METAL-CATALYZED CARBON-CARBON BOND FORMING REACTIONS FOR THE SYNTHESIS OF SIGNIFICANT CHIRAL BUILDING BLOCKS

A Dissertation

by

ALEJANDRO BUGARIN CERVANTES

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

May 2011

Major Subject: Chemistry

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Approved by:

Chair of Committee,	Brian T. Connell
Committee Members,	Daniel Romo
	Daniel A. Singleton
	Rayford G. Anthony
Head of Department,	David H. Russell

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ABSTRACT

Metal-Catalyzed Carbon-Carbon Bond Forming Reactions for the Synthesis of Significant Chiral Building Blocks.

(May 2011)

Alejandro Bugarin Cervantes, B.S., Universidad Autonoma de Zacatecas, Mexico;

M.S., The University of Texas at El Paso

Chair of Advisory Committee: Dr. Brian T. Connell

Morita Baylis-Hillman (MBH) reaction a carbon-carbon bond forming reaction between an α,β-unsaturated carbonyl and aldehydes or activated ketones in the presence of a nucleophilic catalyst. The MBH reaction is an atom-economical method of rapid increase of molecular complexity. The development of this process has received considerable attention in recent years. This dissertation presents the development of a new catalytic system for the symmetric and asymmetric MBH reaction. The new system for the racemic version of this reaction was accomplished employing a 1:1:1 ratio of catalytic amounts (10 mol%) of MgI_2, TMEDA and DMAP and proved to be highly effective. For the asymmetric version was developed a highly enantio-selective system based on Fu's planar chiral DMAP derivative (**II**) with *ee´*s up to 98%. Abnormal MBH adducts are obtained employing either ethyl 2,3-butadienoate or ethyl propiolate in good yields, in the presence if MgI_2 and either a tertiary amine or phosphine as the nucleophile. The α,β-unsaturated carbonyls where prepared by a modified direct α-

methylenation using paraformaldehyde, diisopropylammonium trifluoroacetate, and catalytic acid or base with excellent yields for several carbonyls compounds.

The Negishi cross-coupling reaction is the Pd or Ni-catalyzed stereoselective cross-coupling or organozincs and aryl-, alkenyl-, or alkynyl halides. Enantioselective Negishi cross-coupling of aryl zincs and α-bromo ketones was accomplished employing a NCN Pincer complex as the catalyst with *ee´*s up 99%. The required pincer complexes have been prepared by the oxidative addition of pincer ligands with palladium or nickel.

Additionally, It has been developed a direct and highly active, (NCN)-Pd catalytic system for the α-arylation of ketones with a variety of aryl bromides using the air and moisture stable [*t*-BuPheBox-Me_2]PdBr (**XVI**) as the catalyst. The adducts are obtained in excellent yields (92% average for 20 examples) in only 1 hour using 1 mol% of catalyst loading. Perhaps more importantly, the work described here shows that **XVI** is highly reactive, highly selective, even on substrates bearing challenging functional groups such alkenes.

DEDICATION

Teniendo siempre en la memoria la imagen
de mí ángel y estrella de la suerte,
deseo dedicar esta obra a:

Noé Alfredo Bugarin
Clementina Cervantes

mis padres
por un sin fin de razones

Alfredo Bugarin
Marlen Bugarin
Noé Bugarin

mis hermanos
motivo de orgullo y amor

Emir
a mi gran amor
por todo lo que he pasado con ella...

Ale Bugarin

ACKNOWLEDGEMENTS

I would like to thank my advisor and committee chair, Dr. Brian T. Connell for his support during my Ph.D. journey and my committee members; Dr. Romo, Dr. Singleton, and Dr. Anthony for their guidance and support throughout the course of this research. I'm also extremely indebted to Dr. Simon W. North for his advice, help, and friendship during our collaborations. I would like to express a special thanks to the Connell's group and Dr. Joseph H. Reibenspies for the X-Ray structure data acquired.

Thanks also go to my friends, colleagues, students, the department faculty and staff for making my time at Texas A&M University a great experience. Special thanks go to Mrs. Sandy Manning for all her assistance. The financial support provided by the Welch foundation and Bio-defense is greatly appreciated. My appreciation also goes out to the Department of Chemistry of Texas A&M University for giving me the opportunity to develop and prove myself. Ultimately, thanks to my mother and father for their encouragement, patience, and love. In general, thanks to thus who believe in me.

Additionally, I would like to thank my *Schnecke* for being with me all the time I needed her, especially at the end of this journey and for her unselfish help and support during the process through getting this degree. I'm very proud of her.

NOMENCLATURE

COD	Cyclooctadiene
EtOAc	Ethyl Acetate
DABCO	1,4-diazabicyclic[2.2.2]octane
DBU	1,8-diazabicyclic[5.4.0]undec-7-ene
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	Dimethyl sulfoxide
MBH	Morita Baylis Hillman
Me	Methyl
Ni	Nickel
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
PheBox	Phenyl oxazoline core
$Pd_2(dba)_3$	Tris(dibenzylideacetone)dipalladium
Pyr	Pyridine
rt	Room temperature (18–22 ºC)

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CHAPTER I

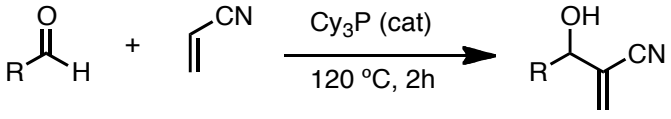
INTRODUCTION

1.1 MgI_2 Catalyzed Symmetric and Asymmetric MBH Reaction

The development of efficient and selective carbon-carbon bond-forming reactions, particularly with control of absolute stereochemistry, continues to be an area of intense research in organic chemistry. The Morita-Baylis-Hillman (MBH) reaction, first reported in 1968,[1] is an important carbon-carbon bond-forming reaction between electron-deficient alkenes, such as α,β-unsaturated ketones, and carbonyl compounds (aldehydes or ketones). This transformation is usually catalyzed by nucleophilic tertiary amines or phosphines.[2]

In the seminal report,[1] Morita and coworkers reported the first nucleophilic triggered acrylic α-substitution catalyzed by phosphines. Treatment of acrylonitrile with catalytic amounts of tricyclohexylphosphine in the presence of aldehydes produced the corresponding adducts (scheme 1.1). However, the chemical yields were only modest (<23%) and substrate scope was limited. If one equivalent of Ph_3P was used instead, the corresponding Wittig products predominated (*E*-alkenes).

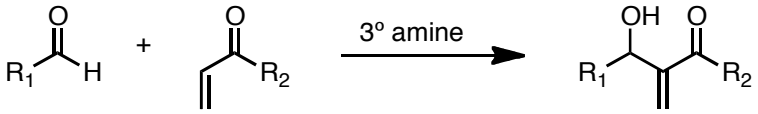
Scheme 1.1 Phosphine catalyzed MBH reaction.



This dissertation follows the style of *Journal of American Chemistry Society*.

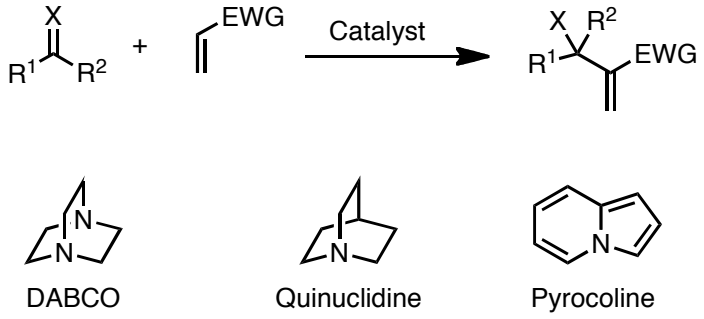
In 1972, a German patent filled by A. B. Baylis and M. E. D. Hillman from the Celanese Corporation described a new method for the synthesis of acrylic compounds, which involved the reaction of α,β-unsaturated carboxylic acid derivatives and aldehydes catalyzed by tertiary amines (Scheme 1.2).[3] The Baylis-Hillman approach featured high conversions and yields, broad scope with respect to substrates and catalysts tolerance, as well as wide temperature range (0-200 ºC). However, the rate of reactions at room temperature or lower was slow (days).

Scheme 1.2 Amine catalyzed MBH reaction.



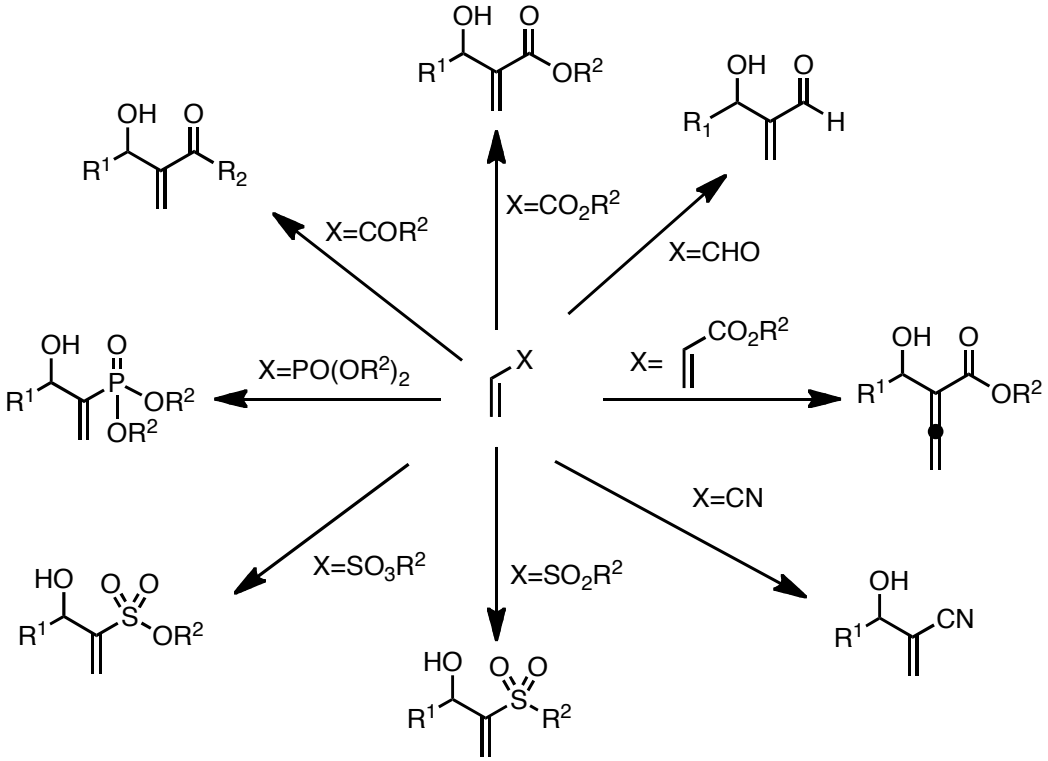
Over the last three decades,[2,4] the MBH reaction has evolved into one of the most useful carbon-carbon bond-forming reactions in organic synthesis and several variations of the three essential components have been reported, including several enantioselective variants. The three essential components are an activated alkene, an electrophile and a nucleophilic catalyst (Scheme 1.3). The most effective catalysts are nucleophilic unhindered tertiary amines like DABCO, quinuclidine and pyrocoline.[2]

Scheme 1.3 Components of the MBH reaction.



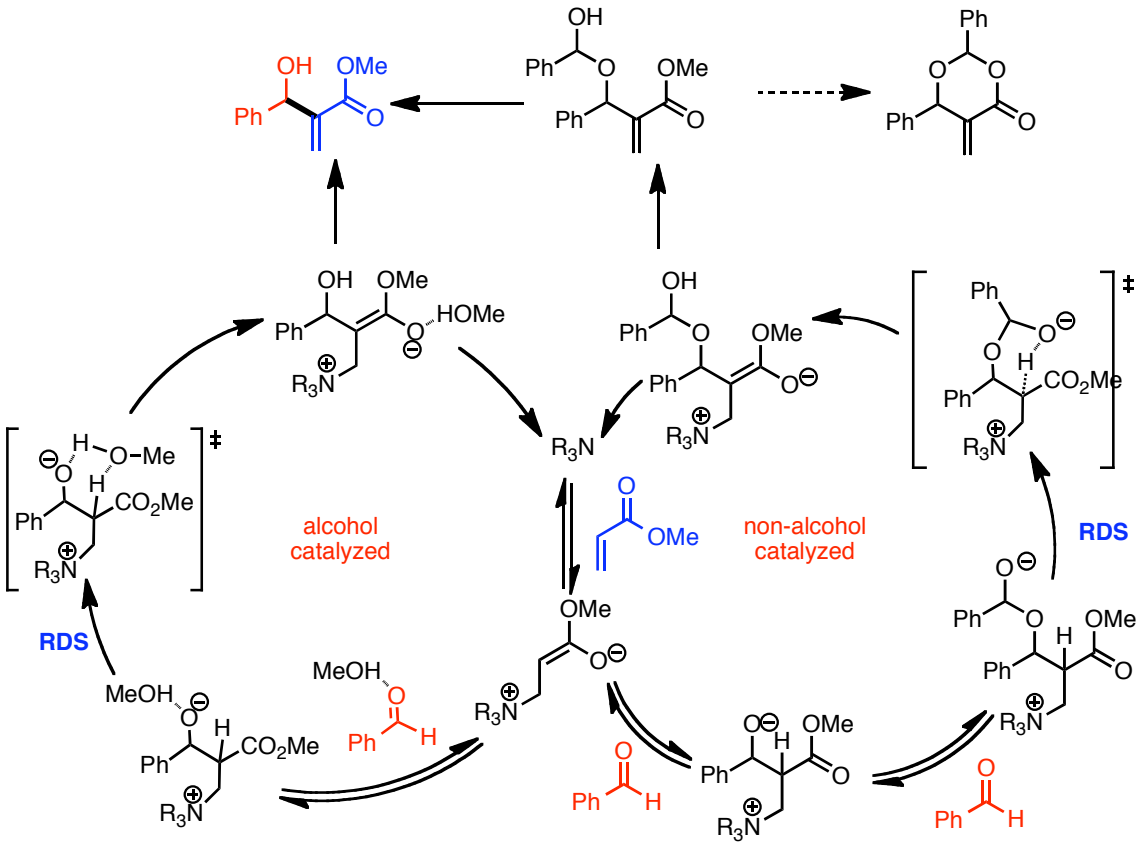
The MBH reaction has a broad scope and tolerates several activated alkenes including alkyl vinyl ketones,[5-7] alkyl and aryl acrylates,[8-10] acrolien,[11,12] allenic esters,[13] acrylonitriles,[6,14] vinyl sulfones and sulfonates,[15,16] as well as vinyl phosphonates[17] on reactions with aldehydes at atmospheric pressure and using tertiary amines like DABCO as catalyst (Scheme 1.4). As can be expected, β-substituted alkenes with bulky groups require higher pressures and extended reaction times. On the electrophilic component, aldehydes, α-keto-esters and fluorinated ketones are known to react at atmospheric pressure; however, ketones are inert at this pressure and often require high pressures.

Scheme 1.4. Scope of the MBH reaction with several activated alkenes.



Some of the advantages of the MBH reaction include formation of carbon-carbon bond under mild conditions, broad scope of substrates (both alkenes and electrophiles). It is atom economical and the products of MBH reactions are usually highly functionalized and hence can be used as components of further transformations such as aldol, Michael, and Diels-Alder reactions, or 1,2- additions, among others. This in turn can lead to the synthesis of complex molecules including natural products and other biologically important materials. The mechanism of the MBH reaction is believed to proceed through a conjugate addition followed by an aldol addition, and then β-elimination (Scheme 1.5).[18]

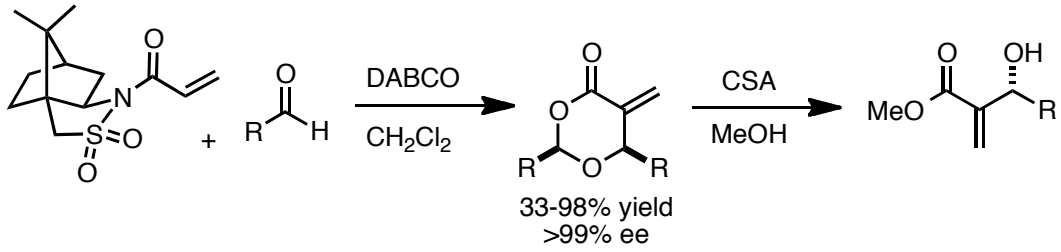
Scheme 1.5. Mechanism of the MBH reaction.



The first step in the catalytic cycle is a Michael-type addition of the tertiary amine or phosphine to the activated alkene that produces a zwitterionic enolate, which then adds to the aldehyde. After a proton transfer, the product and catalyst are released by a β-elimination (Scheme 1.5).

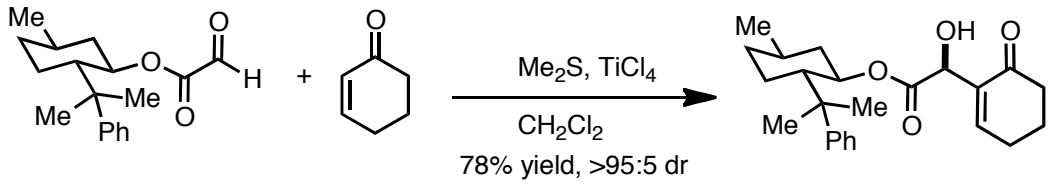
Since the MBH reaction forms a new stereogenic center, any of three essential components; the activated alkene, the electrophile or the nucleophilic catalyst, can be used to control the absolute stereochemistry. Chiral auxiliaries have been combined with activated alkenes and successfully applied in asymmetric MBH reactions. One of the most impressive examples is that of Leahy,[19] in which the use of camphor derived sultam and two equivalents of aldehyde formed the corresponding dioxanone. In this transformation the chiral auxiliary was cleaved *in situ*. The dioxanone was then converted into the MBH adduct by treatment with mild acids in methanol (Scheme 1.6).

Scheme 1.6 Substrate control in the MBH reaction.



Chiral non-racemic electrophiles have been used as well in the asymmetric MBH. A chiral glycoxylate derived from 8-phenylmenthol was shown to induce good diasteroselectivities and also provided high yields in diastereoselective MBH reactions under Kataoka modified reaction conditions (Scheme 1.7).[20]

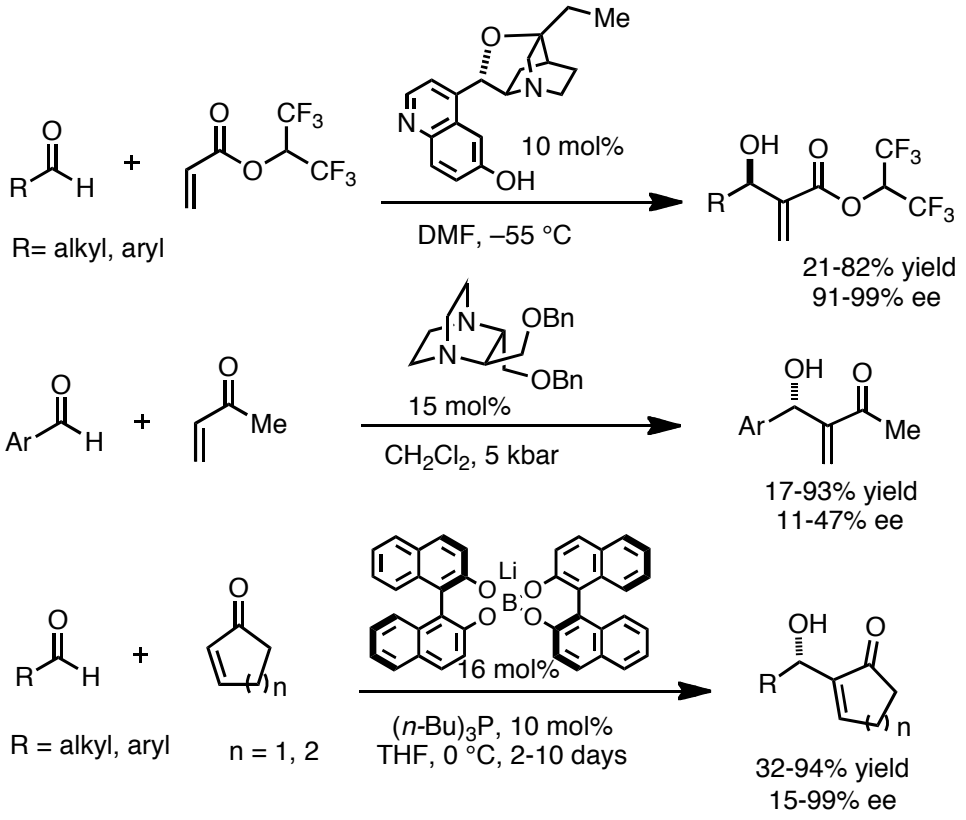
Scheme 1.7 Chiral auxiliaries in the MBH reaction.



Various attempts to accelerate this reaction through the use of chiral catalysts, cocatalysts, and a chiral medium have been studied.[4] Hatakeyama reported a chiral quinidine-derived catalyst for the reaction of a highly activated acrylate with aldehydes, providing the corresponding adducts with *ee* values up to 99%.[21] Connon was the first to use thioureas to accelerate the DABCO-promoted MBH reaction.[22] Recently, several other thiourea-derived[23-27] and BINOL-derived[28-30] systems have been reported. Each of these methods has been limited in substrate scope to varying extents.

By far, the most appealing approach to the asymmetric MBH reaction is the use of chiral catalysts. However, most of the catalytic systems reported so far are not general and suffer from low yields and enantioselectivities as well as the need for high pressures and long reaction times. Among the best catalyst reported to date are Cinchona alkaloid derivatives,[21] C-2 symmetric DABCO derivatives[31] and some chiral Lewis acids[32,33] (Scheme 1.8).

Scheme 1.8. Catalytic asymmetric MBH reactions.



In general, all of these approaches faces certain limitations, and although there have been significant improvements in this area. A general enantioselective version of the MBH reaction has yet to be developed.

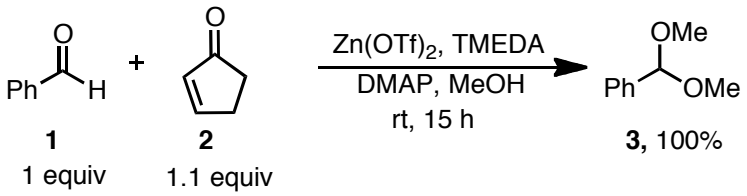
1.2 Results and Discussion

1.2.1 Acceleration of the MBH Reaction

The possibility of improvements in the chemistry of the MBH reaction prompted us to develop a catalytic system for the MBH reaction, which would be amenable to asymmetric catalysis in a straightforward manner (i.e., by using a chiral catalyst). In our initial studies, we identified several Lewis acidic metal salts, which were capable of catalyzing the reaction of benzaldehyde (**1**) with cyclopentenone (**2**) in the presence of TMEDA and a catalytic Lewis base (DMAP). Several metal salts $NiCl_2$, $PdCl_2$, $SnCl_4$, LiCl, $LiClO_4$, $Cu(OTf)_2$, and SmI_2 were found to catalyze MBH reaction under these conditions; however, the yields were generally low and/or required extended reaction times. No reactions were observed when Zn(II) halides were employed. When the more reactive $Zn(OTf)_2$ was used, quantitative dimethylacetalization of **1** was observed (Scheme 1.9).

To our delight, we found Mg(II) salts to be quite reactive, with MgI_2 being more reactive than its congeners $MgBr_2$ and $MgCl_2$.

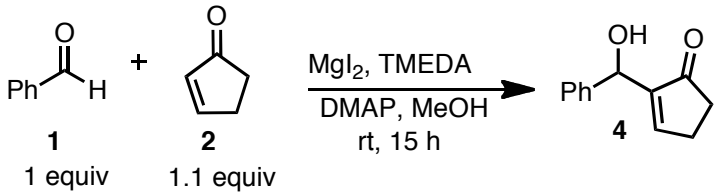
Scheme 1.9 Dimethylacetalization of benzaldehyde.



1 1 equiv **2** 1.1 equiv **3,** 100%

We then focused our attention to find potential nucleophilic catalysts that were compatible with the combination of Lewis acidic MgI_2 and TMEDA. Our initial screening included DABCO, DBU, triethylamine, Hünig's base, and pyridine. We observed that the strong base DBU deactivated the catalyst, whereas weak nucleophiles like triethylamine and pyridine showed very low reaction rates and Hünig's base did not promoted the reaction at all. We were pleased to find that the use of MgI_2 and DMAP as catalytic partners dramatically accelerated the MBH reaction.

Table 1.1. MBH reaction between cyclopenten-2-one and benzaldehyde in the presence of MgI_2, TMEDA, and DMAP.[a]



Entry	MgI_2 (%)	TMEDA (%)	DMAP (%)	Yield[b] (%)
1	–	–	10	NR
2	–	10	–	NR
3	–	10	10	NR
4	**10**	**10**	**10**	**91**
5	10	20	–	54
6	10	–	20	36

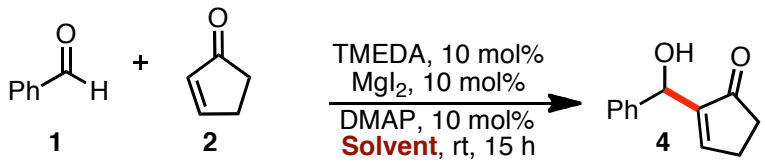
[a] The reactions were performed with 0.5 mmol of **1**, 1.1 equiv of **2**, in 1.5 mL of MeOH at rt for 15 h. [b] Isolated yield after purification by silica gel chromatography.

No reaction was observed between **1** and **2** in the absence of MgI_2 (10 mol% DMAP or 10 mol% TMEDA) in MeOH (Table 1.1). However, the addition of 10 mol% MgI_2 to the reaction mixture afforded the adduct (**4**) in low yield when combined with either 10 mol% DMAP (36% yield) or 10 mol% TMEDA (54% yield). Increasing the amount of DMAP present provided no improvement in reaction yields. On the other

hand, the use of equimolar amounts of Lewis acid, ligand, and Lewis base in the system afforded the adduct in 91% yield (Table 1.1, entry 4).

After we identified the optimal Lewis acid and nucleophile catalysts for the MBH reaction between **1** and **2**, the effect various solvent systems was investigated. We observed that the reaction was faster in protic solvents like MeOH than in THF, EtOAc, CH_2Cl_2 or dioxane. Although beneficial in other systems,[34] a mixed solvent system of MeOH–H_2O also afforded lower yields in this system (Table 1.2).

Table 1.2. Solvent optimization.[a]



1 (1 equiv) + **2** (1.1 equiv) → **4**

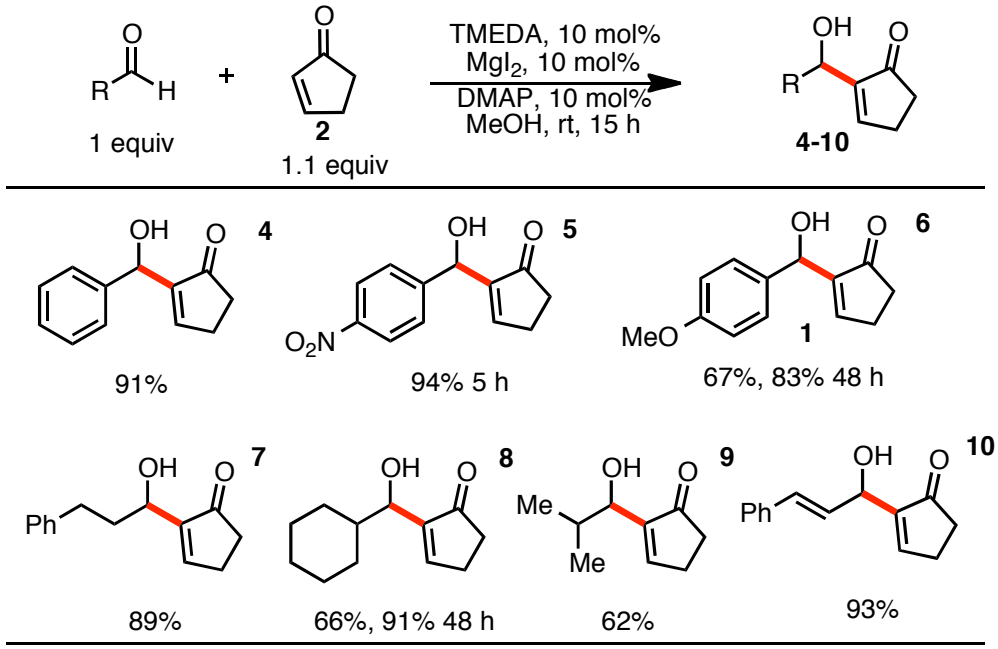
Entry	Solvent	Yield[a] (%)	Entry	Solvent	Yield[b] (%)
1	Toluene	9	7	Et_2O	69
2	Benzene	12	8	EtOAc	72
3	THF	28	9	H_2O	NR
4	CH_2Cl_2	39	10	MeOH/H_2O	76
5	MeCN	46	12	EtOH	63
6	Pyr	54	13	**MeOH**	**91**

[a] The reactions were performed with 0.5 mmol of **1**, 1.1 equiv of **2**, 0.1 equiv of each catalyst, in 1.5 mL of solvent at rt for 15 h. [b] Isolated yield after purification by silica gel chromatography.

Having optimized the reaction conditions for the MBH reaction between **1** and **2**, we then investigated the scope of the MgI_2/TMEDA/DMAP-catalyzed MBH reaction by exploring a variety of electrophiles (Table 1.3). For electron-deficient aldehydes, the system was very efficient; the MBH adduct of *p*-nitrobenzaldehyde and cyclopentenone (**5**) was obtained after only 5 hours in 94% yield. Additionally, this system afforded reasonable yields for electron-rich aldehydes. The MBH adduct for the aromatic aldehyde *p*-methoxybenzaldehyde (**6**) was obtained in 67% yield, and the MBH adducts

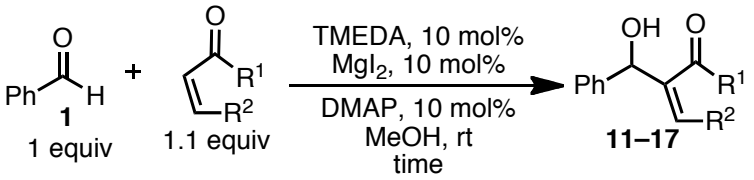
for the aliphatic aldehydes cyclohexane carboxaldehyde (**8**) and isobutyraldehyde (**9**) were obtained in 66% and 62% yield, respectively (Table 1.3). The system was also efficient for α,β-unsaturated aldehydes; the MBH adduct for *trans*-cinammaldehyde (**10**) was obtained in 93 % yield. It is worth to mention that the lower yields obtained for several of the MBH adducts was the result of incomplete reaction. The presence of starting materials was observed after 15 hours for all entries with yields lower that 90%. This reaction time of 15 hour was used as benzaldehyde, a moderately reactive aldehyde with neither electron-rich nor electron-poor characteristics, was completely consumed after this time period. By performing all reactions in this 15 hours time window, we could compare the effects of electron-donating or electron-withdrawing functionalities on the rate of reaction.

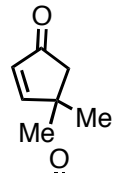
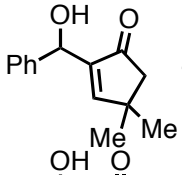
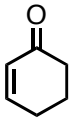
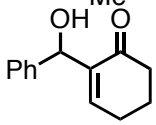
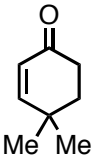
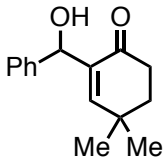
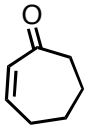
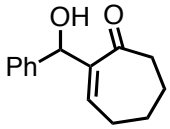
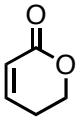
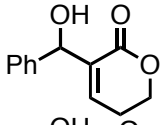
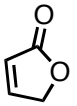
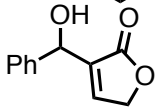
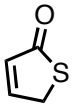
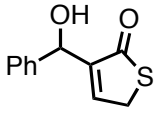
Table 1.3. Scope of the MBH reaction of cyclopenten-2-one.[a,b]



[a] The reactions were performed with 0.5 mmol of aldehyde, 1.1 equiv of **2**, 0.1 equiv of each catalyst, in 1.5 mL of MeOH at rt for 15 h. [b] Isolated yield after purification by silica gel chromatography.

Table 1.4. MBH reaction of benzaldehyde.[a]



Entry	Enone/Enoate	Product (#)	Time (h)	Yield[b] (%)
1		 **11**	15	86
2		 **12**	15 48	84 89
3		 **13**	15 48	75 91
4		 **14**	15	56
5		 **15**	15 48	47 78
6[c]		 **16**	2	53
7[c,d]		 **17**	1	92

[a] The reactions were performed with 0.5 mmol of benzaldehyde, 1.1 equiv of enone/enoate, 0.1 equiv of each catalyst, in 1.5 mL of MeOH at rt for 15 h. [b] Isolated yield after purification by silica gel chromatography.[c] EtOH solvent; [d] Reaction performed at –15 °C.

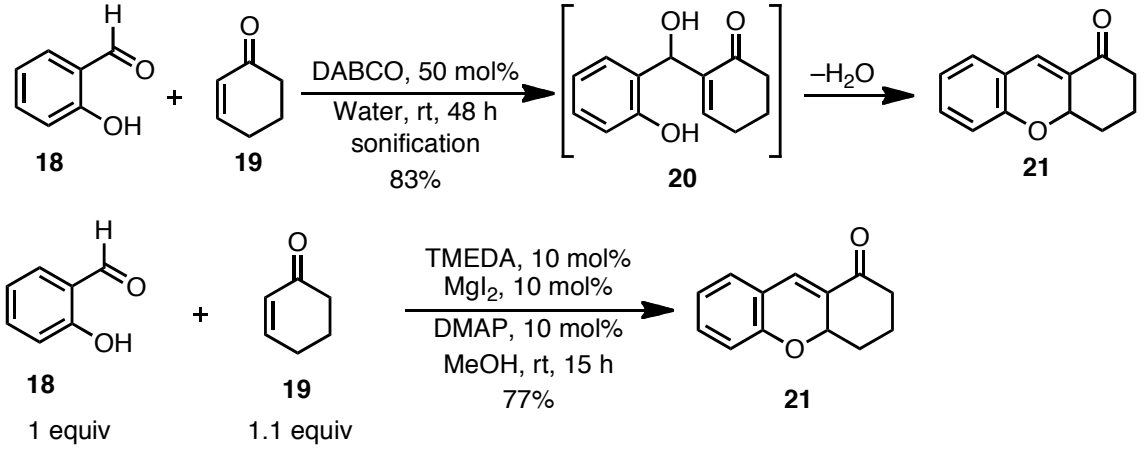
To further examine the scope and utility of these catalytic reaction conditions, a variety of α,β-unsaturated ketones, esters and thioesters were treated with **1** under our optimized reaction system conditions (Table 1.4). Again, most reactions were quenched after 15 hours for comparison purposes, although starting material was still remaining. In

all cases, the reaction proceeded smoothly in the presence of catalytic amounts of equimolar Lewis acid, ligand, and the nucleophile and afforded the corresponding adducts in good to high yields at room temperature.

Notable examples from Table 1.4 included reactions with γ-disubstituted enones such as 4,4-dimethylcyclopenten-2-one and 4,4-dimethylcyclohexen-2-one (Table 1.4, entries 1 and 3), which gave 86% and 75% yield respectively, after 15 hours.

The reactivity of the MBH reaction was also demonstrated for cyclic enones, which contain five, six and seven member rings (Table 1.4) in moderate to high yields of 91%, 84%, and 56%, respectively.

Scheme 1.10 Reaction of cyclohexen-2-one and salicylaldehyde.



Bräse and coworkers have previously reported the synthesis of xanthenes starting from 2-hydroxybenzaldehydes and 2-cyclohexenone using DABCO as catalyst.[35] He employed DABCO (50 mol%) as a catalyst in water under sonification conditions to obtain 2,3,4,4a-tetrahydro-1H-xanthen-1-one (**21**) in 83% yield after 48 h by a presumed sequence of MBH, conjugate addition, and elimination reactions. When we investigated

this sequence under our reaction conditions, we obtained the product **21** in 77% yield in significantly less time (15 hours) and under milder reaction conditions (Scheme 1.10).

Scheidt and coworkers had published several articles regarding the addition of silyloxyallenes to aldehydes trying to solve the poor reactivity of enones, specially β–substituted.[36-38] We envisioned that our catalytic partner could also help to solve this limitation. Unfortunately the dual catalytic system was not capable of accelerating the Morita-Baylis-Hillman reaction of acylic enones or acrylates with aldehydes.

1.2.2 Enantioselective MBH Reaction

The development of an asymmetric version of the MBH reaction has attracted considerable interest in recent years,[4] driven by the easy accessibility of starting materials and the potential of the poly-functionalized adducts, that can be used as components of further transformations in the synthesis of complex molecules.

The mechanism of the MBH reaction allows the use of a Lewis acid cocatalyst to increase reaction rates.[18,39-41] For example, In 2009 we reported a mild reaction system employing a 1:1:1 ratio of catalytic amounts (10 mol%) of MgI_2, TMEDA and DMAP to accelerate the rates of the MBH reaction between cyclic enones and enoates with aldehydes in methanol.[42] Based on this protocol, we studied an enantioselective process utilizing cyclopentenone as a substrate. MBH adducts of cyclopentenone have potential utility towards the total synthesis of natural products containing cyclopentenone or

cyclopent(en)yl moieties, including Lathyranoic acid A and Euphorbia factor L_{11},[43] as well as Acutaxyline A and B (Figure 1.1).[44]

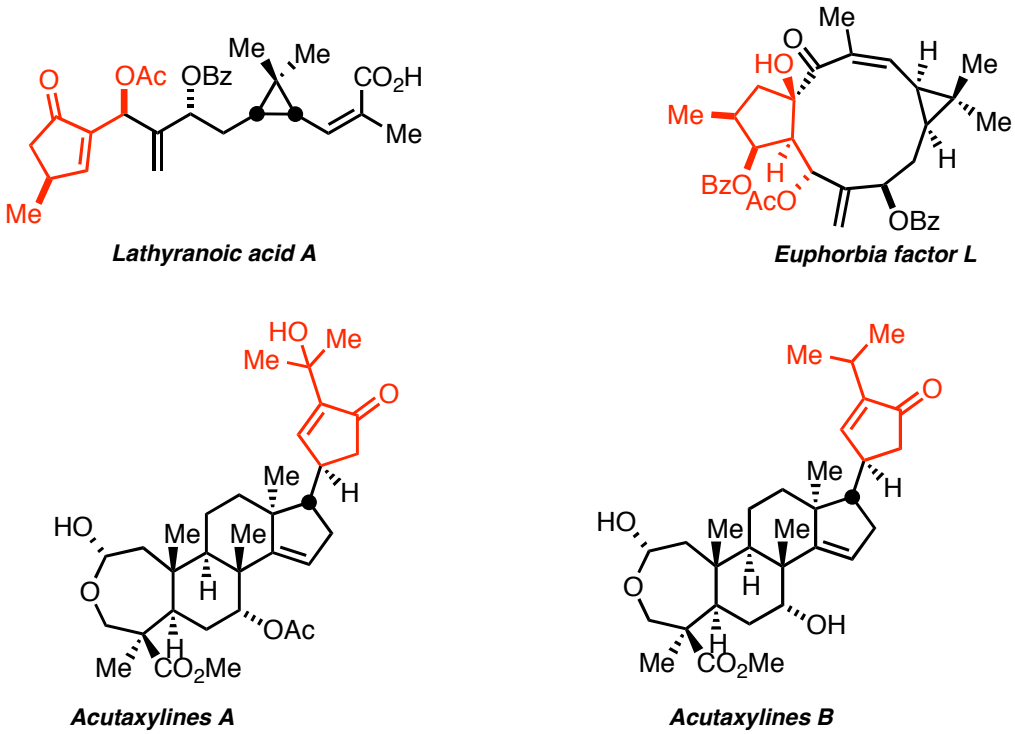


Figure 1.1 Natural Products containing cyclopentenone or cyclopent(en)yl moieties.

Our initial studies identified chiral nucleophiles (Figure 1.2), which were capable of catalyzing the reaction of *trans*-cinnamaldehyde with cyclopentenone in the presence of catalytic MgI_2 (Table 1.5). TMEDA and several chiral TMEDA-equivalent ligands[45] were also screened, but they resulted in low enantioselectivity due to a reasonably high background reaction rate. Lewis acids other than MgI_2, including $NiCl_2$, $SnCl_4$, LiCl, $LiClO_4$, $Cu(OTf)_2$, and $Zn(OTf)_2$, showed poor or no reactivity under these conditions.

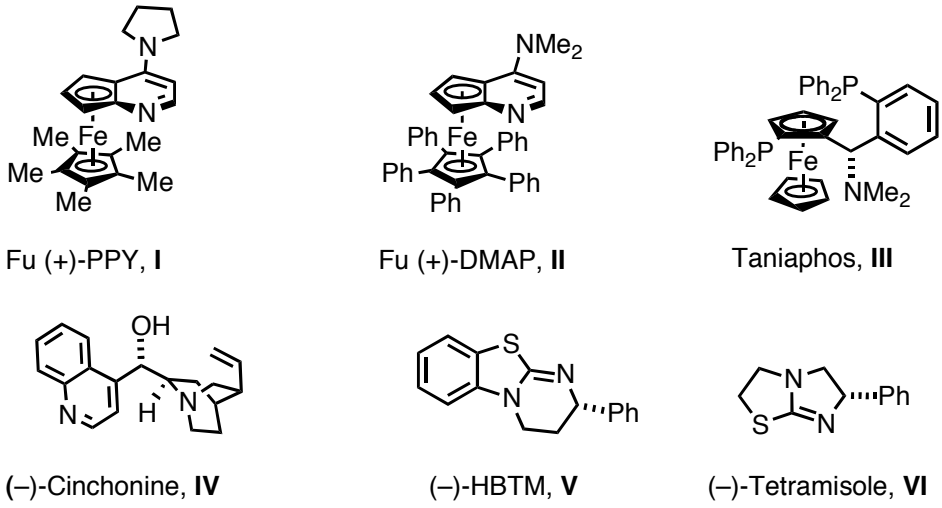
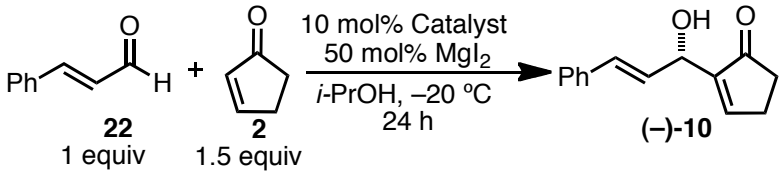


Figure 1.2. Chiral amine catalysts examined as nucleophiles.

Table 1.5 shows the catalytic activity of several chiral nucleophiles (**I**-**VI**)[46-50] towards the asymmetric MBH coupling of *trans*-cinnamaldehyde with cyclopentenone in the presence of 50 mol% MgI_2. The reaction mediated by the most nucleophilic catalyst (Fu's chiral PPY **I**) occurred with the highest yield (98%) but lower *ee* (81%) (Table 1.5, entry 1) than Fu's less nucleophilic **II**, which delivered the product in a 96% yield and 94% *ee* (Table 1.5, entry 2) Other catalytic nucleophiles showed lower enantioselectivity and reactivity (Table 1.5, entries 3-6). The chiral thiourea derived [(–)-HBTM **V** and (–)-tetramisole **VI**] were also notably less reactive (Table 1.5, entries 5-6) than the DMAP derivatives **I** and **II**.

Table 1.5. Enantioselective MBH reaction between cyclopenten-2-one and *trans*-cinnamaldehyde.[a]



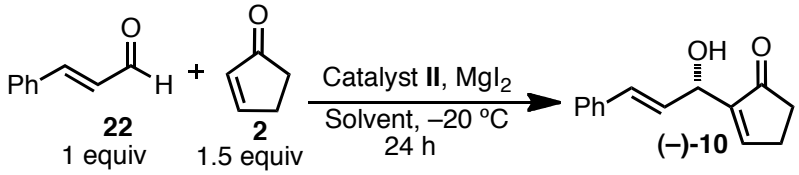
Entry	Catalyst	Yield[b] (%)	ee[c] (%)
1	I	98	81
2	**II**	**96**	**94**
3	III	45	54
4	IV	89	45
5	V	5	63
6	VI	19	48

[a] The reactions were performed with 0.075 mmol of **22**, 1.5 equiv of **2**, 0.1 equiv of catalyst, 0.5 equiv of MgI_2, in 1.5 mL of *i*-PrOH at –20 ºC for 24 h. [b] Isolated yield after purification by silica gel chromatography.[c] Enantiomeric excess determined by chiral HPLC.

With these results in hand, optimization of the reaction conditions utilizing catalyst **II** was carried out (Table 1.6). At –20 °C, no reaction was observed between *trans*-cinnamaldehyde and cyclopentenone in the absence of MgI_2 (Table 1.6, entry 1). However, increasing the amount of MgI_2 from 10 mol% to 50 mol% increased the yield of the reaction from 45% to 96% yield without having a dramatic effect on the *ee* (92% vs 94%) (entries 2 and 5). Intermediate quantities of MgI_2 provided intermediate yields (entries 3 and 4). *i*-PrOH proved to be the best solvent, delivering the product in excellent yield while maintaining a high level of enantioselectivity as compared to MeOH and EtOH (entries 6 and 7). The use of less catalyst **II** (5 mol%) afforded a slower reaction but no loss of *ee* (entry 8), while 20 mol% of catalyst **II** was no better than 10 mol% (entry 5 vs 9). Higher reaction concentration had a negligible effect on the reaction (entry 10) while higher temperatures eroded the observed *ee* (entries 11 and 12).

Lower temperature slowed the reaction with no marked increase in enantioselectivity (entry 13).

Table 1.6 Optimization of the enantioselective MBH reaction.[a]



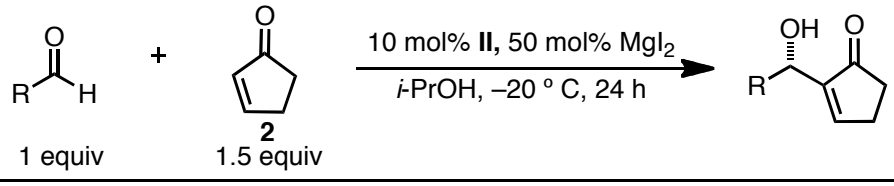
Entry	MgI_2 (mol %)	II (mol %)	Solvent	Yield[b] (%)	ee[c] (%)
1	0	10	*i*-PrOH	NR	NA
2	5	10	*i*-PrOH	21	80
3	10	10	*i*-PrOH	45	92
4	20	10	*i*-PrOH	57	93
5	50	10	*i*-PrOH	96	94
6	50	10	EtOH	89	77
7	50	10	MeOH	98	53
8	50	10	*i*-PrOH	60	94
9	50	5	*i*-PrOH	93	94
10[d]	50	20	*i*-PrOH	92	94
11[e]	50	10	*i*-PrOH	97	70
12[f]	50	10	*i*-PrOH	94	91
13[g]	50	10	*i*-PrOH	39	95

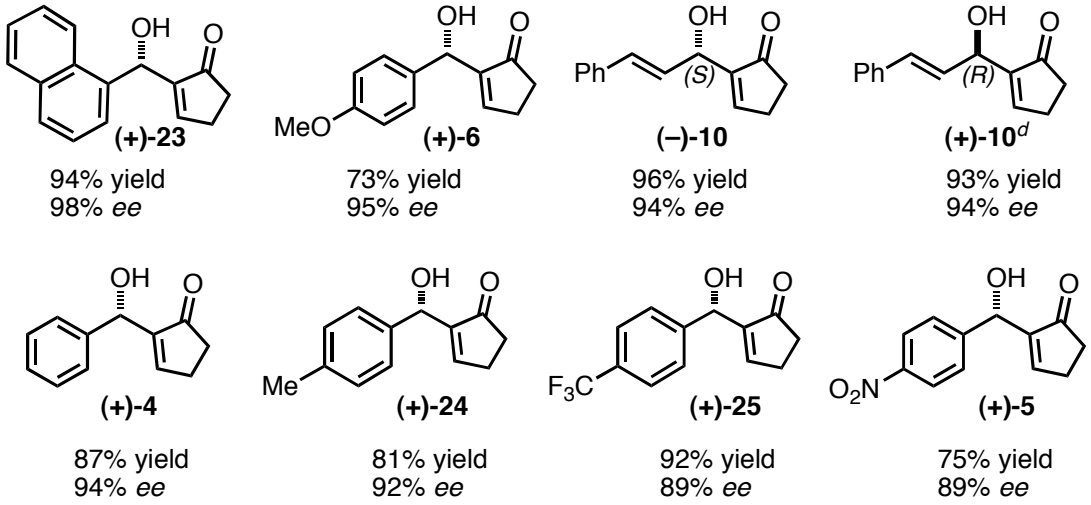
[a] The reactions were performed with 0.075 mmol of **22**, 1.5 equiv of **2**, 0.1 equiv of catalyst **II**, 0.5 equiv of MgI_2, in 1.5 mL of *i*-PrOH at –20 ºC for 24 h. [b] Isolated yield after purification by silica gel chromatography. [c] Enantiomeric excess determined by chiral HPLC [d] [c] = 0.1 M instead of 0.05 M. [e] Reaction performed at 20 °C. [f] Reaction performed at 0 °C. [g] Reaction performed at –50 °C.

We then investigated the scope of this enantioselective MBH reaction by examining a variety of electrophiles (Table 1.7). For aromatic aldehydes, the system was very efficient. The MBH reaction of 1-naphthaldehyde and cyclopentenone delivered the product in 94% yield and 98% ee (Table 1.7, entry 1). The adduct of electron-rich *p*-methoxybenzaldehyde was obtained in 73% yield and 95% ee (Table 1.7, entry 2). The electron-poor *p*-nitrobenzaldehyde afforded a lower yield (75%), likely due to solubility of the aldehyde in *i*-PrOH (Table 1.7, entry 8). Additionally, this chiral DMAP/MgI_2 mixture afforded reasonable yields (54–68%) and moderate *ee*'s (53–63% for the

aliphatic aldehydes (Table 1.8). The lower yields obtained in these cases were the result of incomplete reaction, and extended reaction times will likely provide increased yields.

Table 1.7. Enantioselective MBH reaction with various aromatic aldehydes.[a,b,c]

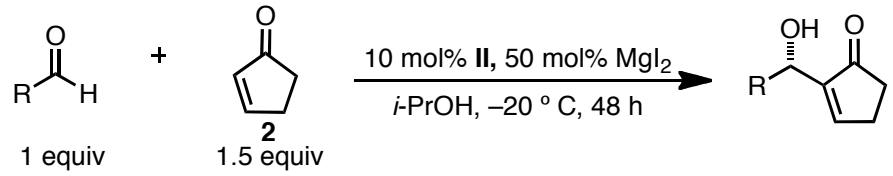




[a] The reactions were performed with 0.075 mmol of aldehyde, 1.5 equiv of **2**, 0.1 equiv of catalyst **II**, 0.5 equiv of MgI_2, in 1.5 mL of *i*-PrOH at –20 ºC for 24 h. [b] Isolated yield after purification by silica gel chromatography [c] Enantiomeric excess determined by chiral HPLC [d] The (–)-enantiomer of catalyst **II** was used.

To further extent the scope and utility of these reaction conditions, a variety of cyclic and acyclic α,β-unsaturated ketones and esters were treated with benzaldehyde, but no significant reaction occurred. Similar to other reported MBH catalytic systems (vide supra), the present system demonstrates a limited scope with respect to the nucleophilic component, so a careful analysis of substrates is necessary when evaluating various MBH reaction catalysts.

Table 1.8 Enantioselective MBH reaction with aliphatic aldehydes.[a,b,c]



(–)-7	(–)-8	(–)-9
68% yield	54% yield	59% yield
53% *ee*	58% *ee*	63% *ee*

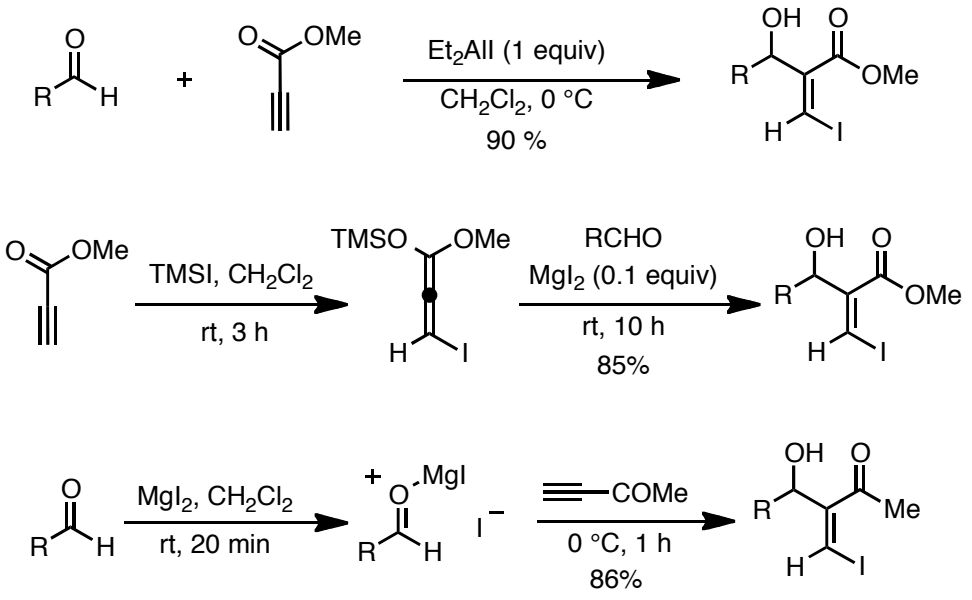
[a] The reactions were performed with 0.075 mmol of aldehyde, 1.5 equiv of **2**, 0.1 equiv of catalyst **II**, 0.5 equiv of MgI_2, in 1.5 mL of *i*-PrOH at –20 ºC for 24 h. [b] Isolated yield after purification by silica gel chromatography [c] Enantiomeric excess determined by chiral HPLC.

1.2.3 1,3-Allylic Transpositions of β-Iodo BH Adducts

Morita-Baylis-Hillman type (MBH-type) couplings have emerged as important carbon-carbon bond forming processes in organic synthesis in recent years. Highly functionalized BH adducts can be subjected to a large number of further transformations for the synthesis of natural products and synthetic derivatives. In 2002, Paré and coworkers developed new approaches for the synthesis of substituted α-(hydroxymethyl)-β-iodoacrylates and ketones as shown in scheme 1.11.[51,52] The main advantage that these approaches offered was the fact that β-substituted acrylate olefins could be used as substrates in these BH-type reactions, which had been proven poor substrates in the original MBH reaction. However, Et_2AlI is a moisture-sensitive reagent, which is difficult to handle, and the alternative route *via* the intermediary iodo-allene

suffered from long reaction times, in contrast to the synthesis of ketones,[53] which proceeded both rapidly and efficiently.

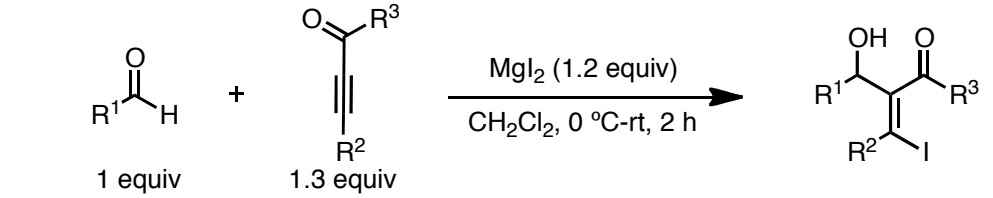
Scheme 1.11 Paré's approach to the synthesis of β-iodo Baylis Hillman adducts.

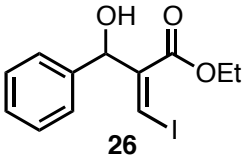
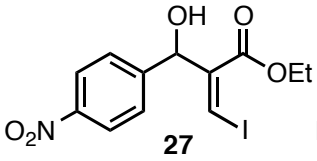
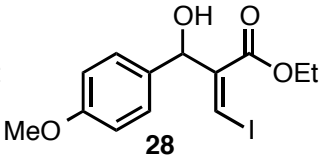
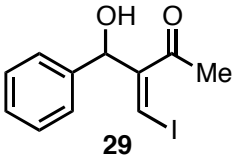
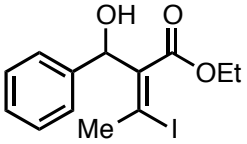
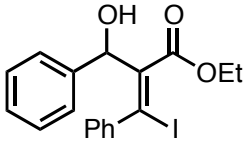
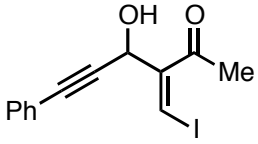
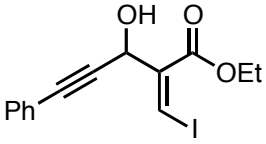
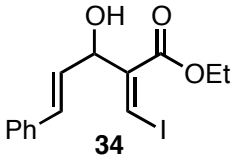
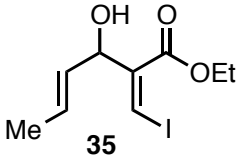
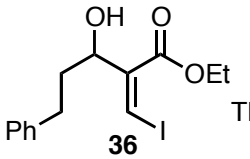
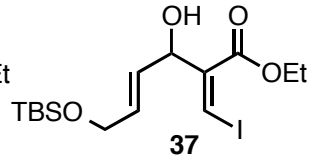
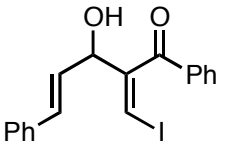
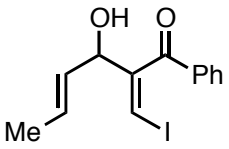
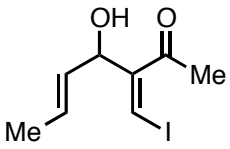
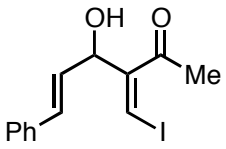


We were interested in extending our reaction conditions developed for the symmetric and asymmetric Morita-Baylis-Hillman reaction[54,55] to the synthesis of β-iodo Baylis-Hillman adducts. Our study started utilizing the same protocol reported by Paré and co-workers.[53] We synthesized several β-iodo Baylis Hillman adducts (Table 1.9). All adducts were obtained as the *Z* isomers. We found that the aldehyde and MgI_2 had to be mixed in CH_2Cl_2 at room temperature for 20 min before addition of the propargylic ester. Under these conditions, the reaction between **1** and methyl prop-2-ynoate (**42**) was complete within 1 h, and the desired product (**26**) was obtained in 92% yield with a Z/E

ratio of >95:5 (Table 1.9). The high yields obtained under these conditions were attributed to the lower Lewis acidity of MgI_2 compared to Et_2AlI, which minimizes the production of side products.

Table 1.9 Synthesis of β-iodo Baylis Hillman adducts.[a,b]

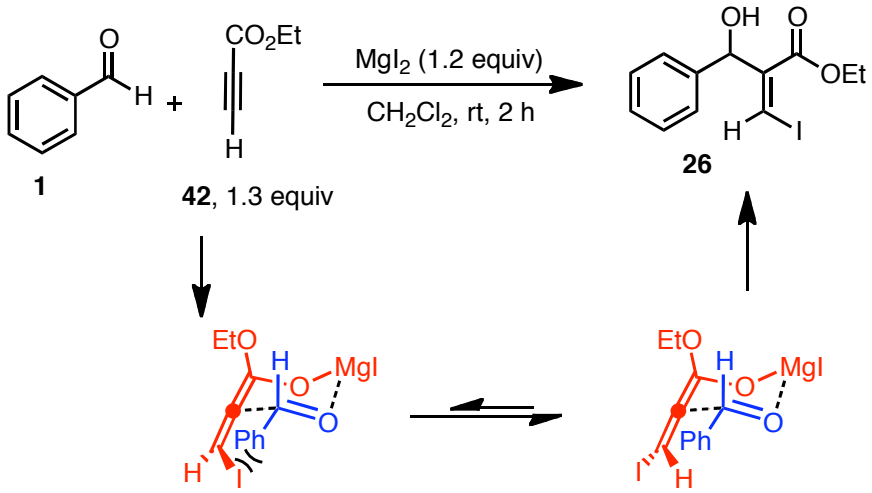


 **26** 92% yield	 **27** 94% yield	 **28** 89% yield	 **29** 95% yield
 **30** 65% yield	 **31** 71% yield	 **32** 88% yield	 **33** 85% yield
 **34** 91% yield	 **35** 86% yield	 **36** 85% yield	 **37** 89% yield
 **38** 96% yield	 **39** 93% yield	 **40** 92% yield	 **41** 90% yield

[a] The reactions were performed with 0.367 mmol of aldehyde, 1.3 equiv of ynone/ynoate, 1.2 equiv of MgI_2, in 4 mL of CH_2Cl_2 at rt for 2 h. [b] Isolated yield after purification by silica gel chromatography.

The high *Z*-selectivity was rationalized to arise from the close transition state on the reaction mechanism, in which, the iodide substituent is away from the phenyl group on the aldehyde (Scheme 1.12).

Scheme 1.12 Mechanism and selectivity of the β-iodo Baylis Hillman adducts.



We were able to assign the *Z* geometry of the tetrasubstituted olefin unambiguously by single crystal X-Ray analysis of the β-iodo Baylis Hillman Adduct **31** (Figure 1.3).

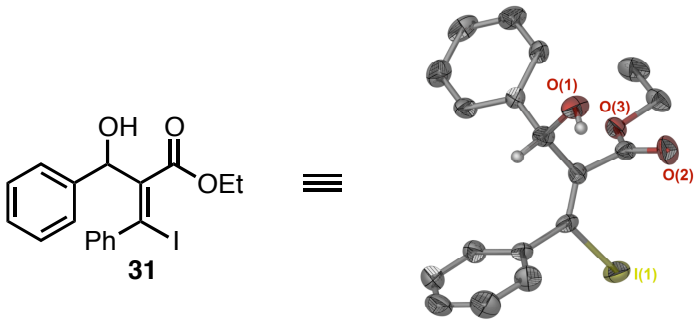
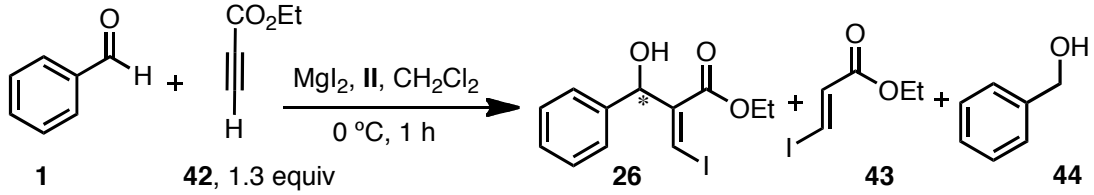


Figure 1.3 X-Ray structure of the β-iodo Baylis Hillman adduct **31**.

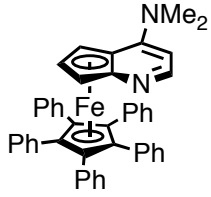
We then applied our reaction conditions developed for the asymmetric Morita-Baylis-Hillman reaction.[55] When CH_2Cl_2 was used as the solvent the expected β-iodo BH adducts were obtained (Table 1.10, entry 1). Adding to this mixture a catalytic amount of Fu's chiral DMAP **II**, the product was obtained in only 2% *ee*. The low enantioselectivity was due to the fact that the background reaction was faster than the catalyzed by the chiral DMAP **II** Catalyst. Other solvents and reaction conditions were screened as well, however no increase on the enantioselectivity was observed.

Table 1.10 Attempted asymmetric synthesis of β-iodo Baylis Hillman adducts.



1 **42**, 1.3 equiv **26** **43** **44**

Entry	Solvent	MgI_2 (mol %)	II (%)	Yield[b] (%)	ee (%)
1	CH_2Cl_2	120	–	80	NA
2	CH_2Cl_2	120	5	75	2%
3	CH_2Cl_2	–	5	NR	NA
4	*i*-PrOH	120	–	A	NA
5	*i*-PrOH	120	5	A	NA
6	*i*-PrOH	–	5	NR	NA
7	*i*-PrOH	0	100[c]	NR	NA
8	*i*-PrOH	5	100[c]	A+B	NA
9	*i*-PrOH	120	100[c]	B	NA



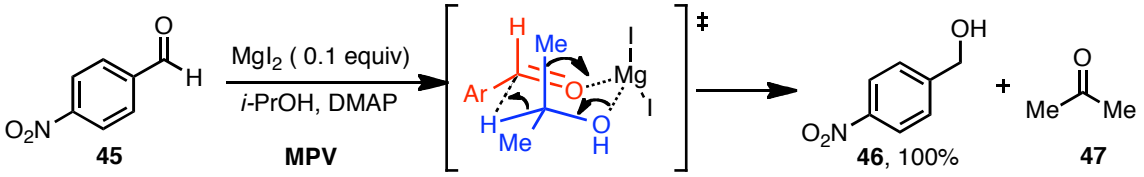
Fu (+)-DMAP, **II**

[a] The reactions were performed with 0.367 mmol of **1**, 1.3 equiv of **42**, 1.2 equiv of MgI_2, in 4 mL of CH_2Cl_2 at 0 ºC for 1 h. [b] Isolated yield after purification by silica gel chromatography [c] Racemic DMAP was used.

While screening different solvents it was found that using isopropanol, the sole product observed was (*E*)-ethyl 3-iodoacrylate (**43**), which was the product of the addition of iodide to ethyl propiolate. Also, it was found that in the presence of stoichiometric DMAP and MgI_2 the major product was benzyl alcohol (**44**). This alcohol

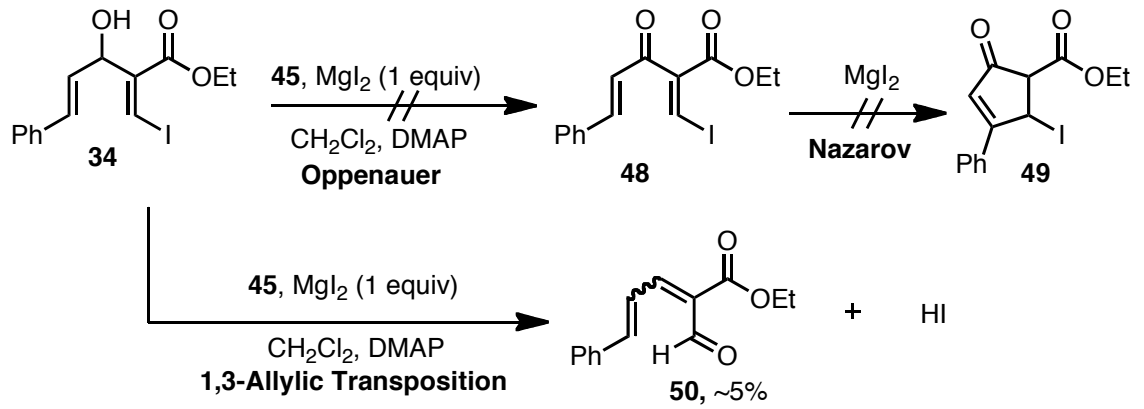
was the product of and Meerwein-Ponndorf-Verley (MPV) redox reaction between benzaldehyde and isopropanol with the aid of MgI_2.[56] To validate this observation, we subjected of *p*-nitrobenzaldehyde to the same reaction conditions excluding the enoate, and the MVP redox reaction was again observed in quantitative yield (Scheme 1.13).

Scheme 1.13 Meerwein-Ponndorf-Verley redox of *p*-nitrobenzaldehyde and isopropanol.



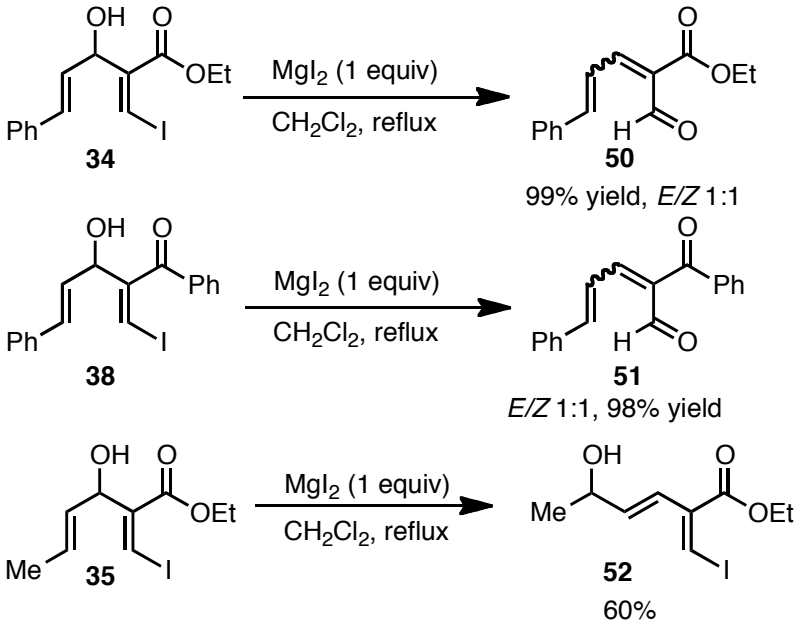
While this Oppenauer redox reaction was certainly unwanted, we were encouraged by the possibility of using this side reaction as an entry to access cyclopentenones of the type of **49** through a tandem Oppenauer-Nazarov sequence of reactions. In the event, however, no cyclopentenone was observed, instead; a 1:1 mixture of aldehydes **50** were observed, along with recovered starting material (Scheme 1.14). The formation of the aldehyde product is the result of a Lewis acid mediated 1,3-allylic transposition of the hydroxyl group, followed by the elimination of the elements of HI.

Scheme 1.14 Attempted tandem Oppenauer-Nazarov reaction.



Intrigued by these observations, we then subjected the β-iodo Baylis-Hillman adduct **34** to several reaction conditions to optimize the formation of aldehyde **50**. We found that treatment of **34** with one equivalent of MgI_2 in refluxing CH_2Cl_2 provided a clean and quantitative conversion to the corresponding aldehyde **50** as 1:1 mixture of E/Z isomers (Scheme 1.15). Others β-iodo Baylis-Hillman adducts were also subjected to these conditions. Compound **38** afforded the corresponding aldehyde **51** in 98% yield as a 1:1 mixture of E/Z isomers. Interestingly, when the phenyl group was replaced by a methyl group (**35**), the regiochemistry of the 1,3-allylic transposition changed, and afforded the allylic diene **52** in 60% yield (Scheme 1.15).

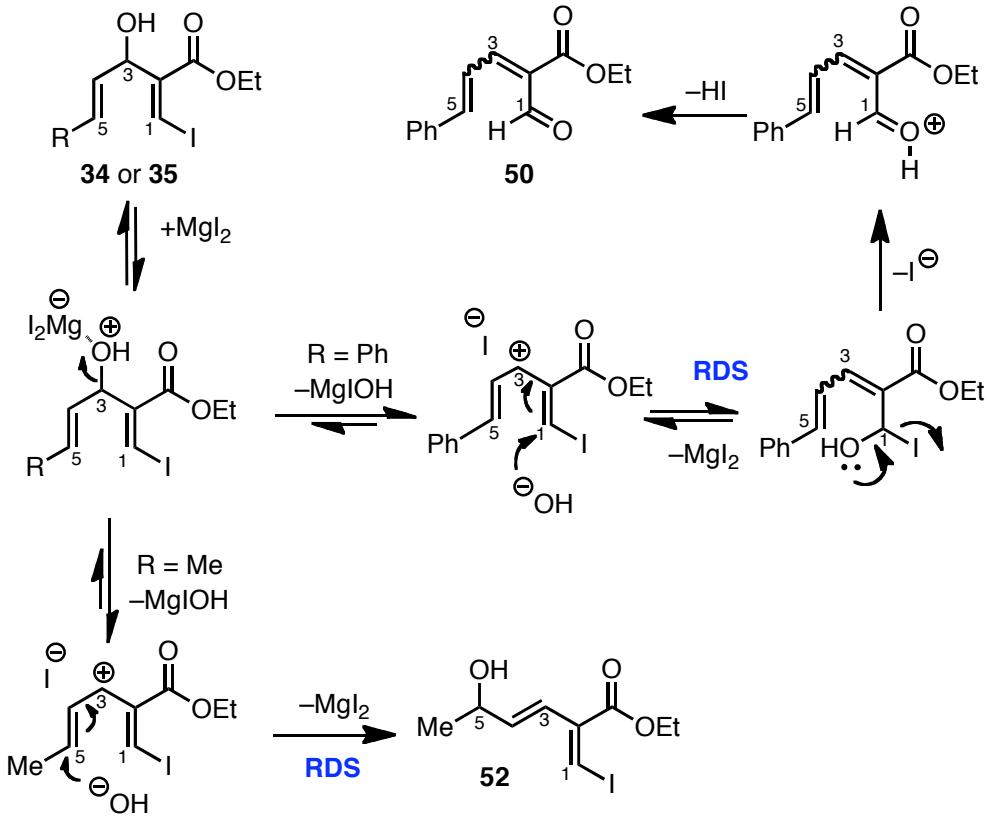
Scheme 1.15 1,3-Allylic transpositions of β-iodo Baylis-Hillman adducts.



Our proposed reaction mechanism for the 1,3-allylic transposition is shown on scheme 1.16. Initial activation of the hydroxyl group by MgI_2 leads to the formation of a stabilized carbocation, the hydroxy then add regioselective to either C1 or C5 depending

on the substituent at C5. If a phenyl group is attached to C5 then the 1,3-allylic transposition occurs at C1 possible due to stabilization of the carbocation by resonance of the phenyl. Also this addition leads to a higher level of conjugation (Scheme 1.16, right). On the other hand, when a methyl group is present at C5, the 1,3-allylic transposition occurs at C5. This could be likely to less hindrance in the molecule (Scheme 1.16, left). This information shows that the rate-determining step should be the hydroxy addition since the 1,3-allylic transposition depends on the nature of the system.

Scheme 1.16 Proposed reaction mechanism for the 1,3-allylic transpositions of β-iodo Baylis-Hillman adducts.



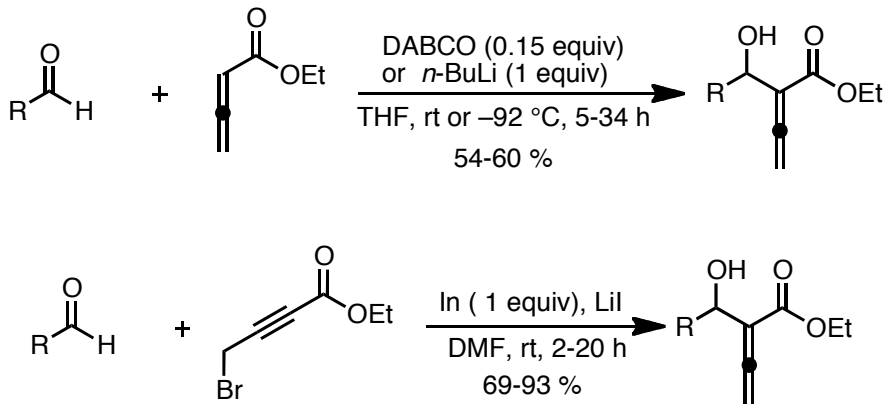
We hope to further explore the scope of this 1,3 allylic transpositions of β-iodo Baylis-Hillman adducts in the near future, since the products of these reactions are quite functionalized and are amenable for subsequent transformations such as aldol, Michael, and Diels-Alder reactions, or 1,2- additions, cross-couplings, among others. Also this approach offers a unique entry to differentiated 1,3 carbonyls (**50**, **51**) as well as β-iodo-dienoates (**52**).

1.2.4 Abnormal MBH Reactions of Allenic Esters

The synthesis of highly functionalized α-hydroxyalkyl allenic esters continues to attract the interest of synthetic chemists due to the fact that this structural motif is often encounter in many natural products and also are useful building blocks in synthetic chemistry. Several catalytic methods employing amines as nucleophilic triggers have emerged recently for the synthesis of these type molecules (Scheme 1.17).[13]

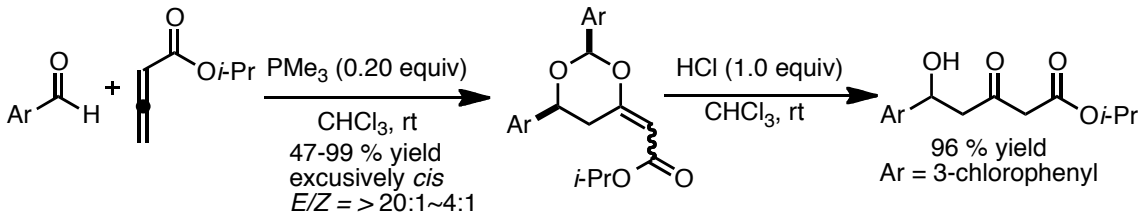
Another approach to the synthesis of α-hydroxyalkyl allenic esters is the indium mediated coupling of aldehydes with 3-(ethoxycarbonyl)propargyl bromide (Scheme 1.17),[57] however, these reactions needed 1 equivalent of In, 3 equivalents of LiI and a long reaction times (up to 20 h).

Scheme 1.17 Approaches to the synthesis of α-hydroxyalkyl allenic esters.



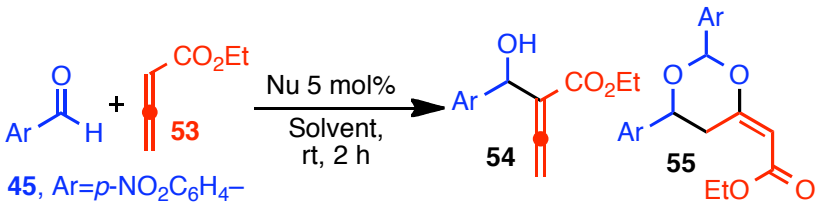
Despite the abundance of coupling reactions between allenes and various electrophiles under nucleophilic catalysis, there is only one report on phosphine-catalyzed reactions between allenes and aldehydes reported by Kwon and coworkers in 2005,[58] in which they reported the reaction of allenoates with aldehydes to produce 2,6-disubstituted-1,3-dioxan-4-ylidene-acetates in excellent to moderate yields with complete diasteroselectivity (exclusively *cis*) and high *E/Z*-selectivities. This phosphine-mediated annulation reactions to form heterocycles offers a powerful reaction to construct masked δ-hydroxy-β-ketoester, which can be released by hydrolysis under acidic conditions in excellent yields (Scheme 1.18).

Scheme 1.18 Phosphine catalyzed reaction of allenoates with aldehydes.



We were encouraged to investigate preparative methods of functionalized α-hydroxyalkyl allenic esters. Our method employing ethyl 2,3-butadienoate, showed a remarkable regiochemistry when a specific combination of nucleophile and solvent is used, switching between α or γ additions (Table 1.11).

Table 1.11 Synthesis of abnormal Baylis Hillman adducts.[a,b]

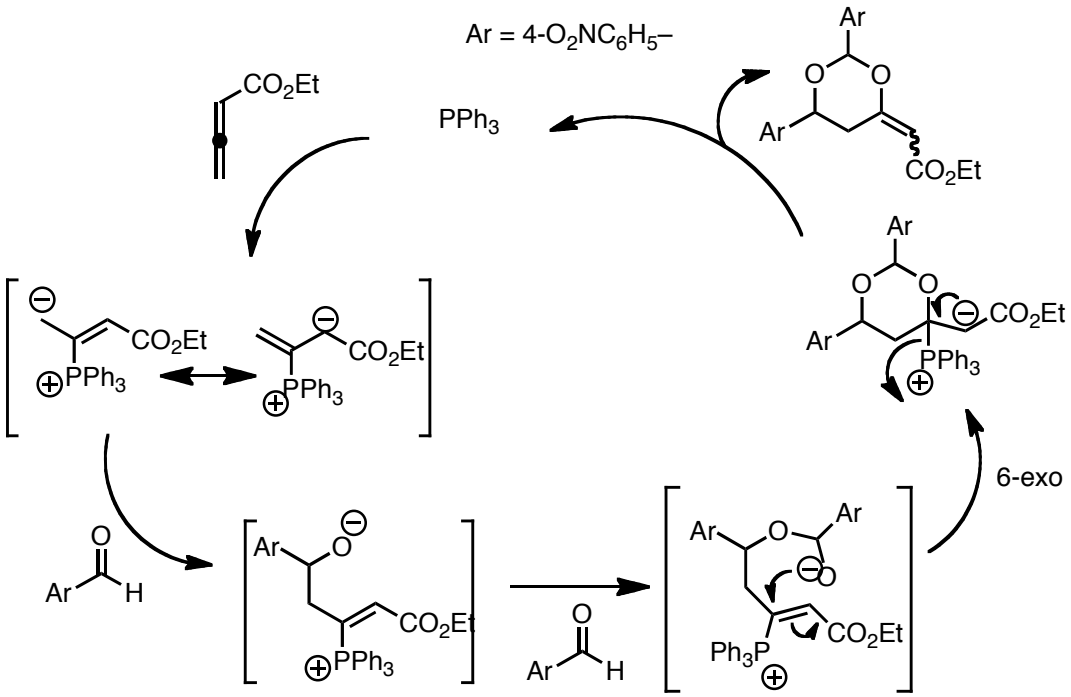


Entry	Nucleophile	Solvent	Conversion[b] 100%
1	DMAP	CH_2Cl_2	**54**
2	PPh_3	CH_2Cl_2	**55**
3	DMAP	EtOH	**54**
4	PPh_3	EtOH	**54**

[a] The reactions were performed with 0.367 mmol of **45**, 1.3 equiv of **53**, 0.5 equiv of nucleophile, in 4 mL of CH_2Cl_2 at rt for 2 h. [b] calculated by ^1H NMR.

When *p*-nitrobenzaldehyde (**45**) was reacted with ethyl 2,3-butadienoate (**53**) in CH_2Cl_2 in the presence of catalytic DMAP (5 mol %), the normal BH adduct was obtained in only 2 h at room temperature. On the other hand, when PPh_3 was employed a complete different reactivity was observed giving the 2,6-disubstituted-1,3-dioxan-4-ylidene-acetate as the sole product. If EtOH is used as solvent, the outcome for the two nucleophiles is similar with the normal BH adduct as the only product. A plausible mechanism is proposed on scheme 1.19 for the 1,4-addition.

Scheme 1.19 Proposed mechanism for the formation of 1,3-dioxan-4-ylidene.

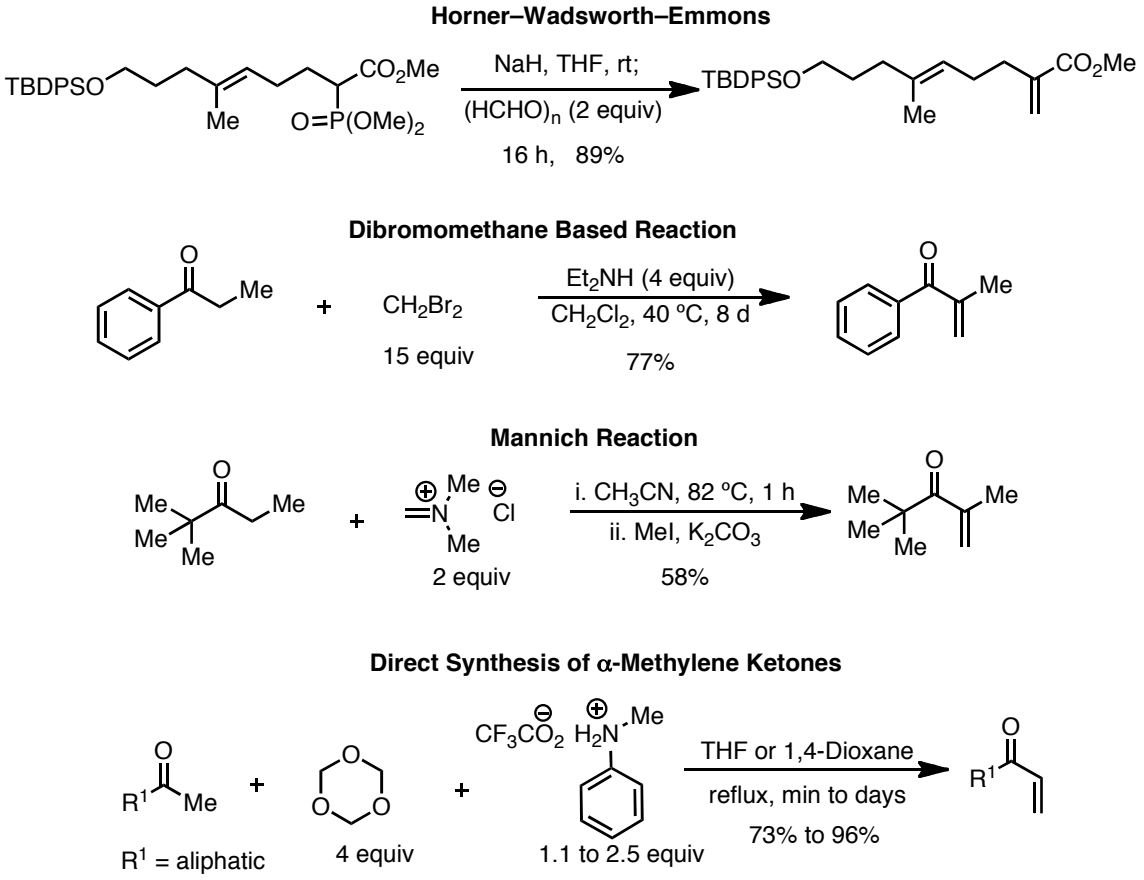


1.2.5 Direct α-Methylenation of Carbonyl Compounds

Molecules containing the α,β–unsaturated carbonyl functionality are commonly utilized as substrates for a range of chemical transformations including nucleophilic addition,[59-61] Michael addition,[62,63] the Morita-Baylis-Hillman,[2,64-67] Diels-Alder,[68,69] and several organocatalytic reactions.[70-73] The importance of the α-methylene is amplified by its presence in numerous biologically active natural products. α-Methylenation has attracted attention because it is generally an atom economical method for conversion of simple carbonyls compounds to their α,β-unsaturated derivatives.

Several methods have been developed for the α–methylenation of carbonyls (Scheme 1.20), but a practical approach has yet to be generalized and optimized.[74-82] Pihko recently reported an α-methylenation of aldehydes in aqueous media employing catalytic pyrrolidine and propionic acid,[83,84] but for the synthesis of complex, functionalized α,β–unsaturated carbonyls, the three step Mannich reaction/alkylation/elimination procedure with dimethylmethylideneammonium iodide (Eschenmoser's salt) has been the most popular choice,[85] where the mild reaction conditions are more important than the shortest possible sequence.[86-90] Gras had earlier reported a direct one step α-methylenation of ketonic compounds using *N*-methylanilinium trifluoroacetate as a catalyst with 1,3,5-trioxane in a refluxing aprotic solvent (THF or 1,4-dioxane).[91,92] This reaction affords α,β-unsaturated carbonyls by way of a Mannich-type reaction on a transiently formed methyleneammonium salt.

Scheme 1.20 Approaches for the α–methylenation of carbonyls.



We were attracted to this simple method but needed a more robust system with greater substrate scope and better reproducibility to reliably deliver a wide range of unsaturated substrates that would be used on our Morita-Baylis-Hillman ongoing projects. In our initial study, we screened a variety of ammonium salts for the α-methylenation of acetophenone (Figure 1.4).

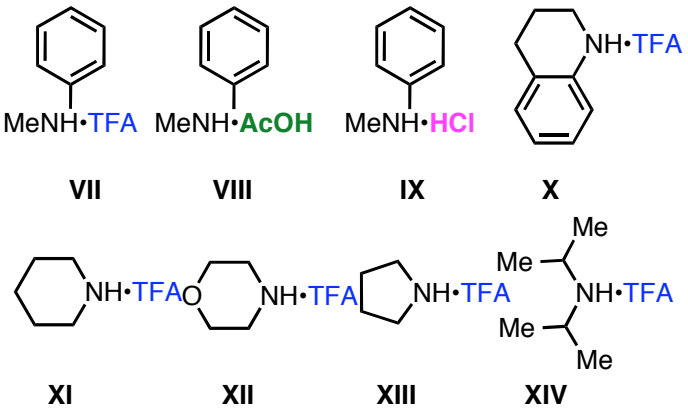
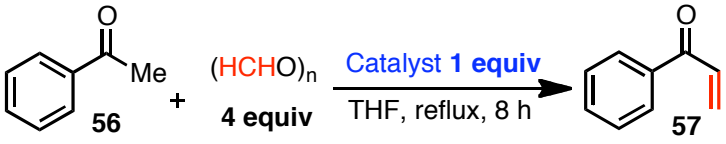


Figure 1.4 Aminomium salts screened as catalysts.

Diisopropylammonium trifluoroacetate (**XIV**) was found to be the optimal amine component in a reaction between acetophenone and paraformaldehyde in refluxing THF affording a 92% yield (Table 1.12).

Table 1.12 Screening of ammonium salts as catalyst.[a,b]

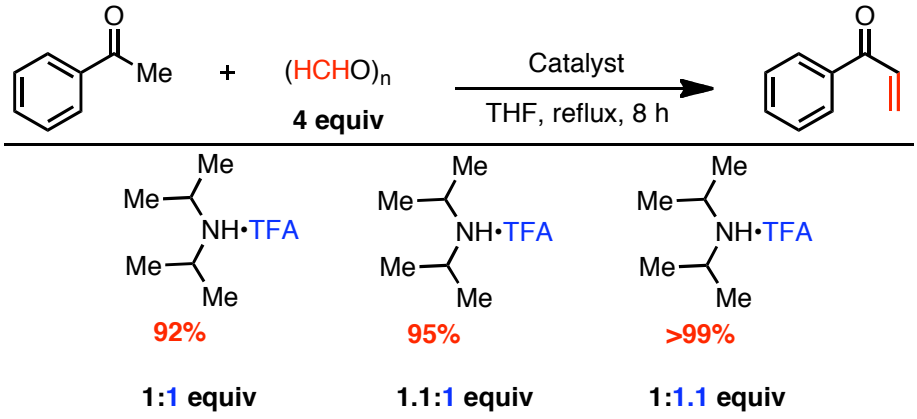


Entry	Catalyst	Yield[b] (%)
1	VII	82
2	VIII	5
3	IX	50
4	X	34
5	XI	45
6	XII	89
7	XIII	78
8	**XIV**	**92**

[a] The reactions were performed with 1 mmol of **56**, 4 equiv of paraformaldehyde, 1 equiv of catalyst, in 1.0 mL of THF at 67 °C for 8 h. [b] Determined by GC.

We then optimized the reaction conditions using diisopropylamine as the catalyst (Table 1.13). Addition of 10 mol% of diisopropylamine in the catalytic system increased the yield from 92% to 95%. On the other hand, addition of 10 mol% of trifluroacetic acid (TFA) raised the yield to >99%.

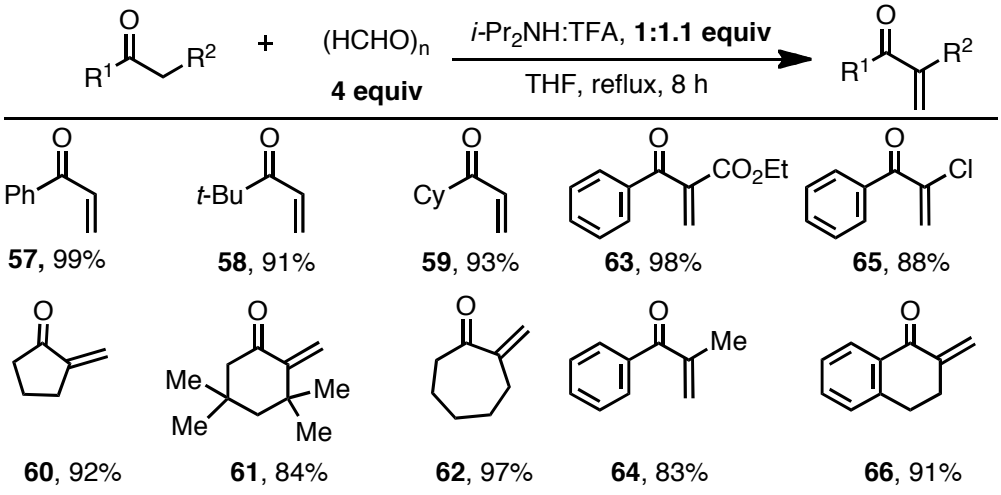
Table 1.13 Optimization of the reaction conditions.[a,b,c]



[a] The reactions were performed with 1 mmol of acetophenone, 4 equiv of paraformaldehyde, 1 equiv of catalyst, in 1.0 mL of THF at 67 °C for 8 h. [b] Determined by GC. [c] 4 equiv of paraformaldehyde added at once gave 83% yield.

We were pleased to find that with ammonium salt **XIV** complete conversion of the starting material to the α,β–unsaturated carbonyl could be obtained in 8 h. The scope of this reaction was then assessed with a representative selection of aldehydes, ketones and esters (Table 1.14).

Table 1.14 Synthesis of α,β-unsaturated carbonyls from cyclic and acyclic ketones.[a,b]



[a] The reactions were performed with 1 mmol of ketone, 4 equiv of paraformaldehyde, 1 equiv of catalyst, in 1.0 mL of THF at 67 °C for 8 h. [b] Isolated yield after purification by silica gel chromatography.

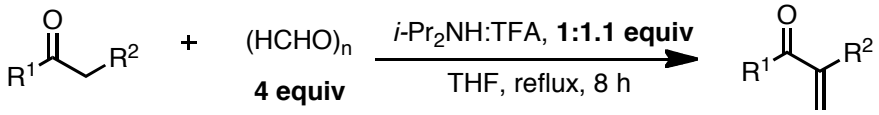
As shown in Table 1.14, a wide variety of aliphatic and aromatic ketones can be reliably converted to the corresponding α,β–unsaturated ketones in good to excellent yields with catalyst **XIV**. Also cyclic symmetrical ketones were good substrates for this transformation, affording exclusively the mono-methylenated product in good yields. Sterically demanding ketones are also tolerated as evidenced by 2,2,5,5-tetramethylcyclohexanone affording an 84% yield of the desired product **61**. Furthermore, no isomerization of the double bond could be detected in any of these adducts by ^{1}H NMR spectroscopy.

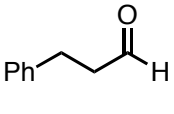
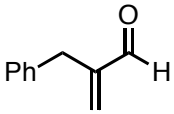
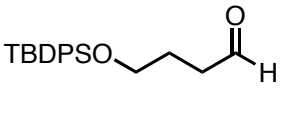
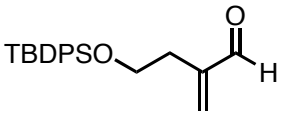
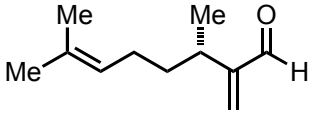
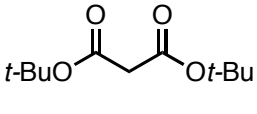
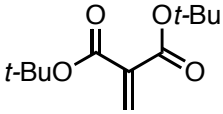
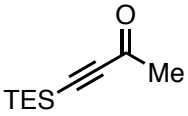
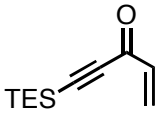
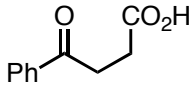
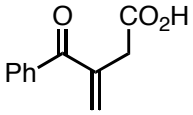
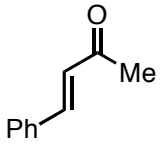
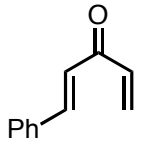
Aldehydes are easy converted to acroleins using this catalytic system. 3-Phenylpropional afforded a 95% yield (Table 1.15). The TBDPS protecting group is stable to these reaction conditions. Several reactions produced similar or higher yields of products when the reaction conditions were buffered with additional *i*-Pr_2NH instead of additional TFA. For example, when the TES protected methyl acetylene ketone (4-(triethylsilyl)but-3-yn-2-one) was treated under our standard reaction conditions, no desired product was observed. But, by adding 1 equiv *i*-Pr_2NH, the desired adduct **71** was obtained in 2 h in 62% yield.

These reaction conditions are mild as evidenced by the variety of functional groups which compatible with this system. For example, β-ketoesters reacted cleanly affording a 98% yield of the desired product. Hydroxy groups are also tolerated by these conditions. Interestingly, 2-hydroxyacetophenone underwent intramolecular conjugate addition after initial α-methylenation to form 4-chromanone which then underwent a second α-methylenation to afford adduct **74** in 85%. For phenoxyacetone, almost

exclusively the adduct 2-phenoxybut-1-en-3-one was obtained in 85% yield. Inseparable traces of 1-phenoxybut-3-en-2-one were observed as well. Such regioselectivity can be explained by the selective reaction of the thermodynamic enol (Table 1.16, entry 4).

Table 1.15 Synthesis of α,β-unsaturated carbonyls from aldehydes, alkynylketones and diesters.[a]

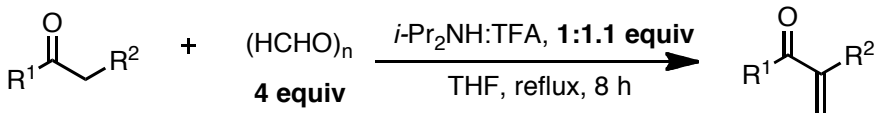


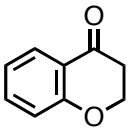
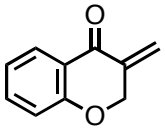
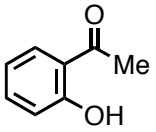
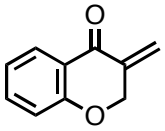
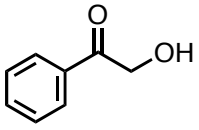
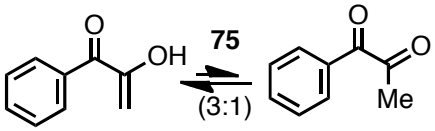
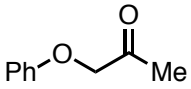
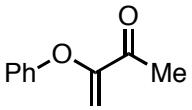
Entry	Substrate	Product (#)	Yield[b] (%)
1			**67** 95
2			**68** 99
3	(*S*)-citronellal		**69** 92
4			**70** 81
5			**71** 62
6[c]			**72** 62
7			**73** 96

[a] The reactions were performed with 1 mmol of carbonyl compound, 4 equiv of paraformaldehyde, 1 equiv of catalyst, in 1.0 mL of THF at 67 °C for 8 h. [b] Isolated yield after purification by silica gel chromatography.[c] $(HCHO)_n$ 2 equiv, 2 h, catalyst ratio *i*-Pr_2NH:TFA (2:1).

As a final note, several reactions that we tried were significantly slower when a catalytic amount (10-50 mol%) of *i*-Pr_2NH•TFA was utilized. Given the modest cost and convenience of this reagent, we have not further explored the application of catalytic reaction conditions.

Table 1.16 Synthesis of α,β-unsaturated carbonyls from functionalized ketones.[a]



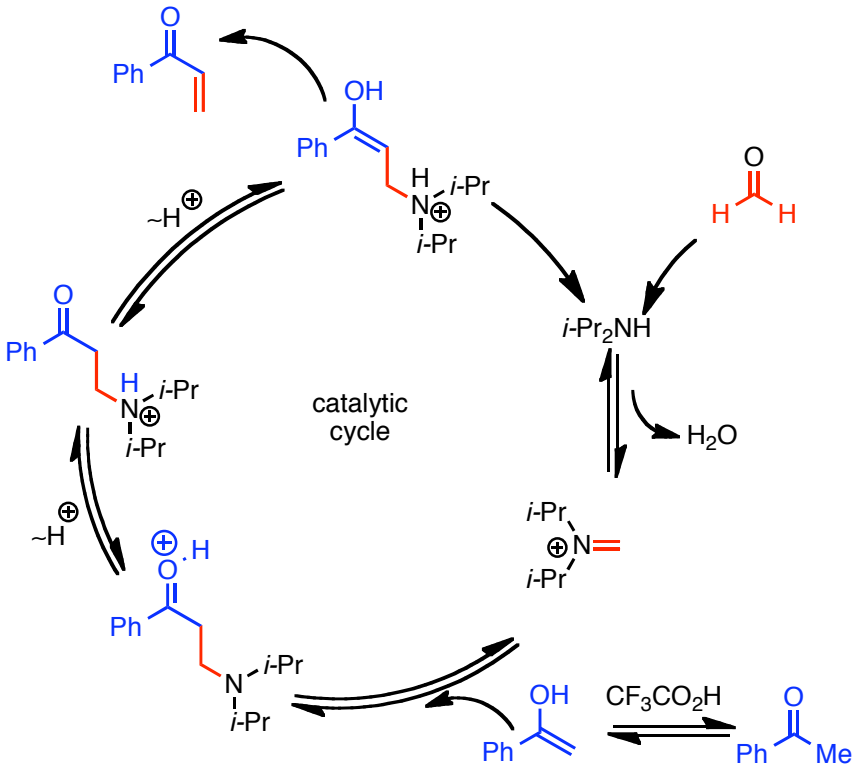
Entry	Substrate	Product (#)	Yield[b] (%)
1		 **74**	94
2		 **74**	85
3[c]		 **75** (3:1)	84
4		 **76**	85

[a] The reactions were performed with 1 mmol of carbonyl compound, 4 equiv of paraformaldehyde, 1 equiv of catalyst, in 1.0 mL of THF at 67 °C for 8 h. [b] Isolated yield after purification by silica gel chromatography. [c] A 3:1 ratio of enol:methyl ketone is observed.

The proposed mechanism for the formation of α,β-unsaturated carbonyls is shown on scheme 1.21 and proceeds through the expected iminium intermediate, followed by Mannich reaction. After a tautomerization and β-elimination, the desired α–β-unsaturated carbonyl compound is obtained.

We anticipate that this method will be of wide use in organic synthesis due to the mildness of the reaction conditions as well as the inexpensive cost of the reagents and most important, to the tolerance of several functional groups in the substrates.

Scheme 1.21 Proposed mechanism for the formation of α,β-unsaturated carbonyls.



1.3 Experimental Section

1.3.1 General Information

All reactions were carried out under an argon atmosphere in oven-dried glassware with magnetic stirring. All commercially obtained reagents were used as received. All aldehydes were distilled before use. Any impure starting material from stock was purified by distillation, column chromatography, or recrystallization. Solvents were distilled under its specific drying agent or obtained from a purification system. Water was distilled and deoxygenated under nitrogen flush.

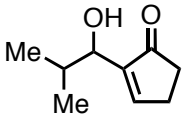
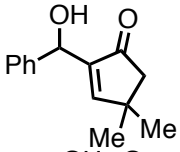
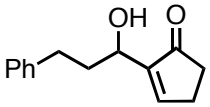
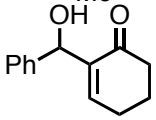
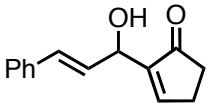
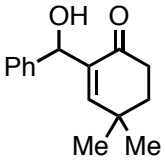
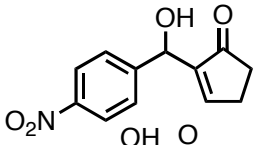
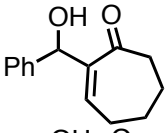
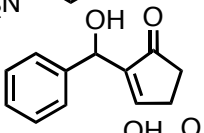
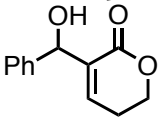
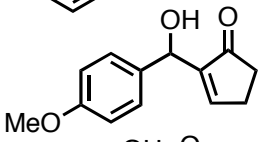
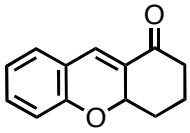
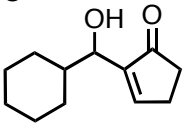
Cooling was accomplished using an ice bath or an isopropanol bath. Heating was accomplished by either a heating mantle or silicone oil bath. Purification of reaction products was carried out by flash column chromatography using silica gel, distillation or by recrystallization. Visualization was accompanied with UV light and/or ceric ammonium molybdate or potassium permanganate staining.

^{1}H NMR spectra were recorded on a 300 MHz instrument and recorded relative to the deuterated solvent used, in ppm units. ^{1}H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). Proton-decoupled ^{13}C NMR spectra were recorded at 75 MHz. High-resolution mass spectra (HRMS) were obtained at Texas A&M. Infrared spectra were recorded on a spectrometer using a thin film on NaCl plates.

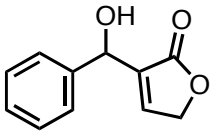
1.3.2 Acceleration of the MBH Reaction

General procedure for the synthesis of Baylis-Hillman adducts **4**-**17**: To a stirred mixture of aldehyde (0.5 mmol) and activated alkene (0.55 mmol) in MeOH (1.2 mL) at room temperature under argon atmosphere was added a solution of MgI_2 (13.9 mg, 0.05 mmol) and TMEDA (8.3 mg, 0.05 mmol) in MeOH (0.2 mL), followed by dropwise addition of a solution of DMAP (6.1 mg, 0.05 mmol) in MeOH (0.1 mL). After, the mixture was stirred for 15 h at rt under argon atmosphere. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (1.0 mL). The solution mixture was extracted twice with dichloromethane (5.0 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (20% EtOH/Hexanes or CH_2Cl_2) (Table 1.17).

Table 1.17 References to known compounds (MBH adducts).[93-99]

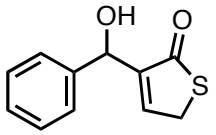
Adduct (#)	Product	Reference	Adduct (#)	Product	Reference
9		97	**11**		95
7		96	**12**		93
10		93	**13**		93
5		94	**14**		93
4		93	**15**		98
6		94	**21**		99
8		96			

Details for the Unknown Adducts **16** and **17**.



3-(hydroxy(phenyl)methyl)furan-2(5*H*)-one (**16**): To a stirred mixture of benzaldehyde (53 mg, 0.5 mmol) and furan-2(5*H*)-one (46.2 mg, 0.55 mmol) in EtOH (1.2 mL) at room temperature under argon was added a solution of magnesium iodide (13.9 mg, 0.05 mmol) and TMEDA (8.3 mg, 0.05 mmol) in EtOH (0.2 mL) was added

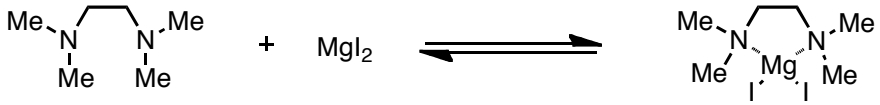
followed by dropwise addition of a solution of dimethylaminepyridine (6.1 mg, 0.05 mmol) in EtOH (0.1 mL). After, the mixture was stirred for 2 h at rt under argon. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (1.0 mL). The solution mixture was extracted twice with dichloromethane (5.0 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (dichloromethane) to give compound **16** (50.4 mg, 53%) as a colorless oil; IR (thin film) ν 3424, 2869, 1745, 1201 cm^{-1}; ^1H NMR ($CDCl^3$, 300 MHz) δ 7.43–7.31 (m, 5 H), 7.19 (q, *J* = 1.55 Hz, 1 H), 5.56 (s, 1 H), 4.78 (t, *J* = 2.0 Hz, 2 H), 3.45 (d, *J* = 4.0 Hz, 1 OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 146.0, 140.0, 136.3, 128.5, 128.2, 126.3, 70.5, 69.0. MS (ESI) calcd for $C_{11}H_{10}O_3$ + Li requires m/z 197.0790, found 197.0795.



3-(hydroxy(phenyl)methyl)thiophen-2(5*H*)-one (**17**): To a stirred mixture of benzaldehyde (53 mg, 0.5 mmol) and thiophen-2(5*H*)-one (55 mg, 0.55 mmol) in EtOH (1.2 mL) at –15 ºC under argon was added a solution of magnesium iodide (13.9 mg, 0.05 mmol) and TMEDA (8.3 mg, 0.05 mmol) in EtOH (0.2 mL) was added followed by dropwise addition of a solution of dimethylamine-pyridine (6.1 mg, 0.05 mmol) in EtOH (0.1 mL). After, the mixture was stirred for 1 h at –15 ºC under argon. The reaction was quenched by addition of saturated aqueous NH4Cl solution (1.0 mL). The solution mixture was extracted twice with dichloromethane (5.0 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified

by flash silica gel column chromatography (dichloromethane) to give compound **17** (94.8 mg, 92%) as a pale yellow oil; IR (thin film) ν 3419, 2918, 1659, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42-7.32 (m, 5 H), 7.16 (m, 1 H), 5.63 (s, 1 H), 3.98 (t, *J* = 1.08 Hz, 2 H), 3.20 (d, *J* = 3.63 Hz, 1 OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 148.9, 147.7, 140.6, 128.6, 128.1, 126.4, 70.1, 35.5. MS (ESI) calcd for $C_{11}H_{10}O_2S$ + Li requires *m/z* 213.0562, found 213.0573.

1.3.3 NMR Studies of Complex TMEDA–MgI_2



E-1 **E-2**

NMR Studies of TMEDA (**E-1**):

A solution of TMEDA (20 mg, 0.172 mmol) (**E-1**) in 1 mL of $CDCl_3$ or CD_3OD was analyzed by ^1H NMR and ^{13}C NMR.

TMEDA. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.388 (s, 4H), 2.245 (s, 12H)

TMEDA. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 57.604, 45.806.

TMEDA. ^1H NMR (CD_3OD, 300 MHz) δ 2.469 (s, 4H), 2.261 (s, 12H)

TMEDA. ^{13}C NMR (CD_3OD, 75 MHz) δ 58.017, 45.938.

NMR Studies of TMEDA/MgI_2 (**E-2**):

To a stirred mixture of MgI_2 (47.9 mg, 0.172 mmol) in 1 mL of $CDCl_3$ or CD_3OD at room temperature under argon atmosphere was added TMEDA (20 mg, 0.172 mmol), the mixture was stirred for 5 min at rt under argon atmosphere. Then, analyzed by ^1H NMR and ^{13}C NMR.

TMEDA + MgI_2. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.596 (s, 4H), 2.364 (s, 12H)

TMEDA + MgI_2. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.422, 45.359.

TMEDA + MgI_2. ^1H NMR (CD_3OD, 300 MHz) δ 2.541 (s, 4H), 2.311 (s, 12H)

TMEDA + MgI_2. ^{13}C NMR (CD_3OD, 75 MHz) δ 57.529, 45.752.

1.3.4 Enantioselective MBH Reaction

General procedure for the synthesis of enantiomeric enriched BH adducts: To a stirred mixture of (*R*)-(+)-4-dimethylaminopyrindinyl(pentaphenylcyclopentadienyl) iron (**II**) (5 mg, 0.0075 mmol, 10 mol%), MgI_2 (10 mg, 0.038 mmol, 50 mol%) in *i*-PrOH (1.5 mL) was added the aldehyde (0.075 mmol) at room temperature under argon. Then, the reaction mixture was cooled down to –20 ºC followed by the addition of cyclopent-2-enone (**2**) (9 mg, 0.11 mmol, 1.5 equiv). After, the mixture was stirred for 24 h at –20 ºC under argon atmosphere. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (1.0 mL). The solution mixture was extracted twice with CH_2Cl_2 (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography using 20% EtOH/hexanes or CH_2Cl_2 as the eluents to afford the respective adducts (Table 1.18). HPLC was used to verify the enantiomeric excess for each adduct (Table 1.19).

Table 1.18 References to known compounds (enantioenriched adducts).[33,42,93-97,100,101]

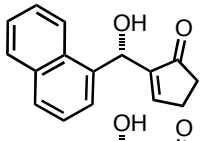
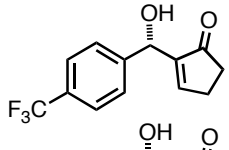
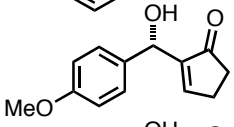
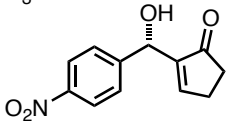
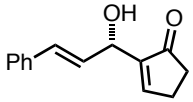
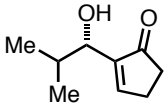
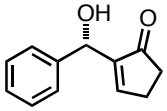
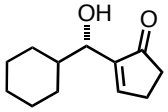
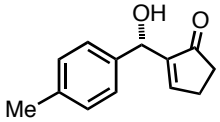
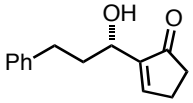
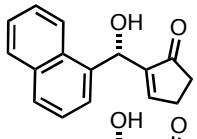
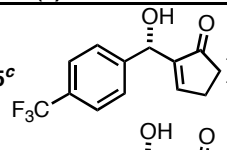
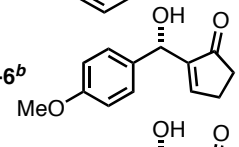
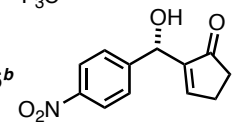
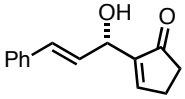
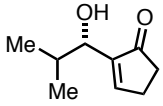
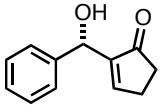
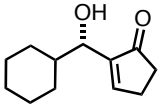
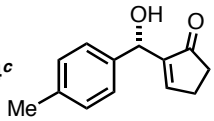
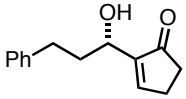
Compound No.	Product	Reference (racemic)	Reference (nonracemic)	Compound No.	Product	Reference (racemic)	Reference (nonracemic)
(+)-23		–	–	**(+)-25**		95	–
(+)-6		94	–	**(+)-5**		94	101
(–)-10		95	100	**(–)-9**		97	33
(+)-4		93	33	**(–)-8**		96	33
(+)-24		94	–	**(–)-7**		96	33

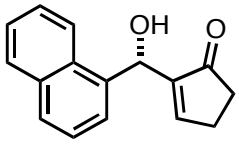
Table 1.19 HPLC data (enantioenriched MBH adducts).

Adduct (#)	Product	HPLC RT	ee (%)	$[\alpha]_D^{22}$ [d]	Adduct (#)	Product	HPLC RT	ee (%)	$[\alpha]_D^{22}$ [d]
(+)-23[a]		t_{major} = 30.60 min t_{minor} = 27.25 min	98	+66.1	**(+)-25**[c]		t_{major} = 17.61 min t_{minor} = 20.33 min	89	+17.3
(+)-6[b]		t_{major} = 22.23 min t_{minor} = 24.29 min	95	+26.7	**(+)-5**[b]		t_{major} = 21.45 min t_{minor} = 24.70 min	89	+38.5
(–)-10[a]		t_{major} = 23.67 min t_{minor} = 26.64 min	94	–22.7	**(–)-9**[c]		t_{major} = 8.79 min t_{minor} = 9.19 min	63	–25.4
(+)-4[b]		t_{major} = 12.39 min t_{minor} = 13.49 min	94	+18.2	**(–)-8**[c]		t_{major} = 7.94 min t_{minor} = 8.51 min	58	–21.7
(+)-24[c]		t_{major} = 24.68 min t_{minor} = 25.94 min	92	+15.8	**(–)-7**[b]		t_{major} = 10.47 min t_{minor} = 10.83 min	53	–18.9

[a] Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (hexane/*i*PrOH = 90/10), 1.0 mL/min, 254 nm. [b] Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (hexane/*i*PrOH = 85/15), 1.0 mL/min, 254 nm. [c] Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (hexane/*i*PrOH = 95/5), 1.0 mL/min, 254 nm.[d] Optical rotation at (*c* 1.00, $CHCl_3$).

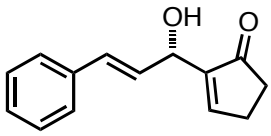
The absolute (*S*) configuration of products **(–)-4**, **(–)-5**, **(–)-7**, **(–)-8**, **(–)-9** and **(–)-10** was determined by comparison of the sign of optical rotation with the known compounds (see previous page). Other absolute configurations are assigned by analogy.

Procedures and characterization data for the asymmetric BH adducts: Compounds **(+)-5**, **(+)-6**, **(–)-7**, **(–)-8**, **(–)-9**, **(–)-10**, **(+)-24** and, **(+)-25** are known compounds (Table 1.18). Compound **(+)-23** is a new compound. Full tabulated data is available below for the new compound **(+)-23** and the adduct of the optimization reaction **(–)-10**.



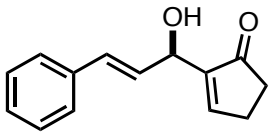
(*S*)-2-(hydroxy(naphthalen-1-yl)methyl)cyclopent-2-enone (**(+)-23**): To a stirred mixture of (*R*)-(+)-4-dimethylaminopyrindinyl-(pentaphenylcyclopentadienyl) iron (**II**) (5 mg, 0.008 mmol), MgI_2 (10.4 mg, 0.038 mmol) in *i*-PrOH (1.5 mL) was added 1-naphthaldehyde (12 mg, 0.075 mmol) at room temperature under an argon atmosphere. Then the reaction mixture was cooled down to –20 ºC followed by the addition of cyclopent-2-enone (9 mg, 0.11 mmol, 1.5 equiv). After, the mixture was stirred for 24 h at –20 ºC under argon atmosphere. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL). The mixture was extracted twice with CH_2Cl_2 (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography to give compound **(+)-23** (14 mg, 94%) as a colorless oil (CH_2Cl_2); IR (thin film) ν 3403, 3028, 2920, 1695, 1611, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.93-7.88 (m, 2H), 7.82 (d, J = 8.7 Hz, 1H), 7.76 (d, J = 7.2 Hz, 1H), 7.70-7.46 (m, 3H), 7.02 (m, 1H), 6.30 (s, 1H), 3.79 (s, 1OH), 2.50 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.1, 161.1, 147.2, 136.6, 133.8, 130.4, 128.8, 128.4, 126.1, 125.6, 125.5, 124.4, 123.7, 66.5, 35.2, 26.6. HRMS (ESI)

calcd for $C_{16}H_{14}O_2$ + Li requires m/z 245.0409, found 245.0411. $[\alpha]_{22}^{D}$ = +66.09 (*c* 1.0, $CHCl_3$). Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (hexane/*i*PrOH = 90/10), 1.0 mL/min, 254 nm, t_{major}= 30.60 min, t_{minor}= 27.25 min; 98% *ee*.



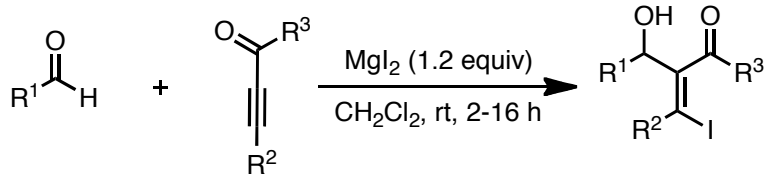
(*S*,*E*)-2-(1-hydroxy-3-phenylallyl)cyclopent-2-enone (**(–)-10**): To a stirred mixture of (*R*)-(+)-4-dimethylaminopyrindinyl-(pentaphenylcyclopentadienyl) iron (**II**) (5 mg, 0.0075 mmol, 10 mol%), MgI_2 (10 mg, 0.038 mmol, 50 mol%) in *i*-PrOH (1.5 mL) was added *trans*-cinnamaldehyde (10 mg, 0.075 mmol) at room temperature under an argon atmosphere. Then the reaction mixture was cooled down to –20 ºC followed by the addition of cyclopent-2-enone (9 mg, 0.11 mmol, 1.5 equiv). After, the mixture was stirred for 24 h at –20 ºC under an argon atmosphere. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL). The solution mixture was extracted twice with CH_2Cl_2 (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography to give compound **(–)-10** (16 mg, 96%) as a colorless oil (CH_2Cl_2); IR (thin film) ν 3400, 3026, 2921, 1691, 1605, 970 cm-1; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (td, *J* = 1.1 Hz, 1.4 Hz, 3.1 Hz, 1H), 7.41 (m, 2H), 7.27-7.17 (m, 3H), 6.70 (dd, *J* = 1.1 Hz, 14.8 Hz, 1H), 6.35 (dd, *J* = 6.5Hz, 9.8 Hz, 1H), 5.17 (d, *J* = 6.7 Hz, 1H), 3.31 (d, *J* = 4.1 Hz, 1OH), 2.65 (m, 2H), 2.49 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.6, 158.8, 146.3, 136.3, 131.1, 128.6, 128.5, 127.8, 126.5, 68.4, 35.1, 26.7. HRMS (ESI)

calcd for $C_{14}H_{14}O_2$ + Li requires *m/z* 221.115, found 221.114. $[\alpha]^{22}_D$ = -22.66 (*c* 1.0, $CHCl_3$). Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (hexane/*i*-PrOH = 90/10), 1.0 mL/min, 254 nm, t_{major}= 23.67 min, t_{minor}= 26.64 min; 94% *ee*.



When (*S*)-(+)-4-dimethylaminopyrindinyl-(pentaphenylcyclo-pentadienyl) iron (**II**) was used the values obtained for **(+)-10** are: (15 mg, 93%) as a colorless oil (CH_2Cl_2); IR (thin film) ν 3400, 3026, 2921, 1691, 1605, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55 (td, *J* = 1.1 Hz, 1.4 Hz, 3.1 Hz, 1H), 7.41 (m, 2H), 7.27-7.17 (m, 3H), 6.70 (dd, *J* = 1.1 Hz, 14.8 Hz, 1H), 6.35 (dd, *J* = 6.5Hz, 9.8 Hz, 1H), 5.17 (d, *J* = 6.7 Hz, 1H), 3.31 (d, *J* = 4.1 Hz, 1OH), 2.65 (m, 2H), 2.49 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.6, 158.8, 146.3, 136.3, 131.1, 128.6, 128.5, 127.8, 126.5, 68.4, 35.1, 26.7. HRMS (ESI) calcd for $C_{14}H_{14}O_2$ + Li requires *m/z* 221.115, found 221.114. $[\alpha]^{22}_D$ = +22.66 (*c* 1.0, $CHCl_3$). Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (hexane/*i*-PrOH = 90/10), 1.0 mL/min, 254 nm, t_{minor}= 23.67 min, t_{major}= 26.64 min; 94% *ee*.

