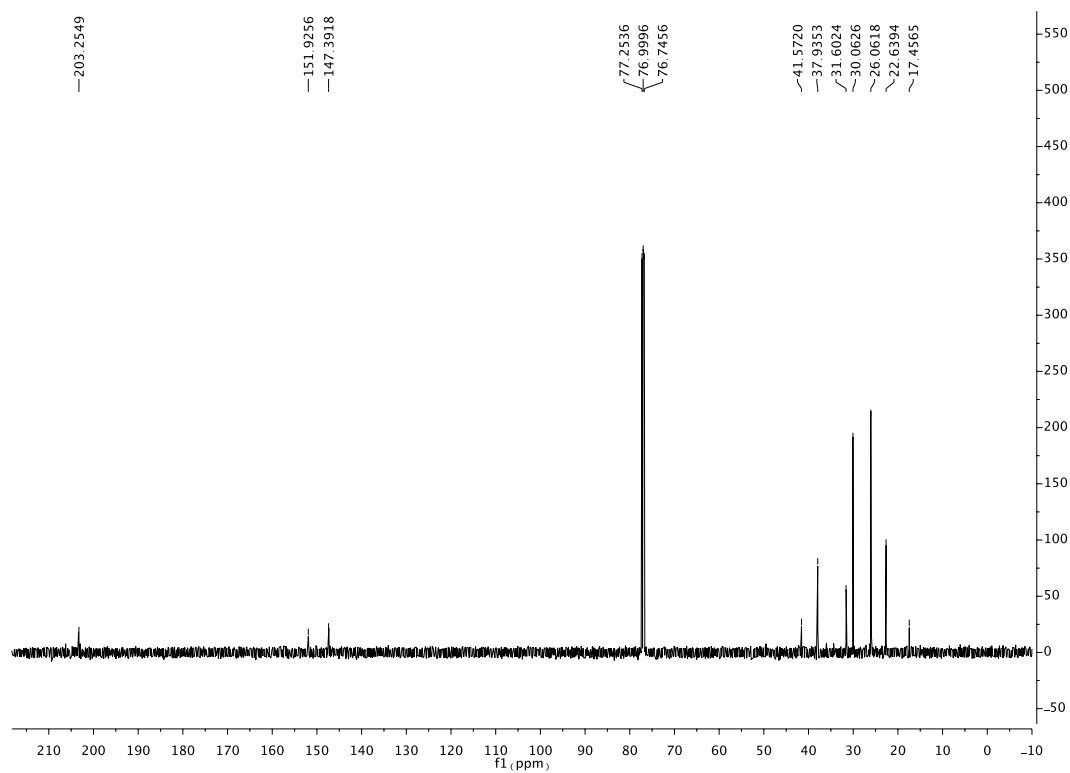
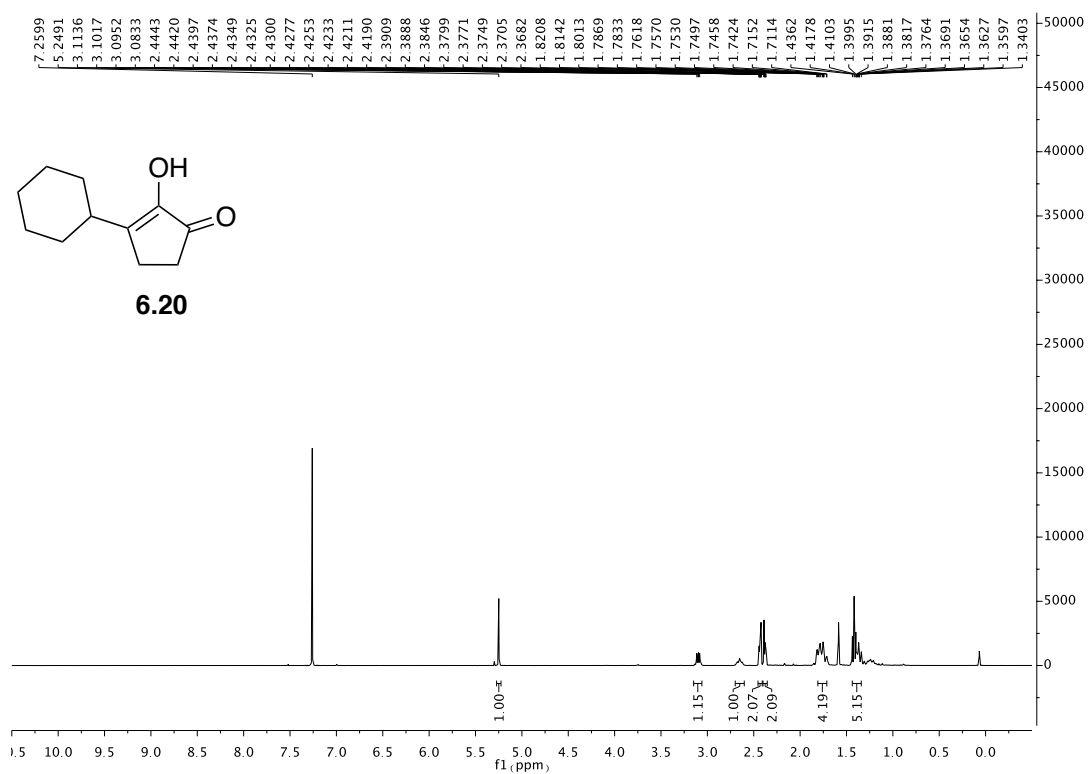


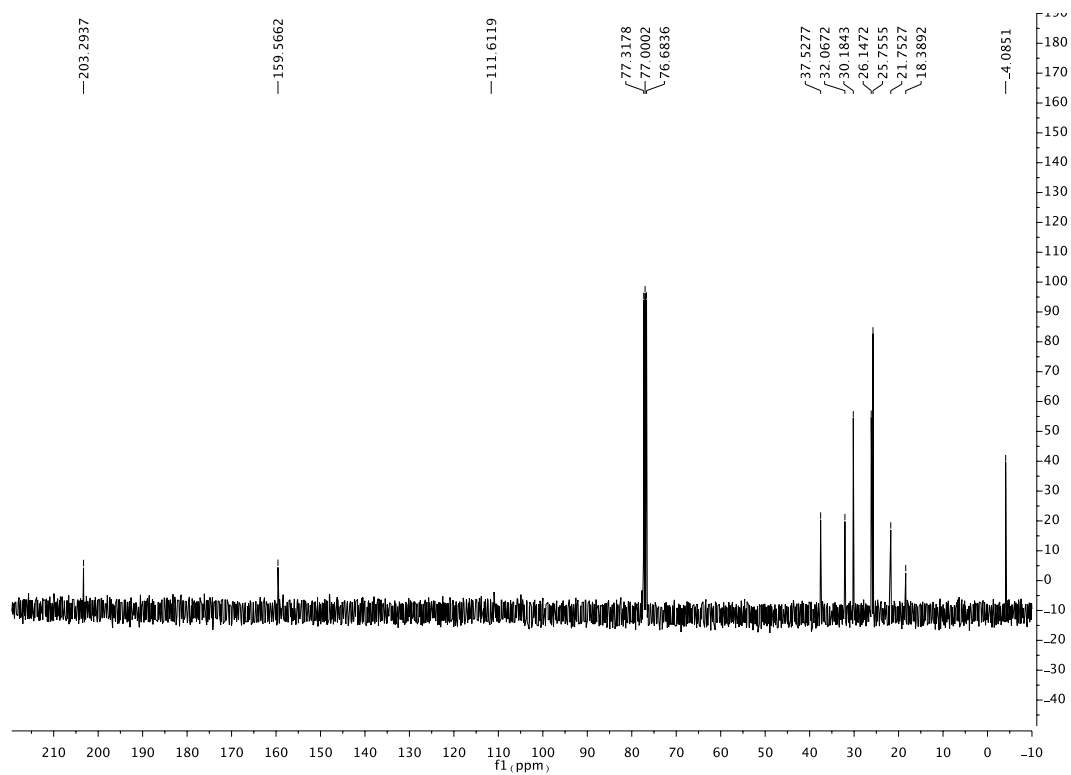
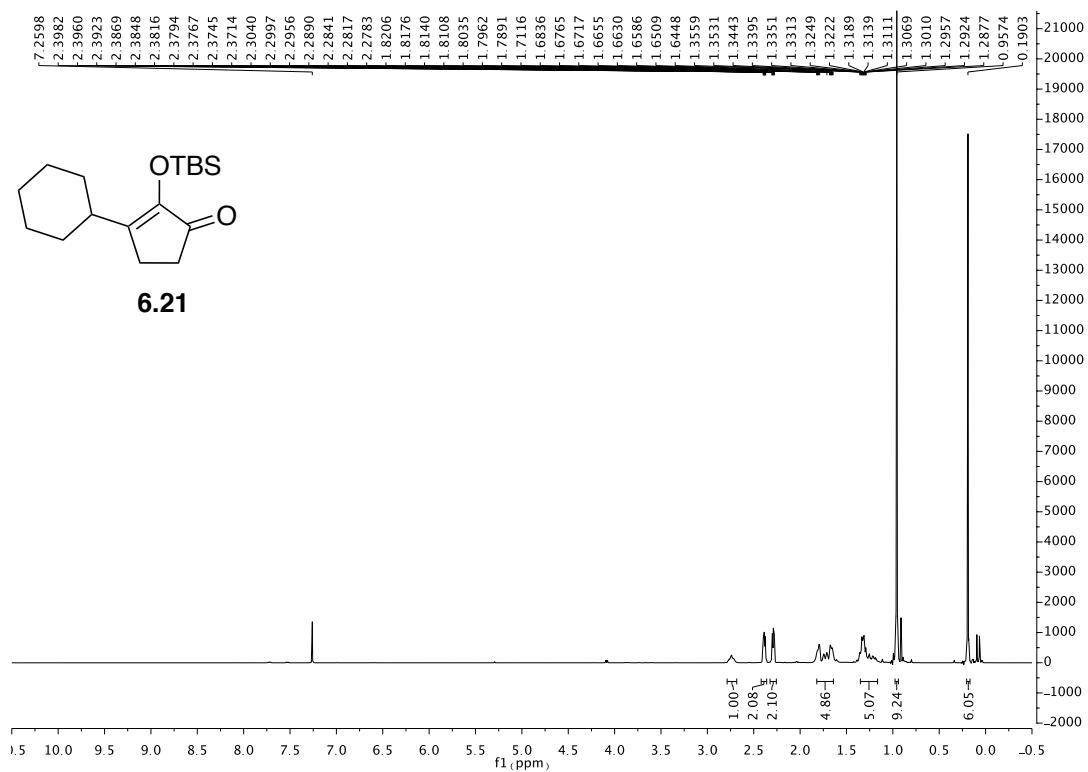


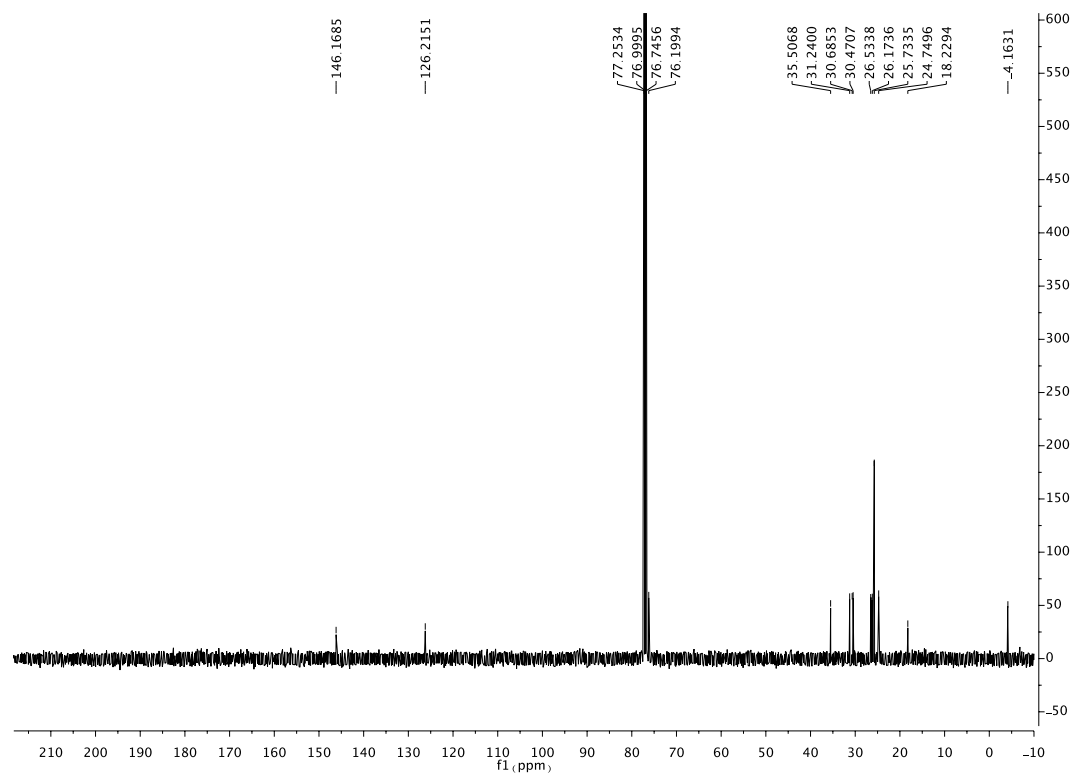
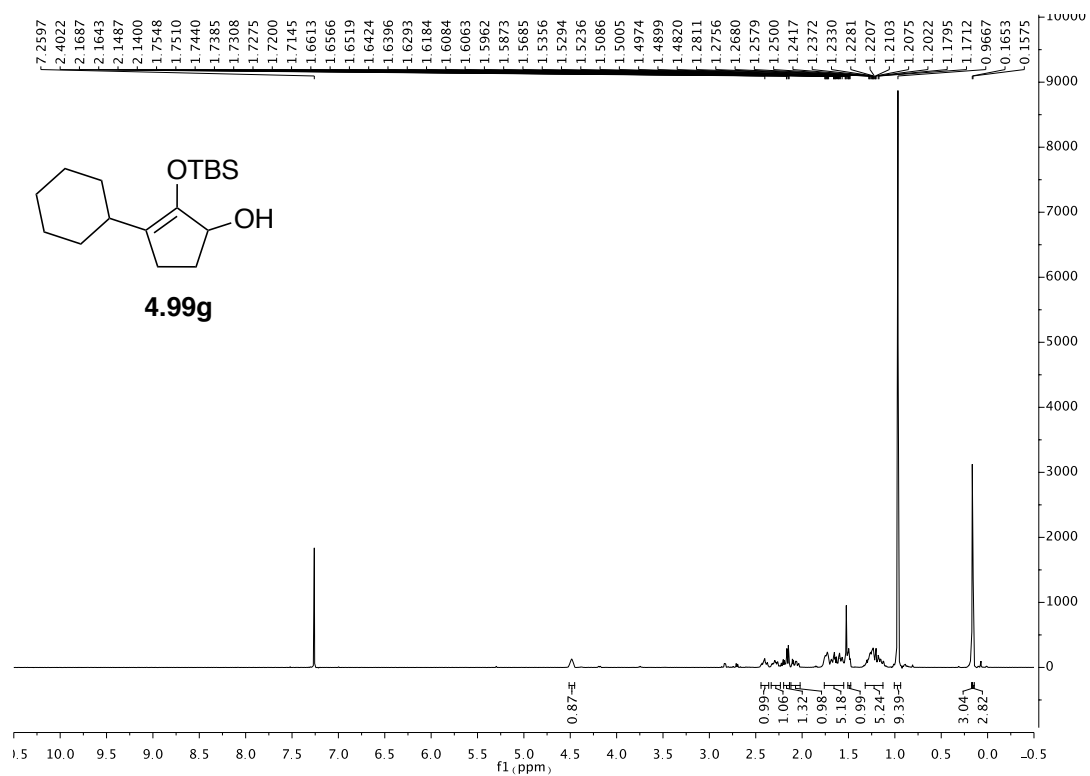


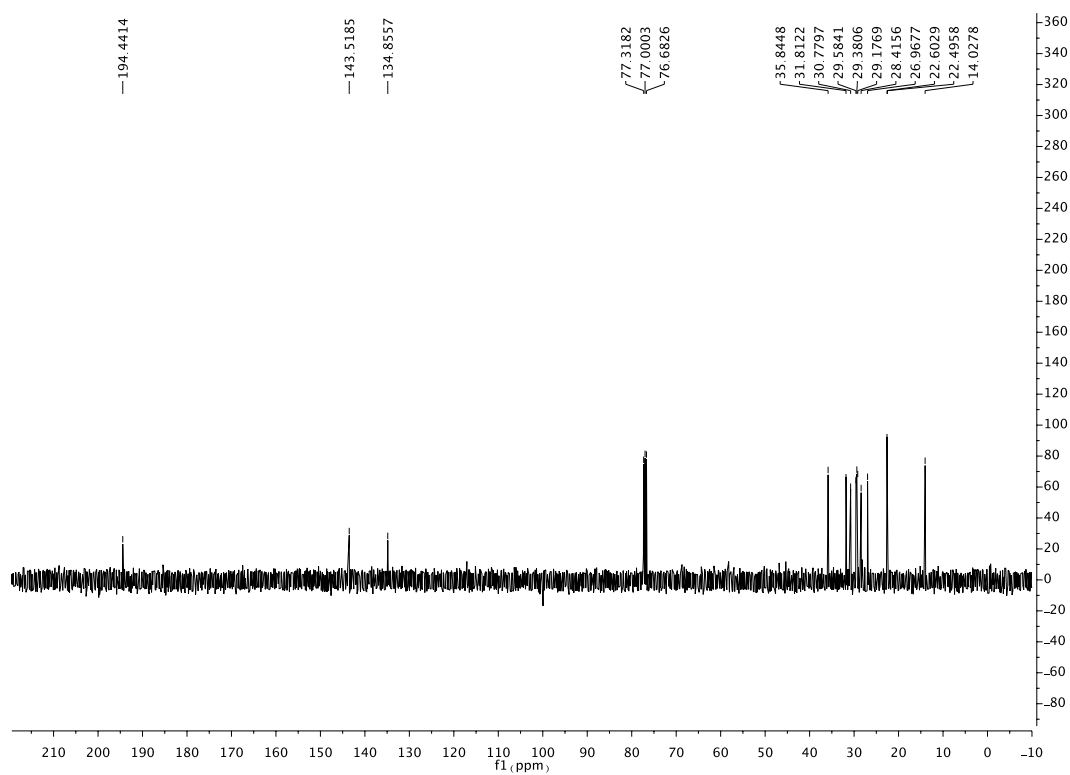
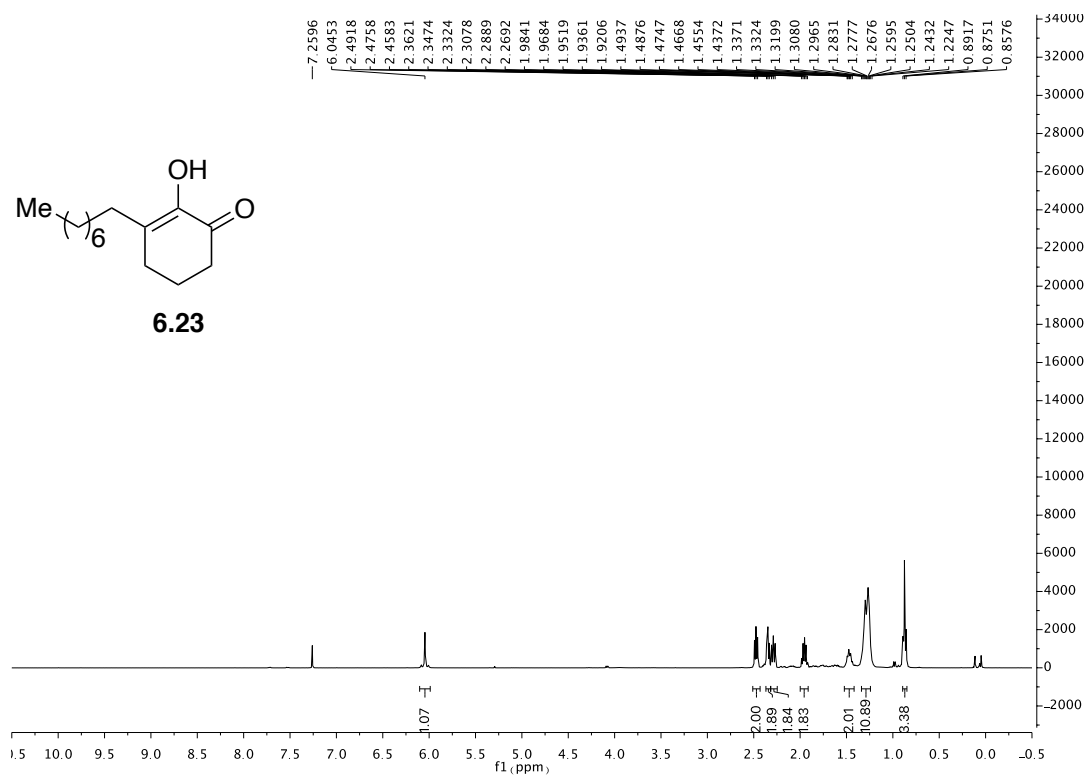


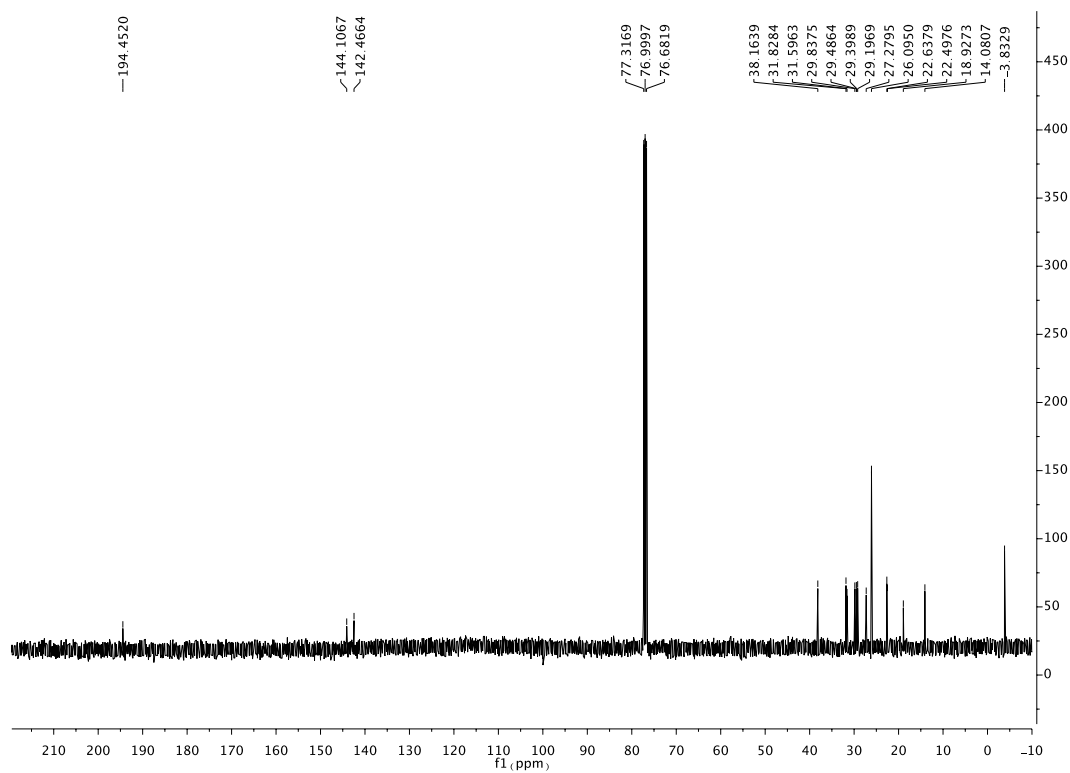
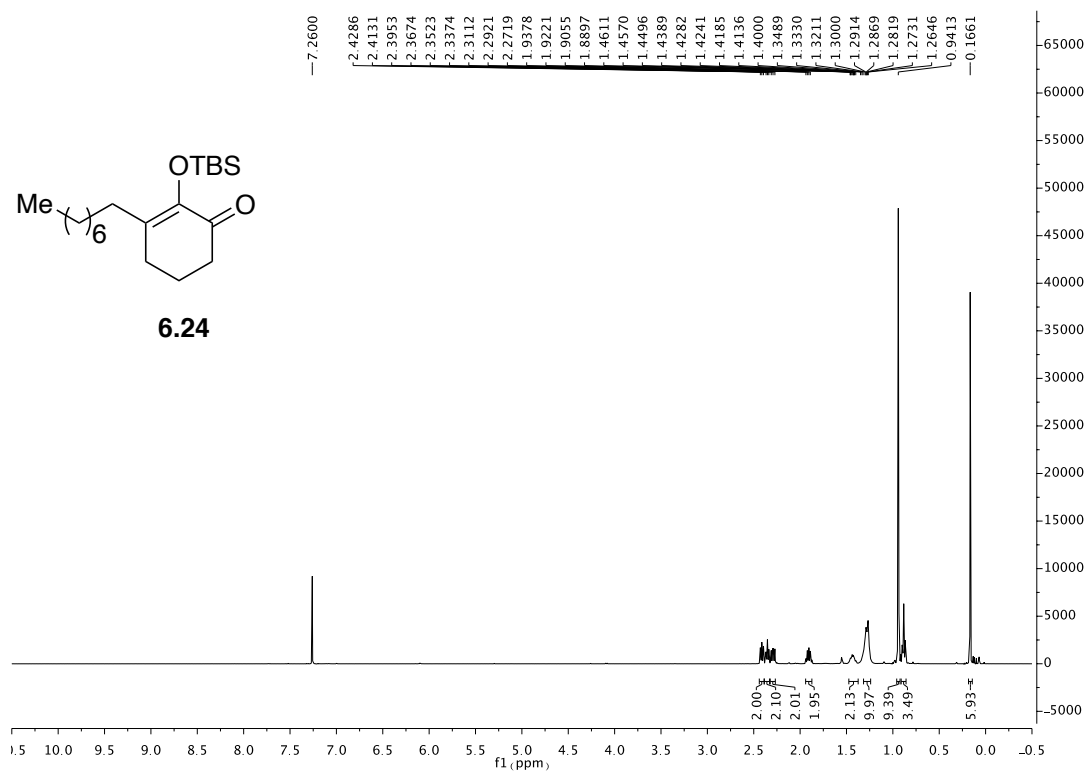


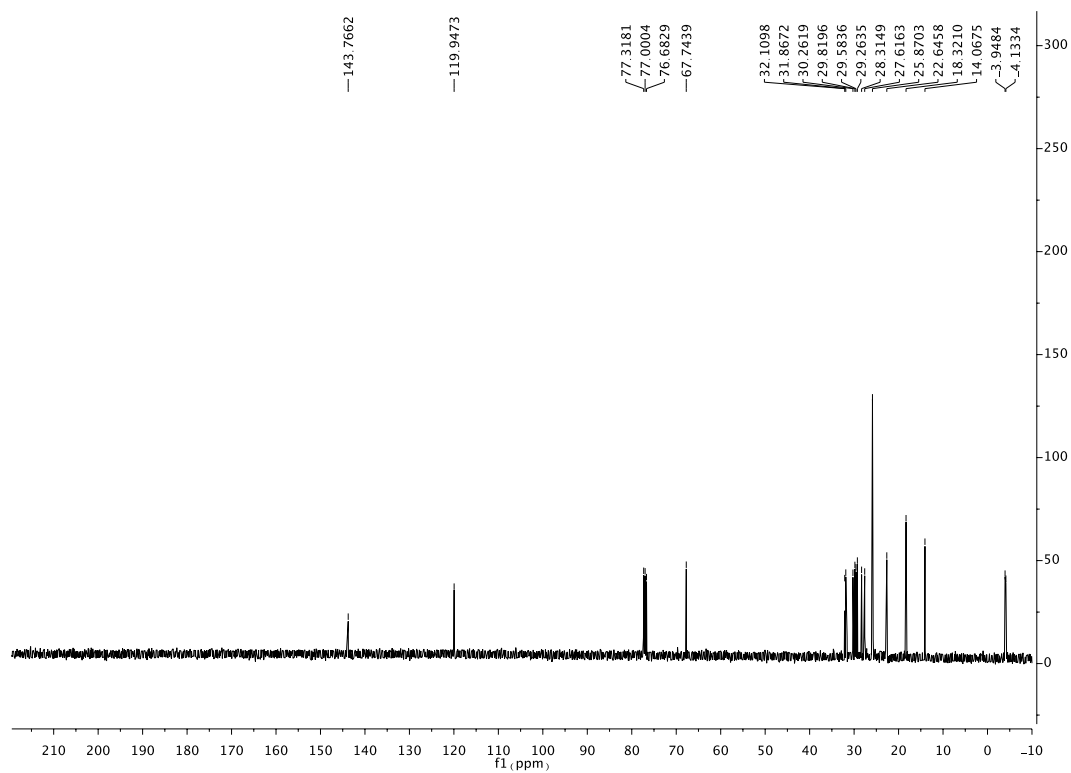
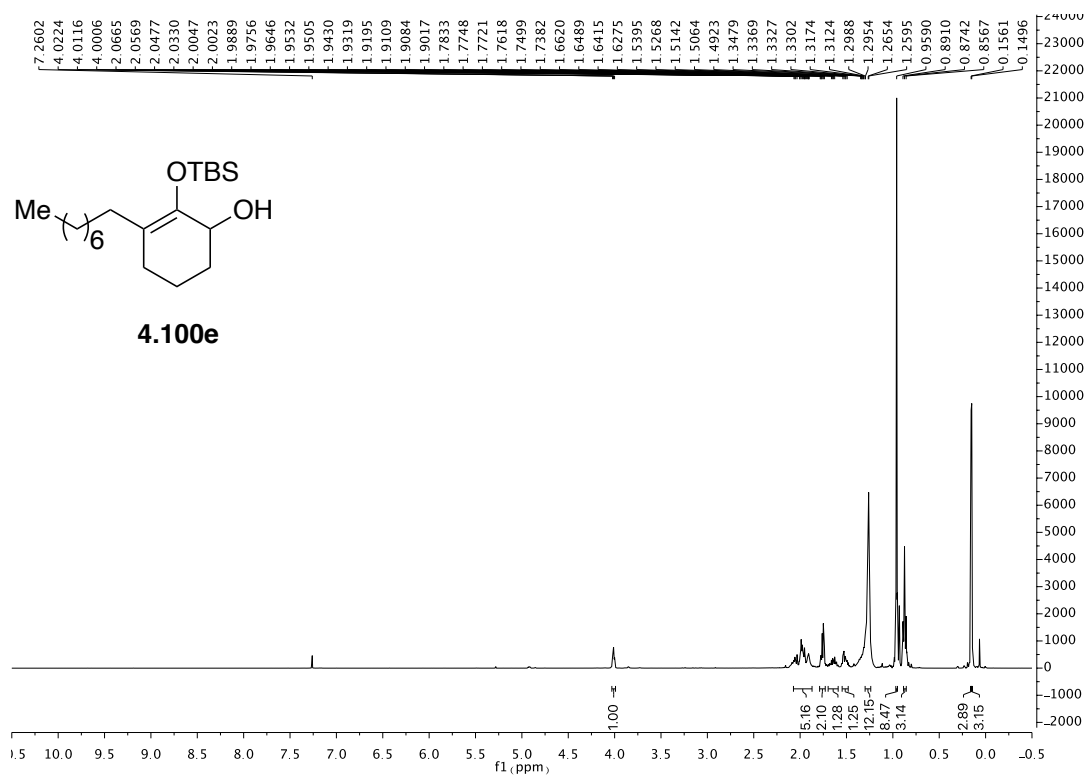


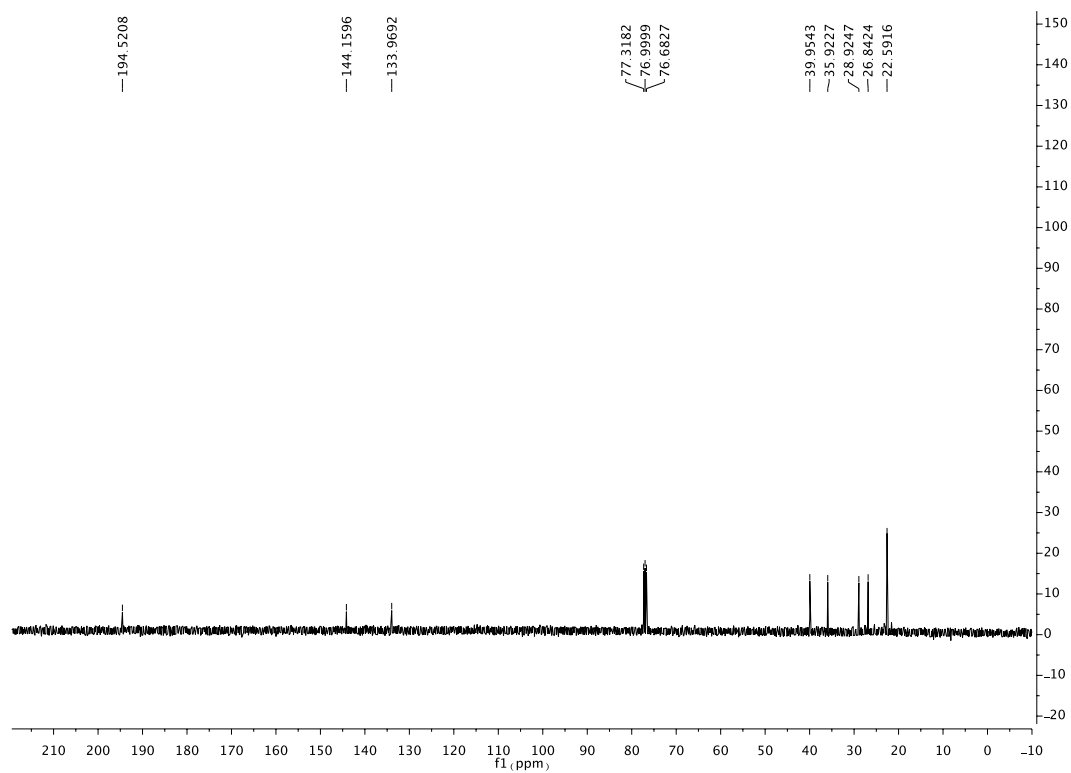
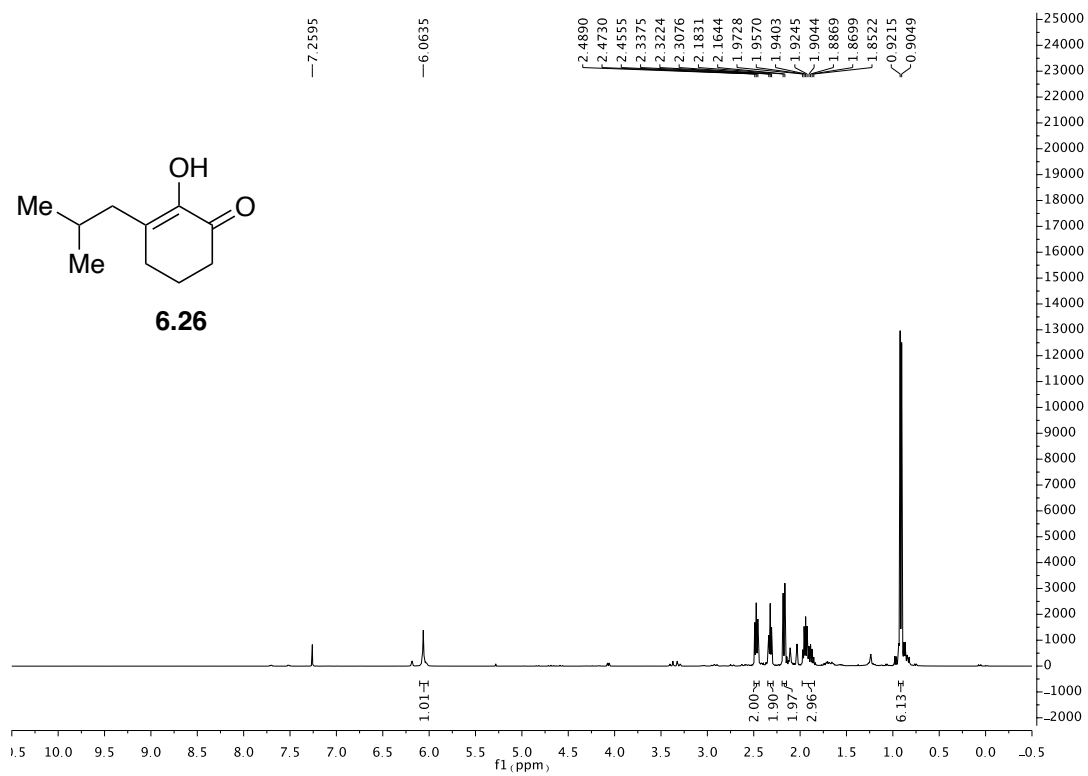


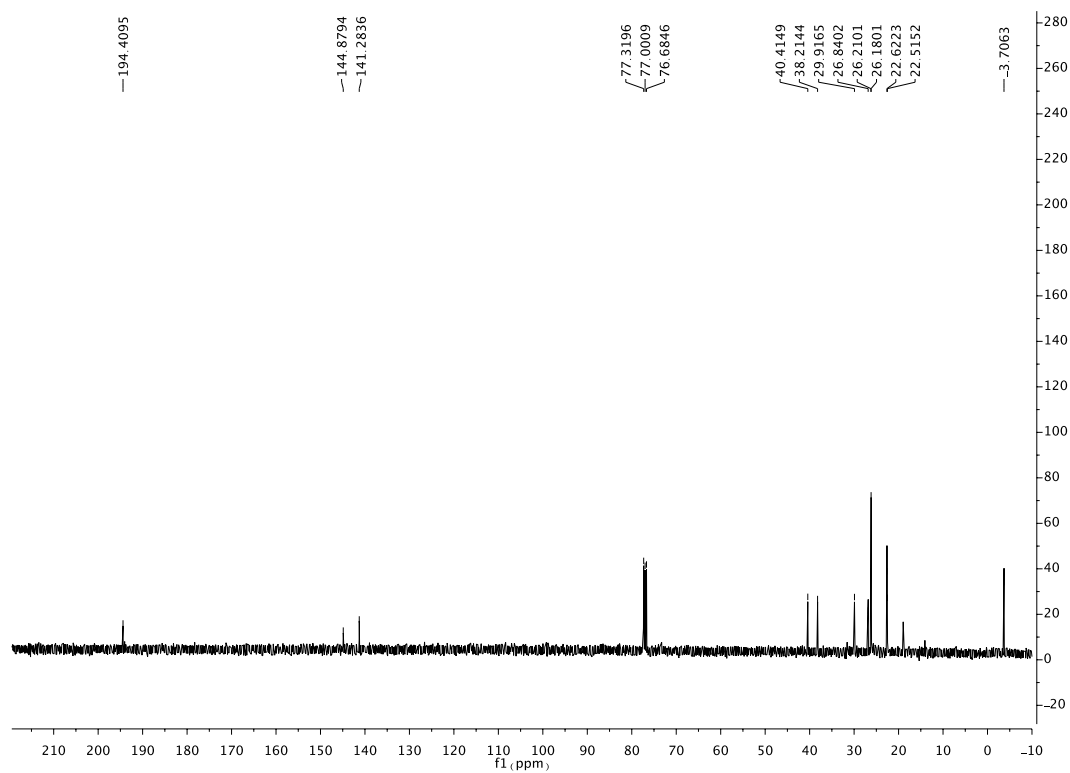
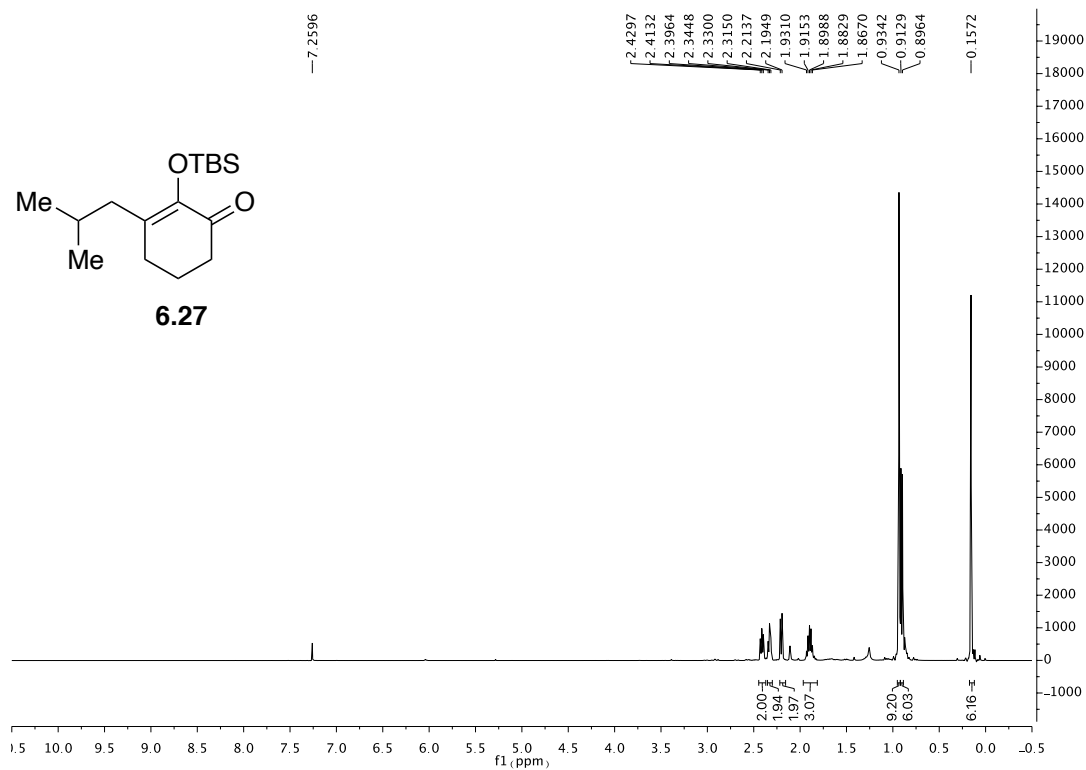


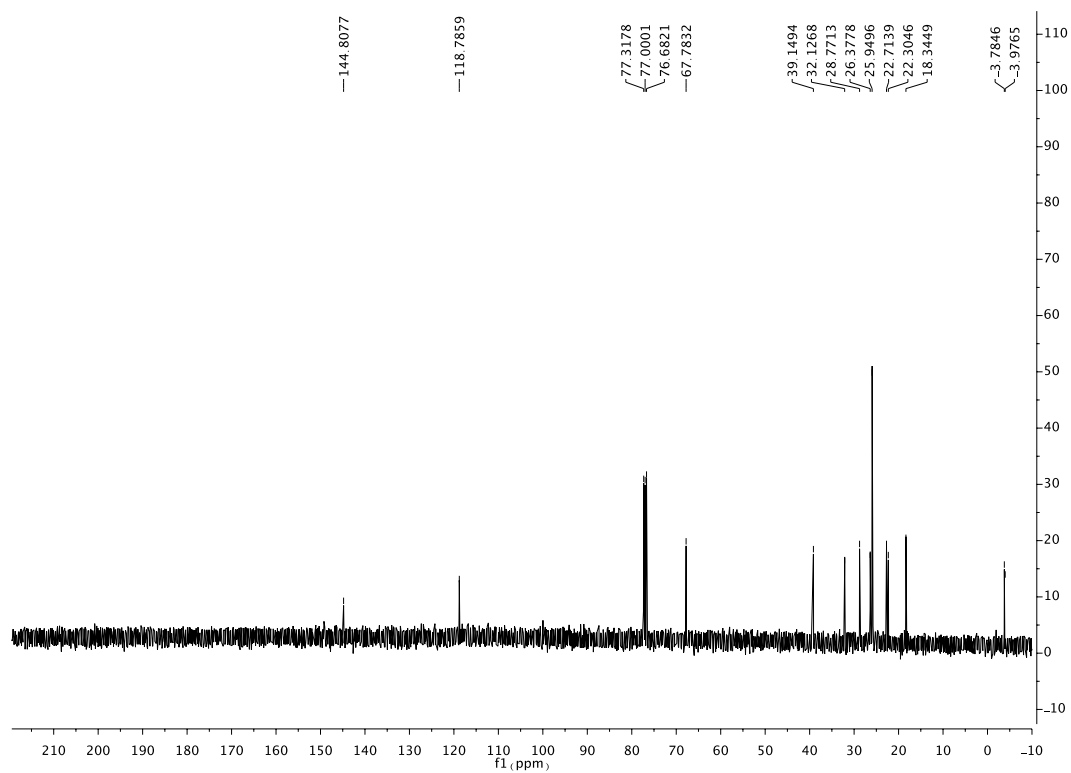
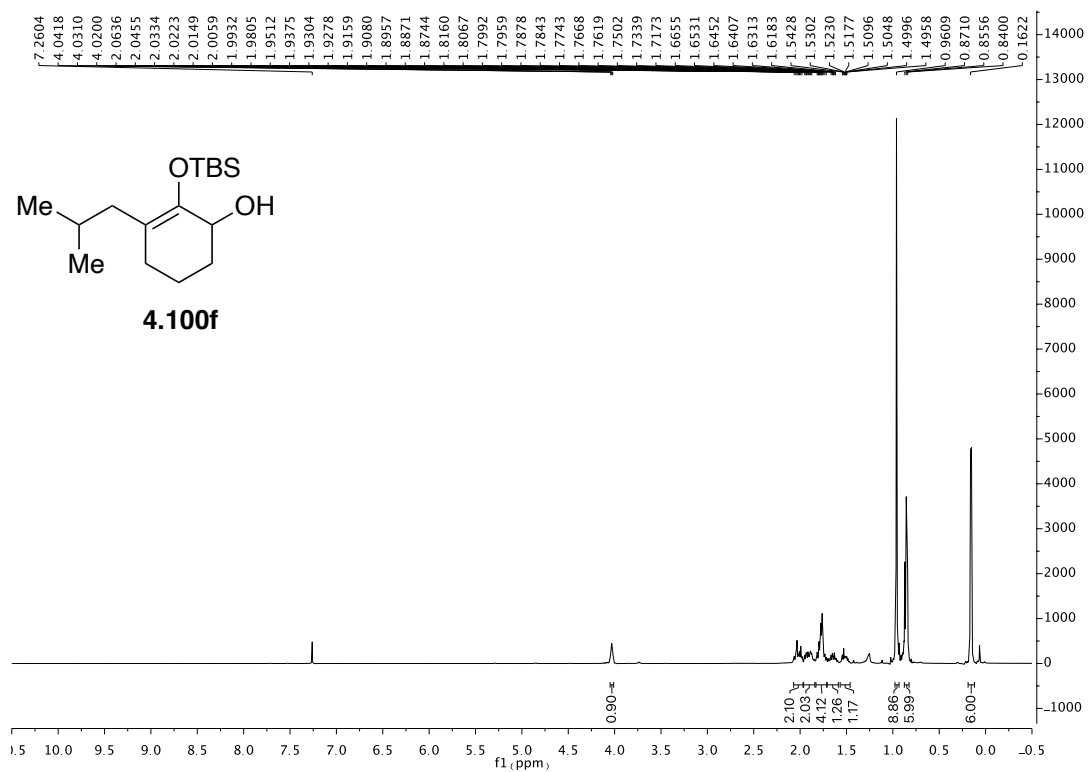


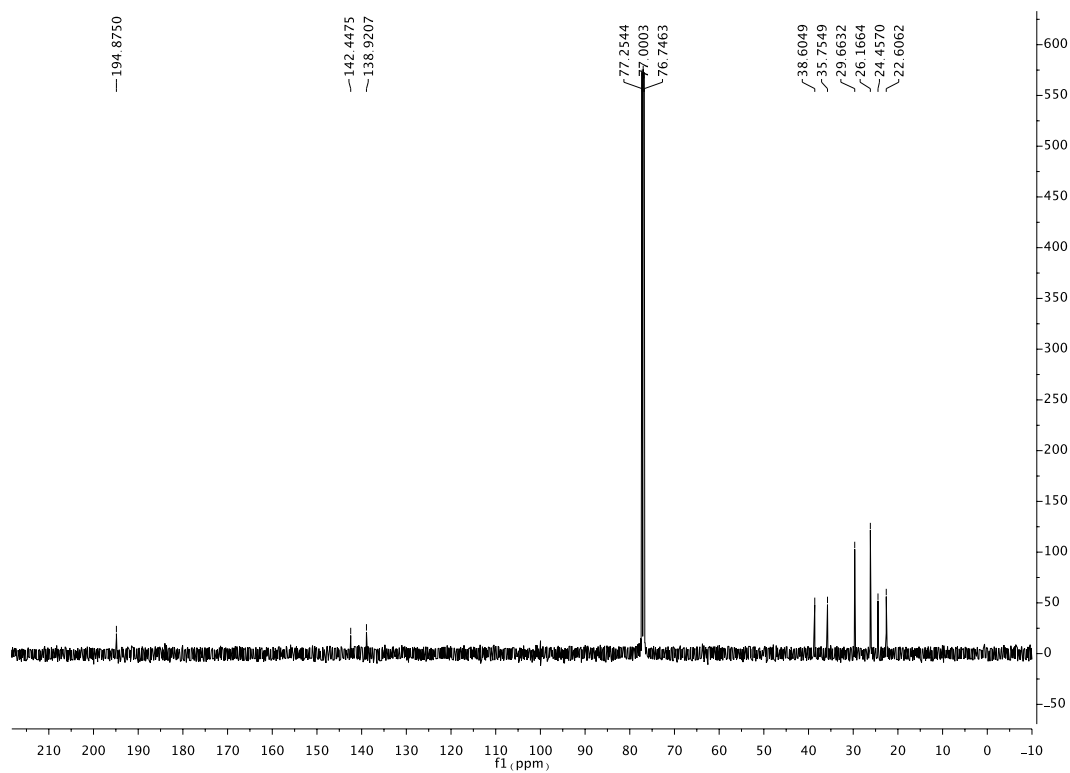
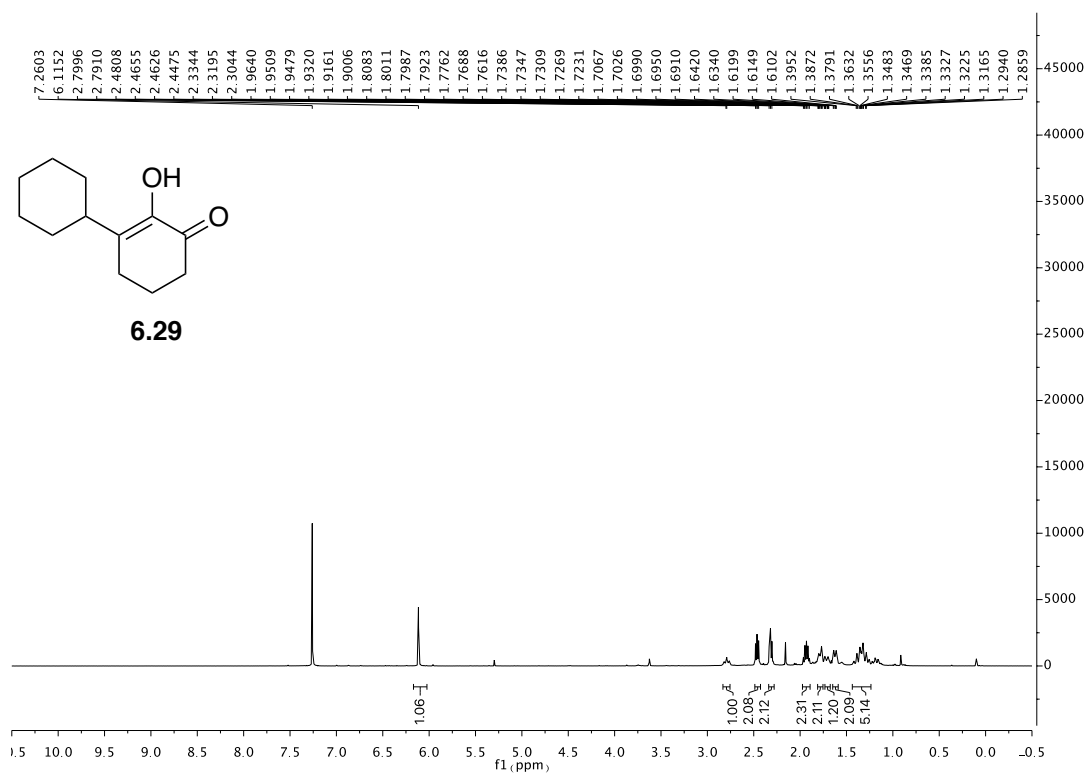


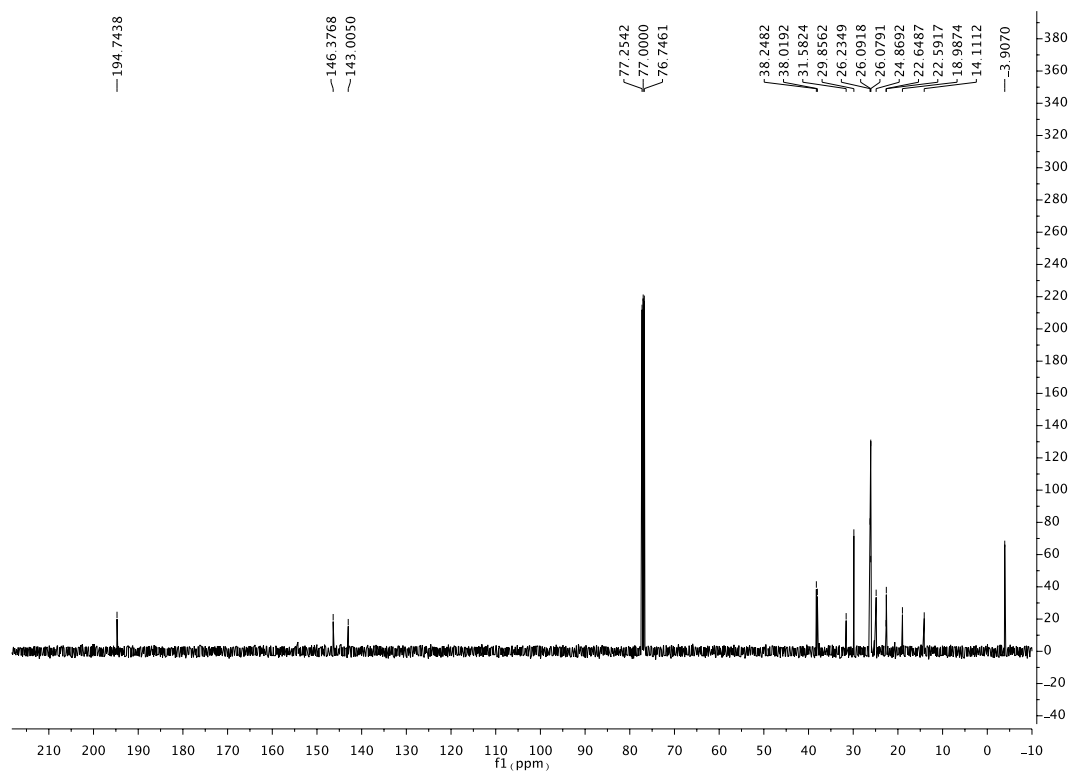
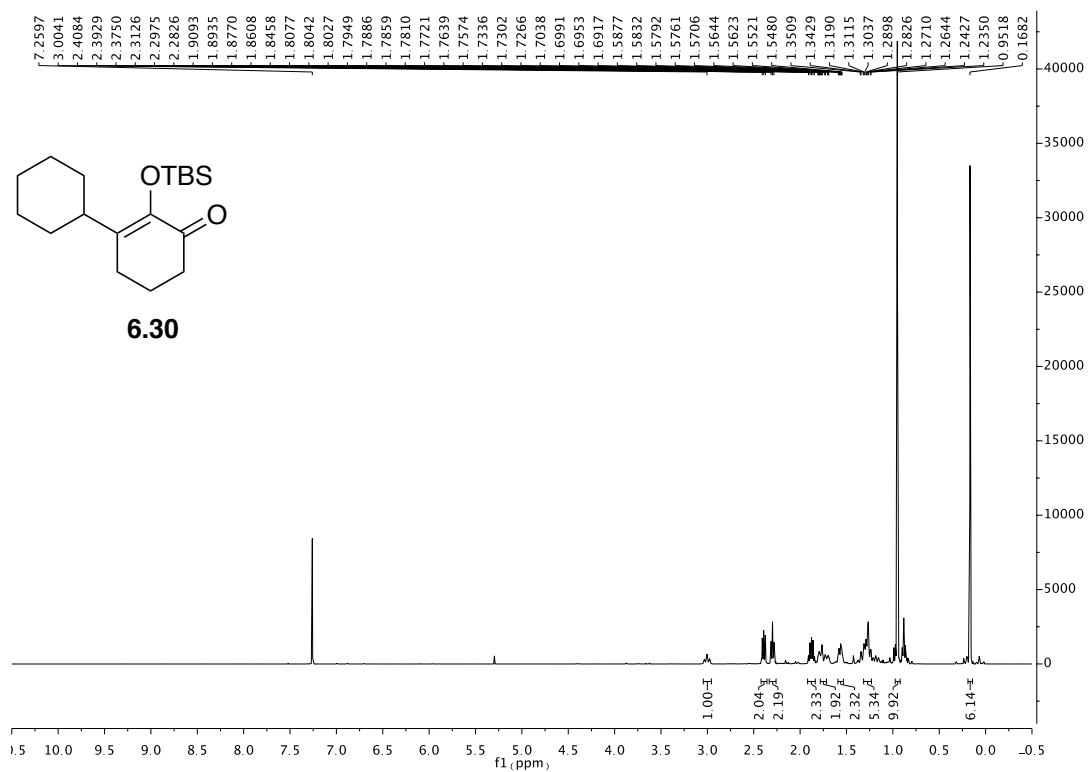


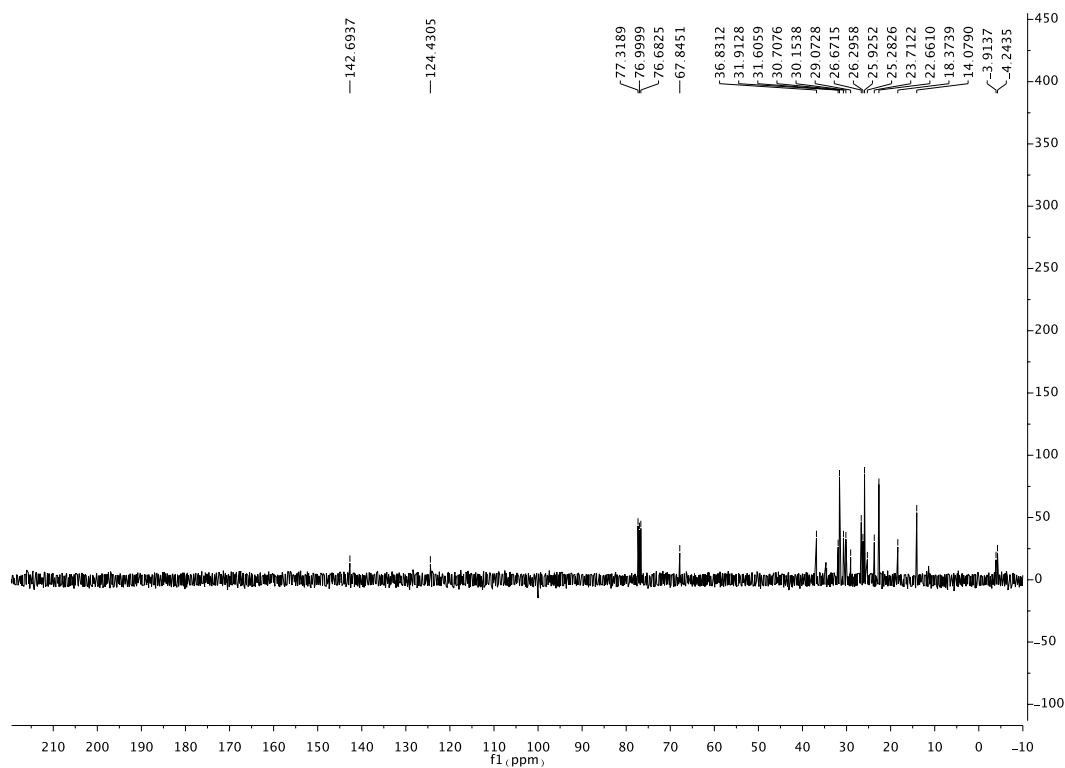
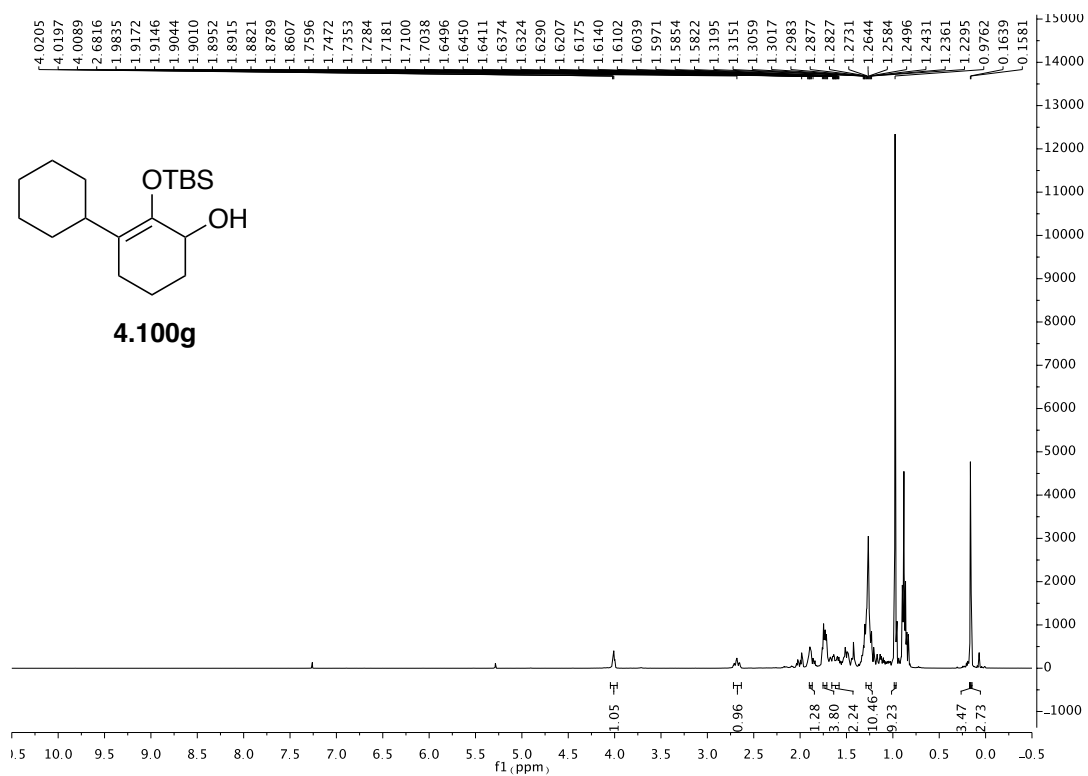


