

DEVELOPMENT OF TRANSITION-METAL CATALYZED CARBON-CARBON BOND FORMING  
REACTIONS

Brendan C. Lainhart

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Approved by:

Erik J. Alexanian

Jeffrey S. Johnson

Simon J. Meek

Jillian L. Dempsey

Matthew R. Lockett

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## ABSTRACT

Brendan C. Lainhart: DEVELOPMENT OF TRANSITION-METAL CATALYZED CARBON-CARBON  
BOND FORMING REACTIONS  
(Under the direction of Erik J. Alexanian)

**Chapter One** discusses our efforts towards a Rhodium-catalyzed [4 + 2 + 2] cycloaddition of diene-allenes with exogenous allenes. Our efforts began with the development of a racemic reaction achieving high yields through the use of Rh-phosphoramidite and Rh-phosphite catalyst systems. Further, we discuss the challenging development of an enantioselective variant and the methods we used to avoid the problematic [4 + 2] side reaction. We demonstrate that in these reactions, a Rh-H<sub>8</sub>-monophos complex can produce highly enantioenriched cyclooctanoid products in decent yield. The chapter finishes with a discussion of the potential reaction mechanisms and the evidence thereof.

**Chapter Two** describes the initial efforts towards three Pd-catalyzed C-C bond forming reactions of alkyl halides: 1) The improvement of the alkyl-Heck type cyclization of alkyl iodides; 2) The development of the alkyl-Heck type cyclization of primary alkyl bromides; 3) Efforts towards the enantioselective carbonylation of alkyl iodides using both steric selectivity and directing group based selectivity.

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## LIST OF ABBREVIATIONS AND SYMBOLS

Å	Angstrom
Ac	acetyl
AgCl	silver chloride
AgOAc	silver acetate
AgO <sub>2</sub> CCF <sub>3</sub>	silver trifluoroacetate
AgOMs	silver methanesulfonate
AgOTf	silver trifluoromethanesulfonate
AgOTs	silver toluenesulfonate
AgPF <sub>6</sub>	silver hexafluorophosphate
Ar	aryl
atm	atmosphere
9-BBN	9-Borabicyclo[3.3.1]nonane
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
binol	1,1'-Bi-2-naphthol
Bn	benzyl
Bpin	pinacolatoboryl
BuOH	<i>n</i> -butanol
CDCl <sub>3</sub>	<i>d</i> <sub>1</sub> -chloroform
CHCl <sub>3</sub>	chloroform
cod	cyclooctadiene
coe	cyclooctene
Cp	cyclopentadiene
Cp*	pentamethyl cyclopentadiene

Cs <sub>2</sub> CO <sub>3</sub>	cesium carbonate
Cy	cyclohexyl
Cy <sub>2</sub> NMe	<i>N,N</i> -dicyclohexylmethanamine
D	deuterium
DCE	1,2-dichloroethane
DCM	dichloromethane
diglyme	bis(2-methoxyethyl) ether
DIPEA	<i>N,N</i> -diisopropyl ethylamine
dippf	bis(diisopropylphosphino)ferrocene
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
dcypf	bis(dicyclohexylphosphino)ferrocene
dppf	bis(diphenylphosphino)ferrocene
dtbdppf	1-diphenylphosphino-1'-(di- <i>tert</i> -butylphosphino)ferrocene
dtbpf	bis(di- <i>tert</i> -butylphosphino)ferrocene
Et	ethyl
Et <sub>3</sub> N	triethylamine
Et <sub>2</sub> O	diethyl ether
EtOAc	ethyl acetate
equiv	equivalents
GC/MS	gas chromatography/mass spectrometry
H <sub>8</sub> -binol	5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol
H <sub>8</sub> -monophos	(8,9,10,11,12,13,14,15-Octahydro-3,5-dioxo-4-phosphacyclohepta[2,1- <i>a</i> ;3,4- <i>a'</i> ]dinaphthalen-4-yl)dimethylamine

Hex	hexanes
HPLC	High Pressure Liquid Chromatography
h $\nu$	light promoted
Hz	hertz
IMes	1,3-bis(2,4,6-trimethylphenyl)-imidazolium
<sup>i</sup> Pr	isopropyl
KOtBu	potassium tert-butoxide
LC/MS	Liquid chromatography/mass spectrometry
m	meter
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mm	millimeter
mmol	millimole
monophos	3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)dimethylamine
Ms	methane sulfonyl
nbd	norbornadiene
<sup>n</sup> Bu	n-butyl
<sup>n</sup> Oct	n-octyl

NHC	<i>N</i> -heterocyclic carbene
NIS	<i>N</i> -iodosuccinimide
nm	nanometer
NMP	<i>N</i> -methylpyrrolidinone
NMR	Nuclear Resonance Spectroscopy
Nuc	nucleophile
OAc	acetate
PCy <sub>3</sub>	tricyclohexyl phosphine
Pd	palladium
[Pd(allyl)Cl] <sub>2</sub>	allylpalladium(II) chloride dimer
Pd <sub>2</sub> dba <sub>3</sub>	tris(dibenzylideneacetone)dipalladium(0)
Pd <sub>2</sub> (MeO-dba) <sub>3</sub>	tris(di- <i>p</i> -methoxy-benzylideneacetone)dipalladium(0)
Pd(OAc) <sub>2</sub>	palladium(II) acetate
Pd(PPh <sub>3</sub> ) <sub>4</sub>	tetrakis(triphenylphosphino)palladium(0)
Pent	<i>n</i> -pentane
Ph	phenyl
PhCF <sub>3</sub>	$\alpha,\alpha,\alpha$ -trifluorotoluene
PhH	benzene
PhMe	toluene
PMP	1,2,2,6,6-pentamethylpiperidine
P(OEt) <sub>3</sub>	triethylphosphite
P(NMe) <sub>3</sub>	hexamethylphosphortriamide
P( <sup>n</sup> Bu) <sub>3</sub>	tri- <i>n</i> -butylphosphine

ppm	parts per million
Pr	propyl
P( <sup>t</sup> Bu) <sub>3</sub>	tri- <i>tert</i> -butylphosphine
pyr	pyridine
RT	room temperature
SET	single electron transfer
SIMes	1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
S <sub>N</sub> 2	bimolecular nucleophilic substitution
TADDOL	$\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-dioxolane-4,5- dimethanol
TBS	tertbutyl dimethylsilyl
<sup>t</sup> Bu	tertbutyl
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxy radical
TEMT	triethyl methanetricarboxylate
TES	triethylsilane
Tf	trifluoromethane sulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilane
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	4-methylbenzene sulfonyl
TsN	<i>p</i> -toluenesulfonamide
UV	Ultraviolet
°C	Degrees Celsius

$\alpha$	alpha
$\beta$	beta
$\Delta$	reflux
$\mu\text{L}$	microliter

## **CHAPTER 1:Development of an enantioselective Rh-catalyzed [4 + 2 + 2] cycloaddition of diene-allenes and allenes**

### **1.1 Introduction**

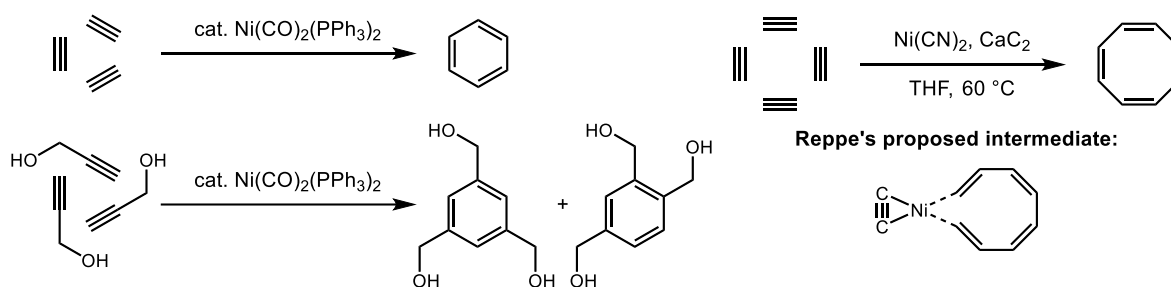
#### **1.1.1 Multicomponent cycloadditions**

The formation of valuable small molecules is an ongoing challenge in synthetic research, namely the ability to construct complex carbocycle cores in a convergent, cost effective manner. There are two methods for the formation of cyclic molecules: the stepwise formation and cyclization of linear compounds or the cycloaddition of multiple discrete components. The latter has an innate advantage in that it maximizes convergency through the formation of multiple C-C bonds in a single step.

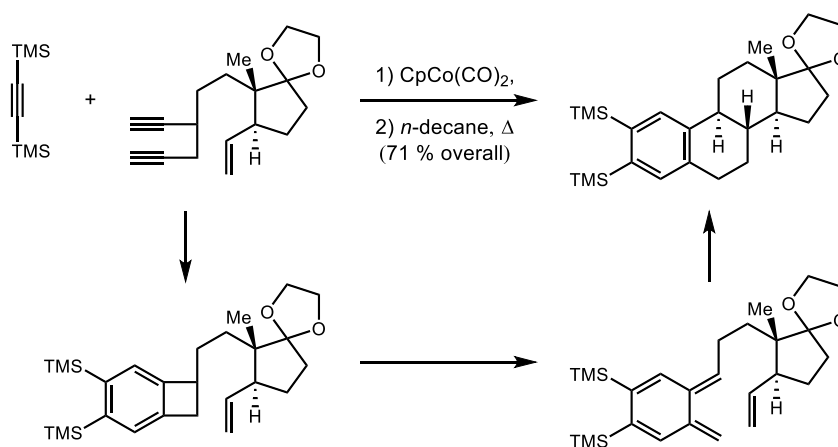
The ability to construct several important bonds in one step makes cycloadditions of simple  $\pi$ -components invaluable tools in chemical synthesis. The Diels-Alder reaction has been the most used cycloaddition in synthesis, as it is a facile route to ubiquitous six-membered rings.<sup>1,2</sup> The reaction has long served as a benchmark for efficiency, producing two new C-C bonds and up to four contiguous stereocenters. Additionally through many years of examination, much is known about the fundamentals of this type of reactivity. Furthermore, many asymmetric methods have been developed, including chiral Lewis acid,<sup>3,4</sup> organocatalytic,<sup>5,6</sup> and ligand-controlled transition metal catalysis.<sup>7,8</sup>

Higher order, multicomponent [ $m + n + o$ ] cycloadditions offer a significant advantage over traditional two-component cycloadditions in that a minimum of three new C-C  $\sigma$ -bonds are formed during the course of the reaction.<sup>9</sup> This feature allows for the use of simpler starting

materials; instead of using a diene as a  $4\pi$ -component in a  $[4 + 2]$  cycloaddition, the use of two  $2\pi$ -components results in a  $[2 + 2 + 2]$  cycloaddition.<sup>10</sup> These reactions were initially reported by Walter Reppe in 1948 with the disclosure the cyclotrimerization of acetylene derivatives with a Ni-catalyst (**Figure 1**).<sup>11,12</sup> In addition to this, he reported the  $[2 + 2 + 2 + 2]$  cyclotetramerization of acetylene to form cyclooctatetraene.<sup>13</sup>



**Figure 1.** Early examples of transition metal catalyzed higher order cycloadditions.



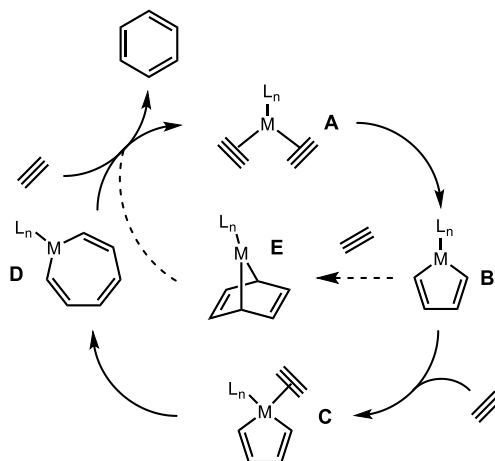
**Figure 2.** The tandem  $[2 + 2 + 2]/[4 + 2]$  cycloadditions in Vollhardt's synthesis of esterone.

Since their discovery by Walter Reppe, multicomponent cycloadditions have been developed for the formation of six,<sup>10,14,15</sup> seven,<sup>16</sup> eight,<sup>17,18</sup> and nine<sup>19,20</sup> membered rings. The landmark example of this type of reaction in total synthesis was demonstrated by Vollhardt and



coworkers in their synthesis of estrone<sup>21</sup> (**Figure 2**). The synthesis involved a Co-catalyzed [2 + 2 + 2] cycloaddition of three alkynes to form a fused cyclobutabenzenoid system. Following the strain relieving 4- $\pi$  electrocyclic ring opening, the resulting xylylene underwent a ring forming Diels-Alder reaction. Overall this powerful transformation furnished three of the four rings in the steroid core in a single reaction step.

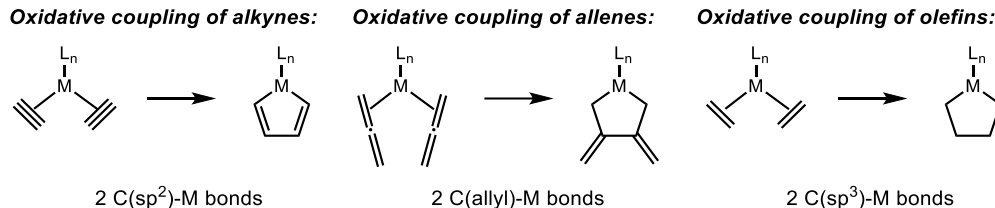
Reppe was the first to suggest a metallacyclic intermediate in his report on acetylene tetramerization (**Figure 1**).<sup>22</sup> Since that time, this has been accepted as the operative intermediate in multicomponent cycloadditions.<sup>23</sup> The proposed mechanisms of [2 + 2 + 2] cycloadditions are illustrated in **Figure 3**.<sup>24</sup> Coordination of two  $\pi$ -components affords complex **A**, which is proposed to undergo an oxidative cyclization to form metallacycle **B**. At this juncture, two pathways have been proposed for the completion of the reaction. The first pathway involves coordination of the third alkyne then a migratory insertion to expanded metallacycle **D** followed by product forming reductive elimination. The second pathway involves a [4 + 2] cycloaddition with the  $\pi$ -component and metallacycle to form metallabicycle **E** with a bridgehead metal species. This intermediate can then undergo a reductive demetallation to produce the benzene and turn over the catalyst.



**Figure 3.** A generalized depiction of proposed mechanisms for  $[2 + 2 + 2]$  cycloadditions.

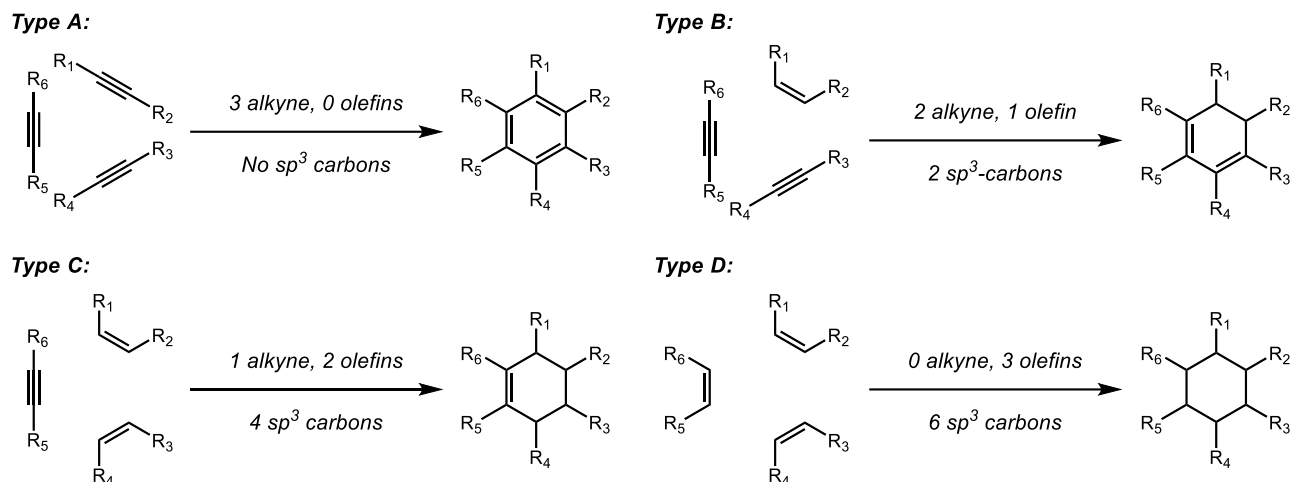
### 1.1.2 Allenes in transition metal catalyzed cycloadditions

The use of alkyne is pervasive in transition metal catalyzed cycloadditions. Given the proposed mechanism of these cycloadditions shown in **Figure 3**, the reactivity of alkynes can be rationalized. The initial C-C bond is formed from the oxidative coupling of two  $\pi$ -components, forming a metallacycle. It is, therefore, pertinent to discuss metallacycle stability, as a high energy intermediate may render a pathway kinetically unattainable. A metallacarbocycle, which is a metallacycle containing no heteroatoms, necessarily contains two C-M bonds. The accessibility of these intermediates is likely related to the stability of the C-M bonds (**Figure 4**). The nature of the C-M bond is that it is typically polarized with the electron density lying largely towards the carbon. Consequently, the electronegativity, and therefore hybridization, of carbon-bound ligands play a pivotal role in the strength of the bond. Bond strengths in C-M bonds follows the trend of  $C_{\text{alkynyl}}-M > C_{\text{vinyl}}-M > C_{\text{alkyl}}-M$ .<sup>25,26</sup> The coupling of alkynes form  $C(sp^2)$ -bound carbon ligands in the metallacycle, which are more stable than the corresponding alkyl metallacycle formed from the oxidative coupling of olefins.



**Figure 4.** Formation of metallacycles through oxidative cyclization.

The incorporation of alkynes in  $[m + n + o]$  cycloadditions forms endocyclic olefins in the cycloadducts, which can be valuable synthetic handles. Additionally, the  $[2 + 2 + 2]$  coupling of three alkynes (Type A as illustrated in **Figure 5**) can furnish very valuable arene products. However, an overreliance on alkyne is a barrier to furnishing stereocomplex cyclic products. Whilst the utility of reactions of Type A and Type B have been demonstrated, reactions of Type C and Type D have been rare. The hypothetical coupling of three alkenes, Type D, would furnish a cyclohexane derivative with the impressive potential for six stereogenic carbons. Nevertheless, the difficulty of the metallacyclopentane-forming oxidative coupling necessary for this transformation hinders its practical realization.

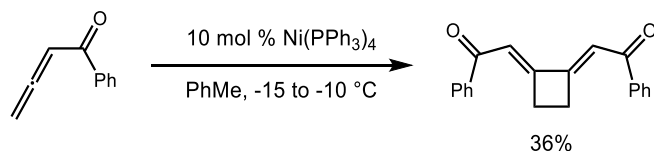


**Figure 5.** A representation of the uses of alkyne in  $[m + n + o]$  cycloadditions.

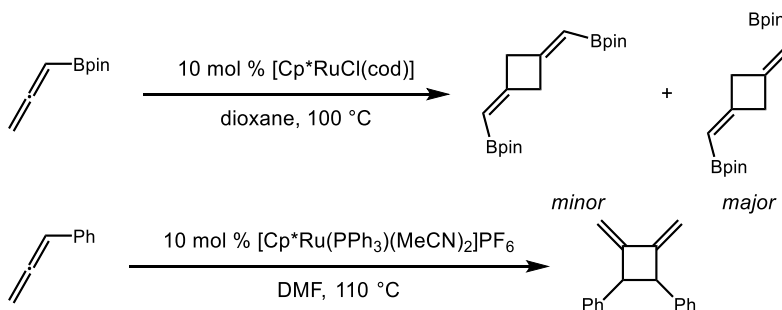
An alternative to alkynes in these reactions are allenes, or 1,2-dienes, which have been shown to react in transition-metal catalyzed cycloadditions. Allenes have the benefit of having similar reactivity compared to alkynes, including a small amount of additional strain energy (3-5 kcal),<sup>27</sup> but also contain two  $sp^2$  carbon atoms, which could be converted to  $sp^3$  carbons in a cycloaddition reaction. An interesting attribute of metalation of allenes is the formation of either an allylic or vinylic metal intermediate. Therefore the oxidative coupling of two allenes will furnish a stabilized metal species that contains two  $sp^3$  carbons, which is more stable than a saturated metallacycle form from the oxidative coupling of two olefins.

Unlike alkynes, the two  $\pi$ -bonds in allenes are not necessarily degenerate and create a situation in which a reagent must discern between the two for selective reactivity. This can be illustrated through the transition metal catalyzed  $[2 + 2]$  coupling of allenes. For monosubstituted allenes, the internal  $\pi$ -component is considered the “head” whereas the terminus is “tail.” Using an electron rich nickel(0) catalyst Saito and Yamamoto demonstrated the tail-to-tail  $[2 + 2]$

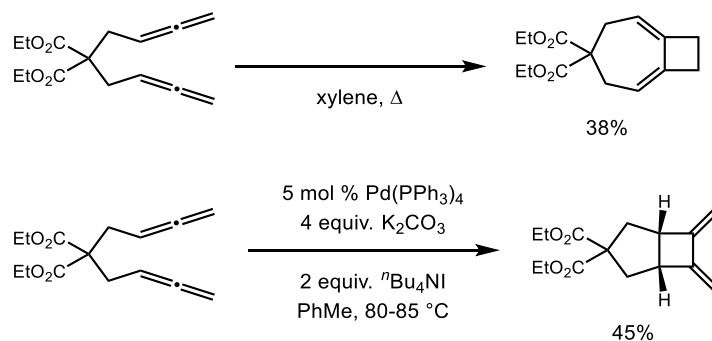
dimerization of electron deficient allenes (**Figure 6**).<sup>28</sup> Similar reactivity was observed in the dimerization of Bpin-allene under Ru-catalysis (**Figure 7, top**),<sup>29</sup> however this tail-to-tail coupling places the exocyclic olefin distal to each other as opposed to vicinal. Interestingly, the same catalytic system produced a head-to-head dimerization of phenylallene (**Figure 7, bottom**). In a report by the Ma group (**Figure 8**), it has been shown that 1,6-bisallenes undergo tail-to-tail dimerization under thermal conditions.<sup>30</sup> However, under Pd-catalysis, the same bisallenes will couple in a head-to-head fashion. A lack of comprehensive comparisons in the literature makes it difficult to make overall assertions about the reactivity of these systems. Nevertheless, it is evident that allenes have a diverse set of reactivity with transition metal catalysts that varies based on the metal used and the stereoelectronic properties of the allene. This is particularly important with respect to the oxidative coupling of allenes to form metallacycles.



**Figure 6.** The tail-to-tail dimerization of electron deficient allenes.

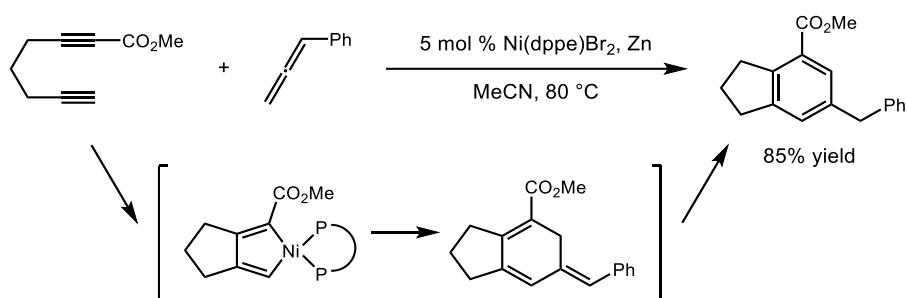


**Figure 7.** The dimerization of allenes using ruthenium catalysis.

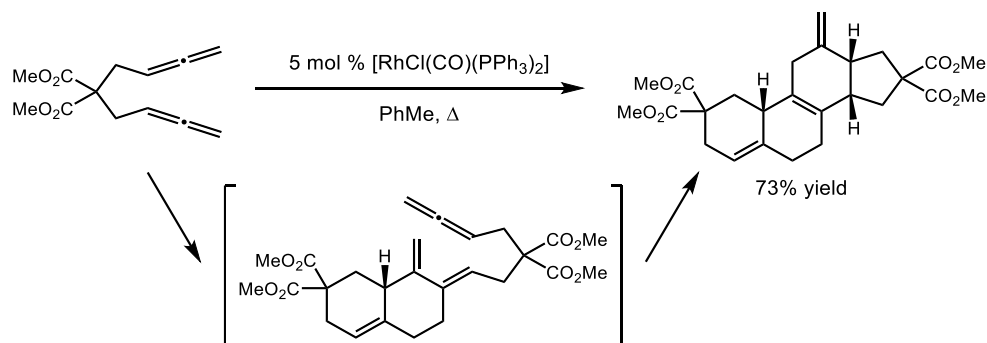


**Figure 8.** The switch of regioselectivity of allene dimerizations in thermal and metal catalyzed reactions.

The use of allenes in multicomponent  $[m + n + o]$  cycloadditions has previously been demonstrated. Cheng and coworkers have used allenes in a  $[2 + 2 + 2]$  cycloaddition with 1,6-diynes.<sup>31</sup> The resulting cycloadduct undergoes an aromatizing tautomerization to form benzenoid products (**Figure 9**). Ma and coworkers have shown the ability of 1,5-bisallenes to undergo Rh-catalyzed  $[2 + 2 + 2]$  cycloadditions with exogenous allenes.<sup>32</sup> Interestingly, this reaction is thought to go through an initial head-to-tail oxidative coupling of the bis-allene before incorporation of the exogenous allene to afford  $[4.4.0]$  cycloadduct featuring an exocyclic diene. Additionally, they were able to demonstrate the utility of the exogenous diene with the dimerization of 1,5-bisallenes to form a tetracyclic, steroid-like core from a tandem  $[2 + 2 + 2]/[4 + 2]$  cycloaddition (**Figure 10**).<sup>33</sup> Importantly, this reaction sets a stereocenter at the ring fusion which differentiates this reaction from the canonical  $[2 + 2 + 2]$  cycloaddition of three alkynes.



**Figure 9.** The [2 + 2 + 2] cycloaddition of enyne and allenes reported by Cheng.



**Figure 10.** The tandem [2 + 2 + 2]/[4 + 2] cycloadditions for the formation of steroid-like cores.

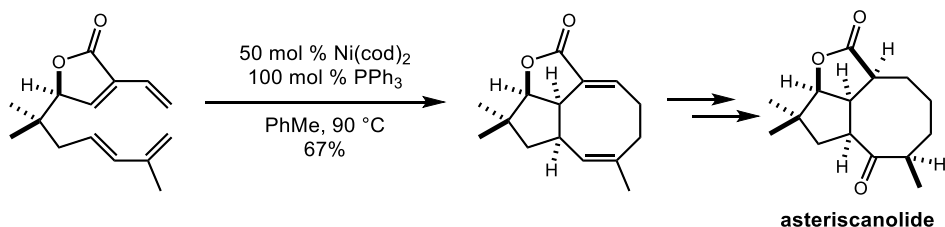
Previously, our group has reported two applications of allenes in [2 + 2 + 2] cycloadditions wherein ene-allenes are coupled with exogenous allenes and olefins (**Figure 11**).<sup>34,35</sup> Using a cationic Rh/bisphosphine catalyst system, trans-hydrindanes are furnished. The resultant bicycles contain an exocyclic diene and up to four stereocenters, typically as single diastereomers. The use of enantiopure Rh/H<sub>8</sub>-binap results in the formation of enantioenriched bicycles with good selectivity. The work described herein explores the extension of our prior studies towards the formation of eight-membered cyclooctanoids through a [4 + 2 + 2] cycloaddition. Further, to date allenes have not been applied to [4 + 2 + 2] cycloadditions.



**Figure 11.** Rhodium(I) catalyzed [2 + 2 + 2] of ene-allenes and exogenous allenes.

### 1.1.3 Eight-membered rings through cycloadditions

The formation of medium-sized rings has been a longstanding challenge in synthetic chemistry.<sup>36,37</sup> The kinetics of medium-sized ring closure are markedly slower<sup>38</sup> and medium-sized rings have more ring strain than five- and six-membered rings as well. Multicomponent cycloadditions avoid the entropic and enthalpic penalties of medium-sized ring closure because they form and maintain cyclic intermediates that undergo ring expansion through migratory insertion and ultimately terminate with reductive elimination. Several cyclooctanoid-forming two-component cycloadditions, including [4 + 4], [6 + 2],<sup>39–41</sup> and [7 + 1]<sup>42</sup> cycloadditions have been previously demonstrated. These cycloadditions have been applied to the total synthesis of a number of natural products, including asteriscanolide (**Figure 12**).<sup>43</sup> However, the division of these reactions into smaller  $\pi$ -components coupled in higher order,  $[m + n + o]$  cycloadditions would result in more convergent syntheses.

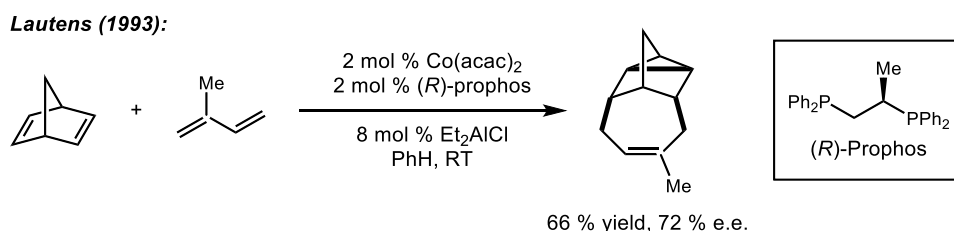


**Figure 12.** The key Ni-catalyzed [4 + 4] cycloaddition in Wender's synthesis of asteriscanolide.



Though the number of eight-membered carbocyclic natural products is small compared to those with five- and six-membered carbocycles, cyclooctanoid compounds have garnered considerable attention for their biomedical uses. Most noteworthy amongst them are the oncological medication taxol and the antibiotic pleuromutilin. Additionally, increasing the synthetic avenues to eight-membered ring formation would potentially increase their presence in medicinal chemical libraries.

The first  $[4 + 2 + 2]$  cycloaddition, which was reported nearly half a century ago, exploited the ring strain in norbornadiene to couple its two olefinic moieties with a diene. The low loadings of simple Fe(III)-catalyst system provided selectivity for the  $[4 + 2 + 2]$  pathway over the corresponding  $[2 + 2 + 2]$  pathway. Lautens and coworkers later developed a Co-catalyzed asymmetric variant of this reaction using (*R*)-Prophos (**Figure 13**).<sup>44</sup>

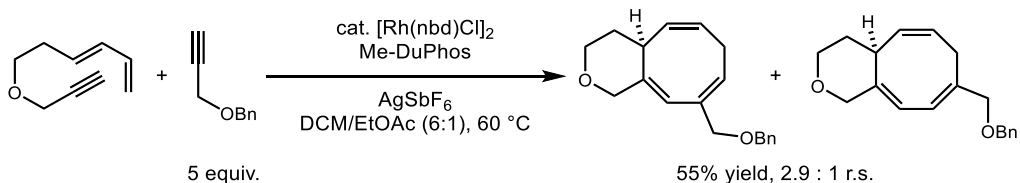


**Figure 13.** Rhodium(I) catalyzed  $[4 + 2 + 2]$  of dienes and norbornadiene.

The field progressed to utilize non-strained  $\pi$ -components when Gilbertson et al., whilst studying the rhodium-catalyzed  $[4 + 2]$  cycloisomerization<sup>7</sup> of tethered diene-alkynes in 2002, observed a  $[4 + 2 + 2]$  dimerization cycloaddition.<sup>45–47</sup> The addition of an exogenous alkyne led to the formation of bicyclic cyclooctatrienes with up to two stereocenters, all as single diastereomers. Unfortunately, insertion of the exogenous alkyne component occurred in high regioselectivity only with terminal substitution of the diene (**Figure 14**). Hilt and coworkers

disclosed a fully intermolecular variant of this reaction in which a cobalt catalyst mediates the coupling of simple 1,3-dienes with two equivalents of alkynes to form monocyclic cyclooctatrienes.<sup>48</sup>

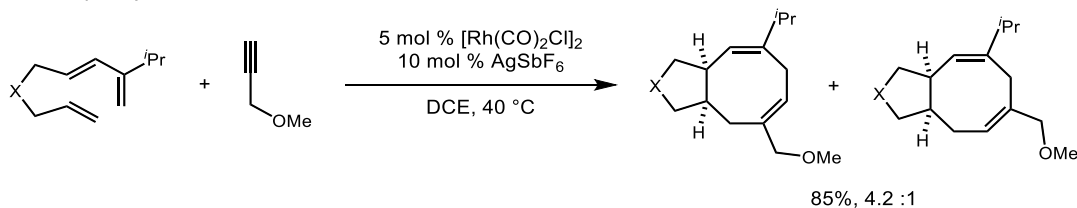
**Gilbertson (2002):**



**Figure 14.** Rh(I)-catalyzed [4 + 2 + 2] cycloaddition of diene-ynes and exogenous alkynes.

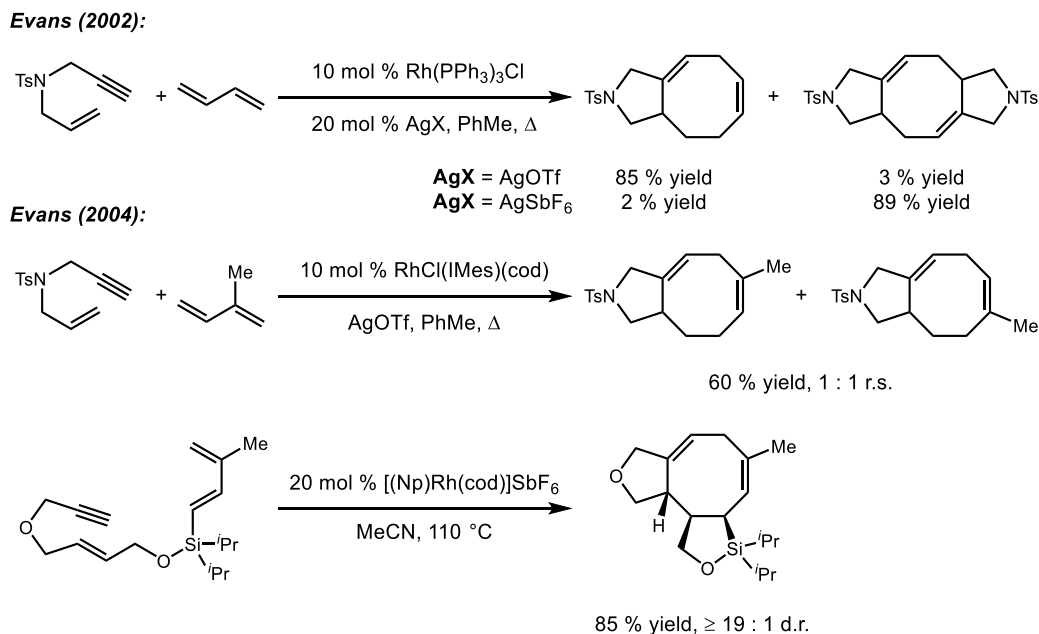
Wender and coworkers developed a similar reaction in which a 1,3,8-triene, or ene-diene, is coupled with an alkyne to form cyclooctadiene products (**Figure 15**).<sup>49</sup> Similar to other work in the field, this reaction is catalyzed by cationic Rh-catalysts; however, it does not use phosphine or carbene ligands. Instead this catalyst has two carbonyl ligands, which are not incorporated into the cycloadducts. These reactions furnish single diastereomers of cyclooctanoid products with up to three stereogenic centers. All products of these reactions are produced with two stereocenters at the ring fusion and were formed with cis-selectivity, including challenging ring-fusion quaternary centers.

**Wender (2006):**



**Figure 15.** Rhodium(I) catalyzed [4 + 2 + 2] of trienes and exogenous alkynes.

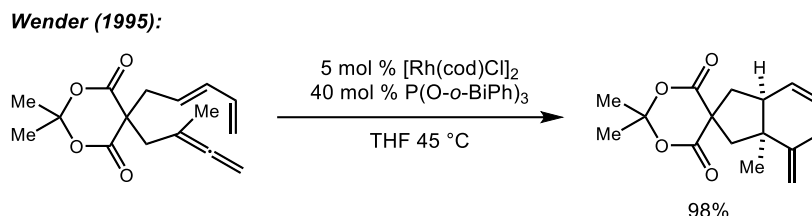
Evans and coworkers discovered an alternative [4 + 2 + 2] in which a 1,6-enyne was coupled with exogenous dienes using cationic Wilkinson's catalyst (**Figure 16**).<sup>50,51</sup> Interestingly, the chemoselectivity of the reaction was highly dependent on counterion, whereby the use of <sup>-</sup>OTf anion was highly selective for the [4 + 2 + 2] product and SbF<sub>6</sub><sup>-</sup> selected for a [2 + 2 + 2 + 2] dimerization of the enyne. Despite achieving high selectivity for the desired cyclooctanoid, asymmetrically substituted dienes were incorporated with poor selectivity. However, this limitation was overcome through the use of removable siloxy tethers which provided the desired products as a single regioisomer with respect to the diene and high diastereoselectivity.<sup>52</sup>



**Figure 16.** Rhodium(I) catalyzed [4 + 2 + 2] of enynes with exogenous dienes.

A number of Rh-catalyzed [4 + 2 + 2] cycloadditions have been reported, each with a different catalyst system. Unfortunately, the diversity of conditions prevent a clear observation of

patterns with respect to catalyst choice. However, some trends are evident. Most catalysts are cationic with non-coordinating counter-ions and most effective catalyst systems contain strong  $\sigma$ -donor ligands. Additionally, examples of enantioselective  $[4 + 2 + 2]$  carbocycloadditions are limited to the use of norbornadiene and a single result reported by Gilbertson.



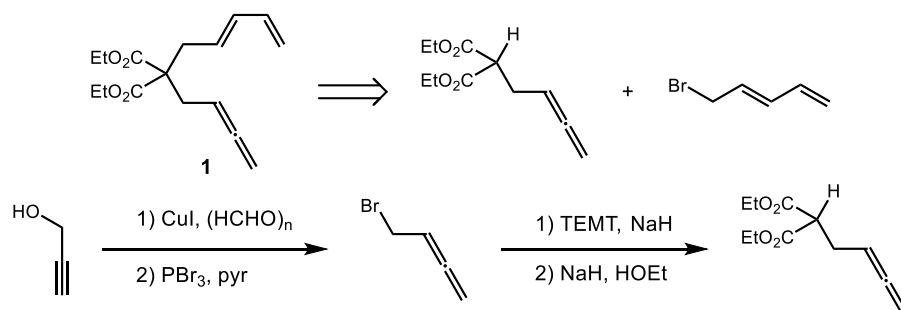
**Figure 17.** The Rh-catalyzed  $[4 + 2]$  cycloisomerization of diene-allenes.

It was expected that the major hurdle in developing a  $[4 + 2 + 2]$  cycloaddition of diene-allenes with exogenous allenes would be an intramolecular  $[4 + 2]$  cycloadditions. An analogous  $[4 + 2]$  cycloaddition using diene-allenes has been previously reported to occur under rhodium(I)-phosphite catalysis (**Figure 17**).<sup>53</sup> The resulting cis-hydrindane products are formed in high yields as single diastereomers; however, all decalin-type products are formed with only modest stereoselectivity. Indeed rhodium(I)-catalyzed  $[4 + 2]$  cycloadditions have been well established and include intramolecular cycloisomerization of trienes, diene-alkene, and diene-allenes. However, we hypothesized that the unique reactivity of allenes, making them capable of undergoing a migratory insertion and outcompeting reductive elimination, would lead to the development of an efficient  $[4 + 2 + 2]$  cycloaddition.

## 1.2 Rhodium-catalyzed [4 + 2 + 2] cycloaddition of diene-allenes and allenes

### 1.2.1 Discovery of initial eight-membered cycloadduct

Due to the success of prior [4 + 2 + 2] cycloadditions and our prior Rh-catalyzed cycloadditions of allenes, we hypothesized that a Rh-catalyst could effect a cycloaddition between diene-allene substrates and exogenous allenes. Most diene-allenes discussed herein were synthesized through alkylation of diethyl allenylmalonate, which was synthesized via a sequential alkylation and decarboxylation of triethyl methanetricarboxylate (TEMT). Allenyl bromide was prepared through an initial Crabbé reaction on propargyl alcohol followed by bromination. Using this sequence, diene-allene **1** was prepared (**Figure 18**).

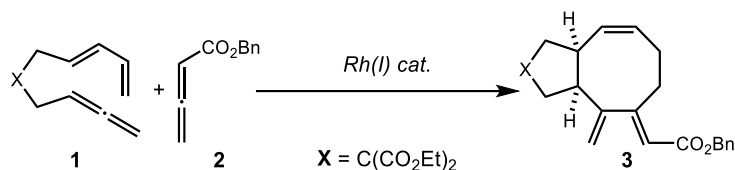


**Figure 18.** Synthetic route to diene-allene substrates.

Initial efforts towards the synthesis of cyclooctanoid products (**Table 1**) began with the conditions used in our [2 + 2 + 2] cycloadditions. Under these conditions, none of the desired cyclooctanoid was observed (entry 1). An unquantified amount of [4 + 2] cycloadduct was observed with the use of both cationic and neutral Rh/binap catalysts (entries 1-2). The application of Wilkinson's catalyst, which bears only monodentate ligands, produced a complex mixture of products (entry 3), potentially due to the propensity of allenates to react with unbound PPh<sub>3</sub>. A similar reaction, the [4 + 2 + 2] cycloaddition of diene-isocyanates and

alkynes, reported by the Rovis group used a rhodium-phosphoramidite catalyst system.<sup>54</sup> Using a monodentate phosphoramidite-bound rhodium catalyst system provided cycloadduct **3** in good yield (entry 4). Additional phosphoramidite ligand (2:1 ligand to metal) provided a lower yield of the desired cycloadduct (entry 5). Switching from the phosphoramidite ligand to a simple phosphite ligand (triethylphosphite) provided an increased yield of the cyclooctanoid (entry 6). Control reactions confirm that cyclooctanoid products are not formed without rhodium (entry 7) and that the phosphorus ligands are critical for reactivity (entry 8). Notably, trace amounts of [4 + 2] cycloadduct can be observed in the absence of Rh-catalyst at 100 °C. The following studies were conducted with phosphoramidite ligands due to the prevalence of commercially available chiral phosphoramidite ligands.

**Table 1.** Optimization of racemic Rh-catalyzed [4 + 2 + 2] cycloaddition.



entry <sup>a</sup>	precatalyst	ligand	additive	temp (°C)	yield <sup>b</sup> (%)
1	[Rh(coe) <sub>2</sub> Cl] <sub>2</sub>	6 mol % binap	5 mol % AgOTf	100	< 2
2	[Rh(coe) <sub>2</sub> Cl] <sub>2</sub>	6 mol % binap	-	100	< 2
3	Rh(PPh <sub>3</sub> ) <sub>4</sub> Cl	-	-	100	< 2
<b>4</b>	<b>[Rh(coe)<sub>2</sub>Cl]<sub>2</sub></b>	<b>6 mol % monophos</b>	-	<b>75</b>	<b>70</b>
5	[Rh(coe) <sub>2</sub> Cl] <sub>2</sub>	10 mol % monophos	-	75	54
6	[Rh(coe) <sub>2</sub> Cl] <sub>2</sub>	6 mol % P(OEt) <sub>3</sub>	-	75	76
7	-	-	-	100	< 2
8	[Rh(coe) <sub>2</sub> Cl] <sub>2</sub>	-	-	75	< 2

<sup>a</sup>Reaction conditions: 1 equiv. diene-allene, 2 equiv. allenoate, 2.5 mol % precatalyst, PhMe.  
<sup>b</sup>Isolated yield

Structural evidence for **3** provided by 1D and 2D <sup>1</sup>H and <sup>13</sup>C NMR experiments were confirmed through the comparison of NMR data and X-ray crystallographic examination of

analogous compound **25** (see **Table 4**). Interestingly, this reaction gave an unexpected isomer of the cyclooctanoid, which differs from what would be expected based on our previous work. Both reactions yield fused bicyclic products; however, rather than the trans-fused hydrindanes seen in our [2 + 2 + 2] cycloadditions (**Figure 11**), cis-fused [6.3.0] bicycles are observed. Additionally, the terminal portion of the allene is incorporated into the ring which is in contrast to our previous work. The mechanistic implications of this will be discussed later in Section 1.4.

### 1.2.2 Ligand Optimization

With an initial product in hand, we decided to investigate other phosphoramidite ligands. Phosphoramidite ligands are readily synthesized from diols and amines in as little as a single step and have been successfully applied to enantioselective methods. The effect these ligands have on the general efficiency of the reaction will be discussed herein; however, they have been applied to the enantioselective variant of this reaction will be discussed later in Section 1.3.

Initial ligand modification began with the examination of the effect of the amine moiety (**Table 2**). Monophos contains dimethylamine, which represents the smallest dialkyl substituted amine possible. Therefore, ligands with larger alkyl groups were examined. Ligands containing the cyclic amines piperidine and pyrrolidine gave lower yields (entries 2-3). Increasing steric bulk through the appendage of a phenyl ring led to an increase in yield to 82 % (entry 4). However, an isomer of this ligand, containing  $\alpha$ -methylbenzylamine, proved to be less effective in this reaction (entry 5). Further increase of the size of the amide to bis- $\alpha$ -methylbenzylamine formed a completely inactive catalyst (entry 6).

Next the backbone portion of the ligand was modified. Partial hydrogenation of the binol to a bis-tetrahydronaphthol backbone increases the dihedral angle of the bis-aryl backbone and often affects reactivity. The application of H<sub>8</sub>-monophos resulted in a slightly lowered yield (entry 7). Subsequently, alteration of the amine on this hydrogenated phosphoramidite was

explored. Increasing the size of the amine resulted in a slight decrease in yield (entries 7-8), even with the N-benzylmethylamine (entry 9) which was shown to be beneficial before (entry 4). Using a 2,2'-bis(diphenylphosphino)binaphthol, which is known to act as a bidentate phosphoramidite-phosphine ligand, stymied substrate conversion (entry 10). Moving away from binol-type backbones, TADDOL-based phosphoramidite resulted in significantly less cyclooctanoid formation (entry 11). However, replacing the phenyl ring with smaller methyl groups resulted in a good yield (entry 12), suggesting the steric bulk of the phenyl rings were problematic to the reaction. Further optimization details with respect to chemo- and enantioselectivity will be discussed later in Section 1.3.

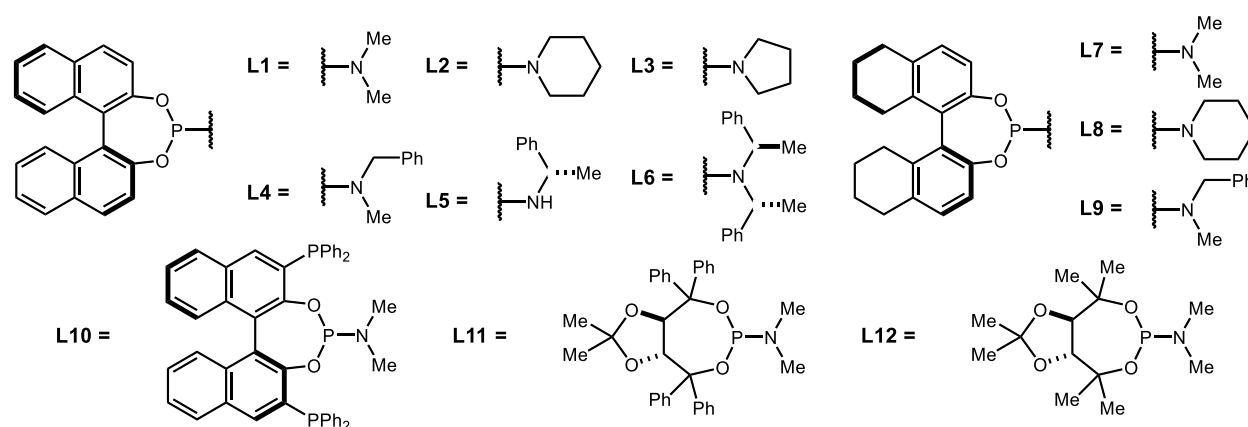
**Table 2.** Ligand optimization of [4 + 2 + 2] cycloaddition.

$\text{X} = \text{C}(\text{CO}_2\text{Et})_2$

entry <sup>a</sup>	ligand	yield <sup>b</sup> 3 (%)	entry <sup>a</sup>	ligand	yield <sup>b</sup> 3 (%)
1	<b>L1</b>	70	7	<b>L7</b>	65
2	<b>L2</b>	61	8	<b>L8</b>	57
3	<b>L3</b>	70	9	<b>L9</b>	59
4	<b>L4</b>	82	10	<b>L10</b>	n.r.
5	<b>L5</b>	51	11	<b>L11</b>	19
6	<b>L6</b>	n.r.	12	<b>L12</b>	73

<sup>a</sup>Reaction conditions: 1 equiv. diene-allene, 2 equiv. allenoate, 2.5 mol % [Rh(coe)<sub>2</sub>Cl]<sub>2</sub>, 6 mol % ligand, PhMe, 75 °C. <sup>b</sup>Isolated yield





**Figure 19.** Phosphoramidite ligands used in catalyst optimization.

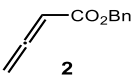
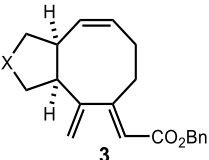
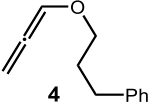
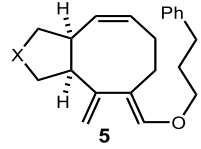
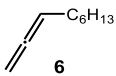
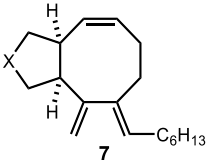
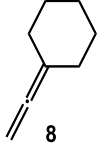
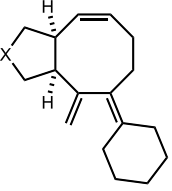
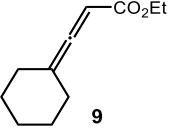
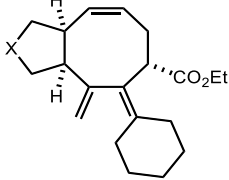
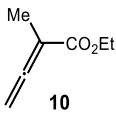
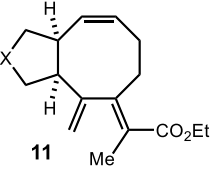
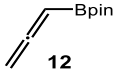
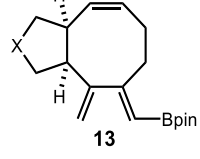
### 1.2.3 Scope of Exogenous Allene

Our initial target for investigations into the substrate tolerance was the added allene component (**Table 3**). In our prior work on the [2 + 2 + 2] reaction, it was seen that only electron deficient allenes performed well in the reaction. Additionally, given that dimerization of our diene-allene is not observed under our conditions, it would seem unlikely that a broad allene scope would be observed. However, the reaction at the unsubstituted terminus of the allene was observed, whereas in our prior work the substituted portion of the allene was seen to react, which indicates that stereoelectronic properties of the allene substitution might not play a large role in the reaction.

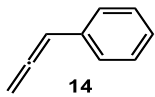
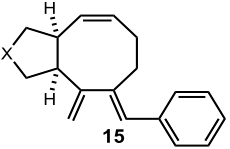
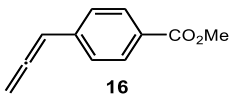
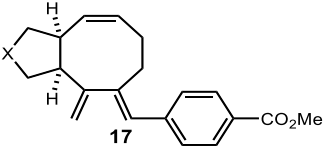
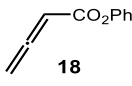
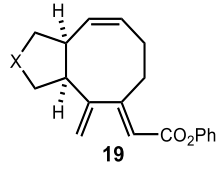
Under our rhodium-phosphoramidite catalyst system, it was observed that electron rich allenic ether **4** was incorporated into the cyclooctanoid product **5** in modest, but meaningful yield (entry 2). Alkyl allene **6** was also shown to be competent in this reaction, affording cyclooctanoid **7** in moderate yield (entry 3-4). The use of 1,1-dialkyl substituted allenes were shown to be ineffective under the standard conditions (entry 5). The addition of an activating, electron withdrawing group, as in trisubstituted allene **9** does not lead to formation of product

(entry 6). 1,1-Disubstituted allenolate **10**, however, was incorporated with the use of  $\text{P}(\text{OEt})_3$  and elevated temperature (entry 7). The use of pinacolatoboranylallene **12** was also successful under these conditions, and the boronate ester expressed in the product can be further used in a cross coupling reaction to modify the product (entry 8). Unfortunately, unlike our prior work, phenylallene (**14**) only produced a moderate yield of cycloadduct **15** (entry 9). As expected, adding an electron withdrawing substituent to the arene was very well tolerated (entry 10). An even more electron deficient allenolate, phenyl allenolate **18**, proceeded with good efficiency (entry 11). Electron-withdrawing substituents were, overall, beneficial for this reaction; however, electron rich allenes were shown to be competent under our conditions. Going forward, benzyl allenolate (**2**) was selected for use in substrate scoping due to its ease of synthesis, UV-active nature, and propensity to undergo facile reactivity under these conditions.

**Table 3.** Scope of added allene in [4 + 2 + 2] cycloaddition.

entry <sup>a</sup>	allene	product	yield <sup>b</sup> (%)
1	 <b>2</b>	 <b>3</b>	70
2	 <b>4</b>	 <b>5</b>	29
3	 <b>6</b>	 <b>7</b>	44
4 <sup>c</sup>			40
5	 <b>8</b>	 <b>9</b>	0
6	 <b>9</b>	 <b>10</b>	0
7 <sup>c,d</sup>	 <b>10</b>	 <b>11</b>	40
8 <sup>c,e</sup>	 <b>12</b>	 <b>13</b>	47

**Table 3 cont.** Scope of added allene in [4 + 2 + 2] cycloaddition.

9			53 <sup>f</sup>
10 <sup>c</sup>			78
11 <sup>c</sup>			67
<sup>a</sup> Reaction conditions: 1 equiv. diene-allene, 2 equiv. allenolate, 2.5 mol % [Rh(coe) <sub>2</sub> Cl] <sub>2</sub> , 6 mol % monophos, PhMe, 75 °C. <sup>b</sup> Isolated yield. <sup>c</sup> 6 mol % P(OEt) <sub>3</sub> instead of monophos. <sup>d</sup> 130 °C. <sup>e</sup> 100 °C. <sup>f</sup> Isolated as 2.7:1 mixture of cyclooctanoid to cyclohexanoid byproduct.			

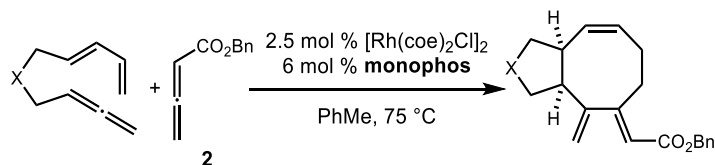
### 1.2.4 Substrate Scope

Our initial examination began with the study of the tether between the diene and allene of the substrates (**Table 4**). The diethyl malonate tether which has been included into our initial diene-allene (entry 1), has a considerable effect on the bond angles at the central carbon. This effect, which is commonly known as the Thorpe-Ingold effect, occurs when two large, geminal groups repulse each other thus reducing the angle between the two other geminal substituents.<sup>55</sup> This has been shown to be beneficial to the kinetics of ring closures and couplings of these substituents. Tethered  $\pi$ -systems linked exclusively by methylene units are rare in prior [4 + 2 + 2] chemistry. Nevertheless, methylene-tethered diene-allene **20** was submitted to Rh/monophos catalyst system and gave the resulting cyclopentane-fused cyclooctanoid **21** in good yield (entry 2). Interestingly, these tethers have proven successful in a related report on the Rh/phosphoramidite catalyzed [4 + 2 + 2] cycloadditions of diene-isocyanates and alkynes.

Unfortunately, extension of the tether by one methylene unit provide a diene-allene that was recalcitrant under these conditions (**Figure 20**).

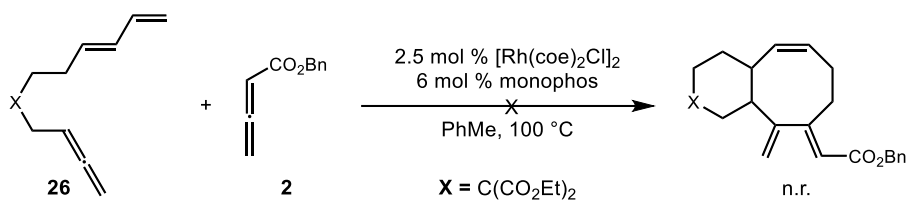
Heteroatom tethers were also explored to synthesize hetero-bicyclic products. Ether-tethered diene-allene **22** proved as efficient as the carbon-based tethered substrates and furnished tetrahydrofuran-fused cyclooctanoid **23** (entry 3). Nitrogen-based tethers require a protecting group due to the reactivity of amines with transition-metal catalysts. Therefore, tosylamide-tethered substrate **24** was subjected to these cycloadditions conditions and converted to pyrrolidine-fused cyclooctanoid **25** in good yield (entry 4). Despite the success of heteroatom and methylene-tethered diene-allenes, diethyl malonate-tethered substrates were chosen for further studies due to their ease of synthesis.

**Table 4.** Effect of tether on [4 + 2 + 2] cycloaddition.



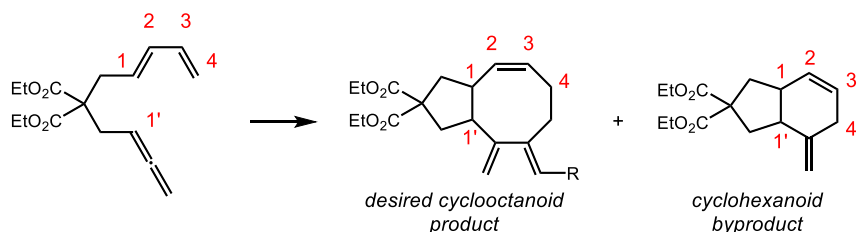
entry	X =	product	yield (%)	entry	X =	product	yield (%)
1	C(CO <sub>2</sub> Et) <sub>2</sub> ( <b>1</b> )	<b>3</b>	70	3	O ( <b>22</b> )	<b>23</b>	70
2	CH <sub>2</sub> ( <b>20</b> )	<b>21</b>	75	4	NTs ( <b>24</b> )	<b>25</b>	59

<sup>a</sup>Reaction conditions: 1 equiv. diene-allene, 2 equiv. allenolate, 2.5 mol % [Rh(coe)<sub>2</sub>Cl]<sub>2</sub>, 6 mol % monophos, PhMe, 75 °C. <sup>b</sup>Isolated yield.



**Figure 20.** Rh-catalyzed [4 + 2 + 2] cycloaddition with a four-carbon tether.

Initial studies of substitution on the  $\pi$ -components of the diene-allene substrates began with examination of substitution on the diene. **Figure 21** illustrates the nomenclature that will be used in discussing these substrates wherein the positions on the diene will be referred to by number, starting with “1” on the tether-connected terminus sequentially outward to “4”.



**Figure 21.** Nomenclature for the description of diene-allenes and cycloadducts.

Our studies began with methyl substitution at each position on the diene-allene (**Table 5**). Unfortunately, 1-Me substituted diene-allene **27** proved to be a recalcitrant substrate with both monophos and triethyl phosphite, even at elevated temperature (entry 3-4). However, 2-Me substituted diene-allene **28** was converted to cyclooctanoid **29** in poor yield due to low conversion, but with only a minuscule amount of cyclohexanoid byproduct (entry 5). However, the use of  $\text{P}(\text{OEt})_3$  resulted in a good yield of product with no observable byproduct (entry 6). Interestingly, there is a discrepancy between the reactivity of the internal diene substitutions whereas 3-Me substituted diene-allene **30** produced cyclooctanoid **31** in a diminished yield and a significant amount of cyclohexanoid byproduct (entry 7), though this was also corrected with the use of  $\text{P}(\text{OEt})_3$  (entry 8). Terminal substitution was likewise problematic (entry 9), giving a lowered yield. However, cyclohexanoid product was not observed, rather it is believed that  $\beta$ -hydride elimination from a possible metallacycle intermediate could be the cause of the lower yield. The use of  $\text{P}(\text{OEt})_3$  provided a higher yield of cyclooctanoid **33** (entry 10). Through the study of simple methyl-substituted diene-allene isomers it has been shown that the location of

diene substitution has a large effect on the efficiency of the reaction, which was remedied using the sterically unencumbering ligand P(OEt)<sub>3</sub>. After this cursory analysis of positional effect of methyl substitutions, more advanced hydrocarbon substitution was examined. In all cases, having multiple alkyl substitutions resulted in no formation of the desired cyclooctanoid product (entries 11-12). Additionally, substitution on the allene was shown to be viable in this reaction as diene-allene **36** bearing a 1,1-disubstituted allene was shown to produce all-carbon quaternary center containing cyclooctanoid **37** with no observable cyclohexanoid byproduct (entries 13-14).

**Table 5.** Methyl substitution scope of Rh-catalyzed [4 + 2 + 2] cycloaddition.

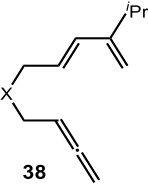
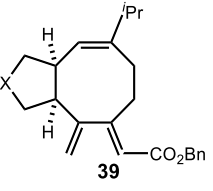
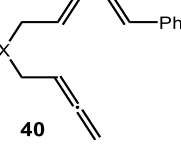
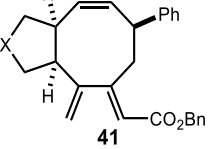
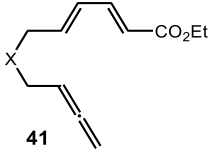
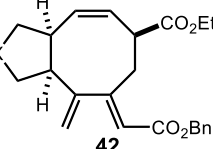
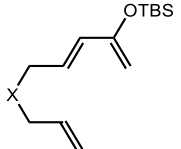
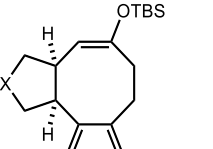
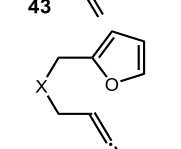
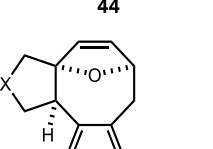
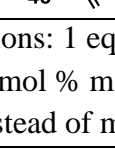
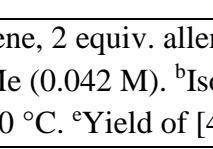
entry <sup>a</sup>	substrate	product	yield <sup>b</sup> (%)	entry <sup>a</sup>	substrate	product	yield <sup>b</sup> (%)
1			70	9 <sup>d</sup>			32
2 <sup>c</sup>			76	10 <sup>c,d</sup>			55
3 <sup>d</sup>			0	11			0
4 <sup>c,d</sup>			0	12			0
5			29	13 <sup>d</sup>			55
6 <sup>c,d</sup>			50	14 <sup>c,d</sup>			59
7			49				
8 <sup>c,d</sup>			59				

<sup>a</sup>Reaction conditions: 1 equiv. diene-allene, 2 equiv. allenolate, 2.5 mol % [Rh(coe)<sub>2</sub>Cl]<sub>2</sub>, 6 mol % monophos, PhMe (0.042 M). <sup>b</sup>Isolated yield. <sup>c</sup>P(OEt)<sub>3</sub> used instead of monophos. <sup>d</sup>100 °C.

With our understanding of positional effects gained from the exploration of methyl substitutions, we sought to further explore the substrate scope with other substitutions (**Table 6**). Substrates that contained larger alkyl groups at the 3-position were tolerated (entry 1), albeit at lower yields than those seen with methyl substitution (**Table 5**, entries 7-8). After demonstrating the effect of alkyl substitution on the reaction, we then moved on to an examination of the functional group tolerance. The appendage of a phenyl ring at the terminus of the diene halted the reaction completely (entry 2). Typically, electron withdrawing functionality is well tolerated in transition-metal catalyzed cycloadditions. Whilst terminal methyl-substitution resulted in diminished yield, terminal ester substitution furnished cyclooctanoid product in good yield (entries 3-4). Electron-donating substituents have not been applied as commonly. Silyl enol ether containing substrate **43** was tolerated under these conditions to yield a silyl enol ether in the resulting product (entry 5). Silyl enol ethers are versatile functionalities that can be used in a number of reactions.<sup>56</sup> Furan was examined as the diene component in this reaction, as furans would produce interesting tricyclic products and have been shown to function as competent dienes in the Diels-Alder reaction. Unfortunately, no cyclooctanoid product was observed, rather a substantial amount of the [4 + 2] cycloadduct was observed (entry 6).



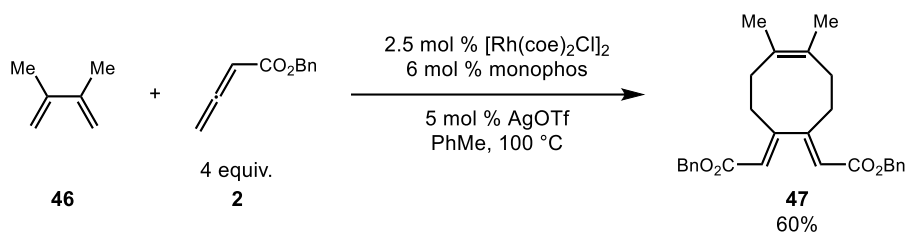
**Table 6.** Substrate scope of racemic Rh-catalyzed [4 + 2 + 2] cycloaddition.

entry <sup>a</sup>	substrate	product	yield <sup>b</sup> (%)
1			27
2 <sup>d</sup>			n.r.
3 <sup>d</sup>			48
4 <sup>c,d</sup>			63
5 <sup>d</sup>			34
6 <sup>c</sup>			0 (55 <sup>e</sup> )
<sup>a</sup> Reaction conditions: 1 equiv. diene-allene, 2 equiv. allenolate, 2.5 mol % [Rh(coe) <sub>2</sub> Cl] <sub>2</sub> , 6 mol % monophos, PhMe (0.042 M). <sup>b</sup> Isolated yield. <sup>c</sup> P(OEt) <sub>3</sub> used instead of monophos. <sup>d</sup> 100 °C. <sup>e</sup> Yield of [4 + 2] byproduct.			

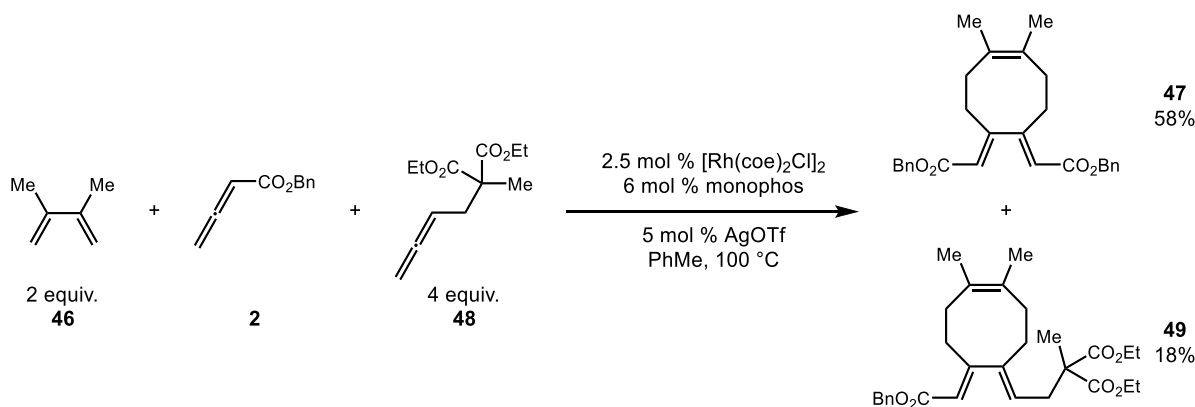
### 1.2.5 Noteworthy Miscellaneous [4 + 2 + 2] Cycloadditions

Previous work has demonstrated the ability of cobalt catalysis to perform a fully intermolecular [4 + 2 + 2] cycloaddition with a diene and two equivalents of an alkyne. This concept was applied to this work using rhodium catalysis to perform the analogous reaction using allenes as replacements for alkyne.<sup>48</sup> Applying a cationic rhodium-monophos catalyst system to 2,3-dimethylbutadiene **46** and allenolate **2** produced monocyclic cyclooctanoid **47** in 60 % yield. Additionally, these conditions were applied to a system containing two unique,

electronically disparate allenes to form a monocyclic cyclooctanoid **49** in a low, but meaningful yield.

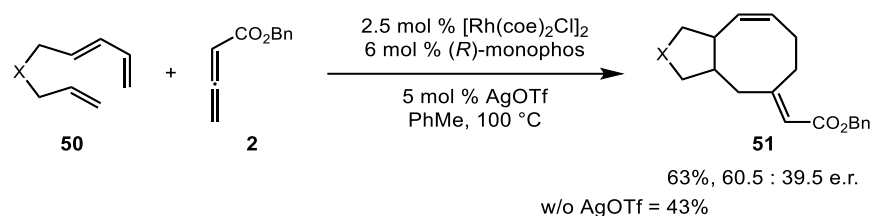


**Figure 22.** Intermolecular Rh-catalyzed [4 + 2 + 2] with allenoates and diene.

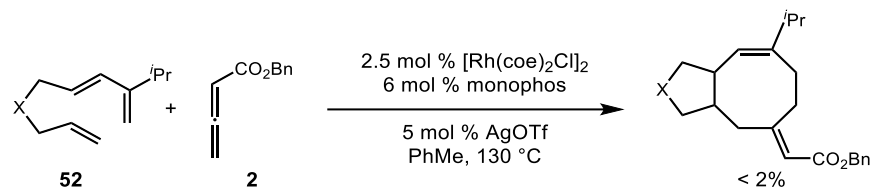


**Figure 23.** Intermolecular Rh-catalyzed [4 + 2 + 2] with three unique components.

The ability of 1,3,8-trienes to react with exogenous allenes under these conditions was briefly explored. Under cationic-rhodium catalysis conditions, triene **50** was coupled with allenoate **2** to form cyclooctanoid **51** in 63 % yield. Notably, the cationic rhodium catalyst performed better than the neutral catalyst employed in our diene-allene-allene [4 + 2 + 2] reaction (**Figure 24**). It was seen that this triene bearing an unsubstituted diene has a similar enantioselectivity to the corresponding diene-allene (discussed later, Section 1.3). Unfortunately other substrates could not be examined as substitution on the diene rendered the substrate recalcitrant (**Figure 25**).



**Figure 24.** Rh-catalyzed [4 + 2 + 2] cycloaddition of a triene and allenolate.



**Figure 25.** Substitution effect on triene in [4 + 2 + 2] cycloaddition.

### 1.2.6 Summary

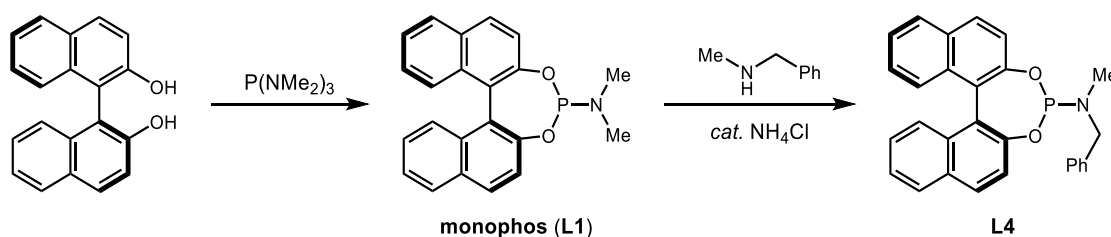
We have shown that the rhodium(I)-catalyzed [4 + 2 + 2] cycloaddition of diene-allenes with exogenous allenes proceeds efficiently to form cyclooctanoid products. The optimal catalysts were found to be monodentate phosphite or phosphoramidite complexes of rhodium with an inverse relationship between reaction yield and steric bulk of the ligand. Specifically, we have found triethyl phosphite and monophos to be particularly effective. This reaction has been shown to tolerate a variety of allene substitution patterns, including electron rich allenes, albeit with lower yields. Substitution on the diene-allene substrates was tolerated, although the reaction efficiency was effected greatly by the location and size of the substitution.

### 1.3 Enantioselective [4 + 2 + 2] cycloaddition of diene-allenes and allenes

With the ability of rhodium-phosphite and rhodium-phosphoramidite catalysts to efficiently produce cyclooctanoids demonstrated, the enantioselectivity of these reaction was then explored. The asymmetric variant of the [4 + 2 + 2] cycloaddition was examined concurrently with the racemic studies. It is important to note that the same parameters that affect the enantioselectivity also play an intimate role in the chemoselectivity of the reaction. Thus despite the focus on enantioselectivity, both issues will be discussed in this chapter.

#### 1.3.1 Effect of Ligand on Chemo- and Enantioselectivity

Only a handful of monophosphoramidite ligands are commercially available; however, they are readily synthesized from commercially available compounds. The synthesis of these ligands begins with an enantioenriched diol and phosphorus triamide, which produces the parent ligand ‘monophos’ (**L1**). The volatility of dimethylamine is beneficial for diversification of the amine moiety. The reaction of monophos with catalytic ammonium salt and a primary or secondary amine under a stream of argon produces a new phosphoramidite ligand (**Figure 26**).



**Figure 26.** Synthetic route for the synthesis and diversification of phosphoramidite ligands.

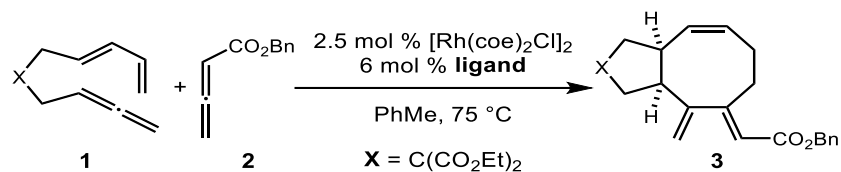
Initial studies examined the use of these ligands on the diene-allene **1**, bearing no substitution on the diene moiety (**Table 7**). The application of monophos proved unsuccessful in imparting stereochemical information as nearly racemic products were obtained (entry 1). The

use of cyclic amine moieties on the ligand gave similar results (entries 2-3), with the exception of a small decrease in yield for **L2**. Increasing the size of the amine through appendage of a phenyl ring resulted in a small increase in enantioselectivity (entry 4). An isomer of this ligand, bearing (*S*)-(-)- $\alpha$ -methyl benzylamine as the amine moiety, resulted in a decrease in both the yield and enantioselectivity (entry 5). Notably, the other diastereomer of this ligand was not examined, therefore we cannot rule out the possibility of a “matched/mismatched” situation.

Using the H<sub>8</sub>-binol backbone (**L7**), an increase in enantioselectivity was observed with only a minor decrease in yield as (entry 6). Again, the amine component was reinvestigated. It was observed that neither piperidine (**L8**) nor benzylmethylamine (**L9**) on the ligand produces a meaningful change in yield or selectivity (entries 7-8).

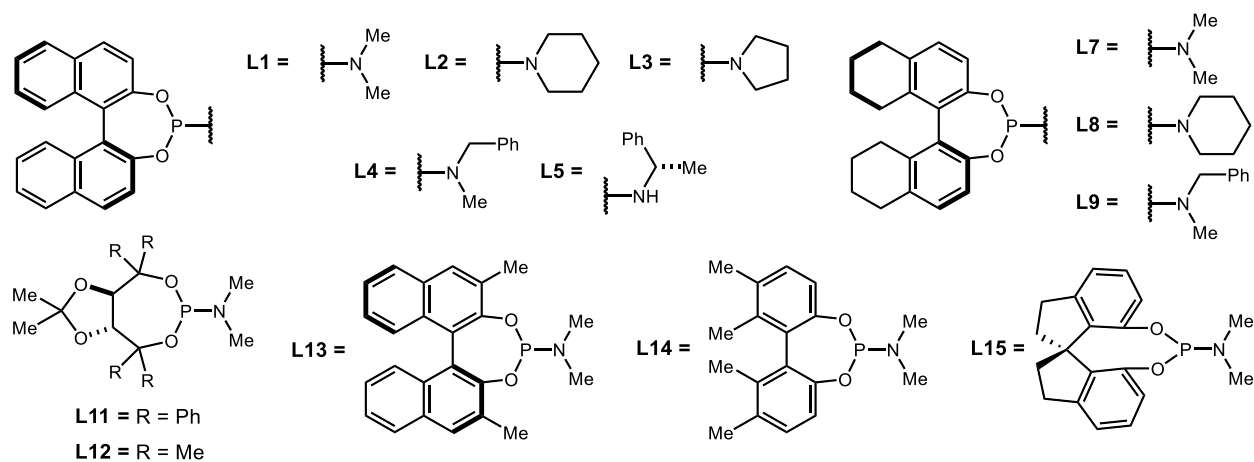
We also explored the use of other diol backbones with drastically different steric profiles. The use of a TADDOL backbone (**L11**, entry 9) gave moderate enantioselectivity (80 : 20 e.r.), but at the expense of chemoselectivity (19% yield). Replacing the phenyl rings on the ligand with a smaller substituent, methyl, resulted in a complete erosion of enantioselectivity (entry 10).

