CHROMIUM-CATALYZED HOMOALDOL EQUIVALENT REACTION, INDIUM-MEDIATED CYCLOISOMERIZATION, AND PALLADIUM-CATALYZED CROSS-COUPLING REACTION

A Dissertation

by

JUN YONG KANG

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

August 2011

Major Subject: Chemistry

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Committee Members,	Daniel Romo
	Kevin Burgess
	Daniel Shantz
Head of Department,	David H. Russell

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ABSTRACT

Chromium-Catalyzed Homoaldol Equivalent Reaction, Indium-Mediated Cycloisomerization, and Palladium-Catalyzed Cross-Coupling Reaction. (August 2011)

Jun Yong Kang, B.S., Konyang University, Korea; M.S., San Francisco State University; M.S., Texas A&M University

Chair of Advisory Committee: Dr. Brian T. Connell

The homoaldol reaction is one of the most powerful methods for the construction of C–C bonds as well as 1,4-oxygenated compounds yet this reaction remains a challenging task due to the instability of homoenolates which spontaneously cyclize to the cyclopropanolate. A regioselective catalytic homoaldol equivalent reaction of 3-bromo vinyl acetate with aldehydes under $Cr^{(III)}$-$Mn^{(0)}$ redox condition is developed. This homoaldol equivalent reaction allows access to the 1,4-oxygenated compounds that are not possible by a conventional aldol process. Mild hydrolysis of the vinyl acetate and reduction of the homoaldol adducts generate diols and lactols in high yield (99%). Further manipulation including stereoselective epoxidation and cyclopropanation is achieved in an efficient manner.

Furans, found in many natural products and utilized in drug discovery, have been well studied but current synthetic methods toward furans have some limitations in functional group tolerance, substrate scope, and low product yield in many cases. A highly efficient and catalytic cycloisomerization reaction that transforms acetylenic α,β-

epoxides to 2,3,5-tri-substituted furans under $InCl_3$ catalysis is developed. This reaction sequence allows access to rapid construction of highly valuable, tri-substituted furan derivatives.

Cross-coupling reactions utilizing transition metals and Lewis acids are important synthetic tools for the formation of C–C and C–N bonds and a number of cross-coupling reactions between α-bromo carbonyl compounds and metal reagents such as aryl metals, alkenyl metals, and alkyl metals are reported. Transition metal-catalyzed cross-coupling reaction for the construction of α-alkynyl carbonyl compounds is reported in a limited case. The first approach to secondary α-alkynyl carbonyl compounds from secondary α-bromo esters and amides with tributyl(phenylethynyl)stannane under palladium-catalyzed cross-coupling reaction conditions is developed. This synthetic method allows access to secondary α-alkynyl carbonyl compounds which are valuable precursors in pharmaceuticals and agricultural applications.

DEDICATION

To my wife, parents, and sisters

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my advisor, Brian T. Connell, for his concrete support and general concern for my development as an organic chemist. As an advisor, he has always encouraged me to explore new ideas and he has guided me in the right direction. Brian's excellent teaching skills, willingness and openness to discussion in the classroom and in his office, motivated me to join the group. It has been a pleasure to work under his guidance during my Ph.D. journey.

I would like to thank Dr. Daniel Romo, Dr. Kevin Burgess, and Dr. Daniel Shantz for their valuable time and suggestions over the years.

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Finally, I would like to take the opportunity to especially thank my wife, my mother, my father, sisters, and brother for their everlasting love and continual support.

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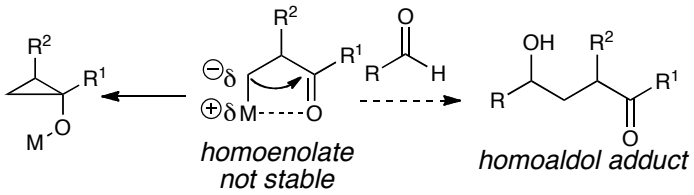
CHAPTER I

INTRODUCTION: CHROMIUM-CATALYZED HOMOALDOL EQUIVALENT REACTIONS

1.1 Introduction and Background of Homoaldol Equivalent Reactions

The power of homoaldol reactions[1,2] in synthetic methodology have been demonstrated by their own convenient access to useful building blocks containing 1,4 oxygenated subunits that are often found in natural products.[3] These products are not accessible by conventional aldol process[4] and can be applied to development of versatile and valuable transformations such as stereoselective epoxidation,[5] stereoselective cyclopropanation,[6] lactol formation, and 1,4-diol synthesis. While aldol reactions have been extensively studied for making carbon-carbon bonds over the past decades,[7] one carbon homologated aldol reaction, referred to as the homoaldol reaction, has been less studied due to the stability of homoenolate[7] that posses both nucleophilic and electrophilic sites and undergoes rapid cyclization to the oxy anionic isomers (Scheme 1.1). Although the early observation of homoenolate anion date back in 1962,[8] the homoenolate remains as a synthon with no examples in literature.

Scheme 1.1. Homoenolate possessing both nucleophilic and electrophilic sites

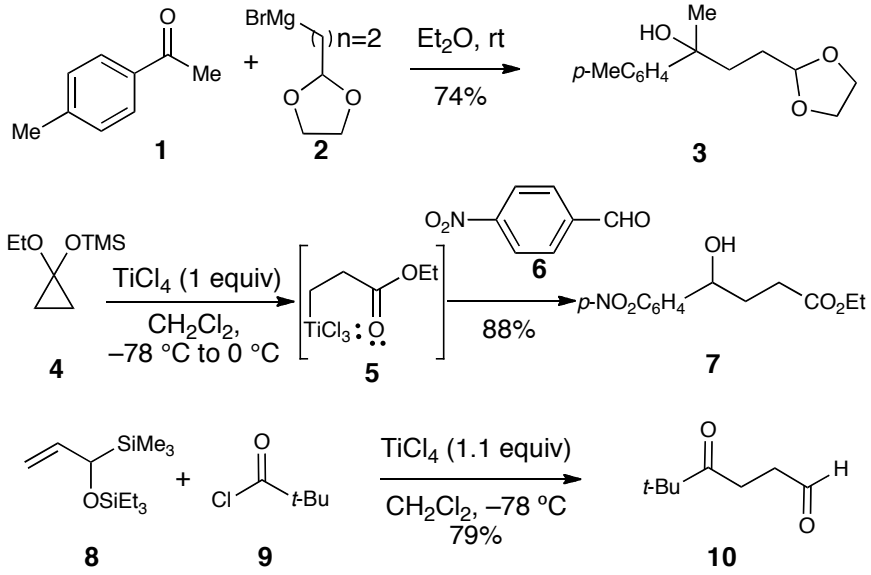


This dissertation follows the style of *Journal of the American Chemical Society*.

Since Nickon's discovery of homoenolate equivalent reagents, there have been many strategies for accessing homoenolate equivalents. In early work employing homoaldol equivalent reactions, stoichiometric amounts of catalyst were used in homoaldol equivalent reactions. Büechi and Wuest in 1969[9] utilized Grignard reagents **2** of homoenolate equivalents and carbonyl compounds **1** to afford the acetal protected tertiary alcohol **3** which could proceed to homoaldol equivalent adducts after hydrolysis of acetal protecting group (Scheme 1.2). However, this method employing the Grignard reagent has the potential for cyclopropyl ether formation by a 1,3-cycloelimination of the Grignard reagent **2**.

In 1977, Nakamura and Kuwajima reported the first example of an ester homoenolate equivalent generated from silyloxy cyclopropane and titanium tetrachloride ($TiCl_4$) for homoaldol equivalent reactions.[10] The silyloxy cyclopropane **4** was treated with $TiCl_4$ to generate titanium homoenolate ester **5** which consequently was reacted with aldehyde **6**, producing the γ-hydroxy ester **7** of homoaldol equivalent adduct (Scheme 1.2). One year later, Sakurai *et al.* employed α-siloxy allylsilane for homoenolate equivalent formation and acid chloride to afford γ-keto aldehydes of the desired homoaldol equivalent adduct (Scheme 1.2).[11] Treatment of α-siloxy allylsilane **8** with acid chloride **9** under $TiCl_4$ (1.1 equiv) produced the γ-keto aldehydes **10**. These reactions, however, employed stoichiometric amount of $TiCl_4$ to induce homoenolate equivalent reagents. Instability of the anions, formation of the Brook rearrangement byproducts, and lack of regioselectivity are all potential problems of α-siloxy allylsilane **8**.

Scheme 1.2. Stoichiometric Homoaldol Equivalent Reaction

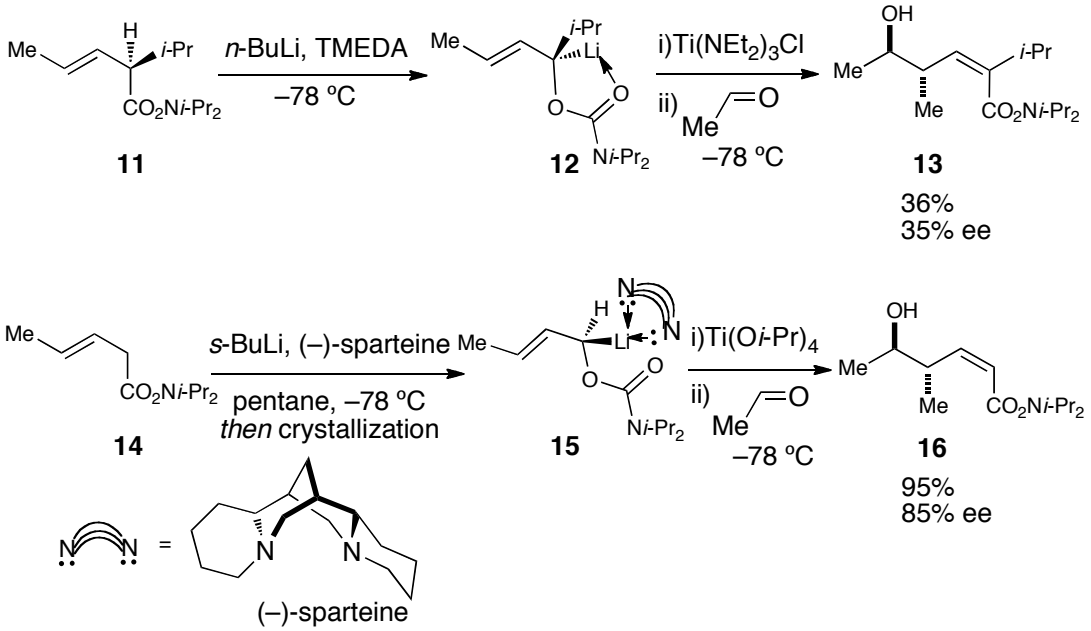


Utilization of Grignard reagent **2** and $TiCl_4$ for generation of homoenolate equivalent reagents from silyloxy cyclopropane **4** and α-siloxy allylsilane **8** revealed several issues, including both decomposition of Grignard reagents and stoichiometric use of titanium reagents. Recognizing these problems, Hoppe approached these issues by enantioselective deprotonation of alkenylcarbamate.[12]

Hoppe's research toward homoaldol equivalent formation focused on α-deprotonation of 2-alkenylcarbamate **11** with *n*-BuLi to generate lithiated alkenylcarbamate **12**, which subsequently underwent lithium-titanium exchange addition of the carbonyl compound to construct the homoaldol equivalent adduct **13** (Scheme 1.3). This procedure presents a successful deprotonation of the alkenylcarbamate **11** with retention of stereochemistry and affords the stereoselective homoaldol equivalent adducts. Nonetheless, this method suffers from low yields with

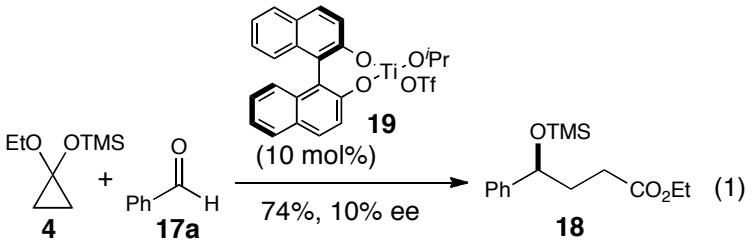
poor enantioselectivity and requires chiral carbamate substrates. The racemization of the lithium complex **12** is one plausible reason for low enatioselectivity in this reaction.

Scheme 1.3. Enantioselective Homoaldol Equivalent Reaction

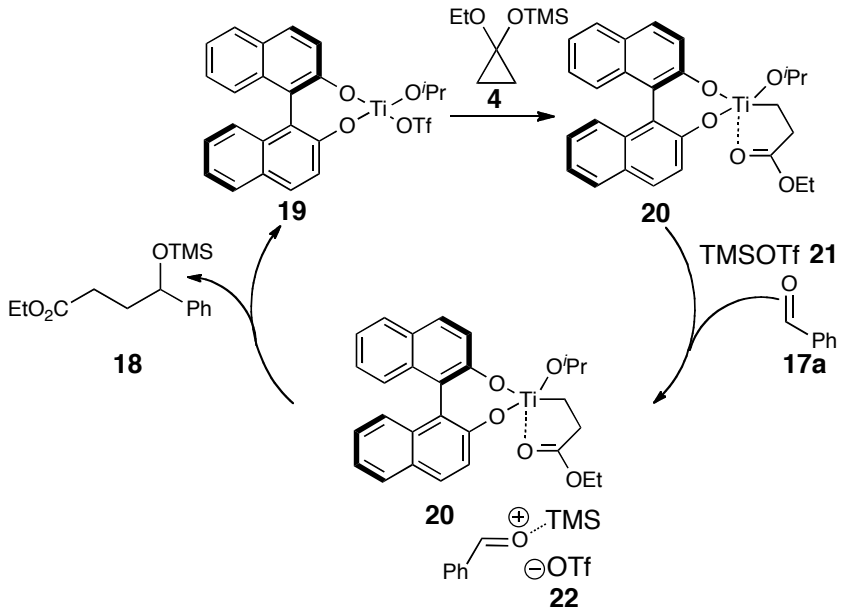


Employing chiral diamine (–)-sparteine and *s*-BuLi for stereoselective lithiation of prochiral butenyl carbamates **14**,[13] Hoppe and Zchage improved both selectivity and product yields of the asymmetric homoaldol equivalent reaction. Crystallization of diamine complexes produced only the desired diamine complex **15**. This complex underwent transmetallation with Ti(O*i*-Pr)$_4$ generating a stable titanium complex which was then treated with aldehyde to afford the *anti* homoaldol adduct **16** (Scheme 1.3). However, this homoaldol equivalent reaction has limited substrate scope and still requires stoichiometric amount of titanium reagents.

The catalytic homoaldol equivalent reaction describing formation of γ-hydroxy esters **18** from silyloxy cyclopropane **4** and benzaldehyde **17a** under titanium catalyst **19** was reported by Gleason in 1999 (eq 1).[14] A proposed catalytic cycle of titanium-catalyzed transformation of silyloxy cyclopropane **4** and benzaldehyde **17a** to γ-hydroxy esters **18** is described in Scheme 1.4. Ring opening of silyloxy cyclopropane **4** under titanium catalyst **19** generates the alkoxy thitanium homoenolate **20**. The homoenolate equivalent **20** undergoes addition to aldehyde **17a**, activated by a co-catalyst of trimethylsilyl triflate **21** forming intermediate **22** and affording the homoaldol equivalent adducts **18** in the catalytic cycle (Scheme 1.4).



Scheme 1.4. Proposed Catalytic Cycle of Titanium-Catalyzed Transformation

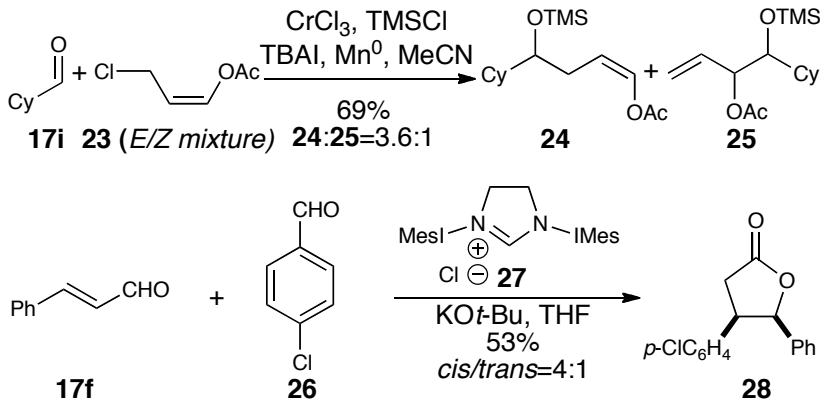


Since Gleason reported the first catalytic generation of homoenolate equivalents, a number of different approaches to homoaldol equivalent reactions employing various catalytically generated homoenolates have been reported. For instance, Lombardo and co-workers in 2002 introduced chromium-catalyzed homoaldol equivalent reactions utilizing 3-chloro-propenyl ester **23** and carbonyl compound **17i** under chromium catalyst ($CrCl_3$) to afford homoaldol equivalent adducts **24** (Scheme 1.5).[15] Chromium (II) oxidatively added to 3-chloro-propenyl ester **23**, in which allylchromium (III) complex was generated. The allylic chromium complex was added to carbonyl compound **17i** to produce homoaldol equivalent adducts **24** and 1,2-diol moieties **25**. Formation of 1,2-diol moieties **25** caused low yield of the desired homoaldol equivalent product **24**. Regioselectivity of this reaction was influenced by solvents. Replacement of

DMF by acetonitrile increased reaction rate but regioselectivity was reversed in favor of diol derivatives. In addition, this reaction requires the use of a catalytic amount of tetrabutylammonium iodide (TBAI) to generate 3-iodo-propenyl esters in situ. This reaction has demonstrated oxidative addition of Cr(II) to allylic halides under Nozaki-Hiyama-Kishi type reaction conditions but yield and regioselectivity remains low.

Recently, Christian and Glorius in 2004 disclosed a catalytic generation of homoenolate equivalents and further reported their application to homoaldol equivalent reactions. *N*-Heterocyclic carbenes **27**, which can catalyze formation of homoenolate equivalents, is a new strategy for generating homoenolate for use with homoaldol equivalent reaction.[16] This reaction protocol has allowed use of organocatalyzed, stereoselective homoaldol equivalent reactions of α,β-unsaturated aldehydes **17f** with aromatic aldehyes **26** to afford γ-butyrolactones **28** (Scheme 1.5). However, the reaction, generating homoenolate equivalents via previously unprecedented procedure, exhibits low product yield and stereoselectivity. In spite of the fact that very significant contributions to the homoaldol equivalent reaction have been made, efficient, mild, and catalytic methods for generation of homoenolates for use in homoaldol equivalent reaction need to be developed.

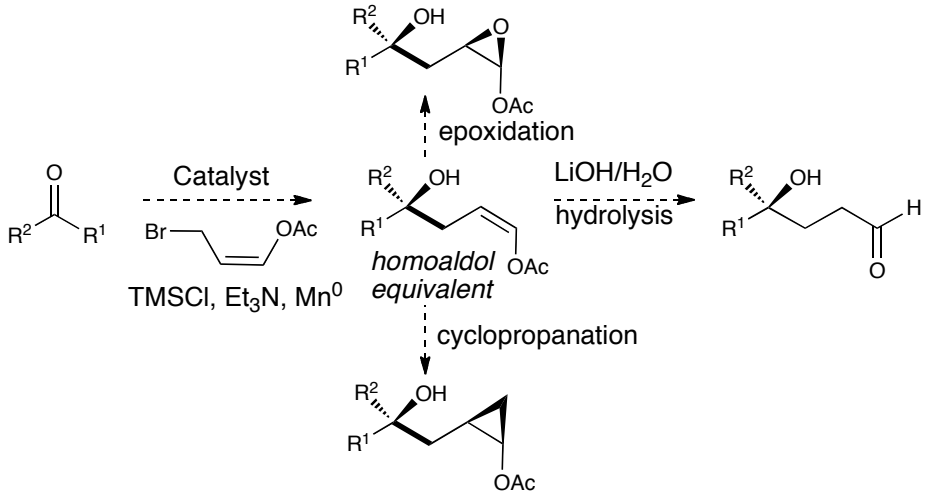
Scheme 1.5. Catalytic Homoaldol Equivalent Reaction



1.2 Specific Aim

The purpose of this project is to develop a synthetic method for regioselective, catalytic homoaldol equivalent reactions that can generate hydroxy vinyl acetates of homoaldol equivalent adducts suitable for further various manipulation to hydroxyl-directed epoxidations, hydroxyl-directed cyclopropanations, and hydrolysis to generate the homoaldol equivalent adducts (Scheme 1.6). This chapter describes the development of synthetic methods for generating homoaldol equivalent products and further manipulation of these homoaldol adducts to make valuable building blocks in organic synthesis.

Scheme 1.6 Proposed Generation of Homoaldol Adducts and Manipulation



1.3 Cr-Catalyzed Homoaldol Equivalent Reaction

Chromium-mediated additions of allylic nucleophiles to electrophiles such as aldehydes, in the Takai–Utimoto[17] and Nozaki–Hiyama–Kishi[18] reactions (Scheme 1.7), as well as the catalytic variant reported by Fürstner,[19] are well-developed processes. We have developed a mild, efficient, catalytic method for generation of homoenolate equivalents mediated by a chromium catalyst and applied this method to highly regioselective intermolecular homoaldol equivalent reactions (Table 1.1).

Scheme 1.7. Chromium-Mediated Coupling Reactions

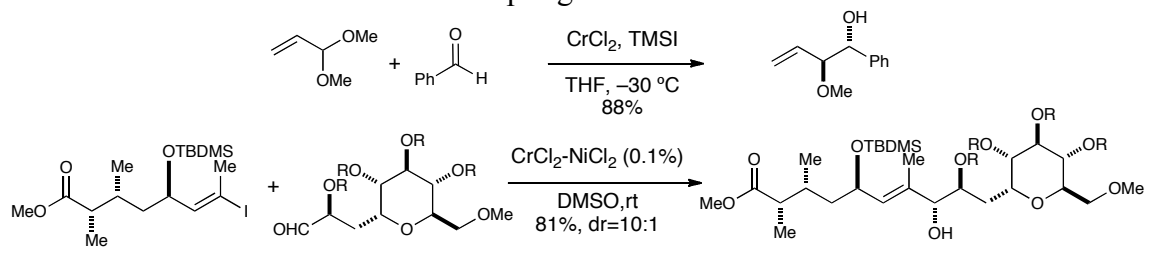
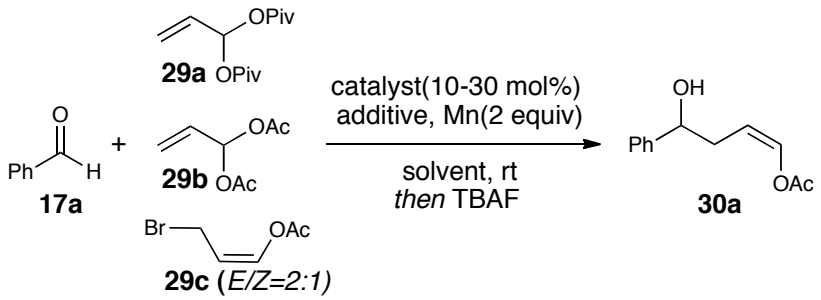


Table 1.1. Initial Screening Results of Homoaldol Equivalent Reaction[a]



entry	nucleophile	catalyst	solvent	additive	yield (%)[b]
1	**29a**	$CrCl_2$	THF	DIPEA, TMSCl	0
2	**29a**	$CrCl_3$	THF	TEA, TMSCl	0
3	**29a**	$CrCl_3$	THF	DIPEA, TMSCl	0
4	**29a**	$CrCl_3$	MeCN	DIPEA, TMSCl	0
5	**29a**	$CrCl_3$	MeCN		0
6	**29a**	$CoBr_2$	MeCN	DIPEA, TMSCl	0
7	**29a**	$CoBr_2$	MeCN		30
8	**29b**	$CrCl_3$	THF	DIPEA, TMSCl	0
9	**29b**	$CoBr_2$	MeCN	DIPEA, TMSCl	0
10	**29b**	$CoBr_2$	MeCN		30
11	**29c**	$CrCl_3$	THF	TMSCl	45[c]
12	**29c**	$CrCl_3$	THF	TMEDA, TMSCl	44[c]
13	**29c**	$CrCl_3$	THF	$(H_2NCH_2)_2$, TMSCl	71[c]
14	**29c**	$CrCl_3$	THF	DIPEA, TMSCl	90[c]
15	**29c**	$CrCl_3$	MeCN	TEA, TMSCl	50[c]
16	**29c**	$CrCl_3$	THF	TEA, TMSCl	99[c]

[a] Reactions were performed using nucleophiles (**29a, 29b,** or **29c** (0.64 mmol)), aldehydes **17a** (0.32 mmol), catalysts ($CrCl_3$ (0.032 mmol), $CrCl_2$ (0.032 mmol), $CoBr_2$ (0.096 mmol)), Mn^0 (0.64 mmol), base (TEA (0.048 mmol), DIPEA (0.048 mmol)) and TMSCl (0,64 mmol) in THF (2 mL) or MeCN (2 mL) at rt for 20 h and quenched with saturated aqueous $NaHCO_3$ solution. [b] Isolated yield. [c] yield after deprotection of TMS protecting group with TBAF.

As Lombardo's early studies had revealed that acetoxyallyl chlorides are not efficient nucleophiles in chromium-catalyzed additions to aldehydes,[15] we employed masked carbonyls **29a** and **29b**, and the presumably more reactive allyl bromide **29c** (3-

bromopropenyl acetate) as nucleophiles for addition to benzaldehyde **17a** (Table 1.1). We began these studies with chromium-mediated addition of homoenolate equivalent to aldehydes to introduce homoaldol equivalent products. Our preliminary results in this study led us investigate the chromium catalyst $CrCl_3$ with 3-bromo vinyl acetate **29c** for this homoladol equivalent reaction. Nucleophiles **29a** and **29b** did not proceed in the homoladol equivalent product with $CrCl_3$ and additives of bases and trimethylsilyl chloride (TMSCl) (Table 1.1, entries 2 and 8) yet led to 30% yield with $CoBr_2$ without additives (Table 1.1, entries 7 and 10). Addition of additives of bases and TMSCl in the reaction with nucleophiles **29a** and **29b** under $CoBr_2$ did not afford the homoladol equivalent products (Table 1.1, entries 6 and 9). It was observed that nucleophiles **29a** and **29b** under $CoBr_2$ proceed in homoaldol equivalent products without additives in polar solvent such as acetonitrile (Table 1.1, entries 7 and 10). On the other hand, nucleophile **29c** provided 99% yield under the reaction conditions (Table 1.1, entry 16).[20]

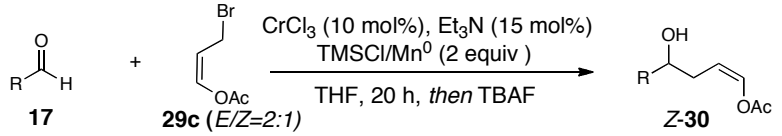
Interestingly, we observed significant acceleration of reaction rate with triethylamine (TEA) as an additive (Table 1.1, entry 16). In order to optimize choice of base, we explored different bases raging from bidentate bases to monodentate bases in the homoaldol equivalent reactions. Bidentate bases such as tetramethylethylenediamine (TMEDA) and ethylenediamine provided the homoaldol equivalent adducts in 44% and 71% respectively (Table 1.1, entries 12 and 13). Monodentate bases including diisopropylethylamine (DIPEA) and triethylamine (TEA), however, afforded the homoaldol equivalent products in 90% and 99% respectively (Table 1.1, entries 14 and

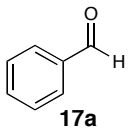
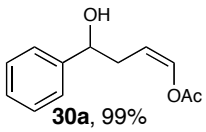
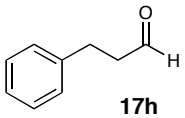
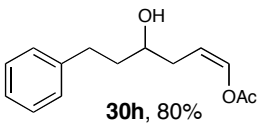
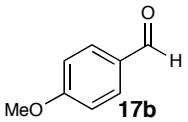
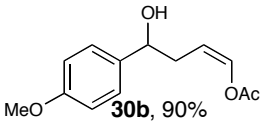
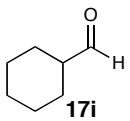
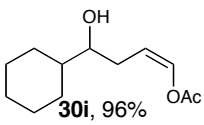
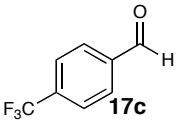
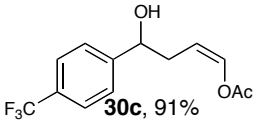
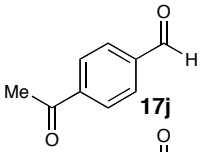
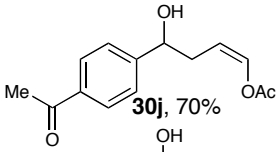
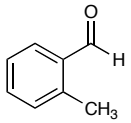
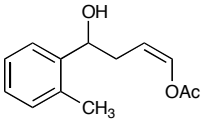
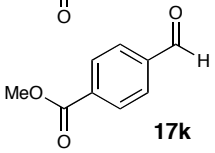
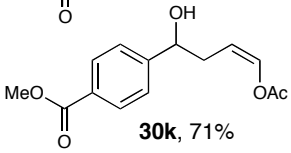
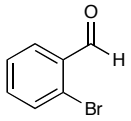
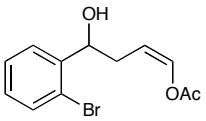
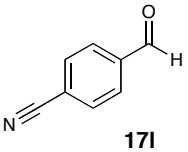
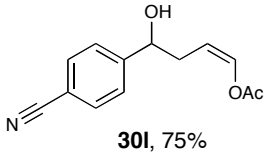
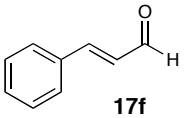
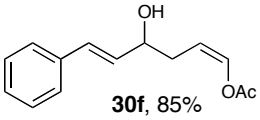
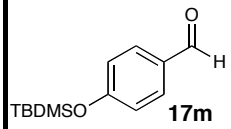
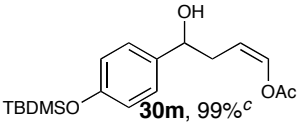
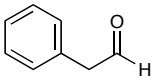
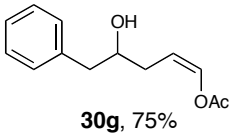
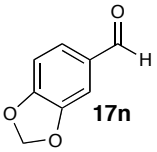
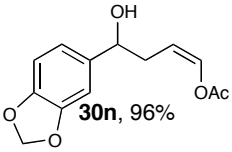
16). This result revealed that sterics are crucial factors for successful homoaldol equivalent reactions requiring sterically less demanding bases.

Experiments to probe the influence of this additive were undertaken in two different reaction flasks, one with TEA and the other one without TEA. The rate of reactions without the TEA additive is very slow and the reaction without TEA does not go to completion under the standard reaction condition (20 h). Other bases such as chelating diamines were less effective.

With these optimized catalytic reaction conditions in hand, various aldehydes with 3-bromo vinyl acetate **29c** were screened under the standard reaction conditions shown in Table 1.2. Aromatic aldehydes **17a**, **17b**, **17c** (Table 1.2) afford higher yield than aliphatic aldehydes **17g**, **17h** (Table 1.2) yet the unsubstituted parent aromatic aldehyde **17a** provided the highest yield (99%).[20] It was observed that steric effects were more crucial than electronic effects regarding the product yield. *Ortho*-substituted aldehydes, including 2-methylbenzaldehyde **17d** and 2-bromobenzaldehyde **17e**, generate lower product yield than *para*-substituted aldehydes such as 4-methoxybenzaldehyde **17b** and 4-trifluorobenzaldehyde **17c** (Table 1.2). Evidence of this idea is supported by the fact that employment of 2,6-dimethylbenzaldehyde as an electrophile leads to very slow conversion and low yield (<50%). It is noteworthy that *para*-nitrobenzaldehyde generates low product yield (<50%) probably due to lack of solubility.

Table 1.2. Scope of Homoaldol Equivalent Reaction[a]

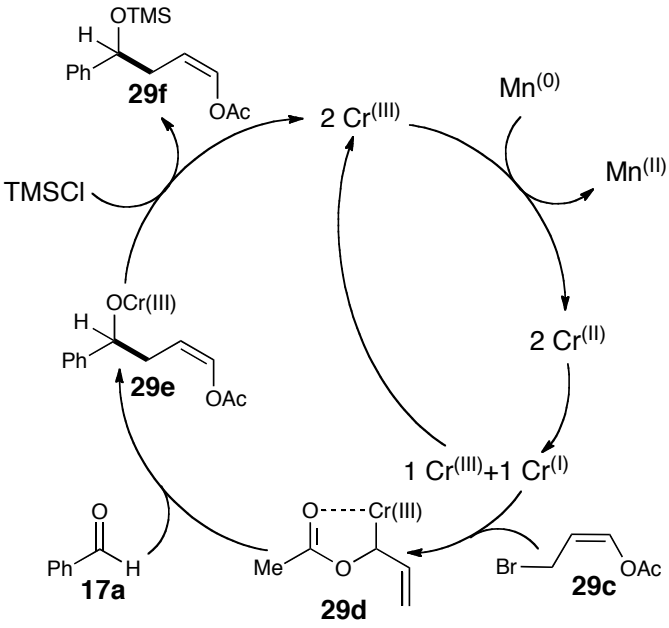


SM	product[b]	SM	product[b]
 **17a**	 **30a**, 99%	 **17h**	 **30h**, 80%
 **17b**	 **30b**, 90%	 **17i**	 **30i**, 96%
 **17c**	 **30c**, 91%	 **17j**	 **30j**, 70%
 **17d**	 **30d**, 82%	 **17k**	 **30k**, 71%
 **17e**	 **30e**, 78%	 **17l**	 **30l**, 75%
 **17f**	 **30f**, 85%	 **17m**	 **30m**, 99%[c]
 **17g**	 **30g**, 75%	 **17n**	 **30n**, 96%

[a] Reactions were performed using **29c** (0.64 mmol), aldehydes **17** (0.32 mmol), $CrCl_3$ (0.032 mmol), Mn^0 (0.64 mmol), Et_3N (0.048 mmol), and TMSCl (0.64 mmol) in 2 mL THF at rt for 20 h, quenched with saturated aqueous $NaHCO_3$ solution, and deprotected with TBAF. [b] Isolated yield. [c] 24 h reaction.

We also have examined functional group tolerance in presence of the aldehydes. Through the investigation of these studies, functional group tolerances using these conditions were found to be high. For example, we found that *para*-silyl-protected hydroxybenzaldehyde **17m** converted to the desired homoaldol equivalent product **30m** in 99% yield (Table 1.2) and also 3,4-(methylenedioxy)benzaldehyde **17n** proceeded efficiently to afford the desired homoaldol equivalent product **30n** in 96% yield. Interestingly, functional group tolerance of other moieties such as ketone **17j**, ester **17k**, and nitrile **17l** lead to diminished but still synthetically acceptable yields (70%, 71%, and 75% yields, respectively (Table 1.2)).[20]

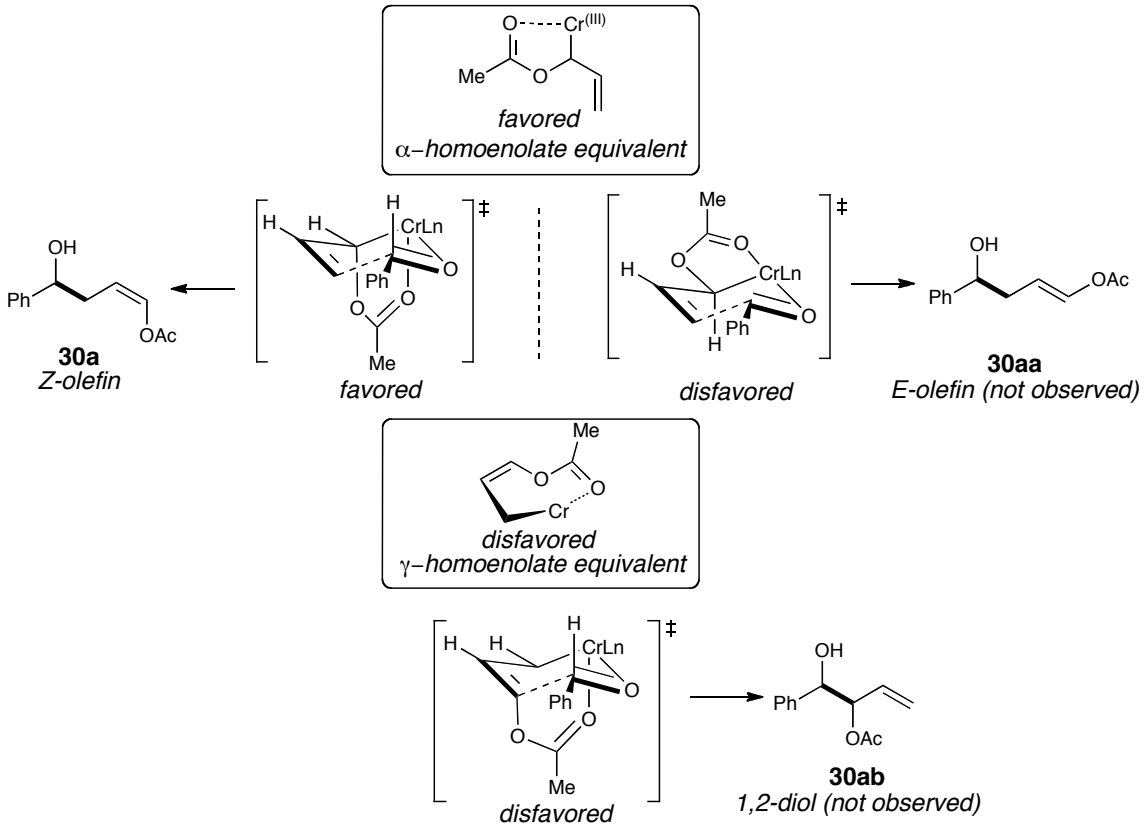
Scheme 1.8. Proposed Mechanism of the Homoaldol Equivalent Reaction



Although more comprehensive studies are required to describe a mechanism of the homoaldol equivalent reaction and the transition state arrangement, we proposed a plausible reaction mechanism based on the observed experimental results and literature precedent.[19] First, chromium (III) is being reduced with Mn (0) to chromium (II), which undergoes redox interconversion to generate chromium (III) and chromium (I),[21-23] in which chromium (I) undergoes oxidative addition with 3-bromopropenyl acetate **29c** to form organochromium complex **29d**. Second, the organochromium complex **29d** undergoes addition to benzaldehyde **17a** to afford organochromium complex **29e**. Finally, transmetallation of organochromium complex **29e** with TMSCl generates TMS-protected homoaldol equivalent adduct **29f** (Scheme 1.8).

In all cases, we have observed only the desired homoaldol adducts without formation of possible 1,2-oxygenated regioisomeric product **30ab** and the *trans*-vinyl acetate product **30aa**. We believe that these observations of highly regio-and chemo-selective reaction can be explained by a transition state arrangement as describe in Scheme 1.9, in which the formation of a 5-membered ring chelate between the chromium center and the acetate subunit as part of a well-established 6-membered ring is crucial for explaining regio- and chemo-selective C–C bond formation. When the acetate subunit is located at equatorial position on 6-membered ring which could respond to unobserved *trans*-vinyl acetate product **30aa**, the formation of a 5-membered ring chelate between the chromium center and the acetate subunit is not plausible because the acetate subunit is not reachable to chelate chromium center.

Scheme 1.9. Proposed 6-membered Ring Transition State Arrangement

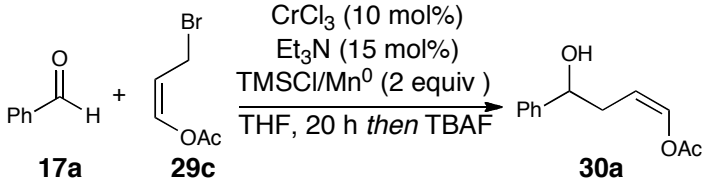


The 5-membered chelate ring formation between the chromium center and the acetate subunit is more stable complex than 7-memberd chelate ring formation corresponding to unobserved 1,2-oxygenated regioisomeric product **30ab**. Accordingly, the *cis*-alkene geometry and regiochemistry of the homoaldol addition products were rationalized by this transition state arrangement (Scheme 1.9).[20]

Due to the potential application of this process for the generation of chiral building blocks applicable in total synthesis, we explored larger-scale reactions described in Table 1.3. With use of 2 mmol of benzaldehyde **17a**, the reaction proceeded

smoothly to afford the homoaldol adducts **30a** in 99% yield (Table 1.3, entry 2). When 5 mmol of benzaldehyde **17a** was subjected to the standard reaction, low yield of product (51%) obtained (Table 1.3, entry 3). For larger reaction scales, the use of freshly washed Mn^0 with HCl, which could eliminate any presence of MnO_2, was required to obtain high yields. On 5 mmol (Table 1.3, entry 4) or 20 mmol (Table 1.3, entry 5) scale reactions with fresh Mn^0, the isolated yield of product **30a** is 90% or 85%, respectively (Table 1.3).

Table 1.3. Large Scale Reaction of Homoaldol Equivalent Reaction[a]



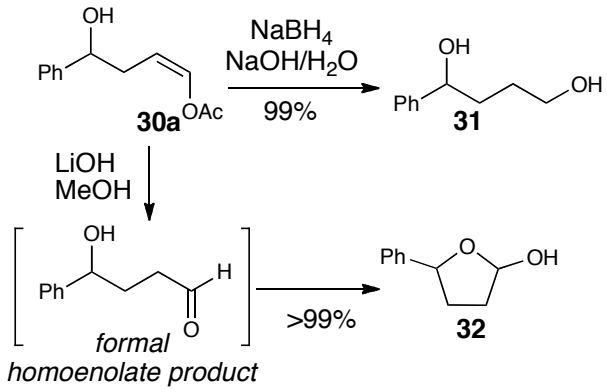
17a **29c** **30a**

entry	mmol (**17a**)	isolated yield (%)[b]
1	1	99
2	2	99
3	5	51
4[c]	5	90
5[c]	20	85

[a] Reactions were performed using **29c** (2 equiv), aldehydes **17a** (1 equiv), $CrCl_3$ (10 mol%), Mn^0 (2 equiv), Et_3N (15 mol%), and TMSCl (2 equiv) in THF at rt for 20 h, quenched with saturated aqueous $NaHCO_3$ solution, and deprotected with TBAF. [b] Isolated yield. [c] Entry 1, 2, and 3 followed GP1. Entry 4 and 5 used activated Mn^0 (325 mesh) that was prepared by sequentially washing with 5% HCl, EtOH, and Et_2O, and then dried under high vacuum and used according to GP1.

We next performed hydrolysis and reduction of the homoaldol equivalent adducts to afford diol **31** and lactol **32** respectively (Scheme 1.10). Treatment of the homoaldol equivalent adducts with $NaBH_4$ in NaOH provided diol **31** in excellent yield (99%). Mild hydrolysis condition (LiOH/MeOH) of the homoaldol equivalent adducts provides the formal homoaldol product, which is isolated after spontaneous cyclization to lactol **32** in quantitative yield.[20]

Scheme 1.10. Hydrolysis and Reduction of Homoaldol Equivalent Product **30a**

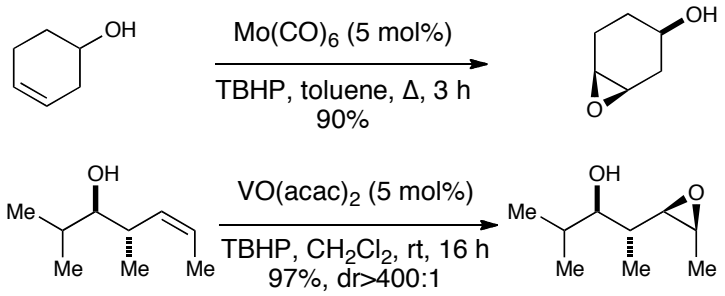


1.4 Functionalization of Homoaldol Equivalent Products and Stereochemical Assignment

Surprisingly, hydroxyl-directed[5] epoxidations and cyclopropanations of vinyl acetates have not been previously reported. Hydroxyl-directed epoxidations of homoallylic alcohols were successful only for specific types of homoallylic alcohols. For example, hydroxyl-directed epoxidation of homoallylic alcohols[24] in cyclic systems have proven possible (Scheme 1.11), yet acyclic homoallylic alcohols have not been

successful in the hydroxyl-directed epoxidation. Directed-epoxidation of homoallylic alcohols bearing alkene α-stereocenters exhibit high stereoselectivity (Scheme 1.11).[25] To the best of our knowledge, we reported the first highly diastereoselective epoxidations of acyclic homoallylic alcohols where no α-stereocenters of the olefins are present, providing over 90% de.

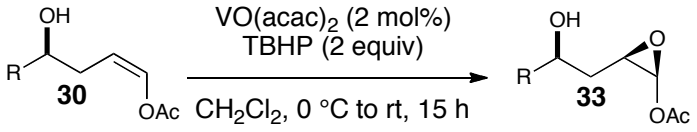
Scheme 1.11. Hydroxyl-Directed Epoxidation of Cyclic Homoallylic Alcohols

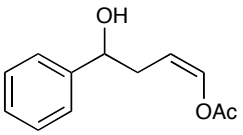
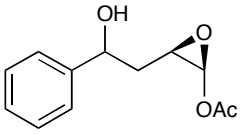
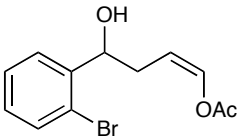
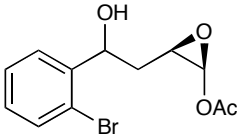
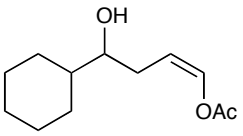
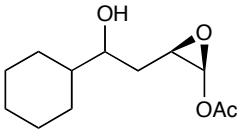


To demonstrate the value of the proximal hydroxyl and vinyl acetate groups of the homoaldol products, conversion of homoaldol equivalent adducts into very valuable compounds was pursued. When the homoaldol adducts were treated with *m*-CPBA, an equal ratio of diastereomeric epoxides was obtained. As a result, we explored transition metal catalyzed epoxidation of homoallylic alcohols.[26] We employed VO(O*i*-Pr)$_3$ (2 mol%) as a catalyst for directed epoxidation of homoallylic alcohols with hydrogen peroxides such as TBHP (70% in water), CHP, and TBHP (5.5 M in decane) but the highest yield from the catalyst was less than 50% (dr = 10:1). The preliminary results of directed-epoxidation of homoallylic alcohols with vanadium catalyst provided promising

results in selectivity (dr = 10:1) but the chemical yield was low. As a result, we utilized $VO(acac)_2$ (2 mol%) and TBHP (5.5M in decane). The directed epoxidation with $VO(acac)_2$ (2 mol%) and TBHP (2 mmol) installed the epoxide/acetal, providing the 1,2,4-oxygenated α-acetoxy-δ-hydroxy α,β-epoxide **33a** in 82% yield as primarily the *syn* diastereomer (dr = 13:1, Table 1.4, entry 1). With the optimal conditions in hand, the substrate scope of the hydroxyl-directed epoxidation of homoallylic alcohol was examined. Highly selective epoxidation of homoallylic alcohols was demonstrated in the reaction of hydroxy phenyl butenyl acetate **30a** (Table 1.4, entry 1) as well as epoxidation of bromophenyl hydroxy butenyl acetate **30e** (Table 1.4, entry 2) and cyclohexyl hydroxy buenyl acetate **30i** (Table 1.4, entry 3), providing high yield and selectivity of 80% yield (dr = >15:1) and 82% (dr = 10:1) respectively. This hydroxyl-directed epoxidation of homoallylic alcohols allows us to approach β-hydroxy epoxide in stereoselectivity (dr = >15:1, Table 1.4, entry 2).[20]

Table 1.4. Hydroxyl-Directed Epoxidation of Vinyl Acetates[a]



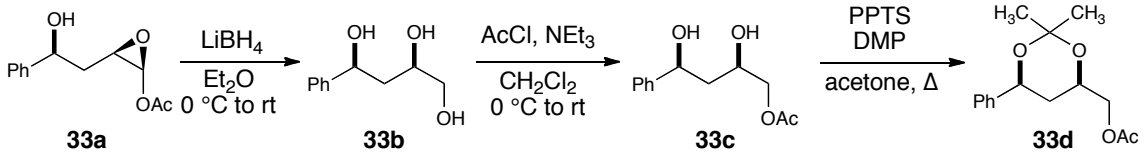
SM	product[b]
 **30a**	 **33a**, 80%, dr[c]=13:1
 **30e**	 **33e**, 80%, dr=>15:1
 **30i**	 **33i**, 82%, dr=10:1

[a] Reagents: $VO(acac)_2$ (2 mol%), adducts **30** (1 mmol), TBHP (5.5 M solution) (2 mmol) in CH_2Cl_2 at rt for 15 h. [b] Isolated yield. [c] dr (*syn:anti*) was determined by ^1H NMR spectroscopy.

In order to confirm the *syn*-epoxide products, we employed [^{13}C] acetonide methods previously developed by Rychnovsky. Rychnovsky and co-workers have established a general method to determine stereochemistry of *syn*- and *anti*-1,3-diol acetonides by ^{13}C chemical shifts of acetyl methyl groups.[27] The epoxide product **33a** was treated with $LiBH_4$ affording triol **33b** in which the primary alcohol was protected with acetyl chloride, providing **33c** (Scheme 1.12). The 1,3-diol **33c** was converted into acetonide **33d**.[18] The vicinal methyl groups of the *syn*-1,3-diol acetonide resulted in a

diastereotopic group posessing different chemical shifts for the two methyl groups (δ = 30.2, 21.0 ppm), confirming the *syn*-epoxide product **33a**.

Scheme 1.12. Stereochemical Analysis of Hydroxyl-Directed Epoxides

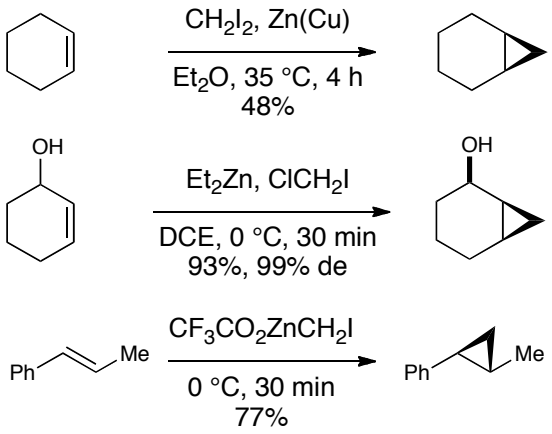


33a **33b** **33c** **33d**

With these promising results using hydroxyl-directed epoxidation of homoallylic alcohols, we were interested in studying the stereoselective conversion of the homoaldol adducts to cyclopropane subunits. This was of interest not only due to the challenge of selective cyclopropation of homoallylic alcohols but also their presence in a wide variety of natural products and biological active compounds.[28]

Since the pioneering research by Simmons and Smith for cyclopropanation was reported[29,30] it has became the most widely used reaction of three-membered ring synthesis, and employs Zn(Cu)/diiodomethane reagent. Recently, several alternative methods for the generation of the reactive reagent ($RZnCH_2I$) in cyclopropanation were introduced by Denmark[31] ($ClZnCH_2I$) and Shi ($CF_3CO_2ZnCH_2I$) (Scheme 1.13).[32]

Scheme 1.13. Cyclopropanation of Olefins

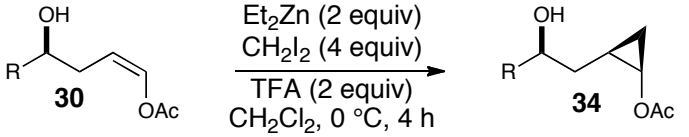


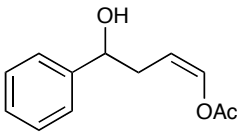
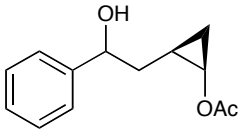
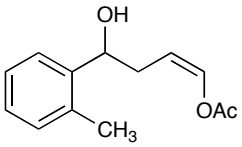
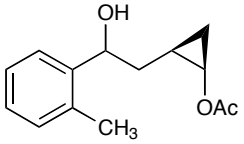
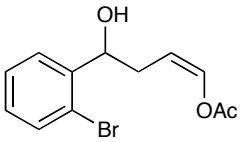
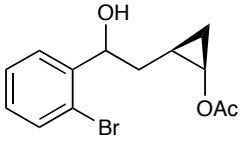
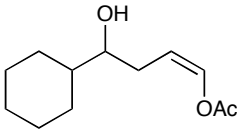
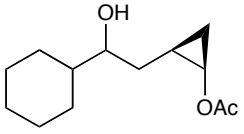
Results form examination of stereoselective cyclopropanation of the homoaldol equivalent adducts employing the Simmons-Smith reagent ($IZnCH_2I$) were rather disappointing, providing 40% (dr = 1.6:1). When the Denmark reagent ($ClZnCH_2I$) was employed, the product yield was improved (73%), yet selectivity was still low (dr = 1.6:1). Remarkably, Shi's cyclopropanation reagent ($CF_3CO_2ZnCH_2I$) afforded the best result for selective cyclopropanation (95%, dr = 6.6:1, Table 1.5, entry 1) of homoallylic alcohols. [20]

With these optimized reaction conditions in hand, the substrate scope was examined. The hydroxyl-directed cyclopropanation of homoallylic alcohols proceeded well in both aromatic and aliphatic homoaldol adducts, yet the best yield (95%, Table 1.5, entry 1) and selectivity (dr = 6.6:1, Table 1.5, entry 1) were derived from the parent homoaldol adduct **30a**. We observed a noticeable decrease of selectivity from 2-bromophenyl hydroxyethyl cyclopropyl acetate **34e** (dr = 3.8:1, Table 1.5, entry 3) probably due to interaction between the zinc reagent and halogen of the olefin **30e**. To

best of our knowledge, this is the first highly *syn*-selective cyclopropanation of homoallylic alcohols in acyclic systems leading to excellent yields (95%) and selectivity (dr = 6.6:1) even though selective cyclopropantions of allylic alcohols[33] and homoallylic alcohols in cyclic system have been previously reported.[34]

Table 1.5. Hydroxyl-Directed Cyclopropanation of Vinyl Acetates[a]

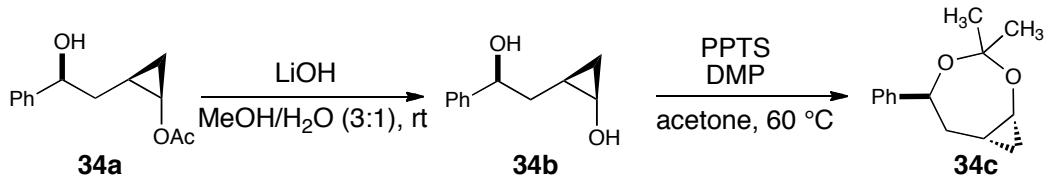


SM	product[b]
 **30a**	 **34a**, 95%, dr[c]=6.6:1
 **30d**	 **34d**, 84%, dr=5:1
 **30e**	 **34e**, 80%, dr=3.8:1
 **30i**	 **34i**, 88%, dr=6:1

[a]All reactions were performed using Et_2Zn (1 mmol), CH_2I_2 (2 mmol), TFA (1 mmol), olefin **30** (0.5 mmol) in CH_2Cl_2 at 0 °C for 4 h. [b] Isolated yield. [c] dr (*syn:anti*) was determined by HPLC.

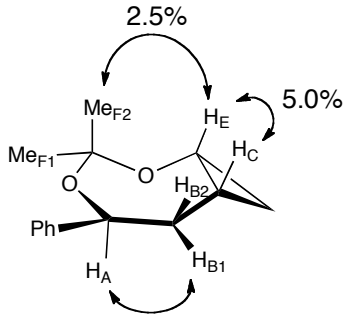
The stereochemical outcome of the hydoxyl-directed cyclopropanation was rationalized by the use of NOE measurements after cyclization of the diol intermediate **34b** to bicyclic cyclopropane **34c** (Scheme 1.14). NOE data strongly supports the conclusion that cyclopropanation of the homoaldol adducts was directed by the hydorxyl group (Table 1.6).[20]

Scheme 1.14. Stereochemical Analysis of Hydroxyl-Directed Cyclopropanation Product



34a **34b** **34c**

Table 1.6. Key NOE Enhancements in **34c**



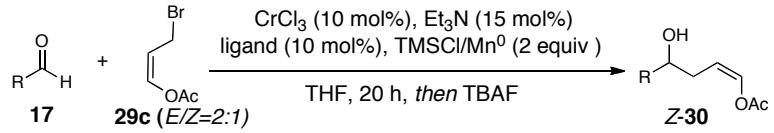
Irradiated H	Observed H	% nOe
A	B1	3.1
A	F	3.1
A	H	2.9
E	F2	2.5
E	C	5.0

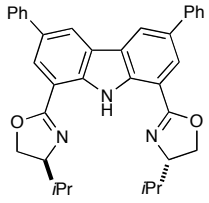
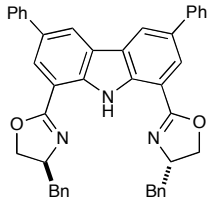
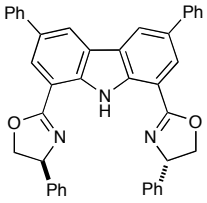
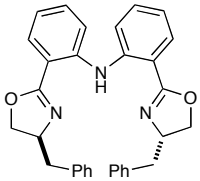
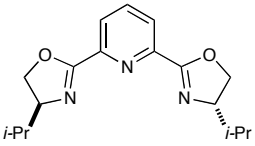
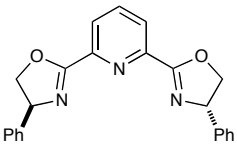
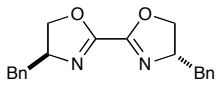
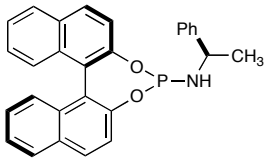
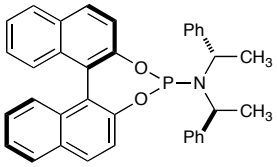
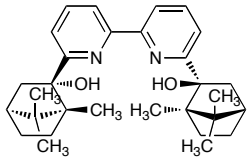
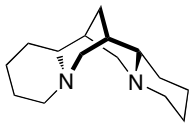
1.5 Asymmetric Homoaldol Equivalent Reactions

Although chromium-catalyzed enantioselective addition of allylic bromides to ketones[35] and aldehydes[36] to afford homoallylic alcohols has been well studied, asymmetric homoaldol reactions remain in difficult tasks reported in few cases.[12,13] For example, Hoppe reported asymmetric homoaldol equivalent reaction employing chiral diamine (–)-sparteine and *s*-BuLi for stereoselective lithiation of prochiral butenyl carbamates which underwent transmetallation with $Ti(Oi\text{-}Pr)_4$ generating titanium complex that added to aldehydes to afford enantioselective synthesis of homoaldol products[13]. This method, however, limited in carbamate substrates and utilized stoichiometric amount of titanium reagents.