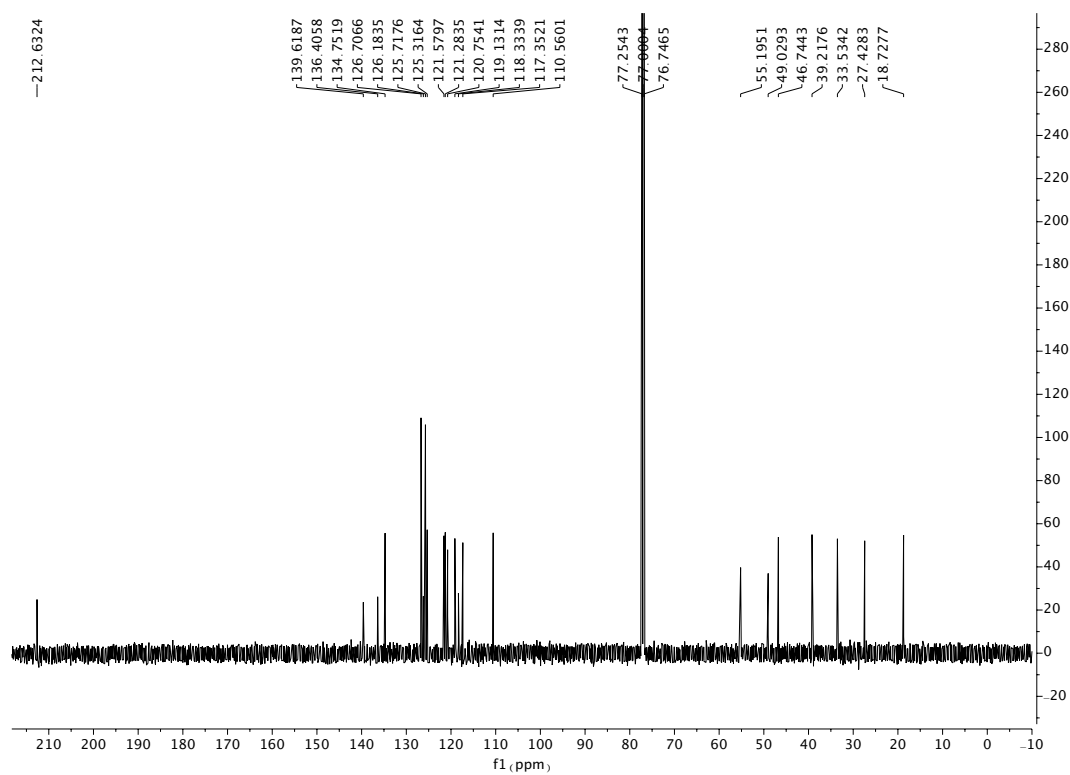
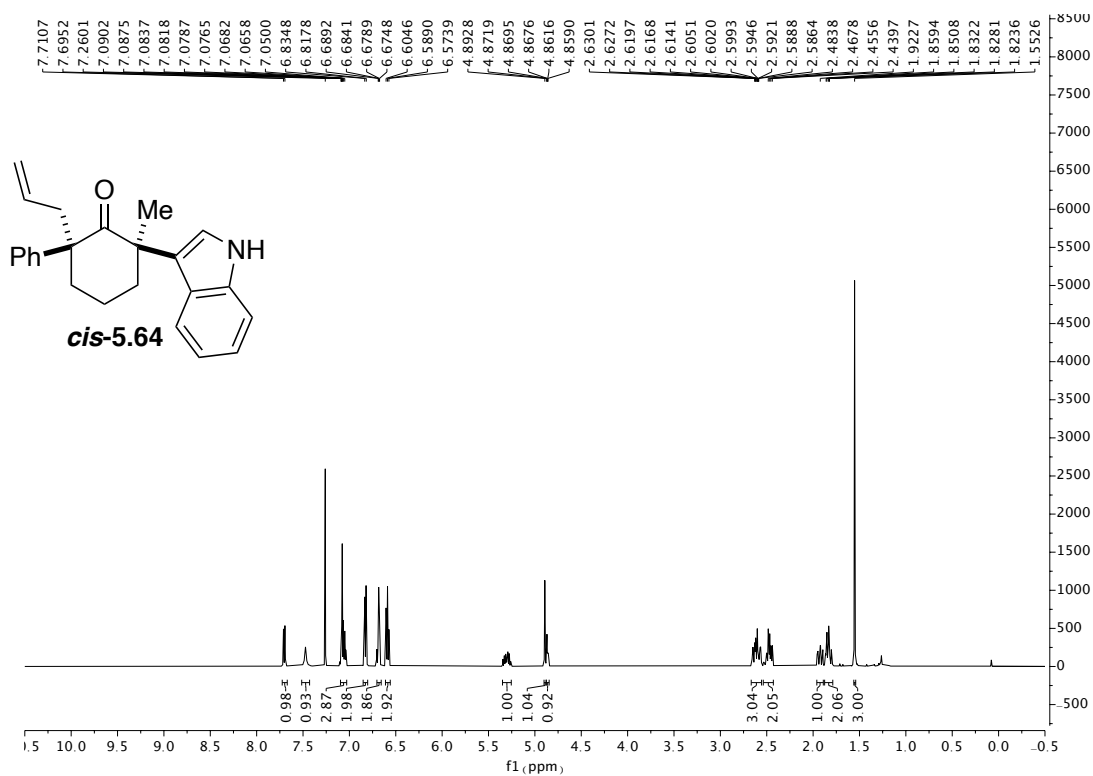


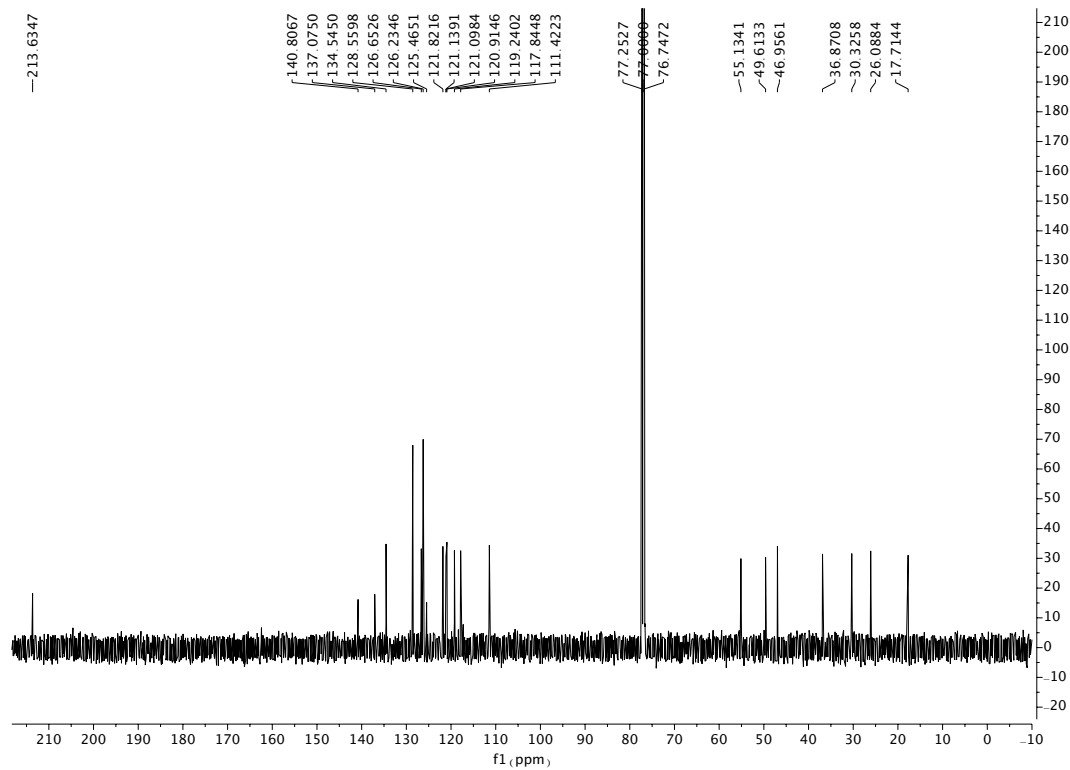
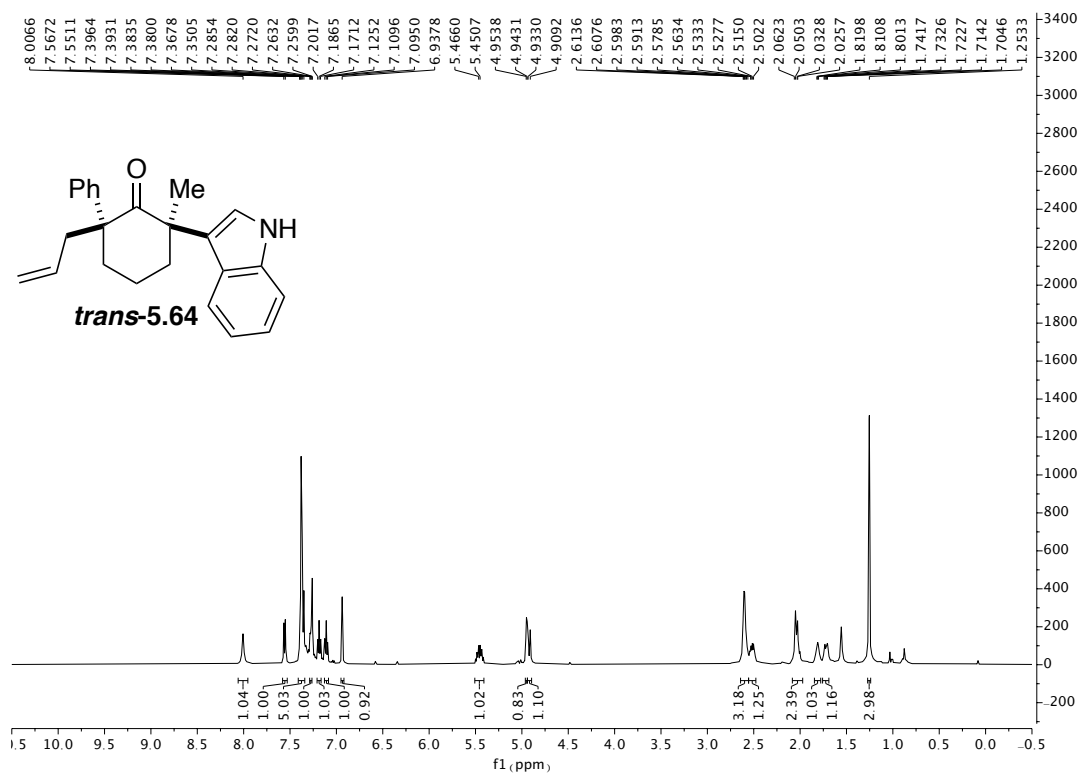


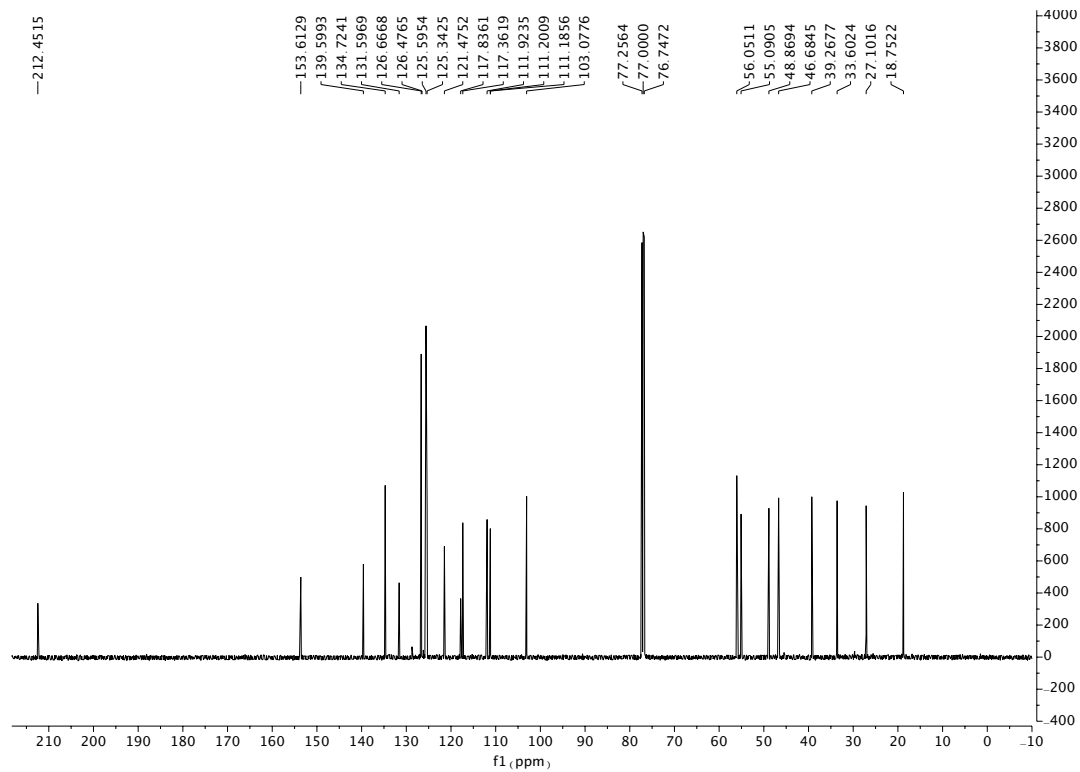
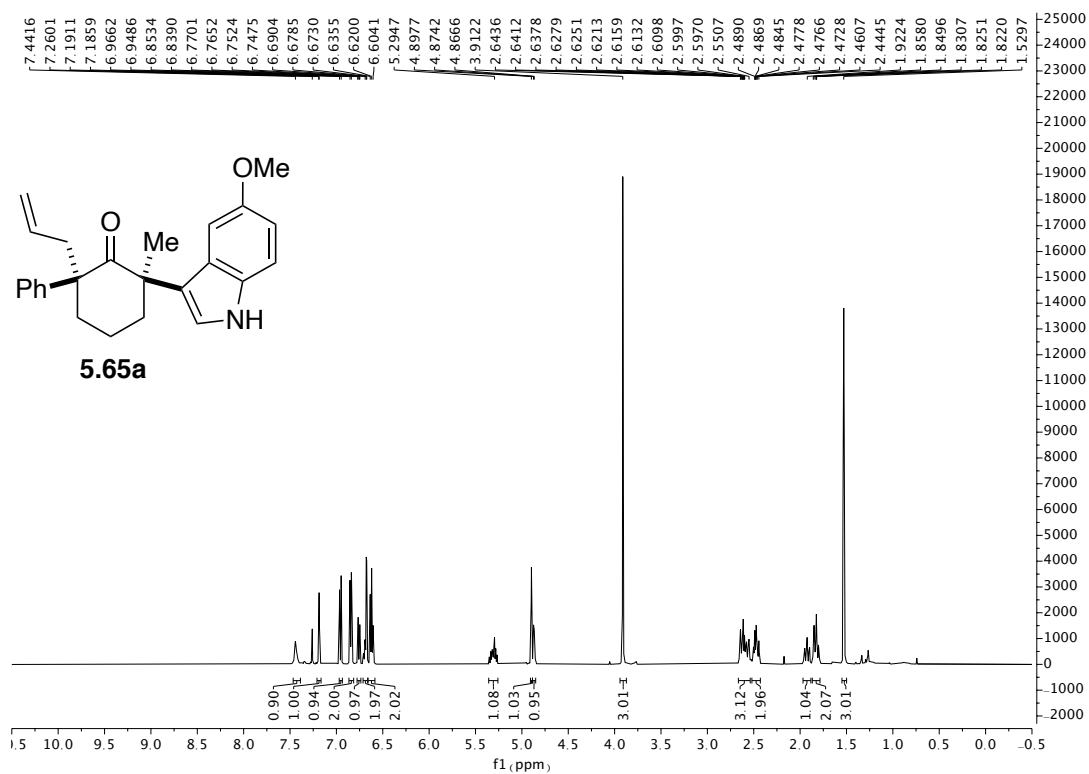


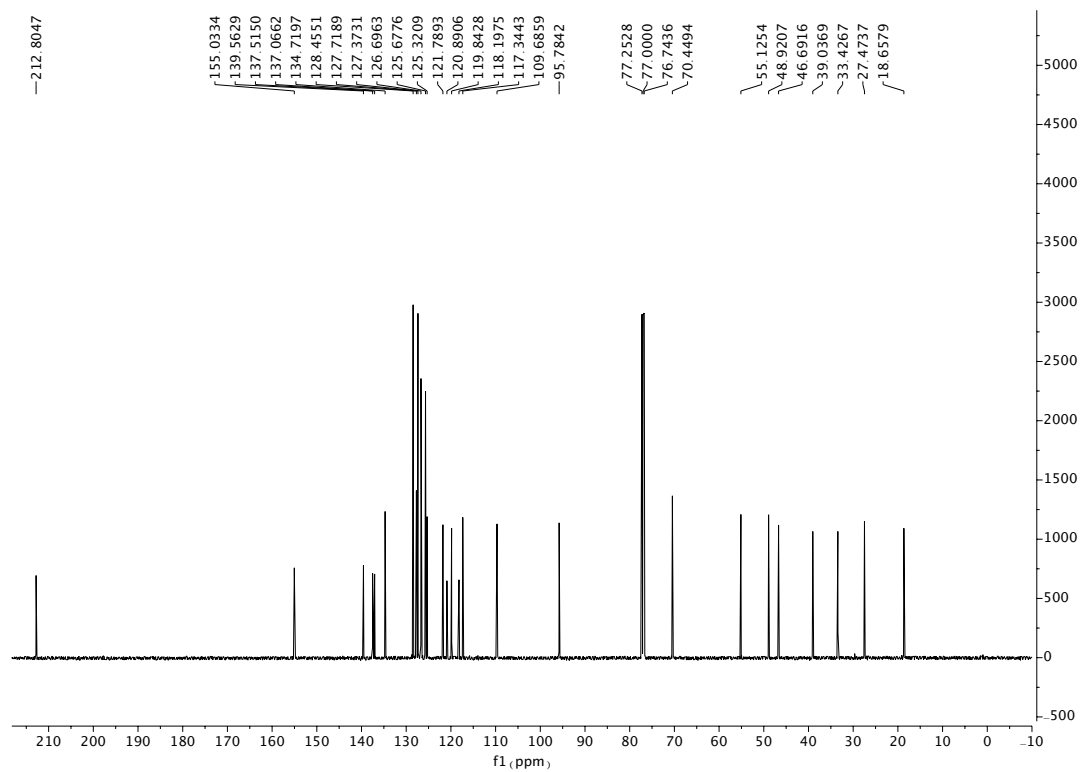
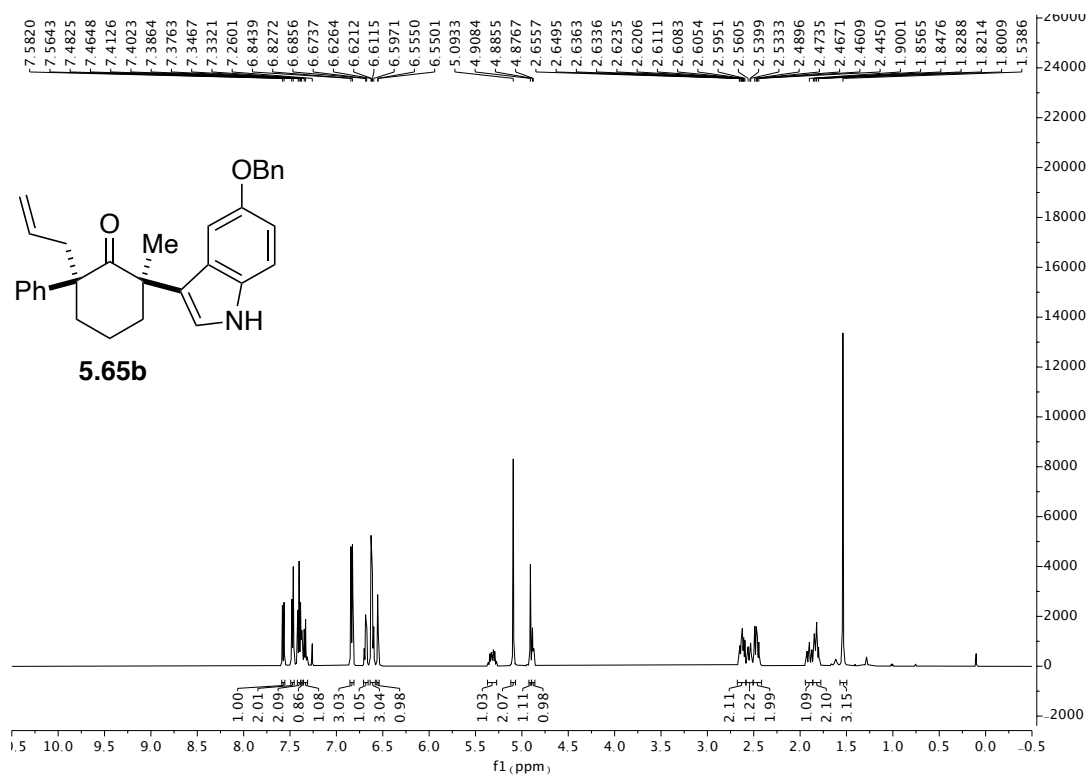


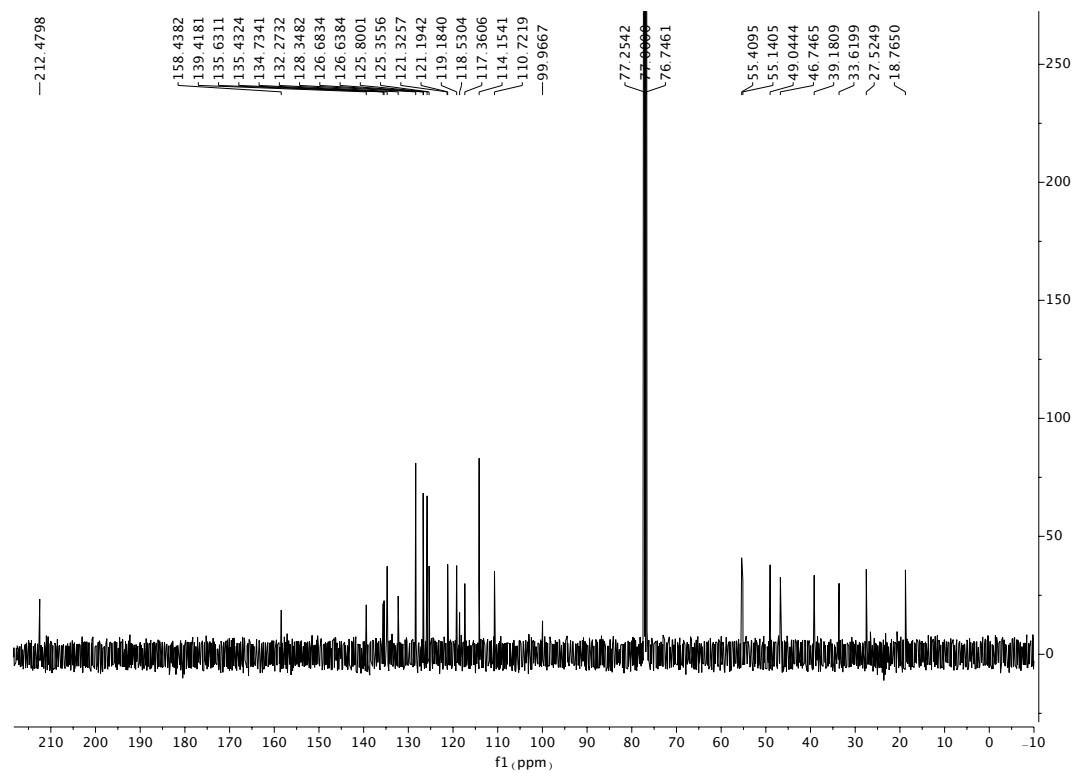
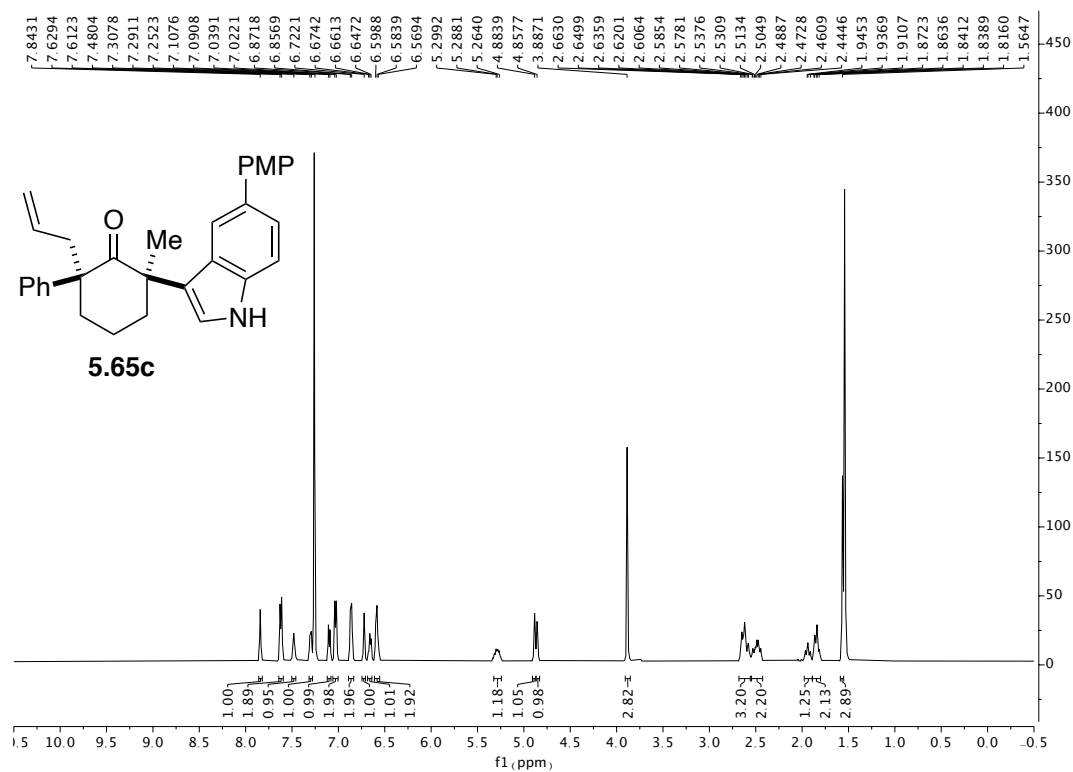


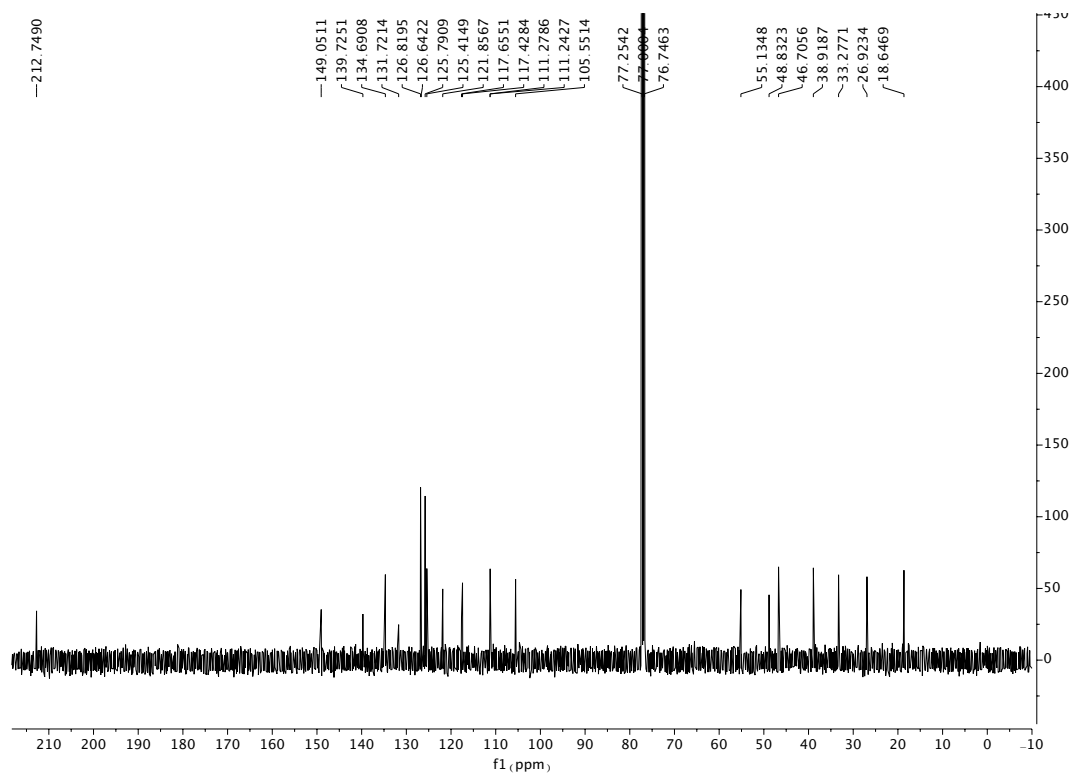
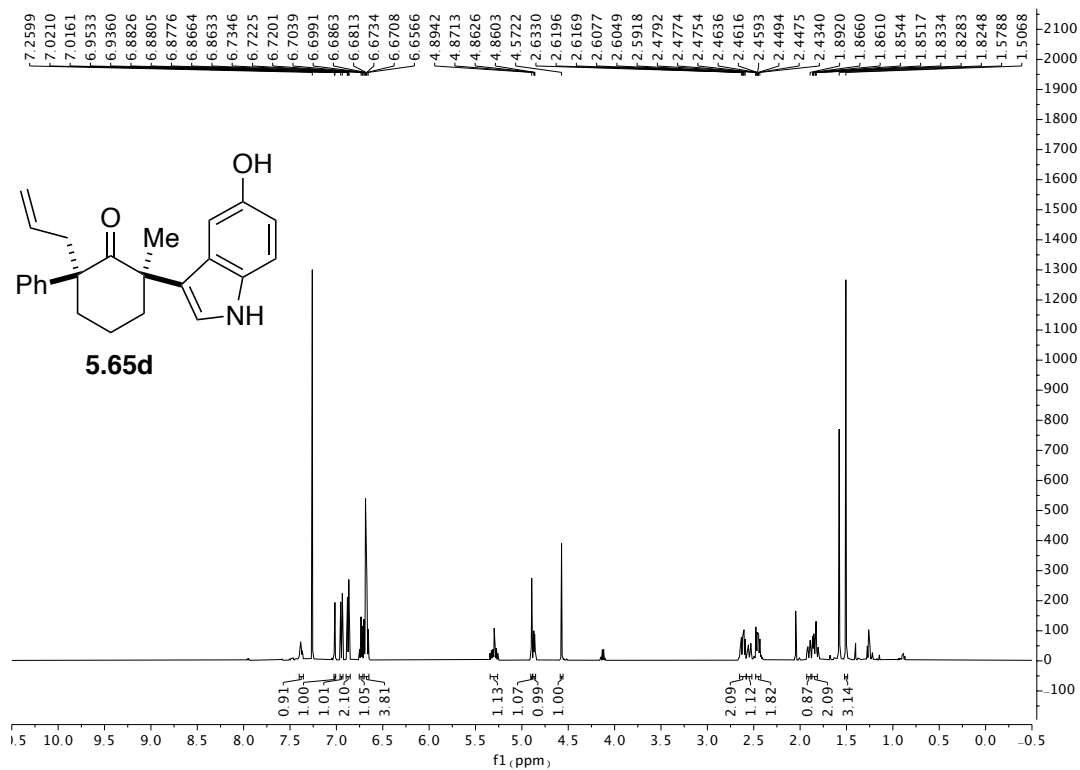


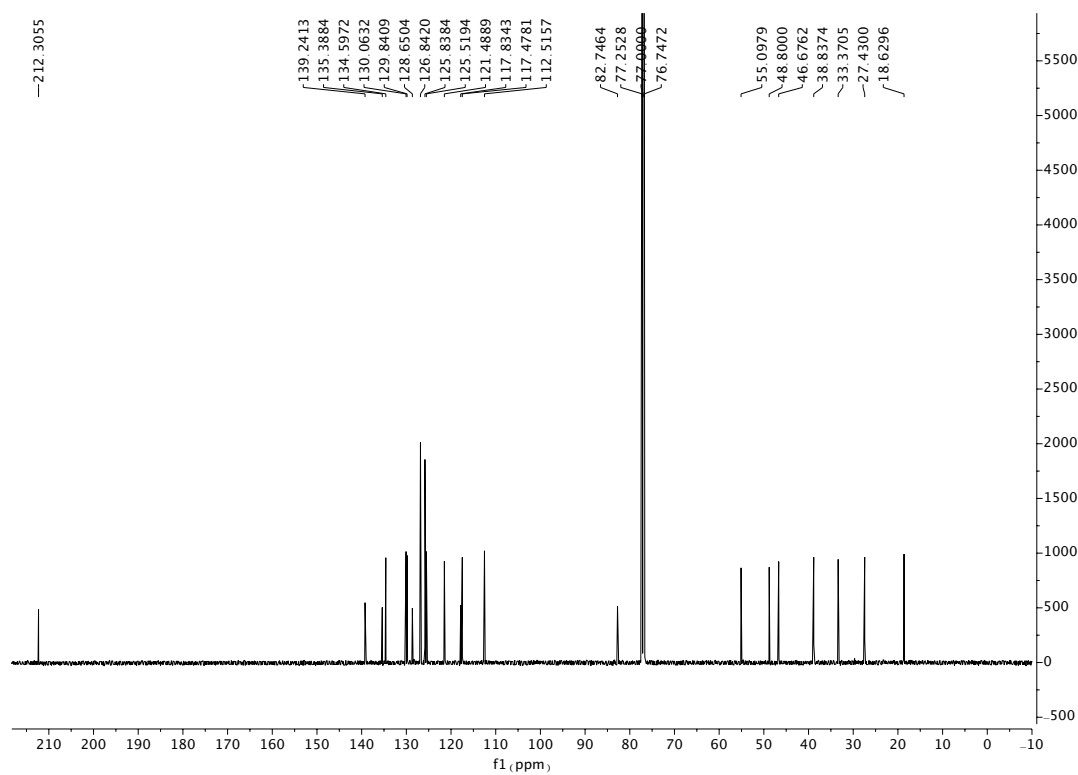
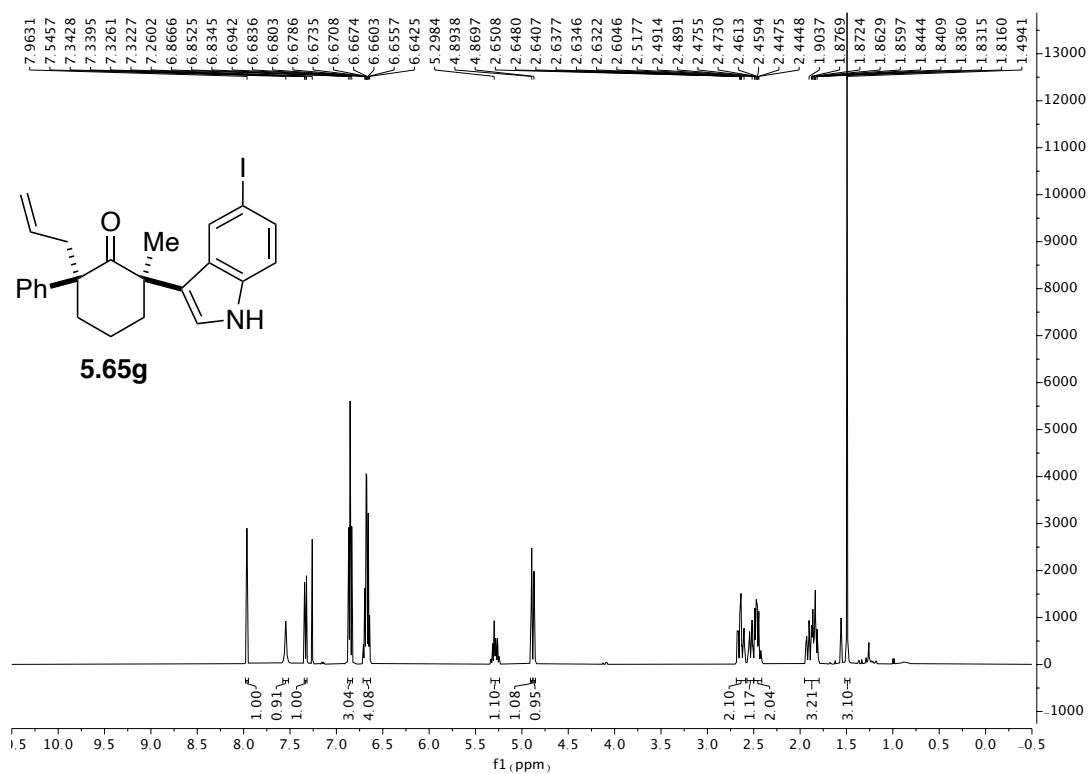


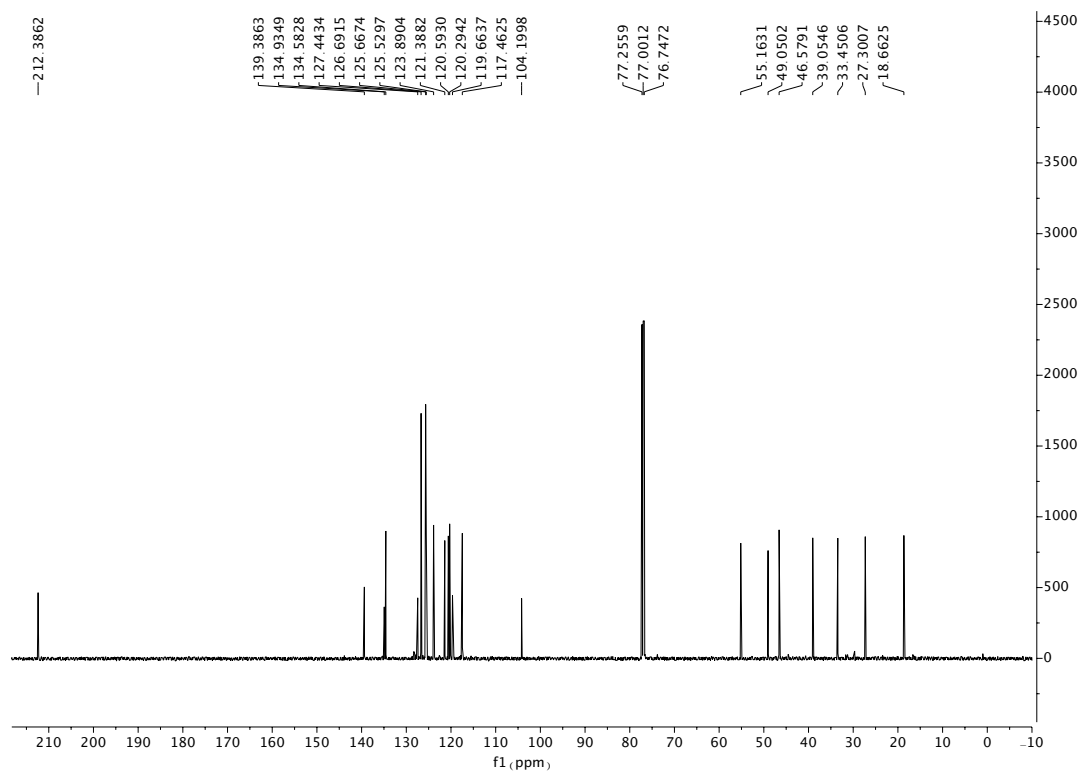
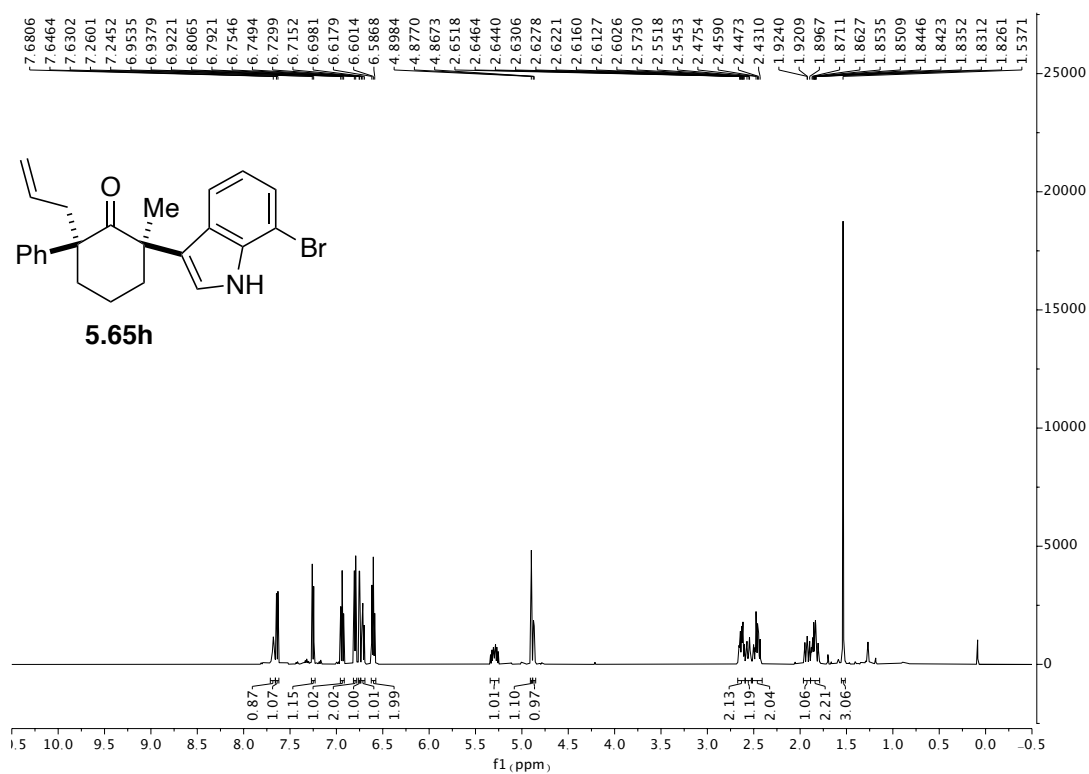


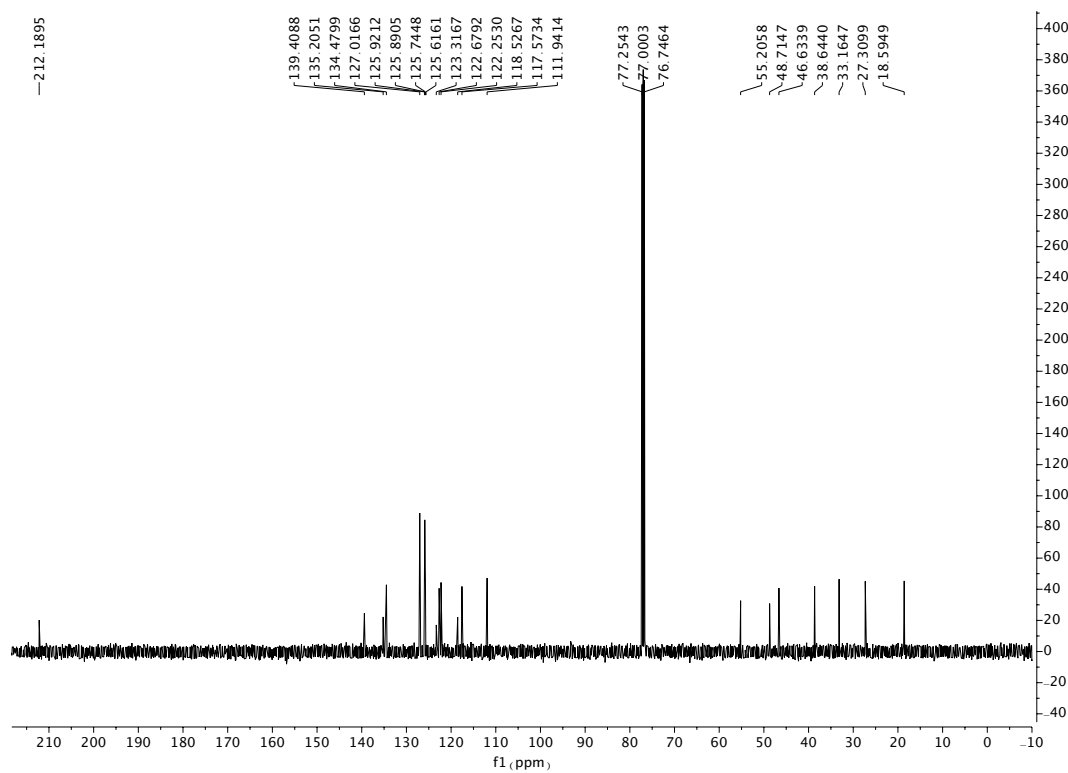
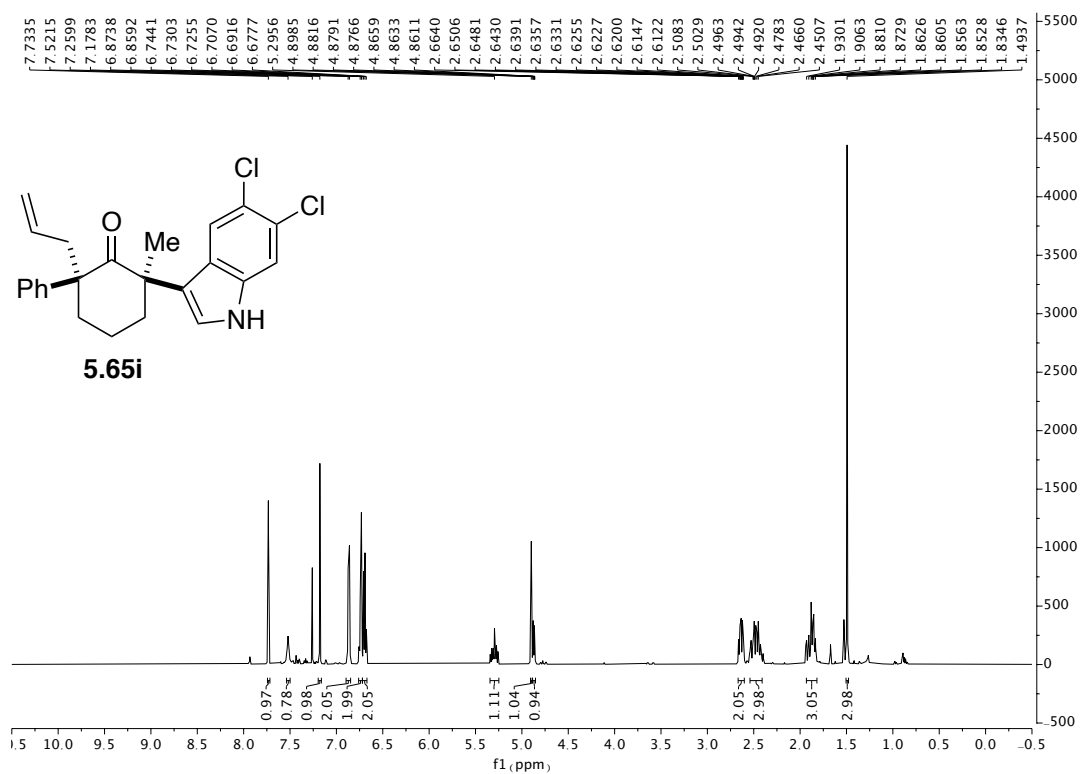


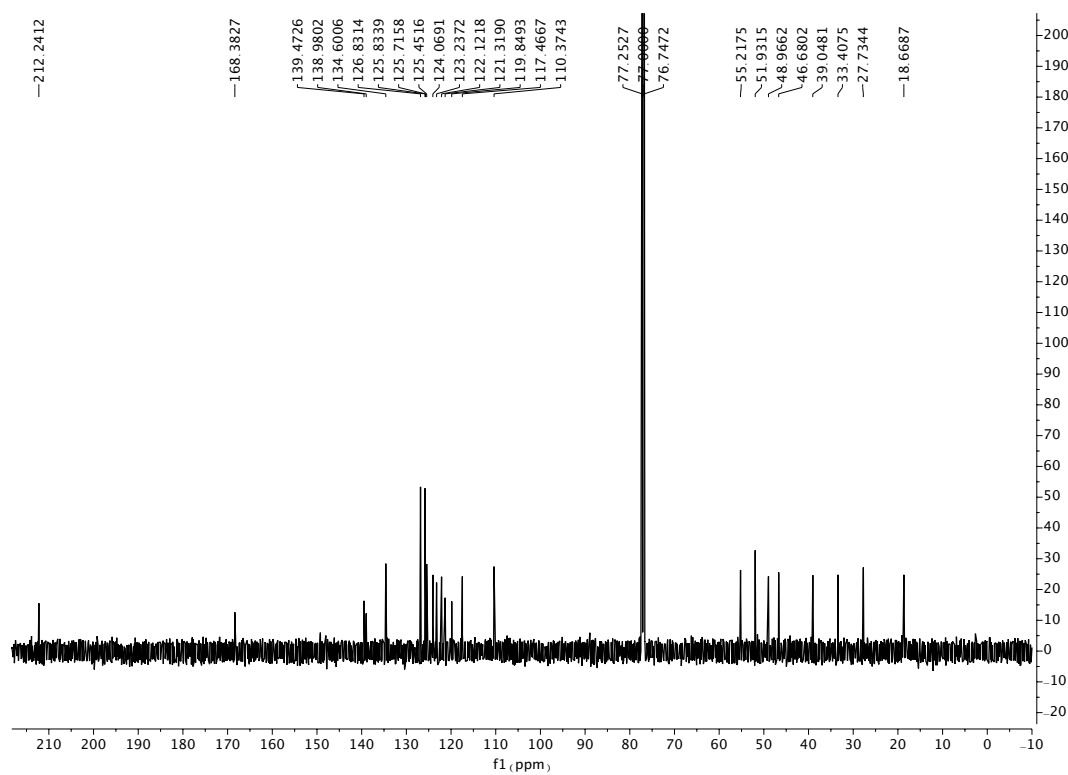
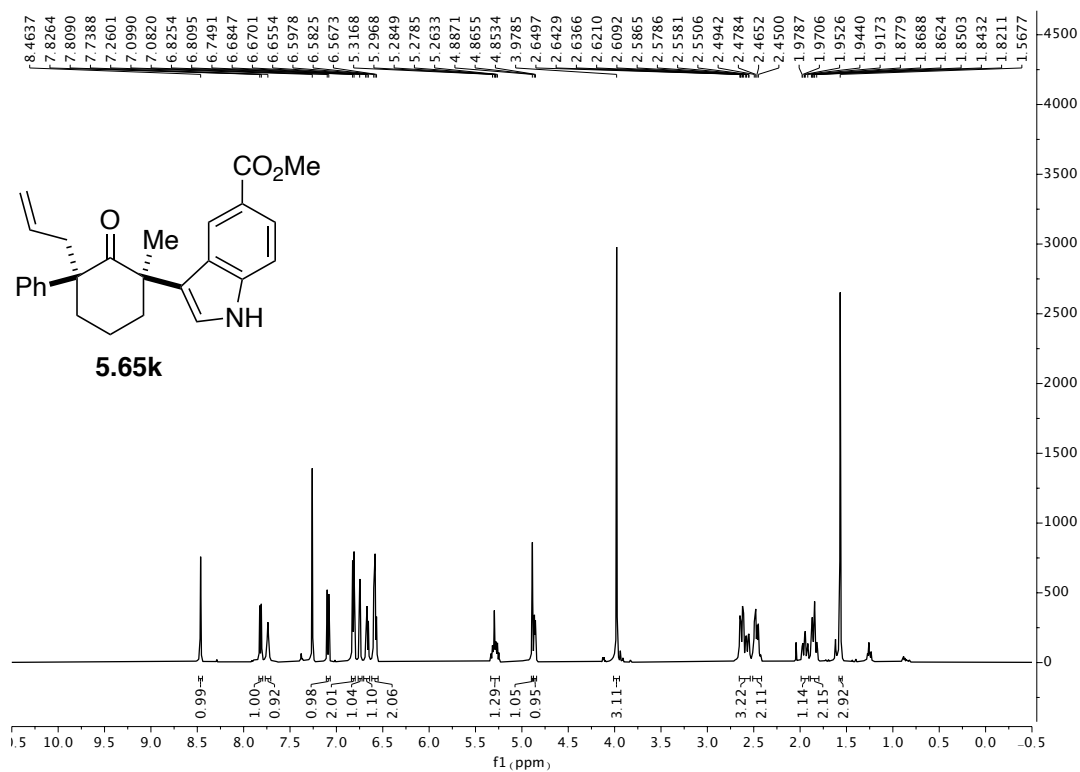


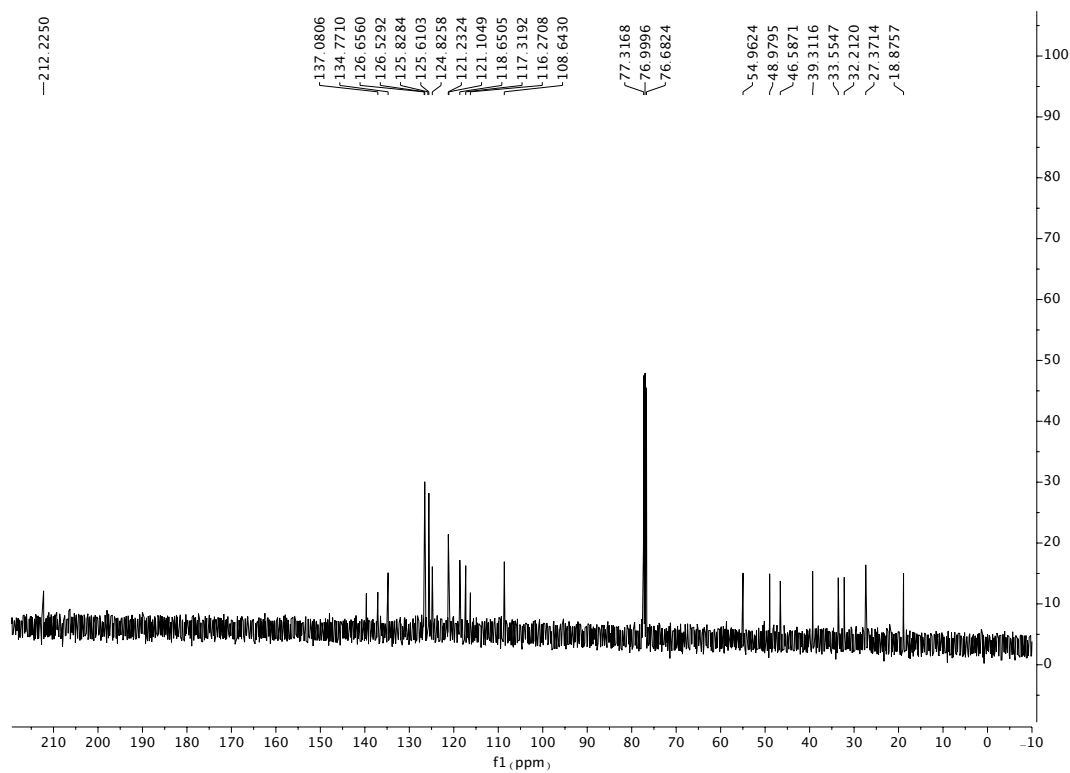
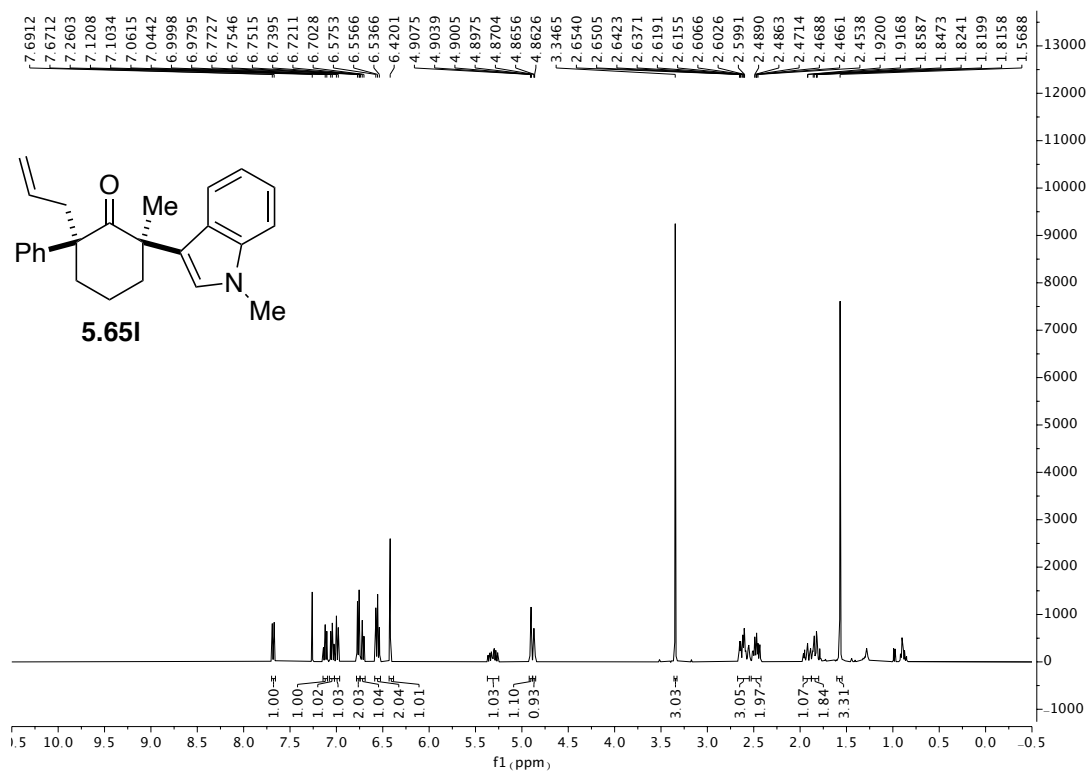


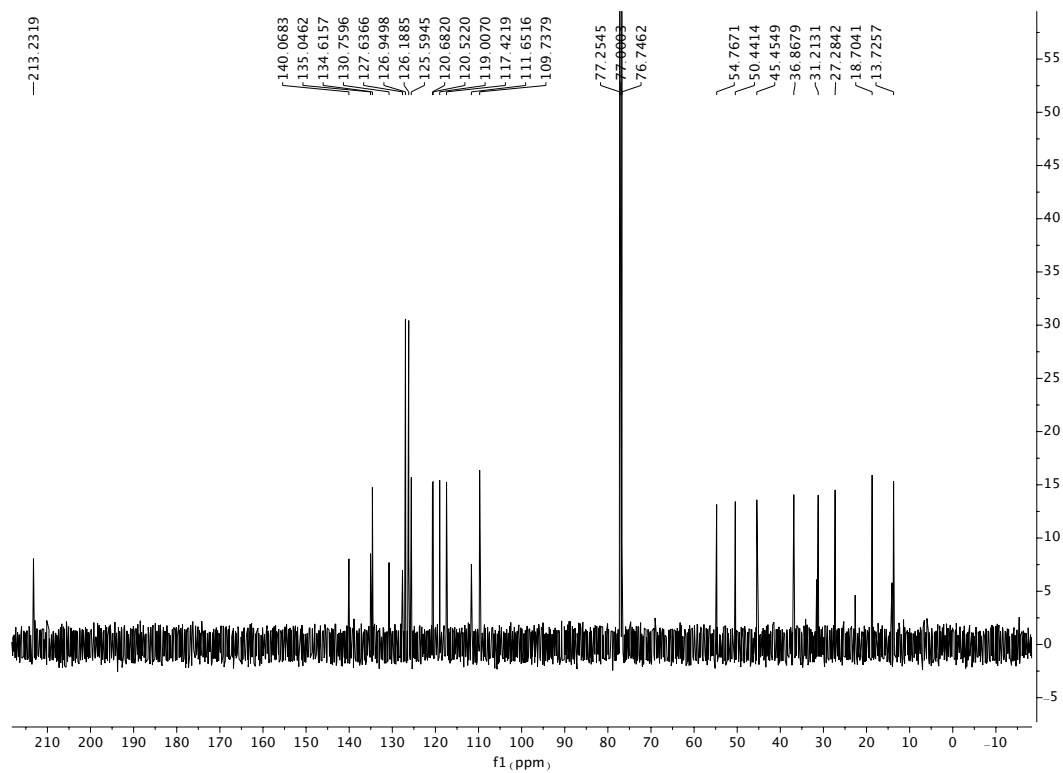
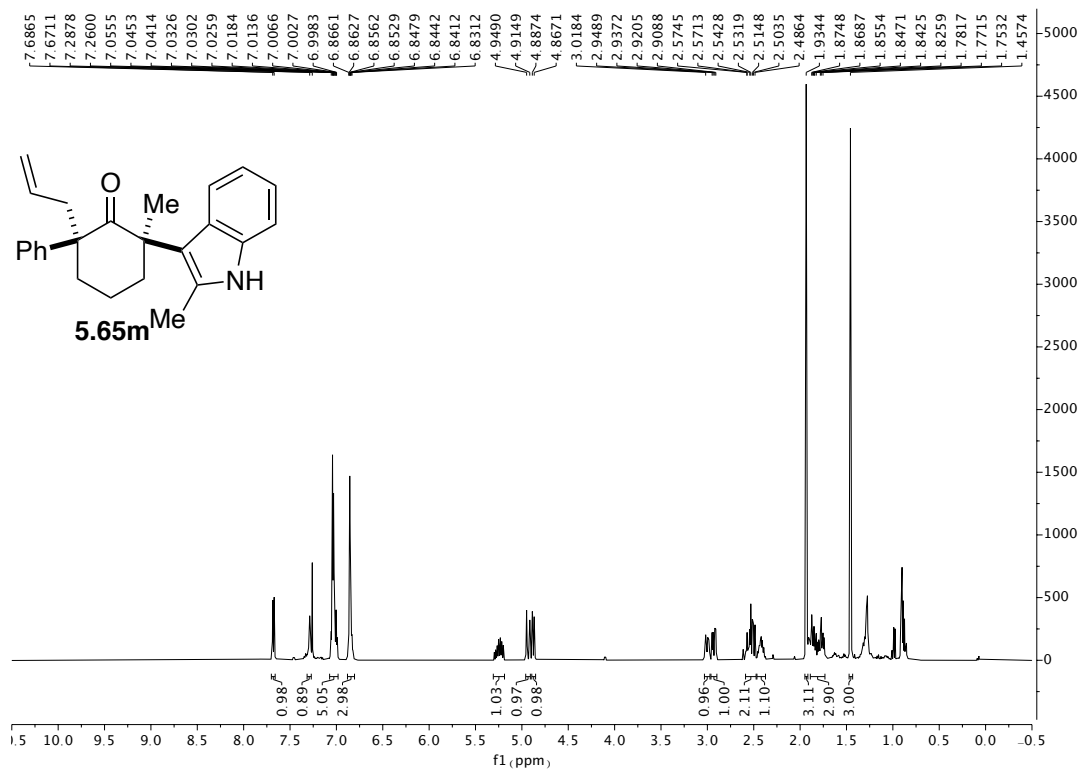