**Table 7.** Ligand screen for the asymmetric Rh-catalyzed [4 + 2 + 2] cycloaddition.



entry <sup>a</sup>	ligand	yield <sup>b</sup> <b>3</b> (%)	e.r.
1	<b>L1</b>	70	54 : 46
2	<b>L2</b>	61	54 : 46
3	<b>L3</b>	70	53 : 47
4	<b>L4</b>	82	58.5 : 41.5
5	<b>L5</b>	51	52 : 48
6	<b>L7</b>	65	59 : 41
7	<b>L8</b>	57	58.5 : 41.5
8	<b>L9</b>	59	61.5 : 38.5
9	<b>L11</b>	19	80 : 20
10	<b>L12</b>	73	52.5 : 47.5

<sup>a</sup>Reaction conditions: 1 equiv. diene-allene, 2 equiv. allenolate, 2.5 mol %  $[\text{Rh}(\text{coe})_2\text{Cl}]_2$ , 6 mol % ligand, PhMe, 75 °C.  
<sup>b</sup>Isolated yield



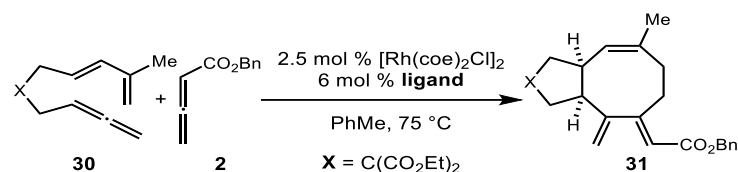
**Figure 27.** Ligands used for asymmetric Rh-catalyzed [4 + 2 + 2] cycloaddition.

### 1.3.2 Ligand Optimization with Substituted Diene-Allenes

While we explored modifying the structure of the ligand to improve enantioselectivity, modification of the diene-allene structure was also investigated. We began our studies on **30** with Me substitution on the 3-position (**Table 8**). The use of monophos was shown to impart good enantioselectivity on the resulting cyclooctanoid. We therefore examined ligand modification using this substrate.

Increasing the size of the amide moiety of the ligand, as in **L2** and **L4**, elevated the enantioselectivity, but at the expense of cyclooctanoid yield. Next, modification of the ligand backbone was studied. The use of high-steric profile backbone TADDOL resulted in no observable formation of the cyclooctanoid, as did **L13**, which bears a 2,2'-dimethylbisnaphthol backbone. However, the use of H<sub>8</sub>-monophos (**L7**), with a partially hydrogenated backbone, was found to be very beneficial to the yield of cyclooctanoid without decreasing the enantioselectivity.

**Table 8.** Ligand screen for the asymmetric Rh-catalyzed [4 + 2 + 2] cycloaddition with diene-allene **30**.

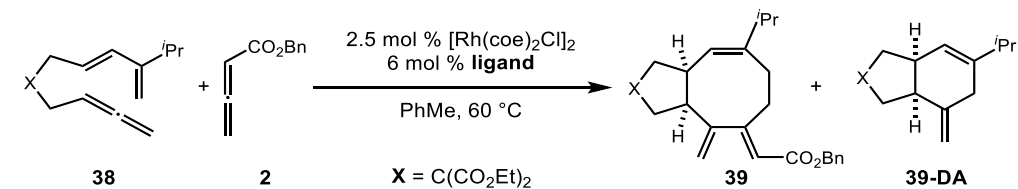


entry <sup>a</sup>	ligand	yield <sup>b</sup> <b>31</b> (%)	e.r.
1	<b>L1</b>	38	90 : 10
2	<b>L2</b>	27	95.5 : 94.5
3	<b>L4</b>	32	91.5 : 8.5
4	<b>L7</b>	51	89 : 11
5	<b>L11</b>	< 2	-
6	<b>L13</b>	< 2	-

<sup>a</sup>Reaction conditions: 1 equiv. diene-allene, 2 equiv. allenoate, 2.5 mol % [Rh(coe)<sub>2</sub>Cl]<sub>2</sub>, 6 mol % ligand, PhMe, 75 °C. <sup>b</sup>Isolated yield

Increasing the size of the substitution at the 3-position from Me (**Table 8**, entry 1) to *i*Pr (**Table 9**, entry 1) results in higher enantioselectivity, but lower chemoselectivity. The high enantioenrichment of this product was promising and prompted examination of the reaction temperature. Lowering the reaction temperature to 60 °C resulted in an increase in chemoselectivity without compromising enantioselectivity. Further examination of ligands gave similar results (**Table 9**), in which it was discovered that the use of H<sub>8</sub>-monophos resulted in the right balance of chemo- and enantioselectivity. Therefore, we sought to investigate further increasing the dihedral angle of the diol. Slight increase in dihedral angle resulted in a lower yield (entry 6), while retaining high enantioselectivity. However, a drastic increase, as seen in siphos (**L15**, entry 7), resulted in only a trace amount of observable cyclooctanoid **39**.

**Table 9.** Ligand screen for the asymmetric Rh-catalyzed [4 + 2 + 2] cycloaddition with diene-allene **38**.



entry <sup>a</sup>	ligand	yield <sup>b</sup> <b>39</b> (%)	e.r.	yield <sup>c</sup> <b>39-DA</b> (%)
1 <sup>d</sup>	<b>L1</b>	27	98 : 2	43
2	<b>L1</b>	39	97.5 : 2.5	31
3	<b>L2</b>	20	99 : 1	55
4	<b>L4</b>	25	97 : 3	39
5	<b>L7</b>	47	96.5 : 3.5	29
6	<b>L14</b>	36	97 : 3	23
7	<b>L15</b>	< 2	-	n.d.

<sup>a</sup>Reaction conditions: 1 equiv. diene-allene, 2 equiv. allenolate, 2.5 mol % [Rh(coe)<sub>2</sub>Cl]<sub>2</sub>, 6 mol % ligand, PhMe, 60 °C. <sup>b</sup>Isolated yield. <sup>c</sup>Yield determined by <sup>1</sup>H NMR spectroscopy. <sup>d</sup>75 °C

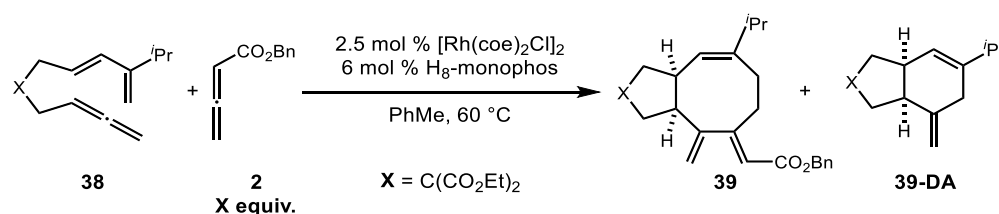


### 1.3.3 Optimization of Chemo- and Enantioselectivity

Moving forward, other reaction parameters were investigated to further improve the reaction efficiency and selectivity, including exogenous allene stoichiometry, precatalyst, solvent, and counter-ion.

The competitive nature between the [4 + 2 + 2] and [4 + 2] cycloaddition pathways leads to a reasonable suggestion that the side reaction can be suppressed through an increase in allenolate equivalency. To test this, the reaction was performed using a slight excess of allenolate (1.2 equiv.). This results in a similar chemoselectivity, but with a lower yield. Conversely, doubling the amount of allene (4 equiv.) in the reaction led to a marginal increase in chemoselectivity, which arose from the suppression of [4 + 2] with no increase in yield for the [4 + 2 + 2] pathway. Another possible way to increase the chemoselectivity is through the increase of relative stoichiometry of the allene through the slow addition of the substrate. However, the addition of **38** over 4.5 h at 75 °C produced similarly poor chemoselectivity (33:67, **38**:**39**).

**Table 10.** The effect of allene stoichiometry on chemoselectivity.



entry <sup>a</sup>	equiv	yield <sup>b</sup>	yield <sup>c</sup>	ratio
1	1.2	36	20	1.8 : 1
2	2	47	29	1.6 : 1
3	4	45	22	2.1 : 1

<sup>a</sup>Reaction conditions: 1 equiv. diene-allene, 2 equiv. allenolate, 2.5 mol %  $[\text{Rh}(\text{coe})_2\text{Cl}]_2$ , 6 mol % ligand, PhMe, 60 °C. <sup>b</sup>Isolated yield. <sup>c</sup>Yield determined by  $^1\text{H}$  NMR spectroscopy.

This reaction requires the disassociation of the olefins from the precatalyst before the reaction can occur, therefore the identity of this precatalyst could play a role in the selectivity of this reaction. Throughout this investigation,  $[\text{Rh}(\text{coe})_2\text{Cl}]_2$  has been used as precatalyst. The use of two other commercially available Rh-precatalysts,  $[\text{Rh}(\text{cod})\text{Cl}]_2$  and  $[\text{Rh}(\text{nbd})\text{Cl}]_2$ , were employed in this reaction. However, no difference was observed in the yield and enantioenrichment of the cyclooctanoid product, indicating that the precatalyst does not play a role in the reaction selectivity.

We next sought to investigate the effect of solvent on the chemo- and enantioselectivity of the reaction (**Table 11**). Using the more polar solvent trifluorotoluene, the cyclooctanoid was produced in nearly the same yield and enantioselectivity. A lower yield was observed when using the ethereal solvent 1,4-dioxane; however, the enantioselectivity was unaffected. Similar results were observed with the use of the chlorinated solvent DCE, but with slightly lower chemo- and enantioselectivity. Based on these observations, solvent does not play a significant role in the selectivity of this reaction and further studies continued in toluene.

**Table 11.** Solvent screen for asymmetric Rh-catalyzed [4 + 2 + 2] cycloaddition.

Reaction scheme: Diene **38** (with substituent X) + Dienophile **2** (CO<sub>2</sub>Bn)  $\xrightarrow[\text{solvent, 60 } ^\circ\text{C}]{2.5 \text{ mol } \% [\text{Rh}(\text{coe})_2\text{Cl}]_2, 6 \text{ mol } \% \text{H}_8\text{-monophos}}$  Products **39** and **39-DA**. X = C(CO<sub>2</sub>Et)<sub>2</sub>.

entry <sup>a</sup>	solvent	yield <sup>b</sup> <b>39</b> (%)	e.r.	yield <sup>c</sup> <b>39-DA</b> (%)	ratio <b>39/39-DA</b>
1	PhMe	47	96.5 : 3.5	29	1.6 : 1
2	PhCF <sub>3</sub>	51	95 : 5	30	1.7 : 1
3	Dioxane	38	97 : 3	25	1.6 : 1
4	DCE	41	93 : 7	32	1.3 : 1

<sup>a</sup>Reaction conditions: 1 equiv. **39**, 2 equiv. **2**, 2.5 mol %  $[\text{Rh}(\text{coe})_2\text{Cl}]_2$ , 6 mol % H<sub>8</sub>-monophos, PhMe, 60 °C. <sup>b</sup>Isolated yield. <sup>c</sup>Yield determined by <sup>1</sup>H NMR spectroscopy.

Using silver salts, the chloride ligand can be abstracted from the rhodium-catalyst and precipitated as AgCl. This has the effect of exchanging the original silver counter-ion with the chloride on the rhodium catalyst. Counter-ion manipulation have been shown to have tremendous effect on the chemoselectivity of rhodium-catalyzed cycloadditions.

Initial examination of counter-ions were conducted with the carboxylate class of anions (**Table 12**). Strongly coordinating acetate anion slowed the reaction marginally and resulted in a shift in chemoselectivity slightly towards the cyclohexanoid product. Trifluoroacetate, which is much less coordinating, slows the rate of reaction, but significantly increases the chemoselectivity favoring the cyclooctanoid product nearly five-fold over the cyclohexanoid byproduct. The heptafluorobutyrate anion is known to be much less coordinating; however, it does not continue the trend of increasing the chemoselectivity.

**Table 12.** Silver salt screen for asymmetric Rh-catalyzed [4 + 2 + 2] cycloaddition.

$\text{38} + \text{2} \xrightarrow[\text{5 mol \% AgOTf, PhMe, 60 } ^\circ\text{C, 3 d}]{\text{2.5 mol \% [Rh(coe)}_2\text{Cl]}_2, \text{6 mol \% H}_8\text{-monophos}}$ 
 $\text{39} + \text{39-DA}$

$\text{X} = \text{C}(\text{CO}_2\text{Et})_2$

entry <sup>a</sup>	Ag salt	conv. <sup>c</sup> (%)	yield <sup>b</sup> 39 (%)	e.r.	yield <sup>c</sup> 39-DA (%)	ratio 39/39-DA
1	None	98	39	97.5 : 2.5	31	1.3 : 1
2	AgOAc	93	34	n.d.	37	0.9 : 1
3	AgO <sub>2</sub> CCF <sub>3</sub>	77	34	n.d.	7	4.8 : 1
4	AgO <sub>2</sub> CCF <sub>3</sub>	78	29	82.5 : 17.5	16	1.8 : 1
5	AgOMs	60	29	n.d.	5	5.4 : 1
6	AgOTs	66	31	56.5 : 43.5	3.5	11 : 1
7	AgOTf	91	45	67.5 : 32.5	6	8 : 1
8	AgPF <sub>6</sub>	81	36	55 : 45	6	5 : 1
AgNTf <sub>2</sub> , AgBF <sub>4</sub> , AgSbF <sub>6</sub> – very low conversion						

<sup>a</sup>Reaction conditions: 1 equiv. **39**, 2 equiv. **2**, 2.5 mol % [Rh(coe)<sub>2</sub>Cl]<sub>2</sub>, 6 mol % H<sub>8</sub>-monophos, PhMe, 60 °C. <sup>b</sup>Isolated yield. <sup>c</sup>Yield determined by <sup>1</sup>H NMR spectroscopy.

Similar trends in chemoselectivity were observed with the sulfonate class of anions. In general, sulfonates are less coordinating than carboxylates.<sup>57</sup> Mesylate and tosylate both resulted in lower conversion whereas triflate did not have as great of an effect. All three of the sulfonate counter-ions increased the chemoselectivity with tosylate and triflate giving high selectivity for the cyclooctanoid product. Unfortunately, a substantial decrease in the enantioselectivity was observed. Similar results were seen with the hexafluorophosphate anion, which increased the chemoselectivity of the reaction, but at the expense of the enantioselectivity.

### 1.3.4 Substrate Scope of Optimized Enantioselective Conditions

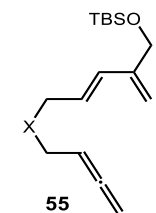
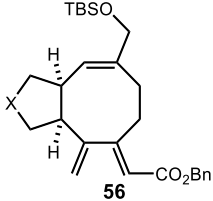
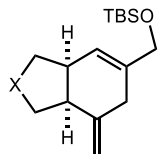
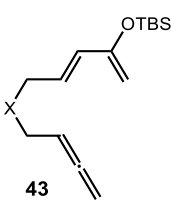
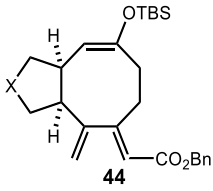
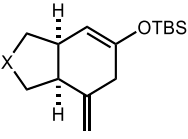
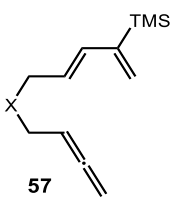
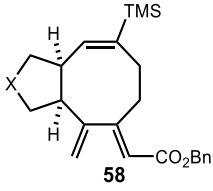
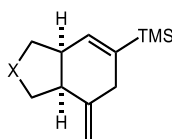
With conditions optimized to afford the highest combination of chemo- and enantioselectivity, a final examination of substrate scope was performed to demonstrate the utility of this transformation. 3-Me substituted diene-allene **30** was converted to cyclooctanoid **31** with good yield in about a 3:1 selectivity over the corresponding cyclohexanoid byproduct **31-DA**. The location of this substitution was shown to have a large impact on both chemoselectivity, as well as the reactions of 2-Me and 4-Me substituted dienes allenes, **28** and **32** respectively, proceeded with good chemoselectivity, but only modest enantioselectivity. Diene-allene **36**, bearing a 1,1-disubstituted allene, also reacted with good chemoselectivity and modest enantioselectivity to provide the quaternary carbon containing cyclooctanoid **37**. However, a synergistic effect can be seen when a 1,1-disubstituted allene is used with a 3-Me substitution on the diene with diene-allene **53**. This substrate is converted to cyclooctanoid **54** with very high enantioselectivity.

Given the large effect that diene substitution at the 3-position has on the chemo- and enantioselectivity, substrates were explored that feature a variety of function groups at this position. Larger alkyl groups, like 3-*i*Pr, increase the effect seen with 3-Me substitution. The resulting highly enantioenriched cycloadduct **39** is formed in a synthetically relevant yield. Protected alcohols were shown to be viable in the reaction as **56** is produced in good yield with moderate enantioenrichment. Interestingly, an electron rich diene-allene **43** bearing a silyl enol ether is converted into the analogous cyclooctanoid **44** in high enantioselectivity. The lower yield and chemoselectivity of this reaction is likely due to the increased temperature necessary for the reaction to proceed rather than the size of the substituent. Vinyl silanes are similarly tolerated as seen with the formation of cyclooctanoid **58**, which is produced in a lower yield than the similar entry 7, but still with high enantioselectivity.

**Table 13.** The asymmetric Rh-catalyzed [4 + 2 + 2] cycloaddition of diene-allenes and exogenous allenes.

entry <sup>a</sup>	substrate	[4 + 2 + 2] product	yield <sup>b</sup> (%)	e.r.	[4 + 2] product	yield <sup>c</sup> (%)
1			60	85 : 15		23
2			55	67.5 : 32.5		2
3 <sup>d</sup>			37	67.5 : 32.5		n.d.
4			55	65 : 35		< 2
5 <sup>d</sup>			33	97.5 : 2.5		27
6			47	96.5 : 3.5		30

Table 12 cont.

7			67	80 : 20		n.d.
8 <sup>d</sup>			34	95.5 : 4.5		23
9			34	96 : 4		47

<sup>a</sup>Reaction conditions: 1 equiv. diene-allene, 2 equiv. allenolate, 2.5 mol % [Rh(coe)<sub>2</sub>Cl]<sub>2</sub>, 6 mol % H<sub>8</sub>-monophos, PhMe, 60 °C. <sup>b</sup>Isolated yield. <sup>c</sup>Yield determined by <sup>1</sup>H NMR spectroscopy. <sup>d</sup>100 °C

### 1.3.5 Summary

It has been observed that the asymmetric Rh/phosphoramidite catalyzed [4 + 2 + 2] cycloaddition can proceed efficiently with high functional group compatibility. Notably, this reaction is highly sensitive towards steric considerations on both the substrate and the ligand. Often this requires a balance between high chemoselectivity and high enantioselectivity, in which large steric interactions diminish the yield of [4 + 2 + 2] cycloadduct while imparting very high levels of enantioselectivity. Despite the number of possible stereoisomers, however, this reaction only furnished one diastereomer of one regioisomer of the cyclooctanoid product.

## 1.4 On the mechanism of the rhodium-catalyzed [4 + 2 + 2] cycloaddition

The high enantioenrichment observed in the cyclooctanoid product inspired us to investigate the enantioselectivity of the cyclohexanoid forming [4 + 2] pathway. To investigate this, a benzyl malonate tethered substrate was synthesized to include a UV-absorbing tag on the cyclohexanoid product. We observed that the cyclooctanoid product was formed in high enantioenrichment, whereas the cyclohexanoid was produced in only moderate enantioenrichment. Further, in the absence of allene, the enantioselectivity eroded and interestingly, the other enantiomer became most prominent.

**Table 14.** The enantioselectivity of the cyclohexanoid byproduct.

$\text{59} + \text{2} \xrightarrow[\text{PhMe, 60 } ^\circ\text{C}]{\text{2.5 mol \% [Rh(coe)}_2\text{Cl]}_2, \text{6 mol \% H}_8\text{-monophos}}$ 
 $\text{60} + \text{61}$

$\text{X} = \text{C}(\text{CO}_2\text{Bn})_2$

allene	yield <sup>b</sup> 60 (%)	e.r. 60	yield <sup>b</sup> 61 (%)	e.r. 61
2 equiv.	48	96.5 : 3.5	37	77.5 : 22.5
0 equiv.	-	-	84	42 : 58

<sup>a</sup>Reaction conditions: 1 equiv. **59**, 2.5 mol % [Rh(coe)<sub>2</sub>Cl]<sub>2</sub>, 6 mol % H<sub>8</sub>-monophos, PhMe, 60 °C. <sup>b</sup>Isolated yield.

Given the discrepancy between the enantiomeric ratios of the cyclooctanoid product and cyclohexanoid byproducts, it is prudent to examine the mechanism of the reaction. It should be noted, however, that detailed kinetic studies have not been performed. Instead, the investigation herein considers evidence gained through the optimization and substrate scope studies that have been previously described.

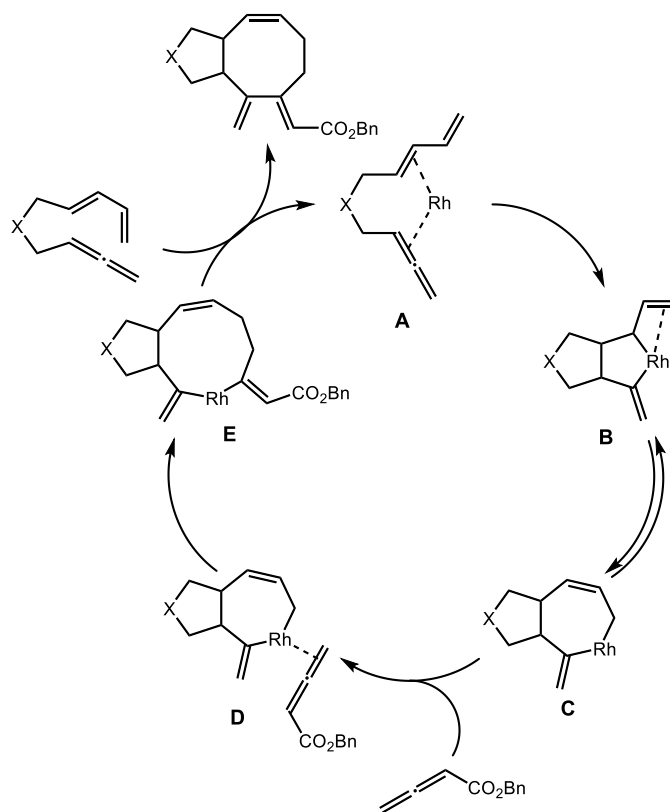
In all catalytic cycles that we propose, the active catalyst is proposed to be the same, a monophosphoramidite-bound rhodium(I) chloride. Initially, a dimeric precatalyst, [Rh(coe)<sub>2</sub>Cl]<sub>2</sub>,



is dissolved along with unbound phosphoramidite. Under the standard conditions, these are stirred together for 30 minutes and a color change is observed from orange to yellow. The observed yellow color is consistent with previously observed Rh(cod)Cl/phosphoramidite complexes. The reactions can then proceed with the substitution of cyclooctene ligands with the starting materials.

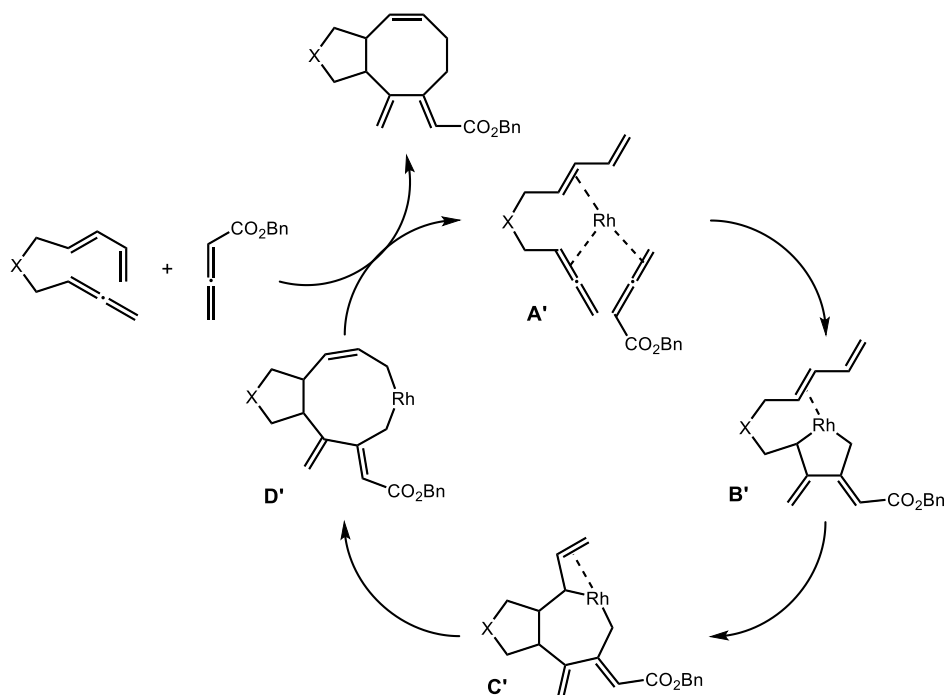
#### 1.4.1 Potential Catalytic Cycles

One plausible mechanism, which will be referred to as Cycle A (**Figure 28**), initiates with an intramolecular oxidative coupling with the tethered allene and the internal portion of the diene. This forms a [3.3.0] metallabicyclic (**B**) with an  $\eta^1$ -bound allyl group that can undergo isomerization to an  $\eta^3$ -allyl species before isomerizing to the terminal-bound  $\eta^1$ -allyl [3.5.0] metallabicyclic (**D**). It is at this point that the [4 + 2 + 2] and [4 + 2] pathways diverge. Reductive elimination of the [3.5.0] metallabicyclic forms the [4 + 2] hydrindane product. Alternatively, migratory insertion of the exogenous allene results in the formation of an expanded, [3.7.0] metallabicyclic (**E**). Reductive elimination of this complex results in the formation of the desired cyclooctanoid product.



**Figure 28.** Cycle A: a plausible mechanism for the [4 + 2 + 2] cycloaddition.

The second plausible mechanism, which will be referred to as Cycle B (**Figure 29**), begins with an intermolecular oxidative coupling of the tethered allene and the exogenous allene. The resulting intermediate is a bis-allyl metallacycle **B'** with the tethered diene coordinated. The diene can undergo insertion into the metallacycle to form the metallabicyclic intermediate **D'**, which can undergo reductive elimination to form the desired cyclooctanoid product. This mechanism, however, provides no pathway from which the cyclohexanoid byproduct can be obtained. It is, therefore, assumed for this work that the [4 + 2] cycloaddition pathway proceeds via Cycle A.

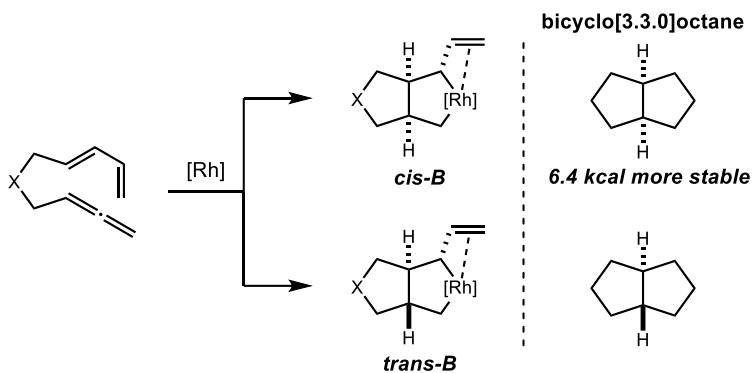


**Figure 29.** Cycle B: a plausible mechanism for the [4 + 2 + 2] cycloaddition.

### 1.4.2 Experimental Evidence

Our mechanistic examination will begin with investigation of the diastereoselectivity. The [4 + 2 + 2] and the [4 + 2] pathways both produce bicyclic product with perfect cis-selectivity at the ring fusion. This is a departure from our prior work<sup>34</sup> in which trans-hydrindanes are formed. In all published examples of rhodium-catalyzed [4 + 2] cycloadditions that form saturated ring junctions, only cis-ring fusions are observed. This agrees with the idea that the [4 + 2] cycloadditions go through a process similar to Cycle A with an initial intramolecular oxidative coupling. The trans-ring junction is observed in [4 + 2] cycloadditions are under gold-catalysis, which are proposed to go through a mechanism that does not proceed through a metallacycle. Instead, the ring is formed in a stepwise fashion initiating with the nucleophilic attack on the Au-bound allene.<sup>58,59</sup>

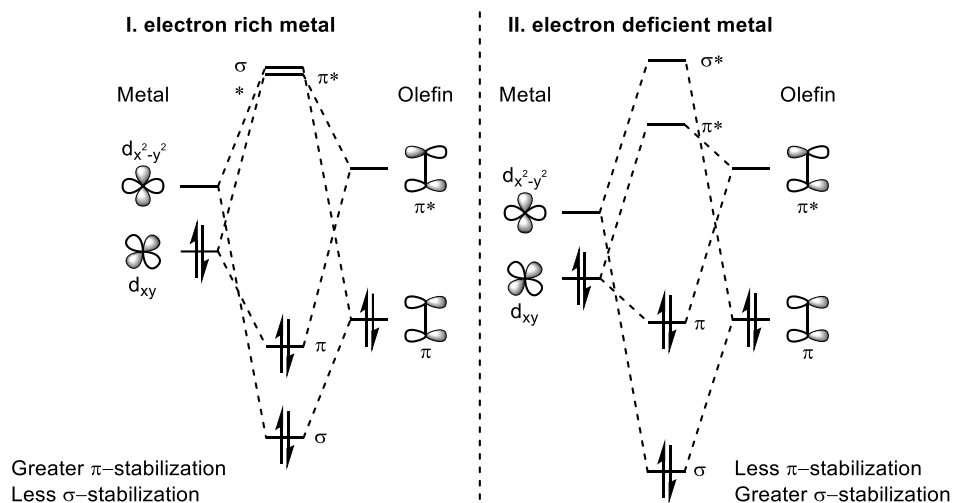
Most significantly, the hydrindane products formed from Wender's  $[4 + 2]$  cycloadditions of diene-allenes are also cis-fused. Wender suggests the selectivity is a consequence of an initial intramolecular oxidative coupling to form metallacycle **cis-B** (**Figure 30**). The cycloalkane analog to this, cis-bicyclo[3.3.0]octane, is 6.4 kcal lower in energy than its trans-counterpart.<sup>60</sup> It can therefore be inferred that there is a similar difference in energy between the two metallabicycles, thus leading to a high diastereoselectivity. In contrast, the insertion of an alkene into metallacycle **B'** (Cycle B, **Figure 29**) proceeds in a manner that sets a trans-fused ring as seen in our prior  $[2 + 2 + 2]$  cycloaddition,<sup>34</sup> which should be similar to the way a diene inserts. This is not only evidence that diene-allenes can go through intramolecular oxidative coupling, but also that the cis-ring fusion indicates that Cycle A is operative in the  $[4 + 2 + 2]$  cycloaddition.



**Figure 30.** Potential metallabicyclic intermediates of Rh-catalyzed cycloaddition and the strain energy of related hydrocarbon structures.

Additional evidence for Cycle A comes from the comparison of allene insertion in this work and our prior  $[2 + 2 + 2]$  cycloadditions.<sup>34</sup> This discussion first requires background on the coordination chemistry of  $\pi$ -components. The coordination of  $\pi$ -components to transition metal is affected by two major orbital interactions (**Figure 31**): the  $\sigma$ -overlap of the metal  $d_{x^2-y^2}$  orbital

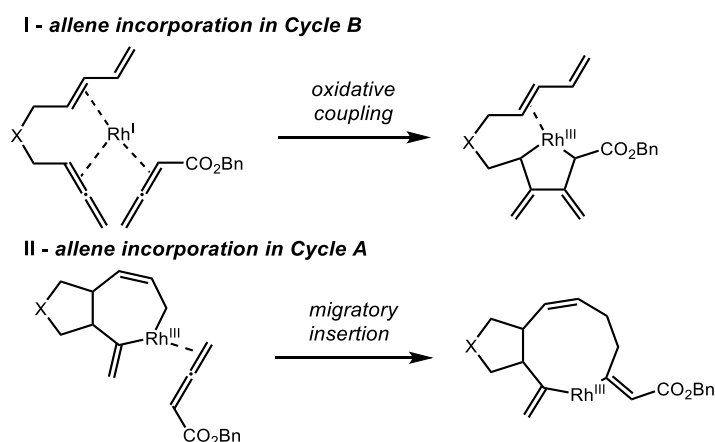
with the  $\pi$ -bonding orbital of the ligand and the metal  $d_{xy}$  orbital with the  $\pi^*$ -antibonding orbital of the ligand. Which of these interactions dominates is highly dependent on the oxidation state of the metal and the substitution on the ligand. An appropriate case study for olefin binding is the coordination of olefins to an electron rich nickel(0) complex. In this case, electron deficient olefins, like maleic anhydride, outcompete coordination of electron rich olefins, like cis-2-hexene.<sup>61,62</sup> This signifies that  $\pi$ -backbonding from the metal d-orbitals into the  $\pi^*$ -antibonding orbitals is the predominating interaction in this coordination. However, in the study of the equilibria of olefin coordination with palladium(II) complexes it was observed that the binding of electron rich olefin propene was favorable over the binding of electron deficient methyl acrylate by factor of  $10^3$ .<sup>63</sup>



**Figure 31.** Molecular orbital diagrams of metal-olefin coordination for I) electron rich metals and II) electron deficient metals.

If we assume, as evidence indicates, that our prior  $[2 + 2 + 2]$  cycloaddition operates through a process resembling cycle B, the exogenous allene is initially incorporated into the metallacycle during the oxidative coupling step. Therefore, before this step the allene is bound to

an electron rich rhodium(I) complex, in which it would be assumed that the electron deficient  $\pi$ -system of the allenolate would be bound (**Figure 32-I**). Indeed, it is observed that the electron deficient  $\pi$ -bond is the  $\pi$ -bond that is incorporated in this reaction. Conversely, in this work the unsubstituted terminus of the allenolate is incorporated into the ring. This lends credence to the idea that, prior to incorporation, the allenolate is bound by its terminal  $\pi$ -component, presumably to a more electron deficient rhodium(III) complex (**Figure 32-II**). This indicates that the allenolate is not involved in the initial oxidative coupling, suggesting that Cycle B is inoperative.



**Figure 32.** Migratory insertion of allenolate into the M-C bond of A) electron rich Rh(I) and an electron deficient Rh(III) species.

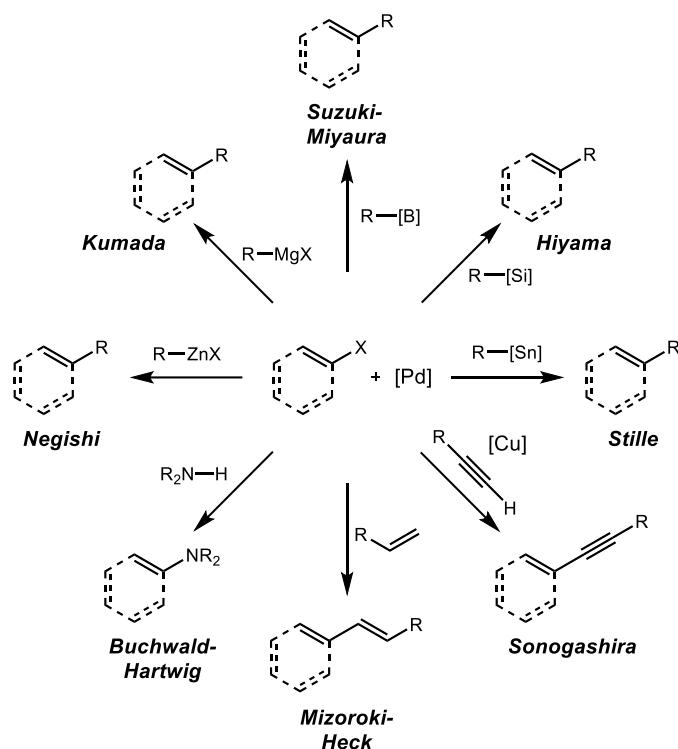
### 1.4.3 Summary

It is tempting to say that the difference in enantioenrichment of the [4 + 2 + 2] cycloadducts and the [4 + 2] cycloadduct precludes that the two are formed from the same pathway and that the C-C bonds are formed in different ways. At this time, however, we believe that both the [4 + 2 + 2] cycloaddition and the [4 + 2] cycloaddition operate through Cycle A, or a slight variant of Cycle A.

## CHAPTER 2: Palladium-Catalyzed Carbon-Carbon Bond Forming Reactions

### 2.1 Introduction to Palladium-Catalyzed Carbon-Carbon Bond Forming Reactions

The ability to form covalent carbon-carbon bonds efficiently is essential in chemical synthesis. Transition-metal catalyzed cross coupling reactions of organic halides and pseudohalides are amongst the most powerful carbon-carbon bond forming reactions in use today.<sup>64,65</sup> The scope of these reactions is impressively broad with respect to the nucleophile, including many organometallic groups as well as amines and olefins as illustrated in **Figure 33**. These cross coupling reactions have enabled synthetic chemists to create convergent routes to highly complex molecular scaffolds.

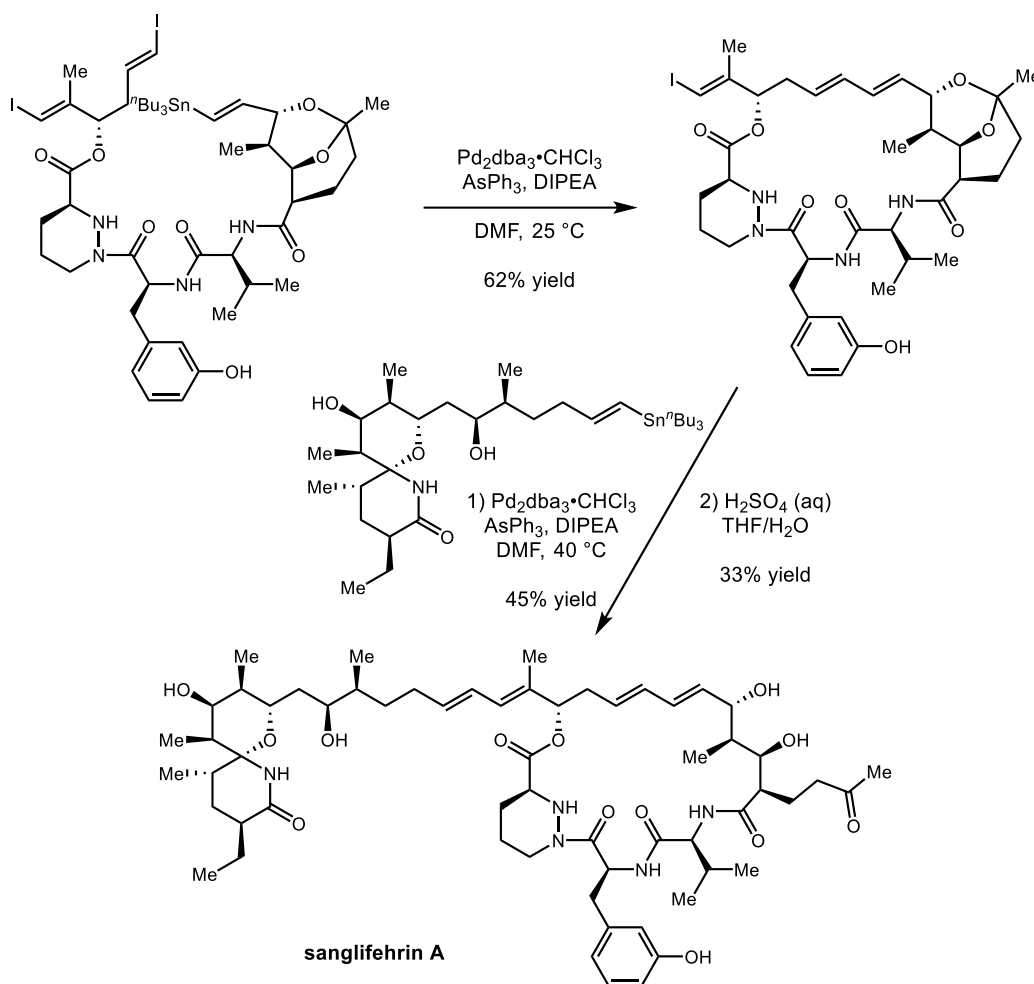


**Figure 33.** The variety of known Pd-catalyzed cross coupling reactions of organohalides.

The mild nature of these transition metal-catalyzed reactions make them widely applicable in late stage synthesis.<sup>66</sup> This is perhaps best exemplified in the synthesis of the immunosuppressant agent sanglifehrin A by the Nicolaou group, in which two of the last three steps are palladium-catalyzed cross coupling reactions (**Figure 34**).<sup>67</sup> This begins with a Stille macrocyclization of the vinyl iodide and vinyl stannane. Interestingly, this coupling is selective for oxidative addition of the disubstituted vinyl iodide over the more hindered trisubstituted vinyl iodide. Additionally, this reaction is unaffected by the diverse set of functionality present in the substrate. Next, an intermolecular Stille reaction to append the western portion of this molecule, demonstrating the potential for convergency that these cross couplings allow. A single step, which opens the acetal and reveals a 1,3-diol and ketone, provides the target molecule. This synthesis demonstrates many of the attributes that make the palladium-catalyzed cross coupling



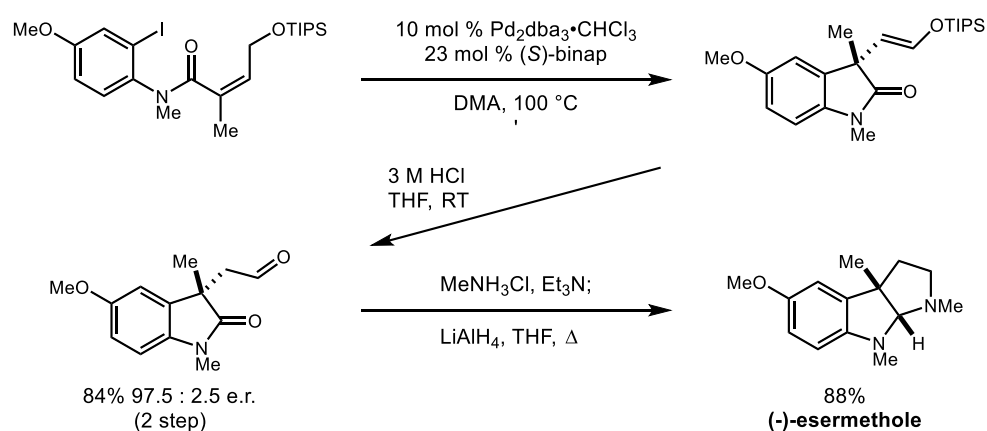
such an impressive reaction, including low reaction temperatures, high functional group tolerance, and impressive selectivity.



**Figure 34.** Late-stage Stille couplings in Nicolaou's synthesis of sanglifehrin A.

The Mizoroki-Heck reaction is particularly useful as, unlike other cross-coupling reactions, it does not require the use of prefunctionalized nucleophiles (i.e. organic stananes, boranes, silanes). Rather this reaction couples organic halides with olefins, which are often commodity chemicals that are readily available through commercial outlets. The Mizoroki-Heck reaction has been applied in the total synthesis of natural products through intramolecular cyclizations and intermolecular couplings.<sup>68</sup> An interesting example of this comes from the

synthesis of (–)-esermethole by the Overman group (**Figure 35**).<sup>69</sup> The key step in this synthesis is the Mizoroki-Heck cyclization of the aryl iodide into an olefin. This reaction proceeds with selectivity of the 5-exo cyclization over the polarization of the acrylamide, which would lead to 6-endo cyclization. Deprotection of the silyl enol ether reveals the penultimate compound in the synthesis bearing a highly enantioenriched all-carbon quaternary center at the ring junction. Last, a reductive amination step afforded the target compound in good yield. This synthesis demonstrates the power of the Mizoroki-Heck reaction to convert simple starting materials into complex small molecules through the construction of pivotal C-C bonds.

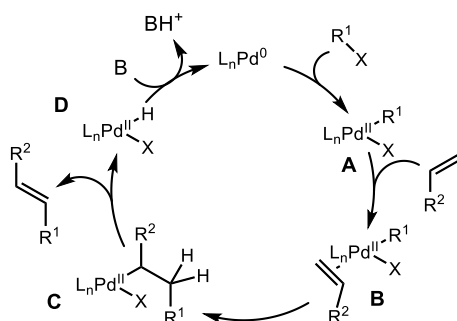


**Figure 35.** An asymmetric Mizoroki-Heck reaction in Overman’s synthesis of (–)-esermethole.

### 2.1.1 Cross-Couplings of Alkyl Electrophiles

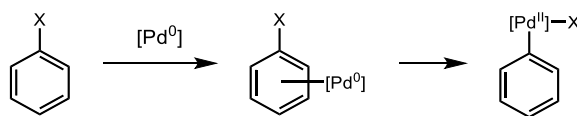
Traditionally, the scope of the Mizoroki-Heck reaction has been limited to  $\text{sp}^2$ -electrophiles, namely aryl and vinyl halides and pseudohalides. Discussing this limitation in detail first requires an examination of the reaction mechanism. Investigation of the mechanism has revealed a very detailed understanding of this reaction; however, herein we will look at a generalized reaction illustrated in **Figure 36**.<sup>70</sup> The reaction initiates with the oxidative addition

of the organic halide to the palladium(0) to form organometallic complex **A**. Next, an open coordination site is required to bind the olefin. Migratory insertion of the olefin into the Pd-C bond forms the new C-C bond (**C**). This complex next must undergo  $\beta$ -hydride elimination to form an olefin-bound hydridopalladium(II) complex. Reductive deprotonation of the hydridopalladium(II) complex reforms the active palladium(0) catalyst.



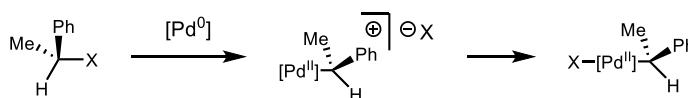
**Figure 36.** The proposed catalytic cycle for the Mizoroki-Heck reaction.

The competence of  $sp^2$ -electrophiles is due in part to the facile oxidative addition (**Figure 37**). This process begins with the coordination of the palladium to the  $\pi$ -system of the electrophile after which a three-center, concerted oxidative addition occurs.<sup>71</sup> Alkyl electrophiles do not benefit from the same precoordination with the metal center that aryl and vinyl electrophiles have, and therefore palladium complexes undergo oxidative addition with these electrophiles more slowly.



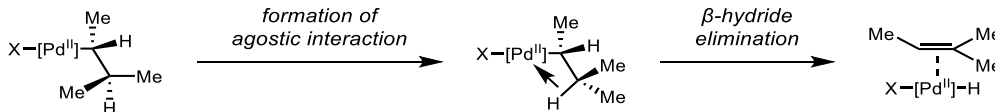
**Figure 37.** Oxidative addition of an aryl halide to Pd.

Alternatively, oxidative addition into the majority of alkyl electrophile is thought to occur through an  $S_N2$  process, in which the metal center acts as a nucleophile (**Figure 38**).<sup>72</sup> This two electron process occurs in the same way as the canonical substitution where electrons from the metal attack the  $\sigma^*$ -orbital of the C-X bond. This results in an inversion of stereochemistry, which has been demonstrated through the stereoinvertive carbonylation of  $d_1$ -benzyl bromide by the Stille group.<sup>73</sup>



**Figure 38.** Oxidative addition of an alkyl halide to Pd.

The success of the oxidative addition of an alkyl halide to a metal center results in an aliphatic organometallic complex. The major degradation pathway of these complexes is through a  $\beta$ -hydride elimination (**Figure 39**).<sup>74</sup> The process of  $\beta$ -hydride elimination requires an open coordination site on the metal, which is necessary for the formation of an agostic interaction with a  $\beta$ -hydrogen. This agostic interaction directly precedes a deinsertion of an olefin and produce a hydridopalladium complex.



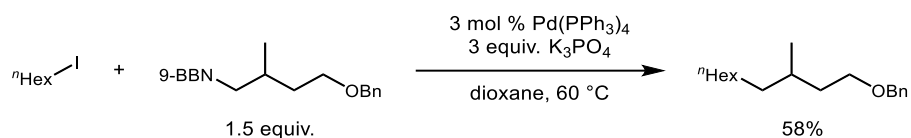
**Figure 39.** Reductive elimination from an aliphatic organopalladium complex.

Traditionally, the Mizoroki-Heck reaction requires an unsaturated coordination sphere to coordinate the olefin before migratory insertion can occur. This is contrary to the mechanism of other cross coupling reactions that use organometallic nucleophiles, which incorporate the nucleophile through a transmetallation process. During the transmetallation, an X-type ligand is exchanged for the carbon-based nucleophile, obviating the need for an open coordination site. Not only is this open coordination site required for bonding of the olefin, but it is also necessary for the  $\beta$ -hydride elimination following olefin migratory insertion. Therefore, efficient alkyl-Heck type cross coupling avoids  $\beta$ -hydride elimination before olefin insertion and then executing it after insertion of the olefin.

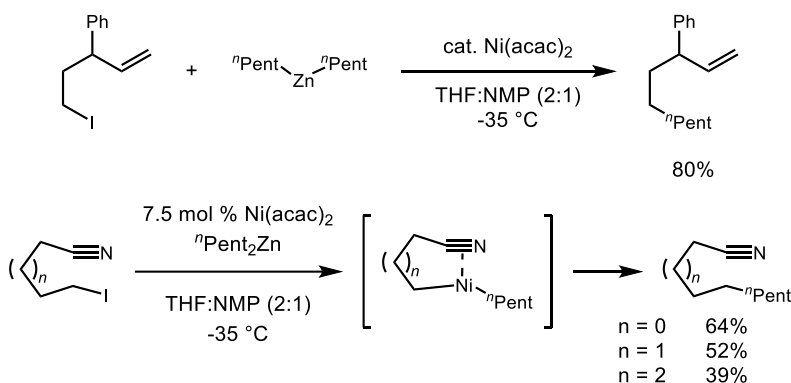
The competence of aryl and vinyl electrophiles can also be described through examination of the organometallic intermediates. Once an alkyl-palladium organometallic complex is formed it may undergo a facile  $\beta$ -hydride elimination. Conversely, aryl and vinyl ligands do not possess accessible  $\beta$ -hydrogens. Consequently, it was only recently that the viability of alkyl electrophiles in palladium-catalyzed cross couplings has been demonstrated despite the great potential use of these reactions in chemical synthesis.

Prior work has shown that these two major barriers to the use of  $sp^3$ -electrophiles can be overcome through tailoring of substrates. Slow oxidative addition can be accelerated through the introduction of activating groups to make the C-X bond more electrophilic. This manifests itself through the use of allylic<sup>75</sup> and benzylic electrophiles,<sup>76,77</sup> as well as  $\alpha$ -halocarbonyls.<sup>78</sup> Additionally,  $\beta$ -hydride elimination can be avoided through the use of electrophiles with no  $\beta$ -hydrogens<sup>79</sup> or inaccessible  $\beta$ -hydrogens,<sup>80</sup> namely substrates that do not possess the rotational freedom to adopt a syn-coplanar conformation. Despite these important works, the use of unactivated alkyl electrophiles remains a major challenge.

The first report of alkyl cross-couplings was disclosed by the Suzuki group in 1992, in which they were able to couple unactivated alkyl iodides with organoboranes using  $\text{Pd}(\text{PPh}_3)_4$  as a catalyst (**Figure 40**).<sup>81</sup> Unsurprisingly,  $\beta$ -hydride elimination was a major byproduct. In the late 1990s, the Knochel group reported a fascinating  $\text{sp}^3$ - $\text{sp}^3$  cross coupling reaction.<sup>82</sup> Their nickel catalyzed Negishi coupling of primary alkyl iodides with organozinc compounds proceeds in good yields, overcoming the potential dehydrohalogenation. Interestingly, each of the substrates includes an appended olefin or nitrile. Indeed, it was discovered that the position of this group is important to the yield of the reaction (**Figure 41**). It was postulated that the unsaturated appendage forms a chelate with the nickel catalyst upon oxidative addition. Interestingly, the use of palladium resulted in a reductive cyclization instead of the Negishi coupling.

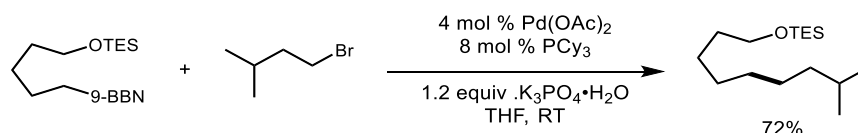


**Figure 40.** The first example of an alkyl-alkyl Suzuki-Miyaura coupling.



**Figure 41.** The use of chelation to effect an alkyl-alkyl Negishi coupling.

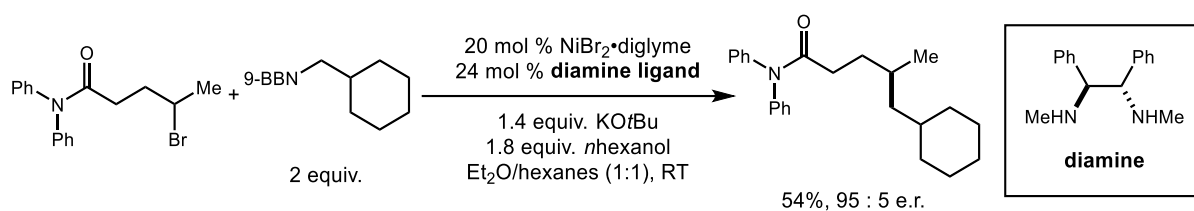
Following these reports, the turn of this century saw a veritable eruption of reports of alkyl cross couplings. Many reports in this field have come out of the Fu group, who first reported an improved alkyl-Suzuki reaction in 2001 using a palladium-phosphine catalyst system (**Figure 42**).<sup>83</sup> It was found that PCy<sub>3</sub> (cone angle: 179°) was crucial for efficient production of the coupled product. Only electron rich phosphine ligands produced coupling product, whereas no triarylphosphine ligands provided coupling product. Interestingly, the cone angle was also shown to be critical, as increasing the cone angle with P(<sup>t</sup>Bu)<sub>3</sub> (182°) and decreasing the cone angle with P(<sup>n</sup>Bu)<sub>3</sub> (136°) both produced mostly dehydrohalogenation products. Since then, the Fu group and others have demonstrated the ability of unactivated alkyl electrophiles to undergo a variety of cross couplings, including Hiyama,<sup>84</sup> Kumada,<sup>85</sup> Negishi,<sup>86,87</sup> Sonogashira,<sup>88</sup> Stille,<sup>89</sup> and additional Suzuki-Miyaura<sup>90</sup> couplings.



**Figure 42.** The use of bulky, electron rich phosphines to affect an alkyl-alkyl Suzuki-Miyaura coupling.

Previously, with sp<sup>2</sup>-electrophiles, enantioselective cross couplings were limited to the formation of atropisomers, desymmetrization and facial selectivity of the olefin in Mizoroki-Heck reactions.<sup>68</sup> The introduction of alkyl halides to pool of potential cross coupling electrophiles also introduces new possibilities for enantioselectivity in these reactions. The use of secondary and tertiary alkyl halides allows for the formation of chiral tertiary and quaternary centers at the electrophilic carbon.

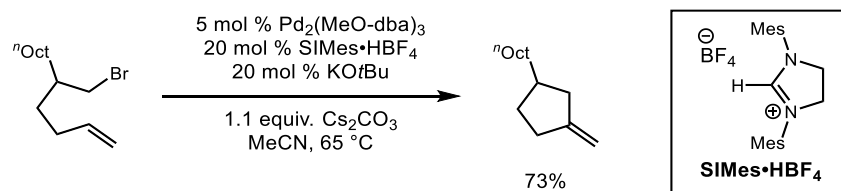
Recently, the Fu group has reported a number of enantioselective alkyl cross couplings.<sup>85,87,91–94</sup> Using an enantioenriched Ni-diamine catalysts with a number of activated and unactivated alkyl halides, several variants of asymmetric Suzuki-Miyaura reaction have been developed (**Figure 43**).<sup>95</sup> These reactions use strategic placement of directing groups to coordinate the nickel catalyst for enantioinduction. In addition, they have also developed variants of this reaction using other organometallic nucleophiles.



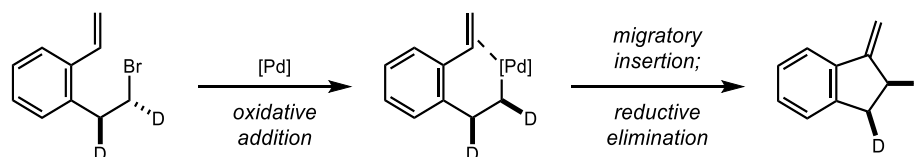
**Figure 43.** Nickel-diamine catalyzed asymmetric alkyl-Suzuki-Miyaura.

The first reported alkyl-Heck type reaction with unactivated electrophiles came from the Fu group in 2007 (**Figure 44**).<sup>96</sup> The use of a palladium-NHC catalyst resulted in the efficient cyclization of alkyl bromides and chlorides onto terminal olefins. Unfortunately, the substrate scope was limited to primary halides and terminal olefins. They proved that their reaction was proceeding via the canonical S<sub>N</sub>2 oxidative addition of the alkyl bromide through their use of deuterium labeled starting materials. It was observed that the stereocenter at the electrophilic center was inverted in the product (**Figure 45**).





**Figure 44.** Pd-NHC catalyzed alkyl-Heck cyclization of primary bromides.

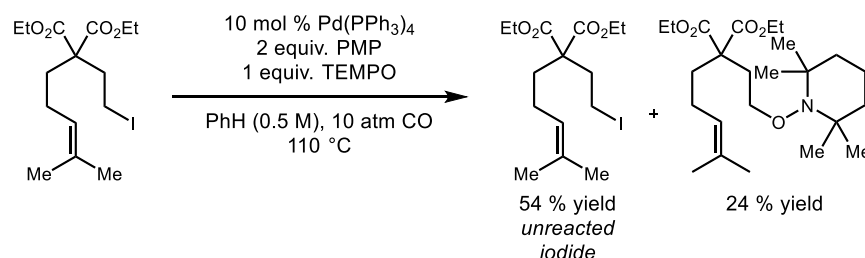


**Figure 45.** The  $S_N2$  oxidative addition of primary bromides as shown via isotopic labelling.

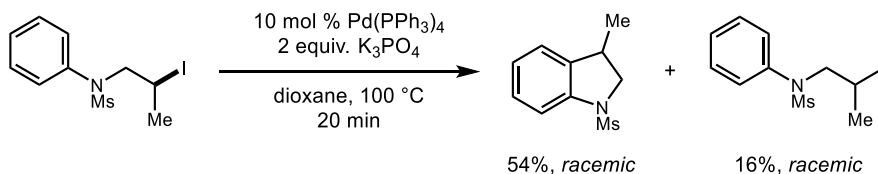
Our group has further demonstrated the utility of alkyl-Heck type reactions. In our seminal work, it was shown that alkyl iodides could be efficiently activated by palladium catalysis and in turn were able to cyclize into a tethered olefin.<sup>97</sup> The resulting cyclic and bicyclic compounds were formed in good yield. In addition to this work, we have developed an intermolecular variant.<sup>98</sup> Further, our lab has demonstrated the viability of cyclizing alkyl iodide into arene rings through palladium catalysis.<sup>99</sup>

Understanding how to improve this reactivity and make it more broadly applicable, mechanistic studies have been undertaken. An examination of these reactions with the addition of known radical trap TEMPO resulted in the observation of a TEMPO-adduct of the starting material after low conversion and no observed cyclization product (**Figure 46**). This indicated an intermediate where a carbon-centered radical is formed from the cleavage of the C-I bond. It is likely that this occurs through an initial single electron transfer (SET) from the palladium catalyst to the C-I bond. This forms a three-electron two center radical anion, which cleaves to form an alkyl radical and the iodide anion. Further evidence to support this idea can be found in

the arylation reaction (**Figure 47**). The introduction of an enantiopure iodide into the reaction provides racemic product, as well as a recovery of racemic starting material. If the reaction were to proceed through an  $S_N2$  mechanism, it would be expected that this stereocenter would be inverted. Rather, the stereocenter was racemized, suggesting a stereoablative, planar intermediate, like a carbocation or a carbon centered radical. Additionally, the recovery of racemic starting material suggests that, at least in the arylation reaction, C-I bond breaking might be reversible.



**Figure 46.** TEMPO-trapping study demonstrating the ability of Pd to activate alkyl halides through SET.



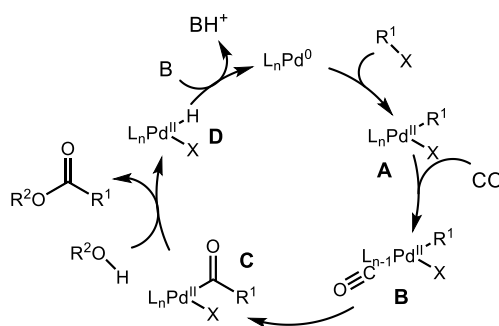
**Figure 47.** Racemization of enantioenriched iodides in Pd-catalyzed alkyl halide arylation.

### 2.1.2 Carbonylation of Organic Halides

Transition metal catalyzed carbonylations of organic molecules are industrially important processes for the synthesis of valuable carbonyl-containing small molecules. Carbon monoxide is the most important  $\text{C}_1$  building block in use today for the functionalization of chemical

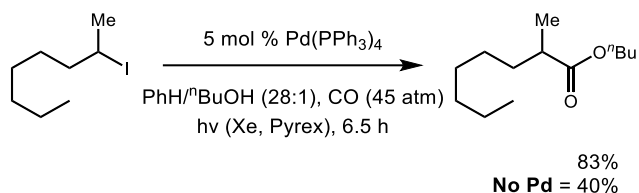
feedstocks.<sup>100</sup> Specifically, carbonylations of organic halides using transition metal catalysis have been used for the formation of aldehydes, amides, carboxylic acids, esters, and ketones.

Carbonylations of  $sp^2$ -halides are well preceded to occur under palladium-catalysis conditions.<sup>100</sup> These reactions are thought to proceed through a mechanism (**Figure 48**) that, similar to that of cross coupling reactions, begins with oxidative addition.<sup>101</sup> The difference is that after forming an organopalladium complex (**A**), carbon monoxide is inserted into the Pd-C bond and nucleophilic attack of the acyl-palladium complex form the desired product. The carbonylation of alkyl halides, however, is markedly less common.



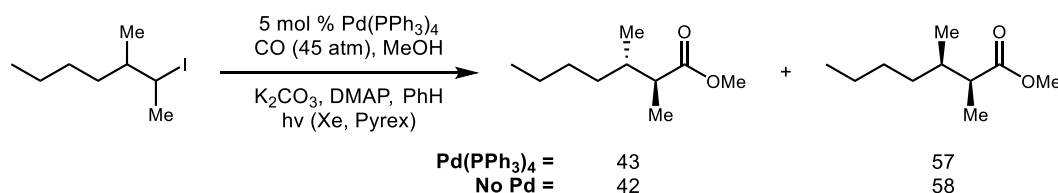
**Figure 48.** Proposed mechanism for the Pd-catalyzed carbonylation of organohalides.

The Ryu group has pioneered a new generation of palladium catalyzed carbonylation of alkyl halides through the use of visible light promotion.<sup>102</sup> Under their conditions, alkyl iodides were efficiently converted into the corresponding esters in good yield (**Figure 49**).<sup>103</sup> It is noteworthy that without the palladium catalyst, the reaction still proceeds, but in drastically lower yield. Interestingly, employing a catalyst with greater electron density on the metal center allowed for the formation of  $\alpha$ -ketoamides resulting from the double carbonylation of the alkyl iodide.<sup>104</sup>



**Figure 49.** The carbonylation of alkyl iodides using light promoted Pd-catalysis.

It is likewise believed that these reactions go through an alkyl radical intermediate, and the role of palladium in the reaction is as of now unclear. It was shown that under these conditions, the presence of palladium did not affect the diastereomeric ratios of the products, as nearly identical results were observed in the purely light promoted reaction (**Figure 50**).



**Figure 50.** The diastereoselectivity of Pd-catalyzed and metal-free carbonylation of alkyl iodides.

In addition to this work, the Ryu group has demonstrated a variety of carbonylative cross coupling reactions, including a carbonylative Sonogashira coupling to form alkynyl ketones,<sup>105</sup> a carbonylative Suzuki-Miyaura coupling to form aryl ketones,<sup>106</sup> and a tandem carbonylative alkyl-Heck-carbonylation for form  $\gamma$ -ketoesters.<sup>107</sup> This impressive portfolio demonstrates the potential that the palladium catalyzed carbonylations hold; however, the requirement of light and high pressures of carbon monoxide are problematic. Specifically, most high pressure reaction equipment is constructed of opaque steel, and the transparent, thick-walled glass reaction vessels typically only tolerate up to 10 atm of pressure. Therefore, this chemistry must be performed

using highly specialized equipment that can be impractical both on an industrial and laboratory scale.

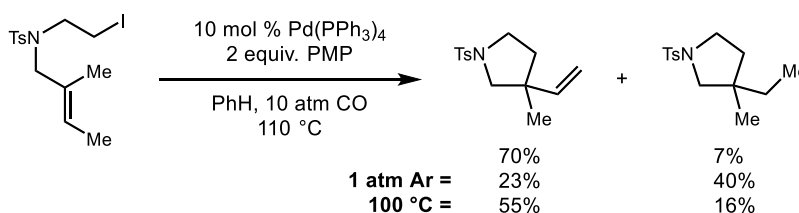
In addition to our alkyl-Heck cyclization, we propose that the stereoablative nature of SET activation of alkyl halides can lead to the asymmetric formation of a C-C bond through carbonylation. We hypothesize that this can be accomplished through the use of palladium complexes with enantioenriched ligands. Given the ambiguity of the role of palladium in these reactions. At very high pressures of carbon monoxide (45 atm), it is possible that palladium is not involved in the reaction after initiation, thus leading to the results seen in **Figure 50**. We therefore set out to investigate the carbonylation of alkyl iodides further with the aim of developing reactions for the formation of enantioenriched carbonyl compounds with lower pressures of carbon monoxide in section 2.3.

## 2.2 Palladium-catalyzed cyclization of alkyl halides

The cyclization of alkyl halides has been previously investigated with former group member Dr. Kayla Bloome and the current efforts are based off of this work.<sup>108</sup> The ongoing research into this reaction has been performed with Alexander Venning.

### 2.2.1 Cyclizations of alkyl iodides

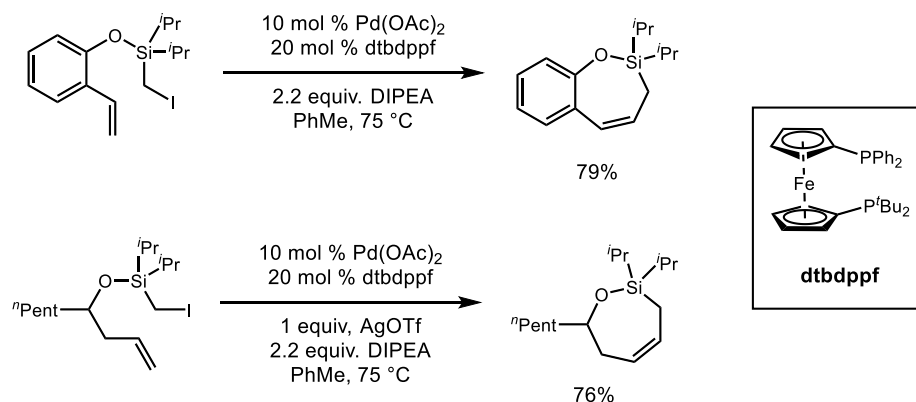
In our prior work on the alkyl-Heck type cyclization of alkyl iodides, a large dependence on carbon monoxide pressure was observed. A primary iodide bearing a trisubstituted olefin was shown to efficiently undergo a Heck-type cyclization to form a pyrrolidinoid product with the use of a palladium(0) catalyst at elevated temperatures under 10 atm of carbon monoxide (**Figure 51**). Replacing the carbon monoxide with 1 atm of an inert gas, argon, resulted in a greatly lowered yield of cyclized product and a large increase in a reductive cyclization product. Additionally, a decrease in reaction temperature of only 10 °C also resulted in a lowered yield and a more than doubling of reductive cyclization product.



**Figure 51.** The dependence on CO pressure of our prior work in alkyl iodide cyclization.

The utility of this methodology is diminished by the harshness of the conditions; therefore, we have set out to optimize this chemistry. The use of high pressure of carbon monoxide for reactions in which it is not incorporated makes the method less practical due to the requirement

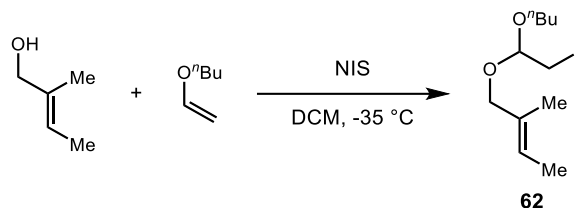
of specialty glassware. Additionally, using reaction temperatures reaching 110 °C limits its efficiency and substrate scope through the degradation of starting materials and products. A report out of the Gevorgyan group demonstrated a similar transformation with Heck-type cyclization of alkyl iodides (**Figure 52**).<sup>109</sup> The catalyst system was quite different from our prior work, using a one-to-two ratio of metal to ligand, dtbdppf. This report demonstrated the reactivity of two distinct classes of substrates: styrenyl substrates that tether to the iodide through the aromatic ring and olefins that are connected through aliphatic tethers. The use of an equivalent of AgOTf was found to be optimal for the cyclization of the aliphatic-tethered iodides.



**Figure 52.** The cyclization of silyl-methyl alkyl iodides under Pd-catalysis.

The success of dtbdppf in Gevorgyan's alkyl-Heck type cyclizations prompted us to examine this ligand in our chemistry (**Table 15**). We chose iodide **62** for our studies due to its facile, scalable synthesis from commercially available starting materials in one step (**Figure 53**). Further, once cyclized it only produces one alkene isomer, thus simplifying the identification and quantification of products. It was observed that the reaction did not proceed at a good rate at 75

°C. However, at 100 °C more product than starting material was observed. Notably, at both temperatures the addition of AgOTf slowed the reaction considerably. This is noteworthy because Gevorgyan's report shows this additive was required for unactivated olefins. With complete conversion observed, further optimization was undertaken.



**Figure 53.** Synthesis of primary iodide starting material.

**Table 15.** Cyclization of alkyl iodides using Pd-dtbdppf catalyst systems.



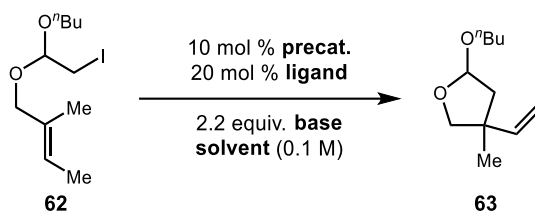
entry	additive	temp (°C)	ratio <sup>a</sup> 62:63
1	-	75	1 : 2
2	1 equiv. AgOTf	75	1 : 7.5
3	-	100	> 19 : 1
4	1 equiv. AgOTf	100	1.9 : 1
<sup>a</sup> Ratio determined by <sup>1</sup> H NMR spectroscopy.			

Our optimization studies began with a screen of bisphosphinoferrocene ligands (**Table 16**). This began with the use of the more common dppf, which led to no conversion of starting material. Switching to the successful dtbdppf ligand resulted in a 70% yield of the desired product with a 86 : 14 d.r., a comparable result to our prior work (**Figure 55**). The use of more



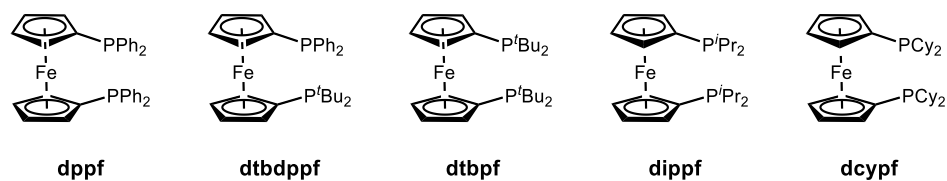
electron rich ligand dtbpf resulted in complete conversion but no observed product. Interestingly, the use of other bisalkylphosphinoferrocene ligands, dcypf and dippf, resulted in no conversion of starting materials. With a clear optimal ligand in hand, further optimization proceeded. A screen of bases revealed that Hunig's base performed better than similarly bulky amine bases and an inorganic phosphate base. Reaction concentration was next investigated, switching from 0.1 M to 0.25 M resulted in a slight decrease in yield. At this new concentration, the more polarized PhCF<sub>3</sub> resulted in an increase in yield, as did 1,4-dioxane. DMF, a very polar solvent, resulted in lower yields. A breakthrough came with the use of [Pd(allyl)Cl]<sub>2</sub> as a precatalyst, which led to a 83% yield.

**Table 16.** Optimization of Pd-catalyzed primary iodide cyclization.

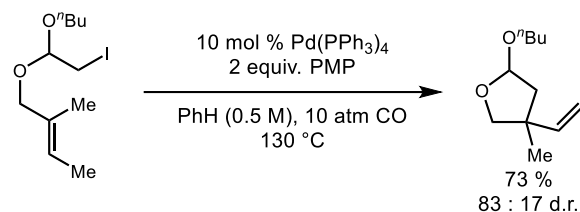


entry	precatalyst	ligand	Base	Solvent	Yield <sup>a</sup> 63 (%)
1	Pd(OAc) <sub>2</sub>	dppf	DIPEA	PhMe	n.r.
2	Pd(OAc) <sub>2</sub>	dtbdppf	DIPEA	PhMe	70
3	Pd(OAc) <sub>2</sub>	dtbpf	DIPEA	PhMe	0
4	Pd(OAc) <sub>2</sub>	dippf	DIPEA	PhMe	n.r.
5	Pd(OAc) <sub>2</sub>	dcypf	DIPEA	PhMe	n.r.
6	Pd(OAc) <sub>2</sub>	dtbdppf	Cy <sub>2</sub> NMe	PhMe	29
7	Pd(OAc) <sub>2</sub>	dtbdppf	PMP	PhMe	27
8	Pd(OAc) <sub>2</sub>	dtbdppf	K <sub>3</sub> PO <sub>4</sub>	PhMe	53
9 <sup>b</sup>	Pd(OAc) <sub>2</sub>	dtbdppf	DIPEA	PhMe	63
10 <sup>b</sup>	Pd(OAc) <sub>2</sub>	dtbdppf	DIPEA	PhCF <sub>3</sub>	71
11 <sup>b</sup>	Pd(OAc) <sub>2</sub>	dtbdppf	DIPEA	Dioxane	71
12 <sup>b</sup>	Pd(OAc) <sub>2</sub>	dtbdppf	DIPEA	DMF	54
13 <sup>b</sup>	[Pd(allyl)Cl] <sub>2</sub>	dtbdppf	DIPEA	PhMe	83

<sup>a</sup>Yield determined by <sup>1</sup>H NMR spectroscopy. <sup>b</sup>0.25 M.



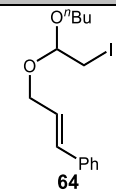
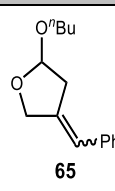
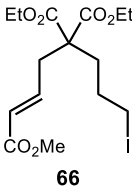
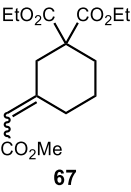
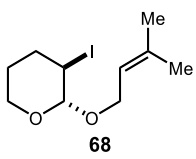
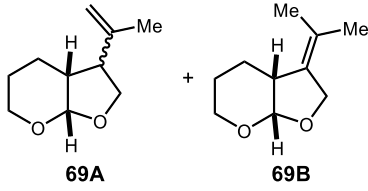
**Figure 54.** Bisphosphinoferrocene ligands.

