PALLADIUM-CATALYZED REACTIONS OF UNACTIVATED ALKYL ELECTROPHILES

Kayla Sue Bloome

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Approved by:

Erik J. Alexanian

Albert A. Bowers

Jeffrey S. Johnson

Alexander J. M. Miller

David A. Nicewicz

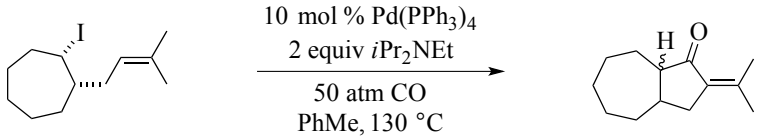
ABSTRACT

KAYLA SUE BLOOME: Palladium-Catalyzed Reactions of Unactivated Alkyl Halides
(Under the direction of Erik J. Alexanian)

I. Palladium-Catalyzed Reactions of Unactivated Alkyl Electrophiles

An overview of palladium-catalyzed reactions with sp^3-hybridized electrophiles is presented. Cross-coupling reactions and carbonylations with alkyl halides and sulfonates are discussed in detail.

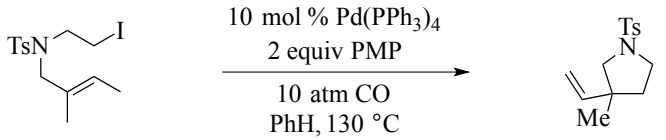
II. Carbonylative Alkyl-Heck Type Cyclization of Alkyl Iodides



82% yield
1.6:1 dr

A palladium-catalyzed carbonylative Heck-type cyclization of alkyl halides is described. Treatment of a range of primary and secondary alkyl iodides with catalytic palladium(0) under CO pressure forms a variety of synthetically versatile enone products. The reactivity described represents a rare example of a palladium-catalyzed Heck-type cyclization involving unactivated alkyl halides with β-hydrogens. Alkene substitution is well tolerated, and mono- and bicyclic carbocycles may be easily accessed.

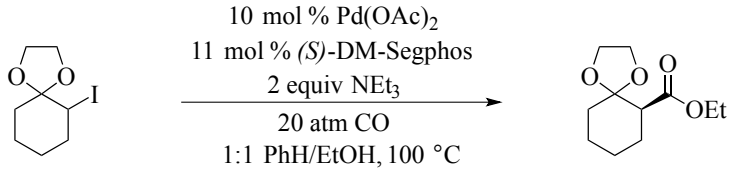
III. Alkyl-Heck Type Cyclizations of Alkyl Halides



70% yield

A palladium-catalyzed Heck-type reaction of unactivated alkyl iodides is described. This process displays broad substrate scope with respect to both alkene and alkyl iodide components and provides efficient access to a variety of cyclic products. The reaction is proposed to proceed via a hybrid organometallic-radical mechanism, facilitating the Heck-type process with alkyl halide coupling partners.

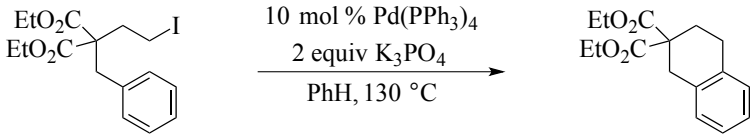
IV. Palladium-Catalyzed Enantioselective Carbonylation of Alkyl Iodides



50% yield
21% ee

A palladium-catalyzed enantioselective carbonylation of unactivated secondary alkyl iodides is reported. Preliminary results serve as proof-of-principle that hybrid radical-organometallic reactivity enables the stereoselective synthesis of α-chiral carbonyl compounds.

V. Palladium-Catalyzed Ring Forming C-H Alkylations of Aromatic Systems



73%

A palladium-catalyzed intramolecular C-H alkylation of heteroarenes and arenes with unactivated alkyl halides is described. Preliminary results suggest this process is applicable to primary alkyl bromides and iodides and tolerates electron-rich and –poor aromatic systems. Our goal to be able to readily synthesize medium-ring fused aromatic structures so they can be readily applied to a variety of biologically active compounds.

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To my parents
for their unwavering love, support, and encouragement

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LIST OF ABBREVIATIONS & SYMBOLS

2D-NMR	two-dimensional nuclear magnetic resonance
9-BBN	9-borabicyclo(3.3.1)nonane
Ac	acetate
Acac	acetylacetone
Ad	adamantyl
Ar	aryl
atm	atmospheres
aq	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	benzyloxycarbonyl
br s	broad singlet
^{t}Bu	*tert*-butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
cat	catalytic amount or catalyst
C-C	carbon-carbon bond
C-H	carbon-hydrogen bond
Chiraphos	Bis(diphenylphosphino)butane
Cl-OMe-BIPHEP	5,5'-Dichloro-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl
^{13}C NMR	carbon nuclear resonance spectroscopy

COSY	correlated spectroscopy
*m*CPBA	*meta*-chloroperoxybenzoic acid
CTAB	hexadecyltrimethylammonium bromide
CTH-BINAM	2,2'-Bis(N-diphenylphosphinoamino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl
CTH-P-Phos	2,2',6,6'-Tetramethoxy-4,4'-bis(diphenylphosphino)-3,3'-bipyridine
C-X	carbon-halide bond
Cy	cyclohexyl
Cyp	cyclopentyl
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIOP	4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane
DLP	dilauroyl peroxide
DMA	dimethylacetamide
DMAP	4-*N,N*-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

DM-Segphos	5,5'-bis[di(3,5-xylyl)phosphino]-4,4'-bi-1,3-benzodioxole
DMSO	dimethylsulfoxide
dppb	1,3-bis(diphenylphosphino)butane
dppe	1,3-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
dt	doublet of triplets
DTMB-Segphos	5,5'-Bis[di(3,5-di-t-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole
EDG	electron donating group
ee	enantiomeric excess
eq	equation
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
FID	flame ionization detector
h	hour
H_8-BINAP	2,2'-Bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1, 1'-binaphthyl

HAS	homolytic aromatic substitution
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HPLC	high performance liquid chromatography
Hz	hertz
IR	infared spectroscopy
J	coupling constant
kcal	kilocalorie
L	ligand
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LRMS	low resolution mass spectroscopy
M	metal or molarity
m	multiplet
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
Monophos	(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)dimethylamine
mp	melting point

Ms	methanesulfonyl
MTBE	methyl *tert*-butyl ether
n	number of atoms or counterions
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NIS	*N*-bromosuccinimide
NMI	1-methylimidazole
NMP	*N*-methylpyrrolidone
NOESY	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
Ph	phenyl
PMP	1,2,2,6,6-pentamethylpiperidine
ppm	parts per million
^{i}Pr	*iso*-propyl
q	quartet
R	substitutent
R_f	retention factor
rac	racemic
rt	room temperature
s	singlet
Segphos	5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
SET	single electron transfer
SIMes	1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene

S_N2	biomolecular nucleophilic substitution
T	temperature
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEMPO	tetramethylpiperidine-*N*-oxide
THF	tetrahydrofuran
TLC	thin layer chromatography
TMU	tetramethylurea
Tol	tolyl
Ts	*para*-toluenesulfonyl
UV	ultraviolet
X	anionic ligand, halide, or substitutent
Xylyl-BINAP	1,1'-Binaphthalene-2,2'-diylbis[bis(3,5-dimethylphenyl)phosphine
Xylyl-OMe-BIPHEP	2,2'-Bis[di((3,5-dimethylphenyl)phosphine]-6,6'-dimethoxy-1,1'-biphenyl
Å	Ångstrom
δ	chemical shift
μL	microliter

CHAPTER 1

Palladium-Catalyzed Reactions of Unactivated Alkyl Electrophiles

1.1 Introduction

Transition metal-catalyzed cross couplings are among the premier methods of carbon-carbon bond forming reactions as is exemplified by their essential role in the synthesis of organic building blocks and pharmaceutical and agrochemical targets.[1-5] Their appeal is chiefly derived from their efficiency and selectivity, tolerance of several functional groups, and mild reaction conditions. One of the most commonly employed metal sources is palladium. Several palladium-catalyzed cross-couplings have been developed to allow concise generation of targets of high importance in both academia and industry (Figure 1-1). This is reflected by the 2010 Nobel Prize in chemistry that was awarded to pioneers in palladium-catalyzed carbon-carbon bond formation.[6]

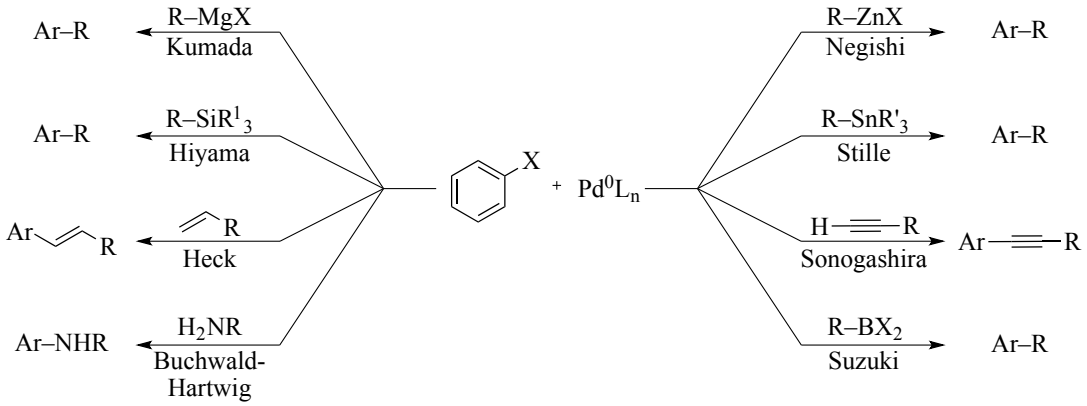


Figure 1-1. Palladium-Catalyzed Cross-Coupling Reactions

The majority of developed reactions for palladium-catalyzed cross-couplings involve the use of sp^2-hybridized electrophiles.[7-10] In contrast, examples employing sp^3-hybridized electrophiles are more scarce due to the synthetic challenges they present, which includes slow oxidative addition to the metal species (Figure 1-2).[11-13] Furthermore, once generated, the transient alkyl-metal species will readily participate in unproductive side reactions, namely β-hydride elimination (Scheme 1-1).[14-16]

Oxidative addition for aryl and vinyl halides typically proceeds through a three-centered transition state as they cannot react by an S_N2 pathway and are typically too electron rich to react via nucleophilic aromatic substitution (Figure 1-2).[17] The oxidative addition of sp^2-hybridized electrophiles to coordinatively unsaturated palladium(0) occurs by initial coordination of the arene or olefin, followed by insertion of the metal into the carbon-halide bond. Conversely, a S_N2 pathway is believed to be operative for oxidative addition for the majority of alkyl halides.[18] These reactions are accelerated in polar solvents and demonstrate inversion in stereochemistry at the carbon in an appropriately substituted alkyl halide. In the polar mechanism, a pair of electrons from the metal center directly attacks the C-X σ* orbital, generating alkyl palladium species **1.2**. Recombination of the ion pair is accomplished through ligand exchange to furnish alkyl palladium **1.3**.

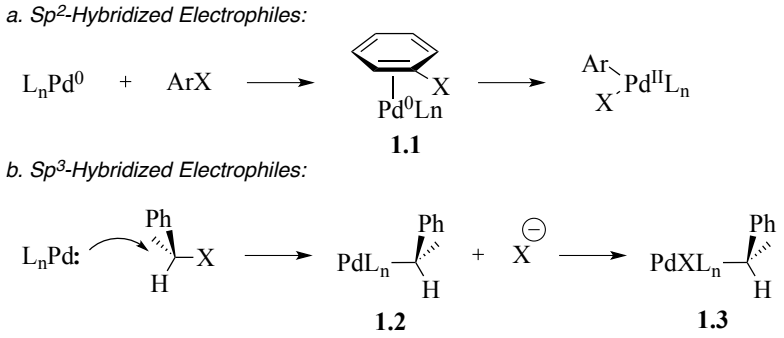
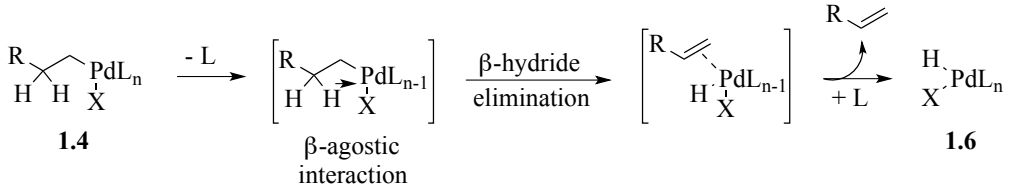


Figure 1-2. Mechanisms for Oxidative Addition of Palladium to sp^2- and sp^3-Hybridized Electrophiles

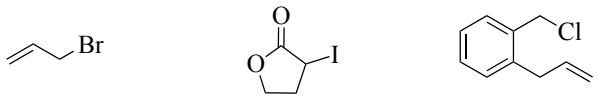
A pathway for β-hydride elimination of palladium-alkyl species **1.4** is depicted in Scheme 1-1. The product of oxidative addition forms the coordinatively unsaturated palladium-alkyl species **1.4**. The vacant site on palladium is filled by an agostic interaction from a C-H bond on the carbon β– to the palladium-metal center, allowing for a co-planar arrangement that results in rapid collapse via β-hydride elimination to form an olefin and palladium-hydride **1.5**.



Scheme 1-1. Mechanism for β-Hydride Elimination of Alkylpalladium Species

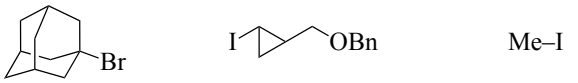
A number of substrate modifications have been used to mitigate the challenges that oxidative addition and β-hydride elimination present. These 'activated' alkyl electrophiles either increase the rate of oxidative addition (Figure 1-3a) or do not have accessible β-hydrogens (Figure 1.3-b).

a. Alkyl Halides that Increase the Rate of Oxidative Addition



ref 1.19 **ref 1.20** **ref 1.21**

b. Alkyl Halides without Accessible β-Hydrogens



ref 1.22 **ref 1.23** **ref 1.24**

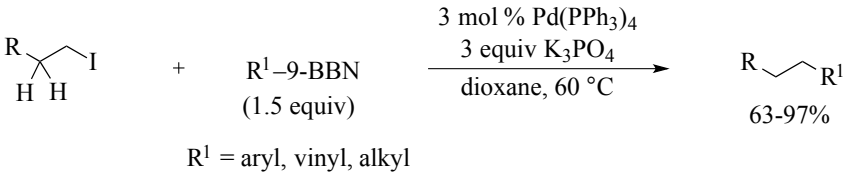
Figure 1-3. Examples of Activated Alkyl Electrophiles

1.2 Palladium-Catalyzed Cross Couplings of sp^3-Hybridized Electrophiles

Within the past ten years, unactivated alkyl electrophiles have been successfully employed in several cross-coupling reactions. General catalytic systems have been developed that prove that the aforementioned synthetic challenges can be overcome, and mechanistic studies have begun to provide insight into these catalyst systems. Examples of these powerful transformations are discussed herein.

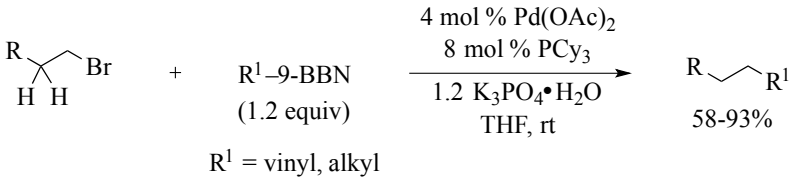
1.2.1. Alkyl Suzuki Cross-Coupling

In 1992, Suzuki reported the first cross-coupling reaction that utilized unactivated alkyl electrophiles (Scheme 1-2).[25] This pioneering methodology coupled aliphatic iodides with organoboranes by using commercially available $Pd(PPh_3)_4$. The reaction proved tolerant of several functional groups, but secondary alkyl iodides were not viable in the reaction. Notably, β-hydride elimination was generally inhibited, and substantial amounts of dehydrohalogentation of the iodide were observed.



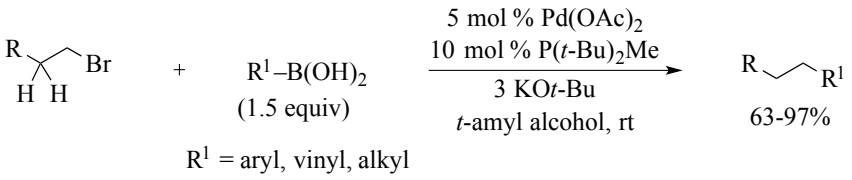
Scheme 1-2. Seminal Cross-Coupling of Unactivated Electrophiles Reported by Suzuki and Co-workers

In 2001, the Fu lab was able to readily employ alkyl bromides in the Suzuki cross-coupling reaction (Scheme 1-3).[26] Their method was reliant upon the use of the tricyclohexylphosphine ligand. The application of trialkylphosphines in couplings of alkyl electrophiles was inspired by previous investigations in the Fu laboratory, which utilized aryl chlorides in palladium-catalyzed cross-coupling reactions.[27] Like alkyl electrophiles, they were considered poor coupling partners due to their reluctance to undergo oxidative addition, but were successfully reacted when bulky, electron-rich phosphines were utilized. Interestingly, trialkylphosphines with similar steric and electronic properties (e.g. $P(^tBu)_3$ and $P(^nBu)_3$) were significantly less effective in the Suzuki reaction of alkyl bromides, generating <2% yield of the desired product and producing increased amounts of β-hydride elimination. In this study, functional group compatibility was exemplified by the use of amines, alkynes, esters, acetals, ethers, cyanides, and alkyl chlorides. Methods have also been reported that allow for the facile use of alkyl chlorides[28] and tosylates[29] in the Suzuki coupling reaction.



Scheme 1-3. Suzuki Coupling of Alkyl Bromides Utilizing Alkyl Phosphines

The Fu group also reported the Suzuki cross-coupling reaction of alkyl bromides and boronic acids (Scheme 1-4).[30] Boronic acids are desirable coupling partners as, unlike their organoborane counterparts, they are air stable. Moreover, several boronic acid derivatives are commercially available. Cross-coupling was realized at room temperature with conditions similar to those developed for coupling with boronates. In this case, KO^{t}Bu was found to be a superior activator when compared to other Lewis bases such as $K_3PO_4 \bullet H_2O$, KF, and NaOMe, and a polar protic solvent was utilized.

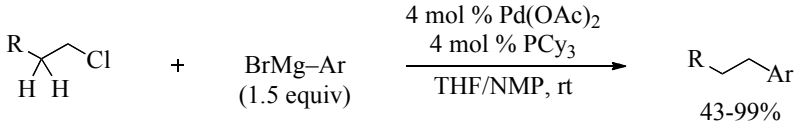


Scheme 1-4. Suzuki Cross-Coupling of Alkyl Bromides and Boronic Acids

1.2.2. Alkyl Kumada Cross-Coupling

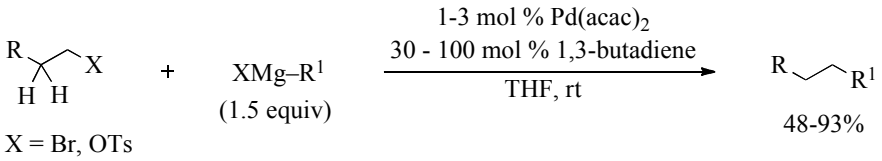
The Kumada coupling, a metal-catalyzed coupling of an electrophile and a grignard reagent, was one of the first reported cross-coupling reactions. In 2002, Beller reported the first palladium-catalyzed coupling of aryl grignards and alkyl chlorides (Scheme 1-5).[31] While Grignard reagent's high nucleophilicity as well as Brønsted

basicity limit the functionality that is compatible with Kumada couplings, cyanides, esters, amides, and acetals proved to be tolerant to the reaction conditions. NMP was found to be crucial to the success of the reaction. It is proposed that NMP weakly coordinates to the palladium, saturating the metal center and therefore out-competing β-hydride elimination of the initially formed alkyl palladium species.



Scheme 1-5. Seminal Palladium-Catalyzed Kumada Coupling Utilizing Alkyl Chlorides

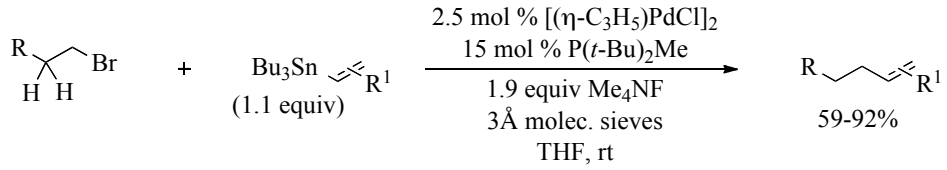
In 2003, Kambe was able to extend the substrate scope to include alkyl bromides and tosylates (Scheme 1-6).[32] Catalytic $Pd(acac)_2$ with 1,3-butadiene as an additive was able to effect coupling with both aryl and alkyl Grignard reagents. Interestingly, the palladium exhibited higher chemoselectivites in favor of the tosylates when compared to bromides and chlorides.



Scheme 1-6. Palladium-Catalyzed Kumada Coupling of Aliphatic Bromides and Tosylates

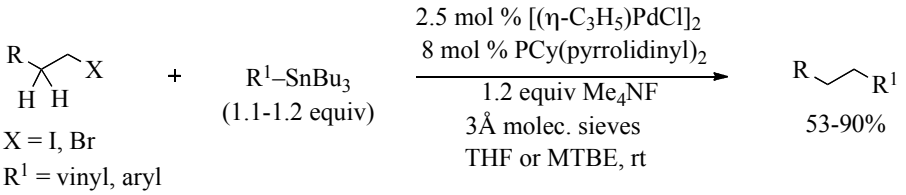
1.2.3. Alkyl Stille Cross-Coupling

The Stille reaction utilizes palladium to cross-coupling organostannanes with electrophiles. The Fu lab described the coupling of alkyl bromides with vinyl stannanes (Scheme 1-7).[33] Similar conditions to their alkyl Suzuki reaction were employed, but required the addition of tetramethylammonium fluoride, which acts as a Lewis base in the activation of the tin towards transmetalation. Additionally, 3 Å molecular sieves were effective in raising the efficiency of the reaction.



Scheme 1-7. Stille Cross-Coupling of Primary Alkyl Halides with Vinyl Tin Reagents

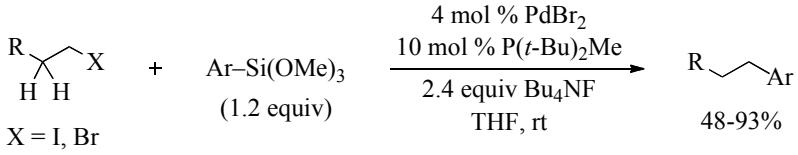
Arylations of β-perfluoroalkyl-substituted alkyl iodides with aryl stannanes have been catalyzed by $PdCl_2(PPh_3)_2$ catalysis; however, high catalyst loadings were required (up to 50 mol %) and moderate yields were observed.[34] The Fu lab reported a method that was generally applicable to unactivated alkyl electrophiles (Scheme 1-8). By varying the ligand in conditions developed for the coupling of alkyl electrophiles with vinyl stannanes, arylation products were efficiently accessed from unactivated alkyl bromides and iodides.[35]



Scheme 1-8. Stille Cross-Couplings of Alkyl Iodides and Bromides with Vinyl and Aryl Stannanes

1.2.4. Alkyl Hiyama Cross-Coupling

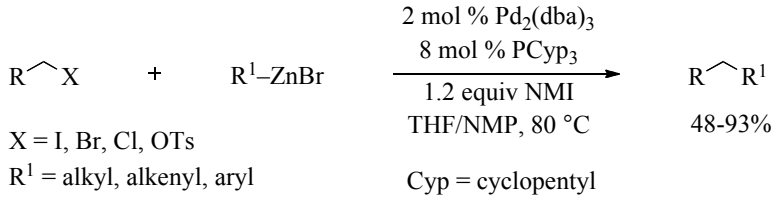
The Hiyama coupling is a palladium-catalyzed cross-coupling of an electrophile to an organosilane. Typically fluoride is added to the reaction, presumably to generate a hypervalent silicate intermediate that is more reactive towards transmetalation than its tetravalent organosilane precursor. Under identical conditions to those previously employed in the coupling of alkyl electrophiles to organostannanes, the Fu group did not observe any conversion with aryl silanes (Scheme 1-9);[36] however, addition of a different fluoride source allowed the reaction to proceed cleanly at room temperature. The reaction proved tolerant of functional groups including esters, cyanides, acetals, and ketones on the alkyl bromide. Electronically varied aryl groups were employed with electronic-deficient aryl silanes providing lower yields.



Scheme 1-9. Hiyama Cross-Coupling of Unactivated Alkyl Haides

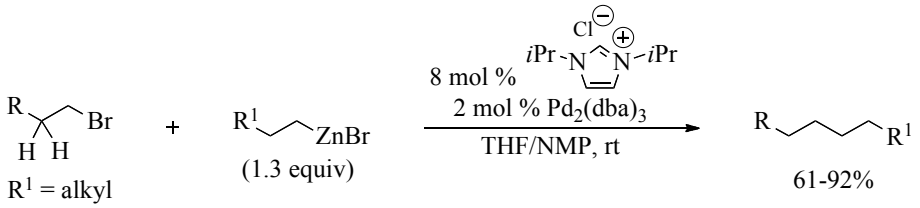
1.2.5. Alkyl Negishi Cross-Coupling

The Negishi cross-coupling utilizes catalytic palladium or nickel to couple an organic halide and an organozinc. The Fu group reported the first example of a palladium-catalyzed Negishi reaction that employed alkyl iodides, bromides, chlorides, and tosylates (Scheme 1-10).[37] In addition to a wide variety of electrophiles, alkene, ether, nitrile, amide, and ester functionalities are compatible with the reaction conditions. The N-methylimidazole (NMI) is proposed to facilitate transmetalation via activation of the organozinc halide.



Scheme 1-10. Negishi Cross-Coupling of Alkyl Electrophiles

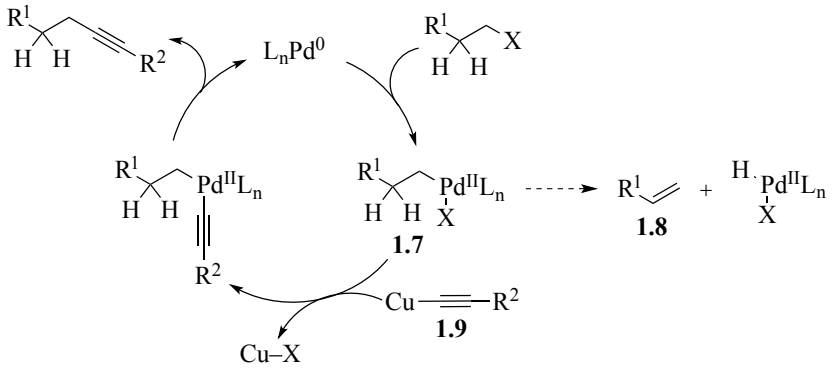
The first Negishi cross-coupling of unactivated alkyl bromides in the presence of a N-heterocyclic carbene (NHC) ligand was reported by the Organ group (Scheme 1-11).[38] NHC ligands have similar σ-donor properties as the trialkylphosphine ligands from which the Fu group has enjoyed a large amount of success.[39,40] By employing a NHC ligand, the reaction did not require the NMI additive or heating. In addition to the mild reaction conditions, the reaction proved tolerant of acetal, ester, amide, alkyne, and nitrile functional groups.



Scheme 1-11. Mild Negishi Cross-Coupling of Alkyl Bromides and Alkyl Zinc Reagents

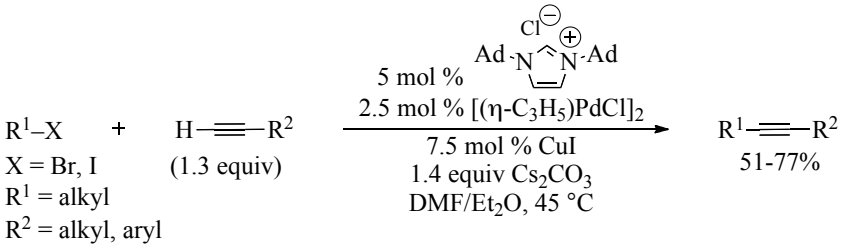
1.2.6. Alkyl Sonogashira Cross-Coupling

The Sonogashira reaction, employs palladium and copper catalysts to facilitate cross-coupling to a terminal alkyne and is proposed to undergo transmetalation with a copper acetylide (Scheme 1-12).[41] Species **1.9** is produced in situ from a low catalyst loading of copper. This is in contrast to the aforementioned cross-coupling reactions, which employ a stoichiometric amount of an organometallic reagent (organoboron, -zinc, -magnesium, -silicon, or -tin). Moreover, higher concentrations of the organometallic coupling partner helps to efficiently favor transmetalation product **1.7** over β-hydride elimination **1.8**. Therefore, the substiochiometric concentration of **1.9** generates a significant challenge in promoting the desired reaction when an alkyl electophile are utilized.



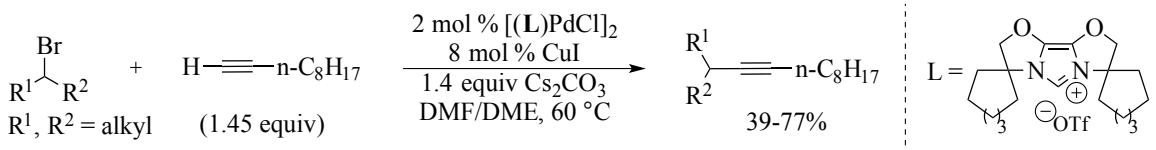
Scheme 1-12. Potential Pathway for a Sonogashira reaction

To date, there are no reported examples of a palladium-catalyzed Sonogashira reaction in the presence of phosphine ligands. All known examples in the literature rely upon NHC ligands. In 2003, the Fu group reported seminal work employing primary alkyl bromides and iodides (Scheme 1-13).[42] The absence of a harsh base and high temperature enabled excellent functional group tolerance including ester, nitrile, chloro, and acetal functionalities, olefins, and unprotected hydroxy groups; however, the substitution pattern of the alkyne had a pronounced effect on reaction outcome, and the reaction conditions had to be adjusted accordingly.



Scheme 1-13. Sonogashira Coupling of Primary Alkyl Halides

In 2006, the Glorius group reported the first Sonogashira reactions of secondary alkyl bromides (Scheme 1-14).[43] The reaction employs similar reaction conditions as those previously utilized by the Fu group; however, higher reaction temperatures and polarity were required. A bioxazoline-derived NHC ligand was employed; this ligand family is electron-rich and sterically demanding, but exhibits a high degree of conformational flexibility.[44] The reaction exhibited excellent levels of functional group tolerance with olefins, acetates, esters, and epoxides installed on the alkyl bromides. Notably, the use of enantiomerically pure (*R*)-2-bromooctane led to complete formation of the racemic product.

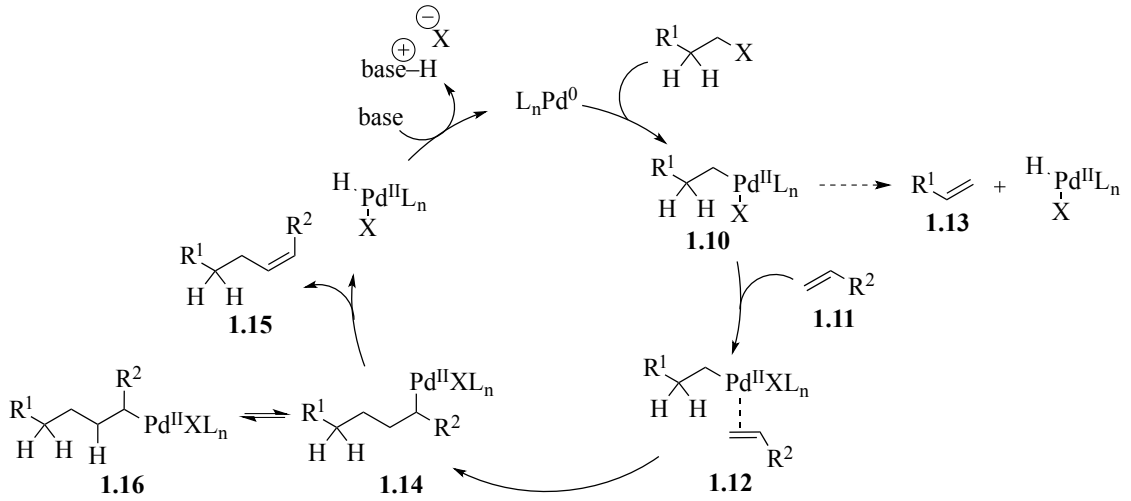


Scheme 1-14. Sonogashira Coupling of Secondary Alkyl Bromides

1.2.7. Alkyl Heck Cross-Coupling

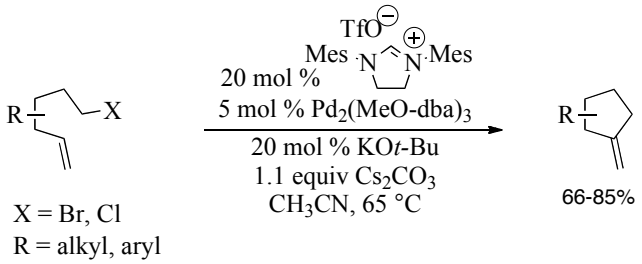
The Heck reaction is the palladium-catalyzed cross-coupling of sp^2-hybridized halides or sulfonates with alkenes. The use of an unfunctionalized coupling partner results in a significantly different mechanism (Scheme 1-15). The alkene **1.11** must undergo coordination to the metal, species **1.12**, prior to undergoing insertion to generate alkyl palladium species. This requires the use of a coordinatively unsaturated palladium species; however, the open coordination site on palladium will facilitate rapid β-hydride elimination. Moreover, in order to generate the product **1.15**, β-hydride elimination is

required. In order to successfully employ sp^3-hybridized electrophiles in the reaction, the rate of insertion must be faster than the rate of the initial β-hydride elimination



Scheme 1-15. Plausible Catalytic Cycle for an Alkyl-Heck Reaction

In 2007, the Fu laboratory reported the only known organometallic alkyl-Heck reaction (Scheme 1-16).[45] They relied upon the intramolecular 5-*exo* cyclization to outcompete the initial β-hydride elimination. Primary alkyl bromides and chlorides were cyclized with mono-substituted to alkenes to provide cyclopentene products. Pd_2(MeO-dba)$_3$ was employed as the precatalyst in the reaction as electron rich dba ligands have resulted in a more active catalyst; a bench stable NHC ligand was also utilized; however, this method's substrate scope is quite limited as secondary halides and further olefin substitution were not tolerated.