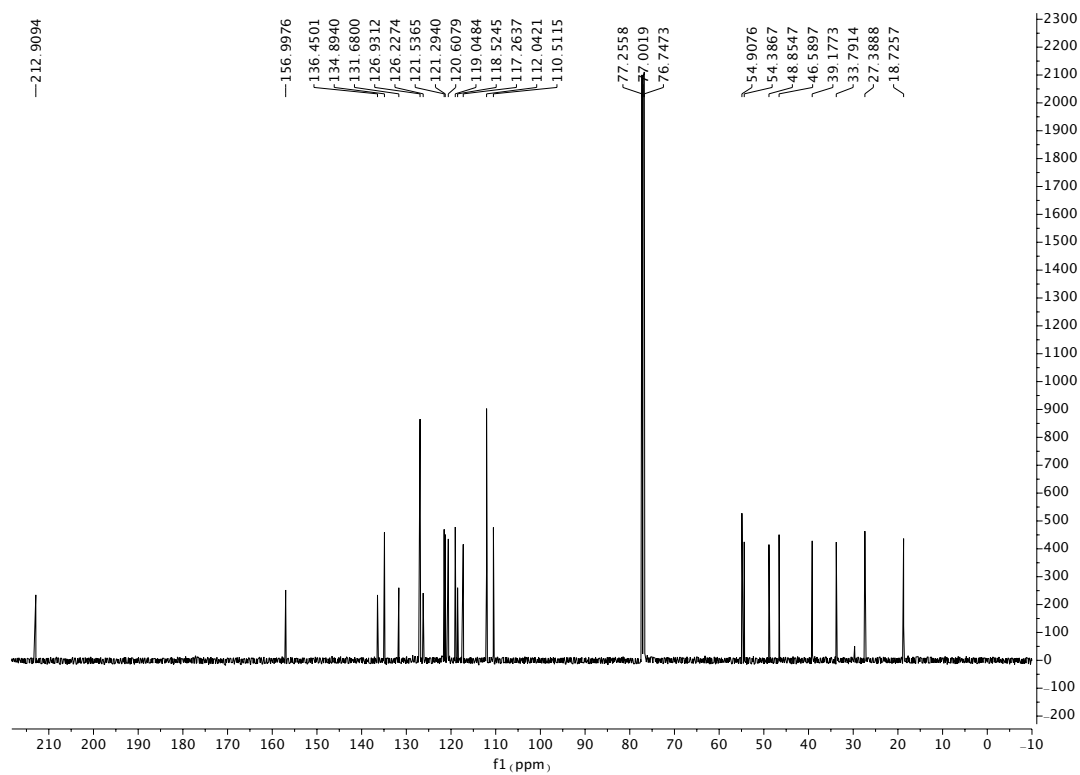
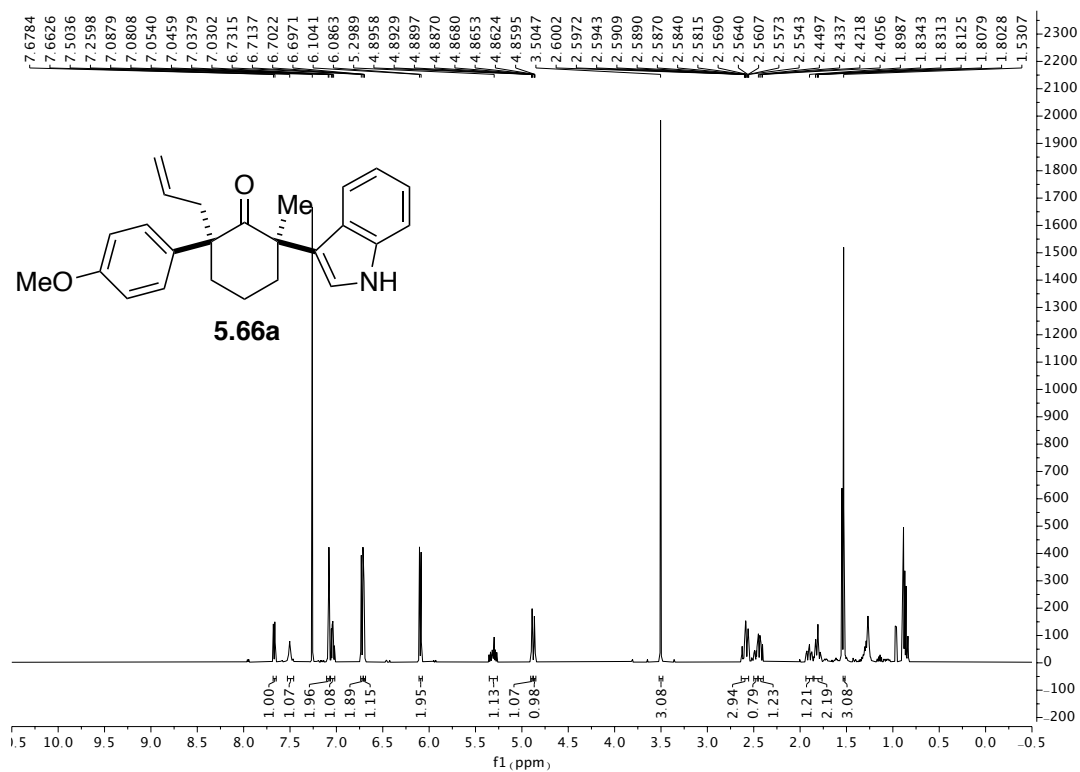


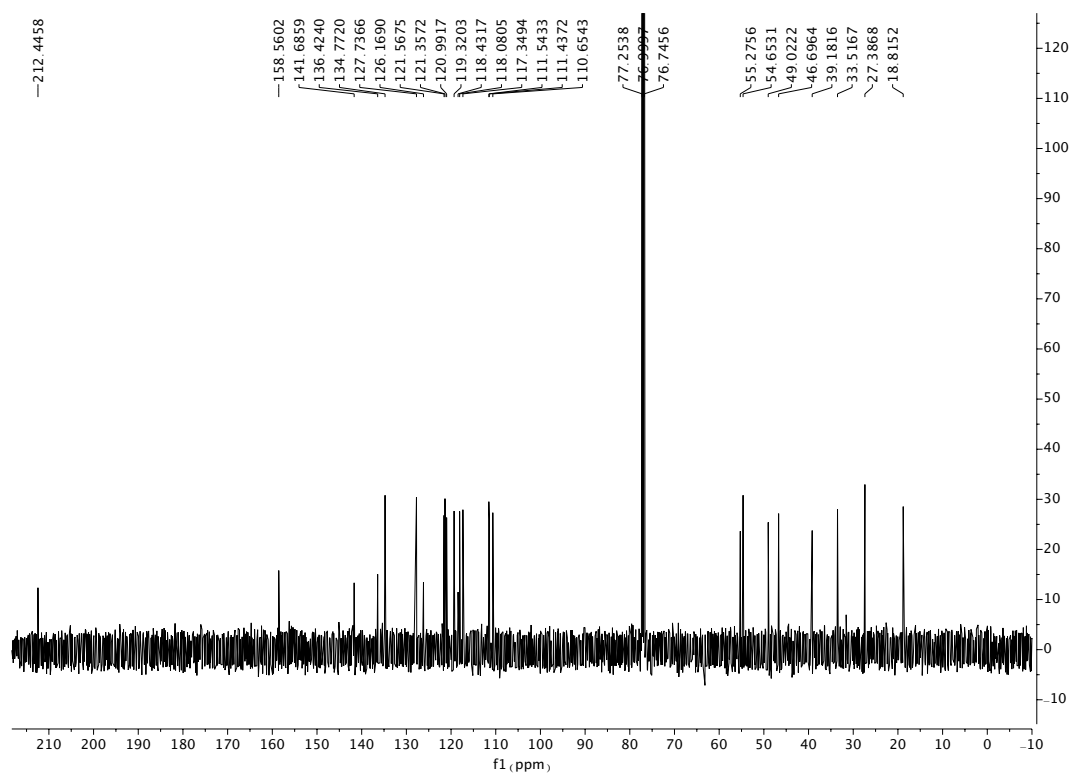
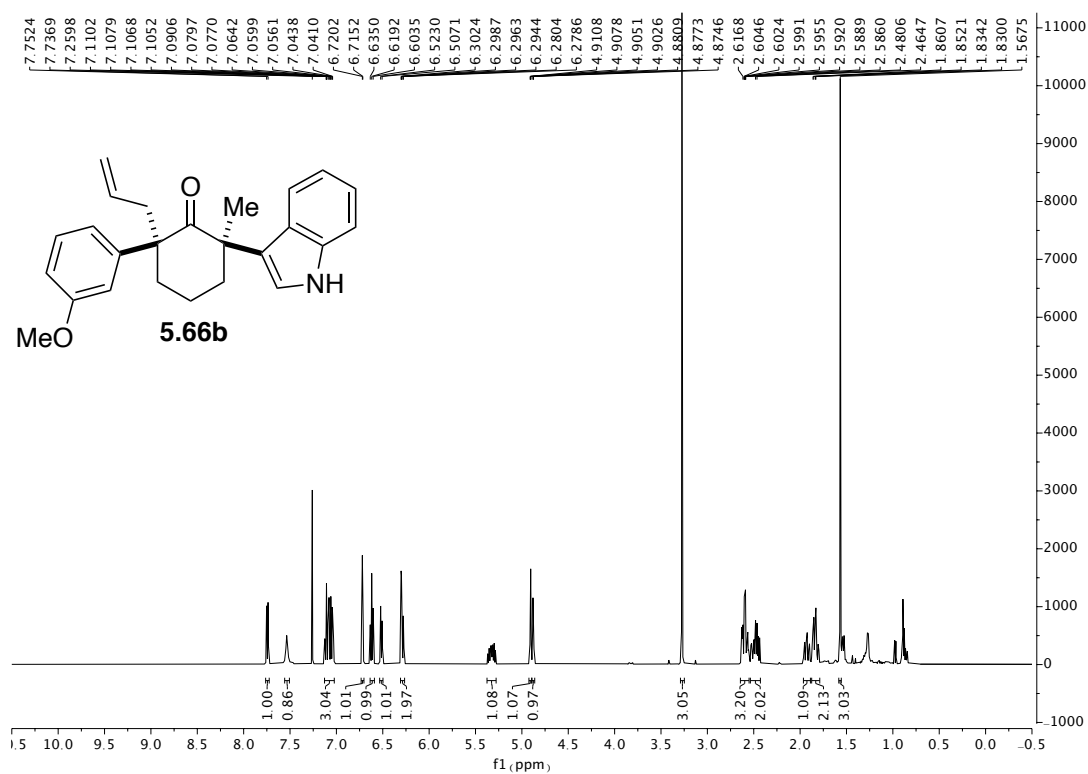


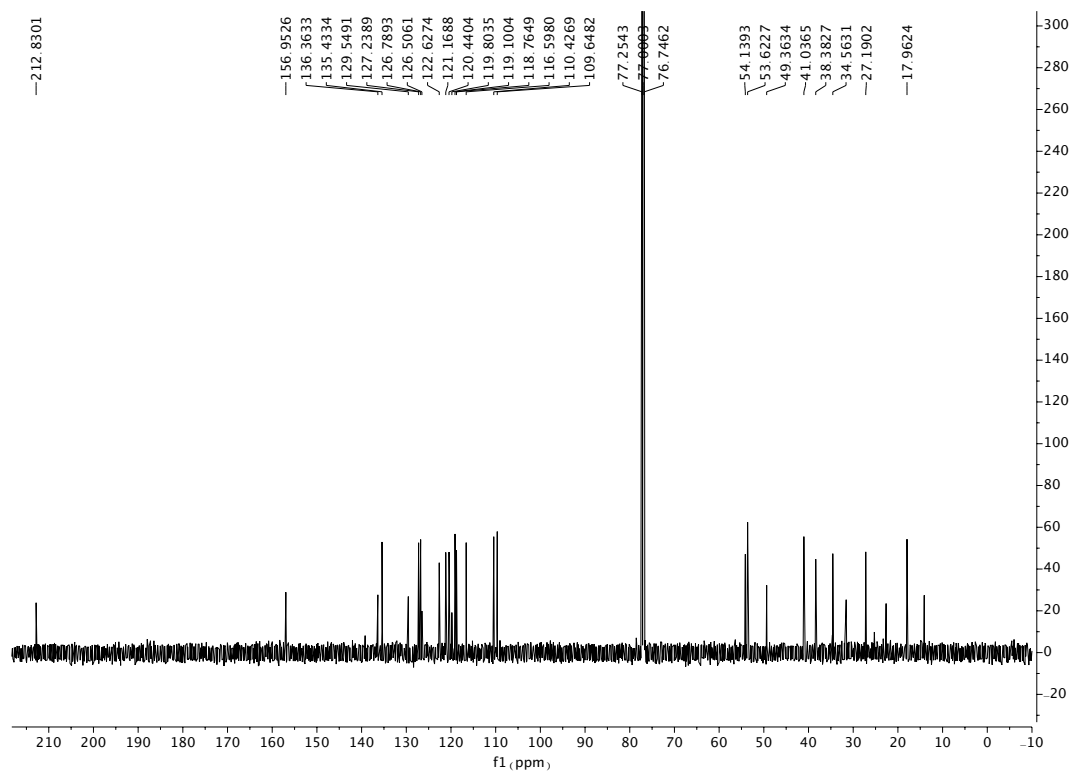
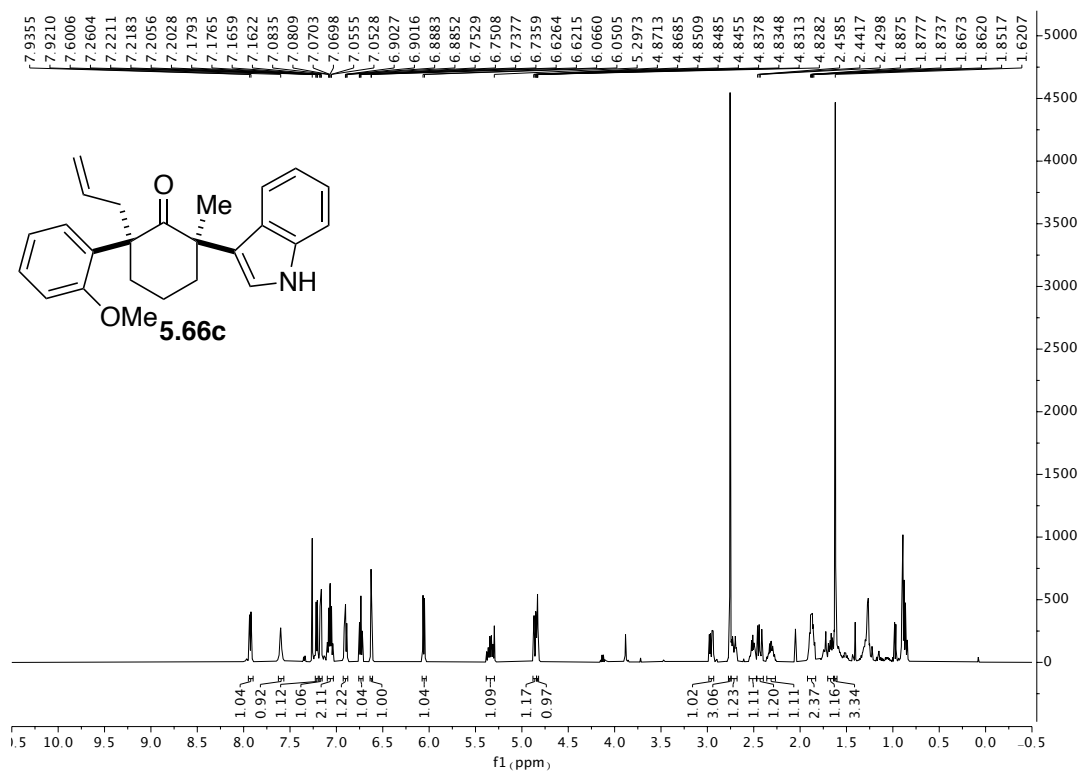


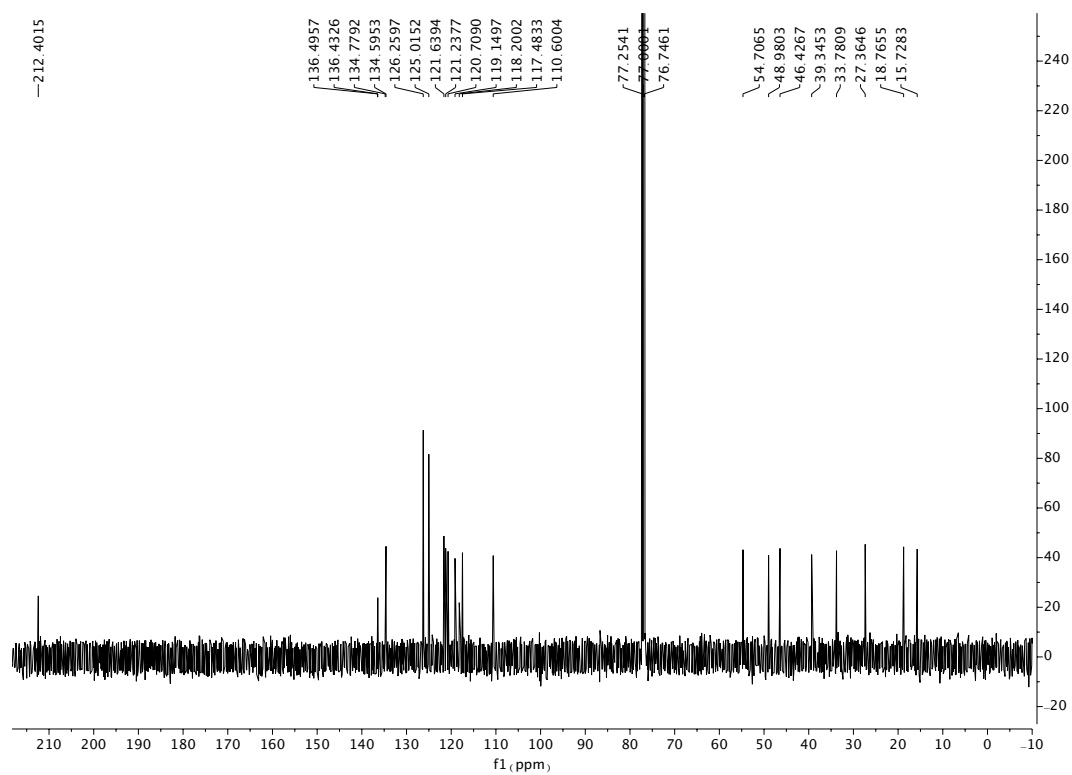
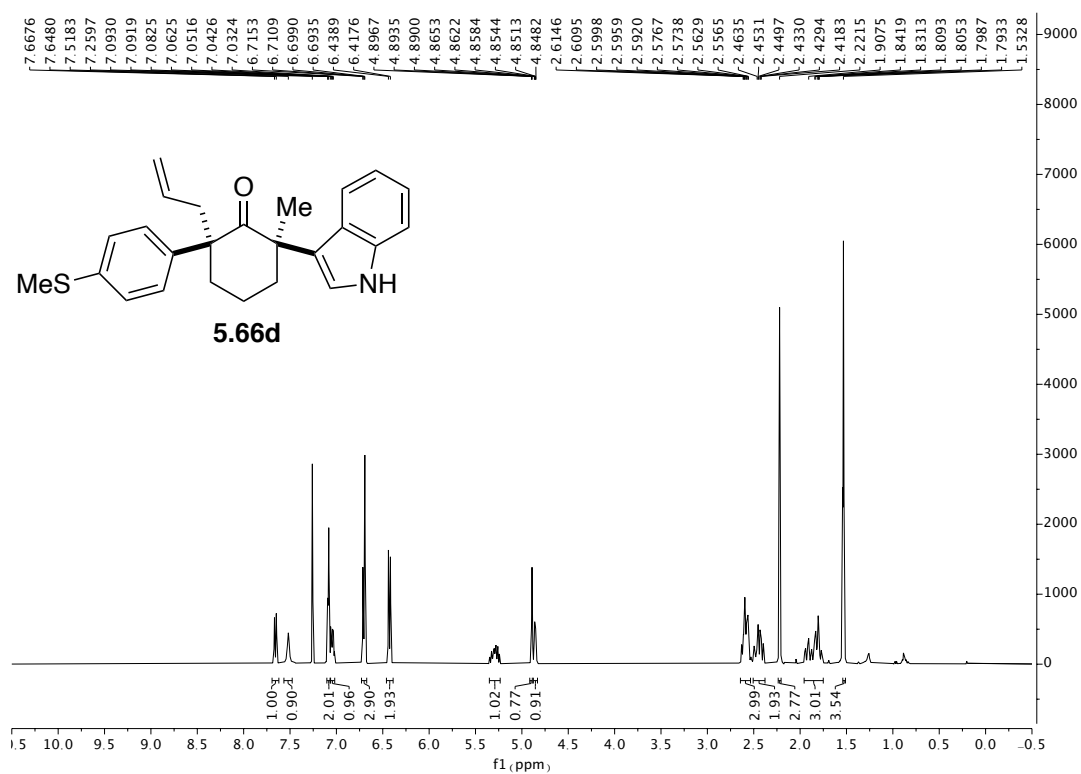


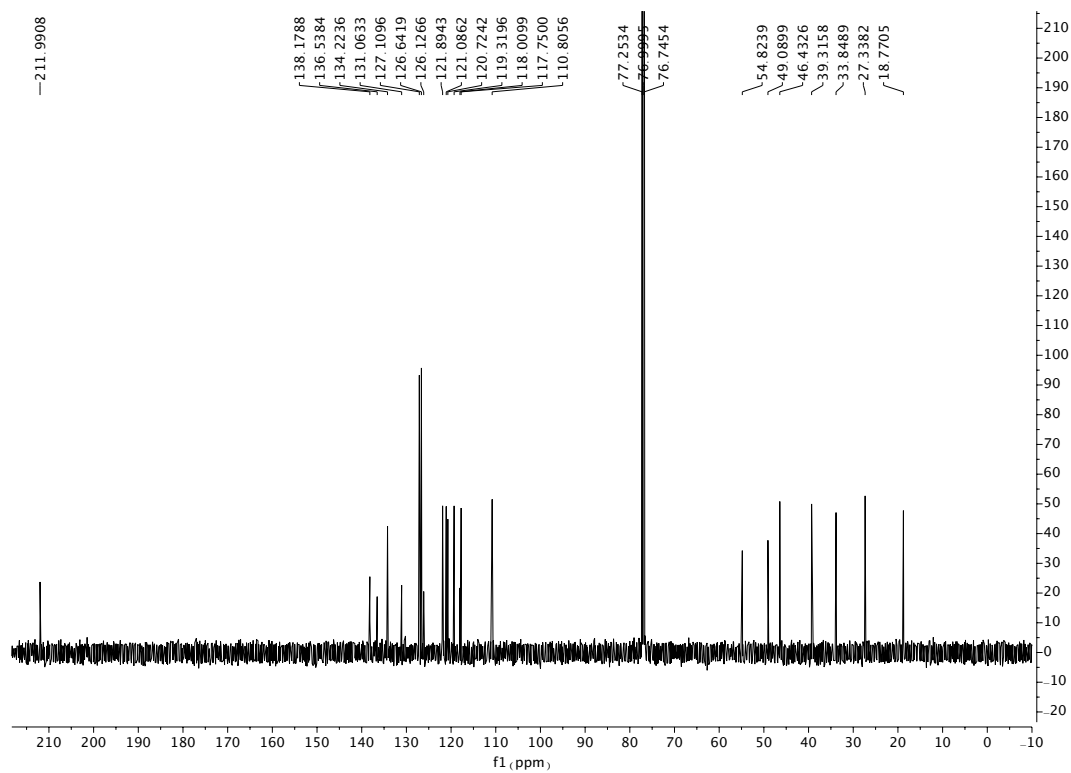
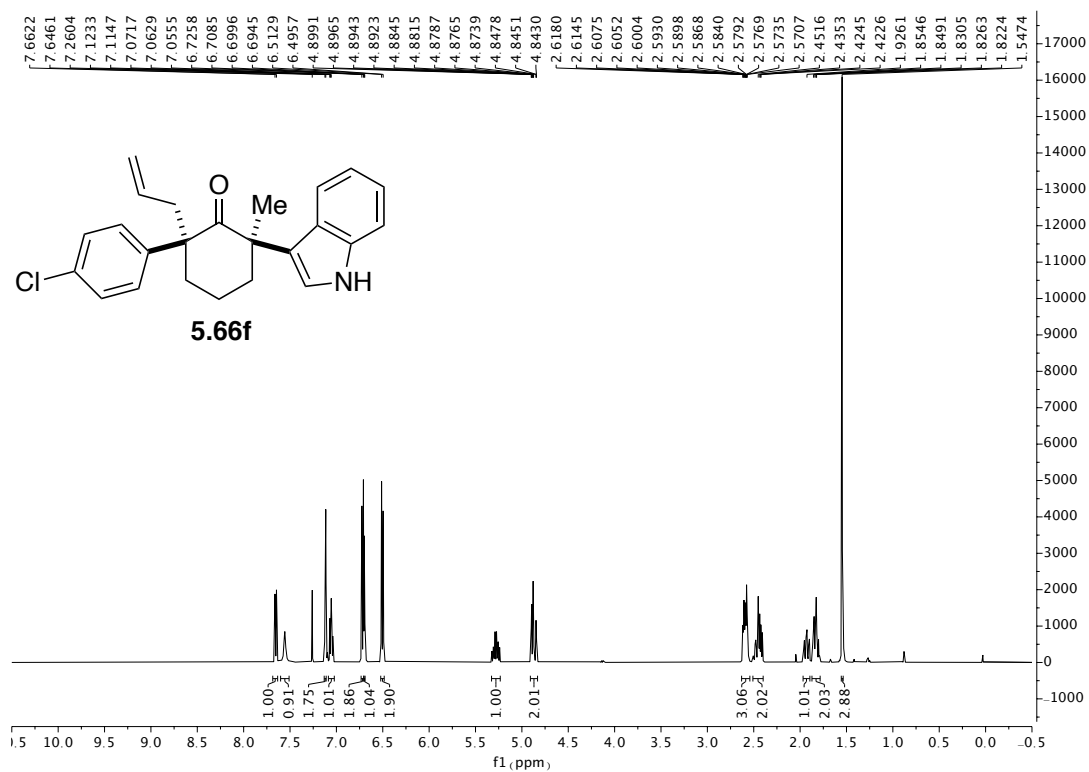


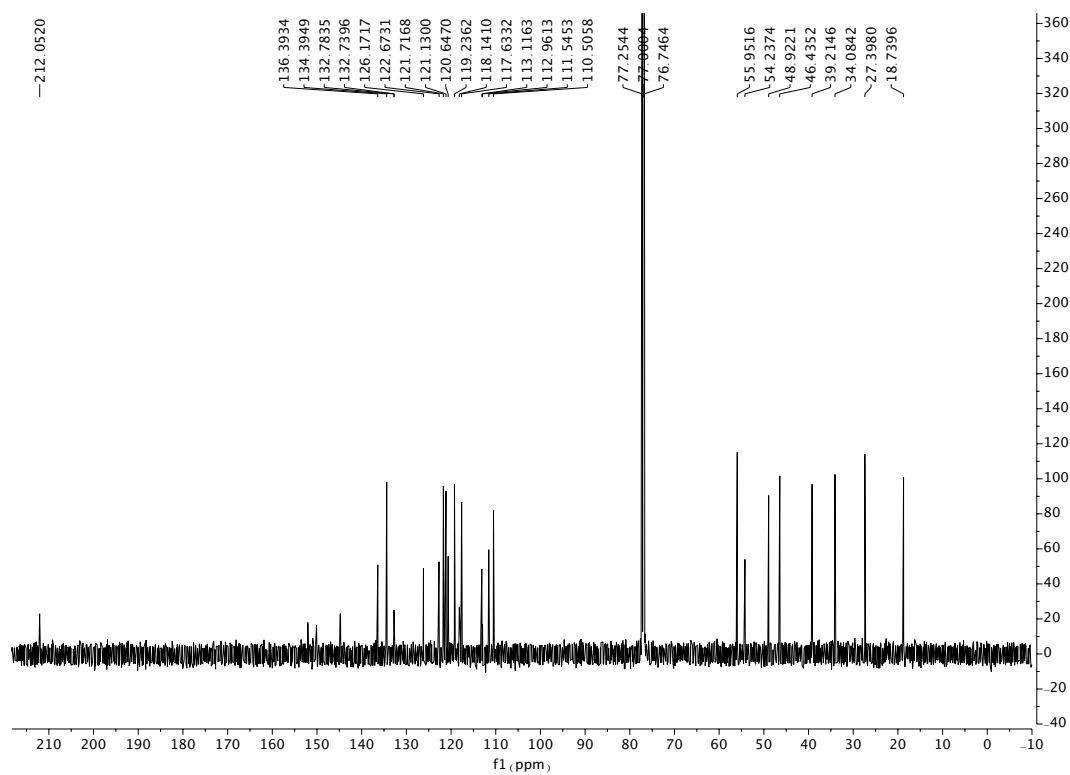
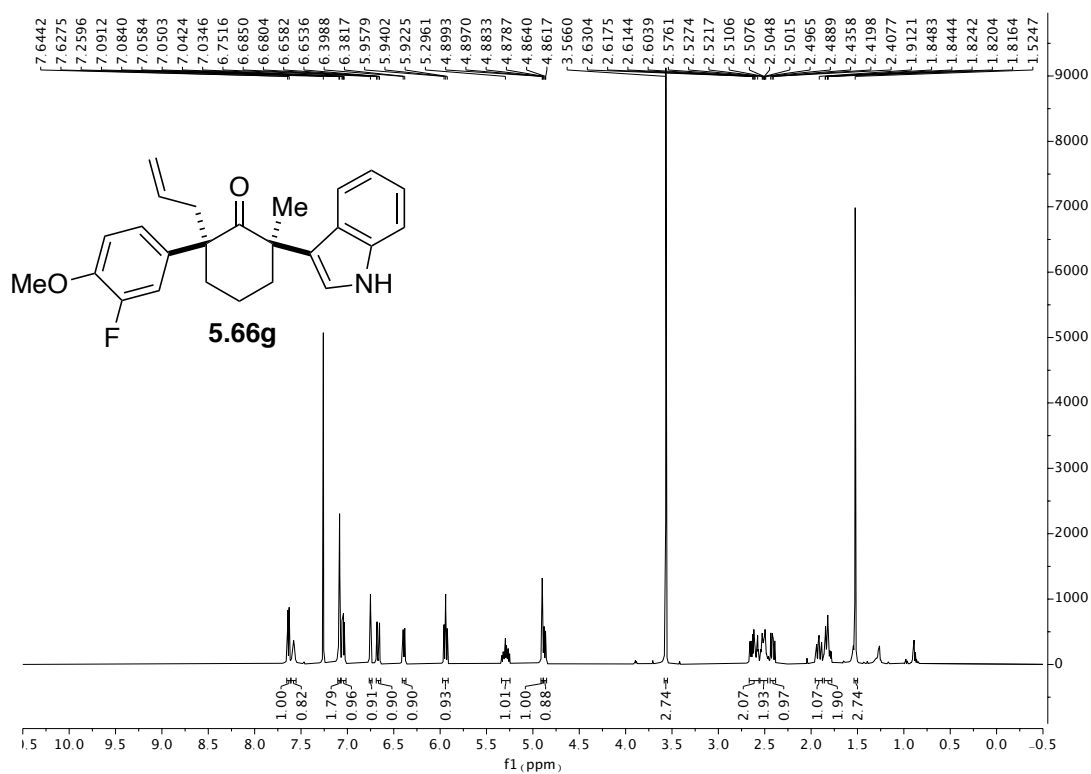


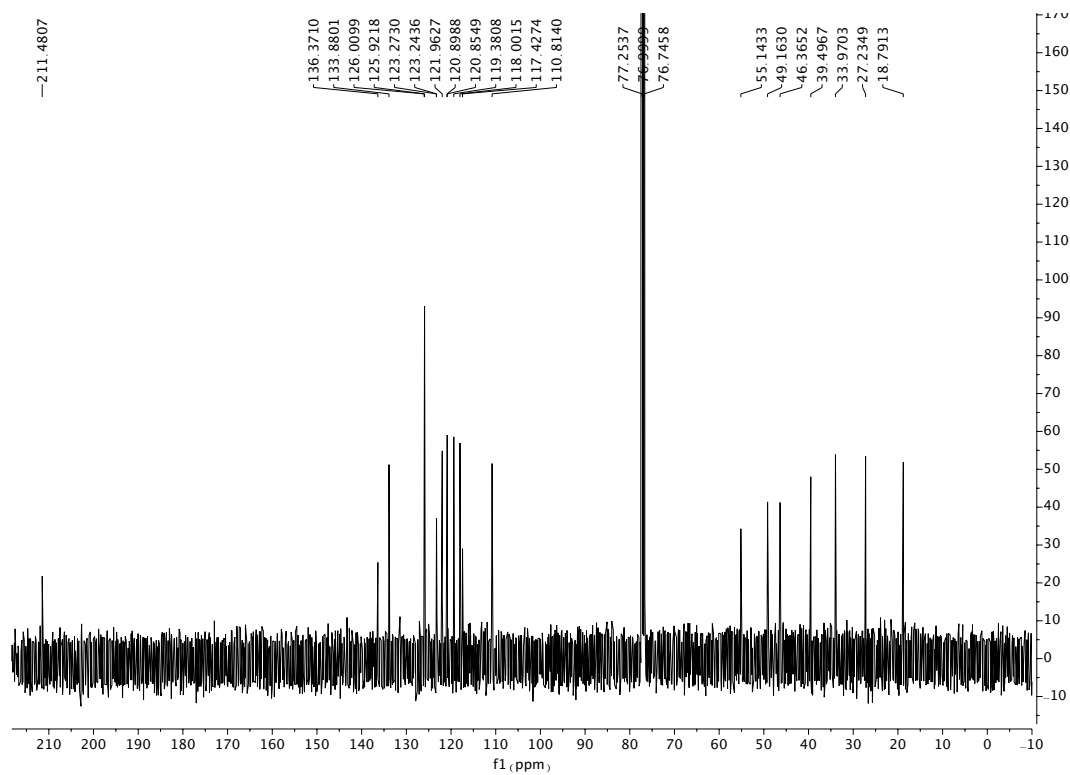
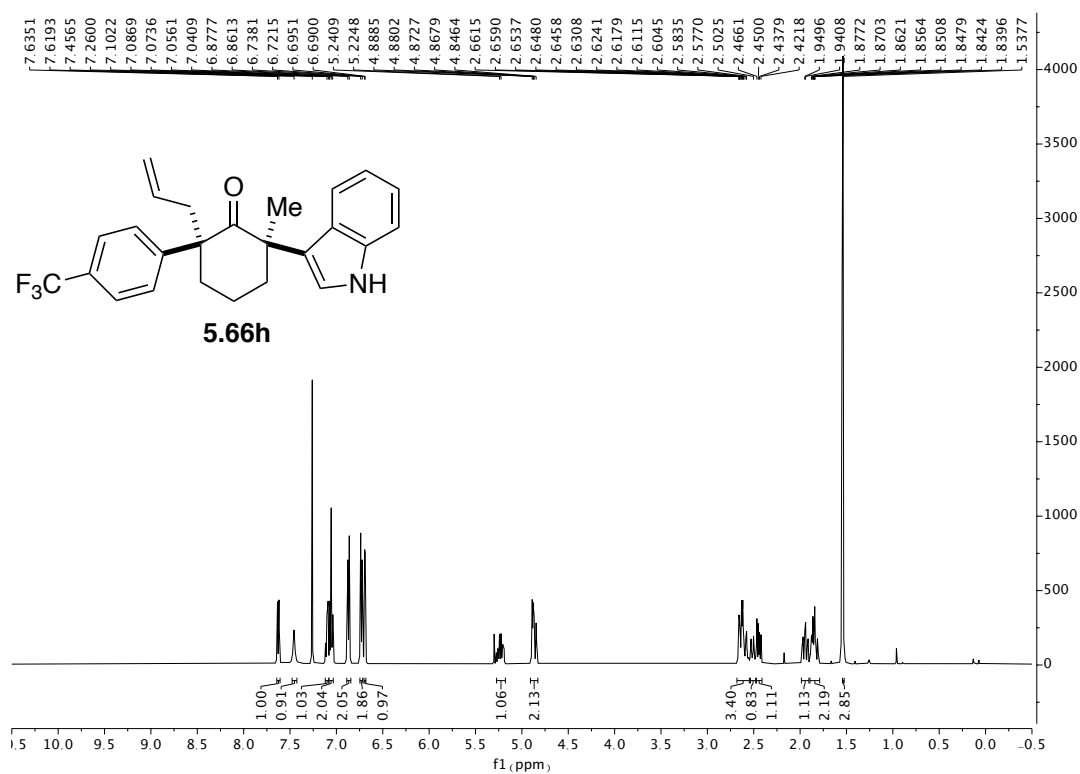


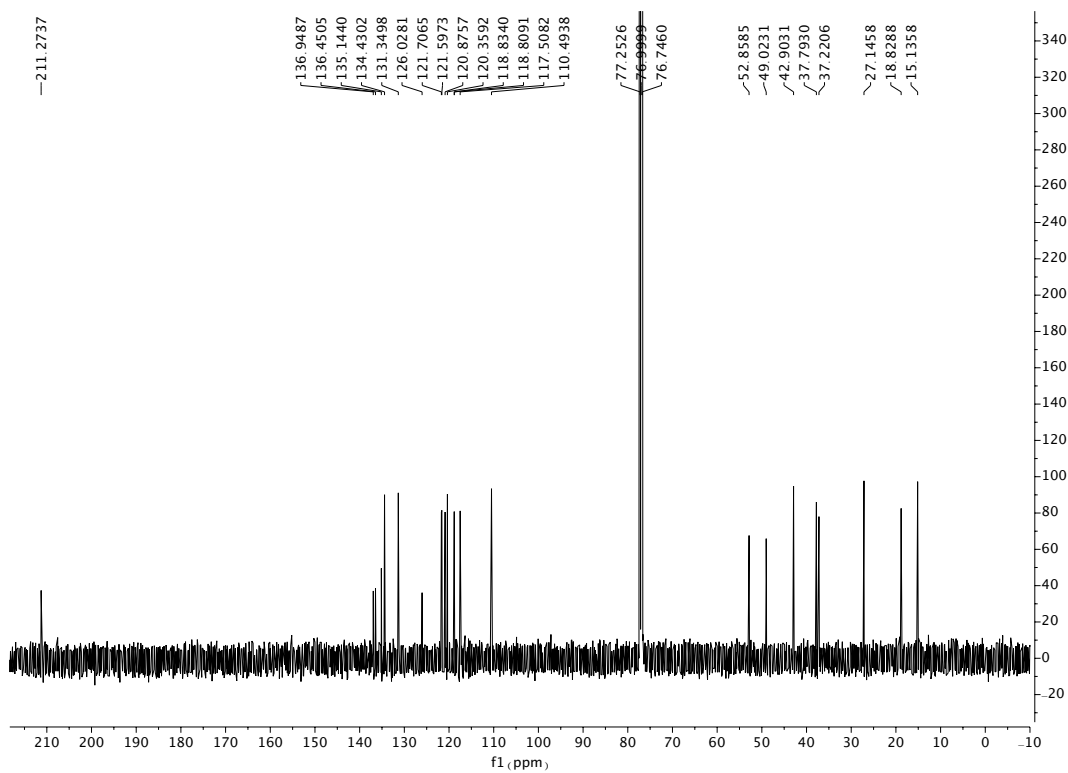
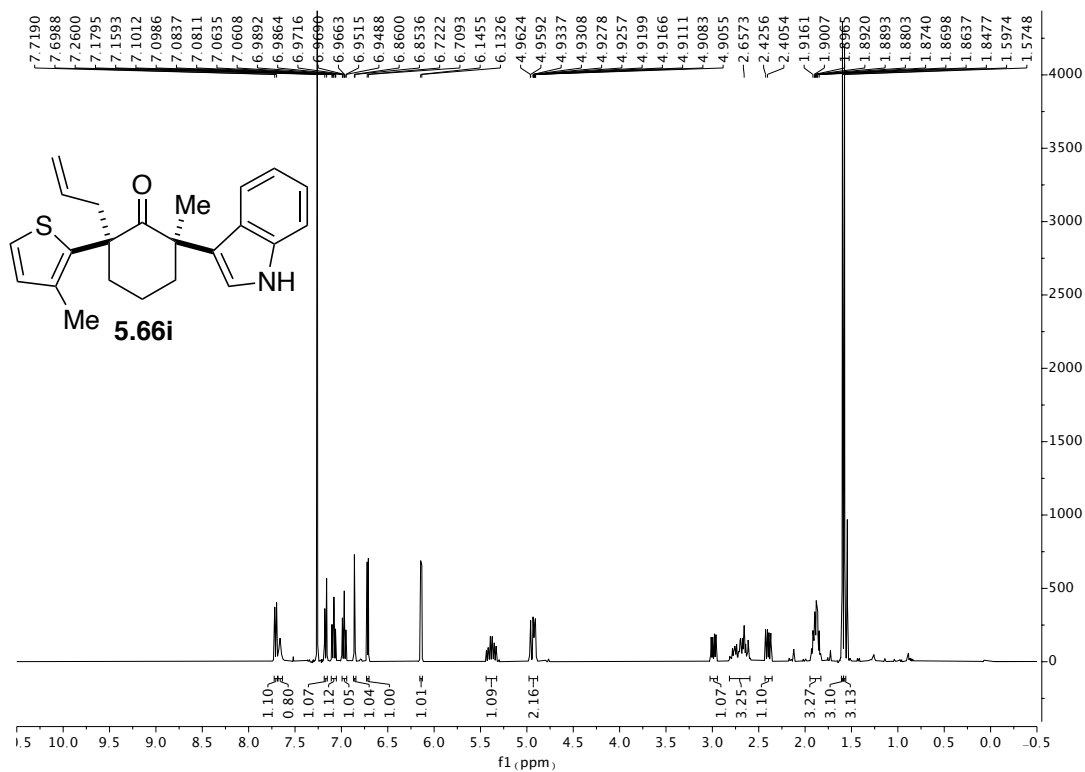


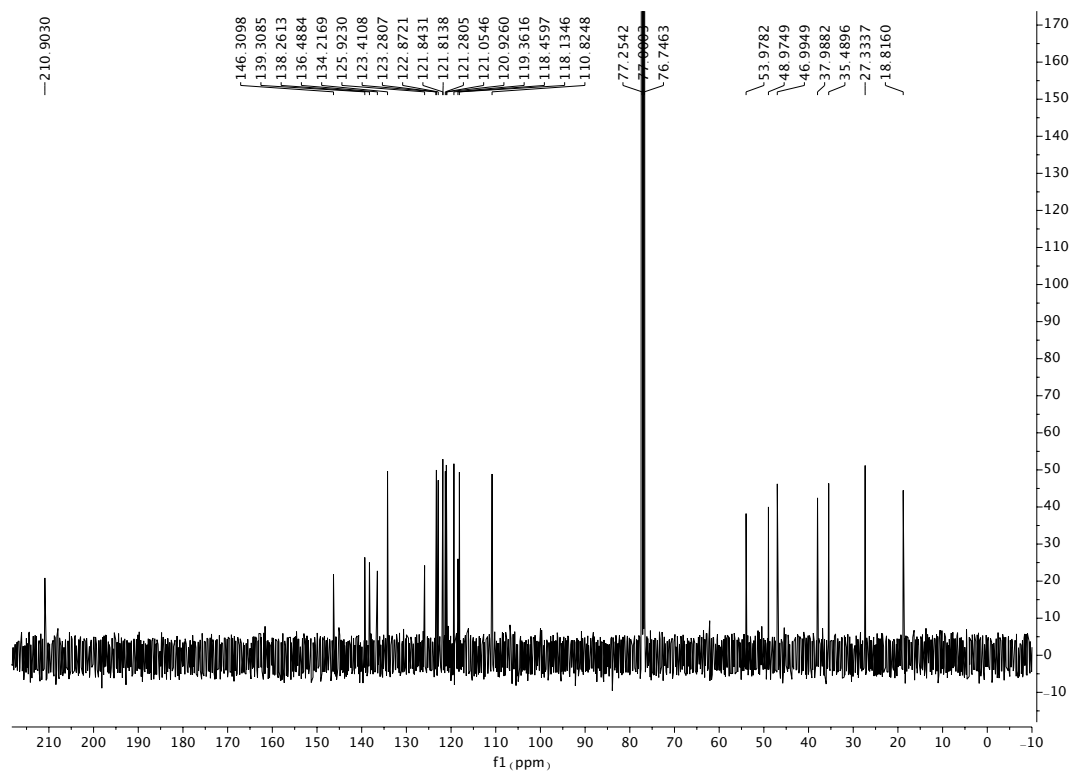
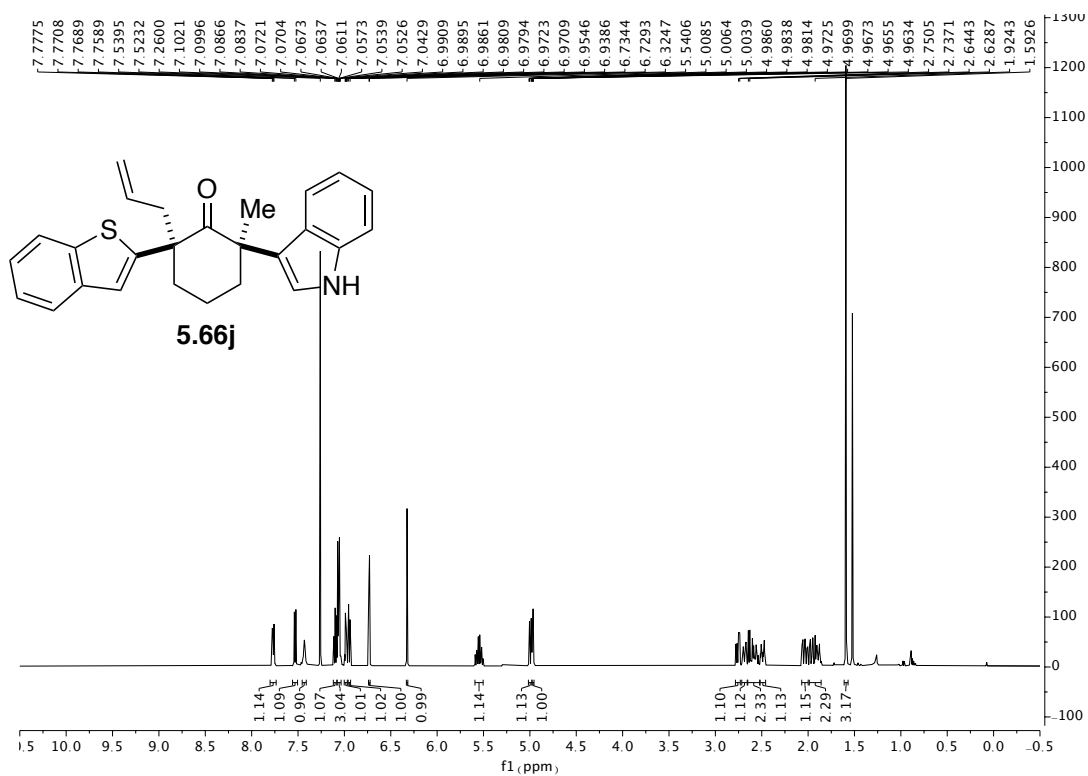


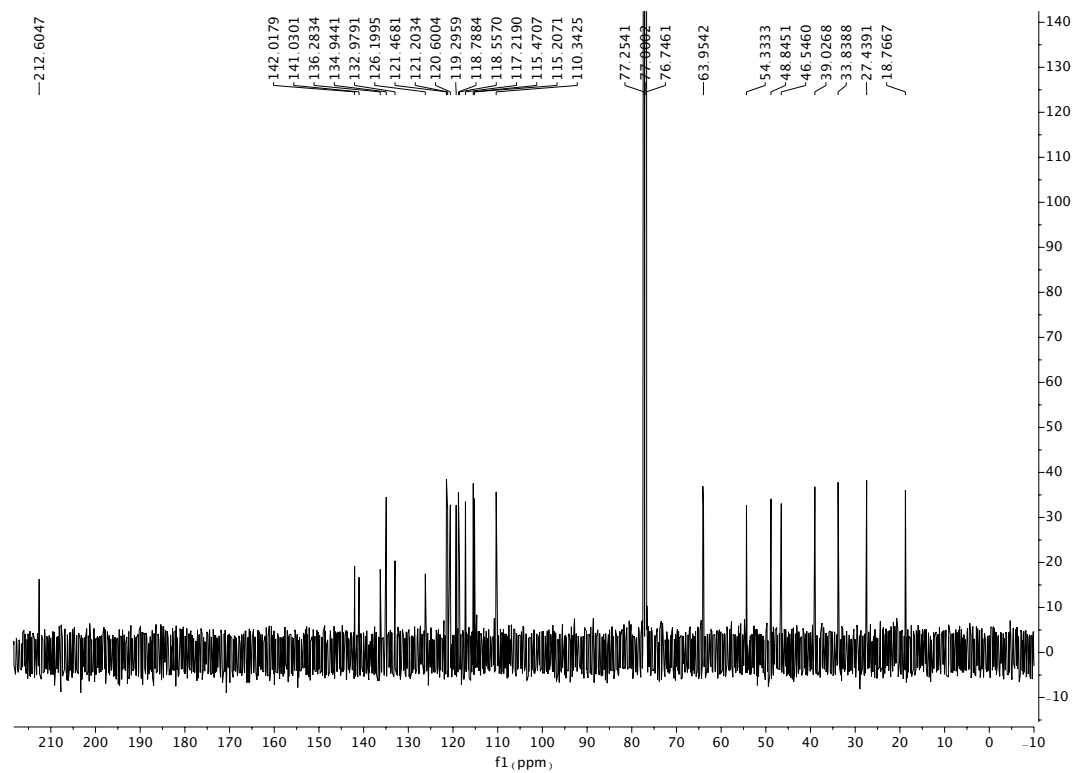
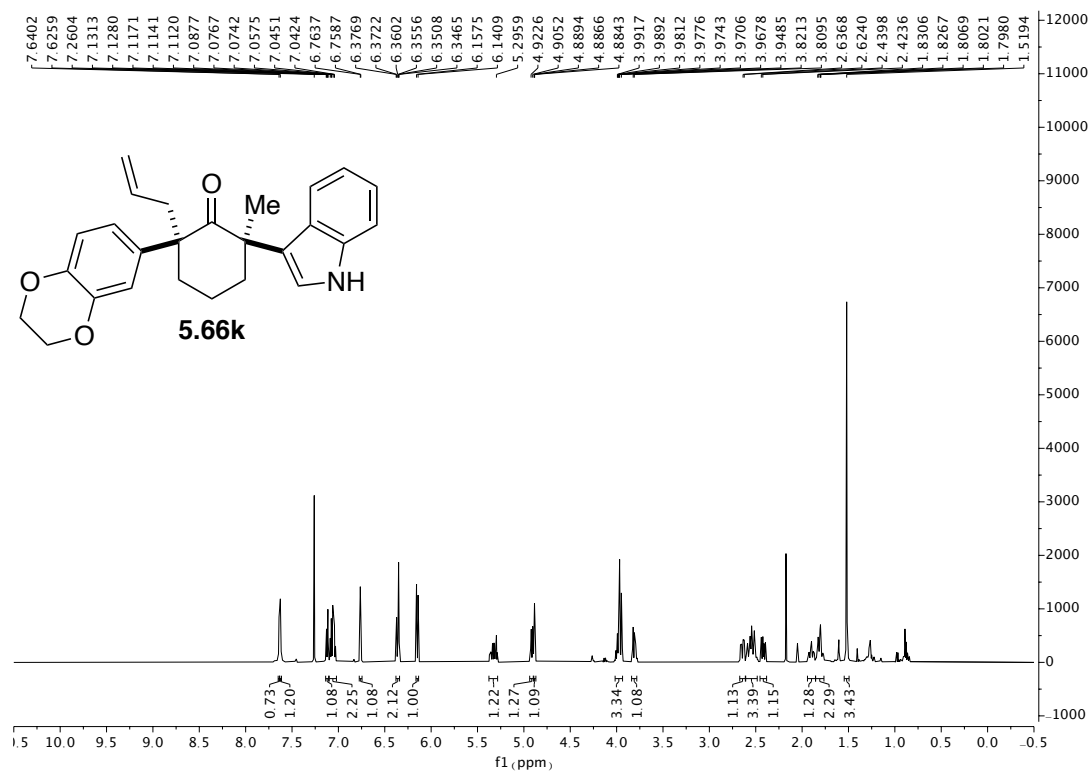


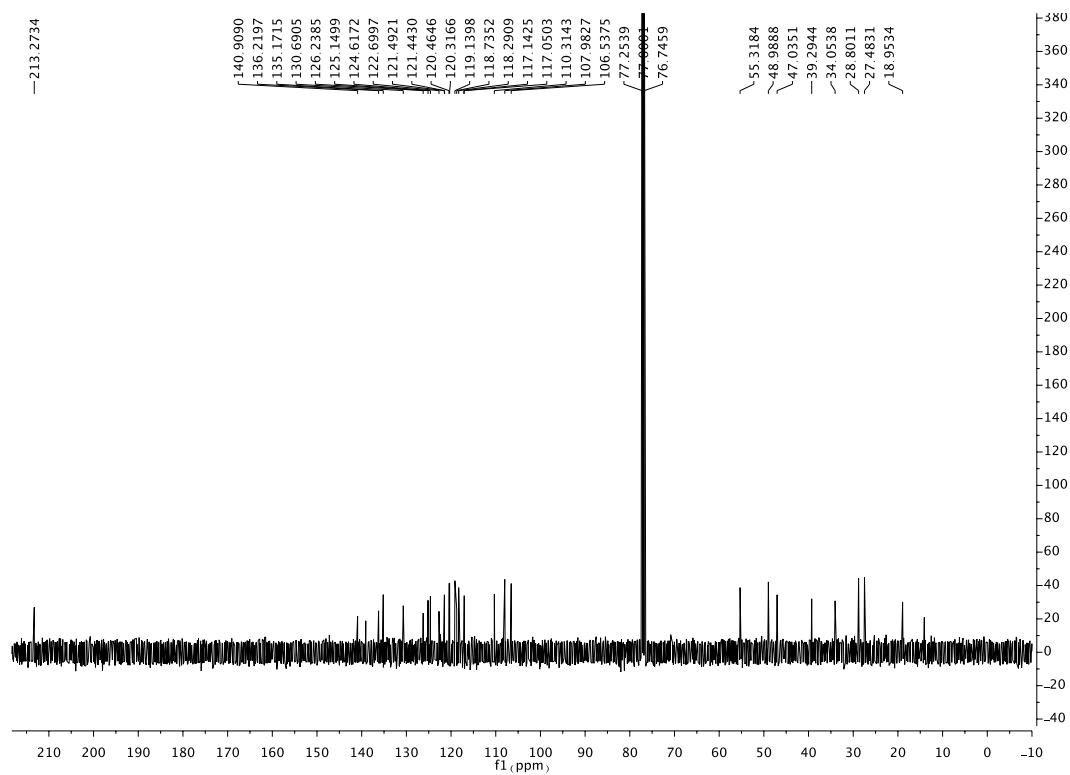
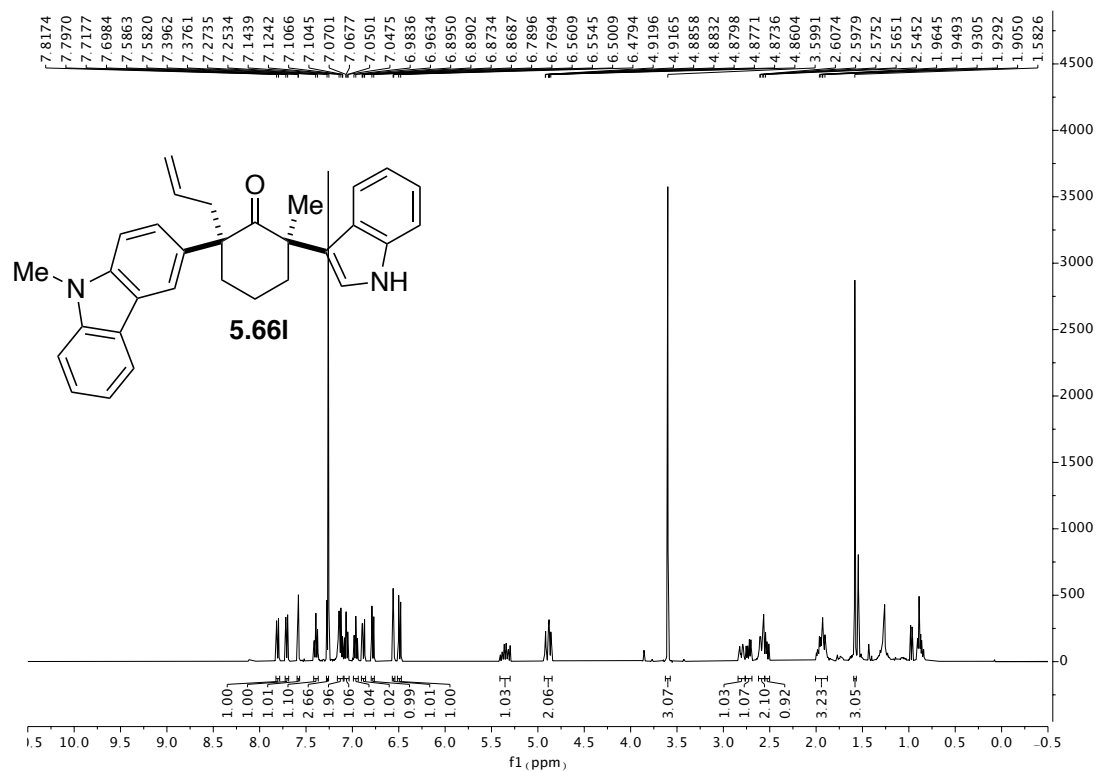