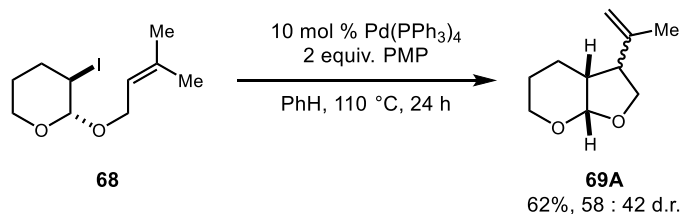


**Figure 55.** Prior published result for the cyclization of **62** under CO pressure.

Concurrent with our optimization studies, a small substrate scope (**Table 17**) was performed using the conditions from entry 2. It was found that styrenyl iodide **64** was converted to cyclized product in a synthetically relevant yield. The use of acrylate iodide **66** underwent a challenging 6-exo cyclization to form cyclohexanoid product **67**. Additionally, secondary iodide **68** was converted into bicyclic compounds **69A** and **69B** in higher yield than with our prior conditions (**Figure 56**). Further expansion of the substrate scope is necessary, but we have already shown that these new conditions can affect the cyclization of a variety of alkyl iodide substrates efficiently.

**Table 17.** The application our Pd-dtbdppf system to diverse alkyl iodides.

entry <sup>b</sup>	iodide	product	yield <sup>b</sup> (%)
1	 <b>64</b>	 <b>65</b>	44%
2	 <b>66</b>	 <b>67</b>	47%
3	 <b>68</b>	 <b>69A</b> + <b>69B</b>	86% (97 : 3)
<sup>a</sup> Reaction conditions: 1 equiv. iodide, 10 mol % Pd(OAc) <sub>2</sub> , 20 mol % dtbdppf, 2 equiv. DIPEA, PhMe (0.1 M), 100 °C. <sup>b</sup> Yield determined by <sup>1</sup> H NMR spectroscopy.			

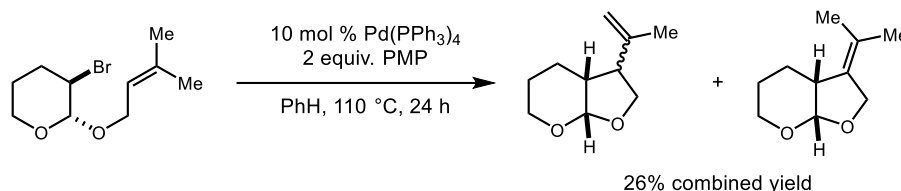


**Figure 56.** Alkyl-Heck type cyclization of **68** using Pd(PPh<sub>3</sub>)<sub>4</sub>.

## 2.2.2 Cyclizations of alkyl bromides

The success of dtbdppf with primary alkyl iodide substrates prompted an examination of the electron poor alkyl bromides with the previously untested ligands. In our prior work, alkyl bromides were difficult substrates (**Figure 57**). The reduction of C-I bond is more facile than the

C-Br bond. Therefore, assuming this reaction initiates with SET from the metal, alkyl bromides should be more challenging substrates and primary alkyl bromides should be particularly challenging.



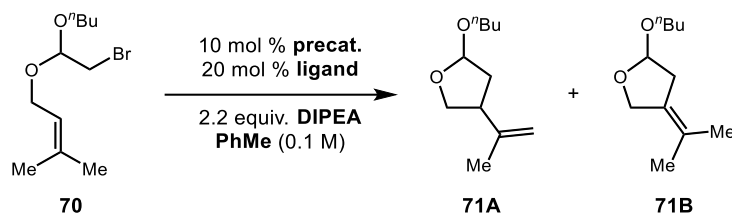
**Figure 57.** Prior result for the cyclization of alkyl bromides.

Our investigation of alkyl bromides was performed using primary bromide **70** (Table 18), which is easily synthesized in a halo-etherification reaction as mentioned previously. Our investigation began with the conditions that were successful for primary iodides, using the uniquely successful ligand dtbdppf. Unfortunately, the reaction only proceeded with modest conversion and provided a low yield of our desired cyclization product. The use of  $\text{Pd}(\text{PPh}_3)_4$  led to lower conversions with no observed product. Using a precatalyst that is known to more efficiently produce palladium(0),  $[\text{Pd}(\text{allyl})\text{Cl}]_2$ , with dtbdppf led to similar results as with  $\text{Pd}(\text{OAc})_2$ . The use of the strong  $\sigma$ -donating ligand, IMes, resulted in low conversion and no observed product.

Moving forward we decided to investigate bisphosphinoferrocene ligands that were even more electron rich than dtbdppf. This started with the investigation of dtbpf, which produces a 30% yield at nearly half conversion after 24 h. Extending the reaction time to 48 h resulted in higher conversion and proportionally higher yield. Emboldened by these results, we decided to investigate similar ligands. Unfortunately, neither the use of dippf nor dcypf resulted in any observed product. Identifying dtbpf as the optimal ligand, we then attempted to hasten the

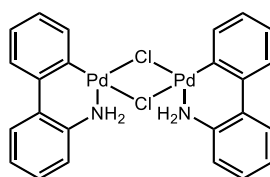
reaction through using different precatalysts. Using a palladium dimer invented by the Buchwald group (**Figure 58**), a slightly higher conversion and yield were observed. Further, using  $[\text{Pd}(\text{allyl})\text{Cl}]_2$ , near complete conversion was observed with a combined yield of 70% of the combined isomers.

**Table 18.** Optimization of alkyl bromide cyclization reaction.



entry	precat. (10 mol %)	ligand (20 mol %)	time (h)	conv. (%)	yield <sup>a</sup> 71A (%)	yield <sup>a</sup> 71B (%)
1	$\text{Pd}(\text{OAc})_2$	dtbdppf	24	34	5	-
2	$\text{Pd}(\text{PPh}_3)_4$	-	24	16	-	-
3	$[\text{Pd}(\text{allyl})\text{Cl}]_2$	dtbdppf	24	29	7	-
4	$[\text{Pd}(\text{allyl})\text{Cl}]_2$	IMes	24	15	-	-
5	$\text{Pd}(\text{OAc})_2$	dtbpf	24	47	30	3
6	$\text{Pd}(\text{OAc})_2$	dtbpf	48	75	44	15
7	$\text{Pd}(\text{OAc})_2$	dippf	48	25	-	-
8	$\text{Pd}(\text{OAc})_2$	dcypf	48	29	-	-
9	Buchwald's dimer	dtbpf	48	80	50	n.d.
10	$[\text{Pd}(\text{allyl})\text{Cl}]_2$	dtbpf	48	96	58	12

<sup>a</sup>Yield determined by  $^1\text{H}$  NMR spectroscopy.



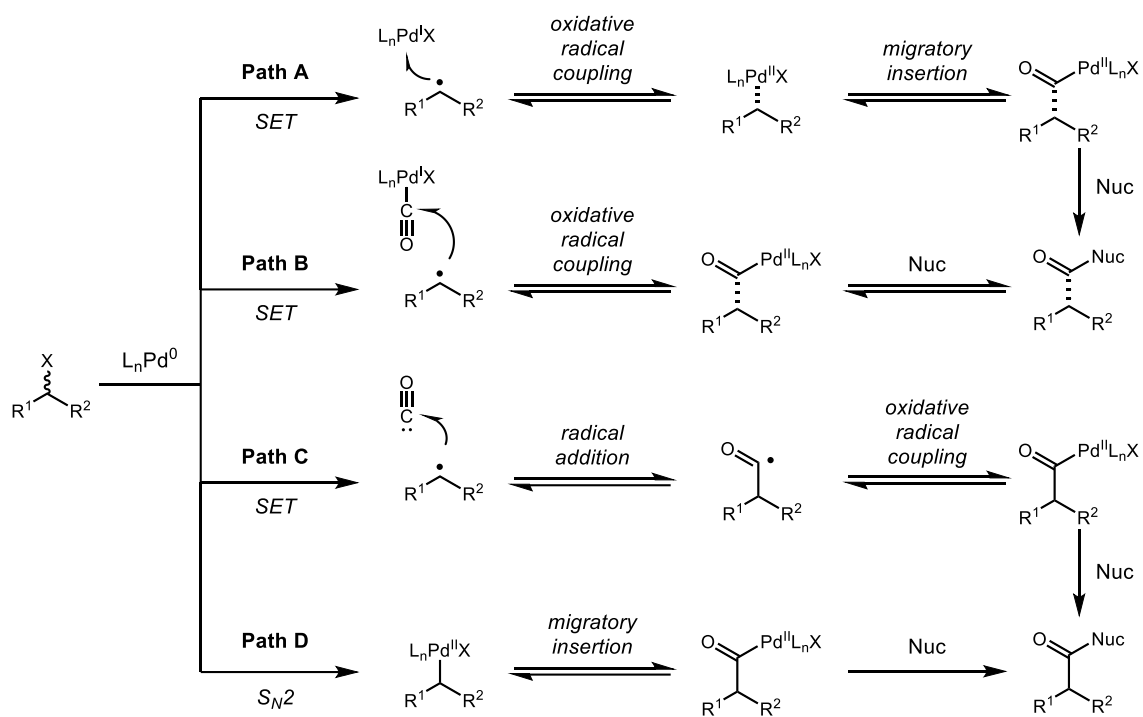
**Figure 58.** Buchwald's precatalyst dimer.

## 2.3 Palladium-catalyzed carbonylation of alkyl halides

The enantioselective carbonylation of alkyl halides has been investigated with former group member, Dr. Kayla Bloome.<sup>108</sup> The ongoing research into this reaction has been performed alongside racemic studies of the same reaction investigated by Brendon Sargent.

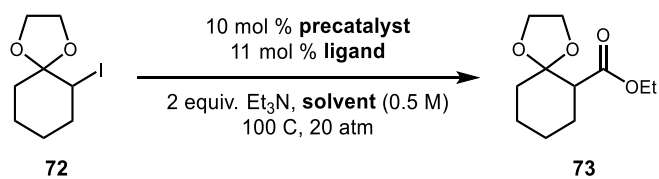
Single electron transfer to alkyl halides represents an interesting avenue for enantioselective reactivity. The formation of a carbon-centered radical is a stereoablative process. Therefore, we hypothesize that using chiral palladium catalysts for the carbonylation of alkyl halides can result in the formation of enantioenriched  $\alpha$ -stereogenic carbonyl compounds.

We suggest that this reaction could proceed through one or more of four possible pathways (**Figure 59**). If the initiation of the reaction does produce an alkyl radical, then interaction with the palladium complex before or during carbonylation (Path A and B, respectively) is essential for stereoiduction. If the radical carbonylates from free carbon monoxide in solution, it is highly unlikely any enantioenrichment will be seen in the products. The amount of carbon monoxide in solution is highly dependent on the pressure of the reaction. Additionally, the stereoinvertive nature of  $S_N2$  oxidative addition will result in a racemic product should the reaction go to completion. However, should one enantiomer of the alkyl halide react faster than the other, it is possible that this could produce a kinetic resolution.



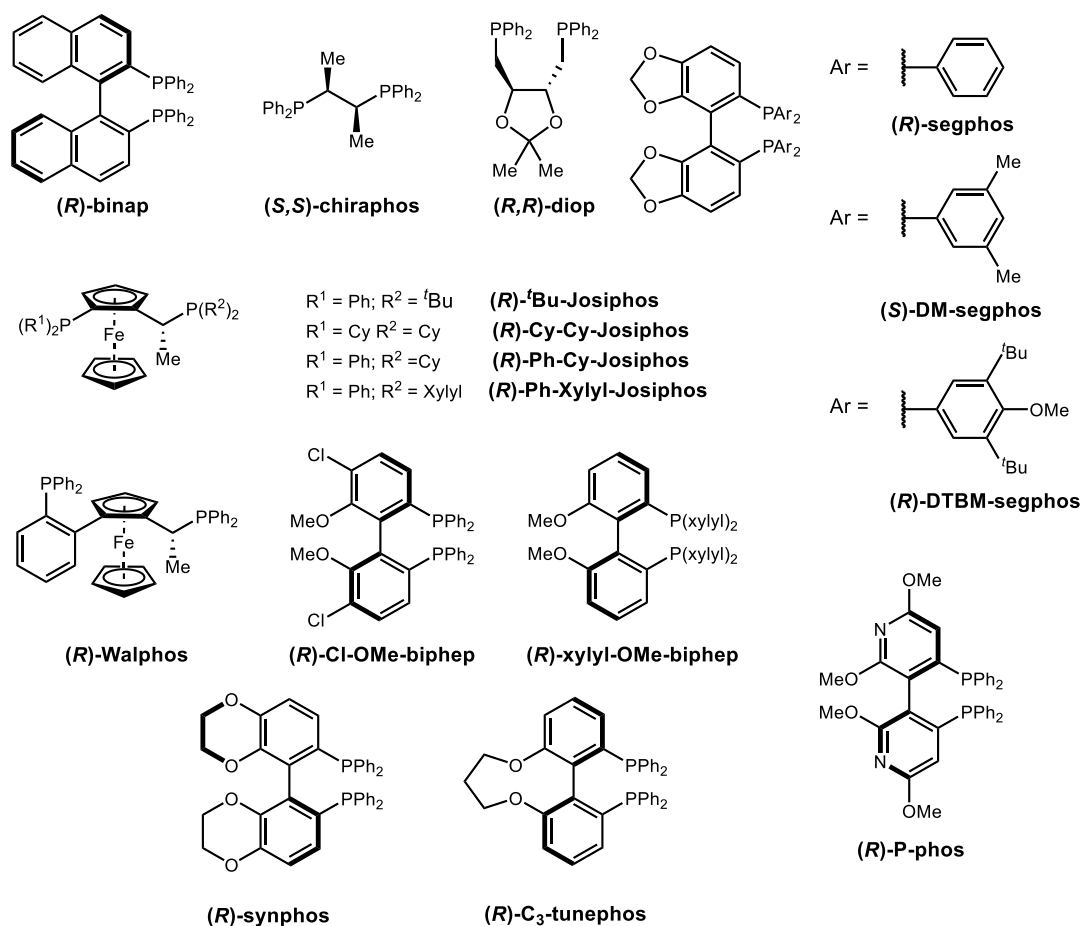
**Figure 59.** Plausible reaction pathways for the carbonylation of alkyl halides.

**Table 19.** Asymmetric carbonylation of cyclic secondary iodide **72**.



entry	precatalyst	ligand	Solvent (1:1)	e.r.
1	Pd(OAc) <sub>2</sub>	( <i>R</i> )-binap	PhH : EtOH	50 : 50
2	Pd(OAc) <sub>2</sub>	( <i>S,S</i> )-chiraphos	PhH : EtOH	50 : 50
3	Pd(OAc) <sub>2</sub>	( <i>R,R</i> )-diop	PhH : EtOH	50 : 50
4	Pd(OAc) <sub>2</sub>	( <i>R</i> )-segphos	PhH : EtOH	50 : 50
5	Pd(OAc) <sub>2</sub>	( <i>S</i> )-DM-segphos	PhH : EtOH	60.5 : 39.5
6	Pd(OAc) <sub>2</sub>	( <i>R</i> )-DTMB-segphos	PhH : EtOH	55 : 45
7	Pd(OAc) <sub>2</sub>	( <i>R</i> )- <sup>t</sup> Bu-Josiphos	PhH : EtOH	57.5 : 42.5
8	Pd(OAc) <sub>2</sub>	( <i>R</i> )-Cy-Cy-Josiphos	PhH : EtOH	50 : 50
9	Pd(OAc) <sub>2</sub>	( <i>R</i> )-Ph-Cy-Josiphos	PhH : EtOH	50 : 50
10	Pd(OAc) <sub>2</sub>	( <i>R</i> )-Ph-xylyl-Josiphos	PhH : EtOH	50 : 50
11	Pd(OAc) <sub>2</sub>	( <i>R</i> )-Walpos	PhH : EtOH	50 : 50
12	Pd(OAc) <sub>2</sub>	( <i>R</i> )-Cl-OMe-biphep	PhH : EtOH	53.5 : 46.5
13	Pd(OAc) <sub>2</sub>	( <i>R</i> )-Xylyl-OMe-biphep	PhH : EtOH	55 : 45
14	Pd(OAc) <sub>2</sub>	( <i>R</i> )-Synphos	PhH : EtOH	52.5 : 47.5
15	Pd(OAc) <sub>2</sub>	( <i>R</i> )-C <sub>3</sub> -tunephos	PhH : EtOH	50.5 : 49.5
16	Pd(OAc) <sub>2</sub>	( <i>R</i> )-P-phos	PhH : EtOH	52 : 48
17	Pd(OAc) <sub>2</sub>	( <i>R</i> )-DM-segphos	C <sub>6</sub> F <sub>6</sub> : EtOH	52.5 : 47.5
18	Pd(OAc) <sub>2</sub>	( <i>R</i> )-DM-segphos	PhCF <sub>3</sub> : EtOH	50 : 50
19	[Pd(allyl)Cl] <sub>2</sub>	( <i>R</i> )-DM-segphos	PhH : EtOH	50.5 : 49.5
20	PdCl <sub>2</sub>	( <i>R</i> )-DM-segphos	PhH : EtOH	51 : 49
21	[Pd(MeCN) <sub>4</sub> ](BF <sub>4</sub> ) <sub>2</sub>	( <i>R</i> )-DM-segphos	PhH : EtOH	57.5 : 42.5
22	Pd(OAc) <sub>2</sub>	( <i>R</i> )-DM-segphos	PhH : EtOH	57 : 43
23	[Pd(MeCN) <sub>4</sub> ](BF <sub>4</sub> ) <sub>2</sub>	( <i>R</i> )-DM-segphos	PhH : EtOH	55 : 45
24	Pd <sub>2</sub> (dba) <sub>3</sub>	( <i>R</i> )-DM-segphos	PhH : EtOH	50 : 50





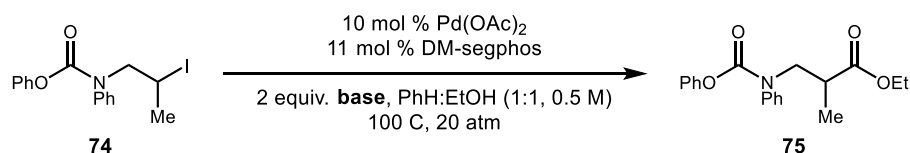
**Figure 60.** Ligands used in the asymmetric carbonylation of alkyl iodides.

Our efforts towards an enantioselective carbonylation of alkyl iodides started with the carbonylation of cyclic iodide **72** (**Table 19**). It was hoped that the  $\alpha$ -acetal group would provide sufficient steric differentiation to interact with the chiral catalyst. We initially targeted palladium complexes bisphosphine ligands (**Figure 60**) due to the vast number of commercially available. Unfortunately, most of the ligands gave near racemic products (entries 1-16). However, the ligand DM-segphos performed markedly better than most other ligands and therefore was selected for further optimization. It was found that both solvent (entries 17-18) and precatalyst (entries 19-21) played a role in the enantioselectivity of the reaction; however, no improved results were observed.

Lastly, doubling the amount of ligand used slightly lowered the enantioenrichment of the resulting esters.

In addition to our work with steric selectivity, we attempted to use a carbamate as a directing group for the carbonylation of iodide **74**. First, we set to find some optimal conditions using as our standard conditions did not provide sufficient yield of the desired ester (**Table 20**). We found that DIPEA was proficient and moved forward using it in our asymmetric reactions. It was found that Pd/segphos and Pd/binap catalysts produce modest enantioenrichment in the formation of **75**. Additionally, to investigate if perhaps ligand coordination was not occurring in full, a premade Pd/binap catalyst was applied to the reaction. This resulted in only an insignificant increase in enantioselectivity. Nevertheless, we have here demonstrated the proof of concept that enantioenriched esters can be products through the carbonylation of alkyl iodides with palladium catalysts.

**Table 20.** The effect of base on yield of the carbonylation of alkyl iodide **74**.

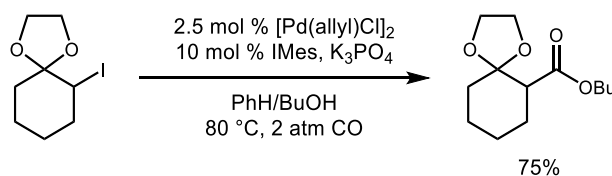


entry	base	yield <sup>a</sup> (%)
1	Et <sub>3</sub> N	40
2	PMP	54
3	DIPEA	61
<sup>a</sup> Yield determined by <sup>1</sup> H NMR spectroscopy.		

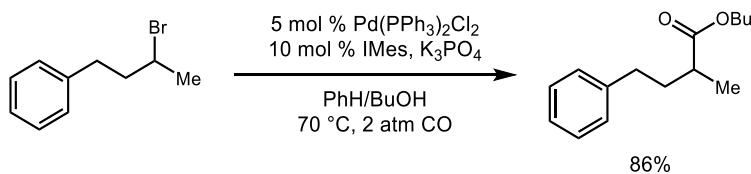
**Table 21.** The asymmetric carbonylation of secondary iodides bearing a carbamate directing group.

entry	precatalyst	ligand	e.r.
1	Pd(OAc) <sub>2</sub>	( <i>R</i> )-DM-Segphos	55 : 45
2	Pd(OAc) <sub>2</sub>	( <i>R</i> )-binap	54 : 46
3	Pd(binap)Cl <sub>2</sub>	-	57 : 43

Efforts are ongoing in our group to optimize the racemic variant of this reaction. We hypothesize that the high pressure of carbon monoxide used in these studies might lead to an increased frequency of carbonylation of free carbon monoxide (**Figure 59**, Path C). Further, high temperatures commonly decrease the enantioselectivity of a reaction. Therefore, the ongoing efforts are aimed at creating a milder environment for the reaction. More recently, we have achieved a low temperature, low pressure carbonylation reaction using a Pd/NHC catalyst system (**Figure 61** and **Figure 62**). This has the additional benefit of opening up a new class of chiral ligands to be explored. Future efforts will begin with these new conditions and take advantage of known chiral NHC ligands.



**Figure 61.** Improved catalyst system for the carbonylation of cyclic iodides.



**Figure 62.** The carbonylation of secondary alkyl bromides under mild conditions.

## 2.4 Summary

In closing, we have improved upon the conditions of our prior work on the Heck cyclizations of alkyl iodides. These new conditions avoid the use of the high pressure of a carbon monoxide atmosphere, which were previously required for cyclization of primary iodides. Our new conditions involve the use of a unique bisphosphine ligand, dtbdppf. Using Pd-complexes of this ligand, we were able to demonstrate the efficient cyclization of styrenyl iodides and secondary alkyl iodides, as well as demonstrate the 6-exo cyclization onto activated alkenes. Additionally, our study of electron rich bisphosphinoferrocenes led to the development of a Pd-dtbdppf catalyst system for the cyclization of alkyl bromides. Future work will examine the scope of alkyl-Heck type cyclizations using these new conditions.

This work has been accompanied by the development of asymmetric carbonylations of racemic alkyl iodides. We proposed that using enantioenriched Pd-bisphosphine complexes, alkyl iodides could be converted into enantioenriched esters. We have demonstrated that low levels of enantioenrichment can be seen using substrates tailored to examine both steric selectivity and directing group-based selectivity. This serves as our proof of concept for further studies. Through our work in carbonylations using achiral or racemic ligands, we have determined that Pd-NHC complex can catalyze these reactions at low pressures and temperatures. Future work will, therefore, investigate the use of chiral NHC ligands for our asymmetric carbonylation reactions.

## CHAPTER 3:Appendix

### 3.1 General Methods

Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. HPLC spectra were obtained using an Agilent 1200 series HPLC with detection at 210, 230, 250 and 254 nm using a Chiralpak IC column using a flow rate of 1mL per minute. The solvent system used for HPLC resolution of enantiomers was hexanes (A1) and isopropanol (B2) unless stated otherwise. Proton and carbon magnetic resonance spectra ( $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR) were recorded on a Bruker model DRX 400 ( $^1\text{H}$  NMR 400 MHz) or a Bruker AVANCE III 600 CryoProbe ( $^1\text{H}$  NMR 600 MHz,  $^{13}\text{C}$  NMR at 150 MHz) spectrometer with solvent resonance as the internal standard for proton and carbon ( $^1\text{H}$  NMR:  $\text{CDCl}_3$  at 7.26 ppm;  $^{13}\text{C}$  NMR:  $\text{CDCl}_3$  at 77.16 ppm). Multiplicity data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization unless otherwise noted ( $\dagger$  = GC/MS analysis was performed with an Agilent G4350A GC/MSD system containing a 7820A GC with an HP-5MS column (length 30m; I. D. 0.250 mm) connected to an Agilent 5975 MSD or  $\ddagger$  = LC/MS analysis was performed with a PerkinElmer Flexar SQ 300 LC/MS system with elution of MeOH and  $\text{H}_2\text{O}$  through an agilent Eclipse Plus C18 column). Thin layer chromatography (TLC) was performed on SiliaPlate 250  $\mu\text{m}$  thick silica gel plates purchased from Silicycle. Visualization was accomplished with short wave UV light (254 nm), aqueous basic

potassium permanganate solution, or ethanolic acidic *p*-anisaldehyde solution followed by heating. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63  $\mu\text{m}$ ) or SiliaFlash T60 silica gel (5-20  $\mu\text{m}$ ) purchased from Silicycle. Tetrahydrofuran, toluene, and acetonitrile were dried by passage through a column of activated neutral alumina under nitrogen prior to use. Toluene was also sparged with Argon for a minimum of two hours prior to storage in a glove box. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted. Absolute configuration was not determined for any of the compounds.

## 3.2 Experimental Procedures and Analytical Data for Chapter 1.

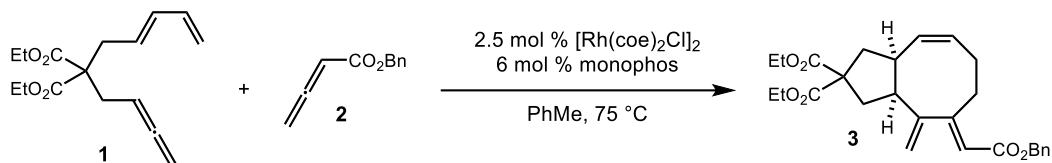
The following compounds were made according to literature procedures: **2**,<sup>110</sup> **6**,<sup>111</sup> **8**,<sup>112</sup> **9**,<sup>113</sup> **10**,<sup>113</sup> **14**,<sup>111</sup> **18**,<sup>114</sup> **50**.<sup>115</sup> **12** was purchased from Sigma-Aldrich and used without purification. **46** (stabilized with BHT) was purchased from Alfa Aesar and used without purification. Allenes **4** and **48** were prepared by Andrew Brusoe and can be found in his thesis.<sup>116</sup> Buta-3,4-dienylmalonate was prepared according to literature procedure.<sup>117</sup>

### 3.2.1 Rh-Catalyzed [4 + 2 + 2] Cycloaddition Procedures and Analytical Data

**General Procedure A:** A solution of [Rh(coe)<sub>2</sub>Cl]<sub>2</sub> (0.0022 mmol, 2.5 mol%) in toluene (0.7 mL) was added to Ligand (0.0053 mmol, 6 mol%) in an oven dried vial under inert atmosphere and stirred for 30 minutes. To this catalyst solution was added a solution of substrate (0.088 mmol, 1 equiv) and allene (0.18 mmol, 2 equiv) in toluene (1.4 mL). Reaction was sealed and heated. The reaction was cooled to room temperature, filtered through celite (EtOAc rinse), and concentrated. The reaction was purified using flash chromatography with EtOAc and hexanes.

**General Procedure B:** To a bulk solution of [Rh(coe)<sub>2</sub>Cl]<sub>2</sub> (0.0022 mmol, 2.5 mol%) in toluene (0.7 mL) in an oven dried vial was added triethyl phosphite (0.06 equiv). The catalyst mixture was stirred for 30 min. Allene in toluene (0.7 mL) transferred to substrate in an oven dried vial with a rinse of toluene (0.7 mL). To the solution of allene and substrate was added 0.7 mL of the catalyst solution. The reaction was then heated and stirred. The reaction was cooled to room temperature, filtered through celite and concentrated. The reaction was then purified with flash chromatography with EtOAc and hexanes.

**[4 + 2 + 2] Cycloaddition forming 3.**



0.088 mmol scale: Reaction performed according to General Procedure A with 24.5 mg (0.0880 mmol) of diene-allene **1** and 30.7 mg (0.176 mmol, 2 equiv) of allene **2**. After 2.5 hours, the reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cyclooctanoid **3** was isolated as a colorless oil massing 27.8 mg (0.0614 mmol, 70%).

0.5 mmol scale: Reaction performed according to General Procedure B with 139 mg (0.500 mmol) of diene-allene **1** and 174 mg (1.00 mmol, 2 equiv) of allene **2**. After 72 hours, the reaction was purified with a gradient flash chromatography from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cyclooctanoid **3** was isolated as a colorless oil massing 168 mg (0.370 mmol, 75%).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.40-7.32 (m, 5H), 5.76-5.69 (m, 1H), 5.69 (s, 1H), 5.30 (ddd,  $J = 10.8, 8.8, 1.3$  Hz, 1H), 5.16 (s, 2H), 4.86 (d,  $J = 1.3$  Hz, 1H), 4.81 (d,  $J = 1.8$  Hz, 1H), 4.26-4.18 (m, 4H), 3.75-3.71 (m, 1H), 3.27 (q,  $J = 7.2$  Hz, 1H), 2.79 (dt,  $J = 12.8, 6.2$  Hz, 1H), 2.53 (dd,  $J = 14.3, 7.3$  Hz, 1H), 2.42-2.26 (m, 3H), 2.17-2.02 (m, 3H), 1.71 (s, 3H), 1.27 (t,  $J = 7.2$  Hz, 3H), 1.26 (t,  $J = 7.2$  Hz, 3H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 192.90, 172.67, 166.38, 165.70, 151.91, 136.30, 132.99, 130.58, 128.68, 128.37, 128.28, 115.19, 111.93, 65.88, 61.76, 61.74, 58.91, 52.03, 39.74, 39.10, 35.69, 34.52, 27.67, 14.19. **LRMS**: Calc: 452.22, Found: 453.42 [M+H]. **IR**: 2980.5, 2934.2, 1727.9,



1645.0, 1616.1, 1449.2, 1367.3, 1253.5, 1157.1, 1099.2, 1026.9, 1002.8, 901.6, 870.7, 746.3, 698.1.

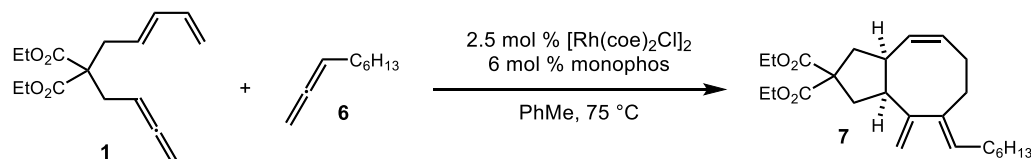
**[4 + 2 + 2] Cycloaddition forming 5.**



Reaction performed according to General Procedure A with 24.5 mg (0.0880 mmol) of diene-allene **1** and 36.3 mg (85% in ether, 0.176 mmol) of allene **4**. After 72 hours at 75 °C, the reaction was purified with a gradient pipette column from 1.25% EtOAc in hexanes to 2.5% EtOAc in hexanes. Cyclooctanoid **5** was isolated as a colorless oil 9.8 mg (0.022 mmol, 25%).

**$^1\text{H}$  NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.32-7.28 (m, 2H), 7.22-7.20 (m, 3H), 5.90 (s, 1H), 5.69 (q,  $J = 8.6$  Hz, 1H), 5.29 (t,  $J = 9.7$  Hz, 1H), 4.86 (s, 1H), 4.77 (s, 1H), 4.21 (q,  $J = 6.9$  Hz, 4H), 3.73 (td,  $J = 6.4, 2.8$  Hz, 2H), 3.27 (q,  $J = 7.0$  Hz, 1H), 2.86 (dt,  $J = 12.4, 4.4$  Hz, 1H), 2.72 (t,  $J = 7.7$  Hz, 3H), 2.56 (dd,  $J = 14.1, 7.3$  Hz, 1H), 2.38 (dd,  $J = 13.0, 5.8$  Hz, 1H), 2.32 (d,  $J = 14.2$  Hz, 1H), 2.18-2.05 (m, 3H), 1.99-1.89 (m, 3H), 1.27 (t,  $J = 7.1$  Hz, 6H).

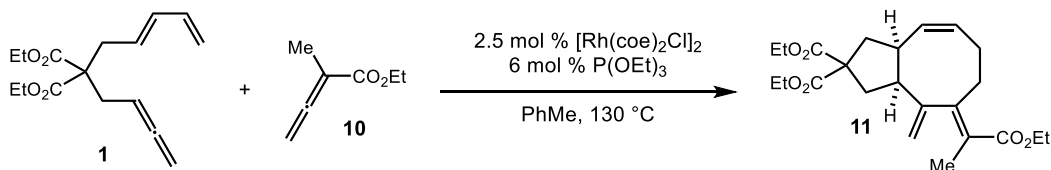
**[4 + 2 + 2] Cycloaddition forming 7.**



Reaction performed according to General Procedure A with 24.5 mg (0.0880 mmol) of diene-allene **1** and 21.9 mg (0.176 mmol) of allene **6**. After 1 h 10 min at 75 °C, the reaction was purified with a gradient pipette column from 1.25% EtOAc in hexanes to 2.5% EtOAc in hexanes. Cyclooctanoid **7** was isolated as a colorless oil 15.6 mg (0.0320 mmol, 44%).

**<sup>1</sup>H NMR** (600 MHz, CHLOROFORM-*d*)  $\delta$  ppm 5.72-5.67 (m, 1H), 5.29 (ddd,  $J$  = 10.7, 9.1, 1.5 Hz, 1H), 5.15 (t,  $J$  = 7.3 Hz, 1H), 4.73 (s, 1H), 4.67 (s, 1H), 4.23-4.17 (m, 4H), 3.10 (q,  $J$  = 7.3, 1H), 2.80 (dt,  $J$  = 12.9, 6.2 Hz, 1H), 2.65 (ddd,  $J$  = 12.5, 5.7, 2.0 Hz, 1H), 2.53 (dd,  $J$  = 14.1, 7.2 Hz, 1H), 2.37 (dd,  $J$  = 12.8, 5.9 Hz, 1H), 2.33 (d,  $J$  = 14.3 Hz, 1H), 2.16-2.11 (m, 1H), 2.08-1.96 (m, 3H), 1.90-1.86 (m, 1H), 1.38-1.22 (m, 18H), 0.90-0.88 (m, 3H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 172.99, 172.72, 153.46, 142.99, 132.99, 130.39, 125.52, 110.03, 61.47, 61.45, 59.04, 53.67, 39.81, 38.96, 35.65, 32.59, 31.72, 29.83, 29.05, 27.77, 27.34, 22.62, 14.05, 14.03. **LRMS**: Calc: 402.28, Found: 403.43 [M+H]. **IR**: 2926.5, 2856.1, 1731.8, 1448.3, 1367.3, 1251.6, 1176.4, 1104.1, 1063.6, 1029.8, 891.0, 863.0, 755.0, 720.3.

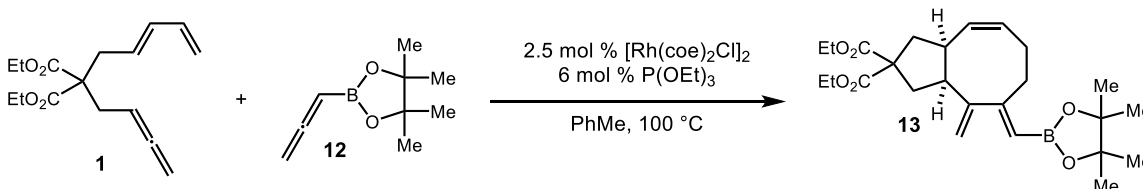
**[4 + 2 + 2] Cycloaddition forming 11.**



Reaction performed according to General Procedure B with 24.5 mg (0.0880 mmol) of diene-allene **1** and 22.2 mg (0.176 mmol) of allene **10**. After 72 hours at 130 °C, the reaction was purified with a gradient pipette column from 5% EtOAc in hexanes to 10% EtOAc in hexanes. Cyclooctanoid **11** was isolated as a colorless oil 14.1 mg (0.0349 mmol, 40%).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 5.74 (q,  $J$  = 9.1 Hz, 1H), 5.33 (t,  $J$  = 9.7 Hz, 1H), 4.91 (s, 1H), 4.83 (s, 1H), 4.28-4.14 (m, 4H), 3.11 (q,  $J$  = 7.1 Hz, 1H), 3.04-2.99 (m, 1H), 2.80 (dt,  $J$  = 12.8, 6.2 Hz, 1H), 2.51 (dd,  $J$  = 14.4, 7.1 Hz, 1H), 2.44-2.35 (m, 2H), 2.32-2.08 (m, 3H), 1.86 (t,  $J$  = 12.5 Hz, 1H), 1.82 (s, 3H), 1.31 (t,  $J$  = 7.1 Hz, 3H), 1.27 (t,  $J$  = 7.1 Hz, 3H), 1.26 (t,  $J$  = 7.1 Hz, 3H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 173.01, 172.76, 170.15, 151.32, 151.23, 132.95, 130.95, 124.19, 112.47, 61.732, 61.70, 60.47, 58.72, 50.95, 39.53, 39.25, 37.25, 35.63, 27.12, 16.84, 16.82, 14.42, 14.19. **LRMS**: Calc: 404.22, Found: 405.37 [M+H]. **IR**: 2980.5, 2931.3, 2868.6, 1729.8, 1447.3, 1256.4, 1177.3, 1137.8, 1100.2, 1066.4, 899.3, 862.0.

**[4 + 2 + 2] Cycloaddition forming 13.**

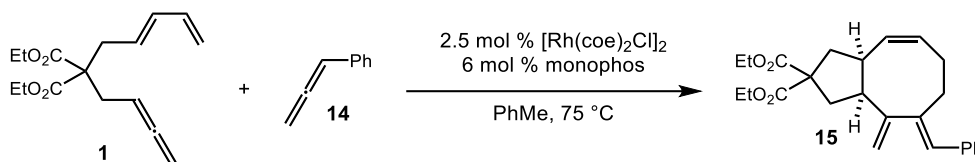


Reaction performed according to General Procedure B with 24.5 mg (0.0880 mmol) of diene-allene **1** and 32  $\mu$ L (0.176 mmol) of allene **12**. After 24 hours at 100 °C, the reaction was purified with a gradient pipette column from 1.25% EtOAc in hexanes to 2.5% EtOAc in hexanes. Cyclooctanoid **13** was isolated as a colorless oil 18.2 mg (0.0410 mmol, 47%).

**<sup>1</sup>H NMR** (600 MHz, CHLOROFORM-*d*)  $\delta$  ppm 5.71 (dd,  $J$  = 10.6, 1.5 Hz, 1H), 5.29 (ddd,  $J$  = 10.6, 9.2, 1.5 Hz, 1H), 5.10 (s, 1H), 4.75 (s, 1H), 4.65 (s, 1H), 4.23-4.18 (m, 4H), 3.21 (ddd,  $J$  = 11.3, 5.6, 1.8 Hz, 1H), 3.05 (q,  $J$  = 7.3 Hz, 1H), 2.85 (dt,  $J$  = 12.9, 6.2 Hz, 1H), 2.53 (dd,  $J$  = 14.5, 7.2 Hz, 1H), 2.38 (dd,  $J$  = 13.0, 5.7 Hz, 1H), 2.32 (d,  $J$  = 14.3 Hz, 1H), 2.25-2.20 (m, 1H), 2.07-1.95 (m, 3H), 1.28-1.25 (m, 18H). **<sup>13</sup>C NMR** (151MHz,

CHLOROFORM-*d*)  $\delta$  ppm 172.90, 168.73, 154.60, 133.23, 130.61, 109.25, 82.98, 61.64, 61.63, 59.19, 52.08, 39.78, 39.04, 37.45, 35.59, 28.98, 25.12, 24.99, 24.78, 14.19. **LRMS:** Calc: 444.27, Found: 445.40 [M+H]. **IR:** 2978.5, 2930.3, 1730.8, 1609.3, 1447.3, 1364.4, 1318.1, 1253.5, 1145.5, 1107.9, 970.0, 851.4.

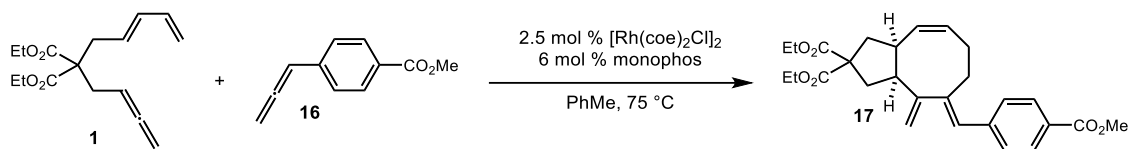
**[4 + 2 + 2] Cycloaddition forming 15.**



Reaction performed according to General Procedure B with 24.5 mg (0.0880 mmol) of diene-allene **1** and 20.4 mg (0.176 mmol) of allene **14**. After 4.5 hours at 75 °C, the reaction was purified with a gradient pipette column from 1.25% EtOAc in hexanes to 2.5% EtOAc in hexanes. Cyclooctanoid **15** was isolated as an inseparable mixture with **15-DA** as a colorless oil 17.1 mg (0.0410 mmol, 47%).

**<sup>1</sup>H NMR** (600 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.38-7.32 (m, 2H), 7.28-7.21 (m, 3H), 6.28 (s, 1H), 5.77 (q,  $J$  = 9.9 Hz, 1H), 5.37 (t,  $J$  = 8.9 Hz, 1H), 4.88 (s, 1H), 4.80 (s, 1H), 4.25-4.17 (m, 4H), 3.25 (q,  $J$  = 7.4 Hz, 1H), 2.94-2.89 (m, 2H), 2.58 (dd,  $J$  = 14.3, 7.3 Hz, 1H), 2.46 (dd,  $J$  = 12.8, 5.3 Hz, 1H), 2.39 (dd,  $J$  = 14.3, 1.3 Hz, 1H), 2.29-2.24 (m, 2H), 2.13 (t,  $J$  = 13.2 Hz, 1H), 2.10-2.03 (m, 1H), 1.29 (t,  $J$  = 7.2 Hz, 3H), 1.28 (t,  $J$  = 7.2 Hz, 3H).

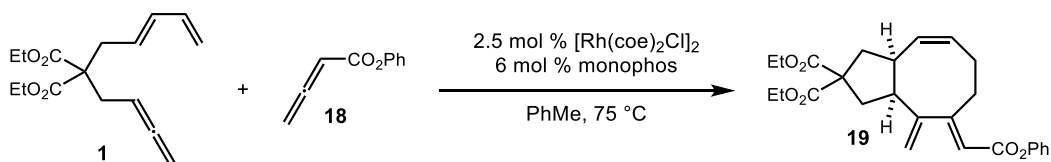
**[4 + 2 + 2] Cycloaddition forming 17.**



Reaction performed according to General Procedure B with 24.5 mg (0.0880 mmol) of diene-allene **1** and 30.7 mg (0.176 mmol) of allene **16**. After 72 hours, the reaction was purified with a gradient pipette column from 1.25% EtOAc in hexanes to 2.5% EtOAc in hexanes. Cyclooctanoid **17** was isolated as a colorless oil 31.1 mg (0.687 mmol, 78%).

**<sup>1</sup>H NMR** (600 MHz, CHLOROFORM-*d*)  $\delta$  ppm 8.00 (d,  $J$  = 8.4 Hz, 2H), 7.29 (d,  $J$  = 8.1 Hz, 2H), 6.28 (s, 1H), 5.75 (dtd,  $J$  = 7.3, 5.1, 0.7 Hz, 1H), 5.37 (dd,  $J$  = 6.8, 6.4 Hz, 1H), 4.88 (s, 1H), 4.81 (s, 1H), 4.27-4.18 (m, 4H), 3.92 (s, 3H), 3.22 (q,  $J$  = 7.3 Hz, 1H), 2.93-2.85 (m, 2H), 2.57 (dd,  $J$  = 14.3, 7.3 Hz, 1H), 2.44 (dd,  $J$  = 13.0, 5.7 Hz, 1H), 2.39 (d,  $J$  = 14.3 Hz, 1H), 2.28-2.24 (m, 2H), 2.12 (t,  $J$  = 13.0 Hz, 1H), 2.09-2.04 (m, 1H), 1.27 (t,  $J$  = 7.2 Hz, 3H), 1.27 (t,  $J$  = 7.2 Hz, 3H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 173.01, 172.77, 167.08, 153.03, 148.52, 142.55, 133.41, 130.02, 129.67, 128.76, 128.09, 124.93, 111.02, 61.71, 61.70, 59.02, 53.39, 52.17, 39.84, 39.17, 35.89, 33.51, 27.72, 14.32, 14.18. **LRMS**: Calc: 452.22, Found: 453.36 [M+H]. **IR**: 2930.3, 2861.8, 1727.9, 1606.4, 1439.6, 1277.6, 1179.3, 1107.9, 1060.7, 1020.2, 890.0, 762.7, 738.6, 707.7.

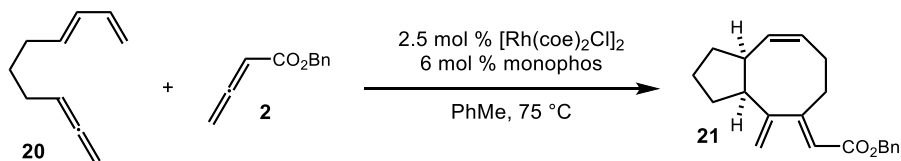
**[4 + 2 + 2] Cycloaddition forming 19.**



Reaction performed according to General Procedure B with 24.5 mg (0.0880 mmol) of diene-allene **1** and 28.2 mg (0.176 mmol) of allene **16**. After 72 hours at 60 °C, the reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cyclooctanoid **19** was isolated as a colorless oil 26.0 mg (0.0593 mmol, 67%).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.41 (t,  $J$  = 8.0 Hz, 2H), 7.25 (t,  $J$  = 8.0 Hz, 1H), 7.15 (d,  $J$  = 8.0 Hz, 2H), 5.90 (s, 1H), 5.80-5.73 (m, 1H), 5.34 (t,  $J$  = 10 Hz, 1H), 4.95 (d,  $J$  = 1 Hz, 1H), 4.90 (d,  $J$  = 1.6 Hz, 1H), 4.25 (q,  $J$  = 7.1 Hz, 4H), 3.78 (dd,  $J$  = 9.4, 6.3 Hz, 1H), 2.96 (q,  $J$  = 7.2 Hz, 1H), 2.93-2.86 (m, 1H), 2.60 (dd,  $J$  = 14.4, 7.2 Hz, 1H), 2.47 (dd,  $J$  = 14.4, 7.2 Hz, 1H), 2.41 (d,  $J$  = 14.4 Hz), 2.36-2.29 (m, 1H), 2.23-2.09 (m, 3H), 1.30 (t,  $J$  = 1.30 Hz, 3H), 1.30 (t,  $J$  = 1.30 Hz, 3H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 172.8, 172.5, 168.0, 164.8, 151.7, 150.6, 132.9, 130.5, 129.4, 125.7, 121.7, 114.4, 112.1, 61.7, 61.7, 58.8, 51.8, 39.6, 39.0, 35.6, 34.7, 27.0, 14.1.

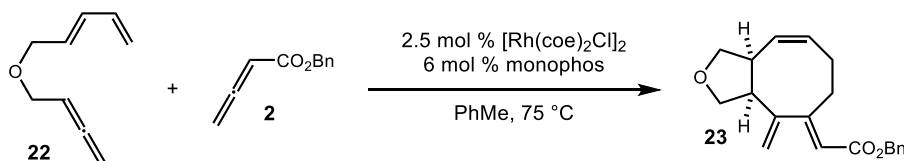
**[4 + 2 + 2] Cycloaddition forming 21.**



Reaction performed according to General Procedure A with 11.8 mg (0.0880 mmol) of diene-allene **20** and 30.7 mg (0.176 mmol, 2 equiv) of allene **2**. After 2.25 hr at 75 °C, the reaction was purified with a gradient pipette column from 1.25% EtOAc in hexanes to 2.5% EtOAc in hexanes. Cyclooctanoid **21** was isolated as a colorless oil 20.4 mg (0.0662 mmol, 75%).

**<sup>1</sup>H NMR** (600 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.41-7.32 (m, 5H), 5.72-5.68 (m, 1H), 5.69 (s, 1H), 5.26-5.22 (m, 1H), 5.17 (d,  $J = 12.5$  Hz, 1H), 5.15 (d,  $J = 12.5$  Hz, 1H), 4.83 (s, 1H), 4.81 (s, 1H), 3.71 (ddd,  $J = 11.3, 6.0, 1.8$  Hz, 1H), 2.97 (q,  $J = 7.1$  Hz, 1H), 2.60 (dt,  $J = 11.9, 6.1$  Hz, 1H), 2.28 (dddd,  $J = 13.6, 7.9, 5.9, 2.4$  Hz, 1H), 2.22-2.17 (m, 1H), 2.14-2.09 (m, 1H), 1.77-1.69 (m, 1H), 1.64-1.59 (m, 1H), 1.53-1.45 (m, 1H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 166.89, 166.57, 153.67, 136.41, 134.40, 129.44, 128.68, 128.37, 128.26, 114.76, 111.11, 65.82, 532.19, 39.95, 34.60, 31.08, 27.31, 26.49, 22.61. **LRMS**: Calc: 308.18, Found: 331.41<sup>+</sup> [M+Na]. **IR**: 2949.6, 2870.5, 1714.4, 1615.1, 1451.2, 1377.9, 1280.5, 1160.0, 999.9, 874.6, 745.4, 698.1.

**[4 + 2 + 2] Cycloaddition forming 23.**

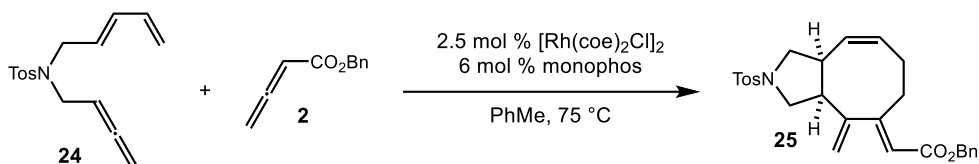


Reaction performed according to General Procedure A with 13.5 mg (0.0880 mmol) of diene-allene **22** and 30.7 mg (0.176 mmol, 2 equiv) of allene **2**. After 1.5 hours 75 °C, the reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cyclooctanoid **5** was isolated as a colorless oil massing 19.0 mg (0.0612 mmol, 70%).

**<sup>1</sup>H NMR** (600 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.41-7.34 (m, 5H), 5.86-5.82 (m, 1H), 5.72 (s, 1H), 5.41 (ddd,  $J = 10.3, 9.0, 0.9$  Hz, 1H), 5.17 (s, 2H), 4.91 (d,  $J = 1.5$  Hz, 1H), 4.68 (d,  $J = 1.8$  Hz, 1H), 3.99-3.96 (m, 2H), 3.85 (dd,  $J = 8.4, 0.7$  Hz, 1H), 3.72 (dd,  $J = 9.4, 6.4$  Hz, 1H), 3.68 (dd,  $J = 10.6, 8.1$  Hz, 1H), 3.19-3.16 (m, 1H), 3.08-3.03 (m, 1H), 2.37-2.32 (m,

1H), 2.21-2.15 (m, 2H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*) δ ppm 166.33, 165.21, 149.20, 136.23, 131.56, 131.21, 128.73, 128.42, 128.36, 115.67, 112.57, 74.10, 68.13, 66.00, 51.62, 40.66, 33.89, 27.37. **LRMS**: Calc: 310.16, Found: 311.24 [M+H]. **IR**: 2926.5, 2865.7, 1714.4, 1617.0, 1452.1, 1158.0 1072.2, 1009.6, 897.7, 741.5, 698.1.

**[4 + 2 + 2] Cycloaddition forming 25.**

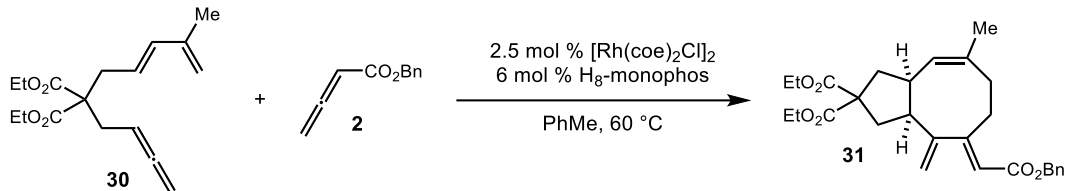


Reaction performed according to General Procedure A with 25.4 mg (0.0880 mmol) of diene-allene **24** and 30.7 mg (0.176 mmol, 2 equiv) of allene **2**. After 2.5 hours 75 °C, the reaction was purified with a gradient pipette column from 5% EtOAc in hexanes to 10% EtOAc in hexanes. Cyclooctanoid **25** was isolated as a colorless solid 23.9 mg (0.0516 mmol, 59%).

**<sup>1</sup>H NMR** (600 MHz, CHLOROFORM-*d*) δ ppm 7.75 (d, *J* = 8.3Hz), 7.38-7.31 (m, 7H), 5.75-5.69 (m, 1H), 5.60 (s, 1H), 5.14 (s, 2H), 4.94-4.89 (m, 1H), 4.86 (d, *J* = 1.7 Hz, 1H), 4.69 (d, *J* = 2.0 Hz, 1H), 3.69 (dd, *J* = 9.8, 5.9 Hz, 1H), 3.51 (dd, *J* = 9.5, 7.3 Hz, 1H), 3.37 (d, *J* = 3.2 Hz, 2H), 3.14 (dd, *J* = 11.0, 9.8 Hz, 1H), 3.07-3.05 (m, 1H), 2.78-2.72 (m, 1H), 2.45 (s, 3H), 2.32-2.26 (m, 1H), 2.11-1.98 (m, 2H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*) δ ppm 165.99, 164.24, 148.95, 143.68, 136.02, 134.13, 131.98, 129.93, 129.64, 128.71, 128.44, 128.40, 18.32, 127.46, 115.83, 113.05, 66.04, 53.26, 50.00, 47.95, 39.11, 34.34, 27.14, 21.69. **LRMS**: Calc: 463.18, Found: 464.28 [M+H]. **IR**: 2925.5, 2858.0, 1713.4, 1617.0, 1453.1, 1346.1, 1160.0, 1039.4, 1015.3, 905.4, 877.5, 810.9, 738.6, 701.0, 699.2, 585.3, 547.7.



**[4 + 2 + 2] Cycloaddition forming **31**.**



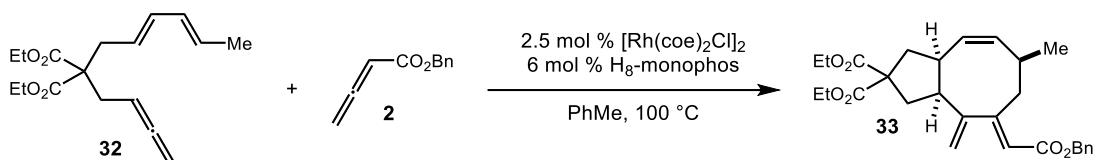
Racemic ( $L = (\pm)$ -Monophos): reaction performed according to General Procedure A with 25.7 mg (0.0880 mmol) of diene-allene **30** and 30.7 mg (0.176 mmol, 2 equiv) allene **2**. After 24 hours at  $60\text{ }^\circ\text{C}$ , reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cycloadduct **31** was isolated as a colorless oil 20.0 mg (0.0429 mmol, 49%). The fraction eluting before the product were combined and concentrated. Trimethoxybenzene (3.0 mg, 0.018 mmol) was added as an internal NMR standard, indicating 0.025 mmol (28%) of [4+2] cycloadduct.

Asymmetric ( $L = (S)$ - $\text{H}_8$ -Monophos): reaction performed according to General Procedure A with 25.7 mg (0.0880 mmol) of diene-allene **30** and 30.7 mg (0.176 mmol, 2 equiv) allene **2**. After 72 hours at  $60\text{ }^\circ\text{C}$ , reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cycloadduct **31** was isolated as a colorless oil 24.7 mg (0.0529 mmol, 60%). The fraction eluting before the product were combined and concentrated. Trimethoxybenzene (1.2 mg, 0.0071 mmol) was added as an internal NMR standard, indicating 0.020 mmol (23%) of [4+2] cycloadduct.

**$^1\text{H}$  NMR** (600 MHz,  $\text{CHLOROFORM-}d$ )  $\delta$  ppm 7.40-7.32 (m, 5H), 5.67 (s, 1H), 5.16 (s, 2H), 5.04 (d,  $J = 8.4\text{ Hz}$ , 1H), 4.80 (s, 1H), 4.78 (s, 1H), 4.27-4.18 (m, 4H), 3.71 (dd,  $J = 11.0, 5.1\text{ Hz}$ , 1H), 2.96 (q,  $J = 7.3\text{ Hz}$ , 1H), 2.76-2.72 (m, 1H), 2.52 (dd,  $J = 14.3, 7.3\text{ Hz}$ , 1H), 2.36 (dd,  $J = 13.0, 5.7\text{ Hz}$ , 1H), 2.33-2.27 (m, 2H), 2.14-2.05 (m, 3H), 1.71 (s, 3H), 1.27 (t,  $J = 7.0\text{ Hz}$ , 3H), 1.26 (t,  $J = 7.0\text{ Hz}$ , 3H).  **$^{13}\text{C}$  NMR** (151MHz,  $\text{CHLOROFORM-}d$ )  $\delta$  ppm 172.98,

172.73, 166.41, 165.78, 152.05, 138.09, 136.30, 128.67, 128.34, 128.26, 126.66, 115.09, 111.53, 65.84, 61.71, 58.87, 52.27, 40.21, 39.32, 35.74, 33.27, 32.35, 24.86, 14.19. **LRMS:** Calc: 466.24, Found: 467.37 [M+H]. **IR:** 2931.3, 1727.9, 1616.1, 1445.4, 1368.3, 1252.5, 1160.0, 1094.4, 1004.7, 873.6, 737.6, 698.1. **HPLC:** Chiralpak IC, 99:1 Hexanes/IPA, er 85:15.

**[4 + 2 + 2] Cycloaddition forming 33.**



Reaction performed according to General Procedure B with 25.7 mg (0.0880 mmol) of diene-allene **32** and 30.7 mg (0.176 mmol) of allene **2**. After 72 hours 100 °C, the reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cyclooctanoid **33** was isolated as a colorless oil 22.4 mg (0.0480 mmol, 55%).

**<sup>1</sup>H NMR** (600 MHz, CHLOROFORM-*d*) δ ppm 7.40-7.31 (m, 5H), 5.36 (ddd, *J* = 10.8, 7.4, 1.4 Hz, 1H), 5.25-5.19 (m, 1H), 5.16 (s, 2H), 4.84 (d, *J* = 1.0 Hz, 1H), 4.82 (d, *J* = 1.5 Hz, 1H), 4.26-4.18 (m, 4H), 3.55 (dd, *J* = 11.1, 1.8 Hz, 1H), 3.05 (m, 1H), 2.81 (dt, *J* = 12.8, 6.2 Hz, 1H), 2.52 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.44-2.33 (m, 3H), 2.06 (t, *J* = 13.1 Hz, 1H), 1.95 (t, *J* = 11.3 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*) δ ppm 172.76, 172.54, 166.27, 164.58, 151.74, 137.53, 136.11, 130.79, 128.55, 128.25, 128.15, 115.28, 111.59, 65.76, 61.61, 61.59, 58.83, 52.62, 43.12, 40.20, 38.86, 35.54, 33.52, 22.56, 14.04. **LRMS:** Calc: 466.24, Found:

467.37 [M+H]. **IR:** 2978.5, 1727.9, 1615.1, 1454.1, 1329.2, 1262.2, 1160.0, 1096.3, 1028.8, 1002.8, 900.6, 875.5, 749.2, 699.1.

**[4 + 2 + 2] Cycloaddition forming 37.**



Racemic: reaction performed according to General Procedure B with 25.7 mg (0.0880 mmol) of diene-allene. After 72 hours, the reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. The product was isolated as a colorless oil 24.2 mg (0.0519 mmol, 59%).

Asymmetric: reaction performed according to General Procedure A with 36.0 mg (0.0880 mmol) of diene-allene **36** and 30.7 mg (0.176 mmol, 2 equiv) allene **2**. After 72 hours, the reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cycloadduct **37** was isolated as a colorless oil 22.7 mg (0.0487 mmol, 55%). The fraction eluting before the product contained [4+2] cycloadduct (0.5 mg, 0.001 mmol, 2%).

**<sup>1</sup>H NMR** (600 MHz, CHLOROFORM-*d*) δ ppm 7.40-7.32 (m, 5H), 5.75 (s, 1H), 5.58 (dt, *J* = 11.1, 6.3 Hz, 1H), 5.34-5.31 (m, 1H), 5.17 (d, *J* = 12.6 Hz, 1H), 5.14 (d, *J* = 12.6 Hz, 1H), 4.90 (s, 1H), 4.87 (s, 1H), 4.24-4.19 (m, 4H), 3.40-3.36 (m, 1H), 2.96 (t, *J* = 14.3, 7.2 Hz, 1H), 2.85-2.80 (m, 2H), 2.61 (d, *J* = 13.6 Hz, 1H), 2.35-2.27 (m 2H), 2.18-2.12 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 6H), 1.07 (s, 3H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*) δ ppm 172.92, 172.72, 166.19, 164.05, 157.00, 136.06, 132.43, 130.09, 128.53, 128.28, 128.15, 118.59, 112.75, 85.79, 61.78, 61.68, 58.08, 53.61, 45.64, 42.45, 38.37, 30.91, 27.61, 25.38, 14.00.

**LRMS:** Calc: 466.24, Found: 467.37 [M+H]. **IR:** 2978.5, 1728.9, 1620.9, 1455.0, 1254.5, 1155.2, 1108.9, 1007.6. **HPLC:** Chiralpak IC, 99:1 Hexanes/IPA, er 65:35.

**[4 + 2 + 2] Cycloaddition forming **39**.**



0.088 mmol scale: Reaction performed according to General Procedure A with 28.2 mg (0.0880 mmol) of diene-allene **38** and 30.7 mg (0.176 mmol, 2 equiv) allene **2**. After 72 hours, the reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cycloadduct **39** was isolated as a colorless oil 20.3 mg (0.0410 mmol, 47%). The fraction eluting before the product were combined and concentrated. Trimethoxybenzene (1.6 mg, 0.0095 mmol) was added as an internal NMR standard, indicating 0.026 mmol (30%) of [4+2] cycloadduct.

0.500 mmol scale: Reaction performed according to General Procedure A with 160 mg (0.500 mmol) of diene-allene **38** and 174 mg (1.00 mmol, 2 equiv) allene **2**. After 72 hours, the reaction was purified with a gradient flash chromatography from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cycloadduct **39** was isolated as a colorless oil 119 mg (0.241 mmol, 48%).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.40-7.32 (m, 5H), 5.68 (s, 1H), 5.16 (s, 2H), 5.03 (d,  $J$  = 8.8 Hz, 1H), 4.80 (s, 1H), 4.75 (s, 1H), 4.26-4.19 (m, 4H), 3.81 (dd,  $J$  = 11.0, 5.5 Hz, 1H), 2.94 (q,  $J$  = 7.1 Hz, 1H), 2.77-2.73 (m, 1H), 2.53 (dd,  $J$  = 14.1, 7.2 Hz, 1H), 2.36 (dd,  $J$  = 13.0, 5.7 Hz, 1H), 2.32 (dd,  $J$  = 14.3 Hz, 1H), 2.27-2.22 (m, 2H), 2.14 (t,  $J$  = 12.8

Hz, 1H), 2.08 (t,  $J = 13.0$  Hz, 1H), 2.05-2.01 (m, 1H), 1.27 (t,  $J = 7.1$  Hz, 3H), 1.26 (t,  $J = 7.1$  Hz, 3H), 0.98 (d,  $J = 7.7$  Hz, 3H), 0.96 (d,  $J = 7.7$  Hz, 3H).  **$^{13}\text{C}$  NMR** (151MHz, CHLOROFORM- $d$ )  $\delta$  ppm 172.83, 172.56, 166.24, 165.78, 151.76, 147.03, 136.15, 128.48, 128.17, 128.06, 124.36, 114.65, 110.97, 65.65, 61.54, 61.50, 58.78, 51.91, 39.53, 39.35, 36.82, 35.41, 34.43, 28.61, 21.97, 21.75, 14.03, 14.02. **LRMS**: Calc: 494.27, Found: 495.33 [M+H]. **IR**: 2959.2, 2870.5, 2870.5, 1727.9, 1646.9, 1616.1, 1458.9, 1365.4, 1252.5, 1158.0, 1099.32, 1002.8, 874.6, 745.4, 698.1. **HPLC**: Chiralpak IC, 99:1 Hexanes/IPA, er 96.5:3.5.

**[4 + 2 + 2] Cycloaddition forming 39.**

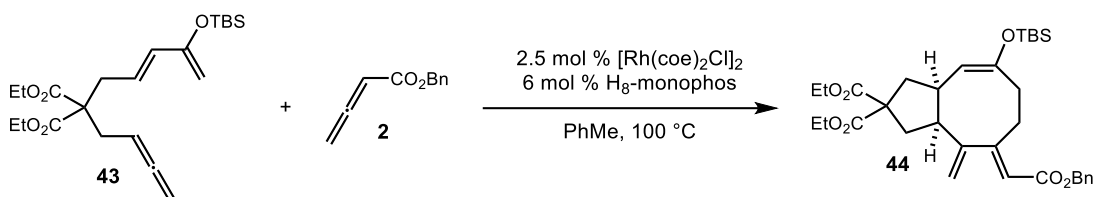


Reaction performed according to General Procedure B with 30.8 mg (0.0880 mmol) of diene-allene **41** and 30.7 mg (0.176 mmol) of allene **2**. After 72 hours at 100 °C, the reaction was purified with a gradient pipette column from 5% EtOAc in hexanes to 10% EtOAc in hexanes. Cyclooctanoid **42** was isolated as a colorless oil 29.3 mg (0.0559 mmol, 63%).

**$^1\text{H}$  NMR** (600 MHz, CHLOROFORM- $d$ )  $\delta$  ppm 7.40-7.31 (m, 5H), 5.73 (s, 1H), 5.73 (ddd,  $J = 10.8, 7.9, 1.7$  Hz, 1H), 5.41 (ddd,  $J = 10.7, 9.1, 1.5$  Hz, 1H), 5.17 (s, 2H), 4.90 (d,  $J = 1.5$  Hz, 1H), 4.87 (d,  $J = 1.8$  Hz, 1H), 4.25-4.16 (m, 6H), 3.92 (dd,  $J = 11.6, 2.0$  Hz, 1H), 3.26 (ddt,  $J = 11.6, 8.1, 1.7$  Hz, 1H), 2.99 (q,  $J = 7.2$  Hz, 1H), 2.82 (dt,  $J = 12.8, 6.3$  Hz, 1H), 2.51 (dd,  $J = 14.5, 7.2$  Hz, 1H), 2.43-2.38 (m, 2H), 2.06 (t,  $J = 13.1$  Hz, 1H), 2.36 (t,  $J = 11.7$  Hz, 1H), 2.05 (t,  $J = 13.2$  Hz, 1H), 1.28 (t,  $J = 7.2$  Hz, 3H), 1.26 (t,  $J = 7.2$  Hz, 6H).  **$^{13}\text{C}$  NMR** (151MHz, CHLOROFORM- $d$ )  $\delta$  ppm 173.99, 172.76, 172.56, 165.98, 161.68, 150.81, 136.13,

133.48, 128.89, 128.70, 128.42, 128.34, 117.14, 112.78, 66.08, 61.84, 61.17, 58.90, 52.76, 44.26, 40.40, 38.85, 37.90, 35.71, 14.35, 14.18. **LRMS:** Calc: 524.24, Found: 525.32 [M+H]. **IR:** 2981.41, 1729.8, 1647.9, 1617.0, 1452.1, 1259.3, 1159.0, 1091.5, 1029.8, 854.0.

**[4 + 2 + 2] Cycloaddition forming **44**.**

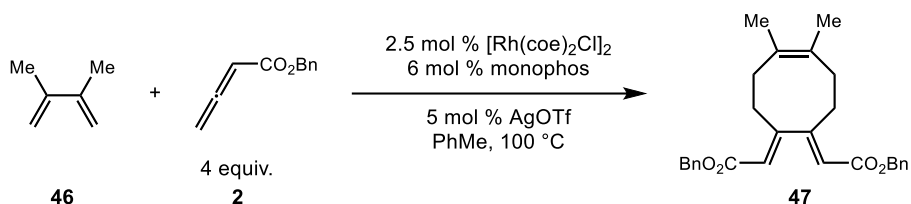


Reaction performed according to General Procedure A with 36.0 mg (0.0880 mmol) of diene-allene **43** and 30.7 mg (0.176 mmol, 2 equiv) allene **2**. After 72 hours, the reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cycloadduct **44** was isolated as a colorless oil 17.6 mg (0.0302 mmol, 34%). The fraction eluting before the product were combined and concentrated. Trimethoxybenzene (3.2 mg, 0.019 mmol) was added as an internal NMR standard, indicating 0.020 mmol (23%) of [4+2] cycloadduct.

**<sup>1</sup>H NMR** (600 MHz, CHLOROFORM-*d*) δ ppm 7.40-7.31 (m, 5H), 5.68 (s, 1H), 5.15 (s, 2H), 4.86 (s, 1H), 4.85 (d, *J* = 1.5 Hz, 1H), 4.44 (d, *J* = 8.5 Hz, 1H), 4.24-4.17 (m, 4H), 3.73-3.69 (m, 1H), 2.86 (q, *J* = 7.2 Hz, 1H), 2.72 (dt, *J* = 12.5, 6.0 Hz, 1H), 2.49 (dd, *J* = 14.2, 7.1 Hz, 1H), 2.41-2.37 (m, 2H), 2.34-2.26 (m, 3H), 2.23-2.15 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*) δ ppm 172.81, 172.56, 166.16, 165.18, 153.12, 151.65, 136.10, 128.52, 128.20, 128.12, 115.06, 112.21, 106.67, 65.72, 61.56, 61.53, 58.58, 52.25, 39.79, 39.72, 35.47, 33.31, 32.94, 25.64, 17.95, 14.05, 14.01, -4.33, -4.98. **LRMS:** Calc: 582.30, Found: 605.29 [M+Na]. **IR:** 2954.5, 2932.2, 2858.0, 1728.9, 1651.7, 1617.0, 1444.4, 1253.5, 1160.0, 1065.5,

1024.0, 999.9, 861.1, 840.8, 780.1, 743.4, 698.1. **HPLC:** Chiralpak IC, 99:1 Hexanes/IPA, er 95.5:4.5.

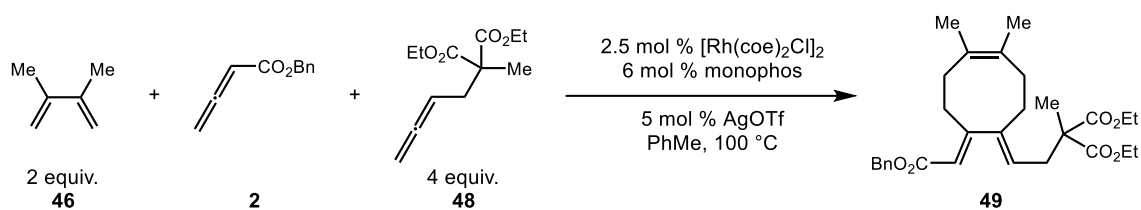
**[4 + 2 + 2] Cycloaddition forming 47.**



A solution of  $[\text{Rh}(\text{coe})_2\text{Cl}]_2$  (1.6 mg, 0.0022 mmol, 2.5 mol%) in toluene (0.7 mL) was added to monophos (1.9 mg, 0.0053 mmol, 6 mol%) in an oven dried vial under inert atmosphere and stirred for 30 minutes. AgOTf (1.1 mg, 0.0044 mmol, 5 mol %) in toluene (0.7 mL) was added and the resulting solution was stirred for 10 minutes with the formation of a white-grey precipitate. To this catalyst solution was added a solution of 2,3-dimethylbutadiene (**46**) (7.2 mg, 0.088 mmol, 1 equiv) and allenolate **2** (61.3 mg, 0.356 mmol, 4 equiv) in toluene (0.7 mL). Reaction was sealed and heated to 100 °C for 17 h. The reaction was cooled to room temperature, filtered through celite (EtOAc rinse), and concentrated. The reaction was purified using flash chromatography with EtOAc and hexanes. The product **47** was obtained as a colorless oil massing 22.8 mg (0.053 mmol, 60%).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.40-7.31 (m, 10H), 5.65 (s, 2H), 5.17 (s, 4H), 2.98-2.95 (m, 4H), 2.27-2.24 (m, 4H), 1.63 (s, 6H).

**[4 + 2 + 2] Cycloaddition forming 48.**

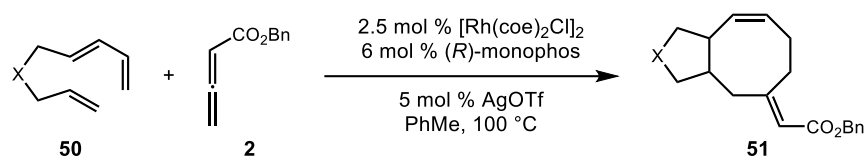


A solution of  $[\text{Rh}(\text{coe})_2\text{Cl}]_2$  (1.6 mg, 0.0022 mmol, 2.5 mol%) in toluene (0.7 mL) was added to monophos (1.9 mg, 0.0053 mmol, 6 mol%) in an oven dried vial under inert atmosphere and stirred for 30 minutes. AgOTf (1.1 mg, 0.0044 mmol, 5 mol %) in toluene (0.7 mL) was added and the resulting solution was stirred for 10 minutes with the formation of a white-grey precipitate. To this catalyst solution was added a solution of 2,3-dimethylbutadiene **46** (14.8 mg, 0.18 mmol, 2 equiv) and allenolate **2** (15.3 mg, 0.088 mmol, 1 equiv) and alkyl allene **48** (74.7 mg, 0.352 mmol, 4 equiv) in toluene (0.7 mL). Reaction was sealed and heated to 100 °C for 22 h. The reaction was cooled to room temperature, filtered through celite (EtOAc rinse), and concentrated. The reaction was purified using flash chromatography with EtOAc and hexanes. The product **49** was obtained as a colorless oil massing 7.6 mg (0.016 mmol, 18%). Additionally, byproduct **47** was obtained as a colorless oil massing 11.0 mg (0.025 mmol, 29%).

$^1\text{H}$  NMR (400 MHz,  $\text{CHCl}_3$ - $d$ )  $\delta$  ppm 7.38-7.31 (m, 5H), 5.56 (s, 1H), 5.14 (s, 2H), 5.01 (t,  $J = 7.5$  Hz, 1H), 4.18 (qd,  $J = 7.1, 3.1$  Hz, 4H), 2.94-2.92 (m, 2H), 2.63 (d,  $J = 7.5$  Hz, 2H), 2.30-2.21 (m, 4H), 2.15-2.12 (m, 2H), 1.62, (s, 3H), 1.61 (s, 3H), 1.36 (s, 3H), 1.25 (t,  $J = 7.2$  Hz, 6H).

**[4 + 2 + 2] Cycloaddition forming 51.**

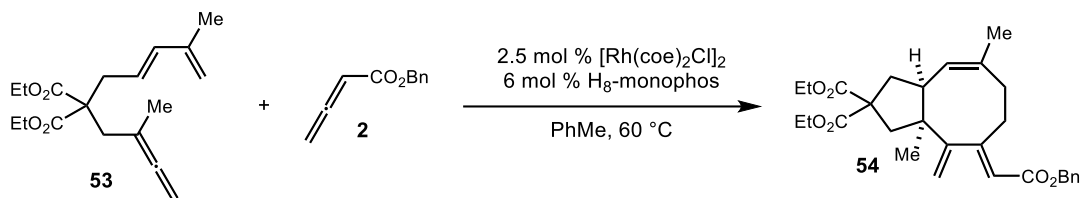




A solution of  $[\text{Rh}(\text{coe})_2\text{Cl}]_2$  (1.6 mg, 0.0022 mmol, 2.5 mol%) in toluene (0.7 mL) was added to (*R*)-monophos (1.9 mg, 0.0053 mmol, 6 mol%) in an oven dried vial under inert atmosphere and stirred for 30 minutes. AgOTf (1.1 mg, 0.0044 mmol, 5 mol %) in toluene (0.7 mL) was added and the resulting solution was stirred for 10 minutes with the formation of a white-grey precipitate. To this catalyst solution was added a solution of triene **50** (23.4 mg, 0.088 mmol, 1 equiv) and allenolate **2** (30.7 mg, 0.176 mmol, 2 equiv) in toluene (0.7 mL). Reaction was sealed and heated to 100 °C for 16 h. The reaction was cooled to room temperature, filtered through celite (EtOAc rinse), and concentrated. The reaction was purified using flash chromatography with EtOAc and hexanes. The product **51** was obtained as a colorless oil massing 24.9 mg (0.057 mmol, 64%).