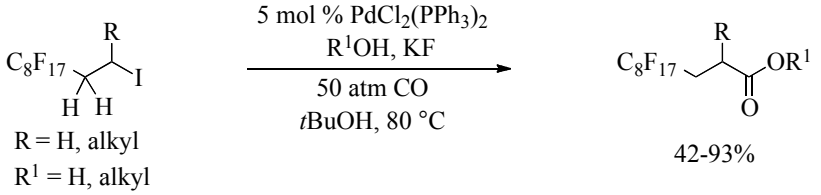
Scheme 1-16. Intramolecular Heck Cyclization of Alkyl Bromide and Chlorides

1.3 Palladium-Catalyzed Carbonylations of sp^3-Hybridized Electrophiles

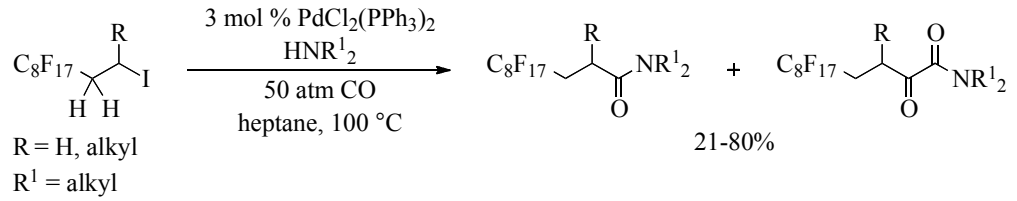
Carbonylation of alkyl halides is one of the most important industrial processes.[46] Palladium-catalyzed carbonylation can allow for the direct synthesis of carboxylic acids, aldehydes, ketones, esters, and amides. Although generally, the use of alkyl electrophiles is limited to methyl, benzyl, and allyl halides.[47,48]

The first palladium-catalyzed carbonylation of alkyl iodides was reported in 1989 by Fuchikami (Scheme 1-17). Carboxylic acids and esters were generated from primary and secondary polyfluorinated iodides when KF or NEt_3 were present in the reaction.[49,50] Interestingly, when secondary amines were used as the nucleophile, a mixture of amide and α-ketoamides was isolated.[51]

Synthesis of Carboxylic Acids of Esters:

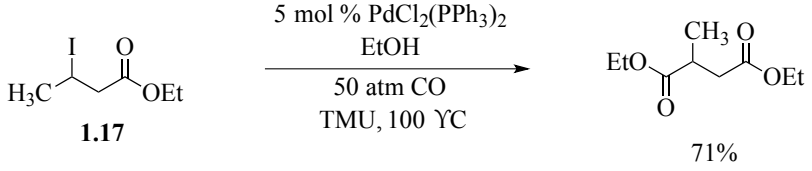


Synthesis of Amides and a-Ketoamides:



Scheme 1-17. Palladium-Catalyzed Carbonylation of Perfluoroalkyl Iodides

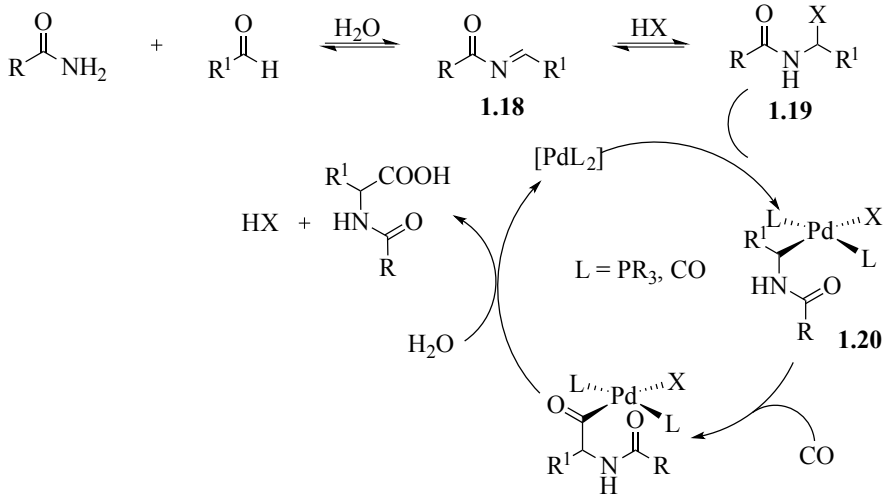
It was found that employing TMU, DMI, or DMPU instead of a commonly employed amine or inorganic bases allowed base-sensitive compounds such as **1.17** to be carbonylated in good yields (Scheme 1-18).[52] It was also found that molecular sieves could facilitate the reaction as well.[53]



Scheme 1-18. Base-Free Carbonylation of Alkyl Iodides

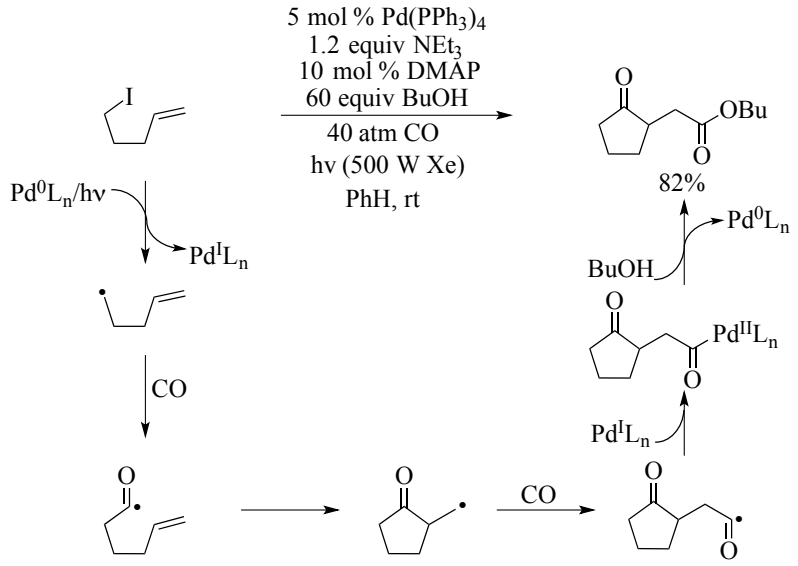
Palladium-catalyzed carbonylation of alkyl halides have also been used to access *N*-acyl α-amino acids via a three-component coupling reaction (Scheme 1-19).[54] Amidocarbonylation is an atom-efficient coupling of an amide, an aldehyde, and carbon monoxide. Palladium-catalyzed activation of α-halo *N*-acylamine **1.19** is followed by

carbonylation and nucleophilic displacement of the palladium complex[55] to provide a wide range of α-amino acids such as hydantoins and aryl glycines.[56-60]



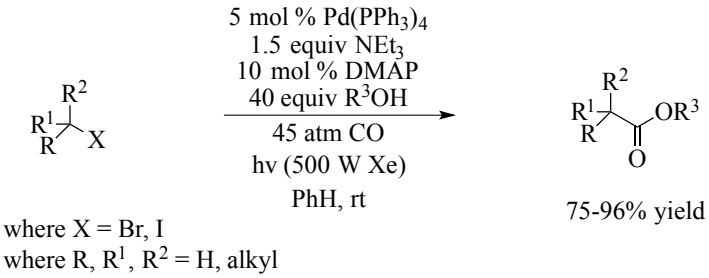
Scheme 1-19. Palladium-Catalyzed Amidocarbonylation

Ryu and co-workers reported a photo-accelerated palladium-catalyzed carbonylative cyclization of alkyl iodides (Scheme 1-20).[61] The carbonylative cascade reaction was able to generate dicarbonylated carbocycles from aliphatic iodides. In contrast to the previous examples, Ryu's method was proposed to proceed by single electron transfer oxidative addition of the alkyl halide to generate a carbon-centered radical. Radical-mediated carbonylation and cyclization was followed by nucleophilic displacement of the acyl-palladium intermediate to furnish product.



Scheme 1-20. Palladium-Catalyzed Carbonylative Cyclization of Alkyl Iodides via a Radical/Metal Pathway

Ryu and co-workes have also published a carbonylation of primary, secondary, and tertiary alkyl halides (Scheme 1-21).[62] While commercially available $Pd(PPh_3)_4$ routinely afforded good to excellent yields of product, palladium dimer $[Pd_2(CNMe)_6][PF_6]_2$ provided similar yields. The reaction was proposed to proceed via a palladium/light mediated mechanism as well, beginning with generation of the carbon-centered free radical from the halide precursor. Free-radical carbon-carbon bond formation is followed by generation of the acylpalladium species, which, upon nucleophilic displacement by the nucleophile, affords the product. Additionally the reaction boasted high functional group compatibility and could also generate amide products in addition to ester products when a secondary amine was employed as the nucleophile.



Scheme 1-21. Palladium-Catalyzed Carbonylation of Primary, Secondary, and Tertiary Alkyl Halides

1.4 Summary and Outlook

Despite significant challenges, alkyl electrophiles have been employed in several palladium-catalyzed reactions including important organometallic cross-coupling reactions as well as carbonylation reactions. Typically bulky, electron-rich alkyl phosphines or NHC ligands are employed to achieve these processes. While primary alkyl electrophiles have been used in several couplings with organoboron, -magnesium, -tin, -zinc, -silicon, and -zinc reagents, the use of secondary alkyl electrophiles is considerably more scarce.

Nevertheless, there are several interesting challenges that have not been successfully met. The alkyl-Heck reaction reported by Fu and co-workers has a limited substrate scope. Extension of this methodology would prove highly desirable, particularly for secondary alkyl electrophiles (Chapter 2 and 3). To date, examples of palladium-catalyzed carbonylation of secondary alkyl electrophiles are also rare. Development of a general catalytic carbonylation method, that can provide access to enantiopure α-chiral carbonyl compounds from racemic alkyl halides would prove invaluable for the synthesis of chiral carbonyl compounds that would otherwise take several steps to synthesize (Chapter 4). Finally, extending the known cross-couplings of sp^3-hybridized electrophiles to reactions with inert C-H bonds would facilitate expedient

synthesis of a wide variety of bioactive natural products that contain a polycyclic aromatic core (Chapter 5). Novel synthetic methodologies have been developed to meet these challenges and are described herein.

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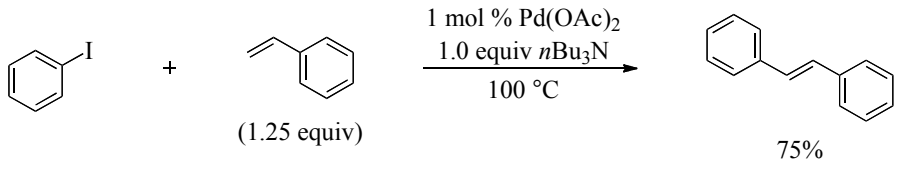
Chapter 2

Palladium-Catalyzed Carbonylative Heck-Type Cyclizations of Alkyl Iodides

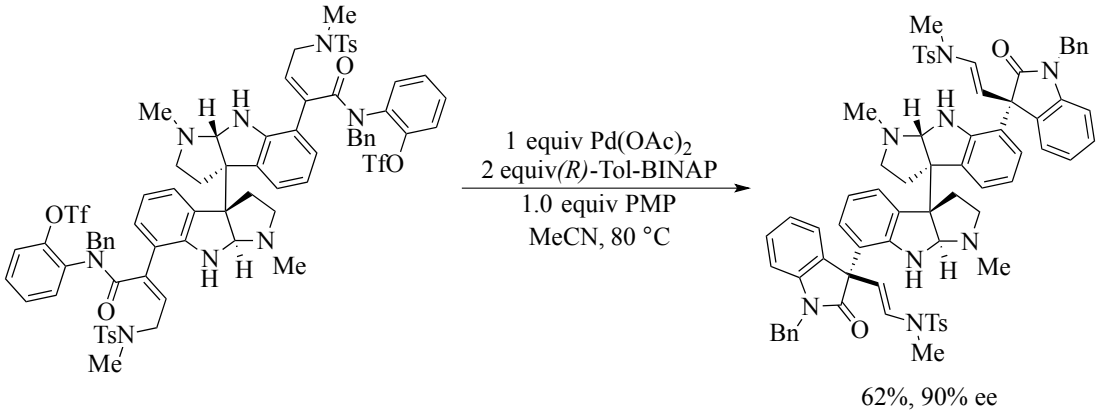
2.1 Introduction

Palladium-catalyzed cross-coupling reactions have had a profound impact on carbon-carbon bond forming processes.[1,2] This is reflected by the 2010 Nobel Prize in chemistry that was awarded to pioneers in palladium-catalyzed carbon-carbon bond synthesis.[3] The palladium-catalyzed Heck reaction, which couples aryl or vinyl halides or sulfonates with simple alkenes, has emerged as a premier method for carbon-carbon bond construction.[4] The Heck reaction boasts excellent functional group tolerance, obviates the need for prefunctionalization of the coupling partner, and generates an olefin product can be readily utilized in subsequent transformations. In 1972, seminal work for the Heck reaction described the palladium-catalyzed coupling of aryl halides with styrenes or acrylates in the presence of an amine base (Scheme 2-1).[5]



Scheme 2-1. Seminal Example of the Heck Reaction

Over the past forty years, the utility of the Heck reaction has been well demonstrated in synthesis, finding widespread applications in various fields of chemical science, which includes more than 100 different syntheses of natural products and bioactive compounds.[6,7] One remarkable example was disclosed by the Overman lab in their syntheses of psycholeine and quadrigemine C, in which an enantioselective double Heck cyclization provided two quaternary centers with excellent regioselectivity and stereoselectivity (Scheme 2-2);[8] however, despite the broad applicability of the Heck reaction, there are significant fundamental limitations associated with the reaction scope, as the Heck reaction is not generally applicable to alkyl electrophiles. As such, it is our goal to develop synthetic strategies, which will enable this important transformation.



Scheme 2-2. Application of the Enantioselective Heck Reaction in the Total Syntheses of Psychloleine and Quadrigemine C

2.2 Background

Extension of the Heck reaction to include alkyl electrophiles would be extremely beneficial; however, there are inherent issues impeding such a realization (Figure 2-1). First, alkyl electrophiles are generally reluctant to undergo oxidative addition,[9-13] and,

second, once the alkyl palladium species is generated, it typically undergoes rapid β-hydride elimination.[14,15] Previously, palladium-catalyzed Heck reactions of alkyl halides has been accomplished by either by employing activated substrates such as benzylic,[16-18] allylic,[19] and α-halo carbonyl[20,21] compounds to enable oxidative addition or utilizing alkyl electrophiles without accessible β-hydrogens.[22]

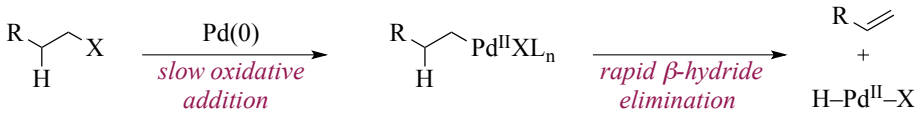


Figure 2-1. Challenges in Developing Alkyl-Heck Processes

In 2007, the first example that relied upon catalyst control to overcome the aforementioned issues was reported. The Fu laboratory described a palladium-catalyzed intramolecular Heck cyclization of primary alkyl bromides and chlorides with mono-substituted alkenes (Figure 2-2).[23] In these transformations $Pd_2(MeO\text{-}dba)_3$ was utilized as the precatalyst. The electron rich dba ligand variant is an especially active catalyst because of its weaker affinity for the metal, which allows for more facile dissociation.[24,25] An NHC ligand was successful as it shares the same σ-donation properties as the trialkyl phosphine ligands that the Fu lab has successfully utilized in other palladium-catalyzed cross-couplings with alkyl electrophiles.[26,27] This metal/ligand combination was able to effectively mitigate β-hydride elimination after oxidative addition and promote β-hydride elimination after cyclization. This was attributed to the increased steric bulk around the metal after cyclization, which promoted dissociation of the palladium(II) species. While

these preliminary findings are encouraging, this method is limited to cyclopentene synthesis with primary halides and mono-substituted alkenes.

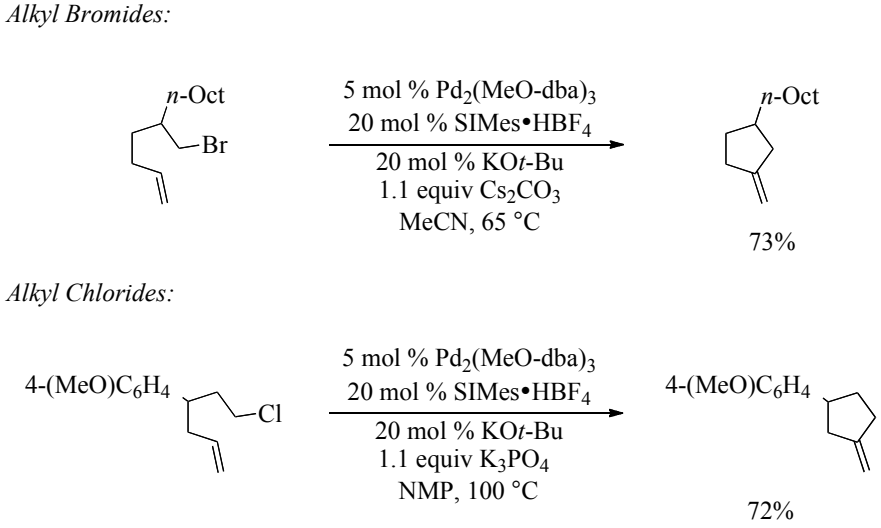


Figure 2-2. Palladium-Catalyzed Heck Cyclization of Aliphatic Bromides and Chlorides

Other research groups have reported useful alkyl Heck-type processes that possess free radical intermediates. Lebedev and Beletskaya reported a Ni-mediated method that couples alkyl bromides with styrene in the presence of zinc.[28] Kambe described a titanocene-catalyzed system that requires stoichiometric grignard addition.[29] Oshima has also reported a cobalt-catalyzed method that coupled alkyl iodides, bromides, and chlorides in the presence of stoichiometric Grignard reagent.[30]

We hypothesized trapping an alkyl palladium species by migratory carbon monoxide insertion would allow access to carbonylative Heck-type products (Figure 2-3). Carbonylative Heck-type reactions have been reported; however, they are limited to aryl or vinyl electrophiles.[31-33] Furthermore, carbonylative cyclization products would

provide synthetically useful enone products which are important building blocks for organic synthesis.[34]

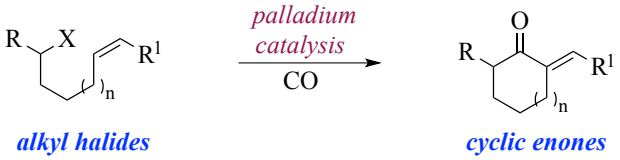
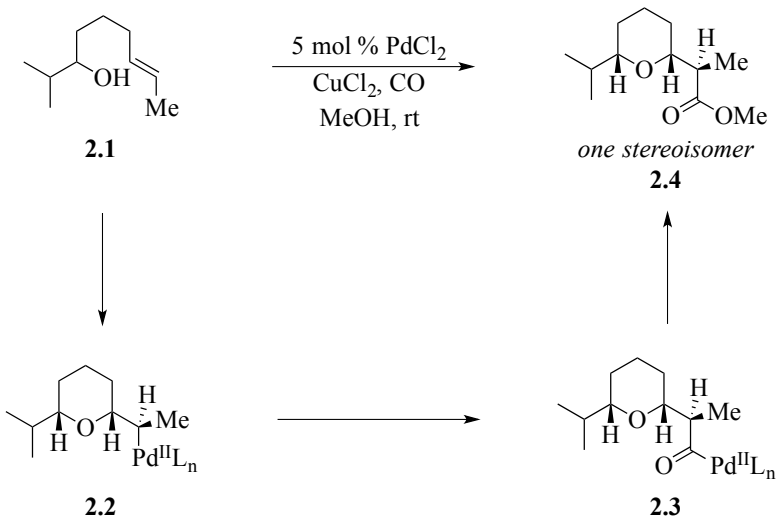


Figure 2-3. Proposed Palladium-Catalyzed Carbonylative Alkyl-Heck Cyclization

Migratory insertion of carbon monoxide ligands has been shown to outcompete β-hydride elimination from the unstable alkyl palladium species generated upon reaction with an alkyl halide.[35] This was demonstrated by the Semmelhack lab as alkoxypalladiation of **2.1** generated alkylpalladium species **2.2** that underwent migratory CO insertion to generate acyl palladium **2.3,** instead of undergoing β-hydride elimination. Methanolysis then displaced palladium, generating ester **2.4** as a single stereoisomer (Scheme 2-3).[36] Herein, we demonstrate that a commercially available palladium catalyst is capable of catalyzing carbonylative Heck-type reactions of unactivated alkyl iodide electrophiles.

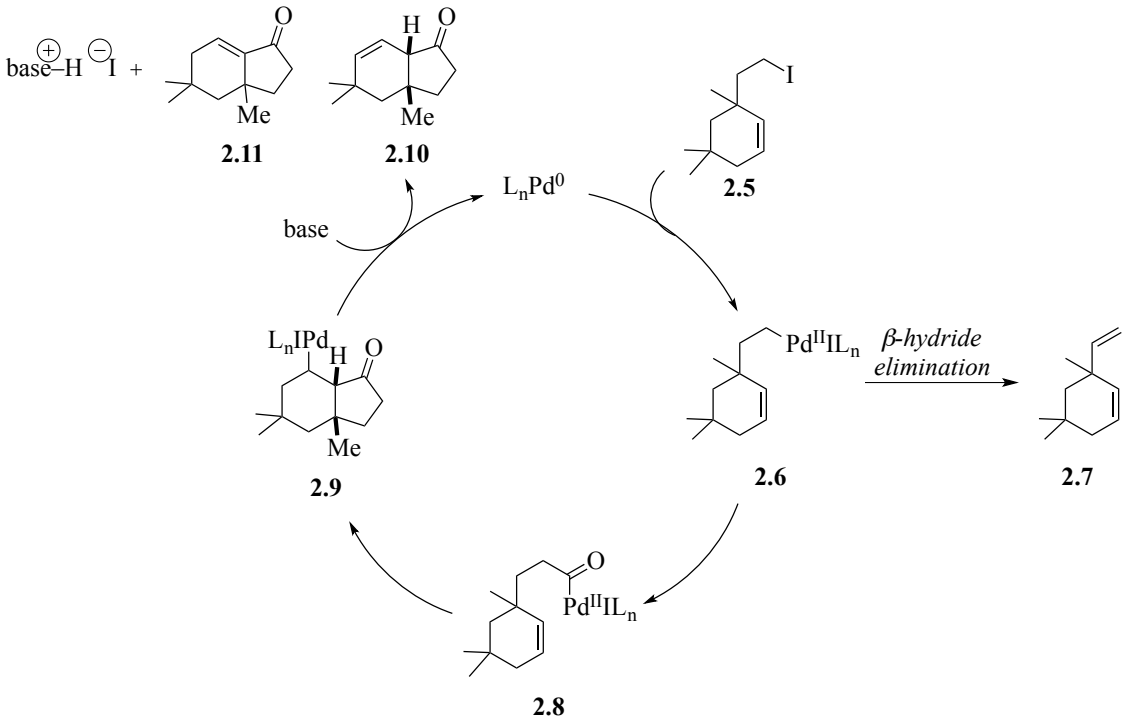


Scheme 2-3. Precedence for Palladium-Catalyzed Migratory CO Insertion Out-Competing β-Hydride Elimination

2.3 Results and Discussion

2.3.1 Reaction Development

Our studies commenced with alkyl iodide **2.5**. Iodide substrate **2.5** was chosen as it includes a number of control elements that will allow facile analysis of the reaction outcome. Our preliminary proposed mechanism is show in Scheme 2-4. Please refer to Scheme 2-8 or Scheme 2-9 for our current hypothesis. If β-hydride elimination were to occur to provide **2.7**, the methylene installed on the alkyl tether would prevent isomerization of the resulting terminal olefin. Cyclization of alkyl-palladium **2.6** to form cyclobutane is highly unlikely; however, rapid 5-*exo* cyclization should occur if acyl-palladium **2.8** is generated. The dimethyl substitution was employed to limit the number of alkene isomers that could be formed if reinsertion of the eliminated hydrido-palladium species into products **2.10** or **2.11** occurs.

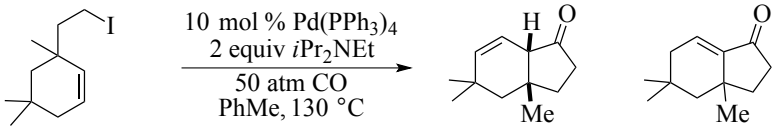


Scheme 2-4. Potential Reaction Pathway for Palladium-Catalyzed Carbonylative Alkyl Heck Cyclization

Optimization studies began with commercially available $Pd(PPh_3)_2Cl_2$ as a catalyst. $Pd(PPh_3)_2Cl_2$ has successfully catalyzed intramolecular carbonylative Heck reactions employing aryl iodides.[33] Upon heating to 130 °C in the presence of 10 mol % palladium catalyst with 2.0 equiv of *i*Pr_2NEt in toluene under 50 atm CO for 5 hours, the desired enone products were observed in a 60% combined yield (Table 2-1, entry 1). Employing commercially available tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) further increased the yield to 79% (entry 2). Reactions utilizing other palladium catalyst systems resulted in decreased yields (entries 3 and 4), and no product formation was observed in the absence of $Pd(PPh_3)_4$ (entry 5). When the reaction temperature was lowered to 100 °C, the reaction efficiency decreased (entry 6). Higher temperatures are likely needed to achieve oxidative addition of the palladium(0) to the alkyl iodide.

Similarly, decreasing the reaction pressure resulted in a less effective reaction (entry 7). We also found that inorganic bases such as Cs_2CO_3 proved inferior to amine bases (entry 8). This is likely due to the decreased solubility of the inorganic base in nonpolar solvent. Notably, substrate dehydrohalogenation (Scheme 2-4, 2.7) was not a significant side reaction in these experiments; however, polar solvents systems were much less effective due to the increased formation of phosphonium salt byproducts (entry 9).

Table 2-1. Influence of Reaction Conditions on the Carbonylative Cyclization

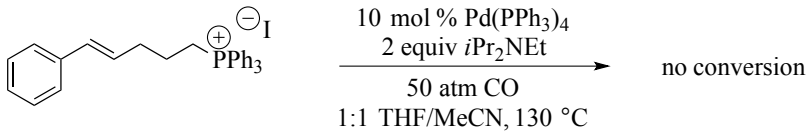


2.5 **2.10** **2.11**

Entry	Variation from standard conditions above	%Yield[a]
1	10 mol % $Pd(PPh_3)Cl_2$, instead of $Pd(PPh_3)_4$	60
2	none	79
3	10 mol % $Pd(OAc)_2$ and 20 mol % PPh_3, instead of $Pd(PPh_3)_4$	35
4	5 mol % $Pd_2(dba)_3$, instead of $Pd(PPh_3)_4$	2
5	no $Pd(PPh_3)_4$	<2
6	100 °C, instead of 130 °C	20
7	30 atm CO, instead of 50 atm CO	41
8	Cs_2CO_3, instead of iPr_2NEt	12
9	1:1 THF:MeCN, instead of PhMe	28

[a]Determined through GC analysis

It was determined that generation of the phosphonium salt was an unproductive side reaction, as when it was resubmitted to the reaction conditions from which it was generated, product formation was not observed (Scheme 2-5).

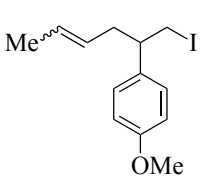
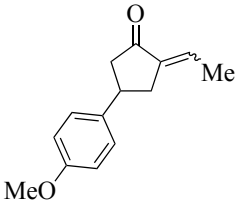
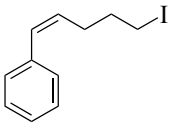
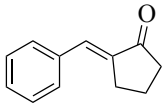
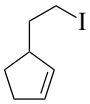
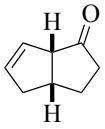
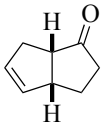
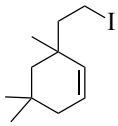
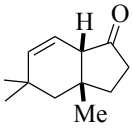
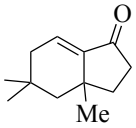
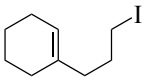
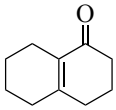


Scheme 2-5. Phosphonium Salt Control Reaction

2.3.2 Substrate Scope Development

We then examined the substrate scope of the reaction with a wide variety of unsaturated alkyl iodides using the optimized reaction conditions (Table 2-1). The study began with primary alkyl iodides. The reaction performed well with simple acyclic substrates as predominantly *(E)*-disubstituted alkyl iodide **2.12** (85:15 *E*:*Z*) (entry 1) provided cyclohexenone **2.13** in 77% yield as a 10:1 mixture of *E*:*Z* isomers. Conjugated alkenes were useful substrates, as (*Z)*-styrenyl substrate **2.14** provided enone **2.15** in 55% yield. We also found that different classes of ring systems were easily accessible. Under the standard conditions, bicyclo[3.3.0]octenones (entry 3) and bicyclo[4.3.0]nonenones (entry 4) were furnished from substrates **2.16** and **2.5**. Notably, this process was not limited to 5-*exo* cyclizations, as bicyclodecenone **2.19** was synthesized in 69% yield from **2.20** via a 6-*endo* cyclization.

Table 2-2. Palladium-Catalyzed Carbonylative Cyclization of Primary Alkyl Iodides[a]

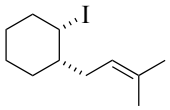
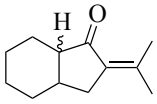
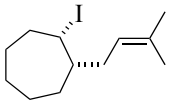
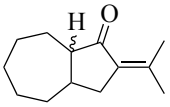
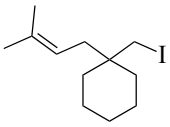
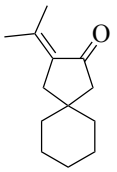
Entry	Substrate	Product	%Yield[b,c]
1	 **2.12**	 **2.13**	77 10:1 *E*:*Z*
2	 **2.14**	 **2.15**	55 >25:1 *E*:*Z*
3	 **2.16**	 **2.17**	 **2.18**	63 1.3:1 **2.17:2.18**
4	 **2.5**	 **2.10**	 **2.11**	74 7.1:1 **2.10:2.11**
5	 **2.19**	 **2.20**	69

[a]All reactions run 0.5 M in PhMe at 130 °C under 50 atm CO in the presence of 10 mol % $Pd(PPh_3)_4$ and 2.0 equiv of iPr_2NEt for 5-12 h. [b]All yields are isolated. [c]The diastereomeric ratios were determined by ^1H NMR spectroscopy of the isolated products.

Secondary alkyl iodides also readily reacted under the standard conditions. Secondary alkyl halides **2.21** (Table 2-3, entry 1) and **2.23** (entry 2) with tri-substituted alkenes generated tetra-substituted enone products in 91% and 82% yields, respectively. Notably, bicyclo[5.3.0]decanone **2.24** was synthesized in good yield, and is a common

motif in bioactive natural products.[37-39] Neopentyl iodide **2.25** efficiently transformed into spriocyclic product **2.26** in 90% yield, demonstrating that sterically hindered alkyl iodides are well tolerated in this system.

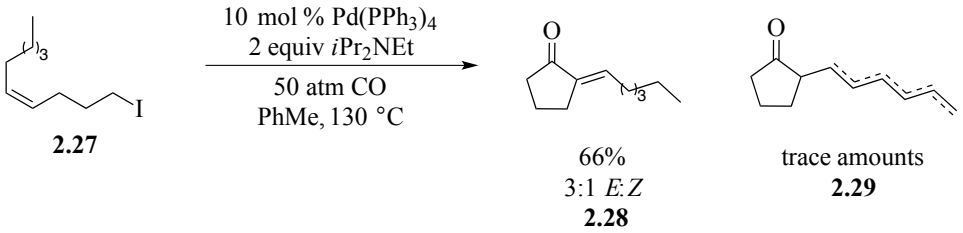
Table 2-3. Palladium-Catalyzed Carbonylative Cyclization of Secondary and Sterically Hindered Secondary Alkyl Iodides

Entry	Substrate	Product	%Yield[b,c]
1	 **2.21**	 **2.22**	91 1.2:1 dr
2	 **2.23**	 **2.24**	82 1.6:1 dr
3	 **2.25**	 **2.26**	90

[a]All reactions run 0.5 M in PhMe at 130 °C under 50 atm CO in the presence of 10 mol % $Pd(PPh_3)_4$ and 2.0 equiv of iPr$_2$NEt for 5-12 h. [b]All yields are isolated. [c]The diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the isolated products.