1.3.5 Synthesis of β-Iodo BH Adducts

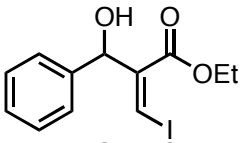
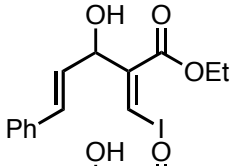
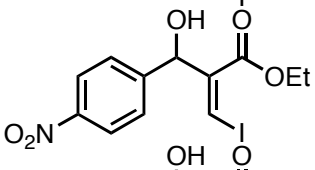
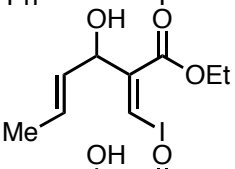
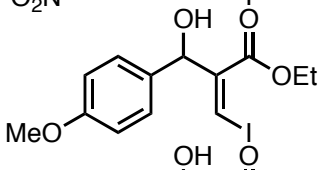
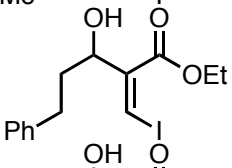
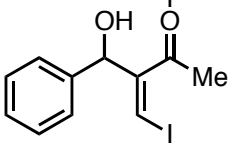
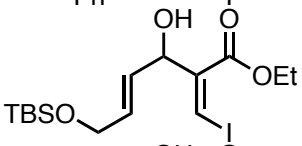
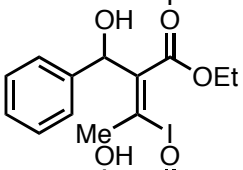
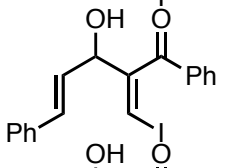
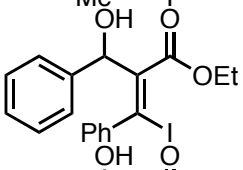
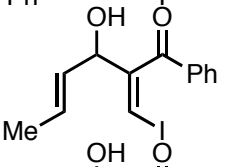
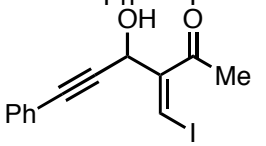
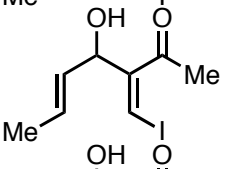
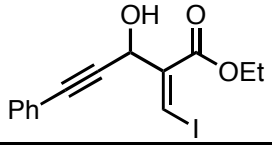
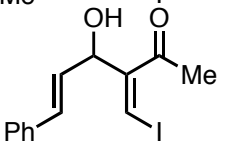


R^1= Alkenyl, Aryl, Alkyl, Akynyl
R^2= H, Me, Ph
R^3= OEt, Me, PH

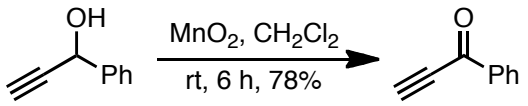
26-41

To an 8 mL glass vial containing a stir bar was added MgI_2 (0.441 mmol, 122.6 mg, 1.2 equiv) and capped with a phenolic cap equipped with a teflon/silicone septa. The vial was filled and purged with argon. A solution of aldehyde (0.367 mmol, 1.0 equiv) in dry dichloromethane (4 mL) was added via syringe under argon. The mixture was stirred for 20 min at room temperature. Then, ynone/ynoate (0.478 mmol, 1.3 equiv) was added via syringe and stirred for 2 h at rt under argon. The reaction mixture was concentrated under reduce pressure. Finally, the residue was loaded to a flash silica gel column chromatography and purified using (0-10% EtOAc-Hexanes) as the eluents to afford the pure adducts **26–41** (Table 1.20).

Table 1.20 References to known compounds (β-Iodo BH adducts).[102-105]

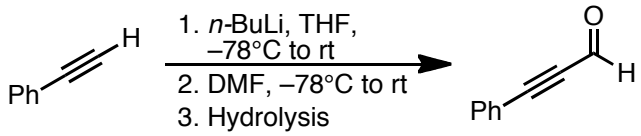
Compound No.	Product	Reference	Compound No.	Product	Reference
26		102	**34**		104
27		102	**35**		104
28		103	**36**		–
29		105	**37**		–
30		–	**38**		–
31		–	**39**		–
32		–	**40**		105
33		–	**41**		105

1.3.6 Synthesis of Carbonyl Starting Materials



E-3 **E-4**

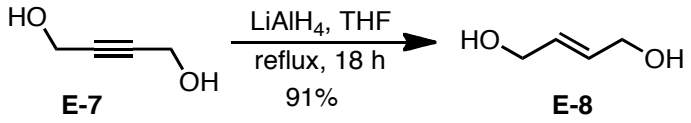
1-phenylprop-2-yn-1-one (**E-4**):[106] In a 25 mL round bottom flask equipped with a stir bar was added MnO_2 (3 equiv) then a solution of 1-phenylprop-2-yn-1-ol (7.5 mmol, 1 g) in dichloromethane (10 mL) was added. After stirring at room temperature for 6 h, the reaction was filtered through a pad of celite to remove the solids. The filtrate was washed sequentially with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford a yellow residue that was purified by flash silica gel column chromatography using (0-10% EtOAc-Hexanes) as the eluents to afford pure **E-4** in 78% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, J = 7.2 Hz, 2H), 7.64 (t, J = 7.8 Hz, 1H), 7.51 (t, J = 7.2 Hz, 2H), 3.46 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3, 136.0, 134.5, 129.6, 128.6, 80.8, 80.2.



E-5 93% **E-6**

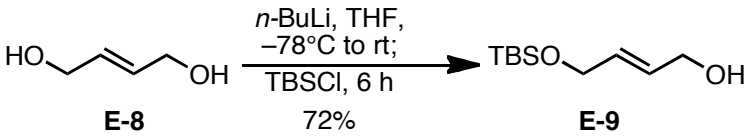
3-phenylprop-2-ynal (**E-6**):[107,108] To a solution of phenyl acetylene (48.9 mmol, 5 g) in 20 mL of THF that had been cooled to –78 °C under argon was added 19 mL of *n*-BuLi (2.57 M in THF, 49 mmol) while stirring. To this solution was added N,N-dimethylformamide (20 mL, excess) dropwise over 10 min. The cooling bath was removed and the solution allowed to warm up to rt. After 1 h of further stirring, the solution was quenched with saturated NH_4Cl and extracted with Et_2O. The organic layer

was washed sequentially with water and brine. Dried over Na_2SO_4. The solvents were removed under reduced pressure to afford a light yellow residue that was purified by flash silica gel chromatography using (0-5% EtOAc-Hexanes) as the eluents to afford pure **E-6** in 93% yield as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.43 (s, 1H), 7.61 (d, *J* = 6.9 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 133.2, 131.3, 128.7, 119.3, 95.1, 88.4.



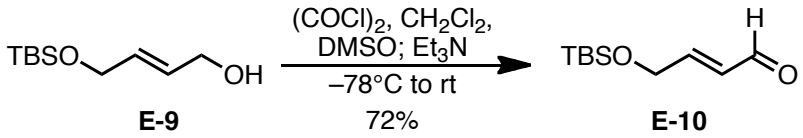
E-7 **E-8**

(*E*)-but-2-ene-1,4-diol (**E-8**):[109] In a 250 mL round bottom flask equipped with stir bar and a condenser was added $LiAlH_4$ (140 mmol, 5.3 g, 1.2 equiv) and dissolved in THF (150 mL) under argon. Then, cooled down to –78 °C. A solution of but-2-yne-1,4-diol (110 mmol, 10 g) in THF (50 mL) was added while stirred vigorously at –78 °C. After the addition the mixture was warmed up slowly to reflux. The reflux was continued for 18 h. The mixture was then cooled down to rt and quenched carefully with saturated NH_4Cl solution. Filtered using a paper filter and the white cake was washed with Et_2O. The solvents were removed under reduced pressure to afford a light yellow residue that was purified by flash silica gel chromatography using (80% EtOAc-Hexanes) as the eluents to afford 9.3 g of pure **E-8** in 91% yield as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (m, 2H), 4.16 (m, 4H), 2.15 (bs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.3, 62.8.



E-8 72% **E-9**

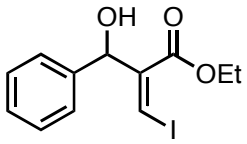
(*E*)-4-(*tert*-butyldimethylsilyloxy)but-2-en-1-ol (**E-9**):[109] In a 250 mL round bottom flask equipped with a stir bar and a septa was added a solution of (*E*)-but-2-ene-1,4-diol (**E-8**) (45 mmol, 4 g) in 100 mL of THF under argon. Cooled down to –78 °C. Then, was added 25 mL of *n*-BuLi (1.8 M in THF, 45 mmol) while stirring. Once the addition was completed, the mixture was allowed to warm up to rt and stirred for 30 min. To this mixture was added a solution of TBSCl (49 mmol, 7.35 g, 1.1 equiv) in 20 mL of THF at rt under argon. After 6 h of further stirring, the solution was quenched with saturated NH_4Cl and extracted with EtOAc. The organic layer was washed sequentially with water and brine. Dried over Na_2SO_4. The solvents were removed under reduced pressure to afford a yellow residue that was purified by flash silica gel chromatography using (20-50% EtOAc-Hexanes) as the eluents to afford 6.6 g of pure **E-9** in 72% yield as light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.82 (m, 2H), 4.18 (m, 2H), 4.15 (m, 2H), 1.68 (bs, 1OH), 0.91 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.7, 128.9, 63.1, 63.0, 25.9, 18.5, -5.3.



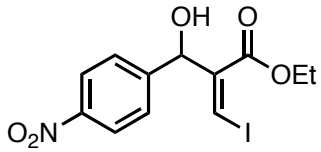
E-9 **E-10**

(*E*)-4-(*tert*-butyldimethylsilyloxy)but-2-enal (**E-10**):[109] In a 250 mL round bottom flask equipped with a stir bar and a septa was added oxalyl chloride (27.2 mmol, 2.36 mL, 1.1 equiv) in 100 mL of DCM at – 78 °C under argon. To this mixture, DMSO (24.7 mmol, 1.75 mL, 1 equiv) was added dropwise and stirred for 30 min. Then, a solution of (*E*)-4-(*tert*-butyldimethylsilyloxy)but-2-en-1-ol (**E-9**) (24.7 mmol, 5 g, 1 equiv) in 20 mL of DCM was added dropwise via syringe and stirred for 10 more min. Finally, a solution of Et_3N (54.3 mmol, 7.52 mL, 2.2 equiv) in 20 mL of DCM was added dropwise via syringe. The mixture was allowed to warm up to rt and stirred for 2 h. Quenched with saturated NH_4Cl and extracted with DCM. The organic layer was washed sequentially with water and brine. Dried over Na_2SO_4. The volatiles were removed under reduced pressure to afford a light brown residue that was purified by flash silica gel chromatography using (20% EtOAc-Hexanes) as the eluents to afford 4.35 g of pure **E-10** in 88% yield as light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.61 (d, J = 8.1 Hz, 1H), 6.89 (dt, J = 3.0, 15.3 Hz, 1H), 6.40 (qt, J = 2.4, 8.1 Hz, 1H), 4.45 (m, 2H), 0.91 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4, 153.5, 130.5, 62.2, 25.7, 18.2, -5.5.

Procedures and characterization data of adducts: Compounds **26–29**, **40** and **41** are known compounds (Table 1.20). Compounds **30–33** and **36–39** are new compounds. Full-tabulated data is available below for all compounds.

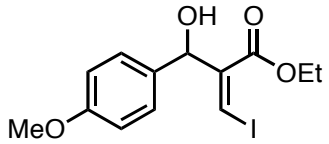


(Z)-ethyl 2-[Hydroxy(phenyl)methyl]-3-iodoprop-2-enoate (**26**): From benzaldehyde and ethyl propiolate as described in the general method (see above). Light yellow oil (92%). IR (thin film) ν 3443, 3070, 2934, 1719 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 5 H), 7.27 (d, *J* = 1.5 Hz, 1 H), 5.55 (s, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 2.92 (bs, 1 OH), 1.22 (t, 12.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 145.0, 140.1, 128.6, 128.2, 126.5, 86.8, 76.2, 61.4, 13.9. HRMS (CI, CH_4) calcd for $C_{12}H_{13}IO_3^+$ requires *m/z* 331.9909, found 331.9906. HPLC values, with a Chiralcel OJ-H column (hexane/*i*-PrOH = 85/15), 1.0 mL/min, 254 nm, t_1= 16.60 min, t_2= 21.50 min.

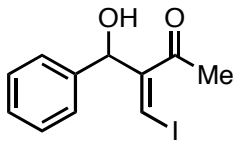


(Z)-ethyl 2-[Hydroxy(4-nitrophenyl)methyl]-3-iodoprop-2-enoate (**27**): From *p*-nitrobenzaldehyde and ethyl propiolate as described in the general method (see above). Light yellow oil (94%). IR (thin film) ν 3448, 3070, 2950, 2835, 1718 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.42 (s, 1H), 5.62 (s, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 3.35 (bs, 1 OH), 1.24 (t, 7.2 Hz, 3H). ^{13}C NMR

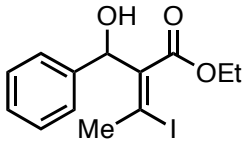
(75 MHz, $CDCl_3$): δ 166.1, 148.1, 147.7, 144.4, 127.9, 124.4, 89.7, 76.3, 62.5, 14.6. HRMS (CI, CH_4) calcd for $C_{12}H_{12}INO_5^+$ requires *m/z* 376.9760, found 376.9759.



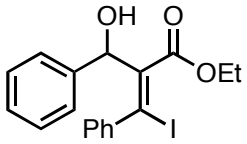
(Z)-ethyl 2-[Hydroxy(4-methoxyphenyl)methyl]-3-iodo-prop-2-enoate (**28**): From *p*-methoxybenzaldehyde and ethyl propiolate as described in the general method (see above). Colorless oil (89%). IR (thin film) ν 3451, 3070, 2934, 2836, 1719 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, *J* = 10.2 Hz, 2H), 7.25 (s, 1H), 6.89 (d, *J* = 4.5 Hz, 2H), 5.52 (s, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 3.82 (s, 3H), 2.73 (bs, 1 OH), 1.25 (t, 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 159.5, 145.3, 132.2, 127.9, 113.9, 86.1, 75.7, 61.4, 55.3, 13.9. HRMS (CI, CH_4) calcd for $C_{13}H_{15}IO_4^+$ requires *m/z* 362.0015, found 362.0013.



(*Z*)-3-(hydroxy(phenyl)methyl)-4-iodobut-3-en-2-one (**29**): From benzaldehyde and but-3-yn-2-one as described in the general method (see above). Colorless oil (95%). IR (thin film) ν 3428, 3061, 2938, 2854, 1701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H), 6.72 (d, *J* = 1.2 Hz, 1H), 5.58 (s, 1 H), 2.71 (bs, 1 OH), 2.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.3, 154.2, 139.3, 128.1, 126.2, 124.8, 78.7, 76.2, 30.2. HRMS (CI, CH_4) calcd for $C_{11}H_{11}IO_2$+ requires *m/z* 301.9804, found 301.9809.

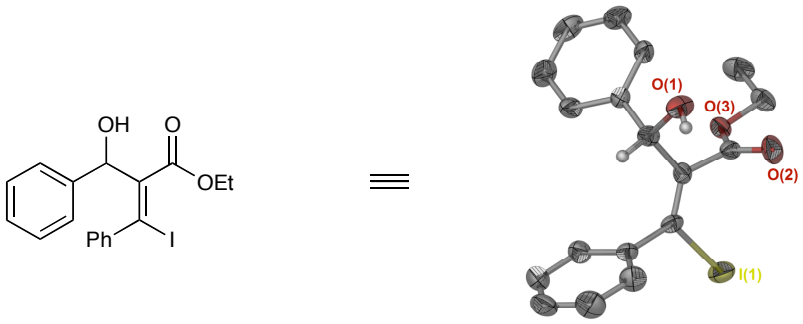


(*Z*)-ethyl 2-(hydroxy(phenyl)methyl)-3-iodobut-2-enoate (**30**): From benzaldehyde and ethyl but-2-ynoate as described in the general method (see above), except this reaction was reacted overnight at reflux dichloromethane. Colorless oil (65%). IR (thin film) ν 3445, 3039, 1715 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (m, 5 H), 5.78 (d, *J* = 4.6, 1 H) 4.20 (q, *J* = 7.2 Hz, 2 H), 3.21 (d, *J* = 5.4, 1 OH), 2.75(s, 3H), 1.16 (t, 12.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 141.1, 139.8, 128.5, 128.1, 127.5, 124.5, 70.1, 61.2, 30.5, 13.6. HRMS (CI, CH_4) calcd for $C_{13}H_{15}IO_3$+ requires *m/z* 346.0066, found 346.0059.

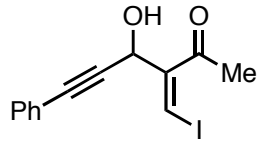


(*Z*)-ethyl 2-(hydroxy(phenyl)methyl)-3-iodo-3-phenylacrylate (**31**): From benzaldehyde and ethyl 3-phenylpropiolate as described in the general method (see above) except this reaction was reacted overnight at reflux dichloromethane. Colorless oil (71%). A sample suitable for X-Ray was obtained from a slow evaporation of a biphasic mixture of dichloromethane / hexanes. IR (thin film) ν 3439, 3042, 1721 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 4 H), 7.28 (m, 6 H), 5.28 (d, *J* = 4.6, 1 H) 4.07 (q, *J* = 7.2 Hz, 2 H), 3.41 (d, *J* = 5.4, 1 OH), 1.02 (t, 12.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 143.2, 142.5, 141.14, 128.4, 128.1, 125.8, 125.5, 104.1, 81.7, 72.1,

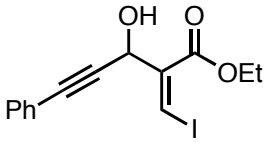
61.5, 31.2, 13.8. HRMS (CI, CH_4) calcd for $C_{18}H_{17}IO_3$+ requires *m/z* 408.0222, found 408.0225.



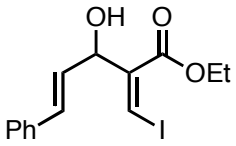
X-Ray Crystal Structure Data for (*Z*)-ethyl 2-(hydroxy(phenyl)methyl)-3-iodo-3-phenylacrylate (**31**): $C_{18}H_{17}IO_3$, M = 408.22, colorless plate, 0.30 x 0.20 x 0.20 mm^3, monoclinic, space group *C2/c*, a = 20.654(10), b = 7.358(4), c = 22.576(6) Å, b = 98.350(6)°, V = 3395(3) $Å^3$, Z = 8, D_c = 1.598 g/cm^3, F_{000} = 1616, MWPC area detector, CuKa radiation, l = 0.71069 Å, T = 110(2)K, $2q_{max}$ = 120.0º, 14935 reflections collected, 2902 unique (R_{int} = 0.0278). Final *GooF* = 1.002, *R1* = 0.0405, *wR2* = 0.0797, *R* indices based on 1451 reflections with I >2sigma(I) (refinement on F^2), 200 parameters, 1 restraint. Lp and absorption corrections applied, m = 1.896 mm^{-1}. Absolute structure parameter = -0.6(7) (Flack, H. D. *Acta Cryst*. **1983**, *A39*, 876-881). Displacement ellipsoid plot (50% probability) of **31** is shown above with all atoms numbered. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (deg): I(1)-C(1) 2.131(5), C(1)-C(2) 1.481(6), C(1)-C(8) 1.324(6), C(8)-C(9) 1.531(6), C(8)-C(16) 1.496(6), C(8)-C(1)-C(2) 126.8(4), C(8)-C(1)-I(1) 120.3(3), C(2)-C(1)-I(1) 112.9(3), C(9)-C(8)-C(1) 123.4(4), C(16)-C(8)-C(1) 121.5(4), C(9)-C(8)-C(16) 115.1(4).



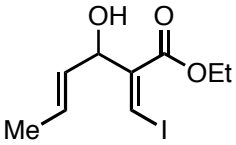
(*Z*)-4-hydroxy-3-(iodomethylene)-6-phenylhex-5-yn-2-one (**32**): From 3-phenylprop-2-ynal (**E-6**) and but-3-yn-2-one as described in the general method (see above). Colorless oil (88%). IR (thin film) ν 3433, 3061, 2938, 1705 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.1 Hz, 2H), 7.35 (m, 3H), 7.30 (d, *J* = 1.2 Hz, 1H), 5.40 (s, 1 H), 2.82 (bs, 1 OH), 2.62 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.8, 150.4, 131.9, 129.2, 128.5, 121.7, 88.5, 85.4, 82.9, 65.8, 30.4. HRMS (CI, CH_4) calcd for $C_{13}H_{11}IO_2$+ requires *m/z* 325.9804, found 325.9809.



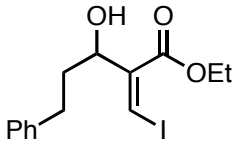
(*Z*)-ethyl 3-hydroxy-2-(iodomethylene)-5-phenylpent-4-ynoate (**33**): From 3-phenylprop-2-ynal (**E-6**) and ethyl propiolate as described in the general method (see above). Colorless oil (85%). IR (thin film) ν 3444, 3037, 1719 cm^{-1}. $^{1}HNMR$ (300 MHz, $CDCl_3$): δ 7.72 (d, *J* = 1.2 Hz, 1H), 7.45 (m, 2H), 7.34 (m, 3H), 5.44 (d, *J* = 1.2 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2 H), 3.12 (d, *J* = 6.6 Hz, 1 OH), 1.40 (t, 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 141.7, 131.7, 128.5, 128.3, 121.7, 89.6, 87.8, 85.5, 65.2, 61.8, 14.1. HRMS (CI, CH_4) calcd for $C_{14}H_{13}IO_3$+ requires *m/z* 355.9909, found 355.9905.



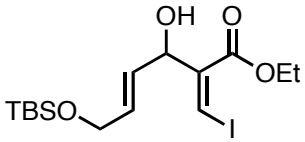
(2Z,4E)-ethyl 3-hydroxy-2-(iodomethylene)-5-phenylpent-4-enoate (**34**): From *trans*-cinnamaldehyde and ethyl propiolate as described in the general method (see above). Light yellow oil (91%). IR (thin film) ν 3443, 3070, 2934, 1719 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 6 H), 6.66 (dd, *J* = 1.2, 14.7 Hz, 1 H), 6.21 (dd, *J* = 6.6, 9.3 Hz, 1 H), 5.13 (d, *J* = 5.4 Hz, 1 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 2.95 (bs, 1 OH), 1.35 (t, 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 144.6, 135.9, 132.3, 128.6, 128.1, 127.7, 126.6, 86.5, 74.9, 61.6, 14.1. HRMS (ESI) calcd for $C_{14}H_{15}IO_3$ - H requires *m/z* 356.9982, found 356.9981.



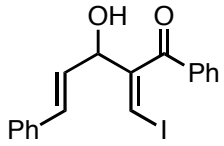
(2Z,4E)-ethyl 3-hydroxy-2-(iodomethylene)hex-4-enoate (**35**): From *trans*-crotonaldehyde and ethyl propiolate as described in the general method (see above). Colorless oil (86%). IR (thin film) ν 3434, 3094, 2924, 2850, 1718 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, *J* = 3.3 Hz, 1 H), 5.76 (m, 1 H), 5.48 (m, 1 H), 4.86 (d, *J* = 5.1 Hz, 1 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 2.62 (bs, 1 OH), 1.70 (d, *J* = 6.6 Hz, 3 H), 1.35 (t, 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 145.3, 129.8, 129.5, 85.3, 74.9, 61.4, 17.7, 14.1. HRMS (ESI) calcd for $C_9H_{13}IO_3$ - H requires *m/z* 294.9826, found 294.9822.



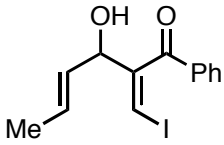
(*Z*)-ethyl 3-hydroxy-2-(iodomethylene)-5-phenylpentanoate (**36**): From 3-phenylpropanal and ethyl propiolate as described in the general method (see above). Light yellow oil (85%). IR (thin film) ν 3441, 3059, 2934, 1719 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 2 H), 7.18 (m, 3 H), 7.09 (s, 1 H), 4.39 (t, *J* = 5.4 Hz, 1 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 2.73, (m, 2 H), 2.65 (bs, 1 OH), 1.94 (q, *J* = 7.3 Hz, 2 H), 1.34 (t, 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 146.6, 141.3, 128.6, 128.5, 126.1, 84.8, 74.3, 61.6, 37.6, 31.8, 14.2. HRMS (ESI) calcd for $C_{14}H_{17}IO_3$ - H requires *m/z* 359.0139, found 359.0138.



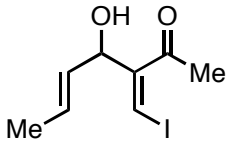
(2*Z*,4*E*)-ethyl 3-hydroxy-2-(iodomethylene)hex-4-enoate (**37**): From (*E*)-4-(*tert*-butyl-dimethylsilyloxy)but-2-enal (**E-10**) and ethyl propiolate as described in the general method (see above). Light yellow oil (89%). IR (thin film) ν 3443, 3094, 2925, 2848, 1719 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, *J* = 1.2 Hz, 1 H), 5.81 (m, 2 H), 4.97 (s, 1 H), 4.28 (q, *J* = 7.6 Hz, 2 H), 4.16 (m, 2 H), 2.71 (bs, 1 OH), 1.34 (t, 7.2 Hz, 3H), 0.89 (s, 9 H), 0.05 (s, 6 H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 144.9, 132.7, 128.3, 86.2, 74.5, 62.8, 61.6, 26.0, 18.5, 14.3, -5.2. HRMS (ESI) calcd for $C_{15}H_{27}IO_4Si$ - H requires *m/z* 425.0640, found 425.0638.



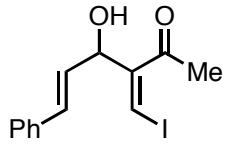
(2*Z*,4*E*)-3-hydroxy-2-(iodomethylene)-1,5-diphenylpent-4-en-1-one (**38**): From *trans*-cinnamaldehyde and 1-phenylprop-2-yn-1-one (**E-4**) as described in the general method (see above). Light yellow solid (96%). IR (thin film) ν 3433, 3060, 2938, 1703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.2 Hz, 2 H), 7.59 (m, 1 H), 7.48 (m, 3 H), 7.29 (m, 4 H), 6.92 (d, *J* = 0.9 Hz, 1 H), 6.66 (d, *J* = 15.9 Hz, 1 H), 6.24 (dd, *J* = 7.2, 8.7 Hz, 1 H), 5.18 (s, 1 H), 2.77 (bs, 1 OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.8, 152.5, 135.8, 134.5, 133.9, 132.8, 129.9, 129.0, 128.5, 128.1, 127.2, 126.6, 79.8, 76.0. HRMS (ESI) calcd for $C_{18}H_{15}IO_2$ - H requires *m/z* 389.0033, found 389.0037.



(2*Z*,4*E*)-3-hydroxy-2-(iodomethylene)-1-phenylhex-4-en-1-one (**39**): From *trans*-crotonaldehyde and 1-phenylprop-2-yn-1-one (**E-4**) as described in the general method (see above). Light yellow solid (93%). IR (thin film) ν 3425, 3065, 2932, 1702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, *J* = 5.7 Hz, 2 H), 7.63 (t, *J* = 4.9 Hz, 1 H), 7.48 (t, *J* = 7.2 Hz, 2 H), 6.83 (d, *J* = 1.5 Hz, 1 H), 5.76 (m, 1 H), 5.55 (dd, *J* = 8.7, 6.3 Hz, 1 H), 4.93 (d, *J* = 6.9 Hz, 1 H), 2.27 (bs, 1 OH), 1.66 (d, *J* = 6.3 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.2, 152.8, 133.9, 130.3, 129.9, 129.5, 128.8, 83.5, 79.0, 76.1, 17.6. HRMS (ESI) calcd for $C1_3H_{13}IO_2$ - H requires *m/z* 326.9876, found 326.9873.



(3*Z*,5*E*)-4-hydroxy-3-(iodomethylene)hept-5-en-2-one (**40**): From *trans*-crotonaldehyde and but-3-yn-2-one as described in the general method (see above). Light yellow solid (92%). IR (thin film) ν 3423, 3060, 2938, 1700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (d, *J* = 1.2 Hz, 1 H), 5.78 (m, 1 H), 5.50 (m, 1 H), 4.78 (d, *J* = 6.8 Hz, 1 H), 2.46 (s, 3 H), 2.35 (d, *J* = 6.3 Hz, 1 OH), 1.73 (d, *J* = 4.4 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.3, 154.4, 130.3, 129.7, 78.5, 75.7, 30.4, 17.8. HRMS (ESI) calcd for $C_8H_{11}IO_2$ - H requires *m/z* 264.9720, found 264.9719.

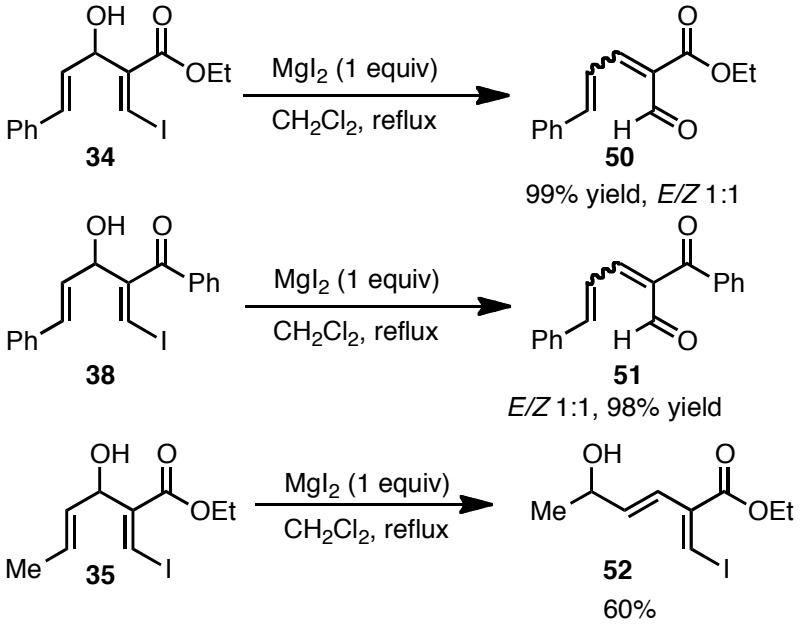


(3*Z*,5*E*)-4-hydroxy-3-(iodomethylene)-6-phenylhex-5-en-2-one (**41**): From *trans*-cinnamaldehyde and but-3-yn-2-one as described in the general method (see above). Light yellow solid (90%). IR (thin film) ν 3421, 3064, 2936, 1701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 5 H), 6.87 (d, *J* = 1.2 Hz, 1 H), 6.68 (d, *J* = 15.9 Hz, 1 H), 6.21 (dd, *J* = 7.1, 8.9 Hz, 1 H), 5.13 (t, *J* = 7.2 Hz, 1 H), 2.54 (s, 3 H), 1.62 (s, 1 OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.1, 153.8, 135.9, 132.9, 128.8, 128.4, 127.5, 126.8, 79.9, 75.8, 30.5. HRMS (ESI) calcd for $C_{13}H_{13}IO_2$ - H requires *m/z* 326.9876, found 326.9879.

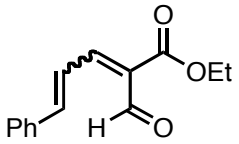
1.3.7 1,3-Allylic Transposition of β-Iodo BH Adducts

A β-iodo Baylis-Hillman adduct **34, 35** or **38** (0.1 mmol; 1.0 equiv) was added to a solution of MgI_2 (28 mg, 0.1 mmol; 1.0 equiv) in dichloromethane (5 mL) at room temperature under argon. The mixture was then stirred for 6 h at reflux dichloromethane. Then, the reaction was quenched with saturated ammonium chloride (5 mL). The reaction mixture was diluted with Et_2O (20 mL), washed with distilled water (10 mL) and brine (10 mL), dried over sodium sulfate, and concentrated under reduce pressure. The crude products were purified by flash silica gel column chromatography using (0-10% EtOAc-Hexanes) as the eluents to afford the pure adducts **50-52**.

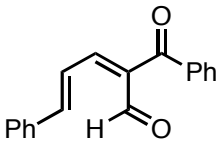
Scheme 1.22 1,3-Allylic transposition adducts and yields.



Procedures and characterization data of 1,3 allylic transposition adducts: Compounds **50–52** are new compounds. Full-tabulated data is available below for all compounds.

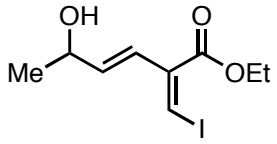


(4*E*)-ethyl 2-formyl-5-phenylpenta-2,4-dienoate (**50**): From adduct **34** as described in the general procedure (see above). Light yellow oil (99%). 1:1 mixture of isomers: IR (thin film) ν 3076, 3026, 2871, 2789, 1692 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.21 (d, *J* = 3.0 Hz, (*Z*) *isomer*, 1 CHO), 9.95 (s, (*E*) *isomer*, 1 CHO), 8.30 (dd, *J* = 9.0, 3.3 Hz, 1 H), 7.95 (dd, *J* = 12.0, 3.6 Hz, 1 H), 7.64 (dd, *J* = 1.8, 10.9 Hz, 1 H), 7.56 (m, 5 H), 7.37 (m, 6 H), 7.27 (s, 1 H), 7.21 (s, 1 H), 4.36 (m, 4 H), 1.38 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.4, 189.7, 166.1, 164.9, 151.1, 150.8, 149.9, 135.3, 135.2, 130.7, 130.6, 129.1, 128.9, 128.8, 128.5, 128.3, 126.3, 124.4, 124.0, 123.6, 61.0, 60.9, 14.2. HRMS (ESI) calcd for $C_{14}H_{14}O_3$ + Li requires *m/z* 237.1103, found 237.1104.



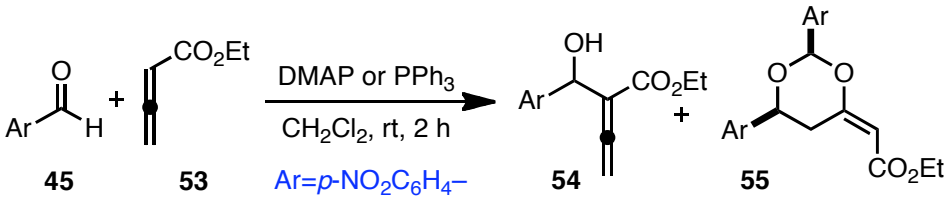
(2*E*,4*E*)-5-phenyl-2-(phenylcarbonyl)penta-2,4-dienal (**51**): From adduct **38** as described in the general procedure (see above). Light yellow oil (98%). 5:1 mixture of isomers: IR (thin film) ν 3066, 3018, 2875, 2783, 1731, 1692 cm^{-1}. (*E*) *isomer*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (s, (*E*) *isomer*, 1 CHO), 7.90 (m, 2 H), 7.61 (tt, *J* = 1.2, 7.5 Hz, 1 H), 7.50 (m, 3H), 7.42 (m, 2H), 7.33 (m, 3H), 7.19 (d, *J* = 15.3 Hz, 1 H), 6.99 (dd,

J = 11.4, 3.9 Hz, 1 H) . ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.5, 190.4, 150.8, 146.4, 139.4, 136.7, 135.1, 134.0, 130.4, 129.5, 128.9, 128.8, 128.0, 123.1. HRMS (ESI) calcd for $C_{18}H_{14}O_2$ + Li requires *m/z* 269.1154, found 269.1149.



(2*Z*,3*E*)-ethyl 5-hydroxy-2-(iodomethylene)hex-3-enoate (**52**): From adduct **35** as described in the general procedure (see above). Light yellow oil (60%). IR (thin film) ν 3434, 3094, 2924, 2850, 1719 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (s, 1 H), 6.60 (dd, *J* = 5.7, 10.2 Hz, 1 H), 6.40 (d, *J* = 16.0 Hz, 1 H), 4.45 (quintet, *J* = 5.3 Hz, 1 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 1.56 (bs, 1 OH), 1.33 (t, 7.2 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3 H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1, 142.3, 138.7, 125.2, 97.7, 68.7, 61.4, 23.1, 14.1. HRMS (ESI) calcd for $C_9H_{13}IO_3$ - H requires *m/z* 294.9826, found 294.9821 and for $C_9H_{13}IO_3$ + H requires *m/z* 296.9988, found 296.9987.

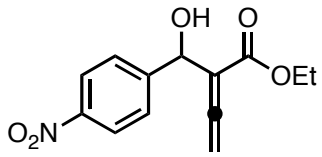
1.3.8 Synthesis of Abnormal BH Adducts



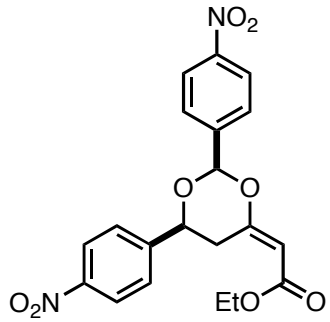
To an 8 mL glass vial containing a stir bar was added the nucleophile (0.018 mmol, 0.05 equiv) and *p*-nitrobenzaldehyde (**45**) (0.367 mmol, 1.0 equiv), then the vial was capped with a phenolic cap equipped with a teflon/silicone septa. The vial was filled

and purged with argon. A solution of ethyl buta-2,3-dienoate (**53**) (0.477 mmol, 1.3 equiv,) in dry dichloromethane (4 mL) was added via syringe under argon. The mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduce pressure. Finally, the residue was loaded to a flash silica gel column chromatography and purified using (0-10% EtOAc-Hexanes) as the eluents to afford the pure adducts **54-55**.

Procedures and characterization data of adducts: Full-tabulated data is available below for compounds **54** and **55**.



Ethyl 2-(hydroxy(4-nitrophenyl)methyl)buta-2,3-dienoate (**54**): From *p*-nitro-benzaldehyde, ethyl buta-2,3-dienoate and DMAP as described in the general method (see above). Light yellow oil (99%). IR (thin film) ν 3465, 2917, 1704 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 1.8, 7.5 Hz, 2 H), 7.50 (dd, *J* = 1.5, 9.0 Hz, 2 H), 5.60 (d, *J* = 6.0 Hz, 1 H), 5.12 (d, *J* = 2.7 Hz, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 3.66 (d, *J* = 2.7 Hz, 1 OH), 1.21 (t, 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.9, 166.6, 148.4, 127.2, 127.1, 123.4, 102.1, 81.6, 71.3, 61.8, 14.1. HRMS (EI) calcd for $C_{13}H_{13}IO_5$ requires *m/z* 263.0794, found 263.0796. HPLC values, with a Chiralcel OJ-H column (hexane/*i*-PrOH = 85/15), 1.0 mL/min, 254 nm, t_1= 14.60 min, t_2= 16.13 min.



(*E*)-ethyl 2-(2,6-bis(4-nitrophenyl)-1,3-dioxan-4-ylidene) ethanoate (**55**): From *p*-nitrobenzaldehyde, ethyl buta-2,3-dienoate and PPh_3 as described in the general method (see above). Light yellow solid (99%). IR (thin film) ν 3070, 2917, 1709 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.31 (m, 4H), 7.85 (d, *J* = 7.5 Hz, 2 H), 7.61 (d, *J* = 7.2 Hz, 2 H), 6.18 (s, 1H), 5.22 (m, 2 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 2.65 (m, 2 H), 1.21 (t, 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9, 164.1, 160.5, 148.1, 146.5, 141.8, 128.1, 127.7, 123.8, 123.1, 104.1, 101.6, 98.1, 59.8, 36.5, 14.1. HRMS (EI) calcd for $C_{13}H_{13}IO_5$ requires *m/z* 263.0794, found 263.0796.

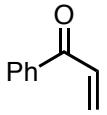
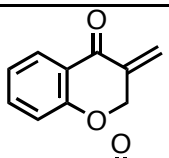
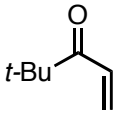
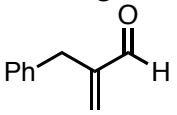
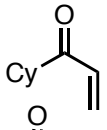
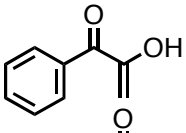
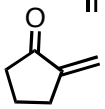
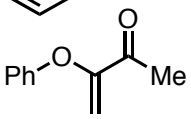
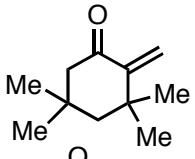
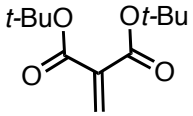
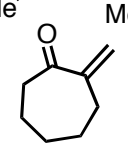
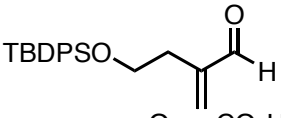
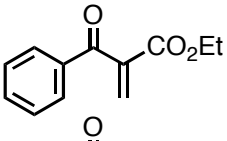
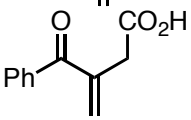
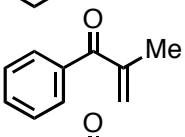
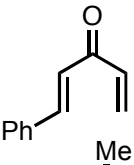
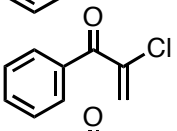
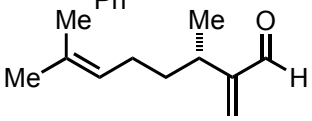
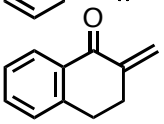
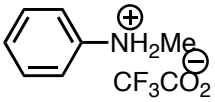
1.3.9 Synthesis of Ammonium Salts (VII-XIV)

To a stirred mixture of secondary amine (100 mmol) in Et_2O (100 mL) at 0 °C is added dropwise the acidic counter-anion (100 mmol). The reaction mixture is stirred at 0 °C for 5 min. The new-formed crystals are filtered and washed with Et_2O (20 mL), dried under vacuum to afford the pure white crystalline salt.

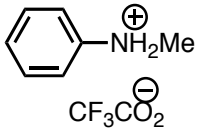
1.3.10 General Procedure for the α-Methylenation

To a mixture of a carbonyl compound (1.0 mmol) and paraformaldehyde (2.0 mmol, 200 mol %) in dry THF (1.0 mL) is added the catalyst (1.0 mmol, 100 mol %) and trifluoroacetic acid (0.1 mmol, 10 mol %). The reaction mixture is stirred at reflux for 2 h, the mixture will become clear, then the reaction mixture is cooled down to room temperature and a second addition of paraformaldehyde (2.0 mmol, 200 mol %) is performed. Next, the reaction mixture is stirred at reflux for an additional 6 h open to the atmosphere. The reaction mixture is cooled down and the solvent is removed under reduce pressure, dissolved with Et_2O and washed with 1N HCl, 1N NaOH, and brine. The solution mixture is dried (Na_2SO_4) and concentrated under vacuum. The crude product is purified by silica gel column chromatography using 5% (Et_2O–Hexanes or EtOAc–Hexanes) as the eluents (Table 1.21).

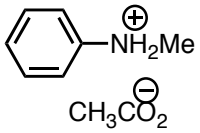
Table 1.21 References to known compounds (α-methylenation).[83,91,110-123]

Adduct (#)	Product	Reference	Adduct (#)	Product	Reference
57		83	**74**		123
58		91	**67**		115
59		110	**75**		116
60		111	**76**		117
61		112	**70**		119
62		91	**68**		115
63		113	**72**		118
64		114	**73**		121
65		114	**69**		115
66		122	**VII**		120

1.3.11 Characterization of Ammonium Salts VII-XIV

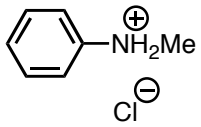


***N*-methylbenzenaminium 2,2,2-trifluoroacetate** (**VII**): To a stirred mixture of *N*-methyl aniline (100 mmol, 10.7 g) in Et_2O (100 mL) at 0 °C was added trifluoroacetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for an additional 5 min. The new-formed crystals were filtered and washed with Et_2O (20 mL), dried under vacuum to afford pure compound **VII** (21.04 g, 96%) as white solid; IR (thin film) ν 3418, 3002, 2717, 2496, 1676, 1601, 1204 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.02 (bs, 2NH), 7.46–7.38 (m, 5H), 2.98 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.6 (q, J = 35 Hz), 137.9, 130.2, 128.9, 121.8, 116.3 (q, J = 288 Hz), 37.6. HRMS (ESI+) calcd for $C_7H_{10}N$ requires *m/z* 108.0808, found 108.0812. HRMS (ESI–) calcd for $C_2F_3O_2$ requires *m/z* 112.9850, found 112.9853.

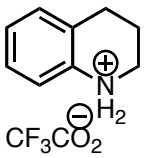


***N*-methylbenzenaminium acetate** (**VIII**): To a stirred neat freshly distilled *N*-methyl aniline (100 mmol, 10.7 g) at 0 °C was added freshly distilled acetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for an additional 5 min to afford pure compound **VIII** (21.8 g, 99%) as colorless oil; IR (thin film) ν 3413, 3051, 2907, 2814, 1713, 1606, 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.23 (t, *J* = 8.2 Hz, 2H), 6.99 (bs, 2NH), 6.76 (t, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 2H), 2.85 (s, 3H), 2.11 (s,

3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.7, 149.0, 129.1, 117.5, 112.7, 30.7, 20.8. HRMS (ESI+) calcd for $C_7H_{10}N$ requires *m/z* 108.0808, found 108.0812. HRMS (ESI–) calcd for $C_2H_3O_2$ requires *m/z* 59.0139, found 59.0138.

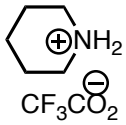


***N*-methylbenzenaminium chloride** (**IX**)[.] To a stirred mixture of *N*-methyl aniline (100 mmol, 10.7 g) in Et_2O (100 mL) at 0 °C was bubbled excess hydrochloric acid gas (from ammonium chloride and sulfuric acid) for 10 min. The reaction mixture was stirred at 0 °C for an additional 5 min. The new-formed crystals were filtered and washed with Et_2O (20 mL), dried under vacuum to afford pure compound **IX** (8.54 g, 64%) as colorless crystals; IR (thin film) ν 3417, 2689, 2458, 1600, 1497 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.23 (bs, 2NH), 7.50 (d, *J* = 5.5 Hz 2H), 7.26 (m, 3H), 2.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.8, 129.8, 129.2, 122.3, 37.7. HRMS (ESI+) calcd for $C_7H_{10}N$–Cl requires *m/z* 108.0808, found 108.0812.

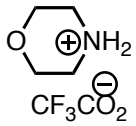


1,2,3,4-tetrahydroquinolinium 2,2,2-trifluoroacetate (**X**): To a stirred mixture of 1,2,3,4-tetrahydroquinoline (100 mmol, 13.3 g) in Et_2O (100 mL) at 0 °C was added trifluoroacetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for and additional 5 min. The new-formed crystals were filtered and washed with Et_2O (20 mL), dried under vacuum to afford pure compound **X** (22.3 g, 91%) as white

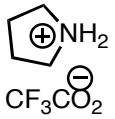
solid; IR (thin film) ν 3424, 2945, 2750, 1503, 1663, 1190 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.05 (bs, 2NH), 7.36-7.19 (m, 4H,), 3.48 (t, *J* = 5.5 Hz, 2H), 2.91 (t, *J* = 6.7 Hz, 2H), 2.18 (q, *J* = 5.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.6 (q, *J* = 37 Hz), 131.3, 130.4, 130.3, 128.2, 127.4, 122.8, 116.4 (q, *J* = 288 Hz), 42.3, 25.0, 19.6. HRMS (ESI+) calcd for $C_9H_{12}N$ requires *m/z* 134.0964, found 134.0969. HRMS (ESI–) calcd for $C_2F_3O_2$ requires *m/z* 112.9850, found 112.9853.



Piperidinium 2,2,2-trifluoroacetate (**XI**): To a stirred mixture of piperidine (100 mmol, 8.5 g) in Et_2O (100 mL) at 0 °C was added trifluoroacetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for an additional 5 min. The new-formed crystals were filtered and washed with Et_2O (20 mL), dried under vacuum to afford pure compound **XI** (16.15 g, 82%) as white solid; IR (thin film) ν 3430, 2966, 2867, 2550, 1697, 1203 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.03 (bs, 2NH), 3.03 (m, 4H), 1.76 (m, 4H), 1.60 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.2 (q, *J* = 35 Hz), 116.5 (q, *J* = 293 Hz), 44.4, 22.4, 22.2. HRMS (ESI+) calcd for $C_5H_{12}N$ requires *m/z* 86.0964, found 86.0960. HRMS (ESI–) calcd for $C_2F_3O_2$ requires *m/z* 112.9850, found 112.9853.

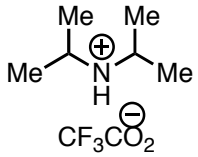


Morpholin-4-ium 2,2,2-trifluoroacetate (**XII**): To a stirred mixture of morpholine (100 mmol, 8.7 g) in Et_2O (100 mL) at 0 °C was added trifluoroacetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for an additional 5 min. The new-formed crystals were filtered and washed with Et_2O (20 mL), dried under vacuum to afford pure compound **XII** (16.71 g, 84%) as white solid; IR (thin film) ν 3426, 3004, 2872, 2513, 1681, 1204 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.39 (bs, 2NH), 3.89 (m, 4H), 3.16 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3 (q, J = 35 Hz), 116.5 (q, J = 290 Hz), 63.6, 43.2. HRMS (ESI+) calcd for $C_4H_{10}NO$ requires *m/z* 88.0757, found 88.0752. HRMS (ESI–) calcd for $C_2F_3O_2$ requires *m/z* 112.9850, found 112.9853.



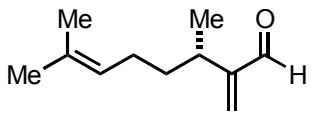
Pyrrolidinium 2,2,2-trifluoroacetate (**XIII**): To a stirred mixture of pyrrolidine (100 mmol, 7.1 g) in Et_2O (100 mL) at 0 °C was added trifluoroacetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for an additional 5 min. The new-formed crystals were filtered and washed with Et_2O (20 mL), dried under vacuum to afford pure compound **XIII** (17.01 g, 93%) as white solid; IR (thin film) ν 3413, 2994, 2785, 2491, 1676, 1202 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.57 (bs, 2 NH), 3.20 (t, J = 6.15 Hz, 4 H), 1.97 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1 (q, J = 34.4 Hz), 116.5 (q, J = 292 Hz), 44.9, 24.1. HRMS (ESI+) calcd for $C_4H_{10}N$ requires *m/z*

72.0808, found 72.0809. HRMS (ESI–) calcd for $C_2F_3O_2$ requires *m/z* 112.9850, found 112.9853.



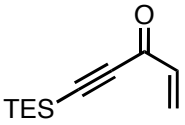
Diisopropylammonium 2,2,2-trifluoroacetate (**XIV**): To a stirred mixture of diisopropylamine (100 mmol, 10.1 g) in Et_2O (100 mL) at 0 °C was added trifluoroacetic acid dropwise (100 mmol, 11.2 g). The reaction mixture was stirred at 0 °C for an additional 5 min. The new-formed crystals were filtered and washed with Et_2O (20 mL), dried under vacuum to afford pure compound **XIV** (20.23, 95%) as white solid; IR (thin film) ν 3436, 3048, 2794, 2503, 1675, 1601, 1190 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.91 (bs, 2NH), 3.35 (h, *J* = 6.5 Hz, 2H), 1.31 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.6 (q, *J* = 35.5 Hz), 116.5 (q, *J* = 288 Hz), 46.8, 18.7. HRMS (ESI+) calcd for $C_6H_{16}N$ requires *m/z* 102.1283, found 102.1286. HRMS (ESI–) calcd for $C_2F_3O_2$ requires *m/z* 112.9850, found 112.9853.

1.3.12 Characterization of the Unknown Adducts 69 and 71



(*S*)-3,7-Dimethyl-2-methylene-6-octanal (**69**). The reaction was carried out following the general procedure using (*S*)-citronellal to yield 153 mg (92%) of **69** as colorless oil.

Lit. $[\alpha]^{20}_{D}$ = +5.2 (*c* = 13.4 in $CHCl_3$).[115] Obtained $[\alpha]^{20}_{D}$ = +5.35 (*c* = 1.00 in CHCl3); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.53 (s, 1H); 6.22 (s, 1H); 5.98 (s, 1H); 5.07 (tt, 1H, *J* = 1.2, 7.2 Hz); 2.71 (sextet, 1H, *J* = 6.8 Hz); 1.93 (m, 2H); 1.66 (s, 3H); 1.56 (s, 3H); 1.51 (m, 1H); 1.37 (m, 1H) 1.06 (d, 3H, *J* = 6.8 Hz) ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.6, 155.5, 132.9, 131.6, 124.1, 35.5, 30.9, 25.7, 25.6, 19.5, 17.6.



5-(triethylsilyl)pent-1-en-4-yn-3-one (**71**): To a mixture of a 4-(triethylsilyl)but-3-yn-2one (58 mg, 0.313 mmol) and paraformaldehyde (17 mg, 0.626 mmol) in dry THF (3 mL) was added salt **XIV** (68 mg, 0.313 mmol) and *i*-$PrNH_2$ (89 μL, 0.626 mmol) at room temperature. The reaction mixture was stirred at reflux until completion (2 h). Then, the reaction mixture was cooled down to room temperature and the solvent was removed under reduce pressure. The crude mixture was purified by silica gel column chromatography using 10% (EtOAc–Hexanes) as the eluent, to afford pure compound **71** (38 mg, 62% yield) as colorless oil; IR (thin film) ν 2958, 2877, 1655, 1612, 1275, 1243, 991, 819, 729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.62 (dd, *J* = 1.25, 17.4 Hz, 1H), 6.41 (dd, *J* = 1.03, 17.4 Hz, 1H), 6.22 (dd, *J* = 1.24, 10.3 Hz, 1H), 1.05 (t, *J* = 8.33 Hz, 9H), 0.72 (q, *J* = 8.03 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.6, 137.9, 133.9, 100.9, 97.5, 7.3, 3.5. HRMS (ESI+) calcd for $C_{11}H_{19}OSi$ requires *m/z* 195.1205, found 195.1202.

CHAPTER II

CHIRAL NICKEL AND PALLADIUM NCN-PINCER COMPLEXES AND THEIR APPLICATION IN CROSS–COUPLING

2.1 Introduction and Background

The development of chiral Lewis acid catalysts for the formation of carbon–carbon (C–C) bonds is currently a challenging, but yet attractive endeavor in organic chemistry.[124,125] Chelating aryl ligands have been utilized on metal centers that are catalytically active in a variety of C–C and C-X bond forming reactions.[124,126] One such class of chelating ligands is the phebox ligand framework.[127] Phebox ligands have three donor sites, one central C and two flanking N-atoms in fixed positions, making them so-called "NCN-pincer" ligands. The chelating sites are bonded to an aryl ring by one sp^2 carbon and two sp^2 nitrogen centers (Figure 2.1).

Figure 2.1 General structure of an "NCN-pincer" ligand (**A**) and an M(NCN)-pincer complex (**B**).

This arrangement results in binding to metal centers that are predicted to be less flexible than other aryldiamine ligands.[128,129] Another interesting feature of this class of ligands is the ease with which a number of chiral analogues can be synthesized from readily available homochiral amino alcohols.[124,130] Organometallic pincer complexes of

the general structure **B** are multipurpose, often air-stable compounds that have attracted interest in catalysis.[131] These pincer ligands can coordinate a variety of transition metals, including Ni,[132,133] Pd,[126,134-136] Pt,[132,135,137] and Rh,[124,130] to form complexes with C_2-symmetry. The modular nature of these structures allow for straightforward modification of the activity of the metal center via steric and electronic effects. For example, metal complexes of these ligands can be transformed into cationic complexes for use in Lewis acid catalyzed reactions.[127,132]

Shortly after the first report of the original pincer complexes in 1970s by Shaw[138] and van Koten,[139] a large number of different pincer complexes has been synthesized and studied in miscellaneous catalytic applications, specially on palladium catalysis.[140,141] The synthesis of palladium pincer complexes is sometimes considerated the limited factor for their application in catalysis due to proligands and complexes syntheses.

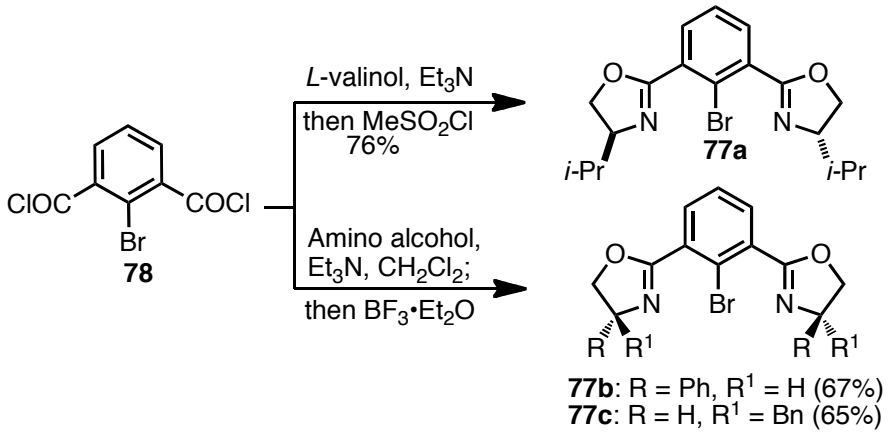
We were inspired to develop a straightforward synthesis of air and moisture stable chiral NCN pincer complexes using short and simple reaction conditions. Also, the complexation with Pd(II) and Ni(II) to form NCN-pincer complexes was explored. Finally, they were applied to the highly selective α-arylation of ketones with a variety of aryl bromides and other metal catalyzed C-C bond-forming reactions.

2.2 Results and Discussion

2.2.1 Pincer Ligand Syntheses

Thirteen chiral phebox ligands were synthesized using modified literature procedures.[124,130,142,143] All the chiral phebox ligands were derived from the aminoalcohols *L*-valine, *L*-phenylalanine and *D*-phenylglycine. The synthesis of [(*S,S*)-phebox-*i*-Pr]Br (**77a**) was performed via the combination of methodologies reported by Nishiyama[124] in 2001 and Kanazawa in 2006 (Scheme 2.1).[130] 2-Bromoisophthalic chloride (**78**) was obtained from 2-bromo-*m*-xylene using the reported protocol[124] and coupled to two equivalents of *L*-valinol to form a bisamide,[144] followed by $MeSO_2Cl/NEt_3$-promoted cyclization[130] to furnish the pincer ligand **77a** in 76% yield.

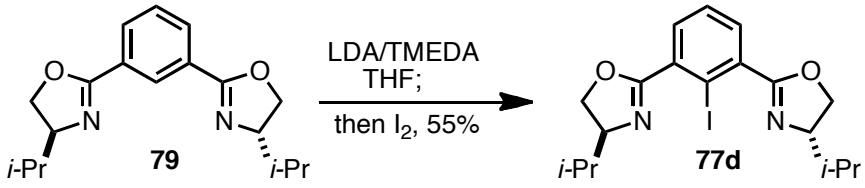
Scheme 2.1 Synthesis of [(*S,S*)-phebox-*i*-Pr]Br (**77a**)**,** [(*R,R*)-phebox-Ph]Br (**77b**) and [(*S,S*)-phebox-Bn]Br (**77c**).



Pincer ligands [(*R,R*)-phebox-Ph]Br (**77b)** and [(*S,S*)-phebox-Bn]Br (**77c**) were synthesized using a similar procedure from acyl chloride **78** and *D*-phenylgycinol[144] or *L*-phenylalaninol,[144] respectively, to give the corresponding bisamides, from which bis(oxazolines) were formed using methodology reported by Davies *et al*,[145] that utilizes BF_3•Et_2O to induce the cyclization to give **77b** and **77c**, in 67% and 65% yields, respectively (Scheme 2.1).

The pincer ligand **77d** was derived form commercially available isophthaloyl dichloride, which was transformed to the known pincer precursor (*S*,*S*)-phebox-*i*-Pr (**79**) using the known procedure.[130] The resulting pincer ligand **79** was halogenated using the methodology of Richards *et al*[132] by treatment of (*S*,*S*)-phebox-*i*-Pr (**79**) with LDA/TMEDA, followed by the addition of iodine to give [(*S*,*S*)-phebox-*i*-Pr]I (**77d**) (Scheme 2.2). Although bromine was initially employed as the electrophile in this halogenation, iodine resulted in a better yield for this transformation (11% vs 55%, respectively).

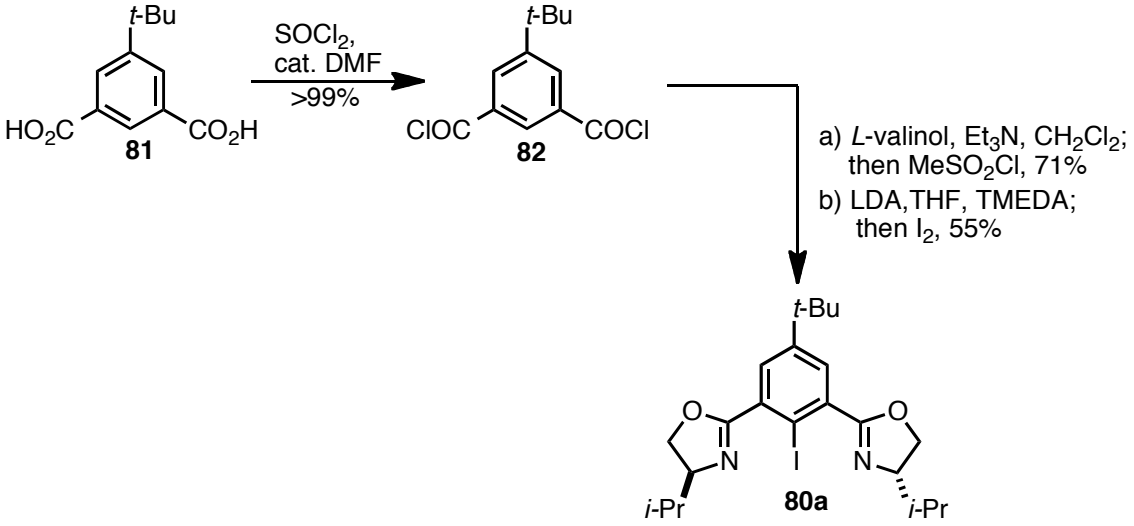
Scheme 2.2 Synthesis of [(*S,S*)-phebox-*i*-Pr]I (**77d**).

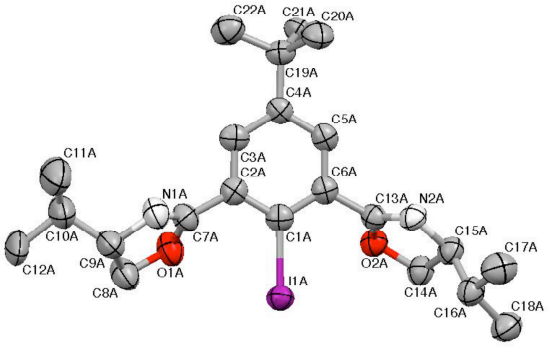


The pincer ligand **80a** was derived form commercially available 5-*tert*-butyl-isophthalic acid **81**, which was transformed to the acyl chloride **82** with $SOCl_2$[146] before condensation with *L*-valinol. The resulting diamide was cyclized employing $MeSO_2Cl$ to

afford the corresponding (*S*,*S*)-*t*-Buphebox-*i*-Pr **E-11** in 71% yield. Halogenation of the resulting bis(oxazoline) was again performed using the methodology of Richards[147] (LDA/TMEDA then I_2) to give [(*S*,*S*)-*t*-Bu-phebox-*i*-Pr]I (**80a**) in 55% yield (Scheme 2.3). A single crystal X-ray structure of **80a** was obtained to corroborate the identity of this pincer ligand (Figure 2.2).

Scheme 2.3 Synthesis of [(S,S)-phebox-*i*-Pr]I (**80a**).

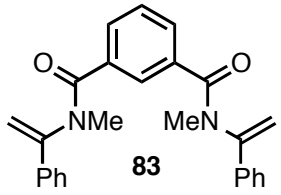




[*t*-BuPheBox*i*-Pr]I

Figure 2.2 X-Ray structure of [(S,S)-phebox-*i*-Pr]I (**80a**).

Unfortunately, synthesis of similar pincer ligands **80b** and **80c**, each containing acidic benzylic protons, could not incorporate the same final halogenation as used in the synthesis of **80a** because deprotonation and ring opening of the oxazolines afforded the undesired bis(enamine). Stark *et al* in 2003 reported a similar finding, where compound **83** was isolated from the corresponding bis(oxazoline) upon treatment with LDA/TMEDA, then iodomethane (Figure 2.3).[126]

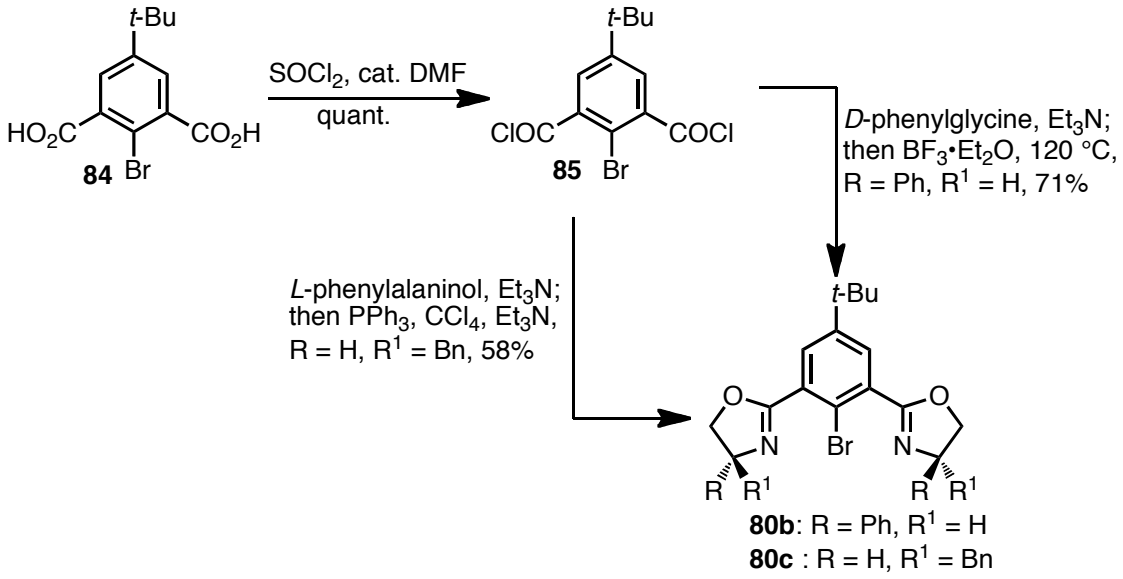


83

Figure 2.3 Undesired bis(enamine).

To avoid this problem, we incorporated the halogen at the beginning of the synthesis. We utilized the procedure of Field *et al*[148] to synthesize 2-bromo-5-*tert*-butyl-isophthalic acid (**84**) from 5-*tert*-butyl-m-xylene by bromination then oxidation (Scheme 2.4). A modified solvent system of 1:1 *t*-BuOH:H_2O was necessary for smooth oxidation of the intermediate 5-*tert*-butyl-2-bromo-*m*-xylene to **84.** Diacid **84** was then treated with $SOCl_2$ to obtain **85**, which was condensed independently with two β-amino alcohols (*L*-phenylalaninol and *D*-phenylgycinol), to give the corresponding bisamides. Finally, bis(oxazoline) formation to give **80b** in 71% yield was accomplished using a BF_3•Et_2O-promoted cyclization, whereas compound **80c** was most efficiently prepared by utilizing using PPh_3/CCl_4, following the procedure of Vorbrüggen, albeit in only 58% yield.[143]

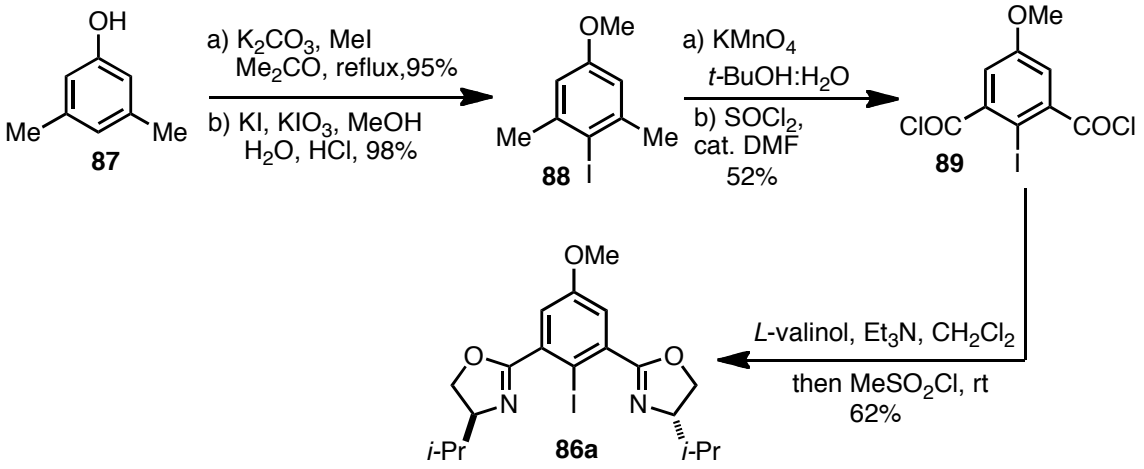
Scheme 2.4 Synthesis of [(*R,R*)-*t*-Buphebox-Ph]Br (**80b**) and [(*S,S*)-*t*-Buphebox-Bn]Br (**80c**).



The synthesis of monomethoxy ligand **86a** began with a modification of a U.S. patent procedure[149] used to synthesize 3,5-dimethyl-4-iodoanisole (**88**). This modification consisted of the inversion of the two reaction steps, to increase the overall yield from 11% to 93%. In our step one, the methylation of 3,5-dimethyl-phenol (**87**) using iodomethane was promoted by potassium carbonate in refluxed acetone to give 3,5-dimethyl-anisole in 95% yield. Treatment of the resulting anisole with potassium iodide and potassium iodate in acidic water gave **88** in 98% yield. The oxidation of the **88** and chlorination of the resultant isophthalic acid proceeded similarly to the procedures describe above to obtain **89** (Scheme 4). An important observation in the cyclization step to form **86a** from the uncylclized bis(amide) intermediate is that for compounds possessing a methoxy group in the aryl ring, BF_3•Et_2O was not tolerated. Demethylation of the phenylmethyl ethers occurs when the bis(amide) is heated in the

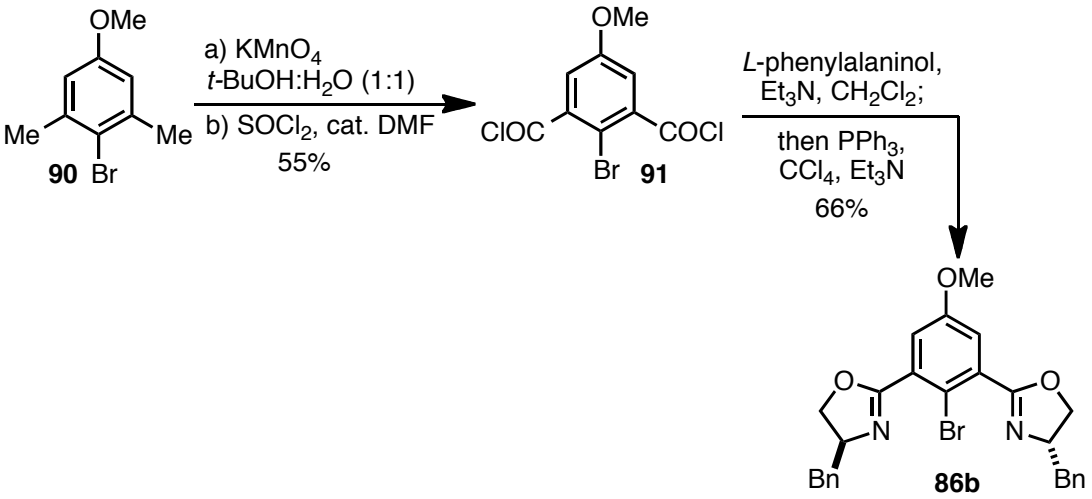
presence of BF_3•Et_2O. For this reason, it was necessary to cyclize using $MeSO_2Cl/Et_3N$, which provided **86a** in 62% yield.

Scheme 2.5 Synthesis of [(*S,S*)-MeO-phebox- *i*-Pr]I (**86a)**.



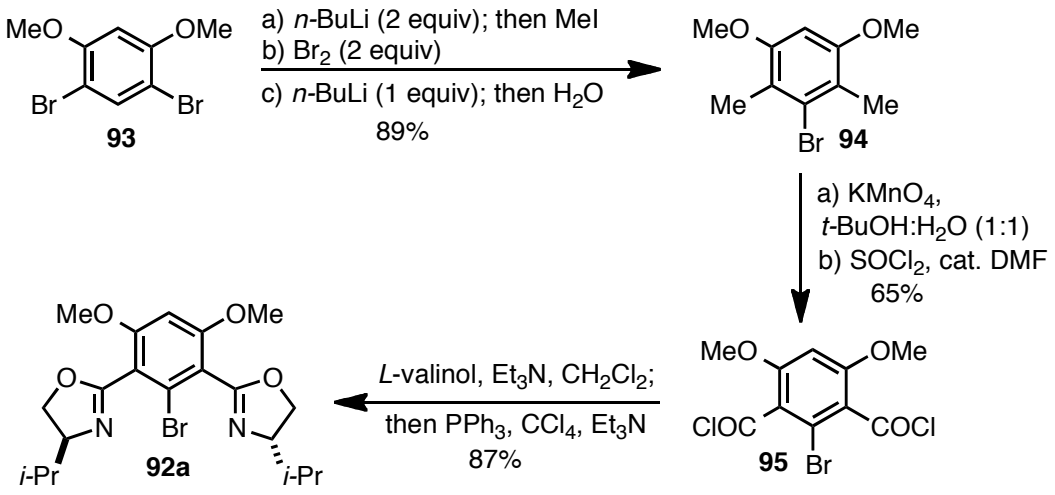
A method analogous to the synthesis of ligand **86a** was employed to synthesize **86b**. Bromination of 3,5-dimethylanisole gave **90** in 66% yield.[150] The oxidation of the **90** with $KMnO_4$ followed by chlorination of the resulting isophthalic acid with $SOCl_2$ gave bis(acyl chloride) **91** in 55% yield (Scheme 2.6). Condensation to provide the bis(amide) was uneventful. However, we again noted that BF_3•Et_2O was not tolerated for the cyclization of this oxygenated bis(amide). Unfortunately, treatment with $MeSO_2Cl/Et_3N$ was also unable to induce the desired cyclization to provide product **86b**. However, we were able to cyclize the bis(amide) using PPh_3/CCl_4, which furnished [(*S,S*)-MeO-phebox-Bn]Br (**86b**) in 62% yield (Scheme 2.6).[143]

Scheme 2.6 Synthesis of [(*S,S*)-MeO-phebox-Bn]Br (**86b)**.



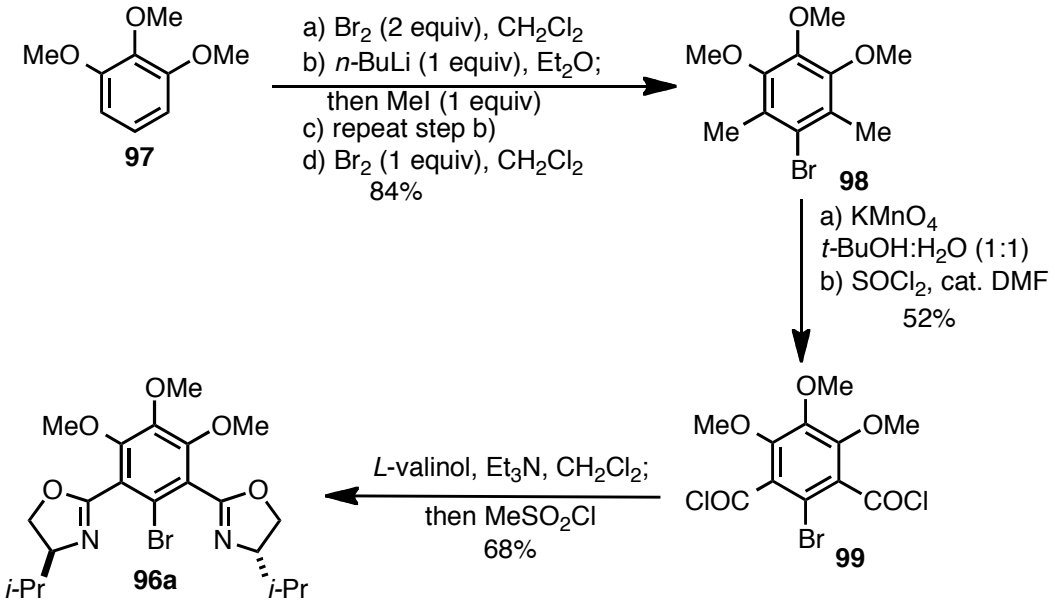
The synthesis of pentasubstituted benzene ligand precursor **92a** was challenging due to the regiochemistry of the methoxy groups and the halogen on the benzene ring. Several routes toward this compound were attempted, but the following synthesis proved to be the most viable. The sequence started with treatment of 1,3-dimethoxybenzene with 2 equiv of Br_2 to afford dibromide **93** (Scheme 2.7).[151] Metal-halogen exchange of **93** with *n*-BuLi followed by MeI delivered the corresponding 1,3-dimethoxy-4,6-dimethylbenzene. An additional 2 equiv of Br_2 provided the fully substituted 2,5-dibromo-1,3-dimethoxy-4,6-dimethylbenzene. Site-selective debromination via metal-halogen exchange with *n*-BuLi afforded **94** in 89% yield for the three steps. Oxidation of **94** with $KMnO_4$ in *t*-BuOH:water gave 2-bromo-4,6-dimethoxy-isophthalic acid, which was then treated with $SOCl_2$ to obtain bis(acyl chloride) **95** in 65% yield. This acid chloride was treated with *L*-valinol, and the resulting bis(amide) was cyclized with PPh_3/CCl_4 to give [(*S,S*)-$(MeO)_2$-phebox-*i*-Pr]Br (**92a**) in 87% yield for the two steps.

Scheme 2.7 Synthesis of [(*S,S*)-(MeO)$_2$-phebox-*i*-Pr]Br (**92a**).



The synthesis of fully substituted aryl pincer ligand **96a** was similar to the dimethoxy pincer ligand **92a** synthesis (Scheme 2.8). The reaction of 1,2,3-trimethoxybenzene **97** with 2 equiv of Br_2 afforded 4,6-dibromo-1,2-3-trimethoxybenzene. This dibromide, in one reaction flask, was treated sequentially with 1 equiv of *n*-BuLi followed by 1 equiv of MeI and then again with 1 equiv of *n*-BuLi followed by 1 equiv of MeI to give 4,5,6-trimethoxy-*m*-xylene. Treatment of the *m*-xylene with 1 equiv of Br_2 afforded the fully substituted benzene **98** in 84% yield. Oxidation of **98** with $KMnO_4$ followed by chlorination with $SOCl_2$ gave **99** in 52% yield. Bis(acid chloride) **99** was treated with *L*-valinol to give corresponding bis(amide), followed by $MeSO_2Cl/NEt_3$ to give [(*S,S*)-(MeO)$_3$-phebox-*i*-Pr]Br (**96a**) in 68% yield.

Scheme 2.8 Synthesis of [(*S,S*)-$(MeO)_3$-phebox-*i*-Pr]Br (**96a**).

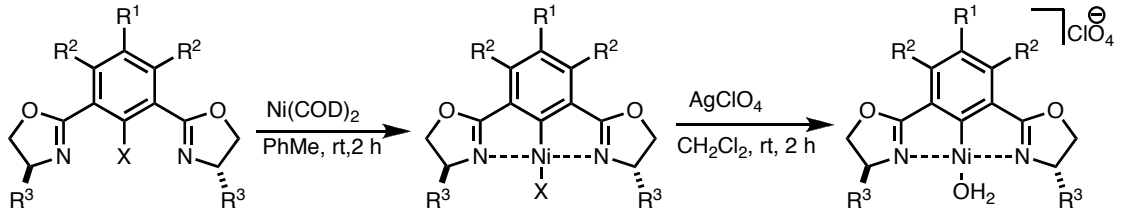


2.2.2 Synthesis of Ni(II) and Pd(II) Pincer Complexes

A method similar to that reported by Richards[152] was used to synthesize Ni(II) and Pd(II) pincer complexes of these ligands. Treatment of pincer ligands [PheBox-Ph]Br (**77b**), [*t*-BuPheBox-Ph]Br (**80b**) or [*t*-BuPheBox-*i*-Pr]I (**80a**) with $Ni(COD)_2$ in PhMe at rt resulting in a slow change of the color of the solution from yellow to orange over 2 hr and provided the nickel complexes [PheBox-Ph]NiBr (**101**), [*t*-BuPheBox-Ph]NiBr (**104**) and [*t*-BuPheBox-*i*-Pr]NiI (**103**) respectively (Scheme 2.9). The identity of each of these nickel compounds was confirmed by X-ray structure analysis of a crystal obtained by slow evaporation from a CH_2Cl_2 solution in air. The resulting bright

orange crystals have been stored in air at room temperature for several months without decomposition. Anion exchange was accomplished by treatment of the (Phebox)NiX complexes **100-108** with $AgClO_4$. After filtering and concentration in vacuo, the cationic complexes were obtained in quantitative yield. The X-ray structure of the nickel complex [PheBox-*i*-Pr]$NiClO_4$•H_2O (**109**), is shown in Figure 2.4.

Scheme 2.9 Synthesis of neutral and cationic nickel pincer complexes.



77a: $R^1 = R^2 = H$, R^3 = *i*-Pr, X = Br
77b: $R^1 = R^2 = H$, R^3 = Ph, X = Br
77c: $R^1 = R^2 = H$, R^3 = Bn, X = Br
80a: R^1 = *t*-Bu, $R^2 = H$, R^3 = *i*-Pr, X = I
80b: R^1 = *t*-Bu, $R^2 = H$, R^3 = Ph, X = Br
80c: R^1 = *t*-Bu, $R^2 = H$, R^3 = Bn, X = Br
86a: R^1 = OMe, $R^2 = H$, R^3 = *i*-Pr, X = I
92a: $R^1 = H$, R^2 = OMe, R^3 = *i*-Pr, X = Br
96a: $R^1 = R^2$ = OMe, R^3 = *i*-Pr, X = Br

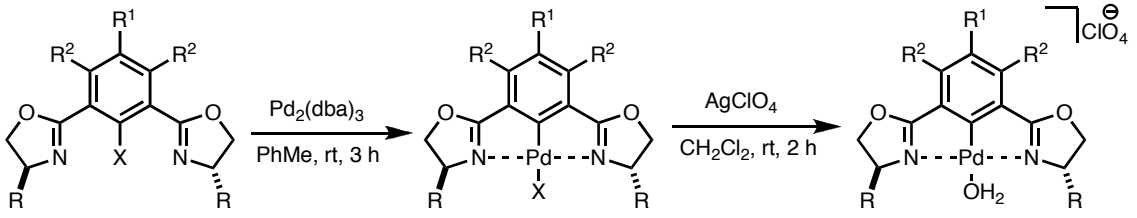
100: $R^1 = R^2 = H$, R^3 = *i*-Pr, X = Br
101: $R^1 = R^2 = H$, R^3 = Ph, X = Br
102: $R^1 = R^2 = H$, R^3 = Bn, X = Br
103: R^1 = *t*-Bu, $R^2 = H$, R^3 = *i*-Pr, X = I
104: R^1 = *t*-Bu, $R^2 = H$, R^3 = Ph, X = Br
105: R^1 = *t*-Bu, $R^2 = H$, R^3 = Bn, X = Br
106: R^1 = OMe, $R^2 = H$, R^3 = *i*-Pr, X = I
107: $R^1 = H$, R^2 = OMe, R^3 = *i*-Pr, X = Br
108: $R^1 = R^2$ = OMe, R^3 = *i*-Pr, X = Br

109: $R^1 = R^2 = H$, R^3 = *i*-Pr
110: $R^1 = R^2 = H$, R^3 = Ph
111: $R^1 = R^2 = H$, R^3 = Bn
112: R^1 = *t*-Bu, $R^2 = H$, R^3 = *i*-Pr
113: R^1 = *t*-Bu, $R^2 = H$, R^3 = Ph
114: R^1 = *t*-Bu, $R^2 = H$, R^3 = Bn
115: R^1 = OMe, $R^2 = H$, R^3 = *i*-Pr
116: $R^1 = H$, R^2 = OMe, R^3 = *i*-Pr
117: $R^1 = R^2$ = OMe, R^3 = *i*-Pr

A similar protocol for the synthesis of cationic palladium complexes was employed. A mixture of the pincer ligands: [*t*-BuPheBox*i*-Pr]I (**80a**) or [*t*-BuPheBoxBn]Br (**80b**) and $Pd_2(dba)_3$ was combined in PhMe. The reaction mixture was filtered through silica gel, eluting with toluene to remove the dba. The silica gel was then washed separately with ethyl acetate to give a yellow solution which was collected and the solvent was removed under reduce pressure to give the pincer complex as a yellow solid. Column chromatography was employed to purify the palladium complexes [*t*-

BuPheBox*i*-Pr]PdI (**121**) and [*t*-BuPheBoxBn]PdBr (**123**). Samples suitable for X-ray analysis of [*t*-BuPheBox*i*-Pr]PdI (**121**) and [*t*-BuPheBoxBn]PdBr (**123**) were prepared by slow evaporation of a dichloromethane solution in air to give light yellow crystals. Their X-ray structure is shown in Figure 2.4. The resulting light yellow crystals have been stored in air at room temperature for several months without decomposition.

Scheme 2.10 Synthesis of neutral and cationic palladium pincer complexes.



77a: $R^1 = R^2 = H$, $R^3 = i$-Pr, X = Br
77b: $R^1 = R^2 = H$, $R^3 = Ph$, X = Br
77c: $R^1 = R^2 = H$, $R^3 = Bn$, X = Br
80a: $R^1 = t$-Bu, $R^2 = H$, $R^3 = i$-Pr, X = I
80b: $R^1 = t$-Bu, $R^2 = H$, $R^3 = Ph$, X = Br
80c: $R^1 = t$-Bu, $R^2 = H$, $R^3 = Bn$, X = Br
86a: $R^1 = OMe$, $R^2 = H$, $R^3 = i$-Pr, X = I
92a: $R^1 = H$, $R^2 = OMe$, $R^3 = i$-Pr, X = Br
96a: $R^1 = R^2 = OMe$, $R^3 = i$-Pr, X = Br

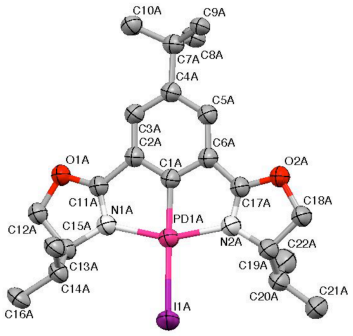
118: $R^1 = R^2 = H$, $R^3 = i$-Pr, X = Br
119: $R^1 = R^2 = H$, $R^3 = Ph$, X = Br
120: $R^1 = R^2 = H$, $R^3 = Bn$, X = Br
121: $R^1 = t$-Bu, $R^2 = H$, $R^3 = i$-Pr, X = I
122: $R^1 = t$-Bu, $R^2 = H$, $R^3 = Ph$, X = Br
123: $R^1 = t$-Bu, $R^2 = H$, $R^3 = Bn$, X = Br
124: $R^1 = OMe$, $R^2 = H$, $R^3 = i$-Pr, X = I
125: $R^1 = H$, $R^2 = OMe$, $R^3 = i$-Pr, X = Br
126: $R^1 = R^2 = OMe$, $R^3 = i$-Pr, X = Br

127: $R^1 = R^2 = H$, $R^3 = i$-Pr
128: $R^1 = R^2 = H$, $R^3 = Ph$
129: $R^1 = R^2 = H$, $R^3 = Bn$
130: $R^1 = t$-Bu, $R^2 = H$, $R^3 = i$-Pr
131: $R^1 = t$-Bu, $R^2 = H$, $R^3 = Ph$
132: $R^1 = t$-Bu, $R^2 = H$, $R^3 = Bn$
133: $R^1 = OMe$, $R^2 = H$, $R^3 = i$-Pr
134: $R^1 = H$, $R^2 = OMe$, $R^3 = i$-Pr
135: $R^1 = R^2 = OMe$, $R^3 = i$-Pr

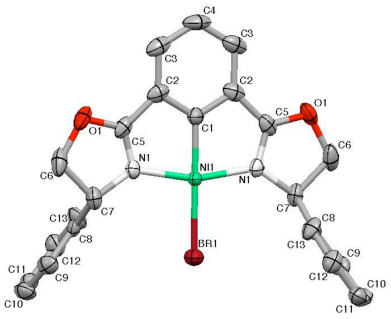
2.2.2.1 Structural Properties of Pincer Complexes

Single crystals, suitable for X-ray crystallography, were obtained by slow evaporation from dichloromethane (Figure 2.4). The structure of nickel pincer complexes [PheBox-Ph]NiBr (**101**), [*t*-BuPheBox-Ph]NiBr (**104**) and [*t*-BuPheBox-*i*-Pr]NiI (**103**) is correlated to the previously reported structures of (PheBox-Me_2)NiI[132]

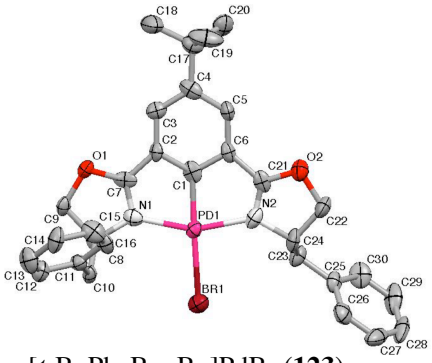
and [(*S,S*)-PheBox-*i*-Pr]NiBr.[133] The square-planar Ni(II) center in these new pincer complexes are four-coordinate, NCN and halogen.



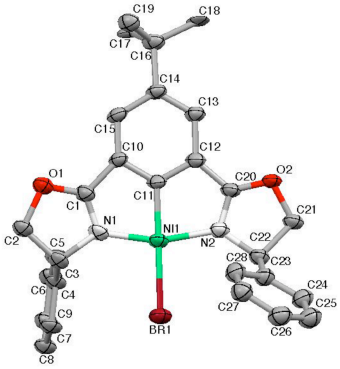
[*t*-BuPheBox-*i*-Pr]PdI (**121**)



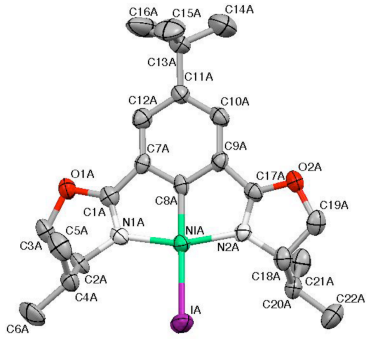
[PheBoxPh]NiBr (**101**)



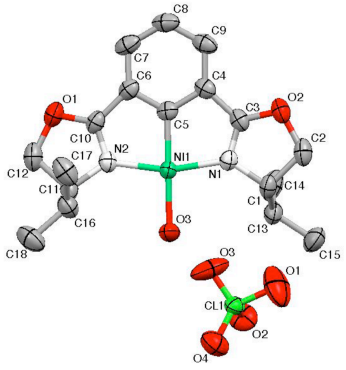
[*t*-BuPheBoxBn]PdBr (**123**)



[*t*-BuPheBoxPh]NiBr (**104**)



[*t*-BuPheBox*i*-Pr]NiI (**103**)



[PheBox*i*-Pr]NiClO$_4$•H$_2$O (**109**)

Figure 2.4 Crystal structures of M(NCN)-pincer complexes.

The M–C bond length in [PheBox-Ph]NiBr (**101**), [*t*-BuPheBox-Ph]NiBr (**103**), [*t*-BuPheBox-*i*-Pr]NiI (**104**), [PheBox-*i*-Pr]$NiClO_4$•H_2O (**109**), [*t*-BuPheBox-*i*-Pr]PdI (**121**), and [*t*-BuPheBoxBn]PdBr (**123**) follows the general trend as expected (Ni–C < Pd–C) (Table 2.1). For example, for complex [(*S,S*)-*t*-BuPheBox-*i*-Pr]NiI (**103**) has a Ni–C bond length of 1.841 Å, where its congener [(*S,S*)-*t*-BuPheBox-*i*-Pr]PdI (**121**) has a Pd–C bond length of 1.944 Å. Another structure feature is the effect of the electron donating groups on the benzene core, it is observed that [(*R,R*)-*t*-BuPheBoxPh]NiBr (**104**) has a Ni–C bond length of 1.835 Å, whereas [(*R,R*)-PheBoxPh]NiBr (**101**) has a Ni–C bond length of 1.844 Å. The *tert*-butyl group shortens the distance between the aryl group and the metal center by electron donation. The trans influence,[153] or lengthening of the bonds trans to each other, can be seen by comparing the complex [(*R,R*)-*t*-BuPheBoxPh]NiBr (**104**) with a Ni–Br bond length of 2.3443 Å versus [(*R,R*)-PheBoxPh]NiBr (**101**) with a Ni–Br bond length of 2.3164 Å. Is noticeable that the Ni–Br bond is longer for the complex with an electron donating groups in the benzene core. The relative importance of the trans influences depends on the formal electron configuration of the metal center,[153] proving our hypothesis of electro-donation to the metal center is possible by incorporation of electron donating groups in the benzene core of the pincer complex resulting in more electron rich complexes. Complex [(*S,S*)-PheBox-*i*-Pr]$NiClO_4$•H_2O (**109**) also has differences from its precursor [(*S,S*)-PheBox-*i*-Pr]NiBr (**100**), some of the differences are the Ni–C bond length, been shorter for the aqueous complex **109** and vice versa for the Ni–X bond length, been longer for the

halogenated complex **100**. These bond lengths variations are explained by the trans influence as well.

Table 2.1 Selected bond lengths and bond angles of the nickel and palladium pincer complexes.

Entry	M(NCN) Complex	M–N(1)	M–C	M–N(2)	M–X	Angle C–M–X
1	[*t*-BuPheBox-*i*-Pr]PdI (**121**)	2.073(11)	1.944(12)	2.077(11)	2.6846(18)	178.5(4)
2	[*t*-BuPheBoxBn]PdBr (**123**)	2.071(7)	1.951(8)	2.074(7)	2.5226(10)	178.2(2)
3	[*t*-BuPheBox-*i*-Pr]NiI (**103**)	1.946(5)	1.841(6)	1.929(5)	2.5301(16)	177.25(19)
4	[*t*-BuPheBoxPh]NiBr (**104**)	1.896(8)	1.835(10)	1.929(8)	2.3443(18)	178.4(3)
5	[PheBoxPh]NiBr (**101**)	1.9371(19)	1.844(3)	1.9371(19)	2.3164(5)	180.0
6[a]	[PheBox-*i*-Pr]NiBr (**100**)	1.908(2)	1.841(19)	1.910(2)	2.3572(4)	178.10(6)
7	[PheBox-*i*-Pr]NiClO$_4$•H$_2$O (**109**)	1.9195(13)	1.8333(4)	1.9101(13)	1.9403(12)	177.35(6)

[a] Previously reported by Van Koten in 2007.

2.2.2.2 Lewis Acidity of the Pincer Complexes

Figure 2.5 shows how the Lewis acidity of the pincer complexes can be tailored by incorporating substituents on the aryl group. Electron withdrawing groups will increase the Lewis acidity of the complex due to electron deficient metal center (Figure 2.5, left). On the other hand, the new complexes with an electron-donating groups on the aryl ring will increase electron density at the metal center, thus presumably decreasing the Lewis acidity of the complex (Figure 2.5, right).

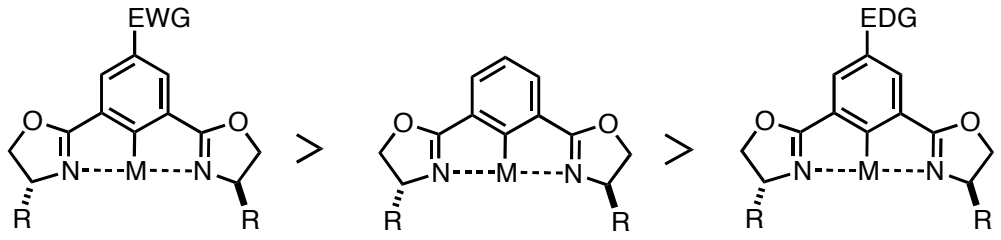


Figure 2.5 Decreasing Lewis acidity of pincer complexes.

The relative Lewis acidity of these pincer complexes can be measured by how tightly a Lewis base, such as MeCN, coordinates to the metal center (Figure 2.6).

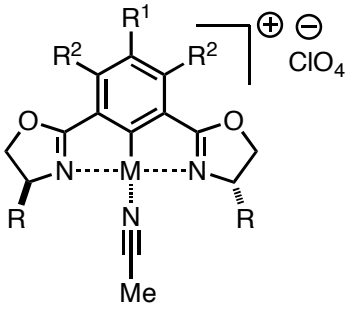


Figure 2.6 MeCN complexation by the cationic pincer complexes.

This electron donation from MeCN to the metal can be indirectly measured by a shift in the ^{1}H NMR of the methyl group of the MeCN. The downfield shift in the signal, relative to free MeCN, will be proportional to the Lewis acidity of the pincer complexes. According to the procedure of Richards,[132] 1.0 equiv of pincer complex was combined with 0.9 equiv of MeCN in $CDCl_3$ (approximately 0.013 M) and the resulting solutions were analyzed by 300 MHz ^{1}H NMR. Insignificant Lewis acidity was discovered for pincer complexes where X was a nondissociating anion (Br and I) with values lower

than 0.001 ppm (Table 2.2, Entries: 2, 3, 14, and 15). On the other hand, complexes where X was exchanged for a less coordinating counterion (ClO_4) showed increased Lewis acidity. For example, [*t*-BuPheBox-*i*-Pr]$NiClO_4$ (**112**) shows a shift at 2.381 ppm, 0.024 smaller than [PheBox-*i*-Pr]$NiClO_4$ (**109**). [$(MeO)_3$PheBox-*i*-Pr]$NiClO_4$ (**117**) shows a shift at 2.362, 0.043 smaller than [PheBox-*i*-Pr]$NiClO_4$ (**109**). Although the palladium pincer complexes shown less Lewis acidity than the Ni(II) complexes, due to the greater inherent electronegativity of Ni(II) vs Pd(II),[154-156] these complexes follow the same general pattern of electronegativity that the Ni(II) pincer complexes show, that is decreasing Lewis acidity as the number of electron donating group on the ligand is increased. For example, the nickel complex [PheBox-*i*-Pr]$NiClO_4$ (**109**) has a shift of 2.405 and palladium complex [PheBox-*i*-Pr]$PdClO_4$ (**127**) has a shift at 2.138 ppm.

Table 2.2 Relative Lewis acidity of Ni(II) and Pd(II) pincer complexes.

Entry	Ni(NCN) Complex	^{1}H NMR of $NCCH_3$[a]	Entry	Pd(NCN) Complex	^{1}H NMR of $NCCH_3$[a]
1	none	2.020	13	none	2.020
2	[PheBoxPh]NiBr (**101**)	2.021	14	[PheBoxPh]PdBr (**119**)	2.020
3	[*t*-BuPheBox-*i*-Pr]NiI (**103**)	2.020	15	[*t*-BuPheBox-*i*-Pr]PdI (**121**)	2.019
4	[PheBox*i*-Pr]$NiClO_4$ (**109**)	2.405	16	[PheBox*i*-Pr]$PdClO_4$ (**127**)	2.138
5	[PheBoxPh]$NiClO_4$ (**110**)	2.381	17	[PheBoxPh]$PdClO_4$ (**128**)	2.184
6	[PheBoxBn]$NiClO_4$ (**111**)	2.385	18	[PheBoxBn]$PdClO_4$ (**129**)	2.207
7	[*t*-BuPheBox-*i*-Pr]$NiClO_4$ (**112**)	2.381	19	[*t*-BuPheBox-*i*-Pr]$PdClO_4$ (**130**)	2.053
8	[*t*-BuPheBoxPh]$NiClO_4$ (**113**)	2.350	20	[*t*-BuPheBoxPh]$PdClO_4$ (**131**)	2.166
9	[*t*-BuPheBoxBn]$NiClO_4$ (**114**)	2.354	21	[*t*-BuPheBoxBn]$PdClO_4$ (**132**)	2.165
10	[(MeO)PheBox-*i*-Pr]$NiClO_4$ (**115**)	2.379	22	[(MeO)PheBox-*i*-Pr]$PdClO_4$ (**133**)	2.135
11	[$(MeO)_2$PheBox-*i*-Pr]$NiClO_4$ (**116**)	2.366	23	[$(MeO)_2$PheBox-*i*-Pr]$PdClO_4$ (**134**)	2.133
12	[$(MeO)_3$PheBox-*i*-Pr]$NiClO_4$ (**117**)	2.362	24	[$(MeO)_3$PheBox-*i*-Pr]$PdClO_4$ (**135**)	2.130

[a] broad singlet

2.3 Applications of the Pincer Complexes

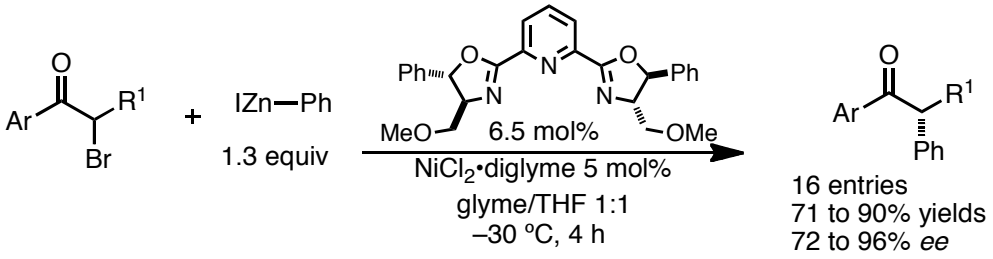
Since several air and moisture stable Palladium complexes were synthesized via oxidative addition to PheBox pincer ligands with $Ni(COD)_2$ or Pd_2dba_3. We decided to utilize them for C–C bond forming reactions such as: Negishi cross-coupling and α-arylation of ketones.

2.3.1 Negishi Cross-coupling Reaction

In 1976, E. Negishi and co-workers reported the first stereospecific Ni-catalyzed alkenyl-alkenyl and alkenyl-aryl cross-coupling of organoaluminums with alkenyl- or aryl halides. After extended research, they found that organozinc reagents showed better reaction rate, yields and stereoselectivity.[157,158] In 2010, E. Negishi received the Nobel price in chemistry for his work on Pd- and Ni-catalyzed stereoselective cross-coupling or organozincs and aryl-, alkenyl-, or alkynyl halides, the so call Negishi reaction.

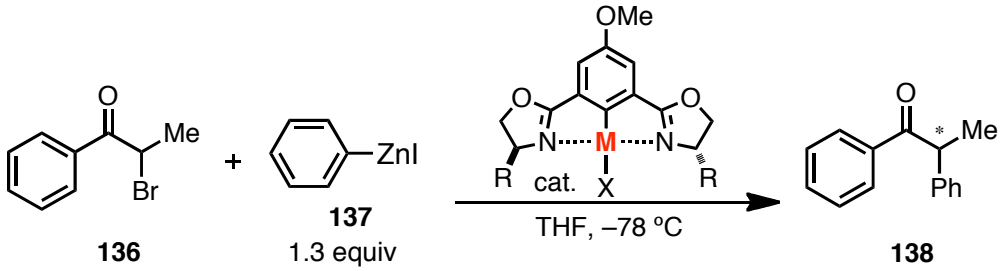
In 2009, G. Fu, reported a nickel complex capable of catalyzed the Negishi reaction between several α-bromoketones and organozinc reagents.[159] He reported moderate to good yields and *ee*'s (Scheme 2.11).

Scheme 2.11 Fu's approach to α-aryl ketones.



With this available information we decided to employ our Nickel- and Palladium- NCN-pincer complexes to catalyzed the Negishi reaction between racemic 2-bromopropiophenone (**136**) and phenyl zinc iodide (**137**) to afford the adduct 1,2-diphenylpropan-1-one (**138**) potentially with high enatiomeric excess (Scheme 2.12).

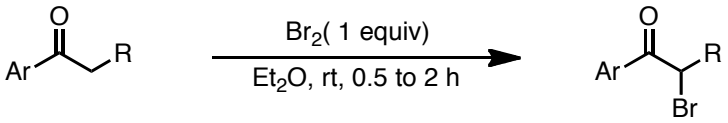
Scheme 2.12 Proposed Negishi cross-coupling reaction.

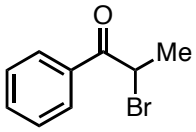
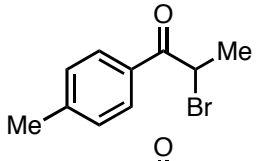
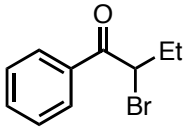
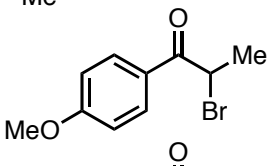
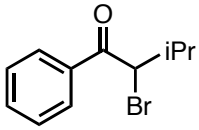
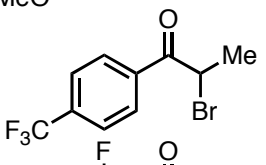
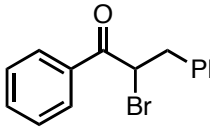
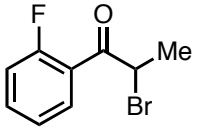
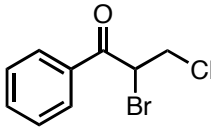
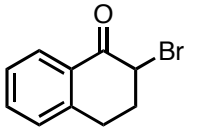
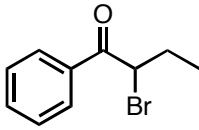
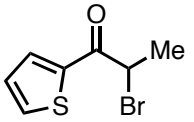


2.3.2 Synthesis of α-Bromoketones

Due to the need of α-bromoketones, we started by synthesizing a library of these molecules using bromine to α-brominate their corresponding aryl ketones precursors (Table 2.3). All the adducts were obtained in good to excellent yields (59-96%).

Table 2.3 Synthesis of α-bromoketones.[a]



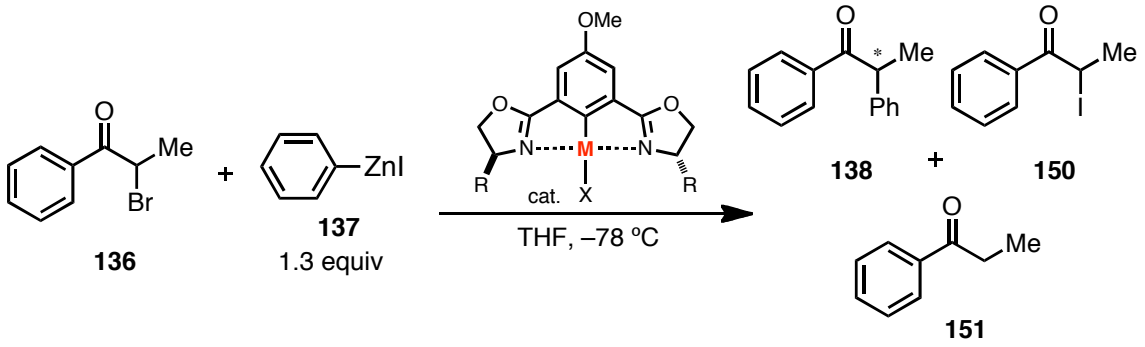
Entry	Product	(#)	Yield (%)[b]	Entry	Product	(#)	Yield (%)[b]
1		**136**	N/A	7		**144**	96
2		**139**	92	8		**145**	94
3		**140**	88	9		**146**	83
4		**141**	93	10		**147**	95
5		**142**	85	11		**148**	59
6		**143**	84	12		**149**	78

[a] The reactions were performed with 6 mmol of ketone, 1.05 equiv of bromine, in 15 mL of Et_2O at rt for 0.5 to 2 h. [b] Isolated yield after purification by silica gel chromatography.

The Negishi reaction turned out to be more complex than expected due to several factors including: the synthesis of arylzinc reagents, dimerization of starting material, byproduct formation, and debromination of the starting material. The outcome or ratio of product : byproducts was dependent on the reaction conditions (Scheme 2.13). The main byproduct formed was 2-iodopropiophenone (**150**), which in turn mislead us in view of the fact that compound **150** has the same retention time (13.99 min) when passed

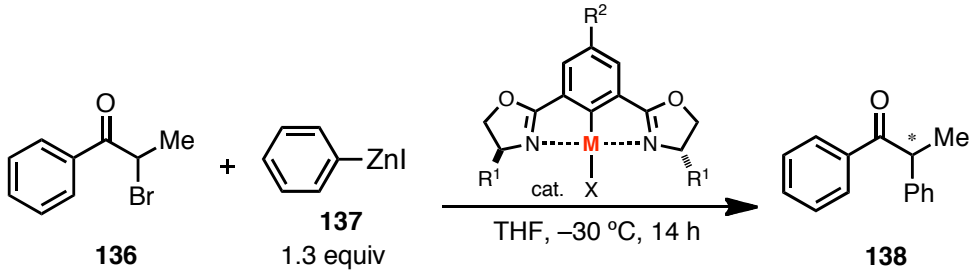
through the chiralcel OJ-H HPLC column (hexane/*i*PrOH = 98/2), 1.0 mL/min, 254 nm) than one of the enantiomers of 1,2-diphenylpropan-1-one (**138**). This misinterpretation of a higher enantiomeric excess was corrected once the adduct **150** was isolated and characterized.

Scheme 2.13 Outcome of the α-arylation of **136**.



After extended research, it was found that palladium pincer complexes afford the adduct **138** in low yield, while nickel pincer complexes delivered the adduct **138** in excellent yields. However, neither the palladium or nickel pincer complexes were successful to catalyze the asymmetric Negishi cross-coupling. It was demonstrated that all pincer complexes were unable to afford significant levels of enantioselectivity (Table 2.4).

Table 2.4 Results of the α-arylation of ketones (Negishi).[a]



136 **137** 1.3 equiv **138**

Entry	Catalyst (5 mol%)	Cat. (#)	Yield (%)[b]	ee (%)[c]
1	$AgClO_4$	–	NR	NA
2	[PheBox*i*-Pr]PdBr	**118**	37	5
3	[*t*-BuPheBoxBn]$PdClO_4$	**132**	36	14
4	[MeOPheBox*i*-Pr]$PdClO_4$	**133**	39	8
5	[PheBox*i*-Pr]NiBr	**109**	55	18
6	[*t*-BuPheBox*i*-Pr]$NiClO_4$	**112**	88	30
7	[*t*-BuPheBoxPh]$NiClO_4$	**113**	79	28
8	[*t*-BuPheBoxBn]$NiClO_4$	**114**	84	23
9	[MeOPheBox*i*-Pr]$NiClO_4$	**115**	93	35

[a] The reactions were performed with 0.25 mmol of **136**, 1.3 equiv of **137**, 0.5 equiv of catalyst, in 4 mL of THF at –30 ºC for 14 h. [b] Isolated yield after purification by silica gel chromatography. [c] Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (hexane/*i*PrOH = 98/2), 1.0 mL/min, 254 nm.

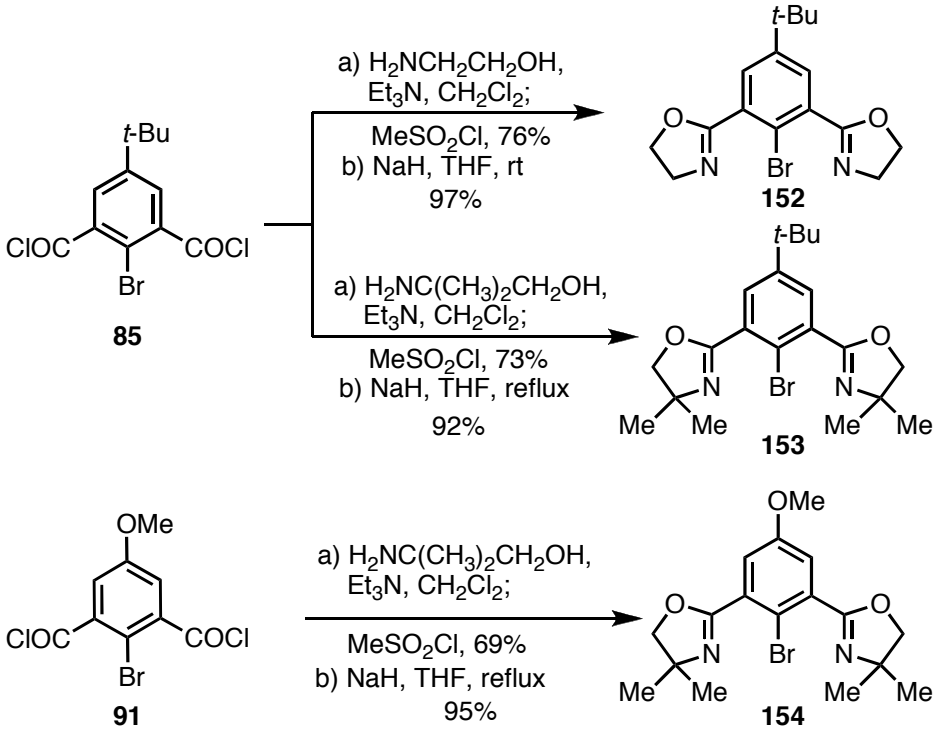
Unfortunately, the attempted enantioselective Negishi cross-coupling using our nickel or palladium pincer complexes was unsuccessful. However, we continued our research to further develop an easier and practical path to synthesize α-aryl ketones. This study is presented in the next pages.

2.4 α-Arylation of Ketones Using Pd (II) Pincer Complexes

In modern organic synthesis palladium catalysis has become one of the most important synthetic tools. A specially appealing synthetic characteristic of Pd catalysis is its extensive synthetic scope and the capability to control the selectivity of the

reactions.[160-162,163] A perfect catalyst has to be stable and highly selective, but also very active to guarantee high turnover numbers and allow low catalyst loadings. Furthermore, it needs to be simple and easy to synthesize. These issues can usually be addressed by an appropriate choice of ligands. One of the successful strategies is to use tridentate ligands, such as pincer ligands, to accomplish a well-defined metal-ligand bonding. In the lates 1970s, Shaw[138] and van Koten,[139] reported the first pincer complexes. Since then, a large number of different pincer complexes has been synthesized and studied in miscellaneous catalytic applications, specially on palladium catalysis.[140,141]

Scheme 2.14 Synthesis of NCN pincer ligands **152-154**.

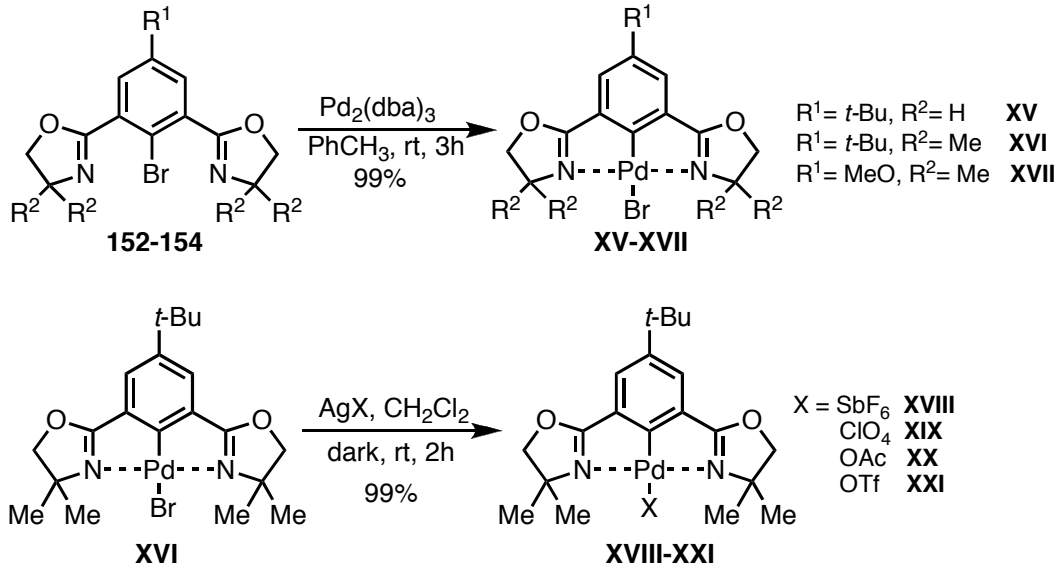


The synthesis of palladium pincer complexes is sometimes considered the limited factor for their application in catalysis due to proligands and complexes syntheses.

Recently, we reported a straightforward synthesis of air and moisture stable chiral NCN pincer complexes using short and simple reaction conditions.[164] Here, the synthesis of new achiral NCN pincer ligands and complexation with Pd (II) to form NCN-pincer complexes are reported. Also, their highly selective α-arylation of ketones with a variety of aryl bromides is reported.

The synthesis of pincer ligands took place from the known 2-bromo isophthalic acids **84** and **90**[164] which, were treated with $SOCl_2$ to obtain the 2-bromo isophthalic dichlorides **85** and **91**. The latter acids chloride were reacted with 2-amino-2-mehtyl-1-propanol or ethanolamine, to give the corresponding bisamide. The resulting bisamides were halogenated employing $MeSO_2Cl$. Finally, the oxazoline formation was accomplished using sodium hydride to afford the NCN Pincer ligands **152-154** (97%, 92%, and 95% yield respectively (Scheme 2.14).

Scheme 2.15 Synthesis of Pd (II) NCN pincer catalysts **XV-XXI**.



The palladium pincer complexes **XV-XXI** were synthesized via oxidative addition of $Pd_2(dba)_3$ to PheBox Pincer ligands **152-154** in 99% yields (Scheme 2.15, top). X-ray of complex **XVI** was taken (Figure 2.7). To obtain the cationic complexes **IV-VII** a mixture of **XVI** and a silver salt was stirred in dry dichloromethane for 2 h at room temperature to give **XVIII-XXI** as a yellow solid in quantitative yield (Scheme 2.15, bottom).

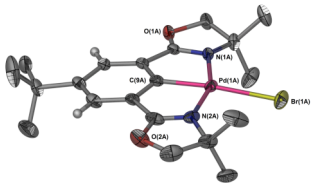
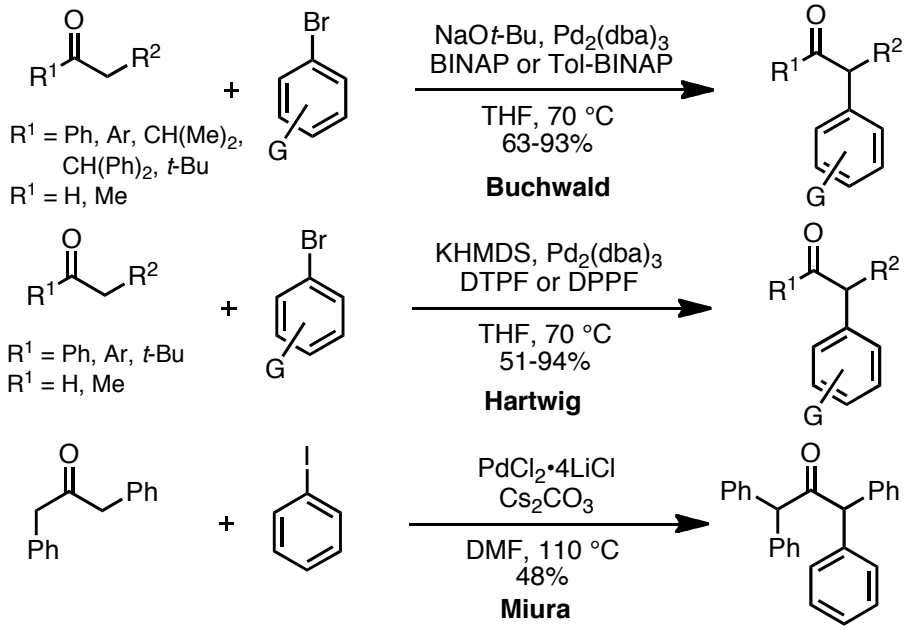


Figure 2.7 X-Ray structure of [*t*-BuPhebox-Me_2]PdBr **XVI**.

The firsts reports over palladium mediated α-arylation of carbonyl compounds appeared independently in 1997 by Buchwald,[165] Hartwig,[166] and Miura[167] (Scheme 2.16). All these methods employ either an excess of the phosphine base ligand or an inorganic catalyst in concentrated reaction mixtures to accelerate the reaction.[168] Since then, more methods are been reported for the α-arylation of carbonyl compounds,[169,170] such methods use Pd,[171-175] Ni,[176] and Cu[177] as the transition metals. In addition to phosphine ligands[178-181] some methods utilize binap derivatives,[182] carbenes,[183] modified ferrocenes,[184] quinine and chinchonidine,[185] proline derivatives,[186] or phosphine pincer ligands[187] to have higher selectivity, broader substrate scope and milder reaction conditions to increase the reaction rate of this metal catalyzed C-C bond transformation. Others attempts to archive this transformation have been reported through the use of

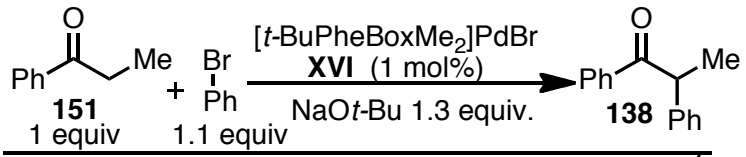
photoinduced S_N1 reaction,[188] solid phase[189] or coupling with diaryl iodonium salts.[190] Although some of these methods are user-friendly, attractive, and successful at some extent. They could be problematic in certain cases due to the hazard of the reaction conditions and also each of these methods has been limited in substrate scope to varying extents.