**$^1\text{H}$  NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.38-7.30 (m, 5H), 5.87 (q,  $J$  = 8.9 Hz, 1H), 5.77 (s, 1H), 5.34 (t,  $J$  = 9.7 Hz, 1H), 5.14 (s, 2H), 4.23-4.17 (m, 4H), 3.77 (dd,  $J$  = 11.5, 5.8 Hz, 1H), 2.92 (q,  $J$  = 7.2 Hz, 1H), 2.48-2.26 (m, 5H), 2.18-2.03 (m, 2H), 1.89 (t,  $J$  = 11.9 Hz, 2H), 1.74 (t,  $J$  = 13.1 Hz, 1H), 1.25 (t,  $J$  = 7.2 Hz, 6H).

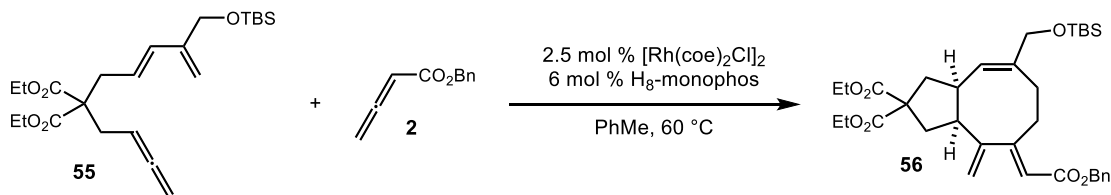
#### [4 + 2 + 2] Cycloaddition forming **54**.



Reaction performed according to General Procedure A with 27.0 mg (0.0880 mmol) of diene-allene **53** and 30.7 mg (0.176 mmol, 2 equiv) allene **2**. After 72 hours, the reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cycloadduct **54** was isolated as a colorless oil 14.0 mg (0.0291 mmol, 33%). The fraction eluting before the product were combined and concentrated. Trimethoxybenzene (5.5 mg, 0.033 mmol) was added as an internal NMR standard, indicating 0.024 mmol (27%) of [4+2] cycloadduct.

**<sup>1</sup>H NMR** (600 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.40-7.31 (m, 5H), 5.69 (s, 1H), 5.18 (d,  $J$  = 12.5 Hz, 1H), 5.14 (d,  $J$  = 12.5 Hz, 1H), 5.10 (d,  $J$  = 5.6 Hz, 1H), 4.86 (s, 1H), 4.78 (s, 1H), 4.23 (d,  $J$  = 7.1 Hz, 2H), 4.22 (d,  $J$  = 7.1 Hz, 2H), 3.62-3.59 (m, 1H), 2.81 (dd,  $J$  = 14.3, 6.8 Hz, 1H), 2.76 (t,  $J$  = 7.5 Hz, 1H), 2.46 (ddd,  $J$  = 12.9, 10.5, 1.8 Hz, 1H), 2.37 (dd,  $J$  = 14.9, 10.1 Hz, 1H), 2.27-2.22 (m, 2H), 1.99 (ddd,  $J$  = 14.8, 8.9, 2.0 Hz, 1H), 1.67 (s, 3H), 1.27 (t,  $J$  = 7.2 Hz, 3H), 1.26 (t,  $J$  = 7.2 Hz, 3H), 1.07 (s, 3H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 172.98, 172.86, 166.19, 163.91, 157.10, 137.15, 136.12, 128.53, 128.26, 128.15, 127.24, 118.59, 112.03, 65.78, 61.75, 61.66, 58.29, 53.64, 46.04, 42.41, 38.34, 31.84, 31.19, 25.23, 25.16, 14.01. **LRMS**: Calc: 480.25, Found: 481.38 [M+H]. **IR**: 2978.5, 1728.9, 1614.1, 1450.2, 1376.0, 1254.5, 1105.0, 1006.7, 885.2, 698.1. **HPLC**: Chiralpak IC, 99:1 Hexanes/IPA, er 97.5:2.5.

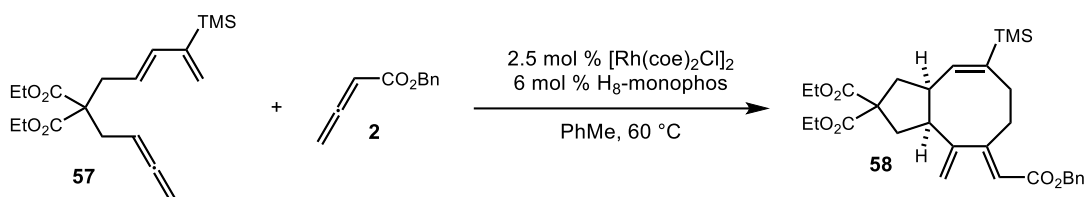
**[4 + 2 + 2] Cycloaddition forming 56.**



Reaction performed according to General Procedure A with 37.2 mg (0.0880 mmol) of diene-allene **55** and 30.7 mg (0.176 mmol, 2 equiv) allene **2**. After 72 hours, the reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cycloadduct **56** was isolated as a colorless oil 35.2 mg (0.0590 mmol, 67%).

**<sup>1</sup>H NMR** (600 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.40-7.30 (m, 5H), 5.70 (s, 1H), 5.29 (d,  $J = 9.2$  Hz, 1H), 5.17 (s, 1H), 4.81 (d,  $J = 1.2$  Hz, 1H), 4.78 (d,  $J = 1.6$  Hz, 1H), 4.30-4.18 (m, 4H), 4.02 (s, 2H), 3.82 (dd,  $J = 9.6, 2.0$  Hz, 1H), 3.02 (q,  $J = 8.0$  Hz, 1H), 2.83-2.75 (m, 1H), 2.55 (dd,  $J = 14.4, 7.2$  Hz, 1H), 2.41-2.37 (m, 2H), 2.24-2.04 (m, 4H), 1.30-1.27 (m, 6H), 0.91 (s, 9H), 0.06 (s, 6H).

**[4 + 2 + 2] Cycloaddition forming **58**.**

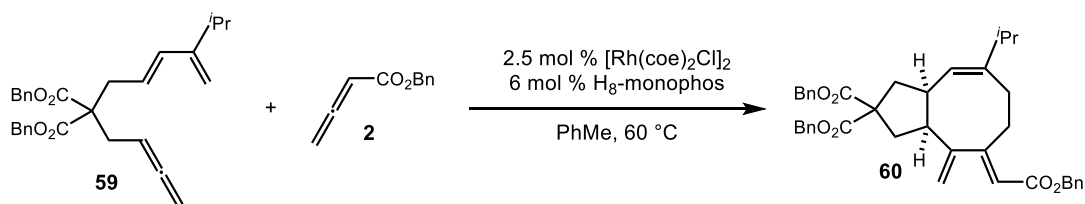


Reaction performed according to General Procedure A with 30.9 mg (0.0880 mmol) of diene-allene **57** and 30.7 mg (0.176 mmol, 2 equiv) allene **2**. After 72 hours, the reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. Cycloadduct **58** was isolated as a colorless oil 15.8 mg (0.0301 mmol, 34%). The fraction eluting before the product were combined and concentrated. Trimethoxybenzene (7.4 mg, 0.044 mmol) was added as an internal NMR standard, indicating 0.042 mmol (47%) of [4+2] cycloadduct.

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.40-7.31 (m, 5H), 5.67 (s, 1H), 5.58 (dd,  $J = 8.7, 1.3$  Hz, 1H), 5.16 (s, 2H), 4.79 (d,  $J = 1.2$  Hz, 1H), 4.75 (d,  $J = 1.5$  Hz, 1H), 4.26-4.18 (m, 4H), 3.82 (ddd,  $J = 11.3, 6.2, 1.6$  Hz, 1H), 3.10 (q,  $J = 7.3$  Hz, 1H), 2.78 (dt,  $J = 13.2,$

5.9 Hz, 1H), 2.55 (dd,  $J = 14.4, 7.1$  Hz, 1H), 2.46-2.35 (m, 3H), 2.20 (t,  $J = 13.0$  Hz, 1H), 2.07 (t,  $J = 13.1$  Hz, 1H), 1.94-1.88 (m, 1H), 1.28 (t,  $J = 7.2$  Hz, 3H), 1.27 (t,  $J = 7.2$  Hz, 3H), 0.04 (s, 9H).  **$^{13}\text{C}$  NMR** (151MHz, CHLOROFORM- $d$ )  $\delta$  ppm 172.81, 172.52, 166.24, 165.85, 151.66, 143.33, 141.10, 136.15, 128.51, 128.21, 128.10, 114.81, 111.09, 65.68, 61.61, 61.58, 58.88, 51.96, 40.47, 38.93, 35.52, 34.32, 28.68, 14.05, 14.03, -1.67. **LRMS**: Calc: 524.26, Found: 525.16 [M+H]. **IR**: 2953.5, 1728.9, 1615.1, 1452.1, 1366.3, 1249.7, 1159.0, 1080.9, 1028.8, 836.0, 746.3, 696.2. **HPLC**: Chiralpak IC, 99:1 Hexanes/IPA, er 96:4.

**[4 + 2 + 2] Cycloaddition forming 60.**

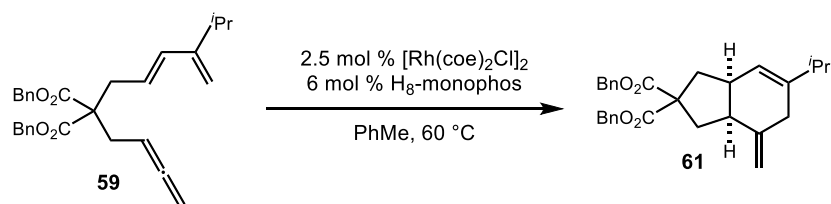


Reaction performed according to General Procedure A with 39.1 mg (0.0880 mmol) of diene-allene **59** and 30.7 mg (0.176 mmol, 2 equiv) allene **2**. After 72 hours, the reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. [4+2+2] Cycloadduct **60** was isolated as a colorless oil 26.0 mg (0.0328 mmol, 48%). [4+2] Cycloadduct **61** was isolated as a colorless oil 14.6 mg (0.0328 mmol, 37%).

**$^1\text{H}$  NMR** (600 MHz, CHLOROFORM- $d$ )  $\delta$  ppm 7.41-7.37 (m, 3H), 7.35-7.30 (m, 6H), 7.29-7.25 (m, 6H), 5.66 (s, 1H), 5.20-5.10 (m, 6H), 4.99 (d,  $J = 12.5$  Hz, 1H), 4.79 (s, 1H), 4.73 (s, 1H), 3.81 (dd,  $J = 10.6, 5.5$  Hz, 1H), 2.94 (q,  $J = 7.2$  Hz, 1H), 2.75 (dt,  $J = 12.6, 6.0$  Hz, 1H), 2.57 (dd,  $J = 14.3, 7.0$  Hz, 1H), 2.41 (dd,  $J = 13.0, 5.7$  Hz, 1H), 2.36 (d,  $J = 14.3$  Hz, 1H), 2.26-2.19 (m, 2H), 2.12 (t,  $J = 12.8$  Hz, 2H), 2.04-2.01 (m, 1H), 0.96 (d,  $J = 7.0$  Hz, 3H),

0.94 (d,  $J = 7.0$  Hz, 3H).  **$^{13}\text{C}$  NMR** (151MHz, CHLOROFORM- $d$ )  $\delta$  ppm 172.48, 172.21, 166.25, 165.72, 151.61, 147.20, 136.16, 135.47, 135.42, 128.51, 128.49, 128.26, 128.23, 128.20, 128.10, 128.03, 127.99, 124.21, 114.71, 111.05, 67.27, 67.26, 65.68, 58.93, 51.90, 39.53, 39.49, 36.79, 35.49, 34.39, 28.61, 21.97, 21.75. **LRMS**: Calc: 618.30, Found: 619.43 [M+H]. **IR**: 3064.3, 3034.4, 2958.3, 2870.5, 1728.9, 1646.9, 1616.1, 1497.5, 1455.0, 1376.9, 1254.5, 1159.0, 1055.8, 1000.9, 903.5, 737.6, 698.1. **HPLC**: Chiralpak IC, 99:1 Hexanes/IPA, er 97:3.

**[4 + 2] Cycloaddition forming 61.**



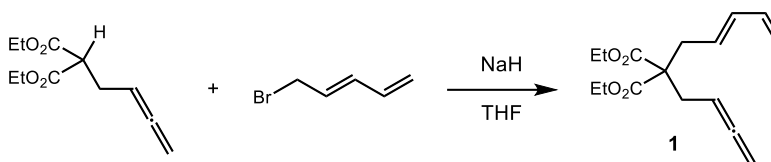
Reaction performed according to General Procedure A with 39.1 mg (0.0880 mmol) of diene-allene **59**. After 72 hours, the reaction was purified with a gradient pipette column from 2.5% EtOAc in hexanes to 5% EtOAc in hexanes. [4+2] Cycloadduct **60** was isolated as a colorless oil 32.9 mg (0.074 mmol, 84%).

**$^1\text{H}$  NMR** (600 MHz, CHLOROFORM- $d$ )  $\delta$  ppm 7.34-7.30 (m, 6H), 7.29-7.24 (m, 4H), 5.18 (s, 1H), 5.13 (s, 2H), 5.10 (s, 2H), 4.79 (d,  $J = 5.9$  Hz, 2H), 2.89-2.78 (m, 3H), 2.60 (d,  $J = 18.1$  Hz, 1H), 2.52 (dd,  $J = 13.5, 7.3$  Hz, 1H), 2.38 (q,  $J = 13.5$  Hz, 1H), 2.36 (q,  $J = 13.0$  Hz, 1H), 2.23 (dd,  $J = 13.5, 3.9$  Hz, 1H), 2.14 (sept,  $J = 6.8$  Hz, 1H), 0.98 (d,  $J = 6.9$  Hz, 6H).  **$^{13}\text{C}$  NMR** (151MHz, CHLOROFORM- $d$ )  $\delta$  ppm 172.68, 171.80, 145.77, 142.37, 135.78, 135.71, 128.65, 128.61, 128.35, 128.30, 128.11, 128.01, 121.24, 108.88, 67.25, 67.19, 59.83,

45.59, 42.09, 40.63, 37.27, 34.77, 31.35, 21.28, 21.14. **LRMS:** Calc: 444.23, Found: 445.40 [M+H]. **IR:** 3067.2, 3033.5, 2959.2, 1732.7, 1455.0, 1375.0, 1231.3, 1161.9, 890.0, 737.6, 697.1. **HPLC:** Chiralpak IC, 99.5:0.5 Hexanes/IPA: with 2 equiv of allene **2**: er 77.5:22.5, without allene **2**: er 42:58.

### 3.2.2 Synthesis and Analytical Data for Diene-Allenes and Related Substrates

#### Synthesis of diene-allene **1**.



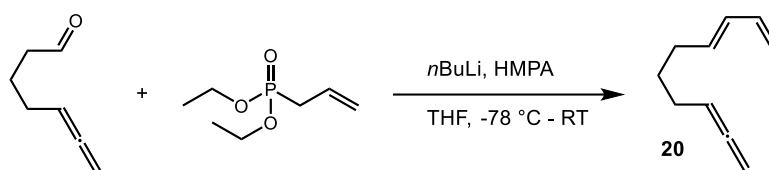
In a dry round bottom flask under and argon atmosphere, NaH (60 % in mineral oil, 78.5 mg, 1.96 mmol) was suspended in THF (11 mL). The reaction was cooled to 0 °C and malonate (396.7 mg, 1.87 mmol) in THF (2.4 mL) was added dropwise. The reaction was allowed to stir 30 minutes while warming to room temperature. Bromide (81 % in ether, 475 mg, 2.62 mmol) was then added and the reaction was stirred at room temperature overnight.

The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and the organic layer was extracted with EtOAc (3x). The organic layers were combined and washed with saturated aqueous sodium bicarbonate, water, and NaCl brine. The organic layer was then dried with MgSO<sub>4</sub>, filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **1** was isolated as a colorless oil massing 310 mg (1.11 mmol, 60 %, 6.1:1 E:Z mixture).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*) δ ppm 6.28 (dt, *J* = 16.9, 10.3 Hz, 1H), 6.10 (dd, *J* = 15.1, 10.5 Hz, 1H), 5.53 (dt, *J* = 15.1, 7.6 Hz, 1H), 5.12 (d, *J* = 16.8 Hz, 1H), 5.02 (d, *J*

= 10.5 Hz, 1H), 5.00-4.92 (m, 1H), 4.67 (dt,  $J = 6.7, 2.4$  Hz, 2H), 4.19 (q,  $J = 7.1$  Hz, 4H), 2.71 (d,  $J = 7.8$  Hz, 2H), 2.61 (dt,  $J = 8.0, 2.4$  Hz, 2H), 1.25 (t,  $J = 7.2$  Hz, 6H).  **$^{13}\text{C}$  NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 210.08, 170.56, 136.60, 135.16, 127.81, 116.37, 84.20, 74.60, 61.30, 57.73, 35.62, 31.98, 14.10. **LRMS:** Calc: 278.15, Found: 279.21 [M+H]. **IR:** 2981.4, 2936.1, 1956.4, 1732.7, 1442.5, 1367.3, 1280.5, 1241.0, 1203.4, 1072.3, 1006.7, 904.5, 853.3.

### Synthesis of diene-allene **20**.

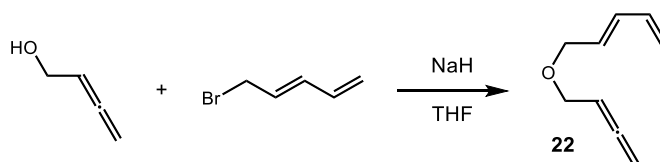


Phosphonate (917.8 mg, 5.15 mmol, 1.2 equiv) dissolved in THF (10.7 mL) under argon and taken to -78 °C. *n*BuLi (2.4 M in hexanes, 2.15 mL, 1.2 equiv) was added dropwise and the reaction was stirred for 30 minutes. HMPA (2.24 mL, 12.9 mmol, 3 equiv) was then added and the reaction was stirred for a further 30 minutes. A solution of aldehyde (531.3 mg, 4.29 mmol, 1 equiv) in THF was then added and the reaction was stirred overnight, warming to room temperature.

The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the organic layer was extracted with pentane (3x). The organic layers were combined and washed with saturated aqueous sodium bicarbonate, water (2x), and NaCl brine. The organic layer was then dried with  $\text{MgSO}_4$ , filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with pentane. Diene-allene **20** was isolated as a colorless oil massing 58.1 mg (0.433 mmol, 10%, 17:1 E:Z ratio).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 6.32 (dt,  $J$  = 17.2, 10.3 Hz, 1H), 6.07 (dd,  $J$  = 15.2, 10.5 Hz, 1H), 5.71 (dt,  $J$  = 15.0, 7.0 Hz, 1H), 5.12-5.08 (m, 2H), 4.97 (d,  $J$  = 10.6 Hz, 1H), 4.67 (dt,  $J$  = 6.6, 3.3 Hz, 2H), 2.14 (q,  $J$  = 7.2 Hz, 2H), 2.02 (dtd,  $J$  = 10.8, 7.1, 3.3 Hz, 2H), 1.54 (quin,  $J$  = 7.43 Hz, 2H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 208.56, 137.23, 134.86, 131.26, 114.81, 89.68, 74.75, 31.88, 28.51, 27.64. **IR:** 2921.6, 2851.2, 1712.5, 1660.4, 1634.4, 1384.6, 1263.2, 1112.7, 1018.2, 802.2, 719.3.

### Synthesis of diene-allene **22**.



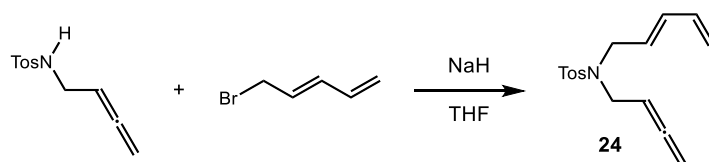
In a dry round bottom flask under and argon atmosphere, NaH (60% in mineral oil, 393.8 mg, 9.84 mmol, 1.15 equiv) was suspended in THF (66 mL). The reaction was cooled to 0 °C and alcohol (80% in ether, 750 mg, 8.56 mmol) was added drowise. The reaction was allowed to stir 30 minutes while warming to room temperature. Bromide (86% in ether, 2.122 g, 12.4 mmol, 1.45 mmol) was then added and the reaction was stirred at room temperature overnight.

The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and the organic layer was extracted with pentane (3x). The organic layers were combined and washed with saturated aqueous sodium bicarbonate, water (3x), and NaCl brine. The organic layer was then dried with MgSO<sub>4</sub>, filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2% Et<sub>2</sub>O in pentane. Diene-allene **22** was isolated as a colorless oil massing 759.5 mg (5.58 mmol, 65%, 7.2:1 E:Z ratio).



**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 6.36 (dt,  $J = 16.7, 10.3$  Hz, 1H), 6.27 (dd,  $J = 15.2, 10.4$  Hz, 1H), 5.79 (dd,  $J = 15.4, 6.2$  Hz, 1H), 5.25 (quin,  $J = 6.8$  Hz, 1H), 5.22 (d,  $J = 16.9$  Hz, 1H), 5.11 (d,  $J = 9.9$  Hz, 1H), 4.80 (dt,  $J = 6.6, 2.4$  Hz, 2H), 4.05 (dd,  $J = 6.1, 0.9$  Hz, 2H), 4.03 (dt,  $J = 7.0, 2.4$  Hz, 2H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 209.29, 136.28, 133.41, 129.79, 117.61, 87.65, 75.66, 69.90, 67.84. **LRMS**: Calc: 136.09, Found: 136.1 [M]. **IR**: 3356.4, 2922.6, 2853.2, 1656.6, 1632.5, 1463.7, 1018.2.

### Synthesis of diene-allene **24**.

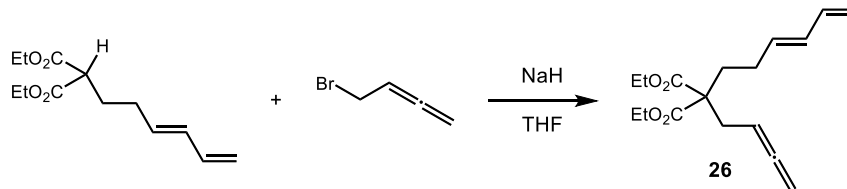


In a dry round bottom flask under and argon atmosphere, NaH (60% in mineral oil, 2.15 mmol, 1.2 equiv) was suspended in THF (18 mL). The reaction was cooled to 0 °C and tosylamine (400 mg, 1.79 mmol) was added dropwise. The reaction was allowed to stir 30 minutes while warming to room temperature. Bromide (81% in ether, 390 mg, 2.15 mmol, 1.2 equiv) was then added and the reaction was stirred at room temperature overnight.

The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and the organic layer was extracted with EtOAc (3x). The organic layers were combined and washed with saturated aqueous sodium bicarbonate, water (3x), and NaCl brine. The organic layer was then dried with MgSO<sub>4</sub>, filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 10% EtOAc in hexanes. Diene-allene **24** was isolated as a colorless waxy solid massing 328 mg (1.13 mmol, 63%, 9.1:1 E:Z ratio).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.71 (d,  $J$  = 8.0 Hz, 2H), 7.30 (d,  $J$  = 8.0 Hz, 2H), 6.27 (dt,  $J$  = 16.7, 10.3 Hz, 1H), 6.12 (dd,  $J$  = 15.0, 10.8 Hz, 1H), 5.54-5.47 (m, 1H), 5.18 (d,  $J$  = 16.3 Hz, 1H), 5.10 (d,  $J$  = 10.6 Hz, 1H), 4.91 (quin,  $J$  = 6.8 Hz, 1H), 4.70 (dt,  $J$  = 6.4, 2.3 Hz, 2H), 3.89 (d,  $J$  = 6.8 Hz, 2H), 3.85 (dt,  $J$  = 7.0, 2.4 Hz, 2H), 2.44 (s, 3H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 209.53, 143.23, 137.36, 135.81, 134.84, 129.62, 127.59, 127.14, 117.91, 85.60, 76.11, 48.30, 45.69, 21.47. **LRMS**: Calc: 289.11, Found: 290.19 [M+H]. **IR**: 2922.6, 1954.5, 1599.7, 1440.6, 1341.3, 1158.0, 1093.4, 1004.7, 952.7, 907.3, 851.7, 815.7, 750.2, 659.5, 547.7.

### Synthesis of diene-allene 26.



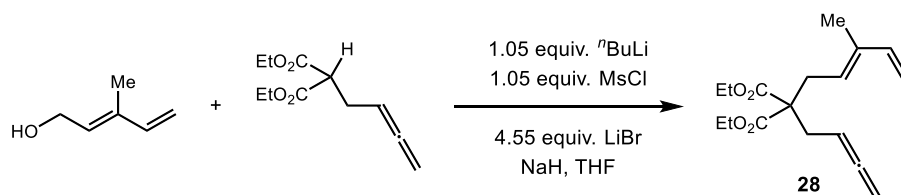
In a dry round bottom flask under and argon atmosphere, NaH (60 % in mineral oil, 64.2 mg, 1.61 mmol) was suspended in THF (6.5 mL). The reaction was cooled to 0 °C and malonate (367.1 mg, 1.53 mmol) was added drowise. The reaction was allowed to stir 30 minutes while warming to room temperature. Bromide (66% in ether, 338.6 mg, 1.68 mmol) was then added and the reaction was stirred at room temperature overnight.

The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and the organic layer was extracted with EtOAc (3x). The organic layers were combined and washed with saturated aqueous sodium bicarbonate, water, and NaCl brine. The organic layer was then dried with MgSO<sub>4</sub>, filtered through cotton and concentrated. The resulting residue was purified with flash

chromatography with 2.5% EtOAc in Hexanes. Diene-allene **26** was isolated as a colorless oil massing 339.6 mg (1.16 mmol, 76 %).

<sup>1</sup>H NMR (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 6.30 (dt,  $J$  = 16.9, 10.2 Hz, 1H), 6.06 (dd,  $J$  = 15.1, 10.4 Hz, 1H), 5.69-5.64 (m, 1H), 5.11 (dd,  $J$  = 17.0, 1.3 Hz, 1H), 4.99 (dd,  $J$  = 10.2, 1.4 Hz, 1H), 4.98-4.91 (m, 1H), 4.67 (dt,  $J$  = 6.7, 2.4 Hz, 2H), 4.19 (q,  $J$  = 7.1 Hz, 4H), 2.64 (dt,  $J$  = 8.0, 2.4 Hz, 2H), 2.03-2.02 (m, 4H), 1.26 (t,  $J$  = 7.1 Hz, 6H).

### Synthesis of diene-allene **28**.



In a dry round bottom flask under argon, dry THF (2.76 mL) was added to dissolve alcohol (74 % in ether, 200 mg, 1.52 mmol). The reaction was taken to  $-78\text{ }^{\circ}\text{C}$  and *n*-BuLi (2.5 M in hexanes, 0.64 mL, 1.59 mmol, 1.05 equiv) was added dropwise and the reaction was stirred 15 minutes. MsCl (123  $\mu\text{L}$ , 1.59 mmol, 1.05 equiv) was added dropwise and stirred 15 minutes. LiBr (599 mg in 1.4 mL THF, 6.90 mmol, 4.55 equiv) added to reaction. The reaction was allowed to stir while warming to room temperature.

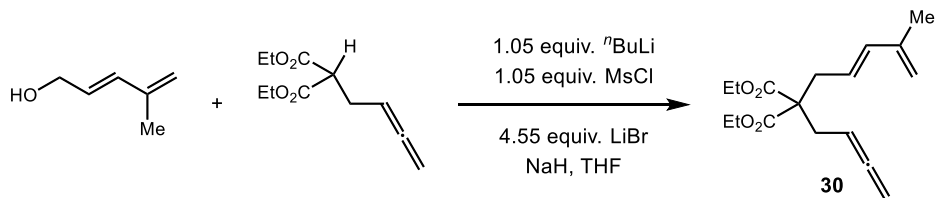
In a dry flask containing NaH (60% dispersion in mineral oil, 61 mg, 1.52 mmol, 1 equiv) under argon, THF (2.1 mL) was added to the flask. Malonate (293 mg, 1.38 mmol, 0.91 equiv) added dropwise at  $0\text{ }^{\circ}\text{C}$  and stirred 30 minutes. The reaction was then taken to  $-78\text{ }^{\circ}\text{C}$  and bromide solution was added. The reaction was allowed to stir at room temperature overnight.

The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the organic layer was extracted with  $\text{Et}_2\text{O}$  (3x). The organic layers were combined and washed with NaCl brine. The

organic layer was then dried with MgSO<sub>4</sub>, filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **28** was isolated as a colorless oil massing 279 mg (0.96 mmol, 70 %).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 6.34 (dd,  $J = 17.3, 10.8$  Hz, 1H), 5.33 (t,  $J = 7.8$  Hz, 1H), 5.12 (t,  $J = 17.3$  Hz, 1H), 4.99-4.92 (m, 1H), 4.89 (s, 1H), 4.66 (dt,  $J = 6.5, 2.5$  Hz, 2H), 4.23-4.15 (m, 4H), 2.80 (d,  $J = 7.5$  Hz, 2H), 2.61 (dt,  $J = 8.0, 2.4$  Hz, 2H), 1.76 (s, 3H), 1.26 (t,  $J = 7.2$  Hz, 6H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 210.01, 170.77, 141.20, 137.19, 125.67, 111.74, 84.33, 74.59, 61.32, 57.63, 32.03, 31.09, 14.06, 11.90. **LRMS**: Calc: 292.17, Found: 293.28 [M+H]. **IR**: 2983.3, 1956.4, 1732.7, 1443.5, 1367.3, 1281.5, 1228.4, 1197.6, 1076.1, 897.7, 854.3.

### Synthesis of diene-allene **30**.



In a dry round bottom flask under argon, dry THF (2.76 mL) was added to dissolve alcohol (74 % in ether, 200 mg, 1.52 mmol). The reaction was taken to  $-78$  °C and *n*-BuLi (2.5 M in hexanes, 0.64 mL, 1.59 mmol, 1.05 equiv) was added dropwise and the reaction was stirred 15 minutes. MsCl (123  $\mu$ L, 1.59 mmol, 1.05 equiv) was added dropwise and stirred 15 minutes. LiBr (599 mg in 1.4 mL THF, 6.90 mmol, 4.55 equiv) added to reaction. The reaction was allowed to stir while warming to room temperature.

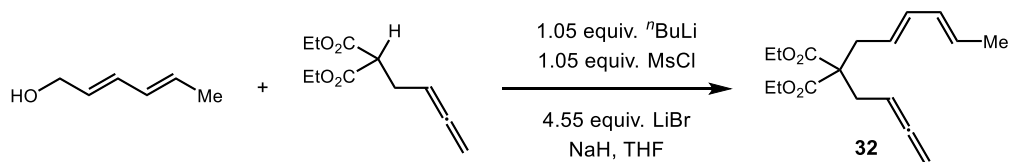
In a dry flask containing NaH (60% dispersion in mineral oil, 61 mg, 1.52 mmol, 1 equiv) under argon, THF (2.1 mL) was added to the flask. Malonate (293 mg, 1.38 mmol, 0.91 equiv)

added dropwise at 0 °C and stirred 30 minutes. The reaction was then taken to -78 °C and bromide solution was added. The reaction was allowed to stir at room temperature overnight.

The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and the organic layer was extracted with Et<sub>2</sub>O (3x). The organic layers were combined and washed with NaCl brine. The organic layer was then dried with MgSO<sub>4</sub>, filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **30** was isolated as a colorless oil massing 279.4 mg (0.956 mmol, 70 %).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*) δ ppm 6.19 (d, *J* = 15.6 Hz, 1H), 5.48 (dt, *J* = 15.5, 7.6 Hz, 1H), 5.01-4.94 (m, 1H), 4.91 (s, 1H), 4.89 (s, 1H), 4.67 (dt, *J* = 6.6, 2.6 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 4H), 2.74 (d, *J* = 7.6 Hz, 2H), 2.61 (dt, *J* = 8.0, 2.5 Hz, 2H), 1.80 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 6H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*) δ ppm 210.09, 170.62, 141.63, 137.10, 123.51, 115.71, 84.26, 74.56, 61.27, 57.84, 35.79, 32.04, 18.52, 14.10. **LRMS**: Calc: 292.17, Found: 293.29 [M+H]. **IR**: 3081.7, 2981.41, 2838.0, 1956.4, 1732.7, 1442.5, 1368.3, 1270.9, 1240.0, 1199.5, 1096.3, 1073.2, 1040.4, 97.0, 887.1, 854.3.

### Synthesis of diene-allene **32**.



This procedure was adapted from Wender and Christy.

In a dry round bottom flask under argon, dry THF (9.3 mL) was added to dissolve (2E,4E)-hexa-2,4-dien-1-ol (80% in ether, 625 mg, 5.09 mmol). The reaction was taken to –78 °C and *n*-BuLi (2.5 M in hexanes, 2.14 mL, 5.35 mmol, 1.05 equiv) was added dropwise

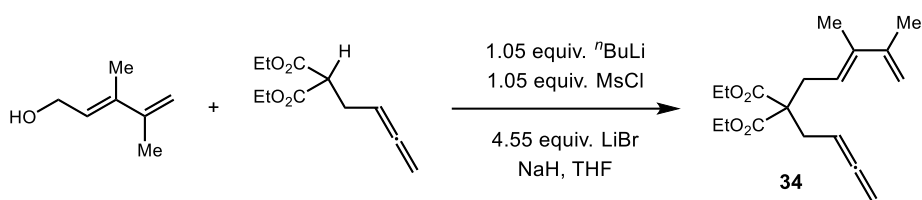
and the reaction was stirred 15 minutes. MsCl (414  $\mu$ L, 5.35 mmol, 1.05 equiv) was added dropwise and stirred 15 minutes. LiBr (2.01 g in 4.6 mL THF, 23.2 mmol, 4.55 equiv) added to reaction. The reaction was allowed to stir while warming to room temperature.

In a dry flask containing NaH (60% dispersion in mineral oil, 204 mg, 5.09 mmol, 1 equiv) under argon, THF (7 mL) was added to the flask. Buta-3,4-dienylmalonate (984 mg, 4.64 mmol, 0.91 equiv) added dropwise at 0 °C and stirred 30 minutes. The reaction was then taken to -78 °C and bromide solution was added. The reaction was allowed to stir at room temperature overnight.

The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the organic layer was extracted with  $\text{Et}_2\text{O}$  (3x). The organic layers were combined and washed with NaCl brine. The organic layer was then dried with  $\text{MgSO}_4$ , filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **32** was isolated as a colorless oil massing 979 mg (3.35 mmol, 72%).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CHLOROFORM-}d$ )  $\delta$  ppm 6.13-5.98 (m, 2H), 5.67-5.58 (m, 1H), 5.41-5.33 (m, 1H), 4.98 (tt,  $J$  = 8.0, 6.6 Hz, 1H), 4.68 (dt,  $J$  = 6.8, 2.5 Hz, 2H), 4.21 (q,  $J$  = 7.2 Hz, 4H), 2.70 (d,  $J$  = 7.8 Hz, 2H), 2.62 (dt,  $J$  = 8.0, 2.5 Hz, 2H), 1.75 (s, 3H), 1.27 (t,  $J$  = 7.2 Hz, 6H).  **$^{13}\text{C}$  NMR** (151MHz,  $\text{CHLOROFORM-}d$ )  $\delta$  ppm 207.70, 171.06, 134.63, 131.44, 128.53, 124.92, 93.64, 74.70, 61.33, 57.68, 35.64, 20.17, 18.16, 14.21. **LRMS:** Calc: 292.17, Found: 292.23. **IR:** 2981.4, 2935.1, 1956.4, 1732.7, 1442.5, 1367.3, 1279.5, 1198.5, 1074.2, 991.2, 854.3.

### Synthesis of diene-allene **34**.



This procedure was adapted from Wender and Christy.

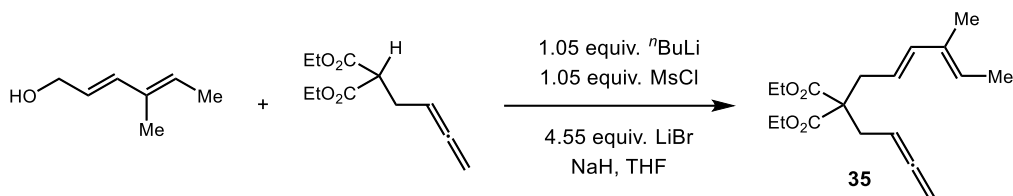
In a dry round bottom flask under argon, dry THF (2.4 mL) was added to dissolve the dienol (150 mg, 1.337 mmol). The reaction was taken to  $-78\text{ }^{\circ}\text{C}$  and *n*-BuLi (2.5 M in hexanes, 0.54 mL, 1.40 mmol, 1.05 equiv) was added dropwise and the reaction was stirred 15 minutes. MsCl (110  $\mu\text{L}$ , 1.40 mmol, 1.05 equiv) was added dropwise and stirred 15 minutes. LiBr (528 g in 1.2 mL THF, 6.09 mmol, 4.55 equiv) added to reaction. The reaction was allowed to stir while warming to room temperature.

In a dry flask containing NaH (60% dispersion in mineral oil, 53.5 mg, 1.34 mmol, 1 equiv) under argon, THF (7 mL) was added to the flask. Buta-3,4-dienylmalonate (258 mg, 1.22 mmol, 0.91 equiv) added dropwise at  $0\text{ }^{\circ}\text{C}$  and stirred 30 minutes. The reaction was then taken to  $-78\text{ }^{\circ}\text{C}$  and bromide solution was added. The reaction was allowed to stir at room temperature overnight.

The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the organic layer was extracted with  $\text{Et}_2\text{O}$  (3x). The organic layers were combined and washed with NaCl brine. The organic layer was then dried with  $\text{MgSO}_4$ , filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **34** was isolated as a colorless oil and that mass was unquantified.

**$^1\text{H}$  NMR** (400 MHz,  $\text{CHLOROFORM-}d$ )  $\delta$  ppm 5.46 (t,  $J = 7.6\text{ Hz}$ , 1H), 5.03 (s, 1H), 4.99 (t,  $J = 7.6\text{ Hz}$ , 1H), 4.93 (s, 1H), 4.67 (d,  $J = 6.4\text{ Hz}$ , 1H), 4.21 (q,  $J = 7.2\text{ Hz}$ , 4H), 2.82 (d,  $J = 7.6\text{ Hz}$ , 2H), 2.64 (d,  $J = 8\text{ Hz}$ , 2H), 1.89 (s, 3H), 1.84 (s, 3H), 1.27 (t,  $J = 7.2\text{ Hz}$ , 6H).

### Synthesis of diene-allene **35**.



This procedure was adapted from Wender and Christy.

In a dry round bottom flask under argon, dry THF (8.1 mL) was added to dissolve the dienol (500 mg, 4.46 mmol). The reaction was taken to  $-78\text{ }^{\circ}\text{C}$  and *n*-BuLi (2.5 M in hexanes, 1.80 mL, 4.68 mmol, 1.05 equiv) was added dropwise and the reaction was stirred 15 minutes. MsCl (360  $\mu\text{L}$ , 4.68 mmol, 1.05 equiv) was added dropwise and stirred 15 minutes. LiBr (1.76 g in 4.1 mL THF, 20.3 mmol, 4.55 equiv) added to reaction. The reaction was allowed to stir while warming to room temperature.

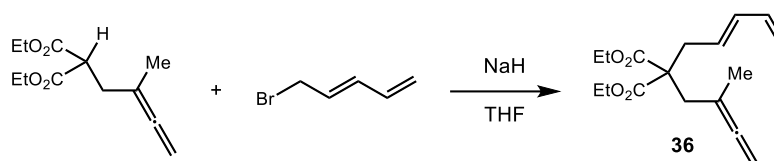
In a dry flask containing NaH (60% dispersion in mineral oil, 178 mg, 4.46 mmol, 1 equiv) under argon, THF (6.7 mL) was added to the flask. Buta-3,4-dienylmalonate (861 mg, 4.06 mmol, 0.91 equiv) added dropwise at  $0\text{ }^{\circ}\text{C}$  and stirred 30 minutes. The reaction was then taken to  $-78\text{ }^{\circ}\text{C}$  and bromide solution was added. The reaction was allowed to stir at room temperature overnight.

The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the organic layer was extracted with  $\text{Et}_2\text{O}$  (3x). The organic layers were combined and washed with NaCl brine. The organic layer was then dried with  $\text{MgSO}_4$ , filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **35** was isolated as a colorless oil massing 979 mg (3.35 mmol, 72%).



**$^1\text{H}$  NMR** (600 MHz, CHLOROFORM-*d*)  $\delta$  ppm 6.12 (d,  $J$  = 15.6 Hz, 1H), 5.48 (q,  $J$  = 6.7 Hz, 1H), 5.35 (dt,  $J$  = 15.5, 7.6 Hz, 1H), 5.01-4.96 (m, 1H), 4.68 (dt,  $J$  = 6.6, 2.5, 2H), 4.21 (q,  $J$  = 7.2 Hz, 4H), 2.73 (d,  $J$  = 7.7 Hz, 2H), 2.62 (dt,  $J$  = 8.0, 2.4 Hz, 2H), 1.72 (d,  $J$  = 7.2 Hz, 3H), 1.70 (s, 3H), 1.27 (t,  $J$  = 1.27 Hz, 6H).  **$^{13}\text{C}$  NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 211.3, 172.0, 140.4, 135.4, 127.4, 120.8, 85.6, 75.8, 62.5, 59.8, 37.0, 33.1, 15.4, 15.0, 13.3.

### Synthesis of diene-allene **36**.



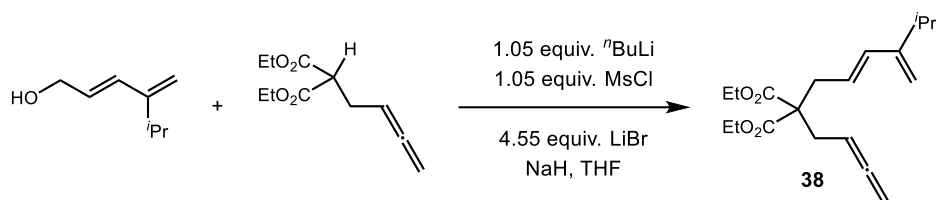
In a dry round bottom flask under and argon atmosphere, NaH (60 % in mineral oil, 78.5 mg, 1.96 mmol) was suspended in THF (11 mL). The reaction was cooled to 0 °C and malonate (396.7 mg, 1.87 mmol) in THF (2.4 mL) was added drowise. The reaction was allowed to stir 30 minutes while warming to room temperature. Bromide (81 % in ether, 475 mg, 2.62 mmol) was then added and the reaction was stirred at room temperature overnight.

The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the organic layer was extracted with EtOAc (3x). The organic layers were combined and washed with saturated aqueous sodium bicarbonate, water, and NaCl brine. The organic layer was then dried with  $\text{MgSO}_4$ , filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **36** was isolated as a colorless oil massing 310 mg (1.11 mmol, 60 %).

**$^1\text{H}$  NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 6.30 (dt,  $J$  = 16.9, 10.3 Hz, 1H), 6.10 (dd,  $J$  = 14.9, 10.4 Hz, 1H), 5.58 (dt,  $J$  = 15.1, 7.5 Hz, 1H), 5.13 (d,  $J$  = 16.6 Hz, 1H), 5.02 (d,  $J$

= 10.3 Hz, 1H), 4.63-4.60 (m, 2H), 4.25-4.13 (m, 4H), 2.80 (d,  $J = 7.6$  Hz, 2H), 2.63 (d,  $J = 2.4$  Hz, 2H), 1.27 (t,  $J = 7.2$  Hz, 6H).  **$^{13}\text{C}$  NMR** (151MHz,  $\text{CHLOROFORM-}d$ )  $\delta$  ppm 207.70, 171.06, 134.63, 131.44, 131.44, 128.53, 124.92, 93.64, 74.70, 61.33, 57.68, 35.64, 35.54, 20.17, 18.16, 14.21. **LRMS**: Calc: 292.17, Found: 293.35 [M+H]. **IR**: 2981.4, 2931.3, 1958.4, 1733.7, 1445.4, 1368.3, 1301.7, 1263.2, 1207.2, 1161.9, 1095.4, 1040.41, 1006.7, 903.5, 857.2.

### Synthesis of diene-allene 38.



In a dry round bottom flask under argon, dry THF (2.9 mL) was added to dissolve alcohol (200 mg, 1.585 mmol). The reaction was taken to  $-78\text{ }^{\circ}\text{C}$  and *n*-BuLi (2.4 M in hexanes, 0.69 mL, 1.664 mmol, 1.05 equiv) was added dropwise and the reaction was stirred 15 minutes. MsCl (0.13 mL, 1.664 mmol, 1.05 equiv) was added dropwise and stirred 15 minutes. LiBr (626.3 mg in 1.4 mL THF, 7.211 mmol, 4.55 equiv) added to reaction. The reaction was allowed to stir while warming to room temperature.

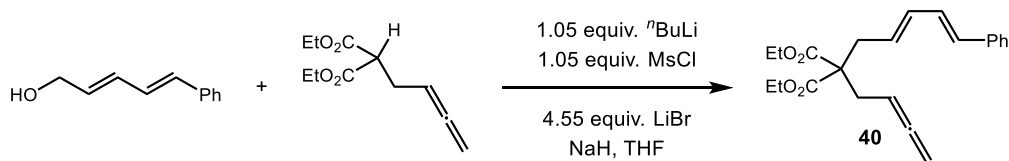
In a dry flask containing NaH (60% dispersion in mineral oil, 63.4 mg, 1.585 mmol, 1 equiv) under argon, THF (7 mL) was added to the flask. Malonate (306 mg, 1.442 mmol) added dropwise at  $0\text{ }^{\circ}\text{C}$  and stirred 30 minutes. The reaction was then taken to  $-78\text{ }^{\circ}\text{C}$  and bromide solution was added. The reaction was allowed to stir at room temperature overnight.

The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the organic layer was extracted with  $\text{Et}_2\text{O}$  (3x). The organic layers were combined and washed with NaCl brine. The organic layer was then dried with  $\text{MgSO}_4$ , filtered through cotton and concentrated. The

resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **38** was isolated as a colorless oil massing 309 mg (0.963 mmol, 67%).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 6.08 (d,  $J$  = 15.8 Hz, 1H), 5.57 (dt,  $J$  = 15.6, 7.6 Hz, 1H), 4.98 (tt,  $J$  = 8.0, 6.7 Hz, 1H), 4.89 (s, 2H), 4.67 (dt,  $J$  = 6.5, 2.5 Hz, 2H), 4.19 (q,  $J$  = 7.3 Hz, 4H), 2.73 (dd,  $J$  = 7.5, 1.3 Hz, 2H), 2.62 (dt,  $J$  = 8.0, 2.4 Hz, 2H), 2.52 (sept,  $J$  = 6.8 Hz, 1H), 1.26 (t,  $J$  = 7.2 Hz, 6H), 1.06 (d,  $J$  = 6.8 Hz, 6H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 210.09, 170.66, 152.28, 136.15, 122.36, 111.37, 84.28, 74.57, 61.27, 61.27, 57.89, 36.02, 29.32, 22.10, 14.09. **LRMS**: Calc: 320.20, Found: 321.38 [M+H]. **IR**: 2965.0, 2873.4, 1956.4, 1732.7, 1463.7, 1443.5, 1367.3, 1272.8, 1241.0, 1198.5, 1094.4, 1040.4, 972.0, 891.0, 852.4.

#### Synthesis of diene-allene **40**.



This procedure was adapted from Wender and Christy.

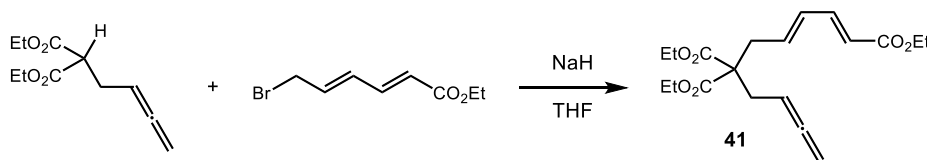
In a dry round bottom flask under argon, dry THF (3.4 mL) was added to dissolve dienol (300 mg, 1.87 mmol). The reaction was taken to  $-78^{\circ}\text{C}$  and *n*-BuLi (2.5 M in hexanes, 0.79 mL, 2.00 mmol, 1.05 equiv) was added dropwise and the reaction was stirred 15 minutes. MsCl (0.15 mL, 2.00 mmol, 1.05 equiv) was added dropwise and stirred 15 minutes. LiBr (740 mg in 1.7 mL THF, 8.52 mmol, 4.55 equiv) added to reaction. The reaction was allowed to stir while warming to room temperature.

In a dry flask containing NaH (60% dispersion in mineral oil, 74.9 mg, 1.87 mmol, 1 equiv) under argon, THF (2.5 mL) was added to the flask. Buta-3,4-dienylmalonate (362 mg, 1.70 mmol) added dropwise at 0 °C and stirred 30 minutes. The reaction was then taken to -78 °C and bromide solution was added. The reaction was allowed to stir at room temperature overnight.

The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and the organic layer was extracted with Et<sub>2</sub>O (3x). The organic layers were combined and washed with NaCl brine. The organic layer was then dried with MgSO<sub>4</sub>, filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **40** was isolated as a colorless waxy solid massing 503 mg (83%).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.29 (m, 5H), 6.73 (m, 1H), 6.46 (d, *J* = 15.5 Hz, 1H), 6.26 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.64 (dt, *J* = 15.1, 7.7 Hz, 1H), 4.97 (m, 1H), 4.69 (dt, *J* = 6.59, 2.39 Hz, 2H), 4.21 (q, *J* = 6.98 Hz, 1H), 2.77 (d, *J* = 7.5 Hz, 2H), 2.63 (dt, *J* = 8.0, 2.5 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 6H)

#### Synthesis of diene-allene **41**.



In a dry round bottom flask under argon, dry THF (9.3 mL) was added to dissolve alcohol (80 % in ether, 625 mg, 5.09 mmol). The reaction was taken to -78 °C and *n*-BuLi (2.5 M in hexanes, 2.14 mL, 5.35 mmol, 1.05 equiv) was added dropwise and the reaction was stirred 15 minutes. MsCl (414  $\mu$ L, 5.35 mmol, 1.05 equiv) was added dropwise and stirred 15 minutes.

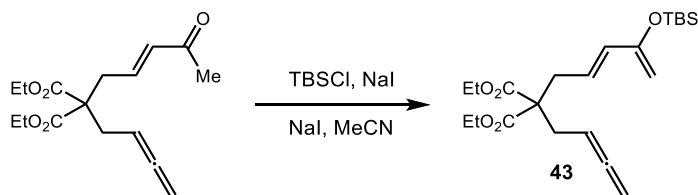
LiBr (2.01 g in 4.6 mL THF, 23.18 mmol, 4.55 equiv) added to reaction. The reaction was allowed to stir while warming to room temperature.

In a dry flask containing NaH (60% dispersion in mineral oil, 204 mg, 5.09 mmol, 1 equiv) under argon, THF (7 mL) was added to the flask. Malonate (984 mg, 4.636 mmol, 0.91 equiv) added dropwise at 0 °C and stirred 30 minutes. The reaction was then taken to -78 °C and bromide solution was added. The reaction was allowed to stir at room temperature overnight.

The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and the organic layer was extracted with Et<sub>2</sub>O (3x). The organic layers were combined and washed with NaCl brine. The organic layer was then dried with MgSO<sub>4</sub>, filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **41** was isolated as a colorless oil massing 979 mg (3.35 mmol, 72 %).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*) δ ppm 6.13-5.98 (m, 2H), 5.67-5.58 (m, 1H), 5.41-5.33 (m, 1H), 4.98 (tt, *J* = 8.0, 6.6 Hz, 1H), 4.68 (dt, *J* = 6.8, 2.5 Hz, 2H), 4.21 (q, *J* = 7.2 Hz, 4H), 2.70 (d, *J* = 7.8 Hz, 2H), 2.62 (dt, *J* = 8.0, 2.5 Hz, 2H), 1.75 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 6H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*) δ ppm 210.05, 170.65, 134.70, 131.15, 128.59, 124.19, 84.28, 74.54, 61.24, 57.83, 35.59, 31.84, 18.00, 14.10. **LRMS**: Calc: 292.17, Found: 292.23. **IR**: 2981.4, 2935.1, 1956.4, 1732.7, 1442.5, 1367.3, 1279.5, 1198.5, 1074.2, 991.2, 854.3.

### Synthesis of diene-allene **43**.

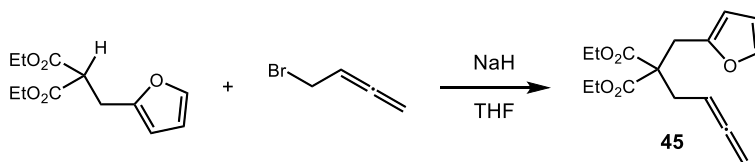


In a dry round bottom flask under and argon atmosphere, enone (136.6 mg, 0.464 mmol) and Et<sub>3</sub>N (0.12 mL, 1.9 equiv) were dissolved in MeCN (0.54 mL). The reaction was cooled to 0 °C and TBSCl (50% in toluene, 0.27 mL, 0.775 mmol, 1.67 equiv) in MeCN (0.54 mL) was added dropwise. NaI (127.3 mg, 0.849 mmol, 1.83 equiv) in MeCN (1.0 mL) was then added and the reaction was stirred overnight, warming to room temperature.

The reaction was quenched with saturated aqueous sodium bicarbonate and the organic layer was extracted with pentane and diethyl ether (1:1, 3x). The organic layers were combined, dried with MgSO<sub>4</sub>, filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5%-5% EtOAc in Hexanes. Diene-allene **43** was isolated as a colorless oil massing 168.0 mg (0.411 mmol, 89%).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*) δ ppm 5.96 (d, *J* = 15.2 Hz, 1H), 5.83 (dt, *J* = 15.2, 7.8 Hz, 1H), 5.01-4.94 (m, 1H), 4.68 (dt, *J* = 6.7, 2.4 Hz, 2H), 4.28 (s, 1H), 4.25 (s, 1H), 4.23-4.18 (m, 4H), 2.76 (d, *J* = 7.5 Hz, 2H), 2.62 (dt, *J* = 8.0, 2.5 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 6H), 0.98 (s, 9H), 0.18 (s, 6H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*) δ ppm 210.05, 170.50, 154.55, 132.12, 124.50, 95.18, 84.25, 74.60, 61.29, 57.71, 34.99, 31.87, 25.77, 18.19, 14.09, -4.74. **LRMS**: Calc: 408.23, Found: 295.21 [M-TBS<sup>+</sup>+2H<sup>+</sup>].

### Synthesis of diene-allene **45**.



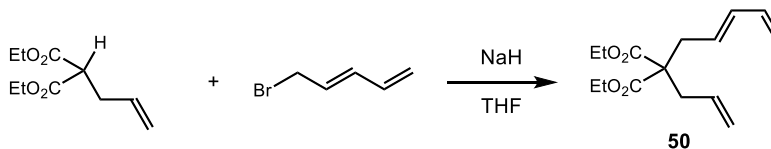
In a dry round bottom flask under and argon atmosphere, NaH (60% in mineral oil, 91.6 mg, 2.29 mmol) was suspended in THF. Malonate (500 mg, 2.08 mmol) was added

dropwise at room temperature. The reaction was allowed to stir 30 minutes while warming to room temperature. Allenyl bromide (192 mg, 0.879 mmol) was then added and the reaction was stirred at room temperature overnight.

The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the organic layer was extracted with  $\text{Et}_2\text{O}$  (3x). The organic layers were combined, dried with  $\text{MgSO}_4$ , filtered through cotton and concentrated. The resulting residue was purified with a plug of silica, rinsing with  $\text{EtOAc}$ . Diene-allene **45** was isolated as a colorless, waxy solid massing 178 mg (0.292 mmol, 61%).

$^1\text{H}$  NMR (400 MHz,  $\text{CHLOROFORM-}d$ )  $\delta$  ppm 7.31 (s, 1H), 6.29 (s, 1H), 6.09 (s, 1H), 5.05 (m, 1H), 4.71 (d,  $J = 4$  Hz, 2H), 4.21 (q,  $J = 6.8$  Hz, 4H), 3.35 (s, 2H), 2.59 (dt,  $J = 8.0, 2.4$  Hz, 2H), 1.27 (t,  $J = 7.1$  Hz, 6H).

### Synthesis of triene **50**.



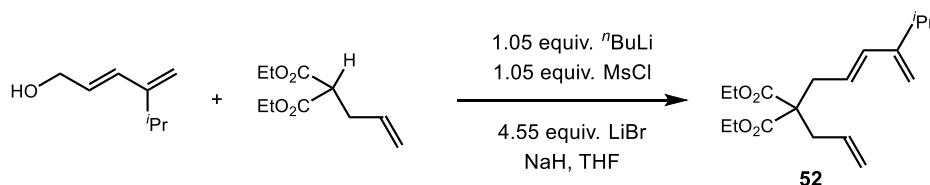
In a dry round bottom flask under and argon atmosphere, NaH (60% in mineral oil, 209.8 mg, 5.24 mmol) was suspended in THF (26 mL). Malonate (1.00 g, 4.99 mmol) was added dropwise at room temperature. The reaction was allowed to stir 30 minutes while warming to room temperature. Bromide (1.13 mg, 72% in ether, 5.49 mmol) was then added and the reaction was stirred at room temperature overnight.

The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the organic layer was extracted with  $\text{Et}_2\text{O}$  (3x). The organic layers were combined, dried with  $\text{MgSO}_4$ , filtered

through cotton and concentrated. The resulting residue was purified with a plug of silica, rinsing with EtOAc. Diene-allene **50** was isolated as a colorless, waxy solid massing 784 mg (2.94 mmol, 59%).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 6.29 (dt,  $J = 16.9, 10.2$  Hz, 1H), 6.10 (dd,  $J = 15.0, 10.5$  Hz, 1H), 5.67 (td,  $J = 17.3, 7.4$  Hz, 1H), 5.53 (dt,  $J = 15.2, 7.7$  Hz, 1H), 5.14-5.13 (m, 2H), 5.10 (s, 1H), 5.02 (d,  $J = 10.2$  Hz, 1H), 4.19 (q,  $J = 7.1$ , 4H), 2.66 (dd,  $J = 11.8, 7.5$  Hz, 4H), 1.25 (t,  $J = 7.2$  Hz, 6H)

### Synthesis of triene **52**.



This procedure was adapted from Wender and Christy.

In a dry round bottom flask under argon, dry THF (7.2 mL) was added to dissolve (*E*)-4-iso-propylpenta-2,4-dien-1-ol (500 mg, 3.96 mmol). The reaction was taken to  $-78$  °C and *n*-BuLi (2.5 M in hexanes, 1.66 mL, 4.16 mmol, 1.05 equiv) was added dropwise and the reaction was stirred 15 minutes. MsCl (0.32 mL, 4.16 mmol, 1.05 equiv) was added dropwise and stirred 15 minutes. LiBr (1.57 mg in 3.6 mL THF, 18.0 mmol, 4.55 equiv) added to reaction. The reaction was allowed to stir while warming to room temperature.

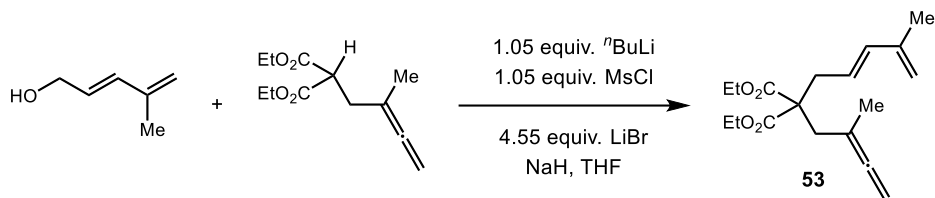
In a dry flask containing NaH (60% dispersion in mineral oil, 158.5 mg, 3.96 mmol, 1 equiv) under argon, THF (5.4 mL) was added to the flask. Allylmalonate (722 mg, 3.61 mmol) added dropwise at  $0$  °C and stirred 30 minutes. The reaction was then taken to  $-78$  °C and bromide solution was added. The reaction was allowed to stir at room temperature overnight.



The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the organic layer was extracted with  $\text{Et}_2\text{O}$  (3x). The organic layers were combined and washed with NaCl brine. The organic layer was then dried with  $\text{MgSO}_4$ , filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **52** was isolated as a colorless oil massing 679 mg (2.20 mmol, 56%).

$^1\text{H NMR}$  (400 MHz,  $\text{CHLOROFORM-}d$ )  $\delta$  ppm 6.08 (d,  $J = 15.6$  Hz, 1H), 5.74-5.56 (m, 2H), 5.16 (d,  $J = 1.6$  Hz, 1H), 5.12 (s, 1H), 4.91 (s, 2H), 4.21 (q,  $J = 6.8$  Hz, 4H), 2.71-2.66 (m, 4H), 2.54 (sept,  $J = 6.8$  Hz, 1H), 1.27 (t,  $J = 7.0$  Hz, 6H), 0.90 (d,  $J = 6.8$  Hz, 6H).

### Synthesis of diene-allene **53**.



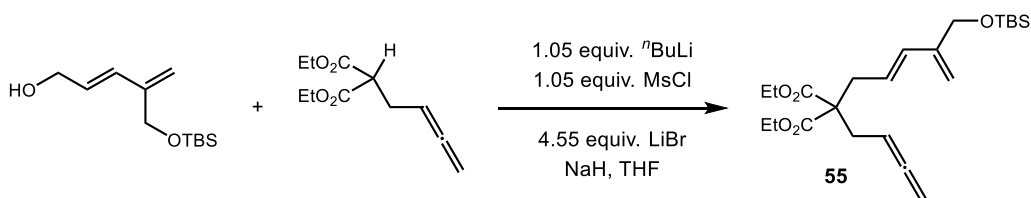
In a dry round bottom flask under argon, dry THF (9.3 mL) was added to dissolve alcohol (80 % in ether, 625 mg, 5.09 mmol). The reaction was taken to  $-78^\circ\text{C}$  and  $n\text{-BuLi}$  (2.5 M in hexanes, 2.14 mL, 5.35 mmol, 1.05 equiv) was added dropwise and the reaction was stirred 15 minutes.  $\text{MsCl}$  (414  $\mu\text{L}$ , 5.35 mmol, 1.05 equiv) was added dropwise and stirred 15 minutes.  $\text{LiBr}$  (2.01 g in 4.6 mL THF, 23.18 mmol, 4.55 equiv) added to reaction. The reaction was allowed to stir while warming to room temperature.

In a dry flask containing  $\text{NaH}$  (60% dispersion in mineral oil, 204 mg, 5.09 mmol, 1 equiv) under argon, THF (7 mL) was added to the flask. Malonate (984 mg, 4.636 mmol, 0.91 equiv) added dropwise at  $0^\circ\text{C}$  and stirred 30 minutes. The reaction was then taken to  $-78^\circ\text{C}$  and bromide solution was added. The reaction was allowed to stir at room temperature overnight.

The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the organic layer was extracted with  $\text{Et}_2\text{O}$  (3x). The organic layers were combined and washed with NaCl brine. The organic layer was then dried with  $\text{MgSO}_4$ , filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **53** was isolated as a colorless oil massing 73.3 mg (0.239 mmol, 26 %).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CHCl}_3$ - $d$ )  $\delta$  ppm 6.17 (d,  $J$  = 15.4 Hz, 1H), 5.51 (dt,  $J$  = 15.2, 7.7 Hz, 1H), 4.90 (s, 1H), 4.87 (s, 1H), 4.61-4.59 (m, 2H), 4.23-4.11 (m, 4H), 2.79 (d,  $J$  = 7.8 Hz, 2H), 2.62 (br. s, 2H), 1.80 (s, 3H), 1.66 (t,  $J$  = 3.1 Hz, 3H), 1.25 (t,  $J$  = 7.1 Hz, 6H).  **$^{13}\text{C}$  NMR** (151MHz,  $\text{CHCl}_3$ - $d$ )  $\delta$  ppm 207.73, 171.03, 141.89, 136.97, 124.26, 115.66, 93.64, 74.71, 61.36, 57.66, 35.89, 35.76, 20.13, 18.70, 14.19. **LRMS**: Calc: 306.18, Found: 307.36 [M+H]. **IR**: 3018.7, 2980.5, 2938.0, 1958.4, 1732.7, 1609.3, 1445.4, 1369.2, 1299.8, 1265.1, 1237.1, 1186.0, 1096.3, 1041.4, 970.0, 886.1, 858.2.

### Synthesis of diene-allene **55**.



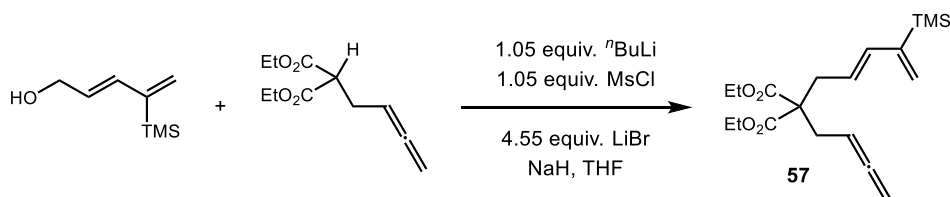
In a dry round bottom flask under argon, dry THF (1.2 mL) was added to dissolve alcohol (147 mg, 0.643 mmol). The reaction was taken to  $-78\text{ }^\circ\text{C}$  and  $n\text{-BuLi}$  (2.6 M in hexanes, 0.26 mL, 0.68 mmol, 1.05 equiv) was added dropwise and the reaction was stirred 15 minutes.  $\text{MsCl}$  (52  $\mu\text{L}$ , 0.68 mmol, 1.05 equiv) was added dropwise and stirred 15 minutes.  $\text{LiBr}$  (254 mg in 0.60 mL THF, 2.92 mmol, 4.55 equiv) added to reaction. The reaction was allowed to stir while warming to room temperature.

In a dry flask containing NaH (60% dispersion in mineral oil, 25.7 mg, 0.643 mmol, 1.0 equiv) under argon, THF (0.96 mL) was added to the flask. Malonate (124.1 mg, 0.58 mmol, 0.91 equiv) added dropwise at 0 °C and stirred 30 minutes. The reaction was then taken to -78 °C and bromide solution was added. The reaction was allowed to stir at room temperature overnight.

The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and the organic layer was extracted with Et<sub>2</sub>O (3x). The organic layers were combined and washed with NaCl brine. The organic layer was then dried with MgSO<sub>4</sub>, filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **55** was isolated as a colorless oil massing 96.7 mg (0.229 mmol, 39%).

<sup>1</sup>H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 6.13 (d, *J* = 16.0 Hz, 1H), 5.50 (dt, *J* = 16.0, 8.0 Hz, 1H), 5.24 (d, *J* = 1.6 Hz, 1H), 5.03 (s, 1H), 5.03-4.94 (m, 1H), 4.68 (dt, *J* = 6.8, 2.5 Hz, 2H), 4.28 (s, 2H), 4.20 (q, *J* = 7.2 Hz, 4H), 2.72 (d, *J* = 7.6 Hz, 2H), 2.62 (dt, *J* = 8.0, 2.5 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 6H), 0.92 (s, 9H), 0.08 (s, 6H).

### Synthesis of diene-allene **57**.



In a dry round bottom flask under argon, dry THF (1.6 mL) was added to dissolve alcohol (94 % in ether, 150 mg, 0.903 mmol). The reaction was taken to -78 °C and *n*-BuLi (2.4 M in hexanes, 0.40 mL, 0.948 mmol, 1.05 equiv) was added dropwise and the reaction was stirred 15 minutes. MsCl (73 μL, 0.948 mmol, 1.05 equiv) was added dropwise and stirred 15 minutes.

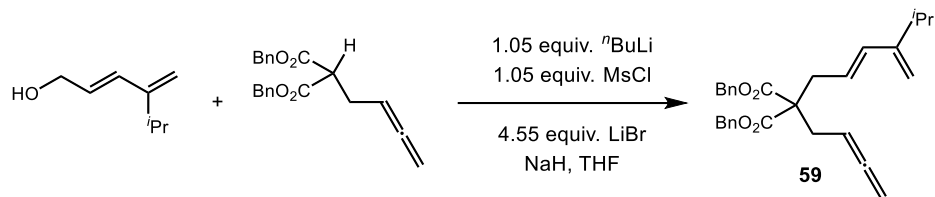
LiBr (357 mg in 0.82 mL THF, 4.11 mmol, 4.55 equiv) added to reaction. The reaction was allowed to stir while warming to room temperature.

In a dry flask containing NaH (60% dispersion in mineral oil, 36.1 mg, 0.903 mmol, 1.0 equiv) under argon, THF (1.3 mL) was added to the flask. Malonate (174.5 mg, 0.822 mmol, 0.91 equiv) added dropwise at 0 °C and stirred 30 minutes. The reaction was then taken to -78 °C and bromide solution was added. The reaction was allowed to stir at room temperature overnight.

The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl and the organic layer was extracted with Et<sub>2</sub>O (3x). The organic layers were combined and washed with NaCl brine. The organic layer was then dried with MgSO<sub>4</sub>, filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **57** was isolated as a colorless oil massing 170.5 mg (0.487 mmol, 59%).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*) δ ppm 6.21 (d, *J* = 15.9 Hz, 1H), 5.64 (d, *J* = 3.2 Hz, 1H), 5.56 (dt, *J* = 16.8, 8.0 Hz, 1H), 5.36 (d, *J* = 3.2 Hz, 1H), 5.00-4.93 (m, 1H), 4.67 (dt, *J* = 6.7, 2.4 Hz, 2H), 4.23-4.16 (m, 4H), 2.72 (d, *J* = 7.6 Hz, 2H), 2.62 (dt, *J* = 8.1, 2.5 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 6H), 0.15 (s, 9H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*) δ ppm 210.07, 170.63, 148.75, 139.13, 127.51, 125.57, 84.31, 74.59, 61.29, 57.87, 36.27, 32.03, 14.13, -0.93. **LRMS**: Calc: 350.19, Found: 351.35 [M+H]. **IR**: 2960.2, 1956.4, 1733.7, 1442.5, 1367.3, 1271.8, 1248.7, 1197.6, 1095.4, 971.0, 840.8, 759.8.

### Synthesis of diene-allene **59**.



In a dry round bottom flask under argon, dry THF (1.4 mL) was added to dissolve (*E*)-4-*iso*-propylpenta-2,4-dien-1-ol (100 mg, 0.792 mmol). The reaction was taken to  $-78\text{ }^{\circ}\text{C}$  and *n*-BuLi (2.6 M in hexanes, 0.32 mL, 0.83 mmol, 1.05 equiv) was added dropwise and the reaction was stirred 15 minutes. MsCl (64  $\mu\text{L}$ , 0.83 mmol, 1.05 equiv) was added dropwise and stirred 15 minutes. LiBr (313 mg in 0.72 mL THF, 3.61 mmol, 4.55 equiv) added to reaction. The reaction was allowed to stir while warming to room temperature.

In a dry flask containing NaH (60% dispersion in mineral oil, 31.7 mg, 0.792 mmol, 1 equiv) under argon, THF (1.2 mL) was added to the flask. Buta-3,4-dibenzylmalonate (205 mg, 0.721 mmol, 0.91 equiv) added dropwise at  $0\text{ }^{\circ}\text{C}$  and stirred 30 minutes. The reaction was then taken to  $-78\text{ }^{\circ}\text{C}$  and bromide solution was added. The reaction was allowed to stir at room temperature overnight.

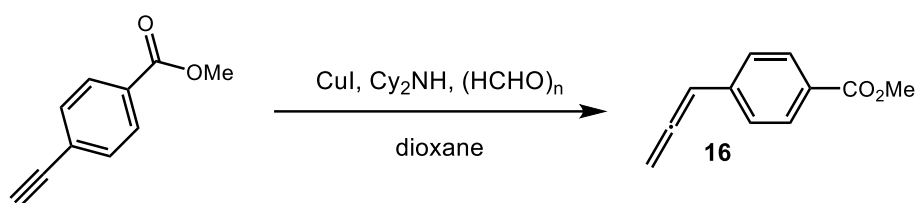
The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the organic layer was extracted with  $\text{Et}_2\text{O}$  (3x). The organic layers were combined and washed with NaCl brine. The organic layer was then dried with  $\text{MgSO}_4$ , filtered through cotton and concentrated. The resulting residue was purified with flash chromatography with 2.5% EtOAc in Hexanes. Diene-allene **59** was isolated as a colorless oil massing 228 mg (0.512 mmol, 71%).

**$^1\text{H}$  NMR** (400 MHz,  $\text{CHLOROFORM-}d$ )  $\delta$  ppm 7.34-7.32 (m, 6H), 7.29-7.28 (m, 4H), 6.02 (d,  $J = 15.7\text{ Hz}$ , 1H), 5.46 (dt,  $J = 15.7, 7.8\text{ Hz}$ , 1H), 5.13 (d,  $J = 12.5\text{ Hz}$ , 1H), 5.11 (t,  $J = 12.5\text{ Hz}$ , 1H), 4.92 (quin,  $J = 7.2\text{ Hz}$ , 1H), 4.87 (s, 1H), 4.84 (s, 1H), 4.62-4.61 (m, 2H), 2.76 (d,  $J = 7.7\text{ Hz}$ , 2H), 2.65 (d,  $J = 8.1\text{ Hz}$ , 2H), 2.39 (sept,  $J = 6.8\text{ Hz}$ , 1H), 1.01 (d,  $J = 6.3\text{ Hz}$ ,

6H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 210.09, 170.35, 152.20, 136.41, 128.51, 128.48, 128.29, 128.25, 122.01, 111.56, 84.08, 74.70, 67.06, 58.08, 36.04, 32.02, 29.15, 22.09. **LRMS**: Calc: 444.23, Found: 445.40 [M+H]. **IR**: 3065.3, 3033.5, 2962.1, 1955.5, 1733.7, 1455.0, 1375.0, 1270.9, 1191.8, 1069.3, 971.0, 893.8, 846.6, 747.3, 697.1.

### 3.2.3 Synthesis and Analytical Data for Allenes

#### Synthesis of allene 16.



CuI (417 mg, 2.19 mmol, 0.5 equiv) and (HCHO)<sub>n</sub> (236 mg, 7.87 mmol, 1.8 equiv) were suspended in dry dioxane (22 mL) under Ar. Methers 4-ethynylbenzoate (700 mg, 4.37 mmol, 1 equiv) and dicyclohexyl (2.2 mL, 10.9 mmol, 2.5 equiv) added at room temperature. The reaction was heated to reflux for 5.5 hr.

The reaction was cooled to room temperature and diluted with Et<sub>2</sub>O. The reaction was washed with H<sub>2</sub>O (3x), which was then backextracted with Et<sub>2</sub>O. The organic layers were combined and washed with 1N HCl (3x), H<sub>2</sub>O and brine. Reaction purified with flash chromatography with 5%-10% EtOAc in hexanes. The pure product was a waxy yellow solid massing 350 mg (2.01 mmol, 46%).

**<sup>1</sup>H NMR** (400 MHz, CHLOROFORM-*d*)  $\delta$  ppm 7.98 (d, *J* = 8.25 Hz, 2H), 7.36 (d, *J* = 8.25 Hz, 2H), 6.21 (t, *J* = 6.8 Hz, 1H), 5.21 (d, *J* = 6.8 Hz, 2H), 3.91 (s, 3H). **<sup>13</sup>C NMR** (151MHz, CHLOROFORM-*d*)  $\delta$  ppm 210.63, 166.89, 139.00, 129.92, 128.40, 126.51, 93.60, 79.22,

52.02. **LRMS:** Calc: 174.07, Found: 174.0 [M]<sup>†</sup>. **IR:** 2949.6, 1929.1, 1720.2, 1607.4, 1435.7, 1311.4, 1279.5, 1176.4, 1107.9, 855.3, 773.3, 703.9.

### 3.3 Experimental Procedures and Analytical Data for Chapter 2.

The following compounds were made according to literature procedures: **62**,<sup>97</sup> **64**,<sup>118</sup> **68**,<sup>119</sup> **70**,<sup>120</sup> **72**.<sup>121</sup> Palladium precatalysts and ligands were purchased and used without purification.