Despite these significant advancements, there were also limitations to the substrate scope as well. While the majority of the products favored the generation of conjugated enones, alkene isomerization was noted in certain cases (Scheme 2-6). When acyclic alkyl iodide **2.27** was subjected to the standard conditions, trace amounts of alkene isomers **2.29** were noted by ^{1}H and ^{13}C NMR in addition to conjugated enone

product **2.28**. Alkene isomerization was also found to increase with reaction time as well.



2.27 | 66% 3:1 *E*:*Z* **2.28** | trace amounts **2.29**

Scheme 2-6. Isomerization of the Enone Products

When primary alkyl iodides with mono-substituted alkenes were subjected to the standard reaction conditions, < 20% yield was observed (Scheme 2-6). Initially, the low boiling point of **2.30** was believed to be partially responsible for the low yield; however, iodide **2.31** possesses a substantially higher boiling point and resulted in a similar outcome. Significant amounts of unidentified decomposition were noted by ^{1}H NMR, indicating that an unstable intermediate may have been present.

2.30 **2.31**

Figure 2-4. Substrate Limitations with Respect to Alkene Substitution

Furthermore, primary alkyl bromides were unreactive under the standard conditions (Figure 2-5, entry 1). This is most likely attributed the higher bond strength of a carbon–bromide bond in comparison to a carbon–iodide bond. Attempts were made to generate the iodide in situ through the addition of 20 mol % sodium iodide (entry 2) and 50 mol % tetrabutylammonium iodide (entry 3); however, these attempts were

unsuccessful, likely because the reaction was conducted in a non-polar solvent, significantly decreasing the rate of the polar substitution reaction.

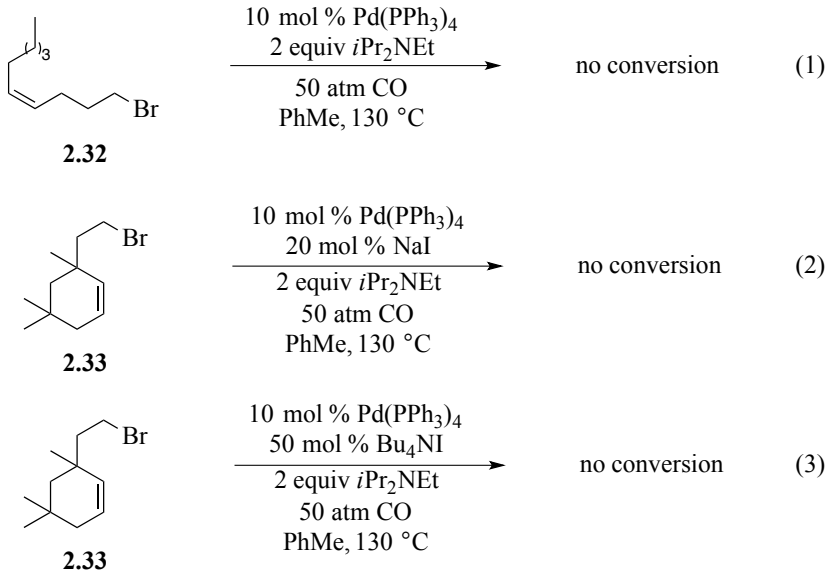
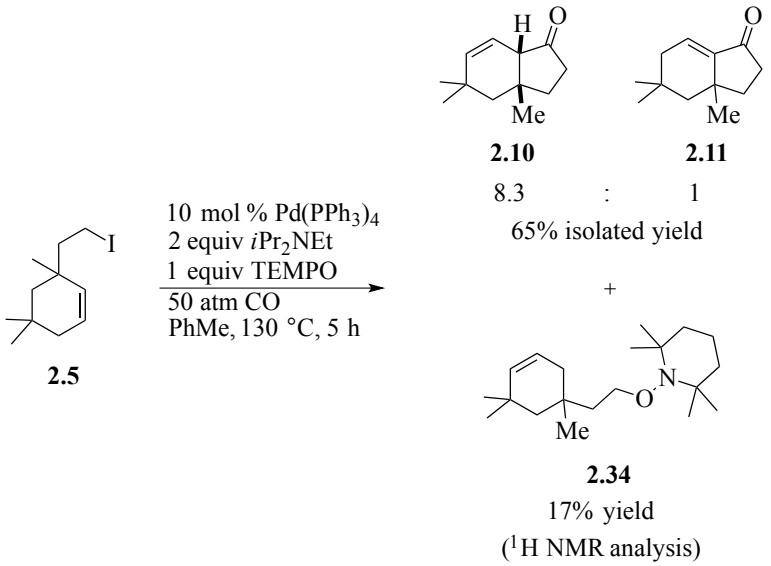


Figure 2-5. Attempted Reactions of Alkyl Bromides Substrates

2.3.3 Mechanistic Studies

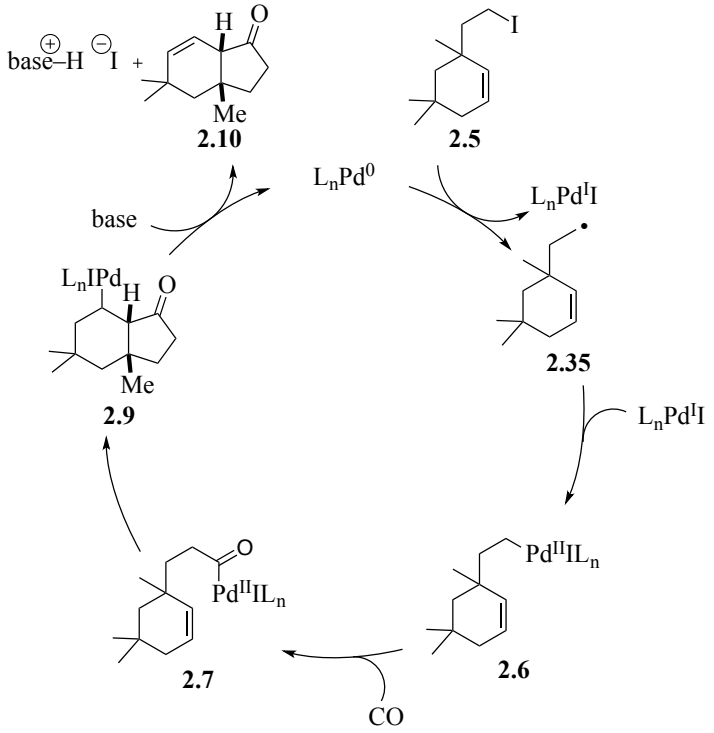
The ability of palladium(0) to react with alkyl iodides by S_N2[40,41] as well as through single-electron pathways,[42,43] opens the door to a number of mechanistic possibilities. To understand more about this reaction, we subjected enone **2.5** to the standard reaction conditions as well as one equivalent of TEMPO (Scheme 2-7). TEMPO has been previously utilized to trap radical intermediates in nickel-catalyzed reactions involving alkyl iodides.[44] The reaction produced 65% of enone products **2.10** and **2.11** as well as 17% of TEMPO adduct **2.34**. Although the efficiency of the reaction is comparable to that of the reaction performed in the absence of TEMPO, these results suggest the involvement of carbon-centered radicals in the reaction.



Scheme 2-7. Reaction Run in the Presence of a Radical Trap

Hybrid organometallic-radical mechanisms have been proposed in reactions involving the palladium-catalyzed carbonylation of alkyl iodides;[45-47] however, photoirradiation is required to achieve oxidative addition via single electron transfer to generate a carbon-centered radical. It is possible that in our system, the oxidative addition occurs thermally instead of photolytically. A possible catalytic cycle for the reaction could begin with oxidative addition of the palladium(0) to alkyl iodide **2.5** via a single-electron transfer, which could generate carbon-centered radical **2.35** and a putative palladium(I) species (Scheme 2-8). Generation of **2.35** would account for the presence of the TEMPO adduct **2.34**. Carbon-centered radical **2.35** could then reaction with the react with the palladium(I) species. Alkyl palladium species **2.6** could then undergo migratory carbon monoxide insertion, generating acyl palladium **2.8**. 5-*exo* cyclization to alkyl palladium **2.9** would be immediately followed by β-hydride elimination to furnish enone

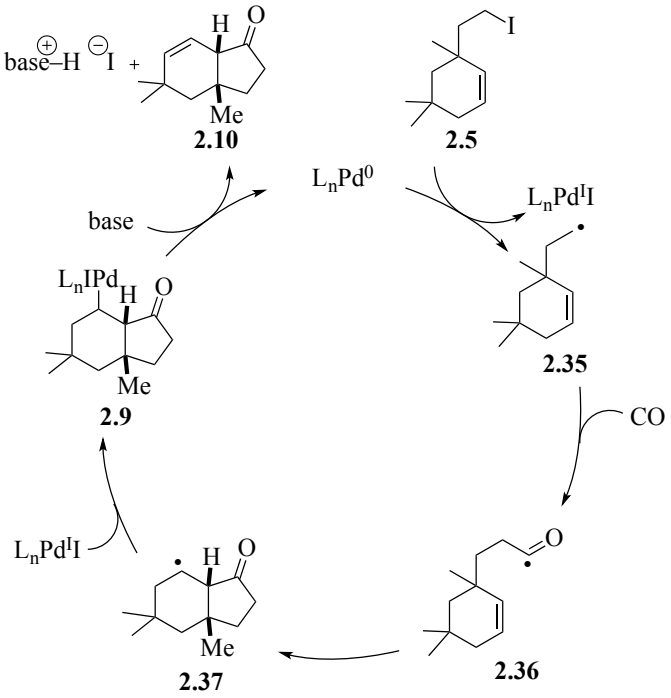
2.10. Base could then regenerate the active catalyst. The absence of any other TEMPO adducts supports this catalytic cycle.



Scheme 2-8. Plausible Organometallic-Radical Hybrid Mechanism for the Carbonylative Cyclization of Alkyl Iodides

Another potential mechanism could occur by the same oxidative addition via single electron transfer to generate carbon-centered radical **2.35**. Trapping of the radical with carbon monoxide could generate acyl radical **2.36**, which could undergo then 5-*exo* cyclization to generate **2.37**. Formation of alkyl palladium **2.9** could be accomplished through reaction with palladium(I). β-hydride elimination could then provide enone **2.10**. Although an appreciable amount of any other TEMPO-trapped adduct was not observed, it is possible that other radical intermediates participate in the mechanism. 5-*exo* cyclization could occur too quickly for TEMPO to intercept **2.36**. A radical cyclization would also account for the observed low diastereomeric ratios of **2.22** and **2.24** (1.2:1 and

1.6:1, respectively) **(**(Table 2-3, entries 1 and 2). The success of secondary halides (Table 2-3, entries 1, 2, and 3) in the reaction may be additional evidence for the formation of a carbon-centered radical via single electron transfer oxidative addition.



Scheme 2-9. Plausible Organometallic-Radical Hybrid Mechanism with Increased Radical Character for the Carbonylative Cyclization of Alkyl Iodides

2.4 Summary

In conclusion, we have developed a palladium-catalyzed intramolecular carbonylative Heck-type cyclization of unactivated alkyl iodides. The reaction possesses a broad substrate scope as primary and secondary iodides and substituted alkenes are efficiently reacted to generate synthetically valuable mono- and bicyclic enones. Notably, the isolation of trapped carbon-centered radicals indicates that the reaction proceeds via a hybrid organometallic-radical pathway, although further studies will be required to elucidate the precise reaction pathway.

2.5 Experimental

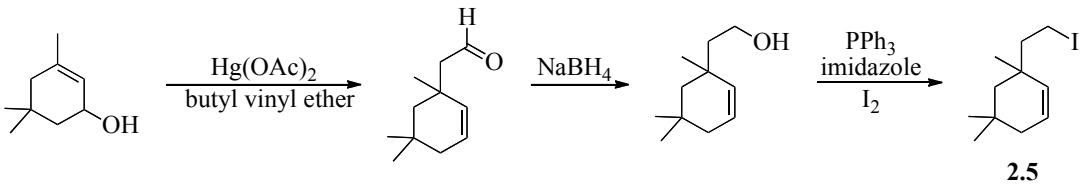
2.5.1 General Methods

Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 or 500 or a Bruker AMX 300 (^{1}H NMR at 300 MHz, 400 MHz or 500 MHz and ^{13}C NMR at 100 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.28 ppm, ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), coupling constants (Hz), and integration. Mass spectra were obtained either using a positive ion mode flow injection ESI (electrospray ionization) on a Bruker Daltonics, Inc., Billerica, MA, USA, BioToF Mass Spectrometer or electron impact ionization on an Agilent Technologies, Inc., Santa Clara, CA, USA, GCMS, 5973N Mass Selective Detector, using a HP-5MS, 30mx0.25mmx0.25um capillary column. Visualization was accomplished with short wave UV light (254 nm), aqueous basic potassium permanganate solution, or ethanolic acidic *p*-anisaldehyde solution followed by heating. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63 μm) purchased from Silicycle. Tetrahydrofuran, diethyl ether, and toluene were dried by passage through a column of neutral alumina under nitrogen prior to use. Carbon Monoxide, Research Purity 99.998% was purchased from Matheson Tri-Gas. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted. The pressure reactors used were purchased from Parr Instrument

Company that included a 4310 Gage Block Assembly and a GP VS 22 mL A SKT 316SS ST CLS.

2.5.2 Preparation of Iodide and Bromide Substrates

Note: As a precaution alkyl iodides were immediately stored in a dark, inert atmosphere at -40 °C upon purification.



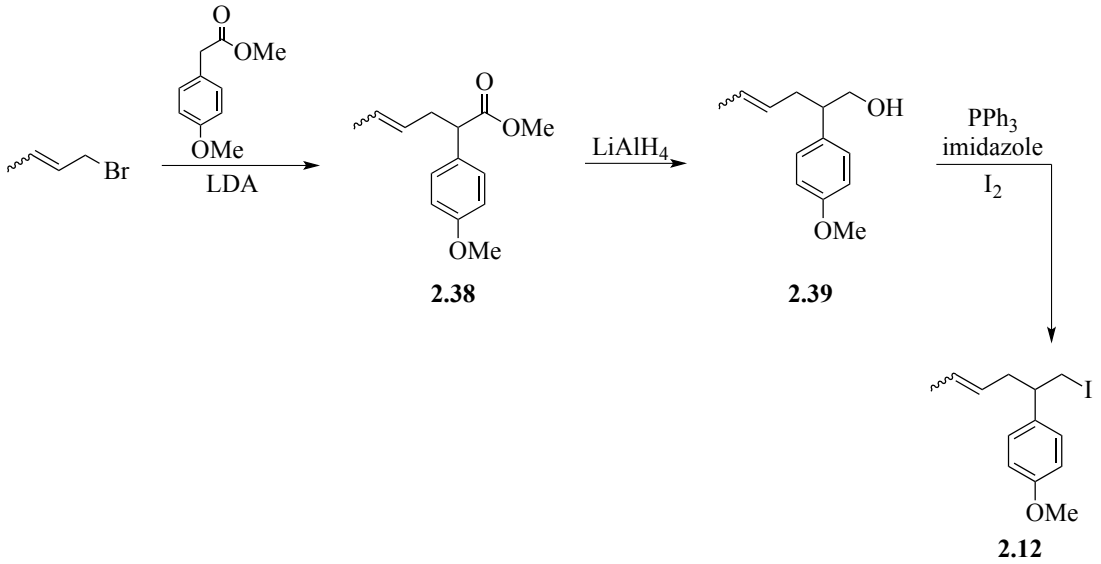
2.5

3-(2-iodoethyl)-3,5,5-trimethylcyclohex-1-ene (2.5, Table 2-2, entry 4). The title compound was synthesized according to a literature Claisen rearrangment procedure,[49] followed by a standard sodium borohydride reduction, and an iodination.

For 2-(1,5,5-trimethylcyclohex-2-enyl)acetaldehyde, physical and spectral data were in accordance with literature data.[50] For 2-(1,5,5-trimethylcyclohex-2-enyl)ethanol, physical and spectral data were in accordance with literature data.[51]

To a 0 °C solution of alcohol (1.00 g, 5.94 mmol), triphenylphosphine (1.87 g, 7.13 mmol), and pyridine (910 uL, 11.29 mmol) in DCM (45.7 mL) was added iodine (1.81 g, 7.13 mmol) under Ar. The reaction mixture was stirred at 0 °C for 1 hr. The reaction as then washed with 1 N HCl, sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (100:1 Hexanes/EtOAc) to provide **2.5** (1.12 g, 4.03 mmol, 68%) as a colorless oil. Analytical data for **2.5**: **IR** (thin film, cm^{-1}) 3011, 2950,

2903, 2866, 1455, 1363, 1171, 413; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.62 (dt, *J* = 10, *J* = 4 Hz, 1 H), 5.34 (d, *J* = 10 Hz, 1 H), 3.11 (m, 2 H), 1.99 – 1.88 (m, 2 H), 1.72 (m, 2 H), 1.39 (d, *J* = 13.75 Hz, 1 H), 1.23 (d, *J* = 13.75 Hz, 1H), 1.02, (s, 3 H), 0.95 (s, 6 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 133.38, 124.93, 49.37, 46.47, 38.55, 37.97, 31.68, 29.83, 28.60, 27.69, 1.14; **GCMS** calculated for [M] 278.05, found 278.



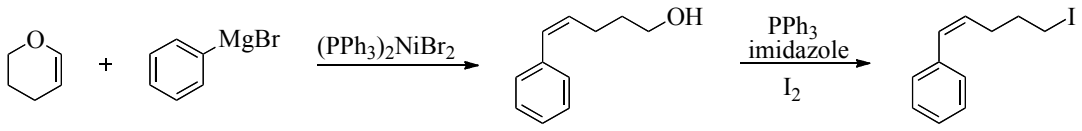
1-(1-iodohex-4-en-2-yl)-4-methoxybenzene (2.12, Table 2-2, entry 1). To a 0 °C solution of *i*Pr_2NH (2.9 mL, 21.0 mmol) in THF (90 mL) was added *n*BuLi (13.8 mL, 22.0 mmol, 1.6 M in hexanes) dropwise under Ar. The reaction mixture was stirred for 10 minutes and then cooled to –78 °C. Methyl 2-(4-methoxyphenyl)acetate (3.6 g, 20.0 mmol) was added dropwise in THF (10 mL). The reaction mixture was stirred for 30 minutes and then treated with crotyl bromide (3.24 g, 24.0 mmol, 85% pure from Acros). The reaction was then warmed to room temperature and stirred overnight. The reaction mixture was then diluted with EtOAc, washed with sat. NH_4Cl, dried with $MgSO_4$, and concentrated *in vacuo* to give a crude oil that was purified by flash chromatography (20:1

Hexanes/EtOAc) to provide (3.33 g, 14.21 mmol, 71% yield) **2.38** as a colorless oil. Analytical data for **2.38**: **IR** (thin film, cm^{-1}) 2999, 2951, 2915, 2855, 2836, 1737, 1612, 1512, 1436, 1302, 1250, 1179, 1160, 1035, 969, 833, 793; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (m, 2 H), 6.88 (m, 2 H), 5.52 (m, 1 H), 5.39 – 5.28 (m, 1 H), 3.81 (s, 3 H), 3.68 – 3.66 (m, 3 H), 3.56 (m, 1 H), 2.82 (m, 0.17 H), 2.75 (m, 0.85 H), 2.52 (m, 0.17 H), 2.43 (m, 0.85 H), 1.65 – 1.59 (m, 3 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ ppm 174.42, 174.36, 130.89, 130.86, 128.95, 128.92, 127.77, 127.57, 126.87, 126.26, 113.95, 60.40, 55.22, 51.93, 51.88, 51.09, 50.68, 36.67, 31.01, 17.97, 14.21, 12.84; **LRMS** (ESI) calculated for $[C_{14}H_{18}O_3+Na]^+$ 257.12, found 257.10.

To a 0 °C solution of lithium aluminum hydride (810 mg, 21.34 mmol) in THF (80 mL) was added **2.38** dropwise in THF (20 mL) under Ar. The reaction mixture was stirred for 1 hr at 0 °C. It was then quenched by the slow, dropwise addition of 810 μL H_2O, followed by 1.62 mL 10 wt % NaOH, and then 2.43 mL H_2O. The reaction mixture was stirred vigorously until a white solid appeared. The white precipitate was filtered, and the filtrate was concentrated *in vacuo*. The resulting oil was purified by flash chromatography (3:1 Hexanes/EtOAc) to provide (2.22 g, 10.76 mmol, 76% yield) **2.39** as a colorless oil. Analytical data for **2.39: IR** (thin film, cm^{-1}) 3376, 2998, 2915, 2835, 1513, 2058, 1301, 1242, 1178, 1036, 968, 912, 829; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.15 (m, 2 H), 6.87 (m, 2 H), 5.49 – 5.41 (m, 1 H), 5.37 – 5.30 (m, 1 H), 3.77 (s, 3 H), 3.75 – 3.61 (m, 2 H), 2.76 (m, 1 H), 2.48 (m, 0.18 H), 2.41 – 2.33 (m, 0.86 H), 2.32 – 2.23 (m, 1 H), 2.04 (s, 0.07 H), 1.97 (s, 0.95 H), 1.62 – 1.57 (m, 3 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ ppm 158.10, 158.05, 134.09, 134.03, 128.69, 127.93, 126.53, 125.04, 113.73, 66.80,

66.75, 54.98, 47.52, 47.47, 35.42. 29.59, 17.76, 12.68; **LRMS** (ESI) calculated for $[C_{13}H_{18}O_2+Na]^+$ 229.12, found 229.10

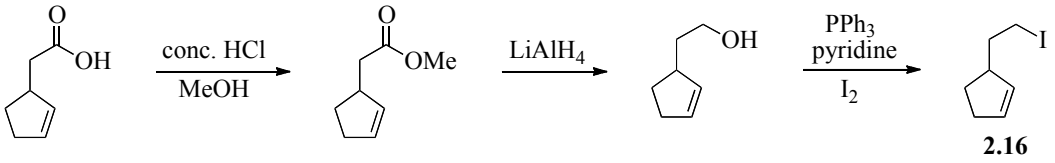
To a room temperature solution of alcohol **2.39** (2.0 g, 9.70 mol) in acetonitrile (15 mL) and diethyl ether (58 mL) under Ar, triphenylphosphine (5.09 g, 19.39 mmol), imidazole (1.32 g, 19.39 mmol) and iodine (4.92 g, 19.39 mmol) were added successively. The reaction mixture was stirred approximately fifteen minutes. SiO_2 was then added, and the mixture was concentrated *in vacuo.* The crude iodide was purified by column chromatography (30:1 Hex:EtOAc) to provide **2.12** (2.25 g, 7.12 mmol, 79% yield) as a colorless oil an as inseparable mixture of stereoisomers (85:15) with cis as the major isomer. Analytical data for **2.12**: **IR** (thin film, cm^{-1}) 2998, 2954, 2933, 2912, 2833, 1611, 1583, 1512, 1461, 1439, 1302, 1249, 1178, 1036, 967, 828, 804, 556, 453; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.12 – 7.08 (m, 2 H), 6.90 – 6.87 (m, 2 H), 5.54 – 5.47 (m, 1 H), 5.32 – 5.25 (m, 1 H), 3.81 (s, 3 H), 3.47 – 3.40 (m 1 H), 3.40 – 3.33 (m, 1 H), 2.91 – 2.81 (m, 1 H), 2.68 – 2.61 (m, 0.19 H), 2.52 – 2.46 (m, 0.9 H), 2.40 – 2.34 (m, 1 H), 1.64 – 1.59 (m, 3 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 158.33, 158.27, 134.83, 134.74, 128.26, 128.22, 127.91, 127.52, 127.24, 125.87, 113..68, 113.65, 55.08, 47.17, 47.00, 38.71, 33.03, 17.91, 14.14, 13.88, 12.96; **LRMS** (ESI) calculated for $[C_{13}H_{17}IO+H]^+$ 317.04, found 317.04.



2.14

(*Z*)-(5-iodopent-1-en-1-yl)benzene (2.14, Table 2-2, entry 2). The title compound was prepared according to a literature procedure by Kulawiec, *et. al*.[52] and iodination as described below.

To a room temperature solution of alcohol (670 mg, 4.13 mmol) in acetonitrile (6 mL) and diethyl ether (24 mL) under Ar, Triphenylphosphine (2.17 g, 8.26 mmol), imidazole (562 mg, 8.26 mmol), and iodine (2.1 g, 8.26 mmol) were added successively. The reaction mixture was stirred approximately fifteen minutes. SiO_2 was then added, and the mixture was concentrated *in vacuo*. The crude iodide was purified by column chromatography (40:1 Hex:EtOAc) to provide **2.14** (700 mg, 2.57 mmol, 63%) as a colorless oil. Physical and spectral data for **2.14** were in accordance with literature data.[53]

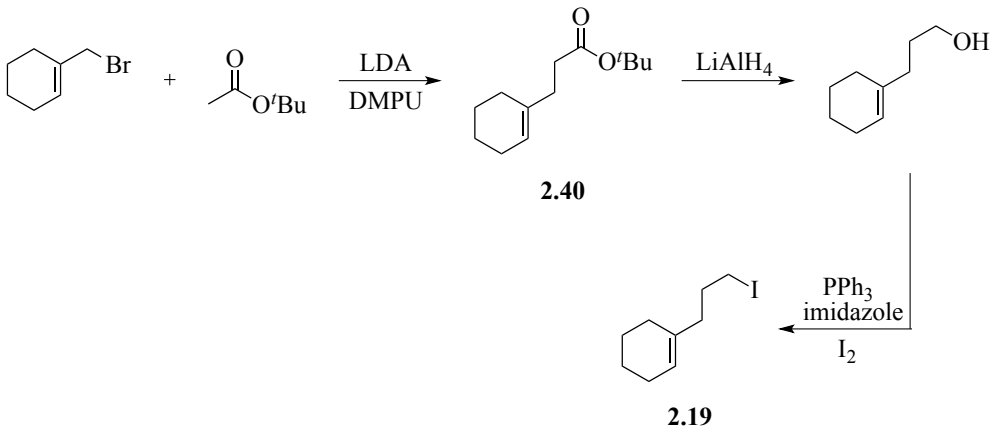


2.16

3-(2-iodoethyl)cyclopent-1-ene (2.16, Table 2-2, entry 3). The title compound was prepared via esterification and reduction according to the literature procedure by Lopp *et. al*[54] followed by iodination.

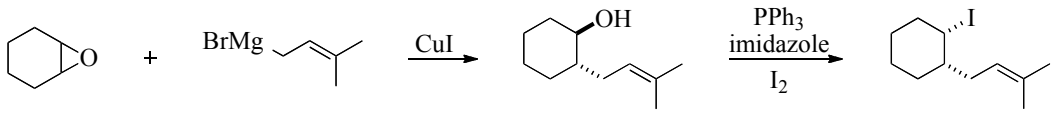
To a 0 °C solution of alcohol (1.33 g, 11.86 mmol), triphenylphosphine (3.73 g, 14.23 mmol), and pyridine (1.8 mL, 22.53 mmol) in DCM (90 mL) was added iodine (3.61 g, 14.23 mmol) under Ar. The reaction mixture was stirred at 0 °C for 1 hr. The reaction was diluted with DCM and then washed with 1 N HCl, sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (100:1 Hexanes/EtOAc) to

provide **2.16** (2.04 g, 9.19 mmol, 78% yield) as a colorless oil. Physical and spectral data were in accordance with the literature data.[55]



1-(3-iodopropyl)cyclohex-1-ene (2.19, Table 2-2, entry 5). The title compound was synthesized via an alklylation[56], followed by a standard LAH reduction, and an iodination[57].

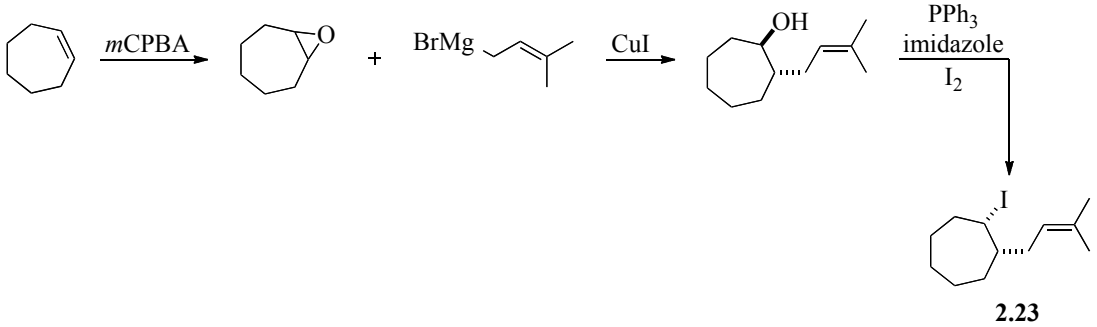
Analytical data for **tert-butyl 3-(cyclohex-1-en-1-yl)propanoate (2.40)**: **IR** (film) 3423, 2977, 2931.27, 2835, 1730, 1448, 1367, 1294, 1256, 1152, 827, 420 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 5.38 (s, 1H), 2.28 (t, J = 7.5 Hz, 2 H), 2.18, (t, J = 7.5 Hz, 2 H), 1.94 (m, 2H), 1.89 (m, 2 H), 1.58 (m, 2 H), 1.50 (m, 2 H), 1.41 (s, 9 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ ppm 172.92, 136.13, 121.37, 79.89, 33.98, 33.19, 28.09, 25.09, 28.02, 22.83, 22.38; **LRMS** (ESI) calculated for $[C_{13}H_{22}O_2+H]^+$ 211.17, found 211.08. Physical and spectral data in accordance with literature data for 3-(cyclohex-1-en-1-yl)propan-1-ol.[58] Physical and spectral data were in accordance with the literature data for **2.19**.



2.21

***(cis)*-1-iodo-2-(3-methylbut-2-en-1-yl)cyclohexane (2.21, Table 2-3, entry 1).** The title compound was prepared by conjugate addition to cyclohexene[59] to generate an alcohol whose physical and spectra data were in accordance with literature data[60] followed by an iodination.

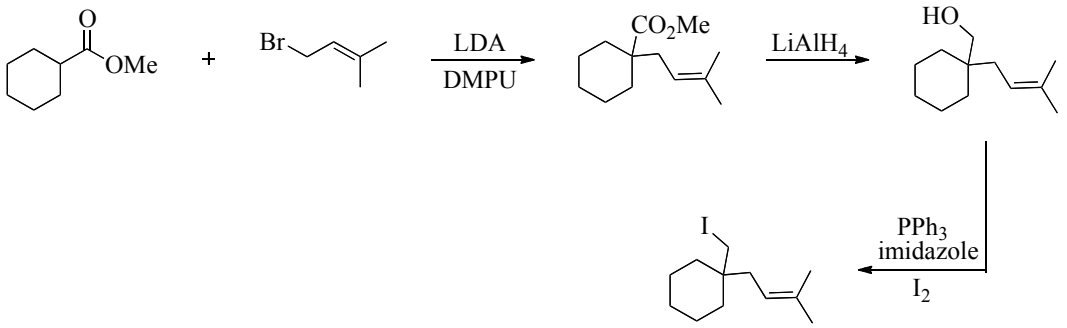
Triphenylphosphine (1.87 g, 7.13 mmol), imidazole (485 mg, 7.13 mmol), and iodine (1.81 g, 7.13 mmol) in DCM (11 mL) were combined at 0 °C under Ar and stirred for 15 min. A solution of alcohol (800 mg, 4.75 mmol) in DCM (11 mL) was then added dropwise. The reaction mixture was stirred at 0 °C for 30 min. The reaction was then quenched with H_2O and extracted with DCM three times. The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (50:1 Hexanes/EtOAc) to provide **XX** (925 mg, 3.33 mmol, 70%) as a colorless oil. Analytical data for **2.21**: **IR** (thin film, cm^{-1}) 2927, 2852, 1708, 1637, 1446; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.06 (m, 1 H), 4.72 (m, 1 H), 2.19 (m, 1 H), 1.93 (m, 1 H), 1.86 (m, 1 H), 1.78 – 1.68 (m, 5 H) 1.65 (s, 3 H), 1.55 (m, 1 H), 1.47(m, 1 H), 1.33 – 1.25 (m, 3 H), 0.43 (m, 1 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 133.32, 121.47, 48.42, 43.45, 36.89, 36.71, 28.83, 25.87, 25.58, 22.78, 22.58, 22.78, 18.32; **LRMS** (ESI) calculated for [$C_{11}H_{19}I$] 278.05, found 278.



2.23

***(trans)*-1-iodo-2-(3-methylbut-2-en-1-yl)cycloheptane (2.23, Table 2-3, entry 2).** The title compound was synthesized via an oxidation of cycloheptene oxide[61] and conjugate addition to the resulting epoxide.[59]

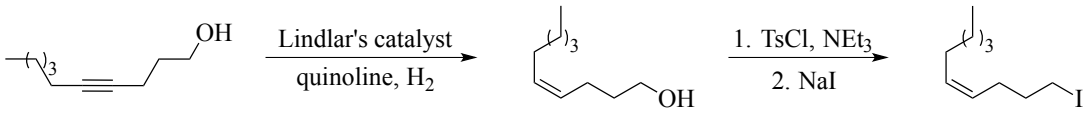
Triphenylphosphine (1.04 g, 3.97 mmol), imidazole (270 mg, 3.97 mmol), and iodine (1.01 g, 3.97 mmol) in DCM (6 mL) were combined at 0 °C under Ar and stirred for 15 min. A solution of alcohol (482 mg, 2.64 mmol) in DCM (6 mL) was then added dropwise. The reaction mixture was stirred at 0 °C for 30 min. The reaction was then quenched with H_2O and extracted with DCM three times. The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (50:1 Hexanes/EtOAc) to provide **2.23** (541 mg, 1.85 mmol, 70%) as a colorless oil. Analytical data for **2.23**: **IR** (thin film, cm^{-1}) 2964, 2926, 2855, 1446, 1375, 485; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.04 (t, J = 7.25 Hz, 1H), 4.70 (t, J = 2.8 Hz, 1H), 2.26 (m, 1H), 2.02 – 1.82 (m, 3H), 1.76 – 1.68 (m, 7 H), 1.62 – 1.50 (m, 3 H), 1.43 – 1.35 (m, 1 H), 0.80 – 0.74 (m, 1H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 133.55, 122.41, 49.67, 46.20, 36.49, 32.86, 27.00, 26.36, 25.90, 25.65, 18.33; **GCMS** calculated for [$C_{12}H_{21}I$] 292.07, found 292.



