Development of Transition Metal-Catalyzed Migratory Transformations

BY

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THESIS

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LIST OF ABBREVIATIONS

Ac	acetyl
Alk	alkyl
aq	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
n-Bu	butyl
t-Bu	*tert*-butyl
Calcd	calculated
cat.	catalytic amount
COD	1,5-cyclooctadiene
δ	chemical shifts in parts per million downfield from tetramethylsilane (NMR)
2D	two-dimensional (NMR)
d	doublet
dba	dibenzylidene acetone
DCM	dichloromethane
DCE	1,2-dichloroethane
DCE	1,2-dichloroethane
DEPT	distortionless enhancement by polarization transfer

LIST OF ABBREVIATIONS (continued)

DFT	Density Functional Theory
DMA	dimethylacetamide
DMB	2,4-dimethoxybenzyl
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDG	electron-donating group
EE	ethoxyethyl
EI	electron impact ionization (in mass spectrometry)
Et	ethyl
eq, equiv.	molar equivalent
EWG	electron-withdrawing group
G	group, Gibbs free energy
g	gram
GC	gas chromatography
h, hrs	hour(s)
HMBC	heteronuclear multiple-bond correlation spectroscopy (NMR)
HMQC	heteronuclear multiple-quantum coherence spectroscopy (NMR)
HR	high resolution (mass spectrometry)
Hz	Hertz
IPr	1,3-bis(2,6-diisopropylphenyl) imidazole-2-ylidene
J	spin-spin coupling constant (NMR)
L	ligand

LIST OF ABBREVIATIONS (continued)

LDA	lithiumdiisopropyl amide
m	multiplet (NMR)
mp	melting point
μ	micro
[M]	metal
M	molar
MS	mass spectrometry
MS	molecular sieves
Me	methyl
Mes	mesityl
MIDA	*N*-methyliminodiacetic acid
mg	milligram
min	minute
mL, ml	milliliter
mm	millimeter
mmol	millimole
mol	mole
MHz	megahertz
m/z	mass to charge ratio
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Ph	phenyl

LIST OF ABBREVIATIONS (continued)

PIDA	Pinen-derived iminodiacetic acid
Piv	pivaloyl, trimethylacetyl
PMB	*p*-methoxybenzyl
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl
q	quartet (NMR)
quint	quintet (NMR)
rt	room temperature
s	singlet (NMR)
sept	septet (NMR)
t	triplet (NMR)
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol, tol	tolyl
Ts	*p*-toluenesulfonyl
TDMPP	tris (2,5-dimethoxyphenyl) phosphine

SUMMARY

This thesis describes the development of transition metal-catalyzed regio- and stereodivergent isomerization and cycloisomerization reactions of acyclic substrates into acyclic products including 1,3-ynones and 1,3-dienes, as well as heterocyclic compounds such as borylated furans.

Chapter 1 describes the development of a regioselective gold-catalyzed transposition reaction of 1,3-ynones and diynones. Supported by computations, experimental studies of this reaction show that the equilibrium between regioisomeric 1,3-ynones can be shifted toward a more stable isomer, thus, allowing to obtain a single reaction product. Two regioselectivity-controlling factors for the transposition of 1,3-ynones were identified. First, by employing an α-substituted aryl group at ketone moiety, the gold-catalyzed reaction provides its arylalkyne regioisomer as a sole product, where an interrupted conjugation between the ketone group of ynone moiety and the aryl group substituent drives this transformation toward more conjugated regioisomer. Second, it is shown that extension of conjugation can render the regioselective transposition of ynone moiety. Thus, the reaction of skipped diynones in the presence of a gold catalyst produced the conjugated diynones via a 1,3-ynone transpositon reaction. The significance of this method is highlighted in the synthesis of various regioisomeric five- and six-membered alkynylated heterocycles.

The development of novel regiodivergent Cu- and Au-catalyzed cycloisomerization reactions of boryl-substituted alkynyl epoxides into C2- or C3-borylated furans is presented in Chapter 2. In the presence of a copper catalyst, the 1,2-MIDA-boronate group migration followed by cycloisomerization reaction occurs to form

C3-borylated furans. In addition, it was found that a more efficient gold-catalyzed version of this reaction is regiodivergent, where depending on the choice of ligand and counterion, the regioisomeric boryl furans can be selectively obtained. Thus, phosphite gold complex with triflate counterion strongly favors a 1,2-boryl migration during the cycloisomerization process to produce C3-borylated furans. In contrast, employment of NHC gold hexafluoroantimonate affords C2-borylated furans, exclusively.

Chapter 3 discloses a transition metal-catalyzed stereodivergent synthesis of functionalized 1,3-dienes from easily accessible propargylic phosphates. It was shown that the 1,3-phosphatyloxy migration in α-halo propargylic phosphates can be followed by a regioselective 1,3-chlorine, 1,3-bromine, and prior unknown 1,3-iodine migration to form the functionalized 1-phosphate, 2-halo substituted 1,3-dienes. This cascade reaction is stereodivergent. Thus, in the presence of a copper catalyst, the (Z)-1,3-diene is formed, where the coordination of the phosphate group in allenyl phosphate intermediate to the copper species is believed to dictate the observed *Z*-stereoselectivity. Whereas, the steric interaction between the phosphate group in allenyl phosphate intermediate and the gold catalyst renders the *E*-selectivity in this transformation. It was also shown that the obtained (*Z*)-1,3-dienes are valuable substrates for a various functionalization reactions, including Diels-Alder reactions (at diene moiety) and cross-coupling reactions (at vinyl bromide and vinyl phosphates) to produce a variety of acyclic and cyclic products.

CONTRIBUTION OF AUTHORS

Several parts of this thesis are reproduced from previously published research and review articles co-authored with collaborators, who contributed significantly to the presented work.

The first part of this thesis is written based on the previously published article ("Gold-Catalyzed 1,3-Transposition of Yones" Kazem Shiroodi, R.; Soltani, M.; Gevorgyan, V. *J. Am. Chem. Soc*. **2014**, *136*, 9882). Thus, as a major contributor of this work, I designed and performed experiments (chapters two and three), and wrote the manuscript. Dr. Mohammad Soltani, a visiting researcher of our group at the time, partially contributed to the synthetic part of the project (chapters 3.2.1 and 3.3.1). Prof. Vladimir Gevorgyan guided the research and contributed to the discussion of the results and manuscript writing.

The second part of the thesis is also reproduced from a previously published research article ("1,2-Boryl Migration Empowers Regiodivergent Synthesis of Borylated Furans " Kazem Shiroodi, R.; Koleda, O.; Gevorgyan, V. *J. Am. Chem. Soc.* **2014***, 136*, 13146), in which I conceive the project and discovered the initial results (chapters seven and eight). Olesja Koleda, a graduate student of our group at the time, discovered part of this project (chapters 6.1 and 6.3) and had significant contribution in execution of the project (chapter seven). Prof. Vladimir Gevorgyan guided the research and contributed to the discussion of the results and manuscript writing.

The third part of the thesis includes material from two previous publications. Chapter nine reproduced from previously published review article ("Metal-catalyzed double migratory cascade reactions of propargylic esters and phosphates." Kazem

Shiroodi, R.; Gevorgyan, V. *Chem. Soc. Rev*. **2013**, *42*, 4991), in which I was the only author besides my advisor, Prof. Vladimir Gevorgyan. Chapters ten and eleven describe results of a published work ("Stereocontrolled 1,3-Phosphatyloxy and 1,3-Halogen Migration Relay toward Highly Functionalized 1,3-Dienes" Kazem Shiroodi, R.; Dudnik, A. S.; Gevorgyan, V. *J. Am. Chem. Soc*. **2012**, *134*, 6928). I was the major contributor of this project. Thus, I executed the project (chapters ten and eleven), and wrote the manuscript. Dr. Alexander Dudnik, a senior graduate student of our group at the time, performed the experiments at the early stage of the project including optimization of reaction conditions (Chapter 10.1). All authors participated in the discussion of the results. My advisor, Prof. Vladimir Gevorgyan, guided the research and contributed to the discussion of the results and manuscript writing.

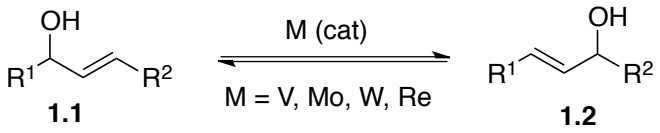
PART ONE

GOLD-CATALYZED 1,3-TRANSPOSITION OF YNONES AND DIYNONES

1. INTRODUCTION

1.1. 1,3-Transposition of Allylic Alcohols

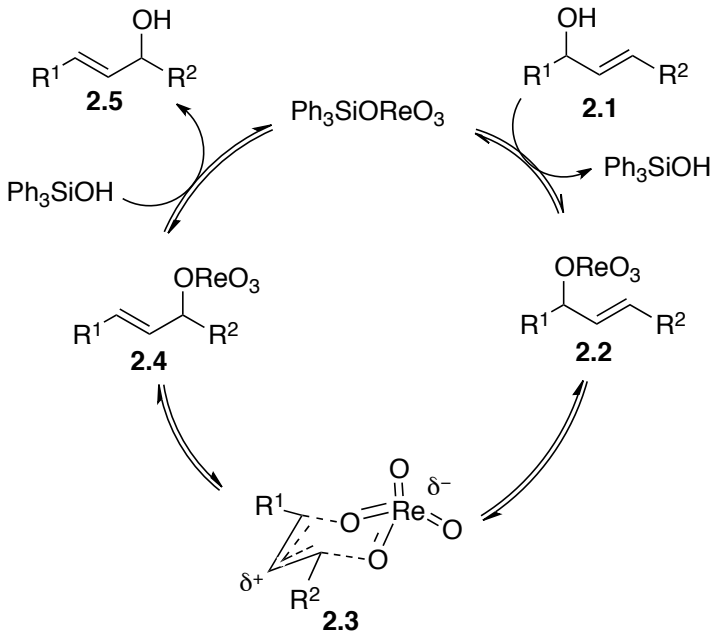
Transition metal-catalyzed transposition reactions are interesting transformations. Among them, the 1,3-transposition of allylic alcohols,[1] which was first reported by Chabardes in 1970,[2] is the synthetically most useful and well-studied transformation. This reaction is a reversible process producing a thermodynamic mixture of regioisomers **1.1** and **1.2** in the presence of a transition metal catalyst (Scheme 1). The initially discovered vanadium-catalyzed version of this isomerization reaction[2] was further developed[3] by employing other metal complexes such as W,[4] Mo,[5] and Re.[6] The high oxidation state rhenium complex $Ph_3SiOReO_3$, however, has been shown to be the catalyst of the choice for this transformation.[6e,f] In addition, this oxometal complex does not participate in the competing oxidation reaction of substrates, which is a common problem with other transition metal catalysts.



Scheme 1.

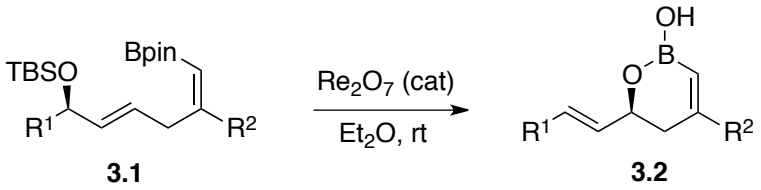
Followed by Osborn's initial mechanistic proposal,[3a] Grubbs and co-workers recently suggested a mechanism for the Re-catalyzed transposition reaction of allylic alcohol **2.1** into the isomer **2.5** (Scheme 2).[7] By ligand exchange substrate **2.1** forms rhennate ester **2.2**, which upon a [3,3]-sigmatropic rearrangement via the chair like transition structure

2.3 affords compound **2.4**. Displacement of allylic alcohol from the latter with either Ph_3SiOH or **2.1** furnishes the transposed isomer **2.5**. Recombination of triphenyl phosphinesilanol with the trioxo-rhenium catalyst regenerates the active catalyst for the catalytic cycle.



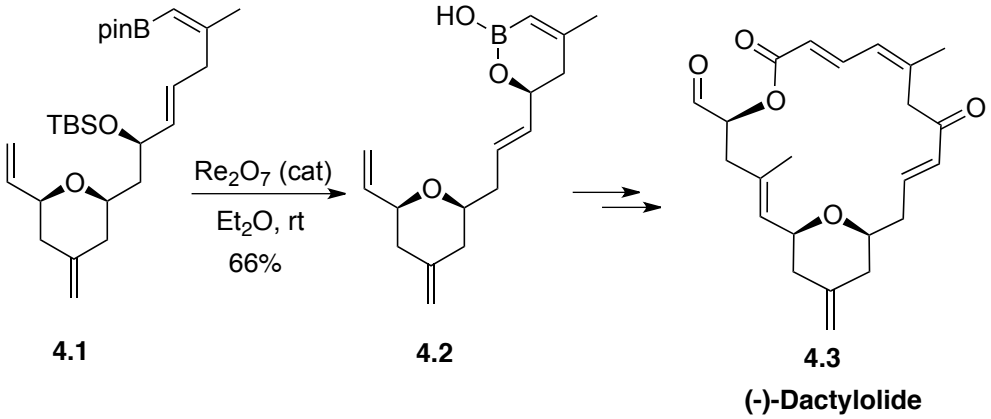
Scheme 2.

Remarkably, creative strategies have recently been developed to control the regioselectivity of this transition metal-catalyzed reversible process to selectively obtain one of the allylic alcohols.[8] For instance, Lee and co-workers showed that allylic silyl ether **3.1**, possessing tethered vinyl boronate in the presence of a rhenium catalyst undergoes a regioselective 1,3-transposition of allylic alcohol moiety to form cyclic boronate **3.2** where formation of thermodynamically favored boron-oxygen bond is believed to be the driving force for this reaction (Scheme 3).[8f] The synthetic utility of this



Scheme 3.

method was demonstrated in the total synthesis of (-)-dactylolide (Scheme 4).[9] Thus, substrate **4.1**, possessing a silyl-protected allylic alcohol moiety undergoes a regioselective isomerization reaction to produce the bicyclic system **4.2**, which upon a sequence of steps efficiently produce the natural product **4.3**.

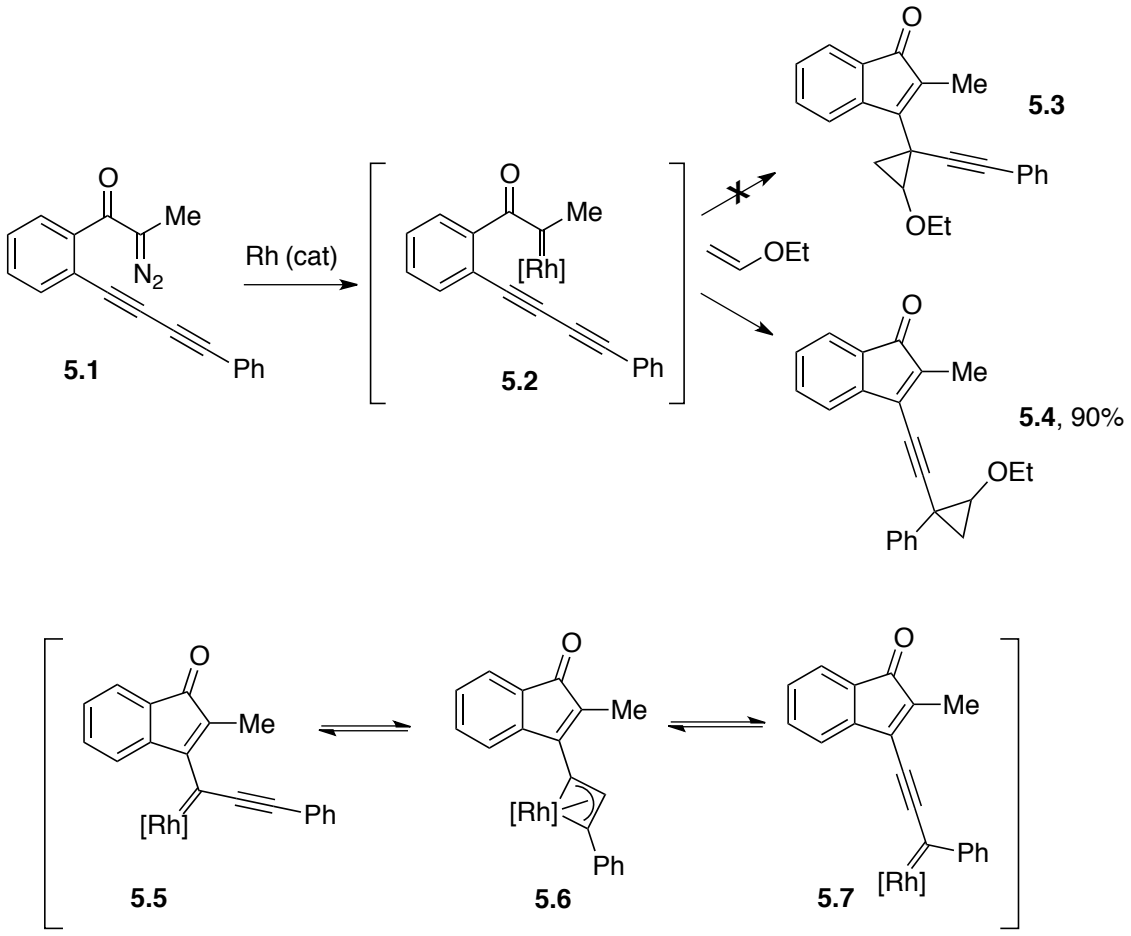


Scheme 4.

1.2. 1,3-Transposition of Alkynyl Metal Carbenes

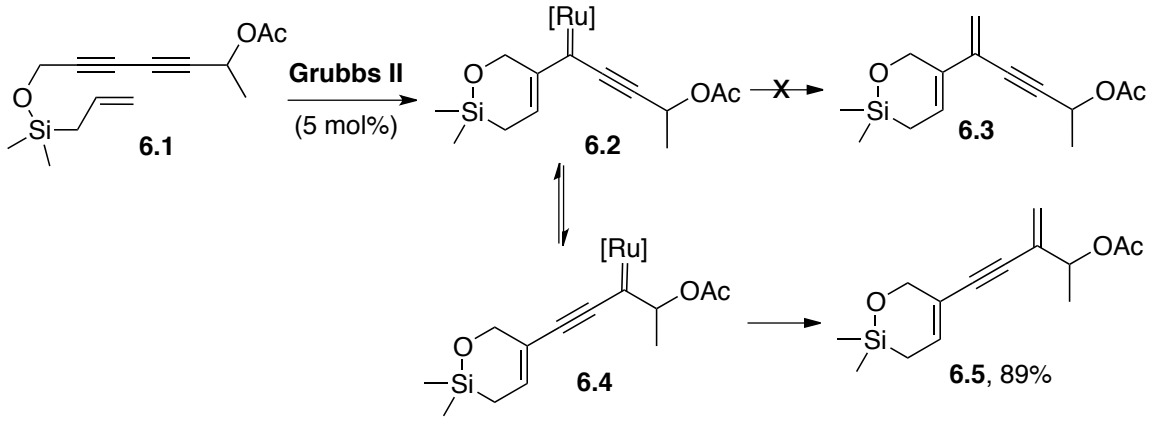
The catalytically-generated alkynyl metal carbenes, possessing metals such as Rh,[10] Ru,[11] Au,[12] Pt,[13] and Cu,[14] as well as stoichiometric analogues involving Ti,[15] Cr,[16] and W[17] metals, have been shown to undergo a 1,3-transposition reaction.[18] Seminal studies of transposition in alkynyl rhodium alkylidenes, as well as its well-studied ruthenium version, are discussed below.

In 1993, Padwa and co-workers reported the first example of a 1,3-transposition reaction of alkynyl metal carbene functionality.[10] Using the diyne-tethered α-diazoketone **5.1** in the presentence of a rhodium catalyst, the generated metal carbene **5.2** underwent a cyclopropanation reaction exclusively at the distal rather than proximal alkynyl moiety to produce **5.4** selectively over **5.3** (Scheme 5). Accordingly, it was proposed that upon alkyne-carbene metathesis of **5.2**, carbene **5.5** (precursor of **5.3**) is generated, which then undergoes a 1,3-transposition reaction to form regioisomeric carbene **5.7** (precursor of **5.4**) via the intermediacy of a four-membered metallacycle **5.6**. It is believed that a combination of the disfavored steric hindrance between the rhodium carbene and indenone moieties in **5.5** and the favored conjugation in **5.7** is the driving force for this transposition reaction.



Scheme 5.

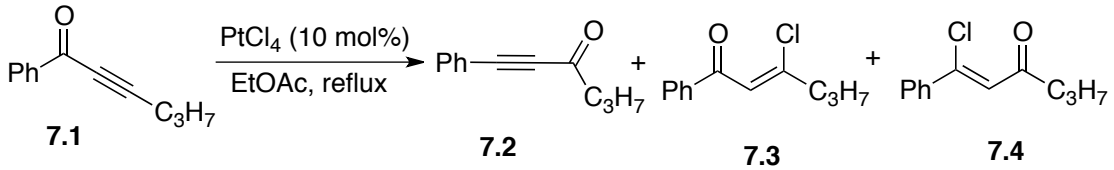
Lee group disclosed a cascade reaction of diyne **6.1** catalyzed by the Grubbs catalyst to from product **6.5** (Scheme 6).[11a] It was found that the allylsilyl-protected diynol **6.1** in the presence of the Grubbs-II (ruthenium) catalyst undergoes the ring closing metathesis (RCM) reaction to generate the cross-conjugated alkynyl ruthenium carbene **6.2**. The latter does not produce the corresponding enyne **6.3**, instead it undergoes a 1,3-transposition reaction to the regioisomeric alkynyl carbene **6.4**, which then produces the product **6.5** in 89% yield.



Scheme 6.

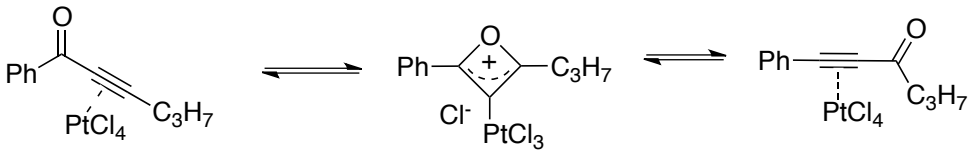
1.3. 1,3-Transposition of Ynones

Blum and co-workers reported that ynone **7.1** in the presence of the platinum (IV) chloride catalyst produces a mixture of regioisomeric ynones **7.1** and **7.2** along with chloroenones **7.3** and **7.4** (Scheme 8).[19] Enones **7.3** and **7.4** are believed to form via a non-catalytic hydrochlorination of alkyne functionality of both regioisomers **7.1** and **7.2**, where the origins of chlorine and hydrogen are the catalyst and the solvent, respectively. The low regioselectivity and efficiency of this reaction was mostly attributed to the



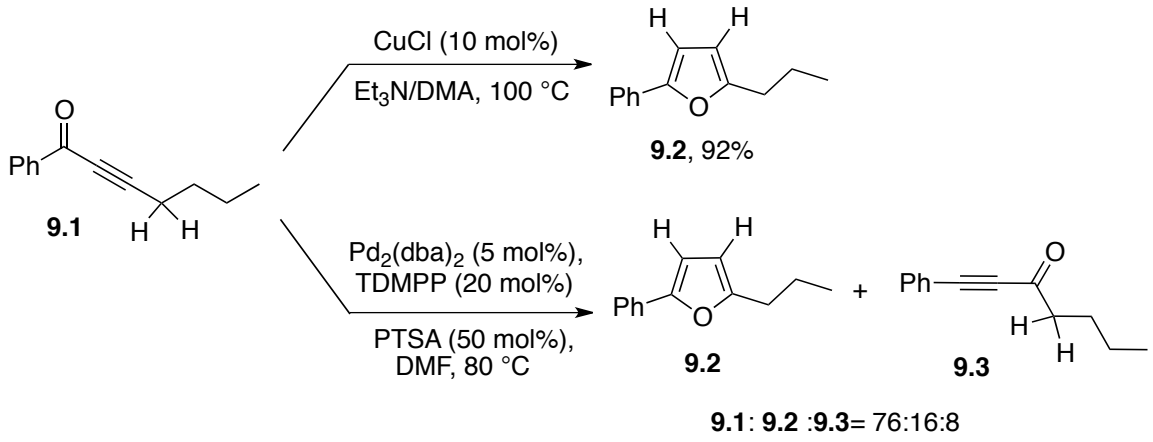
Scheme 7.

reversibility of the 1,3-transposition process. Thus, it was suggested[19,20] that intramolecular nuclophilic attack of the oxygen at the activated alkyne moiety of **8.1** generates the four-membered intermediate **8.2**, which further rearranges to the regioisomer **8.3** (Scheme 8).



Scheme 8.

Recently, our group has shown that ynone **9.1** in the presence of a copper catalyst undergoes a cycloisomerization reaction to efficiently produce furan **9.2** (Scheme 7).[21] Interestingly, during the optimization process of cyclization of **9.1** to furan **9.2**, it was found that the palladium-catalyzed version of this reaction produced a detectable amount of transposed ynone regioisomer **9.3** although with a low efficiency. This 1,3-transposition reaction was further explored and described in the next section.

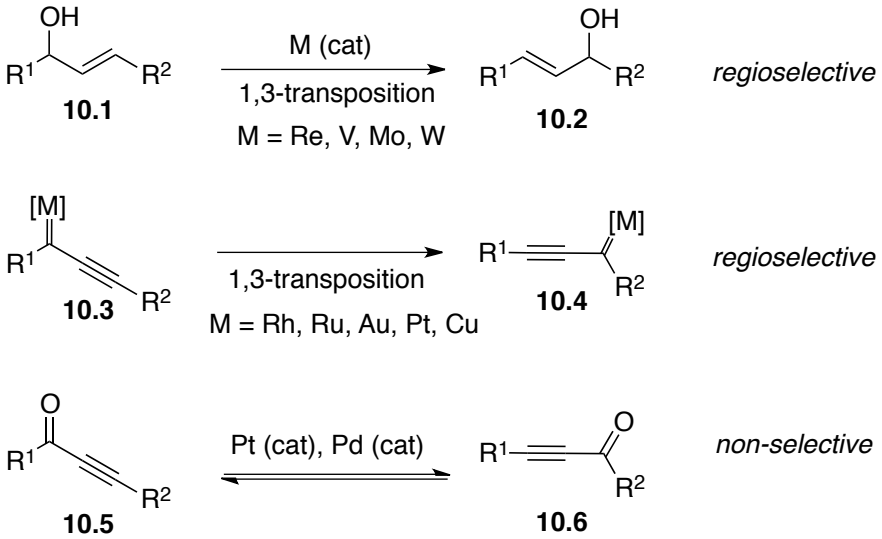


Scheme 9.

1.4. Summary

In summary, transition metal-catalyzed 1,3-transposition reactions are emerging areas of research in synthetic organic chemistry. Earlier, it was shown that allylic alcohols in the presence of transition metals exist in a thermodynamic equilibrium with the 1,3-transposed isomer. Subsequently, creative strategies have been developed to

control the efficiency of this transformation. Thus, a various allylic alcohols **10.1** were converted into the corresponding isomers **10.2** via a regioselective 1,3-transposition reaction (Scheme 10). Likewise, the regioselective transformations involving the 1,3-transposition of alkynyl metal carbenes **10.3** to **10.4** have been well studied.[22] The unselective and low-yielding 1,3-transposition reaction of alkynyl ketones (ynones) **10.5** to the regioisomeric ynones **10.6** has also been reported.



Scheme 10.

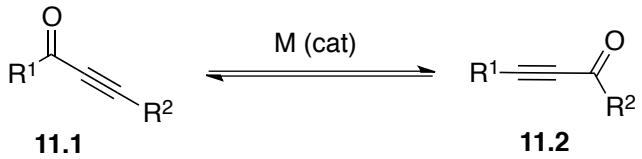
Based on observations, it was suggested that regioisomeric ynones **10.5** and **10.6** exist in equilibrium. However, no regioselectivity-controlling strategy for this transformation has been developed so far.

2. REGIODIVERGENT 1,3-TRANSPOSITION OF YNONES AND DIYNON

Ynones are widely used in total synthesis of natural products.[23] In addition, they are valuable reaction partners in the synthesis of a wide array of heterocycles.[24] Although reported, the corresponding regioselective 1,3-transposition reaction of ynones is yet to be developed. Intrigued by our group's early observation (*vide supra*), we decided to further explore a regioselective and efficient 1,3-transposition reaction of ynones.

2.1. Computation-Assisted Discovery of Regiocontrolling Factors

It was suggested that in the presence of transition metals, regioisomeric ynones **11.1** and **11.2** exist as a thermodynamic mixture (Scheme 11).[19]



11.1 **11.2**

Scheme 11.

According to the simplified Boltzman's equation (eq 1), the ratio of **11.2**:**11.1** in equilibrium depends on the ground state energy difference between these these two isomers.

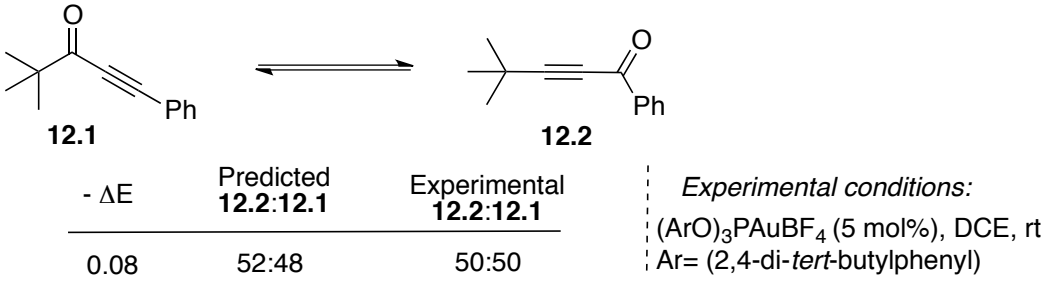
$$\mathbf{11.2/11.1} = \exp(-\Delta E_{\mathbf{11.2\text{-}11.1}}/RT) \qquad \text{(eq 1)}$$

Accordingly, if the ground state energy difference between two isomers ($\Delta E_{\mathbf{11.2\text{-}11.1}}$) is more than 2.9 kcal/mol, a >>99:1 ratio of **11.2**:**11.1** is predicted, meaning that the existing equilibrium would virtually completely be pushed toward the more stable isomer **11.2** (Scheme 11). Thus, in order to get some insight into the effect of different substitutions (*i.e.* R^1 and R^2) of ynones on the position of the equilibrium between **11.1** and **11.2**, we performed DFT calculations of the ground state energies of **11.1** and **11.2** at

the B3LYP/6-31G* level. The theoretical ratios of **11.2**:**11.1** were predicted based on calculated ΔE (eq 1), which were then compared to the experimentally-obtained ratios.

2.1.1. Consideration of Steric Effect

First, we considered the equilibrium between two regioisomers **12.1** (the more bulky *t*-Bu substituent next to the carbonyl group) and **12.2** (the less bulky phenyl substituent next to the carbonyl group) in the 1,3-transposition reaction (Scheme 12). The DFT calculation shows 0.08 kcal/mol difference between the ground energies of these two isomers, thus, suggesting a 47:53 ratio of **12.2**:**12.1**. Expectedly, the reaction of ynone **12.1** in the presence of a π-philic metal catalyst such as [tris(2,4-di-tertbutylphenylphosphite]gold tetrafluoroborate (for optimization of the catalyst see Table 1) reached the equilibrium with isomer **12.2** after 30 min to produce a ~50:50 mixture of regioisomers.

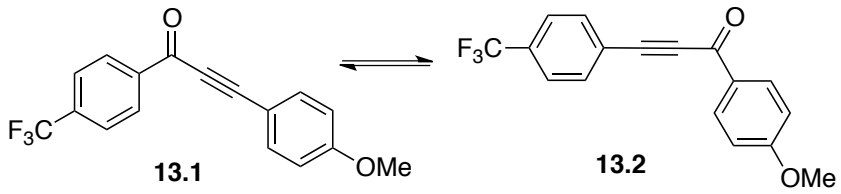


Scheme 12.

This observation confirms that the transposition reaction of ynones indeed is a reversible process. In addition, it suggests that the steric effect of *t*-Bu over phenyl group does not have any noticeable effect on the regioselectivity of the 1,3-ynone transposition.

2.1.2. Consideration of Electronic Factor

Next, the equilibrium between the electronically push-pull system **13.1** and **13.2** was considered (Scheme 13). Computations suggested that ynone **13.1** is 0.8 kcal/mol more stable than its regioisomer **13.2**. Therefore, a 79:21 ratio of isomers was predicted, where the equilibrium between the two isomers was slightly shifted toward **13.2**. Indeed, the reaction of alkynyl ketone **13.1** in the presence of the gold-catalyzed (for optimization of the catalyst see Table 1) produced a 74:26 mixture of **13.2**:**13.1**.



- ΔE	Predicted **13.2**:**13.1**	Experimental **13.2**:**13.1**
0.8	79:21	74:26

Experimental conditions:
$(ArO)_3PAuBF_4$ (5 mol%), DCE, rt
Ar= (2,4-di-*tert*-butylphenyl)

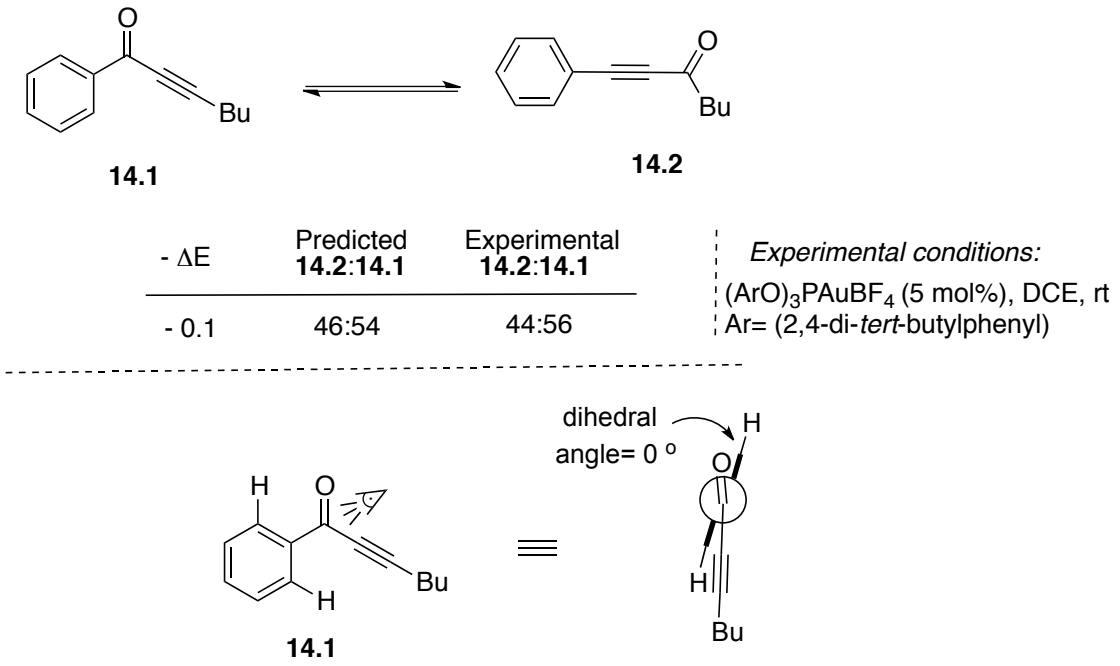
Scheme 13.

The experimental observation, which is in accordance with the theoretical prediction shows that the electronic nature of the p-substituent on the phenyl group of ynone moiety does not have a significant affect on the position of equilibrium between two regioisomers.

2.1.3. Consideration of Interrupted Conjugation Factor

After finding that neither steric nor electronic factors have significant influence on the equilibrium between regioisomeric ynones, we considered the conjugation factor. First, we looked at the equilibrium between ynones **14.1** and **14.2** possessing alkyl and aryl substitutions (Scheme 14). Expectedly, the ground energy difference between the

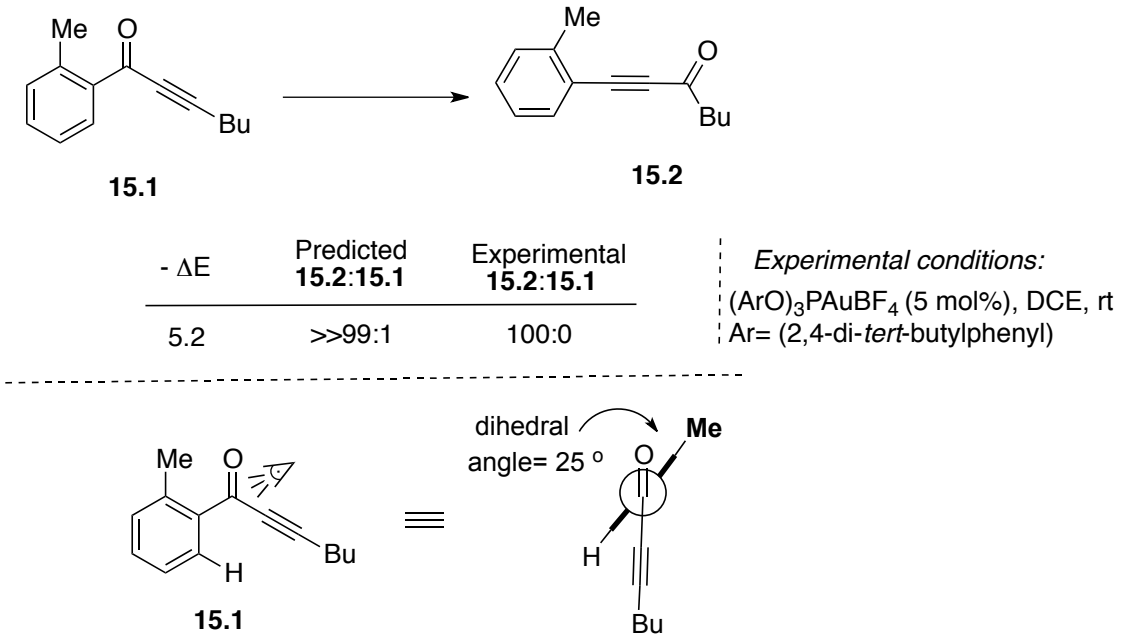
two isomers was negligible (0.1 kcal/mol). Thus, both theoretical prediction and the following experimental observation of the gold-catalyzed reaction of **14.1** showed almost the same thermodynamic ratios of **14.2**:**14.1**. Expectedly, the optimized structure of **14.1** showed co-planar orientation of the ketone and phenyl moieties, which is a requisite for a maximal orbital overlapping and hence for a conjugation between theses two groups. Obviously, the ynone **14.1** is almost as stable as the transposed isomer **14.2**, in which conjugation of phenyl and acetylene groups is apparent.



Scheme 14.

Next, we thought that by employing ynone **15.1** (analogue of **14.1**), possessing a methyl substituent at the *ortho* position of phenyl group, the dihedral angle between aryl and ketone moieties would be changed (Scheme 14). Thus, the orbital overlapping between these two groups would decrease consequently leading to the destabilization of **15.1**. Hence, the existing equilibrium would shift toward the more stable regioisomeric ynone **15.2**. Indeed, the optimized structure showed the dihedral angle between aryl and

ketone groups of **15.1** to be 25 degrees. Accordingly, computations show that the isomer **15.2** is 5.2 kcal/mol more stable than isomer **15.1**, thus, predicting a >>99:1 ratio of **15.2:15.1**. To our delight, when the ynone **15.1** was subjected to the gold-catalyzed reaction, an exclusive formation of **15.2** was observed with no traces of **15.1** detected.



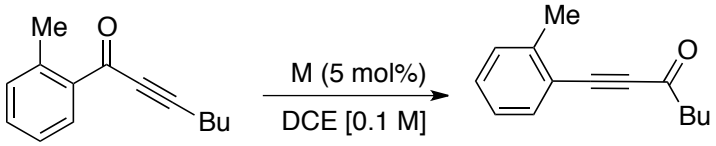
Scheme 15.

2.1.3.1 Scope of 1,3-Transposition Reaction of Ynones by Interrupted Conjugation Factor

Inspired by our initial finding on the *o*-tolyl-type handle (interrupted conjugation) to control the regioselectivity of 1,3-transposition of ynones (Scheme 15), we examined the transformation of **15.1** into the regioisomer **15.2** in the presence of different transition metals (Table I). First, the reaction was tested under the Pd-catalyzed conditions (Scheme 9). Thus, a 94:6 ratio of **15.2**:**15.1** was observed albeit with a modest yield (entry 1). The platinum (IV)-catalyed version of this reaction[19] was neither efficient nor regioselective (entry 2).[19] It was found that **15.1** was unreactive in the presence of gold (I)

chloride bearing phosphine and NHC ligands (entries 3, 4). Likewise, poor conversion was achieved in the presence of a gold (III) chloride (entry 5). However, employment of

Table I. OPTIMIZATION OF 1,3-TRANSPOSITION REACTION OF **15.1** to **15.1**



15.1 **15.2**

Entry	Catalyst	*T*, °C	**15.2**:**15.1**[a]	Isolated Yield (%)
1	$Pd_2(dba)_3$[b]	80	94:6	60
2	$PtCl_4$	100	12:88[c]	-
3	Ph_3PAuCl	100	0:100[d]	-
4	IPrAuCl	100	0:100[d]	-
5	LAuCl[e]	100	25:75[c]	-
6	$Ph_3PAuCl + AgSbF_6$	25	100:0	85
7	Ar_3PAuCl[f] + $AgSbF_6$	25	100:0	56
8	$IPrAuCl + AgSbf_6$	25	100:0	92
9	$(ArO)_3PAuCl$[g] + $AgSbF_6$	25	100:0	92
10	**$(ArO)_3PAuCl$[g] + $AgBF_4$**	**25**	**100:0**	**95**
11	$AgBF_4$	100	0:100[d]	-

[a] Ratios were reported based on ^1H NMR.

[b] TDMPP (20 mol%), PTSA (50 mol%) in DMF, 17 h.

[c] Ratios were reported based on GC/MS.

[d] Substrate **15.1** stayed intact.

[e] L=2-pyridinecarboxylato.

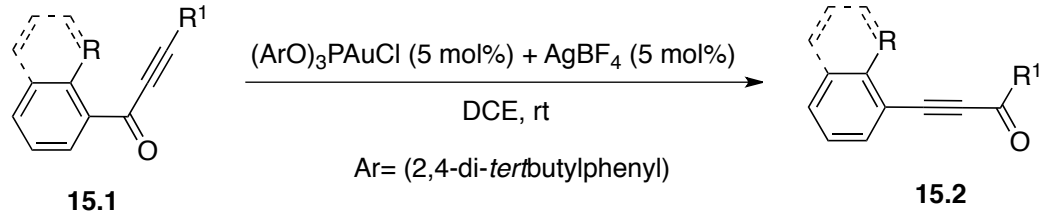
[f] 2-dicyclohexylphosphino-2', 4', 6', triisopropylbiphenyl.

[g] Ar=(2,4-di-*t*-Bu-C_6H_3).

gold hexafluoroantimonate complexes at room temperature led to exclusive formation of the rearranged product **15.2** (entries 6-9). Finally, employment of a cationic gold catalyst possessing phosphite ligand and tetrafluoroborate counter ion led to the 1,3-transposed ynone **15.2** in 95% yield (entry 10). Control experiment indicated that silver tetrafluoroborate did not catalyze this reaction even at high temperature (entry 11).

With the optimized conditions in hands, we examined the scope of this transformation in the transposition of differently-substituted 1,3-ynones (Table II). Thus, ynones **15.1a-c** bearing acyclic substituents reacted smoothly to produce the rearranged products **15.2a-c** (entries 1-3). In addition, substrates **15.2d-f** having 3-, 5-, and 6-membered carbocycles afforded the transposed products in good to excellent yields (entries 4-6). Phenyl- and thiophenyl-substituted ynones **15.1g** and **15.1h** were also competent reactants in this transformation (entries 7 and 8). Expectedly, methyl substituent at *ortho* position of phenyl ring of **15.1i** governed the regioselectivity of transposition reaction over the *meta*-substituted phenyl to produce product **15.2i** in an excellent yield (entry 9). Transposition of F- and OMe-containing ynones **15.1j** and **15.1k** proceeded uneventfully as well (entries 10,11). Expectedly, not only the methyl substituent at the *ortho* position of the phenyl group of ynones but also a variety of other groups were effective to impose the controlling stereoelectronic effect. Thus, aryl ynones **15.1l**-**q** bearing phenyl (entry 12), trimethylsilyl (entry 13), halogens (entries 15-17), and naphthyl groups showed excellent regioselectivity, affording the rearranged products **15.2l**-**q** exclusively and in high to excellent yields. Notably, 3-metylated indole **15.1r** can also be efficiently employed in this reaction to produce **15.2r** (entry 18).

Table II. GOLD-CATALYZED 1,3-TRANSPOSITION OF YNONES



15.1 **15.2**

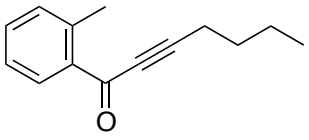
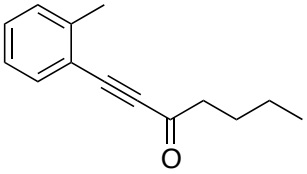
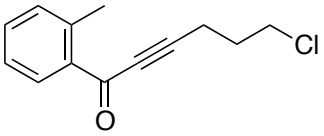
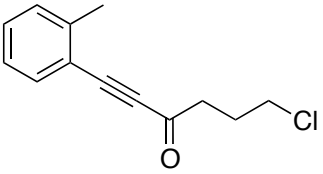
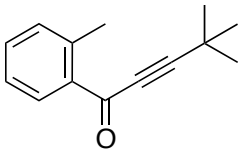
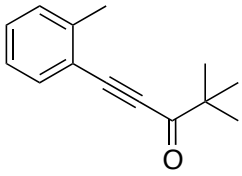
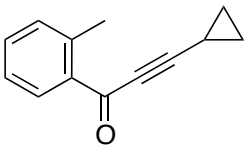
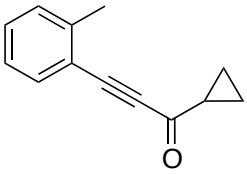
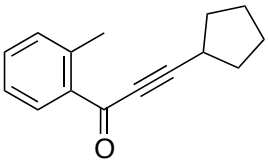
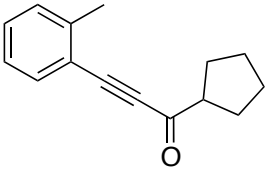
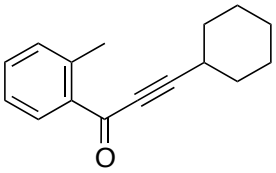
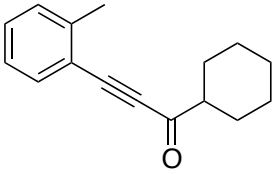
Entry	Substrate		Product		Yield (%)[a,b]
1		**15.1a**		**15.2a**	95
2		**15.1b**		**15.2b**	90
3		**15.1c**		**15.2c**	98
4		**15.1d**		**15.2d**	90
5		**15.1e**		**15.2e**	91
6		**15.1f**		**15.2f**	79

Table III. GOLD-CATALYZED 1,3-TRANSPOSITION OF YNONES (continued)

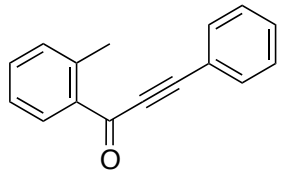
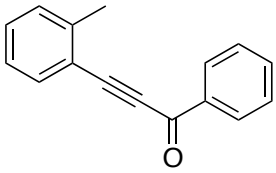
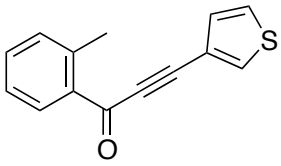
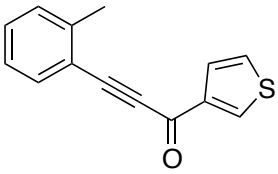
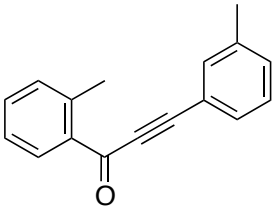
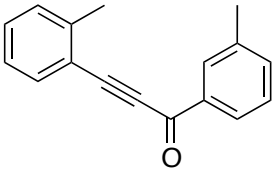
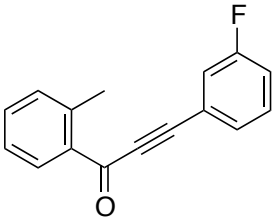
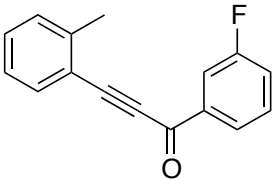
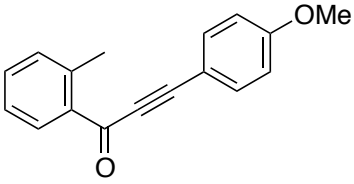
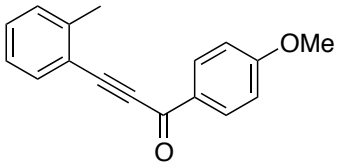
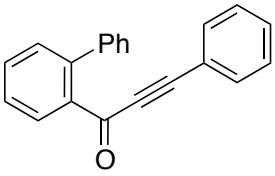
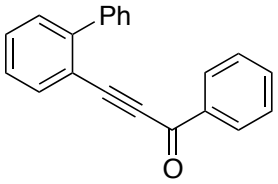
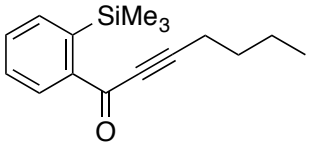
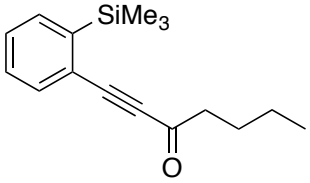
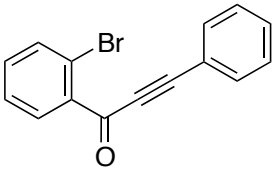
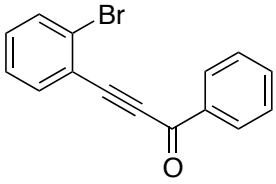
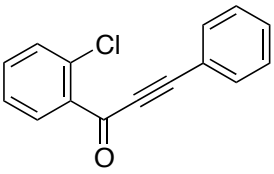
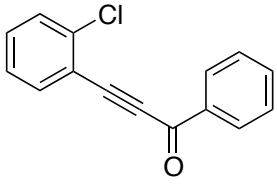
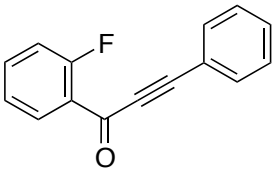
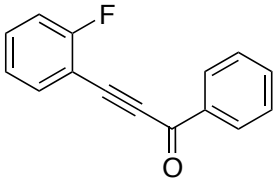
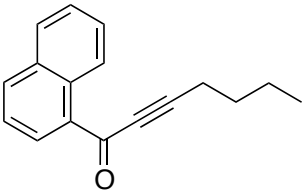
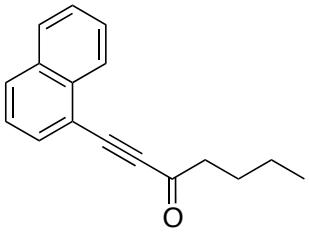
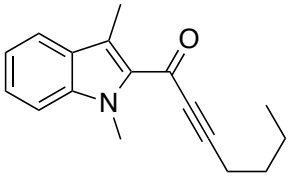
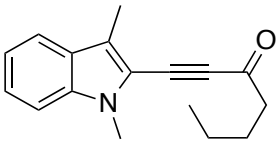
Entry	Substrate		Product	Yield (%)[a,b]	Entry
7		**15.1g**		**15.2g**	88
8		**15.1h**		**15.2h**	88
9		**15.1i**		**15.2i**	92
10		**15.1j**		**15.2j**	97
11		**15.1k**		**15.2k**	81
12		**15.1l**		**15.2l**	91

Table IV. GOLD-CATALYZED 1,3-TRANSPOSITION OF YNONES (continued)

Entry	Substrate		Product		Yield (%)[a,b]	Entry
13		**15.1m**		**15.2m**	91[c]	
14		**15.1n**		**15.2n**	92	
15		**15.1o**		**15.2o**	89	
16		**15.1p**		**15.2p**	83	
17		**15.1q**		**15.2q**	85	
18		**15.1r**		**15.2r**	90	

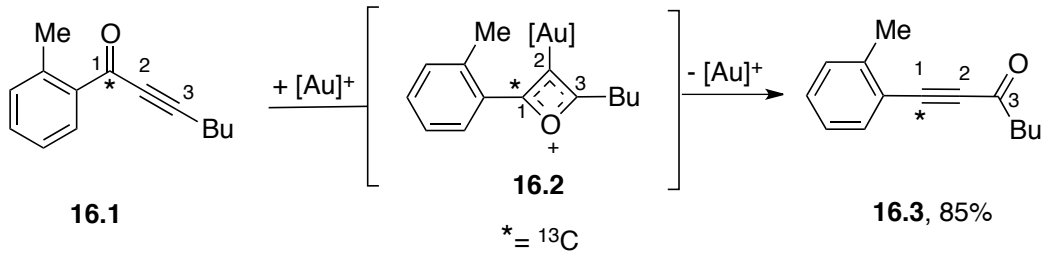
[a] Isolated yield.

[b] Reactions were performed on 0.2 – 0.5 mmol scale.

[c] IPrAuCl (5 mol%) + $AgSbF_6$ (5 mol%) were used as catalytic system.

2.1.3.2 Carbon-Labeling Studies

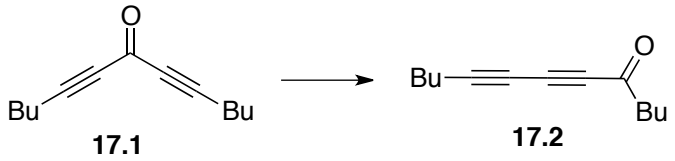
To verify if this transformation proceeds with or without skeletal rearrangement, which are often observed in the gold-catalyzed transformations,[25] C1-labebeled ynone **16.1** was prepared and subjected to the standard reaction conditions (Scheme 16). Thus, upon he 1,3-transposition reaction, the regioisomer **16.3** was formed possessing the labeled carbon at the alkyne moiety. This observation indicates that the ynone transposition reaction does not involve C–C bond disconnection and most likely proceeds through intermediacy of a four-membered heterocycles **16.2**.[19, 20]



Scheme 16.

2.1.4. Consideration of Extended Conjugation Factor

We considered the possibility of the extended conjugation serving as a regioselectivity-controlling factor in this transformation (Scheme 17). Computations predicted that conversion of the cross-conjugated diynone **17.1** to the conjugated isomer **17.2** would be thermodynamically favored by releasing 8.0 kcal/mol energy. Thus, this effect would completely push the equilibrium toward the more thermodynamically stable ynone **17.2**. Inspired by this prediction, we subjected the diynone **17.1** to the gold-catalyzed reaction. We were pleased to find that **16.1** was completely converted to the regioisomeric diynone **17.2**.



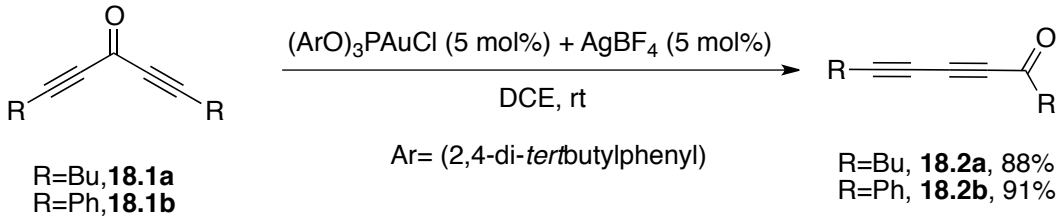
- ΔE	Predicted **17.2**:**17.1**	Experimental **17.2**:**17.1**
8.0	>>99:1	100:0

Experimental conditions:
$(ArO)_3PAuBF_4$ (5 mol%), DCE, rt
Ar= (2,4-di-*tert*-butylphenyl)

Scheme 17.

2.1.4.1. Scope of 1,3-Transposition Reaction of Ynones by Extended Conjugation Factor

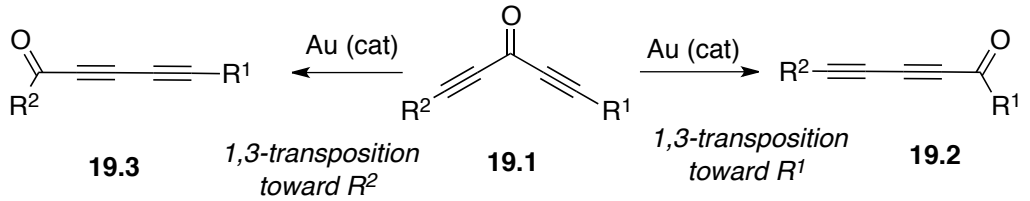
Intrigued by finding the second regioselective-controlling factor in the 1,3-transposition of ynones *i.e.* extended conjugation (Scheme 16), we examined the reaction of symmetrically substituted diynones **18.1a, b** under the optimized reaction conditions. Thus, the 1,3-transposition reaction occurred smoothly to afford conjugated diynones **18.2a, b** in excellent yields.



Scheme 18.

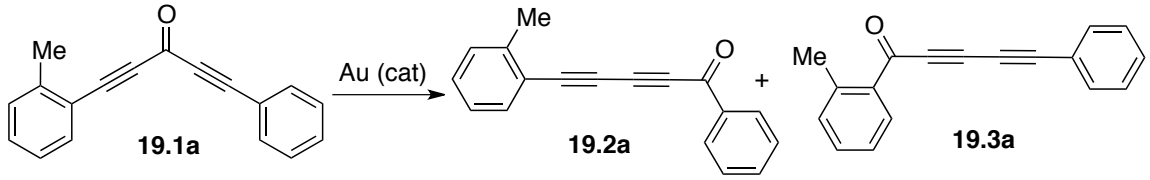
We were interested in the development of 1,3-transposition reaction toward synthetically more attractive unsymmetrical conjugated diynones. However, by employing an unsymmetrical substrate such as **19.1**, a gold catalyst can activate either of

alkynyl groups. Thus, the reaction would lead to a mixture of products **19.2** (result of 1,3-transposition toward R^1) and **19.3** (result of 1,3-transposition toward R^2).



Scheme 19.

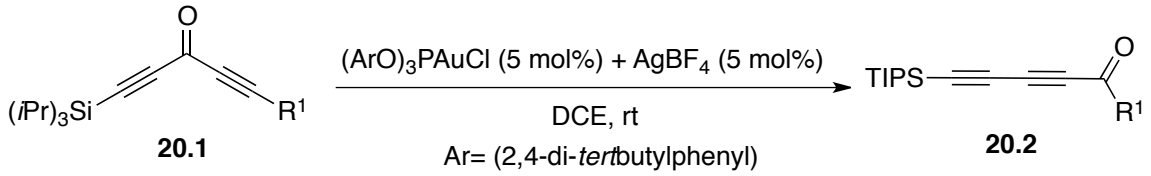
To solve this problem, we first speculated that by employing the unsymmertical diynone **19.1a**, bearing an *o*-tolyl moiety, the interrupted conjugation effect (*vide supra*) would render a selective transposition toward phenyl group, thus formation of **19.2a** would be expected over **19.3a** (Scheme 20). However, by performing this reaction at room temperature, both alkyne moieties of **19.1a** were involved in the transposition reaction to produce a 58:42 mixture of rearranged products **19.2a** and **19.3a**. Gratifyingly, at elevated temperature, the thermodynamically more stable isomer **19.2a** was obtained exclusively in 79%.

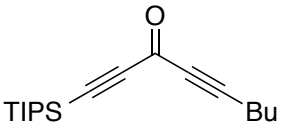
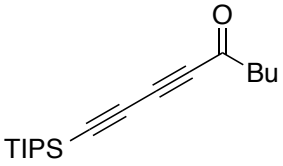
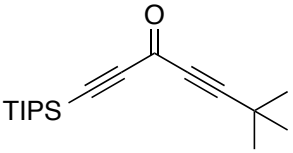
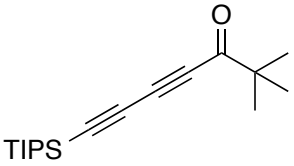
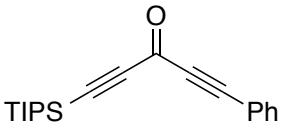
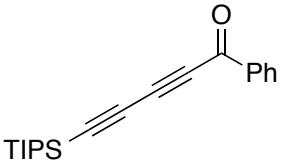
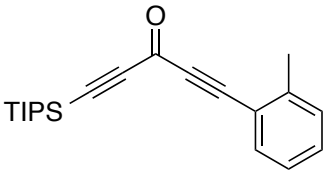
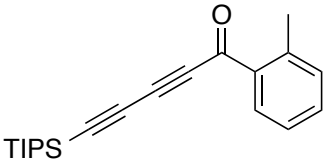
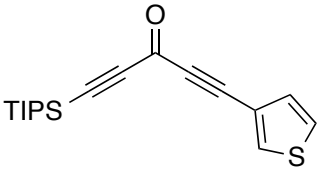
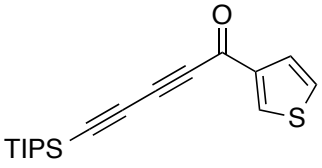


Scheme 20.

Next, we speculated that employing a skipped diynone **20.1**, possessing a bulky triisopropylsilyl (TIPS) terminus would impose steric hindrance at the proximal triple bond, thus the distal alkyne would selectively be activated by the gold catalyst toward the

Table V. GOLD-CATALYZED 1,3-TRANSPOSITION REACTION OF DIYNONES



Entry	Substrate		Product		Yield (%)[a,b]
1		**20.1a**		**20.2a**	86
2		**20.1b**		**20.2b**	83
3		**20.1c**		**20.2c**	93
4		**20.1d**		**20.2d**	91
5		**20.1e**		**20.2e**	90[c]

[a] Isolated yield.

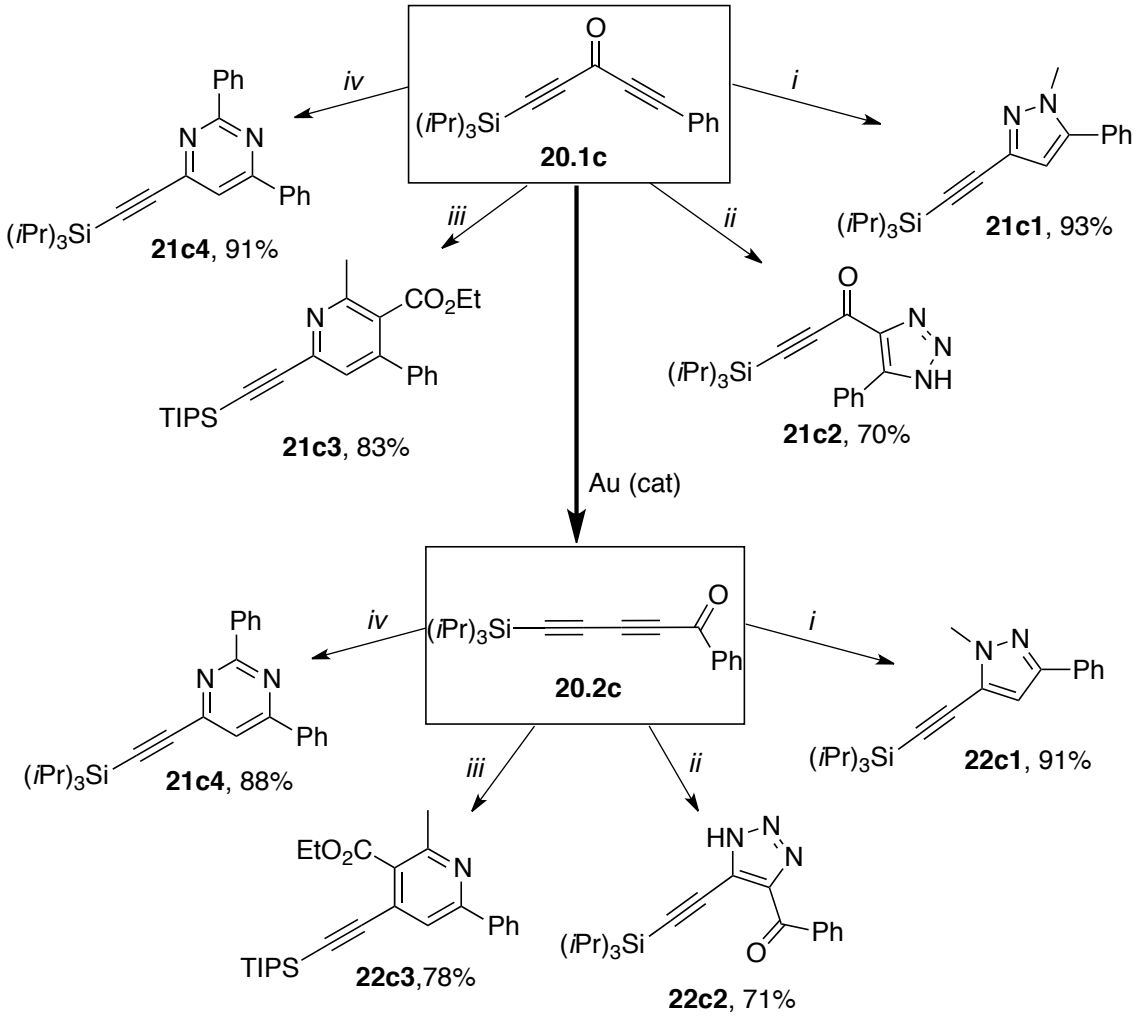
[b] Reactions were performed on 0.2 – 0.5 mmol scale.

[c] Reaction was performed at 100 °C.

1,3-transposition reaction hence producing the conjugated diynone **20.2** (Table III). Indeed, the transposition of skipped diynones **20.1a-e** efficiently afforded the unsymmetrical conjugated diynones **20.2a-e** bearing a variety of alkyl, aryl, and heteroaryl substituents (entries 1-5).

2.1.4.2. Synthesis of Regioisomeric Alkynylated Heterocycls

Having established the regioselective synthesis of conjugated diynones from easily available skipped diynones, we speculated that heterocyclization reactions of both of those unsymmetrically-substituted **20.1** and **20.2** should allow for obtaining regioisomeric heterocycles. It was expected that the bulky TIPS group in **20.1** would impose steric hindrance hence controlling the heterocyclization at another ynone miety. Indeed, the reaction of skipped **20.1c** with methylhyrazine produced pyrazole **21c1** in 93% yield, where TIPS-acetylene moiety did not involve in this regioselective reaction (Scheme 21).[26] Likewise, a [3+2] cyclization of **20.1c** with sodium azide afforded the novel TIPS-acetylene-containing triazole **21c2** in a good yield. A condensation reaction of **20.1c** with ethylacetoacetate and ammonium acetate furnished the tetrasubstituted pyridine **21c4** in 83% yield.[26b] In addition, alkynylated pyrimidine was efficiently synthesized by reaction of **20.1c** with benzimidine hydrochloride.[26] Next, we were eager to verify whether the conjugated diynones **20.2** would be competent substrates for these heterocyclization, as to the best of us knowledge no such selective reactions were reported.[27] Remarkably, after the gold-catalyzed transposition of **20.1** to **20.2**, the heterocyclization reaction under the same conditions produced regioisomeric alkynylated heterocycles. Therefore, pyrazole **22c1** (regioisomer of **21c1**), triazole **22c2** (regioisomer **of 21c2**), and pyridine **22c3** (regioisomer of **21c3**) were obtained in good to excellent



Scheme 21.

i. $MeNHNH_2$ (3.0 equiv), MeCN, rt.

ii. NaN_3 (1.1 equiv, DMF, rt.

iii. Benzamidine hydrochloide (1.2 equiv), Na_2CO_3 (2.4 equiv), MeCN:H_2O= 7:1, 80 °C.

iv. Ethylacetoacetate (1.7 equiv), NH_4OAc (5.0 equiv), EtOH, reflux.

yields. The reaction of symmetrical benzimidine hydrochlodie with **20.2c** produced pyrimidine **21c4** (same product of reacting with **20.1c**) albeit in a slightly lower yield.

2.2. Summary

In summary, we developed the first efficient and regioselective 1,3-transposition reaction of ynones and diynones. It was found that steric and electronic nature of substituents at ynone miety did not have significant influence on the position of equilibrium between regioisomeric ynones in this thermodynamically-controlled transformation. However, we found that interrupted- and extended conjugation effects can efficiently control the regioselectivity of this reaction. The synthetic usefulness of this method was demonstrated by synthesis of various regioisomeric five- and six-membered heterocyclic scaffolds possessing an alkyne moiety.

3. EXPERIMENTAL SECTION

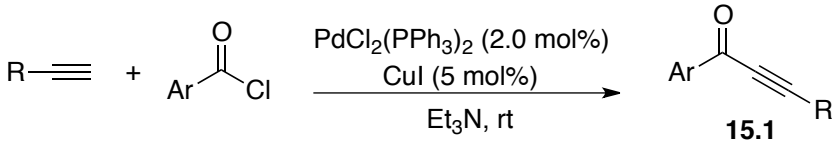
3.1. General Information

NMR spectra were recorded on Bruker Avance DRX-500 (500 MHz) or DRX-400 (400 MHz) instruments. GC/MS analysis was performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). Column chromatography was carried out employing Silicycle silica gel (Kieselgel 60, 63-200 μm). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography. All manipulations with transition metal catalysts were conducted under inert atmosphere using a combination of glovebox and standard Schlenk techniques. Anhydrous toluene, tetrahydrofuran, ether, and dichloromethane purchased from Aldrich were additionally purified on PureSolv PS-400-4 by Innovative Technology, Inc. purification system. Anhydrous solvents other than listed above were purchased from Aldrich and stored over calcium hydride. All other reagents were purchased from Aldrich, Strem Chemicals Inc., Alfa Aesar or Acros Organics, or synthesized via known literature procedures. Reactions were typically run in oven-dried glassware under inert atmosphere.

3.2. 1,3-Transposition Reaction of Ynones

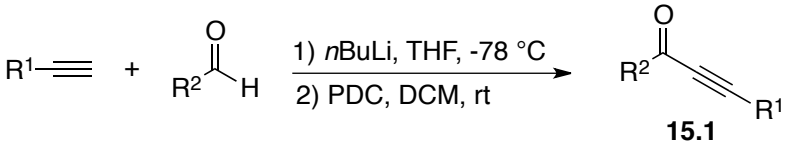
3.2.1. Synthesis of Ynone Substrate

***Method A*:**[28]



In a 5.0 mL round bottom flask containing stirring bar, $PdCl_2(PPh_3)_2$ (2.0 mol%, 0.04 mmol, 28 mg) and copper(I) iodide (5.0 mol%, 0.1 mmol, 20 mg) were added under argon atmosphere. Et_3N (2.0 mL) and alkyne (1.02 equiv) were added and reaction mixture allowed to stir for 5 minutes. The aryloyl chloride (1.0 equiv) was added and the reaction mixture stirred at room temperature until judged completed by GC/MS. The reaction mixture was then poured into saturated ammonium chloride solution and extracted three times with ethyl acetate. Combined organic extracts were dried over anhydrous Na_2SO_4, solvents were removed under reduced pressure, and the residue was purified by flash chromatography (Hex/EtOAc= 40/1) to give the corresponding ynone **15.1**.

***Method B*:**



*n*BuLi solution (1.0 equiv, 2.0 mmol) was added to the solution of terminal alkyne (1.1 equiv, 2.2 mmol) in THF (5 mL) at -78 °C. The reaction stirred 15 min at -78 °C followed by adding the aldehyde (1.0 equiv, 2.0 mmol). The reaction mixture was

allowed to warm to room temperature and stirred for an additional 1 h. After completion, reaction mixture was poured into saturated ammonium chloride solution and extracted three times with dichloromethane. Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure and the residue without purification transferred to a 25 mL round bottom flask. Dichloromethane (10 mL), Celite® (~ 200 mg), and pyridinium dichromate (1.0 equiv) were added. After completion judged by GC/MS, the reaction was extracted three times with dichloromethane. Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure and the residue was purified by flash chromatography (Hex/EtOAc= 40/1) to give the corresponding ynone **15.1**.

1-*o*-tolylhept-2-yn-1-one (15.1a) Method A, (80%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.18 (apparent d, *J* = 7.5 Hz, 1 H), 7.40-7.38 (m, 1 H), 7.29-7.27 (m, 1 H), 7.20-7.19 (m, 1 H), 2.60 (s, 3 H), 2.45-7.43 (m, 2 H), 1.61 (sex, *J* = 7.4 Hz, 2 H), 1.46 (sex, *J* = 7.4 Hz, 2 H), 0.93 (t, *J* = 7.5 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 179.9, 140.2, 135.7, 133.2, 132.6, 132.0, 125.7, 95.4, 81.2, 29.8, 22.0, 21.9, 18.8, 13.5.

6-chloro-1-*o*-tolylhex-2-yn-1-one (15.1b) Method B, (55% over two steps) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.16 (apparent d, *J* = 7.7 Hz, 1 H), 7.41-7.39 (m, 1 H), 7.31-7.28 (m, 1 H), 7.22-7.19 (m, 1 H), 3.66 (t, *J* = 6.2 Hz, 2 H), 2.65 (t, *J* = 6.9 Hz, 2 H), 2.59 (s, 3 H), 2.07 (quin, *J* = 6.6 Hz, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 179.6, 140.3, 135.5, 133.2, 132.8, 132.1, 125.8, 92.8, 81.7, 43.4, 30.5, 21.9, 16.6. **HRMS** (EI) calcd. for $C_{13}H_{13}ClO$ [M]+: 220.0655, found: 220.0657.

4,4-dimethyl-1-*o*-tolylpent-2-yn-1-one (15.1c)[29] Method A (95%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.18-8.16 (m, 1 H), 7.42-7.40 (m, 1 H), 7.33-7.31 (m, 1 H), 7.24-7.21 (m, 1 H), 2.62 (s, 3 H), 1.36 (s, 9 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 180.2, 140.2, 136.0, 133.0, 132.6, 132.0, 125.7, 102.4, 79.7, 30.1, 27.9, 21.9.

3-cyclopropyl-1-*o*-tolylprop-2-yn-1-one (15.1d) Method A (95%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.12 (apparent d, J = 7.7 Hz, 1 H), 7.41-7.39 (m, 1 H), 7.30-7.28 (m, 1 H), 7.22-7.20 (m, 1 H), 2.60 (s, 3 H), 1.51-1.47 (m, 1 H), 1.01 - 0.97 (m, 4 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 179.7, 140.0, 135.9, 132.9, 132.5, 132.0, 125.7, 99.6, 21.8, 9.7, 8.7, -0.1. **HRMS** (EI) calcd. for $C_{13}H_{12}O$ [M]+: 184.0888, found: 184.0883.

3-cyclopentyl-1-*o*-tolylprop-2-yn-1-one (15.1e) Method A (93%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.16 (apparent d, J = 7.7 Hz, 1 H), 7.42-7.39 (m, 1 H), 7.29-7.27 (m, 1 H), 7.22-7.20 (m, 1 H), 2.88 - 2.86 (m, 1 H), 2.61 (s, 3 H), 2.04 - 1.99 (m, 2 H), 1.81 - 1.74 (m, 4 H), 1.65 - 1.60 (m, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 180.1, 140.2, 135.9, 133.1, 132.6, 132.0, 125.7, 99.5, 80.8, 80.8, 77.4, 77.1, 76.9, 33.3, 30.2, 25.2, 21.9. **HRMS** (EI) calcd. for $C_{15}H_{16}O$ [M]+: 212.1201, found: 212.1206 .

3-cyclohexyl-1-*o*-tolylprop-2-yn-1-one (15.1f) Method A (67%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.20-8.18 (m, 1 H), 7.43-7.40 (m, 1 H), 7.32-7.29 (m, 1 H), 7.23-7.21 (m, 1 H), 2.70 - 2.65 (m, 1 H), 2.62 (s, 3 H), 1.91 - 1.88 (m, 2 H), 1.76 - 1.72 (m, 2 H), 1.63 - 1.35 (m, 6 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 180.1, 140.2, 135.9, 133.1, 132.6,

132.0, 125.7, 98.9, 81.1, 31.7, 29.3, 25.7, 24.7, 21.9. HRMS (EI) calcd. for $C_{16}H_{18}O$ [M]+: 226.1358, found: 226.1357.

3-phenyl-1-*o*-tolylprop-2-yn-1-one (15.1g)[30] Method A (75%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.32 (apparent d, *J* = 7.7 Hz, 1 H), 7.67-7.64 (m, 2 H), 7.48-7.45 (m, 2 H), 7.42-7.40 (m, 2 H), 7.38-7.36 (m, 1 H), 7.29-7.27 (m, 1 H), 2.69 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 179.7, 140.5, 135.7, 133.2, 132.9, 132.2, 130.6, 128.7, 125.9, 120.3, 91.8, 88.4, 22.0.

3-(thiophen-3-yl)-1-*o*-tolylprop-2-yn-1-one (15.1h) Method B (45%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.27 (apparent d, *J* = 7.9 Hz, 1 H), 7.79-7.77 (m, 1 H), 7.45-7.43 (m, 1 H), 7.36-7.33 (m, 2 H), 7.28 - 7.24 (m, 2 H), 2.67 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 179.7, 140.4, 135.7, 133.5, 133.1, 132.9, 132.2, 130.2, 126.2, 125.9, 119.6, 88.6, 87.3, 21.9. **HRMS** (EI) calcd. for $C_{14}H_{10}OS$ [M]+: 226.0452, found: 226.0452.

3-*m*-tolyl-1-*o*-tolylprop-2-yn-1-one (15.1i) Method A (85%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.32 (apparent d, *J* = 7.5 Hz, 1 H), 7.47 - 7.45 (m, 3 H), 7.38-7.36 (m, 1 H), 7.31 - 7.26 (m, 3 H), 2.69 (s, 3 H), 2.37 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 179.8, 140.4, 138.5, 135.8, 133.4, 133.2, 132.9, 132.2, 131.6, 130.1, 128.6, 125.9, 120.1, 92.2, 88.2, 22.0, 21.2. **HRMS** (EI) calcd. for $C_{17}H_{14}O$ [M]+: 233.0966, found: 233.0965.

3-(3-fluorophenyl)-1-*o*-tolylprop-2-yn-1-one (15.1j) Method A, (70%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.28 (apparent d, *J* = 7.7 Hz, 1 H), 7.48 - 7.42 (m, 2 H), 7.39 - 7.35 (m, 2 H), 7.34-7.31 (m, 1 H), 7.28-7.26 (m, 1 H), 7.18-7.14 (m, 1 H), 2.67 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 179.3, 162.2 ($^{1}J_{C\text{-}F}$ = 248.2 Hz), 140.6, 135.4, 133.2 ($^{3}J_{C\text{-}F}$ = 17.6 Hz), 132.2, 130.3 ($^{4}J_{C\text{-}F}$ = 8.8 Hz), 128.8, 126.0, 122.1($^{4}J_{C\text{-}F}$ = 8.8 Hz), 119.4 ($^{3}J_{C\text{-}F}$ = 23.9 Hz), 118.0 ($^{3}J_{C\text{-}F}$ = 21.4 Hz), 89.8 ($^{5}J_{C\text{-}F}$ = 3.8 Hz), 88.6, 22.0. **HRMS** (EI) calcd. for $C_{16}H_{11}FO$ [M]+: 237.0716, found: 237.0717.

3-(4-methoxyphenyl)-1-*o*-tolylprop-2-yn-1-one (15.1k) [1] Method A, (98%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.29-8.28 (m, 1 H), 7.63-7.61 (m, 2 H), 7.47-7.45 (m, 1 H), 7.37-7.36 (m, 1 H), 7.27 (apparent d, *J* = 6.8 Hz, 1 H), 6.93-6.91 (m, 2 H), 3.84 (s, 3 H), 2.68 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 179.9, 161.6, 140.2, 136.0, 135.0, 132.9, 132.7, 132.1, 125.8, 114.4, 112.1, 93.0, 88.4, 55.4, 21.9.

1-([1,1'-biphenyl]-2-yl)-3-phenylprop-2-yn-1-one (15.1l) Method A, (69%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.99 (apparent d, *J* = 7.7 Hz, 1 H), 7.61-7.60 (m, 1 H), 7.48-7.47 (m, 1 H), 7.46 - 7.42 (m, 4 H), 7.40 - 7.34 (m, 2 H), 7.30 - 7.26 (m, 4 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 180.6, 142.7, 140.4, 138.0, 133.0, 132.2, 131.1, 130.5, 130.1, 129.6, 128.4, 128.3, 127.8, 127.4, 120.1, 93.8, 88.9. **HRMS** (EI) calcd. for $C_{21}H_{14}O$ [M]+: 281.0966, found: 281.0967.

1-(2-(trimethylsilyl)phenyl)hept-2-yn-1-one (15.1m) Method B, (52% over two steps) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.35 (apparent d, *J* = 7.5 Hz, 1 H), 7.75-7.73 (m, 1

H), 7.57-7.55 (m, 1 H), 7.53-7.52 (m, 1 H), 2.51 (t, J = 7.2 Hz, 2 H), 1.72 - 1.64 (m, 2 H), 1.57 - 1.48 (m, 2 H), 0.98 (t, J = 7.3 Hz, 3 H), 0.33 (s, 9 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 179.8, 142.4, 141.6, 135.8, 133.1, 132.5, 128.9, 96.4, 80.2, 29.9, 22.1, 18.9, 13.5, 0.1.

1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (15.1n)[31] Method A, (60%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.08-8.05 (m, 1 H), 7.69 (apparent d, J = 7.9 Hz, 1 H), 7.65-7.63 (m, 2 H), 7.49 - 7.45 (m, 2 H), 7.42 - 7.36 (m, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 177.5, 137.5, 134.9, 133.4, 133.1, 132.8, 131.0, 128.7, 127.4, 121.2, 120.0, 94.2, 88.0.

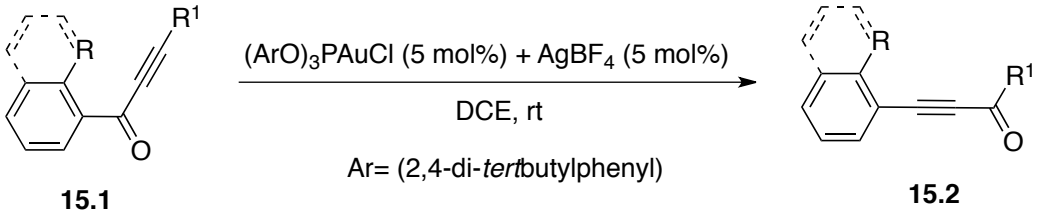
1-(2-chlorophenyl)-3-phenylprop-2-yn-1-one (15.1o)[32] Method A, (70%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.31 (apparent d, J = 7.5 Hz, 2 H), 7.73-7.71 (m, 1 H), 7.68 - 7.61 (m, 1 H), 7.57 - 7.48 (m, 3 H), 7.44-7.41 (m, 1 H), 7.36 - 7.30 (m, 1 H). **^{13}CNMR** (126 MHz, $CDCl_3$) δ ppm 176.7, 133.45, 133.1, 132.6, 131.5, 131.0, 128.7, 126.9, 120.0, 93.9, 88.3.

1-(2-fluorophenyl)-3-phenylprop-2-yn-1-one (15.1p)[33] Method A, (85%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.08-8.05 (m, 2 H), 7.64-7.60 (m, 2 H), 7.56 - 7.52 (m, 2 H), 7.46 - 7.41 (m, 1 H), 7.38 - 7.34 (m, 2 H), 7.25-7.24 (m, 1 H), 7.16 - 7.11 (m, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 174.1, 162.0 ($^{1}J_{C\text{-}F}$ = 262.0 Hz), 135.6 ($^{3}J_{C\text{-}F}$ = 8.8 Hz), 133.2, 131.8, 131.0, 128.7, 125.5 ($^{3}J_{C\text{-}F}$ = 7.6 Hz), 124.2 ($^{4}J_{C\text{-}F}$ = 5.0 Hz), 120.0, 117.1 ($^{2}J_{C\text{-}F}$ = 22.7 Hz), 93.0, 88.5.

1-(naphthalen-1-yl)-3-phenylprop-2-yn-1-one (15.1q)[34] Method A, (70%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 9.27 (apparent d, *J* = 8.8 Hz, 1 H), 8.66 (apparent d, *J* = 7.2 Hz, 1 H), 8.09 (apparent d, *J* = 8.3 Hz, 1 H), 7.91 (apparent d, *J* = 8.1 Hz, 1 H), 7.71 - 7.67 (m, 3 H), 7.62 - 7.57 (m, 2 H), 7.49-7.48 (m, 1 H), 7.45-7.42 (m, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 179.7, 135.1, 134.6, 133.9, 133.0, 130.8, 130.6, 129.0, 128.7, 128.6, 126.8, 126.0, 124.5, 120.4, 91.7, 88.5.

1-(1,3-dimethyl-1H-indol-2-yl)hept-2-yn-1-one (15.1r) Method B, (55% over two steps) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.70 (apparent d, *J* = 8.3 Hz, 1 H), 7.41-7.38 (m, 1 H), 7.32 (apparent d, *J* = 7.5 Hz, 1 H), 7.17-7.15 (m, 1 H), 4.01 (s, 3 H), 2.78 (s, 3 H), 2.52 (t, *J* = 7.2 Hz, 2 H), 1.67 (quin, *J* = 7.5 Hz, 2 H), 1.51 (sxt, *J* = 7.5 Hz, 2 H), 0.97 (t, *J* = 7.5 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 169.9, 139.3, 127.3, 126.9, 125.7, 121.3, 120.8, 120.0, 110.1, 96.3, 82.8, 32.5, 29.7, 22.1, 19.1, 13.5, 11.2. **HRMS** (EI) calcd. for $C_{17}H_{19}NO$ [M]+ 253.1453, found: 253.1465.

3.2.2. Gold-Catalyzed 1,3-Transposition of Ynones



15.1 **15.2**

An oven dried 5 mL V-shape vial equipped with magnetic stir bar was loaded with commercially available chloro[tris(2,4-di-*tert*-butylphenyl)phosphite] gold (5.0 mol%, 22 mg) and silver tetraflouroborate (5.0 mol%, 4.8 mg) in the glove box. The vial was capped and taken out of glove box. 1,2-dichloroethane (4 mL) was added and reaction mixture was stirred for 5 min at room temperature. Ynone **15.1** (0.5 mmol) as a solution in 1,2-dichloroethane (1 mL) was then added through cannula and the reaction mixture stirred at room temperature until judged completed by GC/MS. The reaction mixture was then passed through a small pad of Celite®, solvents were removed under reduced pressure, and the residue was purified by flash chromatography using silica gel (Hex/EtOAc= 40/1) to give the rearranged ynone **15.2** product.

1-*o*-tolylhept-1-yn-3-one (15.2a) (95%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.53 (apparent d, *J* = 7.7 Hz, 1 H), 7.35-7.33 (m, 1 H), 7.27-7.24 (m, 1 H), 7.21-7.18 (m, 1 H), 2.68 (t, *J* = 7.5 Hz, 2 H), 2.49 (s, 3 H), 1.78 - 1.72 (m, 2 H), 1.45 - 1.37 (m, 2 H), 0.95 (t, *J* = 7.5 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 188.3, 142.1, 133.5, 130.7, 129.8, 125.8, 119.9, 91.7, 89.7, 45.4, 26.4, 22.2, 20.6, 13.8. **HRMS** (EI) calcd. for $C_{14}H_{16}O$ [M]+: 200.1201, found: 200.1203.

6-chloro-1-*o*-tolylhex-1-yn-3-one (15.2b) 90%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.53 (apparent d, *J* = 7.7 Hz, 8 H), 7.36-7.37 (m, 1 H), 7.26-7.24 (m, 1 H), 7.121-7.19 (m, 1 H), 3.63 (t, *J* = 6.3 Hz, 2 H), 2.89 (t, *J* = 7.1 Hz, 2 H), 2.49 (s, 3 H), 2.20 (quin, *J* = 6.7 Hz, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 186.3, 142.2, 133.6, 130.9, 129.8, 125.9, 119.6, 91.5, 90.4, 44.0, 42.4, 26.7, 20.6. **HRMS** (EI) calcd. for $C_{13}H_{13}ClO$ [M]+: 220.0655, found: 220.0658.

4,4-dimethyl-1-*o*-tolylpent-1-yn-3-one (15.2c) (98%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.18-8.15 (m, 1 H), 7.44-7.41 (m, 1 H), 7.33-7.32 (m, 1 H), 7.22 (apparent d, *J* = 7.7 Hz, 1 H), 2.62 (s, 3 H), 1.36 (s, 9 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 180.2, 140.2, 136.0, 133.0, 132.6, 132.0, 125.7, 102.4, 79.7, 30.1, 27.9, 21.9. **HRMS** (EI) calcd. for $C_{14}H_{16}O$ [M]+: 200.1201, found: 200.1200.

1-cyclopentyl-3-*o*-tolylprop-2-yn-1-one (15.2d) 91%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.55-7.52 (m, 1 H), 7.35-7.33 (m, 1 H), 7.26-7.24 (m, 1 H), 7.21-7.18 (m, 1 H), 3.07 - 3.02 (m, 1 H), 2.50 (s, 3 H), 2.05 - 1.95 (m, 4 H), 1.74 - 1.64 (m, 4 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 191.0, 142.0, 133.5, 130.6, 129.8, 125.8, 120.0, 91.1, 90.2, 53.9, 29.2, 26.0, 20.7. **HRMS** (EI) calcd. for $C_{15}H_{16}O$ [M]+ 212.1201, found: 212.1202.

1-cyclopropyl-3-*o*-tolylprop-2-yn-1-one (15.2e) (90%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.52 (apparent d, *J* = 7.7 Hz, 1 H), 7.34-7.32 (m, 1 H), 7.27-7.24 (m, 1 H), 7.121-7.19 (m, 1 H), 2.48 (s, 3 H), 2.19 - 2.12 (m, 1 H), 1.35 - 1.32 (m, 2 H), 1.12 - 1.08 (m, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 188.4, 141.9, 133.5, 130.6, 129.8, 125.9, 119.8,

89.8, 89.4, 77.3, 77.0, 76.8, 24.7, 20.7, 11.0. **HRMS** (EI) calcd. for $C_{13}H_{12}O$ [M]+: 184.088, found: 184.0887.

1-cyclohexyl-3-*o*-tolylprop-2-yn-1-one (15.2f) (79%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.54 (apparent d, *J* = 7.5 Hz, 1 H), 7.35-7.33 (m, 1 H), 7.26-7.24 (m, 1 H), 7.20-7.19 (m, 1 H), 5.29 (s, 1 H), 2.50 (s, 1 H), 2.08 - 2.05 (m, 2 H), 1.82 (td, *J* = 13.0, 3.5 Hz, 2 H), 1.70 - 1.67 (m, 1 H), 1.57 - 1.49 (m, 2 H), 1.39 - 1.33 (m, 2 H), 1.31 - 1.23 (m, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 191.5, 142.0, 133.5,130.6, 130.5, 129.8, 125.8,120.0, 91.0, 90.4, 52.4, 28.4, 25.8, 25.4, 20.7. **HRMS** (EI) calcd. for $C_{16}H_{18}O$ [M]+: 226.1358, found: 226.1362.

1-phenyl-3-*o*-tolylprop-2-yn-1-one (15.2g)[35] (88%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.25 (apparent d, *J* = 7.3 Hz, 1 H), 7.67 - 7.62 (m, 2 H), 7.55-7.52 (m, 1 H), 7.39-7.37 (m, 1 H), 7.29 (apparent d, *J* = 7.5 Hz, 1 H), 7.26-7.20 (m, 1 H), 2.60 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 178.0, 142.2, 137.0, 134.1, 133.7, 130.8, 129.9, 129.5, 128.6, 126.0, 120.0, 92.2, 90.8, 20.9.

1-(thiophen-3-yl)-3-*o*-tolylprop-2-yn-1-one (15.2h) (88%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.37-8.35 (m, 2 H), 7.71-7.67 (m, 2 H), 7.63 (apparent d, *J* = 7.5 Hz, 1 H), 7.37 - 7.36 (m, 2 H), 7.31-7.29 (m, 1 H), 7.25-7.21 (m, 1 H), 2.58 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 171.4, 143.1, 142.0, 135.1, 133.6, 130.8, 129.9, 126.9, 126.8, 126.0, 119.9, 91.2, 90.3, 20.9. **HRMS** (EI) calcd. for $C_{14}H_{10}OS$ [M]+: 226.0452, found: 226.0453.

1-*m*-tolyl-3-*o*-tolylprop-2-yn-1-one (15.2i) (92%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.09 - 8.03 (m, 2 H), 7.66 (apparent d, *J* = 7.5 Hz, 1 H), 7.46 - 7.41 (m, 1 H), 7.41-7.37 (m, 1 H), 7.29 (apparent d, *J* = 7.5 Hz, 1 H), 7.27-7.24 (m, 1 H), 2.60 (s, 3 H), 2.45 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 178.2, 142.1, 138.5, 137.1, 134.9, 133.6, 130.8, 129.9, 128.5, 127.0, 125.9, 120.1, 91.9, 90.9, 21.3, 20.9. **HRMS** (EI) calcd. for $C_{17}H_{14}O$ [M]+: 233.0966, found: 233.0971.

1-(3-fluorophenyl)-3-*o*-tolylprop-2-yn-1-one (15.2j) (97%) ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.04 (apparent d, *J* = 7.7 Hz, 1 H), 7.89 (apparent d, *J* = 7.5,1 H), 7.65 (apparent d, *J* = 7.5 Hz, 1 H), 7.53-7.50 (m, 1 H), 7.41-7.38 (m, 1 H), 7.35 - 7.33 (m, 1 H), 7.31-7.29 (m, 1 H), 7.26 - 7.23 (m,1 H), 2.59 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 176.6, 162.8 ($^{1}J_{C\text{-}F}$ = 249.5 Hz), 142.3, 133.8, 131.0, 130.3 ($^{4}J_{C\text{-}F}$ = 7.6 Hz), 129.9, 126.0, 125.3, 121.0 ($^{3}J_{C\text{-}F}$ = 21.4 Hz), 119.7, 115.9, ($^{3}J_{C\text{-}F}$ = 22.7 Hz), 92.8, 90.4, 20.9. **HRMS** (EI) calcd. for $C_{16}H_{11}FO$ [M]+: 238.0783, found: 238.0793.

1-(4-methoxyphenyl)-3-*o*-tolylprop-2-yn-1-one (15.2k) (81%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.21 (apparent d, *J* = 8.8 Hz, 2 H), 7.64 (apparent d, *J* = 7.5 Hz, 1 H), 7.37-7.35 (m, 1 H), 7.28-7.29 (m, 1 H), 7.25-7.22 (m, 1 H), 6.99 (apparent d, *J* = 9.0 Hz, 2 H), 3.90 (s, 3 H), 2.58 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 176.7, 164.4, 142.0, 133.5, 131.9, 130.6, 130.4, 129.8, 125.9, 120.2, 113.9, 91.3, 90.8, 55.6, 20.9.

3-(biphenyl-2-yl)-1-phenylprop-2-yn-1-one (15.2l) (91%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.84 (apparent d, *J* = 7.7 Hz, 1 H), 7.74 (apparent d, *J* = 7.3 Hz, 1 H), 7.63 - 7.58

(m, 1 H), 7.57 - 7.52 (m, 1 H), 7.52 - 7.45 (m, 1 H), 7.44 - 7.40 (m, 1 H), 7.34-7.31 (m, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 177.9, 146.2, 140.1, 136.8, 135.0, 133.8, 131.0, 129.7, 129.6, 129.4, 128.4, 128.4, 127.9, 127.5, 118.9, 92.8, 89.7. **HRMS** (EI) calcd. for $C_{21}H_{14}O$ [M]+: 281.0966, found: 281.0966.

1-(2-(trimethylsilyl)phenyl)hept-1-yn-3-one (15.2m) (91%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.61 (apparent d, *J* = 7.5 Hz, 1 H), 7.55 (d, *J* = 7.3 Hz, 1 H), 7.43-7.40 (m, 1 H), 7.38-7.35 (, 1 H), 2.67 (t, *J* = 7.4 Hz, 2 H), 1.73 (quin, *J* = 7.5 Hz, 2 H), 1.40 (sxt, *J* = 7.4 Hz, 2 H), 0.95 - 0.94 (m, 1 H), 0.95 (t, *J* = 7.3 Hz, 3 H), 0.41 (s, 9 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 187.8, 144.7, 134.4, 134.2, 129.6, 128.9, 125.0, 91.6, 90.6, 45.1, 26.1, 22.2, 13.8, -1.0. **HRMS** (EI) calcd. for $C_{16}H_{22}OSi$ [M]+: 258.1440, found: 258.1444.

3-(2-bromophenyl)-1-phenylprop-2-yn-1-one (15.2n) (89%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.33 (apparent d, *J* = 7.2 Hz, 2 H), 7.73 - 7.63 (m, 3 H), 7.55-7.52 (m, 2 H), 7.39 - 7.32 (m, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 177.8, 136.8, 135.3, 134.2, 132.8, 131.8, 129.9, 128.7, 127.4, 126.8, 122.7, 90.5, 90.4. **HRMS** (EI) calcd. for $C_{15}H_9BrO$ [M]+: 283.9837, found: 283.9837.

3-(2-chlorophenyl)-1-phenylprop-2-yn-1-one (15.2o)[36] (89%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.31 (apparent d, *J* = 7.5 Hz, 2 H), 7.72 (apparent d, *J* = 7.7 Hz, 1 H), 7.68 - 7.60 (m, 1 H), 7.57 - 7.47 (m, 3 H), 7.44-7.40 (m, 1 H), 7.34-7.32 (m, 1 H). **^{13}C NMR**

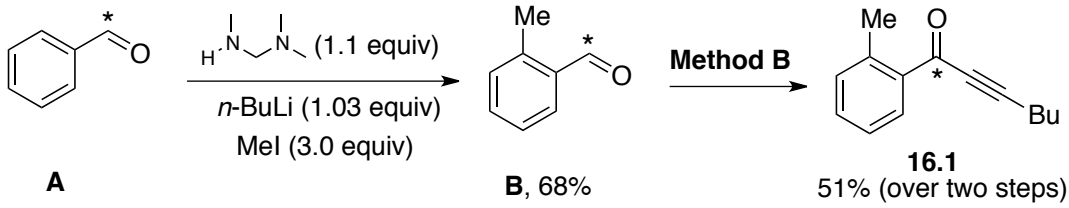
(126 MHz, $CDCl_3$) δ ppm 177.8, 137.5, 136.8, 135.1, 134.2, 131.8, 129.8, 129.7, 128.7, 126.9, 120.5, 91.0, 89.0.

3-(2-fluorophenyl)-1-phenylprop-2-yn-1-one (15.2p)[37] (83%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.26 (apparent d, *J* = 7.5 Hz, 2 H), 7.68 - 7.63 (m, 2 H), 7.54 - 7.46 (m, 3 H), 7.22 - 7.16 (m, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 177.7, 163.8 ($^1J_{C\text{-}F}$ = 255.8 Hz), 136.7, 134.8, 134.3, 132.8 ($^3J_{C\text{-}F}$ = 7.6 Hz), 129.7, 128.7,124.4 ($^4J_{C\text{-}F}$ = 3.8 Hz), 115.9 ($^2J_{C\text{-}F}$ = 20.1 Hz), 109.0 ($^2J_{C\text{-}F}$ = 14.9 Hz), 91.4 (d, *J* = 2.5 Hz), 86.2.

3-(naphthalen-1-yl)-1-phenylprop-2-yn-1-one (15.2q)[38] (85%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.44 (apparent d, *J* = 8.3 Hz, 2 H), 8.35-8.32 (m, 2 H), 7.99-7.96 (m, 2 H), 7.95-7.91 (m, 2 H), 7.68 - 7.65 (m, 4 H), 7.60 - 7.55 (m, 6 H), 7.53 - 7.49 (m, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 178.0, 137.1, 134.2, 133.7, 133.2, 133.1, 131.5, 129.6, 128.7, 128.6, 127.8, 127.0, 125.8, 125.2, 117.7, 91.7, 91.5.

1-(1,3-dimethyl-1H-indol-2-yl)hept-1-yn-3-one (15.2r) (90%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.59 (apparent d, *J* = 8.1 Hz, 1 H), 7.38-7.33 (m, 1 H), 7.27 (apparent d, *J* = 8.1 Hz, 1 H), 7.16-7.11 (m, 1 H), 3.81 (s, 3 H), 2.72 (t, *J* = 7.4 Hz, 2 H), 2.49 (s, 3 H), 1.80 (quin, *J* = 7.5 Hz, 2 H), 1.45 (sxt, *J* = 7.5 Hz, 2 H), 0.98 (t, *J* = 7.3 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 187.4, 138.3, 127.0, 125.2, 123.6, 120.1, 119.9, 117.2, 109.6, 98.3, 83.6, 45.0, 30.8, 26.6, 22.2, 13.9, 10.0. **HRMS** (EI) calcd. for $C_{17}H_{19}NO$ [M]+: 253.1467, found: 253.1468.

3.2.3. Carbon-Labeling Studies



Synthesis of ^{13}C-Labeled *o*-Tolylaldehyde B:[39]

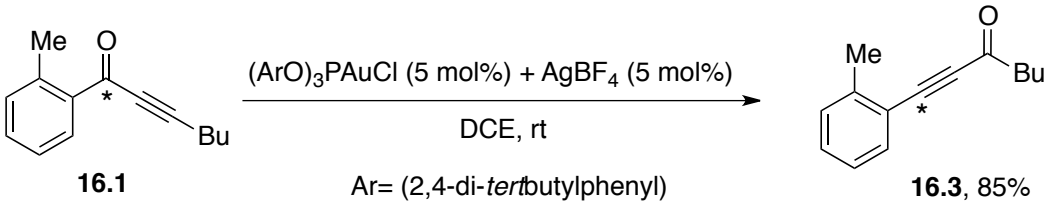
A flame-dried round bottom flask equipped with a stirring bar was charged with trimethylethylenediamine (1.1 equiv, 1.1 mmol, 143 μL) under argon. THF (5 mL) was added and the solution was cooled to –20 °C. *n*-butyl lithium (1.03 equiv, 1.03 mmol, 2.63 M, 390 μL) was added dropwise to the cold reaction mixture and the resulting solution was stirred for 15 min. The labeled benzaldehyde **A**[40] (1.0 equiv, 1 mmol, 102 μL, ~10% enrichment) was then added and the reaction was stirred for 15 min at –20 °C. Second portion of *n*-butyl lithium (3.1 equiv, 3.1 mmol, 2.63 M, 1.2 mL) was added to the solution and the reaction was stored in a freezer at -20 °C for 14 h. The reaction mixture was then cooled down to –40 °C and MeI (3.0 equiv, 3 mmol, 187 μL) was added dropwise. The reaction stirred for 30 min at –40 °C and then 30 min at rt. The reaction was diluted with diethyl ether (10 mL) and saturated ammonium chloride was added. The reaction mixture was extracted with diethyl ether and washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude material was subjected to column chromatography (pure hexane to Hex:EtOAc=20:1) to afford **B** as a yellow oil (68%).

Synthesis of the ^{13}C-labeled 1-o-tolylhept-2-yn-1-one (16.1)

The obtained labeled o-tolyladehyde **B** was subjected to the **Method B** to afford the labeled **16.1**.

^{13}C-labeled 1-o-tolylhept-2-yn-1-one (16.1) (51% over two steps) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.19 (apparent d, *J* = 7.7 Hz, 5 H), 7.43-7.41 (tm, 1 H), 7.33-7.29 (m, 1 H), 7.25-7.22 (m, 1 H), 2.62 (s, 3 H), 2.47 (t, *J* = 7.2 Hz, 2 H), 1.64 (quin, *J* = 7.3 Hz, 2 H), 1.49 (sex, *J* = 7.4 Hz, 2 H), 0.99 - 0.92 (m, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm **180.0** (**labeled**), 140.3, 135.8, 133.2, 132.6, 132.0, 125.7, 95.4, 81.2, 29.8, 22.1, 21.9, 18.8, 13.5.

1,3-Transposition Reaction of ^{13}C-Labeled Ynone:



16.1 **16.3**, 85%

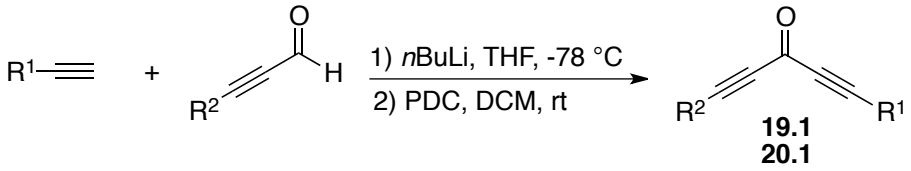
The gold-catalyzed reaction of ketone-labeled ynone **16.1** (vide supra) afforded the alkyne-labeled regioisomer **16.3**.

^{13}C-labeled 1-*o*-tolylhept-1-yn-3-one (16.3) (85%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.53 (apparebt d, *J* = 7.0 Hz, 1 H), 7.38-7.35 (m, 1 H), 7.26-7.24 (m, 1 H), 7.21-7.19 (m, 1 H), 2.68 (t, *J* = 7.4 Hz, 2 H), 2.50 (s, 3 H), 1.75 (quin, *J* = 7.5 Hz, 2 H), 1.46 - 1.39 (m, 3 H), 0.97 - 0.94 (m, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 188.3, 142.1, 133.5, 130.7, 129.8, 125.9, 119.9, **89.7** (**labeled**), 45.4, 26.4, 22.2, 20.6, 13.8. **HRMS** (EI) calcd. for $C_{21}H_{28}OSi$ [M+]: 201.1235, found: 201.1239.