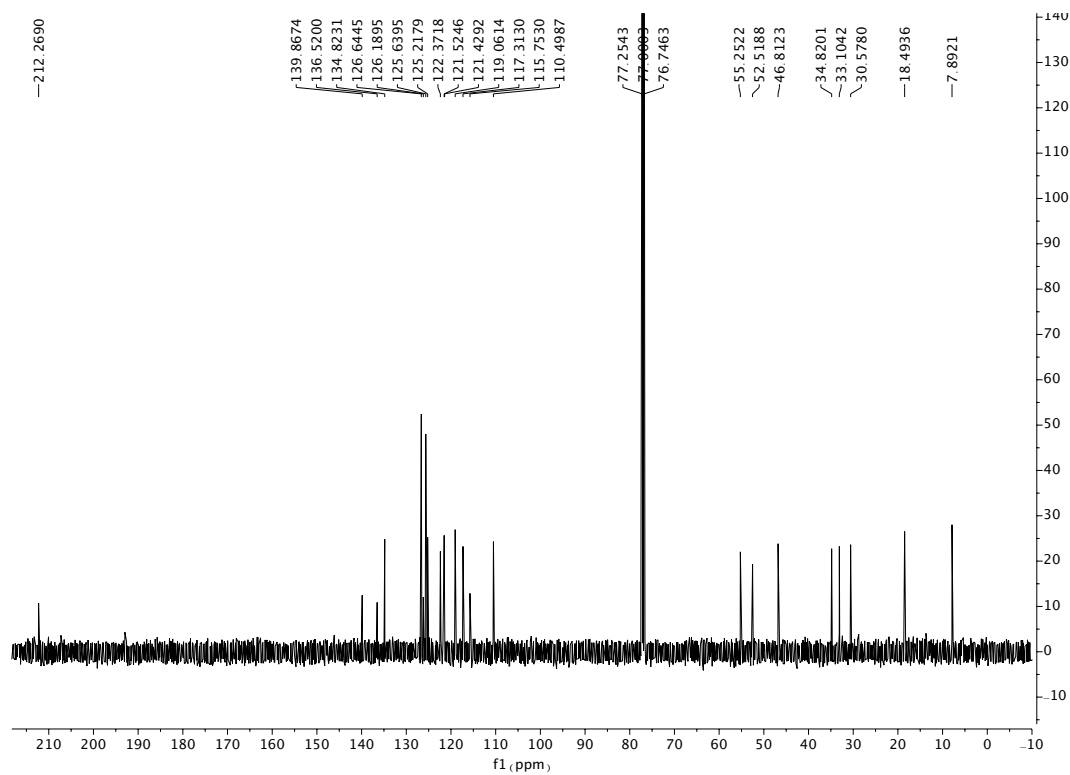
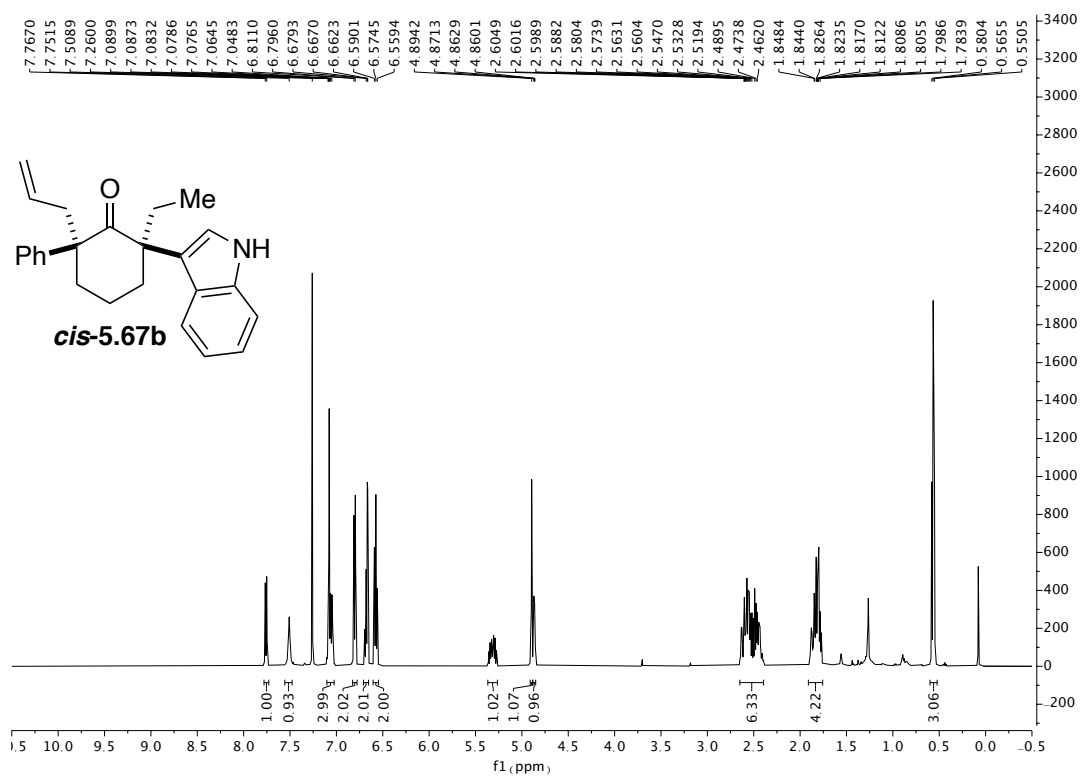


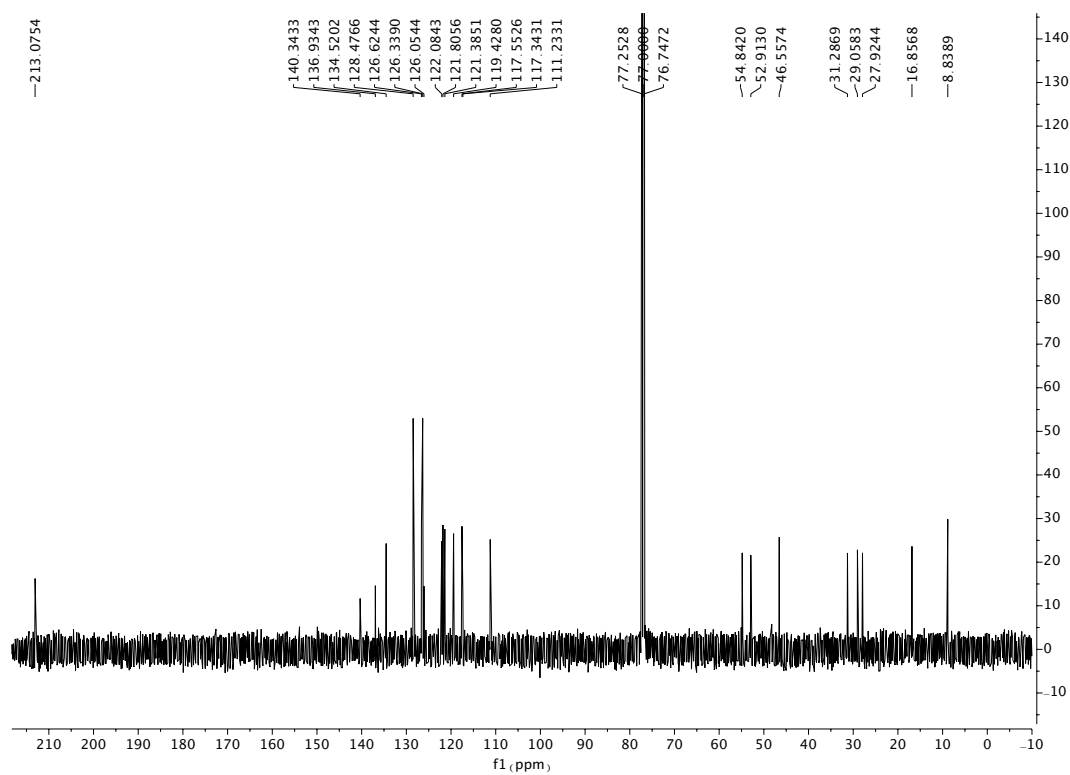
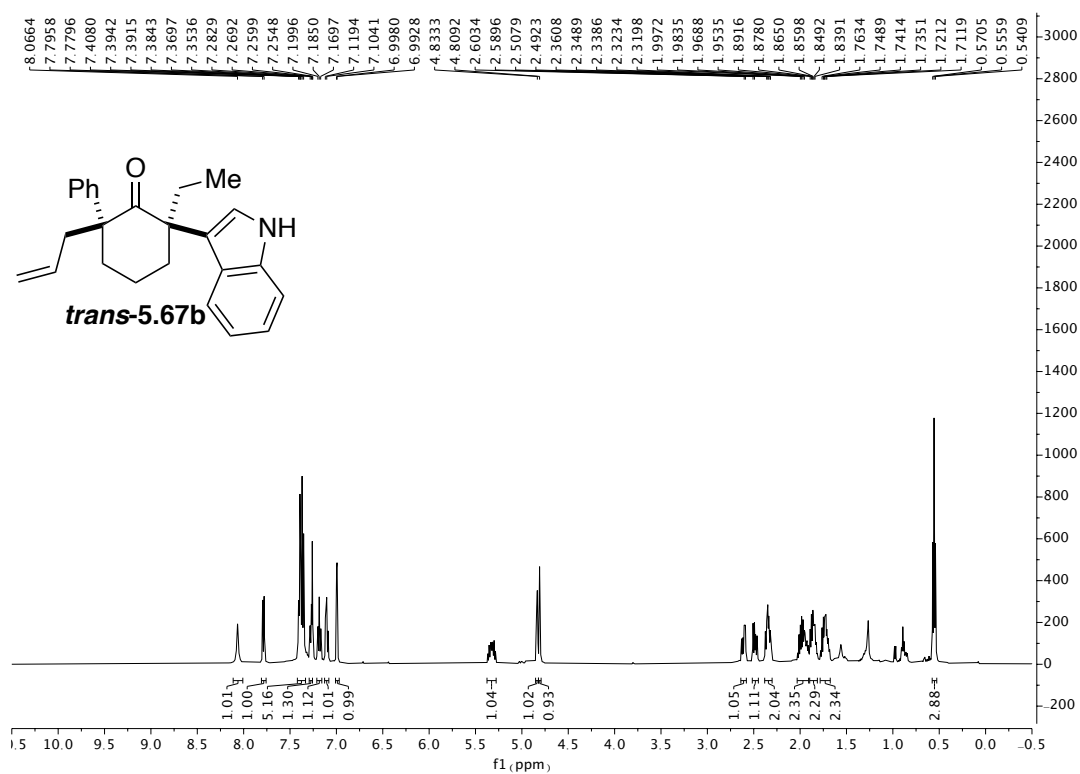


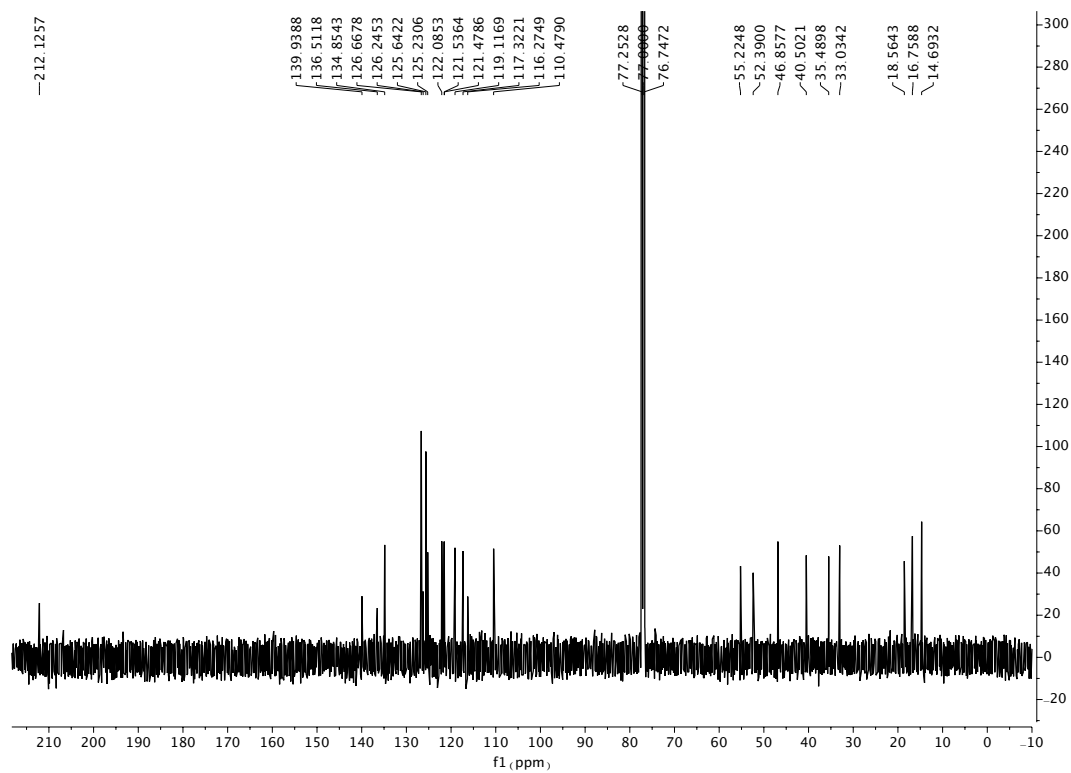
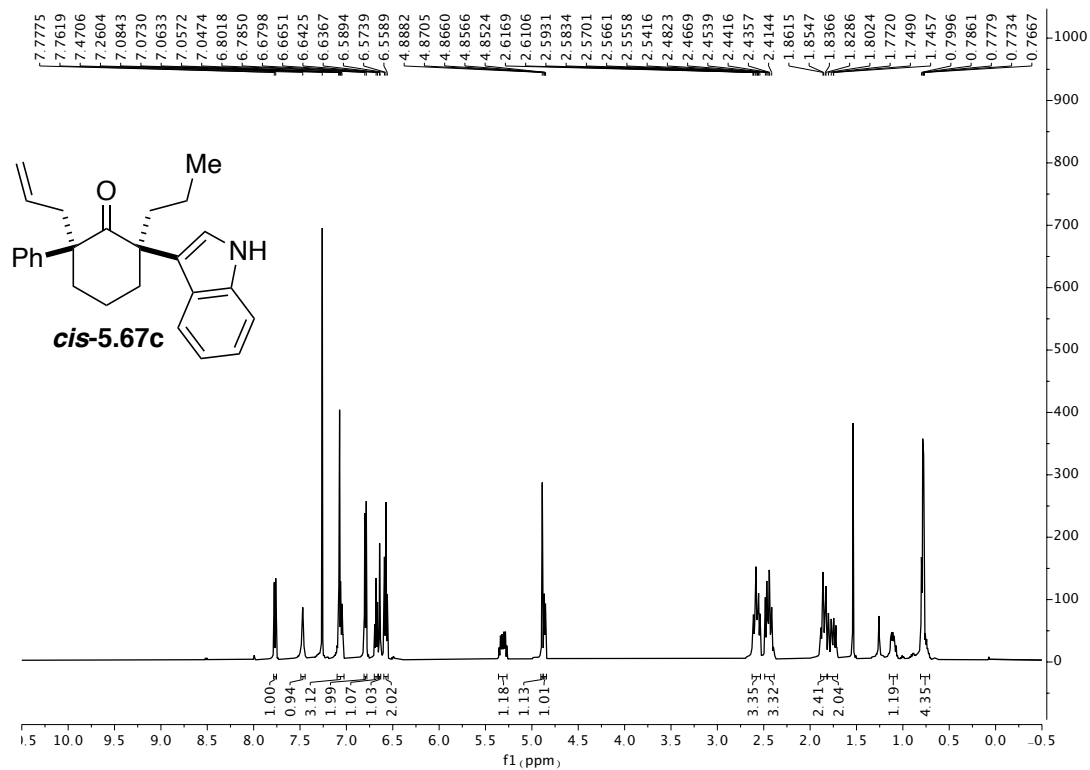


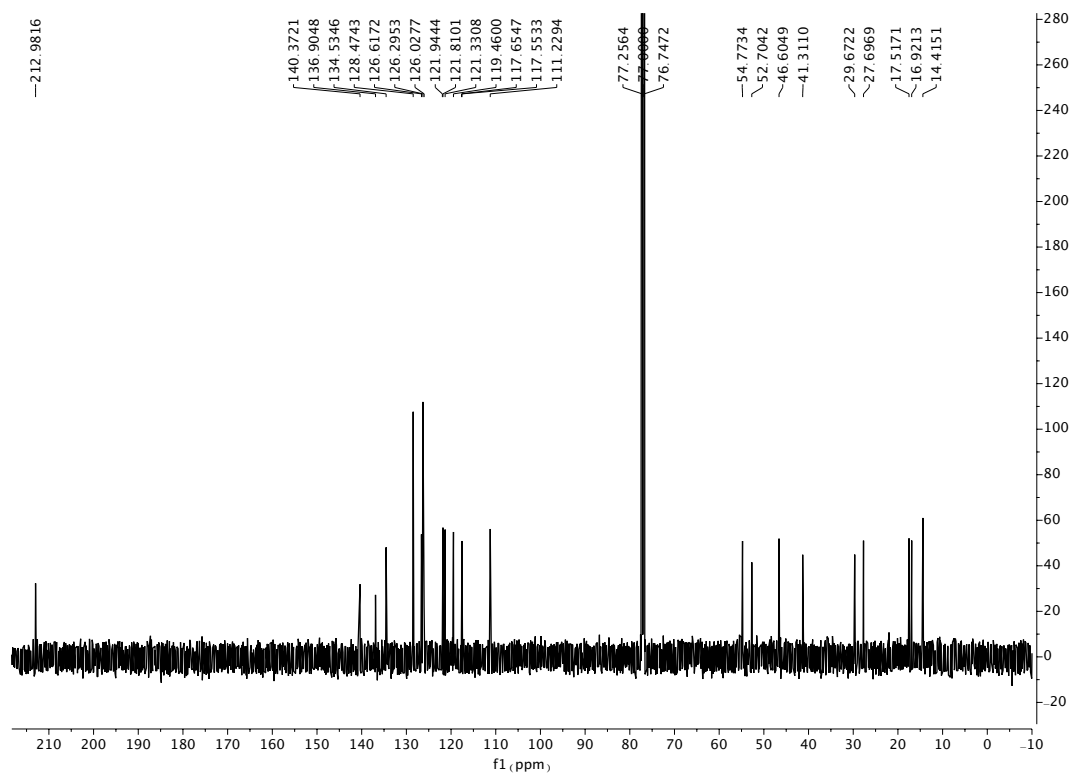
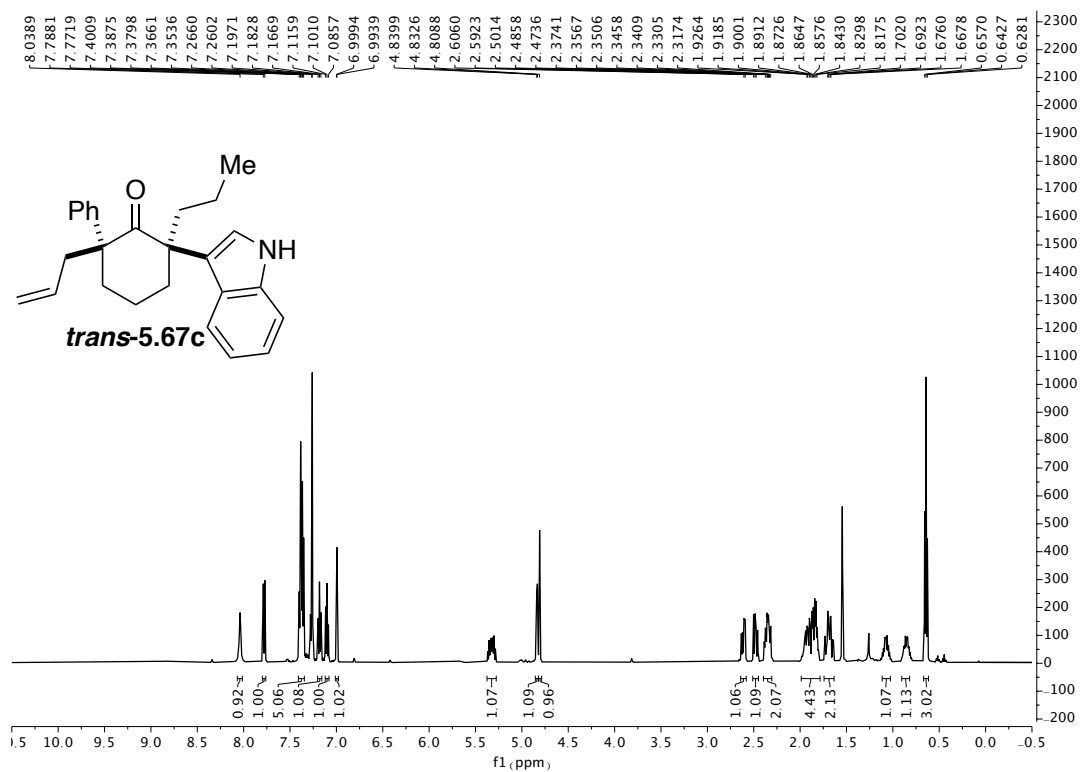


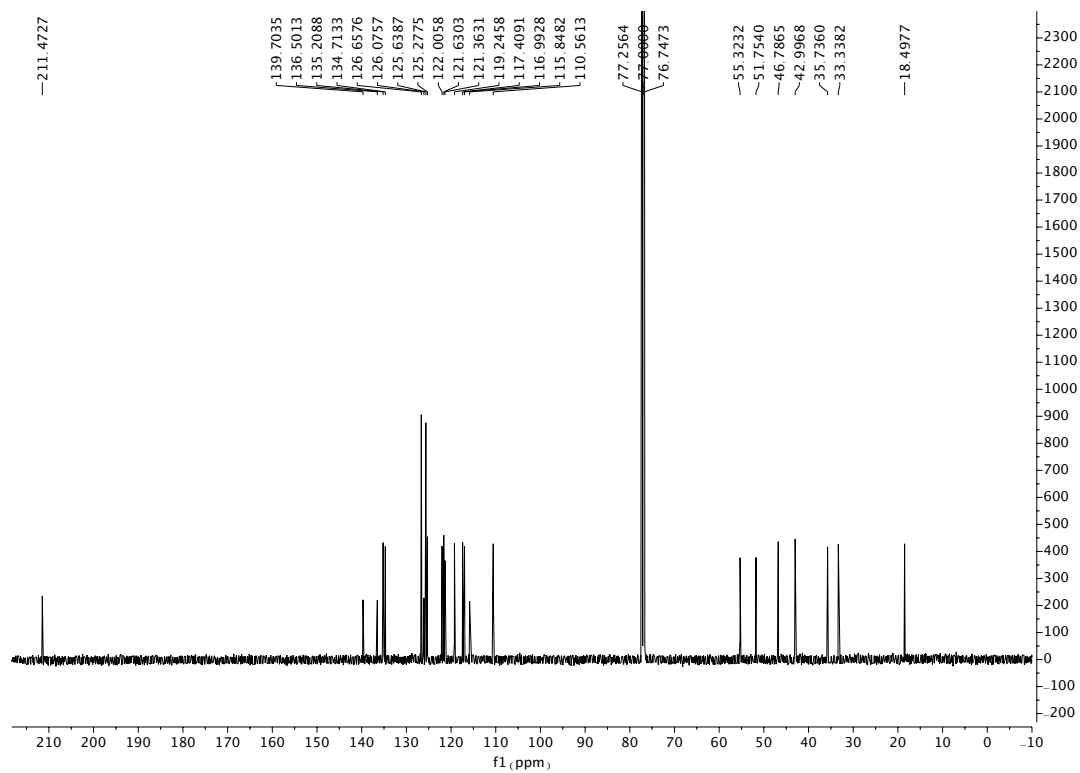
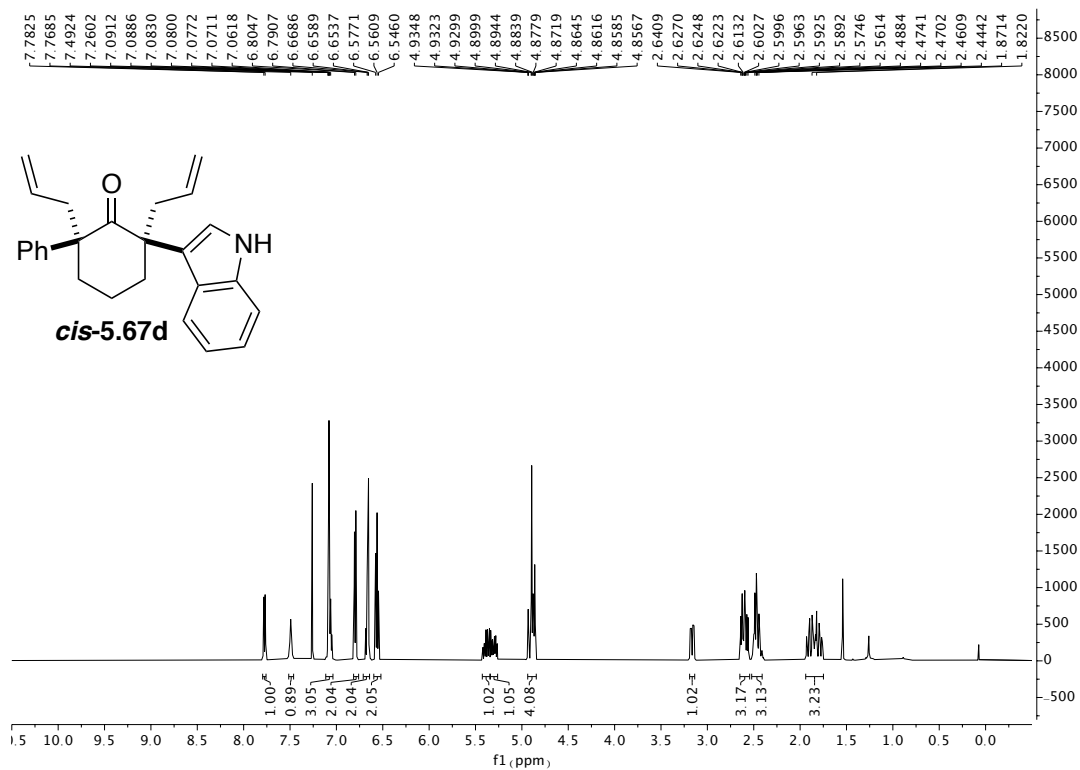


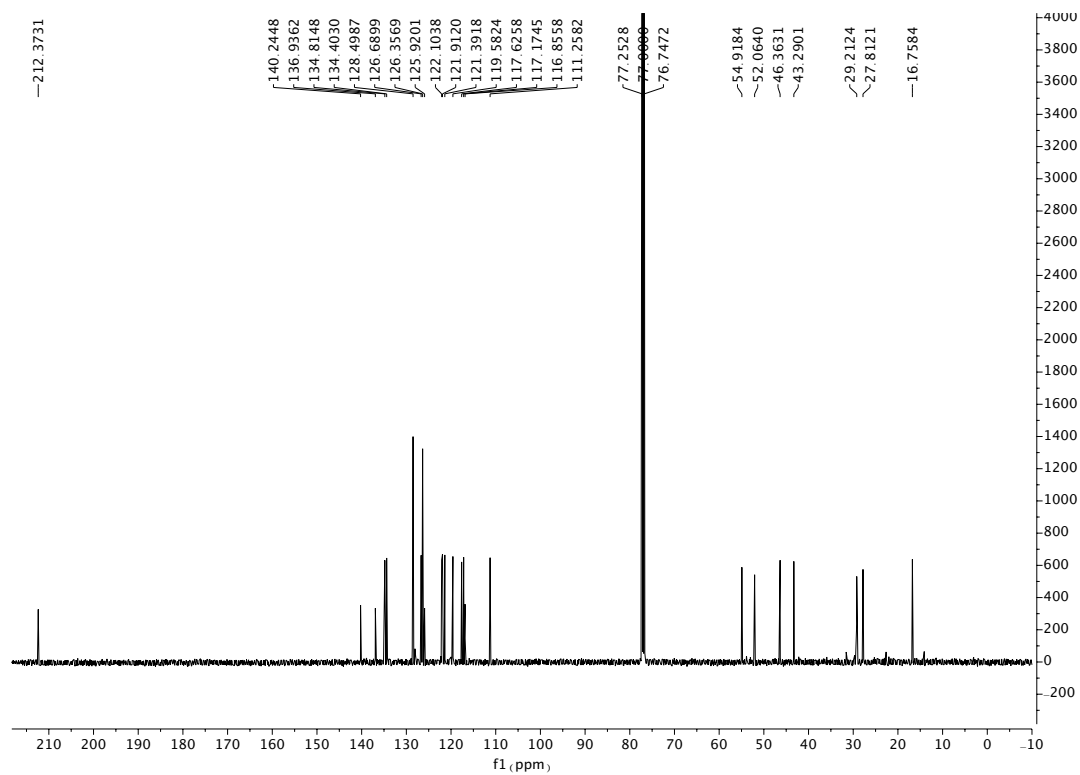
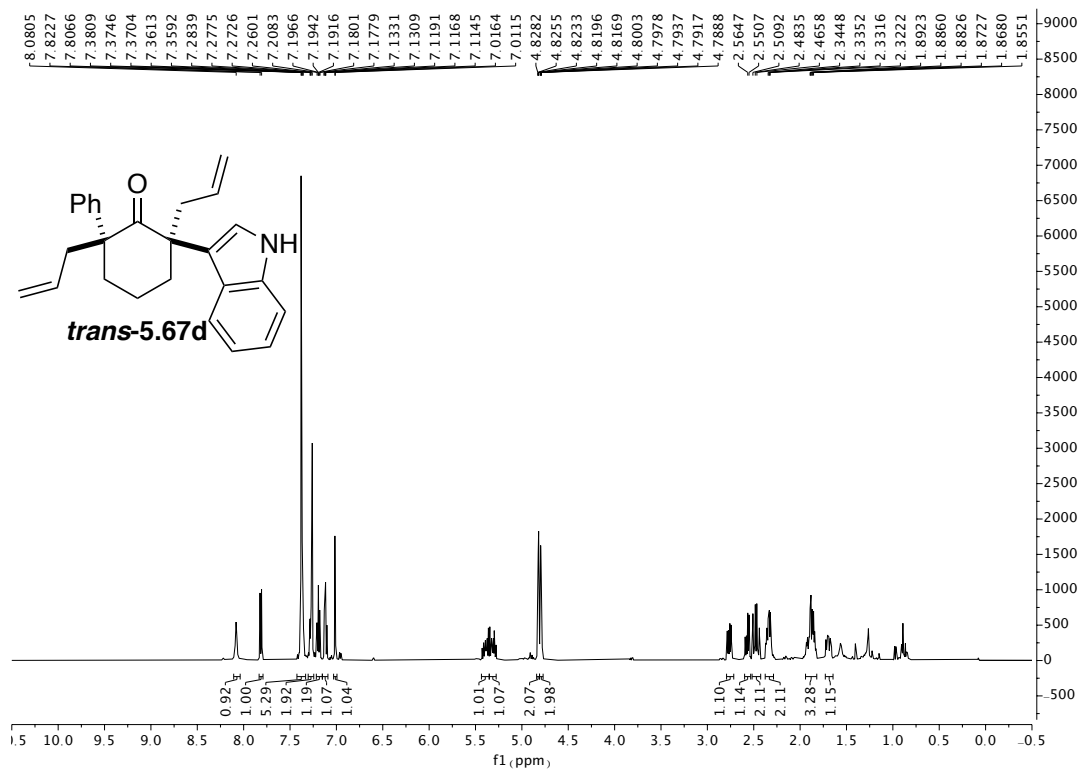


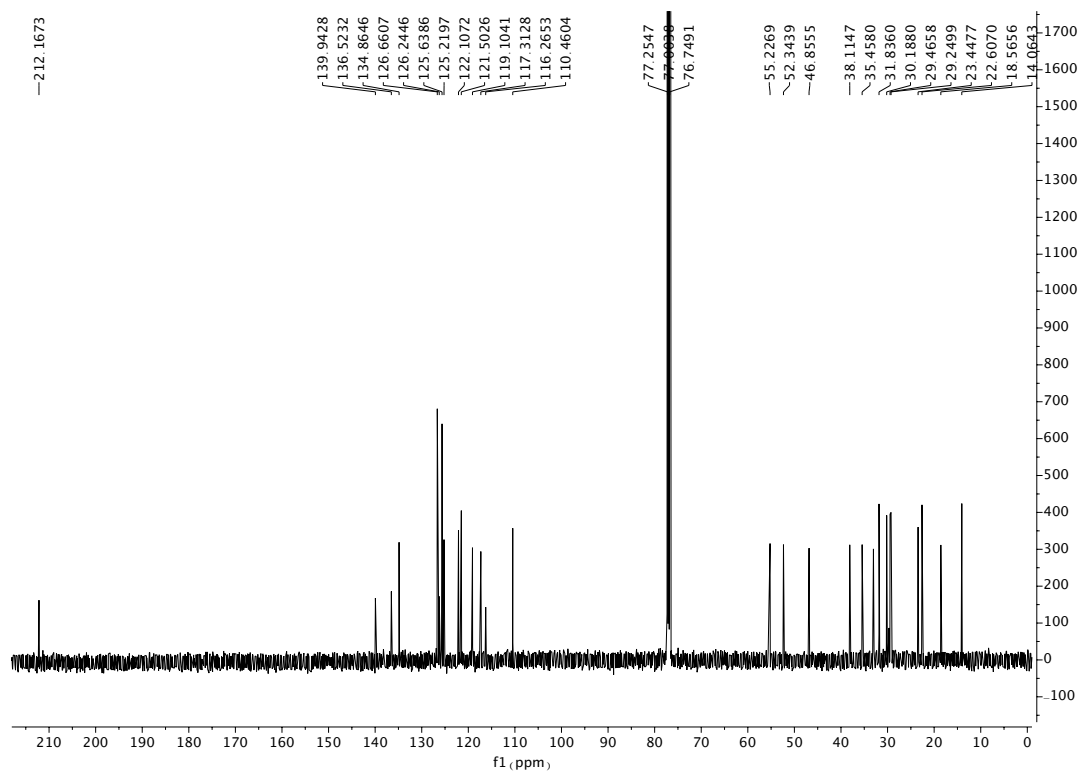
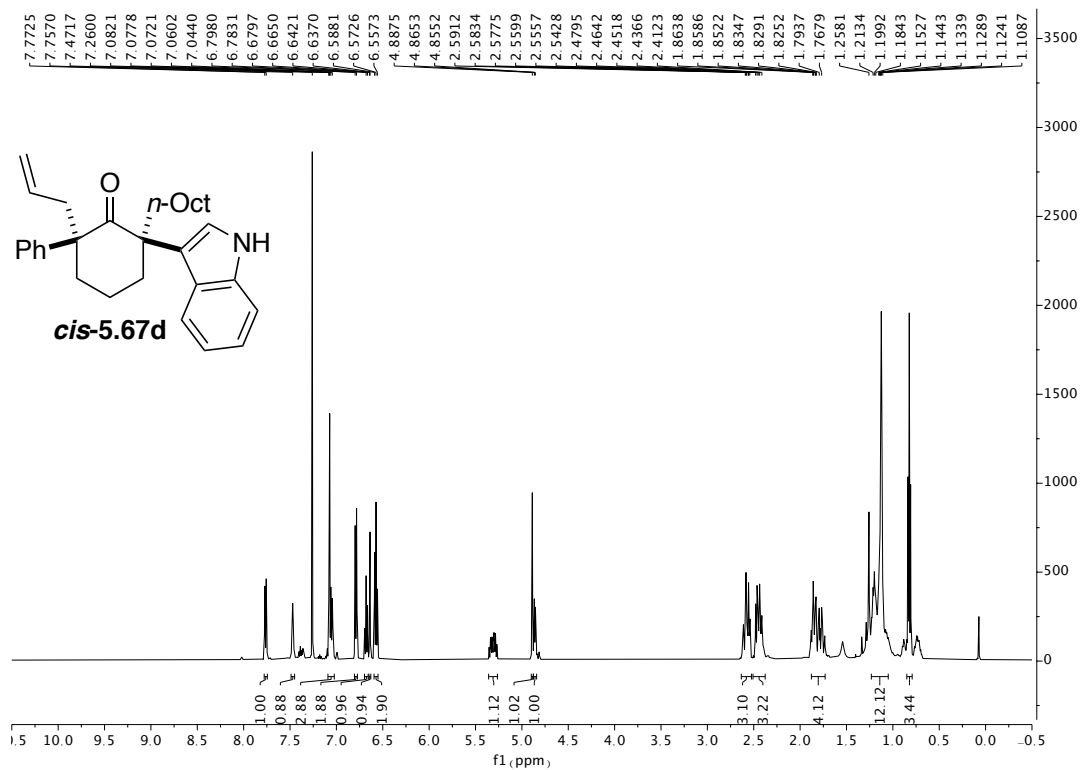


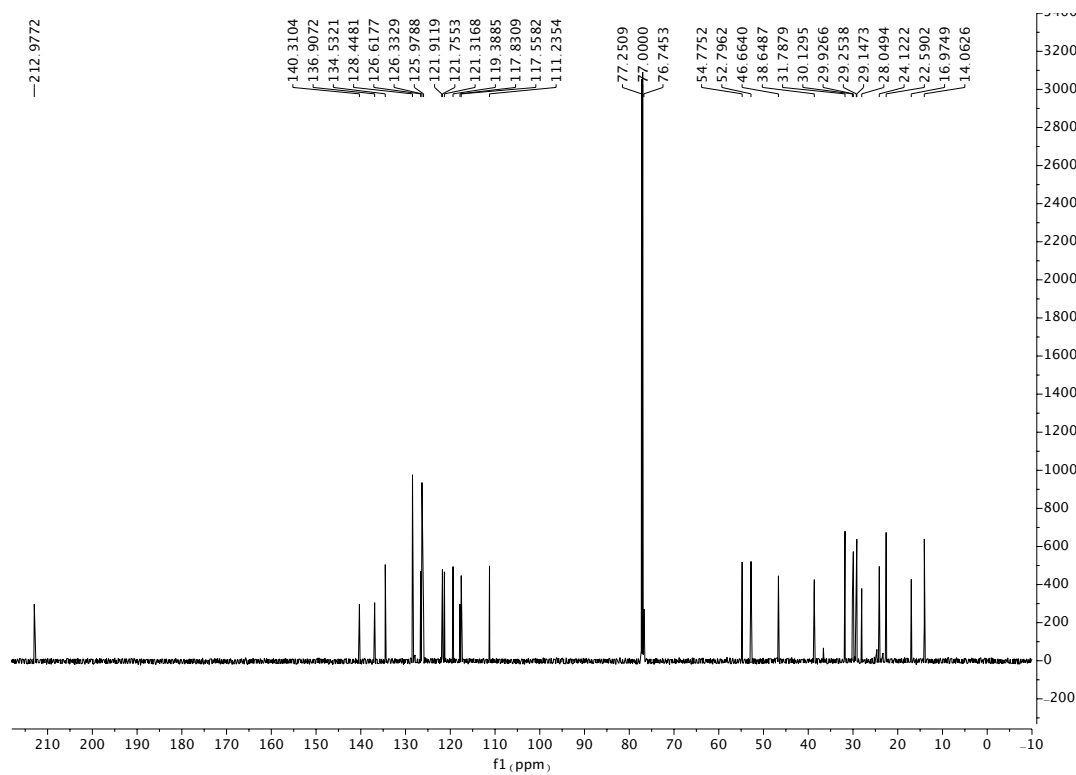
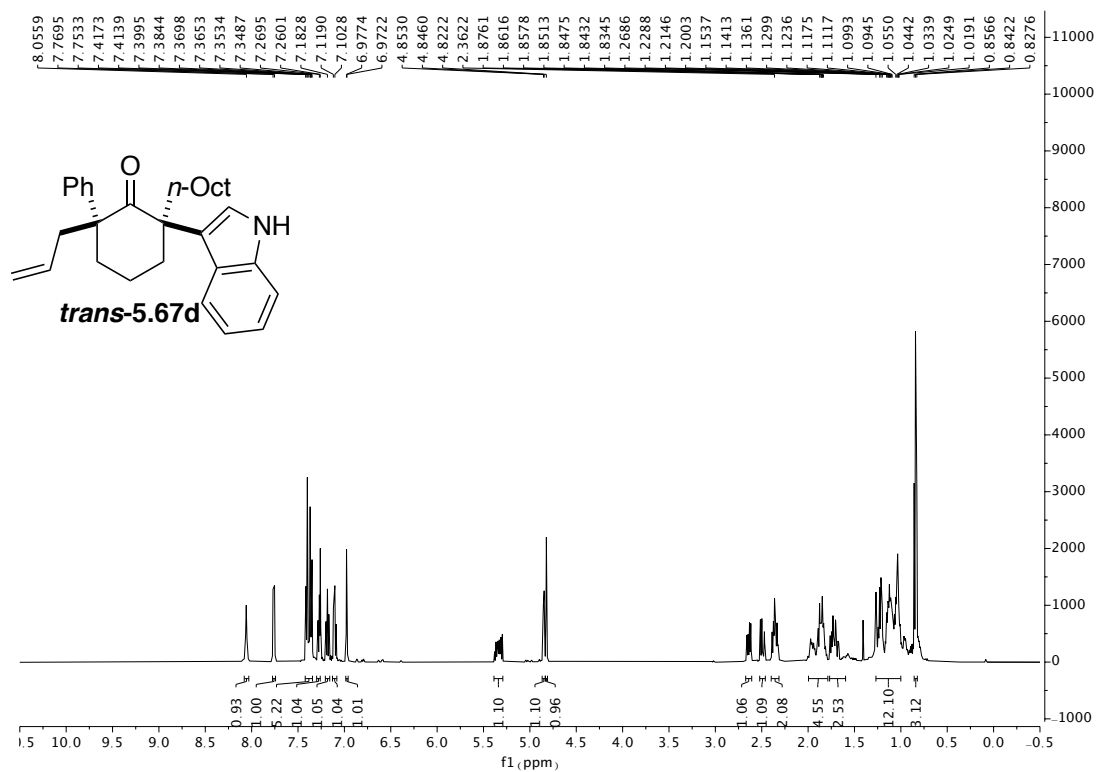


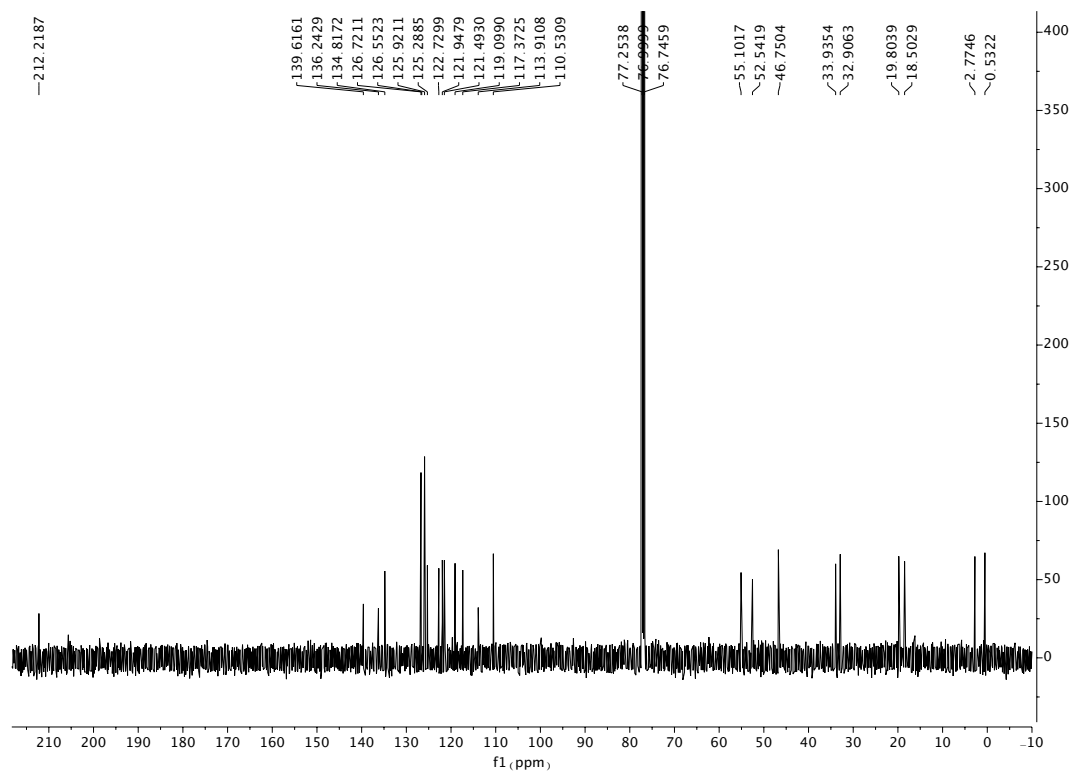
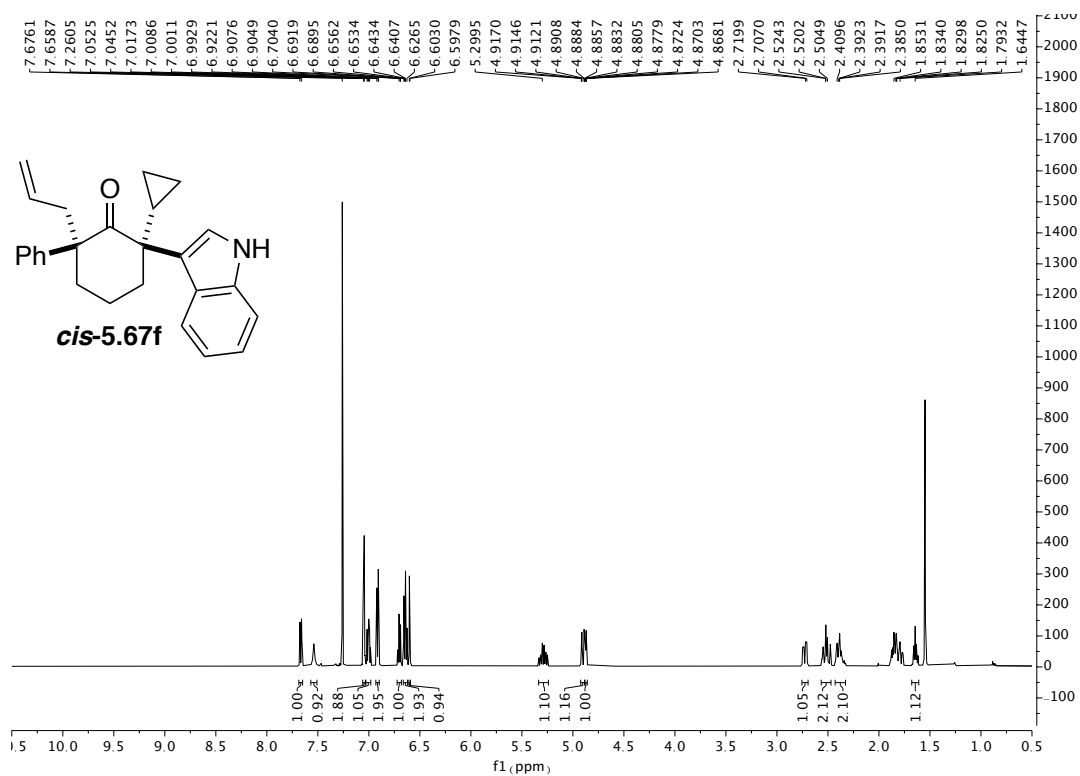


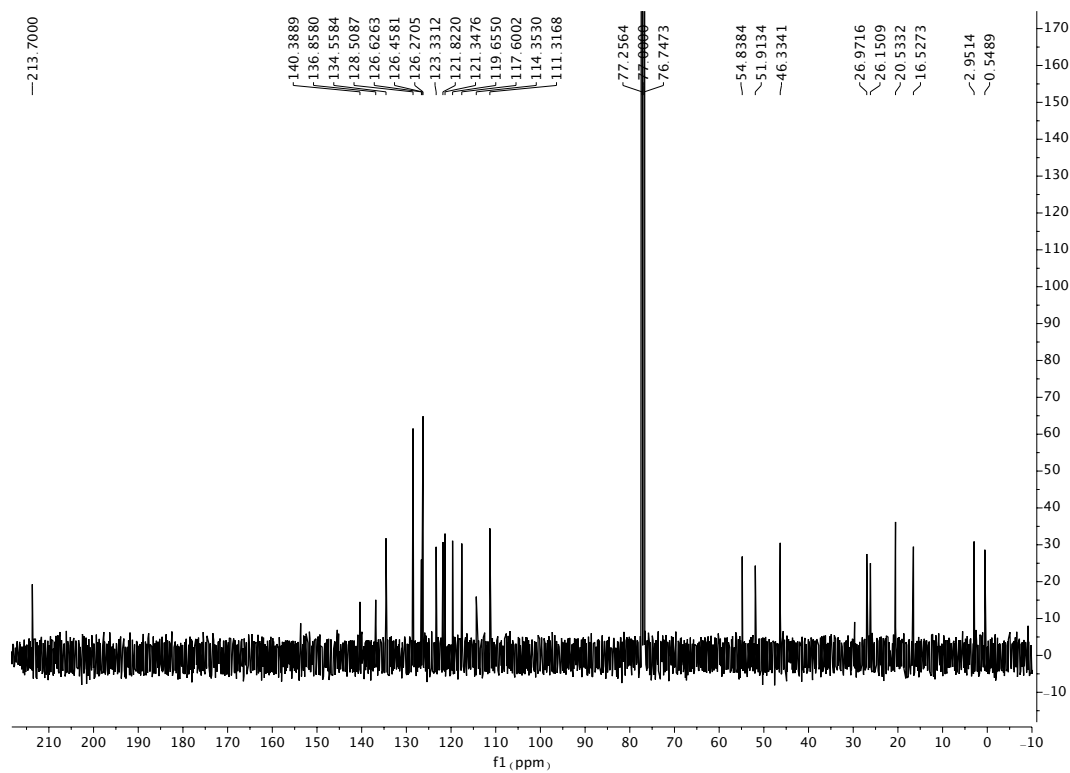
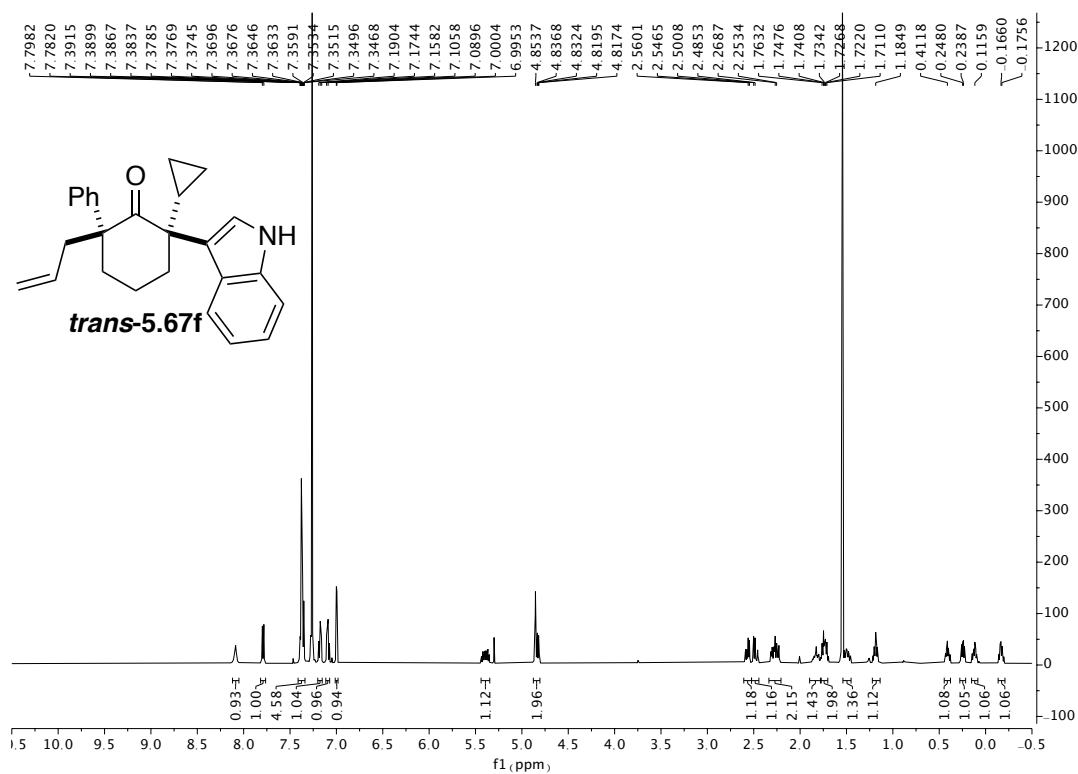


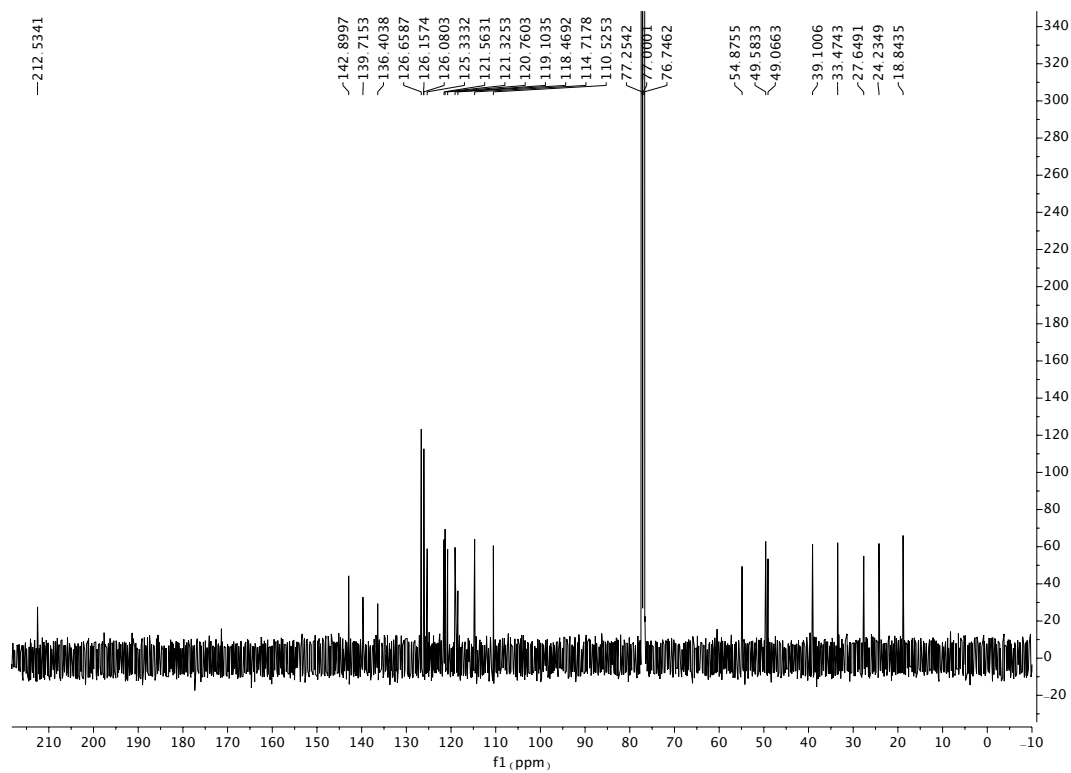
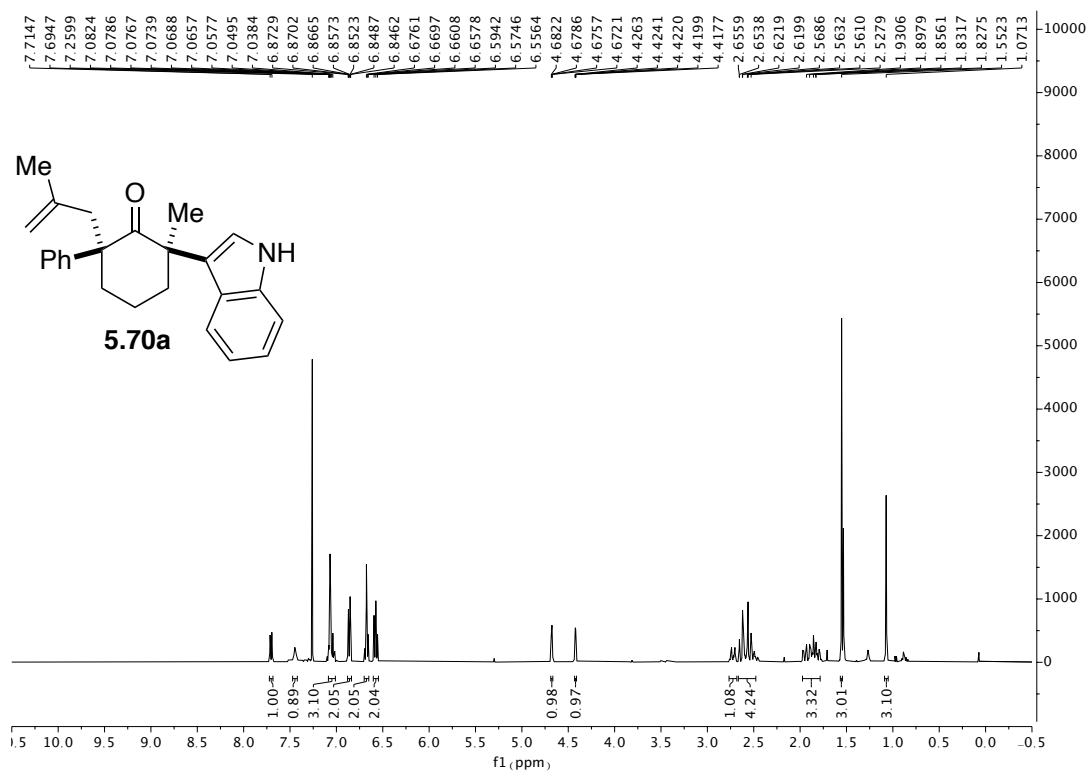


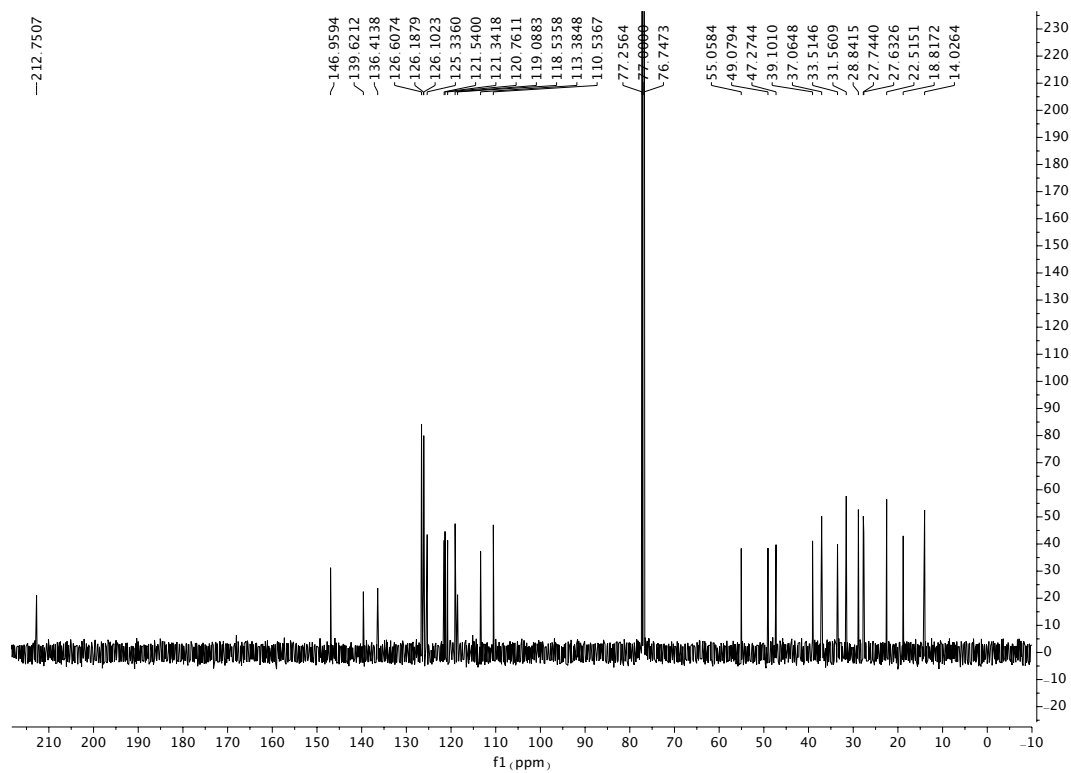
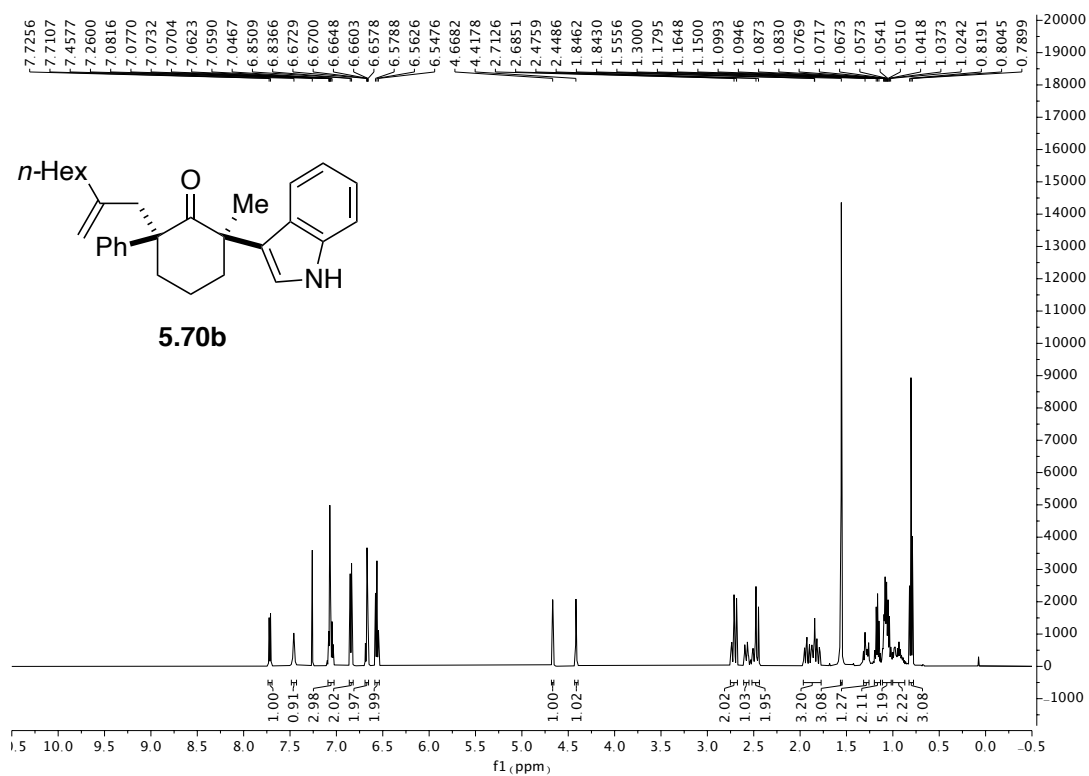