2.25

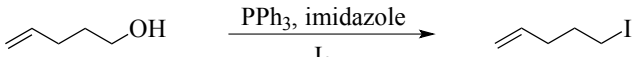
1-(iodomethyl)-1-(3-methylbut-2-en-1-yl)cyclohexane (2.25, Table 2-3, entry 3). The title compound was synthesized by an alkylation reaction[62] followed by a standard LAH reduction, and an iodination reaction.

Triphenylphosphine (908 mg, 3.46 mmol) was added to a 0 °C solution of (1-(3-methylbut-2-en-1-yl)cyclohexyl)methanol (234 mg, 1.28 mmol) and imidazole (332 mg, 4.88 mmol) in THF (15 mL) under Ar. The reaction mixture was stirred 10 minutes, followed by addition of iodine (845 mg, 3.33 mmol). The reaction mixture was then warmed to room temperature and stirred overnight. The solution was quenched with $Na_2S_2O_3$ and extracted with Et_2O (x 3). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified using flash chromatography (30:1 Hexanes/EtOAc) to provide **2.25** (179 mg, 0. 613 mmol, 48%) as a colorless oil. Analytical data for **2.25**: **IR** (thin film, cm^{-1}) 2926, 2855, 1453, 412; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.06 (t, J = 7.65 Hz, 1 H), 3.24 (s, 2 H), 2.02 (d, J = 7.6 Hz, 2 H), 1.71 (s, 3 H), 1.66 (s, 3 H), 1.48 – 1.33 (m, 10 H) ; **^{13}C NMR** (500 MHz, $CDCl_3$) δ 134.32, 118.99, 36.25, 34.96, 26.22, 26.07, 22.56, 21.93, 18.39; **LRMS** (ESI) calculated for [$C_{12}H_{21}I$] 292.07, found 292.



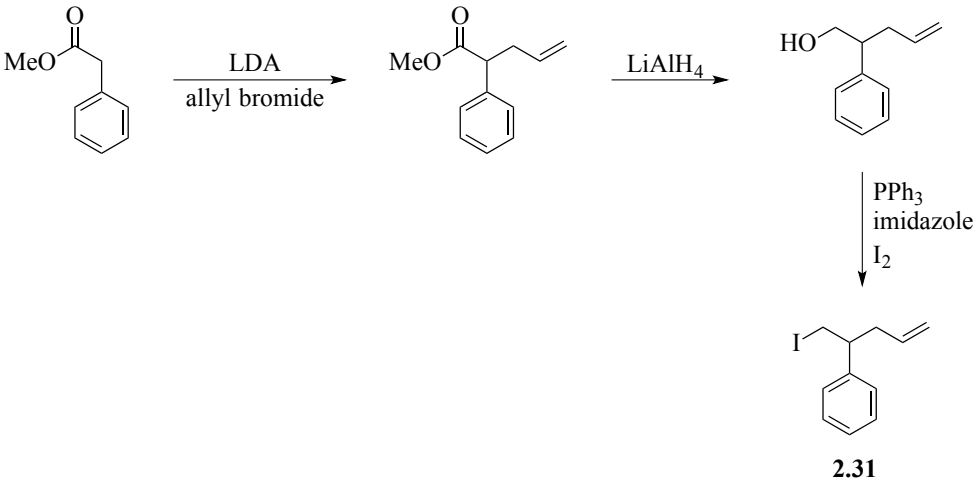
2.27

(*Z*)-1-iododec-4-ene (2.27, Scheme 2-6). The title compound was prepared according to a literature procedure by Yadav and co-workers.[63]



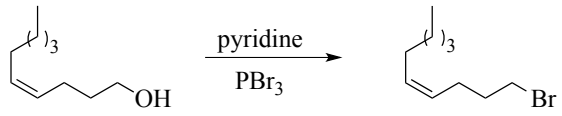
2.30

5-iodopent-1-ene (2.30, Figure 2-4). The title compound was prepared by an iodination reaction.[64]



2.31

(1-iodopent-4-en-2-yl)benzene (2.31, Figure 2-4). The title compound was synthesized by an alkylation[65] followed by a standard LAH reduction, and an iodination reaction.[66]

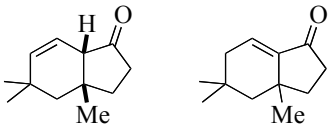


2.32

(*Z*)-1-bromodec-4-ene (2.32, Figure 2-5). The title compound was prepared by a bromination reaction.[67]

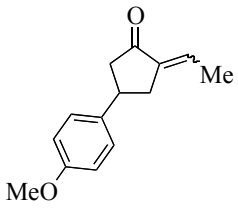
2.5.3 Intramolecular Carbonylative Alkyl Heck Results

General Procedure for the Intramolecular Carbonylative Alkyl Heck Reaction: In a glovebox, the alkyl iodide (1.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), *i*Pr_2NEt (2.0 equiv), and toluene (0.5 M) were combined in a 20 mL Parr reactor. The reactor was sealed and then removed from the glovebox. The Parr reactor was purged with carbon monoxide at 150 psi and then charged with 735 psi carbon monoxide. The reaction vessel was then placed in a 130 °C oil bath for 12 hr, after which, it was allowed to cool to room temperature before depressurizing. The Parr reactor was then opened and the reaction mixture was transferred out of the vessel by subsequent rinses with Et_2O. The combined organic layers were washed with brine. The aqueous layer was then extracted with Et_2O three times. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting enone was purified by flash chromatography with the specified solvent system.



2.10 **2.11**

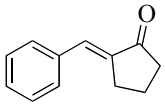
(*cis*)-3a,5,5-trimethyl-2,3,3a,4,5,7a-hexahydro-1H-inden-1-one (2.10, Table 2-2, entry 4) and 3a,5,5-trimethyl-2,3,3a,4,5,6-hexahydro-1H-inden-1-one (2.11, Table 2-2, entry 4). The title compounds were synthesized according to the general procedure using **2.5** (70 mg, 0.25 mmol), but the reaction time was 5 hr. The resulting enones were purified by flash chromatography (20:1 Hexanes:EtOAc) to afford **2.10** and **2.11** (33.0 mg, 0.185 mmol, 74% yield) as a yellow oil. The two regioisomers were partially separable. Analytical data for **2.10**: **IR** (thin film, cm^{-1}) 3011, 2918, 2848, 1443, 1226, 1176, 689; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.58 (m, 2 H), 2.35 (s, 1 H), 2.29 (m, 2 H), 1.90 (m, 1 H), 1.65 (m, 1 H), 1.39 (s, 2 H), 1.21 (s, 3 H), 1.06 (s, 3 H), 0.97 (s, 3 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 219.53, 138.63, 118.71, 56.28, 44.66, 38.25, 35.92, 35.17, 32.59, 32.03, 30.18, 28.41; **GCMS** calculated for [M] 178.14, found 178. Analytical data for **2.11**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 6.57 (t, J = 4.4 Hz, 1 H), 2.44 – 2.19 (m, 2 H), 2.03 (m, 2 H), 1.90 - 1.95 (m, 1 H), 1.69 (m, 1 H), 1.47 – 1.44 (m, 1 H), 1.23 (m, 1 H), 1.16 (s, 3 H), 1.06 (s, 3 H), 0.98 (s, 3 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 207.04, 145.42, 130.54, 49.94, 39.41, 37.55, 35.60, 35.27, 31.26, 31.16, 30.09, 25.96.



2.13

2-ethylidene-4-(4-methoxyphenyl)cyclopentanone (2.13, Table 2-2, entry 1). The title compound was synthesized according to the general procedure using **2.12** (150 mg, 0.474 mmol). The resulting enone was purified by flash chromatography (30:1

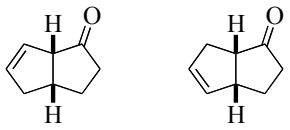
Hexanes/EtOAc) to afford **2.13** (79.0 mg, 0.365 mmol, 77% yield) as an inseparable mixture of stereoisomers (10:1 trans:cis) as a pale yellow oil. Analytical data for **2.13-*cis isomer***: **IR** (thin film, cm^{-1}) 2925, 2855, 1720, 1652, 1612, 1513, 1249, 1035, 829; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 6.09 (m, 1 H), 3.79 (s, 3 H), 3.33 (m, 1 H), 2.96 (dd, *J* = 15.3, *J* = 7 Hz, 1 H), 2.77 – 2.63 (m, 2 H), 2.47 (dd, *J* =17.6, *J* = Hz, 1 H), 2.16 (d, *J* = 7.2, 3 H); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 206.92, 158.37, 136.20, 135.64, 135.38, 127.59, 114.08, 55.28, 48.14, 40.04, 38.7, 14.49; **LRMS** (ESI) calculated for $[C_{14}H_{16}O_2+Na]^+$ 239.10, found 239.10. Analytical data for **2.13-*trans isomer***: **IR** (thin film, cm^{-1}) 2925, 2854, 1721, 1652, 1513, 1248, 1203, 1180, 1035, 829; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 6.68 (m, 1 H), 3.79 (s, 3 H), 3.34 (p, *J* = 8.7 Hz, 1 H), 3.07 (dd, *J* = 16.3 Hz, *J* = 7.75 Hz, 1 H), 2.74 (dd, *J* = 17.7 Hz, *J* = 7.6 Hz, 1 H), 2.63 – 2.40 (m, 2 H), 1.82 (d, *J* = 6.9 Hz, 3 H); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 205.23, 158.23, 138.35, 135.78, 131.34, 127.56, 113.98, 55.21, 46.34, 38.16, 35.24, 15.16; **LRMS** (ESI) calculated for $[C_{14}H_{16}O_2+Na]^+$ 239.10, found 239.10.



2.15

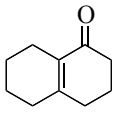
(*E*)-2-benzylidenecyclopentanone (2.15, Table 2-2, entry 2). The title compound was synthesized according to the general procedure using **2.14** (70 mg, 0.257 mmol). The resulting enone was purified by flash chromatography (20:1

hexanes/EtOAc) to afford **2.14** (24.3 mg, 0.141 mmol, 55% yield) as a pale yellow oil. Physical and spectral data were in accordance with the literature data.[68]



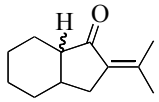
2.17 **2.18**

(*cis*)-2,3,3a,4-tetrahydropentalen-1(6aH)-one (2.17, Table 2-2, entry 3) and (*cis*)-3,3a,6,6a-tetrahydropentalen-1(2H)-one (2.18, Table 2-2, entry 3). The title compounds were synthesized according to the general procedure using **2.16** (200 mg, 0.90 mmol). The resulting enones were purified by flash chromatography (15:1 Pentane/Et_2O) to afford a 1.3:1 inseparable mixture of **2.17** and **2.18** (67.7 mg, 0.554 mmol, 62% yield) as a yellow oil. *Warning: volatile compound.* Physical and spectral data were in accordance with the literature data.[69]



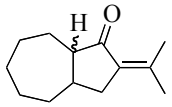
2.20

3,4,5,6,7,8-hexahydronaphthalen-1(2H)-one (2.20, Table 2-2, entry 5.) The title compound was synthesized according to the general procedure using **2.19** (150 mg, 0.60 mmol). The resulting enone was purified by flash chromatography (20:1 Hexanes/EtOAc) to afford **2.20** (63.6 mg, 0.423 mmol, 70% yield) as a yellow oil. Physical and spectral data for **2.20** were in accordance with the literature data.[70]



2.22

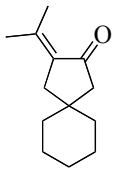
2-(propan-2-ylidene)octahydro-1H-inden-1-one (2.22, Table 2-3, entry 1). The title compound was synthesized according to the general procedure using **2.21** (70 mg, 0.25 mmol). The resulting enone was purified by flash chromatography (25:1 hexanes/EtOAc) to afford **2.22** (41.0 mg, 0.230 mmol, 92% yield) as an inseparable mixture of *cis* and *trans* stereoisomers as a colorless oil. Analytical data for **2.22**: **IR** (thin film, cm^{-1}) 2927, 2852, 1708, 1637, 1446; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.63, (dd, J = 14.8, J = 6.2, Hz 1 H), 2.52 (m, 1 H), 2.31 – 0.77 (m, 22 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 207.63, 206.83, 147.77, 146.19, 131.19, 130.18, 56.80, 50.96, 40.65, 34.39, 33.91, 33.02, 32.34, 29.66, 26.10, 25.71, 25.52, 24.27, 24.23, 24.09, 23.07, 22.71, 20.43, 20.37; **LRMS** (ESI) calculated for $[C_{12}H_{18}O+Na]^+$ 201.13, found 201.12.



2.24

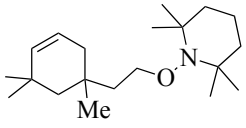
2-(propan-2-ylidene)octahydroazulen-1(2H)-one (2.24, Table 2-3, entry 2). The title compound was synthesized according to the general procedure using **2.23** (100 mg, 0.34 mmol). The resulting enone was purified by flash chromatography (30:1 hexanes/EtOAc) to afford **2.24** (53.4 mg, 0.277 mmol, 82% yield) as an inseparable mixture of *cis* and *trans* stereoisomers as a colorless oil. Analytical data for **2.24**: **IR** (thin film, cm^{-1}) 2924, 2851, 1704, 1636; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.78 – 2.66 (m, 1 H), 2.48 – 1.19 (m, 19 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 209.79, 208.48, 146.51.,

145.87, 131.51, 131.12, 56.49, 55.31, 40.40, 37.54, 36.48, 35.71, 35.68, 33.95, 31.44, 28.44, 28.25. 28.21, 27.98, 27.60, 27.18, 26.89, 24.28, 24.19, 20.44, 20.40; **LRMS** (ESI) calculated for $[C_{13}H_{20}O+H]^+$ 193.16, found 193.15.



2.26

3-(propan-2-ylidene)spiro[4.5]decan-2-one (2.26, Table 2-3, entry 3). The title compound was synthesized according to the general procedure using **2.25** (64.0 mg, 0.22 mmol). The resulting enone was purified by flash chromatography (20:1 hexanes/EtOAc) to afford **2.26** (38.1 mg, 0.198 mmol, 90% yield) as a colorless oil. Analytical data for **2.26**: **IR** (thin film, cm^{-1}) 2925, 2853, 1708, 1633; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.40 (t, *J* = 1.5 Hz, 2 H), 2.20 (s, 2 H), 2.19 (t, *J* = 1.9 Hz, 3 H), 1.80 (s, 3 H), 1.49 = 1.35 (m, 10 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 207.12, 147.40, 130.87, 37.63, 36.23, 25.94, 24.3, 22.83, 20.50 ; **LRMS** (ESI) calculated for $[C_{13}H_{20}O+Na]^+$ 215.14, found 215.11.



2.34

2,2,6,6-tetramethyl-1-(2-(1,5,5-trimethylcyclohex-2-en-1-yl)ethoxy)piperidine (TEMPO reaction byproduct) (2.35, Scheme 2-7). The title compound was synthesized according to the procedure using **2.5** (111.3 mg, 0.41 mmol), but required the

addition of TEMPO (64.1 mg, 0.41 mmol) and using a 5 hr reaction time. The resulting product was purified by flash chromatography (50:1 Hexanes/EtOAc) to afford **2.35**. The yield was obtained using 1,4-dinitrobenzene as an internal NMR standard. Analytical data for **2.35**: **IR** (thin film, cm^{-1}) 2929, 2869, 2360, 2342, 1455, 1373, 1359; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.56 – 5.52 (m, 1 H), 5.39 (d, *J* = 10 Hz, 1 H), 3.76 (m, 2 H), 1.79 – 1.68 (m, 2 H), 1.59 – 1.22 (m , 10 H), 1.15 (s, 6 H), 1.07 (s, 6 H), 1.02 (s, 3 H), 0.94 (s, 6 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 135.23, 123. 48, 73.86, 59.50, 47.57, 42.09, 39.52, 38.64, 34.31, 33.03, 33.00, 31.44, 29.89, 29.16, 28.56, 20.20, 20.17, 17.13; **LRMS** (ESI) calculated for $[C_{20}H_{37}NO+H]^+$ 308.30, found 308.29.

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Chapter 3

Palladium-Catalyzed Heck-Type Cyclizations of Alkyl Iodides

3.1. Introduction

The palladium-catalyzed Heck reaction is a fundamental synthetic transformation in chemical synthesis, which enables the direct cross-coupling of aryl or vinyl halides or sulfonates and simple alkenes.[1] The utility of this process has been well demonstrated in synthesis;[2-4] however, the Heck reaction has not been generally applicable to alkyl electrophiles.[5] The challenge in developing a Heck reaction that employs alkyl electrophiles has been largely attributed to the general reluctance of sp^3-hybridized alkyl halides to undergo oxidative addition processes with low-valent transition metals,[6-10] as well as the predisposition of the putative alkyl palladium species to undergo β-hydride elimination, resulting in overall dehydrohalogenation (Figure 3-1).[11,12]

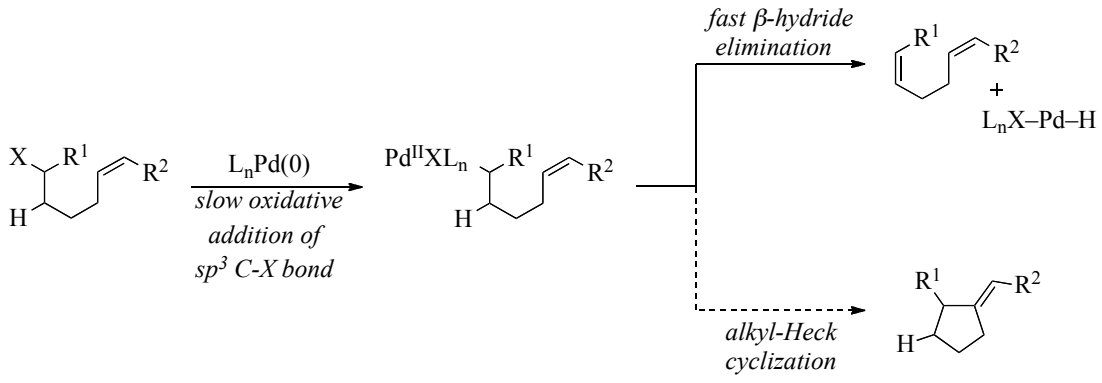
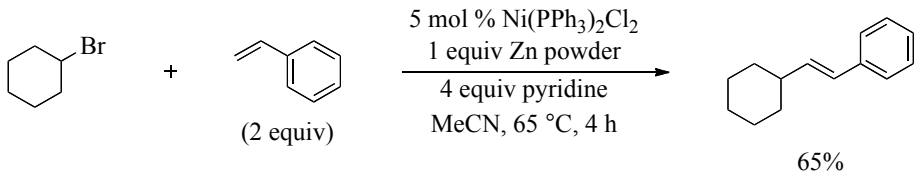


Figure 3-1. Challenges in Developing Alkyl-Heck Processes

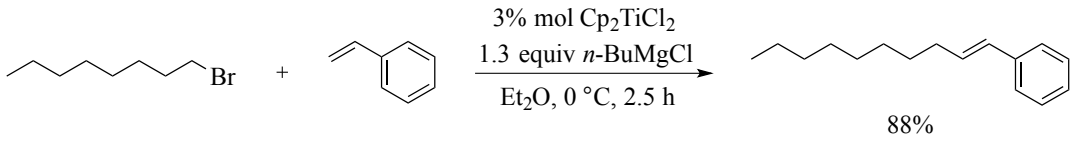
3.2 Background

Despite the challenges that have impeded the development of a palladium-catalyzed alkyl Heck transformation, useful strategies have emerged that facilitate alkyl Heck-type transformations utilizing metals other than palladium. Nickel was found to catalyze an alkyl Heck-type reaction of alkyl bromides with styrene and methyl acrylate (Scheme 3-1).[13] Stoichiometric zinc was required to regenerate the active catalyst.



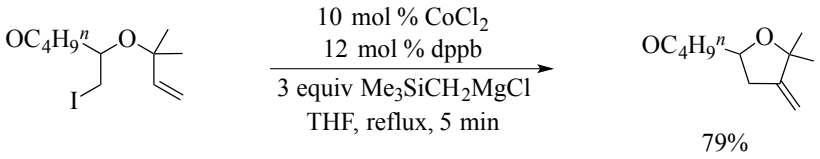
Scheme 3-1. Nickel-Catalyzed Alkyl Heck-Type Reaction

Kambe and co-workers reported a titanocene mediated alkyl-Heck-type reaction (Scheme 3-2).[14,15] Primary and secondary alkyl bromides as well as secondary alkyl chlorides were suitable electophiles to provide the corresponding *E*-alkenes; however, stoichiometric highly reactive Grignard reagents were required, greatly limiting the substrate scope of the reaction.



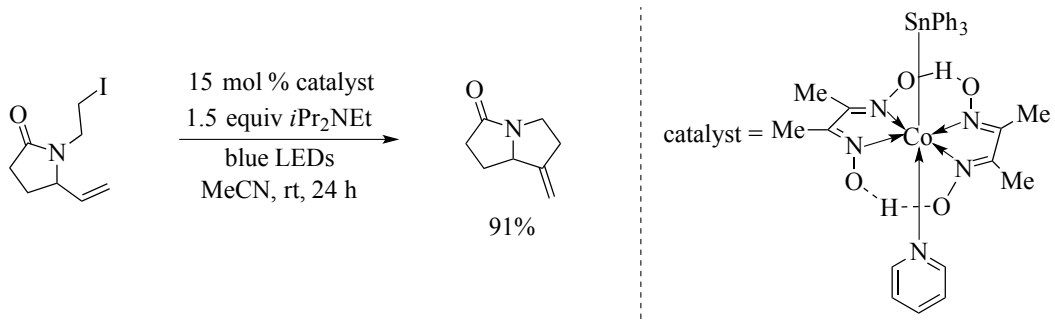
Scheme 3-2. Titanocene-Catalyzed Alkyl Heck-Type Reaction

Oshima and coworkers reported a cobalt-catalyzed intramolecular Heck-type cyclization for alkyl iodides and bromides (Scheme 3-3).[16] This transformation has been proposed to be radical mediated, and requires stoichiometric quantities of alkyl Grignard reagents to regenerate the active catalyst. An intermolecular reaction that utilizes the same reaction conditions was also reported.



Scheme 3-3. Cobalt-Catalyzed Alkyl Heck-Type Cyclization

The Carreira lab reported a cobalt-catalyzed intramolecular alkyl-Heck-type cyclization of alkyl iodides (Scheme 3-4).[17] The transformation did not require a Grignard reagent to regenerate the catalyst. As such, the scope of the reaction included enones and acrylates. A cobaloxime catalyst was employed that could be regenerated from hydridocobalt with amine base. This method relied upon blue LED's to introduce the homolytic cleavage of the cobalt-tin bond. An isopropyl group could be utilized instead of the tin ligand, albeit providing the majority of the products in lower yields.



Scheme 3-4. Cobalt-Catalyzed Intramolecular Cyclization of Alkyl Iodides Employing Stannyl Cobaloximes and Blue LEDs

Seminal work by the Fu lab demonstrated the ability of palladium to catalyze an intramolecular alkyl-Heck reaction (Schem 3-2).[18] $Pd_2(MeO\text{-}dba)_3$ was employed as a precatalyst because the more electronically rich dba ligands have shown to dissociate from the metal as a higher rate, allowing for the active catalyst to be more efficiently generated; however, the scope of this reaction is limited to cyclopentene synthesis, utilizing only primary halides and mono-substituted alkenes.

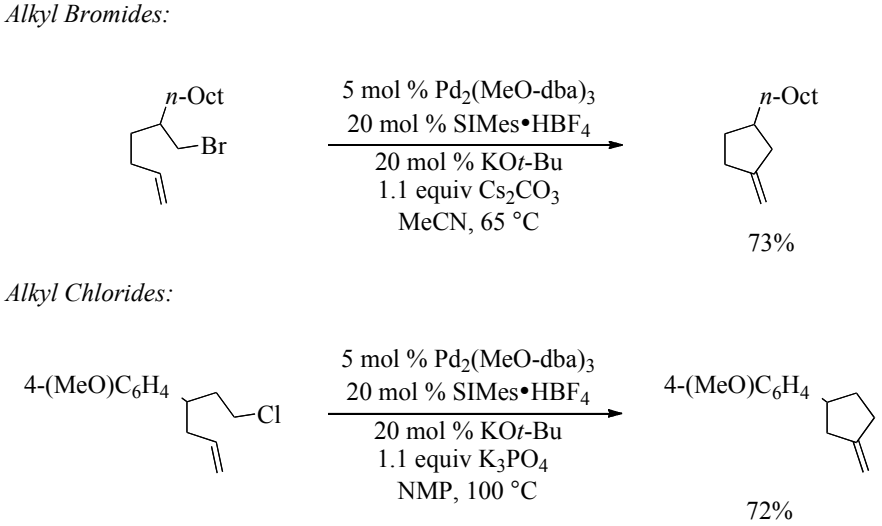
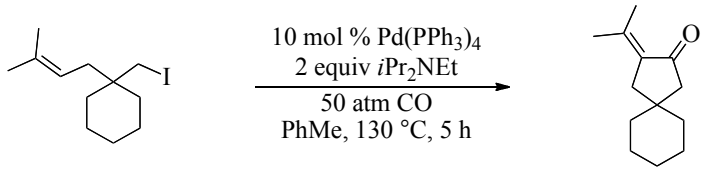


Figure 3-2. Palladium-Catalyzed Heck Reaction of Primary Halides with Monosubstituted Alkenes

Alkyl-Heck-type processes of broad substrate scope, capitalizing on the mild conditions afforded by palladium(0) catalysis while leveraging the synthetic accessibility of alkenes and alkyl halides, would constitute powerful transformations for organic synthesis. We recently reported our initial efforts toward the development of alkyl Heck-type processes in the form of a palladium(0)-catalyzed carbonylative cyclization of simple unsaturated alkyl iodides, providing expedient access to numerous classes of cycloalkenones (Scheme 3-5).[19]



Scheme 3-5. Palladium-Catalyzed Carbonylative Heck-Type Reaction of Alkyl Iodides

Herein, we demonstrate that commercially available reagents readily facilitate an alkyl Heck-type reaction. We found that mono- and bicyclic Heck products could be readily accessed from a wide variety of alkyl iodides, and substitution of the alkene was well tolerated.

3.3 Results and Discussion

3.3.1 Reaction Development

Our studies commenced with acyclic primary iodide **3.1** (Figure 3-3). This

substrate was examined to determine if a 5-*exo* alkyl Heck-type process would outcompete a possible 6-*exo* carbonylative alkyl-Heck-type cyclization.[20] Iodide **3.1** was subjected to identical conditions to those previously employed in our laboratory to generate carbonylative alkyl Heck-type products. Upon reaction, cyclopentene **3.3** was formed in good yield from an alkyl-Heck-type process, and *no formation of carbonylative cyclization product **3.2** was observed* (Figure 3-3).

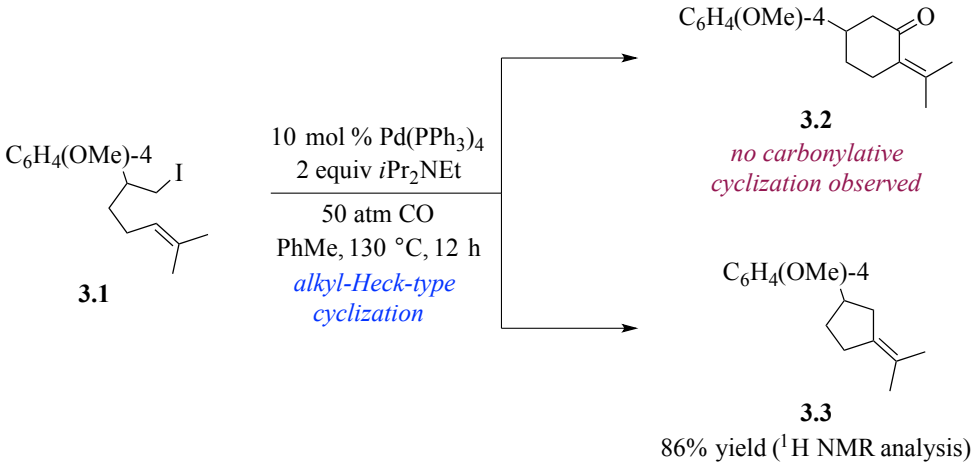
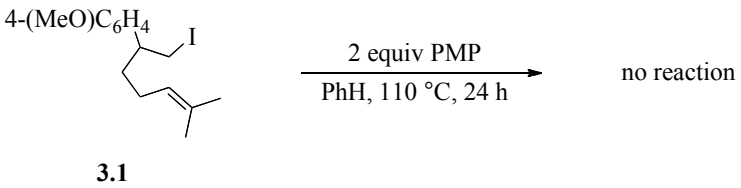


Figure 3-3. Competition Experiment Between a 5-*exo* Alkyl Heck-Type Cyclization and a 6-*exo* Carbonylative Alkyl-Heck-Type Cyclization

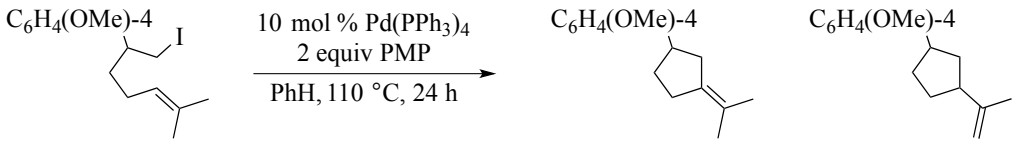
Furthermore, no product formation was observed in the absence of palladium (Scheme 3-6).



Scheme 3-6. Carbocyclization Reaction Attempted in the Absence of Palladium

Following this promising result, we sought to determine whether CO was necessary for the success of the cyclization reaction. When iodide **3.1** was reacted in the presence of varying pressures of carbon monoxide, a significant difference in the amount of alkene isomerization was noted. In the absence of carbon monoxide, alkene isomers **3.3** and **3.4** were formed with a slight preference for the more substituted alkene **3.3** (Table 3-1, entry 1). Running the reaction under increasing amounts of carbon monoxide minimized the formation of alkene isomer **3.4** (entries 2 and 3); however, no benefit was observed over 10 atm of CO (entry 4).

Table 3-1. Effect of Carbon Monoxide upon Alkene Isomer Formation



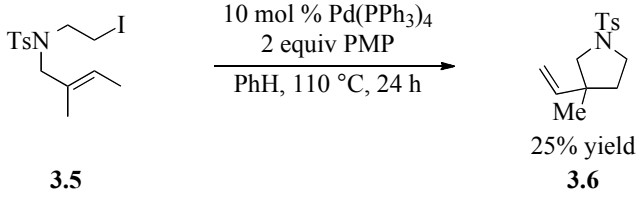
3.1 **3.3** **3.4**

CO (atm)	%Yield	Ratio of Alkene Isomers (**3.3**:**3.4**)
0 (1 atm Ar)	76[a]	2.8 : 1
2	85[a]	8.3 : 1
10	84[b]	20.8 : 1
50	86[a]	20.5 : 1

[a]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield. [c]Ratios determined from crude ^{1}H NMR spectroscopy.

Furthermore, the presence of CO was noted to significantly improve yields for certain substrates such as pyrrolidine **3.5**. When carbon monoxide was not present, **3.6**

was generated in low yield, and significant amounts of unidentifiable decomposition were observed. (Scheme 3-7).

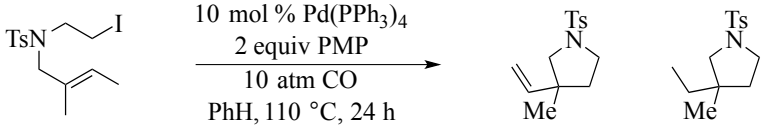


3.5 **3.6**

Scheme 3-7. Palladium-Catalyzed Carbocyclization to a Pyrrolidine in the Absence of CO

Further optimization studies were required for the alkyl iodide **3.5** as there were large quantities of reduced product **3.7** being generated in addition to pyrrolidine **3.6**. Running the reaction under 10 atm of carbon monoxide greatly increased the efficiency of the reaction (entries 1 and 2). It was found that lowering the temperature from 110 °C to 100 °C caused increased reduction formation (Table 3-2, entry 3). Toluene was found to generate more reduction than when benzene was utilized, most likely attributed to facile benzylic hydrogen abstraction (entry 4). Using a weaker base also resulted in more reduction formation (entry 5).

Table 3-2. Optimization Efforts to Limit Reduction of Alkyl Iodides



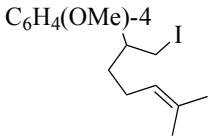
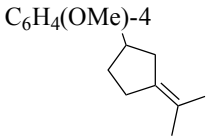
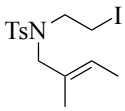
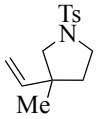
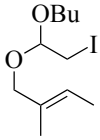
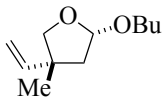
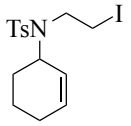
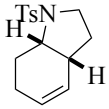
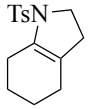
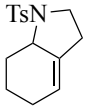
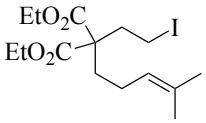
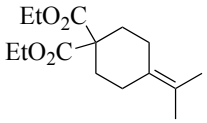
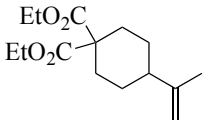
3.5 **3.6** **3.7**

Entry	Variation from standard conditions above	%yield **3.6**[a]	%yield **3.7**[a]
1	none	70	7
2	1 atm Ar instead of 10 atm CO	23	40
3	100 °C instead of 110 °C	55	16
4	Toluene instead of benzene	47	19
5	*i*Pr_2NEt instead of PMP	40	16

[a]Yield determined by ^{1}H NMR analysis usign 1,3,5-trimethoxybenzene as an internal standard.