3.3. 1,3-Transposition Reaction of Diynones

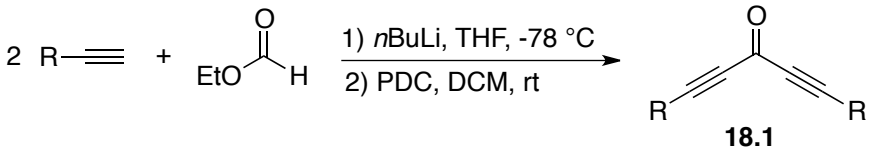
3.3.1. Synthesis of Skipped Diynone Substrates

Method B:



*n*BuLi solution (1.0 equiv, 2.0 mmol) was added to the solution of terminal alkyne (1.1 equiv, 2.2 mmol) in THF (5 mL) at -78 °C. The reaction stirred 15 min at -78 °C followed by adding the alkynyl aldehyde (1.0 equiv, 2.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. After completion, reaction mixture was poured into saturated ammonium chloride solution and extracted three times with dichloromethane. Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure and the residue without purification transferred to a 25 mL round bottom flask. Dichloromethane (10 mL), Celite® (~ 200 mg), and pyridinium dichromate (1.0 equiv) were added. After completion judged by GC/MS, the reaction was extracted three times with dichloromethane. Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure and the residue was purified by flash chromatography (Hex/EtOAc= 40/1) to give the corresponding ynone **19.1**.

***Method C*:**



*n*BuLi solution (2.2 equiv, 4.4 mmol) was added to a solution of the acetylene (2.2 equiv, 4.4 mmol) in THF (5 mL) at -78 ^{o}C. After stirring for 30 min at this temperature, ethyl formate (1.0 equiv, 2 mmol) was added via syringe. The reaction was stirred for 1 h and allowed to warm up to room temperature. Saturated ammonium chloride solution was then added and the reaction mixture was extracted three times with ethyl acetate. Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure and the residue was purified by flash chromatography (Hex/EtOAc= 40/1) to give the symmetrical ynone.

Trideca-5,8-diyn-7-one (18.1a)[41] Method C, (73%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 2.37 (t, *J* = 7.1 Hz, 4 H), 1.56 (quin, *J* = 7.3 Hz, 4 H), 1.42 (sxt, *J* = 7.4 Hz, 4 H), 0.90 (t, *J* = 7.5 Hz, 6 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 161.4, 94.6, 82.3, 29.5, 21.9, 18.7, 13.4.

1,5-diphenylpenta-1,4-diyn-3-one (18.1b)[42] Method C, (69%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.66-7.59 (m, 4 H), 7.51 - 7.46 (m, 2 H), 7.43-7.40 (m, 4 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 160.8, 133.4, 131.3, 128.7, 119.5, 91.7, 89.5.

1-(*o*-tolyl)nona-1,4-diyn-3-one (19.1a) Method B, (68% over two steps) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.64 (apparent d, *J* = 7.2 Hz, 2 H), 7.62-7.60 (m, 1 H), 7.52 - 7.47 (m, 1 H), 7.44-7.40 (m, 2 H), 7.39 - 7.36 (m, 1 H), 7.30-7.26 (m, 1 H), 7.27-7.20 (m, 1 H), 2.55 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 160.8, 142.9, 133.8, 133.3, 131.3,

131.2, 129.9, 128.7, 126.0, 119.6, 119.2, 93.3, 91.5, 91.2, 89.5, 20.6. **HRMS** (EI) calcd. for $C_{16}H_{16}O$ [M]+: 244.0888, found: 244.0889.

1-(triisopropylsilyl)nona-1,4-diyn-3-one (20.1a) Method B, (70% over two steps) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 2.39 (t, *J* = 7.0 Hz, 2 H), 1.58 - 1.53 (m, 2 H), 1.46 - 1.41 (m, 2 H), 1.09 (m, 21 H), 0.91 (t, *J* = 7.5 Hz , 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 160.6, 105.1, 96.0, 95.7, 82.4, 29.5, 21.8, 18.8, 18.4, 13.4, 11.0. **HRMS** (EI) calcd. for $C_{18}H_{30}OSi$ [M]+: 290.2066, found: 290.2072.

6,6-dimethyl-1-(triisopropylsilyl)hepta-1,4-diyn-3-one (20.1b) Method B, (42% over two steps) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.30 (s, 9 H), 1.12 (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 161.0, 105.3, 103.0, 96.5, 86.1, 29.8, 27.9, 18.4, 11.0. **HRMS** (EI) calcd. for $C_{18}H_{30}OSi$ [M]+: 290.2066, found: 290.2065.

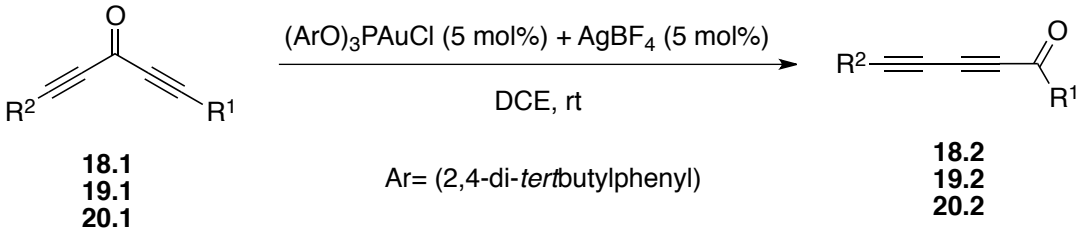
1-phenyl-5-(triisopropylsilyl)penta-1,4-diyn-3-one (20.1c) Method B, (56% over two steps) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.60 (apparent d, *J* = 7.5 Hz, 2 H), 7.50-7.46 (m, 1 H), 7.45-7.38 (m, 2 H), 1.15 (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 160.4, 133.4, 131.2, 128.7, 119.5, 105.1, 97.7, 91.5, 89.5, 18.5, 11.0. **HRMS** (EI) calcd. for $C_{20}H_{26}OSi$ [M]+: 310.1753, found: 310.1755.

1-(o-tolyl)-5-(triisopropylsilyl)penta-1,4-diyn-3-one (20.1d) Method B, (67% over two steps) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.55 (apparent d, *J* = 7.7 Hz, 1 H), 7.39-7.35 (m, 1H), 7.27-7.25 (m, 1H), 7.24-7.21 (m, 1 H), 2.51 (s, 3 H), 1.1 (s, 21 H). **^{13}C NMR**

(126 MHz, $CDCl_3$) δ ppm 160.3, 143.0, 133.9, 131.3, 129.9, 125.9, 119.3, 105.2, 97.2, 93.5, 91.0, 53.4, 97.2, 20.5, 18.5, 11.0. **HRMS** (EI) calcd. for $C_{21}H_{28}OSi$ [M]+: 324.1909, found: 324.1914.

1-(thiophen-3-yl)-5-(triisopropylsilyl)penta-1,4-diyn-3-one (20.1e) Method B, (41% over two steps) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.79 (apparent d, *J* = 1.1 Hz, 1 H), 7.35-7.33 (m, 1 H), 7.24-7.20 (m, 1 H), 1.14 - 1.11 (m, 40 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 134.9, 130.3, 126.4, 105.1, 18.5, 11.0.

3.3.2. Gold-Ctalyzed 1,3-Transposition of Skipped to Conjugated Diynones



18.1
19.1
20.1

18.2
19.2
20.2

An oven dried 5 mL V-shape vial equipped with magnetic stir bar was loaded with commercially available chloro[tris(2,4-di-*tert*-butylphenyl)phosphite] gold (5.0 mol%, , 22 mg) and silver tetraflouroborate (5.0 mol%, 4.8 mg). 1,2-dichloroethane (4 mL) was added and reaction mixture was stirred for 5 min at room temperature. Ynone **18.1** (0.5 mmol) as a solution in 1,2-dichloroethane (1 mL) was then added through cannula and the reaction mixture stirred at room temperature until judged completed by GC/MS. The reaction mixture was then passed through a small pad of Celite®, solvents were removed under reduced pressure, and the residue was purified by flash

chromatography using silica gel (Hex/EtOAc= 40/1) to give the rearranged ynone **18.2** product.

Trideca-6,8-diyn-5-one(18.2a) (88%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 2.55 (t, *J* = 7.4 Hz, 2 H), 2.38 - 2.33 (m, 2 H), 1.64 (quin, *J* = 7.5 Hz, 2 H), 1.58 - 1.52 (m, 2 H), 1.47 - 1.40 (m, 3 H), 1.38 - 1.30 (m, 2 H), 0.91 (dt, *J* = 7.3, 4.5 Hz, 6 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 187.3, 90.6, 76.1, 72.2, 63.8, 45.2, 29.8, 26.0, 22.1, 21.9, 19.3, 13.7, 13.4. **HRMS** (EI) calcd. for $C_{13}H_{18}$[M]+: 190.1358, found: 190.1357.

1,5-diphenylpenta-2,4-diyn-1-one (18.2b)[43] (91%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.17 (dd, *J* = 8.3, 1.1 Hz, 2 H), 7.65 - 7.63 (m, 1 H), 7.59 (dd, *J* = 7.5, 2.5 Hz, 2 H), 7.52 (t, *J* = 7.8 Hz, 2 H), 7.48 - 7.45 (m, 1 H), 7.39 (t, *J* = 7.5 Hz, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 176.9, 136.6, 134.5, 133.1, 130.5, 129.6, 128.7, 128.7, 120.2, 86.4, 77.8, 77.5, 72.5.

1-o-tolylnona-1,3-diyn-5-one (19.2a) (79%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.18 (apparent d, *J* = 7.7 Hz, 2 H), 7.69 - 7.62 (m, 1 H), 7.57-7.54 (m, 1 H), 7.54 - 7.49 (m, 2 H), 7.37 - 7.32 (m, 1 H), 7.26 (s, 1 H), 7.22-7.17 (m, 1 H), 2.51 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 177.0, 142.7, 136.6, 134.5, 133.5, 130.5, 129.8, 129.7, 128.7, 125.9, 120.1, 85.6, 78.5, 77.7, 75.9, 20.7. **HRMS** (EI) calcd. for $C_{16}H_{16}O$ [M]+: 244.0888, found: 244.0890.

1-(triisopropylsilyl)nona-1,3-diyn-5-one (20.2a) (86%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 2.78 - 2.39 (m, 2 H), 1.69 - 1.61 (m, 2 H), 1.39 - 1.32 (m, 3 H), 1.14 - 1.07 (m, 21

H), 0.93 - 0.90 (m, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 187.0, 94.9, 87.5, 75.2, 72.4, 45.1, 25.9, 22.0, 18.4, 13.7, 11.1. **HRMS** (EI) calcd. for $C_{18}H_{30}OSi$ [M]+:290.2066 , found: 290.2066.

2,2-dimethyl-7-(triisopropylsilyl)hepta-4,6-diyn-3-one (20.2b) (83%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.21 (s, 9 H), 1.11 (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 193.1, 94.5, 87.5, 76.9, 71.0, 45.0, 25.8, 18.4, 11.1. **HRMS** (EI) calcd. for $C_{18}H_{30}OSi$ [M]+: 290.2066, found: 290.2058.

1-phenyl-5-(triisopropylsilyl)penta-2,4-diyn-1-one (20.2c) (93%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.13 (apparent d, J = 7.5 Hz, 1 H), 7.66-7.62 (m, 1 H), 7.53-7.49 (m, 2 H), 1.14 - 1.11 (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 176.91, 136.4, 134.5, 129.6, 128.7, 95.3, 87.7, 77.6, 71.7, 18.5, 11.2. **HRMS** (EI) calcd. for $C_{20}H_{26}OSi$ [M]+: 310.1722, found: 310.1750.

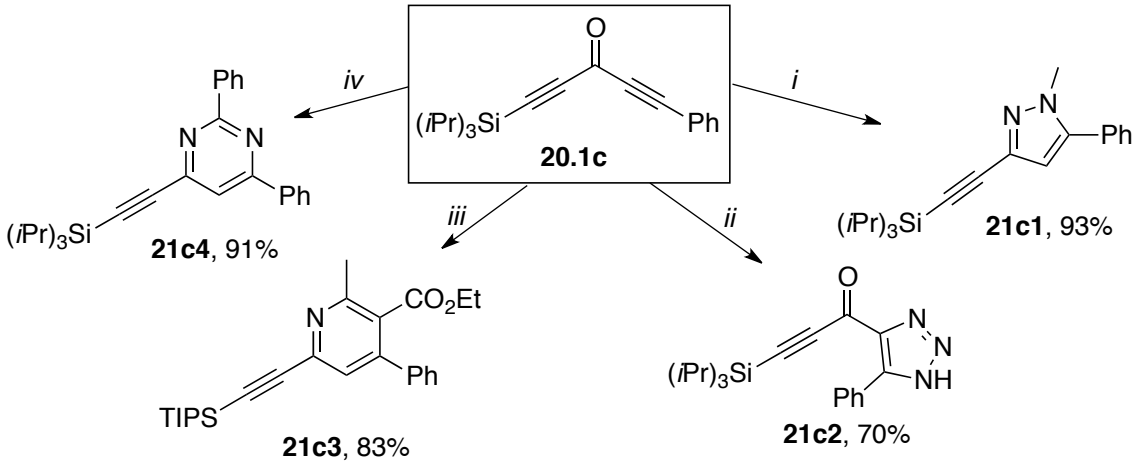
1-*o*-tolyl-5-(triisopropylsilyl)penta-2,4-diyn-1-one (20.2d) (91%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.19 (apparent d, J = 7.5 Hz, 1 H), 7.49-7.44 (m, 3 H), 7.39-7.35 (m, 1 H), 7.25 (apparent d, J = 8.3 Hz, 1 H), 2.62 (s, 3 H), 1.13 - 1.08 (m, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 178.4, 140.7, 133.7, 133.3, 132.2, 126.0, 94.9, 87.8, 76.6, 72.9, 21.9, 18.5, 11.2.

1-(thiophen-3-yl)-5-(triisopropylsilyl)penta-2,4-diyn-1-one (20.2e) (90%) ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.31 (apparent d, J = 1.2 Hz, 1 H), 7.64-7.59 (m, 1 H), 7.35-

7.31 (m, 1 H), 1.15 (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 170.1, 136.2, 127.0, 126.5, 95.0, 87.6, 75.8, 72.0, 18.5, 11.2.

3.3.3. Synthesis of Regioisomeric Alkynylated Heterocycles

3.3.3.1 Synthesis of Heterocycles from Skipped Diynones



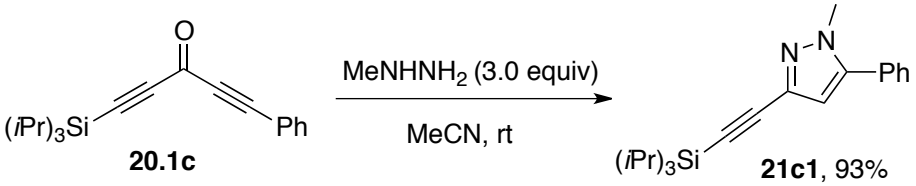
i) NH_2NH_2 (3.0 equiv), MeCN, rt.

ii) NaN_3 (1.1 equiv), DMF, rt.

iii) benzamidine hydrochloide (1.2 equiv), Na_2CO_3 (2.4 equiv), MeCN:H_2O= 7:1, 80 °C.

iv) Ethylacetoacetate (1.7 equiv), NH_4OAc (5.0 equiv), EtOH, reflux.

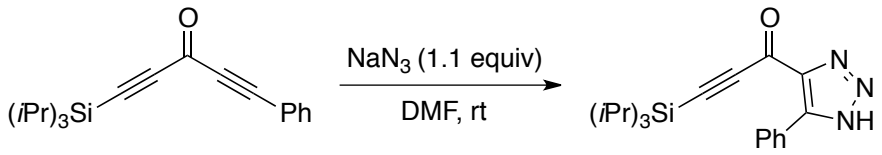
Synthesis of 1-methyl-5-phenyl-3-((triisopropylsilyl)ethynyl)-1*H*-pyrazole (21c1)[44]



To a 3 mL V-shaped vial containing 2,2-dimethyl-7-(triisopropylsilyl)hepta-4,6-diyn-3-one (**20.1c**) (0.15 mmol, 43.5 mg) was added MeCN (2.0 mL) and

methylhydrazine (3.0 equiv, 0.45 mmol, 14 μL). The solution was stirred overnight at room temperature. Ammonium chloride (sat.) was added and solution was then extracted with dichloromethane. After removal of solvents, the residue was subjected to column chromatography (Hexane:EtOAc= 20:1 to 2:1) to produce **21c1** as a yellow oil (93%, 47 mg). The position of NH moiety in product was proposed according to that in reported procedures. [44, 45, 46]

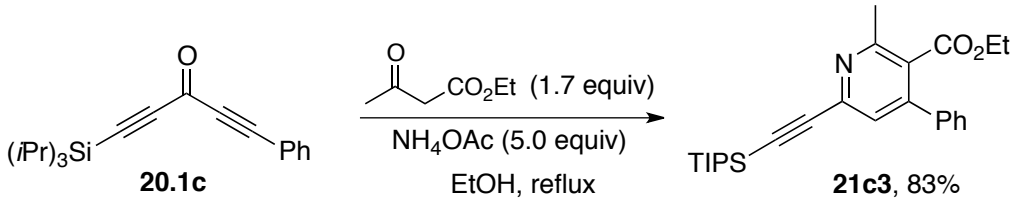
Synthesis of 1-(5-phenyl-1*H*-1,2,3-triazol-4-yl)-3-(triisopropylsilyl)prop-2-yn-1-one (21c2)[2]



20.1c **21c2**, 70%

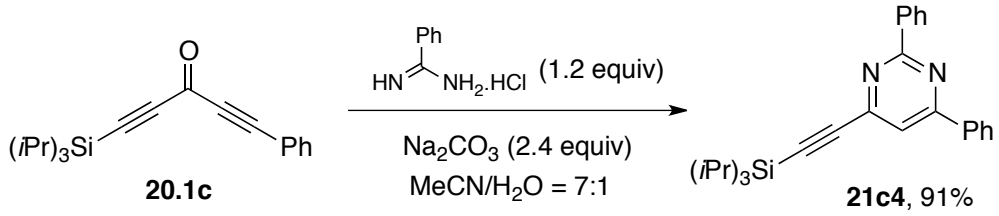
To a 3 mL V-shaped vial containing diynone **20.1c** (0.2 mmol, 62 mg) was added DMF (2.0 mL) and sodium azide (1.1 equiv, 0.22 mmol, 14.5 mg). After stirring for 3 h at at room temperature, water (5 mL) was added and solution was extracted with dichloromethane. The solvents were then removed under reduced pressure and the residue was subjected to column chromatography (Hexane:EtOAc= 20:1 to 2:1) to produce **21c2** as a yellow oil (71%, 49 mg). The position of NH moiety in product was proposed according to that in reported procedures.

Synthesis of ethyl 2-methyl-4-phenyl-6-((triisopropylsilyl)ethynyl)nicotinate (21c3)



To a 10 mL round bottom flask equipped with stirring bar and a reflux condenser was sequentially added **20.1c** (0.2 mmol, 62 mg), ethyl acetoacetate (1.7 equiv, 0.34 mmol, 44 μl), ammonium acetate (5.0 equiv, 1 mmol, 77 mg), and ethanol (4 mL). The reaction was refluxed overnight. After cooling to room temperature, the solvents were removed under reduced pressure. Saturated sodium bicarbonate (10 mL) was added and the reaction was extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate, filtered through a pad of cotton, and then concentrated under reduced pressure. The crude oil was purified via silica gel chromatography (pure hexanes to Hex:EtOAc=10:1) to afford **21c3** as yellow oil (83%, 70 mg).

Synthesis of 2,4-diphenyl-6-((triisopropylsilyl)ethynyl)pyrimidine (21c4)[47]



To a 3 mL V-shaped vial containing **20.1c** (0.15 mmol, 46.5 mg), bezimidamide hydrochloride (1.2 equiv, 0.18 mmol, 28 mg) and sodium carbonate (2.4 equiv, 0.36 mmol, 51 mg) was added MeCN (2 mL) and water (300 μL). The reaction stirred at 80 °C until judged completed by GC/MS. After cooling down, water (5 mL) was added and the mixture was extracted with dichloromethane. The combined extracts were then dried

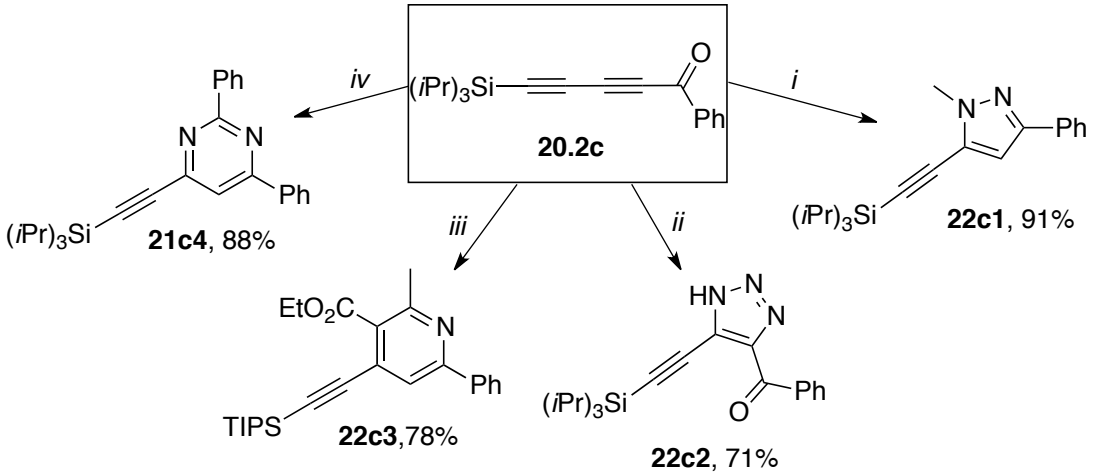
over sodium sulfate, concentrated under reduced pressure, and the residue was subjected to column chromatography (pure hexanes to Hex:EtOAc=10:1) to give **21c4** as a yellow oil (91%, 57 mg)

1-methyl-5-phenyl-3-((triisopropylsilyl)ethynyl)-1*H*-pyrazole (21c1) (93%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.59 - 7.19 (m, 5 H), 6.46 (s, 1 H), 3.86 (s, 3 H), 1.14 (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 144.0, 134.2, 129.9, 128.8, 128.6, 125.5, 110.4, 99.3, 91.6, 37.7, 18.7, 11.3. **HRMS** (EI) calcd for $C_{18}H_{32}N_2Si$ [M]+: 339.2257, found: 339.2253.

1-(5-phenyl-1*H*-1,2,3-triazol-4-yl)-3-(triisopropylsilyl)prop-2-yn-1-one (21c2) (70%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.45 - 7.39 (m, 2 H), 7.38 - 7.35 (m, 2 H), 7.33 (s, 1 H), 1.23 - 0.95 (m, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 170.5, 141.7, 130.1, 129.2, 128.5, 103.8, 99.8, 18.5, 11.1.

2,4-diphenyl-6-((triisopropylsilyl)ethynyl)pyrimidine (21c4) (91%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.63 - 8.61 (m, 2 H), 8.25 - 8.23 (m, 2 H), 7.69 (s, 1 H), 7.53 (m, 6 H), 1.22 (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 164.8, 164.0, 151.4, 137.5, 136.6, 131.1, 130.8, 128.9, 128.5, 128.4, 127.2, 117.3, 104.9, 96.2, 18.7, 11.3. **HRMS** (EI) calcd. for C27H32N2Si [M]+: 412.2335, found: 412.2335.

3.3.3.2 Synthesis of Heterocycles from Conjugated Diynones



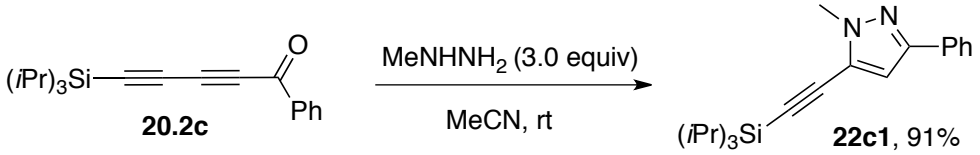
i) NH_2NH_2 (3.0 equiv), MeCN, rt.

ii) NaN_3 (1.1 equiv), DMF, rt.

iii) benzamidine hydrochloide (1.2 equiv), Na_2CO_3 (2.4 equiv), MeCN:H_2O= 7:1, 80 °C.

iv) Ethylacetoacetate (1.7 equiv), NH_4OAc (5.0 equiv), EtOH, reflux.

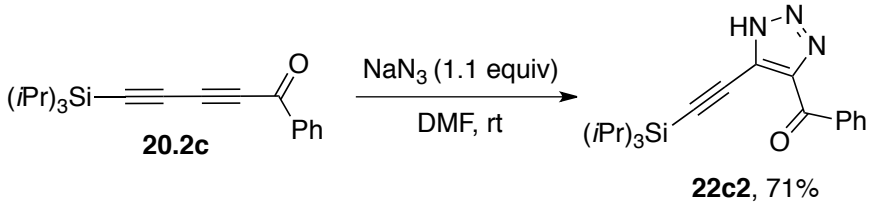
Synthesis of 1-methyl-3-phenyl-5-((triisopropylsilyl)ethynyl)-1*H*-pyrazole (22c1)[48]



To a 3 mL V-shaped vial containing 2,2-dimethyl-7-(triisopropylsilyl)hepta-4,6-diyn-3-one (**20.2c**) (0.15 mmol, 43.5 mg) was added MeCN (2.0 mL) and methylhydrazine (3.0 equiv, 0.45 mmol, 14 μL). The solution was stirred overnight at room temperature. Ammonium chloride (sat.) was added and solution was then extracted with dichloromethane. After removal of solvents, the residue was subjected to column chromatography (Hexane:EtOAc= 20:1 to 2:1) to produce **22c1** as a yellow oil (91%, 46

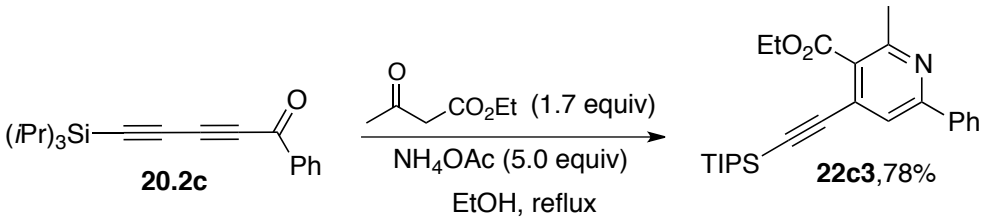
mg). The position of NH moiety in product was proposed according to that in reported procedures. [44, 49, 50]

Synthesis of phenyl(5-((triisopropylsilyl)ethynyl)-1*H*-1,2,3-triazol-4-yl)methanone (22c2)[2]



To a 3 mL V-shaped vial containing diynone **20.2c** (0.2 mmol, 62 mg) was added DMF (2.0 mL) and sodium azide (1.1 equiv, 0.22 mmol, 14.5 mg). After stirring for 3 h at at room temperature, water (5 mL) was added and solution was extracted with dichloromethane. The solvents were then removed under reduced pressure and the residue was subjected to column chromatography (Hexane:EtOAc= 20:1 to 2:1) to produce **21c2** as a yellow oil (71%, 49 mg). The position of NH moiety in product was proposed according to that in reported procedures.

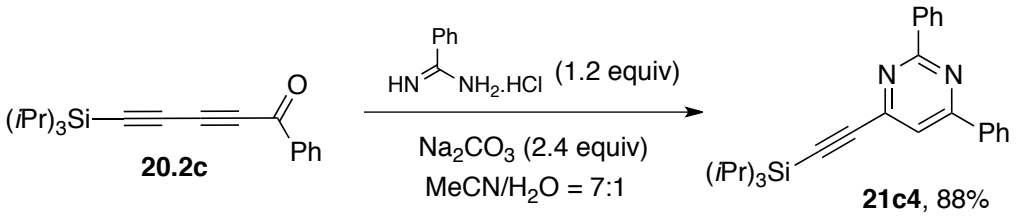
Synthesis of ethyl 2-methyl-6-phenyl-4-((triisopropylsilyl)ethynyl)nicotinate (22c3)[45]



To a 10 mL round bottom flask equipped with stirring bar and a reflux condenser was sequentially added **20.2c** (0.2 mmol, 62 mg), ethyl acetoacetate (1.7 equiv, 0.34

mmol, 44 μl), ammonium acetate (5.0 equiv, 1 mmol, 77 mg), and ethanol (4 mL). The reaction was refluxed overnight. After cooling to room temperature, the solvents were removed under reduced pressure. Saturated sodium bicarbonate (10 mL) was added and the reaction was extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate, filtered through a pad of cotton, and then concentrated under reduced pressure. The crude oil was purified via silica gel chromatography (pure hexanes to Hex:EtOAc=10:1) to afford **22c3** as yellow oil (78%, 66 mg).

Synthesis of 2,4-diphenyl-6-((triisopropylsilyl)ethynyl)pyrimidine (21c4)[51]



To a 3 mL V-shaped vial containing **20.2c** (0.15 mmol, 46.5 mg), bezimidamide hydrochloride (1.2 equiv, 0.18 mmol, 28 mg) and sodium carbonate (2.4 equiv, 0.36 mmol, 51 mg) was added MeCN (2 mL) and water (300 μL). The reaction stirred at 80 °C until judged completed by GC/MS. After cooling down, water (5 mL) was added and the mixture was extracted with dichloromethane. The combined extracts were then dried over sodium sulfate, concentrated under reduced pressure, and the residue was subjected to column chromatography (pure hexanes to Hex:EtOAc=10:1) to give **21c4** as a yellow oil (88% from **21.1c**, 54 mg).

1-methyl-3-phenyl-5-((triisopropylsilyl)ethynyl)-1*H*-pyrazole 22c1 (93%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.84 - 7.72 (m, 2 H), 7.39 (t, *J* = 7.7 Hz, 2 H), 7.34 - 7.28 (m, 1

H), 4.00 (s, 3 H), 1.15 (br. s., 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 150.3, 133.0, 128.6, 127.8, 127.1, 125.5, 107.1, 99.8, 94.5, 37.4, 18.6, 11.2. **HRMS** (EI) calcd for $C_{18}H_{32}N_2Si$ [M]+: 339.2257, found: 339.2255.

phenyl(5-((triisopropylsilyl)ethynyl)-1*H*-1,2,3-triazol-4-yl)methanone (22c2) (70%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.12 (apparent d, *J* = 7.5 Hz, 2 H), 7.61 - 7.58 (m, 1 H), 7.49-7.45 (m, 2 H), 1.05 (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 185.9, 136.4, 133.6, 130.4, 128.4, 102.4, 92.8, 18.5, 11.1. **HRMS** (EI) calcd. for $C_{20}H_{27}N_3OSi$[M]+: 354.2002, found: 354.2002.

Ethyl 2-methyl-6-phenyl-4-((triisopropylsilyl)ethynyl)nicotinate (78%) **^{1}H NMR** (500 MHz, CDCl3) d ppm 7.99 (apparent d, *J* = 7.5 Hz, 2 H), 7.63 (s, 1 H), 7.49-7.46 (m, 2 H), 7.44-7.41 (m, 1 H), 4.42 (q, *J* = 7.5 Hz, 2 H), 2.65 (s, 3 H), 1.41 (t, *J* = 7.5 Hz, 3 H), 1.15 (s, 21 H). **^{13}C NMR** (126 MHz, CDCl3) d ppm 167.7, 157.4, 155.4, 138.3, 130.0, 129.5, 128.9, 128.8, 127.1, 120.7, 102.1, 99.7, 61.7, 23.1, 18.6, 14.1, 11.2. **HRMS** (EI) calcd. for C26H35NO2Si [M]+: 421.2437, found: 421.2438.

2,4-diphenyl-6-((triisopropylsilyl)ethynyl)pyrimidine (21c4) (88%) **^{1}H NMR** (500 MHz, CDCl3) d ppm 8.63 - 8.61 (m, 2 H), 8.25 - 8.23 (m, 2 H), 7.69 (s, 1 H), 7.53 (m, 6 H), 1.22(s, 21 H). **^{13}C NMR** (126 MHz, CDCl3) d ppm 164.8, 164.0, 151.4, 137.5, 136.6, 131.1, 130.8, 128.9, 128.5, 128.4, 127.2, 117.3, 104.9, 96.2, 18.7, 11.3. **HRMS** (EI) calcd. for $C_{27}H_{32}N_2Si$ [M]+: 412.2335, found: 412.2335.

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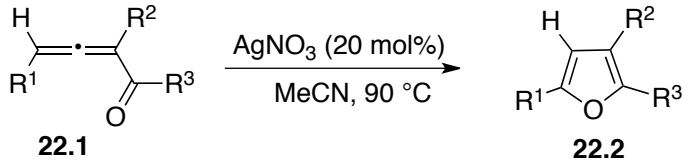
PART TWO

REGIOSELECTIVE SYNTHESIS OF C2- AND C3-BORYLATED FURANS

5. INTRODUCTION

5.1. Transition Metal-Catalyzed Cycloisomerization Approach in Synthesis of Furans

Furan is a highly important motif existing in a broad range of biologically active natural products and drugs.[1] It has broad applications as synthetic intermediates[2] and are used in materials science.[3] Accordingly, a vast number of efficient methodologies toward this important scaffold have been developed.[4] Among these methods, the *transition metal-catalyzed cycloisomerization* reaction of easily accessible acyclic substrates is one of the powerful approaches.[1,5] Thus, a range of acyclic substrates in the presence of various transition metals undergo this cascade transformation to efficiently produce furans with diverse substitution pattern. For instance, in 1990, Marshall and Robinson showed that acyclic allenyl ketone **22.1** in the presence of catalytic amounts of silver salt cycloisomerizes into the furan **22.2** (Scheme 22).[6]



22.1 **22.2**

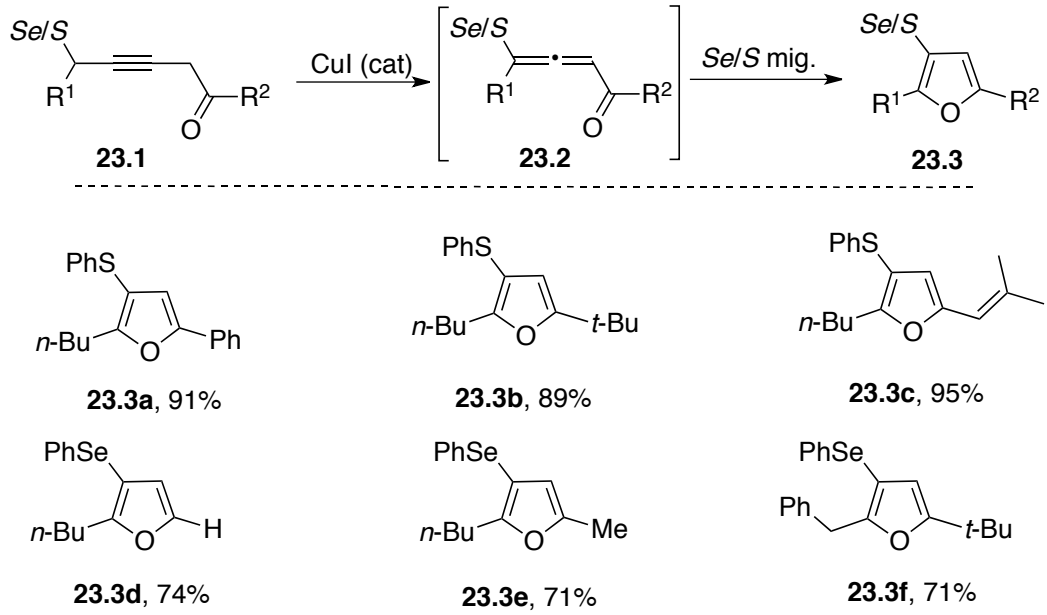
Scheme 22.

5.2. Transition Metal-Catalyzed Migratory Cycloisomerization toward Substituted Furans

Transition metal-catalyzed cycloisomerization reactions toward furans typically involve cyclization of acyclic substrates possessing sp-hybridized carbon moieties such as alkynyl or allenyl systems.[4] Thus, expectedly, this method gives access to furan products with at least one unsubstituted carbon. In order to solve this problem *en route* to fully substituted furans, migratory cycloisomerization reaction has been introduced, where the cyclization process is accompanied with migration of functional groups to the neighboring atoms.[5] This method offers mild and selective assembly of functionalized furans with diverse substitution patterns.

5.2.1. Migration of Sulfur- and Selenium-Containing Groups

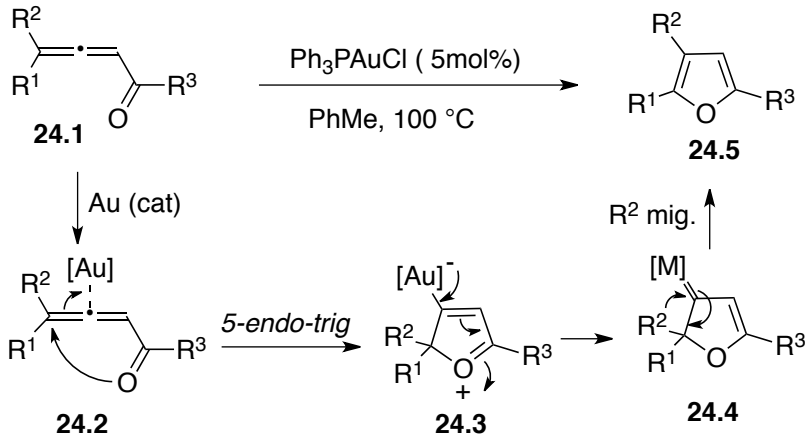
Gevorgyan and co-workers reported an efficient copper-catalyzed synthesis of C3-functionalized furan **23.3** from the hompropargylic ketone **23.1** (Scheme 23).[7] The transformation is believed to occur via a 1,3-protrotropic isomerization to produce the allenyl ketone **23.2**, which upon sulfur or selenium group migration during the cycloisomerization process produces furan **23.3**.



Scheme 23.

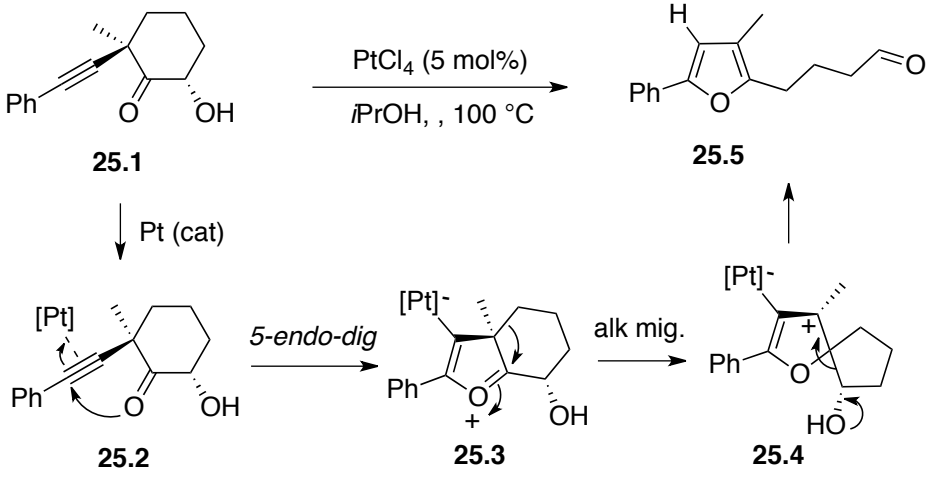
5.2.2. Migration of Carbon-Containing Groups

In 2007, Gevorgyan group described that allenyl ketones **24.1** in the presence of catalytic amounts of transition metals, such as gold and silver, can be converted into furan **24.5** via a migratory cycloisomerization reaction (Scheme 24).[7b,8] It was suggested that the gold catalyst activates the allene moiety of substrate **24.1** to form **24.2**, which upon a *5-endo-trig* cyclization produces oxocycle **24.3**. Flow of electron from gold to oxygen in the latter generates **24.4**, where a 1,2-R^2 migration to the carbene center affords the trisubstituted furan **24.5**.



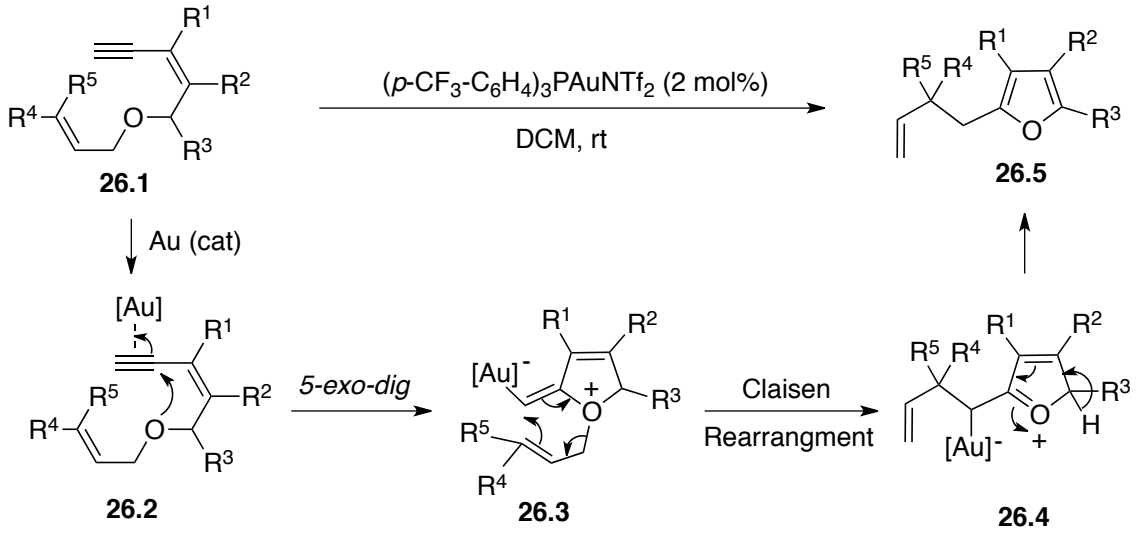
Scheme 24.

It was shown by Kirsh and co-workers that skipped propargylic ketone **25.1** can be a competent substrate for the Pt-catalyzed cycloisomerization reaction to produce furan **25.5** (Scheme 25).[9] Thus, a *5-endo-dig* cyclization reaction of activated **25.2** furnishes the bicyclic oxonium ion **25.3**. A ring contraction in the latter via a 1,2-akyl migration to the neighboring cationic carbon center of **25.3** leads to the allylic cation-containig spiro system **25.4**, which upon a pinacol-type ring opening produces furan **25.5** possessing a tethered carbonyl functionality.



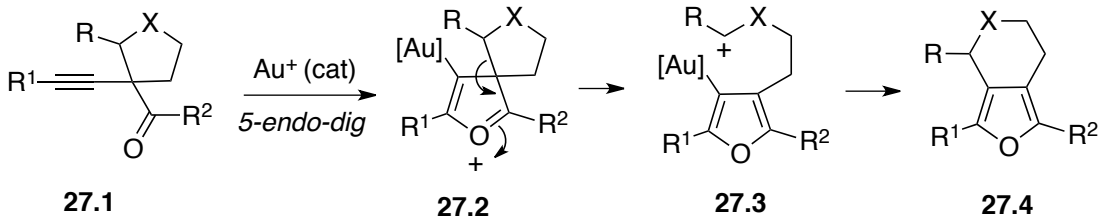
Scheme 25.

In 2011, Gagosz *et al.* reported the gold-catalyzed cycloisomerization reaction of ynenyl allyl ether **26.1** into tetrasubstituted furan **26.5** via an oxygen-to-carbon allyl group migration (Scheme 26).[10] It was suggested that activation of substrate **25.1** with the gold catalyst gives **26.2**, which upon the following nucleophilic attack of etheric oxygen at the alkyne moiety produces the cyclic oxonium compound **26.3**, possessing an exocyclic vinyl gold species. The latter undergoes a Claisen-type rearrangement to give heterocycle **26.4**, where a new C-C bond is formed. A sequence of protonation/protodemetallation in **26.4** then delivers the furan **26.5**, possessing a homoallylic miety at the C2 position.



Scheme 26.

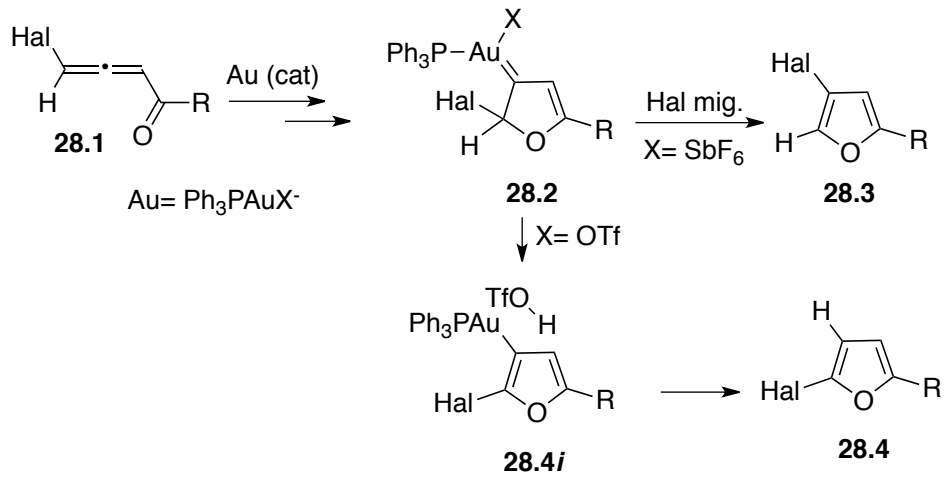
Recently, Zhang's group reported a gold-catalyzed transformation of skipped propargylic ketones **27.1** into the 3,4-fused furans **27.4** (Scheme 27).[11] It is believed that activation of the π-system of substrate and the following *5-endo-dig cyclization* process generates the spiro-oxacycle **27.2**. Ring opening of the latter generates the stabilized cation **27.3**, which upon the nucleophilic attack of furyl gold moiety produces fused furan **27.4**.



Scheme 27.

5.2.3. Migration of Halogen Atoms

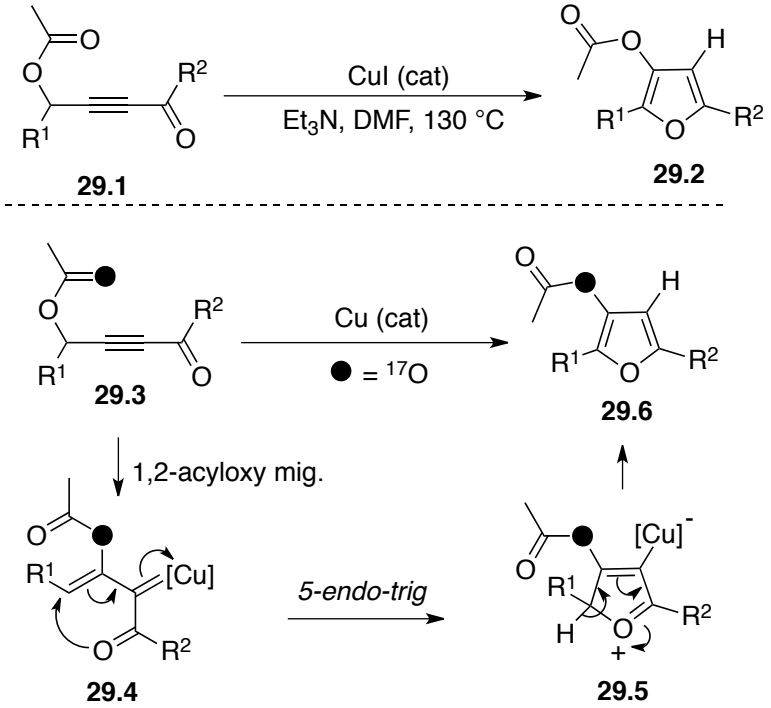
A regiodivergent gold-catalyzed cycloisomerizaion of halogenated allenyl ketones **28.1** to C2- or C3-halofurans **28.2** and **28.3** was reported by Gevorgyan and co-workers (Scheme 28).[12] Iodine, bromine, and chlorine migrated during this cycloismerization reaction. The computation-assisted mechanistic studies of this transformation revealed the crucial role of the counterion in determining the regioselectivity of this reaction. Thus, after formation of the gold carbene **28.2**, the gold catalyst with the non-coordinating hexafluoroanimonate renders the kinetically-favored 1,2-halogen migration over the hydride shift to produce the C3-holeganted furan **28.3**. Alternatively, the more basic triflate counterion assists the proton transfer to the C3-furyl gold species **28.4i** to form the C2-halogenated furan **28.4**.



Scheme 28.

5.2.4. Migration of Oxygen-Containing Groups

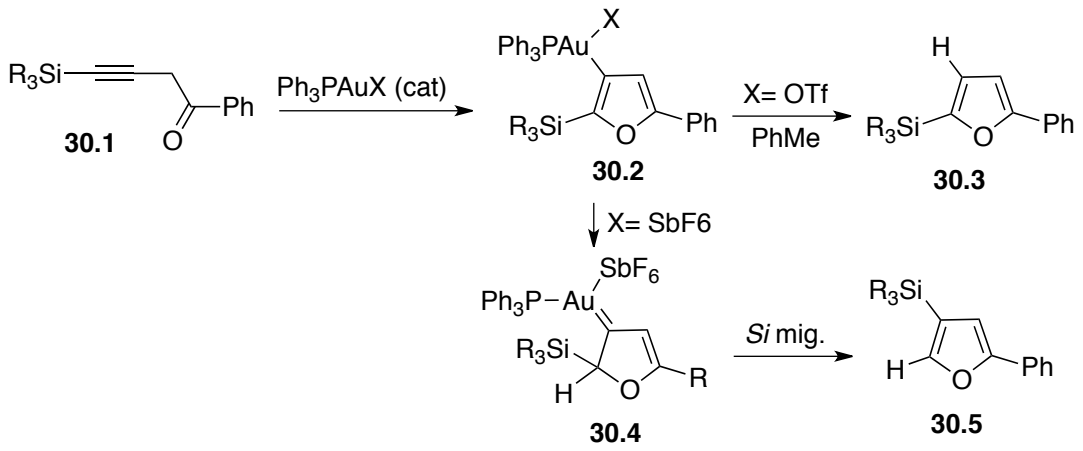
In 2004, Gevorgyan and co-workers disclosed synthesis of acyloxylated furans **29.2** via a copper-catalyzed migratory cycloisomerization of easily accessible propargylic esters **29.1** (Scheme 29).[13] Detailed mechanistic investigations were further revealed[13b] by employing the propargylic ester **29.3**, possessing the ^{17}O-label at the carbonyl of acetoxy group. Thus, the copper-catalyzed reaction of the latter produced furan **29.6**, where the bridged oxygen of acetoxy miety is labeled. Accordingly, it was proposed that the copper catalyst renders the 1,2-acyloxy migration in **29.3** via a Rautenstrauch rearrangement to form carbene **29.4**. It then undergoes a nucleophilic attack of carbonyl group at the alkene moiety via a *5-endo-trig* cyclization to generate oxonium ion **29.5**, which upon a sequence of deprotonation/protometallation steps produces furan **29.6**.



Scheme 29.

5.2.5. Migration of Silicon-Containing Groups

Having established the effect of counterion in the regioselective synthesis of halofurans,[12] Gevorgyan *et al*. reported a regiodivergent synthesis of silylated furans **30.3** and **30.5** from **30.1** (Scheme 30).[14] Both, their computation and experimental results suggest that after the gold-catalyzed cycloisomerization of skipped alkynyl ketone **30.1** into the key furyl gold species **30.2**, the counterion is the regioselectivity-controlling element. Therefore, a basic trifilate counterion in a nonprotic solvent such as toluene favors protodemetalation of **30.2** to form the C2-silylated furan **30.3**. On the other hand, SbF_6 counterion renders the β–protonation of the vinyl gold species in **30.2** to gold carbene **30.4**, which upon a kinetically-favored 1,2-silicon group migration affords the regioisomeric C3-silylated furan **30.5**.

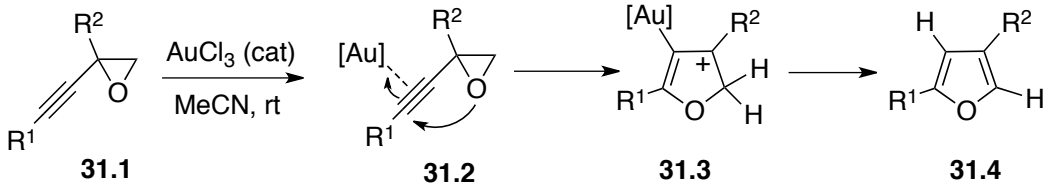


Scheme 30.

5.3. Cycloisomerization and Migratory Cycloisomerization of Alkynyl Epoxides and Aziridines in Synthesis of Heterocycles

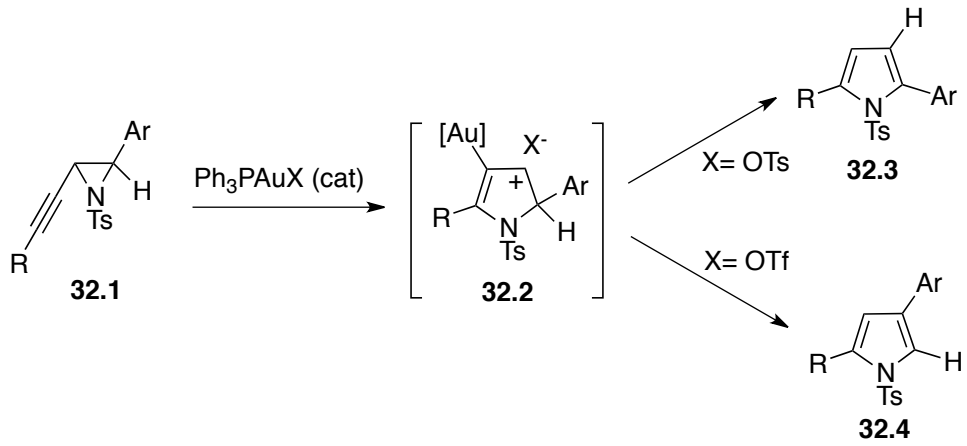
Propargylic oxiranes have been shown to be excellent substrates to undergo cycloisomerization reaction into furans in the presence of various transition metal

catalysts such as Hg,[15] Mo,[16] Ru,[17] Pt,[18] Ag,[19] and Au.[20] For example, the cycloisomerization of alkynyl epoxides **31.1** into furans **31.4** under the gold-catalyzed conditions was first reported by Hashmi and Sinha (Scheme 31).[21] It is believed that gold-activation of the π-system of substrate **31.1** gives **31.2**, in which a nucleophilic attack of oxygen of epoxide at the activated alkyne moiety generates the cation **31.3**. A sequence of deprotonation/protodematalation in the latter furnishes the disubstituted furan **33.4**.



Scheme 31.

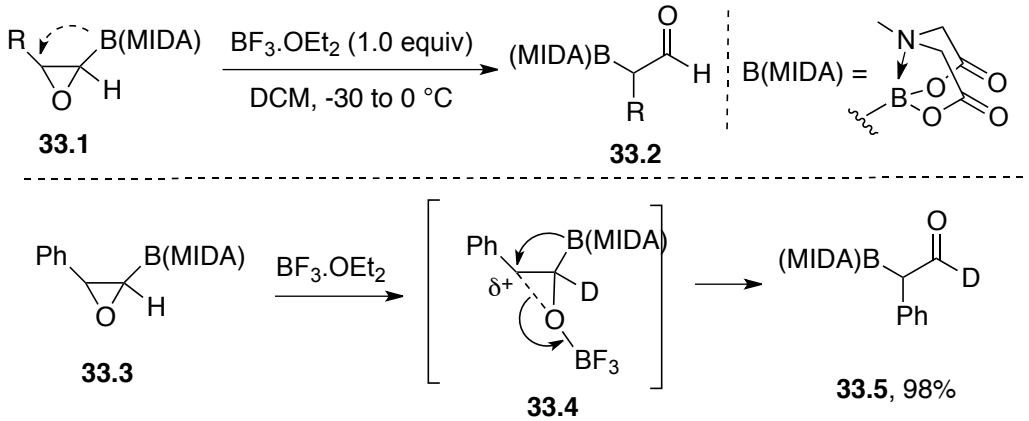
Taking into account a great reactivity of alkynyl epoxides in the metal-catalyzed cycloisomerization reactions toward furans,[15-21] it is surprising that no migratory cycloisomerization reaction of these easily accessible substrates into furans has been reported so far. However, the migratory cycloisomerization reactions of their analogues alkynyl aziridines into pyrroles have been shown.[22] For instance, Davies and Martin reported a regiodivergent migratory cycloisomerization reaction of alkynyl aziridine **32.1** in the presence of a gold catalyst to produce C2- and C4-arylated pyrroles **32.3** and **32.4** (Scheme 32).[22b] The regiochemical outcome of this reaction is dependent on the choice of counterion used. Thus, the generated intermediate **32.2** (analogue of **32.3**) in the presence of a sufficiently basic tosylate counterion undergoes a proton elimination to favor formation of C2-arylated pyrroles **32.3**. Whereas, using a less basic triflate led to pyrrole **32.3** via an aryl migration.



Scheme 32.

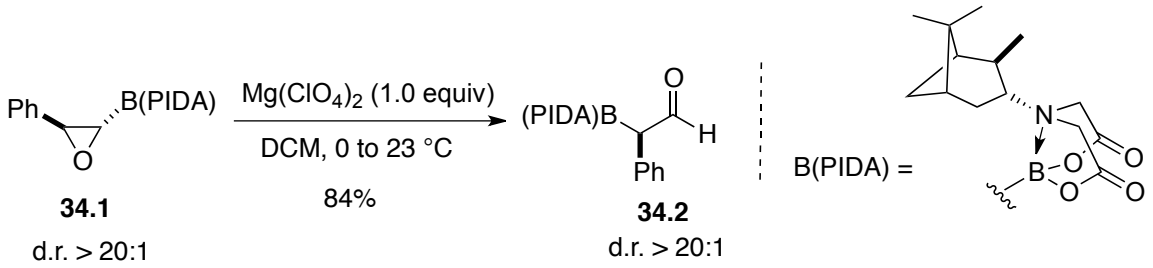
5.4. Lewis Acid-Mediated Boryl Migration in Synthesis of Acyclic Products Acid-Mediated

In 2011, Yudin demonstrated that *N*-methyliminodiacetyl (MIDA) boronated epoxides **33.1** in the presence of stoichiometric amounts of $BF_3.OEt_2$ undergo a 1,2-boryl migration to form α-boryl aldehydes **33.2** (Scheme 33).[23] For mechanistic clarification, the deuterium-labeled epoxide **33.3** was subjected to the reaction conditions to form **33.5** with exclusive D-incorporation at the carbonyl moiety, which suggests a 1,2-boryl shift in intermediate **33.4**.



Scheme 33.

In an independent study, Burke group also showed that stereodefined epoxide **34.1**, possessing a pinene-derived iminodiacetic acid (PIDA) boronate group, in the presence of magnesium perchlorate undergoes a 1,2-boryl migration to form α-boryl aldehydes **34.2** with preservation of stereochemical purity (Scheme 34).[24]



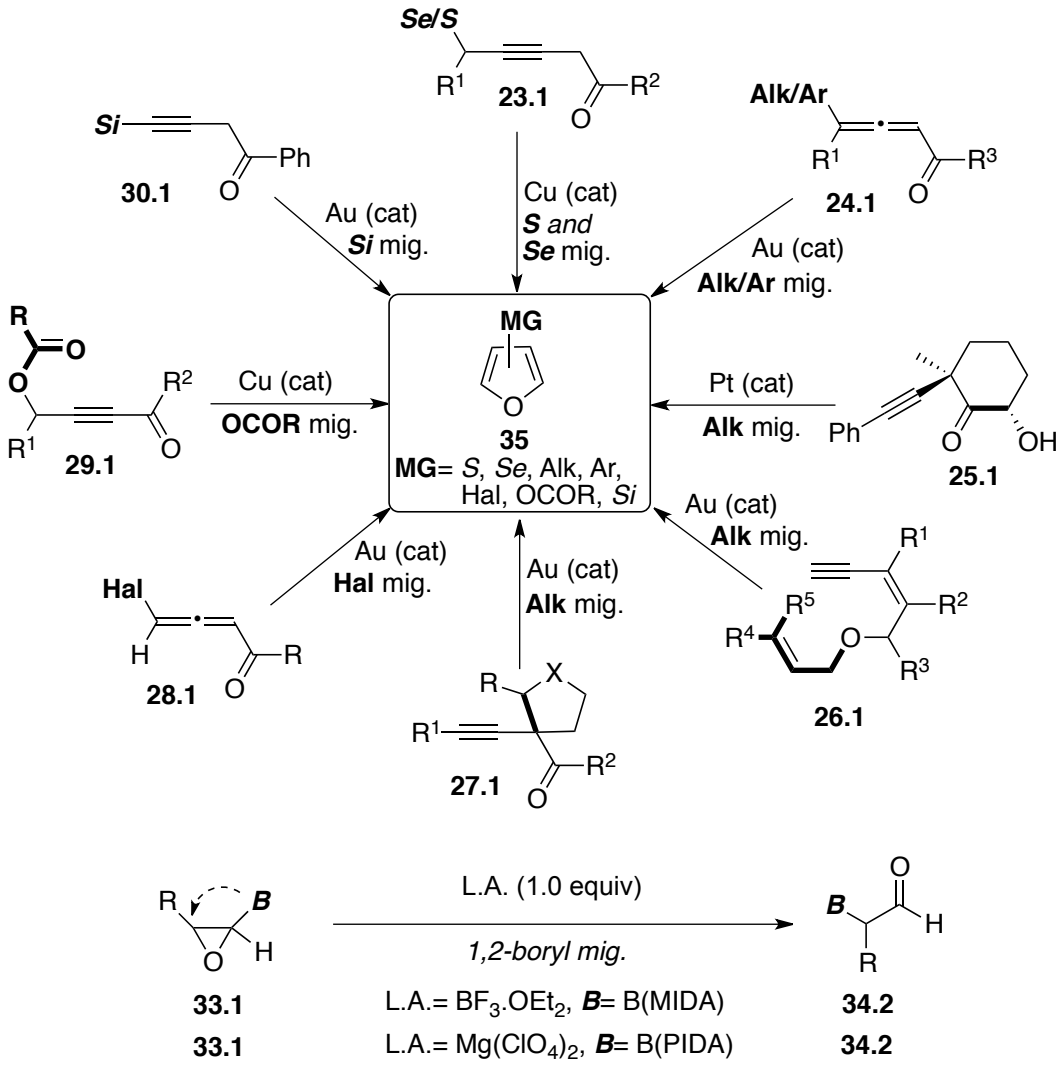
Scheme 34.

5.5. Summary

In summary, the transition metal-catalyzed migratory cycloisomerization approach is a powerful method for efficien synthesis of various substituted furans with diverse substation patterns. It has been shown that during cycloisomerization reaction, a variety of groups including sulfur, selenium, carbon, halogen, acyloxy, and silicon can migrate to the neighboring carbon atom to produce functionalized furan **35** (Scheme 35). The metal-activated acyclic substrates **23.1**-**30.1** have been employed in migratory cycloisomerization reactions toward furans **35** with diverse substitution patterns. However, the potential rearrangement of easily accessible alkynyl epoxides into functionalized furans proceeding via this cascade migratory reaction in the presence of transition metals has not been examined.

The Lewis acid-mediated 1,2-boryl migration in acyclic epoxides **33.1** and **34.1** to form α-borylated aldehydes **33.2** and **34.2** have been shown (Scheme 35). It has been demonstrated that both MIDA and PIDA boronate are capable of migrating in these

systems. However, the transition metal-catalyzed migratory cycloisomerization reactions of boryl-containing acyclic substrates into borylated heterocycles are unknown transformations at this point.



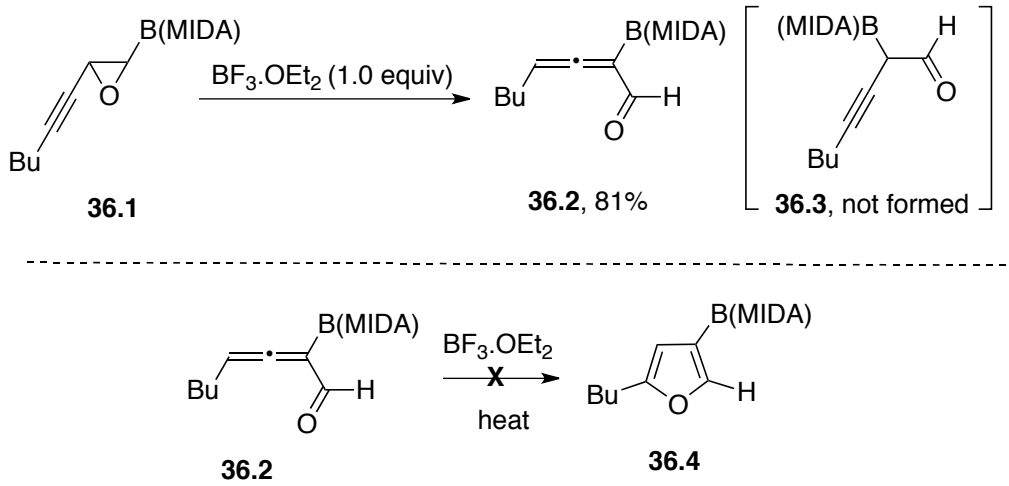
Scheme 35.

6. REGIOSELCTIVE SYNTHESIS OF C2- AND C3-BORYLATED FURANS

Borylated heterocycles are important motifs, which have wide applications in medicine and materials science.[25] Due to their high potential for further functionalizations, they are also useful intermediates in synthetic organic chemistry.[25] Inspired by works of Yudin[23] and Burke,[24] who showed migration of a boryl group in borylared epoxides, as well as by works of Hashmi[21] and Davies[22b] on cycloisomerization in alkynyl epoxides and aziridines to form heterocycles, we thought that development of an efficient and regioselective method for the synthesis of borylated furans is feasible.

6.1. Attempts to Synthesize C3-Borylated Furans via a Lewis Acid-Mediated Reaction

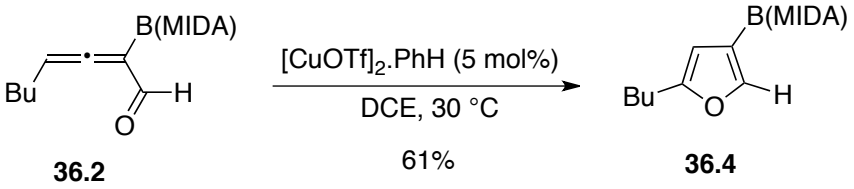
First, we were curious if the MIDA boronate-containing alkynyl epoxide **36.1** under Yudin's conditions[23] would produce skipped propargylic ketone **36.3**, which have been shown to be an excellent precursor for synthesis of furan rings (*vide infra*) (Scheme 36). However, the $BF_3.OEt_2$-promoted reaction of **36.1** did not provide **36.3**; allenyl aldehyde **36.2** was efficiently formed instead, which may or may not be obtained via **36.3**. All attempts to cyclize allenyl ketone **36.2**, which has been shown to be a competent substrate for cycloisomerization reaction (*vide infra*), into furan **36.4** under forcing reaction conditions failed.



Scheme 36.

6.2. Copper-Catalyzed Synthesis of C3-Borylated Furans

Intrigued by our group's experience in the copper-catalyzed cycloisomerization reaction of allenyl ketones into furans (*vide infra*),[26] we subjected formed intermediate **36.2** to cyclize in the presence of $[CuOTf]_2$•PhH catalyst (Scheme 37). Indeed, the C3-borylated furan **36.4** was formed in 61% yield!

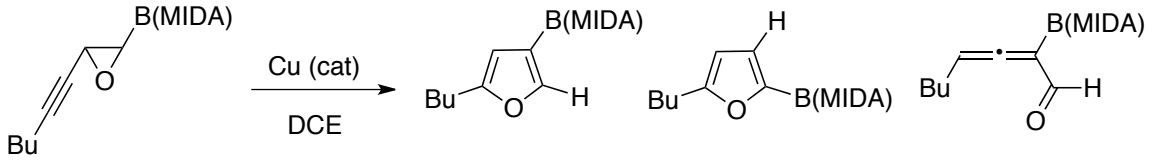


Scheme 37.

Next, we explored the possibility of the direct transformation of alkynyl epoxide **36.1** into furan **36.4** in the presence of copper catalysts (Table IV). The reaction of substrate **36.1** in the presence of CuI catalyst produced the furan **36.4**. However, some detectable amount of C2-borylated **36.5** was also observed (entry 1). It was found that the copper acetate-catalyzed reaction was not efficient (entry 2). did not provide any product (entry 3). Gratifyingly, the cycloisomerization reaction of **36.1** in the presence of

$[CuOTf]_2$.PhH catalyst afforded the C3-borylated furan **36.4** with an excellent regioselectivity (entry 3).

Table VI. OPTIMIZATION OF CU-CATALYZED REACTION OF 36.1[a]



36.1 **36.4** **36.5** **36.2**

Entry	Cu Catalyst	**36.1:36.4:36.5:36.6**[b]	Yield (%)[c]
1	CuI	0:88:12:0	5
2	CuOAc	38:59:3:0	56
3	**$[CuOTf]_2$•PhH**	**80 (0:97:3:0)**	**80**[d]

[a] Reactions were performed in 0.1 mmol scale.

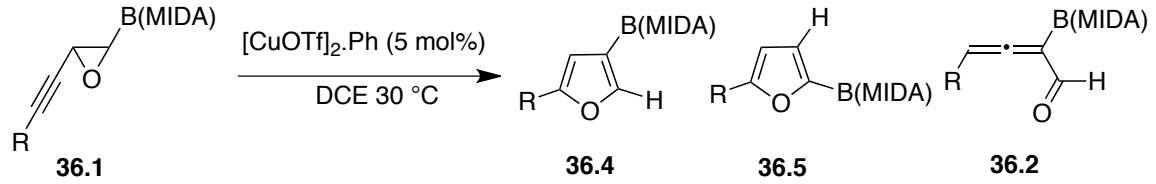
[b] NMR ratios.

[c] Isolated yield.

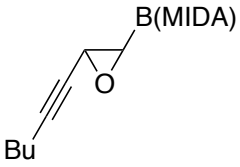
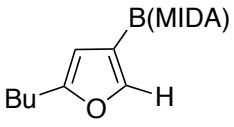
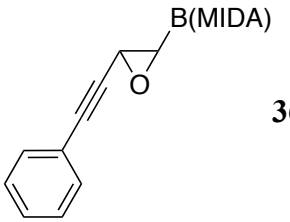
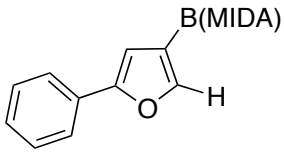
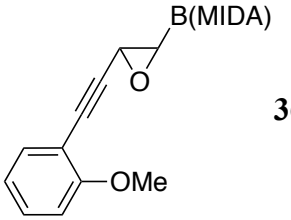
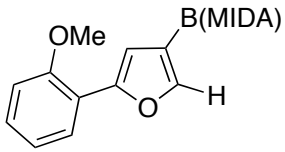
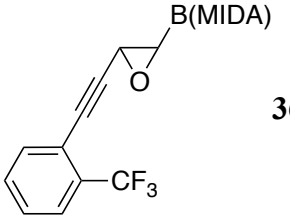
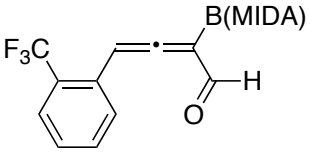
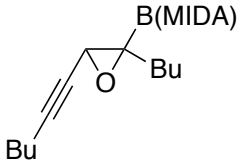
[d] The reaction was performed at 30 °C .

With these conditions in hand, we examined the copper-catalyzed synthesis of C3-borylated furans (Table V). Thus, excellent yield and regioselectivity were obtained in the reaction of **36.1a** (entry 1). Likewise, phenyl substituted alkynyl epoxide **36.1b** produced furan **36.4b** in good regioselectivity albeit in a low yield (entry 2). Cyclization of alkynyl epoxide **36.1c** possessing an electron-rich aryl group proceeded smoothly to produce furan **36.4c** in an excellent regioselectivity (entry 3). However, attempts to cycloisomerize **36.1d** possessing an electron-deficient aryl group failed (entry 4).

Table VII. COPPER-CATALYZED SYNTHESIS OF C3-BORYLATED FURANS



36.1 **36.4** **36.5** **36.2**

Entry	Substrate		Product		**36.4:36.5:36.2**[a]	Yield (%)[b]
1		**36.1a**		**36.4a**	(97:3:0)	80
2		**36.1b**		**36.4b**	(89:11:0)	36
3		**36.1c**		**36.4c**	(99:1:0)	51
4		**36.1d**		**36.4d**	(0:0:100)[c]	96
5		**36.1e**	-	**36.4e**	0[d]	0

[a] NMR ratios.

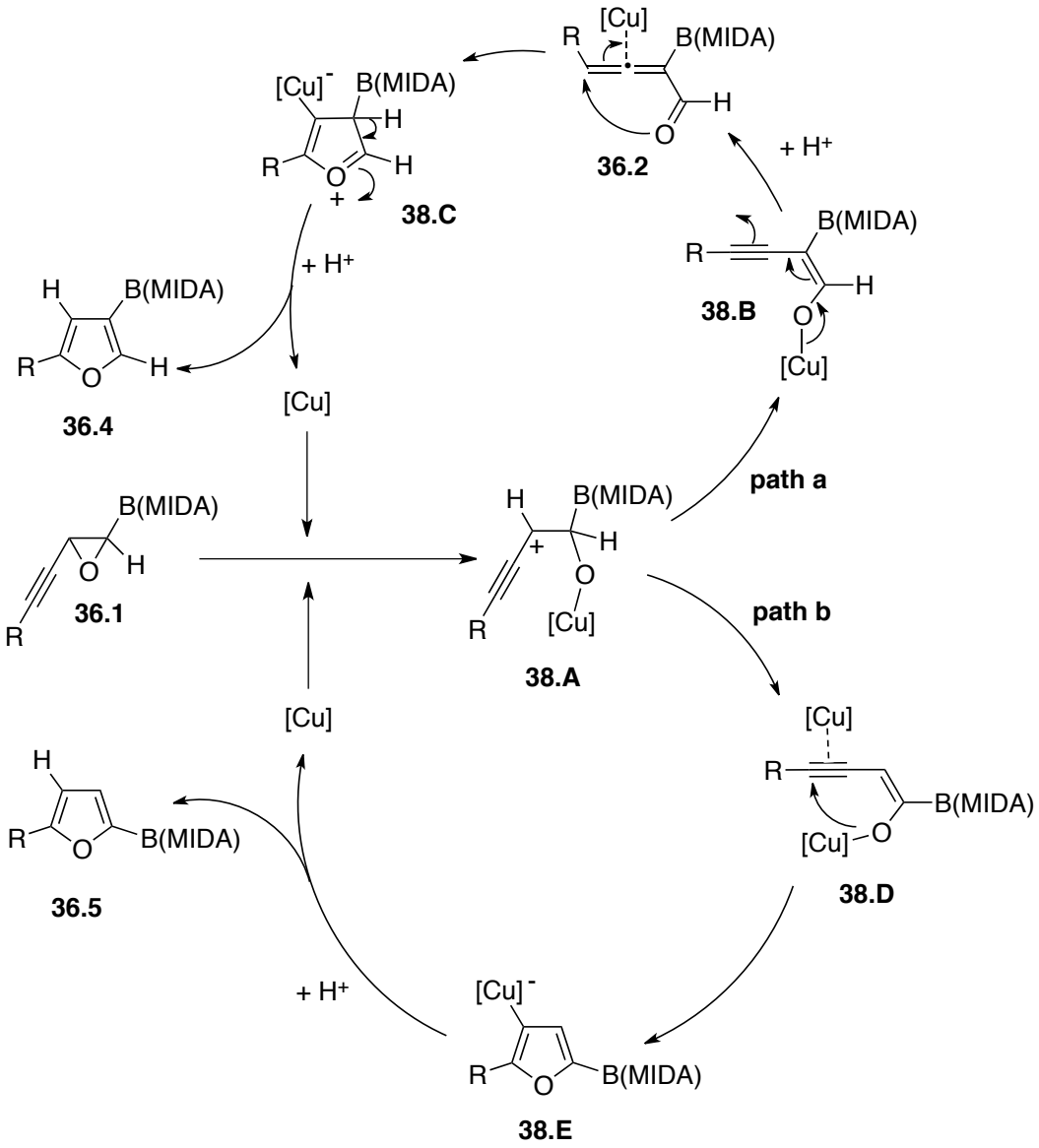
[b] Isolated yields.

[c] heating of the reaction did not lead to furan.

[d] Decomposition of **36.1**.

Employing trisubstituted alkynyl epoxide **36.1e** in this transformation resulted in complete decomposition of starting material (entry 5).

We propose the following mechanism for the copper-catalyzed cycloisomerization of alkynyl epoxide **35.1** into C3- and C2-borylated furans **36.4** and **36.5** (Scheme 38). First, the oxophilic copper catalyst opens the epoxide ring of **36.1** to form propargylic cation **38.A**. According to the **path a**, a favored 1,2-boryl migration to the neighboring carbon atom occurs, which upon a proton loss generates the Cu-enynolate **38.B**. Protonation at the distal carbon of the alkyne group in the latter gives the allenyl ketone intermediate **36.2**, which then cyclizes to **38.C** via a *5-endo-trig* process.[26] The oxonium ion **38.C** undergoes a sequence of protonation/protodemetalation steps to produce the C3-borylated furan **36.4**. Formation of the minor C2-borylated furan can potentially be explained by an alternative **path b**. Thus, a proton loss in **38.A** generates the copper-enynolate **38.D**, which upon attack of the nucleophilic oxygen at the activated akyne moiety gives the furyl copper species **35E**. Protometalation of the latter produces the C2-borylated product **36.5**.



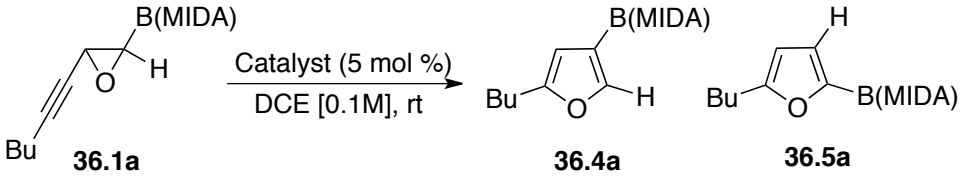
Scheme 38.

6.3. Gold-Catalyzed Regiodivergent Synthesis of C2- and C3-Borylated Furans

Seeking for more general and efficient conditions for regioselective synthesis of borylated furans, we next turned our attention to the π-philic gold catalysts (Table VI).[27] It was found that in the presence of Ph_3PAuCl, the reaction was more regioselective for **36.1a** with triflate counterion (entry 2) compared for that hexafluoroantimonate (entry 1).

Gratifyingly, employment of a gold catalyst possessing electron rich phosphite ligand with triflate led to furan **36.4a** with an excellent regioselectivity and yield (entry 3). Conversely, switching counterion to hexafluoroantimonate favored formation of **36.4a** (entry 4). Analogous results were obtained in the presence of IPrAuCl with triflate counterion (entry 5). Remarkably, employment of the same gold catalyst with hexafluoroantimonate led to furan **36.5a**, exclusively (entry 6). Control gold-free experiments indicated the reactions in the presence of silver triflate (entry 7) and silver hexafluroantimonate (entry 8) were both less efficient and regioselective.

Table VIII. OPTIMIZATION OF AU-CATALYZED REACTION OF **36.1a**



36.1a **36.4a** **36.5a**

Entry	Catalyst	**36.4a:36.5*a*** [a]	Yield (%) [b]
1	$Ph_3PAuCl/ AgSbF_6$	50:50	>99
2	$Ph_3PAuCl/ AgOTf$	82:18	85
3	**$(ArO)_3PAuCl$ [c] / AgOTf** [d,e]	**96:4** [f]	**81** [g]
4	$(ArO)_3PAuCl$ [c] / $AgSbF_6$ [d]	22:78	76
5	IPrAuCl/ AgOTf	33:67	79
6	**IPrAuCl/ $AgSbF_6$**	**0:100**	**81**
7	AgOTf [d]	87:13	39
8	$AgSbF_6$	86:14	39

[a] NMR ratios.

[b] NMR yields.

[c] Ar = 2,4-di-*t*BuPh.

[d] Solution [0.04M].

[e] performed at T = -30 °C.

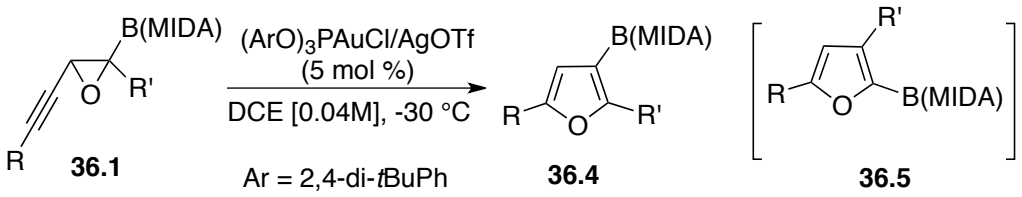
[f] Ratio of 91:9 at rt.

[g] 76% NMR yield at rt.

6.3.1. Scope of Reaction

After finding conditions for regiodivergent synthesis of boryl furans **36.4** and **36.5**, we first examined the scope of the migratory cycloisomerization reaction toward C3-borylated furan **36.4** (Table VII). Thus, C2-alkyl-substituted furans **36.4a**, **36.4f**, and **36.4g** were produced in good yields and excellent regioselectivity. Phenyl-substituted alkynyl epoxide **36.1b** reacted smoothly to afford **36.4b** in 87% yield and good regioselectivity. Likewise, *ortho*-substituted aryl-containing furans **36.4c** and **36.4d** were obtained as sole products in good yields. Analogously, cyclization of alkynyl epoxides **36.1h** and **36.1i** provided furans **36.4h** and **36.4i** possesing para-substituted aryls. Diynyl epoxide **36.1j** afforded alkynylated furan **36.4j** exclusively in 67% yield. Remarkably, employment of trisubstituted oxirane **36.1k** in this transformation led to exclusive formation of furan **36.4**k in 83% yield, thus, indicating overwhelming preference of boryl- versus aryl group migration. Analogously, dialkyl-containing furan **36.1e** was selectively obtained under these conditions.

Table IX. GOLD-CATALYZED SYNTHESIS OF C3-BORYLATED FURANS



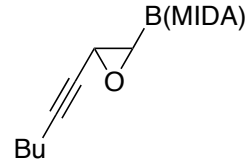
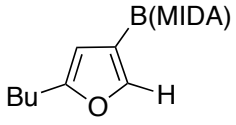
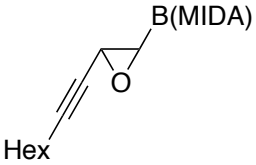
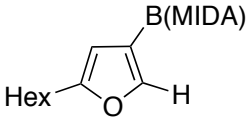
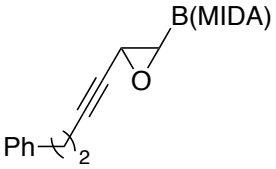
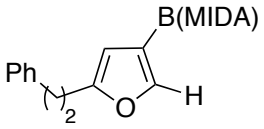
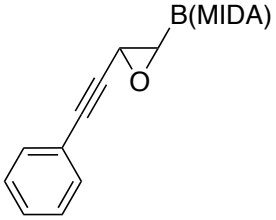
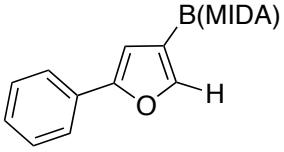
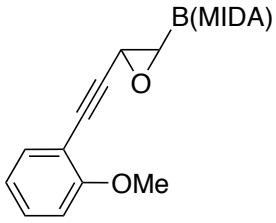
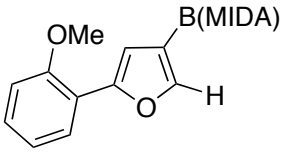
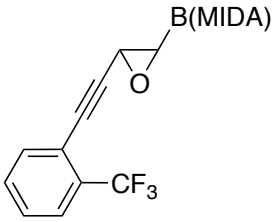
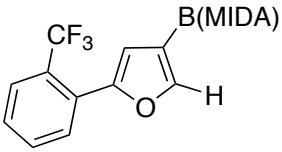
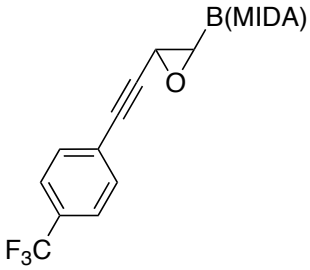
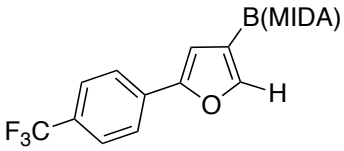
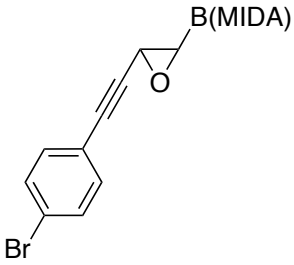
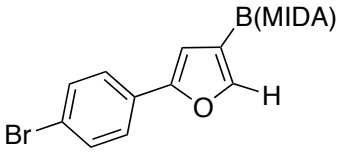
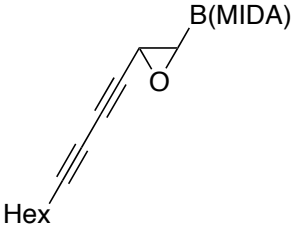
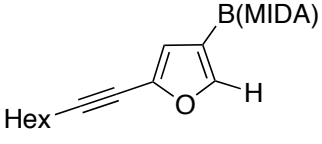
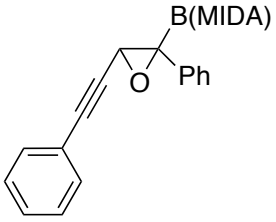
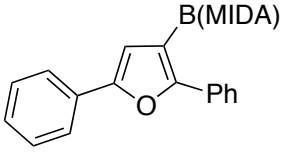
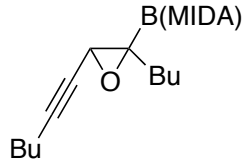
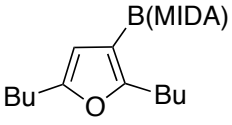
Entry	Substrate		Product		**36.4:36.5** Yield [a]	(%)[b]
1		**36.1a**		**36.4a**	92:8	83
2		**36.1f**		**36.4f**	97:3	67
3		**36.1g**		**36.4g**	96:4	74
4		**36.1b**		**36.4b**	90:10	87
5		**36.1c**		**36.4c**	100:0	81

Table X. GOLD-CATALYZED SYNTHESIS OF C3-BORYLATED FURANS (continued)

Entry	Substrate		Product	**36.4:36.5**[a]	Yield (%)[b]	Entry
6		**36.1d**		**36.4d**	100:0	61
7		**36.1h**		**36.4h**	891:9	65[c]
8		**36.1i**		**36.4i**	95:5	79
9		**36.1j**		**36.4j**	100:0	67
10		**36.1k**		**36.4k**	100:0	83
11		**36.1e**		**36.4e**	100:0	75

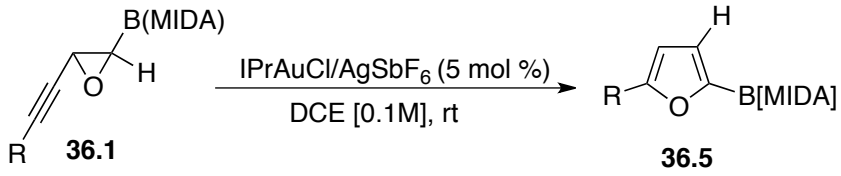
[a] NMR ratios.

[b] Isolated yields.

[c] Reaction was performed at rt.

Next, we investigated the gold-catalyzed cycloisomerization reaction of alkynyl epoxide **36.1** leading to C2-borylated furan **36.5** (Table VIII). Thus, alkyl-containing furans **36.5a**, **36.5f**, and **36.5g** were exclusively obtained in reasonable to good yields. Analogously, alkynyl epoxide **36.1b** possessing phenyl substituent worked well under these reaction conditions. Likewise, electronically different *ortho*- and *para*-substituted aryl-containing furans **36.5c**, **36.5d**, **36.5h**, and **36.5i** were obtained in modest to good yields and excellent regioselectivity. In addition, diynyl epoxide **36.1j** was smoothly converted into alkynylated furan **36.5j** in good yield. Finally, cyclization of **36.1l** afforded mono-substituted boryl furan **36.1l** in 60% yield.[28]

Table XI. GOLD-CATALYZED SYNTHESIS OF C2-BORYLATED FURANS



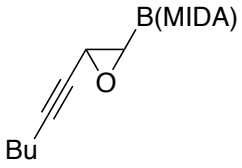
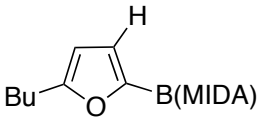
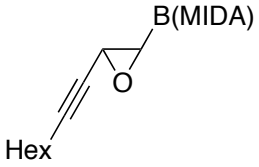
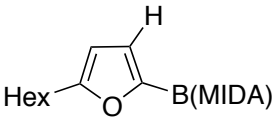
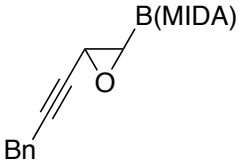
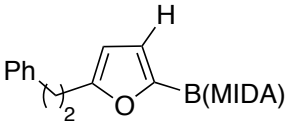
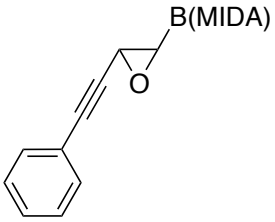
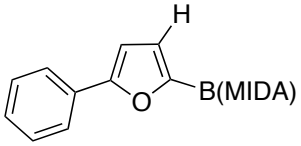
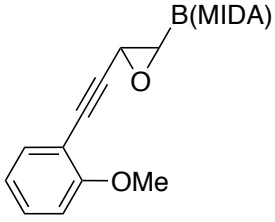
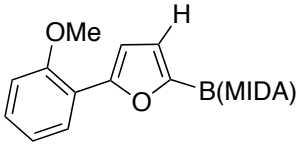
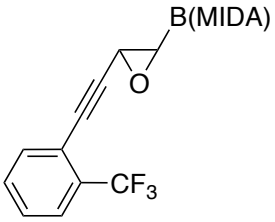
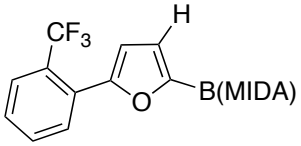
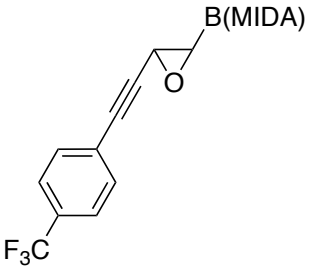
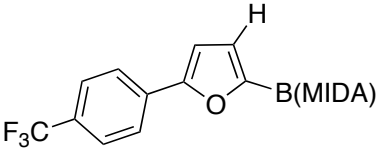
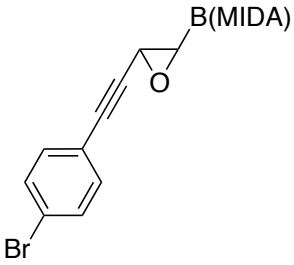
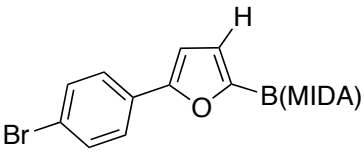
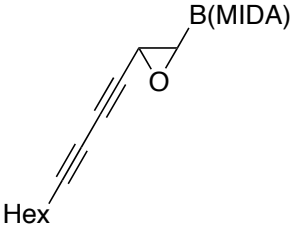
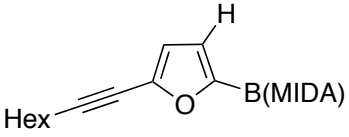
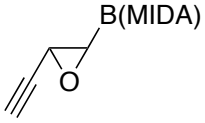
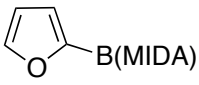
Entry	Substrate		Product		Yield (%)[a,b]
1		**36.1a**		**36.5a**	75
2		**36.1f**		**36.5f**	57
3		**36.1g**		**36.5g**	64
4		**36.1b**		**36.5b**	50
5		**36.1c**		**36.5c**	49[c]

Table XII. GOLD-CATALYZED SYNTHESIS OF C2-BORYLATED FURANS (continued)

Entry	Substrate		Product		Yield (%)[a,b]	Entry
6		**36.1d**		**36.5d**	42[c]	
7		**36.1h**		**36.5h**	65	
8		**36.1i**		**36.5i**	84	
9		**36.1j**		**36.5j**	66	
10		**36.1l**		**36.5l**	75[d,e]	

[a] Isolated yields.

[b] Exclusive formation of C2-borylated furans was observed in all examples.

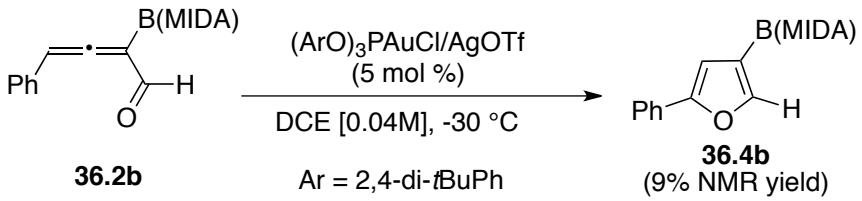
[c] Substantial decomposition of substrate was observed.

[d] THF as the solvent.

[e] NMR yield.

6.3.2. Mechanism of the Gold-Catalyzed Reactions

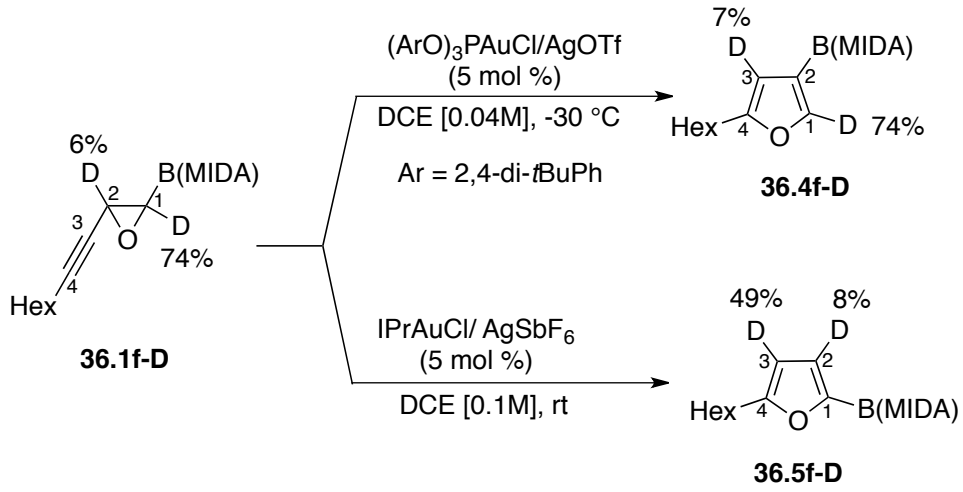
We performed some initial mechanistic experiments for the gold-catalyzed reactions. First, we verified whether the Au-catalyzed reaction proceeds via intermediacy of allene intermediate **36.2b** (Scheme 39). However, subjecting the latter to the reaction conditions produced furan **36.4b** in a very low yield. This indicates that in contrast to the Cu-catalyzed version (*vide supra*), generation of allene intermediate **36.2b** in the gold-catalyzed transformation is less likely.



36.2b **36.4b** (9% NMR yield)

Scheme 39.

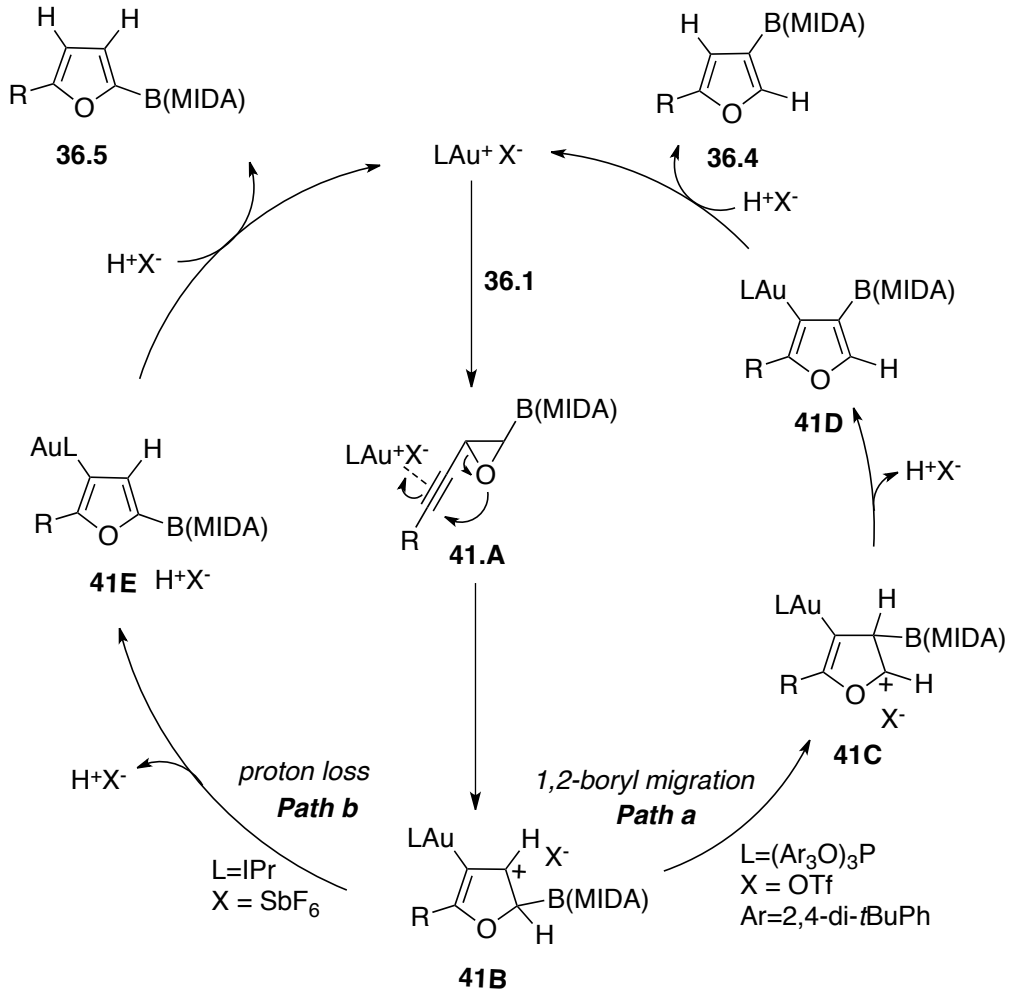
Next, cycloisomerization of a deuterium-labeled alkynyl epoxide **36.1f-D** was examined (Scheme 40). It was found that under the gold-catalyzed migratory conditions, furan **36.4f-D** was formed in which the deuterium label stayed intact at the C1 position. However, subjecting **4f-D** to the non-migratory cycloisomerization conditions produced furan **6f-D** with deuterium label at the C3 position substantially scrambled.[29]



Scheme 40.

Obviously, more detailed studies toward understanding the role of both ligand and counterion on the regioselectivity of this cycloisomerization reaction are required. At this point, based on the above observations, we propose the following working rationale for this regiodivergent transformation (Scheme 41). First, activation of the π system of **36.1** by the gold catalyst triggers a nucleophilic attack of the oxygen at the distal position of alkyne moiety producing the heterocyclic cation **41B**.[27] In the case of triflate counterion (***Path a***), a 1,2-boryl migration to the cationic center of **41B** takes place to generate cation **41C**, which, upon proton loss affords the furyl gold species **41D**. Protiodemetalation of the latter produces the C3-borylated furan **36.4**. Alternatively, in the presence of hexafluoroantimonate counterion (***Path b***), a proton loss[29] in intermediate **41B** takes place to afford the furyl gold species **41E**, which upon protiodeauration produces C2-borylated furan **36.5**. It should be mentioned that the observed counterion effect on the regioselectivity of boryl group versus hydrogen migration is in a sharp contrast with the migration trend for carbon- and silyl group versus hydrogen migration

previously reported by our[12,14] and other[30] groups. Further studies to elucidate the origins of the observed migratory trend are underway in our group.



Scheme 41.

6.4. Summary

In summary, complementary regioselective copper- and gold-catalyzed cycloisomerization reactions of boron-containing alkynyl epoxides toward C2- and C3-borylated furans have been developed. It was found that the copper-catalyzed transformation triggers the initial 1,2-boryl group migration forming an allenyl

derivative, which upon cycloisomerization produces C3-borylated furan. However, the Cu-catalyzed cycloisomerization appeared to be not general. Accordingly, we developed two efficient and general Au-catalyzed protocols, where depending on the choice of ligand and counterion, regioisomeric boryl furans can be selectively obtained. Thus, phosphite gold complex with triflate counterion strongly favors a 1,2-boryl migration during the cycloisomerization process to produce C3-borylated furans. In contrast, employment of NHC gold hexafluoroantimonate affords C2-borylated furans, exclusively. MIDA boronate moiety proven to be a highly valuable group for a variety of useful transformations.[31] Thus, it is believed that the obtained regioisomeric MIDA boronate-containing furans may become useful building blocks for organic synthesis.

7. EXPERIMENTAL SECTION

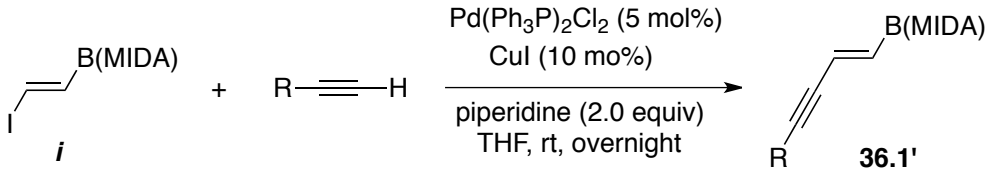
7.1. General Information

NMR spectra were recorded on Bruker Avance DRX-500 (500 MHz) or DRX-400 (400 MHz) instruments. GC/MS analysis was performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). Column chromatography was carried out employing Silicycle silica gel (Kieselgel 60, 63-200 μm). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography. All manipulations with transition metal catalysts were conducted under inert atmosphere using a combination of glovebox and standard Schlenk techniques. Anhydrous toluene, tetrahydrofuran, ether, and dichloromethane purchased from Aldrich were additionally purified on PureSolv PS-400-4 by Innovative Technology, Inc. purification system. Anhydrous solvents other than listed above were purchased from Aldrich and stored over calcium hydride. All other reagents were purchased from Aldrich, Strem Chemicals Inc., Alfa Aesar or Acros Organics, or synthesized via known literature procedures. Reactions were typically run in oven-dried glassware under inert atmosphere. Iodoalkene ***i*** was synthesized via the procedure developed by Burke *et al*.[32]

7.2. Synthesis of Starting Materials

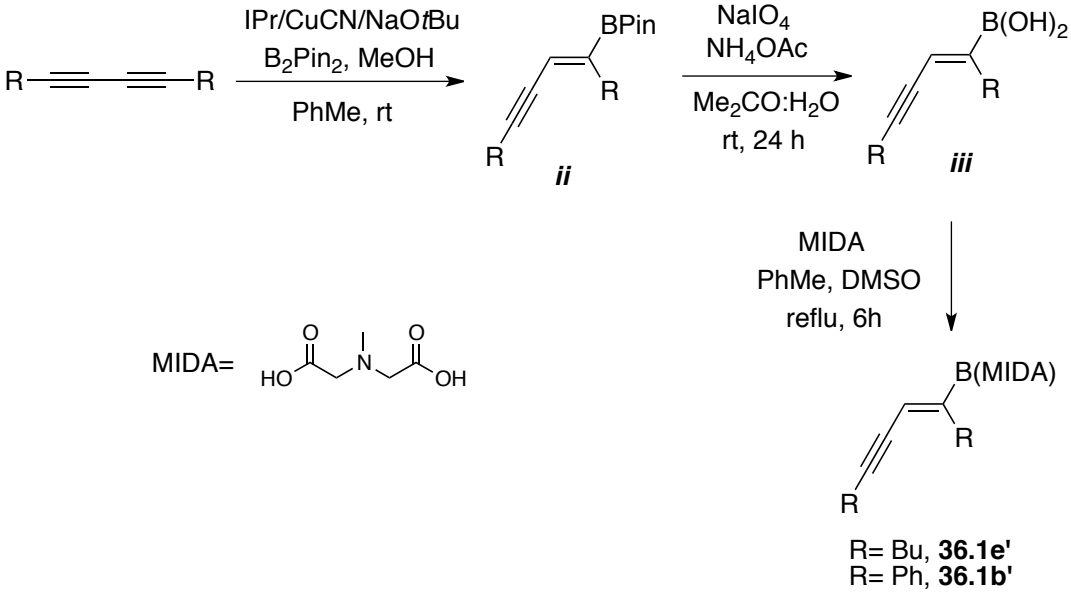
7.2.1. Synthesis of Enynyl Boronates]

***Method A*: Synthesis of Disubstituted Enynyl Boronates** [33]



To a 10-mL round bottom flask in glove box was added $Pd(Ph_3P)_2Cl_2$ (5 mol %), CuI (10 mol%), and vinyl iodide ***i***[32] (1.0 equiv). Ahydrous THF (0.2 M) was added and the reaction stirred at room temperature for 2 min. Piperidine (2.0 equiv) and terminal alkyne (1.2 equiv) were added to the solution sequentially and let the reaction stir overnight at room temperature. The reaction mixture was filtered through a short pad of silica gel and the filter was washed with EtOAc. The filtrate was concentrated under reduced pressured and purified by column chromatography on silica gel (Hex:EtOAc = 10:1 to 1:6) to afford enynyl MIDA-boronate **36.1'**.