Scheme 2.16 Early examples of the catalytic α–arylation of carbonyl compounds.



Never before a NCN pincer complex has been utilized for this transformation, until now. The advantages of our method include: the ready availability of the inexpensive coupling substrates, no excess of ligand, shorter reaction times, diluted mixtures, lower reaction temperature, exclusively monoarylation, and above all the catalyst stability.

Table 2.5 Palladium cross-coupling reaction between propiophenone and bromobenzene.[a]



Entry	Solvent	Temp °C	Time (h)	Yield (%)[b]
1	Toluene	120	1	99
2	Toluene	90	1	97
3	**Toluene**	**70**	**1**	**96**
4	Toluene	50	6	95
5	Toluene	rt	6	11
6	THF	70	1	84
7	1,4-dioxane	70	6	5
8	Toluene	70	2	99
9	Toluene	70	0.5	78
10[c]	Toluene	70	1	98
11[d]	Toluene	70	0.5	97
12[e]	Toluene	70	1	95
13[f]	Toluene	70	1	99

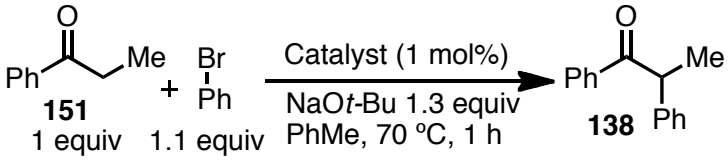
[a] The reactions were performed with 0.33 mmol of **151**, 1.1 equiv of bromobenzene, 1.3 equiv of NaO*t*-Bu, 0.01 equiv of catalyst, in 1.5 mL of solvent (0.22M) . [b] Isolated yield after purification by silica gel chromatography. [c] 0.33mmol/1mL (0.33M) used instead of the usual 0.33mmol/1.5mL [d] [c] 0.33mmol/0.5mL (0.66M) used instead of the usual 0.33mmol/1.5mL [e] 1 equiv. of bromobenzene used. [f] 1.1: 1 ratio of propiophenone : bromobenzene.

Our initial Pd system made use of Pd complex **XVI**, which was capable of catalyzing the reaction of propiophenone with bromobenzene (Table 2.5). We have conducted a thorough optimization of this catalytic system and the results are depicted in Table 2.5 and 2.6. Toluene proved to be the best solvent, delivering the product in excellent yield (Table 2.5, entry 3). THF and 1,4-dioxane were also screened, but they resulted in low reactivity (84% and 5% yield respectively), possible due to a reasonable metal coordination (Table 2.5, entries 6 and 7).

At room temperature, the system allowed for the synthesis of the corresponding adduct **138** in 11% yield after 6 h using 1 mol% of **XVI** (Table 2.5, entry 5). However, increasing the temperature to 50 °C increased the yield from 11% to 95% in 6 h (Table 2.5, entry 4). Further increase of temperature to 70 °C allows for drastic reduction of reaction time to 1 h providing 96% yield (Table 2.5, entry 3). At 70 °C in 30 min. the reaction is already 78% completed while at 2 h the reaction is totally complete (Table 2.5, entries 8 and 9). Additional increase of temperature afforded the adduct in 97% and 99% for 90 °C and 120 °C respectively in 1h (Table 2.5, entries 1 and 2). The use of more concentrated mixture (1mmol/3mL instead of the usual 1mmol/5mL) afforded a faster reaction rate with 98% yield (Table 2.5, entry 10). When 1mmol/1mL was used the corresponding product was obtained in 97% after 30 min. (Table 2.5, entry 11). Also, we verified the stoichiometry of the starting materials. It was found that employing 1:1 ratio of propiophenone:bromobenzene the product was afforded in 95% yield (Table 2.5, entry 12). While, using 1.1:1 ratio 99% yield was obtained (Table 2.5, entry 13).

With these data in hand and in view of the fact that higher reaction concentration and temperatures have a positive effect on the reaction rates. We decided to use milder conditions for further optimization, this means less diluted mixtures, lower catalyst loading, lower temperature, shorted reaction times and only 10 mol% excess of aryl bromide.

Table 2.6 Optimization of catalyst for the cross-coupling between propiophenone and bromobenzene.[a]



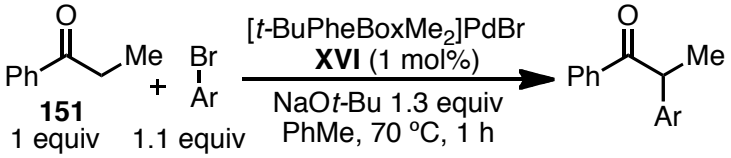
Entry	Catalyst (1 mol%)	Cat. (#)	Yield (%)[b]
1	none	–	0
2	$Pd(OAc)_2$	XXII	48
3	[*t*-BuPheBoxH_2]PdBr	XV	90
4	**[*t*-BuPheBoxMe_2]PdBr**	**XVI**	**96**
5	[MeOPheBoxMe_2]PdBr	XVII	92
6	[*t*-BuPheBoxMe_2]$PdSbF_6$	XVIII	79
7	[*t*-BuPheBoxMe_2]$PdClO_4$	XIX	86
8	[*t*-BuPheBoxMe_2]PdOAc	XX	87
9	[*t*-BuPheBoxMe_2]PdOTf	XXI	77
10[c]	[*t*-BuPheBoxMe_2]PdBr	XVI	36
11[d]	[*t*-BuPheBoxMe_2]PdBr	XVI	95
12[e]	[*t*-BuPheBoxMe_2]PdBr	XVI	86

[a] The reactions were performed with 0.33 mmol of **151**, 1.1 equiv of bromobenzene, 1.3 equiv of NaO*t*-Bu, 0.01 equiv of catalyst, in 1.5 mL of toluene at 70 ºC for 1h . [b] Isolated yield after purification by silica gel chromatography. [c] Reaction performed open to the air. [d] 0.5 mol % of catalyst used instead of the usual 1 mol % and 2 h reaction time. [e] 0.1 mol % of catalyst used instead of the usual 1 mol % and 6 h reaction time.

Table 2.6 depicts the catalytic activity of several Pd complexes (**XV**-**XXII**) towards the α-arylation of propiophenone with bromobenzene in the presence of only 1 mol% of catalyst. The reaction mediated by [*t*-BuPheBox-Me_2]PdBr (**XVI**) occurred with the highest yield (96%) (Table 2.6, entry 4). We have also found that switching from **XVI** to a more electron-rich metal center catalyst **XVIII** afforded slightly lower yield (92%) (Table 2.6, entry 3). The less steric hindered catalyst **XV** showed even lower yield (90%), possible due to be less stable than **XVI** (Table 2.6, entry 3). We compared the differences in performance between neutral and cationic Pd complexes, the formers showed lower reactivity (82% average yield) due to less turnovers of the catalyst in the

system (Table 2.6, entries 6-9). $Pd(OAc)_2$ was also notably less reactive with 48% yield (Table 2.6, entries 2). In the absence of a Pd source the reaction did not proceed (Table 2.6, entry 1). Also, was observed a formation of the corresponding adduct **138** in 36% yield for an aerobic reaction performed open to the air with catalyst **XVI** (Table 2.6, entries 10). To our delight, lower catalyst loading (0.5 mol%) showed high reactivity with 95% yield after only 2 h (Table 2.6, entries 11). Finally, 0.1 mol% of **XVI** gave 86% yield after 6 h (Table 2.6, entries 12), proving the high turnover numbers for this catalytic system using **XVI**.

Table 2.7 Cross-coupling of propiophenone with various aryl bromides.[a]



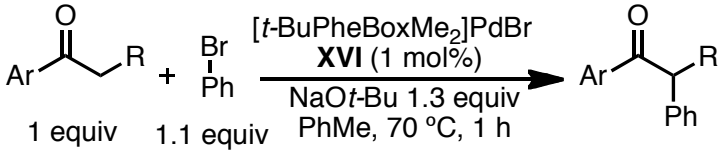
Entry	Ar	Product (#)	Yield (%)[b]
1	Ph	**138**	96
2[c]	2-MeO-C_6H_4	**155**	88
3	3-MeO-C_6H_4	**156**	96
4	4-MeO-C_6H_4	**157**	94
5	3-Me-C_6H_4	**158**	97
6	4-Me-C_6H_4	**159**	95
7	4-F-C_6H_4	**160**	94
8	4-Me_2N-C_6H_4	**161**	91
9	4-MeS-C_6H_4	**162**	89
10	4-CF_3-C_6H_4	**163**	93
11	4-CH_2CH-C_6H_4	**164**	85
12	1-Naphthyl	**165**	87
13[c]	1,3-CF_3-C_6H_4	**166**	92

[a] The reactions were performed with 0.33 mmol of **151**, 1.1 equiv of arylbromide, 1.3 equiv of NaO*t*-Bu, 0.01 equiv of catalyst **XVI**, in 1.5 mL of toluene at 70 ºC for 1h . [b] Isolated yield after purification by silica gel chromatography. [c] 2 mol % of **XVI** was used.

We investigated the scope of this cross-coupling reaction by examining a variety of aryl bromides with propiophenone (**151**). For both electon-deficient and electro-rich

aryl bromides, the system showed to be very efficient (Table 2.7, entries 3-10). The palladium cross-coupling reaction of 1-bromo naphthalene and **151** delivers the product in 87% yield; the yield is slighter lower since the coupling is *ortho* to a substituent (Table 2.7, entry 12). The adduct of the electron-rich 2-bromoanisole is obtained in 49% yield using 1 mol% catayst loading due to steric interactions with the *ortho* methoxy group, but when 2 mol% was used 88% yield was obtained in 1 h (Table 2.7, entry 2). The electron-poor 1-bromo-3,5-bis(trifluoromethyl)benzene afforded a lower yield (55%), due to electron density since it contains two electron withdrawing substituents at the *meta* position. Although, using twice as much catalyst loading the yield was increased up to 92% in the same amound of time (Table 2.7, entry 13). Additionally, this Palladium pincer complex **XVI** was highly chemoselective for the cross-coupling reaction of 4-bromo styrene, affording the adduct in 85% yield (Table 2.7, entry 11).

Table 2.8 Cross-Coupling of bromobenzene with various ketones[ia]



Entry	Ar	R	Product (#)	Yield (%)[b]
1	Ph	Me	**167**	96
2	Ph	Et	**168**	91
3[c]	Ph	*i*-Pr	**169**	95
4	Ph	CH_2Ph	**170**	98
5	4-MeO-C_6H_4	Me	**171**	82
6	4-CF_3-C_6H_4	Me	**172**	99
7	4-MeC_6H_4	Me	**173**	84
8	2-F-C_6H_4	Me	**174**	83

[a] The reactions were performed with 0.33 mmol of ketone, 1.1 equiv of bromobenzene, 1.3 equiv of NaO*t*-Bu, 0.01 equiv of catalyst **XVI**, in 1.5 mL of toluene at 70 ºC for 1h . [b] Isolated yield after purification by silica gel chromatography. [c] 2 mol % of **XVI** was used.

To further examine the scope and utility of these reaction conditions, a variety of ketones were treated with bromobenzene, but no significant differences were observed (Table 2.8). The system was proven to be highly active for several ketones varying electron-poor or electron-rich group in the aromatic part. The electron-deficient 1-(4-(trifluoromethyl)phenyl)propan-1-one showed higher reactivity with 99% yield (Table 2.8, entry 6) versus its counterpart electron-rich 1-(4-methoxyphenyl)propan-1-one with 82% yield (Table 2.8, entry 5). In the aliphatic side of the ketone, several groups where investigated. It was found that isovalerophenone showed lower reaction rate with only 60% yield after 1 h, but using 2 mol% catalyst loading the yield was increased to 95% in the same period of time. This was likely to steric interaction of the isopropyl group with the transient stereocenter. (Table 2.8, entry 3). In general electron-withdrawing groups help to accelerate the reaction rates while electon-donating groups reduce slighty the reaction rate.

In summary, we have developed a direct and highly active, (NCN)-Pd catalytic system for the α-arylation of ketones with a variety of aryl bromides using [*t*-BuPheBox-Me_2]PdBr (**XVI**) as the catalyst. Further efforts are needed to further elucidate the mechanistic details of this reaction system which should in turn allow for future advances to develop an asymmetric variant.

2.5 Experimental Section

2.5.1 General Information

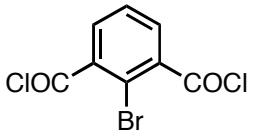
All reactions were carried out under an argon atmosphere in oven-dried glassware with magnetic stirring. All commercially obtained reagents were used as received. Any impure starting material from stock was purified by distillation, column chromatography, or recrystallization. Solvents were distilled under its specific drying agent or obtained from a purification system.

Cooling was accomplished using an ice bath or an isopropanol bath. Heating was accomplished by either a heating mantle or silicone oil bath. Purification of reaction products was carried out by flash column chromatography using silica gel, distillation or by recrystallization. Visualization was accompanied with UV light and/or ceric ammonium molybdate or potassium permanganate staining.

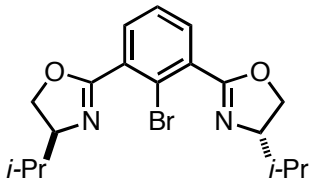
^{1}H NMR spectra were recorded on a 300 MHz instrument and recorded relative to the deuterated solvent used, in ppm units. ^{1}H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). Proton-decoupled ^{13}C NMR spectra were recorded at 75 MHz. High-resolution mass spectra (HRMS) were obtained at Texas A&M. Infrared spectra were recorded on a spectrometer using a thin film on NaCl plates.

2.5.2 Synthesis and Characterization of Pincer Ligands

The procedures and characterization data for the pincer ligands is described in the following pages.

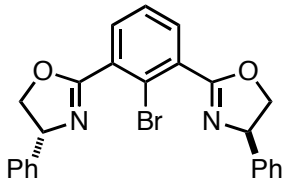


2-bromoisophthalyl dichloride (**78**): To a suspension of 2-bromoisophthalic acid (1 g, 4 mmol) in benzene (40 mL) and a drop of DMF was added $SOCl_2$ (9 mL, 61 mmol) at 0 °C. After the mixture was refluxed for 3 h, excess $SOCl_2$ was removed by distillation, which gave **78** in 99% yield (1.1 g). ^{1}HNMR (300MHz, $CDCl_3$) δ 8.00 (d, 2H), 7.62 (t, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 139.1, 134.5, 127.9, 117.3. MS (CI) LRMS calcd for $C_8H_3BrCl_2O_2$ + H requires *m/z* 280.87, found 280.9 and 282.9.



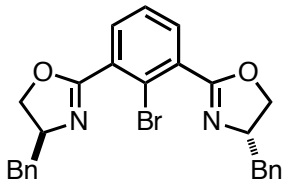
[(*S,S*)-Phebox-*i*-Pr]Br (**77a**): A solution of 2-bromo-isophthaloyl dichloride **78** (1.02 g, 4.0 mmol) in dichloromethane (20 mL) was slowly added to a solution of *L*-valinol (907 mg, 8.8 mmol) and triethylamine (8.1 mL, 60 mmol) in dichloromethane (20 mL) at 0 ºC. The mixture was stirred at room temperature for 5 h. Formation of the intermediate diamide–dialcohol was monitored by TLC examination; Rf = 0.4 (ethyl acetate/methanol = 10 :1). Then, methanesulfonyl chloride (1.003 g, 8.8 mmol) was added at 0 ºC, and the mixture was stirred at room temperature for 16 h. Formation of the product **77a** was monitored by TLC examination; Rf = 0.8 (ethyl acetate/hexane = 3:1). At 0 ºC, aqueous

potassium carbonate (1 N, ca. 30 mL) was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, was dried over sodium sulfate, and concentrated. The crude product was purified by column chromatography (20% EtOAc-Hexanes) to give **77a** in 76% yield (1.27 g, 2.71 mmol) as a colorless solid. $[\alpha]^{19}_{D}$ = –56.62° (*c*= 1 in $CHCl_3$). IR (thin film) ν 1628 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.37 (t, *J* = 8.3 Hz, 1H), 4.42 (m, 2H), 4.18 (m, 4H), 1.92 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 6H), 0.99 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.03, 144.1, 132.57, 132.23, 126.93, 72.85, 70.53, 32.58, 18.75, 18.25. MS (ESI) LRMS calcd for $C_{18}H_{23}BrN_2O_2$ + H requires *m/z* 379.09, found 379.26 and 381.18.

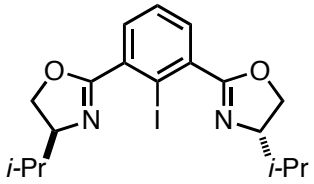


[(*R,R*)-Phebox-Ph]Br (**77b**): A procedure analogous to the synthesis of 1a was employed using 2-bromo-isophthalic acid chloride (**78**) (1.02 g, 4.0 mmol) and (*R*)-phenylglycinol (1.07 g, 7.8 mmol), to yield the uncyclized oxazoline (bisamide) as a white solid. A suspension of the crude bis(amide) in BF_3•Et_2O (10 mL)was heated to 120 °C (the mixture became homogeneous at 75 °C) for 4 h. The solution was allowed to cool down, diluted with dichloromethane (50 mL), and poured into ice-cold 2N NaOH (50 mL). The phases were separated, and dried with sodium sulfate. Concentration of this solution gave crude [(*R,R*)-Phebox-Ph]Br (**77b**), which was purified by column chromatography (20% EtOAc-hexanes). Yield 1.06 g (67% after two steps) of **77b** as a white solid. $[\alpha]^{19}_{D}$ = 67.98° (*c*= 1 in $CHCl_3$). IR (thin film) ν 1651 cm^{-1}. ^{1}HNMR

(300MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.44 (t, *J* = 8.3 Hz, 1H), 7.31-7.40 (m, 10H), 5.45 (t, *J* = 5.6 Hz, 2H) 4.85 (t, *J* = 6.6 Hz, 2H), 4.32 (t, *J* = 5.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.25, 141.72, 132.93, 131.81, 128.6, 127.5, 127.0, 126.6, 121.4, 75.09, 70.25. MS (ESI) LRMS calcd for $C_{24}H_{19}BrN_2O_2$ + H requires *m/z* 447.06, found 447.05 and 449.05.

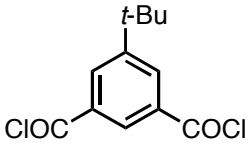


[(*S,S*)-Phebox-Bn]Br (**77c**): A procedure analogous to the synthesis of **77b** was employed using 2-bromo-isophthalic acid chloride (**78**) (1.02 g, 4.0 mmol) and *L*-phenylalaninol (1.238 g, 8.2 mmol), to yield 1.09 g (65% after two steps) of **77c**. $[\alpha]^{19}_D$ = –50.21° (*c*= 1 in $CHCl_3$). IR (thin film) ν 1649 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.38 (t, *J* = 8.3 Hz, 1H), 7.22-7.33 (m, 10H), 4.64-4.67 (m, 2H), 4.41 (t, *J* = 5.6 Hz, 2H), 4.20 (t, *J* = 6.6 Hz, 2H), 3.24 (dd, *J* = 5.6 Hz, 6.8 Hz, 2H). 2.85 (dd, *J* = 5.8 Hz, 4.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 137.5, 132.5, 131.8, 129.2, 128.4, 126.4, 121.2, 72.0, 67.9, 41.3. MS (ESI) LRMS calcd for $C_{26}H_{23}BrN_2O_2$ + H requires *m/z* 475.09, found 475.10 and 477.09.



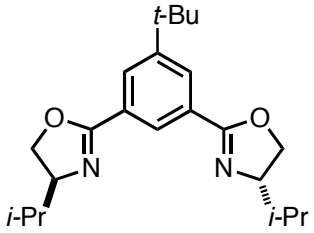
[(*S,S*)-Phebox-*i*-Pr]I (**1d**): To a solution of diisopropylamine (0.34 g, 3.36 mmol) in THF (2 mL), cooled to –78 °C *n*BuLi in hexanes (3.7 mmol) and the resulting mixture

stirred at –78 °C min at room temperature. After re-cooling to –78 °C this was added via cannula to a separate flask, also cooled to –78 °C (*S,S*)-Phebox-*i*-Pr (**79**) (0.39 g, 1.12 mmol) and TMEDA (0.43 g, 3.7mmol) in THF (10 mL). After the addition the resulting deep red solution was stirred at room temperature for 5 h prior to the addition of iodine (1.22 g, 4.8 mmol). The solvent was removed in vacuo and the crude product dissolved in CH_2Cl_2 (50 mL). After washing with aqueous sodium thiosulfate solution (50 mL), this was dried ($MgSO_4$), filtered and the solvent removed in vacuo. Column chromatography of the residue (20% EtOAc-Hexanes) gave [(*S,S*)-Phebox-*i*-Pr]I (**77d**) as a pale yellow oil (0.303g, 52%). $[\alpha]^{19}_D$ = –58.32° (*c*= 1 in $CHCl_3$). IR (thin film) ν 1628 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.39 (t, *J* = 8.1 Hz, 1H), 4.46 (m, 2H), 4.16 (m, 4H), 1.93(m, 2H), 1.07 (d, *J* = 6.8 Hz, 6H), 1.00 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.48, 142.12, 136.63, 131.64, 127.77, 73.03, 70.69, 32.67, 18.96, 18.45. MS (ESI) LRMS calcd for $C_{18}H_{23}IN_2O_2$ + H requires *m/z* 427.08, found 427.079.

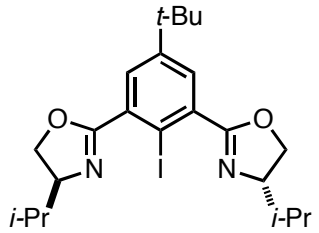


Isophthaloyl dichloride (**82**). To a suspension of 5-*tert*-butyl-isophthalic acid (**81**) (10 g, 56 mmol) in benzene (40 mL) and a drop of DMF was added $SOCl_2$ (30 mL, excess) at 0 °C. After the mixture was refluxed for 5 h, excess $SOCl_2$ was removed by distillation, which gave **82** in 99% yield (11.63 g). IR (thin film) ν 1761 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.41 (s, 2H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$)

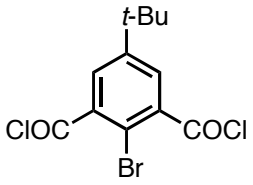
δ 167.6, 153.9, 134.2, 134.0, 131.6, 35.2, 30.9. MS (CI) LRMS calcd for $C_{12}H_{12}Cl_2O_2$ + H requires *m/z* 259.02, found 259.0.



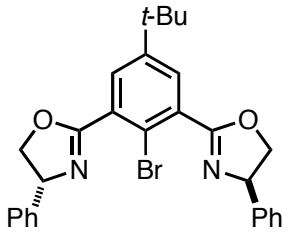
(*S,S*)-*t*BuPhebox-*i*-Pr (**E-11**). A solution of isophthaloyl dichloride **82** (1.55 g, 6.0 mmol) in dichloromethane (20 mL) was slowly added to a solution of *L*-valinol (1.36 g, 13.2 mmol) and triethylamine (12.5mL, 90 mmol) in dichloromethane (20 mL) at 0 ºC. The mixture was stirred at room temperature for 5 h. Formation of the intermediate diamide–dialcohol was monitored by TLC examination; Rf = 0.5 (ethyl acetate/methanol = 10:1). Then, methanesulfonyl chloride (1.25 mL, 13.2 mmol) was added at 0 ºC, and the mixture was stirred at room temperature for 16 h. Formation of the product **E-11** was monitored by TLC examination; Rf = 0.8 (ethyl acetate/hexane = 3:1). At 0 ºC, aqueous potassium carbonate (1 N, ca. 50 mL) was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, was dried over sodium sulfate, and concentrated. The crude product was purified by column chromatography (20% EtOAc-Hexanes) to give (*S,S*)-*t*-BuPhebox-*i*-Pr (**E-11**) in 76 % yield (1.5 g, 4.7 mmol) as a white solid. $[\alpha]^{19}_{D} = -72.56°$ (*c*= 1 in $CHCl_3$). IR (thin film) ν 1648 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.11 (s, 2H), 4.42 (m, 2H), 4.15 (m, 4H), 1.88(m, 2H), 1.38 (s, 3H), 1.04 (d, *J* = 5.8 Hz, 6H), 0.94 (d, *J* = 5.8 Hz, 6H). MS (ESI) LRMS calcd for $C_{22}H_{32}N_2O_2$ + H requires *m/z* 357.25, found 357.2.



[(*S,S*)-*t*BuPhebox-*i*-Pr]I (**80a**). To a solution of diisopropylamine (0.34 g, 3.36 mmol) in THF (2 mL), cooled to –78 °C *n*BuLi in hexanes (3.7 mmol) and the resulting mixture stirred at –78 °C min at room temperature. After re-cooling to –78 °C this was added via cannula to a separate flask, also cooled to –78 °C (S,S)-*t*-BuPhebox-*i*-Pr (**E-11**) (0.4 g, 1.12 mmol) and TMEDA (0.43 g, 3.7mmol) in THF (10 mL). After the addition the resulting deep red solution was stirred at room temperature for 5 h prior to the addition of iodine (1.22 g, 4.8 mmol). The solvent was removed in vacuo and the crude product dissolved in CH_2Cl_2 (50 mL). After washing with aqueous sodium thiosulfate solution (50 mL), this was dried ($MgSO_4$), filtered and the solvent removed in vacuo. Column chromatography of the residue (20% EtOAc-Hexanes) gave [(S,S)-*t*-BuPhebox-*i*-Pr]I (**80a**) as a pale brown crystalline solid (0.313 g, 58%). $[\alpha]^{19}_D = -63.99°$ (*c*= 1 in $CHCl_3$). IR (thin film) ν 1658 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.52 (s, 2H), 4.44 (m, 2H), 4.13 (m, 2H), 1.94 (m, 2H), 1.28 (s, 9H), 1.03 (d, *J* = 6.8 Hz, 6H), 0.98 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.78, 151.2, 136.1, 128.9, 92.0, 73.0, 70.5, 34.5, 32.6, 30.8, 19.0, 18.4. MS (ESI) LRMS calcd for $C_{22}H_{31}IN_2O_2$ + H requires *m/z* 483.14, found 483.31.

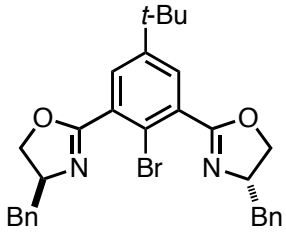


2-bromo-5-tert-butyl-isophthaloyl dichloride (**85**): To a suspension of 2-bromo-5-tert-butyl-isophthalic acid (**84**) (5 g, 15 mmol), in benzene (25 mL) and a drop of DMF was added $SOCl_2$ (25 mL, excess) at 0 °C. After the mixture was refluxed for 3 h, excess $SOCl_2$ was removed by distillation to give 5.55 g of **85** in 99% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 2H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 152.0, 138.5, 131.3, 113.7, 35.12, 30.7. MS (CI) LRMS calcd for $C_{12}H_{11}BrCl_2O_2$ + H requires *m/z* 336.93, found 336.9 and 338.9.



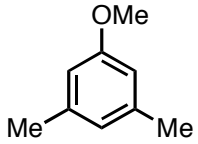
[(*R,R*)-*t*BuPhebox-Ph]Br (**80b**): A solution of isophthaloyl dichloride (**85**) (1 g, 3 mmol) in dichloromethane (10 mL) was slowly added to a solution of (*R*)-phenylglycinol (856 mg, 6.25 mmol) in dichloromethane (10 mL), then a solution of triethylamine (2.06 mL, 15 mmol) in dichloromethane (10 mL) was added slowly at 0 ºC under argon. The mixture was stirred at room temperature for 8 h. Formation of the intermediate diamide–dialcohol was monitored by TLC. After completion the mixture was washed with NH_4Cl, dried with sodium sulfate. The solution is concentrated under reduce pressure to give the corresponding crude bis(amide). MS (ESI) LRMS calcd for $C_{29}H_{31}BrN_2O_4$ + H requires *m/z* 539.15, found 539.14 and 541.14. A suspension of the

crude bis(amide) (1g, 2 mmol) in BF_3•Et_2O (10 mL)was heated to 120 °C (the mixture became homogeneous at 75 °C) for 4 h. The solution was allowed to cool, diluted with dichloromethane (50 mL), and poured into ice-cold 2N NaOH (50 mL). The phases were separated, and dried with sodium sulfate. Concentration of this solution gave crude [(*R*,*R*)-*t*BuPhebox-Ph]Br (**80b**), which was purified by column chromatography (20% EtOAc-hexanes) affording a white solid, 800 mg (86% yield after two steps): $[\alpha]^{19}_D$ = +46.91° (*c*= 1 in $CHCl_3$). IR (thin film) ν 1650 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.31−7.42 (m, 10H), 5.47 (t, *J* = 8.3 Hz 2H), 4.87 (t, *J* = 5.6 Hz, 2H), 4.33 (t, *J* = 6.6 Hz, 2H), 1.37 (s, 9H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 150.5, 141.7, 131.3, 130.1, 128.6, 127.5, 126.7, 118.1, 70.3, 34.6, 30.8. MS (ESI) LRMS calcd for $C_{28}H_{27}BrN_2O_2$ + H requires *m/z* 503.13, found 503.1 and 505.1.



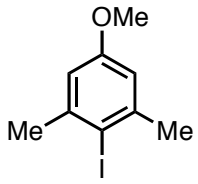
[(*S*,*S*)-*t*BuPhebox-Bn]Br (**80c**): A procedure analogous to the synthesis of **80b** was employed using 2-bromo-5-tertbutyl-isophthalic acid chloride (**85**) (600 mg, 1.78 mmol) and *L*-phenylalaninol (593 mg, 3.93 mmol), to yield the crude uncylized oxazoline (bisamide) as a white solid after removal of volatiles under reducer pressure. Acetonitrile (10 mL), PPh_3 (981 mg, 3.7 mmol), and triethylamine (0.512 mL, 3.7 mmol) were added to the crude bisamide. The temperature was reduced to 0 °C, after which CCl_4 (0.37 mL, 3.7 mmol) was slowly added via syringe. The reaction mixture was warmed to room

temperature overnight, after which the mixture was quenched with H_2O (10 mL) and the volatiles were removed in vacuum. The residue was dissolved in H_2O (50 mL) and dichloromethane (100 mL). After separation of the layers, the organic layer was washed with H_2O (30 mL) and brine (30 mL). The combined aqueous layers were extracted with dichloromethane (100 mL). The combined organic layers were dried on Na_2SO_4 and filtered. After the solvent was removed in vacuum, the crude product was purified by silica gel column chromatography (20% EtOAc-hexanes) to afford **80c** as a white solid, 549 mg (58% yield after two steps). $[\alpha]^{19}_D = -52.15°$ (*c*= 1 in $CHCl_3$). IR (thin film) ν 1658 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.60 (s, 2H), 7.25−7.38 (m, 10H), 4.65 (m, 2H), 4.38 (t, *J* = 6.6 Hz, 2H), 4.22 (t, *J* = 5.6 Hz, 2H), 3.25 (dd, *J* = 5.6 Hz, 6.8 Hz, 2H), 2.88 (dd, *J* = 5.8 Hz, 4.2 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 150.24, 137.4, 131.3, 129.7, 129.3, 128.3, 126.4, 117.8, 71.8, 67.8, 41.2, 34.5, 30.8. MS (ESI) LRMS calcd for $C_{30}H_{31}BrN_2O_2$ + H requires *m/z* 531.16, found 531.16 and 533.16.

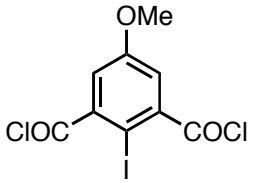


3,5-dimethylanisol (**E-12**): To a solution of 3,5-dimethylphenol **87** (30g, 246 mmol) in acetone (200 mL) was added anhydrous K_2CO_3 (51 g, 369 mmol), and iodomethane (52.4 g, 369 mmol). The mixture was heated at reflux under argon for 24 hr. After cooling the reaction to room temperature, it was filtrated through celite, washed with acetone, and concentrated under reduce pressure. The residue was dissolved in dichloromethane and washed with 1N NaOH. Further simple distillation afforded pure 3,5-dimethylanisol (**E-12**) as a colorless liquid in 95% yield. ^{1}HNMR (300MHz, $CDCl_3$)

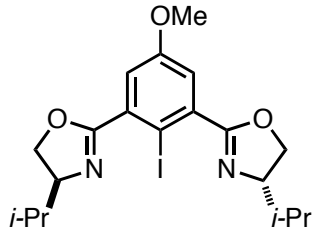
δ 6.99 (s, 1H), 6.63 (s, 2H), 3.85 (s, 3H), 2.38 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 139.9, 122.3, 115.7, 54.9, 21.3. MS (CI) LRMS calcd for $C_9H_{12}O$ + H requires *m/z* 137.09, found 137.10.



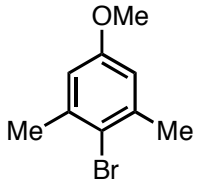
3,5-dimethyl-4-iodoanisol (**88**): To a solution of 3,5-dimethylanisol **E-12** (4 g, 30 mmol) in 40 mL of methanol was added 20 mL of 36% hydrochloric acid, with occasional cooling to maintain the temperature at 20-30 °C. To the resulting solution was added a solution of potassium iodide (3.2 g, 20 mmol) and potassium iodate (2.1 g, 10 mmol) in 25 ml water over a 10-minute period. Note that the solution color changed from colorless to brown and cloudy. After stirring at room temperature overnight, the reaction mixture was extracted with dichloromethane, washed with $Na_2S_2O_3$ and 1N NaOH, dried with Na_2SO_4. The solvent was removed under reduce pressure. The resulting tan solid was recrystallized several times from hot methanol by cooling down to –4 °C to yield 7.7 g (98% yield) of white crystals, which were identified as 3,5-dimethyl-4-iodoanisol (**88**). ^{1}HNMR (300MHz, $CDCl_3$) δ 6.67 (s, 2H), 3.78 (s, 3H), 2.45 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 142.8, 112.8, 96.9. 55.2, 29.7. MS (CI) LRMS calcd for $C_9H_{11}IO$ + H requires *m/z* 262.99, found 263.10.



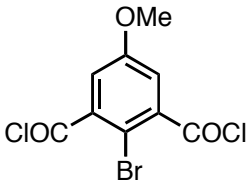
2-iodo-5-methoxy-isophthaloyl dichloride (**89**): In a 250 mL three-necked round-bottom flask equipped with a mechanical stirrer and a reflux condenser was added 2-iodo-5-methoxy-1,3-dimethylbenzene (**88**) (2 g, 8 mmol), dispersed in 30 mL of water and NaOH (1.3 g, 32 mmol). A hot solution of $KMnO_4$ (10.8 g, 72 mmol) in 100 mL of water was added at 100 °C and the reaction mixture was heated at reflux for 8 h. After the mixture was cooled to room temperature, the reaction was filtered using vacuum filtration. The solution was acidified with concentrated HCl. The resulting white precipitate was collected by vacuum filtration and either oven-dried (~80 °C) or dried under high vacuum overnight to give 1.3 g (53% yield) of the 2-iodo-5-methoxy-isophthalic acid. To a suspension of 2-iodo-5-methoxy-isophthalic acid (0.7 g, 2.2 mmol) in benzene (50 mL) and a drop of DMF was added $SOCl_2$ (11 mL, 150 mmol) at 0 °C. The mixture was warmed up to reflux. After the mixture was refluxed for 5 h, the excess $SOCl_2$ was removed by distillation to give 772 mg (99% yield) of the 2-iodo-5-methoxy-isophthalic acid chloride (**89**) as a pale yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (s, 2H), 3.95 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 158.9, 139.5, 119.3, 106.8, 56.3. MS (CI) LRMS calcd for $C_9H_5Cl_2IO_3$ + H requires *m/z* 358.87, found 358.9.



[(*S*,*S*)-MeOPhebox-*i*-Pr]I (**86a**): A solution of 2-iodo-5-methoxy-isophthaloyl dichloride (**89**) (750 mg, 2.09 mmol) in dichloromethane (10 mL) was slowly added to a solution of L-valinol (474 mg, 4.6 mmol), triethylamine (4.25 mL, 31 mmol) in dichloromethane (20 mL) at 0 ºC. The mixture was stirred at room temperature for 5 h. Formation of the intermediate diamide–dialcohol was monitored by TLC. Then, methanesulfonyl chloride (524.4 mg, 4.6 mmol) was added at 0 ºC, and the mixture was stirred at room temperature for 8 h. Formation of the product **86a** was monitored by TLC examination; R_f = 0.4 (60% ethyl acetate/hexane). At 0 ºC, aqueous potassium carbonate (1 N, ca. 30 mL) was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate, and concentrated under reduce pressure. The crude product was purified by column chromatography (20% EtOAc-Hexanes) to give **86a** in 62 % yield after two steps (580 mg, 1.27 mmol) as colorless oil. $[\alpha]^{19}_{D}$ = –62.42° (*c*= 1 in $CHCl_3$). IR (thin film) ν 1650 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.11 (s, 2H), 4.47 (m, 2H), 4.14 (m, 4H), 3.79 (s, 3H), 1.89 (m, 2H), 1.04 (d, *J* = 6.8 Hz, 6H), 0.96 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 159.0, 137.8, 117.7, 84.0, 72.3, 70.6, 55.0, 32.6, 18.9, 18.4. MS (ESI) LRMS calcd for $C_{19}H_{25}IN_2O_3$ + H requires *m/z* 457.091, found 457.085.

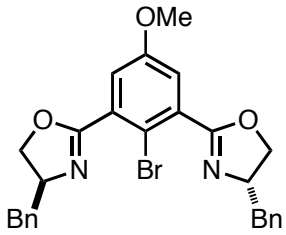


2-bromo-5-methoxy-1,3-dimethylbenzene (**90**): To a stirred solution of 3,5-dimethylanisol (**E-12**) (8.2 g, 60 mmol) in CH_2Cl_2 (100 mL) was added dropwise a 1.0 M solution of bromine in CH_2Cl_2 (9.95 g, 63 mmol) at 0 °C via cannula over a 2-min period of time under argon. The reaction was stirred for 1 hour at room temperature; progress was monitored by TLC analysis. The product was washed with sodium thiosulfate until the organic phase is colorless, dried with sodium sulfate. The solvent was removed under reduce pressure. The residue was purified by simple distillation to give 10.88 g (66%) of pure 2-bromo-5-methoxy-1,3-dimethylbenzene (**90**) as a colorless liquid: ^{1}HNMR (300MHz, $CDCl_3$) δ 6.56 (s, 2H), 3.78 (s, 3H), 2.40 (s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 138.8, 118.8, 113.9, 55.6, 24.2. MS (CI) LRMS calcd for $C_9H_{11}BrO$ + H requires *m/z* 215.0, found 215.1 and 217.1.



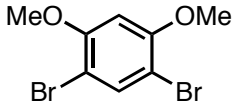
2-bromo-5-methoxy-isophthaloyl dichloride (**91**): In a 250 mL three-necked round-bottom flask equipped with a mechanical stirrer and a reflux condenser was added 2-bromo-5-methoxy-1,3-dimethylbenzene (**90**) (2.5 g, 11.7 mmol), dissolved in 30.0 mL of *t*-BuOH–water (1:1) and $KMnO_4$ (3.7 g, 23.4 mmol). The mixture was set at reflux for 2 h, cool down to room temperature, then more $KMnO_4$ (3.7 g, 23.4 mmol) was added.

The reaction mixture was refluxed for another 16 hours. After the mixture was cooled to room temperature, and filtered using vacuum filtration, the *t*-BuOH was removed under reduce pressure. The solution was acidified with concentrated HCl. The resulting white precipitate was collected by vacuum filtration and either oven-dried (~80 °C) or dried under high vacuum overnight to give 1.79 g (56% yield) of the 2-bromo-5-methoxy-isophthalic acid. To a suspension of 2-bromo-5-methoxy-isophthalic acid (1.0 g, 3.7 mmol) in benzene (50 mL) and a drop of DMF was added $SOCl_2$ (11 mL, 150 mmol) at 0 °C. After the mixture was refluxed for 5 h, the excess $SOCl_2$ was removed by distillation to give 1.12 g (99% yield) of the 2-bromo-5-methoxy-isophthaloyl dichloride (**91**) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 2H), 3.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 158.9, 139.5, 119.3, 106.8, 56.3. MS (CI, CH_4) LRMS calcd for $C_9H_5BrCl_2O_3$ + H requires *m/z* 310.88, found 310.9 and 312.9.



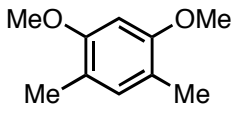
[(*S*,*S*)-MeOPhebox-Bn]Br (**86b**): A solution of 2-bromo-5-methoxy-isophthaloyl dichloride (**91**) (806 mg, 2.6 mmol) in dichloromethane (10 mL) was slowly added to a solution of L-phenylalaninol (824 mg, 5.4 mmol) and triethylamine (1.6 mL, 11.25 mmol) in dichloromethane (20 mL) at 0 ºC. The mixture was stirred at room temperature for 5 h. The volatiles were removed under reduce pressure to afford the crude bisamide that was used without further purification. Acetonitrile (10 mL), PPh_3 (1.52 g, 5.7

mmol), and triethylamine (551 mg, 5.46 mmol) were added to the crude bisamide. The temperature was reduced to 0 °C, after which CCl_4 (840 mg, 5.46 mmol) was slowly added via syringe. The reaction mixture was warmed to room temperature and stirred overnight, after which the mixture was quenched with H_2O (10 mL) and the volatiles were removed under vacuum. The residue was dissolved in H_2O (50 mL) and dichloromethane (100 mL). After separation of the layers, the organic layer was washed with H_2O (30 mL) and brine (30 mL). The combined aqueous layers were extracted with dichloromethane (100 mL). The combined organic layers were dried on Na_2SO_4 and filtered. After the solvent was removed under reducer pressure, the crude product was purified by silica gel column chromatography (20% EtOAc-hexanes) to afford **86b** as colorless oil. 858 mg (66% after two steps). $[\alpha]^{19}_D = -55.68°$ (*c*= 1 in $CHCl_3$). IR (thin film) ν 1645 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.24−7.35 (m, 10H), 7.17 (s, 2H), 4.63 (m, 2H), 4.40 (t, *J* = 7.6 Hz, 2H), 4.20 (t, *J* = 5.6 Hz, 2H), 3.81 (s, 3H), 3.23 (dd, *J* = 5.6 Hz, 6.8 Hz, 2H). 2.86 (dd, *J* = 5.8 Hz, 4.2 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 157.8, 137.4, 132.4, 129.2, 128.5, 128.3, 126.3, 126.4, 118.2, 111.35, 71.9, 67.8, 55.6, 41.2. MS (ESI) LRMS calcd for $C_{27}H_{25}BrN_2O_3$ + H requires *m/z* 505.10, found 505.10 and 507.10.

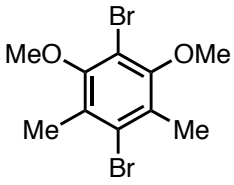


1,5-dibromo-2,4-dimethoxybenzene (**93**). To a stirred solution of 1,3-dimethoxybenzene (15 g, 108 mmol) in CH_2Cl_2 (100 mL) was added dropwise a 1.0 M solution of bromine in CH_2Cl_2 (36 g, 230 mmol) at 0 °C via cannula over a 2-min period

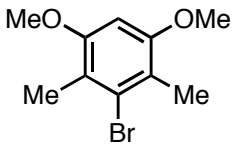
under argon. The reaction was stirred for 30 min., progress was monitored by TLC analysis. The product was washed with sodium thiosulfate until the organic phase is colorless, dried with sodium sulfate, and the solvent was removed under reduced pressure to give 32 g (99%) of pure 1,5-dibromo-2,4-dimethoxybenzene (**93**) as a white solid: ^{1}HNMR (300MHz, $CDCl_3$) δ 7.65 (s, 1H), 6.48 (s, 1H), 3.9 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 135.8, 102.3, 97.3, 56.4. MS (CI, CH_4) LRMS calcd for $C_8H_8Br_2O_2$ + H requires *m/z* 293.89, found 294.0, 295.0, 297.0, and 299.0.



1,5-dimethoxy-2,4-dimethylbenzene (**E-13**). An *n*-BuLi (2.39 g, 37.4 mmol) solution was added to a solution of 1,5-dibromo-2,4-dimethoxybenzene (**93**) (5 g, 17 mmol) in 100 mL of ether at –78 °C under argon, the colorless solution was stirred at –78 °C for 30 min. Iodomethane (4.7 mL, 74.8 mmol) was added slowly at –78 °C under argon via syringe. The mixture was allowed to warm up to room temperature while stirred for 1h. The mixture was quenched with NH_4Cl and washed with 1N NaOH, water and brine. It was dried with sodium sulfate and concentrated under reduce pressure to give 2.8 g (99%) of pure 1,5-dimethoxy-2,4-dimethylbenzene (**E-13**) as white solid: ^{1}HNMR (300MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.43 (s, 1H), 3.83 (s, 6H), 2.13 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 132.3, 117.6, 95.3, 55.69, 15.14. MS (CI, CH_4) LRMS calcd for $C_{10}H_{14}O_2$ + H requires *m/z* 167.10, found 167.10.

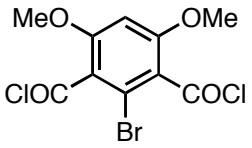


1,4-dibromo-2,6-dimethoxy-3,5-dimethylbenzene (**E-14**). To a stirred solution of 1,5-dimethoxy-2,4-dimethylbenzene (**E-13**) (2.8 g, 17 mmol) in CH_2Cl_2 (70 mL) was added dropwise a 1.0 M solution of bromine (6.7 g, 42 mmol) in CH_2Cl_2 (30 mL) at 0 °C via cannula over a 2-min period under argon. The reaction was stirred for 16 h at room temperature; progress was monitored by TLC analysis. The product was washed with sodium thiosulfate until the organic phase is colorless, dried with sodium sulfate, and the solvent was removed under reduce pressure to give 5.02 g (93%) of pure 1,4-dibromo-2,6-dimethoxy-3,5-dimethylbenzene (**E-14**) as white solid after recrystallization from ether: ^{1}HNMR (300MHz, $CDCl_3$) δ 3.78 (s, 6H), 2.4 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 129.3, 127.7, 112.2, 60.6, 17.3. MS (CI, CH_4) LRMS calcd for $C_{10}H_{12}Br_2O_2$ + H requires *m/z* 322.92, found 323.1, 325.1, and 327.1.



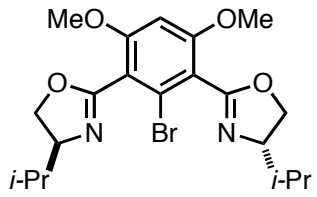
3-bromo-1,5-dimethoxy-2,4-dimethylbenzene (**94**). An *n*-BuLi (795 mg, 12.4 mmol) solution was added to a solution of 1,4-dibromo-2,6-dimethoxy-3,5-dimethylbenzene (**E-14**) (4 g, 12.4 mmol) in 100 mL of ether at –78 °C under argon, the colorless solution was stirred at –78 °C for 1 h. H_2O (50 mg, 25 mmol) in 5 mL of THF was added slowly at –78 °C under argon. The mixture was allowed to warm up to room temperature and stirred for 1h. The mixture was quenched with NH_4Cl and washed with NH_4OH, water

and brine. It was dried with sodium sulfate and concentrated under reduce pressure to give 3.04 g (98%) of pure 3-bromo-1,5-dimethoxy-2,4-dimethylbenzene (**94**) as white solid after recrystallization from ether: ^{1}HNMR (300MHz, $CDCl_3$) δ 6.44 (s, 1H), 3.83 (s, 6H), 2.28 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 129.2, 118.8, 94.7, 56.0, 15.7. MS (CI, CH_4) LRMS calcd for $C_{10}H_{13}BrO_2$ + H requires *m/z* 245.0, found 245.1, and 247.1.



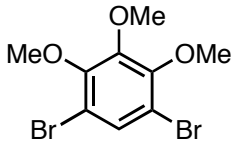
2-bromo-4,6-dimethoxy-isophthaloyl dichloride (**95**). In a 250 mL three-necked round-bottom flask equipped with a mechanical stirrer and a reflux condenser was added 3-bromo-1,5-dimethoxy-2,4-dimethylbenzene (**94**) (2.85 g, 12 mmol), dispersed in 100 mL of a 1:1 mixture of tert-butyl alcohol and water. $KMnO_4$ (11.4 g, 72 mmol) was added, and the reaction mixture was heated to reflux for 2 h. After the mixture was cooled to room temperature, more $KMnO_4$ (11.4 g, 72 mmol) was added and the reaction mixture was refluxed for an additional 16 h. After the mixture was cooled to room temperature, the reaction was filtered through Celite and the filtrate was reduced by 1/3 under reduce pressure. The solution was acidified with concentrated HCl. The resulting white precipitate was collected by vacuum filtration and the precipitate collected and either oven-dried (~80 °C) or high vacuum dried overnight to give 2.30 g (65% yield) of 2-bromo-4,6-dimethoxy-isophthalic acid as yellowish solid: IR (thin film) ν 3463, 1663 cm^{-1}. To a suspension of 2-bromo-4,6-dimethoxy-isophthalic acid (1.5 g, 5 mmol) in benzene (40 mL) and a drop of DMF was added $SOCl_2$ (9 mL, 61 mmol) at 0 °C. After

the mixture was refluxed for 3 h, the excess $SOCl_2$ was removed by distillation, which gave 2-bromo-4,6-dimethoxy-isophthaloyl dichloride (**95**) in 99% yield (1.6 g) as a pale yellow solid. ^{1}HNMR (300MHz, $CDCl_3$) δ 6.49 (s, 1H), 3.97 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 158.3, 123.0, 114.2, 94.6, 56.7. MS (CI, CH_4) LRMS calcd for $C_{10}H_7BrCl_2O_4$ + H requires *m/z* 340.89, found 340.9 and 342.9.

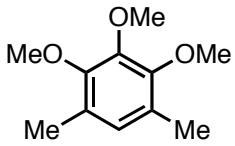


[(*S*,*S*)-(MeO)$_2$Phebox-*i*-Pr]Br (**92a**). A solution of 2-bromo-4,6-dimethoxy-isophthaloyl dichloride (**95**) (110 mg, 0.324 mmol) in dichloromethane (5 mL) was slowly added to a solution of *L*-valinol (70 mg, 0.679 mmol) and triethylamine (0.2 mL, 1.4 mmol) in dichloromethane (5 mL) at 0 ºC. The mixture was stirred at room temperature for 5 h. Formation of the intermediate diamide–dialcohol was monitored by TLC. The volatiles were removed under reduce pressure to afford the crude bisamide that was used without further purification. Acetonitrile (5 mL), PPh_3 (254.6 mg, 0.972 mmol), and triethylamine (98 mg, 0.972 mmol) were added to the crude bisamide. The temperature was reduced to 0 °C, after which CCl_4 (150 mg, 0.972 mmol) was slowly added via syringe. The reaction mixture was warmed to room temperature overnight, after which the mixture was quenched with H_2O (10 mL) and the volatiles were removed in vacuo. The residue was dissolved in H_2O (50 mL) and dichloromethane (100 mL). After separation of the layers, the organic layer was washed with H_2O (30 mL) and brine (30 mL). The combined aqueous layers were extracted with dichloromethane (100 mL).

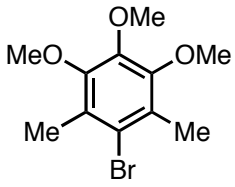
The combined organic layers were dried on Na_2SO_4 and filtered. After the solvent was removed under reduced pressure, the crude product was purified by silica gel column chromatography (20% EtOAc-hexanes) to afford **92a** as colorless oil. 123 mg (87% after two steps). $[\alpha]^{19}_D$ = –64.75° (*c*= 1 in $CHCl_3$). IR (thin film) ν 1652 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 6.39 (s, 1H), 4.39 (m, 2H), 4.14 (m, 4H), 3.82 (s, 6H), 1.93(m, 2H), 1.02 (d, *J* = 6.5 Hz, 6H), 0.92 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 160.3, 124.2, 113.5, 94.0, 72.4, 70.1, 56.1, 32.2, 18.74, 18.19. MS (ESI) LRMS calcd for $C_{20}H_{27}BrN_2O_4$ + H requires *m/z* 439.11, found 439.12 and 441.11.



1,5-dibromo-2,3,4-trimethoxybenzene (**E-15**). To a stirred solution of 1,2,3-trimethoxybenzene (**97**) (4 g, 24 mmol) in CH_2Cl_2 (40 mL) was added dropwise a 1.0 M solution of bromine in CH_2Cl_2 (8.4 g, 53 mmol) at 0 °C via cannula over a 2-min period under argon. The reaction was stirred for 1h at room temperature; progress was monitored by TLC analysis. The product was washed with sodium thiosulfate until the organic phase is colorless and dried with sodium sulfate. The solvent was removed under reduce pressure to give 7.4 g (97%) of pure 1,5-dibromo-2,3,4-trimethoxybenzene (**E-15**) as a colorless liquid after simple distillation: ^{1}HNMR (300MHz, $CDCl_3$) δ 7.49 (s, 1H), 3.94 (s, 3H), 3.9 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 148.2, 129.7, 112.2, 61.2, 60.9. MS (CI, CH_4) LRMS calcd for $C_9H_{10}Br_2O_3$ + H requires *m/z* 324.9, found 324.9, 325.9, and 327.9.

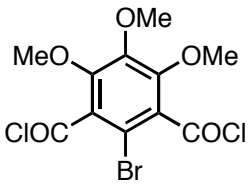


2,3,4-trimethoxy-1,5-dimethylbenzene (**E-16**). An *n*-BuLi (1.66 g, 26 mmol) solution was added to a solution of 1,5-dibromo-2,3,4-trimethoxybenzene (**E-15**) (7 g, 22 mmol) in 100 mL of ether at –78 °C under argon, the cloudy solution was stirred at –78 °C for 30 min. Iodomethane (3.3 mL, 52.8 mmol) was added slowly at –78 °C under argon via syringe. The mixture was allowed to warm up to room temperature and stirred for 1h, the mixture becomes clear. A second addition of *n*-BuLi (1.66 g, 26 mmol) was added at –78 °C under argon and stirred at –78 °C for 30 min. Iodomethane (3.3 mL, 52.8 mmol) was added again slowly at –78 °C under argon via syringe. The mixture was allowed to warm up to room temperature and stirred for 1h. The mixture was diluted with ether (50 mL) and quenched with aqueous NH_4Cl and washed with 1N NaOH, water and brine. It was dried with sodium sulfate and concentrated under reduced pressure to give 4.2 g (99%) of pure 2,3,4-trimethoxy-1,5-dimethylbenzene (**E-16**) as colorless liquid after distillation: ^{1}HNMR (300MHz, $CDCl_3$) δ 6.70 (s, 1H), 3.92 (s, 3H), 3.84 (s, 6H), 2.20 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 146.1, 126.3, 126.1, 60.5, 60.3, 15.3. MS (CI, CH_4) LRMS calcd for $C_{11}H_{16}O_3$ + H requires *m/z* 197.11, found 197.1.



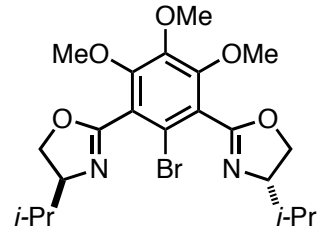
1-bromo-3,4,5-trimethoxy-2,6-dimethylbenzene (**98**). To a stirred solution of 2,3,4-trimethoxy-1,5-dimethylbenzene (**E-16**) (2 g, 10 mmol) in CH_2Cl_2 (20 mL) was added

dropwise a 1.0 M solution of bromine (3.18 g, 11 mmol) in CH_2Cl_2 (10 mL) at 0 °C via cannula over a 2-min period under argon. The reaction was stirred for 2 h at room temperature; progress was monitored by TLC analysis. The product was washed with sodium thiosulfate until the organic phase becomes colorless, dried with sodium sulfate, and the solvent is removed under reduced pressure to give 2.4 g (86%) of pure 1-bromo-3,4,5-trimethoxy-2,6-dimethylbenzene (**98**) as colorless oil after silica gel column chromatography: ^{1}HNMR (300MHz, $CDCl_3$) δ 3.90 (s, 3H), 3.81 (s, 6H), 2.32 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 145.6, 127.7, 121.8, 60.8, 60.7, 16.47. MS (CI, CH_4) LRMS calcd for $C_{11}H_{15}BrO_3$ + H requires *m/z* 275.02, found 275.0 and 277.0.



2-bromo-4,5,6-trimethoxy-isophthaloyl dichloride (**99**). In a 250 mL three-necked round-bottom flask equipped with a mechanical stirrer and a reflux condenser was 1-bromo-3,4,5-trimethoxy-2,6-dimethylbenzene (**98**) (2 g, 7.3 mmol), dispersed in 30 mL water and NaOH (2.34 g, 58.4 mmol), the mixture was heated to 100 °C. Hot solution of $KMnO_4$ (6.95 g, 44 mmol) in 100 mL of water was added, and the reaction mixture was stirred at 100 °C for 8 h. After the mixture was cooled to room temperature, the reaction was filtered through Celite and the filtrate was reduced by 1/3 under reduced pressure. The solution was acidified with concentrated HCl. The resulting white precipitate was collected by vacuum filtration and the precipitate collected and either oven-dried (~80 °C) or high vacuum dried overnight to give 1.42 g (52% yield) of 2-bromo-4,5,6-

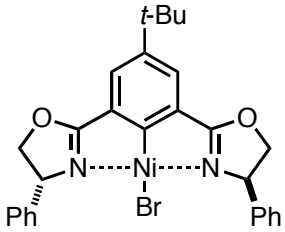
trimethoxy-isophthalic acid as white solid: IR (thin film) ν 3460, 1675 cm^{-1}. To a suspension of 2-bromo-4,5,6-trimethoxy-isophthalic acid (1 g, 3 mmol) in benzene (40 mL) and a drop of DMF was added $SOCl_2$ (9 mL, 61 mmol) at 0 °C. After the mixture was refluxed for 3 h, the excess $SOCl_2$ was removed by distillation, which gave 2-bromo-4,5,6-trimethoxy-isophthaloyl dichloride (**99**) in 99% yield (1.1 g) as a pale yellow oil. ^{1}HNMR (300MHz, $CDCl_3$) δ 4.05 (s, 6H), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.04, 152.34, 145.2, 130.8, 105.7, 62.07, 61.13. MS (CI, CH_4) LRMS calcd for $C_{11}H_9BrCl_2O_5$ + H requires *m/z* 370.9, found 370.9 and 372.9.



[(*S*,*S*)-(MeO)$_3$Phebox-*i*-Pr]Br (**96a**). A solution of 2-bromo-4,5,6-trimethoxy-isophthaloyl dichloride (**99**) (1 g, 2.7 mmol) in dichloromethane (10 mL) was slowly added to a solution of *L*-valinol (1.114 mg, 11 mmol) and triethylamine (6.3 mL, 45 mmol) in dichloromethane (20 mL) at 0 ºC. The mixture was stirred at room temperature for 5 h. Formation of the intermediate diamide–dialcohol was monitored by TLC. Then, methanesulfonyl chloride (1.5 g, 13.2 mmol) was added at 0 ºC, and the mixture was stirred at room temperature for 16 h. Formation of the product **96a** was monitored by TLC. At 0 ºC, aqueous potassium carbonate (1 N, ca. 30 mL) was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product

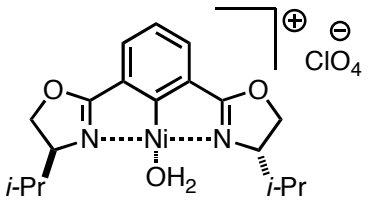
was purified by column chromatography (20% EtOAc-Hexanes) to give [(*S,S*)-$(MeO)_3$Phebox-*i*-Pr]Br (**96a**) in 68 % yield after two steps (862 mg, 1.83 mmol) as a white solid. $[\alpha]^{19}_D$ = –67.86° (*c*= 1 in $CHCl_3$). IR (thin film) ν 1650 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 4.41 (t, *J* = 8.8 Hz, 2H), 4.16 (m, 4H), 3.88 (s, 6H), 3.84 (s, 3H), 1.87 (m, 2H), 1.03 (d, *J* = 4.5 Hz, 6H), 0.98 (d, *J* = 4.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 154.2, 145.5, 122.9, 116.3, 72.8, 70.3, 61.6, 60.8, 32.4, 18.7, 18.39. MS (ESI) LRMS calcd for $C_{21}H_{29}BrN_2O_5$ + H requires *m/z* 469.12, found 469.11 and 471.11.

2.5.3 Synthesis and Characterization of Pincer Complexes

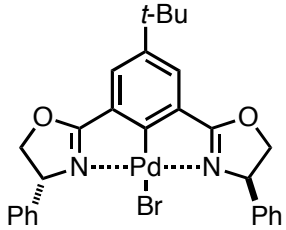


[(*R,R*)-*t*-BuPhebox-Ph]NiBr (**104**): A mixture of [(*R,R*)-*t*-BuPhebox-Ph]Br (**80b**) (385 mg, 0.385 mmol) and $Ni(COD)_2$ (115.2 mg, 0.424 mmol) in dry toluene (9 mL) was stirred for 2 h at room temperature, by which time the reaction was deemed complete by TLC (60% EtOAc-Hexanes). The reaction mixture was filtered through silica gel eluting with ethyl acetate. The yellow band was collected and the solvent was removed under reduce pressure to give **104** as a yellow solid (207 mg, 0.37 mmol) 96% yield. A sample suitable for X-ray analysis was prepared by slow evaporation of dichloromethane solution in air to afford bright yellow crystals. IR (thin film) ν 1650 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.42 (s, 2H), 7.28–7.34 (m, 10H), 5.07 (dd, *J* = 4.3 Hz, 2H), 4.96 (t,

J = 8.6 Hz, 2H), 4.68 (dd, *J* = 4.3 Hz, 2H), 1.36 (s, 9H). MS (ESI) HRMS calcd for $C_{28}H_{27}BrN_2NiO_2$ – Br requires *m/z* 481.1426, found 481.1422.

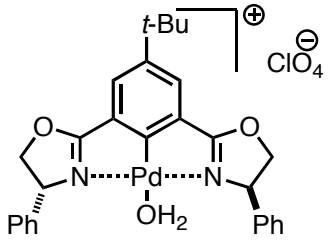


[(*S,S*)-Phebox-*i*-Pr]NiClO$_4$•H$_2$O (**109**): A mixture of [(*S,S*)-Phebox-*i*-Pr]NiBr (**100**) (207 mg, 0.37 mmol)) and $AgClO_4$ (82 mg, 0.42 mmol) was stirred in dry dichloromethane (10 mL) for 2 h at room temperature, under argon and wrapped in aluminum foil to protect the reaction mixture from light by which time the reaction was monitored by TLC (60% EtOAc-Hexanes). The reaction mixture was filtered through celite eluting with dichloromethane. The solvent was removed under reduce pressure to give **109** as a red solid (211 mg, 0.37 mmol) quantitative yield. A sample suitable for X-ray analysis was prepared by slow evaporation of a diethyl ether solution in air to give a greenish yellow crystal. MS (ESI) HRMS calcd for $C_{18}H_{23}ClN_2NiO_6$ – ClO_4 requires *m/z* 357.1113, found 357.1109.



[(*R,R*)-*t*-BuPhebox-Ph]PdBr (**122**): A mixture of [(*R,R*)-*t*-BuPhebox-Ph]Br (**80b**) (50.2 mg, 0.1 mmol) and $Pd_2(dba)_3$ (50 mg, 0.11 mmol) was stirred in dry toluene (5 mL) for 3 h at room temperature, by which time the reaction was deemed complete by

TLC (60% EtOAc-Hexanes). The reaction mixture was filtered through silica eluting with toluene to remove dba. The silica gel was then washed separated with ethyl acetate to give a yellow solution which was collected. The solvent was removed under reduced pressure to give **36** as yellow solid (44 mg, 0.08 mmol) 88% yield. A sample suitable for X-ray analysis was prepared by slow evaporation of a dichloromethane solution in air to give light yellow crystals. IR (thin film) ν 1635 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.50 (s, 2H), 7.29–7.35 (m, 10H), 5.38 (q, *J* = 4.3 Hz, 2H), 5.03 (t, *J* = 5.6 Hz, 2H), 4.77 (q, *J* = 4.3 Hz, 2H), 1.37 (s, 9H). MS (ESI) HRMS calcd for $C_{28}H_{27}BrN_2PdO_2$ – Br requires *m/z* 529.1107, found 529.1109.

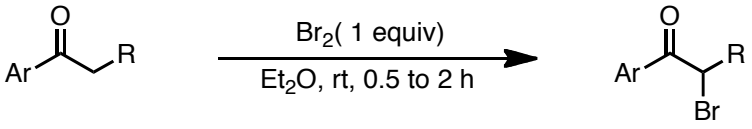


[(*R,R*)-*t*-BuPhebox-Ph]PdClO$_4$•H$_2$O (**131**): A mixture of [(*R,R*)-*t*-BuPhebox-Ph]PdBr (**122**) (20 mg, 0.03 mmol)) and $AgClO_4$ (10.3 mg, 0.05 mmol) was stirred in dry dichloromethane (10 mL) for 2 h at room temperature under argon. Wrapped in aluminum foil to protect the reaction mixture from light by which time the reaction was monitored by TLC (60% EtOAc-Hexanes). The reaction mixture was filtered through celite eluting with dichloromethane. The solvent was removed under reduce pressure to give **131** as a yellow solid (19 mg, 0.03 mmol) quantitative yield. IR (thin film) ν 1645 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.52 (s, 2H), 7.32–7.42 (m, 10H), 5.43 (t, *J* = 6.3 Hz,

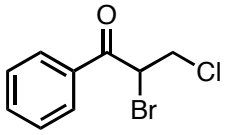
2H), 5.25 (t, J = 8.6 Hz, 2H), 4.64 (t, J = 6.3 Hz, 2H), 1.75 (s, 2H), 1.38 (s, 9H). MS (ESI) HRMS calcd for $C_{28}H_{27}ClN_2PdO_6 - ClO_4$ requires *m/z* 529.1107, found 529.1110.

2.5.4 Synthesis and Characterization of α-Bromoketones

All compounds are known compounds except **142** (Table 2.9). Full-tabulated data is available below for the new compound.



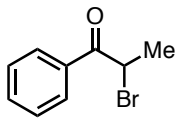
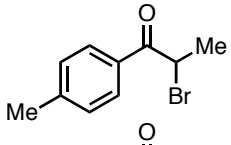
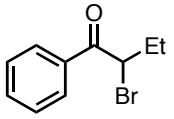
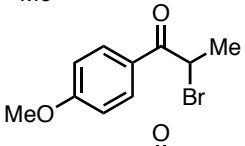
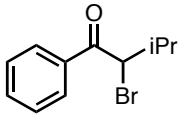
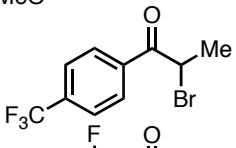
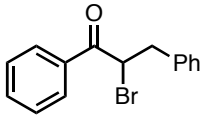
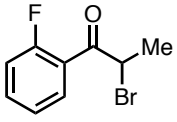
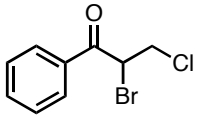
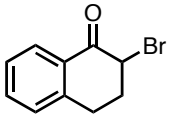
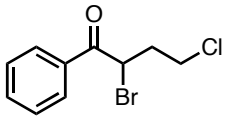
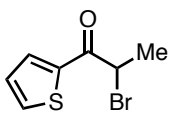
General method for preparation of α-Bromoketones: Bromine (1.05 equiv) was added to an ice cooled solution of a ketone (1.0 equiv, 6 mmol) in 15 mL of Et_2O. The solution was stirred for 30 min. at room temperature, and then the reaction was quenched with 10% aqueous potassium carbonate (10 mL). The organic layer was washed with sodium thiosulfate (10 mL) and brine (10 mL), dried over sodium sulfate, and concentrated. The α-bromoketone was purified by flash silica gel column chromatography (10% CH_2Cl_2/Hexanes).



2-bromo-3-chloro-1-phenylpropan-1-one (**142**)**:** To a ice bath cooled and stirred mixture of 3-chloro-1-phenylpropan-1-one (1.0 g, 5.93 mmol) in 15 mL of Et_2O was added bromine (996 mg, 6.22 mmol, 1.05 equiv). The solution was stirred for 30 min at

room temperature, and then the reaction was quenched with 10% aqueous potassium carbonate (10 mL). The organic layer was washed with sodium thiosulfate (10 mL) and brine (10 mL), dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (10% CH_2Cl_2/hexanes) to give compound **142** (1.24 g, 85%) as a colorless oil. IR (thin film) ν 3403, 3028, 2920, 1695, 1611, 960 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, J = 7.4 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.4 Hz, 2H), 5.30 (dd, J = 4.8 Hz, J = 5.1 Hz, 1H), 4.36 (t, J = 10.1 Hz, 1H), 3.95 (dd, J = 5.1 Hz, J = 5.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.66, 134.23, 134.02, 128.93, 128.90, 42.24, 42.15. HRMS (ESI) calcd for C_9H_8BrClO + Li requires *m/z* 245.9447, found 245.9441.

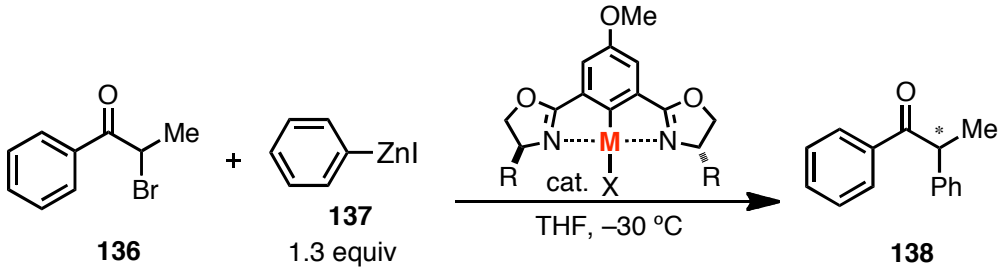
Table 2.19 References to known compounds (α-Bromoketones).[159,191,192]

Compound No.	Product	Yield (%)	Reference	Compound No.	Product	Yield (%)	Reference
136		N/A	159	**144**		96	191
139		92	159	**145**		94	159
140		88	159	**146**		83	159
141		93	159	**147**		96	159
142		85	–	**148**		59	192
143		84	159	**149**		78	159

2.5.5 Asymmetric α-Arylation (Negishi Reaction)

General procedure: A solution of the phenylmagnesium bromide (1.6 mmol; 1.6 equiv) was added to a solution of ZnI_2 (510 mg, 1.6 mmol; 1.6 equiv) in THF (final concentration of PhZnI = 0.20 M) at 0 ºC under argon. The mixture was stirred for 1 h at room temperature (a white precipitate is immediately observed), and then it was cooled to –60 °C. To an oven-dried 10-mL vial was added a pincer complex [(R)PheBoxR^1]MX (0.050 mmol; 0.05 equiv) in 2 mL of THF under argon. Then, the α-bromoketone (0.25 mmol; 1.0 equiv) was added. This solution was cooled to –30 °C. The suspension of PhZnI (2.0 mL, 0.325 mmol; 1.3 equiv) was added dropwise over 3 min, and the reaction mixture was stirred at –30 °C for 14 h. Then, the reaction was quenched with saturated ammonium chloride (10 mL). The reaction mixture was diluted with Et_2O (20 mL), washed with distilled water (10 mL) and brine (10 mL), dried over sodium sulfate, and concentrated. The product **138**[159] was purified by flash silica gel column chromatography.

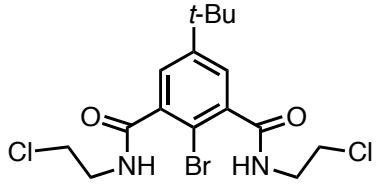
Scheme 2.17 Studied Negishi reaction.



Retention times for the enantiomers of compound **138** was determined by HPLC with a Chiralcel OJ-H column (hexane/*i*PrOH = 98/2), 1.0 mL/min, 254 nm. T_1 = 13.99 min and T_2 = 15.00 min.

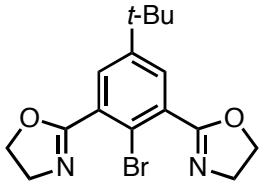
2.5.6 Synthesis of Palladium Pincer Catalysts XV-XXI

Compounds **85** and **91** are known compounds. The rest of the compounds for the synthesis of palladium complexes **XV-XXI** are unknown compounds. Full-tabulated data is available below for all these compounds.

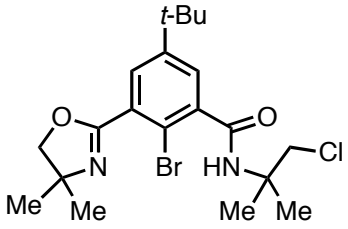


2-bromo-5-*tert*-butyl-N^1,N^3-bis(2-chloroethyl)benzene-1,3-dicarbamide (**E-17**): A solution of isophthaloyl dichloride **85**[42] (0.50 g, 1.48 mmol) in dichloromethane (5 mL) was slowly added to a solution of ethanolamine (190 mg, 3.12 mmol) in dichloromethane (5 mL), then a solution of triethylamine (1.023 mL, 7.4 mmol) in dichloromethane (5 mL) was added slowly at 0 ºC under argon. The mixture was stirred at room temperature for 5 h. Formation of the intermediate diamide–dialcohol was monitored by TLC. Then, methanesulfonyl chloride (1.69 g, 14.8 mmol) was added at 0 ºC, and the mixture was stirred at room temperature for 16 h. Formation of the product S-1 was monitored by TLC. At 0 ºC, aqueous potassium carbonate (1 N, ca. 30 mL) was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate, and concentrated under reduce pressure. The crude product was purified by column chromatography (20% EtOAc-Hexanes) to give **E-17** in 76 % yield (474.6 mg, 1.12 mmol) as a white solid. IR (thin film) ν 3265, 1642 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.57 (s, 2H), 6.35 (t, J = 5.4 Hz, 2 NH), 3.79

(m, 8H), 1.31 (s, 9H). MS (ESI) HRMS calcd for $C_{16}H_{21}BrCl_2N_2O_2$ + H requires *m/z* 423.0163, found 423.0164 and 425.0135.

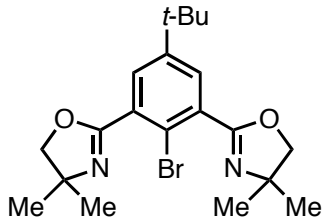


[*t*-BuPheBox-H_2]Br (**152**): To a suspension of NaH (60 mg, 2.5 mmol) in THF (5 mL) under argon was added a solution of dichloro carbamide **E-17** (105.5 mg, 0.25 mmol) in THF (5 mL) at room temperature and stirred for 3h. The mixture was diluted with dichloromethane (50 mL), and washed with saturated NH_4Cl (10 mL) and brine. The organic phase was separated, and dried with sodium sulfate. Concentration of this solution gave [*t*-BuPhebox-H_2]Br (**152**), which was purified by column chromatography (20% EtOAc-hexanes) affording a colorless oil, 85 mg (97% yield): IR (thin film) ν 1655 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.67 (s, 2H), 4.46 (t, *J* = 9.3 Hz, 4H), 4.09 (t, *J* = 9.3 Hz, 4H), 1.37 (s, 9H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 150.3, 131.3, 129.9, 117.9, 67.8, 55.2, 34.6, 30.8. MS (ESI) HRMS calcd for $C_{16}H_{19}BrN_2O_2$ + H requires *m/z* 351.0630, found 351.0635 and 353.0639.



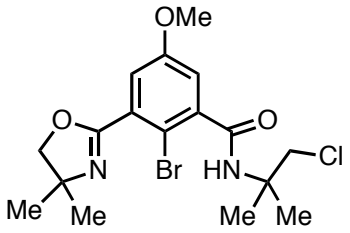
2-bromo-5-*tert*-butyl-*N*-(1-chloro-2-methylpropan-2-yl)-3-(4,4-dimethyl-4,5-dihydr-ooxazol-2-yl)benzamide (**E-18**): A solution of isophthaloyl dichloride **85** (0.50 g, 1.48

mmol) in dichloromethane (5 mL) was slowly added to a solution of 2-amino-2-methyl-1-propanol (291 mg, 3.27 mmol) in dichloromethane (5 mL), then a solution of triethylamine (2.05 mL, 14.8 mmol) in dichloromethane (5 mL) was added slowly at 0 ºC under argon. The mixture was stirred at room temperature for 5 h. Formation of the intermediate diamide–dialcohol was monitored by TLC. Then, methanesulfonyl chloride (1.69 g, 14.8 mmol) was added at 0 ºC, and the mixture was stirred at room temperature for 16 h. Formation of the product S-2 was monitored by TLC. At 0 ºC, aqueous potassium carbonate (1 N, ca. 30 mL) was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate, and concentrated under reduce pressure. The crude product was purified by column chromatography (20% EtOAc-Hexanes) to give **E-18** in 73 % yield (477.5 mg, 1.08 mmol) as a white solid. IR (thin film) ν 3284, 1651 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.7 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 5.81 (s, 1NH), 4.09 (s, 2H), 3.86 (s, 2H), 1.45 (s, 6H), 1.36 (s, 6H), 1.26 (s, 9H). MS (ESI) HRMS calcd for $C_{20}H_{28}BrClN_2O_2$ + H requires *m/z* 443.1023, found 443.1017 and 445.0959.



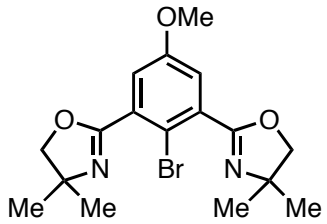
[*t*-BuPheBox-Me$_2$]Br (**153**): To a suspension of NaH (136 mg, 5.6 mmol) in THF (10 mL) under argon was added a solution of chloro benzamide **E-18** (250 mg, 0.56 mmol) in THF (5 mL) at room temperature. Then, the mixture was stirred at reflux for 3 h. The mixture was diluted with dichloromethane (50 mL), and washed with saturated NH_4Cl

(10 mL) and brine. The organic phase was separated, and dried with sodium sulfate. Concentration of this solution gave [*t*-BuPhebox-Me_2]Br (**153**), which was purified by column chromatography (20% EtOAc-hexanes) affording a light yellow oil, 211.2 mg (92% yield): IR (thin film) ν 1656 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.56 (s, 2H), 4.12 (s, 4H), 1.40 (s, 12H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 150.3, 131.6, 129.5, 118.0, 79.3, 68.0, 34.6, 30.9, 28.1. MS (ESI) HRMS calcd for $C_{20}H_{27}BrN_2O_2$ + H requires *m/z* 407.1256, found 407.1257 and 409.1302.

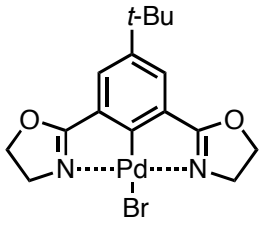


2-bromo-*N*-(1-chloro-2-methylpropan-2-yl)-3-(4,4-dime- thyl-4,5-dihydrooxazol-2-yl)-5-methoxybenzamide (**E-19**): A solution of 2-bromo-5-methoxy-isophthaloyl dichloride **91**[164] (917 mg, 2.96 mmol) in dichloromethane (10 mL) was slowly added to a solution of 2-amino-2-methyl-1-propanol (580 mg, 6.51 mmol) in dichloromethane (10 mL), then a solution of triethylamine (4.095 mL, 29.6 mmol) in dichloromethane (10 mL) was added slowly at 0 ºC under argon. The mixture was stirred at room temperature for 5 h. Formation of the intermediate diamide–dialcohol was monitored by TLC. Then, methanesulfonyl chloride (3.374 g, 29.6 mmol) was added at 0 ºC, and the mixture was stirred at room temperature for 16 h. Formation of the product **E-19** was monitored by TLC. At 0 ºC, aqueous potassium carbonate (1 N, ca. 50 mL) was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine,

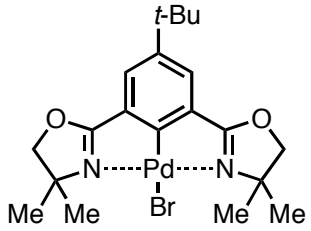
dried over sodium sulfate, and concentrated under reduce pressure. The crude product was purified by column chromatography (20% EtOAc-Hexanes) to give **E-19** in 69 % yield (849.6 mg, 2.04 mmol) as a white solid. IR (thin film) ν 3279, 1657 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.14 (d, *J* = 3.0 Hz, 1H), 7.05 (d, *J* = 3.0 Hz, 1H), 5.74 (s, 1NH), 4.15 (s, 2H), 3.91 (s, 2H), 3.82 (s, 3H), 1.51 (s, 6H), 1.41 (s, 6H). MS (ESI) HRMS calcd for $C_{17}H_{22}BrClN_2O_3$ + H requires *m/z* 417.0502, found 417.0508 and 419.0587.



[MeOPheBox-Me$_2$]Br (**154**): To a suspension of NaH (288 mg, 12 mmol) in THF (10 mL) under argon was added a solution of chloro benzamide **E-19** (500 mg, 1.2 mmol) in THF (10 mL) at room temperature. Then, the mixture was stirred at reflux for 3 h. The mixture was diluted with dichloromethane (50 mL), and washed with saturated NH_4Cl (10 mL) and brine. The organic phase was separated, and dried with sodium sulfate. Concentration of this solution gave crude [MeOPhebox-Me$_2$]Br (**154**), which was purified by column chromatography (20% EtOAc-hexanes) affording **154** in 95% yield (433 mg, 1.14 mmol) as colorless oil, which crystallized to colorless crystals after some period of time. IR (thin film) ν 1665. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.16 (s, 2H), 4.12 (s, 4H), 3.80 (s, 3H), 1.39 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 158.0, 132.8, 118.2, 111.4, 79.5, 68.0, 55.7, 28.1. MS (ESI) HRMS calcd for $C_{17}H_{21}BrN_2O_3$ + H requires *m/z* 381.0736, found 381.0734 and 383.0790.

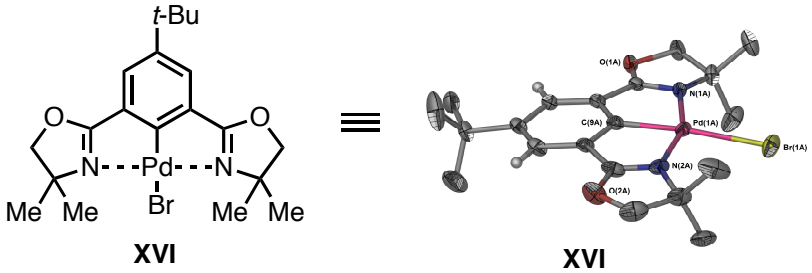


[*t*-BuPheBox-H_2]PdBr (**XV**): A mixture of [*t*-BuPheBox-H_2]Br (**152**) (35 mg, 0.1 mmol) and $Pd_2(dba)_3$ (50 mg, 0.055 mmol) were stirred in dry toluene (4 mL) for 3 h at room temperature, by which time the reaction was deemed complete by TLC (60% EtOAc-Hexanes). The reaction mixture was filtered through silica eluting with toluene to remove dba. The silica gel was then washed separated with ethyl acetate to give a reddish solution which was collected and the solvent was removed under reduce pressure to give **XV** as a reddish solid (45 mg, 0.099 mmol) in 99% yield. IR (thin film) ν 1640, 1559 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.41 (s, 2H), 4.83 (t, *J* = 7.2 Hz, 4H), 4.14 (t, *J* = 7.2 Hz, 4H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 163.8, 143.3, 130.5, 125.3, 82.7, 66.9, 34.9, 31.3. MS (ESI) HRMS calcd for $C_{16}H_{19}BrN_2O_2Pd$ – Br requires *m/z* 377.0481, found 377.0489.



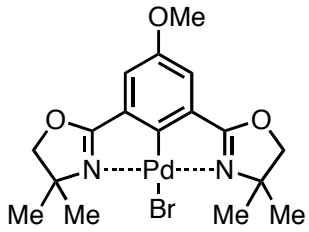
[*t*-BuPheBox-Me_2]PdBr (**XVI**): A mixture of [*t*-BuPheBox-Me_2]Br (**153**) (90 mg, 0.22 mmol) and $Pd_2(dba)_3$ (111 mg, 0.12 mmol) were stirred in dry toluene (6 mL) for 3 h at room temperature, by which time the reaction was deemed complete by TLC (60% EtOAc-Hexanes). The reaction mixture was filtered through silica eluting with toluene

to remove dba. The silica gel was then washed separated with ethyl acetate to give a reddish solution which was collected and the solvent was removed under reduce pressure to give **XVI** as a reddish solid (112 mg, 0.217 mmol) 99% yield. A sample suitable for X-ray analysis was prepared by slow evaporation of a biphasic dichloromethane/ hexanes solution in air to give yellow crystals. IR (thin film) ν 1630, 1558 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.33 (s, 2H), 4.44 (s, 4H), 1.65 (s, 12H), 1.29 (s, 9H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 163.8, 147.9, 129.4, 124.0, 82.7, 65.9, 34.9, 31.3, 28.1. MS (ESI) HRMS calcd for $C_{16}H_{19}BrN_2O_2Pd$ – Br requires *m/z* 433.1107, found 433.1102.

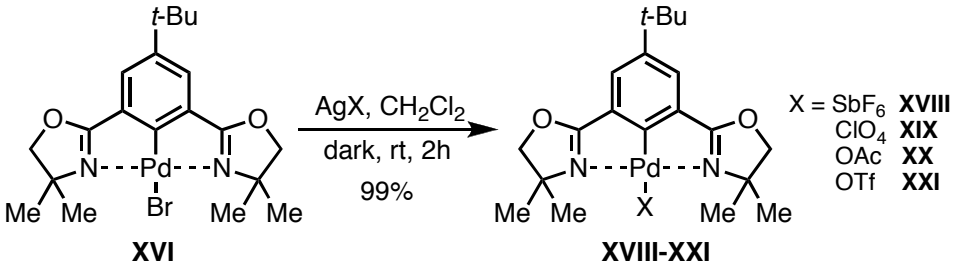


X-Ray Crystal Structure Data for [*t*-BuPheBox-Me$_2$]PdBr (**XVI**): $C_{20}H_{27}BrN_2O_2Pd$, M = 513.75, yellow needle, 0.26 x 0.12 x 0.01 mm^3, monoclinic, space group $P2_1/n$ (No. 14), a = 12.6447(12), b = 21.628(2), c = 15.6491(15) Å, β = 103.716(6)°, V = 4157.7(7) $Å^3$, Z = 8, D_c = 1.641 g/cm^3, F_{000} = 2064, MWPC area detector, Cu Kα radiation, λ = 1.54178 Å, T = 110(2)K, $2\theta_{max}$ = 120.0º, 74692 reflections collected, 6004 unique (R_{int} = 0.0634). Final *GooF* = 1.004, *R1* = 0.0311, *wR2* = 0.0690, R indices based on 5333 reflections with I >2sigma(I) (refinement on F^2), 514 parameters, 18 restraints. Lp and absorption corrections applied, μ = 9.576 mm^{-1}. Absolute structure parameter 0.000(4). Displacement ellipsoid plot (50% probability) of **XVI** is shown above with important atoms numbered. Some hydrogen atoms have been omitted for clarity. Selected bond

distances (Å) and angles (deg): Pd(1A)-C(9A) 1.937(4), Pd(1A)-Br(1A) 2.5278(6), Pd(1A)-N(1A) 2.078(3), Pd(1A)-N(2A) 2.074(4), N(1A)-C(3A) 1.291(5), N(2A)-C(10A) 1.293(6), C(9A)-Pd(1A)-Br(1A) 173.96(11), N(1A)-Pd(1A)-N(2A) 157.79(13), C(9A)-Pd(1A)-N(1A) 79.14(115), C(9A)-Pd(1A)-N(2A) 78.69(16), Br(1A)-Pd(1A)-N(1A) 101.43(9), Br(1A)-Pd(1A)-N(2A) 100.47(10).



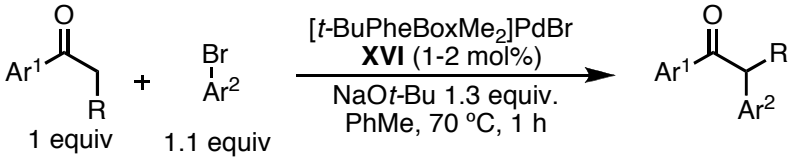
[MeOPheBox-Me$_2$]PdBr (**XVII**): A mixture of [MeOPheBox-Me$_2$]Br (**154**) (90 mg, 0.22 mmol) and $Pd_2(dba)_3$ (111 mg, 0.12 mmol) were stirred in dry toluene (6 mL) for 3 h at room temperature, by which time the reaction was deemed complete by TLC (60% EtOAc-Hexanes). The reaction mixture was filtered through silica eluting with toluene to remove dba. The silica gel was then washed separated with ethyl acetate to give a reddish solution which was collected and the solvent was removed under reduce pressure to give **XVII** as a reddish solid (106 mg, 0.218 mmol) 99% yield. IR (thin film) ν 1620, 1559 cm^{-1}. ^{1}HNMR (300MHz, $CDCl_3$) δ 6.89 (s, 2H), 4.44 (s, 4H), 3.79 (s, 3H), 1.66 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 157.0, 130.0, 128.1, 112.8, 82.7, 66.1, 55.9 28.1. MS (ESI) HRMS calcd for $C_{16}H_{19}BrN_2O_2Pd$ – Br requires *m/z* 407.0587, found 407.0589.



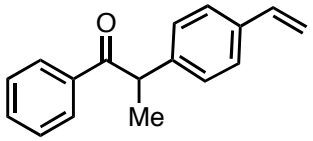
[*t*-BuPheBox-Me$_2$]PdX (**XVIII-XXI**): A mixture of [*t*-BuPheBox-Me$_2$]PdBr (**XVI**) (5.1 mg, 0.01 mmol)) and AgX (1.5 equiv., 0.015 mmol) under argon was stirred in dry dichloromethane (4 mL) for 2 h at room temperature. The mixture was wrapped in aluminum foil to protect the reaction mixture from light during the all reaction time. The reaction mixture was filtered through celite eluting with dichloromethane. The solvent was removed under reduce pressure to give **XVIII-XXI** as a yellow solid (0.01 mmol) in quantitative yield. IR (thin film) ν 1642 cm^{-1}. MS (ESI) HRMS calcd for $C_{16}H_{19}N_2O_2PdX$ – X requires *m/z* 433.1107, found 433.1098.

2.5.7 Procedures and Characterization for the α-Arylation

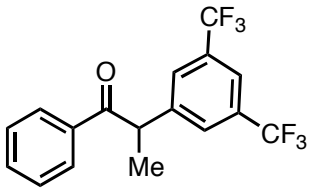
Compounds **138**, **155-163**, **165** and **167-174** are known compounds (Table 2.10). Compounds **164** and **166** are new compounds. Full-tabulated data is available below for the new compounds.



General Procedure for the Selective α-Arylation of Ketones with Aryl Bromides: To an 8 mL glass vial containing a stir bar was added the respective catalyst **XV-XXII** (0.01 equiv, 0.0033 mmol) and capped with a phenolic cap equipped with a teflon/silicone septa. The vial was filled and purged with argon. A solution of sodium tert-butoxide (41.2 mg, 1.3 equiv, 0.429 mmol) in toluene (1.5 mL) was added via syringe under argon. Then, arylbromide (1.1 equiv, 0.363 mmol) was added via syringe followed by the respective ketone (44 mg, 1 equiv, 0.33 mmol) at room temperature. The mixture was stirred for 1 h at 70 ºC under argon. Then it was cooled down to room temperature. The reaction mixture was quenched with saturated ammonium chloride (4 mL), diluted with Et_2O (20 mL), washed with distilled water (10 mL) and brine (10 mL), dried over sodium sulfate, and concentrated under reduce pressure. The product was purified by flash silica gel column chromatography using either (60% toluene-hexanes) or (50% dichloromethane-hexanes) as the eluents.

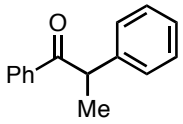
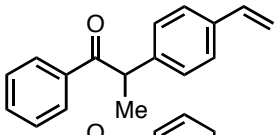
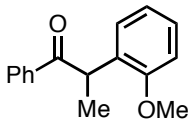
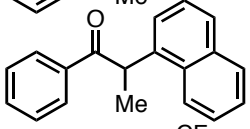
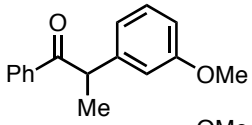
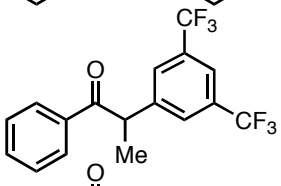
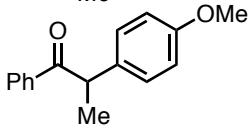
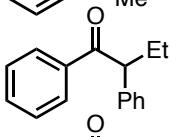
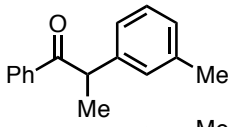
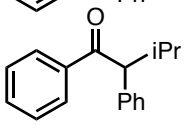
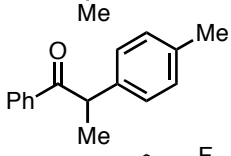
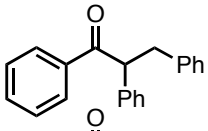
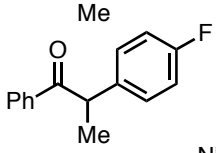
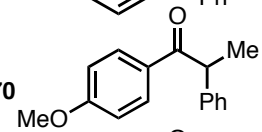
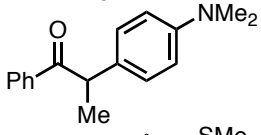
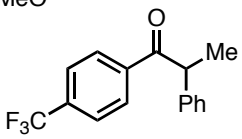
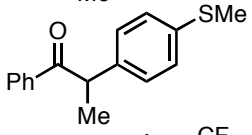
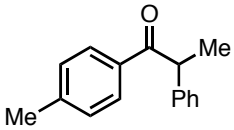
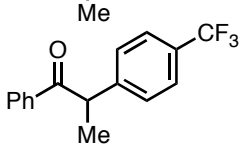
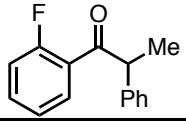


1-phenyl-2-(4-vinylphenyl)propan-1-one (**164**): To an 8 mL glass vial containing a stir bar was added the catalyst **XVI** (1.7 mg, 0.01 equiv, 0.0033 mmol) and capped with a phenolic cap equipped with a teflon/silicone septa. The vial was filled and purged with argon. A solution of sodium tert-butoxide (41.2 mg, 1.3 equiv, 0.429 mmol) in toluene (1.5 mL) was added via syringe under argon. Then, 4-bromostyrene (66.4 mg, 1.1 equiv, 0.363 mmol) was added via syringe followed by propiophenone (**151**) (44 mg, 1 equiv, 0.33 mmol) at room temperature. The mixture was stirred for 1 h at 70 ºC under argon. Then it was cooled down to room temperature. The reaction mixture was quenched with saturated ammonium chloride (4 mL), diluted with Et_2O (20 mL), washed with distilled water (10 mL) and brine (10 mL), and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (50% dichloromethane-hexanes) to give compound **164** (67.6 mg, 85%) as a colorless oil; IR (thin film) ν 3403, 3028, 2920, 1695, 1611, 960 cm1; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, J = 7.6 Hz, 2H), 7.47 (t, J = 7.2 Hz, 1H), 7.47 (m, 4H), 7.26 (d, J = 7.6 Hz, 2H), 6.67 (dd, J = 10.8 Hz, J = 6.4 Hz, 1H), 5.71 (d, J = 17.6 Hz, 1H), 5.22 (d, J = 11.4 Hz, 1H), 4.69 (q, J = 6.8 Hz, 1H), 1.55 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 141.0, 136.4, 136.3, 136.2, 132.7, 128.7, 128.2, 127.9, 126.6, 113.7, 47.5, 19.3. HRMS (ESI) calcd for $C_{17}H_{12}O$ + Li requires *m/z* 243.1361, found 243.1331 (Table 2.10).



2-(3,5-bis(trifluoromethyl)phenyl)-1-phenylpropan-1-one (**166**): To an 8 mL glass vial containing a stir bar was added the catalyst **XVI** (1.7 mg, 0.01 equiv, 0.0033 mmol) and capped with a phenolic cap equipped with a teflon/silicone septa. The vial was filled and purged with argon. A solution of sodium tert-butoxide (41.2 mg, 1.3 equiv, 0.429 mmol) in toluene (1.5 mL) was added via syringe under argon. Then, 1-bromo-3,5-bis(trifluoromethyl)benzene (106.3 mg, 1.1 equiv, 0.363 mmol) was added via syringe followed by propiophenone (**151**) (44 mg, 1 equiv, 0.33 mmol) at room temperature. The mixture was stirred for 1 h at 70 ºC under argon. Then it was cooled down to room temperature. The reaction mixture was quenched with saturated ammonium chloride (4 mL), diluted with Et_2O (20 mL), washed with distilled water (10 mL) and brine (10 mL), and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (50% dichloromethane-hexanes) to give compound **166** (105 mg, 92%) as a colorless oil; IR (thin film) ν 3400, 3026, 2921, 1691, 1605, 970 cm1; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (d, J = 7.4 Hz, 2H), 7.79 (s, 2H), 7.76 (s, 1H), 7.59 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 4.89 (q, J = 11.6 Hz, 1H), 1.62 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 143.5, 135.7, 133.5, 132.05 (q, J = 50.3 Hz, $2CF_3$), 128.8, 128.6, 128.2, 124.9, 121.5, 46.8, 19.6. HRMS (ESI) calcd for $C_{17}H_{12}F_2O$ + Li requires *m/z* 346.0792, found 346.0792 (Table 2.10).

Table 2.10 References to known compounds (α-arylketones).[159,193-196]

Compound No.	Product	Reference (racemic)	Compound No.	Product	Reference (racemic)
138		159	**164**		–
155		159	**165**		196
156		159	**166**		–
157		159	**167**		159
158		159	**168**		159
159		194,195	**169**		159
160		159	**170**		159
161		159	**171**		159
162		159	**172**		193
163		196	**173**		159

CHAPTER III

CONCLUSIONS AND OUTLOOK

We have developed a new catalytic system for the Morita-Baylis-Hillman reaction employing a 1:1:1 ratio of catalytic amounts (10 mol%) of MgI_2, TMEDA and DMAP, which proved to be highly effective at promoting the reaction of a variety of electrophiles, including both electron-poor and electron-rich aldehydes, with various cyclic enones as the nucleophilic substrates in the MBH reaction. Both α,β-unsaturated esters and thioesters were also shown to undergo the MBH sequence even more readily. Furthermore, these studies provided a valuable platform for the development of chiral ligands to promote enantioselective MBH reactions, as chiral TMEDA-equivalent ligands are well known. This newly developed asymmetric MBH reaction involved the effective addition of cyclopentenone to aromatic and aliphatic aldehydes catalyzed by Fu's planar chiral DMAP derivative **II** in conjunction with readily available MgI_2 as a cocatalyst. The products were obtained in good to excellent yields and moderate to excellent enantioselectivity. Perhaps more importantly, the work described here showed that the scope of reactions catalyzed by Fu's planar chiral DMAP catalysts can be increased by employing a simple cocatalyst, a concept which, to our knowledge, had not been documented previously.

We also extended our reaction conditions to the synthesis of β-iodo Baylis-Hillman adducts and to the synthesis of α-hydroxyalkyl allenic esters. Furthermore, we found that some of the β-iodo Baylis-Hillman adducts underwent 1,3-allylic

transpositions. The products of these reactions are quite functionalized and are amenable for subsequent transformations such as aldol, Michael, and Diels-Alder reactions, or 1,2-additions, cross-couplings, among others. Also this approach offers a unique entry to differentiated 1,3 carbonyls as well as β-iodo-dieneoates.

While the Morita-Baylis-Hillman reaction project was ongoing, we also developed an α-methylenation of carbonyls for the synthesis of α,β-unsaturated carbonyls, which in turn served as substrates for the MBH reactions. Using the readily available diisopropylammonium trifluoroacetate salt (**XIV**) as a catalyst, the α-methylenation of carbonyls compounds has been successfully accomplished under mild reaction conditions in good to excellent yields (62 to 99%, 17 of 18 examples above 80%) using various aromatic and aliphatic ketones, aldehydes and esters at 67 ºC in 8 h. No isomerization of the double bond is detected, no over alkylation or polymerization of any adduct was detected and functional group tolerance turned out to be excellent. We believe that this is the simplest and most straightforward method currently available for the α-methylenation of carbonyl compounds.

We anticipate that these new methods will be useful to the general synthetic community for the synthesis of building of significant chiral building blocks as well as in applications to the synthesis of complex molecules, including; but not limited to, Bioactive Natural Products and other pharmaceutically important molecules.

Thirteen PheBox(NCN) pincer ligands were synthesized, varying the electronics of the basic backbone structure, from ready available enantiomeric pure aminoalcohols and aromatic compounds. Air and moisture nickel(II) and palladium(II) bisoxazoline pincer complexes were synthesized via oxidative addition of $Ni(COD)_2$ or $Pd_2(dba)_3$ to PheBox pincer ligands. These pincer complexes were then transformed into cationic complexes by halide abstraction using $AgClO_4$. Their relative Lewis acidity was measured and reported. The identity of several neutral and cationic complexes was confirmed by X-ray crystal structure analysis.

These chiral palladium and nickel "NCN" pincer complexes were subjected to Negishi cross-coupling reactions. They were demonstrated to be very efficient to catalyze the Negishi reactions although not significant enantiomeric excess was obtained. Due to the need of α-bromoketones for the Negishi reaction, several α-bromoketones were prepared using bromine to α-brominate their corresponding aryl ketones with good to excellent yields.

Although, the attempted enantioselective Negishi cross-coupling reaction was fruitless to synthesize enatioenriched α-aryl ketones; afterward, we developed a direct and highly active, (NCN)-Pd catalytic system for the α-arylation of ketones with a variety of aryl bromides using [*t*-BuPheBox-Me_2]PdBr (**XVI**) as the catalyst. The adducts were obtained in excellent yields (92% average) in only 1 hour using 1 mol% of catalyst loading. Perhaps more importantly, the work described here showed that **XVI** is highly reactive, highly selective, even on substrates bearing challenging functional groups such alkenes.

Efforts are underway to further elucidate the mechanistic details of this reaction system, which should in turn allow for future advances to develop an asymmetric variant, as well as to expand the scope of this reaction. We also anticipate that these catalysts will be effective in other related Palladium and Nickel catalyzed cross-couplings.

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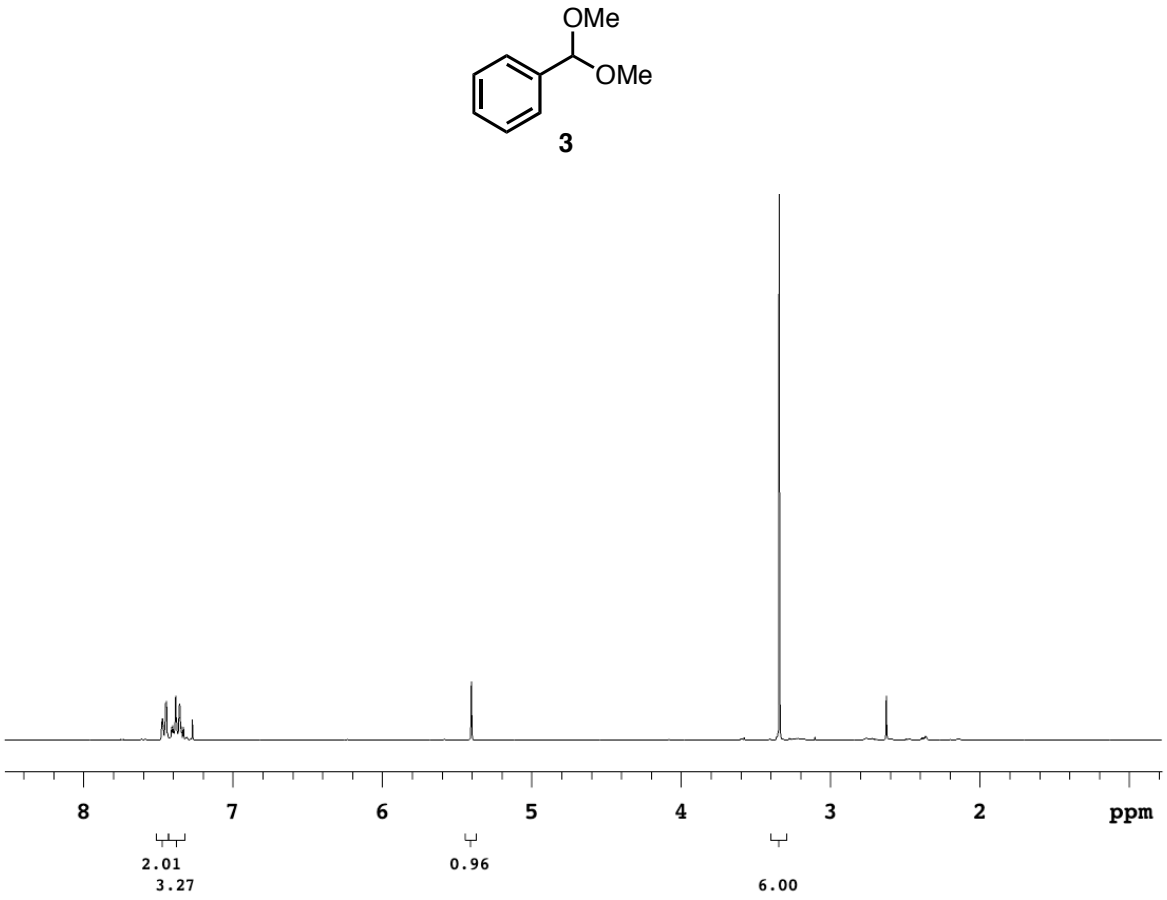
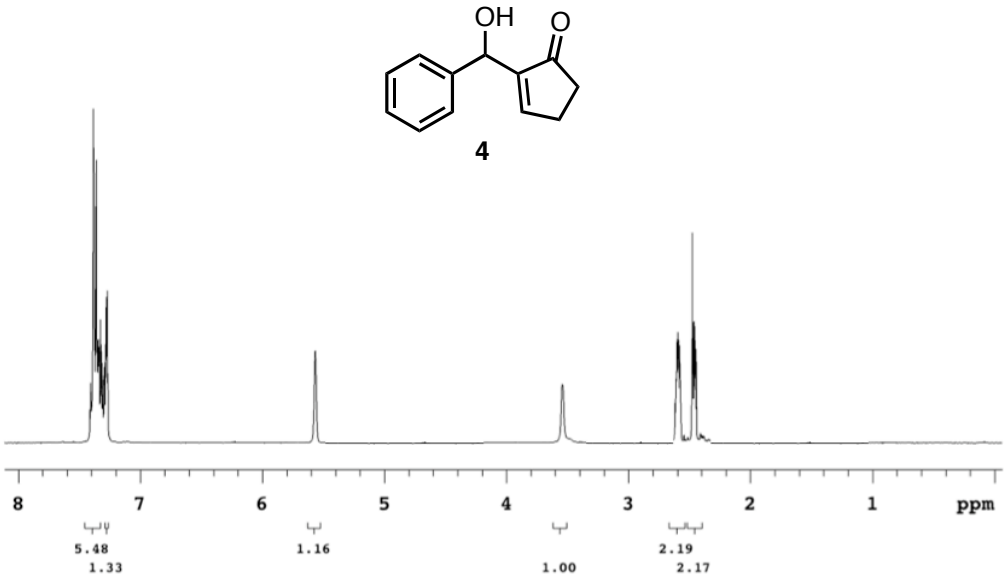
APPENDIX A

^{1}H AND ^{13}C NMR SPECTRA

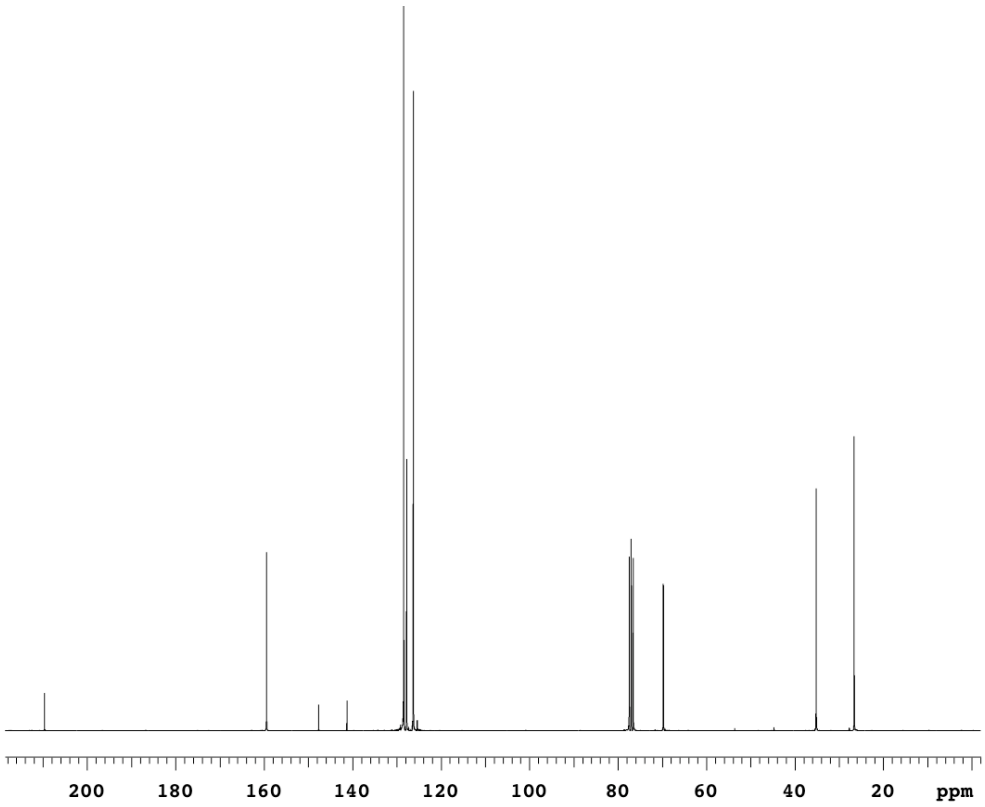
^{1}H NMR ($CDCl_3$, 300 MHz)



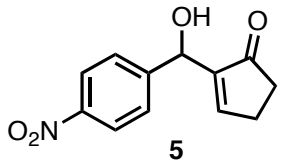
^{1}H NMR ($CDCl_3$, 300 MHz)



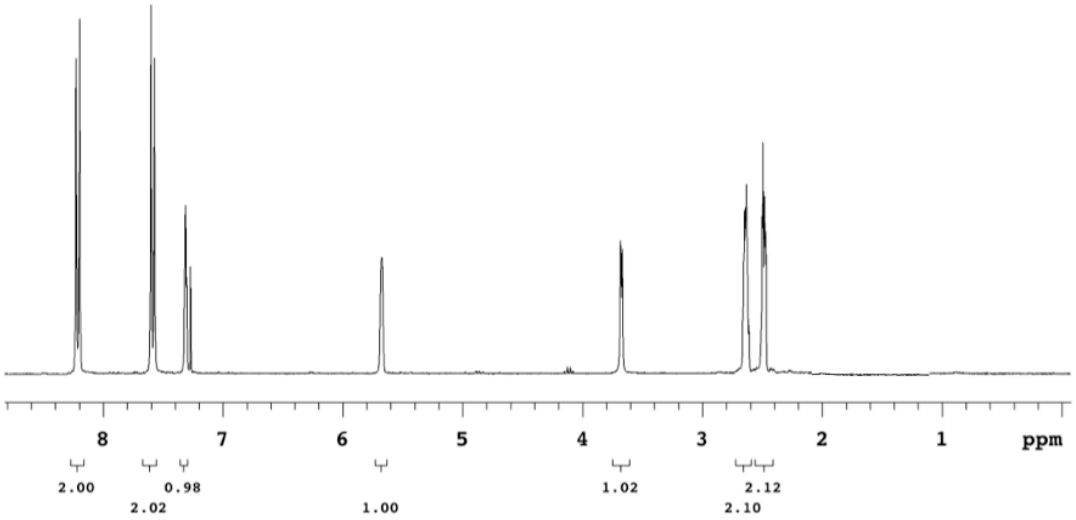
^{13}C NMR ($CDCl_3$, 75 MHz)



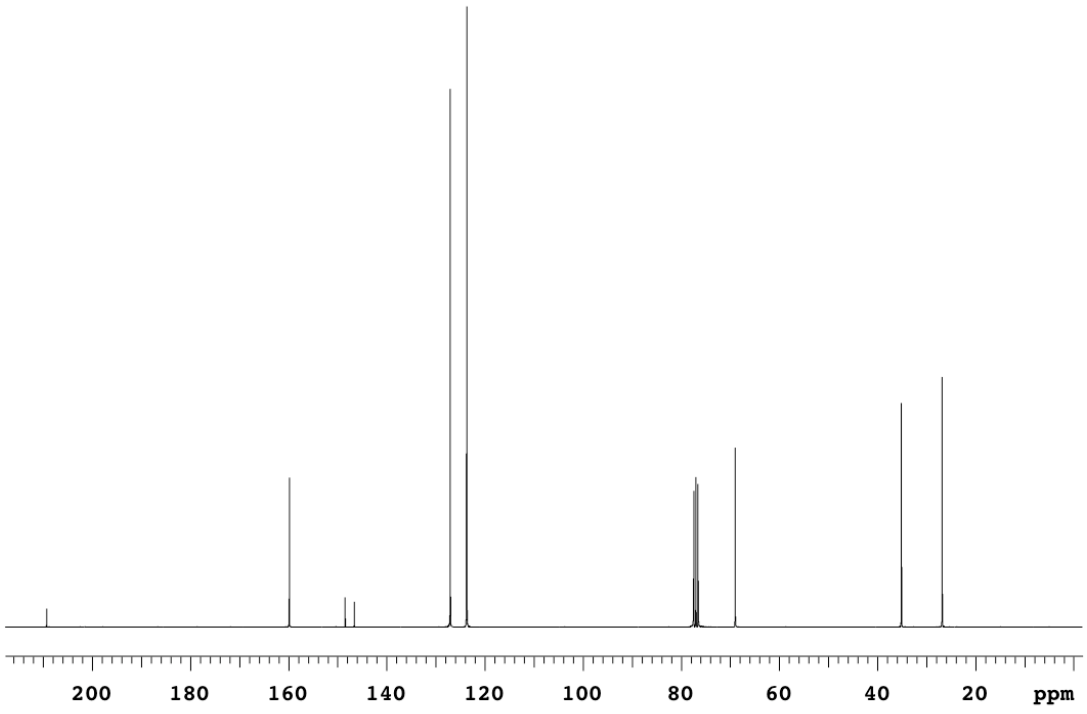
^{1}H NMR ($CDCl_3$, 300 MHz)



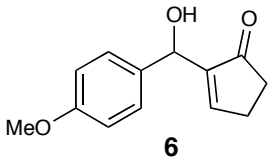
5



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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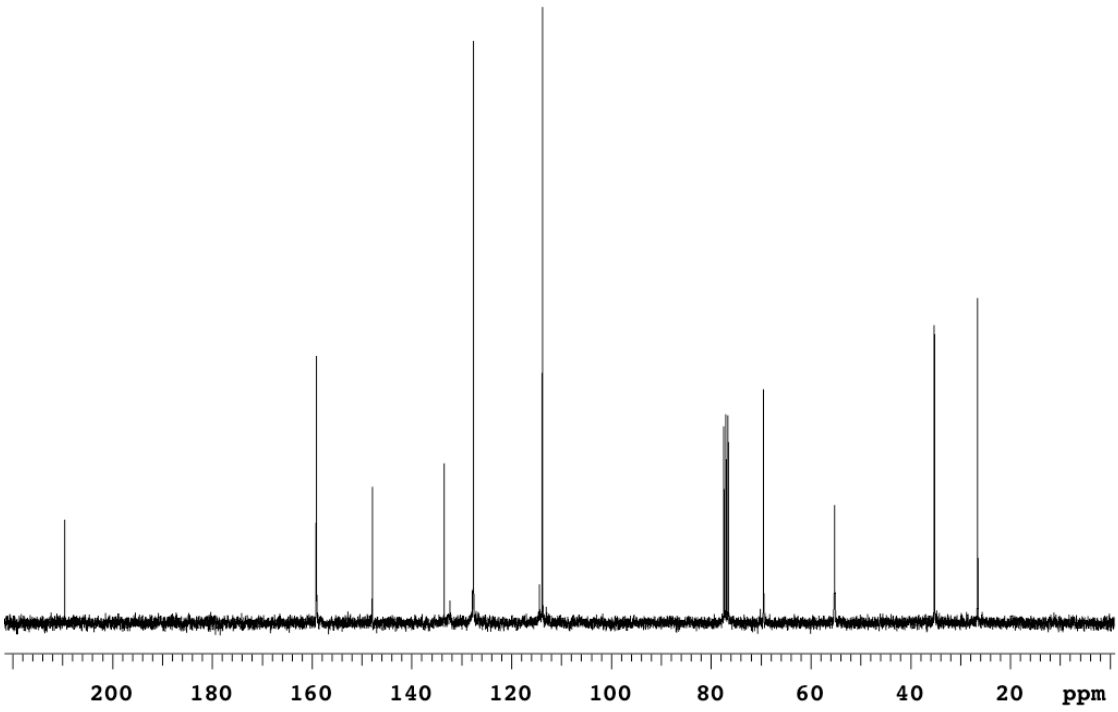
^{13}C NMR ($CDCl_3$, 75 MHz)



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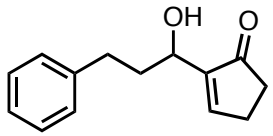

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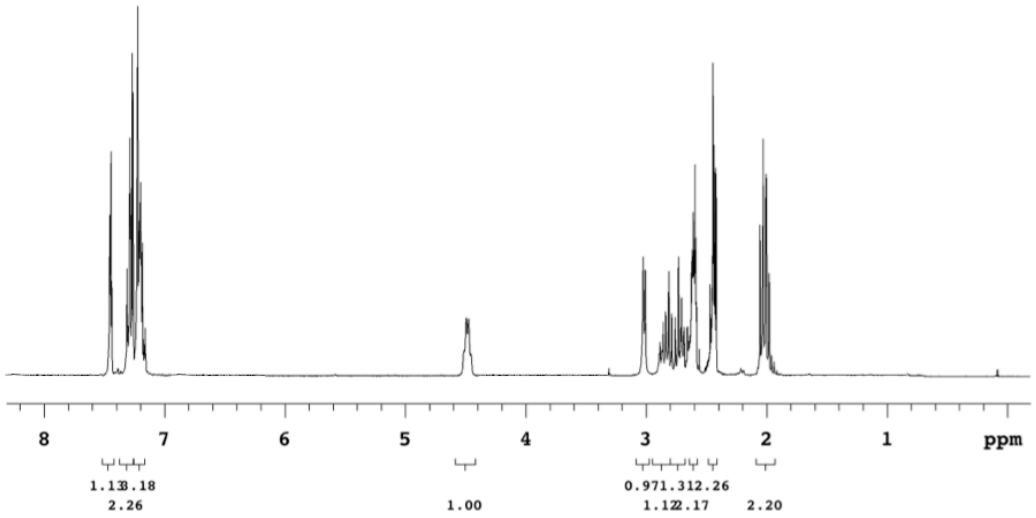
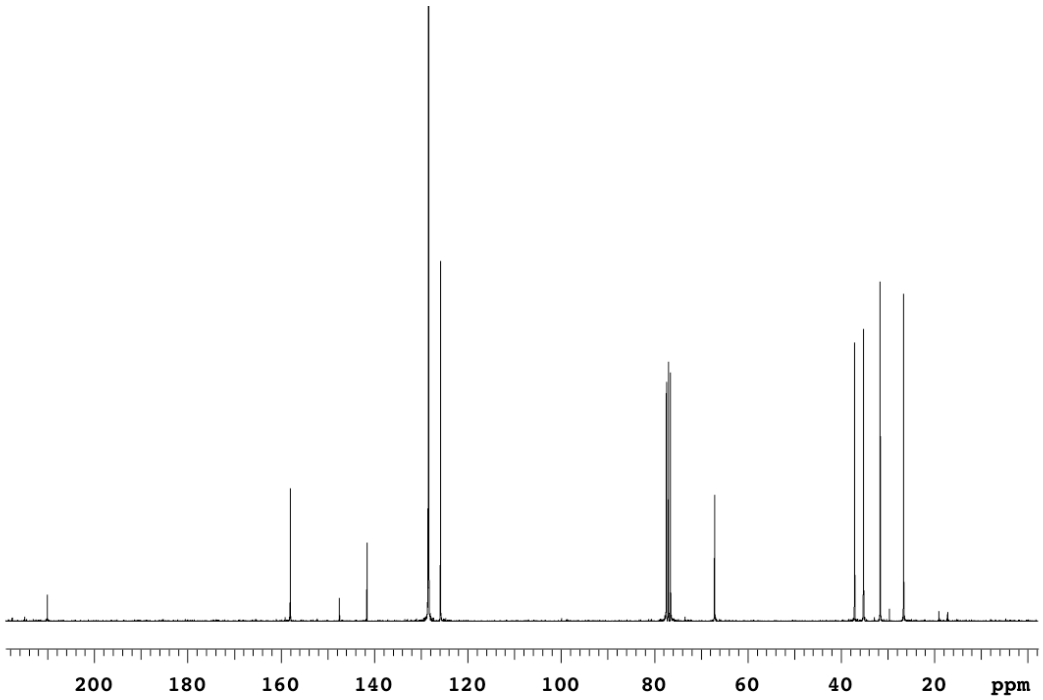
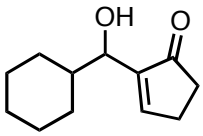