Next, we began to examine the substrate scope. As previously mentioned, acyclic alkyl iodide **3.1** efficiently cyclizes to provide cyclopentene **3.3** in 80% yield (Table 3-3, entry 1). Primary iodide **3.5** with a trisubstituted alkene provided pyrrolidine **3.6**, demonstrating the ability of this carbocyclization to synthesize quaternary centers (entry 2). The ability to form quaternary centers was also showcased in the cyclization of acetal iodide **3.8** to provide substituted tetrahydrofuran **3.9** (entry 3). Bicycles were also easily synthesized via carbocyclization of iodide **3.10** to provide alkene isomers **3.11**, **3.12**, **3.13** in a 74% yield (entry 4). Notably, this process is not limited to cyclopentene synthesis. 6-*exo* cyclization of **3.14** was realized with Thorpe-Ingold diesters installed in the substrate to provide **3.15** and **3.16** in 70% yield.

Table 3-3. Palladium-Catalyzed Carbocyclizations of Primary Alkyl Iodides[a]

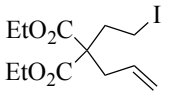
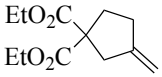
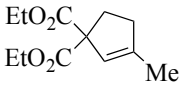
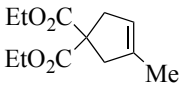
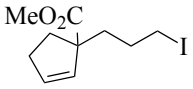
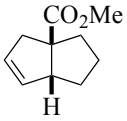
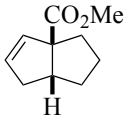
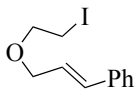
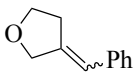
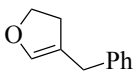
Entry	Substrate	Product	%Yield[b,c]
1	 **3.1**	 **3.3**	80
2	 **3.5**	 **3.6**	70[d]
3	 **3.8**	 **3.9**	73[e] 83:17 dr
4	 **3.10**	 **3.11**  **3.12**  **3.13**	74 9:1.2:1 **3.11**:**3.12**:**3.13**
5	 **3.14**	 **3.15**  **3.16**	70 **3.15**:**3.16** 2.3:1

[a]All reactions run 0.5 M in PhH at 110 °C under 10 atm CO in the presence of 10 mol % $Pd(PPh_3)_4$ and 2.0 equiv of PMP. [b]Yields of isolated product. [c]The product ratios were determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [d]Yield calculated by ^{1}H NMR spectroscopy of crude reaction mixtures using internal standard. [e]Reaction temperature is 130 °C.

While running the reaction under 10 atm of CO pressure generally helped to mitigate the formation of alkene isomers, some substrates still generated multiple alkene

isomers in poor ratios. For example, monosubstituted alkene **3.17** generated alkene isomers **3.18**, **3.19**, and **3.20** in a 5:1.6:1 ratio (Table 3-4, entry 1). The lack of selectivity may be attributed to the relative energies of the tri-substitued alkenes formed. This was also observed in reaction of iodide **3.21** as bicyclic products **3.22** and **3.23** were generated in a 1.5:1 ratio (entry 2). Finally, acyclic iodide **3.24** was reacted, and demonstrated a slight preference was observed for the styrenyl product **3.25** over enol ether product **3.26** (entry 3).

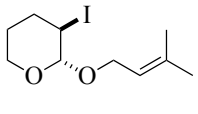
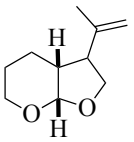
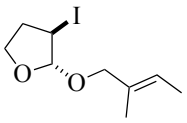
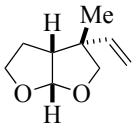
Table 3-4. Palladium-Catalyzed Carbocyclizations Resulting in Significant Alkene Isomerization[a]

Entry	Substrate	Product		%Yield[b,c]
1	 **3.17**	 **3.18**	 **3.19**  **3.20**	72[d,f] 5:1.6:1 **3.18**:**3.19**:**3.20**
2	 **3.21**	 **3.22**	 **3.23**	64[d,e] 1.5:1 **3.22**:**3.23**
3	 **3.24**	 **3.25** 1:1 *E*:*Z*	 **3.26**	42[e,f] 8:1 **3.25**:**3.26**

[a]All reactions run 0.5 M in PhH at 110 °C under 10 atm CO in the presence of 10 mol % $Pd(PPh_3)_4$ and 2.0 equiv of PMP, 2 h. [b]Yields of isolated product. [c]The product ratios were determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [d]Yield calculated by ^{1}H NMR spectroscopy of crude reaction mixtures using internal standard. [e]2.0 equiv iPr$_2$NEt used as base. [f]Reaction time 18 h.

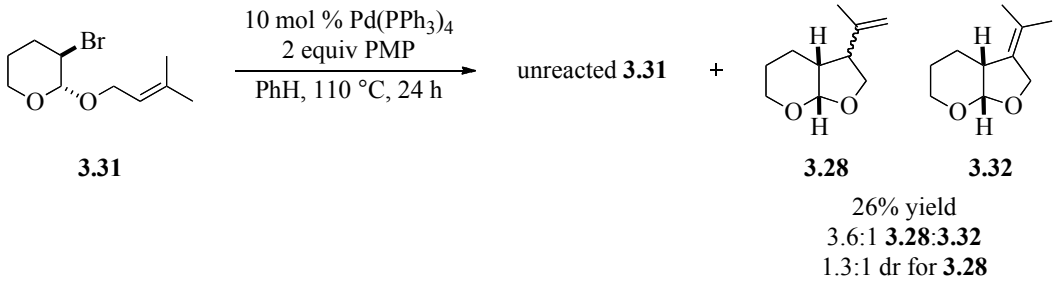
We also explored the potential of a palladium-catalyzed carbocyclization using secondary alkyl halides. Running the reaction under carbon monoxide did not help to increase the efficiency of the reaction. As a result, reactions for secondary alkyl halides were able to be conducted in a glass pressure tube instead of a stainless steel pressure reactor. Secondary alkyl iodide **3.27** was efficiently cyclized to [6,5]-bicycle **3.28** (Table 3-5, entry 1). Iodide **3.29** reacted successfully to produce **3.30** with high stereoselectivity (entry 2).

Table 3-5. Palladium-Catalyzed Carbocyclization for Secondary Alkyl Iodides[a]

Entry	Substrate	Product	%Yield[b,c]
1	 **3.27**	 **3.28**	62 58:42 dr
2	 **3.29**	 **3.30**	66[d] >95:5 dr

[a]All reactions run 0.5 M in PhH at 110 °C under Ar the presence of 10 mol % $Pd(PPh_3)_4$ and 2.0 equiv of PMP. [b]Yields of isolated product. [c]The product ratios were determined by ^1H NMR spectroscopy of crude reaction mixtures. [d]Yield calculated by ^1H NMR spectroscopy of crude reaction mixtures using internal standard.

We also investigated the potential to employ alkyl bromides our palladium-catalyzed carbocyclization; however, reaction of alkyl bromide **3.31** proceeded slowly, providing a 26% ^1H NMR yield of cyclization products **3.28** and **3.29** after 24 hours (Scheme 3-8). Significant amounts of unreacted starting material remained.



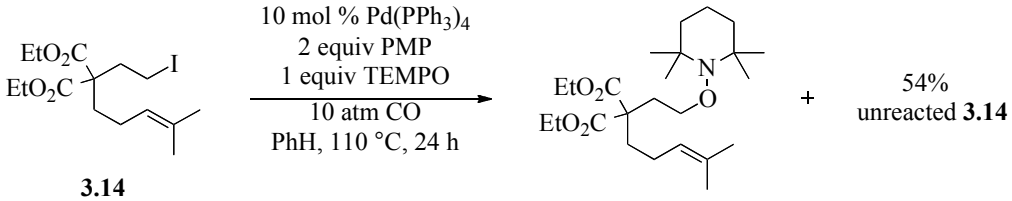
3.31 **3.28** **3.32**

26% yield
3.6:1 **3.28**:**3.32**
1.3:1 dr for **3.28**

Scheme 3-8. Palladium-Catalyzed Carbocyclization of Alkyl Bromides

3.3.2 Mechanistic Studies

Alkyl halides are known to react with palladium(0) via both S_N2[21,22] and single-electron transfer pathways.[23] In order to probe the potential intermediacy of carbon-centered radicals in this reaction, we attempted the cyclization in the presence of TEMPO.[24] We chose to employ iodide **3.14** that undergoes a 6-*exo* cyclization, which is slower than a 5-*exo* cyclization, as a slower cyclization may increase the likelihood of the radical being intercepted (Scheme 3-9). Upon reaction, formation of alkyl-Heck-type products were not observed. Instead, TEMPO adduct **3.33** and a significant amount of unreacted starting material was noted. This result suggests the presence of a carbon-centered radical intermediate in the reaction mechanism.

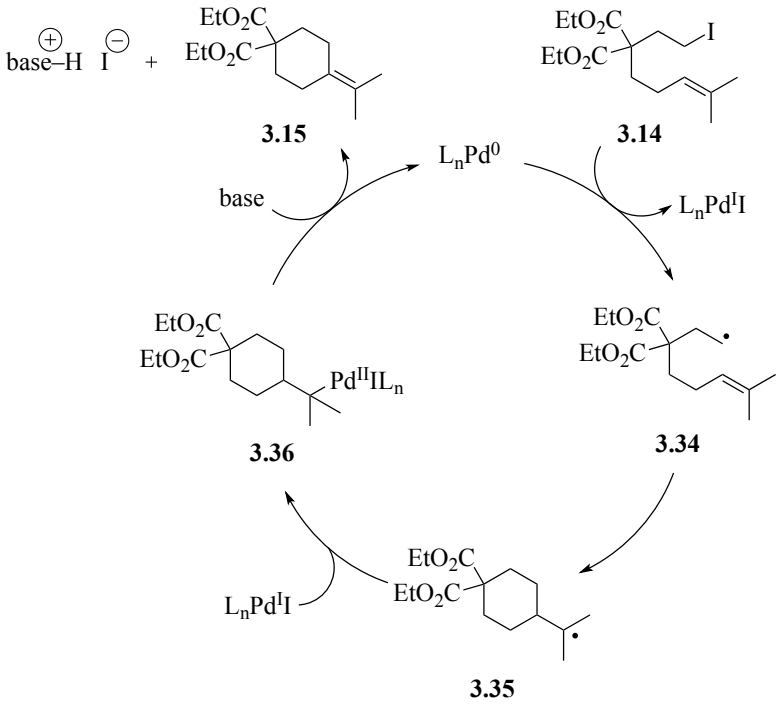


3.14 **3.33**

24% yield (^{1}H NMR analysis)

Scheme 3-9. Palladium-Catalyzed Alkyl-Heck-Type Reaction Run in the Presence of TEMPO

Although the determination of a precise reaction pathway will require more extensive studies, our preliminary mechanistic hypothesis is illustrated in Scheme 3-10. Oxidative addition of palladium(0) to iodide **3.14** could occur via single-electron transfer to generate carbon-centered free radical **3.34**.[25-28] Cyclization of the radical onto the pendant alkene could then generate a second carbon-centered radical **3.35**. Subsequently, the interception of the carbon-centered radical by a putative palladium(I) species generates **3.36**, and β-hydride elimination of alkylpalladium(II) **3.36** provides cyclohexene **3.15**. Lastly, base regenerates the active palladium(0) species. Substrate dehydrohalogenation was not a significant side reaction in the carbocyclization, which is consistent with this mechanism.



Scheme 3-10. Plausible Catalytic Cycle for the Carbocyclization

Presently, the role of carbon monoxide in the reaction is unclear. It is possible that the formation of a less electron-rich $Pd(PPh_3)_x(CO)_y$ species, which are formed under CO pressure,[29-31] results in a more efficient hybrid organometallic-radical process. Other transition-metal-catalyzed reactions have benefited from the presence of carbon monoxide although it is not incorporated into the products.[32-35]

In order to further probe the possibility of the hybrid organometallic-radical pathway, preliminary DFT mechanisitic calculations were employed to determine why a classical Pd(0) to Pd(II) oxidative addition is inoperative. The Baik group at Indiana University performed all calculations. The reaction energy profile for the two-electron process is shown in Figure 3-4; however, the system employed in the DFT calculations is a simplified version of chemistry described. Also trialkylphosphines were studied, not the triphenylphosphines employed in this work. DFT calculations[36-40] correctly indicate that the Pd(0) complex is most stable with two ligands attached to the metal center. The oxidative addition of alkylpalladium species is only slightly uphill energetically, with an increase in 4.5 kcal/mol from the oxidative addition of iodide **3.39** to square-planar palladium(II) complex **3.40**. Rearrangement to trans-palladium species **3.41** would result the oxidative addition step being 4.4 kcal/mol downhill overall. This finding is in agreement with the general propensity of palladium(0) complexes to promote oxidative addition. The reason this traditional pathway is inoperative in this reaction that the lowest energy transition state from complex **3.41** to the desired product **3.43** is **3.42-TS**, which is practically unreachable under standard conditions at 30.8 kcal/mol.

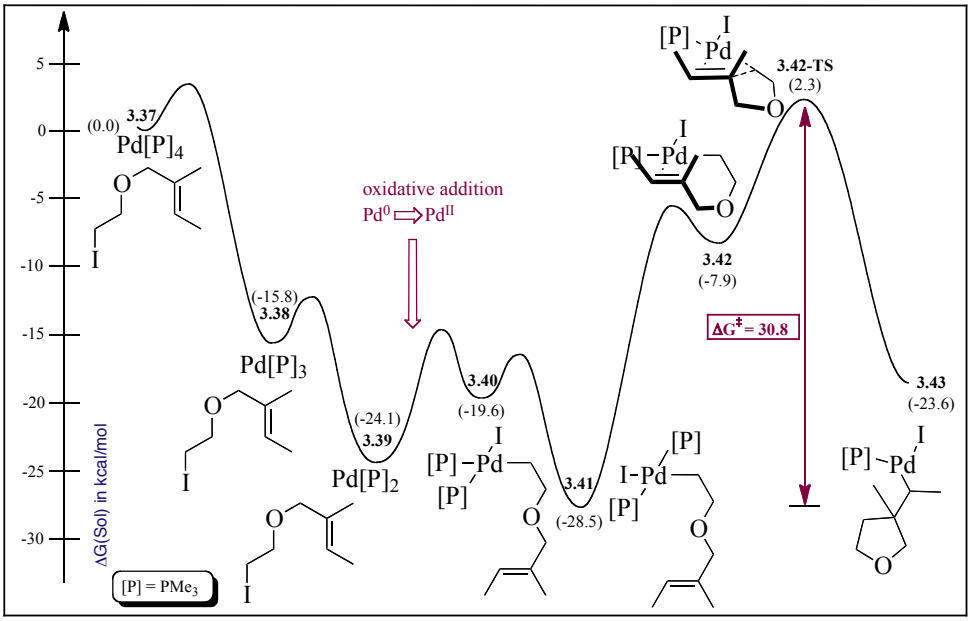


Figure 3-4. Preliminary DFT calculations of Palladium-Catalyzed Alkyl-Heck Reaction via a Two-Electron Pathway

An alternate organometallic-radical pathway, which would proceed through a single-electron oxidative addition process and generate a palladium(I) species, is illustrated in Figure 3-5. Preliminary calculations suggest this process is uphill by 9.1 kcal/mol. The cyclization of resulting carbon-centered radical **3.44** is associated with a reasonable barrier of 21.4 kcal/mol compared to 30.8 kcal/mol for the two-electron pathway. Thus, the two-electron oxidative addition process is not a favored process because accessing the final product is kinetically uphill via this reaction.

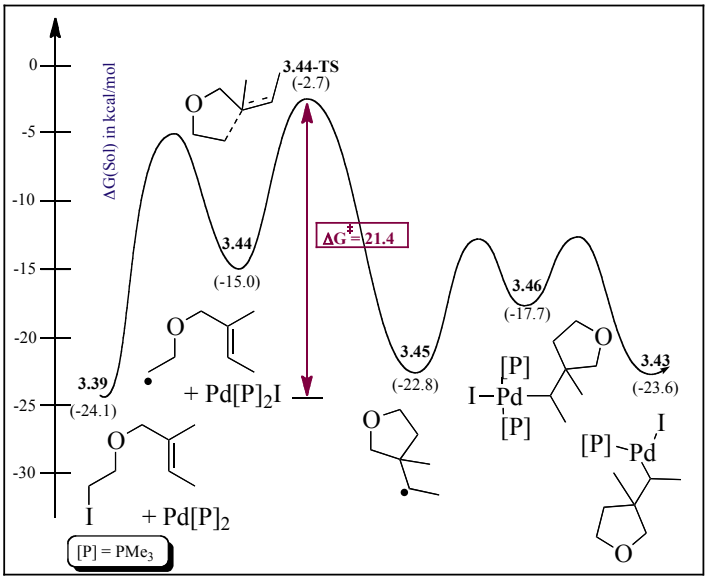


Figure 3-5. Preliminary DFT calculations of Palladium-Catalyzed Alkyl-Heck Reaction via a Single-Electron Pathway

3.4 Summary

In conclusion, we have disclosed a palladium-catalyzed Heck-type reaction of alkyl iodides of broad substrate scope. This process is applicable to the synthesis of many types of common cyclic frameworks and tolerates a variety of substituted alkenes and alkyl iodides. Notably, quaternary centers were easily synthesized. We proposed the wide substrate scope of this transformation results from the hybrid organometallic-radical nature of the process, successfully overcoming the major challenges inherent in the development of palladium-catalyzed Heck reactions employing alkyl halide substrates. Finally, preliminary DFT studies conducted by the Baik group provide mechanistic support for the presence of a hybrid organometical-radical pathway, proposing it is ~10 kcal/mol lower in energy than the classic two-electron oxidative addition process.

3.5 Experimental

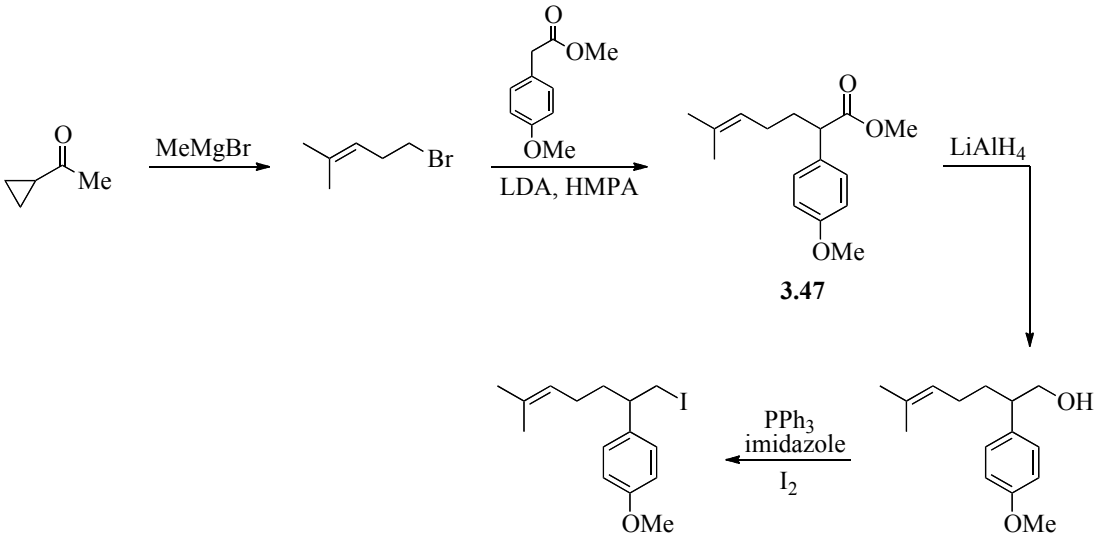
3.5.1 General Methods

Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model AVANCE III 400, 500, or 600 or a Bruker AMX 300 (^{1}H NMR at 300 MHz, 400 MHz, 500 MHz, or 600 MHz and ^{13}C NMR at 100 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.28 ppm, ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), coupling constants (Hz), and integration. Mass spectra were obtained either using a positive ion mode flow injection ESI (electrospray ionization) on a Bruker Daltonics, Inc., Billerica, MA, USA, BioToF Mass Spectrometer or electron impact ionization on an Agilent Technologies, Inc., Santa Clara, CA, USA, GCMS, 5973N Mass Selective Detector, using a HP-5MS, 30mx0.25mmx0.25um capillary column. Micromass (now Waters Corporation, 34 Maple Street, Milford, MA 01757) Quattro-II, Triple Quadrupole Mass Spectrometer, with a Z-spray nano-Electrospray source design, in combination with a NanoMate (Advion, 19 Brown Road, Ithaca, NY 14850) chip based electrospray sample introduction system and nozzle was also used. Visualization was accomplished with short wave UV light (254 nm), aqueous basic potassium permanganate solution, or ethanolic acidic *p*-anisaldehyde solution followed by heating. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63 μm) purchased from Silicycle. Tetrahydrofuran, diethyl ether, and

dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use. Acetone, 99.8%, Extra Dry was purchased from Acros. Carbon Monoxide, Research Purity 99.998% was purchased from Matheson Tri-Gas. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted. The pressure reactors used were purchased from Parr Instrument Company that included a 4310 Gage Block Assembly and a GP VS 22 mL A SKT 316SS ST CLS reaction vessel. The sealed tubes used were purchased from Ace Glass.

3.5.2 Preparation of Alkyl Iodide Substrates

Note: As a precaution alkyl iodides were immediately stored in a dark, inert atmosphere at -40 °C upon purification.

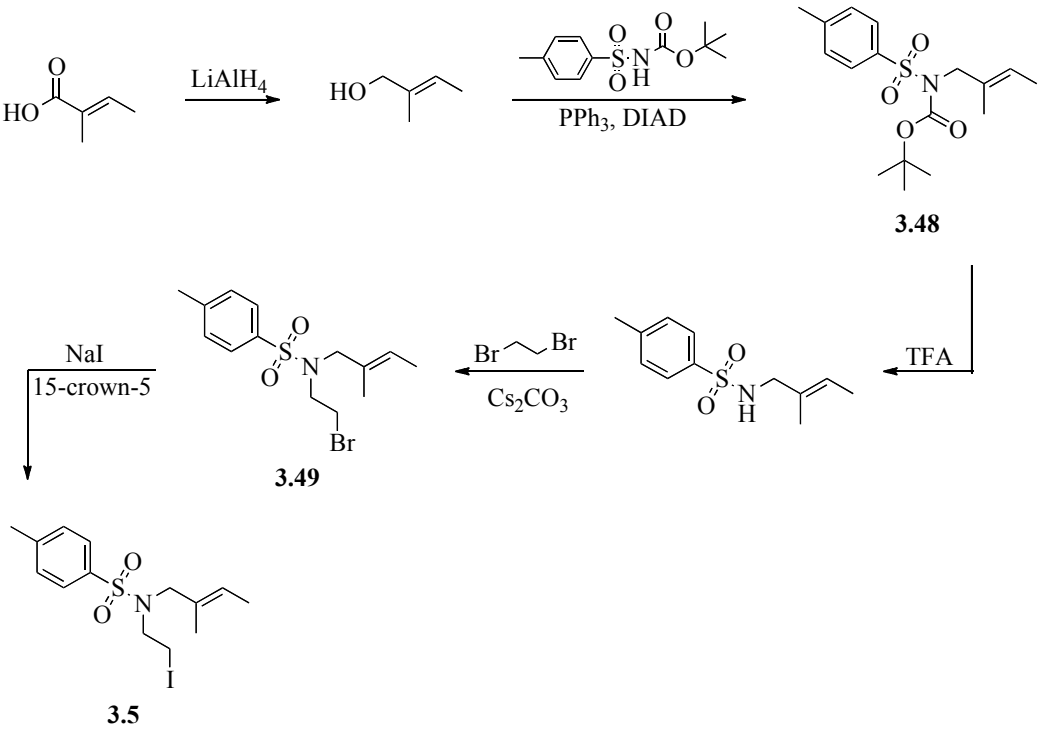


1-(1-iodo-6-methylhept-5-en-2-yl)-4-methoxybenzene (3.1, Table 3-3, entry 1). To a 0 °C solution of *i*Pr_2NH (3.2 mL, 22.48 mmol) in THF (73 mL) was added *n*BuLi (2.5 M in Et_2O, 9.0 mL, 22.48 mmol) dropwise. The reaction mixture was stirred

for 10 minutes, and then cooled to -78 °C. Methyl 4-methoxyphenylacetate (3.68 g, 20.44 mmol) in THF (5 mL) was added dropwise, and the reaction mixture was stirred for 30 minutes. The 1-bromo-4-methyl-3-pentene[41] (4.00 g, 24.53 mmol) was added in THF (5 mL) followed by HMPA (2.2 mL, 12.6 mmol). It was then warmed to room temperature and stirred overnight. The reaction was diluted with 1:1 Et_2O:Hexanes, washed with sat. aq. NH_4Cl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purified by column chromatography (20:1 Hex:EtOAc) to provide 3.11 g (58%) of **3.47** as a colorless oil. Analytical data for **(3.47)**: **IR** (thin film, cm^{-1}) 2951, 2857, 2837, 1738, 1611, 1512, 1248, 1164, 1036, 830.2; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 5.10 (t, *J* = 7.2 Hz, 1 H), 3.81 (s, 3 H), 3.66 (s, 3 H), 3.52 (t, *J* = 7.8 Hz, 1 H), 2.10 (m, 1 H), 1.94 (q, *J* = 7.2 Hz, 2 H), 1.79 (m, 1 H), 1.70 (s, 3 H), 1.54 (s, 3 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 174.8, 158.6, 132.5, 131.1, 128.9, 123.3, 113.9, 55.22, 51.88, 49.97, 33.49, 25.80, 25.72, 17.67; **LRMS** (ESI) calculated for $[C_{16}H_{22}O_3+Na]^+$ 285.15 , found 285.17.

To a 0 °C slurry of $LiAlH_4$ (758 mg, 19.97 mmol) in Et_2O (80 mL) was added a solution of **3.47** (2.62 g, 9.99 mmol) in Et_2O (25 mL) dropwise. After addition, the reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched via the following workup: 758 μL H_2O added slowly, followed by addition of 1.5 mL 10 wt % NaOH solution, and then 2.3 mL H_2O. The reaction was stirred vigorously until a white solid was formed. The reaction mixture was filtered, dried ($MgSO_4$), and concentrated to provide 2.33 g (~quant.) of the alcohol as a colorless oil that was taken on directly to the next reaction.

To a solution of the alcohol (1.3 g, 5.55 mmol) in Et_2O (35 mL) and MeCN (9 mL) was added PPh_3 (2.91 g, 11.10 mmol) and imidazole (756 mg, 11.10 mmol), followed by iodine (2.82 g, 11.10 mmol) under Ar at room temperature. The reaction stirred overnight. It was then diluted with CH_2Cl_2 and washed with aq. $Na_2S_2O_3$ and brine. The reaction mixture was then dried ($MgSO_4$), and concentrated *in vacuo*. Purified by column chromatography (20:1 Hex:EtOAc) to provide 1.54 g (80%) of **3.1** as a colorless oil. **(3.1)**: **IR** (thin film, cm^{-1}) 3445, 1646, 1511, 1248, 1177, 829.2, 506.2; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 5.08 (t, *J* = 6.6 Hz, 1 H), 3.82 (s, 3 H), 3.39 (m, 1 H), 3.34 (m, 1 H), 2.81 (m, 1 H), 1.89 (m, 3 H), 1.68 – 1.64 (m, 4 H), 1.54 (s, 3 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 158.4, 134.9, 132.1, 128.3, 123.6, 113.8, 55.20, 46.83, 35.79, 25.96, 25.70, 17.70, 14.82 ; **LRMS** (ESI) calculated for $[C_{15}H_{21}IO+Na]^+$ 367.05, found 367.00.



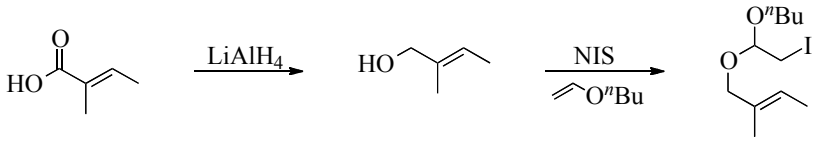
(*E*)-*N*-(2-iodoethyl)-4-methyl-*N*-(2-methylbut-2-en-1-yl)benzenesulfonamide (3.5, Table 3-3, entry 2). Sulfonamide **3.5** was synthesized via a modified Mitsunobu reaction[42] using (*E*)-2-methylbut-2-en-1-ol,[43] followed by Boc deprotection,[44] alkylation,[45] and iodination as described below.

Analytical data for **(3.48)**: **IR** (thin film, cm^{-1}) 3648, 2931, 1715, 1598, 1257, 910.2, 674..9; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 7.8 Hz, 2 H), 5.05 (m, 1 H), 4.40 (s, 2 H), 2.45 (s, 3 H), 1.66 (d, *J* = 7.2 Hz, 3 H), 1.61 (s, 3 H), 1.36 (s, 9 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 151.0, 144.0, 137.1, 130.9, 129.0, 128.1, 121.6, 83.95, 53.29, 27.78, 21.56, 13.72, 13.18; **LRMS** (ESI) calculated for $[C_{17}H_{25}NO_4S+H]^+$ 340.16, found 340.13.

Analytical data for **(3.49)**: **IR** (thin film, cm^{-1}) 2920, 1732, 1540, 1338, 1159, 571.7; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.8 Hz, 2 H), 7.34 (d, *J* = 7.8 Hz, 2 H), 5.42 (m, 1 H), 3.64 (s, 2 H), 3.42 (m, 4 H), 2.45 (s, 3 H), 1.64 (m, 6 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 143.6, 136.0, 130.9, 128.8, 127.1, 125.0, 57.75, 49.10, 29.12, 21.53, 13.68, 13.55; **LRMS** (ESI) calculated for $[C_{14}H_{20}BrNO_2S+Na]^+$ 368.03, found 368.06.

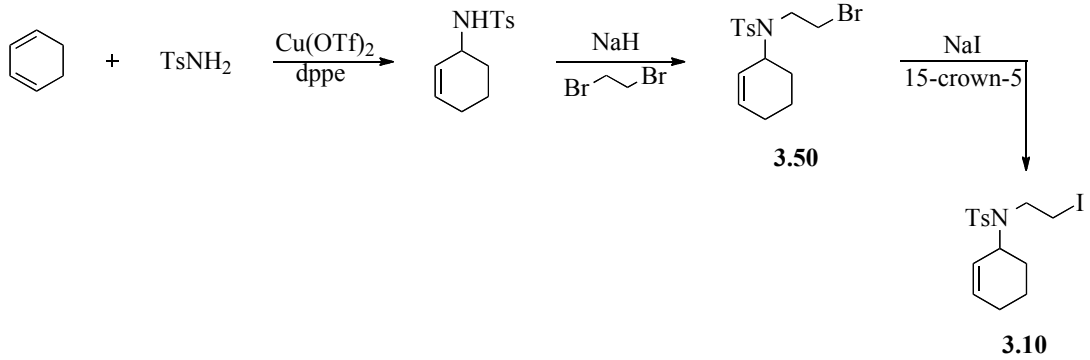
To a solution of **3.49** (422 mg, 1.22 mmol) in dried acetone (4.1 mL) was added NaI (548 mg, 3.66 mmol) and 15-crown-5 (120 μL, 0.61 mmol) at room temperature under Ar. The reaction was then heated to a reflux and stirred overnight. The reaction was cooled to room temperature and diluted with CH_2Cl_2. The reaction mixture was stirred for ~15 minutes. The organic layer was then washed with sat. aq. $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by column chromatography (10:1 Hex:EtOAc) to provide 357 mg (74%) **3.5** as a colorless oil. Analytical data for **(3.5)**: **IR** (thin film, cm^{-1}) 2919, 1597, 1338, 1159, 911.2, 657.6;

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.8 Hz, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 5.41 (m, 1 H), 3.62 (s, 2 H), 3.35 (m, 2 H), 3.16 (m, 2 H), 2.45 (s, 3 H), 1.64 (m, 6 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 143.5, 136.2, 131.0, 129.8, 127.1, 124.9, 57.43, 50.44, 21.53, 13.72, 13.58, 2.05; **LRMS** (ESI) calculated for $[C_{14}H_{20}INO_2S+Na]^+$ 416.02, found 416.04.



3.8

(*E*)-1-(1-butoxy-2-iodoethoxy)-2-methylbut-2-ene (3.8, Table 3-3, entry 3). Iodoacetal **3.8** was synthesized from (*E*)-2-methylbut-2-en-1-ol[43] and butyl vinyl ether according to a modified literature procedure by Renaud *et. al.*[46] Analytical data for **3.8**: **IR** (thin film, cm^{-1}) 3435, 2958, 2932, 2870, 1646, 1456, 1379, 1112, 1033; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.55 (q, *J* = 6.6 Hz, 1 H), 4.63 (t, *J* = 5.4 Hz, 1 H), 4.03 (d, *J* = 11.4 Hz, 1 H), 3.93 (d, *J* = 11.4 Hz, 1 H), 3.62 (m, 1 H), 3.51 (m, 1 H), 3.25 (d, *J* = 5.4 Hz, 2 H), 1.71 (s, 3 H, 1.66 (d, *J* = 6.6 Hz, 3 H), 1.60 (m, 2 H), 1.43 (m, 2 H), 1.95 (t, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 132.2, 123.51, 100.84, 72.88, 66.08, 31.73, 19.32, 13.87, 13.86, 13.24, 5.46; **LRMS** (ESI) calculated for $[C_{11}H_{21}IO_2+Na]^+$ 335.05, found 335.12.