***Method B*: Synthesis of Disubstituted Enynyl Boronates**



Synthesis of Enynyl Pinacol Boronate *ii*:[34] To an oven dried round bottom flask in glovebox was added CuCl (2 mol %), IPr (2 mol %), and *t*-BuONa (12 mol %). Toluene (0.5 M) was added and the mixture was stirred at room temperature for 15 min under argon atmosphere. B_2pin_2 (1.2 equiv) was then added to the solution in glovebox and stirred at room temperature for 5 min. The symmetrical diyne (1.0 equiv) and MeOH (2.0 equiv) were then added sequentially and the reaction was stirred at room temperature until completion (monitored by GC/MS). The reaction mixture was filtered through Celite®. The solvent was removed under reduced pressure and the crude ***ii*** was used in the next step without any purification.

Synthesis of Enynyl Boronic Acid *iii*:[35] To the crude enynyl pinacol boronate ***ii*** (1.0 equiv) acetone/water (2/1) solution (0.1 M) was added. $NaIO_4$ (3.1 equiv) and NH_4OAc (3.1 equiv) were sequentially added to the solution and the mixture was stirred at room temperature. Once completed (monitored by GC-MS), the reaction was treated with water and extracted with EtOAc. Organic layers were combined, washed with brine, and dried over Na_2SO_4. Solvents were removed under reduced pressure and the crude ***iii*** was used in the next step without any purification.

Synthesis of Enynyl MIDA Boronate 36.1e' and 36.1b':[36] To the crude boronic acid ***iii*** (1.0 equiv) methyliminodiacetic acid (1.1 equiv), toluene (0.3 mL), and DMSO (0.12 mL) were added. The Dean-Stark trap filled with toluene fit condenser vented to ambient atmosphere. The reaction mixture was refluxed with azeotropic removal of water for 6 hours. The mixture was then cooled down to room temperature, treated with

EtOAc/acetone mixture, and extracted with water. Aqueous layer was further washed with EtOAc/acetone mixture for two times. The organic layers were combined, washed with brine, and dried over Na_2SO_4. Solvents were removed under reduced pressure and the residue was subjected to column chromatography on silica gel (Hex:EtOAc = 10:1 to 1:6) to obtain enynyl boronates **36.1e' and 36.1b'**.

(*E*)-6-methyl-2-(oct-1-en-3-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.1a') Method A, (45%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.06 (d, *J*=18.9 Hz, 1 H), 5.97 (d, *J*=18.0 Hz, 1 H), 4.06 (d, *J*=16.9 Hz, 2 H), 3.72 (d, *J*=16.9 Hz, 2 H), 2.84 (s, 3 H), 2.30 (td, *J*=7.1 Hz, *J*=1.7 Hz, 2 H), 1.5 (quintet, *J*=7.0 Hz, 2 H), 1.4 (sextet, *J*=7.3 Hz, 2 H), 0.91 (t, *J*=7.3 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.4, 124.6, 92.8, 80.4, 61.6, 47.1, 30.7, 22.0, 19.1, 13.6.

(E)-6-methyl-2-(4-phenylbut-1-en-3-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.1b') Method A, (61%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.44 (apparent d, *J*=6.4, 2 H), 7.33 – 7.31 (m, 3 H), 6.36 (d, *J*=18.0 Hz, 1 H), 6.19 (d, *J*=18.3 Hz, 1 H), 3.91 (d, *J*=16.5 Hz, 2 H), 3.73 (d, *J*=16.5 Hz, 2 H), 2.90 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 167.2, 131.7, 128.4, 124.3, 122.9, 889.0, 84.4, 61.6, 47.0.

(E)-2-(4-(2-methoxyphenyl)but-1-en-3-yn-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.1c') Method A, (62%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.38 (apparent d, *J*=7.7 Hz, 1 H), 7.27-7.21 (m, 1 H), 6.88 – 6.82 (m, 2 H), 6.34 (d, *J*=18.3 Hz, 1 H), 6.19 (d, *J*=18.0 Hz, 1 H), 4.1 (d, *J*=17.2 Hz, 2 H), 3.83 (s, 3 H), 3.77 (d, *J*=17.2 Hz, 2 H),

2.82 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.6, 159.9, 133.7, 130.1, 123.8, 120.6, 12.1, 110.8, 93.4, 87.6, 61.7, 55.8, 47.2.

(E)-6-methyl-2-(4-(2-(trifluoromethyl)phenyl)but-1-en-3-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.1d') Method A, (35%), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.74 (apparent d, *J*=7.7 Hz, 1 H), 7.67 – 7.63 (m, 2 H), 7.58-7.52 (m, 1 H), 6.41 (d, *J*=18.3 Hz, 1 H), 6.28 (d, *J*=18.3 Hz, 1 H), 4.28 (d, *J*=16.9 Hz, 2 H), 4.13 (d, *J*=16.9 Hz, 2 H), 3.08 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 167.9, 134.0, 132.2, 128.6, 126.0 (q, *J*=5.5 Hz), 121.1, 94.9, 85.3, 61.7, 46.7.

(Z)-2-(dodec-5-en-7-yn-5-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.1e') Method B, (63% over 3 steps), **^{1}H NMR** (500 MHz, CDCl3) δ ppm 5.80 (s, 1 H), 4.06 (d, J=17.0 Hz, 2 H), 3.73 (d, J=16.9 Hz, 2 H), 2.77 (s, 3 H), 2.34 (dt, J=1.8 Hz, J=6.8 Hz, 2 H), 2.18 (t, J=7.6 Hz, 2 H), 1.51 (quintet, J=7.2 Hz, 2 H), 1.46 – 1.39 (m, 4 H), 1.32 (quintet, J=7.1 Hz, 2 H), 0.92 – 0.87 (m, 6 H). **^{13}C NMR** (126 MHz, CDCl3) δ ppm 168.5, 118.6, 97.3, 78.3, 61.94, 47.1, 32.4, 31.8, 30.9, 23.2, 21.9, 19.3, 13.9, 13.6.

(*E*)-2-(dec-1-en-3-yn-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.1f') Method A, (54%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.06 (d, *J*=18.0 Hz, 1 H), 5.97 (d, *J*=18.2 Hz, 1 H), 4.06 (d, *J*=17.1 Hz, 2 H), 3.72 (d, *J*=17.0 Hz, 2 H), 2.84 (s, 3 H), 2.3 (t, *J*=7.1 Hz, 2 H), 1.52 (quintet, *J*=7.3 Hz, 2 H), 1.37 (quintet, *J*=7.3 Hz, 2 H), 1.33 – 1.23 (m, 4 H), 0.88 (t, *J*=6.8 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm: 168.4, 124.6, 92.9, 80.4, 61.6, 47.1, 31.3, 28.6, 22.5, 19.5, 14.1.

(E)-6-methyl-2-(6-phenylhex-1-en-3-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.1g') Method A, (68%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.35-7.27 (m, 2 H), 7.27-7.21 (m, 3 H), 6.07 (d, *J*=18.2 Hz, 1 H), 5.99 (d, *J*=18.2 Hz, 1 H), 4.02 (d, *J*=16.9 Hz, 2 H), 3.69 (d, *J*=16.8 Hz, 2 H), 2.84 (t, *J*=7.7 Hz, 2 H), 2.79 (s, 3 H), 2.60 (d, *J*=7.6 Hz, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.3, 140.6, 128.4, 126.4, 124.4, 91.9, 81.1, 61.6, 47.1, 35.0, 21.6.

(E)-6-methyl-2-(4-(4-(trifluoromethyl)phenyl)but-1-en-3-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.1h') Method A, (45%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.58 (apparent d, *J*=8.3 Hz, 2 H), 7.54 (apparent d, *J*=8.2 Hz, 2 H), 6.38 (d, *J*=18.2 Hz, 1 H), 6.25 (d, *J*=18.2 Hz, 1 H), 3.88 (d, *J*=16.3 Hz, 2 H), 3.73 (d, *J*=16.3 Hz, 2 H), 2.92 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 166.5, 131.9, 125.3, 124.0, 97.1, 90.0, 61.6, 46.8.

(E)-2-(4-(4-bromophenyl)but-1-en-3-yn-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.1i') Method A, (38%), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.57 (apparent d, *J*=8.5 Hz, 2 H), 7.39 (apparent d, *J*=8.5 Hz, 2 H), 6.35 (d, *J*=18.2 Hz, 1 H), 6.22 (d, *J*=18.2 Hz, 1 H), 4.28 (d, *J*=16.9 Hz, 2 H), 4.11 (d, *J*=16.6 Hz, 2 H), 3.08 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 167.9, 133.1, 131.8, 122.5, 122.1, 121.3, 90.6, 88.5, 61.6, 46.7.

(E)-2-(dodeca-1-en-3,5-diyn-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.1j') Method A, (51%), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 6.39 (d, *J*=18.2 Hz, 1

H), 6.03 (d, *J*=18.3 Hz, 1 H), 4.26 (d, *J*=16.9 Hz, 2 H), 4.08 (d, *J*=16.9 Hz, 2 H), 3.05 (s, 3 H), 2.37 (t, *J*=7.0 Hz, 2 H), 1.53 (quintet, *J*=7.1 Hz, 2 H), 1.44 – 1.38 (m, 2 H), 1.34 – 1.28 (m, 4 H), 0.89 (t, *J*=6.8 Hz, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 167.9, 120.5, 85.1, 74.8, 64.9, 61.7, 46.7, 31.1, 28.3, 28.0, 22.3, 18.9, 13.4.

(Z)-2-(1,4-diphenylbut-1-en-3-yn-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.1k') Method B, (10% over 3 steps), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.51 – 7.53 (m, 2 H), 7.45-7.39 (m, 2 H), 7.29 – 7.31 (m, 4 H), 7.21 – 7.23 (m, 2 H), 6.40 (s, 1 H), 4.25 (d, *J*=17.0 Hz, 2 H), 3.84 (d, *J*=16.3 Hz, 2 H), 2.93 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 141.1, 131.2, 128.9, 128.4, 128.3, 127.9, 126.9, 123.4, 117.9, 93.5, 88.5, 62.0, 46.8.

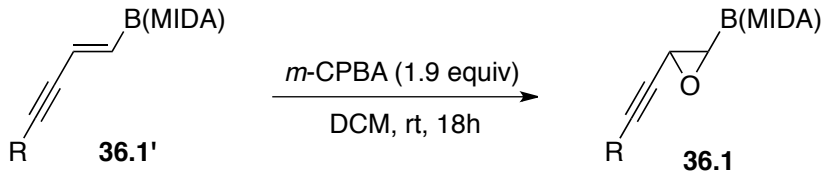
(E)-6-methyl-2-(5-(trimethylsilyl)pent-1-en-3-yn-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.1l'') Method A, (71%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.16 (d, *J*=18.3 Hz, 1 H), 6.09 (d, *J*=19.0 Hz, 1 H), 4.06 (d, *J*=16.9 Hz, 2 H), 3.71 (d, *J*=16.9 Hz, 2 H), 2.85 (s, 3 H), 0.18 (s, 9 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.2, 124.0, 104.6, 96.6, 61.6, 47.2, -0.1.

(*E*)-2-(but-1-en-3-yn-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.1l') Enyne **36.1l''** (1.0 equiv), possessing the TMS group, was dissolved in anhydrous THF (0.25 M) under argon atmosphere. The solution was cooled down to -78 °C and TBAF (1.05 equiv; 1 M sol. in THF) was added dropwise. The reaction was stirred at -78 °C for 1 hour and then warmed up to room temperature. The mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc (2 times). Organic layers were

combined, washed with brine, dried over Na_2SO_4, and filtered. Solvent were removed under reduced pressure and the product was purified by column chromatography on silica gel (Hexanes:EtOAc = 10:1 to 1:6) to give **36.1l'**.

(72%), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 6.31 (d, *J*=18.3 Hz, 1 H), 5.99 (dd, *J*=18.3 Hz, *J*=1.8 Hz, 1 H), 4.26 (d, *J*=16.9 Hz, 2 H), 4.08 (d, *J*=17.2 Hz, 2 H), 3.46 (d, *J*=2.2 Hz, 1 H), 3.04 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ 168.0, 121.0, 78.9, 61.6, 46.6.

7.2.2. Synthesis of Alkynyl Epoxides



Enynyl boronate **36.1'** (1.0 equiv) was dissolved in dichloromethane (0.05 M) and *m*-CPBA (1.9 equiv) was added. The reaction was stirred at room temperature for 18 hours. The reaction mixture was then treated with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 times). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. Solvents were removed under reduced pressure and the crude was subjected to column chromatography on silica gel (Hex:EtOAc = 10:1 to 1:8) to obtain the desired boronated alkynyl epoxide **36.1**.

2-(3-(hex-1-yn-1-yl)oxiran-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.1a)

(60%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 3.98 (d, *J*=17.2 Hz, 1 H), 3.97 (d, *J*=16.5 Hz, 1 H), 3.84 (d, *J*=17.2 Hz, 1 H), 3.75 (d, *J*=16.1 Hz, 1 H), 3.36 (d, *J*=2.9 Hz, 1 H), 3.12 (s,

3 H), 2.45 (d, *J*=2.9 Hz, 1 H), 2.19 (t, *J*=7.2 Hz, 2 H), 1.48 (quintet, *J*=7.1 Hz, 2 H), 1.39 (sextet, *J*=7.3 Hz, 2 H), 0.90 (t, *J*=7.2 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.9, 167.5, 84.7, 77.2, 62.09, 62.02, 46.3, 44.2, 30.4, 21.9, 18.4, 13.5. **HRMS** (ESI) calcd. for $C_{13}H_{18}BNO_5$ $[M+H]^+$: 280.1356, found: 280.1358.

6-methyl-2-(3-(phenylethynyl)oxiran-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.1b) (44%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.42 (dd, *J*=7.5 Hz, *J*=1.9 Hz, 2 H), 7.31 – 7.25 (m, 3 H), 4.04 (d, *J*=17.3 Hz, 1H), 4.02 (d, *J*=16.4 Hz, 1 H), 3.88 (d, *J*=17.0 Hz, 1 H), 3.78 (d, *J*=16.4 Hz, 1 H), 3.61 (d, *J*=2.9 Hz, 1 H), 3.11 (s, 3 H), 2.61 (d, *J*=2.9 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.7, 167.4, 131.9, 128.8, 128.4, 121.9, 86.4, 83.5, 62.2, 62.1, 46.4, 44.4. **HRMS** (ESI) calcd. for $C_{15}H_{14}BNO_5$ $[M+H]^+$: 300.1043, found: 300.1042.

2-(3-((2-methoxyphenyl)ethynyl)oxiran-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.1c) (52%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.39 (dd, *J*=7.5 Hz, *J*=1.7 Hz, 1 H), 7.31 – 7.27 (m, 1 H), 6.89 – 6.85 (m, 2 H), 3.95 (d, *J*=16.9 Hz, 2 H), 3.86 (d, *J*=16.9 Hz, 1 H), 3.86 (s, 3 H), 3.79 (d, *J*=16.1 Hz, 1 H), 3.67 (d, *J*=2.9 Hz, 1 H), 3.12 (s, 3 H), 2.64 (d, *J*2.9 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.2, 166.9, 160.4, 133.9, 130.3, 120.5, 111.1, 110.7, 90.3, 79.9, 62.1, 62.0, 55.8, 46.2, 44.8. **HRMS** (ESI) calcd. for $C_{16}H_{16}BNO_6$ $[M+H]^+$: 330.1149, found: 330.1140.

6-methyl-2-(3-((2-(trifluoromethyl)phenyl)ethynyl)oxiran-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.1d) (48%), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.77

(d, *J*=7.3 Hz, 1 H), 7.70 – 7.65 (m, 2 H), 7.60 (t, *J*=7.4 Hz, 1 H), 7.37 (d, *J*=17.2 Hz, 1 H), 4.30 (d, *J*=16.9 Hz, 1 H), 4.22 (d, *J*=17.2 Hz, 1 H), 4.02 (d, *J*=16.9 Hz, 1 H), 3.55 (d, *J*=2.9 Hz, 1 H), 3.33 (s, 3 H), 2.67 (d, *J*=2.9 Hz, 1 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 168.3, 167.3, 134.5, 132.2, 130.8 (q, *J*=31.4 Hz), 129.1, 126.0 (q, *J*=5.5 Hz), 123.7 (q, *J*=271.9 Hz), 120.2 (d, *J*=3.7 Hz), 9301, 78.1, 62.2, 62.1, 46.3, 42.9. **HRMS** (ESI) calcd. for $C_{16}H_{13}BF_3NO_5$ $[M+H]^+$: 368.0917, found: 368.0913.

2-(2-butyl-3-(hex-1-yn-1-yl)oxiran-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.1e) (63%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 3.92 (d, *J*=17.3 Hz, 1 H), 3.87 (d, *J*=16.1 Hz, 1 H), 3.79 (d, *J*=17.0 Hz, 1 H), 3.74 (d, *J*=16.1 Hz, 1 H), 3.41 (s, 1 H), 3.07 (s, 3 H), 2.19 (t, *J*=6.7 Hz, 2 H), 1.84 – 1.77 (m, 1 H), 1.62 – 1.53 (m, 1 H), 1.53 – 1.20 (m, 8 H), 0.86 (t, *J*=7.2 Hz, 6 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.9, 167.2, 86.6, 75.7, 62.3, 49.9, 46.1, 32.8, 30.4, 27.3, 23.4, 21.9, 18.5, 13.9, 13.5. **HRMS** (ESI) calcd. for $C_{17}H_{26}BNO_5$ $[M+H]^+$: 336.1982, found 336.1977.

6-methyl-2-(3-(oct-1-yn-1-yl)oxiran-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.1f) (60%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 4.01 (d, *J*=17.0 Hz, 1 H), 4.00 (d, *J*=16.1 Hz, 1 H), 3.85 (d, *J*=17.1 Hz, 1 H), 3.74 (d, *J*=16.3 Hz, 1 H), 3.36 (s, 1 H), 3.11 (s, 3 H), 2.45 (d, *J*=2.9 Hz, 1 H), 2.19 (t, *J*=6.6 Hz, 2 H), 1.48 (quintet, *J*=7.1 Hz, 2 H), 1.37 – 1.23 (m, 6 H), 0.87 (t, *J*=6.8 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.8, 167.4, 132.0, 128.5, 84.9, 50.9, 46.3, 44.5, 31.3, 28.6, 28.4, 22.6, 18.8, 14.2. **HRMS** (ESI) calcd. for $C_{15}H_{22}BNO_5$ $[M+H]^+$: 308.1669, found: 308.1674.

6-methyl-2-(3-(4-phenylbut-1-yn-1-yl)oxiran-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.1g) (56%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.31 – 7.28 (m, 2 H), 7.23 – 7.19 (m, 3 H), 3.97 (d, *J*=17.2 Hz, 1 H), 3.95 (d, *J*=16.1 Hz, 1 H), 3.81 (d, *J*=17.2 Hz, 1 H), 3.72 (d, *J*=16.5 Hz, 1 H), 3.36 (d, *J*=2.6 Hz, 1 H), 3.06 (s, 3 H), 2.81 (t, *J*=7.5 Hz, 2 H), 2.48 (t, *J*-7.2 Hz, 2 H), 2.44 (d, *J*=2.9 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.6, 167.3, 140.4, 128.5, 126.4, 83.96, 77.98, 62.08, 62.02, 46.2, 44.3, 34.71, 20.88. **HRMS** (ESI) calcd. for $C_{17}H_{18}BNO_5$ $[M+H]^+$: 328.1356, found: 328.1350.

6-methyl-2-(3-((4-(trifluoromethyl)phenyl)ethynyl)oxiran-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.1h) (44%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.54 – 7.50 (m, 4 H), 4.06 (d, *J*=16.9 Hz, 1 H), 4.03 (d, *J*=16.1 Hz, 1 H), 3.89 (d, *J*=17.2 Hz, 1 H), 3.81 (d, *J*=16.5 Hz, 1 H), 3.64 (d, *J*=2.9 Hz, 1 H), 3.17 (s, 3 H), 2.65 (d, *J*=2.9 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.4, 167.1, 132.1, 130.4 (q, *J*=33.3 Hz), 125.7, 125.3 (q, *J*=3.7 Hz), 123.7 (q, *J*=271.9 Hz), 88.6, 82.1, 62.2, 62.1, 46.4, 44.3. **HRMS** (ESI) calcd. for $C_{16}H_{13}BF_3NO_5$ $[M+H]^+$: 368.0917, found: 368.0921.

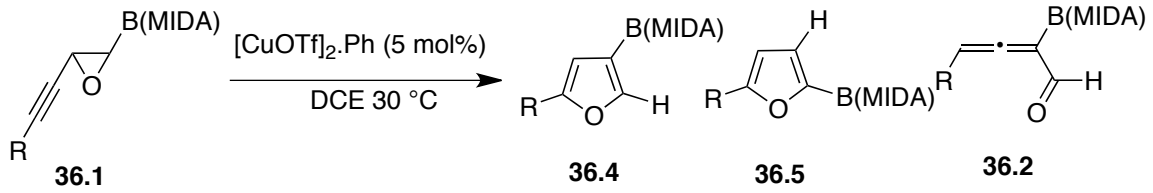
2-(3-((4-bromophenyl)ethynyl)oxiran-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.1i) (34%), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.56 (d, *J*=8.6 Hz, 2 H), 7.40 (d, *J*=8.6 Hz, 2 H), 4.36 (d, *J*=17.2 Hz, 1 H), 4.29 (d, *J*=16.9 Hz, 1 H), 4.21 (d, *J*=17.2 Hz, 1 H), 4.01 (d, *J*=16.9 Hz, 1 H), 3.50 (d, *J*=3.0 Hz, 1 H), 3.31 (s, 3 H), 2.64 (d, *J*=3.0 Hz, 1 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 168.3, 167.3, 133.4, 131.8, 122.6, 121.4, 88.6, 81.2, 62.2, 62.1, 46.3, 42.9. **HRMS** (ESI) calcd. for $C_{15}H_{13}BBrNO_5$ $[M+H]^+$: 378.0148, found: 378.0152.

2-(3-(deca-1,3-diyn-1-yl)oxiran-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.1j) (42%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 4.01 (d, *J*=17.2 Hz, 1 H), 4.00 (d, *J*=16.5 Hz, 1 H), 3.87 (d, *J*=17.1 Hz, 1 H), (d, *J*=16.5 Hz, 1 H), 3.43 (d, *J*=2.7 Hz, 1 H), 3.11 (s, 3 H), 2.28 (d, *J*=2.9 Hz, 1 H), 2.28 (t, *J*=7.1 Hz, 2 H), 1.52 (quintet, *J*=7.1 Hz, 2 H), 1.49 – 1.40 (m, 2 H), 1.32 – 1.25 (m, 4 H), 0.88 (t, *J*=6.9 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.7, 167.3, 81.8, 72.9, 68.7, 64.4, 62.1, 51.1 (C-B, rough, broad), 46.5, 44.0, 31.2, 28.6, 28.1, 22.5, 19.3, 14.1. **HRMS** (ESI) calcd. for $C_{17}H_{22}BNO_5$ $[M+H]^+$: 332.1669, found: 332.1669.

6-methyl-2-(2-phenyl-3-(phenylethynyl)oxiran-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.1k) (28%), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.56 – 7.54 (m, 2 H), 7.38 – 7.35 (m, 2 H), 7.30 – 7.26 (m, 2 H), 4.24 – 7.21 (m, 2 H), 7.00 – 6.98 (m, 2 H), 4.31 (d, *J*=6.8 Hz, 1 H), 4.28 (d, *J*=6.3 Hz, 1 H), 4.08 (d, *J*=16.7 Hz, 1 H), 3.93 (s, 1 H), 3.81 (d, *J*=17.2 Hz, 1 H), 2.00 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 168.0, 167.1, 138.7, 131.6, 128.6, 128.3, 127.7, 127.1, 126.8, 122.1, 85.4, 84.6, 62.6, 62.2, 51.1, 46.8. **HRMS** (ESI) calcd. for $C_{21}H_{18}BNO_5$ $[M+H]^+$: 376.1356, found: 376.1353.

2-(3-ethynyloxiran-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.1l) (45%), ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ ppm 4.34 (d, *J*=17.2 Hz, 1 H), 4.26 (d, *J*=16.9 Hz, 1 H), 4.18 (d, *J*=17.2 Hz, 1 H), 3.97 (d, *J*=16.5 Hz, 1 H), 3.29 (s, 3 H), 3.26 (dd, *J*=2.9 Hz, *J*=1.5 Hz, 1 H), 2.87 (d, *J*=1.8 Hz, 1 H), 2.52 (d, *J*=2.6 Hz, 1 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 168.2, 167.2, 81.7, 72.0, 62.0, 46.2, 42.3. **HRMS** (ESI) calcd. for $C_9H_{10}BNO_5$ $[M+H]^+$: 224.0730, found: 224.0730.

7.3. Copper-Catalyzed Synthesis of C3-Borylated Furans

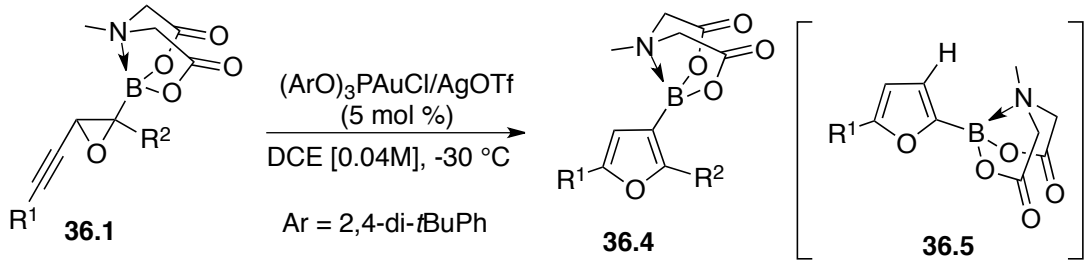


36.1 **36.4** **36.5** **36.2**

To a V-shaped vial in the glovebox was added $[CuOTf]_2.PhH$ (5 mol %, 2.5 mg). The vial was capped and taken out of glovebox. Dry dichloroethane (2.0 mL) was added and the mixture stirred for 2 min at room temperature. Alkynyl epoxide **36.1** (1.0 equiv, 0.1 mmol) as a solution in dichloroethane (0.5 mL) was added dropwise and the mixture was stirred at 30 °C overnight. The reaction mixture was then filtered through Celite® and the solvent was removed under reduced pressure. The crude product was subjected to column chromatography on silica gel (Hexanes:EtOAc = 10:1 to 1:6) to obtain furan **36.4**.

7.4. Gold-Catalyzed Reactions

7.4.1. Gold-Catalyzed Synthesis of C3-Borylated Furans



To a round bottom flask in the glovebox was added commercially available (2,4-di-*t*-BuPhO)$_3$PAuCl (5 mol %, 4.4 mg), AgOTf (5 mol %, 1.3 mg) in the glove box. The flask was capped abd taken out of glove box. Dry dichloroethane (2.0 mL) was added and the mixture was stirred for 5 min at room temperature, which was then cooled down to -30 ºC. Alkynyl epoxide **36.1** (1.0 equiv, 0.1 mmol) as a solution in dichloroethane (0.5 mL) was added dropwise and the mixture was stirred at -30 ºC. After 2 hours, the reaction mixture was filtered through Celite® and the solvent was removed under reduced pressure. The crude product was subjected to column chromatography on silica gel (Hexanes:EtOAc = 10:1 to 1:6) to obtain furan **36.4**.

2-(5-butylfuran-3-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.4a) (83%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.35 (s, 1H), 5.95 (s, 1 H), 4.16 (d, *J*=16.9 Hz, 2 H), 3.79 (d, *J*=16.9 Hz, 2 H), 2.68 (s, 3 H), 2.56 (t, *J*=7.5 Hz, 2 H), 1.57 (quintet, *J*=7.6 Hz, 2 H), 1.32 (sxt, *J*=7.8 Hz, 2 H), 0.9 (t, *J*=7.3 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm

168.9, 158.1, 145.7, 107.2, 61.4, 47.5, 30.1, 27.5, 22.3, 13.8. **HRMS** (ESI) calcd. for $C_{13}H_{18}BNO_5$ $[M+H]^+$: 280.1356, found: 280.1359.

6-methyl-2-(5-phenylfuran-3-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.4b) (87%) ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ ppm 7.72 (apparent d, *J*=8.3 Hz, 2 H), 7.60 (s, 1 H), 7.42-7.38 (m, 2 H), 7.28 – 7.25 (m, 1 H), 6.93 (s, 1 H), 4.33 (d, *J*=16.9 Hz, 2 H), 4.15 (d, *J*=16.9 Hz, 2 H), 2.96 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.6, 155.4, 147.0, 130.5, 128.8, 127.6, 123.9, 107.7, 61.5, 47.6. **^{11}B NMR** (128 MHz, $(CD_3)_2CO$) δ ppm 10.1. **HRMS** (ESI) calcd. for $C_{15}H_{14}BNO_5$ $[M+H]^+$: 300.1043, 300.1042.

2-(5-(2-methoxyphenyl)furan-3-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.4c) (81%) **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.80 (apparent d, *J*=7.7 Hz, 1 H), 7.57 (s, 1 H), 7.28 – 7.24 (m, 1 H), 7.09 (apparent d, *J*=8.4 Hz, 7.04 (s, 1 H), 7.03-6.98 (m, 1 H), 4.31 (d, *J*=16.9 Hz, 2 H), 4.12 (d, *J*=16.9 Hz, 2 H), 3.94 (s, 3 H), 2.96 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.1, 155.3, 151.8, 146.1, 128.3, 126.0, 120.7, 119.41, 112.3, 111.0, 61.5, 55.4, 47.5. **HRMS** (ESI) calcd. for $C_{16}H_{16}BNO_6$ $[M+H]^+$: 330.1149, found: 330.1139.

6-methyl-2-(5-(2-(trifluoromethyl)phenyl)furan-3-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.4d) The reaction was performed at room temperature. (61%), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.88-7.80 (m, 2 H), 7.70 – 7.73 (m, 3 H), 7.65-7.45 (m, 1 H), 6.84 (s, 1 H), 4.34 (d, *J*=16.9 Hz, 2 H), 4.16 (d, *J*=16.9 Hz, 2 H), 2,98 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 168.1, 151.4, 148.0, 132.3, 130.3, 128.2, 126.5 (q, *J*=5.6

Hz), 126.1 (q, *J*=31.4 Hz), 124.3 (q, *J*=271.9 Hz), 113.4, 61.5, 47.2. **HRMS** (ESI) calcd. for $C_{16}H_{13}BF_3NO_5$ $[M+H]^+$: 368.0917, found: 368.0917.

2-(2,5-dibutylfuran-3-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.4e) (81%) **^{1}H NMR** (500 MHz, ($CDCl_3$) δ ppm 5.77 (s, 1 H), 3.98 (d, *J*=16.9 Hz, 2 H), 3.72 (d, *J*=16.5 Hz, 2 H), 2.69 (s, 3 H), 2.60 (t, *J*=7.5 Hz, 2 H), 2.54 (t, *J*=7.5 Hz, 2 H), 1.61 – 1.54 (m. 4 H), 1.36 – 1.26 (m, 4 H), 0.92 – 0.86 (m, 6 H). **^{13}C NMR** (126 MHz, ($CDCl_3$) δ ppm 167.9, 155.3, 107.8, 61.5, 47.1, 31.5, 30.1, 27.9, 27.5, 22.4, 22.3, 13.9, 13.8. **HRMS** (ESI) calcd. for $C_{17}H_{26}BNO_5$ $[M+H]^+$: 336.1982, found: 336.1976.

2-(5-hexylfuran-3-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.4f) (67%), ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.36 (s. 1 H), 5.95 (s, 1 H), 4.09 (d, *J*=16.9 Hz, 2 H), 3.77 (d, *J*=16.9 Hz, 2 H), 2.70 (s. 3 H), 2.57 (t, *J*=7.7 Hz, 2 H), 1.60 (quintet, *J*=7.4 Hz, 2 H), 1.36 – 1.24 (m, 6 H), 0.87 (t, *J*=6.97 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.4, 158.3, 145.8, 107.1, 61.4, 47.4, 31.5, 31.5, 28.9, 28.0, 27.9, 22.6, 14.1. **HRMS** (ESI) calcd. for $C_{15}H_{22}BNO_5$ $[M+H]^+$: 368.0917, found: 368.0921.

6-methyl-2-(5-phenethylfuran-3-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.4g) (74%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.39 (s, 1 H), 7.24 – 7.21 (m, 2 H), 7.16 – 7.11 (m, 3 H), 5.93 (s, 1 H), 4.11 (d, *J*=16.9 Hz, 2 H), 3.72 (d, *J*16.9 Hz, 2 H), 2.93 – 2.88 (m, 4 H), 2.58 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.2, 159.4, 141.0, 128.43, 128.4, 126.1, 119.9, 106.1, 61.5, 47.0, 34.5, 29.5. **HRMS** (ESI) calcd. for $C_{17}H_{18}BNO_5$ $[M+H]^+$: 328.1356, found: 328.1350.

6-methyl-2-(5-(4-(trifluoromethyl)phenyl)furan-3-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.4h) (65%), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.92 (apparent d, *J*=8.1 Hz, 2 H), 7.74 (apparent d, *J*=8.1 Hz, 2 H), 7.70 (s, 1 H), 7.15 (s, 1 H), 4.35 (d, *J*=17.2 Hz, 2 H), 4.17 (d, *J*=16.9 Hz, 2.98 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 168.1, 153.0, 148.1, 134.5, 125.7 (q, *J*=3.7 Hz), 124.5 (q, *J*=270.0 Hz), 123.9, 111.2, 61.5. 47.2. **HRMS** (ESI) calcd. for $C_{16}H_{13}BF_3NO_5$ $[M+H]^+$: 368.0917, found: 368.0918.

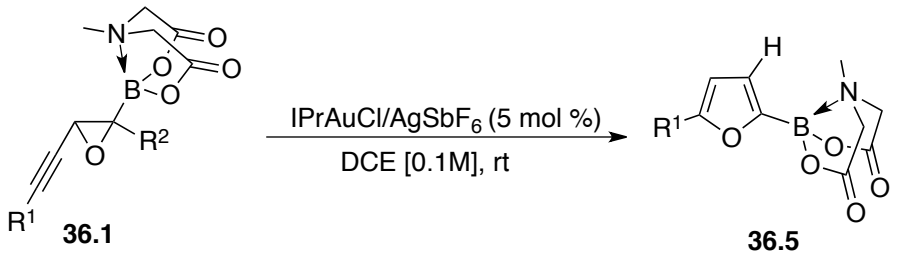
2-(5-(4-bromophenyl)furan-3-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.4i) (79%), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.67 (apparent d, *J*=8.5 Hz, 2 H), 7.62 (s, 1 H), 7.58 (apparent d, *J*=8.6 Hz, 2 H), 6.99 (s, 1 H), 4.33 (d, *J*=17.0 Hz, 2 H), 4.14 (d, *J*=16.9 Hz, 2 H), 2.96 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 168.0, 153.4, 147.3, 131.8, 130.2, 125.4, 120.4, 109.5, 61.5, 47.2. **HRMS** (ESI) calcd. for $C_{15}H_{13}BBrNO_5$ $[M+H]^+$: 378.0148, found: 378.0154.

6-methyl-2-(5-(oct-1-yn-1-yl)furan-3-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.4j) (67%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.42 (s, 1 H), 6.46 (s, 1 H), 4.11 (d, *J*=16.9 Hz, 2 H), 3.77 (d, *J*=16.7 Hz, 2 H), 2.70 (s, 3 H), 2.40 (t, *J*=7.1 Hz, 2 H), 1.88 (quintet, *J*=7.3 Hz, 2 H), 1.44 – 1.38 (m, 2 H), 1.33– 1.25 (m, 4 H), 0.89 (t, 6.8 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.3, 147.0, 139.0, 116.3, 95.6, 70.6, 61.5, 47.6, 31.3, 28.6, 28.3, 22.5, 19.5, 14.1. **HRMS** (ESI) calcd. for $C_{17}H_{22}BNO_5$ $[M+H]^+$: 332.1669, found: 332.1666.

2-(2,5-diphenylfuran-3-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.4k)

(67%) **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.88-7.78 (m, 4 H), 7.44 – 7.41 (m, 4 H), 7.39-7.27 (m, 1 H), 7.33-7.28 (m, H), 6.96 (s, 1 H), 4.28 (d, *J*=17.2 Hz, 2 H), 3.97 (d, *J*=16.9 Hz, 2 H), 2.78 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 167.9, 152.9, 132.6, 130.7, 128.8, 128.4, 128.0, 127.9, 127.3, 123.7, 112.3, 61.9, 46.9. **HRMS** (ESI) calcd. for $C_{21}H_{18}BNO_5$ $[M+H]^+$: 376.1356, found: 376.1355.

7.4.2. Gold-Catalyzed Synthesis of C2-Borylated Furans



To a V-shaped vial in the glovebox was added IPrAuCl (5 mol %, 3.1 mg) and $AgSbF_6$ (5 mol %, 1.7 mg). The flask was capped and taken out of glove box. Dry dichloroethane (2.0 mL) was added and the mixture was stirred for 5 min at room temperature. Alkynyl epoxide **36.1** (1.0 equiv, 0.1 mmol) as a solution in dichloroethane (0.5 mL) was added dropwise and the mixture was stirred at room temperature. After 1-2 hours the reaction mixture was filtered through Celite® and the solvent was removed under reduced pressure. The crude product was subjected to column chromatography on silica gel (Hexanes:EtOAc = 10:1 to 1:6) to obtain furan **36.5**.

2-(5-butylfuran-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.5a) (75%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.63 (d, *J*=2.9 Hz, 1 H), 5.95 (d, *J*=2.9 Hz, 1 H), 4.13 (d, *J*=16.9 Hz, 2 H), 3.82 (d, *J*=16.9 Hz, 2 H), 2.66 (s, 3 H), 2.6 (t, *J*=7.7 Hz, 2 H), 1.57 (quintet, *J*=7.6 Hz, 2 H), 1.33 (sxt, *J*=7.4 Hz, 2 H), 0.9 (t, *J*=7.3 Hz, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.3, 160.7, 119.9, 105.4, 61.6, 47.2, 30.2, 27.8, 22.3, 13.8. **HRMS** (ESI) calcd. for $C_{13}H_{18}BNO_5$ $[M+H]^+$: 280.1356, found: 280.1354.

6-methyl-2-(5-phenylfuran-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.5b) (50%), ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ ppm 7.75 (apparent d, *J*=8.4 Hz, 2 H), 7.45-7.34 (m, 2 H), 7.35-7.25 (m, 1 H), 6.83 (d, *J*=3.3 Hz, 1 H), 6.78 (d, *J*=3.3 Hz, 1 H), 4.39 (d, *J*=16.9 Hz, 2 H), 4.21 (d, *J*=16.9 Hz, 2 H), 2.95 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 168.1, 156.8, 131.1, 128.7, 127.4, 123.9, 120.0, 105.6, 61.6, 47.0. **^{11}B NMR** (128 MHz, $(CD_3)_2CO$) δ ppm 9.3. **HRMS** (ESI) calcd. for $C_{15}H_{14}BNO_5$ $[M+H]^+$: 330.1043, found: 300.1037.

2-(5-(2-methoxyphenyl)furan-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.5c) (49%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.80 (apparent dd, *J*=7.7 Hz, *J*=1.5 Hz, 1 H), 7.20 – 7.24 (m, 1 H), 7.05-6.96 (m, 1 H), 6.93 (apparent d, *J*=8.1 Hz, 1 H), 6.91 (d, *J*=3.3 Hz, 1 H), 6.84 (d, *J*=3.3 Hz, 1 H), 4.10 (d, *J*=4.1 Hz, 2 H), 3.90 (s, 3 H), 3.84 (d, *J*=16.5 Hz, 2 H), 2.68 (s, 3 H). **^{13}C NMR** (126 MHz, $(CDCl_3)$ δ ppm 168.0, 155.35, 153.7, 128.5, 126.2, 121.2, 120.8, 119.7, 111.0, 110.4, 61.6, 55.4, 47.2. **HRMS** (ESI) calcd. for $C_{16}H_{16}BNO_6$ $[M+H]^+$: 330.1149, found: 330.1145.

6-methyl-2-(5-(2-(trifluoromethyl)phenyl)furan-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.5d) The reaction was performed at 60 °C. (42%), ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ ppm 7.84 – 7.82 (m, 2 H), 7.73 – 7.70 (m, 1 H), 7.65-7.49 (m, 1 H), 6.83 (d, *J*=3.3 Hz, 1 H), 6.77 (d, *J*=3.3 Hz, 1 H), 4.4 (d, *J*=16.9 Hz, 4.16 (d, *J*=17.2 Hz, 2 H), 2.94 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 167.9, 153.9, 132.4, 131.8 (d, *J*=3.7 Hz), 130.5, 128.3, 126.6 (q, *J*=5.55 Hz), 124.4 (q, *J*=271.88 Hz), 119.7, 110.37, 64.53, 46.9. **HRMS** (ESI) calcd. for $C_{16}H_{13}BF_3NO_5$ $[M+H]^+$: 368.0917, found: 368.0917.

2-(5-hexylfuran-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.5f) (57%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.64 (d, *J*=2.9 Hz, 1 H), 5.95 (d, *J*=3.3 Hz, 1 H), 4.07 (d, *J*=16.9 Hz, 2 H), 3.83 (d, *J*=16.9 Hz, 2 H), 2.66 (s, 3 H), 2.58 (t, *J*=7.5 Hz, 2 H), 1.58 (quintet, *J*=7.4 Hz, 2 H), 1.34 – 1.26m, 6 H), 0.87 (t, *J*=7.0 Hz, 3 H). **^{13}C NMR** (126 MHz, ($CDCl_3$) δ ppm 168.4, 160.8, 120.0, 105.4, 61.6, 47.1, 31.5, 28.9, 28.2, 28.0, 22.6, 14.1. **HRMS** (ESI) calcd. for $C_{15}H_{22}BNO_5$ $[M+H]^+$: 308.1669, found: 308.1670.

6-methyl-2-(5-phenethylfuran-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.5g) (64%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.23 – 7.26 (m, 2, H), 7.15 – 7.17 (m, 3 H), 6.62 (d, *J*=2.9 Hz, 1 H), 5.98 (d, *J*=2.9 Hz, 1 H), 4.02 (d, *J*=16.9 Hz, 2 H), 3.96 (d, *J*=16.9 Hz, 2 H), 2.98 – 2.90 (m, 4 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.2, 159.4, 141.0, 128.4, 128.4, 126.1, 119.9, 106.0, 61.5, 47.0, 34.5, 29.5. **HRMS** (ESI) calcd. for $C_{17}H_{18}BNO_5$ $[M+H]^+$: 328.1356, found: 328.1352.

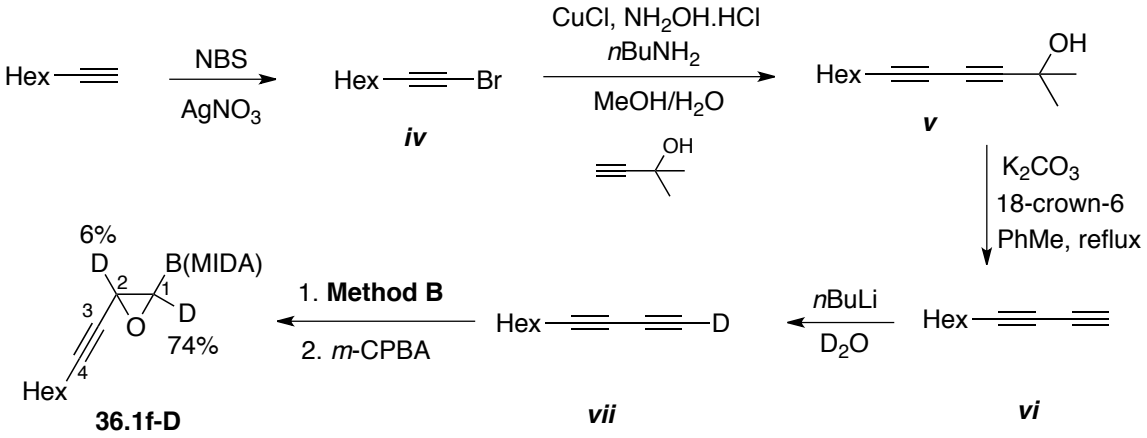
6-methyl-2-(5-(4-(trifluoromethyl)phenyl)furan-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.5h) (65%), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.96 (apparent d, *J*=8.1 Hz, 2 H), 7.73 (apparent d, *J*=8.3 Hz, 2 H), 7.05 (d, *J*=3.4 Hz, 1 H), 6.84 (d, *J*=3.4 Hz, 1 H), 4.41 (d, *J*=17.0 Hz, 2 H), 4.23 (d, *J*=17.0 Hz, 2 H), 2.97 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 168.0, 155.2, 134.6, 128.2 (q, *J*=32.4 Hz), 125.7 (d, *J*=3.7 Hz), 124.5 (q, *J*=271.0 Hz), 124.2, 120.3, 108.1, 61.6, 47.1. **HRMS** (ESI) calcd. for $C_{16}H_{13}BF_3NO_5$ $[M+H]^+$: 368.0917, found: 368.0923.

2-(5-(4-bromophenyl)furan-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.5i) (84%), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.70 (apparent d, *J*=8.8 Hz, 2 H), 7.57 (apparent d, *J*=8.8 Hz, 2 H), 6.90 (d, *J*=3.3 Hz, 1 H), 6.79 (d, *J*=3.3 Hz, 1 H), 4.39 (d, *J*=16.9 Hz, 2 H), 4.21 (d, *J*=16.9 Hz, 2 H), 2.95 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 168.0, 155.6, 131.7, 130.3, 125.7, 120.7, 120.2, 106.5, 61.6, 47.0. **HRMS** (ESI) calcd. for $C_{15}H_{13}BBrNO_5$ $[M+H]^+$: 378.0148, found: 378.0144.

6-methyl-2-(5-(oct-1-yn-1-yl)furan-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (36.5j) (66%), **^{1}H NMR** (500 MHz, $(CDCl_3)$ δ ppm 6.71 (d, *J*=3.1 Hz, 1 H), 6.44 (d, *J*=3.1 Hz, 1 H), 4.07 (d, *J*=16.7 Hz, 2 H), 3.87 (d, *J*=16.9 Hz, 2 H), 2.71 (s, 3 H), 2.40 (t, *J*=7.1 Hz, 2 H), 1.58 (quintet, *J*=7.4 Hz, 2 H), 1.41 (dt, *J*=14.2 Hz, *J*=7.2 Hz, 2 H), 1.34– 1.22 (m, 4 H), 0.89 (t, *J*=6.7 Hz, 3 H). **^{13}C NMR** (126 MHz, $(CDCl_3)$ δ ppm 168.2, 141.0, 120.0, 114.3, 95.9, 71.8, 47.3, 31.3, 28.7, 28.3, 22.5, 19.5, 14.1. **HRMS** (ESI) calcd. for $C_{17}H_{22}BNO_5$ $[M+H]^+$: 332.1669, found: 332.1671.

2-(furan-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (36.5l) Reaction was run in anh. THF. (60% NMR yield), **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ ppm 7.59 (d, *J*=1.5 Hz, 1 H), 7.53 (s, 1 H), 6.5 (d, *J*=1.1 Hz, 1 H), 4.29 (d, *J*=17.2 Hz, 2 H), 4.09 (d, *J*=16.9 Hz, 2 H), 2.89 (s, 3 H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ ppm 168.1, 147.2, 143.3, 112.7, 61.4, 47.0. **HRMS** (ESI) calcd. for $C_9H_{10}BNO_5$ $[M+H]^+$: 224.0730, found: 224.0728.

7.4.3. Mechanistic Investigations



Synthesis of 1-bromooct-1-yne *iv*: 1-Octyne (1.0 equiv, 10 mmol, 1.48 mL) was dissolved in acetone (263 mL) and the reaction flask was covered with alumina foil. $AgNO_3$ (0.3 equiv, 3 mmol, 0.51 g) and *N*-bromosuciinimide (1.4 equiv, 14 mmol, 2.5 g) were added to the reaction mixture. The reaction was stirred at room temperature for 18 h. The reaction was then quenched with H_2O and extracted with hexanes (3 times). Organic layers were combined, washed with brine, dried over Na_2SO_4, and filtered. Solvents were removed under reduced pressure and crude material was purified by column chromatography on silica gel (pure hexanes) to obtain compound ***iv***.

1-bromooct-1-yne (85%, 8.5 mmol, 1.6 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 2.20 (t, *J*=7.2 Hz, 2 H), 1.54 – 1.47 (m, 2 H), 1.41 – 1.34 (m, 2 H), 1.31 – 1.25 (m, 4 H), 0.82 (t, *J*=6.9 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 80.4, 37.4, 31.3, 28.5, 28.3, 22.6, 19.7, 14.1.

Synthesis of 2-methyldodeca-3,5-diyn-2-ol *v*: The mixture of MeOH (1.80 mL), H_2O (0.88 mL), 2-methyl-3-butyne-2-ol (2.0 equiv, 14.4 mmol, 1.4 mL), CuCl (15 mol%, 1.1 mmol, 107 mg) and NH_2OH**.**HCl (0.3 equiv, 2.2 mmol, 153 mg) was cooled down to 0 ºC and ***iv*** (1.0 equiv, 7.2 mmol, 1.36 g) as a solution in MeOH (0.9 mL) was added dropwise. The reaction was stirred at room temperature for 20 hours. The reaction mixture was then quenched with H_2O and extracted with Et_2O (2 times). Organic layers were combined, washed with brine, dried over Na_2SO_4, filtered. Solvents were removed under reduced pressure and the crude material was subjected to column chromatography on silica gel (hexane:EtOAc = 50:1 to 20:1) to obtain compound ***v***.

2-methyldodeca-3,5-diyn-2-ol (73%, 5.3 mmol, 1.0 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 2.36 (s_{br}, 1 H), 2.25 (t, *J*=7.2 Hz, 2 H), 1.50 (s, 3 H), 1.39 – 1.33 (m, 2 H), 1.31 – 1.23 (m, 4 H), 0.87 (t, *J*=7.0 Hz, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 81.8, 79.8, 67.4, 65.5, 64.3, 31.3, 31.1, 28.5, 28.1, 22.5, 19.2, 14.0.

Synthesis of deca-1,3-diyne *vi*: Anhydrous K_2CO_3 (1.0 equiv, 7.2 mmol, 1.0 g) and 18-crown-6 (0.3 equiv, 1.6 mmol, 422 mg) were added to the Shlenk flask. Condenser was attached and the system was flushed with argon. Diyne ***v*** (1.0 equiv, 7.2 mmol, 1.0 g) as a solution in anhydrous toluene (38 mL) was added to the mixture under argon. The

mixtures was stirred under reflux for 18 hours and then cooled down to room temperature. The reaction mixture was then quenched with H_2O and extracted with Et_2O (2 times). Organic layers were combined, washed with brine, dried over Na_2SO_4, and filtered. Solvents were removed under reduced pressure and the crude material was purified by column chromatography on silica gel (pure hexanes) to obtain compound ***vi***.

Deca-1,3-diyne (54%, 3.9 mmol, 522 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 2.24 (t, *J*=7.0 Hz, 2 H), 1.92 (s, 1 H), 1.49 1.56 (m, 2 H), 1.42 – 1.34 (m, 2 H), 1.33 – 1.25 (m, 4 H), 0.88 (t, *J*=7.0 Hz, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 78.3, 68.5, 64.6, 64.3, 31.3, 28.5, 28.0, 22.5, 19.0, 14.0.

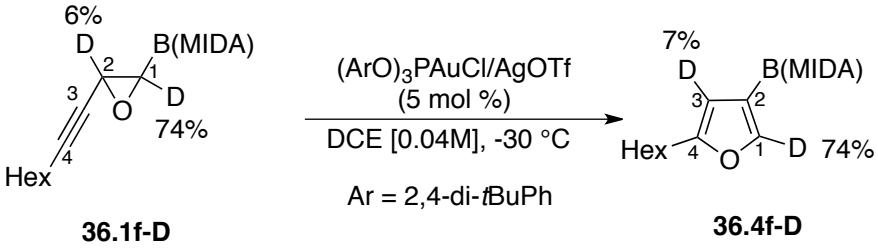
Synthesis of deuterated deca-1,3-diyne *vii*. Terminal diyne ***vi*** (1.0 equiv, 3.9 mmol, 522 mg) was dissolved in anhydrous THF (5.7 mL) and the solution was cooled down to -78 °C. Then *n*BuLi (1.2 equiv, 4.9 mmol) was added dropwise. The reaction was stirred at -78 °C for 30 min then at -30 °C for 30 more min. The reaction was quenched with D_2O (10.0 equiv, 39 mmol, 706 μL), filtered through the short pad Celite®, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (pure hexanes) to obtained the desired deuterated product ***vii***.

Deuterated deca-1,3-diyne (84%, 99% D-incorporation). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 2.26 (t, *J*=7.2 Hz, 2 H), 1.56 – 1.51 (m, 2 H), 1.42 – 1.36 (m, 2 H), 1.34 – 1.26 (m, 4 H), 0.89 (t, *J*=7.2 Hz, 3 H).

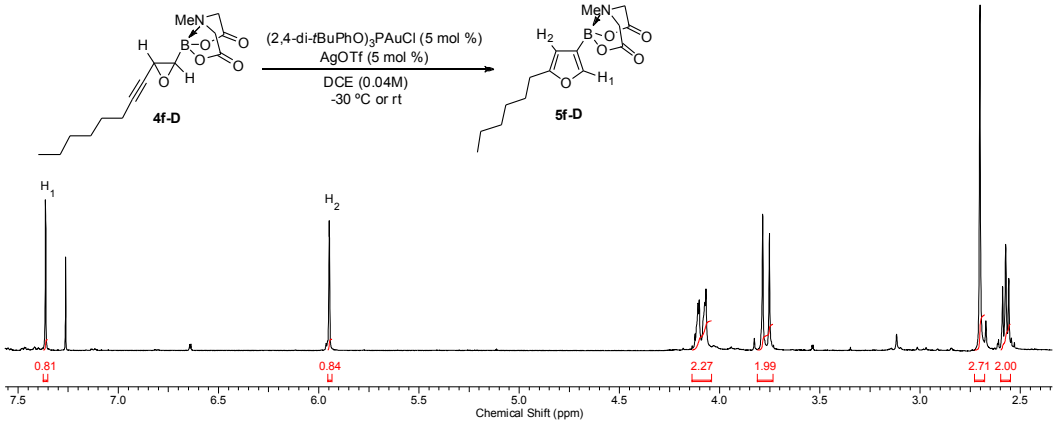
Compound **36.1f-D** was synthesized by subjecting deuterated diyne ***vii*** to **method B** followed by epoxidation (*vide infra*).

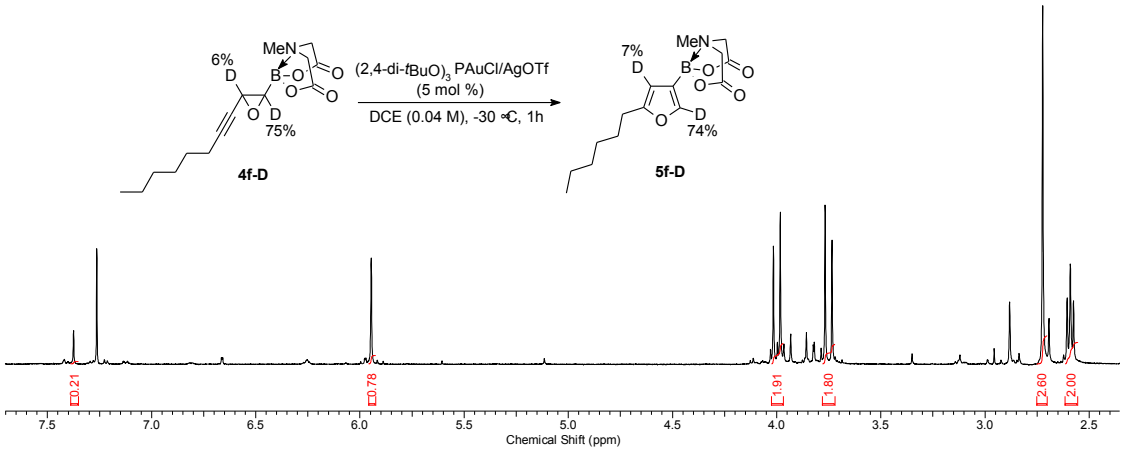
36.1f-D: ^{1}**H NMR** (500 MHz, $CDCl_3$) δ ppm 4.01 (d, *J*=16.5 Hz, 2 H), 3.87 (d, *J*=17.2 Hz, 1 H), 3.74 (d, *J*=16.1 Hz, 1 H), 3.35 (s, 0.85 H), 3.12 (s, 3 H), 2.44 (d, *J*=2.9 Hz, 0.24 H), 2.18 (td, *J*=7.2, 1.3 Hz, 2 H), 1.51 – 1.45 (m, 2 H), 1.38 – 1.22 (m, 6 H), 0.87 (t, *J*=7.0 Hz, 3 H).

A. Reaction of the Deuterated Alkynyl epoxide to form C3-Borylated Furan



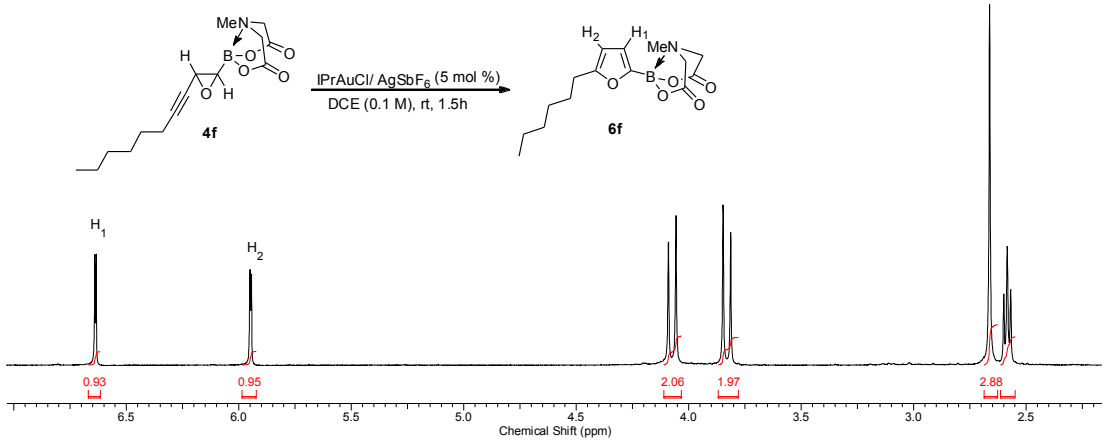
36.1f-D **36.4f-D**

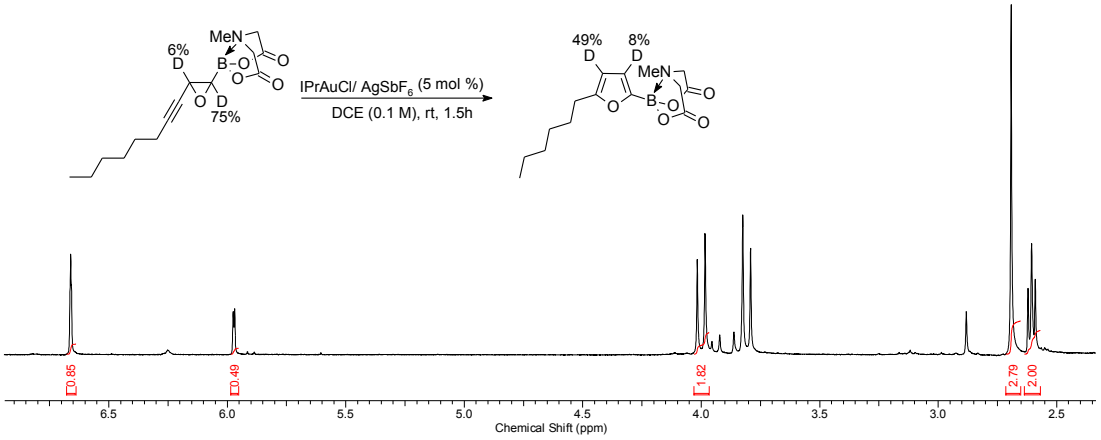




A. Reaction of the Deuterated Alkynyl epoxide to form C2-Borylated Furan

36.1f-D **36.5f-D**





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28. Trisubstituted **36.1k** and **35.1e** afforded products **35.4k** and **35.1e** in 81% and 67%, respectively. No competitive alkyl or aryl migration was observed.

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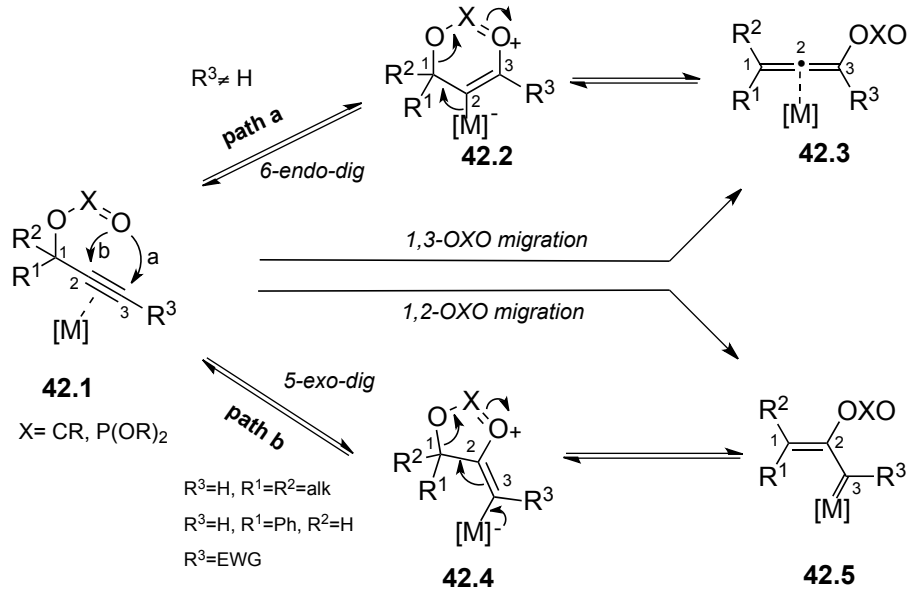
PART THREE

STERREOCONTROLLED METAL-CATALYZED 1,3-PHOSPHATYLOXY/1,3-HALOGEN MIGRATION RELAY TOWARD 1,3-DIENES

9. INTRODUCTION

9.1. Transition Metal-Catalyzed Double Migratory Cascade Reactions of Propargylic Esters and Phosphates

Cascade transformations offer enhancement of molecular complexity and diversity from simpler molecules, which are often accompanied by high degrees of chemo-, regio-, diastereo-, and enantioselectivity.[1] Compared to the stepwise reactions, these step-economical processes represent environmentally and economically more favored approaches. One of the remarkable examples of such transformations is a transition metal-catalyzed molecular rearrangement of readily available propargylic esters and phosphates.[2] Earlier cases include copper-,[3] silver-,[3] zinc-,[4] and palladium-[5] catalyzed reactions. However, extensive studies were triggered by discovery of ruthenium-,[6] platinum-,[7] and gold-[8] catalyzed processes. It is generally accepted that transition metal catalysts can activate the triple bond of **42.1** for further transformations (Scheme 42). Thus, it can undergo a *6-endo-dig* cyclization to produce intermediate **42.2**, which further rearranges into allene **42.3** (**path a**). Overall, this formal [3,3]-rearrangement represents a 1,3-OXO (X = CR, $P(OR)_2$) migration process. Alternatively, the activated substrate **42.1** can undergo a *5-exo-dig* cyclization to form intermediate 42.4, which upon ring opening forms the metal-stabilized carbene **42.5** (**path b**). This process, which involves a 1,2-OXO migration, is often referred to as a Rautenstrauch rearrangement.[5]



Scheme 42.

Generally, the regiochemistry of 1,3-OXO migration to form **42.3** (**path a**) or 1,2-OXO migration to generate **42.5** (**path b**) can be predicted. As a rule of thumb, if substrate **42.1** possesses electronically unbiased internal alkynes ($R^3 \neq H$), the 1,3-OXO migration takes place.[9] Alternatively, for tertiary or benzyl alcohol derived substrate 42.1, possessing terminal alkynes (R^3 = H)10 and electronically biased internal alkynes (R^3 = EWG),[11] the 1,2-OXO migration is preferred. However, other factors, such as the choice of metal catalyst,[12] the substitution pattern at the propargyl moiety,[13] and temperature,[14] in some cases have been reported to govern the regiochemical outcome of these reactions.

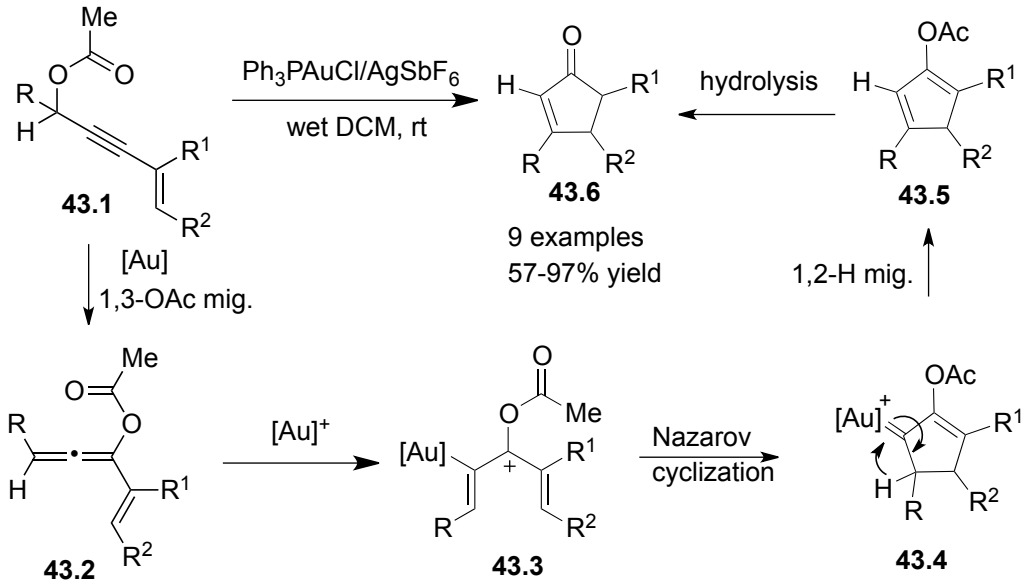
Interestingly, reactive compounds **42.3** and **42.5**, which possess additional functional groups, can undergo further cascade transformations, including intra-[15] or intermolecular[16] trapping, cycloaddition,[2b] cross-coupling,[17] and oxidation reactions.[18] Alternatively, if these intermediates possess appropriately situated migrating groups, then a second migration can occur, thus offering an easy route to diversely functionalized products.

9.2. Double Migratory Transformations with an Initial 1,3-OXO Migration

9.2.1. Cascade 1,3-OXO/Hydrogen migration

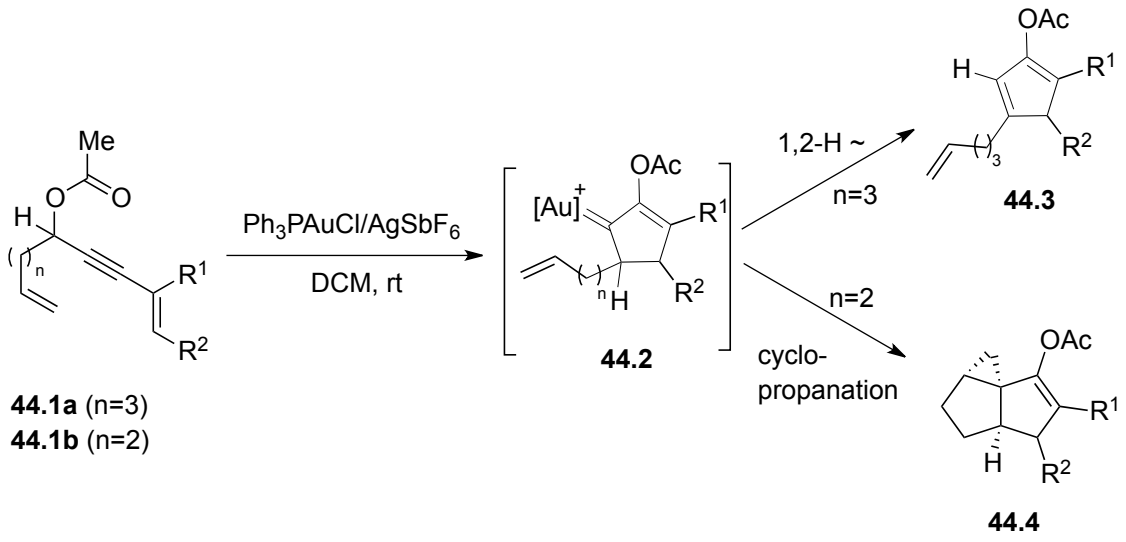
9.2.1.1 Double 1,3-OXO/1,2-H Migration

In 2006, Zhang and co-workers reported the Au(I)-catalyzed cascade reaction of propargylic esters **43.1** into cyclopentenone **43.6** (Scheme 43).[19] This reaction proceeds well with various cyclic and acyclic substrates providing cyclopentanone products in good to excellent yields. The proposed mechanism involves an initial 1,3-acyloxy migration to form allenylacetate **43.2** (*vide supra*), which in the presence of a gold catalyst transforms into the vinyl gold species **43.3**. The Nazarov cyclization of the latter produces cyclic gold-stabilized carbene **43.4**, which upon a subsequent 1,2-hydride shift[20] affords dienyl acetate **43.5**. Hydrolysis of the latter by wet dichloromethane furnishes the cyclopentenone **43.6**.



Scheme 43.

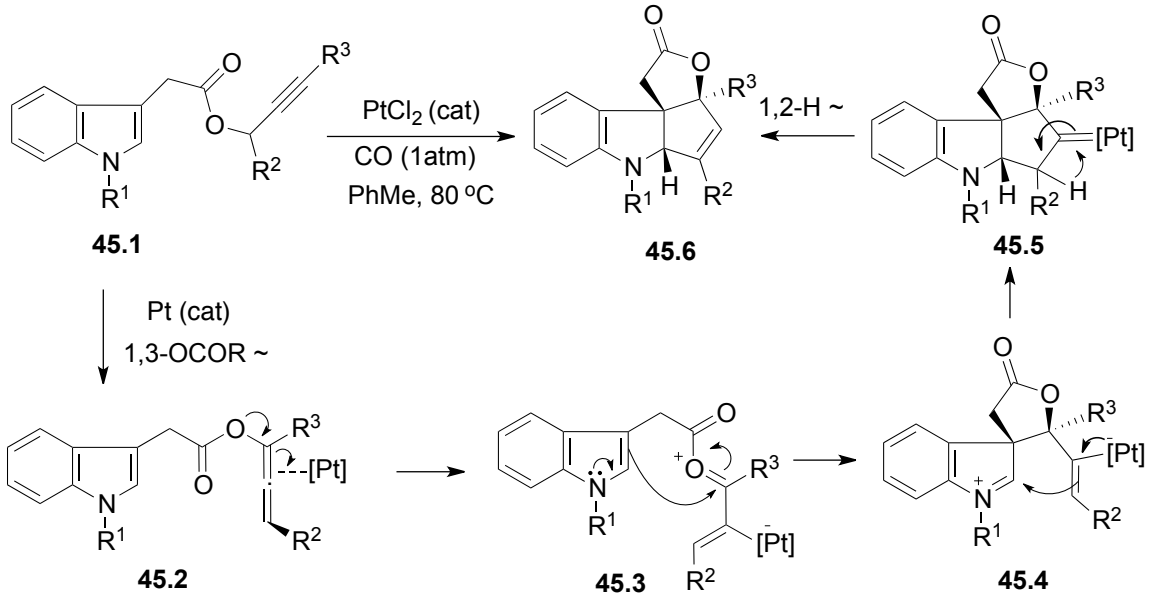
Fensterbank and Malacria disclosed an analogous Au(I)- catalyzed reaction of analogous enynyl acetates **44.1** bearing a tethered olefin at the propargylic position (Scheme 44).[21] It is believed that after the 1,3-OAc migration–Nazarov cyclization sequence, the compound **44.2** (an analogue of **43.4**) is formed. Depending on the length of the tether, different reactivity of the gold-carbene **44.2** was observed. When n=3 (**44.2a**), the above discussed 1,2-hydride shift[19] takes place to produce the cyclopentadienyl acetate **44.3**. However, in the reaction of the substrate with a shorter tether (**44.2b**, n = 2), exclusive formation of tricyclic compound **44.4** via an electrophilic cyclopropanation reaction was observed. DFT calculations supported the cyclopropanation reaction of compound **44.2b** into **44.4**, which is both kinetically and thermodynamically favored over the 1,2-hydride shift that leads to **44.3**.



Scheme 44.

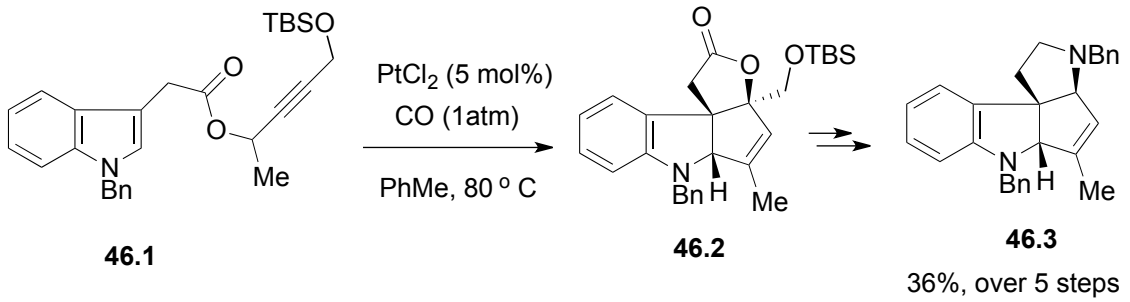
In 2007, Zhang's group developed the Pt(II)-catalyzed synthesis of tetracyclic 2,3-indoline-fused cyclopentenes **45.6** from the propargylic 3-indoleacetates **45.1** (Scheme 45).[22] This reaction exhibites a wide substrate scope, as various groups at the

propargylic position, nitrogen atoms, and terminus alkyne of **45.1** were well-tolerated under the reaction conditions. According to the mechanistic hypothesis, the 1,3-migration of the indoleacetate group produces allene **45.2**, which then in the presence of the platinum catalyst gives the oxocarbenium species **45.3**. Following the C3 attack of the indole moiety at the electrophilic center of the latter, the vinyl platinum **45.4** is formed. A subsequent *5-exo-trig* cyclization of **45.4** produces the platinum carbene-containing tetracyclic compound **45.5**, which undergoes a 1,2-hydride shift to furnish the final tetracyclic product **45.6**.



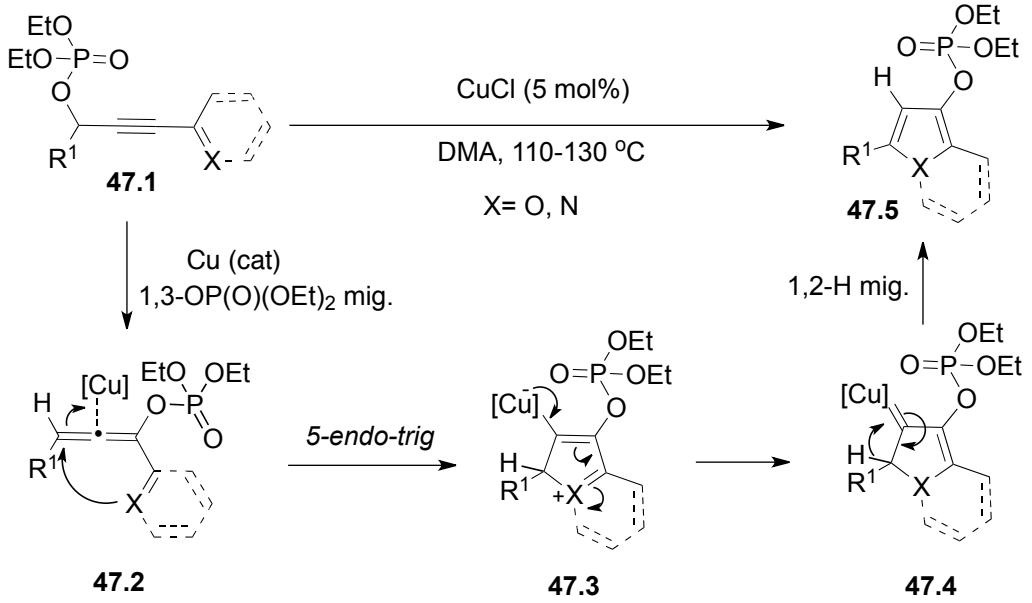
Scheme 45.

Notably, a synthetic utility of this transformation was demonstrated by a short synthesis of compound **46.3**, a tetracyclic core of vindolinine (Scheme 46). Thus, propargylic ester **46.1** under these reaction conditions produced compound **46.2**, which upon sequential functional group interconversion was efficiently transformed into the indoline-containing alkaloid **46.3** in a reasonable overall yield.



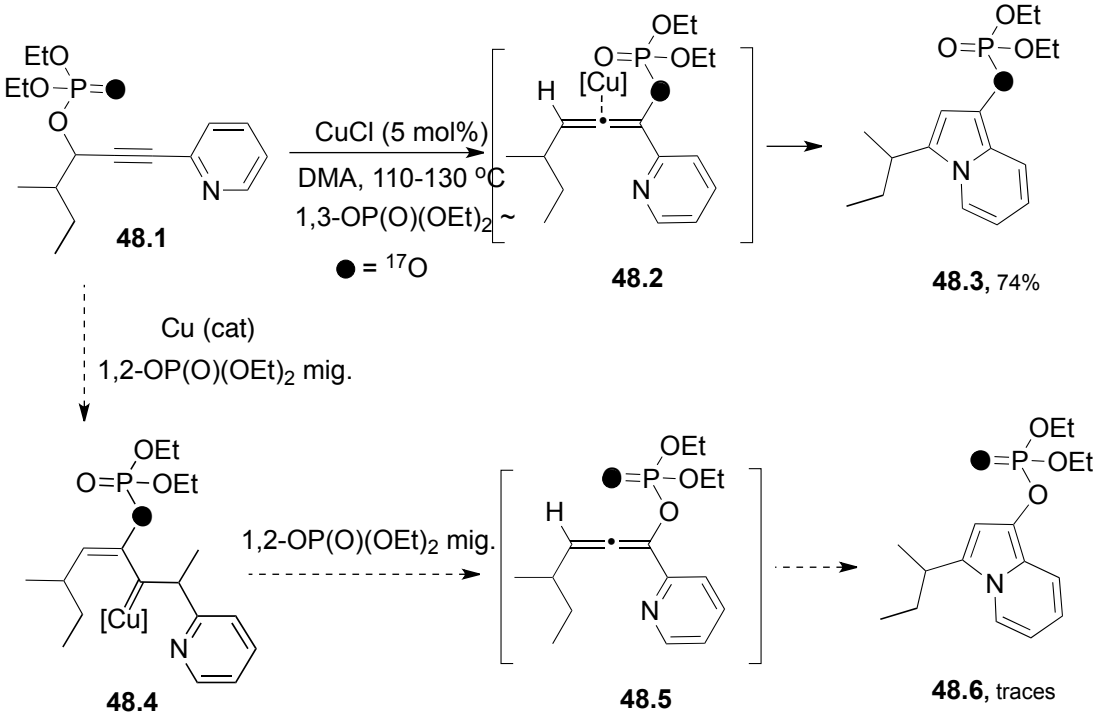
Scheme 46.

Gevorgyan's group demonstrated the copper-catalyzed synthesis of various heterocycles **47.5** from propargylic phosphates **47.1** (Scheme 47).[23] A variety of substituted furanes and indolizines could be efficiently accessed via this cascade transformation. The proposed mechanism involves the Cu-catalyzed 1,3-phosphatyloxy migration to produce allene **47.2**, which upon a nucleophilic attack of the heteroatom at the metal-activated allene via a *5-endo-trig* process generates oxonium ion **47.3**. The latter then converts into the heterocyclic copper carbene **47.4**, which further undergoes a subsequent 1,2-hydride shift to furnish heterocycle **47.5**. Employment of an analogous acyloxy-containing substrate in this reaction was less efficient.



Scheme 47.

To better understand the mechanism of the reaction, the ^{17}O-enriched alkynyl pyridine **48.1** was treated under the reaction conditions (Scheme 48). Subsequently, the corresponding indolizine **48.2** with the labeled bridging phosphate oxygen was isolated as a major isotopomer with traces of **48.6** observed. Thus, this observation strongly supports that migratory cycloisomerization of substrate **48.1** involves the formation of allene **48.2** (the result of 1,3-phosphatyloxy migration) rather than isotopomeric allene **48.5** (the product of two sequential 1,2-phosphathyloxy migrations).

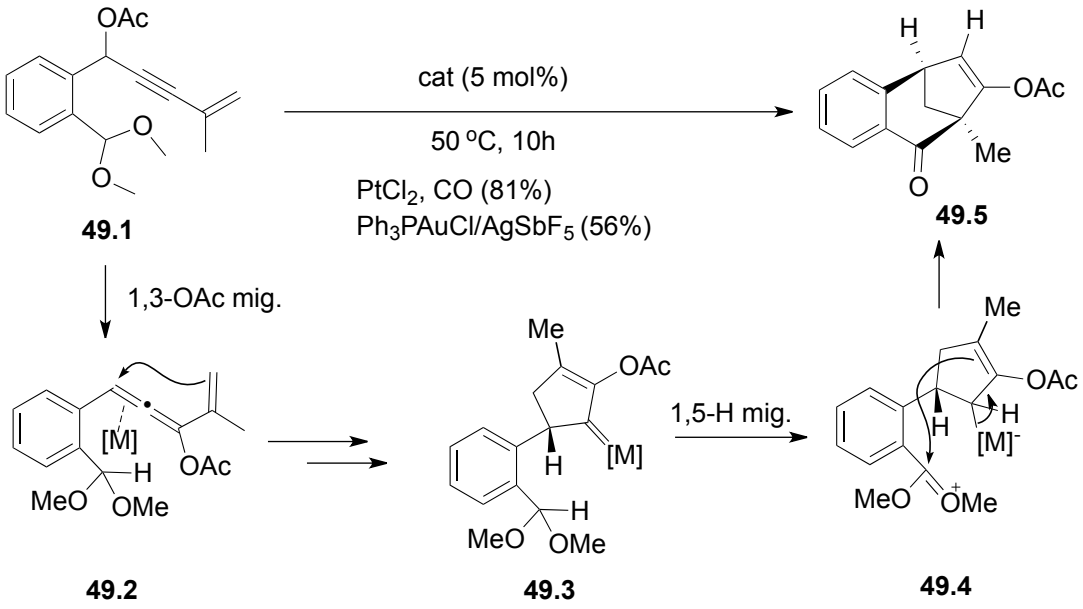


Scheme 48.

9.2.1.2 Double 1,3-OXO/1,5-H Migration

It was shown by Liu's group that propargylic acetate **49.1** could be converted into the tricyclic structure **49.5** in the presence of either gold(I) or platinum(II) catalysts

(Scheme 49).[24] The mechanism of this reaction involves the metal-triggered 1,3-OAc migration to produce allene **49.2**, which upon a *5-endo-trig* cyclization generates the bicyclic metal carbene **49.3**. A following 1,5-hydride shift from the acetal moiety of the latter to the electrophilic metal carbene center produces cation **49.4**, which then undergoes a nucleophilic attack of the allyl metal moiety at the electrophilic oxocarbenium center to furnish the final tricyclic product **49.5**.



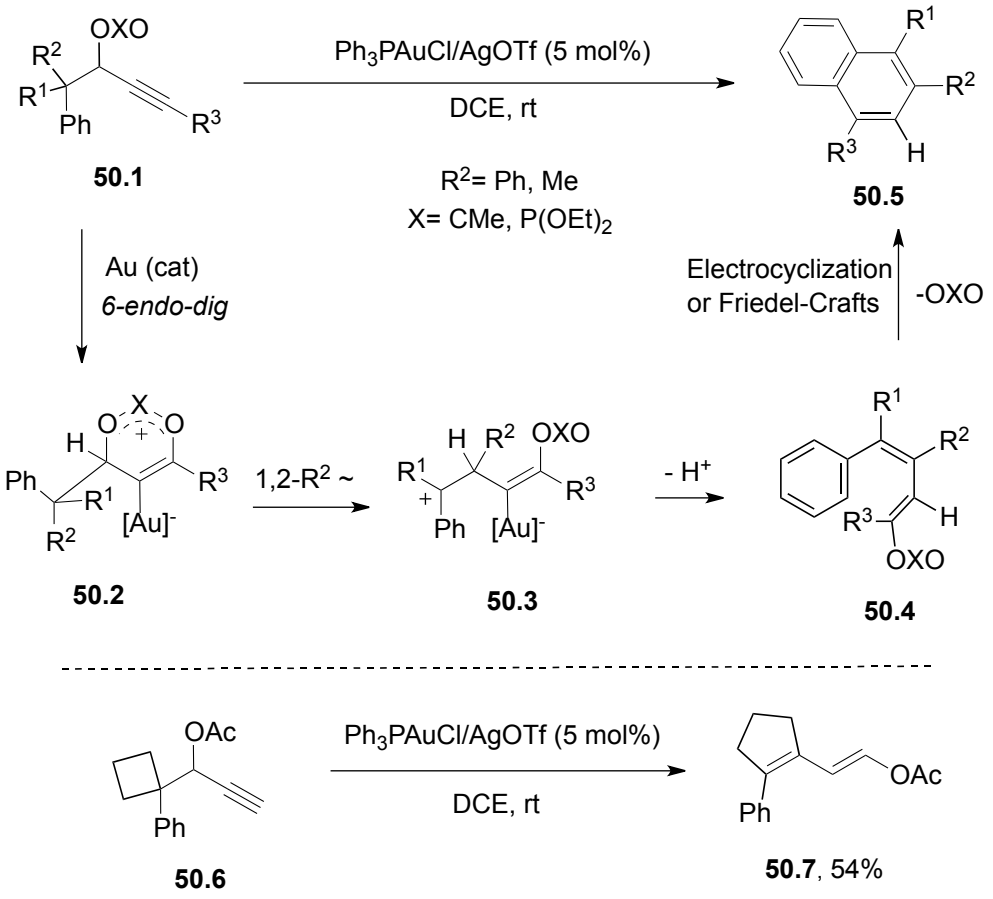
Scheme 49.

9.2.2. Cascade 1,3-OXO/Alkyl migration

9.2.2.1 Double 1,3-OXO/1,2-Alkyl Migration

Gevorgyan and co-workers reported the gold-catalyzed cascade reaction of the propargylic esters and phosphates **50.1** to unsymmetrically substituted naphthalenes **50.5** (Scheme 50).[25,26] It was proposed that substrate **50.1** initially undergoes the gold-catalyzed *6-endo-dig* cyclization to produce the cyclic intermediate **50.2**, in which a 1,2-R^2 migration forms the benzylic carbocation **50.3**. A sequence of proton loss–

protodeauration steps in the latter takes place to give diene **50.4**, which upon cyclization via either 6π-electrocyclization or Friedel-Crafts reactions furnishes the naphthalene product **50.5**. Interestingly, employing the substrate **50.6** (analogue of **50.1**), having a strained cyclobutyl ring at the α-position of the propargylic ester group leads to formation of 1,3-diene **50.7** (analogue of **50.4**) possessing the acetate functionality.

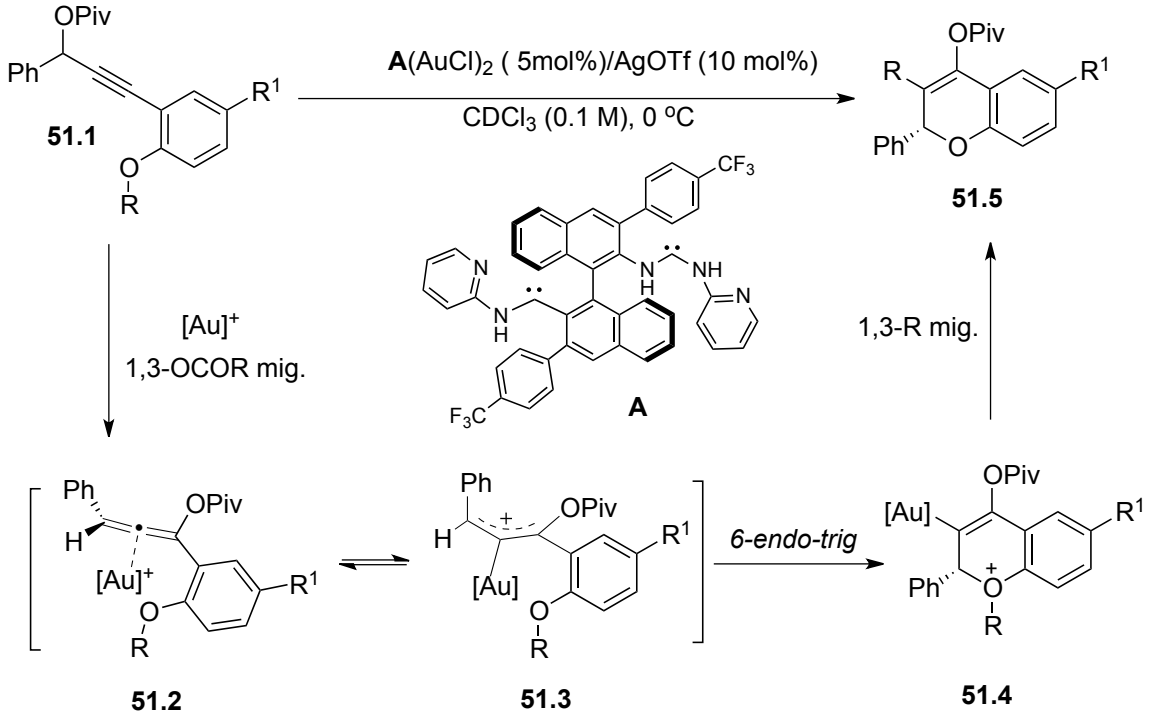


Scheme 50.

9.2.2.2 Double 1,3-OXO/1,3-Alkyl Migration

Toste and co-workers disclosed the gold-catalyzed enantioselective synthesis of chromenyl derivatives **51.5** from the propargylic pivalates **51.1** (Scheme 51).[27] Among all chiral ligands tested, the acyclic 3,3'-functionalized BINAM ligand **A** showed the best

enantioselectivity. The mechanism of the reaction involves an initial 1,3-pivaloxy migration to yield the metal-activated axially chiral allene **51.2**, which in the presence of the gold catalyst transforms into the achiral carbocation **51.3**. The latter, which is stabilized by the oxygen atom of the migrated group, possesses a chiral ligand at the gold moiety. Therefore, the dynamic kinetic asymmetric *6-endo-trig* cyclization leads to the



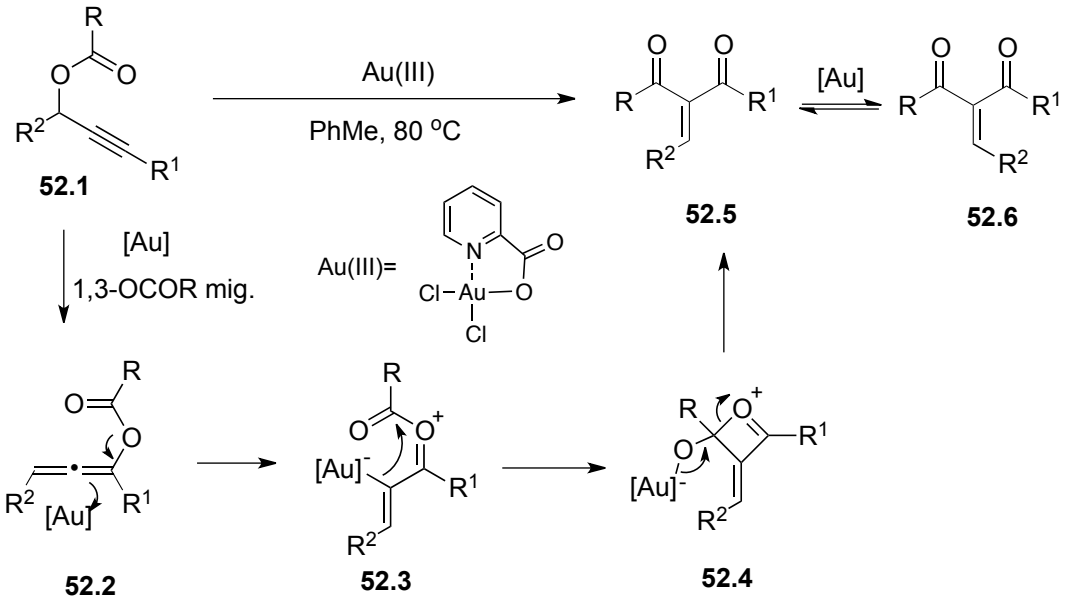
Scheme 51.

oxonium compound **51.2**. Further carbodemetallation of the vinyl gold moiety in the latter via the 1,3-alkyl migration affords the enatioriched C3-substituted chromenyl pivalate **51.5**.

9.2.3. Cascade 1,3-OXO/1,3-Acyl migration

Zhang's group reported the gold(III)-catalyzed cascade reaction of propargylic esters **52.1** into α-ylidene-β-diketones **52.5** and **52.6** (Scheme 52).[28,29] Substrate **52.1**,

possessing different substituents at the terminal alkyne and the propargylic positions, reacted in a highly efficient manner. Notably, not only propargylic pivalates, but also acrylates, benzoates, and carbonates were employed in this double migratory process. According to the mechanistic hypothesis, the propargylic ester **52.1** undergoes a 1,3-acyloxy migration to form the allenyl ester **52.2**, which in the presence of the gold catalyst transforms into a vinyl gold species **52.3**. Intramolecular nucleophilic attack of the vinyl gold moiety at the acylium ion in the latter produces a four membered oxacycle **52.4**, which upon rearrangement affords the (*E*)- α-ylidene-β-diketone **52.5**. The *Z* diastereomer **52.6** is believed to form via isomerization of the *E* analogue in the presence of the Au(III) catalyst.

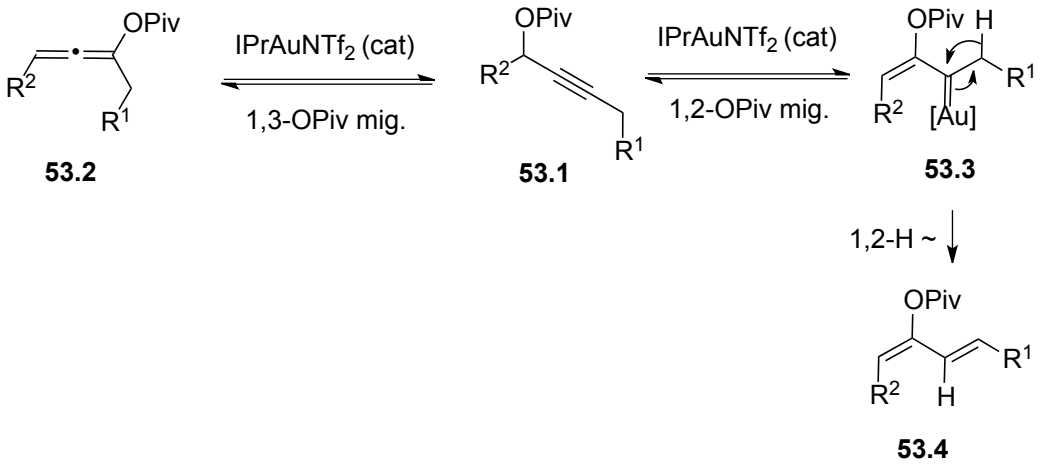


Scheme 52.

9.3. Double Migratory Transformations with an Initial 1,2-OXO Migration

9.3.1. Double 1,2-OXO/1,2-H Migration

In 2008, Zhang's group reported the gold-catalyzed stereoselective reaction of propargylic ester **53.1** toward (1*Z*, 3*E*)-diene **53.4** (Scheme 53).[30] Control over the regioselectivity in this reaction was achieved by taking advantage of the reversible nature of these transformations. Thus, the electronically unbiased propargyl ester **53.1** initially undergoes 1,3-OPiv migration, which is usually preferred for internal alkynes, to produce allene **53.2** (*vide supra*). If the latter does not undergo further reactions,[28] then the

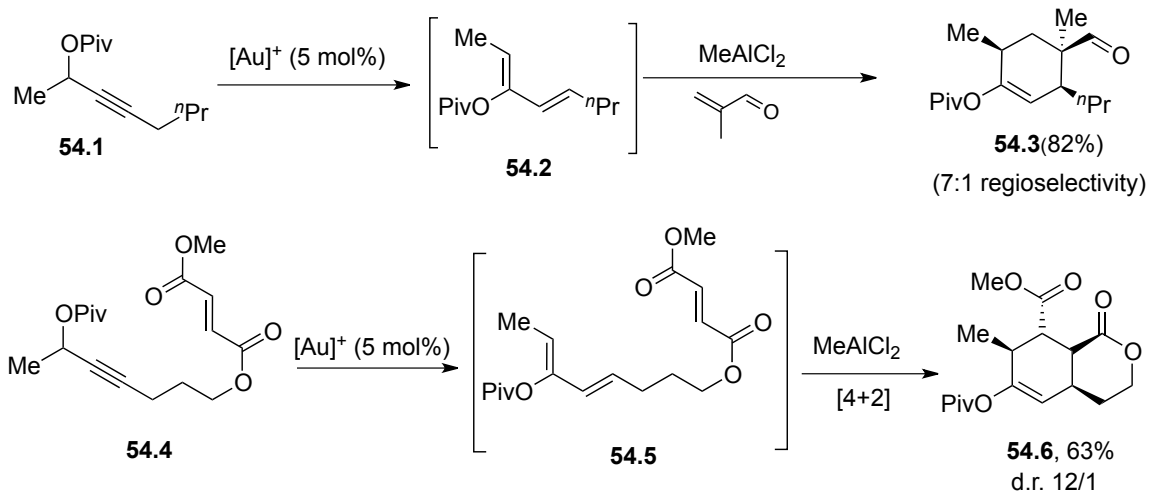


Scheme 53.

equilibrium shifts back to propargylic pivalate **53.1**. The latter then undergoes a 1,2-pivaloxy migration, which is less facile for internal alkynes, to generate the gold carbene **53.3**, which upon an irreversible 1,2-hydride shift produces the 1,3-diene **53.4**.[31]

Notably, the obtained dienes in this chemistry were shown to be good partners in the Diels–Alder reaction (Scheme 54). Under the reaction conditions, the propargylic pivalates **54.1** and **54.4** initially underwent the double migratory cascade reactions to produce expected 1,3-dienes **54.2** and **54.5**, which upon the following inter- and

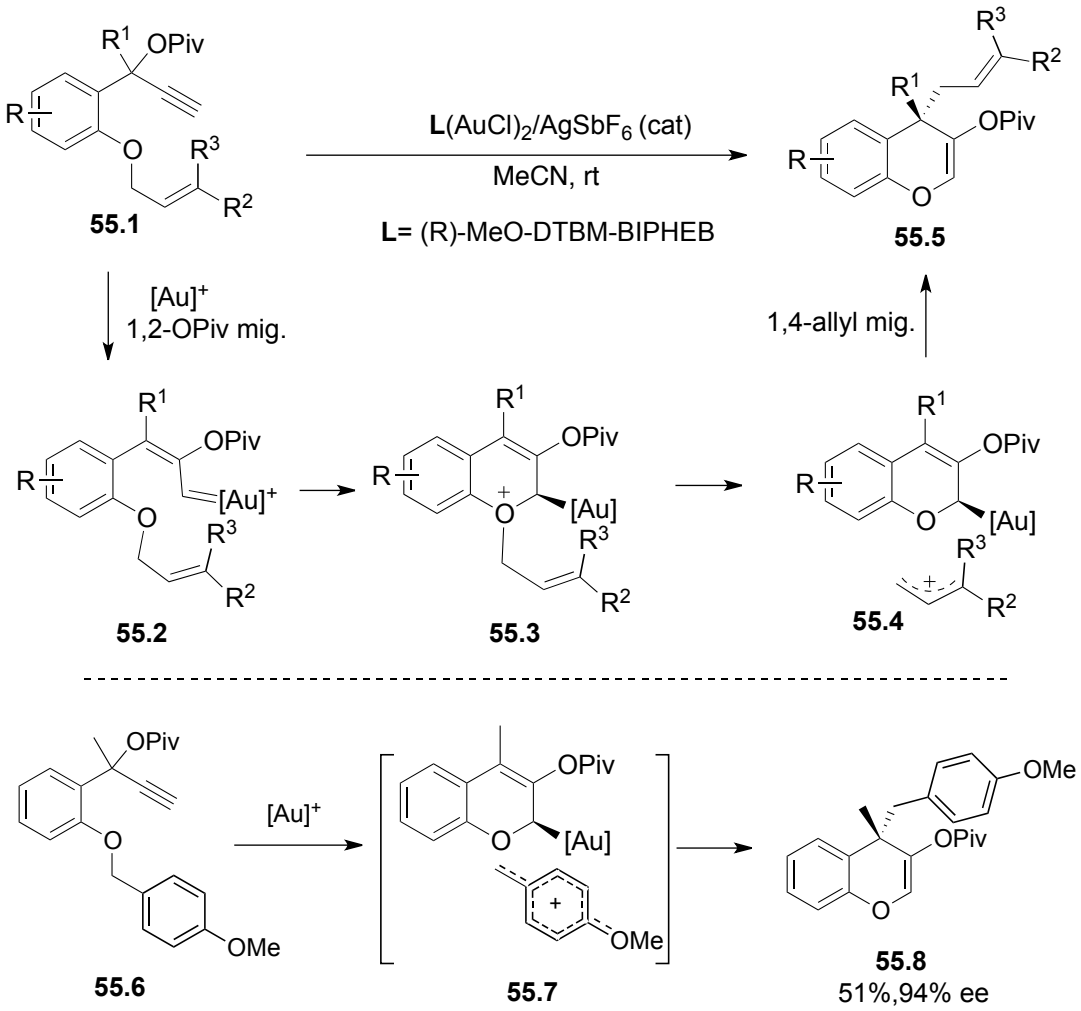
intramolecular Diels–Alder reactions furnished the cycloadducts **54.3** and **54.6**, respectively, in good yields and selectivity.



Scheme 54.

9.3.2. Double 1,2-OXO/1,4-Carbon Migration

It was shown by Toste's group that benzopyran **55.5** can be synthesized via a gold-catalyzed enantioselective cascade 1,2-OPiv-1,4-allyl migration of **55.1** (Scheme 55).[32] Thus, propargyl pivalates **55.1**, possessing a number of different groups at the aromatic ring, the propargylic, and the allylic positions, underwent an efficient and highly enantioselective transformation in the presence of the (R)-MeO-DTBM-BIPHEP-$(AuCl)_2$–$AgSbF_6$ catalyst system. According to the mechanistic hypothesis, substrate **55.1** possessing a terminal alkyne moiety undergoes a gold-promoted 1,2-pivaloxy migration to produce carbene **55.2**, which upon a nucleophilic attack of the ether oxygen atom at the electrophilic center generates the oxonium intermediate **55.3**. Ionization of the allylic group of the latter produces compound **55.4**. The following nucleophilic attack of the allyl gold moiety at the allylic cation furnishes benzopyran **55.5**. [33]



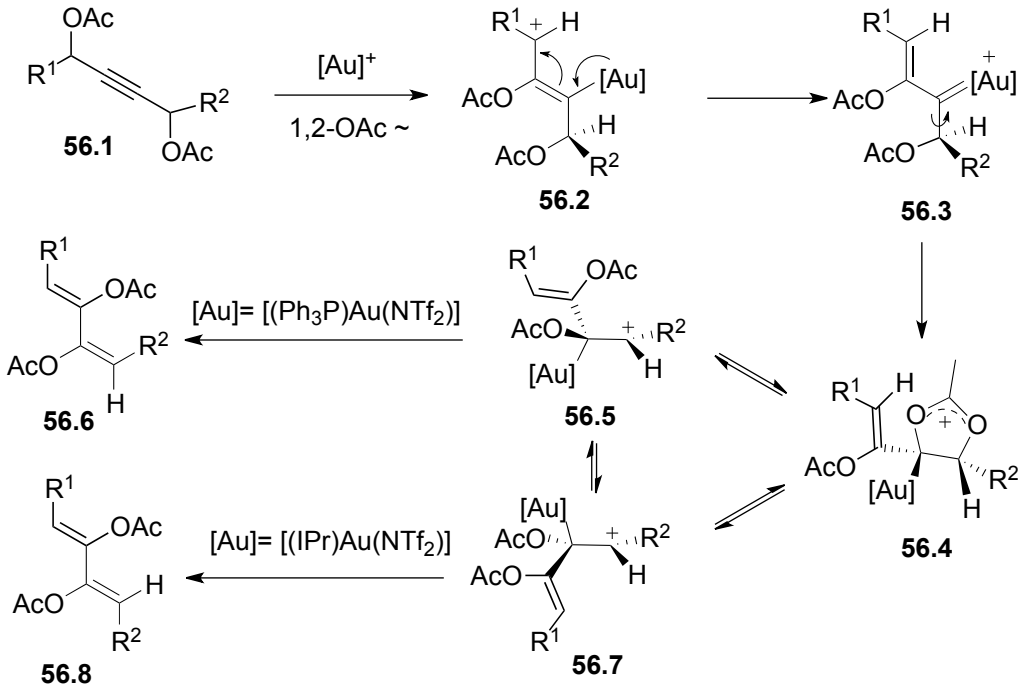
Scheme 55.