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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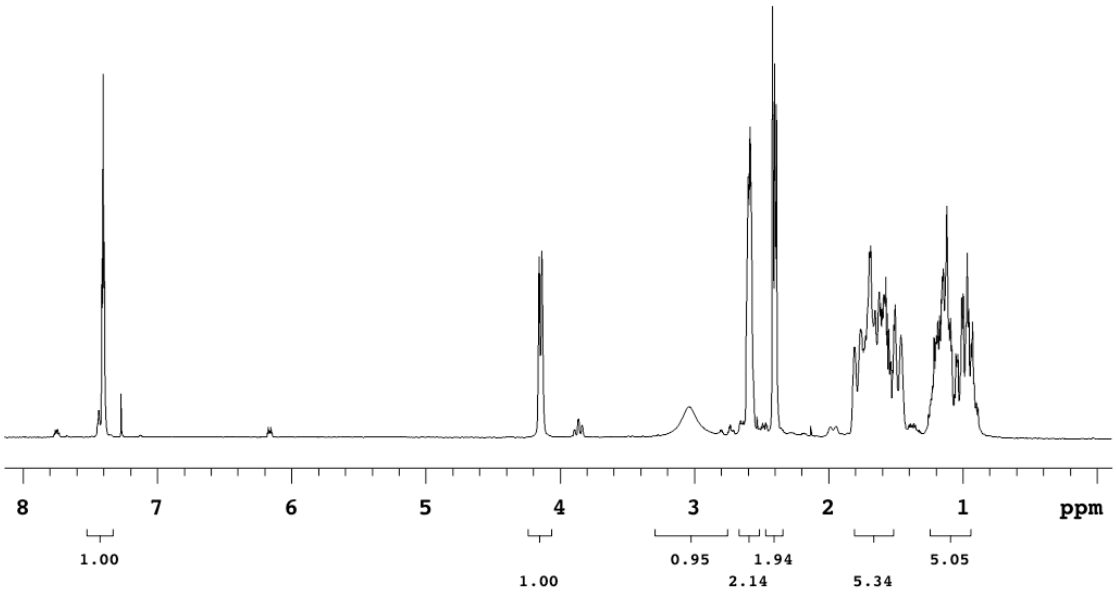
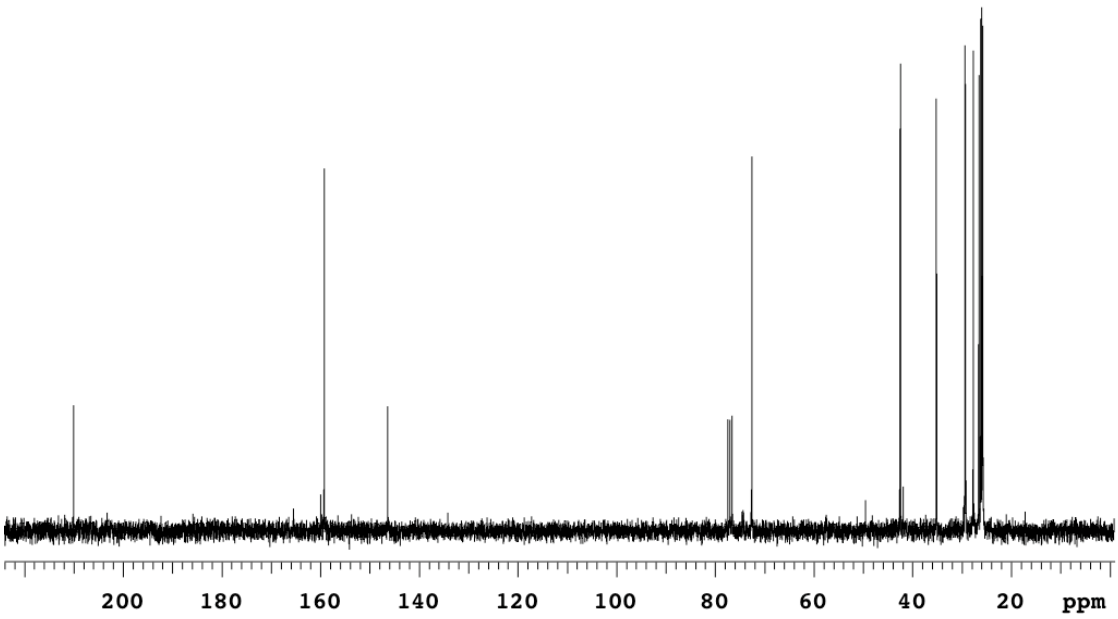
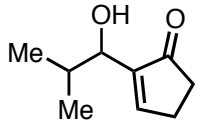


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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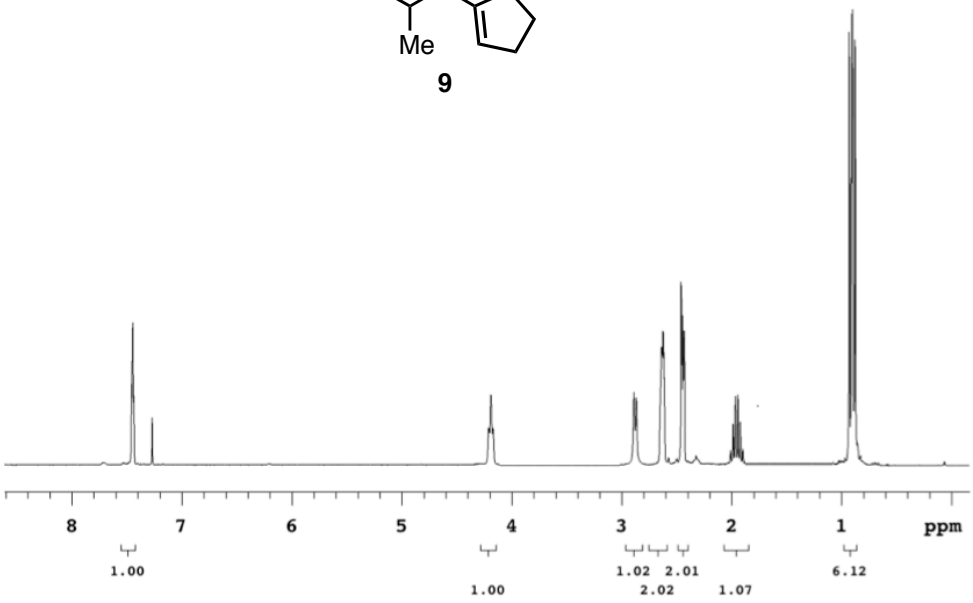
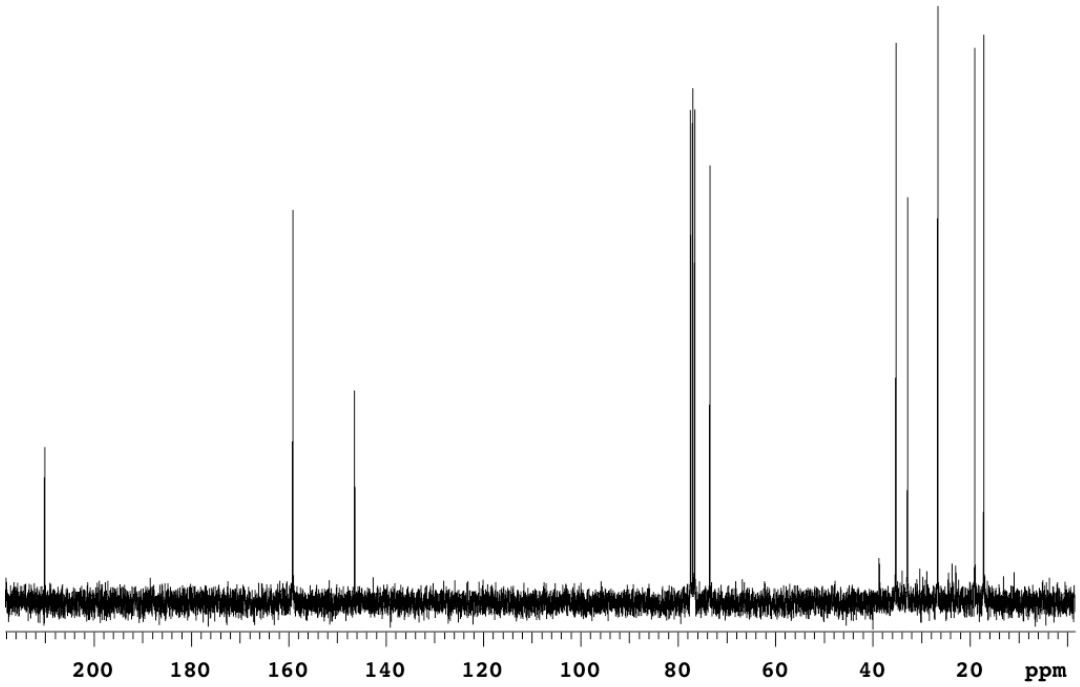


^{13}C NMR ($CDCl_3$, 75 MHz)



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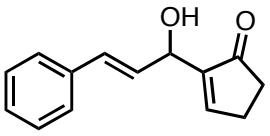

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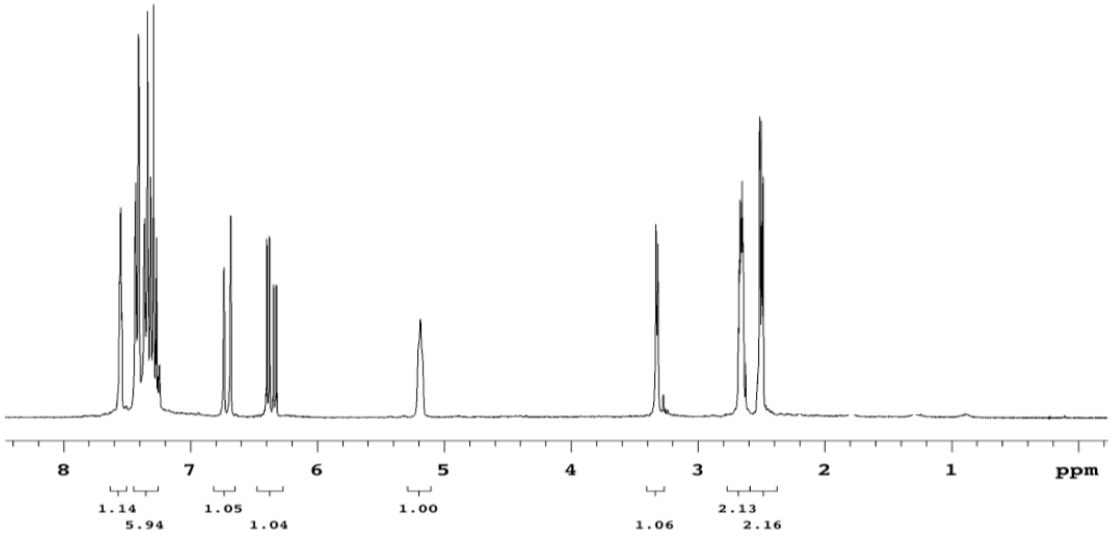
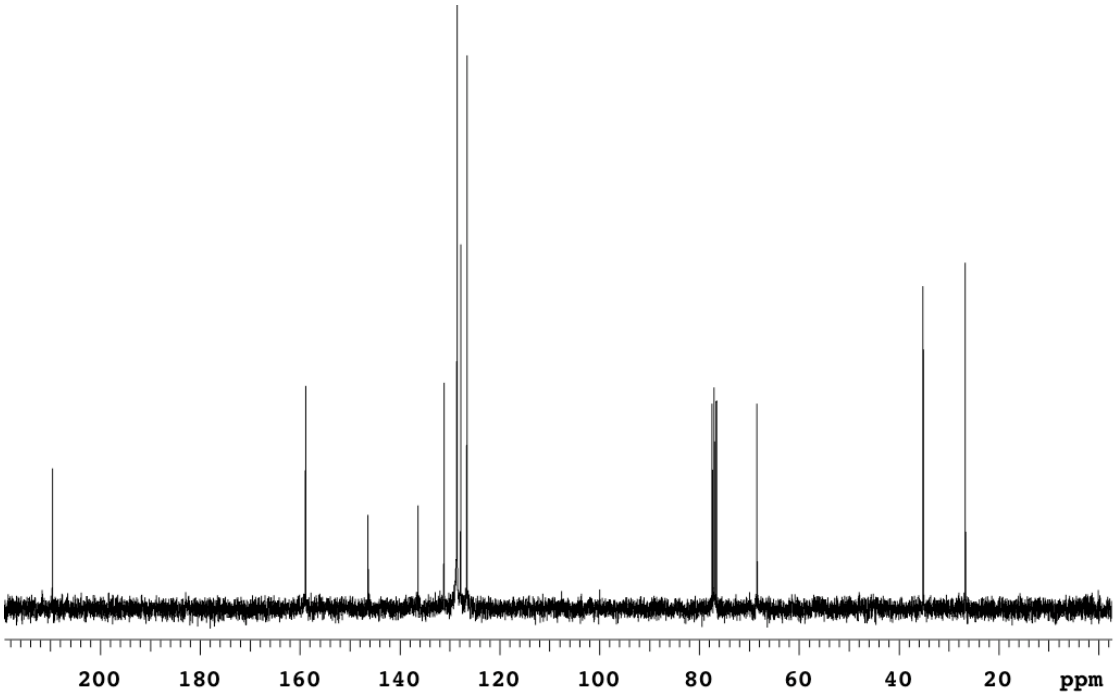
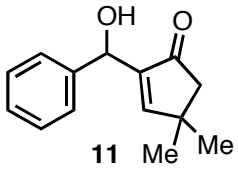


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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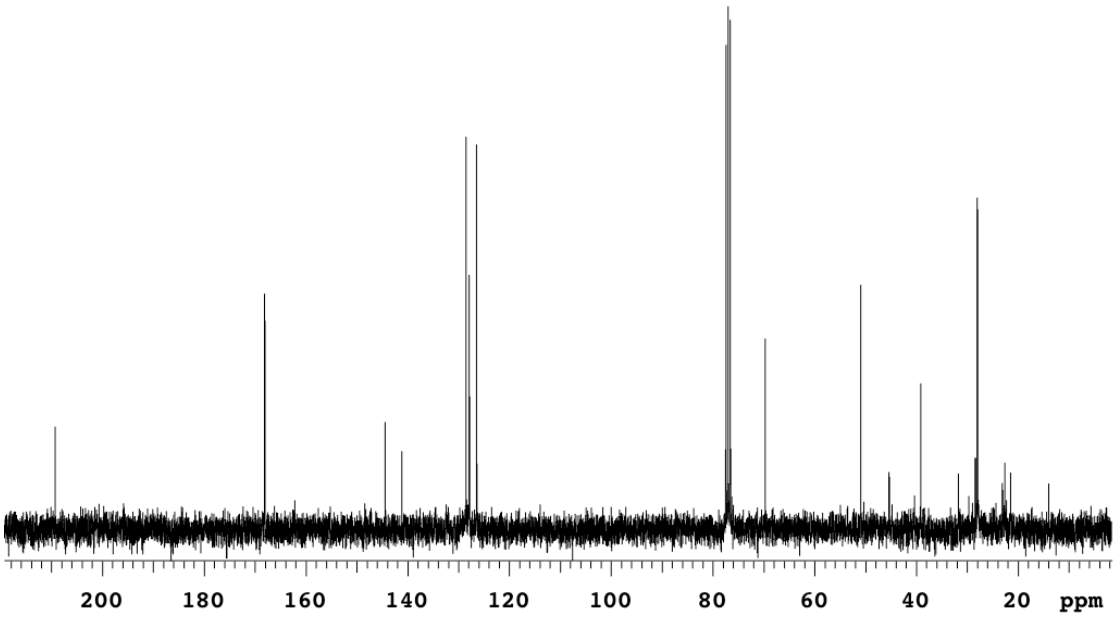
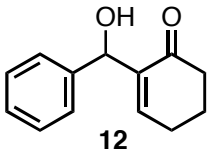
^{13}C NMR ($CDCl_3$, 75 MHz)

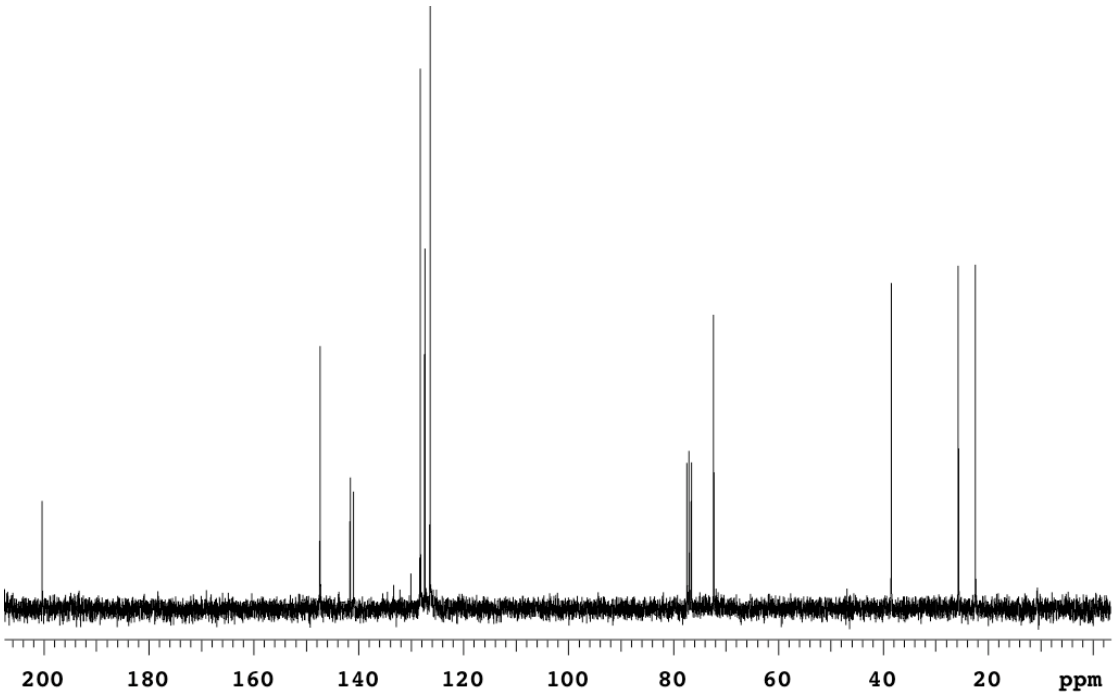


^{1}H NMR ($CDCl_3$, 300 MHz)

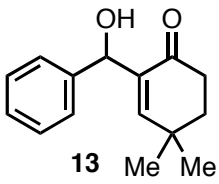


12

^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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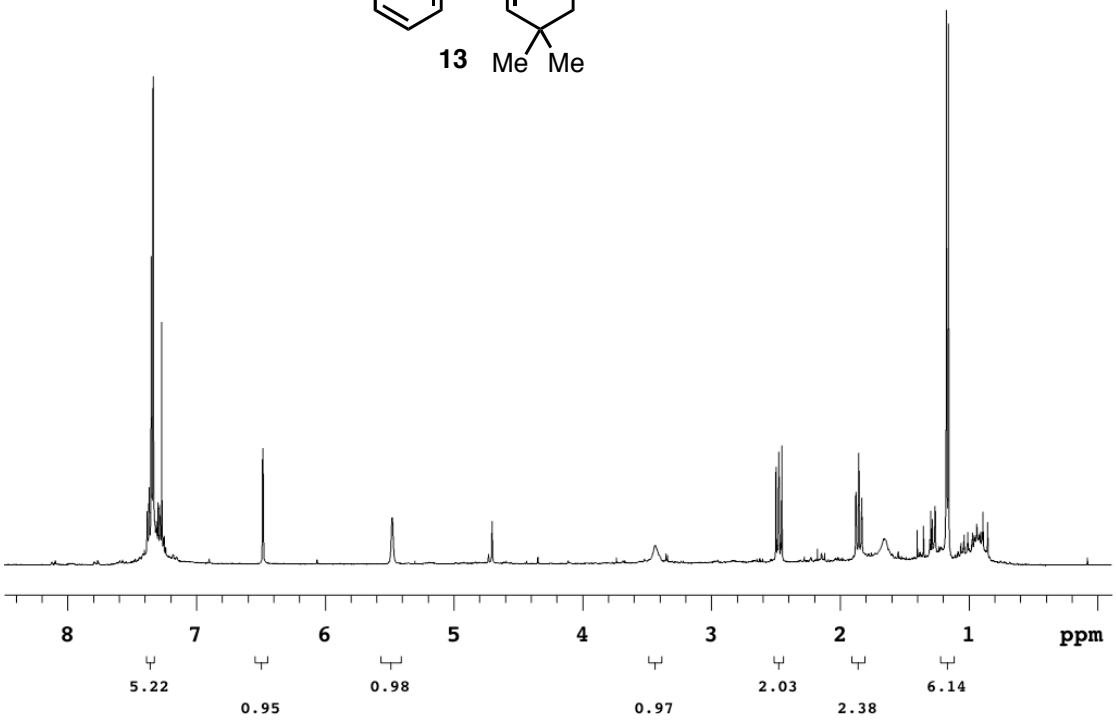
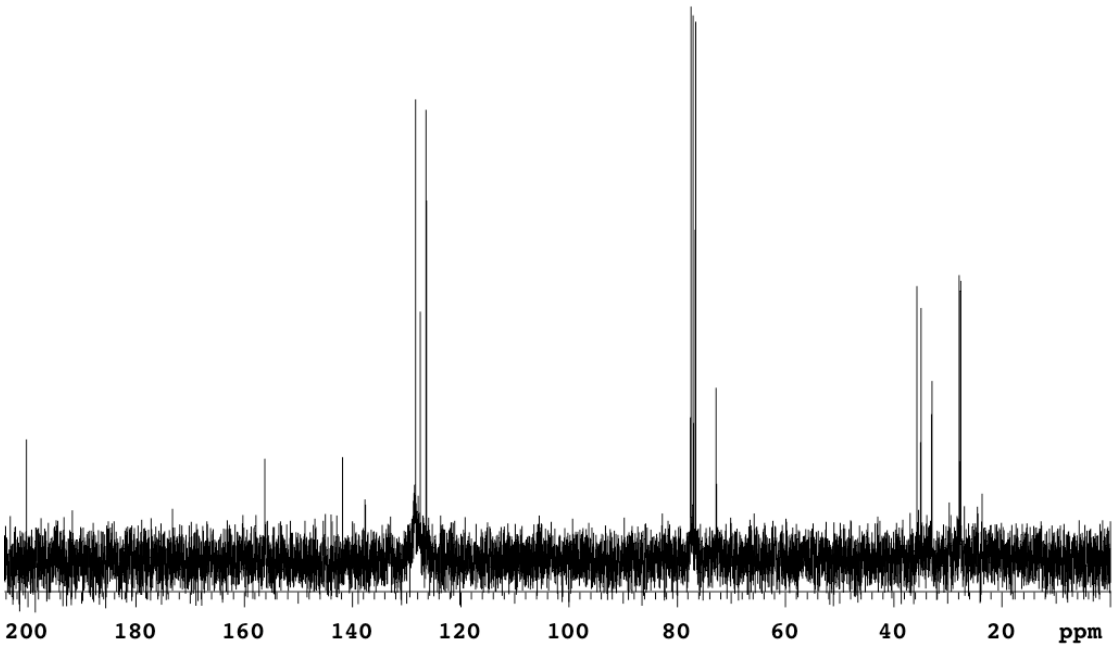
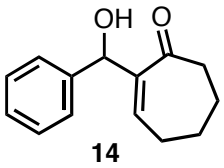


^{13}C NMR ($CDCl_3$, 75 MHz)

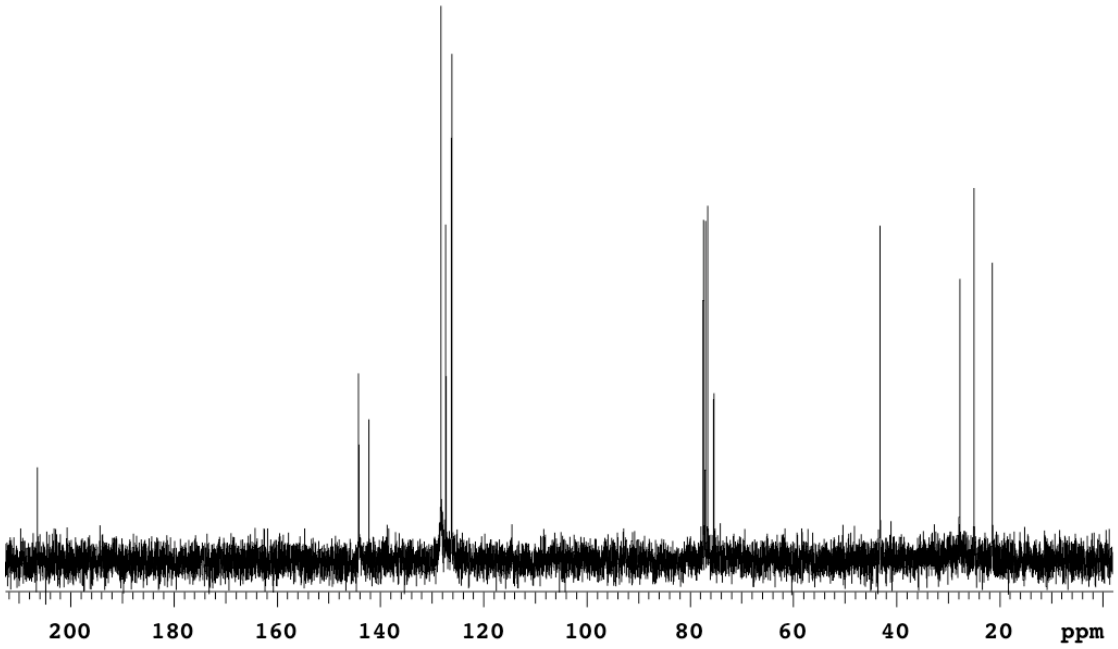


^{1}H NMR ($CDCl_3$, 300 MHz)

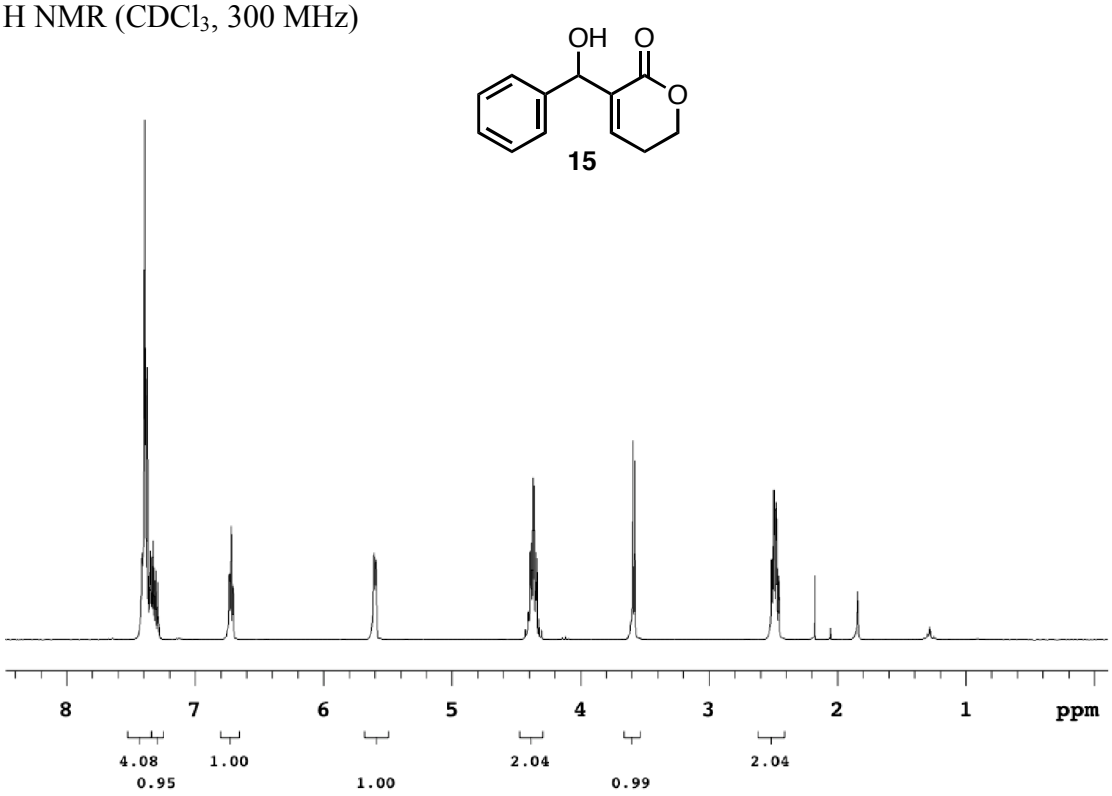


14

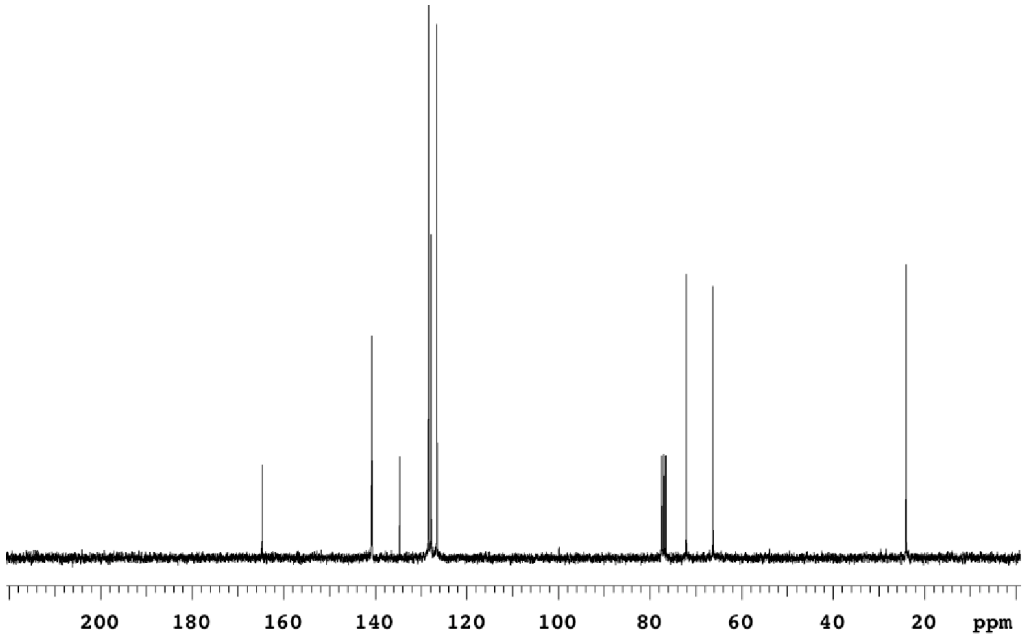
^{13}C NMR ($CDCl_3$, 75 MHz)



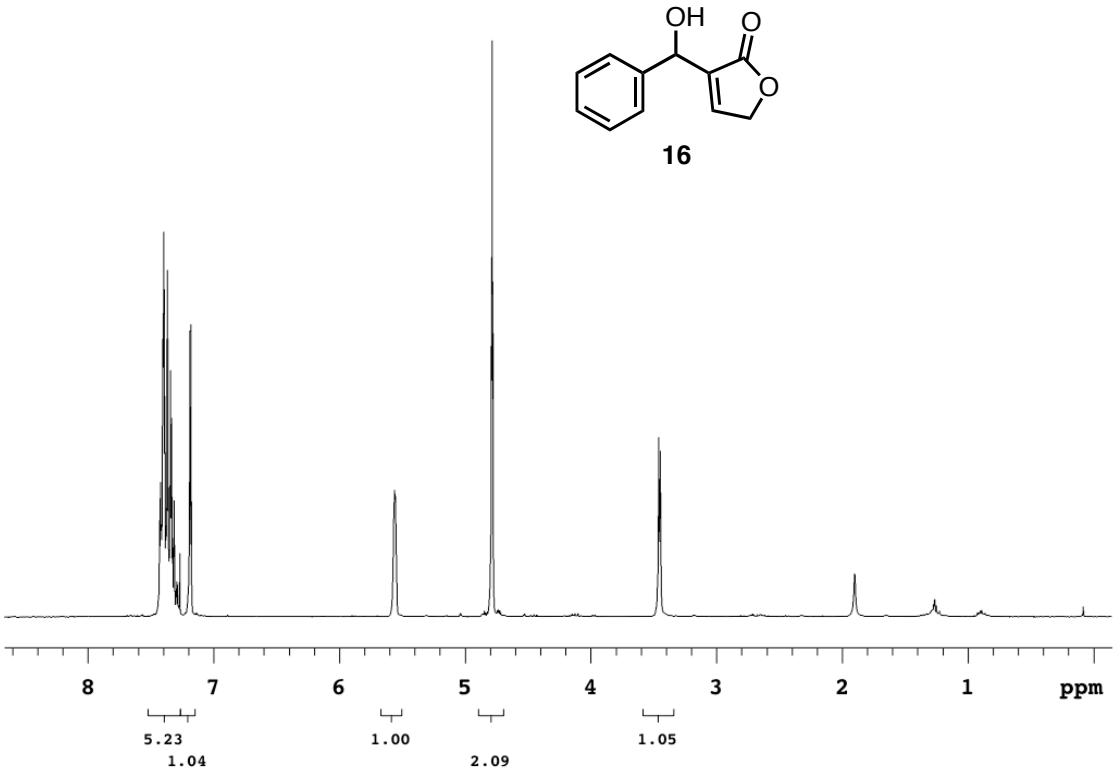
^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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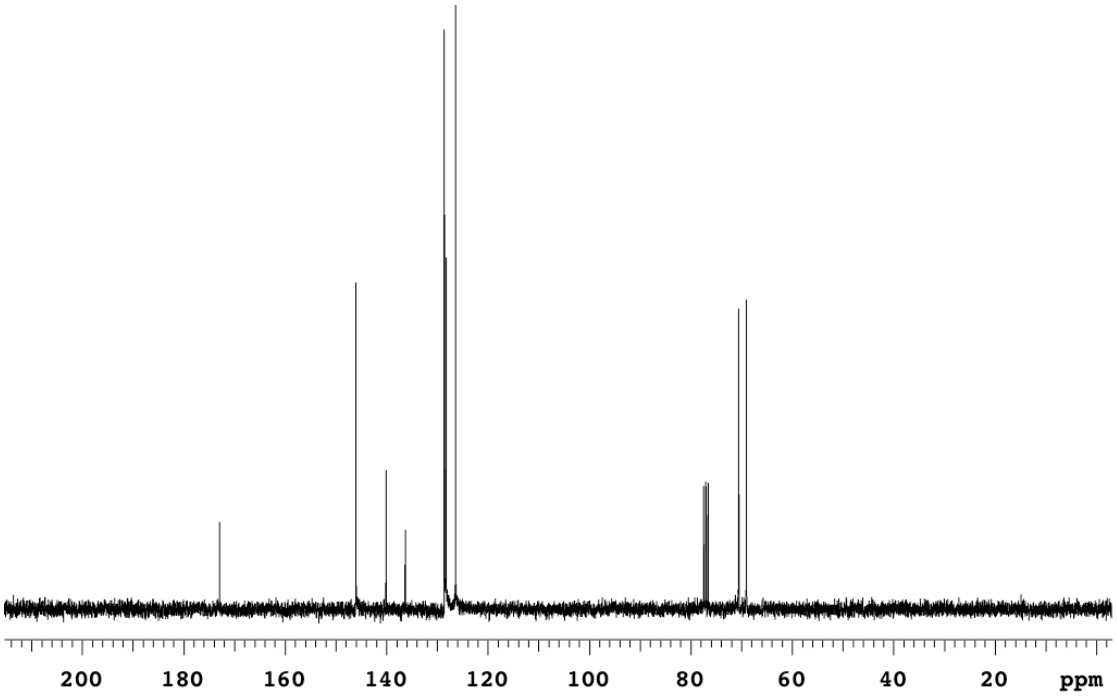
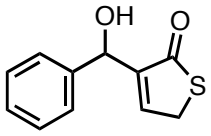


^{1}H NMR ($CDCl_3$, 300 MHz)



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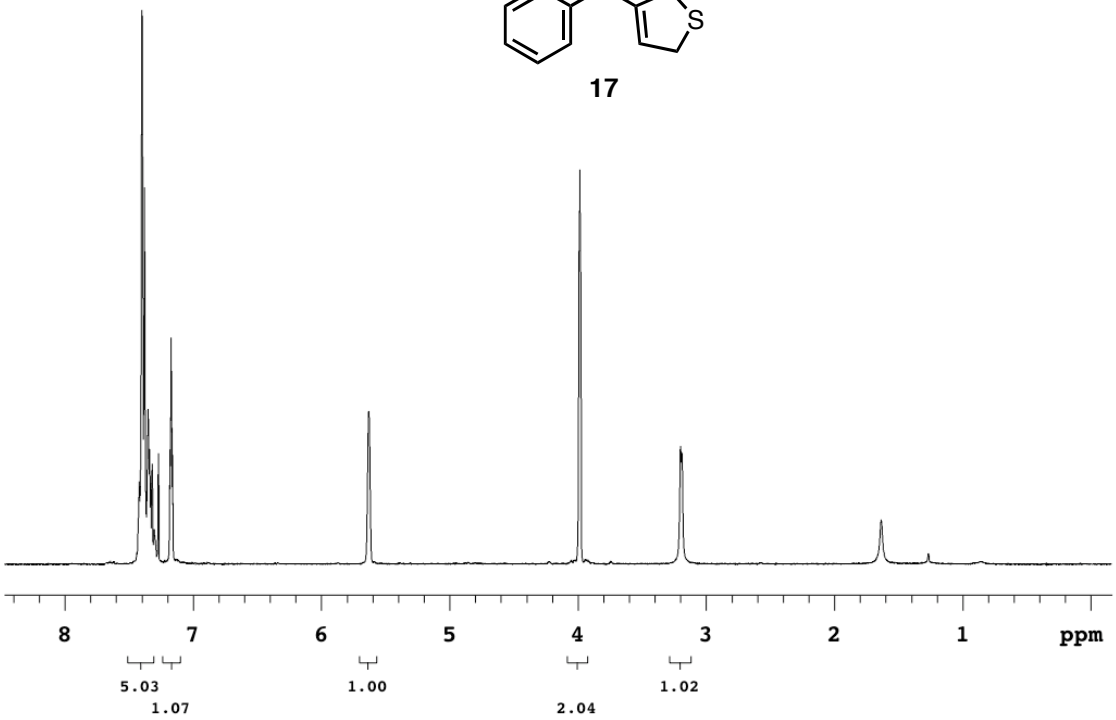
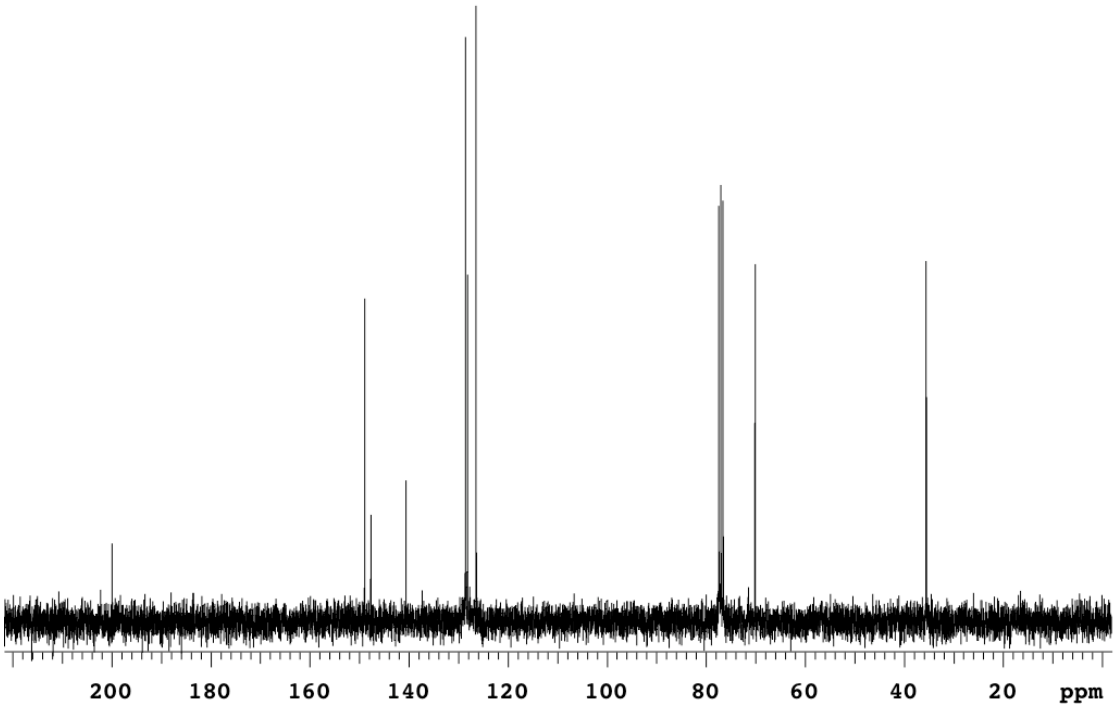
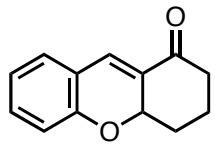


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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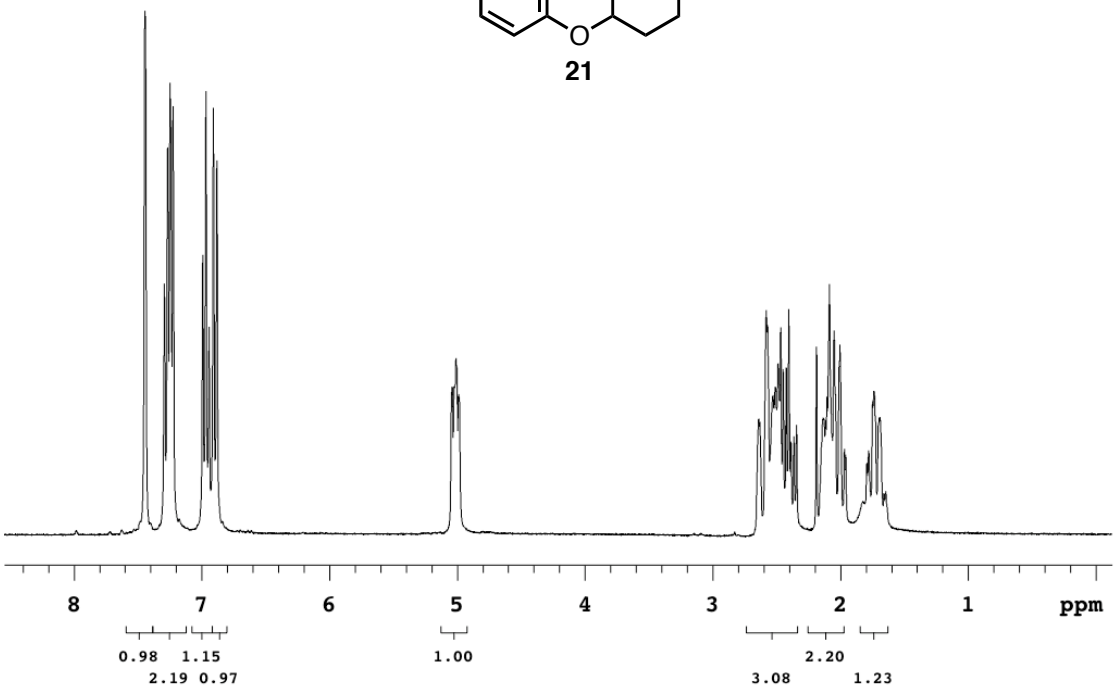
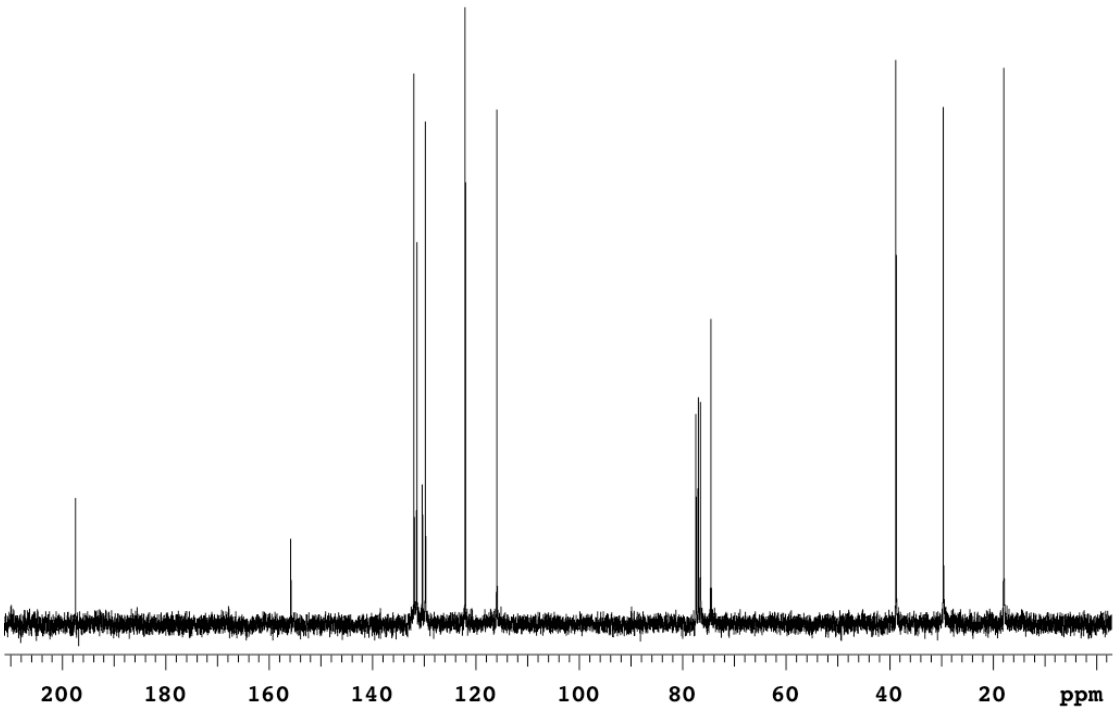
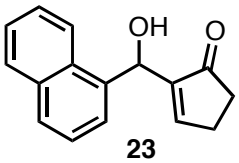


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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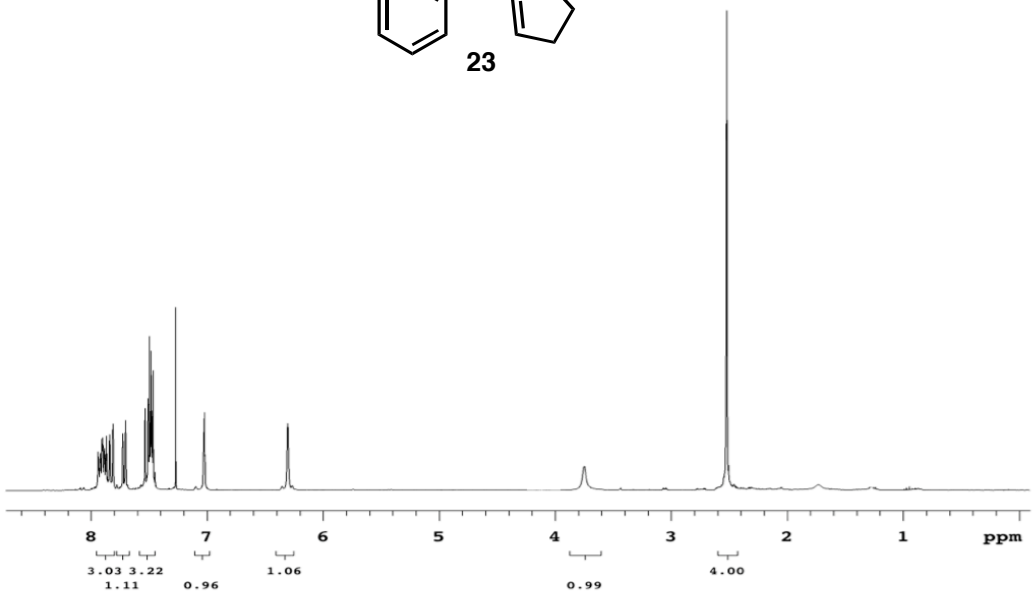
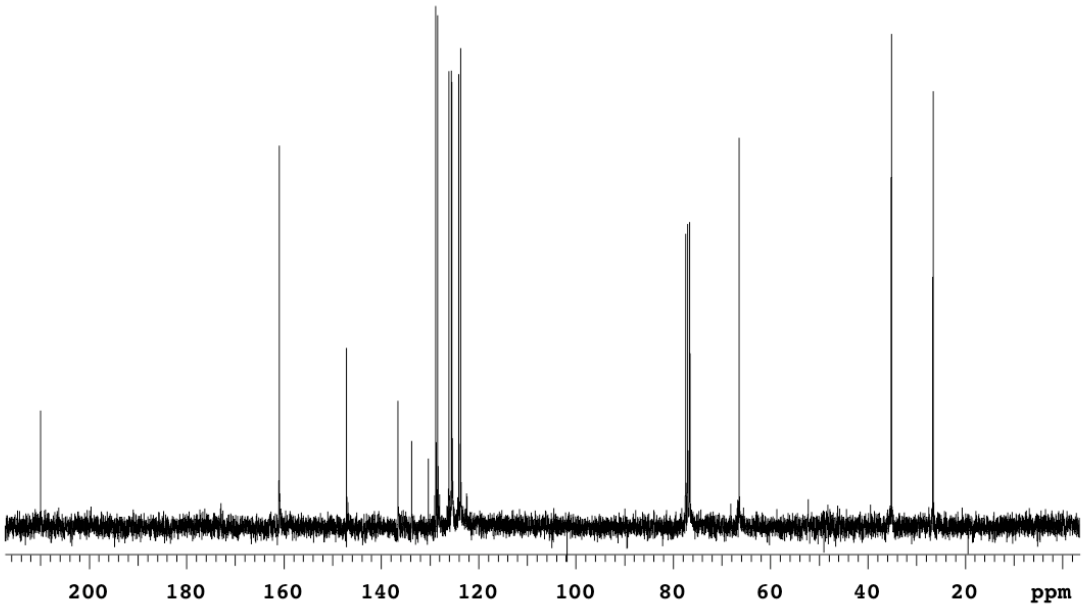
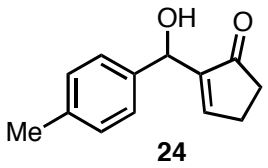


^{13}C NMR ($CDCl_3$, 75 MHz)

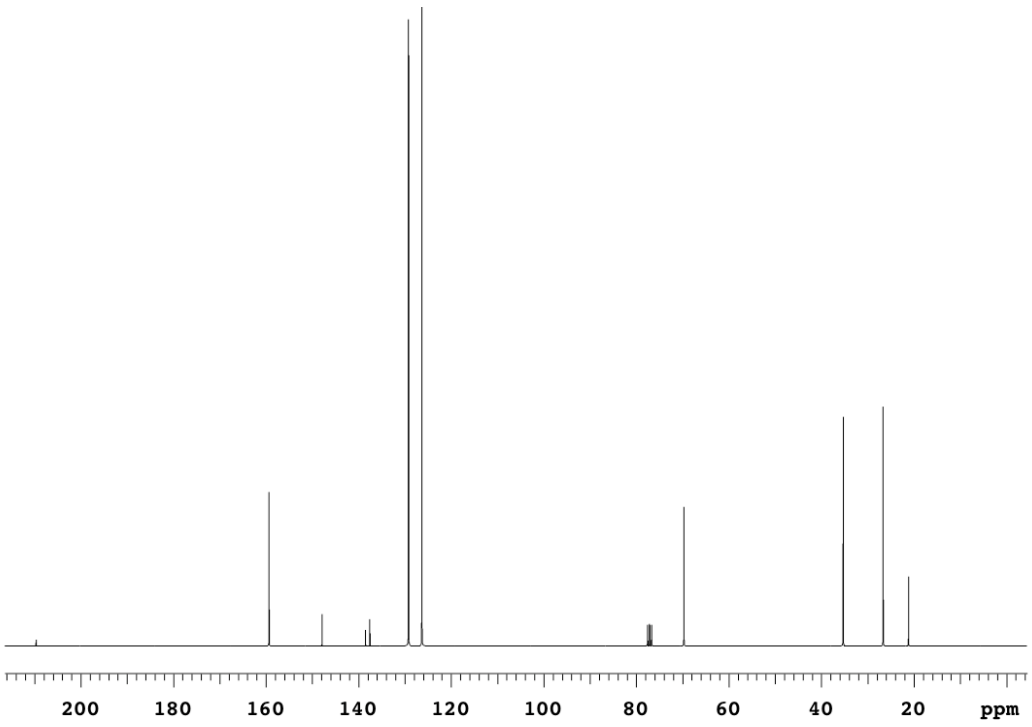


^{1}H NMR ($CDCl_3$, 300 MHz)

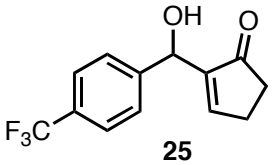


24

^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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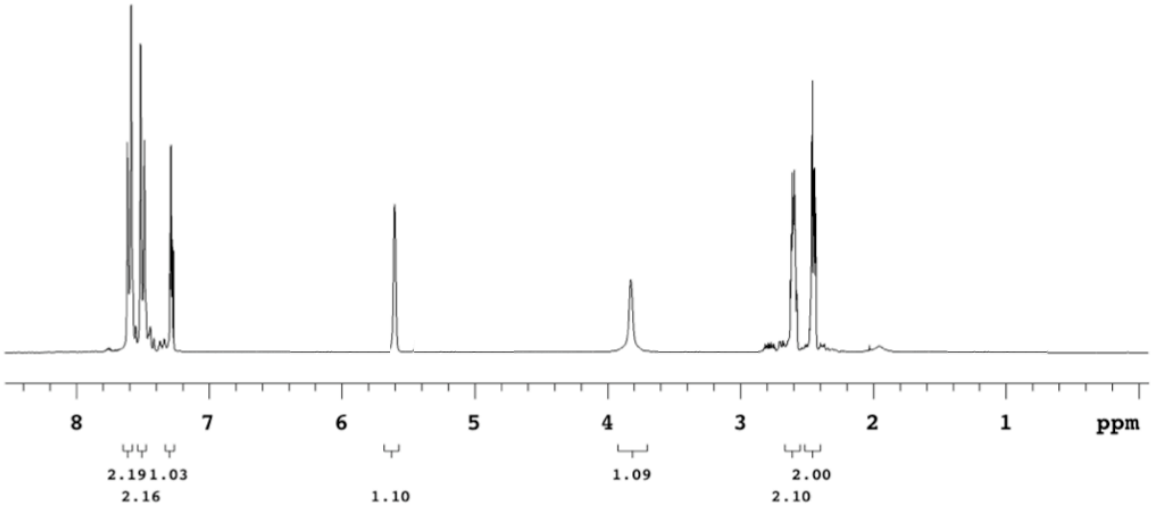
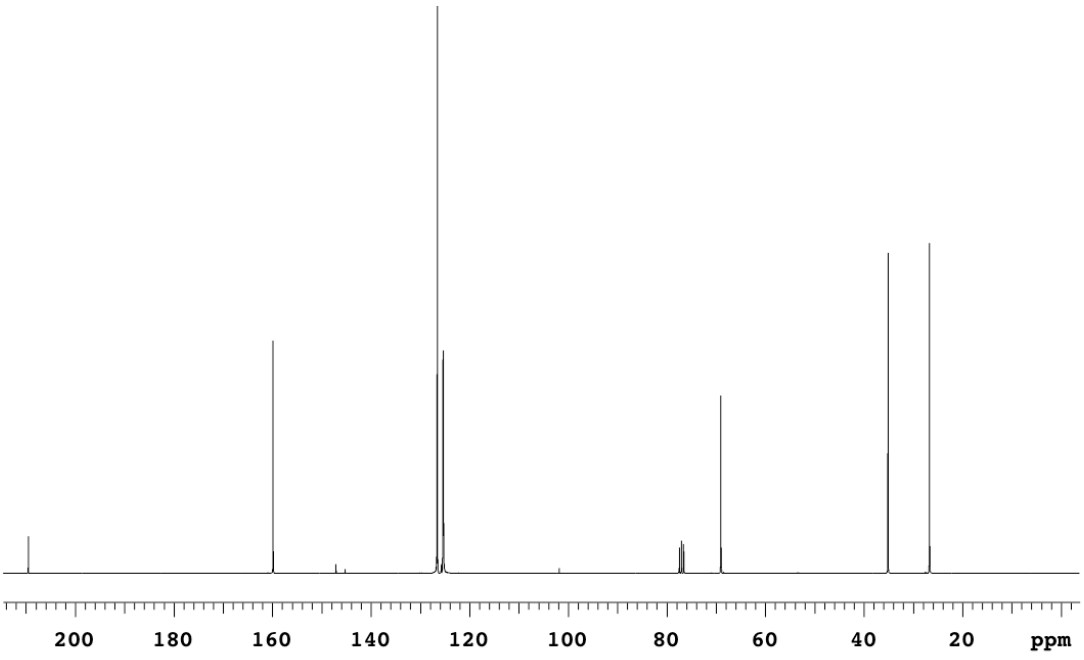
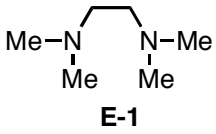


^{13}C NMR ($CDCl_3$, 75 MHz)

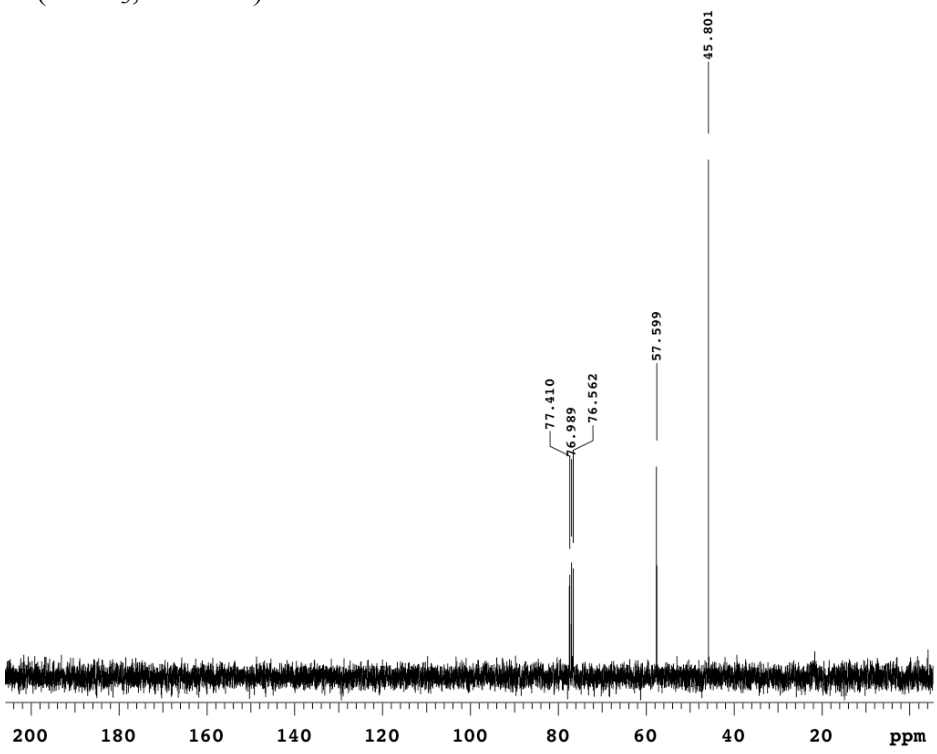


^{1}H NMR ($CDCl_3$, 300 MHz)

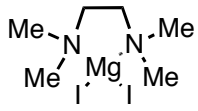


E-1

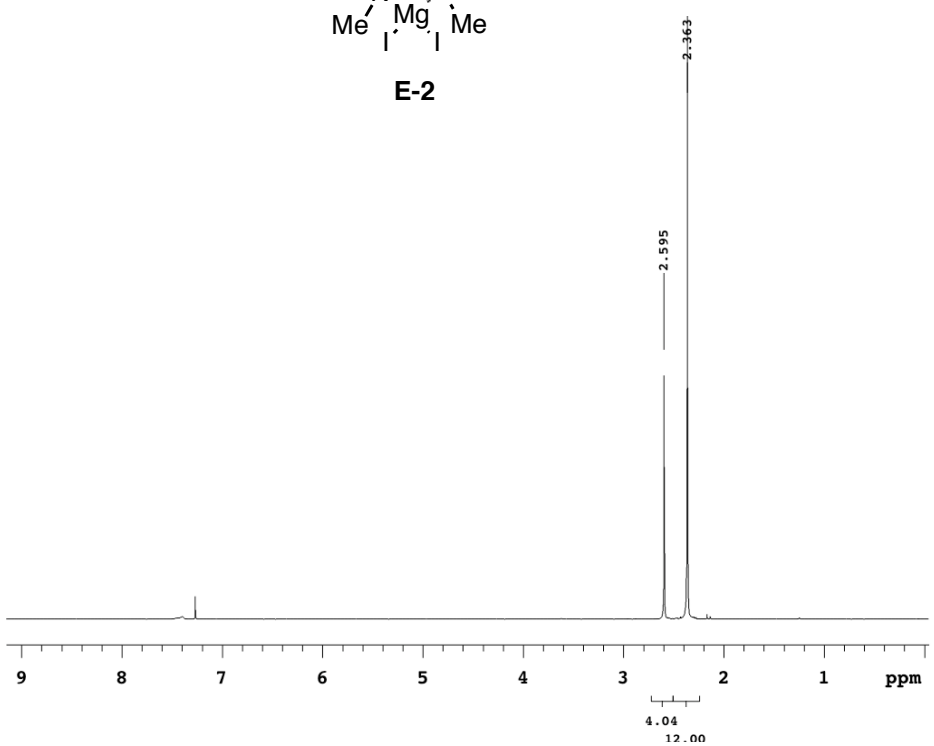
^{13}C NMR ($CDCl_3$, 75 MHz)



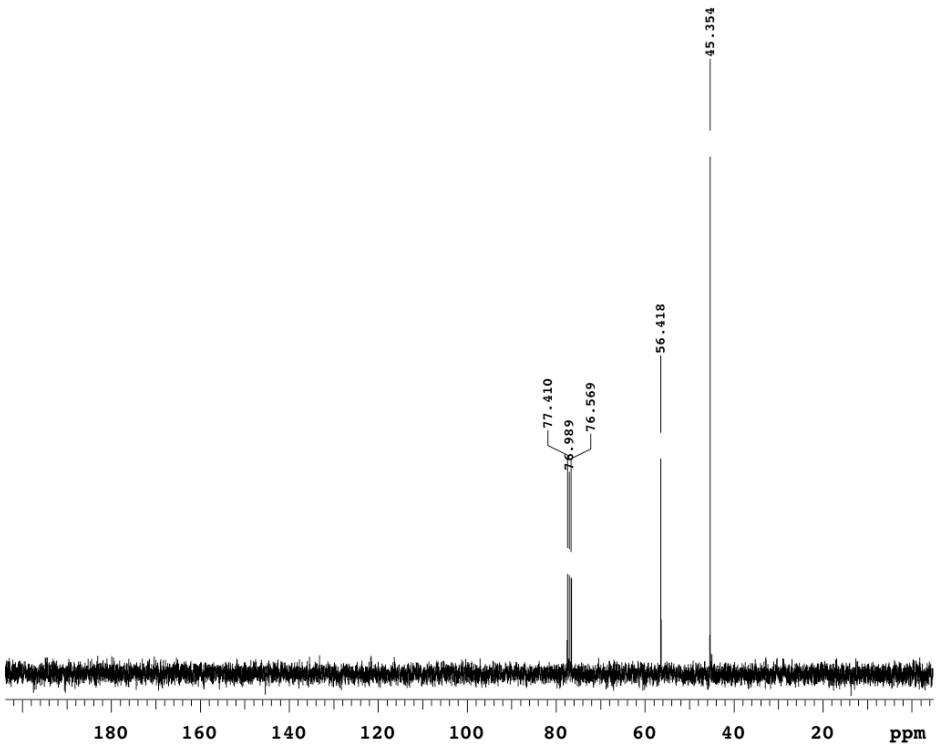
^{1}H NMR ($CDCl_3$, 300 MHz)



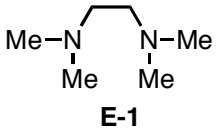
E-2



^{13}C NMR ($CDCl_3$, 75 MHz)

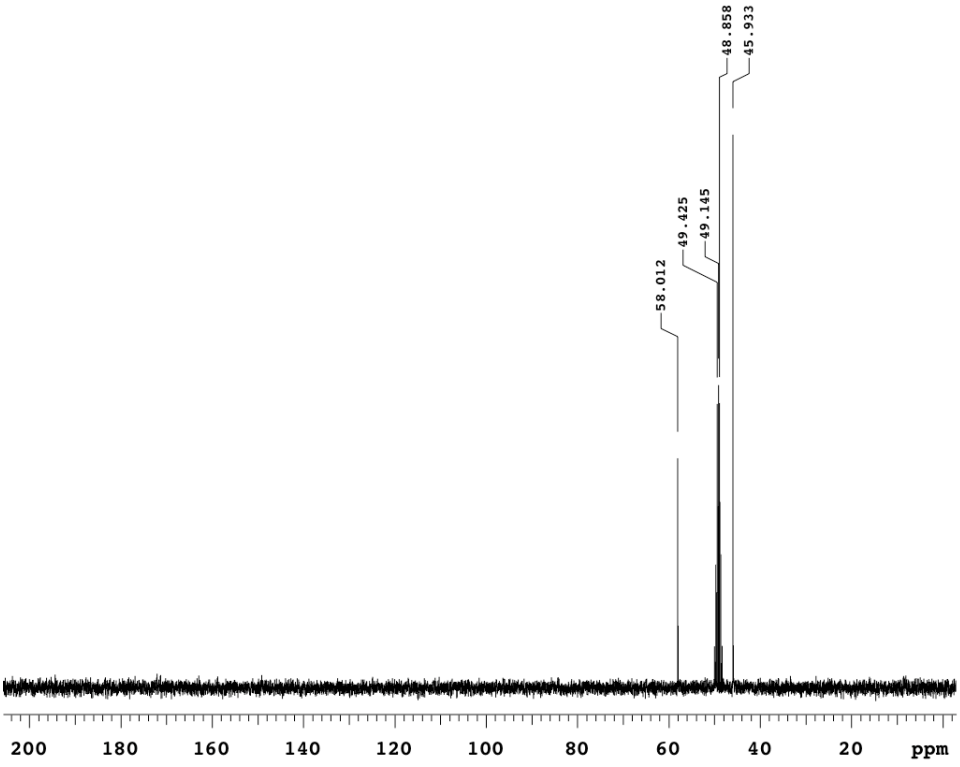


^{1}H NMR (CD_3OD, 300 MHz)

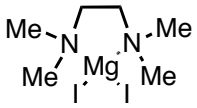


E-1

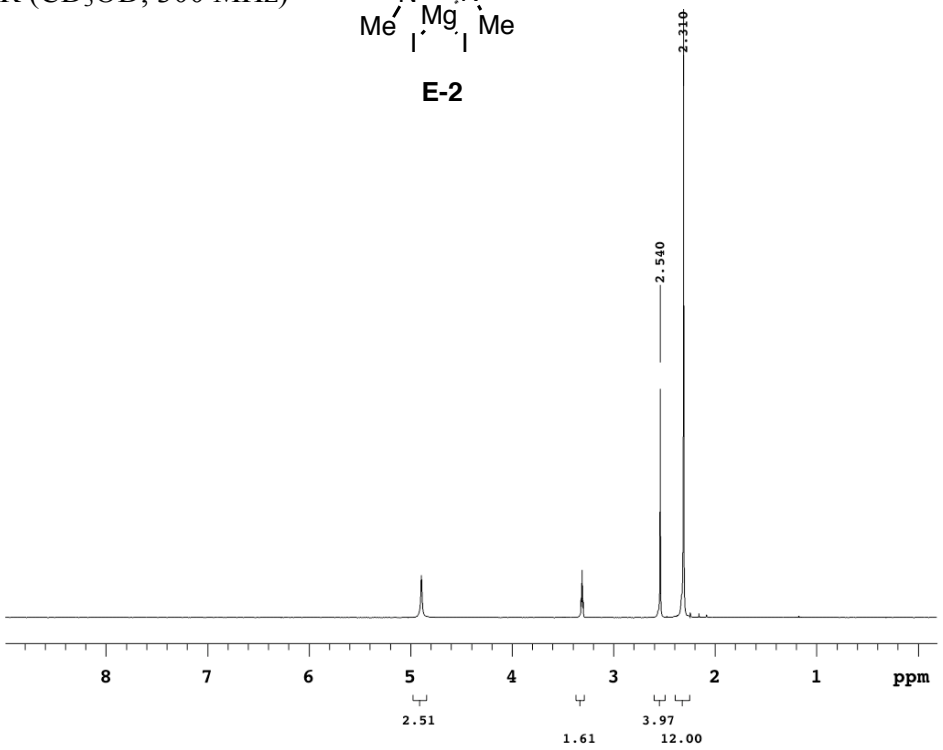
^{13}C NMR (CD_3OD, 75 MHz)



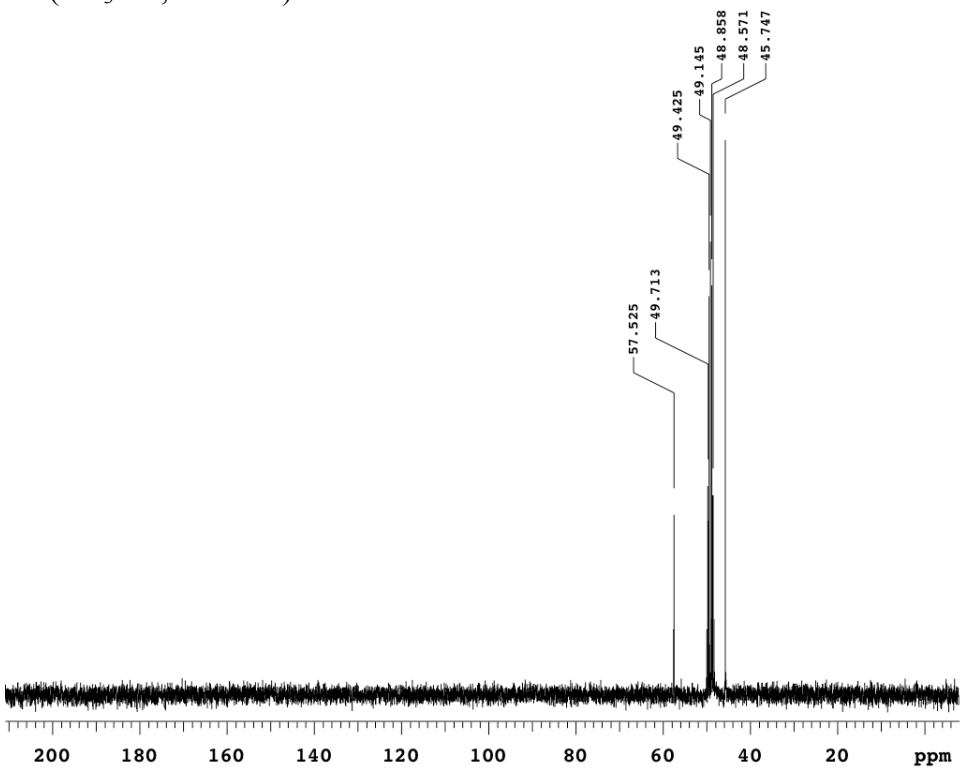
^{1}H NMR (CD_3OD, 300 MHz)



E-2

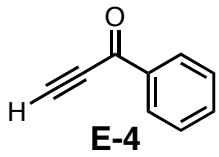


^{13}C NMR (CD_3OD, 75 MHz)

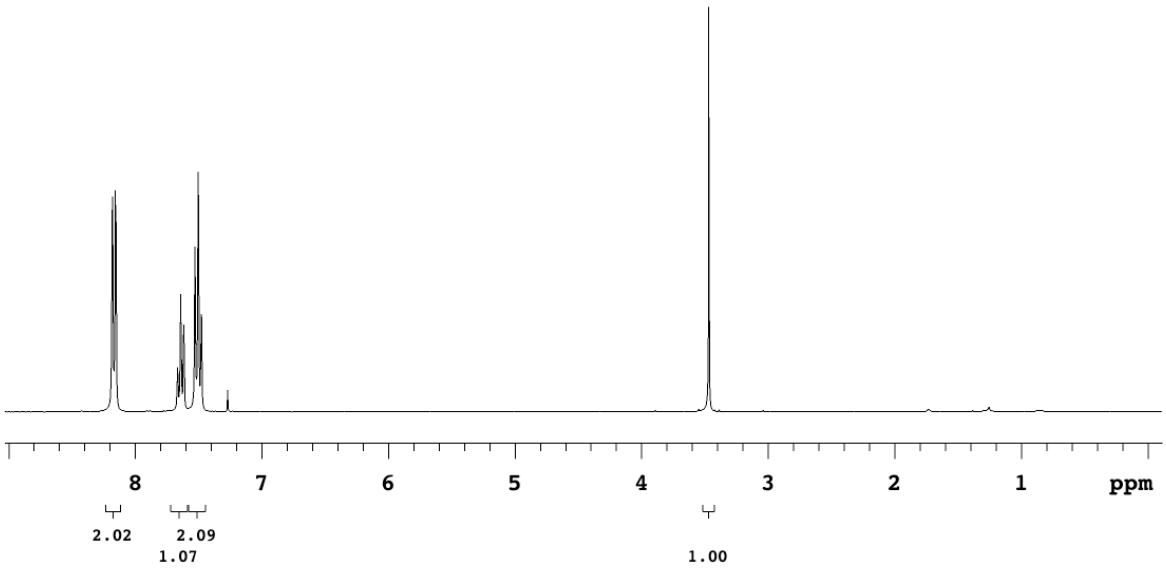


^{1}H and ^{13}C NMR Spectra of Starting Materials

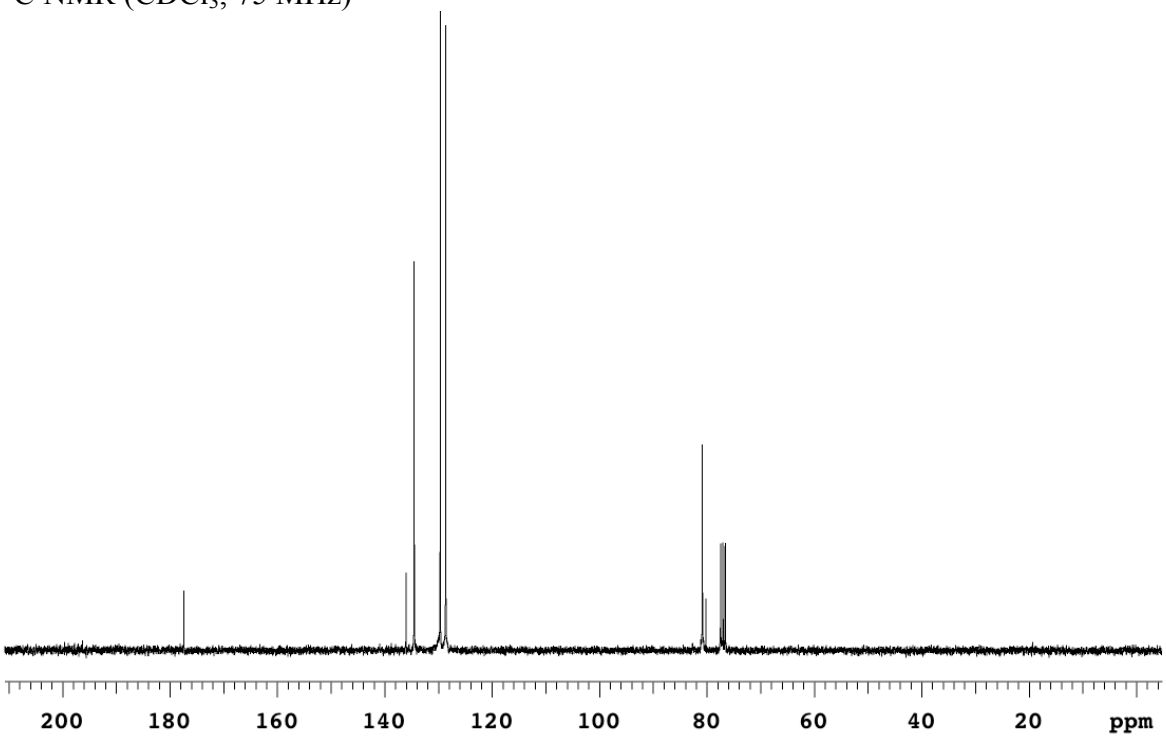
^{1}H NMR ($CDCl_3$, 300 MHz)



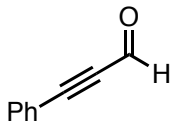
E-4



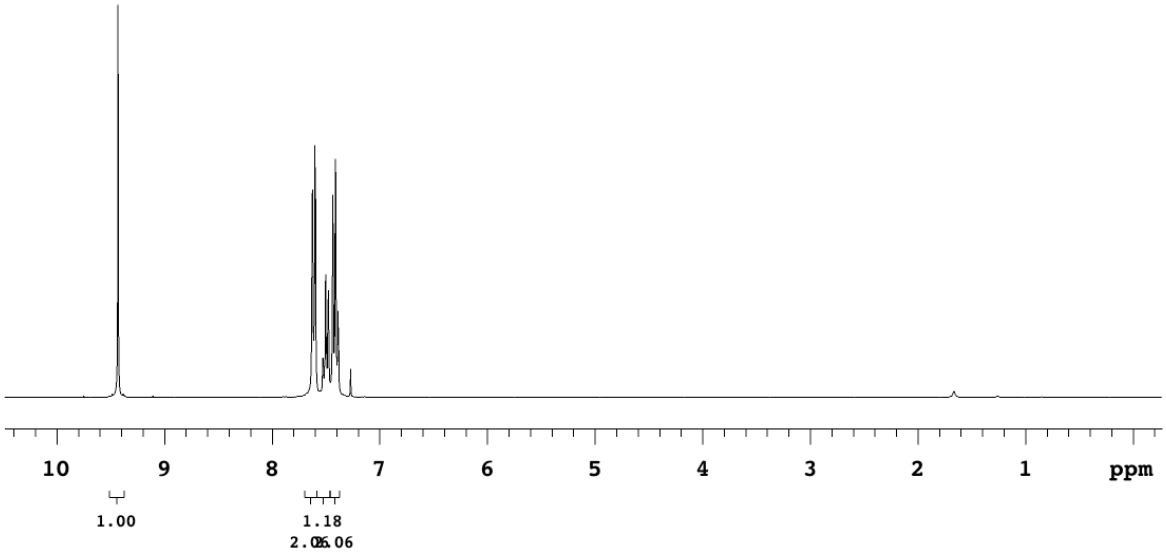
^{13}C NMR ($CDCl_3$, 75 MHz)



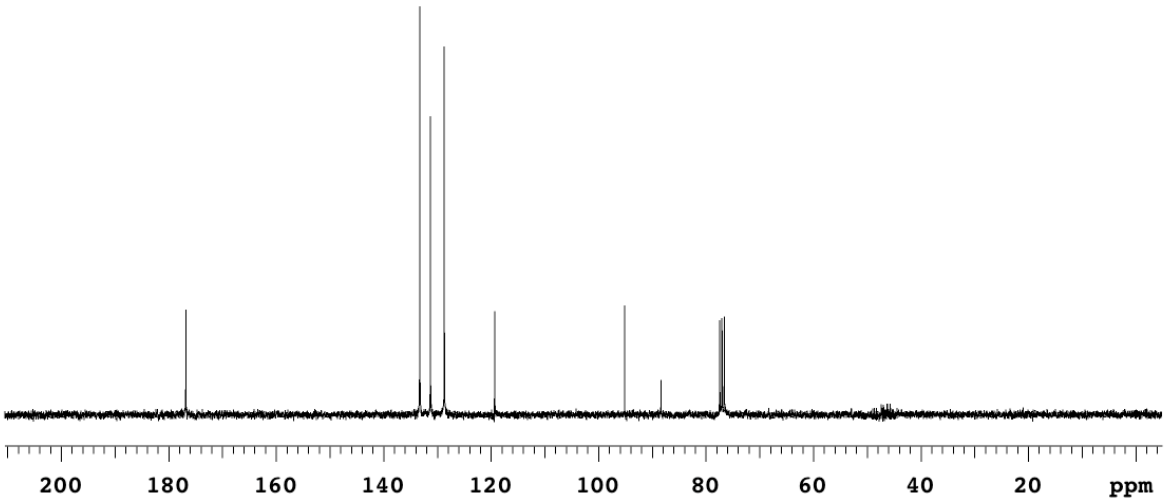
^{1}H NMR ($CDCl_3$, 300 MHz)



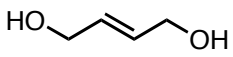
E-6



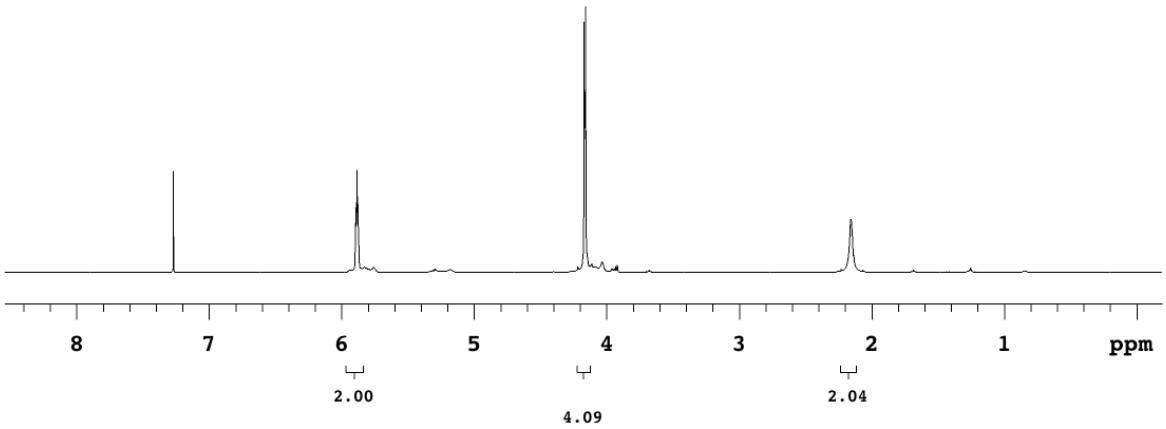
^{13}C NMR ($CDCl_3$, 75 MHz)



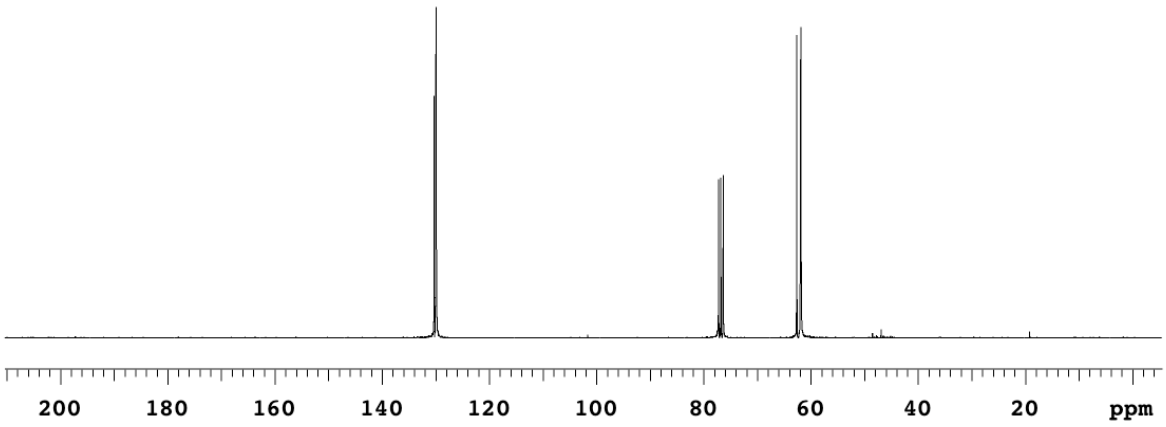
^{1}H NMR ($CDCl_3$, 300 MHz)



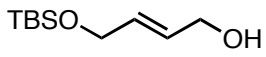
E-8



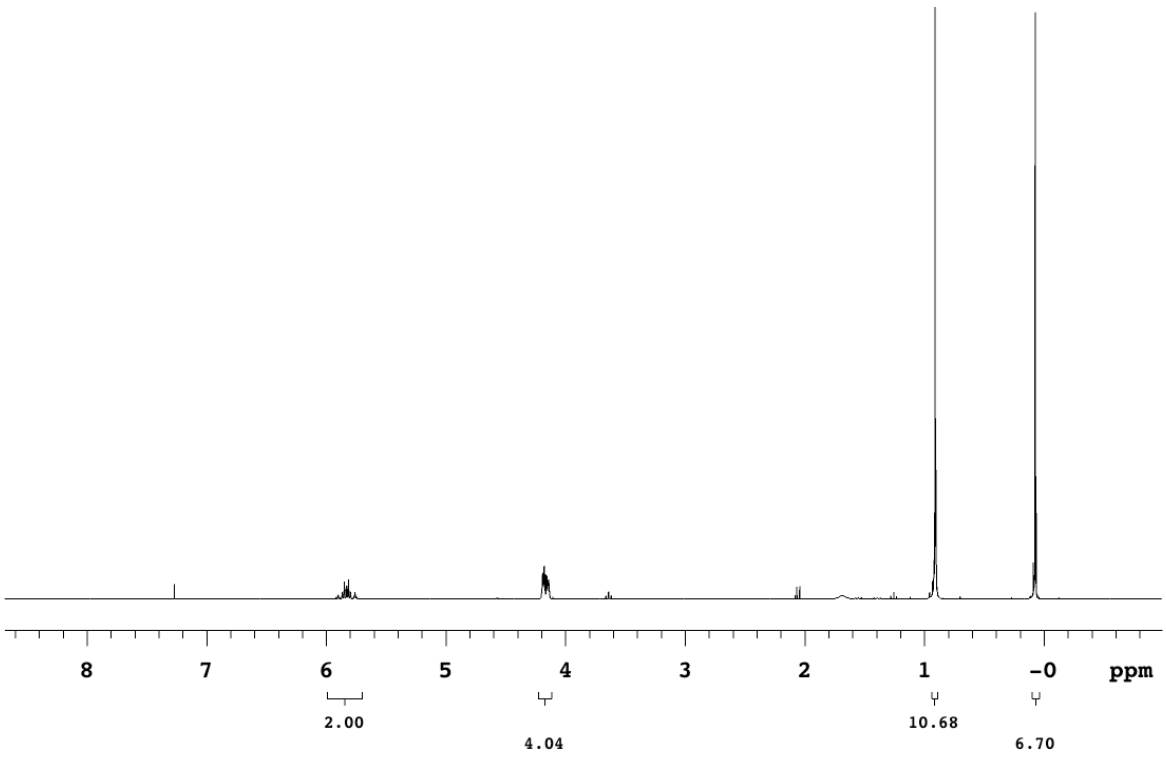
^{13}C NMR ($CDCl_3$, 75 MHz)



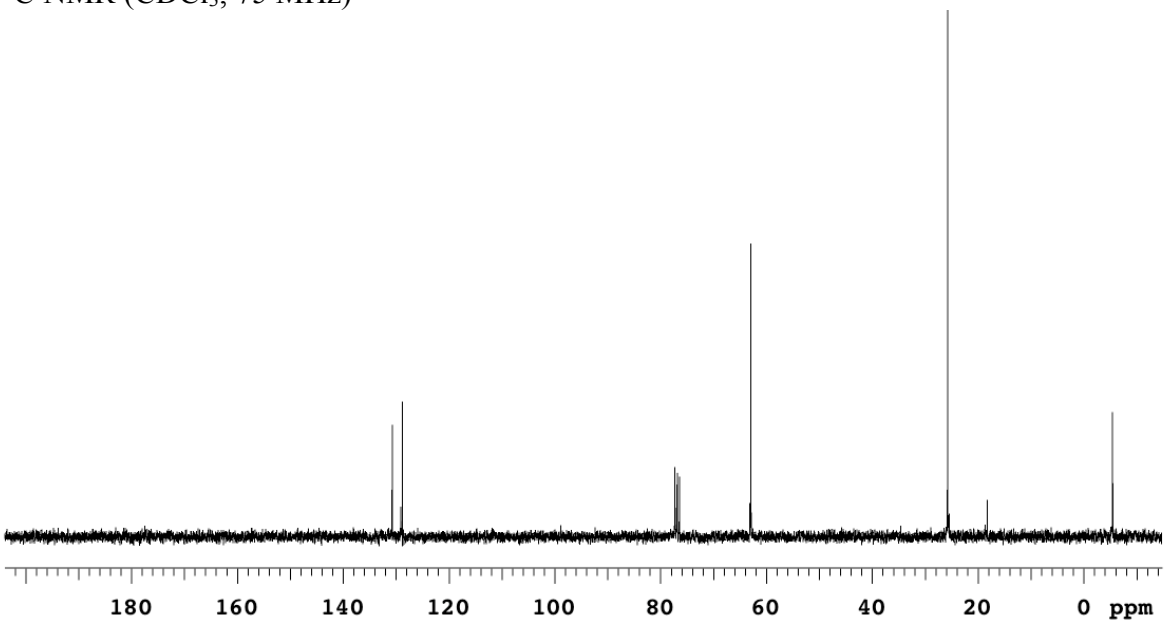
^{1}H NMR ($CDCl_3$, 300 MHz)



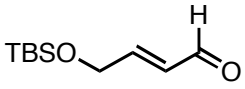
E-9



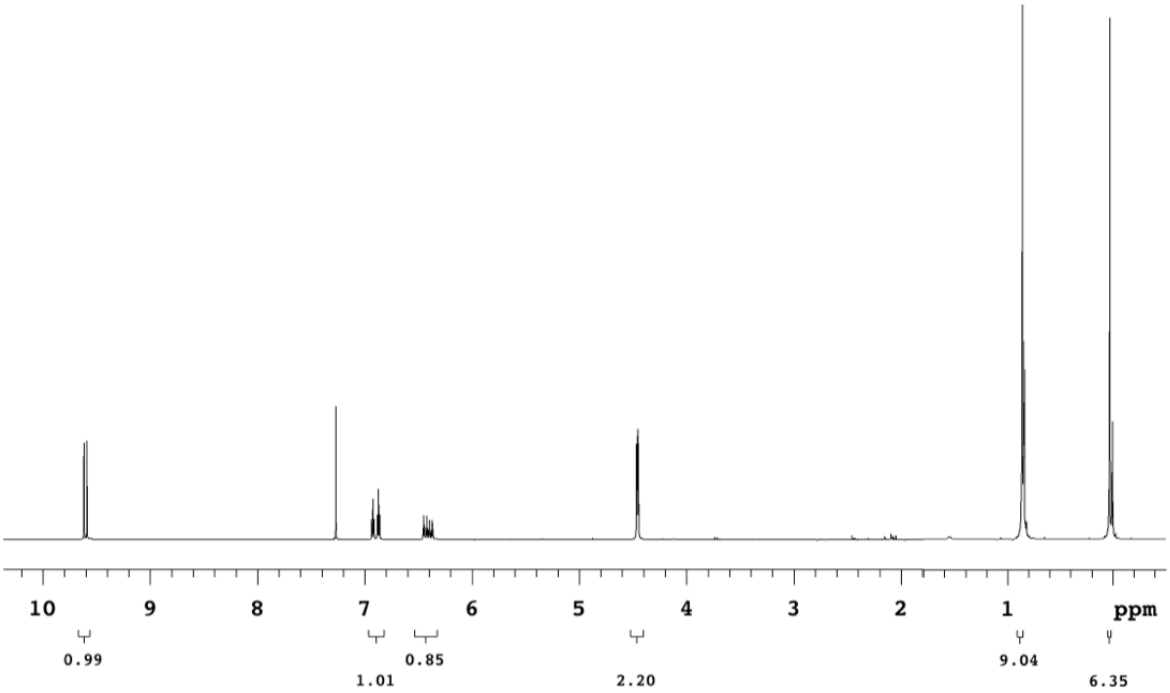
^{13}C NMR ($CDCl_3$, 75 MHz)



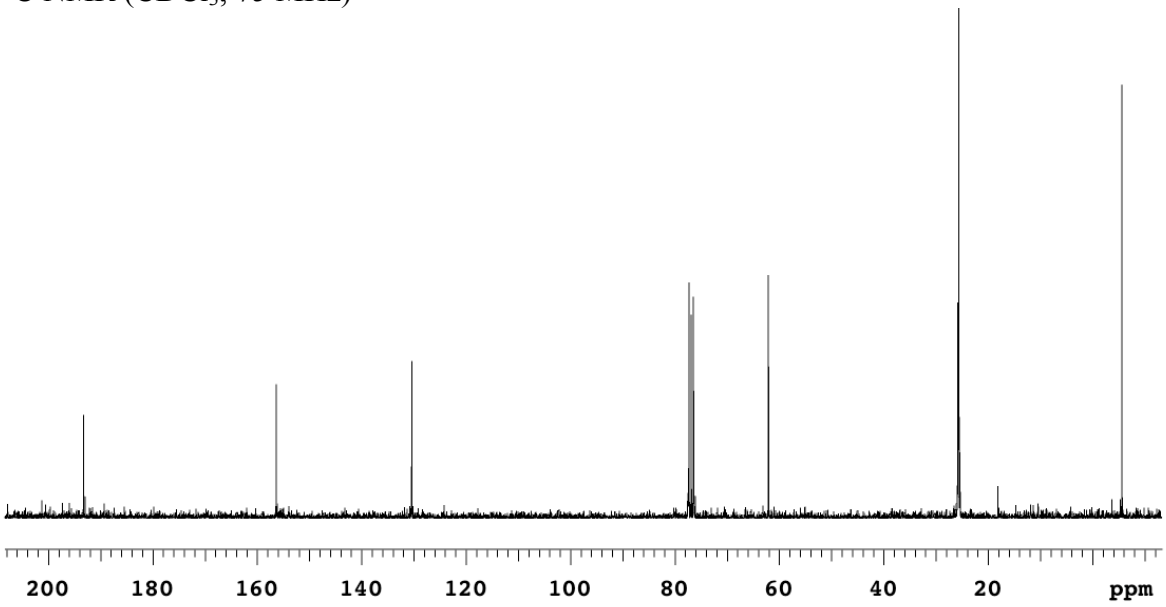
^{1}H NMR ($CDCl_3$, 300 MHz)



E-10

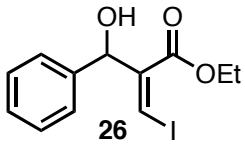


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H and ^{13}C NMR Spectra of Adducts

^{1}H NMR ($CDCl_3$, 300 MHz)



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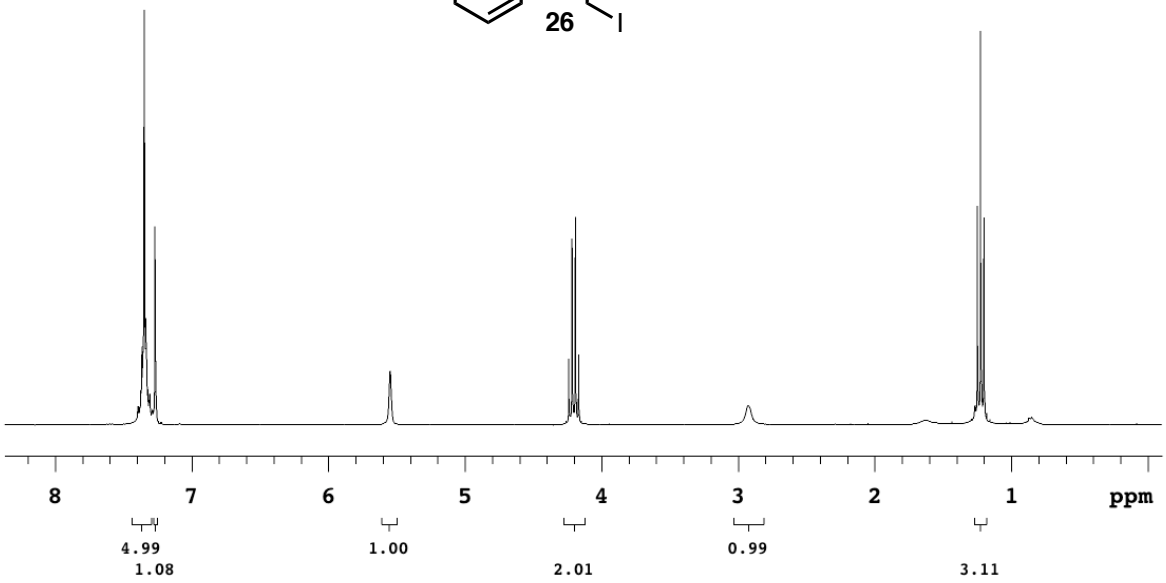
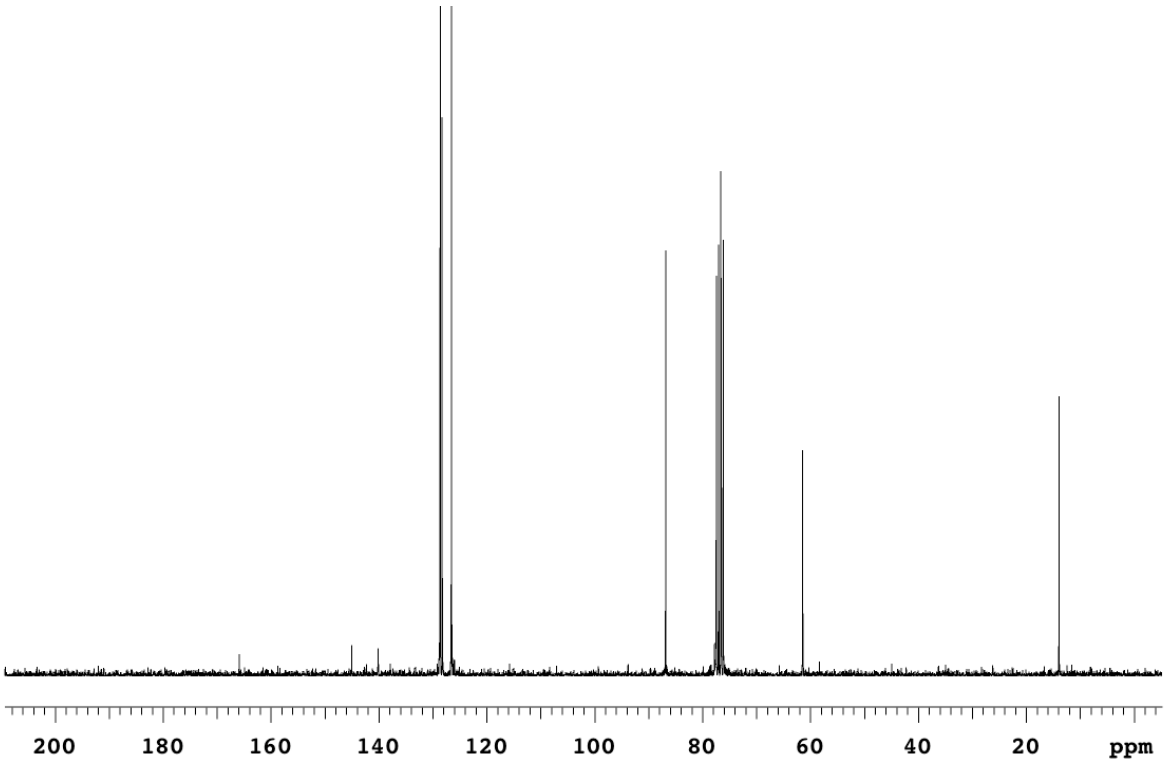
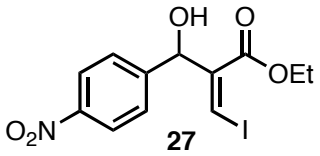


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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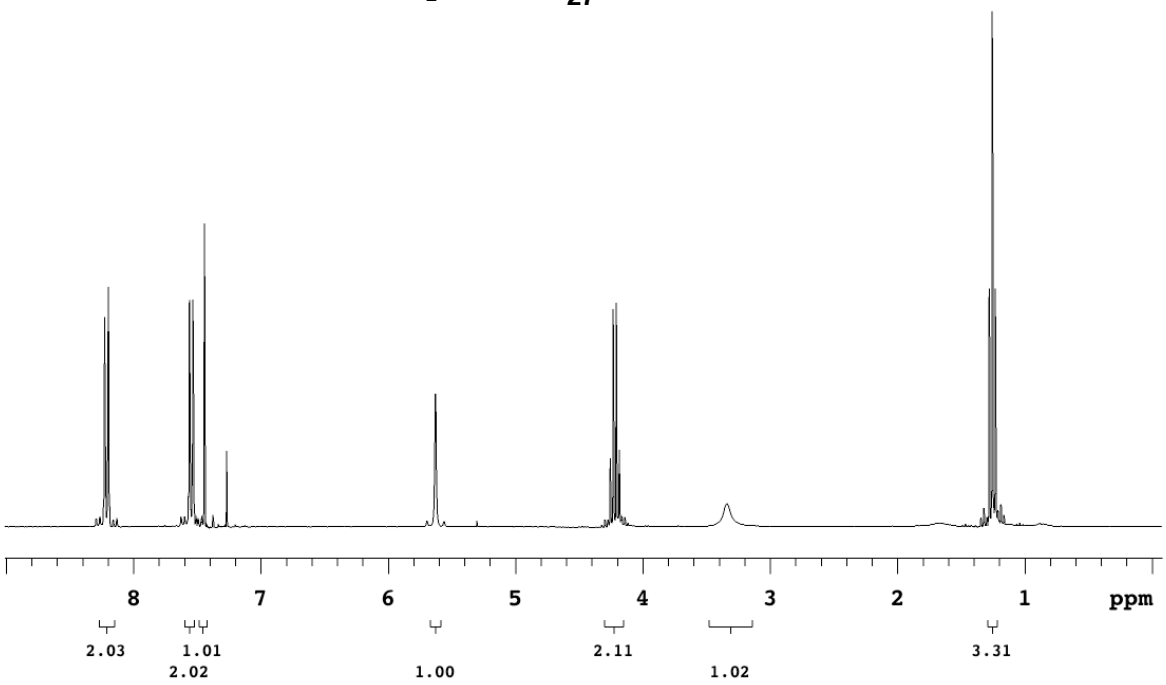
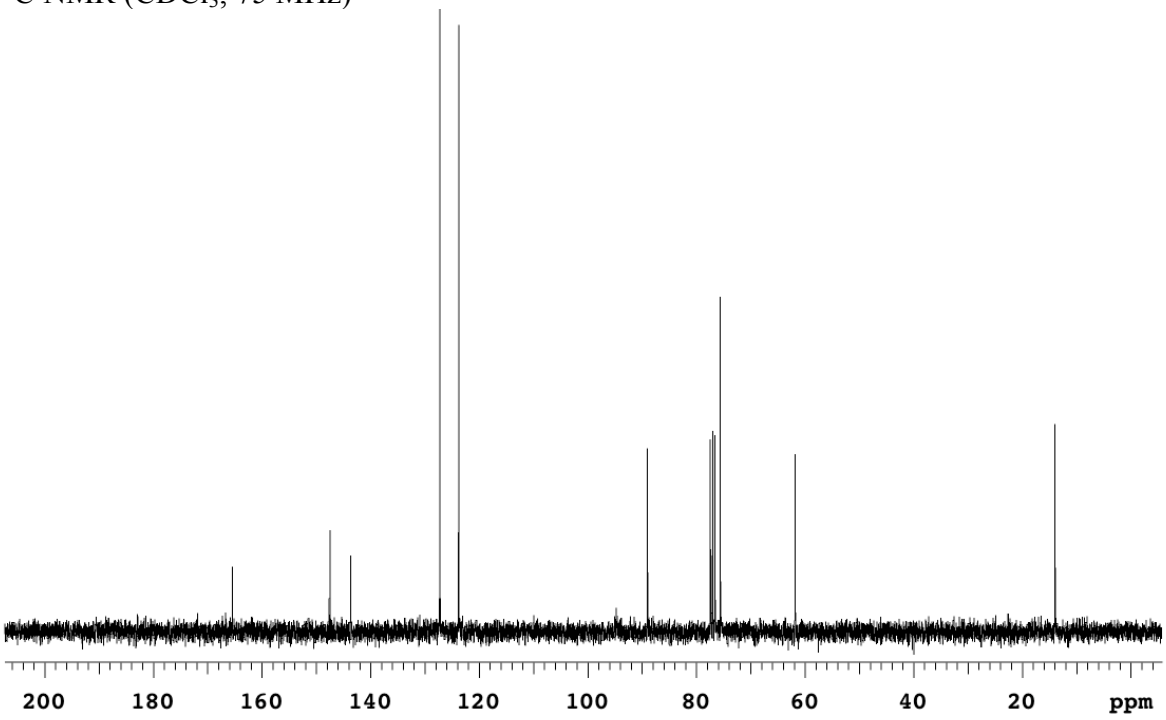
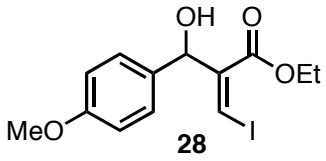


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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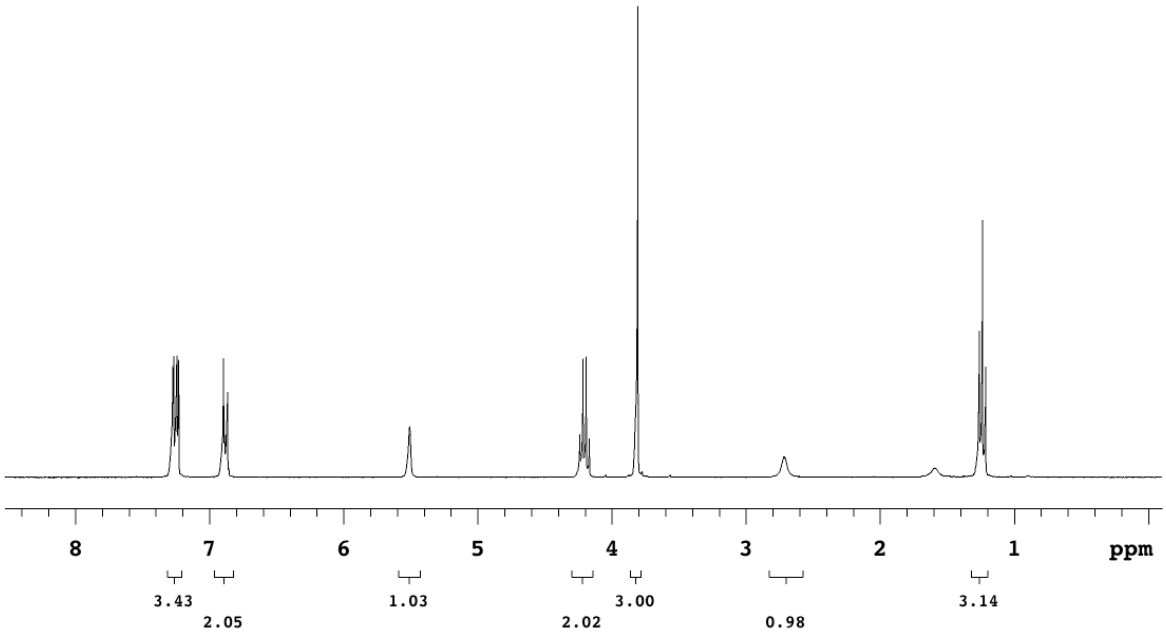
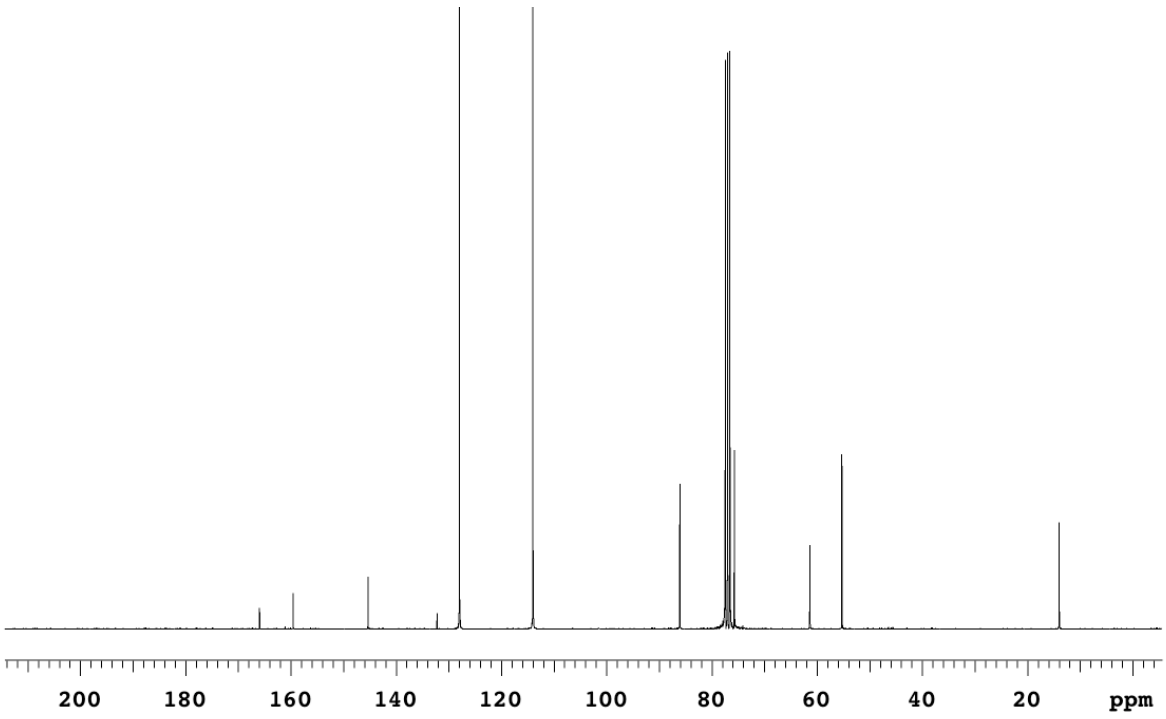
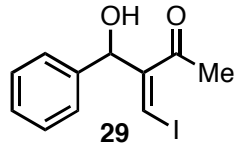


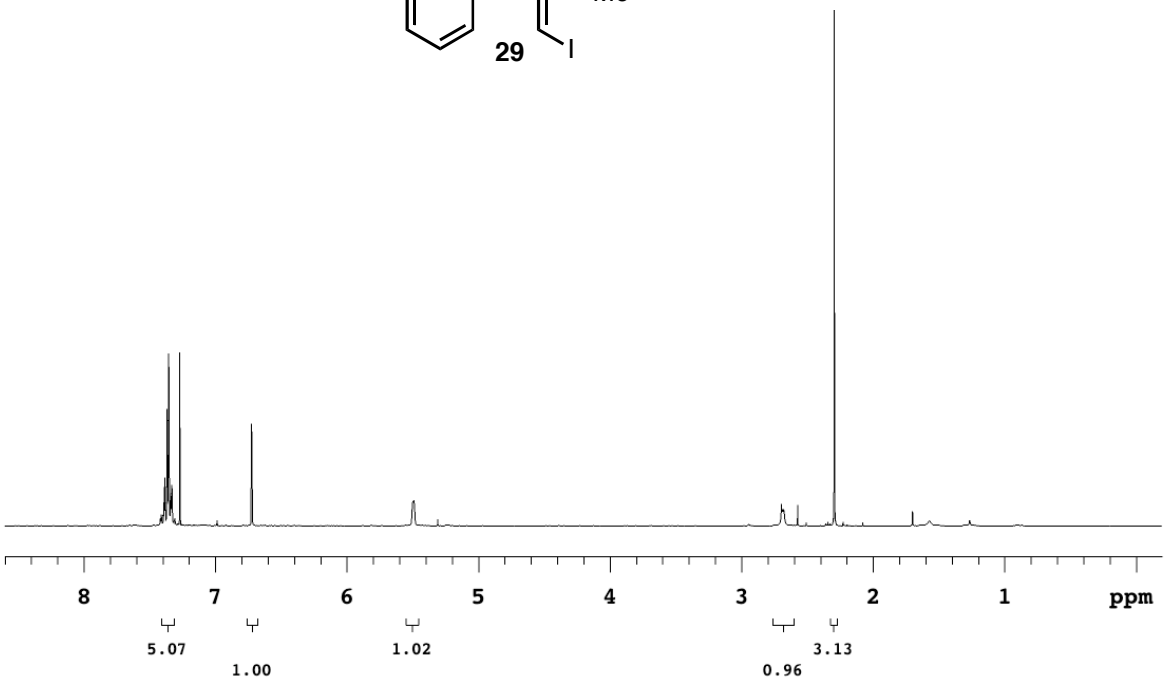
^{13}C NMR ($CDCl_3$, 75 MHz)



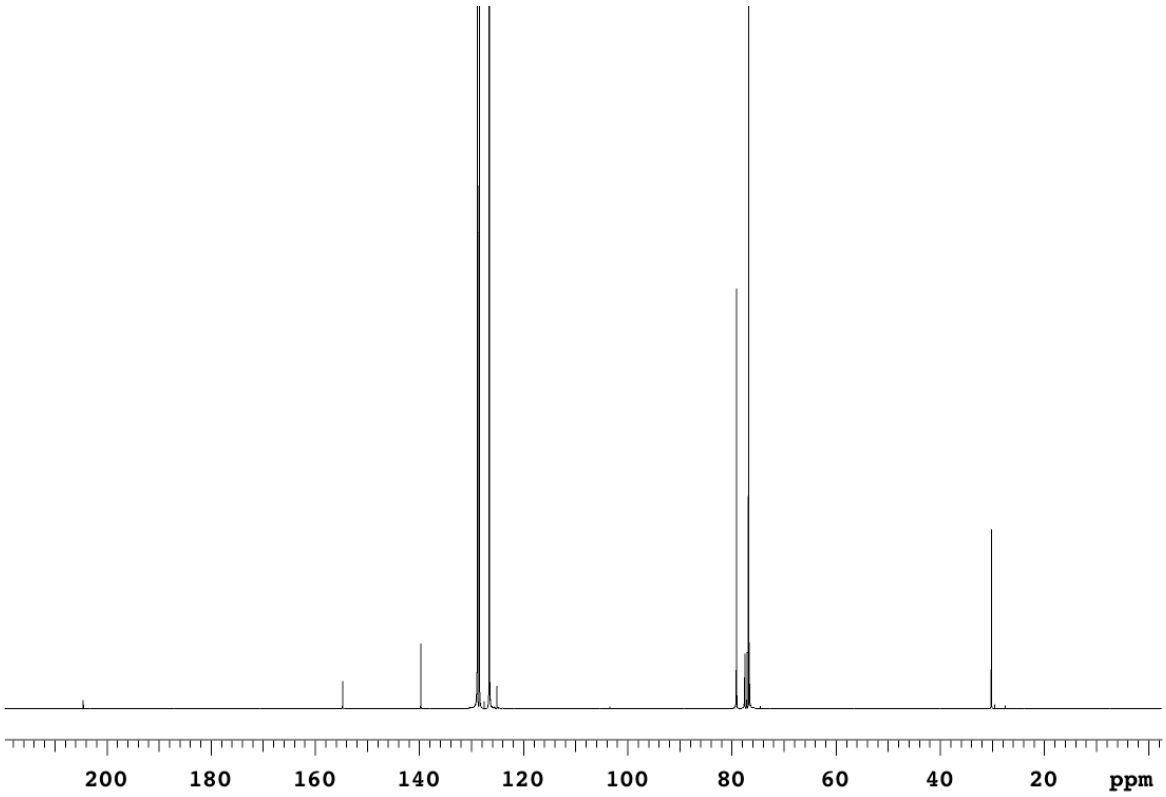
^{1}H NMR ($CDCl_3$, 300 MHz)



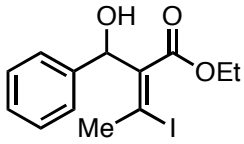
29



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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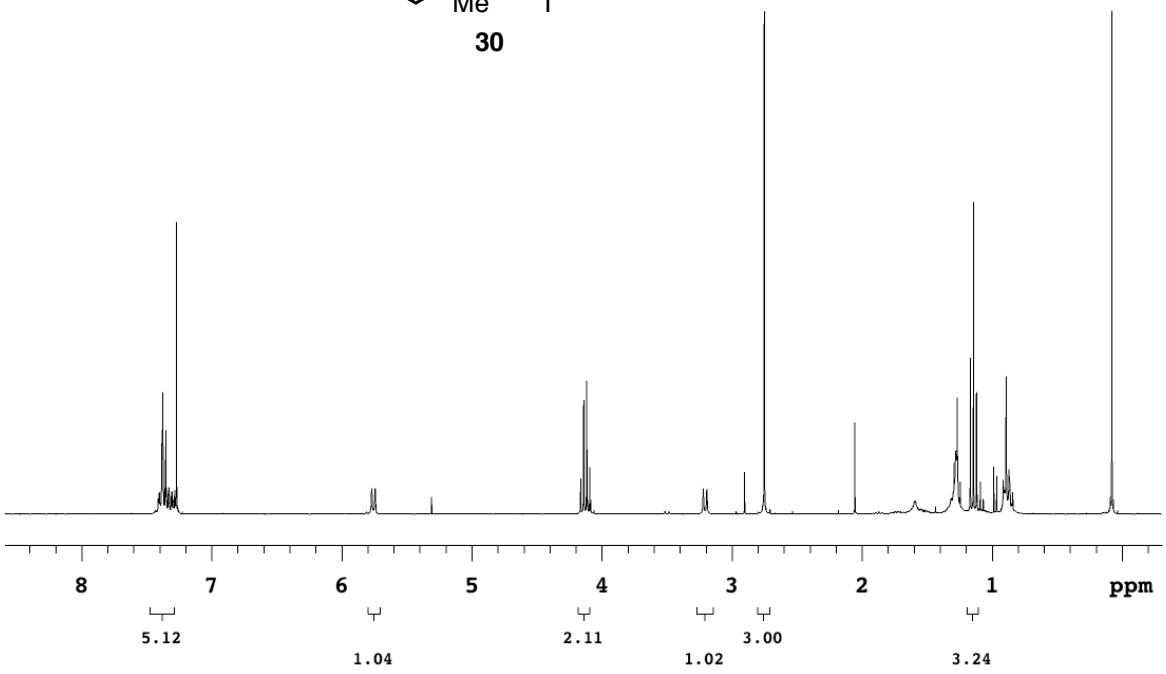
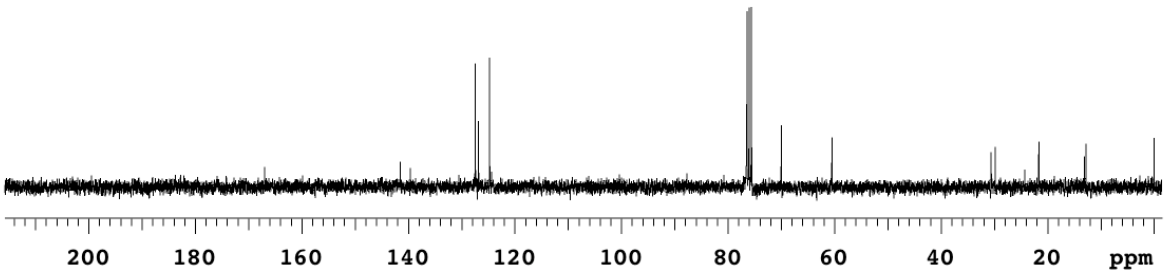
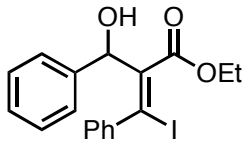


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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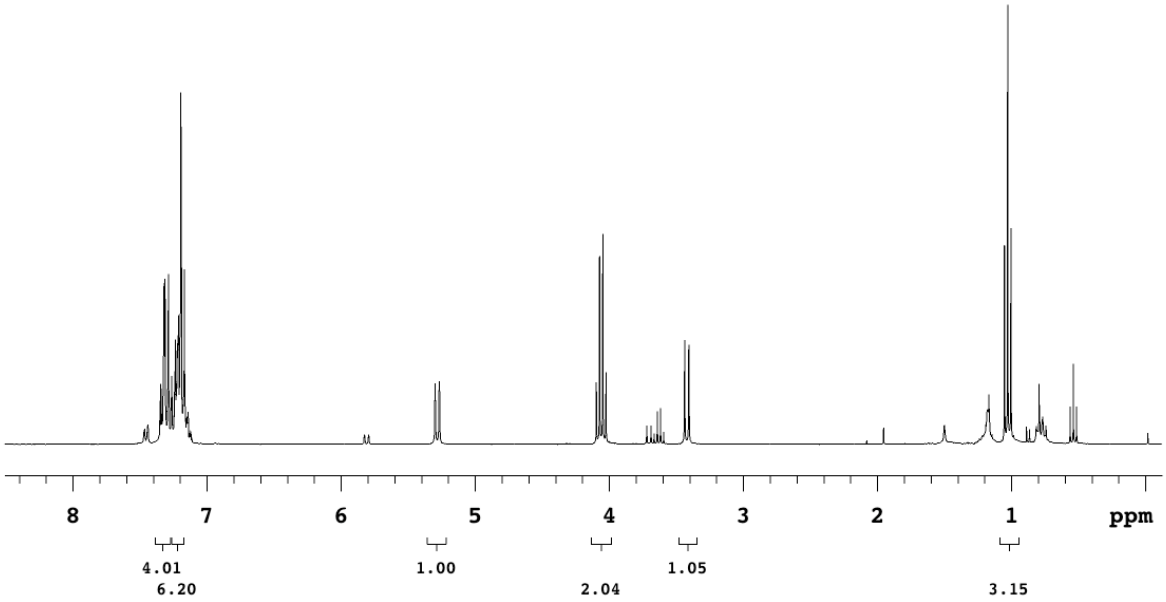
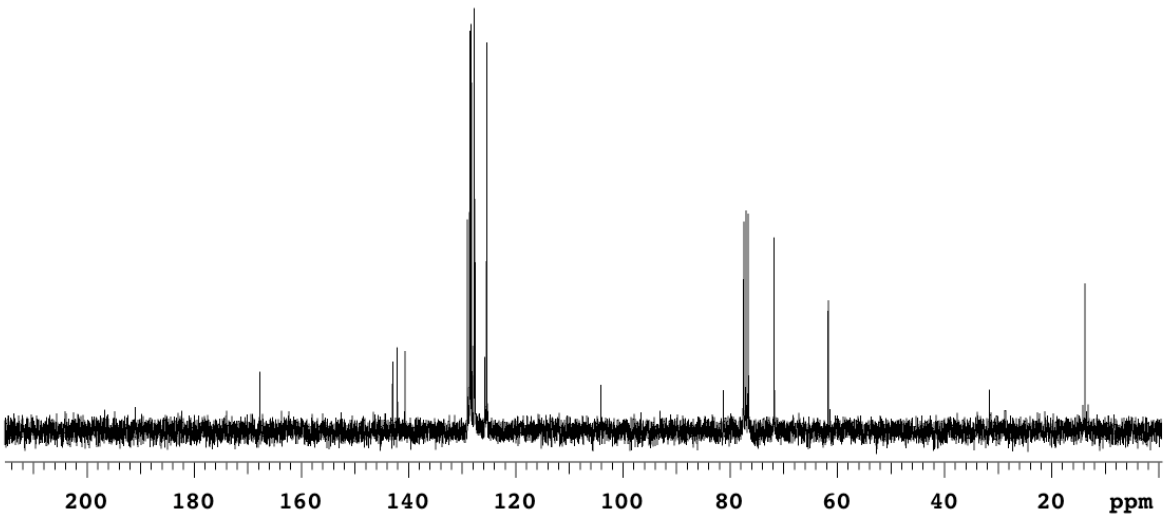
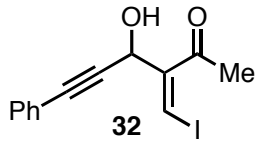