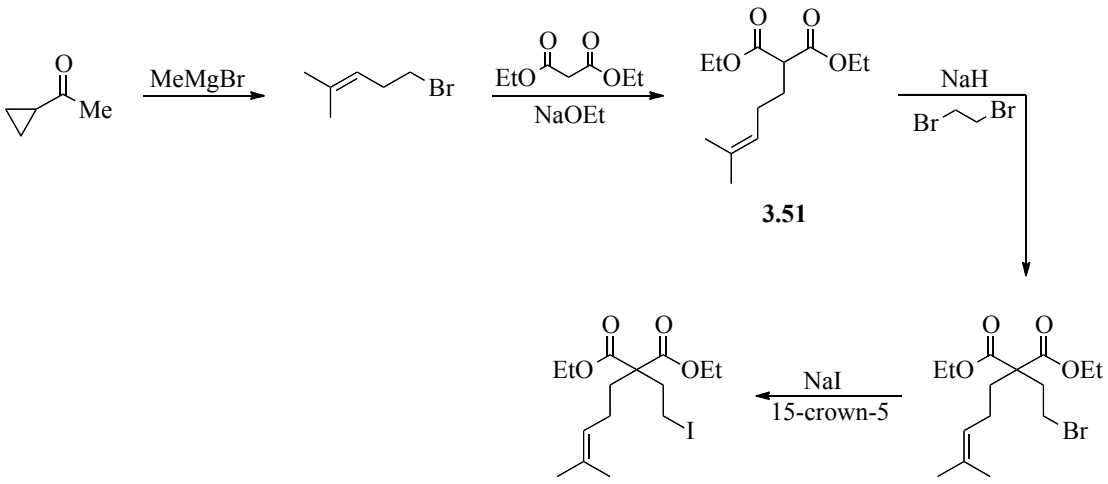


***N*-(cyclohex-2-en-1-yl)-*N*-(3-iodopropyl)-4-methylbenzenesulfonamide (3.10, Table 3-3, entry 4).** The title compound was prepared from *N*-(cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide,[47] followed by alkylation,[48] and iodination as described below.

Analytical data for **(3.50)**: **IR** (thin film, cm^{-1}) 2933, 1597, 1448, 1342, 1160, 585.3; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2 H), 7.33 (d, *J* = 7.8 Hz, 2 H), 5.82 (d, *J* = 4.2 Hz, 1 H), 4.96 (d, *J* = 9.6 Hz, 1 H), 4.47 (brs, 1 H), 3.70 – 3.66 (m, 1 H), 3.48 – 3.41 (m, 2 H), 3.26 (m, 1 H), 2.45 (s, 3 H), 1.97 (m, 2 H), 1.90 (m, 1 H), 1.80 – 1.77 (m, 1 H), 1.64 – 1.57 (m, 1 H), 1.44 (dq, *J* = 12.6 Hz, *J* = 2.4 Hz, 1 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 143.5, 137.1, 133.3, 129.8, 127.0, 136.6, 55.36, 45.56, 31.11, 29.10, 24.31, 21.54, 21.50; **LRMS** (ESI) calculated for $[C_{15}H_{20}BrNO_2S+Na]^+$ 380.03, found 380.09.

To a solution of **3.50** (1.12 g, 2.8 mmol) in dried acetone (9.2 mL) was added NaI (1.25 g, 8.3 mmol) and 15-crown-5 (274 μL, 1.4 mmol) at room temperature under Ar. The reaction was then heated to a reflux and stirred overnight. The reaction was cooled to room temperature and diluted with CH_2Cl_2. The reaction mixture was stirred for ~15 minutes. The organic layer was then washed with sat. aq. $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by column

chromatography (30:1 Hex:EtOAc) to provide 911.3 mg (81%) **7** as a white solid. Analytical data for **(3.10)**: **IR** (thin film, cm^{-1}) 3421, 2932, 1647, 1598, 1448, 1340, 1159, 1006, 585.3, 548.6; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 2 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 5.81 (d, *J* = 9.0 Hz, 1 H), 4.96 (d, *J* = 10.2 Hz, 1 H), 4.45 (s, I H), 3.50 – 3.41 (m, 2 H), 3.30 – 3.23 (m, 2 H), 2.44 (s, 3 H), 1.97 (brs, 2 H), 1.90 (m, 1 H), 1.77 (m, 1 H), 1.60 (m, 1 H), 1.41 (m, 1 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 143.5, 137.2, 133.2, 129.8, 127.0, 126.7, 55.33, 46.92, 29.23, 24.31, 21.55, 21.50, 4.87; **LRMS** (ESI) calculated for $[C_{15}H_{20}INO_2S+Na]^+$ 428.02, found 427.95.

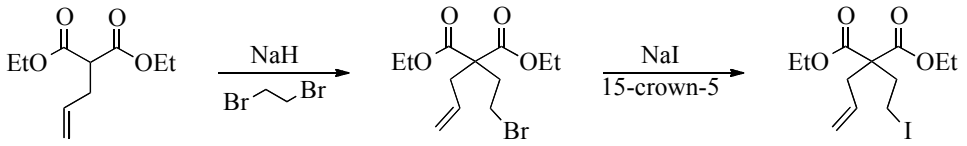


Synthesis of diethyl 2-(2-iodoethyl)-2-(4-methylpent-3-en-1-yl)malonate (3.14, Table 3-3, entry 5). Na (296 mg, 12.88 mmol) was added portionwise to ethanol (10 mL) at room temperature under Ar. Diethylmalonate (1.87 mL, 12.27 mmol) was then added dropwise to the solution of NaOEt. The reaction was warmed to 50 °C and stirred for one hour. 1-bromo-4-methyl-3-pentene[41] (2.0 g, 12.27 mmol) was then added dropwise. The reaction was heated to reflux and stirred for 3 h. The reaction was cooled to room temperature and poured into an ice cold 1:1 solution of sat. aq. NH_4Cl:H_2O,

followed by neutralization of the resulting solution. The reaction mixture was extracted three times with ethyl acetate, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting crude oil was purified by column chromatography (25:1 Hexanes:EtOAc) to provide 2.08 g (70%) **3.51** as a colorless oil. Analytical data for **(3.51)**: **IR** (thin film, cm^{-1}) 2981, 2934, 1732, 1447, 1370, 1254, 1147, 1051; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.09 (t, *J* = 6 Hz, 1 H), 4.21 (q, *J* = 3.6 Hz, 4 H), 3.34 (t, *J* = 7.2 Hz, 1 H), 2.05 (q, *J* = 7.2 Hz, 2 H), 1.94 (q, *J* = 7.2 Hz, 2 H), 1.70 (s, 3 H), 1.60 (s, 3 H), 1.28 (t, *J* = 7.2 Hz); **^{13}C NMR** (600 MHz, $CDCl_3$) d 169.5, `133.2, 122.7, 61.26, 51.37, 28.80, 25.71, 25.68, 17.63, 14.08; **LRMS** (ESI) calculated for $[C_{13}H_{22}O_4+Na]^+$ 265.14, found 265.16.

To a solution of **3.51** (1.24 g, 5.10 mmol) in THF (18.2 mL) at 0 °C under Ar was added NaH (266 mg, 6.65 mmol, 60 wt % mineral oil) portionwise. The reaction was warmed to room temperature and stirred until the emission of H_2(g) was complete. 1,2-dibromoethane (1.77 mL, 20.4 mmol) was added neat. The reaction was then heated to a reflux and stirred for 24 hrs. The reaction was then quenched with 1:1 H_2O/CH_2Cl_2. The reaction was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by column chromatography (10:1 Hex:EtOAc) to provide 1.32 g (74%) **3.52** as a pale yellow oil. Analytical data for **(3.52)**: **IR** (thin film, cm^{-1}) 2979, 2932, 1730, 1446, 1220, 1176, 1025, 512.9; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.08 (brs, 1 H), 4.22 (q, *J* = 7.2 Hz, 4 H), 3.35 (t, *J* = 8.4 Hz, 2 H), 2.49 (t, *J* = 8.4 Hz, 2 H), 1.92 (s, 4 H), 1.69 (s, 3 H), 1.60 (s, 3 H), 1.28 (t, *J* = 7.2 Hz, 6 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 170.6, 132.8, 122.7, 61.48, 57.57, 36.25, 33.11, 27.27, 25.63, 22.82, 17.60, 14.05; **LRMS** (ESI) calculated for $[C_{15}H_{25}BrO_4+Na]^+$ 371.10, found 371.08.

To a solution of **3.52** (2.38 g, 6.8 mmol) in dried acetone (22.7 mL) was added NaI (3.06 g, 20.4 mmol) and 15-crown-5 (330 μL, 1.7 mmol) at room temperature under Ar. The reaction was then heated to a reflux and stirred overnight. The reaction was cooled to room temperature and diluted with CH_2Cl_2. The reaction mixture was stirred for ~15 minutes. The organic layer was then washed with sat. aq. $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by column chromatography (30:1 Hex:EtOAc) to provide 1.60 g (60%) **3.14** as a colorless oil. Analytical data for **(3.14)**: **IR** (thin film, cm^{-1}) 2978, 2933, 1730, 1258, 1233, 1176, 507.2; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.08 (s, 1 H), 4.31 (q, *J* = 7.2 Hz, 4 H), 3.09 (m, 2 H), 2.53 (m, 2 H), 1.90 (m, 4 H), 1.69 (s, 3 H), 1.58 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 6 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 170.5, 132.8, 122.7, 61.44, 59.03, 37.85, 32.80, 25.65, 22.83, 17.61, 14.06, -2.16; **LRMS** (ESI) calculated for $[C_{15}H_{25}IO_4+Na]^+$ 419.07, found 419.04.

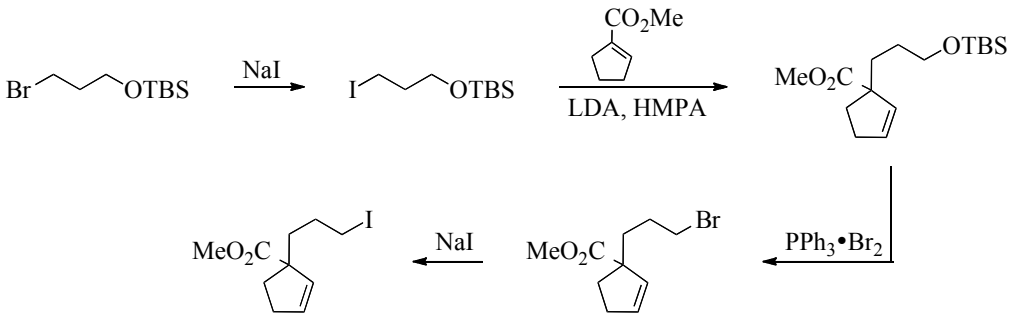


3.17

Diethyl 2-allyl-2-(2-iodoethyl)malonate (3.17, Table 3-4, entry 1). The title compound was synthesized in two steps by an alkylation[49] followed by an iodination as described below.

To a solution of bromide (3.00 g, 9.76 mmol) in dried acetone (32.5 mL) was added NaI (4.4 g, 29.3 mmol) and 15-crown-5 (430 μL, 2.20 mmol) at room temperature under Ar. The reaction was stirred ~10 minutes then heated to a reflux and stirred overnight. The reaction was cooled to room temperature and diluted with CH_2Cl_2. The

reaction was stirred ~15 minutes and washed with sat. aq. $Na_2S_2O_3$ and brine. Next the reaction was dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by column chromatography (20:1 Hex: EtOAc) to provide 2.75 g (80%) **3.17** as a pale yellow oil. Analytical data for **1-(1-iodo-6-methylhept-5-en-2-yl)-4-methoxybenzene (3.17)**: IR (thin film, cm-1) 2981, 2936, 1730, 1239, 1205, 532.2; ^{1}H NMR (600 MHz, CDCl3) δ 5.67 (m, 1 H), 5.15 (m, 2 H), 4.22 (q, *J* = 7.2 Hz, 4 H), 3.12 (m, 2 H), 2.66 (d, *J* = 7.4 Hz, 2 H), 2.50 (m, 2 H), 1.28 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (600 MHz, CDCl3) δ 170.0, 131.8, 119.6, 61.58, 58.99, 37.75, 37.44, 14.07, −2.43; LRMS (ESI) calculated for [C12H19IO4+Na]+ 377.02, found 376.99.



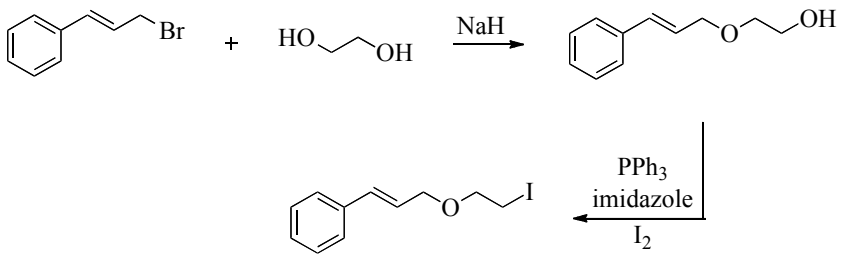
3.21 **3.53**

Methyl 1-(3-iodopropyl)cyclopent-2-enecarboxylate (3.21, Table 3-4, entry 2). The title compound was synthesized by preparation of *tert*-butyl(3-iodopropoxy)dimethylsilane,[50] followed by alkylation,[51] bromination,[52] and iodination as described below.

Analytical data for **methyl 1-(3-bromopropyl)cyclopent-2-enecarboxylate (3.53)**: IR (thin film, cm-1) 2949, 2853, 1730, 1433, 1241, 1163, 559.2; ^{1}H NMR (600 MHz, CDCl3) δ 5.86 (m, 1 H), 5.69 (m, 1 H), 3.70, (s, 3 H), 3.39 (t, *J* = 6.0 Hz, 2 H),

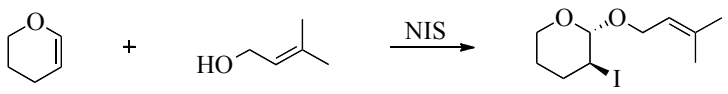
2.49-2.36 (m, 3 H), 1.90-1.74 (m, 5 H); ^{13}C NMR (600 MHz, CDCl3) δ 176.5, 132.9, 132.8, 59.50, 51.98, 37.00, 33.67, 32.76, 31.76, 28.73; LRMS (ESI) calculated for $[C_{10}H_{15}BrO_2+Na]^+$ 269.02, found 269.03.

A solution of **3.53** (746 mg, 3.02 mmol), NaI (1.36 g, 9.06 mmol), and 15-crown-5 (294 μL, 1.51 mmol) in dried acetone (15 mL) was heated to a reflux under Ar. The solution then stirred overnight. The reaction was diluted with CH_2Cl_2 and stirred for 15 minutes, then washed with sat. aq. $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude oil was then purified using column chromatography (30:1 Hex:EtOAc) to provide 808 mg (91%) of **3.21** as a colorless oil. Analytical data for **methyl 1-(3- iodopropyl)cyclopent-2-enecarboxylate (3.21):** IR (thin film, cm-1) 3443, 2948, 1730,1432, 1216, 1161, 727.0, 603.6; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85 (m, 1 H), 5.69 (m, 1 H), 3.70 (s, 3 H), 3.16 (t, J = 6.0 Hz, 2 H), 2.46-2.36 (m, 3 H), 1.85-1.71 (m, 5 H) ; ^{13}C NMR (600 MHz, CDCl3) δ 176.4, 133.0 132.8, 59.42, 51.98, 39.27, 32.79, 31.75, 29.49, 6.49; LRMS (ESI) calculated for $[C_{10}H_{15}IO_2+Na]^+$ 317.00, found 317.02.



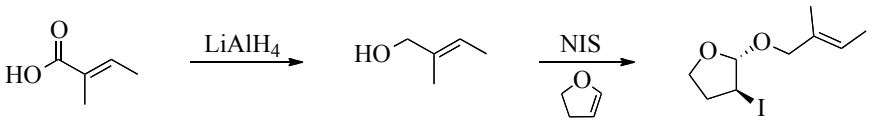
3.24

(*E*)-(3-(2-iodoethoxy)prop-1-en-1-yl)benzene (3.24, Table 3-4, entry 3). The title compound was synthesized from 2-(cinnamyloxy)ethanol[53] by iodination.[54]



3.27

(*trans*)-1-iodo-2-((3-methylbut-2-en-1-yl)oxy)cyclohexane (3.27, Table 3-5, entry 1). The title compound was synthesized according to the literature procedure by Renaud *et. al*.[46]



3.29

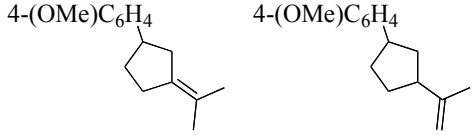
(2*S*,3*R*)-3-iodo-2-(((*E*)-2-methylbut-2-en-1-yl)oxy)tetrahydrofuran (3.29, Table 3-5, entry 2). The title compound was synthesized according to a modified literature procedure by Renaud *et. al*.[46] Analytical data for **3.29**: **IR** (thin film, cm^{-1}) 3434, 1644, 1014, 594.9; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.52 (m, 1 H), 5.36 (s, 1 H), 4.20 (dd, J = 6.0 Hz, J = 2.4 Hz, 1 H), 4.14 (m, 1 H), 4.07 – 4.03 (m, 2 H), 3.86 (d, J = 11.4 Hz, 1 H), 2.65 (m, 1 H), 2.22 (m, 1 H), 1.65 (s, 6 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 132.1, 123.4, 109.4, 73.33, 66.92, 35.63, 24.88, 13.67, 13.26; **LRMS** (ESI) calculated for the sodium-bound dimer $[2(C_9H_{15}IO_2)+Na]^+$ 587.23, found 587.03.

3.5.3 Alkyl-Heck-Type Reaction Results

General Procedure for the Alkyl-Heck-Type Reaction, *Method A:* In a glovebox, the alkyl iodide (1.0 equiv), $Pd(PPh_3)_4$ (10 mol %), 1,2,2,6,6-pentamethylpiperidine (2.0 equiv), and benzene (0.5 M) were combined in a 22 mL Parr reactor with a stir bar added. The pressure reactor was assembled and sealed in the

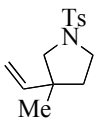
glovebox. Upon removal, the pressure reactor was charged with 10 atm CO from a purged line. The pressure was slowly released, followed by a second pressurization to 10 atm CO. The pressure reactor was then placed into an oil bath at 110 °C. The reaction mixture was stirred for 24 h, after which it was cooled to room temperature and slowly depressurized. The reaction was diluted with Et_2O and washed with 1 N HCl. The reaction was then extracted with Et_2O three times. The combined organic layers were dried ($MgSO_4$), and concentrated. The reaction mixture was then treated with CuCl and dissolved in CH_2Cl_2 in order to remove PPh_3.[55] The product was purified by flash column chromatography with the specified solvent system.

General Procedure for the Alkyl-Heck-Type Reaction, *Method B:* In a glovebox, the alkyl iodide (1.0 equiv), $Pd(PPh_3)_4$ (10 mol %), 1,2,2,6,6-pentamethylpiperidine (2.0 equiv), and benzene (0.5 M) were combined in a sealed tube with a stir bar added. Upon removal from the glovebox, the sealed tube was placed into an oil bath at 110 °C. The reaction mixture was stirred for 24 h, after which it was cooled to room temperature and diluted with Et_2O. The reaction mixture was washed with 1 N HCl. The reaction was then extracted with Et_2O three times. The combined organic layers were dried ($MgSO_4$), and concentrated. The reaction mixture was then treated with CuCl and dissolved in CH_2Cl_2 in order to remove PPh_3.[55] The product was purified by flash column chromatography with the specified solvent system.



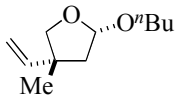
3.3 **3.4**

1-methoxy-4-(3-(propan-2-ylidene)cyclopentyl)benzene (3.3, Table 3-3, entry 1). The title compound was synthesized from **3.1** (80 mg, 0.232 mg) using Method A. The product was purified by flash column chromatography (10:1 Hex/Benzene) to afford **3.3** (42.0 mg, 0.194 mmol, 84% yield) as a colorless oil. Less than 5% of minor alkene isomer **3.4** was observed. Analytical data for **3.3**: **IR** (thin film, cm^{-1}) 3422, 2948, 1512, 1246, 1179, 1038, 827.3; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23 (d, *J* = 9.0 Hz, 2 H), 6.90 (d, *J* = 8.4 Hz, 2 H), 3.83 (s, 3 H), 3.0 (m, 1 H), 2.75 (m, 1 H), 2.50 (m, 1 H), 2.28 (m, 2 H), 2.15 (m, 1 H), 1.76 – 1.69 (m, 7 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 157.7, 137.4, 134.7, 127.8, 121.6, 113.5, 55.19, 44.9, 39.04, 34.66, 30.41, 21.09, 20.77; **LRMS** (ESI) calculated for $[C_{15}H_{20}O+K]^+$ 255.12, found 255.07. Analytical data for **3.3** and **3.4** (inseparable mixture): **IR** (thin film, cm^{-1}) 3422, 2948, 1512, 1246, 1179, 1038, 827.3; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (m, 2 H), 6.88 (m, 2 H), 4.76 (m, 2 H), 3.82 (s, 3 H), 3.15 (m, 0.33 H), 3.06 (m, 0.71 H), 2.81 – 2.63 (m, 0.88 H), 2.68 – 2.63 (m, 0.17 H), 2.48 (dd, J = 16.5 Hz, J = 8.5 Hz, 0.56 H), 2.30 – 2.11 (m, 2.37 H), 2.03 – 1.98 (m, 0.84 H), 1.89 – 1.85 (m, 0.37 H), 1.80 (s, 1.43 H), 1.75 – 1.62 (m, 4.72 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 157.8, 157.2, 157.6, 149.0, 148.7, 138.9, 138.2, 137.5, 134.8, 127.9, 127.8, 121.6, 113.7, 113.6, 108.2, 108.1, 55.25, 47.14, 46.20, 45.00, 44.83, 43.83, 40.62, 39.04, 38.93, 35.27, 34.67, 33.50, 31.87, 30.42, 30.31, 21.14, 21.09, 20.78; **LRMS** (ESI) calculated for $[C_{15}H_{20}O+K]^+$ 255.12, found 255.07.



3.6

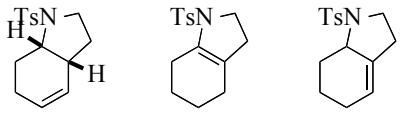
3-methyl-1-tosyl-3-vinylpyrrolidine (3.6, Table 3-3, entry 2). The title compound was synthesized from **3.5** (100 mg, 0.254 mmol) using Method A to afford **3.6** in 70% yield by ^{1}H NMR analysis using 1,3,5-trimethyoxybenzene. Yield by ^{1}H NMR analysis was required due to the presence of a byproduct was inseparable by flash column chromatography. Analytical data for **3.6**: **IR** (thin film, cm^{-1}) 2965, 2360, 1343, 1158, 662.4, 548.6; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 2 H), 7.34 (d, *J* = 7.8 Hz, 2 H), 5.70 (dd, *J* = 17.4 Hz, *J* = 10.2 Hz, 1 H), 4.94 (m, 2 H), 3.36 (m, 2 H), 3.17 (d, *J* = 9.6 Hz, 1 H), 3.06 (d, *J* = 9.6 Hz, 1 H), 2.45 (s, 3 H), 1.76 (m, 1 H), 1.69 (m, 1 H), 0.996 (s, 3 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 143.3, 142.8, 133.8, 129.5, 112.7, 58.15, 46.63, 44.22, 37.48, 22.99, 21.54; **LRMS** (ESI) calculated for $[C_{14}H_{19}NO_2S+H]^+$ 266.12, found 266.09.



3.9

2-butoxy-4-methyl-4-vinyltetrahydrofuran (3.9, Table 3-3, entry 3). The title compound was synthesized from **3.8** (200 mg, 0.640 mmol) using Method A except the reaction temperature was 130 °C and the reaction time was 6 h. The product was purified by flash column chromatography (30:1 Hex:EtOAc) to afford **3.9** (86.3 mg, 0.468 mmol, 73%) as a 83:17 mixture of inseparable diastereomers as a colorless oil. Analytical data for **3.9**: **IR** (thin film, cm^{-1}) 3436, 2935, 2871, 1639, 1348, 1098, 1018, 921.8; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.98 – 5.88 (m, 1.2 H), 5.20 (dd, *J* = 5.4 Hz, *J* = 3.6 Hz, 1 H), 5.15 (dd, *J* = 6.0 Hz, *J* = 3.0 Hz, 0.28 H), 5.08 – 4.99 (m, 2.4 H), 3.74 (d, *J* = 7.8 Hz, 1 H), 3.70 (m, 1.7 H), 3.49 (d, *J* = 7.8 Hz, 1 H), 3.39 (m, 1.3 H), 2.16 (dd, *J* = 13.2 Hz, *J* = 6.0

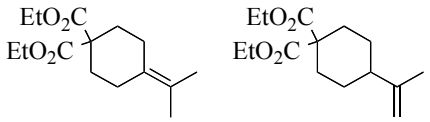
Hz, 0.20 H), 1.96 (dd, *J* = 5.4 Hz, *J* = 0.6 Hz, 1 H), 1.85 (dd, *J* = 13.2 Hz, *J* = 3.6 Hz, 1 H), 1.73 (dd, *J* = 13.2 Hz, *J* = 3.6 Hz, 0.2 H), 1.56 (m, 2.7 H), 1.37 (m, 2.7 H), 1.25 (s, 0.75 H), 1.18 (s, 3 H), 0.922 (t, *J* = 7.2 Hz, 3.9 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 145.1, 143.54, 112.5, 111.1, 104.9, 104.9, 77.51, 77.32, 76.79, 67.67, 46.40, 45.67, 45.12, 44.56, 31.80, 31.78, 23.68, 22.84, 19.34, 19.32, 13.85; **LRMS** (ESI) calculated for $[C_{11}H_{20}O_2+NH_4]^+$ 202.18, found 202.13.



3.11 **3.12** **3.13**

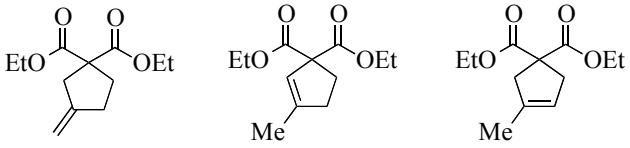
1-tosyl-2,3,3a,6,7,7a-hexahydro-1H-indole (3.11, Table 3-3, entry 4), **1-tosyl-2,3,4,5,6,7-hexahydro-1H-indole (3.12, Table 3-3, entry 4)**, **1-tosyl-2,3,5,6,7,7a-hexahydro-1H-indole (3.13, Table 3-3, entry 4).** The title compounds were synthesized from **3.10** (80 mg, 0.197 mmol) using Method A. It was not necessary to remove PPh_3 prior to purification. The product was purified by flash column chromatography (10:1 Hex/EtOAc) to afford a 9.1:1.2:1 inseparable mixture of (40.6 mg, 0.146 mmol, 74% combined yield) as a colorless oil. Analytical data for **3.11**, **3.12**, and **3.13**: **IR** (thin film, cm^{-1}) 3437, 2925, 1344, 1161, 663.4, 600.7, 549.6; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 (m, 2.5 H), 7.31 (m, 2.5 H), 5.78 (m, 1 H), 5.63 (m, 0.055 H), 3.70 (m, 1H), 3.55 (m, 0.22 H), 3.48 (m, 0.13 H), 3.47 (m, 1 H), 3.41 (m, 0.11 H), 3.35 – 3.30 (m, 0.11 H), 3.16 (m, 1.2 H), 2.50 (m, 0.22 H), 2.44 (s, 4 H), 2.33 (m, 1.1 H), 2.25 (m, 0.19 H), 2.15 – 2.11 (m, 1.2 H), 2.03 – 1.97 (m, 2.5 H), 1.94 – 1.83 (m, 0.49 H), 1.81 – 1.75 (m, 2.3 H), 1.66 (s, 0.42 H), 1.63 – 1.57 (m, 1.55 H), 1.41 – 1.35 (m, 0.41 H), 1.34 – 1.21 (m, 1.1 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 143.3 143.2, 143.0, 137.3, 135.3, 134.8, 134.5, 129.6, 129.6,

129.5, 128.6, 127.5, 127.4, 127.3, 126.7, 125.0, 124.0, 121.1, 59.54, 58.64, 58.32, 47.93, 47.56, 47.17, 38.88, 37.67, 35.34, 30.79, 29.87, 29.85, 27.63, 27.13, 26.25, 24.25, 23.10, 22.50, 21.47, 21.29, 20.22; **LRMS** (ESI) calculated for $[C_{15}H_{19}NO_2S+Na]^+$ 300.10, found 300.08.



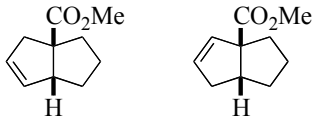
3.15 **3.16**

Diethyl 4-(propan-2-ylidene)cyclohexane-1,1-dicarboxylate (3.15, Table 3-3, entry 5) and **diethyl 4-(prop-1-en-2-yl)cyclohexane-1,1-dicarboxylate (3.16, Table 3-3, entry 5).** The title compounds were synthesized from **3.14** (100 mg, 0.252 mmol) using Method A. The products were purified by flash column chromatography (25:1 Hex/EtOAc) to afford a 2.3:1 inseparable mixture of **3.15** and **3.16** (46.5 mg, 0.174 mmol, 70% combined yield) as a pale yellow oil. Analytical data for **3.15** and **3.16**: **IR** (thin film, cm^{-1}) 3443, 2978, 2937, 1731, 1644, 1233, 1192; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.68 (d, *J* = 9.5 Hz, 2 H), 4.20 (m, 8.76 H), 2.43 (d, *J* = 13.5 Hz, 2 H), 2.24 (m, 3.5 H), 2.04 (m, 3.7 H), 1.92 (m, 1.45 H), 1.81 – 1.57 (m, 14.3 H), 1.36 (m, 1.8 H), 1.25 (m, 14.4 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 172.6, 171.8, 171.0, 148.6, 128.8, 121.8, 108.6, 61.28, 61.15, 61.04, 54.95, 54.55, 43.97, 32.13, 31.23, 27.83, 26.11, 20.84, 19.92, 14.09, 14.06, 14.01; **LRMS** (ESI) calculated for $[C_{15}H_{24}O_4+Na]^+$ 291.16, found 291.13.



3.18 **3.19** **3.20**

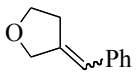
Diethyl 3-methylenecyclopentane-1,1-dicarboxylate (3.18, Table 3-4, entry 1), diethyl 3-methylcyclopent-2- ene-1,1-dicarboxylate (3.19, Table 3-4, entry 1), diethyl 3-methylcyclopent-3-ene-1,1-dicarboxylate (3.20, Table 3-4, entry 1). The title compounds were synthesized from the reaction of **3.17** (80 mg, 0.226 mmol) using Method A. The reaction was run for 18 hours. The product was purified by flash column chromatography (20:1 Hex/EtOAc) to afford a 5:1.6:1 partially separable mixture of **3.18**, **3.19**, and **3.20** (36.7 mg, 0.162 mmol, 72% combined yield) as a clear oil. All physical and spectral data were in accordance with literature data for **3.18**,[18] **3.19**,[56] and **3.20**.[57]



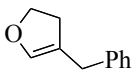
3.22 **3.23**

(*cis*)-methyl 1,2,3,3a,4,6a-hexahydropentalene-3a-carboxylate (3.22, Table 3-4, entry 2) and **(*cis*)-methyl 1,2,3,3a,6,6a-hexahydropentalene-3a-carboxylate (3.23, Table 3-4, entry 2)**. The title compounds were synthesized from **3.21** (100 mg, 0.340 mmol) using Method A, with a reaction time of 2.5 h. The product was purified by flash column chromatography (30:1 Hex/EtOAc) to afford a 1.5:1 inseparable mixture of **3.22** and **3.23** (35.9 mg, 0.216 mmol, 64% combined yield) as clear oil. Analytical data for **3.22** and **3.23**: IR (thin film, cm-1) 3436, 2952, 1731, 1651; ^{1}H NMR (500 MHz, $CDCl_3$)

δ 5.74 (dt, *J* = 5.5 Hz, *J* = 2.5 Hz, 0.51 H), 5.57 (m, 1.48 H), 5.47 (m, 1 H), 3.70 (m, 4.66 H), 3.47 (d, *J* = 8.5 Hz, 1 H), 3.04 (dq, *J* = 17 Hz, *J* = 2 Hz, 1.0 H), 2.98 (m, 0.55 H), 2.75 (qt, *J* = 9 Hz, *J* = 2.5 Hz, 0.53 H), 2.32 (dq, *J* = 17.5 Hz, *J* = 2.5 Hz, 1.0 H), 2.12 (m, 1.1 H), 2.03 (m, 1.1 H), 1.90 (m, 0.60 H), 2.80 (m, 1.1 H), 1.72 (m, 3.78 H), 1.58 – 1.51 (m, 2.7 H), 1.42 (m, 0.70 H); ^{13}C NMR (500 MHz, CDCl3) δ 178.7, 177.6, 133.2, 132.6, 131.8, 128.2, 67.06, 57.72, 56.05, 51.95, 51.90, 45.55, 45.28, 40.78, 39.78, 37.24, 35.89, 32.15, 25.48, 25.21; LRMS (ESI) calculated for $[C_{10}H_{14}O_2+Na]^+$ 189.09, found 189.08.