#### 3.3.1 Alkyl-Heck Type Cyclization Procedures and Analytical Data

##### General procedure for alkyl-Heck type cyclizations:

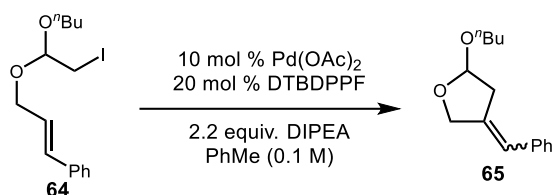
In a glovebox, palladium precatalyst (0.02 mmol, 10 mol %) and ligand (0.04 mmol, 20 mol %) were weighed into an oven dried vial. A solution of alkyl halide (0.2 mmol, 1 equiv.) in toluene (1 mL) was added to catalyst mixture. Additional toluene was used to rinse vial (1 mL). Base (0.40-0.44 mmol, 2.0-2.2 equiv) is added immediately prior to leaving the glovebox. The reaction is heated for 24-48 h in the sealed vial. Upon removal from heat, the vial is cooled to room temperature. 1N HCl is added and the product is extracted with DCM (3x). The organic layers were collected, washed with brine, dried and concentrated. A small amount of 1,3,5-trimethoxybenzene was added for use as internal standard with <sup>1</sup>H NMR.

##### Alkyl-Heck type cyclization forming **63**.



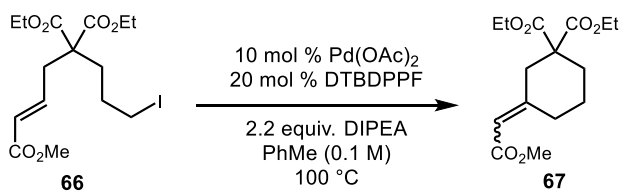
Reaction performed according to the General Procedure with 62.4 mg (0.20 mmol) of iodide **62**. The reaction was heated for 24 h at 100 °C. Yield were determined through NMR yield with an internal standard of 1,3,5-trimethoxybenzene. The product was determined through comparison with a literature spectrum.

#### Alkyl-Heck type cyclization forming **65**.



Reaction performed according to the General Procedure with 72.0 mg (0.20 mmol) of iodide **64**. The reaction was heated for 10.5 h at 100 °C. Yield were determined through NMR yield with an internal standard of 1,3,5-trimethoxybenzene. The product was determined through comparison with a literature spectrum.

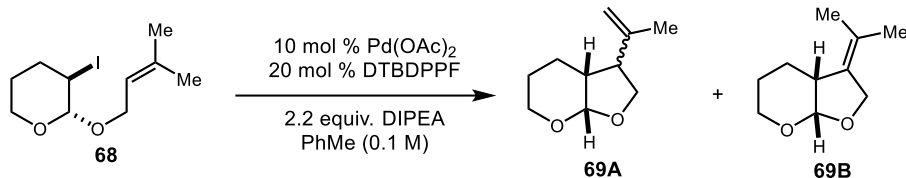
#### Alkyl-Heck type cyclization forming **67**.



Reaction performed according to the General Procedure with 85.2 mg (0.20 mmol) of iodide **66**. The reaction was heated for 24 h at 100 °C. Yield were determined through NMR yield with an internal standard of 1,3,5-trimethoxybenzene.

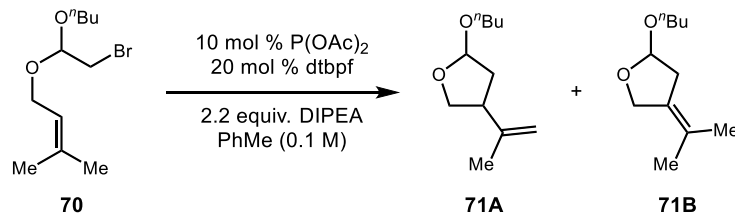


### Alkyl-Heck type cyclization forming **69**.



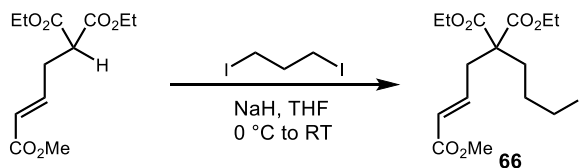
Reaction performed according to the General Procedure with 59.2 mg (0.20 mmol) of iodide **68**. The reaction was heated for 24 h at 100 °C. Yield were determined through NMR yield with an internal standard of 1,3,5-trimethoxybenzene. The product was determined through comparison with a literature spectrum.

### Alkyl-Heck type cyclization forming **71A** and **71B**.



Reaction performed according to the General Procedure with 53.0 mg (0.20 mmol) of iodide **70**. The reaction was heated for 48 h at 100 °C. Yield were determined through NMR yield with an internal standard of 1,3,5-trimethoxybenzene. The product was determined through comparison with a literature spectrum.

### Synthesis of Iodide **66**.



In a dry round bottom flask under an argon atmosphere, NaH (60% in mineral oil, 154 mg, 2.84 mmol) was suspended in THF (19.4 mL). Malonate (1.00 g, 3.87 mmol) was added dropwise at room temperature. The reaction was allowed to stir 30 minutes while warming to room temperature. 1,3-diiodopropane (0.89 mL, 7.74 mmol) was then added and the reaction was stirred at room temperature overnight.

The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  and the organic layer was extracted with  $\text{Et}_2\text{O}$  (3x). The organic layers were combined, dried with  $\text{MgSO}_4$ , filtered through cotton and concentrated. The resulting residue was purified with a plug of silica, rinsing with  $\text{EtOAc}$ . Diene-allene **50** was isolated as a colorless, waxy solid massing 874 mg (2.05 mmol, 53%).

$^1\text{H}$  NMR (400 MHz,  $\text{CHCl}_3$ -*d*)  $\delta$  ppm 6.84-6.76 (m, 1H), 5.90 (d,  $J$  = 15.6 Hz, 1H), 4.22 (q,  $J$  = 7.0 Hz, 4H), 3.74 (s, 3H), 3.16 (t,  $J$  = 6.8 Hz, 2H), 2.78 (dd,  $J$  = 7.8, 1.3 Hz, 2H), 2.01-1.97 (m, 2H), 1.81-1.74 (m, 2H), 1.27 (t,  $J$  = 7.2 Hz, 6H).

### 3.3.2 Alkyl Halide Carbonylation Procedures and Analytical Data

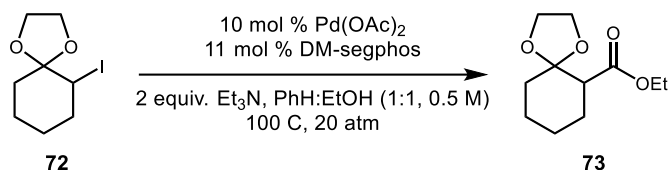
#### General procedure for alkyl halide carbonylations:

In a glovebox, palladium precatalyst (0.02 mmol, 10 mol %) and ligand (0.0275 mmol, 11 mol %) were weighed into a stainless steel Parr pressure vessel. A solution of alkyl halide (0.25 mmol, 1 equiv.) in toluene (0.25 mL) was added to catalyst mixture. Ethanol was used to rinse vial (0.25 mL). Base (0.50 mmol, 2.0 equiv) is added immediately prior to sealing Parr vessel and leaving the glovebox. The pressure vessel is purged twice with CO gas before filling to the desired pressure. The reaction is heated for 4 h in the sealed vial. Upon removal from heat, the vessel is cooled to room temperature, then vented. 1N HCl is added and the product is

extracted with DCM (3x). The organic layers were collected, washed with brine, dried and concentrated. The crude product is then purified with a pipette-sized silica gel column.

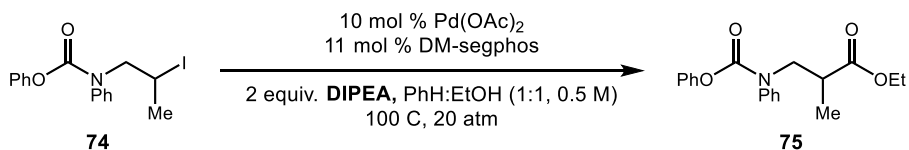
### 3.3.3 Synthesis and Analytical Data for Alkyl Halides

#### Pd-catalyzed carbonylation forming **73**.



Reaction performed according to the General Procedure with 59.2 mg (0.20 mmol) of iodide **72**. The reaction was heated for 24 h at 100 °C. The product was determined through comparison with a literature spectrum. Measurements of enantioenrichment were determined using GC with a chiral column at 120 °C with a flow rate of 1.5 mL/min. GC spectra were obtained using an Agilent 6850 series GC with a Hydrodex-β-6TBDM column.

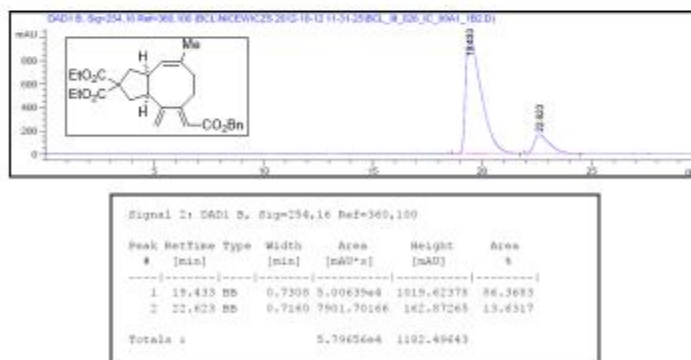
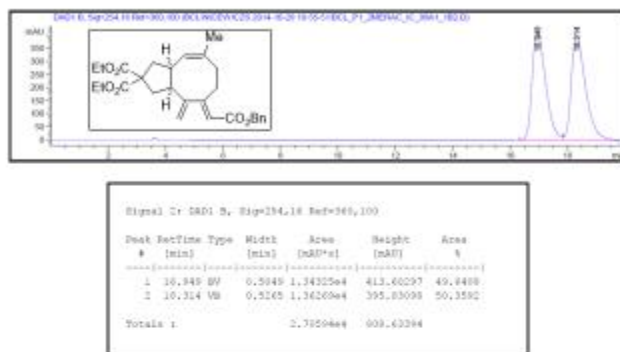
#### Pd-catalyzed carbonylation forming **75**.



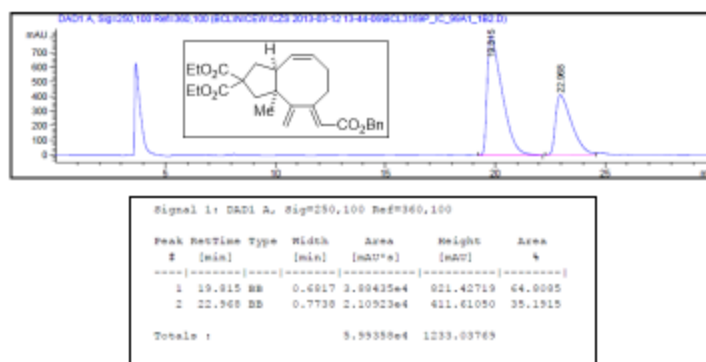
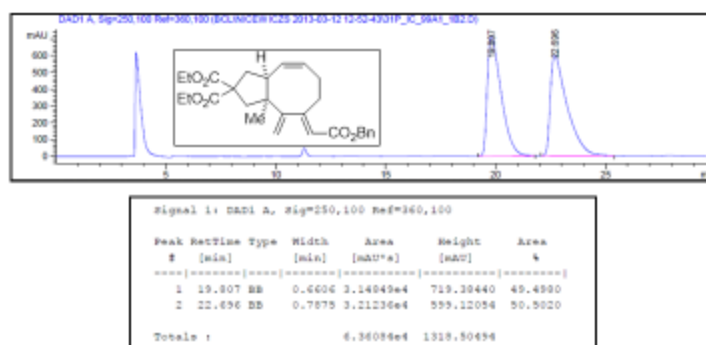
Reaction performed according to the General Procedure with 59.2 mg (0.20 mmol) of iodide **74**. The reaction was heated for 4 h at 100 °C. The products were purified with a short silica column with 10% EtOAc in Hexanes. **HPLC**: Chiralpak IC, 90 : 10 Hexanes/IPA.

### 3.4.1 HPLC Traces for Enantioselective [4 + 2 + 2] Cycloadditions

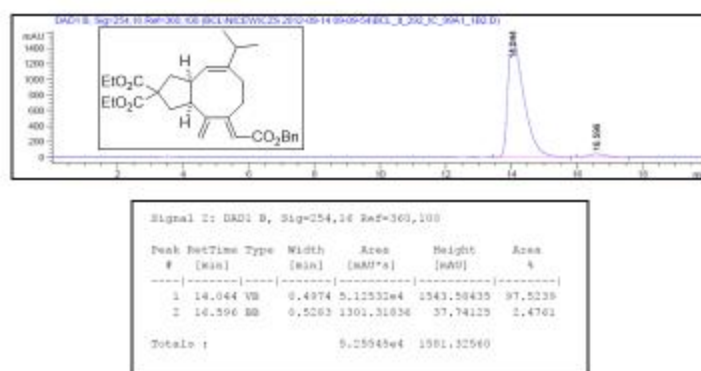
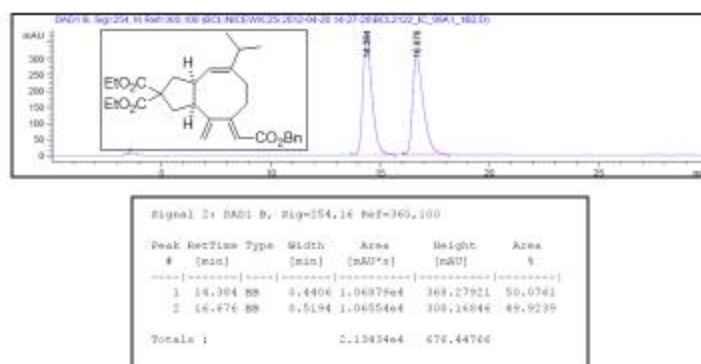
HPLC Spectra of 31



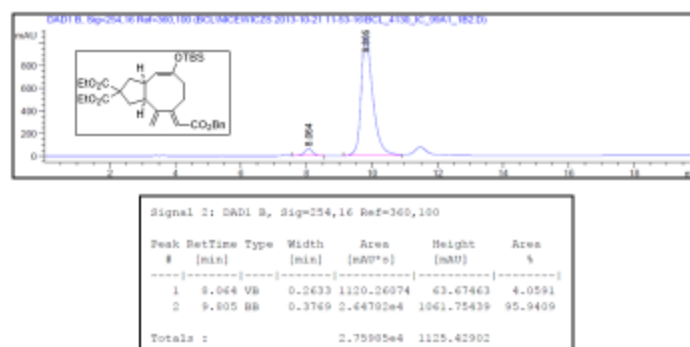
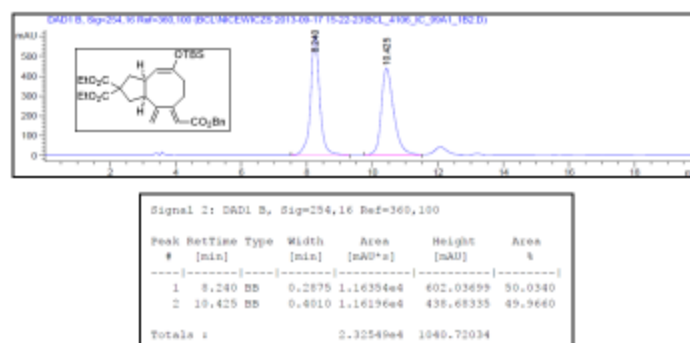
# HPLC Spectra of 37



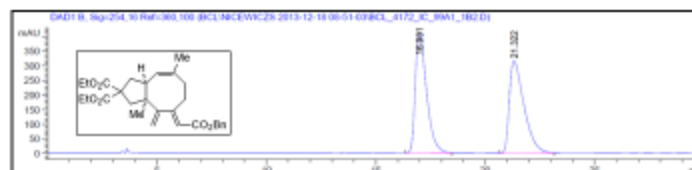
## HPLC Spectra of 39



# HPLC Spectra of 44

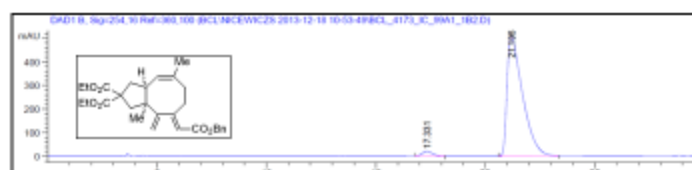


# HPLC Spectra of 54



Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.991	BB	0.5476	1.47039e4	410.02946	50.0590
2	21.322	BB	0.6961	1.46692e4	316.04729	49.9410
Totals :				2.93731e4	727.67566	

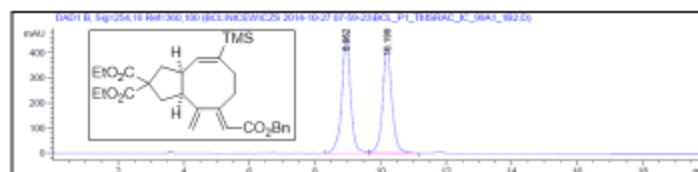


Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.331	BB	0.4084	636.02905	20.03438	2.4747
2	21.196	BB	0.7310	2.50648e4	500.52640	97.5253
Totals :				2.57009e4	520.56098	

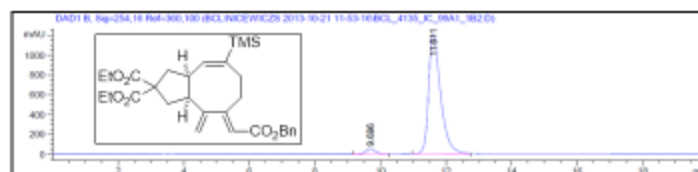


## HPLC Spectra of 58



```
Signal 2: DAD1 B, Sig=254.16 Ref=340.100
```

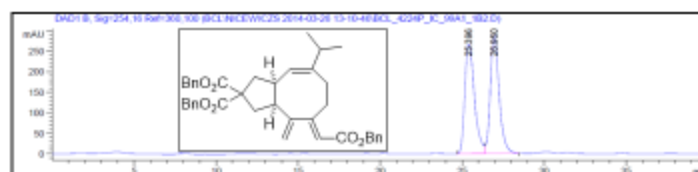
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.952	BV	0.2771	8938.40625	475.06332	51.3083
2	10.198	BV	0.3011	8360.84648	419.45456	49.6117
Totals :				1.71993648	893.51708	



```
Signal 1r: DADI B, Sig=234,16 Ref=360,100
```

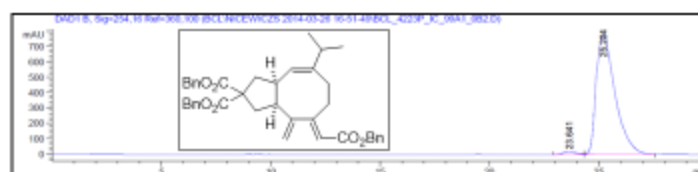
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.696	BD	0.3064	1061.14270	52.37360	3.3532
2	11.611	BD	0.3021	3.95045e4	1204.94805	96.6469
Totals :				3.14645e4	1257.32245	

# HPLC Spectra of 60



Signal 2: DAD1 B, Sig=254,16 Ref=360,100

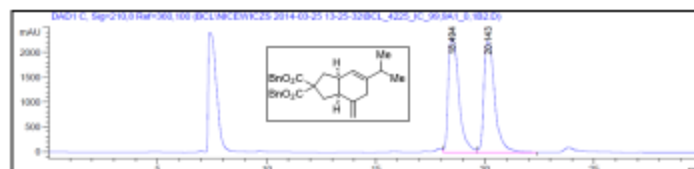
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.396	BV	0.4276	1.59758e4	266.95939	50.2081
2	26.950	VB	0.5444	1.58848e4	289.63397	49.7919
Totals :				2.18606e4	556.63336	



Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.641	BV	0.4108	812.03510	19.22462	1.7042
2	25.204	VB	0.7936	4.69360e4	776.60461	98.2958
Totals :				4.76481e4	795.82923	

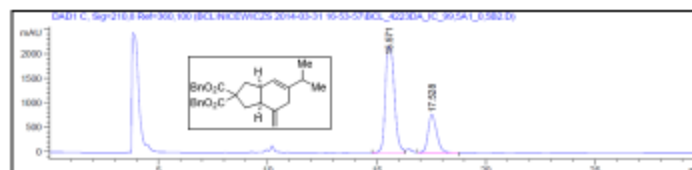
# HPLC Spectra of 61



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

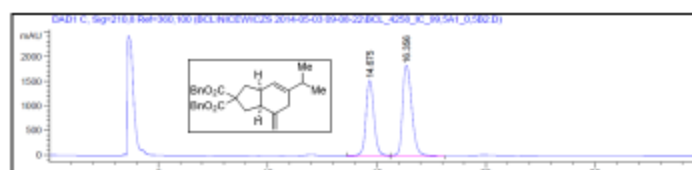
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.494	VV	0.5051	7.91046e4	2271.90381	50.0391
2	20.143	VB	0.5252	7.79824e4	2234.17017	49.9609
Totals :				1.56987e5	4506.07397	

# HPLC Spectra of 61con't



Signal 3: DAD1 C, Sig=210,8 Ref=369,100

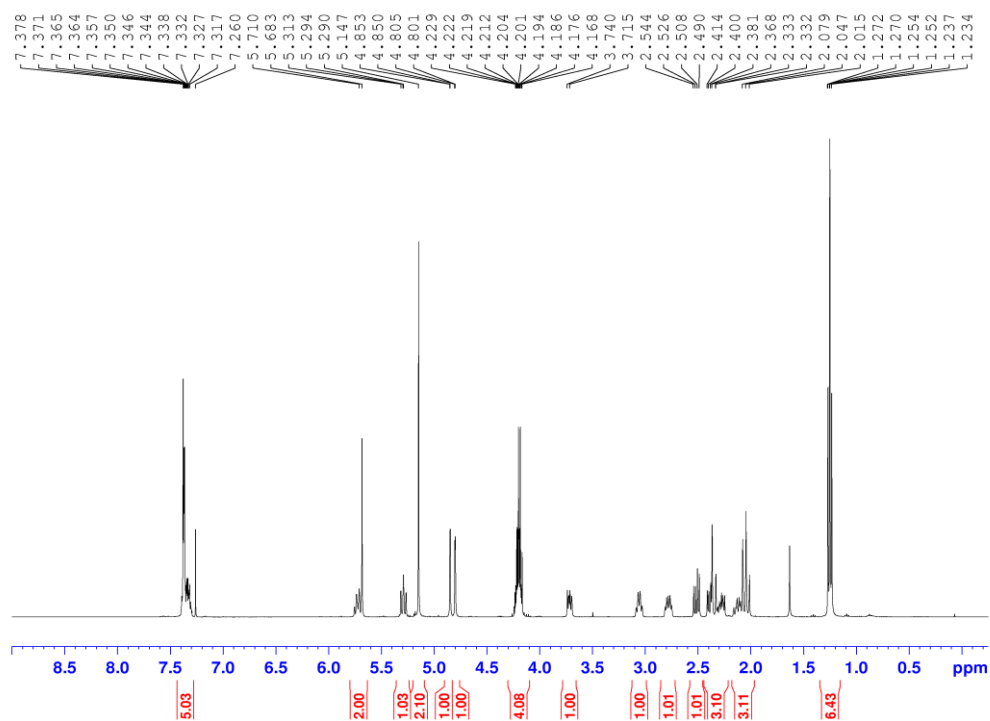
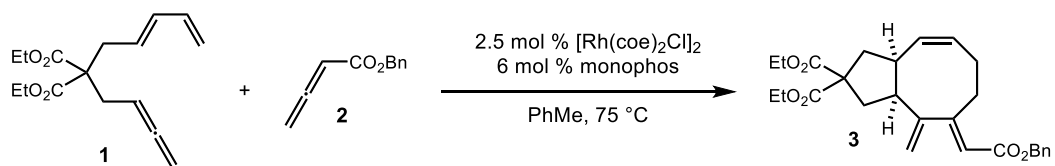
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.571	UV	0.4611	6.29644e4	2162.70369	74.5434
2	17.528	UV	0.4225	2.14682e4	781.45477	25.4566
Totals :				8.43326e4	2944.23846	

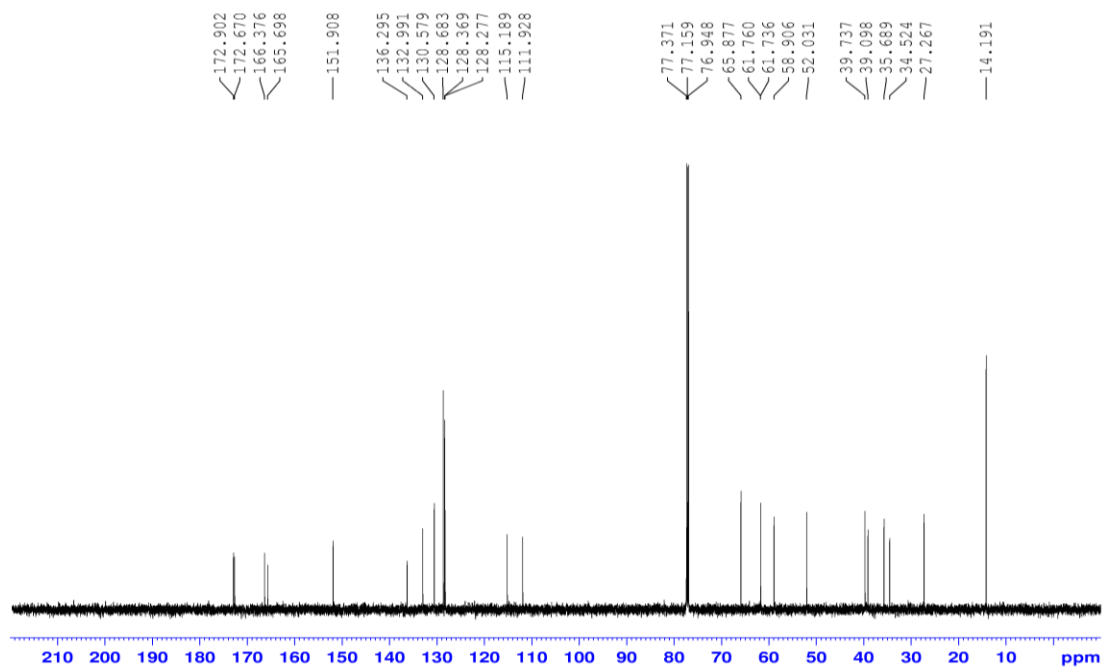


Signal 3: DAD1 C, Sig=210,8 Ref=369,100

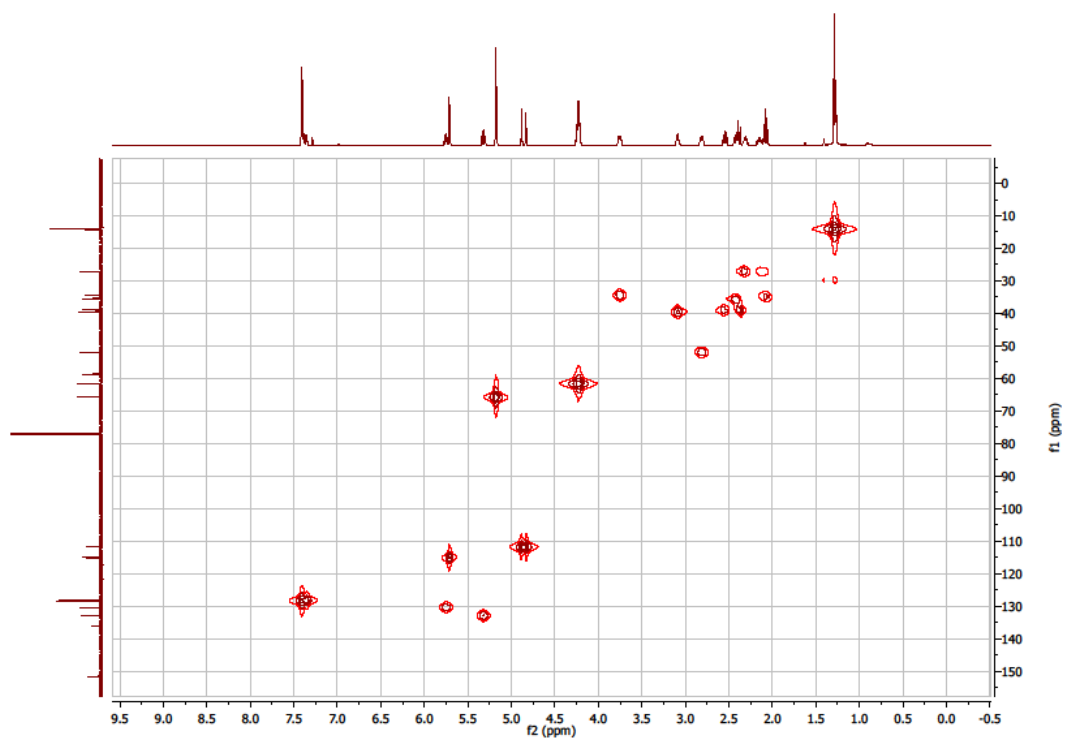
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.675	UV	0.3965	3.91942e4	1531.94924	42.0114
2	16.356	UV	0.4612	5.41090e4	1839.12268	57.9886
Totals :				9.32942e4	3370.97192	

### 3.4.2 NMR Spectra for [4 + 2 + 2] Cycloadditions

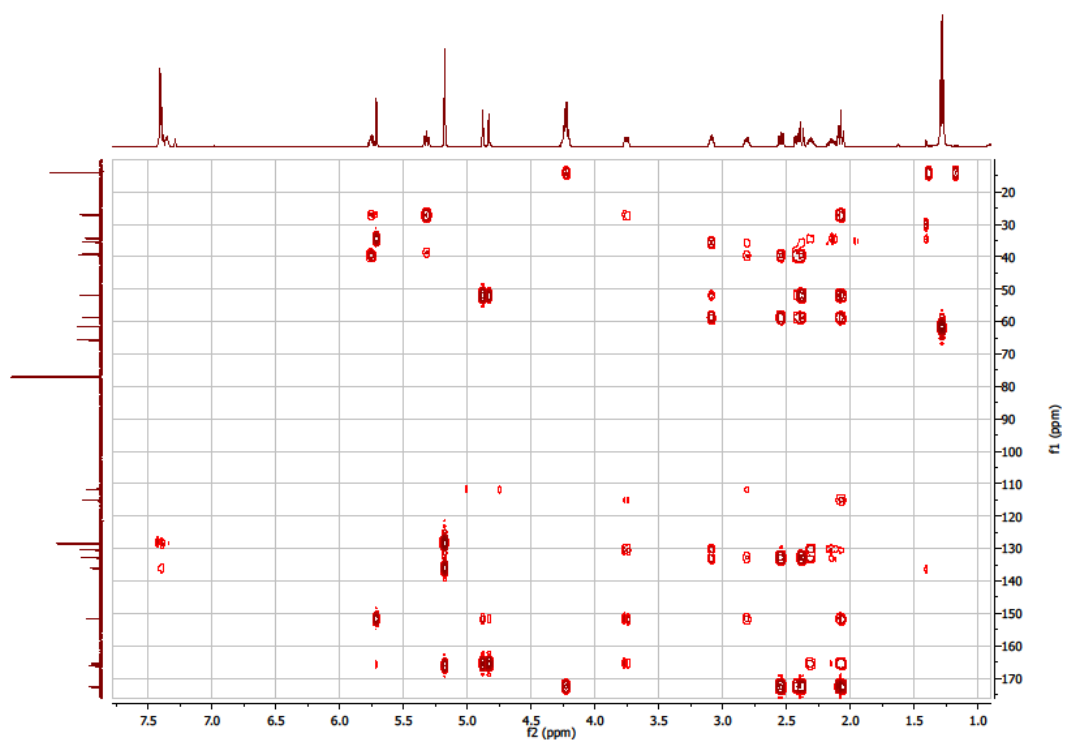




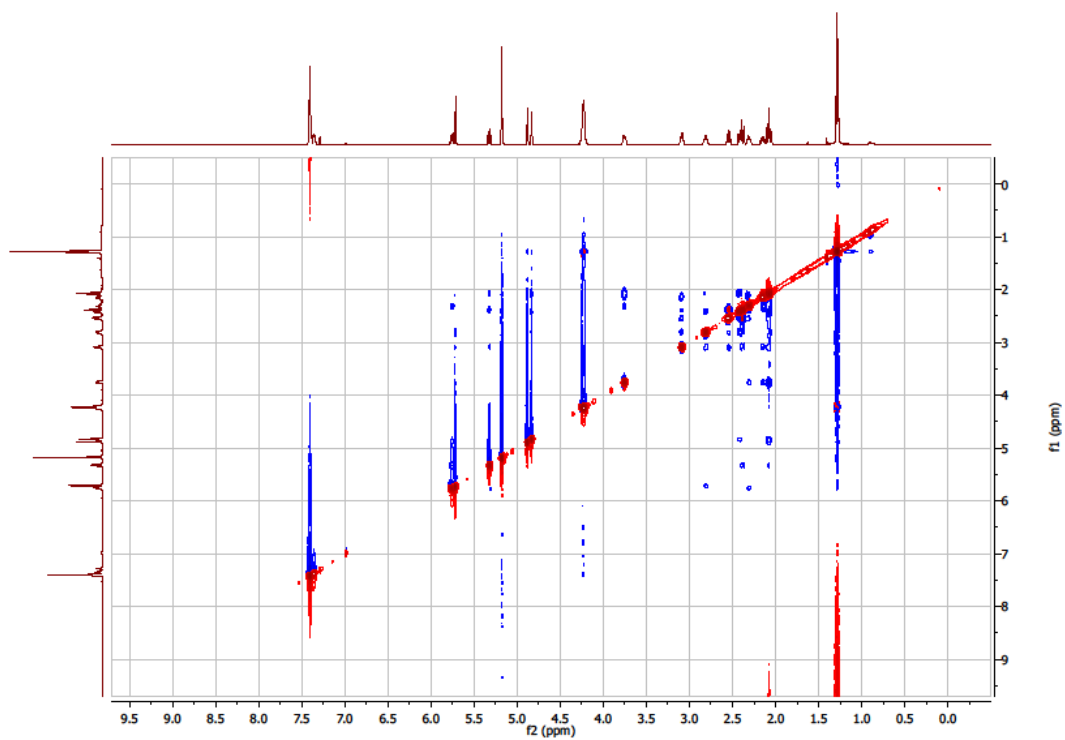
HMQC

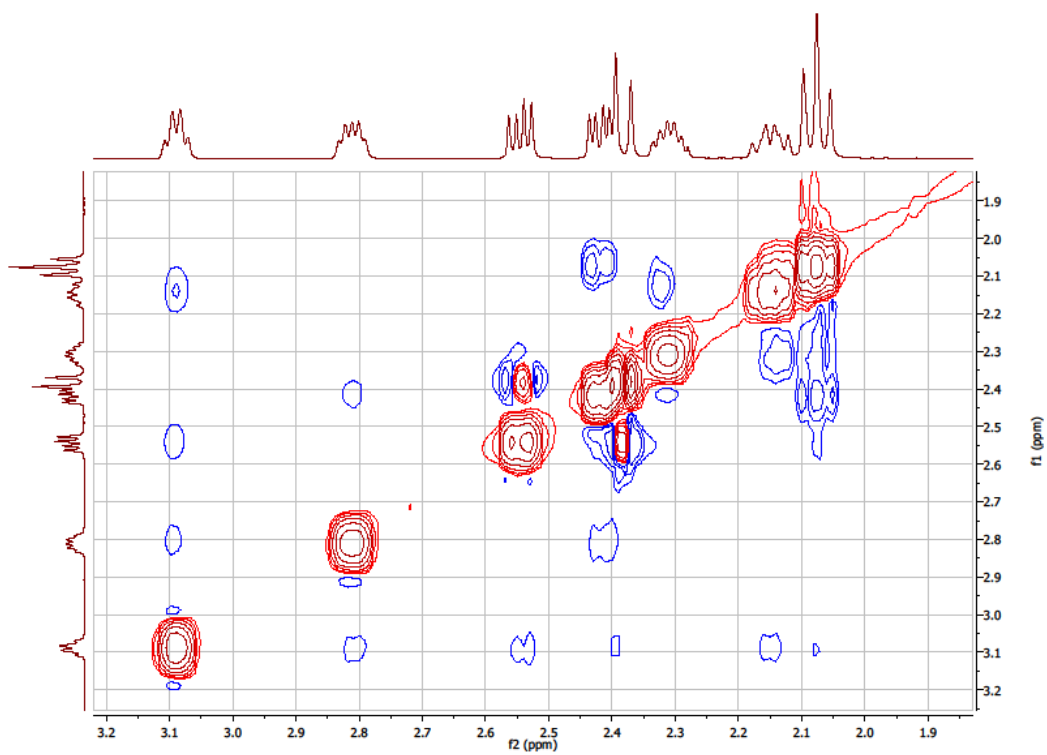


HMBC

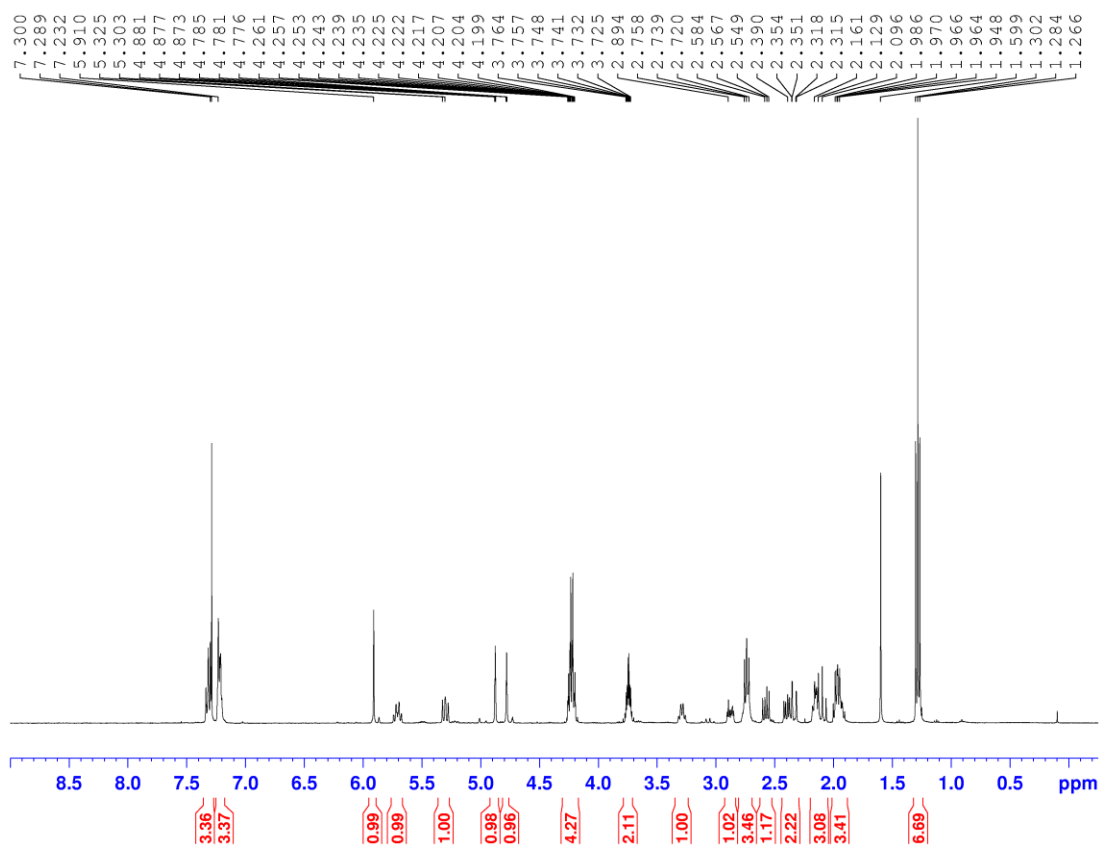
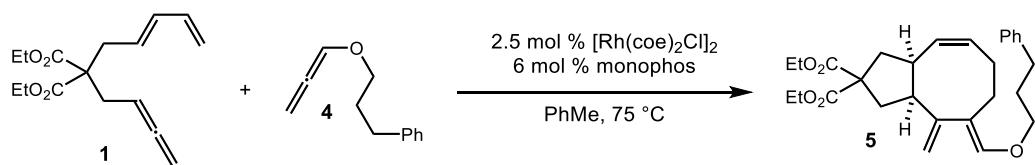


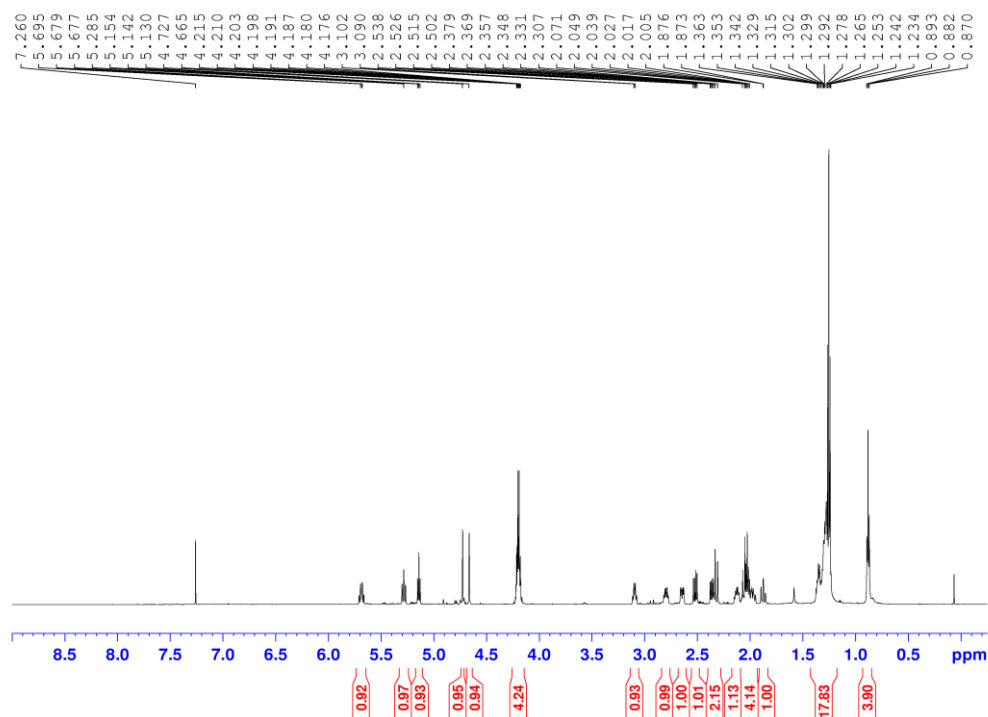
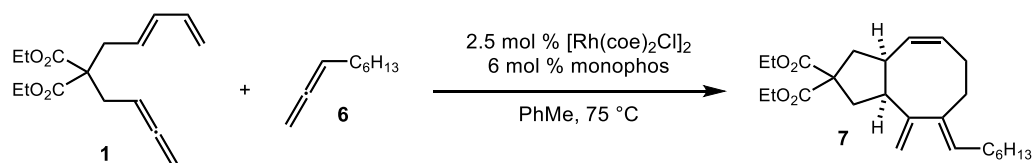
NOESY

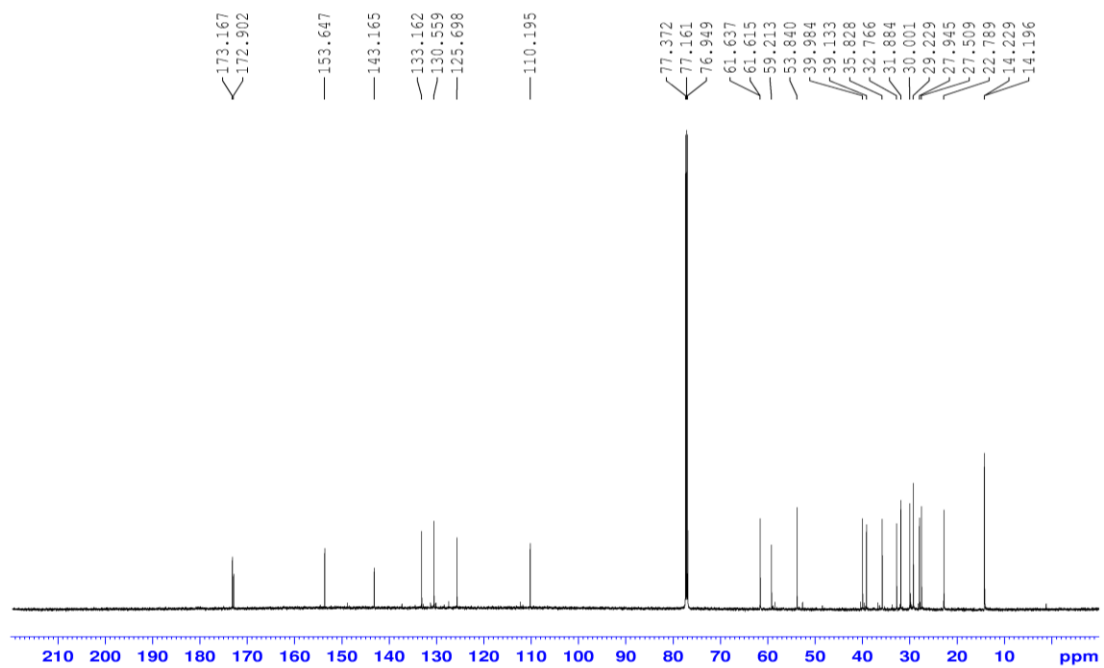


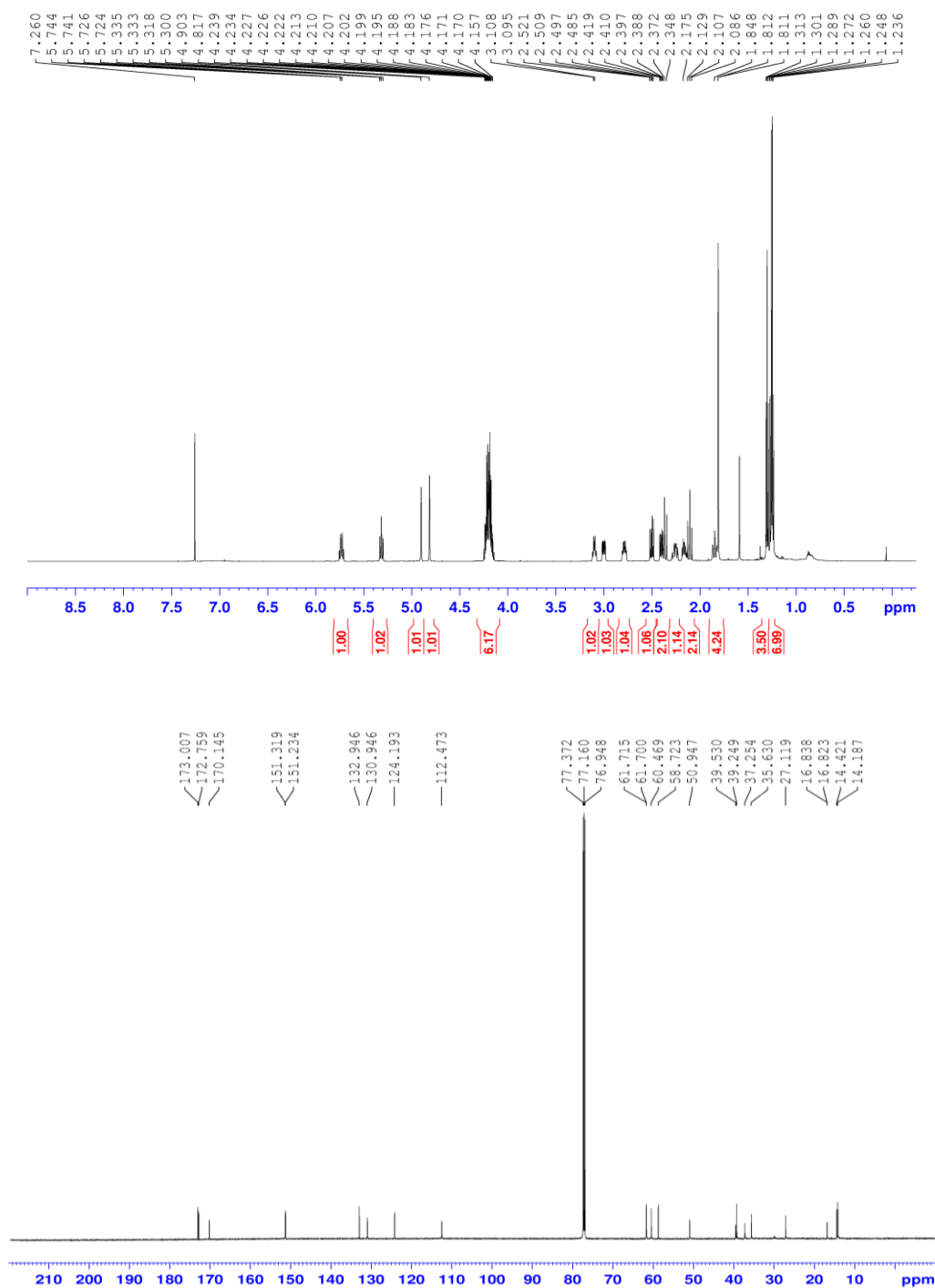
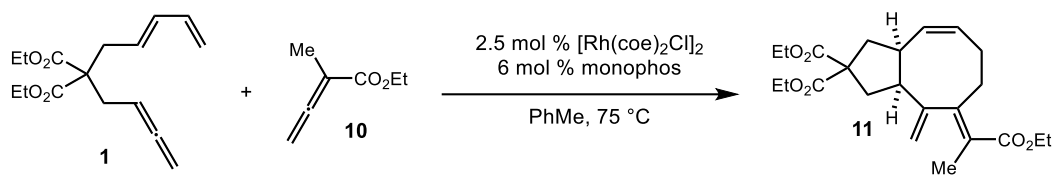


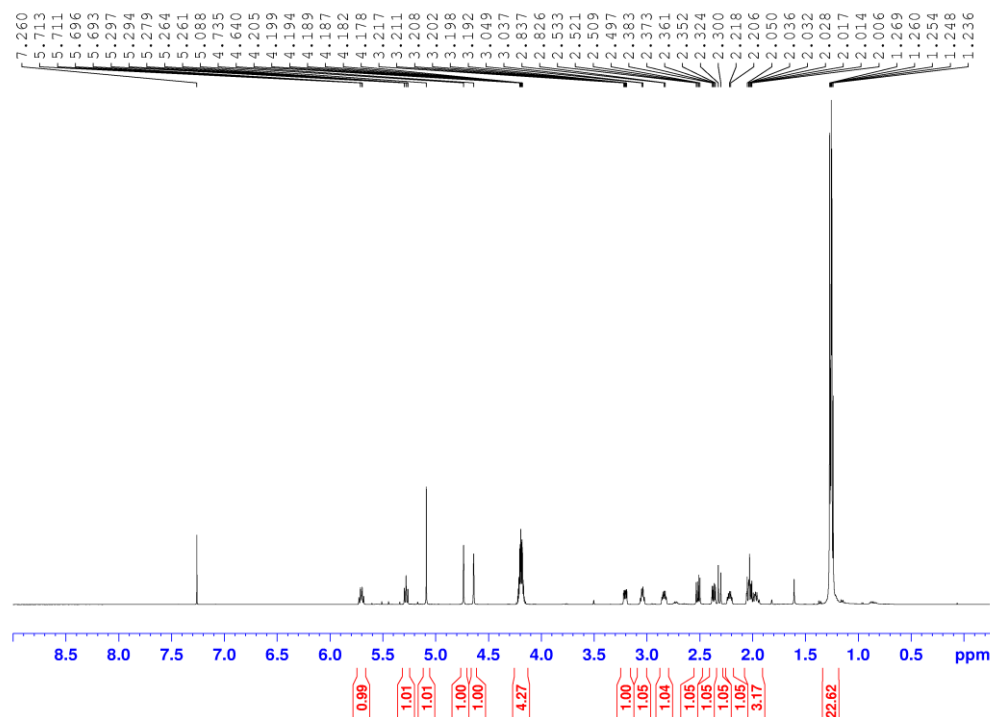
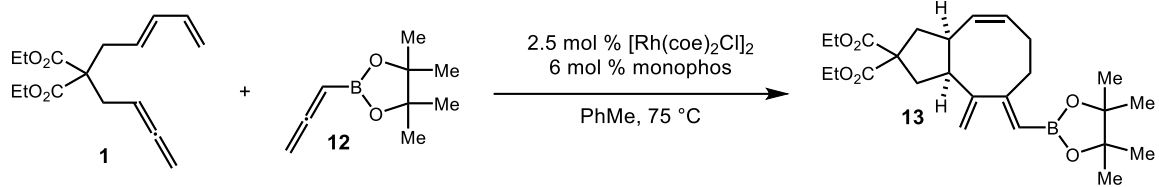


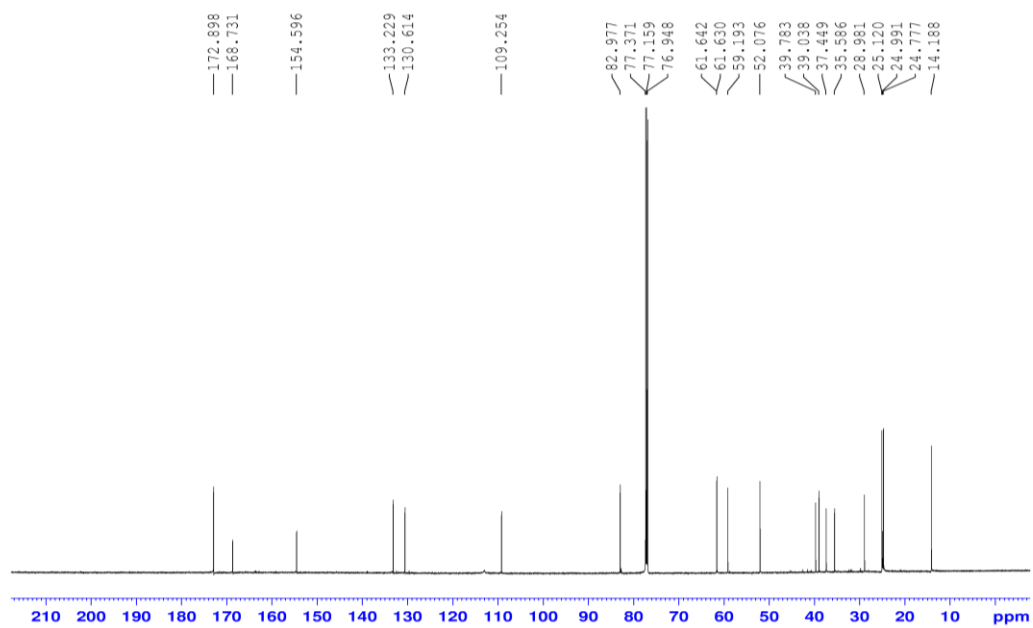


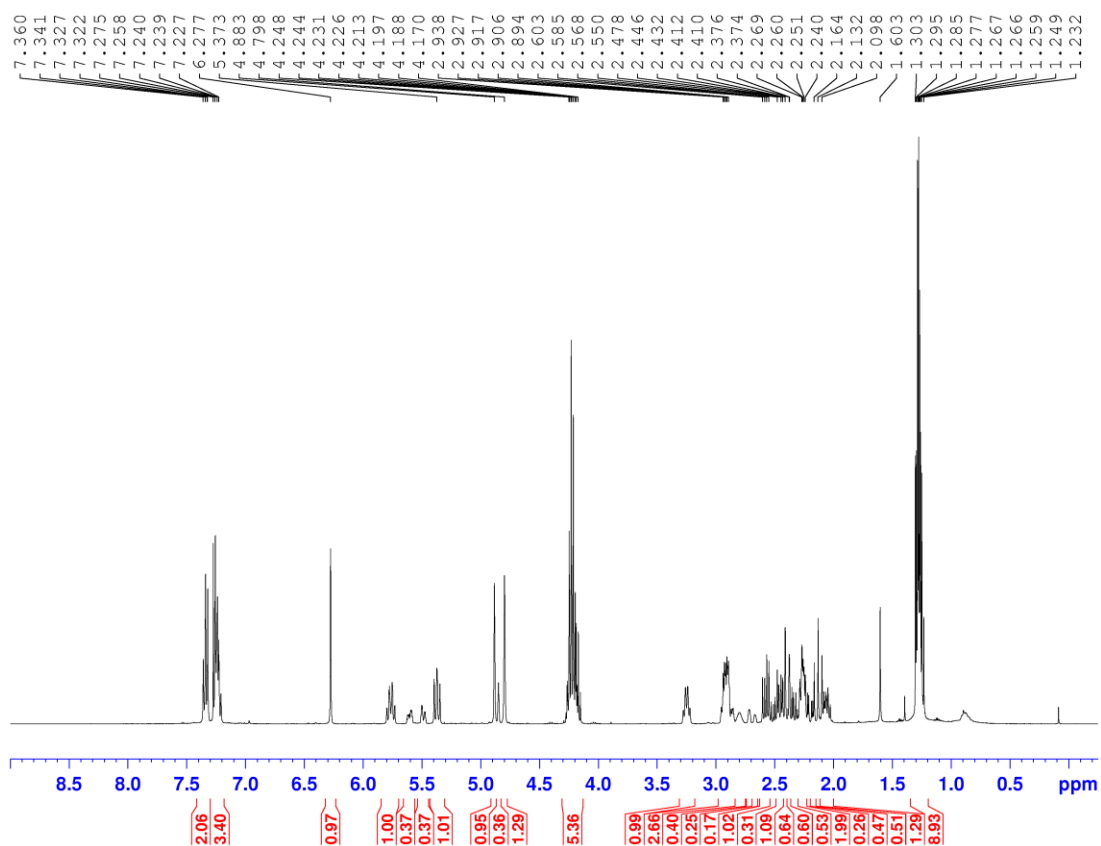
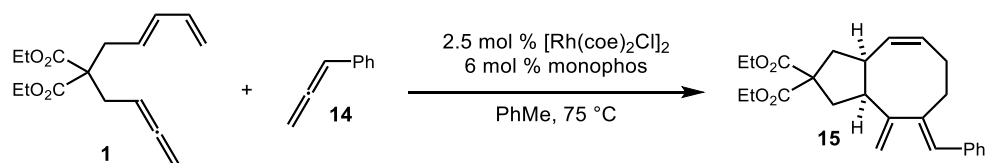


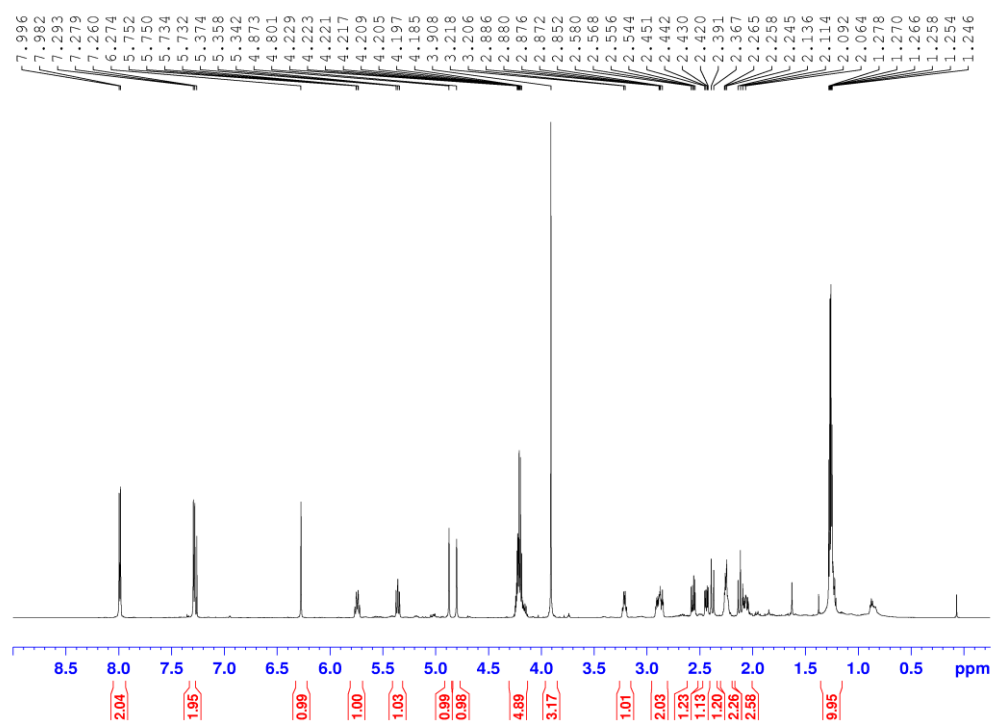
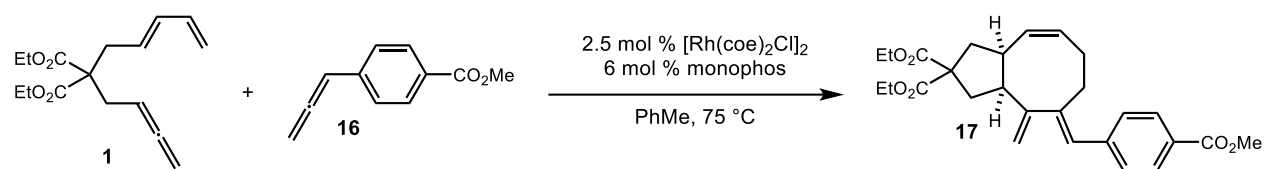




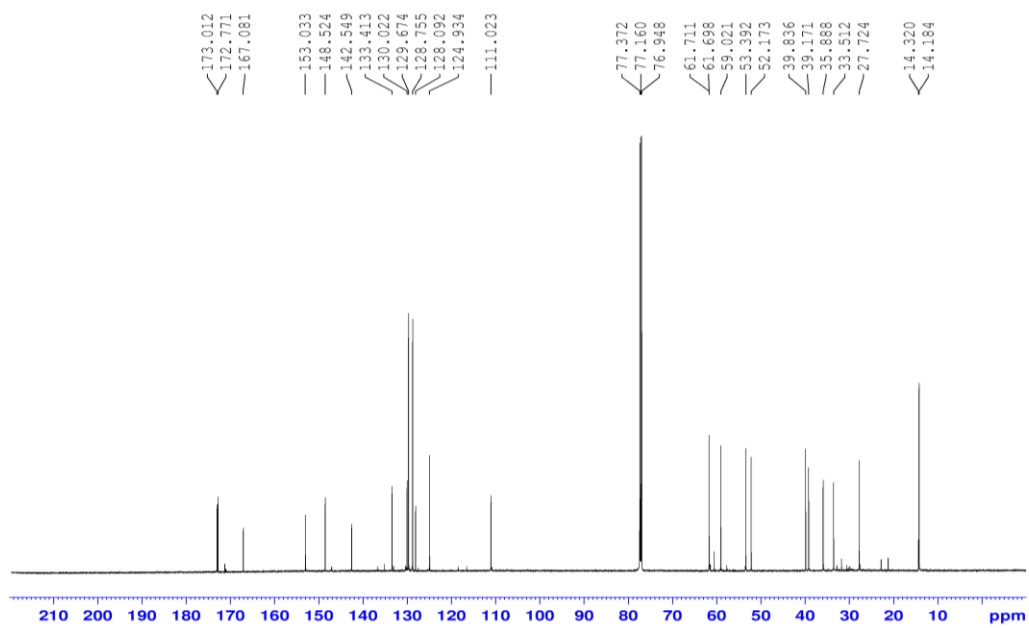


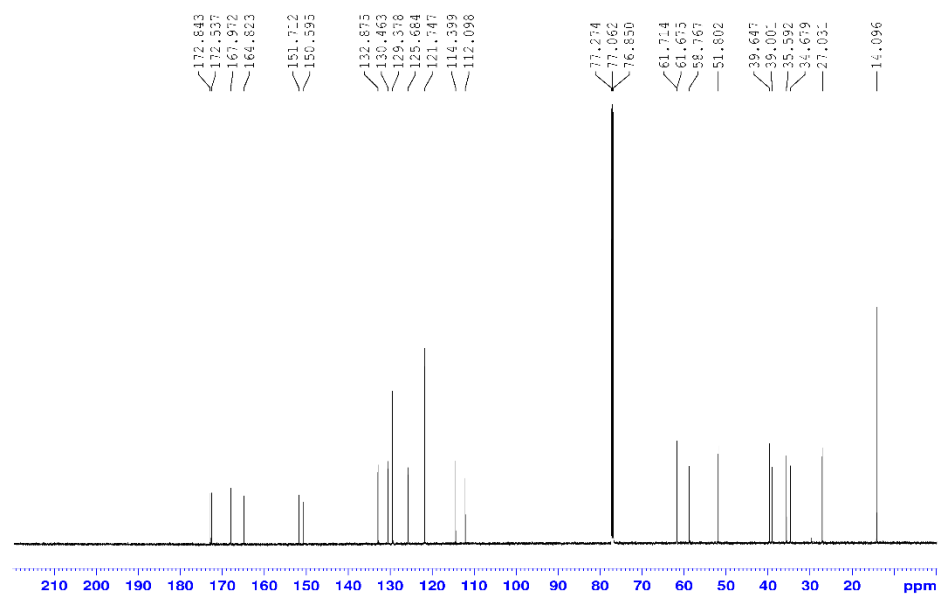
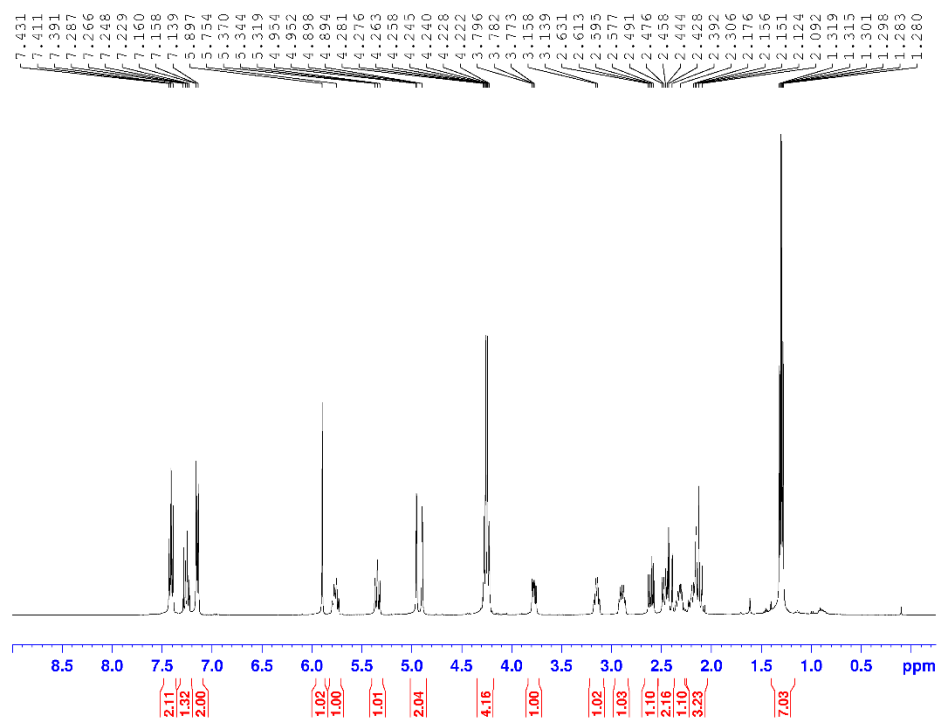
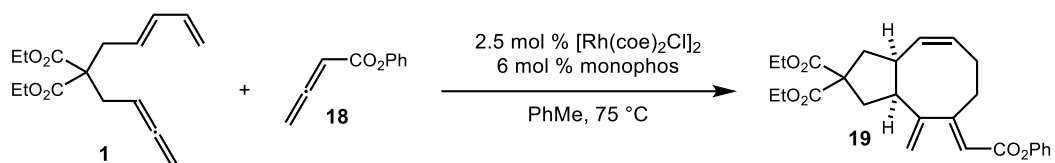


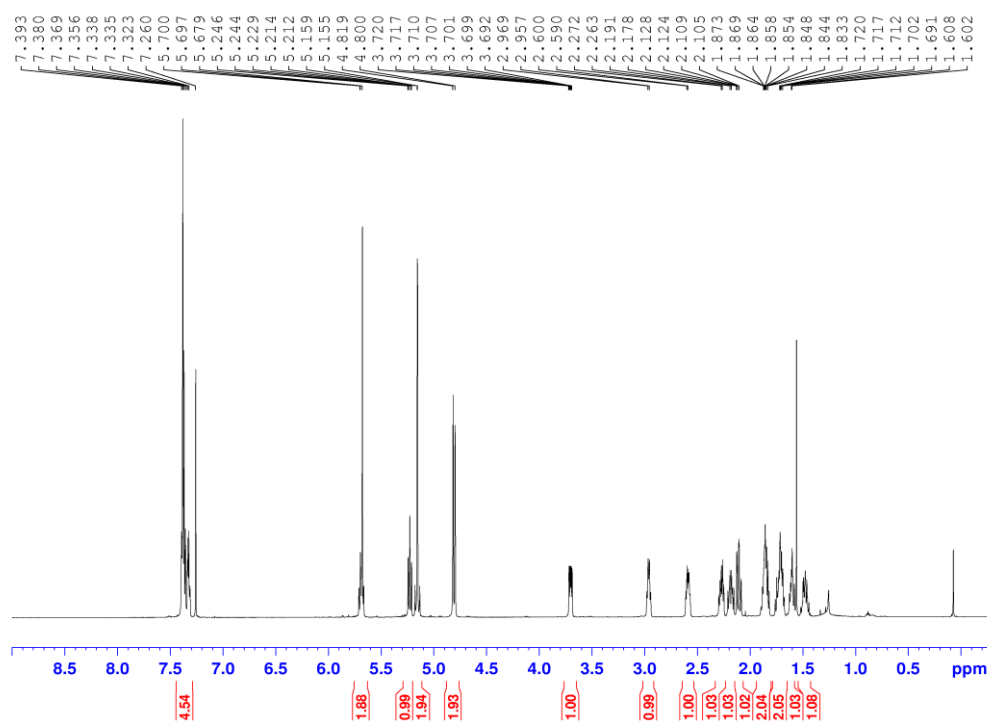
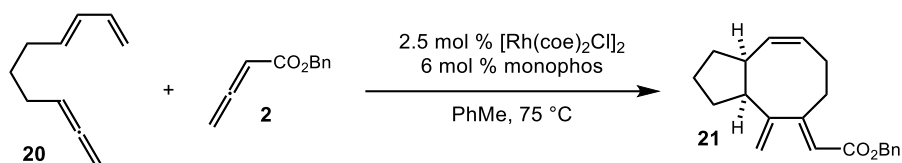


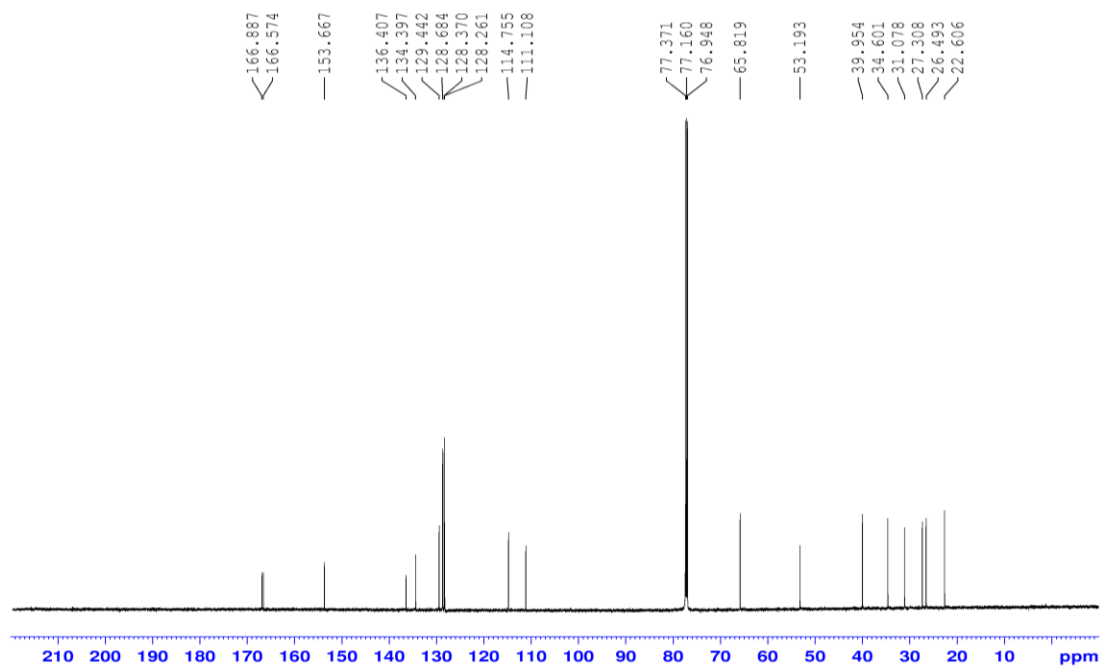


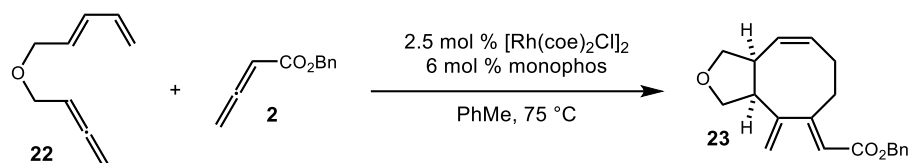


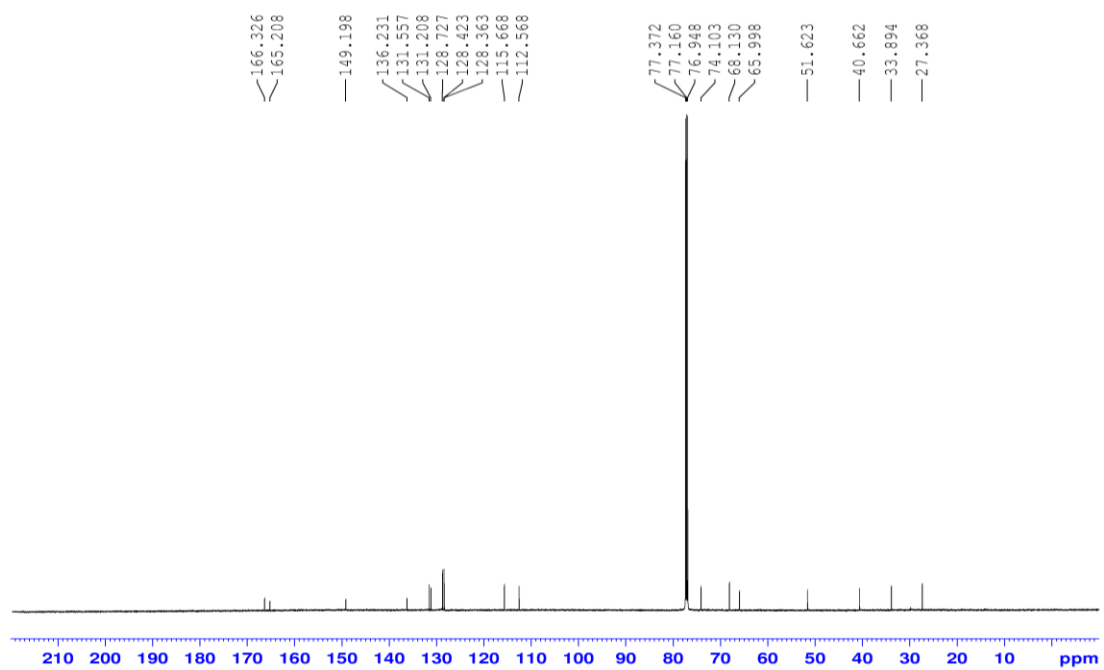


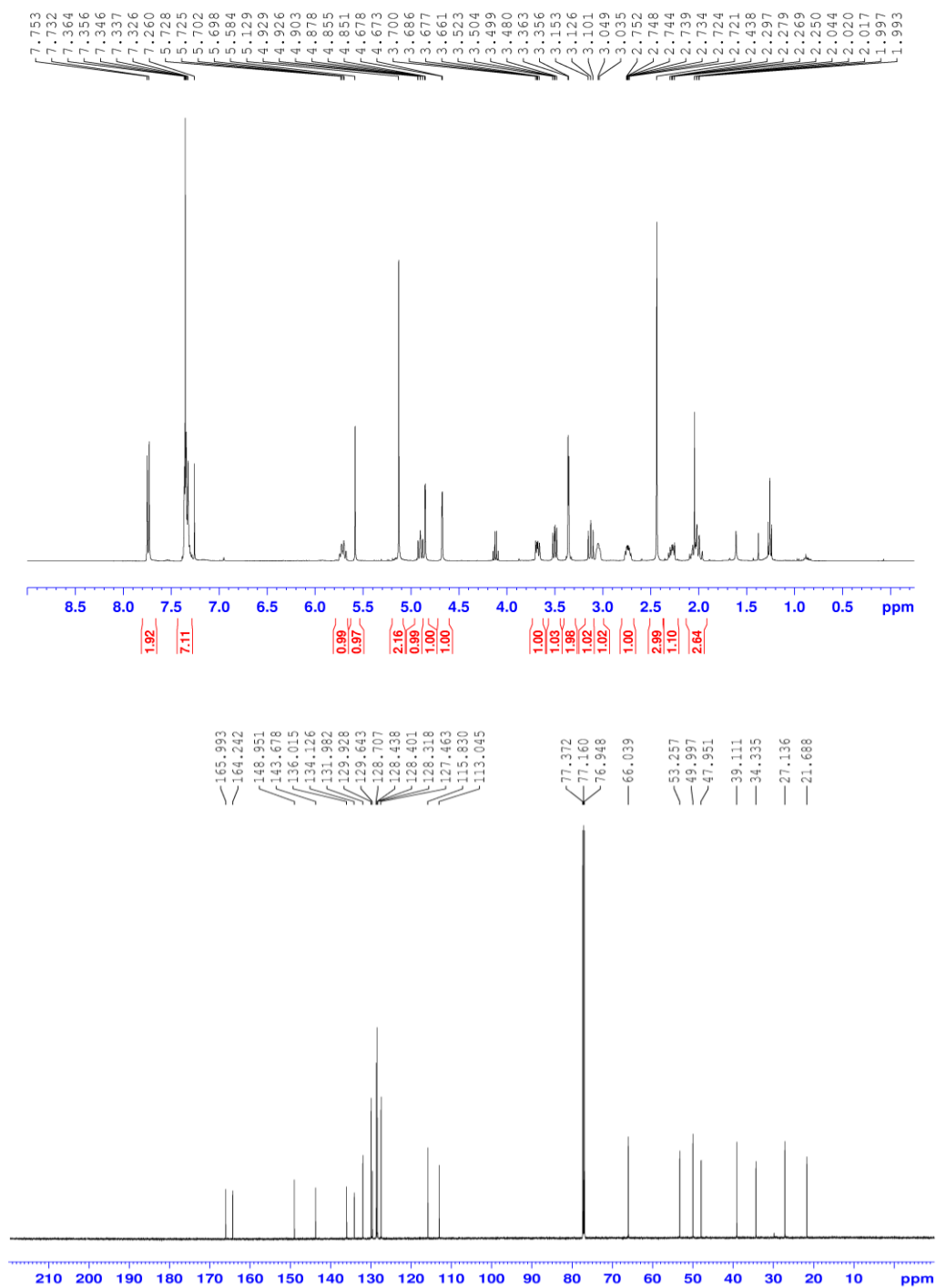
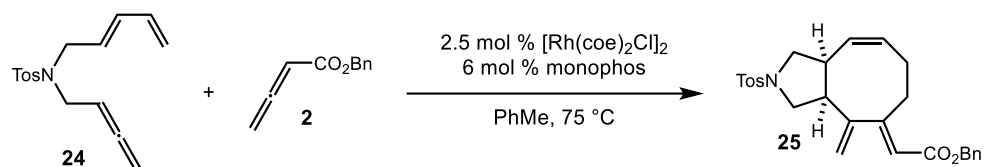