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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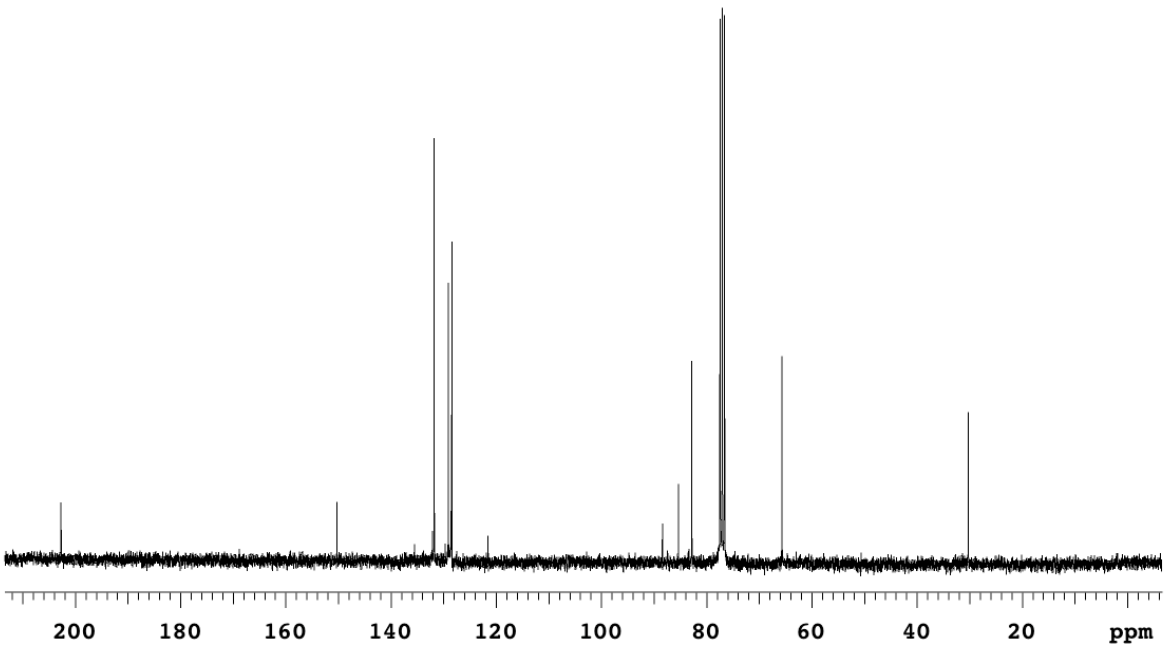
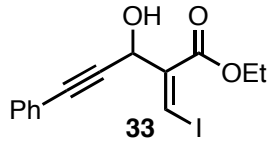
^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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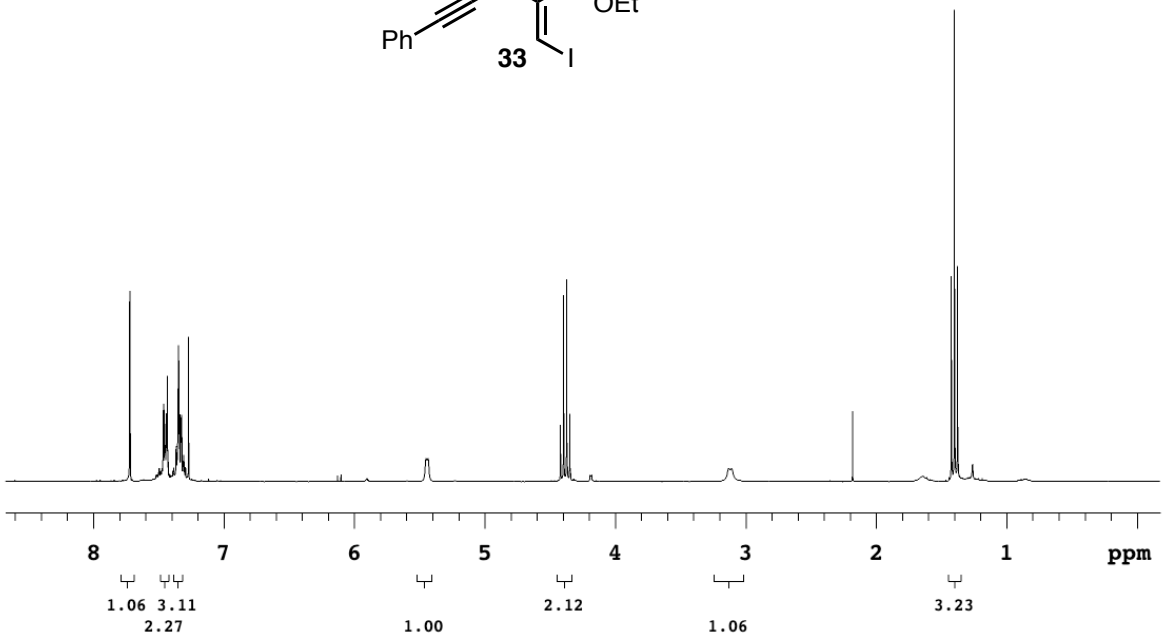
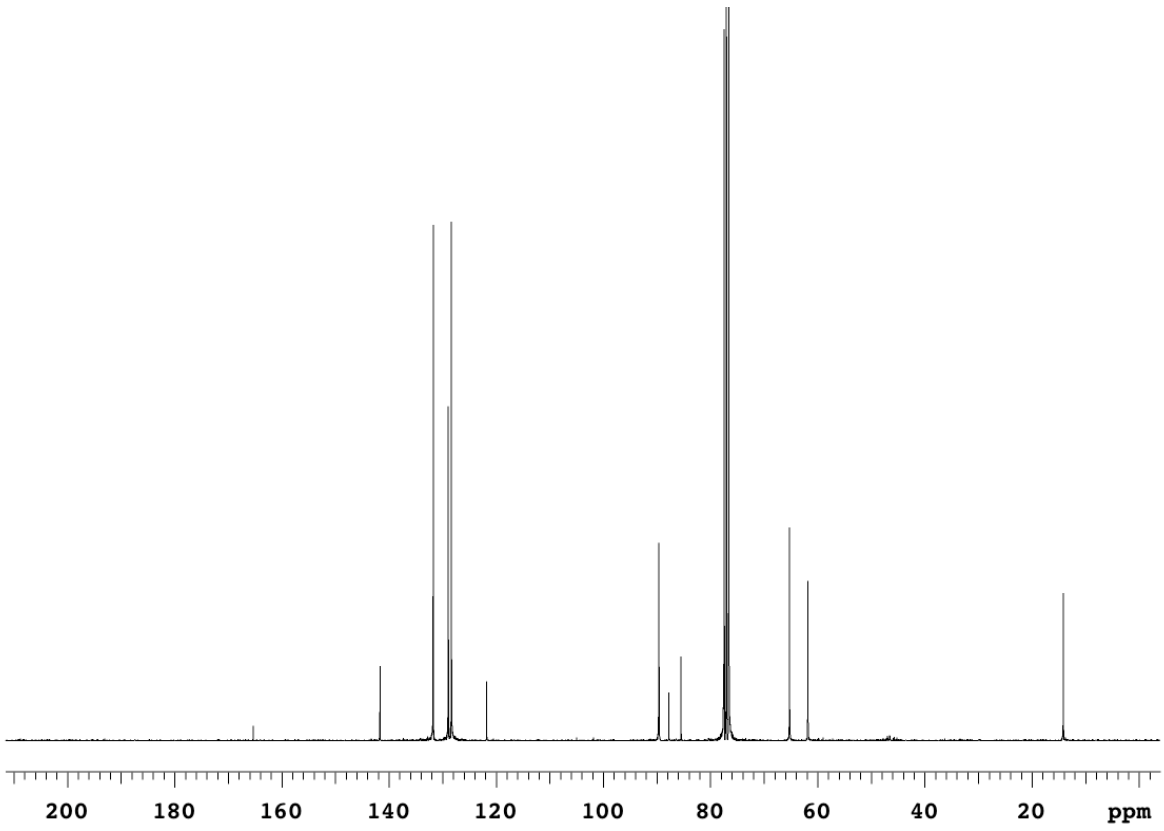
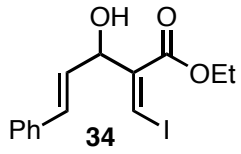


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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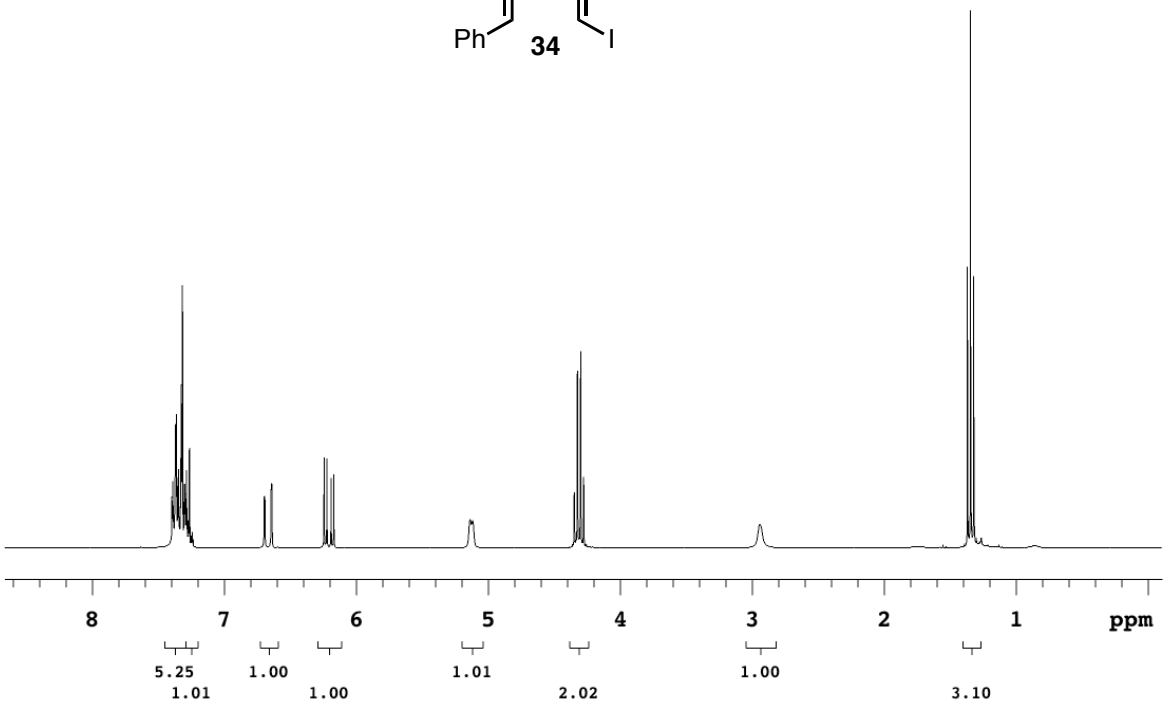
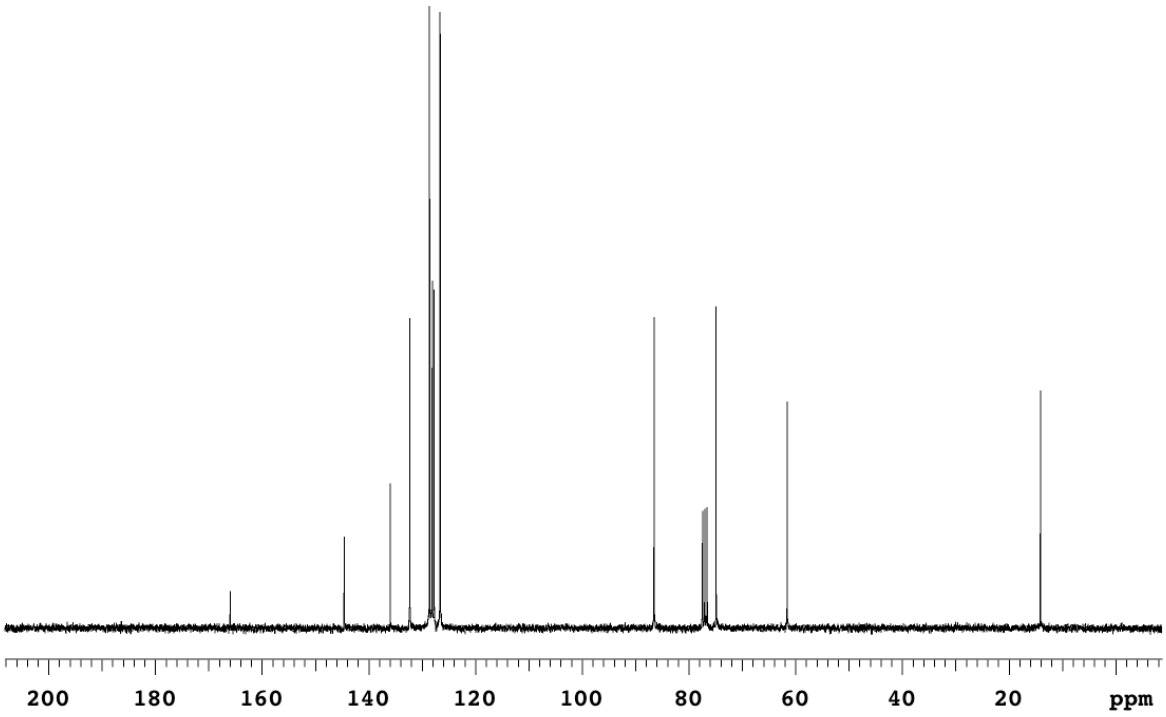
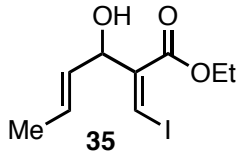


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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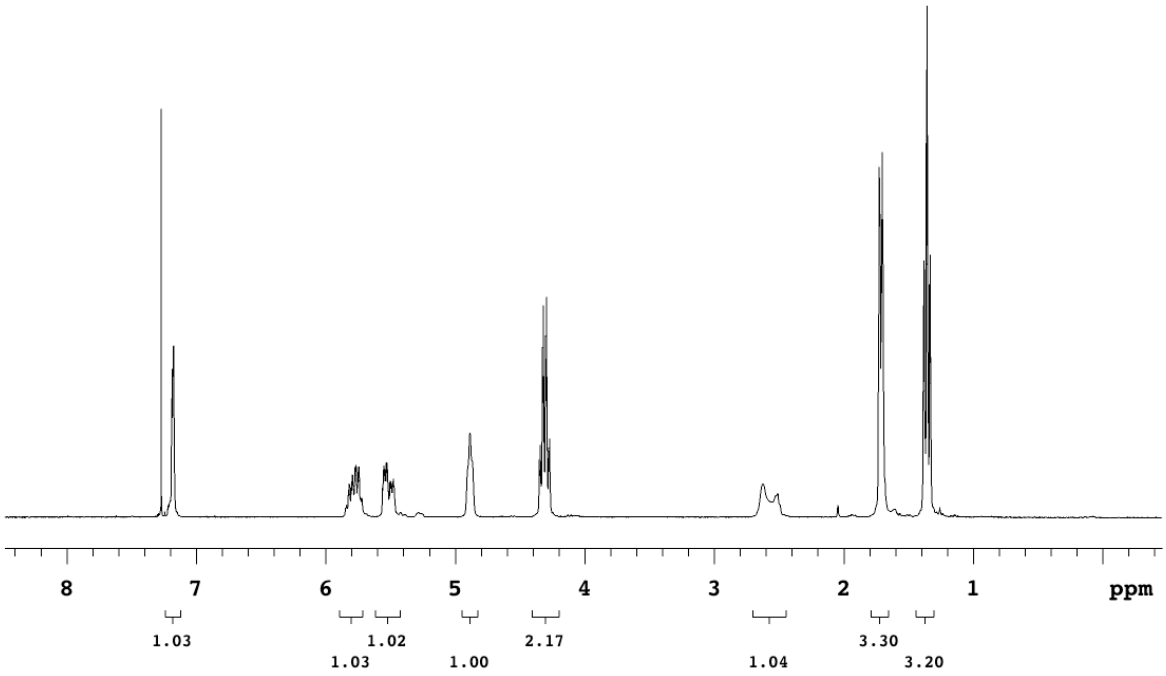
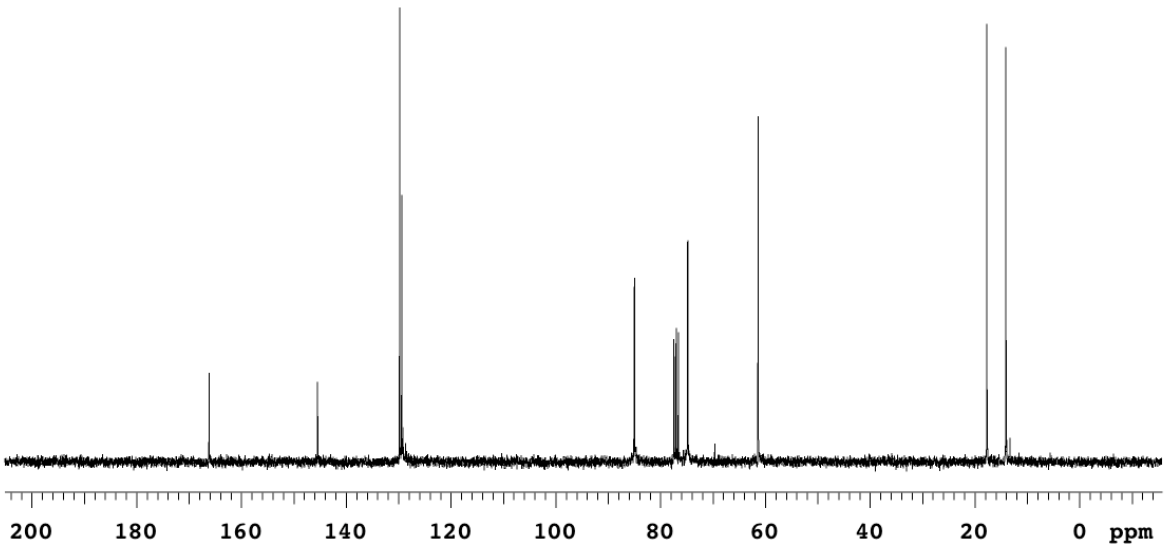
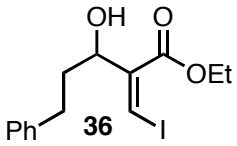


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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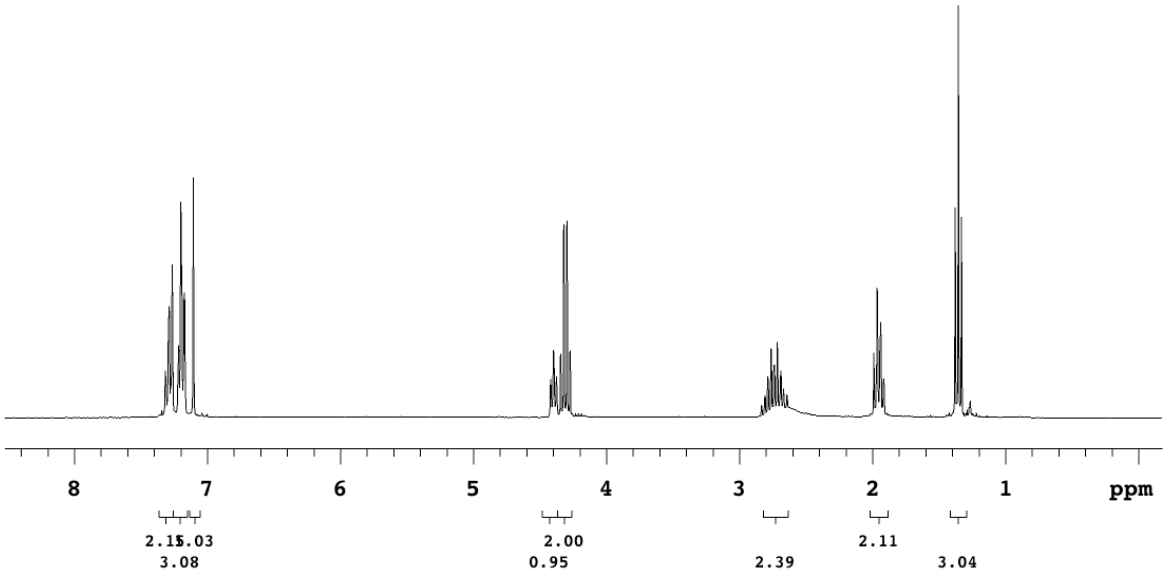
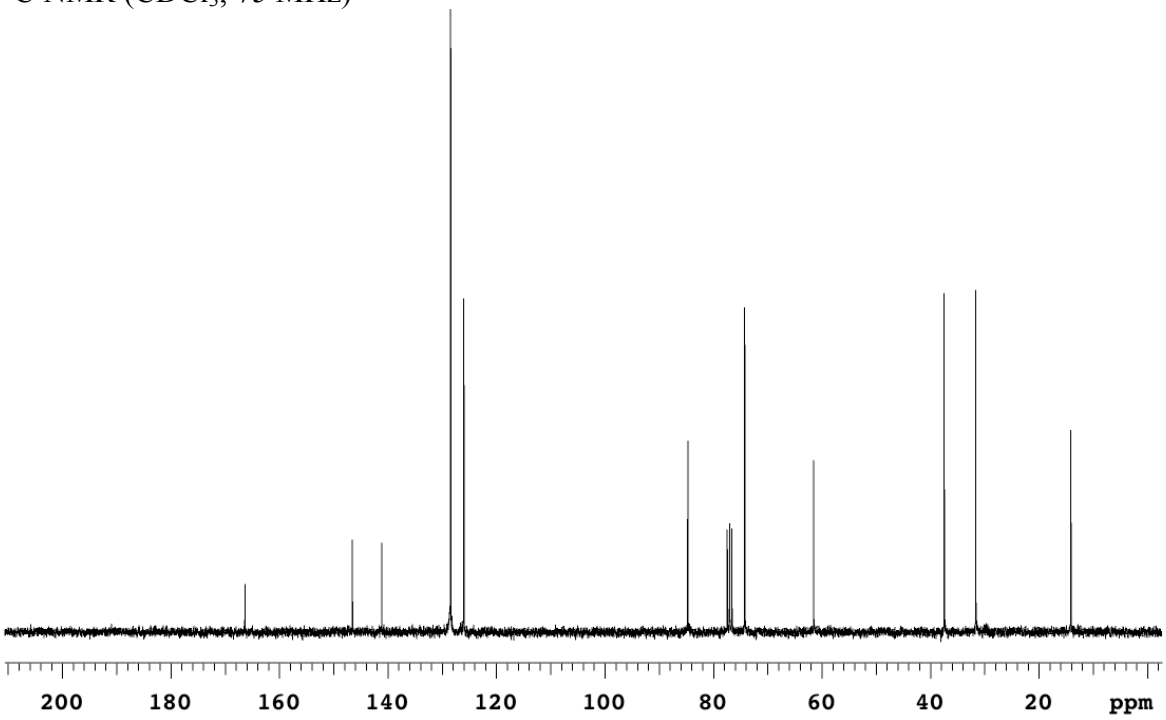
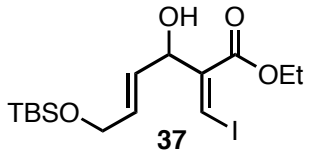


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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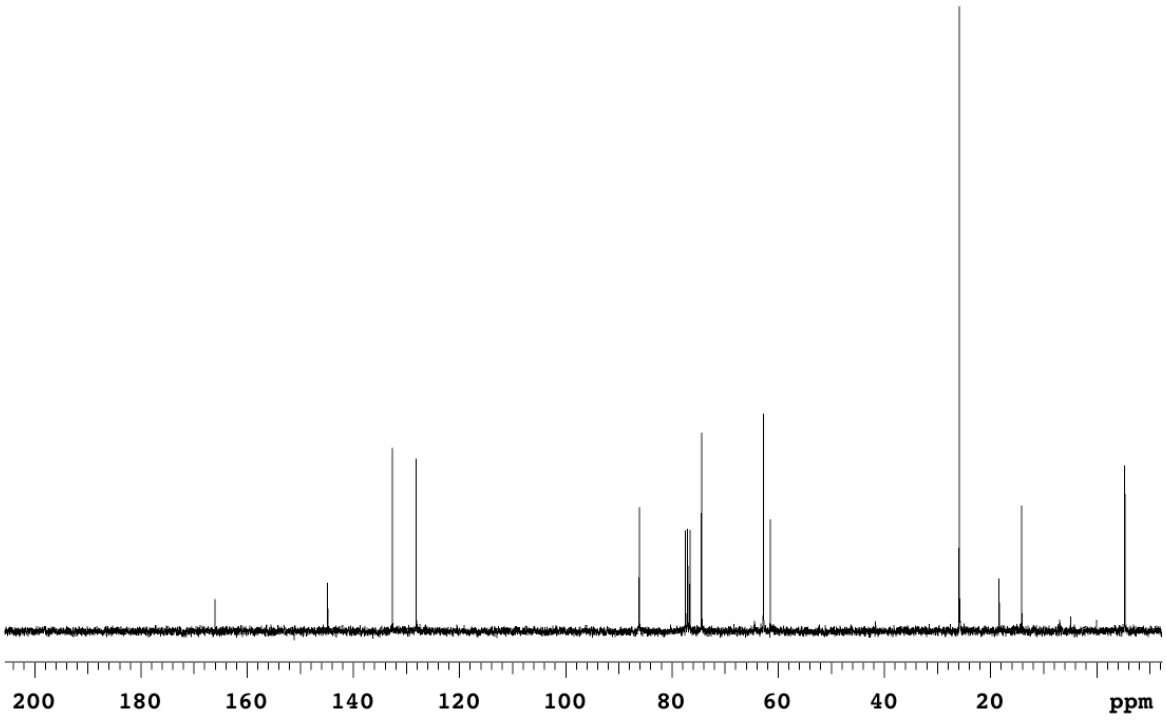
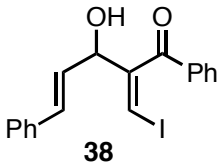
^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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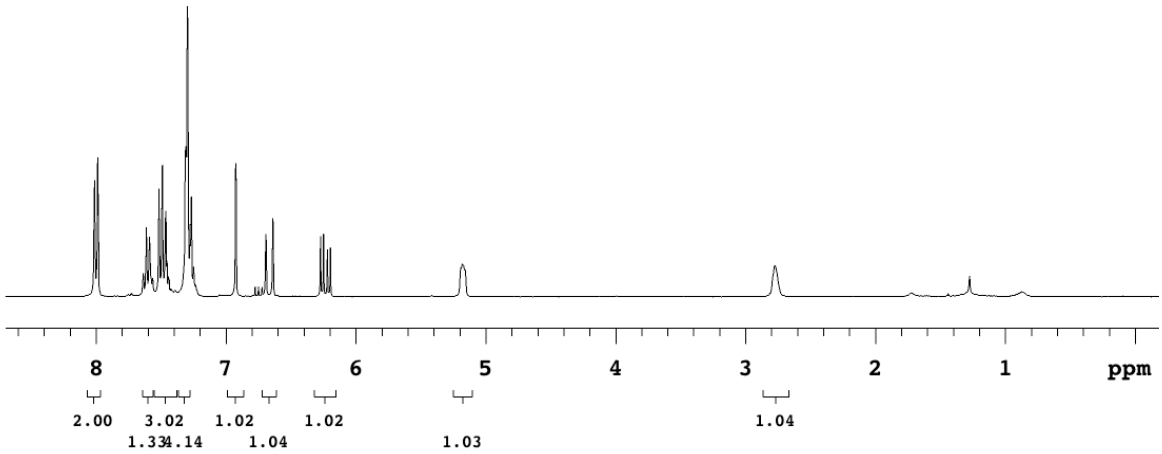

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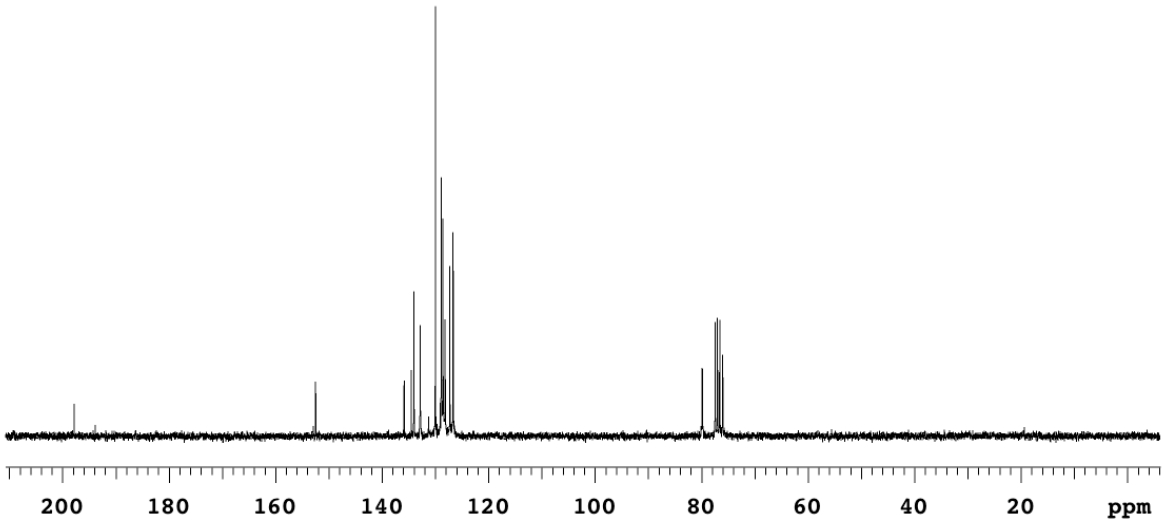
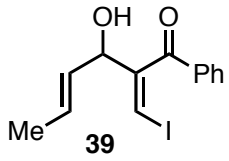


^{1}H NMR ($CDCl_3$, 300 MHz)



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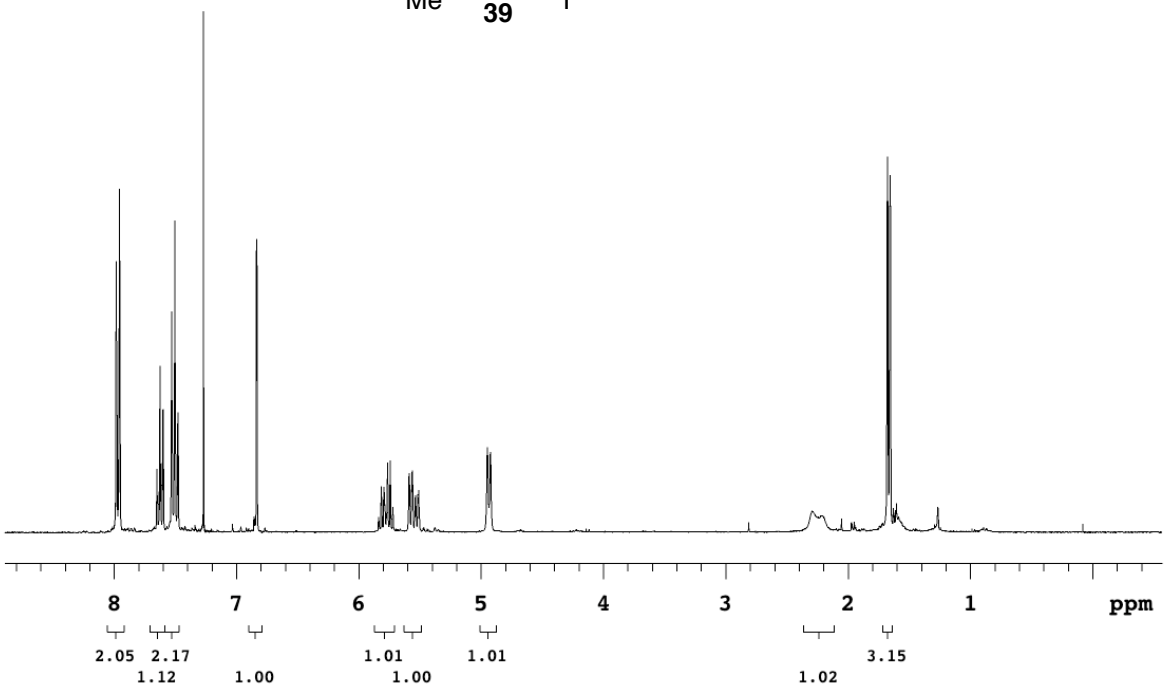
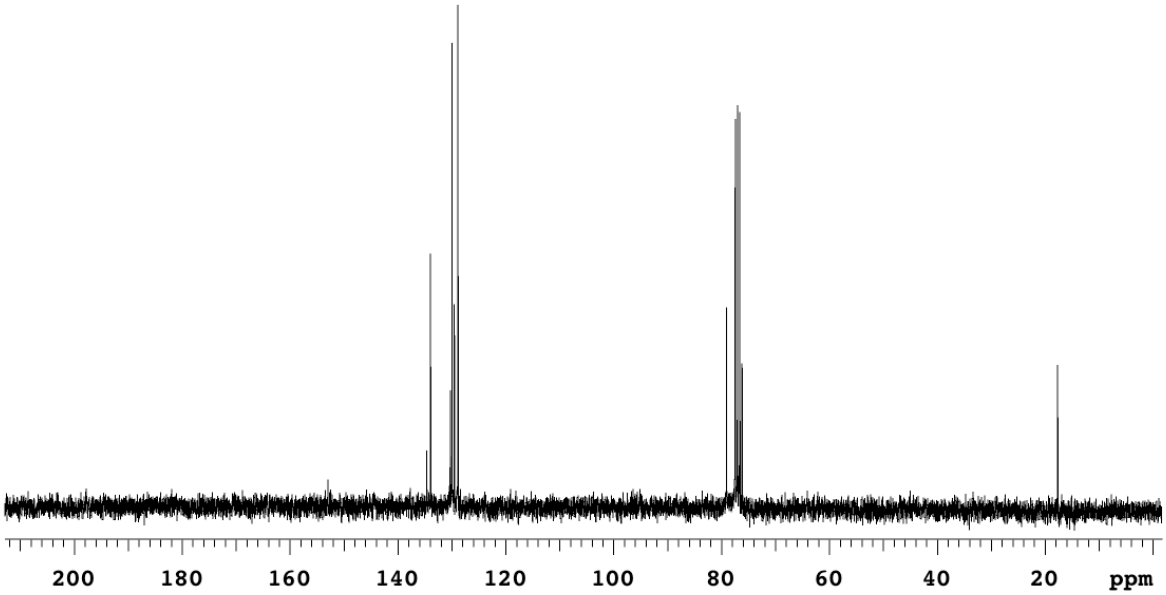
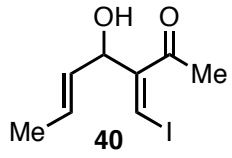


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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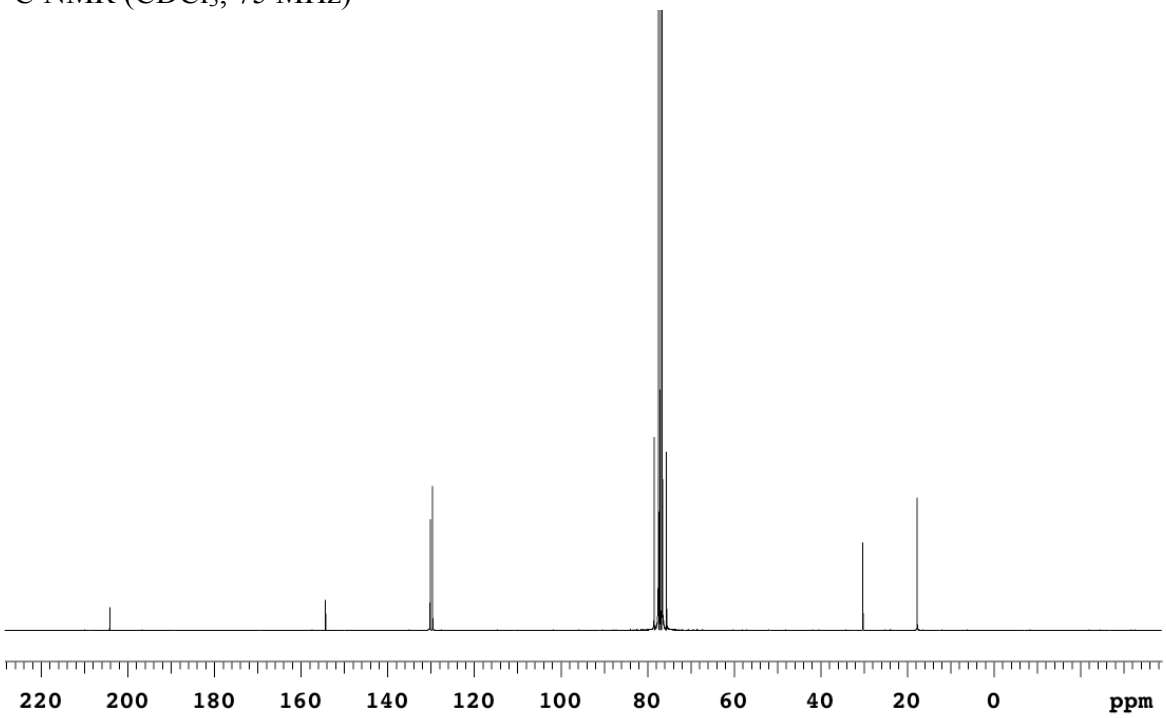
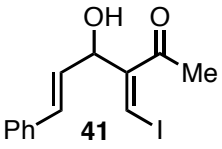
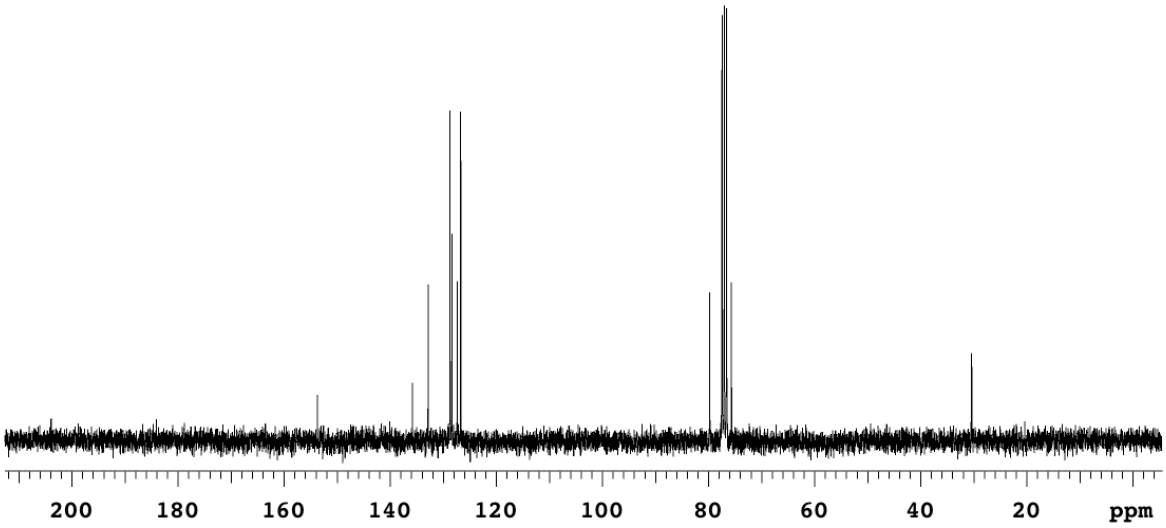
^{13}C NMR ($CDCl_3$, 75 MHz)



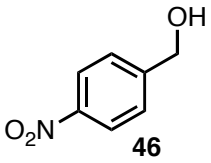
^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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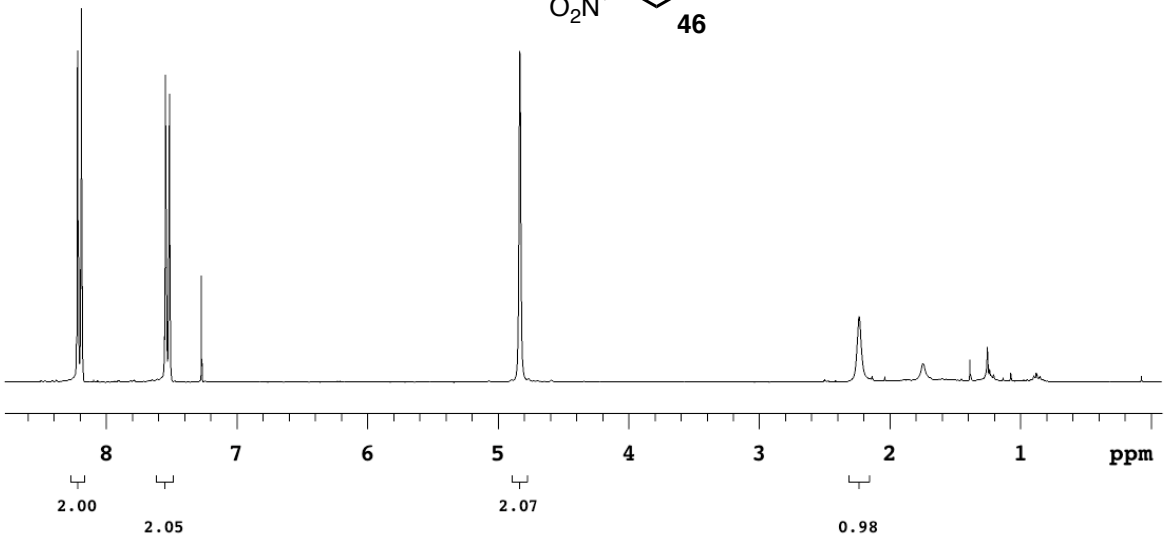
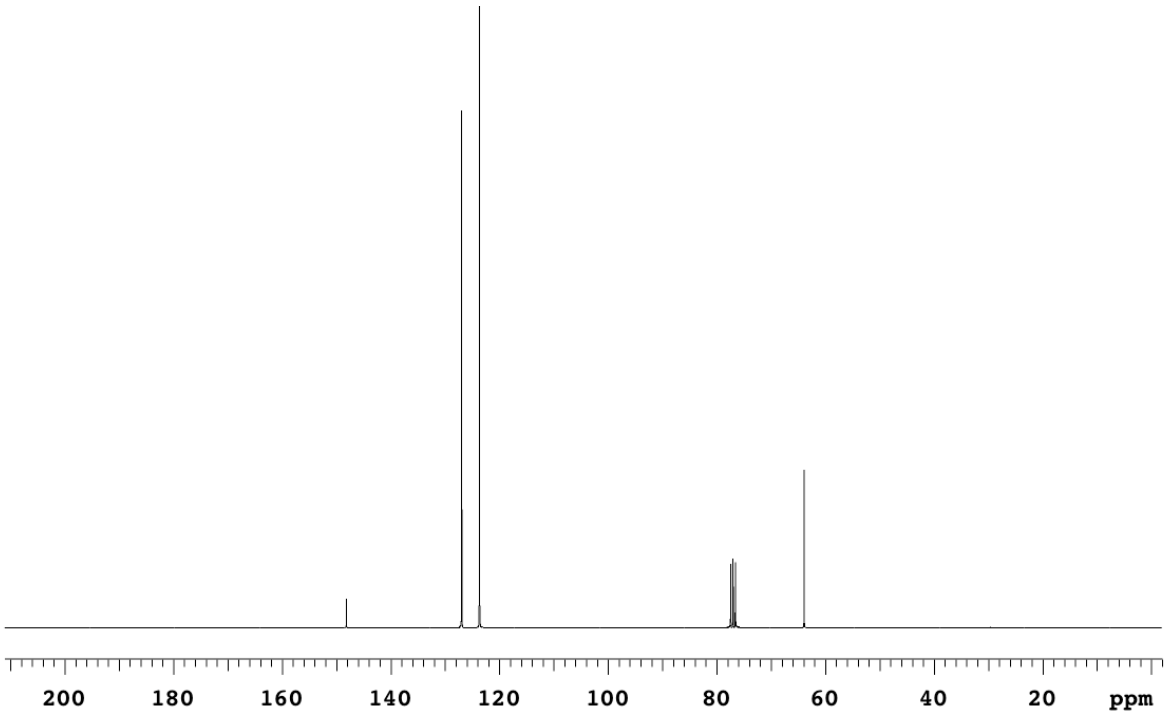
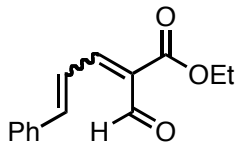


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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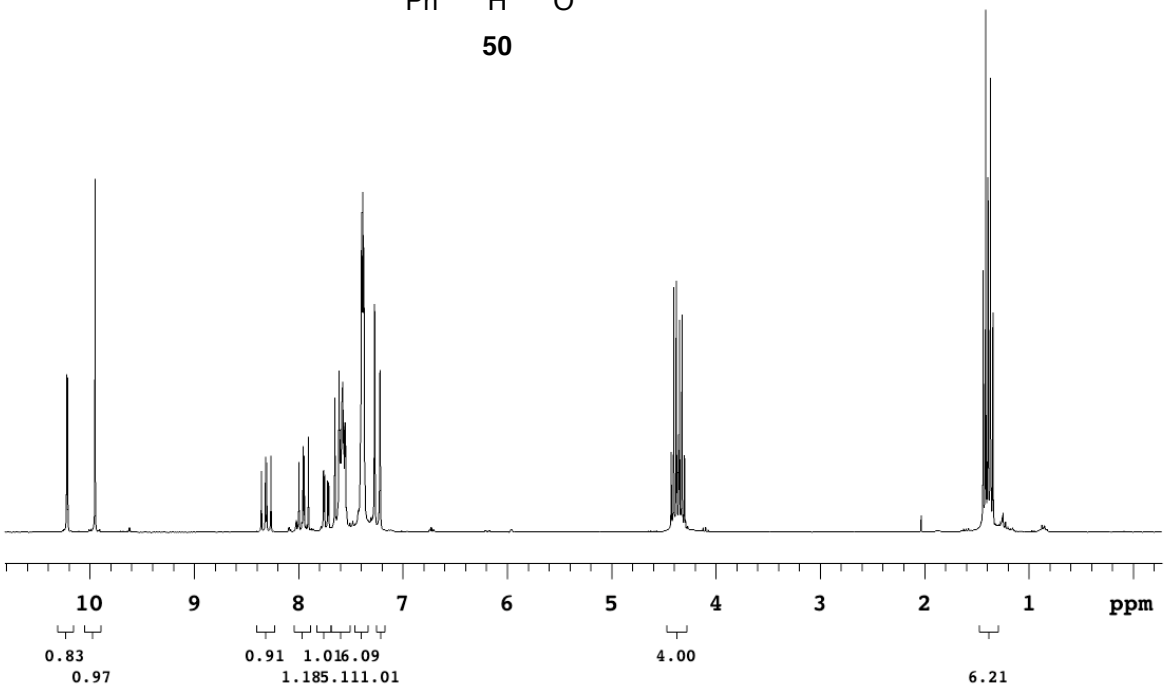
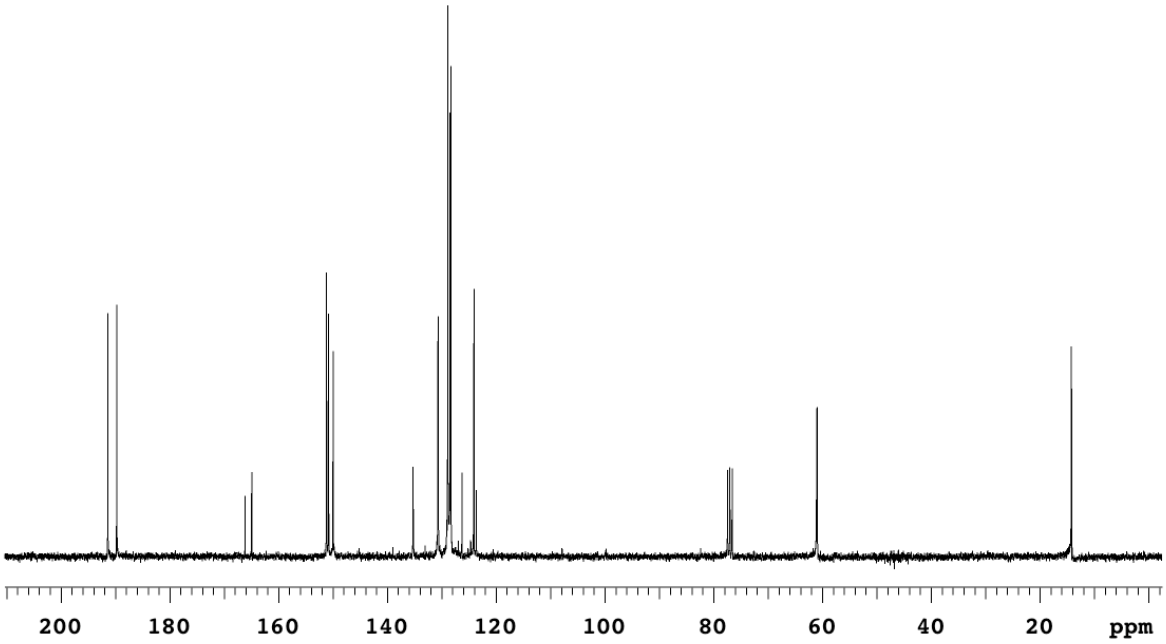
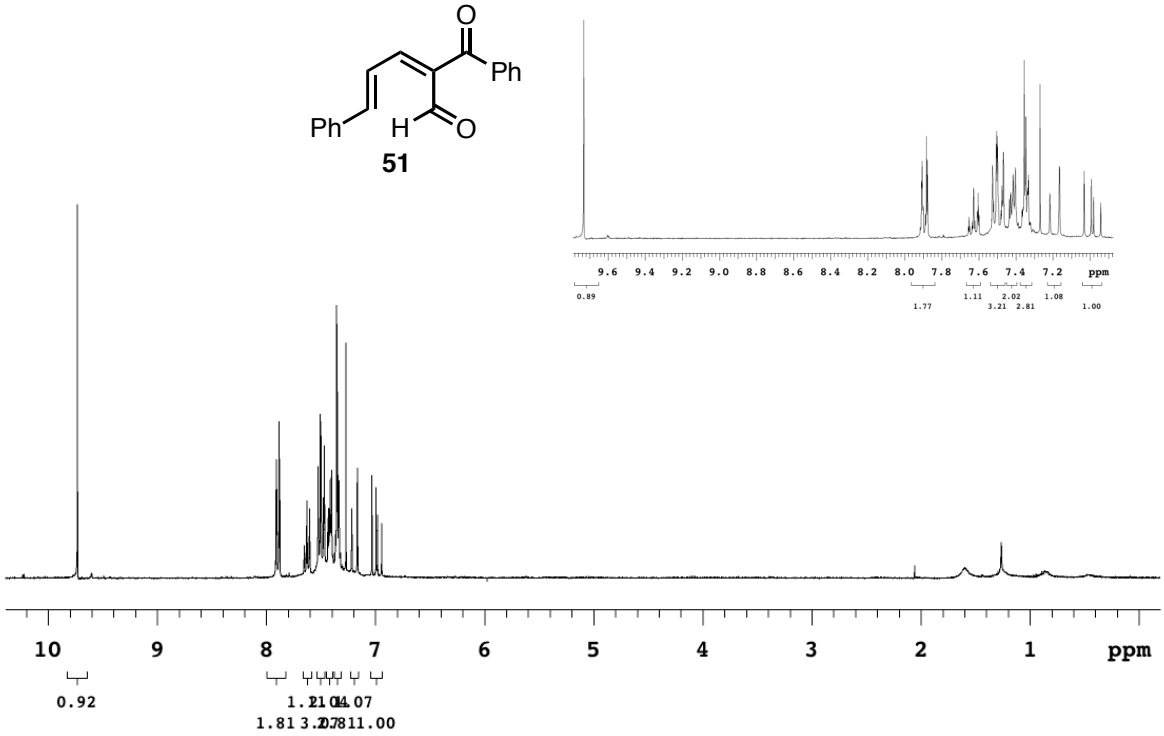


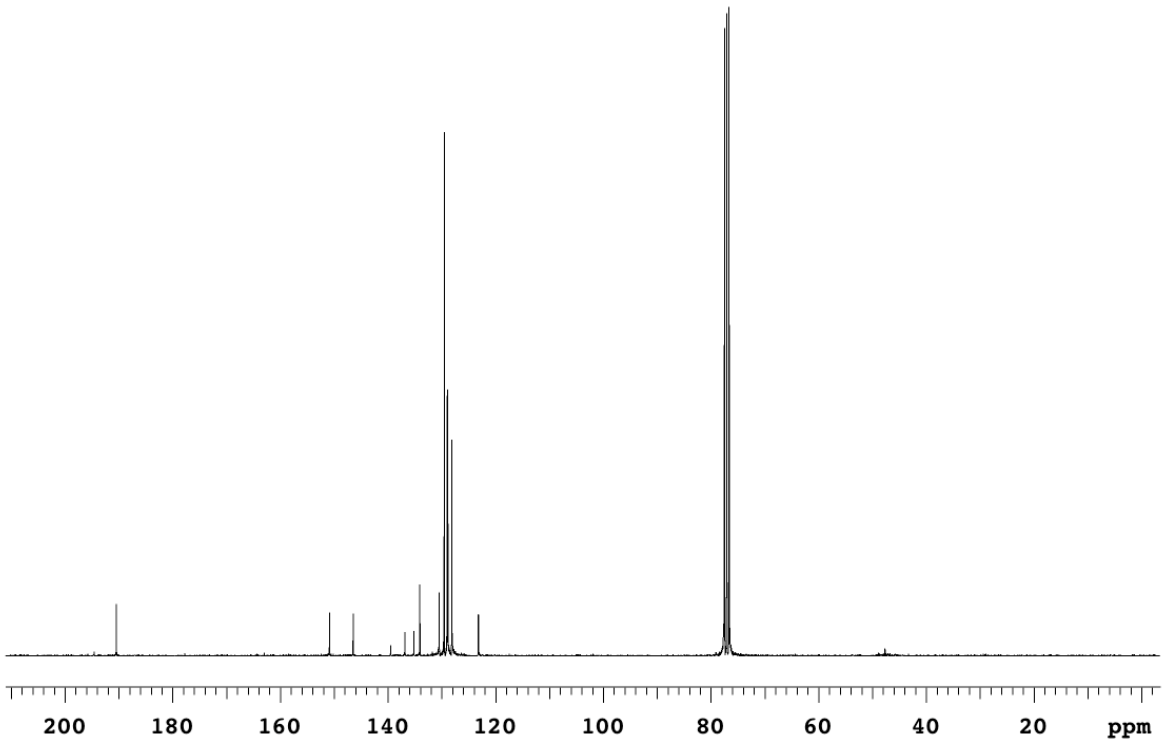
^{13}C NMR ($CDCl_3$, 75 MHz)



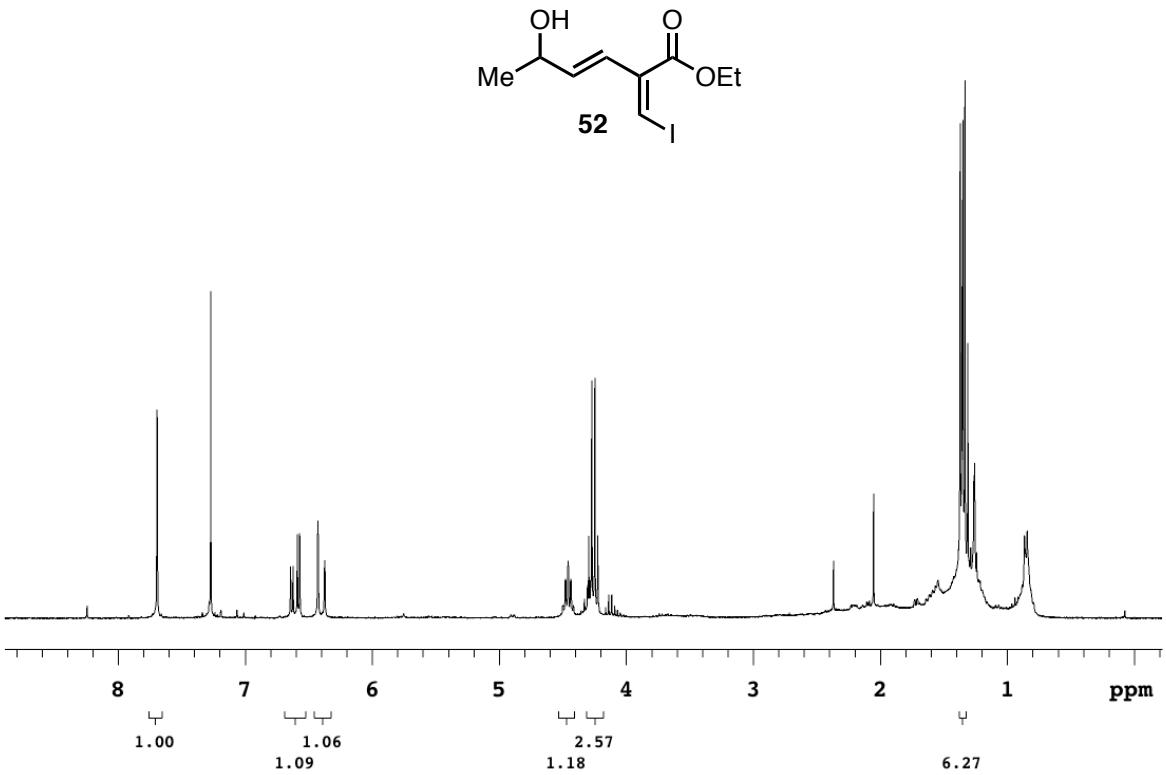
^{1}H NMR ($CDCl_3$, 300 MHz)



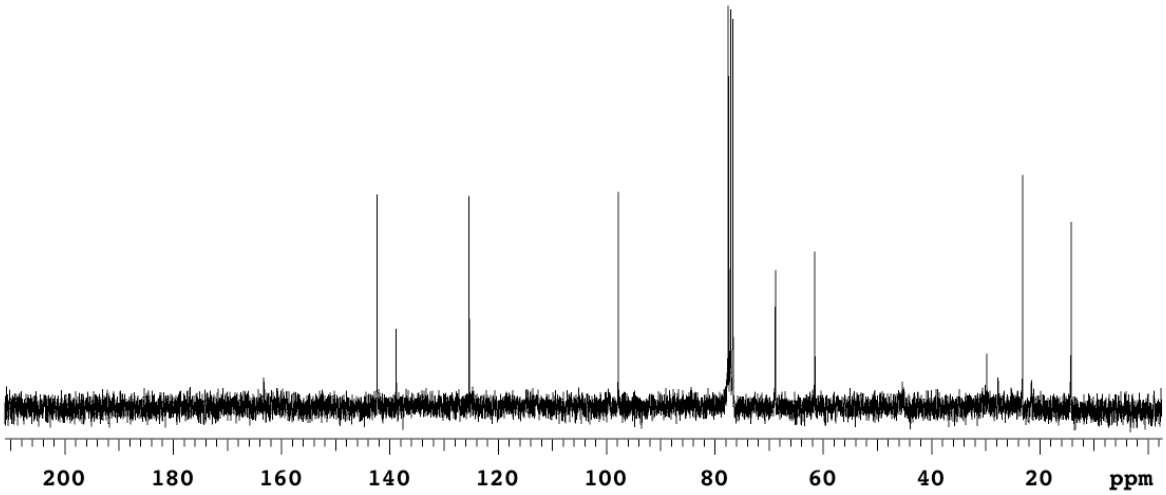
^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)

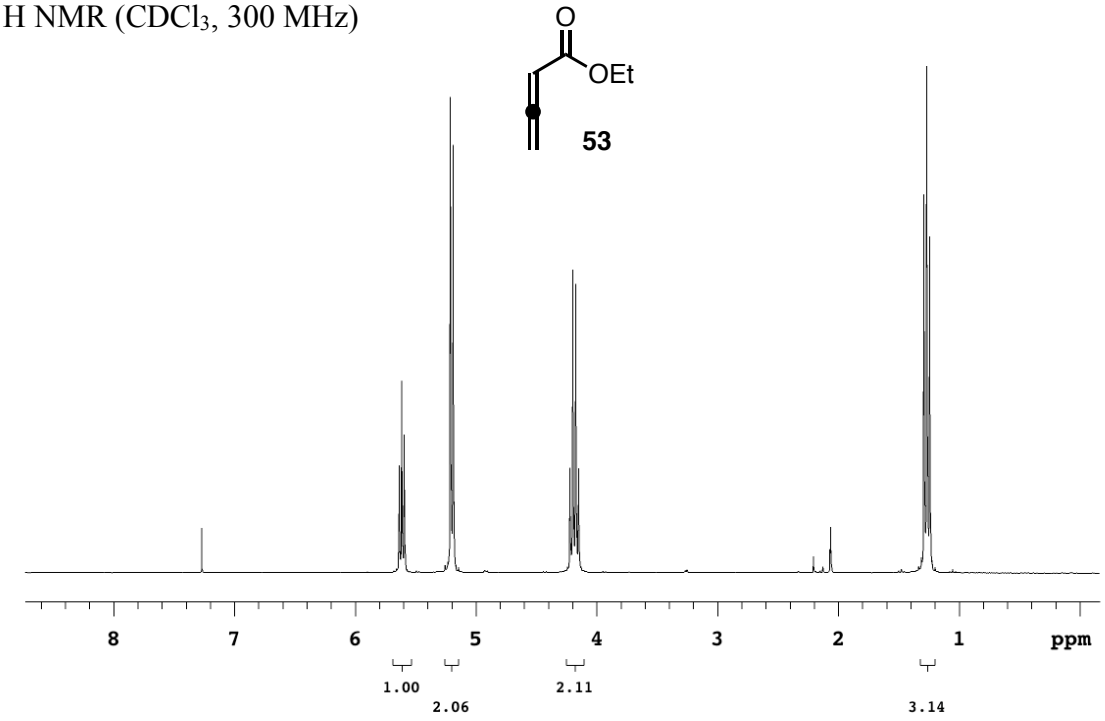


^{13}C NMR ($CDCl_3$, 75 MHz)

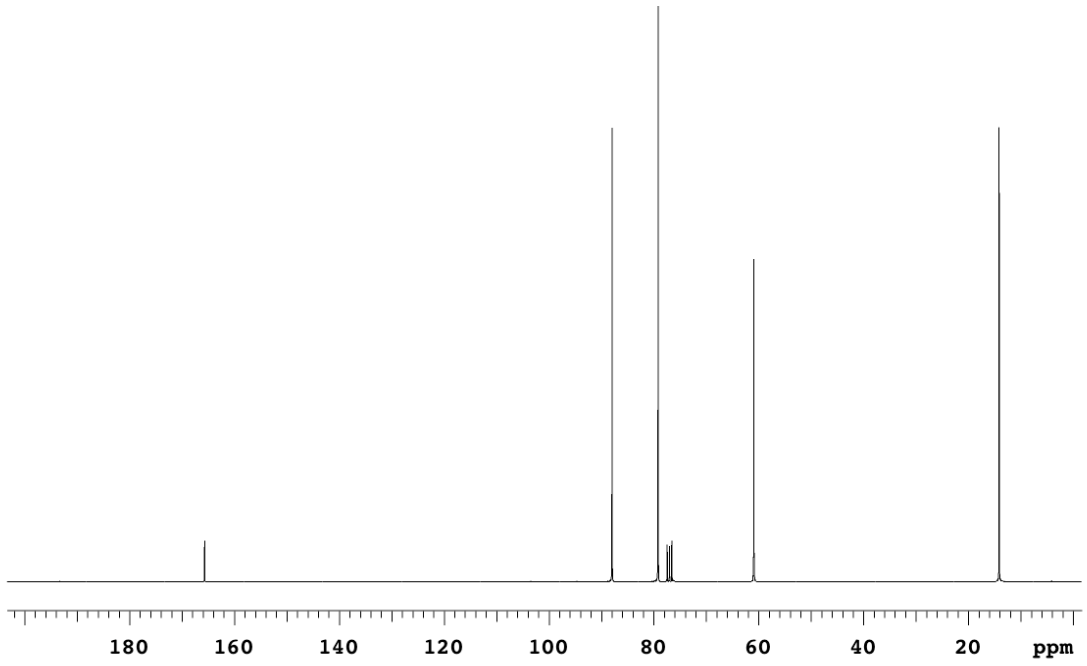


^{1}H and ^{13}C NMR Spectra

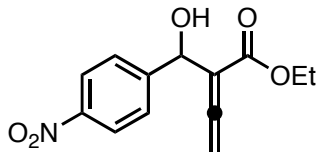
^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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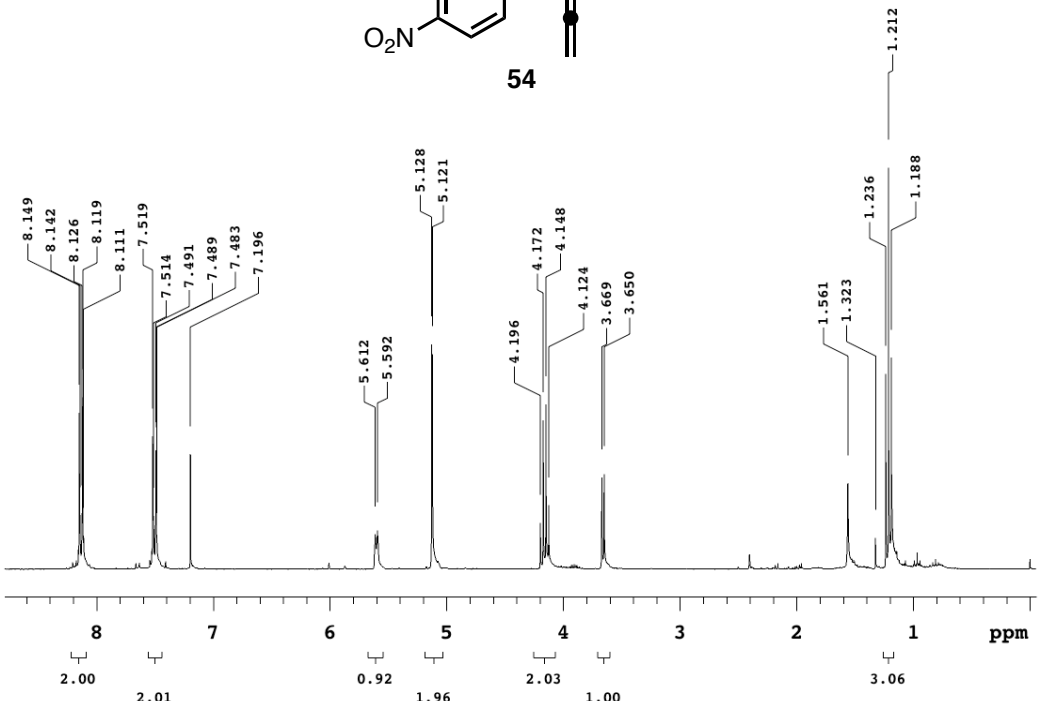
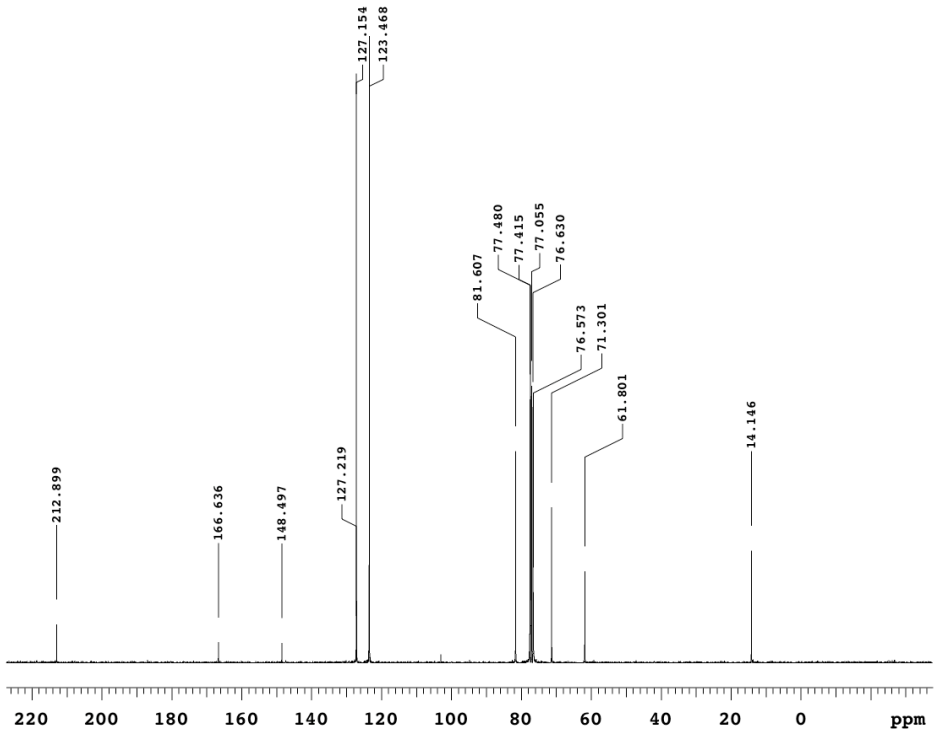
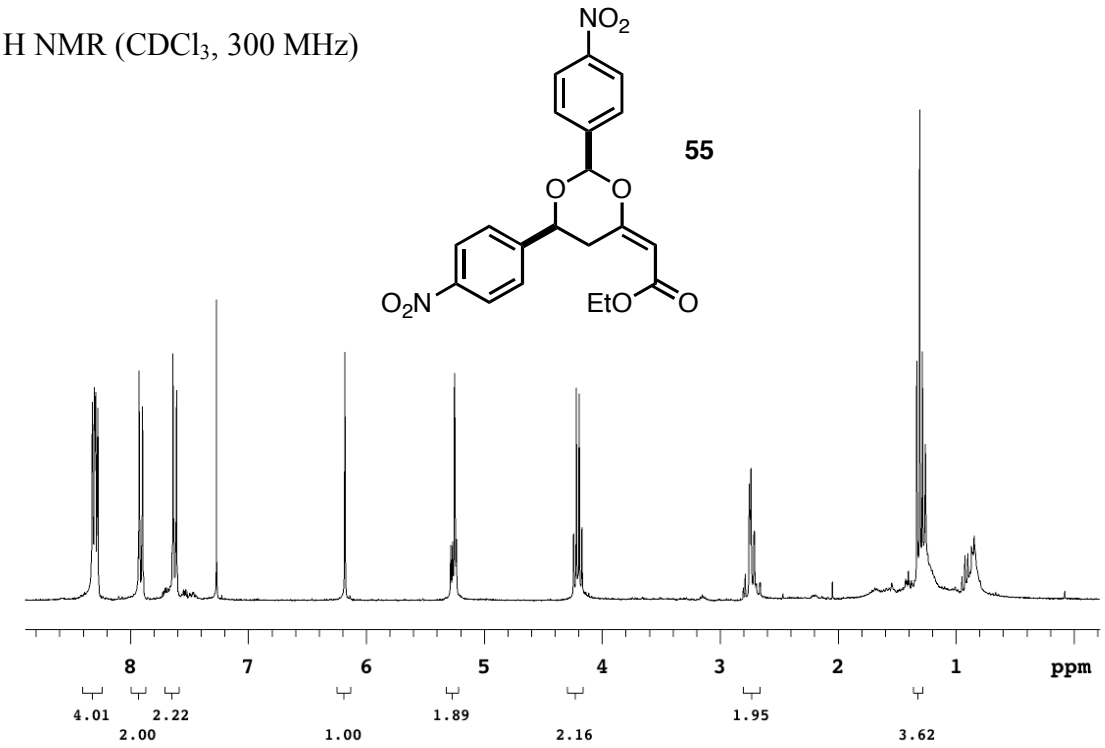


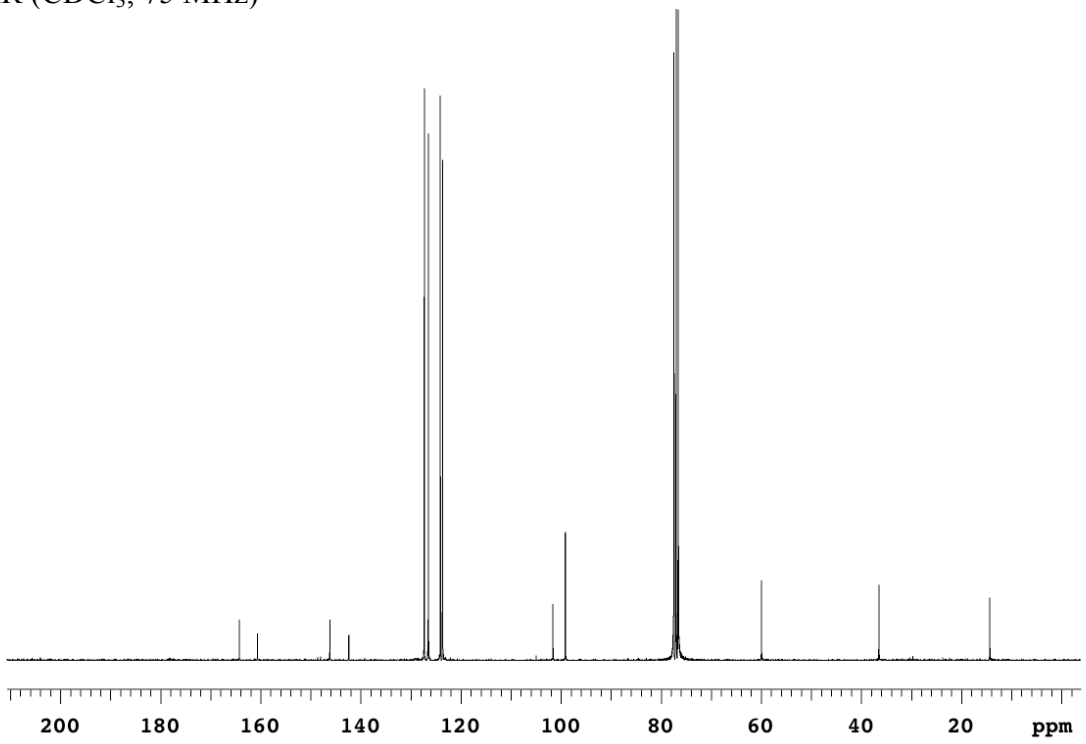
^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)

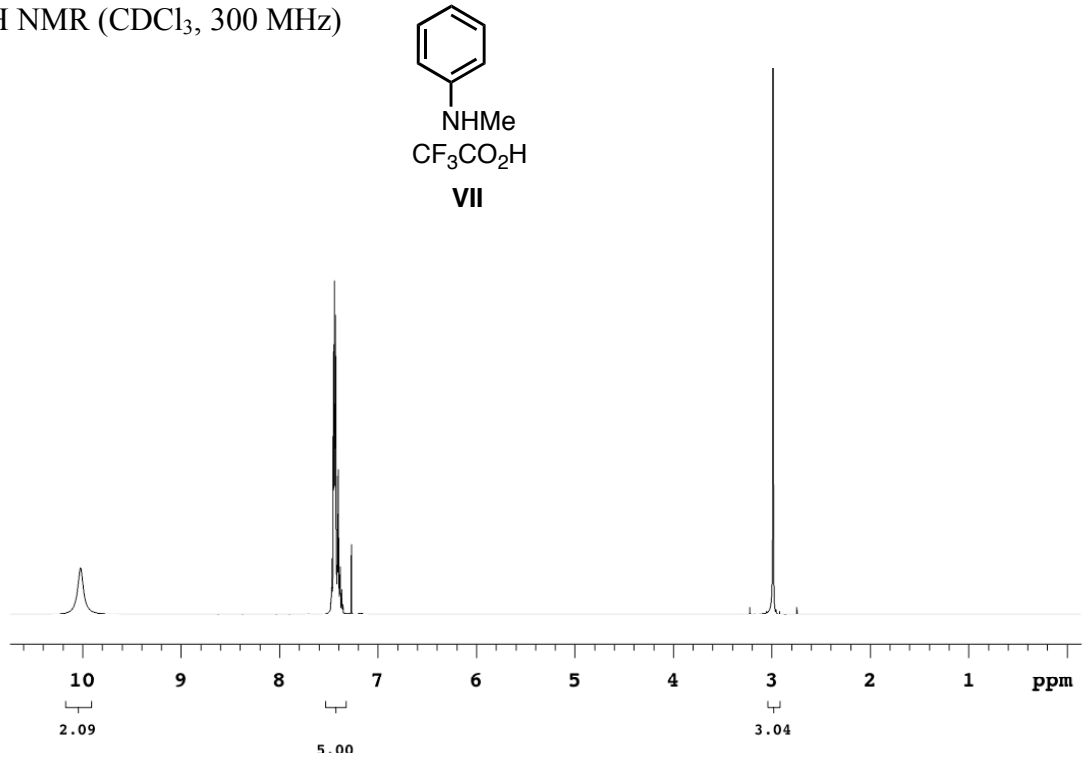


^{13}C NMR ($CDCl_3$, 75 MHz)

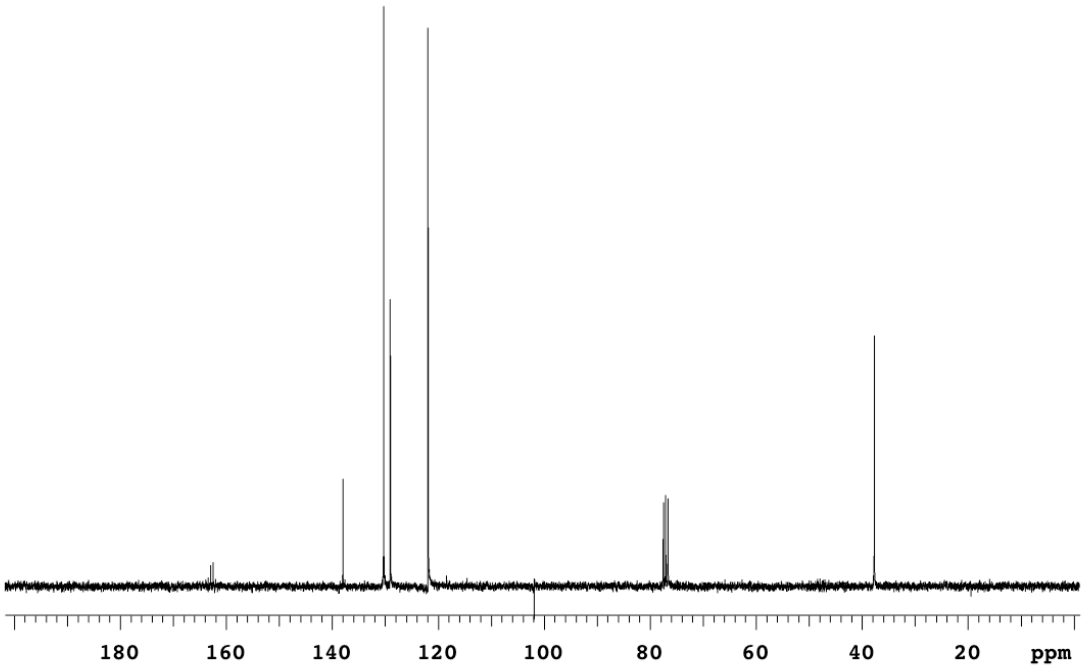


^{1}H and ^{13}C NMR Spectra

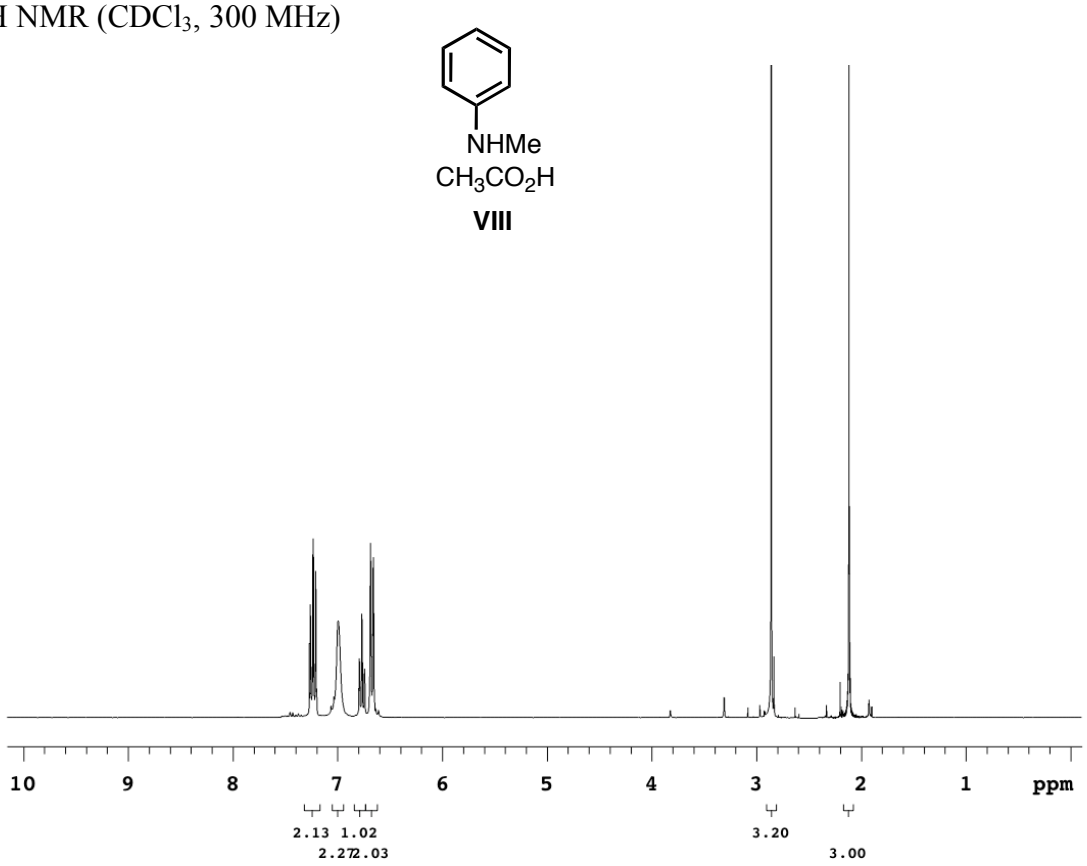
^{1}H NMR ($CDCl_3$, 300 MHz)



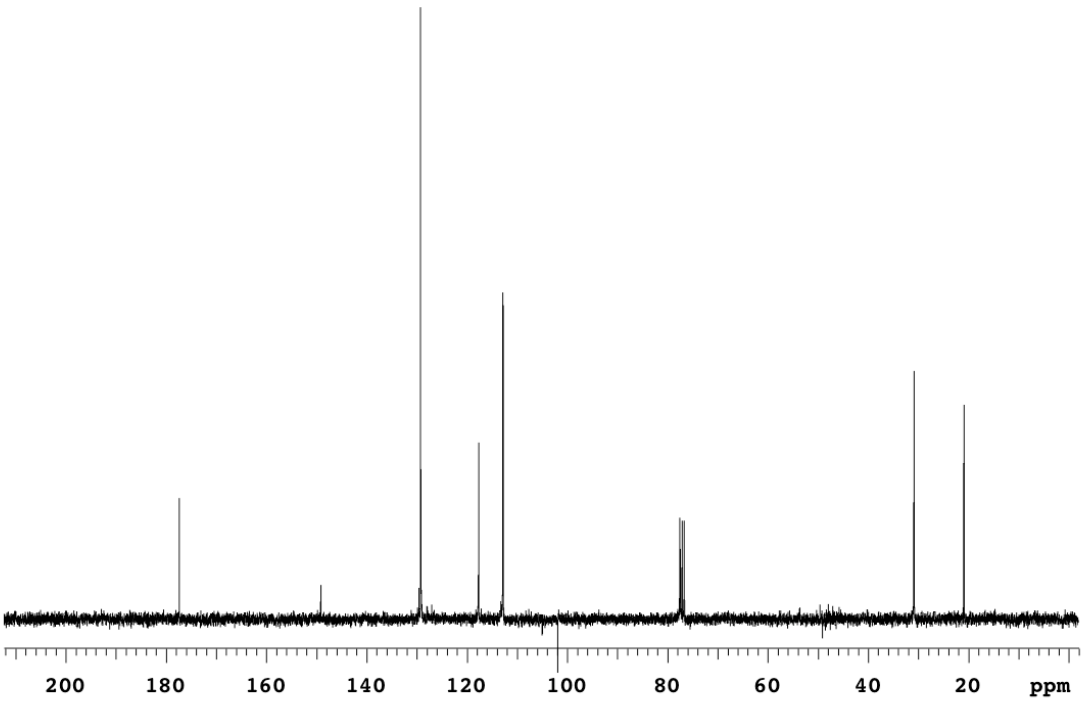
^{13}C NMR ($CDCl_3$, 75 MHz)



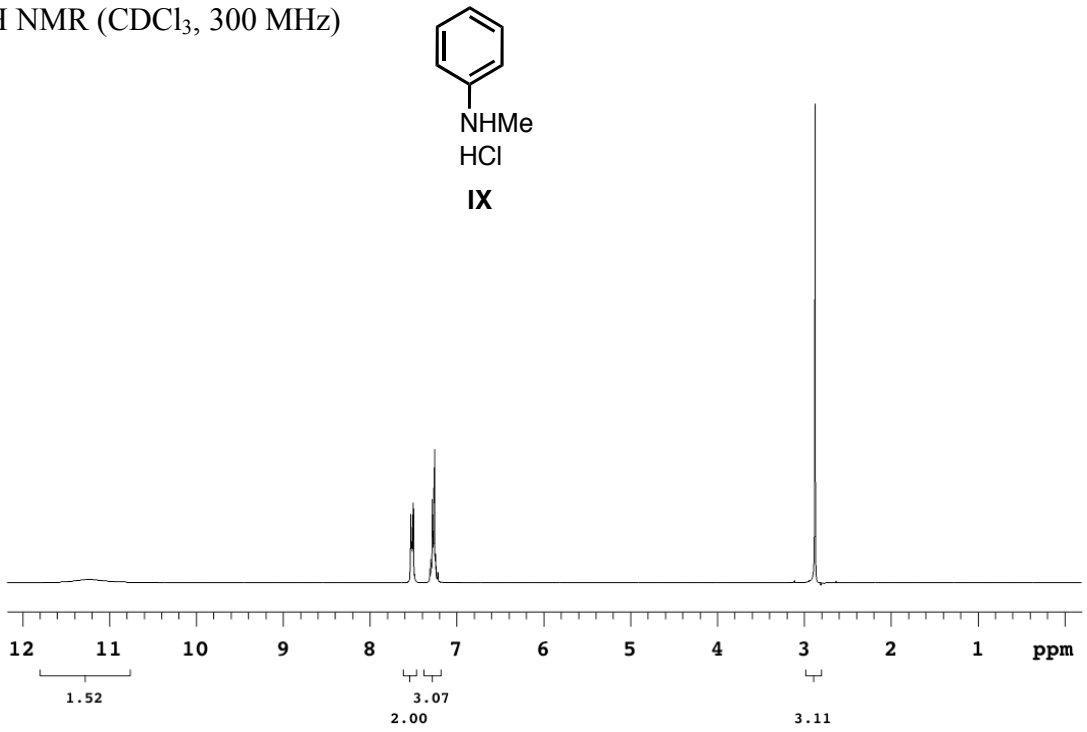
^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)

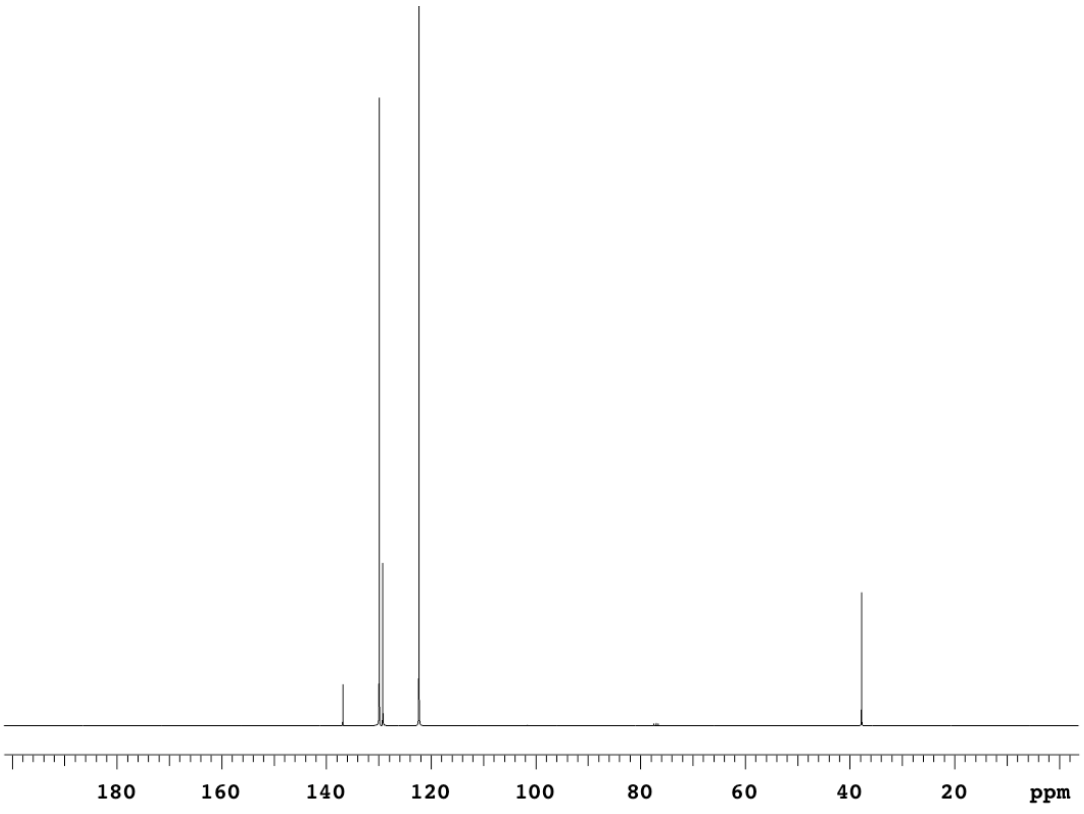


^{1}H NMR ($CDCl_3$, 300 MHz)

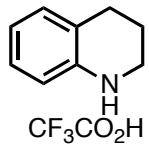


IX

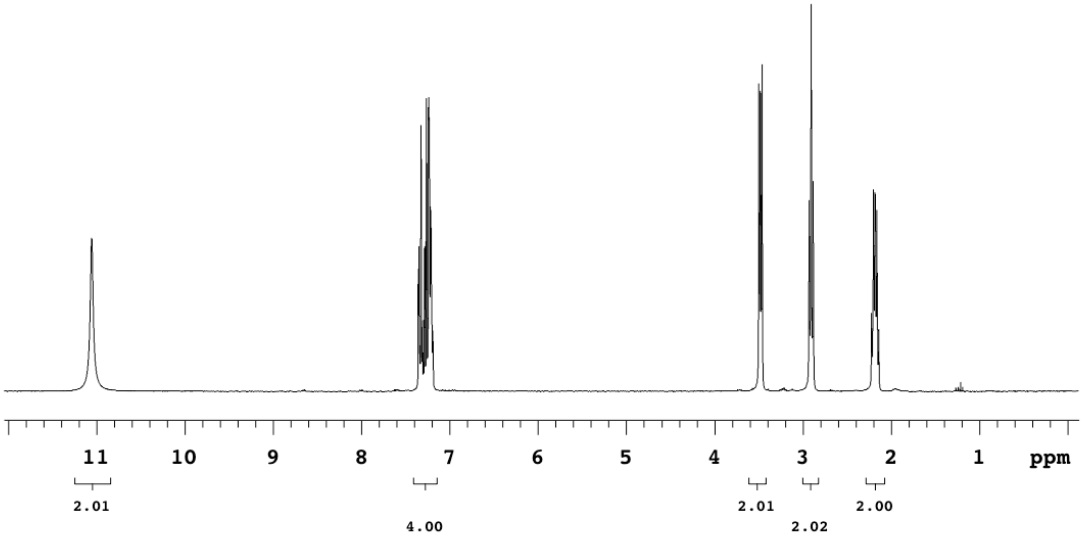
^{13}C NMR ($CDCl_3$, 75 MHz)



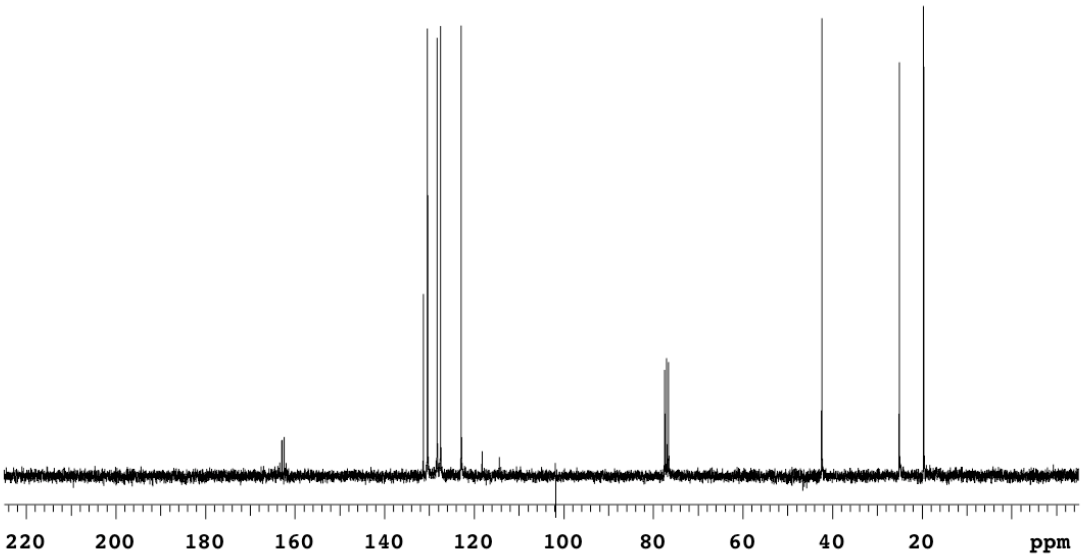
^{1}H NMR ($CDCl_3$, 300 MHz)



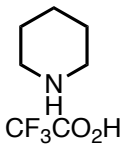
X



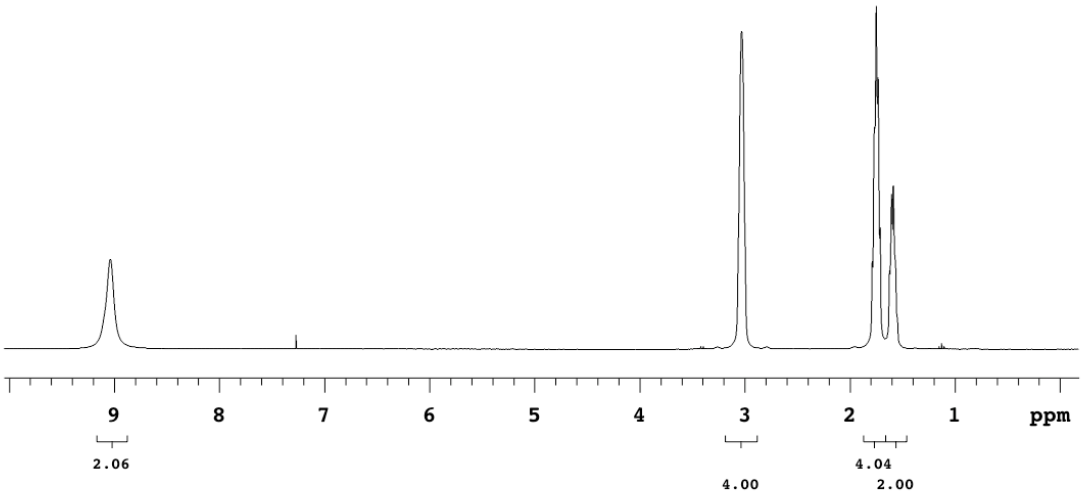
^{13}C NMR ($CDCl_3$, 75 MHz)



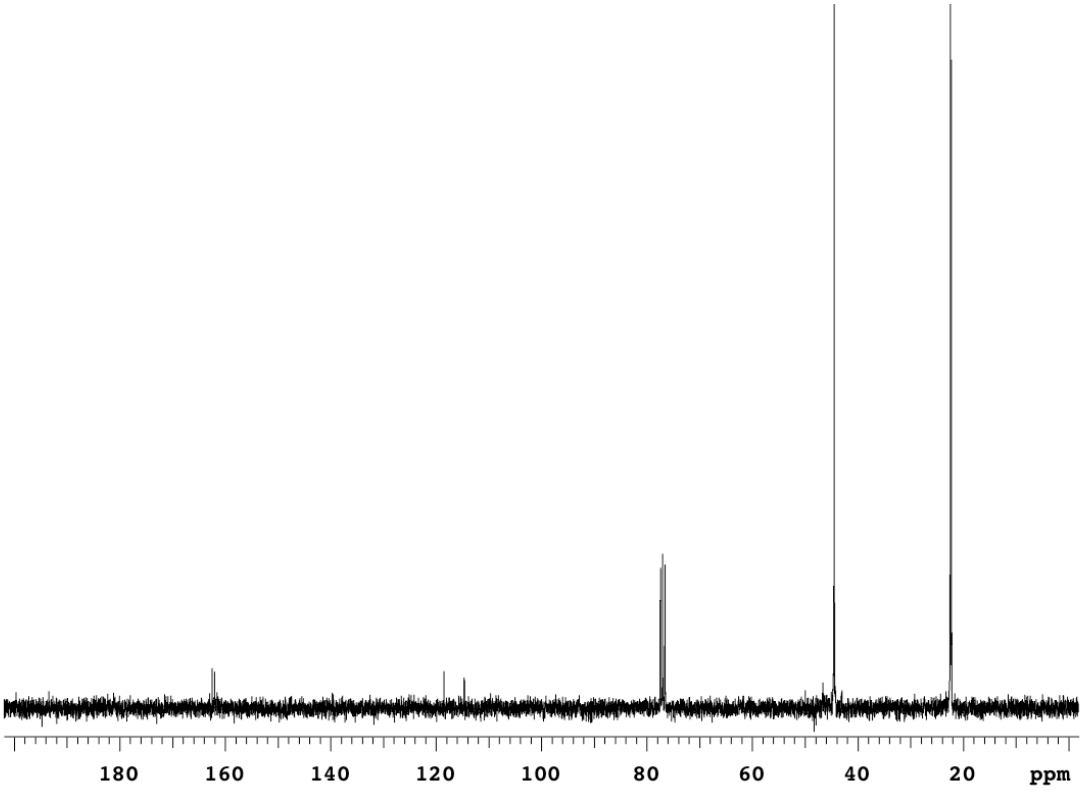
^{1}H NMR ($CDCl_3$, 300 MHz)



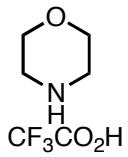
XI



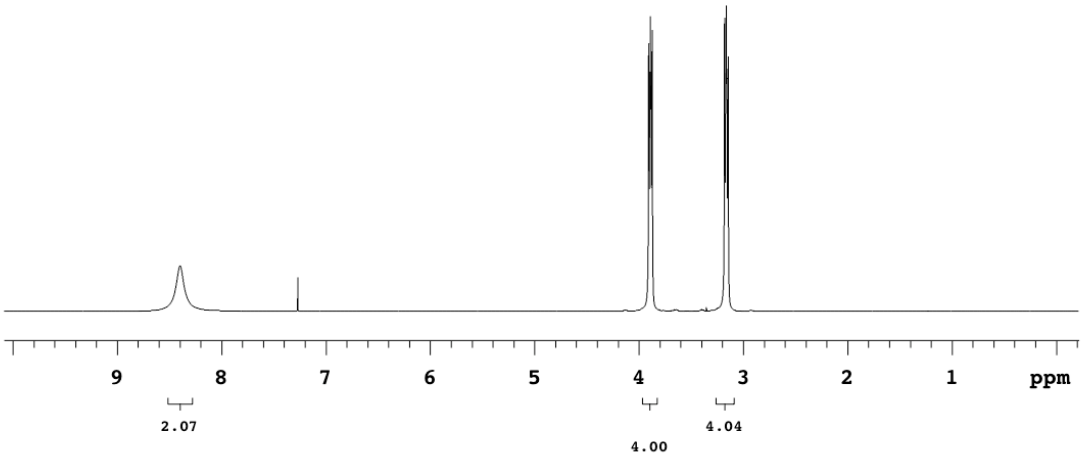
^{13}C NMR ($CDCl_3$, 75 MHz)



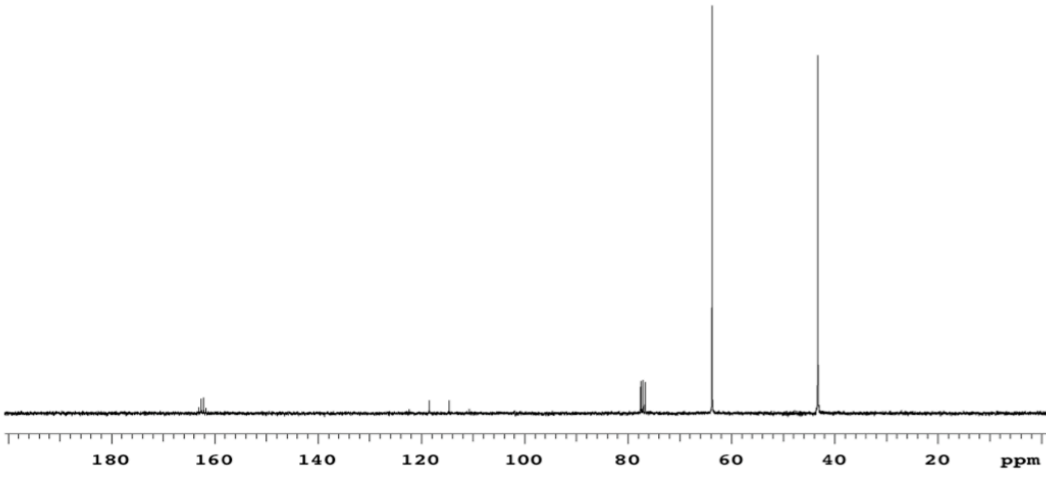
^{1}H NMR ($CDCl_3$, 300 MHz)



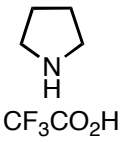
XII



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



XIII

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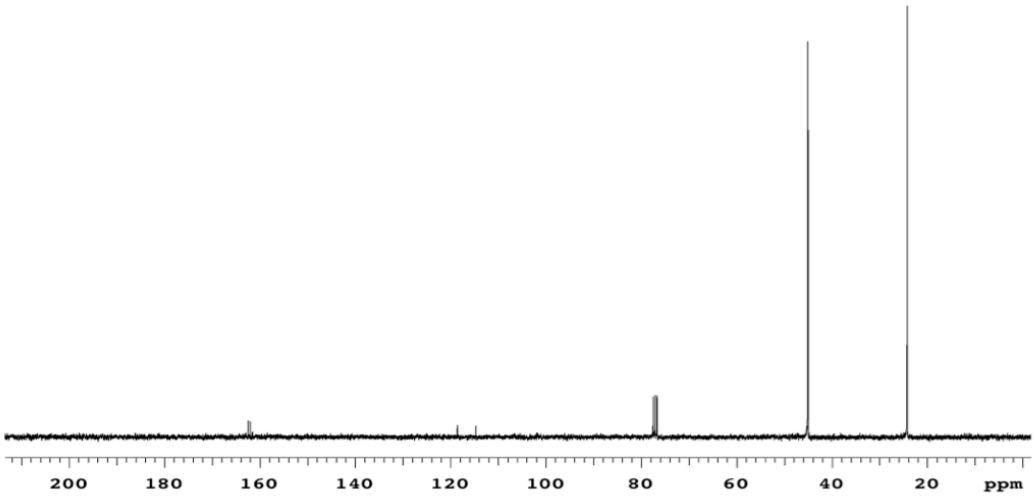
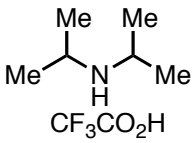
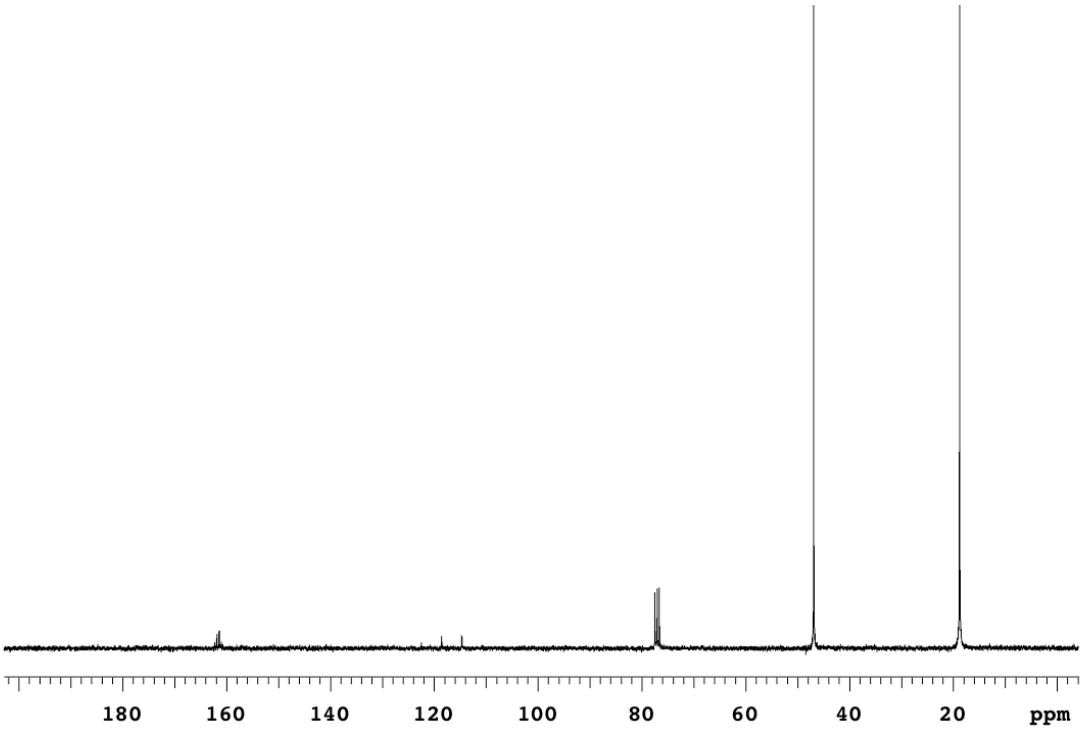


^{1}H NMR ($CDCl_3$, 300 MHz)

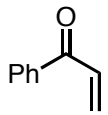


XIV

^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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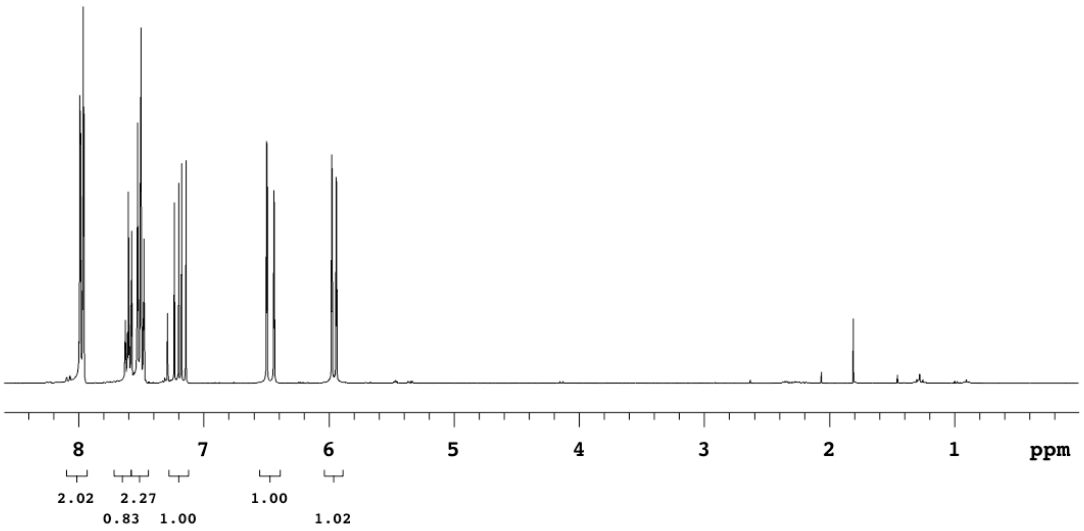

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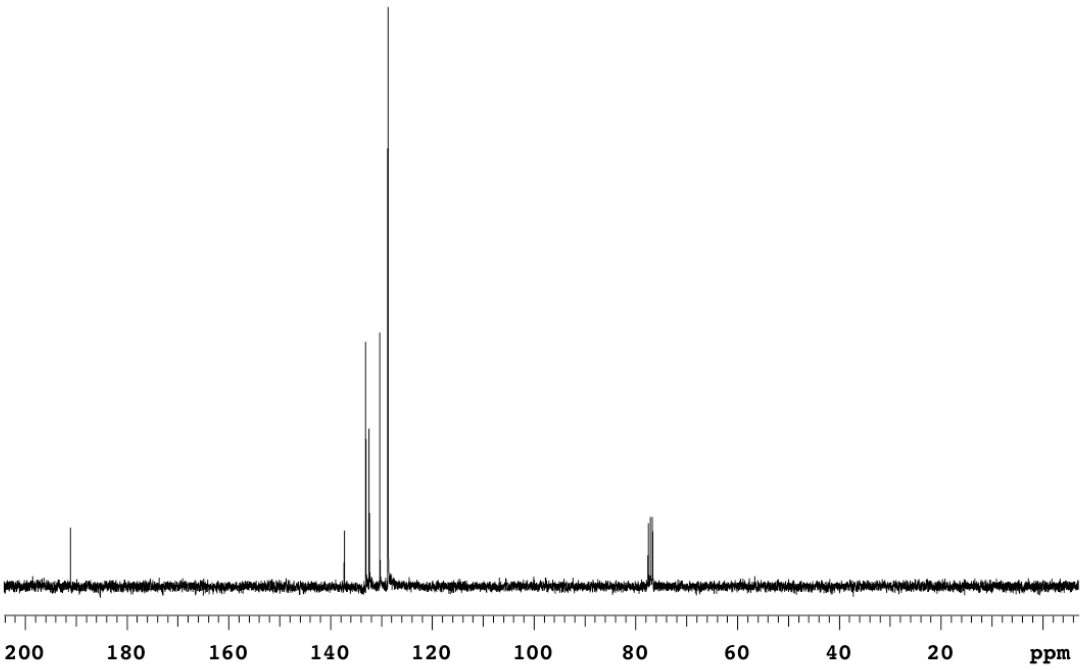

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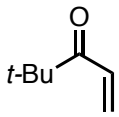

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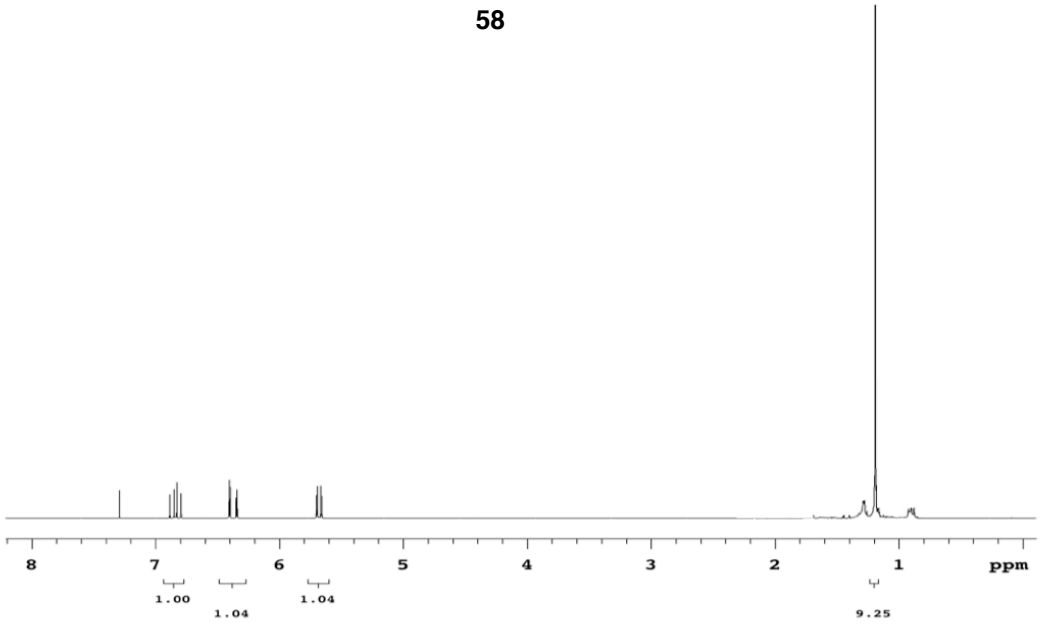

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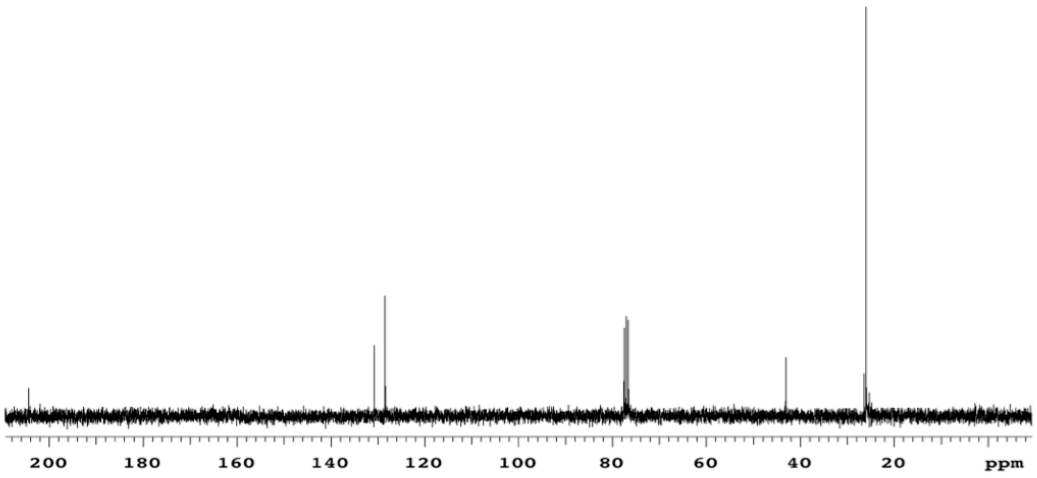

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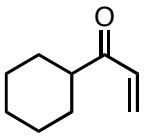

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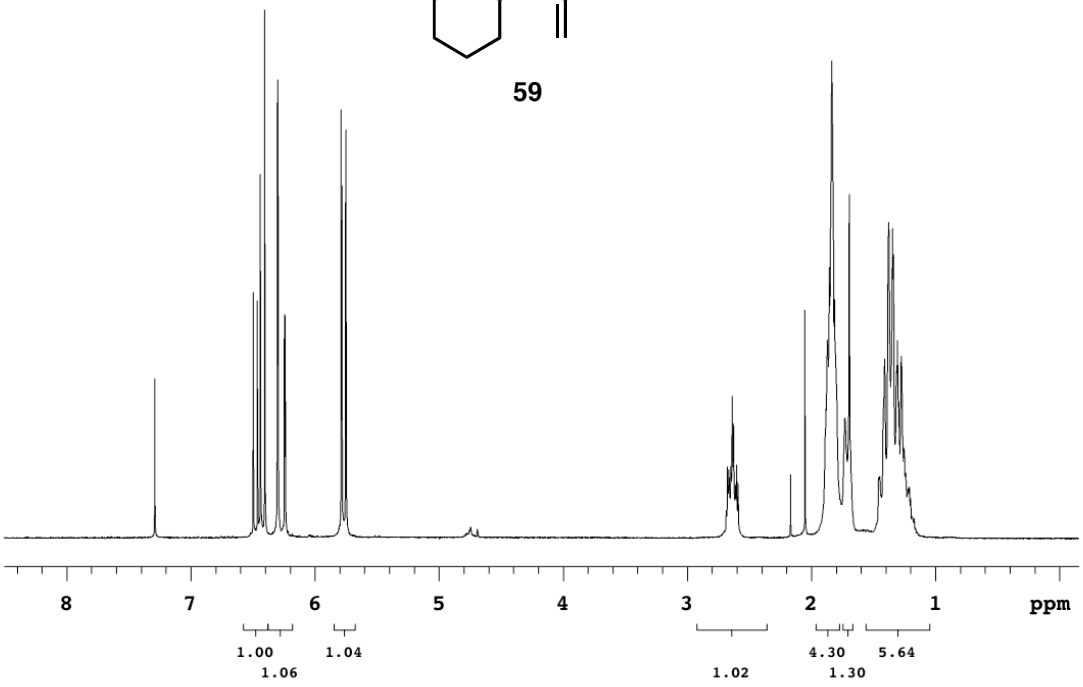

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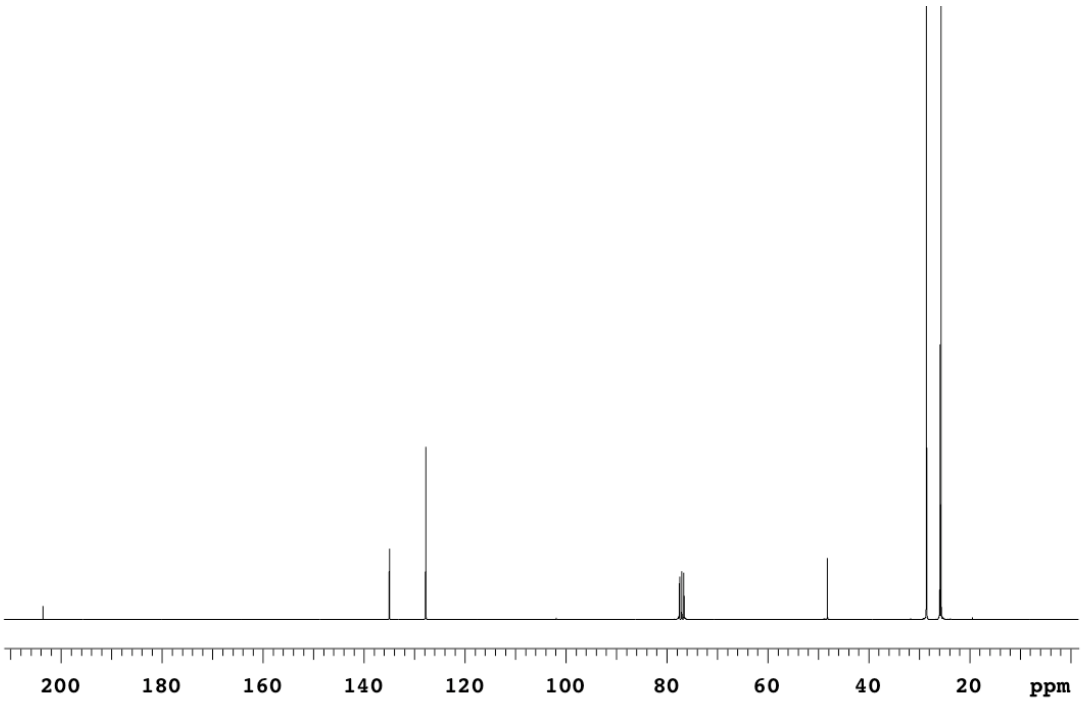