Therefore, we desired to explore asymmetric homoaldol equivalent reactions employing a variety of chiral ligands. The tridentate bis(oxazolinyl)carbazole ligands have been successfully applied for the asymmetric catalysis of Nozaki-Hiyama methallylation and allylation of aldehydes.[37] We employed tridentate bis(oxazolinyl)carbazole ligands, PyBox ligands, and phosphoramidite ligands for the asymmetric homoaldol reactions described in Table 1.7. The results of asymmetric homoaldol reactions employing the ligands, however, show low enantioselectivity (Table 1.7). Among the ligands (Table 1.7), the [PyBox*i*-Pr] ligand exhibited the highest enantioselectivity (11% ee).

Table 1.7. Asymmetric Homoaldol Equivalent Reactions Employing Carbazole and PyBox Ligands[a,b]

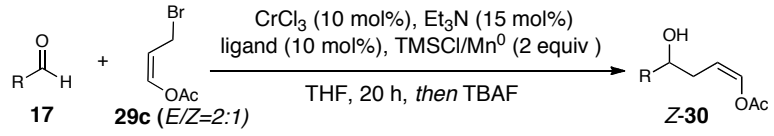


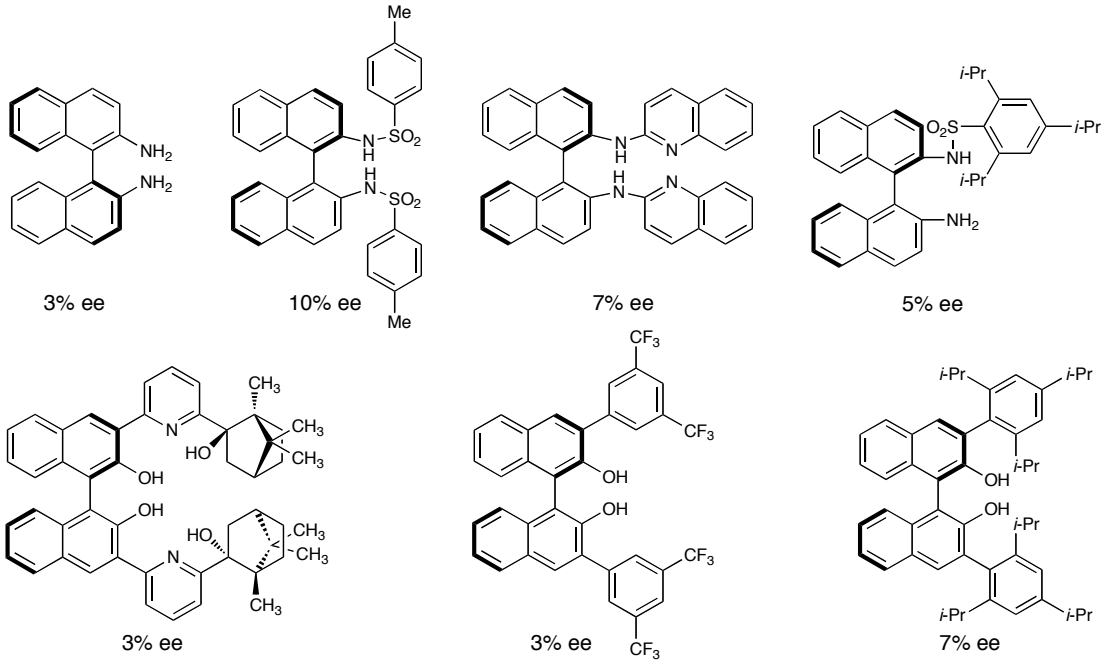
 4% ee	 9% ee	 9% ee	 7% ee
 11% ee	 1% ee	 2% ee	
 7% ee	 0% ee	 4% ee	 0% ee

[a] Reactions were performed using **29c** (0.64 mmol), aldehydes **17** (0.32 mmol), $CrCl_3$ (0.032 mmol), Mn^0 (0.64 mmol), Et_3N (0.048 mmol), ligand (0.032 mmol), and TMSCl (0.64 mmol) in 2 mL THF at rt for 20 h, quenched with saturated aqueous $NaHCO_3$ solution, and deprotected with TBAF. [b] Enantiomeric excess was determined by Chiral HPLC: Chiralcel® OD-H column (hexane/*i*-PrOH = 95/5), 1.0 mL/min, 254 nm, *major diastereoisomer* t_R = 16.0 min, and *minor diastereoisomer* t_R = 19.0 min.

We then utilized DABN[38] (Diamino-1,1′-binaphthalene) and BINOL[39] (Binaphthalene-2,2′-diol) derivative ligands for the asymmetric homoaldol reactions. The results employing DABN and BINOL derivative ligands are described in Table 1.8. The DABN and BINOL derivative ligands were not effective ligands for asymmetric homoaldol reactions providing low enantioselectivity (Table 1.8).

Table 1.8. Asymmetric Homoaldol Equivalent Reactions Employing DABN and BINOL derivative Ligands[a,b]

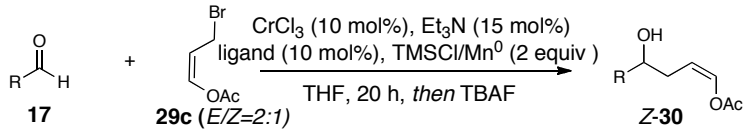


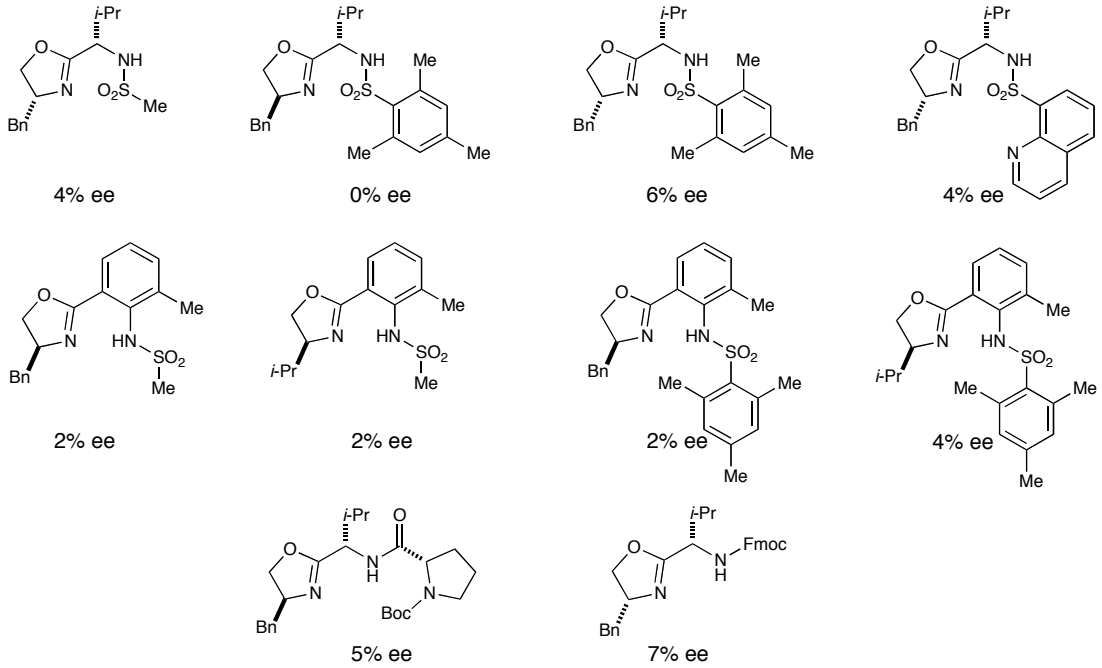


[a] Reactions were performed using **29c** (0.64 mmol), aldehydes **17** (0.32 mmol), $CrCl_3$ (0.032 mmol), Mn^0 (0.64 mmol), Et_3N (0.048 mmol), ligand (0.032 mmol), and TMSCl (0.64 mmol) in 2 mL THF at rt for 20 h, quenched with saturated aqueous $NaHCO_3$ solution, and deprotected with TBAF. [b] Enantiomeric excess was determined by Chiral HPLC: Chiralcel® OD-H column (hexane/*i*-PrOH = 95/5), 1.0 mL/min, 254 nm, *major diastereoisomer* t_R = 16.0 min, and *minor diastereoisomer* t_R = 19.0 min.

Oxazoline-containing ligands[36] and sulfonamide ligands[40] have been used in the enantioselective Nozaki-Hiyama-Kishi reaction. Accordingly, we have employed the ligands for the asymmetric homoaldol equivalent reactions described in Table 1.9. However, we obtained poor enantioselectivity of homoaldol equivalent products from these ligands.

Table 1.9. Asymmetric Homoaldol Equivalent Reactions Employing Oxazoline and Sulfonamide Ligands[a,b]



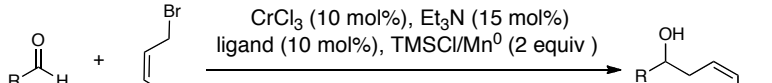


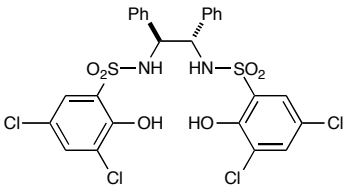
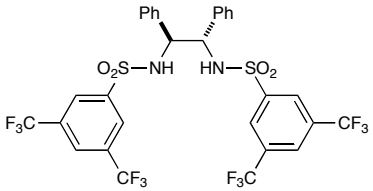
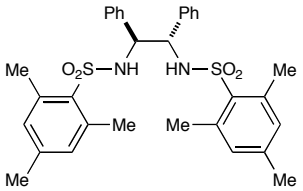
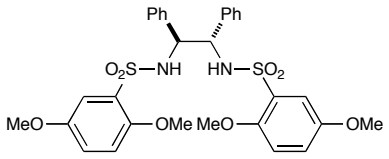
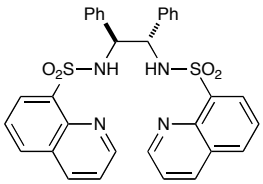
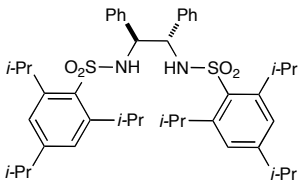
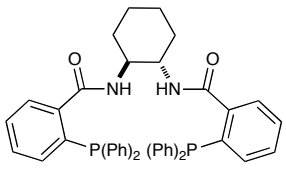
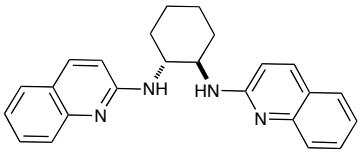
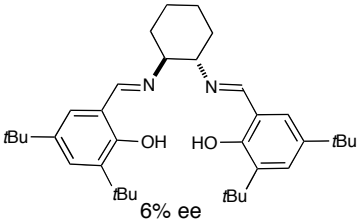
[a] Reactions were performed using **29c** (0.64 mmol), aldehydes **17** (0.32 mmol), $CrCl_3$ (0.032 mmol), Mn^0 (0.64 mmol), Et_3N (0.048 mmol), ligand (0.032 mmol), and TMSCl (0.64 mmol) in 2 mL THF at rt for 20 h, quenched with saturated aqueous $NaHCO_3$ solution, and deprotected with TBAF. [b] Enantiomeric excess was determined by Chiral HPLC: Chiralcel® OD-H column (hexane/*i*-PrOH = 95/5), 1.0 mL/min, 254 nm, *major diastereoisomer* t_R = 16.0 min, and *minor diastereoisomer* t_R = 19.0 min.

When chiral diamine ligands[41] were employed for the asymmetric homoaldol equivalent reactions, we obtained the homoaldol product in 25% ee (Table 1.10). It was observed that bulky substituents such as *iso*-propyl group on the ligand caused an increase in enantioselectivity of the homoaldol equivalent products (Table 1.10).

Based on these results, sulfonamide chiral diamine ligands were the most effective ligands for the asymmetric homoaldol equivalent reactions yet more comprehensive studies toward the asymmetric homoaldol equivalent reactions are necessary to improve enantioselectivity.

Table 1.10. Asymmetric Homoaldol Equivalent Reactions Employing Chiral Diamine Ligands[a,b]



 3% ee	 4% ee	 4% ee
 3% ee	 3% ee	 25% ee
 1% ee	 6% ee	 6% ee

[a] Reactions were performed using **29c** (0.64 mmol), aldehydes **17** (0.32 mmol), $CrCl_3$ (0.032 mmol), Mn^0 (0.64 mmol), Et_3N (0.048 mmol), ligand (0.032 mmol), and TMSCl (0.64 mmol) in 2 mL THF at rt for 20 h, quenched with saturated aqueous $NaHCO_3$ solution, and deprotected with TBAF. [b] Enantiomeric excess was determined by Chiral HPLC: Chiralcel® OD-H column (hexane/*i*-PrOH = 95/5), 1.0 mL/min, 254 nm, *major diastereoisomer* t_R = 16.0 min, and *minor diastereoisomer* t_R = 19.0 min.

1.6 Conclusion

We have reported regioselective, catalytic homoaldol equivalent reactions of 3-bromo vinyl acetate with aldehydes under $Cr^{(III)}$-$Mn^{(0)}$ redox condition. This homoaldol equivalent reaction allows us to access to the 1,4-oxygenated compounds that are not possible by a conventional aldol processes. Mild hydrolysis of the vinyl acetate and reduction conditions of the homoaldol adducts generated the diols and lactols in high yield (99%). Large scale reactions which are often a challenging process in catalytic reactions still led to high yields (20 mmol scale, 85%). Further manipulation of the homoaldol equivalent adducts with $VO(acac)_2$ (2 mol%) and TBHP provided stereoselective β-hydroxy epoxides with excellent selectivity (dr = >15:1). Upon treatment of the homoaldol adducts with Shi's cyclopropanation reagent ($CF_3CO_2ZnCH_2I$), high stereoselective cyclopropanation was observed in high selectivity (dr = 6.6:1). We also have explored asymmetric homoaldol equivalent reactions employing chiral diamine ligands providing 25% ee.

1.7 Experimental Procedure

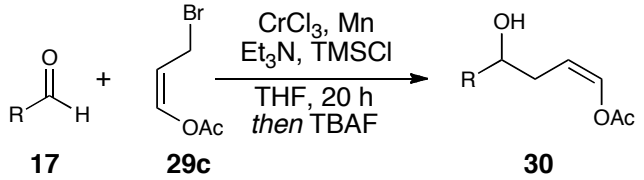
1.7.1 General Information

All reactions were carried out under an argon atmosphere in oven-dried glassware and with magnetic stirring bar. Dry THF was purified by passing through alumina under argon. All commercially obtained reagents were used as received.

Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 1.00 mm glass-backed silica gel 60-F plates. Visualization was performed with UV light or $KMnO_4$ stain solution. Concentration in vacuo refers to the removal of volatile solvent using a rotary evaporator attached to a dry diaphragm pump (10-15 mm Hg) and pumping to a constant weight with an oil pump (<300 mTorr). Heating was accomplished using silicone oil bath. Temperature was controlled by a temperature controller.

^{1}H NMR spectra were recorded on a Varian Inova 300 (at 300 MHz) or a Varian Mercury 300 (at 300 MHz) NMR and are recorded relative to Me_4Si (δ 0.0 ppm). ^{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 on Varian Inova 300 (at 75 MHz) or a Varian Mercury 300 (at 75 MHz) and are reported relative to $CDCl_3$ (δ 77.16 ppm). High-resolution mass spectra (HRMS) were obtained at TAMU. Infrared spectra were recorded on a Bruker Tensor 27 spectrometer as a thin film on NaCl plates.

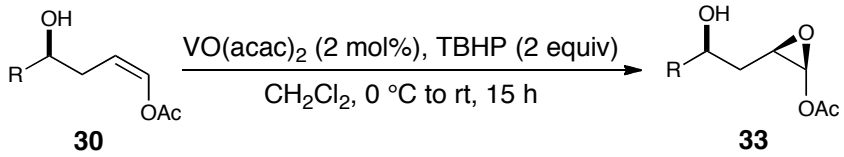
1.7.2 General Procedure 1 (GP1) of Homoaldol Equivalent Reaction



17 **29c** **30**

To 2 dram vial was added $CrCl_3$ (5 mg, 0.032 mmol, 0.1 equiv) and $Mn^{(0)}$ (325 mesh) (35 mg, 0.64 mmol, 2 equiv). The vial was fitted with a Teflon cap, purged with argon, charged with THF (2.0 mL), and allowed to stir for 20 min at rt (18 °C to 22 °C). After 20 min, Et_3N (5 mg, 0.048 mmol, 0.15 equiv) and TMSCl (70 mg, 0.64 mmol, 2 equiv) were added to the reaction mixture. After stirring for 20 min, the reaction color changed to a deep dark color. After 20 min, 3-bromopropenyl acetate **29c** (115 mg, 0.64 mmol, 2 equiv) was added and the reaction mixture stirred for 40 min. After 40 min, aldehyde **17** (0.32 mmol, 1 equiv) was added and the mixture was allowed to stir at rt (18 °C to 22 °C) for 20 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (1.5 mL). After stirring for 30 min, the mixture was passed through a Celite® plug, eluting with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and then treated directly with 1 mL TBAF (1 mol in THF). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography.

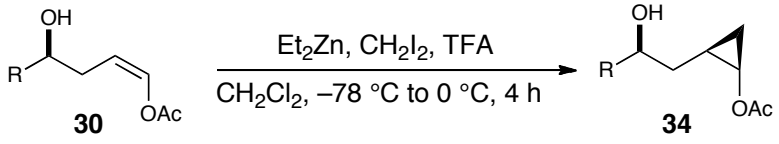
1.7.3 General Procedure 2 (GP2) of Hydroxyl-Directed Epoxidation



30 **33**

A 10 mL round bottom flask was charged with $VO(acac)_2$ (2 mol%, 0.02 equiv) in a dry box. To the flask was added CH_2Cl_2 (5 mL) in an ice bath and a solution of the appropriate olefin **30** (1 mmol, 1 equiv) in CH_2Cl_2 (1 mL). To this solution was added TBHP (5.5 M solution in decane) (2 mmol, 2 equiv) over 1 h by syringe pump at 0 °C and then the reaction mixture was allowed to warm up to rt (18 °C to 22 °C) and stirred for 15 h. After 15 h, the reaction mixture was passed through a Celite® plug eluting with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography.

1.7.4 General Procedure 3 (GP3) of Hydroxyl-Directed Cyclopropanation

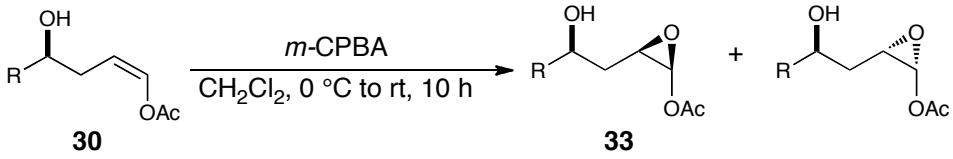


30 **34**

To a solution of Et_2Zn (1 mmol, 2 equiv) in CH_2Cl_2 (3 mL) was added CH_2I_2 (2 mmol, 4 equiv) dropwise at –78 °C and the reaction mixture was allowed to warm up to 0 °C and stirred for 15 min at 0 °C, then TFA (1 mmol, 2 equiv) was added to the

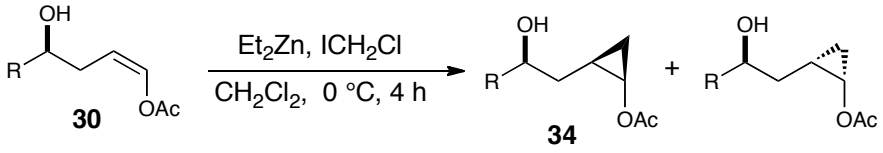
reaction mixture and stirred for another 15 min at 0 °C. To the resulting mixture was added the appropriate olefin **30** (0.5 mmol, 1 equiv) in CH_2Cl_2 (1 mL) over 20 min and the resulting mixture was stirred at 0 °C for 4 h. After 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution at 0 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography.

1.7.5 General Procedure 4 (GP4) of Epoxidation

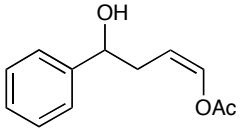


To a solution of the appropriate olefin **30** (0.1 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was added *m*-CPBA (0.12 mmol, 1.2 equiv) dropwise at 0 °C and then the resulting mixture was stirred for 1 hour at the same temperature. The reaction mixture was warm up to rt (18 °C to 22 °C) and stirred for 10 h. The reaction mixture was washed with saturated aqueous Na_2SO_4. The organic layer was extracted with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography.

1.7.6 General Procedure 5 (GP5) of Cyclopropanation

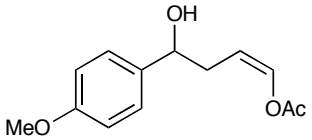


To a solution of Et_2Zn (1 mmol, 2 equiv) in CH_2Cl_2 (3 mL) was added ICH_2Cl (2 mmol, 4 equiv) dropwise at 0 °C and the reaction mixture was stirred for 15 min at 0 °C. To the resulting mixture was added appropriate olefin **30** (0.5 mmol, 1 equiv) in CH_2Cl_2 (1 mL) over 20 min and the resulting mixture was stirred at 0 °C for 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution at 0 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography.

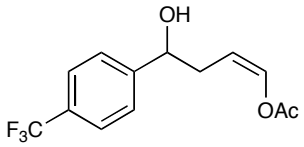


(*Z*)-4-Hydroxy-4-phenylbut-1-enyl acetate (30a). Benzaldehyde **17a** (0.32 mmol, 34 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (115 mg, 0.64 mmol, 2.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography with 1:3 EtOAc/hexanes provided a colorless oil of **30a** (66 mg, 99%). R_f = 0.25; IR (film, cm^{-1}): 3434 (br), 3031, 2907, 1750; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H), 7.07 (d, *J* = 6.3, Hz, 1H), 4.90 (q, *J* = 7.5 Hz, 1H), 4.71 (t, *J* = 6.5 Hz, 1H), 2.70-2.54 (m, 2H), 2.30 (bs, 1H), 2.09 (s, 3H) ; ^{13}C NMR

(75 MHz, $CDCl_3$) δ 168.0, 143.8, 135.9, 128.4 (2), 127.7, 125.8 (2), 109.3, 73.5, 34.2, 20.7; HRMS (ESI) calcd for $C_{12}H_{14}O_3$ $[M+Li]^+$: 213.1103; found: 213.1119

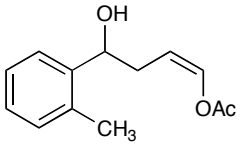


(*Z*)-4-Hydroxy-4-(4-methoxyphenyl)but-1-enyl acetate (30b). 4-Methoxybenzaldehyde **17b** (0.32 mmol, 44 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (115 mg, 0.64 mmol, 2.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography with 1:3 EtOAc/hexanes provided a colorless oil of **30b** (68 mg, 90%). R_f = 0.13; IR (film, cm^{-1}): 3478 (br), 3005, 2940, 2839, 1755, 1610; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 9.13 Hz, 2H), 7.09 (d, *J* = 6.3, Hz, 1H), 6.88 (d, *J* = 9.13 Hz, 2H), 4.89 (q, *J* = 7.5 Hz, 1H), 4.69 (t, *J* = 6.5 Hz, 1H), 3.8 (s, 3H), 2.69-2.54 (m, 2H), 2.11 (s, 3H), 1.99 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 159.2, 135.9 (2), 127.2 (2), 113.8 (2), 109.5, 73.3, 55.4, 34.2, 20.8; HRMS (ESI) calcd for $C_{13}H_{16}O_4$ $[M+Li]^+$: 243.1209; found: 243.1185.

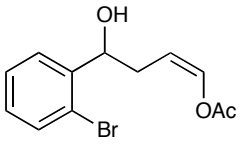


(*Z*)-4-Hydroxy-4-(4-(trifluoromethyl)phenyl)but-1-enyl acetate (30c). 4-Trifluoromethylbenzaldehyde **17c** (0.32 mmol, 56 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (115 mg, 0.64 mmol, 2.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography with 1:4 EtOAc/hexanes provided a colorless oil of **30c** (80 mg, 91%). R_f = 0.21; IR (film, cm^{-1}): 3446 (br), 3102, 3067, 2928, 1755, 1670, 1619; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.2, Hz, 2H), 7.12 (d, *J* = 6.3, Hz,

1H), 4.89 (q, *J* = 7.5 Hz, 1H), 4.80 (t, *J* = 6.5 Hz, 1H), 2.65-2.58 (m, 2H), 2.16 (bs, 1H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 148.2, 136.6, 126.2 (3), 125.5 (3), 108.5, 73.0, 34.5, 20.7; HRMS (ESI) calcd for $C_{13}H_{13}F_3O_3$ $[M+Li]^+$: 281.0977; found: 281.0960.

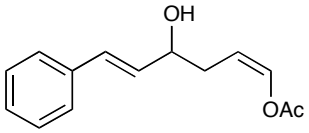


(*Z*)-4-Hydroxy-4-*o*-tolylbut-1-enyl acetate (30d). 2-Methylbenzaldehyde **17d** (0.32 mmol, 38 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (115 mg, 0.64 mmol, 2.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography with 1:5 EtOAc/hexanes provided a colorless oil of **30d** (57 mg, 82%). R_f = 0.22; IR (film, cm^{-1}): 3434 (br), 3061, 3025, 2928, 1755; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.5 Hz, 1H), 7.25-7.09 (m, 4H), 5.02-4.94 (m, 2H), 2.59-2.54 (m, 2H), 2.34 (s, 3H), 2.30 (bs, 1H), 2.16 (bs, 1H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 141.2, 136.1, 134.6, 130.6, 127.6, 126.5, 125.3, 109.8, 70.2, 33.3, 20.9, 19.2; HRMS (ESI) calcd for $C_{13}H_{16}O_3$ $[M+Li]^+$: 227.1259; found: 227.1242.

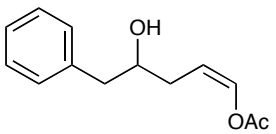


(*Z*)-4-(2-Bromophenyl)-4-hydroxybut-1-enyl acetate (30e). 2-Bromobenzaldehyde **17e** (0.32 mmol, 59 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (115 mg, 0.64 mmol, 2.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography with 1:3 EtOAc/hexanes provided a colorless oil of **30e** (70 mg, 78%). R_f = 0.20; IR (film, cm^{-1}): 3446 (br), 3064, 2922, 1755; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59-7.11 (m, 5H), 5.15 (m,

1H), 5.00 (q, *J* = 7.5 Hz, 1H), 2.74-2.65 (m, 1H), 2.60-2.50 (m, 1H), 2.11 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 142.7, 136.5, 132.8, 129.2, 127.8, 127.6, 122.0, 109.2, 72.4, 32.7, 20.9; HRMS (ESI) calcd for $C_{12}H_{13}BrO_3$ $[M+Li]^+$: 291.0208; found: 291.0143.

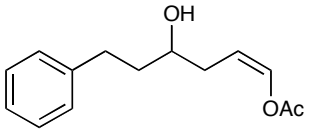


(1*Z*,5*E*)-4-Hydroxy-6-phenylhexa-1,5-dienyl acetate (30f). *Trans*-cinnamaldehyde **17f** (0.32 mmol, 42 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (115 mg, 0.64 mmol, 2.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography with 1:3 EtOAc/hexanes provided a colorless oil of **30f** (63 mg, 85%). R_f = 0.14; IR (film, cm^{-1}): 3467(br), 3055, 2987, 2928, 1747, 1264; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.27 (m, 5H), 7.17 (d, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 16 Hz, 1H), 6.27 (dd, *J* = 16, 6.6 Hz, 1H), 5.01 (q, *J* = 7.5 Hz, 1H), 4.42-4.36 (m, 1H), 2.58-2.51 (m, 2H), 2.17 (s, 3H), 2.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 136.5, 136.1, 131.4, 130.7, 128.7 (2), 127.8, 126.5 (2), 109.0, 72.1, 32.6, 20.8; HRMS (ESI) calcd for $C_{14}H_{16}O_3$ $[M+Li]^+$: 239.1259; found: 239.1216.

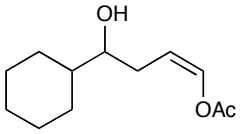


(*Z*)-4-Hydroxy-5-phenylpent-1-enyl acetate (30g). 2-Phenylacetaldehyde **17g** (0.32 mmol, 38 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (115 mg, 0.64 mmol, 2.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography with 1:4 EtOAc/hexanes provided a colorless oil of **30g** (52 mg, 75%). R_f = 0.18; IR (film, cm^{-1}):

3443 (br), 3028, 2916, 2848, 1752, 1670; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.20 (m, 5H), 7.14 (d, *J* = 7.5 Hz, 1H), 5.01 (q, *J* = 7.5 Hz, 1H), 3.98-3.81 (m, 1H), 2.89-2.67 (m, 2H), 2.42-2.37 (m, 2H), 2.14 (s, 3H), 1.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 138.3, 136.1, 129.5, 129.1, 128.7, 126.7, 126.6, 109.6, 72.1, 43.4, 31.9, 20.8; HRMS (ESI) calcd for $C_{13}H_{16}O_3$ $[M+Li]^+$: 227.1259; found: 227.1200.

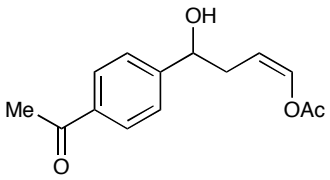


(*Z*)-4-Hydroxy-6-phenylhex-1-enyl acetate (30h). 3-Phenylpropanal **17h** (0.32 mmol, 41 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (115 mg, 0.64 mmol, 2.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography with 1:4 EtOAc/hexanes provided a colorless oil of **30h** (60 mg, 80%). R_f = 0.16; IR (film, cm^{-1}): 3416 (br), 3064, 3023, 2937, 2863, 1758, 1673; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.14 (m, 5H), 7.14 (d, *J* = 7.5 Hz, 1H), 4.94 (q, *J* = 7.5 Hz, 1H), 3.72-3.65 (m, 1H), 2.81-2.66 (m, 2H), 2.38-2.33 (m, 2H), 2.14 (s, 3H), 1.90-1.76 (m, 2H), 1.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 142.0, 136.2, 128.5 (4), 126.0, 109.5, 70.5, 38.5, 32.7, 32.1, 20.8; HRMS (ESI) calcd for $C_{14}H_{18}O_3$ $[M+Li]^+$: 241.1416; found: 241.1327.

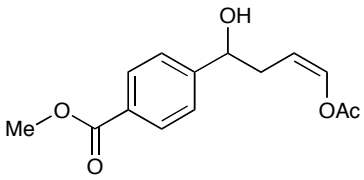


(*Z*)-4-Cyclohexyl-4-hydroxybut-1-enyl acetate (30i). Cyclohexanealdehyde **17i** (0.32 mmol, 36 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (115 mg, 0.64 mmol, 2.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography with 1:5 EtOAc/hexanes provided a colorless oil of **30i** (65 mg, 96%). R_f = 0.23; IR (film, cm^{-1}):

3446 (br), 2925, 2854, 1755; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 7.5 Hz, ıH), 4.97 (q, *J* = 7.5 Hz, 1H), 3.41 (bs, 1H), 2.37-2.30 (m, 2H), 2.14 (m, 2H), 2.14 (s, 3H), 1.92-1.01 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 136.0, 110.4, 75.5, 43.1, 29.6, 29.3, 28.0, 26.5, 26.3, 26.2, 20.9; MS (ESI) 304 $[M+H]^+$; HRMS (ESI) calcd for $C_{12}H_{20}O_3$ $[M+Li]^+$ 219.1572; found 219.1556.

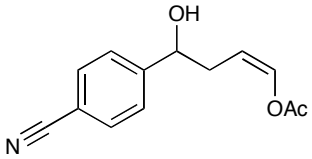


(*Z*)-4-(4-Acetylphenyl)-4-hydroxybut-1-enyl acetate (30j). 4-Acetylbenzaldehyde **17j** (0.32 mmol, 47 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (77 μL, 0.64 mmol, 2 equiv) were subjected to the reaction conditions described in GP1. Flash chromatography with 1:2 EtOAc/hexanes provided a colorless oil of **30j** (55 mg, 70%). R_f = 0.21; IR (film, cm^{-1}): 3464 (br), 2960, 2922, 1750, 1675, 1604; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 3.5 Hz, 2H), 7.40 (d, *J* = 3.5 Hz, 2H), 7.01 (d, *J* = 2.9 Hz, 1H), 4.85 (q, *J* = 7.5 Hz, 1H), 4.76 (t, *J* = 6.1 Hz, 1H), 3.05 (bs, 1H), 2.60-2.55 (m, 2H), 2.52 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 167.8, 149.4, 136.2, 136.0, 128.4 (2), 125.9 (2), 108.8, 72.8, 34.2, 26.5, 20.6; HRMS (ESI) calcd for $C_{14}H_{16}O_4$ $[M+H]^+$: 249.1127; found: 249.1090.

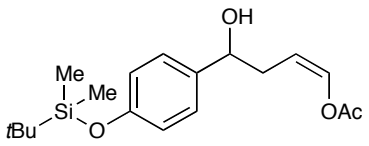


(*Z*)-Methyl4-(4-acetoxy-1-hydroxybut-3-enyl)benzoate (30k). Methyl 4-formylbenzoate **17k** (0.32 mmol, 52 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (77 μL, 0.64 mmol, 2 equiv) were subjected to the reaction conditions

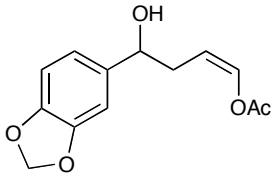
described in GP1. Flash chromatography with 1:2 EtOAc/hexanes provided a colorless oil of **30k** (60 mg, 71%). R_f = 0.38; IR (film, cm^{-1}): 3496 (br), 2954, 2904, 1755, 1720; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 4.0 Hz, 2H), 7.41 (d, *J* = 4.0 Hz, 2H), 7.07 (d, *J* = 3.0 Hz, 1H), 4.88 (q, *J* = 7.5 Hz, 1H), 4.76 (t, *J* = 6.1 Hz, 1H), 3.8 (s, 3H), 2.64-2.57 (m, 2H), 2.54 (s, 1H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 167.0, 149.0, 136.3, 130.0 (2), 129.8, 129.4, 125.8 (2), 108.7, 73.1, 52.2, 34.3, 20.7; HRMS (ESI) calcd for $C_{14}H_{16}O_5$ $[M+H]^+$: 265.1076; found: 265.1068.



(*Z*)-4-(4-Cyanophenyl)-4-hydroxybut-1-enyl acetate (30l). 4-Formylbenzonitrile **17l** (0.32 mmol, 42 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (77 μL, 0.64 mmol, 2 equiv) were subjected to the reaction conditions described in GP1. Flash chromatography with 1:1 EtOAc/hexanes provided a colorless oil of **30l** (55 mg, 75%). R_f = 0.32; IR (film, cm^{-1}): 3478 (br), 3101, 3064, 2925, 1752 1673, 1604; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 3.9 Hz, 2H), 7.47 (d, *J* = 3.9 Hz, 2H), 7.08 (d, *J* = 3.4 Hz, 1H), 4.87 (q, *J* = 7.1 Hz, 1H), 4.80 (t, *J* = 6.2 Hz, 1H), 2.60-2.55 (m, 2H), 2.55 (bs , 1H), 2.09 (s, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 149.2, 136.5, 132.2 (2), 126.5 (2), 118.8, 111.1, 108.2, 72.6, 34.3, 20.6; HRMS (ESI) calcd for $C_{13}H_{13}NO_3$ $[M+H]^+$: 232.0974; found: 232.0808

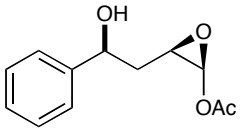


(*Z*)-4-(4-(*Tert*-butyldimethylsilyloxy)phenyl)-4-hydroxybut-1-enyl acetate (30m). 4-(*Tert*-butyldimethylsilyloxy)benzaldehyde **17m** (0.32 mmol, 75 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (77 μL, 0.64 mmol, 2 equiv) were subjected to the reaction conditions described in GP1. Flash chromatography with 1:3 EtOAc/hexanes provided a colorless oil of **30m** (107 mg, 99%). R_f = 0.38; IR (film, cm^{-1}): 3443 (br), 2954, 2931, 2889, 2863, 1758; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 4.6 Hz, 2H), 7.07 (d, *J* = 3.2 Hz, 1H), 6.81 (d, *J* = 4.6 Hz, 2H), 4.88 (q, *J* = 7.3 Hz, 1H), 4.65 (t, *J* = 6.4 Hz, 1H), 2.69-2.48 (m, 2H), 2.14 (bs , 1H), 2.11 (s, 3H), 0.98 (s, 9H), 0.19 (s, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 155.3, 136.6, 135.9, 128.5, 127.1, 120.0, 119.8, 109.6, 73.3, 34.3, 25.7 (3), 20.8, 18.3, -4.4 (2); HRMS (ESI) calcd for $C_{18}H_{28}LiO_4Si$ $[M+Li]^+$: 343.1917; found: 343.1716

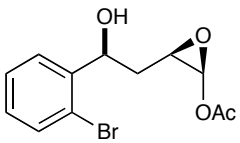


(*Z*)-4-(Benzo[*d*][1,3]dioxol-5-yl)-4-hydroxybut-1-enyl acetate (30n). 1,3-Benzodioxole-5-carbaldehyde **17n** (0.32 mmol, 48 mg, 1.0 equiv) and 3-bromoprop-1-enyl acetate **29c** (77 μL, 0.64 mmol, 2 equiv) were subjected to the reaction conditions described in GP1. Flash chromatography with 1:3 EtOAc/hexanes provided a colorless oil of **30n** (77 mg, 96%). R_f = 0.21; IR (film, cm^{-1}): 3467 (br), 2901, 1752, 1670, 1504, 1489; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, *J* = 6.3 Hz, 1H), 6.84 (s, 1H), 6.75 (d, *J* = 1.5 Hz, 1H) 6.74(s, 1H), 5.91 (s, 2H), 4.84 (q, *J* = 7.4 Hz, 1H), 4.59 (t, *J* = 6.9 Hz, 1H), 2.64-2.44 (m, 2H), 2.38 (bs , 1H), 2.09 (s, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 147.7, 147.0, 138.0,

135.8, 119.3, 109.3, 108.0, 106.4, 101.0, 73.4, 34.2, 20.7 ; HRMS (ESI) calcd for $C_{13}H_{14}LiO_5$ $[M+Li]^+$: 257.1001; found: 257.0851

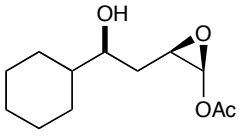


(2*S*,3*R*)-3-((*S*)-2-Hydroxy-2-phenylethyl)oxiran-2-yl acetate (33a). $VO(acac)_2$ (5.3 mg, 0.02 mmol, 0.02 equiv), olefin **30a** (206 mg, 1 mmol, 1 equiv), and TBHP (5.5M solution in decane) (0.36 mL, 2 mmol, 2 equiv) were subjected to the reaction conditions described in GP2. Flash column chromatography with EtOAc/hexanes (1:3) provided a colorless oil of **33a** (182 mg, 82%). R_f = 0.20, dr = 13 : 1 (determined by ^{1}H NMR); IR (film, cm^{-1}): 3449 (br), 3058, 3034, 2925, 1758; ^{1}H NMR (300 MHz, $CDCl_3$) *major diastereoisomer* : δ 7.43-7.26 (m, 5H), 5.50 (d, *J* = 2.64 Hz, 1H), 4.92 (t, *J* = 6.1 Hz, 1H), 3.05 (ddd, *J* = 2.7, 5.2, 7.7 Hz, 1H,), 2.53 (bs, 1H), 2.22-2.01 (m, 2H), 2.09 (s, 3H); *minor diastereoisomer* : δ 7.43-7.26 (m, 5H), 5.55 (d, *J* = 2.64 Hz, 1H), 4.92 (t, *J* = 6.1 Hz, 1H), 3.26 (ddd, *J* = 2.7, 4.4, 7.7 Hz, 1H), 2.60 (bs, 1H), 2.22-2.01 (m, 2H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *major diastereoisomer* : δ 170.7, 143.5, 128.7 (2), 128.0, 125.8 (2), 75.1, 72.4, 54.1, 36.3, 20.9; *minor diastereoisomer* : δ 170.7, 143.8, 128.6 (2), 127.9, 125.7 (2), 75.8, 71.6, 53.9, 36.3, 20.9; HRMS (ESI) calcd for $C_{12}H_{14}O_4$ $[M+Li]^+$: 229.1052; found: 229.1022. *A mixture of diastereoisomers was synthesized from **30a** with m-CPBA following GP4.*



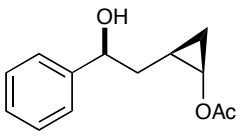
(2*S*,3*R*)-3-((*S*)-2-(2-Bromophenyl)-2-hydroxyethyl)oxiran-2-yl acetate (33e). $VO(acac)_2$ (5.3 mg, 0.02 mmol, 0.02 equiv), olefin

30e (284 mg, 1 mmol, 1 equiv), and TBHP (5.5M solution in decane) (0.36 mL, 2 mmol, 2 equiv) were subjected to the reaction conditions described in GP2. Flash column chromatography with EtOAc/hexanes (1:3) provided a colorless oil of **30e** (194 mg, 85%). R_f = 0.23, dr = >15:1 (determined by ^{1}H NMR); IR (film, cm^{-1}): 3437 (br), 3064, 2937, 1744, 1723; ^{1}H NMR (300 MHz, $CDCl_3$) *major diastereoisomer* : δ 7.61 (d, *J* = 7.91 Hz, 1H), 7.49 (d, *J* = 7.91 Hz, 1H), 7.33 (t, *J* = 8.1 Hz, 1H), 7.13 (t, *J* = 8.12 Hz, 1H), 5.52 (d, *J* = 2.4 Hz, 1H), 5.28 (dd, *J* = 3.83, 8.60 Hz, 1H), 3.24 (ddd, *J* = 2.52, 6.04, 6.04 Hz, 1H), 2.97 (bs, 1H), 2.15-1.97 (m, 2H), 2.07 (s, 3H); *minor diastereoisomer* : δ 7.61 (d, *J* = 7.91 Hz, 1H), 7.49 (d, *J* = 7.91 Hz, 1H), 7.33 (t, *J* = 8.1 Hz, 1H), 7.13 (t, *J* = 8.12 Hz, 1H), 5.52 (d, *J* = 2.4 Hz, 1H), 5.28 (dd, *J* = 3.83, 8.60 Hz, 1H), 3.24 (ddd, *J* = 2.52, 6.04, 6.04 Hz, 1H), 2.97 (bs, 1H), 2.15-1.97 (m, 2H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *major diastereoisomer* : δ 170.7, 142.6, 132.6, 129.1, 127.9, 127.3, 121.4, 74.9, 70.9, 54.2, 35.0, 20.9; *minor diastereoisomer* : δ 170.7, 142.6, 132.2, 129.0, 127.7, 127.1, 121.4, 75.5, 70.2, 53.5, 34.0, 20.9; HRMS (ESI) calcd for $C_{12}H_{13}BrO_4$ $[M+Li]^+$: 307.0157; found: 307.0038. *A mixture of diastereoisomers was synthesized from **30e** with m-CPBA following GP4.*



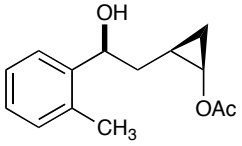
(2*S*,3*R*)-3-((*S*)-2-Cyclohexyl-2-hydroxyethyl)oxiran-2-yl acetate (33i). $VO(acac)_2$ (5.3 mg, 0.02 mmol, 0.02 equiv), olefin **30i** (212 mg, 1 mmol, 1 equiv), and TBHP (5.5M solution in decane) (0.36 mL, 2 mmol, 2 equiv) were subjected to the reaction conditions described in GP2. Flash column chromatography with EtOAc/hexanes (1:5) provided a colorless oil of **33i** (194 mg,

85%). R_f = 0.21, dr = 15 : 1 (determined by ^{1}H NMR); IR (film, cm^{-1}): 3425 (br), 2925, 2851, 1741; ^{1}H NMR (300 MHz, $CDCl_3$) *major diastereoisomer* : δ 5.53 (d, *J* = 2.60 Hz, 1H), 3.61 (ddd, *J* = 3.81, 5.48, 9.19 Hz, 1H), 3.20 (ddd, *J* = 2.72, 5.71, 6.83 Hz, 1H), 2.12 (s, 1H), 2.0 (bs, 1H), 1.89-1.65 (m, 7H), 1.44-1.32 (m, 1H), 1.30-1.14 (m, 3H), 1.11-0.96 (m, 3H); *minor diastereoisomer* : δ 5.58 (d, *J* = 2.60 Hz, 1H), 3.61 (ddd, *J* = 3.81, 5.48, 9.19 Hz, 1H), 3.20 (ddd, *J* = 2.72, 5.71, 6.83 Hz, 1H), 2.12 (s, 1H), 2.0 (bs, 1H), 1.89-1.65 (m, 7H), 1.44-1.32 (m, 1H), 1.30-1.14 (m, 3H), 1.11-0.96 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *major diastereoisomer* :δ 170.7, 75.1, 74.3, 55.0, 43.7, 31.3, 28.8, 28.0, 26.4, 26.1, 26.0, 20.9; *minor diastereoisomer* : δ 170.7, 76.1, 73.4, 54.6, 43.9, 31.3, 29.0, 27.8, 26.4, 26.1, 26.0, 20.9; HRMS (ESI) calcd for $C_{12}H_{20}O_4$ $[M+Li]^+$: 235.1522; found: 235.1461. *A mixture of diastereoisomers was synthesized from* ***30i*** *with m-CPBA following GP4.*



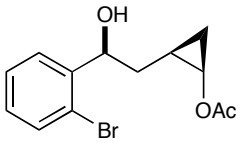
(1*R*,2*S*)-2-((*S*)-2-Hydroxy-2-phenylethyl)cyclopropyl acetate (34a). $Zn(Et)_2$ (123 mg, 1 mmol, 2 equiv), CH_2I_2 (534 mg, 2 mmol, 4 equiv), TFA (114 mg, 1 mmol, 2 equiv), and olefin **30a** (103 mg, 0.5 mmol, 1 equiv) were subjected to the reaction condition described in GP3. Flash column chromatography with Et_2O/hexanes (1:1) provided a colorless oil of **34a** (105 mg, 95%). R_f = 0.28, dr = 6.6:1 (determined by chiral HPLC); IR (film, cm^{-1}): 3428 (br), 3042, 3002, 2934, 1732; ^{1}H NMR (300 MHz, $CDCl_3$) *major diastereoisomer* : δ 7.37-7.24 (m, 5H), 4.77 (t, *J* = 6.48 Hz, 1H), 4.09 (ddd, *J* = 3.39, 6.83, 6.83 Hz, 1H), 2.5 (bs, 1H), 2.04 (s, 3H), 1.86-1.80 (m, 2H), 1.04-0.85 (m, 2H), 0.45 (ddd, *J* = 3.43, 6.11, 6.11 Hz, 1H);

minor diastereoisomer : δ 7.37-7.24 (m, 5H), 4.77 (t, *J* = 6.48 Hz, 1H), 4.09 (ddd, *J* = 3.39, 6.83, 6.83 Hz, 1H), 2.5 (bs, 1H), 2.04 (s, 3H), 1.86-1.80 (m, 2H), 1.04-0.85 (m, 2H), 0.36 (ddd, *J* = 3.43, 6.11, 6.11 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *major diastereoisomer* :δ 172.0, 144.5, 128.4 (2), 127.5, 125.9 (2), 74.4, 52.0, 36.8, 20.8, 13.2, 10.8; *minor diastereoisomer* : 172.0, 144.5, 128.4 (2), 126, 125.8 (2), 74.4, 52.5, 37.0, 20.8, 13.6, 10.7; HRMS (ESI) calcd for $C_{13}H_{16}O_3$ $[M+Li]^+$: 227.1259; found: 227.1292; Chiral HPLC: ChiralPAK® AD-H column, isopropanol:hexanes = 5:95, 1.0 mL/min, λ = 210 nm; *major diastereoisomer* t_R = 18.0 min and 20.4 min, *minor diastereoisomer* t_R = 17.2 min and 19.1 min. *A mixture of diastereoisomers was synthesized from* ***30a*** *with* Et_2Zn *and* ICH_2Cl *following the GP5.*



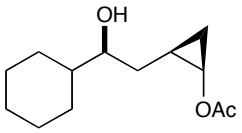
(1*R*,2*S*)-2-((*S*)-2-Hydroxy-2-*o*-tolylethyl)cyclopropyl acetate (34d). Zn(Et)$_2$ (123 mg, 1 mmol, 2 equiv), CH_2I_2 (534 mg, 2 mmol, 4 equiv), TFA (114 mg, 1 mmol, 2 equiv), and olefin **30d** (110 mg, 0.5 mmol, 1 equiv) were subjected to the reaction condition described in the GP3. Flash column chromatography with Et_2O/hexanes (1:1) provided a colorless oil of **34d** (98 mg, 84%). R_f = 0.28, dr = 5:1 (determined by HPLC); IR (film, cm^{-1}): 3446 (br), 3073, 3023, 2992, 1741; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.70, 1.08 Hz, 1H), 7.26-7.09 (m, 3H), 5.0 (dd, *J* = 8.10, 4.86 Hz, 1H), 4.10 (ddd, 6.92, 6.92, 3.34 Hz, 1H), 2.47 (bs, 1H), 2.32 (s, 3H), 2.02 (s, 3H), 1.89-1.68 (m, 2H), 1.08 (ddd, *J* = 7.27, 7.27, 1.87 Hz, 1H), 0.92 (ddd, *J* = 9.38, 9.38, 6.51 Hz, 1H), 0.43 (ddd, *J* = 6.63, 6.63, 3.34 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 142.7, 134.1, 130.2, 127.1, 126.2, 125.2, 70.4, 52.2,

35.9, 20.8, 18.9, 13.2, 11.0; HRMS (ESI) calcd for $C_{14}H_{18}O_3$ $[M+Li]^+$: 241.1416; found: 241.1367; Chiral HPLC: ChiralPAK® AD-H column, isopropanol:hexanes = 2:98, 0.6 mL/min, λ = 210 nm; *major diastereoisomer* t_R = 34.5 min, *minor diastereoisomer* t_R = 36.4 min and 42.4 min. *A The mixture of diastereoisomers was synthesized from* ***30d*** *with* Et_2Zn *and* ICH_2Cl *following the GP5.*



(1*R*,2*S*)-2-((*S*)-2-(2-Bromophenyl)-2-hydroxyethyl)cyclopropyl acetate (34e). $Zn(Et)_2$ (123 mg, 1 mmol, 2 equiv), CH_2I_2 (534 mg, 2 mmol, 4 equiv), TFA (114 mg, 1 mmol, 2 equiv), and olefin **30e** (142 mg, 0.5 mmol, 1 equiv) were subjected to the reaction conditions described in GP3. Flash column chromatography with Et_2O/hexanes (1:1) provided a colorless oil of **34e** (119 mg, 80%). R_f = 0.3, dr = 3.8:1 (determined by HPLC); IR (film, cm^{-1}): 3446 (br), 3067, 3005, 2919, 1744; ^1H NMR (300 MHz, $CDCl_3$) *major diastereoisomer* :δ 7.59 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.50 (dd, *J* = 8.06, 1.19 Hz, 1H), 7.33 (ddd, *J* = 7.52, 7.52, 0.78 Hz, 1H), 7.12 (ddd, 7.94, 7.94, 1.85 Hz, 1H), 5.17 (app bs, 1H), 4.12 (ddd, *J* = 6.91, 6.91, 3.45 Hz, 1H), 2.63 (bs, 1H), 2.04 (s, 3H), 1.87-1.77 (m, 2H), 1.09 (ddd, *J* = 9.66, 7.07, 2.83 Hz, 1H), 0.92 (ddd *J* = 9.66, 9.66, 6.84 Hz, 1H), 0.43 (ddd, *J* = 6.77, 6.77, 5.31 Hz, 1H); *minor diastereoisomer* : δ 7.59 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.50 (dd, *J* = 8.06, 1.19 Hz, 1H), 7.33 (ddd, *J* = 7.52, 7.52, 0.78 Hz, 1H), 7.12 (ddd, 7.94, 7.94, 1.85 Hz, 1H), 5.17 (app bs, 1H), 4.12 (ddd, *J* = 6.91, 6.91, 3.45 Hz, 1H), 2.63 (bs, 1H), 2.01 (s, 3H), 1.87-1.77 (m, 2H), 1.09 (ddd, *J* = 9.66, 7.07, 2.83 Hz, 1H), 0.92 (ddd *J* = 9.66, 9.66, 6.84 Hz, 1H), 0.43 (ddd, *J* = 6.77, 6.77, 5.31 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *major diastereoisomer*

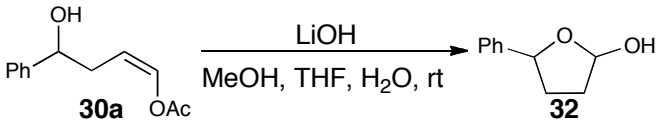
: δ 172.1, 143.4, 132.6, 128.9, 127.7, 127.6, 121.8, 72.6, 52.1, 35.4, 21.1, 12.9, 11.1; *minor diastereoisomer* : δ 172.1, 143.4, 132.5, 128.7, 127.7, 127.3, 121.8, 73.0, 52.6, 35.2, 20.8, 13.4, 10.4; HRMS (ESI) calcd for $C_{13}H_{15}BrO_3$ $[M+Li]^+$: 305.0365; found: 305.0262. Chiral HPLC: Chiralcel® OJ-H column, isopropanol:hexanes = 4:96, 1.0 mL/min, λ = 210 nm; *major diastereoisomer* t_R = 21.6 min and 29.2 min, *minor diastereoisomer* t_R = 27.2 min and 31.2 min. *A mixture of diastereoisomers was synthesized from* ***30e*** *with* Et_2Zn *and* ICH_2Cl *following GP5.*

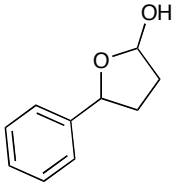


(1*R*,2*S*)-2-((*S*)-2-Cyclohexyl-2-hydroxyethyl)cyclopropyl acetate (34i). $Zn(Et)_2$ (123 mg, 1 mmol, 2 equiv), CH_2I_2 (534 mg, 2 mmol, 4 equiv), TFA (114 mg, 1 mmol, 2 equiv), and olefin **30i** (106 mg, 0.5 mmol, 1 equiv) were subjected to the reaction condition described in the GP3. Flash column chromatography with Et_2O/hexanes (1:1) provided a colorless oil of **34i** (99 mg, 88%). R_f = 0.21, dr = 6 : 1 (determined by ^1H NMR); IR (film, cm^{-1}): 3437 (br), 2925, 2851, 1744; ^1H NMR (300 MHz, $CDCl_3$) *major diastereoisomer* : δ 4.07 (ddd, *J* = 3.42, 6.87, 6.87 Hz, 1H), 3.37 (app q, *J* = 6.54 Hz, 1H), 2.00 (s, 3H), 1.84 (bs, 1H), 1.81-0.86 (m, 15H), 0.41 (ddd, *J* = 3.43, 6.66, 6.66 Hz, 1H); *minor diastereoisomer* : δ 4.07 (ddd, *J* = 3.42, 6.87, 6.87 Hz, 1H), 3.37 (app q, *J* = 6.54 Hz, 1H), 2.00 (s, 3H), 1.84 (bs, 1H), 1.81-0.86 (m, 15H), 0.33 (ddd, *J* = 3.43, 6.66, 6.66 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *major diastereoisomer*: δ 172.0, 75.9, 52.1, 43.4, 31.8, 29.1, 27.9, 26.5, 26.3, 26.1, 20.8, 13.4, 10.8; *minor diastereoisomer*: δ 172.0, 75.9, 52.8, 43.6, 31.5, 29.2, 27.7, 26.5, 26.3, 26.1, 20.8, 13.8, 10.3 ; HRMS (ESI) calcd for $C_{13}H_{22}O_3$ $[M+Li]^+$: 233.1729; found:

233.1652. *A mixture of diastereoisomers was synthesized from* ***30i*** *with* Et_2Zn *and* ICH_2Cl *following GP5.*

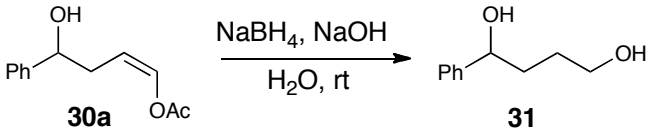
1.7.7 Hydrolysis Procedure of Homoaldol Equivalent Adduct 30a



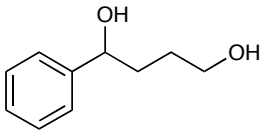


5-Phenyltetrahydrofuran-2-ol (32). To a solution of (*Z*)-4-hydroxy-4-phenylbut-1-enyl acetate **30a** (30 mg, 0.14 mmol, 1 equiv) in $CH_3OH/THF/H_2O$ (4 mL, 1.5:1.5:1) was added LiOH (6 mg, 0.14 mmol, 1 equiv) and the heterogeneous reaction mixture was vigorously stirred at room temperature for 10 min. The organic solvent was evaporated under reduced pressure and the aqueous layer was extracted with THF. The combined organic layers were dried $MgSO_4$ and evaporated under reduced pressure. Purification was accomplished by flash column chromatography (EtOAc/hexanes = 1:1) to give the desired product **32** as colorless oil (24 mg, 99% yield). R_f = 0.5 (EtOAc/hexanes = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.24 (m, 10H) (mixture of diastereomers), 5.75 (dd, *J* = 5.1, 2.0 Hz, 1H), 5.61 (dd, *J* = 5.1, 2.0 Hz, 1H), 5.25 (t, *J* = 7.1 Hz, 1H), 5.01 (t, *J* = 6.1 Hz, 1H), 3.7 (bs, 1H), 3.6 (bs, 1H), 2.52-1.73 (m, 8H) (mixture of diastereomer); ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of diastereomer) δ 142.8, 142.4, 128.4, 127.6, 127.5, 126.5, 125.7, 99.0, 98.6, 83.0, 79.7, 34.5, 33.1, 32.9, 32.8; HRMS (ESI) calcd for $C_{10}H_{12}O_2$ $[M+Li]^+$ 171.0997; found 171.0940.