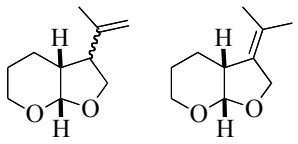


3.25



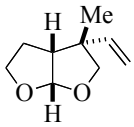
3.26

3-benzylidenetetrahydrofuran (3.25, Table 3-4, entry 3) and **4-benzyl-2,3-dihydrofuran (3.26, Table 3-4, entry 3)**. The title compounds were synthesized according to Method B using **3.24** (80 mg, 0.278 mmol), but *i*PrNEt$_2$ was used as the amine base. Reaction time was 18 hours. **3.25** and **3.26** were produced (18.8 mg, 0.117 mmol, 42% combined yield) as a separable mixture of alkene isomers (8:1) and an inseparable mixture of alkene stereoisomers (1:1) as a colorless oil. The yield was calculated by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard due to the volatility of this compound. All physical and spectral data were in accordance with the literature data.[58]



3.28 **3.32**

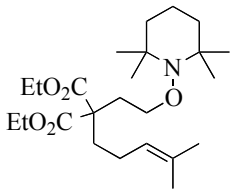
3-(prop-1-en-2-yl)hexahydro-2*H*-furo[2,3-*b*]pyran (3.28, Table 3-5, entry 1). The title compound was synthesized from **3.27** (80 mg, 0.270 mmol) using Method B; however, the reaction time was shortened to 4 h. It was not necessary to remove the PPh_3 prior to purification. The product was purified by flash column chromatography (10:1 Hex/EtOAc) to afford **3.28** (29.6 mg, 0.176 mmol, 65% yield) as an inseparable mixture of stereoisomers (1.4:1) as a yellow oil. Less than 5% of minor alkene isomer **3.32** was observed. All physical and spectral data were in accordance with the literature data for **3.28**.[58] Analytical data for **3.32**: **IR** (thin film, cm^{-1}) 3460, 2937, 1447, 1399, 1156, 1028; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.18 (d, J = 4 Hz, 1 H), 4.48 (d, J = 12.5 Hz, 1 H), 4.28 (d, J = 12.5 Hz, 1 H), 3.85 (td, J = 11 Hz, J = 3 Hz, 1 H), 3.70 (m, 1 H), 2.56 (p, J = 5.5 Hz, 1 H), 1.83, (m, 1 H), 1.68 (s, 3 H), 1.62 – 1.53 (m, 8 H), 1.43 (m, 1 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 133.3, 122.5, 100.7, 66.73, 61.17, 37.83, 24.12, 22.91, 20.72, 19.79; **LRMS** (ESI) calculated for $[C_{10}H_{16}O_2+Na]^+$ 301.02, found 301.13.



3.30

3-methyl-3-vinylhexahydrofuro[2,3-*b*]furan (3.30, Table 3-5, entry 2). The title compound was synthesized from **3.29** (80 mg, 0.283 mmol) using Method B to afford a 66% of **3.30** by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene. ^{1}H NMR

analysis was required due to product instability on silica gel. Analytical data for **3.30**: **IR** (thin film, cm^{-1}) 2925, 2360, 1732, 1456, 1011, 923.7; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 18.0 Hz, *J* = 10.8 Hz, 1 H), 5.80 (d, *J* = 4.8 Hz, 1 H), 5.14 (d, *J* = 11.4 Hz, 1 H), 4.99 (d, *J* =18.0 Hz, 1 H) 3.92 – 3.82 (m, 3 H), 3.62 (d, *J* = 8.4 Hz, 1 H), 2.49 (m, 1 H), 1.88 (m, 2 H), 1.22 (s, 3 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 140.4, 114.5, 109.3, 76.00, 68.80, 53.43, 48.04, 27.46, 26.30; **LRMS** (ESI) calculated for $[C_9H_{14}O_2+H]^+$ 155.11, found 154.99.

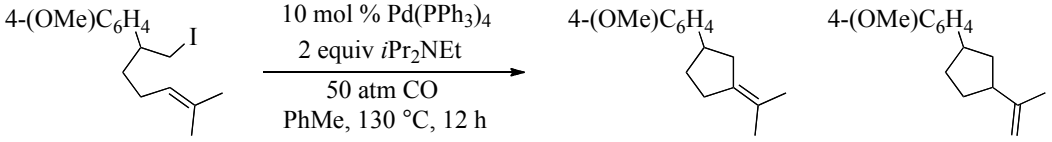


3.33

Diethyl 2-(4-methylpent-3-en-1-yl)-2-(2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)ethyl)malonate (3.33, Scheme 3-9). The title compound was obtained from **3.14** (100 mg, 0.25 mmol) using Method A, but with the addition of TEMPO (39.4 mg, 0.25 mmol). The resulting mixture was purified by flash column chromatography (30:1 Hexanes:EtOAc) to afford **3.33** as a colorless oil. The yield of **3.33** (24%) as well as the amount of unreacted **3.14** (54%) was determined using ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. When this reaction was run without $Pd(PPh_3)_4$ present, **3.33 (**or product **3.15** or **3.16**) was not observed. Analytical data for **3.33**: **IR** (thin film, cm^{-1}) 3444, 2976, 2932, 1732, 1645, 1455, 1374, 1297, 1261, 1195, 1104, 1031; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.10 (t, *J* = 6.5 Hz, 1 H), 4.18 (m, 4 H), 3.73 (t, *J* = 6.9 Hz, 2 H), 2.23 (t, *J* = 7.0 Hz, 2 H), 1.97 (m, 2 H), 1.89 (m, 2 H), 1.68 (s, 3 H), 1.58 (s, 3 H), 1.53 (m, 1 H), 1.43 (m, 4 H), 1.31 (dt, *J* = 12.9 Hz, *J* = 3.0 Hz, 1 H), 1.25 (t,

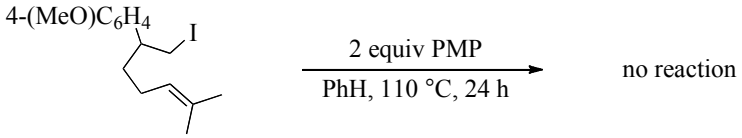
J = 7.0 Hz, 6 H), 1.14 (s, 6 H), 1.07 (s, 3 H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 171.5, 132.2, 123.2, 72.56, 61.10, 59.62, 55.83, 39.53, 32.89, 32.36, 30.75, 25.65, 22.89, 20.05, 17.55, 17.07, 14.05; **LRMS** (ESI) calculated for $[C_{24}H_{43}NO_5+H]^+$ 426.32, found 426.40.

3.5.4 Additional Experiments



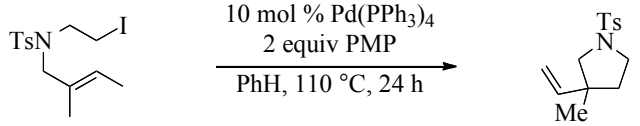
3.1 **3.3** **3.4**

Initial Experiment Using Carbonylative Alkyl-Heck Conditions (Figure 3-3). **3.3** was synthesized from the reaction of **3.1** (100 mg, 0.327 mmol) using Method A, except that *i*Pr_2NEt was the amine base used, toluene was the solvent used, the reaction was run under 50 atm CO, and the reaction temperture was 130 °C. The reaction afforded **3.3** in 86% yield (determined by using the ^{1}H NMR internal standard 1,3,5-trimethoxybenzene). Less than 5% of minor alkene isomer **3.4** was observed. No carbonylative cyclization product was observed.



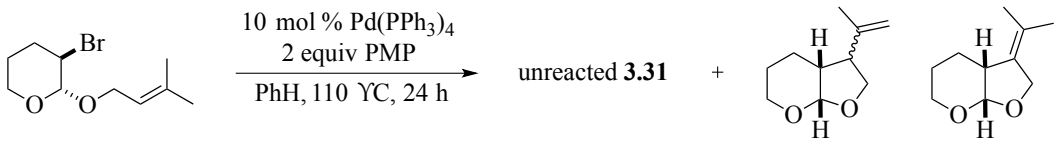
3.1

Control Experiment in the Absence of Pd Catalyst (Scheme 3-6). **3.1** (80 mg, 0.232 mmol) was reacted using Method A in the absence of $Pd(PPh_3)_4$. No product was observed by ^{1}H NMR analysis of the crude reaction mixture.



3.5 **3.6**

Reaction of Iodide 3.5 in the Absence of CO (Scheme 3-7). Reaction of substrate **3.5** was performed using Method B (without CO present) (100 mg, 0.254 mmol) instead of Method A (with 10 atm CO present). The reaction afforded **3.6** in 25% yield determined by using the ^{1}H NMR internal standard 1,3,5-trimethoxybenzene.



3.31 **3.28** **3.32**

Attempted Cyclization Using Alkyl Bromide 3.31 (Scheme 3-8). 3.31 (synthesized according to a procedure by Miura *et. al.*[60]) (80 mg, 0.321 mmol) was reacted under Method B to afford **3.28** and **3.32** (25.6% combined yield, as determined by ^{1}H NMR analysis) as a 3.6:1 mixture of regioisomers and a 1.3:1 mixture of stereoisomers.

3.6 References

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(2) Beletskaya, I. P.; Cheprakov, A. V. "The Heck Reaction as a Sharpening Stone of Palladium-Catalysis." *Chem. Rev.* **2000**, *100*, 3009 – 3066.

(3) Cabri, W.; Candiani, I. "Recent Developments and New Prespectives in the Heck Reaction." *Acc. Chem. Res.* **1995**, *28*, 2 – 7.

(4) Dounay, A. B.; Overman, L. E. "The Asymmetric Intramolecular Heck Reaction in Natural Product Total Synthesis." *Chem. Rev.* **2003**, *103*, 2945 – 2963.

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Chapter 4

Palladium-Catalyzed Enantioselective Carbonylations of Alkyl Iodides

4.1. Introduction

α-Alkylations of carbonyl compounds are essential carbon-carbon bond forming reactions in synthetic chemistry.[1,2] Asymmetric variants are generally reliant upon the use of chiral auxiliaries.[3,4] For practical and fundamental reasons, development of a catalytic asymmetric α-alkylation transformation has been highly sought after.[5] Several distinct strategies for catalytic asymmetric alkylation have been reported that include organocatalysis, Lewis acid activation, and metal-catalyzed cross-coupling.[6-9]

We propose an alternative approach for the synthesis of enantiopure α-chiral carbonyl compounds: enantioselective carbonylations of secondary alkyl halides (Figure 4-1). Realization of this highly modular synthesis would allow access to chiral α-substituted amides, esters, and ketones via a single catalytic step.

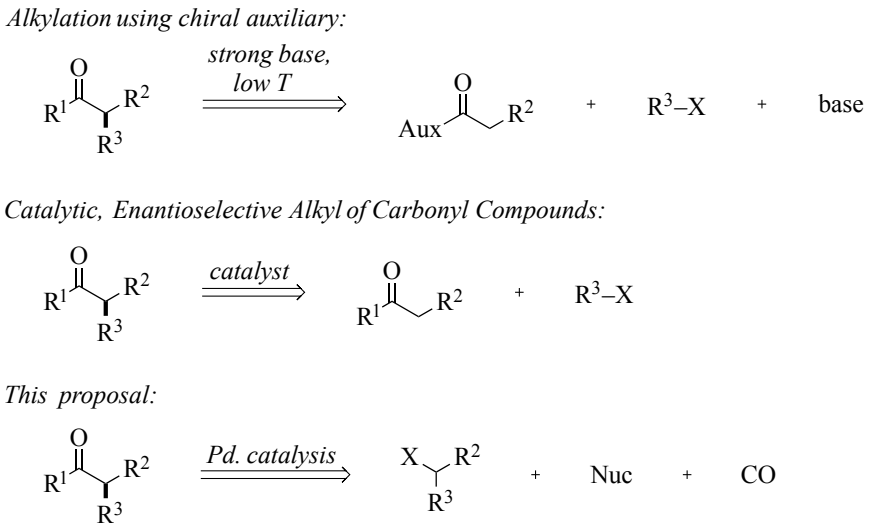


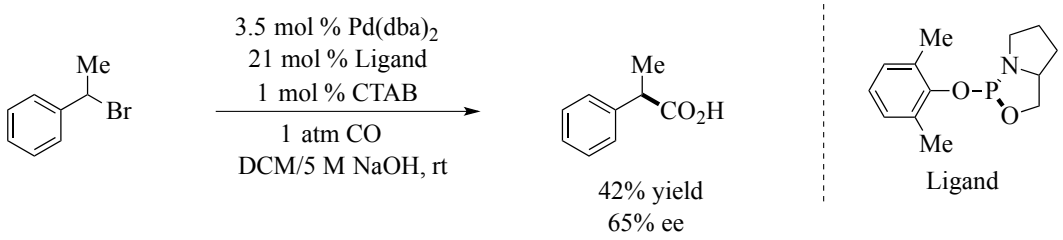
Figure 4-1. General, Enantioselective Approaches to α-Substituted Carbonyl Compounds

4.2. Background

We are proposing the synthesis of chiral α-alkylated carbonyl compounds through a different bond disconnection than are traditionally employed (Figure 4-1). By utilizing a variety of nucleophiles (esterification, amidation, or cross coupling with the resulting acyl-palladium), many enantiopure chiral building blocks could be readily accessed; however, there are significant challenges that need to be addressed concerning this approach.

Despite significant efforts, there are few general examples for the palladium-catalyzed carbonylation of secondary sp^3-hybridized electrophiles,[10-12] due to the general reluctance of secondary electrophiles to undergo oxidative addition;[13,14] however, β-hydride elimination of the resulting the alkylpalladium species, traditionally a challenging issue for the palladium-catalyzed reaction of unactivated alkyl electrophiles, should not be problematic as migratory CO insertion outcompeting β-hydride elimination has been well-precendented.[15,16]

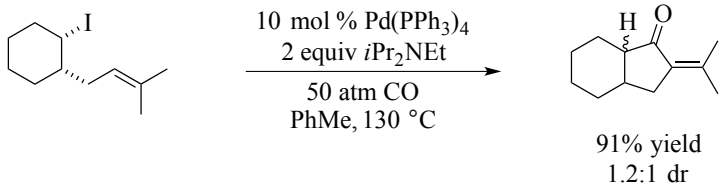
To date, there is only one example of an enantioselective carbonylation facilitated by catalytic palladium (Scheme 4-1).[17] A kinetic resolution of benzyl bromide was reported that was catalyzed by an oxazaphospholane-palladium complex. The kinetic resolution is enabled by a discriminative slow oxidative addition step. Additionally, the reaction was shown to occur at the organic-aqueous interface, although the use of the phase transfer agent hexadecyltrimethylammonium bromide (CTAB) was required to achieve enantiomeric discrimination. α-Methylbenzyl bromide was the only substrate examined, and the chemical yields and stereoselectivities were low for the ligands tested. As such, the general enantioselective carbonylation of alkyl halides has yet to be realized.



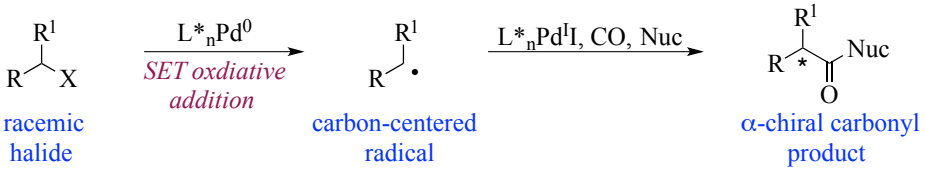
Scheme 4-1. Asymmetric Carbonylation of Benzyl Bromides via a Kinetic Resolution

Our lab has reported the successful palladium-catalyzed carbonylative Heck-type cyclization of primary and secondary alkyl halides (Scheme 4-2).[18] We proposed a reaction pathway where oxidative addition to aliphatic halides occurs via single electron transfer. Generation of the resulting carbon-centered radical was confirmed through trapping experiments employing TEMPO. The mechanism for the proposed transformation displays both radical and organometallic properties, resulting in a unique combination of reactivity that allows access to a wide range of transformations. We

hypothesized that application of this reactivity to the catalytic carbonylation of secondary halides will allow the synthesis of chiral α-alkylated carbonyl compounds (Scheme 4-3).



Scheme 4-2. Palladium-Catalyzed Carbonylative Heck-Type Cyclization of Unactivated Alkyl Iodides



Scheme 4-3. Proposed Palladium-Catalyzed Enantioselective Carbonylation of Racemic Alkyl Halides

Another challenge in developing a general enantioselective carbonylation is that little is understood for the reaction mechanism employing secondary alkyl halides in palladium-catalyzed cross-couplings that invoke a hybrid radical/organometallic mechanism.[14,19] In particular, few details are available regarding the critical carbon-carbon bond-forming step. Palladium-catalyzed esterification has been reported under UV irradiation to proceed via a hybrid radical-organometallic mechanism (Figure 4-2).[20] It was determined that the purely radical catalyzed reaction and the palladium catalyzed reaction shared the same isomeric ratios of the carbonylation products, indicating that the metal was not a participant in the key carbon-carbon bond forming step. The absence of metal makes asymmetric induction highly unlikely.

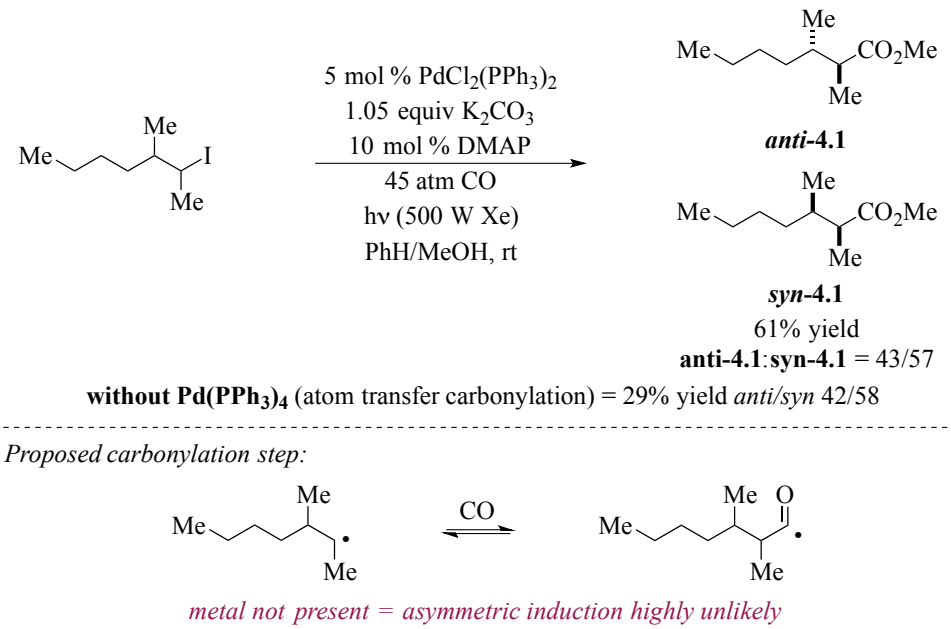


Figure 4-2. Palladium/Light-Accelerated Carbonylation Suggesting Metal Is Not Involved in the Carbon-Carbon Bond Forming Step

Despite these challenges, we set out to determine if it was possible to develop a palladium-catalyzed enantioselective carbonylation of alkyl halides. Realization of this goal would provide expedient access to valuable enantiopure amides, esters, and ketones. Herein, we report our preliminary findings.

4.3 Results and Discussion

In order to develop an enantioselective carbonylation of secondary alkyl halides, the metal must be involved in the critical carbon-carbon bond forming step. There are two general mechanistic scenarios for this to occur. If single electron transfer occurs to generate a putative palladium(I) species and a carbon-centered radical, the carbon-centered radical may add to the palladium in an enantioselective step (Figure 4-3, Path A). Migratory insertion of coordinated carbon monoxide could then generate the carbon

stereocenter, and the product could be furnished through nucleophilic displacement of palladium. Alternatively, single electron transfer could be followed by the enantiodetermining addition of the carbon-centered radical to the metal-bound carbon monoxide (Path B). The resulting enantiopure acylpalladium could then proceed to product; however, if the carbon-centered radical generated via single electron transfer adds to free carbon monoxide, a racemic product would ultimately be generated (Path C). In Path D, two-electron oxidative addition to palladium generates an alkyl metal species, which is followed by migratory CO insertion and nucleophilic displacement of palladium to generate the product; however, the product formed will be racemic as the starting material is racemic and the oxidative addition proceeds through an S_N2-type mechanism.

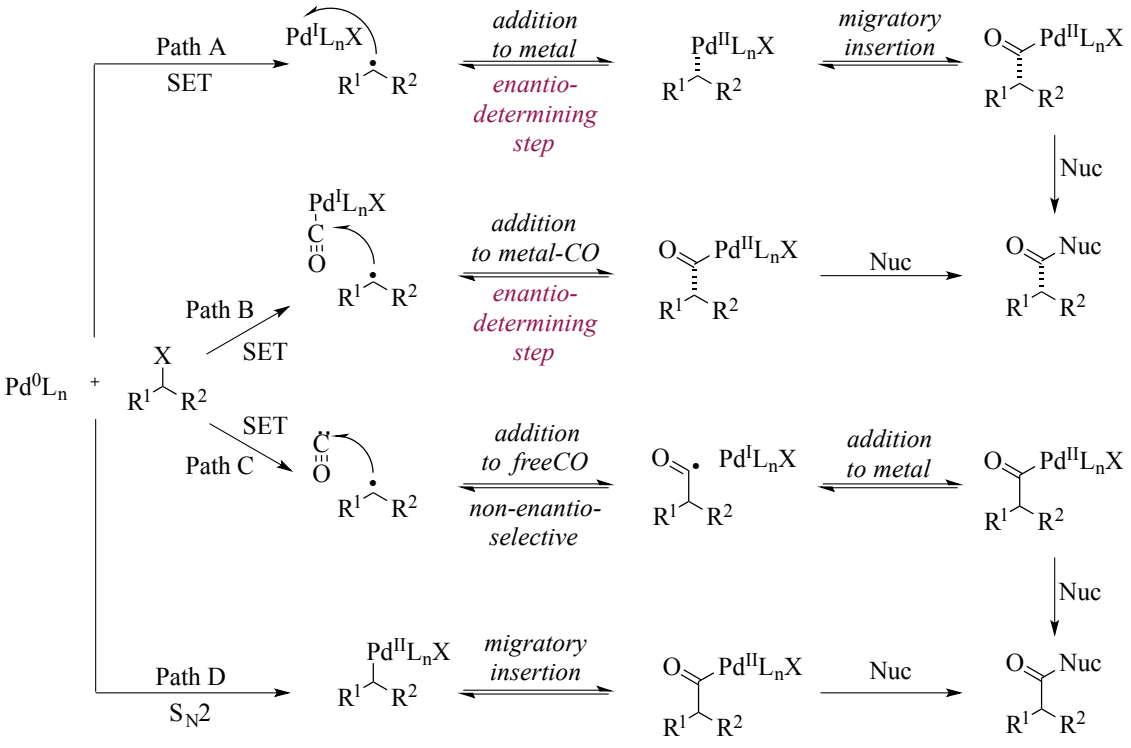


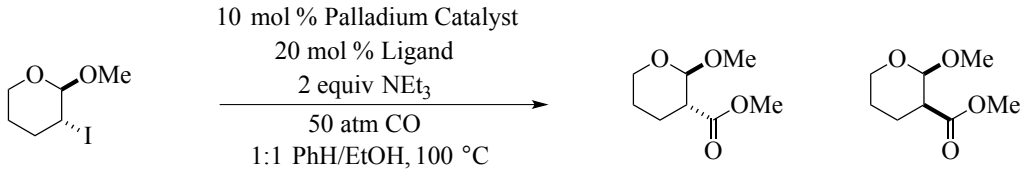
Figure 4-3. Potential Mechanisms for the Enantioselective Palladium-Catalyzed Carbonylation

Little precedent is available to suggest which pathway will be dominant. The reactions of alkyl halides with low-valent transition metals have been shown to occur via both single electron transfer[21,22] and S_N2 pathways;[23,24,25] however, the SET pathway should predominate, but perhaps not exclusively in the case of secondary halides, as the increased steric bulk of the electrophile disfavors the S_N2 pathway. In addition to the oxidative addition step, it is imperative to understand the role of carbon monoxide. A recent report on the mechanism of alkane carbonylation has provided limited guidance as simple metal complexes were studied;[26] however, calculations suggest that in many cases addition of carbon-centered radicals to free carbon monoxide have the lowest energy barrier, but are highly reversible. Addition using a number of metal complexes including $Pd(CO)_4$ is, overall, a more exergonic process. Minimizing the addition to free carbon monoxide (Path C) will be critical to the development of a successful enantioselective reaction.

Our preliminary investigation sought to determine whether Paths A or B were active mechanistic pathways in this reaction. We employed racemic secondary iodide **4.2** in our palladium-catalyzed reaction conditions. Evidence of the metal's involvement in the carbon-carbon bond forming step would result in a different diastereomeric ratio of the carbonylated products than if the metal was absent (i.e. addition of the the carbon centered radical to free CO). Our results are summarized in Table 4-1. We first obtained the diastereomeric ratio of ester products ***anti*-4.3** and ***syn*-4.3** in a purely radical-mediated reaction (entry 1). We observed an approximately ten-point difference in the d.r. of the *syn*- and *anti*-products when the reaction was run in the presence of a palladium catalyst with a variety of ligands (entries 2- 8) with the exception of the NHC

ligand and inorganic base (entry 9). These conditions were similar to those invoked by the Fu laboratory in a purely organometallic reaction with aliphatic bromides and chlorides.[27] Albeit slight, this difference does suggest that the presence of the palladium-catalyst does have an impact on the carbon-carbon bond forming step in the reaction.

Table 4-1. Investigation of the Influence of the Palladium-Catalyst upon the Diastereomeric Ratios of the Carbonylation Reaction



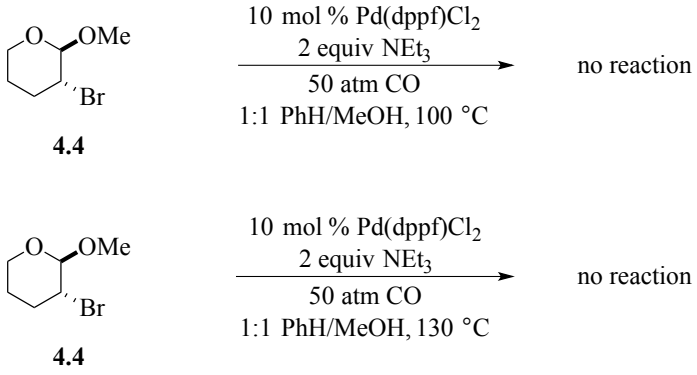
4.2 ***anti*-4.3** ***syn*-4.3**

Entry	Palladum Catalyst	Ligand	d.r.[a]
1	--	--	66:34[b]
2	$Pd(dppf)Cl_2$	--	76:24
3	$Pd(BINAP)Cl_2$	--	75:25
4	$Pd(OAc)_2$	*(R)*-DM-Segphos	77:23
5	$Pd(OAc)_2$	*(R)*-Monophos	73:27
6	$Pd(OAc)_2$	*(R)*-tol-BINAP	75:25
7	$Pd(OAc)_2$	*(R)*-xylyl-BINAP	75:25
8	$Pd(OAc)_2$	Josiphos	75:25
9	$Pd(OAc)_2$	SIMes-HBF_4	66:34[c]

[a]The diastereomeric ratios were determined by ^1H NMR spectroscopy of the crude reaction mixtures. [b]10 mol % $SnBu_3$(allyl) and 25 mol % AIBN. [c]20 mol % KO*t*Bu added.

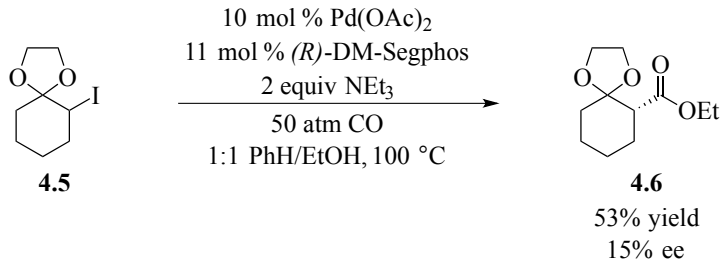
We also endeavored to study the difference in the isomeric ratio of carbonylation products with an alkyl bromide. Carbon-bromine bonds are more difficult to activate

than their iodide counterparts. As such, it is feasible that accessing the carbon-centered radical at a slower rate would allow for a more controlled carbonylation via increased participation of the metal-complex instead of free carbon monoxide.; however, alkyl bromide **4.4** wasn't reactive under our conditions, even at elevated temperature (Scheme 4-4).



Scheme 4-4. Attempted Palladium-Catalyzed Carbonylation of Alkyl Bromides at Various Temperatures

Encouraged by preliminary data, our studies commenced with alkyl iodide **4.5**. Studies commenced with (*R*)-DM-Segphos as it provided the largest difference in d.r. in our previous screen (Table 4-1, entry 4). Under these conditions, there was measurable enantioselectivity in the reaction (Scheme 4-5). We then sought to optimize the enantioselectivity by varying manipulating conditions.



4.5 **4.6**

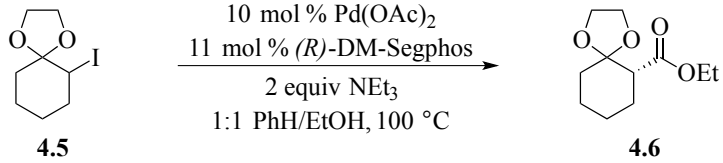
53% yield

15% ee

Scheme 4-5. Preliminary Enantioselective Carbonylation Result

We began by investigating the effect of carbon monoxide pressure had on enantioselectivity. We found that reducing the CO pressure from 50 atm (Table 4-2, entry 1) to 20 atm (entry 2) resulted in an increase of the ee of the reaction to 20 % without a large difference in yield' however, further decreasing the pressure further resulted in significantly lower yields, while similar levels of enantioselectivity were maintained (entries 3 and 4). The decrease in yield can be attributed to an increase in side reactions such as β-hydride elimination and nucleophilic displacement of the iodide with ethanol. In order to validate our results, the reaction was run with the opposite ligand enantiomer (see: additional experiments). Similar results were generated, indicating the enantioselectivity was imparted by the metal-ligand complex; however, the absolute stereochemistry of the product was not obtained.

Table 4-2. Effect of Carbon Monoxide Pressure on the Carbonylation of Secondary Alkyl Iodides



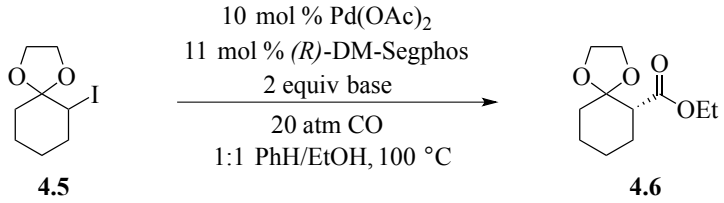
4.5 **4.6**

Entry	CO (atm)	%Yield[a]	ee
1	50	53	15
2	20	47	20
3	10	20	ND
4	5	15	22

[a]Yield calculated by ^{1}H NMR spectroscopy of crude reaction mixtures using 1,3,5-trimethoxybenzene.

Next, we sought to determine the effect of different bases upon the enantioselectivity of the reaction. When a bulkier amine base, Hunig's base, was utilized (Table 4-3, entry 2), there was a significant drop in enantioselectivity. Moreover, no stereoinduction was noted when K_3PO_4 was utilized, and moderate yields were obtained (entry 3). The implementation of a weaker inorganic weaker base resulted in lower yields as well as low levels of enantioselectivity (entry 4). These results were compelling, as the base should have a greater effect upon the yield rather than the ee since its presumed role in the mechanism is to turnover the catalyst. It is possible that the other bases are not as efficient in regenerating the catalyst as triethylamine, and the background radical pathway (Figure 4-3, Path C) becomes more pronounced. The low levels of stereoinduction and poor yields observed with inorganic bases may be attributed to their decreased solubility in benzene.

Table 4-3. Effect of the Base on the Carbonylation of Secondary Alkyl Iodides



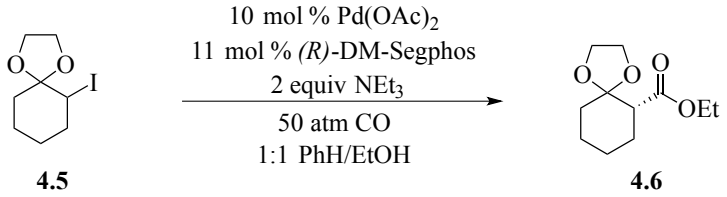
4.5 **4.6**

entry	base	%yield[a]	ee
1	NEt_3	47	20
2	iPr_2NEt	45	5
3	K_3PO_4	50	0[b]
4	NaOAc	20	4

[a]Yield calculated by ^{1}H NMR spectroscopy of crude reaction mixtures using 1,3,5-trimethoxybenzene. [b]Reaction pressure is 50 atm CO.

Next we sought to determine the effect that temperature has upon the stereoselectivity of the reaction. We wanted to lower the temperature in order provide more control in the stereodetermining step; however, when the temperature was decreased to 70 °C, there was a substantial drop in ee. One potential cause for the drop in enantioselectivity is when the temperature is lowered, oxidative addition by an S_N2 mechanism is favored (Figure 4-3, Path D).