Interestingly, when substrate **55.6**, bearing an electron rich para-methoxybenzyl ether moiety, was subjected to the reaction conditions, the benzopyrane **55.8** was formed. This observation provides strong support for the formation of intermediate **55.7** (an analogue of **55.4**), thus suggesting the cationic nature of the second migrating group in this cascade transformation.

9.3.3. Double 1,2-OXO/1,2-OAc migration

Nevado and co-workers disclosed a stereodivergent formation of 1,3-dienes **56.6** and **56.7** via the gold-catalyzed double 1,2-acyloxy migration cascade from the 1,3-bis-

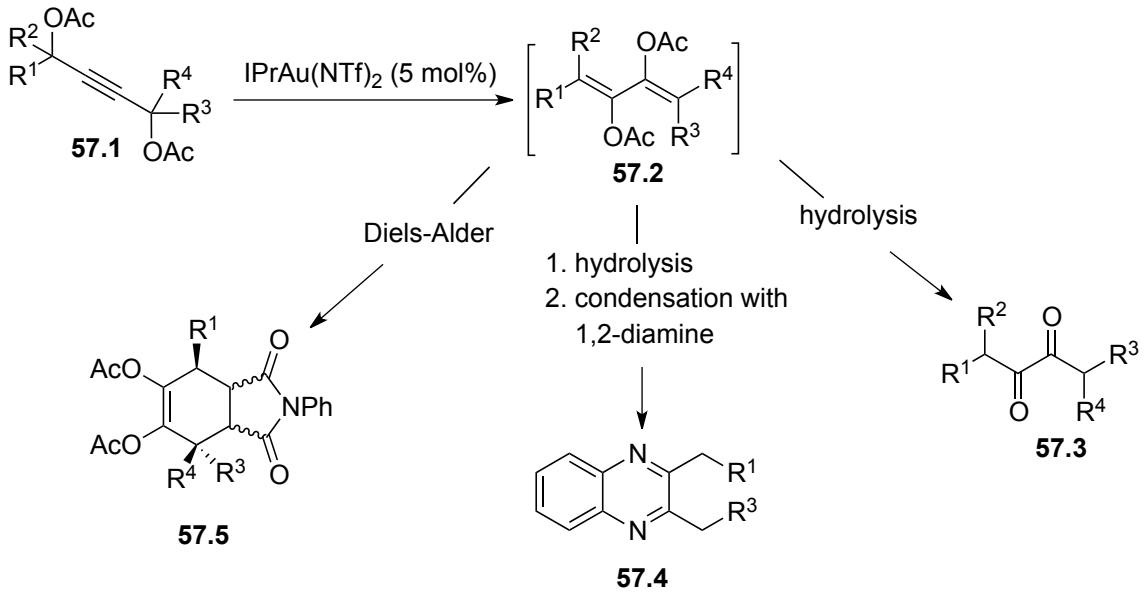
propargyl acetate **56.1** (Scheme 56).[34] Thus, use of the IPrAu(NTf)$_2$ catalyst produces the (*Z*,*Z*)-1,3-dienes **56.6**, while employment of the Ph$_3$PAuNTf$_2$ catalyst gives the (*Z*,*E*)-1,3-diene **56.7**. The proposed mechanism of this reaction involves the gold-promoted 1,2-acyloxy migration to produce cation **56.2**, in which the *Z*-selectivity of the first migration is dictated by avoiding the 1,3-allylic strain between [Au] and R^1 groups. The produced gold carbene **56.3**, upon rotation around the C–C bond and subsequent nucleophilic attack of the adjacent oxygen at the carbene center, gives cyclic intermediate **56.4**. Ring opening of the latter produces cation **56.5**, which in the case of the Ph$_3$PAuNTf$_2$ catalyst directly produces the (*Z*,*E*)-1,3-diene **56.6**. On the other hand, **56.5**, possessing the bulky IPr ligand of [(IPr)Au(NTf)$_2$] isomerizes to the more stable cation **56.7**, which upon elimination of gold species produces the (*Z*,*Z*)-1,3-diene **56.8**. In the following report, the



Scheme 56.

same group clarified more mechanistic details, such as substitution effects at the propargylic position of **56.1** on the stereochemical outcome of this cascade reaction.[34b]

Importantly, the synthetic utility of obtained products via this chemistry was demonstrated (Scheme 57).[34b] Thus, after the double migratory cascade reaction of the 1,4-bis-propargylic acetates **57.1**, the obtained diene **57.2** could be hydrolyzed to produce the unsymmetrical 1,2-diketone **57.3**. A one-pot cascade double migration–hydrolysis followed by condensation with aromatic 1,2-diamines produced quinoxaline **57.4**. The obtained diene was also shown to be a good partner in Diels–Alder reaction with N-phenylmaleimide to produce the cycloadduct **57.4** with moderate endo selectivity.

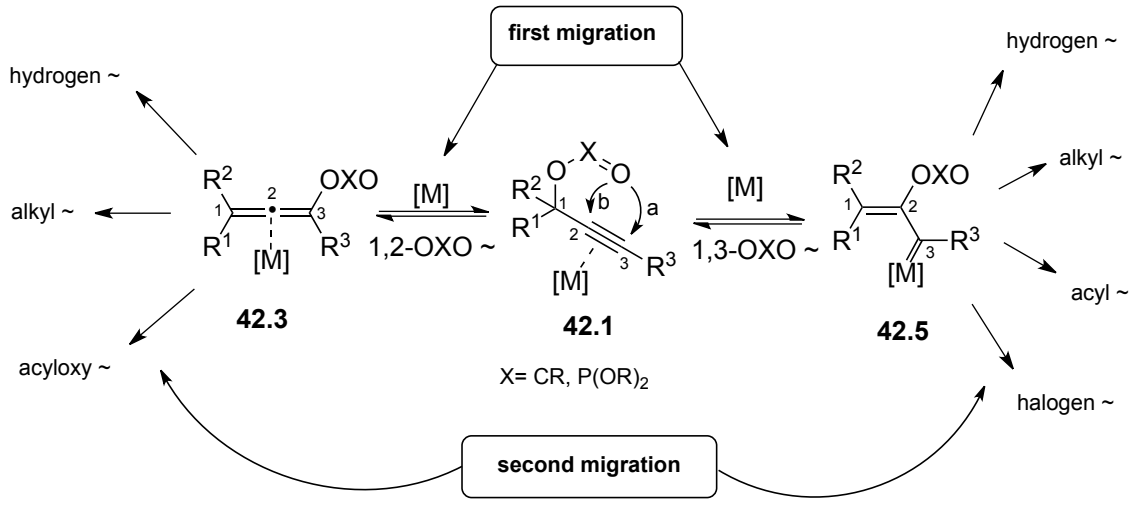


Scheme 57.

9.4. Summary

It was demonstrated that the transition metal-catalyzed 1,3- and 1,2-OXO migrations of propargylic esters and phosphates **42.1**, which produce activated allene

42.3 and metal carbene **42.5**, can efficiently be followed by a second migration of different groups (Scheme 58). It was shown that the 1,2-H migration in the second process leads to mono-,[19,21] bi-,[20] tri-,[24] tetra,[22] and heterocyclic[22,23] scaffolds, as well as to acyclic 1,3-dienes.[30,31] Moreover, employment of an alkyl as the second migrating group in these cascade reactions, gave access to a variety of products including naphthalenes,[25] dienes,[25,26b,26c,33] quinolines,[22d] and substituted chromens.[27,32] In addition, double migratory processes involving acyl and acyloxy migrating groups afford β-[28] and δ-diketones,[29] as well as substituted 1,3-dienes.[34] These cascade reactions are triggered by simple and available catalysts, are highly efficient, and usually take place under mild conditions.

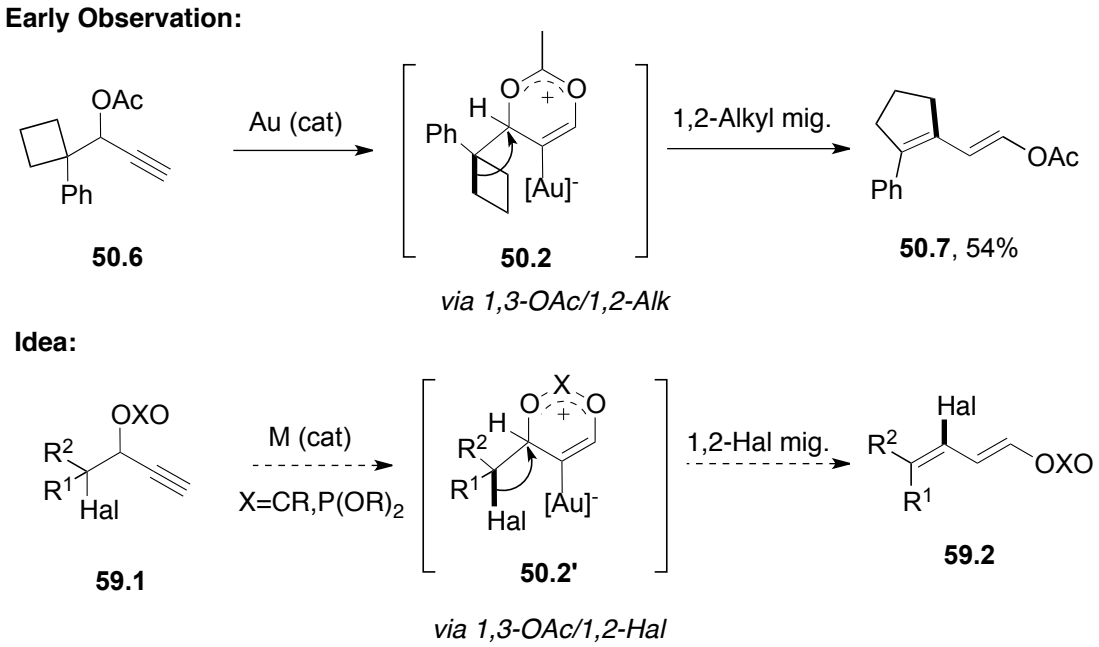


Scheme 58.

A wide range of functional groups such as halogen, allyl, phenoxide, cyclopropane, vinyl silane, olefine, alkyne, acetal, ester, protected alcohol, and protected amine are tolerated in these transformations. Importantly, the products of the double migratory reactions could be further functionalized, thus offering a set of novel powerful tools for organic synthesis.

10. METAL-CATALYZED DOUBLE 1,3-PHOSPHATYLOXY/1,3-HALOGEN MIGRATION CASCADE TOWARD FUNCTIONALIZED DIENES

Processes involving 1,*n*-halogen migrations are powerful tools for obtaining valuable functionalized synthons for organic chemistry. Among known methods are the base-mediated 1,2-migration of halogen atoms to the anionic center (the halogen dance reaction);[35] migrations via halonium,[36] allyl cation,[37] and α-halo metal carbene[38] intermediates; halogen shifts during radical processes;[39] and metal-mediated alkyne−vinylidene isomerizations.[40] Furthermore, various migrations of a range of other functionalizable groups are well-precedented.[41] However, double migration reactions employing two functionalizable groups are exceedingly rare.[42] Inspired by our group's single example on the double 1,3-acetoxy/1,2-alkyl migration reaction in propargylic ester **50.6** to synthesize 1,3-diene **50.7** via intermediacy of **50.2**,[25] we hypothesized that it should be possible to expand the scope of the second migrating group to halogen atoms. Thus, employment of α-halo propargylic ester or phosphate **59.1** (analogue of **50.6**) in the metal-catalyzed reaction should produce **59.2** (analogue of **50.2**). If so, the difunctionalized 1,3-dienes, possessing two valuable vinyl halide and vinyl acetate/phosphate functionalities should be obtained (Scheme 59).

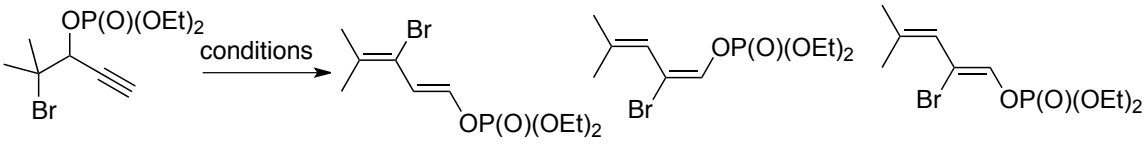


Scheme 59.

10.1. Optimization of the Double Migratory Process

The isomerization reaction of α-bromo propargylic phosphate **59.1a** to 1,3-diene **59.1b** was examined under a variety of conditions (Table IX). It was found that **59.1a** to be unaffected by the original catalytic system used for diene synthesis (entry 1).[25] Likewise, employing gold (I) complexes with alternative counterions such as SbF_6 or BF_4 did not provide product formation at all (entries 2, 3). Similarly, silver and platinum catalysts provided no reaction as well (entries 4, 5). However, employment of gold(I) and gold(III) halides *unexpectedly* produced a mixture of stereoisomeric 1,3-dienes **59.3a** and **59.4a**, the products of double 1,3/1,3-migration sequence (entries 6-8), with no 1,3-diene **59.2a** observed. Employment of Ph_3PAuCl catalyst resulted in good *E*-stereoselectivity of the reaction and moderate yield (entry 9). Use of a more electron deficient phosphine ligand led to E-diene **59.3a** in an excellent yield and good stereoselectivity (entry 10). Further catalyst screening led to another surprising observation: the $[CuOTf]_2$•PhH catalyst

Table XIII. OPTIMIZATION OF DOUBLE MIGRATORY CASCADE REACTION



59.1a **59.2a** **59.3a** **59.4a**

Entry	Catalyst (mol%)	Solvent/*T*, °C	**59:2a:59.3a:59.4a**	Yield (%)[a]
1	$Ph_3PAuOTf$ (5)	DCE/rt	-	0
2	$Ph_3PAuSbF_6$ (5)	DCE/rt	-	0
3	Ph_3PAuBF_4 (5)	DCE/rt	-	0
4	AgOTf (10)	DCE/50	-	0
5	$PtCl_2$ (5)	DCM/40	-	0
6	AuI (5)	PhH/50	0:86:14	ND [c]
7	$AuCl_3$ (5)	PhH/40	0:60:40	ND [c]
8	$LAuCl_2$[b] (5)	DCE/80	0:66:33	ND [c]
9	Ph_3PAuCl (5)	DCE/80	0:90:10	65
10	**(p-$F_3CC_6H_4)_3PAuCl$ (5)**	**PhMe/100**	**0:90:10**	**96**
11	$[CuOTf]_2$•PhH (10)	DCE/50	0:4:96	50
12	**$[CuOTf]_2$•PhH (10)**	**DCE/80**	**0:0:100**	**85**
13	None	PhMe/100	-	0

[a] Isolated yields.

[b] L = 2-pyridinecarboxylato.

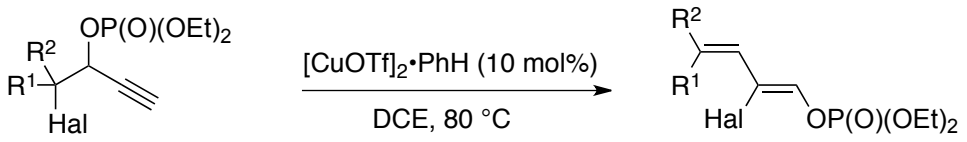
[c] Yield was not determined.

provided the 1,3/1,3-migration product **59.4a** with excellent Z-selectivity (entry 11)! Gratifyingly, performing the reaction at a higher temperature resulted in the efficient and exclusive formation of *Z*-1,3-diene **59.4a** (entry 12). In addition, a control experiment indicated that no product formation occurred in the absence of the catalyst (entry 13).

10.2. Scope of the Copper-Catalyzed Synthesis of (*Z*)-1,3-Dienes

Inspired by these observations, we first investigated the scope of the Cu-catalyzed *Z*-selective reaction under the optimized conditions (Table X). Thus, acyclic compounds **59.1a-c** underwent this tandem transformation to efficiently produce dienes **59.4a-c** (entries 1-3). Chlorine-containing compound **59.1b** gave a better yield of the isomerization product compared to its bromine-bearing analog **59.1a**. Propargylic phosphate possessing cyclic substituent **59.1d** was also effectively converted into the exocyclic diene **59.4d** in both good yield and stereoselectivity. Likewise, heterocyclic compound **59.1e** also provided 1,3-diene **59.4e** as a sole *Z*-isomer in a good yield. To our delight, cyclic ketone-derived substrates **59.1f-j** provided the corresponding products in moderate to excellent yields. Notably, these substrates possessing hydrogen atom adjacent to a halogen provided 1,3-diene **59.4f-j**, *the products of the exclusive halogen over hydrogen atom migration*. Isomerization of five-membered ring-containing substrates **59.1f-g** gave diene products **59.4f-g** as sole stereoisomers in excellent yields (entries 6-7). Similarly, substrates **59.1h-j** bearing six-membered ring furnished the desired products in good yields.[43] Remarkably, compound **59.1j** underwent a 1,3-iodine migration in this tandem transformation to produce the *Z*-diene **59.2j** as a single stereoisomer in moderate yield (entry 10). *To the best of our knowledge, this is the first example of 1,3-migration of iodine*.[36,37,39]

Table XIV. COPPER-CATALYZED SYNTHESIS OF (*Z*)-1,3-DIENES



59.1a **59.4a**

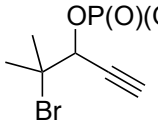
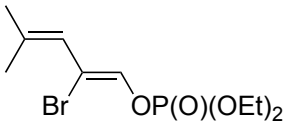
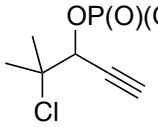
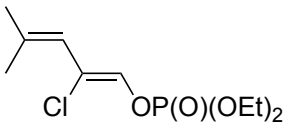
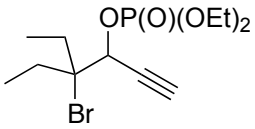
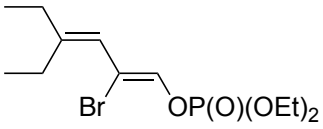
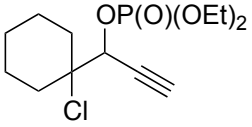
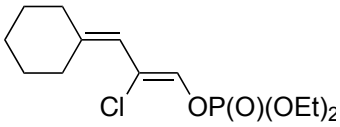
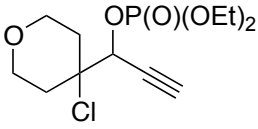
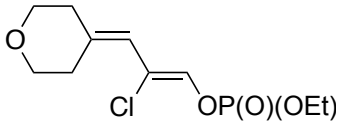
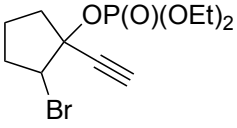
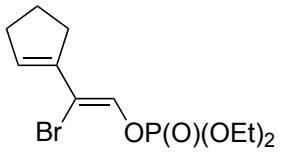
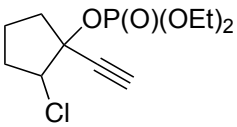
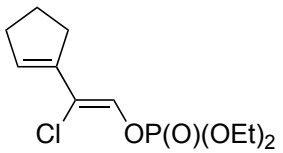
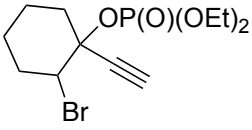
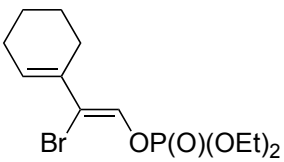
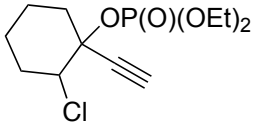
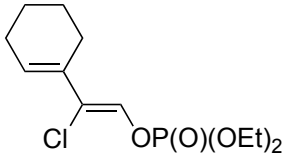
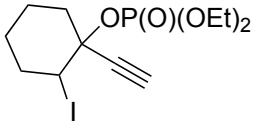
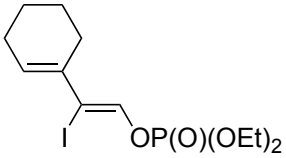
Entry	Substrate		Product[a]		Yield (%)[b]
1		**59.1a**		**59.4a**	86
2		**59.1b**		**59.4b**	95
3		**59.1c**		**59.4c**	69[c]
4		**59.1d**		**59.4d**	75[d]
5		**59.1e**		**59.4e**	77
6		**59.1f**		**59.4f**	91
7		**59.1g**		**59.4g**	95
8		**59.1h**		**59.4h**	79

Table XV. COPPER-CATALYZED SYNTHESIS OF (*Z*)-1,3-DIENES (continued)

Entry	Substrate		Product[a]	Yield (%)[b]	Entry
9		**59.1i**		**59.4i**	86
10		**59.1j**		**59.4j**	64

[a] Major stereoisomer shown.

[b] Isolated yield.

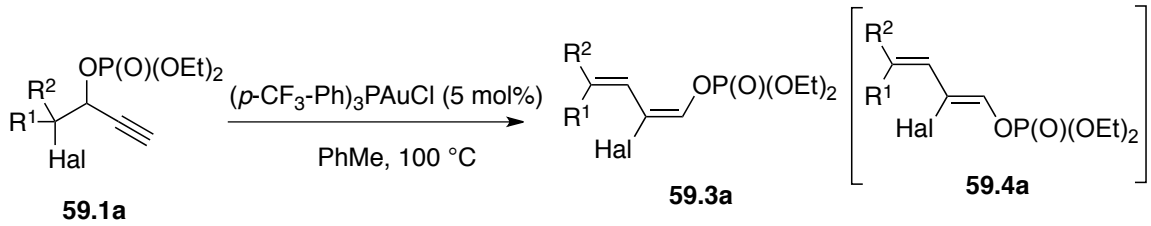
[c] *Z*:*E* =95:5.

[d] *Z*:*E* =90:10.

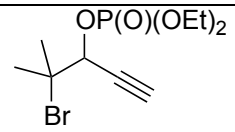
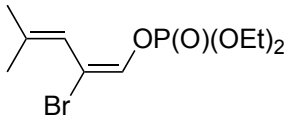
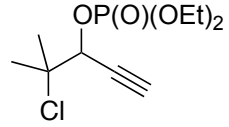
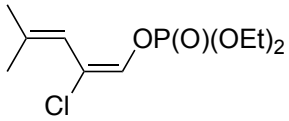
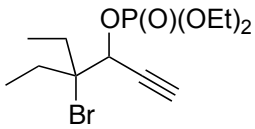
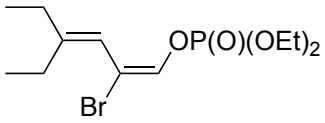
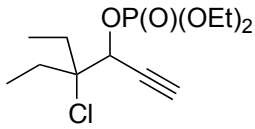
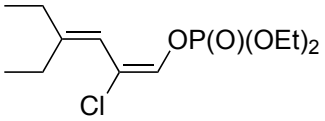
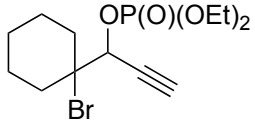
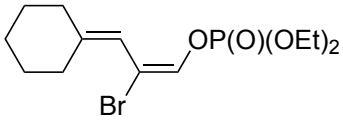
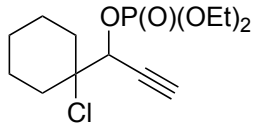
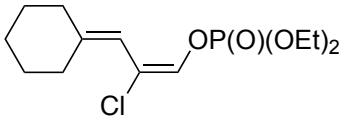
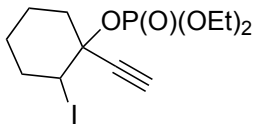
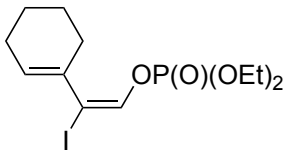
10.3. Scope of the Gold-Catalyzed Synthesis of (*E*)-1,3-Dienes

Next, we investigated the Au-catalyzed cascade 1,3-phosphatyloxy/1,3-halogen double migration reaction leading to *E*-1,3-diene products (Table XI). Several halogenated propargylic phosphates bearing acyclic substituents were converted into the corresponding *E*-dienes **59.3a-c,m** in excellent yields and with good to excellent selectivities (entries 1-4). Likewise, exocyclic *E*-dienes **59.3d,n** could also be efficiently obtained via this transformation. Finally, cyclohexyl-containing substrate **59.1j** underwent this cascade transformation with exclusive 1,3-migration of iodine atom to produce the corresponding 1,3-diene **59.3j** in high yield, albeit with a lower level of stereocontrol.

Table XVI. GOLD-CATALYZED SYNTHESIS OF (*E*)-1,3-DIENES



59.1a **59.3a** **59.4a**

Entry	Substrate		Product[a]		Yield (%)[b] (E:Z ratio)[c]
1		**59.1a**		**59.3a**	95 (90:10)
2		**59.1b**		**59.3b**	89 (84:14)
3		**59.1c**		**59.3c**	97 (89:11)
4		**59.1m**		**59.3m**	98 (93:7)
5		**59.1n**		**59.3n**	91 (90:10)
6		**59.1d**		**59.3d**	90 (95:5)
7		**59.1j**		**59.3j**	89 (60:40)

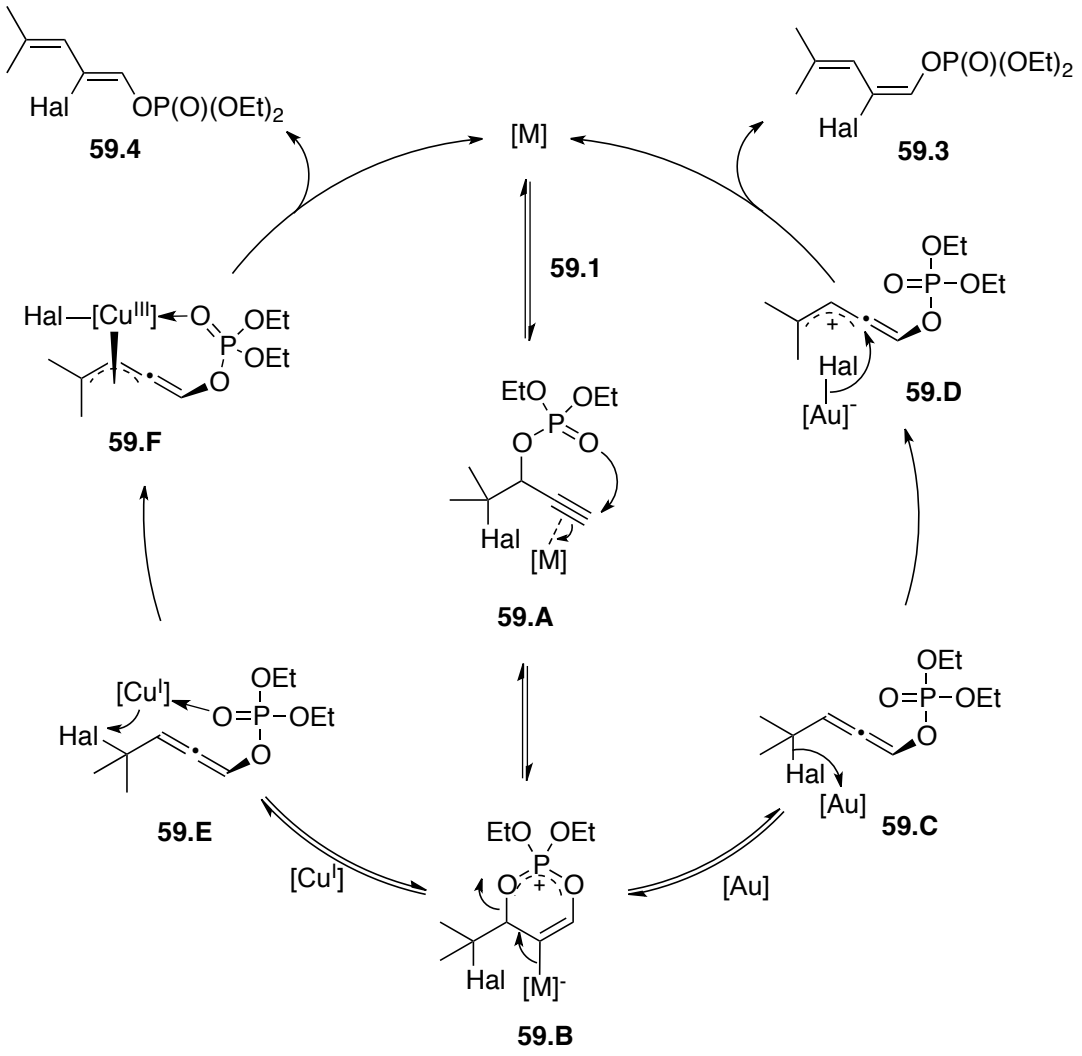
[a] Major stereoisomer shown.

[b] Isolated yield.

[c] NMR ratios.

10.4. Proposed Mechanism for the Reaction

We propose the following plausible mechanism for these cascade transformations (Scheme 60). First, coordination of the metal to the π-system of the alkyne **59.1** renders a 1,3-migration of phosphatyloxy group to produce the cyclic intermediate **59.1B**, which upon elimination of the metal produces allenyl phosphate **59C** or **59E**.[2] In the case of Au catalyst, π-allyl cation **59D**[44] is produced upon a halogen abstraction from **59B**. A subsequent delivery of a halide from gold halide species to **59D** occurs *anti* to the phosphate group giving the *E*-diene **59.3**. Alternatively, in the case of copper catalysis, additional coordination of the metal to the phosphate group of allene takes place (**59E)**. The halogen abstraction by copper produces phosphate-coordinated π-allyl complex **59F**.[45] In this way, a subsequent delivery of the halogen is directed by the phosphate group and occurs *syn* to it, thus producing the corresponding isomeric *Z*-product **59.4**.[46]

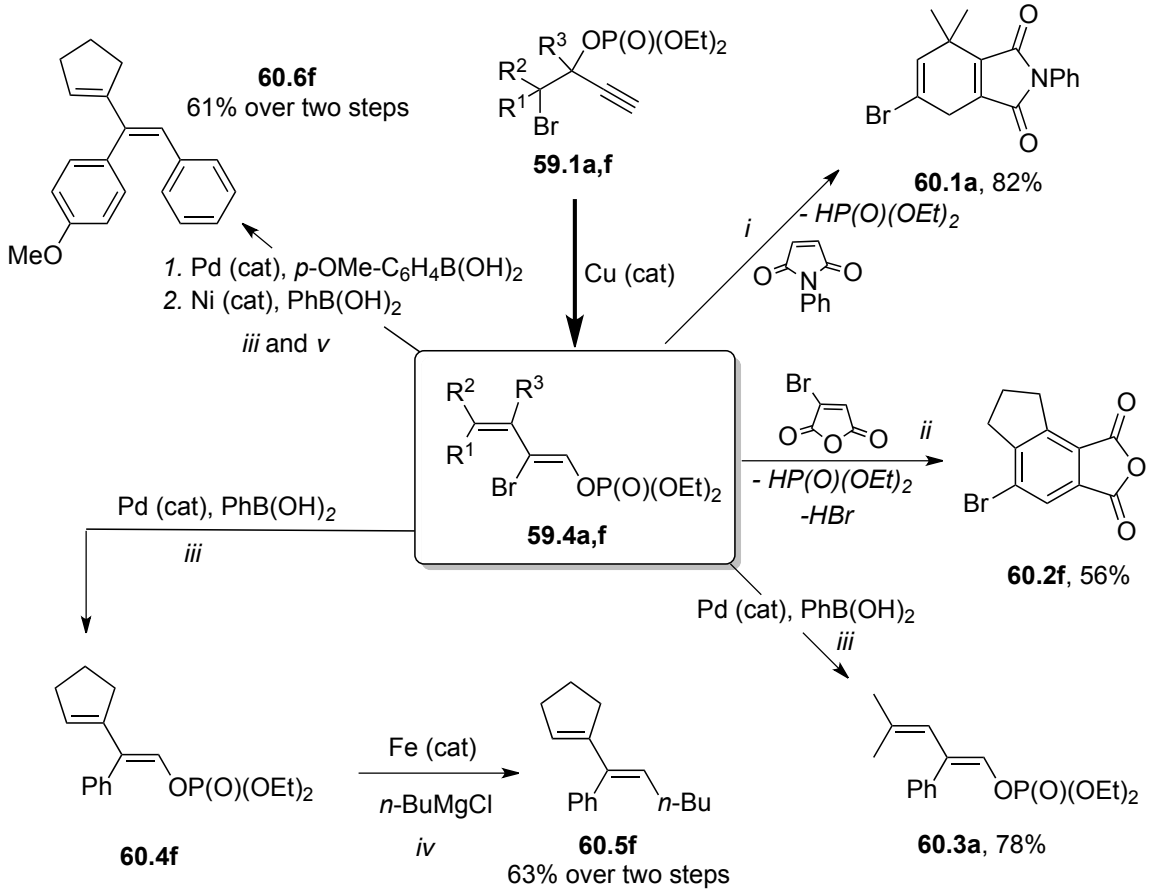


Scheme 60.

10.5. Functionalization of obtained (Z)-1,3-Dienes

Next, synthetic utility of 1,3-dienes **59.4a,f** obtained in the Cu-catalyzed isomerization reactions of **59.1a,f** was examined (Scheme 61). Hence, the Diels−Alder reactions[47] of **59.4a** with *N*-phenylmaleimide and **59.4f** with bromomaleic anhydride efficiently produced cycloadduct **60.1a** and pentasubstituted benzene derivative **60.2f**, respectively. Furthermore, the Miyaura−Suzuki cross-coupling reactions[48] of dienes **59.4a** and **59.4f** with phenylboronic acid proceeded well, giving phenylated 1,3-dienes

60.3a and **60.4f** in 78 and 91% yields, respectively. Notably, the phosphatyloxy terminus of (Z)-diene **60.4f** could also be functionalized after the Miyaura−Suzuki cross-coupling reaction of the vinyl bromide moiety. Thus, the latter underwent the Kumada cross-coupling reaction of the phosphatyloxy moiety in the presence of an iron catalyst[49] to give diene **60.5f**. Finally, a sequential Miyaura−Suzuki reaction on the vinyl bromide and phosphate[50] groups of diene **59.4f** furnished highly functionalized diene **60.6f** in a good overall yield.



Scheme 61.

i. *N*-Phenylmaleimide (1.5 equiv), anisole, 150 °C, 12 h.

ii. Bromomaleic anhydride (1.5 equiv), anisole, 150 °C, 12 h.

iii. $Pd_2(dba)_3$ (4 mol %), XPhos (8 mol %), $ArB(OH)_2$ (2.0 equiv), K_3PO_4 (3.0 eqiv), toluene, 80 °C, 15 h.

iv. $Fe(acac)_3$ (6 mol %), TMEDA (2.0 equiv), *n*-BuMgCl (1.5 equiv), THF, 0 °C.

v. $Ni(cod)_2$ (5 mol %), $PCy_3 \cdot HBF_4$ (10 mol %), $PhB(OH)_2$ (2.0 equiv), K_3PO_4 (3.0 equiv), THF, 75 °C.

10.6. Summary

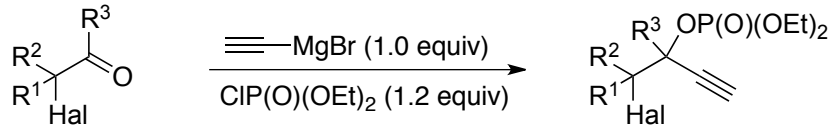
In summary, a stereocontrolled isomerization of α-halosubstituted propargylic phosphates into valuable highly functionalized 1,3-dienes has been developed. This methodology features a double 1,3-phosphatyloxy and 1,3-halogen migration relay. Depending on the choice of catalyst, synthesis of either (*Z*)- or (*E*)-1,3-dienes could be achieved selectively in typically high yields. Thus, (*Z*)-dienes could be obtained exclusively in the presence of a copper catalyst, whereas the use of a gold catalyst afforded predominantly (*E*)-dienes. Notably, these transformations feature an unprecedented 1,3-migration of iodine atoms. Finally, the synthetic utility of the obtained 1,3-dienes was demonstrated in efficient Diels−Alder and cross-coupling reactions.

11. EXPERIMENTAL SECTION

11.1. General Information

NMR spectra were recorded on Bruker Avance DRX-500 (500 MHz) or DRX-400 (400 MHz) instruments. GC/MS analysis was performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). Column chromatography was carried out employing Silicycle silica gel (Kieselgel 60, 63-200 μm). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography. All manipulations with transition metal catalysts were conducted under inert atmosphere using a combination of glovebox and standard Schlenk techniques. Anhydrous toluene, tetrahydrofuran, ether, and dichloromethane purchased from Aldrich were additionally purified on PureSolv PS-400-4 by Innovative Technology, Inc. purification system. Anhydrous solvents other than listed above were purchased from Aldrich and stored over calcium hydride. All other reagents were purchased from Aldrich, Strem Chemicals Inc., Alfa Aesar or Acros Organics, or synthesized via known literature procedures. Reactions were typically run in oven-dried glassware under inert atmosphere. α-bromo,[51] chloro,[52] Fluoro,[53] and iodoaldehydes[54] were synthesized according to literature reports.

11.2. Synthesis of α-Halo Propargylic Phosphates



59.1

Neat α-halo carbonyl compound (or its solution in anhydrous THF) (1.0 equiv) was added dropwise to an ice-cooled flask containing a [1.0 M] solution of ethynylmagnesium bromide in THF (1.0 equiv) while stirring. After addition the reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. Reaction mixture was then placed in an ice-water bath and neat diethylchlorophosphate (1.2 equiv) was added dropwise. Reaction mixture was allowed to warm to room temperature and stirred until judged complete by TLC and GC/MS analyses. After completion, reaction mixture was poured into ammonium chloride solution and extracted three times with ethyl acetate. Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure and the residue was purified by column chromatography (Hex/EtOAc= 1/2) to give the corresponding α-halo propargyl phosphate.

Synthesis of 4-bromo-4-methylpent-1-yn-3-yl diethyl phosphate (59.1a) 2-bromo-2-methylpropanal (30 mmol, 4.53 g), ethynylmagnesium bromide (30 mmol, 0.54 M, 55.5 mL) and neat diethylchlorophosphate (36 mmol, 6.2 g) were used. (55%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.27 - 1.31 (m, 6 H), 1.77 (s, 6H), 2.62 - 2.65 (m, 1 H), 4.07 - 4.17 (m, 4 H), 4.93 - 4.98 (m, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (t, J_{CP}=7.40

Hz), 29.3, 29.6, 62.8 (d, J_{CP}=7.40 Hz), 64.3 (dd, J_{CP}=11.10, 5.55 Hz), 74.9 (d, J_{CP}=5.55 Hz), 76.4, 78.2. **HRMS** (EI) calcd. for $C_{10}H_{18}BrO_4P$: 313.0207, Found: 313.0212.

Synthesis of 4-chloro-4-methylpent-1-yn-3-yl diethyl phosphate (59.1b) 2-chloro-2-methylpropanal (5 mmol, 533 mg), ethynylmagnesium bromide (5 mmol, 0.54 M, 9.3 mL) and neat diethylchlorophosphate (6 mmol, 1.03g) were used. (59%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.30 (m, 6 H), 1.61 (s, 3 H), 1.62 (s, 3 H), 2.61 (d, *J*=2.20 Hz, 1 H), 4.06 - 4.18 (m, 4 H), 4.93 (dd, *J*=7.70, 2.20 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (t, J_{CP}=5.55 Hz), 27.6, 28.1, 64.2 (dd, J_{CP}=9.25, 5.55 Hz), 68.5 (d, J_{CP}=7.4), 74.4 (d, J_{CP}=5.55 Hz), 76.3, 78.1. **HRMS** (EI) calcd. for $C_{10}H_{18}ClO_4P$: 269.0710, Found: 269.0705.

Synthesis of 4-bromo-4-ethylhex-1-yn-3-yl diethyl phosphate (59.1c) 2-bromo-2-ethylbutanal (5 mmol, 895 mg), ethynylmagnesium bromide (5 mmol, 0.54 M, 9.3 mL) and neat diethylchlorophosphate (6 mmol, 1.03g) were used. (63%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.02 (ddd, *J*=7.34, 3.67 Hz, 6 H), 1.29 - 1.36 (m, 6 H), 1.90 - 1.97 (m, 2 H), 1.98 - 2.07 (m, 2 H), 2.63 (d, *J*=2.20 Hz, 3 H), 4.11 - 4.19 (m, 4 H), 5.14 (dd, *J*=7.34, 2.20 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 9.50, 16.1 (t, J_{CP}=7.40 Hz), 30.5, 31.1, 64.2 (d, J_{CP}=7.40 Hz), 72.5 (d, J_{CP}=5.55 Hz), 75.5 (d, J_{CP}=7.41 Hz), 76.7, 78.3. **HRMS** (EI) calcd. for $C_{12}H_{22}BrO_4P$: 341.0517, Found: 341.0514.

Synthesis of 4-chloro-4-ethylhex-1-yn-3-yl diethyl phosphate (1m) 2-chloro-2-ethylpentanal (5 mmol, 673 mg), ethynylmagnesium bromide (5 mmol, 0.54 M, 9.3 mL) and neat diethylchlorophosphate (6 mmol, 1.03g) were used. (65%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm ppm 1.04 (dt, *J*=7.43, 1.65 Hz, 6 H), 1.32 - 1.39 (m, 6 H), 1.95 - 2.02 (m,

4 H) 2.63 (d, *J*=2.20 Hz, 1 H) 4.12 - 4.22 (m, 4 H) 5.15 (dd, *J*=7.70, 2.20 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 8.3, 16.1 (t, J_{CP}=7.40 Hz), 29.4, 30.0, 64.2 (d, J_{CP}=7.40 Hz), 72.3 (d, J_{CP}=7.40 Hz), 76.6, 78.2. HRMS (EI) calcd. for $C_{12}H_{22}ClO_4P$: 297.1023, Found: 297.1016.

Synthesis of 1-(1-bromocyclohexyl)prop-2-yn-1-yl diethyl phosphate (59.1n) 1-bromocyclohexanecarbaldehyde (5 mmol, 955 mg), ethynylmagnesium bromide (5 mmol, 0.54 M, 9.3 mL) and neat diethylchlorophosphate (6 mmol, 1.03g) were used. (67%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.31 - 1.37 (m, 6 H), 1.60 - 1.83 (m, 8 H), 2.03 - 2.23 (m, 2 H), 2.64 (d, *J*=2.20 Hz, 1 H), 4.11 - 4.21 (m, 4 H), 5.02 (dd, *J*=7.70, 2.20 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.1 (t, J_{CP}=7.40 Hz), 22.3 (d, J_{CP}=7.40 Hz) 25.1, 35.8, 64.3 (d, J_{CP}=5.55 Hz), 75.0 (d, J_{CP}=5.55 Hz), 76.4, 78.5. **HRMS** (EI) calcd. for $C_{13}H_{22}BrO_4P$: 353.0517, Found: 353.0516.

Synthesis of 1-(1-chlorocyclohexyl)prop-2-yn-1-yl diethyl phosphate (59.1d) (63%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.26 (t, *J*=7.02 Hz, 6 H), 1.50 - 1.73 (m, 8 H), 1.84 - 1.96 (m, 2 H), 2.60 (s, 1 H), 3.98 - 4.16 (m, 4 H), 4.91 (d, *J*=8.18 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (d, J_{CP}=5.90 Hz), 21.3 (d, J_{CP}=5.90 Hz), 25.0, 34.4, 34.6, 64.2 (t, J_{CP}=5.90 Hz), 74.0 (d, J_{CP}=8.85 Hz), 74.6 (d, J_{CP}=5.90 Hz), 76.8, 78.0. **HRMS** (EI) calcd. for $C_{13}H_{22}ClO_4P$: 309.1023, Found: 309.1011.

1-(4-chlorotetrahydro-2H-pyran-4-yl)prop-2-yn-1-yl diethyl phosphate (59.1e) 4-chlorotetrahydro-2H-pyran-4-carbaldehyde (5 mmol, 743 mg), ethynylmagnesium bromide (5 mmol, 0.54 M, 9.3 mL) and neat diethylchlorophosphate (6 mmol, 1.03g) were used. (69%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.29 - 1.35 (m, 6 H), 1.82 (t,

J=15.13 Hz, 2 H), 2.02 - 2.12 (m, 2 H), 2.66 (d, *J*=2.02 Hz, 1 H), 3.77 (t, *J*=11.65 Hz, 2 H), 3.84 - 3.91 (m, 2 H), 4.08 - 4.19 (m, 4 H), 4.98 (dd, *J*=8.07, 1.47 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (t, J_{CP}=7.40 Hz), 34.4, 34.7, 63.1, 63.2, 64.3 (t, J_{CP}=6.47 Hz), 67.3 (d, J_{CP}=8.32 Hz), 70.9 (d, J_{CP}=8.32 Hz) 74.1 (d, J_{CP}=4.62 Hz). **HRMS** (EI) calcd. for $C_{12}H_{20}ClO_5P$: 311.08371, Found: 311.07961.

Synthesis of 2-bromo-1-ethynylcyclopentyl diethyl phosphate (59.1f) 2-bromocyclopentanone (5 mmol, 815 mg), ethynylmagnesium bromide (5 mmol, 0.54 M, 9.3 mL) and neat diethylchlorophosphate (6 mmol, 1.03g) were used. (53%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.31 (dq, *J*=6.97, 1.10 Hz, 6 H), 1.70 - 1.83 (m, 1 H), 1.89 - 1.98 (m, 1 H), 2.05 - 2.17 (m, 2 H), 2.31 - 2.46 (m, 1 H), 2.61 - 2.75 (m, 2 H), 4.03 - 4.22 (m, 4 H), 4.25 (dt, *J*=7.52, 3.30 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (t, J_{CP}=11.02 Hz), 19.8, 32.9, 36.8, 64.2 (d, J_{CP}=7.40 Hz), 75.7, 80.5, 81.0 (d, J_{CP}=7.40 Hz). **HRMS** (EI) calcd. for $C_{11}H_{18}BrO_4P$: 325.0204, Found: 325.0204.

Synthesis of 2-chloro-1-ethynylcyclopentyl diethyl phosphate (59.1g) 2-chlorocyclopentanone (5 mmol, 593 mg), ethynylmagnesium bromide (5 mmol, 0.54 M, 9.3 mL) and neat diethylchlorophosphate (6 mmol, 1.03g) were used to afford the product as a brown solid. (m.p= 41 °C). (51%), **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.32 - 1.37 (m, 6 H), 1.75 - 1.88 (m, 1 H), 1.93 - 2.09 (m, 2 H), 2.14 - 2.23 (m, 1 H), 2.31 - 2.41 (m, 1 H), 2.64 - 2.71 (m, 1 H), 2.72 (s, 1 H), 4.08 - 4.26 (m, 4 H), 4.30 (dt, *J*=6.60, 2.57 Hz, 5 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.1 (d, J_{CP}=3.70 Hz), 19.1, 32.1, 36.7 64.2 (d, J_{CP}=7.36 Hz), 66.5 (d, J_{CP}=7.40 Hz), 75.9, 81.1 (d, J_{CP}=7.40 Hz). **HRMS** (EI) calcd. for $C_{11}H_{18}ClO_4P$: 281.0710, Found: 281.0707.

Synthesis of 2-bromo-1-ethynylcyclohexyl diethyl phosphate (59.1h) 2-bromocyclohexanone (5 mmol, 885 mg), ethynylmagnesium bromide (5 mmol, 0.54 M, 9.3 mL) and neat diethylchlorophosphate (6 mmol, 1.03g) were used. (62%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.30 (dt, *J*=7.15, 1.10 Hz, 6 H), 1.37 - 1.47 (m, 1 H), 1.56 - 1.76 (m, 4 H), 1.86 - 1.95 (m, 1 H), 1.98 - 2.08 (m, 1 H), 2.15 - 2.23 (m, 1 H), 2.78 (s, 1 H), 4.05 - 4.24 (m, 4 H), 4.50 (s, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (d, J_{CP}=11.10 Hz), 21.5, 32.3, 35.5, 58.3 (d, J_{CP}=7.40 Hz), 63.9 (d, J_{CP}=7.35 Hz), 64.1 (d, J_{CP}=5.55 Hz), 76.5 (d, J_{CP}=7.36 Hz), 81.1. **HRMS** (EI) calcd. for $C_{12}H_{20}BrO_4P$: 339.0361, Found: 339.0360.

Synthesis of 2-chloro-1-ethynylcyclohexyl diethyl phosphate (59.1i) 2-chlorocyclohexanone (5 mmol, 663 mg), ethynylmagnesium bromide (5 mmol, 0.54 M, 9.3 mL) and neat diethylchlorophosphate (6 mmol, 1.03g) were used. (67%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.31 - 1.39 (m, 6 H), 1.54 - 1.61 (m, 2 H), 1.61 - 1.70 (m, 2 H), 2.10 - 2.19 (m, 4 H), 4.09 - 4.25 (m, 4 H), 6.24 (s, 1 H) 6.90 (d, *J*=5.14 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 15.9 (d, J_{CP}=7.40 Hz) 21.5, 31.4, 34.7, 63.8 (dd, J_{CP}=18.50, 5.55 Hz), 64.4 (d, J_{CP}=7.40 Hz), 76.9 (d, J_{CP}=7.40 Hz), 77.3, 81.2. **HRMS** (EI) calcd. for $C_{12}H_{20}ClO_4P$: 295.0866, Found: 295.0868.

Synthesis of diethyl (1-ethynyl-2-iodocyclohexyl) phosphate (59.1j) 2-iodocyclohexanone (5 mmol, 1.12 g), ethynylmagnesium bromide (5 mmol, 0.54 M, 9.3 mL) and neat diethylchlorophosphate (6 mmol, 1.03g) were used. (69%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.25 (t, *J*=6.97 Hz, 6 H), 1.51 - 1.63 (m, 4 H), 1.64 - 1.74 (m, 1 H), 1.82 - 1.91 (m, 1 H), 1.99 - 2.16 (m, 2 H) 2.74 (s, 1 H), 3.93 - 4.02 (m, 1 H), 4.02 - 4.19

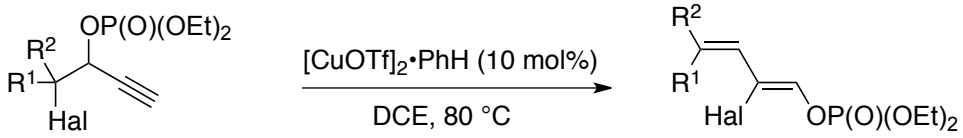
(m, 4 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.1 (d, J_{CP}=6.47 Hz), 21.6, 30.9, 34.4 36.1, 39.9 (d, J_{CP}=5.55 Hz), 63.9 (d, J_{CP}=6.47 Hz), 64.2 (d, J_{CP}=5.55 Hz), 76.6 (d, J_{CP}=8.32 Hz), 81.1. **HRMS** (EI) calcd. for $C_{12}H_{20}IO_4P$: 387.0211, Found: 387.0215.

Synthesis of diethyl (1-ethynyl-2-fluorocyclohexyl) phosphate 2-fluoroclohexanone (5 mmol, 580 mg), ethynylmagnesium bromide (5 mmol, 0.54 M, 9.3 mL) and neat diethylchlorophosphate (6 mmol, 1.03g) were used. (69%) (1:1.2 mixture) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.17 - 1.26 (m, 12 H), 1.30 - 1.66 (m, 8 H), 1.67 - 1.99 (m, 8 H), 2.71 (s, 2 H), 2.75 (s, 2 H), 3.95 - 4.10 (m, 8 H) 4.40 - 4.58 (m, 1 H) 4.80 (d, *J*=49.15 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 15.9 (t, *J*=6.01 Hz), 19.4, 21.4 - 22.2 (m), 27.9 (d, *J*=20.35 Hz), 28.7 (d, *J*=17.57 Hz), 33.9, 36.4, 63.7 (d, *J*=5.55 Hz), 63.9 (d, *J*=6.47 Hz), 77.8 (d, *J*=24.97 Hz), 78.7 (d, *J*=8.32 Hz), 78.9 (d, *J*=9.25 Hz), 79.1, 80.4 (d, *J*=9.25 Hz), 90.6, 92.2 (d, *J*=35.14 Hz), 93.8. **HRMS** (EI) calcd. for $C_{12}H_{20}FO_4P$: 279.1150, Found: 279.1154.

Synthesis of diethyl (1-ethynyl-2-fluorocyclohexyl) phosphate 2-fluorocloheptanone (5 mmol, 651 mg), ethynylmagnesium bromide (5 mmol, 0.54 M, 9.3 mL) and neat diethylchlorophosphate (6 mmol, 1.03g) were used. (69%) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.31 (t, *J*=7.15 Hz, 12 H), 1.41 - 1.81 (m, 12 H), 1.83 - 2.35 (m, 10 H), 2.73, 2.78, 4.04 - 4.19 (m, 8 H), 4.61 (ddd, *J*=47.04, 9.81, 3.30 Hz, 1 H), 5.00 (dd, *J*=47.13, 6.42 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (t, *J*=6.47 Hz), 20.3, 21.0 (d, *J*=12.02 Hz), 21.3, 25.6 (d, *J*=36.07 Hz) 28.2 (d, *J*=21.27 Hz), 28.8 (d, *J*=20.35 Hz), 34.7, 36.1, 63.2 - 65.1 (m), 77.5 (d, *J*=101.73 Hz), 79.3, 80.2, 80.6 (d, *J*=8.32 Hz), 80.8 (d, *J*=9.25

Hz), 82.1 (dd, *J*=19.42, 7.40 Hz), 95.1 (dd, *J*=185.42, 5.09 Hz), 96.9 (dd, *J*=185.42, 6.01 Hz). **HRMS** (EI) calcd. for $C_{13}H_{22}FO_4P$: 293.1318, Found: 293.1314.

11.3. Copper-Catalyzed Synthesis of (*Z*)-1,3-Dienes



59.1a **59.4a**

To an oven dried 10 mL Schlenk flask loaded with commercially available copper (I) trifluoromethanesulfonate benzene complex (10 mol%, 0.05 mmol, 25 mg) equipped with magnetic stir bar was added a solution of halo-propargylicdiethylphosphate (0.5 mmol) in 1,2-dichloroethane (0.05M, 10 mL) via cannula under argon atmosphere. The reaction was then heated to 80 ^{o}C in an oil bath until deemed complete by GC/MS analysis. Once completed, the reaction mixture was allowed to cool to rt, then filtered through a small plug of Celite. The crude mixture was then concentrated by column chromatography (Hex/EtOAc=2/1) to give the (*Z*)-1,3-diene **59.4**.

(*Z*)-2-bromo-4-methylpenta-1,3-dien-1-yl diethyl phosphate (59.4a) (86%) (*Z* only) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.38 (dt, *J*=7.15, 1.10 Hz, 6 H), 1.80 (d, *J*=1.28 Hz, 3 H), 1.81 (d, *J*=1.47 Hz, 3 H), 4.17 - 4.26 (m, 4 H), 5.63 - 5.68 (m, 1 H), 6.75 (dd, *J*=4.95, 1.65 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.1 (d, J_{CP}=5.55 Hz), 19.4, 25.6, 64.8 (d, J_{CP}=5.55 Hz), 107.4, 120.1, 135.1 (d, J_{CP}=3.70 Hz), 140.8. **HRMS** (EI) calcd. for $C_{10}H_{18}BrO_4P$: 312.01260, Found: 312.01098.

(*Z*)-2-chloro-4-methylpenta-1,3-dien-1-yl diethyl phosphate (59.4b) (95%) (*Z* only) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.37 (dt, *J*=7.06, 0.92 Hz, 6 H), 1.80 (d, *J*=1.10 Hz, 3 H), 1.82 (d, *J*=1.47 Hz, 3 H), 4.16 - 4.24 (m, 4 H), 5.55 - 5.59 (m, 1 H), 6.66 (dd, *J*=5.14, 1.47 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.1 (d, J_{CP} =5.55 Hz), 19.6, 26.0, 64.8 (d, J_{CP}=5.55 Hz), 117.6, 118.6, 133.6 (d, J_{CP}=3.7 Hz), 140.5. **HRMS** (EI) calcd. for $C_{10}H_{18}ClO_4P$: 268.06312, Found: 268.06389.

(*Z*)-2-bromo-4-ethylhexa-1,3-dien-1-yl diethyl phosphate (59.4c) (69%) (*Z:E* = 95:5, mixture) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 0.99 - 1.06 (m, 6 H), 1.38 (dt, *J*=7.06, 0.92 Hz, 6 H), 2.12 (dq, *J*=7.40, 1.28 Hz, 2 H), 2.22 (q, *J*=7.70 Hz, 2 H), 4.17 - 4.26 (m, 4 H), 5.62 (s, 1 H), 6.76 (dd, *J*=4.95, 1.65 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 12.3, 13.2, 16.0, 24.3, 28.6, 64.8 (d, J_{CP}=5.55 Hz), 107.3 (d, J_{CP}=11.10 Hz), 117.9, 134.2 (d, J_{CP}=10.45 Hz) 151.99. **HRMS** (EI) calcd. for $C_{12}H_{22}BrO_4P$: 340.04390, Found: 340.04262.

(Z)-2-chloro-3-cyclohexylideneprop-1-en-1-yl diethyl phosphate (59.4d) (75%) (*Z:E*= 91:9, mixture) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.37 (dt, *J*=6.97, 1.10 Hz, 6 H), 1.52 - 1.58 (m, 2 H), 1.58 - 1.64 (m, 2 H), 1.84 - 1.90 (m, 2 H), 1.98 - 2.05 (m, 2 H), 4.14 - 4.26 (m, 4 H), 5.56 (m, 1 H) 6.68 (td, *J*=4.77, 1.10 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (d, J_{CP}=5.55 Hz), 22.2, 22.7, 25.3, 27.3, 42.6, 64.8 (d, J_{CP}=5.55 Hz), 120.3 (d, J_{CP}=11.10 Hz) ,125.5, 131.8 (d, J_{CP}=5.55 Hz), 132.4. **HRMS** (EI) calcd. for $C_{13}H_{22}ClO_4P$: 309.1023, Found: 309.1024.

(Z)-2-chloro-3-(dihydro-2H-pyran-4(3H)-ylidene)prop-1-en-1-yl diethyl phosphate (59.4e) (77%) (*Z* only) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.31 (dt, *J*=7.06, 0.92 Hz, 6 H), 2.23 (t, *J*=5.50 Hz, 2 H), 2.45 (t, *J*=5.50 Hz, 2 H), 3.61 (t, *J*=5.50 Hz, 2 H), 3.66 (t, *J*=5.50 Hz, 2 H), 4.11 - 4.18 (m, 4 H), 5.55 - 5.61 (m, 1 H), 6.63 (dd, *J*=5.14, 1.47 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (d, J_{CP}=6.47 Hz), 31.0, 36.8, 64.8 (d, J_{CP}=6.47 Hz), 68.3, 68.9, 116.2 (d, J_{CP}=11.10 Hz,), 116.9, 133.8 (d, J_{CP}=3.70 Hz), 142.4. **HRMS** (EI) calcd. for $C_{12}H_{20}ClO_5P$: 310.07368, Found: 310.07386.

(Z)-2-bromo-2-(cyclopent-1-en-1-yl)vinyl diethyl phosphate (59.4f) (91%) (*Z* only) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.32 (t, *J*=7.15 Hz, 6 H), 1.90 - 2.04 (m, 2 H), 2.35 - 2.46 (m, 4 H), 4.10 - 4.20 (m, 4 H), 6.06 (s, 1 H), 6.93 (d, *J*=5.50 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (d, J_{CP}=6.47 Hz), 24.1, 32.3, 32.5, 64.9 (d, J_{CP}=6.47 Hz), 109.1 (d, J_{CP}=12.02 Hz), 133.9, 134.6, 137.3. **HRMS** (EI) calcd for $C_{11}H_{18}BrO_4P$: 325.0207, Found: 325.0209.

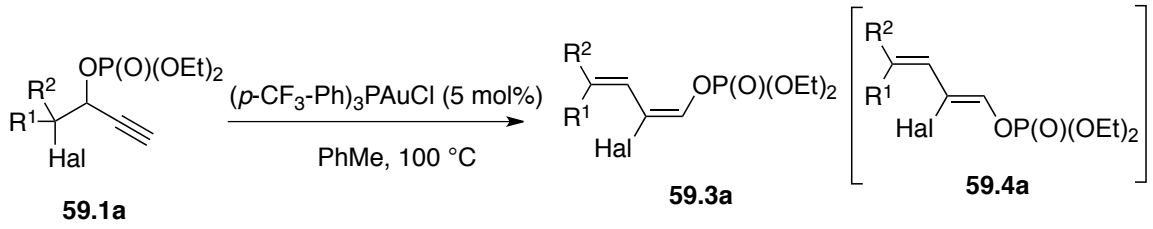
(*Z*)-2-chloro-2-(cyclopent-1-en-1-yl)vinyl diethyl phosphate (59.4g) (95%) (*Z* only) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.37 (dt, *J*=7.06, 0.92 Hz, 6 H), 1.96 - 2.05 (m, 2 H), 2.44 (t, *J*=7.52 Hz, 4 H), 4.16 - 4.25 (m, 4 H), 6.13 (s, 1 H), 6.86 (d, *J*=5.14 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (d, *J*=7.40 Hz), 23.9, 32.2 32.5, 64.9 (d, J_{CP}=5.55 Hz), 118.8 (d, J_{CP}=11.10 Hz), 132.0, 132.8 (d, J_{CP}=3.70 Hz), 136.7. **HRMS** (EI) calcd. for $C_{11}H_{18}ClO_4P$: 280.06312, Found: 280.06440.

(*Z*)-2-bromo-2-(cyclohex-1-en-1-yl)vinyl diethyl phosphate (59.4h) (86%) (*Z* only) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.38 (dt, *J*=7.06, 0.92 Hz, 6 H), 1.55 - 1.63 (m, 2 H), 1.63 - 1.71 (m, 2 H), 2.13 - 2.22 (m, 4 H), 4.16 - 4.26 (m, 4 H), 6.21 (t, *J*=3.85 Hz, 1 H), 7.02 (d, *J*=5.14 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 6.1 (d, J_{CP}=6.47 Hz), 22.0, 22.5 25.8, 26.6, 29.7, 64.8 (d, J_{CP}=6.47 Hz), 115.3, 130.5, 130.9, 132.7 (d, J_{CP}=3.70 Hz). **HRMS** (EI) calcd. for $C_{12}H_{20}BrO_4P$: 338.02825, Found: 338.02681.

(*Z*)-2-chloro-2-(cyclohex-1-en-1-yl)vinyl diethyl phosphate (59.4i) (75%) (*Z* only) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.35 (dt, *J*=7.06, 0.92 Hz 6 H), 1.54 - 1.62 (m, 2 H), 1.62 - 1.71 (m, 2 H), 2.07 - 2.21 (m, 4 H) 4.12 - 4.23 (m, 4 H), 6.24 (s, 1 H), 6.90 (d, *J*=5.14 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (d, J_{CP}=6.47 Hz), 21.9, 22.3 25.6 (d, J_{CP}=6.47 Hz), 64.8 (d, J_{CP}=6.47 Hz), 123.3 (d, J_{CP}=11.10 Hz), 128.4, 129.8, 130.9 (d, J_{CP}=2.78 Hz). **HRMS** (EI) calcd. for $C_{12}H_{20}ClO_4P$: 338.02825, Found: 338.02861.

(Z)-2-(cyclohex-1-en-1-yl)-2-iodovinyl diethyl phosphate (59.4j) (64%) (*Z* only) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.33 (t, *J*=7.15 Hz, 6 H), 1.49 - 1.55 (m, 2 H), 1.57 - 1.63 (m, 2 H), 2.05 - 2.11 (m, 2 H), 2.15 - 2.22 (m, 2 H), 4.11 - 4.20 (m, 4 H), 6.03 (t, *J*=4.03 Hz, 1 H), 6.77 (d, *J*=5.14 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.1 (d, J_{CP}=5.55 Hz), 22.1, 22.7 26.1, 27.7, 64.8 (d, J_{CP}=5.55 Hz), 94.6 (d, J_{CP}=12.95 Hz), 132.4, 132.9, 136.8. **HRMS** (EI) calcd. for $C_{12}H_{20}IO_4P$: 387.0211, Found: 387.0216.

11.4. Gold-Catalyzed Synthesis of (*E*)-1,3-Dienes



59.1a **59.3a** **59.4a**

To an oven dried 10 mL Schlenk flask loaded with commercially available [tris(*para*-trifluoromethylphenyl)phosphine]gold(I) chloride (5 mol%, 0.025 mmol, 175 mg) equipped with magnetic stir bar was added 10 mL toluene (0.05M) via cannula and desired 4-halo-propargylicdiethylphosphate (0.5 mmol) under argon atmosphere. The reaction was then heated to 100 ^{o}C in an oil bath until judged complete by GC/MS analysis. Once completed, the reaction mixture was allowed to cool to rt and then filtered through a small plug of Celite. The crude mixture was then concentrated by column chromatography (Hex/EtOAc=2/1).

(*E*)-2-bromo-4-methylpenta-1,3-dien-1-yl diethyl phosphate (59.3a) (96%) (*E:Z* = 90:10, mixture) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.33 (dt, *J*=7.06, 0.92 Hz, 6 H), 1.72 (d, *J*=1.10 Hz, 3 H), 1.77 - 1.81 (d, *J*=1.10 Hz, 3 H), 4.09 - 4.19 (m, 4 H, **59.3a**+**59.4a**), 5.55 - 5.68 (m, 1 H, **59.3a**+**59.4a**), 6.73 (dd, *J*=5.14, 1.10 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (d, J_{CP}=7.40 Hz, **59.3a**), 19.4 (**59.4a**), 20.2 (**59.3a**), 25.6 (**59.3a**), 64.6 (d, J_{CP}=5.55 Hz, **59.3a**) 64.8 (d, J_{CP}=5.55 Hz, **59.4a**), 107.4 (d, J_{CP}=12.95 Hz, **59.4a**), 109.5 (d, J_{CP}=12.95 Hz, **59.3a**), 118.1 (**59.3a**), 120.1 (**59.4a**), 132.5 (d, J_{CP}=11.10 Hz, **59.3a**), 133.7 (d, J_{CP}=5.55 Hz, **59.3a**), 141.9 (**59.3a**), 140.7 (**59.4a**). **HRMS** (EI) calcd. for $C_{10}H_{18}BrO_4P$: 312.01260, Found: 312.01178.

(*E*)-2-chloro-4-methylpenta-1,3-dien-1-yl diethyl phosphate (59.3b) (95%) (*E:Z* = 86:14, mixture) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.31 - 1.39 (m, 6 H, **59.3b**+**59.4b**), 1.78 (d, *J*=1.10 Hz, 3 H, **59.3b**), 1.79 (d, *J*=1.47 Hz, **59.4b**), 1.81 - 1.83 (m, 3H, **59.3b**+**59.4b**), 4.10 - 4.24 (m, 4 H, **59.3b**+**59.4b**), 5.53 - 5.58 (m, **59.4b**), 5.62 - 5.68 (m, 1 H, **59.3b**), 6.66 (dd, *J*=5.14, 1.10 Hz, 1 H, **59.3b**+**59.4b**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (d, J_{CP}=7.40 Hz, **59.3b**+**59.4b**), 19.6 (**59.4b**), 20.3 (**59.3b**), 26.0 (**2b**), 26.1 (**59.3b**), 64.6 (d, J_{CP}=5.55 Hz, **59.3b**), 64.8 (d, J_{CP}=5.55 Hz, **59.4b**), 116.4 (**59.3b**+**59.4b**), 118.6 (**59.4b**), 120.5 (d, J_{CP}=12.95 Hz, **59.3b**), 132.5 (**59.3b**), 133.6 (d, J_{CP}=3.70 Hz, **59.4b**), 141.8 (**3c**). **HRMS** (EI) calcd. for $C_{10}H_{18}ClO_4P$: 269.0731, Found: 269.0721.

(*E*)-2-bromo-4-ethylhexa-1,3-dien-1-yl diethyl phosphate (59.3c) (97%) (*E:Z* = 89:11, mixture) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 0.94 - 1.07 (m, 6 H), 1.27 - 1.40 (dt, *J*=7.06, 0.92 Hz, 6 H), 2.09 - 2.25 (m, 4 H), 4.10 - 4.19 (m, 4 H), 5.61 (s, 1H), 6.75 (dd, *J*=4.77, 1.47 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 12.1 (**59.3c**), 12.2 (**59.4c**), 12.3 (**59.3c**), 13.1 (**59.4c**), 16.0 (d, J_{CP}=6.47 Hz, **59.3c**), 24.2 (**59.4c**), 24.9 (**59.3c**), 28.5 (**59.3c**), 64.6 (d, J_{CP}=6.5 Hz, **59.4c**), 64.8 (d, J_{CP}=5.55 Hz, **59.4c**), 107.3 (d, J_{CP}=12.02 Hz, **59.4c**), 109.4 (d, J_{CP}=12.95 Hz, **59.3c**), 115.8 (**59.3c**), 117.9 (**59.4c**), 133.7 (d, J_{CP}=4.63 Hz, **59.3c**), 134.1 (d, J_{CP}=3.70 Hz, **59.4c**), 151.9 (**59.4c**), 152.6 (**59.3c**). **HRMS** (EI) calcd. for $C_{12}H_{22}BrO_4P$: 340.04390, Found: 340.04281.

(*E)*-2-chloro-4-ethylhexa-1,3-dien-1-yl diethyl phosphate (59.3m) (98%) (*E:Z* = 13:1, mixture) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.00 - 1.07 (m, 6 H), 1.35 (dt, *J*=7.06, 1.10 Hz, 6H), 1.37 - 1.42 (m, ***Z***), 2.10 - 2.18 (m, 2 H, **59.3m**+***Z***), 2.19 - 2.29 (m, 2 H, **59.3m**+***Z***), 4.10 - 4.25 (m, 4 H, **59.3**+***Z***), 5.54 (s, ***Z***), 5.65 (s, 1 H, **59.3**), 6.63 - 6.72 (m, 1

H, **59.3**+***Z***). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 12.3 (***Z***), 12.5 (d, J_{CP}=14.80 Hz), 16.0, 16.1, 24.4(***Z***), 25.0, 28.92 (***Z***), 29.1, 64.6 (d, J_{CP}=5.55 Hz), 114.1, 116.4, 120.6 (***Z***), 132.6 (d, J_{CP}=5.55 Hz), 152.6. **HRMS** (EI) calcd. for $C_{12}H_{22}ClO_4P$:296.09442, Found: 292.09556.

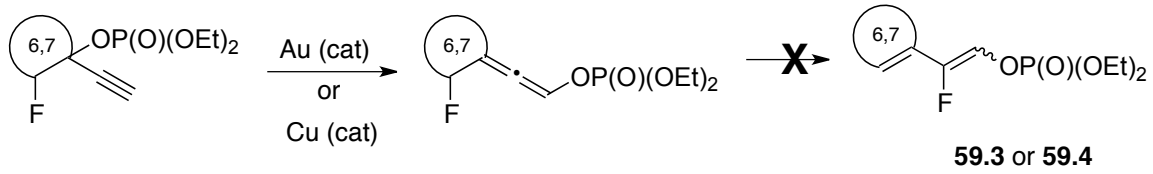
(E)-2-bromo-3-cyclohexylideneprop-1-en-1-yl diethyl phosphate (59.3n) (91%) (*E:Z* = 90:10, mixture) ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.34 (dt, *J*=7.11, 0.83 Hz, 6 H), 1.51 - 1.61 (m, 6 H), 2.12 - 2.21 (m, 4 H), 2.28 (t, *J*=5.50 Hz, ***Z***), 4.05 - 4.24 (m, 4 H), 5.55 (s, 0.78 H, **59.3n**), 5.60 (s, 0.08 H, ***Z***), 6.74 (dd, *J*=5.04, 1.19 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (d, J_{CP}=6.47 Hz, **59.3n**), 26.3 (**59.3n**), 26.4 (***Z***), 27.2 (**59.3n**), 27.8 (***Z***), 28.3 (**59.3n**), 29.8 (***Z***), 30.8 (**59.3n**), 36.6 (**59.3n**), 36.7 (***Z***), 64.6 (d, J_{CP}=5.55 Hz, **59.3n**), 64.8 (d, *J*=6.47 Hz, ***Z***), 109.2 (d, J_{CP}=12.95 Hz, **59.3n**), 114.7 (**59.3n**), 116.6 (***Z***), 133.7 (d, J_{CP}=4.62 Hz, **59.3n**), 134.5 (***Z***), 148.6 (***Z***), 149.4 (**59.3n**). **HRMS** (EI) calcd. for $C_{13}H_{22}BrO_4P$: 352.04390, Found: 352.04201.

(E)-2-chloro-3-cyclohexylideneprop-1-en-1-yl diethyl phosphate (59.3d) (90%) (*E:Z* = 95:5, mixture) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.31 (dt, *J*=7.06, 0.92 Hz, 6 H), 1.48 - 1.61 (m, 6 H), 1.99 (**59.3d**), 2.09 - 2.16 (m, 2 H), 2.20 (t, *J*=5.50 Hz, 2 H), 2.28 (t, *J*=5.50 Hz, **59.4d**), 4.04 - 4.20 (m, 4 H), 5.47 (s, **59.2d**), 5.51 (s, 1 H) 6.50 - 6.70 (m, 1 H, **59.3d**+**59.4d**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (d, J_{CP}=6.47 Hz, **59.3d**), 26.3 (**59.3d**), 26.4 (**59.4d**), 27.4 (**59.3d**), 27.8 (**59.4d**), 28.3 (**59.4d**), 28.4 (**59.3d**), 29.9 (**59.4d**), 30.9 (**59.3d**), 37.0 (**59.3d**), 64.6 (d, J_{CP}=5.55 Hz, **59.3d**), 64.8 (d, J_{CP}=5.55 Hz, **59.4d**), 113.2 (**59.3d**), 115.2 (**59.2d**), 120.2 (d, J_{CP}=12.95 Hz, **59.3d**), 132.6 (d, J_{CP}=4.62

Hz, **59.3d**), 133.1 (d, J_{CP}=3.70 Hz, **59.4d**), 148.4 (**59.4d**) 149.4 (**59.3d**). **HRMS** (EI) calcd. for $C_{13}H_{22}ClO_4P$: 309.1023, Found: 309.1015.

(E)-2-(cyclohex-1-en-1-yl)-2-iodovinyl diethyl phosphate (3j), (Z)-2-(cyclohex-1-en-1-yl)-2-iodovinyl diethyl phosphate (59.3j) (89%) (*E:Z* = 60:40, mixture) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.29 - 1.36 (m, 10 H, **59.3j**+**59.4j**), 1.50 - 1.57 (m, 3 H, **59.3j**+**59.4j**), 1.58 - 1.65 (m, 3 H, **59.3j**+**59.4j**), 2.00 - 2.11 (m, 3 H, **59.3j**+**59.4j**), 2.17 - 2.23 (m, 3 H, **59.3j**+**59.4j**), 4.02 - 4.26 (m, 6 H, **59.3j**+**59.3j**), 5.95 - 6.00 (m, 0.9 H, **59.3j**), 6.02 - 6.07 (m, 0.58 H, **59.4j**), 6.75 (d, *J*=4.77 Hz, 0.76 H, **59.3j**), 6.78 (d, *J*=4.95 Hz, 1 H, **59.4j**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.0 (d, J_{CP}=6.47 Hz, **59.3j**+**59.4j**), 21.7 (**59.3j**), 22.1 (**59.4j**), 22.6 (**59.4j**), 22.7 (**59.3j**), 25.7 (**59.3j**), 26.0 (**59.3j**), 27.7 (**59.3j**), 28.3 (**59.3j**), 64.6 (d, J_{CP}=5.55 Hz, **59.3j**), 64.9 (d, J_{CP}=6.47 Hz, **59.4j**), 90.9 (d, J_{CP}=11.1 Hz, **59.3j**), 94.7 (d, J_{CP}=12.02 Hz, **59.4j**), 131.6 (**59.3j**), 132.4 (**59.4j**), 132.9 (**59.4j**), 133.8 (**59.3j**), 136.1 (d, J_{CP}=4.63 Hz, **59.3j**), 136.8 (d, J_{CP}=2.78 Hz, **59.4j**). **HRMS** (EI) calcd. for $C_{12}H_{20}IO_4P$: 387.0211, Found: 387.0216.

11.5. Copper- and Gold-catalyzed Formation of α-fluoroallenes



59.3 or **59.4**

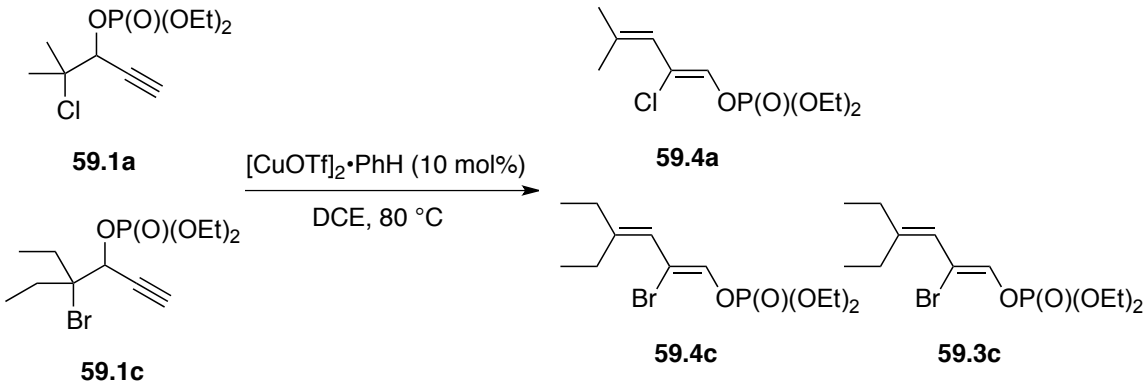
Attempt to isomerize α-fluoro propargylic phosphates only led to the formation of the corresponding α-fluoroallenes via 1,3-phosphatyloxy group migration.

Diethyl (2-(2-fluorocyclohexylidene)vinyl) phosphate (89%) (1.1:1, mixture) **^{1}H NMR** (500 MHz, $CDCl_3$) 1.25 - 1.31 (m, 21 H), 1.40 - 1.51 (m, 2 H), 1.52 - 1.63 (m, 4 H), 1.69 - 1.93 (m, 6 H), 2.06 - 2.19 (m, 2 H), 2.33 - 2.44 (m, 2 H), 4.03 - 4.14 (m, 17 H), 6.60 - 6.71 (m, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) d ppm 15.2 - 17.1 (m), 21.4 (dd, *J*=24.97, 5.55 Hz), 26.0 (d, *J*=5.55 Hz), 29.7 (d, *J*=16.65 Hz), 33.0 (dd, *J*=20.35, 8.32 Hz), 64.2 (d, *J*=5.55 Hz), 87.3 - 90.7 (m), 112.4 (d, *J*=6.47 Hz), 117.3, 189.2. **LRMS** for $C_{12}H_{20}FO_4P$: 279.1.

Diethyl (2-(2-fluorocycloheptylidene)vinyl) phosphate (89%) (1:1, mixture) **^{1}H NMR** (500 MHz, $CDCl_3$) d ppm 1.31 (t, *J*=7.06 Hz, 12 H), 1.49 - 1.79 (m, 12 H), 1.86 - 2.03 (m, 4 H), 2.20 - 2.29 (m, 2 H), 2.31 - 2.44 (m, 2 H), 4.07 - 4.20 (m, 8 H), 5.06 (dt, *J*=22.28, 5.73 Hz, 1 H), 5.15 (dt, *J*=22.47, 5.55 Hz, 1 H), 6.64 - 6.78 (m, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) d ppm 16.0 (d, *J*=6.47 Hz), 22.8 (d, *J*=6.47 Hz), 23.0 (d, *J*=6.47 Hz), 28.1 (d, *J*=24.04 Hz), 28.6 (d, *J*=25.89 Hz), 29.6 (d, *J*=23.12 Hz), 34.1 (d, *J*=14.80 Hz), 34.2 (d, *J*=14.80 Hz), 64.2 (d, *J*=4.62 Hz), 91.5 (d, *J*=8.32 Hz), 92.9 (d, *J*=9.25 Hz), 112.3 (t, *J*=7.40 Hz), 119.8 (d, *J*=7.40 Hz), 119.9 (d, *J*=7.40 Hz), 192.4 - 194.1 (m). **LRMS** for $C_{13}H_{22}FO_4P$: 293.1.

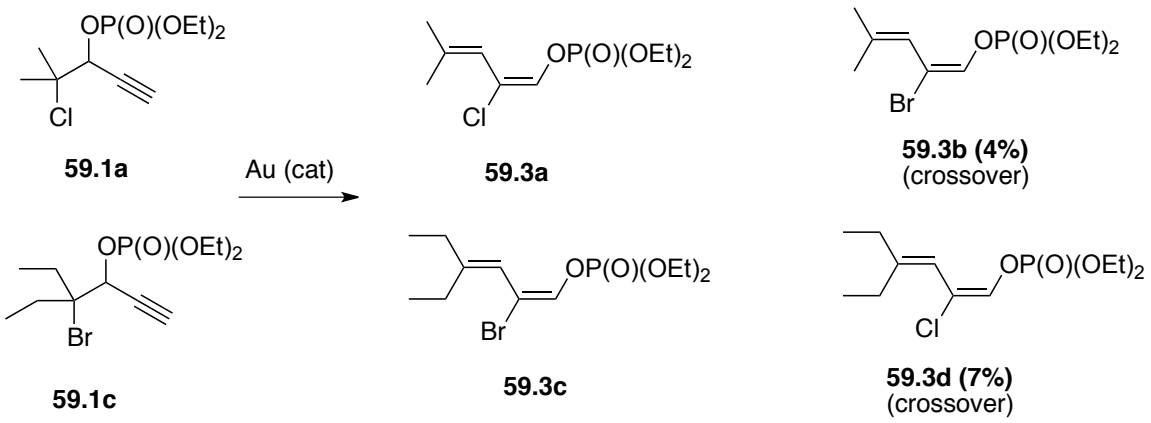
11.6. Crossover Experiments

a) Copper-Catalyzed Reaction



To a 3 mL Wheaton V-vial equipped with spin bar was added copper (I) trifluoromethanesulfonate benzene complex (10 mol%, 0.01 mmol, 5 mg) and pentadecane (10 µl, as an internal standard) under nitrogen atmosphere. A solution of **59.1b** (0.05 mmol, 13 mg) and **59.1c** (0.05 mmol, 17 mg) in dry DCE (2 mL) was transferred through cannula. The reaction was heated to 100 ^{o}C and frequently checked with GC/MS until judged completed. Expected products **59.4b** and **59.4c, 59.3c** were observed with no crossover products detected by GC/MS analysis.

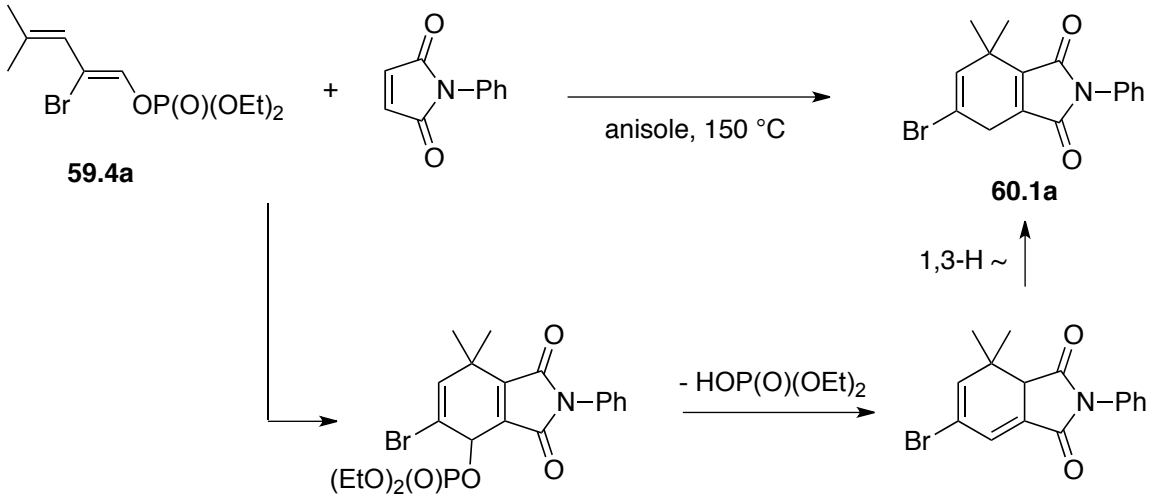
b) Gold-Catalyzed Reaction



To a 3 mL Wheaton V-vial equipped with spin bar was added [tris(*para*-trifluoromethylphenyl)phosphine]gold(I) chloride (5 mol%, 0.005 mmol, 3.5 mg) and pentadecane (10 μl, as an internal standard) under nitrogen atmosphere. A solution of **59.1b** (0.05 mmol, 13 mg) and **59.1c** (0.05 mmol, 17 mg) in dry toluene (2 mL) was transferred through cannula. The reaction was heated to 100 ^{o}C and was checked with GC/MS until judged completed. In addition to the expected products (**59.3b, 59.4b**, **59.3c, 59.4c)**, the crossover products **59.3b** (4%) and **59.3d** (7%) were also detected by GC/MS analysis.

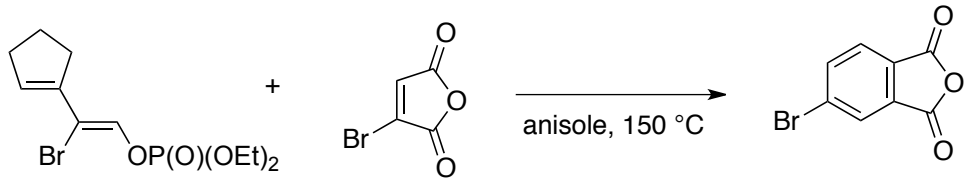
11.7. Functionalization of Obtained (Z)-1,3-Dienes

A) Diels-Alder reaction: Synthesis of 6-bromo-4,4-dimethyl-2-phenyl-4,7-dihydro-1H-isoindole-1,3(2H)-dione (60.1a)



An oven-dried Wheaton V-vial was charged with diene **2a** (0.2 mmol, 63mg), N-phenylmaleimide (1.5 equiv, 0.3 mmol, 52mg) and anisole (0.5 mL). The reaction mixture was stirred overnight at 150 ºC and then cooled to rt. After removing solvent under vacuum, the residue was subjected to column chromatography on silica gel to give product **10** in 82% yield as a white solid (mp=120 ^{o}C). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.46 (s, 6 H), 3.44 (d, *J*=0.92 Hz, 2 H), 5.91 - 6.19 (m, 1 H), 7.30 - 7.40 (m, 3 H), 7.41 - 7.68 (m, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 27.6, 31.6, 37.5, 115.0, 126.0, 127.7, 129.1, 131.4, 136.3, 137.3, 144.2, 168.1. **HRMS** (EI) calcd. for $C_{16}H_{14}BrNO_2$: 332.0286, Found: 332.0282.

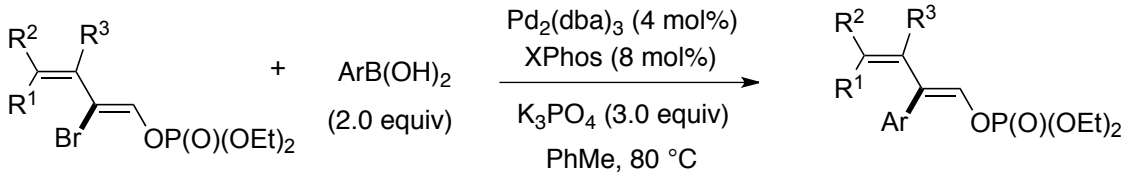
B) Diels-Alder reaction: Synthesis of 5-bromo-7,8-dihydro-1H-indeno[4,5-c]furan-1,3(6H)-dione (60.2f)



59.4f **60.2f**

An oven-dried Wheaton V-vial was charged with diene **2f** (0.2 mmol, 62mg), bromomaleic anhydride (1.5 equiv, 0.3 mmol, 53mg) and anisole (1 mL). The reaction mixture was stirred overnight at 150 ºC and then cooled to rt. After removing solvent under vacuum, the residue was subjected to column chromatography on silica gel to give product **11** in 56% yield as a white solid (mp= 98 ^{o}C). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 2.12 - 2.49 (m, 2 H), 3.10 (t, *J*=7.52 Hz, 2 H), 3.39 (t, *J*=7.43 Hz, 2 H), 7.96 (s, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 24.3, 32.2, 35.2, 125.6, 127.5, 128.3, 131.4, 146.4, 155.6, 162.2, 162.63. **HRMS** (EI) calcd. for $C_{11}H_7BrO_3$: 265.95786 , Found: 265.95874.

C) Suzuki Cross-Coupling Reaction on Vinyl Bromide Moiety



59.4a,f

An oven-dried 5 mL Wheaton V-vial was charged with XPhos (8 mol %), $Pd_2(dba)_3$ (4 mol %), arylboronic acid (2 equiv), 0.8 mmol, 97.4 mg) and anhydrous K_3PO_4 (3equiv, 1.2 mmol, 260 mg) in the glove box. A solution of diene **59.4a** (1.0

equiv) in toluene (4 mL) was added through cannula. The reaction stirred at 80 ^{o}C overnight and then cooled to room temperature. After filtration through a small pad of Celite, solvents were removed under vacuum and the residue was subjected to column chromatography (Hex/EtOAc=2/1) to give the phenylated products **60.1a** in 82% yield.

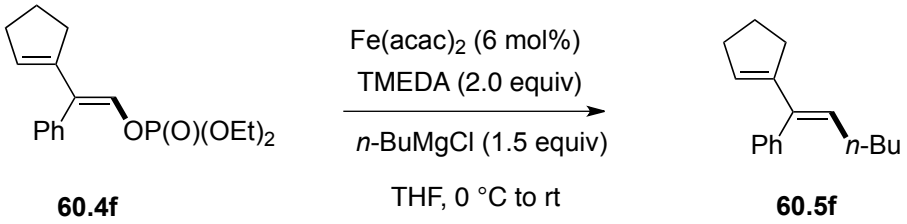
Synthesis of (Z)-diethyl (4-methyl-2-phenylpenta-1,3-dien-1-yl) phosphate (60.3a) (78%) as a yellowish oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.29 (dt, *J*=7.06, 0.92 Hz, 6 H), 1.67 (s, 3 H), 1.83 (s, 3 H), 4.04 - 4.16 (m, 4 H), 5.72 (s, 1 H), 6.56 (d, *J*=4.59 Hz, 1 H), 7.21 - 7.28 (m, 1 H), 7.32 (t, *J*=7.24 Hz, 2 H), 7.42 (d, *J*=7.34 Hz, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$)) δ ppm 16.0 (d, J_{CP}=6.47 Hz), 19.4, 26.2, 64.4 (d, J_{CP}=5.55 Hz), 121.3, 124.3 (d, J_{CP}=10.17 Hz), 127.2, 128.0, 128.8, 134.0 (d, J_{CP}=5.55 Hz), 136.1, 137.40. **HRMS** (EI) calcd. for $C_{16}H_{23}O_4P$: 311.1412, Found: 311.1400.

Synthesis of (Z)-2-(cyclopent-1-en-1-yl)-2-phenylvinyl diethyl phosphate (60.4f) (91%) as a brownish oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.52 (dt, *J*=7.15, 0.73 Hz, 6 H), 2.18 - 2.31 (m, 2 H), 2.53 - 2.68 (m, 2 H), 2.71 - 2.83 (m, 2 H), 4.10 - 4.43 (m, 4 H), 5.68 (br. s., 1 H), 6.98 (d, *J*=4.58 Hz, 1 H), 7.49 - 7.57 (m, 3 H), 7.59 - 7.67 (m, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$)) δ ppm 15.9 (d, J_{CP}=6.47 Hz), 23.3, 32.1, 32.7, 64.3 (d, J_{CP}=6.48 Hz), 127.1, 127.8, 129.49, 131, 132.9 (d, J_{CP}=4.63 Hz), 134.1, 135.7, 140.5. **HRMS** (EI) calcd. for $C_{17}H_{23}O_4P$: 322.13340, Found: 322.13264.

Synthesis of (Z)-2-(cyclopent-1-en-1-yl)-2-(4-methoxyphenyl)vinyl diethyl phosphate (85%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.25 (dt, *J*=7.06, 0.92 Hz, 6 H), 1.90 - 2.01 (m, 2 H), 2.31 - 2.38 (m, 2 H), 2.45 - 2.52 (m, 2 H), 3.81 (s, 3 H) 3.98 - 4.06 (m, 4 H), 5.44 (br. s., 1 H), 6.68 (d, *J*=4.40 Hz, 1 H), 6.84 - 6.92 (m, 2 H), 7.08 -

7.21 (m, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 16.4, 23.8, 32.6, 33.1, 55.57, 64.7 (d, *J*=5.55 Hz), 113.6, 127.14 (d, *J*=11.10 Hz), 128.3, 131.0, 131.2, 133.2, 141.2, 159.1. **HRMS** (EI) calcd. for $C_{18}H_{25}O_5P$: 352.14396, Found: 352.14321.

D) Kumada Cross-Coupling on Vinyl Phosphate Moiety

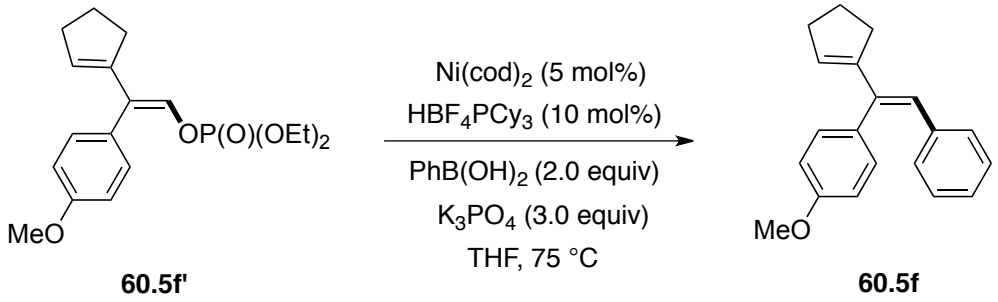


60.4f **60.5f**

An oven-dried 3 mL Wheaton V-vial was charged with $Fe(acac)_3$ (6 mol %, 4.2 mg) and THF (2 mL). TMEDA (2 equiv, 0.4 mmol, 51 mg) and **60.4f** (0.2 mmol, 64 mg) were added to the solution and the vial was then placed in an ice-water bath. A solution of Butylmagnesium chloride in tetrahydrofuran (1.5 equiv, 0.3 mmol) was added to the reaction mixture dropwise. The reaction stirred at 0 ^{o}C for half an hour and then warmed to room temperature. The mixture was then passed through a pad of Celite and the residue was subjected to column chromatography (pure Hexanes) to give product **60.5f** in 70% yield (31 mg) as a yellowish oil.

(*Z*)-(1-(cyclopent-1-en-1-yl)hex-1-en-1-yl)benzene 60.5f: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.84 (t, *J*=7.34 Hz, 3 H), 1.24 - 1.32 (m, 4 H), 1.89 - 2.01 (m, 2 H), 2.31 - 2.43 (m, 2H), 2.55 - 2.64 (m, 2 H) 5.14 (br. s., 1 H), 5.63 (t, *J*=7.70 Hz, 1 H), 7.14 (d, *J*=7.34 Hz, 2 H), 7.26 - 7.31 (m, 1H), 7.36 (t, *J*=7.34 Hz, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 14.3, 22.7, 23.6, 29.3, 32.6, 32.9, 33.5, 126.7, 127.2, 127.5, 128.2, 129.2, 129.4, 129.8, 145.9. **HRMS** (EI) calcd. for $C_{17}H_{22}$: 226.17147, Found: 226.17132.

E) Suzuki Cross-Coupling Reaction on Vinyl Phosphate Moiety



60.5f' **60.5f**

An oven-dried 3 mL Wheaton V-vial was charged with $Ni(cod)_2$ (5 mol %, 1.4 mg), HBF_4PCy_3 (10 mol %, 3.7 mg), phenylboronic acid (2 equiv, 0.2 mmol, 24.5 mg) and anhydrous K_3PO_4 (3equiv, 0.3 mmol, 75 mg) in the glove box. A solution of (Z)-2-(cyclopent-1-en-1-yl)-2-(4-methoxyphenyl)vinyl diethyl phosphate (0.1 mmol, 35 mg) in THF (1 mL) was added through cannula. The reaction stirred at 75 ^{o}C overnight and then cooled to room temperature. After filtration through a small pad of Celite, solvents were removed under vacuum and the residue was subjected to column chromatography (pure Hexane) to give the product **60.5f** in 74% yield (20 mg) as a yellowish oil.

(*Z*)-1-(1-(cyclopent-1-en-1-yl)-2-phenylvinyl)-4-methoxybenzene (60.5f) ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.96 - 2.10 (m, 2 H), 2.39 - 2.50 (m, 2 H), 2.68 - 2.81 (m, 2 H), 3.87 (s, 3 H), 5.42 (br. s., 1 H), 6.52 (s, 1 H), 6.87 - 6.97 (m, 3 H) 7.05 - 7.15 (m, 4 H) 7.25 - 7.32 (m, 1 H) 7.36 - 7.44 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 23.8, 33.1, 33.7, 55.6, 114.3, 126.6, 127.1, 128.2, 129.7, 131.1, 132.4, 132.9, 137.92, 139.7, 147.16, 158.9. **HRMS** (EI) calcd. for $C_{20}H_{20}O$: 276.15142, Found: 276.15067.