1.7.8 Reduction Procedure of Homoaldol Equivalent Adduct 30a

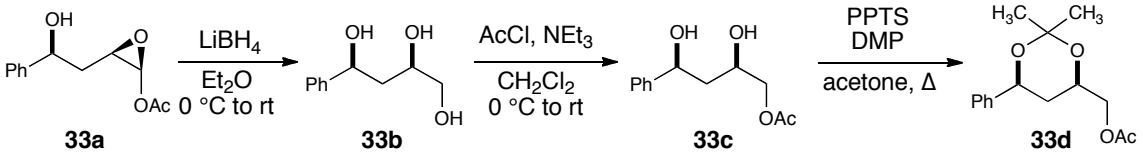


30a **31**

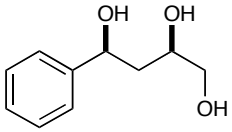


1-Phenylbutane-1,4-diol (31). To a solution of (*Z*)-4-hydroxy-4-phenylbut-1-enyl acetate **30a** (30 mg, 0.14 mmol, 1 equiv) in MeOH (1 mL) was added a solution of $NaBH_4$ (6 mg, 0.16 mmol, 1.1 equiv) in NaOH (1 M solution) (0.145 mL, 0.14 mmol, 1 equiv) and the resulting mixture was stirred for 2 h at room temperature. The organic solvent was evaporated under reduced pressure and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. Purification was accomplished by flash column chromatography eluting with EtOAc/hexanes (1:1). The fractions containing product were combined and concentrated under reduced pressure to give the desired product **31** as colorless oil (24 mg, 99% yield). R_f = 0.22 (EtOAc/hexanes = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H), 4.68 (t, *J* = 6.17 Hz, 1H), 3.69-3.56 (m, 2H), 3.25 (bs, 1H), 2.85 (bs, 1H), 1.86-1.79 (m, 2H), 1.69-1.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 128.5 (2), 127.5, 125.9 (2), 74.4, 62.8, 36.4, 29.7.

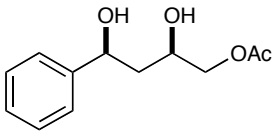
1.7.9 Stereochemical Proofs of Compound 33d and 34c



33a **33b** **33c** **33d**

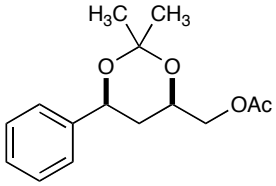


(2*R*,4*S*)-4-Phenylbutane-1,2,4-triol (33b). To a solution of epoxide **33a** (68mg, 0.31 mmol, 1 equiv) in 5 mL Et_2O was added $LiBH_4$ (2 M in THF) (1.02 mmol, 3.3 equiv) over 30 min at 0 °C and then the reaction mixture was allowed to warm up to rt (18 °C to 22 °C). After 30 min stirring, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography eluting with EtOAc/hexanes (3:1) to give the desired product **33b** as colorless oil (22 mg, 40% yield). R_f = 0.14; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 4.91 (dd, *J* = 9.7, 3.4 Hz, 1H), 4.39 (bs, 1H), 4.19 (bs, 1H), 3.94 (bs, 1H), 3.57-3.40 (m, 3H), 2.19-1.83 (m, 1H), 1.73-1.68 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 128.6 (2), 127.8, 125.8 (2), 74.0, 72.2, 66.9, 41.5



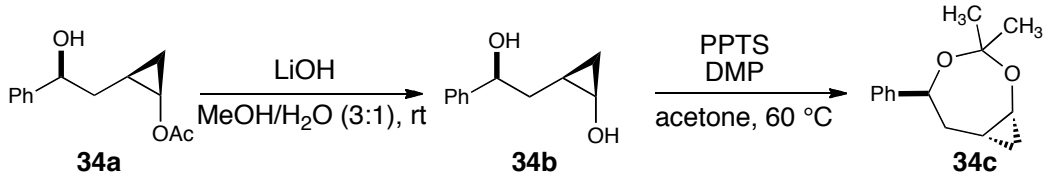
(2*R*,4*S*)-2,4-Dihydroxy-4-phenylbutyl acetate (33c). To a solution of triol **33b** (22 mg, 0.12 mmol, 1 equiv) and Et_3N (37 mg, 0.36 mmol, 3 equiv) in CH_2Cl_2 (1 mL) was added AcCl (10 mg, 0.127 mmol, 1.05 equiv) dropwise at 0 °C and then the reaction mixture was allowed warm up to rt (18 °C to 22 °C). After 3 h stirring at rt (18 °C to 22 °C), water was added. The layers were separated and the organic layer was washed with water and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography, eluting with

EtOAc/hexanes (3:1) to give the desired product **33c** as colorless oil (16 mg, 60% yield). R_f = 0.42; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 4.98 (dd, *J* = 10.59, 3.68 Hz, 1H), 4.16-4.13 (m, 1H), 4.11 (dd, *J* = 11.46, 3.64 Hz, 1H), 4.03 (dd, *J* = 11.55, 6.74 Hz, 1H), 3.43 (bs, 1H), 3.14 (bs, 1H), 2.09 (s, 3H), 1.97-1.90 (m, 1H), 1.80 (app dt, *J* = 2.94, 2.94, 5.73 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 144.0, 128.7 (2), 128.0, 125.8 (2), 74.7, 70.4, 68.5, 41.6, 21.0; HRMS (ESI) calcd for $C_{12}H_{16}O_4$ $[M+Li]^+$ 231.1209; found 231.1091.

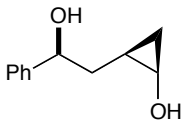


(4*R*,6*S*)-2,2-Dimethyl-6-phenyl-1,3-dioxan-4-yl)methyl acetate (33d). To a solution of diol **33c** (10 mg, 0.045 mmol, 1 equiv) and DMP (13.7 mg, 0.18 mmol, 4 equiv) in acetone (0.5 mL) was added PPTS (0.6 mg, 0.002 mmol, 0.05 equiv) at rt (18 °C to 22 °C). The resulting reaction mixture was refluxed for 24 h. The solvent was removed under reduced pressure and water was added. The layers were separated and the organic layer was washed with water, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography eluting with EtOAc/hexanes (1:10) to give the desired product **33d** as a colorless oil (8 mg, 70% yield). R_f = 0.2; IR (film, cm^{-1}): 3064, 3031, 2996, 2964, 2880, 1741, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 4.94 (dd, *J* = 11.71, 2.73 Hz, 1H), 4.31-4.22 (m, 1H), 4.09 (ddd, *J* = 15.60, 11.58, 4.29 Hz, 1H), 2.09 (s, 3H), 1.74 (app dt, *J* = 2.74, 2.74, 12.98 Hz, 1H), 1.58 (s, 3H), 1.53 (s, 3H), 1.36 (dd, *J* = 52.09, 18.0, 1H); ^{13}C NMR (75

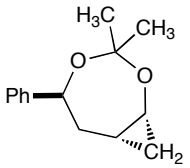
MHz, $CDCl_3$) δ 171.1, 142.0, 128.6 (2), 127.8, 126.0 (2), 99.4, 71.1, 67.6, 67.2, 35.4, 30.2, 21.0, 19.8; HRMS (ESI) calcd for $C_{15}H_{20}O_4$ $[M+Li]^+$ 271.1522; found 171.1385.



34a **34b** **34c**



(1*R*,2*R*)-2-((*S*)-2-Hydroxy-2-phenylethyl)cyclopropanol (34b). To a solution of (1*R*,2*S*)-2-((*S*)-2-hydroxy-2-phenylethyl)cyclopropyl acetate (**34a**) (74 mg, 0.337 mmol, 1 equiv) in MeOH/H_2O (4 mL) was added LiOH (40 mg, 1.687 mmol, 5 equiv) at 0 °C. The resulting reaction mixture was allowed to warm up to rt (18 °C to 22 °C) and stirred for 10 min. The reaction mixture was neutralized with 1N HCl and the solvent removed under reduced pressure. The resulting aqueous phase was extracted with Et_2O. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography eluting with Et_2O/hexanes (2:1) to give the desired product **34b** as colorless oil (60 mg, 99% yield). R_f = 0.28; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.23 (m, 5H), 4.91-4.88 (m, 1H), 3.65 (bs, 1H), 3.50 (bs, 1H), 3.38-3.32 (m, 1H), 2.40-2.16 (m, 1H), 1.18-1.77 (m, 1H), 0.65-0.58 (m, 1H), 0.52-0.40 (m, 1H), 0.26-0.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 128.2 (2), 127.2, 125.8 (2), 73.4, 49.0, 36.1, 13.5, 13.1; HRMS (ESI) calcd for $C_{11}H_{14}O_2$ $[M+Li]^+$ 185.1154; found 185.1148.



(1*R*,5*S*,7*R*)-3,3-Dimethyl-5-phenyl-2,4-dioxabicyclo[5.1.0]octane (34c). To a solution of (1*R*,2*R*)-2-((*S*)-2-hydroxy-2-phenylethyl)cyclopropanol (**34b**) (60 mg, 0.337 mmol, 1 equiv) in acetone (4 mL) was add DMP (103 mg, 1.348 mmol, 4 equiv) and PPTS (4.2 mg, 0.016 mmol, 0.05 equiv) at rt (18 °C to 22 °C). The resulting mixture was refluxed overnight and the solvent was removed under reduced pressure. The resulting aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography eluting with Et_2O/hexanes (1:1) to give the desired product **34c** as colorless oil (18 mg, 25% yield). R_f = 0.78; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.21 (m, 5H), 4.82 (dd, *J* = 9, 4 Hz, 1H), 3.55 -3.40 (m, 1H), 2.27-2.17 (m, 1H), 1.58 (s, 3H), 1.33 (s, 3H), 0.86-0.84 (m, 1H), 0.49-.048 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 128.3 (2), 127.0, 125.9 (2), 102.6, 69.0, 50.4, 37.5, 25.5, 25.4, 11.7; HRMS (ESI) calcd for $C_{14}H_{18}O_2$ $[M+Li]^+$ 225.1467; found 225.1507.

CHAPTER II

INDIUM-CATALYZED CYCLOISOMERIZATION OF ACETYLENIC EPOXIDES TO 2,3,5-TRISUBSTITUTED FURANS

2.1 Introduction and Background of Furan Synthesis

Heterocyclic compounds such as furans, thiofurans, and pyrroles, especially in drug discovery, have become important targets in the organic community due to not only their numerous appearance in natural products[42-45] but also their versatile applications in organic synthesis such as in pesticide synthesis.[46] Furans are some of the most-synthesized heterocyclic compounds because they are frequently found in partial structures of many natural products[42] (Figure 2.1).

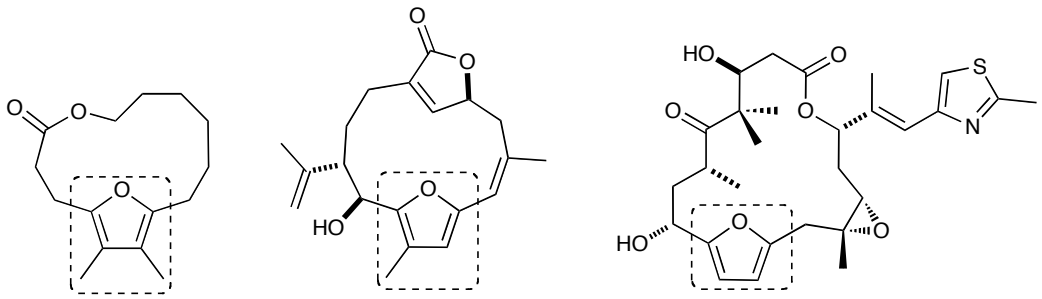
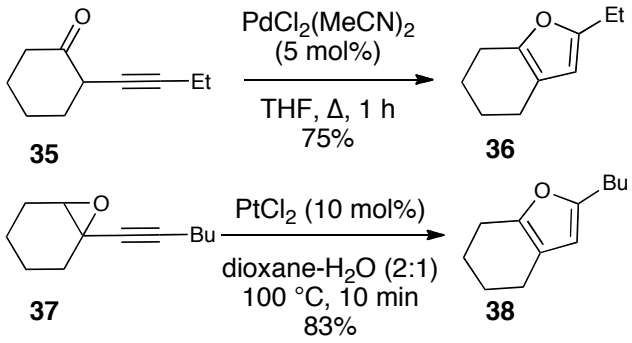


Figure 2.1. Furan-Containing Natural Products.

In 1902 Feist and Benary reported a classic method for generating furans utilizing a condensation reaction between α-haloketones and β-dicarbonyl compounds.[47] Since Feist reported this furan synthesis,[47] a large number of synthetic methods toward furan synthesis have been reported.

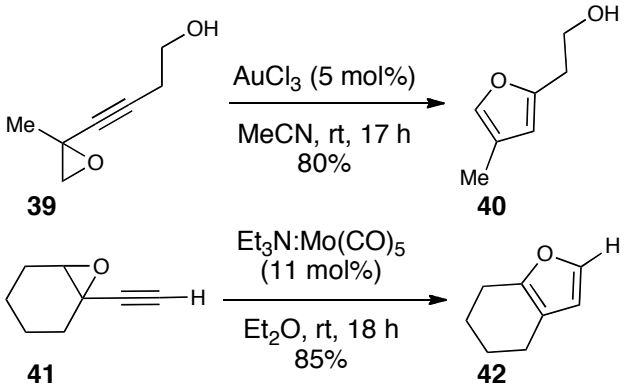
Recent work directed toward furan synthesis featured transition metal-catalyzed reactions and Lewis acid-mediated syntheses. For example, palladium-catalyzed cyclization of acetylenic ketones **35** furnished bicyclic tri-substituted furans **36** as reported by Fukuda and co-workers (Scheme 2.1).[48] Additionally, platinum-catalyzed cyclization of propargylic oxiranes **37** in aqueous media proceeded smoothly to give tri-substituted furans **38** as reported by Yoshida *et al.* in 2009 (Scheme 2.1).[49] However, these transition metal-catalyzed syntheses of furans have suffered from moderate yields under both Pd(II)[48] and Pt(II) catalyzed reaction conditions.[49]

Scheme 2.1. Transition Metal-Catalyzed Furan Synthesis



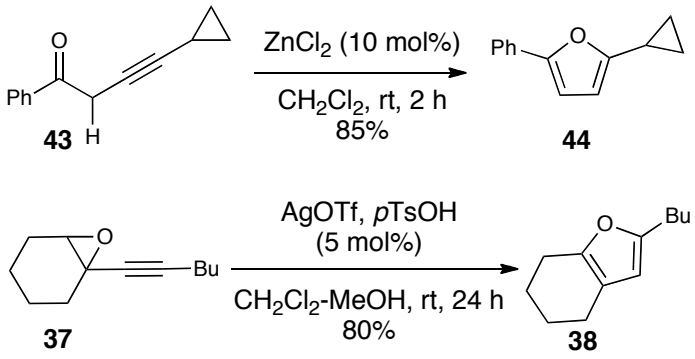
The gold-mediated transformation of alkynyl epoxides **39** to furans **40** has been disclosed by Hashmi (Scheme 2.2)[50] and molybdenum-catalyzed cyclization of propagylic oxiranes **41** to furans **42** as reported by McDonald has been well-established (Scheme 2.2).[51] On the other hand, these Au(III)[50] and Mo(V) catalysts[51] exhibited limited substrate scope for furan synthesis, only providing moderate yields.

Scheme 2.2. Au- and Mo-Catalyzed Furan Synthesis



Lewis acid-mediated syntheses of furans, including use of $ZnCl_2$ for cycloisomerization of alkynyl ketones **43** to cyclopropane substituted furans **44** as introduced by Sniady,[52] and AgOTf-mediated isomerization of alkynyl epoxides **37** to furans **38** as disclosed by Blanc (Scheme 2.3),[53] have now been reported. These Lewis acid-mediated syntheses of furans, however, exhibit poor functional group tolerance.

Scheme 2.3. Lewis Acid-Mediated Furan Synthesis



2.2 Specific Aim

Although numerous methods for furan synthesis have been previously reported, there are some limitations in substrate scope, functional group tolerance, and low product yield in many cases. Thus, a reliable synthetic method toward furans, solving issues with current limitations, needs to be developed due to their versatile application in pharmaceutical industries. In this context, we desired to develop an efficient methodology employing mild and atom-economical reaction conditions affording highly

substituted furans which can serve as valuable precursors in alkaloid natural product synthesis[54,55] and organic synthesis.

2.3 Synthesis of Acetylenic α,β-Epoxides

Acetylenic α,β-epoxides were synthesized using several different methods. For example, Sonogashira cross-coupling reactions[56] between vinyl halides **45** and alkynes **46** afforded tetra-substituted enynes **47**. Epoxidation of olefin **48** furnished the acetylenic α,β-epoxides **49** (Scheme 2.4)[57] and a cascade reaction of alkynyl halides **51** and di-substituted phenones **50** via α-brominated ketone intermediates provided tetra-substituted oxiranes **52** (Scheme 2.4).[58] Furthermore, treatment of α-haloketones **53** and acetylides **54e** generated the acetylenic α,β-epoxides **55** by nucleophilic ring closure of propargylic alcohols (Scheme 2.4).[59,60] These known methods for the synthesis of acetylenic α,β-epoxides require either the use of expensive reagents[56,57] or low product yields.[60] Therefore we wished to develop a highly cost effective and efficient method toward synthesis of acetylenic α,β-epoxides.

Scheme 2.4. Synthesis of Acetylenic α,β-epoxides

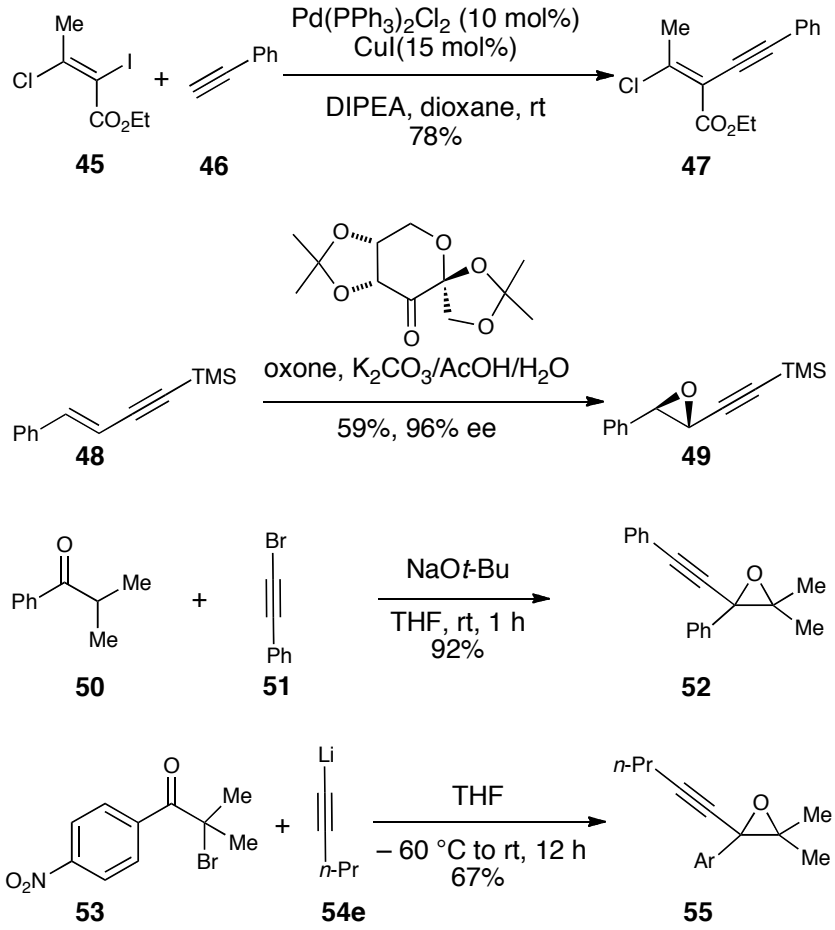
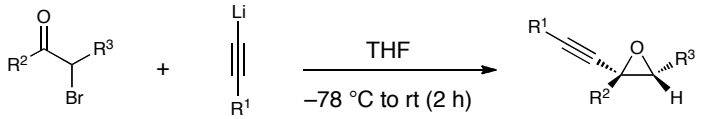
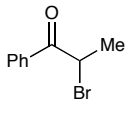
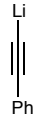
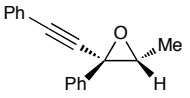
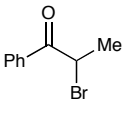
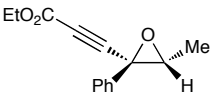
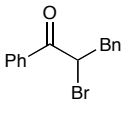
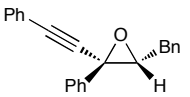
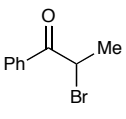
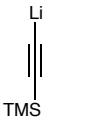
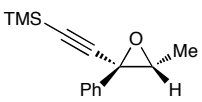
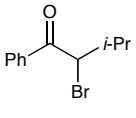
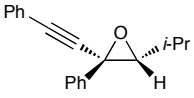
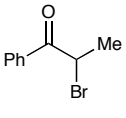
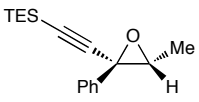
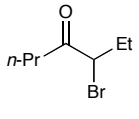
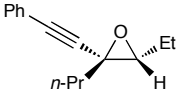
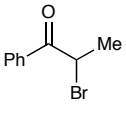
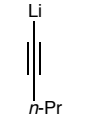
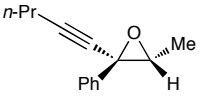


Table 2.1. Epoxides by Treatment of α-Bromo Ketones with Lithium Acetylides[a]



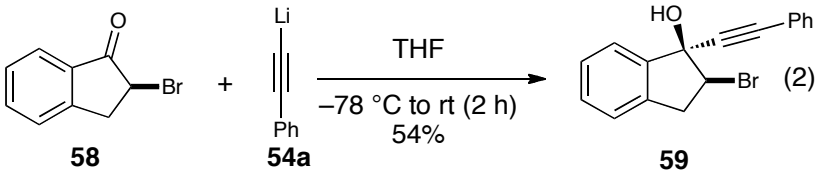
SM		product[b]	SM		product[b]
 **56a**	 **54a**	 **57a**, >99%	 **56a**	 **54b**	 **57e**, 70%
 **56b**	 **54a**	 **57b**, 89%[c]	 **56a**	 **54c**	 **57f**, 95%
 **56c**	 **54a**	 **57c**, 85%[c]	 **56a**	 **54d**	 **57g**, 99%
 **56d**	 **54a**	 **57d**, 90%[c]	 **56a**	 **54e**	 **57h**, 96%

[a] Reactions were performed using α-bromoketones **56** (0.32 mmol) and lithium acetylides **54** (0.35 mmol) in 1 mL THF at rt for 2 h and quenched with saturated aqueous $NaHCO_3$. [b] Isolated yield after column chromatography. [c] Calculated yield accounting for inseparable impurities (See Experimental Procedure for spectra and details of purity).

This project began with preparation of the acetylenic α,β-epoxides, which could undergo cycloisomerization to afford the desired furans. After screening several acetylides, which were prepared from $ZnCl_2$ and Mg, we found that the addition of lithium acetylides to α-bromoketones proceeded very efficiently to generate tri-substituted oxiranes (Table 2.1). Upon treatment of 2-bromopropiophenone **56a** with

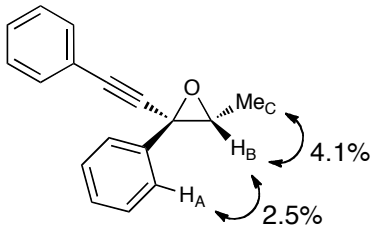
lithium phenyl acetylide **54a**, the desired product of phenyl acetylenic α,β-epoxide **57a** was obtained in quantitative yield (Table 2.1).[61] When β-substituted ketones **56b** and **56c** were subjected to standard reaction conditions (THF, –78 °C to rt, 2 h), furans **57b** and **57c** were also obtained in very high yields (Table 2.1, 89% and 85%, respectively). Aliphatic ketone **56d** and acetylide **54a** also was converted efficiently to the epoxide **57d** in 90% yield. When an acetylide with electron deficient substituent **54b** was employed, a lower yield (70%) of epoxide product **57e** was observed (Table 2.1). We also observed high yield of epoxides **57f** and **57g** in 95% and 99% yields, respectively, when silyl-protected acetylides **54c** and **54d** with **56a** were subjected to these reaction conditions (Table 2.1). Additionally, we were interested in use of aliphatic acetylides to α-bromoketones to access aliphatic acetylenic α,β-epoxides. Accordingly, Aliphatic substituted acetylide **54e** was treated with **56a**, resulted in 96% yield of furan **57h**.

Having now developed this useful transformation of acyclic 2-bromoketones and acetylides to acetylenic α,β-epoxides, 2-bromo-1-indanone **58** was treated with phenylethynyl lithium **54a** using standard reaction conditions. However, it was observed that cyclization of a conformationally restricted cyclic α-haloketone failed to provide the epoxide. It is clear that the required S_N2 replacement of the bromide by the neighboring alkoxide could not occur, because nucleophilic attack of the acetylide **54a** to 2-bromo-1-indanone **58** occurred from the less hindered side of the ketone to produce the unreactive *syn*-hydroxybromide **59** (eq 2).



The stereochemical outcome of the reaction was consistent with Felkin-Anh controlled addition of nucleophile to the ketone and followed by S_N2 displacement of the bromide by alkoxide.[62] The stereochemistry of the tri-substituted oxirane was determined by NOE analysis (Table 2.2).[61]

Table 2.2. Key NOE Enhancements in **57a**



Irradiated H	Observed H	% nOe
B	A	2.5
B	C	4.1
C	B	2.1

2.4 Cycloisomerization of Oxiranes to Furans

Indium is an important element in synthesis and has been employed for many organic transformations including Mannich reactions,[63]allylation of aldehydes,[64] and aldol reactions (Scheme 2.5).[65] Although Indium is a potentially versatile tool in organic synthesis, indium-mediated isomerization and rearrangement have only been reported in

limited cases, such as in the Beckman rearrangement[66] and Ferrier rearrangement (Scheme 2.5).[67] Thus, due to both its exceptional stability to air and water and reasonable cost as a Lewis acid[65] indium attracted our attention when searching for new transformation of cycloisomerization.

Scheme 2.5. Previously Reported Indium-Mediated Organic Reactions

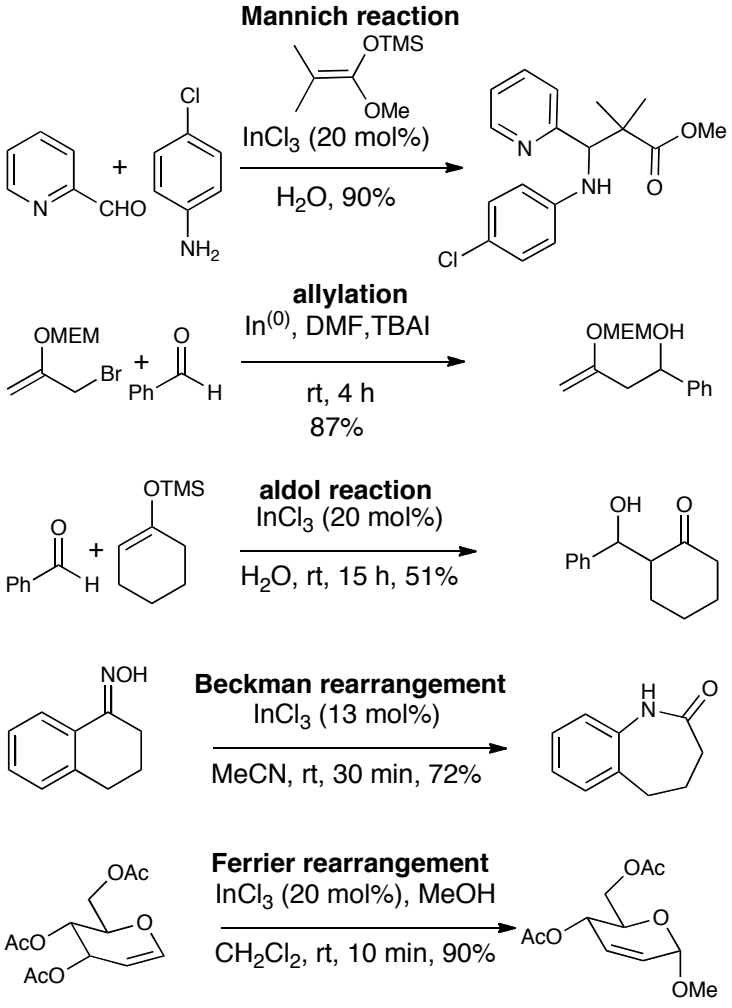
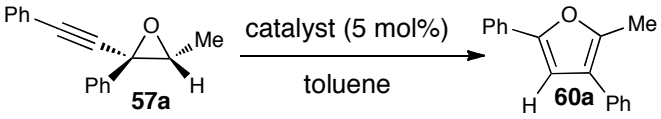


Table 2.3. Initial Cycloisomerization Results[a]



entry	catalyst	temp (°C)	time	yield (%)[b]
1	$Pd_2(dba)_3$, PPh_3	100	48 h	16
2	$Pt[(C_2H_5)_2S]_2Cl_2$	100	48 h	90
3	$AuCl_3$	100	48 h	70
4	CuI	100	48 h	21
5	$InCl_3$	100	20 min	>99
6	$InCl_3$	70	20 min	>99
7	$InCl_3$	50	1 h	95
8	$InCl_3$	40	1 h	10

[a] Reactions were performed using acetylenic α,β-epoxides (0.17 mmol) **57a** and catalysts (0.0085 mmol) in 1 mL toluene and quenched with water. [b] Isolated yield.

The initial cycloisomerization studies of tri-substituted oxiranes are summarized in Table 2.3. Palladium and platinum-catalyzed rearrangement methods are extensively utilized in furan synthesis. For example, Palladium[68] is known to cycloisomerize acetylenic ketones to furans and platinum[49] has been employed for cyclization of propargylic oxiranes to furans. Pd and Pt are known in other reports for generating furans from acetylenic α,β-epoxides via cycloisomerization. However, low yield of products was obtained with Pd catalyst and extended reaction time was necessary for Pt catalyst (Table 2.3, entries 1 and 2). Gold and copper catalysts were employed for this cycloisomerization but they afforded furans in low to moderate yield (Table 2.3, entries 3 and 4).

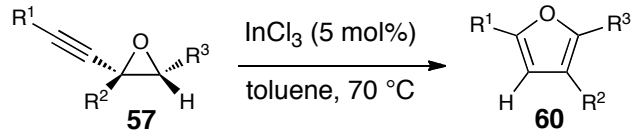
After extensive screening of transition metals and Lewis acids for cycloisomerization of oxiranes to furans, we have developed a highly efficient method applicable toward furan synthesis utilizing indium catalysis via cycloisomerization of acetylenic α,β-epoxides. Indium catalysts, due to their exceptional stability and versatility[65] were applied for cycloisomerization of acetylenic α,β-epoxides. Indium catalyst $InCl_3$ efficiently transformed oxiranes **57a** to furan **60a** in quantitative yield in only 20 min (Table 2.3, entry 5). Reactions at 70 °C provided the same high yield of products (Table 2.3, entry 6). To achieve more mild reaction conditions, reactions were conducted at lower temperature (50 °C and 40 °C) but the reaction proceeded more slowly (Table 2.3, entries 7 and 8). During our studies toluene was the solvent of choice because ethereal solvents such as THF and 1,4-dioxane provide low yield of products and decomposition of oxirane.

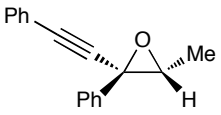
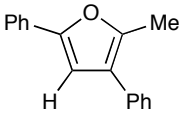
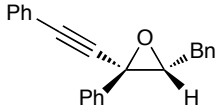
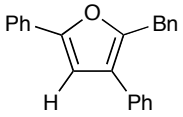
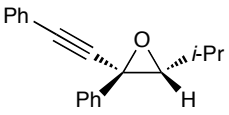
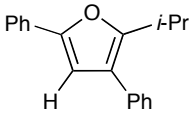
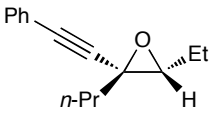
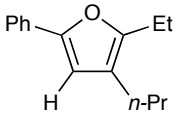
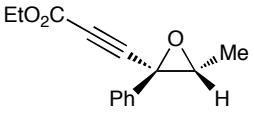
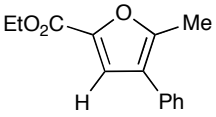
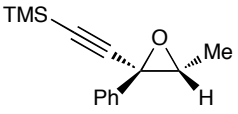
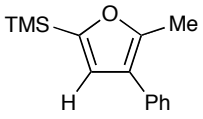
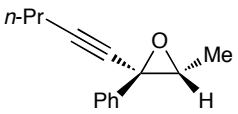
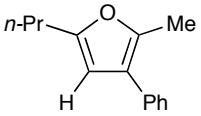
With these optimized reaction conditions in hand, we next investigated the scope of this reaction under indium catalysis using various epoxides. The results of cycloisomerization from the optimized reaction conditions are summarized in Table 2.4. When the parent acetylenic α,β-epoxide **57a** was employed in the standard reaction conditions, the desired product **60a** was obtained in quantitative yield after 20 min at 70 °C (Table 2.4). We were also interested in testing the steric influence on this cycloisomerization reaction. Accordingly, the effect of the β-substituents on epoxides such as benzyl and isopropyl β-substituted epoxides (Table 2.4, **57b** and **57c**) was tested in the reaction conditions (70 °C, 20 min, toluene). Results of cycloisomerization of the β-substituted epoxides indicate that adverse steric interactions appear to be minor in this

reaction, still providing 84% yield of the furan products (Table 2.4, **60b** and **60c**). Treatment of epoxide **57d** with $InCl_3$ (5 mol%) led to furan **60d** in 95% yield (Table 2.4).[61]

To examine the utility of this method with different substituent patterns on the alkyne, the alkynyl epoxide **57e**, which contains an electron-withdrawing alkynyl ester, was treated with $InCl_3$ (5 mol%) under the reaction conditions, providing 90% yield of product **60e** (Table 2.4). When trimethylsilyl-protected alkynyl epoxide **57f** was employed in the reaction conditions, quantitative conversion of the epoxide to the furan **60f** was also observed. However, unexpectedly, it was observed that the structurally related triethylsilyl-protected alkynyl epoxide **57g** (Table 2.1) decomposed upon treatment with $InCl_3$ (5 mol%). Aliphatic alkynyl epoxide **57h**, which could be used to synthesize 1,5-aliphatic furans that often appear in many natural products,[42] also efficiently was converted to furan **60h** in quantitative yield (Table 2.4).

Table 2.4. Scope of the Cycloisomerization Reaction[a]

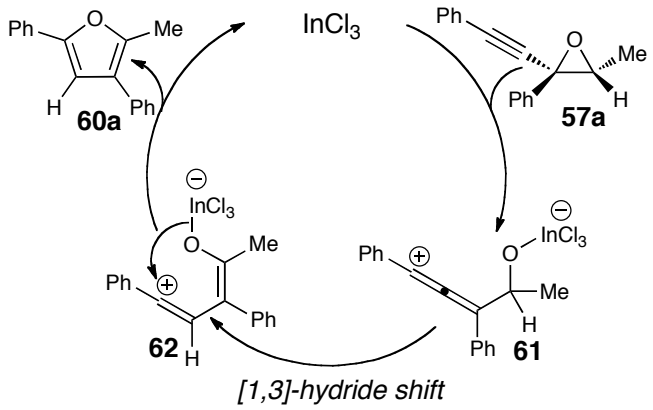


SM	product[b]
 **57a**	 **60a**, >99%
 **57b**	 **60b**, 84%[c]
 **57c**	 **60c**, 84%[c]
 **57d**	 **60d**, 95%
 **57e**	 **60e**, 90%[c]
 **57f**	 **60f**, >99%
 **57h**	 **60h**, >99%

[a] Reactions were performed using acetylenic α,β-epoxides **57** (0.17 mmol) and $InCl_3$ (0.0085 mmol) in 1 mL toluene at 70 °C for 20 min then quenched with water. [b] Isolated yield after column chromatography. [c]Calculated yield accounting for inseparable impurities (See Experimental Procedure for spectra and details of purity).

On the basis of these experimental results, a plausible mechanistic cycle for cycloisomerization of the acetylenic α,β-epoxide to furans is described in Scheme 2.6. First, indium complex is coordinated with the epoxide **57a**. Consequently, the indium epoxide complex undergoes ring-opening to generate zwitterion **61** which can participate in an apparent 1,3-hydride shift[69,70] and generate intermediate benzylic cation/enolate **62**, forming nucleophilic C–O bond, regenerating $InCl_3$, and affording the observed furan product **60a**.[61]

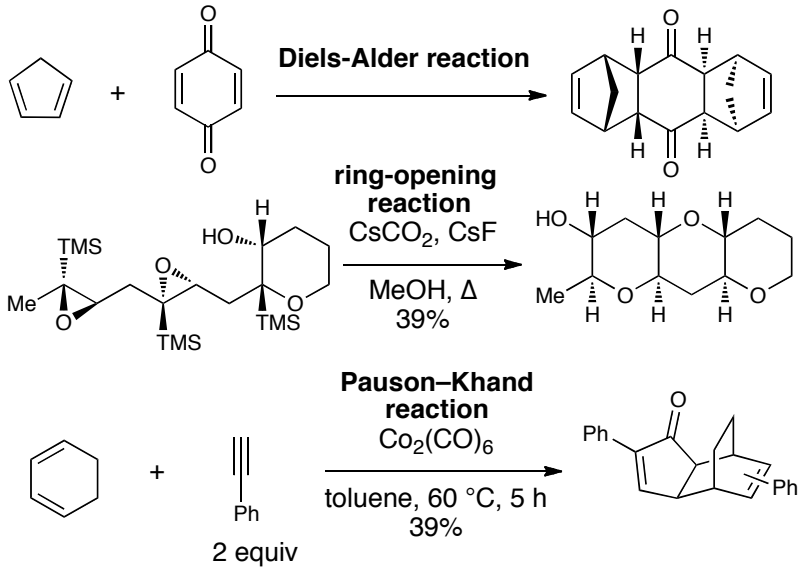
Scheme 2.6. Proposed Mechanistic Cycle for Formation of Furan



2.5 Cascade Reactions to Generate Furans

Cascade reactions,[71] allowing formation of multiple bonds in a single chemical operation, are some of the most attractive chemical processes for synthetic organic chemists due to atom economy decrease in reaction steps, waste, and time. Accordingly, cascade reactions have been utilized in a range of organic synthesis. For example, Diels-Alder reactions,[72] oxirane ring-opening reactions,[72,73] and Pauson–Khand reactions[74] are the several representative reactions that can proceed in cascade process (Scheme 2.7). Therefore, we were interested in generating furans from α-halo carbonyl compounds and acetylides employing cascade process.

Scheme 2.7. Cascade Reactions in Organic Synthesis

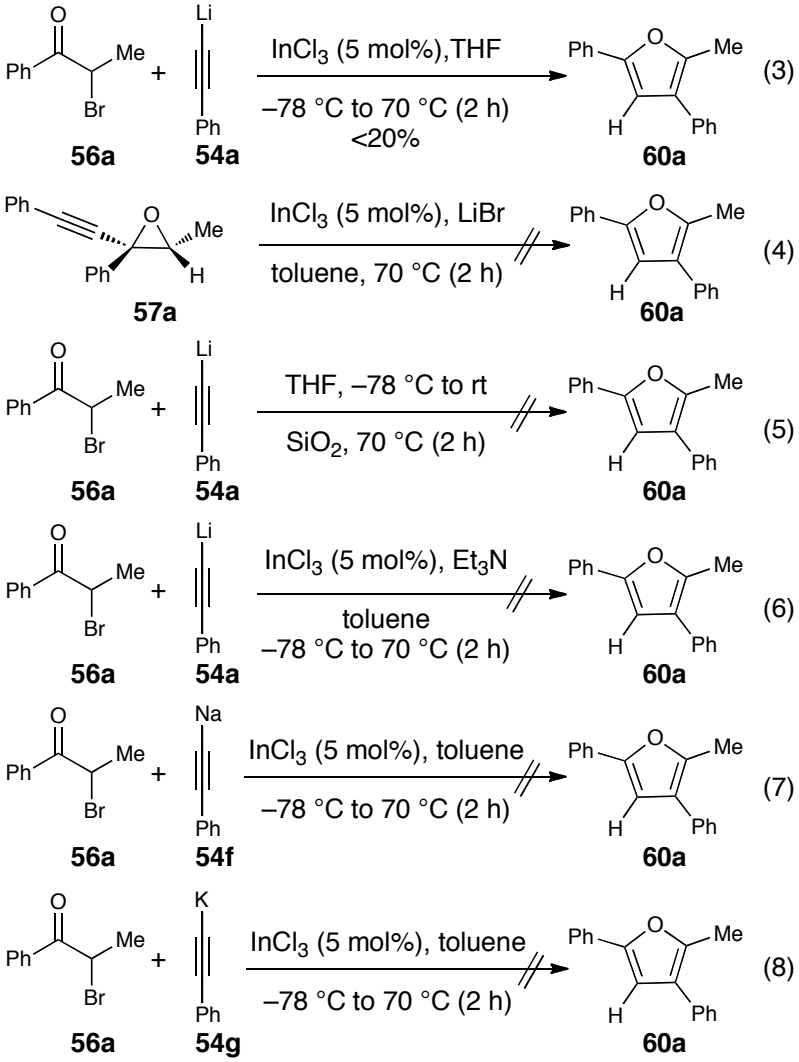


Initial studies of furan synthesis from α-bromoketones and acetylides via cascade processes started with determination of compatible solvents. When THF was used in the

synthesis of furans in this cascade process, furan **60a** was obtained in 20% yield (eq 3). However, no desired furan **60a** was generated employing toluene in the same reaction conditions. It was assumed that LiBr, generated from coupling reaction of α-bromo propiophenone **56a** and phenylethynyl lithium **54a** during the reaction, is responsible for this phenomenon. To test the effect of LiBr on the formation of furan, LiBr was added to the reaction with oxirane (eq 4). Indeed, addition of LiBr to the α,β-acetylenic epoxides **57a** in the standard reaction conditions ($InCl_3$, toluene, 70 °C) resulted in no conversion to furan **60a** (eq 4). With these preliminary results in hand, the reaction conditions were modified. For instance, SiO_2, which could induce oxirane ring opening, was added to the reaction instead of $InCl_3$ catalyst, but the reaction did not proceed to afford product (eq 5). In order to prevent the interference of LiBr in furan formation, in which LiBr could prevent oxirane ring opening which can be catalyzed by $InCl_3$ and subsequently prohibit formation of furan, Et_3N was added to the reaction to precipitate out LiBr•Et_3N complex but the furans still did not obtained (eq 6).

Base on these results, several acetylenic nucleophiles with various cations such as sodium acetylide **54f** and potassium acetylide **54g** were employed under these reaction conditions (eq 7 and 8). However, cation modification of acetylenic nucleophiles still did not allow formation of the desired furans. Generation of LiBr from α-bromo propiophenone and lithium acetylide in the reaction led to LiBr salts which were difficult to remove from the reaction media, hindering the cascade reaction to be rendered as a synthetically useful reaction.

Scheme 2.8. Cascade Reactions for Furan Synthesis



2.6 Conclusion

Furans are extremely important target intermediates among heterocyclic compounds due to both their numerous appearances in biologically active natural products and their versatile applications in organic synthesis. Consequently, while remarkable synthetic methods toward furan synthesis have been continuously reported, improved methods pertaining to substrate scope and product yield are still needed. In this context, we have developed a highly efficient and catalytic cycloisomerization reaction that transforms acetylenic α,β-epoxides to 2,3,5-tri-substituted furans under $InCl_3$ (5 mol%)catalysis. The acetylenic α,β-epoxides were prepared by coupling α-bromo ketones and lithium acetylides to generate a propargylic alcohol which consequently undergoes nucleophilic ring closure. This reaction sequence allows rapid construction of highly valuable, tri-substituted furan derivatives employing mild and atom-economical reaction conditions

2.7 Experimental Procedure

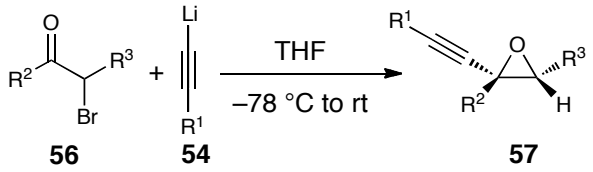
2.7.1 General Information

All reactions were carried out under an argon atmosphere in oven-dried glassware and with magnetic stirring bar. Dry THF was purified by passing through alumina under argon. All commercially obtained reagents were used as received.

Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 1.00 mm glass-backed silica gel 60-F plates. Visualization was performed with UV light or $KMnO_4$ stain solution. Concentration in vacuo refers to the removal of volatile solvent using a rotary evaporator attached to a dry diaphragm pump (10-15 mm Hg) and pumping to a constant weight with an oil pump (<300 mTorr). Heating was accomplished using silicone oil bath. Temperature was controlled by a temperature controller.

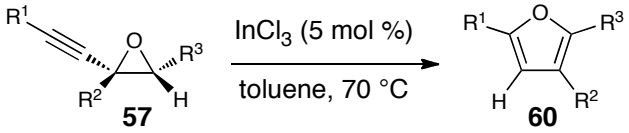
^{1}H NMR spectra were recorded on a Varian Inova 300 (at 300 MHz) or a Varian Mercury 300 (at 300 MHz) NMR and are recorded relative to Me_4Si (δ 0.0 ppm). ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz) and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). Proton-decoupled ^{13}C NMR spectra were recorded on Varian Inova 300 (at 75 MHz) or a Varian Mercury 300 (at 75 MHz) and are reported relative to $CDCl_3$ (δ 77.16 ppm). High-resolution mass spectra (HRMS) were obtained at TAMU. Infrared spectra were recorded on a Bruker Tensor 27 spectrometer as a thin film on NaCl plates.

2.7.2 General Procedure 1 (GP1) of Synthesis of Acetylenic α,β-epoxides



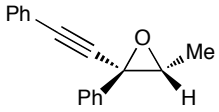
To 2 dram vial was added α-haloketones **56** (0.32 mmol, 1 equiv) and THF (1.0 mL). The vial was cooled to –78 °C and lithium acetylenides **54** (0.35 mmol, 1.1 equiv) was added prepared from acetylene (1.0 equiv) and *n*-BuLi (1.01 equiv) in THF at –78 °C. After complete addition of lithium acetylenides **1**, the reaction mixture was warmed up to rt (18 °C to 22 °C) and stirred for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (1.5 mL). The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography to afford alkynyl oxirane **57**.

2.7.3 General Procedure 2 (GP2) of Cycloisomerization

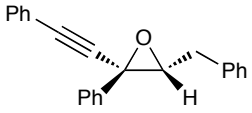


A 2 dram vial was charged with $InCl_3$ (0.0085 mmol, 0.05 equiv) in the dry box. To the vial was added a solution of oxiranes **57** (0.17 mmol, 1.0 equiv) in THF (1 mL). The vial was then placed in a 70 °C oil bath for 20 min. Then cooled to rt (18 °C to 22

°C) and quenched with water. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography to afford furan **60**.

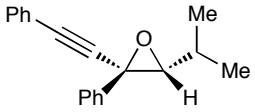


(2*S*,3*R*)-3-Methyl-2-phenyl-2-(phenylethynyl)oxirane (57a). (Phenylethynyl)lithium **54a** (0.35 mmol, 38 mg, 1.1 equiv) and halide **56a** (0.32 mmol, 68 mg, 1.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography on SiO_2 eluting with hexanes:CH_2Cl_2(1:1) provided a colorless oil **57a** (75 mg, quantitative yield). R_f = 0.6 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 2229, 1317, 938, 867; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59-7.57 (m, 2H), 7.51-7.49 (m, 2H), 7.48-7.41 (m, 2H), 7.39-7.33 (m, 4H), 3.74 (q, *J* = 5.5 Hz, 1H), 1.14 (d, *J* = 5.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 132.1 (2), 128.7, 128.3, 128.1 (2), 128.0 (2), 127.1 (2), 122.2, 88.92, 82.9, 63.5, 56.2, 13.4; HRMS (ESI) calcd for $C_{17}H_{15}O$ $[M+H]^+$: 235.1123; found: 235.1131.

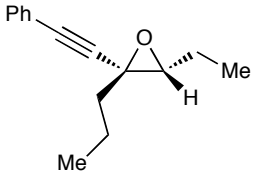


(2*S*,3*R*)-3-Benzyl-2-phenyl-2-(phenylethynyl)oxirane (57b). (Phenylethynyl)lithium **54a** (0.35 mmol, 38 mg, 1.1 equiv) and halide **56b** (0.32 mmol, 92 mg, 1.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography on SiO_2 eluting with hexanes:CH_2Cl_2(1:1) provided a colorless oil **57b** (96 mg, 99%, 89% pure by ^1H and ^{13}C NMR). R_f = 0.83 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 2226, 1317, 938, 879; ^1H NMR

(300 MHz, $CDCl_3$) δ 7.71-7.67 (m, 2H), 7.55-7.26 (m, 11H), 7.26-7.13 (m, 2H), 3.88 (t, *J* = 6.3 Hz, 1H), 2.79 (dd, *J* = 14.8, 6.1 Hz, 1H), 2.63 (dd, *J* = 14.8, 6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 135.5, 132.0 (2), 128.9 (2), 128.8 (2), 128.7 (2), 128.3 (3), 128.2, 127.2 (2), 126.7, 122.1, 88.6, 83.2, 67.5, 56.5, 34.0; HRMS (MALDI) calcd for $C_{23}H_{18}O$ $[M+H]^+$: 311.1436; found: 311.1442.

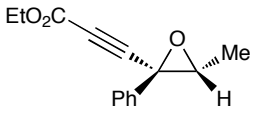


(2*S*,3*R*)-3-Isopropyl-2-phenyl-2-(phenylethynyl)oxirane (57c). (Phenylethynyl)lithium **54a** (0.35 mmol, 38 mg, 1.1 equiv) and halide **56c** (0.32 mmol, 77 mg, 1.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography on SiO_2 eluting with hexanes:CH_2Cl_2(1:1) provided a colorless oil **57c** (80 mg, 95%, 85% pure by ^1H and ^{13}C NMR). R_f = 0.76 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 2226, 1320, 891, 755; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60-7.56 (m, 2H), 7.52-7.47 (m, 2H), 7.45-7.31 (m, 6H), 3.27 (d, *J* = 8.3 Hz, 1H), 1.13 (app s, 4H), 0.82 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 132.0 (2), 128.7, 128.3 (2), 128.1 (2), 128.0, 126.9 (2), 122.3, 89.1, 82.9, 73.0, 56.7, 26.8, 19.6, 17.9; HRMS (MALDI) calcd for $C_{19}H_{18}O$ $[M+H]^+$: 263.1436; found: 263.1428.

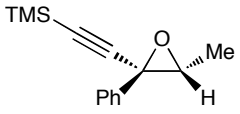


(2*S*,3*R*)-3-Ethyl-2-(phenylethynyl)-2-propyloxirane (57d). (Phenylethynyl)lithium **54a** (0.35 mmol, 38 mg, 1.1 equiv) and halide **56d** (0.32 mmol, 62 mg, 1.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography on SiO_2 eluting

with hexanes:CH_2Cl_2(1:1) provided a colorless oil **57d** (68 mg, >99%, 90% pure by ^{1}H and ^{13}C NMR). R_f = 0.61 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 2226, 1302, 909, 752; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2H), 7.35-7.32 (m, 3H), 3.24 (t, *J* = 6.58 Hz, 1H), 1.47-1.62 (m, 6H), 1.15-1.01 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) d 131.9 (2), 128.6, 128.2 (2), 122.4, 89.1, 82.6, 66.5, 55.3, 33.7, 21.5, 19.2, 14.1, 10.5; HRMS (ESI) calcd for $C_{15}H_{18}O$ $[M+H]^+$: 215.1436; found: 215.1442.

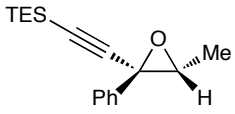


Ethyl 3-((2*S*,3*R*)-3-methyl-2-phenyloxiran-2-yl)propiolate (57e). (3-Ethoxy-3-oxoprop-1-yn-1-yl)lithium **54b** (0.35 mmol, 36 mg, 1.1 equiv) and halide **56a** (0.32 mmol, 68 mg, 1.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography on SiO_2 eluting with hexanes:CH_2Cl_2(2:1) provided a colorless oil **57e** (52 mg, 70%). R_f = 0.64 (hexanes:CH_2Cl_2=2:1); IR (film, cm^{-1}): 2235, 1708, 1220, 953, 870; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.33 (m, 5H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.64 (q, *J* = 5.4 Hz, 1H), 1.28 (t, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 5.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 133.3, 128.5, 128.3 (2), 126.9 (2), 85.9, 74.1, 63.0, 62.2, 54.9, 13.9, 13.0; HRMS (ESI) calcd for $C_{14}H_{14}O_3$ $[M+H]^+$: 231.1021; found: 231.1013.

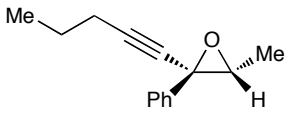


Trimethyl(((2*S*,3*R*)-3-methyl-2-phenyloxiran-2-yl)ethynyl)silane (57f). ((Trimethylsilyl)ethynyl) lithium **54c** (0.35 mmol, 36 mg, 1.1 equiv) and halide **56a** (0.32 mmol, 68 mg, 1.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography on SiO_2 eluting with

hexanes:CH_2Cl_2(1:1) provided a colorless oil **57f** (70 mg, 95%). R_f = 0.75 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 2173, 1249, 938, 844; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.34 (m, 5H), 3.62 (q, *J* = 5.4 Hz, 1H), 1.07 (d, *J* = 5.4 Hz, 3H), 0.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 128.0 (2), 127.9, 127.1 (2), 104.8, 88.1, 63.3, 55.9, 13.2, -0.12 (3); HRMS (ESI) calcd for $C_{14}H_{18}OSi$ $[M+H]^+$: 231.1205; found: 231.1213.

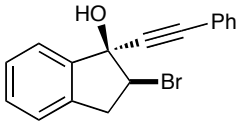


Triethyl(((2*S*,3*R*)-3-methyl-2-phenyloxiran-2-yl)ethynyl)silane (57g). ((Triethylsilyl)ethynyl) lithium **54d** (0.35 mmol, 51 mg, 1.1 equiv) and halide **56a** (0.32 mmol, 68 mg, 1.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography on SiO_2 eluting with hexanes:CH_2Cl_2(1:1) provided a colorless oil **57g** (86 mg, 99%). R_f = 0.70 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 2170, 1240, 938, 864; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.33 (m, 5H), 3.62 (q, *J* = 5.4 Hz, 1H), 1.08 (d, *J* = 5.8 Hz, 3H), 1.03 (t, *J* = 8.3 Hz, 9H), 0.65 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4, 128.0, 127.9 (2), 127.1 (2), 106.1, 85.8, 63.5, 56.0, 13.1, 7.5 (3), 4.3 (3); HRMS (ESI) calcd for $C_{17}H_{24}OSi$ $[M+H]^+$: 273.1675; found: 273.1662.

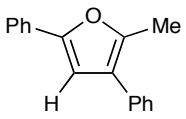


(2*S*,3*R*)-3-Methyl-2-(pent-1-yn-1-yl)-2-phenyloxirane (57h). Pent-1-yn-1-yllithium **54e** (0.35 mmol, 26 mg, 1.1 equiv) and halide **56a** (0.32 mmol, 68 mg, 1.0 equiv) were subjected to the reaction conditions described in GP1. Flash column chromatography on SiO_2 eluting with

hexanes:CH_2Cl_2(1:1) provided a colorless oil **57h** (61 mg, 96%). R_f = 0.60 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 2238, 1448, 867, 752; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51-7.29 (m, 5H), 3.57 (q, *J* = 5.4 Hz, 1H), 2.24 (t, *J* = 7.1 Hz, 2H), 1.64-1.52 (m, 2H), 1.07 (d, *J* = 5.4 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 127.9 (2), 127.8, 127.0 (2), 83.9, 80.1, 63.1, 56.1, 21.9, 20.8, 13.6, 13.3; HRMS (ESI) calcd for $C_{14}H_{16}O$ $[M+H]^+$: 201.1279; found: 201.1282.

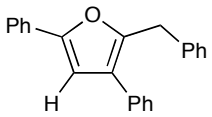


(1*R*,2*S*)-2-Bromo-1-(phenylethynyl)-2,3-dihydro-1*H*-inden-1-ol (59). (Phenylethynyl)lithium **54a** (0.35 mmol, 38 mg, 1.1 equiv) and 2-bromo-indanone **58** (0.32 mmol, 68 mg, 1.0 equiv) were subjected to the reaction conditions described in GP1 for 40 h to afford a colorless oil **59** (54 mg, 54%). R_f = 0.33 (hexanes:Et_2O=5:1); IR (film, cm^{-1}): 3521, 3052, 2228, 1338, 922, 869; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77-7.73 (m, 1H), 7.52-7.44 (m, 2H), 7.42-7.29 (m, 6H), 4.84 (t, *J* = 7.3 Hz, 1H), 3.54-3.39 (m, 2H), 3.08 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 140.2, 132.0 (2), 129.9, 128.9, 128.4 (2), 127.9, 124.8, 124.6, 122.0, 88.0, 85.4, 76.1, 60.3, 39.7; HRMS (MALDI) calcd for $C_{17}H_{13}BrO$ $[M+Na]^+$: 335.0048; found: 335.0037.

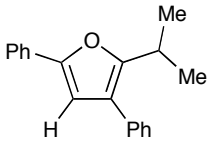


2-Methyl-3,5-diphenylfuran (60a). Oxirane **57a** (0.17 mmol, 40 mg 1.0 equiv) and $InCl_3$ (0.0085 mmol, 1.9 mg, 0.05 equiv) were subjected to the reaction conditions described in GP2 to afford colorless oil **60a** (40 mg, >99%). R_f = 0.83 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 3061, 1599, 1495, 1448, 1018; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76-7.73 (m, 2H), 7.53-7.42 (m, 6H), 7.38-7.27 (m, 2H), 6.85 (s,

1H), 2.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 147.6, 134.1, 130.8, 128.7 (2), 128.6 (2), 127.5 (2), 127.0, 126.5, 123.4 (2), 123.0, 106.4, 13.2 (4); HRMS (ESI) calcd for $C_{17}H_{14}O$ $[M+Na]^+$: 257.0942; found: 257.0949.