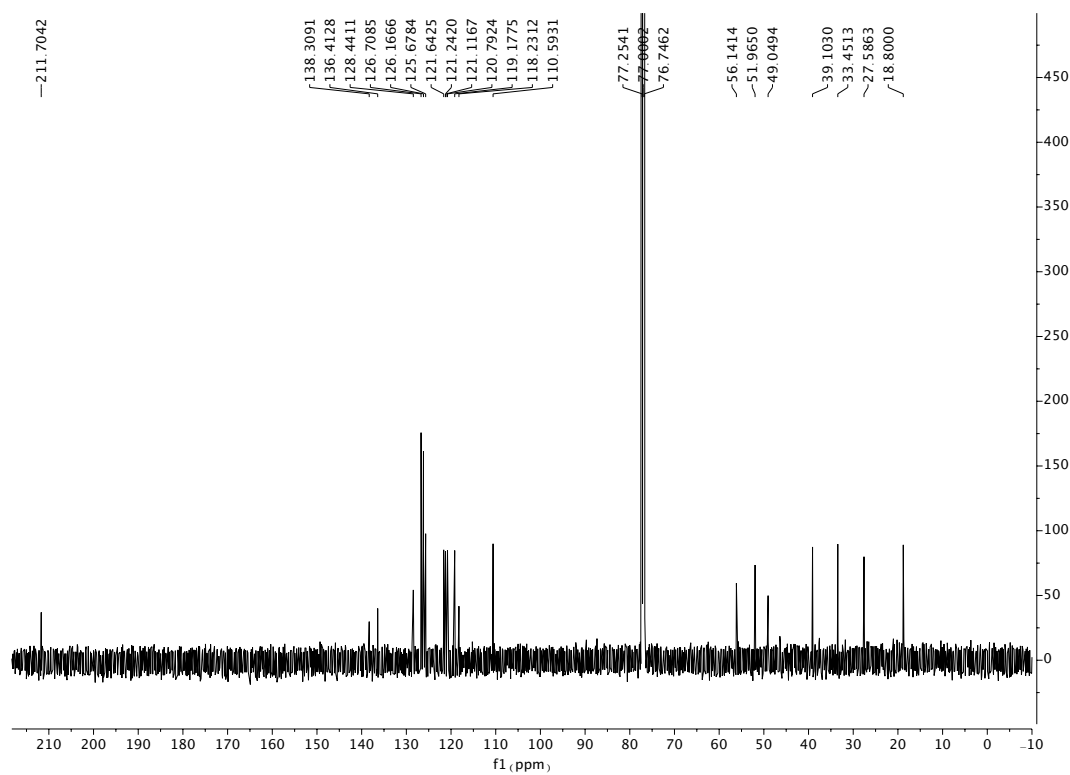
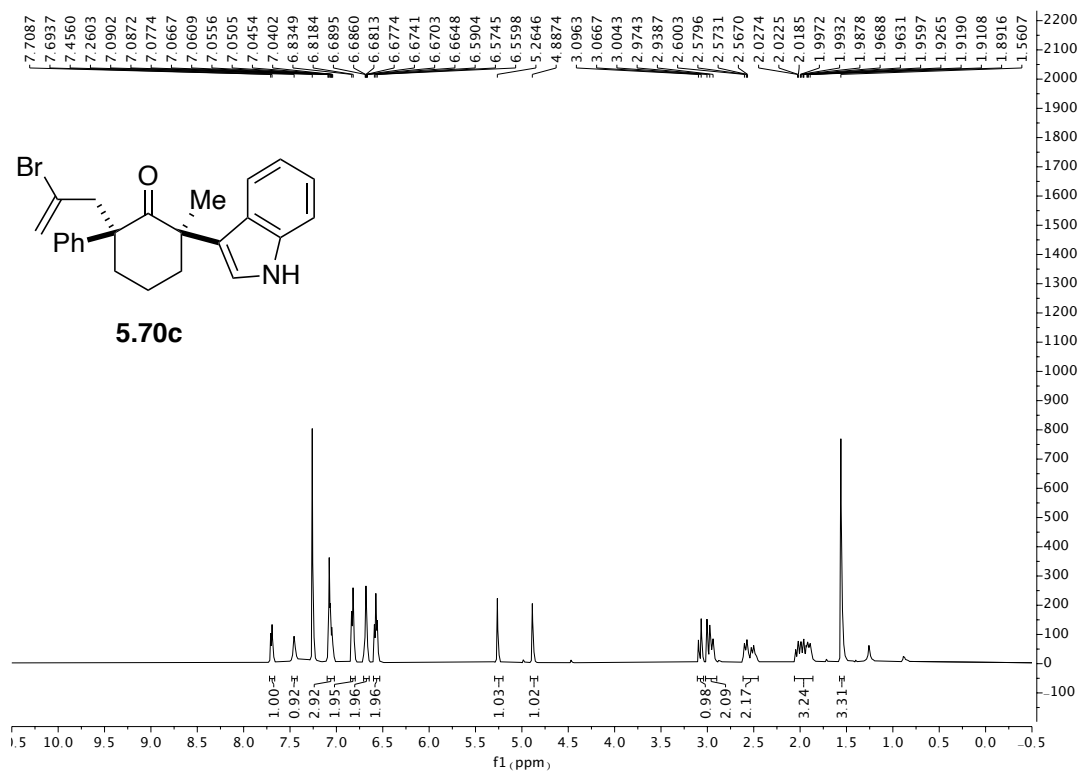


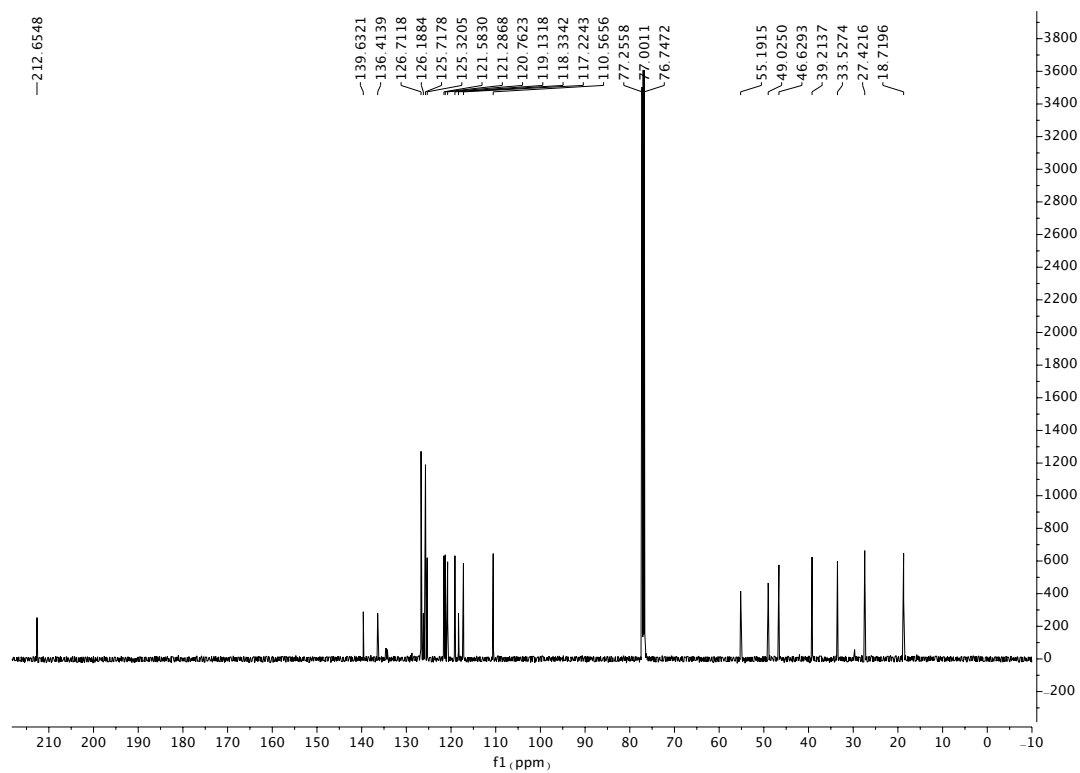
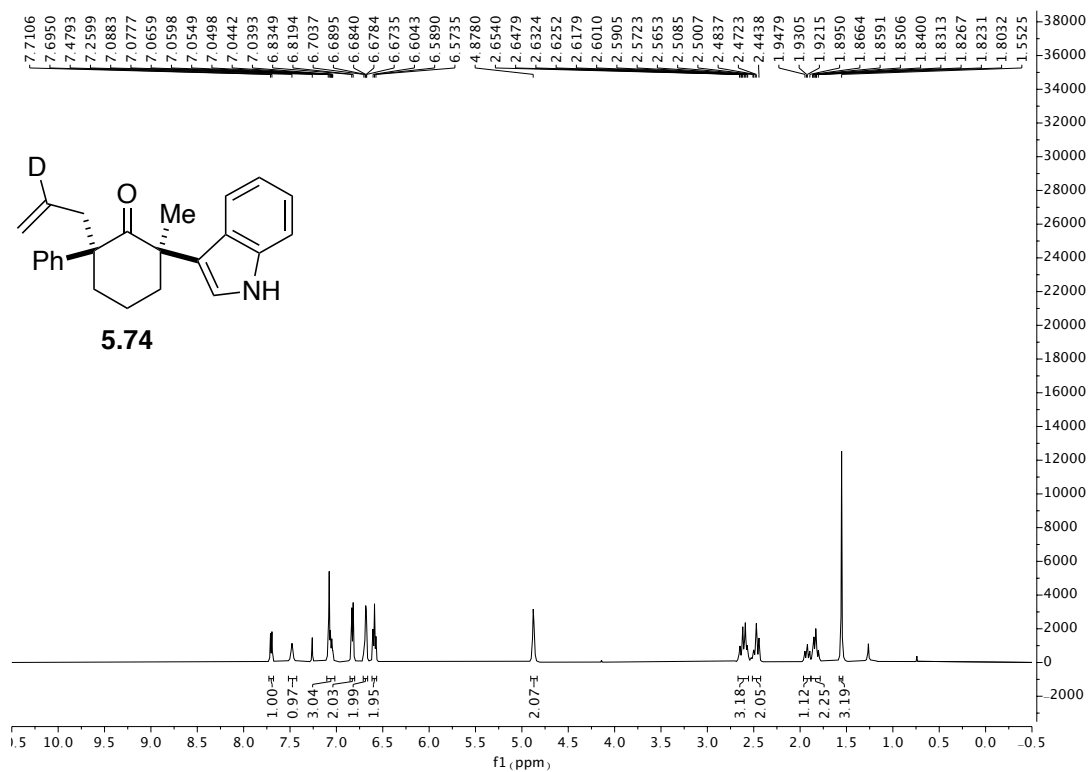


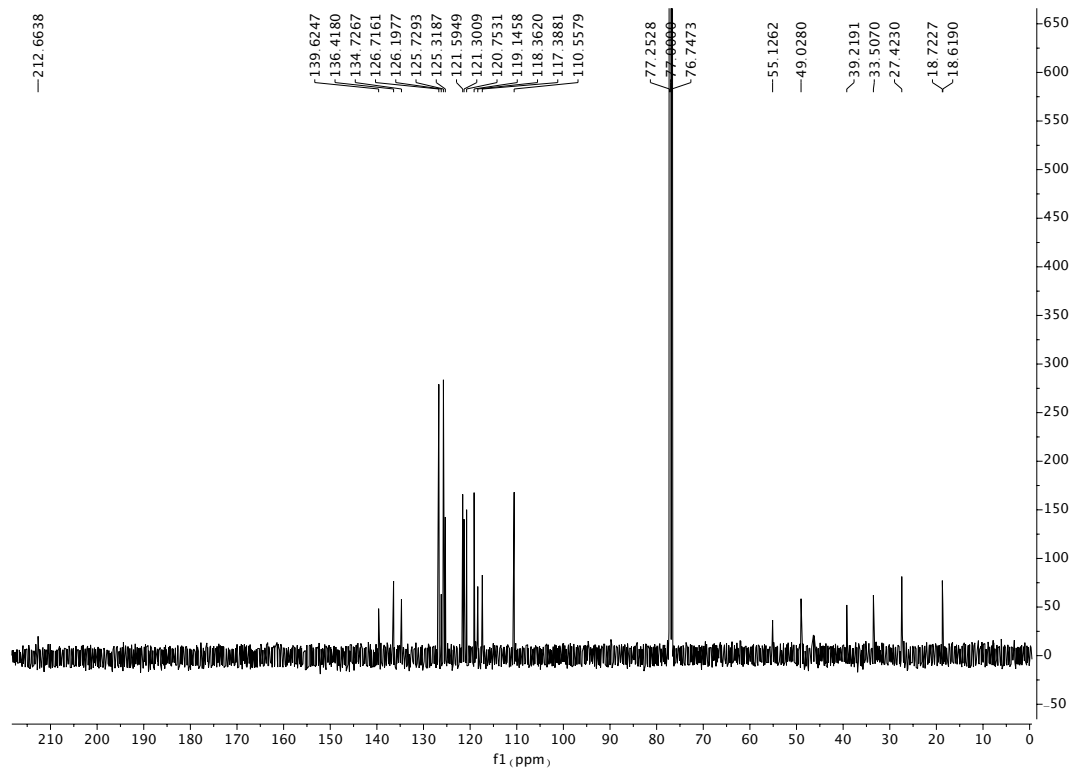
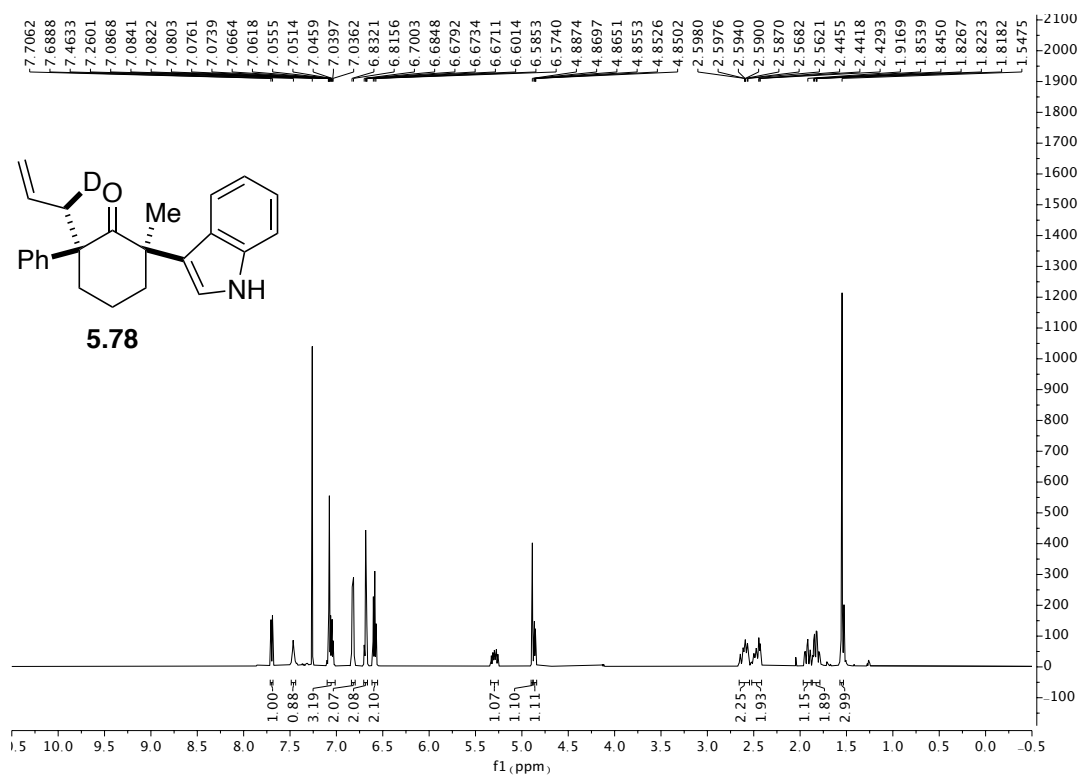


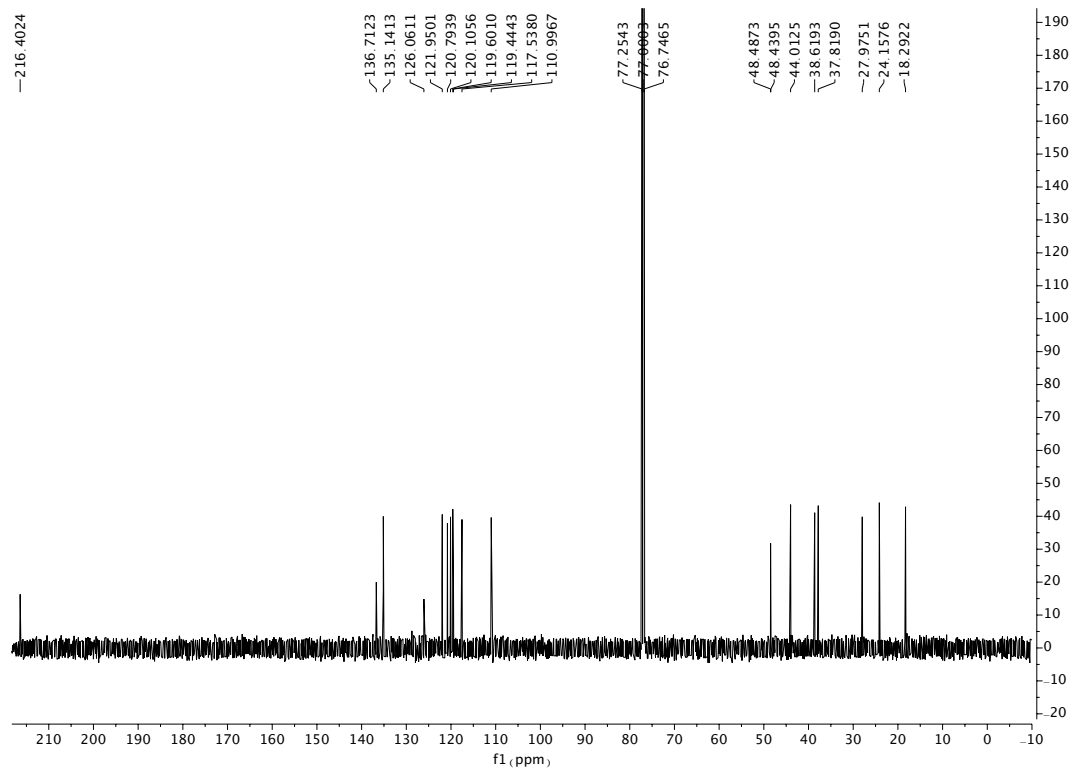
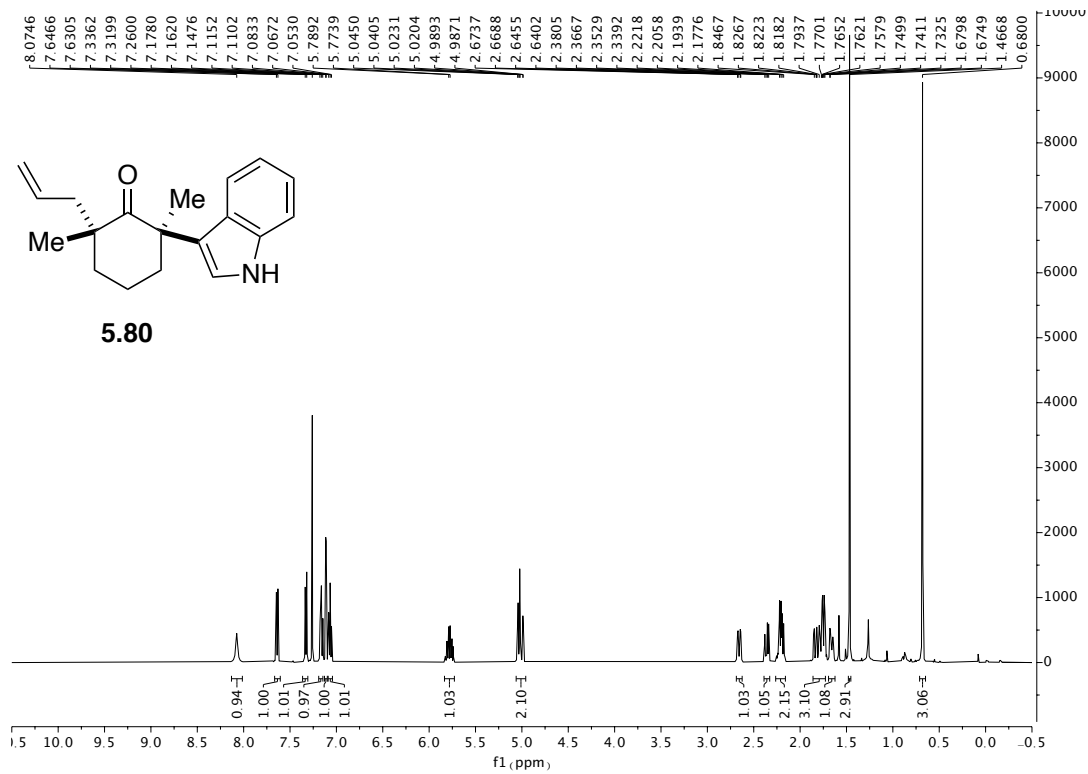


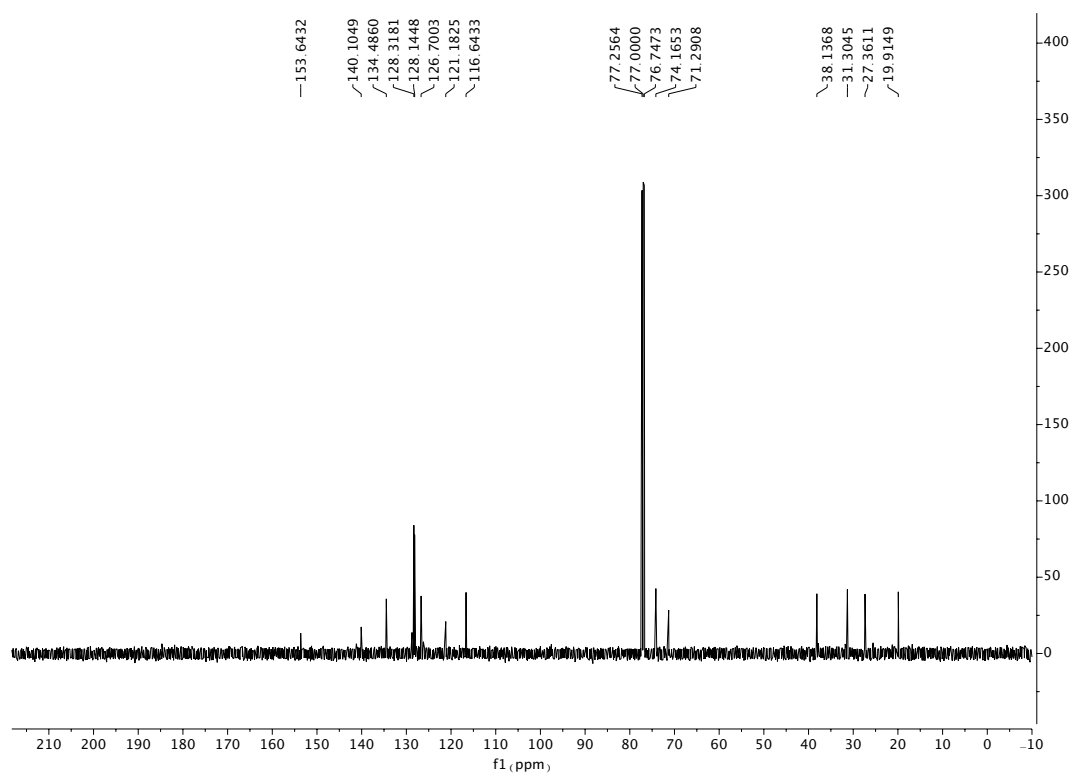
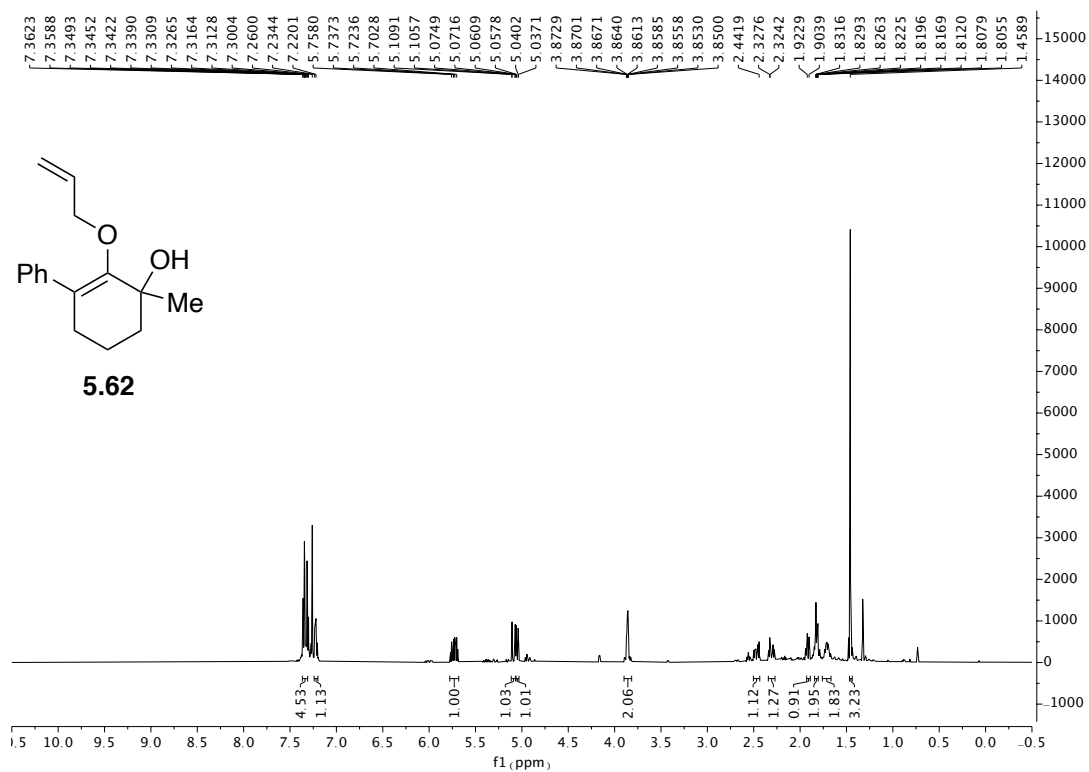


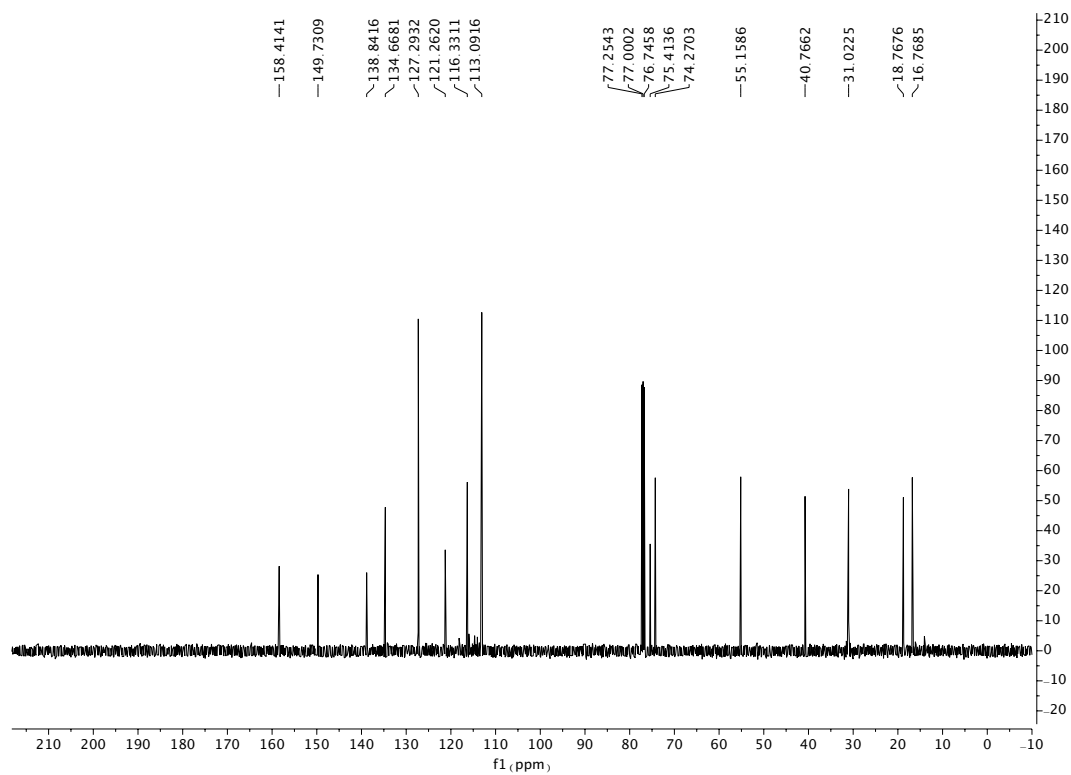
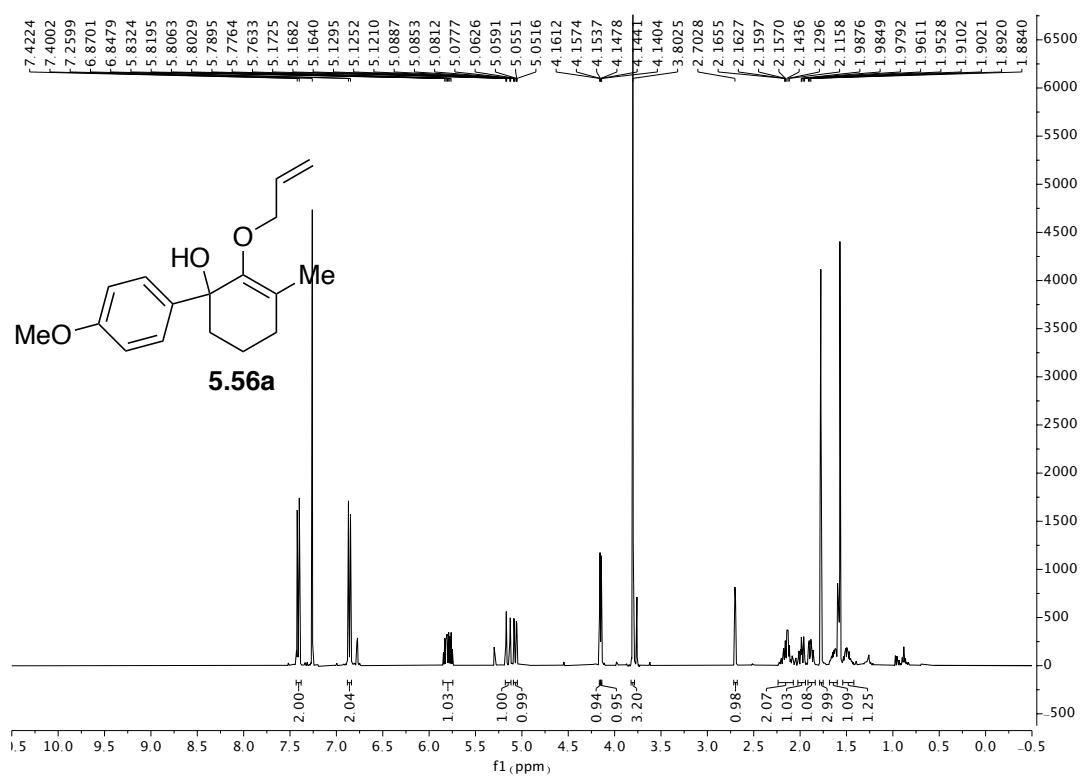


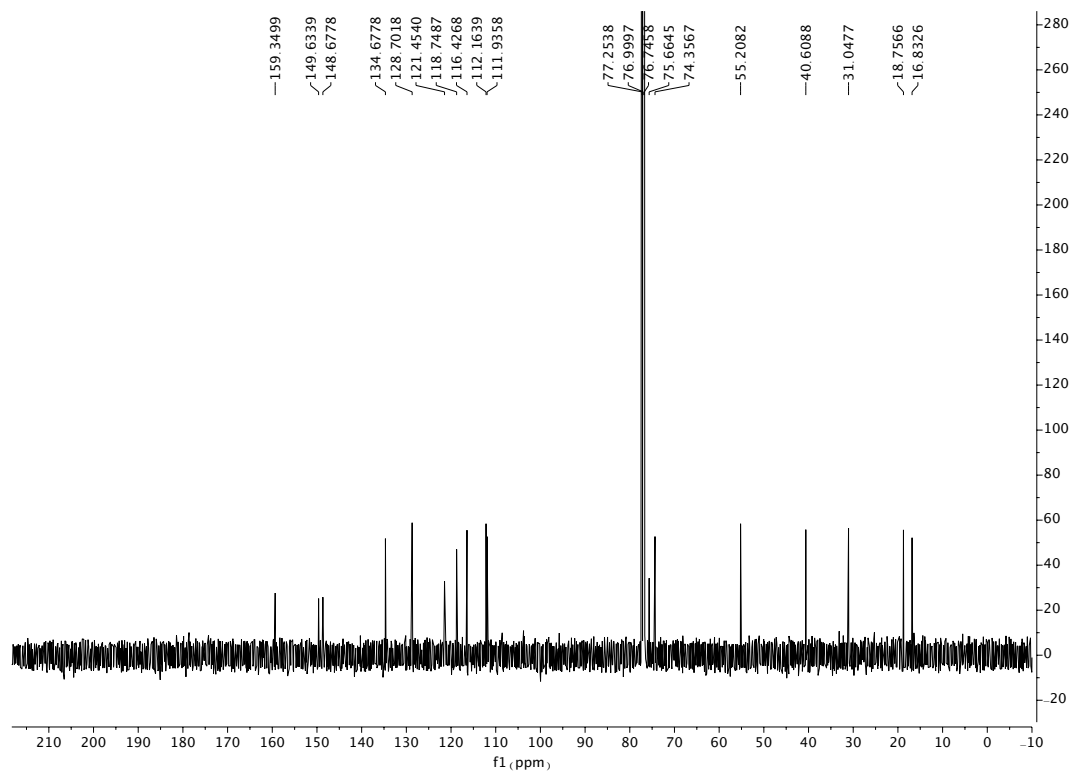
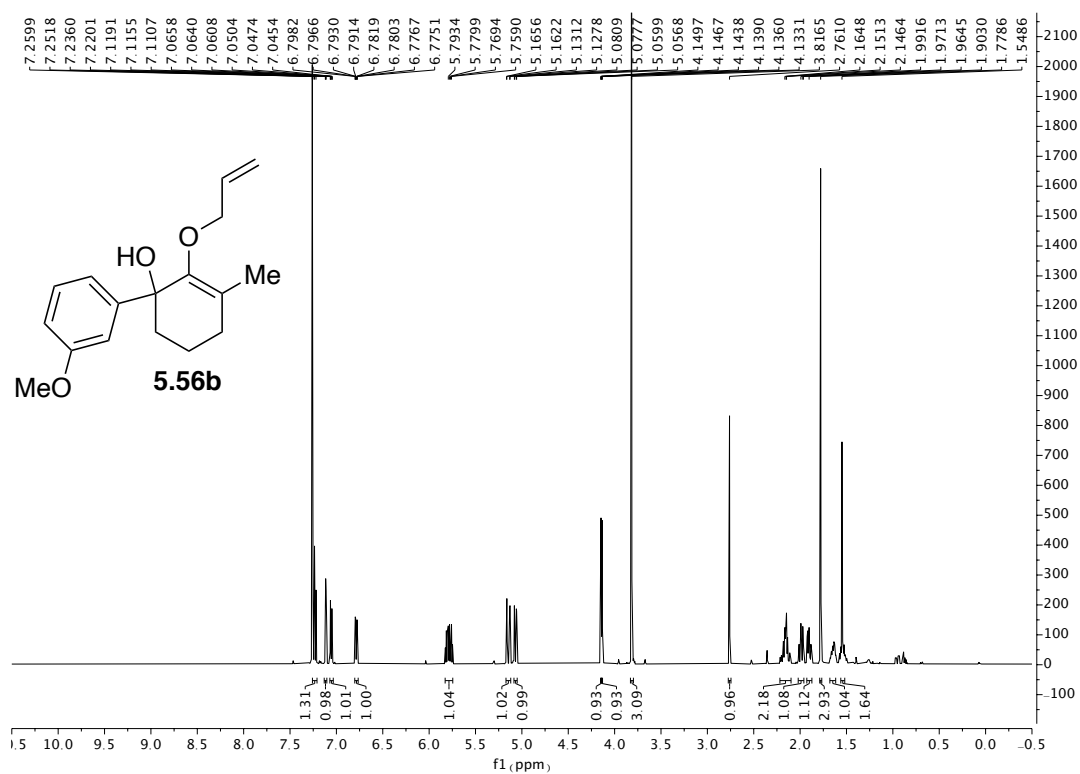


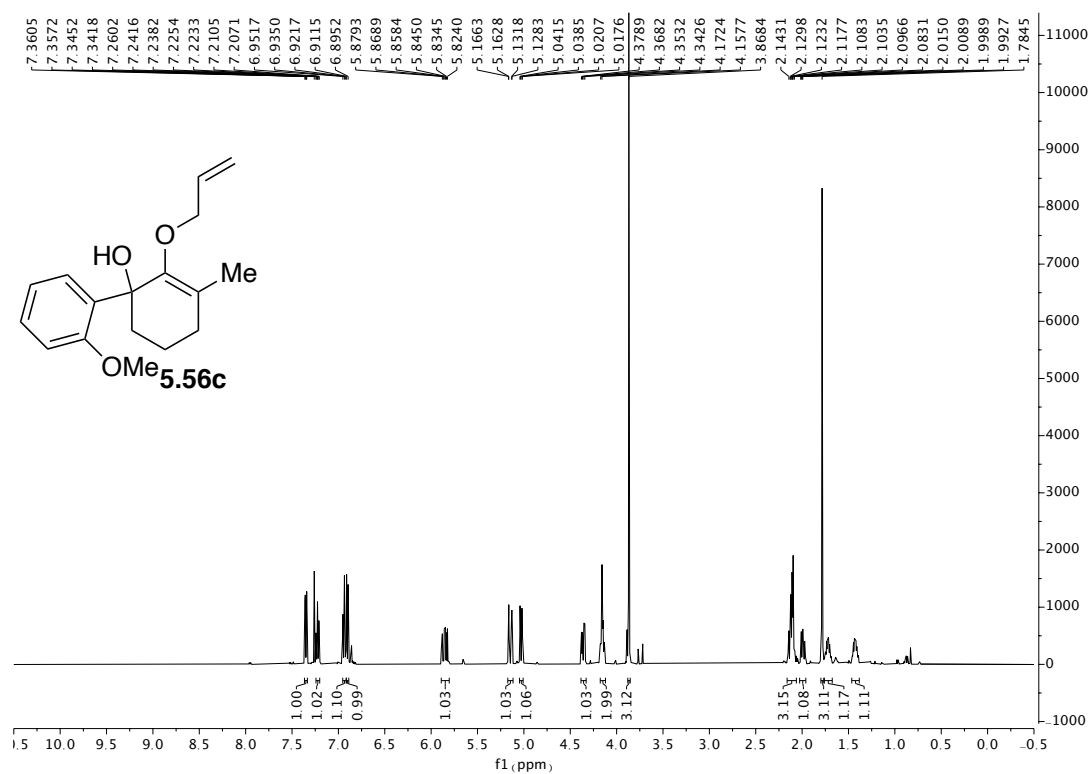


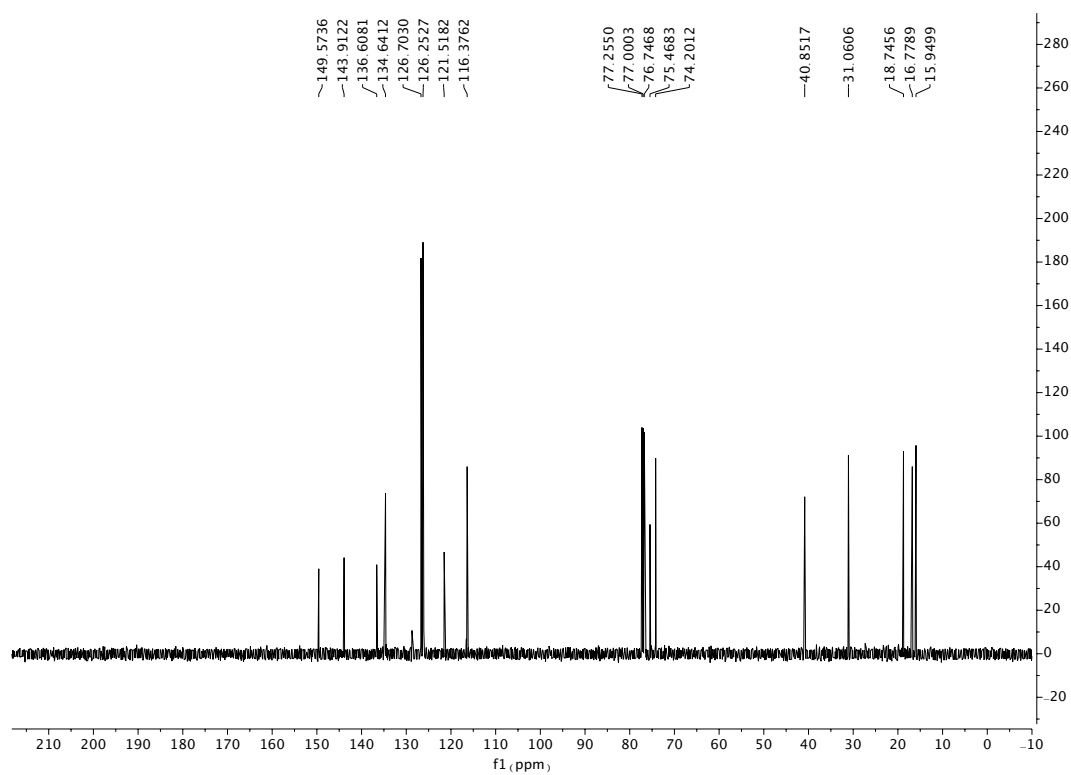
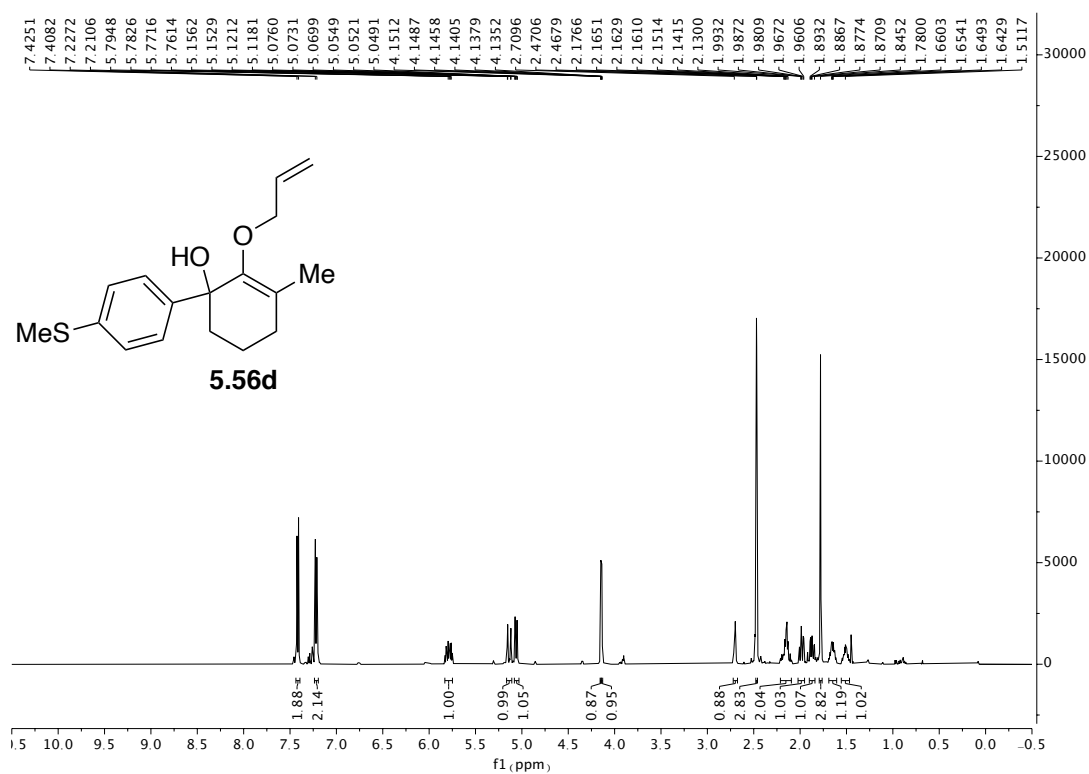


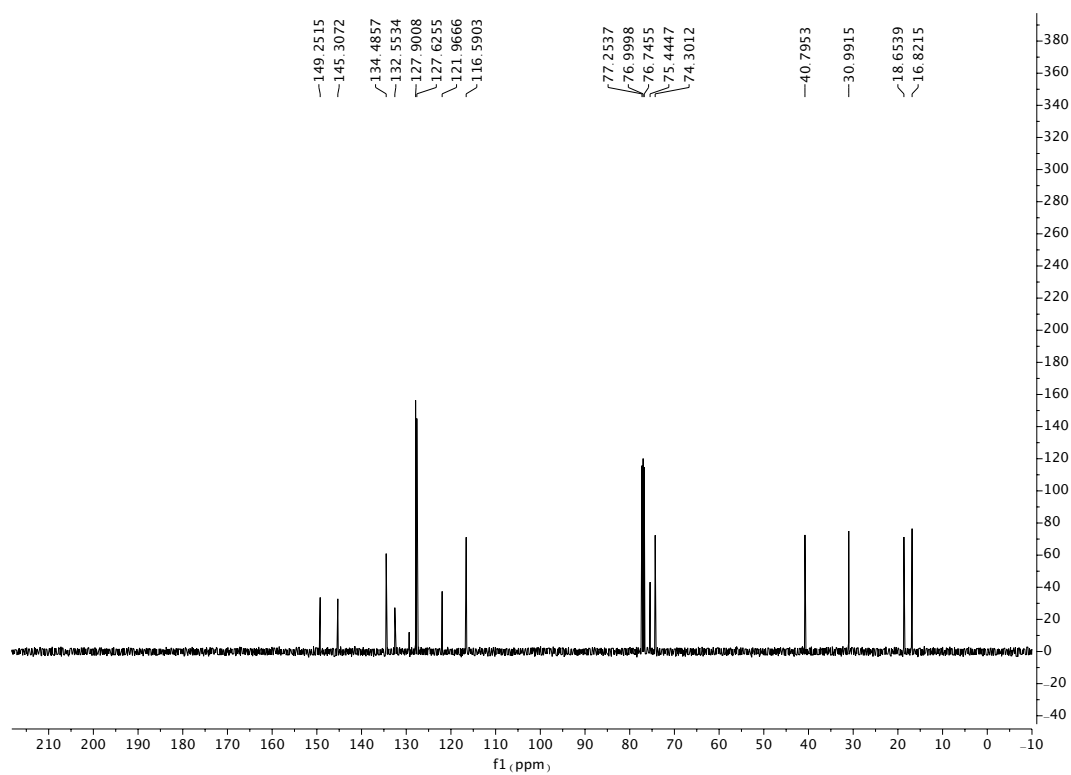
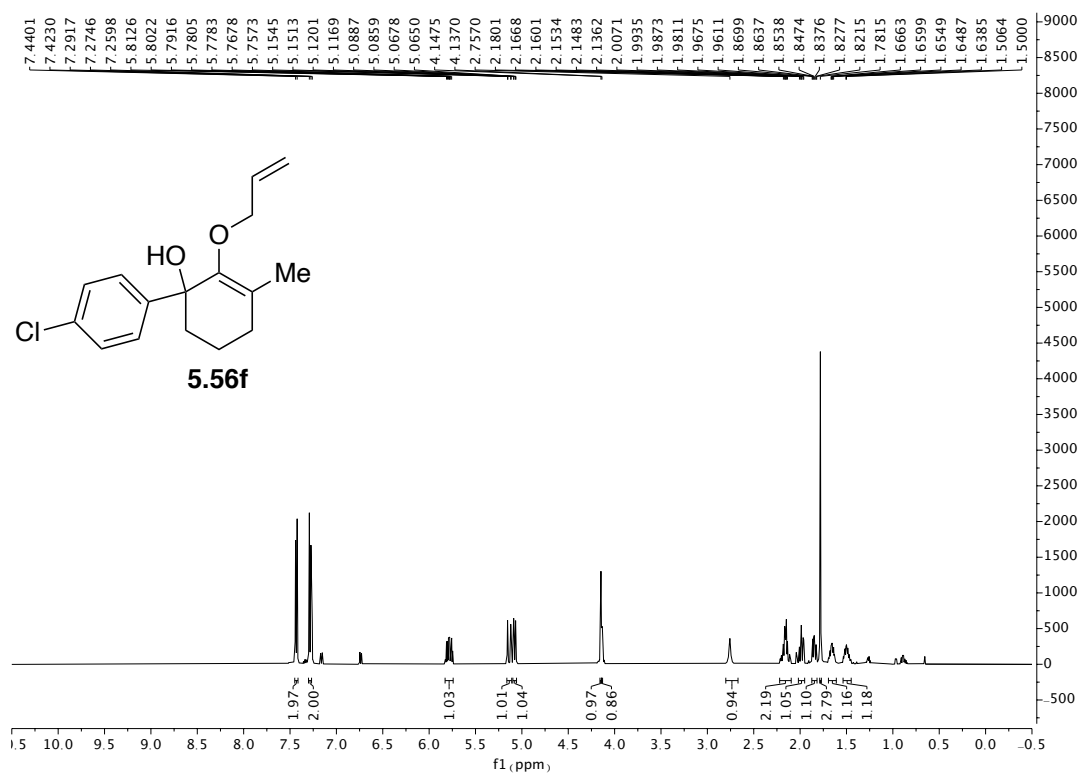


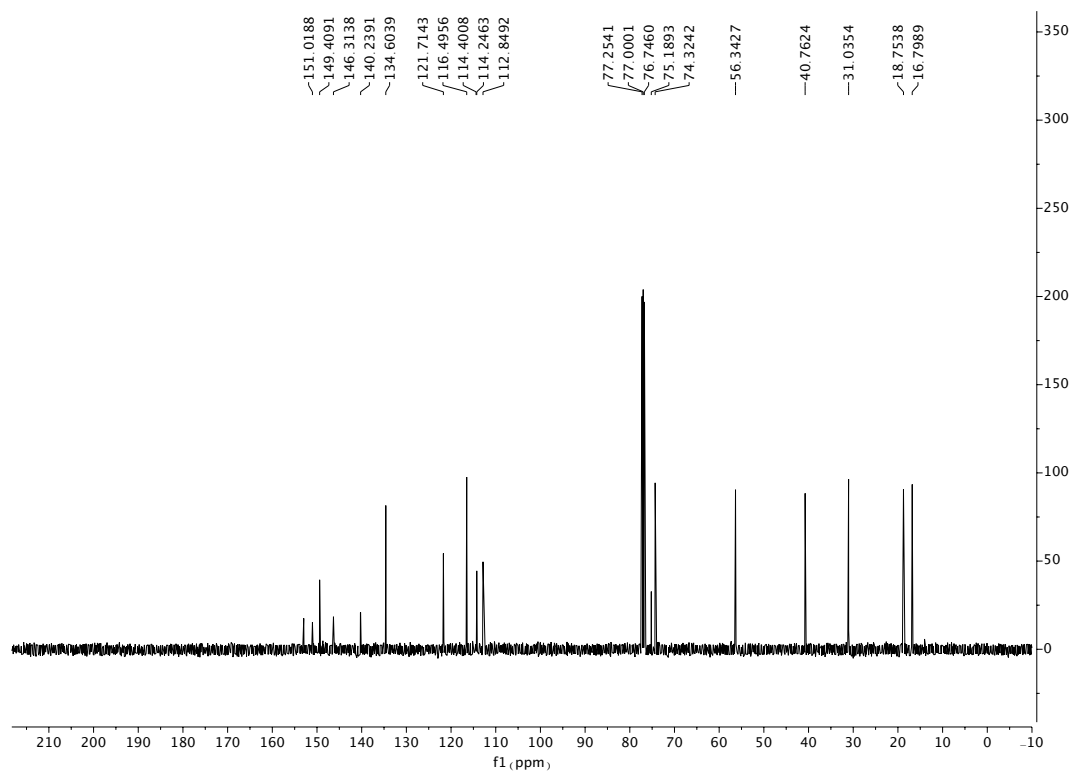
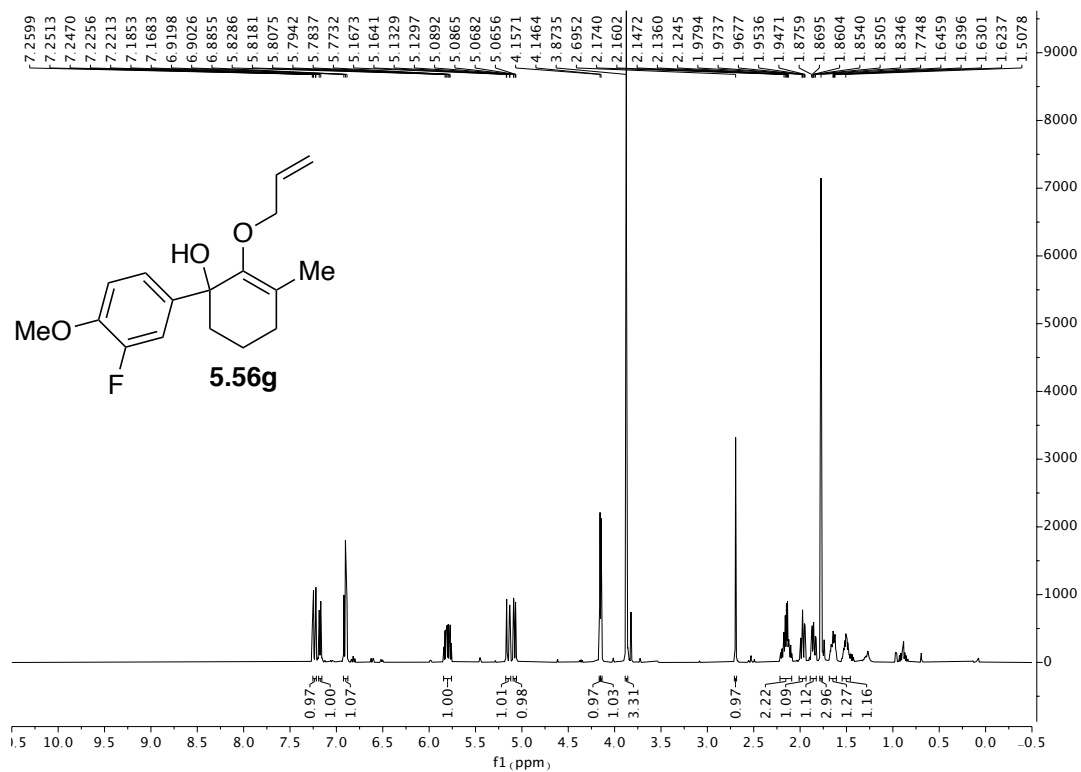


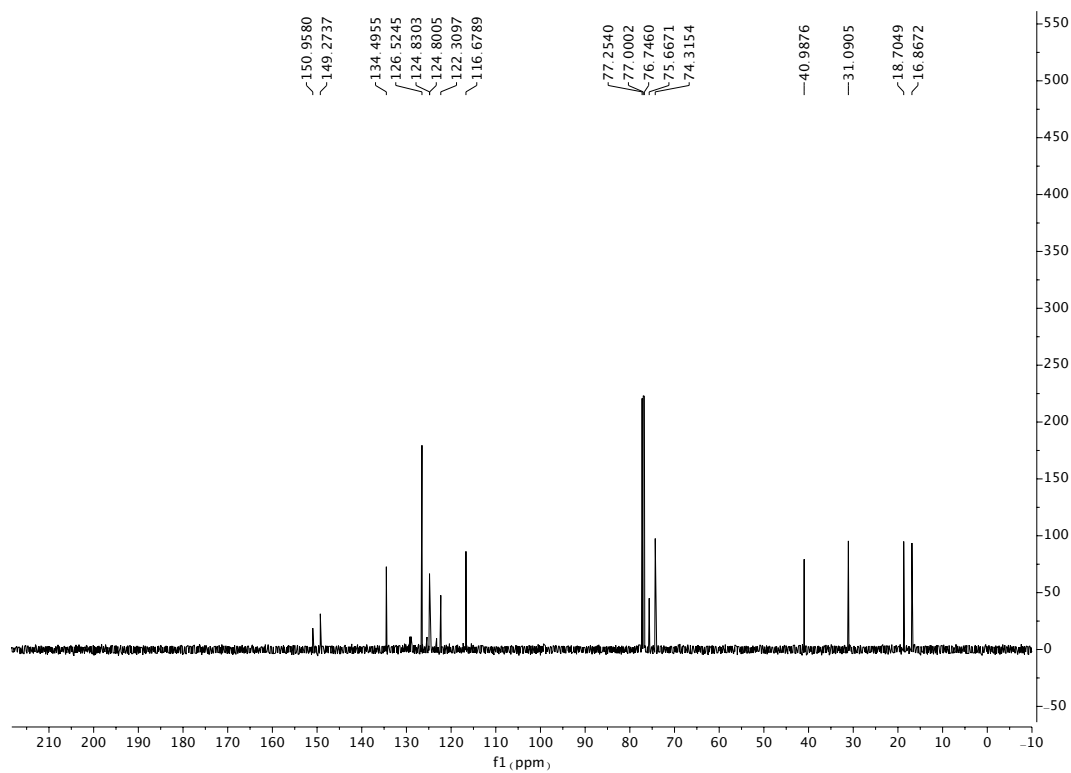
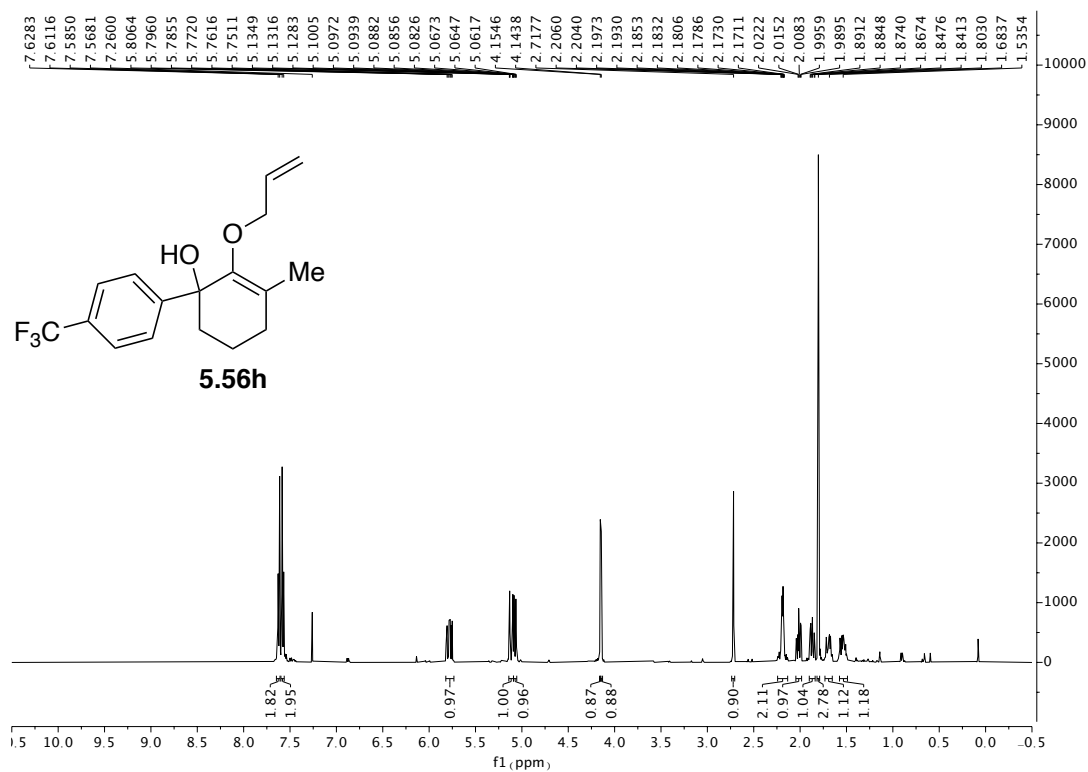


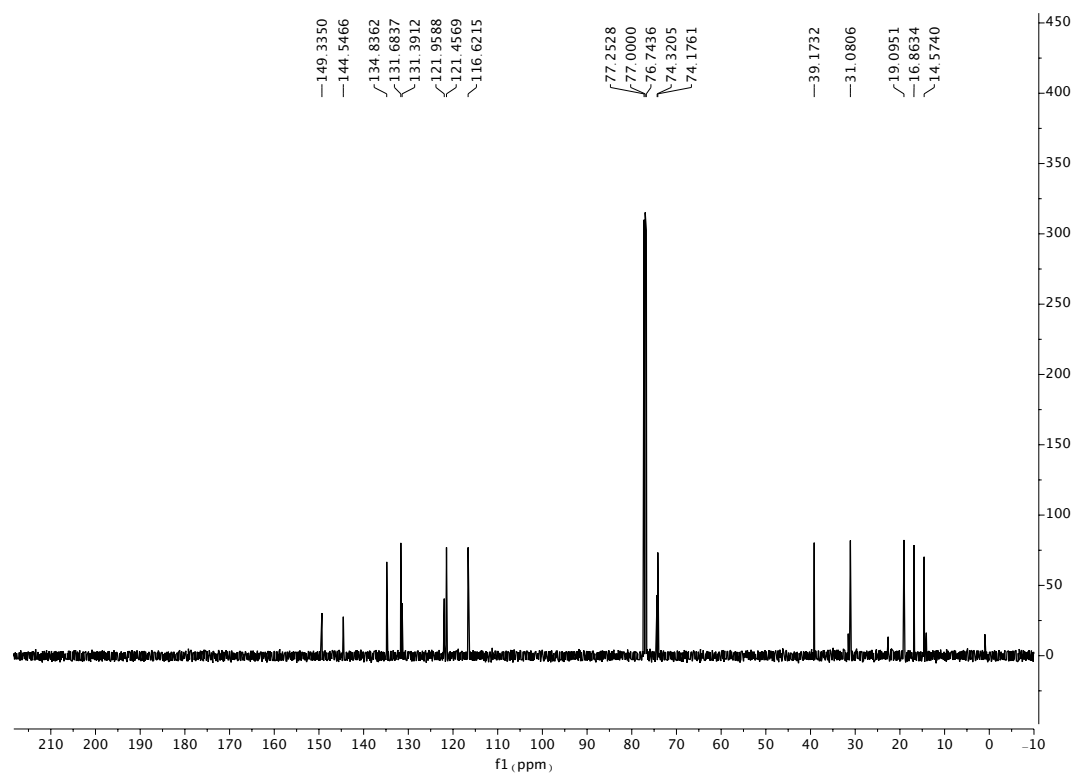
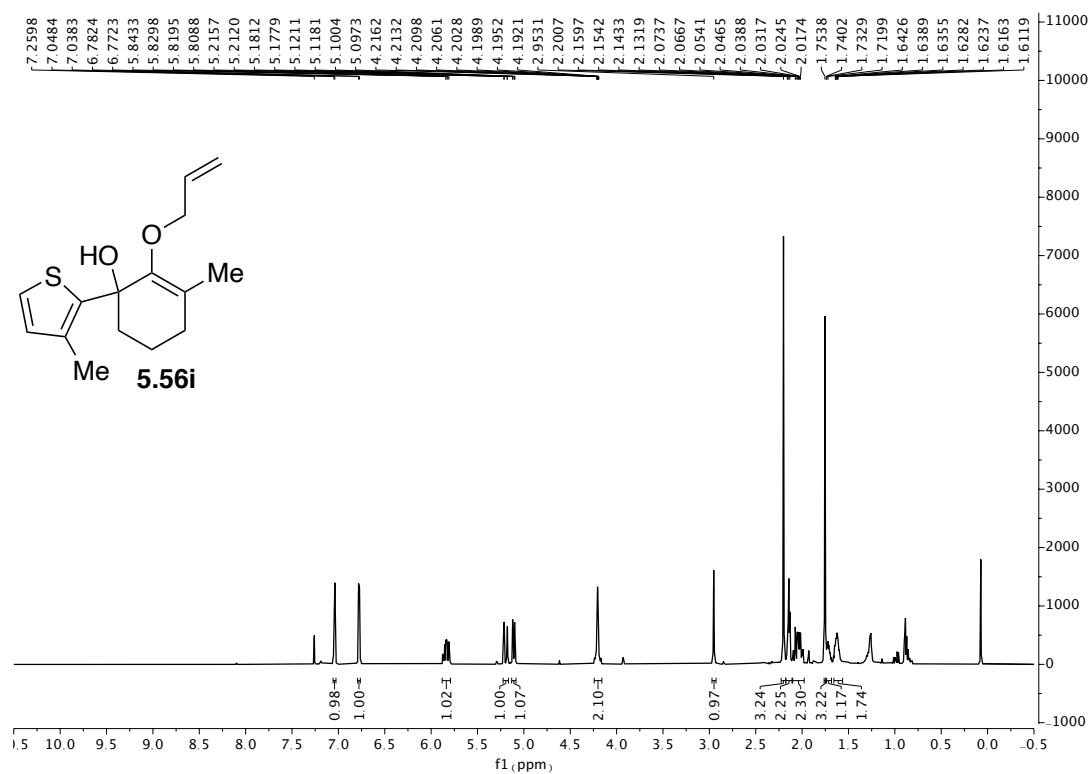