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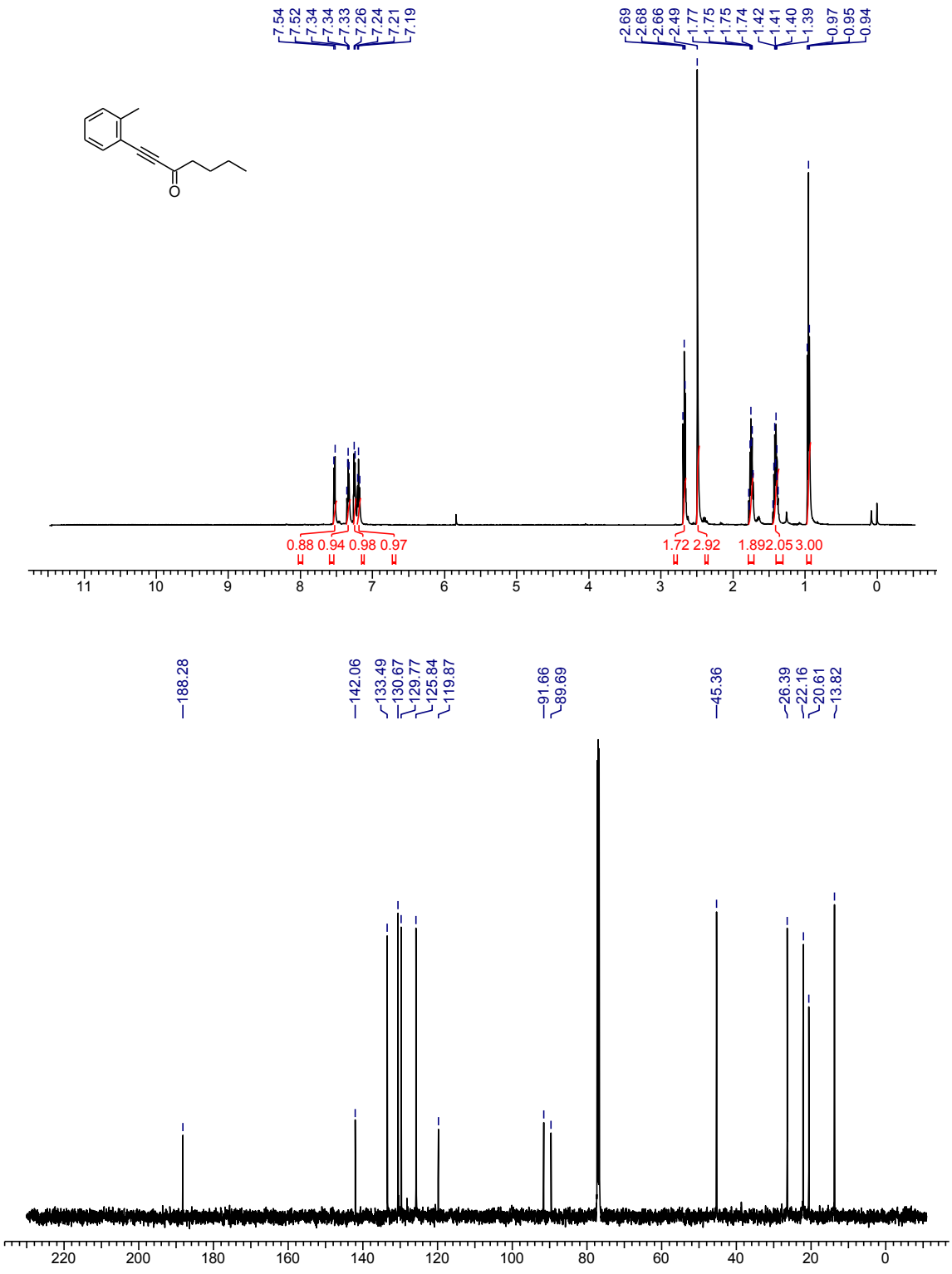
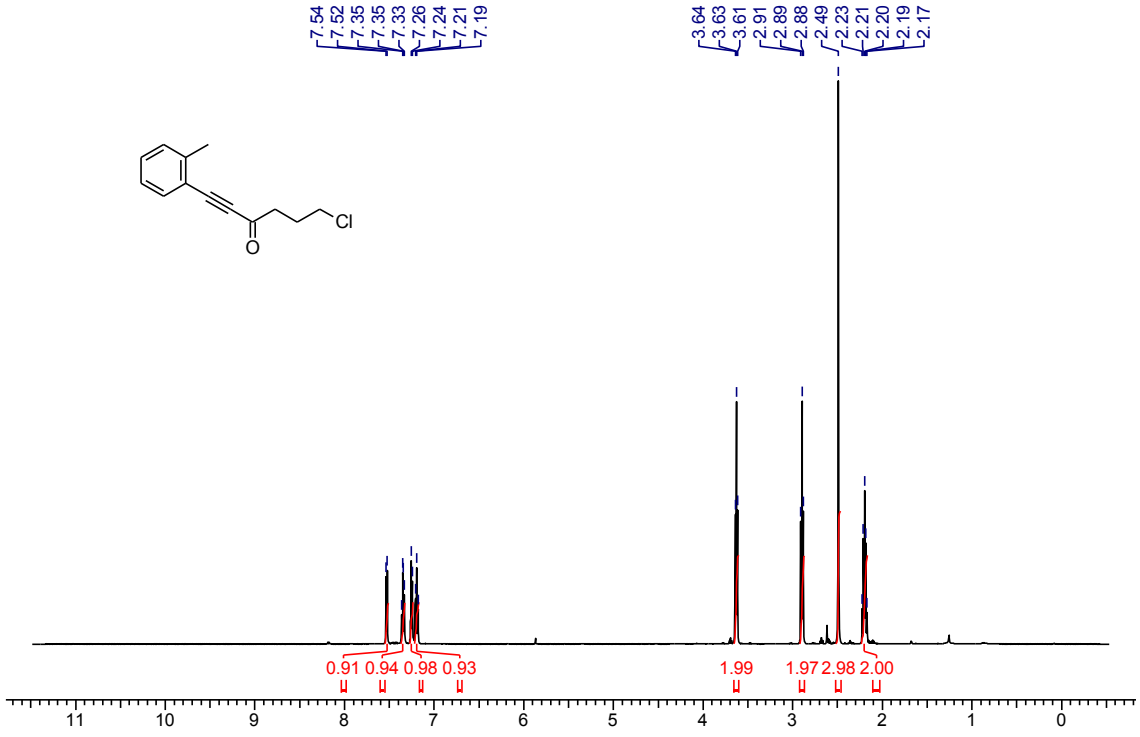
APPENDIX I