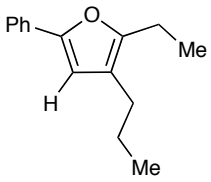


2-Benzyl-3,5-diphenylfuran (60b). Oxirane **57b** (0.17 mmol, 53 mg 1.0 equiv) and $InCl_3$ (0.0085 mmol, 1.9 mg, 0.05 equiv) were subjected to the reaction conditions described in GP2 to afford colorless oil **60b** (53 mg, 99%, 84% pure by ^{1}H and ^{13}C NMR). R_f = 0.56 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 3064, 1599, 1495, 1448; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.73 (m, 2H), 7.52-7.27 (m, 13H), 6.89 (s, 1H), 4.27 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 149.0, 138.6, 133.8, 130.8, 128.8 (2), 128.7 (2), 128.6 (2), 128.4, 127.8 (2), 127.3 (2), 126.9, 126.5, 125.7, 123.7 (2), 106.7, 33.0; HRMS (MALDI) calcd for $C_{23}H_{18}O$ $[M+H]^+$: 311.1436; found: 311.1422.

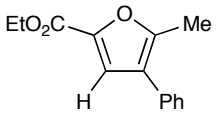


2-Isopropyl-3,5-diphenylfuran (60c). Oxirane **57c** (0.17 mmol, 53 mg 1.0 equiv) and $InCl_3$ (0.0085 mmol, 1.9 mg, 0.05 equiv) were subjected to the reaction conditions described in GP2 to afford colorless oil **60c** (45 mg, 99%, 84% pure by ^{1}H and ^{13}C NMR). R_f = 0.72 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 3058, 1593, 1495; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79-7.72 (m, 2H), 7.51-7.27 (m, 8H), 6.79 (s, 1H), 3.39-3.29 (m, 1H), 1.43 (d, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 151.4, 134.4, 131.1, 128.7 (2), 128.6 (2), 128.1 (2), 127.1, 126.6, 126.0, 123.5 (2),

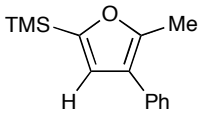
106.7, 26.7, 23.7, 21.9; HRMS (MALDI) calcd for $C_{19}H_{18}O$ $[M+H]^+$: 263.1436; found: 263.1448.



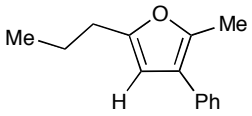
2-Ethyl-5-phenyl-3-propylfuran (60d). Oxirane **57d** (0.17 mmol, 36 mg 1.0 equiv) and $InCl_3$ (0.0085 mmol, 1.9 mg, 0.05 equiv) were subjected to the reaction conditions described in GP2. Flash column chromatography on SiO_2 eluting with hexanes:CH_2Cl_2(20:1) provided colorless oil **60d** (35 mg, 95%). R_f = 0.85 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 3061, 1599, 1486, 1456, 1024; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67-7.65 (m, 2H), 7.41-7.21 (m, 3H), 6.52 (s, 1H), 2.70 (q, *J* = 7.94 Hz, 2H), 2.39 (t, *J* = 7.58 Hz, 2H), 1.68-1.56 (m, 2H), 1.31 (t, *J* = 7.72 Hz, 3H), 1.00 (t, *J* = 7.42 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 151.0, 131.4, 128.6 (2), 126.6, 123.3 (2), 120.5, 107.3, 26.9, 23.9, 19.6, 13.9, 13.5; HRMS (MALDI) calcd for $C_{15}H_{18}O$ $[M+H]^+$: 215.1436; found: 215.1444.



Ethyl 5-methyl-4-phenylfuran-2-carboxylate (60e). Oxirane **57e** (0.17 mmol, 40 mg 1.0 equiv) and $InCl_3$ (0.0085 mmol, 1.9 mg, 0.05 equiv) were subjected to the reaction conditions described in GP2 to afford colorless oil **60e** (40 mg, 99%, 90% pure by ^1H and ^{13}C NMR). R_f = 0.15 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 3061, 1720, 1619, 1187; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.38 (m, 5H), 6.26 (s, 1H), 4.31 (q, *J* = 7.0 Hz, 2H), 2.51 (s, 3H), 1.36 (t, *J* = 7.45 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 130.0, 129.3 (2), 128.8, 128.6 (2), 114.1, 92.9, 61.8, 28.8, 24.4, 14.3; HRMS (ESI) calcd for $C_{14}H_{14}O_3$: 231.1021; found: 231.1010.



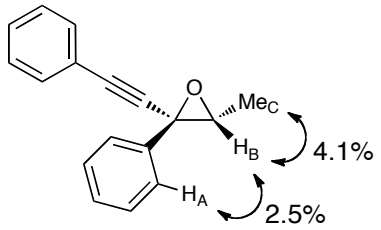
Trimethyl(5-methyl-4-phenylfuran-2-yl)silane (60f). Oxirane **57f** (0.17 mmol, 39 mg 1.0 equiv) and $InCl_3$ (0.0085 mmol, 1.9 mg, 0.05 equiv) were subjected to the reaction conditions described in GP2 to afford colorless oil **60f** (39 mg, >99%). R_f = 0.64 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 3061, 2176, 1909, 1249, 850; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48-7.34 (m, 5H), 4.60 (s, 1H), 2.24 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 134.6, 128.9 (2), 128.0, 127.9 (2), 101.3, 92.5, 53.7, 25.9, 0.0 (3); HRMS (ESI) calcd for $C_{14}H_{18}OSi$ $[M+Na]^+$: 253.1025; found: 253.1014.



2-Methyl-3-phenyl-5-propylfuran (60h). Oxirane **57h** (0.17 mmol, 34 mg 1.0 equiv) and $InCl_3$ (0.0085 mmol, 1.9 mg, 0.05 equiv) were subjected to the reaction conditions described in GP2 to afford colorless oil **60h** (34 mg, >99%). R_f = 0.88 (hexanes:CH_2Cl_2=1:1); IR (film, cm^{-1}): 3061, 1581, 1495, 1448; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48-7.26 (m, 5H), 6.18 (s, 1H), 2.62 (t, J = 7.24 Hz, 2H), 2.47 (s, 3H), 1.81-1.69 (m, 2H), 1.06 (t, J = 7.50 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 145.8, 134.7, 128.6 (2), 127.4 (2), 126.1, 121.2, 106.3, 30.1, 21.5, 13.9, 13.1; HRMS (ESI) calcd for $C_{14}H_{16}O$ $[M+H]^+$: 201.1279; found: 201.1289.

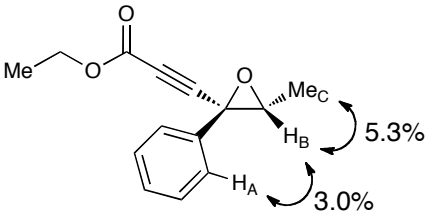
2.7.4 Key NOE Enhancements in 57a, 57e, and 57f

Key NOE Enhancements in **57a**



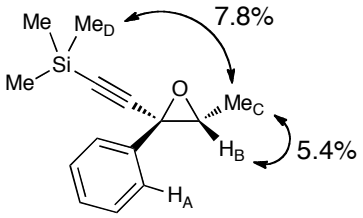
Irradiated H	Observed H	% nOe
B	A	2.5
B	C	4.1
C	B	2.1

Key NOE Enhancements in **57e**



Irradiated H	Observed H	% nOe
B	A	3.0
B	C	5.3
C	B	4.8

Key NOE Enhancements in **57f**



Irradiated H	Observed H	% nOe
B	C	3.0
C	B	5.4
D	C	7.8

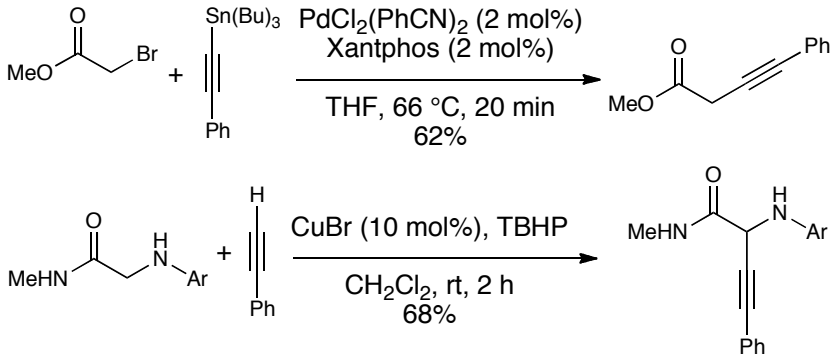
CHAPTER III

CONCLUSION: PALLADIUM-CATALYZED ALKYNYLATION OF SECONDARY α-BROMO CARBONYL COMPOUNDS BY STILLE COUPLING REACTIONS

3.1 Introduction and Background of Cross-Coupling Reaction

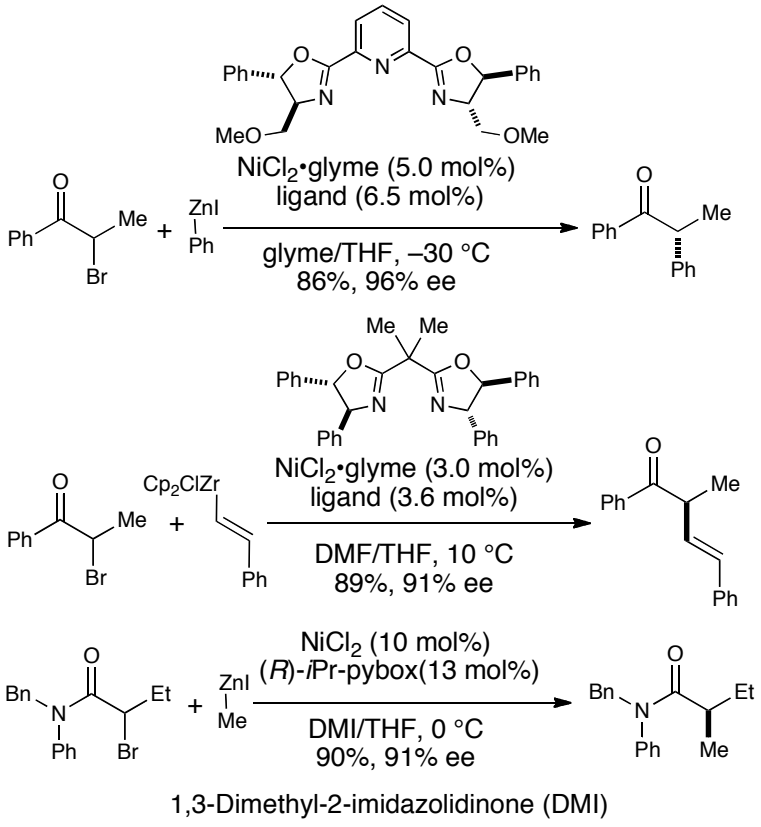
Cross-coupling reactions, specifically utilizing transition metals and Lewis acids, are indispensable synthetic methods for generating C–C and C–N bonds.[75-77] The organometallic nucleophiles of cross-coupling reactions have been extended to a wide range of metals including organolithiums,[78] organozincs,[79] organostannanes,[80] and organozirconiums.[81] As a result, transition metal catalyzed cross-coupling reactions with a variety of metal reagents have been extensively studied. Numerous examples of transition metal-catalyzed cross-coupling reactions of α-halo carbonyl compounds with aryl metals,[82] alkenyl metals,[81] and alkyl metals[83,84] have been successfully reported, but the alkynylation of α-halo carbonyl compounds still remains a difficult task. Few cases of cross-coupling reactions mediated by transition metals and Lewis acids generating α-alkynyl carbonyl compounds have been reported (Scheme 3.1).[85,86] Furthermore, there is currently only one report of transition metal-catalyzed cross-coupling reactions between α-halo carbonyl compounds and alkynyl metals generating α-alkynyl carbonyl compounds.[85] The alkynyl carbonyl compounds have been utilized in a variety of applications to organic synthesis as well as natural product synthesis.[87,88]

Scheme 3.1. Alkynylation of α-Bromo Carbonyl Compounds



Recent works using cross-coupling reactions for α-functionalization of α-bromo carbonyl compounds have featured transition metal-catalyzed reactions. For example, nickel-catalyzed cross-coupling reactions between secondary α-halo carbonyl compounds and aryl zinc reagents furnish α-aryl ketones,[89] nickel-mediated intermolecular cross-coupling reactions of α-bromo ketones with alkenylzirconium reagent proceed successfully to give β,γ-unsaturated ketones,[81] and nickel-catalyzed cross-coupling reactions of α-bromo carbonyl compounds with zinc metal reagents provide α-alkyl carbonyl compounds (Scheme 3.2).[84]

Scheme 3.2. Functionalization of α-Bromo Carbonyl Compounds by Cross-Coupling Reactions

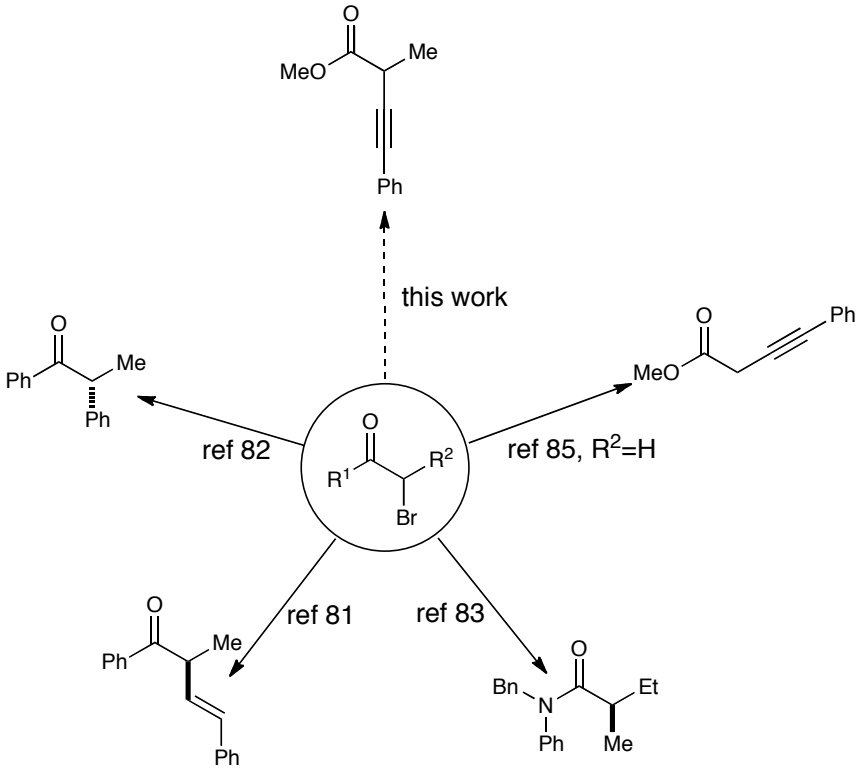


However, alkynylation of α-halo carbonyl compounds with alkynyl metal reagents via cross-coupling reaction have been recognized as a challenging reaction. Indeed, there is only one precedent of transition metal-catalyzed alkynylation of primary α-bromo carbonyl compounds with alkyl metal reagents (Scheme 3.1).[85]

3.2 Specific Aim

α-alkynyl carbonyl compounds are highly valuable precursors for many chemical compounds ranging from pharmaceuticals to agricultural applications.[46] Since there are no straightforward synthetic methods toward secondary α-alkynyl carbonyl compounds, we desired to develop an efficient methodology for cross-coupling reactions producing secondary α-alkynyl carbonyl compounds that could be further studied in both asymmetric alkynylation and cycloisomerization to furans (Scheme 3.3).

Scheme 3.3. Current Synthetic Routes for α-Functionalization of α-Bromo Carbonyl Compounds

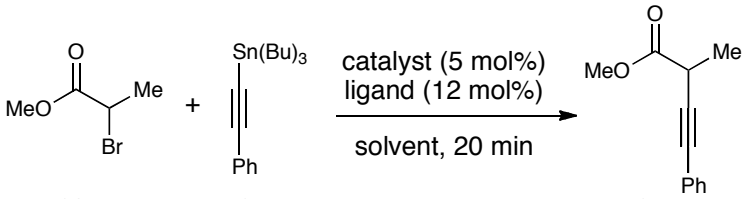


3.3 Pd-Catalyzed Cross-Coupling Reactions of α-Bromo Carbonyl Compounds and Tin Acetylides

This project began with screening of alkynyl metal reagents that could undergo cross-coupling reaction with α-halo carbonyl compounds, generating α-alkynyl carbonyl compounds. After extensive screening of metal reagents ranging from tris(phenylethynyl)indium to tributyl(phenylethynyl)stannane, the desired cross-coupling products were generated in 60 % yield by treatment of α-halo carbonyl compounds and tributyl(phenylethynyl)stannane (Table 3.1, entry 10). Having discovered the optimal metal reagents for the reaction, further optimization of reaction conditions was conducted as described in Table 3.1.

Initial cross-coupling reaction studies of α-bromo esters **63a** and tributyl(phenylethynyl)stannane **64** are summarized in Table 3.1. When a bulky ligand such as Xantphos was used with palladium catalyst $PdCl_2(MeCN)_2$, methyl 2-bromopropanoate **63a**, and tributyl(phenylethynyl)stannane **64** under standard reaction conditions (110 °C, 20 min, toluene), the cross-coupling product of α-alkynyl carbonyl compound **65a** was generated in 31% yield (Table 3.1, entry 1) along with the homocoupled diyne byproduct.[85]

Table 3.1. Initial Screening Results of Cross-Coupling Reactions[a]



63a **64** **65a**

entry	catalyst	ligand	solvent	temp (°C)	yield (%)[b]
1	$PdCl_2(MeCN)_2$	Xantphos	toluene	110	31
2	$PdCl_2(MeCN)_2$	JohnPhos	toluene	110	55
3	$PdCl_2(MeCN)_2$	DavePhos	toluene	110	43
4	$PdCl_2(MeCHN)_2$	TangPhos	toluene	110	42
5	$PdCl_2(MeCN)_2$	PyBox*i*-Pr	toluene	110	50
6	$PdCl_2(MeCN)_2$	BINAP	toluene	110	51
7	$PdCl_2(PhCN)_2$	XPhos	toluene	110	56
8	$NiCl_2$•Glyme		toluene	110	0
9	$Pd(PPh_3)_4$		toluene	110	50
10	$PdCl_2(MeCN)_2$	XPhos	toluene	110	60
11	$PdCl_2(MeCN)_2$	XPhos	THF	70	37
12	$PdCl_2(MeCN)_2$	XPhos	MeCN	80	20[c]

[a] Reactions were performed using catalyst (5 mol %, 0.016 mmol), ligand (12 mol %, 0.038 mmol), α-bromocarbonyl compound **63a** (0.32 mmol, 1 equiv), and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 2 equiv) in solvent (1.0 mL) at 110 °C for 20 min and then quenched with KF solution (1 M, 1.0 mL). [b] Isolated yield after column chromatography. [c] 12 h reaction time.

Other phosphine ligands (Table 3.2) including JohnPhos, DavePhos, TangPhos, and BINAP with $Pd^{(II)}$ catalyst $PdCl_2(MeCN)_2$ were subjected to standard reaction conditions (110 °C, 20 min, toluene) affording cross-coupling products in 55%, 43%, 42%, and 51% yield respectively (Table 3.1, entries 2, 3, 4, and 6). However, the highest yield of cross-coupling products was obtained from combination of $PdCl_2(MeCN)_2$ and

the Xphos ligand, providing 60% yield (Table 3.1, entry 10). Unfortunately, no desired cross-coupling product was generated when NiCl•Glyme, which has previously been successful for other cross-coupling reactions for α-halo carbonyl compounds,[81,84,89] was employed in standard reaction conditions (Table 3.1, entry 8). $Pd(PPh_3)_4$ also provided the cross-coupling product in 50% yield (Table 3.1, entry 9).

Table 3.2. Ligands of Cross-Coupling Reactions

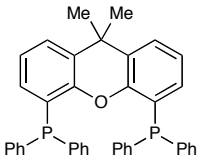
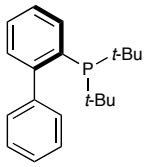
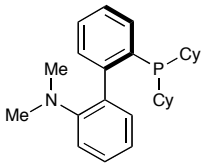
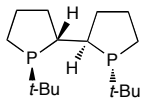
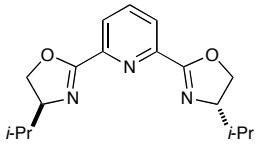
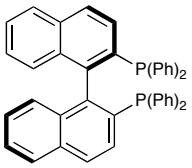
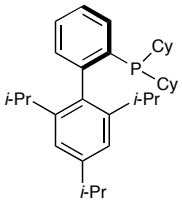
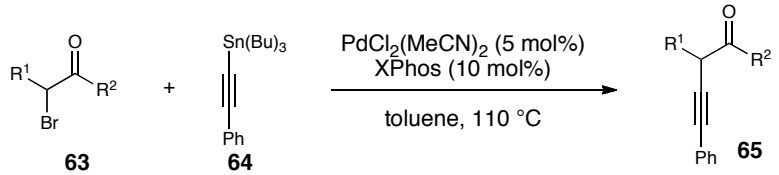
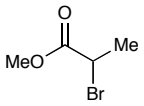
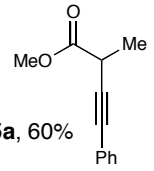
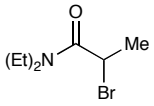
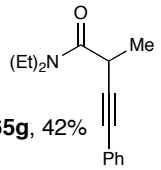
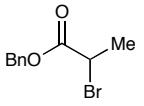
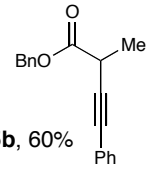
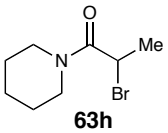
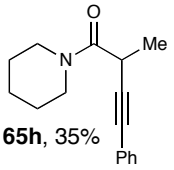
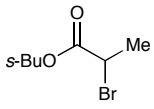
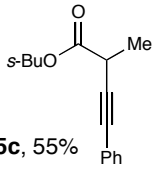
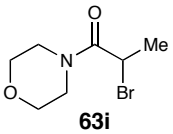
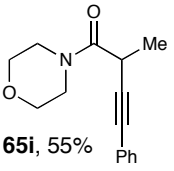
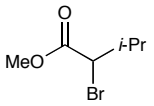
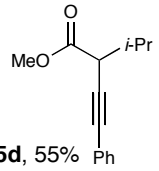
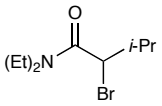
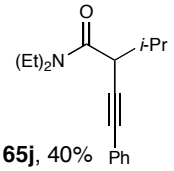
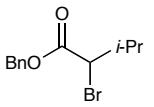
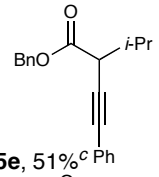
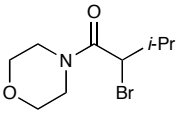
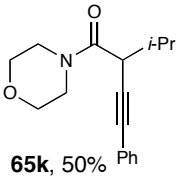
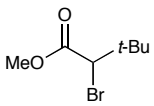
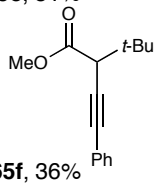
			
Xantphos	JohnPhos	DavePhos	TangPhos
			
PyBox*i*-Pr	BINAP	XPhos	

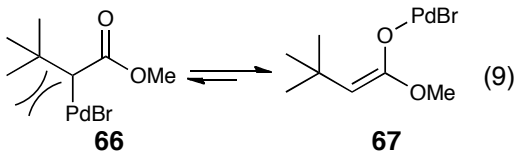
Table 3.3. Scope of the Cross-Coupling Reactions[a]



SM	product[b]	SM	product[b]
 **63a**	 **65a**, 60%	 **63g**	 **65g**, 42%
 **63b**	 **65b**, 60%	 **63h**	 **65h**, 35%
 **63c**	 **65c**, 55%	 **63i**	 **65i**, 55%
 **63d**	 **65d**, 55%	 **63j**	 **65j**, 40%
 **63e**	 **65e**, 51%[c]	 **63k**	 **65k**, 50%
 **63f**	 **65f**, 36%		

[a] Reactions were performed using $PdCl_2(MeCN)_2$ (5 mol %, 0.016 mmol), XPhos (12 mol %, 0.038 mmol), α-bromocarbonyl compound **63** (0.32 mmol, 1 equiv), and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 2 equiv) in toluene (1.0 mL) at 110 °C for 20 min and then quenched with KF solution (1 M, 1.0 mL). [b] Isolated yield after column chromatography. [c] Calculated yield accounting for inseparable impurities (See Experimental Procedure for spectra and details of purity).

With these optimized reaction conditions in hand, we explored the scope of this reaction with various α-bromo esters and amides and the results of the cross-coupling reactions are summarized in Table 3.3. The parent methyl 2-bromopropanoate **63a** and tributyl(phenylethynyl)stannane **64** underwent clean reaction to provide the desired coupling product **65a** in 60% yield after 20 min at 110 °C (Table 3.3). The reactions with α-bromo benzyl ester **63b** and *sec*-butyl ester **63c** also proceed to afford the desired cross-coupling products in 60% and 55% respectively (Table 3.3). To test the effect of the nature of the β-substituents on α-halo carbonyl compounds, the carbonyl compounds with *iso*-propyl **63e** and *tetra*-butyl **63f** groups (Table 3.3) were tested under standard reaction conditions. The bulky β-substituent such as *iso*-propyl and *tetra*-butyl groups on electrophiles decreased the product yields to 5l% (**65e**) and 36% (**65f**) respectively (Table 3.3). A plausible reason for lower product yields with the electrophile **63e** and **63f** could be a result of adverse competition of steric interaction between *carbo*-palladation species **66** and *oxo*-palladation species **67**. For example, in the oxidative addition step, the electrophile **63f** with the bulky *tetra*-butyl substituent does not favor formation of *carbo*-palladation intermediate **66** due to steric interaction between *tetra*-butyl substituent and palladium, but instead prefers to form *oxo*-palladation intermediate **67** (eq 9).



(9)

The α-bromo amides and tributyl(phenylethynyl)stannane **64** also could be transformed to α-alkynyl amide compounds via this intermolecular cross-coupling reaction. Likewise, 2-bromo-*N*,*N*-diethylpropanamide **63g** and tributyl(phenylethynyl)stannane **64** led to cross-coupling product **65g** in 42% yield. It was also observed that electron rich α-bromo amides provide higher yields of coupling product. For example, 2-bromo-1-morpholinopropan-1-one **63i** and 2-bromo-3-methyl-1-morpholinobutan-1-one **63k** with tributyl(phenylethynyl)stannane **64** under standard reaction conditions (110 °C, 20 min, toluene) generated the cross-coupling products **65i** and **65k** in 55% and 50% yield respectively (Table 3.2) (compared to Table 3.2, **65g** (42% yield) **65j** (40% yield)). Treatment of **63k** with tributyl(phenylethynyl)stannane **64** using standard reaction conditions resulted in formation of crystals. We have now confirmed the structure of compound **65k** by single-crystal X-ray analysis (Figure 3.1).

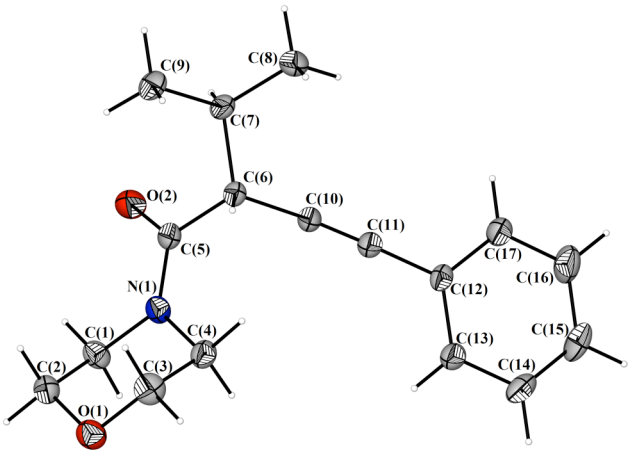
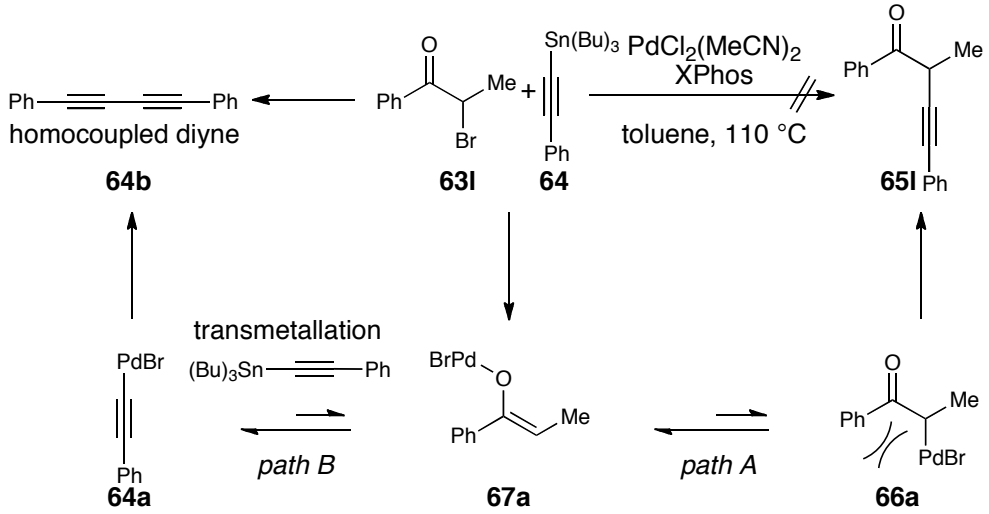


Figure 3.1. Single-Crystal X-ray Structure of Compound **65k**.

During these studies we have demonstrated a successful intermolecular cross-coupling reaction with secondary α-bromo esters and amides with tributyl(phenylethynyl)stannane reagents. In addition, we have explored the limitation of this method using α-bromo aryl ketones as electrophiles and alkynyl metals as nucleophiles for cross-coupling reaction. For example, 2-bromopropiophenone **63l** was treated with tributyl(phenylethynyl)stannane **64** and tris(phenylethynyl)indium under $PdCl_2(MeCN)_2$ catalyst and Xphos ligand but these studies failed to afford the desired cross-coupling products **65l** (path A). It is assumed that the major species from the oxidative addition step could be the *oxo*-palladium intermediate **67a** as opposed to the *carbo*-palladium intermediated **66a** due to both the electron withdrawing phenyl group on the carbonyl group and steric interactions. The intermediate **67a** undergoes transmetallation with **64** to generate **64a** which undergoes a second transmetallation with **64** to form the homocoupled diyne product **64b** in path B (Scheme 3.4).

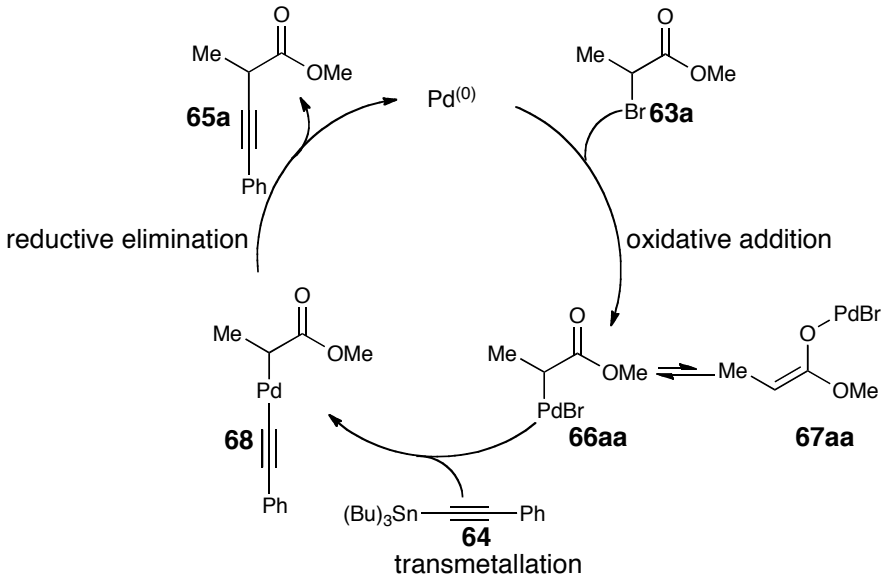
Scheme 3.4. Attempted Cross-Coupling Reaction of 2-Bromopropiophenone **63l**



Additionally, it is noteworthy that when activated α-bromo cyclohexenone was treated with tributyl(phenylethynyl)stannane under standard reaction conditions, no desired product was formed.

Based on the experimental results, a proposed mechanistic cycle for the intermolecular cross-coupling reaction is shown in Scheme 3.5. The electrohphile **63a** undergoes oxidative addition to $Pd^{(0)}$ to form *carbo*-palladium intermediate **66aa** which then undergoes transmetallation with tributyl(phenylethynyl)stannane **64** to form the intermediate **68**. The intermediate **68** is converted to the desired cross-coupling product **65a** after reductive elimination.

Scheme 3.5. Proposed Mechanistic Cycle of Intermolecular Cross-Coupling Reaction



3.4 Conclusion

Cross-coupling reactions employing transition metals and Lewis acids are powerful synthetic tools for the construction of C–C and C–N bonds. Subsequently, a number of cross-coupling reactions between α-bromo ketones and metal nucleophiles such as aryl metals, alkenyl metals, and alkyl metals have been developed yet cross-coupling reactions between α-bromo ketones and alkynyl metals have been reported in a limited study. Our studies toward cross-coupling reactions have focused on generation of secondary α-alkynyl carbonyl compounds. The first approach to secondary α-alkynyl carbonyl compounds was developed under palladium-catalyzed cross-coupling reaction conditions. The secondary α-alkynyl carbonyl compounds was prepared from secondary α-bromo esters and amides with tributyl(phenylethynyl)stannane using $PdCl_2(MeCN)_2$ catalyst and Xphos ligand. This reaction sequence allows rapid access to valuable, secondary α-alkynyl carbonyl derivatives which themselves serve as versatile functional groups.

3.5 Experimental Procedure

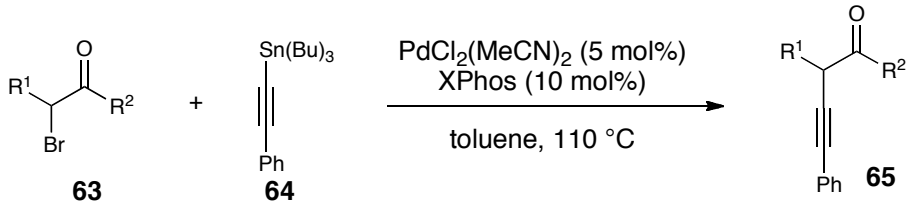
3.5.1 General Information

All reactions were carried out under an argon atmosphere in oven-dried glassware and with magnetic stirring bar. Dry THF was purified by passing through alumina under argon. All commercially obtained reagents were used as received.

Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 1.00 mm glass-backed silica gel 60-F plates. Visualization was performed with UV light or $KMnO_4$ stain solution. Concentration in vacuo refers to the removal of volatile solvent using a rotary evaporator attached to a dry diaphragm pump (10-15 mm Hg) and pumping to a constant weight with an oil pump (<300 mTorr). Heating was accomplished using silicone oil bath. Temperature was controlled by a temperature controller.

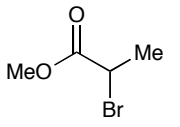
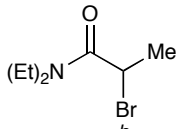
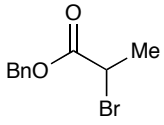
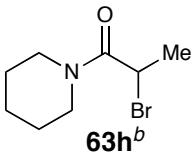
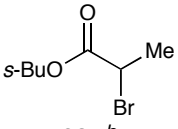
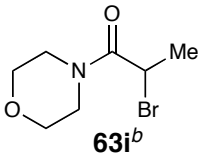
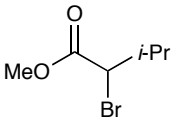
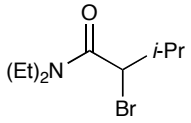
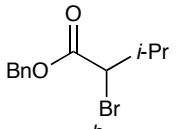
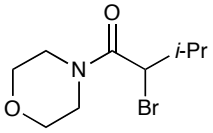
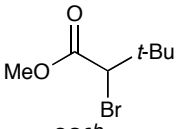
^{1}H NMR spectra were recorded on a Varian Inova 300 (at 300 MHz) or a Varian Mercury 300 (at 300 MHz) NMR and are recorded relative to Me_4Si (δ 0.0 ppm). ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz) and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). Proton-decoupled ^{13}C NMR spectra were recorded on Varian Inova 300 (at 75 MHz) or a Varian Mercury 300 (at 75 MHz) and are reported relative to $CDCl_3$ (δ 77.16 ppm). High-resolution mass spectra (HRMS) were obtained at TAMU. Infrared spectra were recorded on a Bruker Tensor 27 spectrometer as a thin film on NaCl plates.

3.5.2 General Procedure 1 (GP1) of Cross-Coupling Reaction



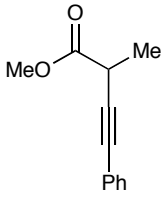
To 2 dram vial was added $PdCl_2(MeCN)_2$ (5 mol %, 0.016 mmol), XPhos (12 mol %, 0.038 mmol), and toluene (1.0 mL), followed by α-bromocarbonyl compound **63** (0.32 mmol, 1 equiv) (Table 3.4) and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 2 equiv). The reaction mixture was heated at 110 °C for 20 min. The reaction mixture was cooled down to rt and was quenched with KF solution (1M, 1.0 mL). The reaction mixture was passed through a Celite® plug, the layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was accomplished by flash column chromatography to afford alkynyl carbonyl compound **65**.

Table 3.4. Reference of Known Compounds **63**

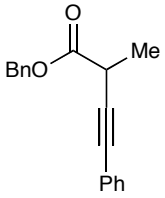
 **63a**[a]	 **63g**[b]
 **63b**[b]	 **63h**[b]
 **63c**[b]	 **63i**[b]
 **63d**[b]	 **63j**[a]
 **63e**[b]	 **63k**[a]
 **63f**[b]	

[a] commercially available compounds: **63a**, **63j**, **63k**

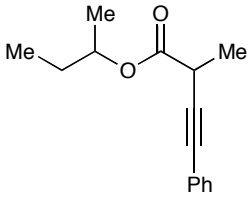
[b] known compounds: **63b**,[90] **63c**,[91] **63d**,[92] **63e**,[93] **63f**,[91] **63g**,[94] **63h**,[95] **63i**[96]



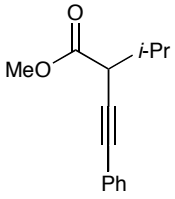
Methyl 2-methyl-4-phenylbut-3-ynoate (65a). α-Bromocarbonyl compound **63aa** (0.32 mmol, 54 mg, 1.0 equiv) and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 250 mg, 2.0 equiv) were subjected to the reaction conditions described in GP1 to afford pale yellow oil **65a** (36 mg, 60% yield). R_f = 0.3 (hexanes:Et_2O=20:1); IR (film, cm^{-1}): 1744, 1199, 758; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.42 (m, 2H), 7.31-7.29 (m, 3H), 3.78 (s, 3H), 3.65 (q, *J* = 7.1 Hz, 1H), 1.54 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 131.7 (2), 128.4 (3), 122.9, 86.9, 82.6, 52.6, 32.7, 18.1; HRMS (ESI) calcd for $C_{12}H_{12}O_2$ $[M+H]^+$: 189.0916; found: 189.0918.



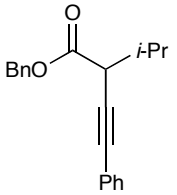
Benzyl 2-methyl-4-phenylbut-3-ynoate (65b). α-Bromocarbonyl compound **63b** (0.32 mmol, 78 mg, 1.0 equiv) and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 250 mg, 2.0 equiv) were subjected to the reaction conditions described in GP1 to afford pale yellow oil **65b** (51 mg, 60% yield). R_f = 0.26 (hexanes:Et_2O=20:1); IR (film, cm^{-1}): 1744, 1489, 1175, 758, 693; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47-7.29 (m, 10H), 5.26 (s, 2H), 3.73 (q, *J* = 7.4 Hz, 1H), 1.60 (d, *J* = 7.0, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 135.7, 131.7 (2), 128.6 (2), 128.4 (2), 128.3 (2), 128.2, 128.0, 123.0, 86.9, 82.8, 67.0, 33.0, 18.0; HRMS (ESI) calcd for $C_{18}H_{16}O_2$ $[M+H]^+$: 265.1229; found: 265.1222.



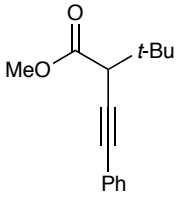
***Sec*-butyl 2-methyl-4-phenylbut-3-ynoate (65c).** α-Bromocarbonyl compound **63c** (0.32 mmol, 67 mg, 1.0 equiv) and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 250 mg, 2.0 equiv) were subjected to the reaction conditions described in GP1 to afford pale yellow oil **3c** (41 mg, 56% yield). R_f = 0.4 (hexanes:Et_2O=20:1); IR (film, cm^{-1}): 1735, 1190, 864, 755, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47-7.43 (m, 2H), 7.34-7.29 (m, 3H), 5.00-4.89 (m, 1H), 3.69 (q, *J* = 7.3 Hz, 1H), 1.72-1.69 (m, 2H), 1.57-1.53 (m, 3H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.01-0.94 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of diastereoisomer) δ 171.1, 171.0, 131.7, 128.2, 128.0, 123.1, 87.4, 87.3, 82.5, 82.4, 73.4, 33.3, 33.1, 28.8, 28.7, 19.4, 19.3, 18.2, 17.9, 9.7, 9.6; HRMS (ESI) calcd for $C_{15}H_{18}O$ $[M+H]^+$: 231.1385; found: 231.1389.



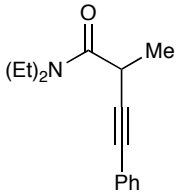
Methyl 2-isopropyl-4-phenylbut-3-ynoate (65d). α-Bromocarbonyl compound **63d** (0.32 mmol, 62 mg, 1.0 equiv) and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 250 mg, 2.0 equiv) were subjected to the reaction conditions described in GP1 to afford pale yellow oil **65d** (38 mg, 55% yield). R_f = 0.3 (hexanes:Et_2O=20:1); IR (film, cm^{-1}): 1744, 1492, 1018, 752, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47-7.41 (m, 2H), 7.31-7.25 (m, 3H), 3.76 (s, 3H), 3.41(d, *J* = 6.5 Hz, 1H), 2.33-2.26 (m, 1H), 1.09 (dd, *J* = 5.3, 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 131.7 (2), 128.1 (3), 123.1, 84.5 (2), 52.3, 46.0, 31.2, 20.8, 19.2; HRMS (ESI) calcd for $C_{14}H_{16}O_2$ $[M+H]^+$: 217.1229; found: 217.1234.



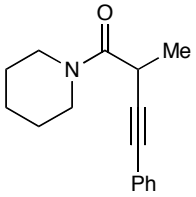
Benzyl 2-isopropyl-4-phenylbut-3-ynoate (65e). α-Bromocarbonyl compound **63e** (0.32 mmol, 87 mg, 1.0 equiv) and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 250 mg, 2.0 equiv) were subjected to the reaction conditions described in GP1 to afford pale yellow oil **65e** (56 mg, 60%, 85% pure by ^{1}H and ^{13}C NMR). R_f = 0.23 (hexanes:Et_2O=20:1); IR (film, cm^{-1}): 1741, 1486, 1166, 755, 693; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.29 (m, 10H), 5.14 (s, 2H), 3.48 (d, *J* = 6.3 Hz, 2H), 2.40-2.30 (m, 1H), 1.11 (t, *J* =6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 135.7, 131.7 (2), 128.5, 128.2, 128.2, 128.1, 128.0 (3), 123.2, 84.7, 84.6 (2), 66.9, 46.2, 31.3, 20.9, 19.2; HRMS (ESI) calcd for $C_{20}H_{20}O_2$ $[M+H]^+$: 293.1542; found: 293.1535.



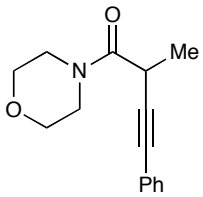
Methyl 2-(*tert*-butyl)-4-phenylbut-3-ynoate (65f). α-Bromocarbonyl compound **63f** (0.32 mmol, 67 mg, 1.0 equiv) and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 250 mg, 2.0 equiv) were subjected to the reaction conditions described in GP1 to afford pale yellow oil **65f** (26 mg, 36% yield). R_f = 0.32 (hexanes:Et_2O=20:1); IR (film, cm^{-1}): 1735, 1146, 755, 687; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.42 (m, 2H), 7.30-7.28 (m, 3H), 3.75 (s, 3H), 3.37 (s, 1H), 1.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 131.7 (2), 128.1 (3), 123.2, 85.2, 84.4, 52.0, 50.1, 35.0, 27.7 (3); EI MS *m/z* calcd for $C_{15}H_{18}O_2$: 230.0; found: 230.0.



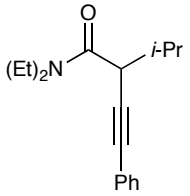
***N,N*-Diethyl-2-methyl-4-phenylbut-3-ynamide (65g).** α-Bromocarbonyl compound **63g** (0.32 mmol, 67 mg, 1.0 equiv) and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 250 mg, 2.0 equiv) were subjected to the reaction conditions described in GP1 to afford pale yellow oil **65g** (31 mg, 42% yield). R_f = 0.22 (hexanes:EtOAc=4:1); IR (film, cm^{-1}): 1646, 1024, 758, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.40 (m, 2H), 7.32-7.29 (m, 3H), 3.72 (q, *J* = 6.0 Hz, 1H), 3.67-3.38 (m, 4H), 1.52 (d, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 6.6 Hz, 3H), 1.17 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 131.8 (2), 128.3 (2), 128.1, 123.5, 88.5, 82.5, 42.1, 40.6, 30.3, 17.9, 14.4, 12.9; HRMS (ESI) calcd for $C_{15}H_{19}NO$ $[M+H]^+$: 230.1545; found: 230.1551.



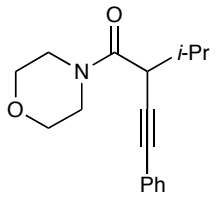
2-Methyl-4-phenyl-1-(piperidin-1-yl)but-3-yn-1-one (65h). α-Bromocarbonyl compound **63h** (0.32 mmol, 70 mg, 1.0 equiv) and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 250 mg, 2.0 equiv) were subjected to the reaction conditions described in GP1 to afford pale yellow oil **65h** (27 mg, 35% yield). R_f = 0.23 (hexanes:EtOAc=4:1); IR (film, cm^{-1}): 1652, 1436, 1003, 758, 687; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.40 (m, 2H), 7.32-7.30 (m, 3H), 3.81-3.73 (m, 2H), 3.71 (q, *J* = 6.7, 1H), 3.55-3.31 (m, 2H) 1.73-1.56 (m, 6H), 1.52 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 131.8 (2), 128.5 (2), 128.1, 123.4, 88.3, 82.9, 47.2, 43.7, 30.5, 26.3, 25.8, 25.2, 17.8; EI MS *m/z* calcd for $C_{16}H_{19}NO$: 241.0; found: 241.0.



2-Methyl-1-morpholino-4-phenylbut-3-yn-1-one (65i). α-Bromocarbonyl compound **63i** (0.32 mmol, 71 mg, 1.0 equiv) and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 250 mg, 2.0 equiv) were subjected to the reaction conditions described in GP1 to afford pale yellow oil **65i** (43 mg, 55% yield). R_f = 0.4 (hexanes:EtOAc=1:1); IR (film, cm^{-1}): 1649, 1027, 758, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.39 (m, 2H), 7.33-7.31 (m, 3H), 3.89-3.50 (m, 8H), 3.67 (q, *J* = 6.9, 1H), 1.53 (d, *J* = 7.6, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 131.8 (2), 128.4 (3), 122.9, 87.6, 83.3, 66.9, 66.6, 46.6, 42.8, 30.3, 17.3; HRMS (ESI) calcd for $C_{15}H_{17}NO_2$ $[M+H]^+$: 244.1338; found: 244.1332.



***N,N*-Diethyl-2-isopropyl-4-phenylbut-3-ynamide (65j).** α-Bromocarbonyl compound **63j** (0.32 mmol, 76 mg, 1.0 equiv) and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 250 mg, 2.0 equiv) were subjected to the reaction conditions described in GP1 to afford pale yellow oil **65j** (33 mg, 40% yield). R_f = 0.32 (hexanes:EtOAc=4:1); IR (film, cm^{-1}): 1652, 1030, 755, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.42 (m, 2H), 7.32-7.30 (m, 3H), 3.65-3.39 (m, 4H), 3.31 (d, *J* = 9.0 Hz, 1H), 2.43-2.33 (m, 1H), 1.29 (t, *J* = 7.3 Hz, 3H), 1.18 (t, *J* = 7.3 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 131.8 (2), 128.2 (2), 128.0, 123.5, 87.0, 83.7, 43.8, 42.3, 40.8, 31.0, 21.3, 20.6, 14.8, 13.0; HRMS (ESI) calcd for $C_{17}H_{23}NO$: 258.1858; found: 258.1863.



2-Isopropyl-1-morpholino-4-phenylbut-3-yn-1-one (65k). α-Bromocarbonyl compound **63k** (0.32 mmol, 80 mg, 1.0 equiv) and tributyl(phenylethynyl)stannane **64** (0.64 mmol, 250 mg, 2.0 equiv) were subjected to the reaction conditions described in GP1 to afford pale yellow solid **65k** (43 mg, 50% yield). R_f = 0.5 (hexanes:EtOAc=1:1); IR (film, cm^{-1}): 1649, 1430, 971, 758, 690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.37 (m, 2H), 7.31-7.26 (m, 3H), 3.85-3.50 (m, 8H), 3.31 (d, *J* = 8.2 Hz, 1H), 2.37-2.25 (m, 1H), 1.19 (d, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 131.7 (2), 128.4 (3), 123.1, 86.0, 85.0, 67.2, 66.9, 47.2, 44.2, 43.0, 30.6, 21.7, 20.6; HRMS (ESI) calcd for $C_{17}H_{21}NO_2$ $[M+H]^+$: 272.1651; found: 272.1656.