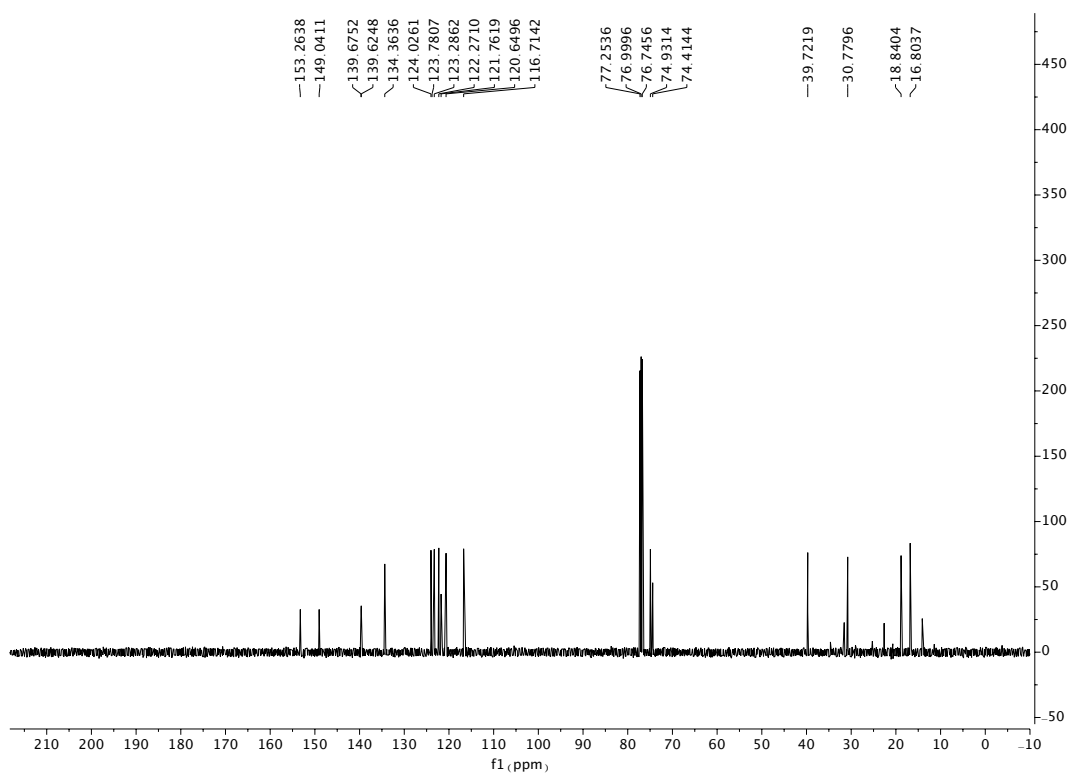
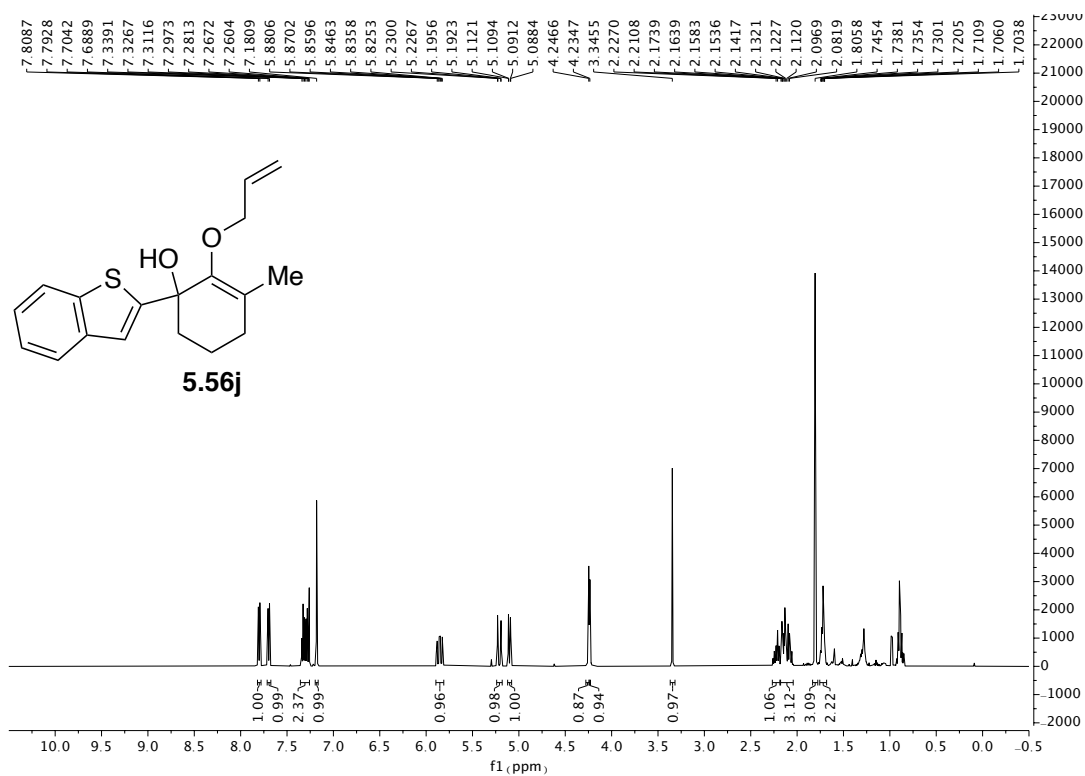


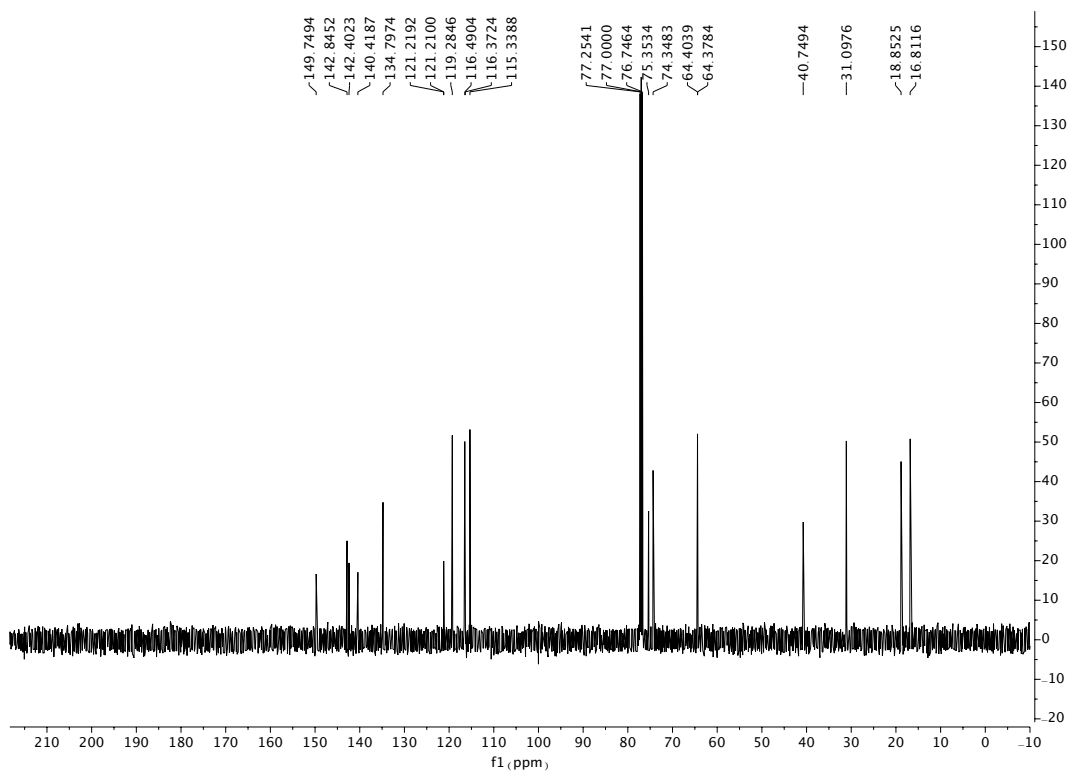
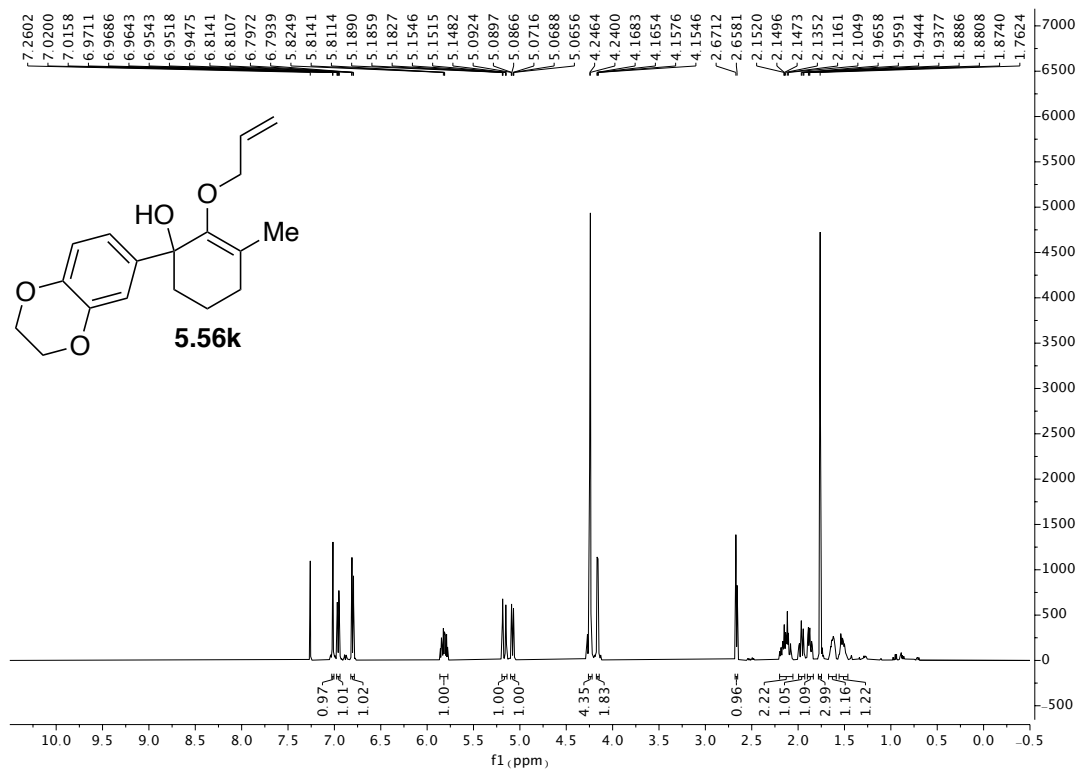


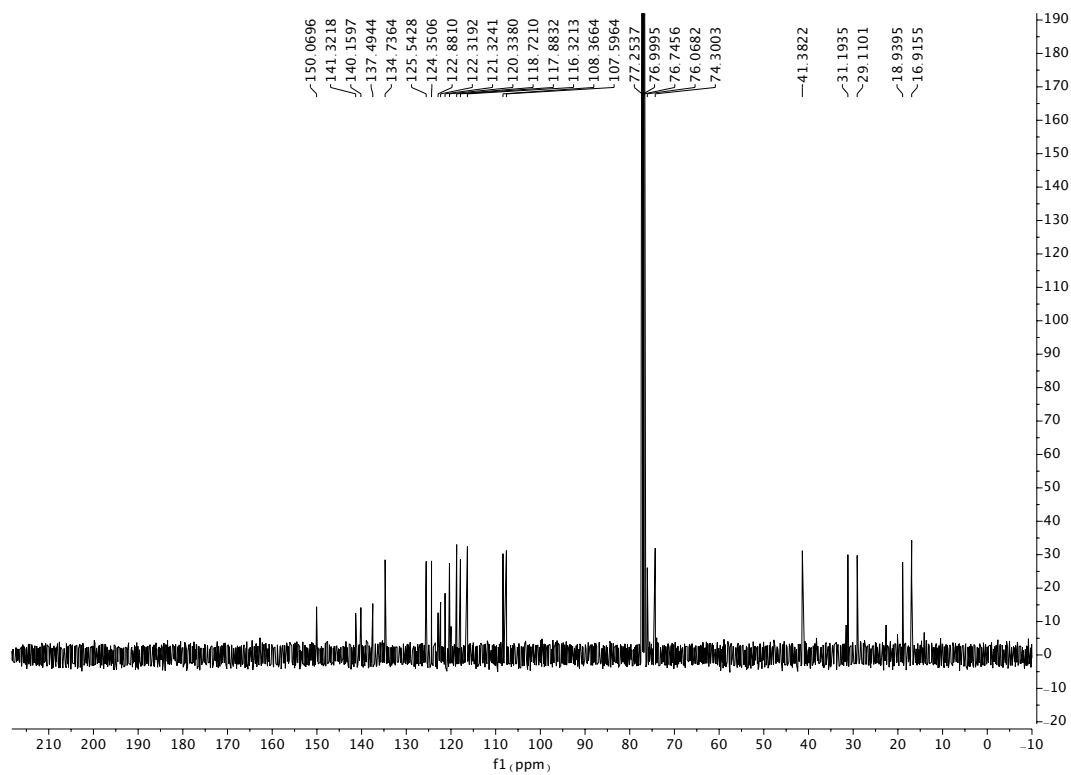
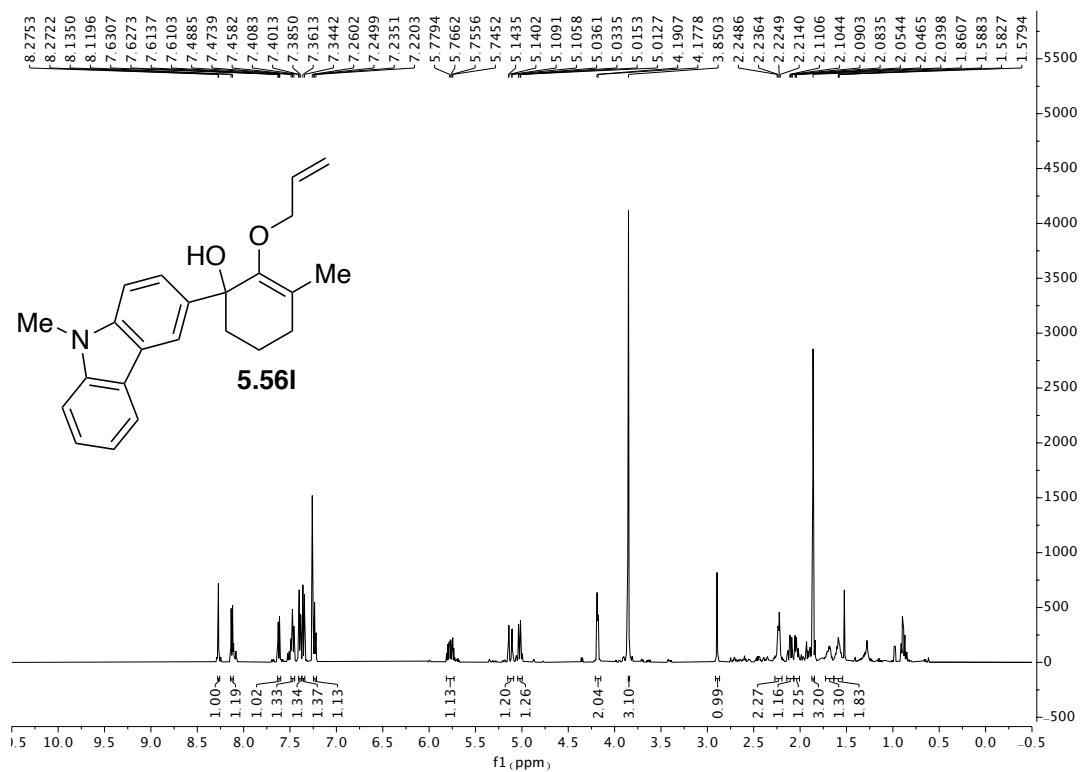


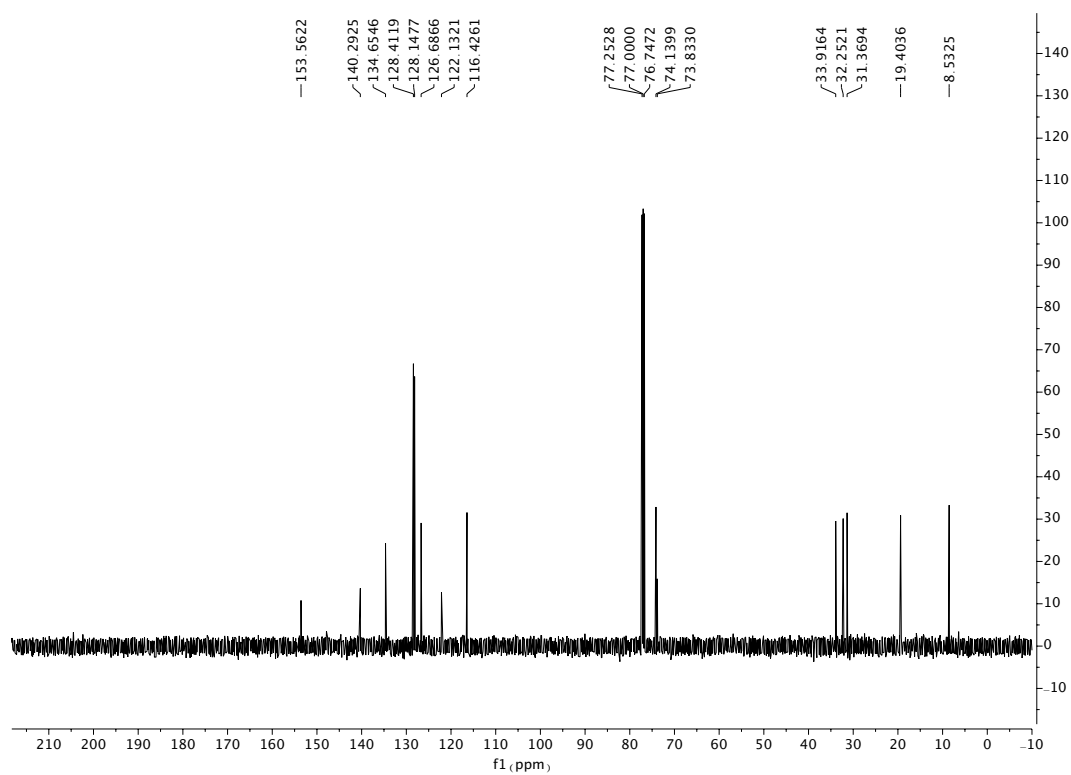
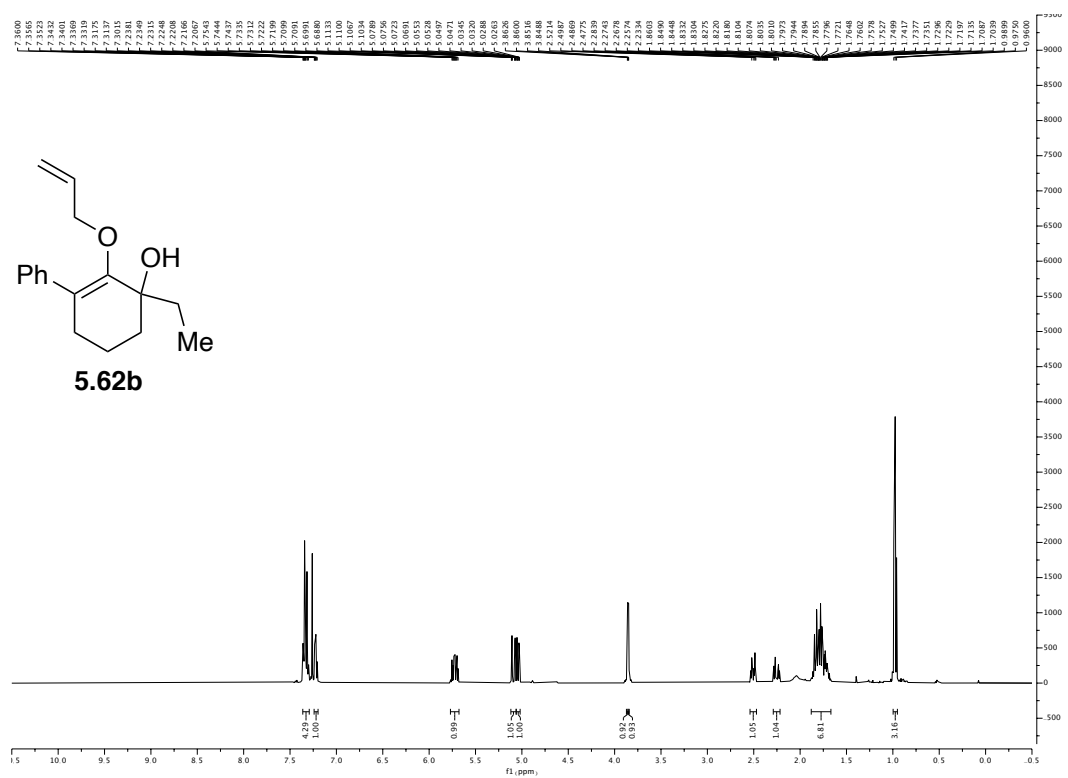


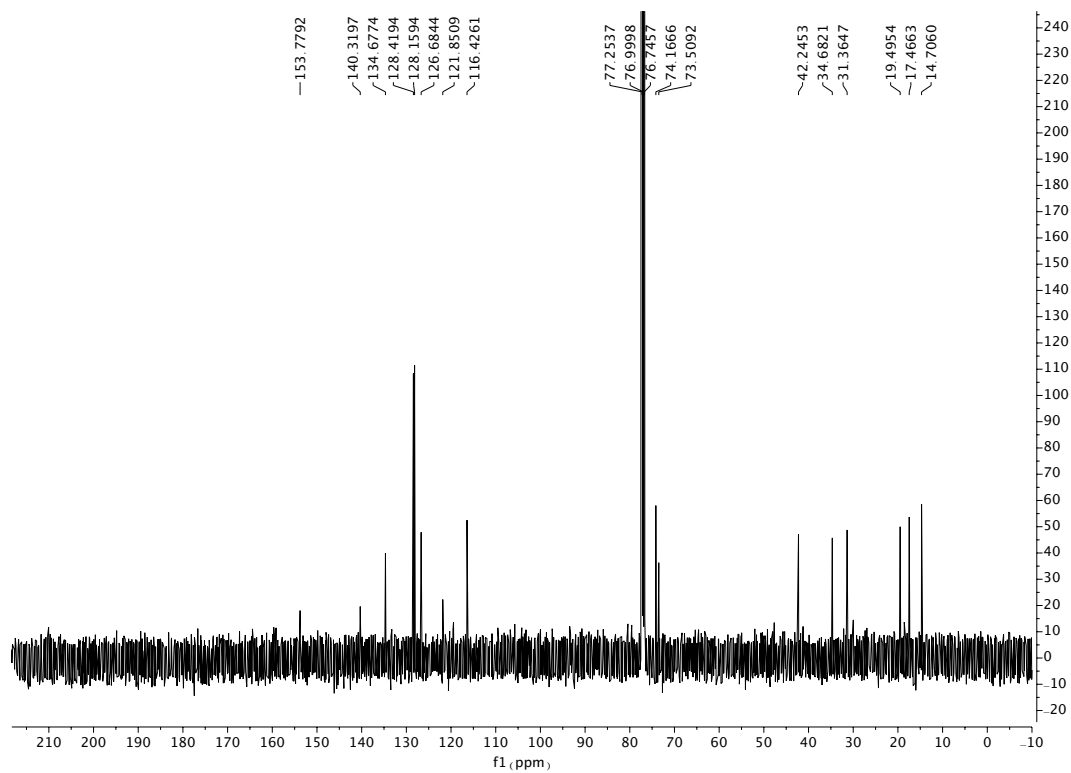
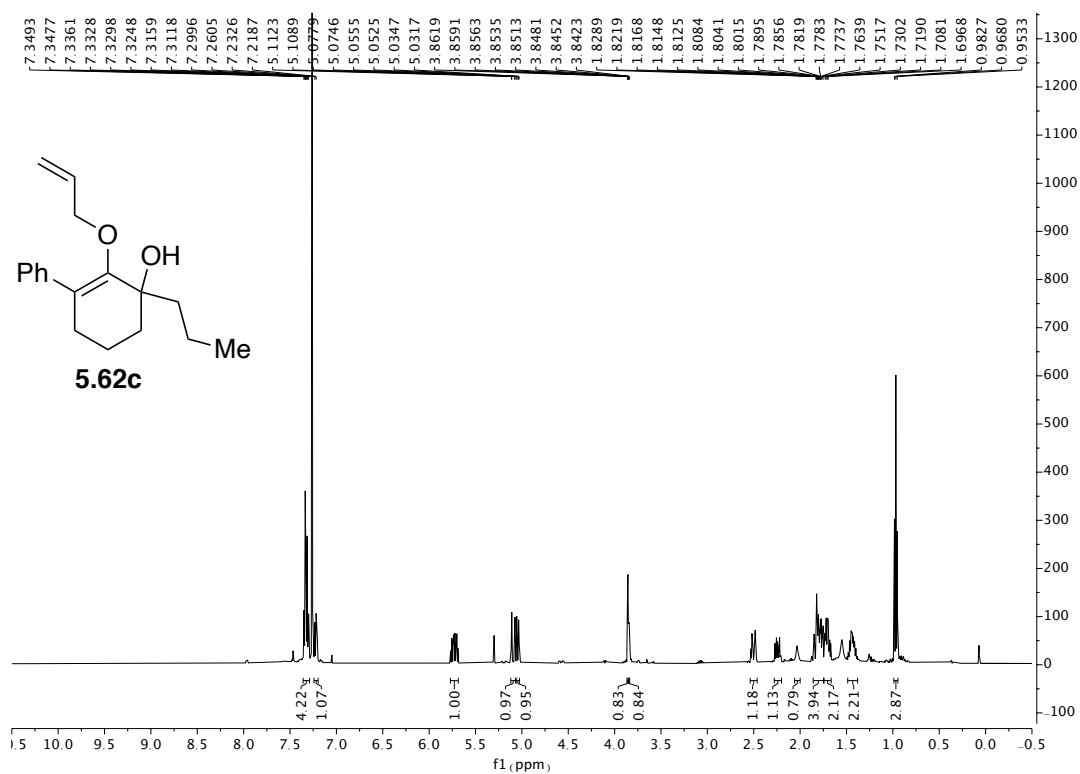


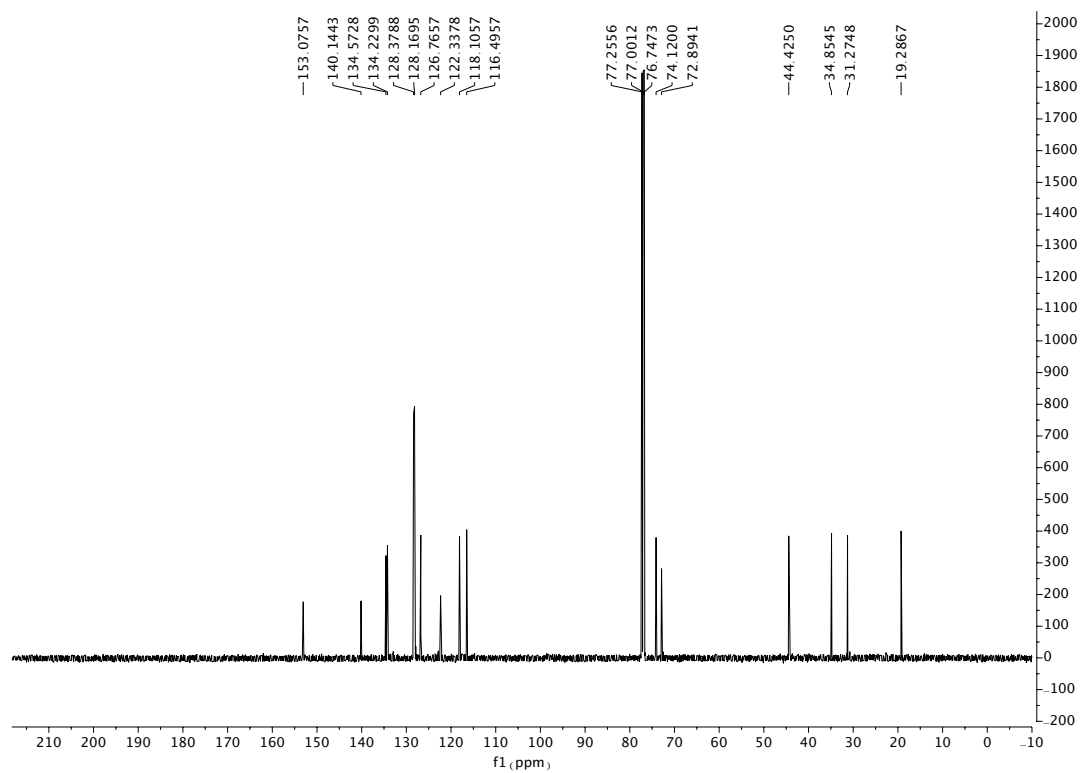
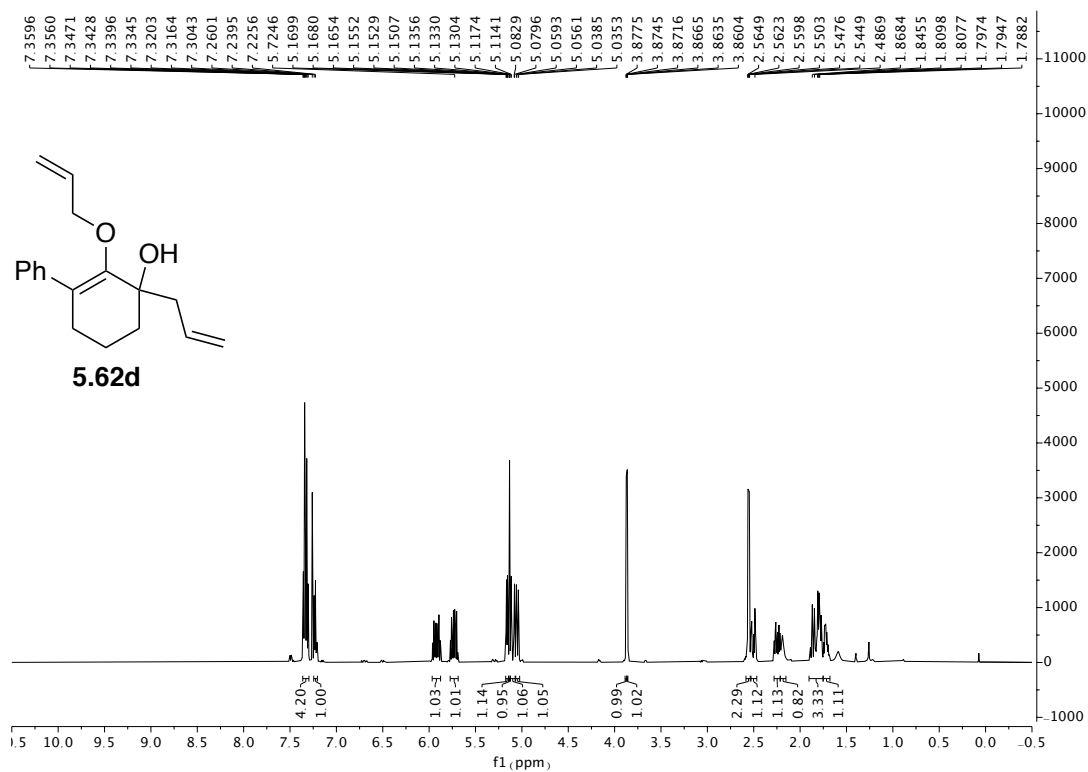


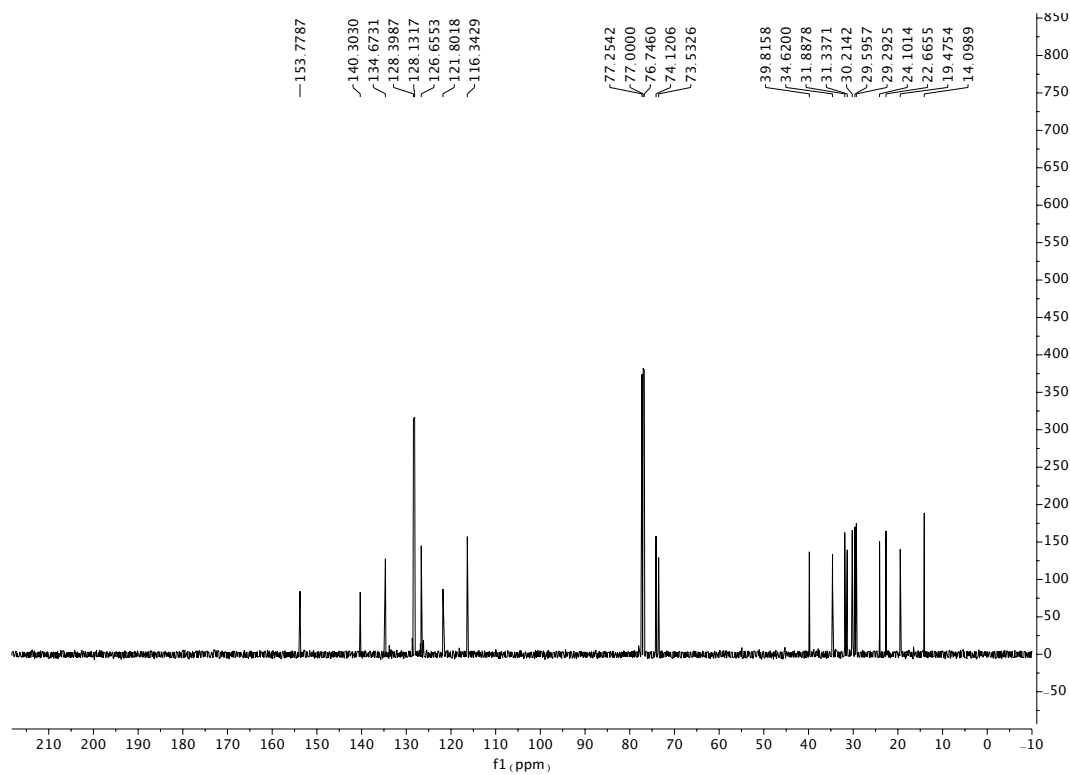
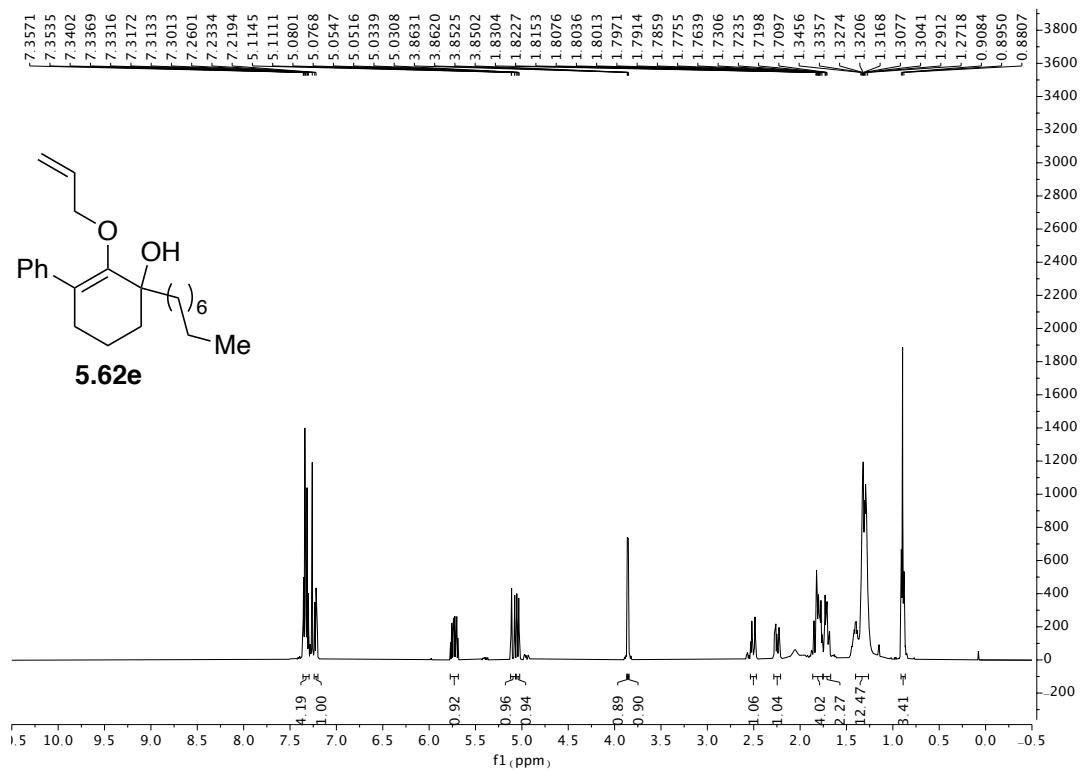


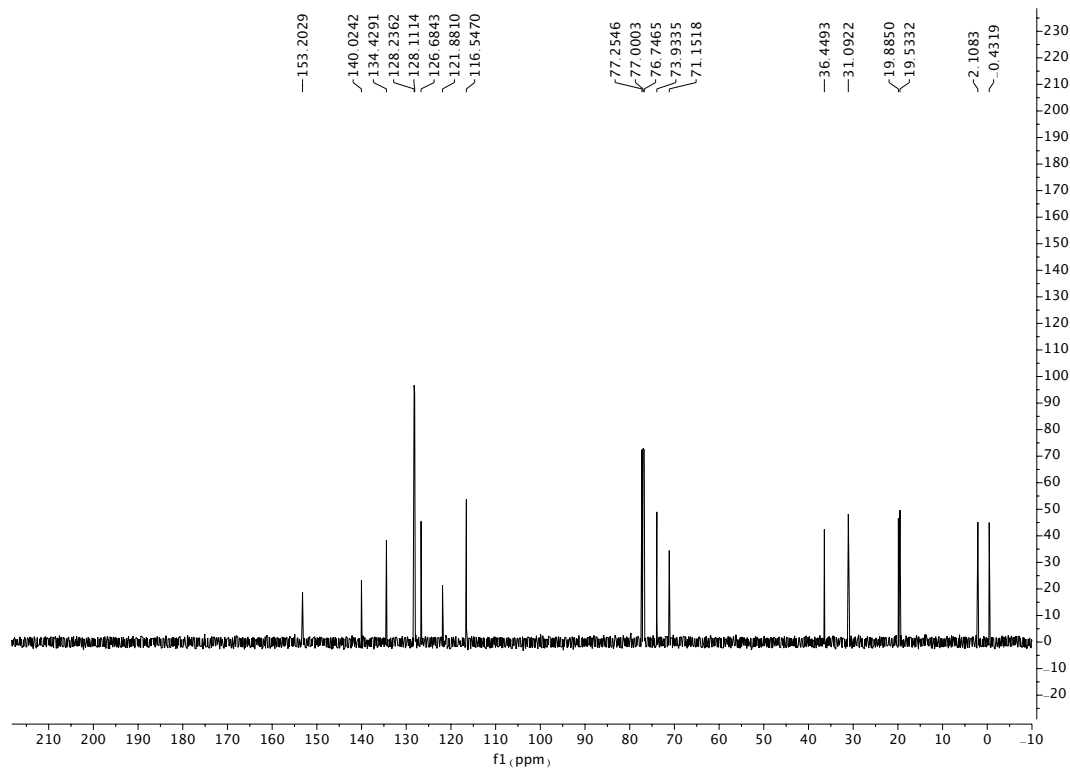
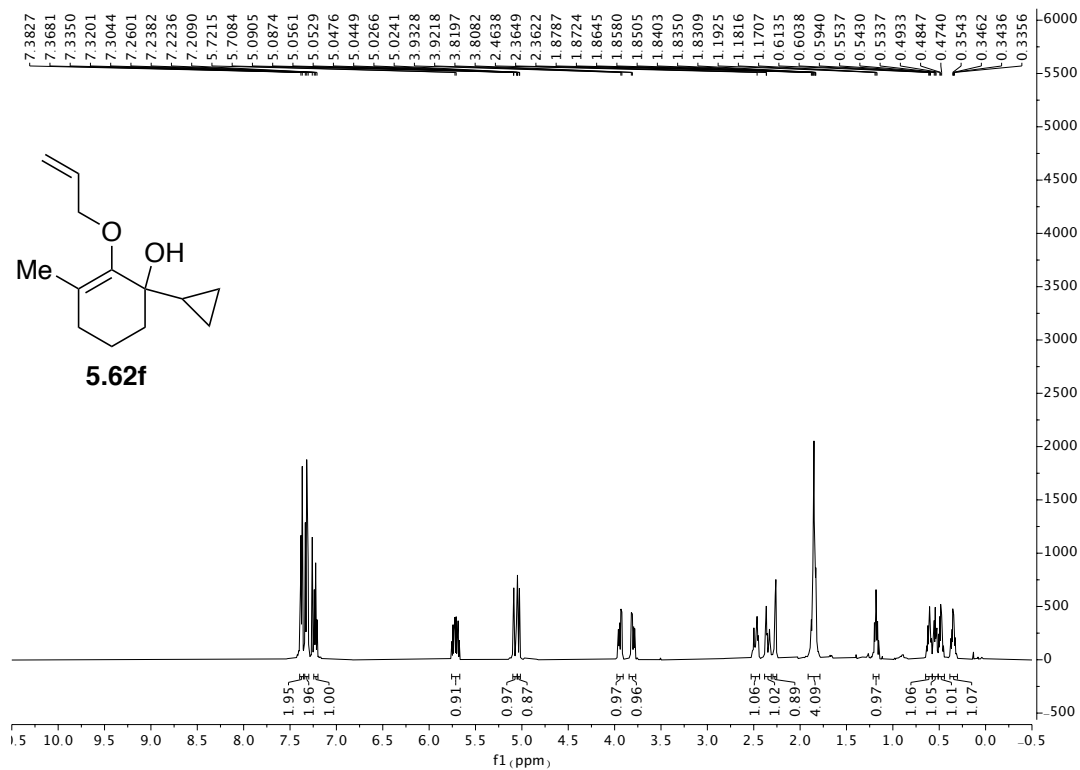


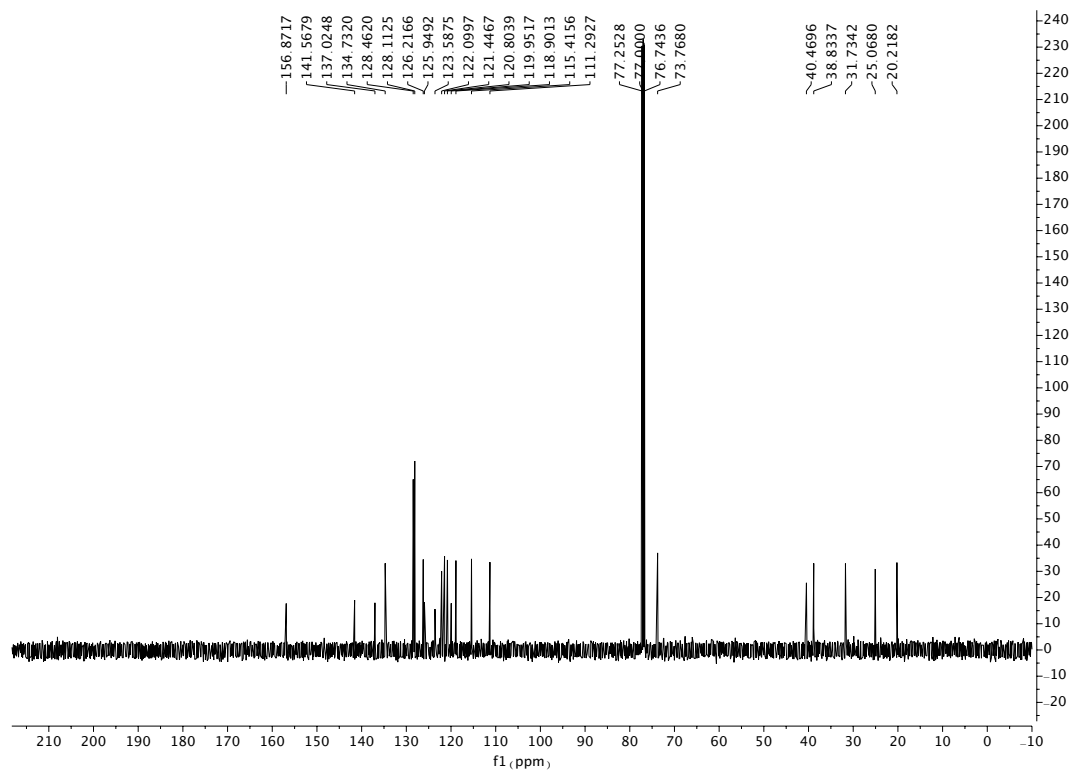
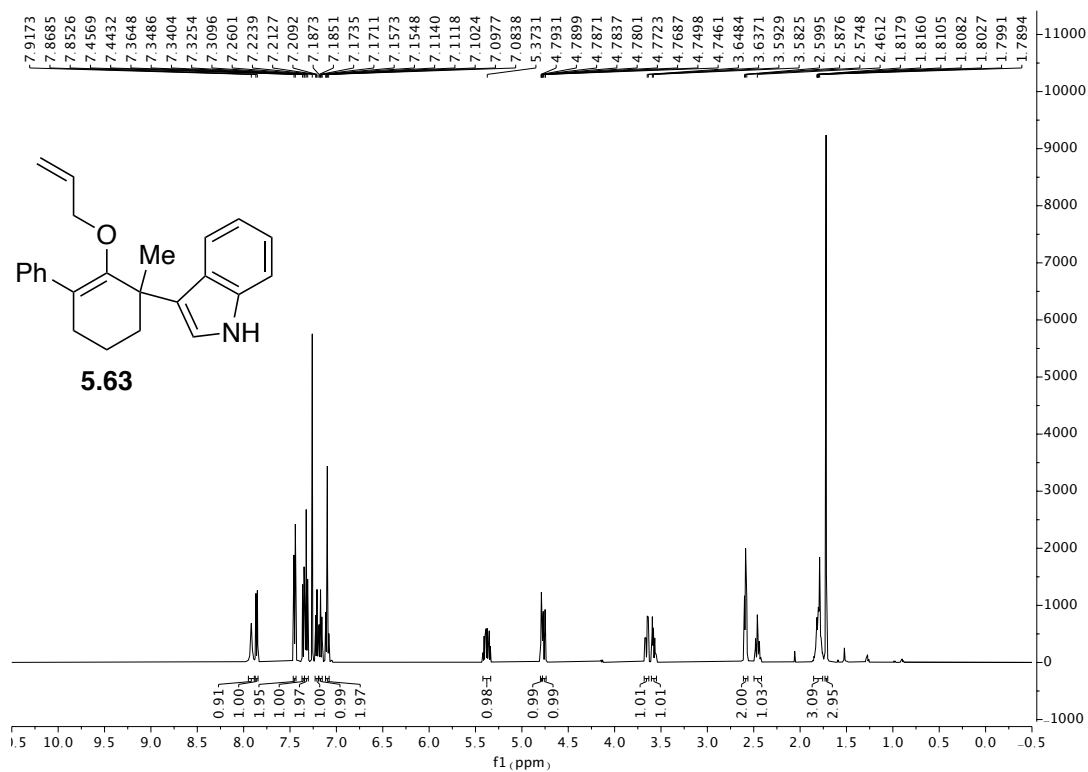


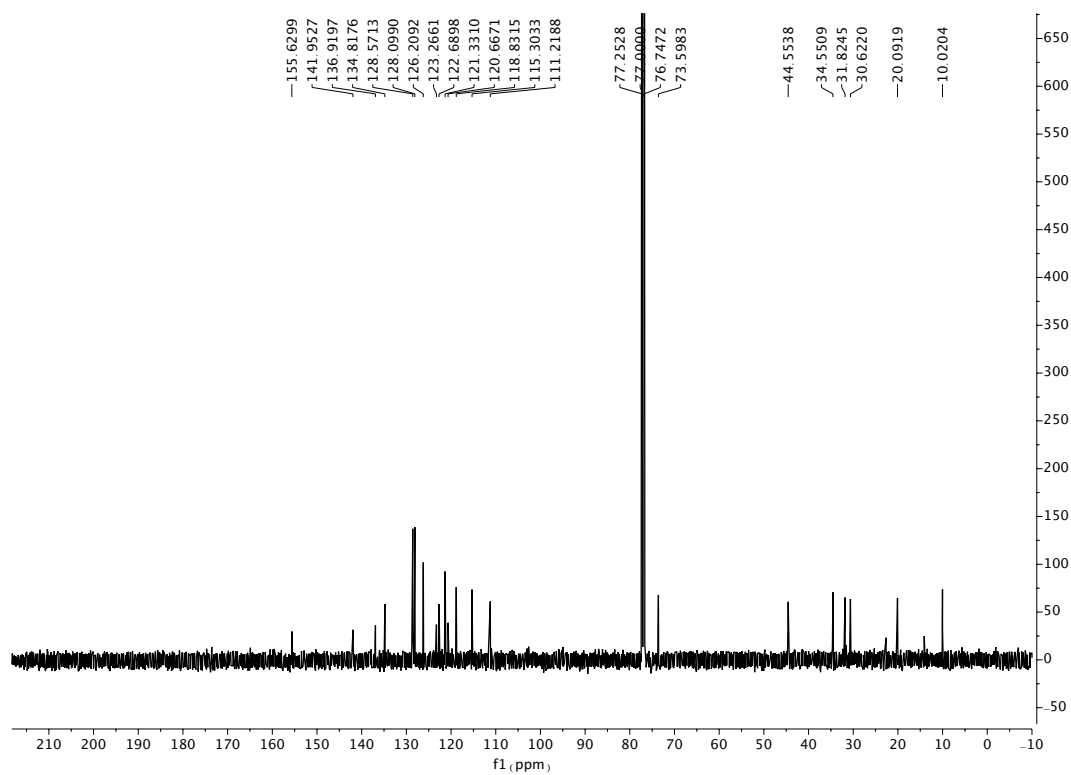
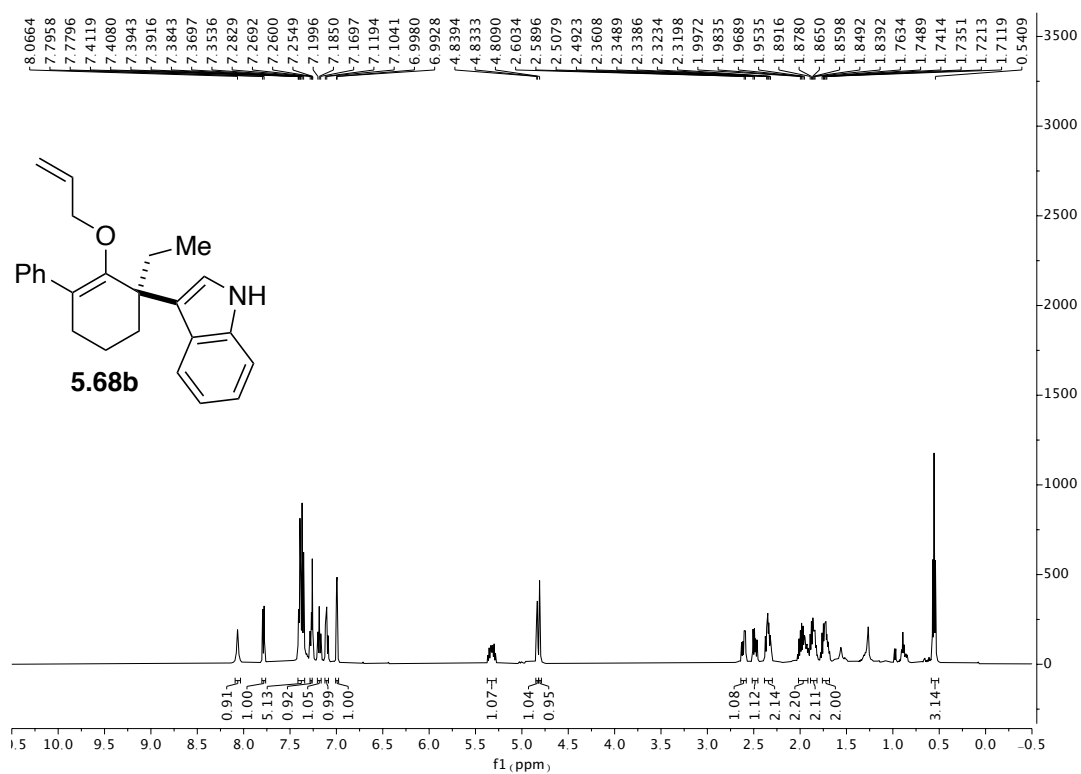


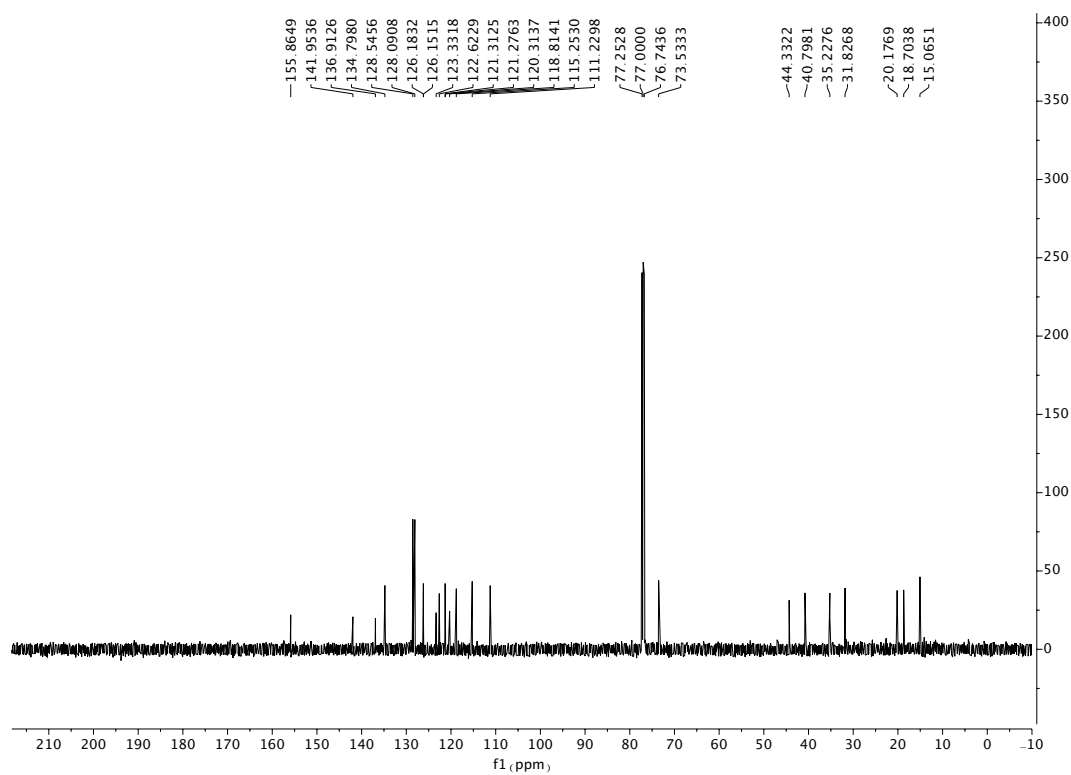
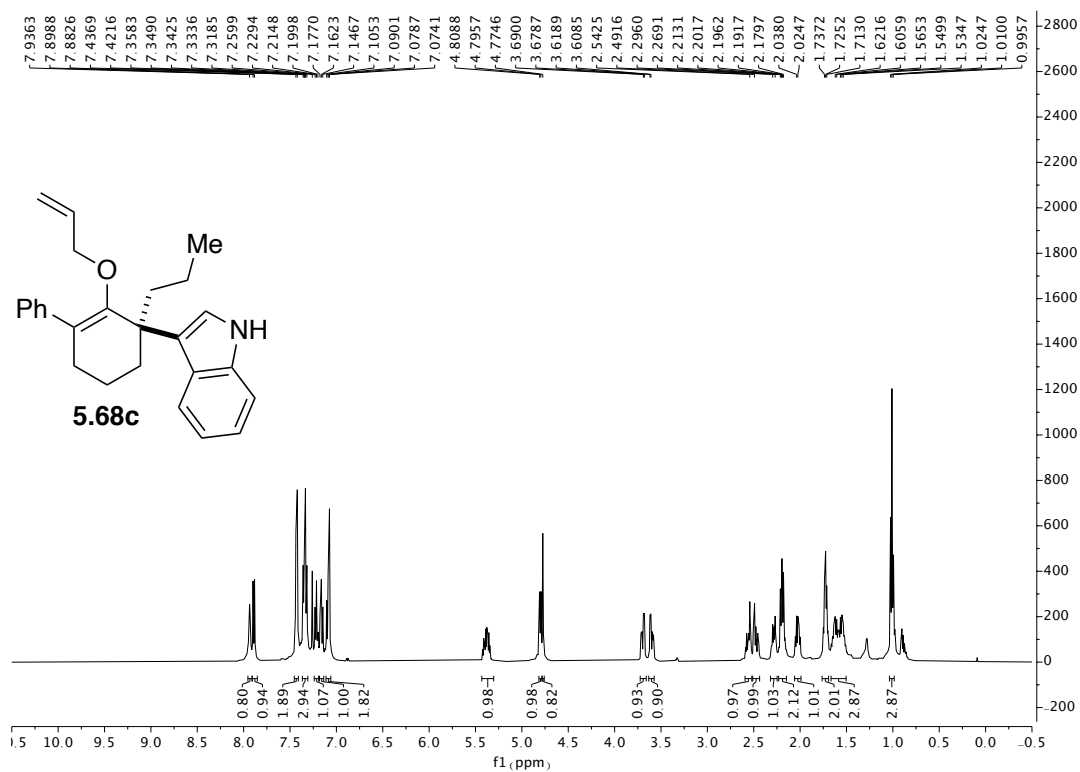