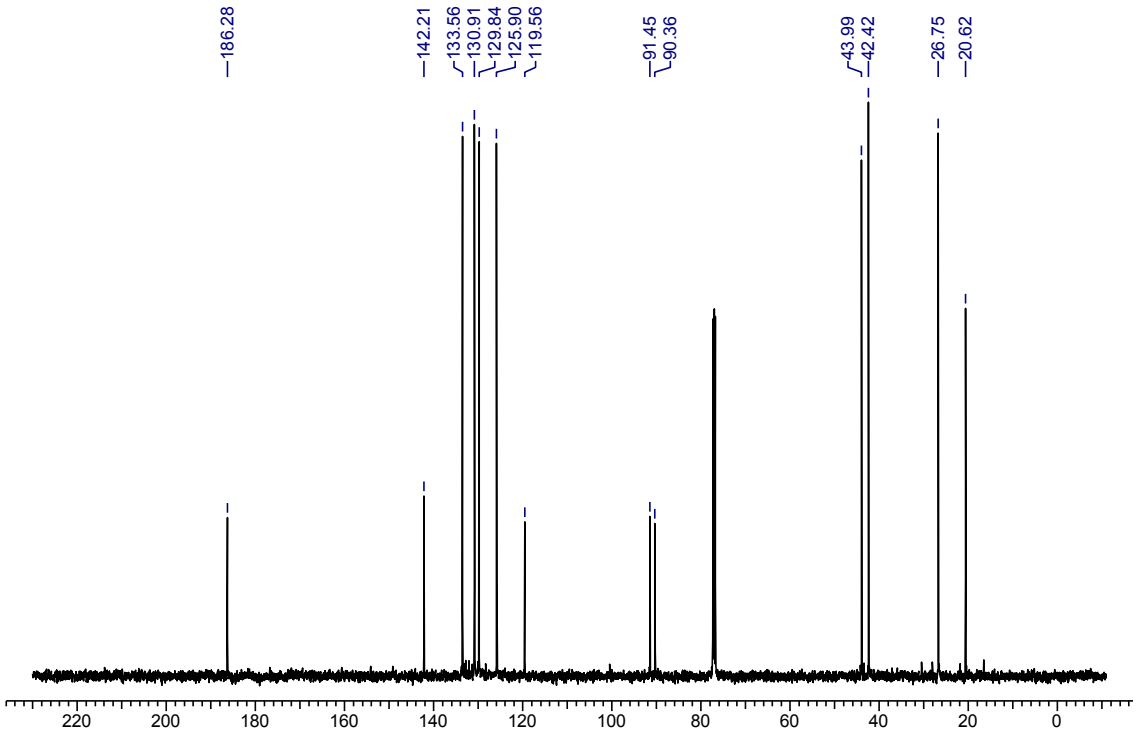
Selected NMR Spectra for Part One

^{1}H and ^{13}C Spectra of **15.2a**

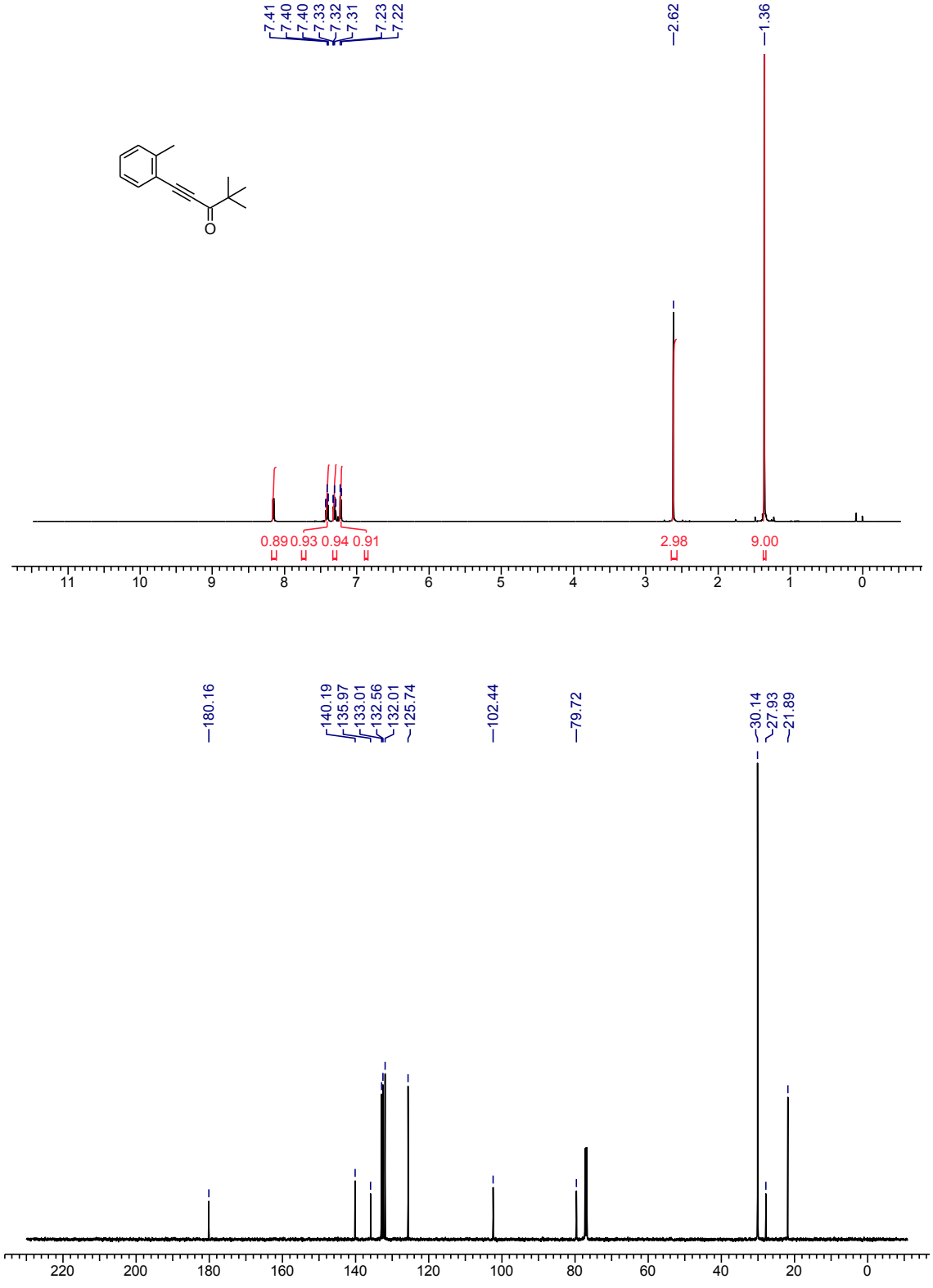


^{1}H and ^{13}C Spectra of **15.2b**

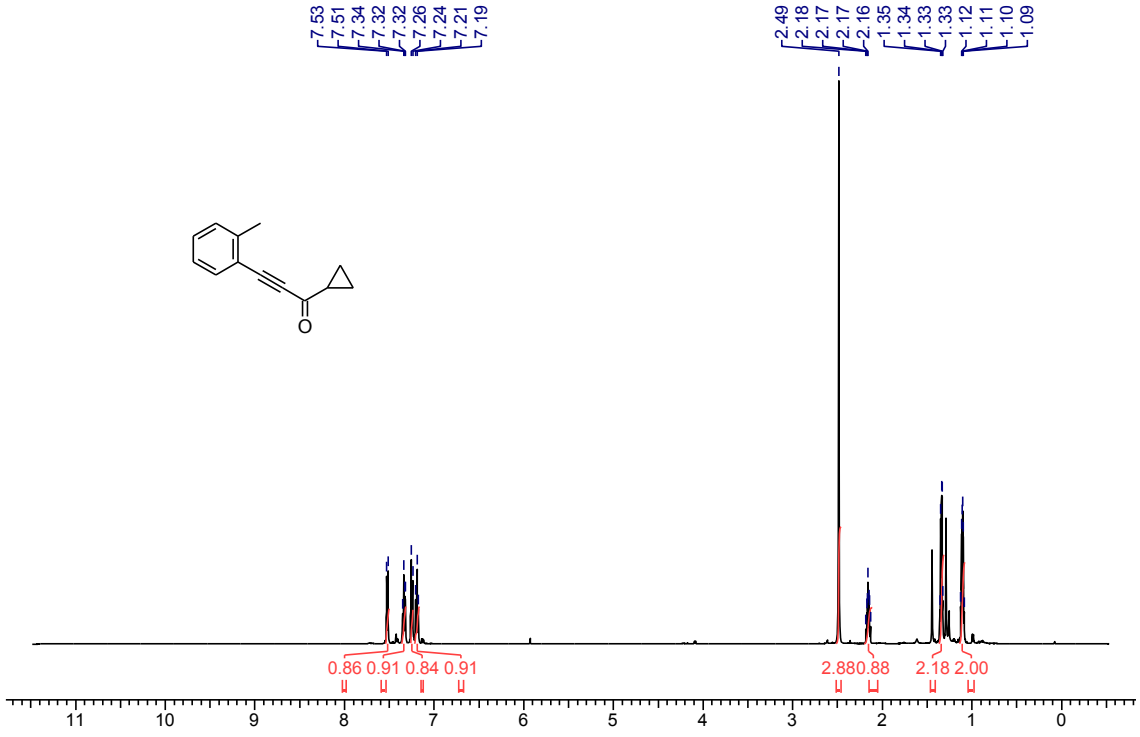


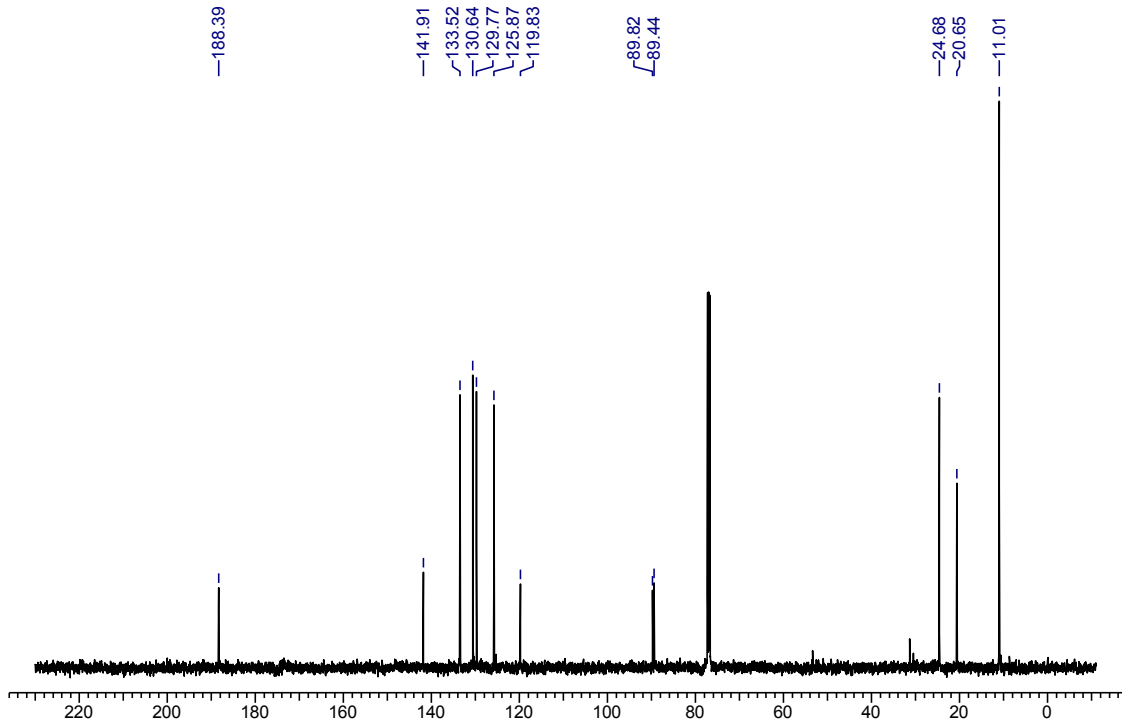


^{1}H and ^{13}C Spectra of **15.2c**

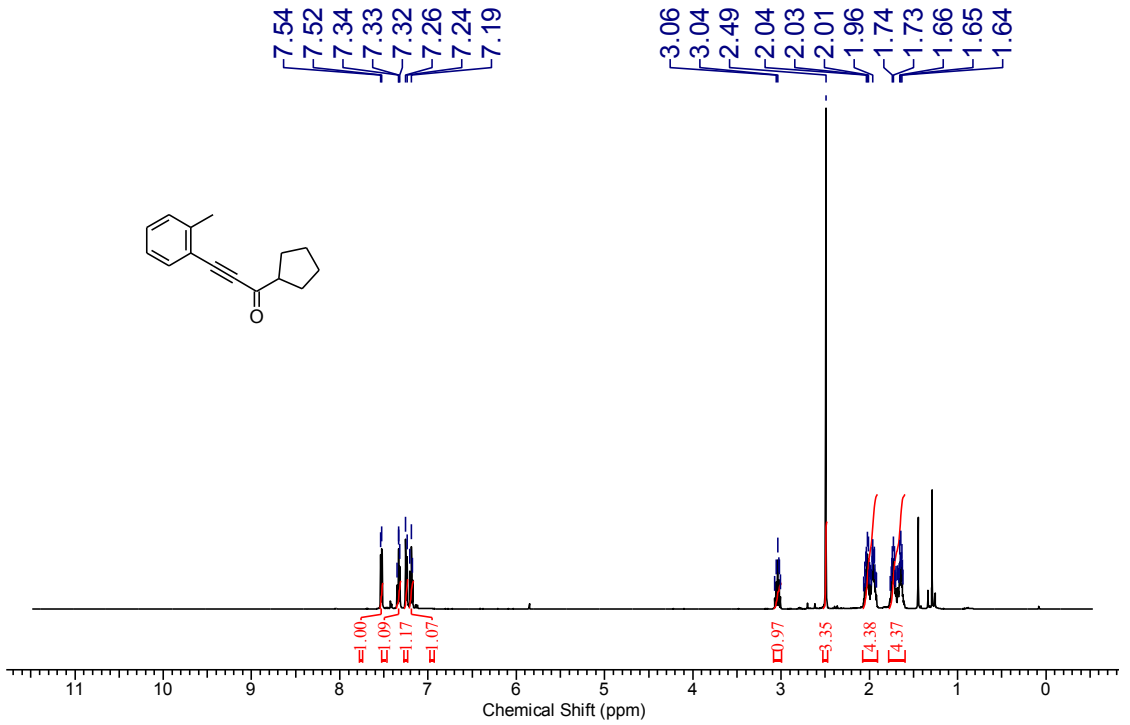


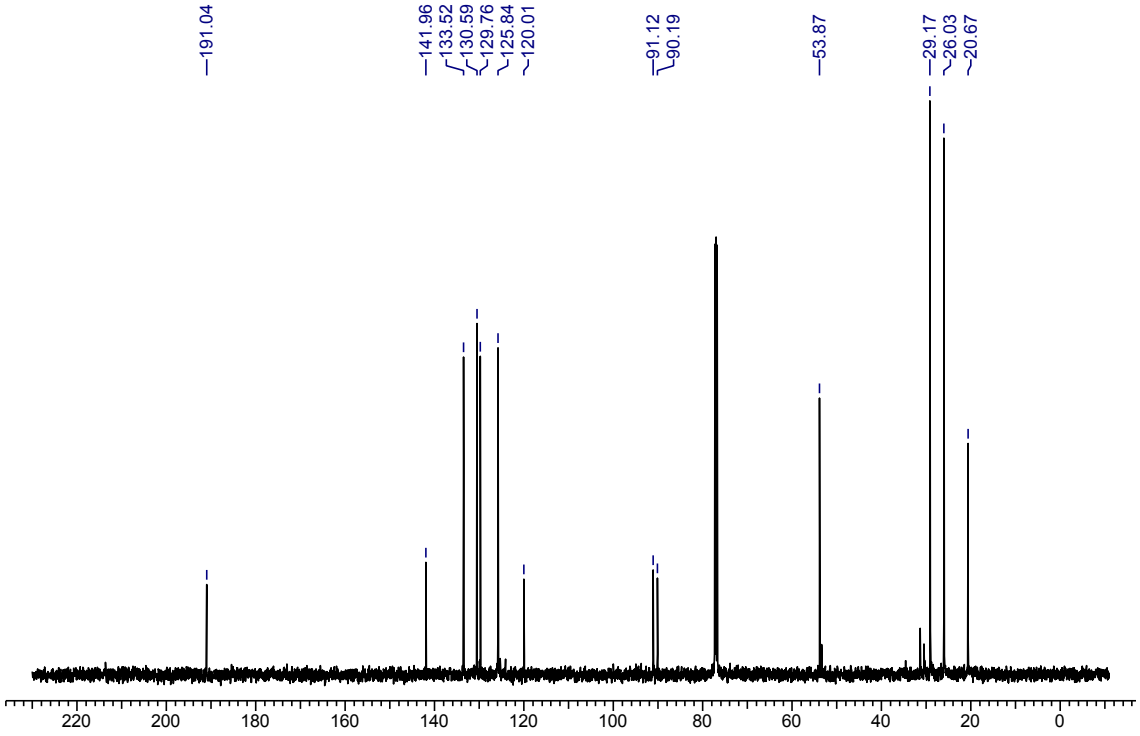
^{1}H and ^{13}C Spectra of **15.2d**



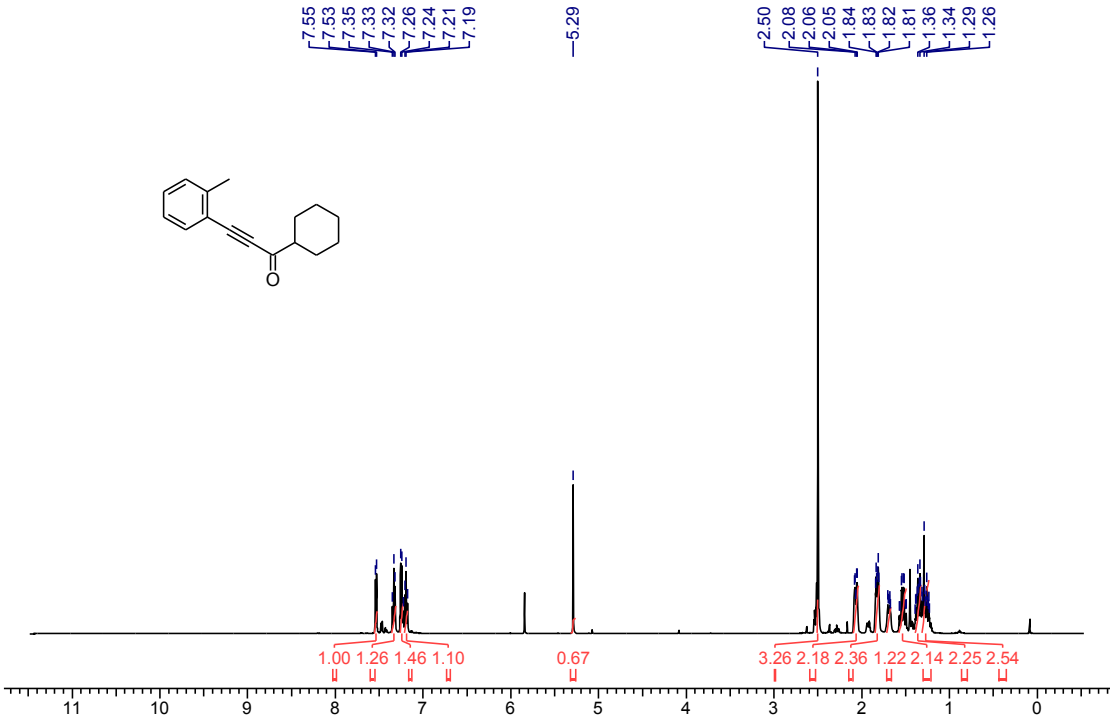


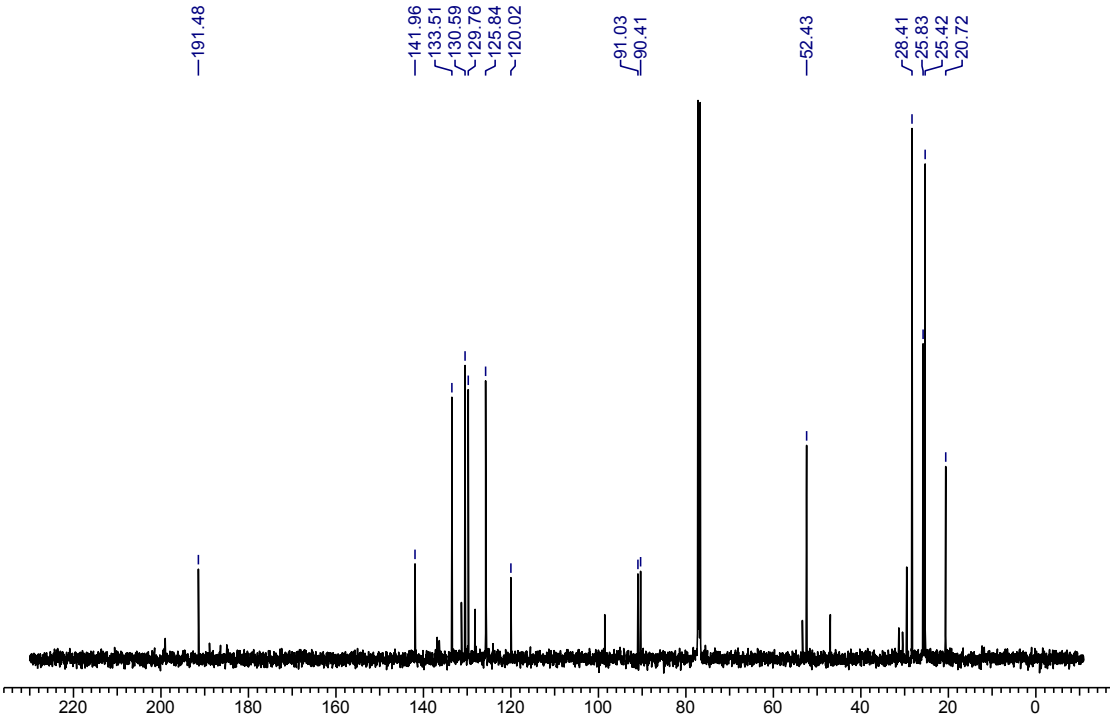
^{1}H and ^{13}C Spectra of **15.2e**



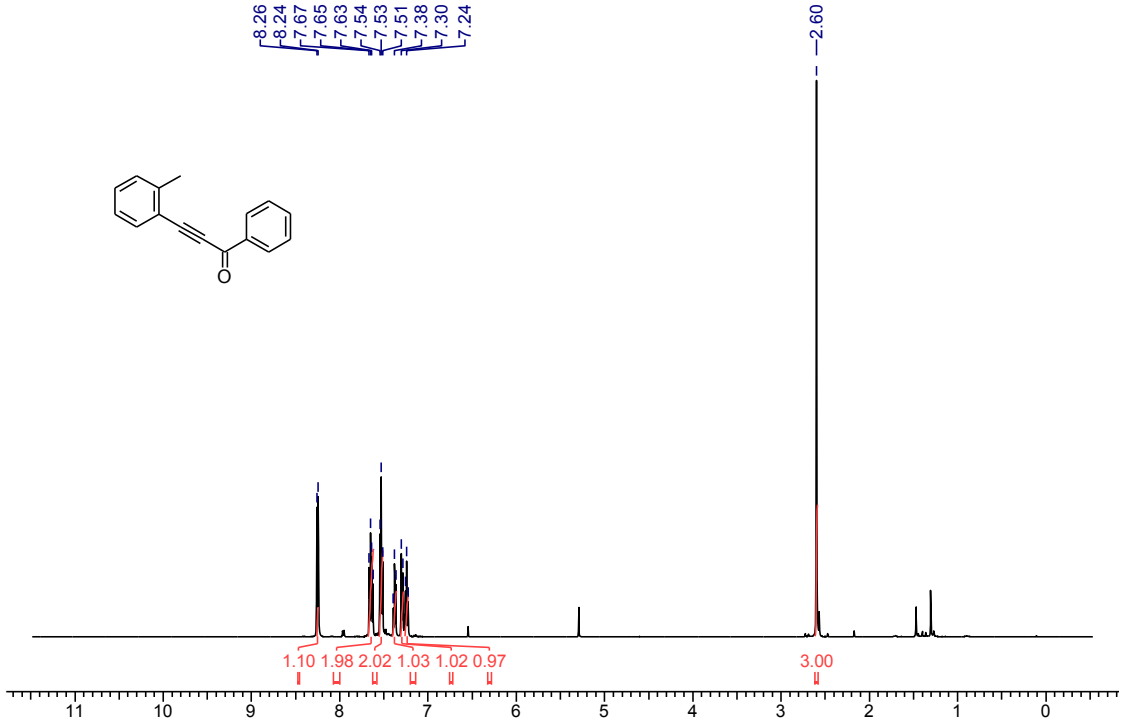


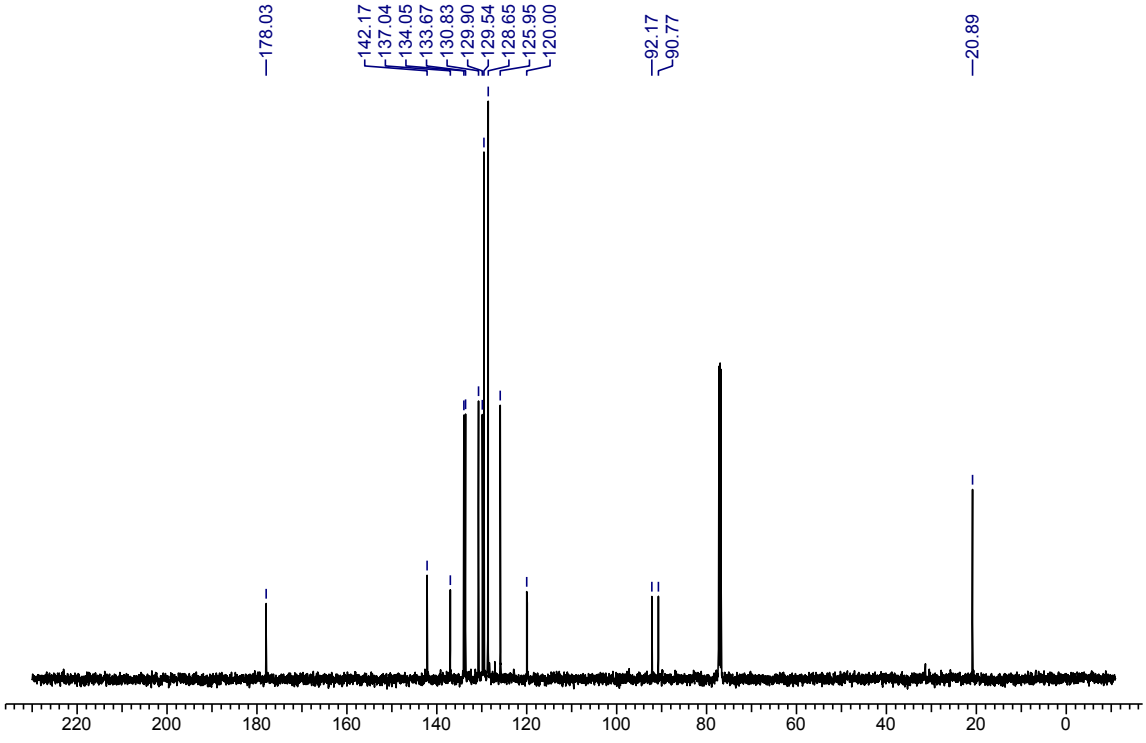
^{1}H and ^{13}C Spectra of **15.2f**



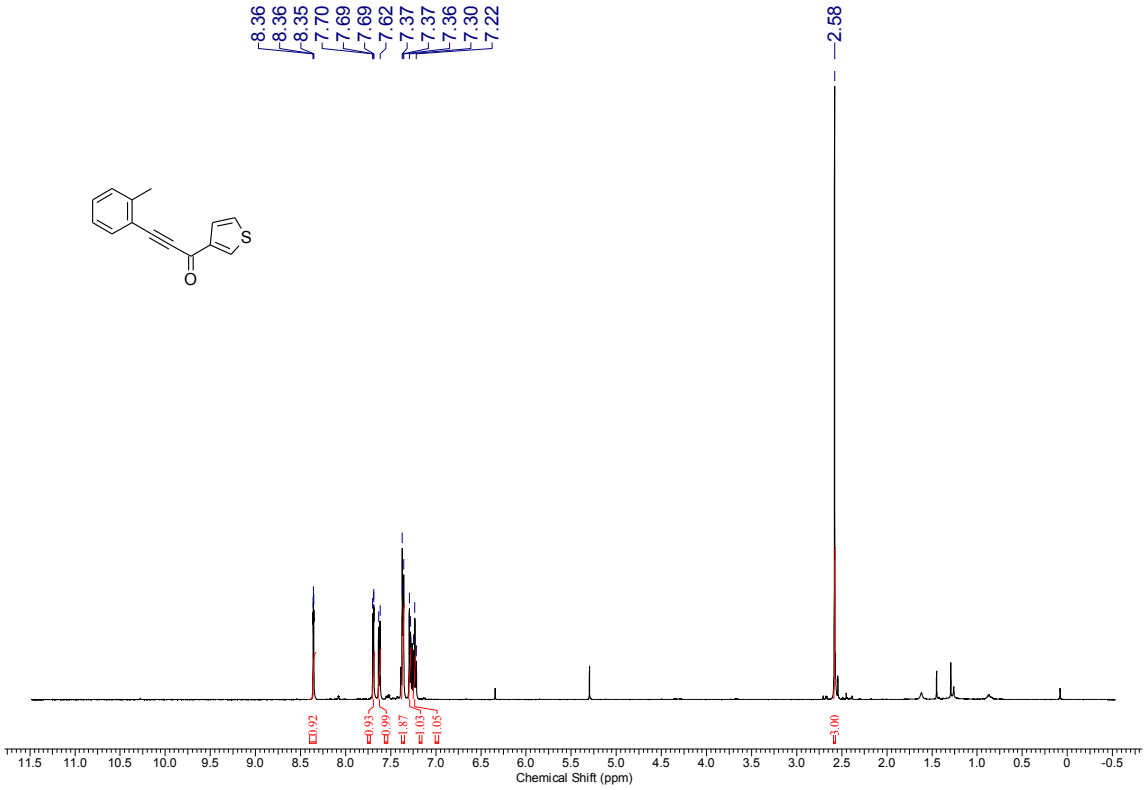


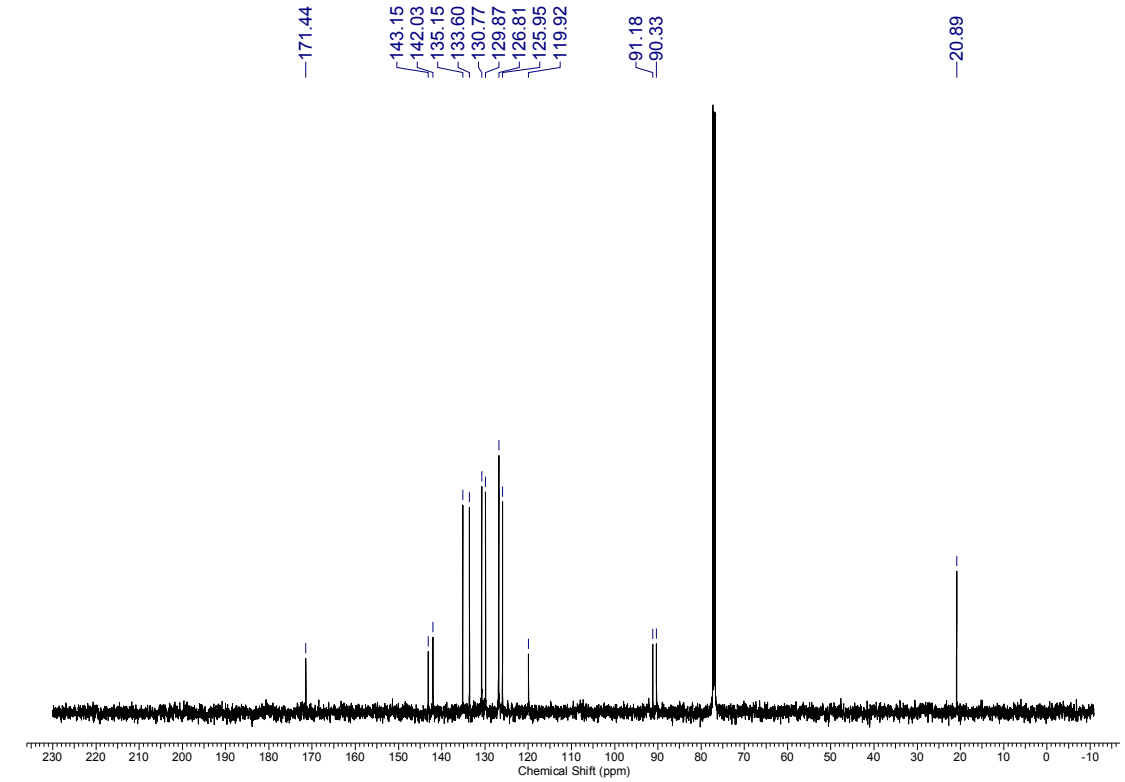
^{1}H and ^{13}C Spectra of **15.2g**



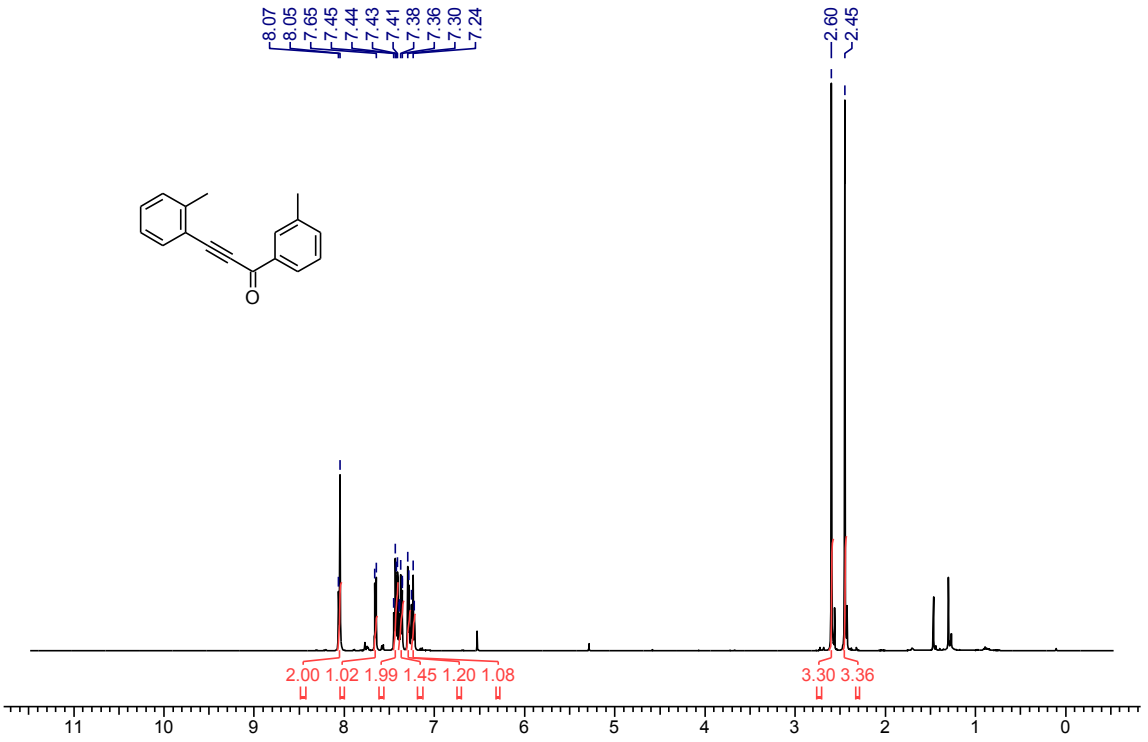


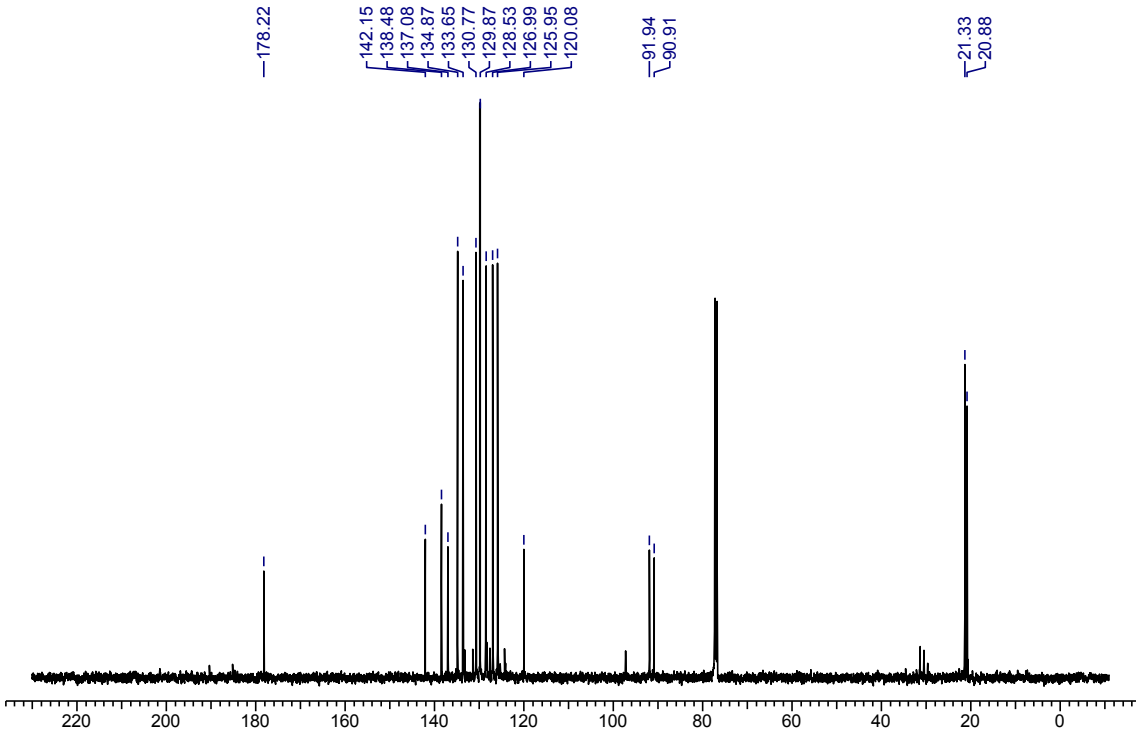
^{1}H and ^{13}C Spectra of **15.2h**



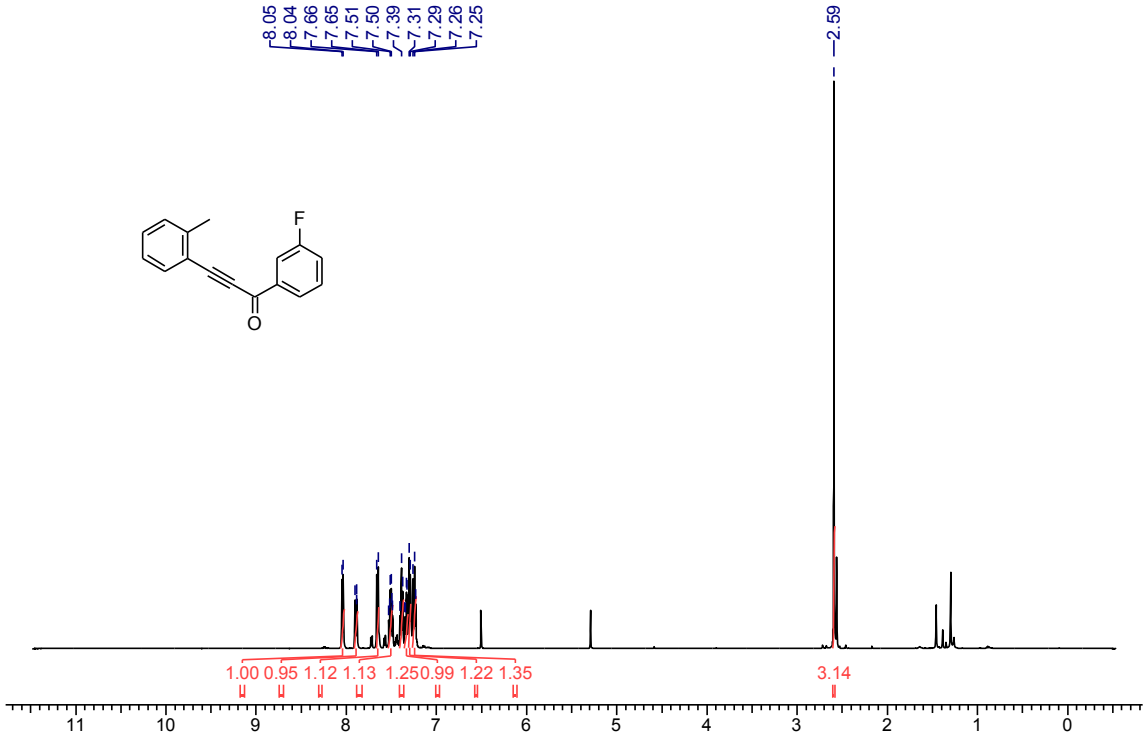


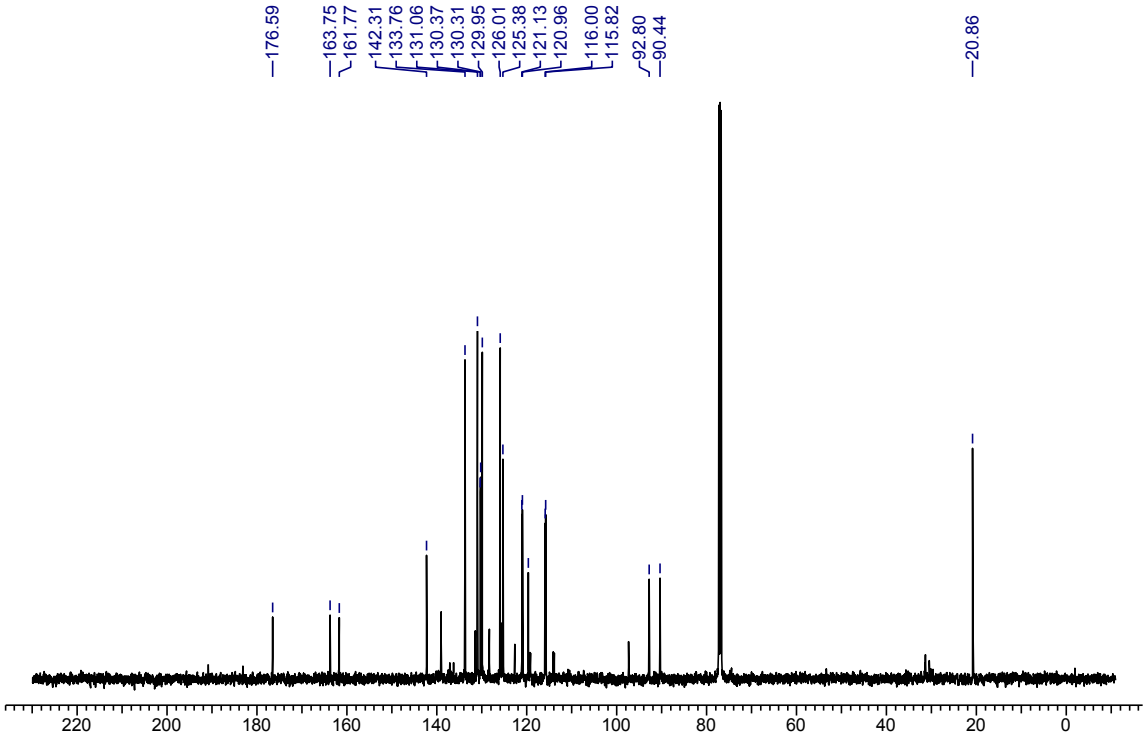
^{1}H and ^{13}C Spectra of **15.2i**



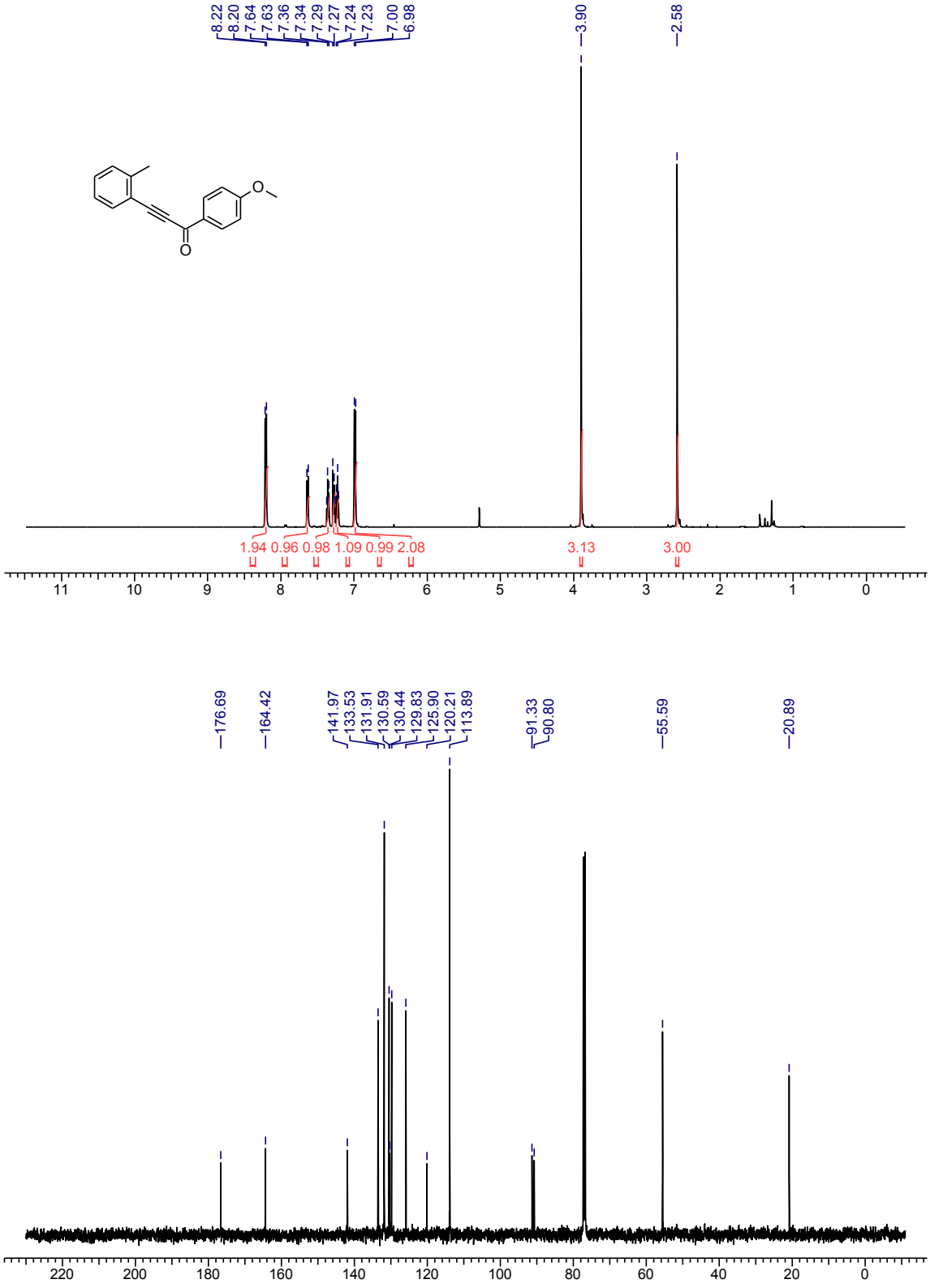


^{1}H and ^{13}C Spectra of **15.2j**

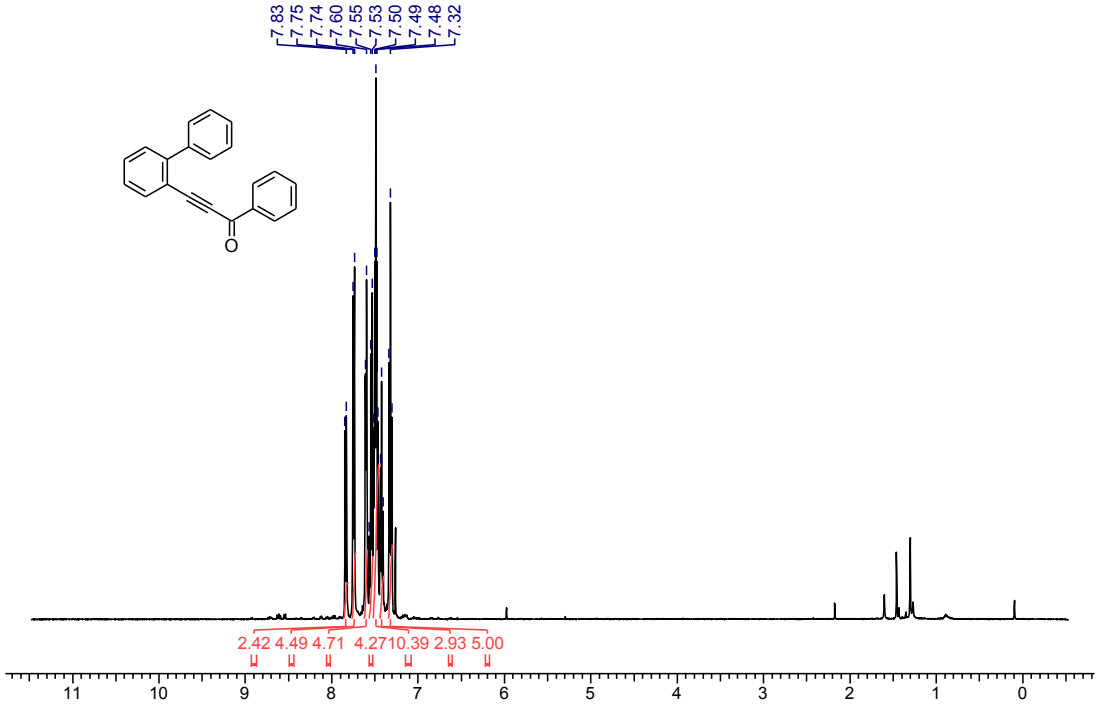


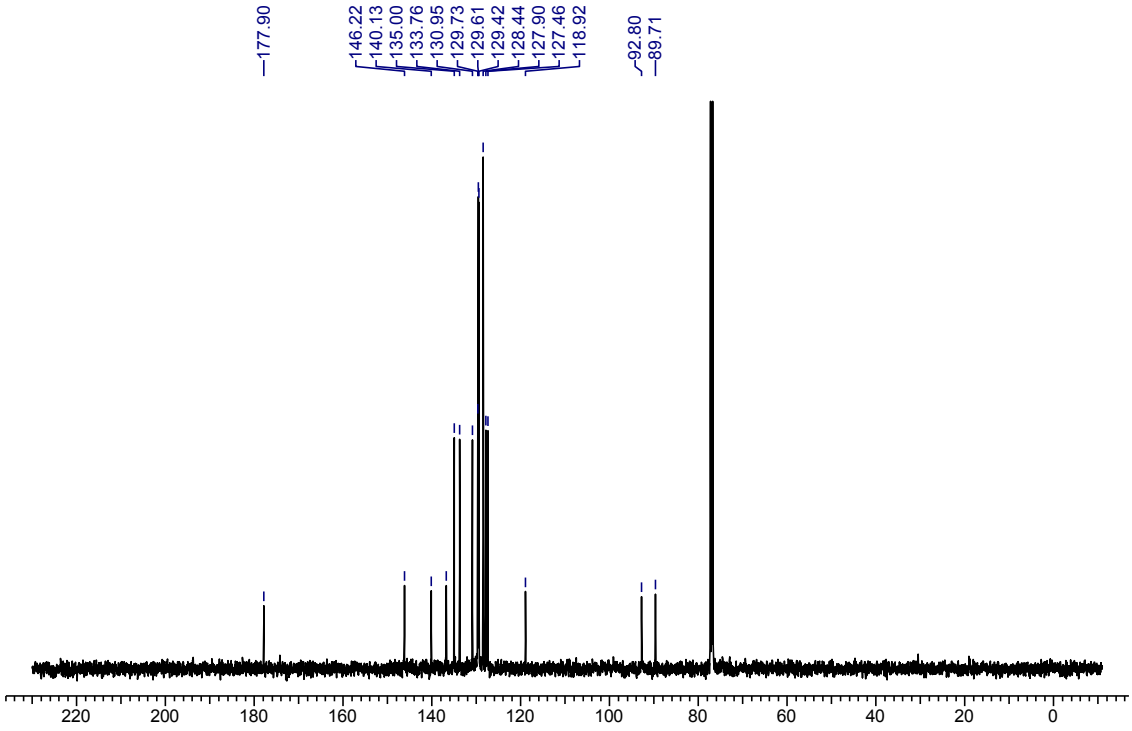


^{1}H and ^{13}C Spectra of **15.2k**

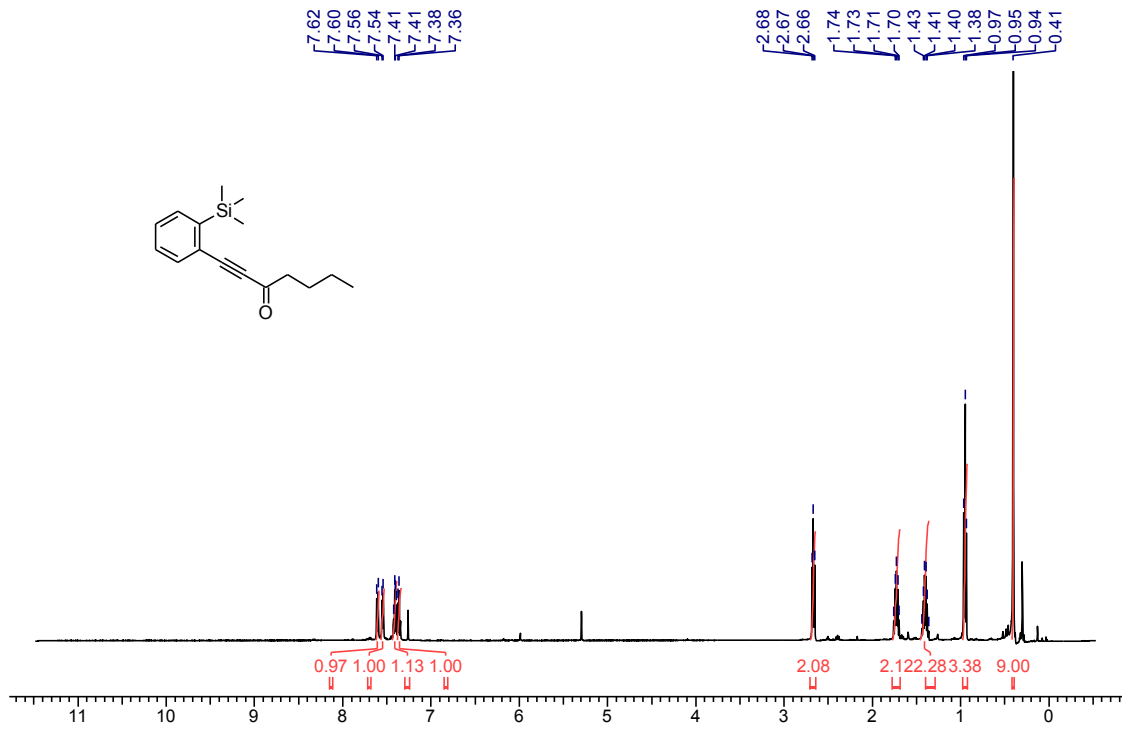


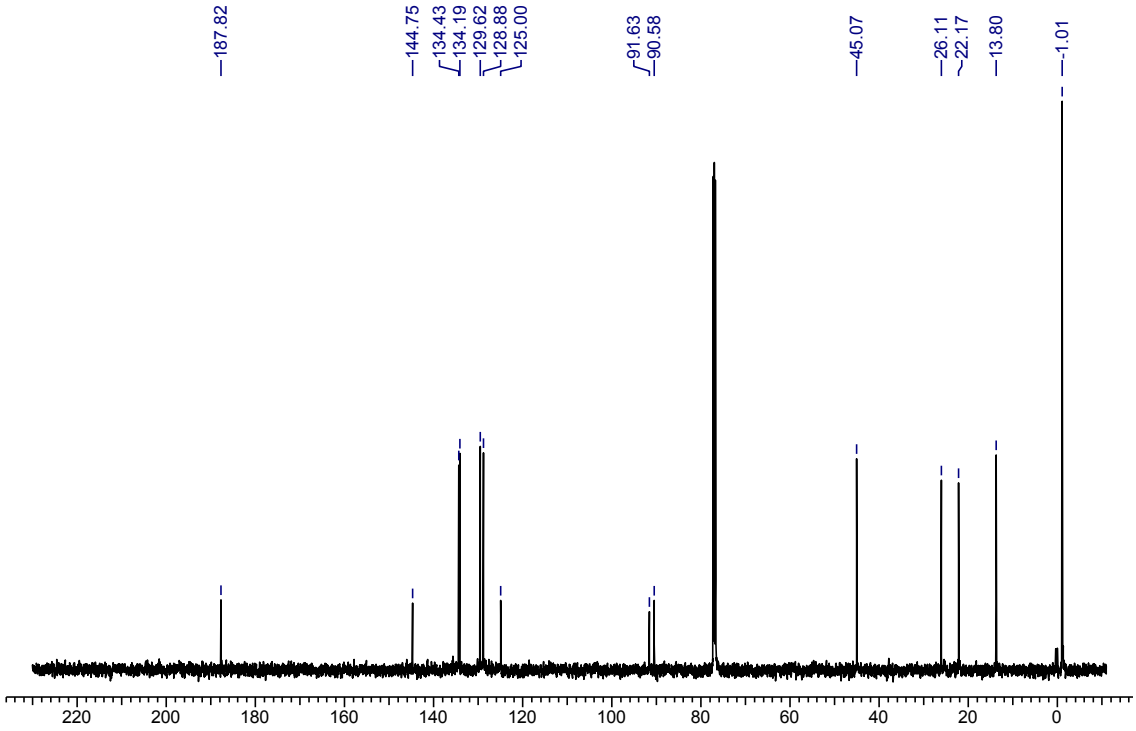
^{1}H and ^{13}C Spectra of **15.2l**



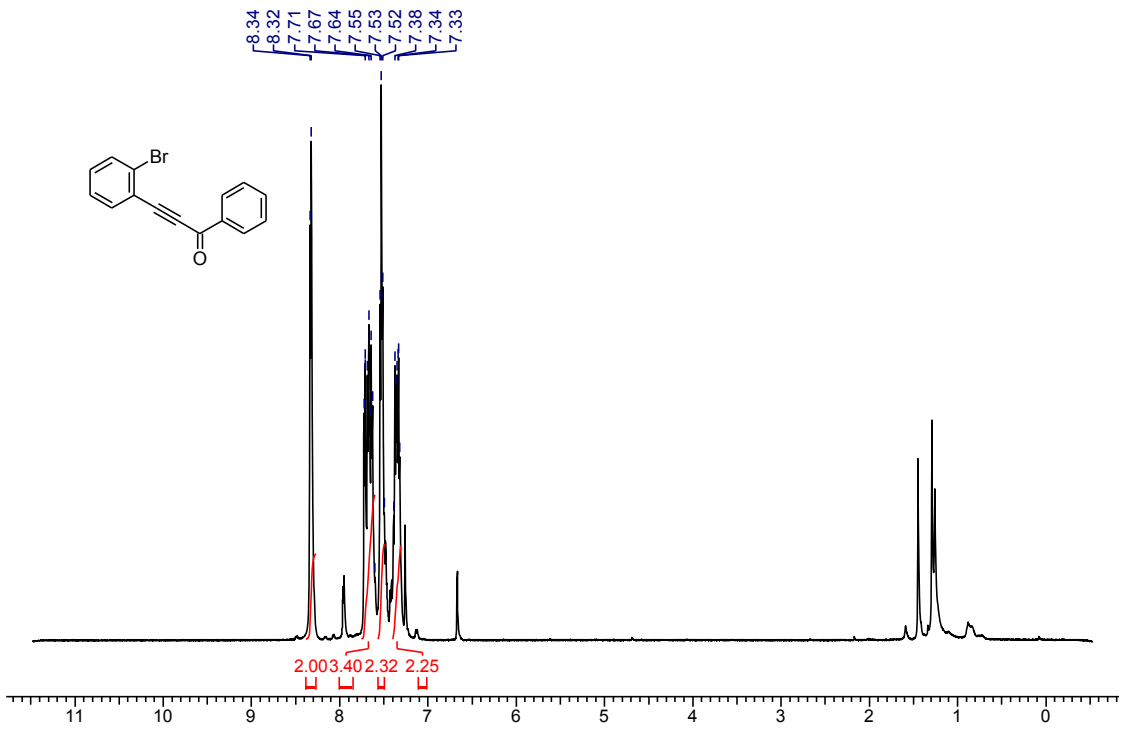


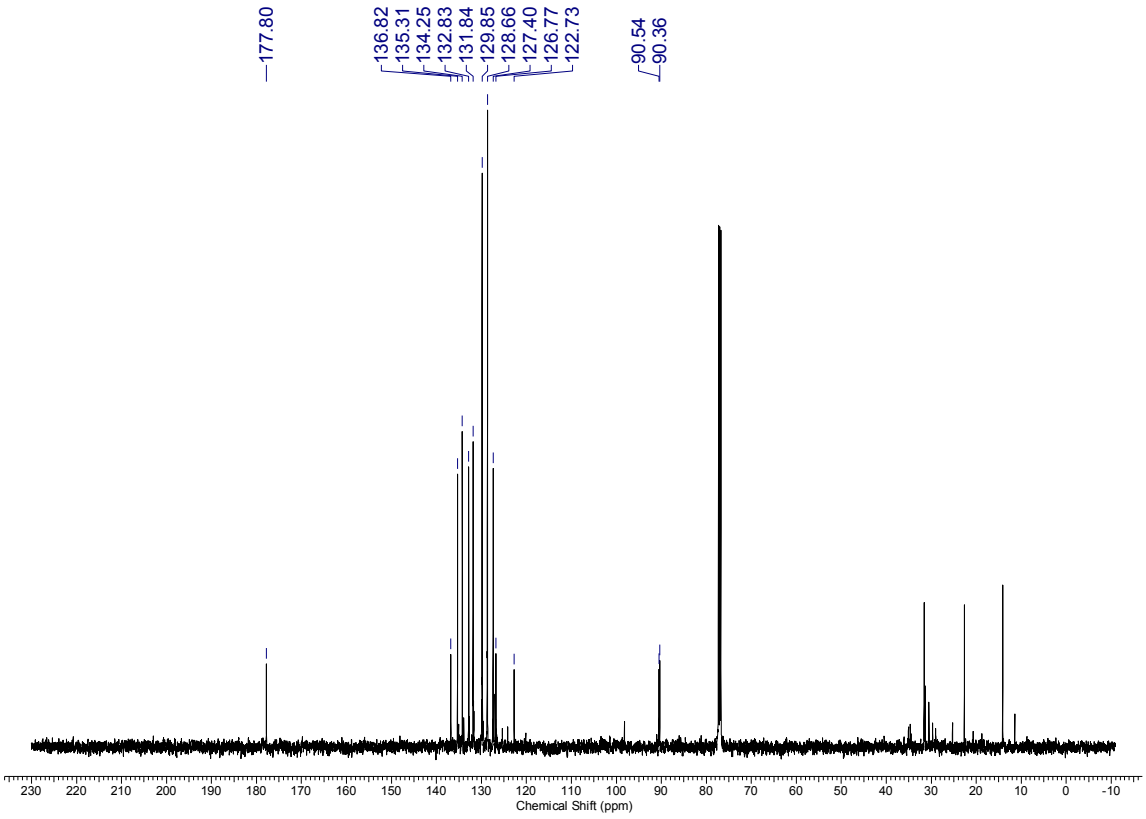
^{1}H and ^{13}C Spectra of **15.2m**



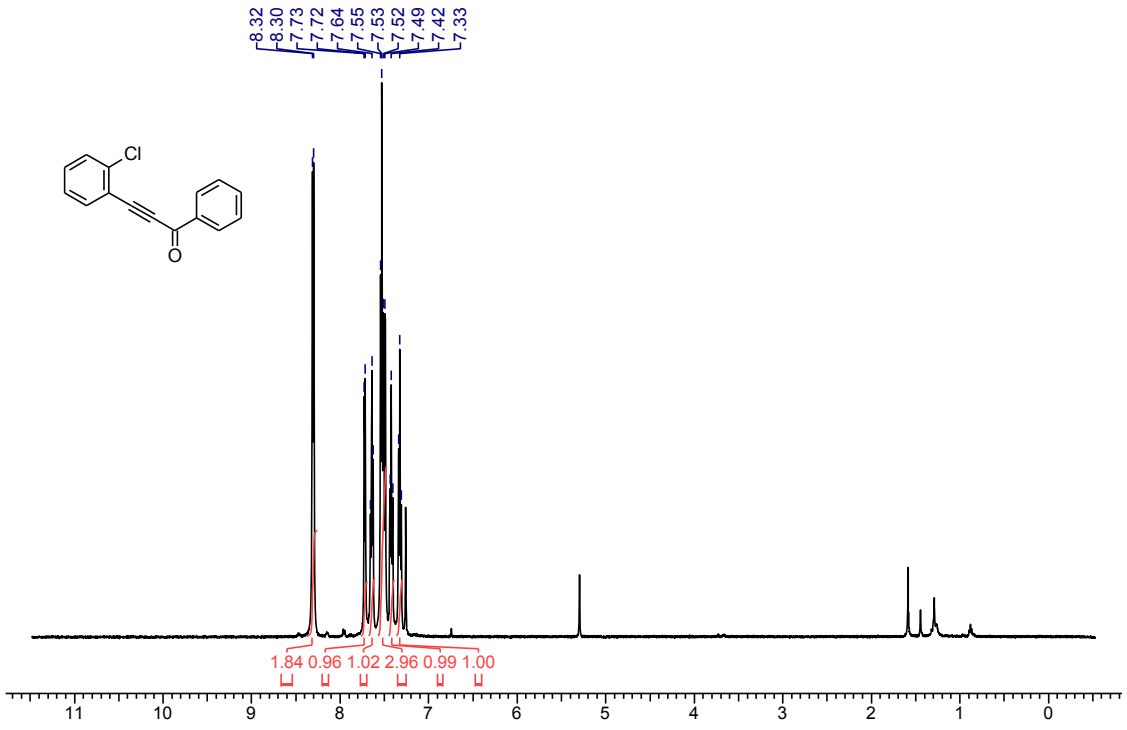


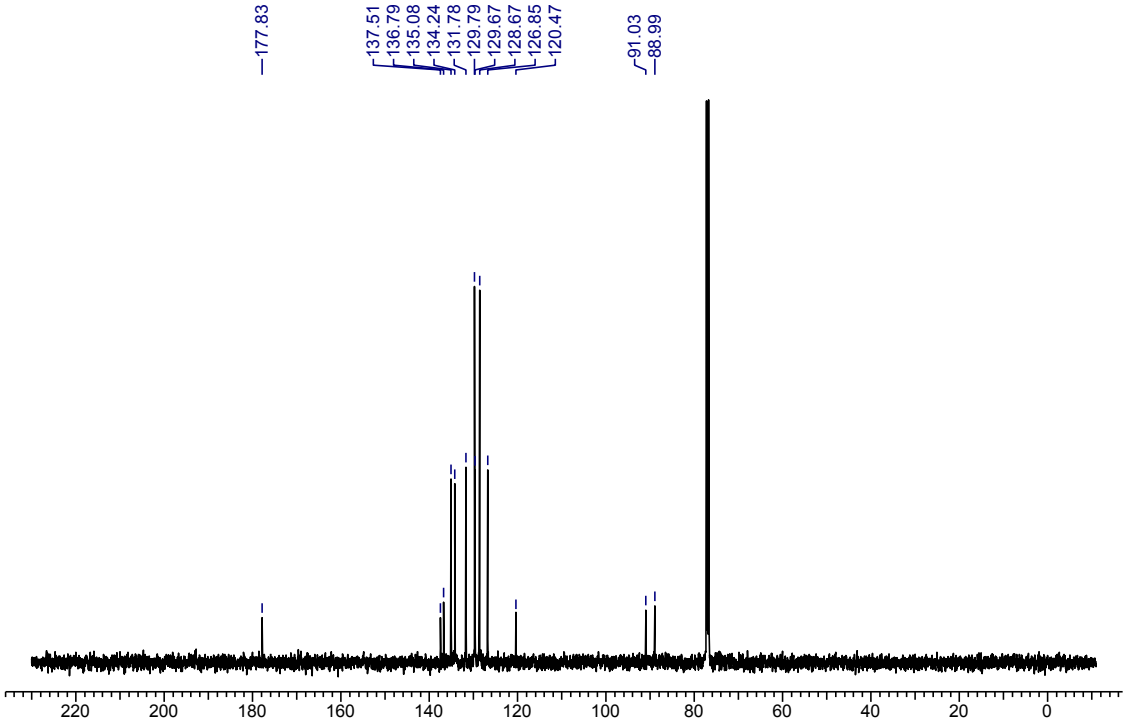
^{1}H and ^{13}C Spectra of **15.2n**



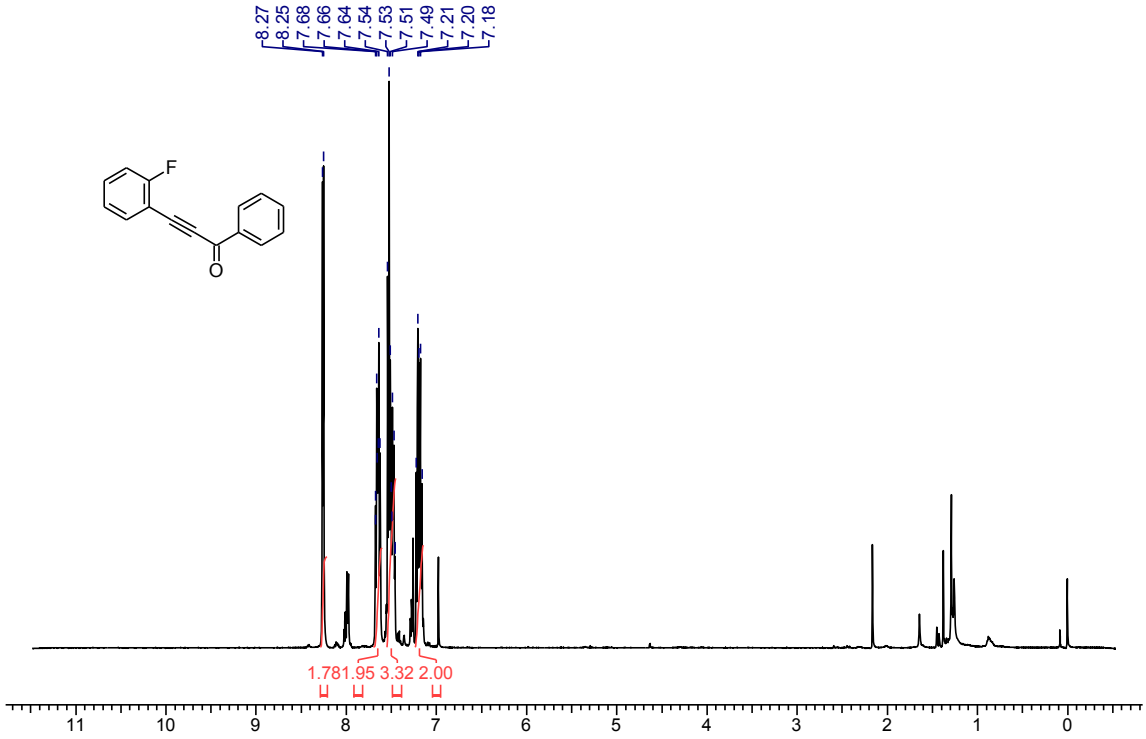


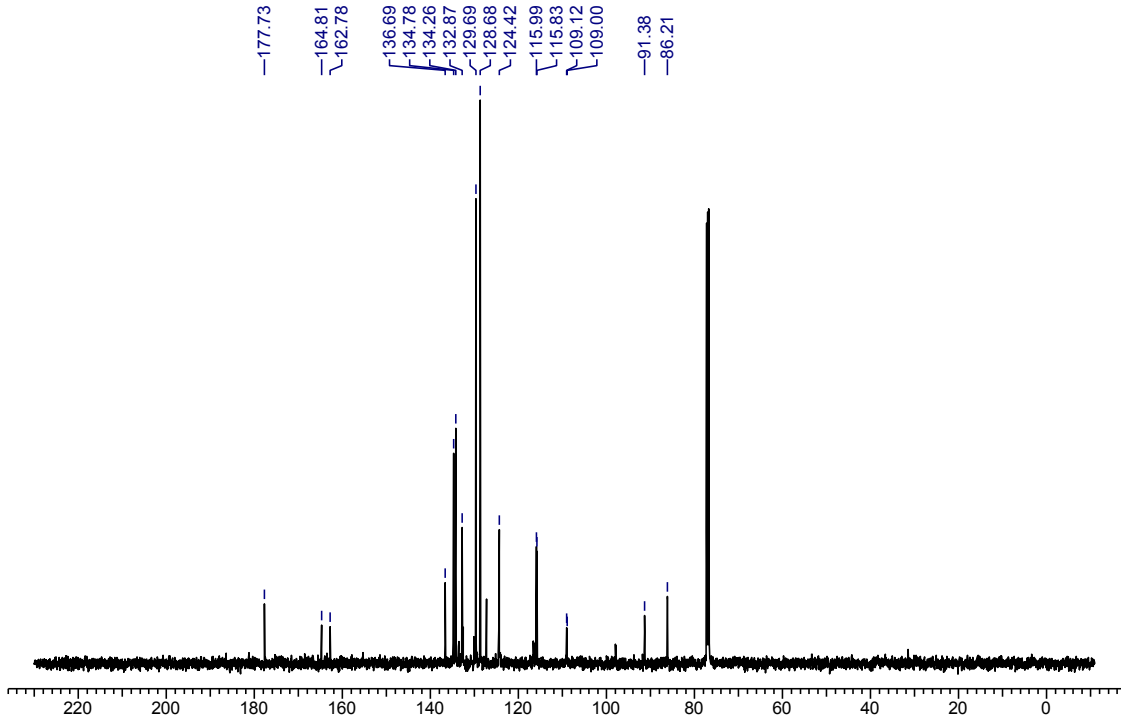
^{1}H and ^{13}C Spectra of **15.2o**



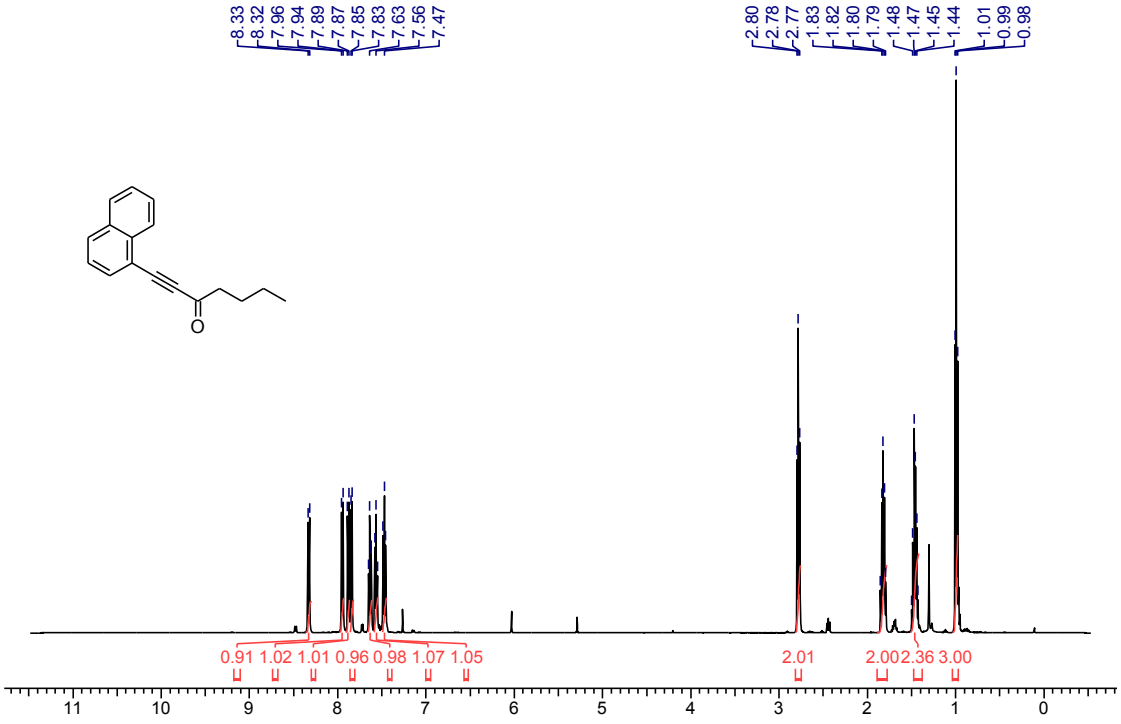


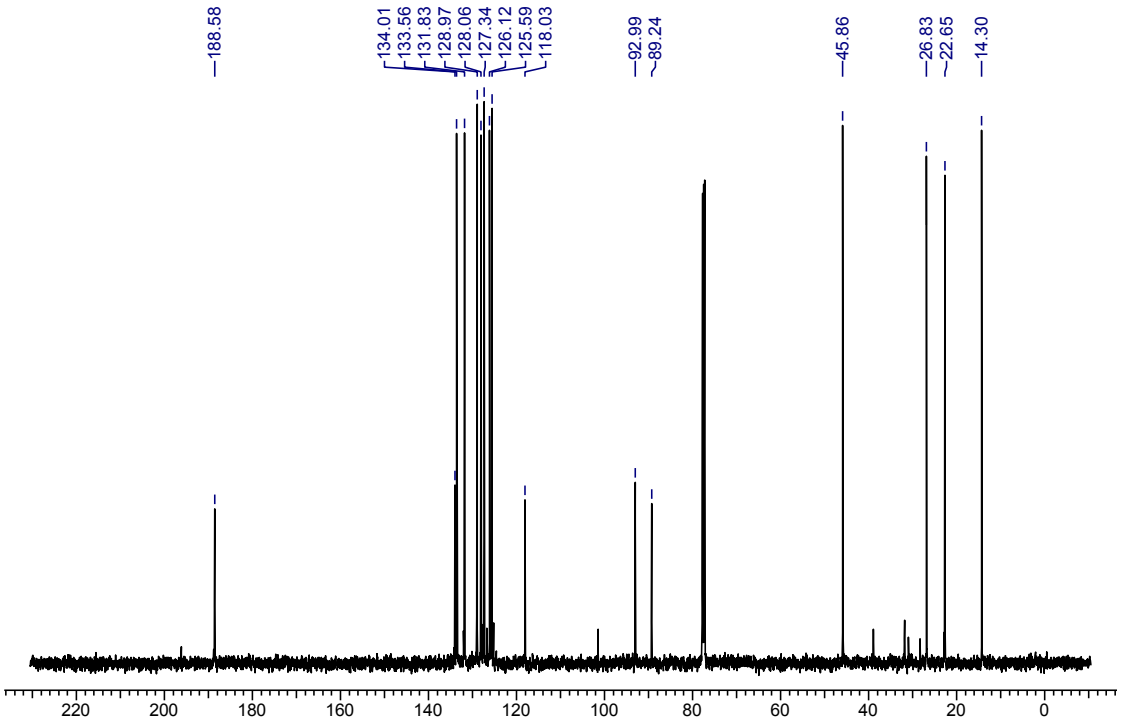
^{1}H and ^{13}C Spectra of **15.2p**



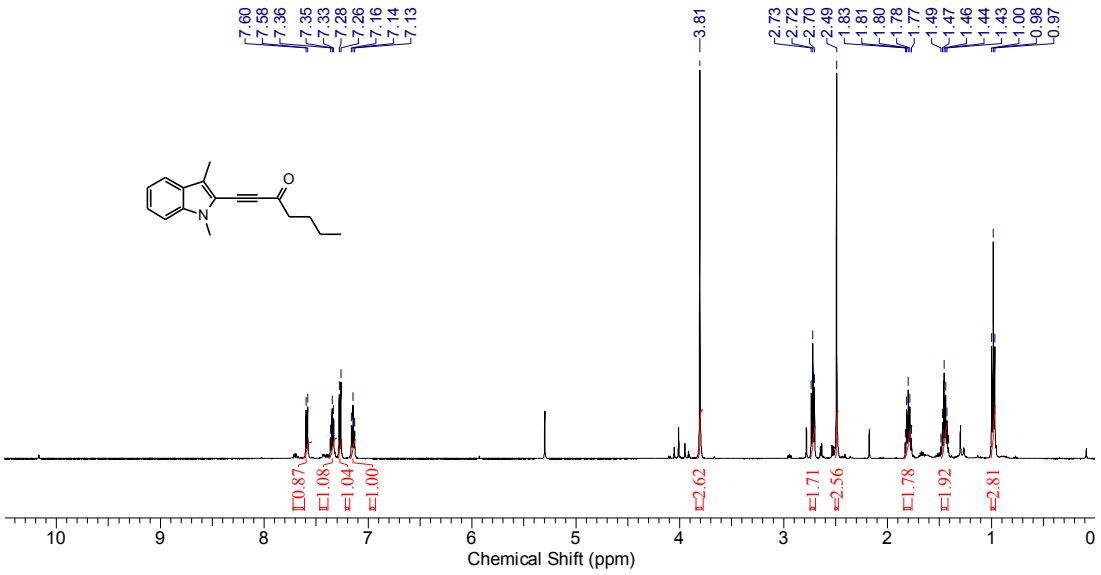


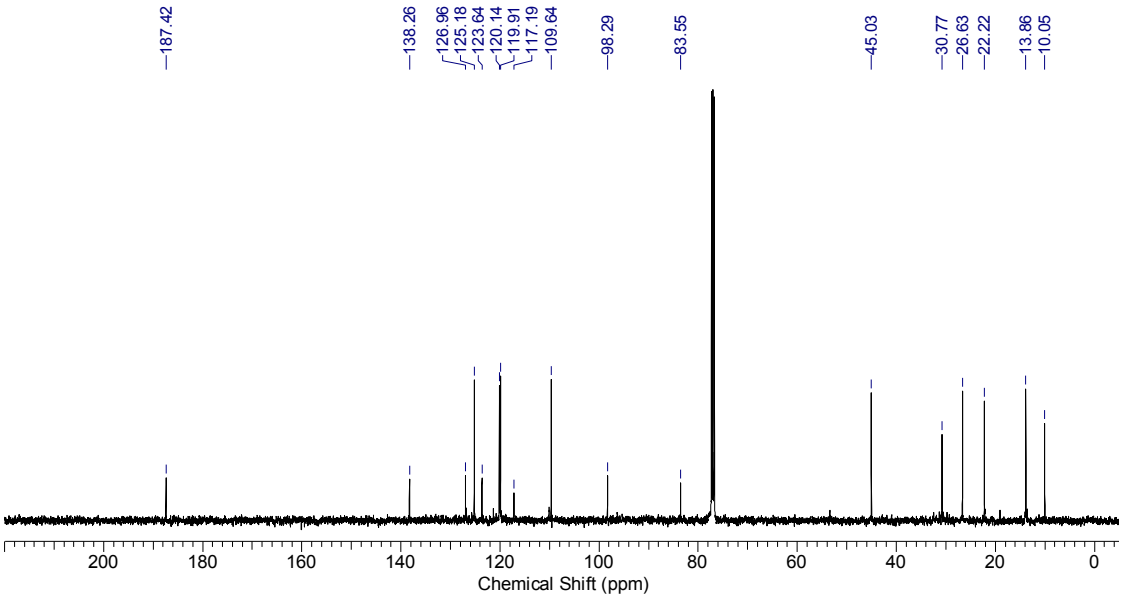
^{1}H and ^{13}C Spectra of **15.2q**



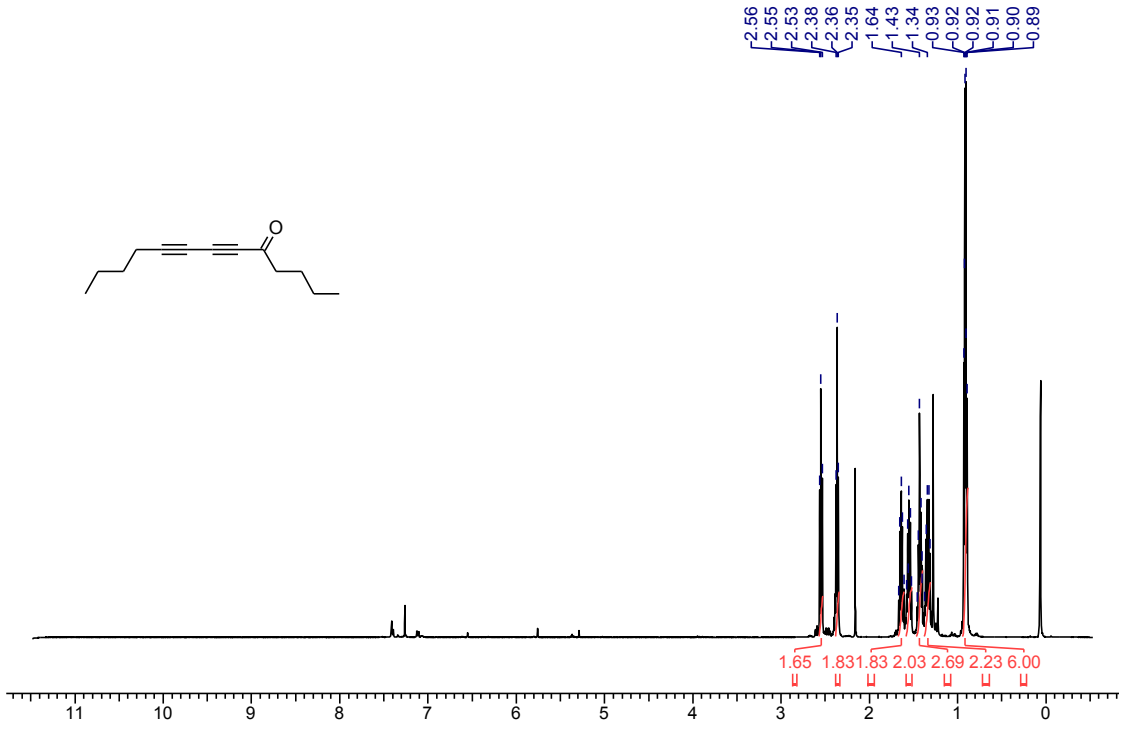


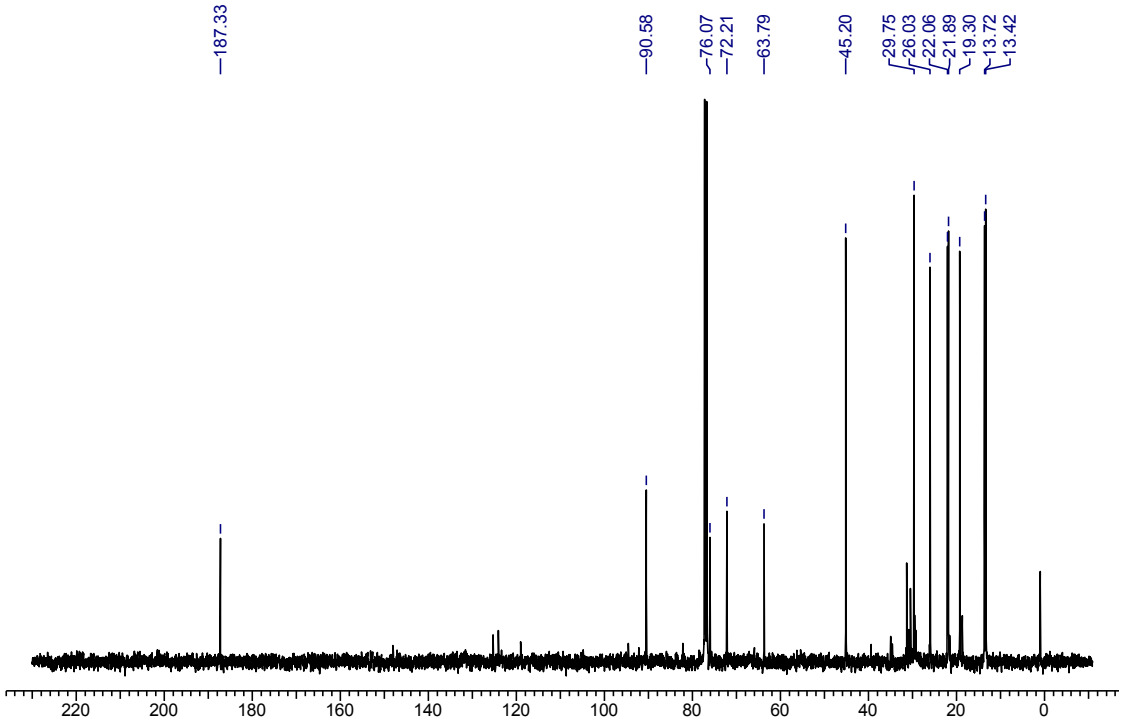
^{1}H and ^{13}C Spectra of **15.2r**



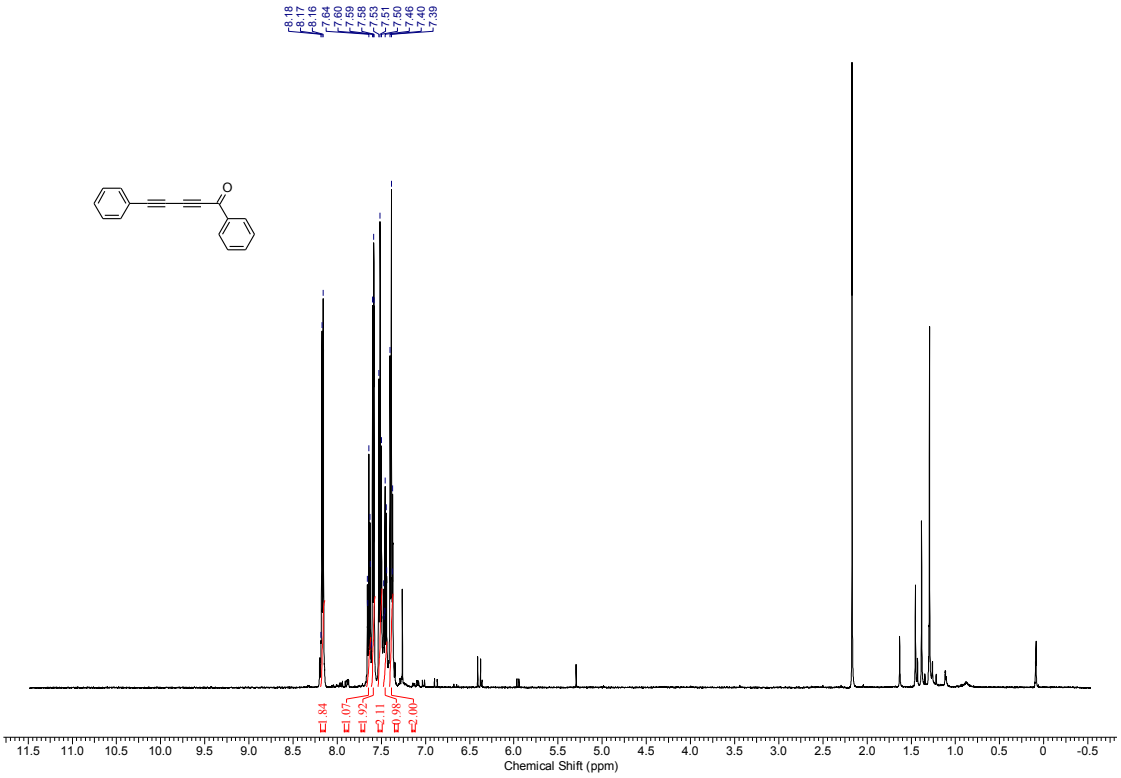


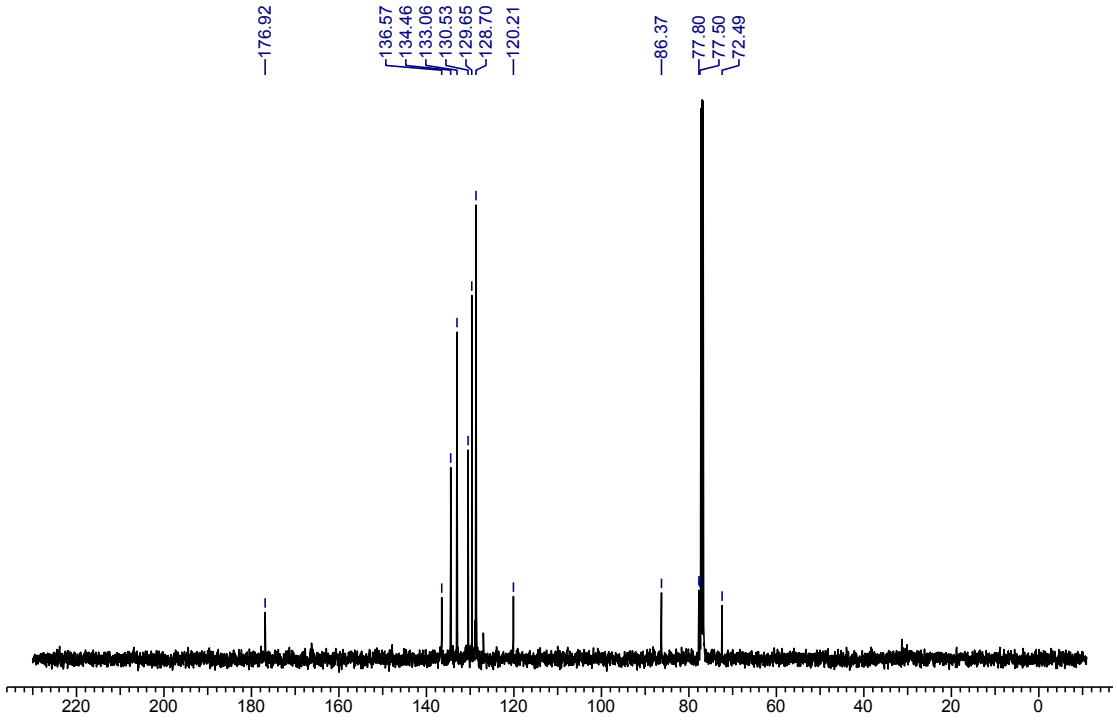
^{1}H and ^{13}C Spectra of **18.2a**



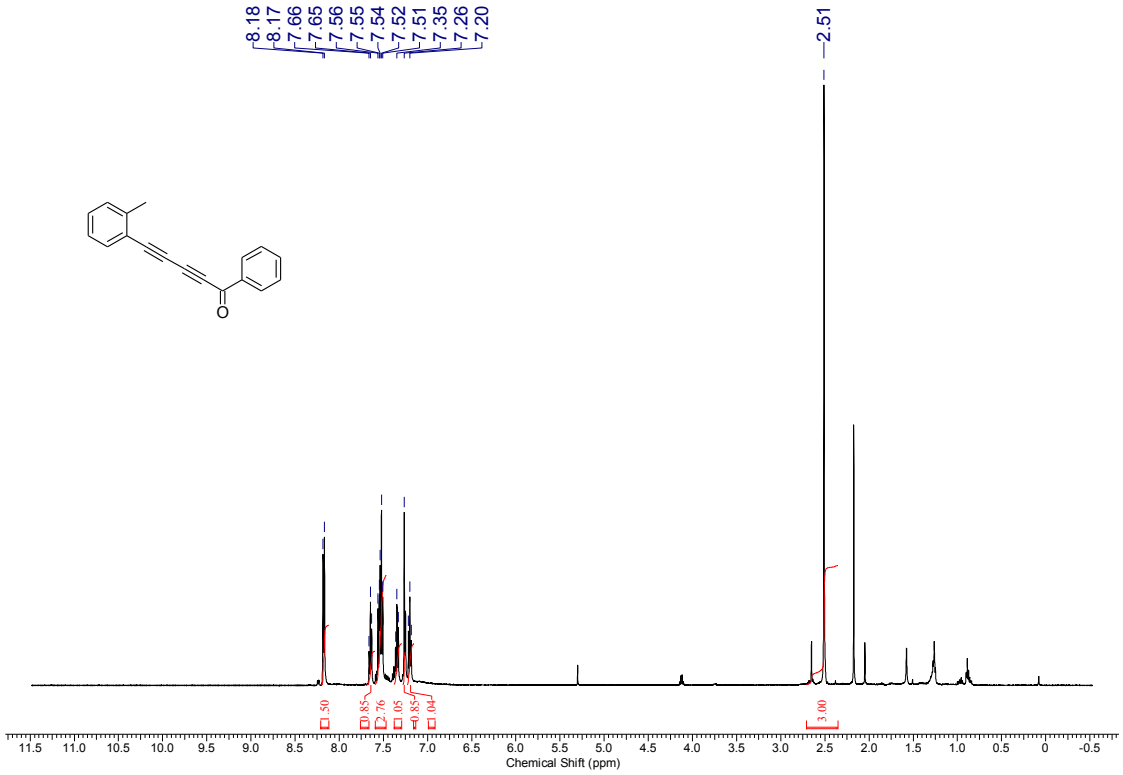


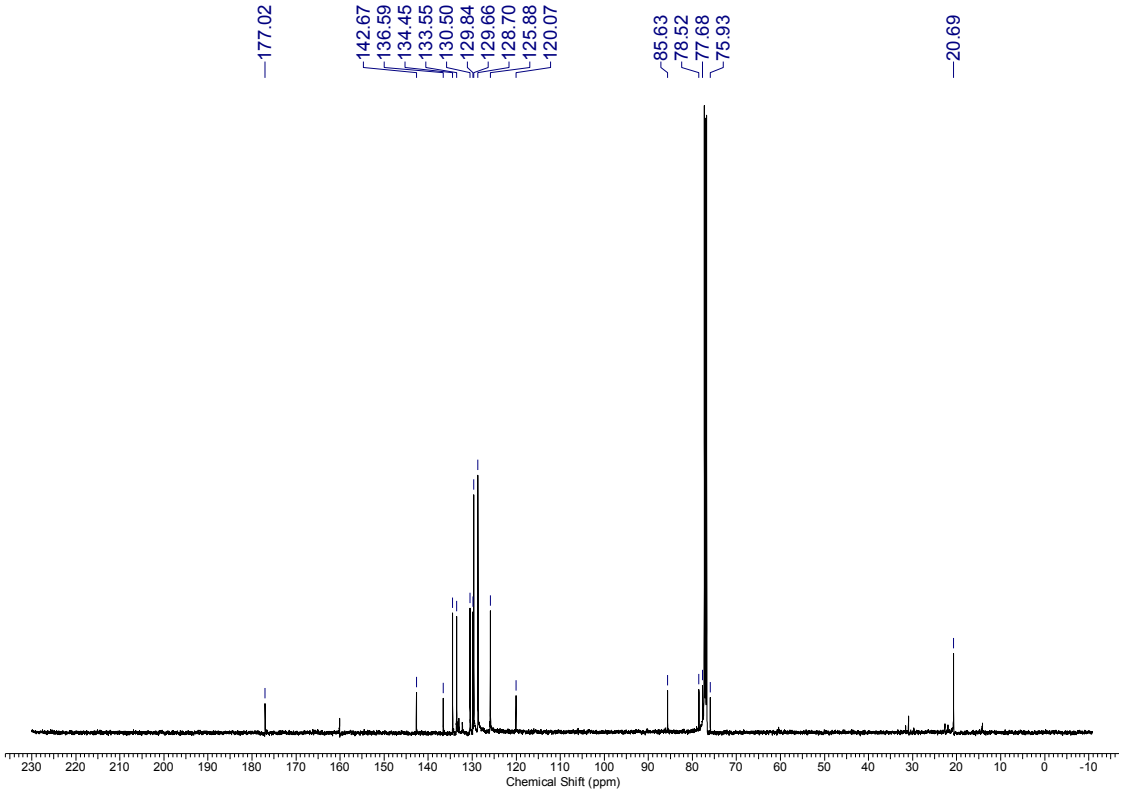
^{1}H and ^{13}C Spectra of **18.2b**



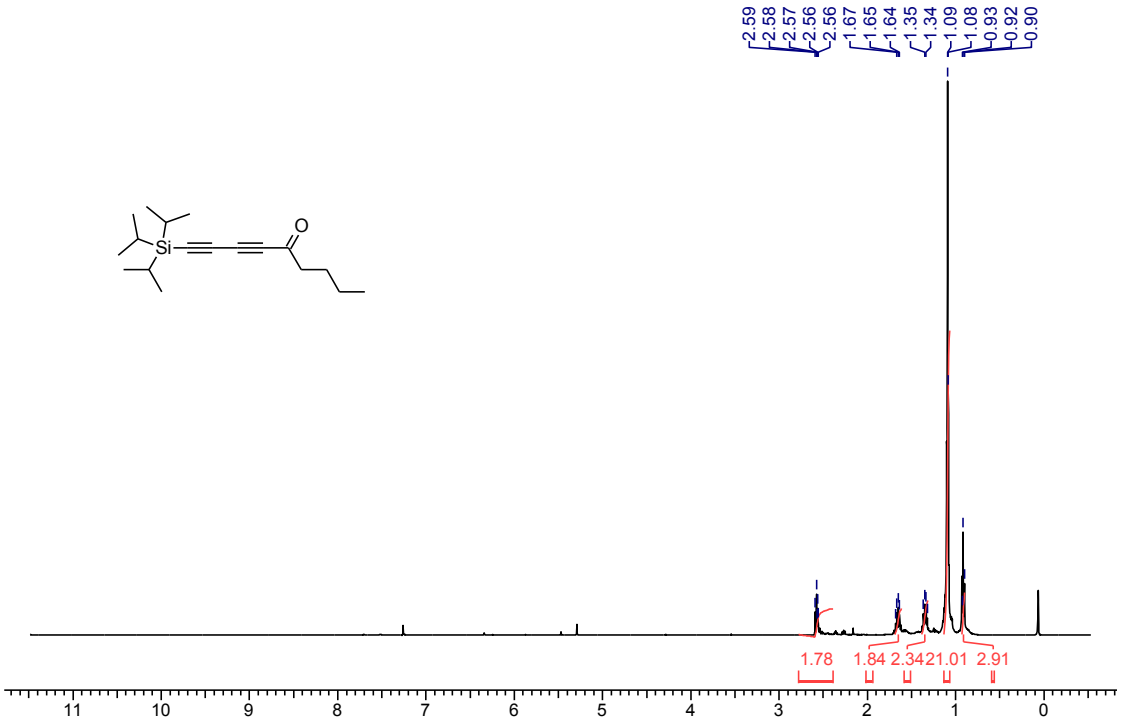


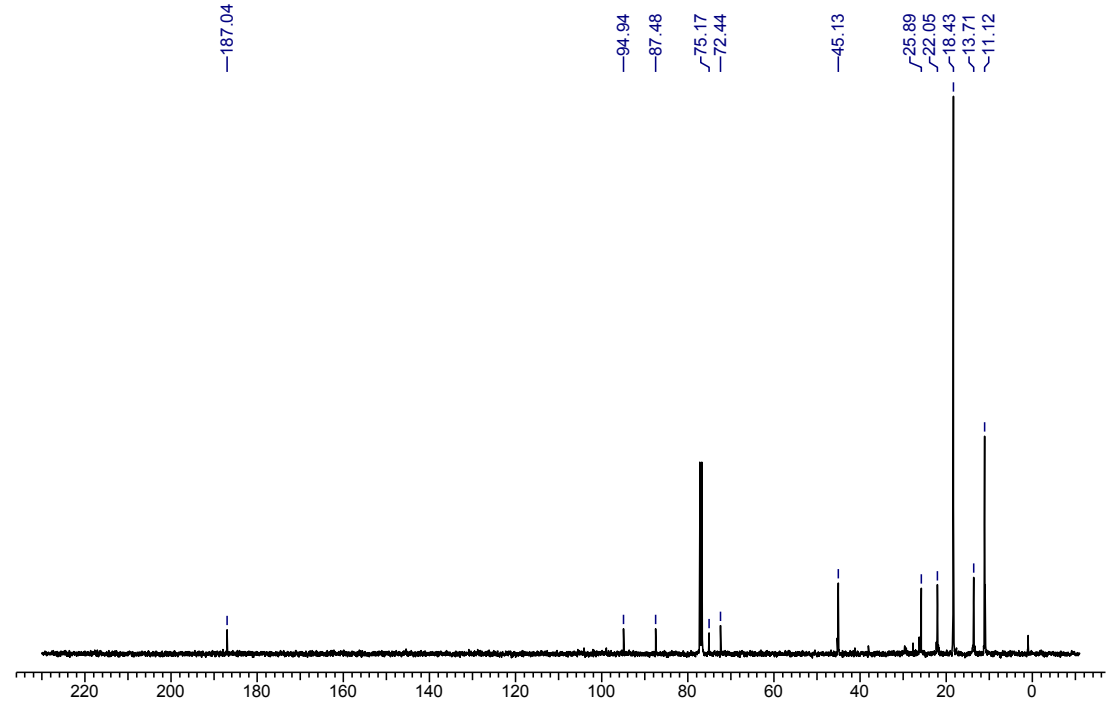
^{1}H and ^{13}C Spectra of **19.2a**



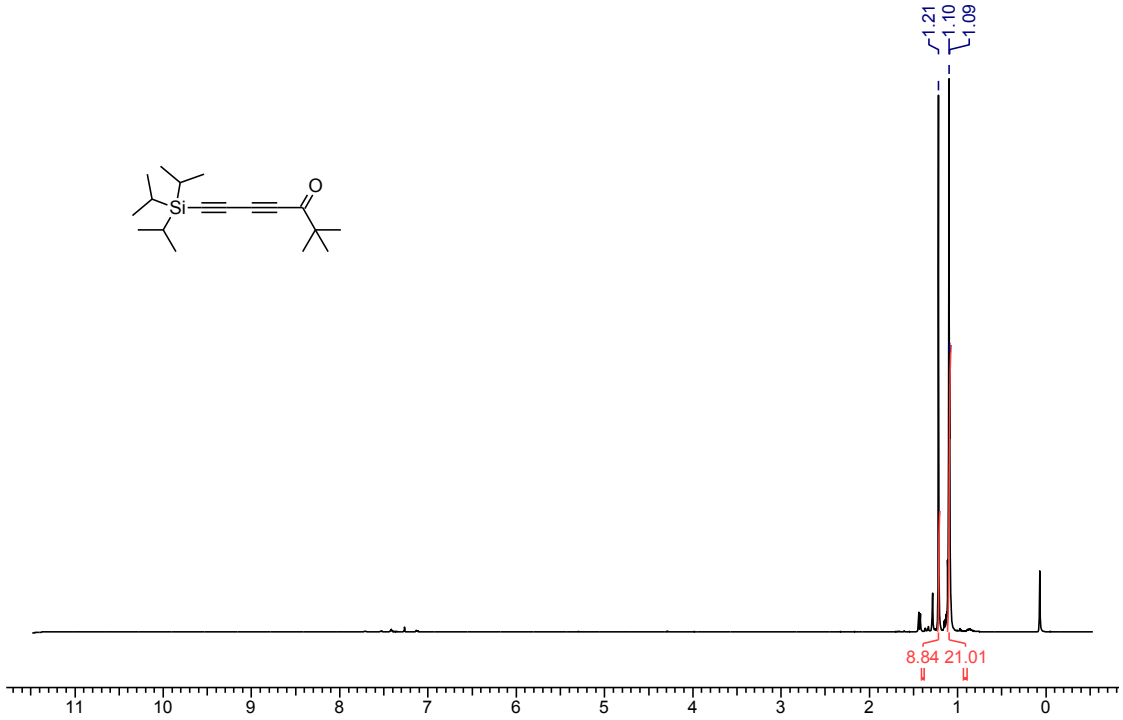


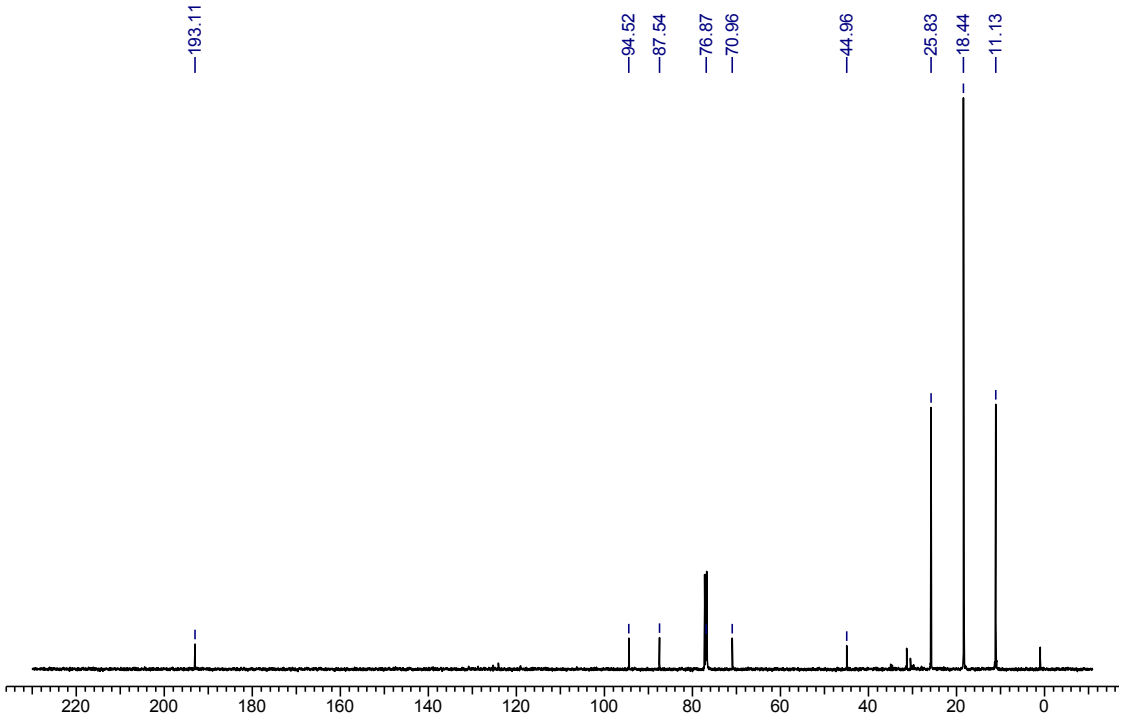
^{1}H and ^{13}C Spectra of **20.2a**



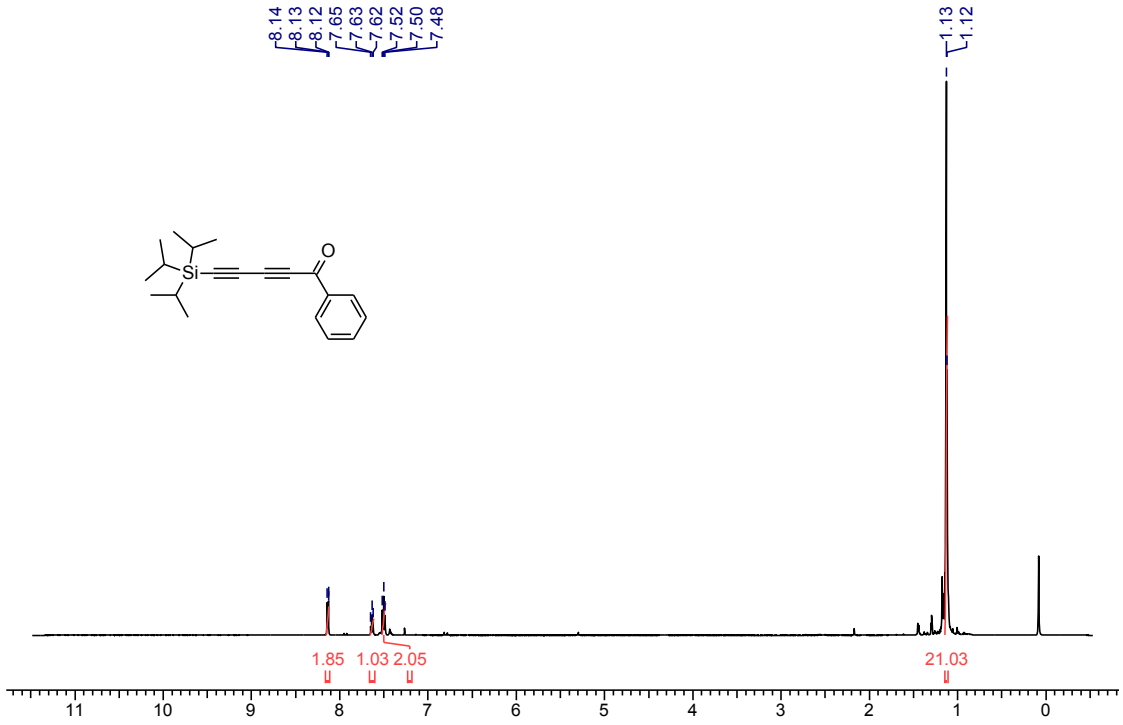


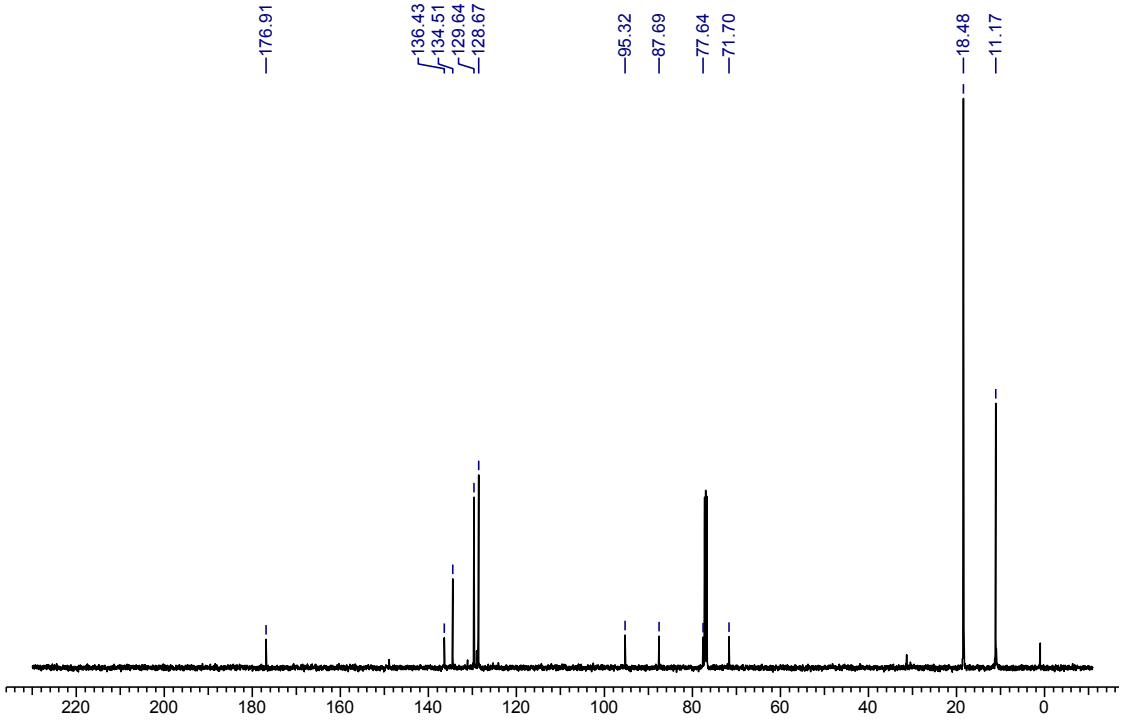
^{1}H and ^{13}C Spectra of **20.2b**



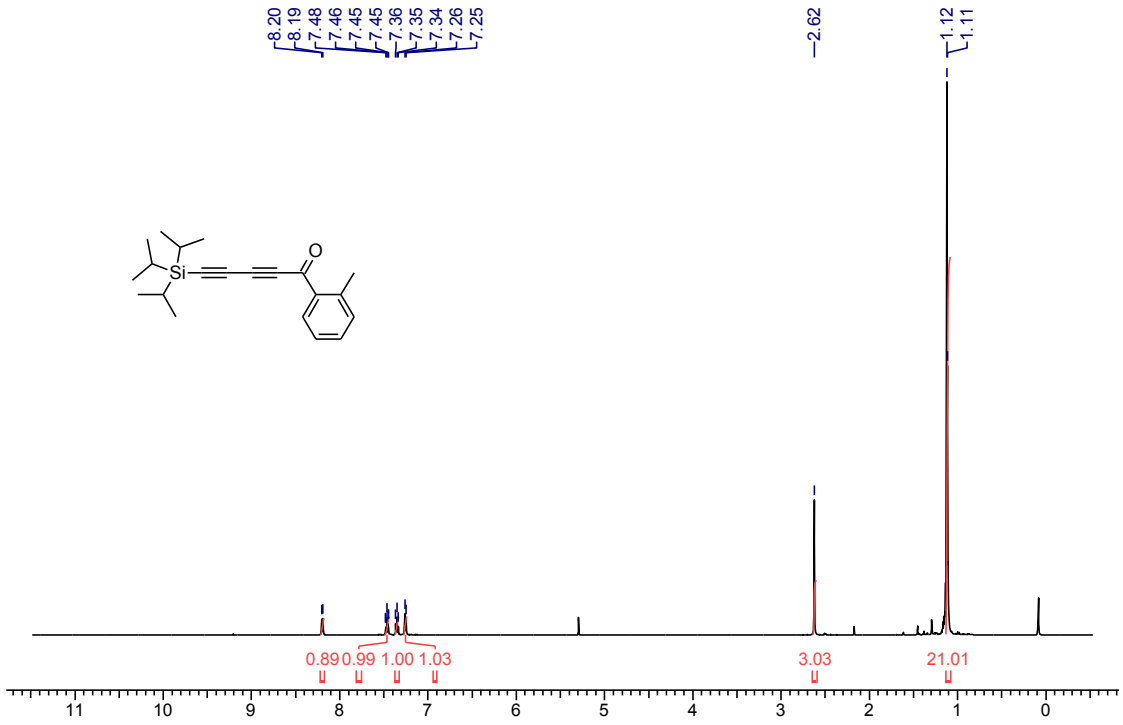


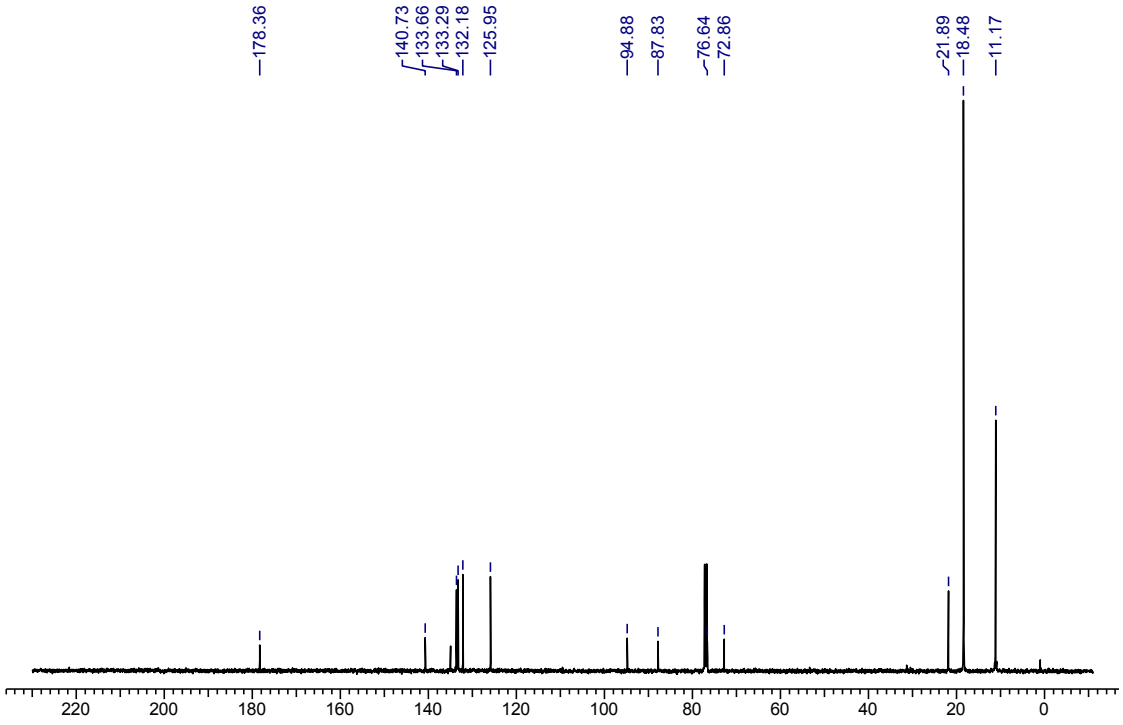
^{1}H and ^{13}C Spectra of **20.2c**



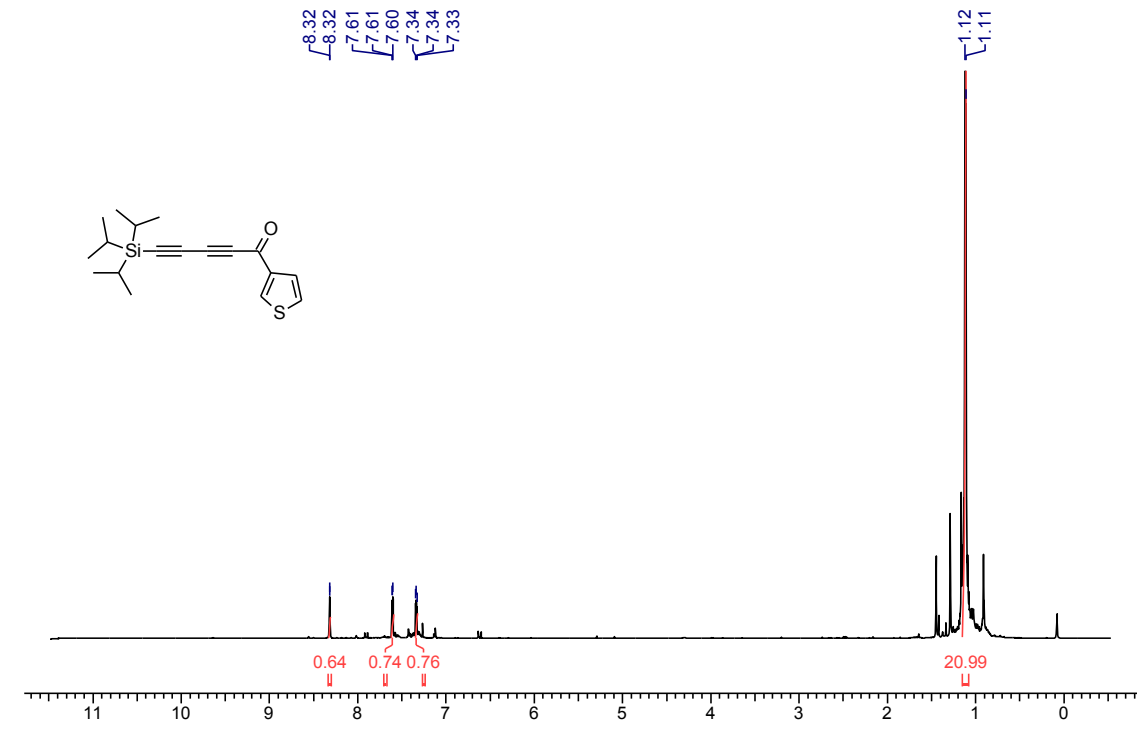


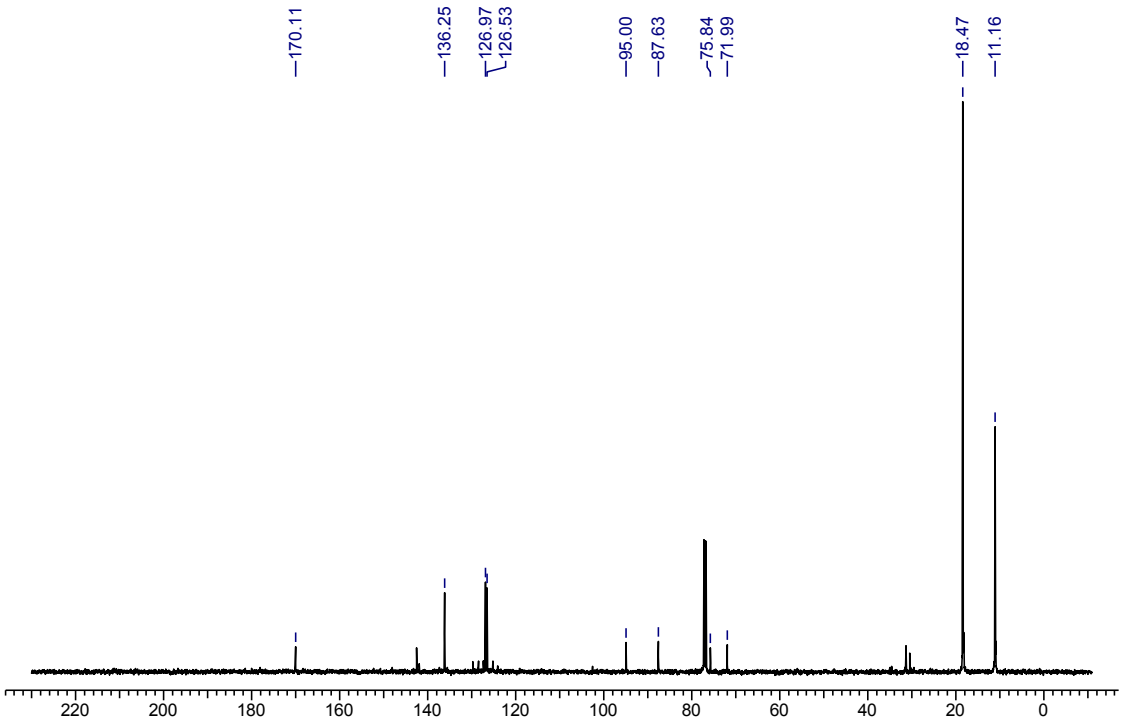
^{1}H and ^{13}C Spectra of **20.2d**



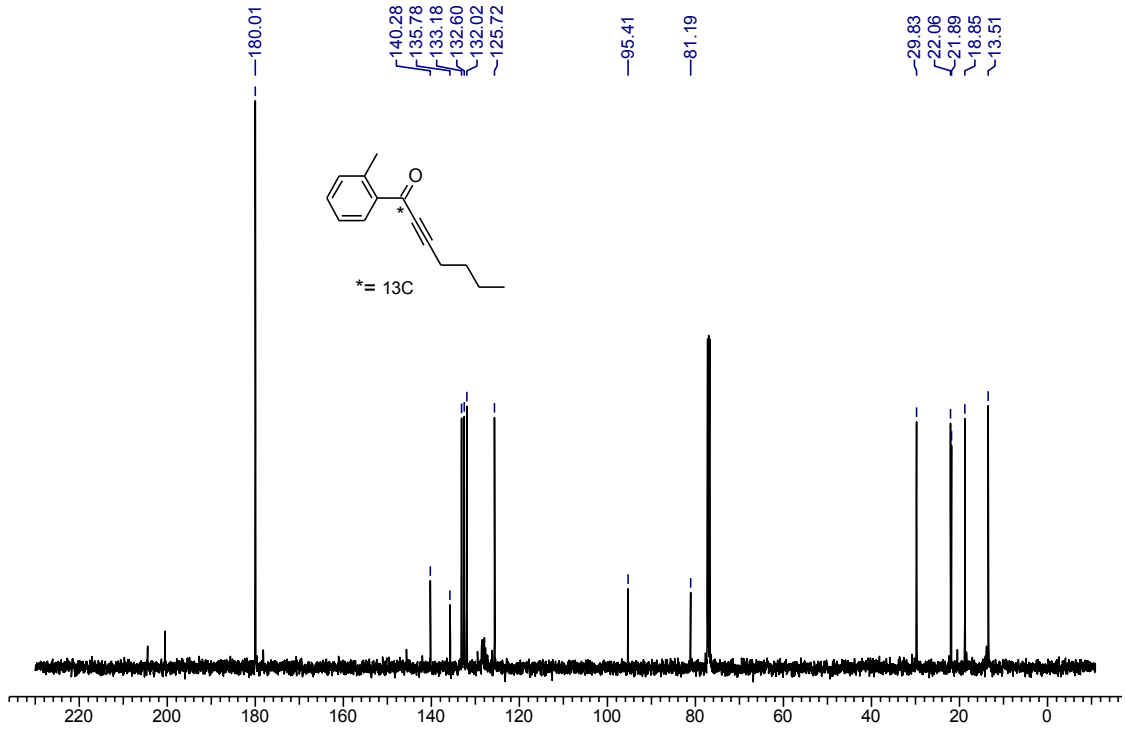


^{1}H and ^{13}C Spectra of **20.2e**

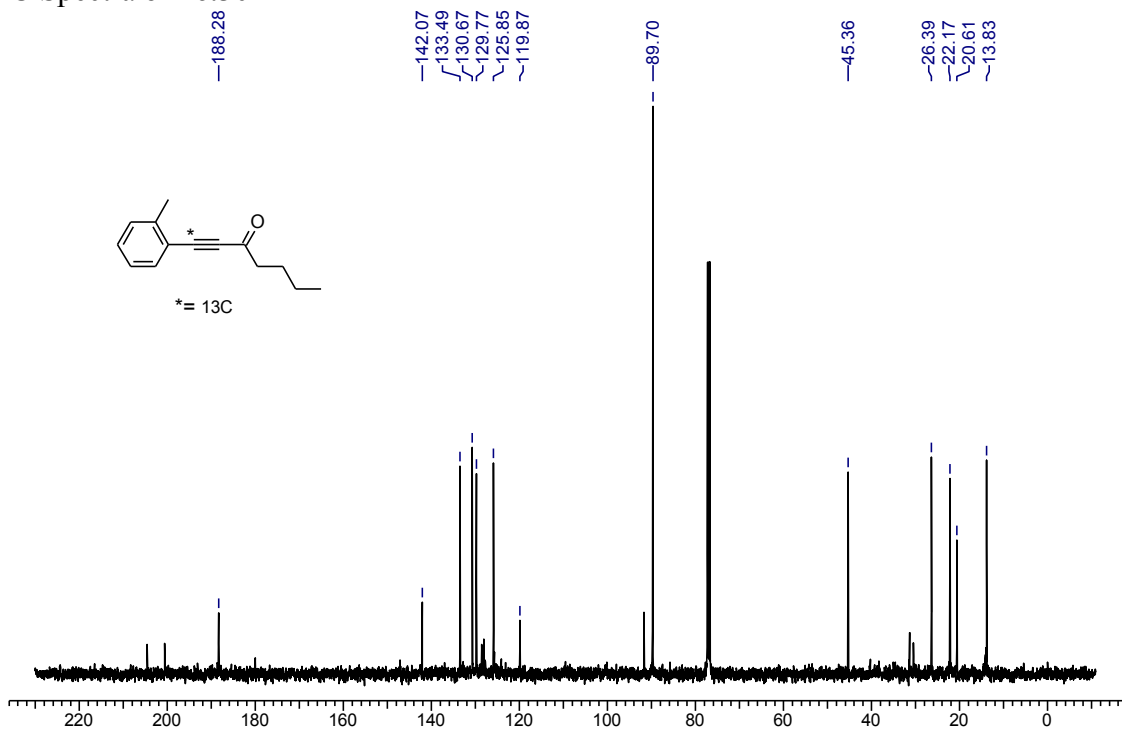




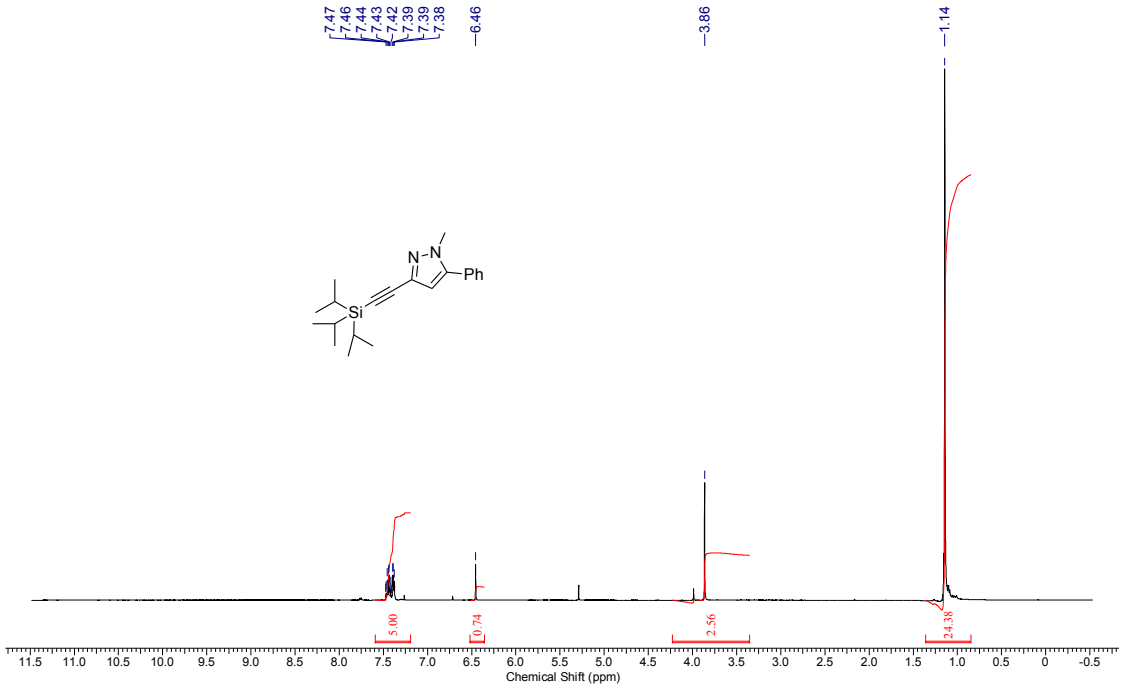
^{13}C Spectra of **16.1**

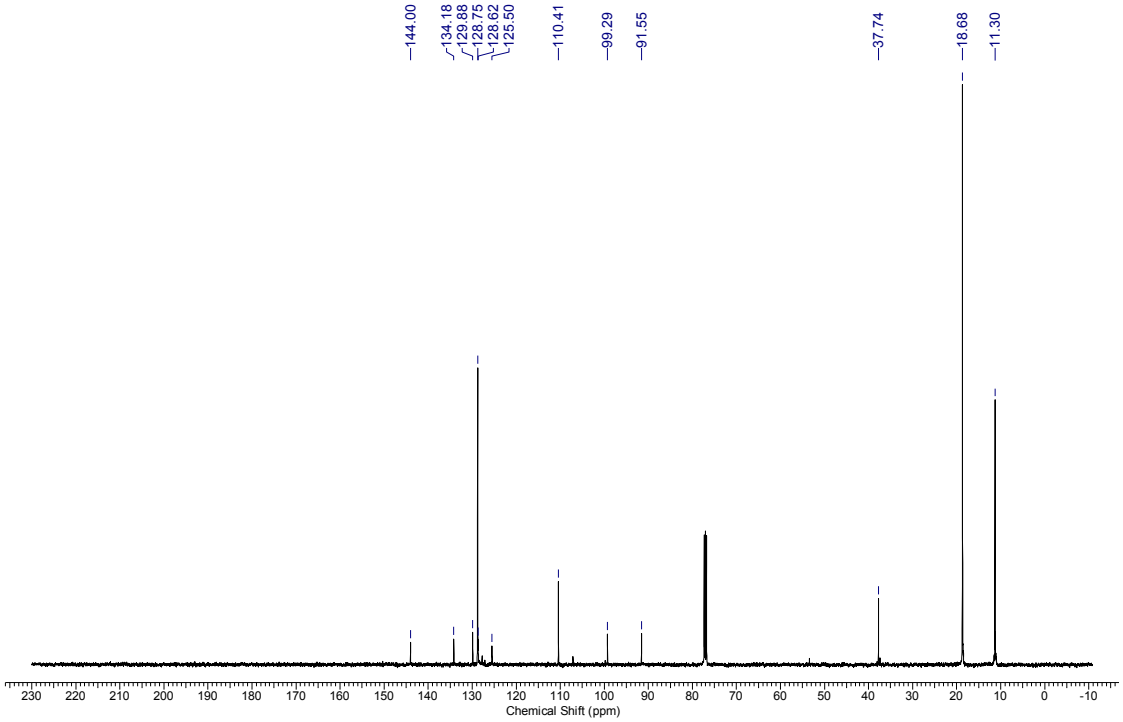


^{13}C Spectra of **16.30**

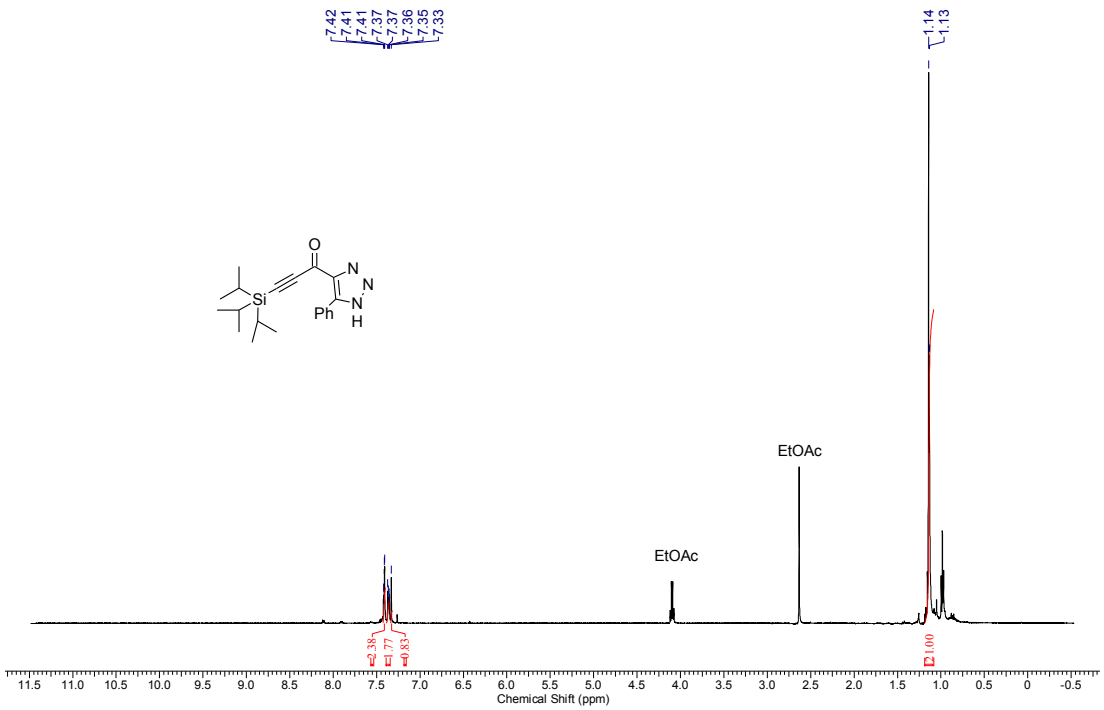


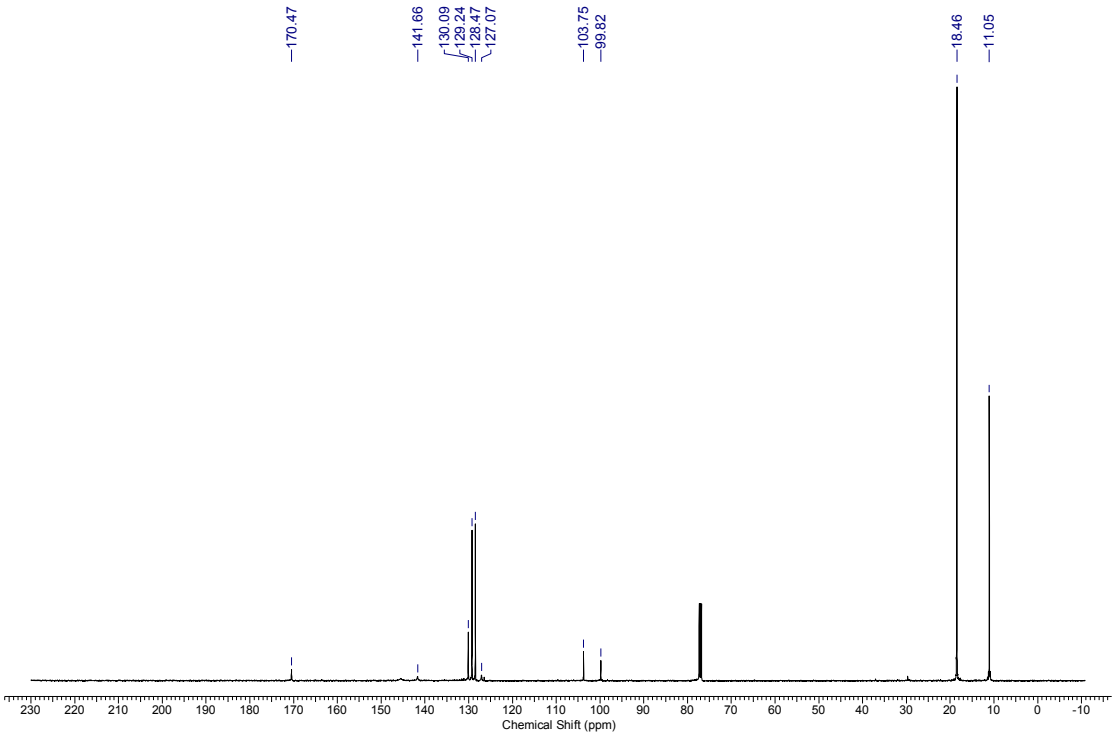
^{1}H and ^{13}C NMR of **21c1**



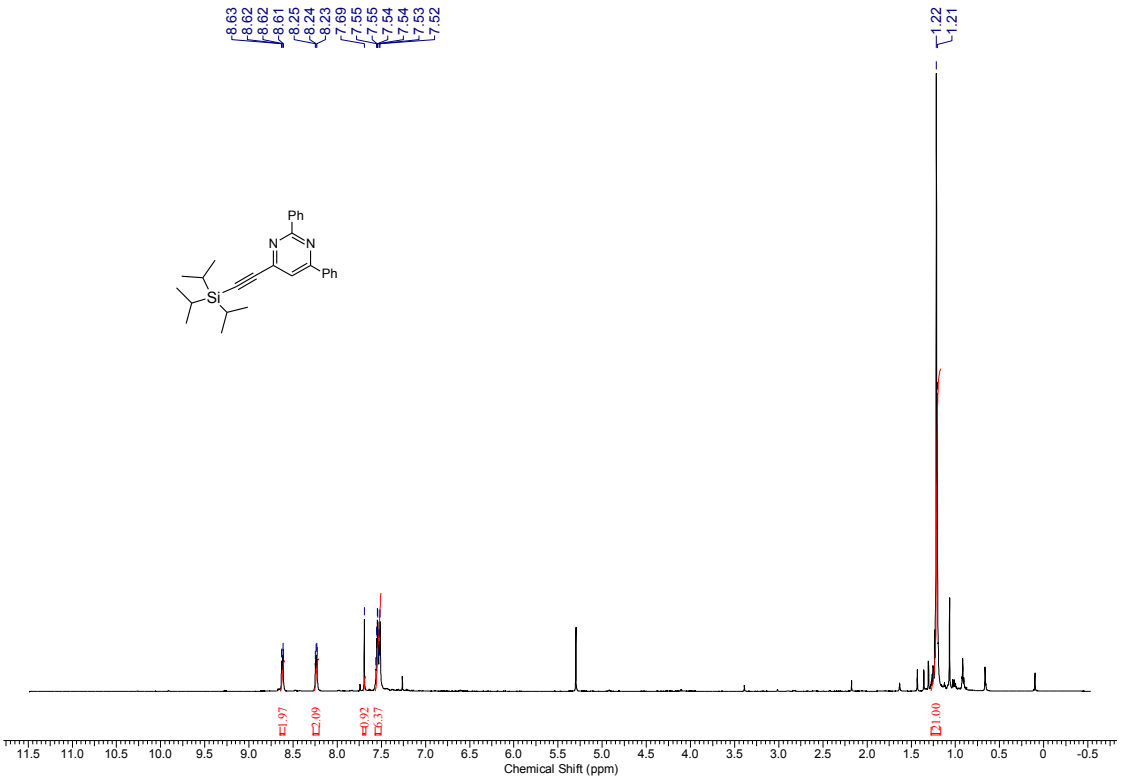


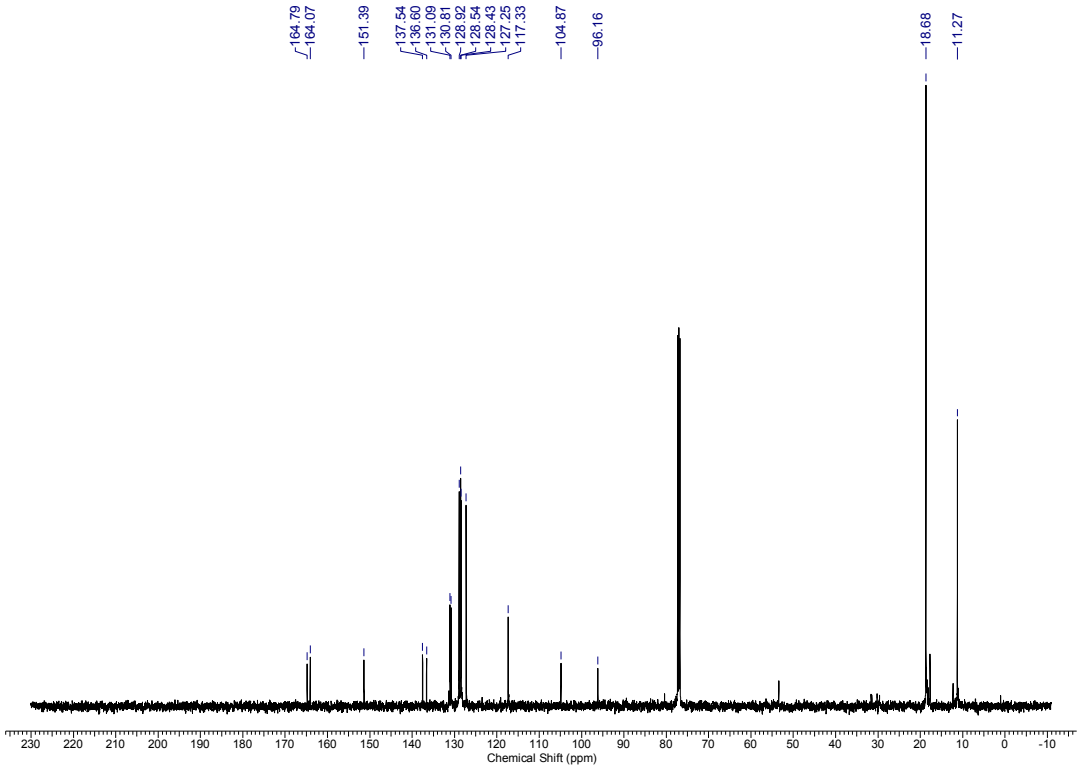
^{1}H and ^{13}C NMR of **21c2**



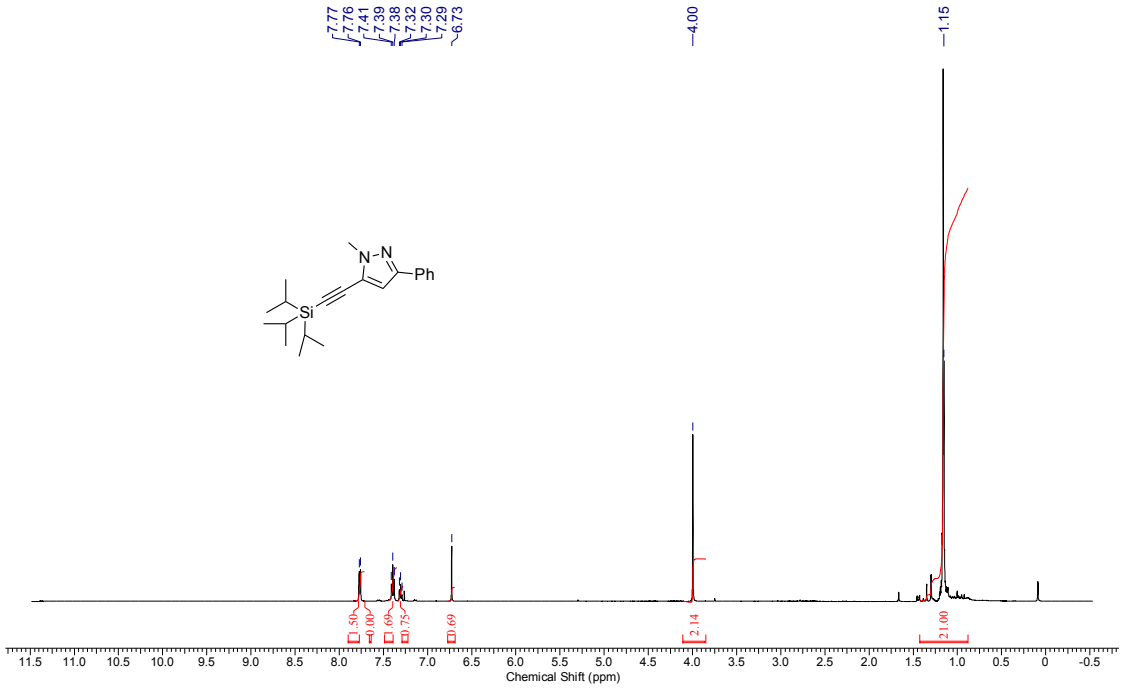


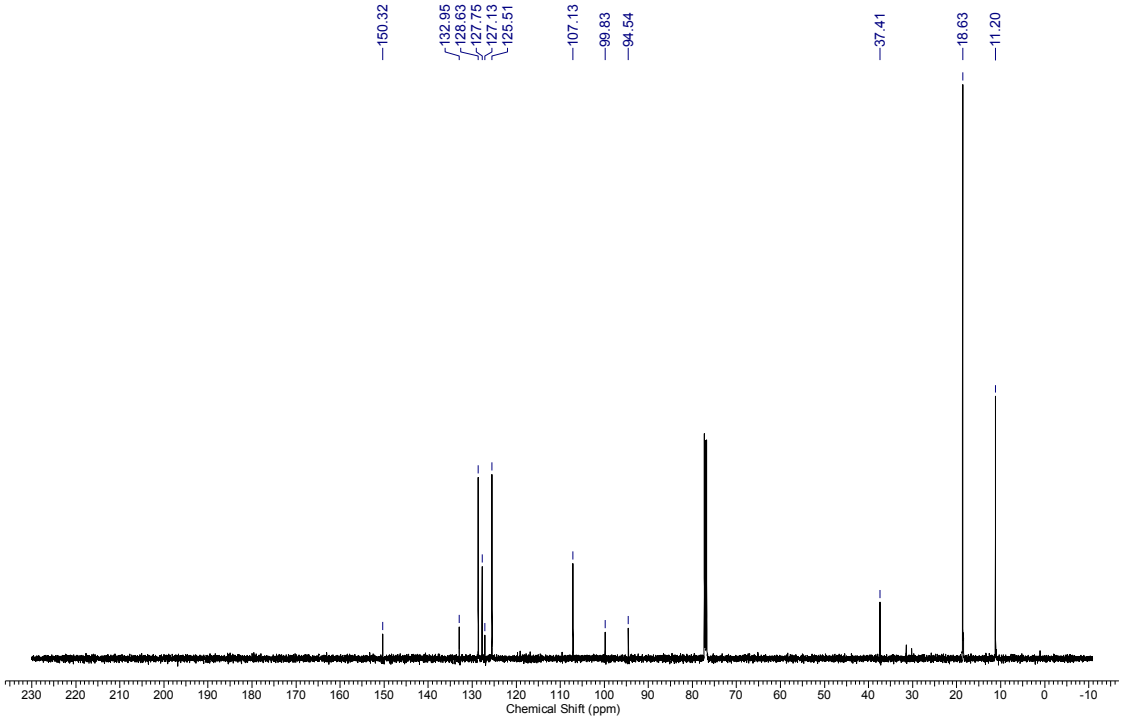
^{1}H and ^{13}C Spectra of **21c4**



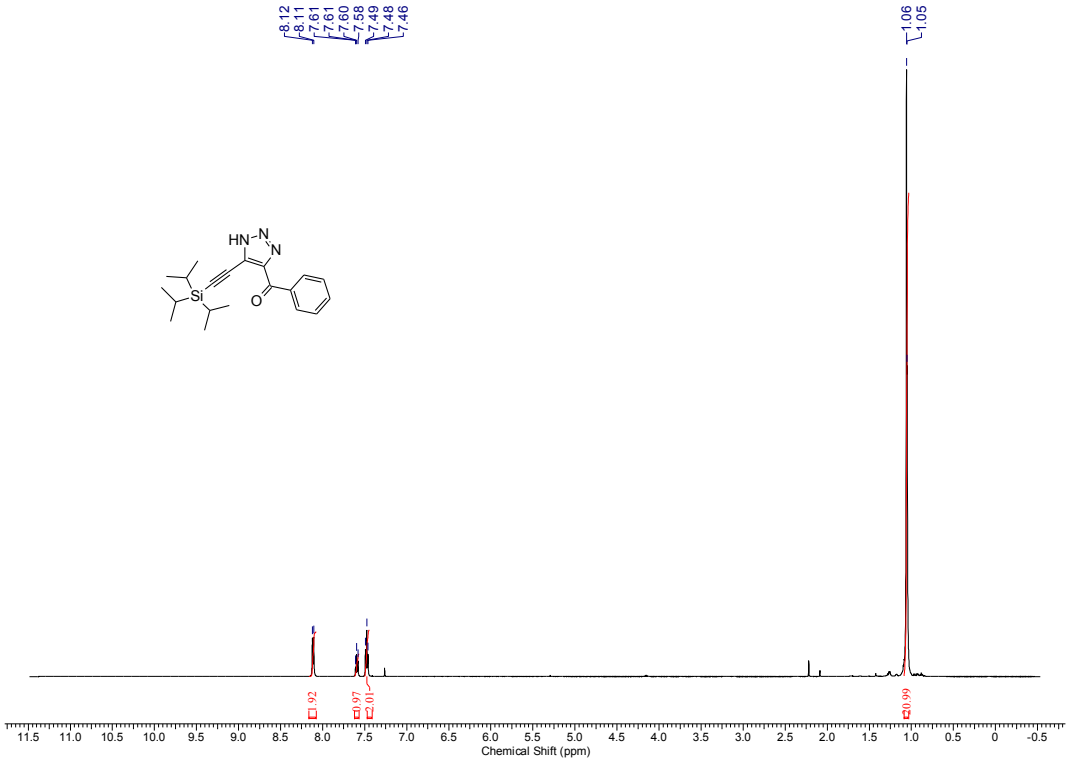


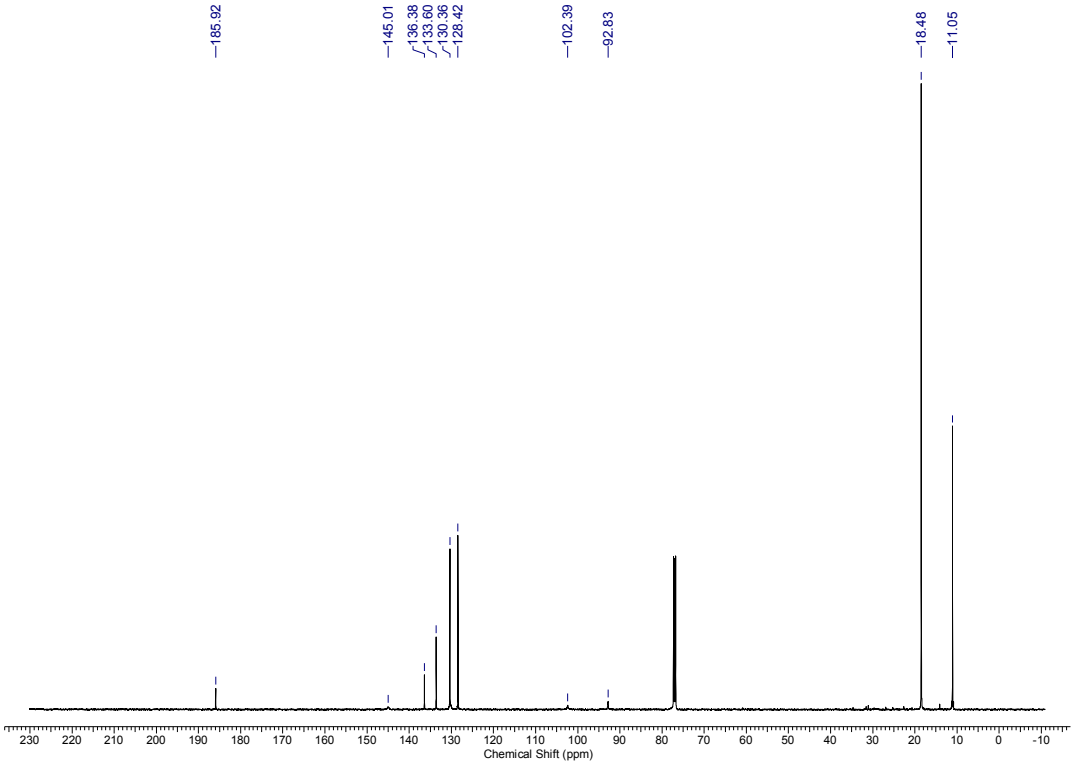
^{1}H and ^{13}C NMR of **22c1**



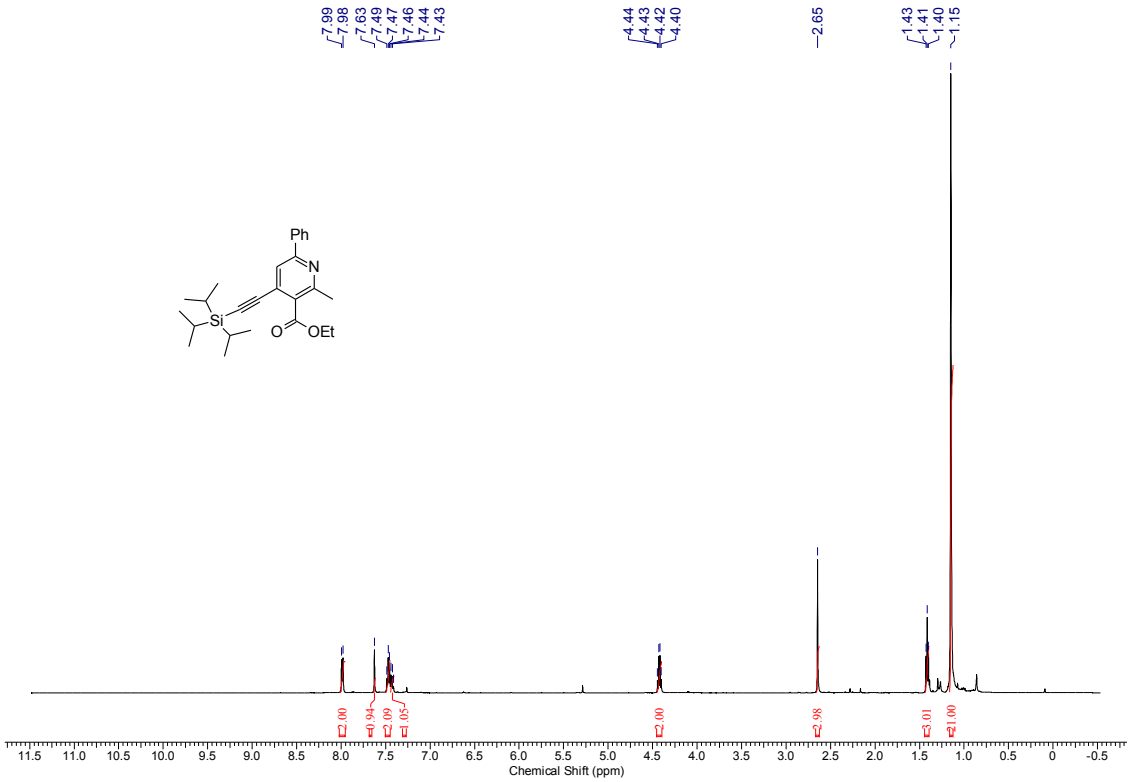


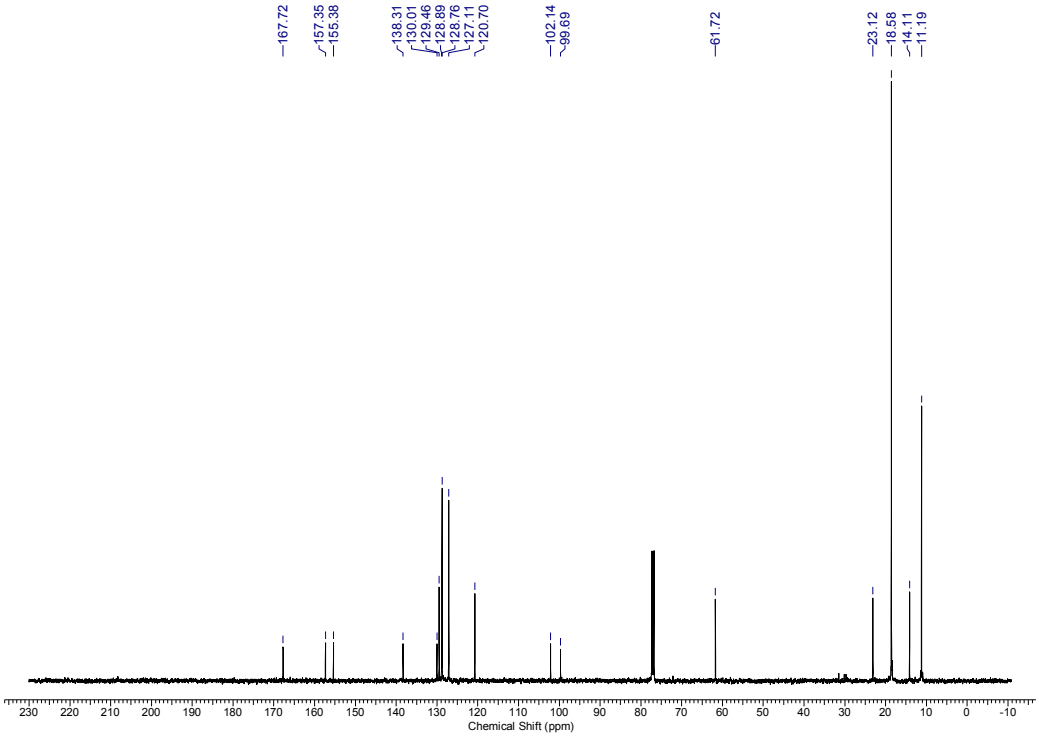
^{1}H and ^{13}C Spectra of **22c2**





^{1}H and ^{13}C Spectra of **22c3**

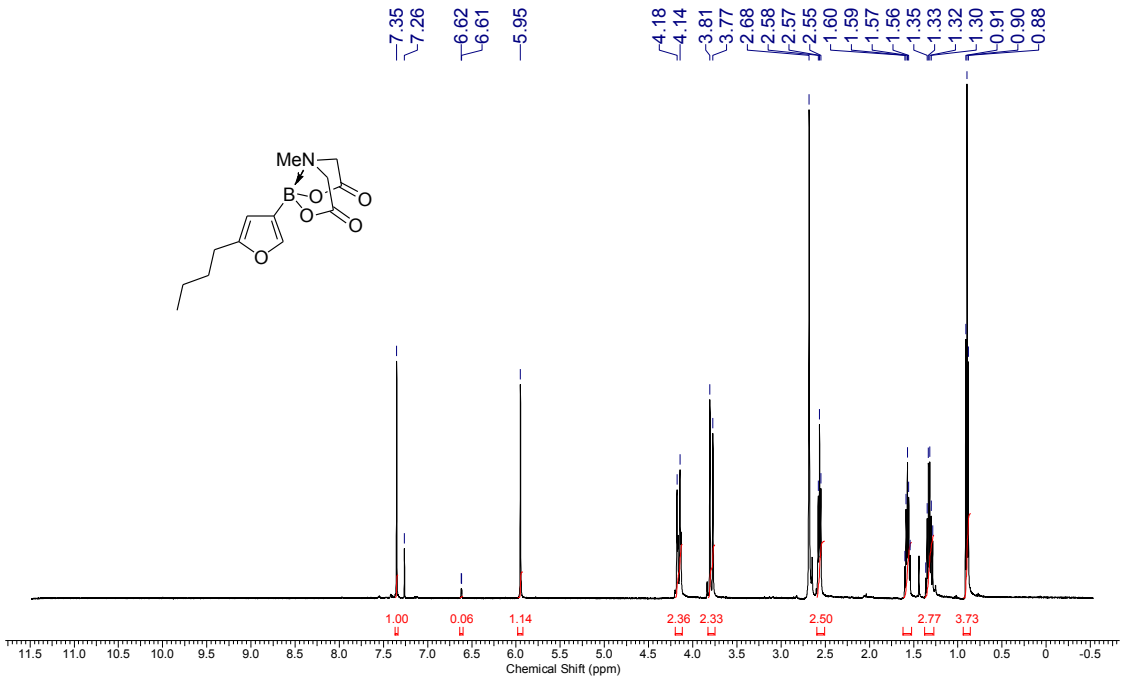


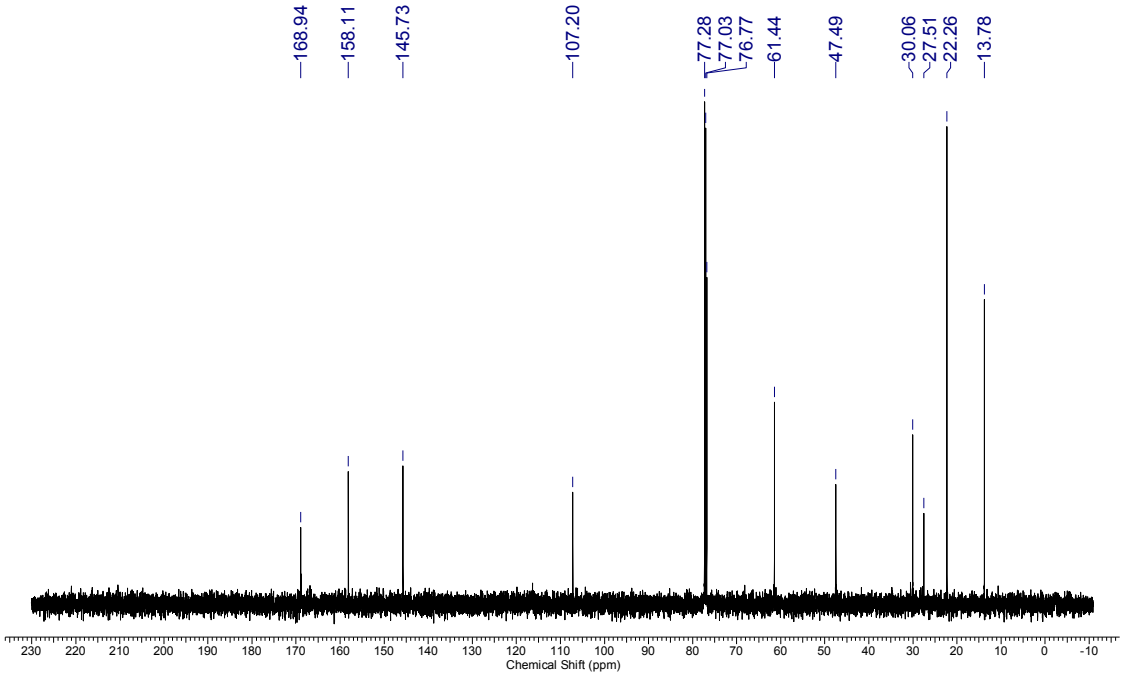


APPENDIX II

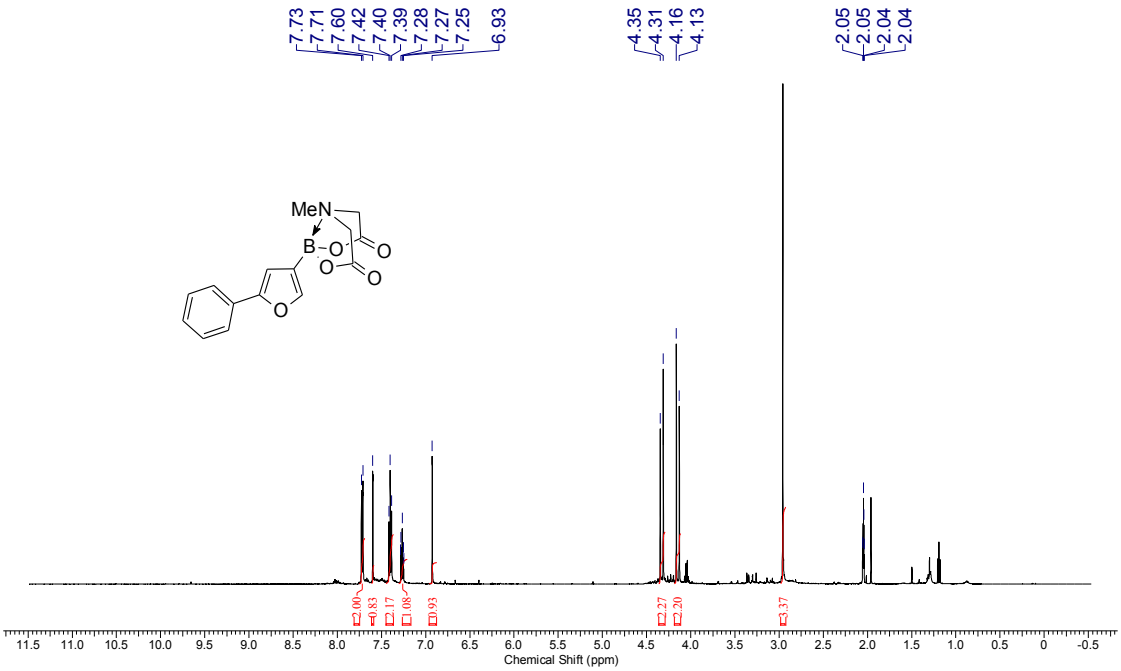
Selected NMR Spectra for Part Two

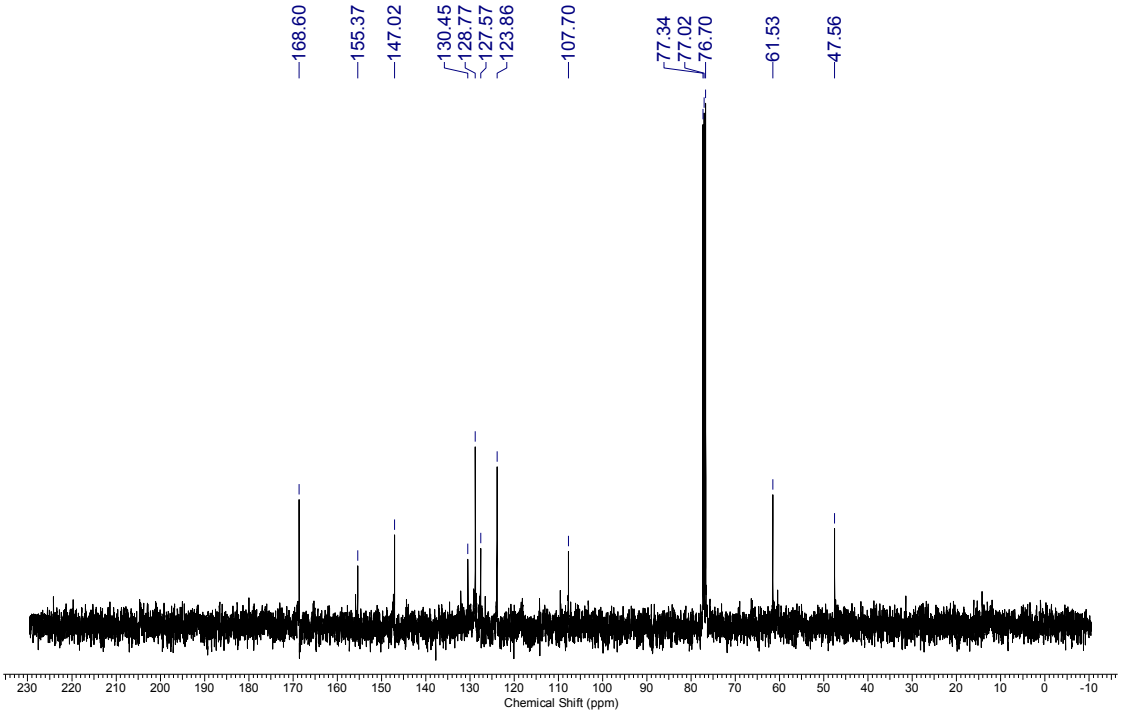
^{1}H and ^{13}C spectra of Spectrum of **36.4a** in $CDCl_3$



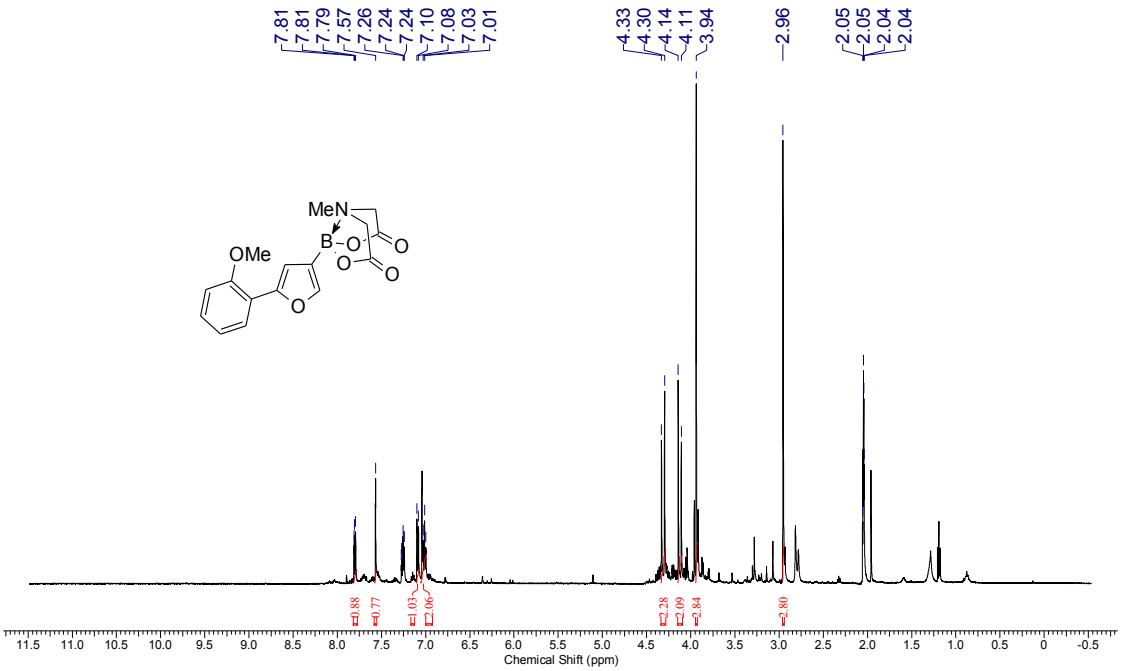


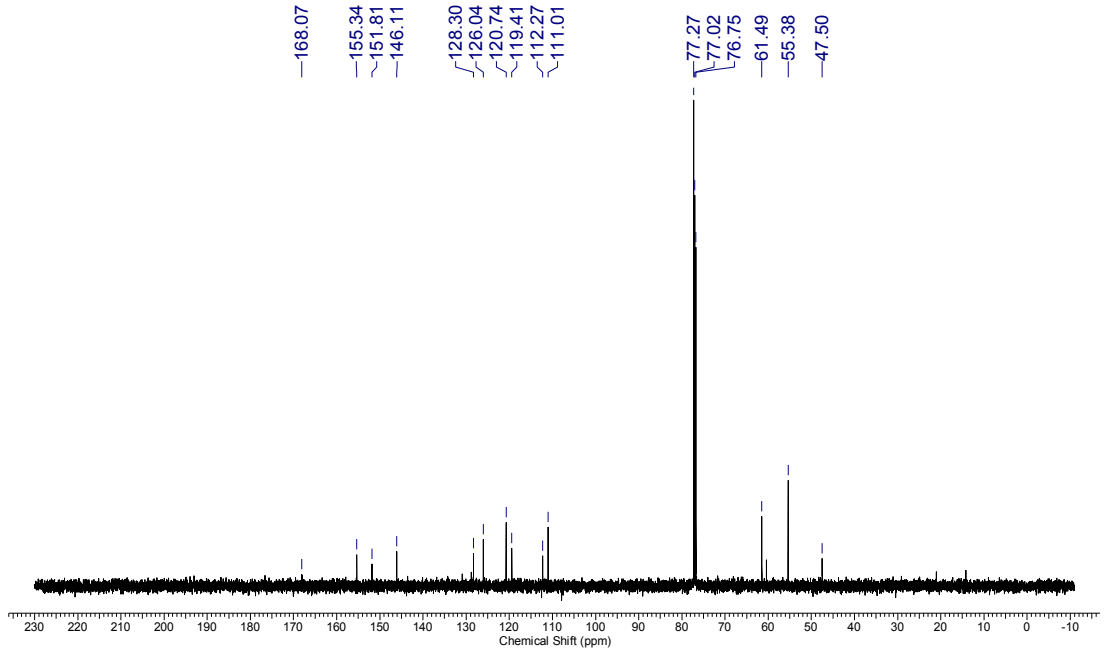
^{1}H and ^{13}C spectra of Spectrum of **36.4b** in $(CD_3)_2CO$



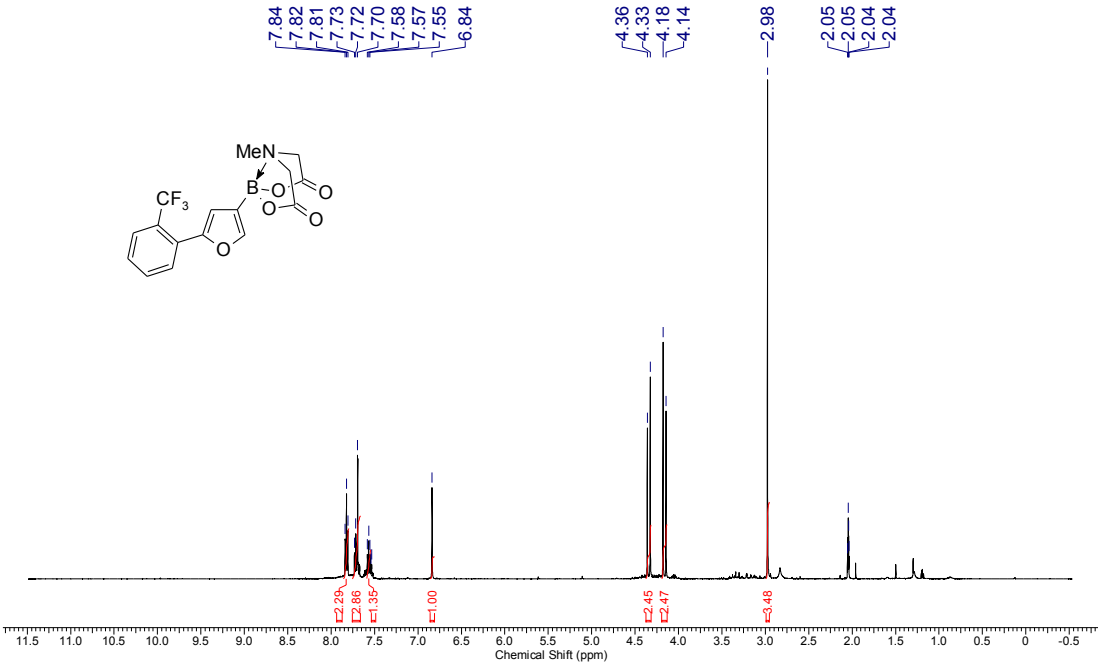


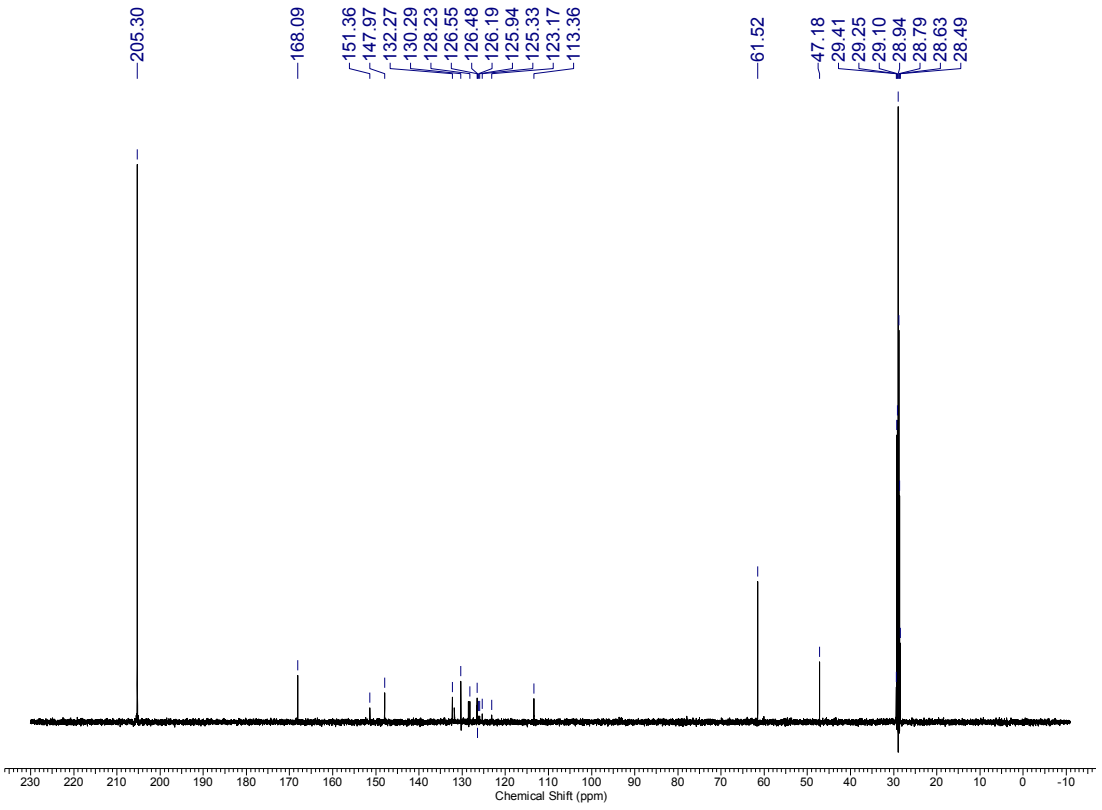
^{1}H and ^{13}C spectra of Spectrum of **36.4c** in $(CD_3)_2CO$



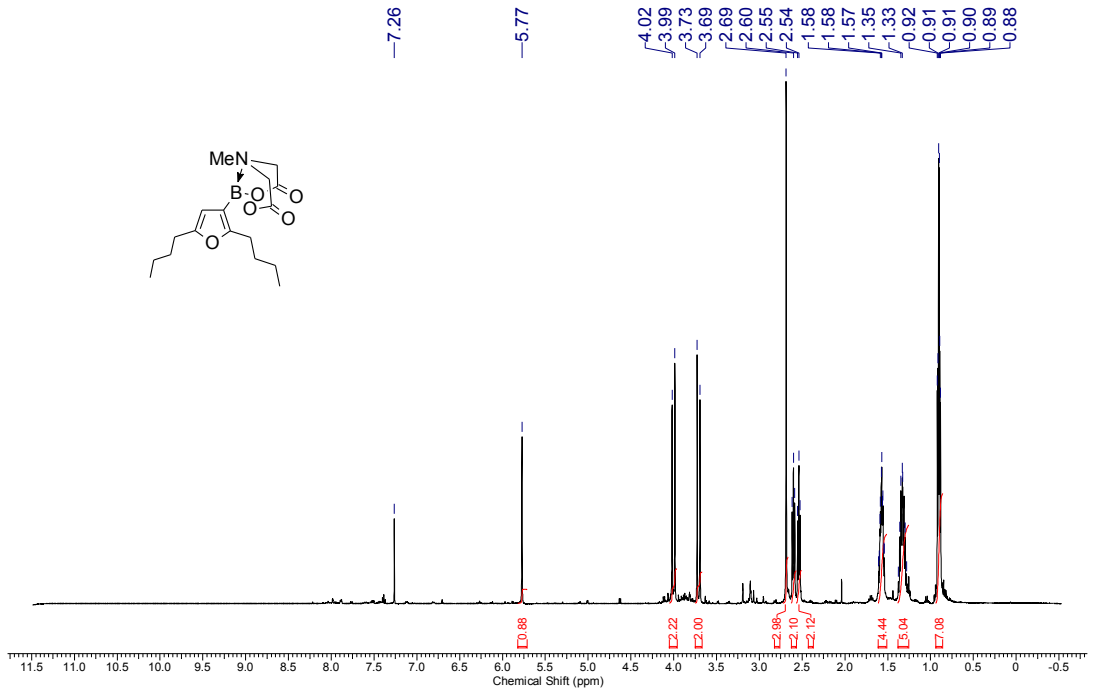


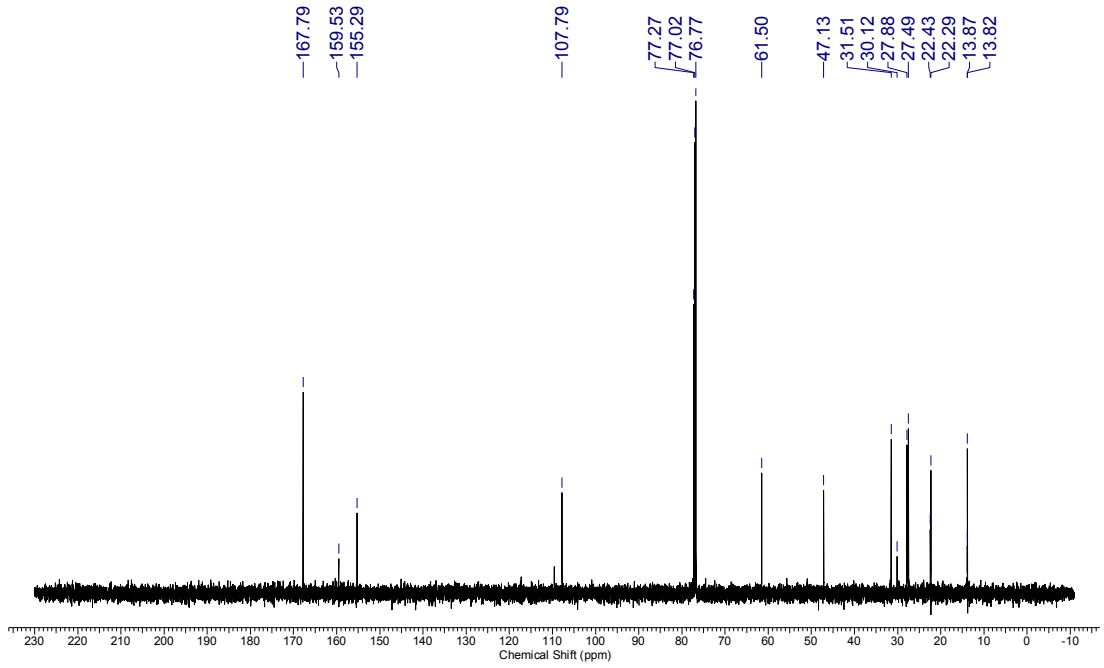
^{1}H and ^{13}C spectra of Spectrum of **36.4d** in $(CD_3)_2CO$



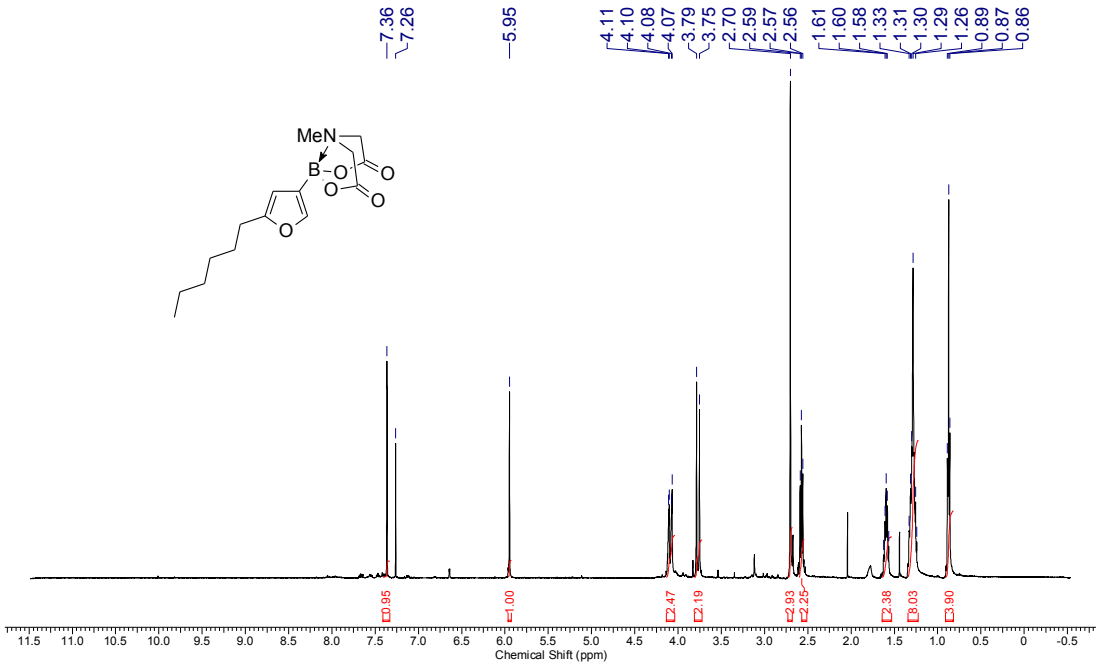


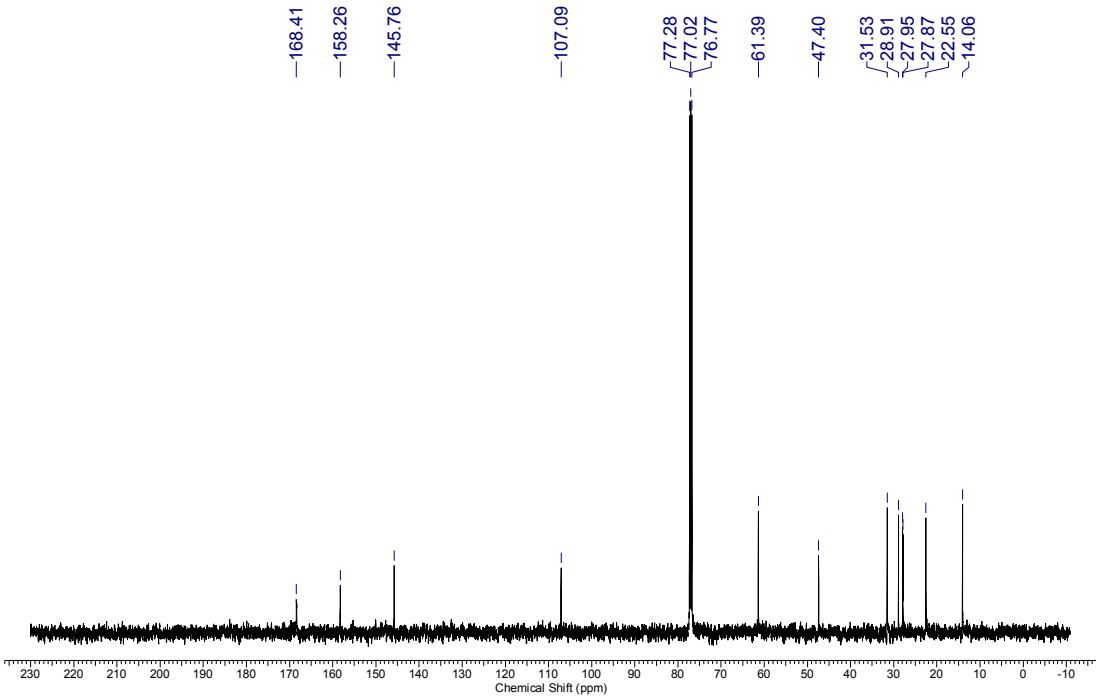
^{1}H and ^{13}C spectra of Spectrum of **36.4e** in $CDCl_3$



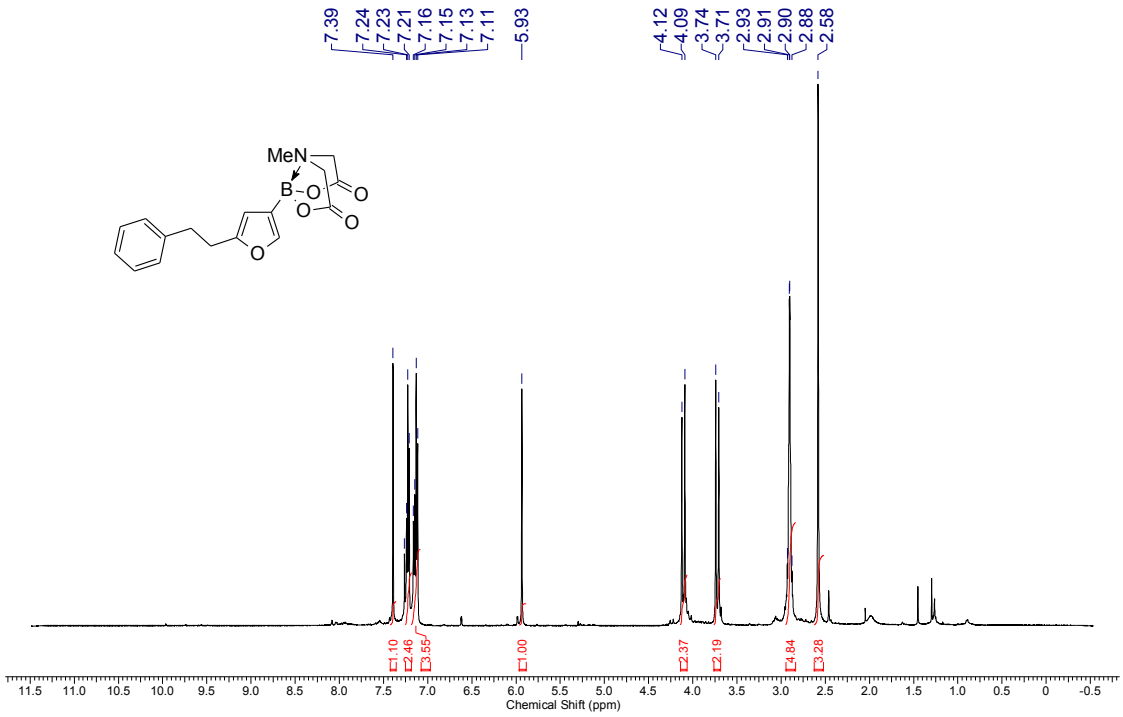


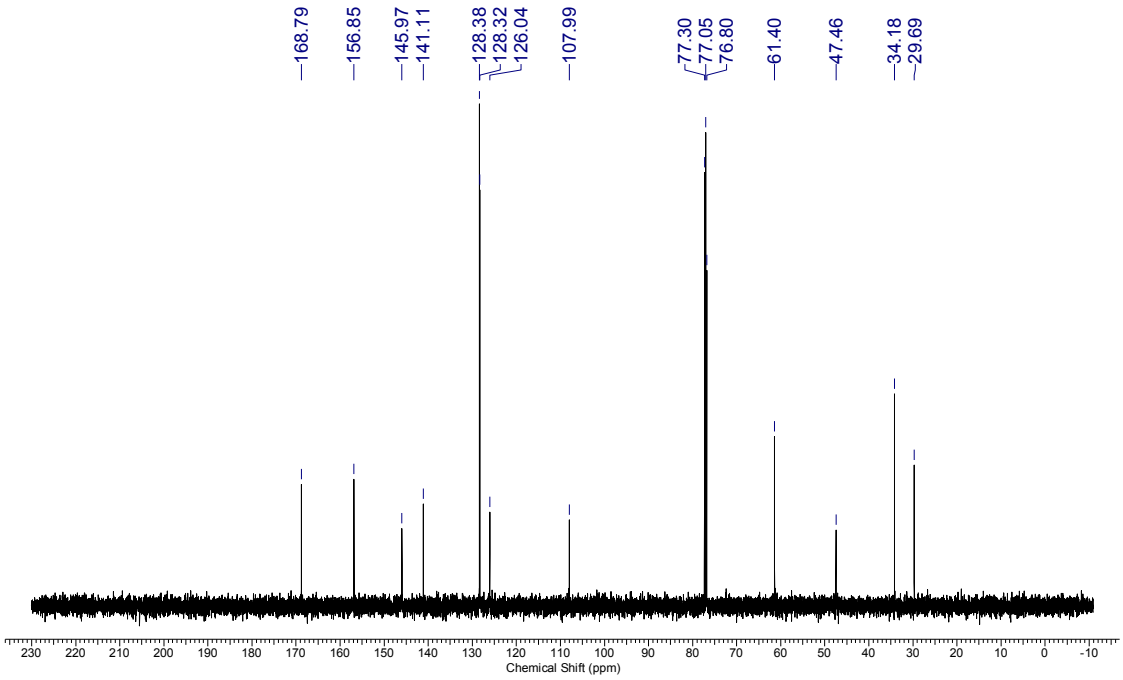
^{1}H and ^{13}C spectra of Spectrum of **36.4f** in $CDCl_3$



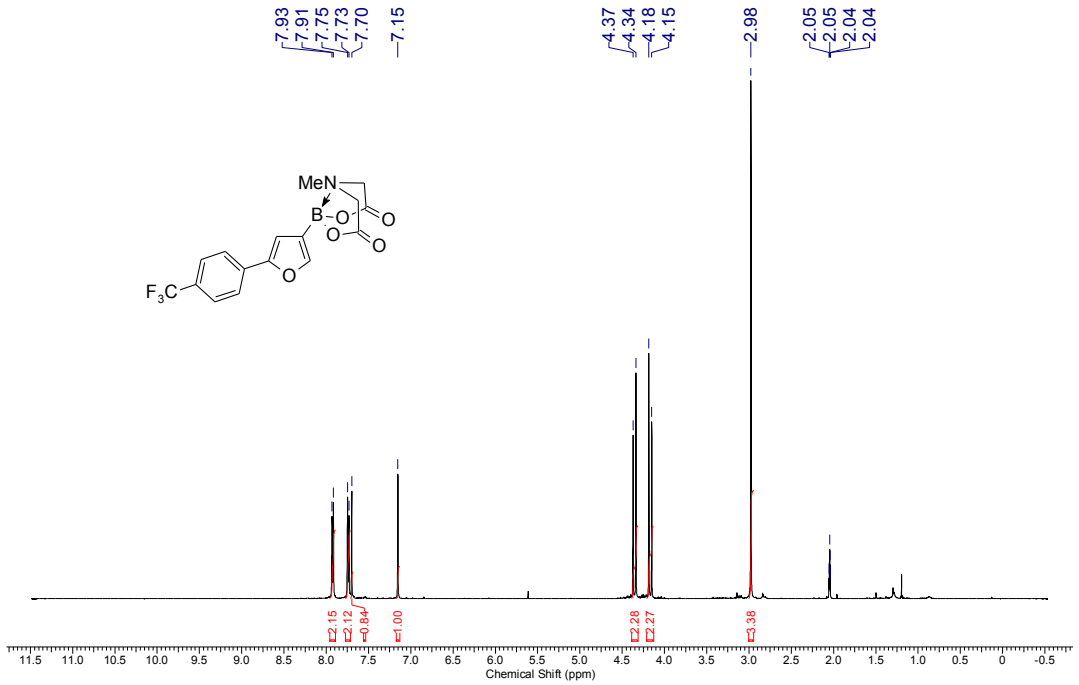


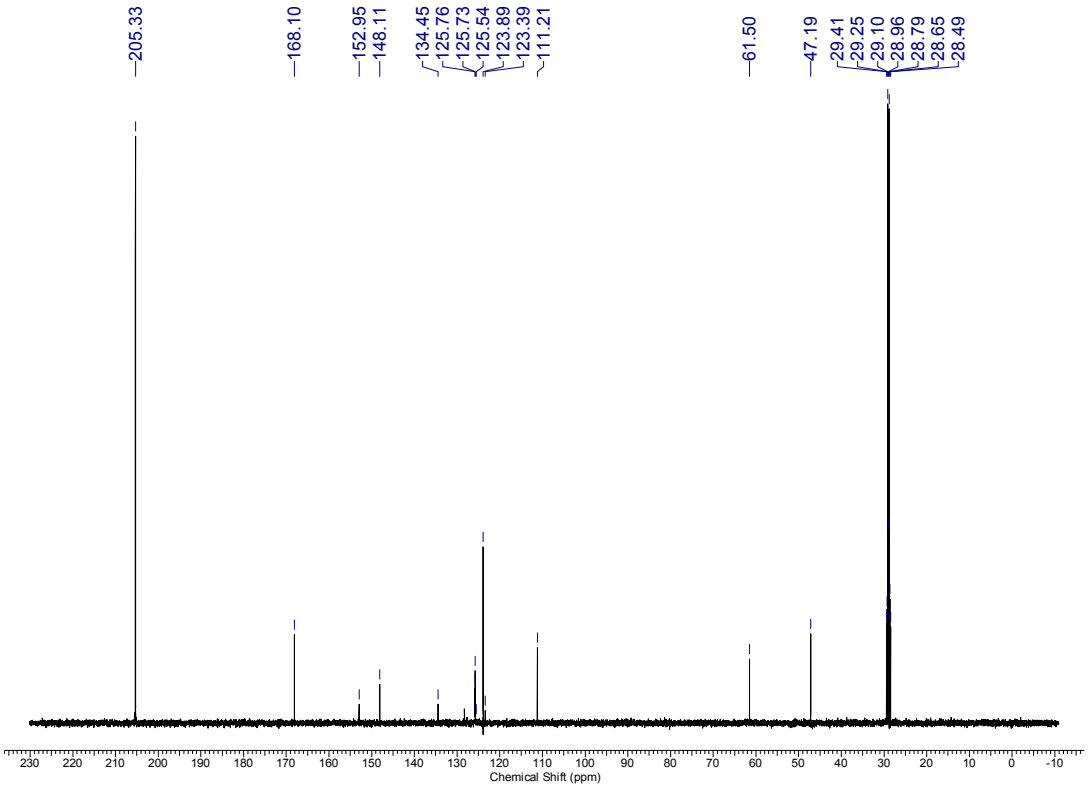
^{1}H and ^{13}C spectra of Spectrum of **36.4g** in $CDCl_3$



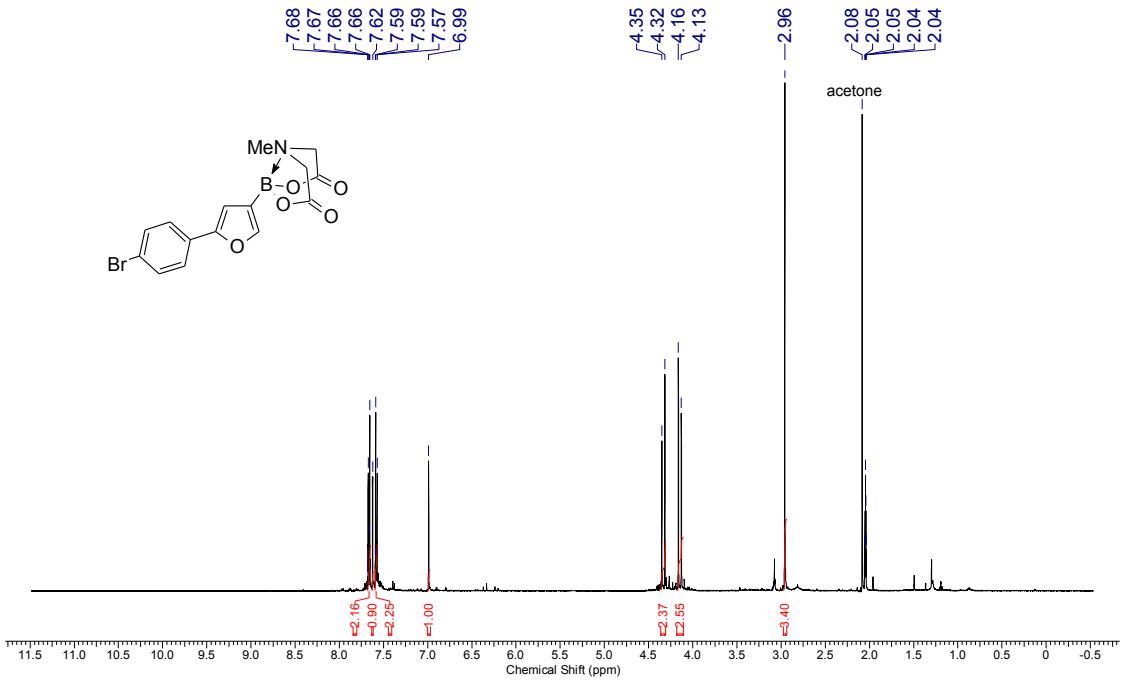


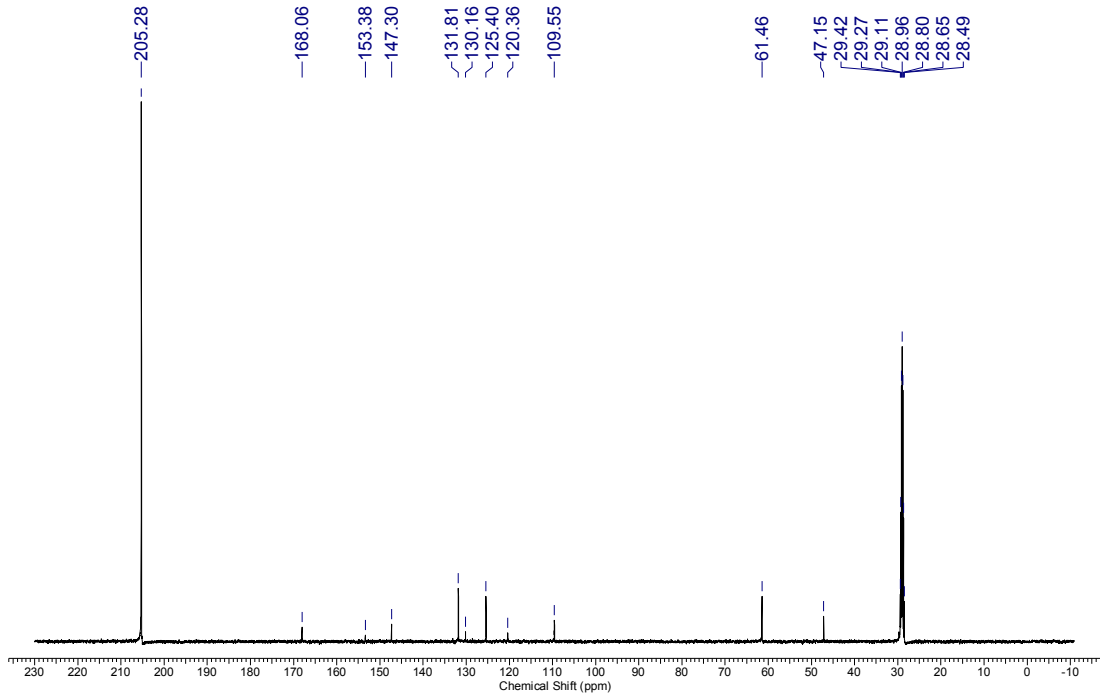
^{1}H and ^{13}C spectra of Spectrum of **36.4h** in $(CD_3)_2CO$



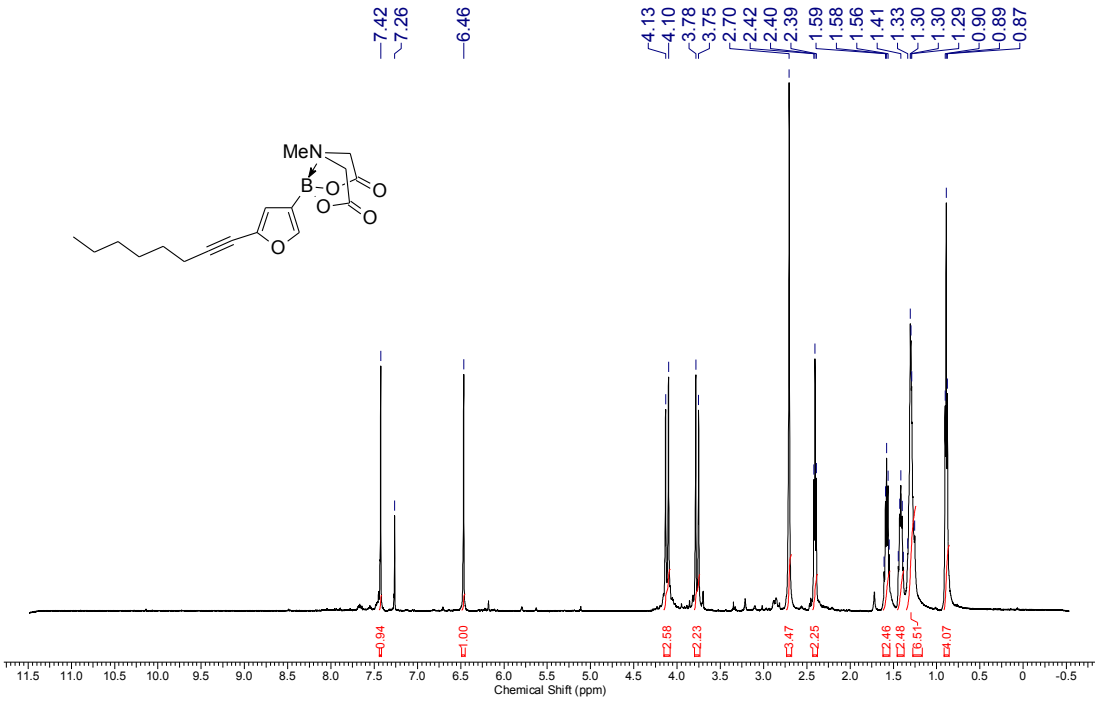


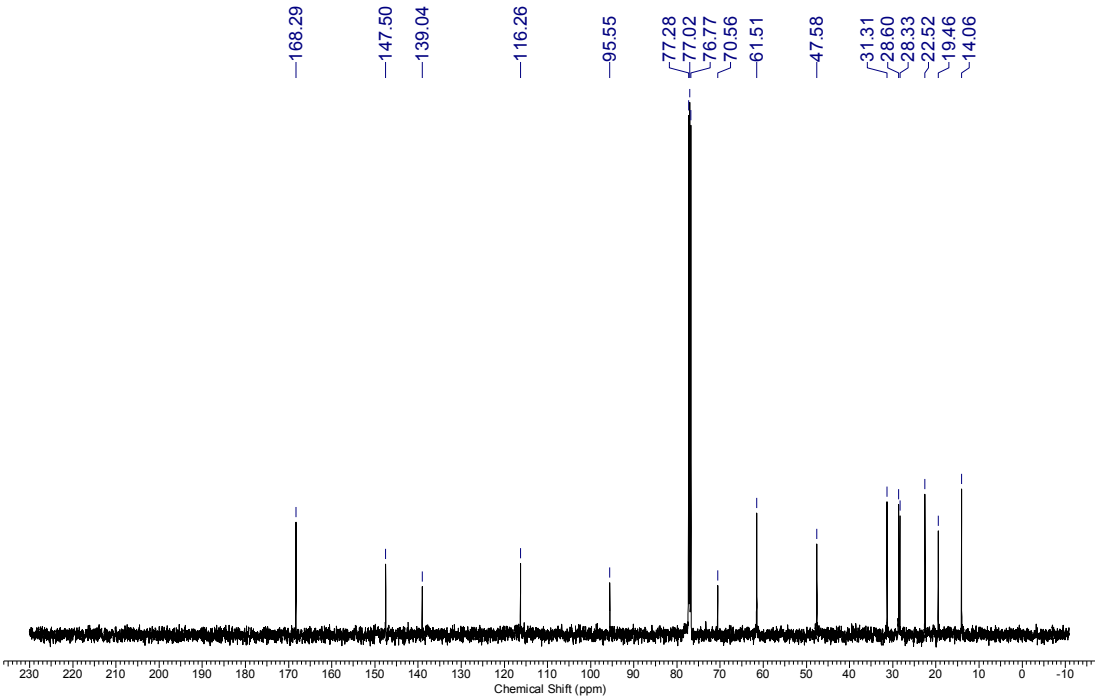
^{1}H and ^{13}C spectra of Spectrum of **36.4i** in $(CD_3)_2CO$