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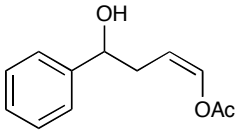
APPENDIX I

SELECTED SPECTRAL DATA

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



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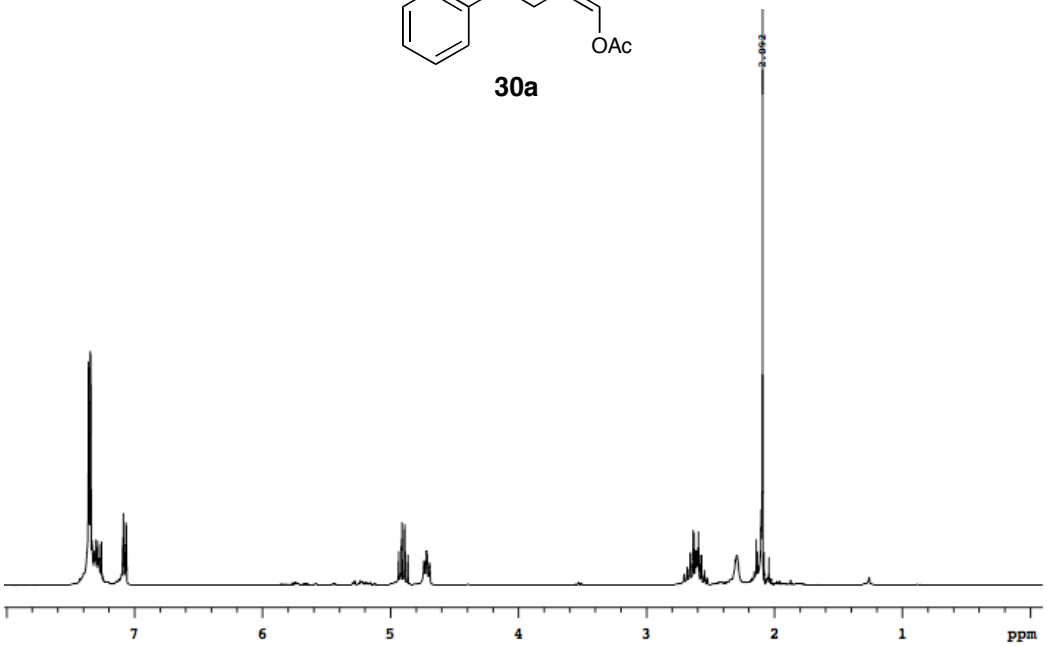
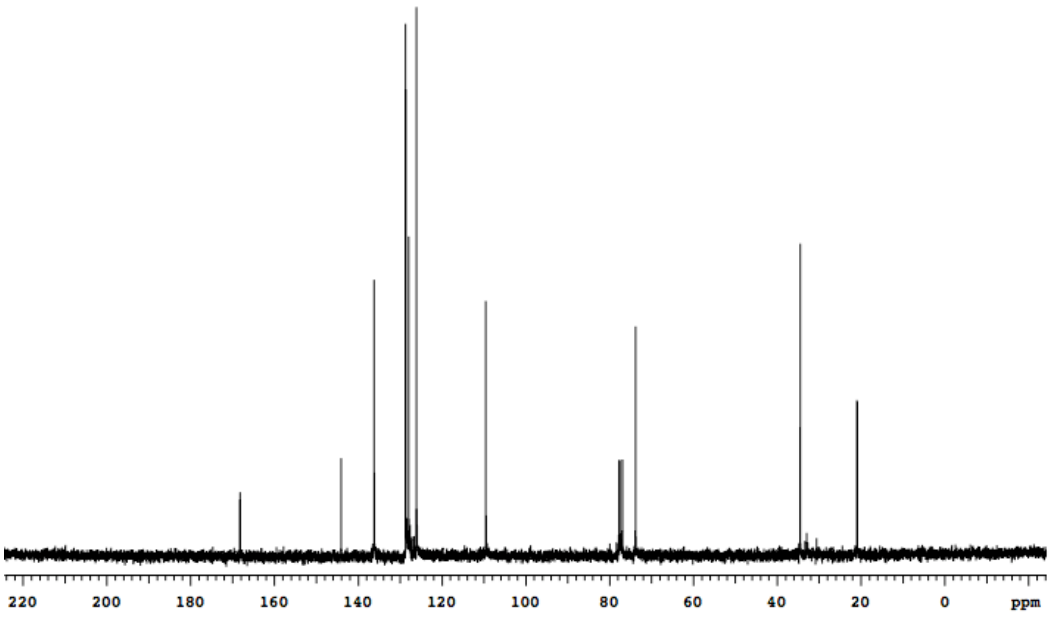


^{13}C NMR (75 MHz) in $CDCl_3$



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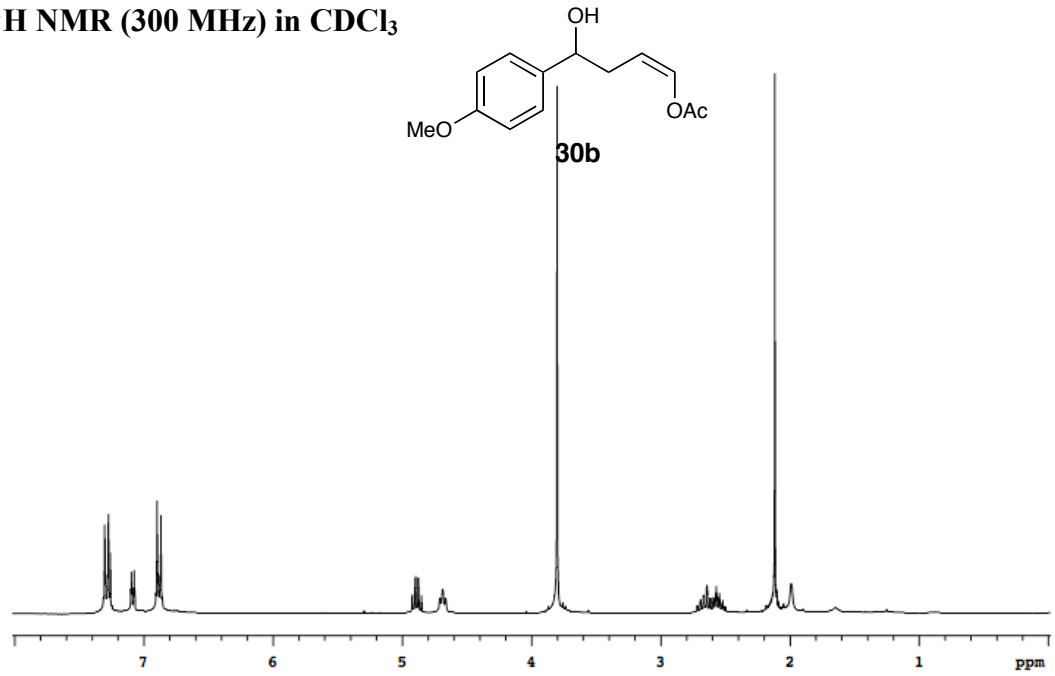

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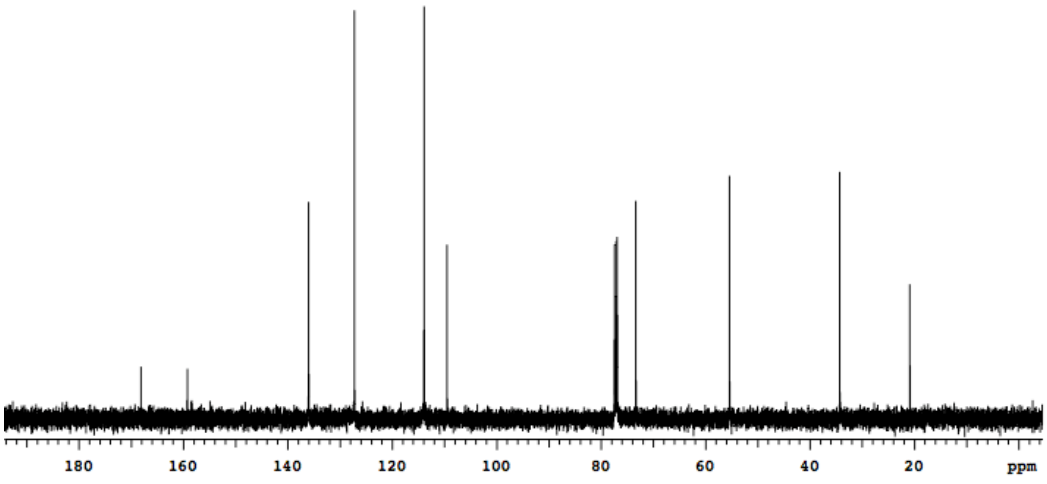

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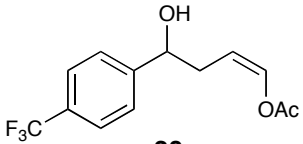

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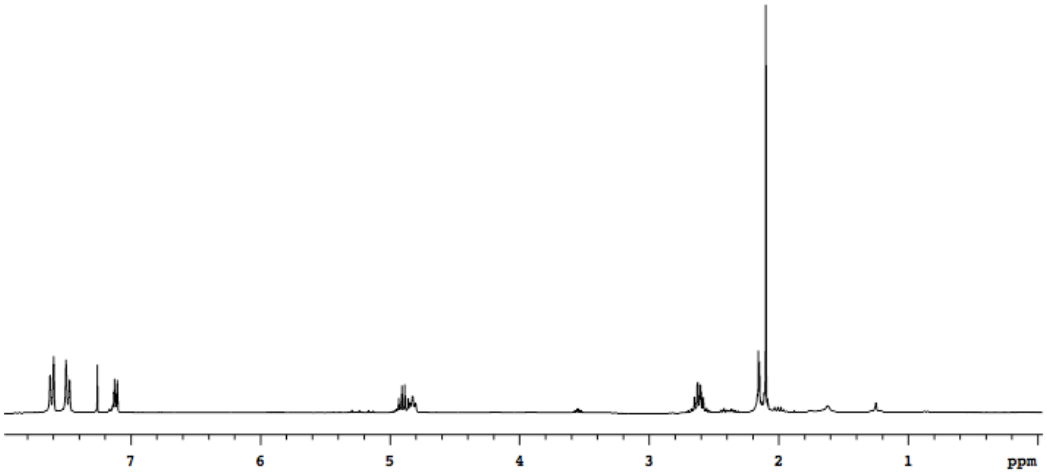
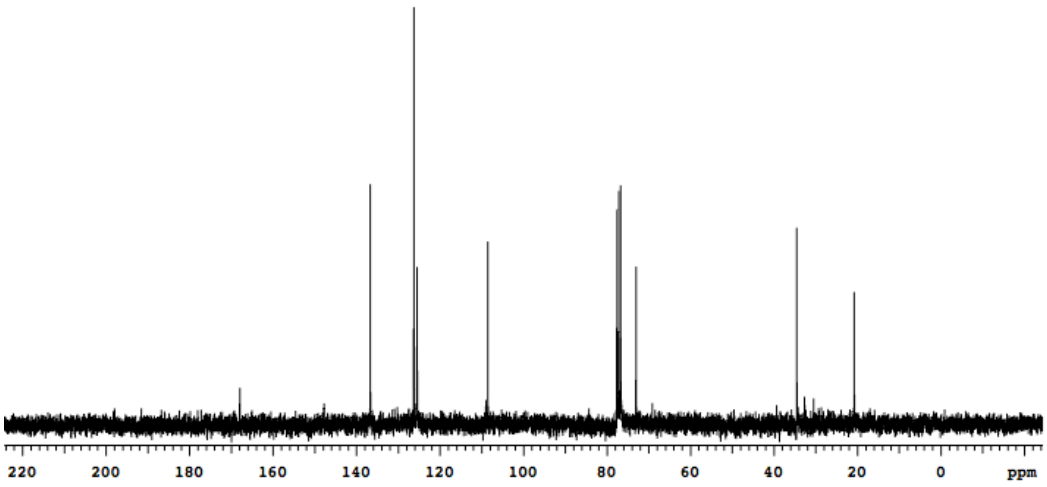


^{13}C NMR (75 MHz) in $CDCl_3$



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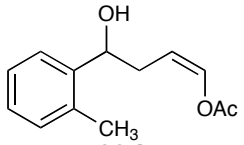

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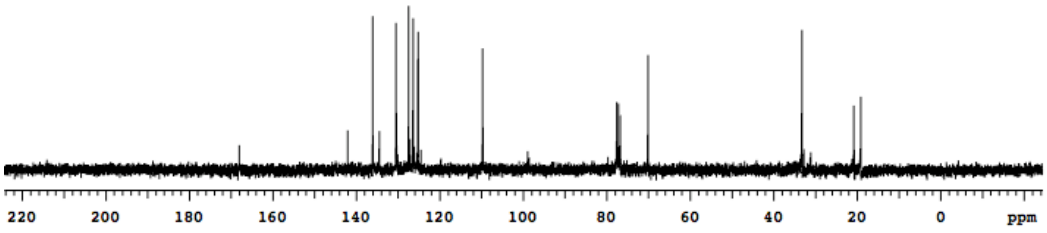

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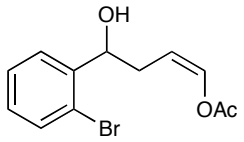

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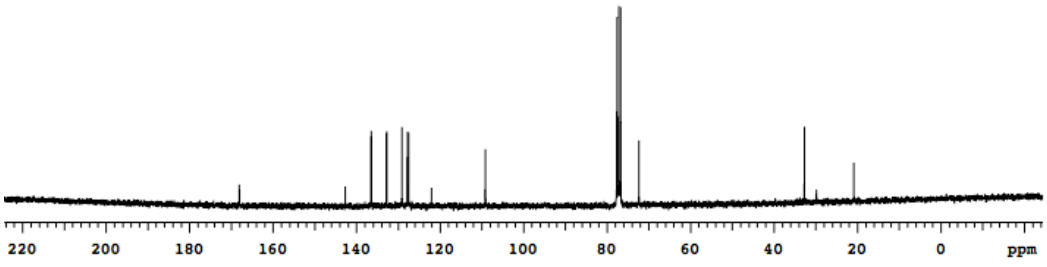

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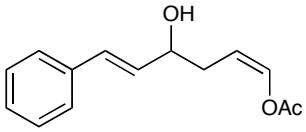

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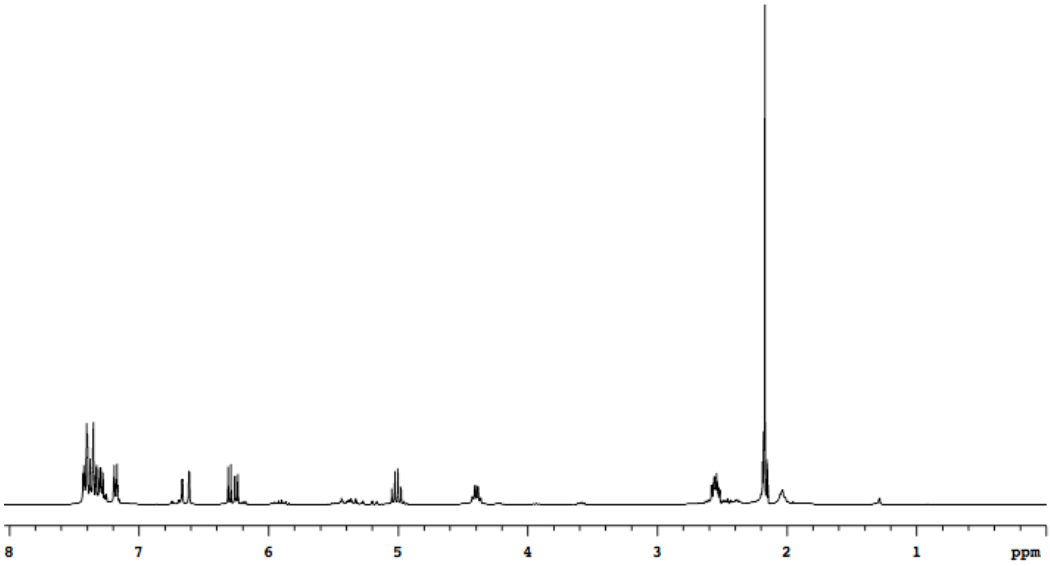

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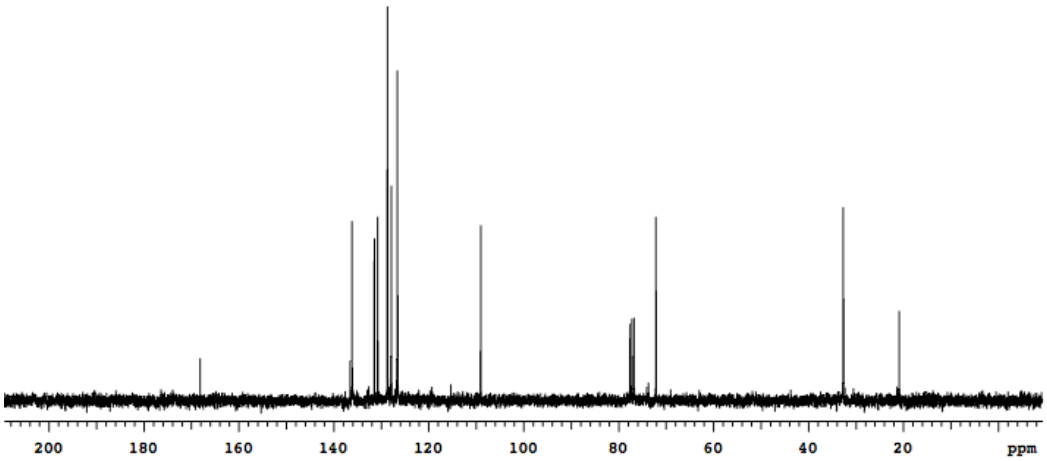

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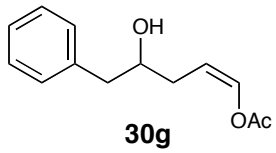

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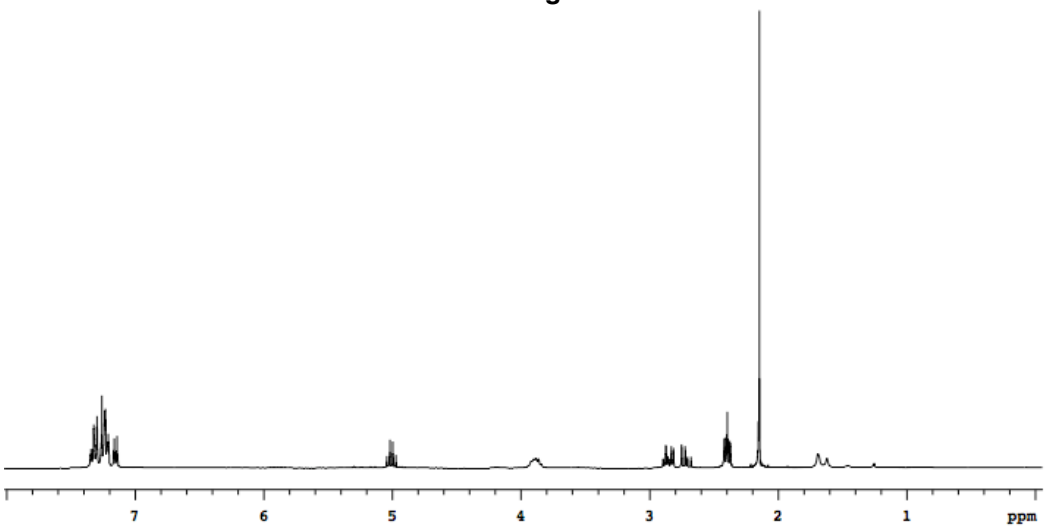

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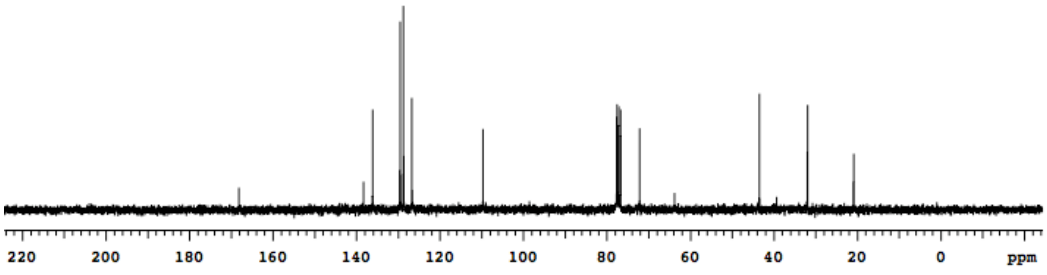

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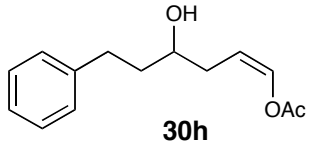

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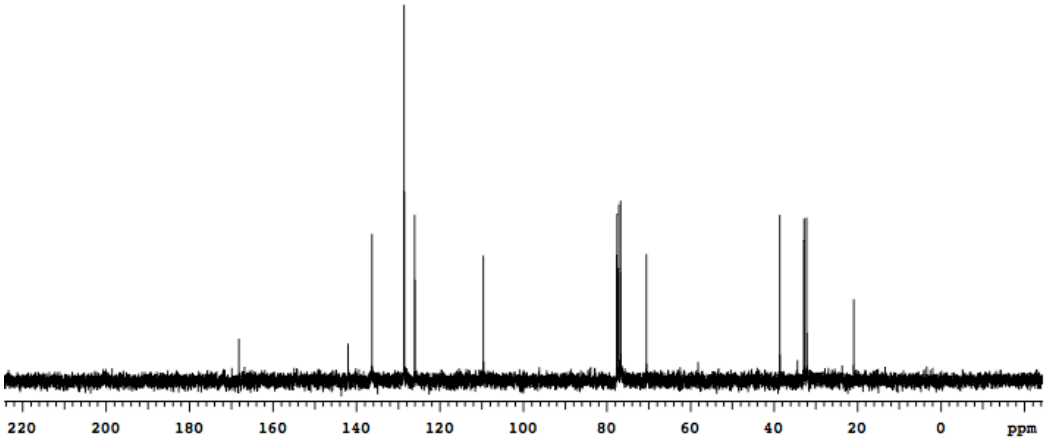

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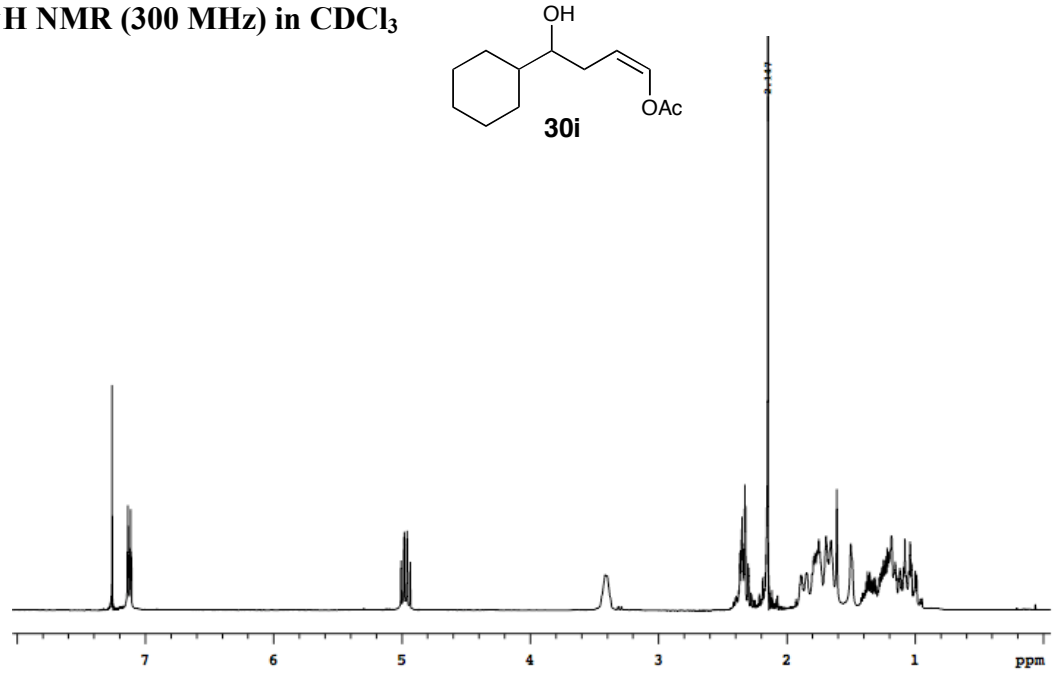

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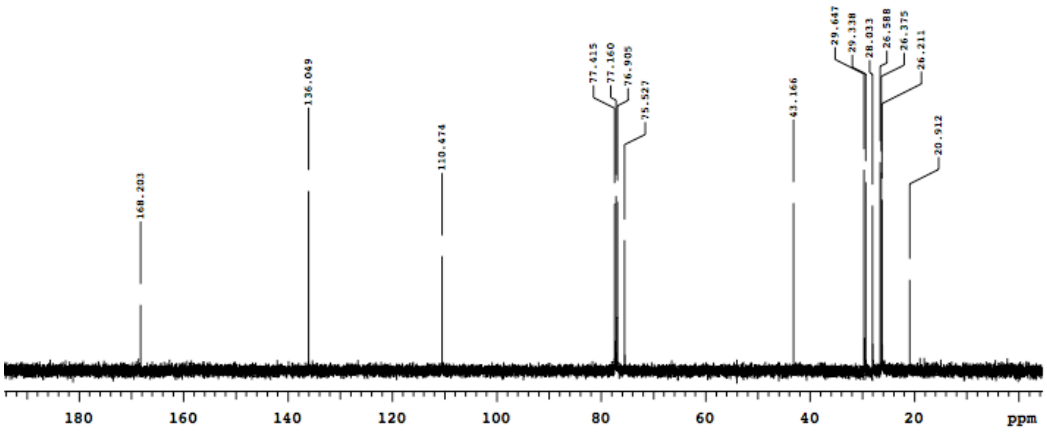

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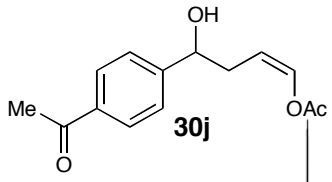

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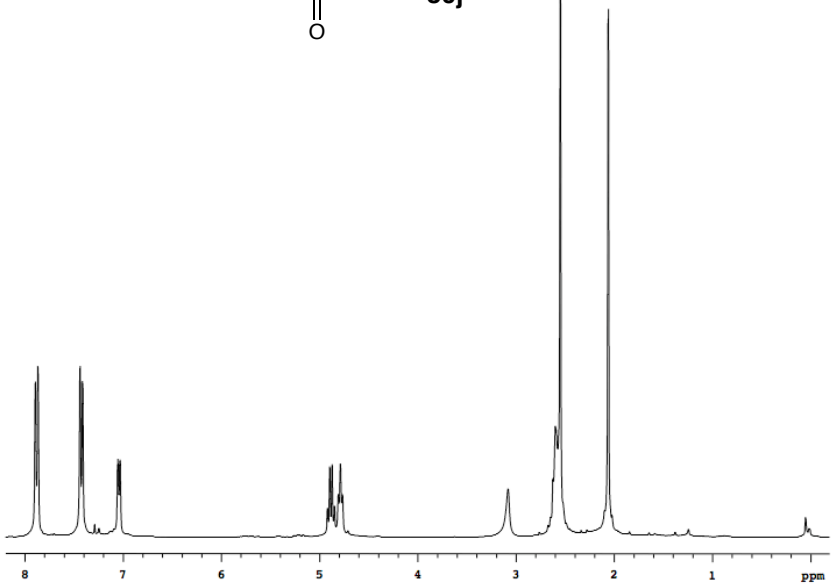

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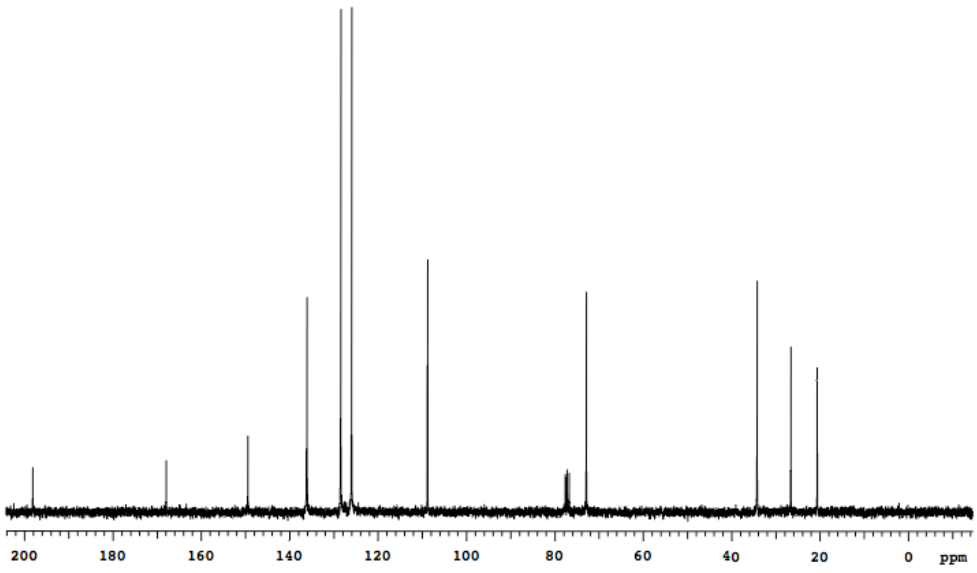

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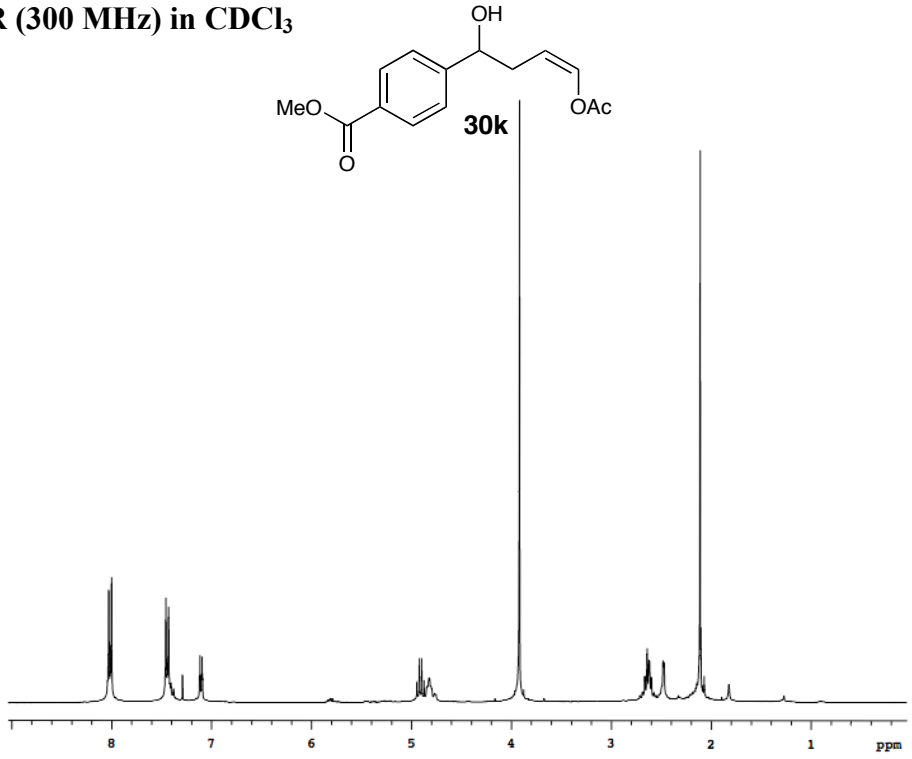

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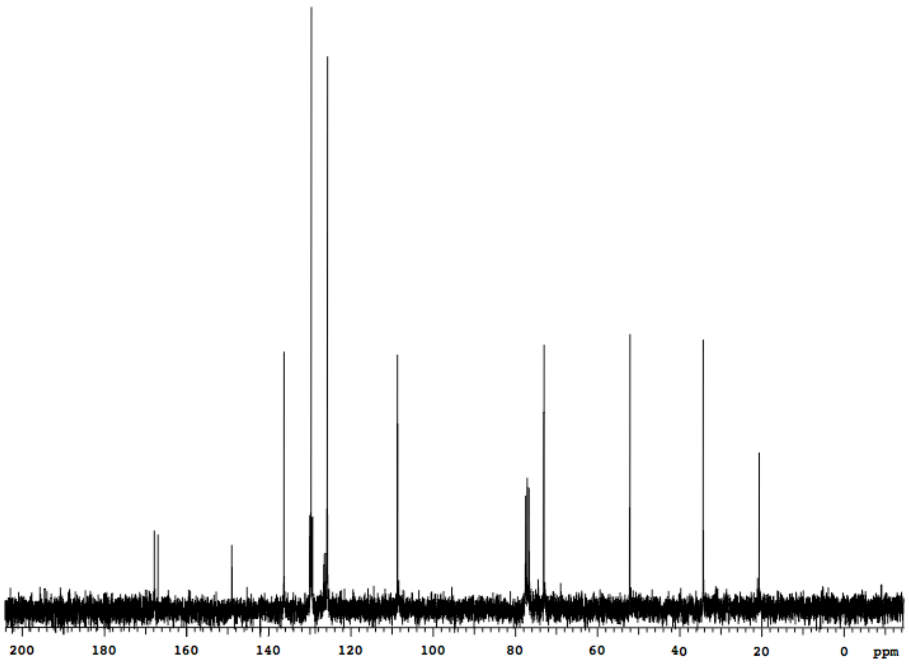

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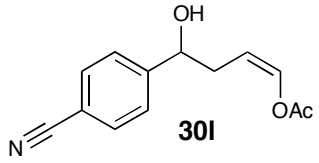

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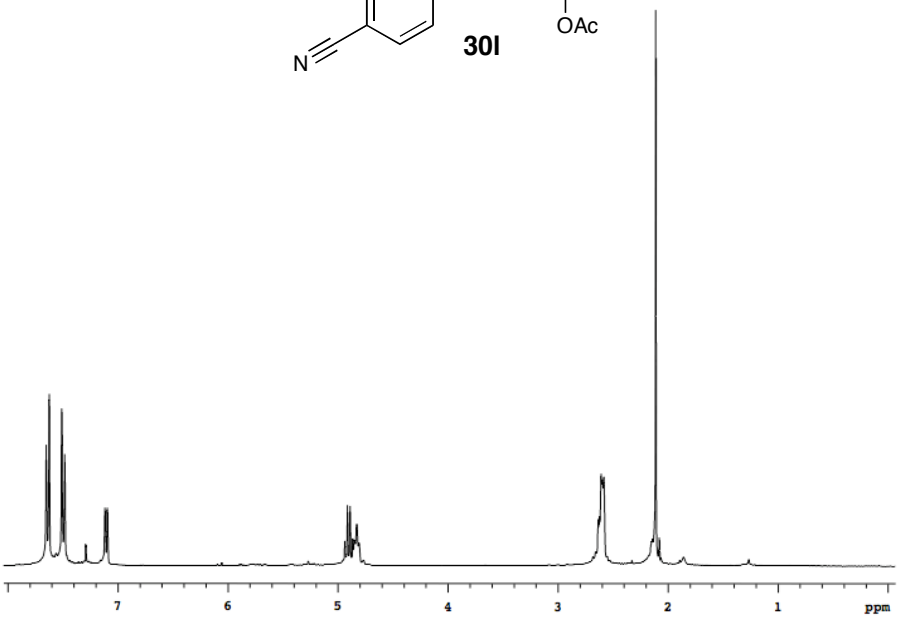

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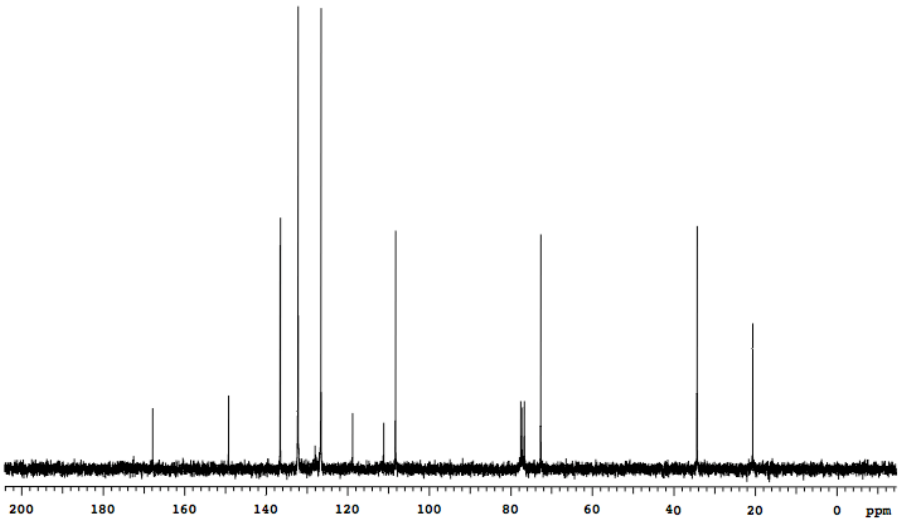

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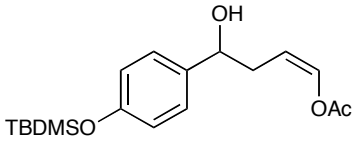

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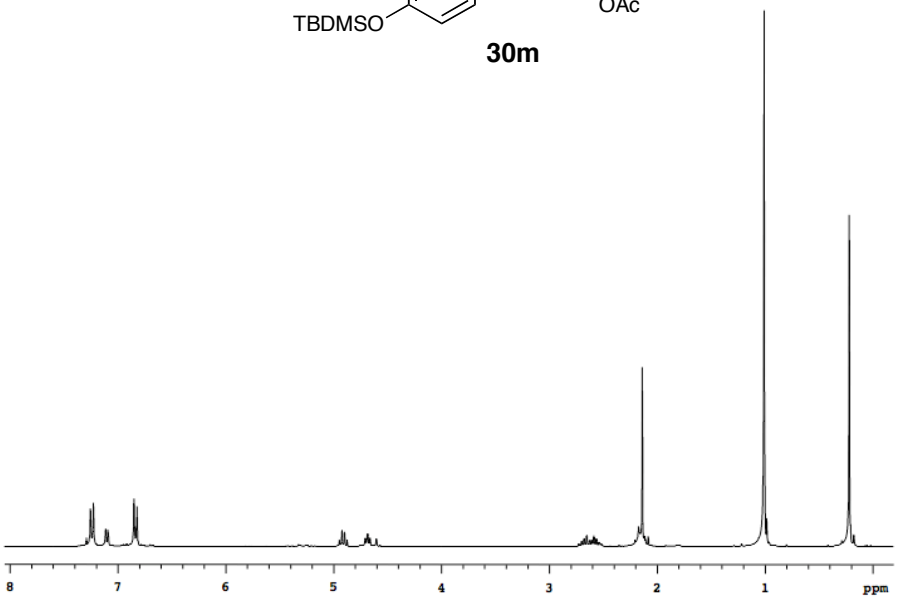

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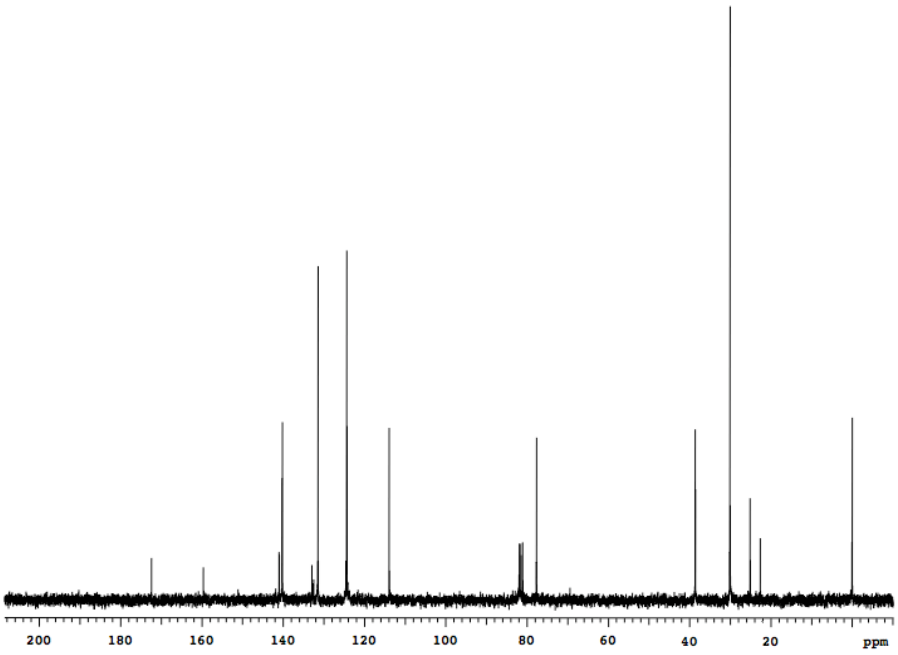

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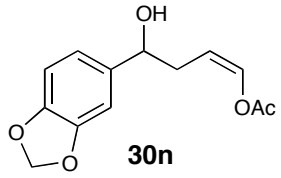

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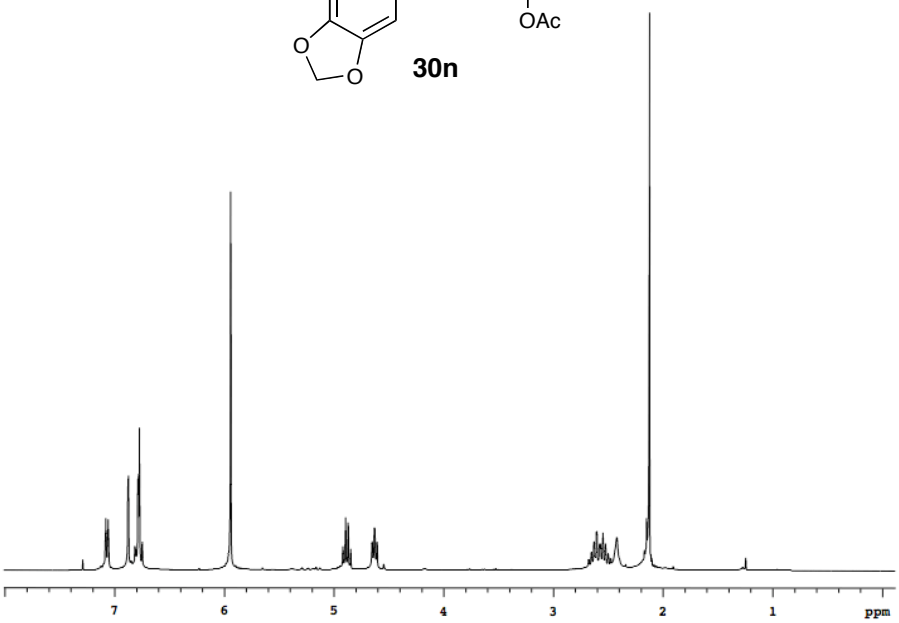

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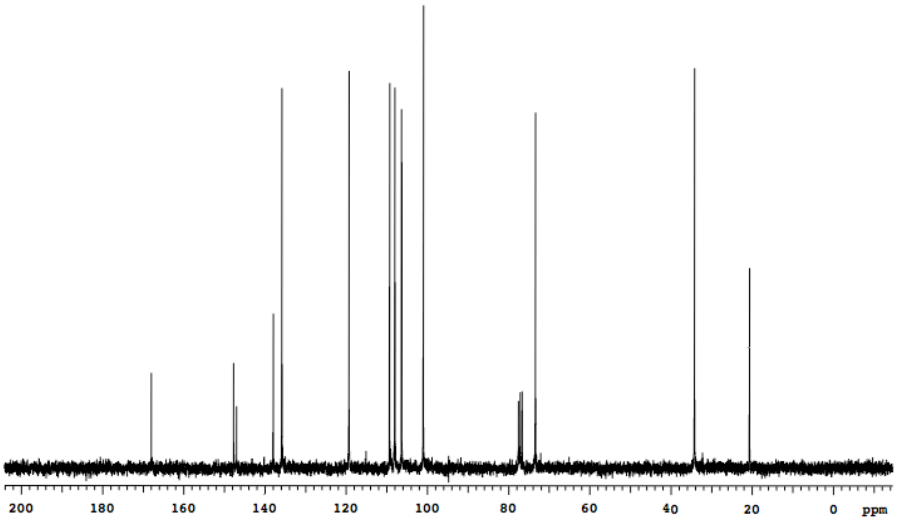

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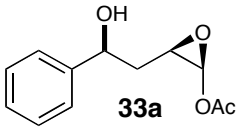

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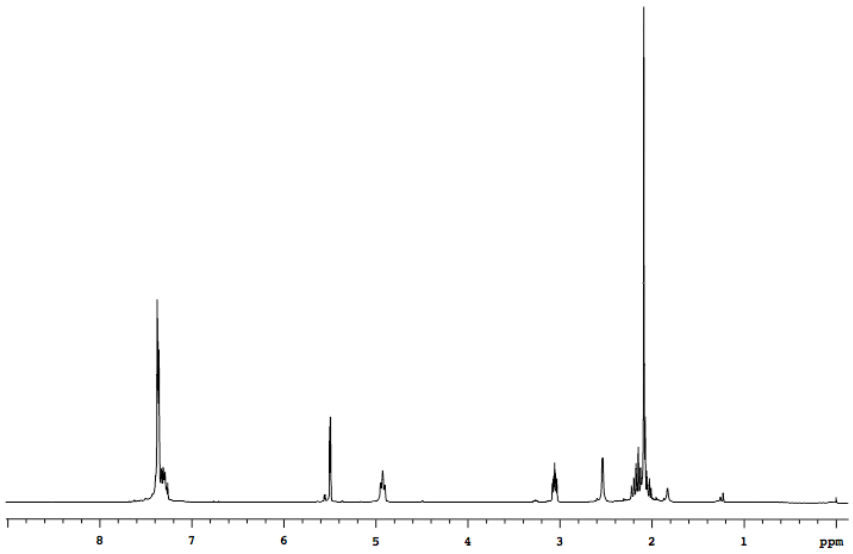

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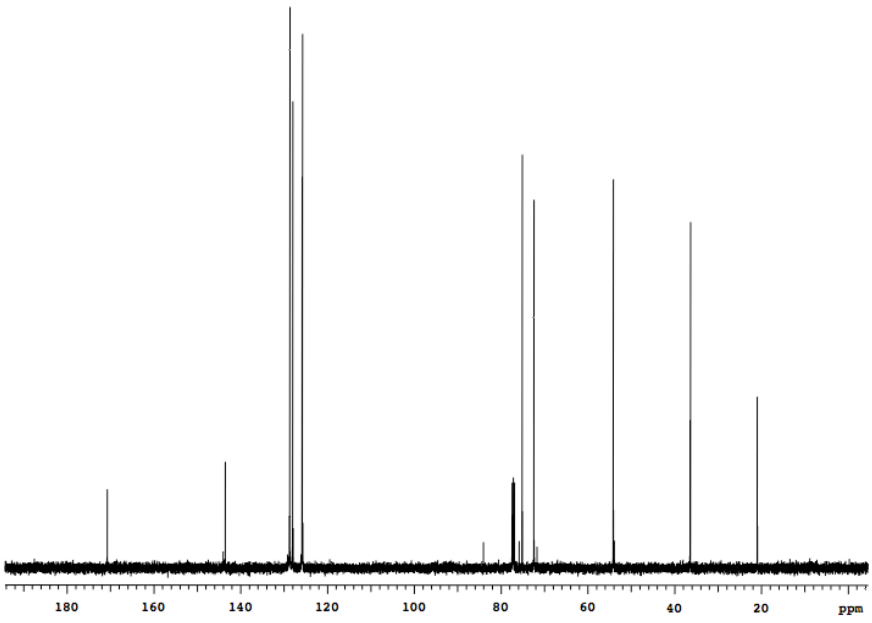

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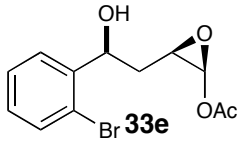

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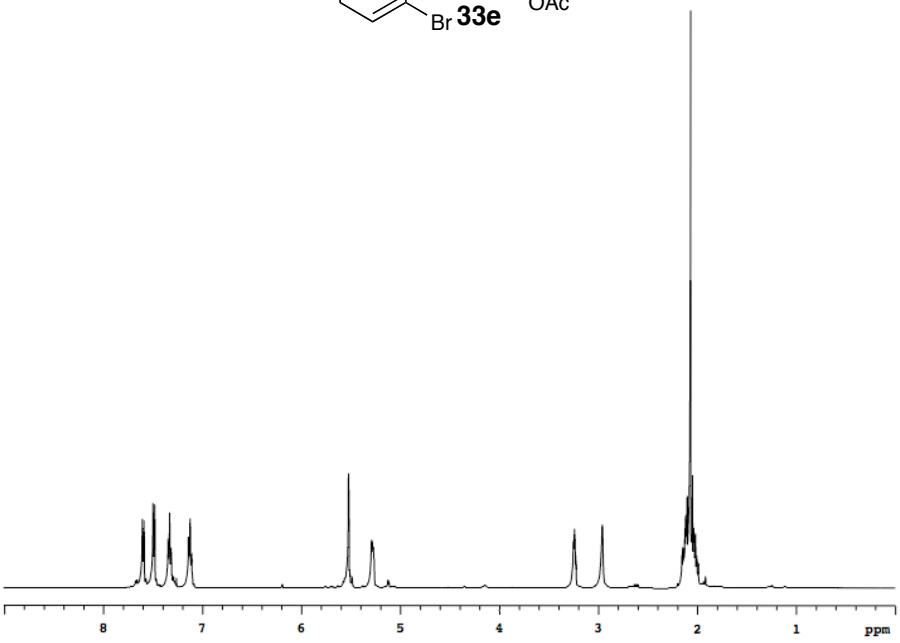
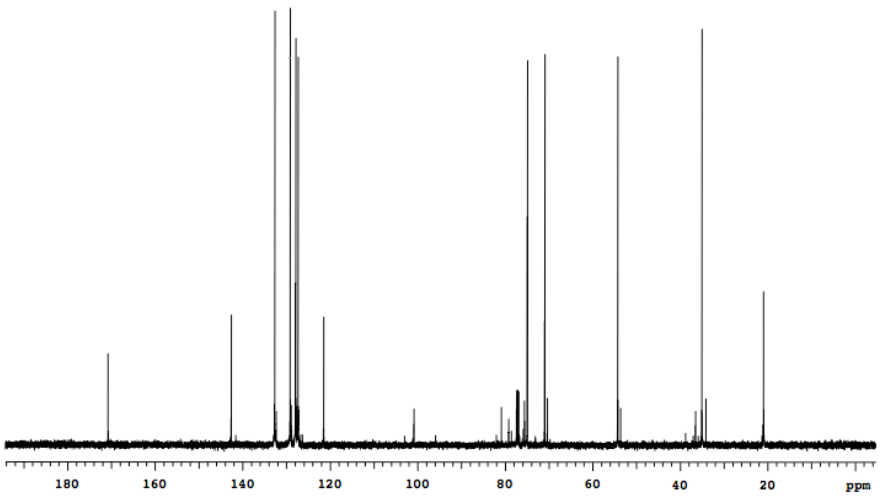


^{13}C NMR (75 MHz) in $CDCl_3$



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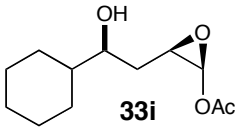

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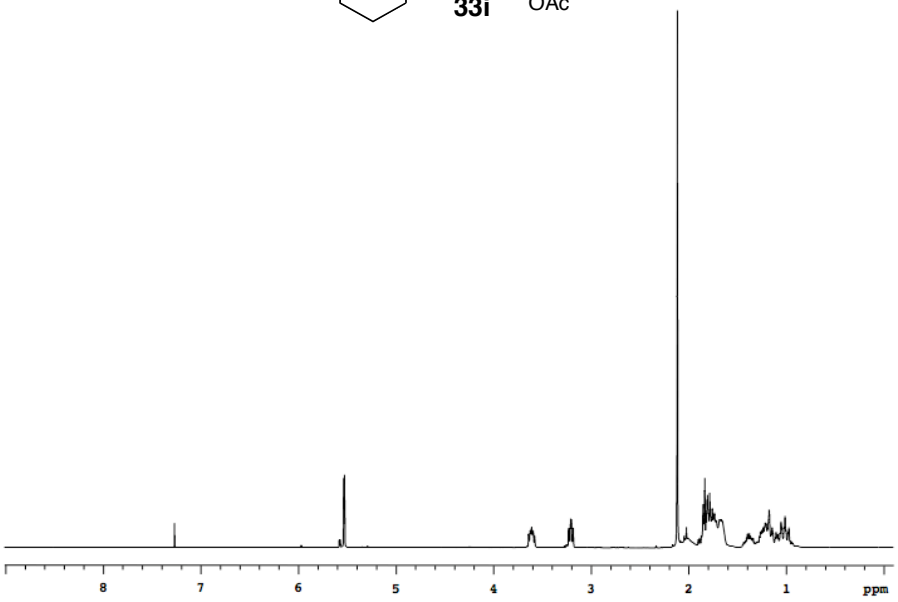

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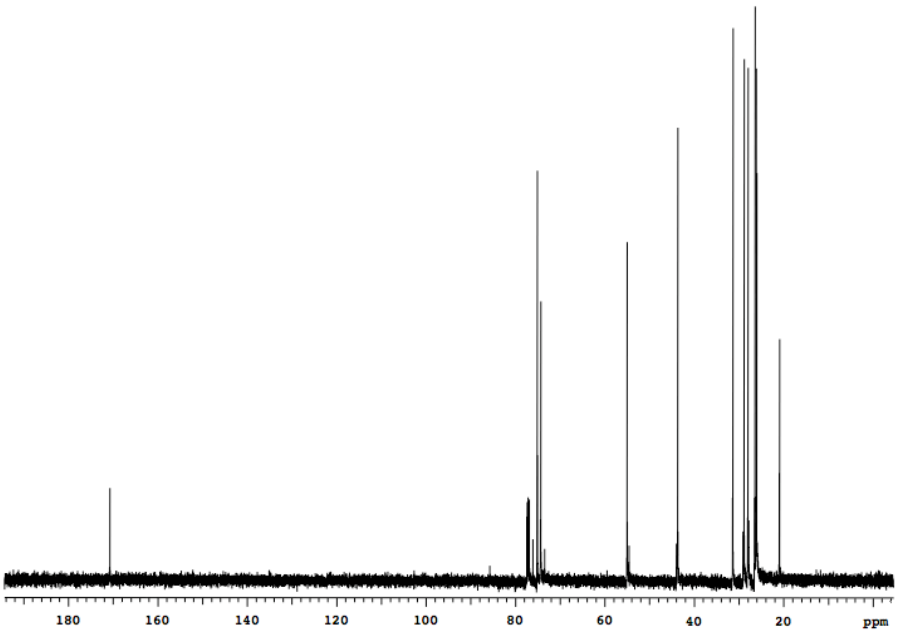

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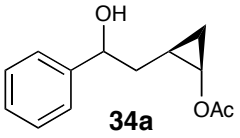

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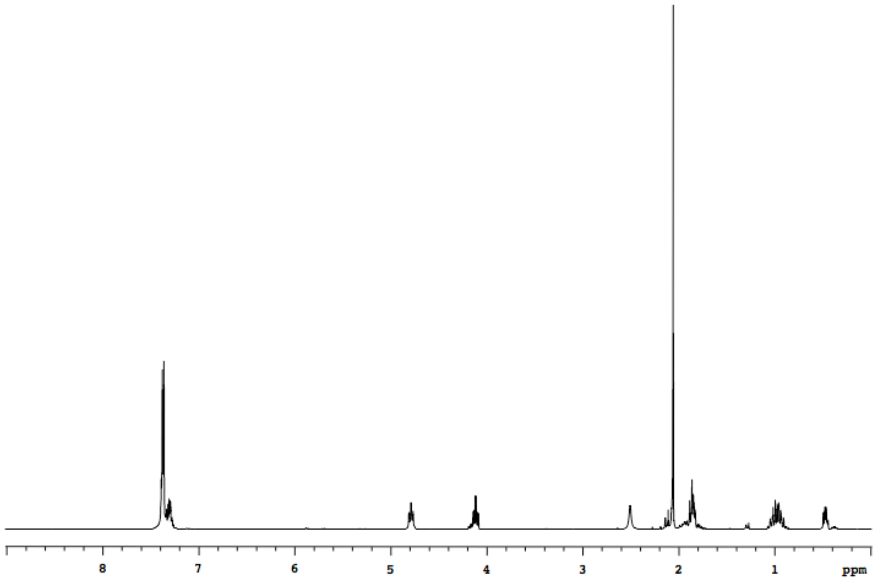

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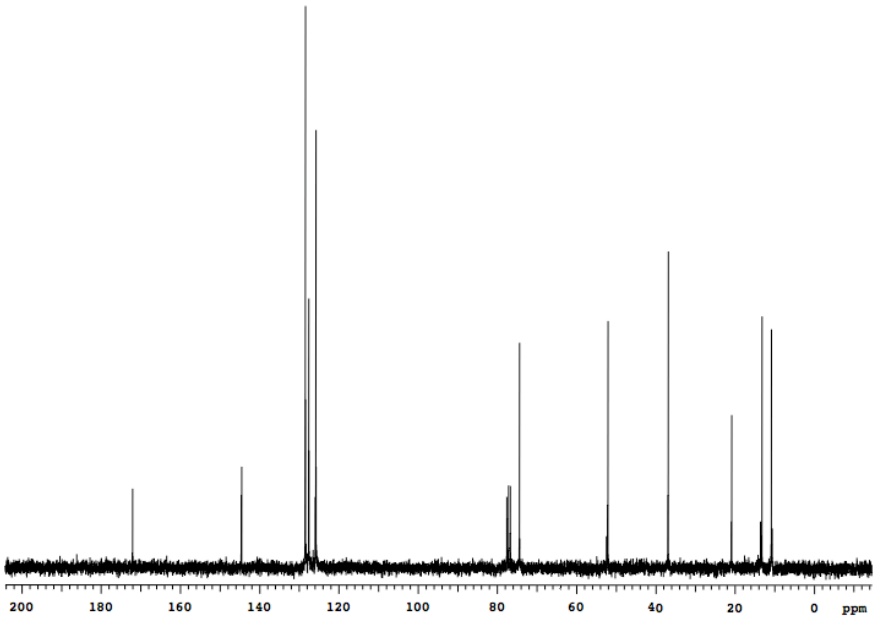

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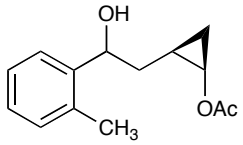

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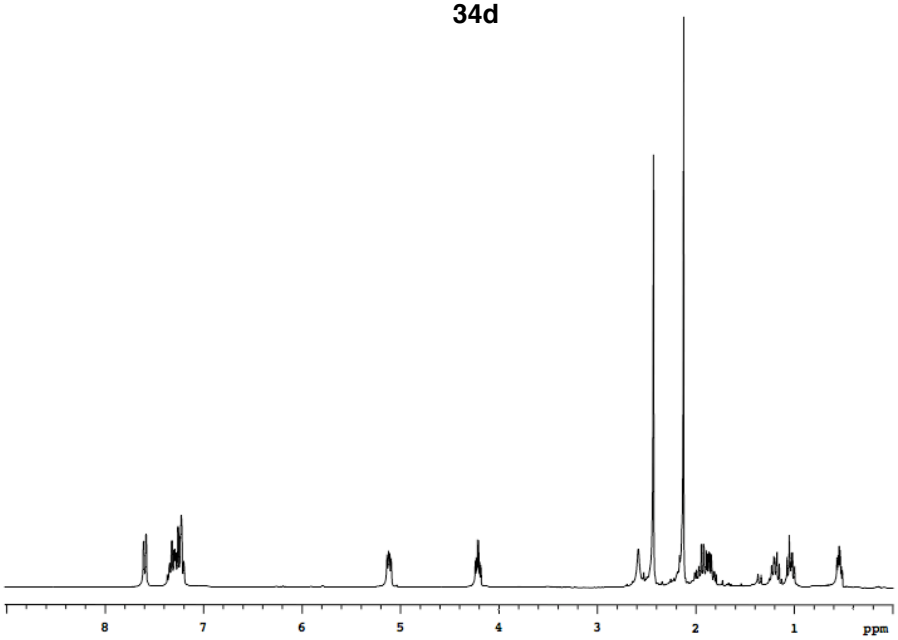
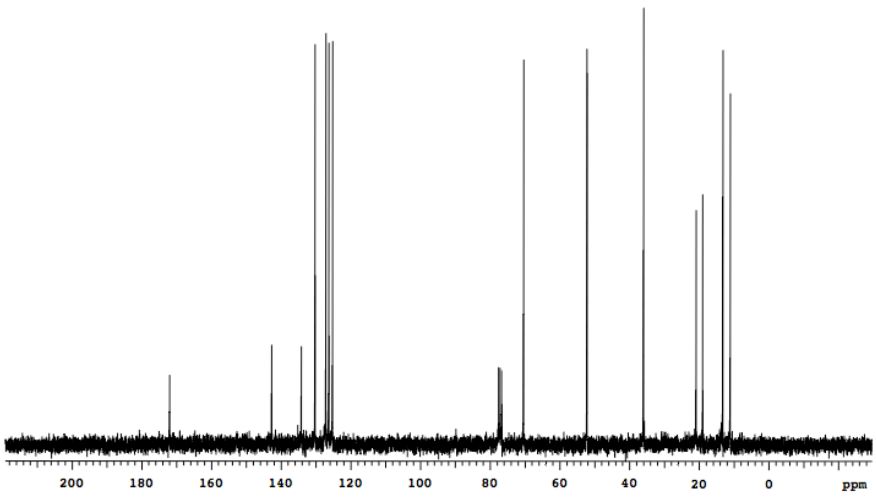
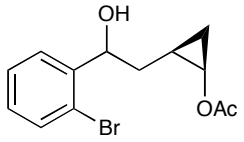


^{13}C NMR (75 MHz) in $CDCl_3$



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



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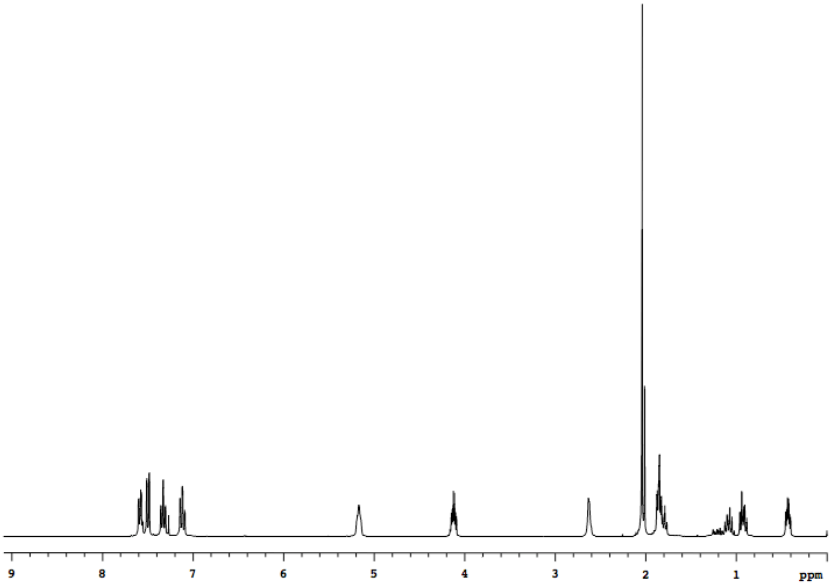
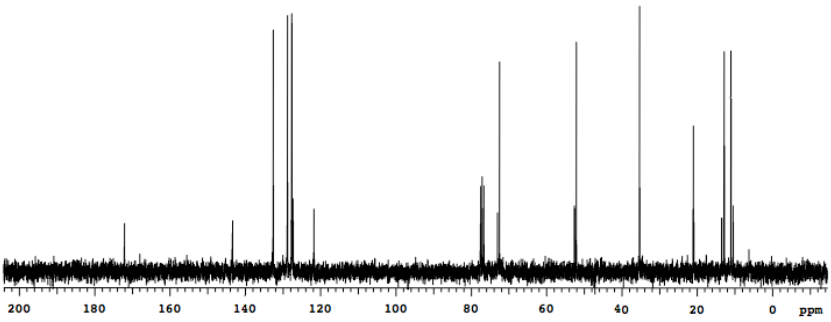
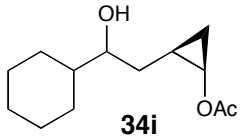


^{13}C NMR (75 MHz) in $CDCl_3$



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



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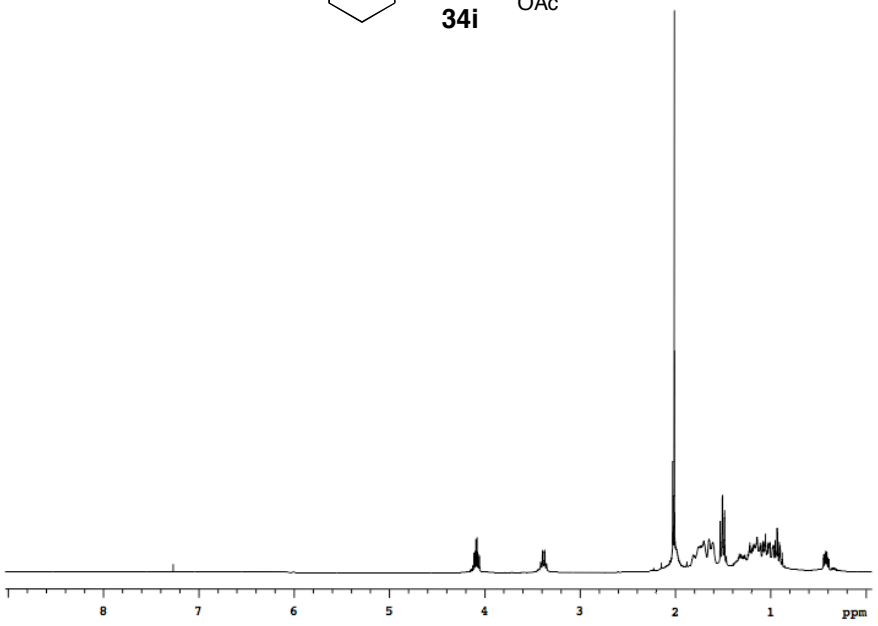
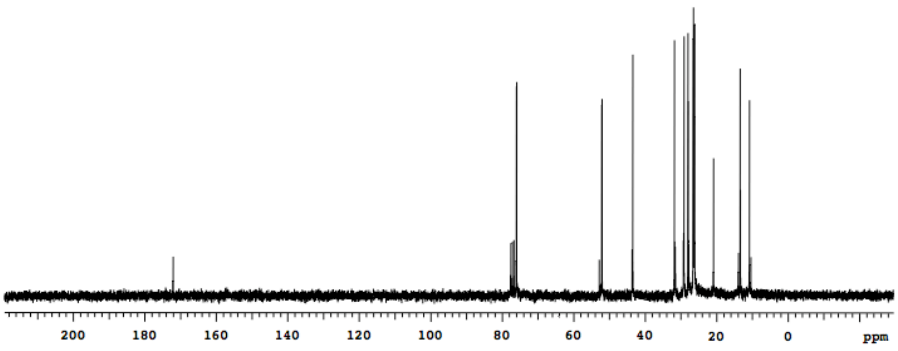
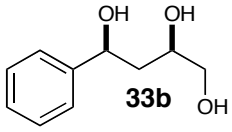