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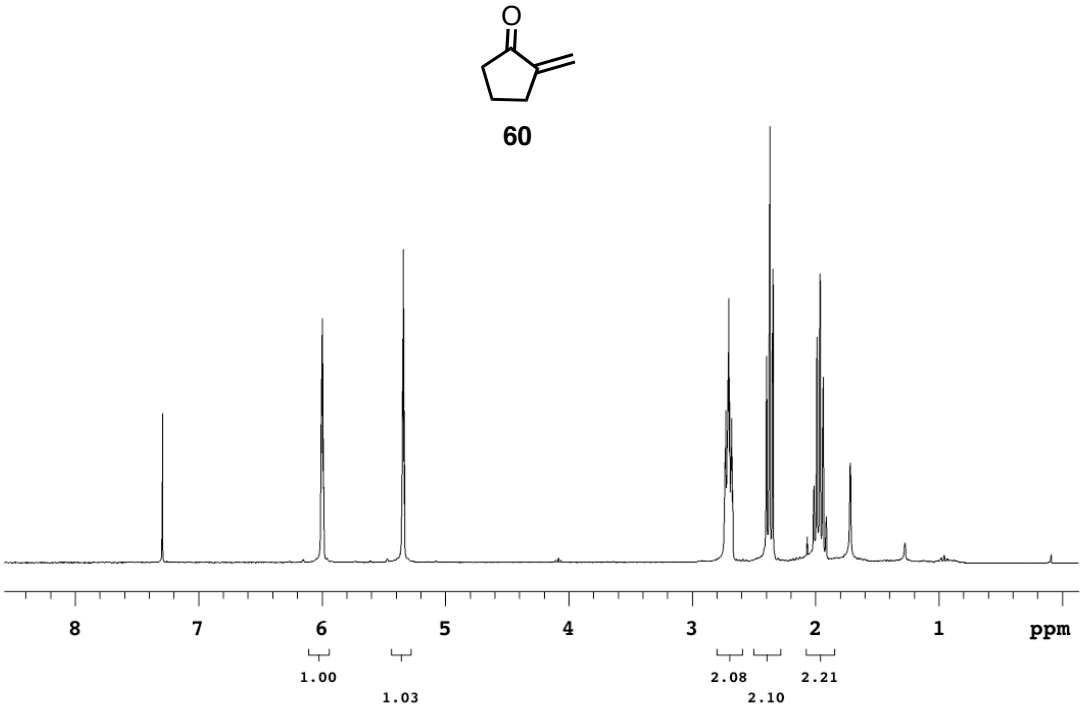

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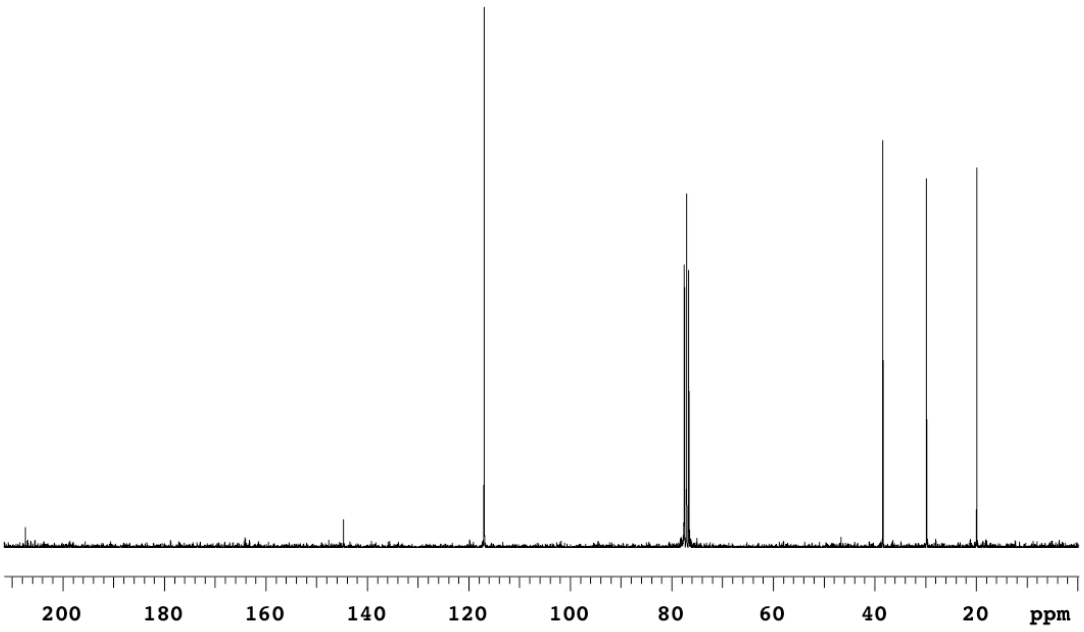

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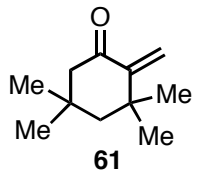

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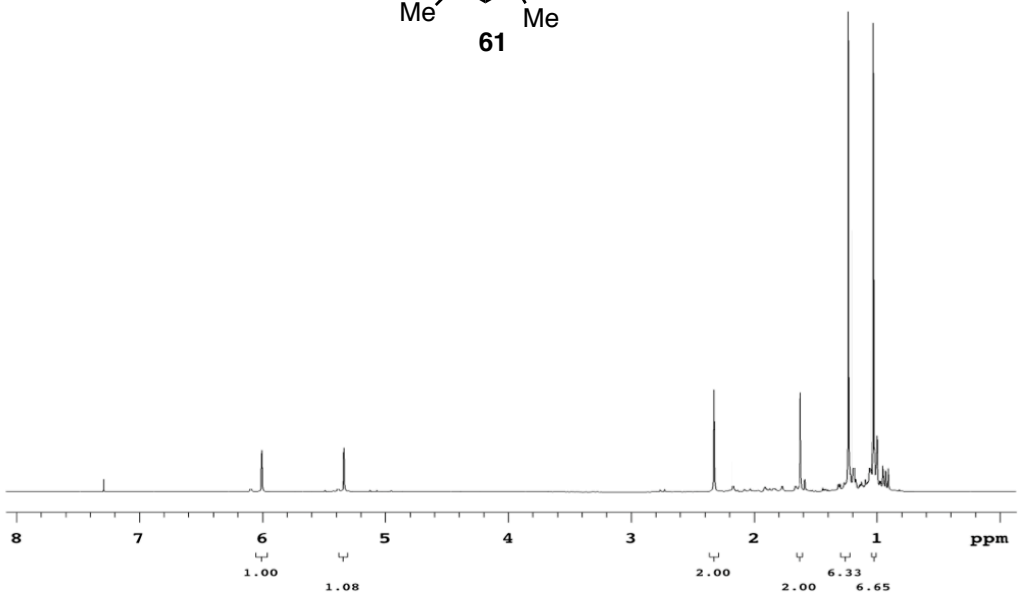

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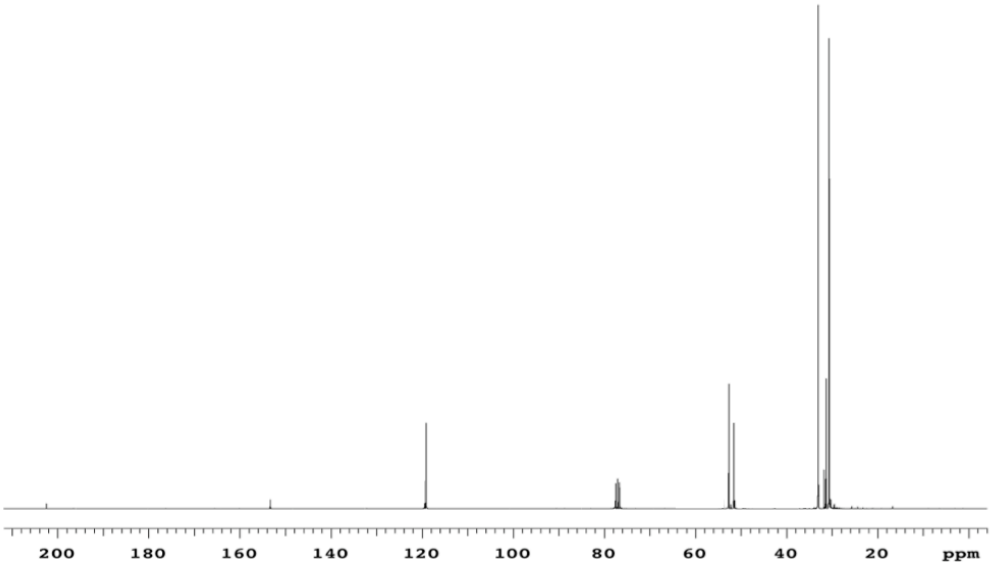

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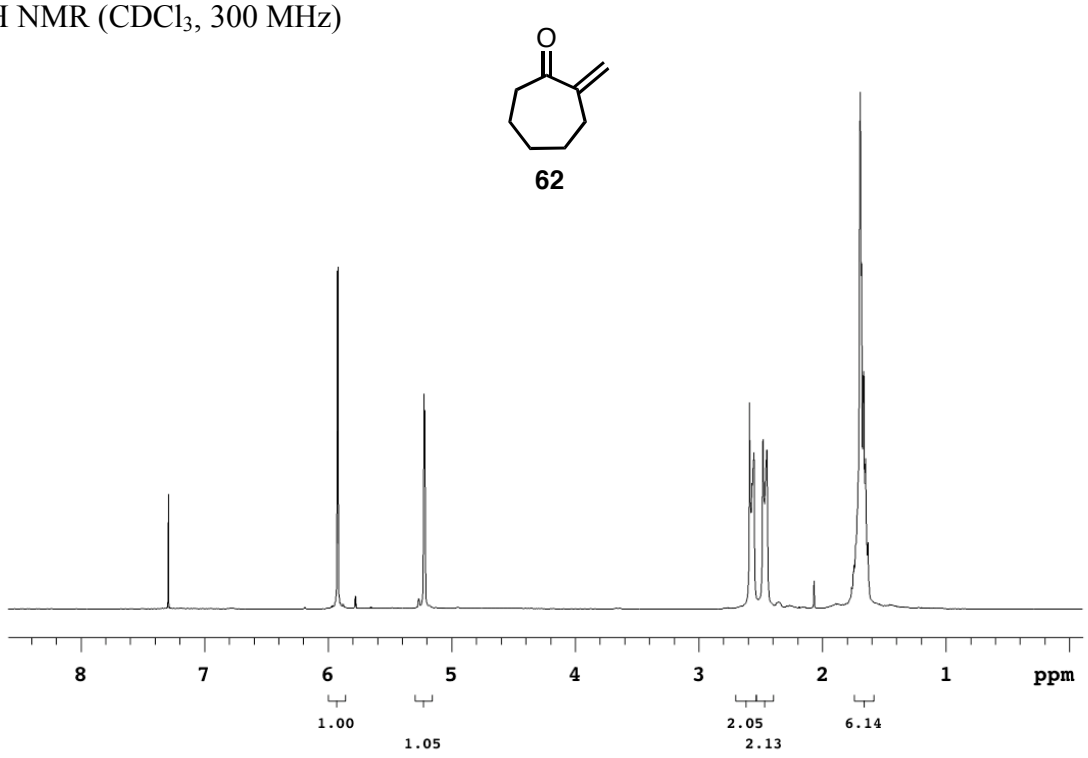

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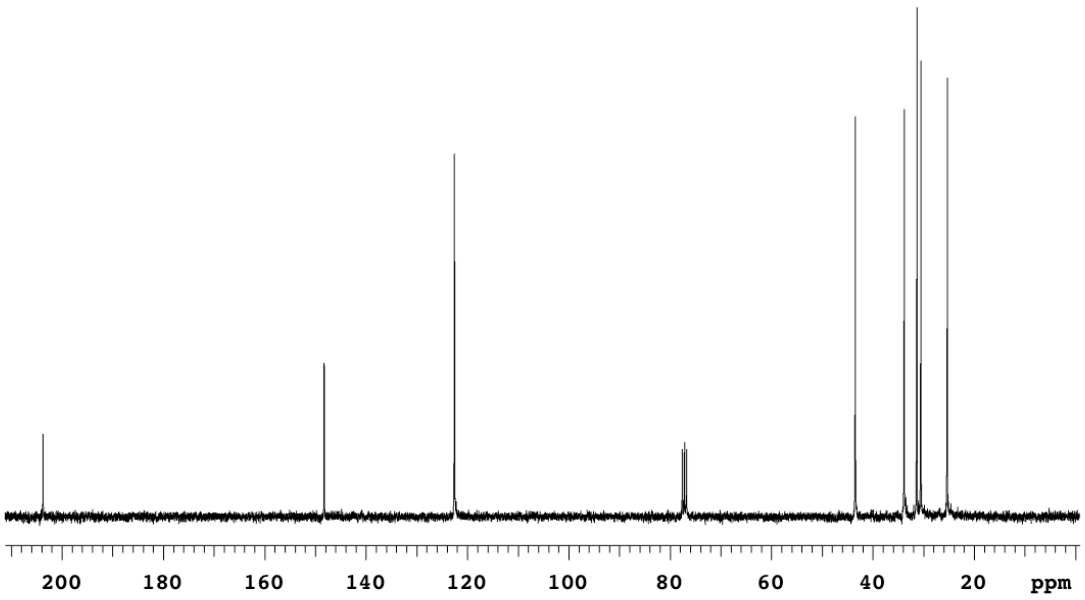

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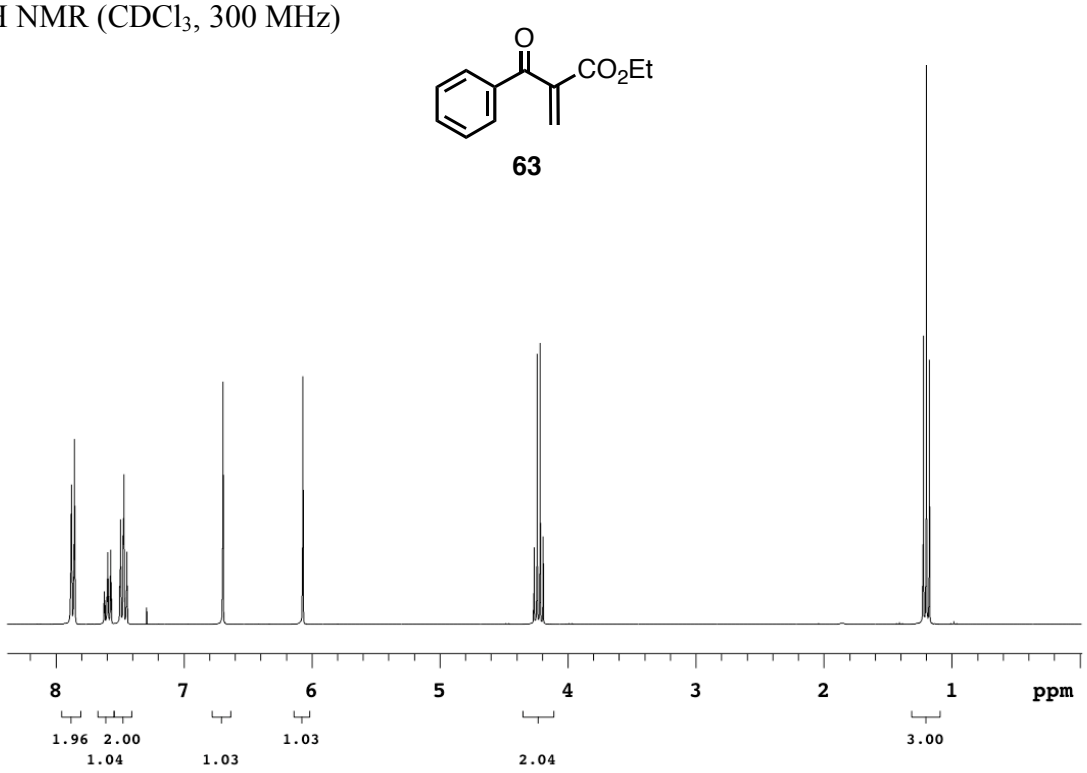

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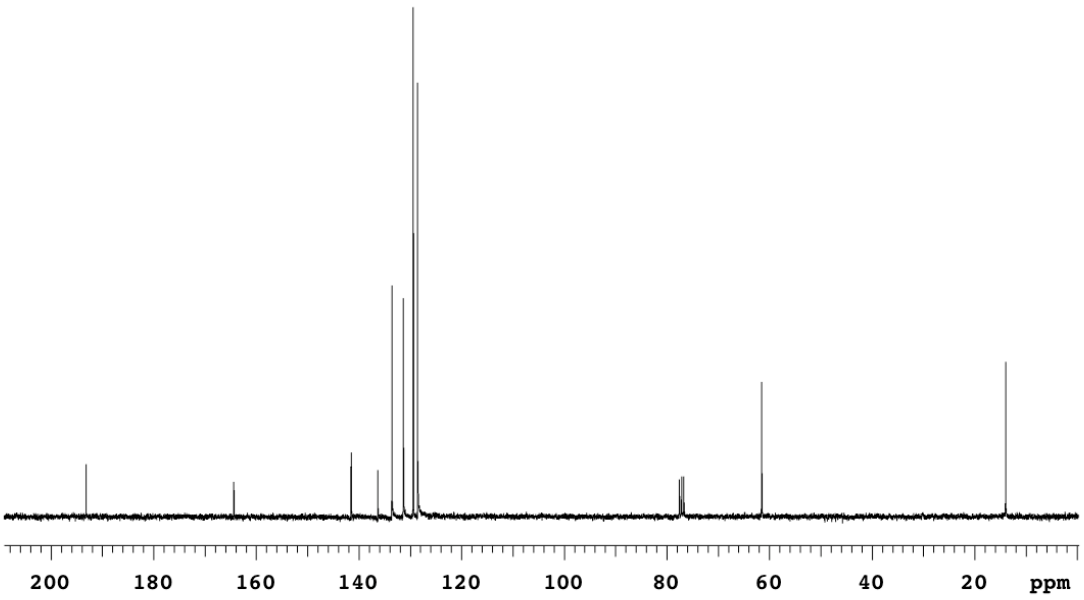

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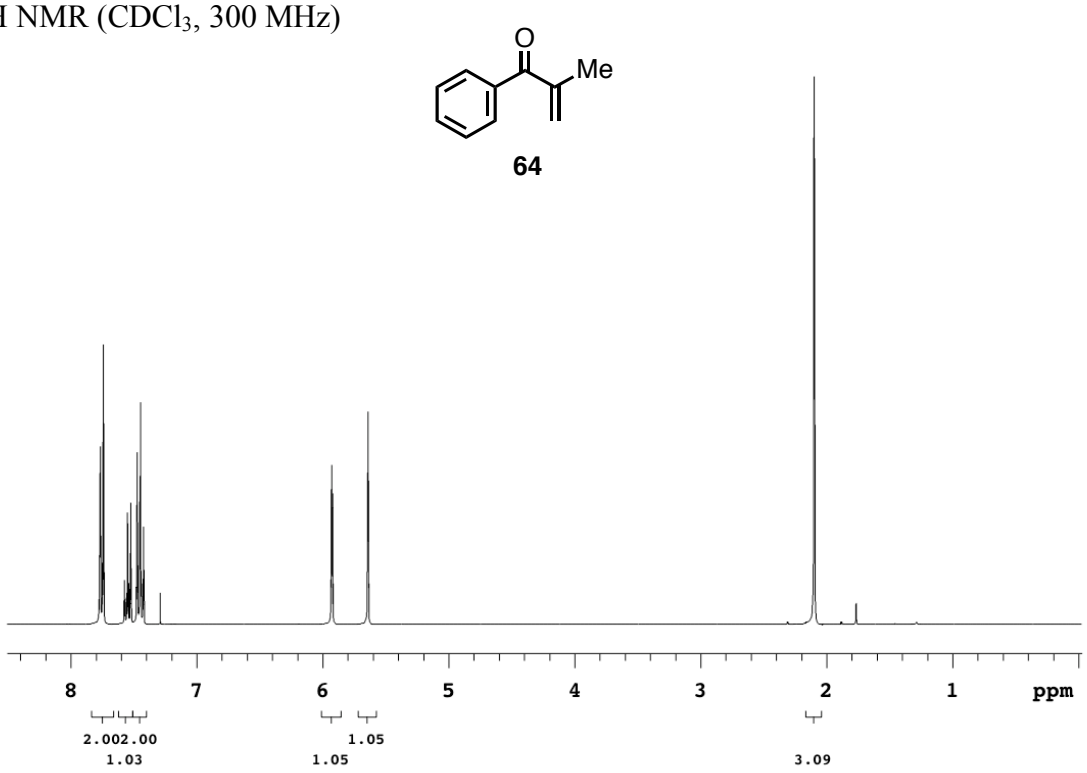

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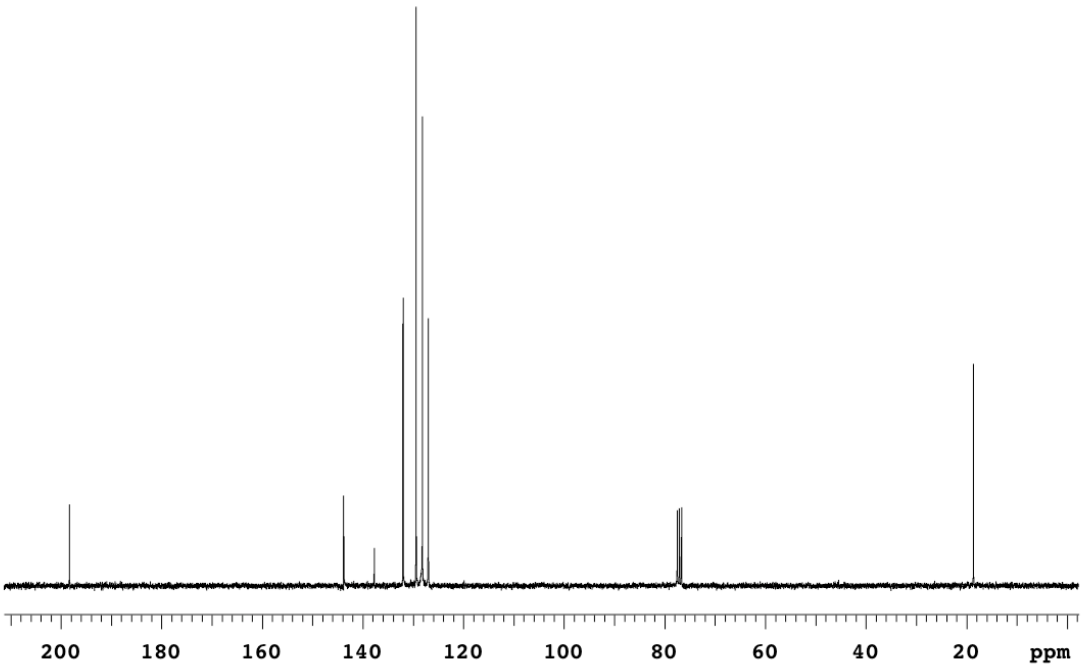

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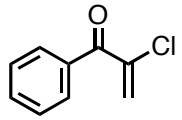

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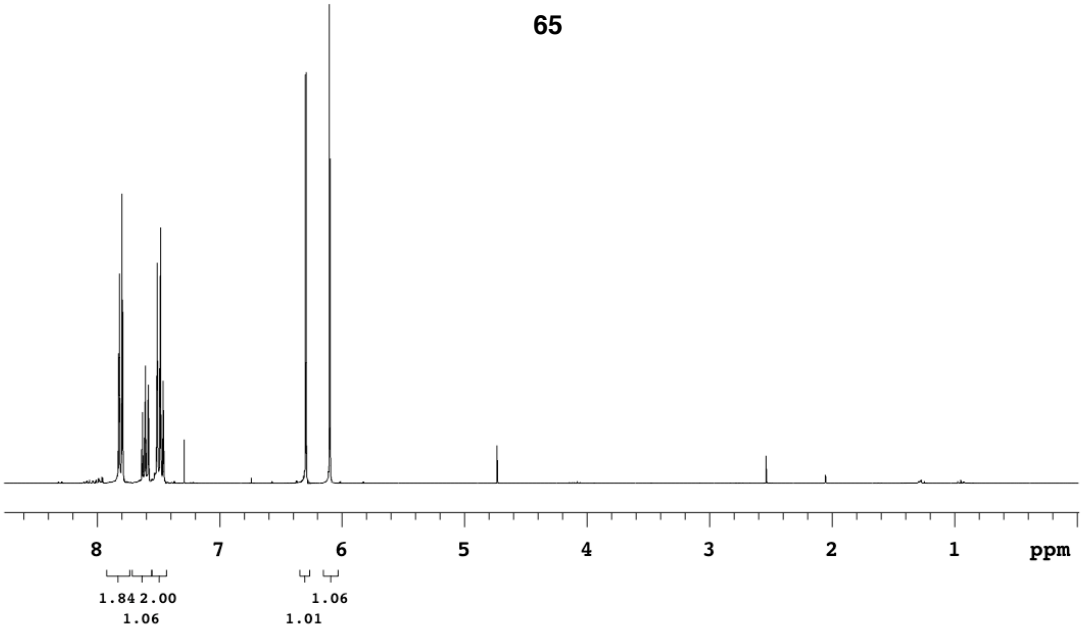

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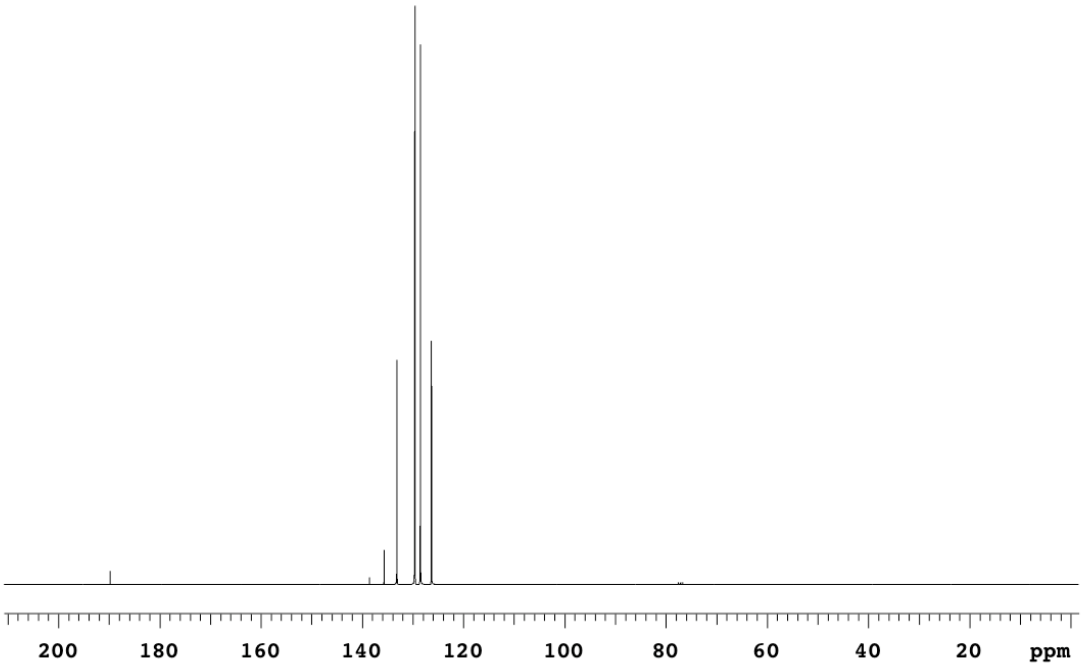

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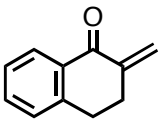

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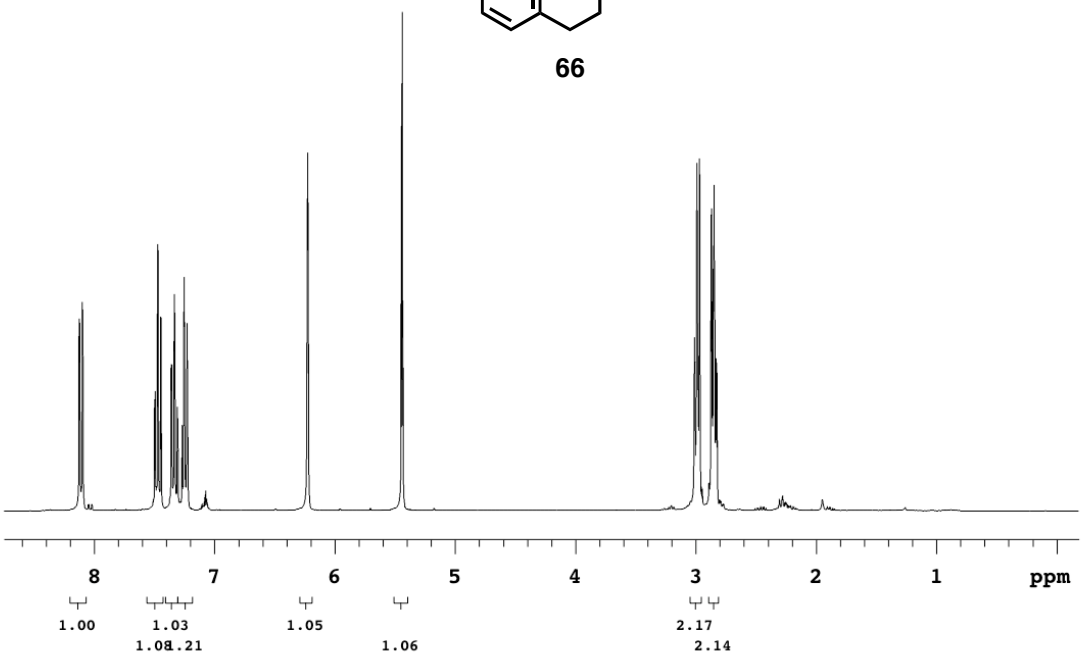

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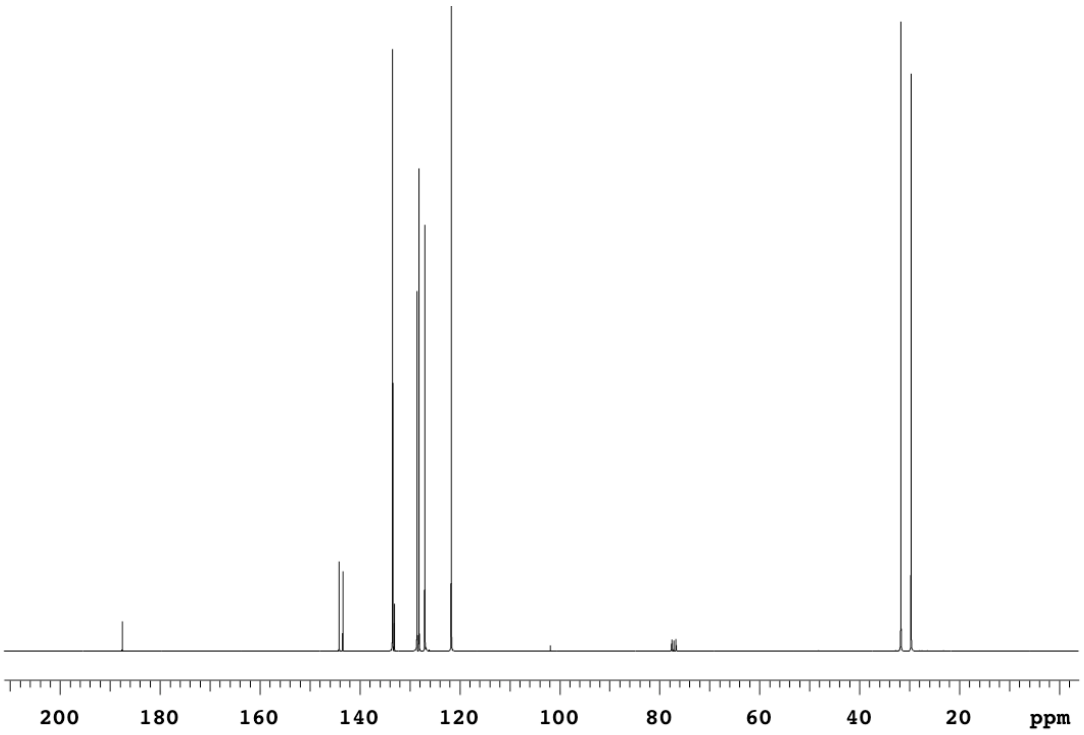

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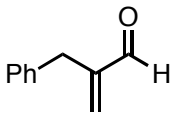

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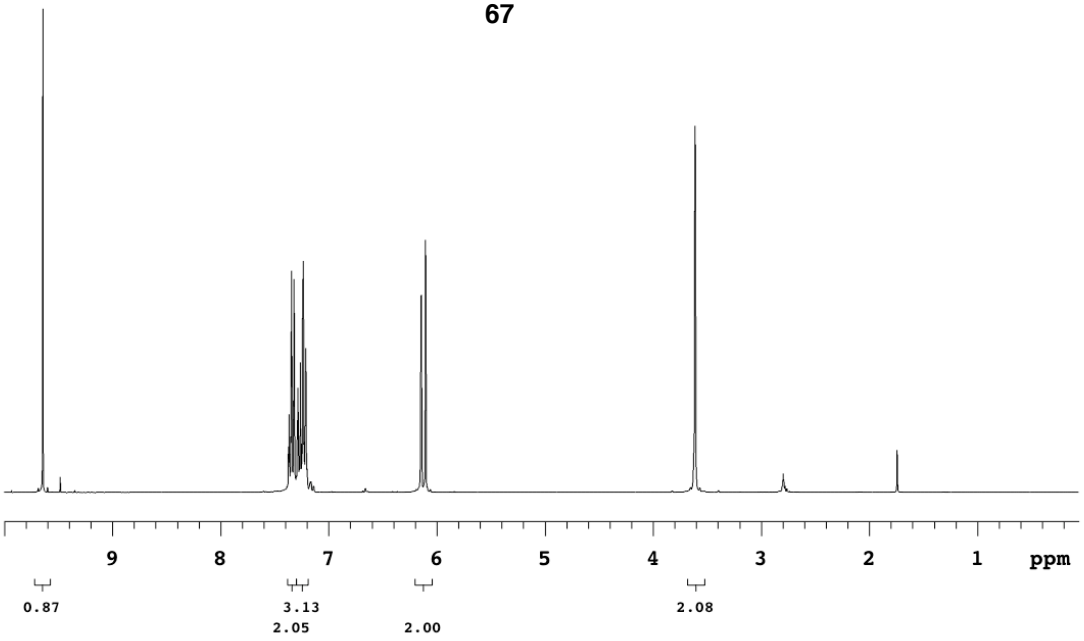

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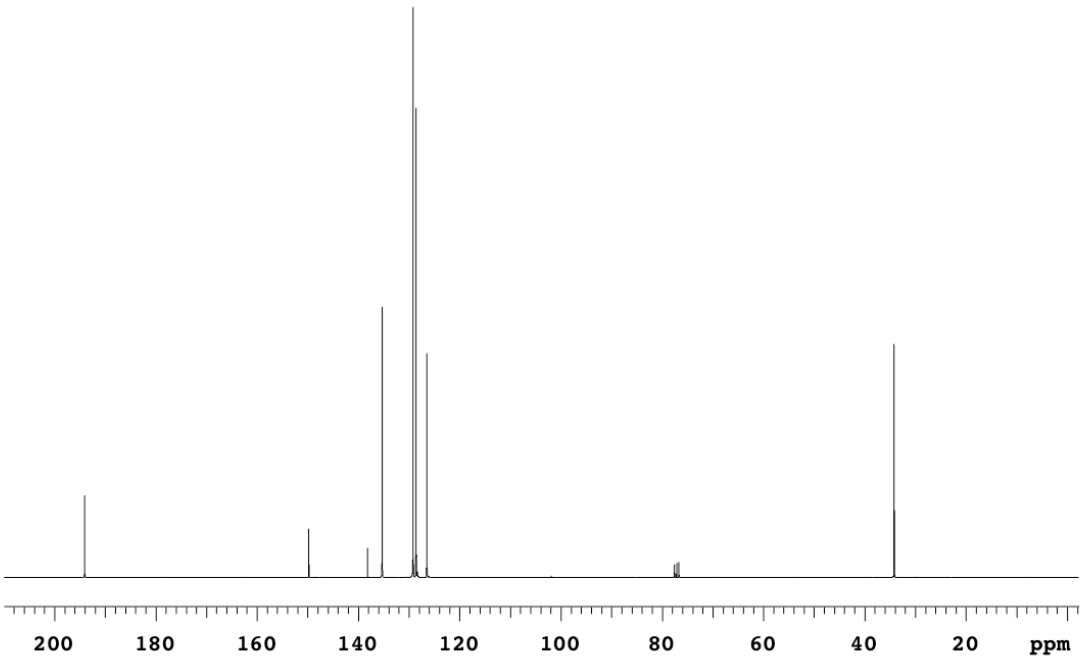

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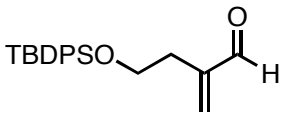

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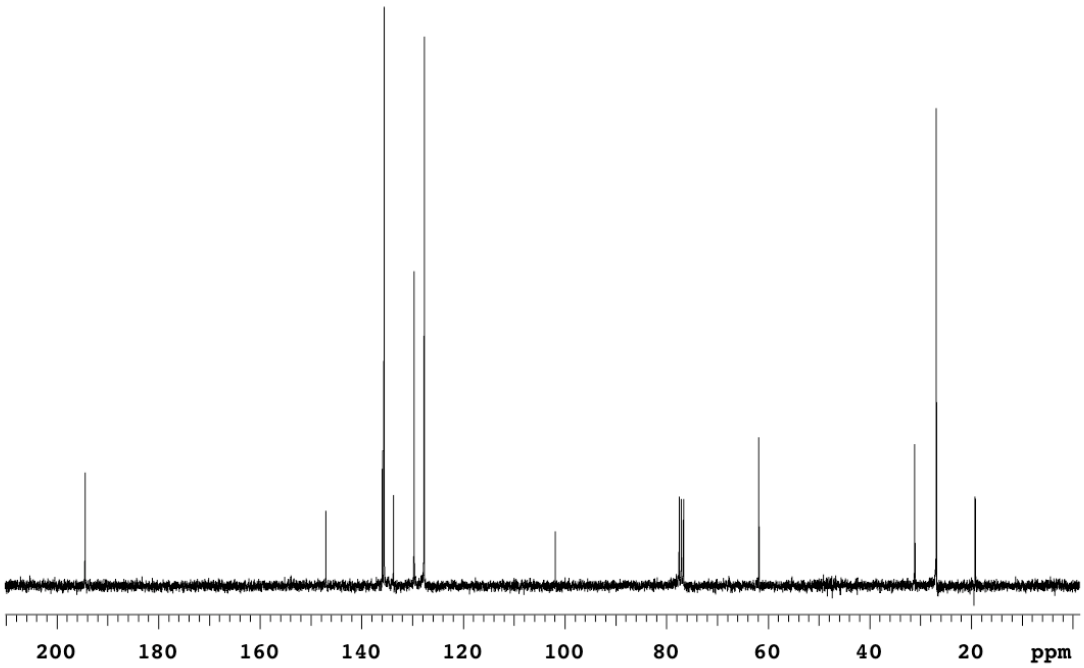

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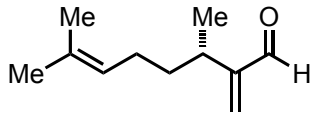

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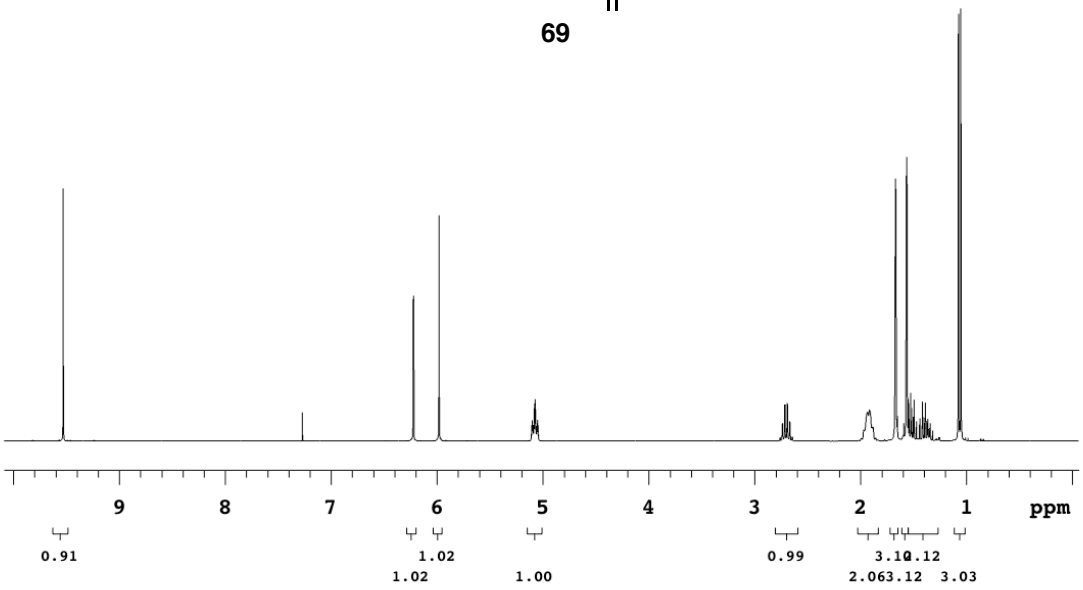

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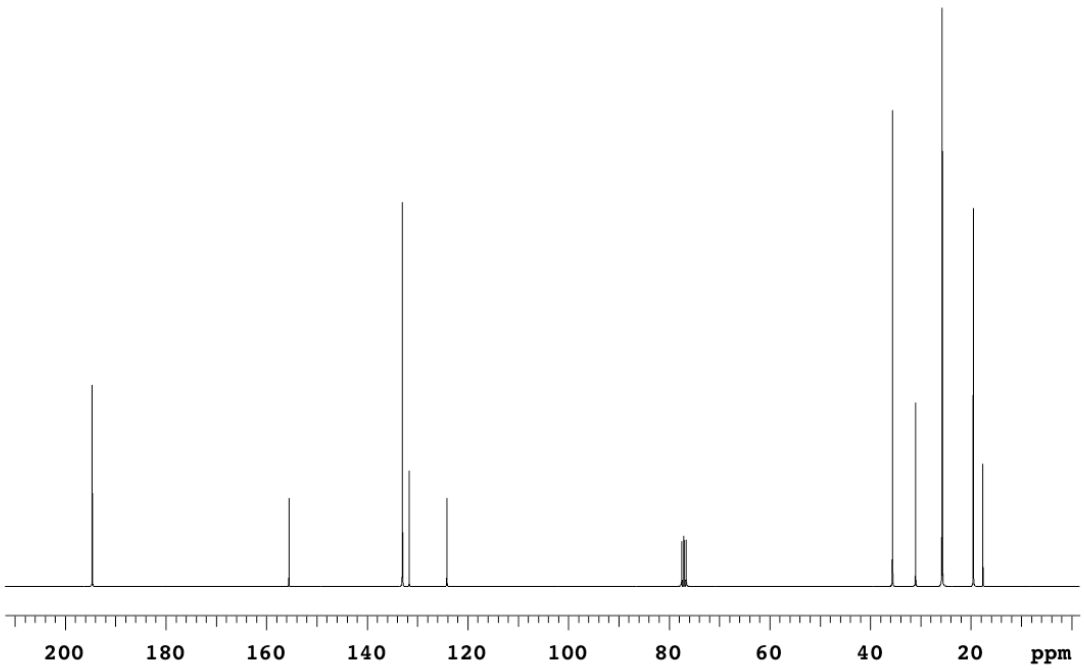

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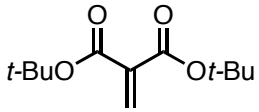

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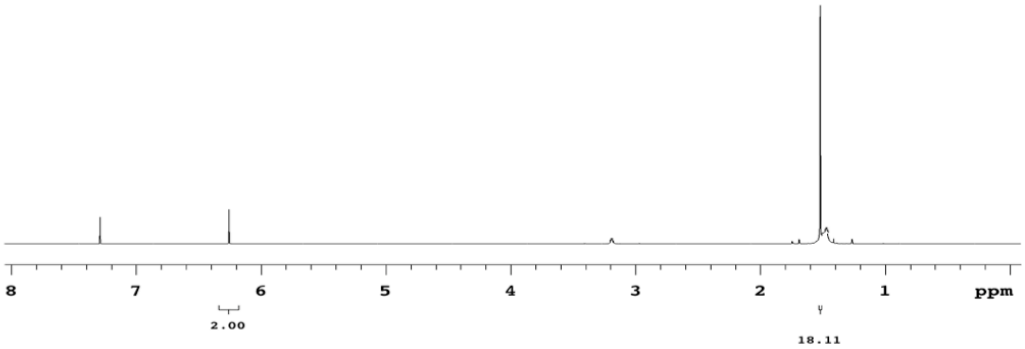

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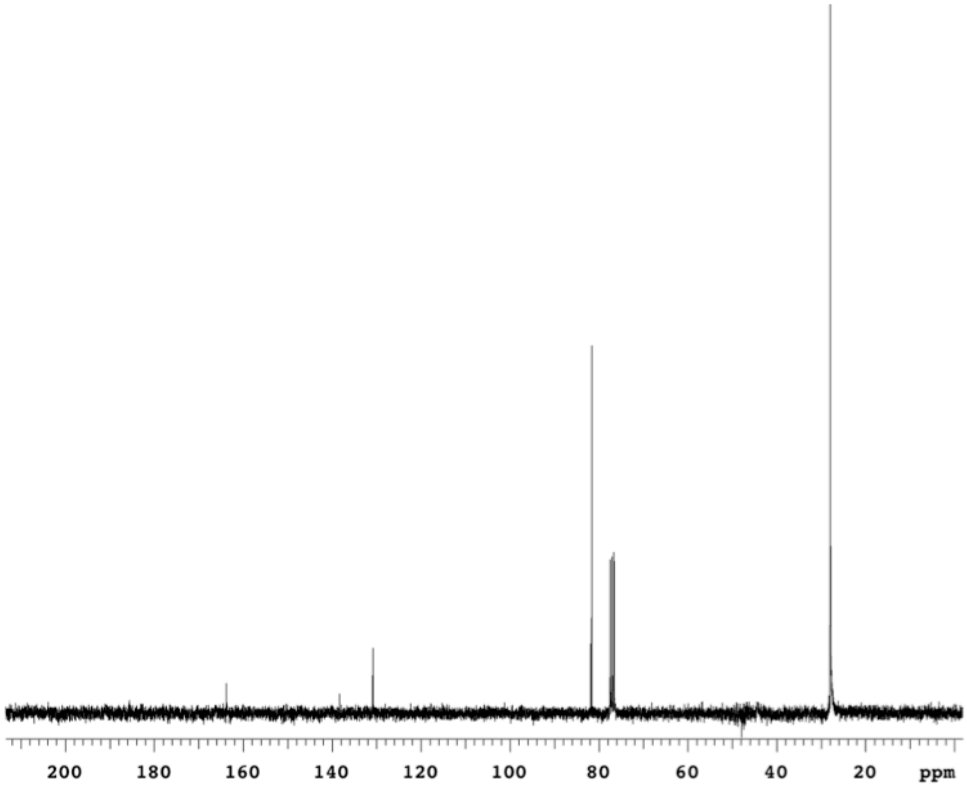
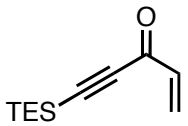


^{1}H NMR ($CDCl_3$, 300 MHz)



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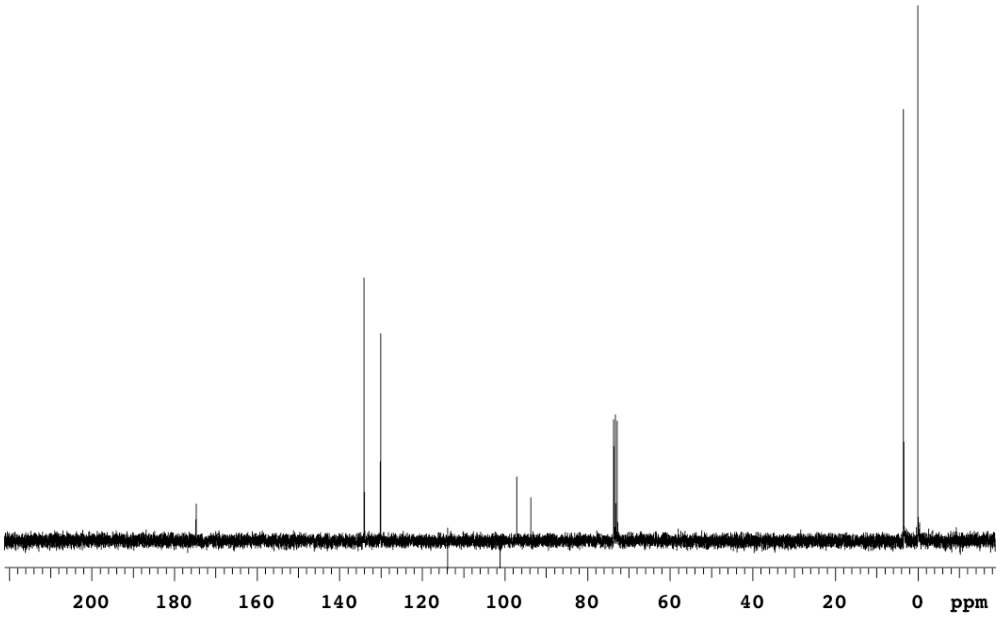

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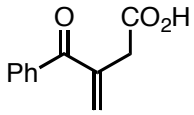

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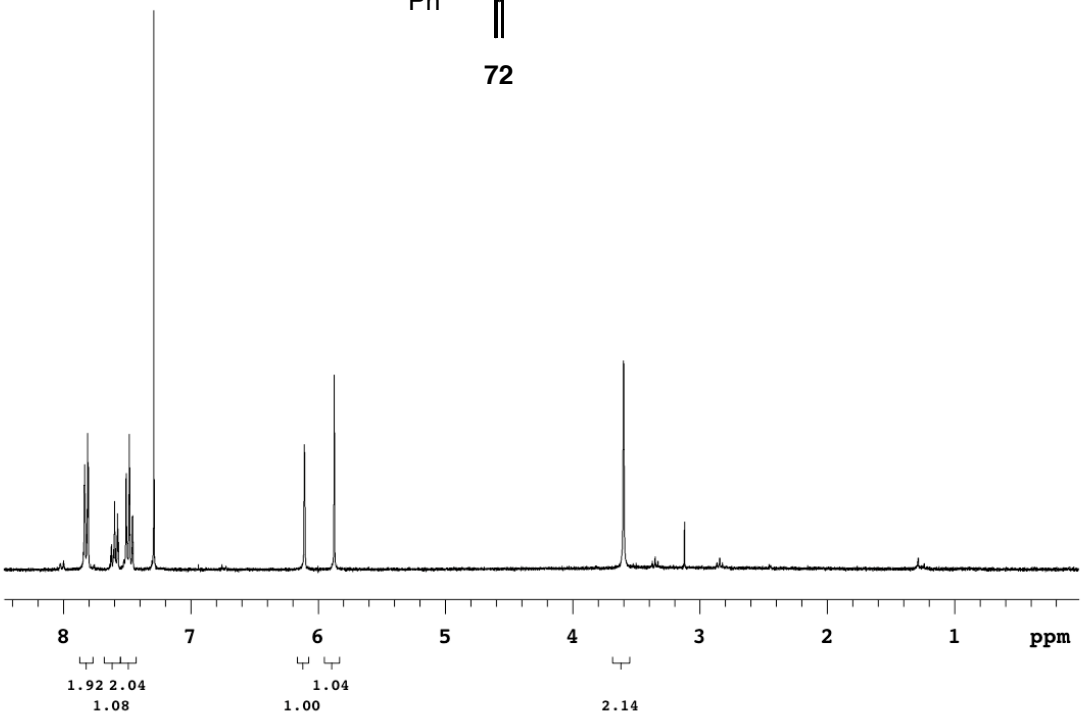
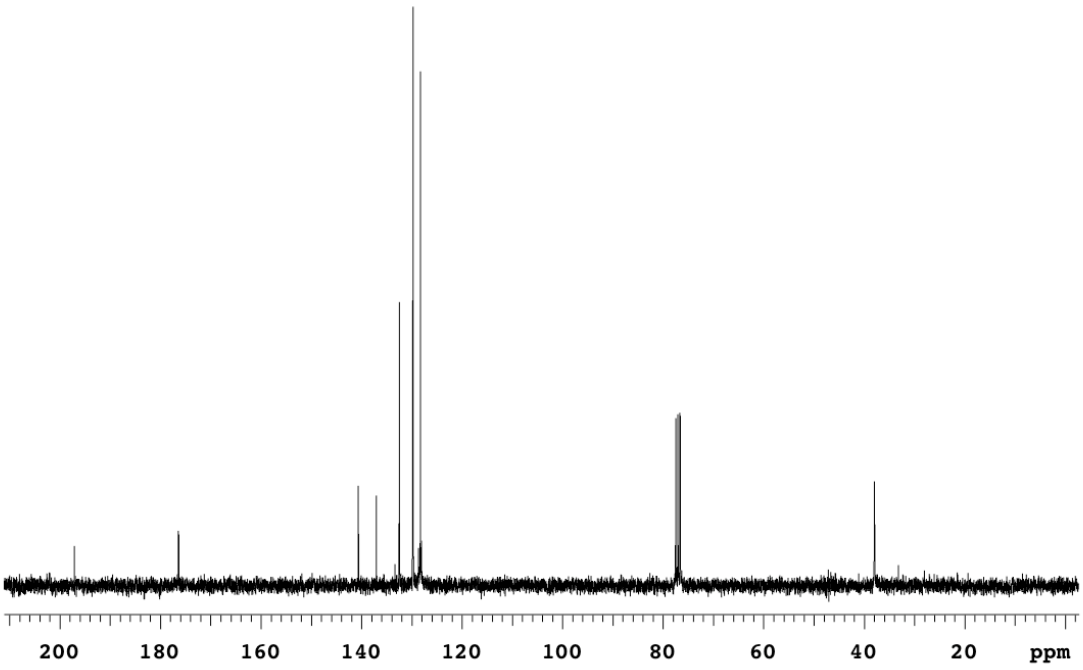
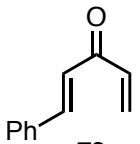


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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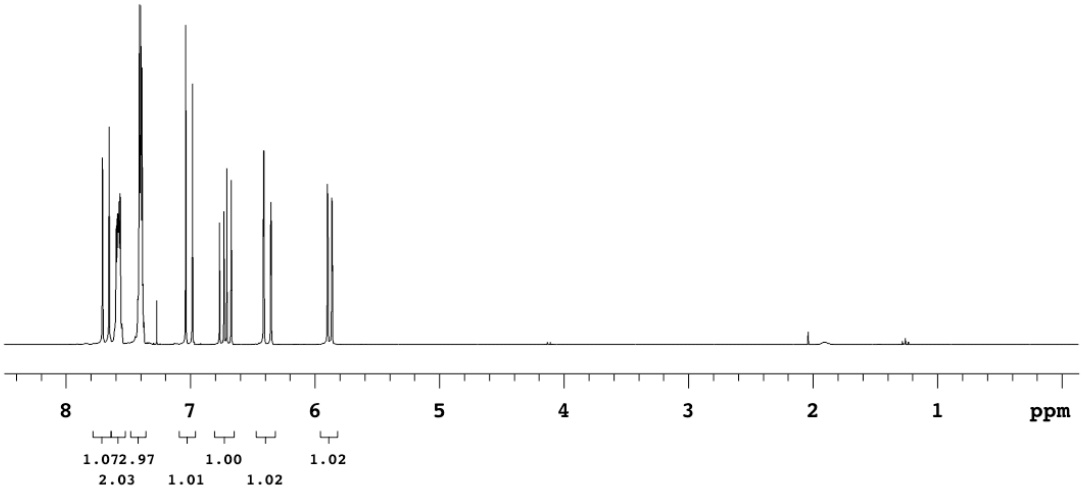
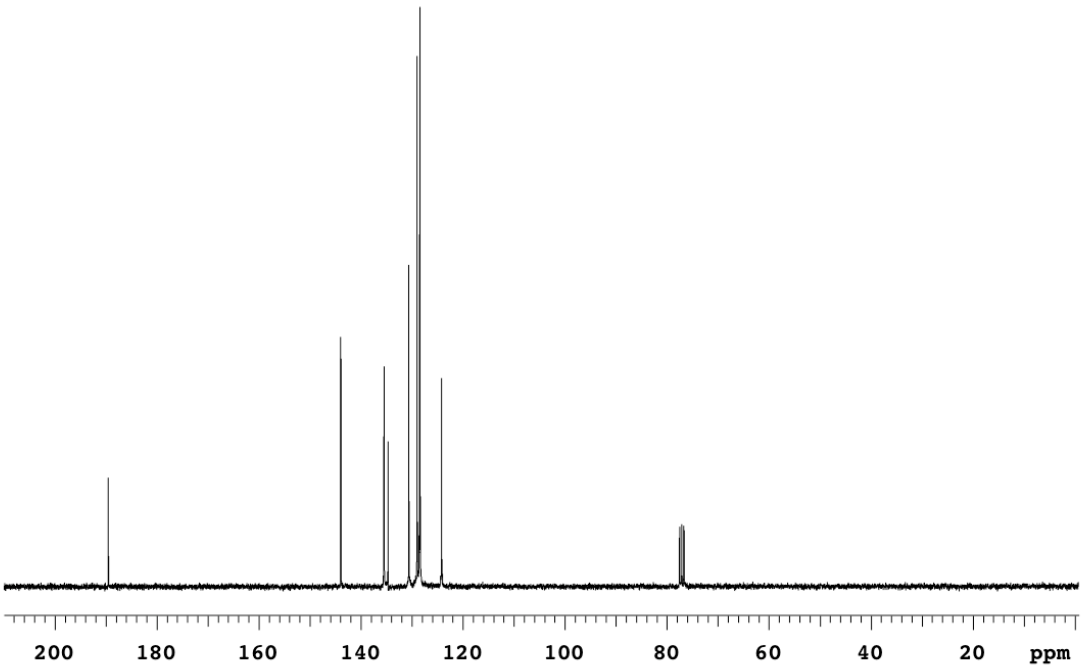
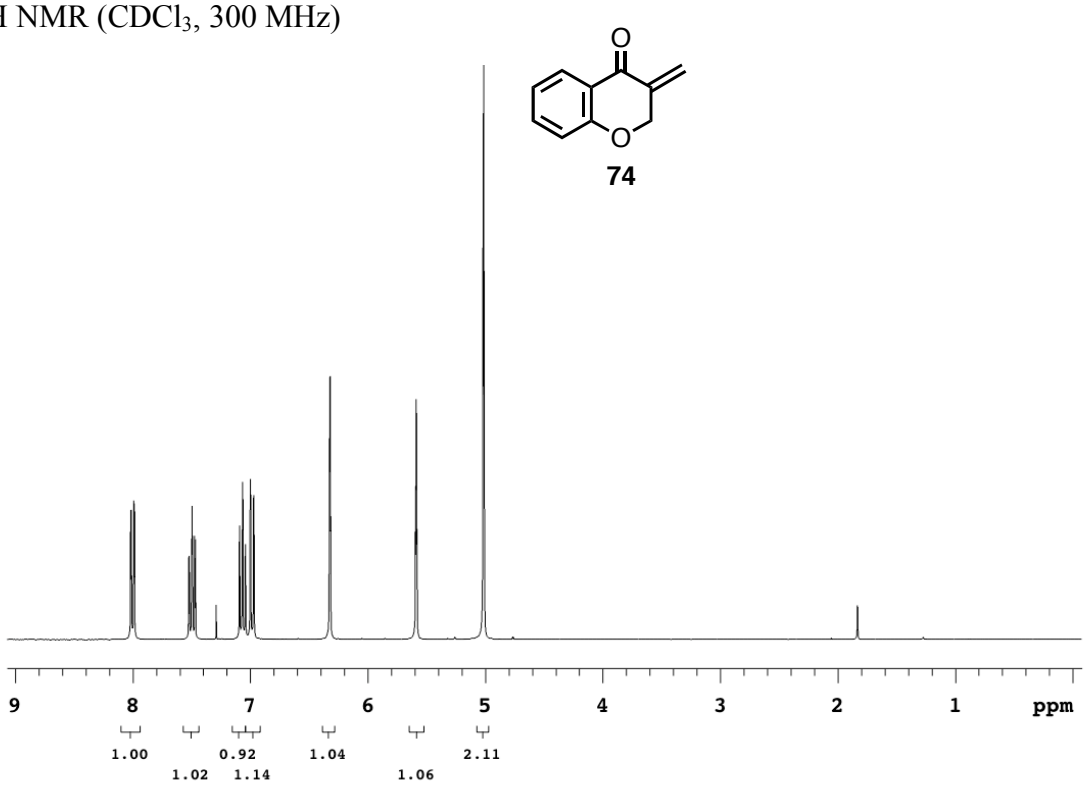


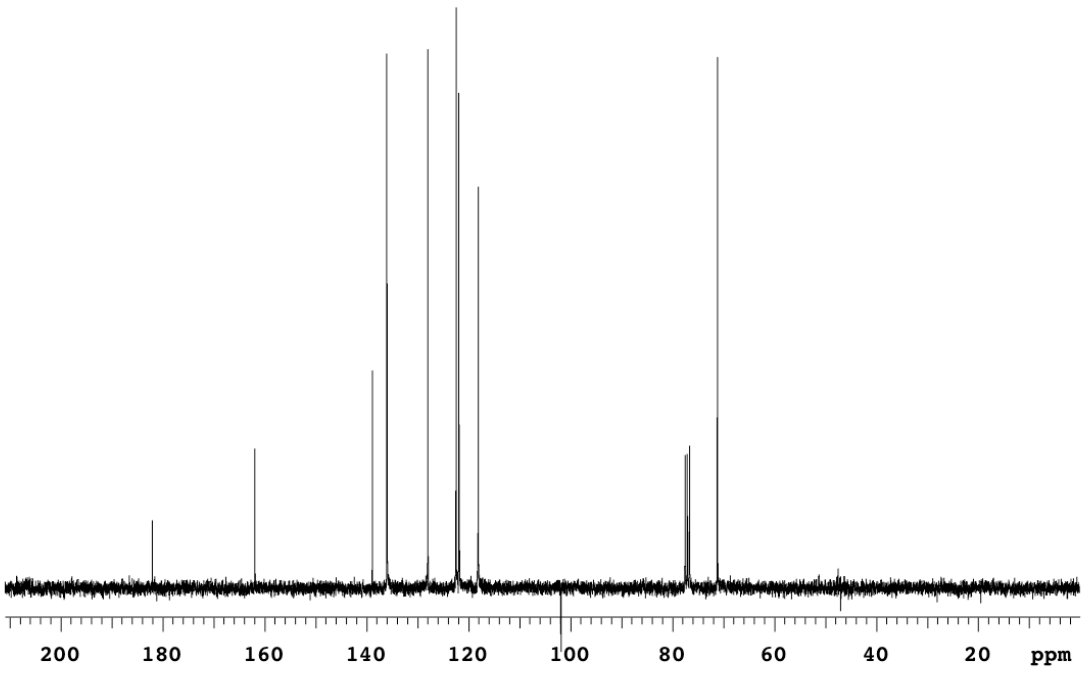
^{13}C NMR ($CDCl_3$, 75 MHz)



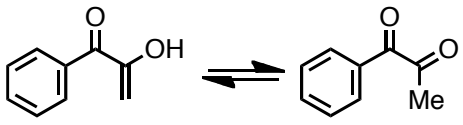
^{1}H NMR ($CDCl_3$, 300 MHz)



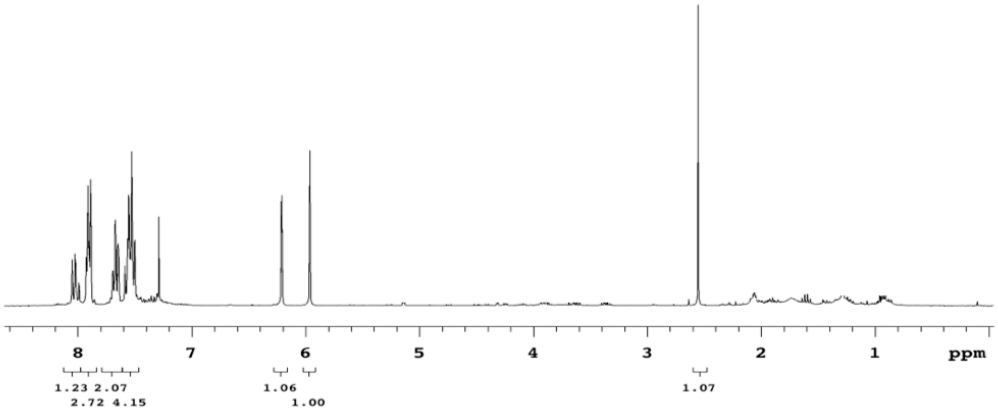
^{13}C NMR ($CDCl_3$, 75 MHz)



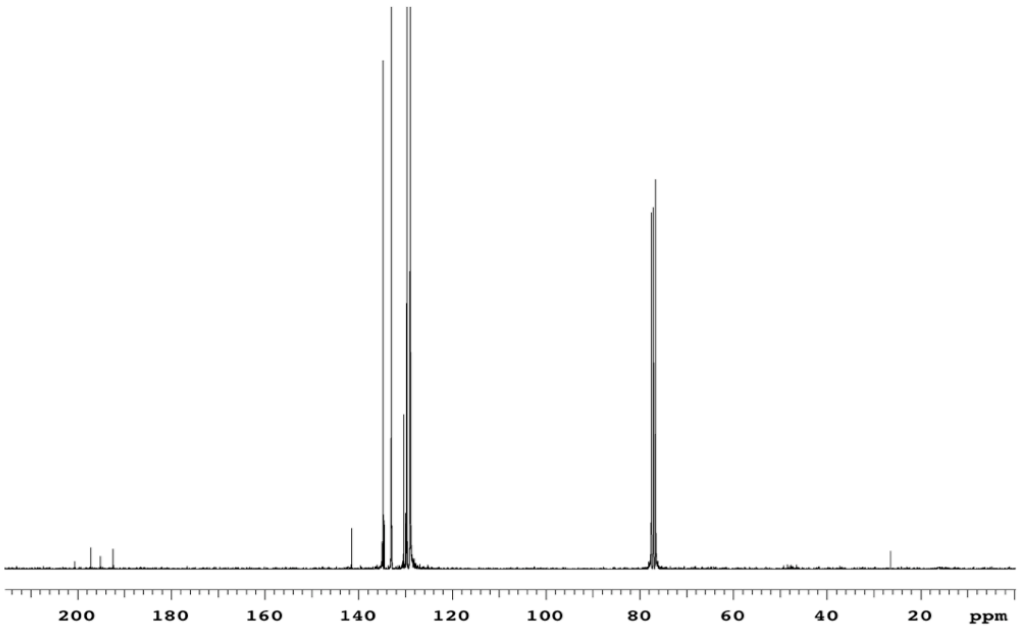
^{1}H NMR ($CDCl_3$, 300 MHz)



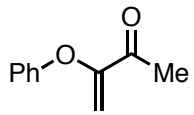
75



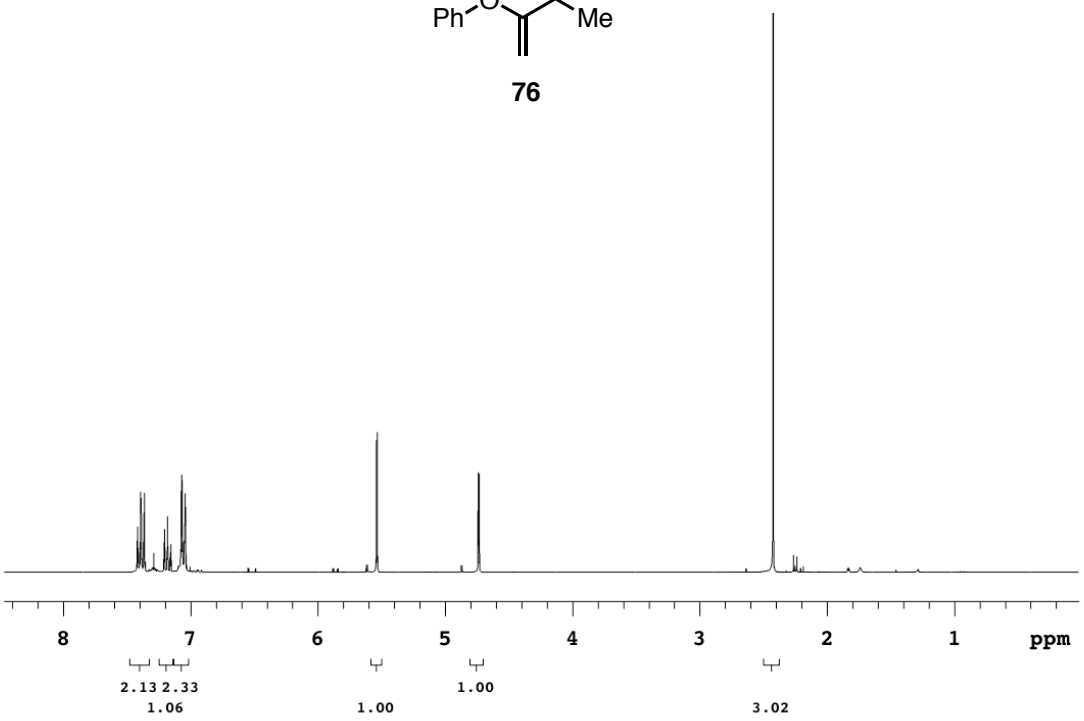
^{13}C NMR ($CDCl_3$, 75 MHz)



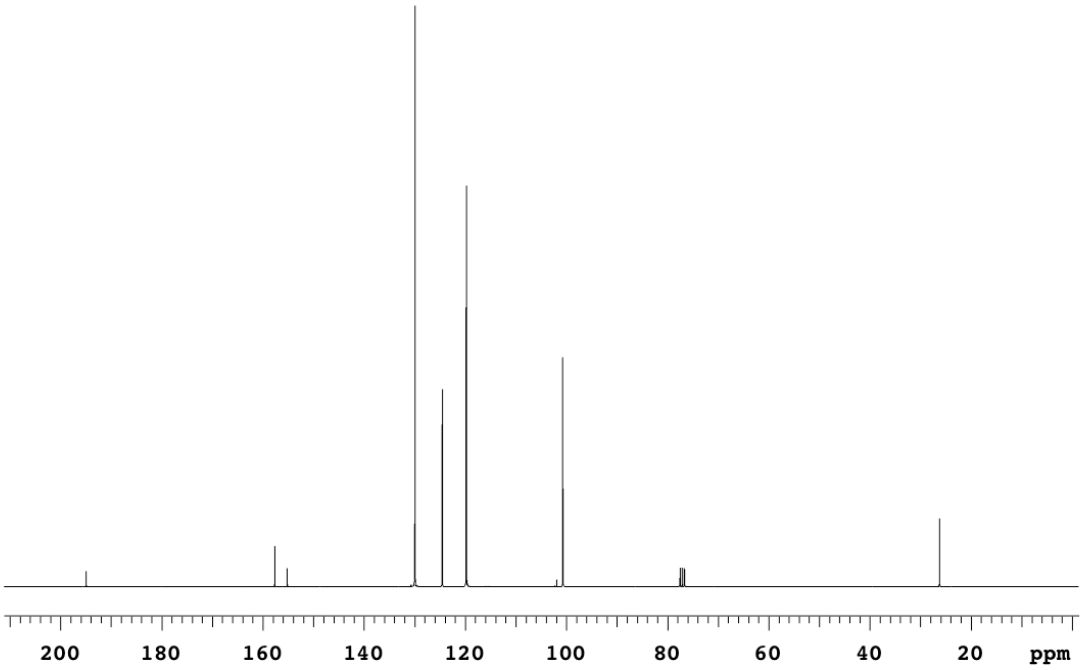
^{1}H NMR ($CDCl_3$, 300 MHz)



76

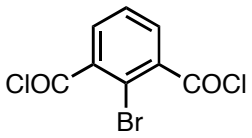


^{13}C NMR ($CDCl_3$, 75 MHz)

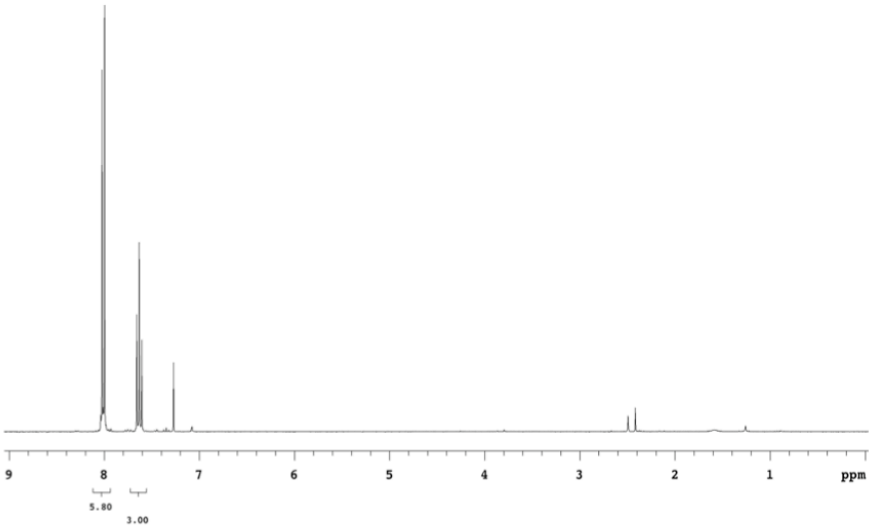


Reproduction of ^{1}H and ^{13}C NMR Spectra

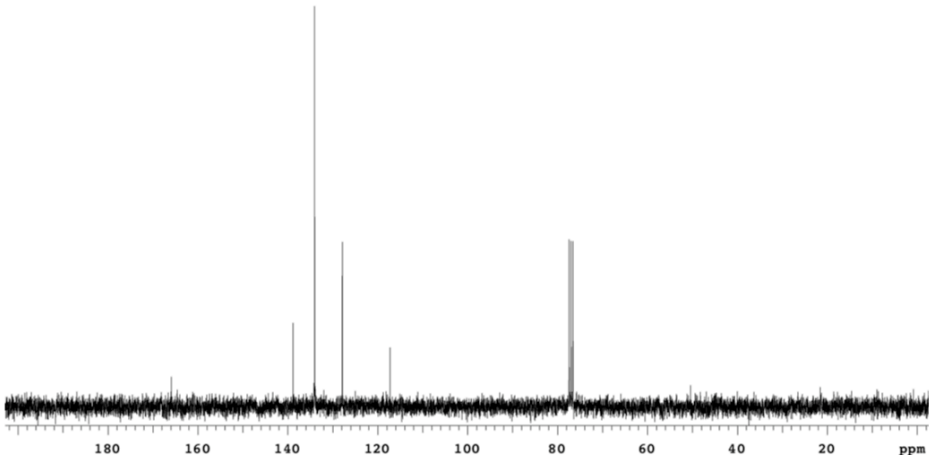
^{1}H NMR ($CDCl_3$, 300 MHz)



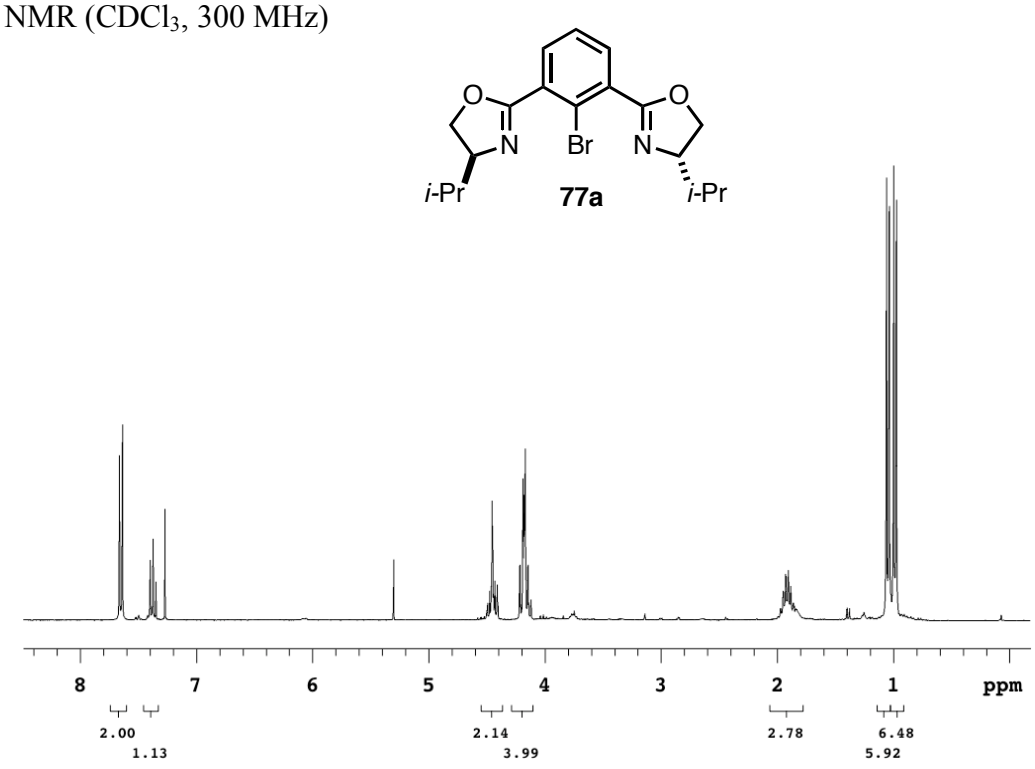
78



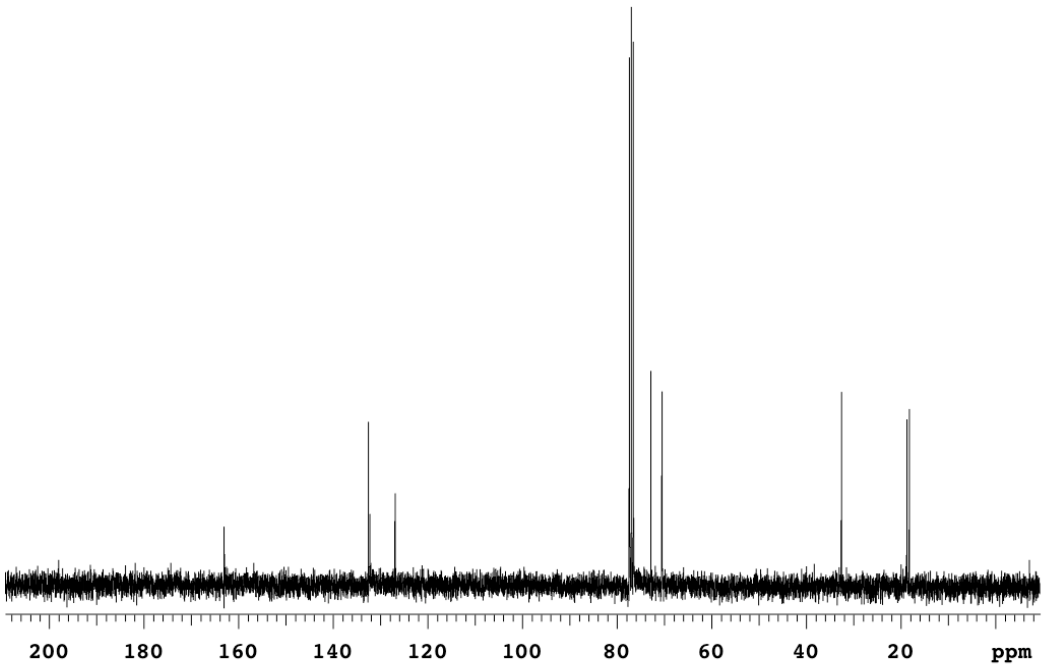
^{13}C NMR ($CDCl_3$, 75 MHz)



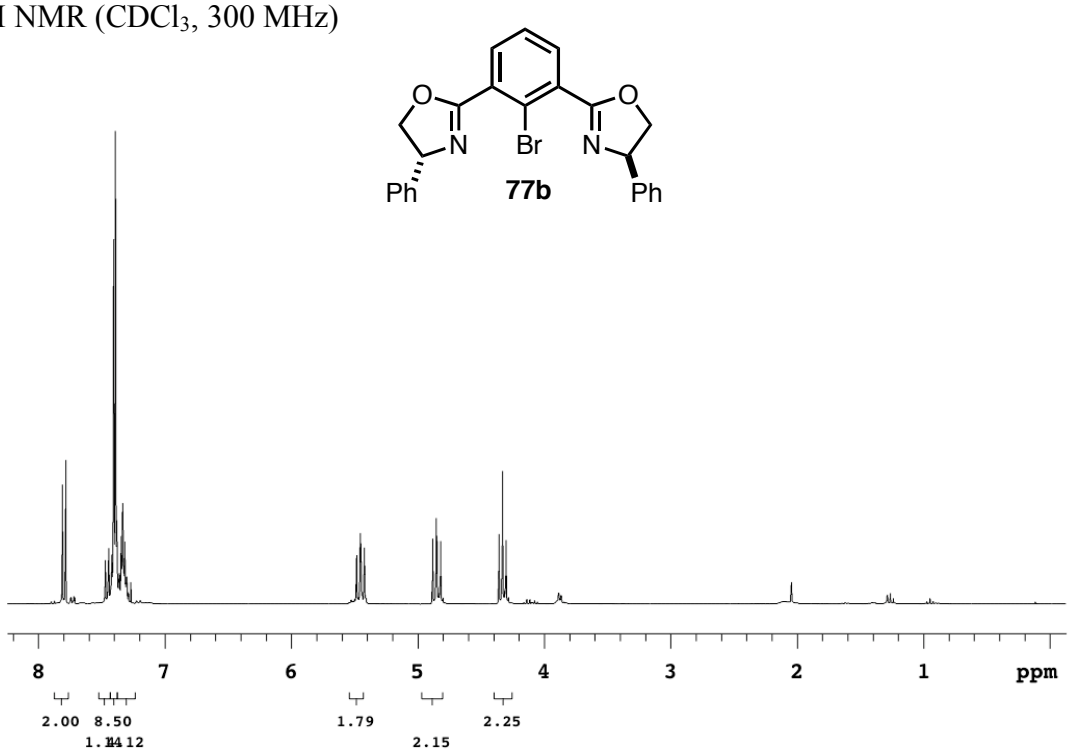
^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)

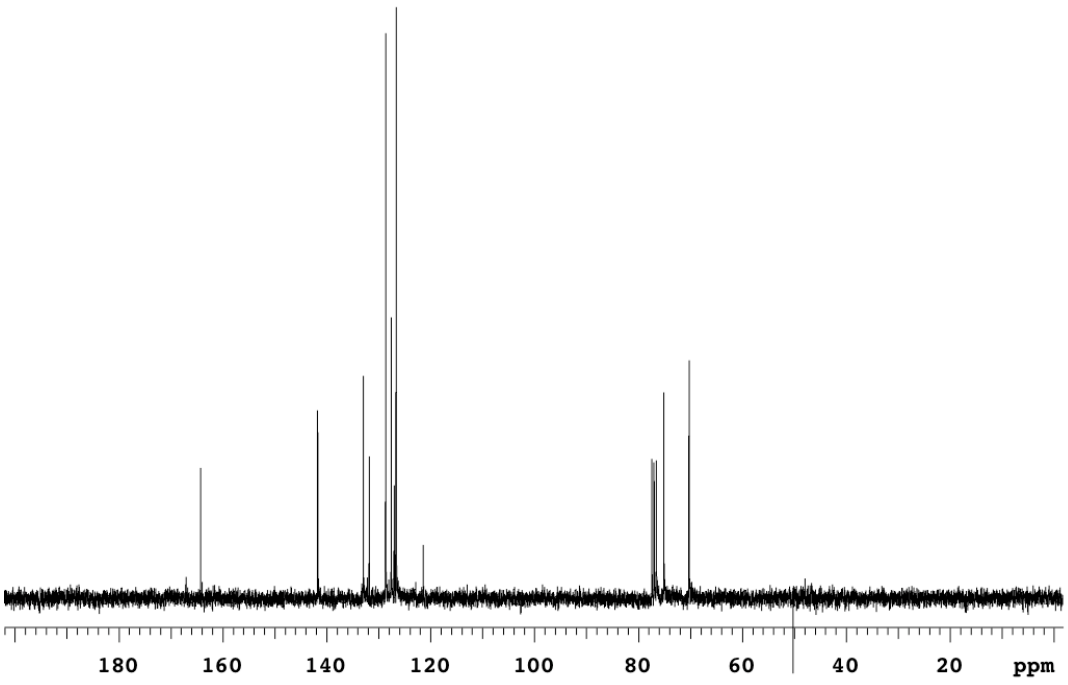


^{1}H NMR ($CDCl_3$, 300 MHz)

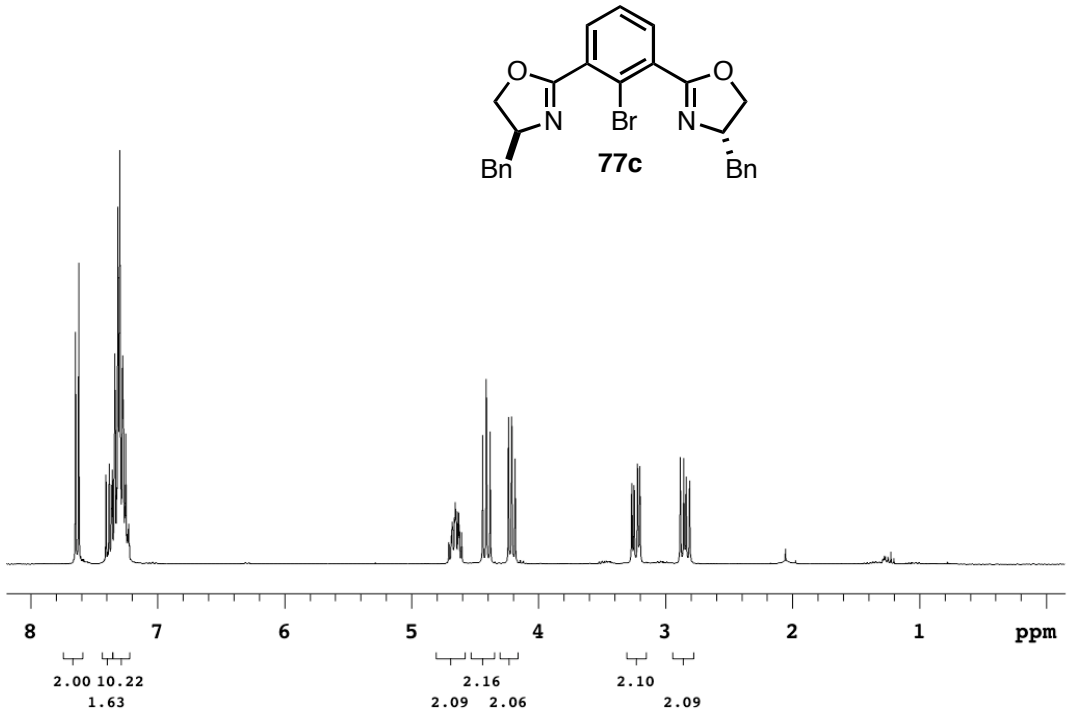


77b

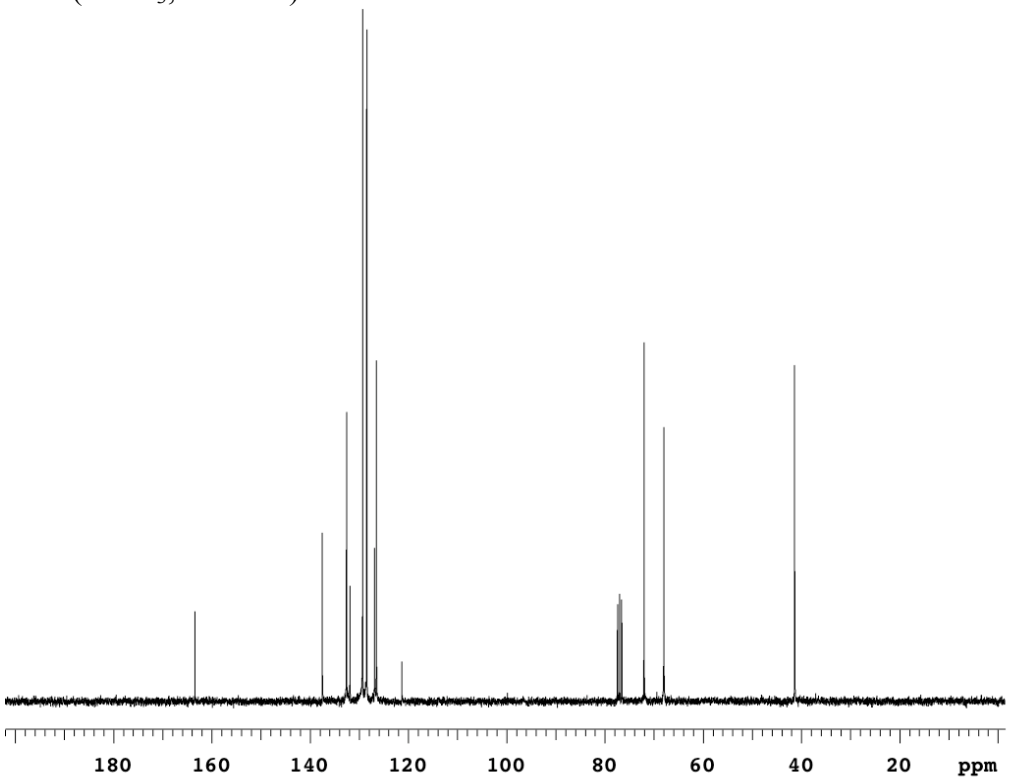
^{13}C NMR ($CDCl_3$, 75 MHz)



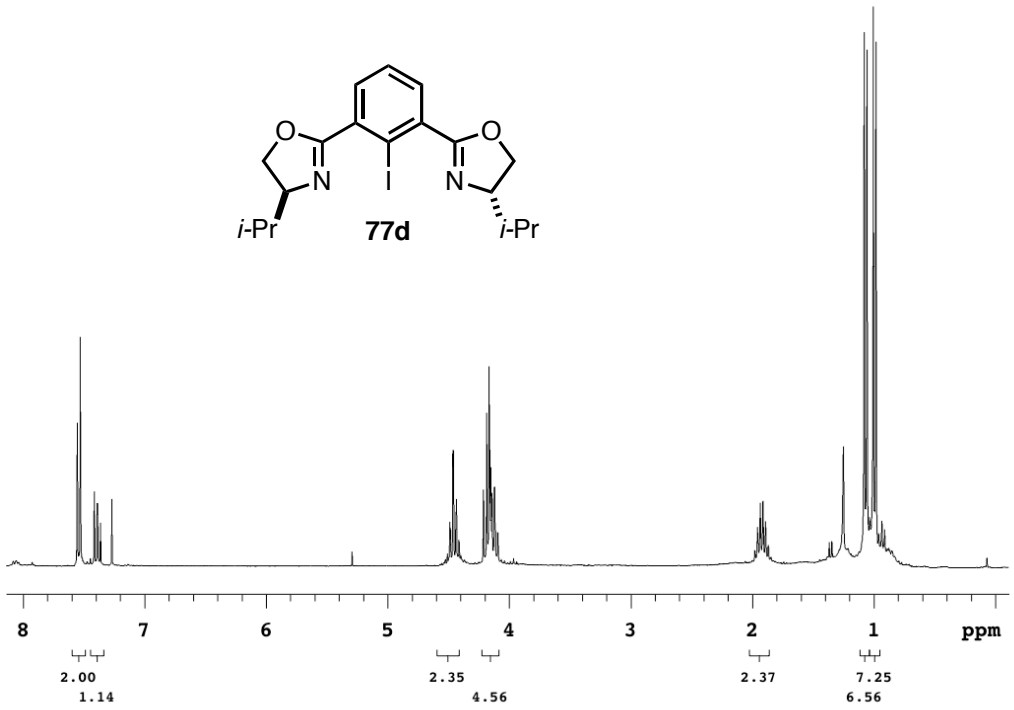
^{1}H NMR ($CDCl_3$, 300 MHz)



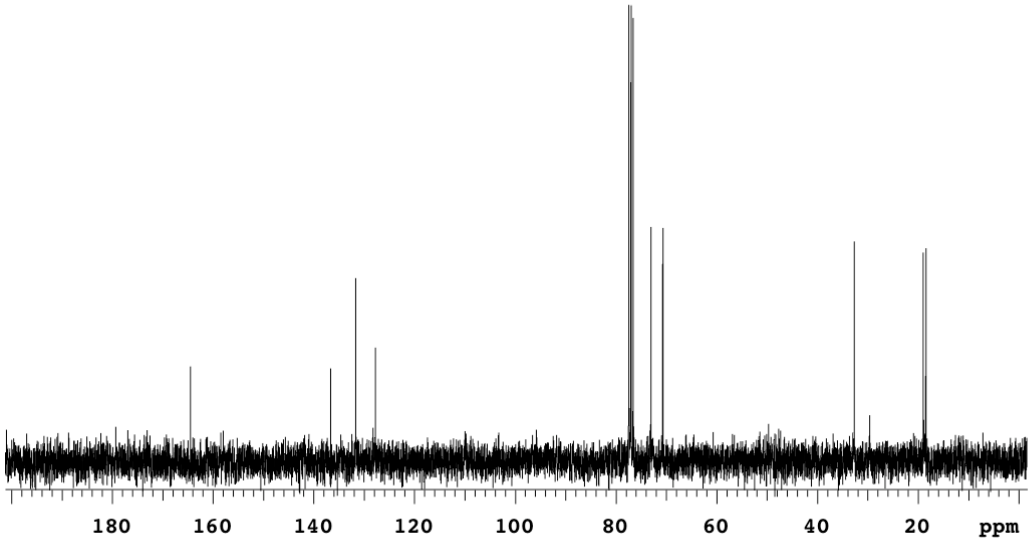
^{13}C NMR ($CDCl_3$, 75 MHz)



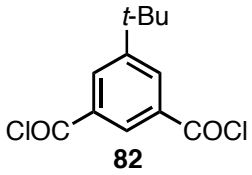
^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)

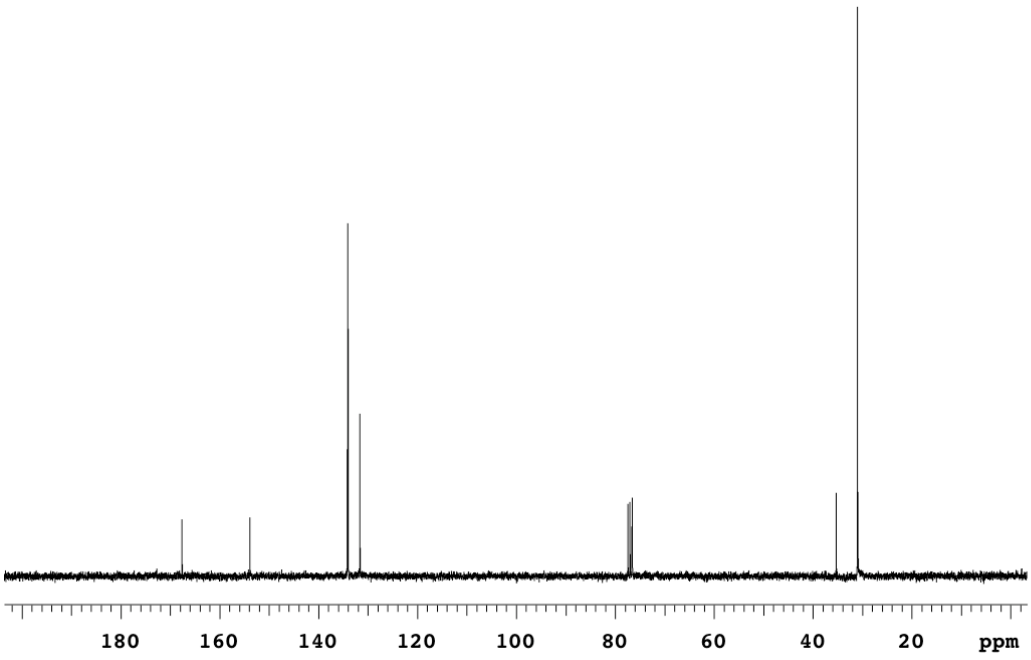


^{1}H NMR ($CDCl_3$, 300 MHz)

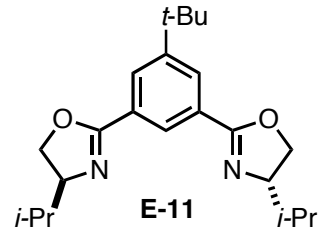


82

^{13}C NMR ($CDCl_3$, 75 MHz)

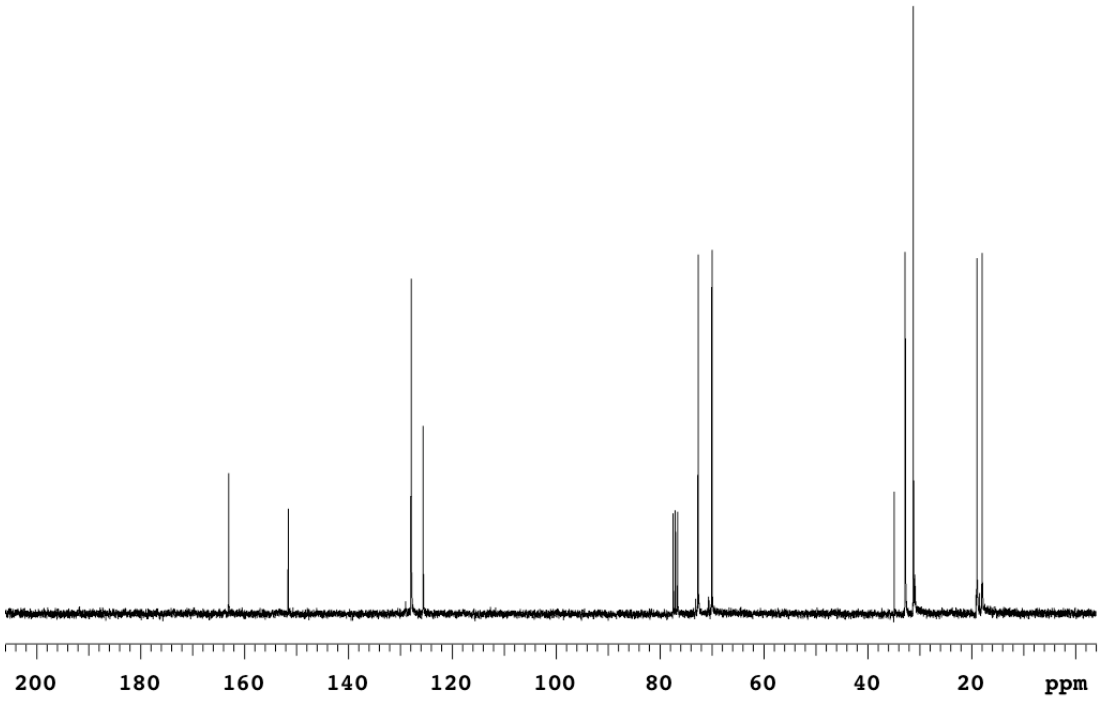


^{1}H NMR ($CDCl_3$, 300 MHz)

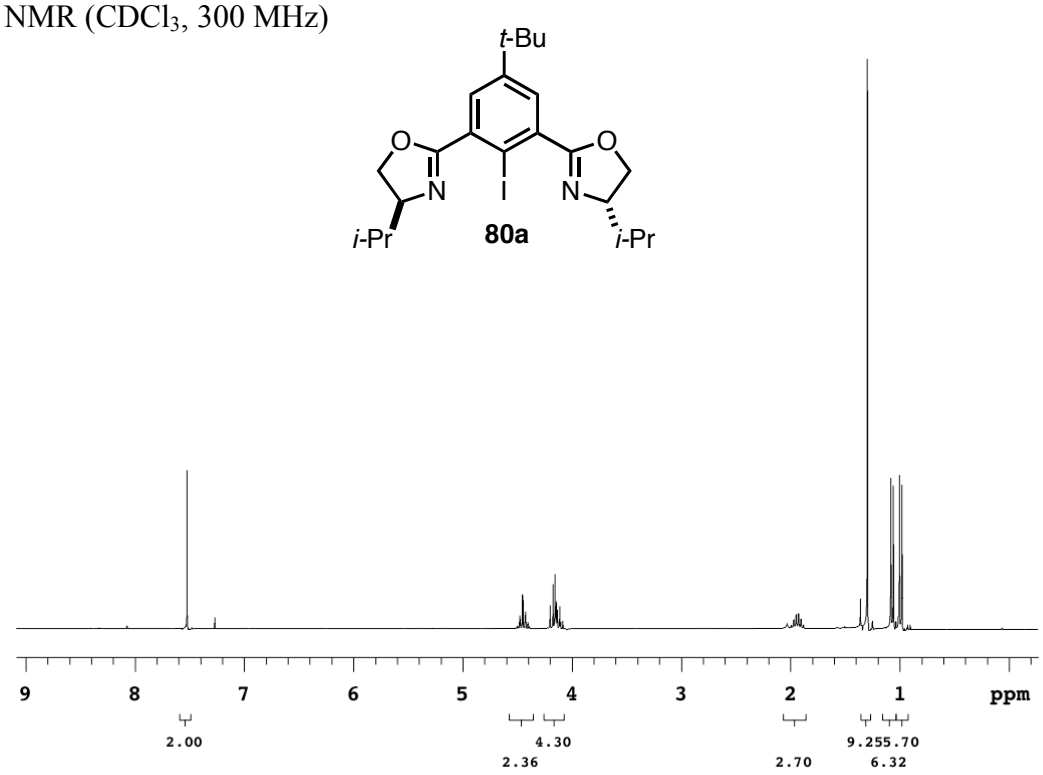


E-11

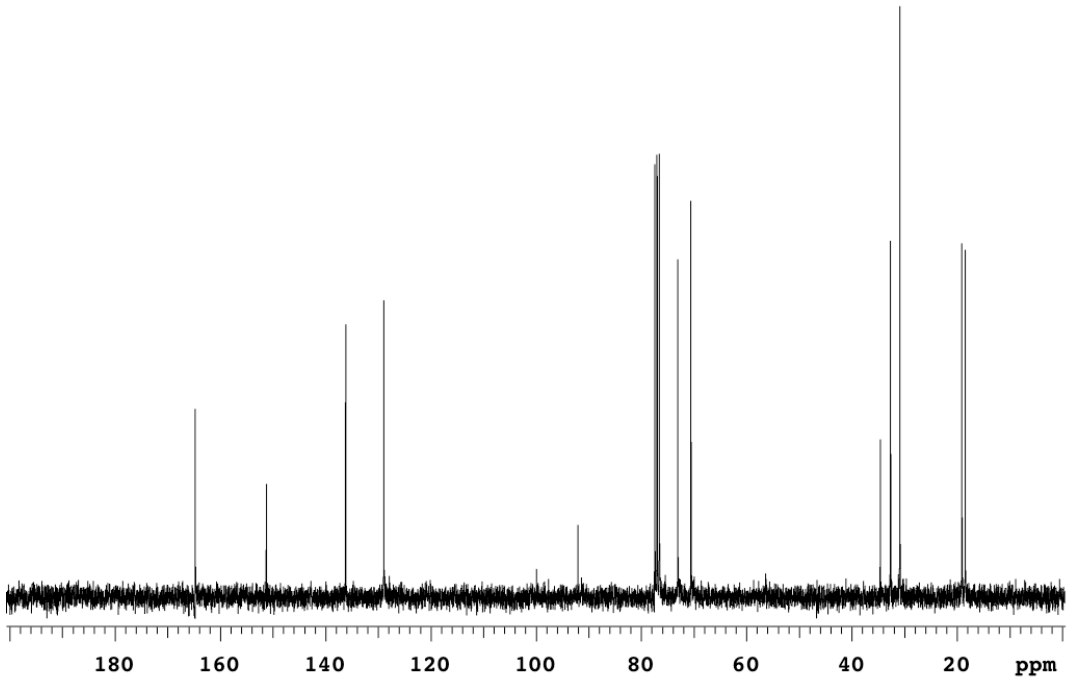
^{13}C NMR ($CDCl_3$, 75 MHz)



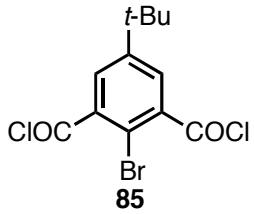
^{1}H NMR ($CDCl_3$, 300 MHz)



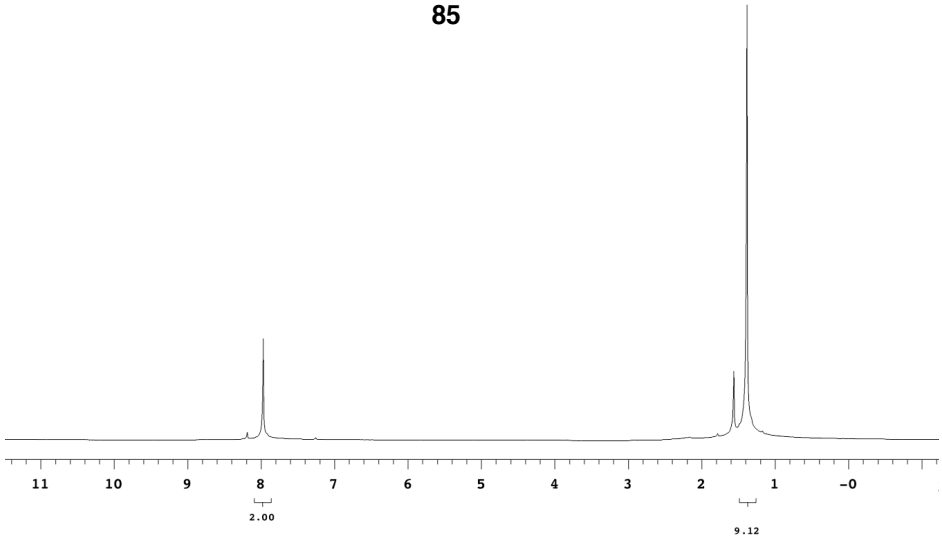
^{13}C NMR ($CDCl_3$, 75 MHz)



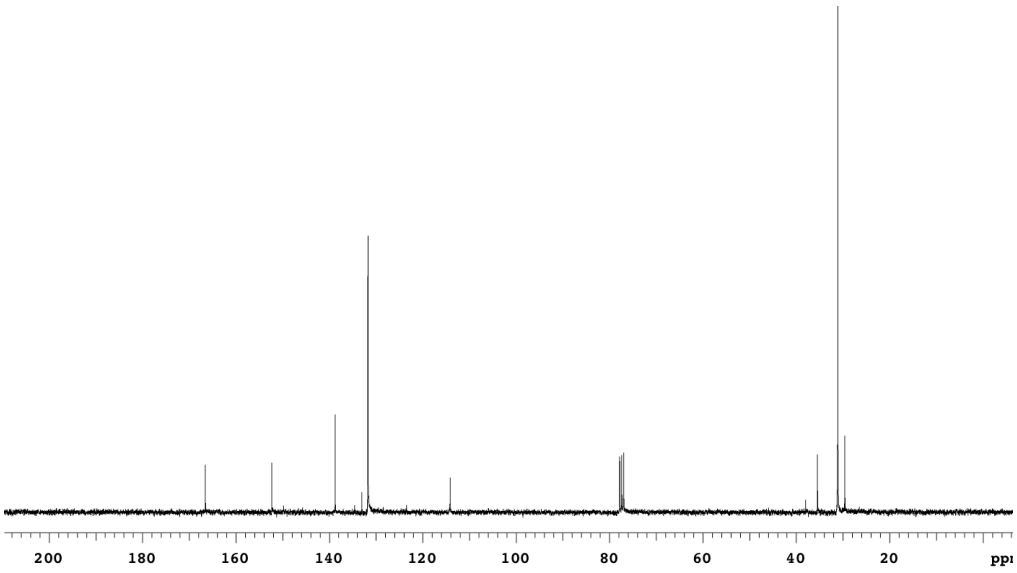
^{1}H NMR ($CDCl_3$, 300 MHz)



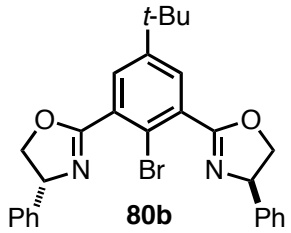
85



^{13}C NMR ($CDCl_3$, 75 MHz)

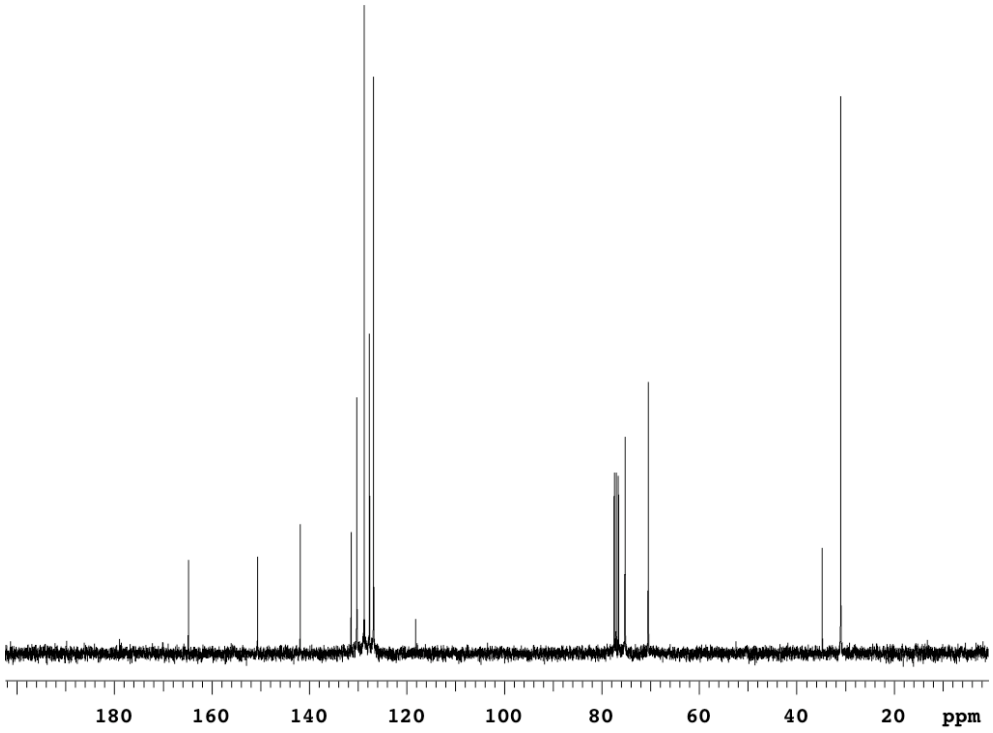


^{1}H NMR ($CDCl_3$, 300 MHz)

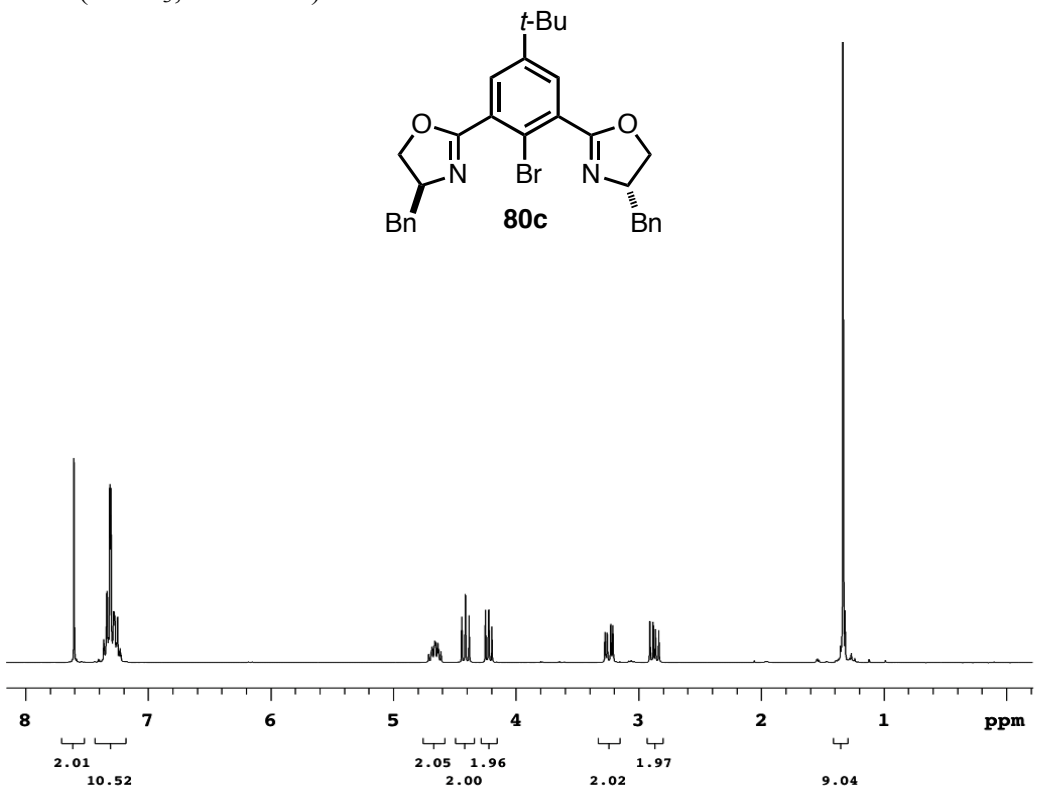


80b

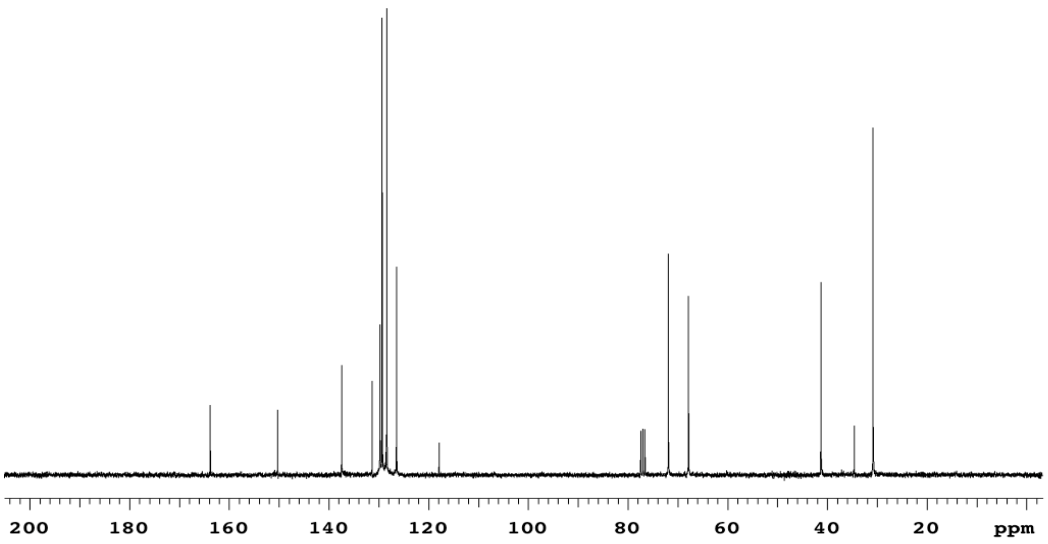
^{13}C NMR ($CDCl_3$, 75 MHz)



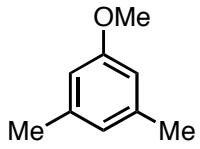
^{1}H NMR ($CDCl_3$, 300 MHz)



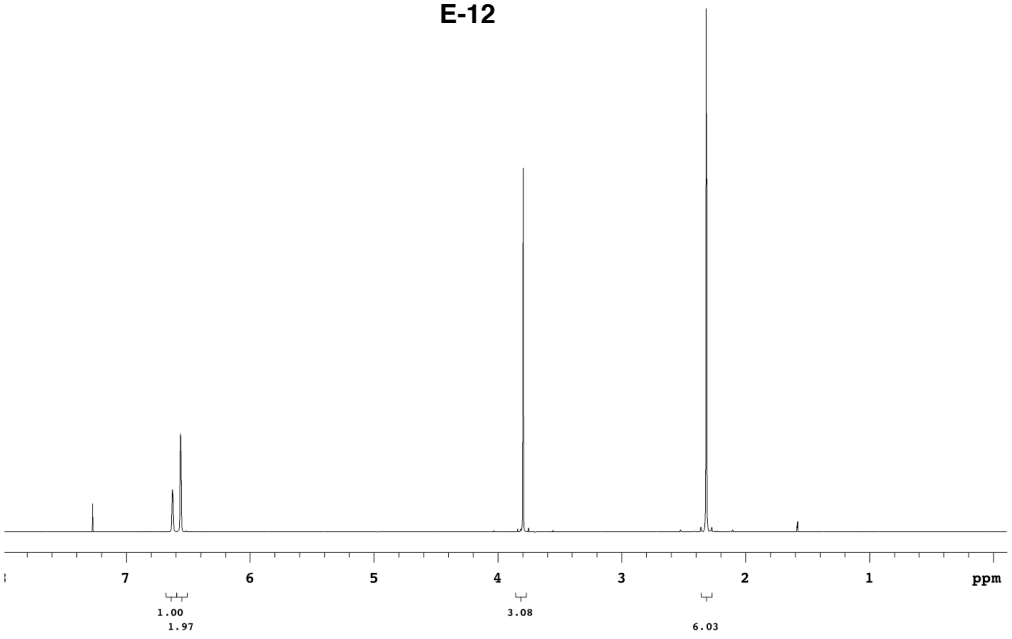
^{13}C NMR ($CDCl_3$, 75 MHz)



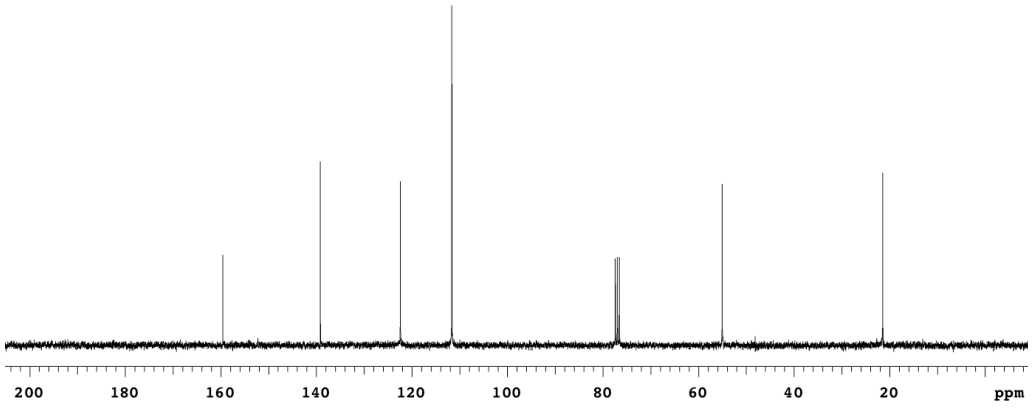
^{1}H NMR ($CDCl_3$, 300 MHz)



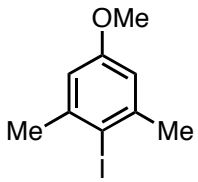
E-12



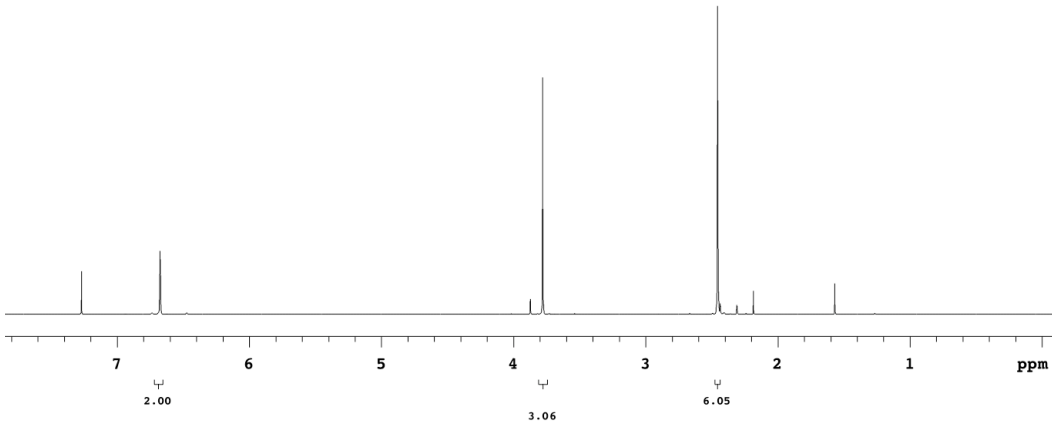
^{13}C NMR ($CDCl_3$, 75 MHz)



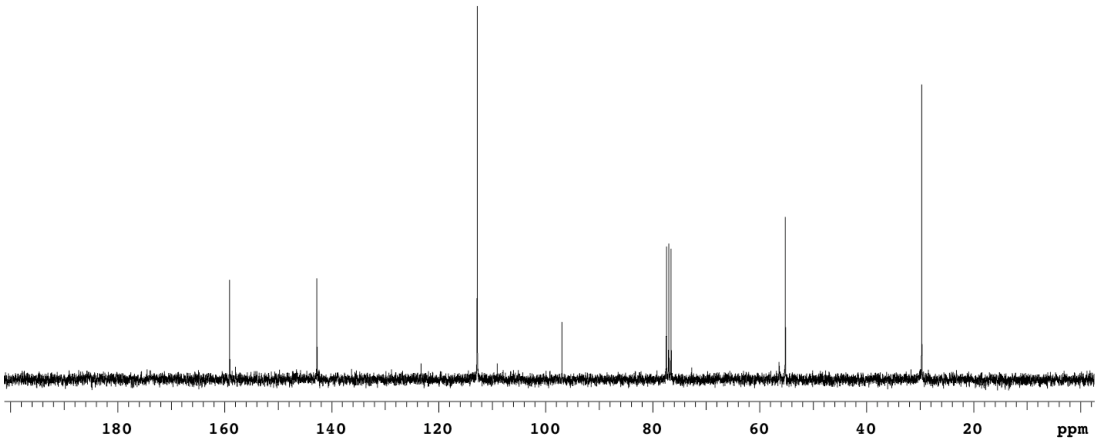
^{1}H NMR ($CDCl_3$, 300 MHz)