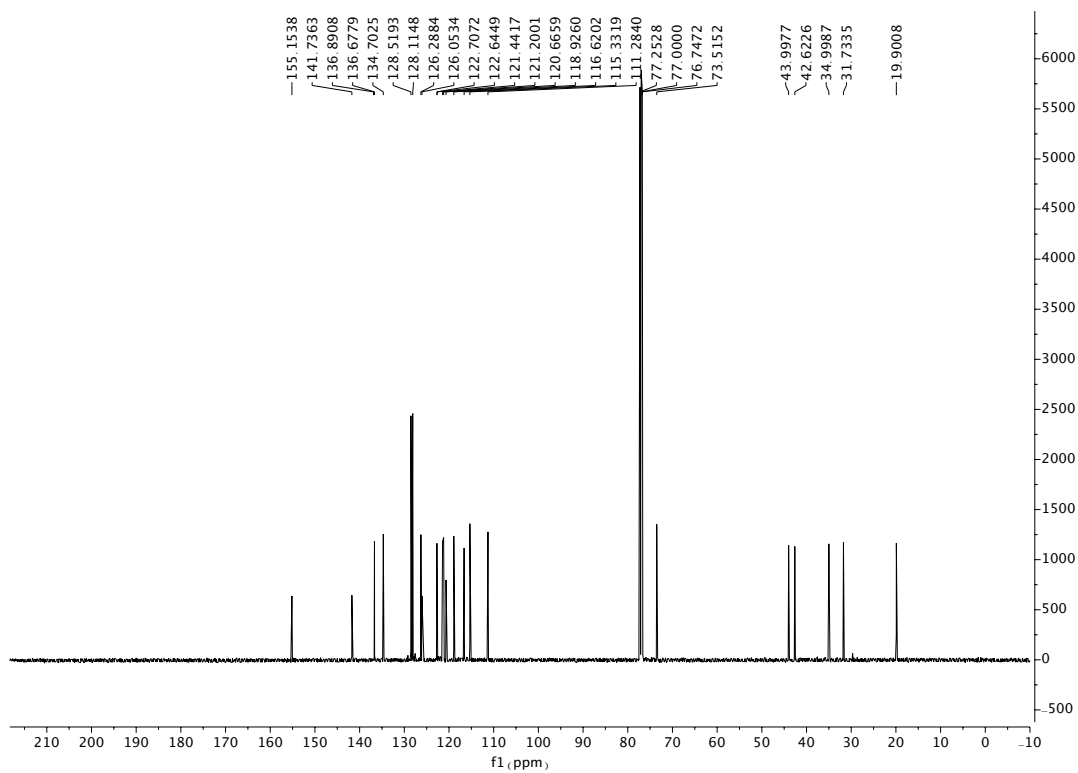
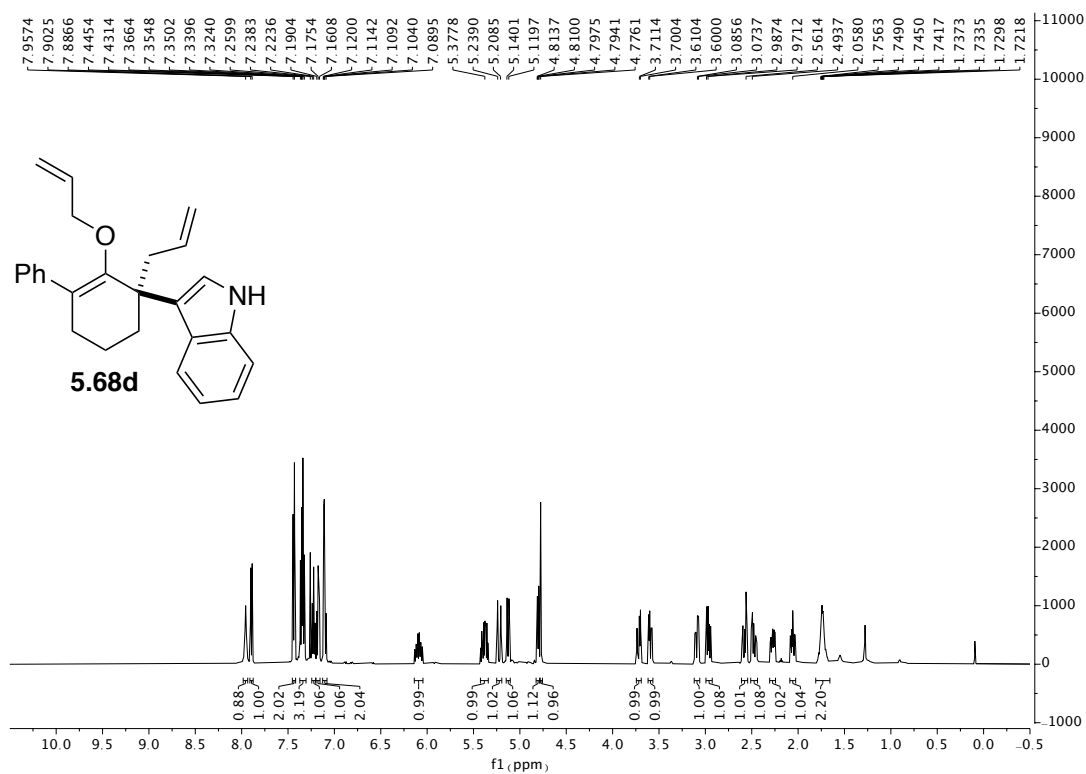


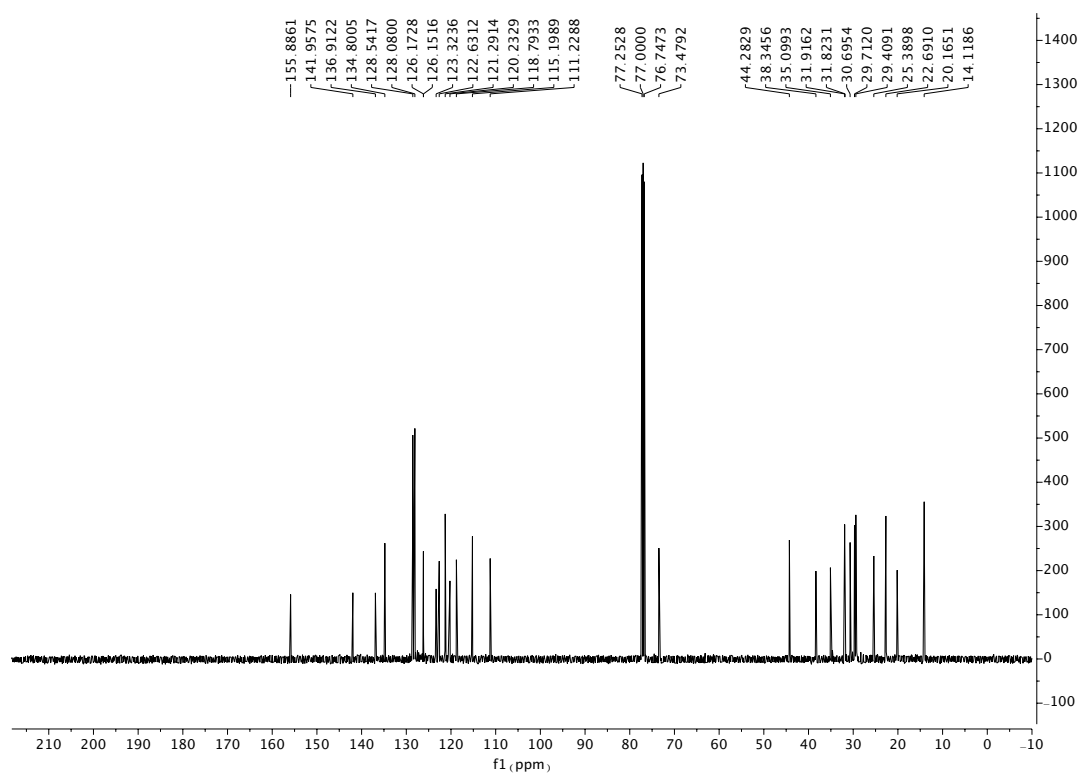
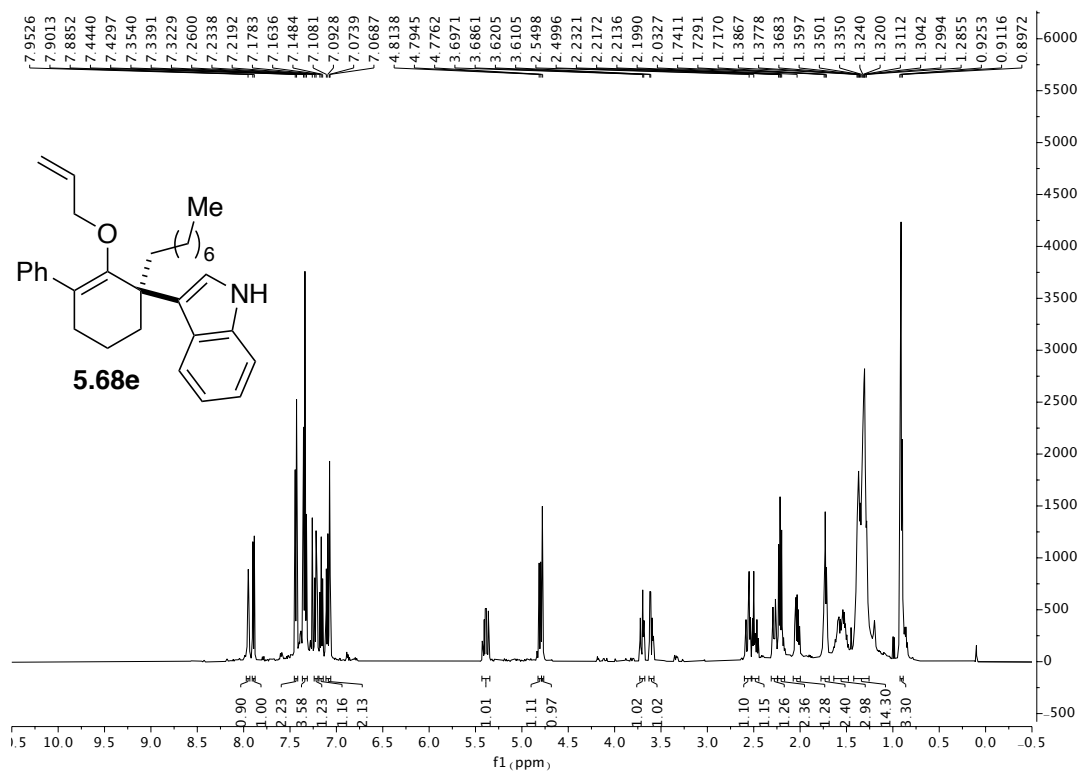


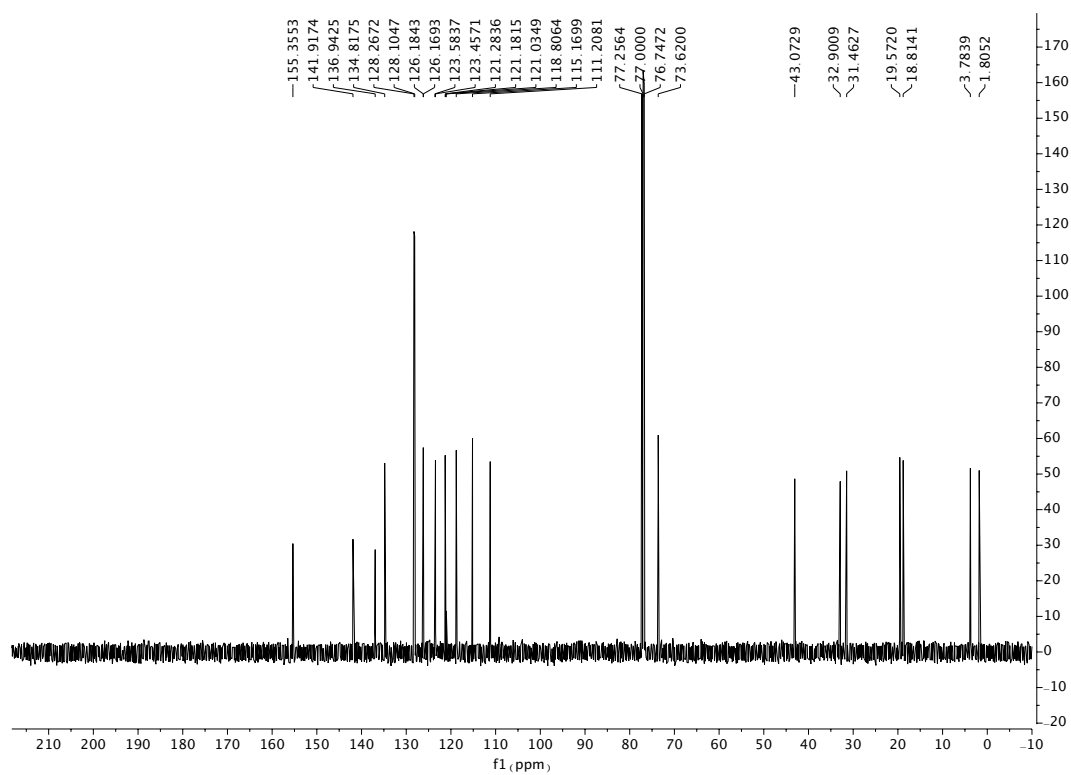
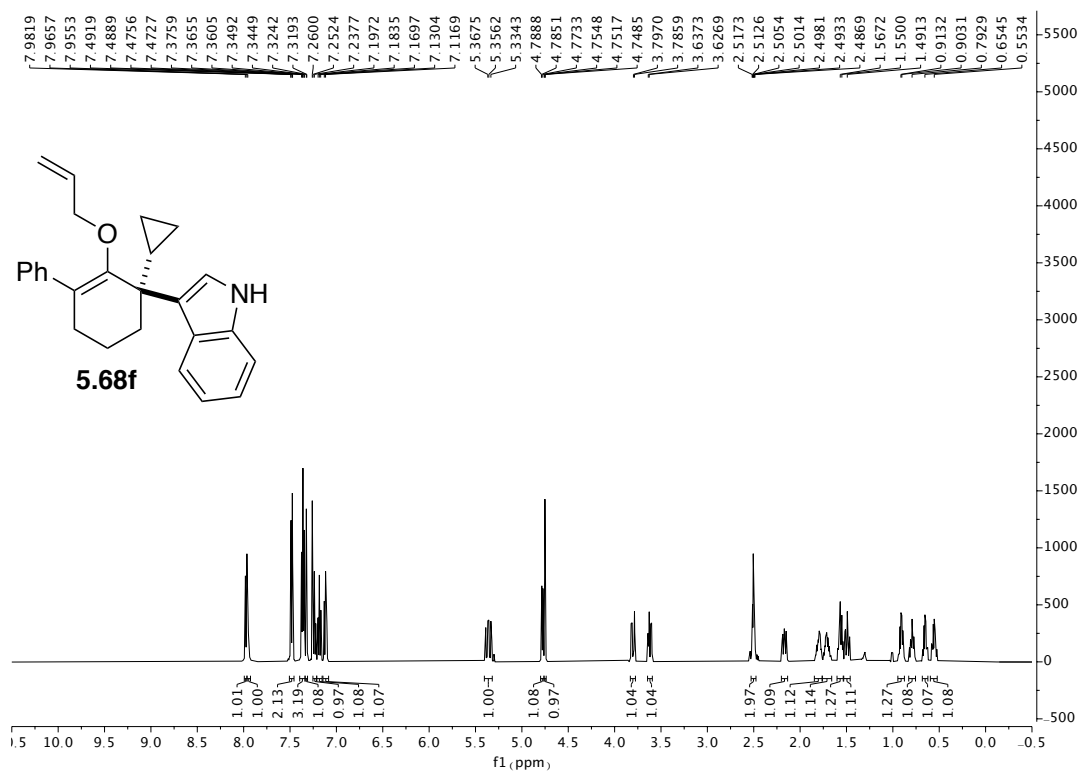


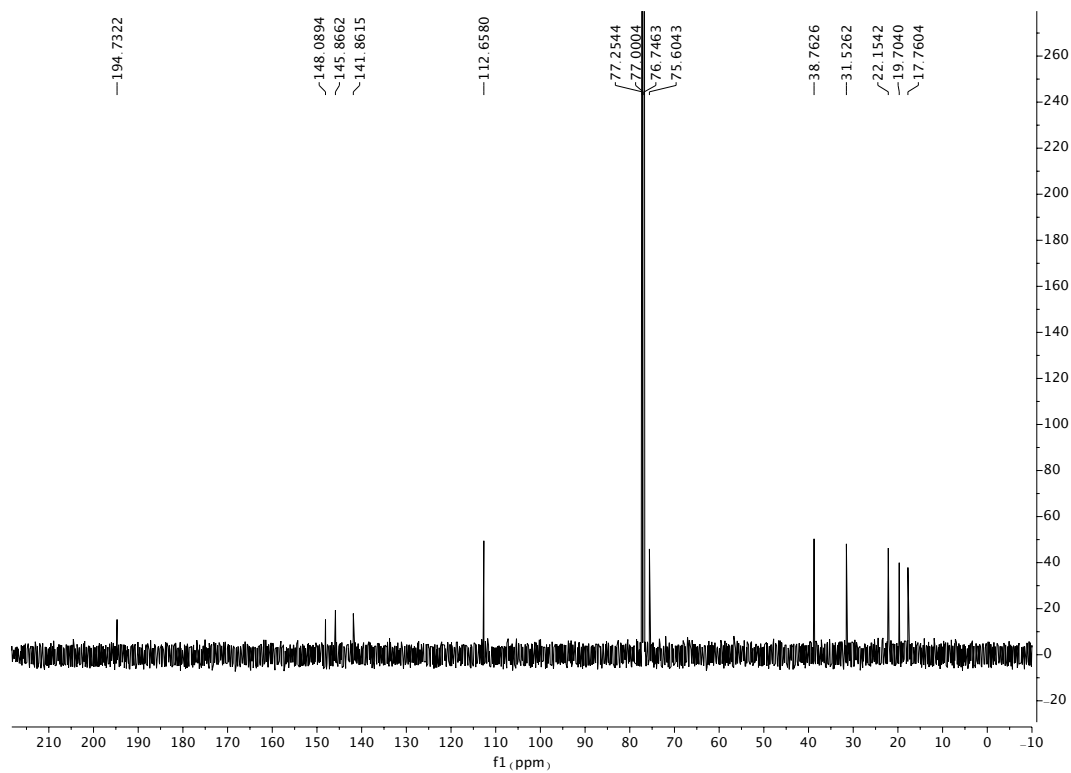
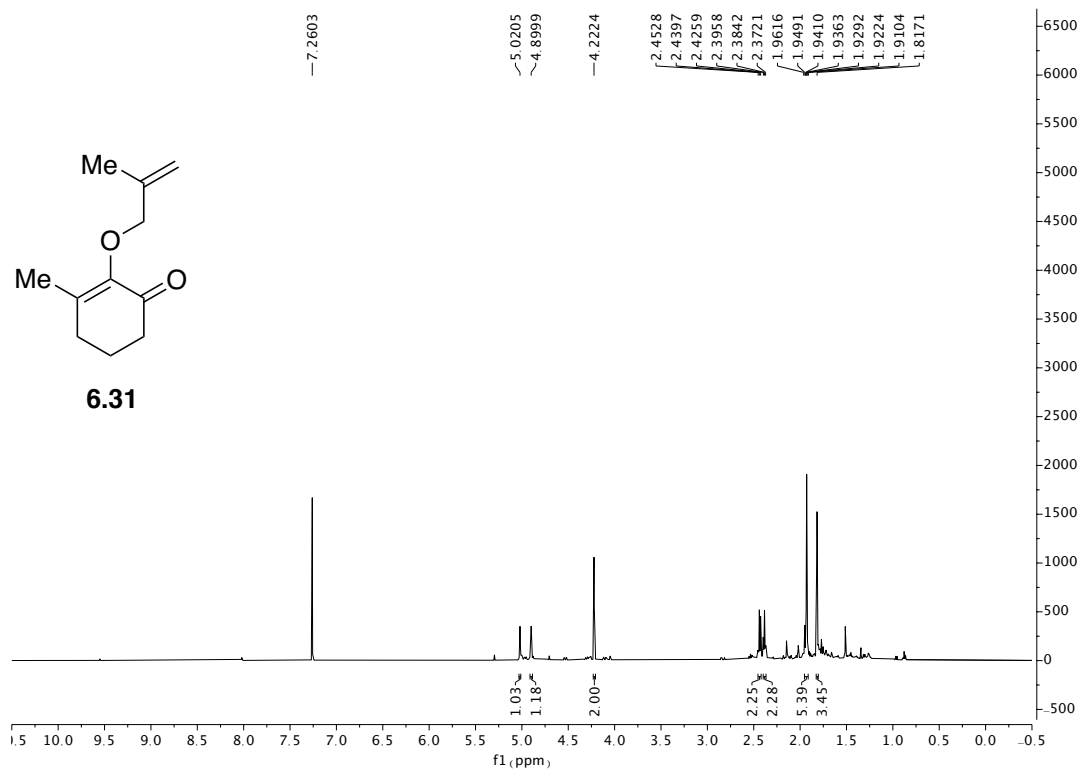


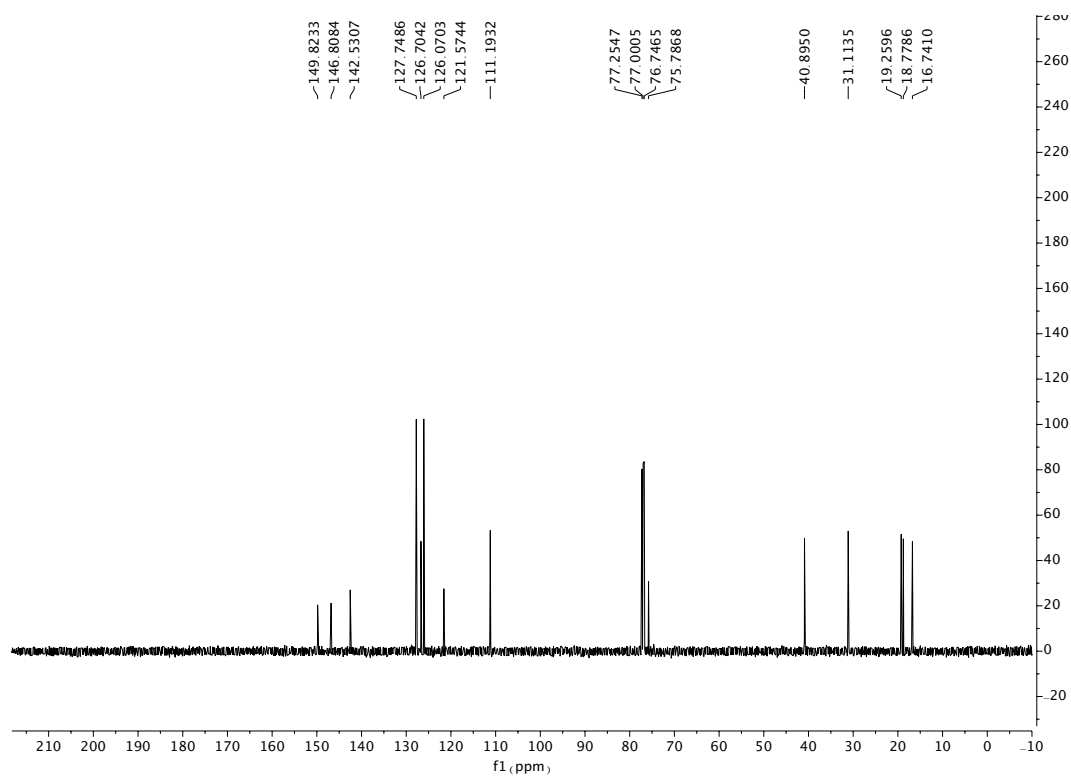
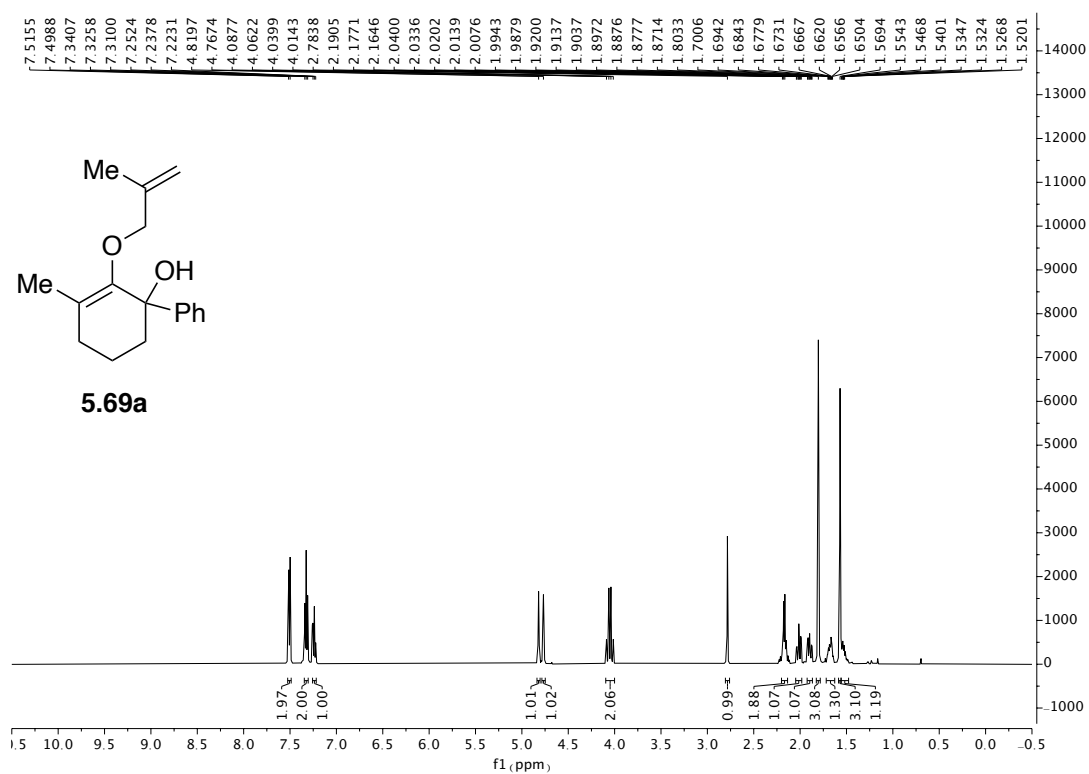


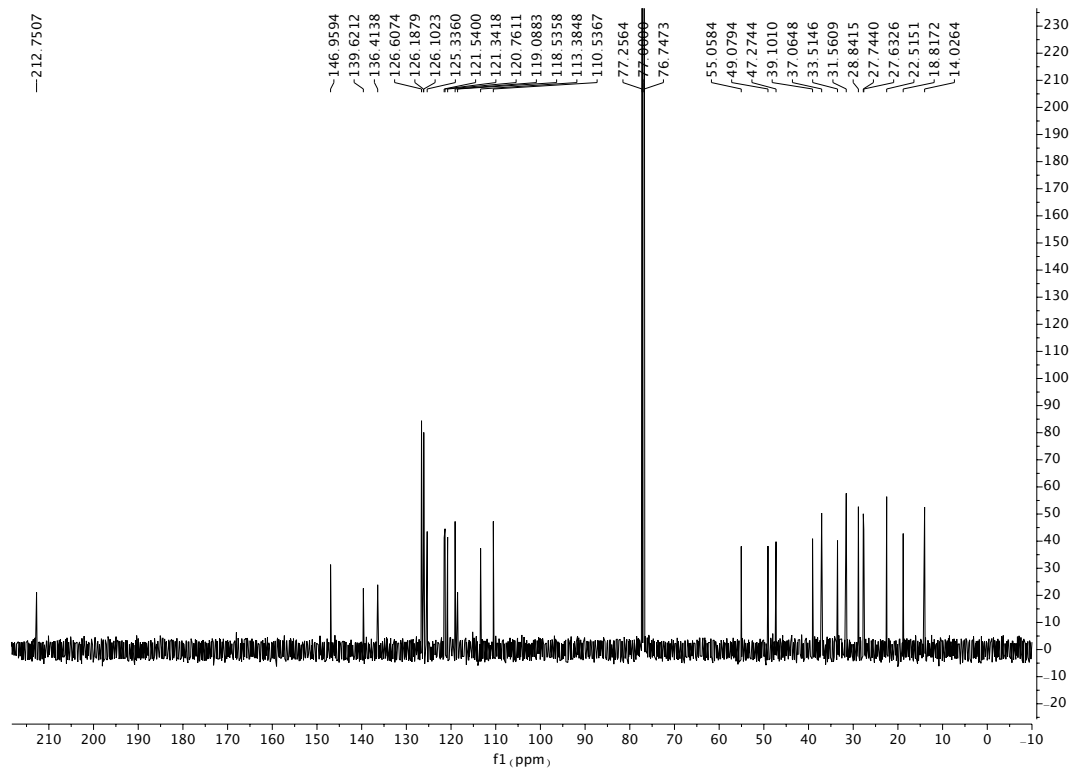
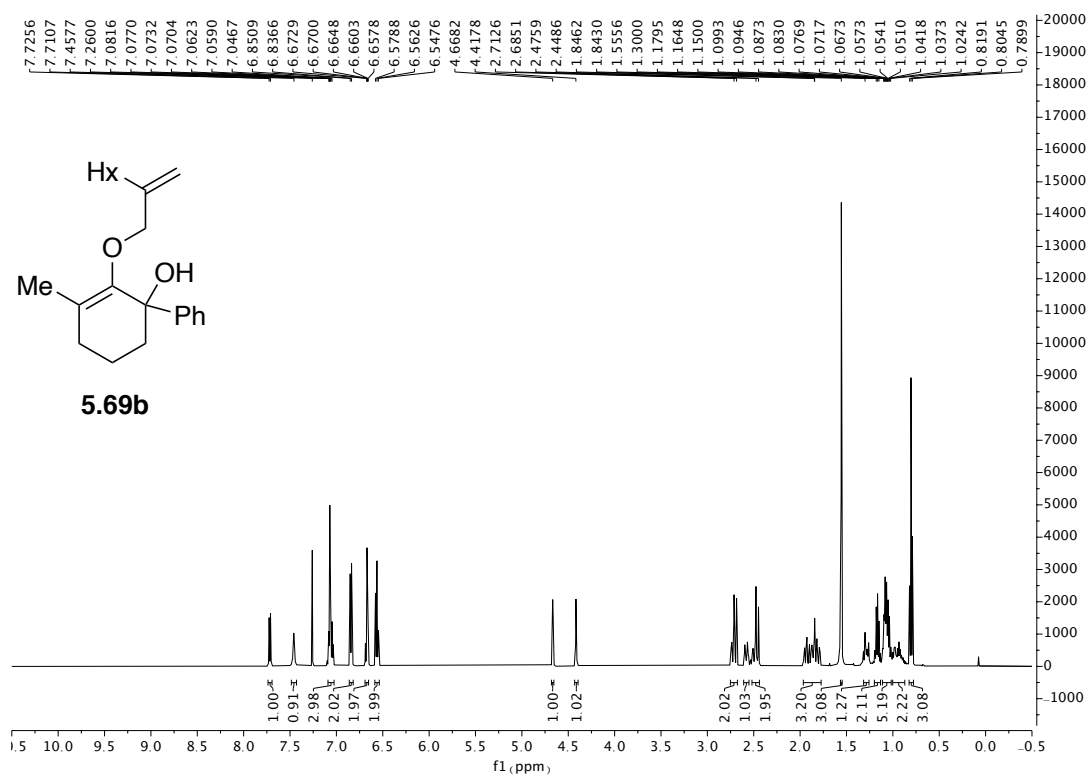


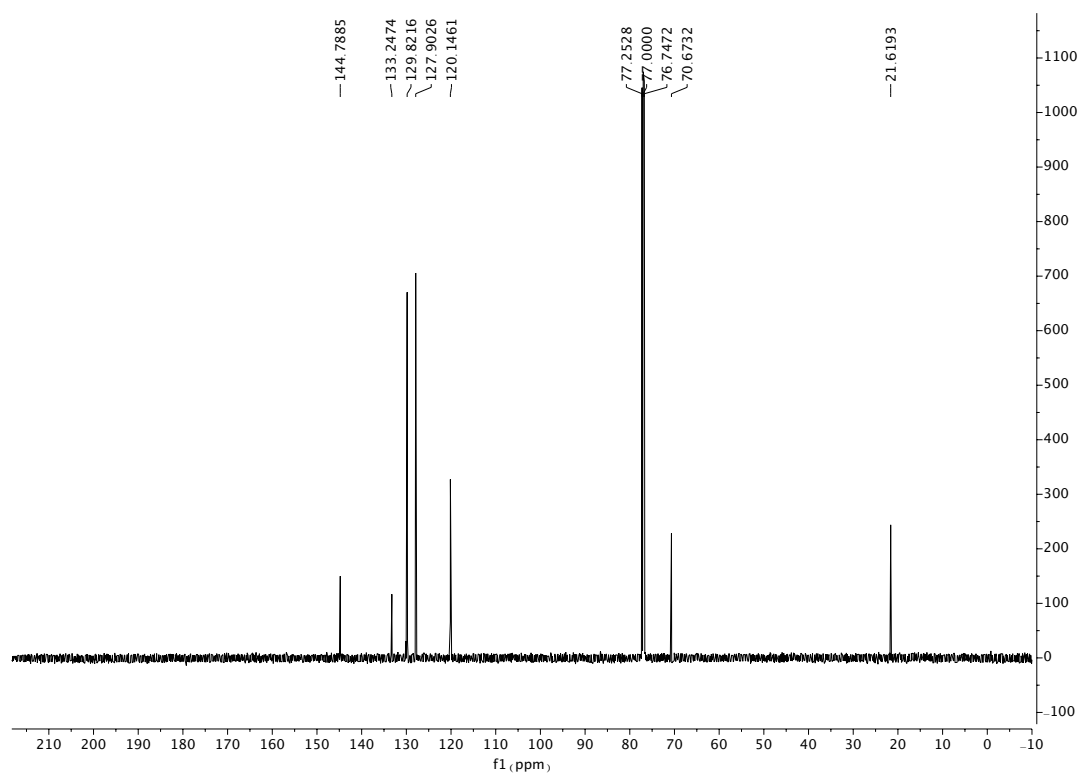
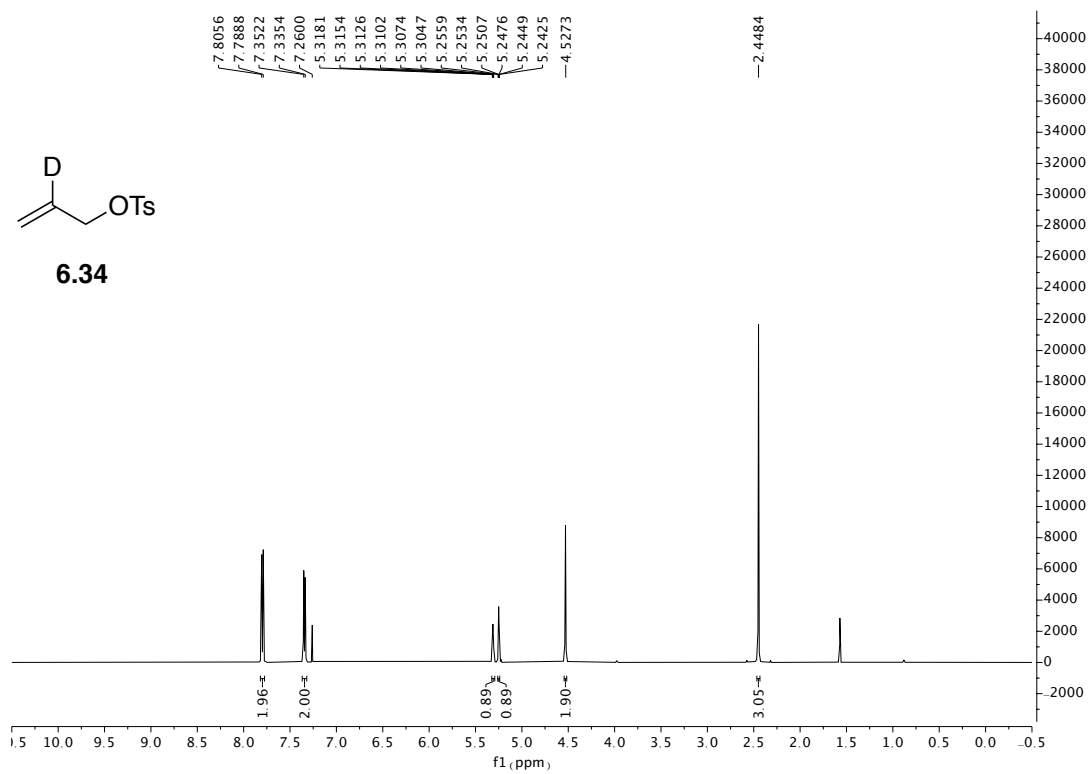


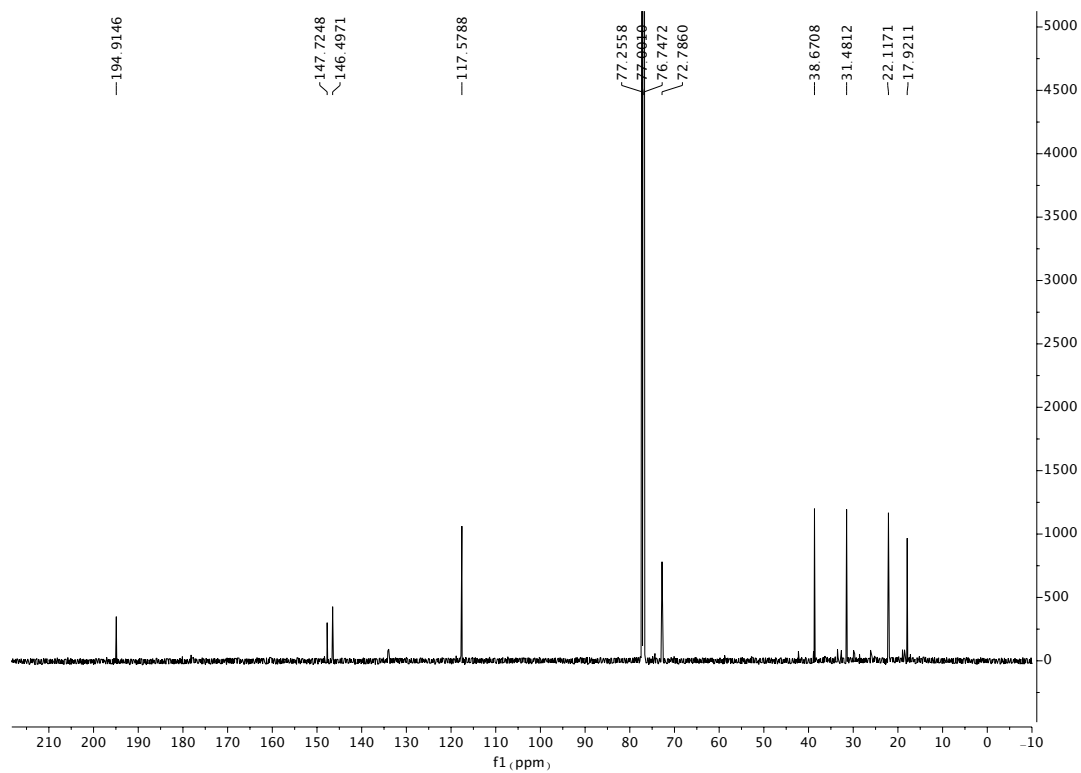
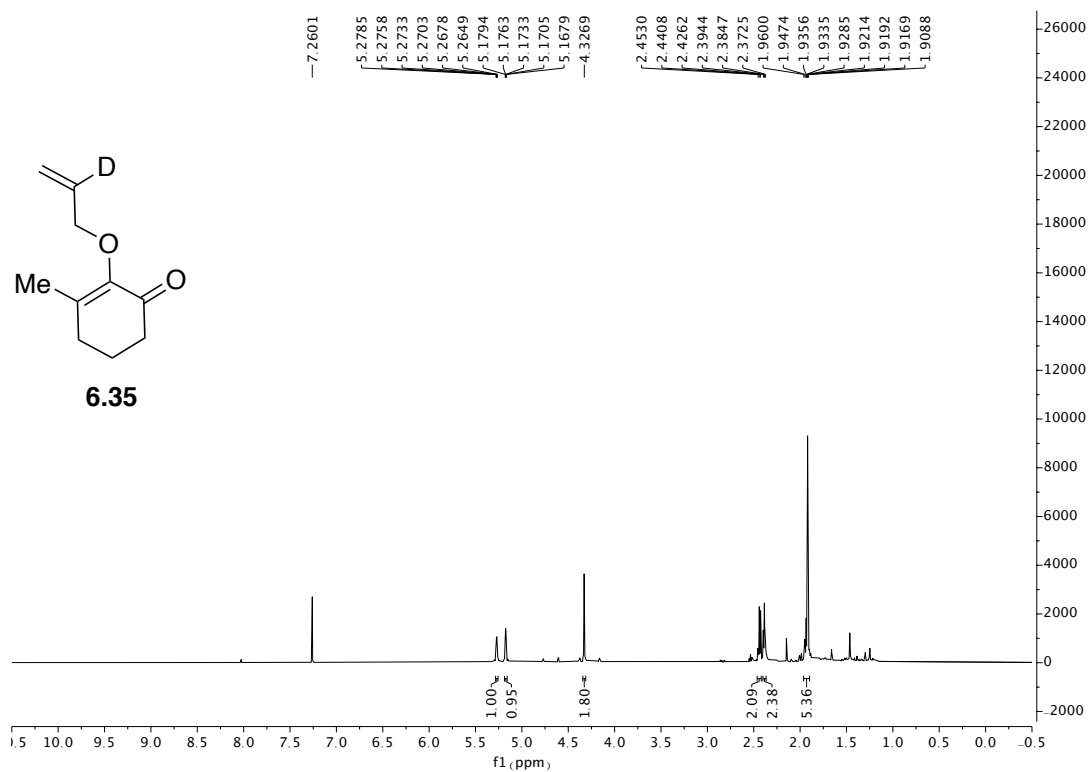


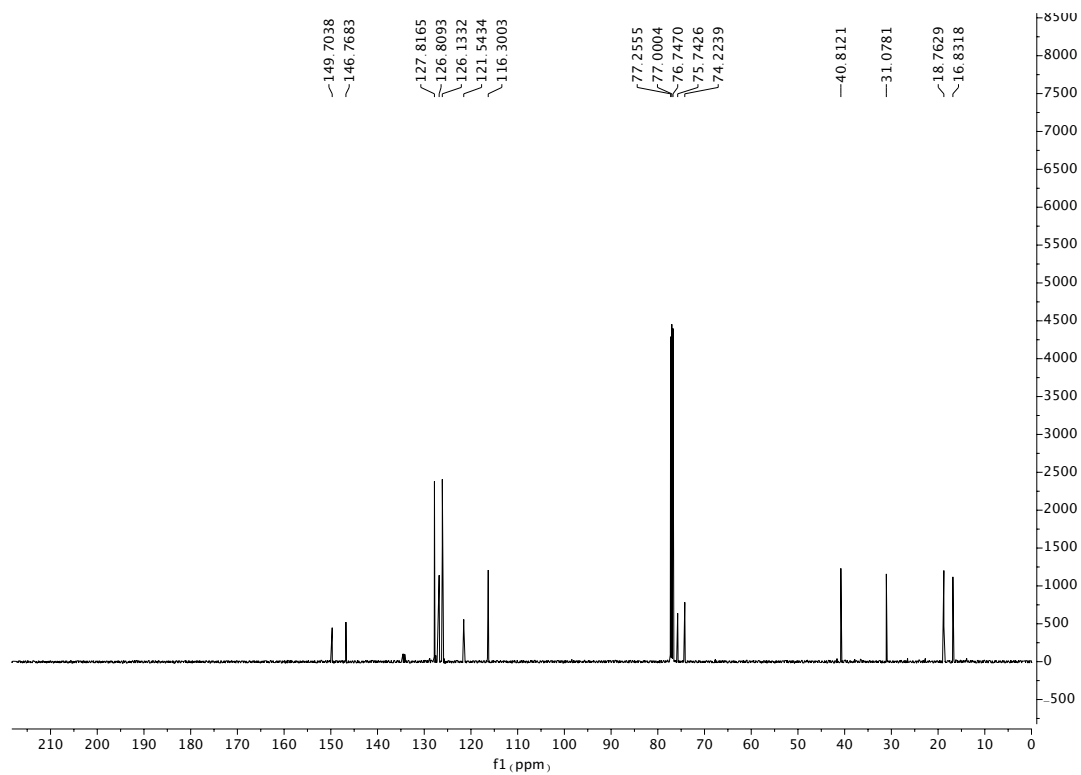
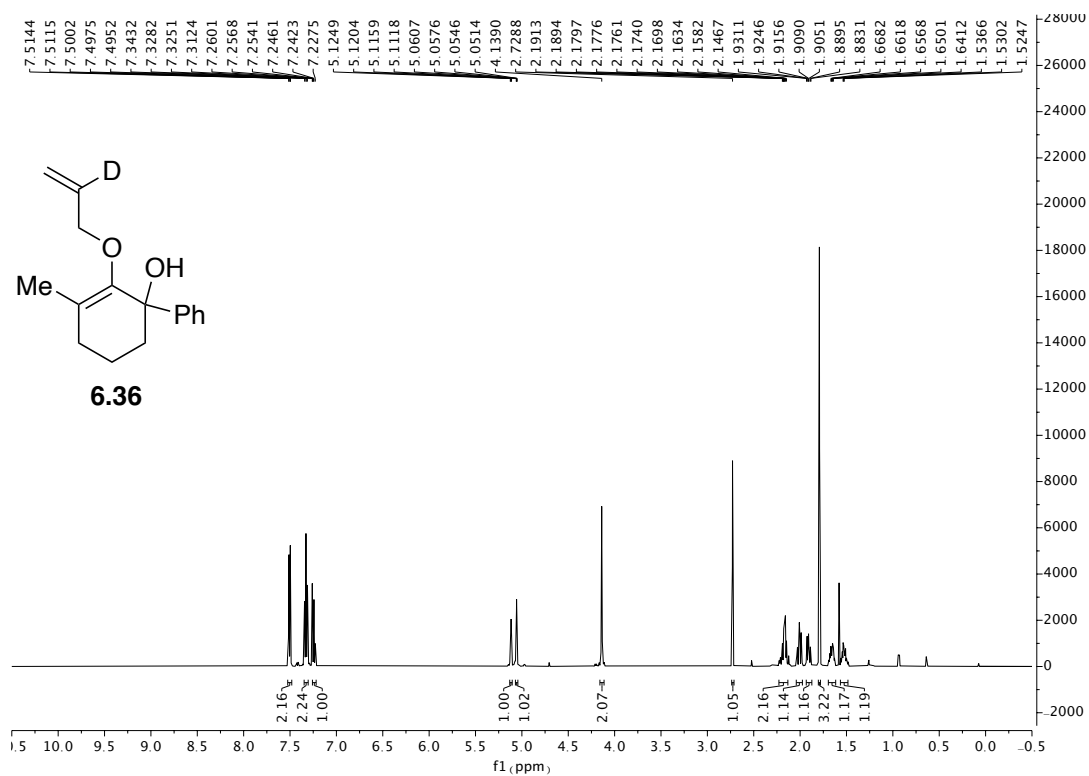


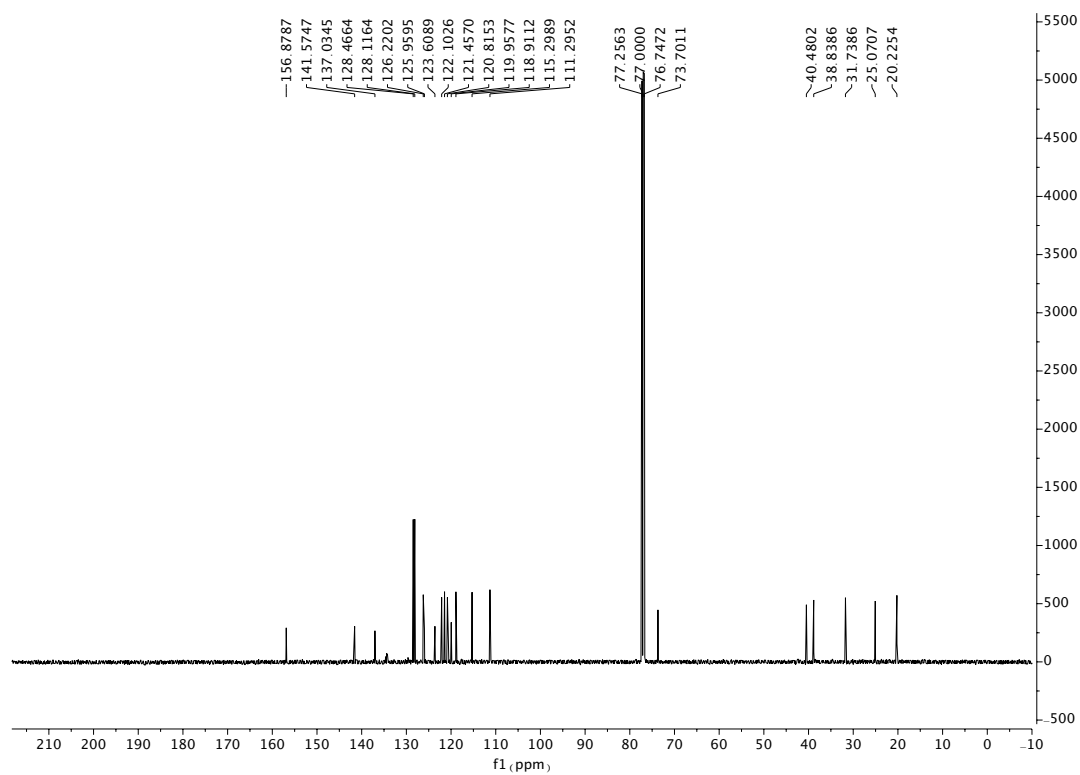
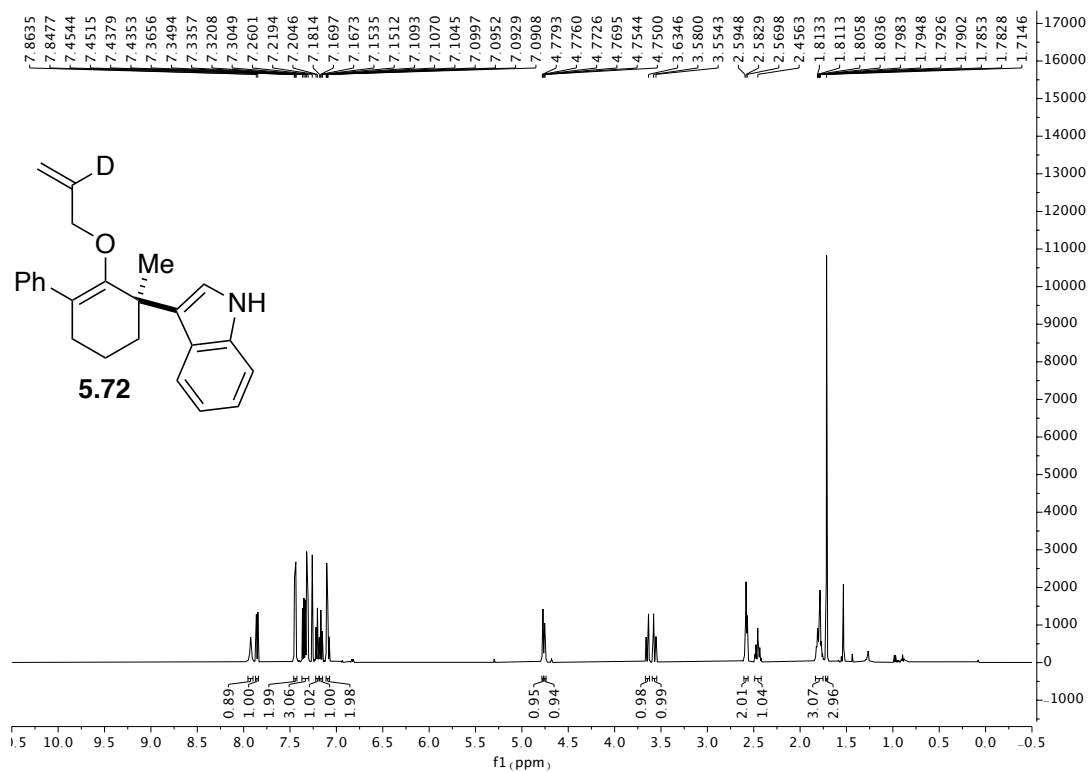


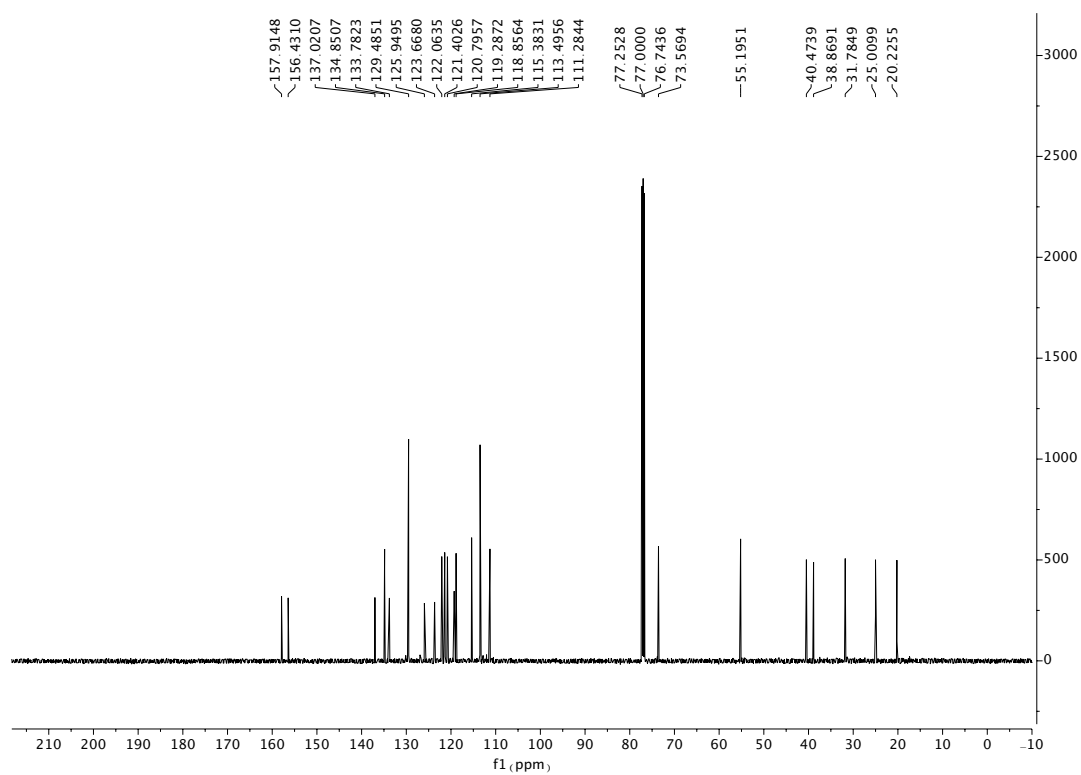
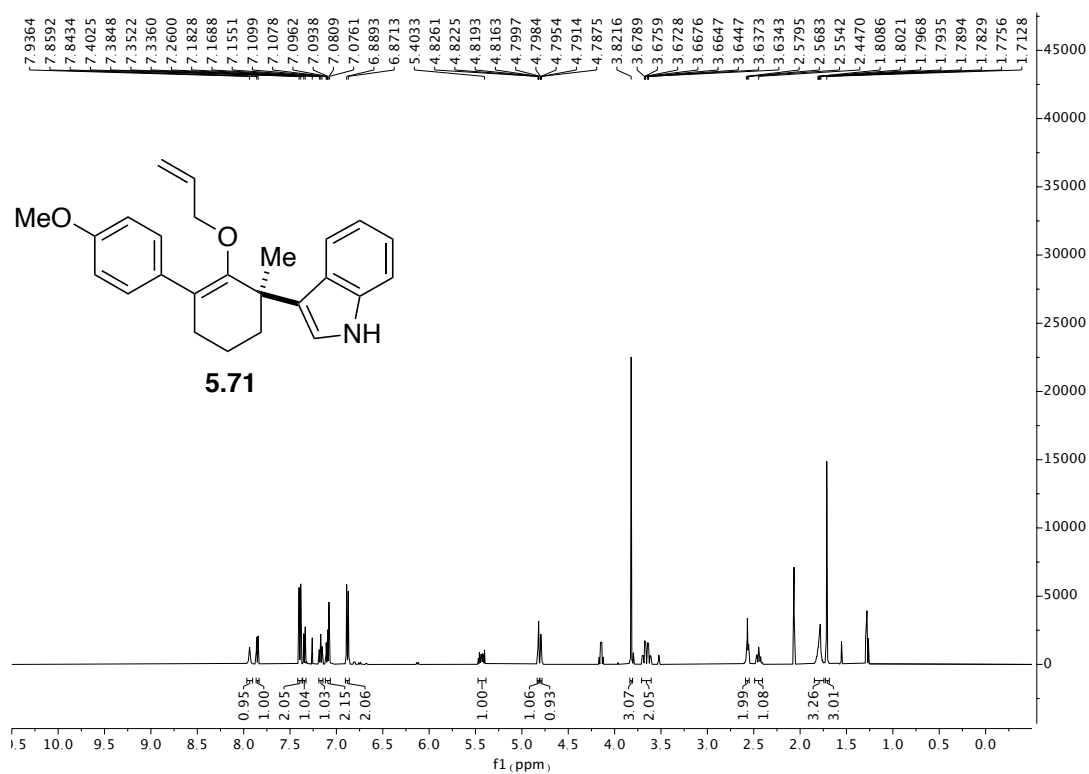


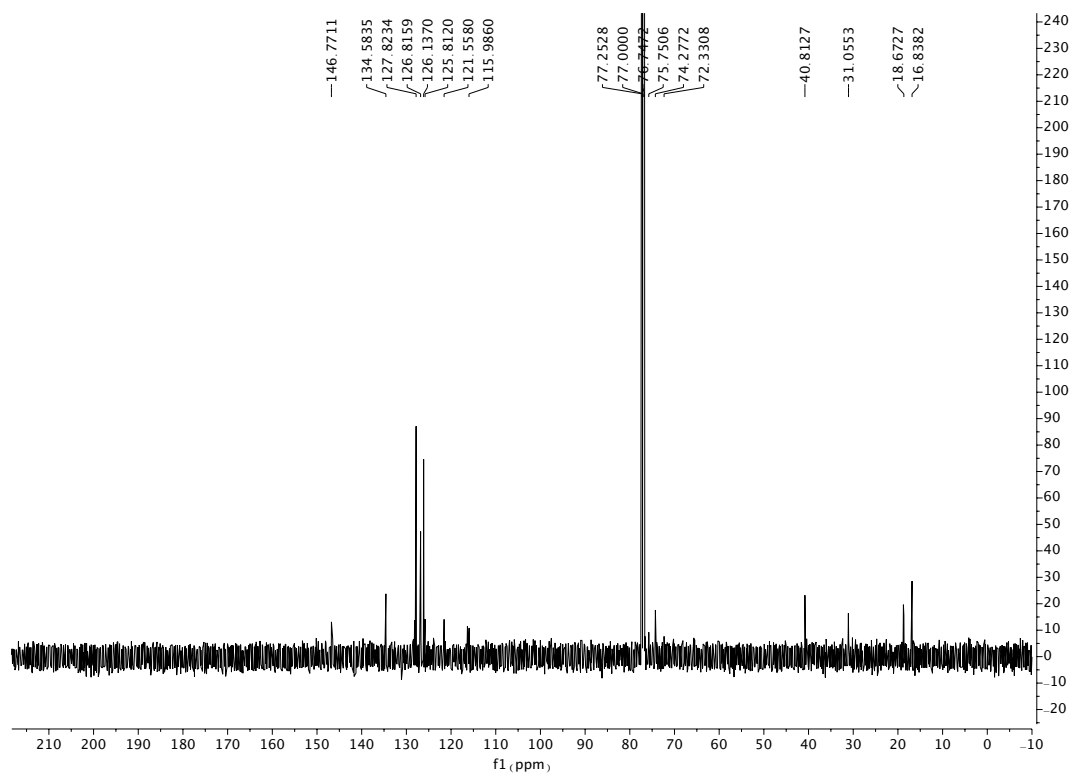
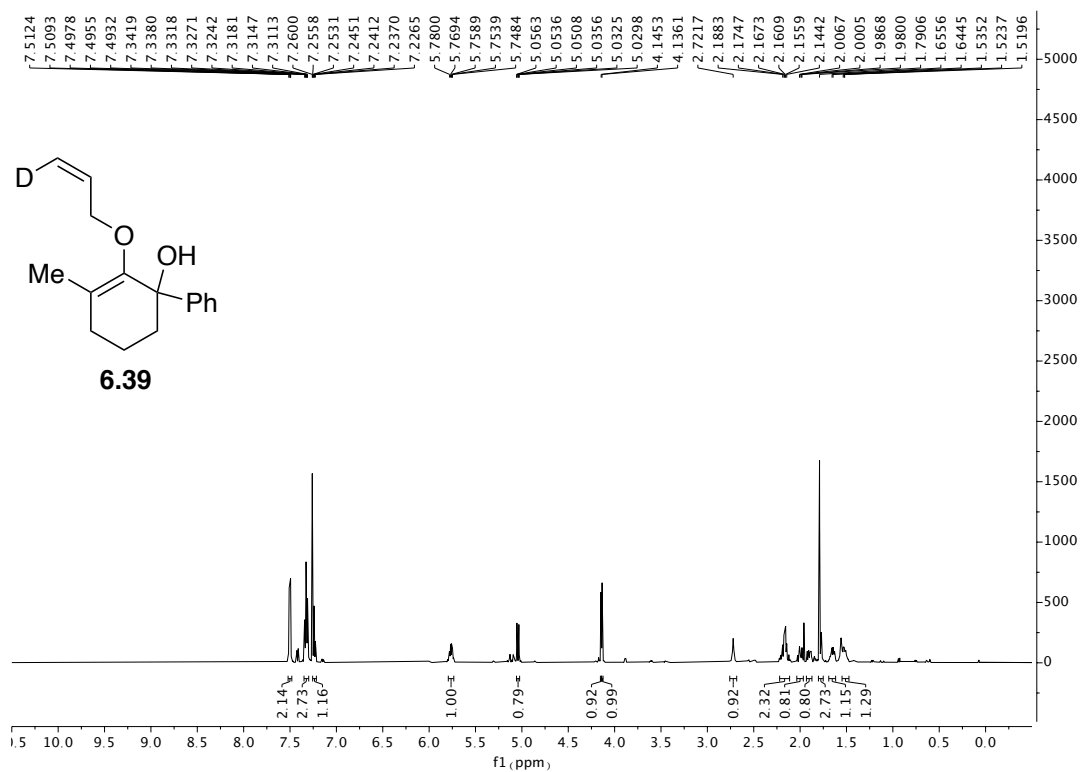