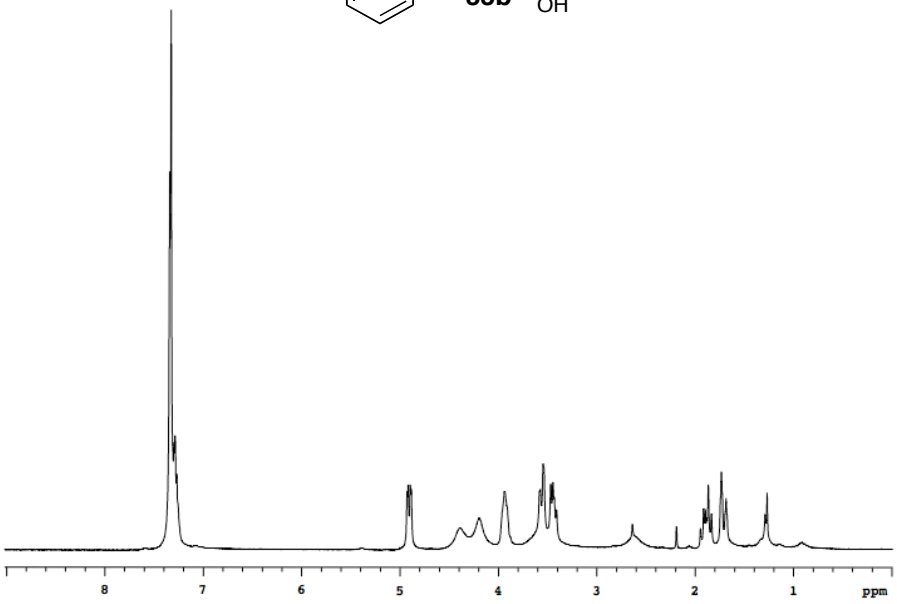
^{13}C NMR (75 MHz) in $CDCl_3$



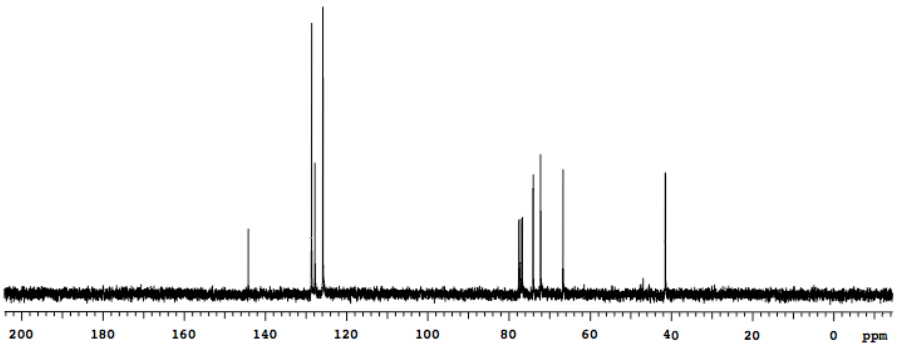
^{1}H NMR (300 MHz) in $CDCl_3$



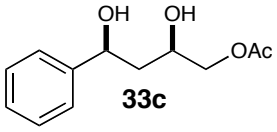
33b



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



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



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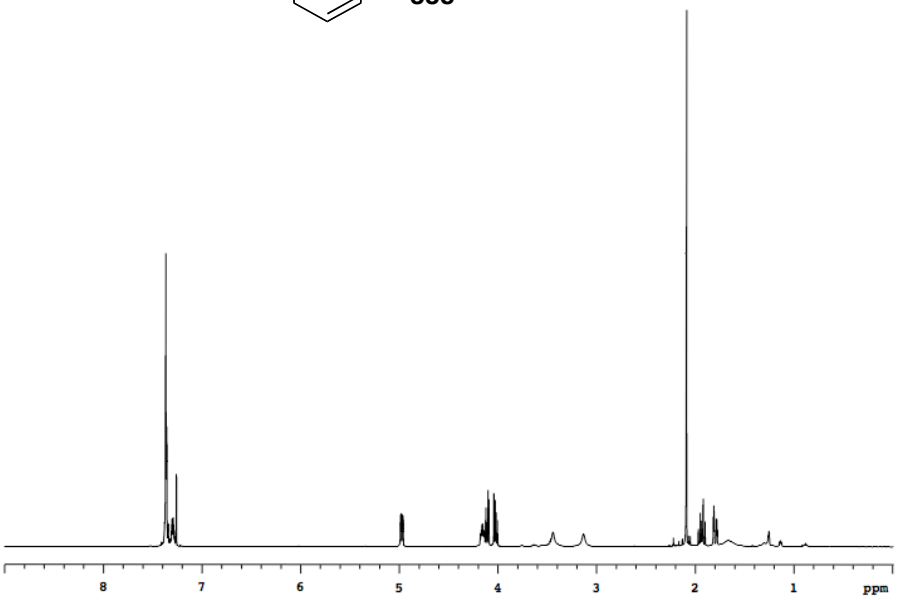
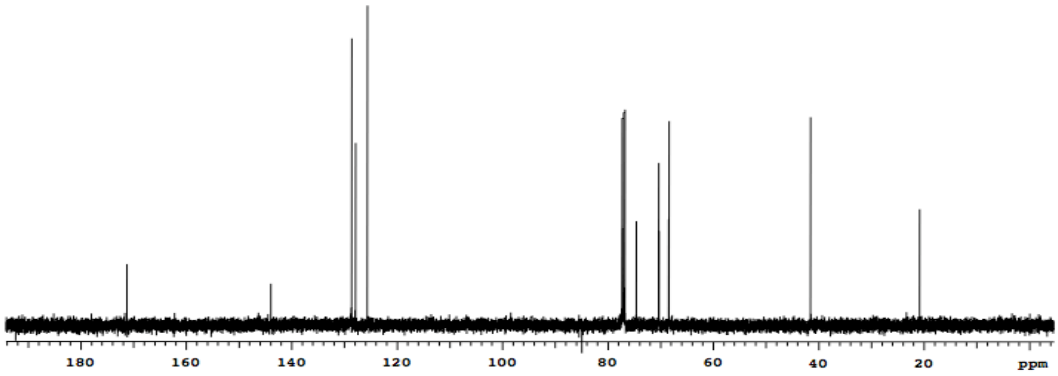
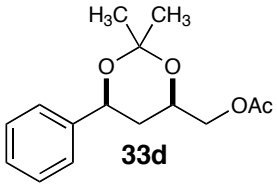


^{13}C NMR (75 MHz) in $CDCl_3$



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



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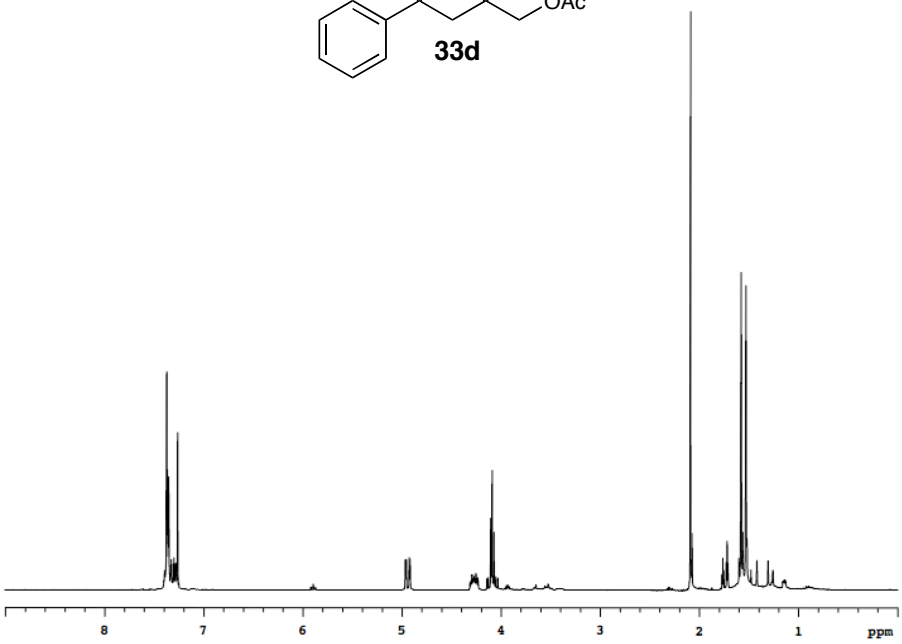
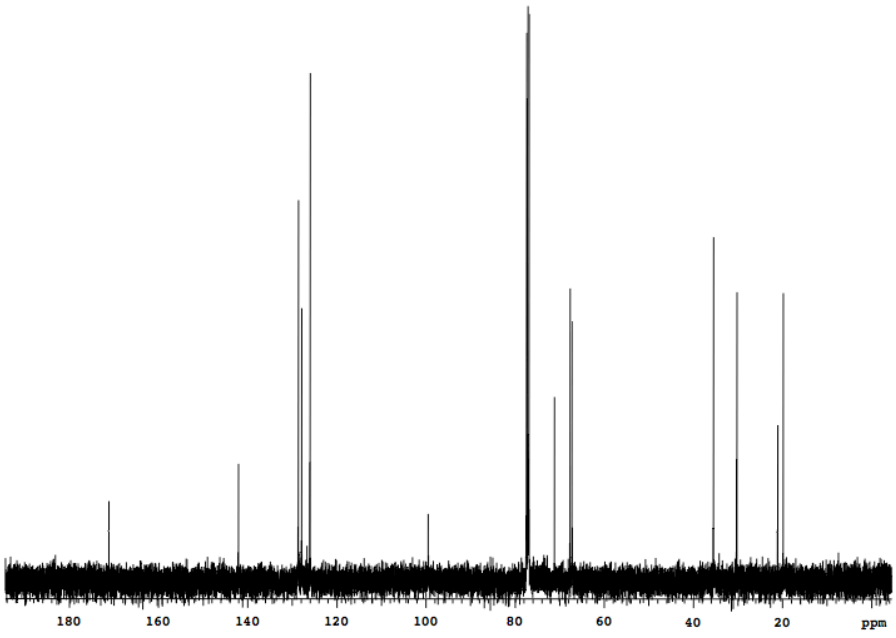
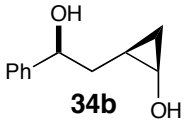


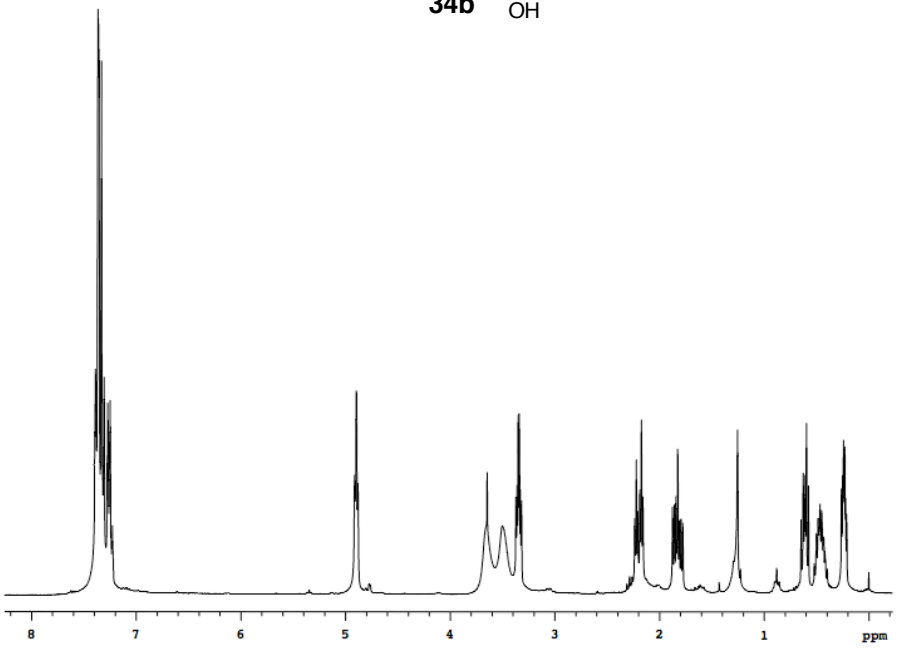
^{13}C NMR (75 MHz) in $CDCl_3$



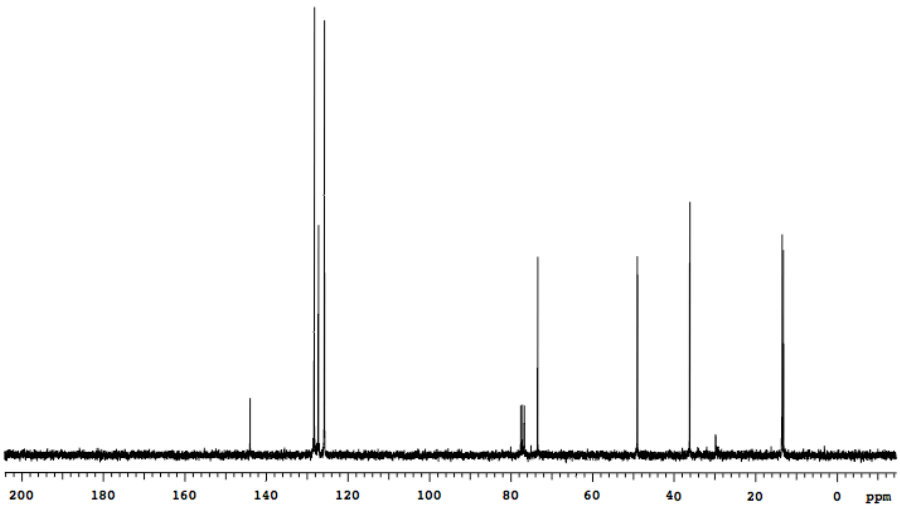
^{1}H NMR (300 MHz) in $CDCl_3$



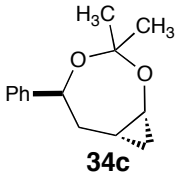
34b



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

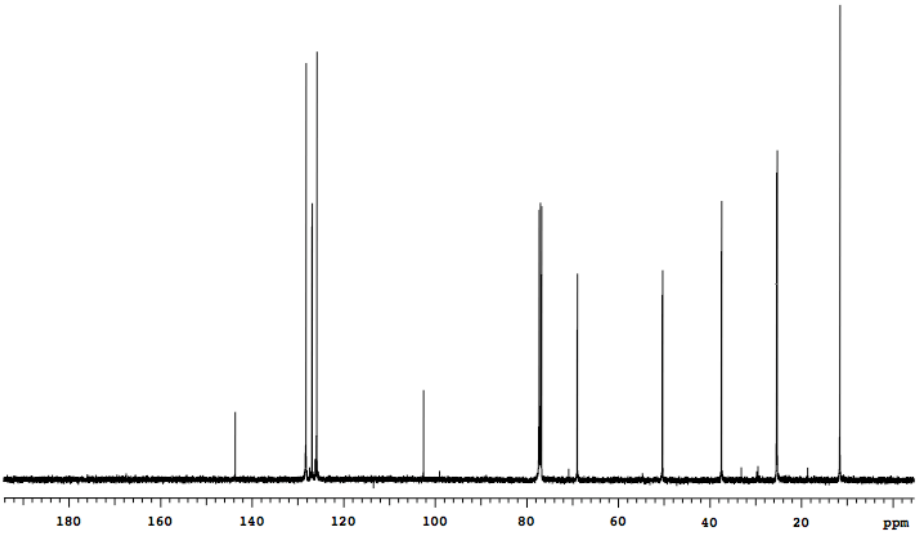


^{1}H NMR (300 MHz) in $CDCl_3$

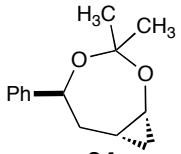


34c

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



^{1}H NMR (500 MHz) COSY in $CDCl_3$



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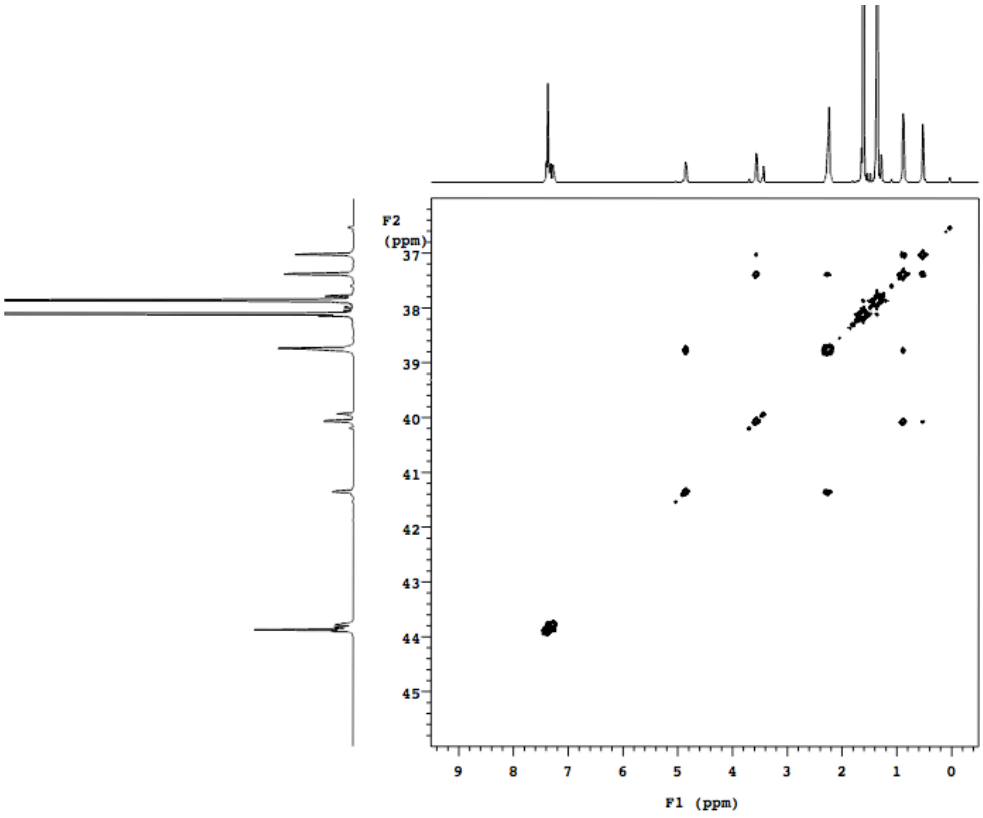
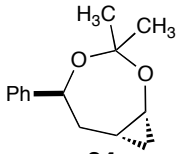


$^{1}H–^{13}C$ NMR (125 MHz) HMQC in $CDCl_3$



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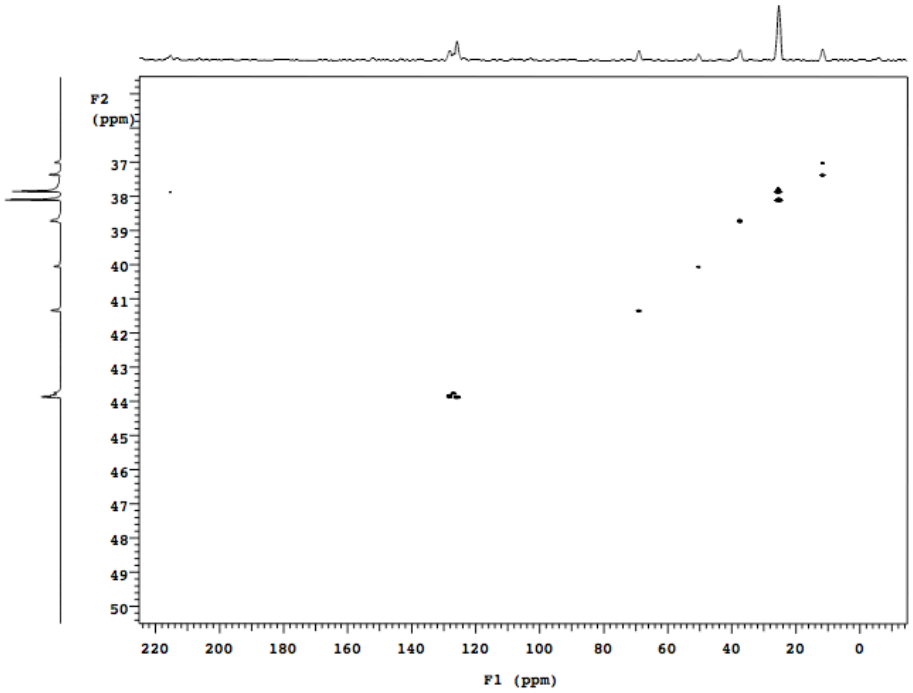
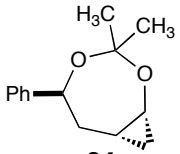


^{13}C NMR (125 MHz) DEPT in $CDCl_3$



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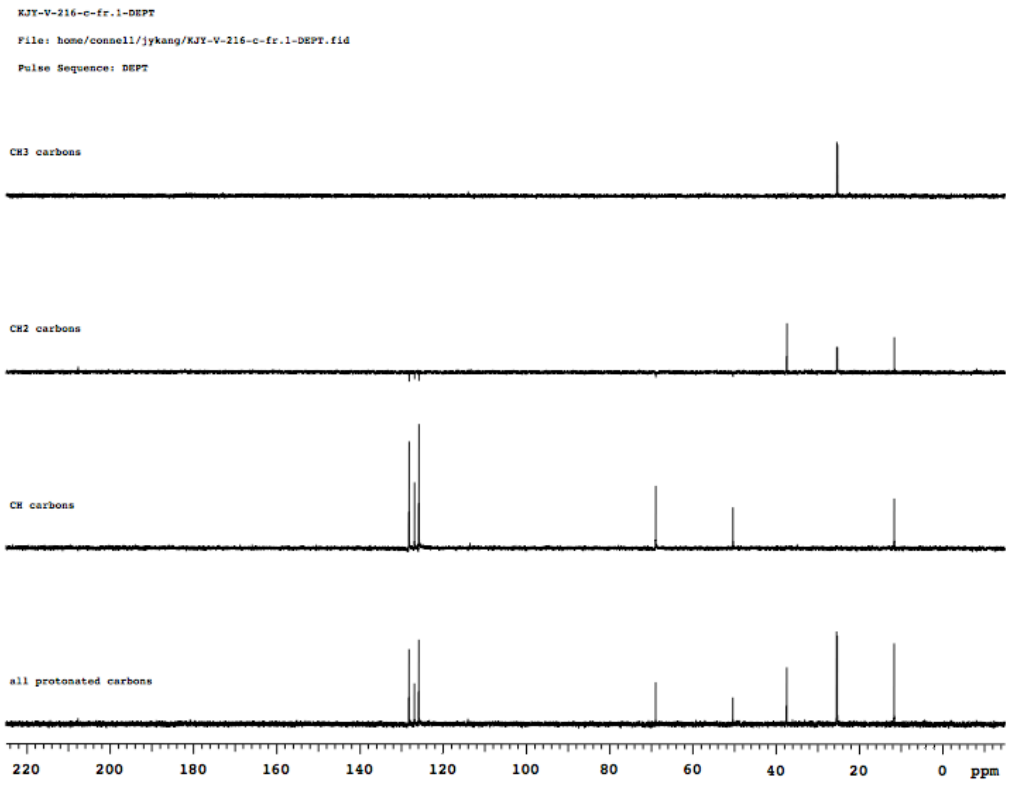
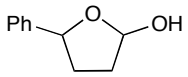
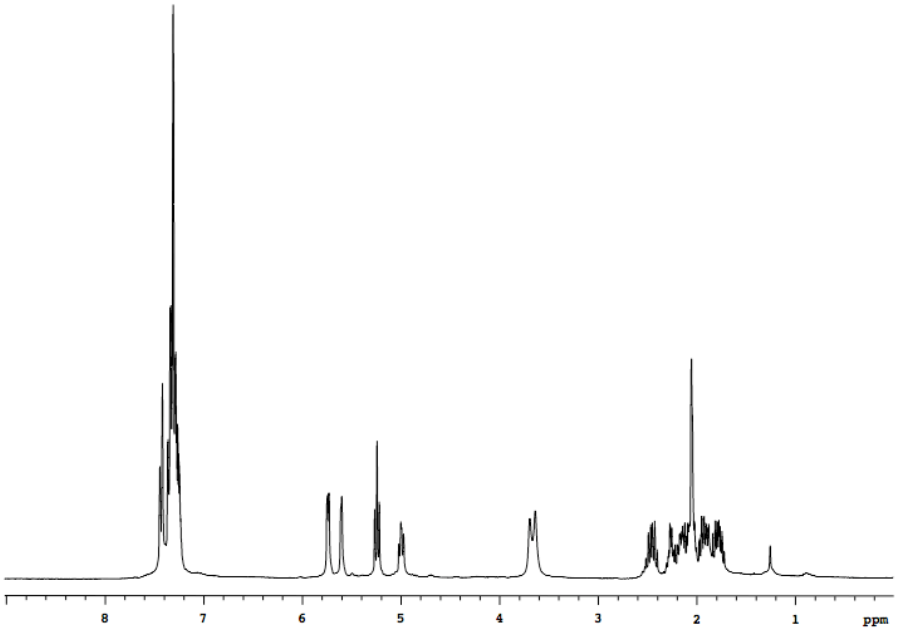


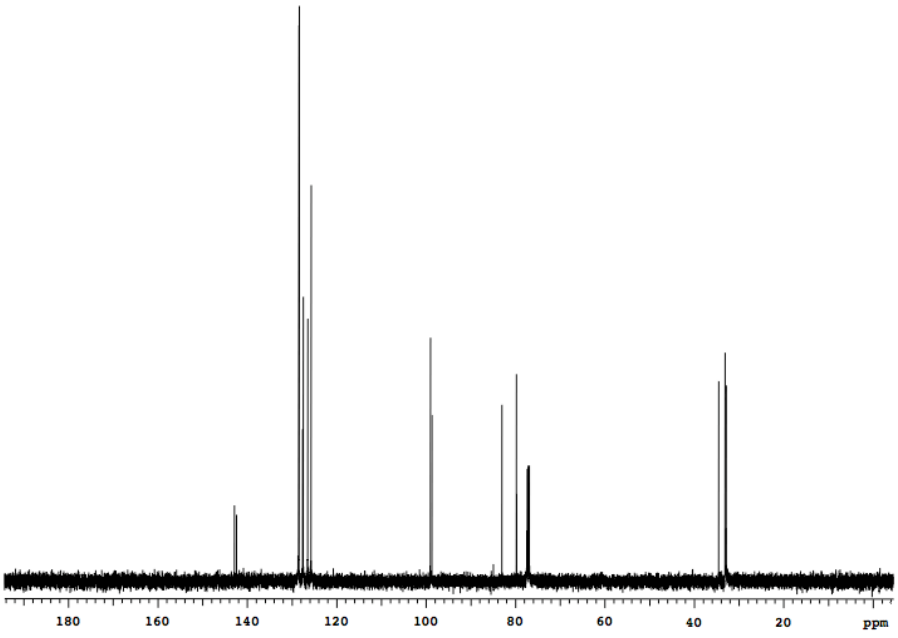
^{1}H NMR (300 MHz) in $CDCl_3$



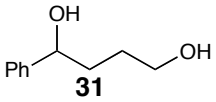
32



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



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



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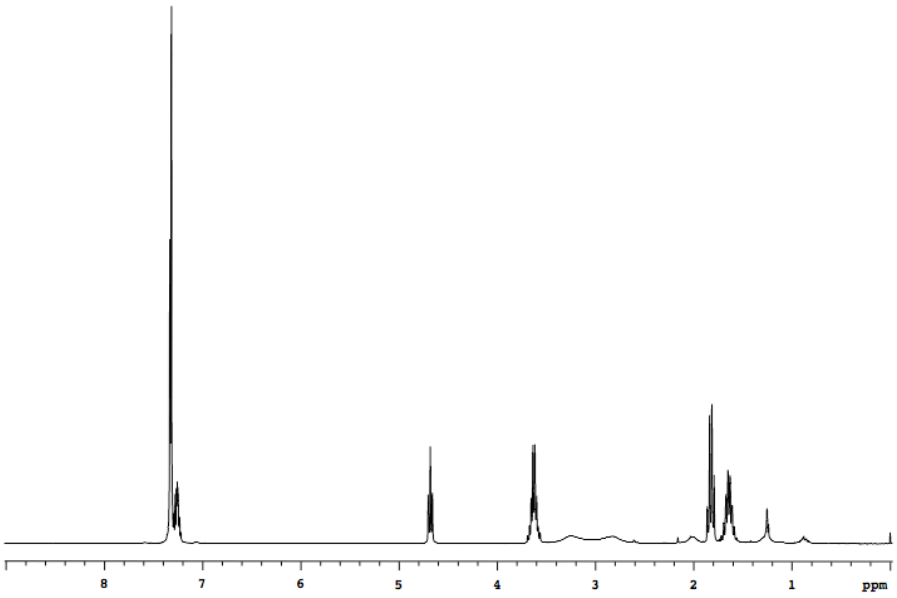
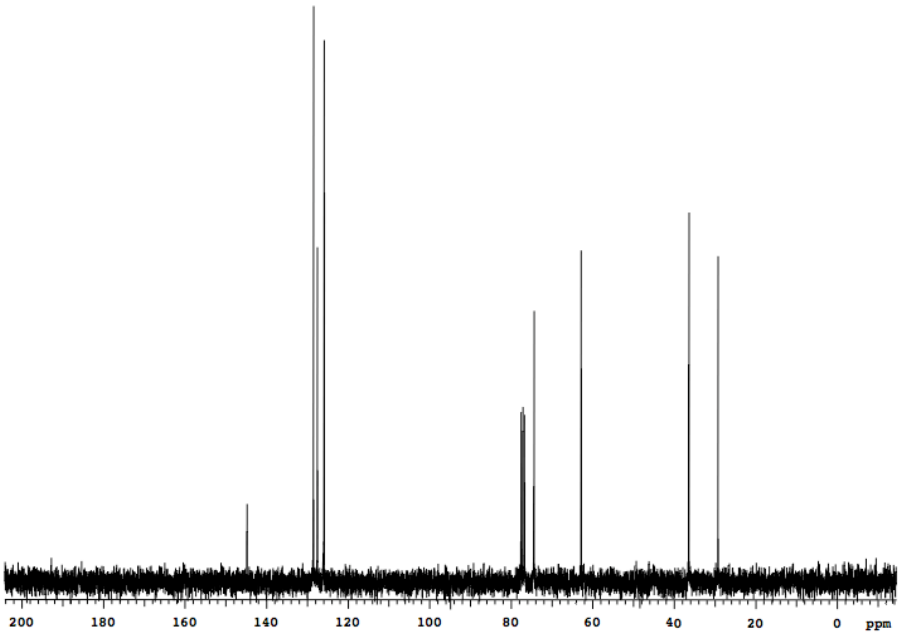
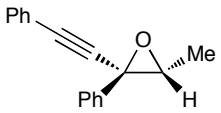


^{13}C NMR (75 MHz) in $CDCl_3$



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



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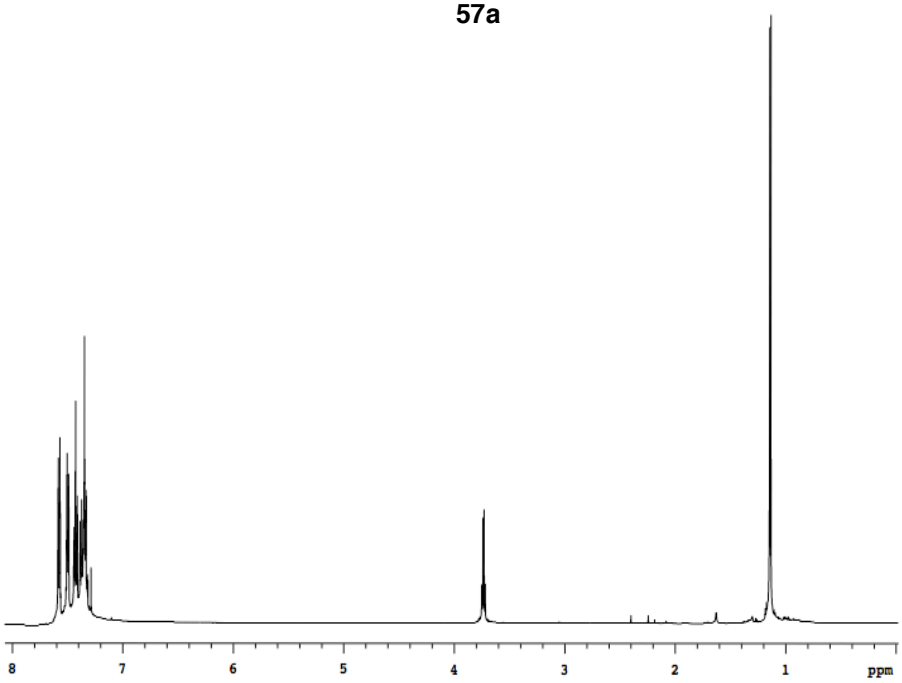
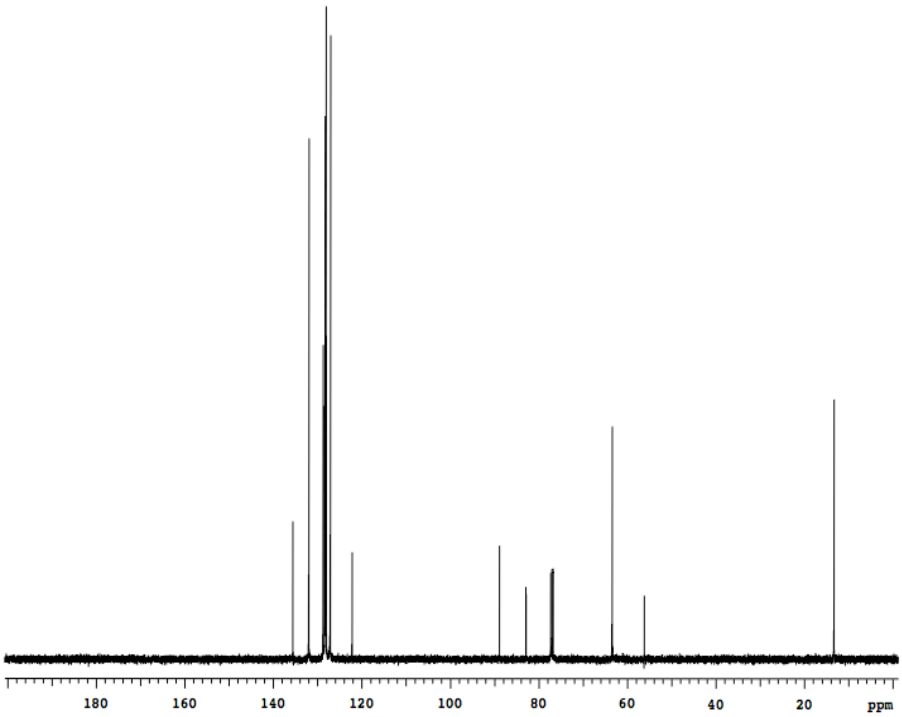
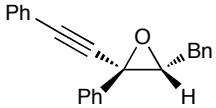


^{13}C NMR (75 MHz) in $CDCl_3$



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



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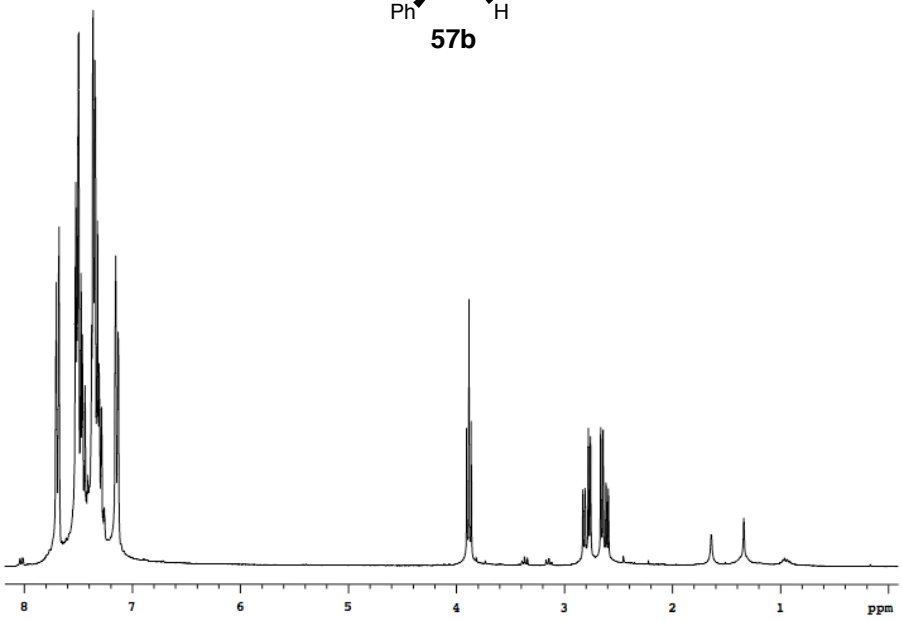
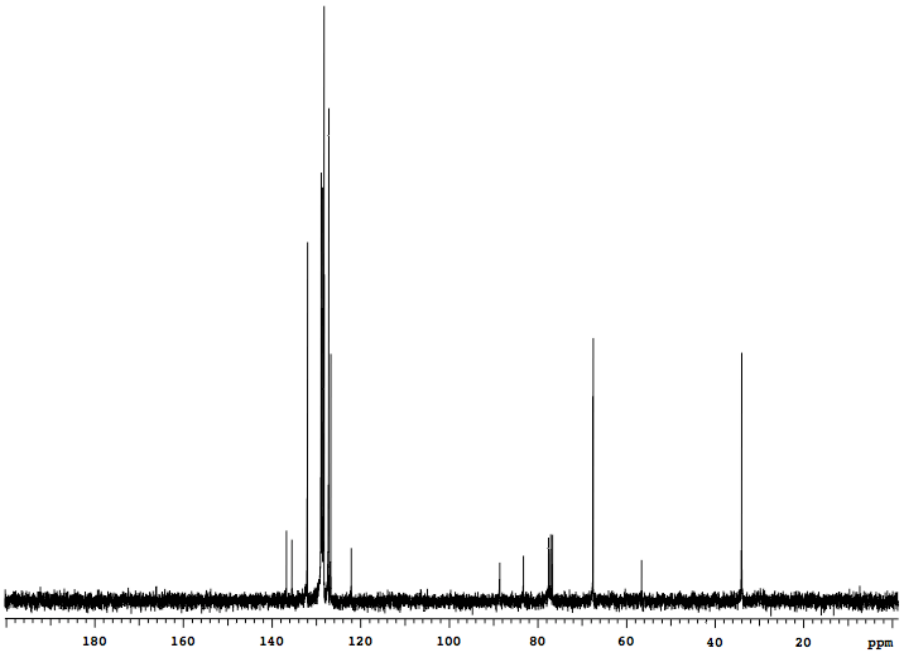
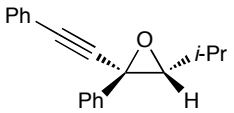


^{13}C NMR (75 MHz) in $CDCl_3$



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



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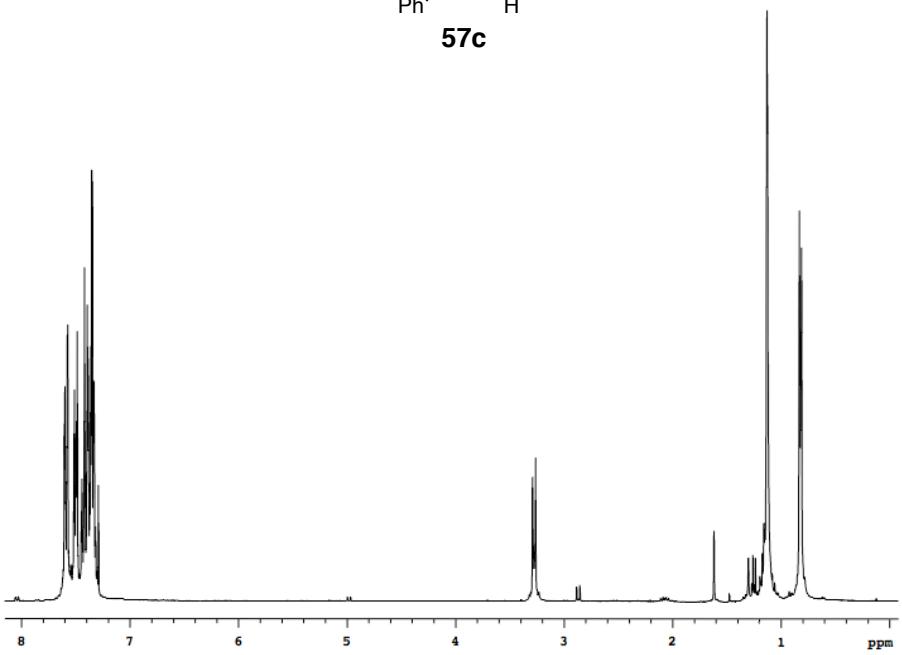
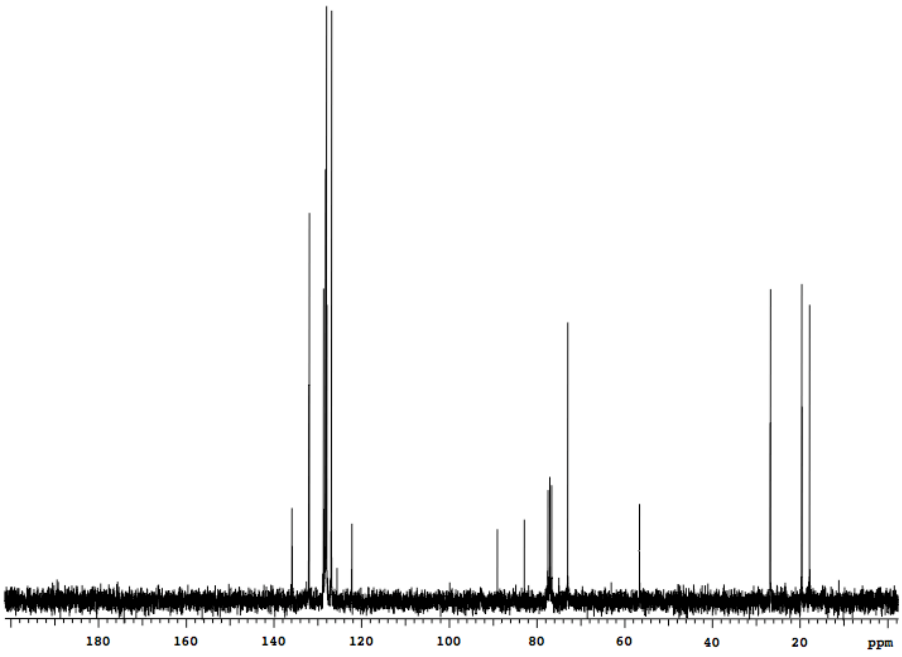
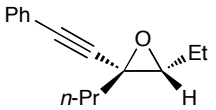


^{13}C NMR (75 MHz) in $CDCl_3$



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



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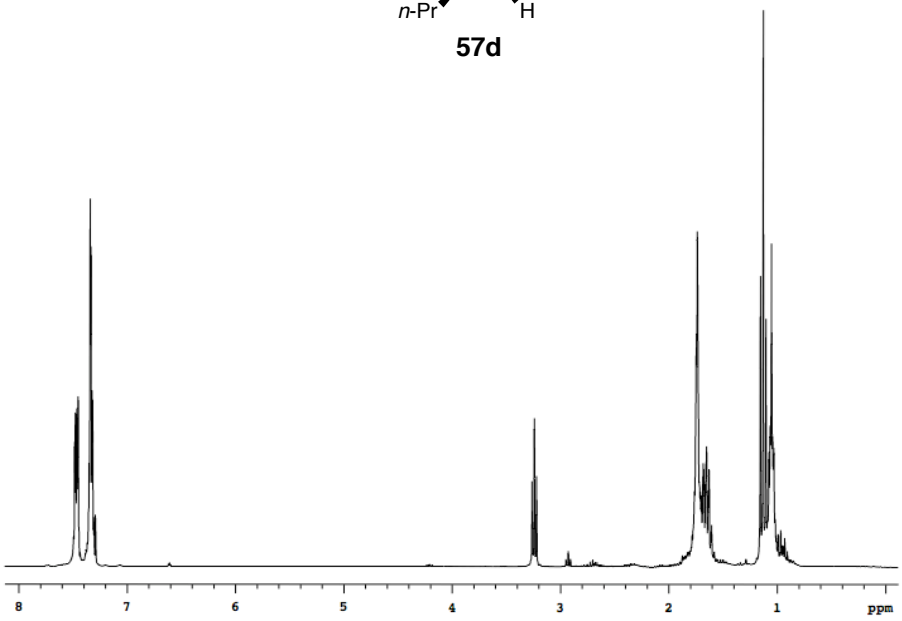
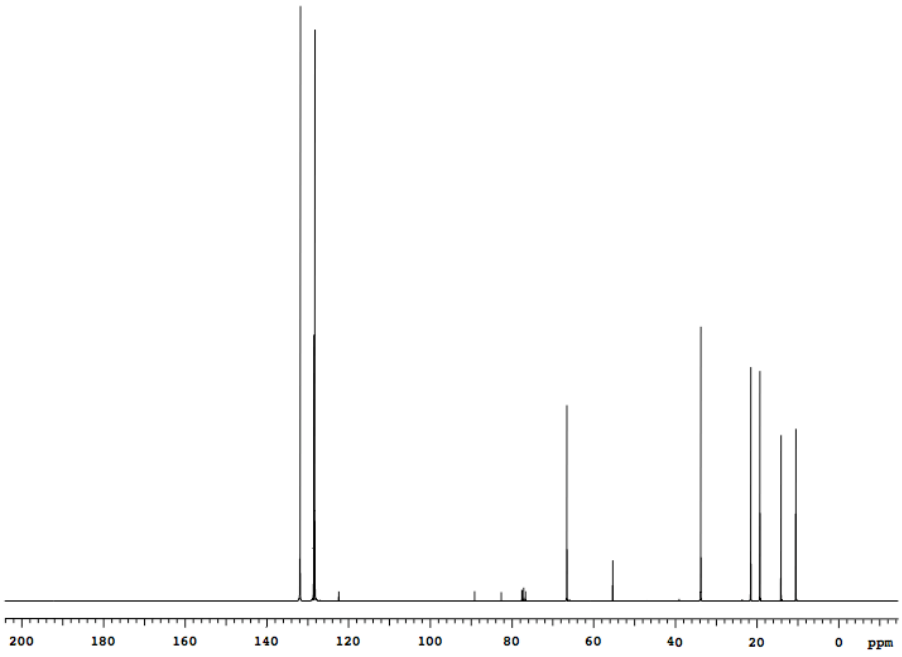
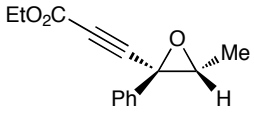


^{13}C NMR (75 MHz) in $CDCl_3$



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



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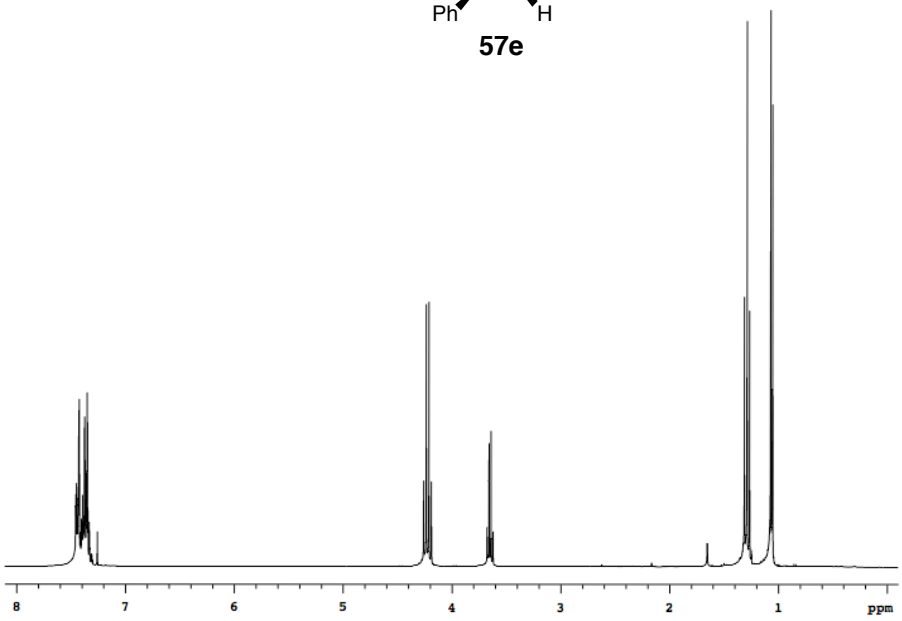
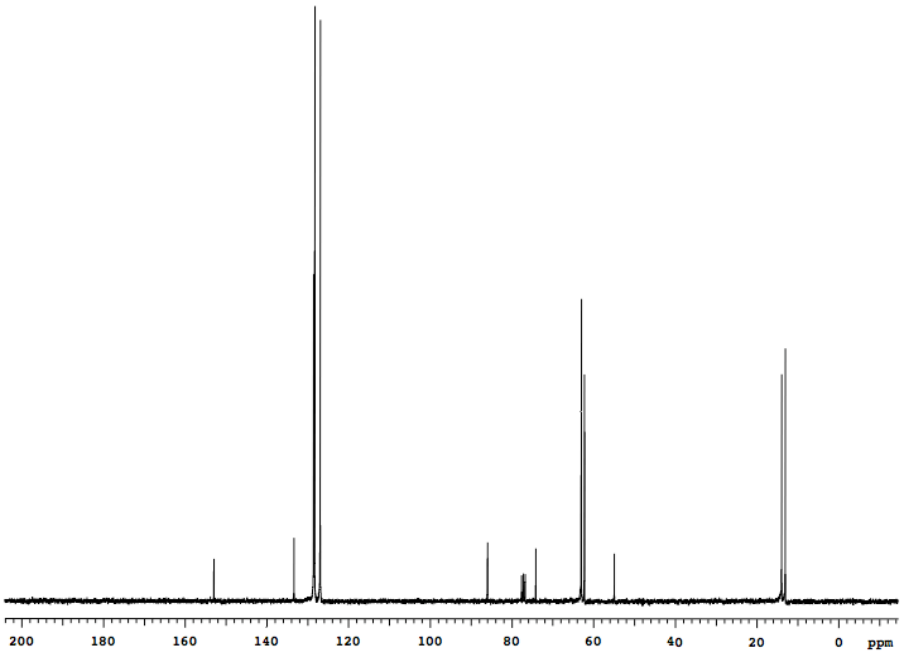
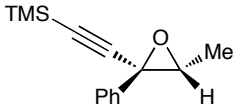


^{13}C NMR (75 MHz) in $CDCl_3$



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



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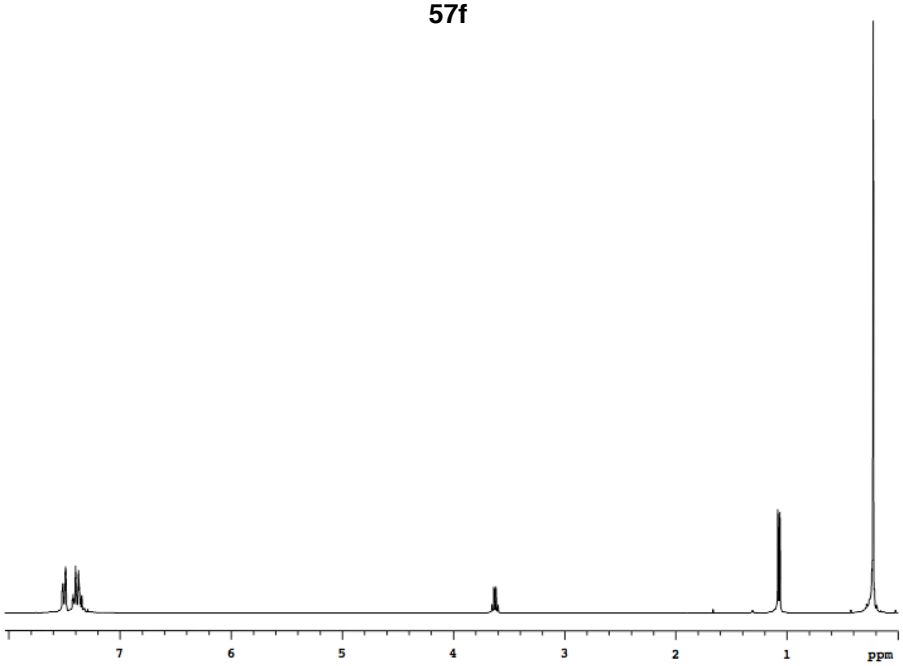
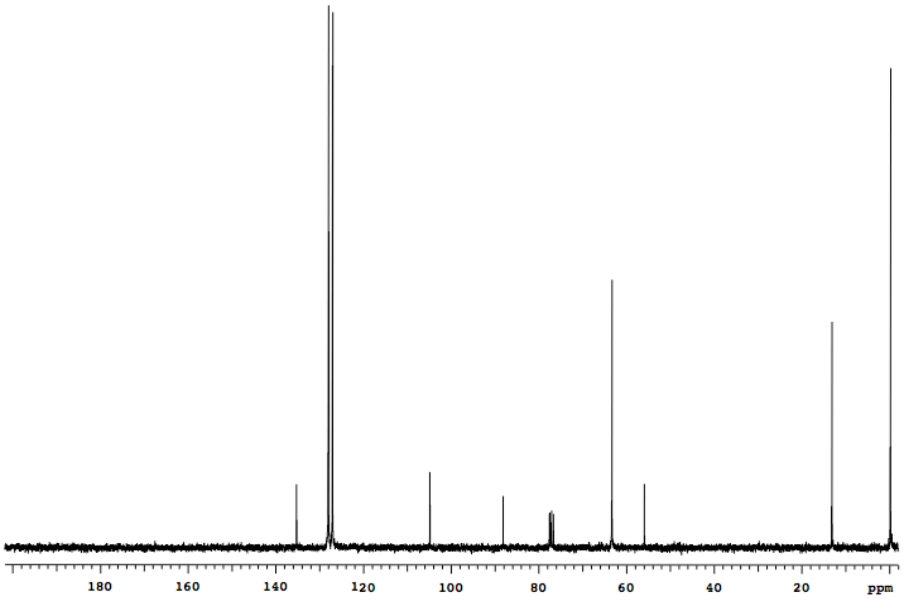
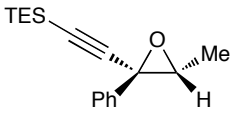


^{13}C NMR (75 MHz) in $CDCl_3$



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



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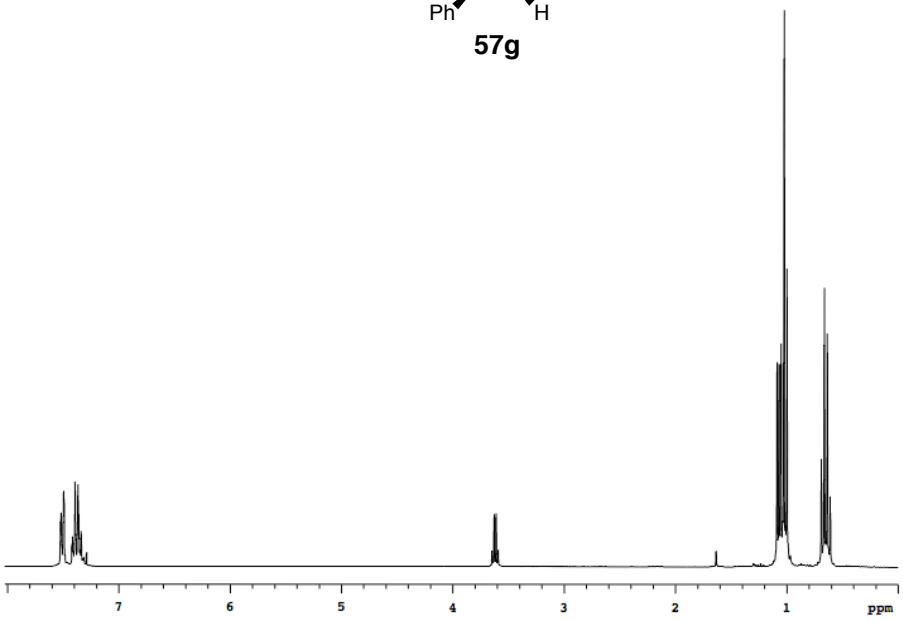
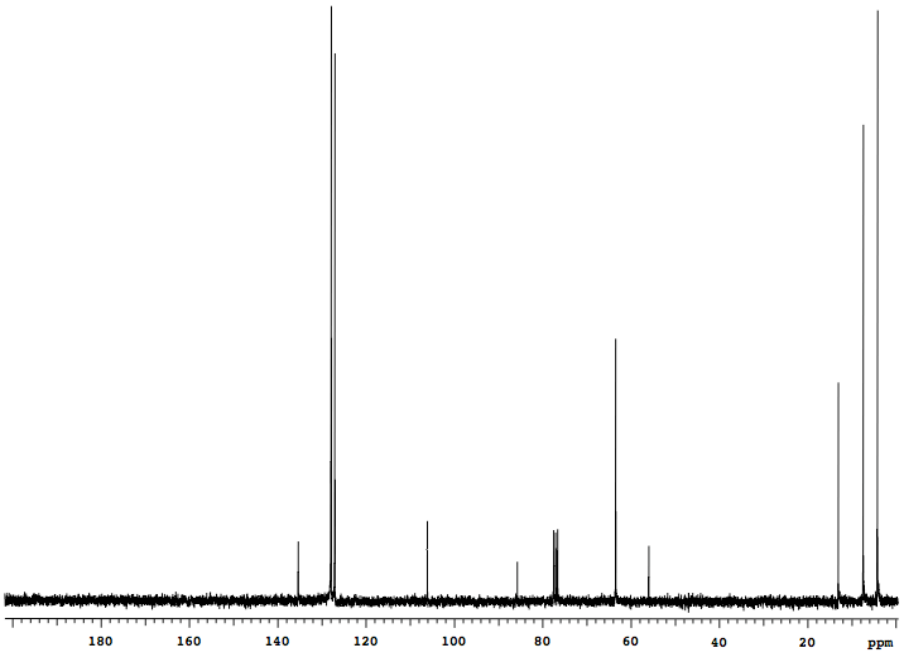
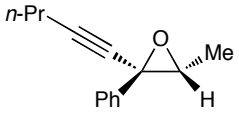