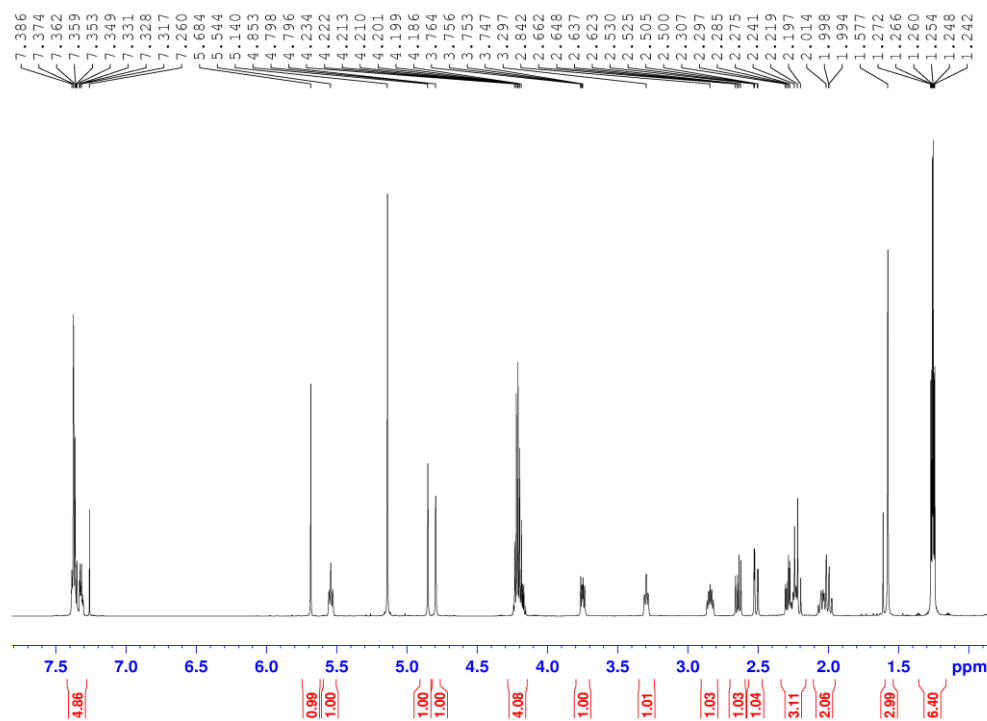
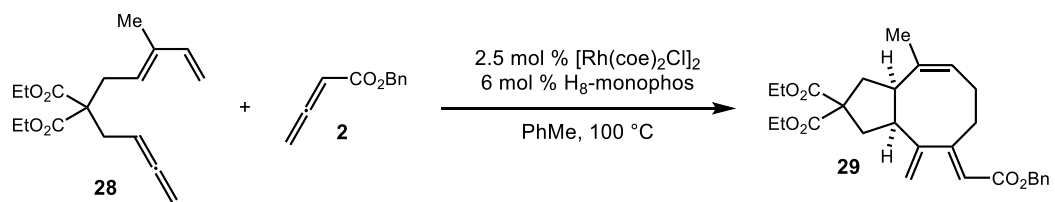




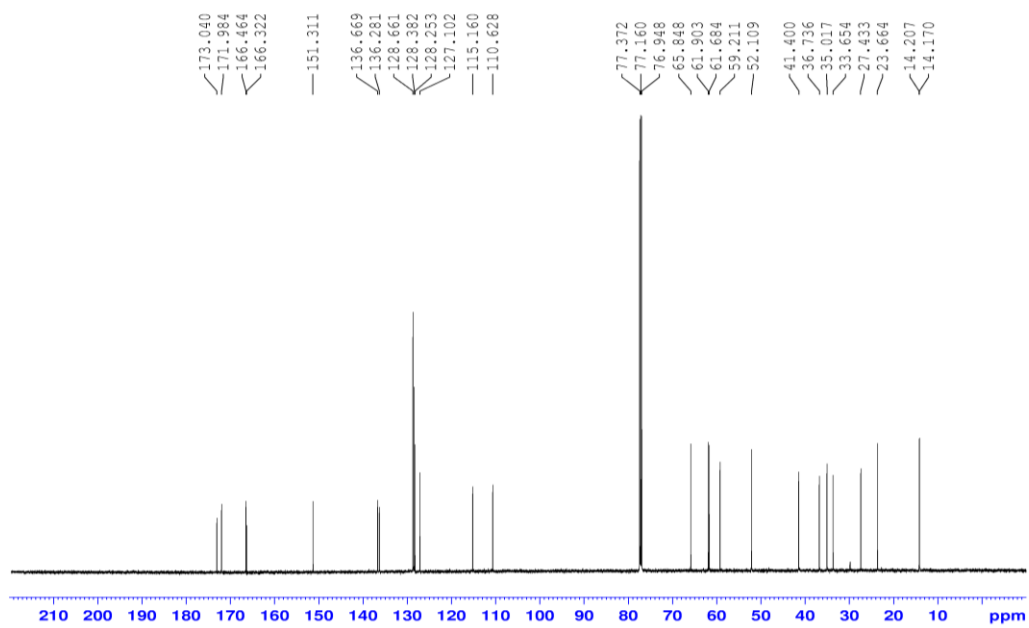


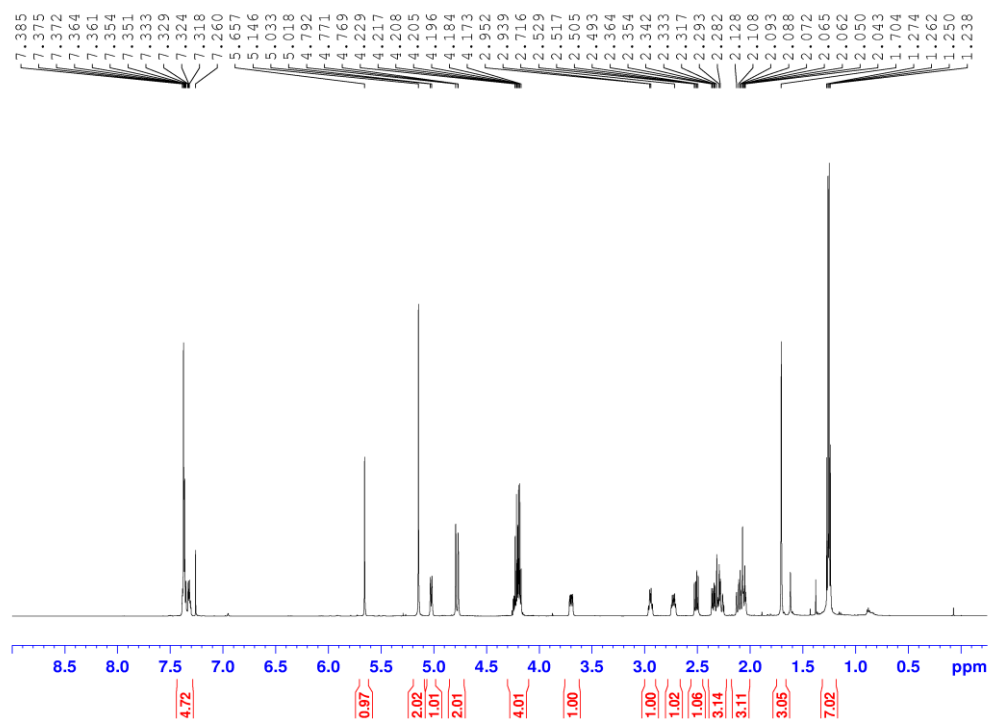
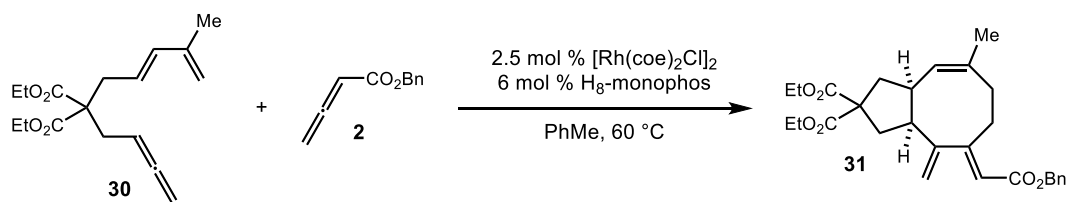


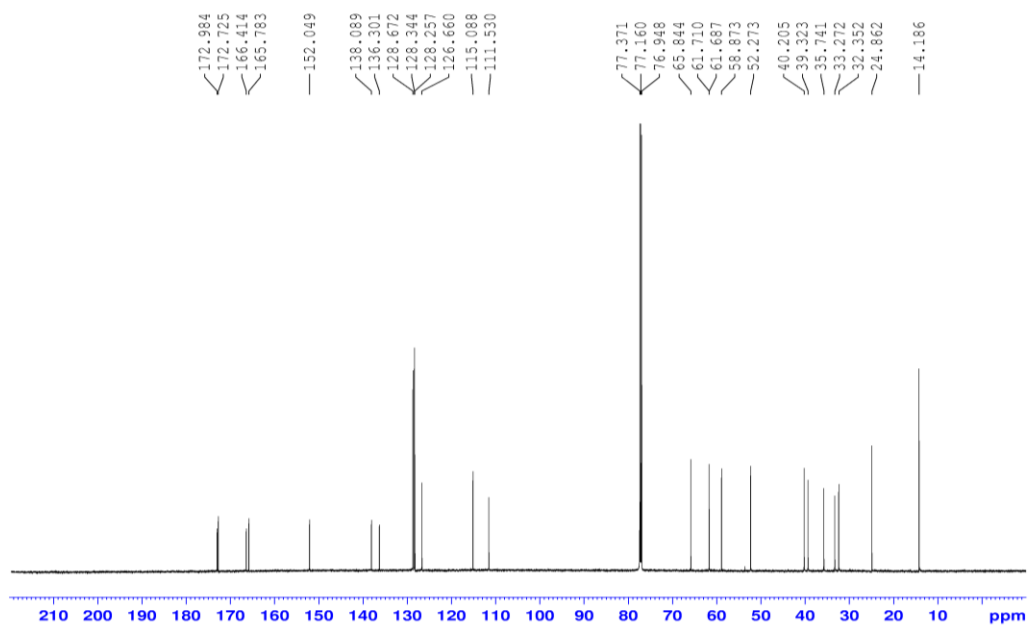




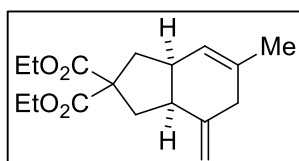
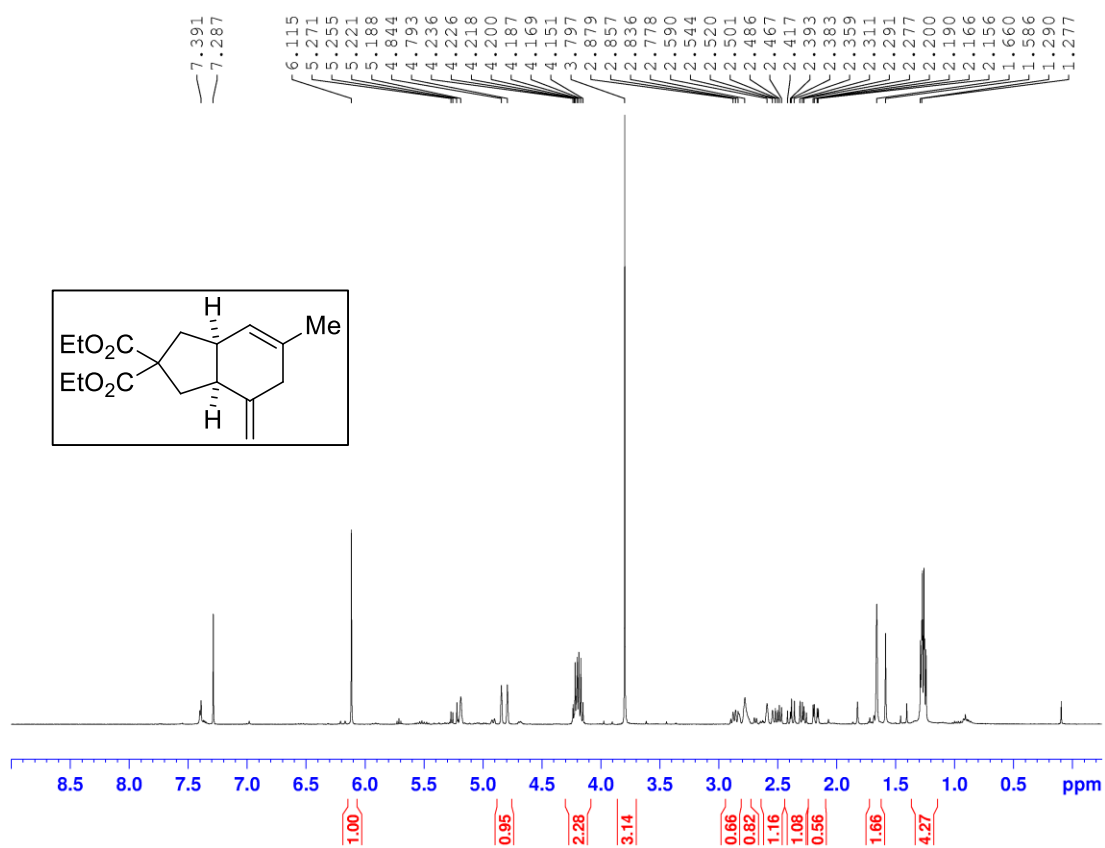


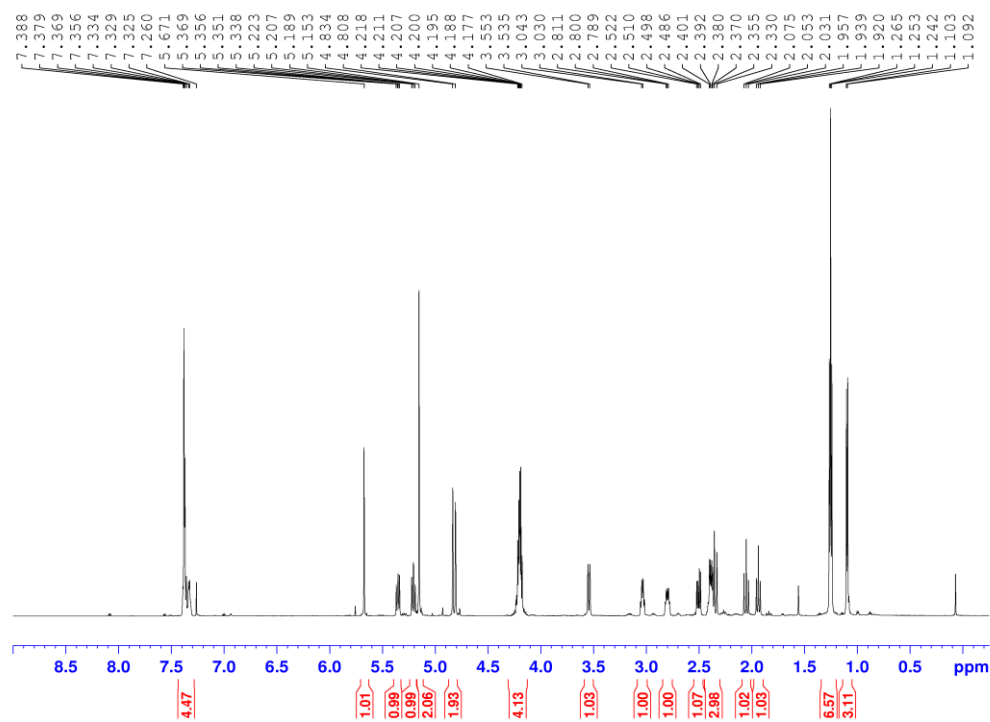
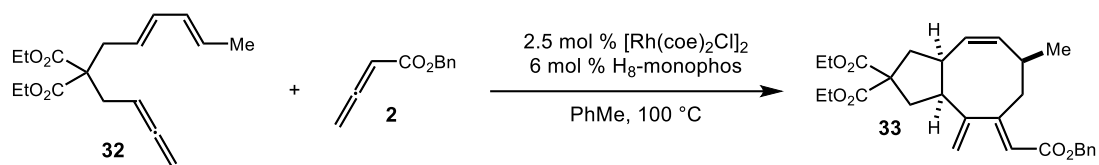


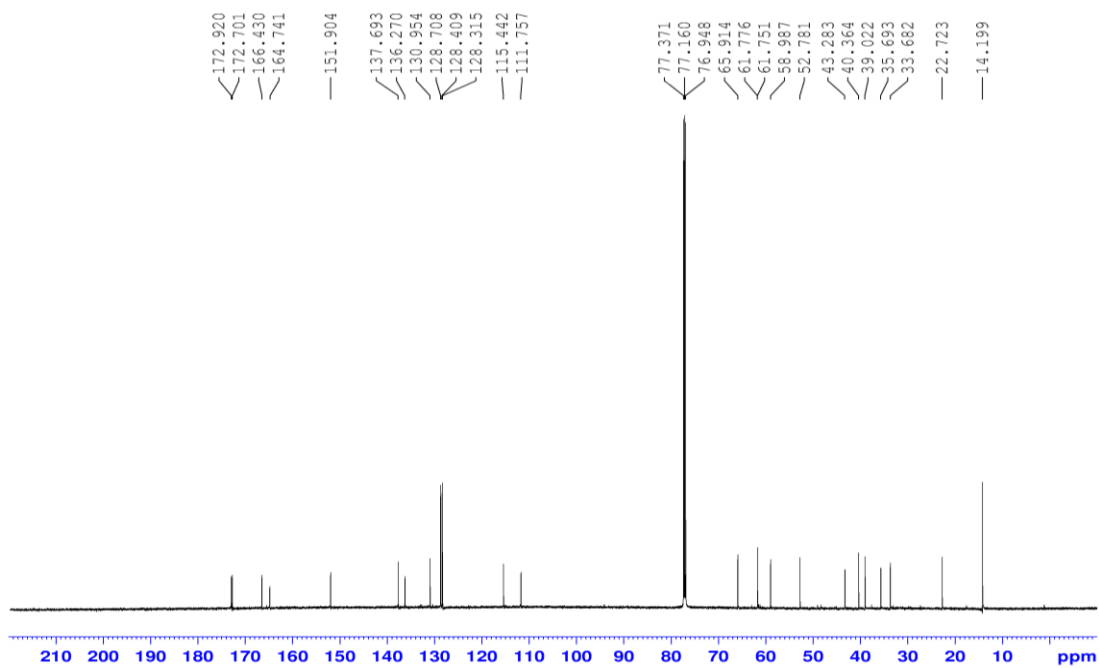




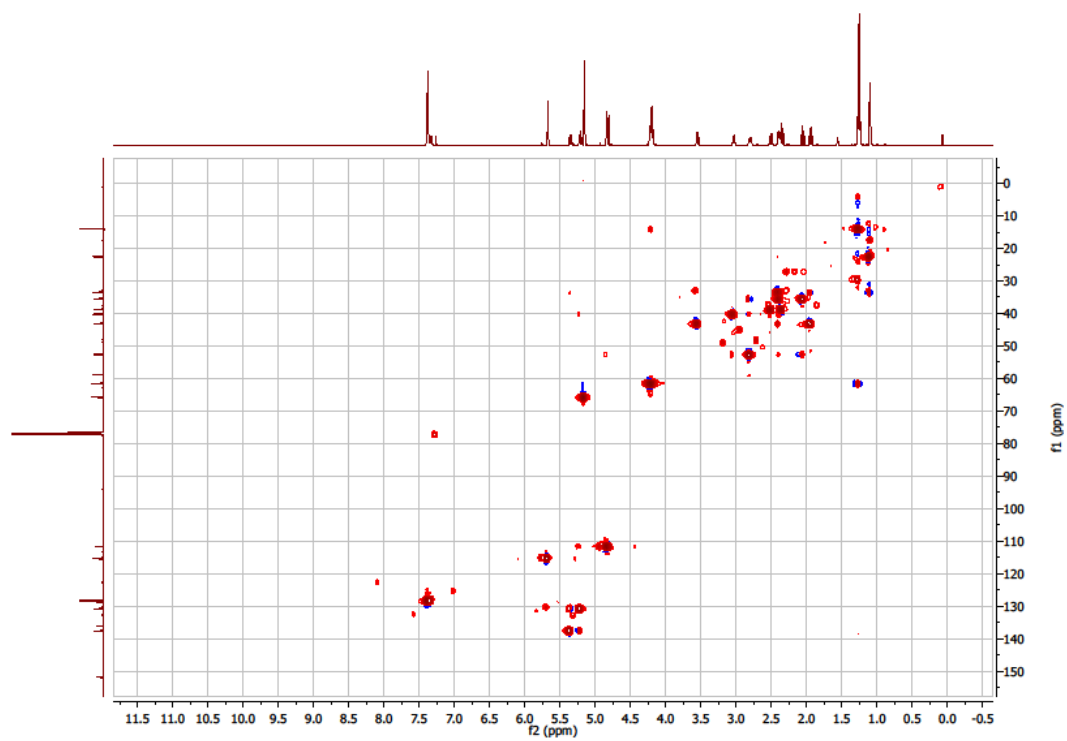
**31-DA**



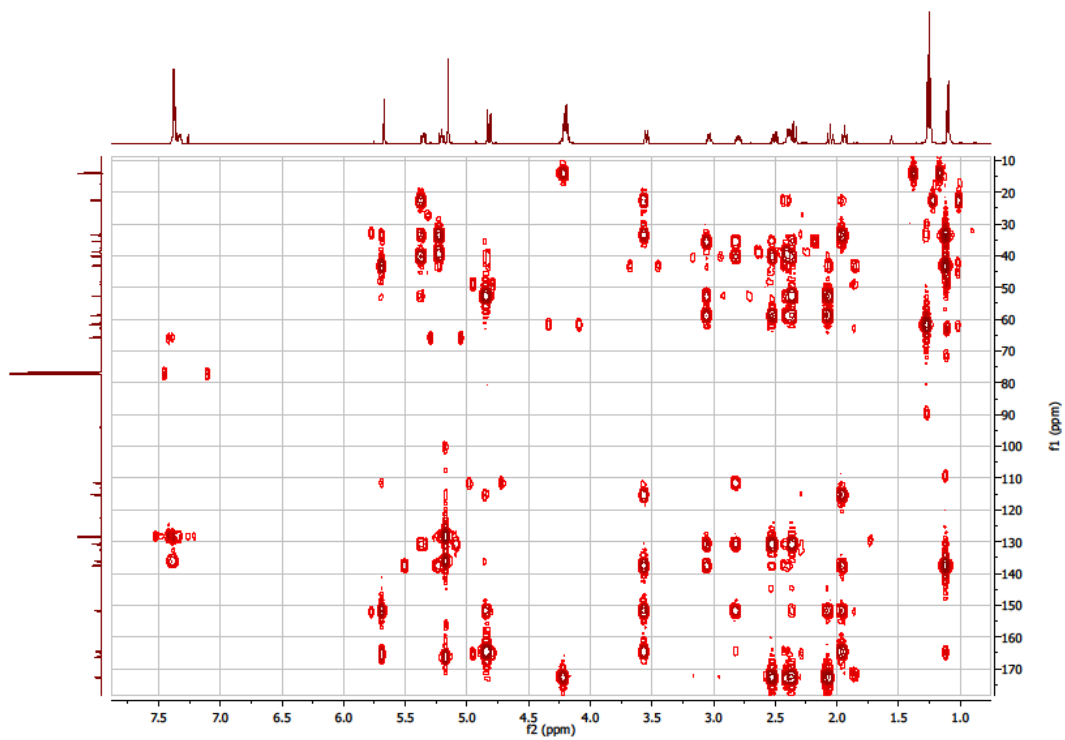




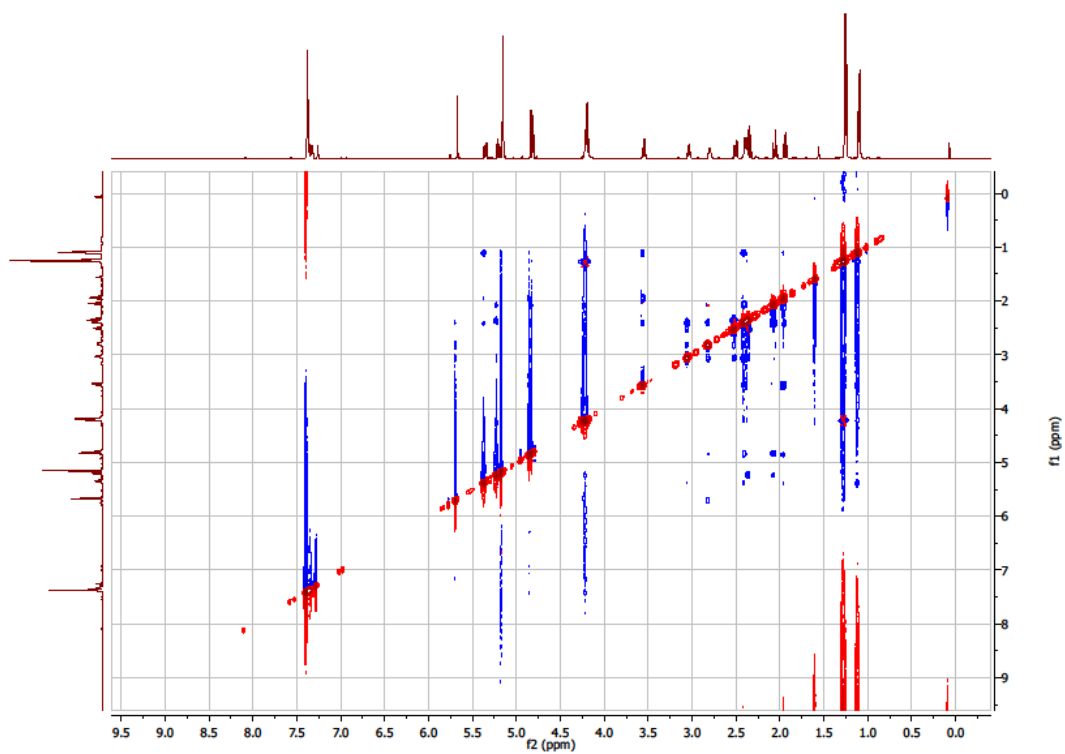
HSQC

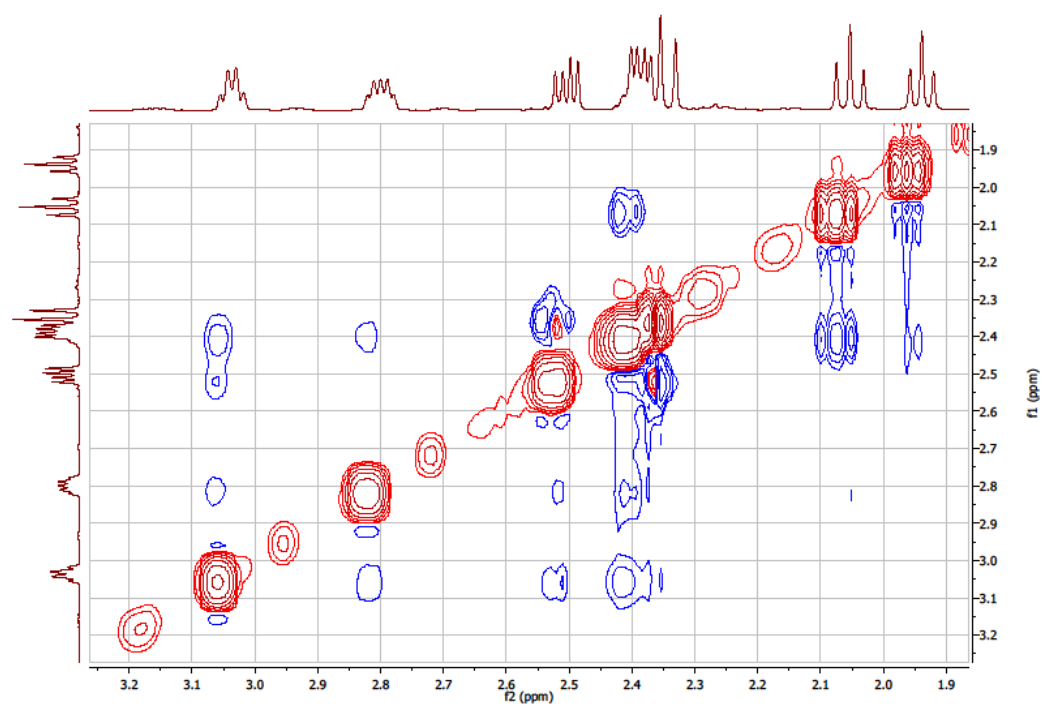


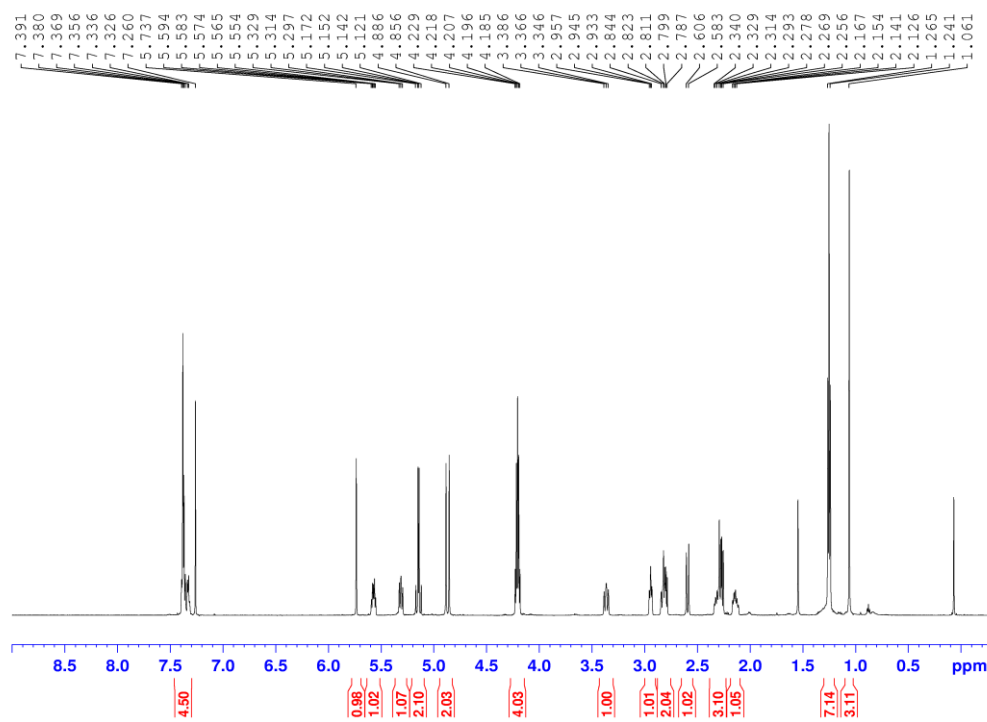
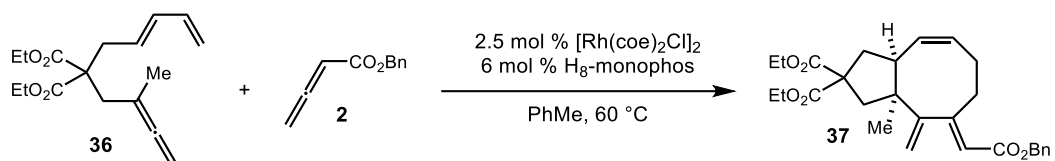
HMBC



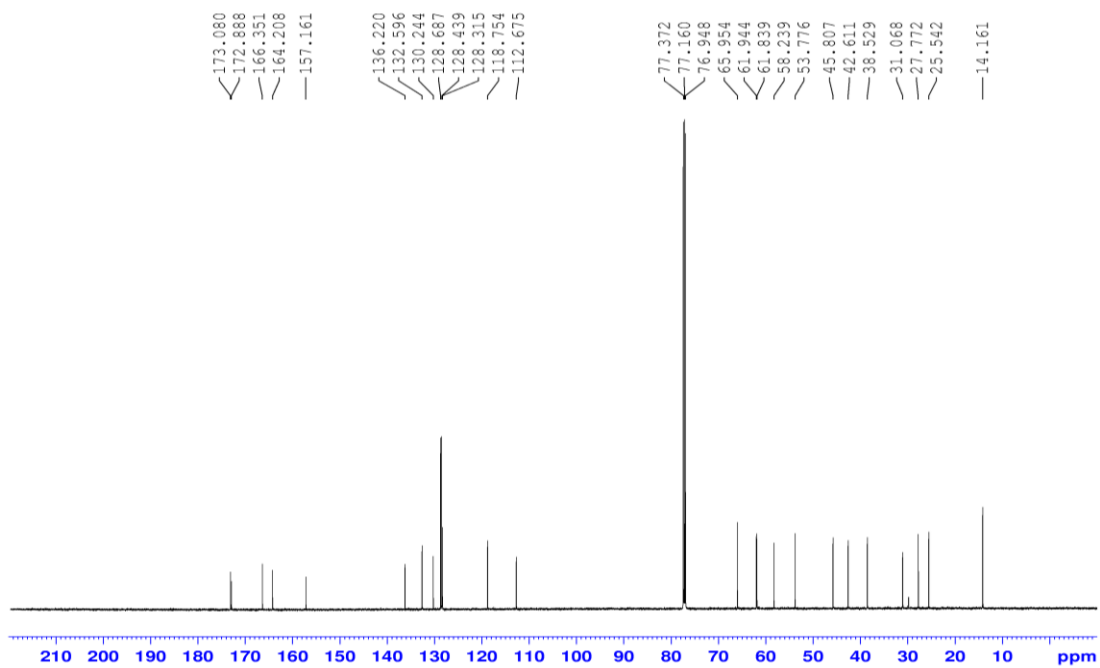
NOESY



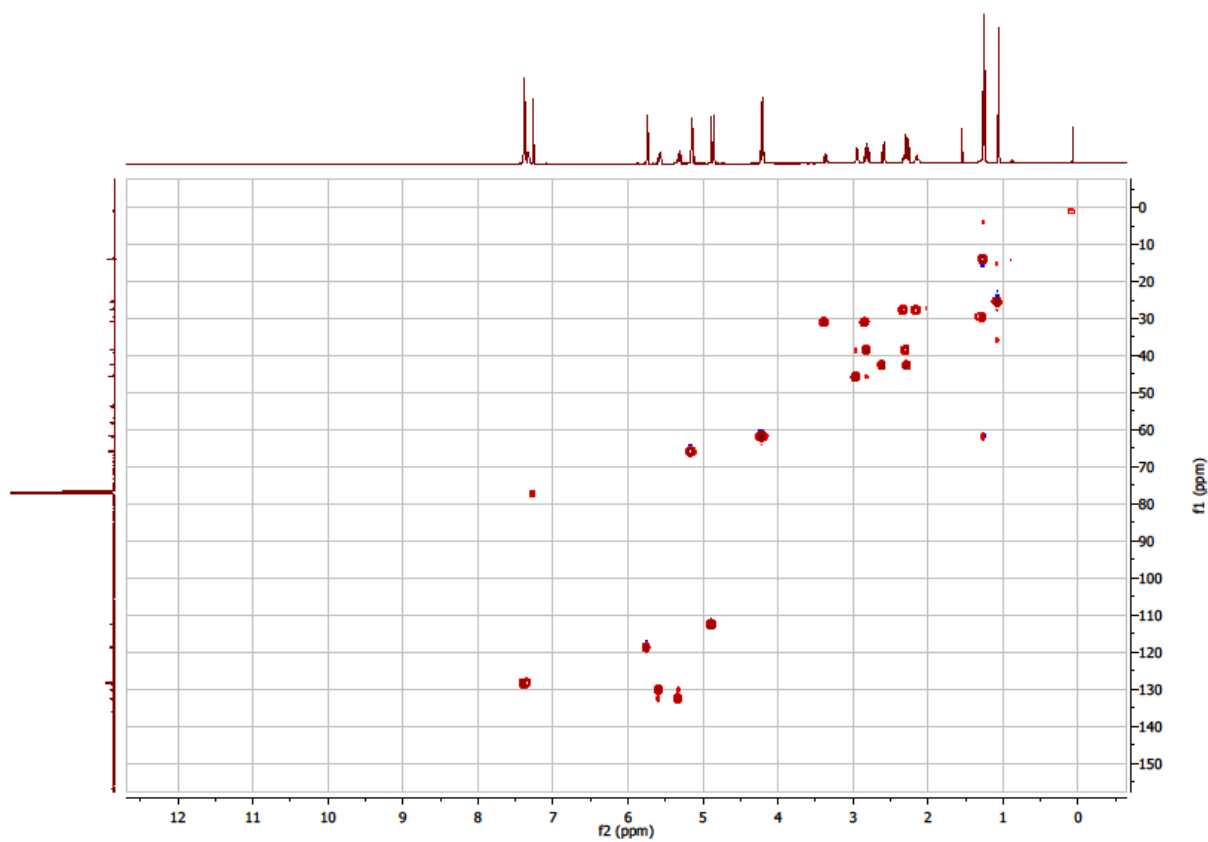






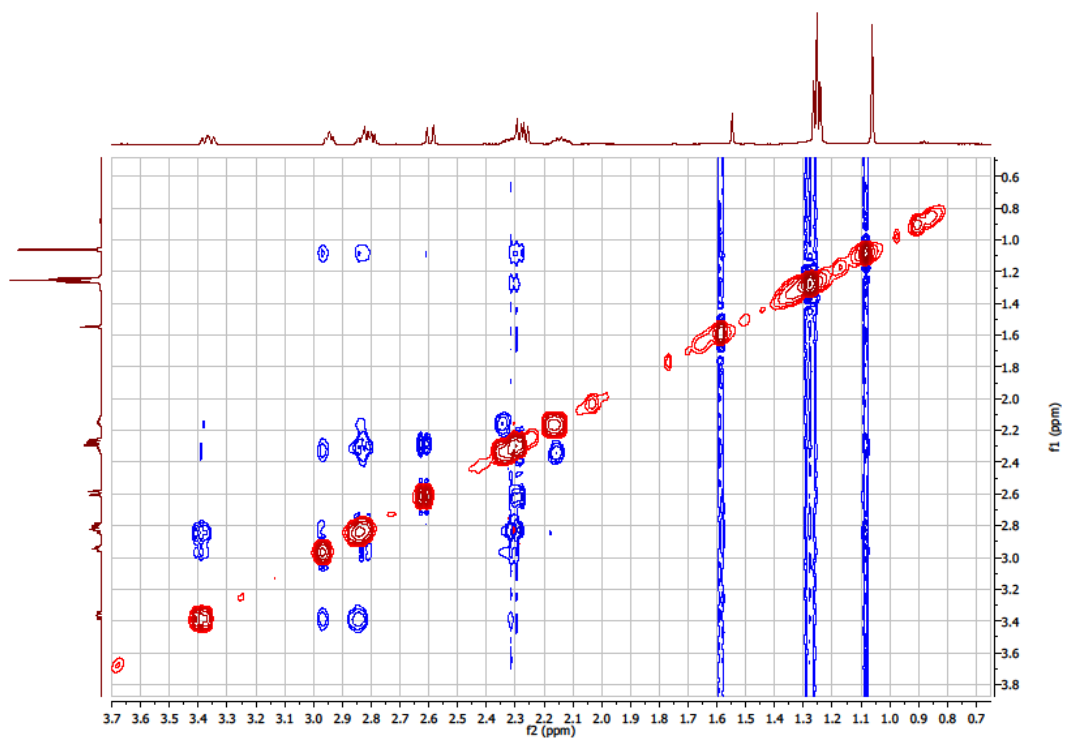
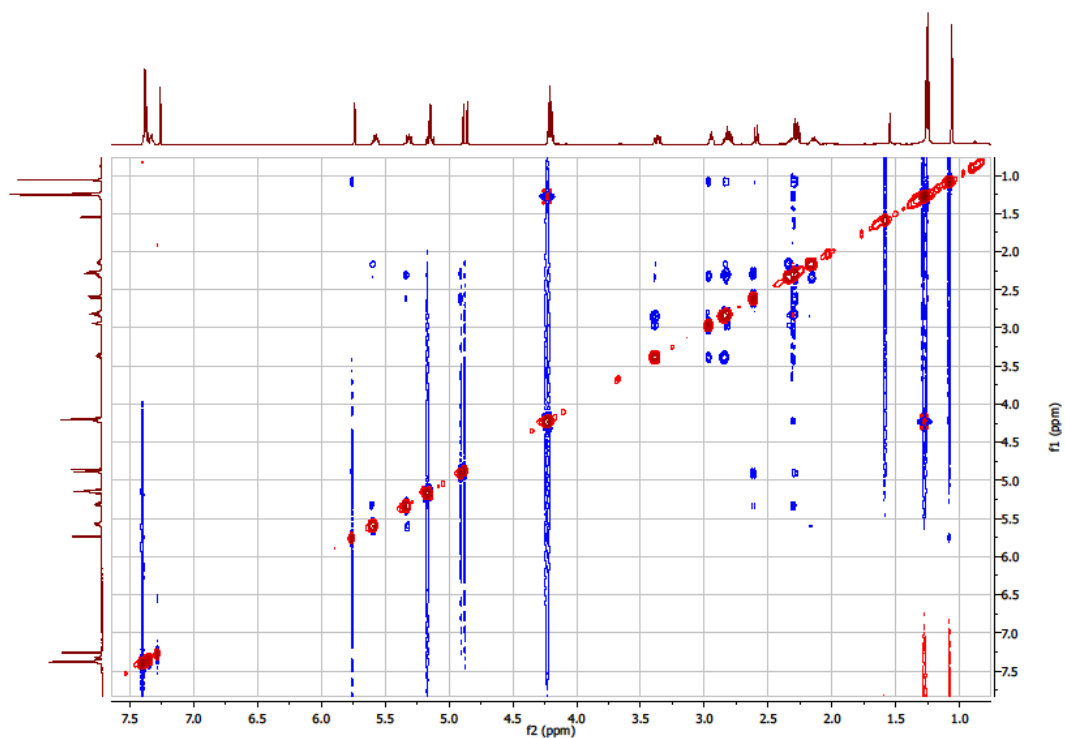


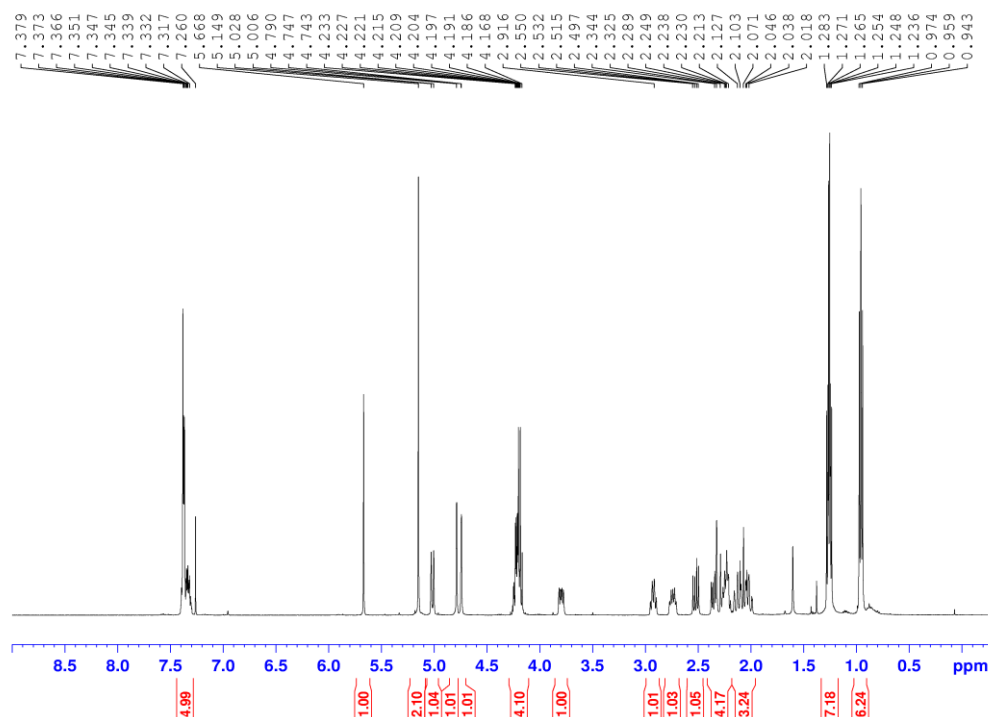
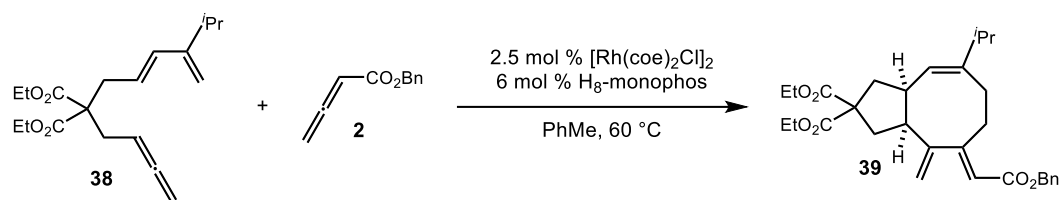
HSQC

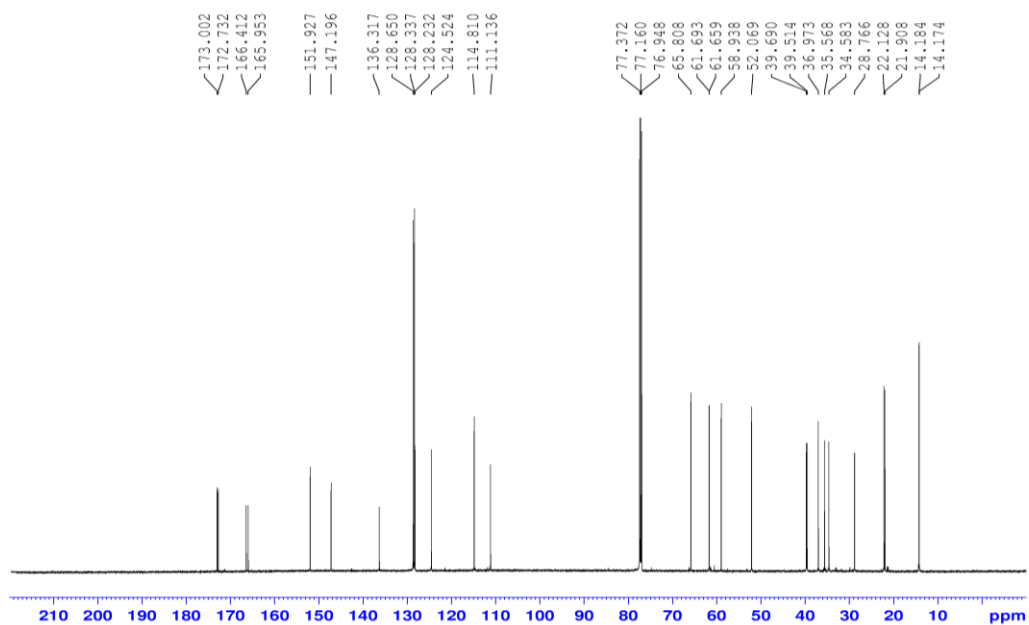




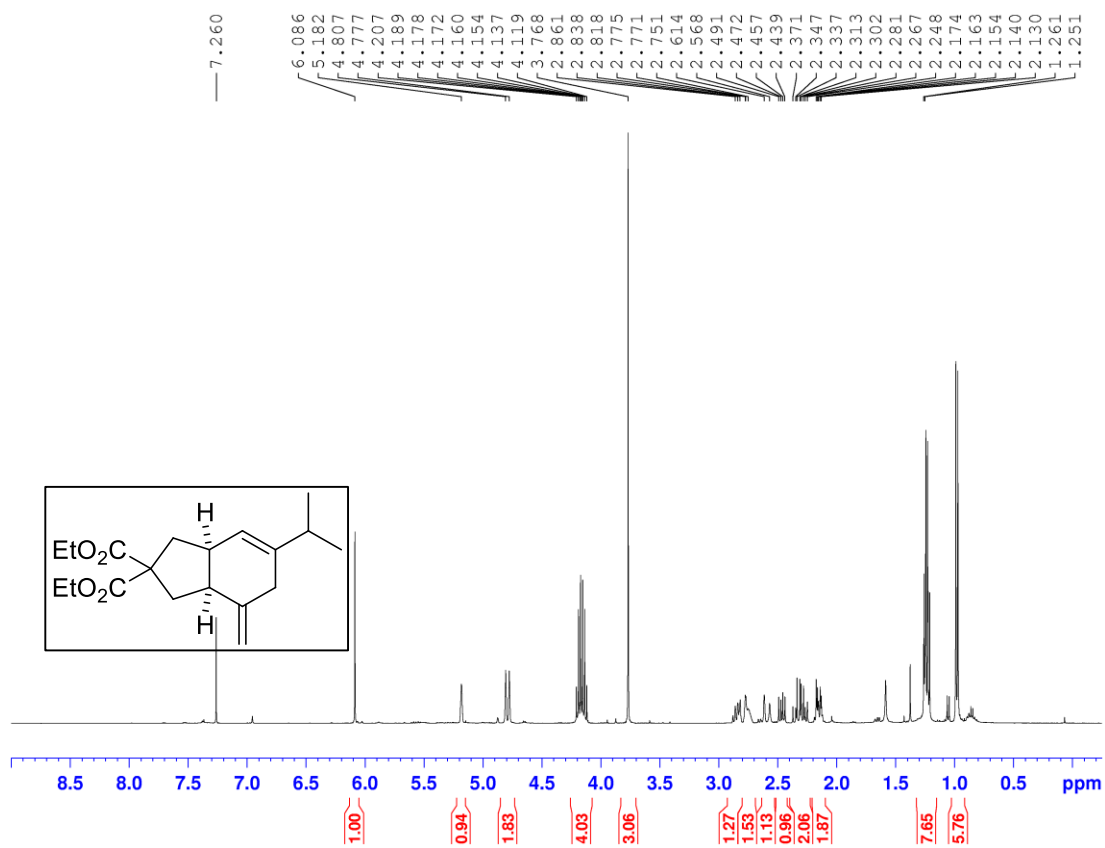
# NOESY

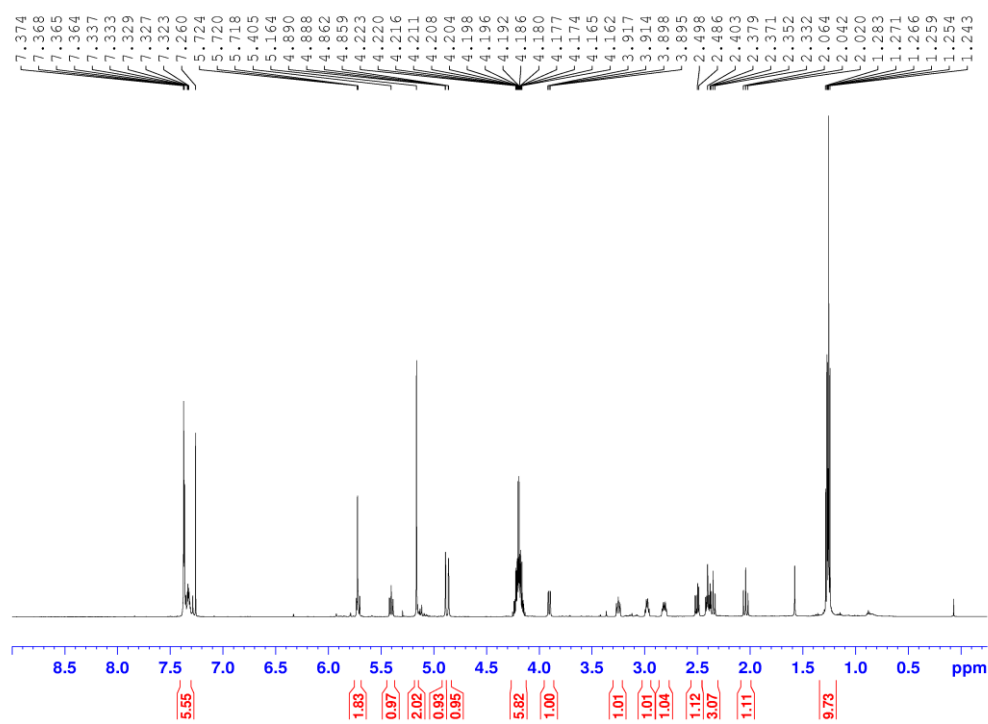
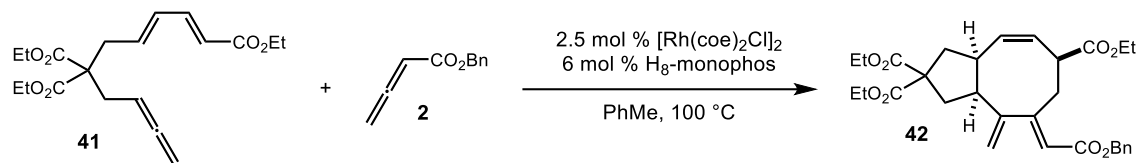


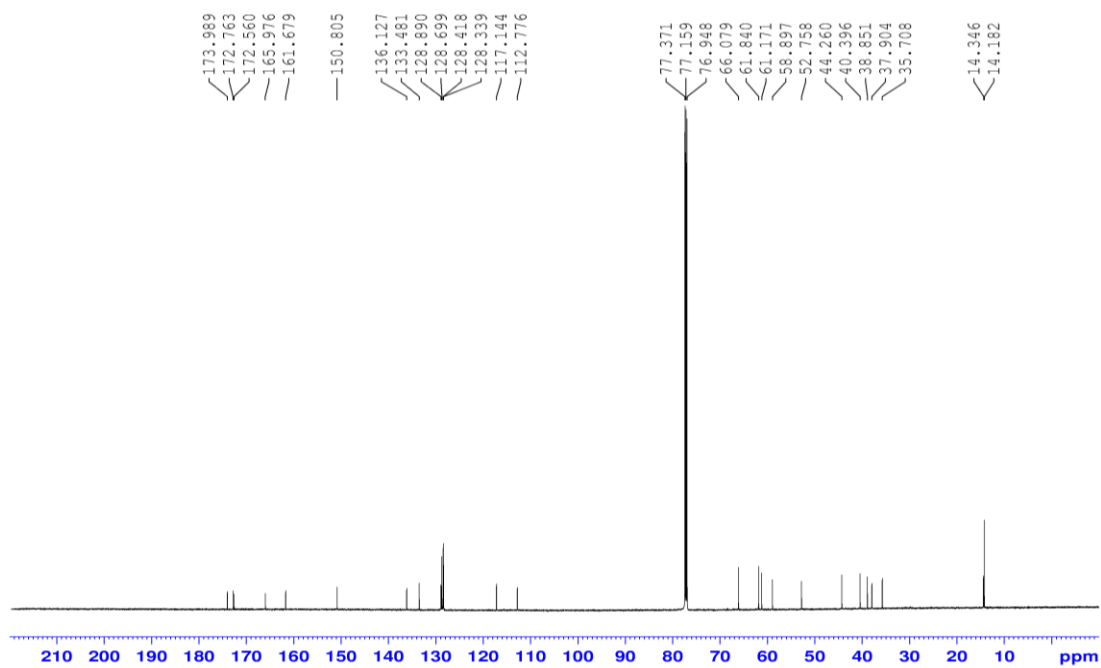




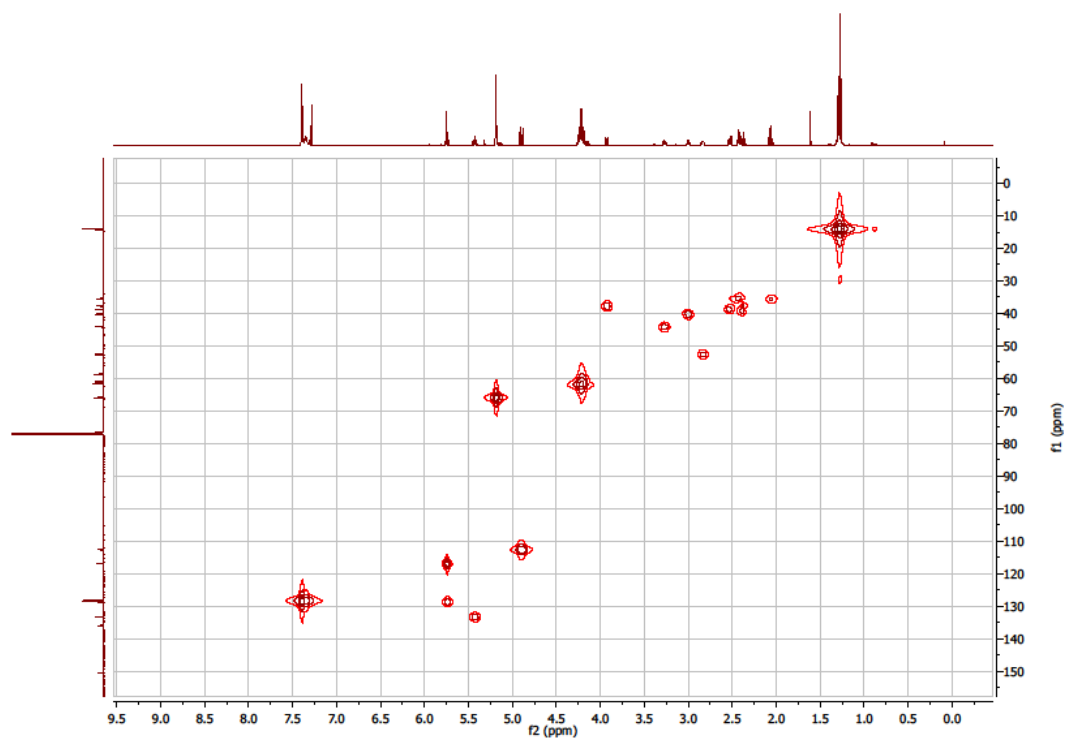
**39-DA**



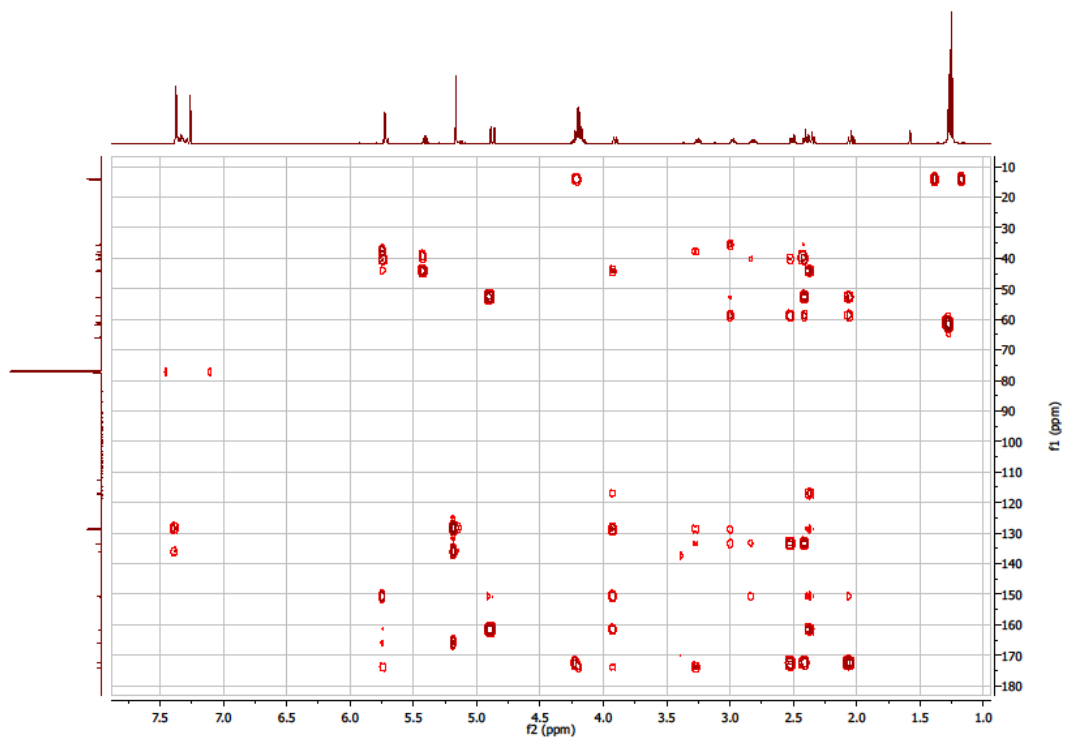




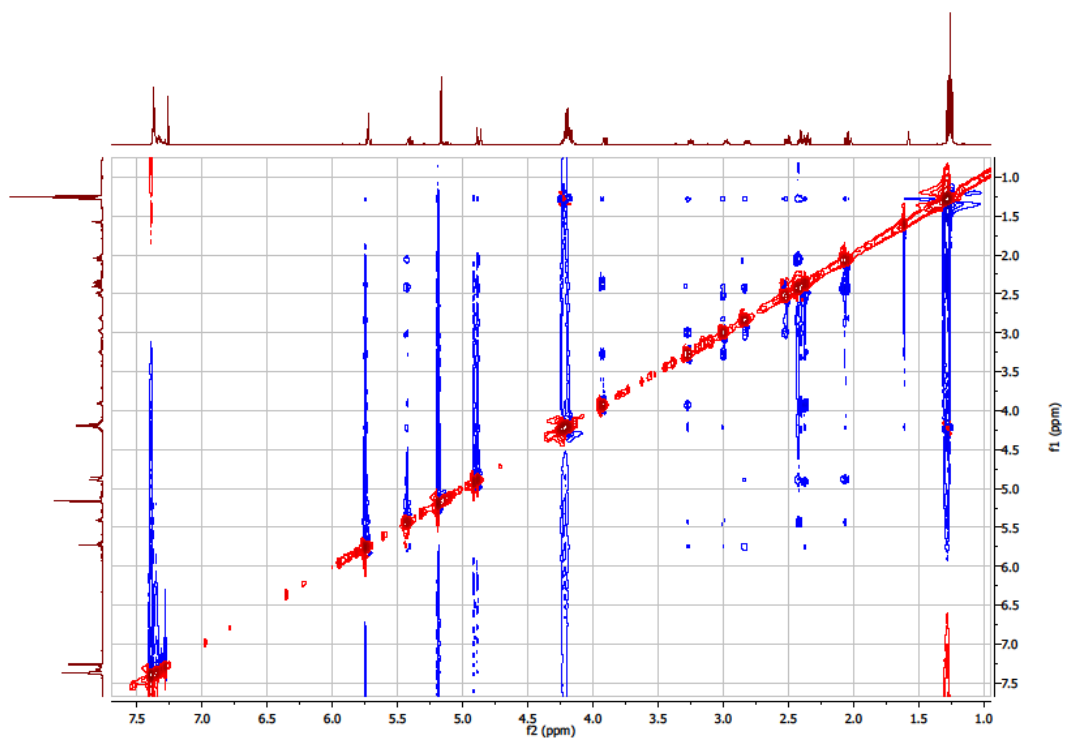
HMQC



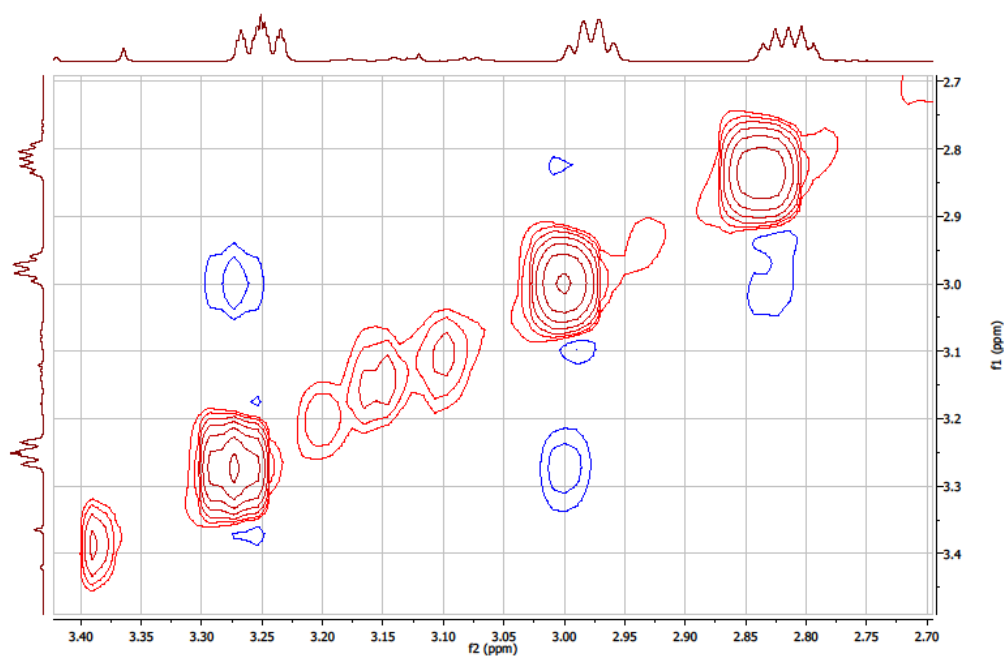
HMBC

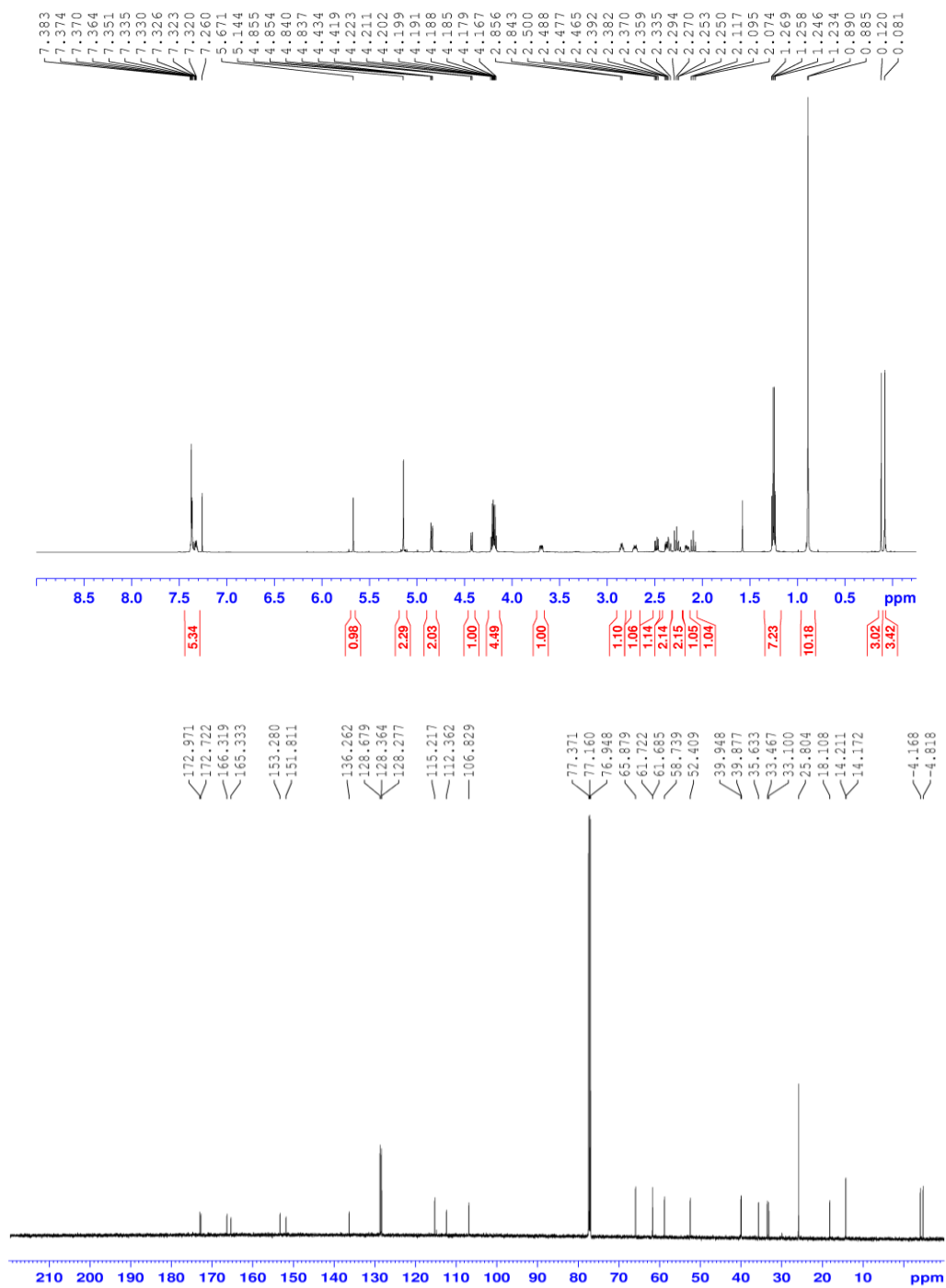
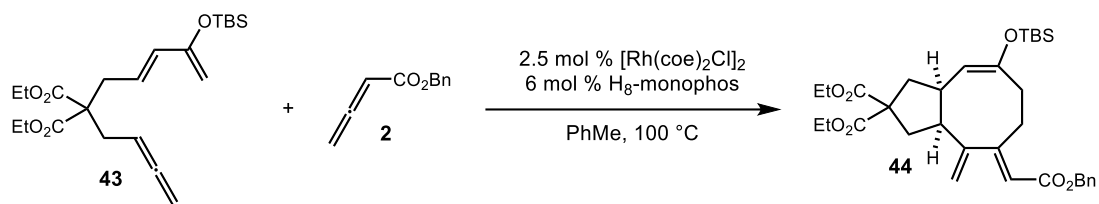


NOESY

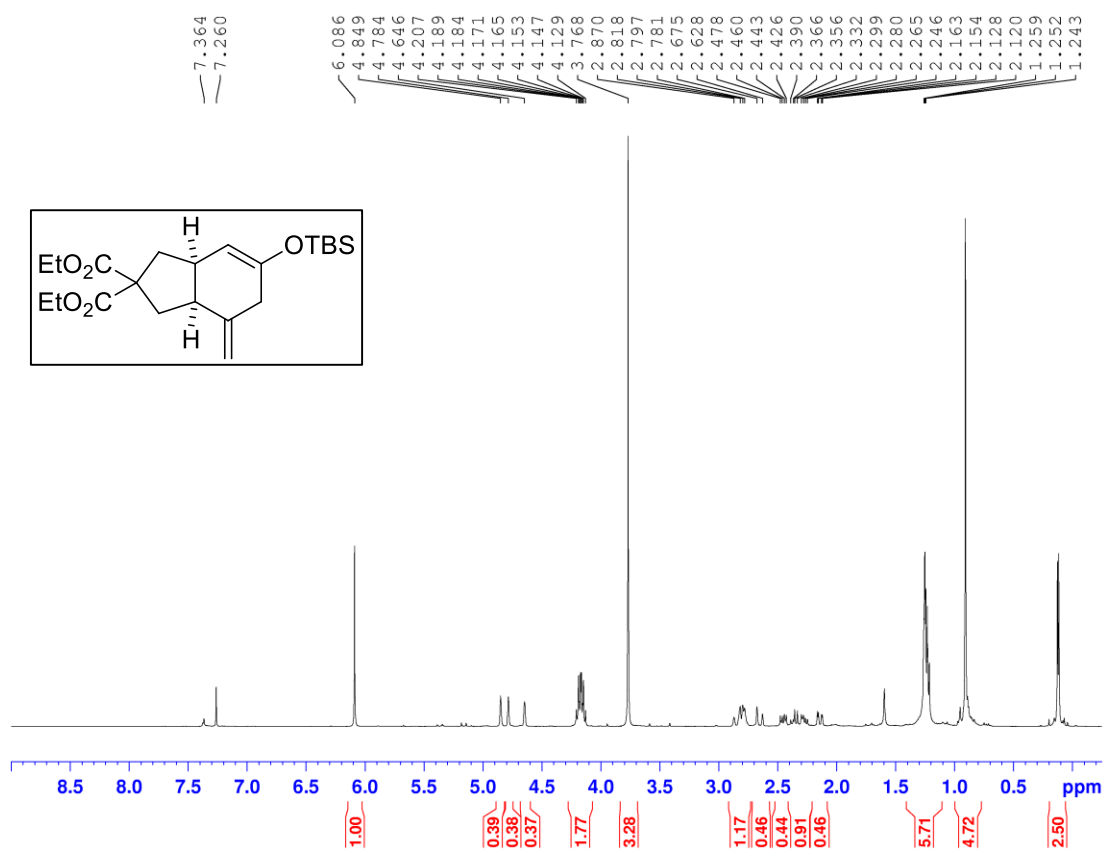


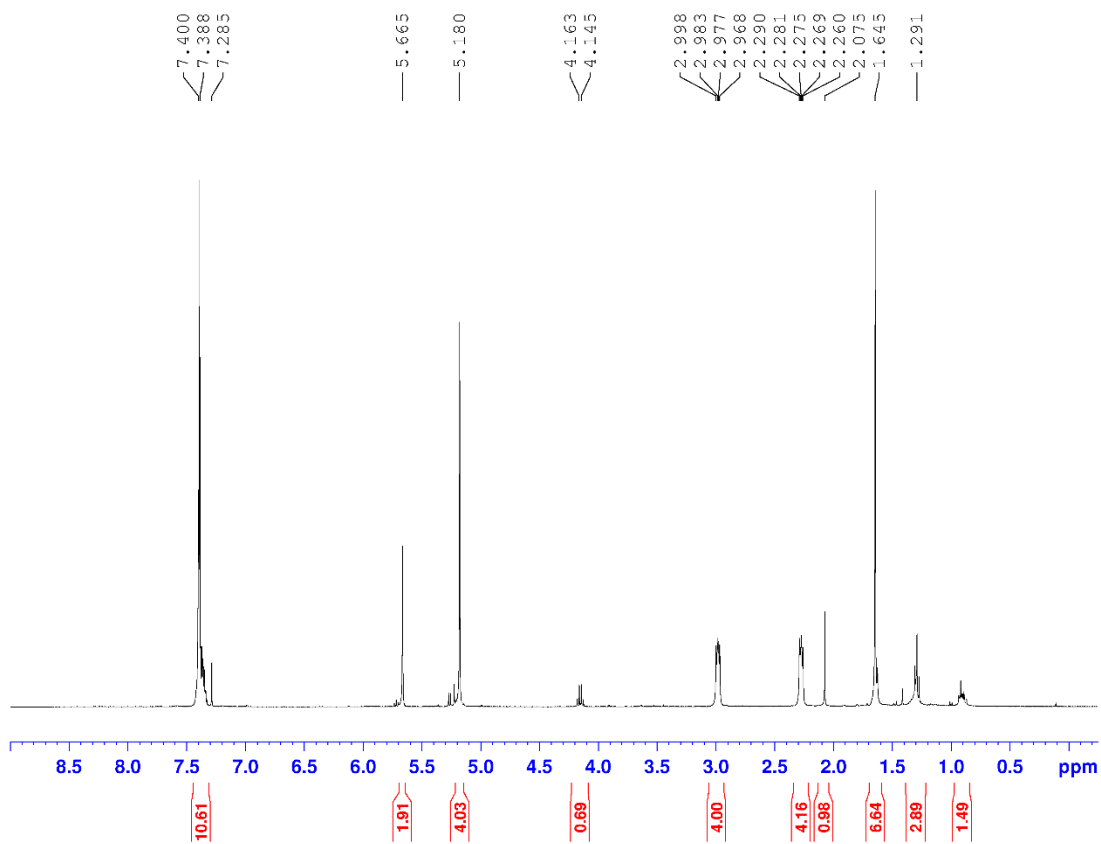
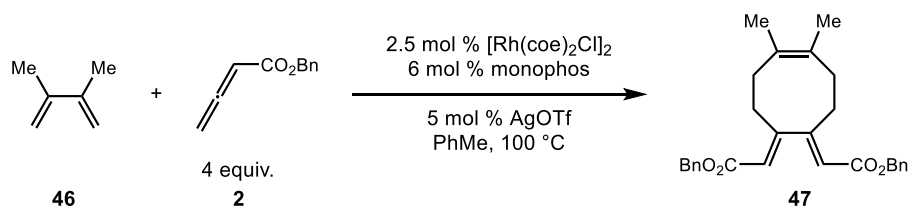