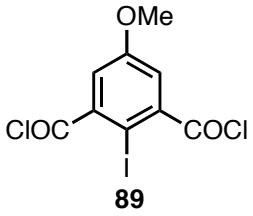
88



^{13}C NMR ($CDCl_3$, 75 MHz)

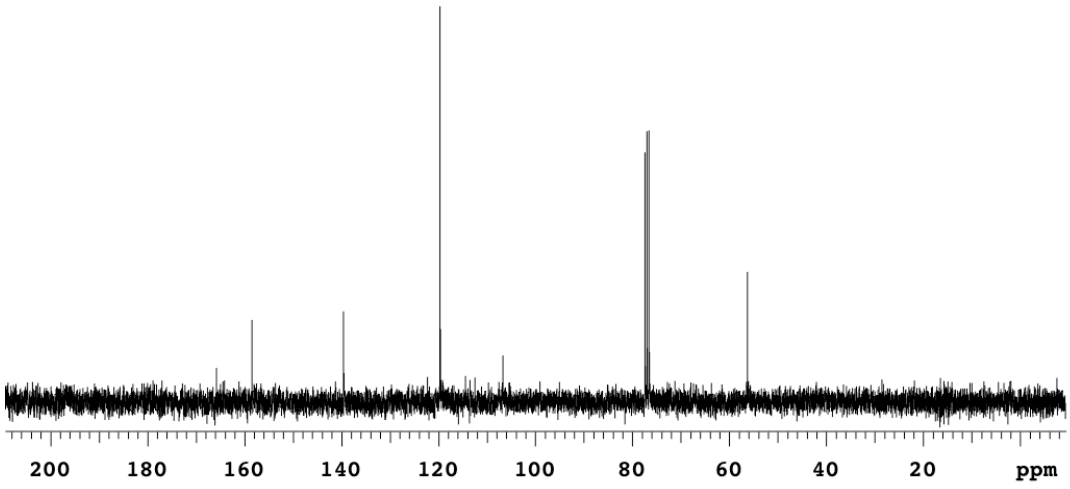


^{1}H NMR ($CDCl_3$, 300 MHz)

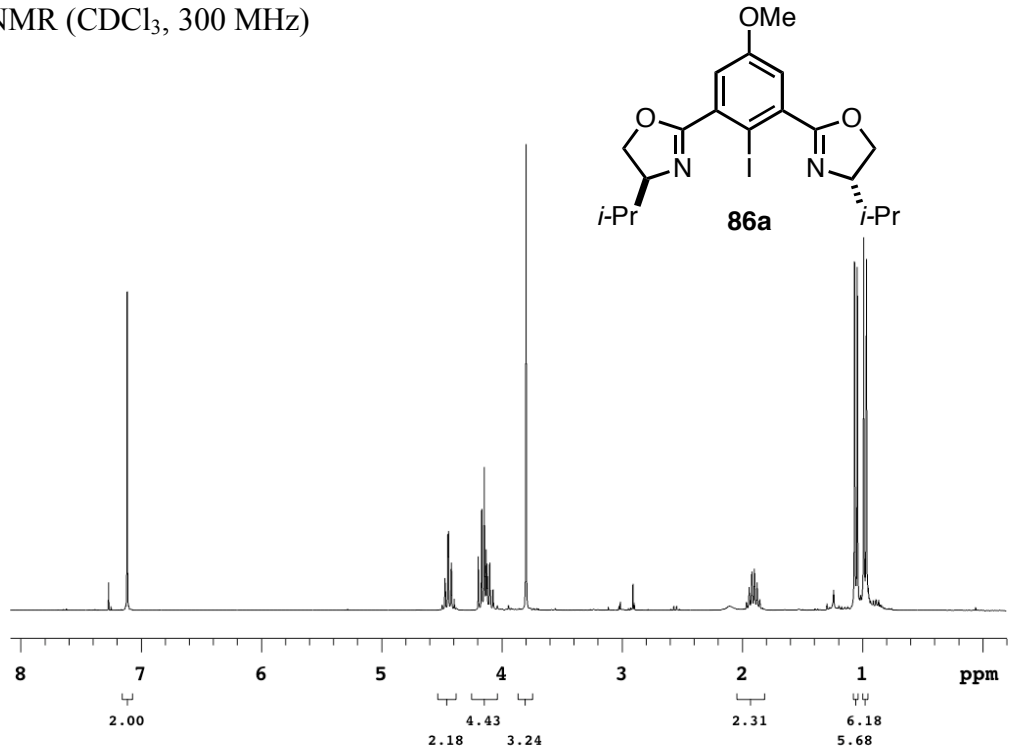


89

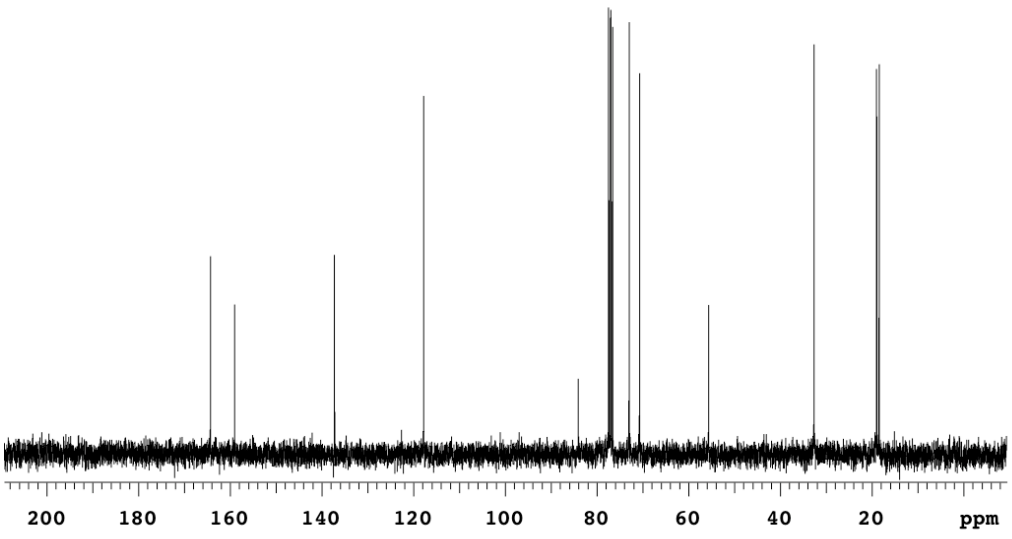
^{13}C NMR ($CDCl_3$, 75 MHz)



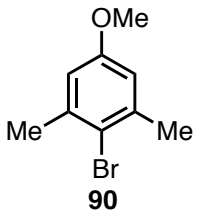
^{1}H NMR ($CDCl_3$, 300 MHz)



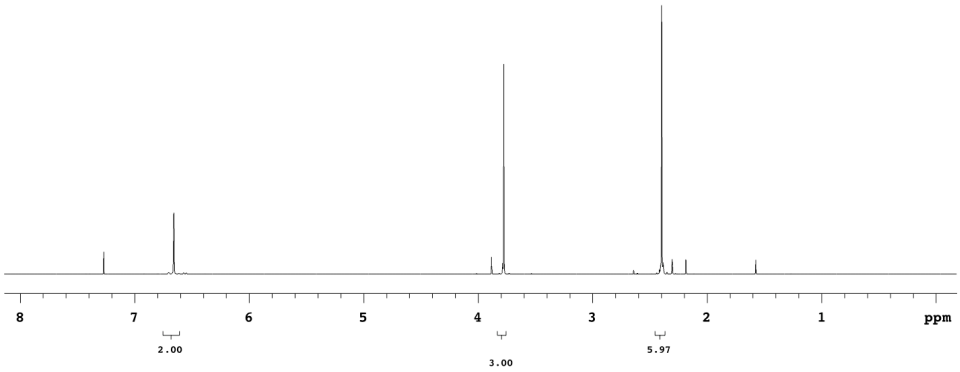
^{13}C NMR ($CDCl_3$, 75 MHz)



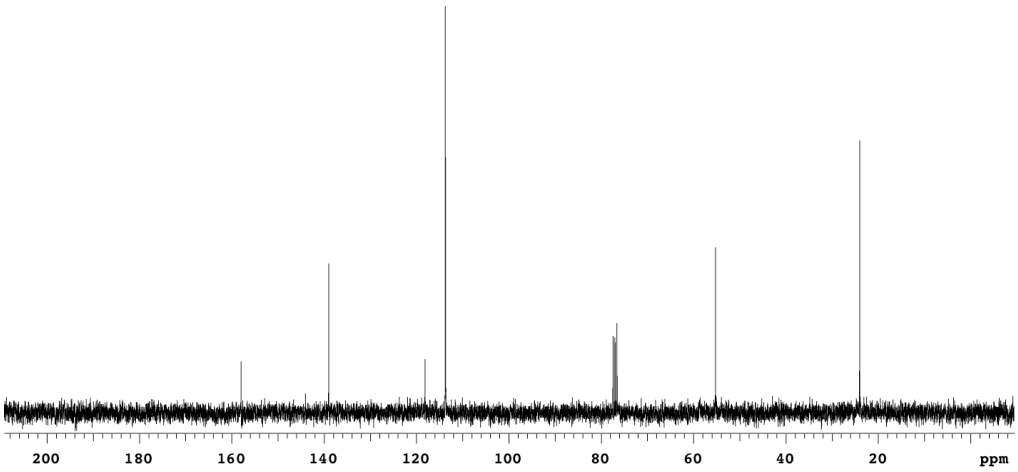
^{1}H NMR ($CDCl_3$, 300 MHz)



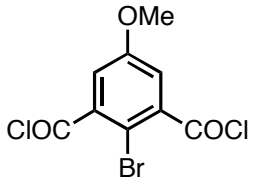
90



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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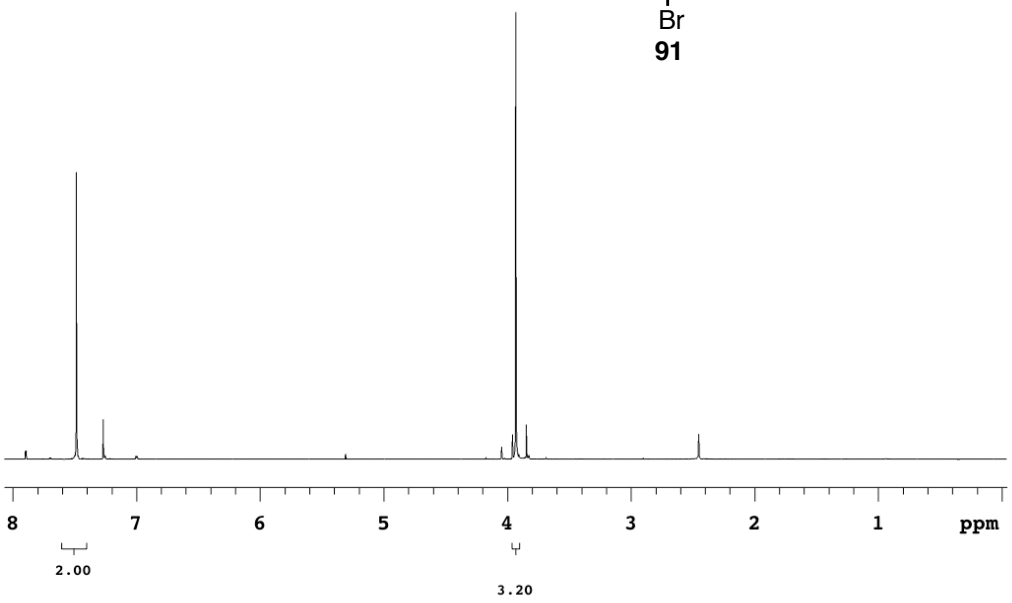
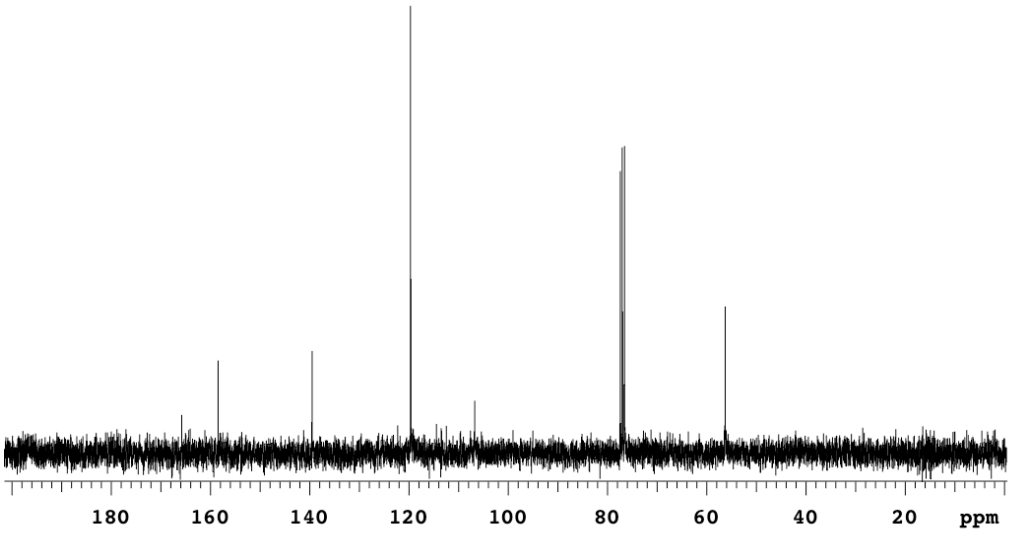
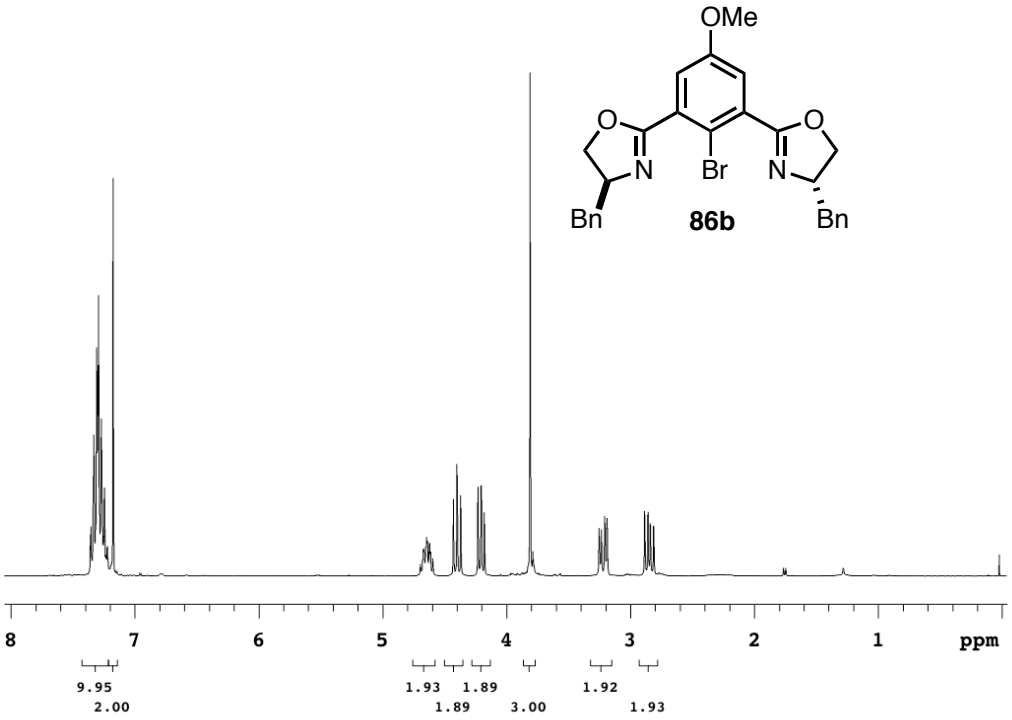


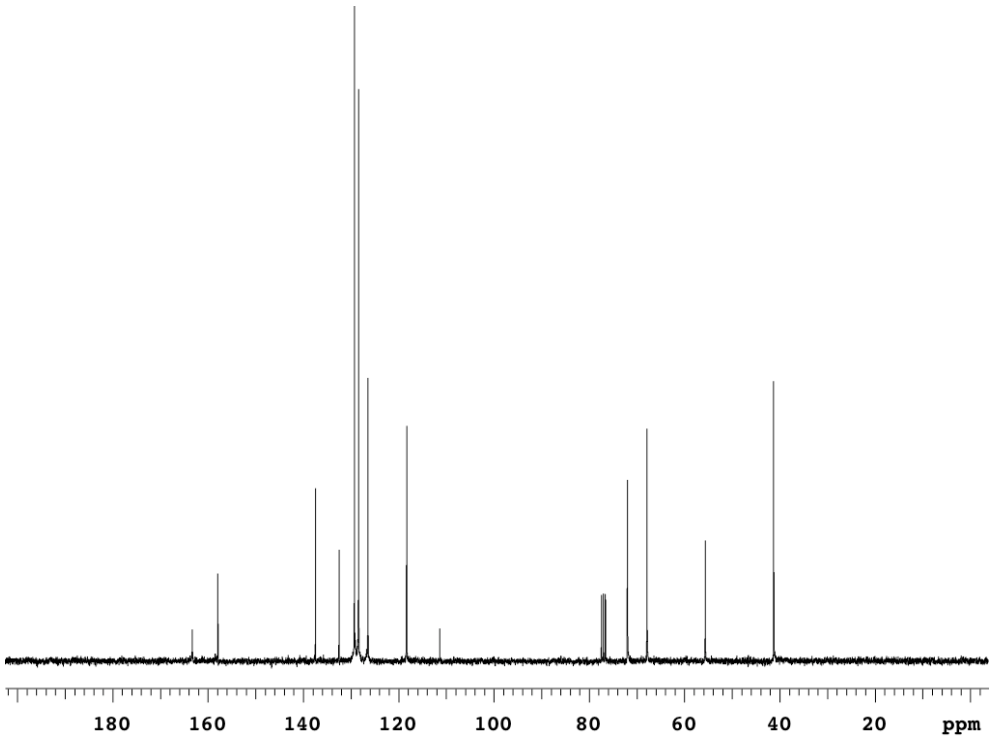
^{13}C NMR ($CDCl_3$, 75 MHz)



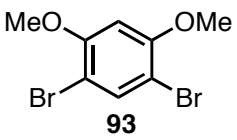
^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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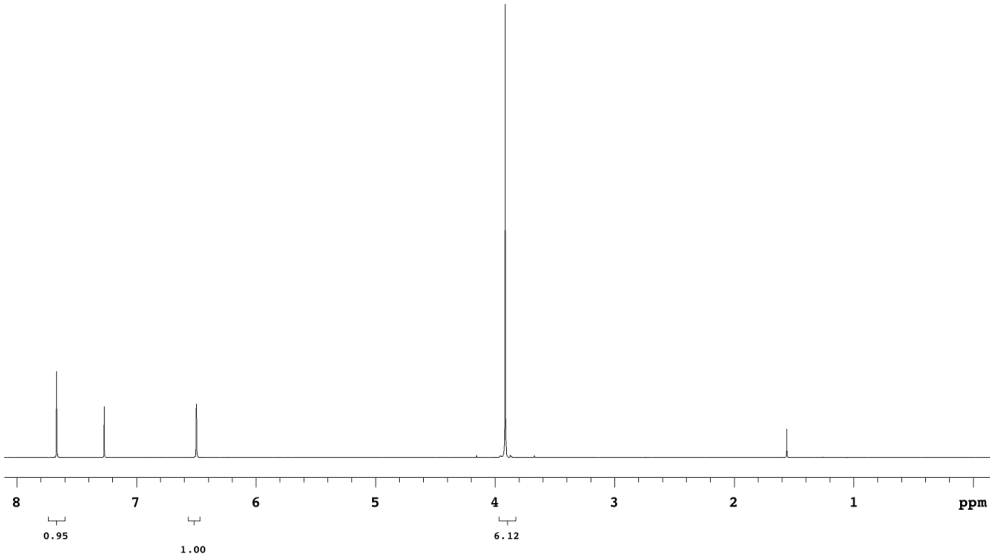
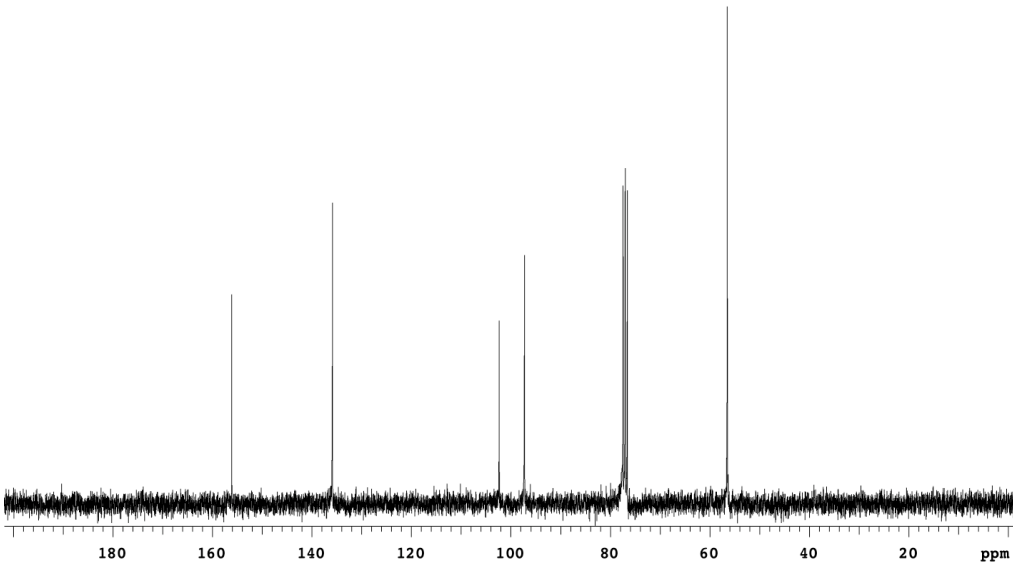
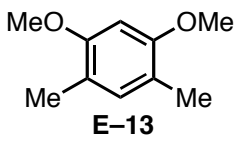


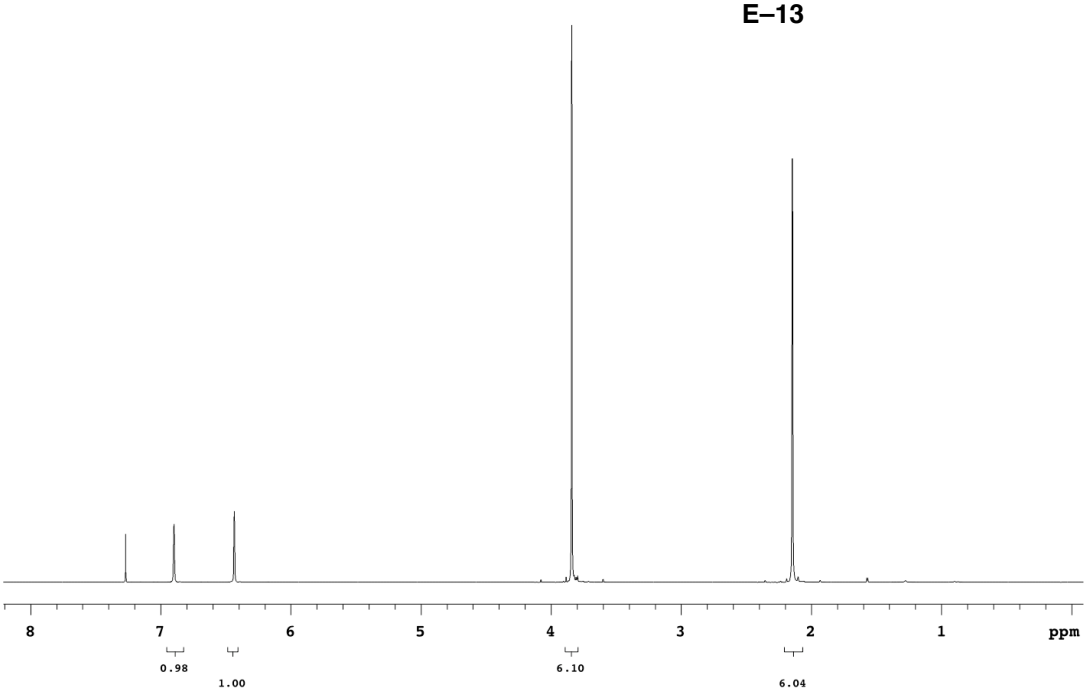
^{13}C NMR ($CDCl_3$, 75 MHz)



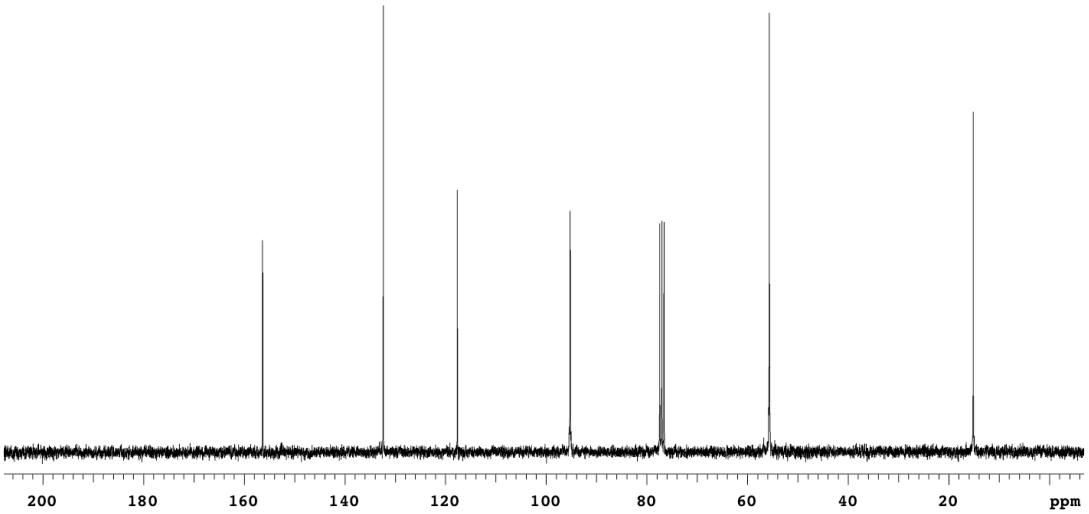
^{1}H NMR ($CDCl_3$, 300 MHz)



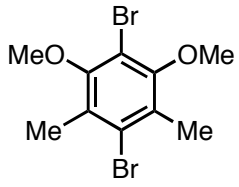
E–13



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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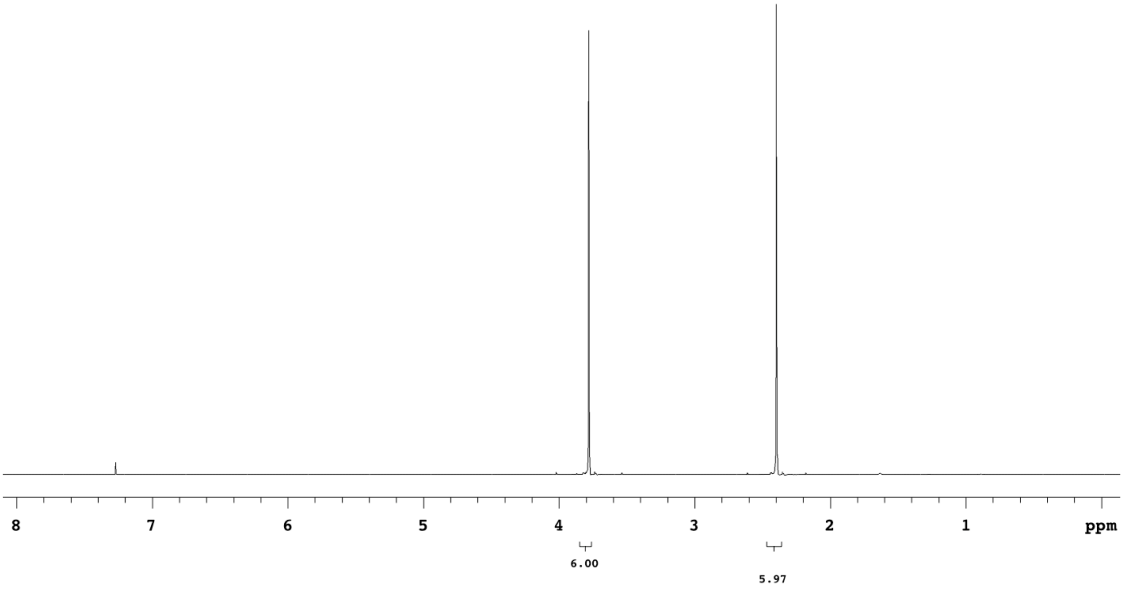
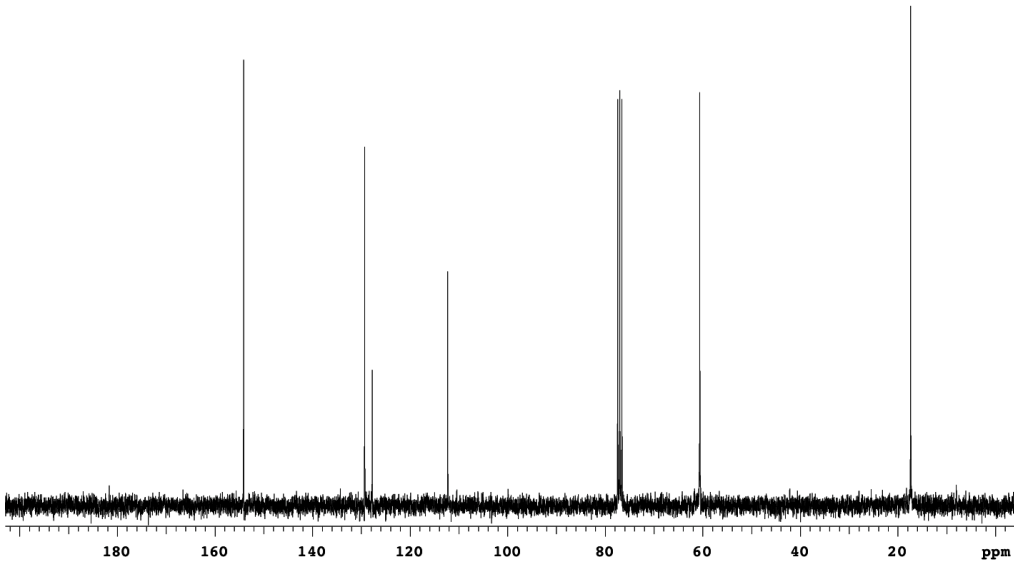
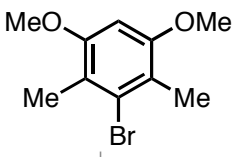


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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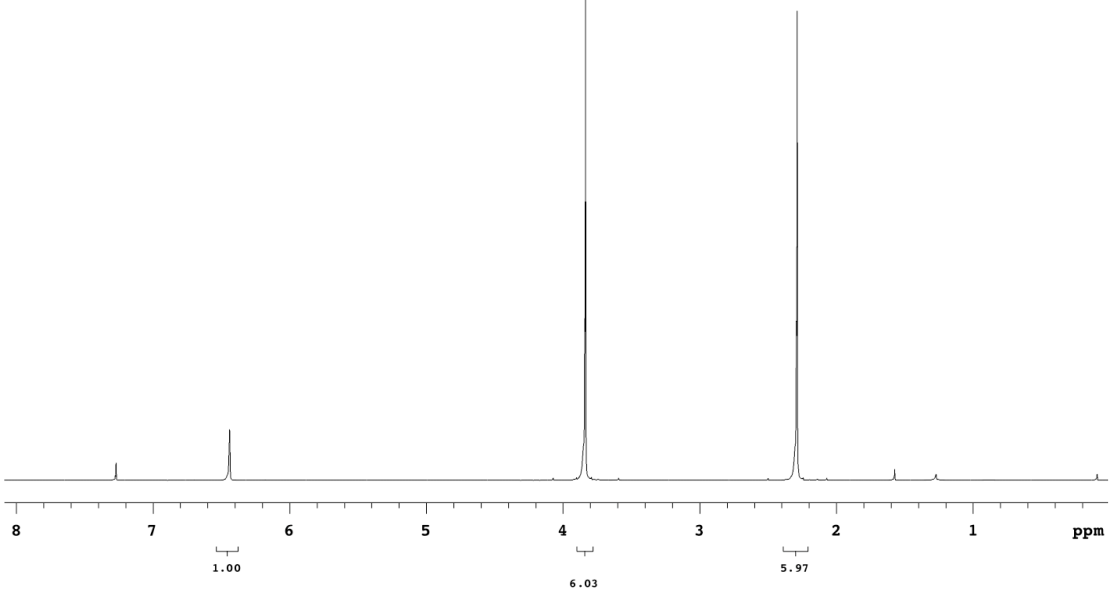
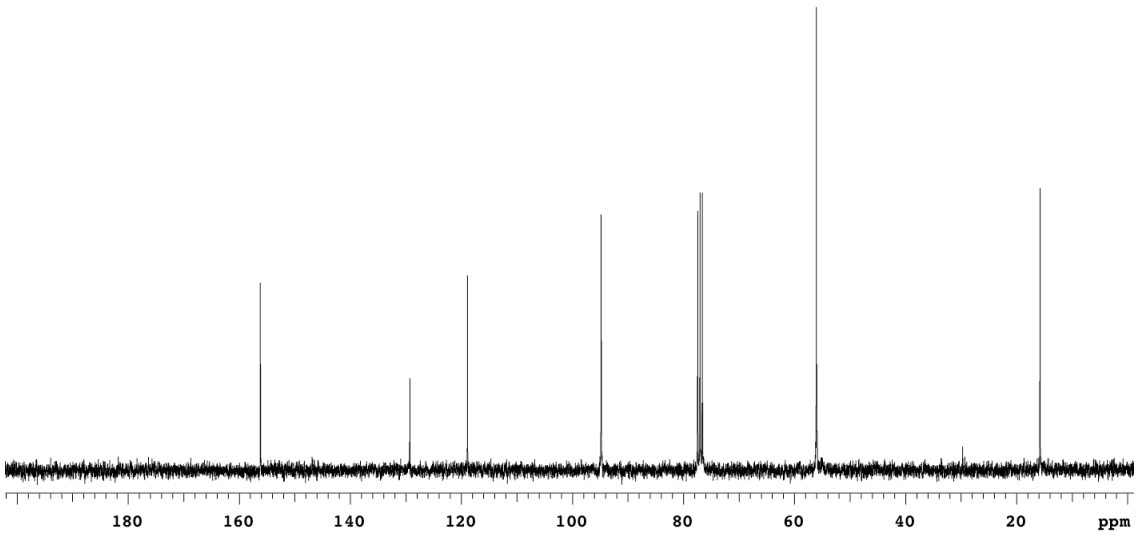
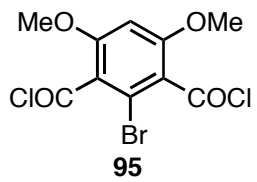


^{13}C NMR ($CDCl_3$, 75 MHz)

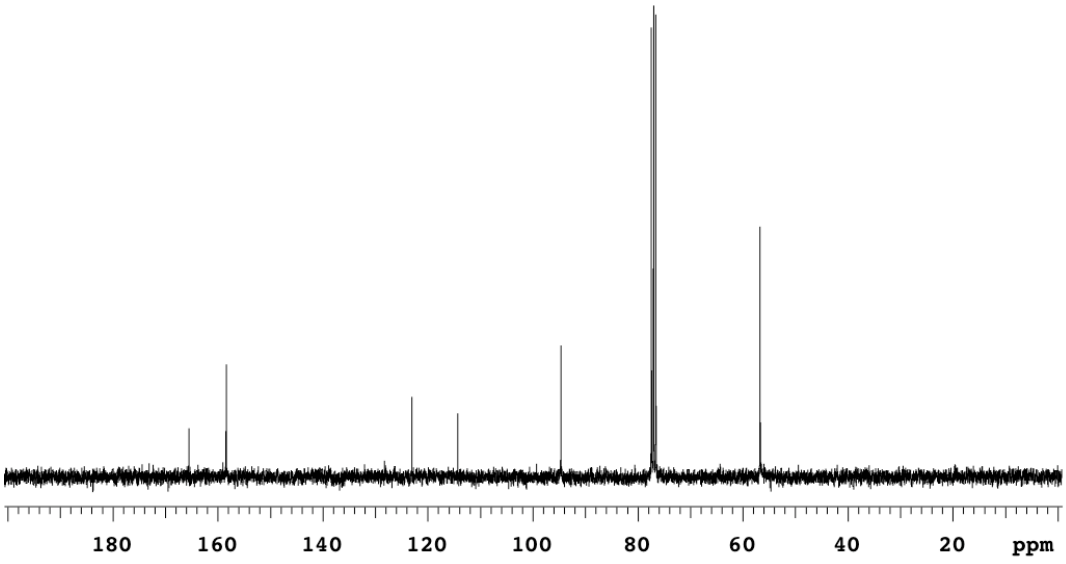


^{1}H NMR ($CDCl_3$, 300 MHz)

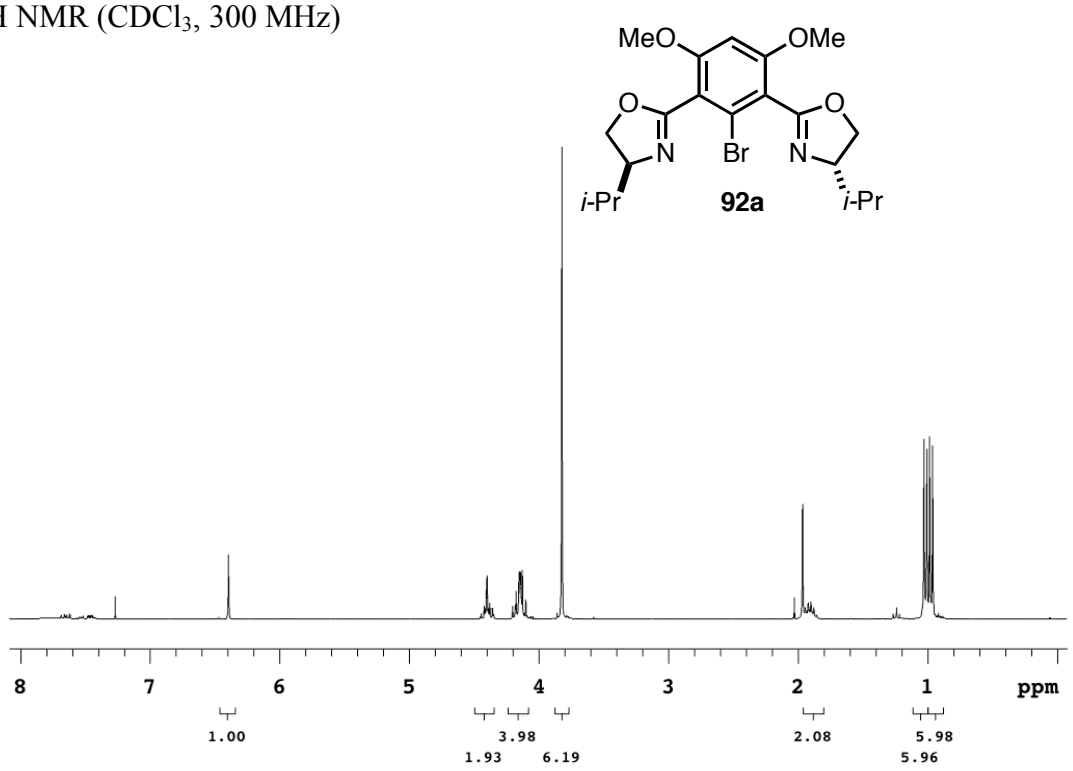


95

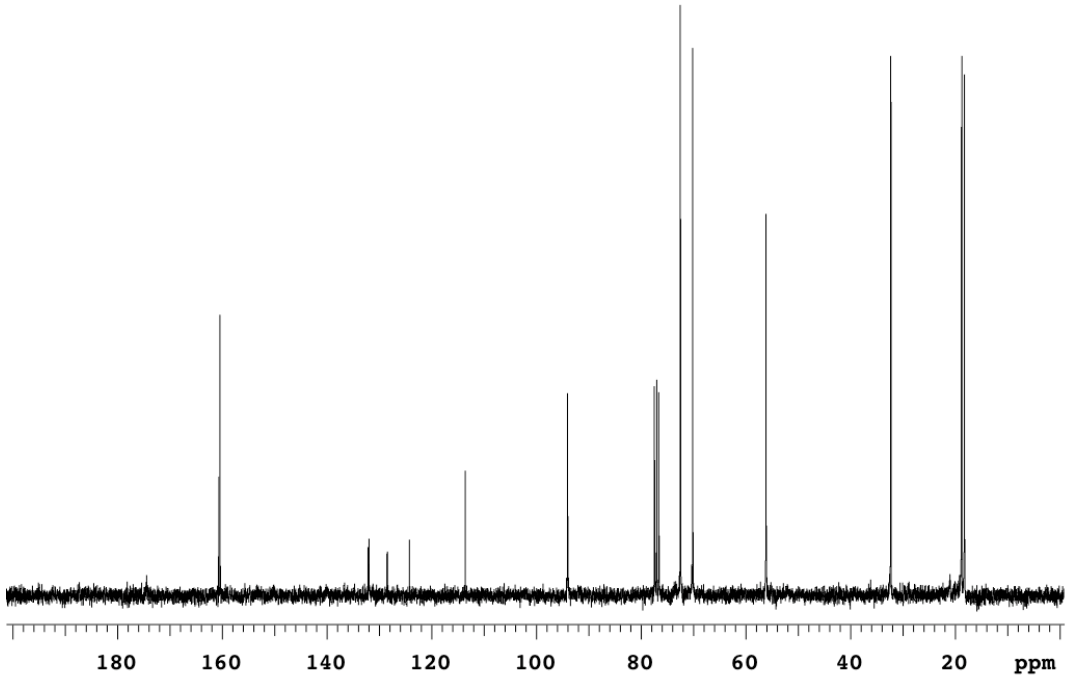
^{13}C NMR ($CDCl_3$, 75 MHz)



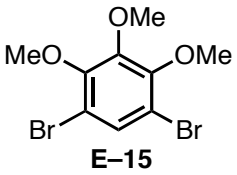
^{1}H NMR ($CDCl_3$, 300 MHz)



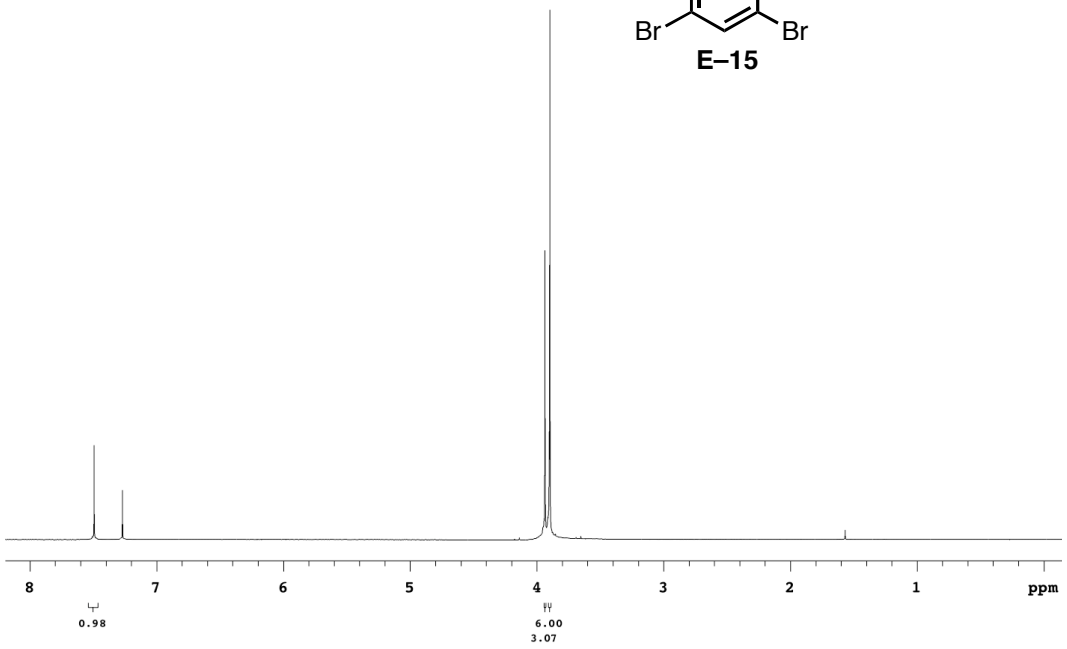
^{13}C NMR ($CDCl_3$, 75 MHz)



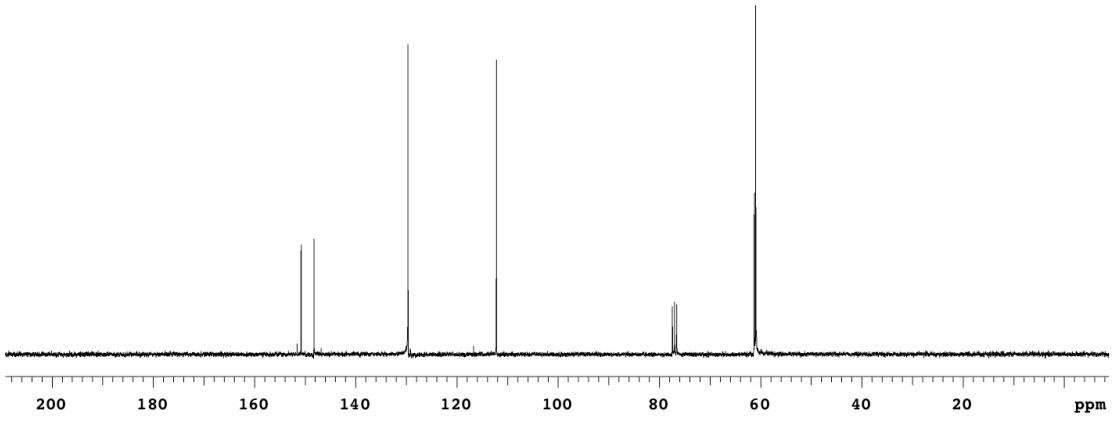
^{1}H NMR ($CDCl_3$, 300 MHz)



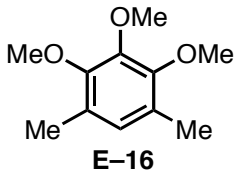
E–15



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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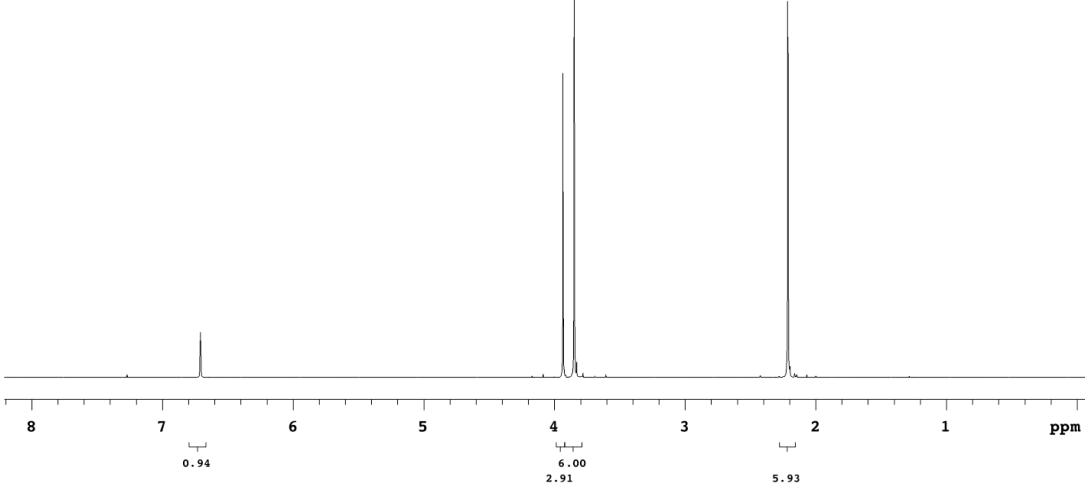
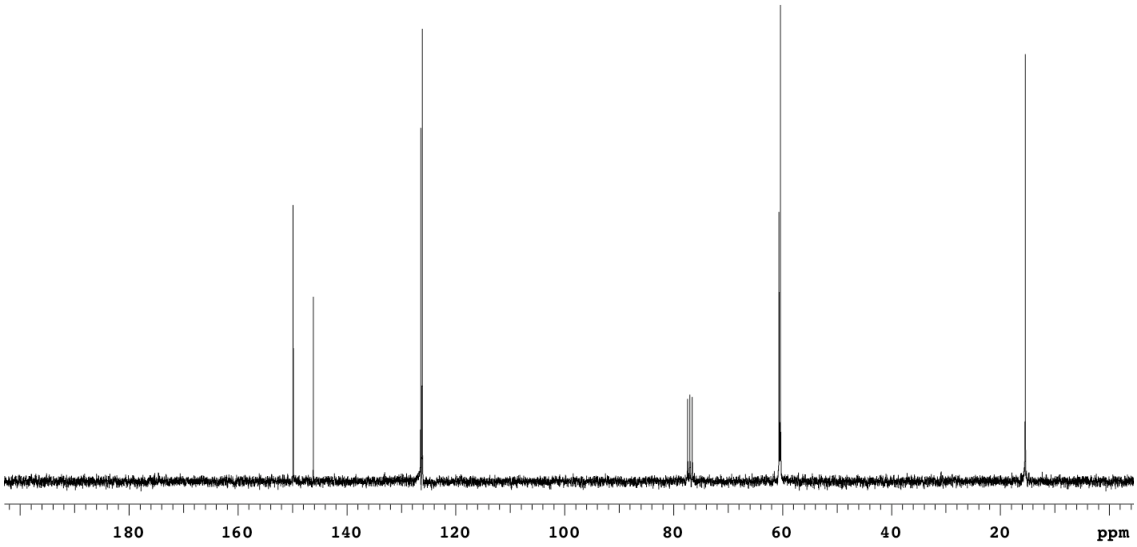
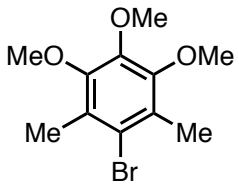


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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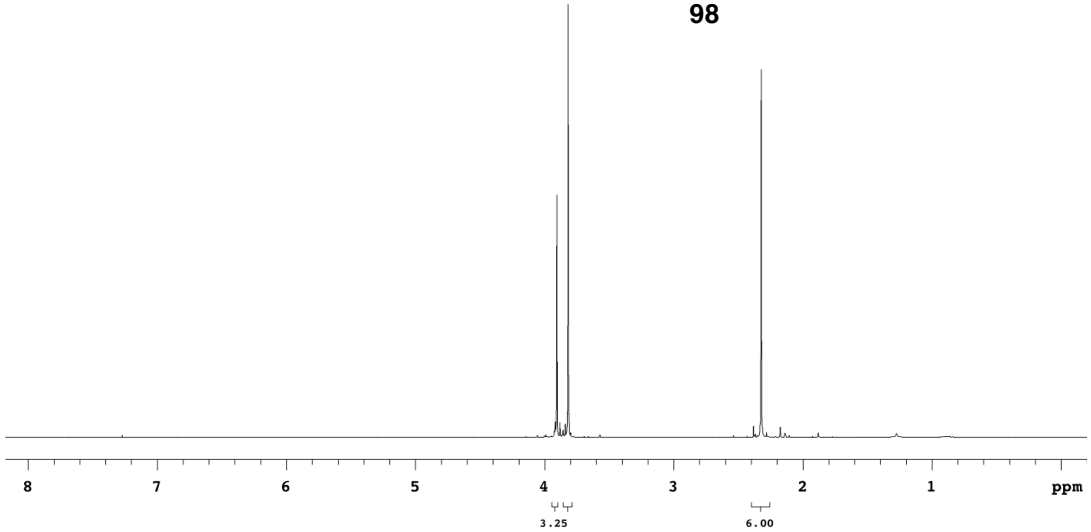
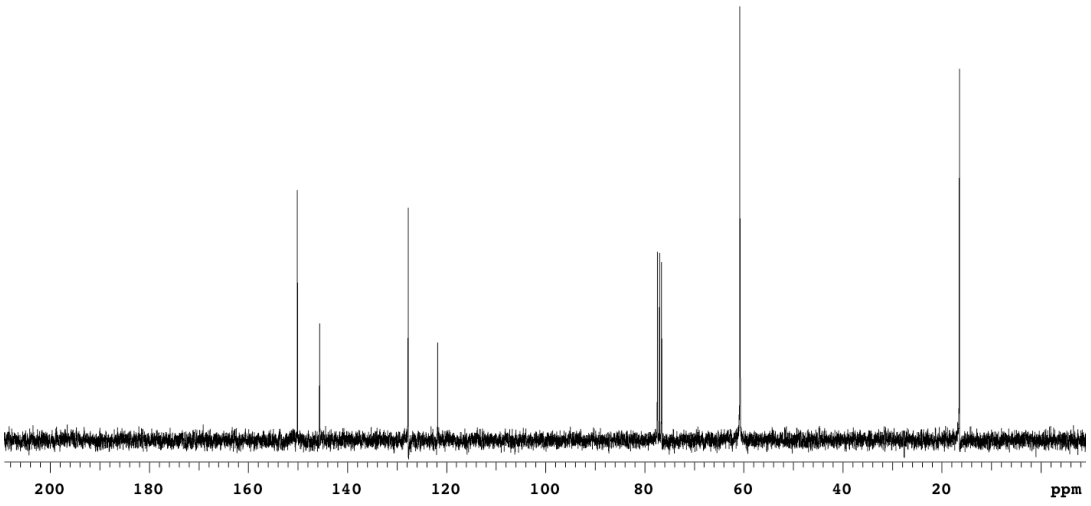
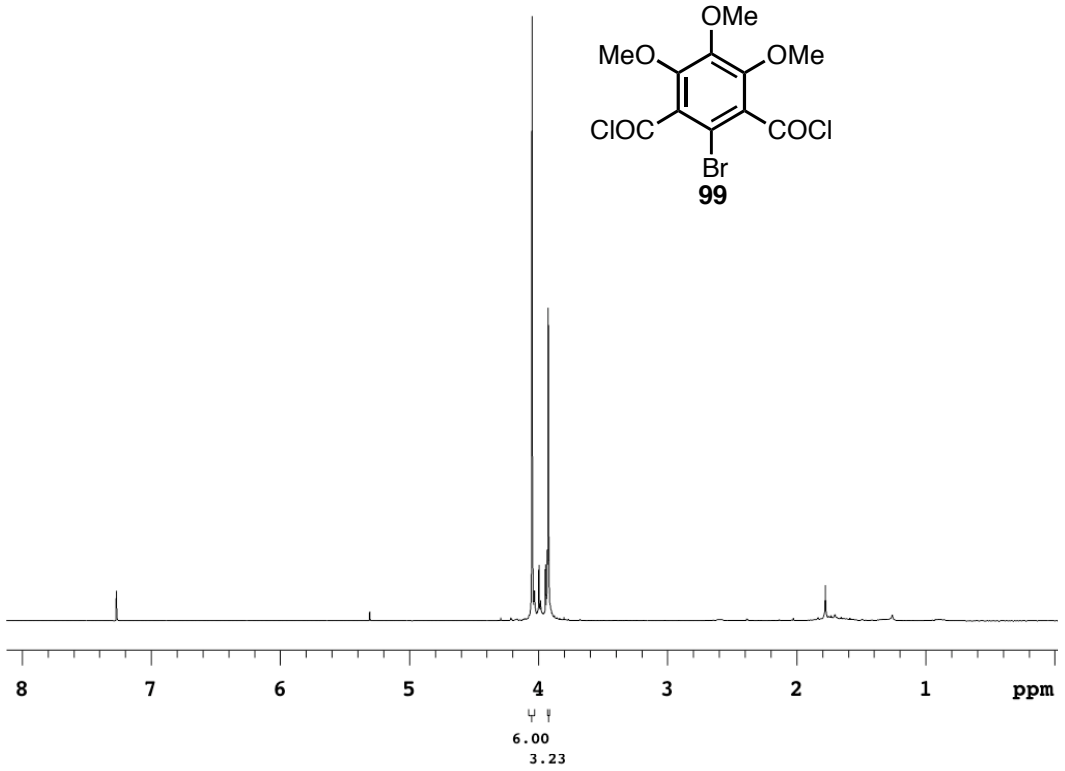


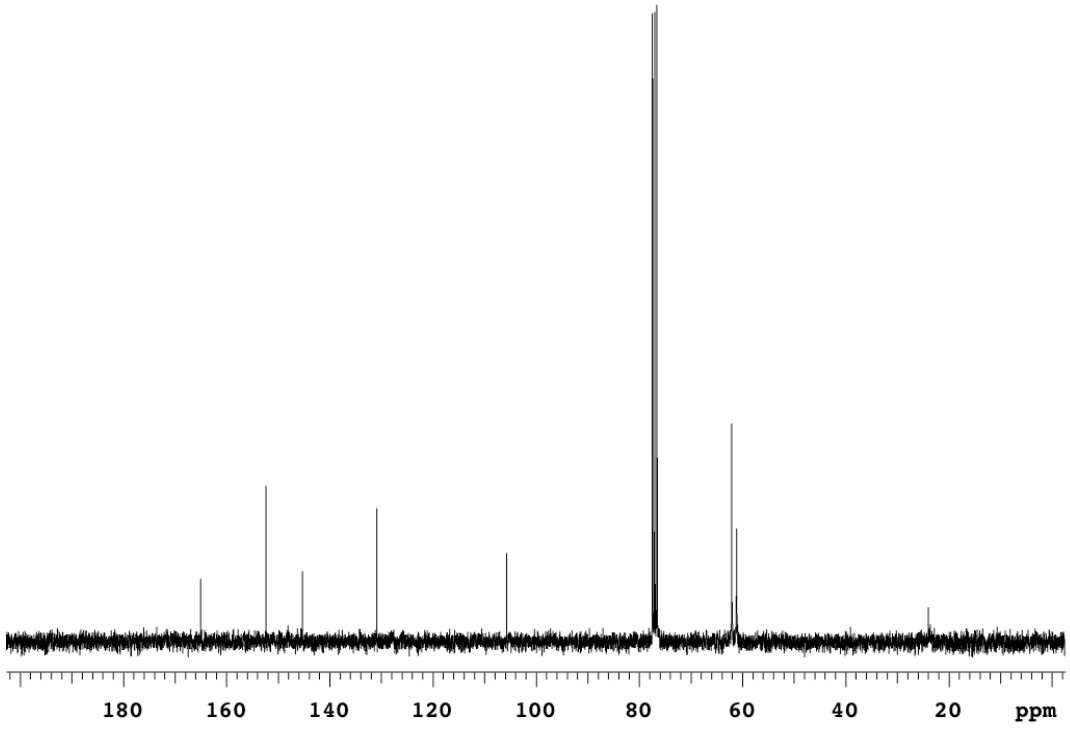
^{13}C NMR ($CDCl_3$, 75 MHz)



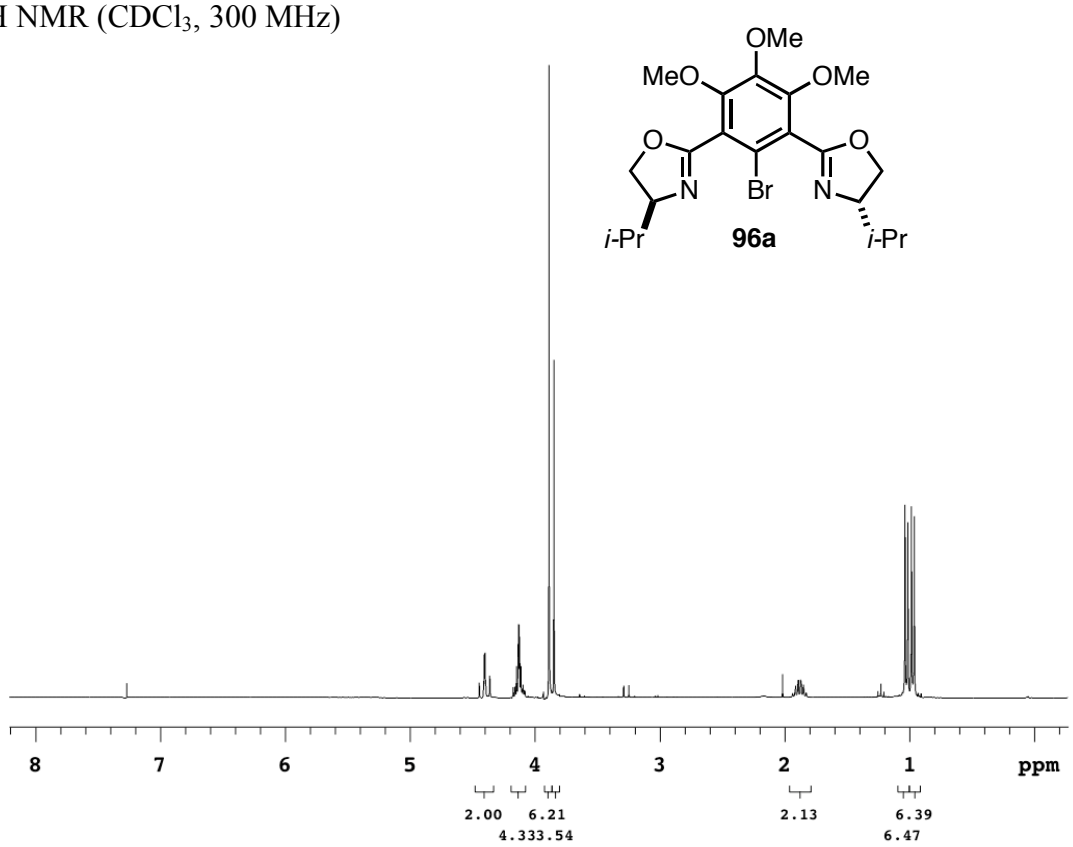
^{1}H NMR ($CDCl_3$, 300 MHz)



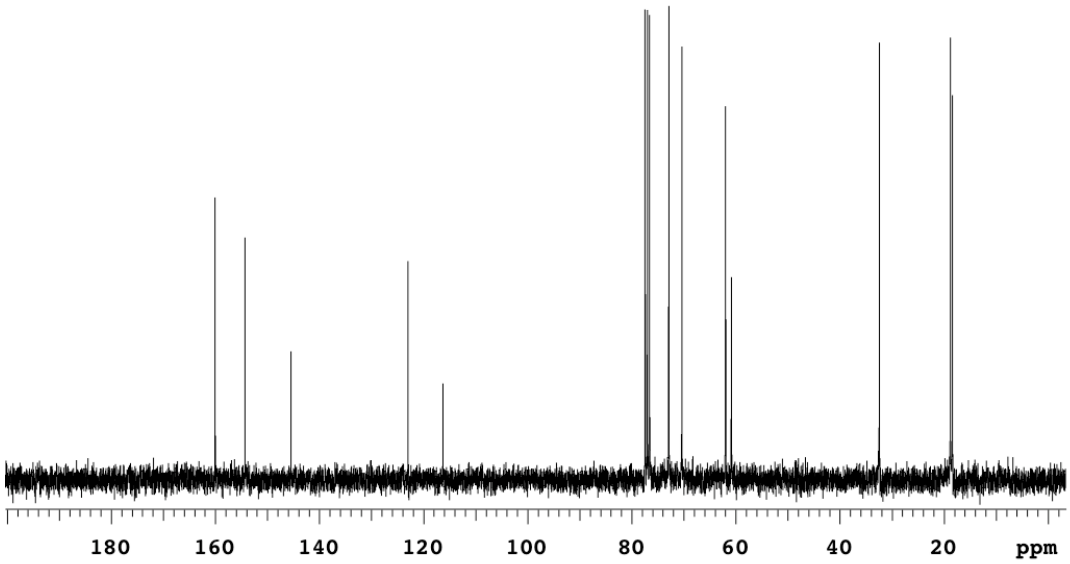
^{13}C NMR ($CDCl_3$, 75 MHz)



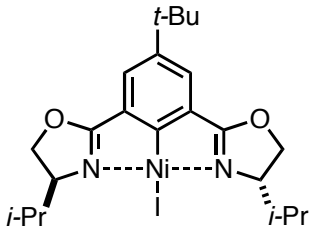
^{1}H NMR ($CDCl_3$, 300 MHz)



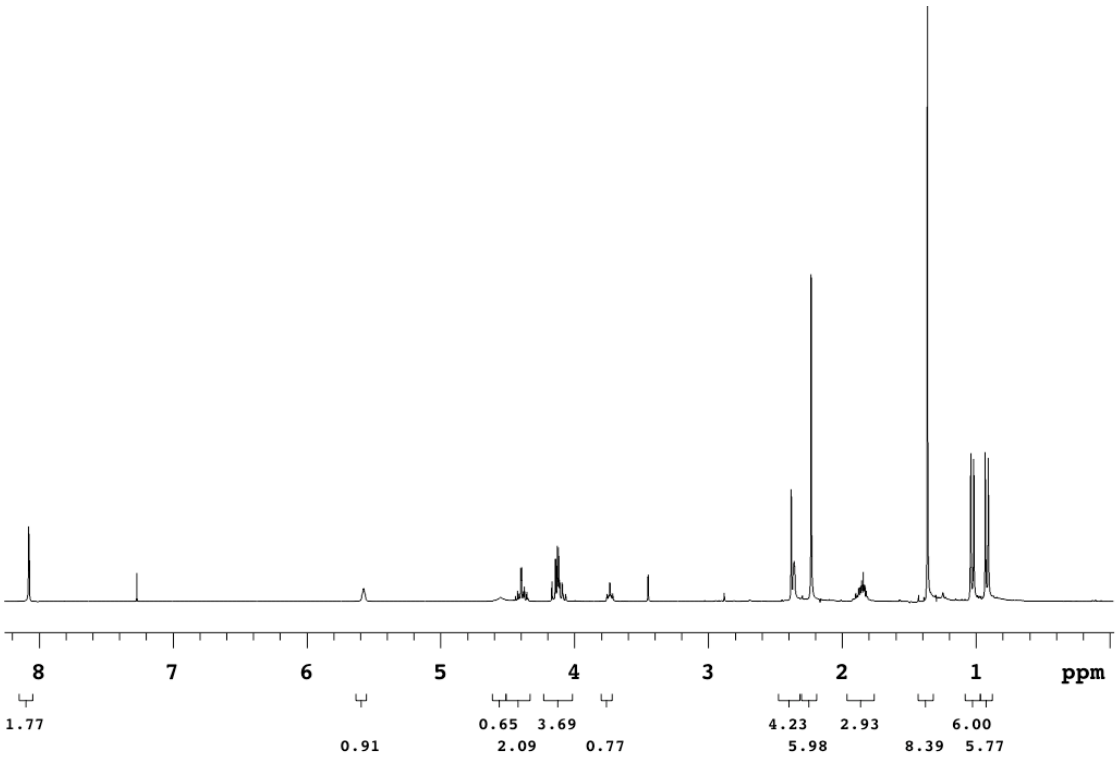
^{13}C NMR ($CDCl_3$, 75 MHz)



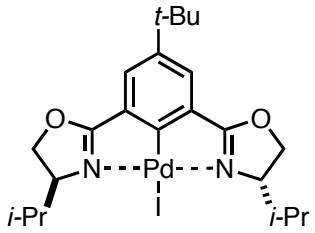
^{1}H NMR ($CDCl_3$, 300 MHz)



103



^{1}H NMR ($CDCl_3$, 300 MHz)



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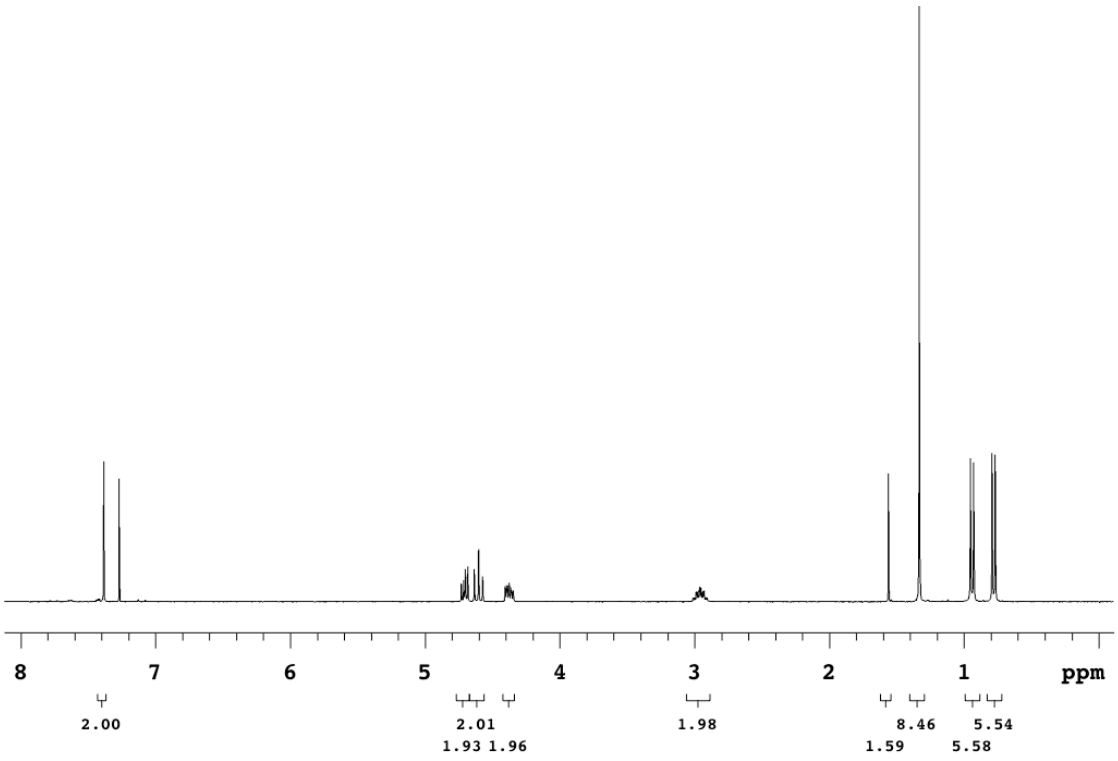
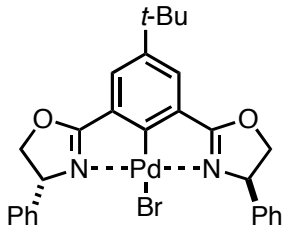


^{1}H NMR ($CDCl_3$, 300 MHz)



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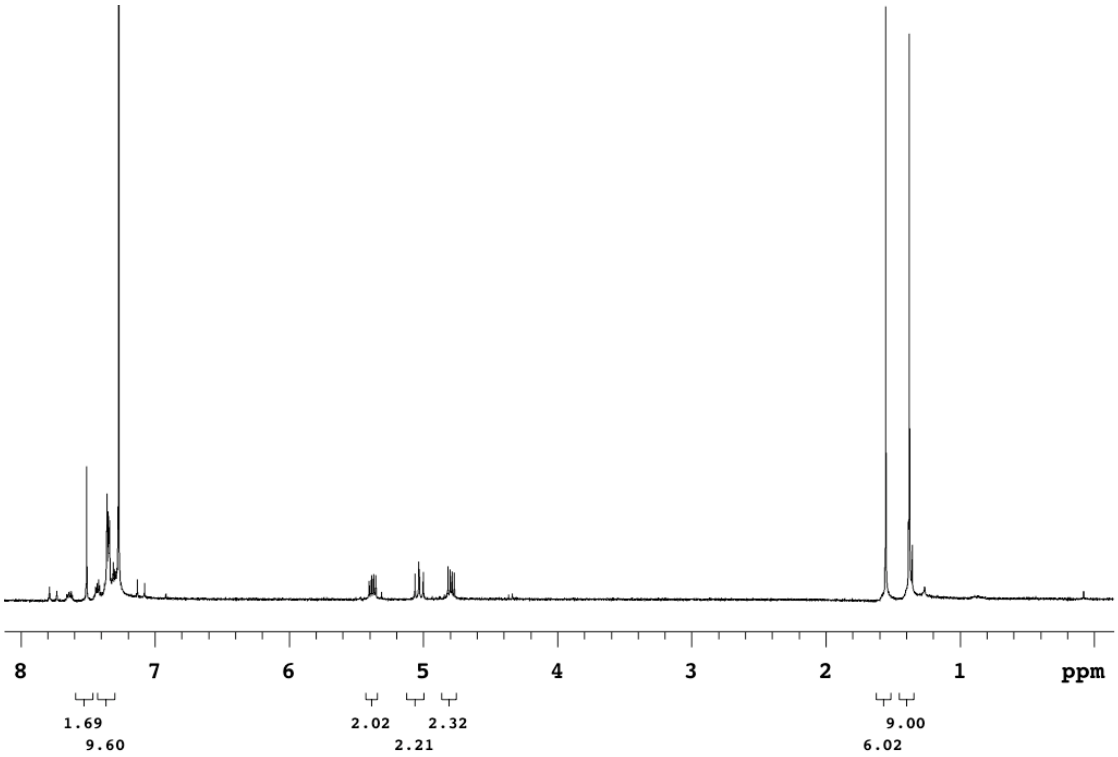
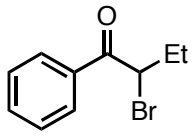


^{1}H and ^{13}C NMR Spectra of α-Bromoketones

^{1}H NMR ($CDCl_3$, 300 MHz)



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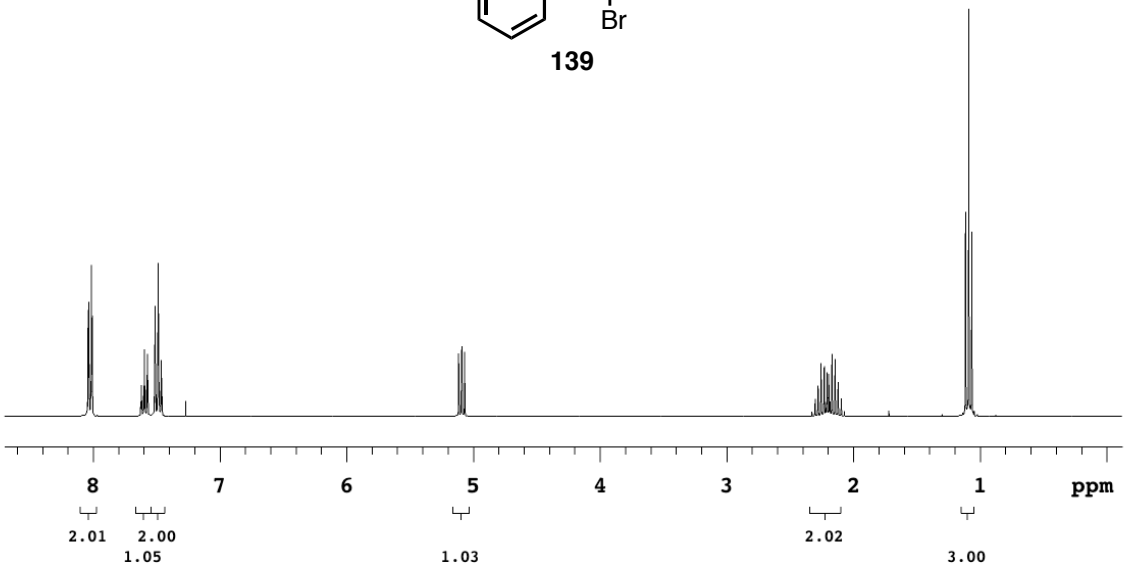
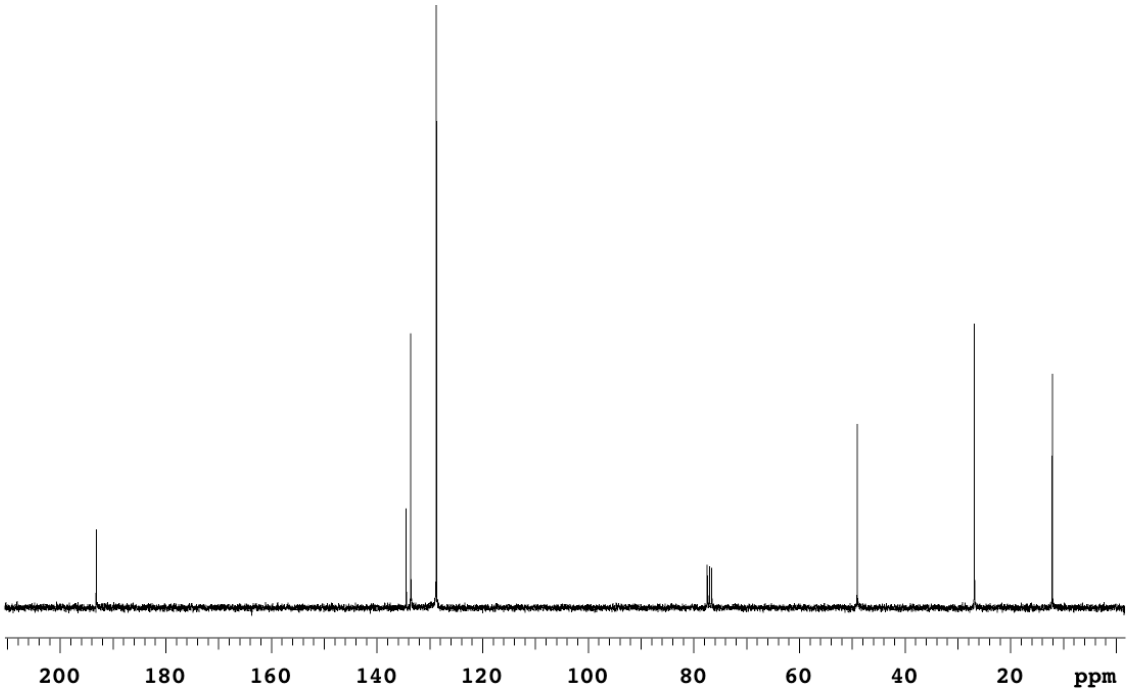
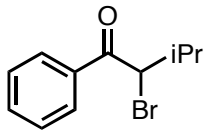


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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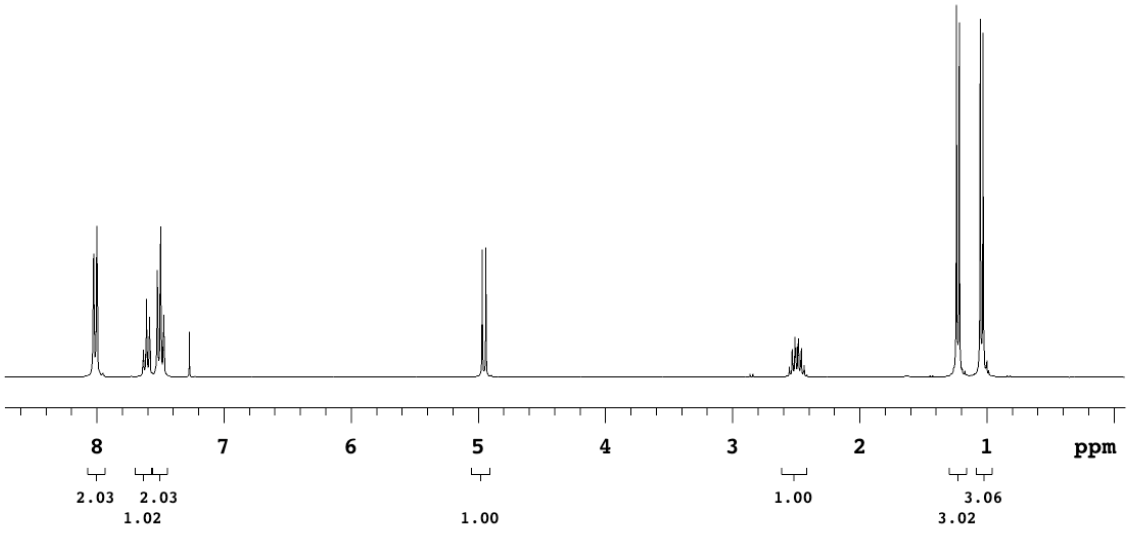
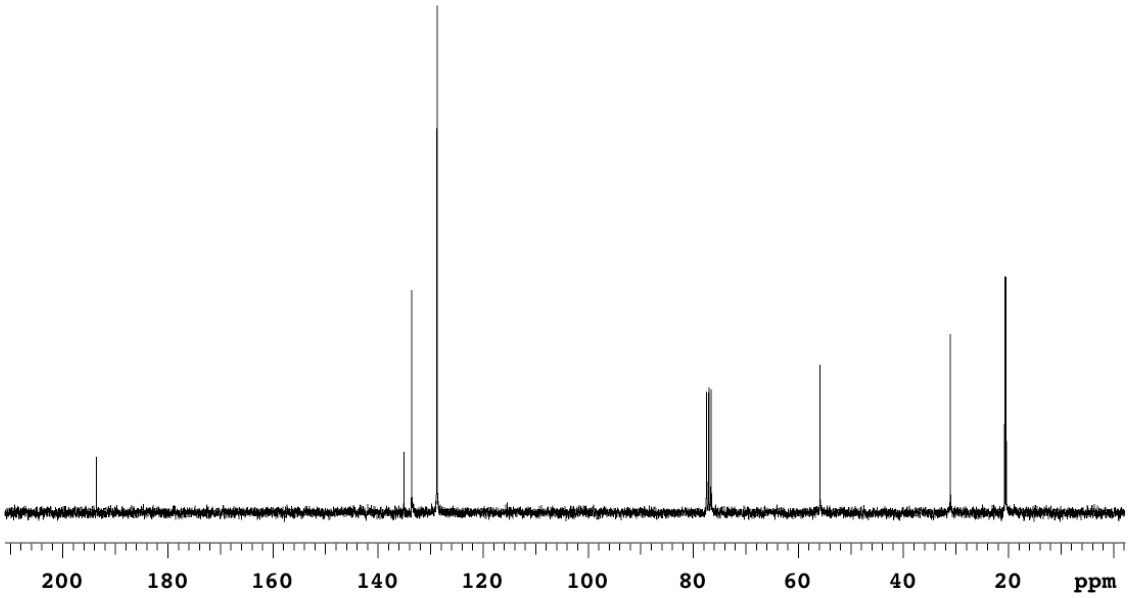
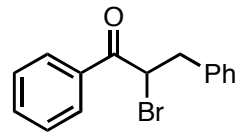


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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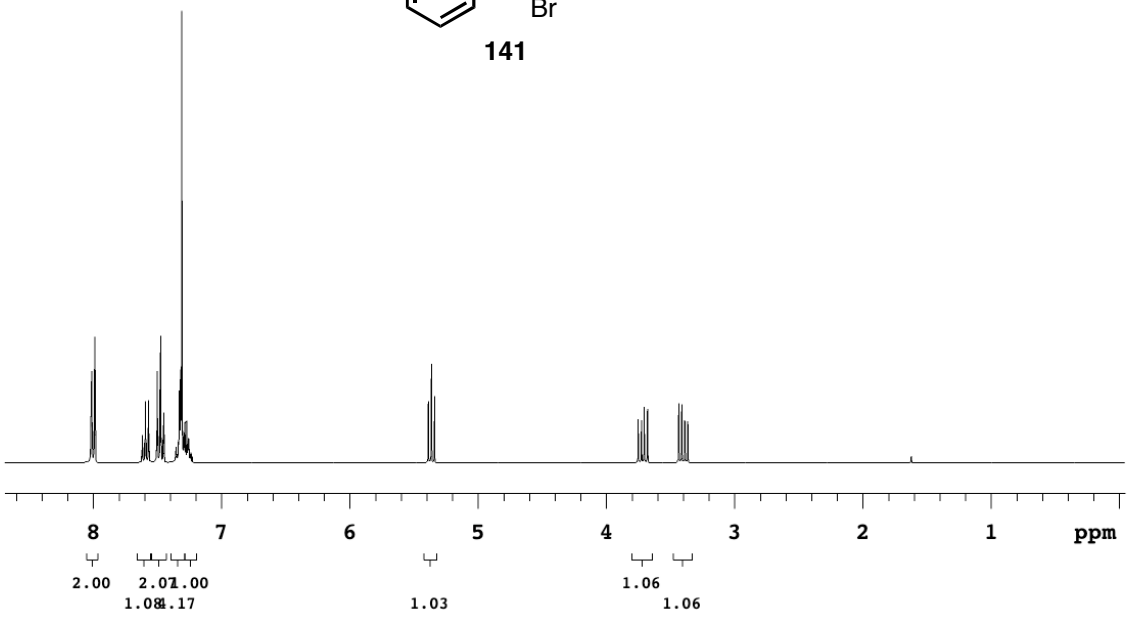
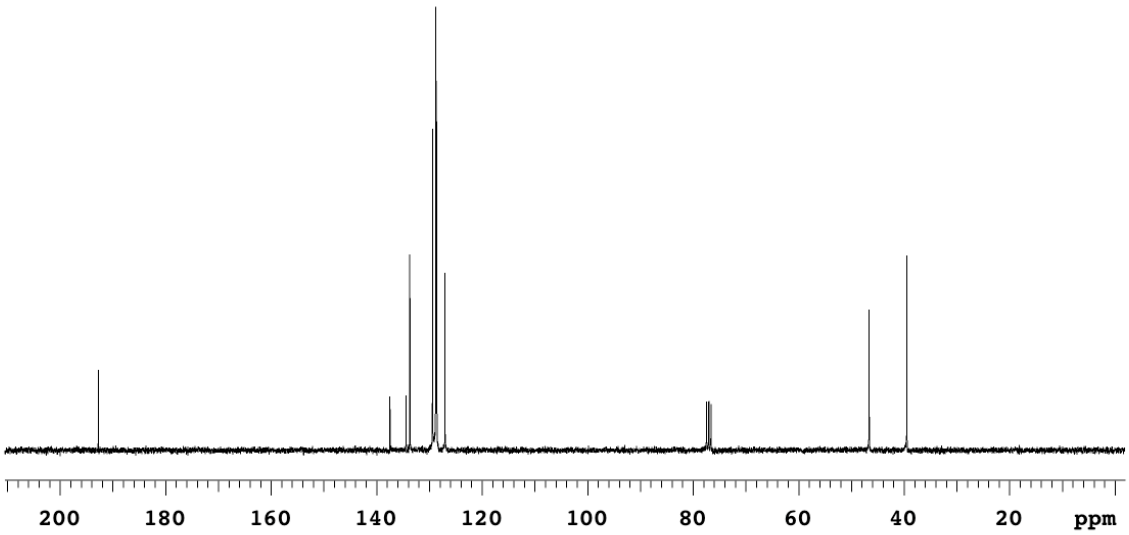
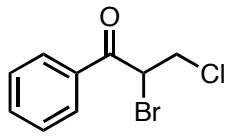


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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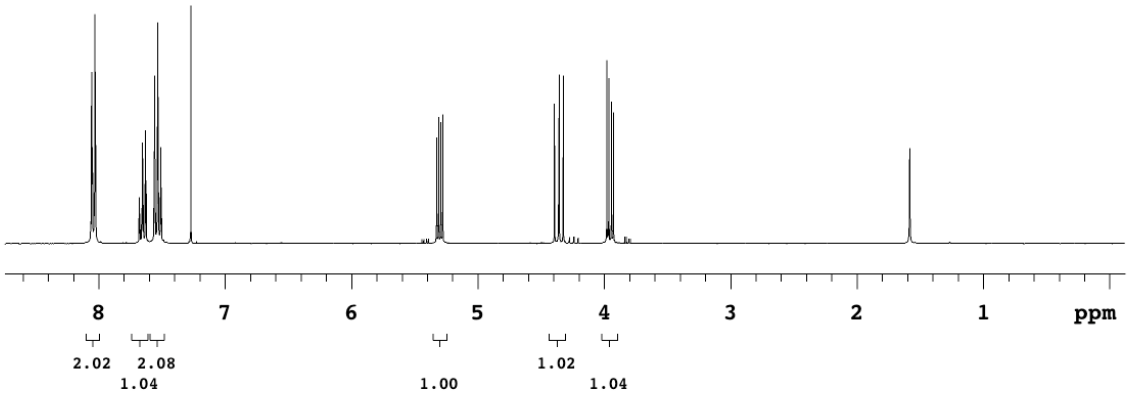
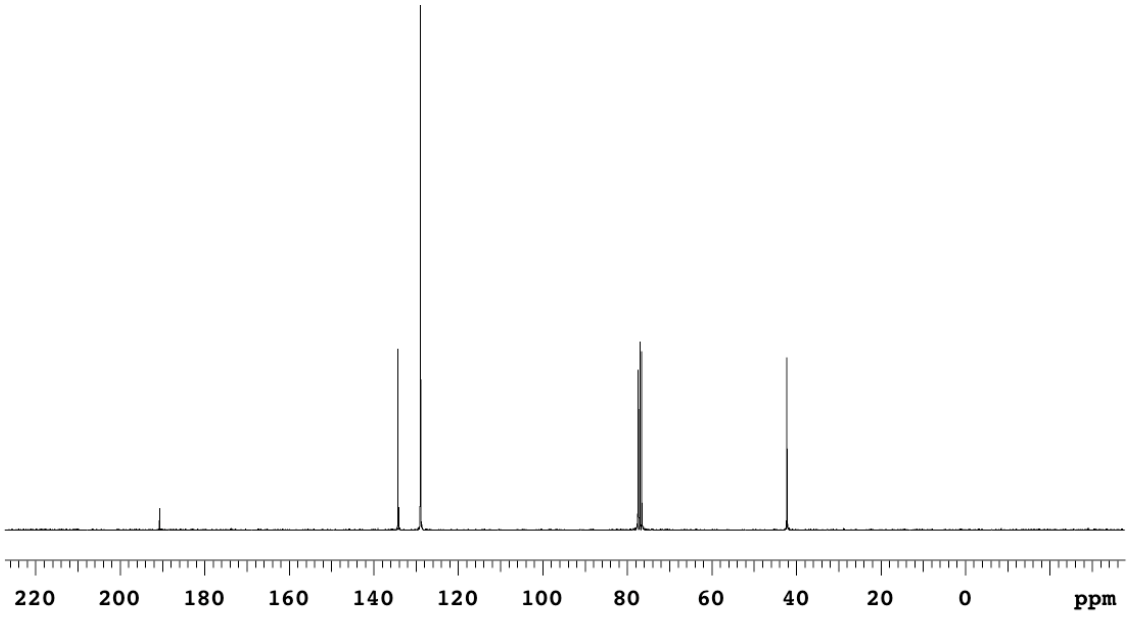
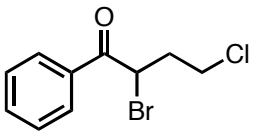


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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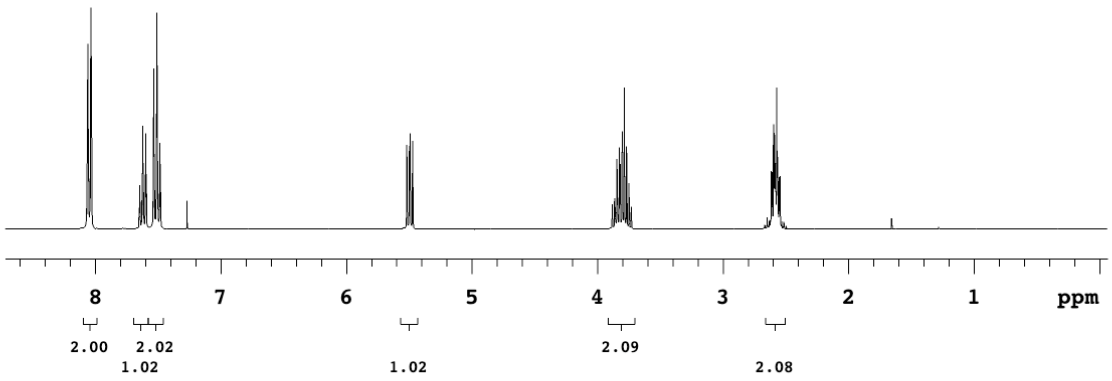
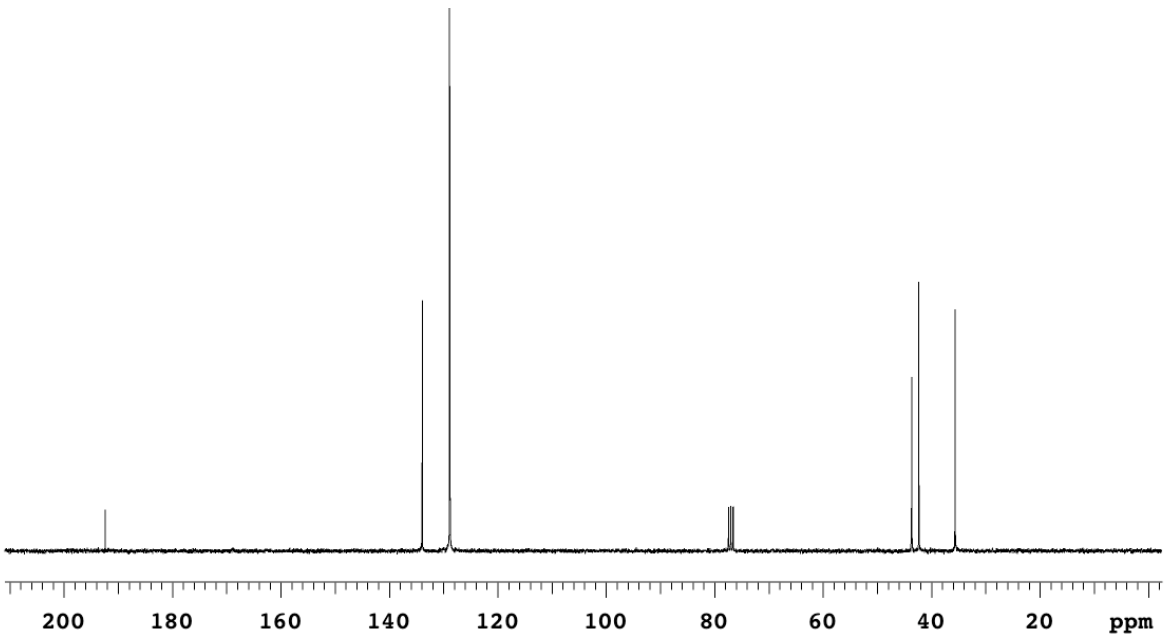
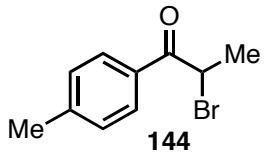


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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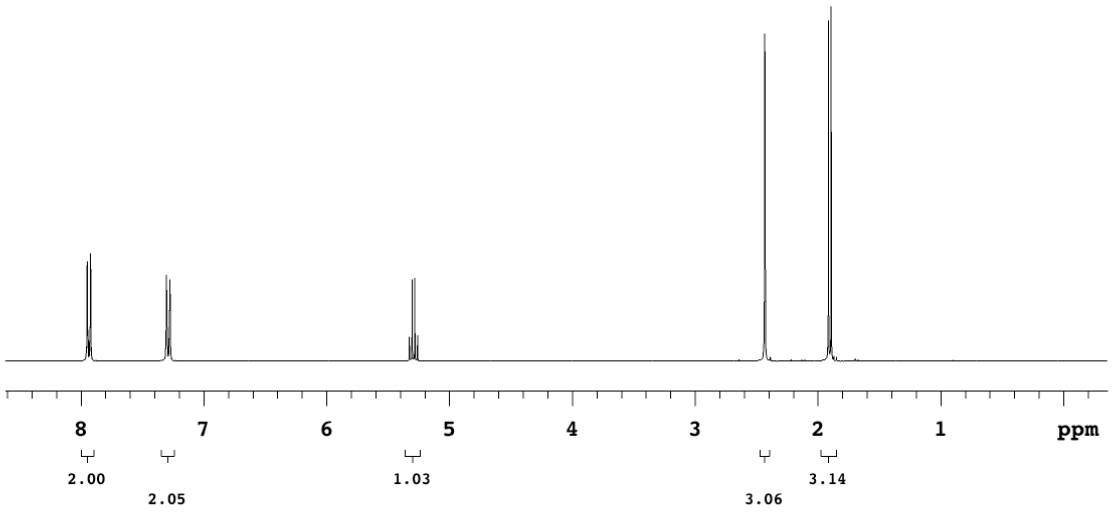
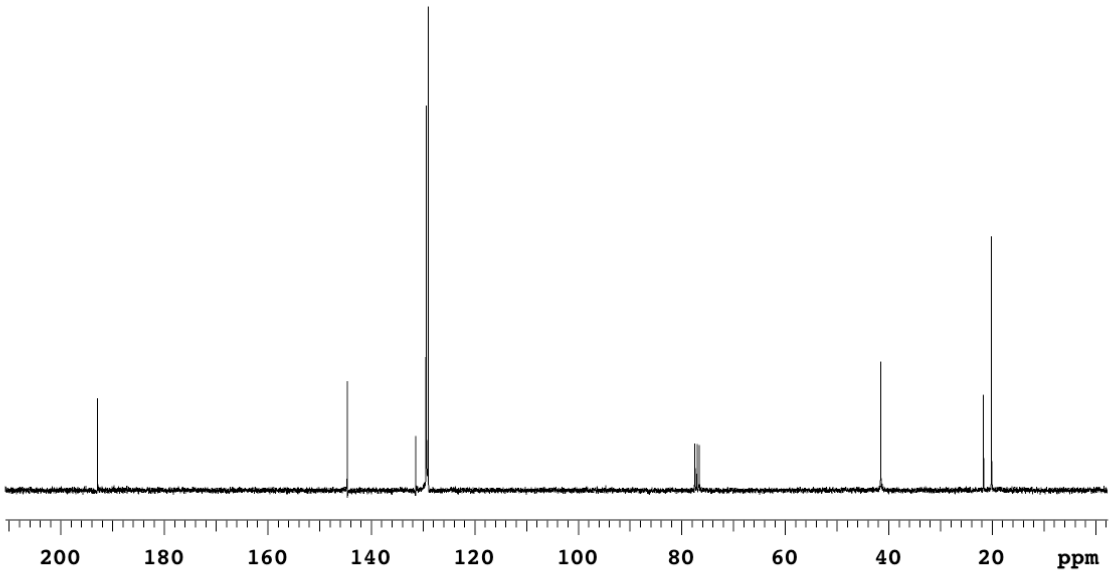
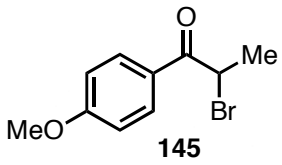


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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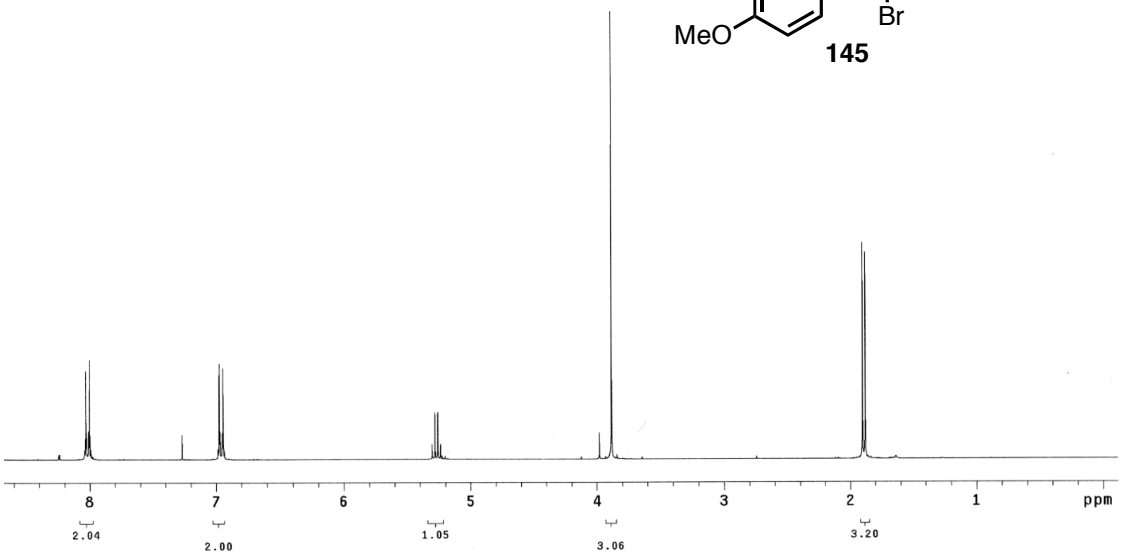
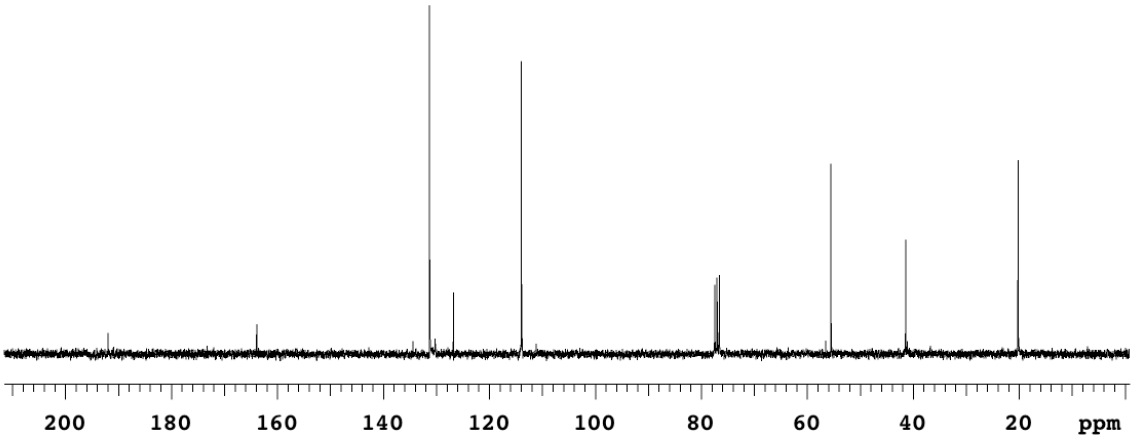
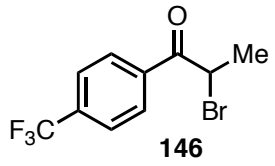


^{13}C NMR ($CDCl_3$, 75 MHz)

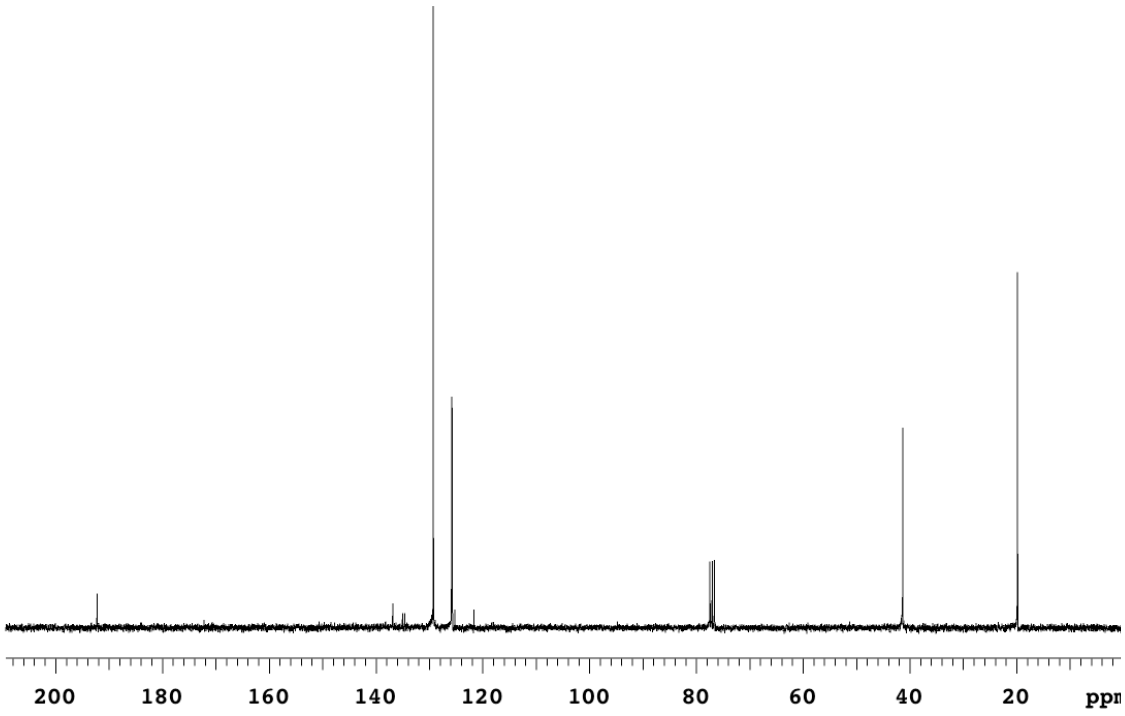


^{1}H NMR ($CDCl_3$, 300 MHz)

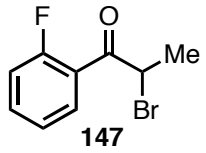


146

^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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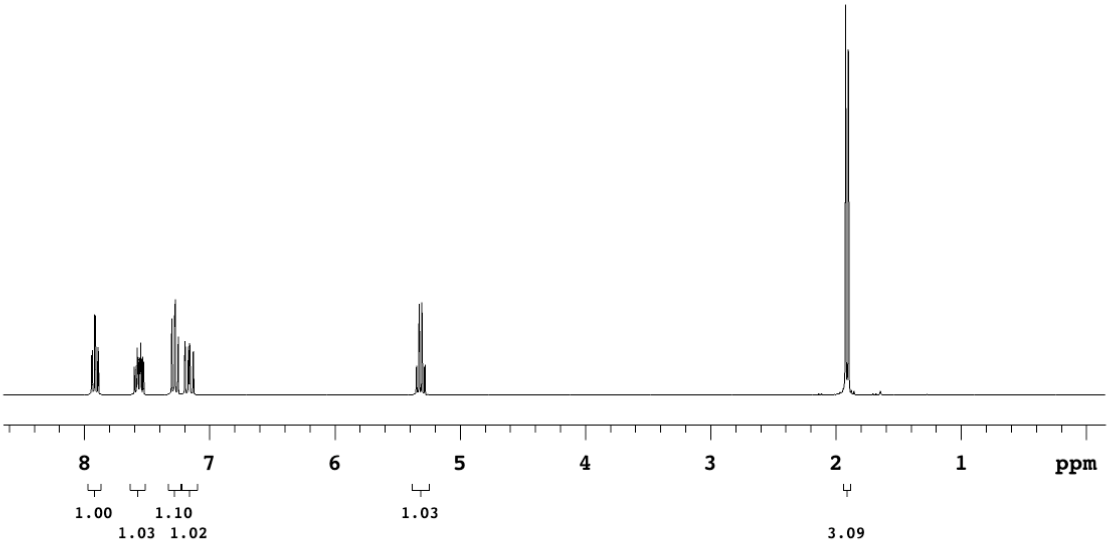
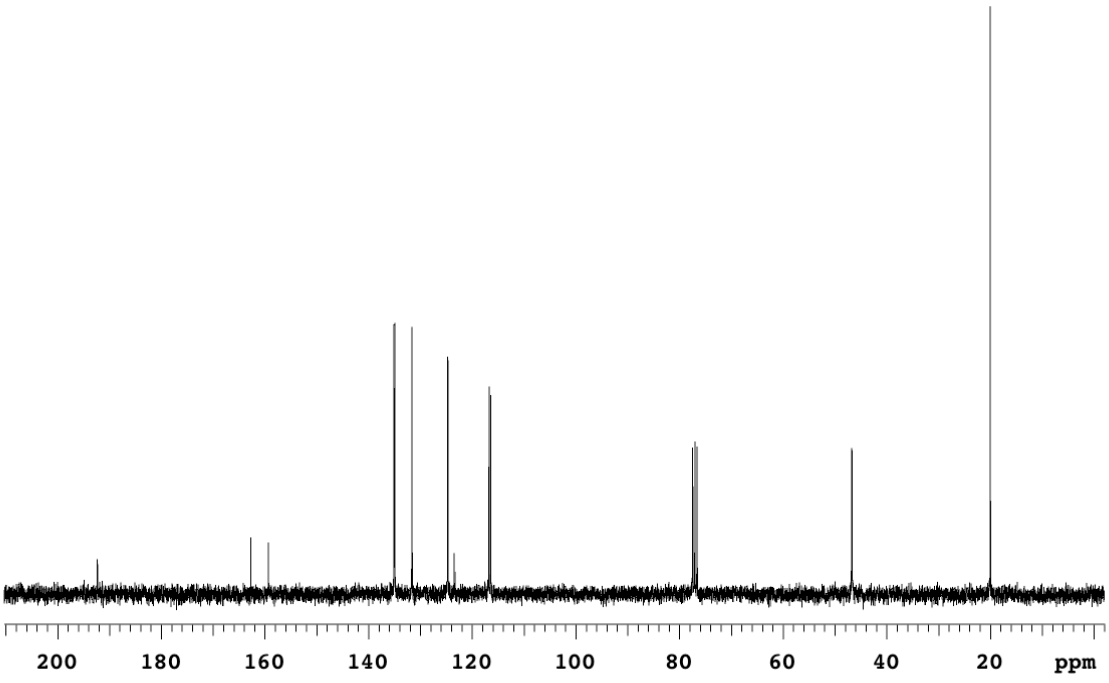
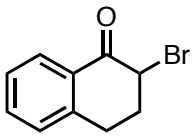


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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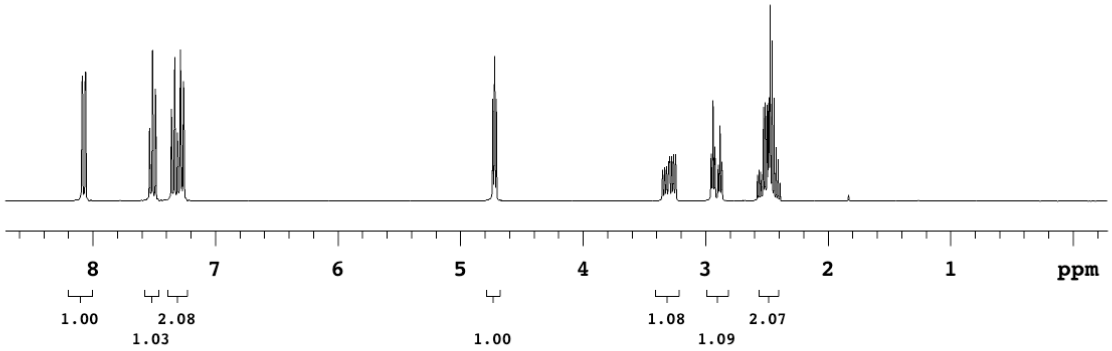
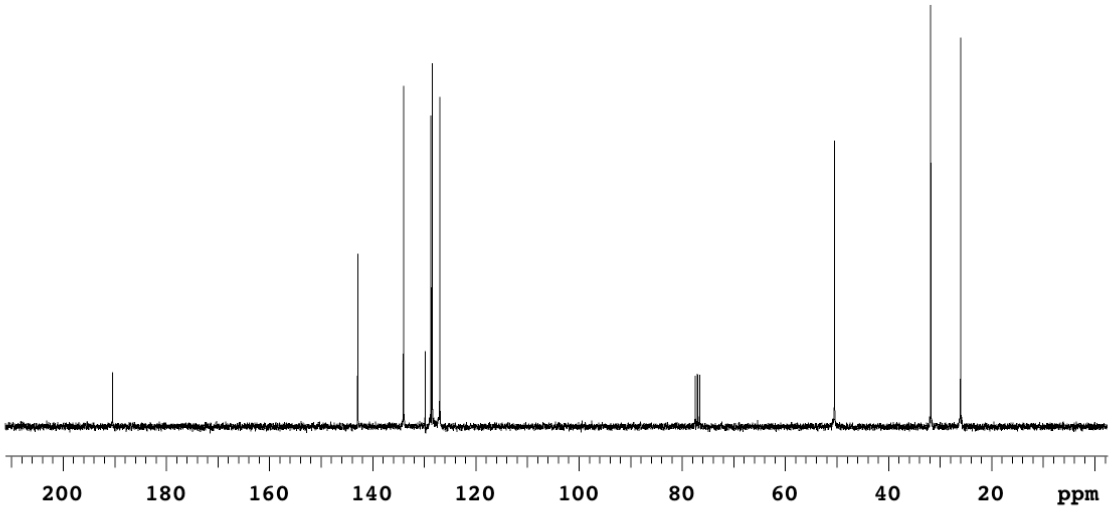
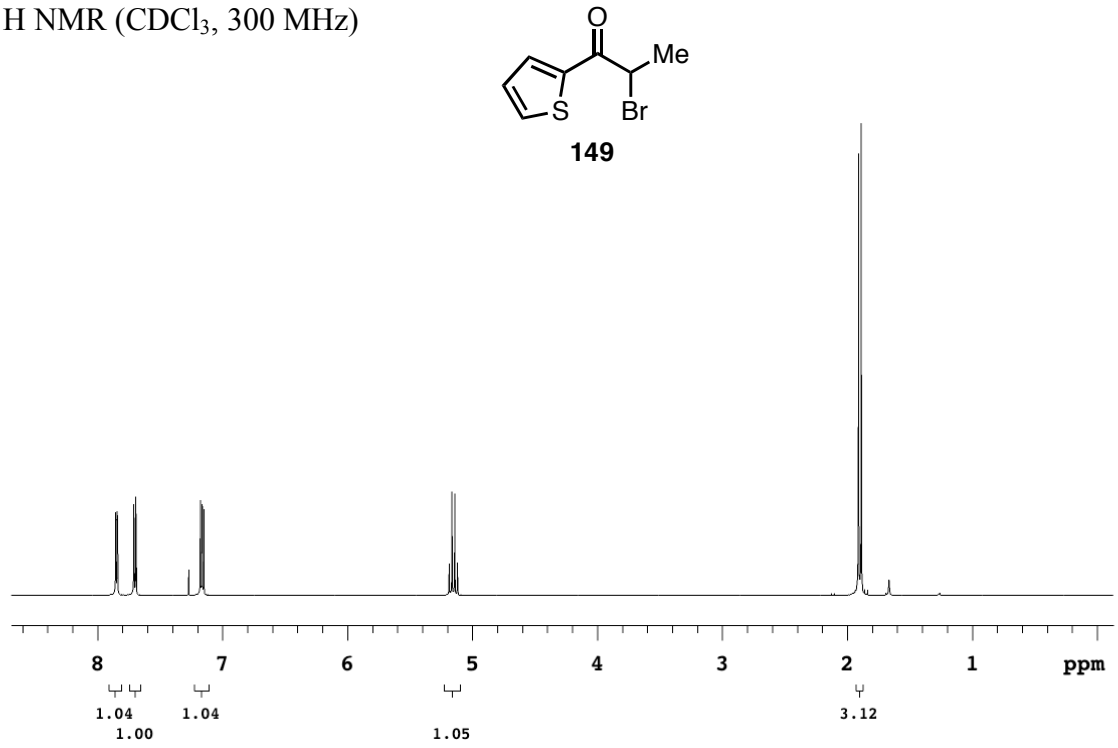


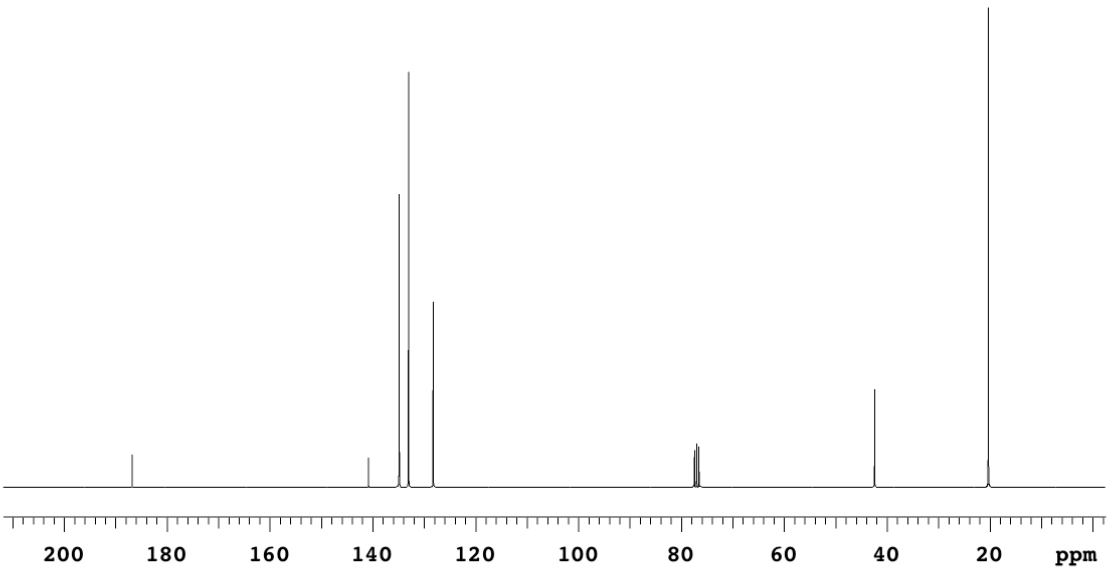
^{13}C NMR ($CDCl_3$, 75 MHz)



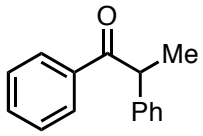
^{1}H NMR ($CDCl_3$, 300 MHz)



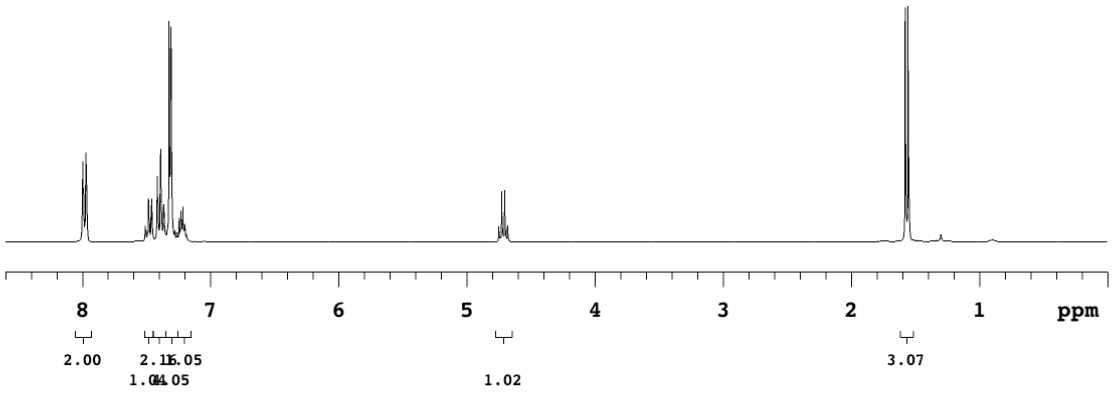
^{13}C NMR ($CDCl_3$, 75 MHz)



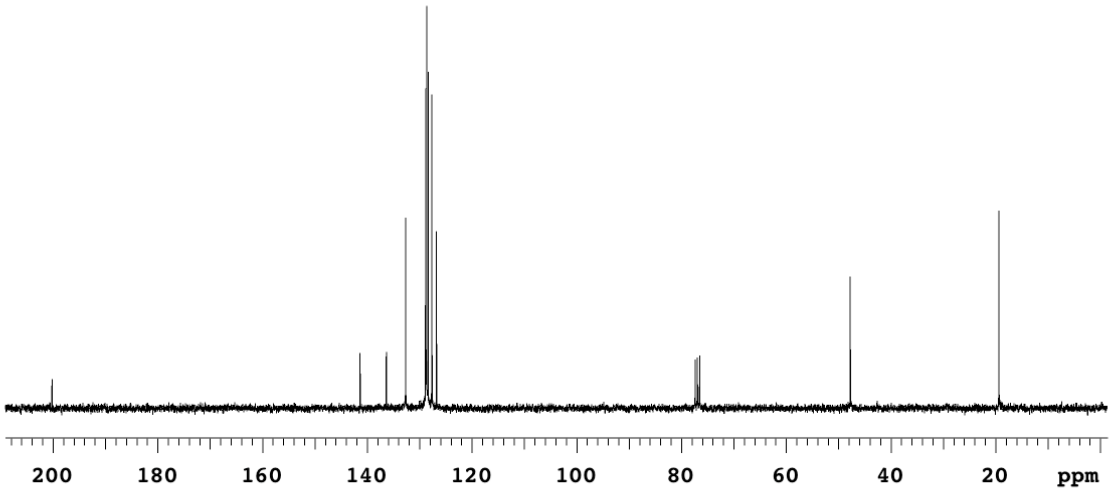
^{1}H NMR ($CDCl_3$, 300 MHz)



138

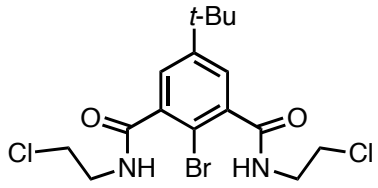


^{13}C NMR ($CDCl_3$, 75 MHz)