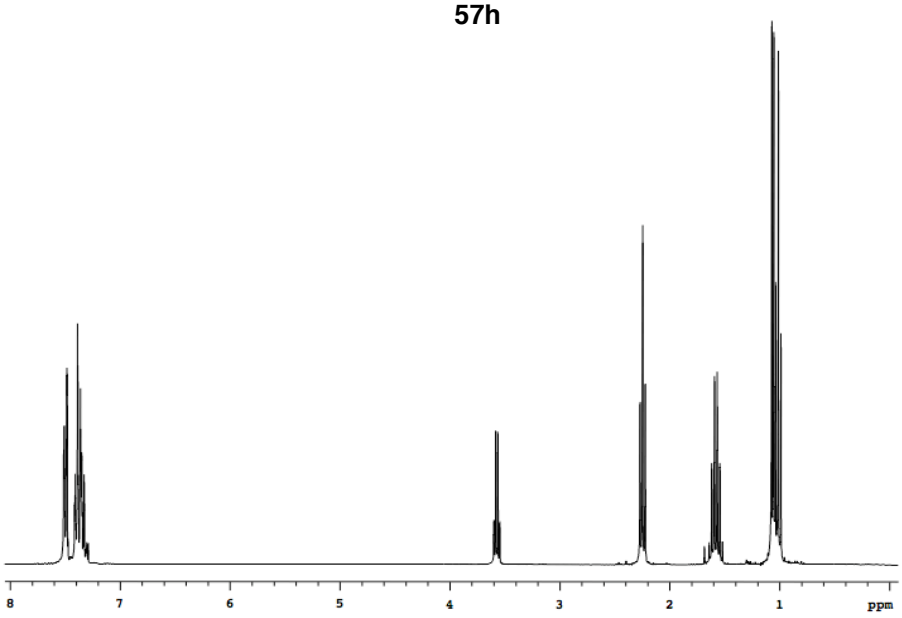
^{13}C NMR (75 MHz) in $CDCl_3$



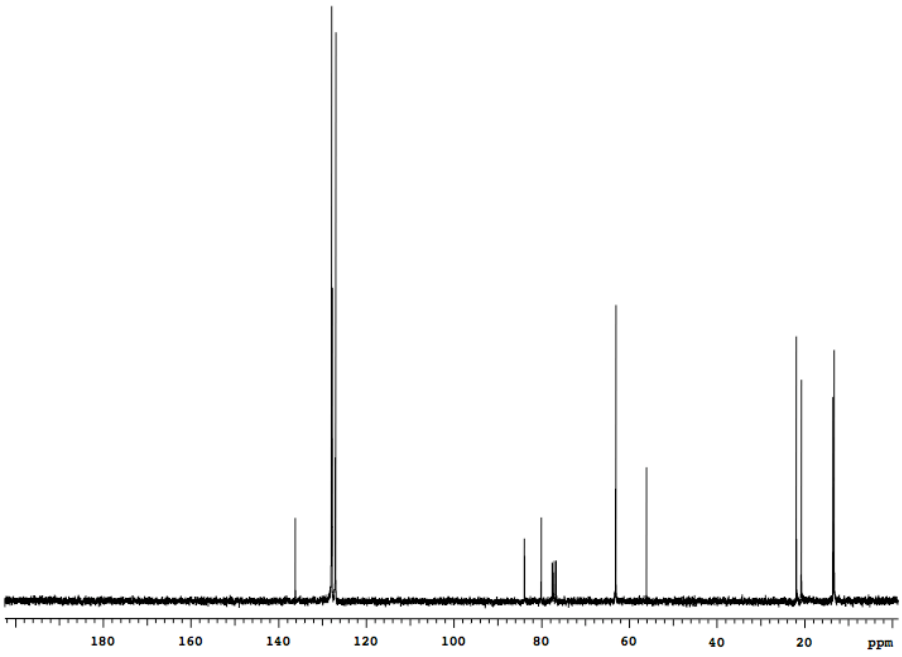
^{1}H NMR (300 MHz) in $CDCl_3$



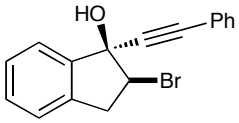
57h



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



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



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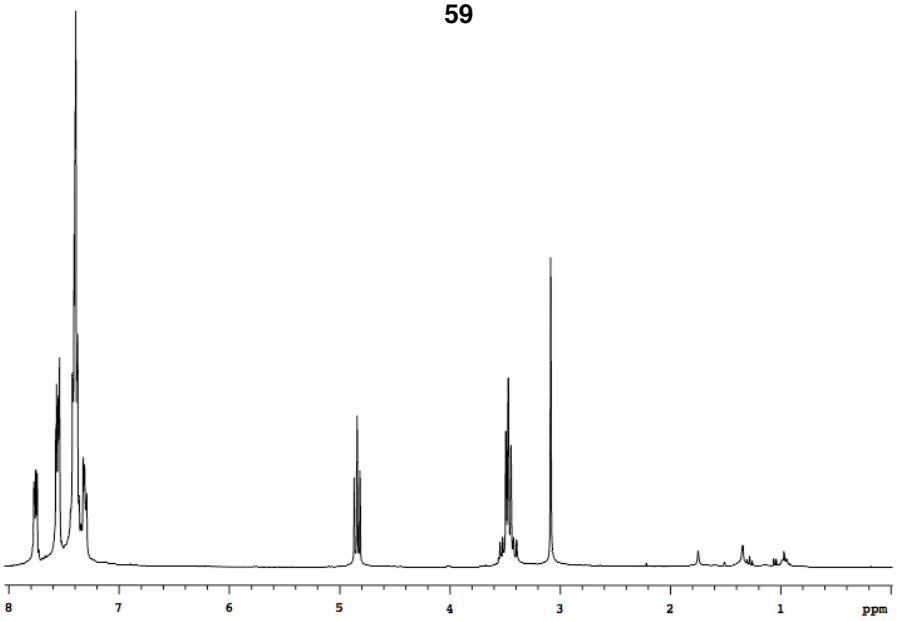
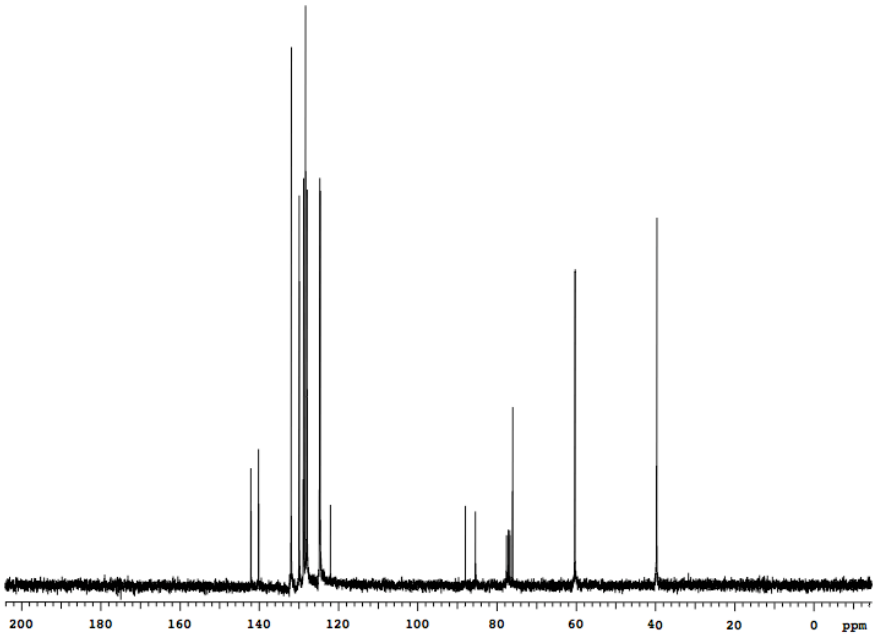


^{13}C NMR (75 MHz) in $CDCl_3$



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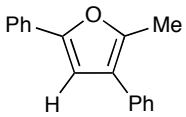

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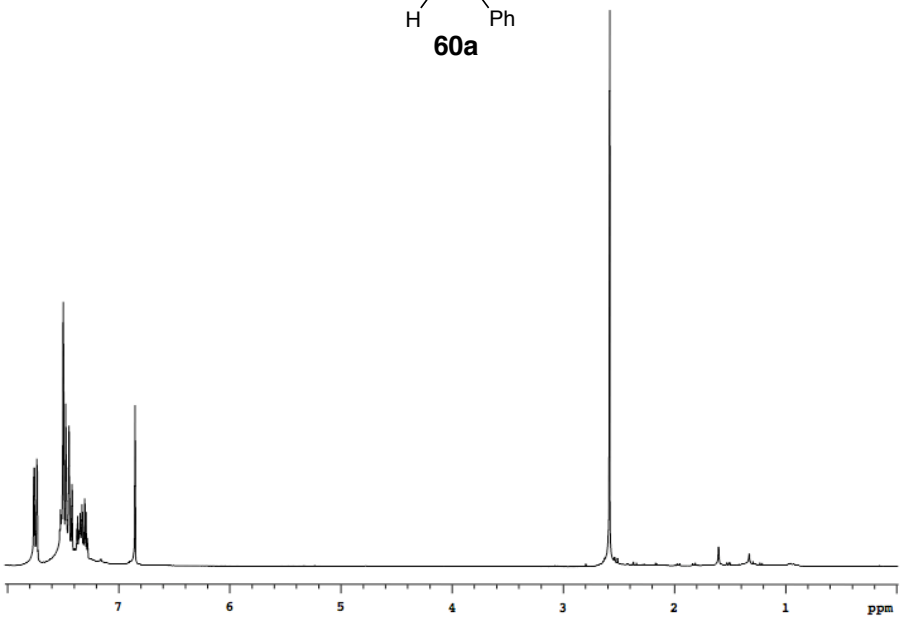
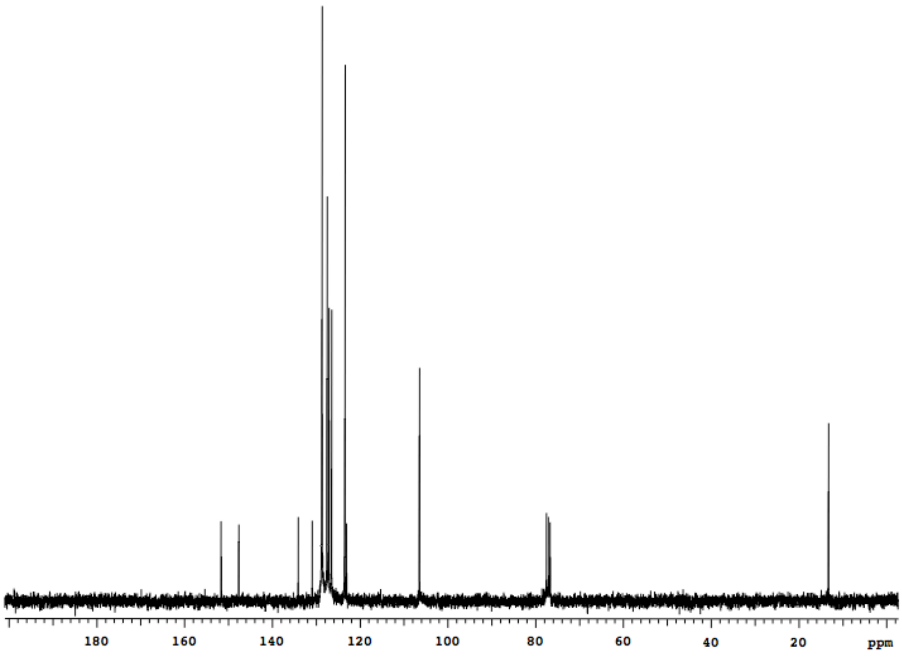
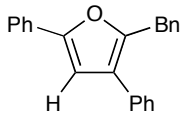


^{13}C NMR (75 MHz) in $CDCl_3$



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



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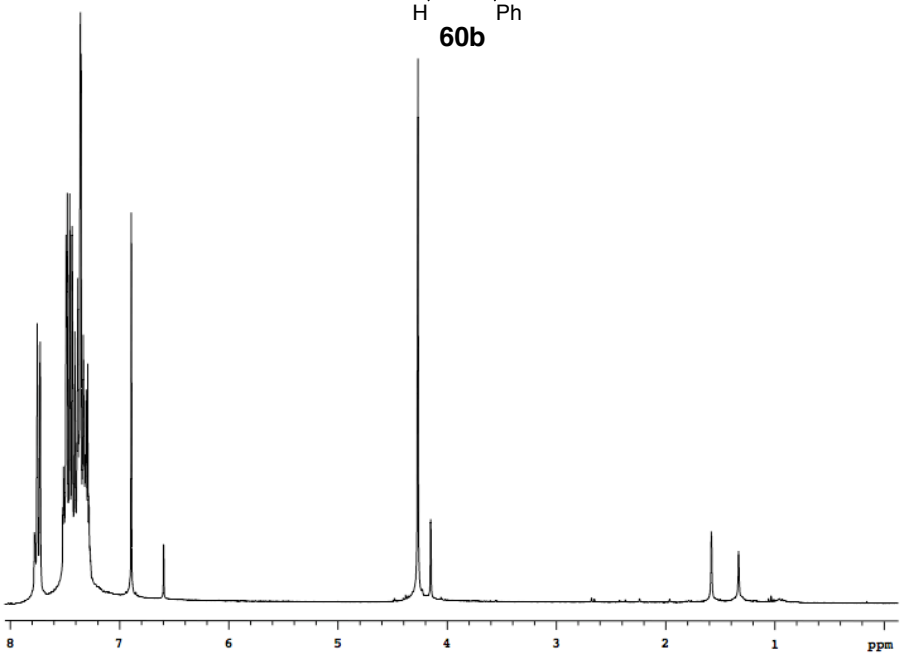
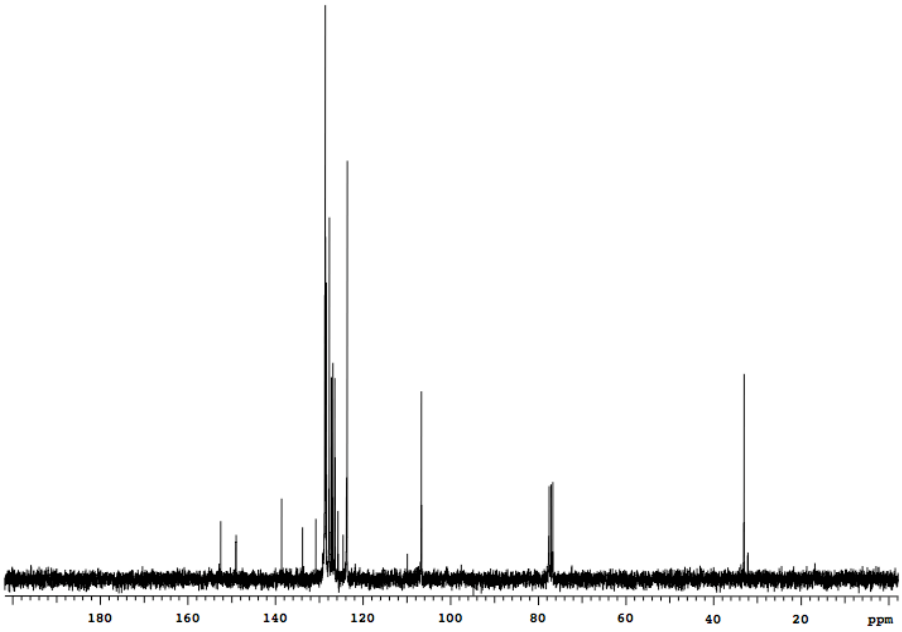


^{13}C NMR (75 MHz) in $CDCl_3$



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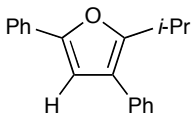

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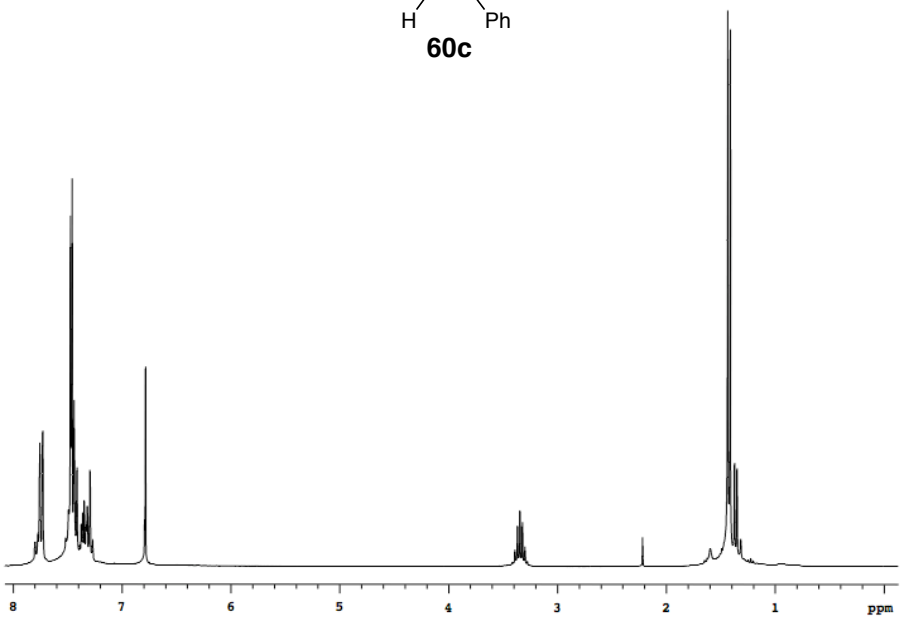
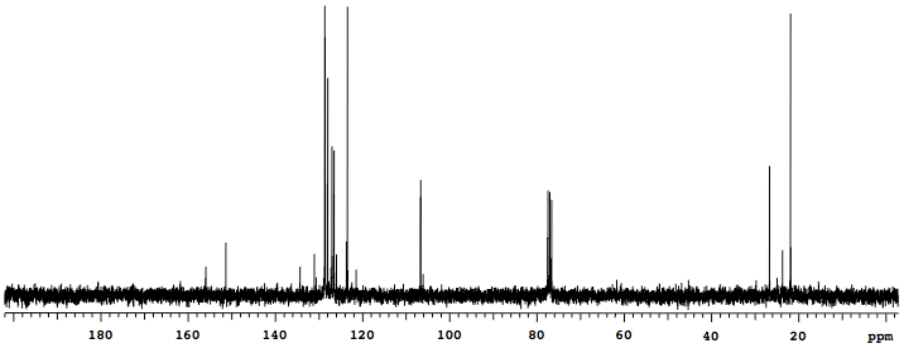


^{13}C NMR (75 MHz) in $CDCl_3$



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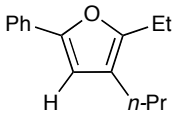

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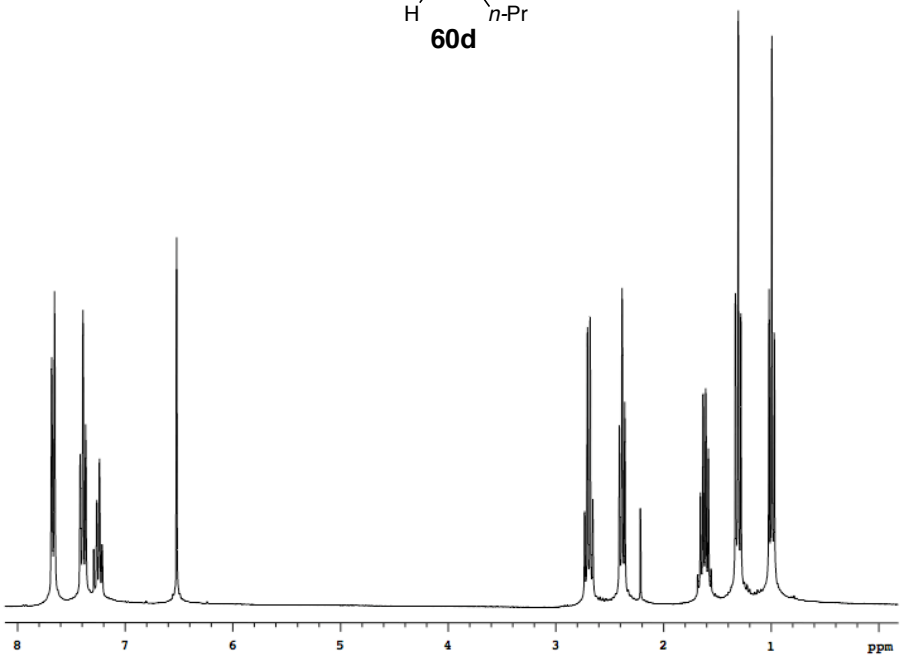
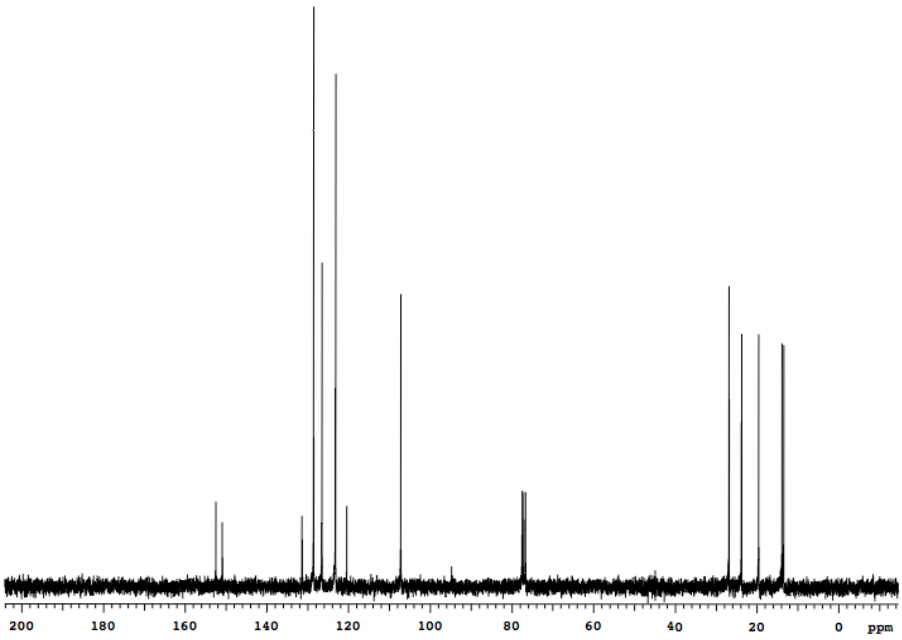
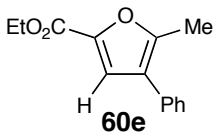


^{13}C NMR (75 MHz) in $CDCl_3$



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



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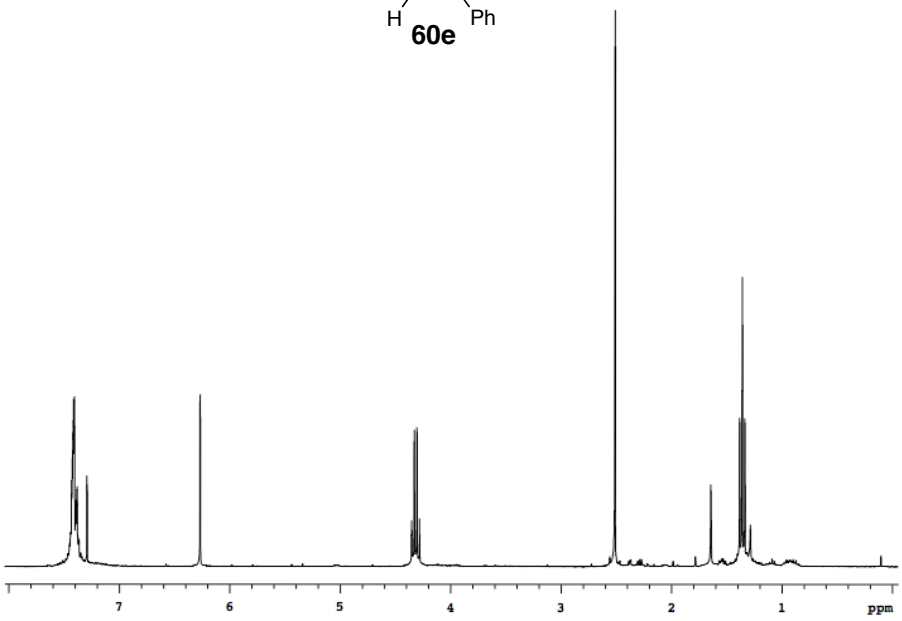
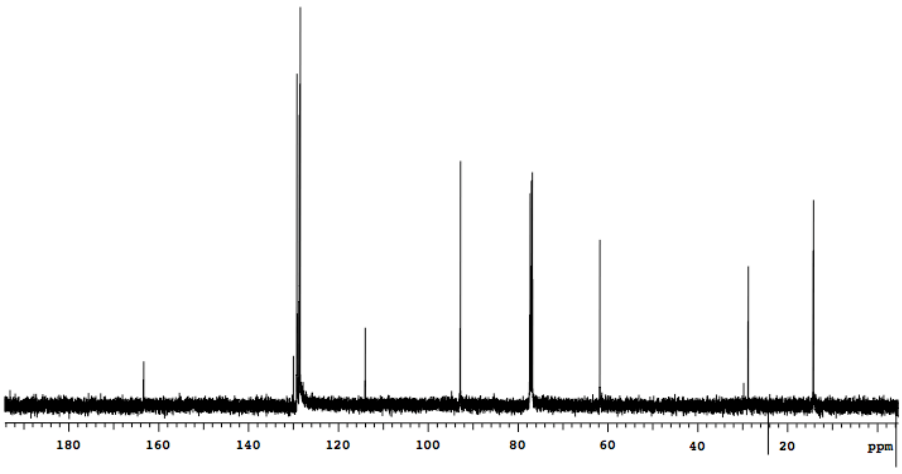
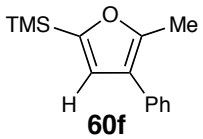


^{13}C NMR (75 MHz) in $CDCl_3$



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



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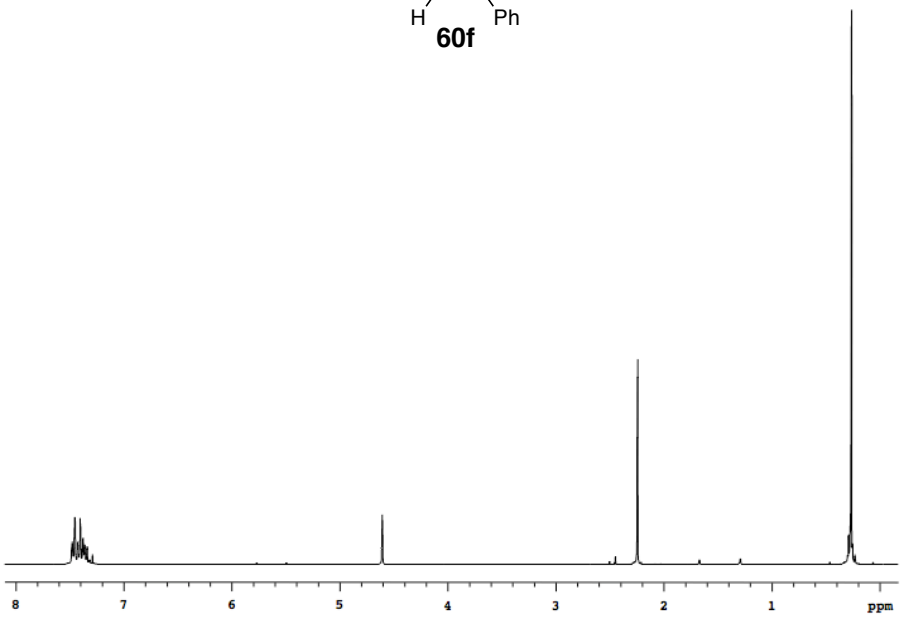
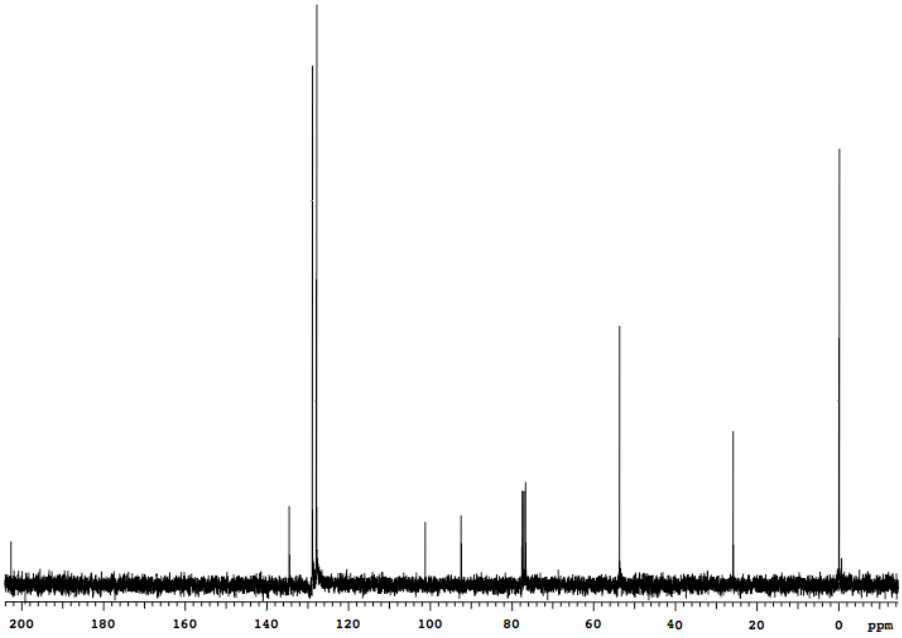


^{13}C NMR (75 MHz) in $CDCl_3$



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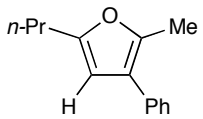

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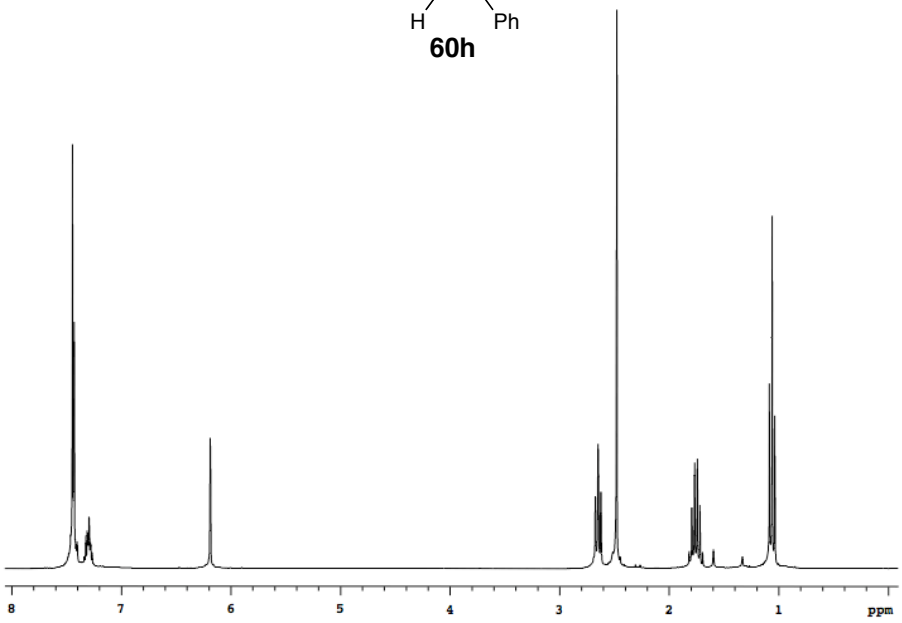
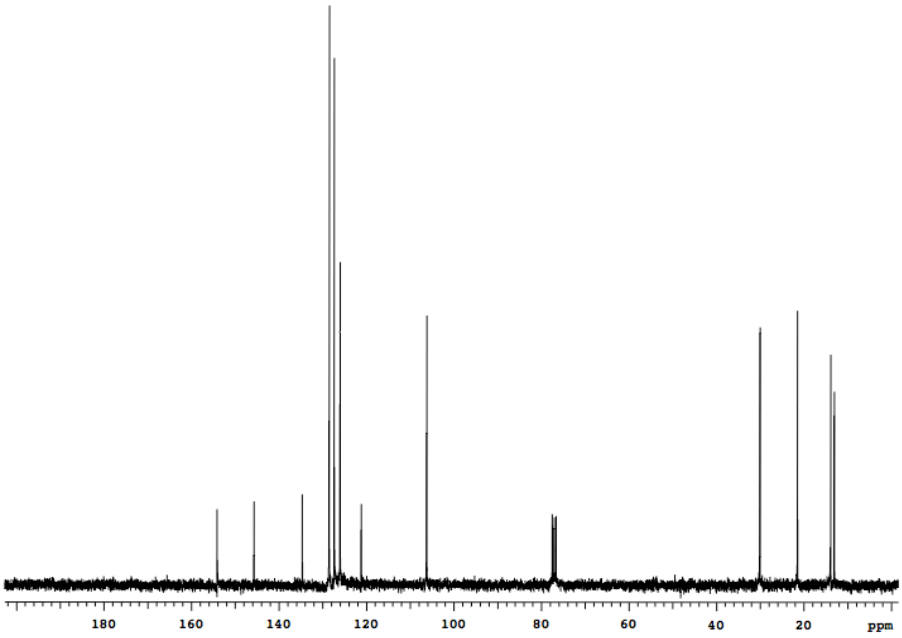


^{13}C NMR (75 MHz) in $CDCl_3$



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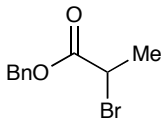

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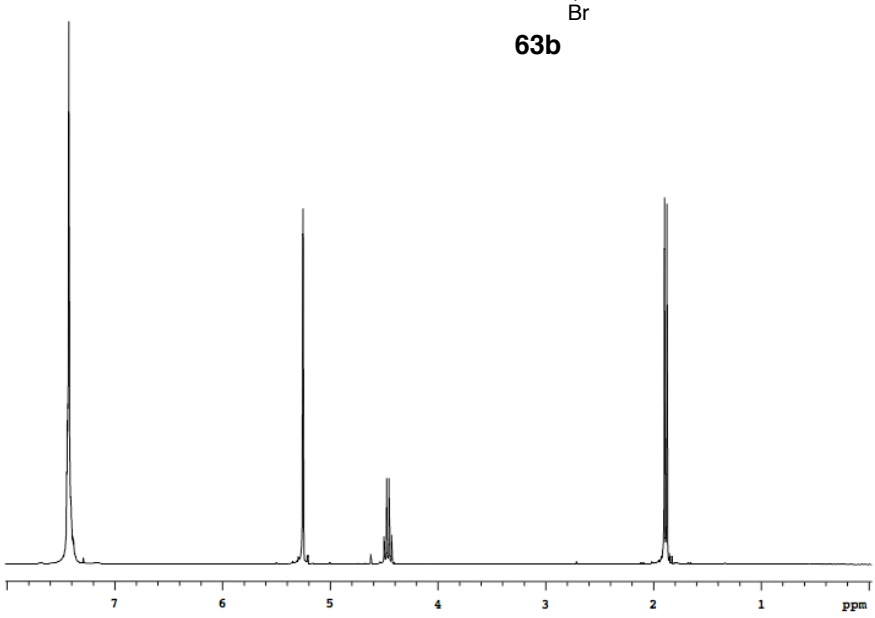
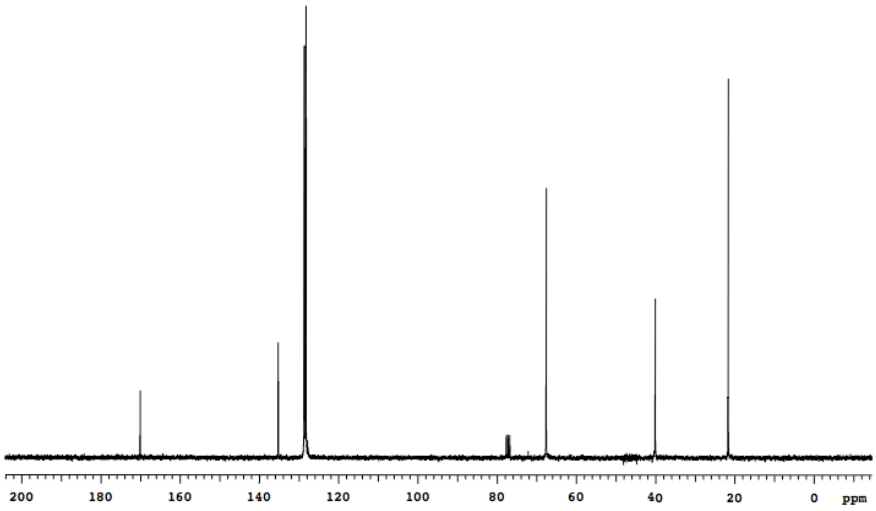


^{13}C NMR (75 MHz) in $CDCl_3$



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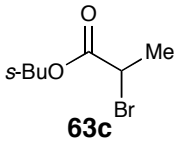

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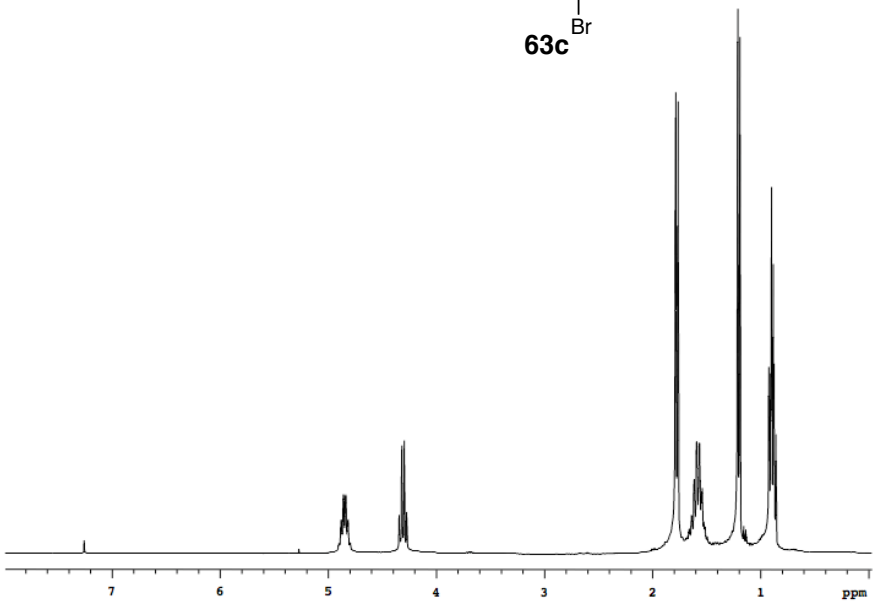
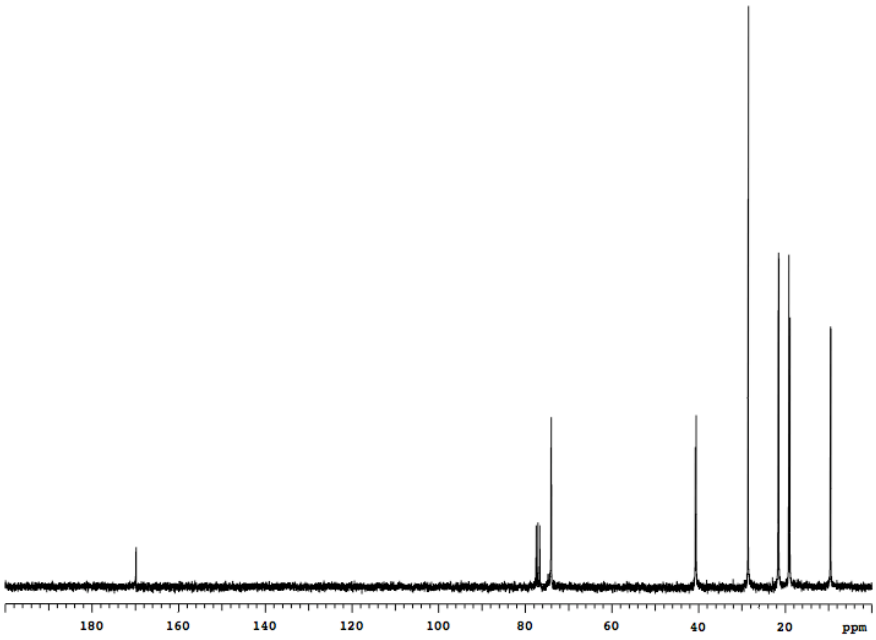


^{13}C NMR (75 MHz) in $CDCl_3$



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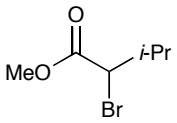

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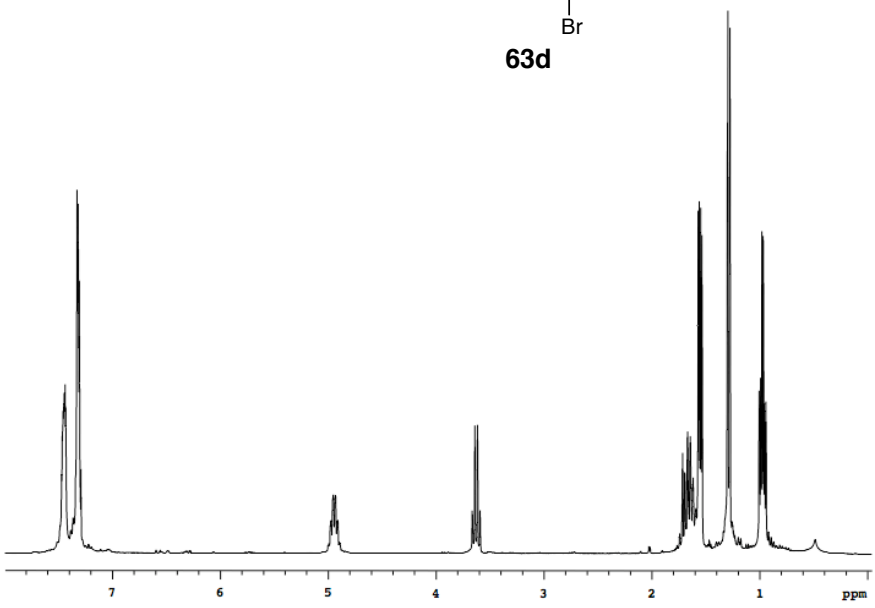
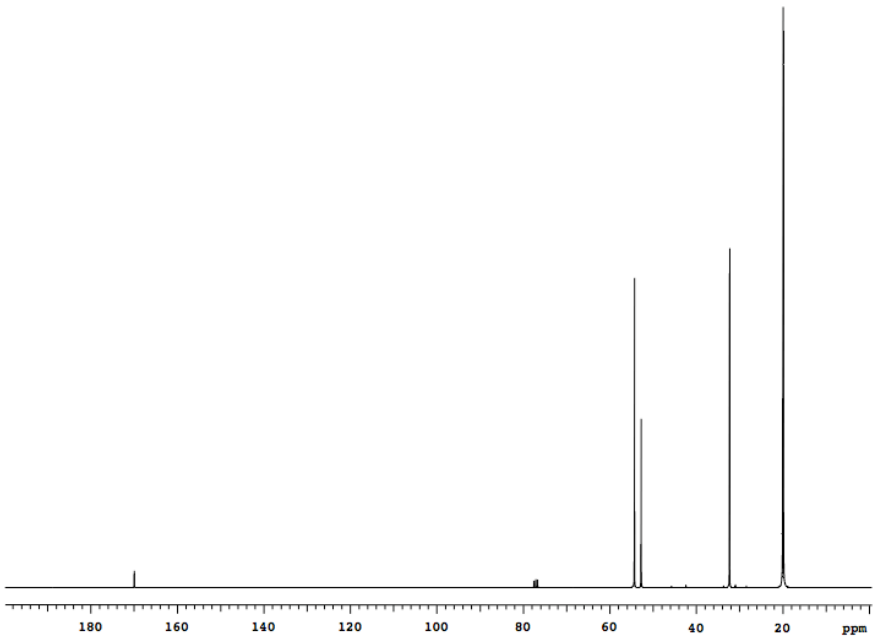


^{13}C NMR (75 MHz) in $CDCl_3$



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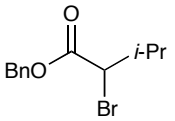

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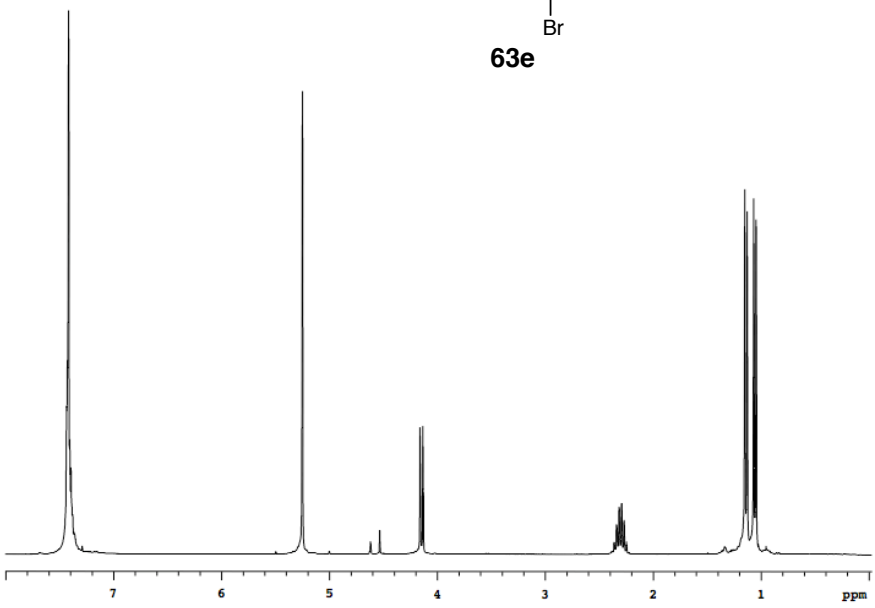
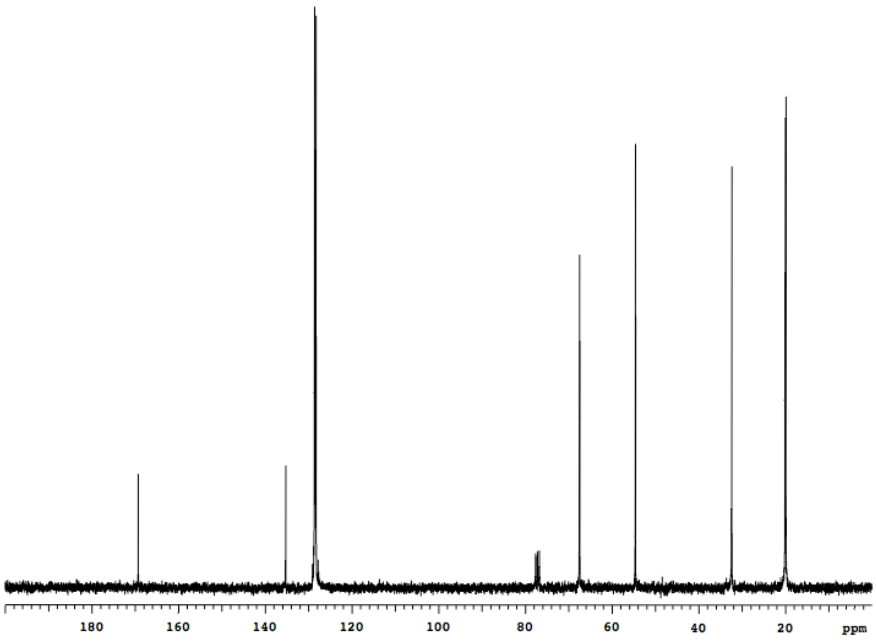


^{13}C NMR (75 MHz) in $CDCl_3$



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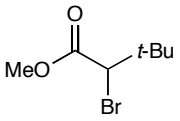

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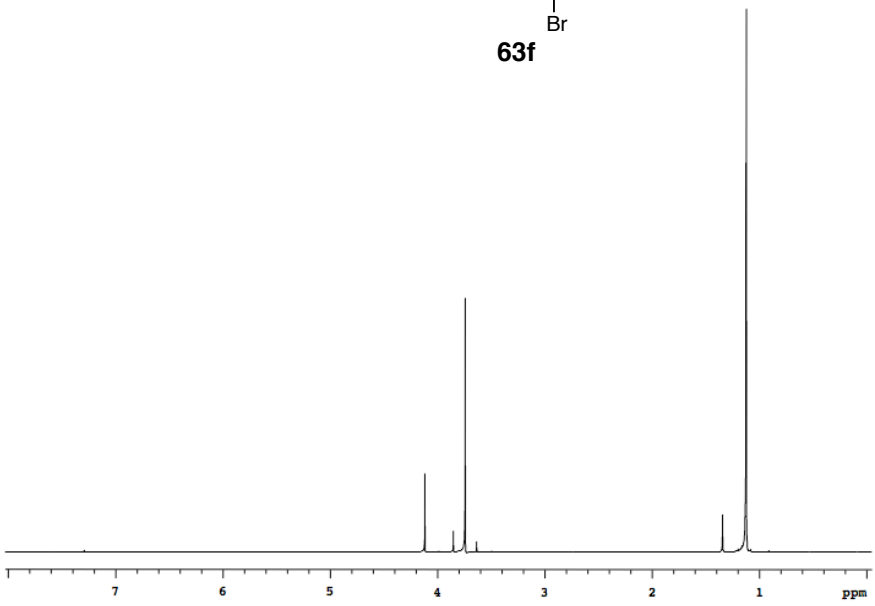
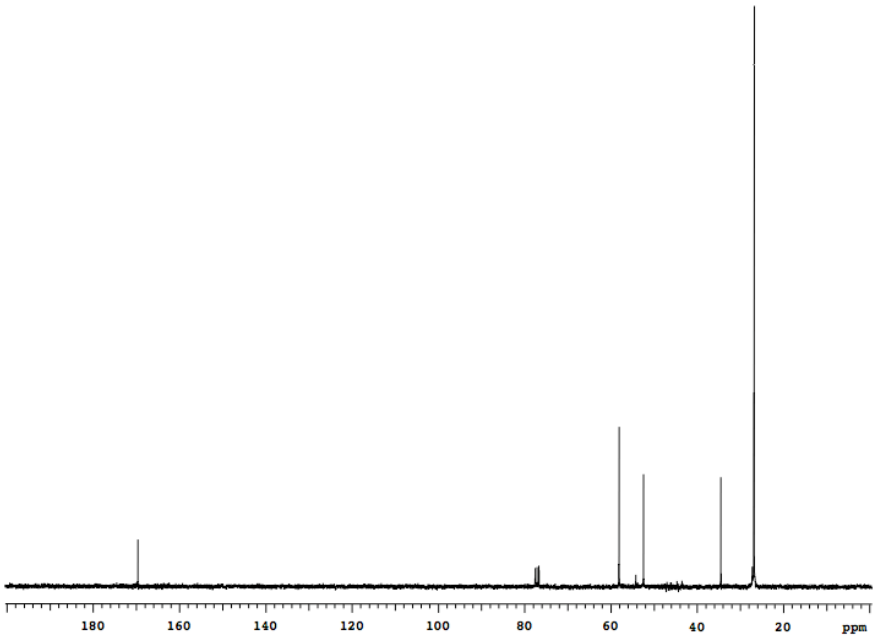
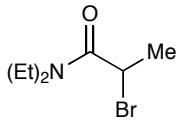


^{13}C NMR (75 MHz) in $CDCl_3$



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



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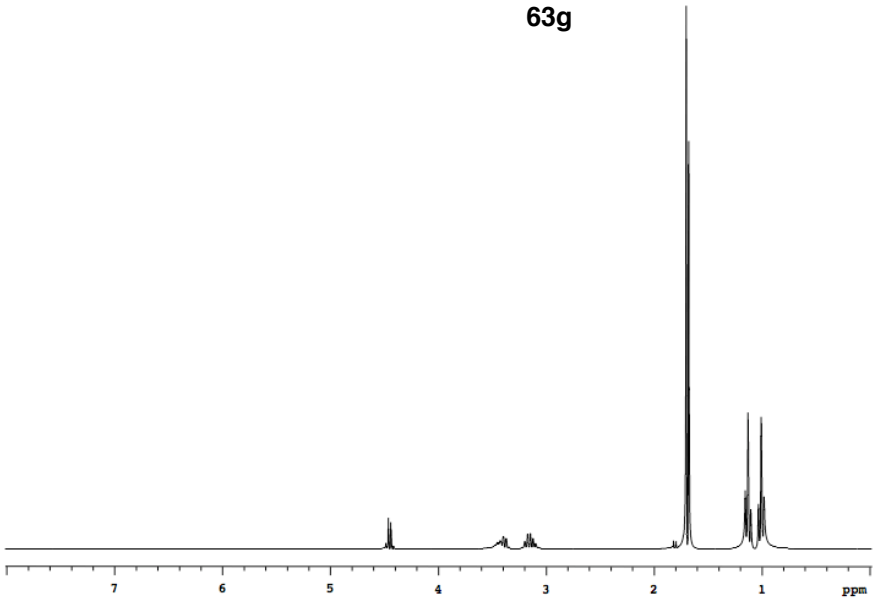
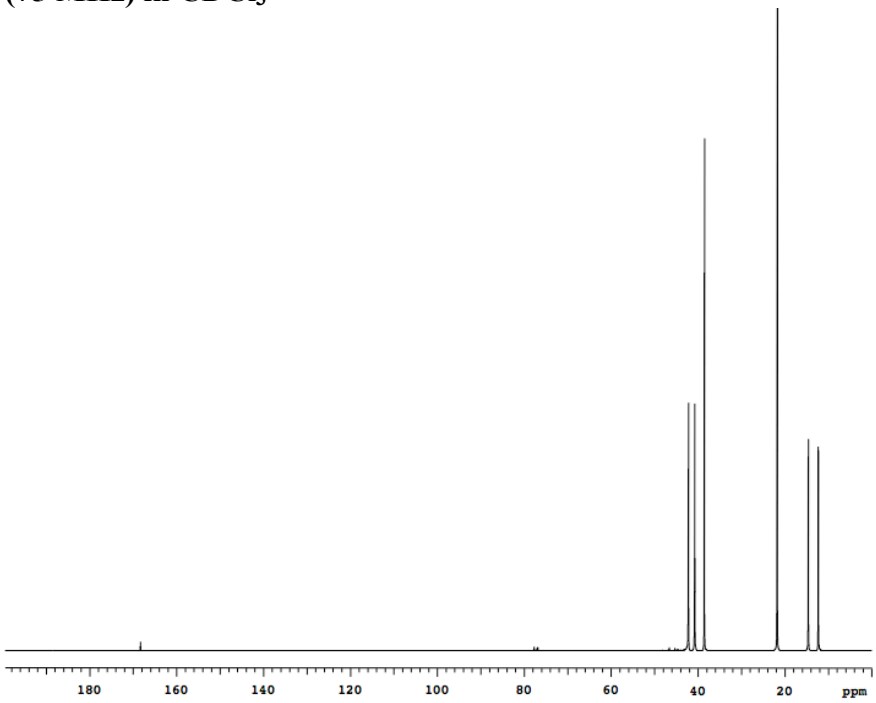


^{13}C NMR (75 MHz) in $CDCl_3$



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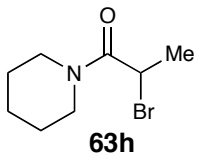

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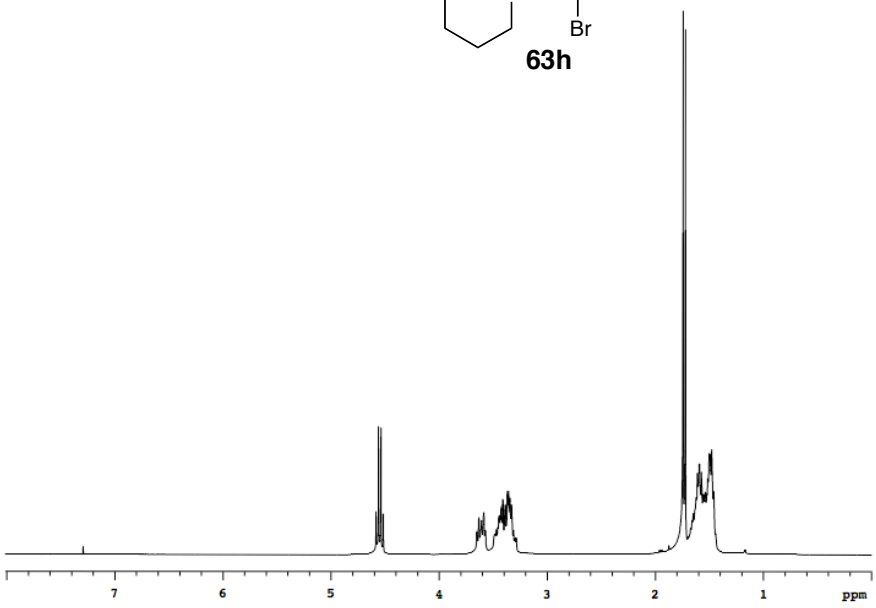

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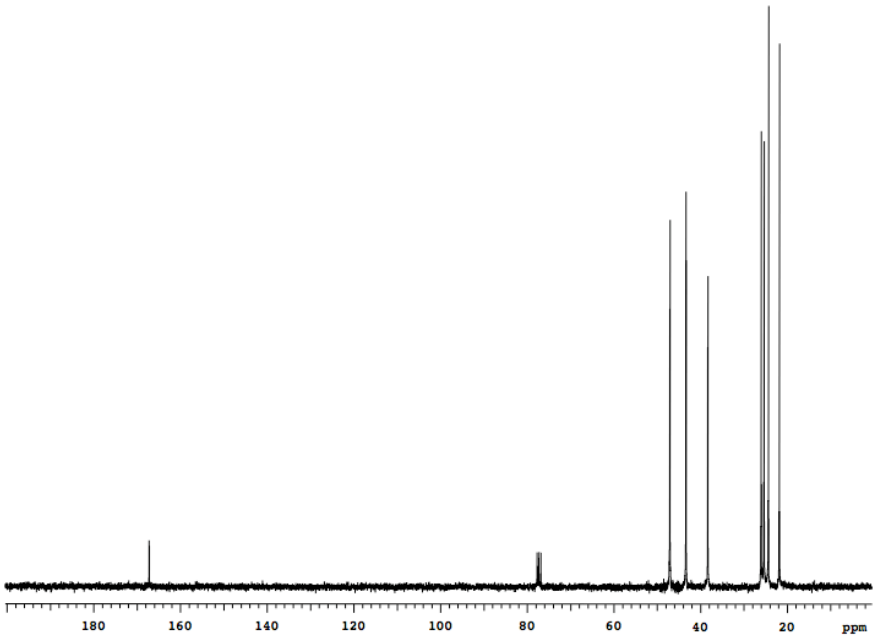