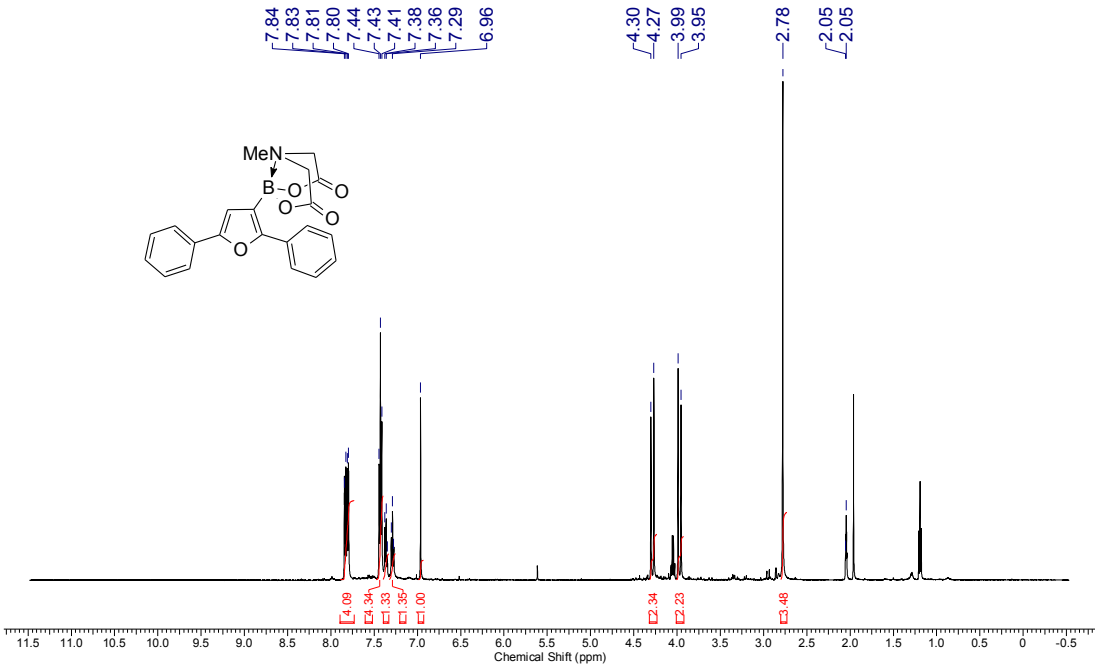


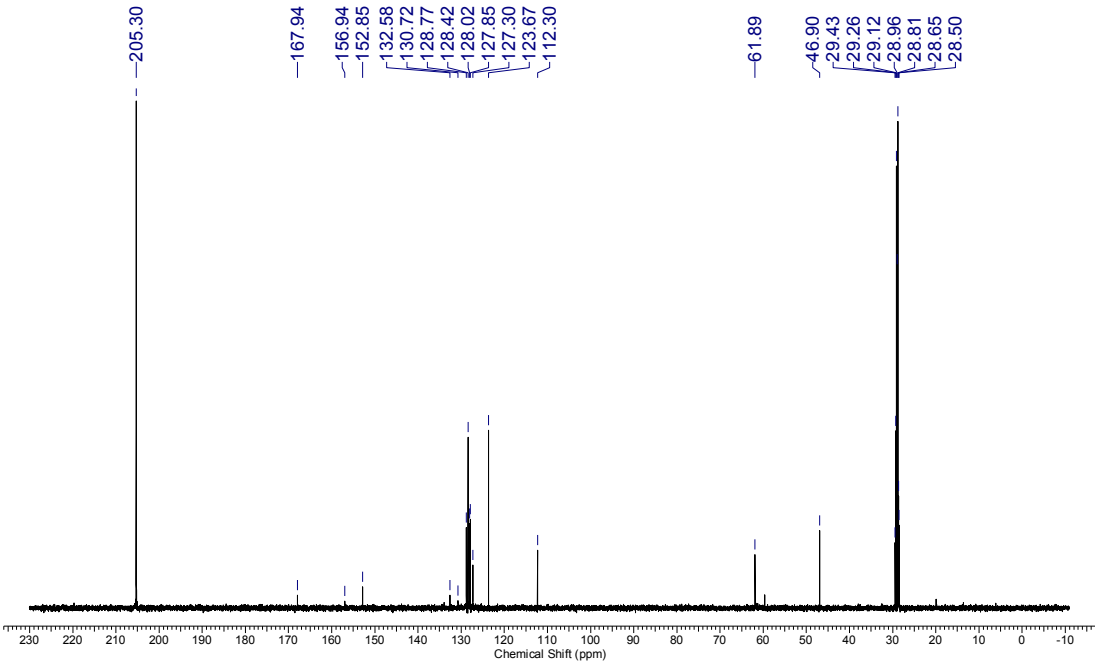
^{1}H and ^{13}C spectra of Spectrum of **36.4j** in $CDCl_3$



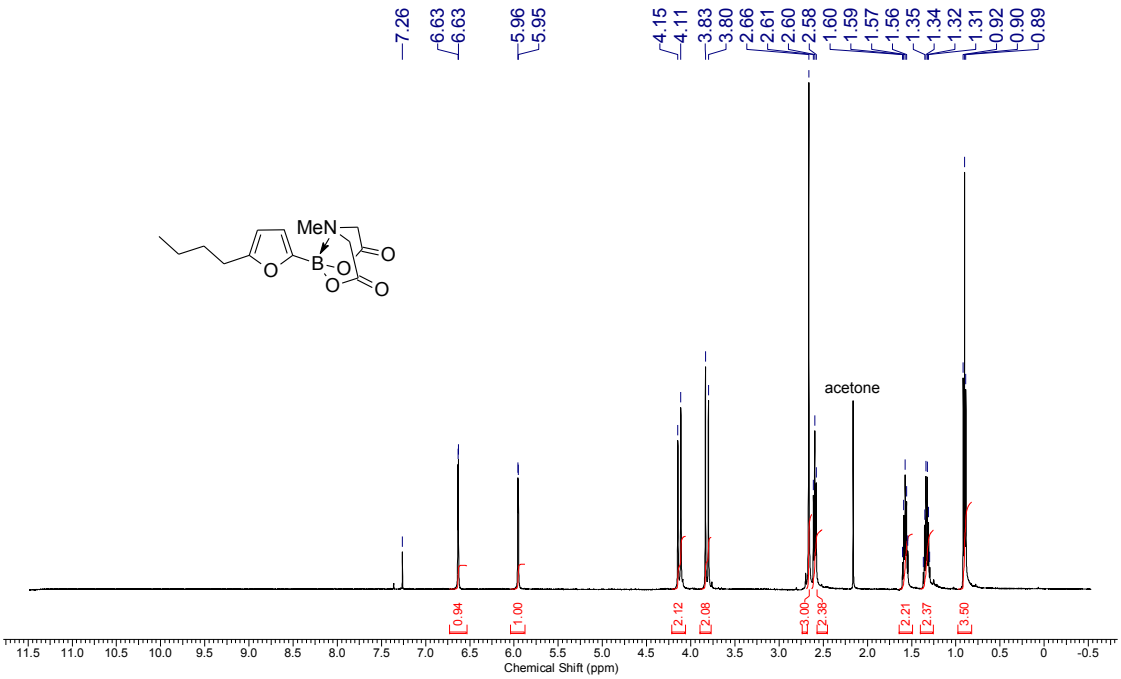


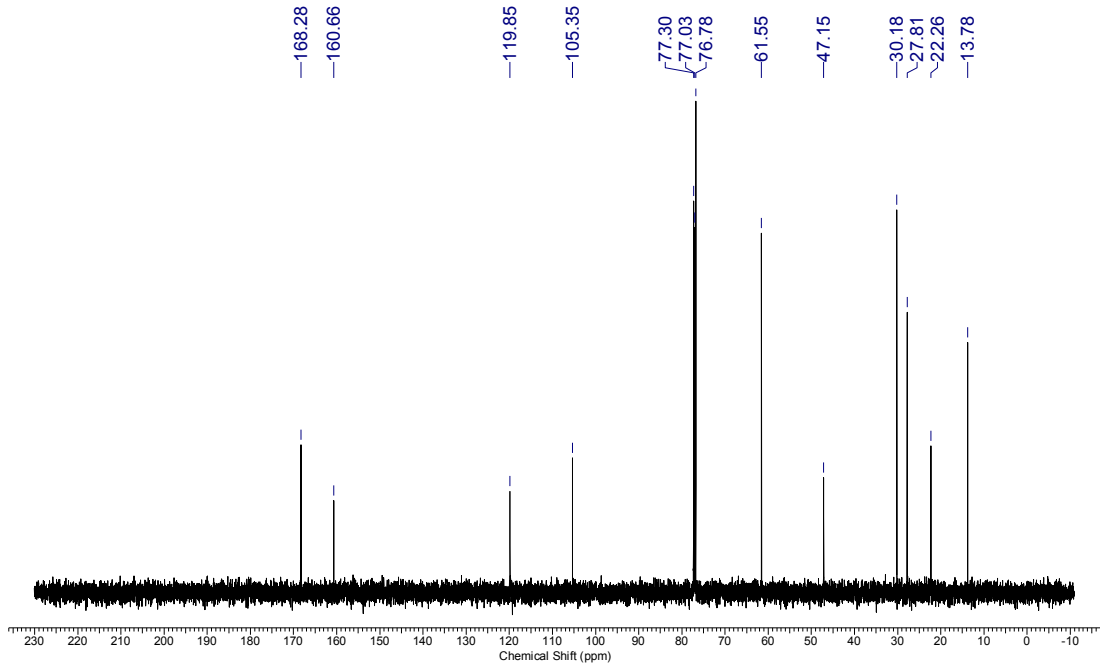
^{1}H and ^{13}C spectra of Spectrum of **36.4k** in $(CD_3)_2CO$



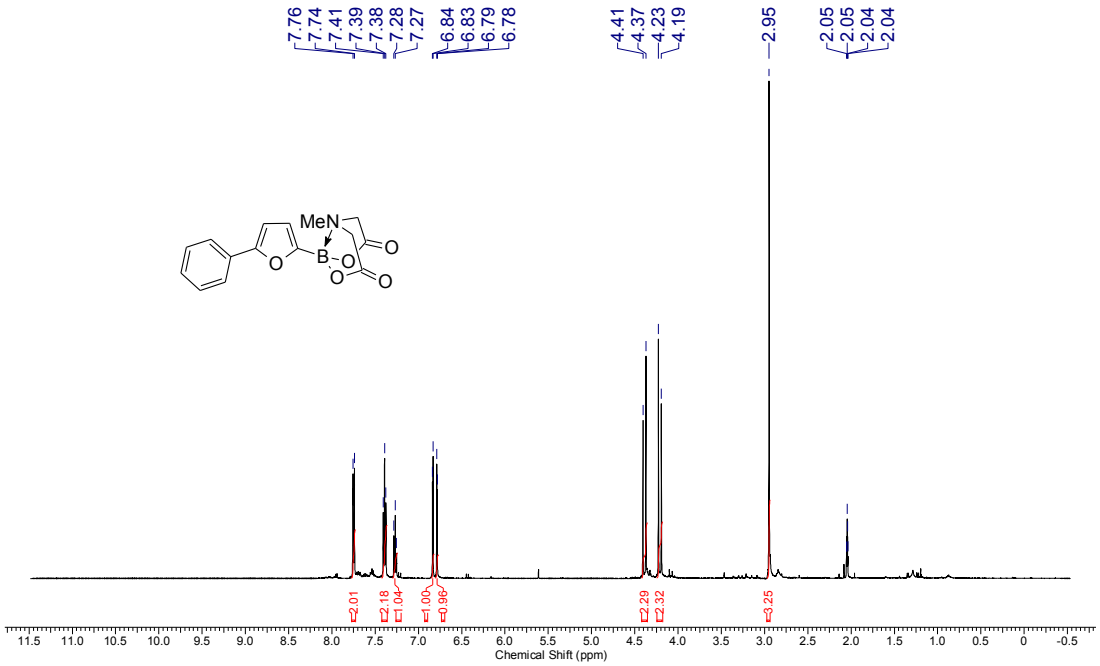


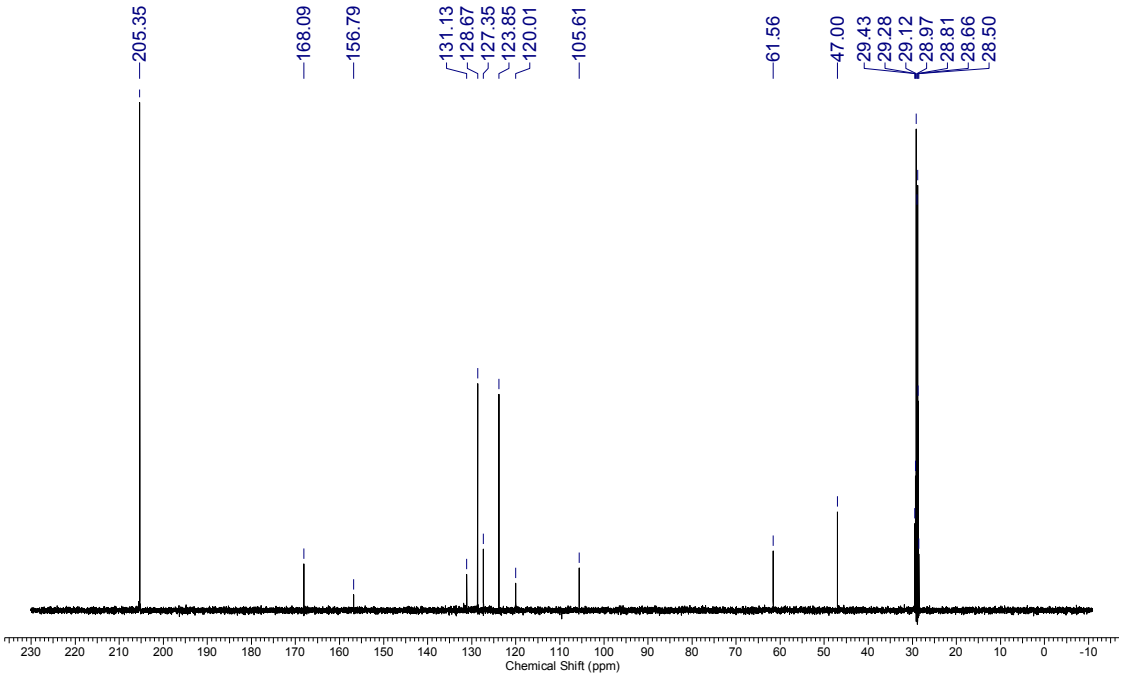
^{1}H and ^{13}C spectra of Spectrum of **36.5a** in $CDCl_3$



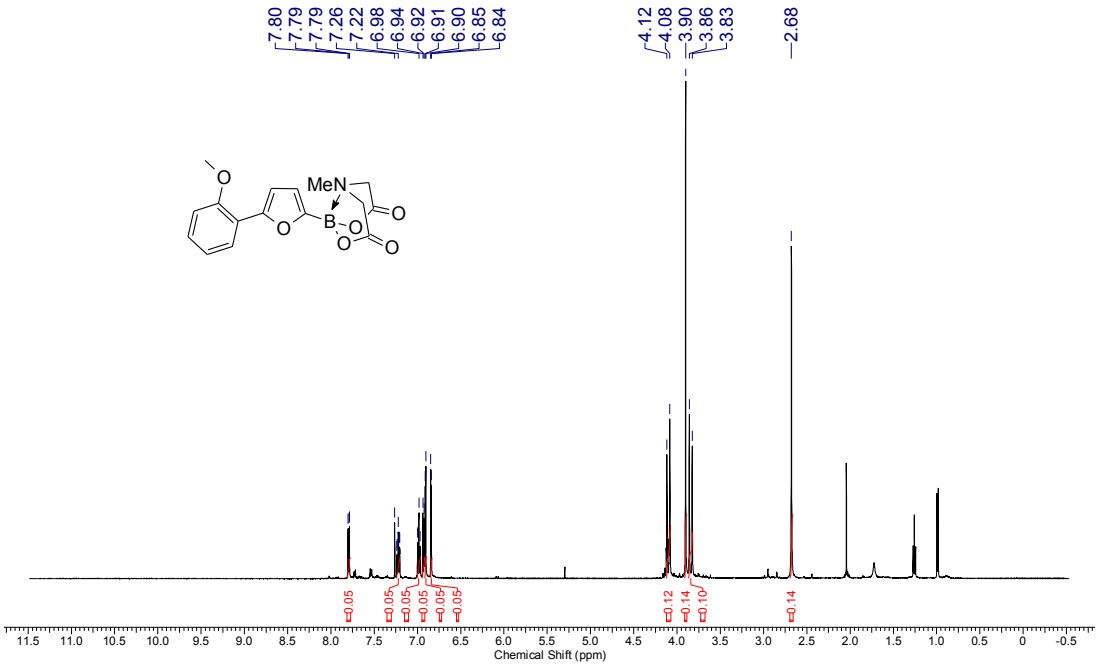


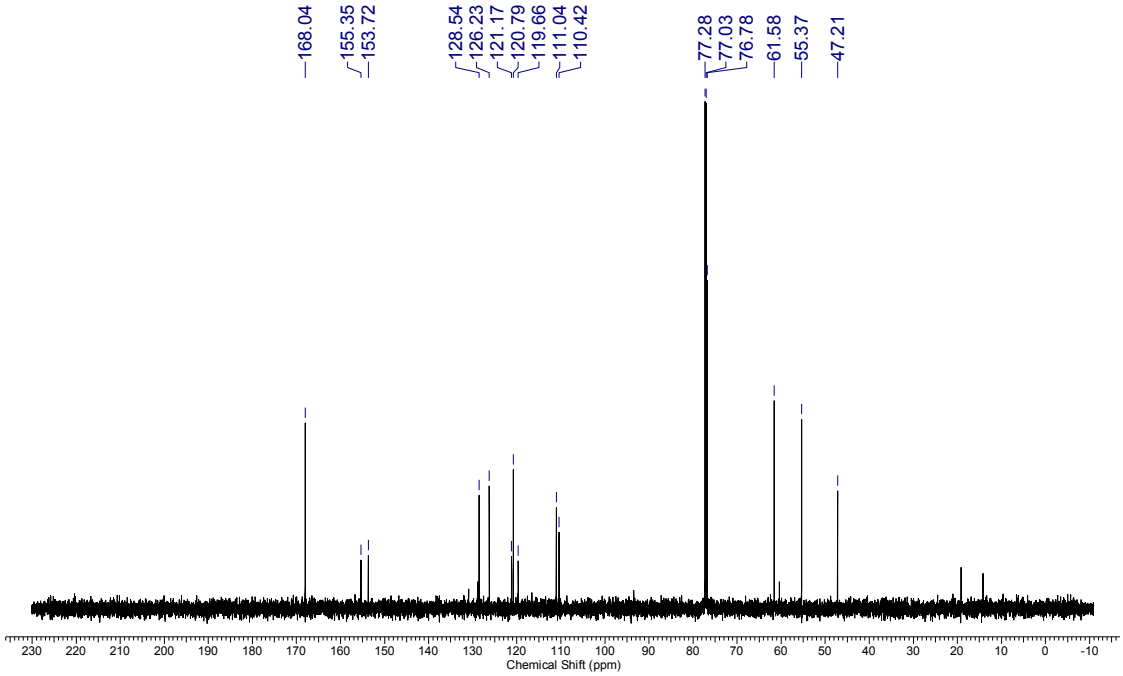
^{1}H and ^{13}C spectra of Spectrum of **36.5b** in $(CD_3)_2CO$



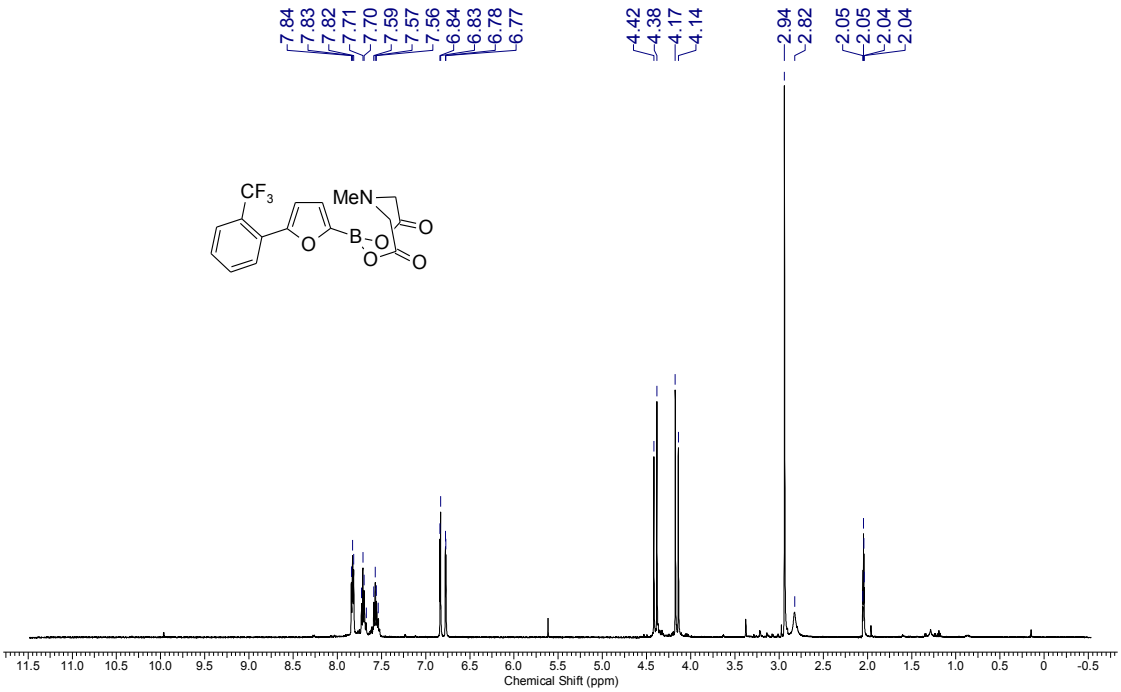


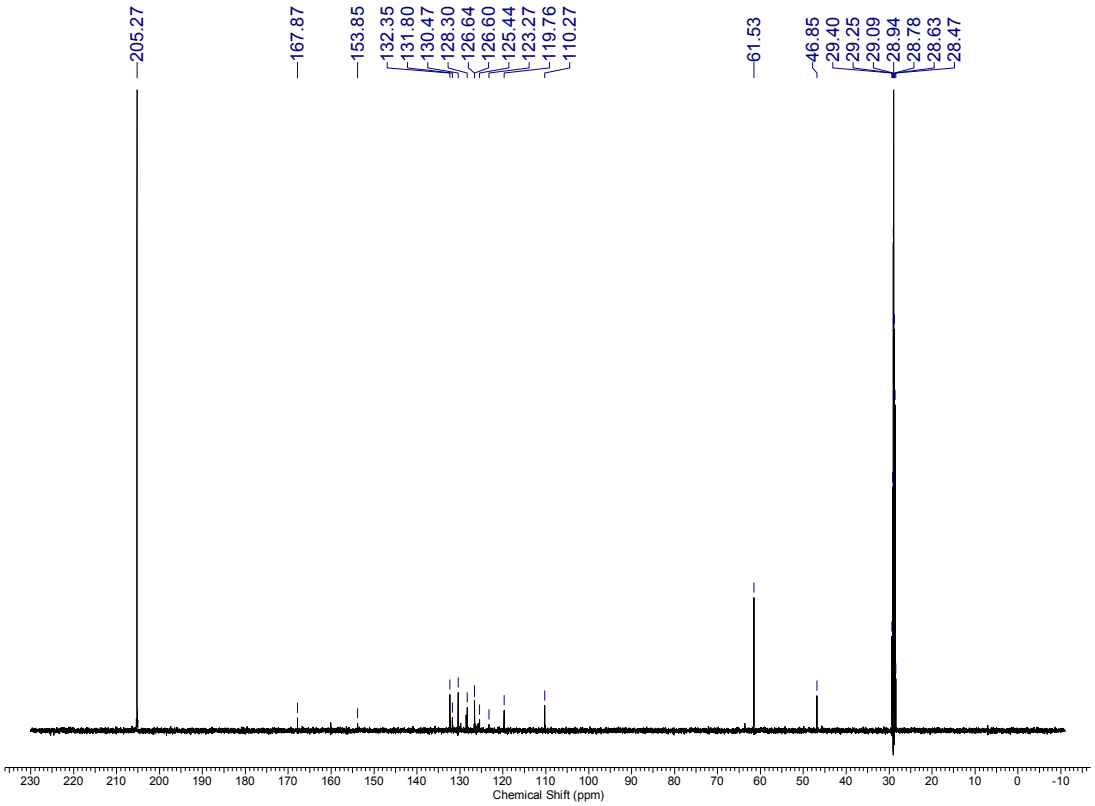
^{1}H and ^{13}C spectra of Spectrum of **36.5c** in $CDCl_3$



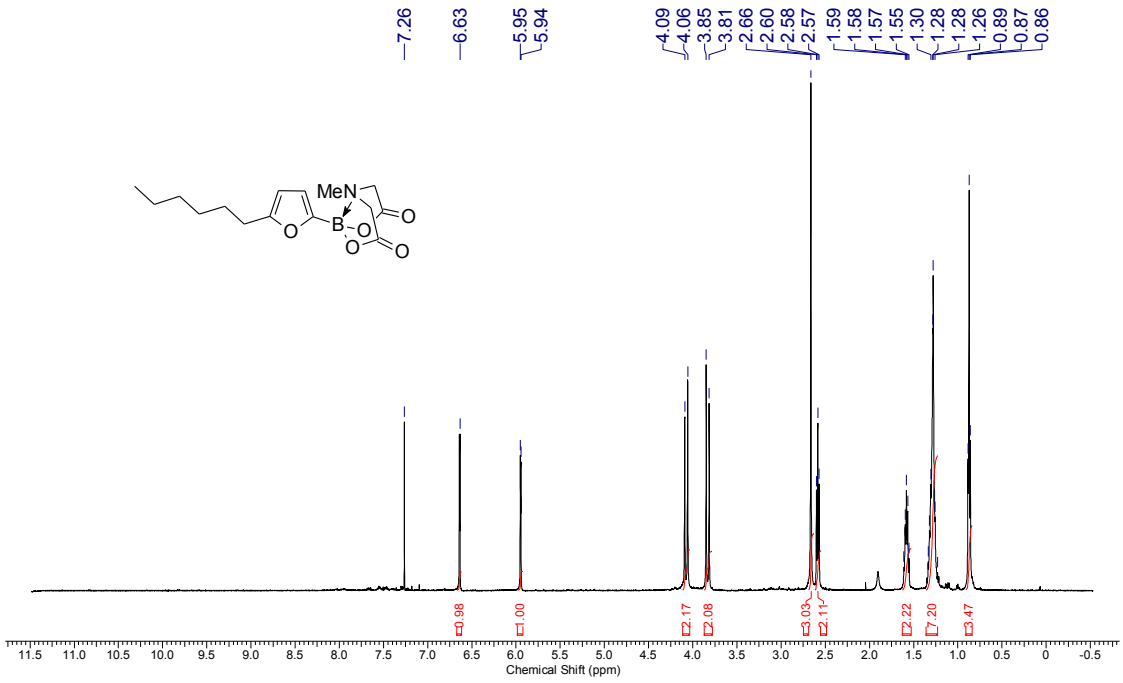


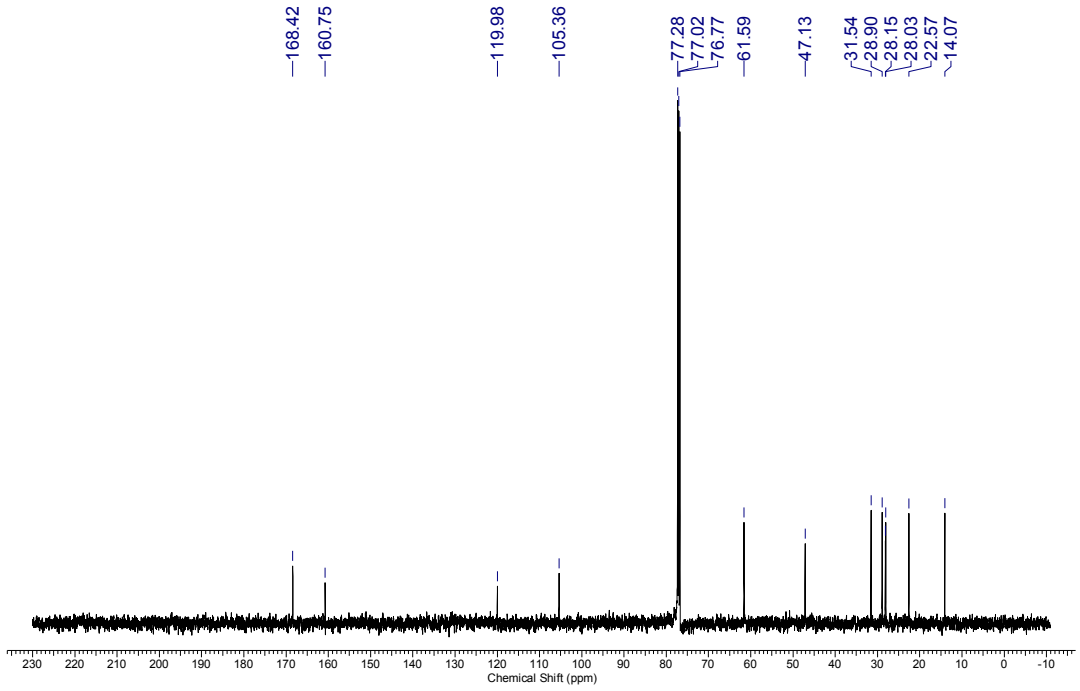
^{1}H and ^{13}C spectra of Spectrum of **36.5d** in $(CD_3)_2CO$



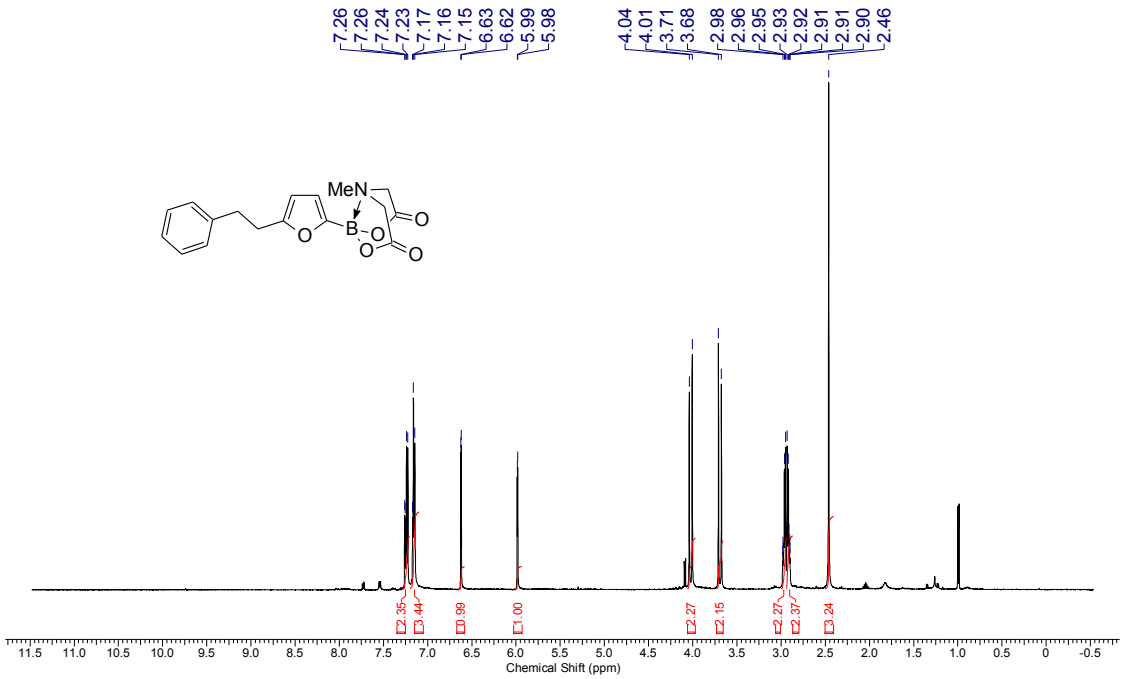


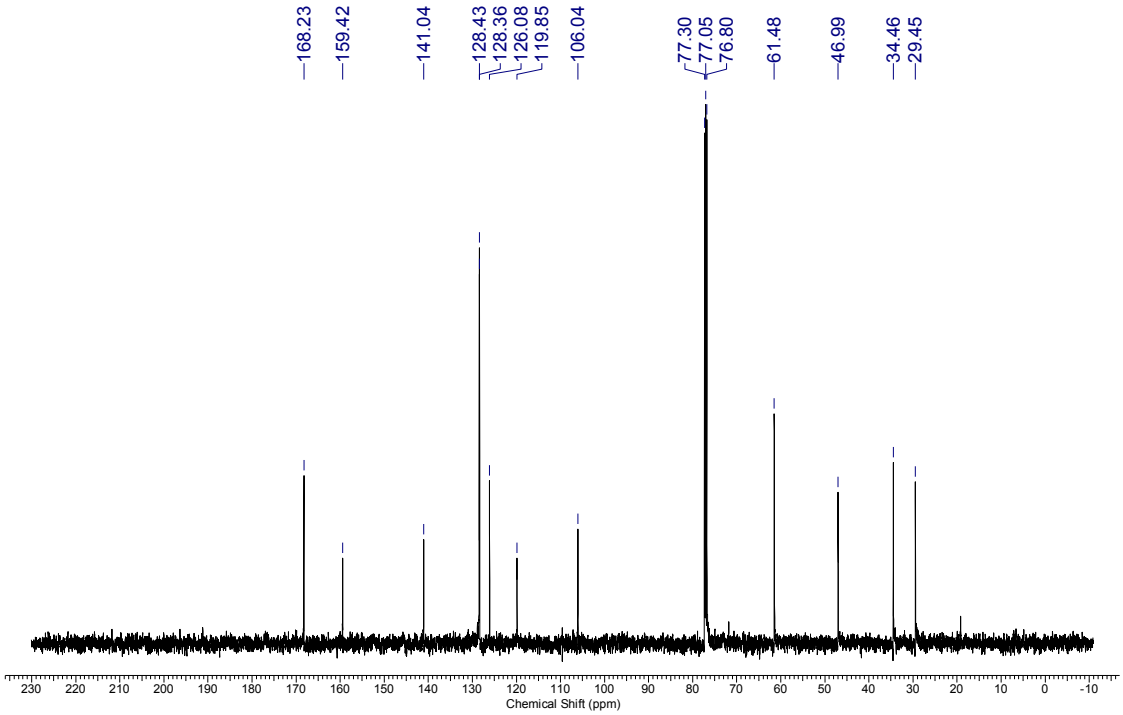
^{1}H and ^{13}C spectra of Spectrum of **36.5f** in $CDCl_3$



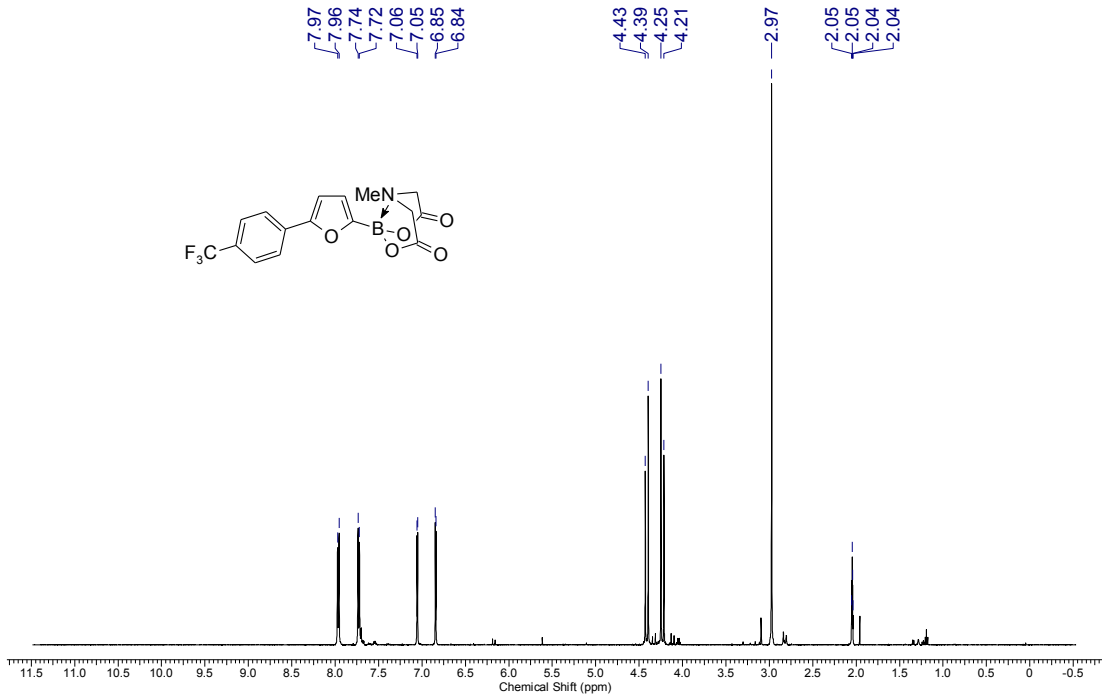


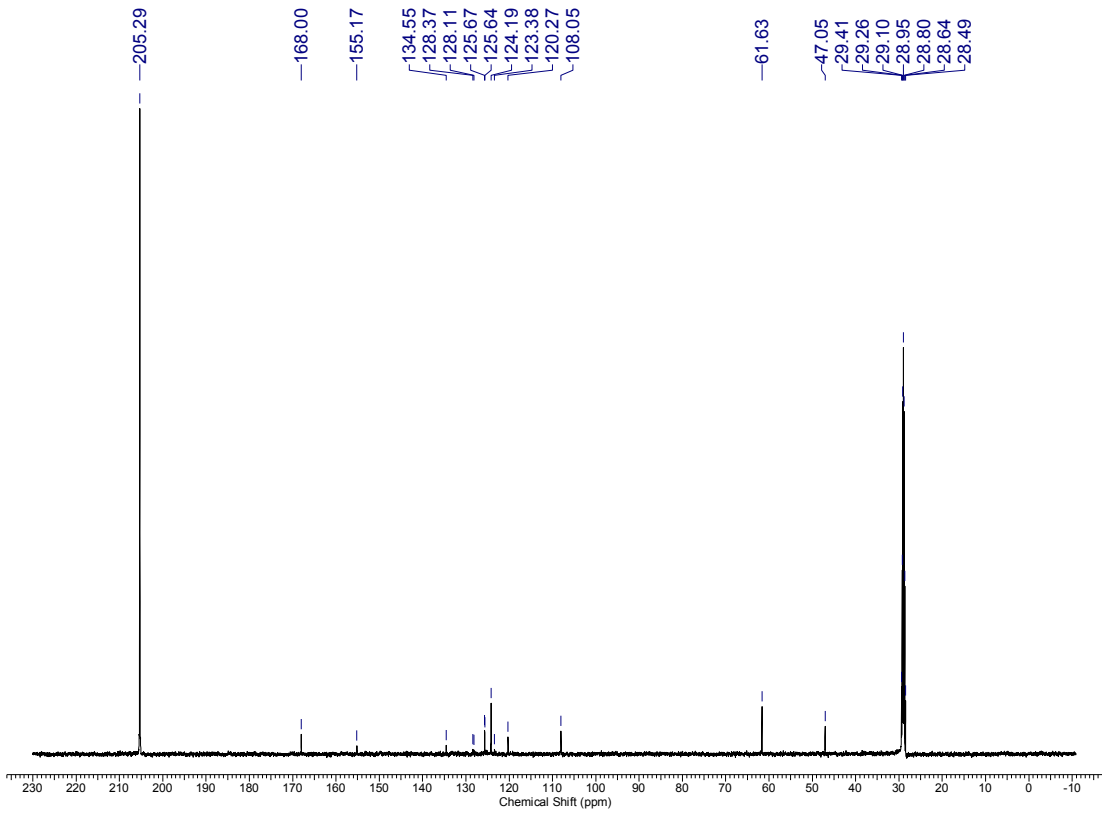
^{1}H and ^{13}C spectra of Spectrum of **36.5g** in $CDCl_3$



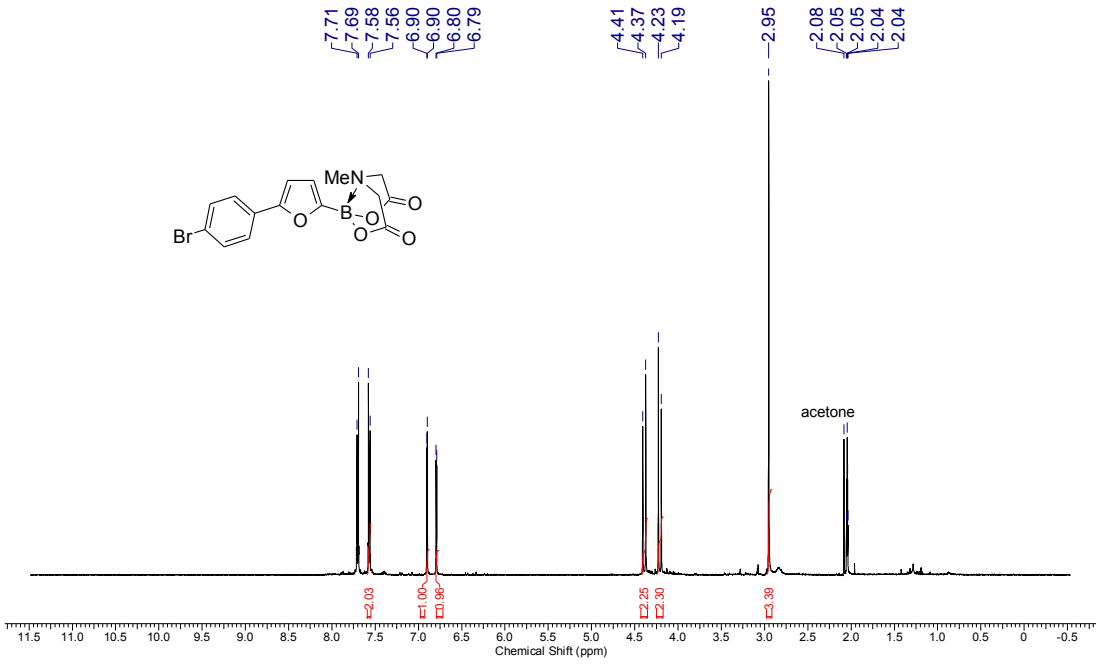


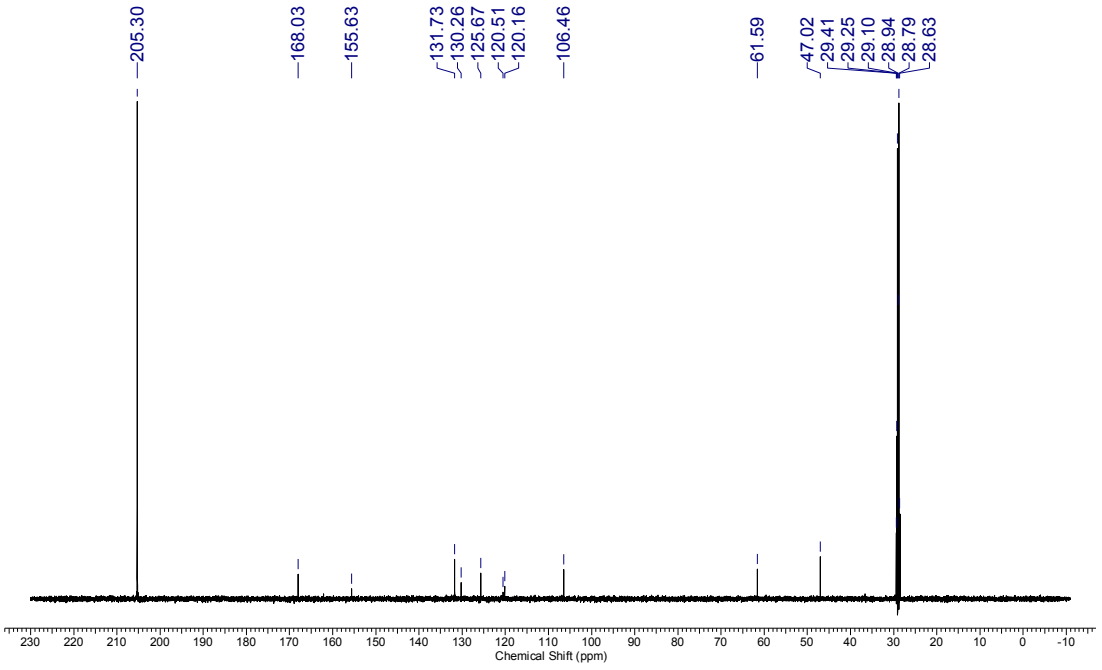
^{1}H and ^{13}C spectra of Spectrum of **36.5h** in $(CD_3)_2CO$



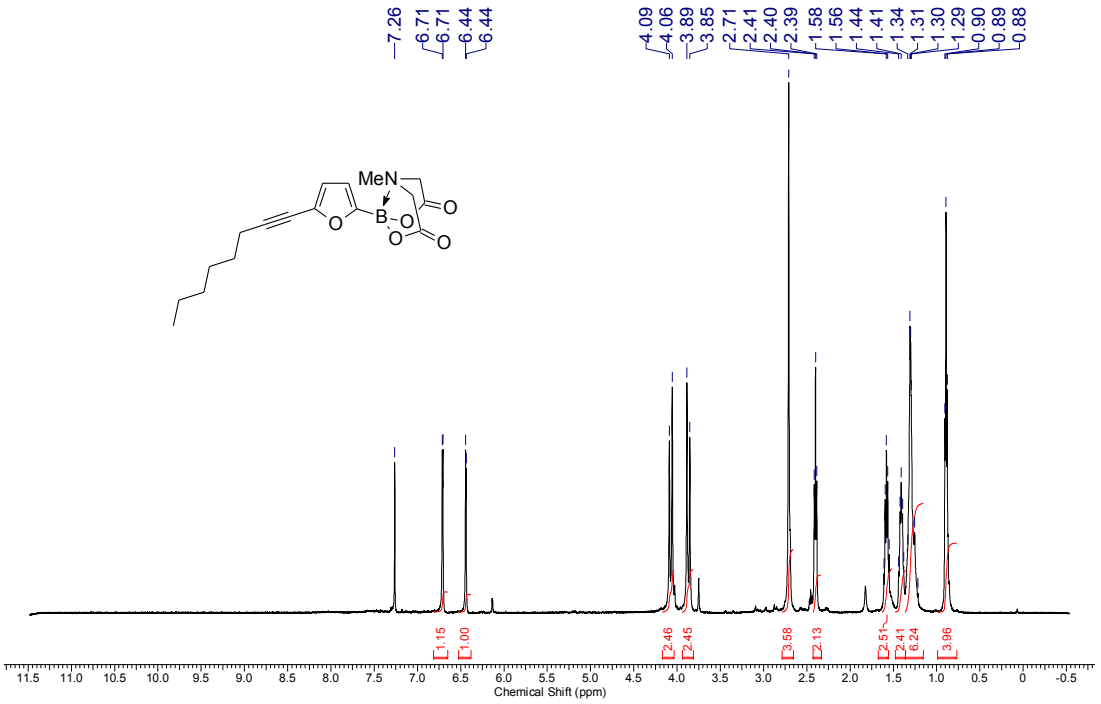


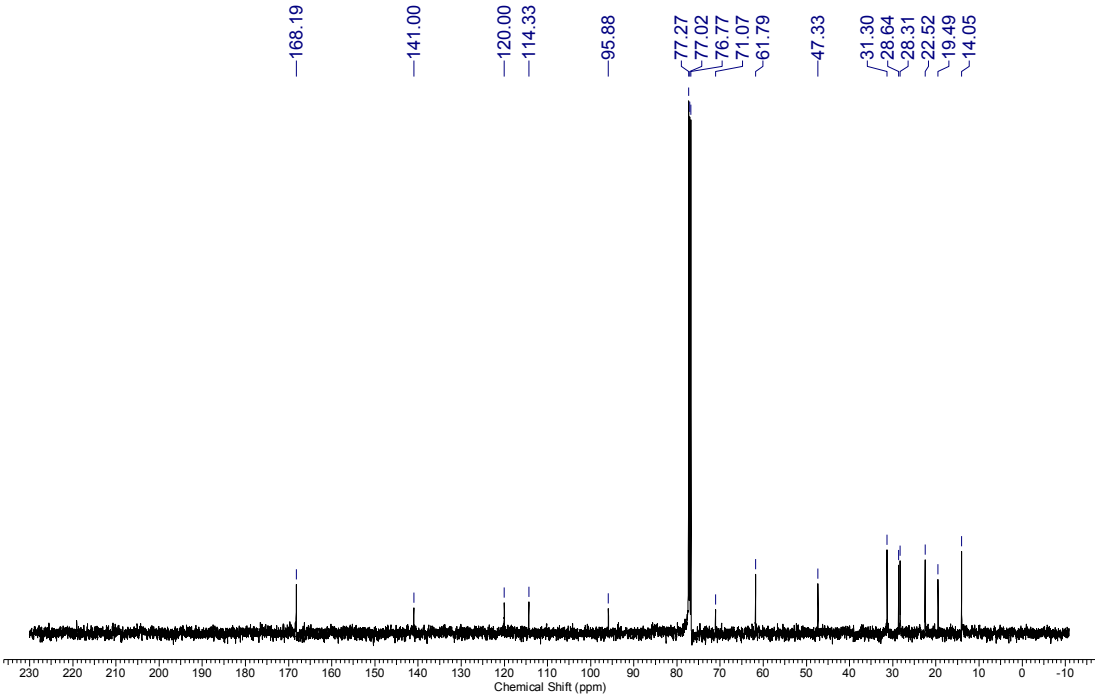
^{1}H and ^{13}C spectra of Spectrum of **36.5i** in $(CD_3)_2CO$



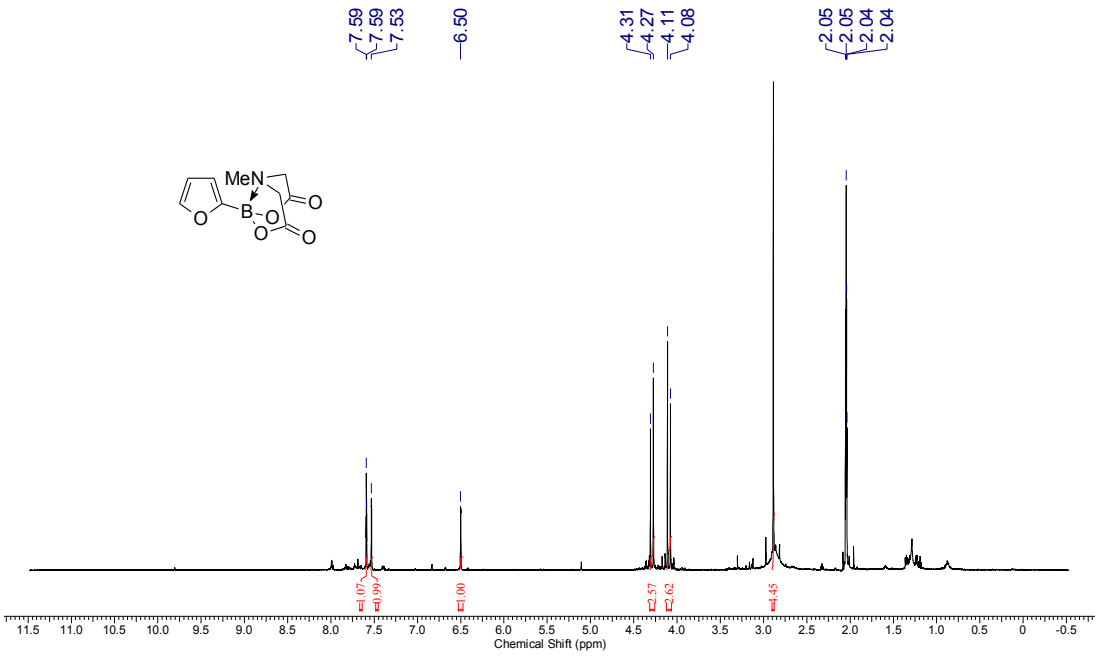


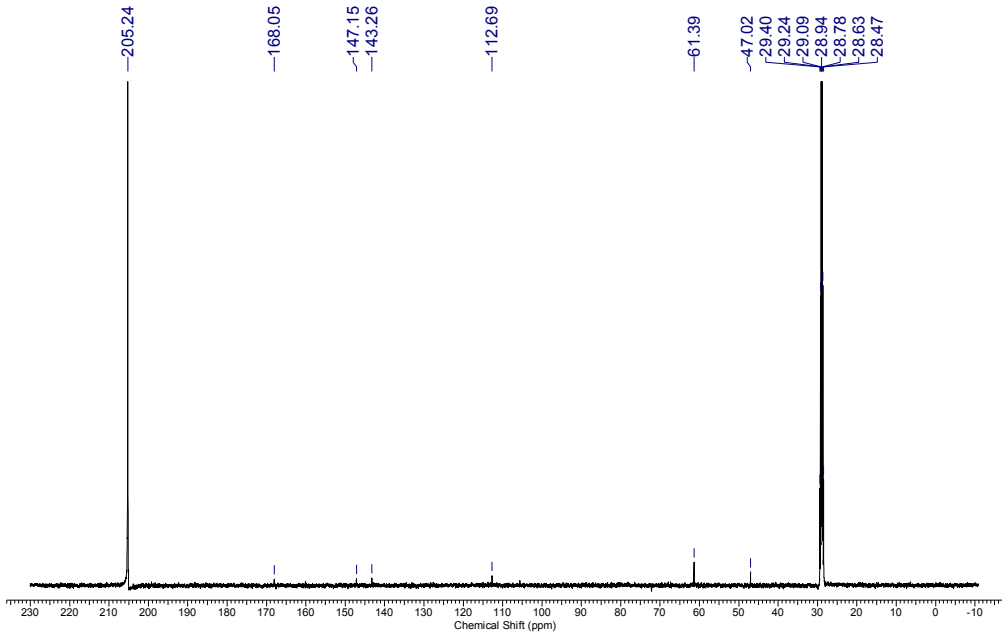
^{1}H and ^{13}C spectra of Spectrum of **36.5j** in $CDCl_3$





^{1}H and ^{13}C spectra of Spectrum of **36.5l** in $(CD_3)_2CO$

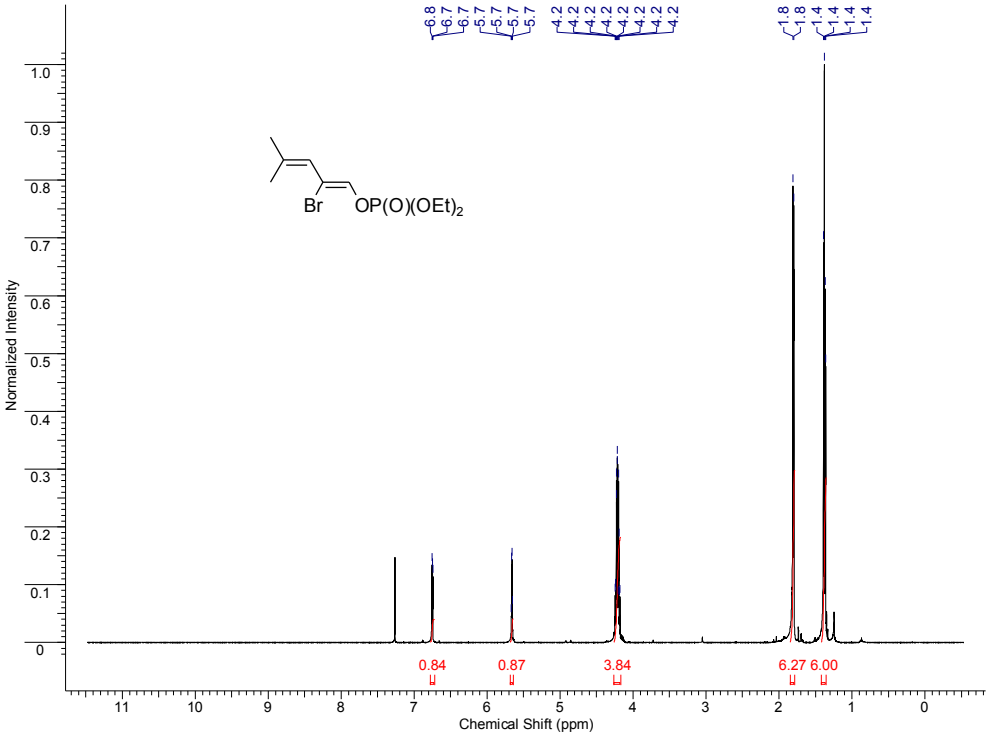


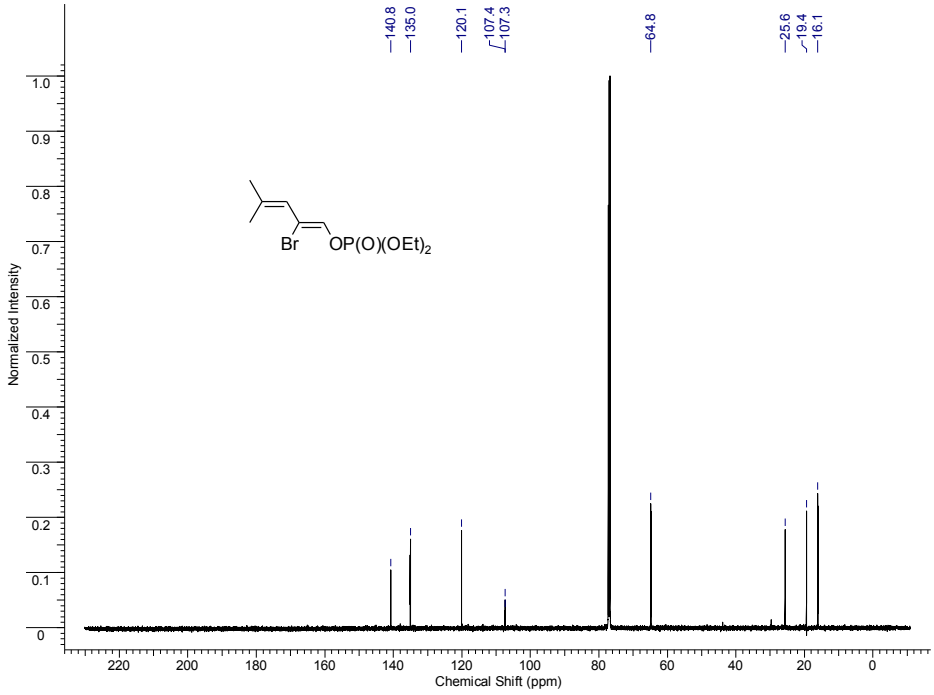


APPENDIX III

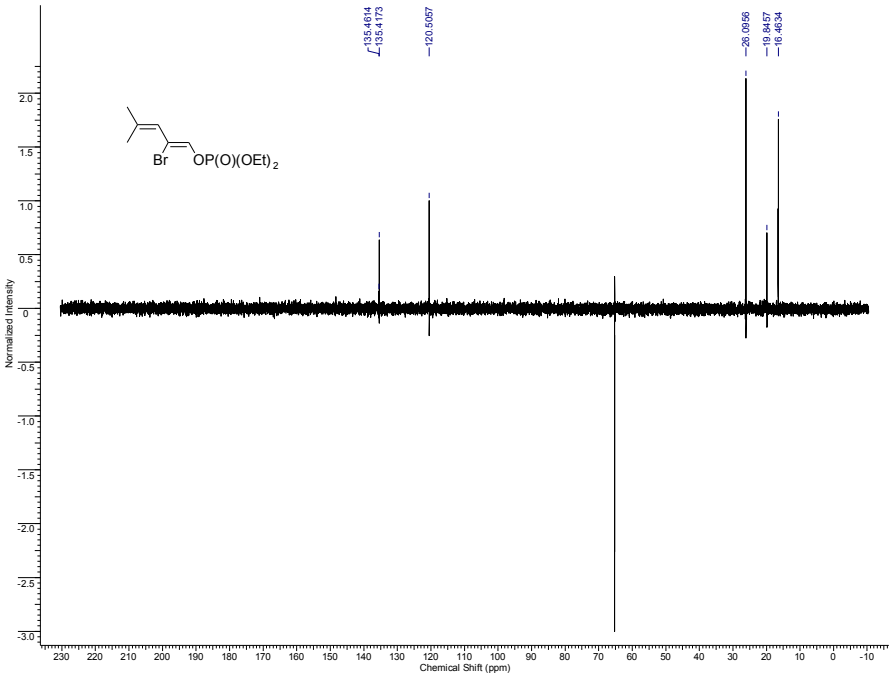
Selected NMR Spectra for Part Three

^{1}H and ^{13}C Spectrum of **59.4a**

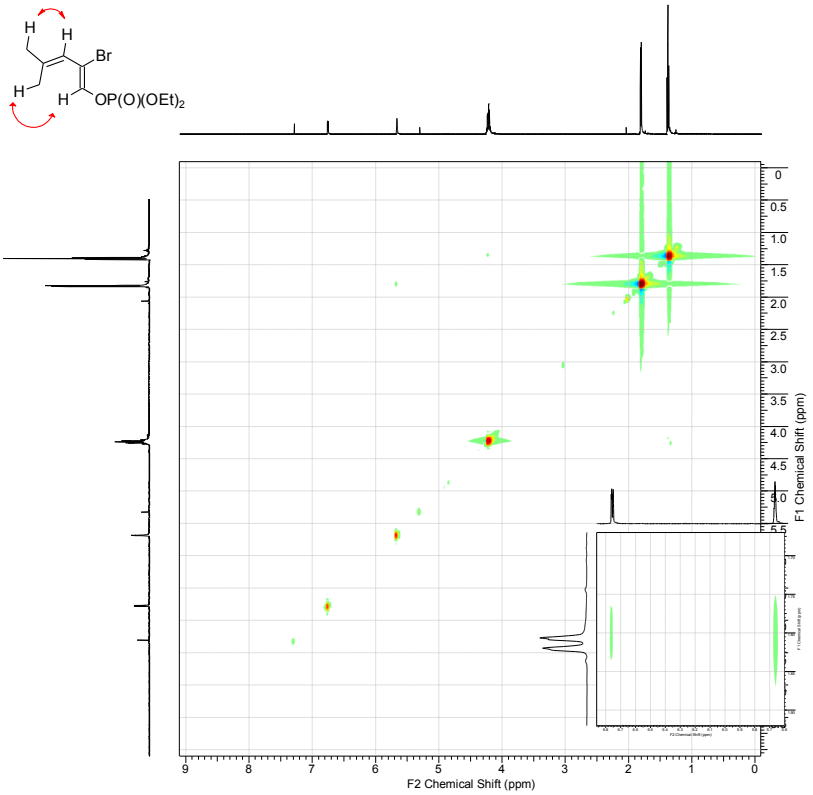




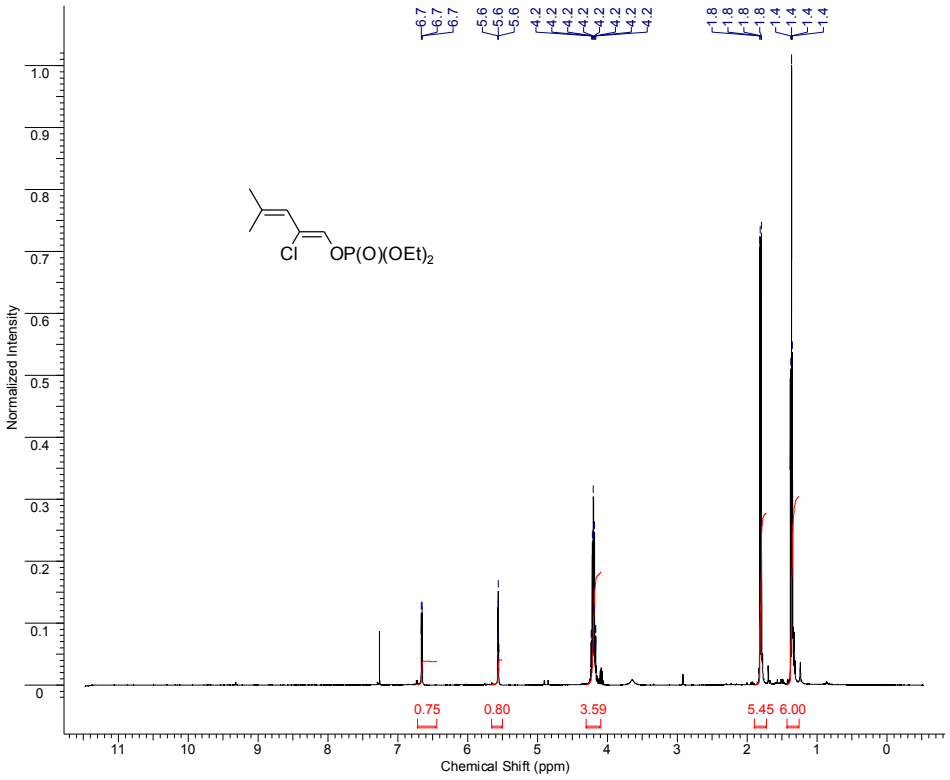
^{13}C-DEPT Spectrum of **59.4a**

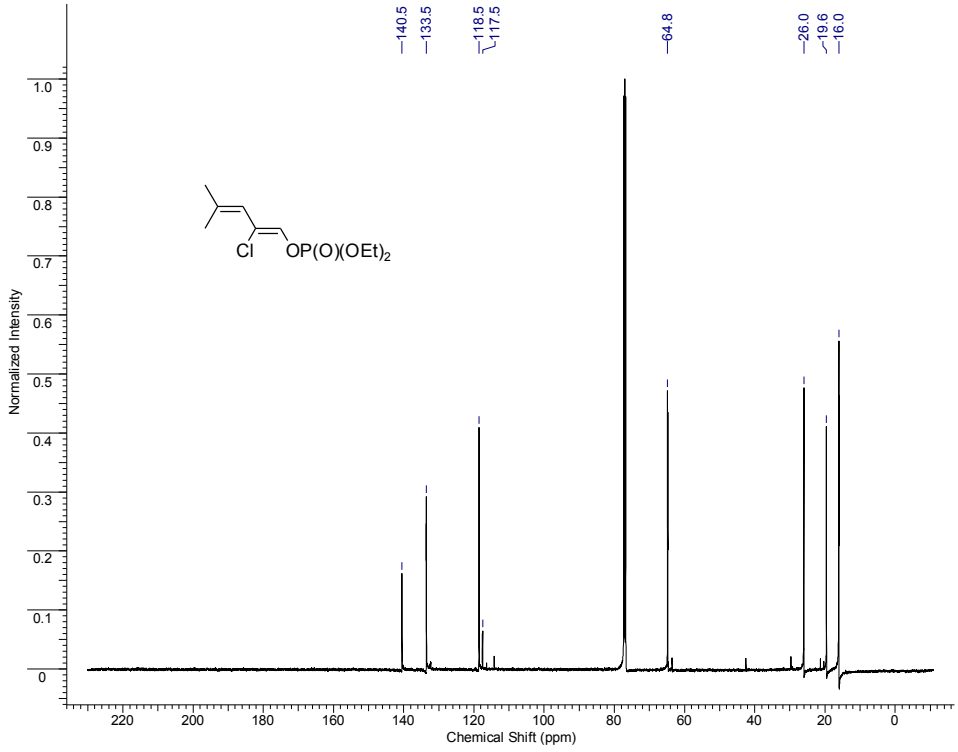


NOESY Spectrum of **59.4a**

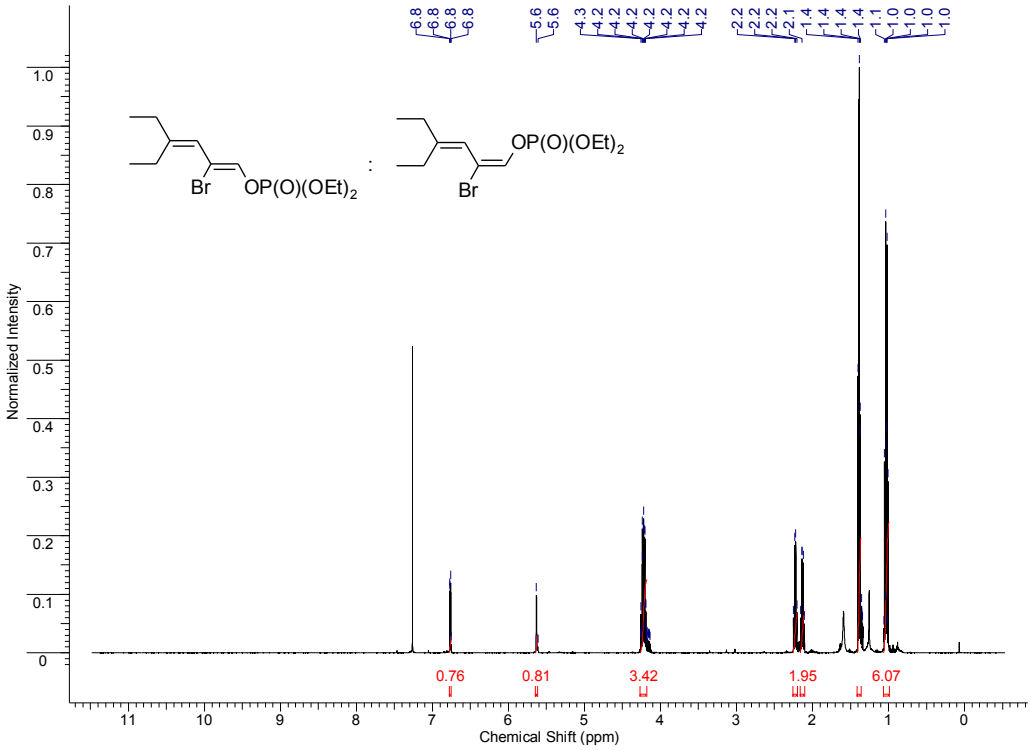


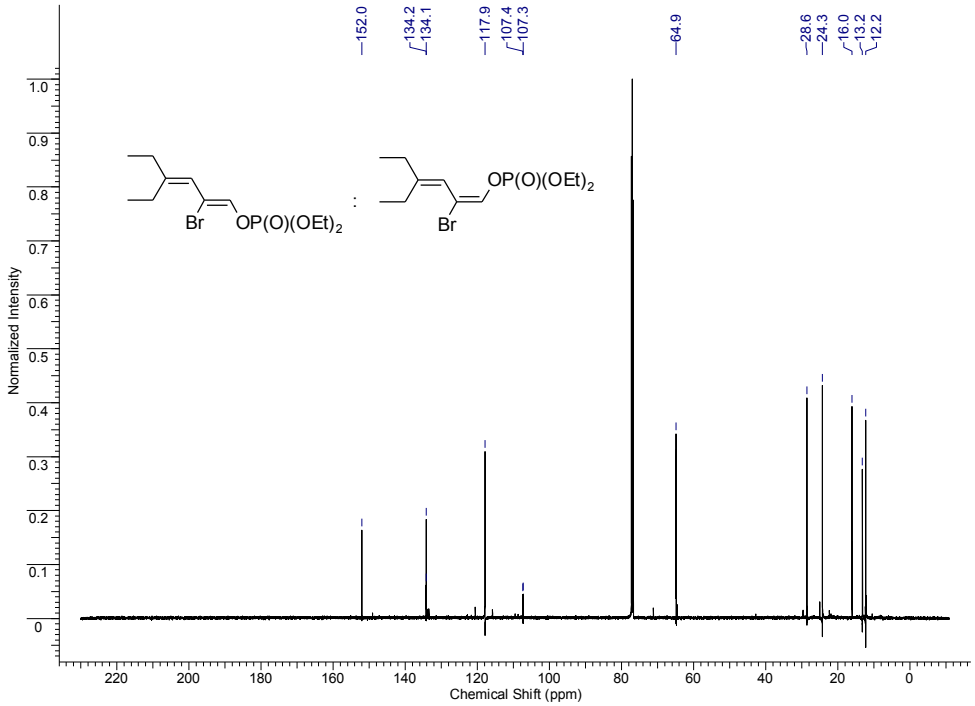
^{1}H and ^{13}C Spectrum of **59.4b**



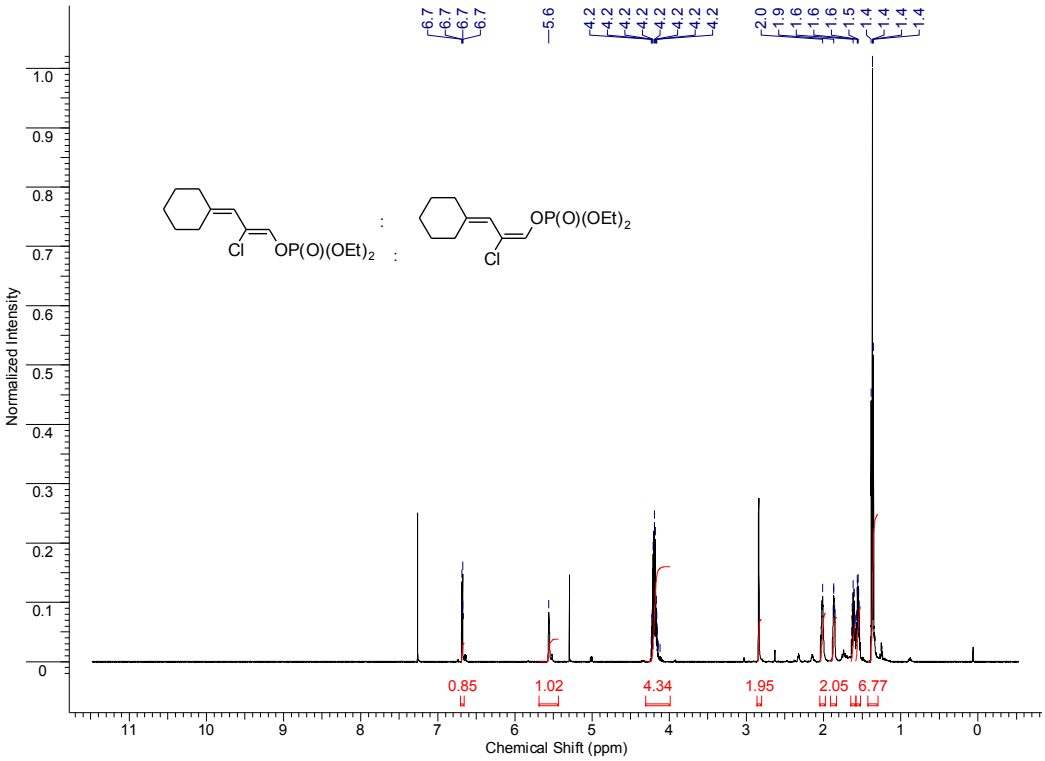


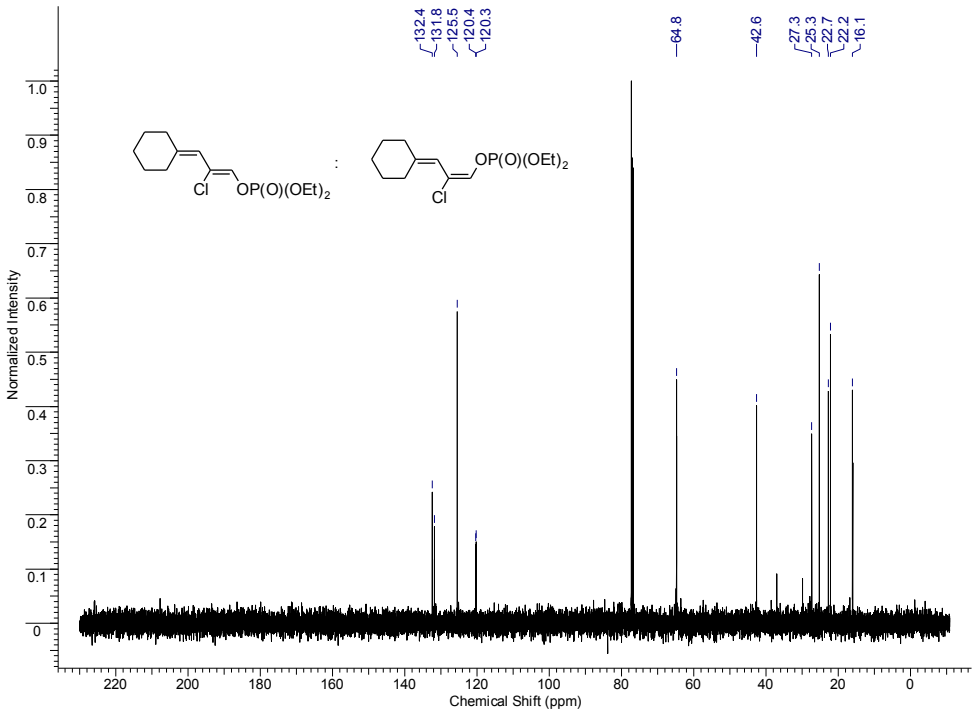
^{1}H and ^{13}C Spectrum of **59.4c +59.3c**



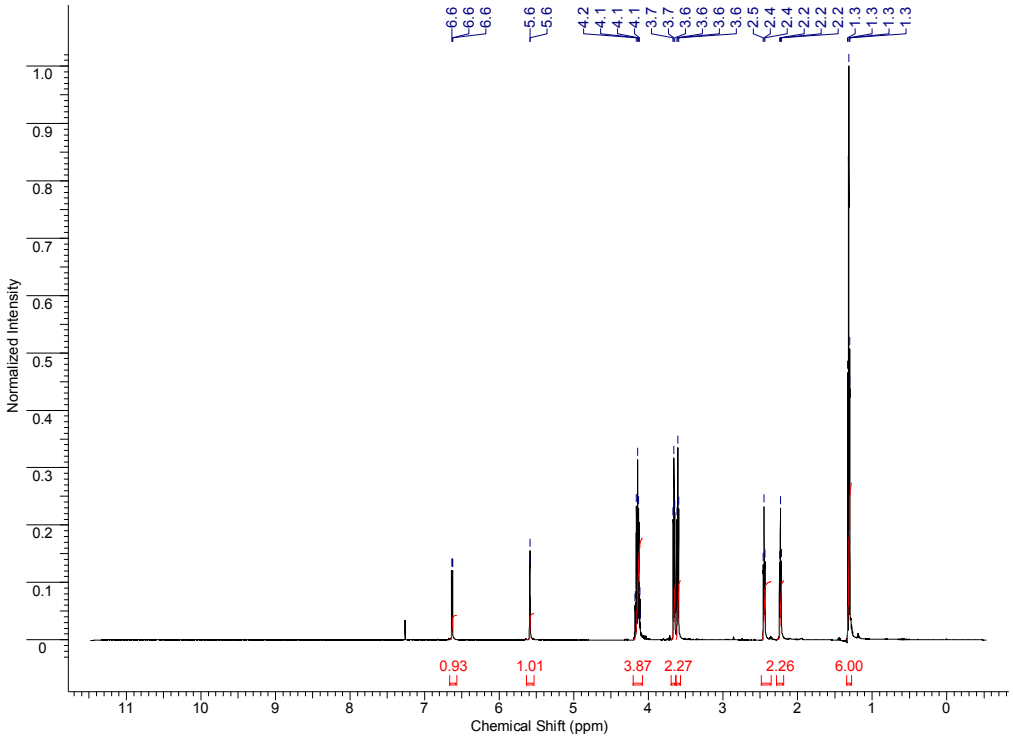


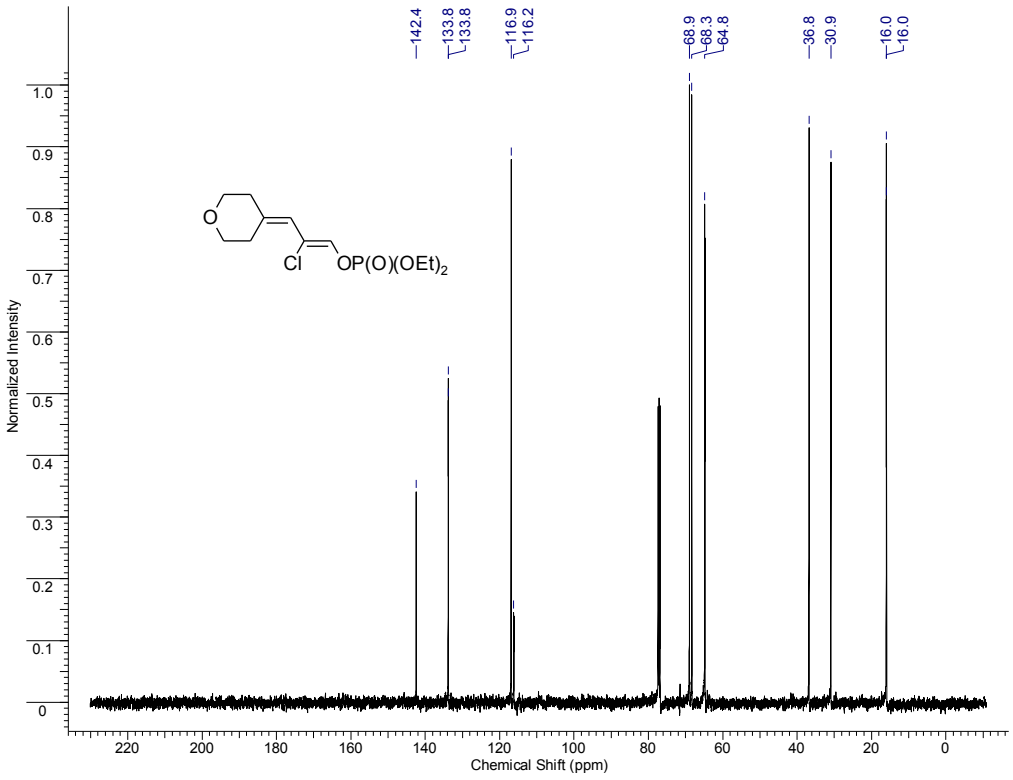
^{1}H and ^{13}C Spectrum of **59.4d + 59.3d**



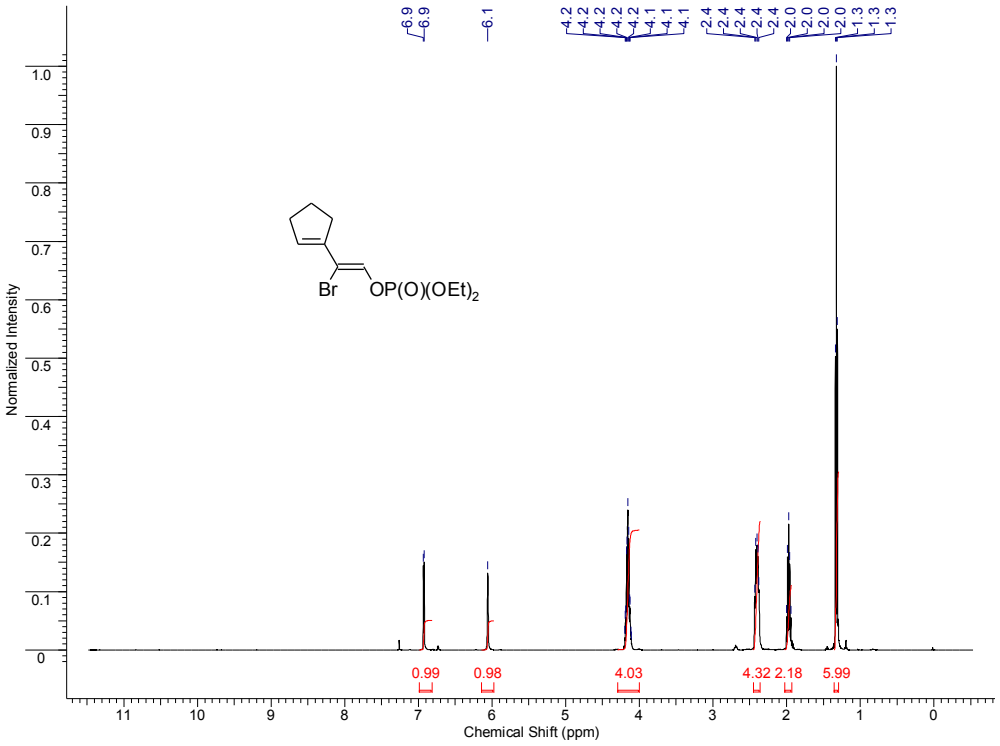


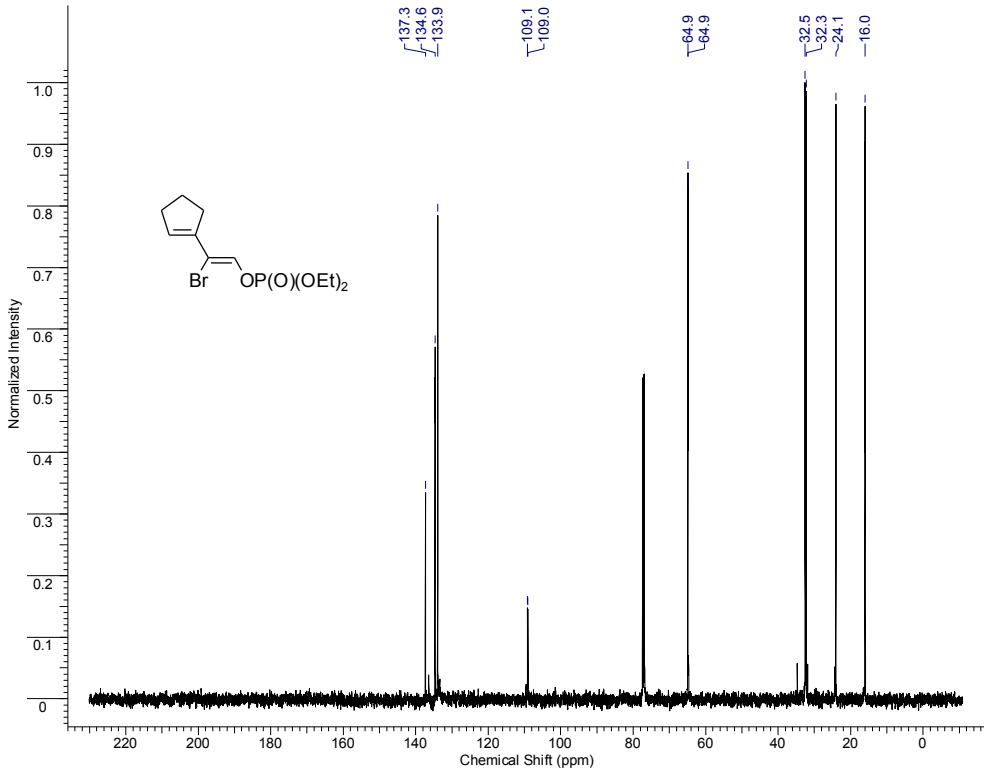
^{1}H and ^{13}C Spectrum of **59.4e**



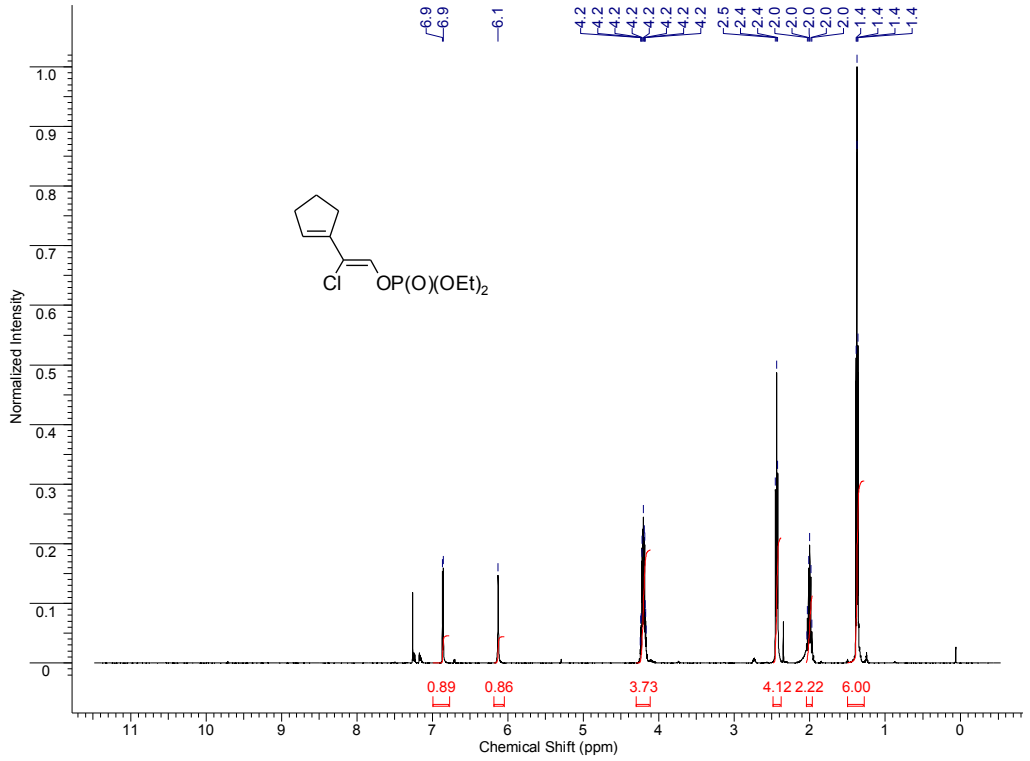


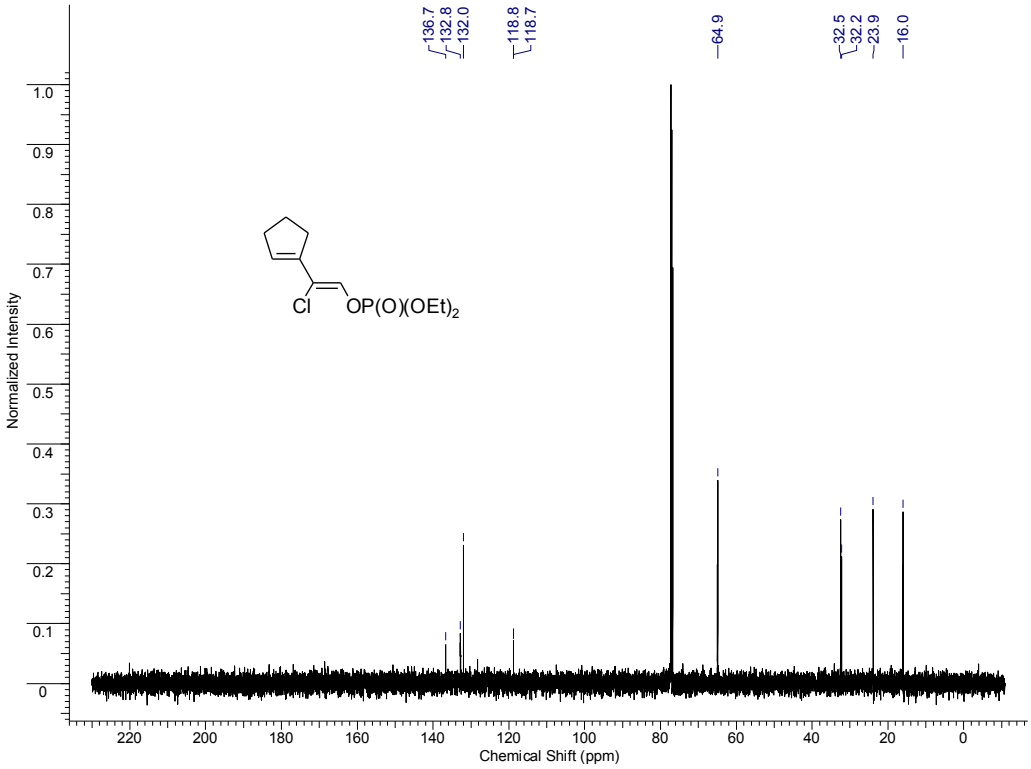
^{1}H and ^{13}C Spectrum of **59.4f**



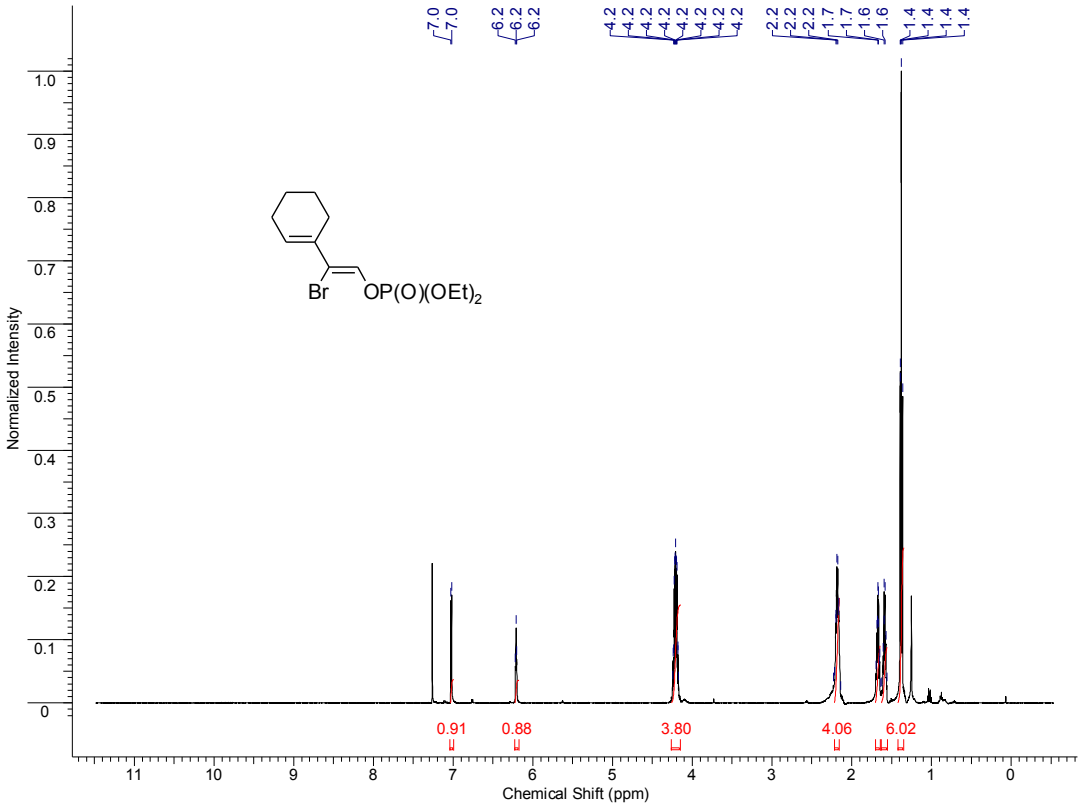


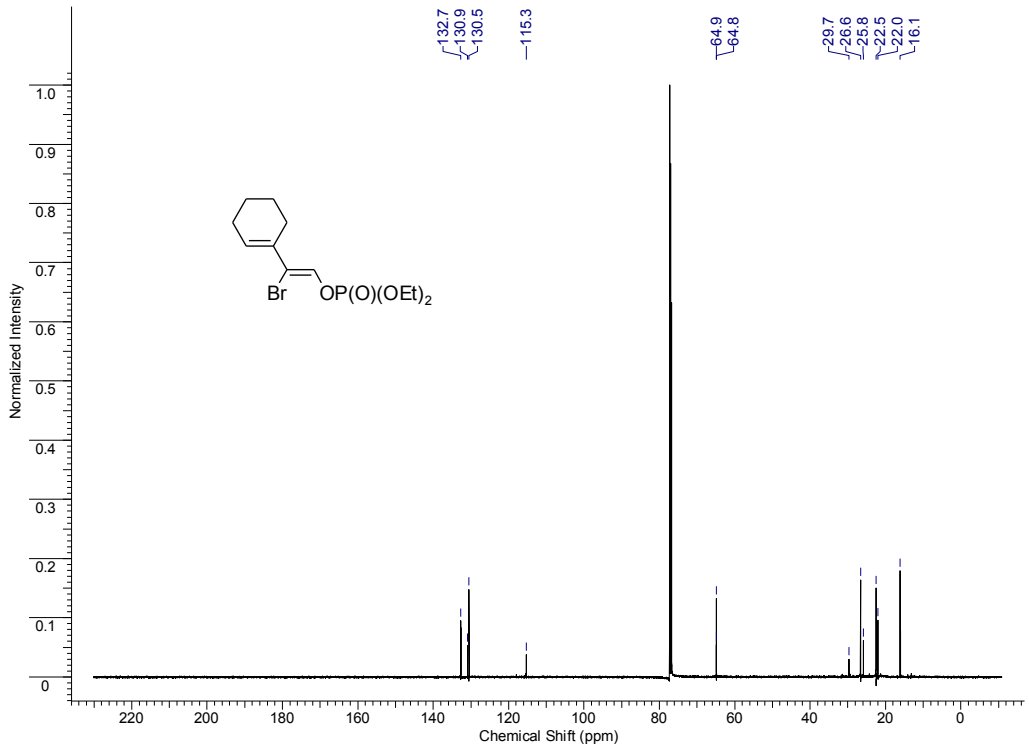
^{1}H and ^{13}C Spectrum of **59.4g**



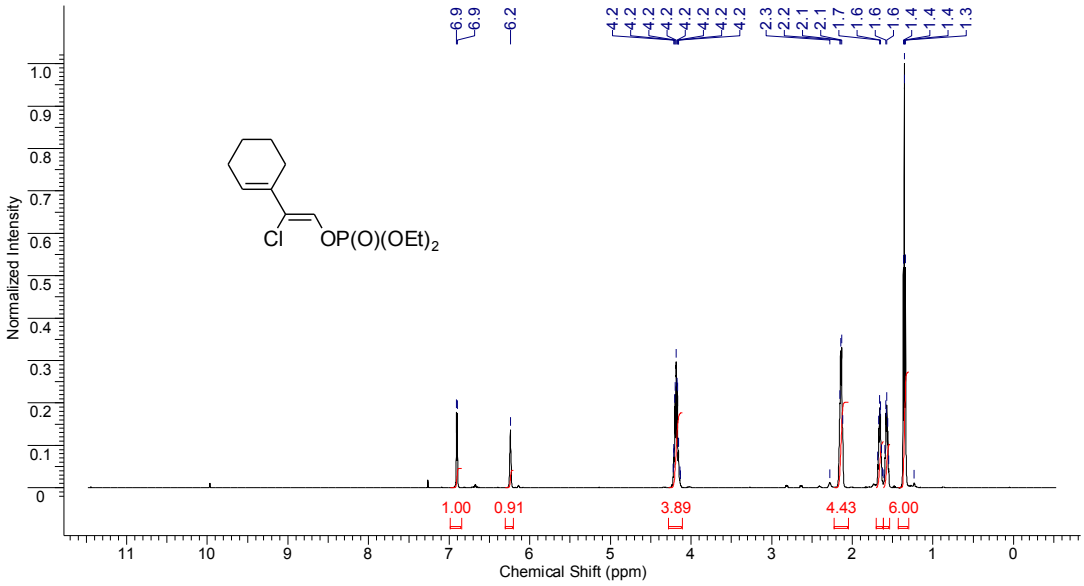


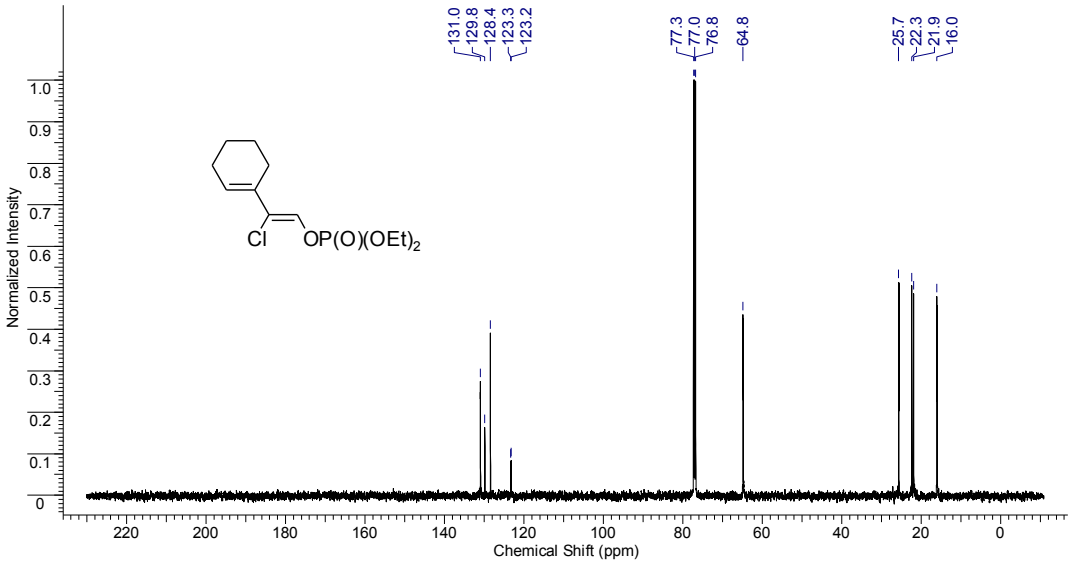
^{1}H and ^{13}C Spectrum of **59.4h**



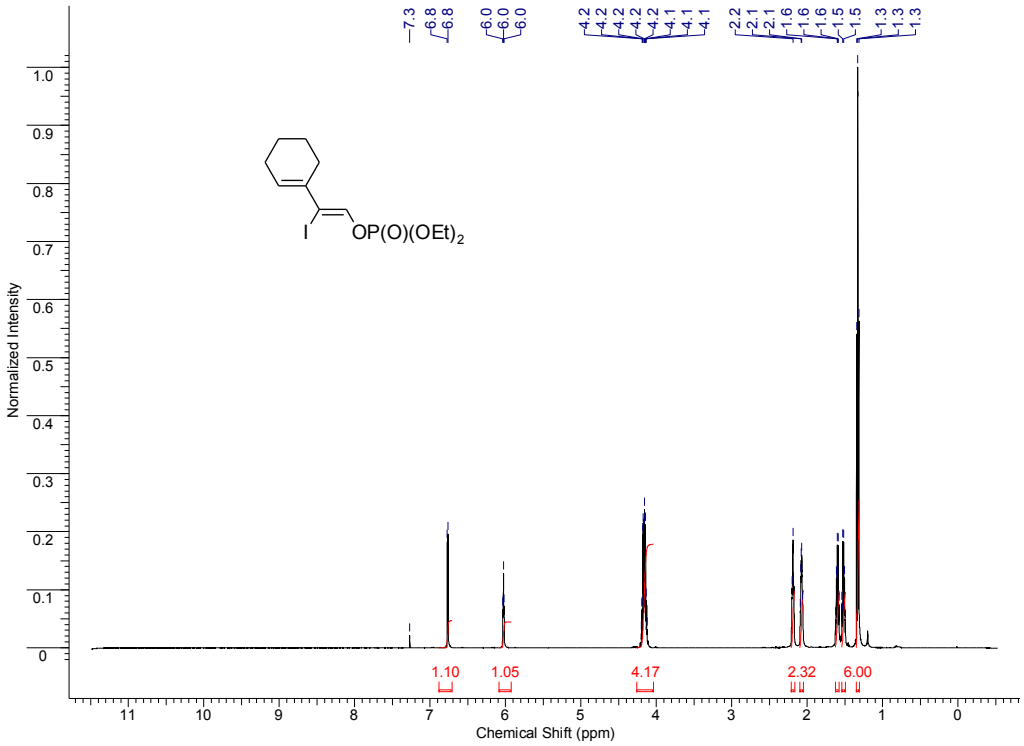


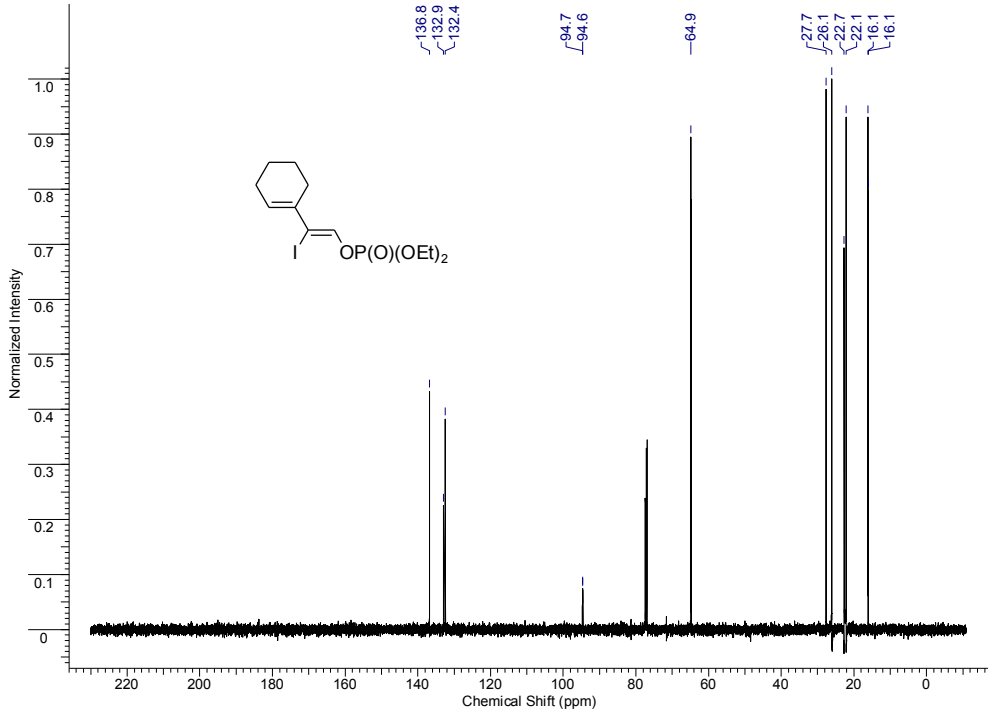
^{1}H and ^{13}C Spectrum of **59.4i**



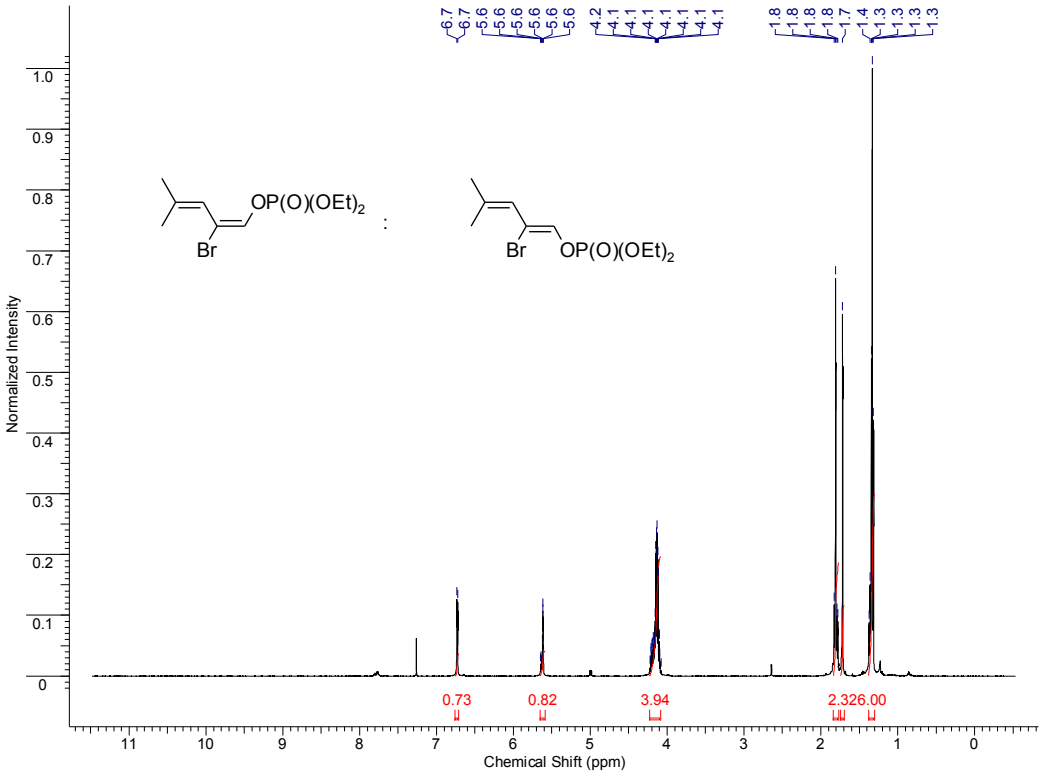


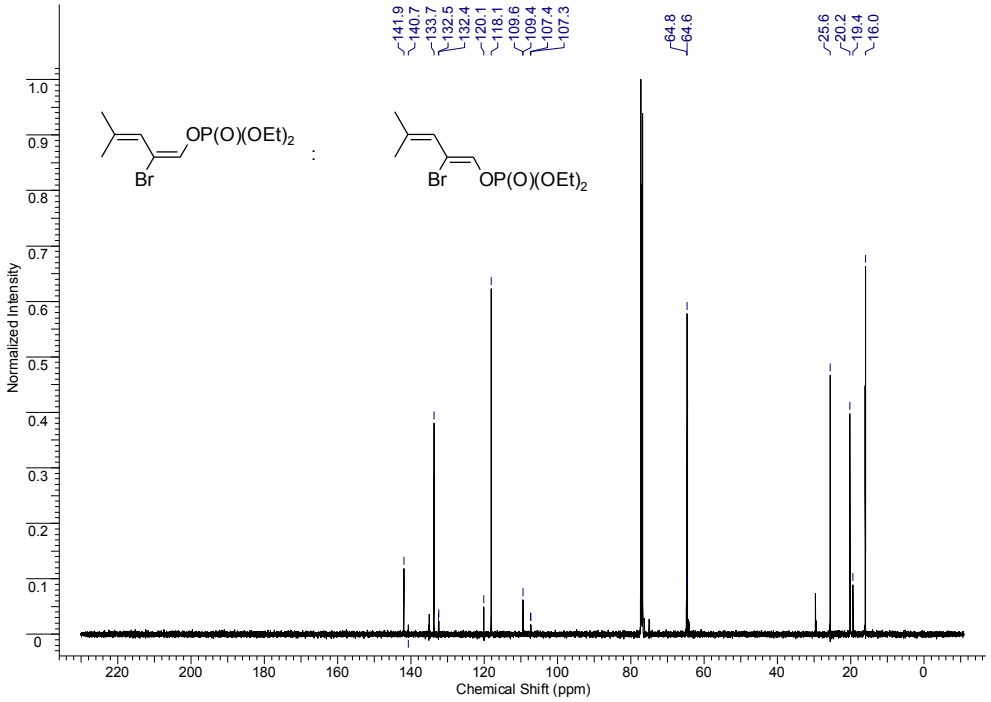
^{1}H and ^{13}C Spectrum of **59.4j**



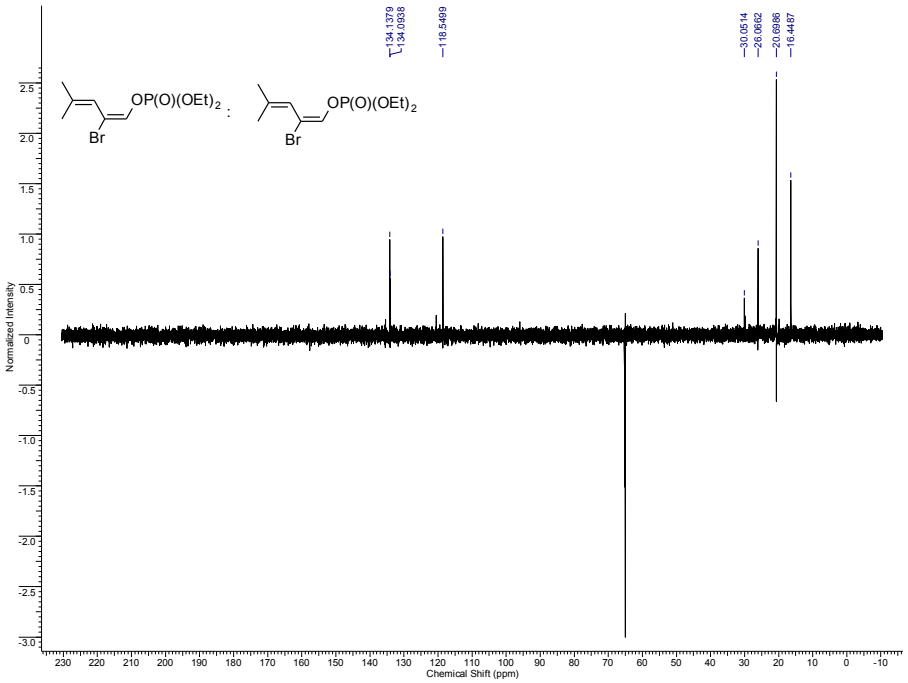


^{1}H and ^{13}C Spectrum of **59.4a + 59.3a**

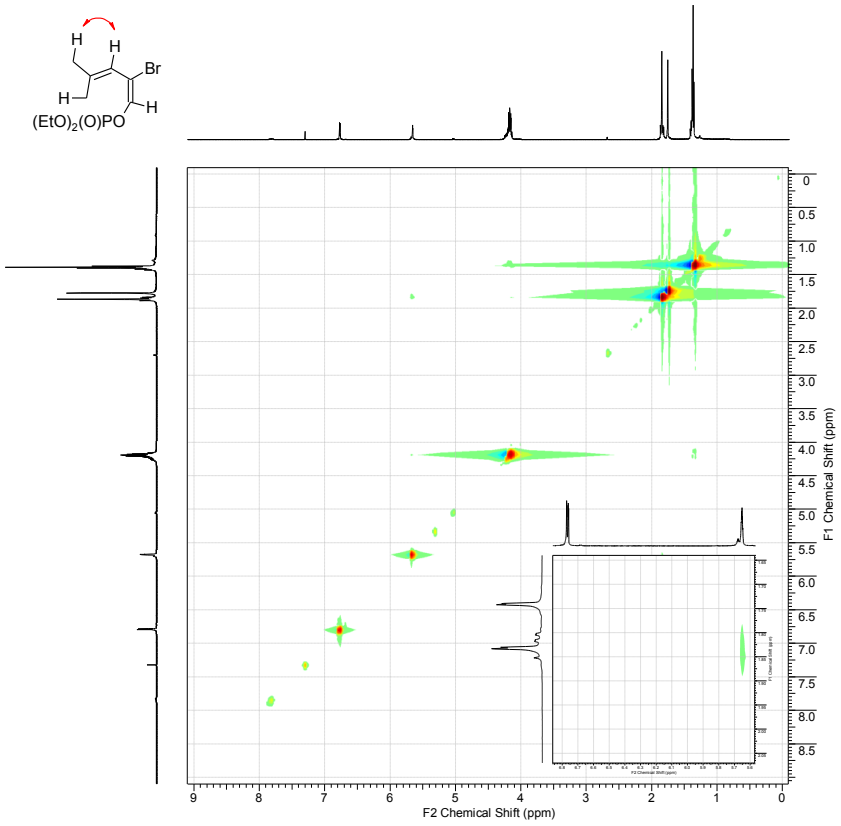




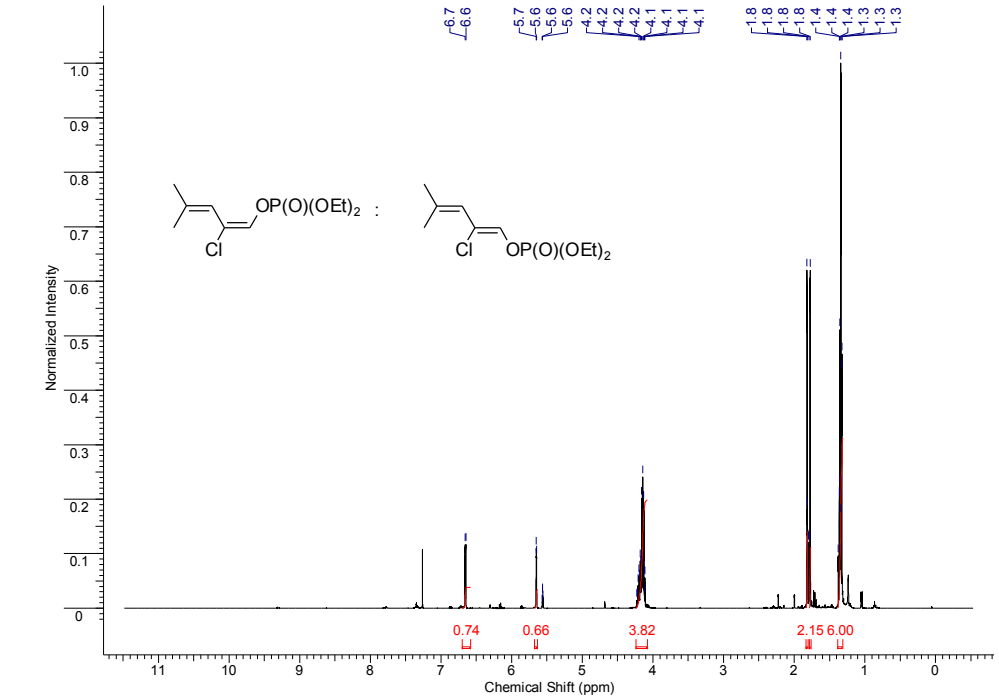
^{13}C-DEPT Spectrum of **59.4a** + **59.3a**