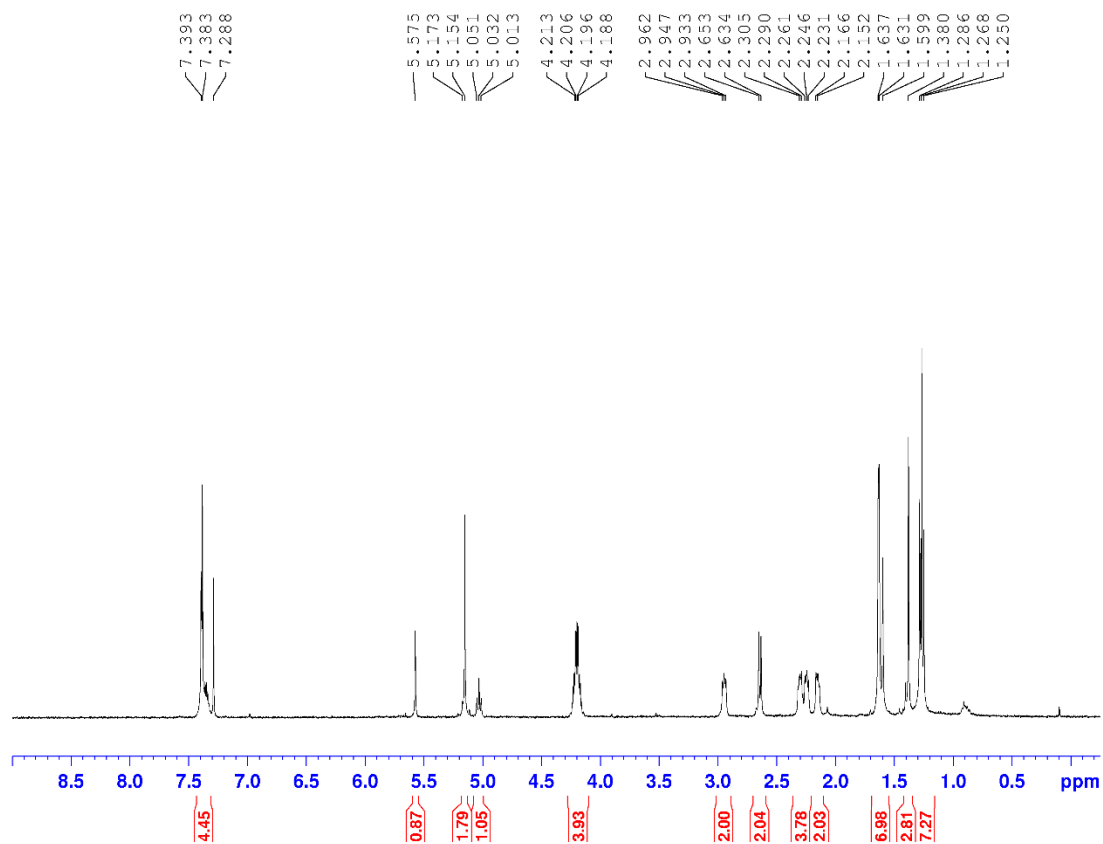
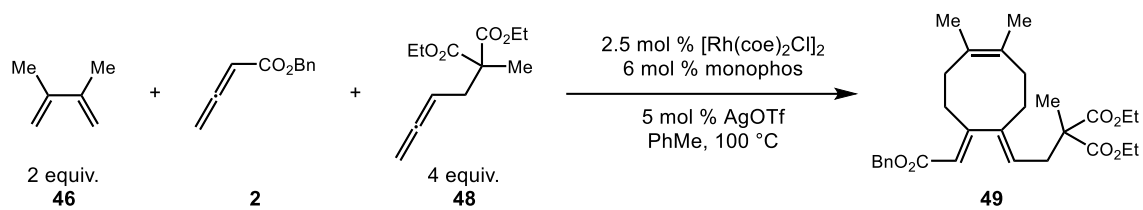


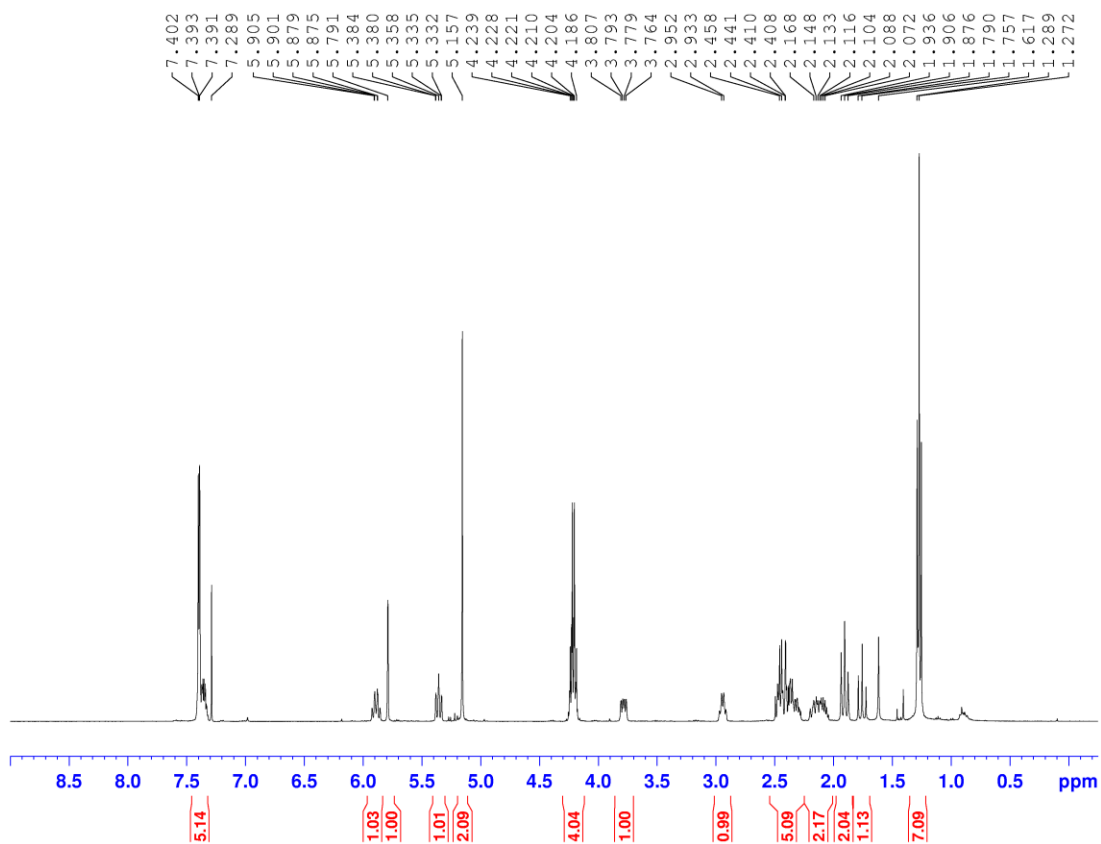
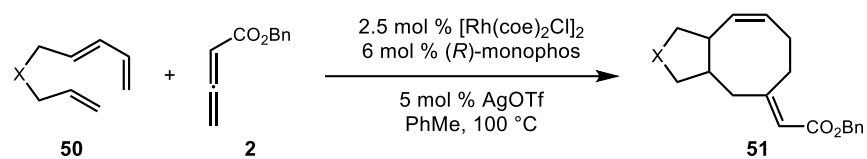


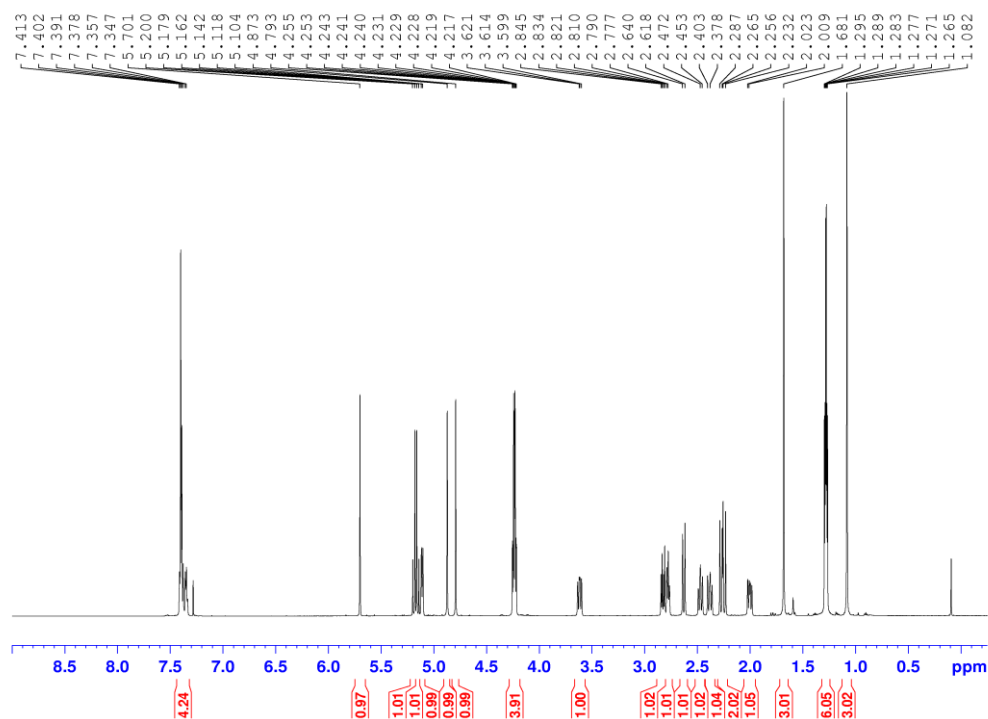
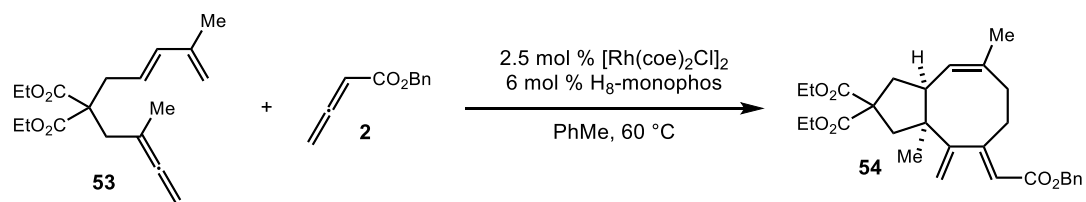
# 44-DA

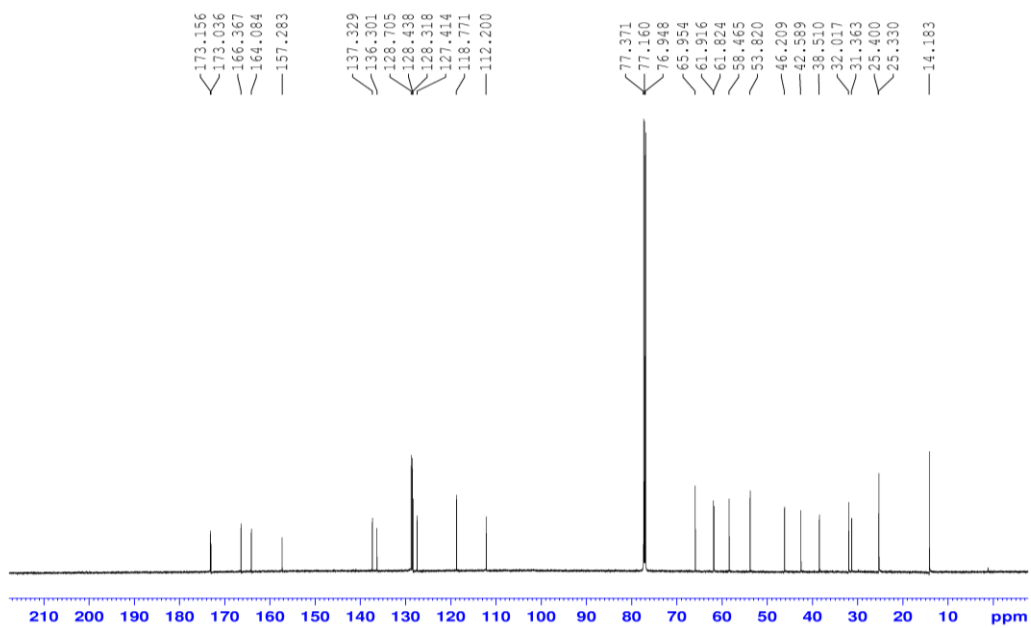




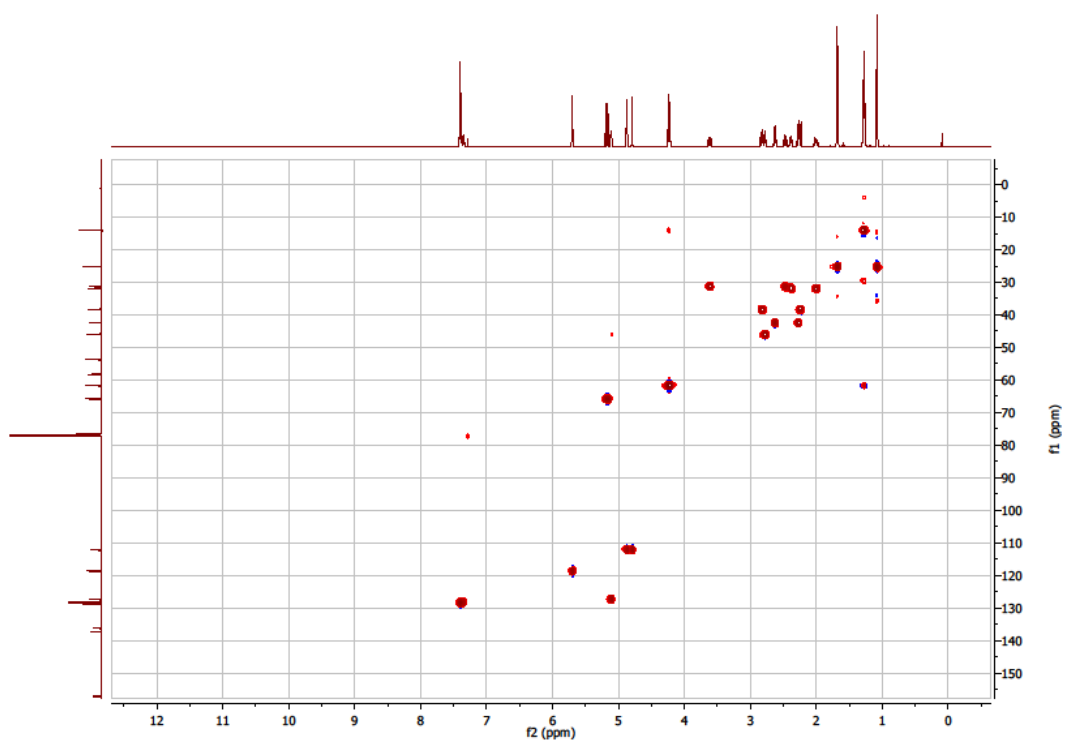






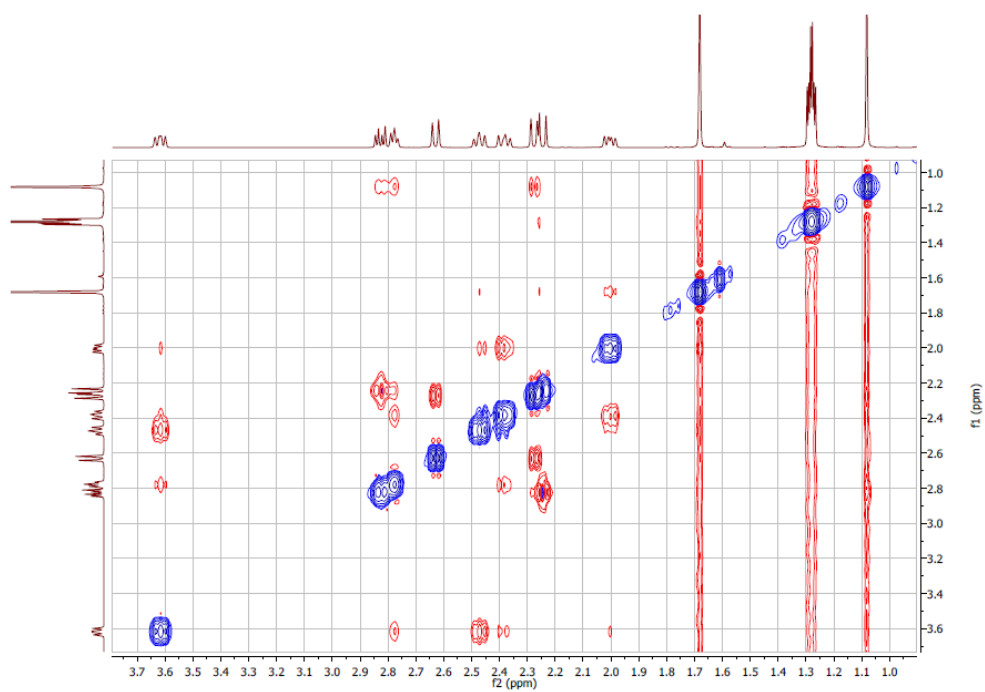
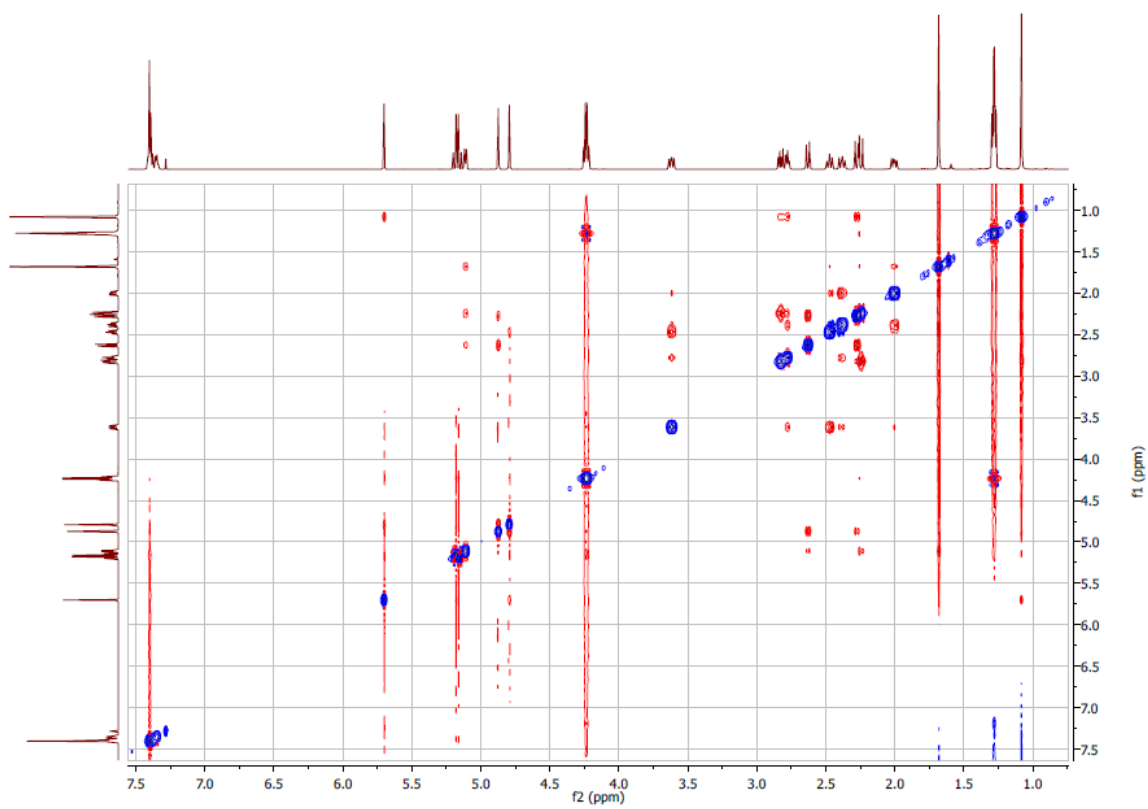


HSQC

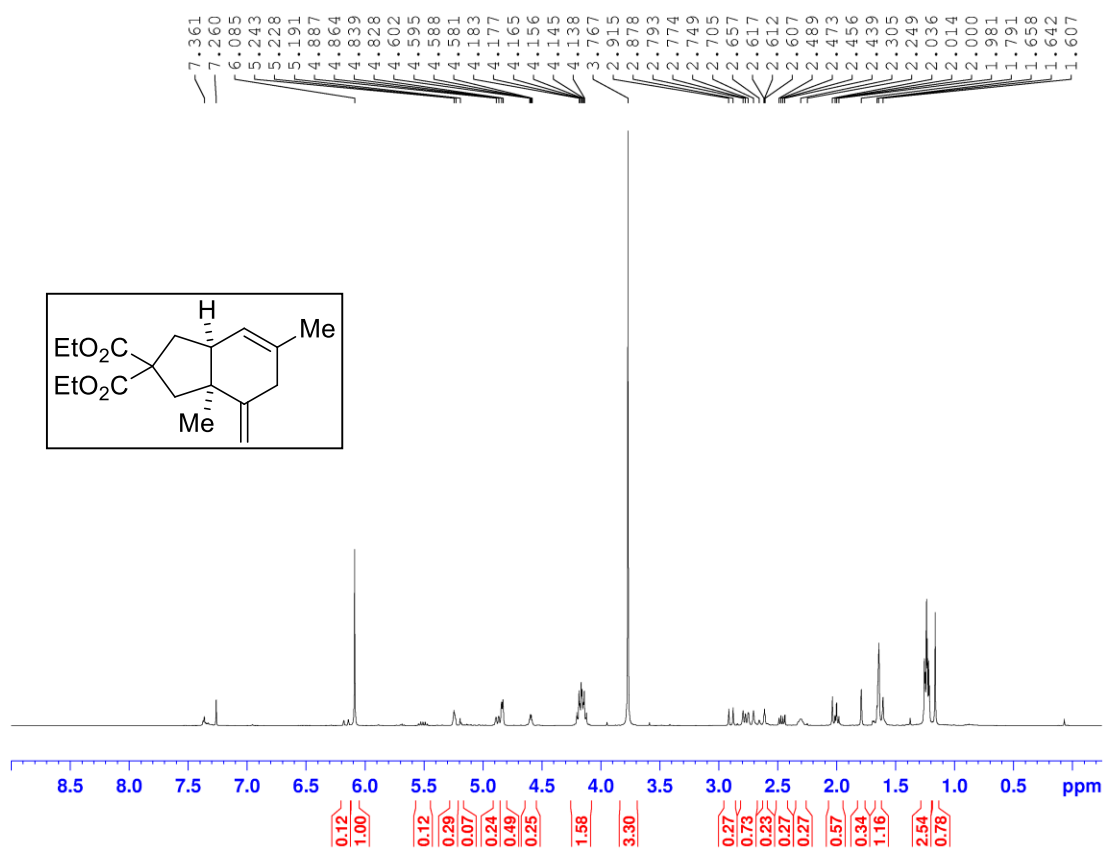


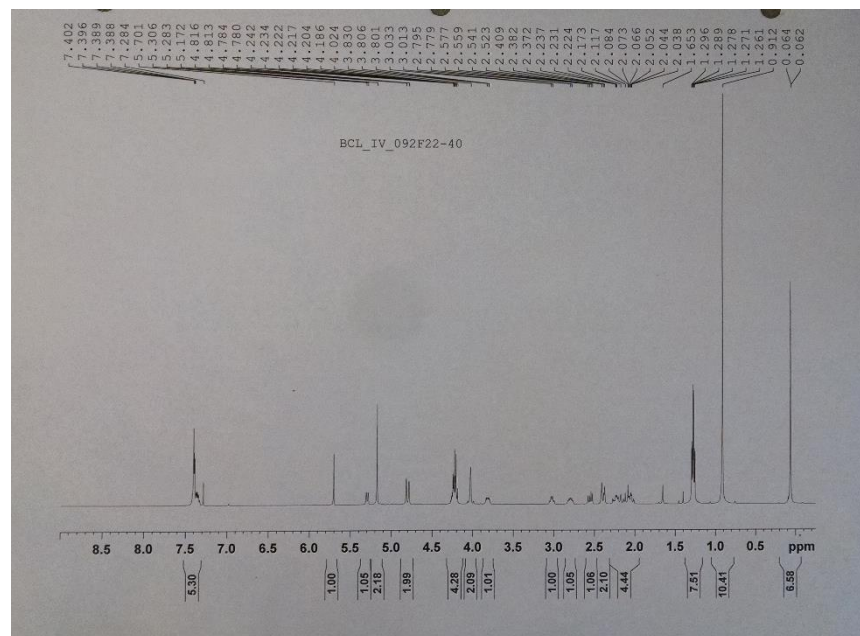


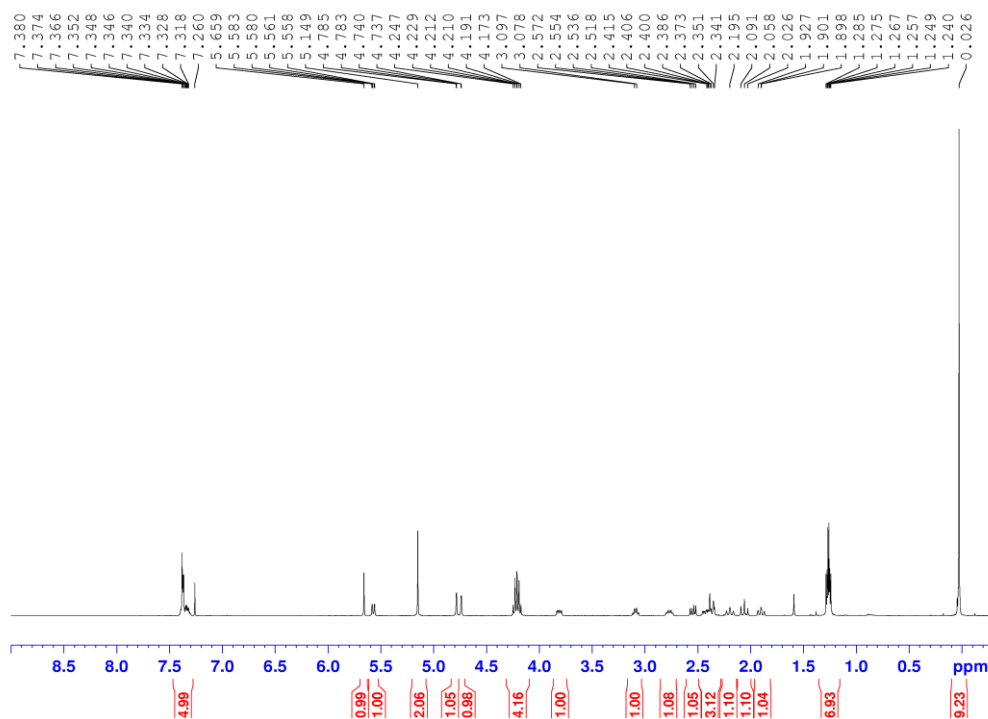
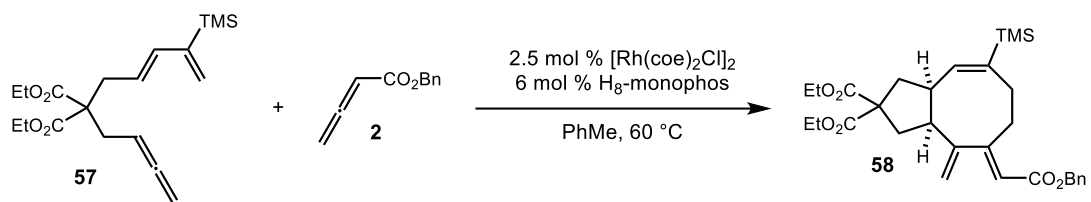
# NOESY

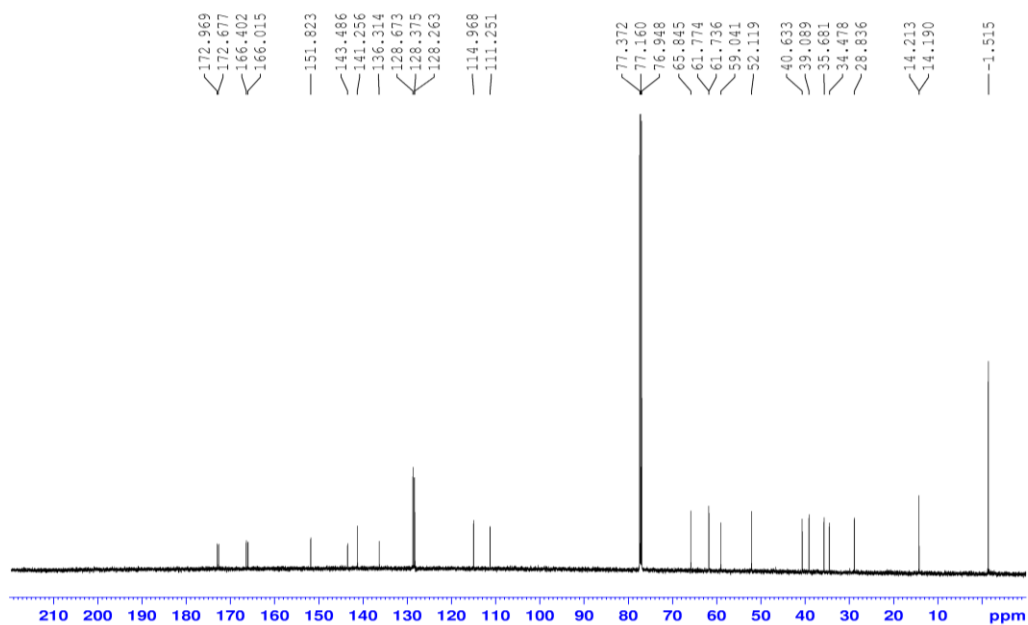


# 54-DA

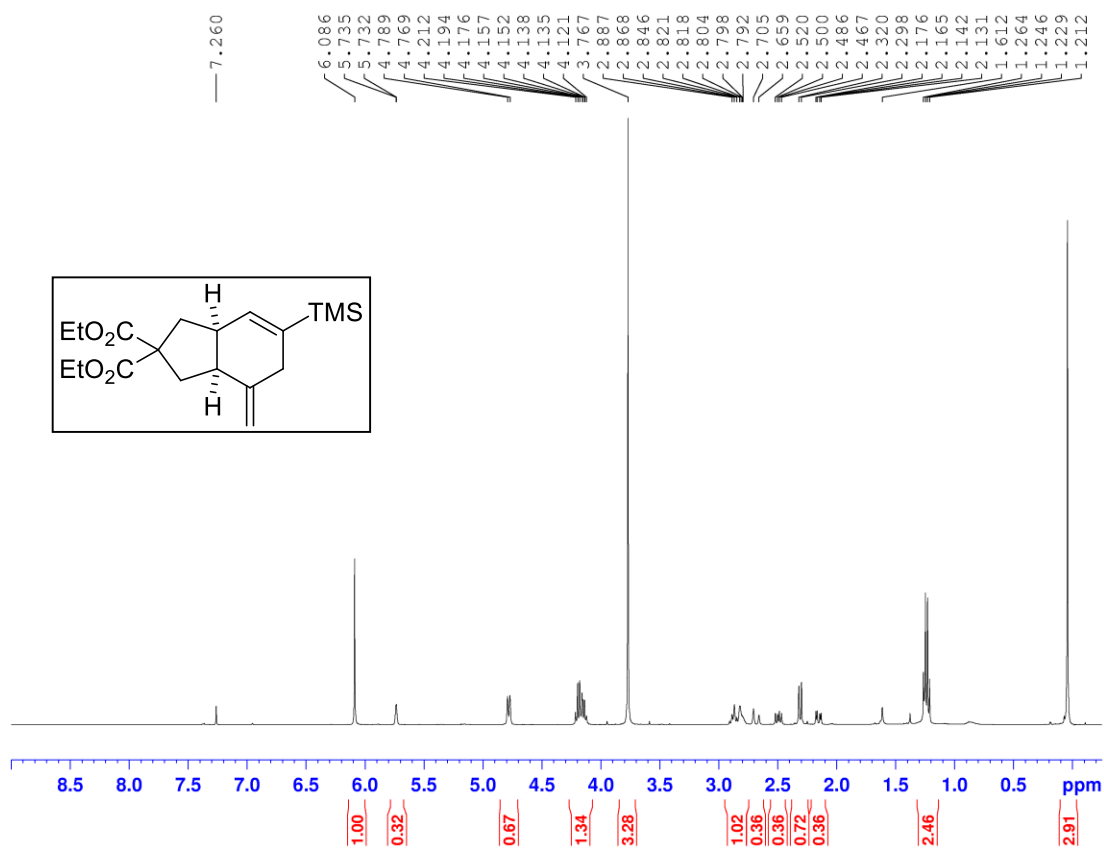


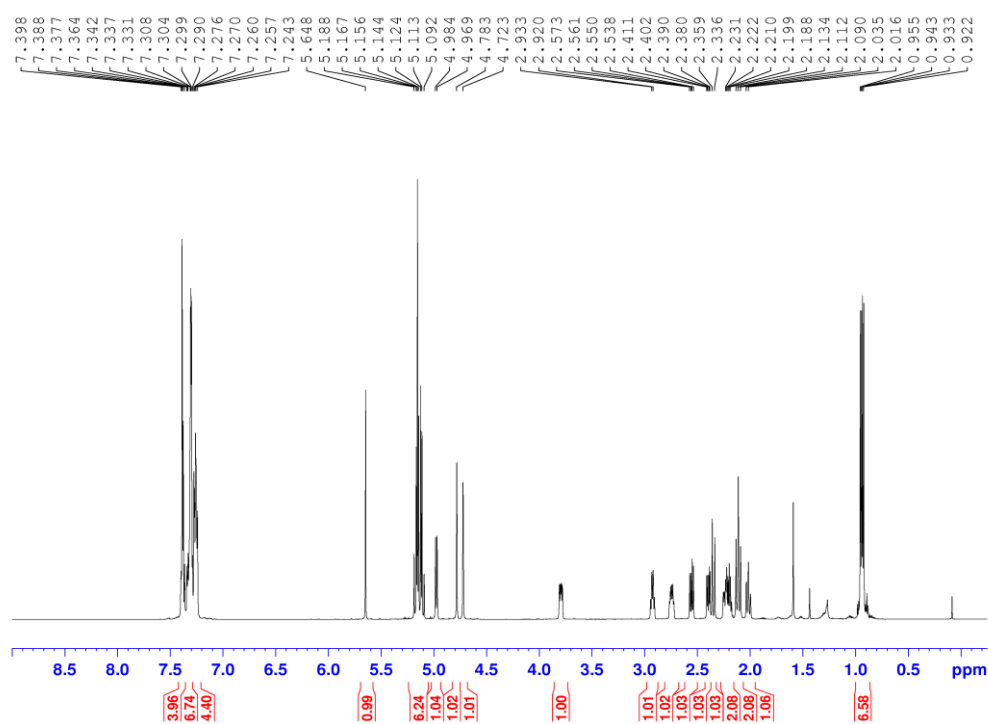
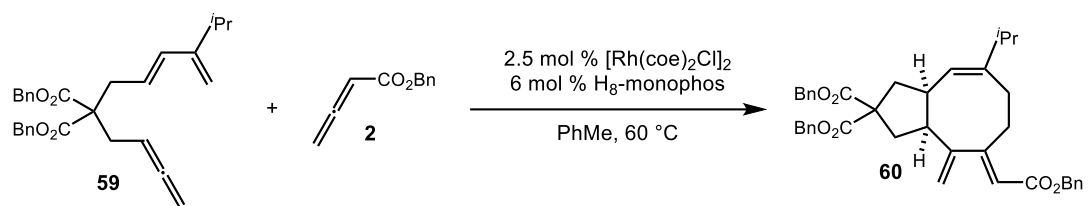


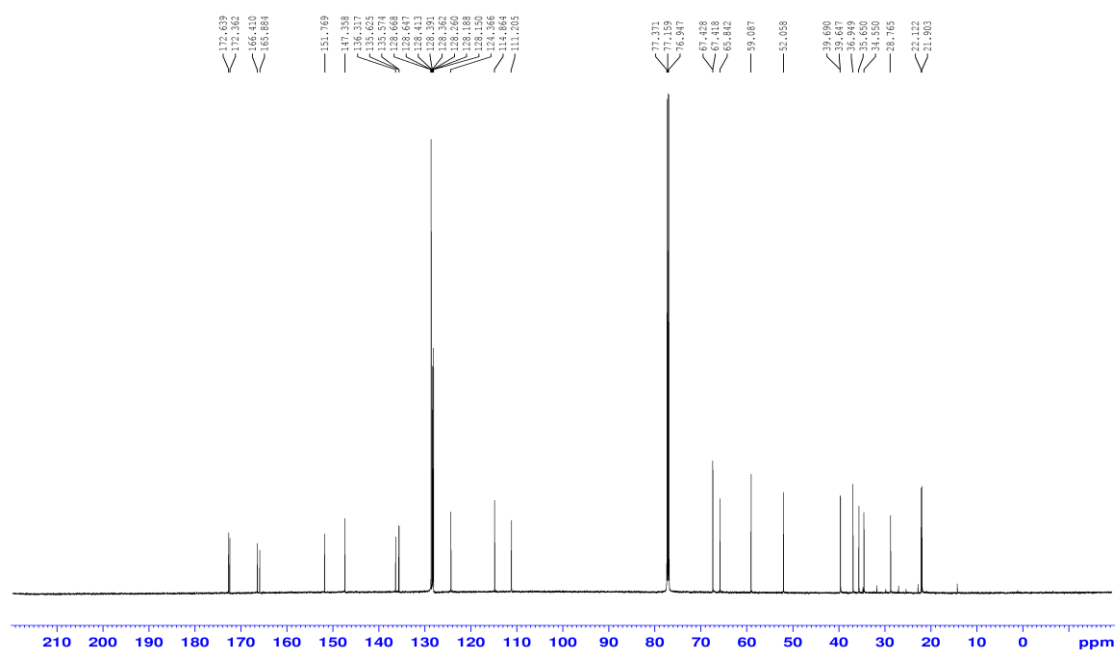


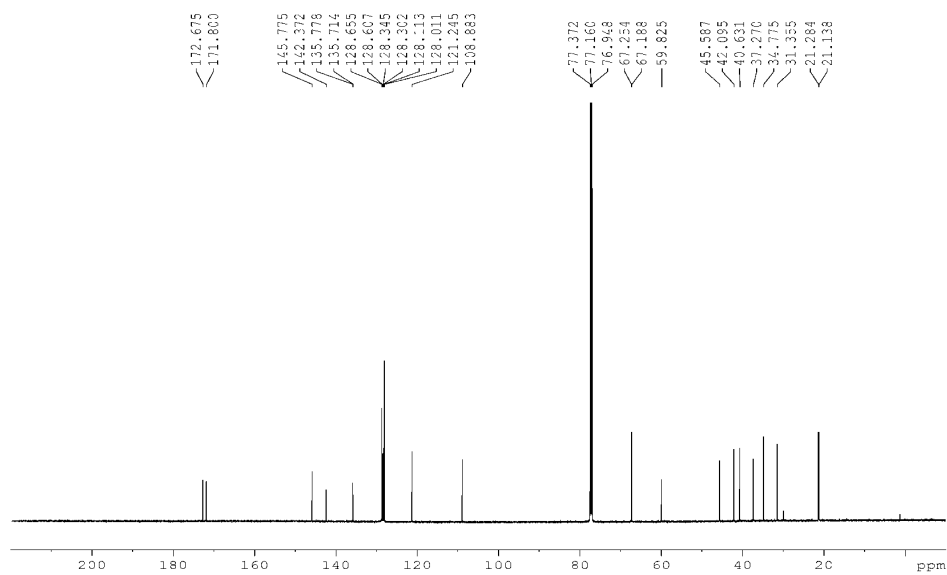
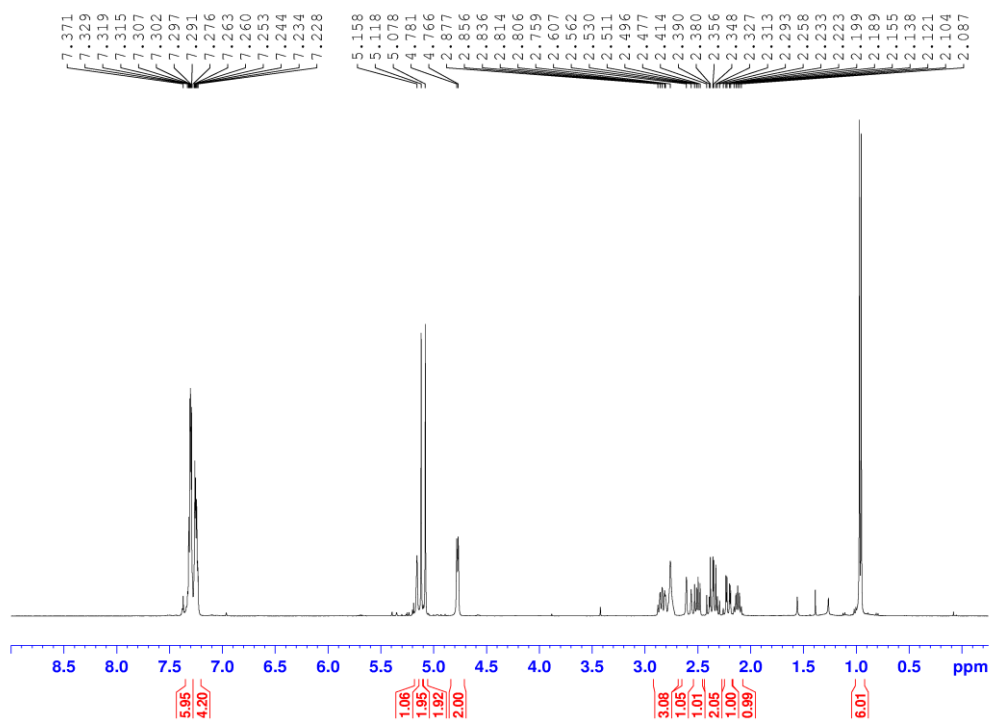
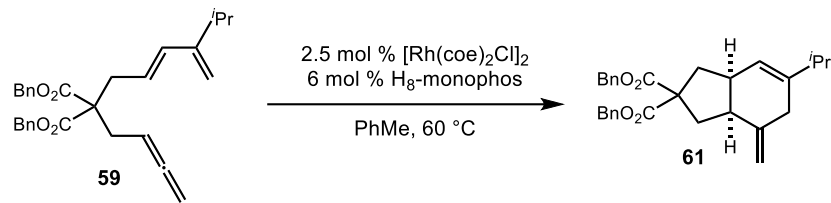


58-DA

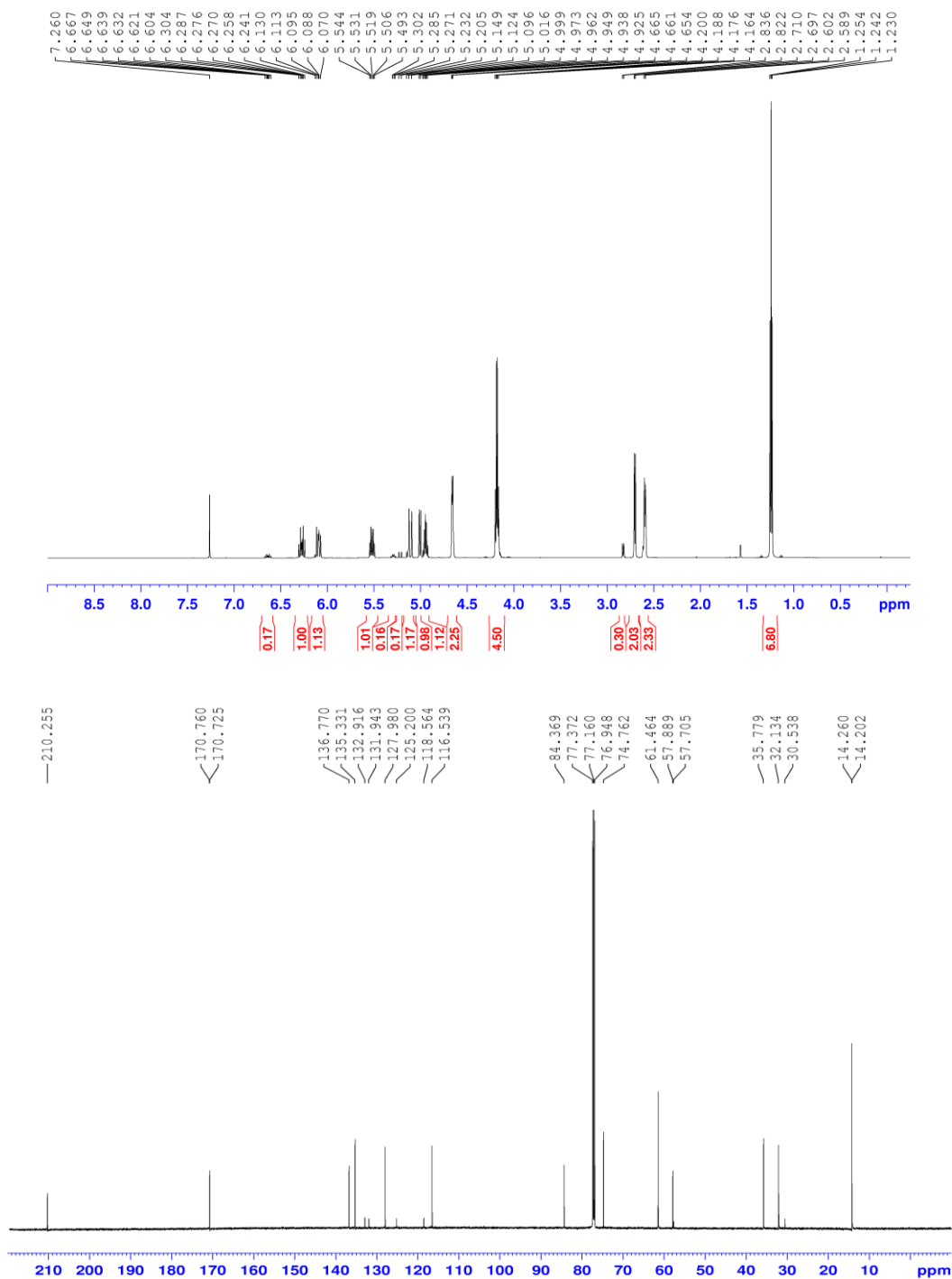
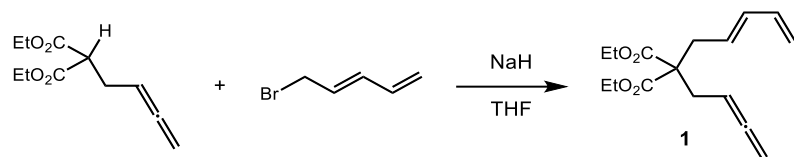


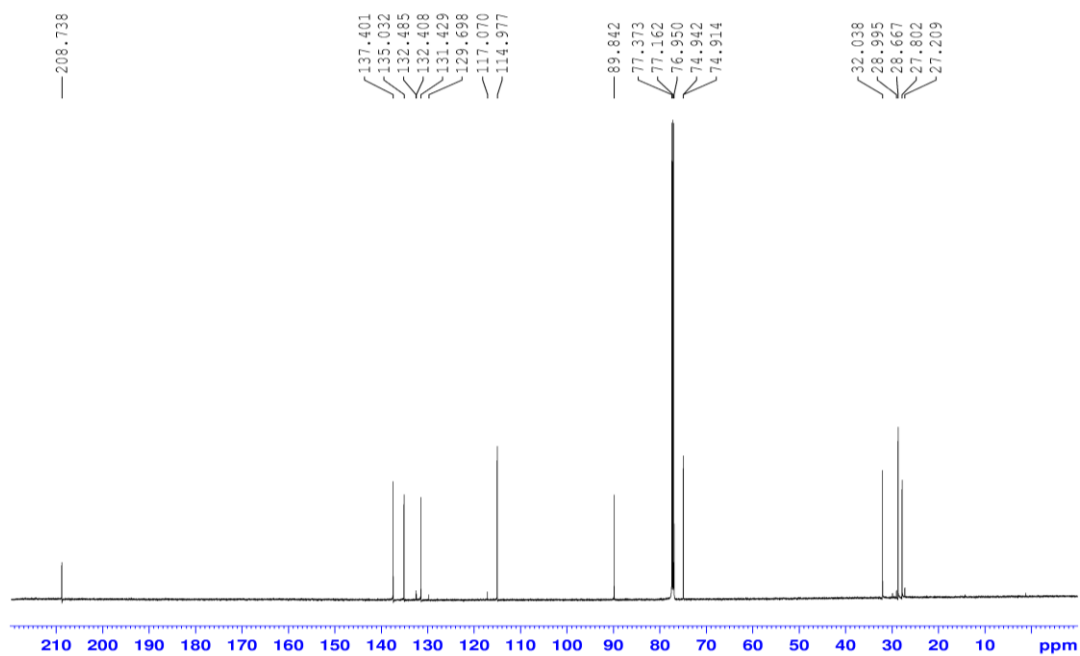
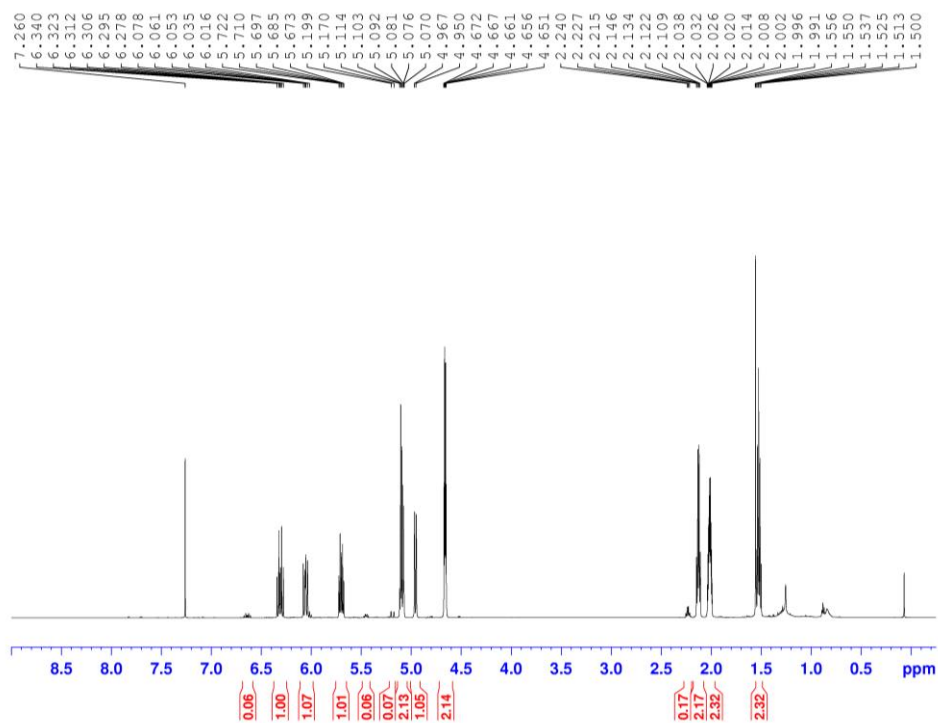
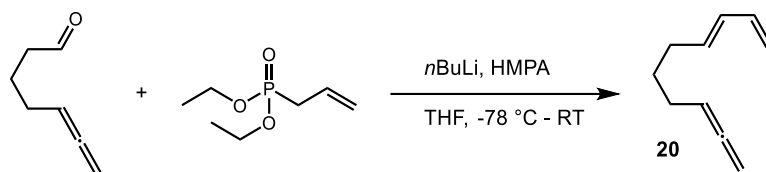


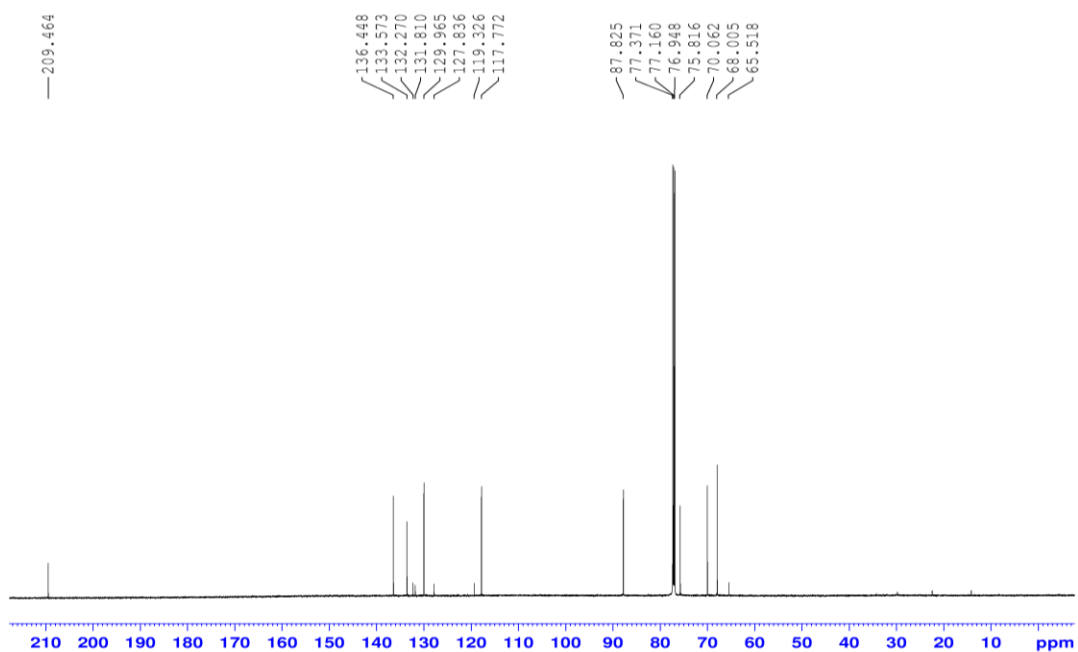
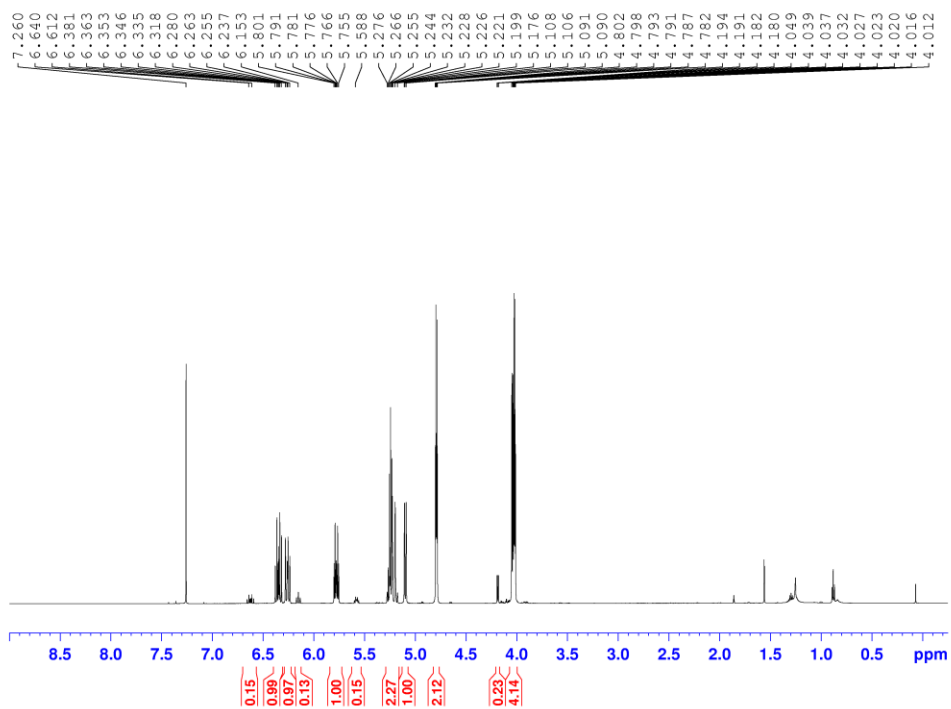
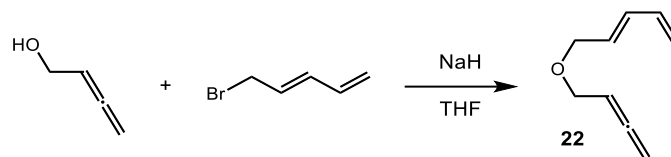


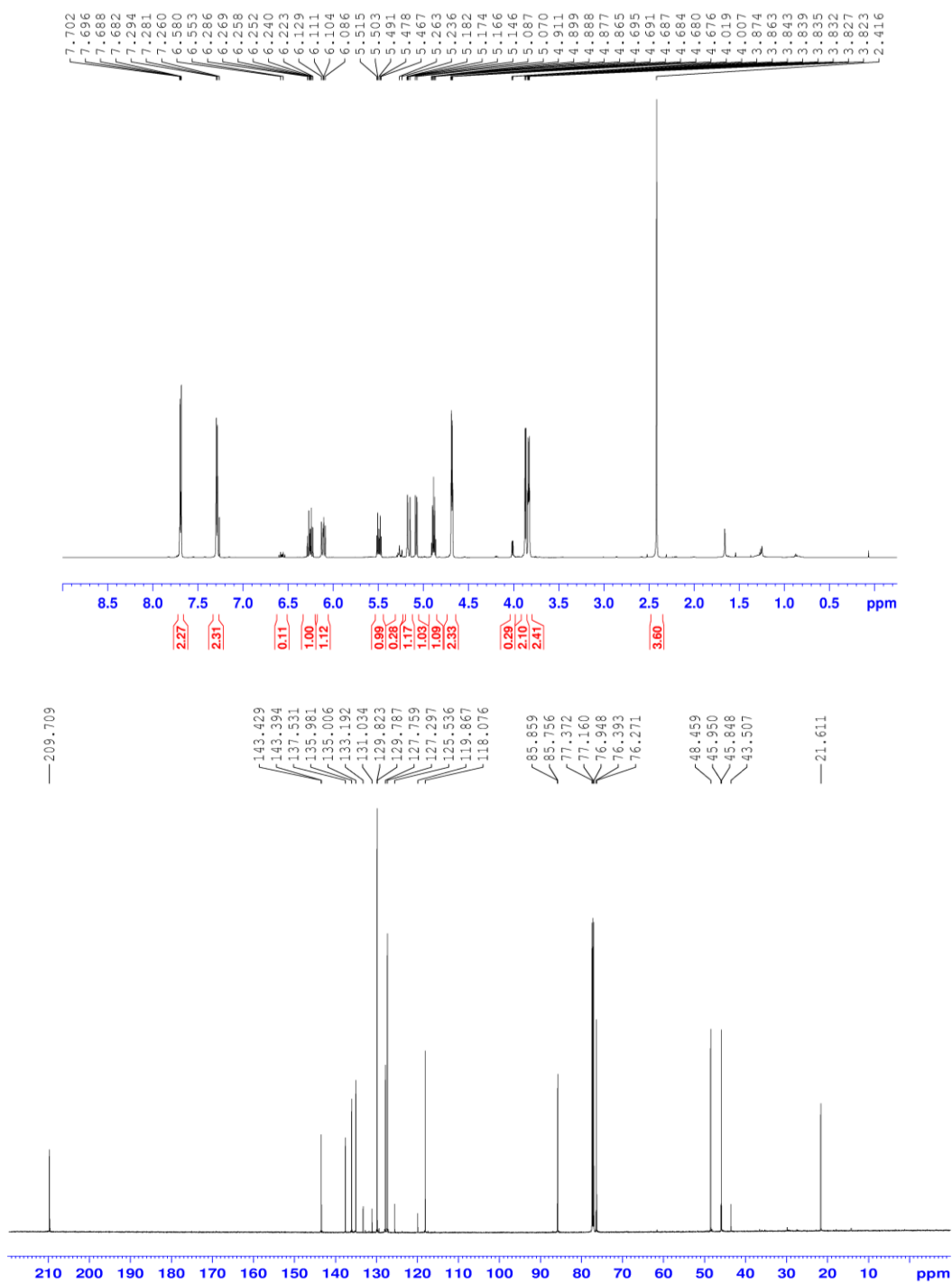
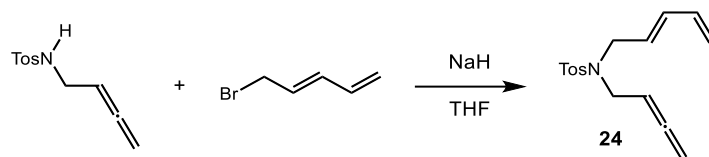


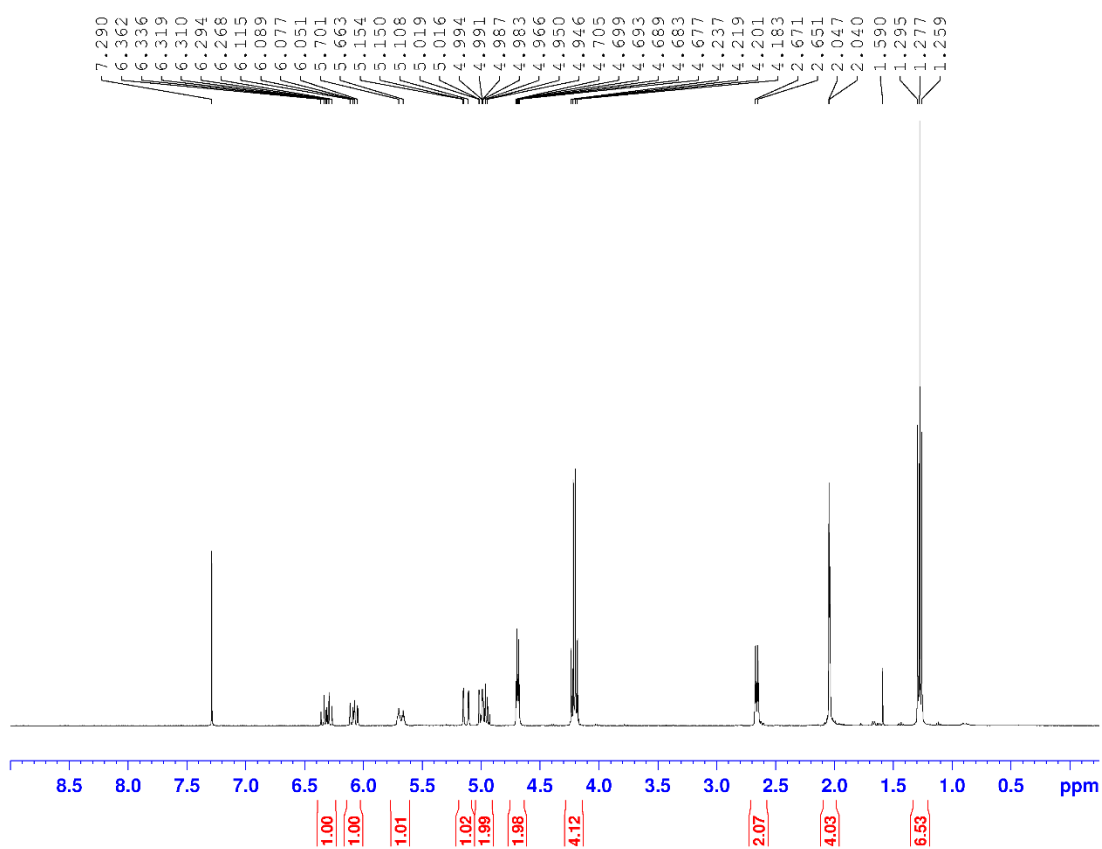
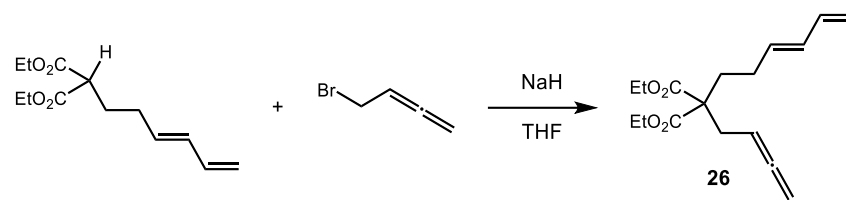


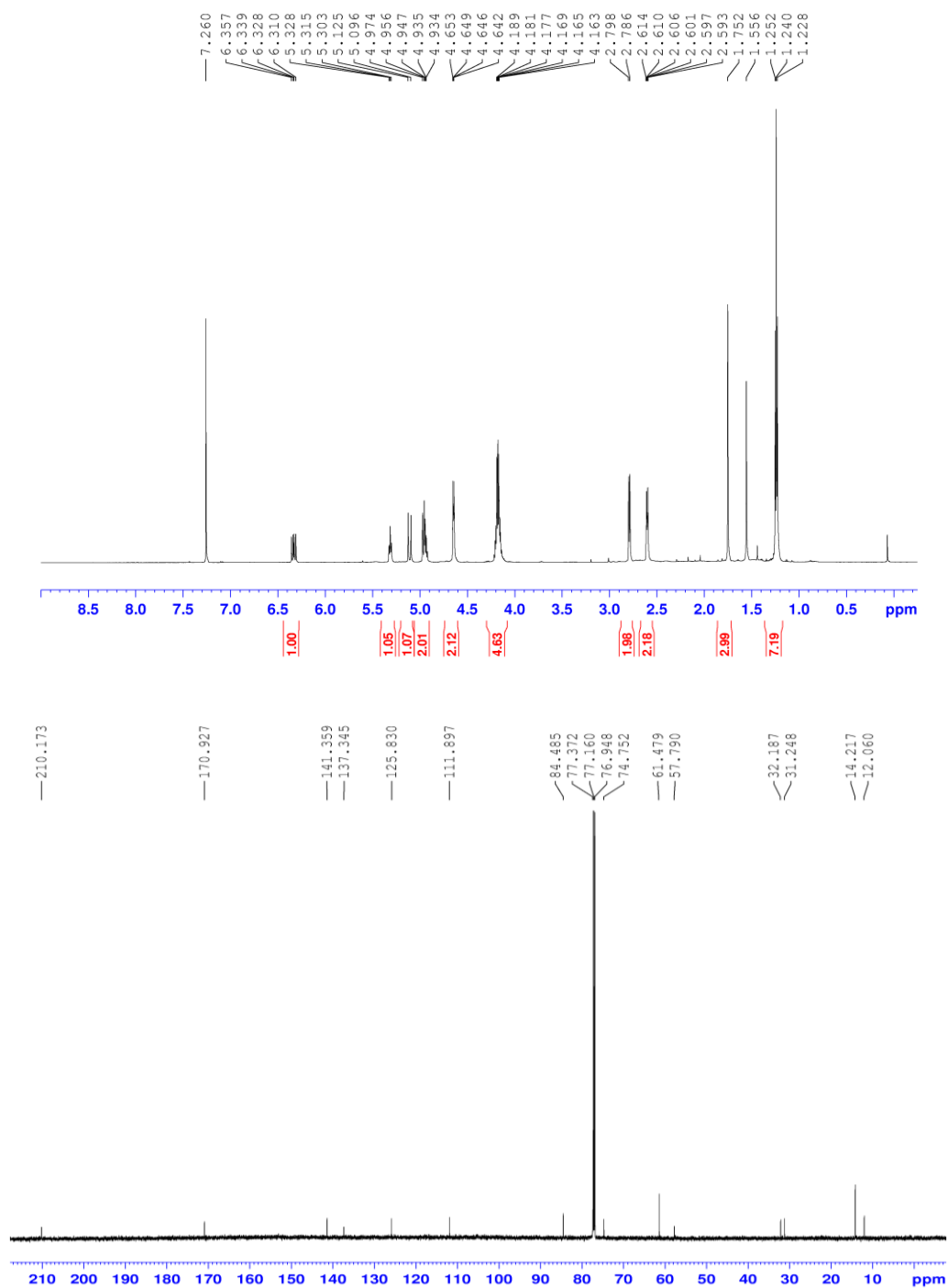
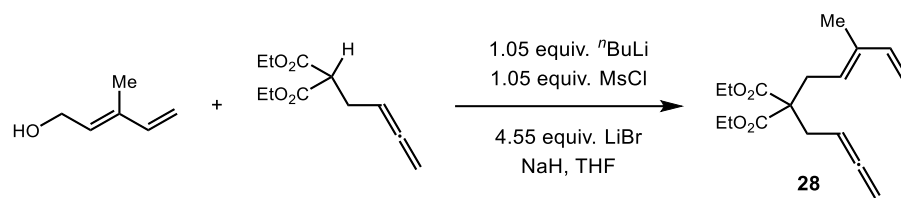


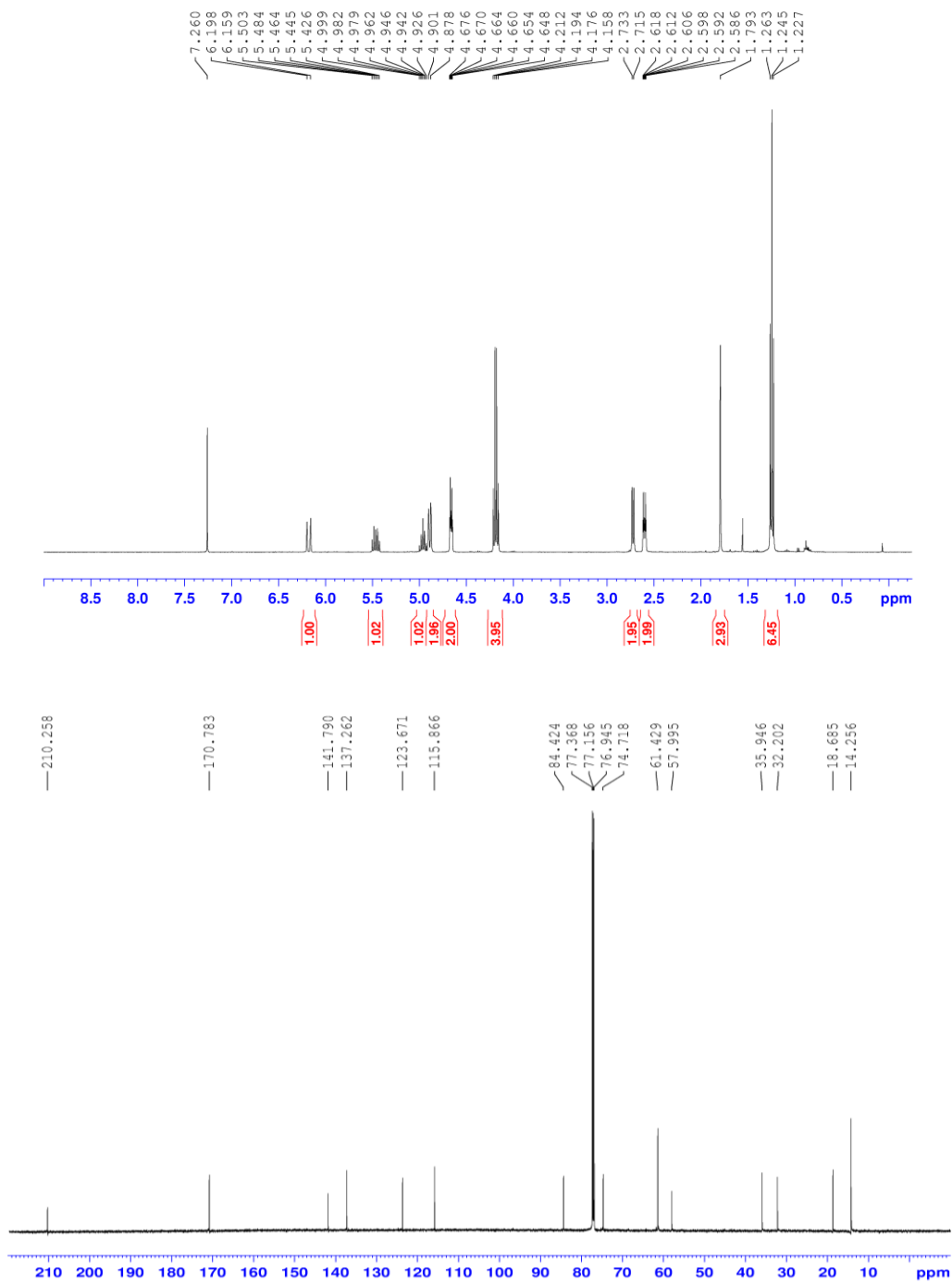
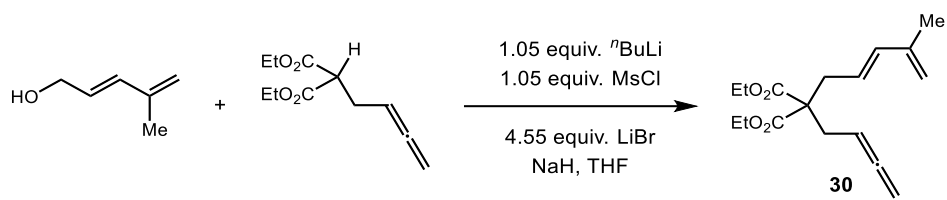