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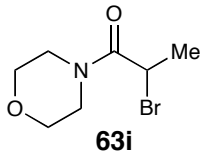

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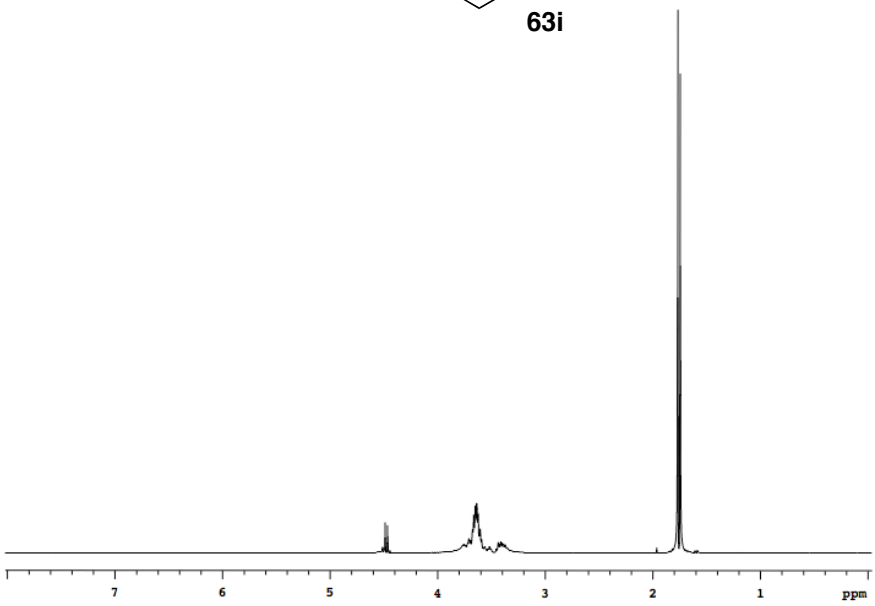
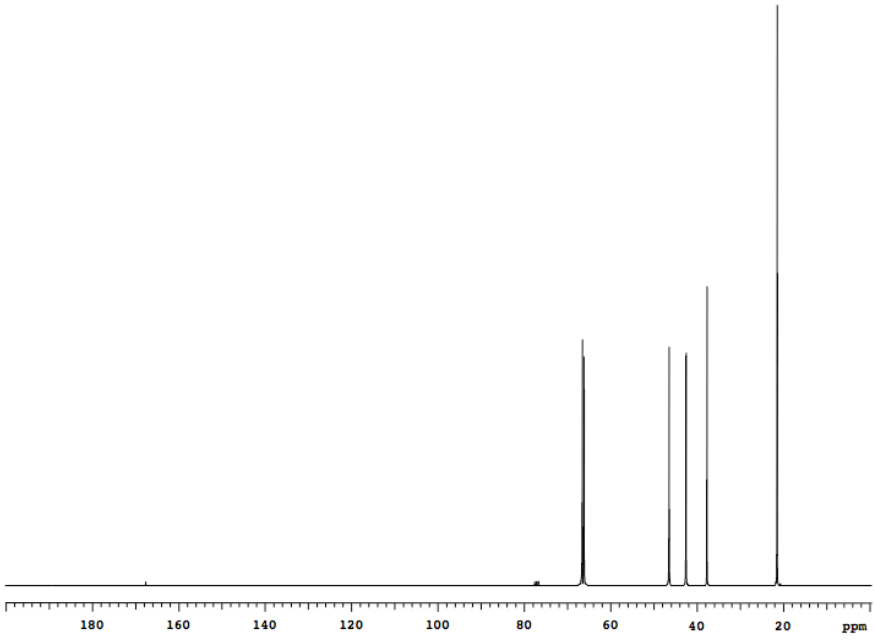


^{13}C NMR (75 MHz) in $CDCl_3$



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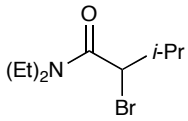

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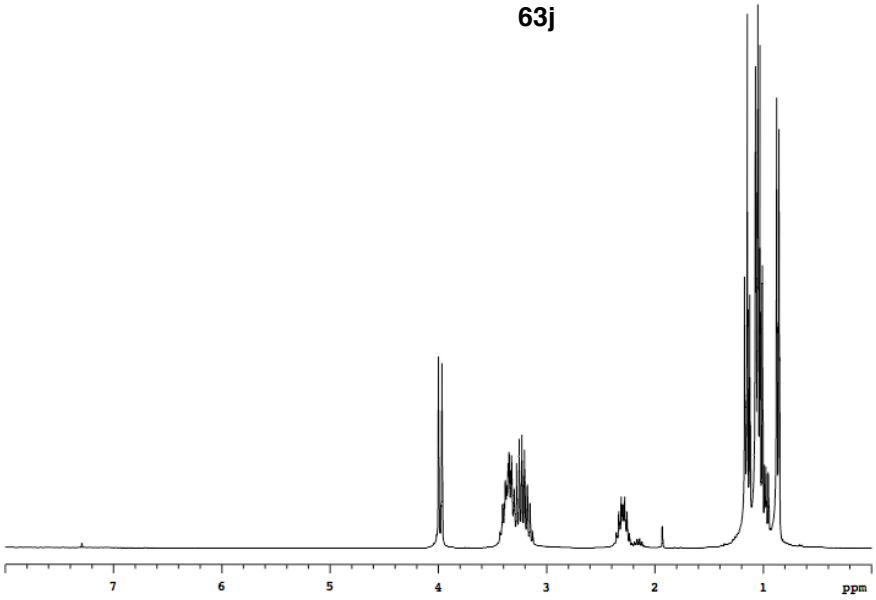
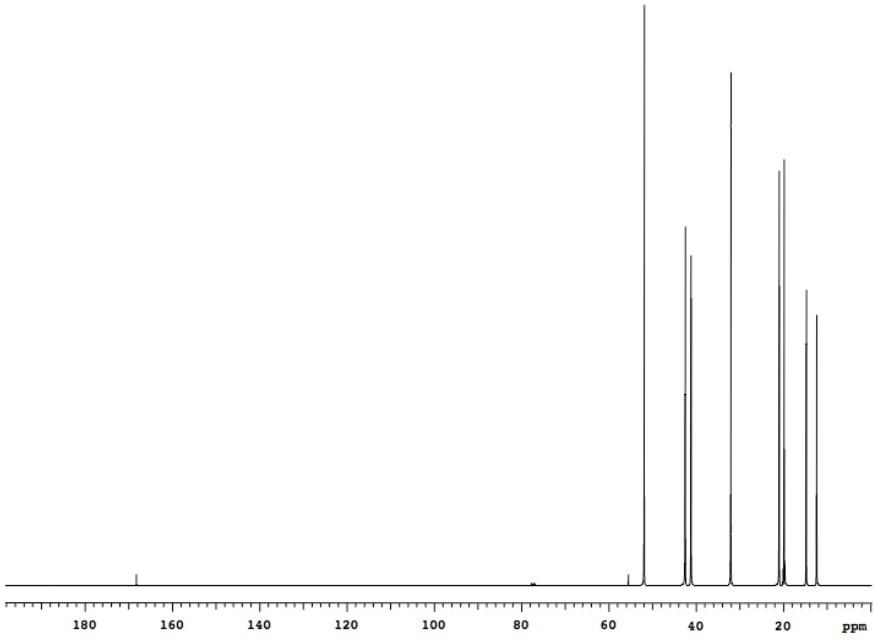
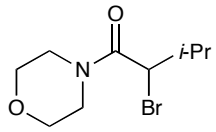


^{13}C NMR (75 MHz) in $CDCl_3$



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



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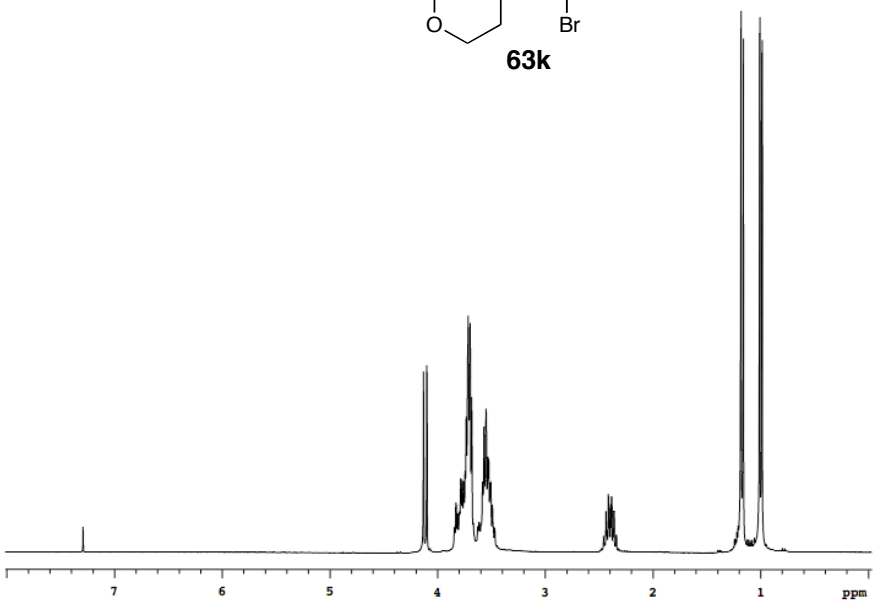
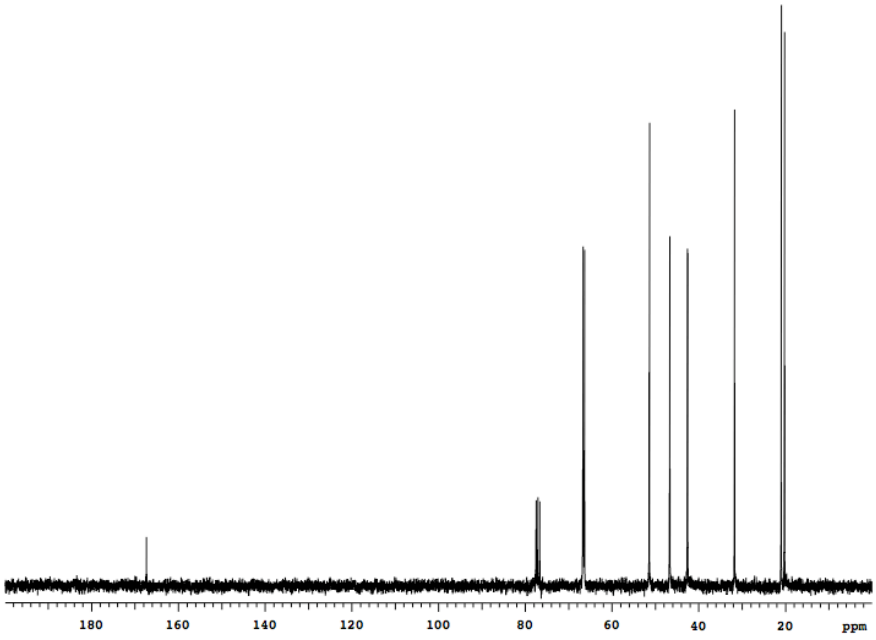
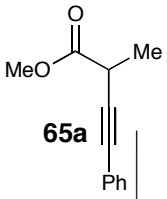
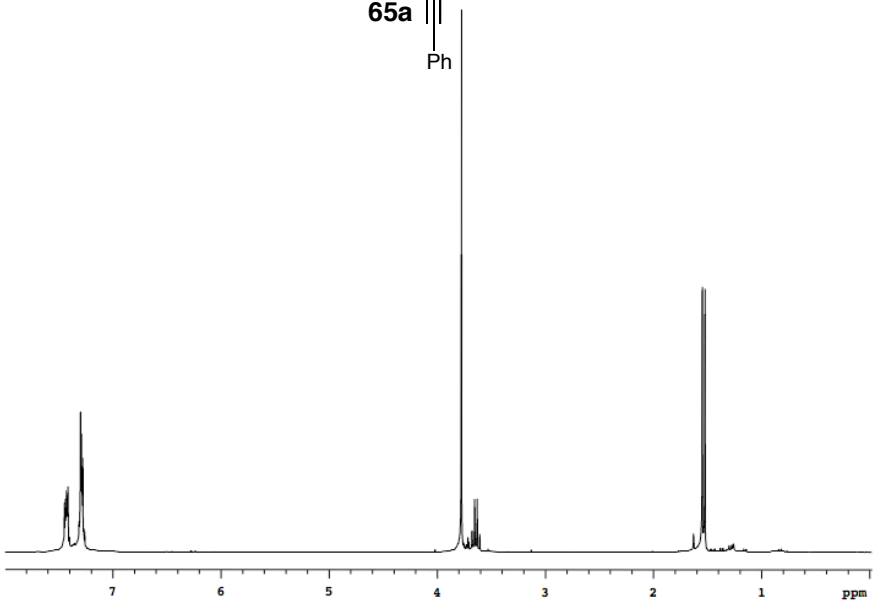


^{13}C NMR (75 MHz) in $CDCl_3$

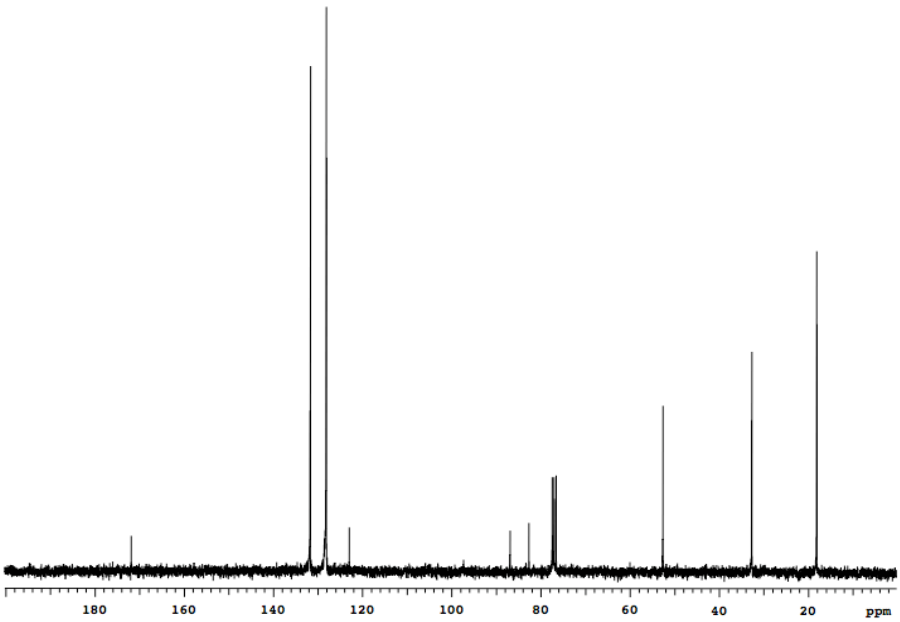


^{1}H NMR (300 MHz) in $CDCl_3$

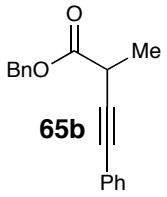




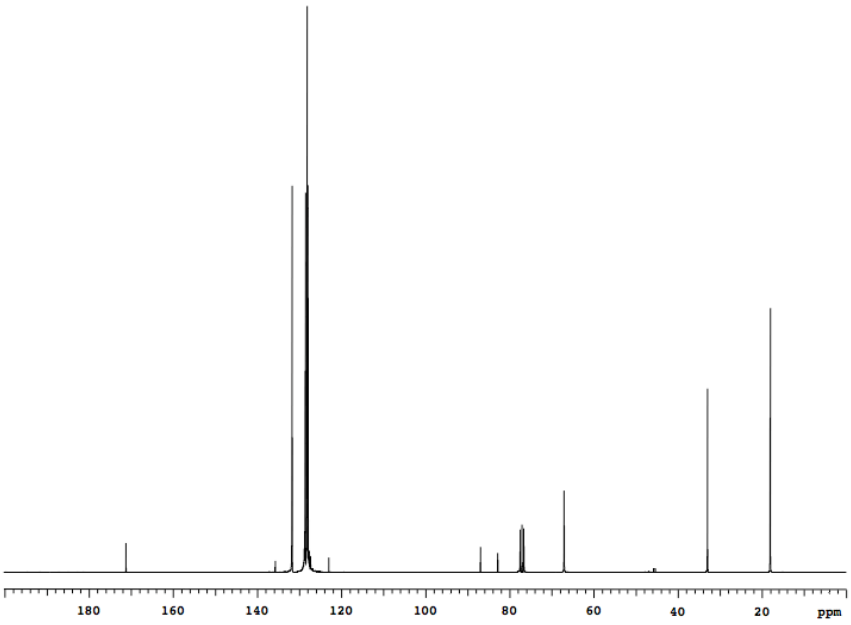
^{13}C NMR (75 MHz) in $CDCl_3$



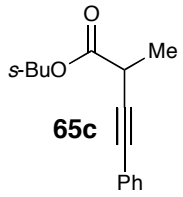
^{1}H NMR (300 MHz) in $CDCl_3$



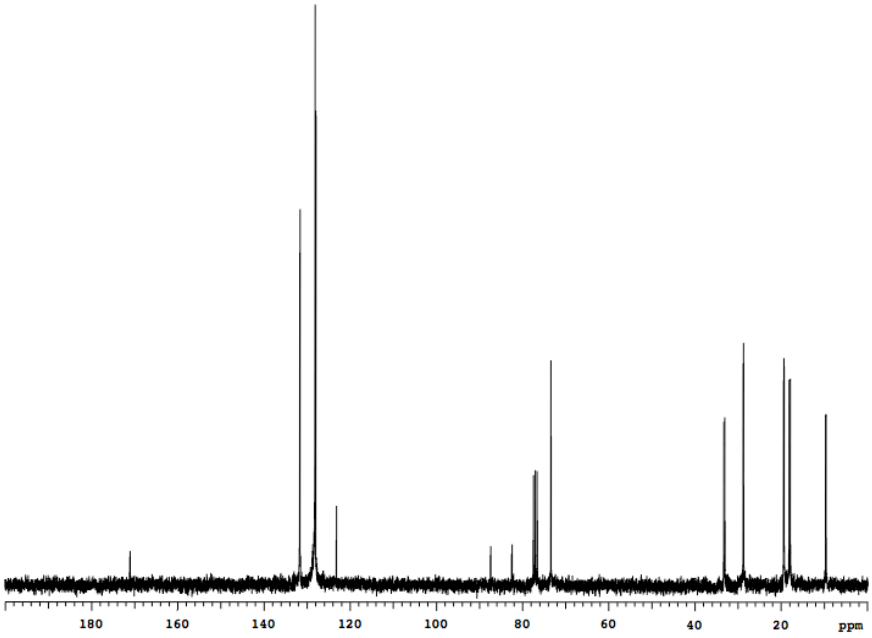
^{13}C NMR (75 MHz) in $CDCl_3$



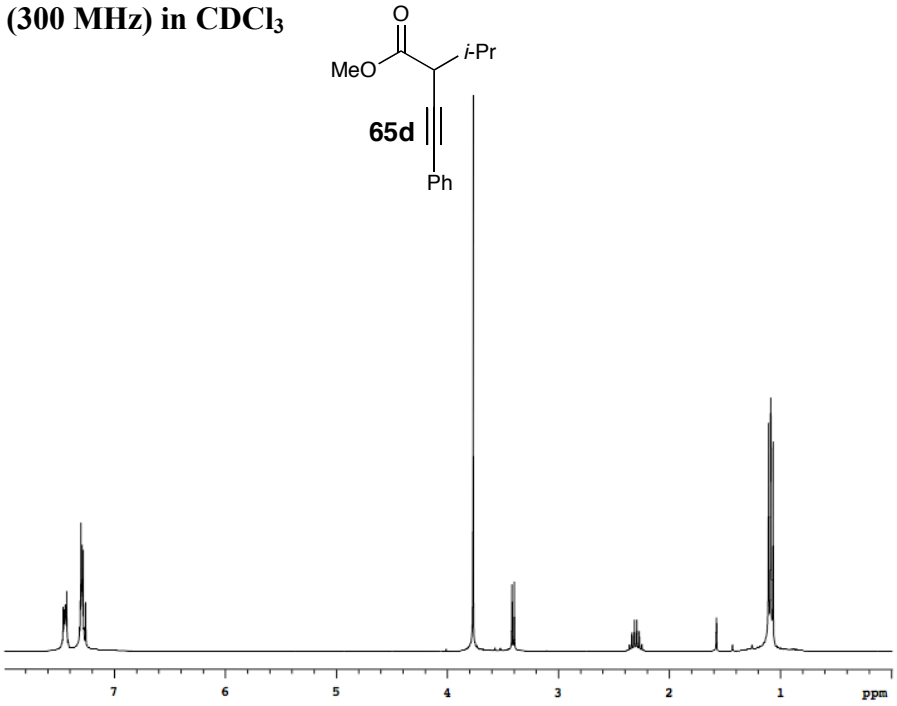
^{1}H NMR (300 MHz) in $CDCl_3$



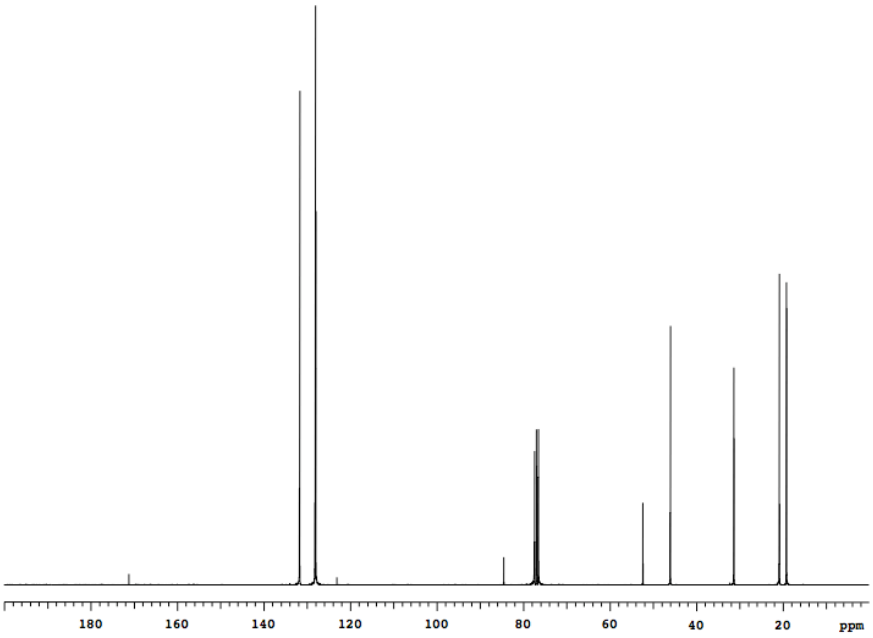
^{13}C NMR (75 MHz) in $CDCl_3$



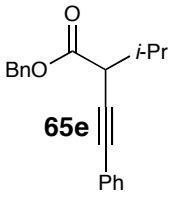
^{1}H NMR (300 MHz) in $CDCl_3$



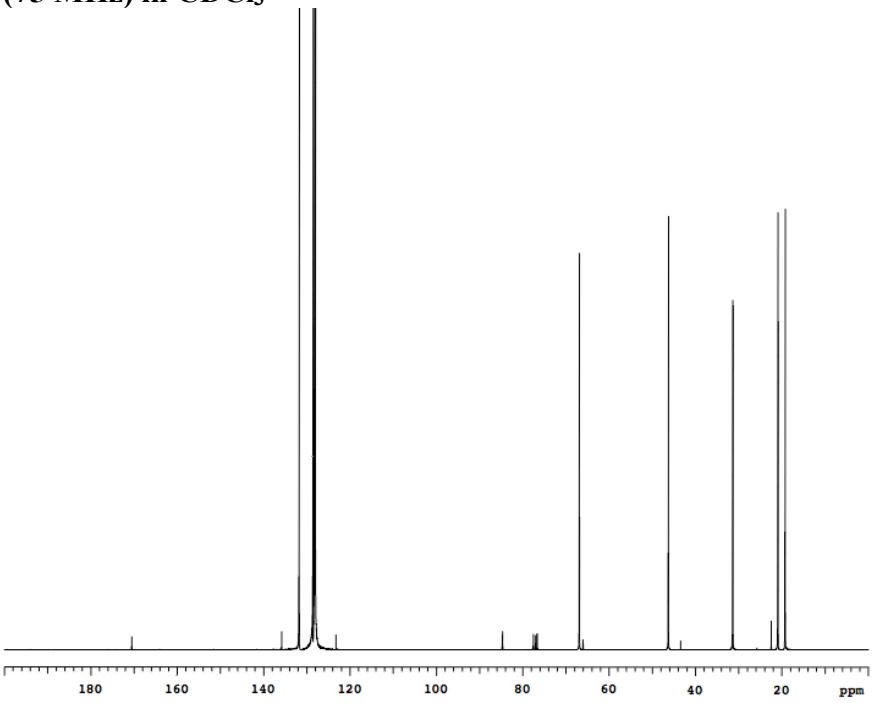
^{13}C NMR (75 MHz) in $CDCl_3$



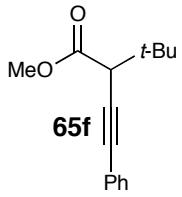
^{1}H NMR (300 MHz) in $CDCl_3$

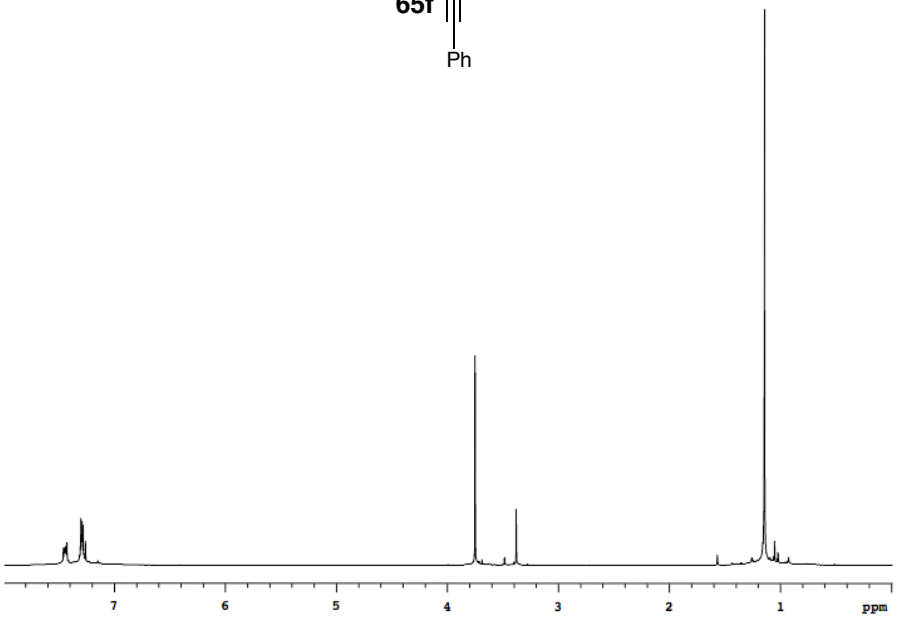


^{13}C NMR (75 MHz) in $CDCl_3$

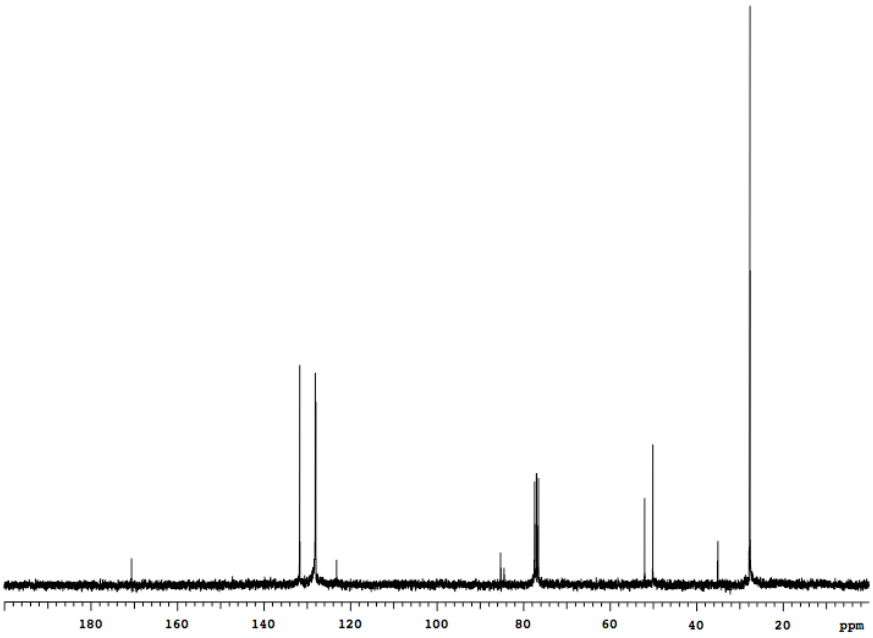


^{1}H NMR (300 MHz) in $CDCl_3$

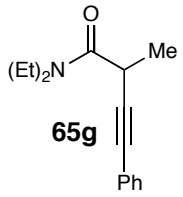




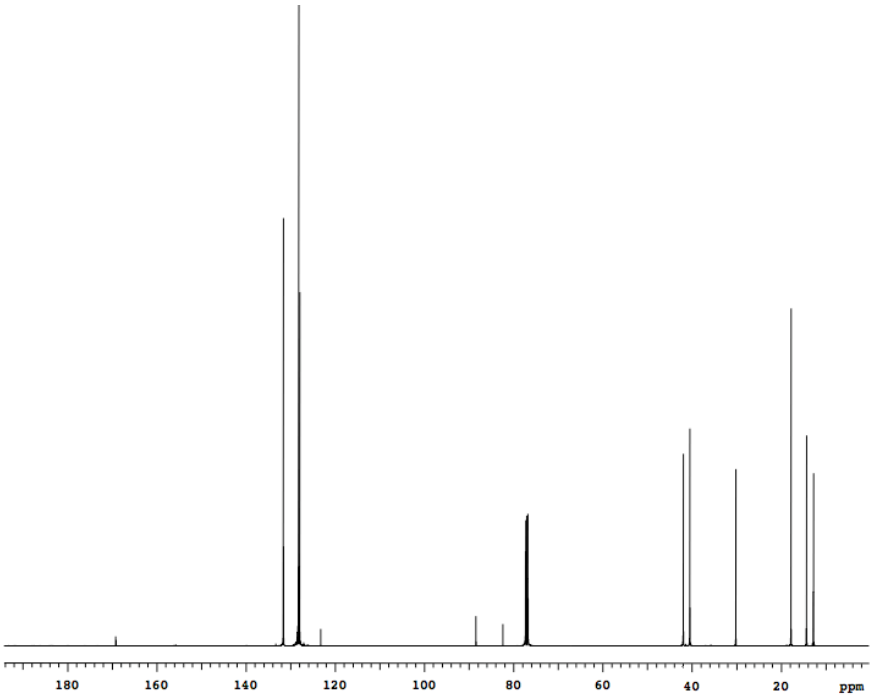
^{13}C NMR (75 MHz) in $CDCl_3$



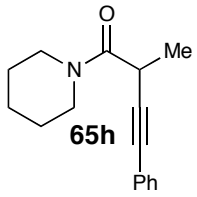
^{1}H NMR (300 MHz) in $CDCl_3$

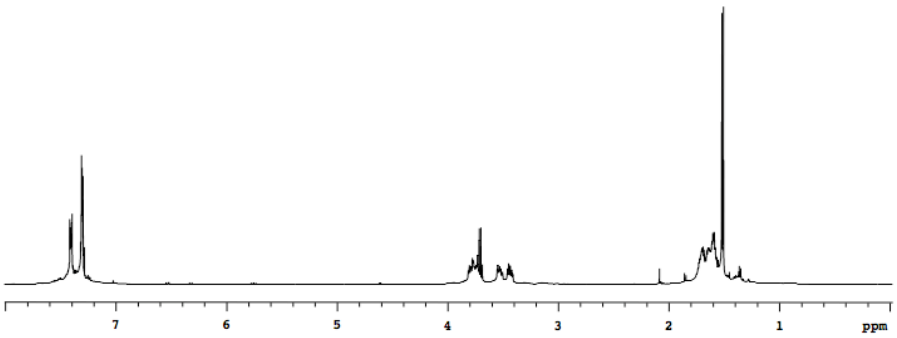


^{13}C NMR (75 MHz) in $CDCl_3$

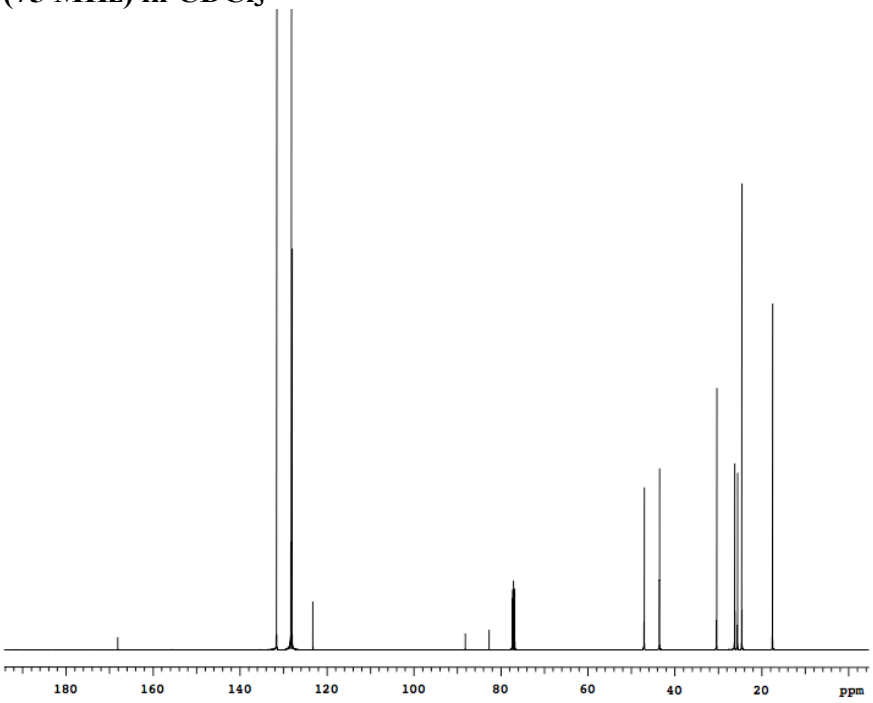


^{1}H NMR (300 MHz) in $CDCl_3$

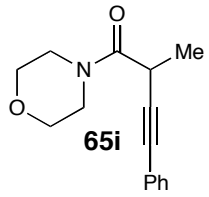




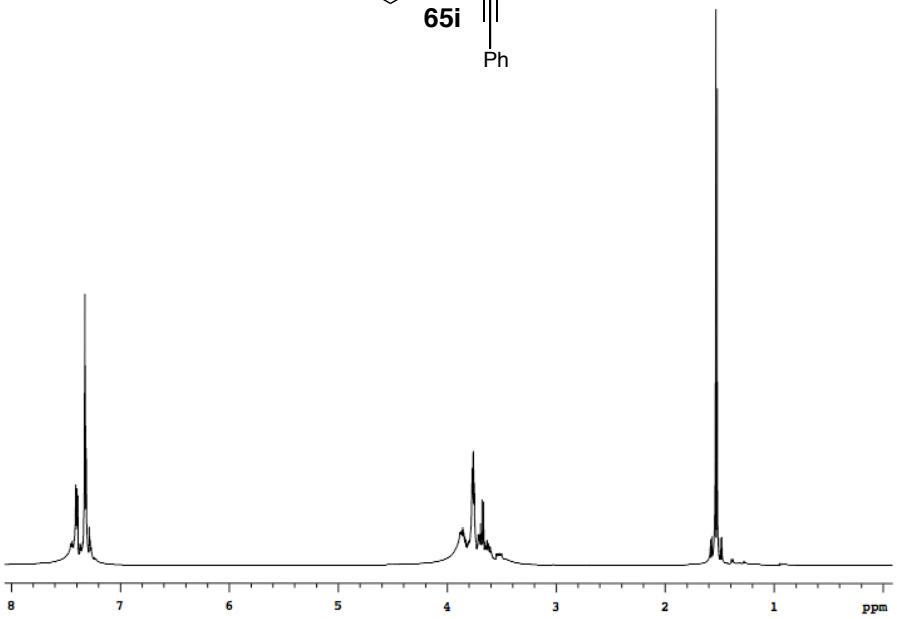
^{13}C NMR (75 MHz) in $CDCl_3$



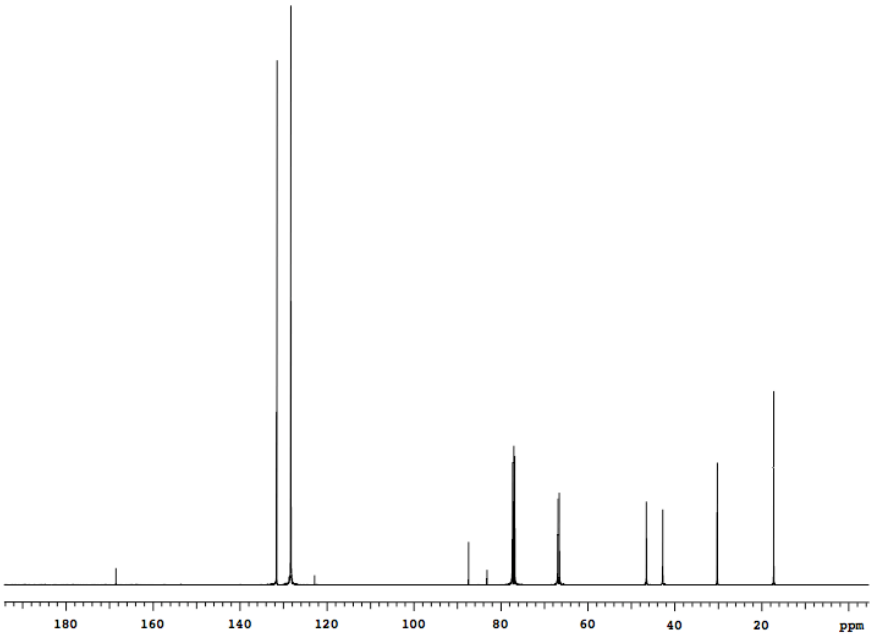
^{1}H NMR (300 MHz) in $CDCl_3$



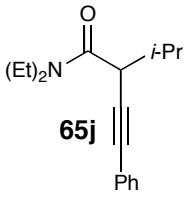
65i



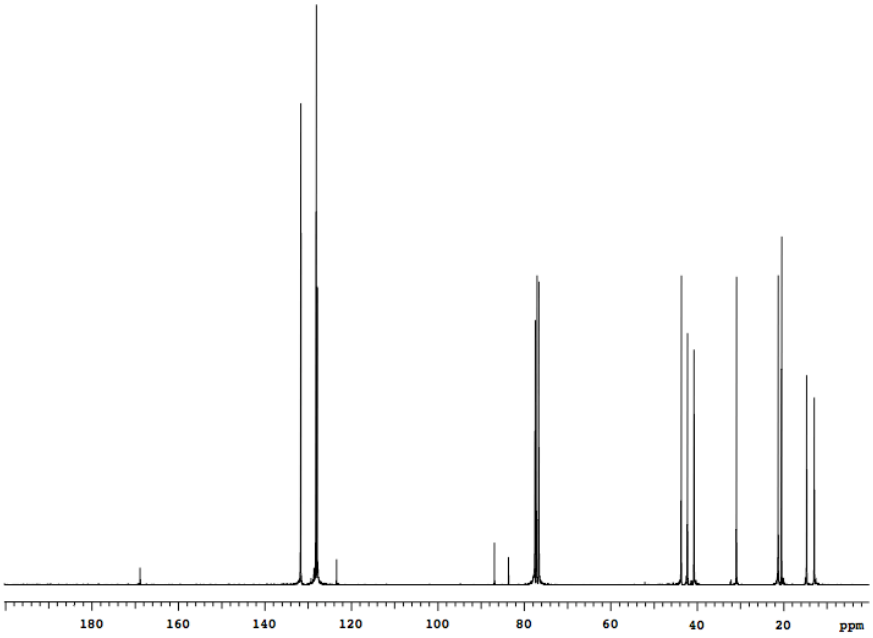
^{13}C NMR (75 MHz) in $CDCl_3$



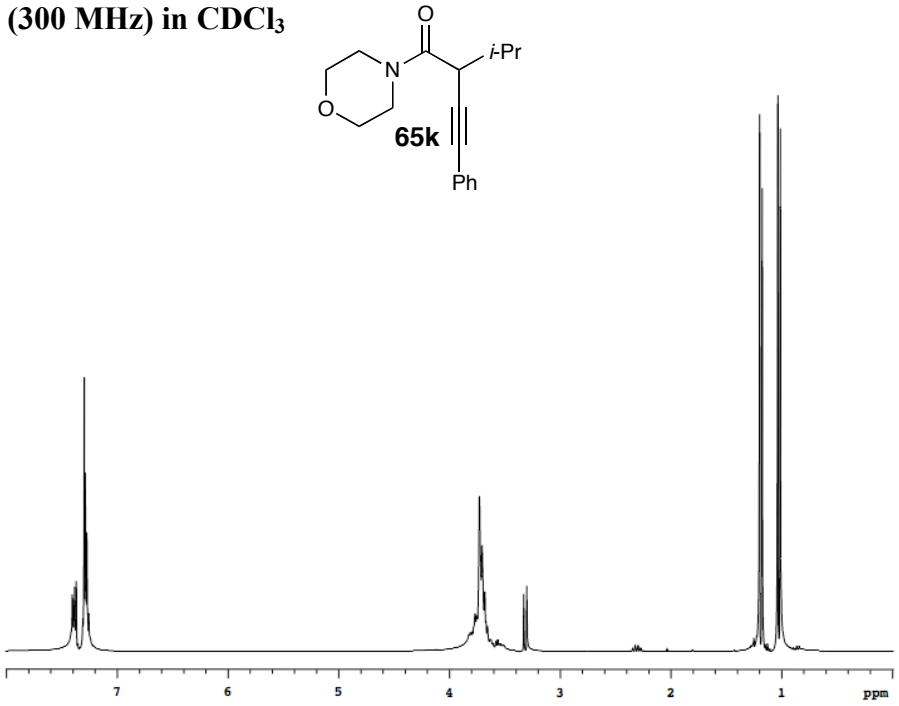
^{1}H NMR (300 MHz) in $CDCl_3$



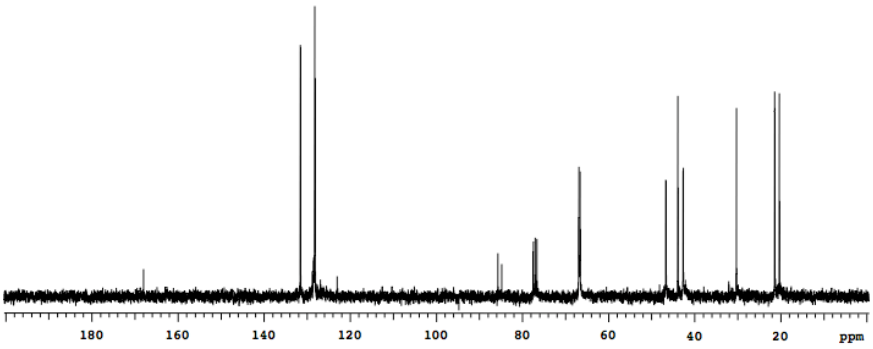
^{13}C NMR (75 MHz) in $CDCl_3$



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



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



APPENDIX II

X-RAY STRUCTURE OF 65k

X-RAY STRUCTURE OF 65k

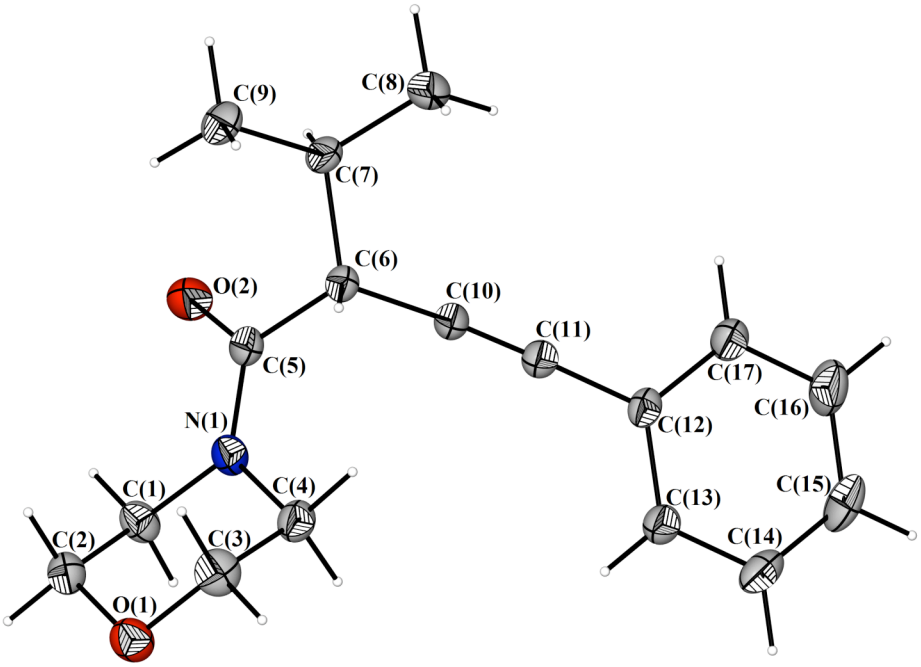


Table 1. Crystal data and structure refinement for compound 65k.

Identification code	brcb190m	
Empirical formula	C17 H21 N O2	
Formula weight	271.35	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.324(8) Å	α= 89.195(19)°.
	b = 10.365(15) Å	β= 84.673(18)°.
	c = 14.32(2) Å	γ = 76.599(17)°.
Volume	765.3(19) $Å^3$	
Z	2	
Density (calculated)	1.178 Mg/m^3	
Absorption coefficient	0.077 mm^{-1}	
F(000)	292	
Crystal size	0.60 x 0.46 x 0.38 mm^3	
Theta range for data collection	1.43 to 27.47°.	
Index ranges	-6<=h<=6, -13<=k<=13, -18<=l<=18	
Reflections collected	7615	
Independent reflections	3402 [R(int) = 0.0287]	
Completeness to theta = 27.47°	97.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9715 and 0.9555	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3402 / 30 / 194	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0422, wR2 = 0.1122	
R indices (all data)	R1 = 0.0520, wR2 = 0.1182	
Largest diff. peak and hole	0.251 and -0.257 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound 65k. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	4222(2)	8030(1)	-30(1)	29(1)
C(2)	1800(2)	7901(1)	-471(1)	31(1)
C(3)	1049(3)	6288(1)	627(1)	35(1)
C(4)	3449(2)	6358(1)	1106(1)	29(1)
C(5)	4273(2)	8517(1)	1641(1)	28(1)
C(6)	3815(3)	8038(1)	2679(1)	23(1)
C(7)	3181(3)	9236(1)	3361(1)	26(1)
C(8)	3359(3)	8790(2)	4381(1)	35(1)
C(9)	448(3)	10065(2)	3230(1)	33(1)
C(6A)	4658(12)	8398(9)	2650(5)	23(1)
C(7A)	1965(12)	8482(7)	3183(4)	26(1)
C(8A)	2123(18)	8471(9)	4244(4)	35(1)
C(9A)	75(15)	9740(8)	2877(7)	33(1)
C(10)	6181(2)	7021(1)	2870(1)	28(1)
C(11)	7976(2)	6115(1)	3003(1)	26(1)
C(12)	10120(2)	5007(1)	3135(1)	24(1)
C(13)	10684(2)	3913(1)	2520(1)	29(1)
C(14)	12804(3)	2865(1)	2631(1)	35(1)
C(15)	14351(3)	2895(1)	3351(1)	43(1)
C(16)	13805(3)	3967(1)	3966(1)	45(1)
C(17)	11705(2)	5023(1)	3861(1)	32(1)
N(1)	3970(2)	7679(1)	966(1)	27(1)
O(1)	1345(2)	6596(1)	-350(1)	34(1)
O(2)	4828(2)	9585(1)	1456(1)	39(1)

Table 3. Bond lengths [Å] and angles [°] for compound 65k.

C(1)-N(1)	1.470(2)
C(1)-C(2)	1.520(2)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-O(1)	1.434(2)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-O(1)	1.434(2)
C(3)-C(4)	1.522(2)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-N(1)	1.466(2)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-O(2)	1.230(2)
C(5)-N(1)	1.353(2)
C(5)-C(6A)	1.478(8)
C(5)-C(6)	1.575(3)
C(6)-C(10)	1.487(2)
C(6)-C(7)	1.546(2)
C(6)-H(6A)	1.0000
C(7)-C(8)	1.530(3)
C(7)-C(9)	1.535(2)
C(7)-H(7A)	1.0000
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(6A)-C(10)	1.513(8)
C(6A)-C(7A)	1.545(5)

C(6A)-H(6AA)	1.0000
C(7A)-C(8A)	1.529(5)
C(7A)-C(9A)	1.537(5)
C(7A)-H(7AA)	1.0000
C(8A)-H(8AA)	0.9800
C(8A)-H(8AB)	0.9800
C(8A)-H(8AC)	0.9800
C(9A)-H(9AA)	0.9800
C(9A)-H(9AB)	0.9800
C(9A)-H(9AC)	0.9800
C(10)-C(11)	1.202(2)
C(11)-C(12)	1.444(2)
C(12)-C(17)	1.401(2)
C(12)-C(13)	1.404(2)
C(13)-C(14)	1.393(2)
C(13)-H(13A)	0.9500
C(14)-C(15)	1.384(2)
C(14)-H(14A)	0.9500
C(15)-C(16)	1.386(3)
C(15)-H(15A)	0.9500
C(16)-C(17)	1.389(2)
C(16)-H(16A)	0.9500
C(17)-H(17A)	0.9500

N(1)-C(1)-C(2)	109.04(11)
N(1)-C(1)-H(1A)	109.9
C(2)-C(1)-H(1A)	109.9
N(1)-C(1)-H(1B)	109.9
C(2)-C(1)-H(1B)	109.9
H(1A)-C(1)-H(1B)	108.3
O(1)-C(2)-C(1)	111.53(10)
O(1)-C(2)-H(2A)	109.3
C(1)-C(2)-H(2A)	109.3
O(1)-C(2)-H(2B)	109.3

C(1)-C(2)-H(2B)	109.3
H(2A)-C(2)-H(2B)	108.0
O(1)-C(3)-C(4)	111.31(11)
O(1)-C(3)-H(3A)	109.4
C(4)-C(3)-H(3A)	109.4
O(1)-C(3)-H(3B)	109.4
C(4)-C(3)-H(3B)	109.4
H(3A)-C(3)-H(3B)	108.0
N(1)-C(4)-C(3)	109.19(10)
N(1)-C(4)-H(4A)	109.8
C(3)-C(4)-H(4A)	109.8
N(1)-C(4)-H(4B)	109.8
C(3)-C(4)-H(4B)	109.8
H(4A)-C(4)-H(4B)	108.3
O(2)-C(5)-N(1)	122.30(13)
O(2)-C(5)-C(6A)	101.3(4)
N(1)-C(5)-C(6A)	135.0(4)
O(2)-C(5)-C(6)	122.45(11)
N(1)-C(5)-C(6)	115.24(14)
C(6A)-C(5)-C(6)	24.1(3)
C(10)-C(6)-C(7)	113.72(12)
C(10)-C(6)-C(5)	106.91(11)
C(7)-C(6)-C(5)	110.09(14)
C(10)-C(6)-H(6A)	108.7
C(7)-C(6)-H(6A)	108.7
C(5)-C(6)-H(6A)	108.7
C(8)-C(7)-C(9)	110.26(12)
C(8)-C(7)-C(6)	111.48(14)
C(9)-C(7)-C(6)	108.97(12)
C(8)-C(7)-H(7A)	108.7
C(9)-C(7)-H(7A)	108.7
C(6)-C(7)-H(7A)	108.7
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5

H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(7)-C(9)-H(9A)	109.5
C(7)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(7)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(5)-C(6A)-C(10)	110.7(5)
C(5)-C(6A)-C(7A)	106.9(5)
C(10)-C(6A)-C(7A)	103.7(5)
C(5)-C(6A)-H(6AA)	111.7
C(10)-C(6A)-H(6AA)	111.7
C(7A)-C(6A)-H(6AA)	111.7
C(8A)-C(7A)-C(9A)	111.3(5)
C(8A)-C(7A)-C(6A)	111.0(5)
C(9A)-C(7A)-C(6A)	108.9(5)
C(8A)-C(7A)-H(7AA)	108.5
C(9A)-C(7A)-H(7AA)	108.5
C(6A)-C(7A)-H(7AA)	108.5
C(7A)-C(8A)-H(8AA)	109.5
C(7A)-C(8A)-H(8AB)	109.5
H(8AA)-C(8A)-H(8AB)	109.5
C(7A)-C(8A)-H(8AC)	109.5
H(8AA)-C(8A)-H(8AC)	109.5
H(8AB)-C(8A)-H(8AC)	109.5
C(7A)-C(9A)-H(9AA)	109.5
C(7A)-C(9A)-H(9AB)	109.5
H(9AA)-C(9A)-H(9AB)	109.5
C(7A)-C(9A)-H(9AC)	109.5
H(9AA)-C(9A)-H(9AC)	109.5
H(9AB)-C(9A)-H(9AC)	109.5

C(11)-C(10)-C(6)	174.04(13)
C(11)-C(10)-C(6A)	160.7(3)
C(6)-C(10)-C(6A)	24.8(3)
C(10)-C(11)-C(12)	178.22(12)
C(17)-C(12)-C(13)	119.16(12)
C(17)-C(12)-C(11)	120.60(12)
C(13)-C(12)-C(11)	120.21(12)
C(14)-C(13)-C(12)	120.11(13)
C(14)-C(13)-H(13A)	119.9
C(12)-C(13)-H(13A)	119.9
C(15)-C(14)-C(13)	120.05(13)
C(15)-C(14)-H(14A)	120.0
C(13)-C(14)-H(14A)	120.0
C(14)-C(15)-C(16)	120.32(13)
C(14)-C(15)-H(15A)	119.8
C(16)-C(15)-H(15A)	119.8
C(15)-C(16)-C(17)	120.30(14)
C(15)-C(16)-H(16A)	119.8
C(17)-C(16)-H(16A)	119.8
C(16)-C(17)-C(12)	120.06(13)
C(16)-C(17)-H(17A)	120.0
C(12)-C(17)-H(17A)	120.0
C(5)-N(1)-C(4)	126.66(12)
C(5)-N(1)-C(1)	120.93(13)
C(4)-N(1)-C(1)	112.39(9)
C(3)-O(1)-C(2)	110.46(9)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for compound 65k. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	34(1)	33(1)	23(1)	4(1)	-3(1)	-12(1)
C(2)	34(1)	29(1)	29(1)	3(1)	-7(1)	-6(1)
C(3)	34(1)	36(1)	36(1)	3(1)	-1(1)	-13(1)
C(4)	31(1)	25(1)	28(1)	4(1)	0(1)	-4(1)
C(5)	28(1)	26(1)	27(1)	0(1)	-6(1)	2(1)
C(6)	22(1)	21(1)	24(1)	1(1)	-4(1)	-3(1)
C(7)	24(1)	22(1)	29(1)	-2(1)	-4(1)	0(1)
C(8)	40(1)	34(1)	27(1)	-5(1)	-4(1)	1(1)
C(9)	26(1)	30(1)	38(1)	-3(1)	-3(1)	5(1)
C(6A)	22(1)	21(1)	24(1)	1(1)	-4(1)	-3(1)
C(7A)	24(1)	22(1)	29(1)	-2(1)	-4(1)	0(1)
C(8A)	40(1)	34(1)	27(1)	-5(1)	-4(1)	1(1)
C(9A)	26(1)	30(1)	38(1)	-3(1)	-3(1)	5(1)
C(10)	33(1)	25(1)	23(1)	0(1)	-4(1)	2(1)
C(11)	28(1)	24(1)	24(1)	1(1)	-2(1)	-3(1)
C(12)	24(1)	21(1)	26(1)	4(1)	0(1)	-3(1)
C(13)	34(1)	24(1)	26(1)	2(1)	-2(1)	-4(1)
C(14)	40(1)	21(1)	39(1)	1(1)	8(1)	-1(1)
C(15)	28(1)	30(1)	65(1)	8(1)	-6(1)	6(1)
C(16)	41(1)	35(1)	61(1)	7(1)	-26(1)	-3(1)
C(17)	37(1)	24(1)	36(1)	1(1)	-11(1)	-4(1)
N(1)	30(1)	28(1)	23(1)	4(1)	-4(1)	-7(1)
O(1)	38(1)	34(1)	32(1)	1(1)	-8(1)	-13(1)
O(2)	51(1)	32(1)	36(1)	-1(1)	-10(1)	-11(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound 65k.

	x	y	z	U(eq)
H(1A)	5769	7432	-356	35
H(1B)	4437	8952	-93	35
H(2A)	285	8560	-181	37
H(2B)	1995	8097	-1149	37
H(3A)	735	5386	698	41
H(3B)	-477	6922	935	41
H(4A)	3165	6187	1786	35
H(4B)	4954	5674	838	35
H(6A)	2307	7610	2722	27
H(7A)	4455	9797	3204	31
H(8A)	2956	9570	4795	53
H(8B)	5118	8274	4458	53
H(8C)	2116	8240	4544	53
H(9A)	34	10829	3659	50
H(9B)	-815	9518	3367	50
H(9C)	380	10376	2582	50
H(6AA)	5489	9100	2865	27
H(7AA)	1325	7692	3007	31
H(8AA)	395	8523	4566	53
H(8AB)	2771	9233	4427	53
H(8AC)	3305	7649	4420	53
H(9AA)	-1639	9802	3213	50
H(9AB)	-53	9699	2200	50
H(9AC)	713	10521	3024	50
H(13A)	9617	3889	2027	34
H(14A)	13187	2129	2212	42
H(15A)	15795	2179	3425	52
H(16A)	14872	3979	4460	54
H(17A)	11342	5756	4283	39

VITA

Name Jun Yong Kang

Education B.S., Food Science and Technology, Konyang University, 1997

M.S., Biochemistry, San Francisco State University, 2005

M.S., Chemistry, Texas A&M University, 2008

Ph.D., Chemistry, Texas A&M University, 2011

Contact Information Jun Yong Kang

c/o Rich Carter

Department of Chemistry, Oregon State University

153 Gilbert Hall Corvallis, Oregon 97331-4003