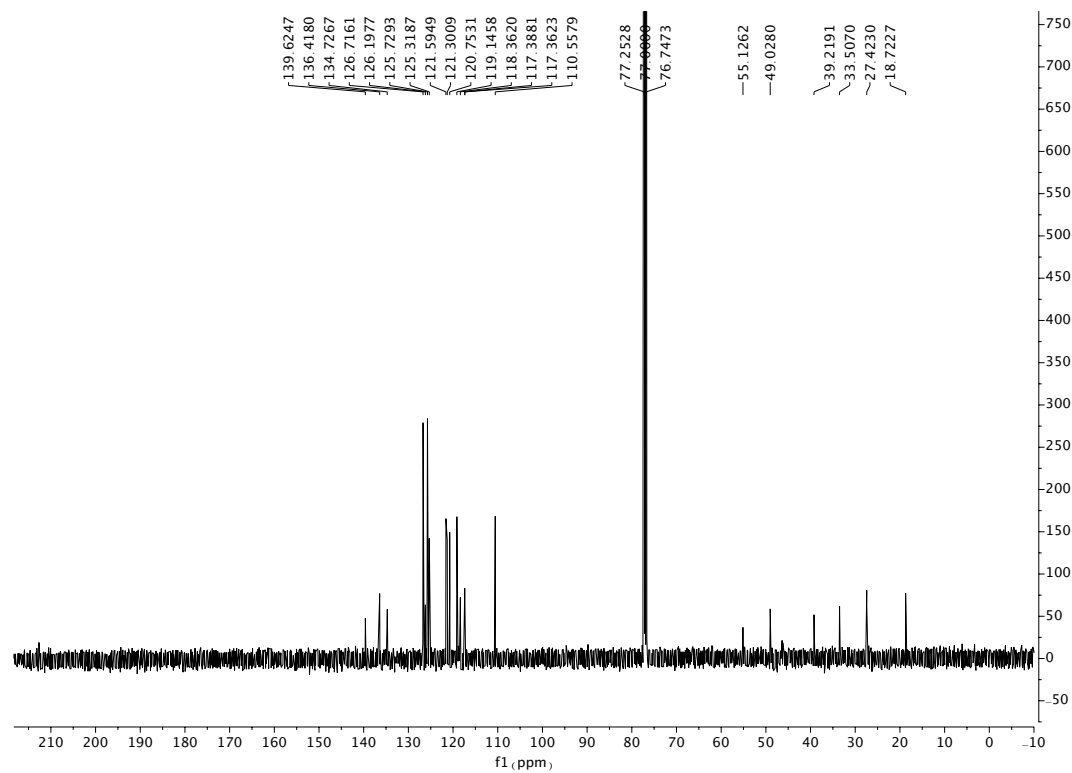
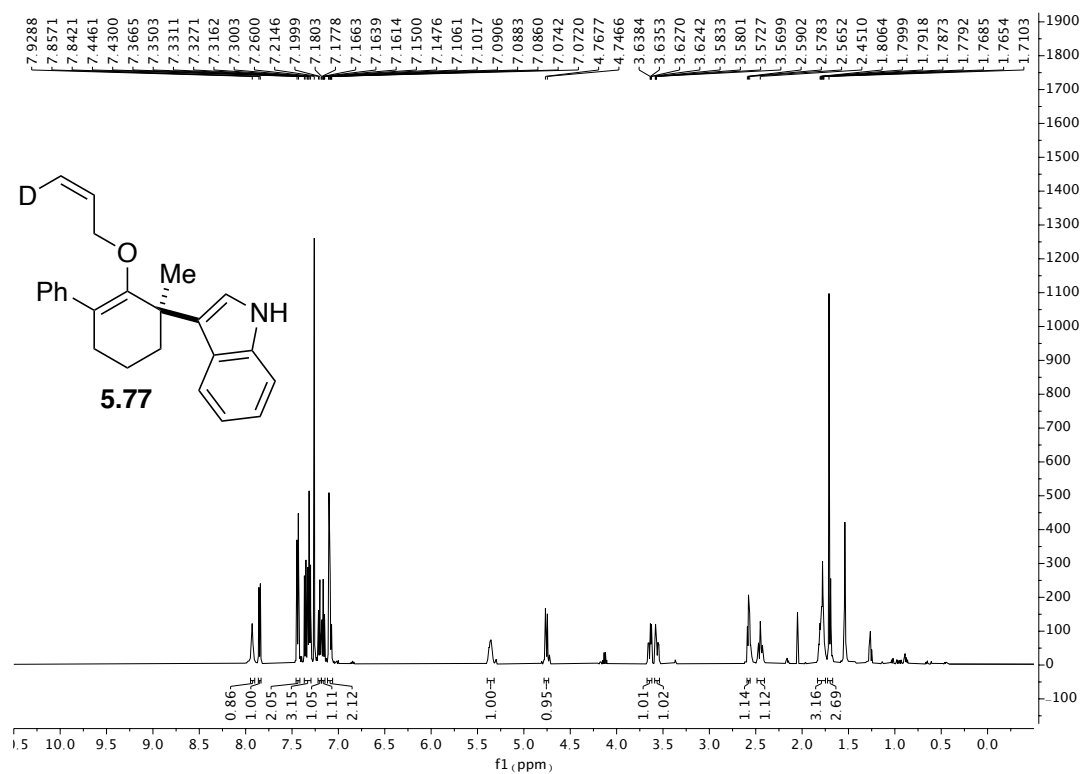


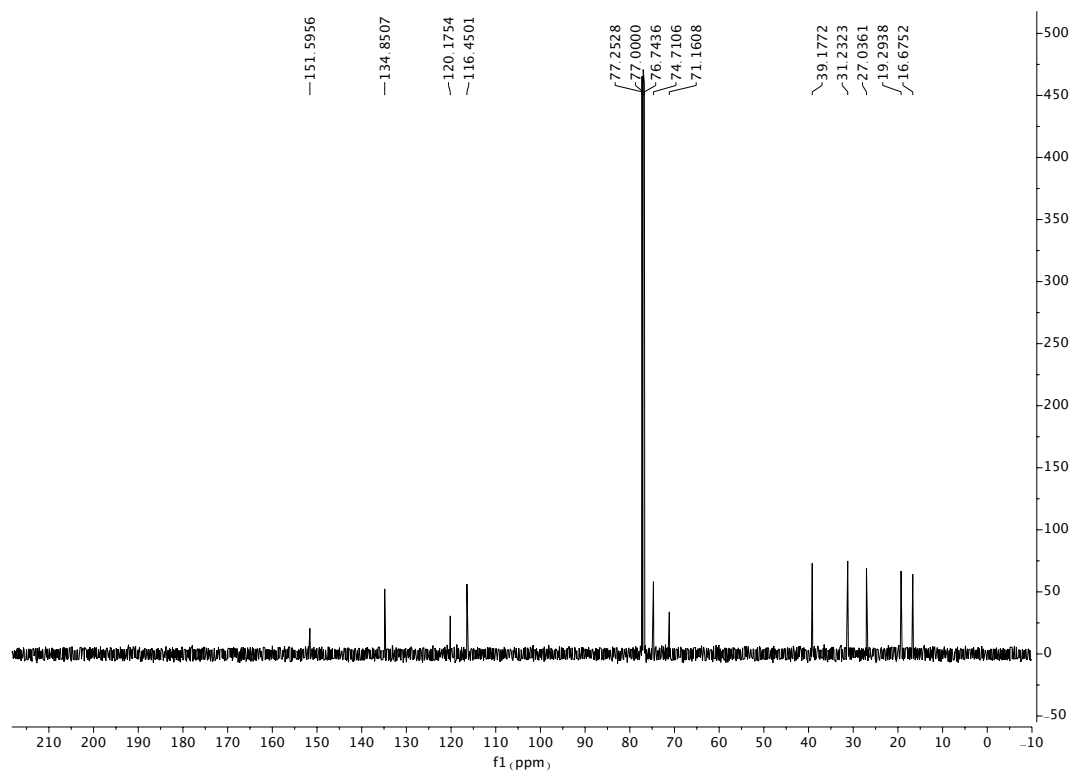
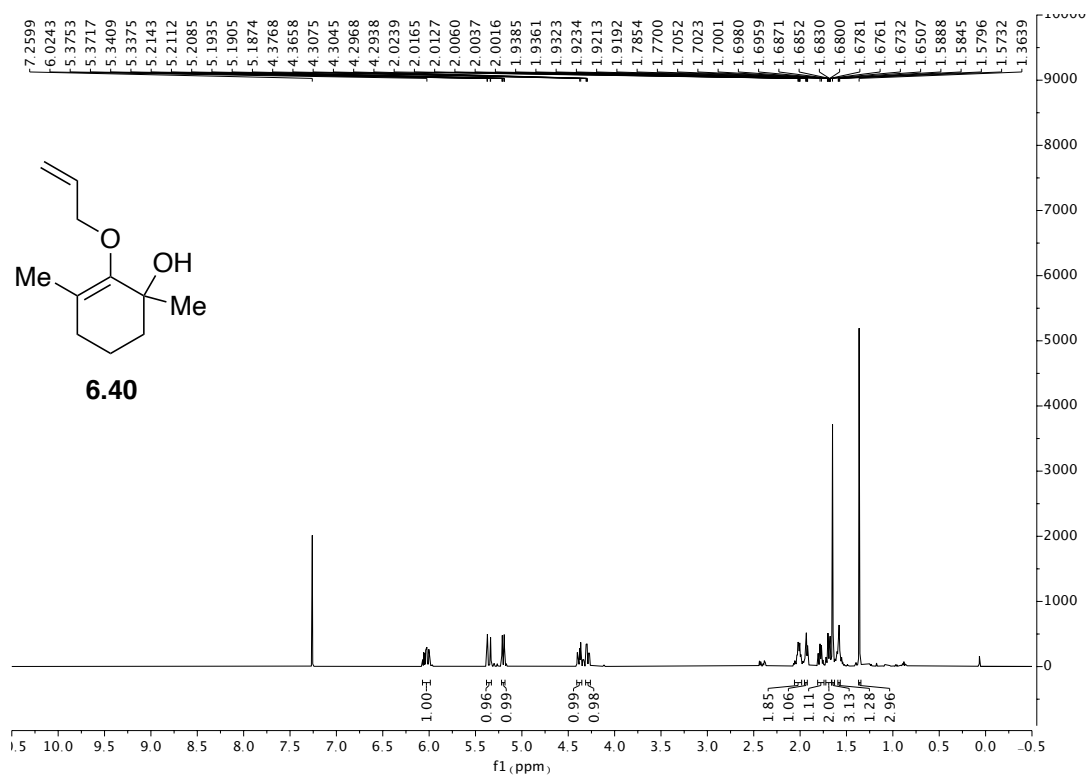


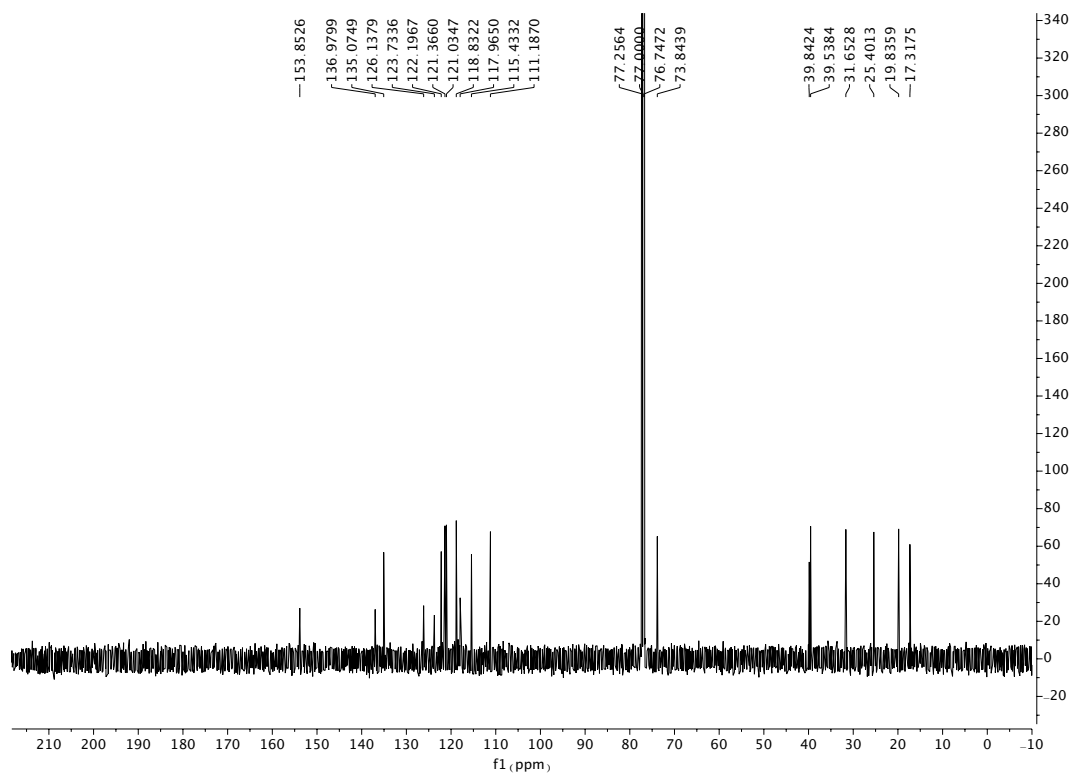
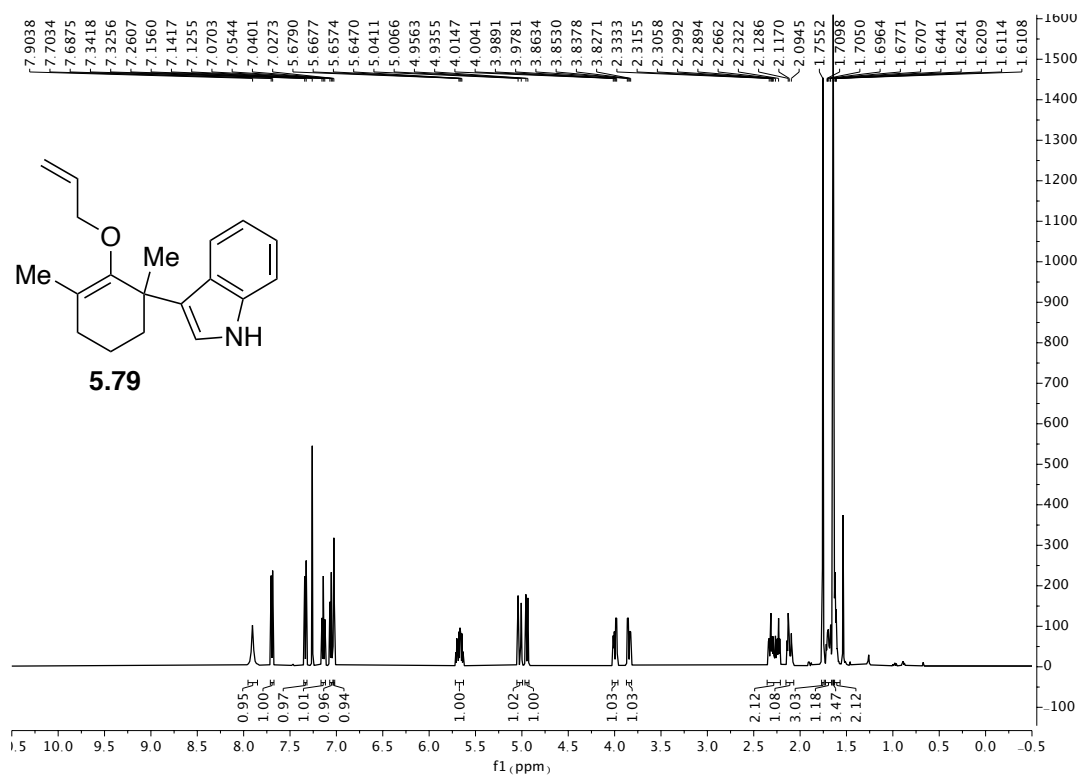












References

1. Chenier, P. J., Favorskii rearrangement in bridged polycyclic compounds. *J. Chem. Educ.* **1978**, *55*, 286.
2. Favorskii, A. E., *J. Russ. Phys. Chem. Soc.* **1894**, 590.
3. Guijarro, D.; Yus, M., The Favorskii Rearrangement: Synthetic Applications. *Curr. Org. Chem.* **2005**, *9*, 1713-1735.
4. Turro, N. J.; Hammond, W. B., Tetramethylcyclopropanone. II. Mechanism of the Favorskii Rearrangement. *J. Am. Chem. Soc.* **1965**, *87*, 3258-3259.
5. Vander Wal, M. N.; Dilger, A. K.; MacMillan, D. W. C., Development of a generic activation mode: nucleophilic α -substitution of ketones via oxy-allyl cations. *Chem. Sci.* **2013**, *4*, 3075-3079.
6. Li, H.; Wu, J., (3+2)-Cycloaddition Reactions of Oxyallyl Cations. *Synthesis* **2015**, *47*, 22-33.
7. Du, J.; Xu, X. X.; Li, Y. F.; Pan, L.; Liu, Q., 3+3 -Cycloaddition Reactions of α -Acidic Isocyanides with 1,3-Dipolar Azomethine Imines. *Org. Lett.* **2014**, *16*, 4004-4007.
8. Hoffmann, H. M. R., The Cycloaddition of Allyl Cations to 1,3-Dienes: General Method for the Synthesis of Seven-Membered Carbocycles. New Synthetic Methods (40). *Angew. Chem. Int. Ed* **1984**, *23*, 1-19.
9. Harmata, M., Exploration of Fundamental and Synthetic Aspects of the Intramolecular 4 + 3 Cycloaddition Reaction. *Acc. Chem. Res.* **2001**, *34*, 595-605.
10. Harmata, M.; Elahmad, S.; Barnes, C. L., Intramolecular 4+3 cycloadditions. Model studies toward the synthesis of ingenanes. *Tetrahedron Lett.* **1995**, *36*, 1397-1400.
11. Nakanishi, W.; West, F. G., Advances in the Nazarov cyclization. *Curr Opin Drug Discov Devel* **2009**, *12*, 732-51.
12. Vaidya, T.; Eisenberg, R.; Frontier, A. J., Catalytic Nazarov Cyclization: The State of the Art. *Chem. Cat. Chem.* **2011**, *3*, 1531-1548.
13. Vinogradov, M. G.; Turova, O. V.; Zlotin, S. G., Nazarov reaction: current trends and recent advances in the synthesis of natural compounds and their analogs. *Org. Biomol. Chem.* **2017**, *15*, 8245-8269.
14. Tang, Q.; Chen, X.; Tiwari, B.; Chi, Y. R., Addition of Indoles to Oxyallyl Cations for Facile Access to α -Indole Carbonyl Compounds. *Org. Lett.* **2012**, *14*, 1922-1925.

15. Liu, C.; Oblak, E. Z.; Vander Wal, M. N.; Dilger, A. K.; Almstead, D. K.; MacMillan, D. W. C., Oxy-Allyl Cation Catalysis: An Enantioselective Electrophilic Activation Mode. *J. Am. Chem. Soc.* **2016**, *138*, 2134-2137.
16. Luo, J.; Jiang, Q.; Chen, H.; Tang, Q., Catalyst-free formation of 1,4-diketones by addition of silyl enolates to oxyallyl zwitterions in situ generated from α -haloketones. *RSC Adv.* **2015**, *5*, 67901-67908.
17. Eaton, P. E.; Cole, T. W., The Cubane System. *J. Am. Chem. Soc.* **1964**, *86*, 962-964.
18. Kuck, D.; Boegge, H., Benzoannelated centropolyquinanes. 2. (all-cis)-Tetrabenzotetracyclo[5.5.1.0⁴,13.0¹⁰,13]tridecane, "fenestrindan". *J. Am. Chem. Soc.* **1986**, *108*, 8107-8109.
19. Mann, J., 3.7 - The Favorskii Rearrangement. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds. Pergamon: Oxford, 1991; pp 839-859.
20. Takeshita, H.; Kawakami, H.; Ikeda, Y.; Mori, A., Synthetic Photochemistry. 65. Synthesis of Hexacyclo[6.4.2.0²,7.0³,11.0⁶,10.0⁹,12]tetradecane. *J. Org. Chem.* **1994**, *59*, 6490-6492.
21. Elford, T. G.; Hall, D. G., Total Synthesis of (+)-Chinensiolid B via Tandem Allylboration/Lactonization. *J. Am. Chem. Soc.* **2010**, *132*, 1488-1489.
22. Liang, G.; Gradl, S. N.; Trauner, D., Efficient Nazarov Cyclizations of 2-Alkoxy-1,4-pentadien-3-ones. *Org. Lett.* **2003**, *5*, 4931-4934.
23. Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J., Chiral Brønsted Acids in the Catalytic Asymmetric Nazarov Cyclization—The First Enantioselective Organocatalytic Electrocyclic Reaction. *Angew. Chem. Int. Ed.* **2007**, *46*, 2097-2100.
24. Spencer III, W. T.; Vaidya, T.; Frontier, A. J., Beyond the Divinyl Ketone: Innovations in the Generation and Nazarov Cyclization of Pentadienyl Cation Intermediates. *Eur. J. Org. Chem.* **2013**, *2013*, 3621-3633.
25. Shoppes, C. W.; Cooke, B. J. A., Intramolecular electrocyclic reactions. Part II. Reactions of 1,5-di-phenylpenta-1,4-dien-3-one. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2271-2276.
26. Shoppee, C. W.; Lack, R. E., Intramolecular electrocyclic reactions. Part I. Structure of 'bromohydroxyphorone': 3-bromo-5-hydroxy-4,4,5,5-tetramethylcyclopent-2-enone. *Journal of the Chemical Society C: Organic* **1969**, 1346-1349.
27. Donmez, S. E.; Soydaş, E.; Aydın, G.; Şahin, O.; Bozkaya, U.; Türkmen, Y. E., Aza-Nazarov Cyclization Reactions via Anion Exchange Catalysis. *Org. Lett.* **2019**, *21*, 554-558.

28. Rasapalli, S.; Sammeta, V. R.; Murphy, Z. F.; Huang, Y.; Boerth, J. A.; Golen, J. A.; Savinov, S. N., Synthesis of C-Ring-Substituted Vasicinones and Luotonins via Regioselective Aza-Nazarov Cyclization of Quinazolinonyl Enones. *Org. Lett.* **2019**, *21*, 9824-9828.
29. Shimada, N.; Ashburn, B. O.; Basak, A. K.; Bow, W. F.; Vicic, D. A.; Tius, M. A., Organocatalytic asymmetric aza-Nazarov cyclization of an azirine. *Chemical Communications* **2010**, *46*, 3774-3775.
30. Riveira, M. J.; Marsili, L. A.; Mischne, M. P., The iso-Nazarov reaction. *Organic & Biomolecular Chemistry* **2017**, *15*, 9255-9274.
31. Corbin, J. R.; Ketelboeter, D. R.; Fernández, I.; Schomaker, J. M., Biomimetic 2-Imino-Nazarov Cyclizations via Eneallene Aziridination. *J. Am. Chem. Soc.* **2020**, *142*, 5568-5573.
32. Tius, M. A.; Chu, C. C.; Nieves-Colberg, R., An imino Nazarov cyclization. *Tetrahedron Letters* **2001**, *42*, 2419-2422.
33. Kim, S.-H.; Cha, J. K., Synthetic Studies Toward caphalotaxine: Functionalization of Tertiary N-Acylhemiaminals by Nazarov Cyclization. *Synthesis* **2000**, *2000*, 2113-2116.
34. Larini, P.; Guarna, A.; Occhiato, E. G., The Lewis Acid-Catalyzed Nazarov Reaction of 2-(N-Methoxycarbonylamino)-1,4-pentadien-3-ones. *Org. Lett.* **2006**, *8*, 781-784.
35. De Simone, F.; Andrès, J.; Torosantucci, R.; Waser, J., Catalytic Formal Homo-Nazarov Cyclization. *Org. Lett.* **2009**, *11*, 1023-1026.
36. Phun, L. H.; Patil, D. V.; Cavitt, M. A.; France, S., A Catalytic Homo-Nazarov Cyclization Protocol for the Synthesis of Heteroaromatic Ring-Fused Cyclohexanones. *Org. Lett.* **2011**, *13*, 1952-1955.
37. Takada, S.; Takaki, N.; Yamada, K.; Nishii, Y., A formal homo-Nazarov cyclization of enantioenriched donor-acceptor cyclopropanes and following transformations: asymmetric synthesis of multi-substituted dihydronaphthalenes. *Org. Biomol. Chem.* **2017**, *15*, 2443-2449.
38. Yadykov, A. V.; Shirinian, V. Z., Recent Advances in the Interrupted Nazarov Reaction. *Adv. Synth. Catal.* **2020**, *362*, 702-723.
39. Dhoro, F.; Tius, M. A., Interrupted Nazarov Cyclization on Silica Gel. *J. Am. Chem. Soc.* **2005**, *127*, 12472-12473.
40. Dhoro, F.; Kristensen, T. E.; Stockmann, V.; Yap, G. P. A.; Tius, M. A., Asymmetric Amine-Intercepted Nazarov Cyclization. *J. Am. Chem. Soc.* **2007**, *129*, 7256-7257.

41. Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G., Highly Diastereoselective Cycloisomerization of Acyclic Trienones. The Interrupted Nazarov Reaction. *J. of Org. Chem.* **1998**, *63*, 2430-2431.
42. William, R.; Wang, S.; Mallick, A.; Liu, X.-W., Interrupting Nazarov Reaction with Different Trapping Modality: Utilizing Potassium Alkynyltrifluoroborate as a σ -Nucleophile. *Org. Lett.* **2016**, *18*, 4458-4461.
43. Grant, T. N.; Rieder, C. J.; West, F. G., Interrupting the Nazarov reaction: domino and cascade processes utilizing cyclopentenyl cations. *Chem. Comm.* **2009**, 5676-5688.
44. Grant, T. N.; West, F. G., Interrupted Nazarov Reactions Using Dichlorocyclopropanes: A Novel Mode of Arene Trapping. *Org. Lett.* **2007**, *9*, 3789-3792.
45. Browder, C. C.; Marmsäter, F. P.; West, F. G., Highly Efficient Trapping of the Nazarov Intermediate with Substituted Arenes. *Org. Lett.* **2001**, *3*, 3033-3035.
46. Wu, Y.-K.; McDonald, R.; West, F. G., Homologous Mukaiyama Reactions via Trapping of the Nazarov Intermediate with Silyloxyalkenes. *Org. Lett.* **2011**, *13*, 3584-3587.
47. Kwon, Y.; McDonald, R.; West, F. G., Organoaluminum-Mediated Interrupted Nazarov Reaction. *Angew. Chem. Int. Ed.* **2013**, *52*, 8616-8619.
48. Basak, A. K.; Tius, M. A., Interrupting the Nazarov Cyclization with Indoles. *Org. Lett.* **2008**, *10*, 4073-4076.
49. Wu, Y.-K.; Dunbar, C. R.; McDonald, R.; Ferguson, M. J.; West, F. G., Experimental and Computational Studies on Interrupted Nazarov Reactions: Exploration of Umpolung Reactivity at the α -Carbon of Cyclopentanones. *J. Am. Chem. Soc.* **2014**, *136*, 14903-14911.
50. Nagaraju, K.; Ma, D., Oxidative coupling strategies for the synthesis of indole alkaloids. *Chem. Soc. Rev.* **2018**, *47*, 8018-8029.
51. Maimone, T. J.; Ishihara, Y.; Baran, P. S., Scalable total syntheses of (-)-hapalindole U and (+)-ambiguine H. *Tetrahedron* **2015**, *71*, 3652-3665.
52. Baran, P. S.; Richter, J. M., Direct Coupling of Indoles with Carbonyl Compounds: Short, Enantioselective, Gram-Scale Synthetic Entry into the Hapalindole and Fischerindole Alkaloid Families. *J. Am. Chem. Soc.* **2004**, *126*, 7450-7451.
53. Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S., Enantiospecific Total Synthesis of the Hapalindoles, Fischerindoles, and Welwitindolinones via a Redox Economic Approach. *J. Am. Chem. Soc.* **2008**, *130*, 17938-17954.

54. Freter, K., Octahydro[1]benzopyrano[3,4-b]indole. *Justus Liebigs Annalen der Chemie* **1978**, 1978, 1357-1364.
55. Liu, C.; Oblak, E. Z.; Vander Wal, M. N.; Dilger, A. K.; Almstead, D. K.; MacMillan, D. W. C., Oxy-Allyl Cation Catalysis: An Enantioselective Electrophilic Activation Mode. *J. Am. Chem. Soc.* **2016**, 138, 2134-2137.
56. Ayala, C. E.; Dange, N. S.; Fronczek, F. R.; Kartika, R., Brønsted Acid Catalyzed α' -Functionalization of Silylenol Ethers with Indole. *Angew. Chem. Int. Ed.* **2015**, 54, 4641–4645.
57. Ayala, C. E.; Dange, N. S.; Stepherson, J. R.; Henry, J. L.; Fronczek, F. R.; Kartika, R., Functionalization of Silyldienol Ethers at the γ -Position via 2-Silyloxypentadienyl Cations. *Org. Lett.* **2016**, 18, 1084-1087.
58. Stepherson, J. R.; Ayala, C. E.; Tugwell, T. H.; Henry, J. L.; Fronczek, F. R.; Kartika, R., Carbazole Annulation via Cascade Nucleophilic Addition–Cyclization Involving 2-(Silyloxy)pentadienyl Cation. *Org. Lett.* **2016**, 18, 3002-3005.
59. Nguyen, T. N.; Setthakarn, K.; May, J. A., Oxyallyl Cation Capture via Electrophilic Deborylation of Organoboronates: Access to α,α' -Substituted Cyclic Ketones. *Org. Lett.* **2019**, 21, 7837-7840.
60. Ayala, C. E.; Dange, N. S.; Fronczek, F. R.; Kartika, R., Brønsted Acid Catalyzed α' -Functionalization of Silylenol Ethers with Indoles. *Angew. Chem. Int. Ed.* **2015**, 54, 4641-4645.
61. Stepherson, J. R.; Fronczek, F. R.; Kartika, R., An expedient synthesis of functionalized 1,4-diketone-derived compounds via silyloxyallyl cation intermediates. *Chem. Commun.* **2016**, 52, 2300-2303.
62. Stepherson, J. R.; Ayala, C. E.; Dange, N. S.; Kartika, R., Nucleophilic Capture of Unsymmetrical Oxyallyl Cations with Indoles under Mild Brønsted Acid Catalysis. *Synlett* **2016**, 27, 320-330.
63. Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C., Enantioselective Organocatalytic Singly Occupied Molecular Orbital Activation: The Enantioselective α -Enolation of Aldehydes. *J. Am. Chem. Soc.* **2007**, 129, 7004-7005.
64. Malone, J. A.; Cleveland, A. H.; Fronczek, F. R.; Kartika, R., Effects of Solvent and Residual Water on Enhancing the Reactivity of Six-Membered Silyloxyallyl Cations toward Nucleophilic Addition. *Org. Lett.* **2016**, 18, 4408-4411.
65. Hughes, E. D.; Ingold, C. K., 55. Mechanism of substitution at a saturated carbon atom. Part IV. A discussion of constitutional and solvent effects on the mechanism, kinetics,

- velocity, and orientation of substitution. *Journal of the Chemical Society (Resumed)* **1935**, 244-255.
66. Solvent Effects on the Rates of Homogeneous Chemical Reactions. In *Solvents and Solvent Effects in Organic Chemistry*, 2010; pp 165-357.
 67. Stepherson, J. R.; Fronczek, F. R.; Kartika, R., An expedient synthesis of functionalized 1,4-diketone-derived compounds via silyloxyallyl cation intermediates. *Chem. Commun.* **2016**, 52, 2300-2303.
 68. Bresnahan, C. G.; Taylor-Edinbyrd, K. A.; Cleveland, A. H.; Malone, J. A.; Dange, N. S.; Milet, A.; Kumar, R.; Kartika, R., Mechanistic Perspectives in the Regioselective Indole Addition to Unsymmetrical Silyloxyallyl Cations. *J. Org. Chem.* **2019**, 84, 7166-7174.
 69. Cernijenko, A.; Risgaard, R.; Baran, P. S., 11-Step Total Synthesis of (-)-Maoecrystal V. *J. Am. Chem. Soc.* **2016**, 138, 9425-9428.
 70. Cox, J. B.; Kimishima, A.; Wood, J. L., Total Synthesis of Herquiline B and C. *J. Am. Chem. Soc.* **2019**, 141, 25-28.
 71. Li, W.-D. Z.; Ma, B.-C., A Simple Biomimetic Synthesis of dl-Chamaejasmine, a Unique 3,3'-Biflavanone. *Org. Lett.* **2005**, 7, 271-274.
 72. Trost, B. M.; Doherty, G. A., An Asymmetric Synthesis of the Tricyclic Core and a Formal Total Synthesis of Roseophilin via an Enyne Metathesis. *J. Am. Chem. Soc.* **2000**, 122, 3801-3810.
 73. Paal, C., Ueber die Derivate des Acetophenonacetessigesters und des Acetonylacetessigesters. *Ber. Dtsch. Chem. Ges.* **1884**, 17, 2756-2767.
 74. Amarnath, V.; Amarnath, K., Intermediates in the Paal-Knorr Synthesis of Furans. *J. Org. Chem.* **1995**, 60, 301-307.
 75. Roman, G., Chemoselective aminomethylation of bifunctional substrates: carbonyl versus phenolic hydroxyl, carbonyl versus pyrazole and pyrrole versus phenolic hydroxyl as competing activating groups. *Tetrahedron Lett.* **2014**, 55, 1229-1233.
 76. Knorr, L., Synthese von Furfuranderivaten aus dem Diacetbernsteinsäureester. *Ber. Dtsch. Chem. Ges.* **1884**, 17, 2863-2870.
 77. Kaleta, Z.; Makowski, B. T.; Soós, T.; Dembinski, R., Thionation Using Fluorous Lawesson's Reagent. *Org. Lett.* **2006**, 8, 1625-1628.
 78. Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M., Microwave-Assisted Paal-Knorr Reaction – Three-Step Regiocontrolled Synthesis of Polysubstituted Furans, Pyrroles and Thiophenes. *Eur. J. Org. Chem.* **2005**, 2005, 5277-5288.

79. Stauffer, F.; Neier, R., Synthesis of Tri- and Tetrasubstituted Furans Catalyzed by Trifluoroacetic Acid. *Org. Lett.* **2000**, *2*, 3535-3537.
80. Raghavan, S.; Anuradha, K., Solid-Phase Synthesis of Heterocycles from 1,4-Diketone Synthons. *Synlett* **2003**, *2003*, 0711-0713.
81. Zhang, F.; Du, P.; Chen, J.; Wang, H.; Luo, Q.; Wan, X., Co-Catalyzed Synthesis of 1,4-Dicarbonyl Compounds Using TBHP Oxidant. *Org. Lett.* **2014**, *16*, 1932-1935.
82. Zhu, X.; Lin, Y.; Sun, Y.; Beard, M. C.; Yan, Y., Lead-Halide Perovskites for Photocatalytic α -Alkylation of Aldehydes. *J. Am. Chem. Soc.* **2019**, *141*, 733-738.
83. Cuccu, F.; Serusi, L.; Luridiana, A.; Secci, F.; Caboni, P.; Aitken, D. J.; Frongia, A., Tandem Wittig Reaction–Ring Contraction of Cyclobutanes: A Route to Functionalized Cyclopropanecarbaldehydes. *Org. Lett.* **2019**, *21*, 7755-7758.
84. Stetter, H., Catalyzed Addition of Aldehydes to Activated Double Bonds—A New Synthetic Approach. *Angew. Chem. Int. Ed* **1976**, *15*, 639-647.
85. Malone, J. A.; Van Houten, J. P.; Ganiu, M. O.; Nepal, B.; Kartika, R., Brønsted Acid Catalyzed Synthesis of Functionalized 1,4- and 1,6-Dicarbonyl Monosilyl Enol Ethers under Operationally Practical Conditions. *J. Org. Chem.* **2017**, *82*, 10659-10664.
86. Esumi, N.; Suzuki, K.; Nishimoto, Y.; Yasuda, M., Synthesis of 1,4-Dicarbonyl Compounds from Silyl Enol Ethers and Bromocarbonyls, Catalyzed by an Organic Dye under Visible-Light Irradiation with Perfect Selectivity for the Halide Moiety over the Carbonyl Group. *Org. Lett.* **2016**, *18*, 5704-5707.
87. Yasuda, M.; Tsuji, S.; Shigeyoshi, Y.; Baba, A., Cross-Coupling Reaction of α -Chloroketones and Organotin Enolates Catalyzed by Zinc Halides for Synthesis of γ -Diketones. *J. Am. Chem. Soc.* **2002**, *124*, 7440-7447.
88. Baran, P. S.; DeMartino, M. P., Intermolecular Oxidative Enolate Heterocoupling. *Angew. Chem. Int. Ed.* **2006**, *45*, 7083-7086.
89. Biju, A. T.; Kuhl, N.; Glorius, F., Extending NHC-Catalysis: Coupling Aldehydes with Unconventional Reaction Partners. *Acc. Chem. Res.* **2011**, *44*, 1182-1195.
90. Esposti, S.; Dondi, D.; Fagnoni, M.; Albini, A., Acylation of Electrophilic Olefins through Decatungstate-Photocatalyzed Activation of Aldehydes. *Angew. Chem. Int. Ed.* **2007**, *46*, 2531-2534.
91. Zhang, J.; Xing, C.; Tiwari, B.; Chi, Y. R., Catalytic Activation of Carbohydrates as Formaldehyde Equivalents for Stetter Reaction with Enones. *J. Am. Chem. Soc.* **2013**, *135*, 8113-8116.

92. Steward, K. M.; Gentry, E. C.; Johnson, J. S., Dynamic Kinetic Resolution of α -Keto Esters via Asymmetric Transfer Hydrogenation. *J. Am. Chem. Soc.* **2012**, *134*, 7329-7332.
93. Yasuda, M.; Katoh, Y.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N., NMR Studies of Five-Coordinate Tin Enolate: An Efficient Reagent for Halo Selective Reaction toward α -Halo Ketone or α -Halo Imine. *J. Org. Chem* **1994**, *59*, 4386-4392.
94. Shin-ichi, U.; Hideki, Y.; Hiroshi, S.; Koichiro, O., Triethylborane Induced Radical Reaction of Gallium Enolates with α -Halo Esters. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2049-2052.
95. DeMartino, M. P.; Chen, K.; Baran, P. S., Intermolecular Enolate Heterocoupling: Scope, Mechanism, and Application. *J. Am. Chem. Soc.* **2008**, *130*, 11546-11560.
96. Stetter, H.; Schreckenber, M., A New Method for Addition of Aldehydes to Activated Double Bonds. *Angew. Chem. Int. Ed* **1973**, *12*, 81-81.
97. Aupoix, A.; Vo-Thanh, G., Solvent-Free Synthesis of Alkylthiazolium-Based Ionic Liquids and their Use as Catalysts in the Intramolecular Stetter Reaction. *Synlett* **2009**, *2009*, 1915-1920.
98. Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A., The Thiazolium-Catalyzed Sila-Stetter Reaction: Conjugate Addition of Acylsilanes to Unsaturated Esters and Ketones. *J. Am. Chem. Soc.* **2004**, *126*, 2314-2315.
99. Christmann, M., New Developments in the Asymmetric Stetter Reaction. *Angew. Chem. Int. Ed.* **2005**, *44*, 2632-2634.
100. Yetra, S. R.; Patra, A.; Biju, A. T., Recent Advances in the N-Heterocyclic Carbene (NHC)-Organocatalyzed Stetter Reaction and Related Chemistry. *Synthesis* **2015**, *47*, 1357-1378.
101. Garapati, V. K. R.; Gravel, M., Oxazolium Salts as Organocatalysts for the Umpolung of Aldehydes. *Org. Lett.* **2018**, *20*, 6372-6375.
102. Harrington, P. E.; Tius, M. A., Synthesis and Absolute Stereochemistry of Roseophilin. *J. Am. Chem. Soc.* **2001**, *123*, 8509-8514.
103. Randl, S.; Blechert, S., Concise Enantioselective Synthesis of 3,5-Dialkyl-Substituted Indolizidine Alkaloids via Sequential Cross-Metathesis–Double-Reductive Cyclization. *J. Org. Chem* **2003**, *68*, 8879-8882.
104. Yasuda, M.; Oh-Hata, T.; Shibata, I.; Baba, A.; Matsuda, H., Facile control of regioselectivity in the reaction of tin enolates with α -halogeno carbonyls by additives. *J. Chem. Soc., Perkin Trans. I* **1993**, 859-865.

105. Baciocchi, E.; Muraglia, E., Synthesis of γ -haloesters and γ -ketoesters by homolytic addition of carbon radicals generated by α -haloesters and triethylborane to alkenes and silyl enol ethers. *Tetrahedron Lett.* **1994**, *35*, 2763-2766.
106. Marx, V. M.; Burnell, D. J., Nazarov Cyclizations of an Allenyl Vinyl Ketone with Interception of the Oxyallyl Cation Intermediate for the Formation of Carbon–Carbon Bonds. *J. Am. Chem. Soc.* **2010**, *132*, 1685-1689.
107. Wu, Y.-K.; West, F. G., Formal Homologous Aldol Reactions: Interrupting the Nazarov Cyclization via Carboalkoxylation of Alkynes. *Org. Lett.* **2014**, *16*, 2534-2537.
108. Kwon, Y.; Schatz, D. J.; West, F. G., 1,4-Diketones from Cross-Conjugated Dienones: Potassium Permanganate-Interrupted Nazarov Reaction. *Angew. Chem. Int. Ed.* **2015**, *54*, 9940-9943.
109. Paal, C., Ueber die Derivate des Acetophenonacetessigesters und des Acetonylacetessigesters. *Berichte der deutschen chemischen Gesellschaft* **1884**, *17*, 2756-2767.
110. Knorr, L., Synthetische Versuche mit dem Acetessigester. II. Mittheilung: Ueberführung des Diacetbernsteinsäureesters und des Acetessigesters in Pyrrolderivate. *Justus Liebigs Ann. Chem.* **1886**, *236*, 290-332.
111. Tracey, M. R.; Hsung, R. P.; Lambeth, R. H., Allylated β -Ketoesters as Precursors in Paal-Knorr-Type Pyrrole Synthesis: Preparations of Chiral and Bispyrroles. *Synthesis* **2004**, *2004*, 918-922.
112. Ferreira, V. F.; de Souza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G., RECENT ADVANCES IN THE SYNTHESIS OF PYRROLES. *Org. Prep. Proced. Int.* **2001**, *33*, 411-454.
113. Balme, G., Pyrrole Syntheses by Multicomponent Coupling Reactions. *Angew. Chem. Int. Ed n* **2004**, *43*, 6238-6241.
114. Kostyanovsky, R. G.; Kadorkina, G. K.; Mkhitarian, A. G.; Chervin, I. I.; Aliev, A. E., New Scope and Limitations in the Knorr–Paal Synthesis of Pyrroles. *Mendeleev Communications* **1993**, *3*, 21-23.
115. Rao, H. S. P.; Jothilingam, S., Facile Microwave-Mediated Transformations of 2-Butene-1,4-diones and 2-Butyne-1,4-diones to Furan Derivatives. *J. Org. Chem.* **2003**, *68*, 5392-5394.
116. Ismail, K. A.; El-Tombary, A. A.; Aboulwafa, O. M.; Omar, A.-M. M. E.; El-Rewini, S. H., Novel Steroidal 1,4-Diketones and Pyridazine Derivatives as Potential Antiestrogens. *Archiv der Pharmazie* **1996**, *329*, 433-437.

117. Dong, Y., Le Quesne, P. W., Total Synthesis of Magnolamide. *Heterocycles* **2002**, *56*, 221-225.
118. Zhang, L.; Zhang, J.; Ma, J.; Cheng, D.-J.; Tan, B., Highly Atroposelective Synthesis of Arylpyrroles by Catalytic Asymmetric Paal–Knorr Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 1714-1717.
119. Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A.; Graham, D. G., Intermediates in the Paal-Knorr Synthesis of Pyrroles. *J. Org. Chem.* **1991**, *56*, 6924-6931.
120. Xu, X. T.; Mou, X. Q.; Xi, Q. M.; Liu, W. T.; Liu, W. F.; Sheng, Z. J.; Zheng, X.; Zhang, K.; Du, Z. Y.; Zhao, S. Q.; Wang, S. H., Anti-inflammatory activity effect of 2-substituted-1,4,5,6-tetrahydrocyclopenta b pyrrole on TPA-induced skin inflammation in mice. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5334-5339.
121. Guan, H.; Laird, A. D.; Blake, R. A.; Tang, C.; Liang, C., Design and synthesis of aminopropyl tetrahydroindole-based indolin-2-ones as selective and potent inhibitors of Src and Yes tyrosine kinase. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 187-190.
122. Bergauer, M.; Hubner, H.; Gmeiner, P., Practical ex-chiral-pool methodology for the synthesis of dopaminergic tetrahydroindoles. *Tetrahedron* **2004**, *60*, 1197-1204.
123. Fatahala, S. S.; Shalaby, E. A.; Kassab, S. E.; Mohamed, M. S., A Promising Anti-Cancer and Anti-Oxidant Agents Based on the Pyrrole and Fused Pyrrole: Synthesis, Docking Studies and Biological Evaluation. *Anti-Cancer Agents Med. Chem.* **2015**, *15*, 517-526.
124. Henne, P.; Zeeck, A.; Grabley, S.; Thiericke, R., Secondary metabolites by chemical screening .35. 6,7-Dihydroxy-4,5,6,7-tetrahydroindole-4-one, a new type of indole-derivative from *Nocardia* sp. *Nat. Prod. Lett.* **1997**, *10*, 43-47.
125. Sun, L.; Tran, N.; Liang, C. X.; Hubbard, S.; Tang, F.; Lipson, K.; Schreck, R.; Zhou, Y.; McMahon, G.; Tang, C., Identification of substituted 3- (4,5,6,7-tetrahydro-1H-indol-2-yl)methylene -1,3-dihydroindol-2-ones as growth factor receptor inhibitors for VEGF-R2 (Flk-1/KDR), FGF-R1, and PDGF-R beta tyrosine kinases. *J. Med. Chem.* **2000**, *43*, 2655-2663.
126. Tarzia, G.; Duranti, A.; Tontini, A.; Spadoni, G.; Mor, M.; Rivara, S.; Plazzi, P. V.; Kathuria, S.; Piomelli, D., Synthesis and structure-activity relationships of a series of pyrrole cannabinoid receptor agonists. *Bioorg. Med. Chem. Lett.* **2003**, *11*, 3965-3973.
127. Feng, Y.; Teng, X.; Gu, J.; Yu, B.; Luo, Y.; Ye, L., Novel anti-cancer agents: design, synthesis, biological activity, molecular docking, and MD simulations of 2, 3, 4, 5-tetrahydro-1H-pyrido-[4,3-b]indole derivatives. *Med. Chem. Res.* **2019**, *28*, 133-142.

128. Mou, X. Q.; Xu, Z. L.; Wang, S. H.; Zhu, D. Y.; Wang, J.; Bao, W.; Zhou, S. J.; Yang, C.; Zhang, D., An Au(I)-catalyzed rearrangement/cyclization cascade toward the synthesis of 2-substituted-1,4,5,6-tetrahydrocyclopenta b pyrrole. *Chem. Commun.* **2015**, *51*, 12064-12067.
129. Marin, L.; Gandon, V.; Schulz, E.; Lebœuf, D., One-Pot Assembly of Highly Functionalized Cyclopenta[b]pyrroles via a Calcium(II)- and Copper(II)-Catalyzed Reaction Sequence. *Adv. Synth. Catal.* **2017**, *359*, 1157-1163.
130. Wu, K.; Wu, P.; Chen, J.; Sun, C.; Yu, Z., Brønsted Acid-Promoted Cascade Alkylation/Cyclization of Pyrroles with N,N-Dimethylaminomethyleneglutaconic Acid Dinitrile: A Concise Route to Cyclopenta[b]pyrroles. *Adv. Synth. Catal.* **2015**, *357*, 3353-3358.
131. Yoshida, M.; Maeyama, Y.; Al-Amin, M.; Shishido, K., Synthesis of Substituted 1,4,5,6-Tetrahydrocyclopenta b pyrroles by Platinum-Catalyzed Cascade Cyclization/Ring Expansion of 2-Alkynyl-1-azaspiro 2.3 hexanes. *J. Org. Chem.* **2011**, *76*, 5813-5820.
132. Andreev, I. A.; Belov, D. S.; Kurkin, A. V.; Yurovskaya, M. A., Synthesis of 4,5,6,7-Tetrahydro-1H-indole Derivatives Through Successive Sonogashira Coupling/Pd-Mediated 5-endo-dig Cyclization. *Eur. J. Org. Chem.* **2013**, 649-652.
133. Andreev, I. A.; Ratmanova, N. K.; Novoselov, A. M.; Belov, D. S.; Seregina, I. F.; Kurkin, A. V., Oxidative Dearomatization of 4,5,6,7-Tetrahydro-1H-indoles Obtained by Metal- and Solvent-Free Thermal 5-endo-dig Cyclization: The Route to Erythrina and Lycorine Alkaloids. *Chem. Eur. J.* **2016**, *22*, 7262-7267.
134. Peters, B. K.; Liu, J.; Margarita, C.; Rabten, W.; Kerdphon, S.; Orebom, A.; Morsch, T.; Andersson, P. G., Enantio- and Regioselective Ir-Catalyzed Hydrogenation of Di- and Trisubstituted Cycloalkenes. *J. Am. Chem. Soc.* **2016**, *138*, 11930-11935.
135. Brayton, D. F.; Jensen, C. M., Solvent free selective dehydrogenation of indolic and carbazolic molecules with an iridium pincer catalyst. *Chem. Commun.* **2014**, *50*, 5987-5989.
136. Malone, J. A.; Toussel, C. E.; Fronczek, F. R.; Kartika, R., Bronsted Acid-Catalyzed Formal 2+2+1 Annulation for the Modular Synthesis of Tetrahydroindoles and Tetrahydrocyclopenta b pyrroles. *Org. Lett.* **2019**, *21*, 3610-3614.
137. Nie, S.; Huang, J.; Hu, J.; Zhang, Y.; Wang, S.; Li, C.; Marcone, M.; Xie, M., Effect of pH, temperature and heating time on the formation of furan in sugar–glycine model systems. *Food Science and Human Wellness* **2013**, *2*, 87-92.
138. Capani, J. S.; Cochran, J. E.; Liang, J., CsF-Mediated in Situ Desilylation of TMS-Alkynes for Sonogashira Reaction. *J. Org. Chem* **2019**, *84*, 9378-9384.

139. Fiorenza, M.; Mordini, A.; Papaleo, S.; Pastorelli, S.; Ricci, A., Fluoride ion induced reactions of organosilanes: the preparation of mono and dicarbonyl compounds from β -ketosilanes. *Tetrahedron Lett.* **1985**, 26, 787-788.
140. Badmus, F. O.; Malone, J. A.; Fronczek, F. R.; Kartika, R., Synthesis of functionalized tetrahydropyrans via cascade cycloaddition involving silyloxyallyl cation intermediates. *Chem. Commun.* **2020**.
141. Claisen, L., Über Umlagerung von Phenol-allyläthern in C-Allyl-phenole. *Berichte der deutschen chemischen Gesellschaft* **1912**, 45, 3157-3166.
142. Claisen, L.; Tietze, E., Über den Mechanismus der Umlagerung der Phenol-allyläther. *Berichte der deutschen chemischen Gesellschaft (A and B Series)* **1925**, 58, 275-281.
143. Berski, S.; Durlak, P., The mechanism of Claisen rearrangement of allyl phenyl ether from the perspective of topological analysis of the ELF. *New J. Chem.* **2016**, 40, 8717-8726.
144. Meyer, M. P.; DelMonte, A. J.; Singleton, D. A., Reinvestigation of the Isotope Effects for the Claisen and Aromatic Claisen Rearrangements: The Nature of the Claisen Transition States. *J. Am. Chem. Soc.* **1999**, 121, 10865-10874.
145. Ganem, B., The Mechanism of the Claisen Rearrangement: Déjà Vu All Over Again. *Angewandte Chemie International Edition in English* **1996**, 35, 936-945.
146. Conroy, H.; Firestone, R. A., THE MECHANISM OF THE PARA-CLAISEN REARRANGEMENT. *J. Am. Chem. Soc.* **1953**, 75, 2530-2531.
147. Martín Castro, A. M., Claisen Rearrangement over the Past Nine Decades. *Chem. Rev.* **2004**, 104, 2939-3002.
148. Majumdar, K. C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B., Recent Advances in the Aza-Claisen Rearrangement. *Synthesis* **2009**, 2009, 2117-2142.
149. Nubbemeyer, U., Recent Advances in Charge-Accelerated Aza-Claisen Rearrangements. In *Natural Products Synthesis II: Targets, Methods, Concepts*, Mulzer, J., Ed. Springer Berlin Heidelberg: Berlin, Heidelberg, 2005; pp 149-213.
150. Thio-Claisen Rearrangement. In *The Claisen Rearrangement*, 2007; pp 431-459.
151. Anisimov, A. V.; Viktorova, E. A., Thio-claisen rearrangement in the synthesis of sulfur-containing heterocyclic compounds (review). *Chem Heterocycl Compd* **1980**, 16, 321-333.
152. The Meerwein–Eschenmoser–Claisen Rearrangement. In *The Claisen Rearrangement*, 2007; pp 367-396.

153. Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A., CLAISEN'sche Umlagerungen bei Allyl- und Benzylalkoholen mit Hilfe von Acetalen des N, N-Dimethylacetamids. Vorläufige Mitteilung. *Helv. Chim. Acta* **1964**, *47*, 2425-2429.
154. Ireland, R. E.; Mueller, R. H., Claisen rearrangement of allyl esters. *J. Am. Chem. Soc.* **1972**, *94*, 5897-5898.
155. Ireland, R. E.; Mueller, R. H.; Willard, A. K., The ester enolate Claisen rearrangement. Stereochemical control through stereoselective enolate formation. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877.
156. Ireland, R. E.; Wipf, P.; Xiang, J. N., Stereochemical control in the ester enolate Claisen rearrangement. 2. Chairlike vs boatlike transition-state selection. *J. Org. Chem* **1991**, *56*, 3572-3582.
157. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R., Simple stereoselective version of the Claisen rearrangement leading to trans-trisubstituted olefinic bonds. Synthesis of squalene. *J. Am. Chem. Soc.* **1970**, *92*, 741-743.
158. Kryshtal, G. V.; Zhdankina, G. M.; Ignat'ev, N. V.; Schulte, M.; Zlotin, S. G., The orthoester Johnson–Claisen rearrangement of allylic terpenols in the presence of acidic ionic liquid. *J. Fluor. Chem.* **2016**, *183*, 23-29.
159. Jaschinski, T.; Hiersemann, M., {1,6}-Transannular Catalytic Asymmetric Gosteli–Claisen Rearrangement. *Org. Lett.* **2012**, *14*, 4114-4117.
160. Cave, R. J.; Lythgoe, B.; Metcalfe, D. A.; Waterhouse, I., Stereochemical aspects of some Claisen rearrangements with cyclic orthoesters. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1218-1228.
161. Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C., Development of a New Lewis Acid-Catalyzed Claisen Rearrangement. *J. Am. Chem. Soc.* **1999**, *121*, 9726-9727.
162. Yoon, T. P.; MacMillan, D. W. C., Enantioselective Claisen Rearrangements: Development of a First Generation Asymmetric Acyl-Claisen Reaction. *J. Am. Chem. Soc.* **2001**, *123*, 2911-2912.
163. Helmboldt, H.; Hiersemann, M., Synthesis and Lewis acid catalyzed Claisen rearrangement of 2-(1,3-oxazolin-2-yl)-substituted allyl vinyl ethers. *Tetrahedron* **2003**, *59*, 4031-4038.
164. Van der Baan, J. L.; Bickelhaupt, F., Palladium(II)-catalyzed claisen rearrangement of allyl vinyl ethers. *Tetrahedron Lett.* **1986**, *27*, 6267-6270.

165. Ollevier, T.; Mwene-Mbeja, T. M., Bismuth triflate catalyzed Claisen rearrangement of allyl naphthyl ethers. *Tetrahedron Lett.* **2006**, *47*, 4051-4055.
166. Tischer, S.; Metz, P., Selective C-6 Prenylation of Flavonoids via Europium(III)-Catalyzed Claisen Rearrangement and Cross-Metathesis. *Adv. Synth. Catal.* **2007**, *349*, 147-151.
167. Yang, D.; Wang, L.; Li, D.; Wang, R., Magnesium Catalysis in Asymmetric Synthesis. *Chem* **2019**, *5*, 1108-1166.
168. Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H., Organoaluminum-promoted Claisen rearrangement of allyl vinyl ethers. *J. Am. Chem. Soc.* **1990**, *112*, 316-322.
169. Sherry, B. D.; Toste, F. D., Gold(I)-Catalyzed Propargyl Claisen Rearrangement. *J. Am. Chem. Soc.* **2004**, *126*, 15978-15979.
170. Mikami, K.; Takahashi, K.; Nakai, T., Diastereocontrol via the phenol- and palladium(II)-catalyzed Claisen rearrangement with cyclic enol ethers. *Tetrahedron Lett.* **1987**, *28*, 5879-5882.
171. Aikawa, K.; Asai, Y.; Hioki, Y.; Mikami, K., Catalytic and highly enantioselective Friedel-Crafts type reactions of heteroaromatic compounds with trifluoropyruvate and glyoxylate by a dicationic palladium complex. *Tetrahedron-Asym.* **2014**, *25*, 1104-1115.
172. Sugiura, M.; Nakai, T., Regiochemical control in the Pd(II)-catalyzed claisen rearrangement via in situ enol ether exchange. *Tetrahedron Lett.* **1996**, *37*, 7991-7994.
173. Hiersemann, M.; Abraham, L., The Cu(OTf)₂- and Yb(OTf)₃-Catalyzed Claisen Rearrangement of 2-Alkoxy carbonyl-Substituted Allyl Vinyl Ethers. *Org. Lett.* **2001**, *3*, 49-52.
174. Balta, B.; Öztürk, C.; Aviyente, V.; Vincent, M. A.; Hillier, I. H., Claisen Rearrangement of Aliphatic Allyl Vinyl Ethers in the Presence of Copper(II) Bisoxazoline. *J. Org. Chem* **2008**, *73*, 4800-4809.
175. Pollex, A.; Hiersemann, M., Catalytic Asymmetric Claisen Rearrangement in Natural Product Synthesis: Synthetic Studies toward (-)-Xeniolide F. *Org. Lett.* **2005**, *7*, 5705-5708.
176. Tan, J.; Cheon, C.-H.; Yamamoto, H., Catalytic Asymmetric Claisen Rearrangement of Enolphosphonates: Construction of Vicinal Tertiary and All-Carbon Quaternary Centers. *Angew. Chem. Int. Ed.* **2012**, *51*, 8264-8267.
177. Cao, T.; Linton, E. C.; Deitch, J.; Bertritt, S.; Kozlowski, M. C., Copper(II)- and Palladium(II)-Catalyzed Enantioselective Claisen Rearrangement of Allyloxy- and

- Propargyloxy-Indoles to Quaternary Oxindoles and Spirocyclic Lactones. *J. Org. Chem.* **2012**, *77*, 11034-11055.
178. Behenna, D. C.; Stoltz, B. M., The Enantioselective Tsuji Allylation. *J. Am. Chem. Soc.* **2004**, *126*, 15044-15045.
179. Numajiri, Y.; Pritchett, B. P.; Chiyoda, K.; Stoltz, B. M., Enantioselective Synthesis of α -Quaternary Mannich Adducts by Palladium-Catalyzed Allylic Alkylation: Total Synthesis of (+)-Sibirinine. *J. Am. Chem. Soc.* **2015**, *137*, 1040-1043.
180. Starkov, P.; Moore, J. T.; Duquette, D. C.; Stoltz, B. M.; Marek, I., Enantioselective Construction of Acyclic Quaternary Carbon Stereocenters: Palladium-Catalyzed Decarboxylative Allylic Alkylation of Fully Substituted Amide Enolates. *J. Am. Chem. Soc.* **2017**, *139*, 9615-9620.
181. Sun, Alexander W.; Hess, S. N.; Stoltz, B. M., Enantioselective synthesis of gem-disubstituted N-Boc diazaheterocycles via decarboxylative asymmetric allylic alkylation. *Chem. Sci.* **2019**, *10*, 788-792.
182. Alexy, E. J.; Zhang, H.; Stoltz, B. M., Catalytic Enantioselective Synthesis of Acyclic Quaternary Centers: Palladium-Catalyzed Decarboxylative Allylic Alkylation of Fully Substituted Acyclic Enol Carbonates. *J. Am. Chem. Soc.* **2018**, *140*, 10109-10112.
183. Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A., Transition Metal-Catalyzed Decarboxylative Allylation and Benzylolation Reactions. *Chem. Rev.* **2011**, *111*, 1846-1913.
184. James, J.; Jackson, M.; Guiry, P. J., Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation: Development, Mechanistic Understanding and Recent Advances. *Adv. Synth. Catal.* **2019**, *361*, 3016-3049.
185. Liao, X.; Weng, Z.; Hartwig, J. F., Enantioselective α -Arylation of Ketones with Aryl Triflates Catalyzed by Difluorophos Complexes of Palladium and Nickel. *J. Am. Chem. Soc.* **2008**, *130*, 195-200.
186. Orlandi, M.; Licini, G., Computational Analysis of Enantioselective Pd-Catalyzed α -Arylation of Ketones. *J. Org. Chem.* **2020**, *85*, 11511-11518.
187. Hao, Y.-J.; Hu, X.-S.; Zhou, Y.; Zhou, J.; Yu, J.-S., Catalytic Enantioselective α -Arylation of Carbonyl Enolates and Related Compounds. *ACS Catalysis* **2020**, *10*, 955-993.
188. Jia, Z.; Gálvez, E.; Sebastián, R. M.; Pleixats, R.; Álvarez-Larena, Á.; Martín, E.; Vallribera, A.; Shafir, A., An Alternative to the Classical α -Arylation: The Transfer of an Intact 2-Iodoaryl from ArI(O₂CCF₃)₂. *Angew. Chem. Int. Ed.* **2014**, *53*, 11298-11301.
189. Peyman, A.; Beckhaus, H.-D.; Rüchardt, C., Intramolecular reactions of 1,5-diaryl-1,5-pentadiyl radicals. *Chem. Ber.* **1988**, *121*, 1027-1031.

190. Nishimura, Y.; Amemiya, R.; Yamaguchi, M., α -Ethynylation reaction of ketones using catalytic amounts of trialkylgallium base. *Tetrahedron Lett.* **2006**, *47*, 1839-1843.
191. Dange, N. S.; Stepherson, J. R.; Ayala, C. E.; Fronczek, F. R.; Kartika, R., Cooperative benzylic–oxyallylic stabilized cations: regioselective construction of α -quaternary centers in ketone-derived compounds. *Chem. Sci.* **2015**, *6*, 6312-6319.
192. Hiersemann, M.; Abraham, L., Catalysis of the Claisen Rearrangement of Aliphatic Allyl Vinyl Ethers. *Eur. J. Org. Chem.* **2002**, *2002*, 1461-1471.
193. Rehbein, J.; Hiersemann, M., Claisen Rearrangement of Aliphatic Allyl Vinyl Ethers from 1912 to 2012: 100 Years of Electrophilic Catalysis. *Synthesis* **2013**, *45*, 1121-1159.

Vita

Joshua Andrew Malone was born in Oswego, New York and grew up in Phoenix, New York. He graduated from State University of New York, Oswego and received his Bachelor of Science, Chemistry degree in December 2014. In his undergraduate career, he performed synthetic organic research and discovered an interest in chemistry. This inspired him to pursue a doctoral degree concentrating in organic chemistry. In 2015, he moved to Baton Rouge, Louisiana and enrolled in the Department of Chemistry at Louisiana State University. He is currently in the lab of Dr. Rendy Kartika as a candidate for Doctor of Philosophy degree in chemistry which will be awarded in May 2021.