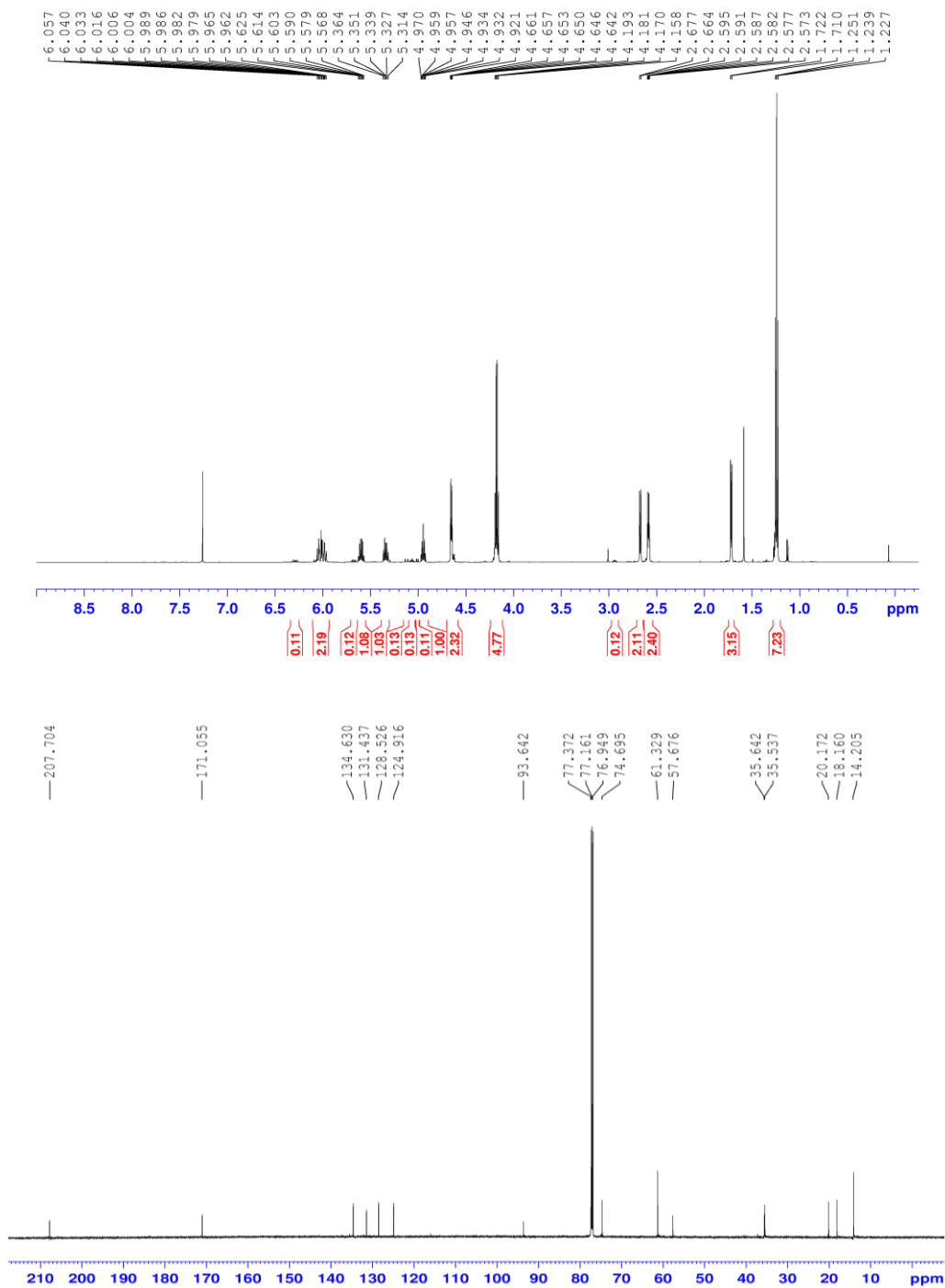
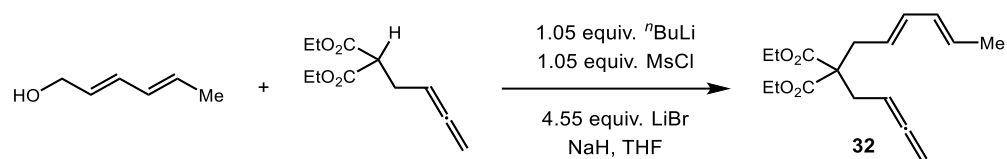




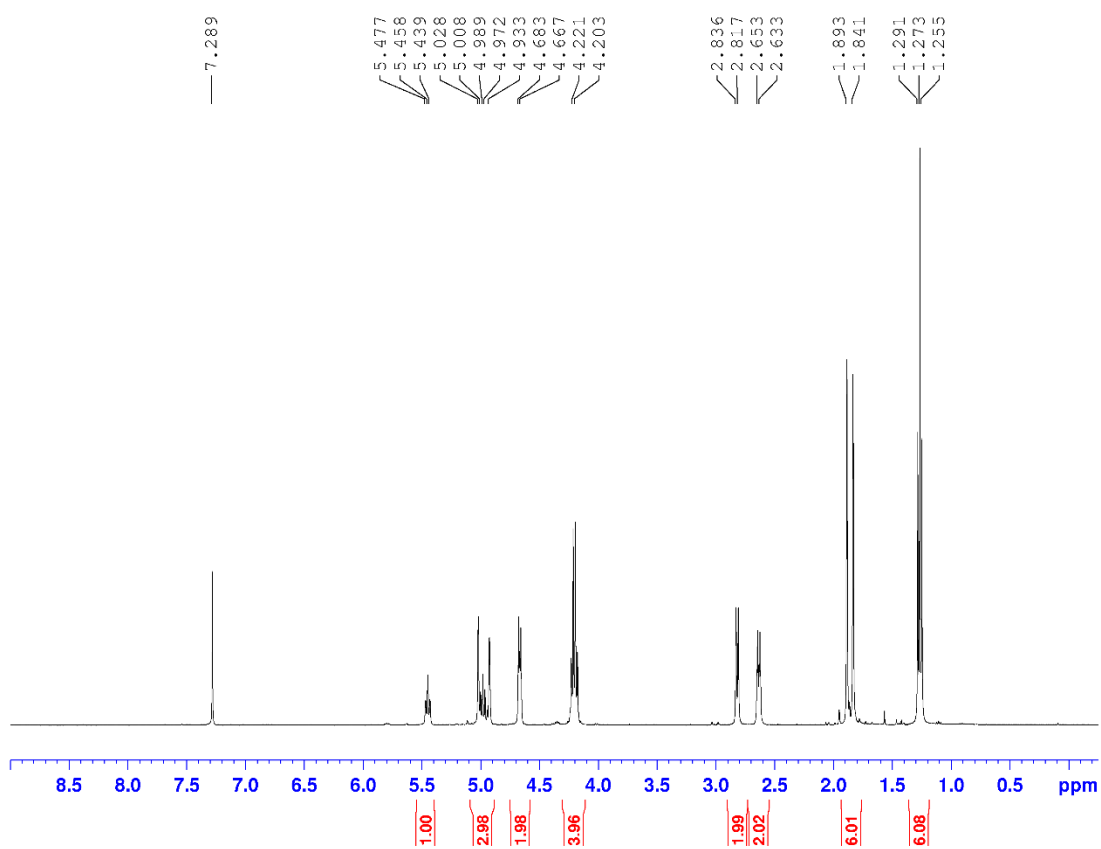
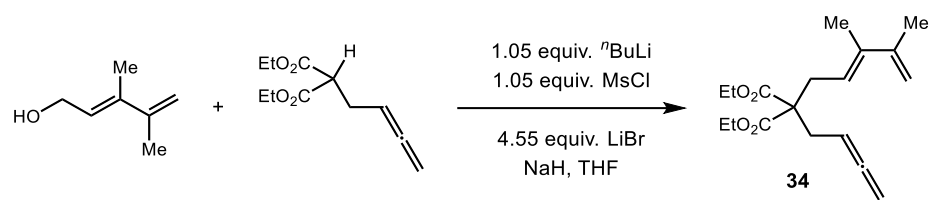


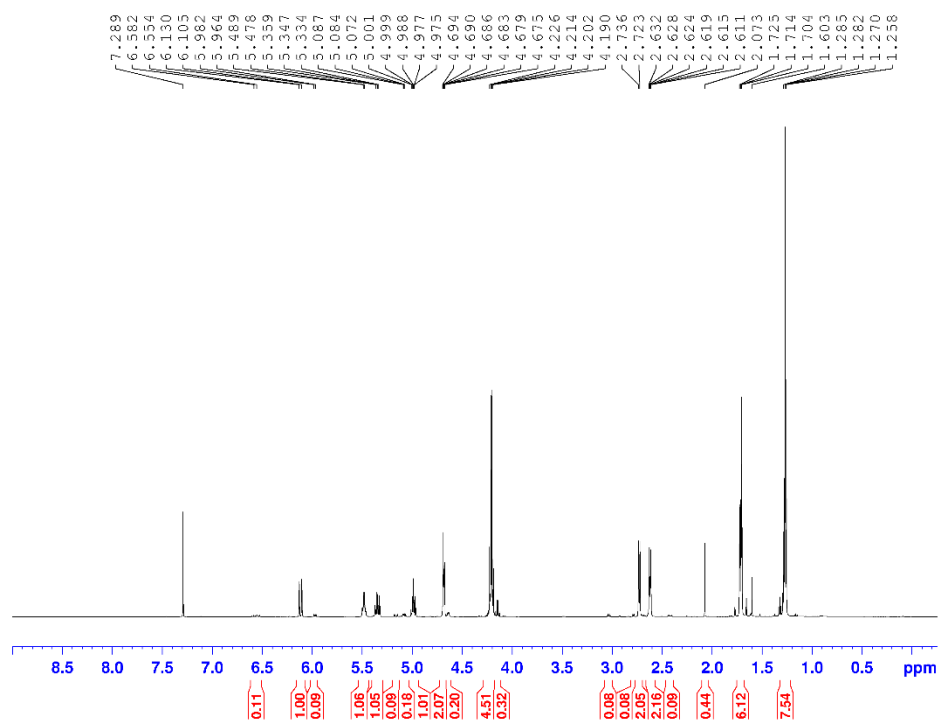
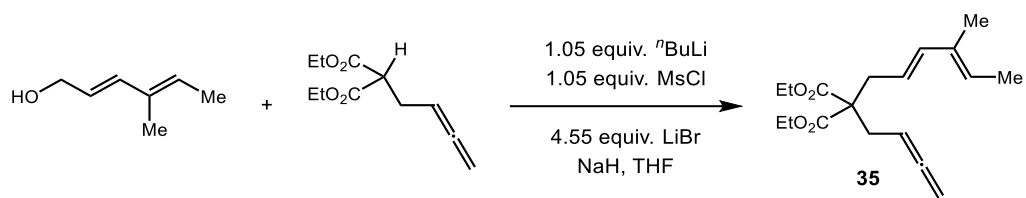


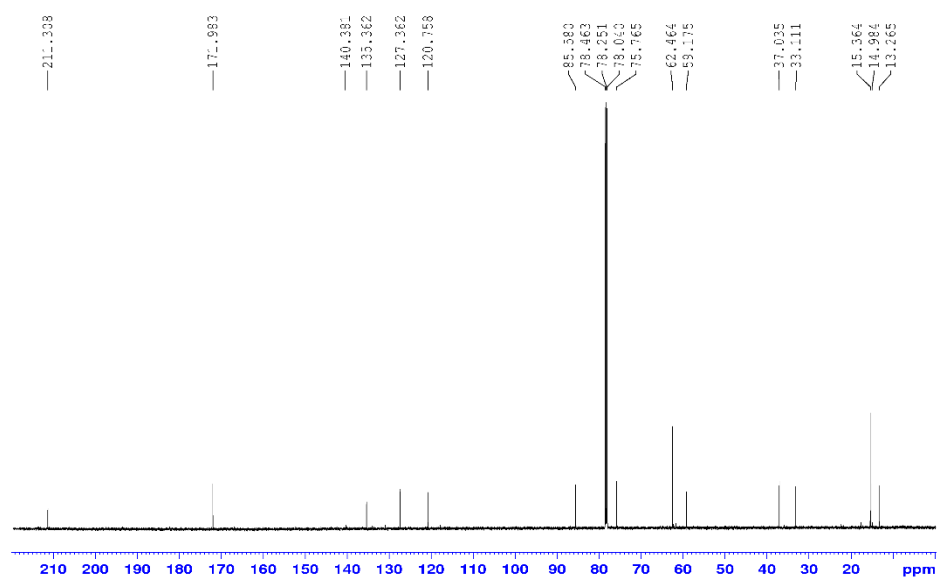


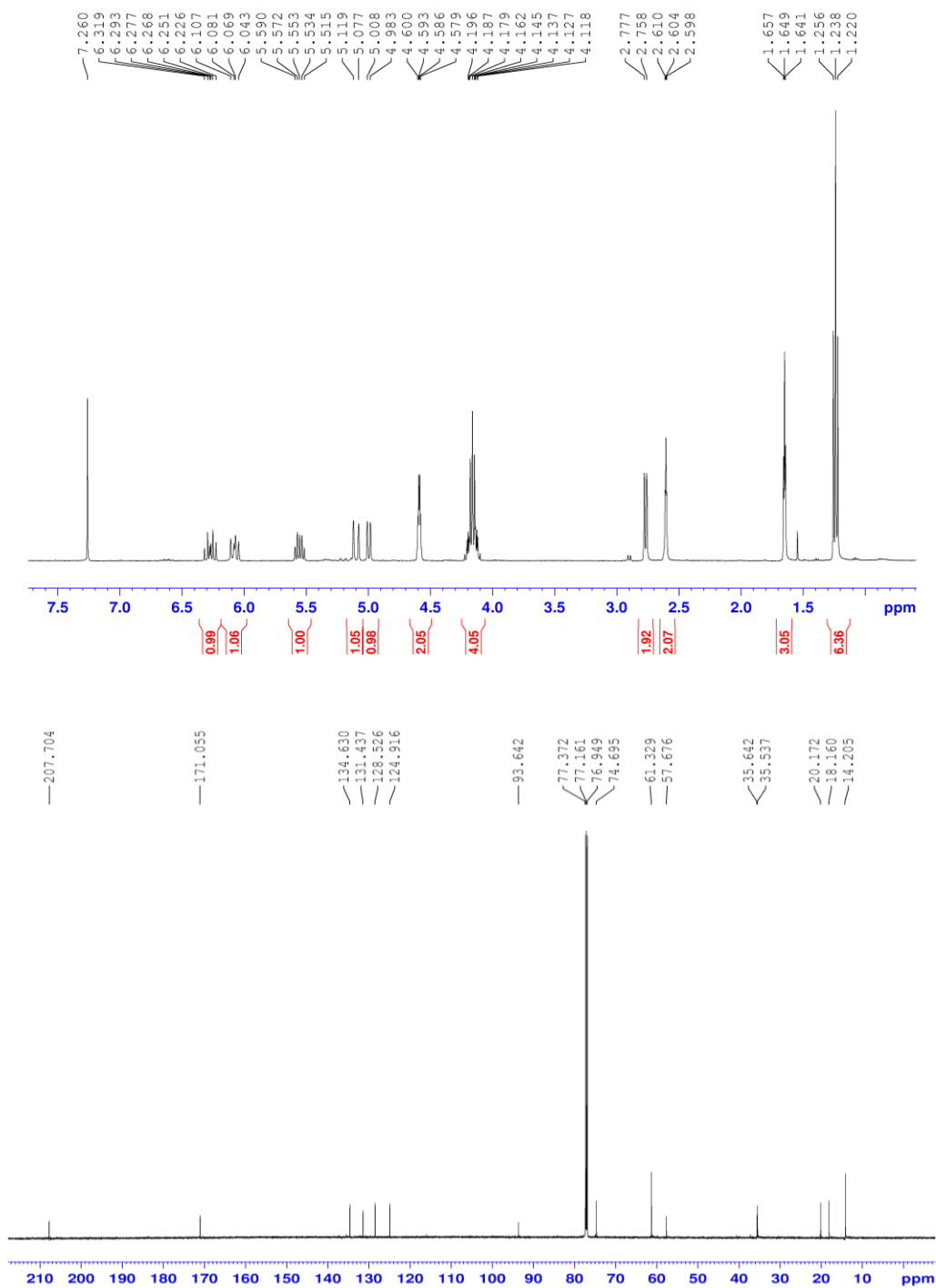
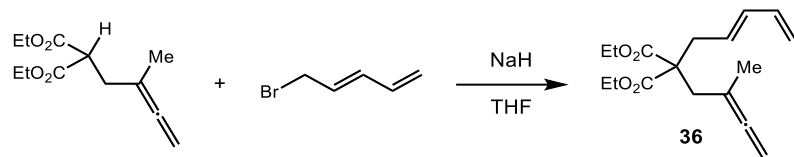


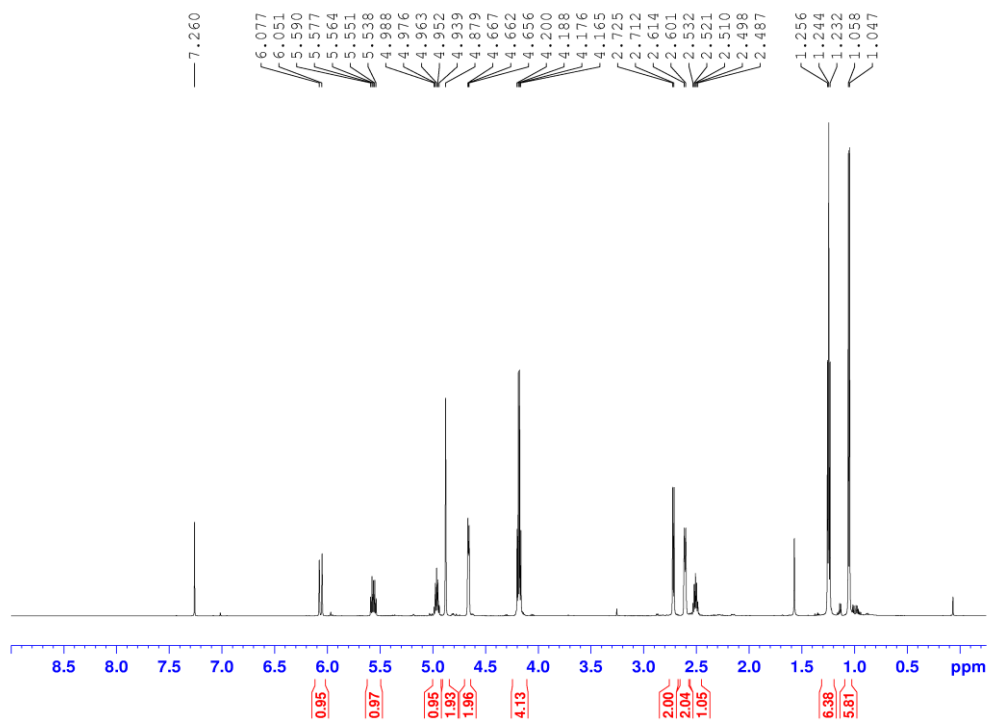
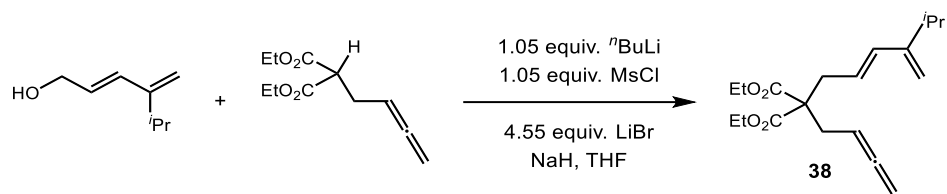


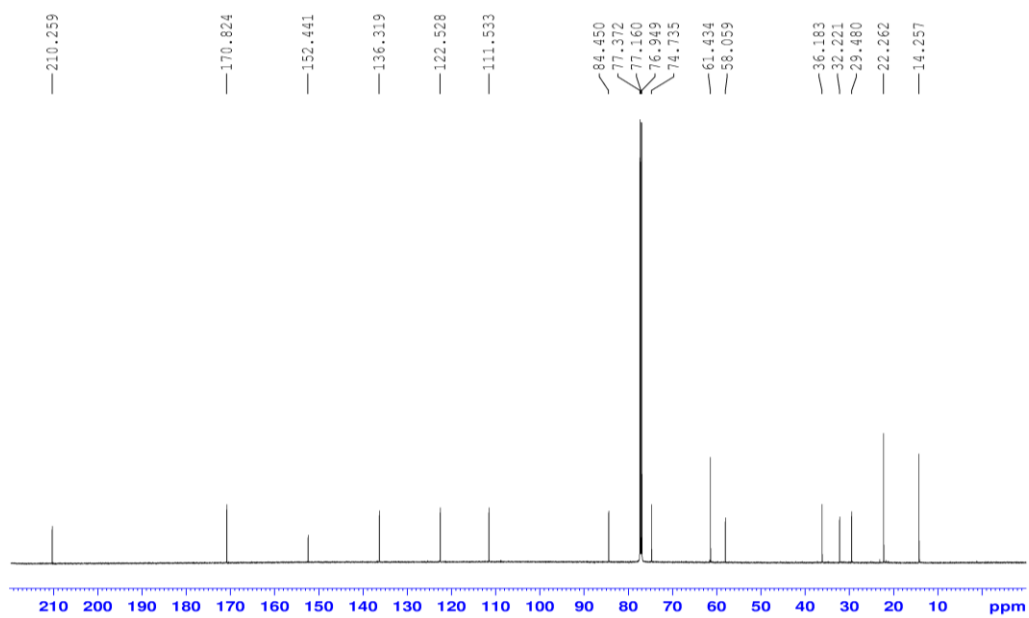


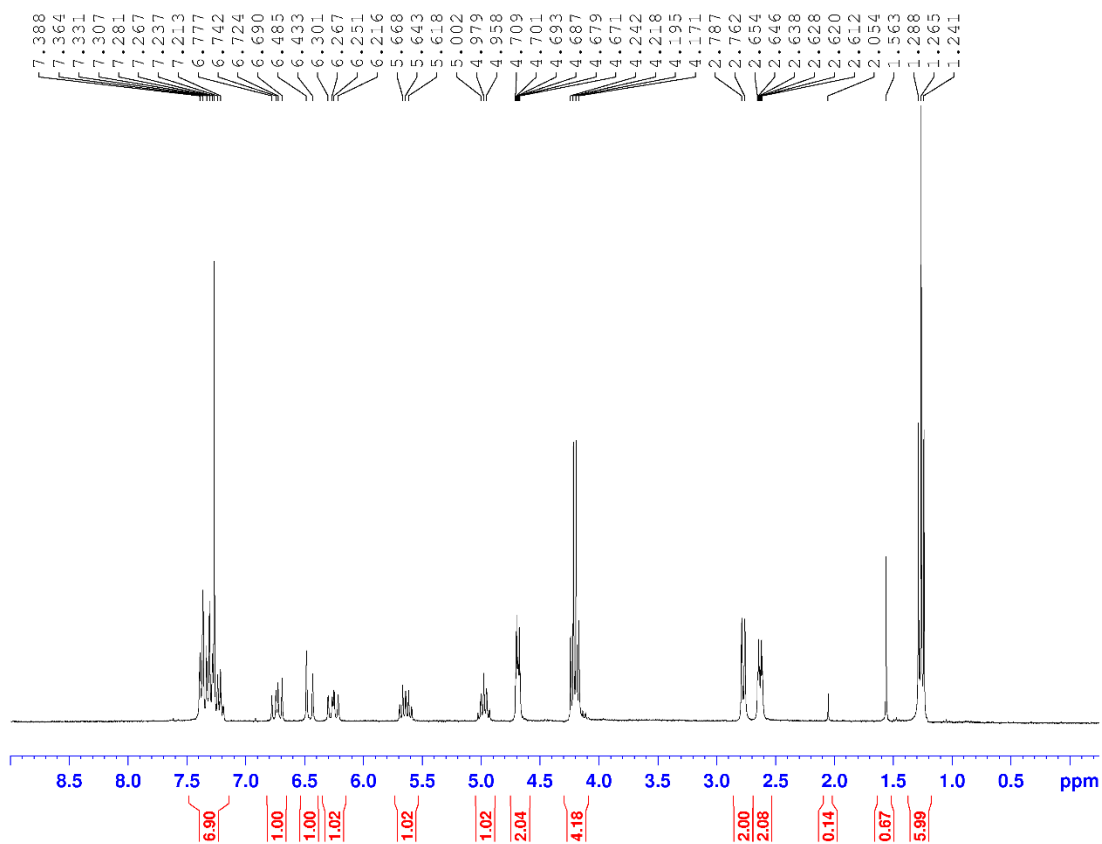
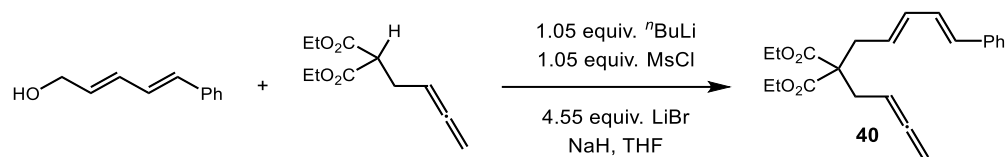


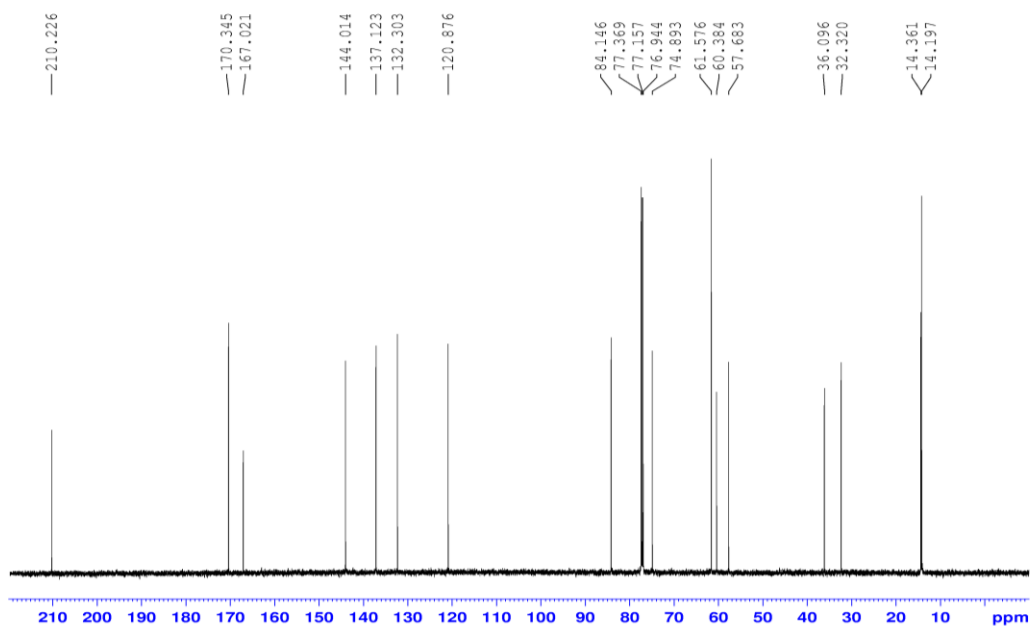
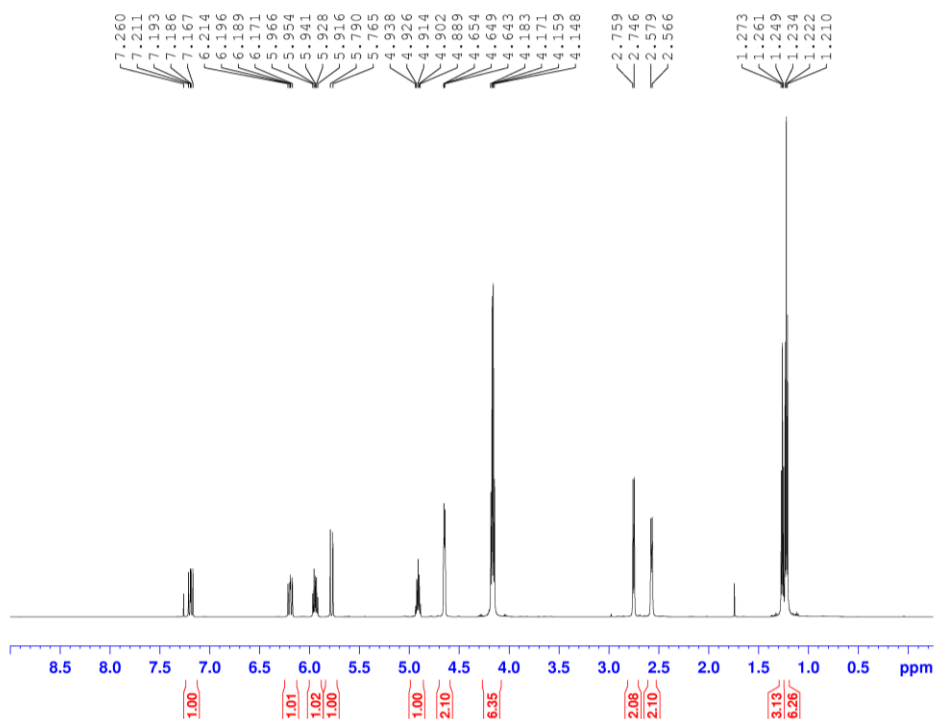
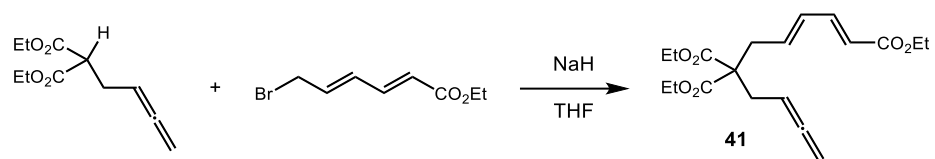




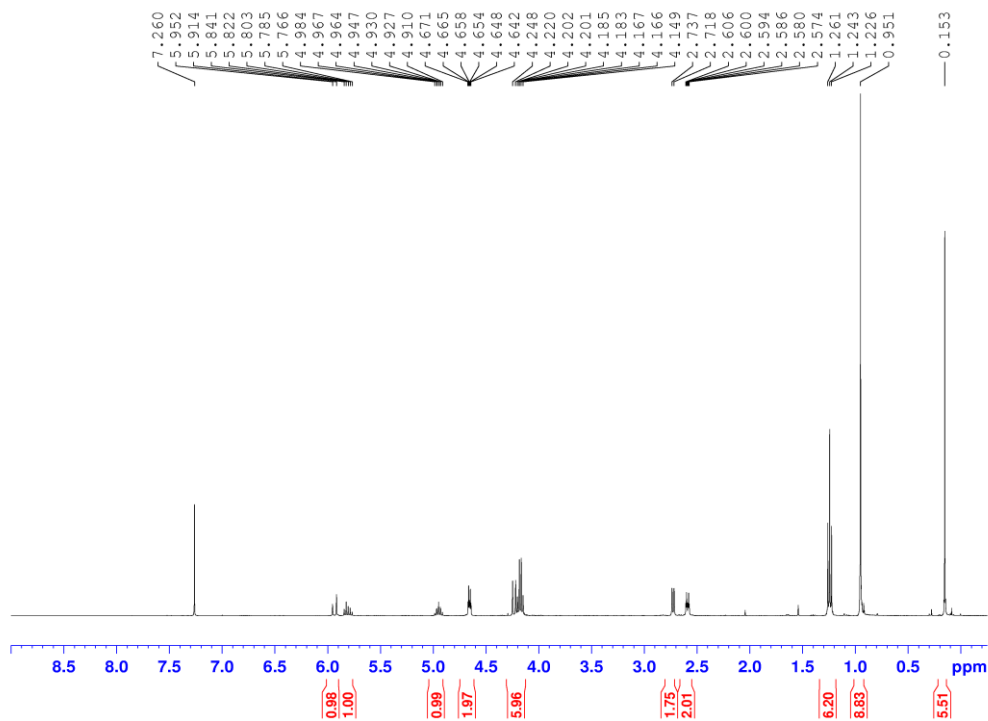
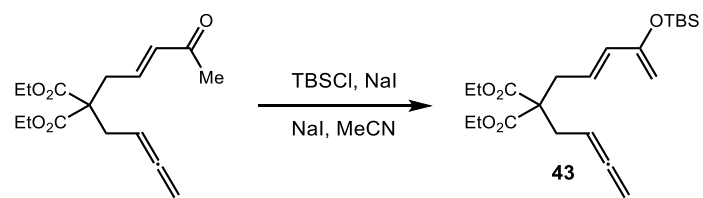


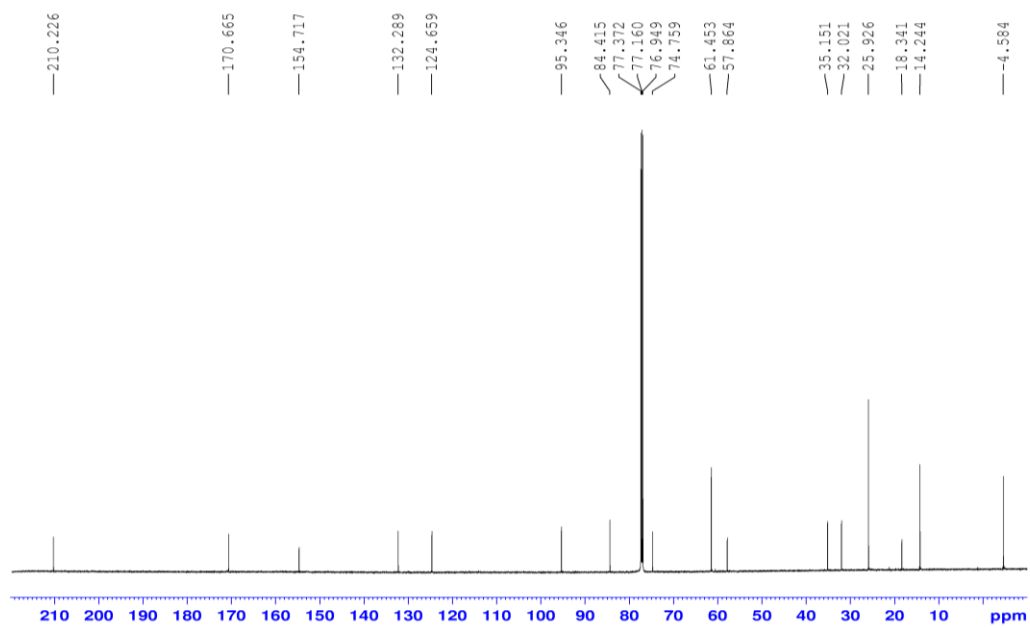


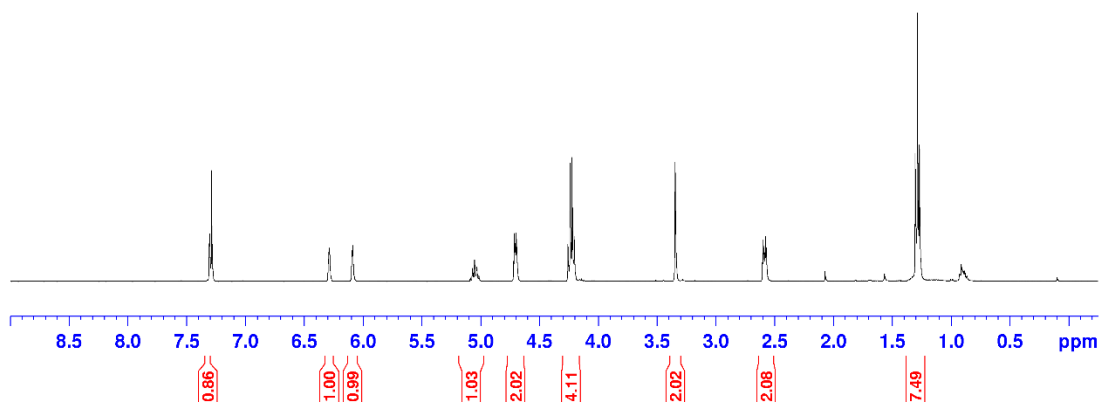
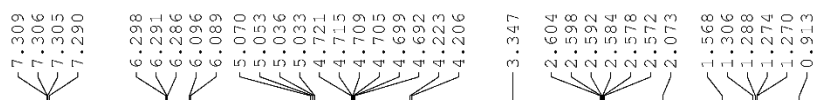
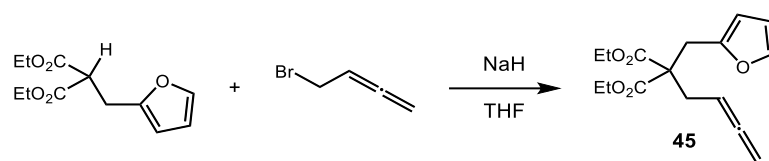


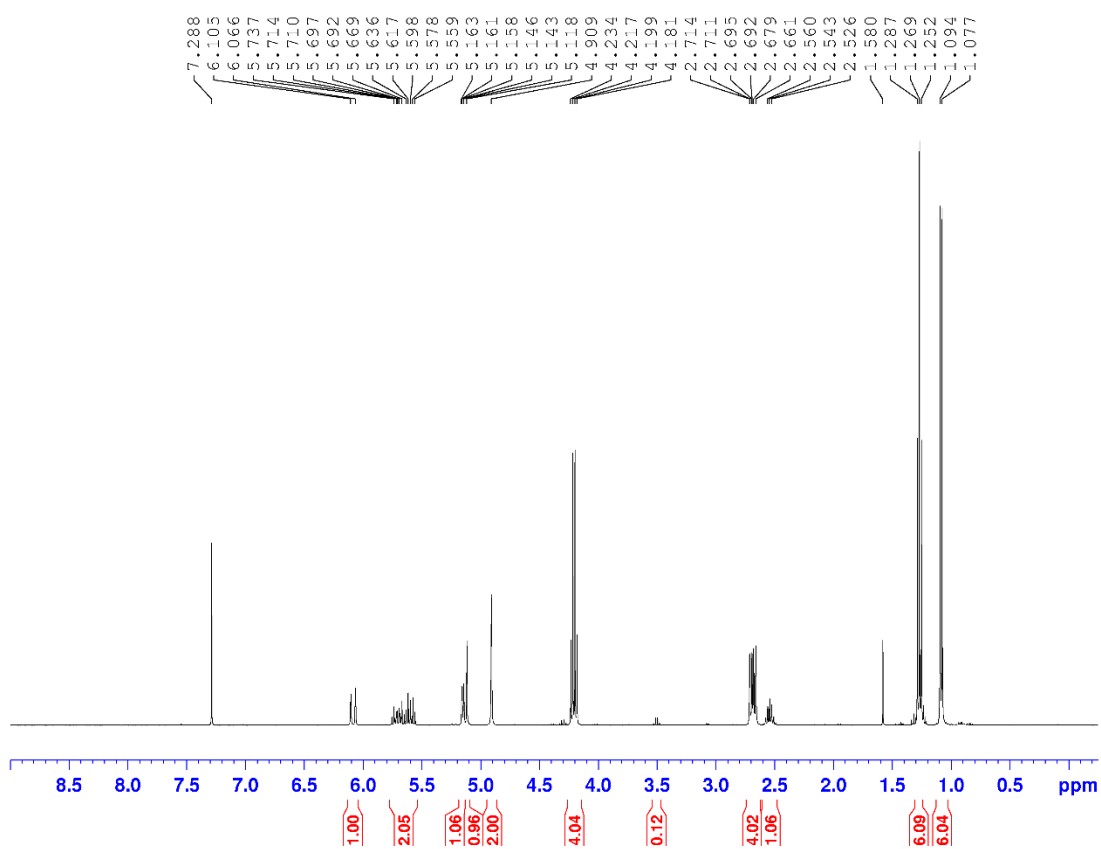
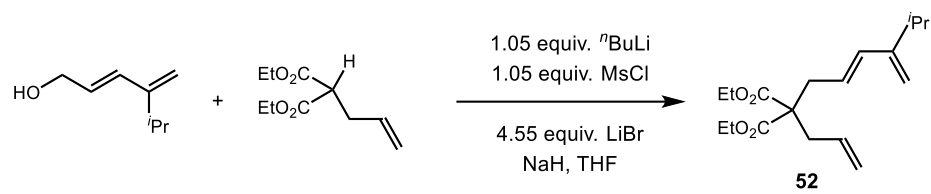


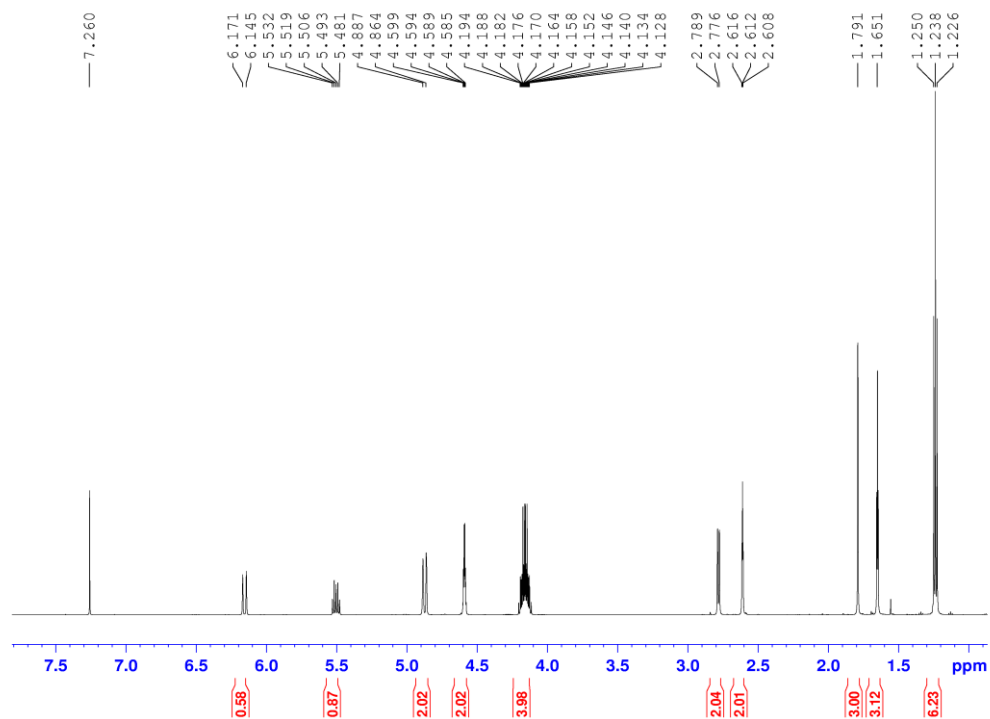
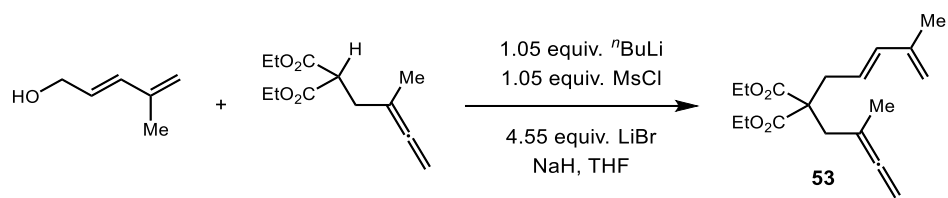


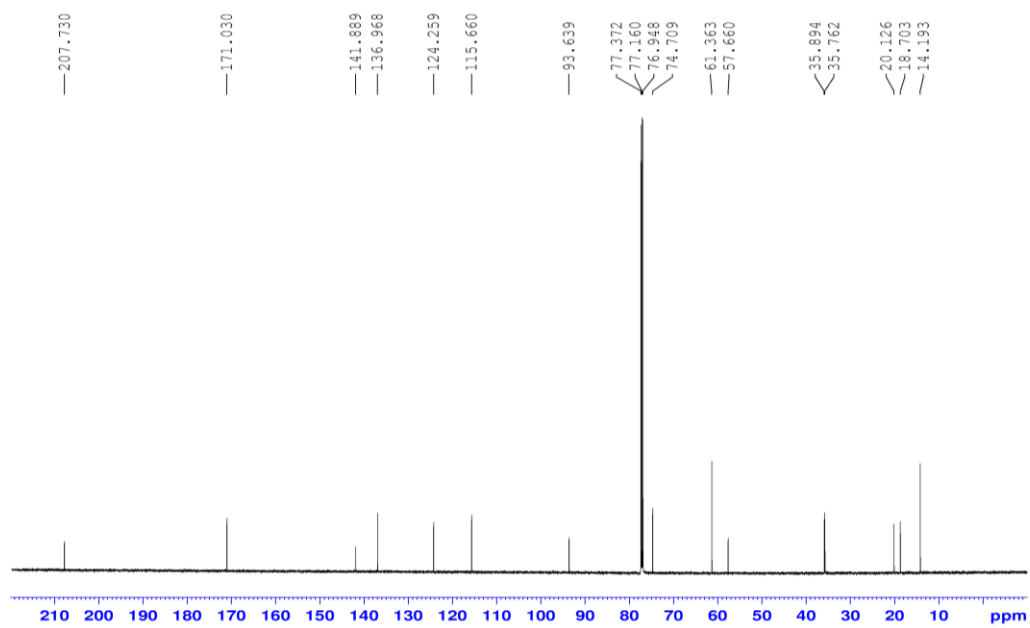


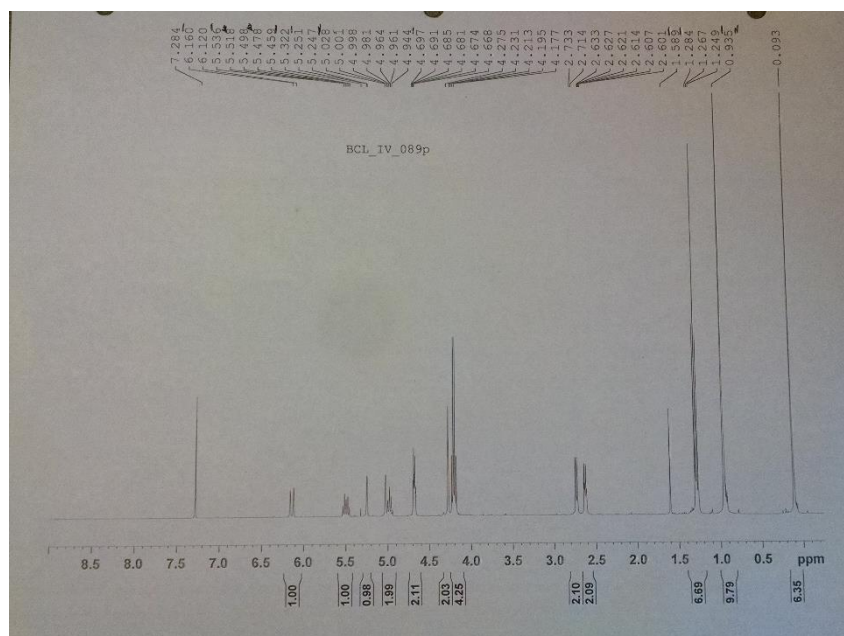
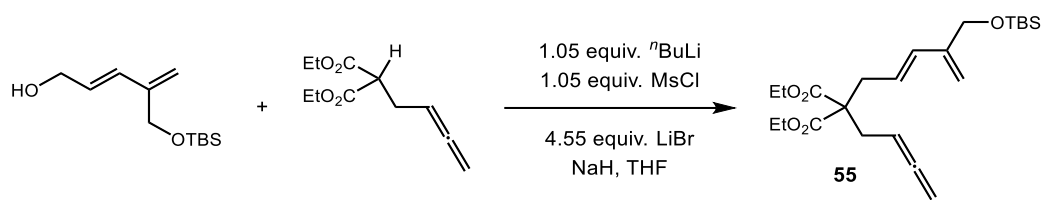


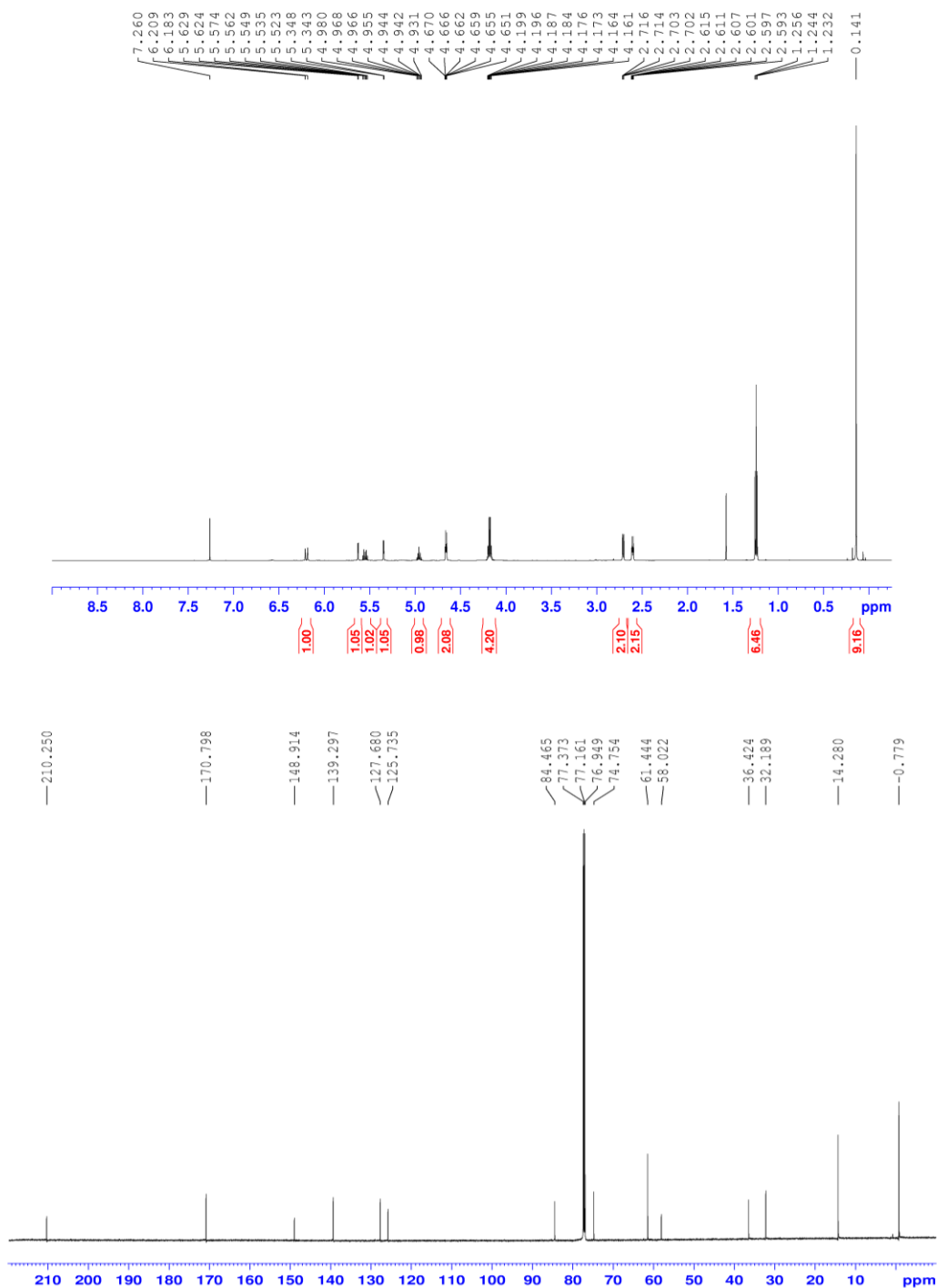
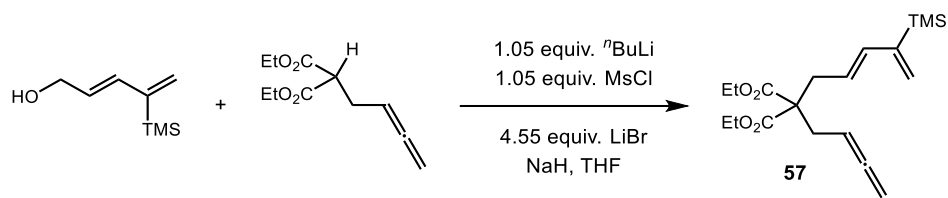




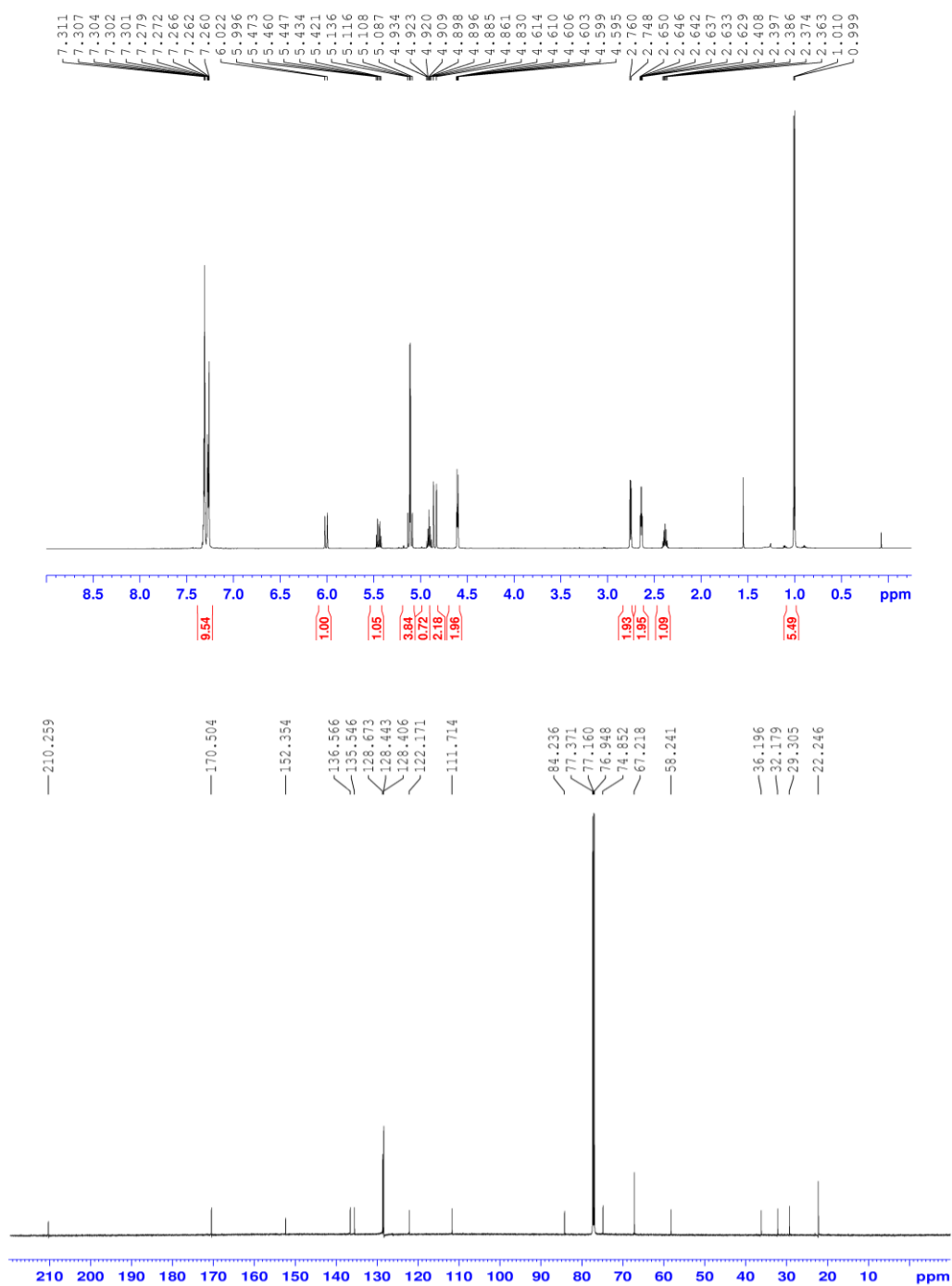
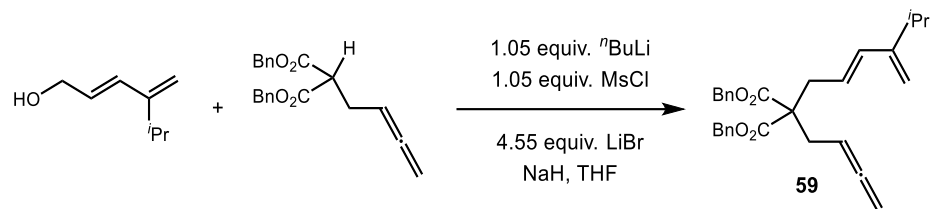






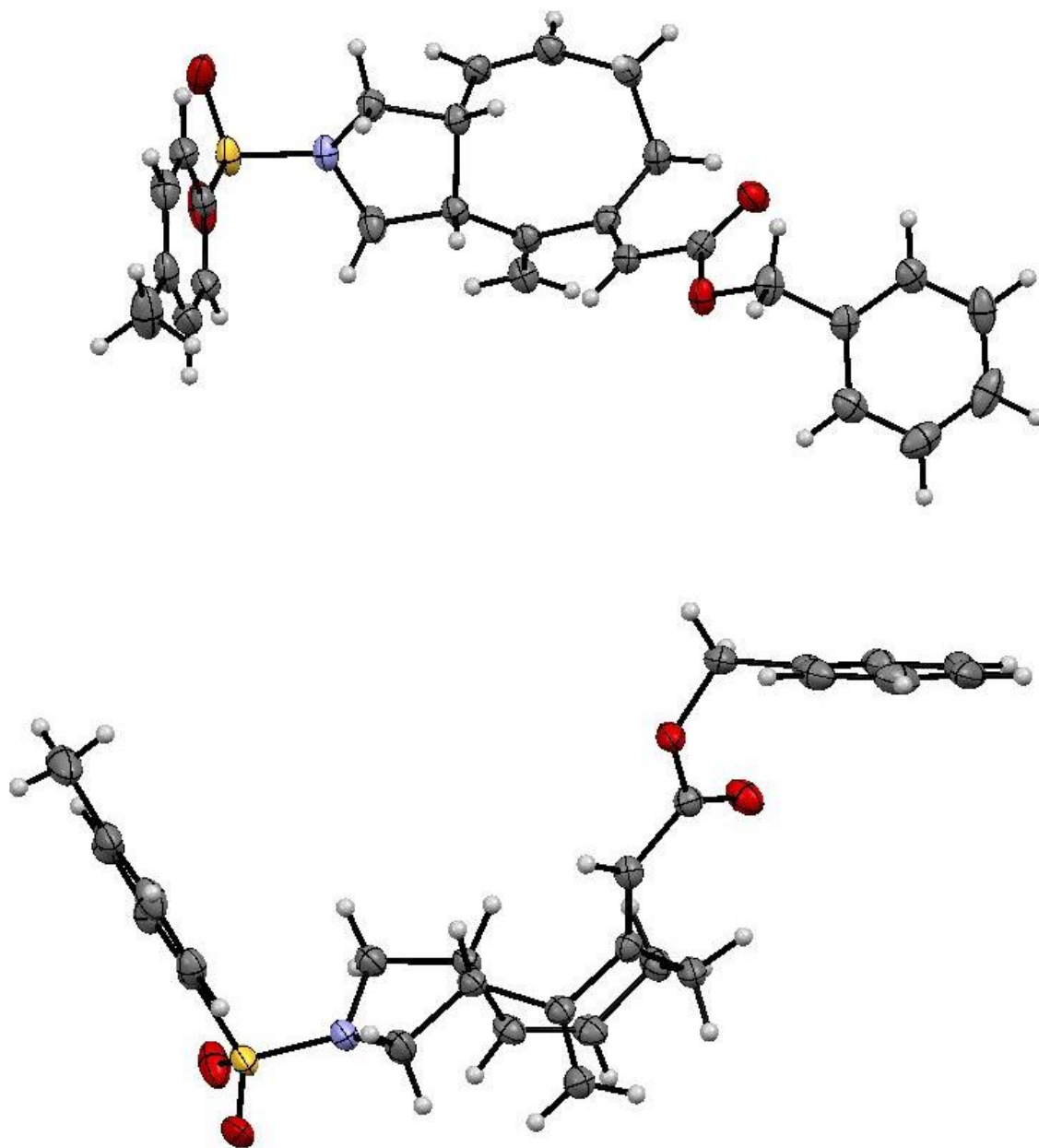




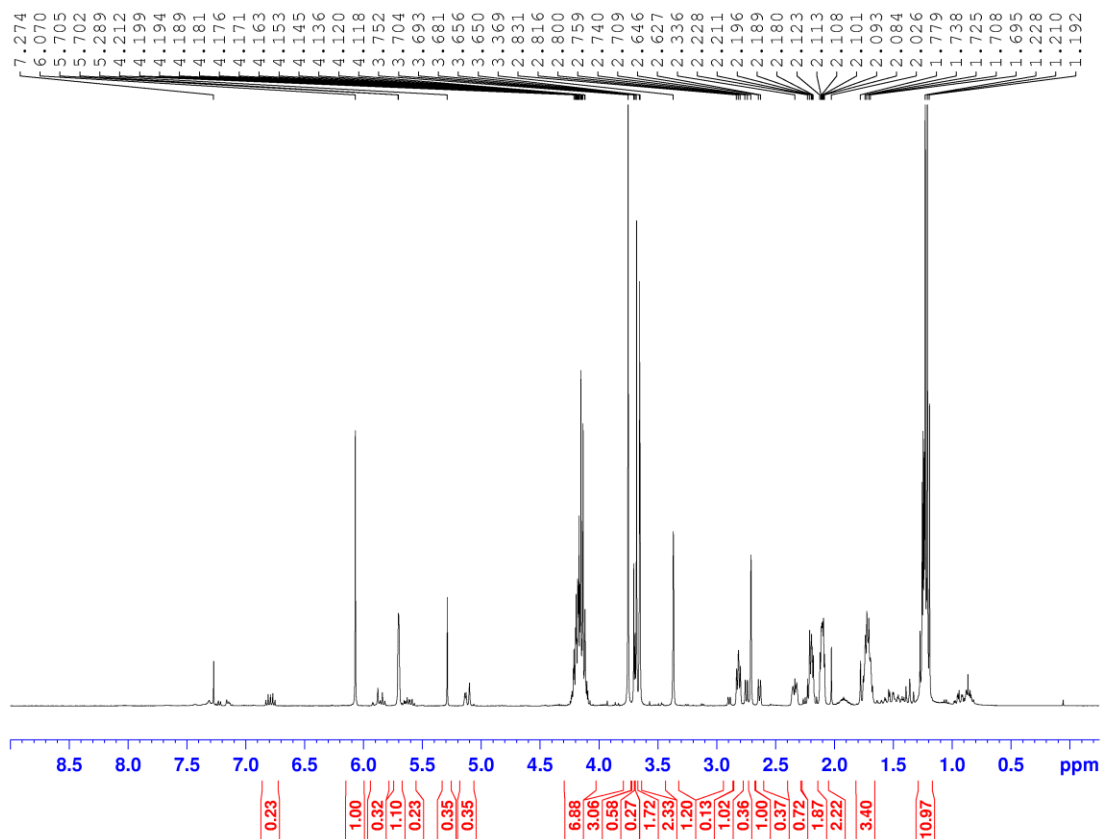
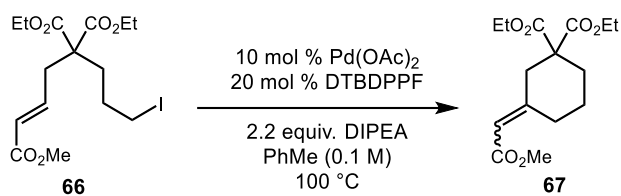


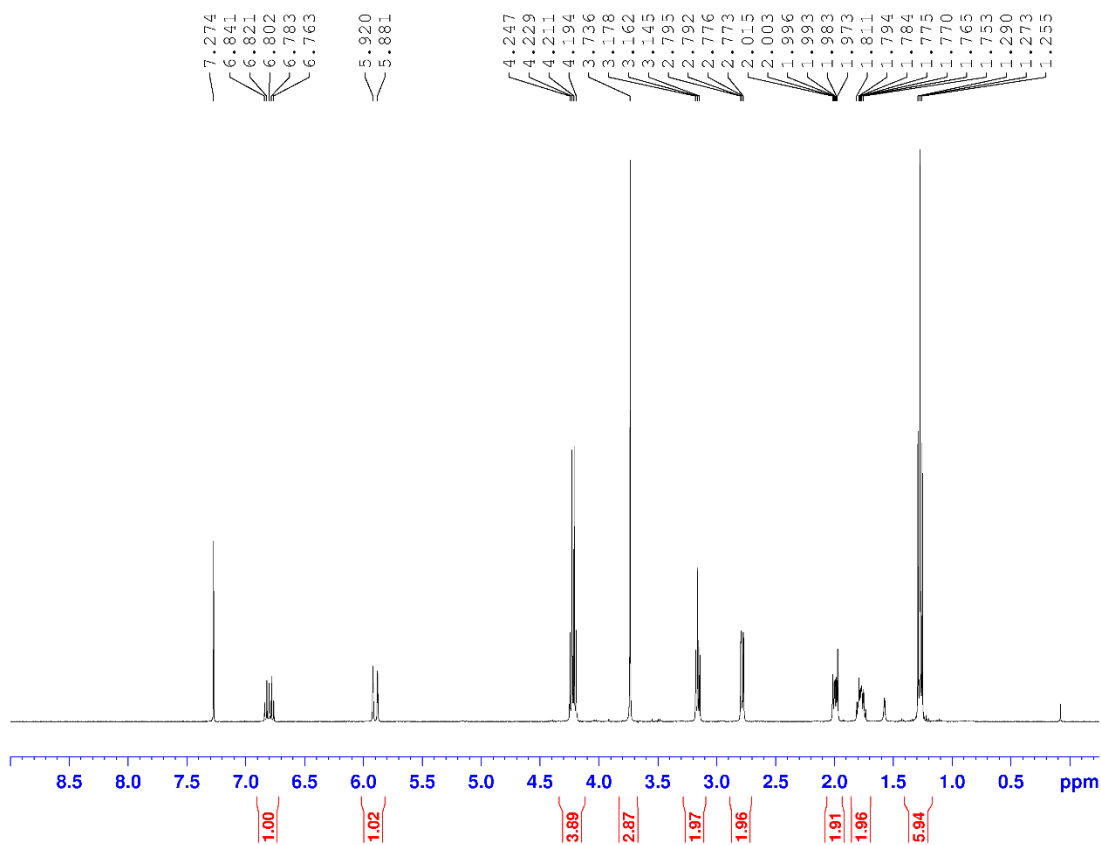
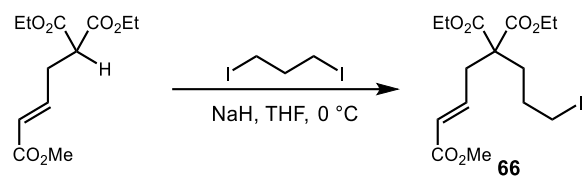
### 3.4.3 Crystal Structure for Compound 25

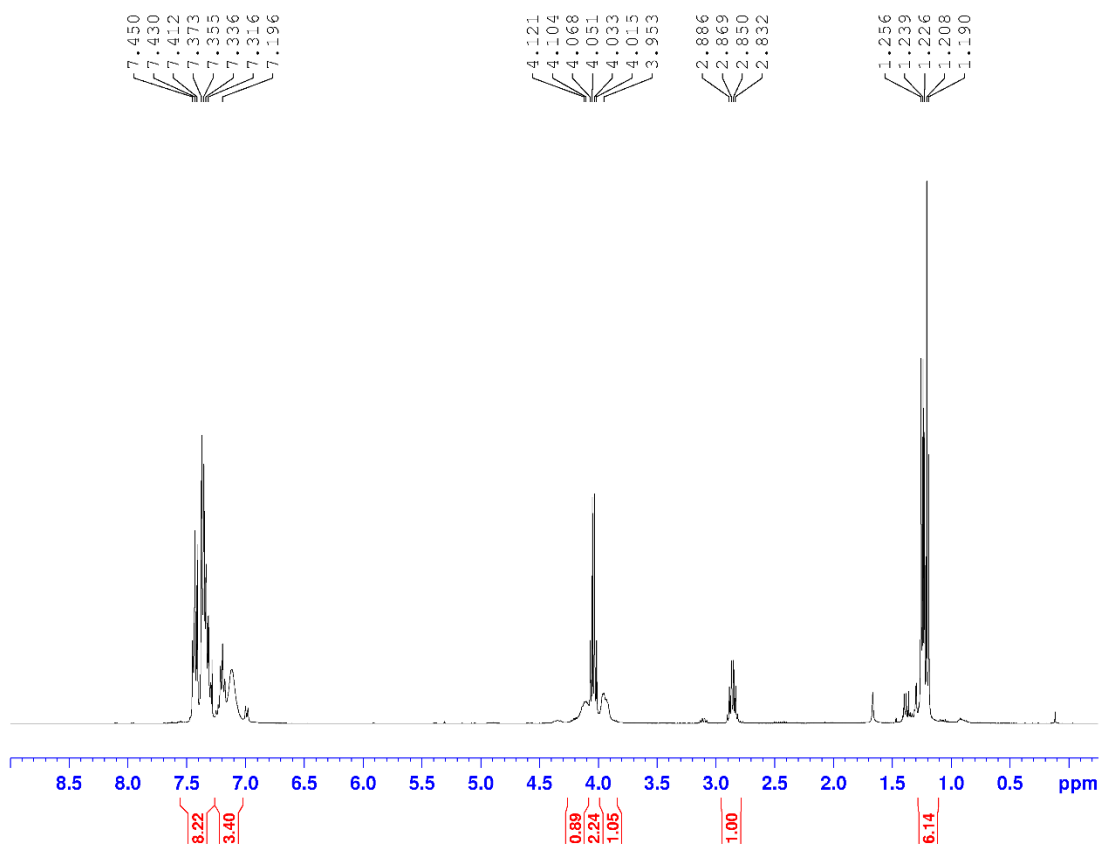
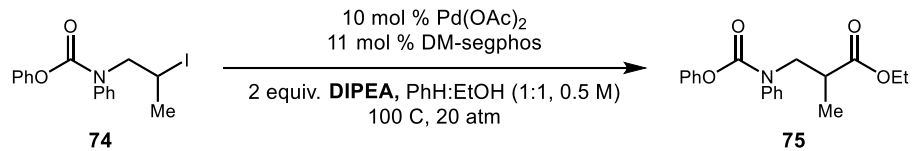
ORTEP diagram of cycloaddition product 7 (thermal ellipsoids set at 50% probability).

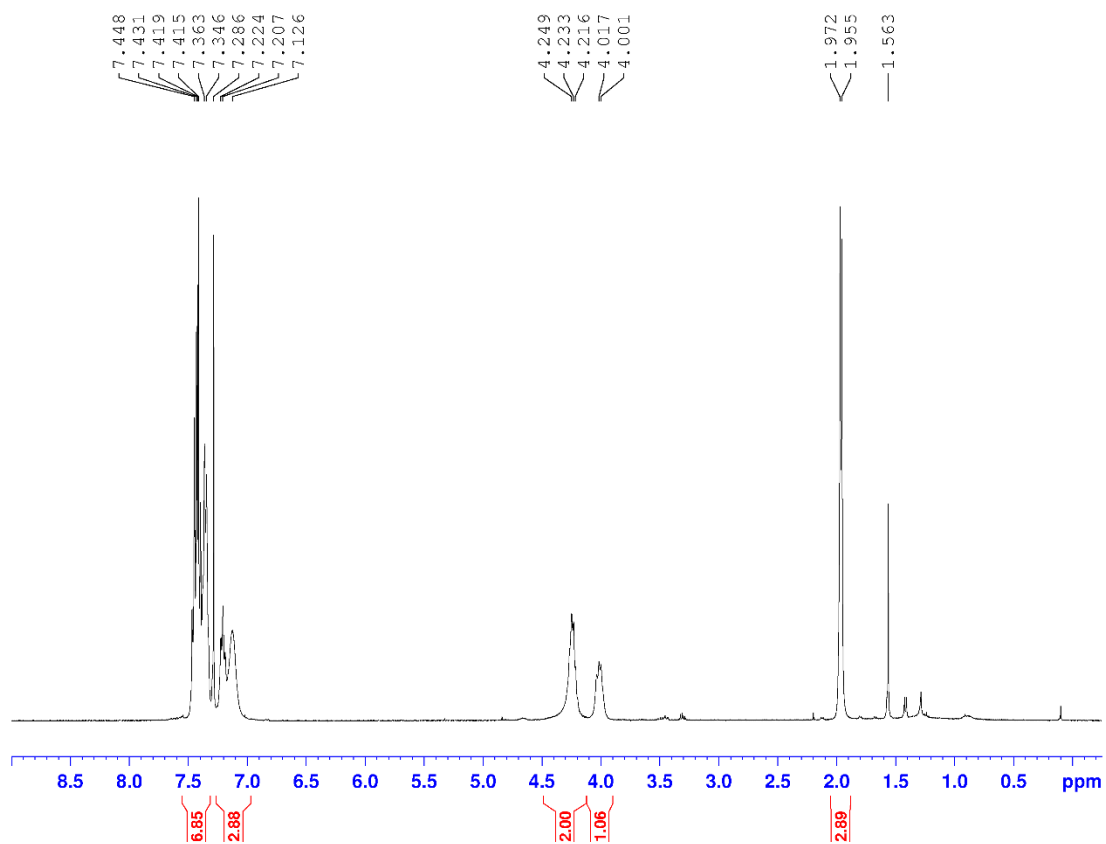
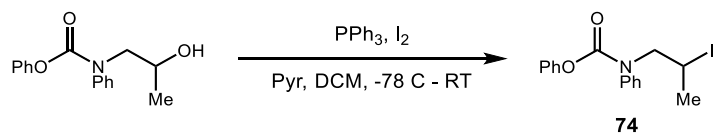


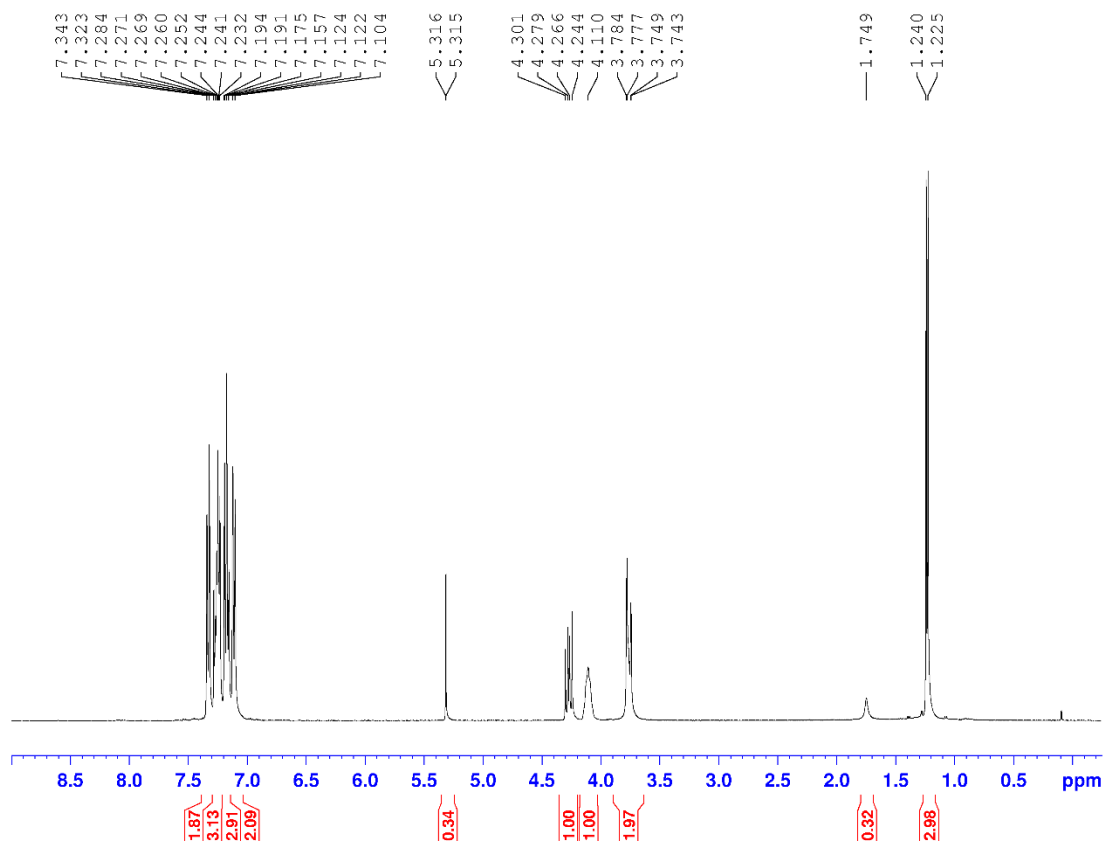
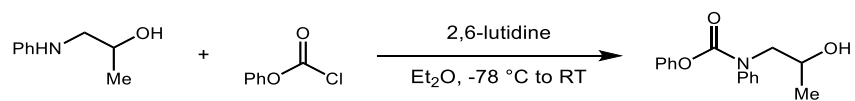
### 3.4.4 NMR Spectra for Pd-Catalyzed Reactions of Alkyl Halides











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