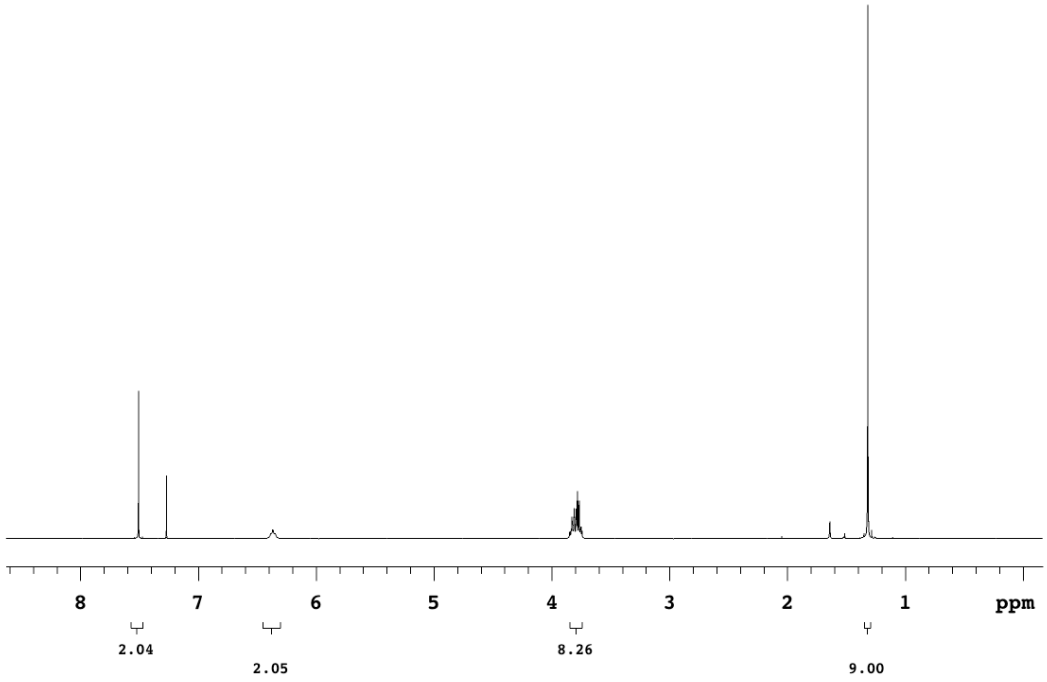


^{1}H and ^{13}C NMR Spectra (α-Arylation)

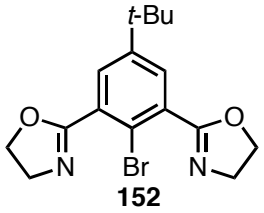
^{1}H NMR ($CDCl_3$, 300 MHz)



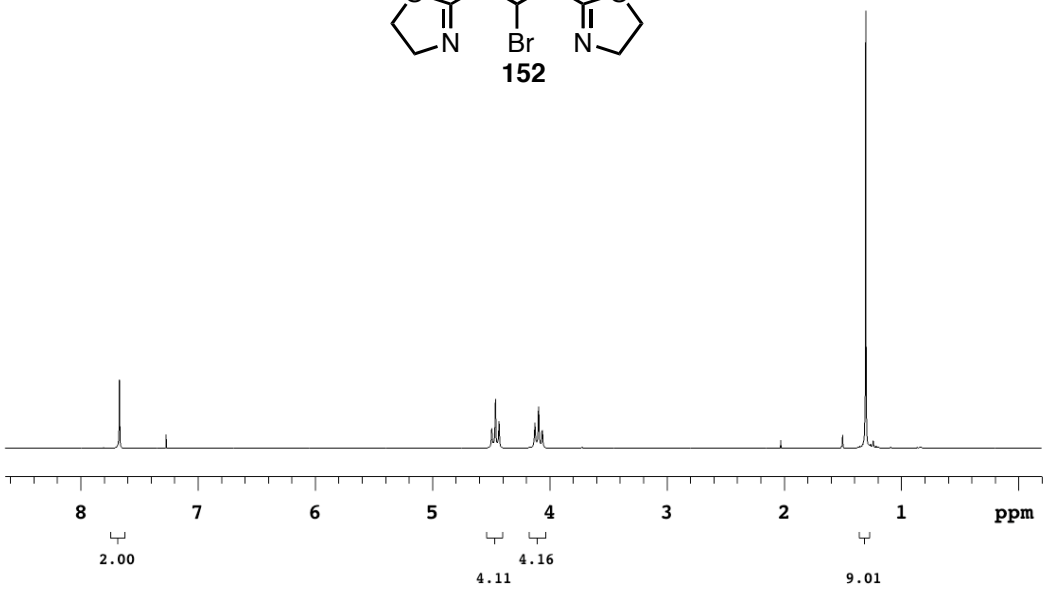
E-17



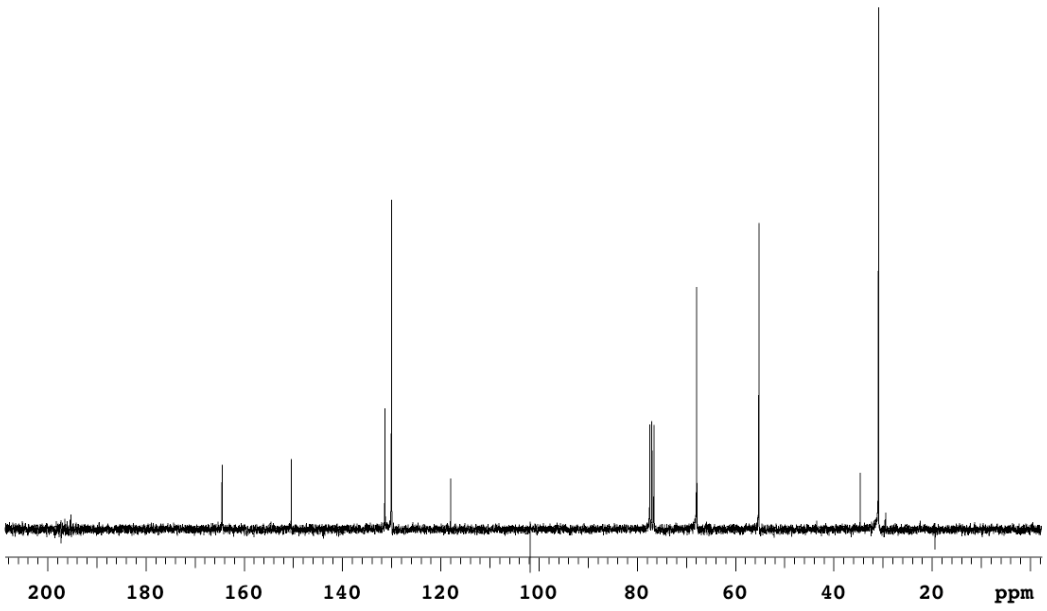
^{1}H NMR ($CDCl_3$, 300 MHz)



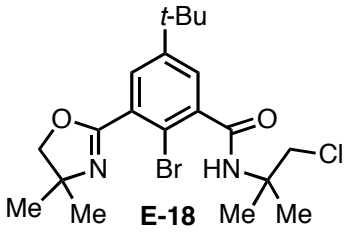
152



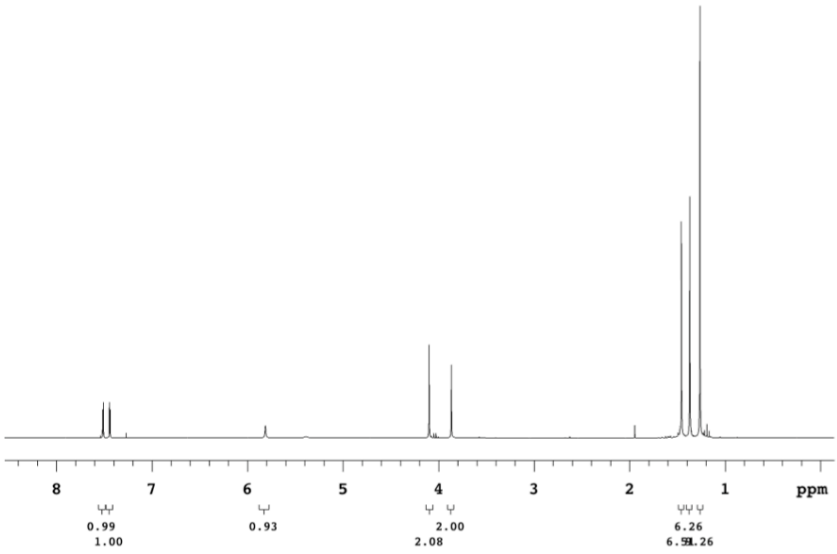
^{13}C NMR ($CDCl_3$, 75 MHz)



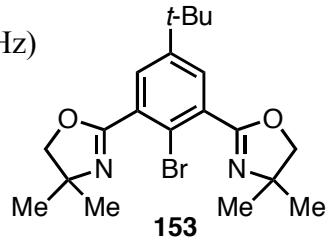
^{1}H NMR ($CDCl_3$, 300 MHz)



E-18

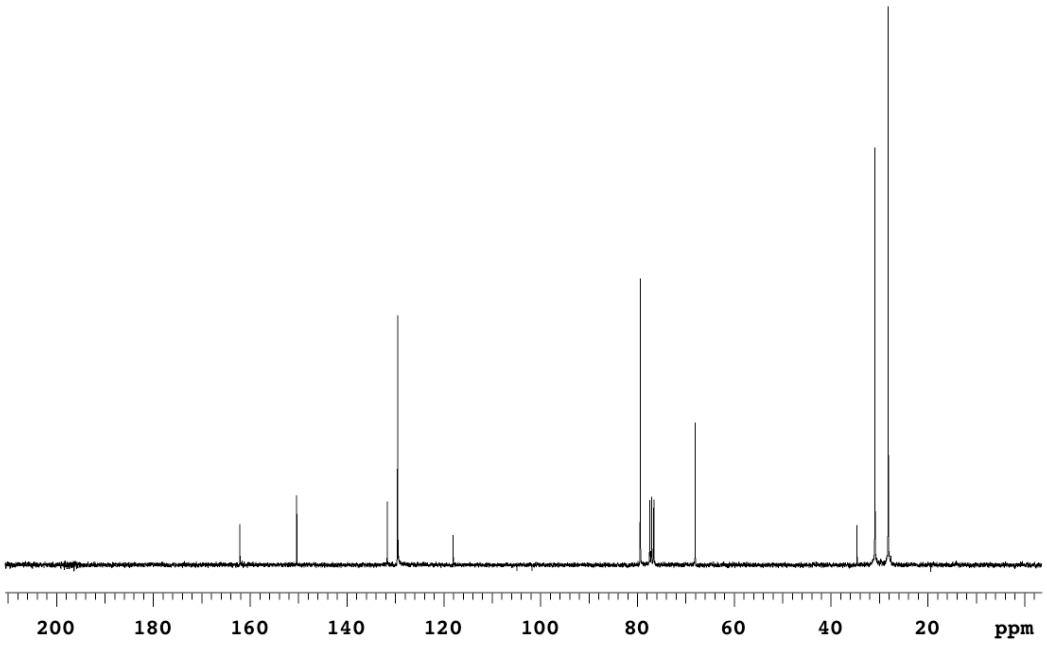


^{1}H NMR ($CDCl_3$, 300 MHz)

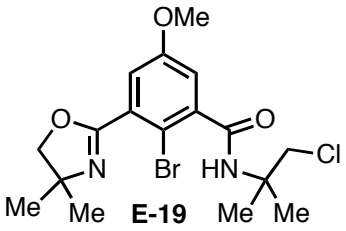


153

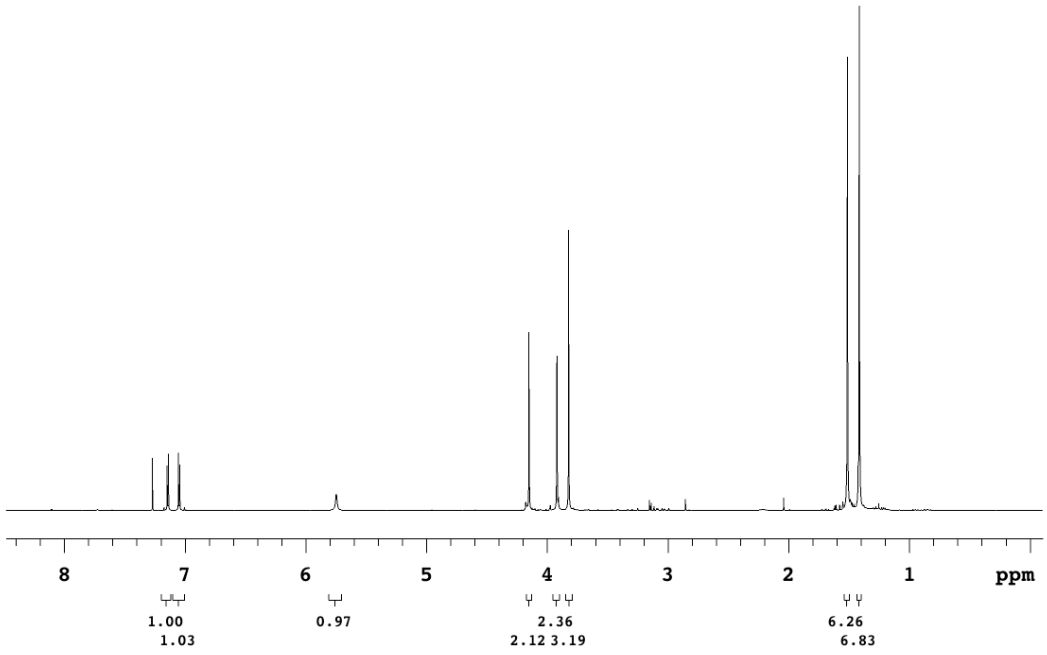
^{13}C NMR ($CDCl_3$, 75 MHz)



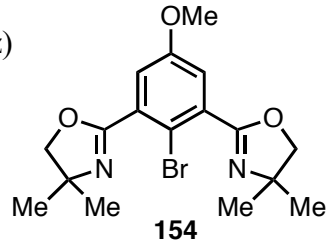
^{1}H NMR ($CDCl_3$, 300 MHz)



E-19

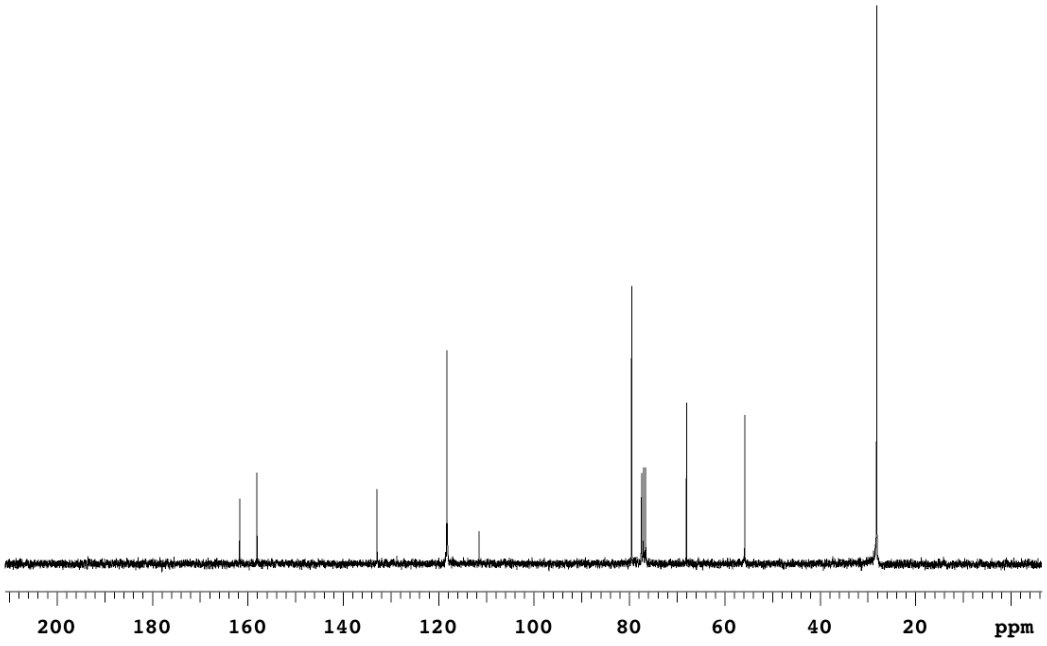


^{1}H NMR ($CDCl_3$, 300 MHz)

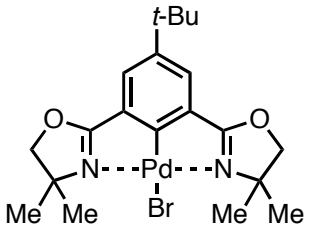


154

^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



XVI

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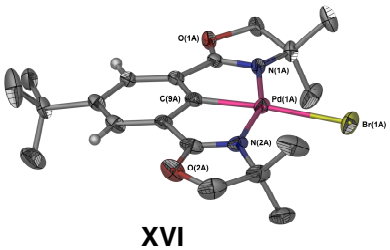
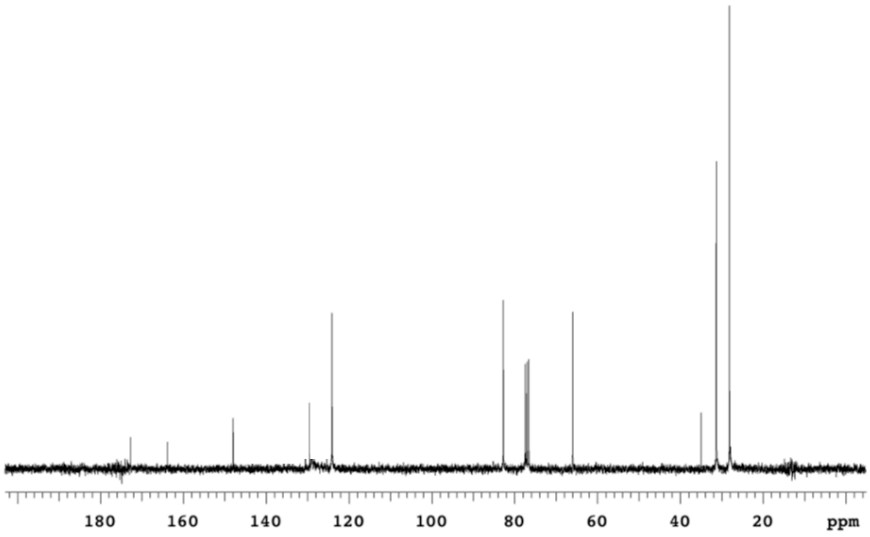
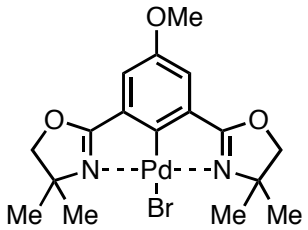


XVI

^{13}C NMR ($CDCl_3$, 75 MHz)

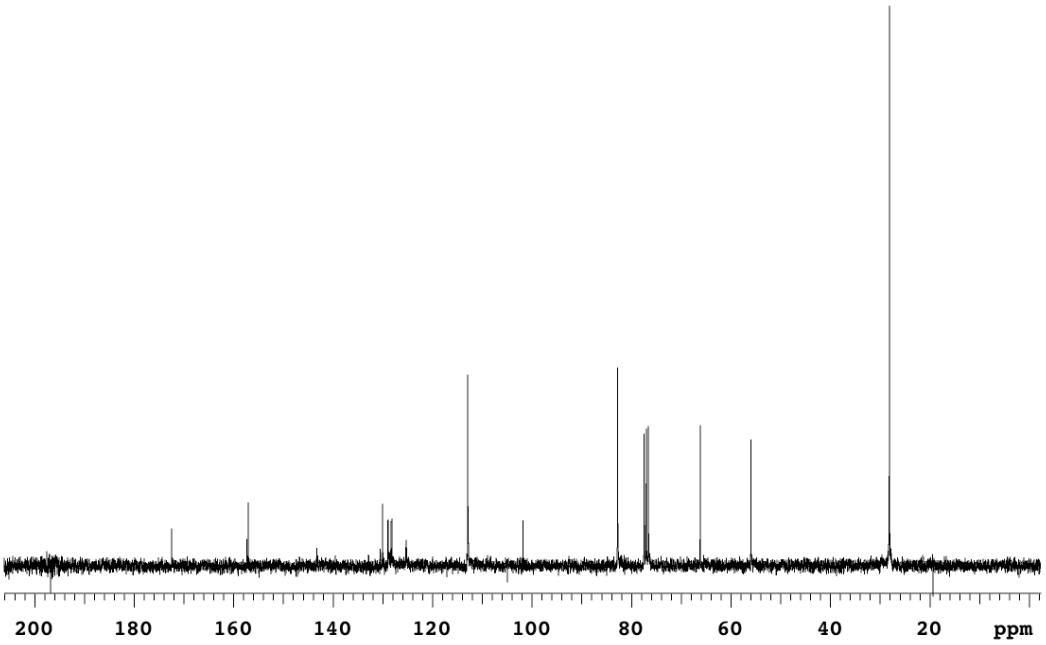


^{1}H NMR ($CDCl_3$, 300 MHz)



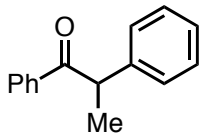
XVII

^{13}C NMR ($CDCl_3$, 75 MHz)

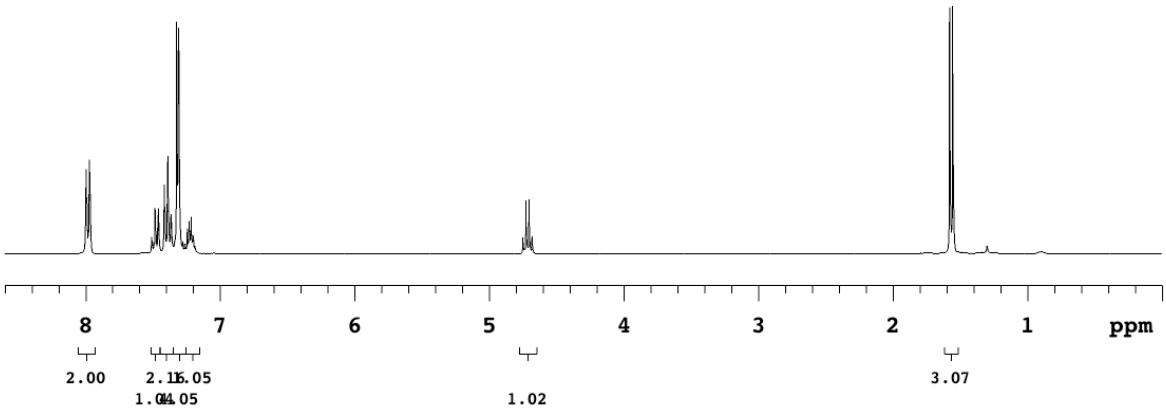


^{1}H and ^{13}C NMR Spectra

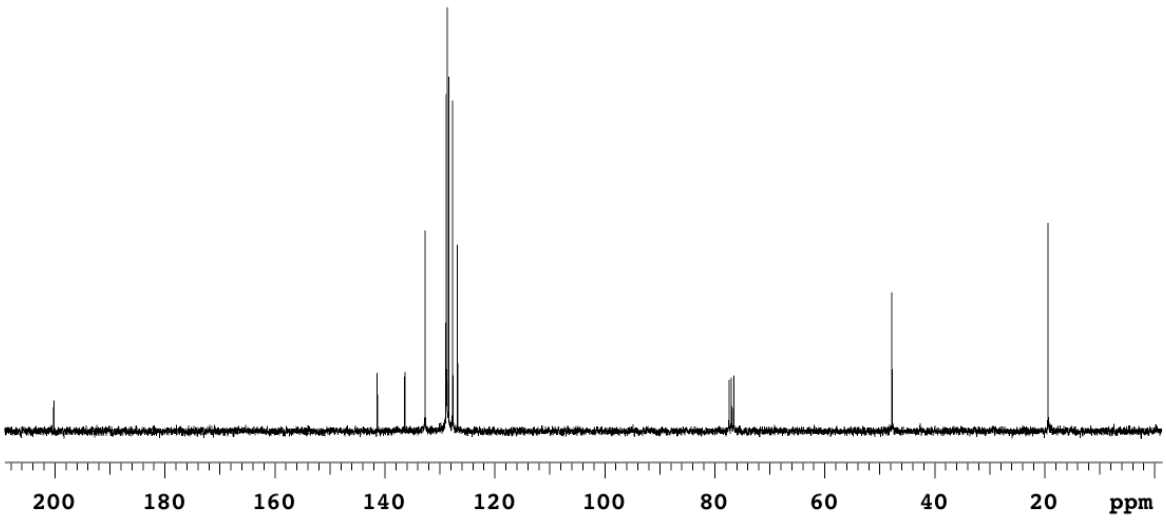
^{1}H NMR ($CDCl_3$, 300 MHz)



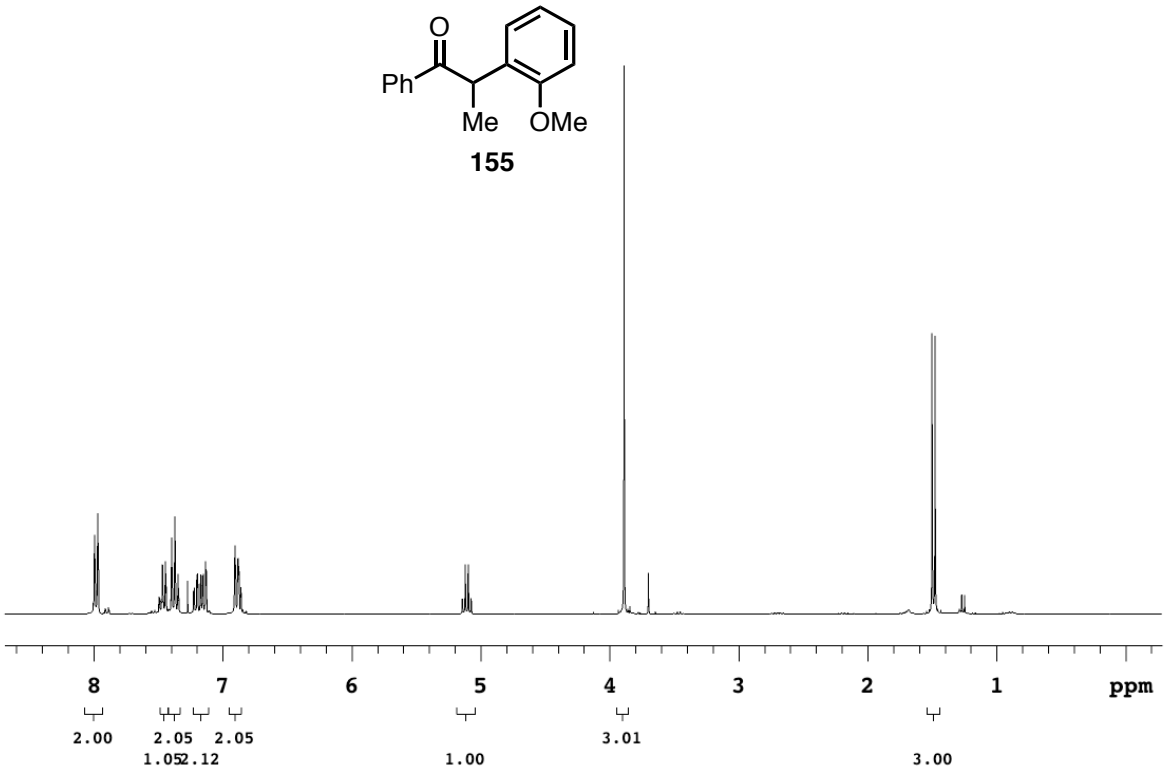
138



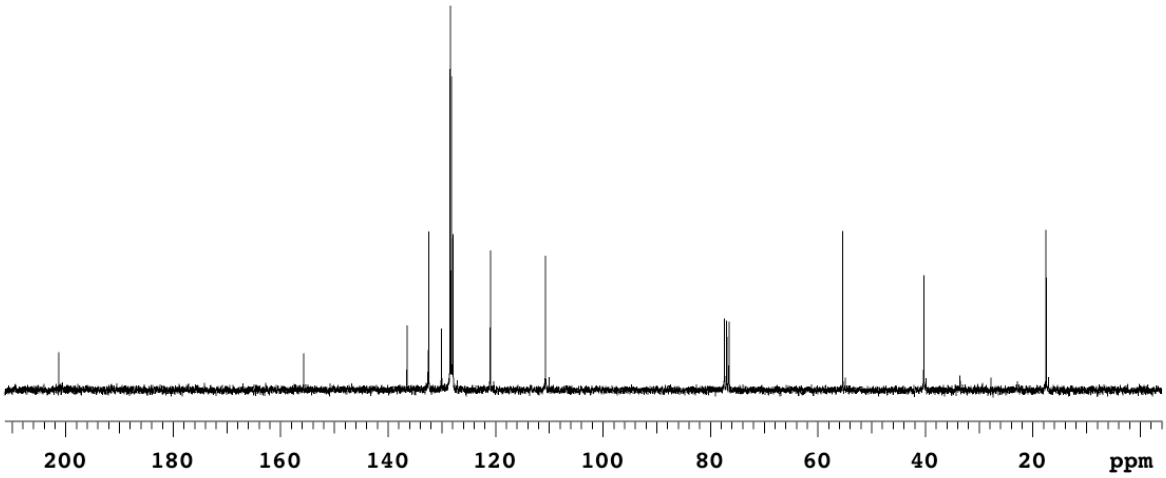
^{13}C NMR ($CDCl_3$, 75 MHz)



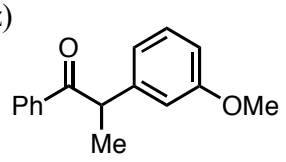
^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)

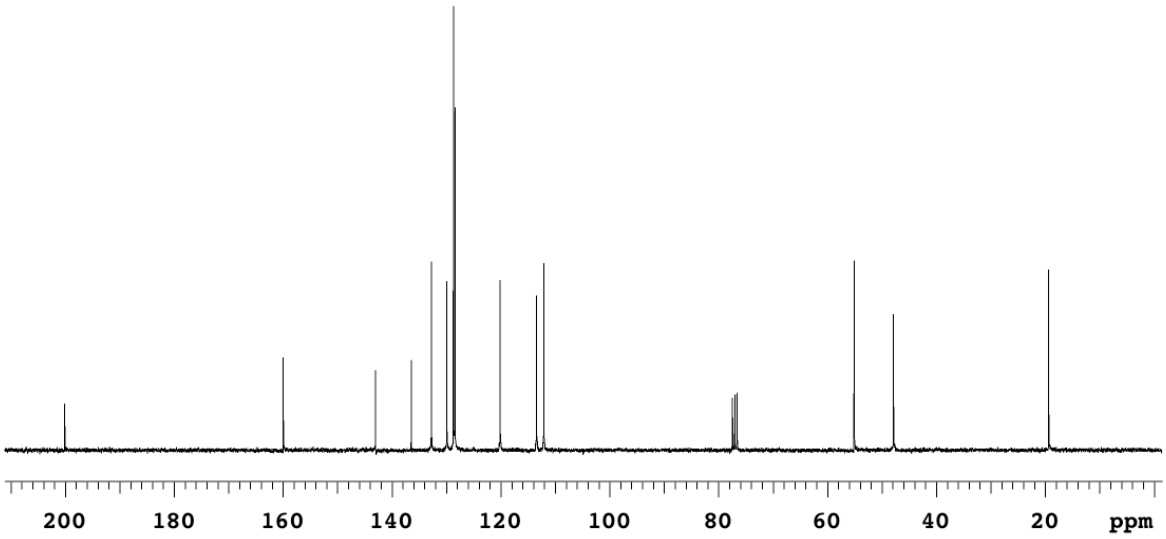


^{1}H NMR ($CDCl_3$, 300 MHz)

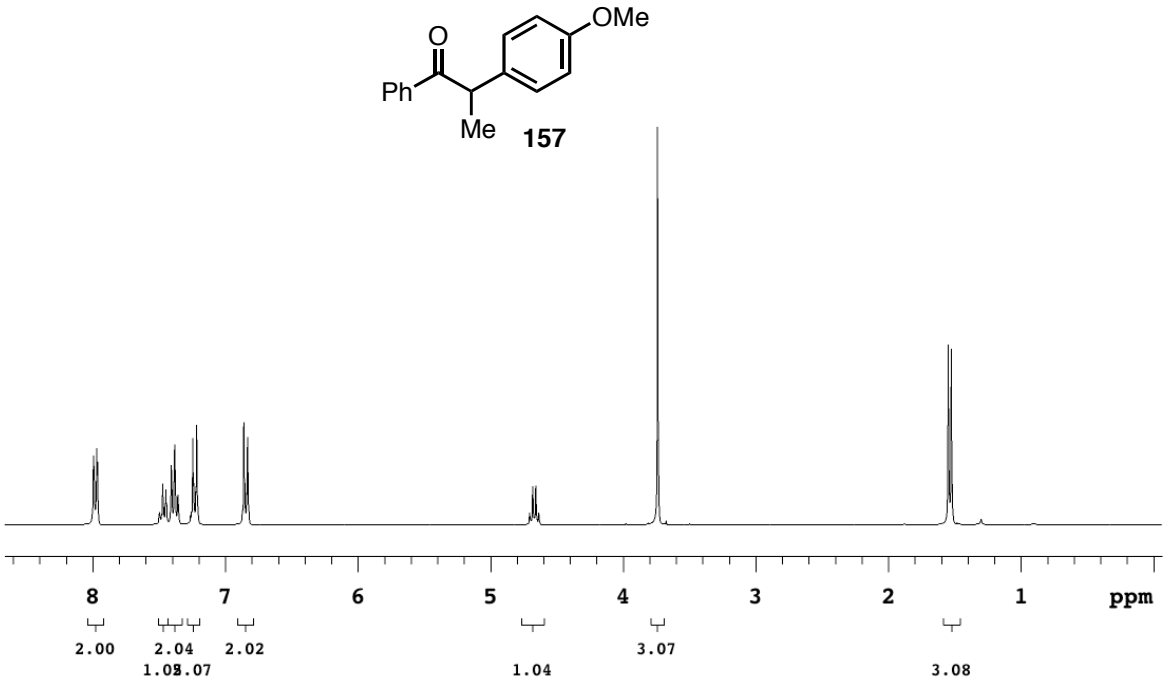


156

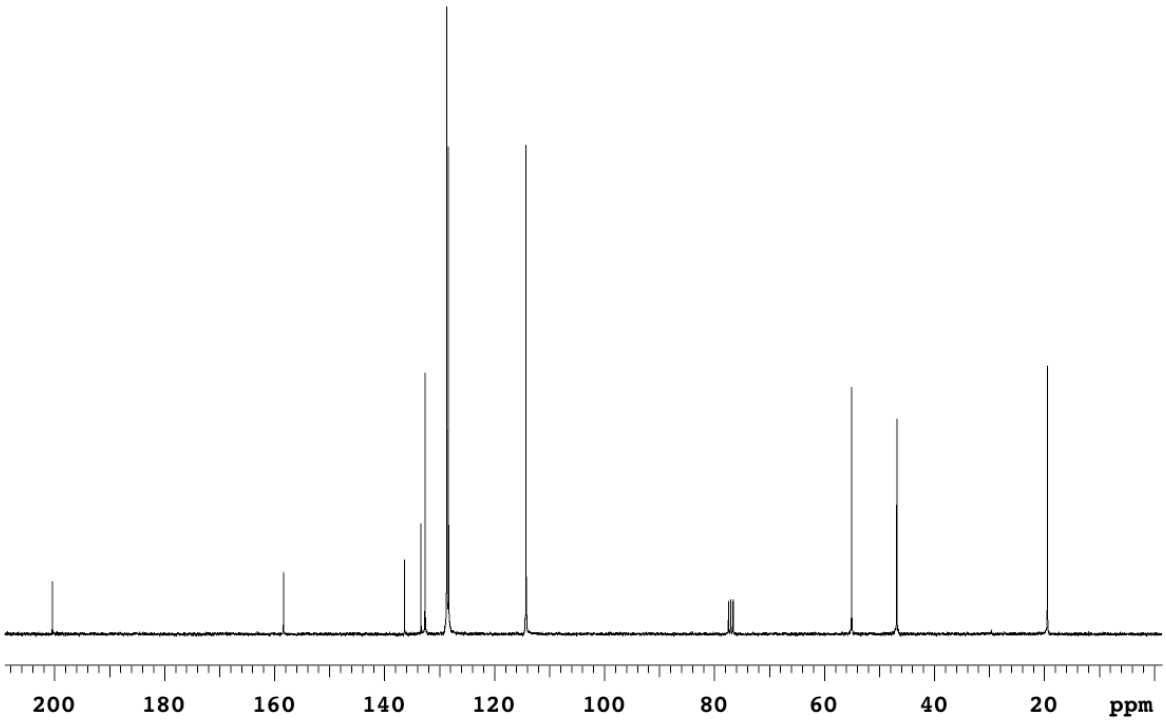
^{13}C NMR ($CDCl_3$, 75 MHz)



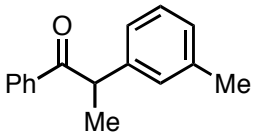
^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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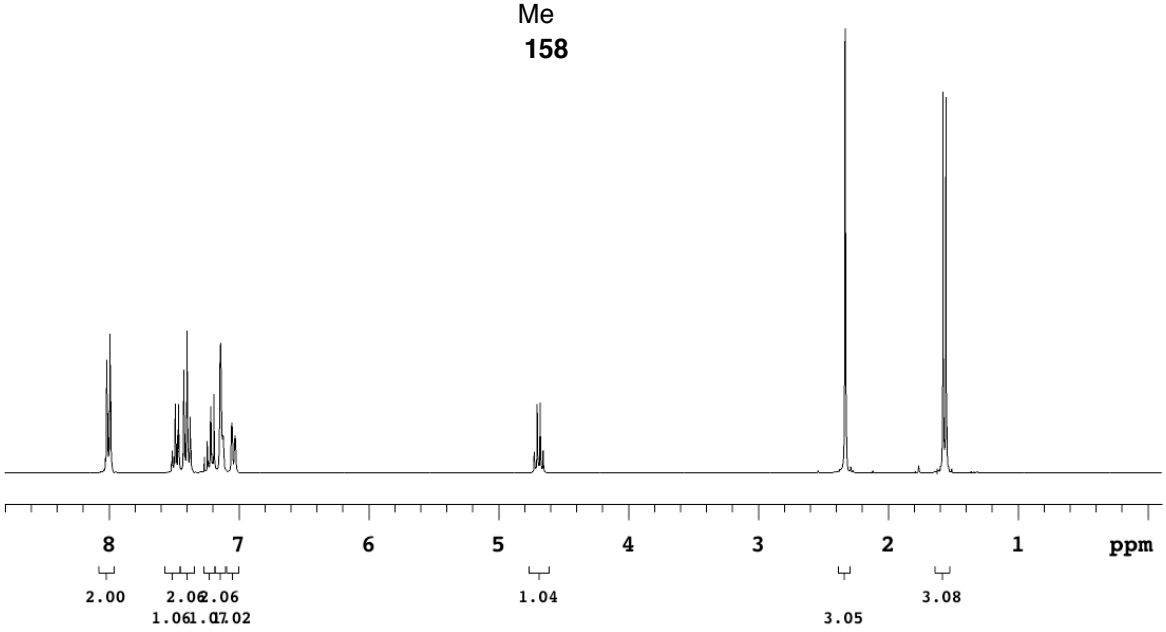
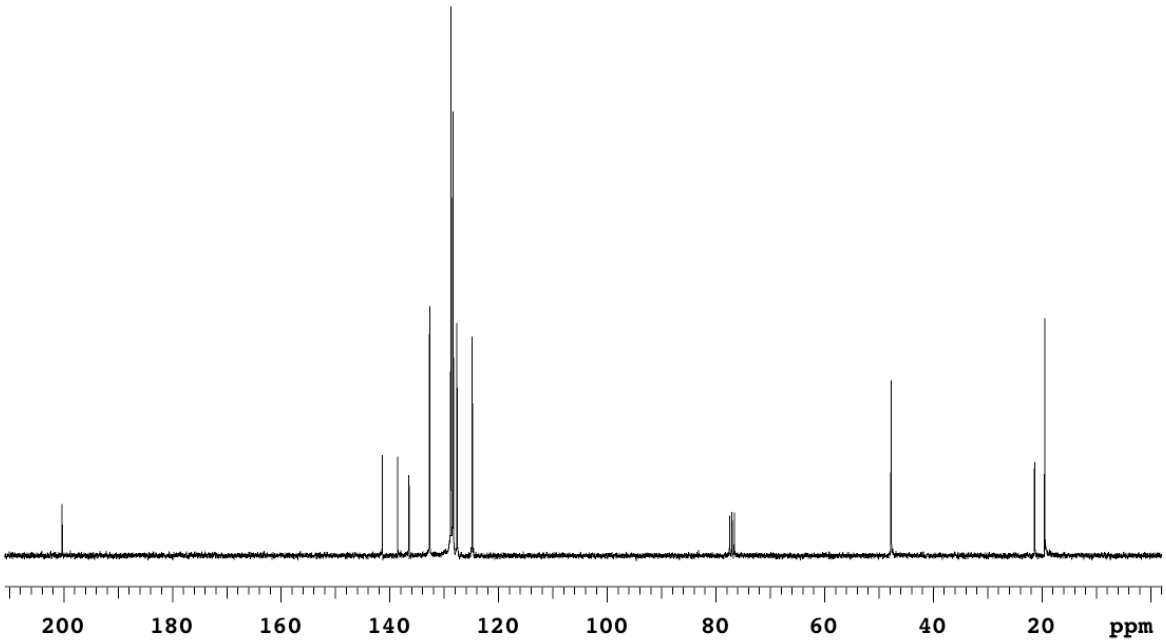
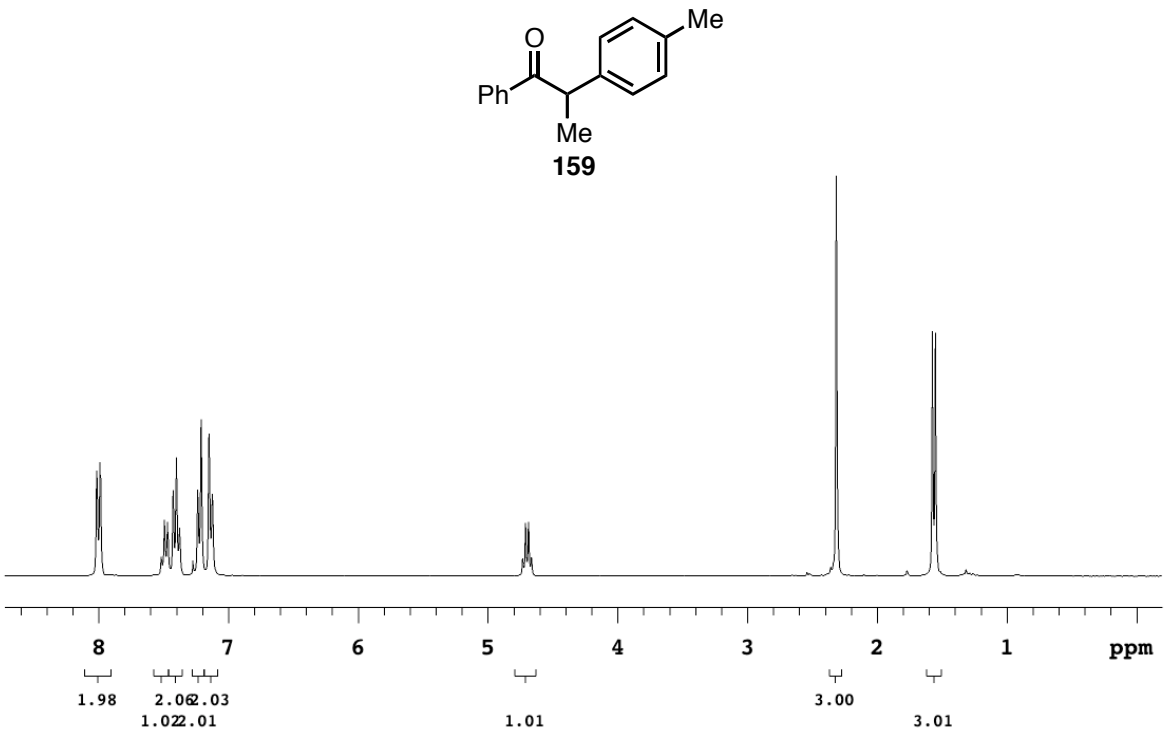


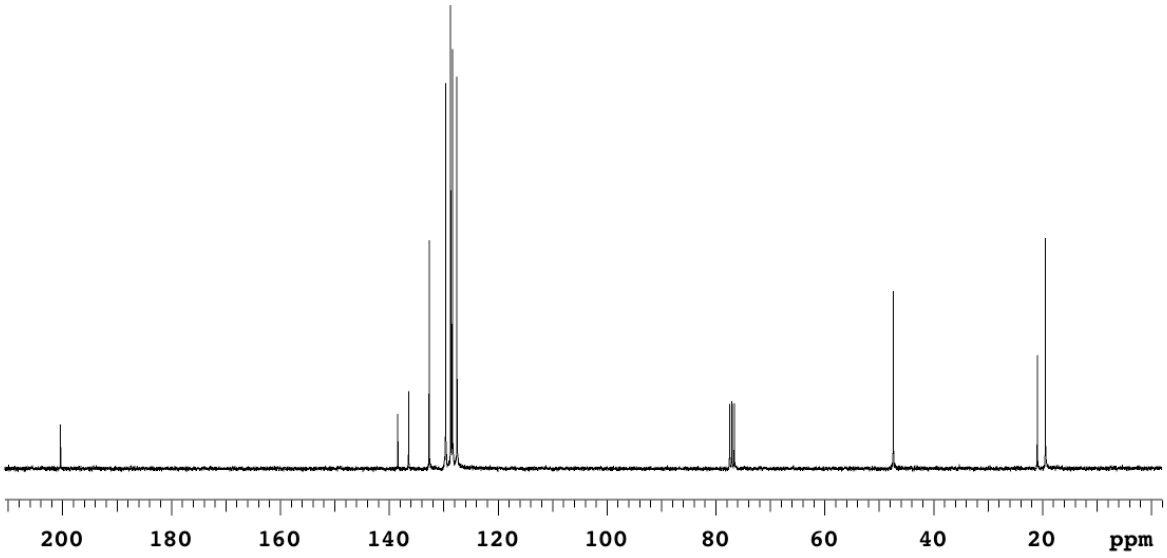
^{13}C NMR ($CDCl_3$, 75 MHz)



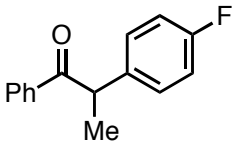
^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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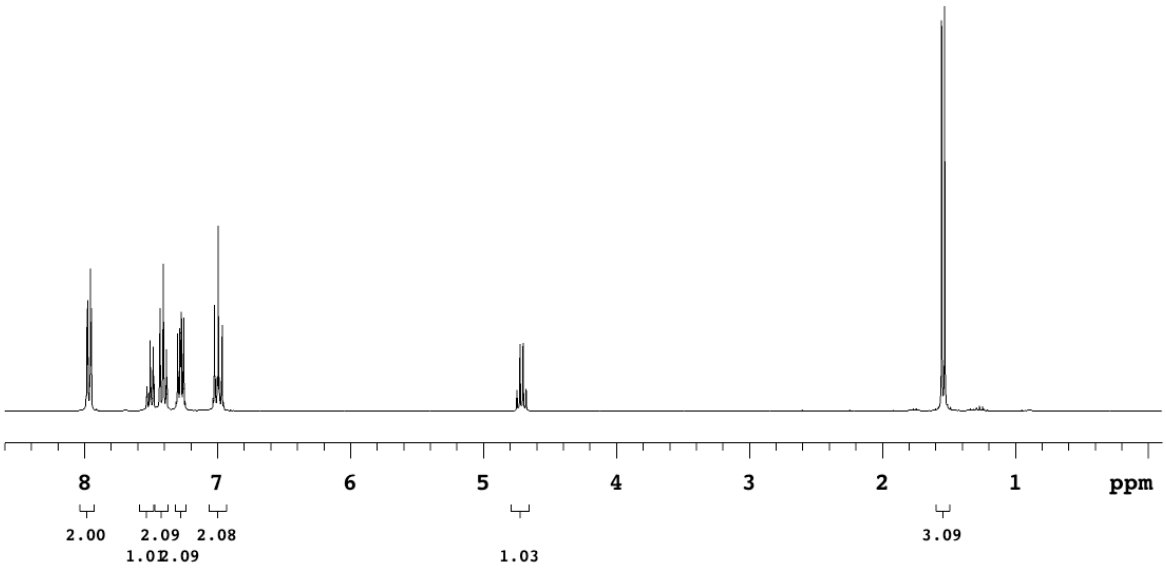
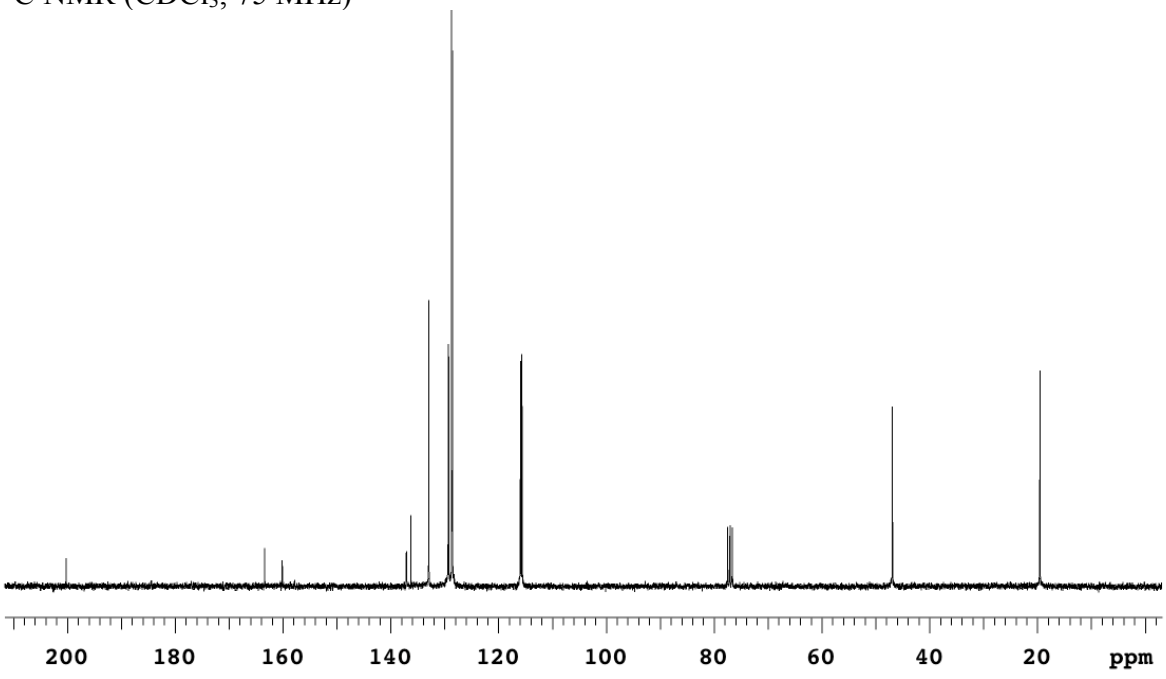
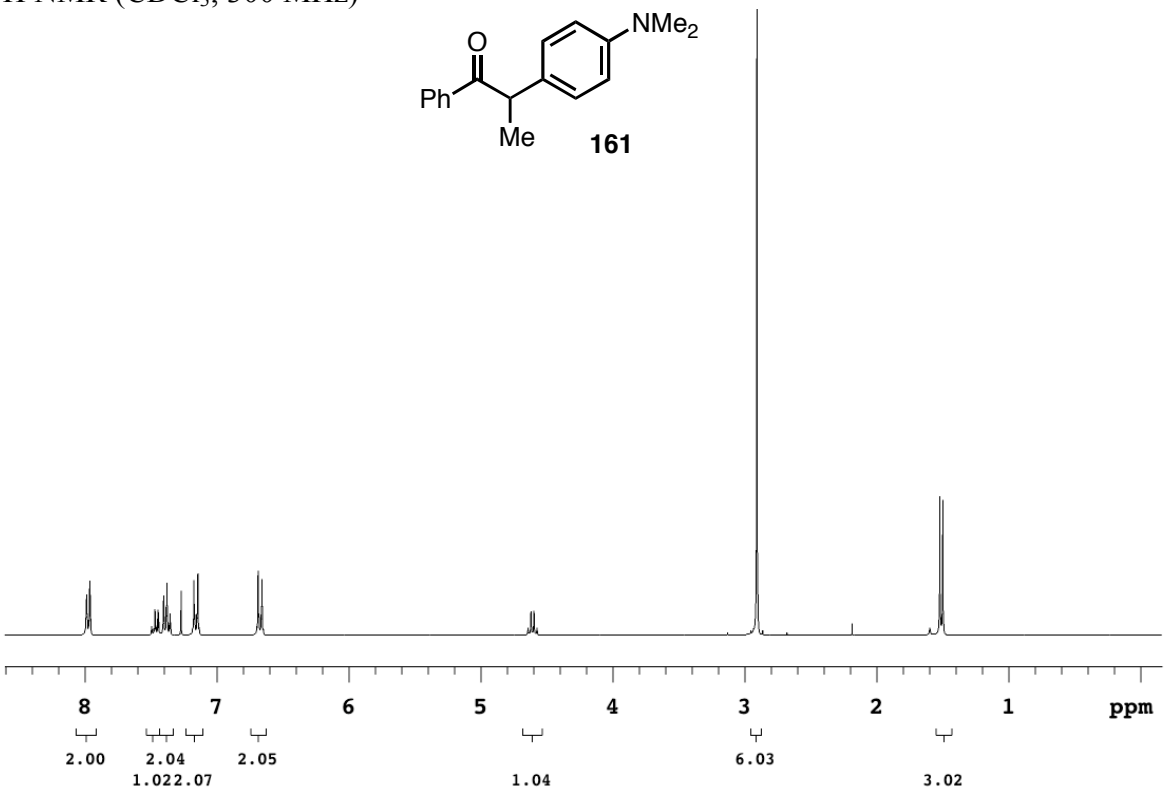


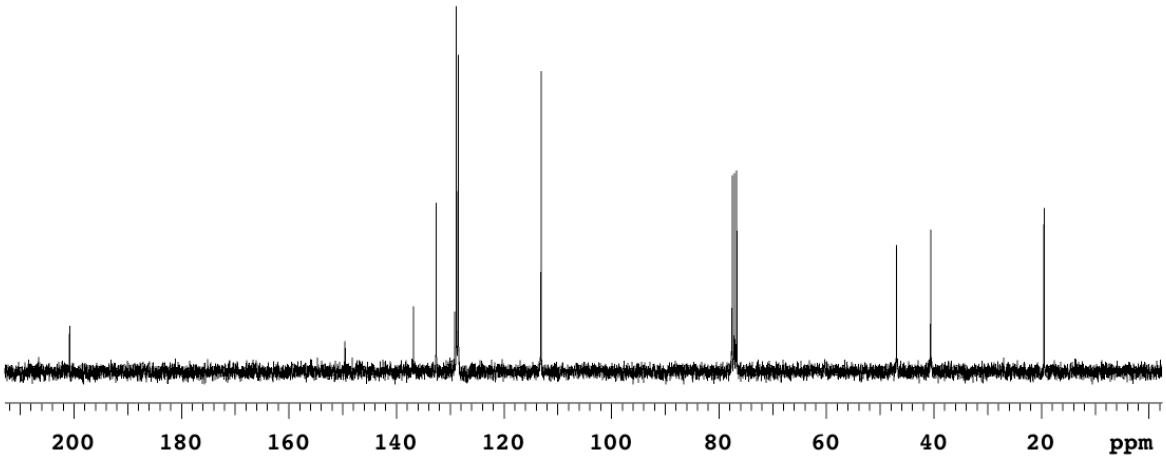
^{13}C NMR ($CDCl_3$, 75 MHz)



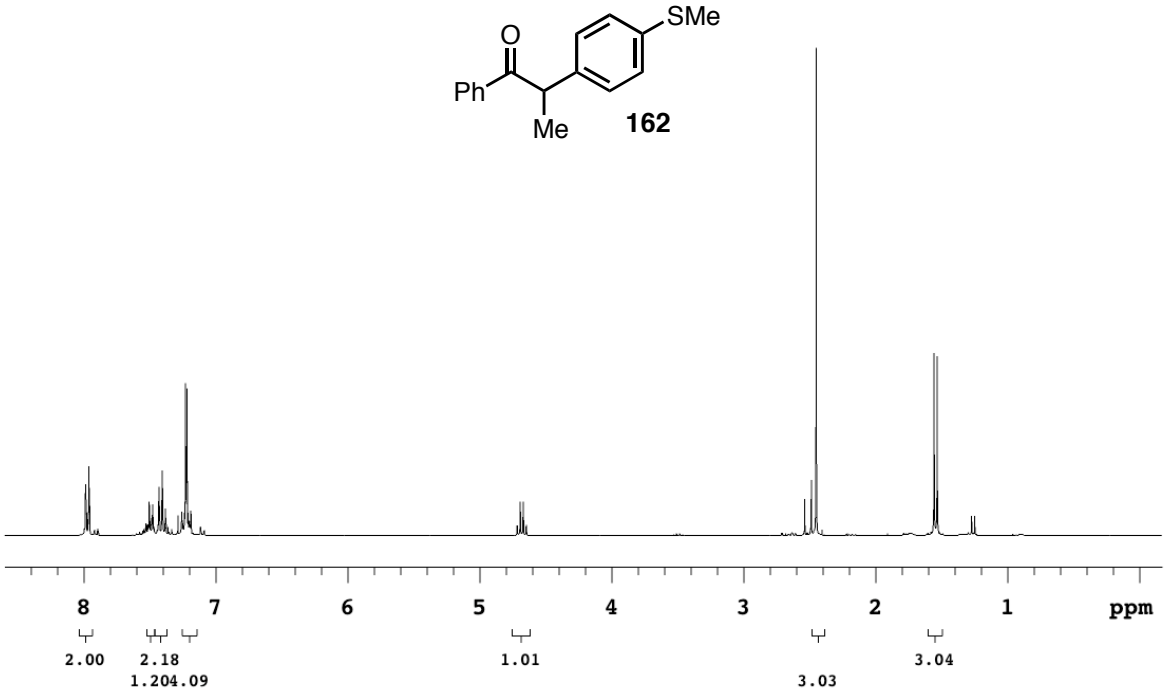
^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)

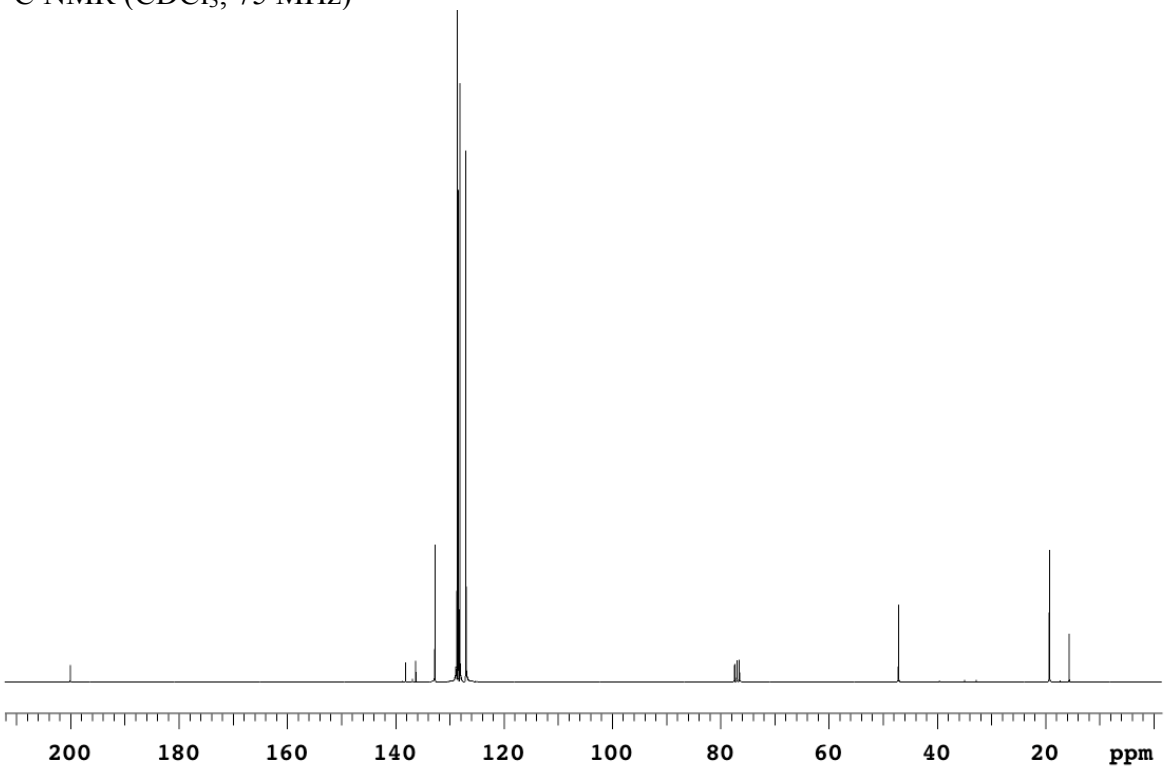


^{1}H NMR ($CDCl_3$, 300 MHz)

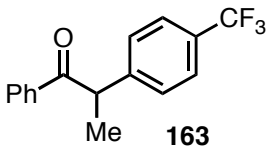


162

^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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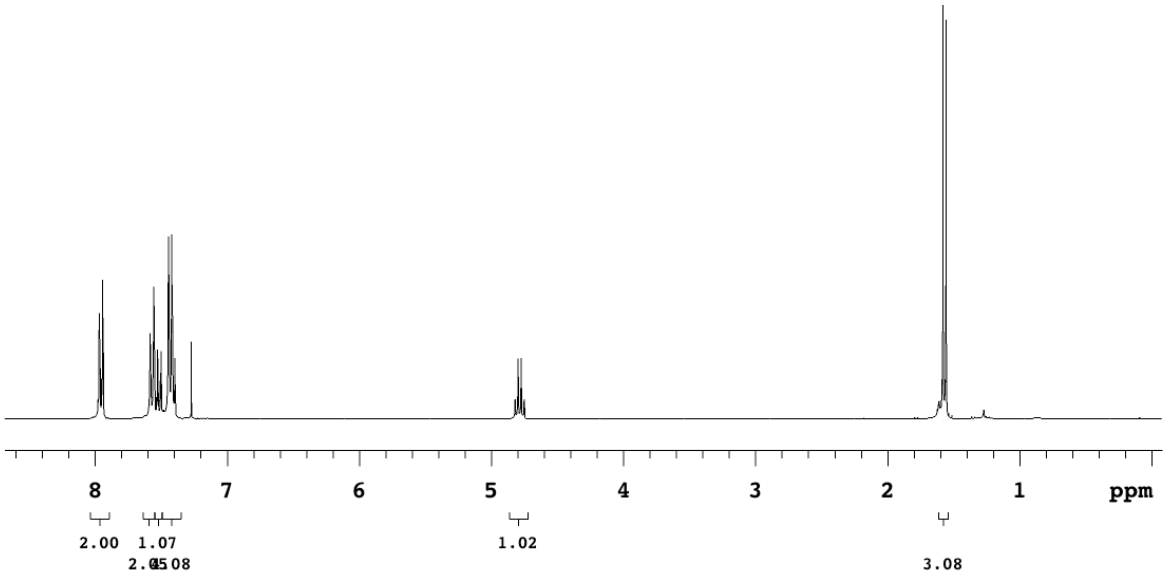
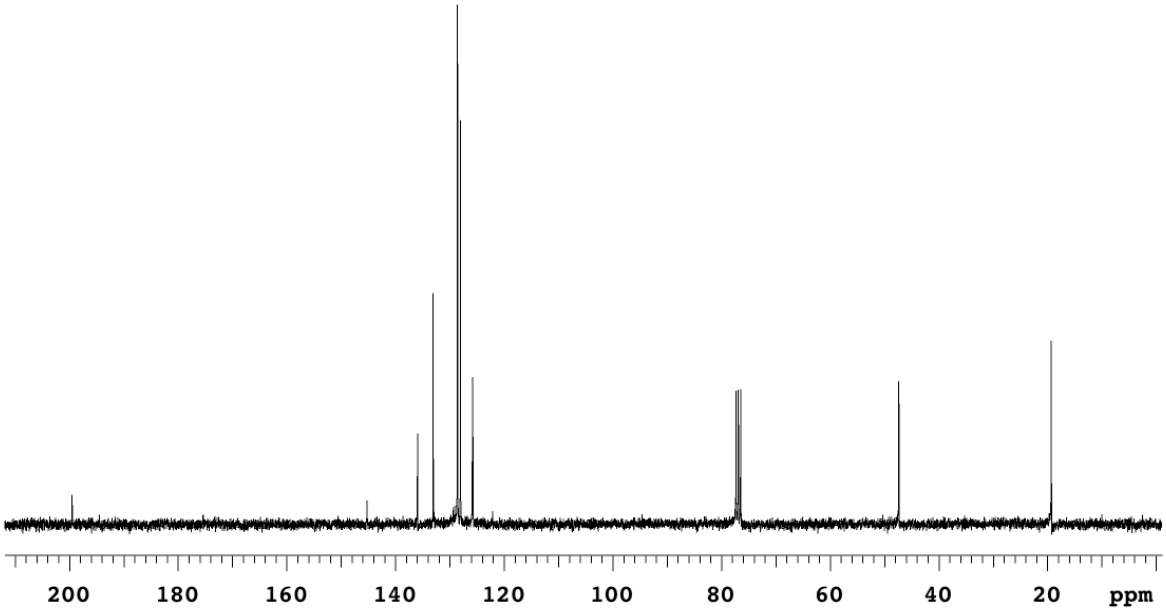
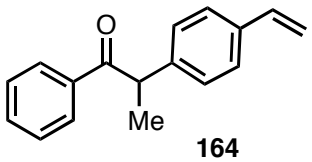


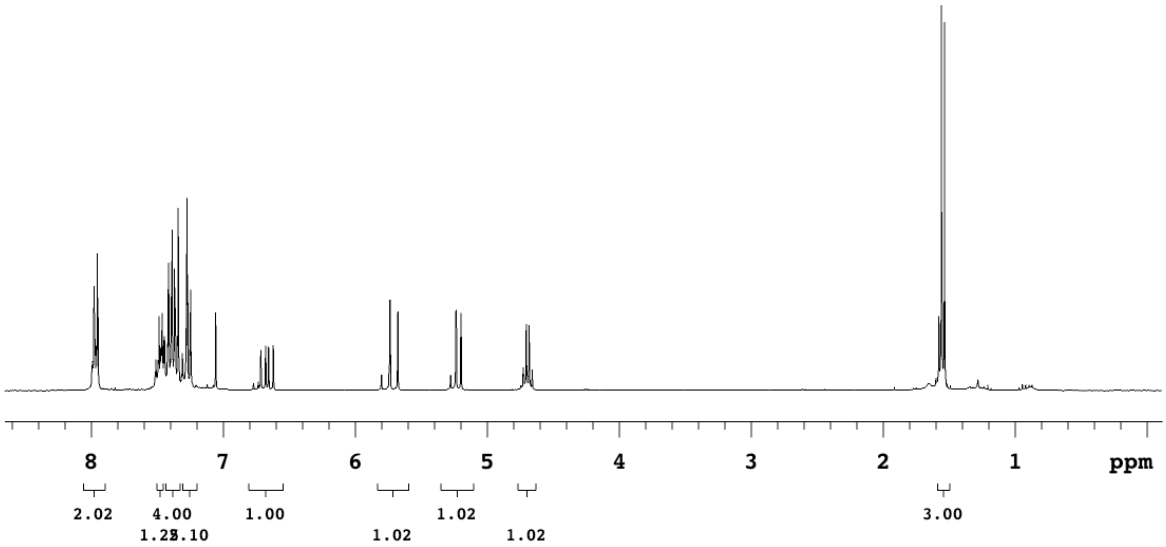
^{13}C NMR ($CDCl_3$, 75 MHz)



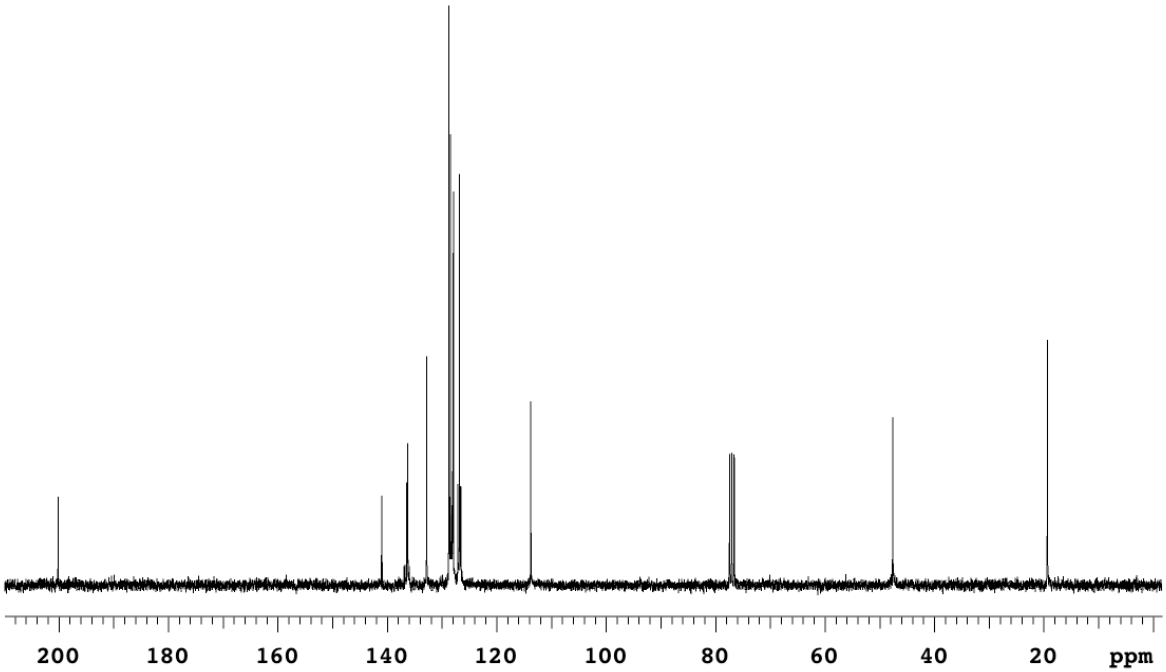
^{1}H NMR ($CDCl_3$, 300 MHz)



164



^{13}C NMR ($CDCl_3$, 75 MHz)



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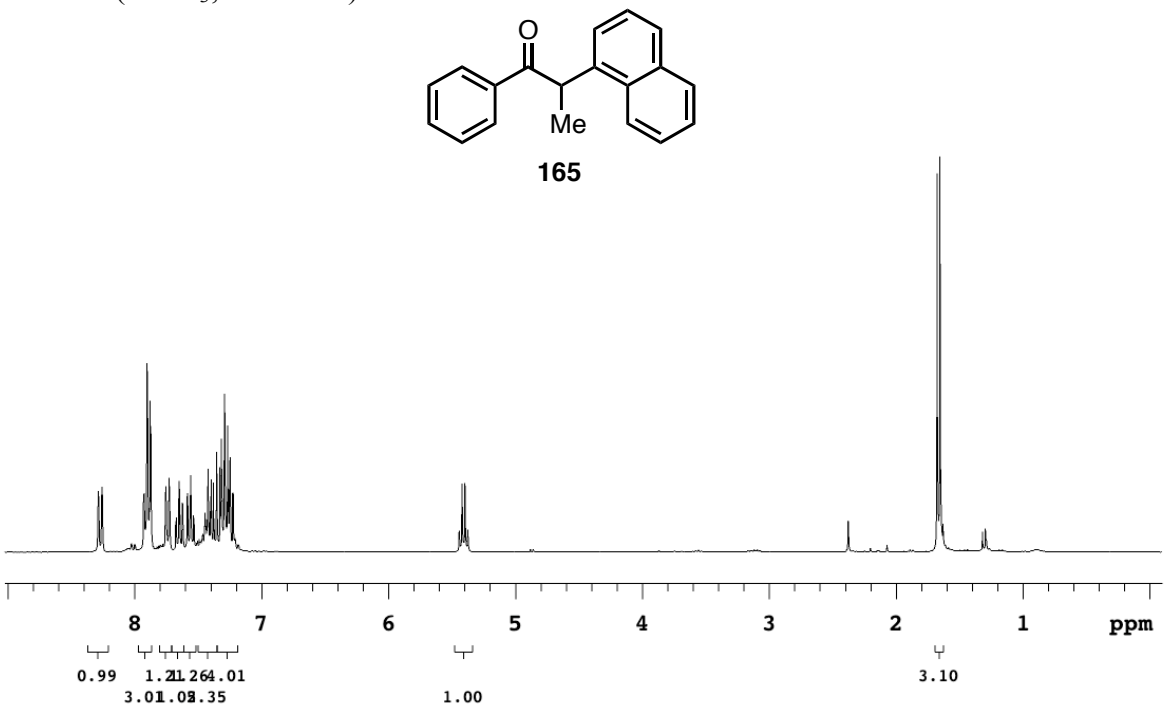
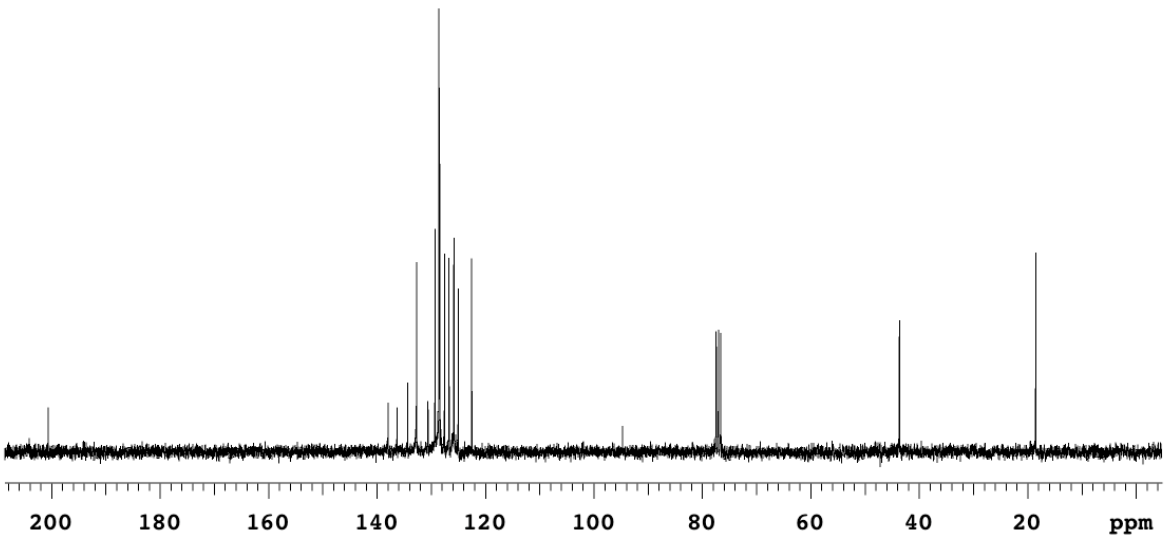
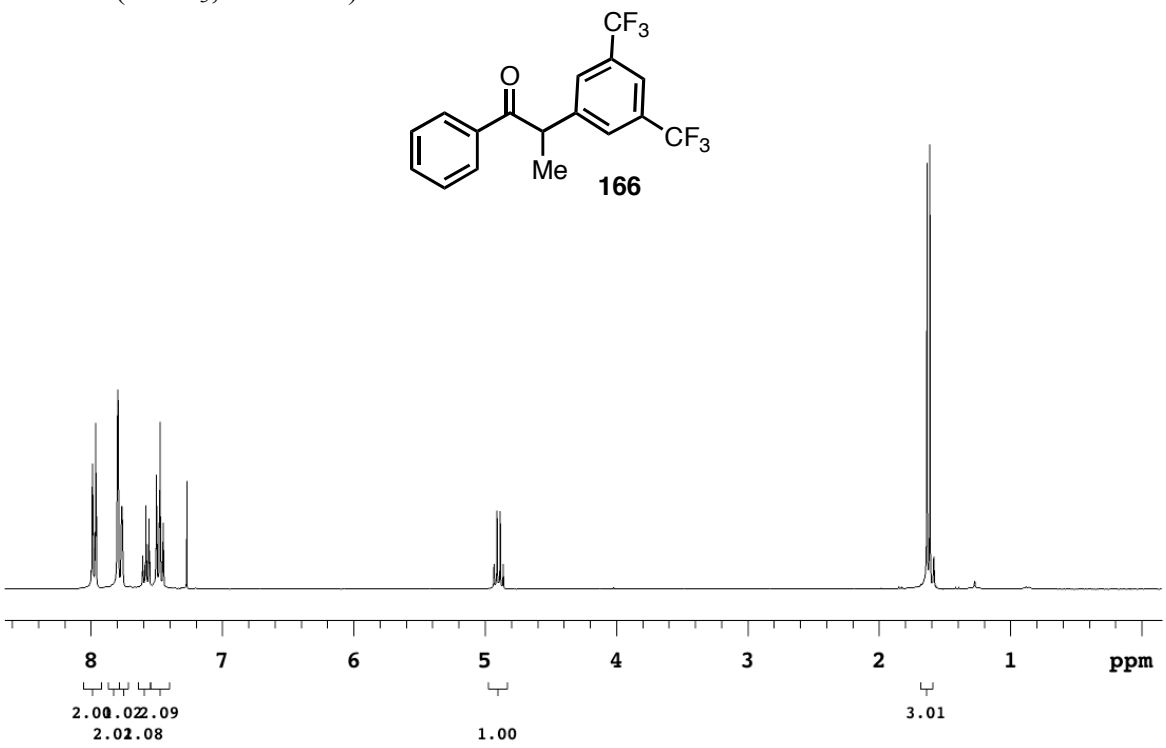


165

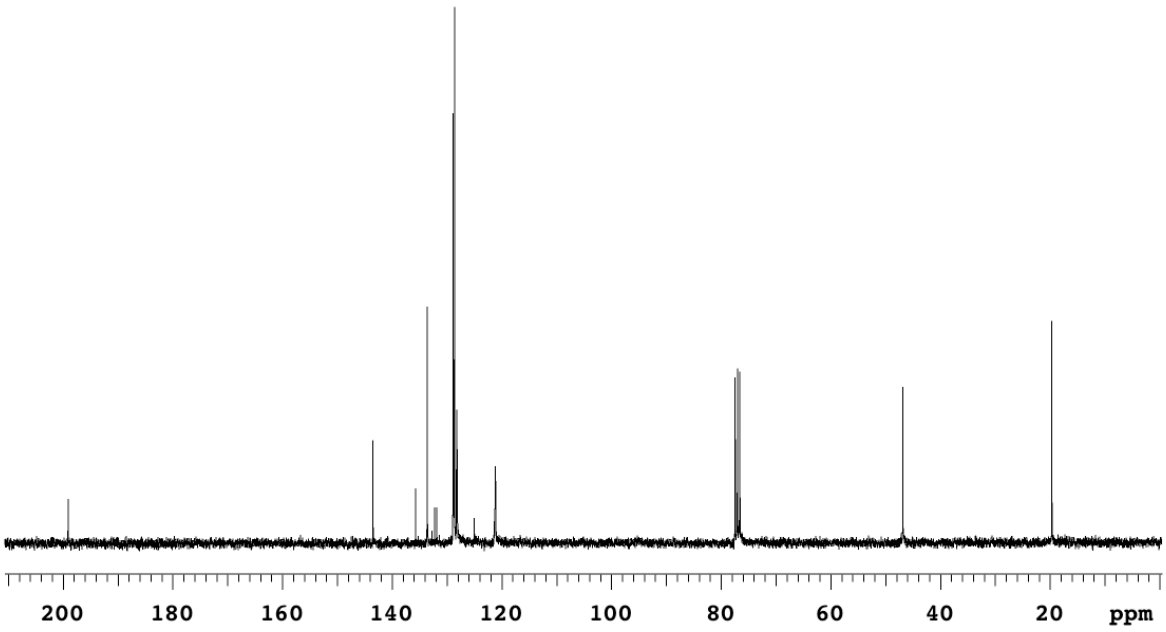
^{13}C NMR ($CDCl_3$, 75 MHz)



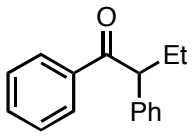
^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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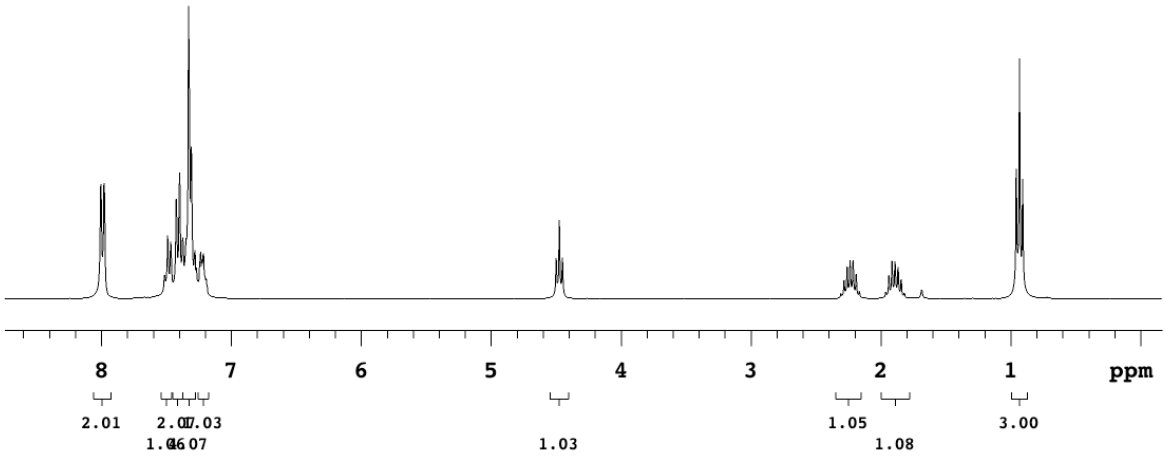
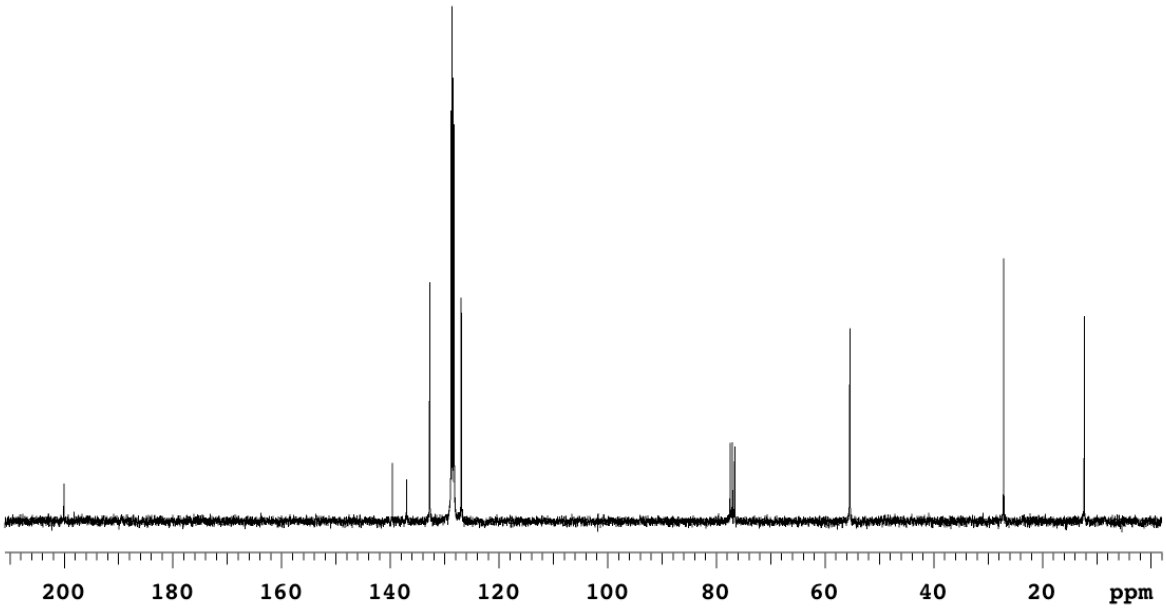
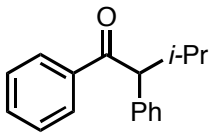


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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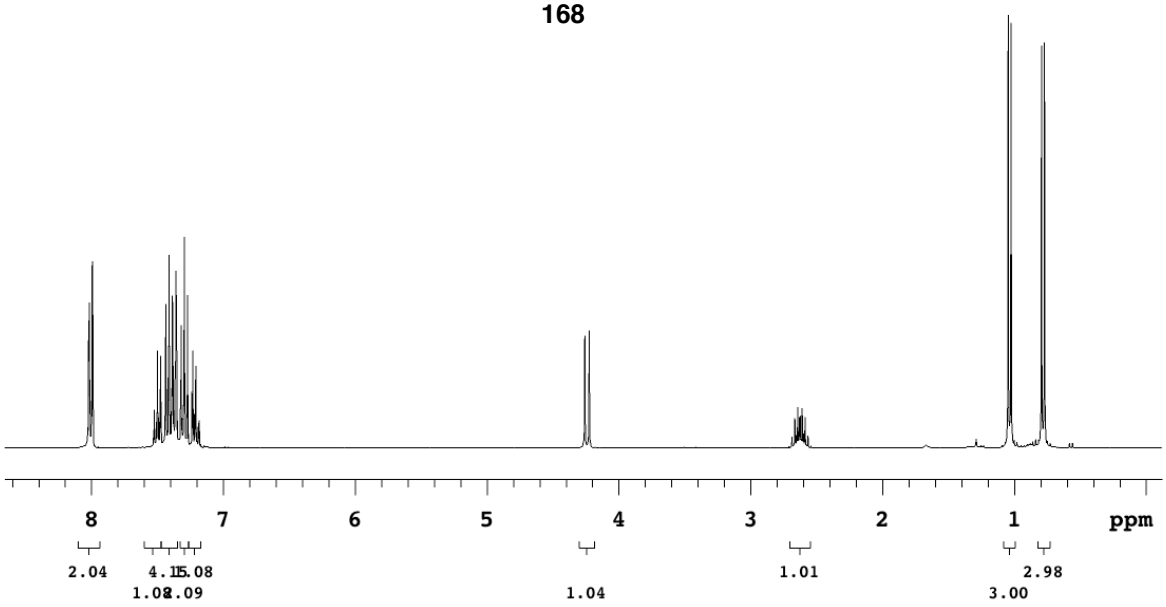
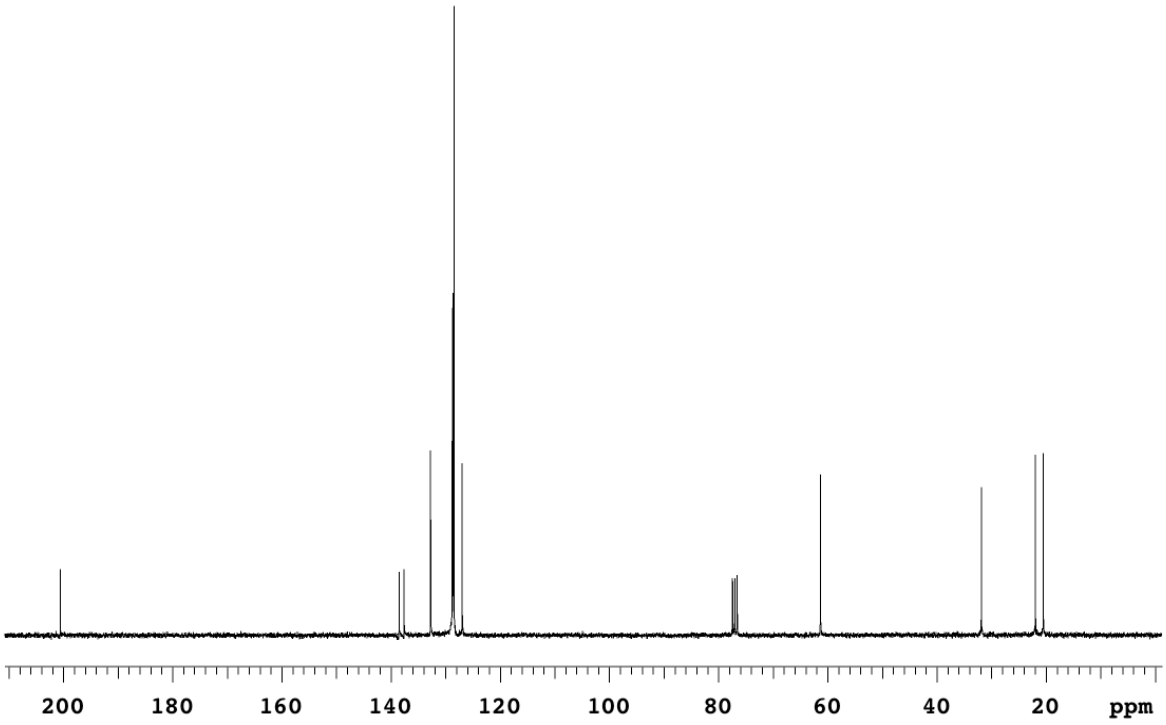
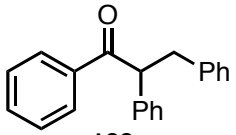


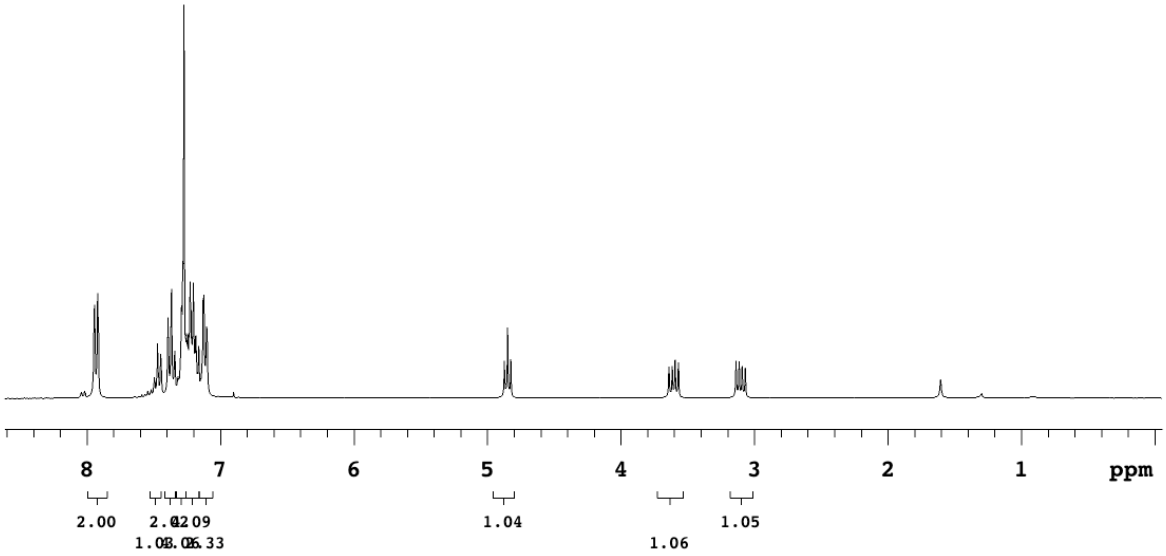
^{13}C NMR ($CDCl_3$, 75 MHz)



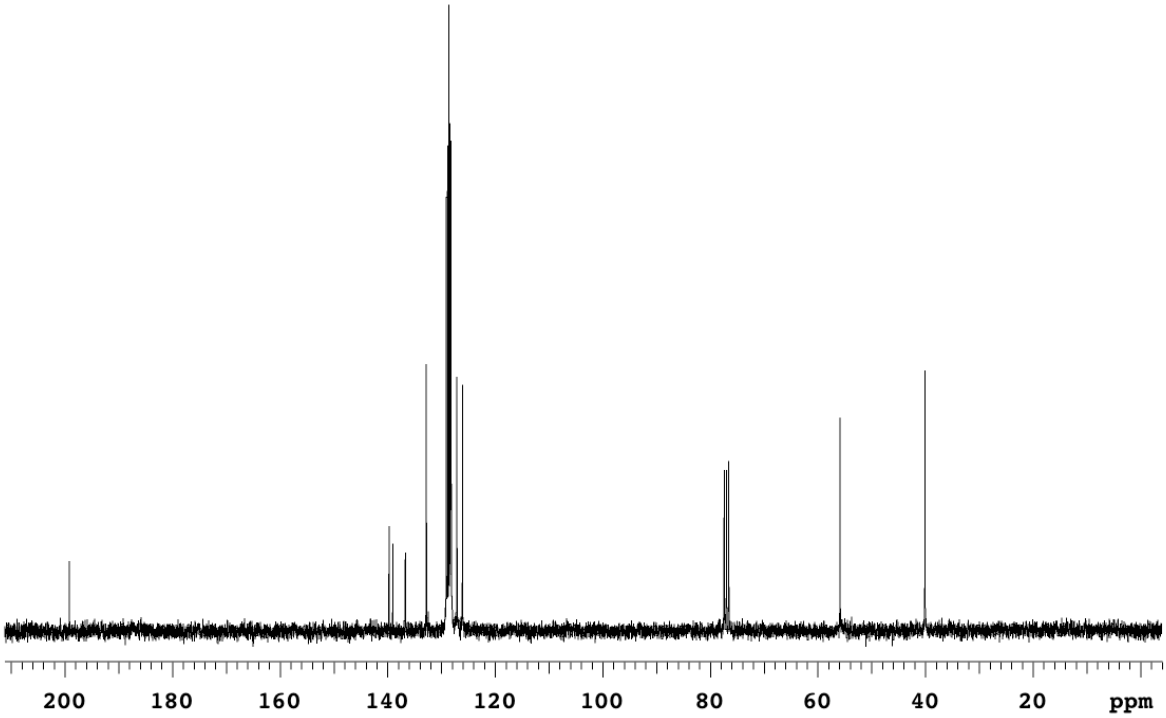
^{1}H NMR ($CDCl_3$, 300 MHz)



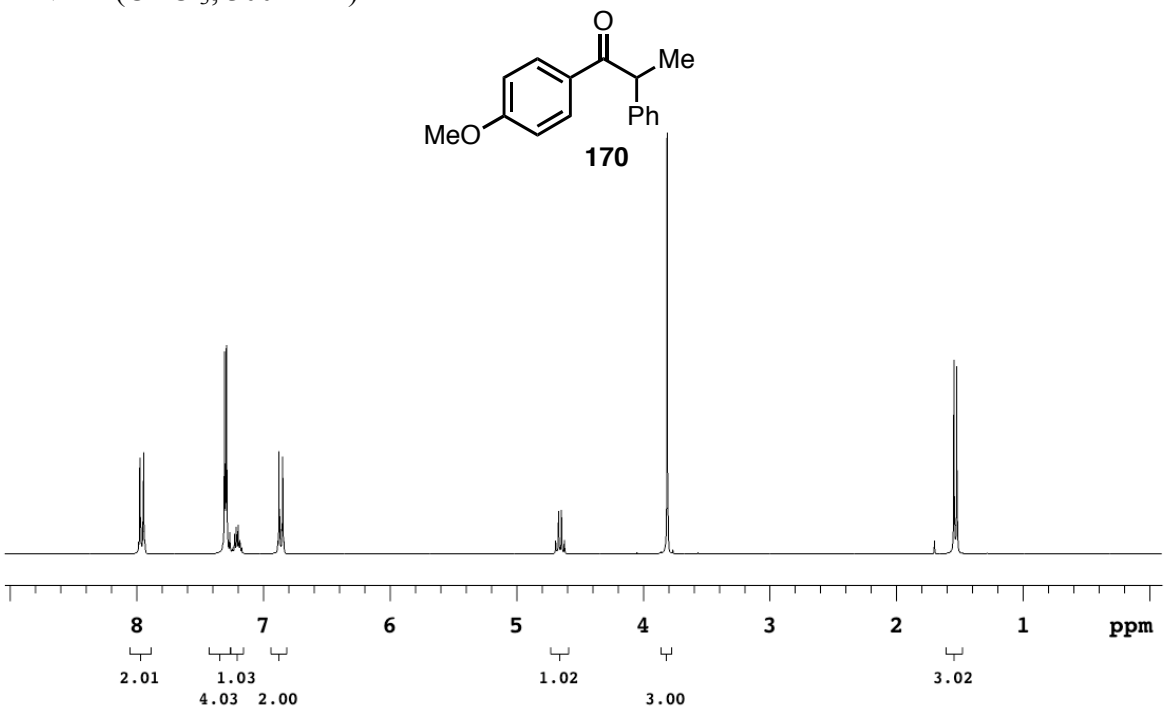
169



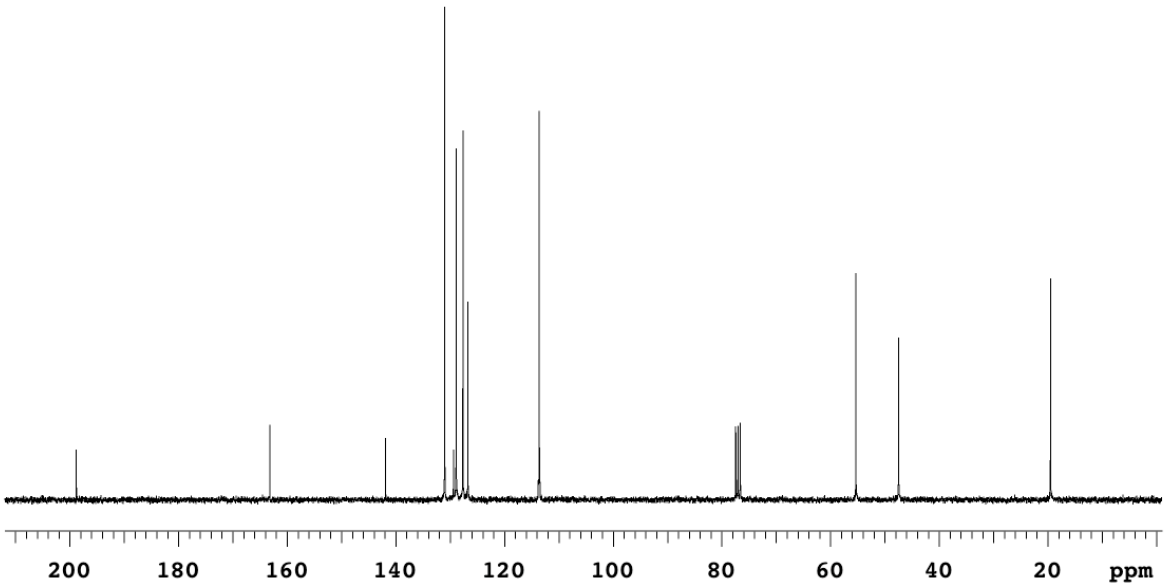
^{13}C NMR ($CDCl_3$, 75 MHz)



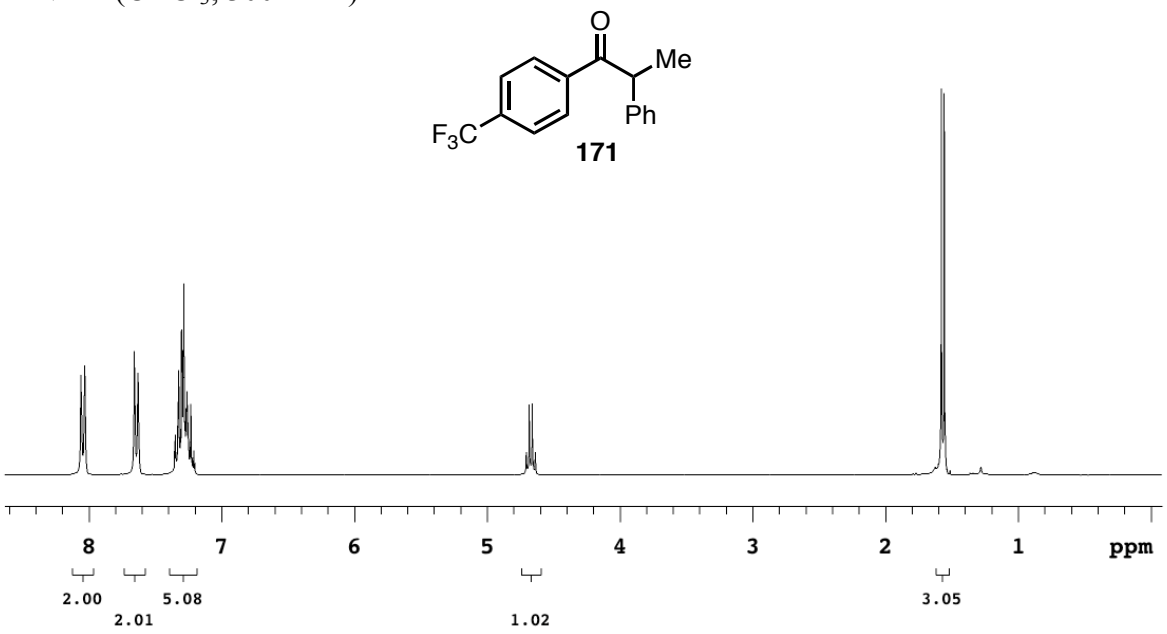
^{1}H NMR ($CDCl_3$, 300 MHz)



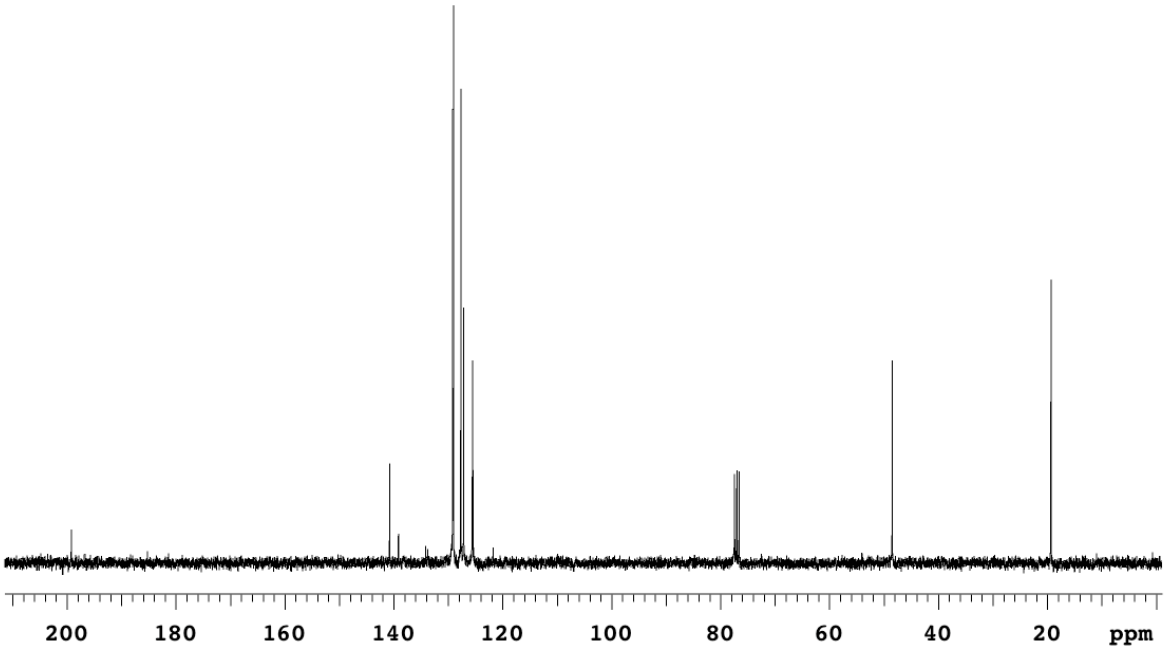
^{13}C NMR ($CDCl_3$, 75 MHz)



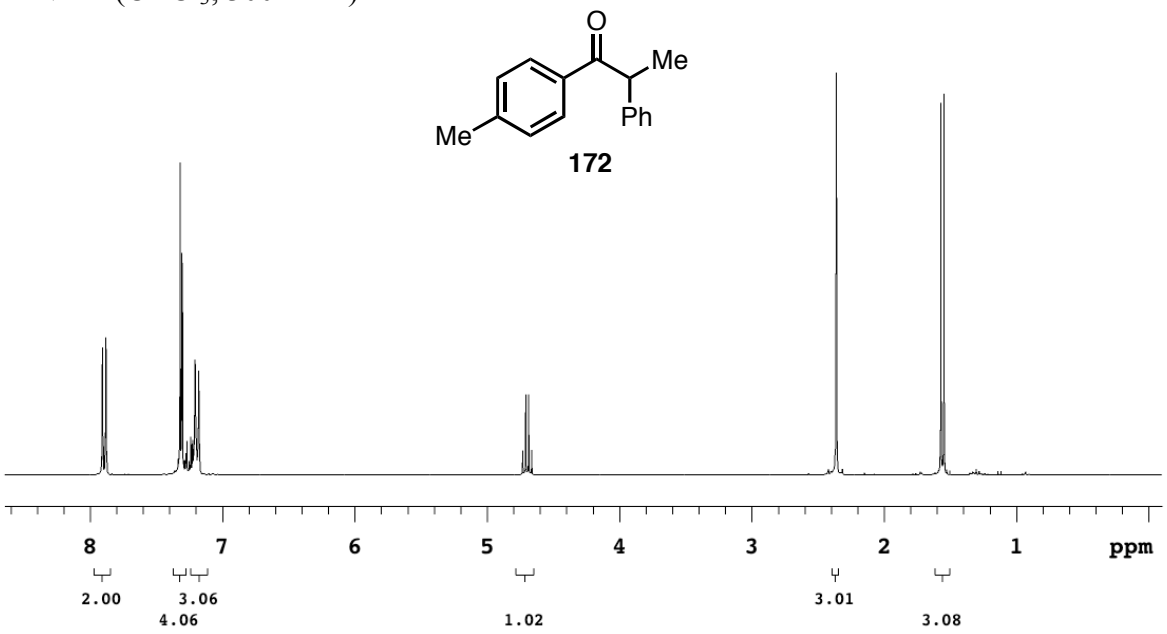
^{1}H NMR ($CDCl_3$, 300 MHz)



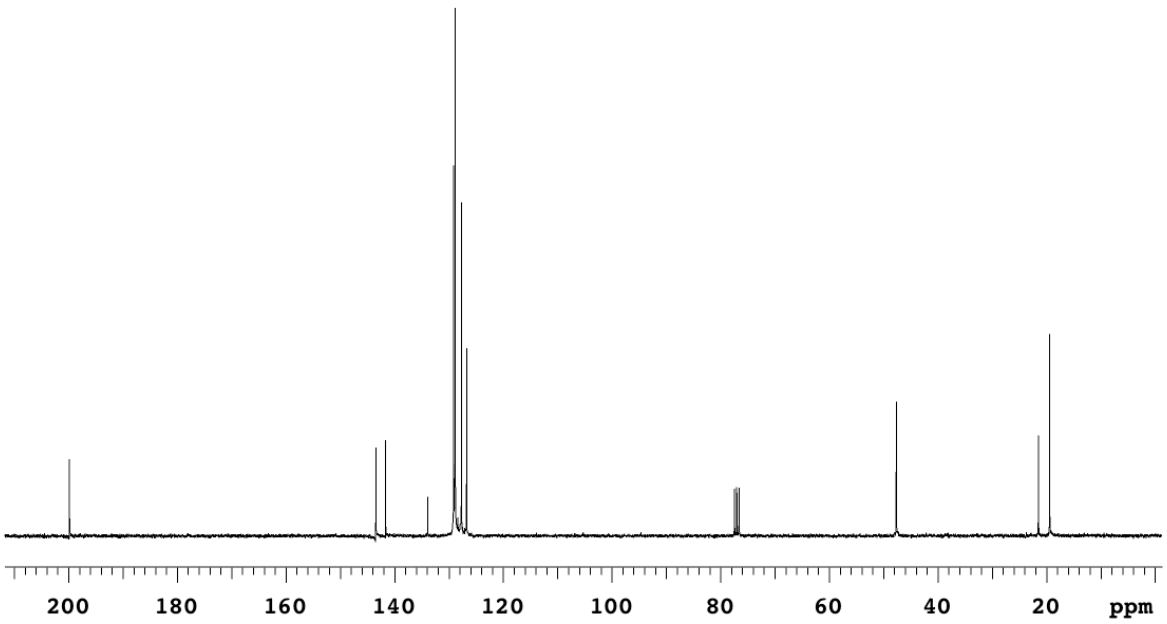
^{13}C NMR ($CDCl_3$, 75 MHz)



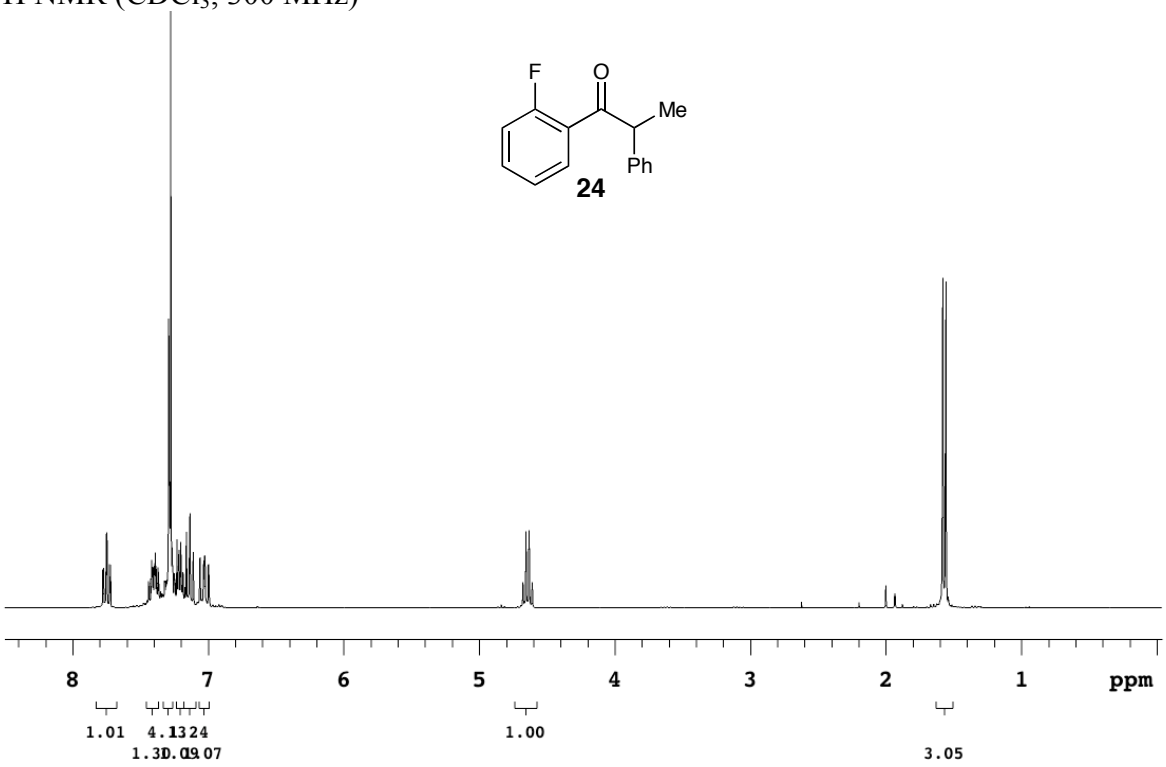
^{1}H NMR ($CDCl_3$, 300 MHz)



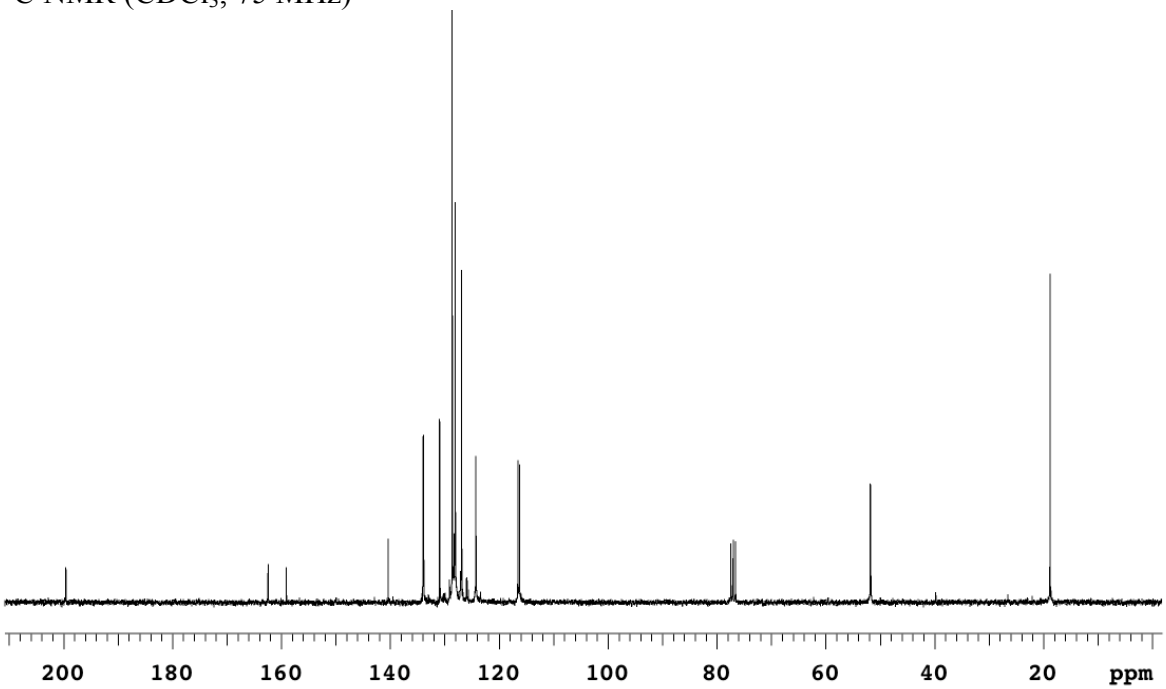
^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



^{13}C NMR ($CDCl_3$, 75 MHz)



APPENDIX B

X-RAY COLLECTION DATA

Table B.1 Crystal and Intensity Collection Data for Nickel Complexes.

	101	**103**	**104**	**109**
Chemica formula	$C_{24}H_{19}BrN_2NiO_2$	$C_{33}H_{46.5}I_{1.5}N_3Ni_{1.5}O_3$	$C_{112}H_{108}Br_4N_8Ni_4O_8$	$C_{18}H_{25}ClN_2NiO_7$
Formula weight	506.03	811.65	2248.54	475.56
Temperature (°K)	110(2)	60(2)	293(2)	90(2)
Wavelength (Å)	1.54178	0.71073	1.54178	0.71073
Crystal system	Orthorhombic	Monoclinic	Orthorhombic	Orthorhombic
Space group	P2(1)2(1)2	P2(1)	P2(1)2(1)2(1)	P2(1)2(1)2(1)
a (Å)	13.1670(9)	5.901(3)	6.2679(8)	6.1341(6)
b (Å)	5.8235(4)	32.739(19)	10.9501(13)	11.6353(10)
c (Å)	13.0951(8)	18.306(10)	35.488(5)	29.016(3)
α (deg)	90	90	90	90
β (deg)	90	95.54(9)	90	90
γ (deg)	90	90	90	90
V (Å^3)	1004.11(12)	3520(3)	2435.7(5)	2070.9(3)
Z	2	4	1	4
ρ_{calc} (mg• m^{-3})	1.674	1.532	1.533	1.525
Absorp coeff (mm^{-1})	3.921	2.161	3.293	1.108
F(000)	512	1644	1152	992
Crystal size (mm^3)	0.09 x 0.06 x 0.01	0.50 x 0.10 x 0.10	0.12 x 0.01 x 0.01	0.26 x 0.12 x 0.12
Scan rage (deg)	3.37 to 59.98	1.67 to 25.00	4.23 to 59.98	2.24 to 28.73
Index ranges	$-14 \le h \le 14$	$-7 \le h \le 7$	$-7 \le h \le 7$	$-8 \le h \le 8$
	$-6 \le k \le 6$	$-38 \le k \le 38$	$-12 \le k \le 11$	$-15 \le k \le 15$
	$-14 \le l \le 14$	$-21 \le l \le 21$	$-39 \le l \le 39$	$-39 \le l \le 38$
Reflections collected	7380	33048	17814	23472
No. of unique refins	1406	12179	3349	4942
R(int)	0.0339	0.0575	0.1626	0.0277
Absorption correction	Semi-empirical	Semi-empirical	Semi-empirical	Semi-empirical
Max. and min. transmission	0.9961, 0.7192	0.8129, 0.74113	0.9678, 0.6856	0.8785, 0.7615
Data/restraints/parameters	1406/0/138	12179/133/813	3349/326/307	4942/48/314
Goodness-of-fit on F^2	1.035	1.029	1.035	1.041
R1[a], wR2[a] [I>2σ(I)]	0.0196, 0.0474	0.0413, 0.0761	0.0720, 0.1645	0.0224, 0.0539
R1[a], wR2[a] (all data)	0.0210, 0.0478	0.0626, 0.0842	0.0854, 0.1728	0.0243, 0.0546
Largest diff. peak / hole (e.Å^{-3})	0.303, -0.175	0.576, -0.480	1.946, -0.939	0.341, -0.171

[a] $R1 = [\sum||F_o|-|F_c|)/\sum|F_o|]$; $wR2 = [\sum(w(F_o^2-F_c^2)^2/\sum(wF_o^4)]^{1/2}$. $S = [\sum(w(F_o^2-F_c^2)^2]/(n-p)^{1/2}$.
n = number of reflections, p = parameters used.

Table B.2 Crystal and Intensity Collection Data for Palladium Complexes.

	121	**123**	**XVI**
Chemica formula	$C_{22}H_{31}IN_2O_2Pd$	$C_{30}H_{31}BrN_2O_2Pd$	$C_{20}H_{27}BrN_2O_2Pd$
Formula weight	588.79	637.88	513.75
Temperature (°K)	110(2)	110(2)	110(2)
Wavelength (Å)	1.54184	1.54178	1.54178
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	P2(1)	P2(1)2(1)2	P2(1)/n
a (Å)	6.0186(12)	6.6808(7)	12.6447(12)
b (Å)	32.173(6)	19.625(2)	21.628(2)
c (Å)	12.237(3)	20.422(2)	15.6494(15)
α (deg)	90	90	90
β (deg)	94.131(9)	90	103.716(6)
γ (deg)	90	90	90
V ($Å^3$)	2363.3(8)	2677.6(5)	4157.7(7)
Z	4	4	8
ρ_{calc} ($mg \cdot m^{-3}$)	1.655	1.582	1.641
Absorp coeff (mm^{-1})	16.731	7.570	9.576
F(000)	1168	1288	2060
Crystal size (mm^3)	0.20 x 0.02 x 0.02	0.10 x 0.01 x 0.01	0.26 x 0.12 x 0.01
Scan rage (deg)	2.75 to 59.96	4.33 to 59.99	4.14 to 60.00
Index ranges	$-6 \le h \le 6$	$-7 \le h \le 7$	$-14 \le h \le 14$
	$-35 \le k \le 36$	$-22 \le k \le 22$	$-24 \le k \le 24$
	$-13 \le l \le 13$	$-22 \le l \le 22$	$-17 \le l \le 17$
Reflections collected	18046	19307	74692
No. of unique refins	6390	3920	6004
R(int)	0.1589	0.0846	0.0634
Absorption correction	Semi-empirical	Semi-empirical	Semi-empirical
Max. and min. transmission	0.7308 , 0.1347	0.9281, 0.5182	0.9103, 0.1897
Data/restraints/parameters	6390/601/505	3920/0/326	6004/18/514
Goodness-of-fit on F^2	1.015	1.005	1.004
R1[a], wR2[a] [I>2σ(I)]	0.0784, 0.1515	0.0453, 0.1079	0.0311, 0.0690
R1[a], wR2[a] (all data)	0.1307, 0.1759	0.0530, 0.1121	0.0364, 0.0707
Largest diff. peak / hole ($e.Å^{-3}$)	1.477, -0.757	2.414, -0.529	1.114, -0.729

[a] $R1 = [\sum | |F_o| - |F_c|) / \sum |F_o|]$; $wR2 = [\sum (w(F_o^2 - F_c^2)^2 / \sum (wF_o^4)]^{1/2}$. $S = [\sum (w(F_o^2 - F_c^2)^2] / (n-p)^{1/2}$. n = number of reflections, p = parameters used.

Table B.3 Crystal and Intensity Collection Data for **80A** and **31**.

	80A	**31**
Chemica formula	$C_{22}H_{31}IN_2O_2$	$C_{18}H_{17}IO_3$
Formula weight	482.39	408.22
Temperature (°K)	163(2)	110(2)
Wavelength (Å)	0.71073	0.71069
Crystal system	Monoclinic	Monoclinic
Space group	P2(1)	C2/c
a (Å)	9.478(6)	20.654(10)
b (Å)	21.389(13)	7.358(4)
c (Å)	11.315(7)	22.576(11)
α (deg)	90	90
β (deg)	95.246(8)	98.350(6)
γ (deg)	90	90
V (Å^3)	2677.6(5)	3395(3)
Z	4	8
ρ_{calc} (mg• m^{-3})	1.403	1.598
Absorp coeff (mm^{-1})	1.420	1.896
F(000)	984	1616
Crystal size (mm^3)	0.40 x 0.10 x 0.10	0.30 x 0.20 x 0.20
Scan rage (deg)	1.81 to 25.00	13.92 to 25.00
Index ranges	$-11 \le h \le 11$	$-24 \le h \le 24$
	$-25 \le k \le 25$	$-8 \le k \le 8$
	$-13 \le l \le 13$	$-26 \le l \le 26$
Reflections collected	18541	14935
No. of unique refins	7590	2902
R(int)	0.0729	0.0278
Absorption correction	Semi-empirical	Semi-empirical
Max. and min. transmission	0.8711, 0.6006	0.7030, 0.6001
Data/restraints/parameters	7590/424/489	2902/0/200
Goodness-of-fit on F^2	1.019	1.002
R1[a], wR2[a] [I>2σ(I)]	0.0461, 0.0862	0.0405, 0.0797
R1[a], wR2[a] (all data)	0.0618, 0.0906	0.0441, 0.0814
Largest diff. peak / hole (e.Å^{-3})	1.720, -0.719	0.633, -1.213

[a] $R1 = [\sum||F_o|-|F_c|)/\sum|F_o|)$; $wR2 = [\sum(w(F_o^2-F_c^2)^2/\sum(wF_o^4)]^{1/2}$. $S = [\sum(w(F_o^2-F_c^2)^2]/(n-p)^{1/2}$. n = number of reflections, p = parameters used.

VITA

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