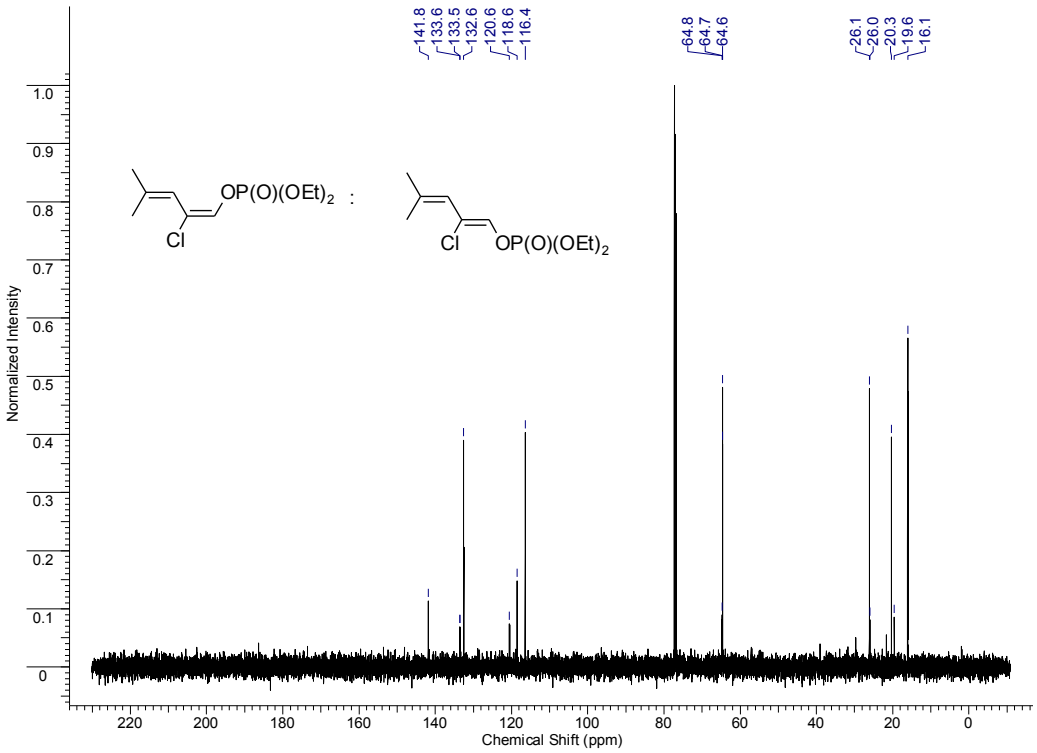


NOESY Spectrum of **59.4a** + **59.3a**

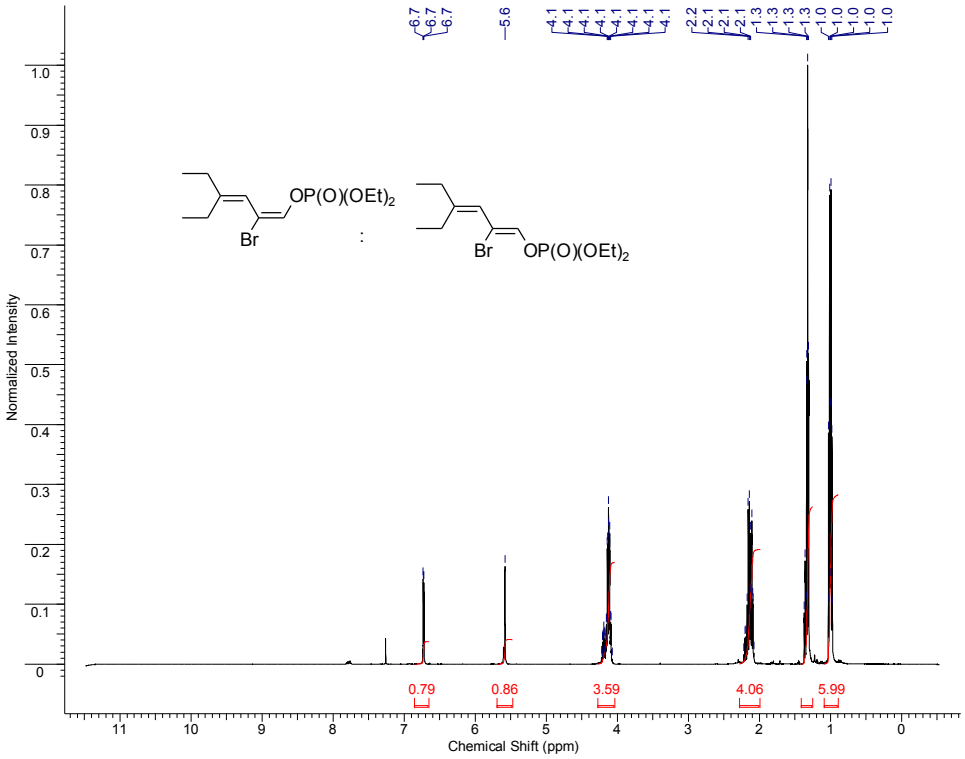


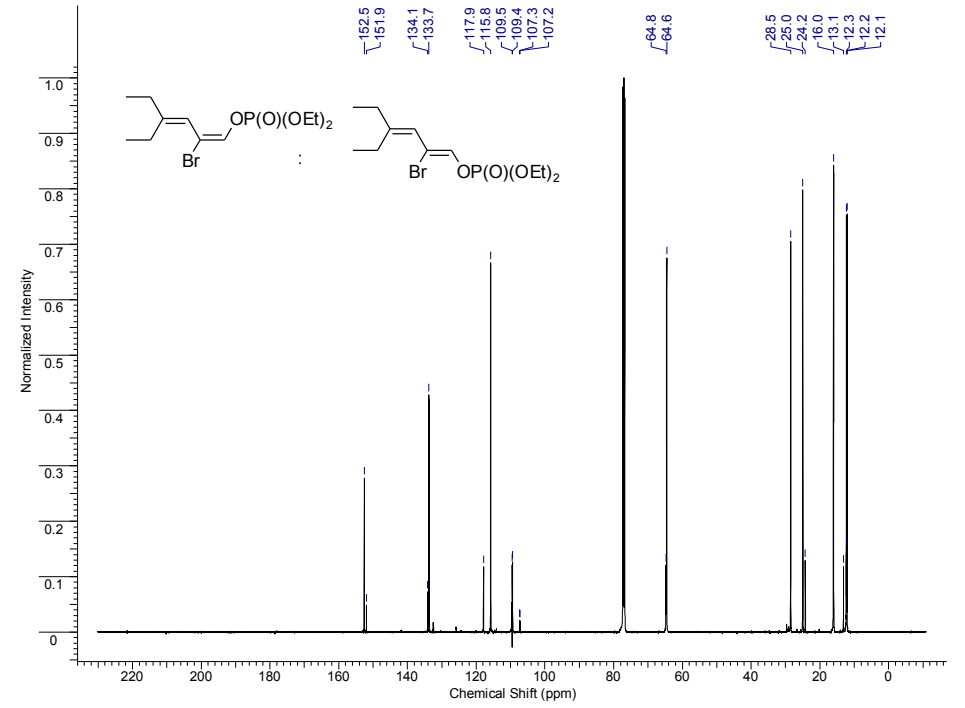
^{1}H and ^{13}C Spectrum of **59.4b + 59.3b**



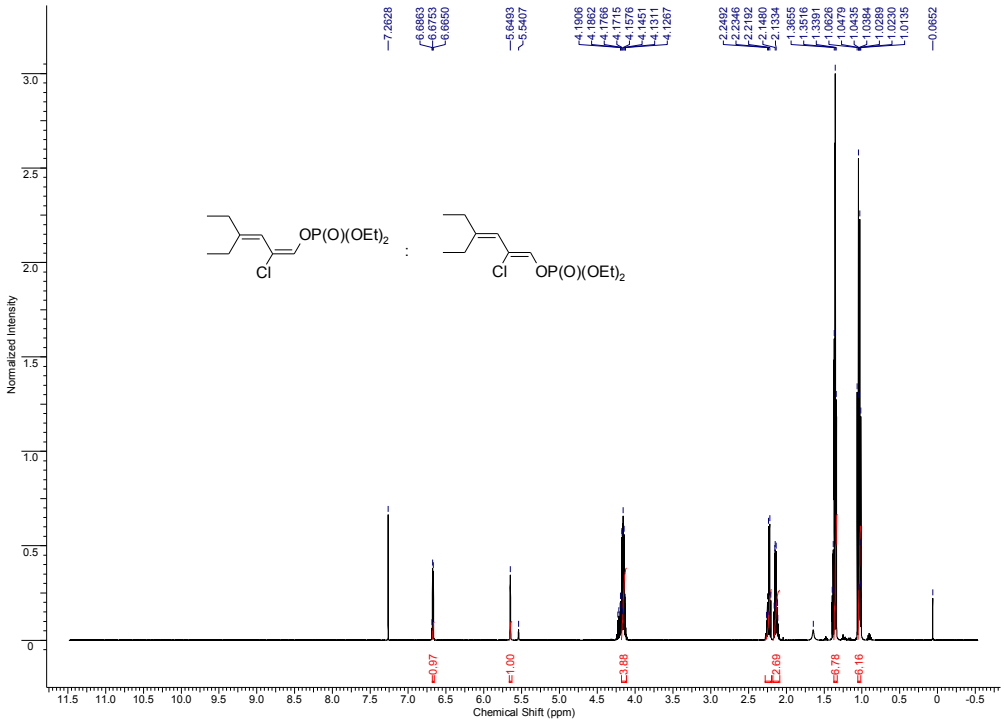


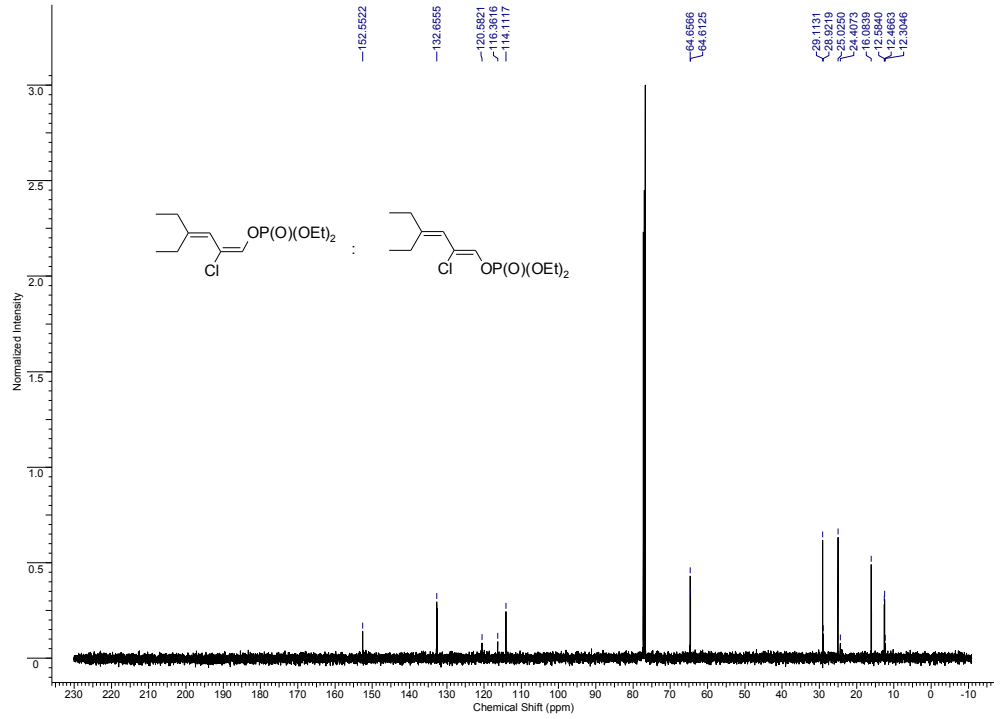
^{1}H and ^{13}C Spectrum of **59.4c + 59.3c**



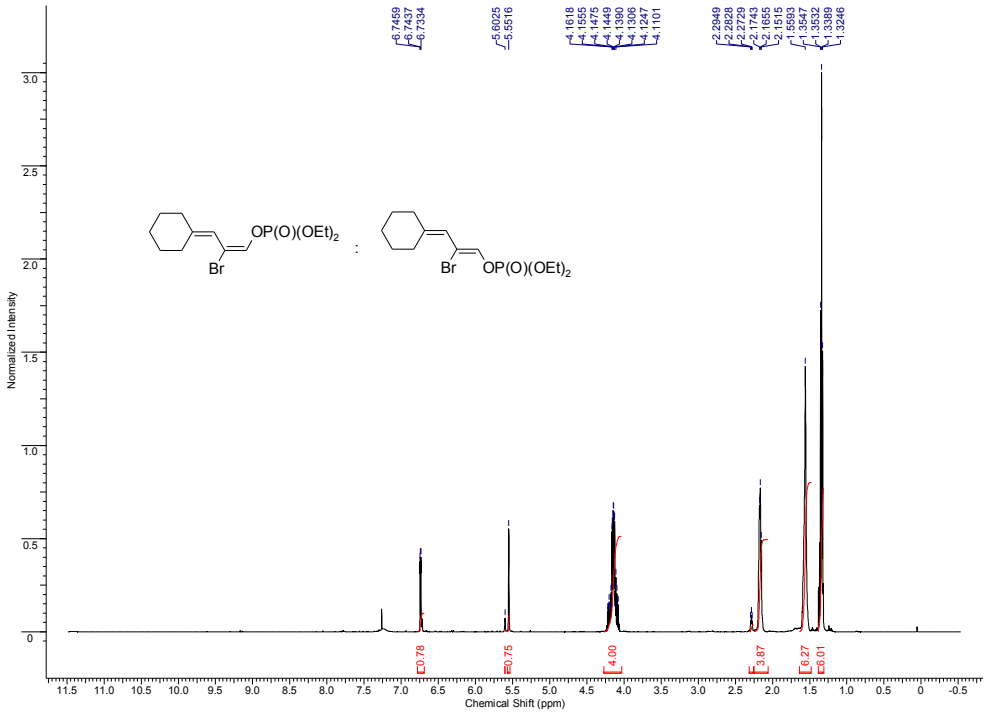


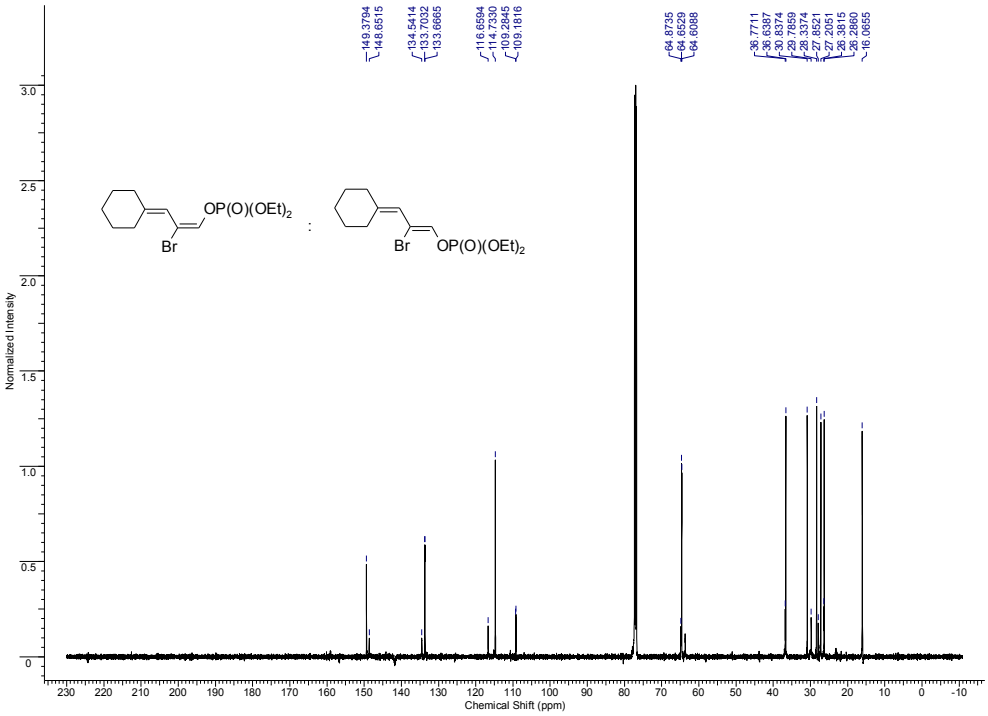
^{1}H and ^{13}C Spectrum of **59.3d** + ***Z*** isomer



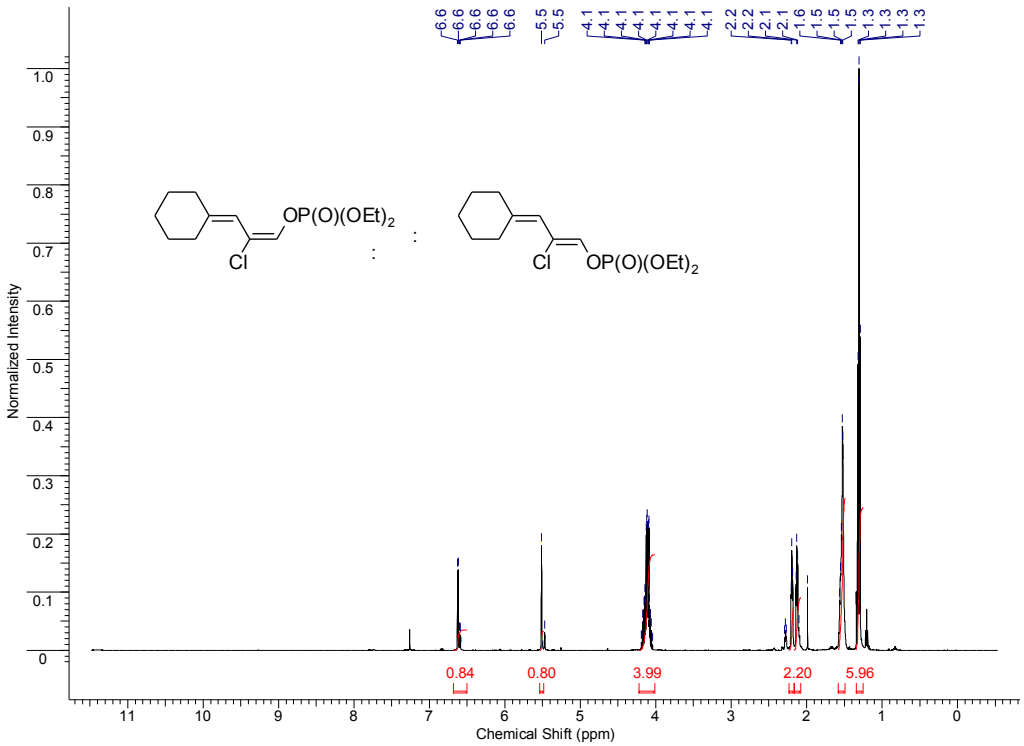


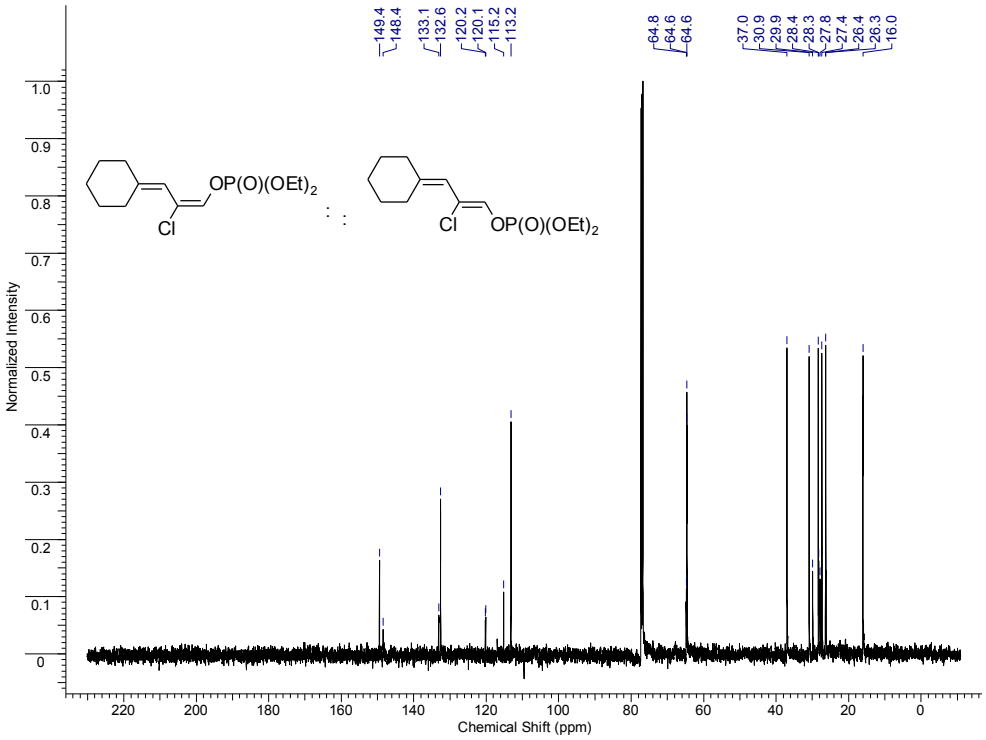
^{1}H and ^{13}C Spectrum of **59.3n** + ***Z*** isomer



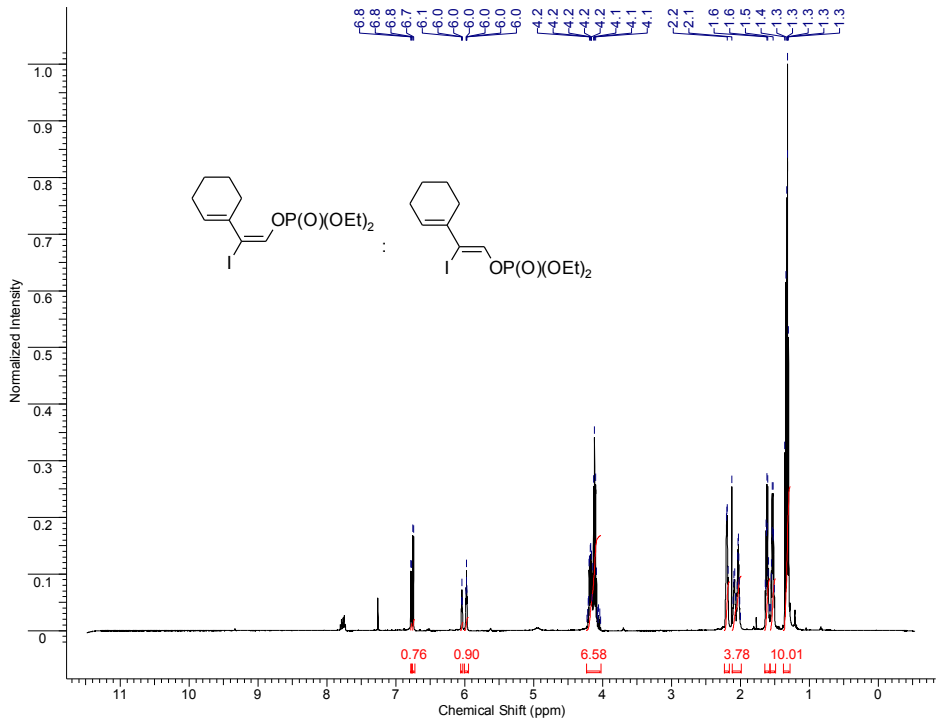


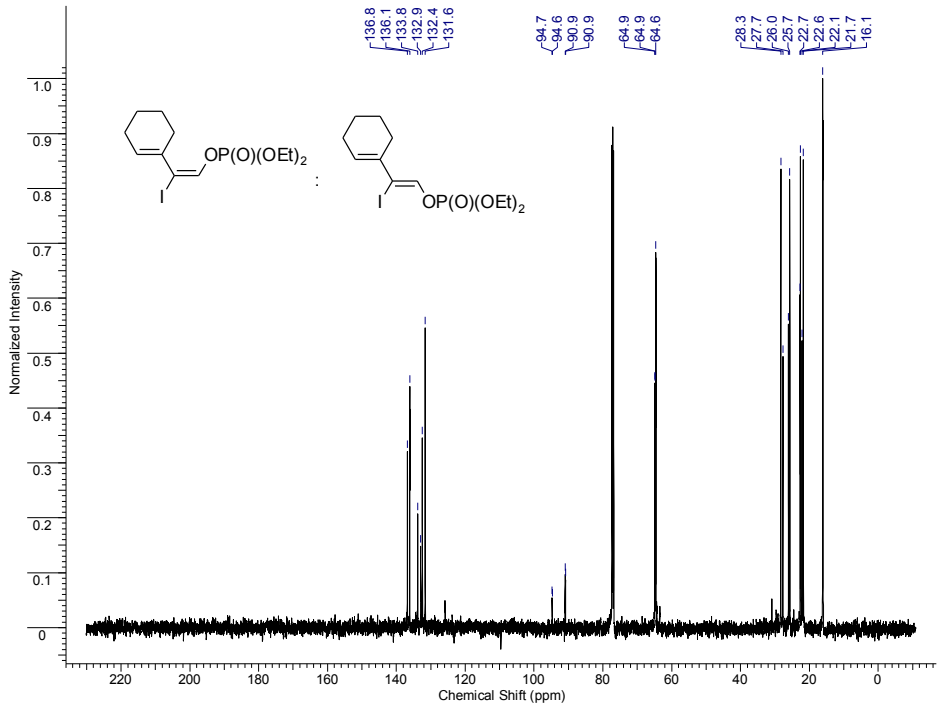
^{1}H and ^{13}C Spectrum of **59.3d + 59.4d**



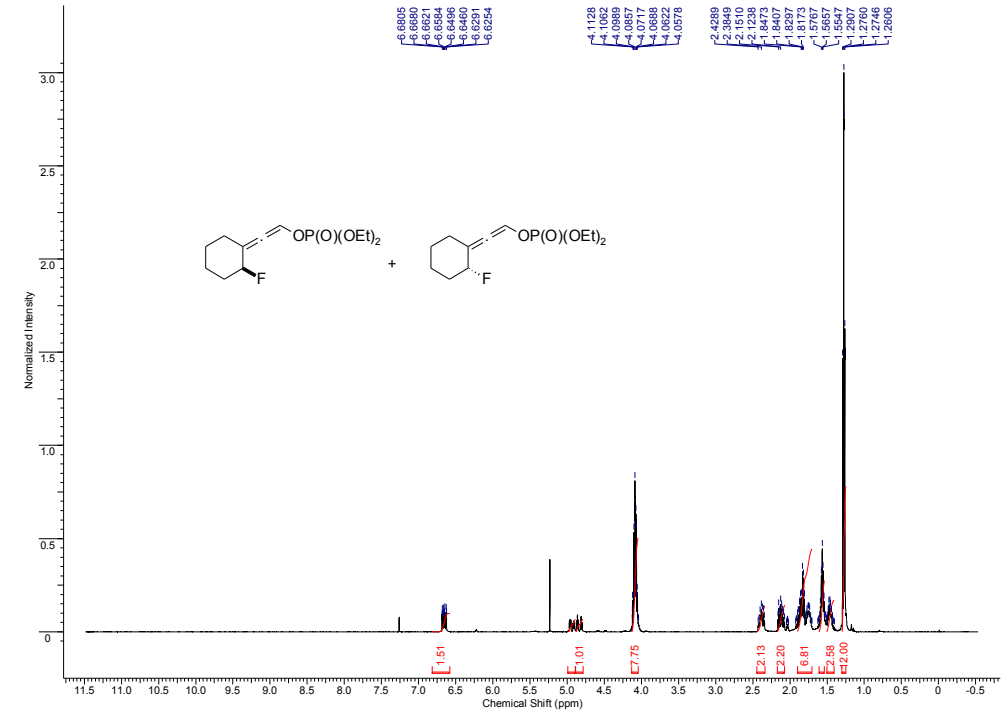


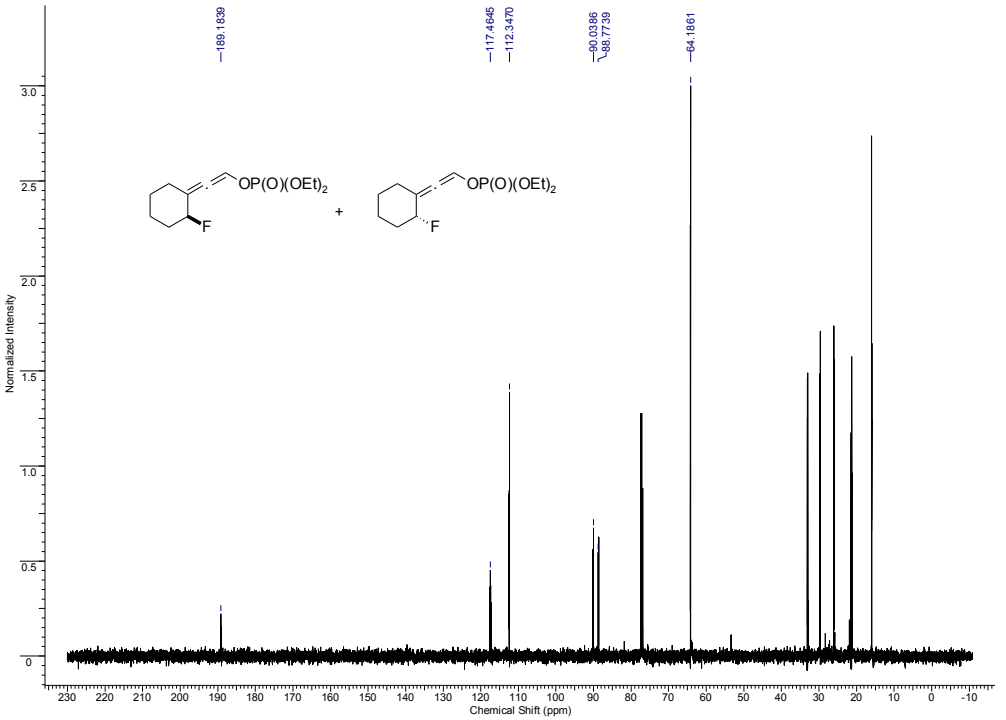
^{1}H and ^{13}C Spectrum of **59.3j** + **59.4j**



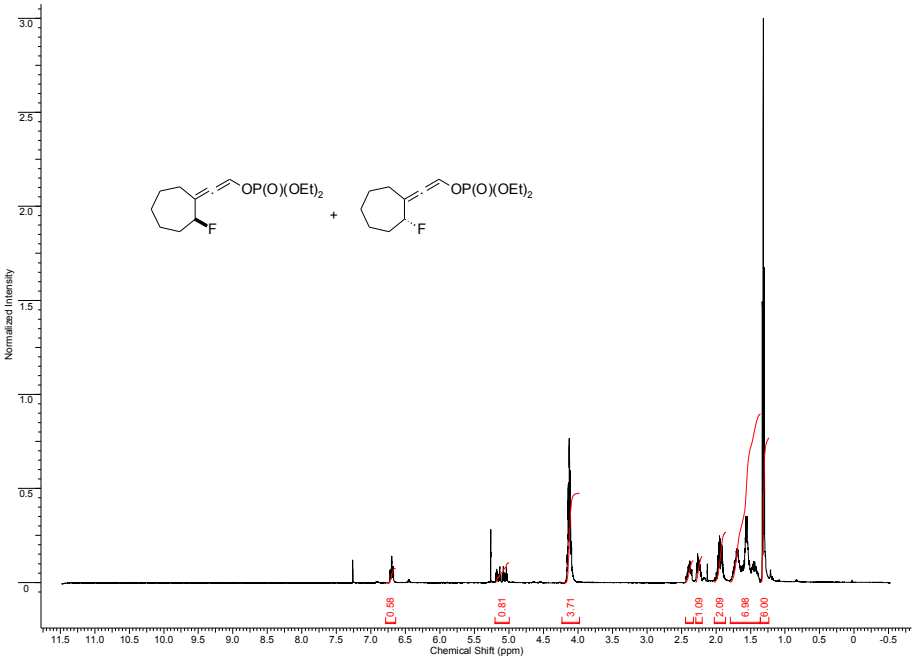


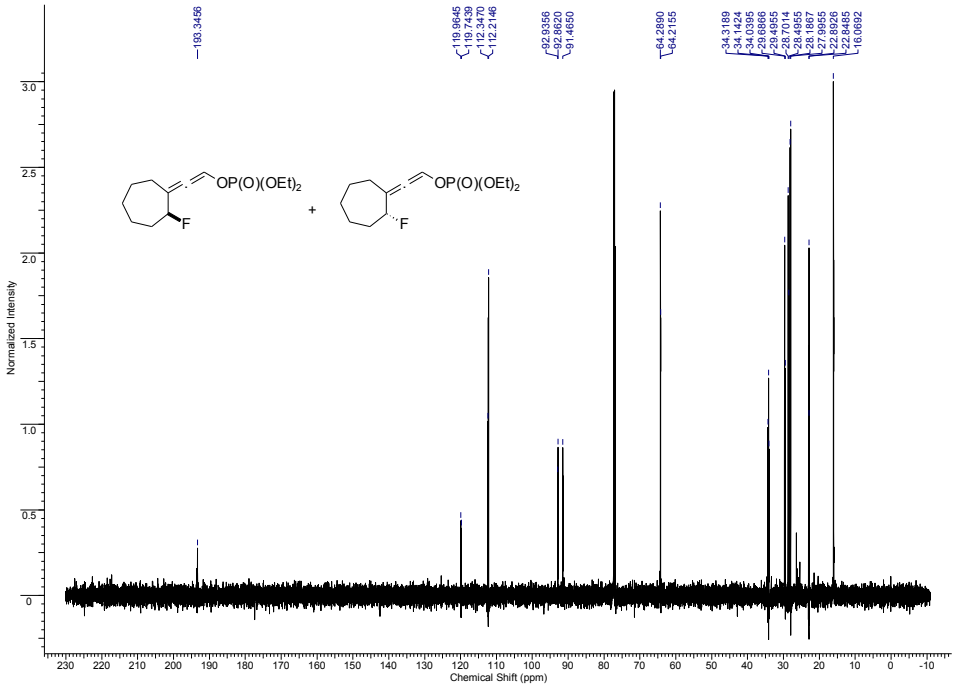
^{1}H and ^{13}C Spectrum of **Diethyl (2-(2-fluorocyclohexylidene)vinyl) phosphate**



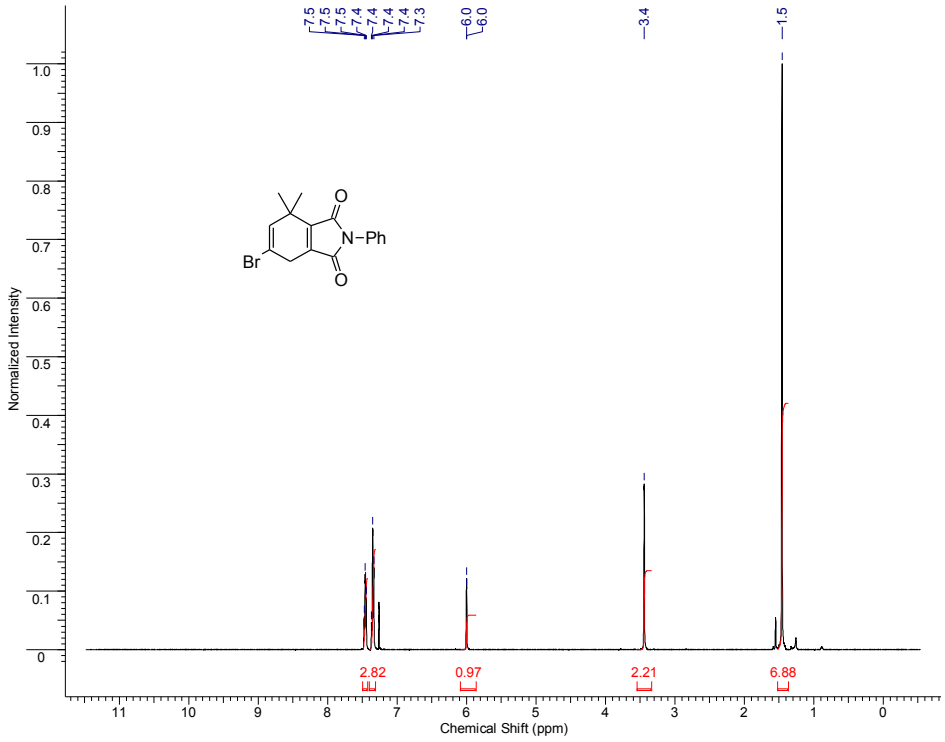


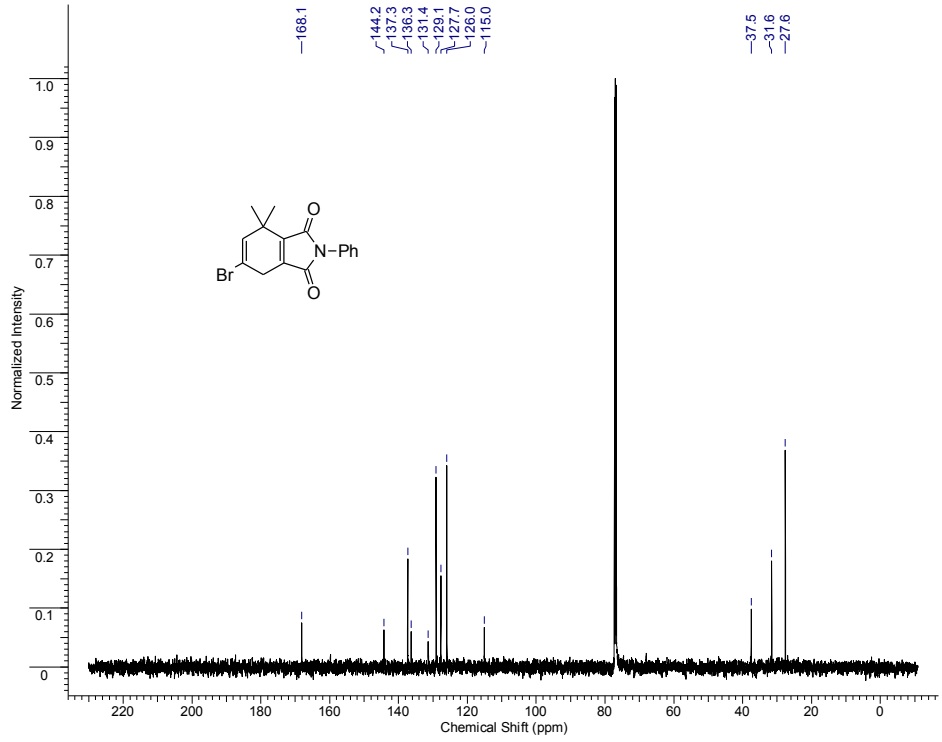
^{1}H and ^{13}C Spectra of **Diethyl (2-(2-fluorocycloheptylidene)vinyl) phosphate**



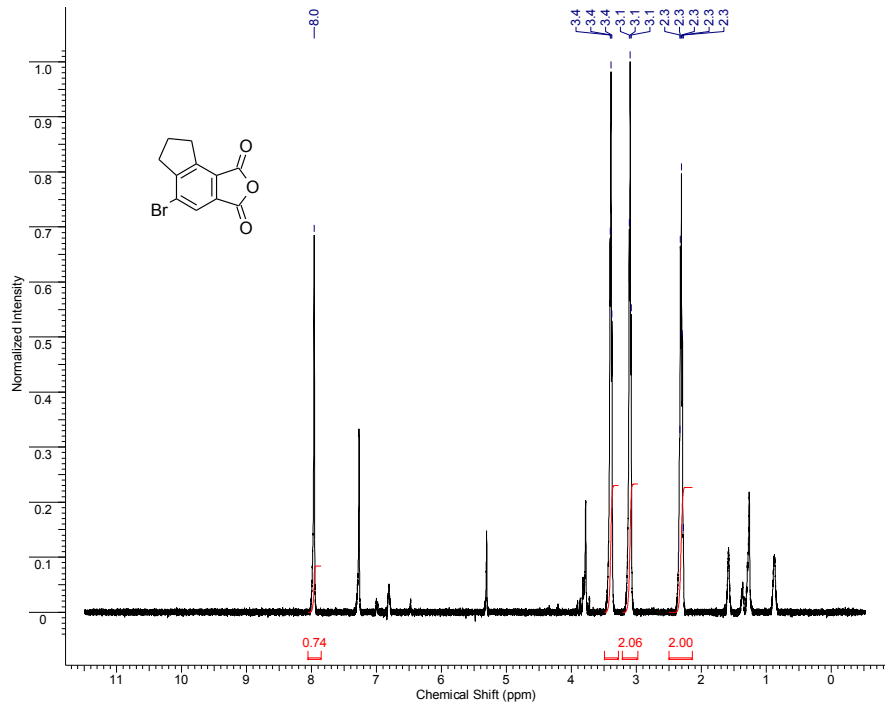


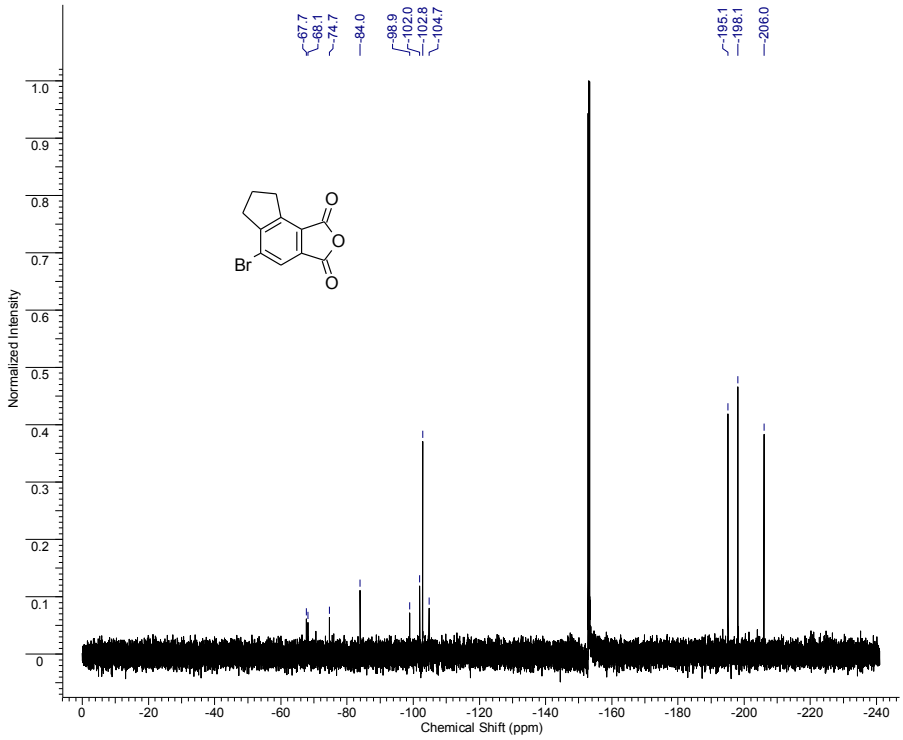
^{1}H and ^{13}C Spectrum of **60.1**



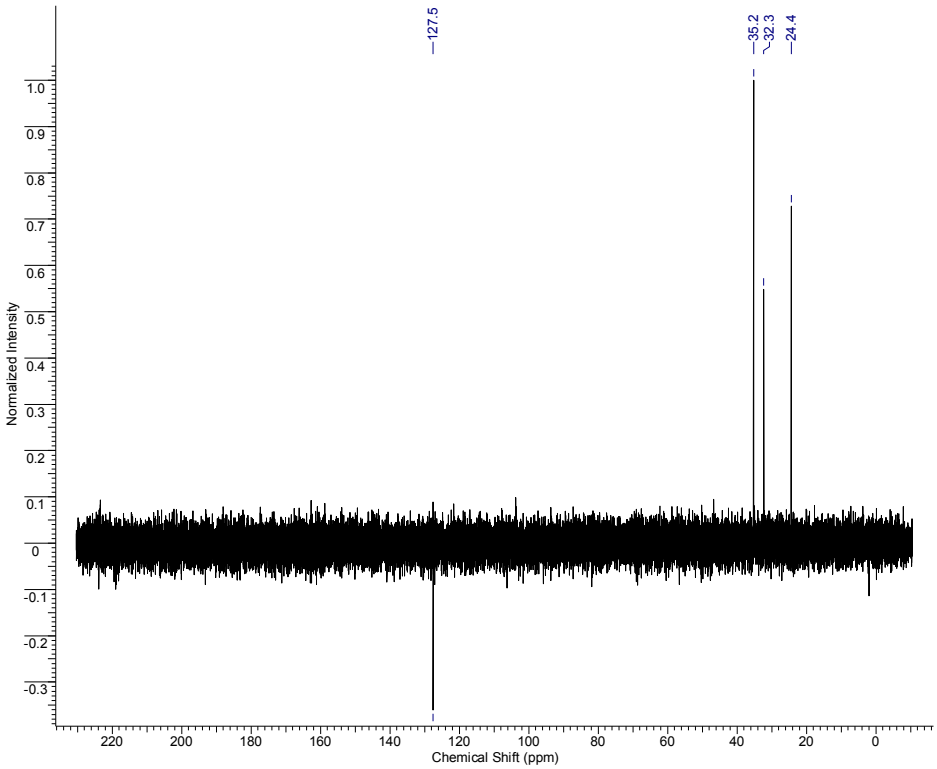


^{1}H and ^{13}C Spectrum of **60.2f**

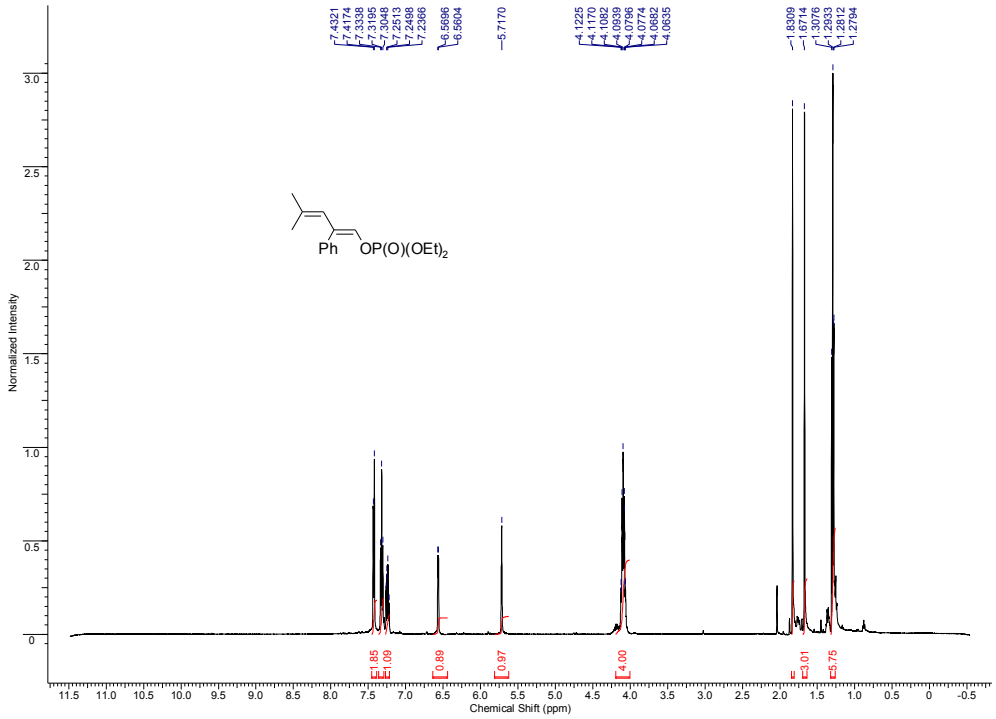


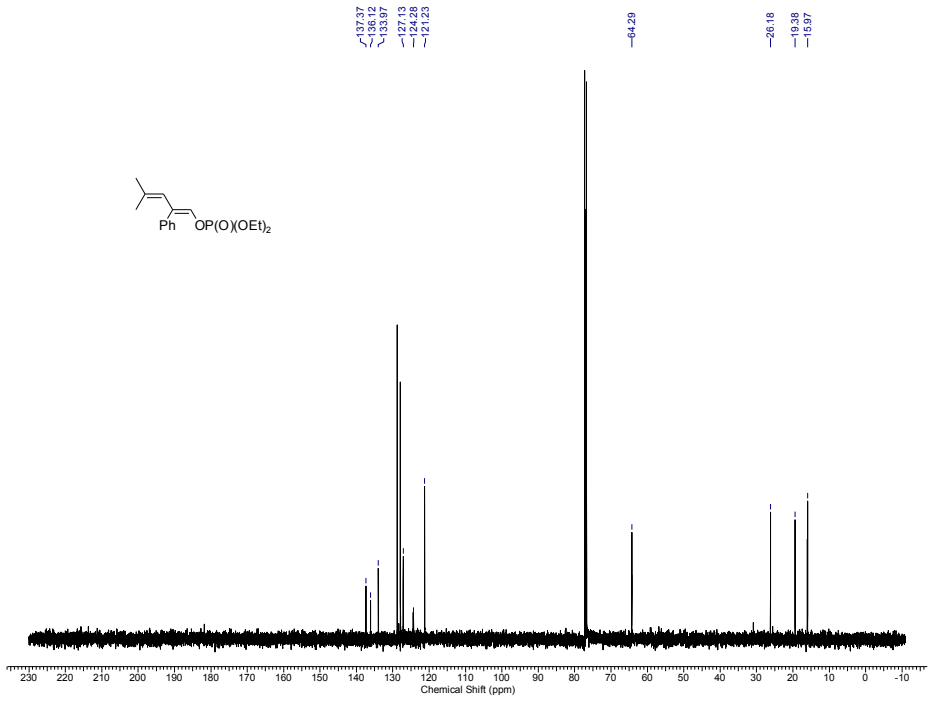


^{13}C-DEPT Spectra of **60.2f**

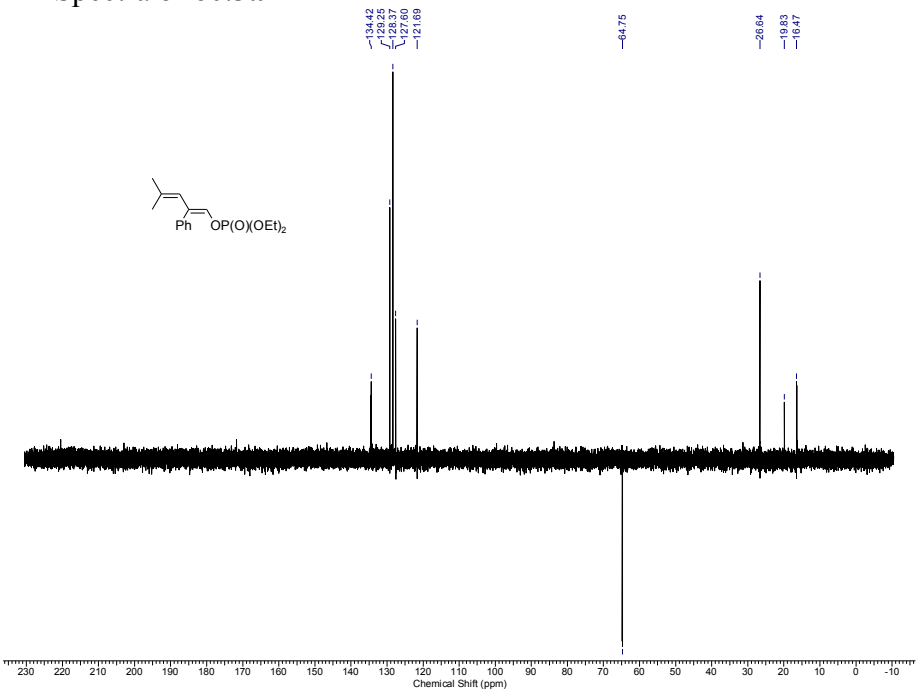


^{1}H and ^{13}C Spectrum of **60.3a**

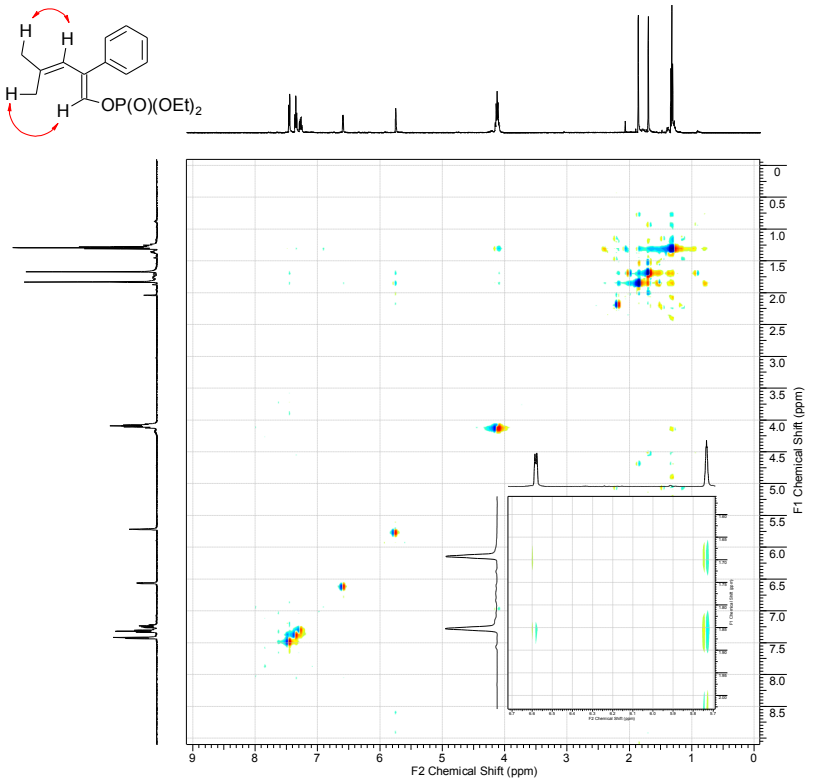




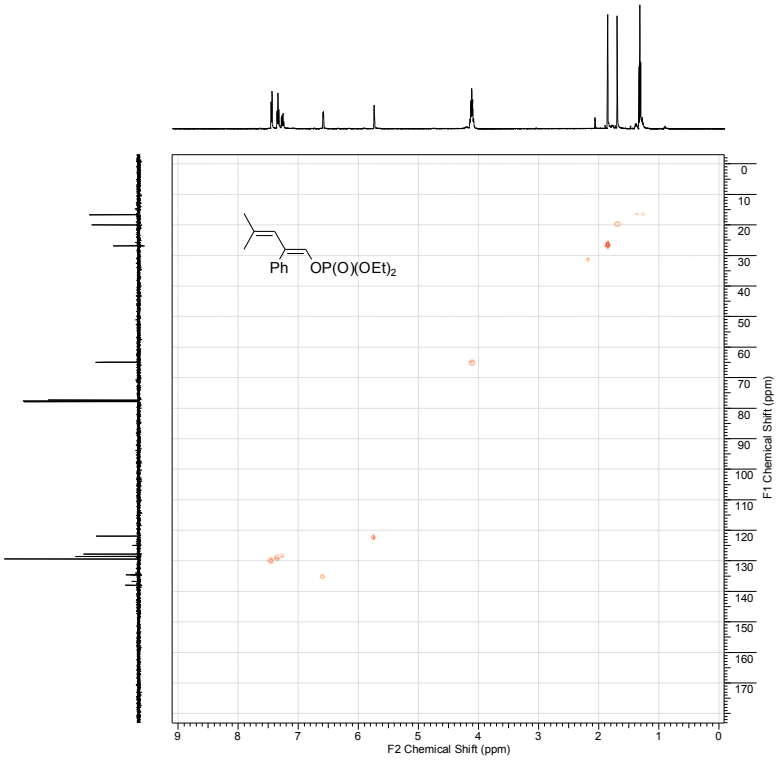
^{13}C-DEPT Spectra of **60.3a**



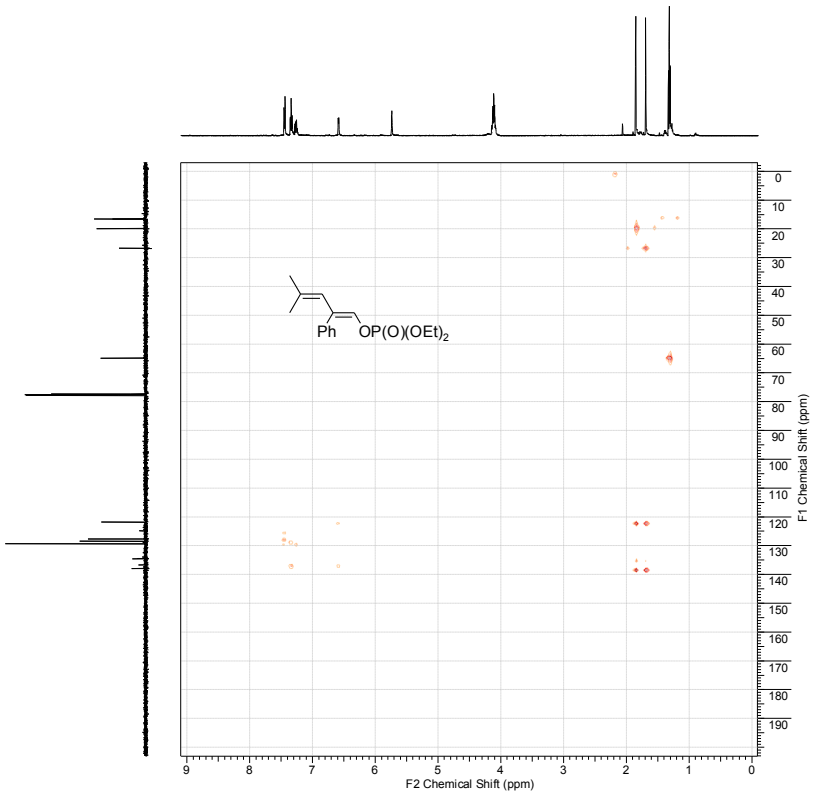
NOESY Spectra of **60.3a**



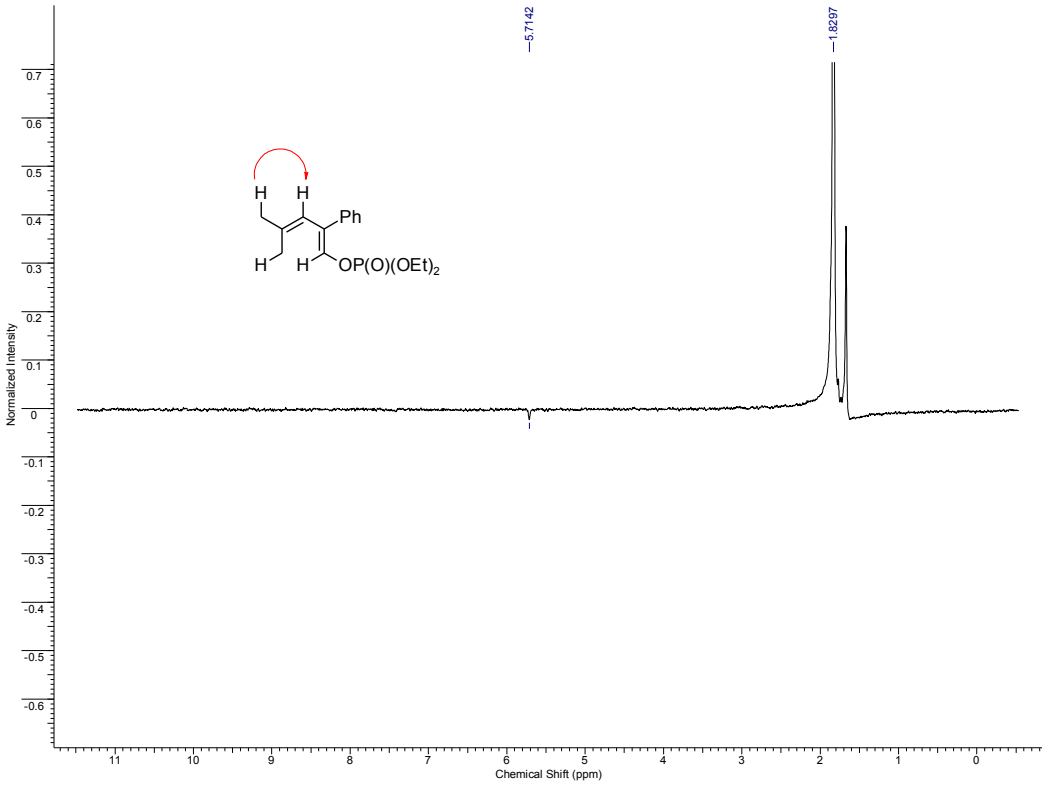
HMQC Spectra of **60.3a**



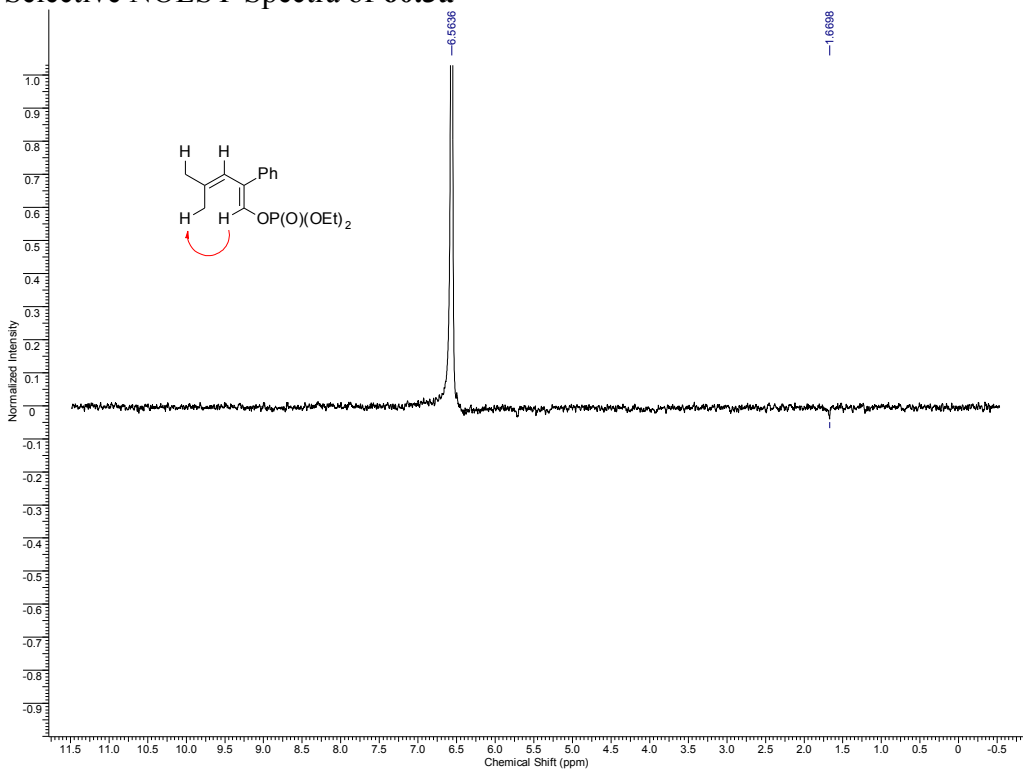
HMBC Spectra of **60.3a**



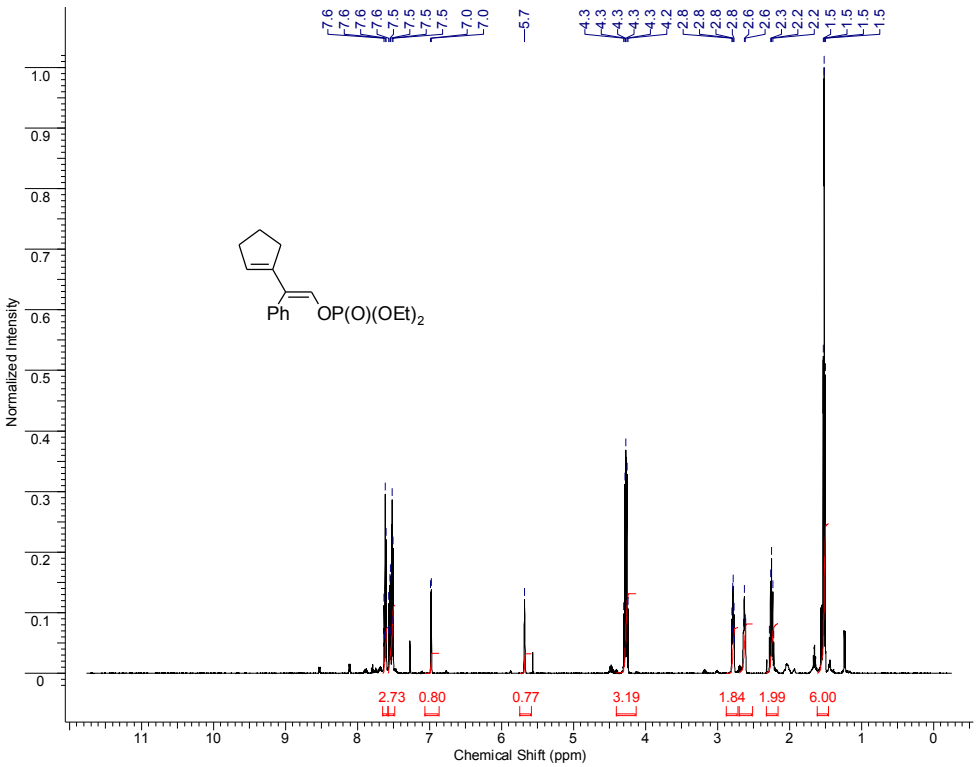
Selective NOESY Spectra of **60.3a**

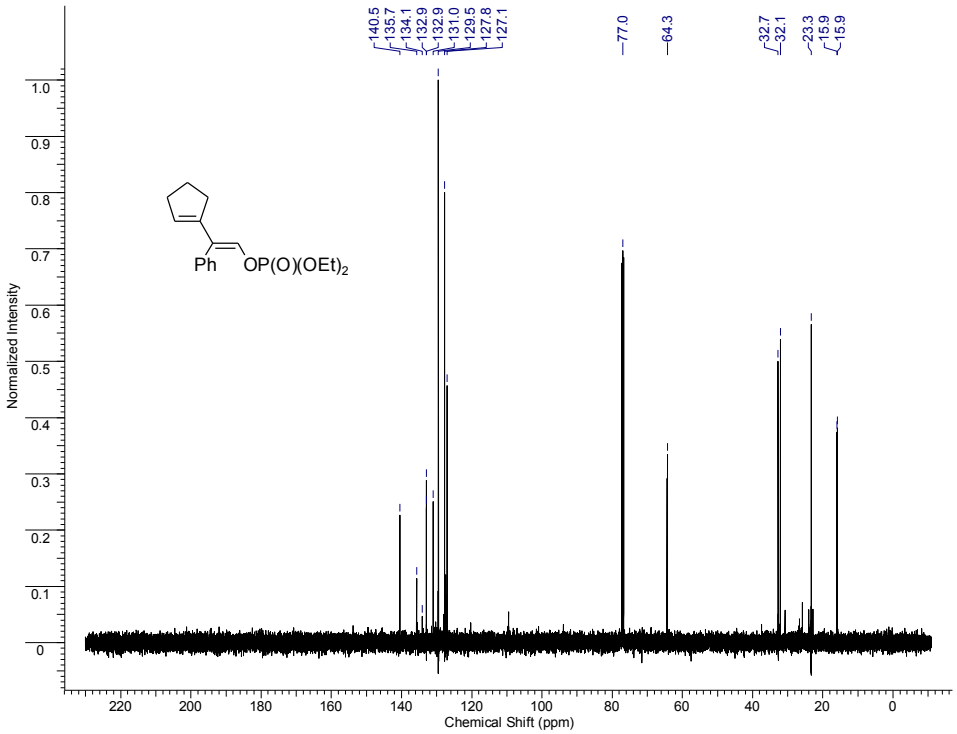


Selective NOESY Spectra of **60.3a**

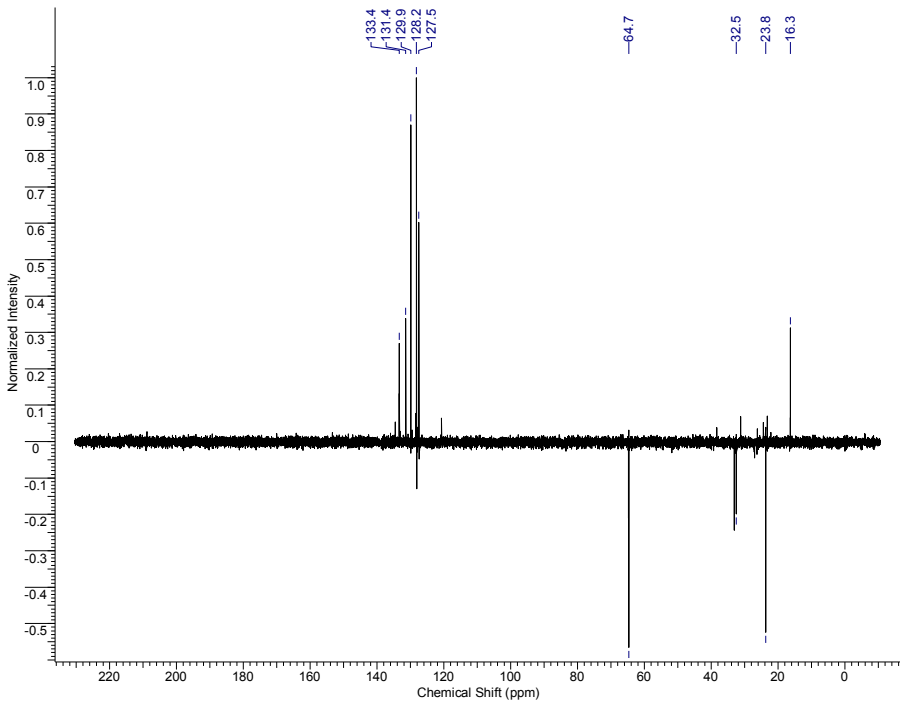


^{1}H and ^{13}C Spectrum of **60.4f**

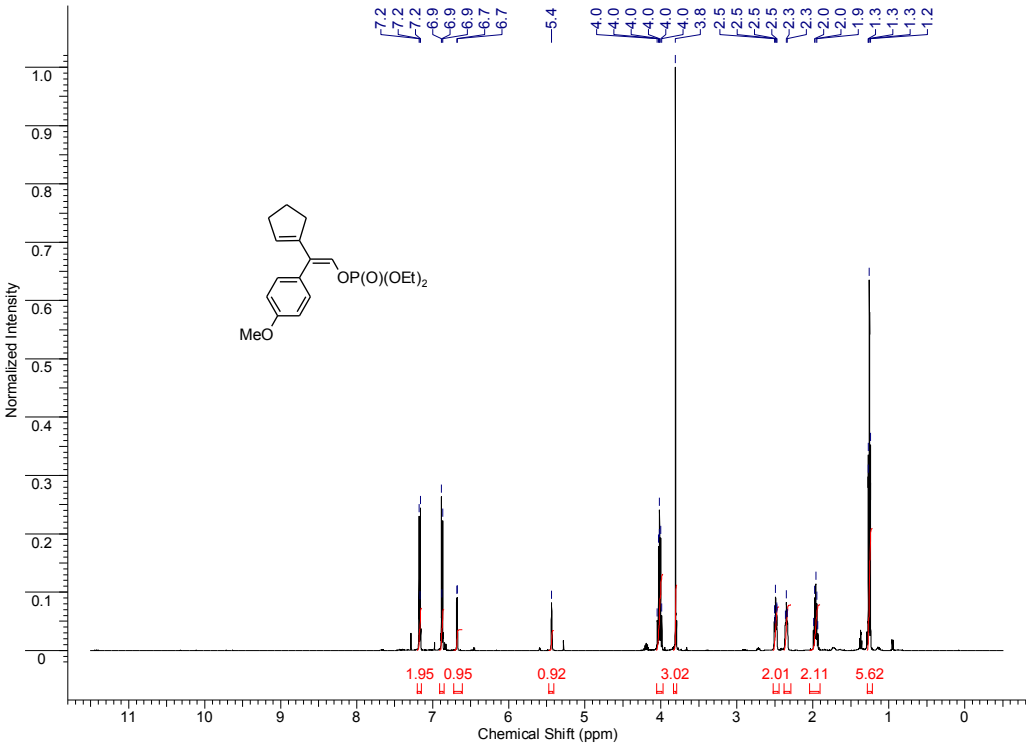


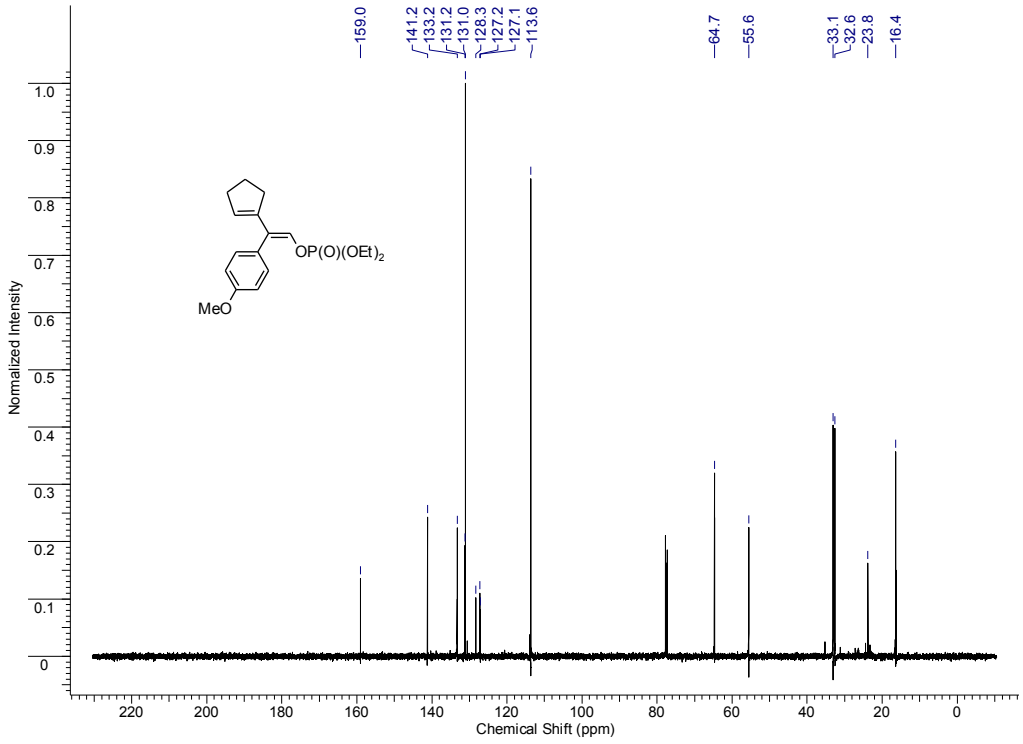


^{13}C-DEPT Spectra of **60.4f**

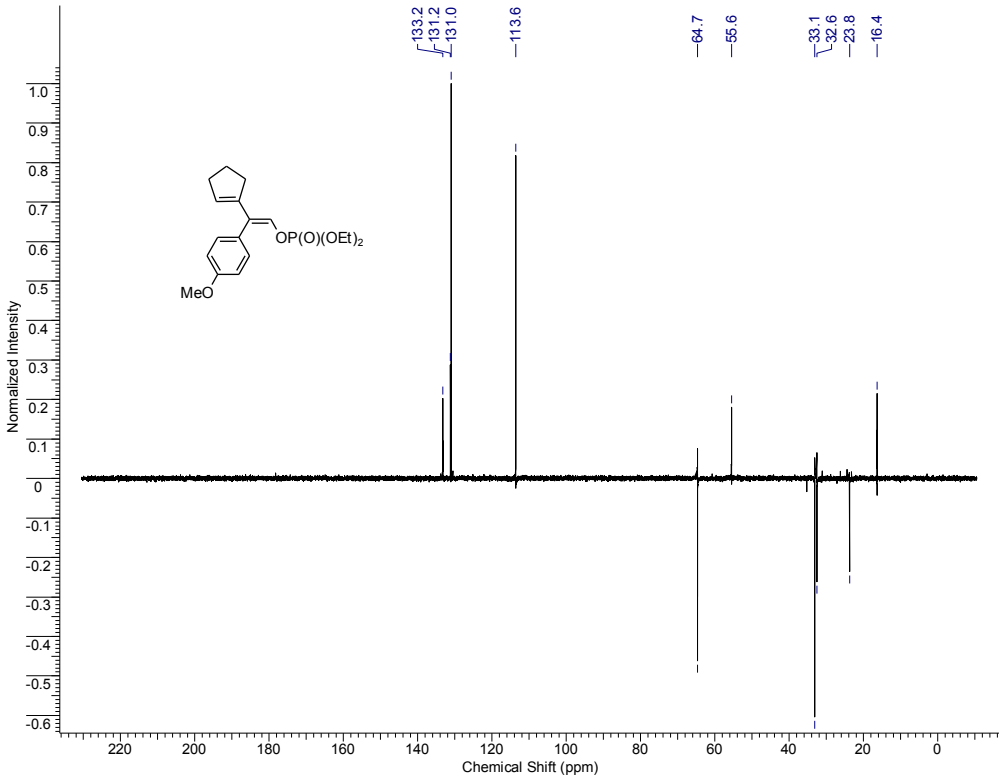


^{1}H and ^{13}C Spectra of **(*Z*)-2-(cyclopent-1-en-1-yl)-2-(4-methoxyphenyl)vinyl diethyl phosphate**

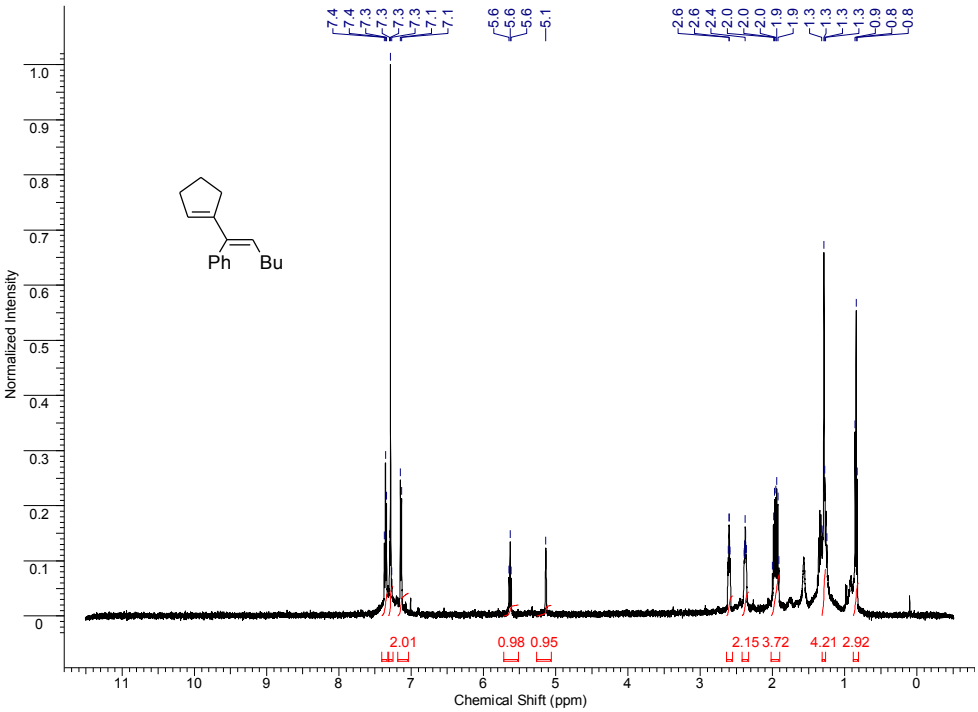


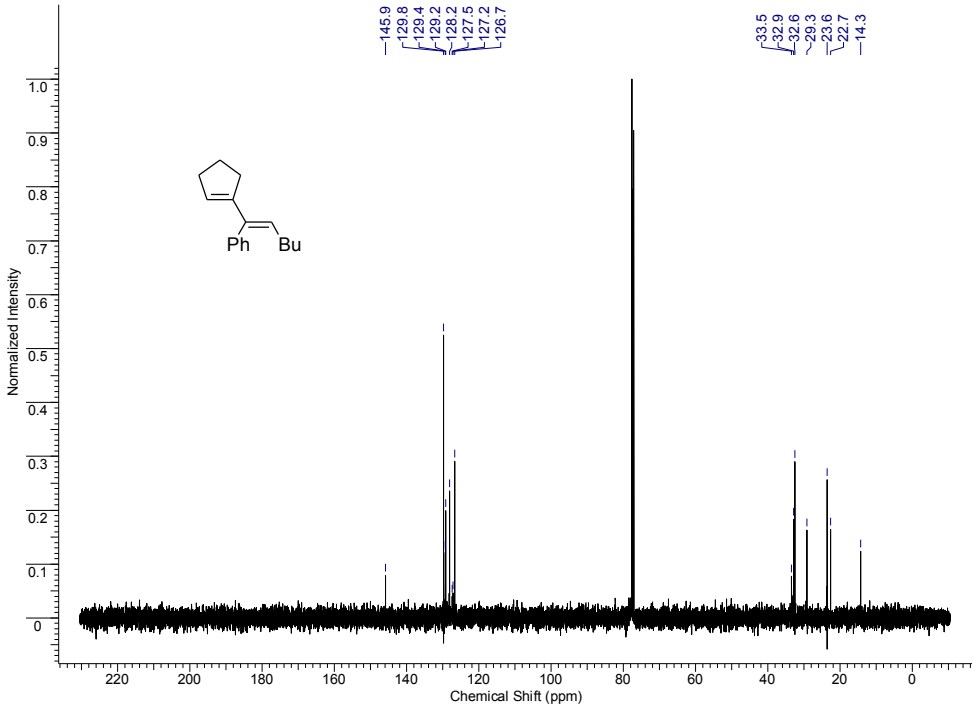


^{13}C-DEPT Spectra of **(*Z*)-2-(cyclopent-1-en-1-yl)-2-(4-methoxyphenyl)vinyl diethyl phosphate**

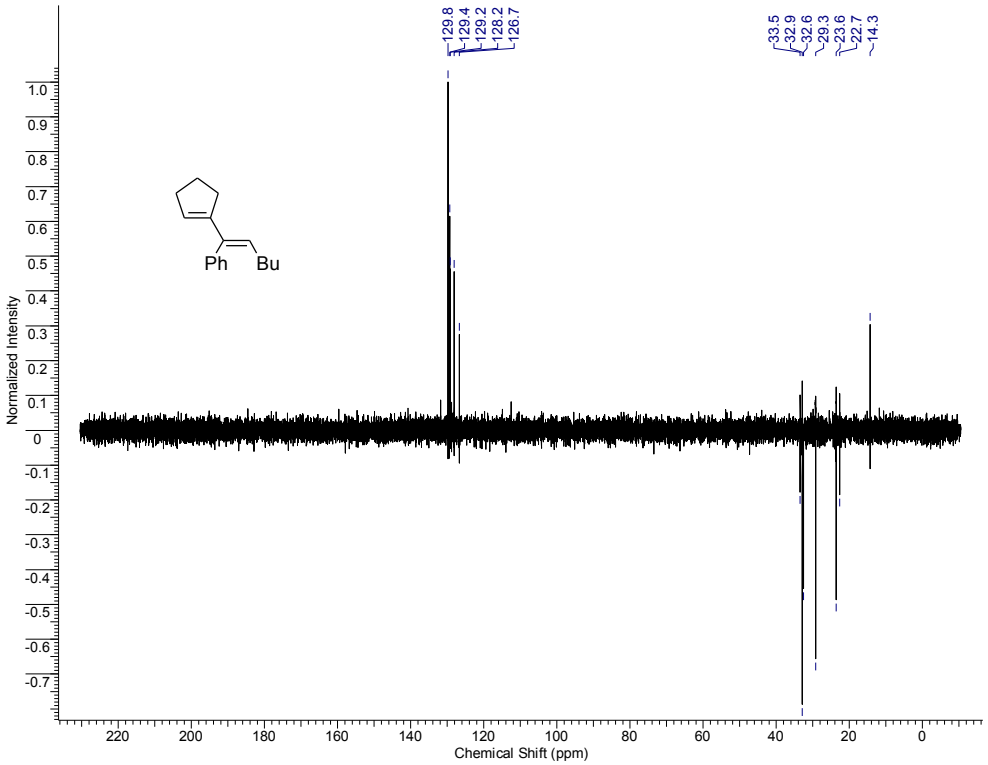


^{1}H and ^{13}C Spectrum of **60.5f**

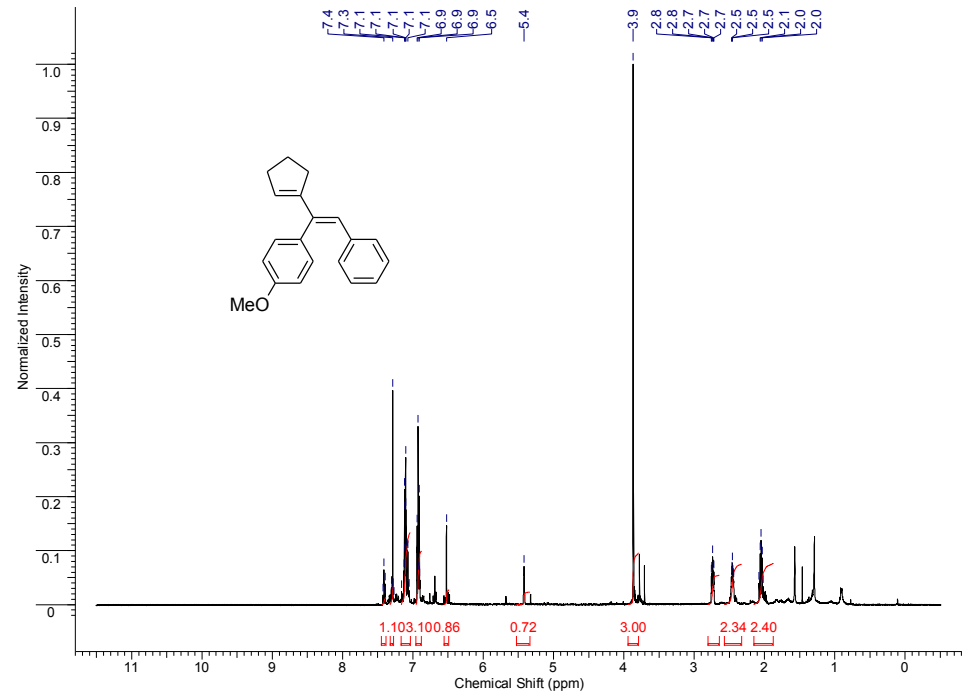


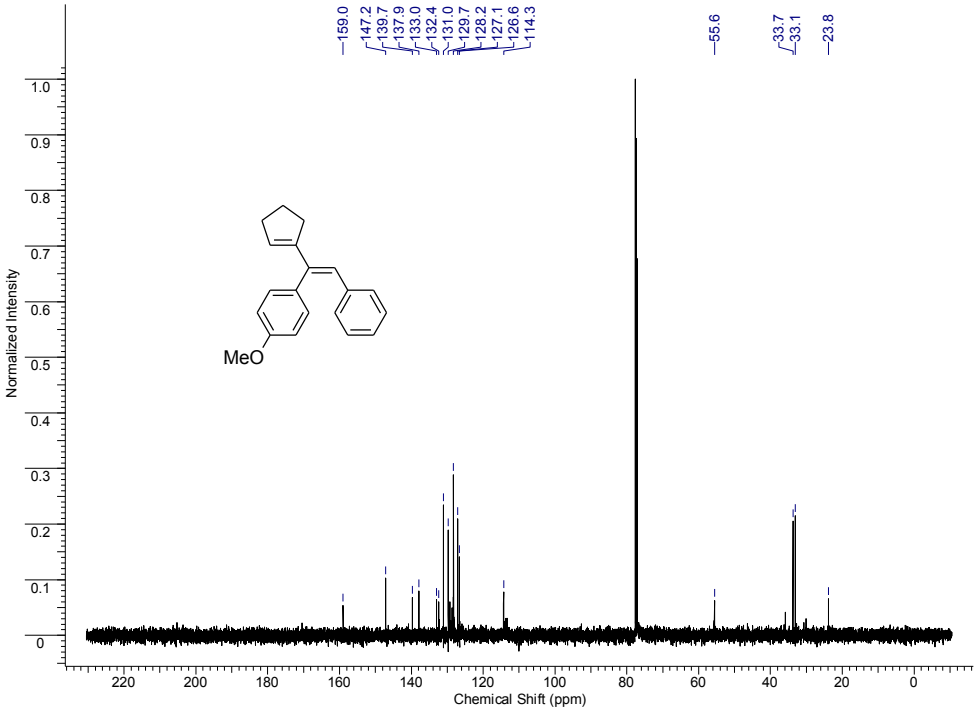


^{13}C-DEPT spectra of **60.5f**

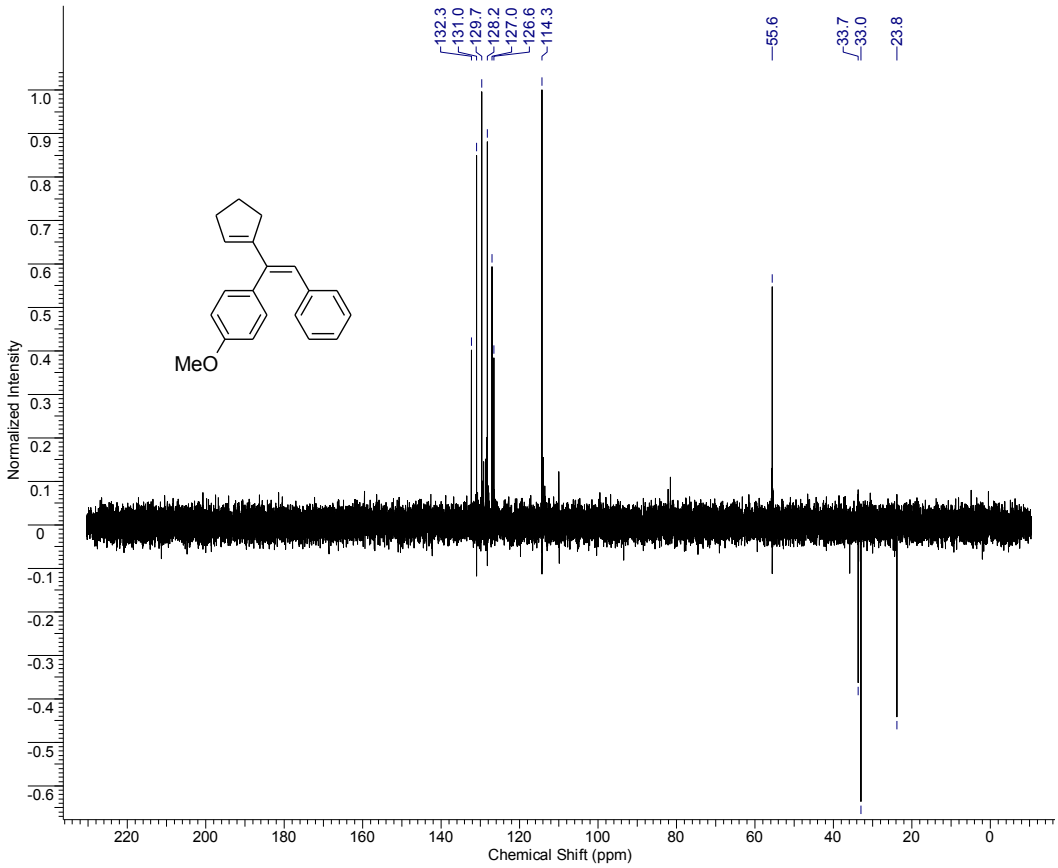


^{1}H and ^{13}C Spectrum of **60.6f**





^{13}C-Dept Spectra of **60.6f**



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Publication: Journal of the American Chemical Society
Publisher: American Chemical Society
Date: Jul 1, 2014
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Publication: Journal of the American Chemical Society

Publisher: American Chemical Society

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Publication: Journal of the American Chemical Society

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R. Kazem Shiroodi and V. Gevorgyan, *Chem. Soc. Rev.*, 2013, **42**, 4991
DOI: 10.1039/C3CS35514D

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