Table 4-4. Effect of Temperature on the Carbonylation of Secondary Alkyl Iodides



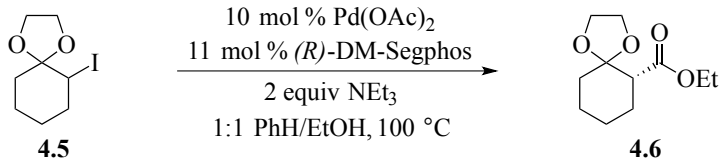
4.5 **4.6**

Entry	Temperature (°C)	%Yield[a]	ee
1	100	53	15
2	70	74	9

[a]Yield calculated by ^{1}H NMR spectroscopy of crude reaction mixtures using 1,3,5-trimethoxybenzene.

We also studied the effect of the amount of nucleophile/solvent ratio had upon the stereoselectivity of the reaction. It was observed that increasing concentrations of nucleophile relative to the solvent progressively increased the stereoselectivity of the reaction (Table 4-5, entries 1, 2, and 3); however, running the reaction in ethanol alone decreased the ee from 20% to 11% (entry 4).

Table 4-5. Effect of the Concentration of the Nucleophile on the Carbonylation of Secondary Alkyl Iodides



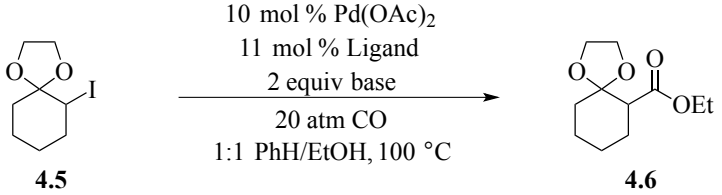
4.5 **4.6**

Entry	PhH:EtOH	%Yield[a]	ee
1	1:1	47	20
2	23:1	ND	9
3	3:1	37	14
4	0:1	59	11

[a]Yield calculated by ^{1}H NMR spectroscopy of crude reaction mixtures using 1,3,5-trimethoxybenzene.

With the reaction conditions optimized, we next examined different ligands (Table 4-6). First we examined different segphos ligands due to our initial success with DM-Segphos. No stereoinduction was observed when Segphos was utilized (entry 2) and the opposite enantiomer was generated with DTMB-Segphos (entry 3). These results indicate that the steric bulk of the ligand has a significant impact on the stereoselectivity of the reaction. A similar trend was noted for BINAP ligands as well (entries 4 and 5), as the ee of the reaction increased with the bulkier xylyl-BINAP ligand. Interestingly, H_8-BINAP delivered similar levels of enantioinduction as DM-Segphos. It is possible that the difference in dihedral angle (~10 degrees) facilitates more efficient stereoinduction.[28] Other phosphine ligands tested were not found to have a significant impact on the enantioselectivity (entries 7 – 17). Structures for the ligands in Table 4-6 are shown in Figure 4-4.

Table 4-6. Effect of the Ligand on the Carbonylation of Secondary Alkyl Iodides

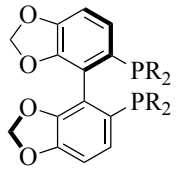


4.5 **4.6**

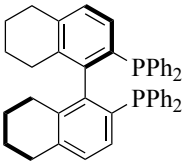
Entry	Ligand	%Yield[a]	ee
1	*(R)*-DM-Segphos	47	20
2	*(R)*-Segphos	58	0
3	*(R)*-DTMB-Segphos	63	10[c]
4	*(R)*-BINAP	75	0[b]
5	*(R)*-xylyl-BINAP	58	7[b]
6	*(R)*-H_8-BINAP	45	23
7	*(S)-(S)*-CHIRAPHOS	ND	0
8	*(R)-(R)*-DIOP	47	0
9	CTH-*(R)*-P-Phos	60	0[b]
10	CTH-*(R)*-BINAM	77	0[b]
11	*t*Bu-Josiphos	40	15
12	Ph-Cy-Josiphos	80	0
13	Cy-Cy-Josiphos	79	0
14	Ph-xylyl-Josiphos	68	0
15	Walphos	38	0
16	*(R)*-Cl-OMe-BIPHEP	46	7
17	*(R)*-xylyl-OMe-BIPHEP	45	11

[a]Yield calculated by ^{1}H NMR spectroscopy of crude reaction mixtures using 1,3,5-trimethoxybenzene. [b]Reaction pressure is 50 atm CO. [c](*S*)-enantiomer generated.

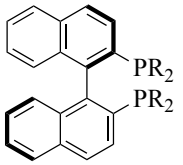
Figure 4-4. Structures for the Ligands in Table 4-6



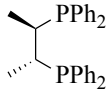
R = Ph, *(R)*-Segphos
R = 3,5-Me_2-Ph, *(R)*-DM-Segphos
R = 4-MeO-3,5-*t*Bu_2-Ph, (*R*)-DTMB-Segphos



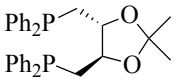
(R)-H_8-BINAP



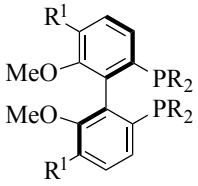
R = Ph, *(R)*-BINAP
R = 3,5-Me_2-Ph, *(R)*-xylyl-BINAP



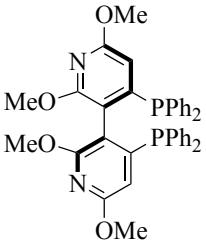
(S)-(S)-CHIRAPHOS



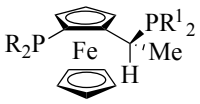
(R)-(R)-DIOP



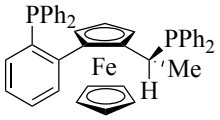
R = 3,5-Me_2-Ph, R^1 = H, *(R)*-xylyl-OMe-Segphos
R = Ph, R^1 = Cl, *(R)*-Cl-OMe-Segphos



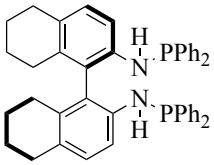
CTH-*(R)*-P-PHOS



R = Ph, R^1 = *t*Bu, *t*Bu-Josiphos
R = Ph, R^1 = Cy, Ph-Cy-Josiphos
R = Cy, R^1 = Cy, Cy-Cy-Josiphos
R = Ph, R^1 = 3,5-Me_2-Ph, Ph-xylyl-Josiphos

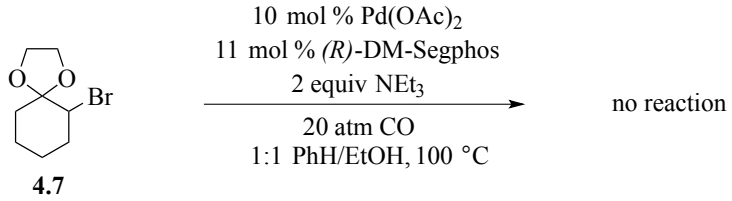


Walphos



CTH-*(R)*-BINAM

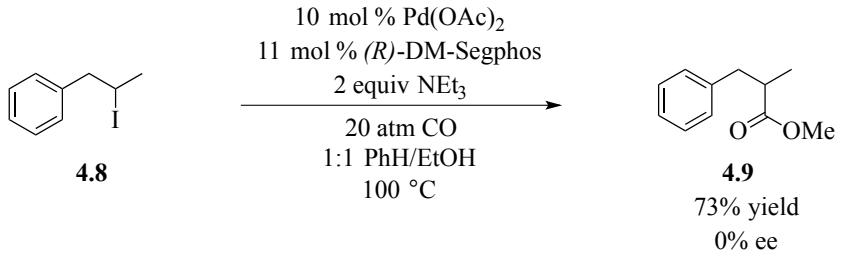
In an attempt to make the reaction more general, we employed alkyl bromide **4.7** under the optimized conditions (Scheme 4-6). Since an alkyl bromide is less activated than an alkyl iodide, the reaction should be slower, resulting in a more controlled reaction. Unfortunately, no reaction was observed.



4.7

Scheme 4-6. Attempted Palladium-Catalyzed Carbonylation Using an Alkyl Bromide

We also wanted to determine if a stereoselective carbonylation could be achieved with a less sterically hindered iodide (Scheme 4-7). Yet, when homo-benzylic iodide **4.8** was reacted under our most promising conditions, no enantioselectivity was observed.



4.8 **4.9**
73% yield
0% ee

Scheme 4-7. Palladium-Catalyzed Carbonylation of Homo-Benzylic Secondary Iodides

4.4. Summary

In conclusion, we have disclosed preliminary results for the asymmetric carbonylation of racemic secondary iodides. These results suggest that ablation of the racemic iodide via palladium catalysis allows for stereoselective synthesis of α-chiral carbonyl compounds. Further optimization of conditions as well as substrate scope investigation will be required to reveal the full potential of this transformation.

4.5. Experimental

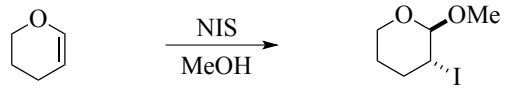
4.5.1. General Methods

HPLC spectra were obtained using an Agilent 1200 series HPLC with detection at 210, 230, 250, and 254 nm using a Chiralpak IB column using a flow rate of 1 mL/min. The solvent system was 99 Hexanes : 1 Isopropanol GC spectra were obtained using an Agilent 6850 series GC with a Hydrodex-β-6TBDM column. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model AVANCE III 400 or 600 (^{1}H NMR at 400 MHz, or 600 MHz and ^{13}C NMR at 100 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.28 ppm, ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), coupling constants (Hz), and integration. Mass spectra were obtained either using a positive ion mode flow injection Visualization was accomplished with short wave UV light (254 nm), aqueous basic potassium permanganate solution, or ethanolic acidic *p*-anisaldehyde solution followed by heating. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63 μm) purchased from Silicycle. Tetrahydrofuran, diethyl ether, and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use. Acetone, 99.8%, Extra Dry was purchased from Acros. Carbon Monoxide, Research Purity 99.998% was purchased from Matheson Tri-Gas. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted. The pressure reactors used were purchased from Parr Instrument Company that included

a 4310 Gage Block Assembly and a GP VS 22 mL A SKT 316SS ST CLS reaction vessel.

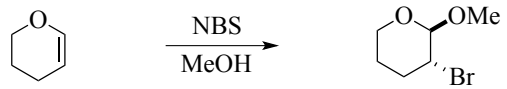
4.5.2 Preparation of Alkyl Halide Substrates

Note: As a precaution alkyl iodides were immediately stored in a dark, inert atmosphere at -40 °C upon purification.



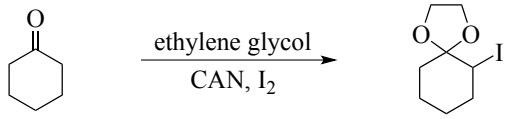
4.2

(*trans*)-3-iodo-2-methoxytetrahydro-2*H*-pyran (4.2, Table 4-1). The title compound was synthesized according to the literature procedure by Oshima and co-workers.[29]



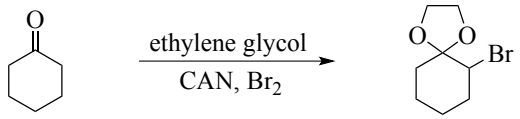
4.4

(*trans*)-3-bromo-2-methoxytetrahydro-2*H*-pyran (4.4, Scheme 4-3). The title compound was synthesized according to the literature procedure by Iwata and co-workers.[30]



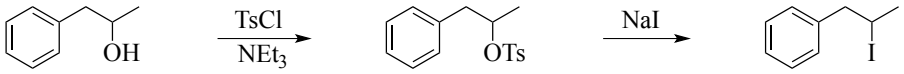
4.5

6-iodo-1,4-dioxaspiro[4.5]decane (4.5). The title compound was prepared according to a procedure by Oshima, *et. al.*[31]



4.7

6-bromo-1,4-dioxaspiro[4.5]decane (4.7, Scheme 4-5). The title compound was prepared according to a procedure by Oshima and co-workers.[31]



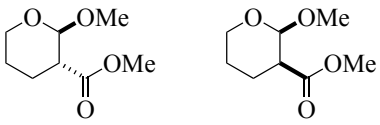
4.8

(2-iodopropyl)benzene (4.8, Scheme 4-6). The title compound was prepared by tosylation of 1-phenyl-2-propanol, followed by iodination.[32] ^{1}H NMR spectral data was in accordance with literature values.[33]

4.5.3. Palladium-Catalyzed Stereoselective Carbonylation Results

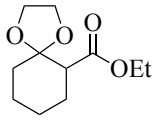
General Procedure: In a glovebox, the alkyl iodide (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), bidentate phosphine ligand (0.2 equiv), NEt_3 (2.0 equiv), and benzene (0.5 M) were combined in a 20 mL Parr reactor. The reactor was sealed and then removed from the glovebox. The Parr reactor was purged with carbon monoxide at 150 psi and then charged with 735 psi carbon monoxide. The reaction vessel was then placed in a 100 °C oil bath for 12 hr, after which, it was allowed to cool to room temperature before depressurizing. The Parr reactor was then opened and the reaction mixture was transferred out of the vessel by subsequent rinses with DCM. The combined organic layers were washed with 1 N HCl. The aqueous layer was then extracted with DCM three times. The combined organic layers were dried ($MgSO_4$) and concentrated in

vacuo. The resulting enone was either analyzed by crude ^{1}H NMR analysis or purified by flash chromatography with the specified solvent system.



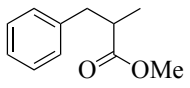
***anti*-4.3** ***syn*-4.3**

Methyl (*anti*)-2-methoxytetrahydro-2*H*-pyran-3-carboxylate (*anti*-4.3, Table 4-1) and methyl (*syn*)-2-methoxytetrahydro-2*H*-pyran-3-carboxylate (*syn*-4.3, Table 4-1). The title compounds were synthesized according to the general procedure using **4.2** (60 mg, 0.25 mmol). Diastereomeric ratios were obtained from the crude reaction mixtures.



4.6

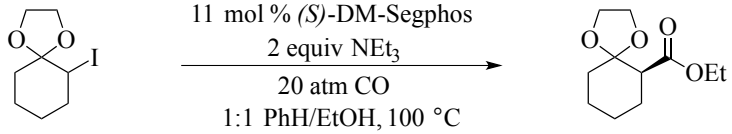
Ethyl 1,4-dioxaspiro[4.5]decane-6-carboxylate (4.6). The title compound was synthesized according to the general procedure using **4.5** (67 mg, 0.25 mmol). The resulting ester was purified by flash chromatography (10:1 Hex:EtOAc). Physical and spectral data were in accordance with the literature.[34] Yields were calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Enantioselectivities were obtained by chiral GC. from a chiral GC at 120 °C with a flow rate of 1.5 mL/min.



4.9

Methyl 2-methyl-3-phenylpropanoate (4.9, Scheme 4-6). The title compound was synthesized according to the general procedure using **4.8** (65 mg, 0.264 mmol). The resulting ester was purified by flash chromatography (10:1 Hex:EtOAc). Physical and spectral data were in accordance with the literature.[35] Yields were calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Enantioselectivity data was obtained by chiral HPLC.

4.5.4 Additional Experiments



4.5 **4.6**
50% yield
21% ee

The title compound was synthesized according to the general procedure using **4.5** (67 mg, 0.25 mmol). The resulting ester was purified by flash chromatography (10:1 Hex:EtOAc). Physical and spectral data were in accordance with the literature.[34] Yields were calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Enantioselectivities were obtained by chiral GC. from a chiral GC at 120 °C with a flow rate of 1.5 mL/min.

4.6. References

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Chapter 5

Palladium-Catalyzed Ring Forming C-H Alkylations of Aromatic Systems

5.1. Introduction

Aryl/heteroaryl sp^2-sp^3 carbon-carbon bond formation has become an indespensible tool in the synthesis of bioactive small molecules containing polycyclic aromatic core structures.[1-3] Traditionally, the syntheses of the arenes/heteroarenes are accomplished through Friedel-Crafts or radical alkylations, both of which are limited to the electronics of the (hetero)aromatic moieties.

However, the Friedel-Crafts reaction has significant limitations in synthesis.[4,5] Namely, the reaction commonly requires the use of a moderately electron rich aromatic component and harsh reaction conditions, namely the use of stoichiometric Lewis acids and high temperatures. The harsh conditions also limit the functional group tolerance of the transformation (e.g. pyridines, alcohols). These aspects severly limit the utility of this transformation.

Conversely, homolytic aromatic substitution (HAS) enjoys broad functional group compatibility;[6-8] however, one significant constraint of the reaction is that electron poor aromatic systems are required for efficient reaction with relatively electron rich radicals. While many HAS reactions commonly require the use of stoichiometric tin reagents, reactions have been developed that employ milder radical initiators. For example, superstoichiometric dilauroyl peroxide (DLP) has been used as radical mediator with

xanthate substrates. Moreover, the synthesis of xanthate precursors is often not a trivial task.

Transition metal-catalyzed cross-coupling reactions have also facilitated sp^3-sp^2 bond carbon-carbon bond formation with (hetero)arenes. Commonly, the substrate scope of these transformations is limited, and the yields are typically low. We wanted to utilize the same mode of activation of alkyl halides previously reported in our lab to facilitate the efficient coupling of unactivated alkyl electrophiles and (hetero)aromatics (Figure 5-1).

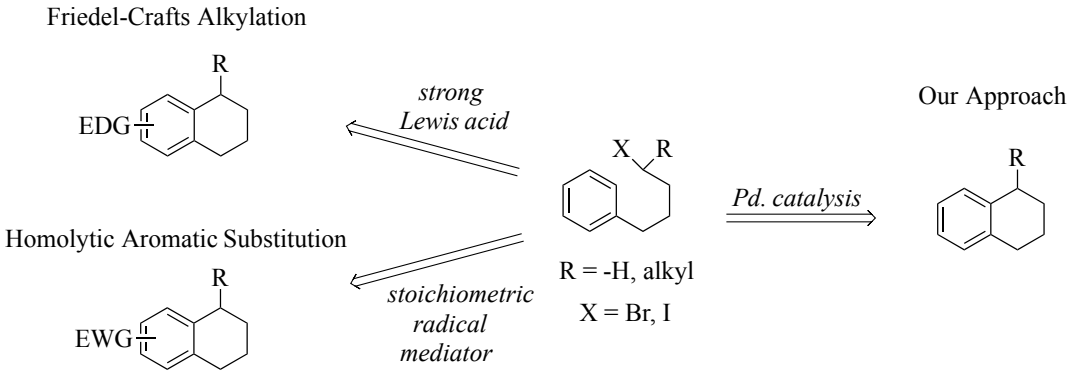


Figure 5-1. General Approaches to C-H Alkylations of (Hetero)aromatics with sp^3-Hybridized Electrophiles

5.2 Background

There are several examples of palladium-catalyzed C-H alkylation of aromatic compounds that employ sp^2-hybridized electrophiles;[9-16] however, examples that employ sp^3-hybridized electrophiles are considerably more scarce. This is due to the general reluctance of alkyl electrophiles to undergo nucleophilic addition,[17-21] and the willingness of the transient alkyl palladium species to participate in rapid β-hydride elimination.[22,23]

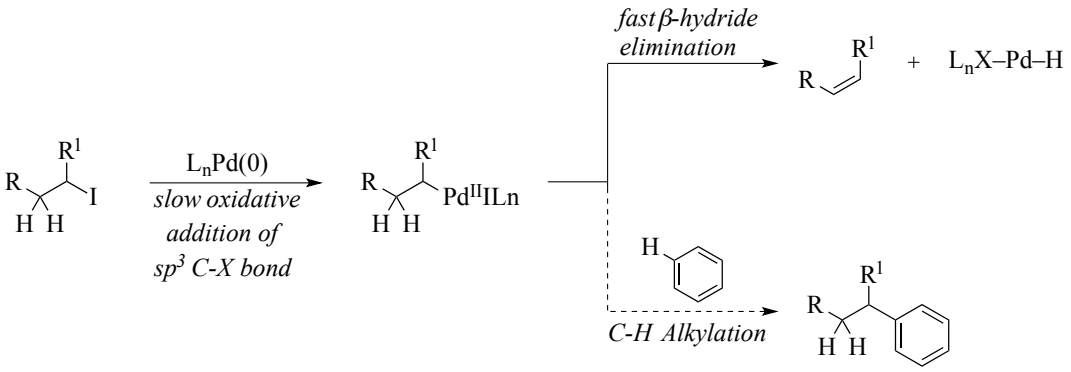
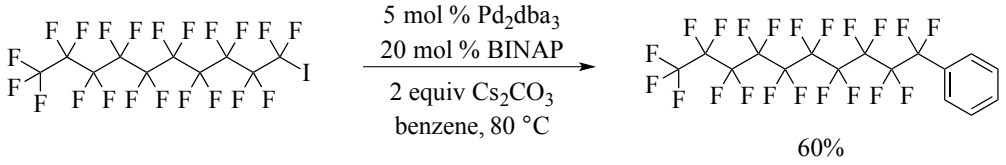


Figure 5-2. Challenges for the Development of a C-H Arylation Using Alkyl Electrophiles

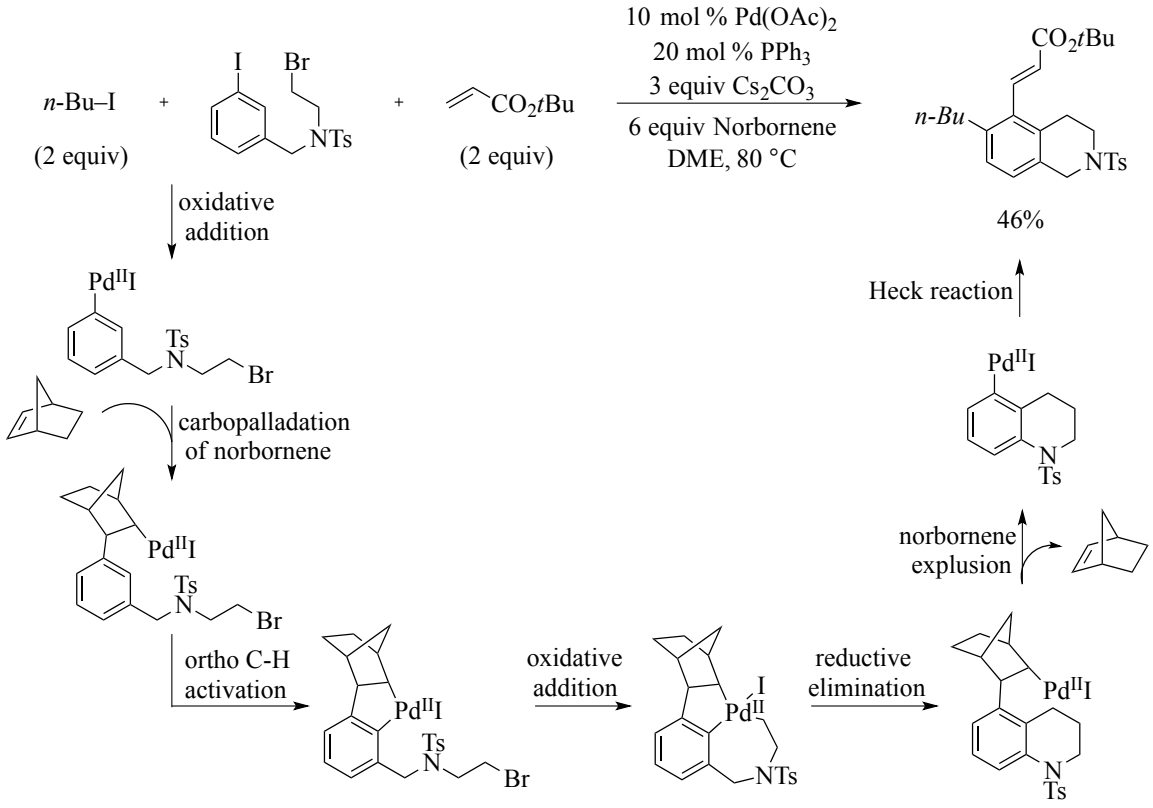
Recently, examples have been reported that utilize sp^3-hybridized electrophiles that do not have accessible β-hydrogens. For example, the Sanford laboratory reported that the palladium-catalyzed perfluoroalkylation of arenes.[24] Preliminary mechanistic data suggests the reaction does not proceed via radical intermediates, implicating an organometallic mechanism. While this transformation is notable, the scope for the iodide is limited to only perfluoroalkyl iodides and a large excess of the arene must be used for an efficient reaction.



Scheme 5-1. Palladium-Catalyzed Arylation of Perfluoroalkyl Iodides

One successful strategy for the reaction of alkyl electrophiles and arenes is the use of norbornene to facilitate domino reactions.[25] In this particular example by Lautens *et. al.*, norbornene is able to mediate sequential C-H alkylation and intermolecular Heck

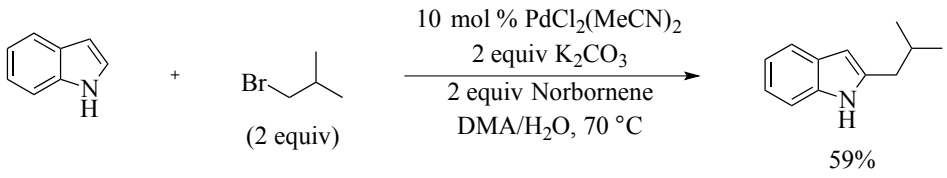
reaction.[26] Norbornene is able to facilitate the reaction for several reasons. Norbornene readily undergoes oxidative addition to relieve significant ring strain. The resulting alkyl palladium-species does not possess accessible β-hydrogens, thus enabling further reaction. Unfavorable steric interactions, presumably results in elimination of norbornene.



Scheme 5-2. Palladium-Catalyzed Intermolecular Alkylations Facilitated by Norbornene

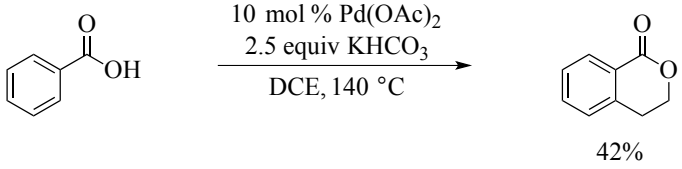
Notably, this strategy was recently employed to alkylate free indoles with alkyl bromides (5-3).[27] The reaction was tolerant of the electronic nature of the indole and was compatible with several functional groups. Furthermore, it was found that use of the free

indole was critical to the success of the reaction, and mechanistic investigations revealed that an *N*-norbornene-type palladacycle is a key intermediate in the synthesis.[28]



Scheme 5-3. Palladium-Catalyzed Intermolecular Alkylation of Unprotected Indoles Enabled by Norbornene

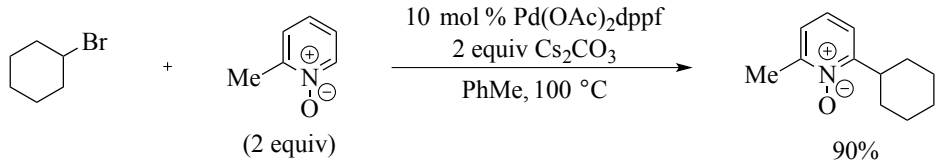
The use of directing groups is another strategy that has been successfully employed to insert C-H alkylation of aromatic systems.[29] A report by Yu and co-workers utilized a carboxylic acid to facilitate ortho-C-H activation, generating γ- and δ-lactones.[30] While a large excess of the alkylating agent was required, the reaction can be run in air.



Scheme 5-4. Palladium-Catalyzed Ortho Alkylation/Lactonization of Benzoic Acids with 1,2-Dichloroethane

Recently, the Fu laboratory reported the first example of a palladium-catalyzed C-H alkylation of aromatic compounds that utilized secondary and tertiary alkyl electrophiles.[31] It was discovered that secondary and tertiary alkyl bromides reacted neatly with pyridine *N*-oxides by employing 10 mol % $Pd(OAc)_2$dppf with an inorganic base at elevated temperatures. The reaction proved to be tolerant of several functional

groups, including substituted olefins and was capable of generating heteroaromatic product on gram-scale. Additionally, preliminary mechanistic studies suggested that this is a radical-type process.



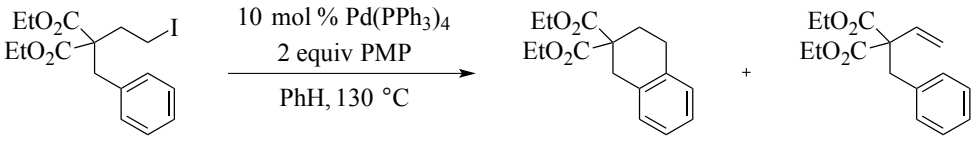
Scheme 5-5. Palladium-Catalyzed C-H Alkylation of Pyridine *N*-Oxides with Secondary and Tertiry Alkyl Bromides

Our lab has demonstrated the potential for both primary and secondary alkyl electrophiles to undergo palladium-catalyzed reactions with alkenes.[32,33] We hoped to apply the palladium-catalyzed activation of sp^3-hybridized electrophiles to C-H alkylations of electronically varied heteroaromatic and aromatic systems. In doing so, we sought to provide expedient access to bioactive small molecules in an atom-economical fashion without the required use of a directing group. Our preliminary findings are reported herein.

5.3 Results and Discussion

With the goal of developing highly reactive conditions to facilitate a broad range of C-C bond forming reactions, we employed an aromatic moiety that did not possess an electronic bias, alkyl iodide **5.1**.[34] Additionally, diesters were installed on the alkyl tether to help promote 6-*exo* cyclization. When primary iodide **5.1** was subjected to conditions previously employed by our group to promote activation of alkyl halides,[33] tetrahydronapthalene **5.2** was formed in 73% yield. Dehydrohalogentation product **5.3**

was also observed. This was of particular interest as β-hydride elimination was not noted to be a significant pathway in reactions that had been previously developed in our laboratory;[32,33] however, the cyclization with the aromatic moiety may be slower than cyclization with alkenes, allowing more time for deleterious side reactions, such as β-hydride elimination, to occur.

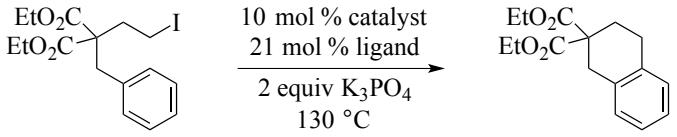


5.1 **5.2** 73% **5.3** 9%

Scheme 5-6. Preliminary results for C-H Alkylation of an Aromatic System by an Unactivated Alkyl Iodide

We hypothesized that employing transition-metals other than palladium may facilitate the same transformation. Our investigation focused on metals that have been utilized to activate primary alkyl halides in atom transfer radical polymerization (ATRP) processes;[35] our findings are summarized in Table 5-1. Wilkinson's catalyst was able to effect a reaction with the aromatic moiety; however, in both non-polar and polar solvents the yield was poor (entries 1 and 2). Catalytic iron systems that were successful for generating carbon-centered radicals from primary halides were not successful in catalyzing the C-H alkylation reaction (entries 3 and 4). Additionally, copper catalysts, one of the most prolific catalysts in ATRP, were unable to promote the reaction. No benefit was observed by employing different metal-ligand ratios (entries 5-10) or by using solvents that have been noted to stabilize radicals species (entries 11-12).

Table 5-1. Capability of Transition-Metals to Catalyze the Intramolecular C-H Alkylation of Primary Alkyl Iodides



5.1 **5.2**

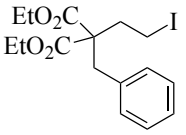
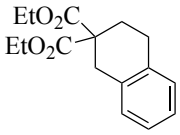
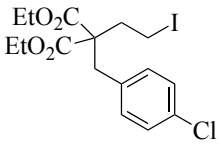
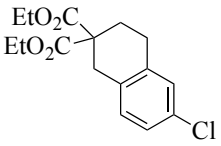
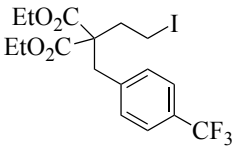
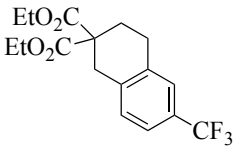
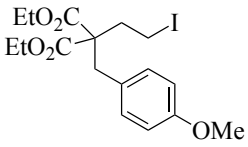
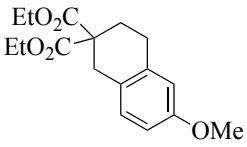
Entry	Catalyst	Ligand	Solvent	%Yield[a]
1	$RhCl(PPh_3)_3$	--	PhH	21
2	$RhCl(PPh_3)_3$	--	$PhCF_3$	20
3	$FeCl_2$	PPh_3	$PhCF_3$	0
4	$FeCl_2$	PCy_3	$PhCF_3$	0
5	CuI	bipy	$PhCF_3$	0[b]
6	CuI	bipy	$PhCF_3$	0
7	CuCl	bipy	$PhCF_3$	0[b]
8	CuCl	bipy	$PhCF_3$	0
9	CuBr	bipy	$PhCF_3$	0[b]
10	CuBr	bipy	$PhCF_3$	0
11	CuBr	bipy	DCM	0
12	CuBr	bipy	DCE	0

[a]Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b]Reaction run with 11 mol % ligand.

Continuing our studies with palladium catalysts, we next sought to determine the effect the electronic nature of the aryl ring had upon the reaction (Table 5-2). When K_3PO_4 was utilized as a base, β-hydride elimination was not observed as a side reaction in the synthesis of tetrahydronapthalene derivative **5.2** (entry 1). Electron poor aromatic moieties gave much lower yields upon reaction, as *para*-chloro-substituted alkyl iodide **5.6** cyclized to **5.7** in 29% yields (entry 2). Trifluoromethyl-substitution on the aromatic

moiety (**5.8**) produced tetrahydronapthlathene derivative, **5.9**, in a similar 25% yield (entry 3). The majority of the remaining mass balance for both reactions was unreacted starting material. Electron-rich aromatic systems reacted more readily, with all starting material being consumed after 24 h (entry 4). When *para*-methoxy-substituted was utilized, cyclization product **5.9** was generated in 46% yield.

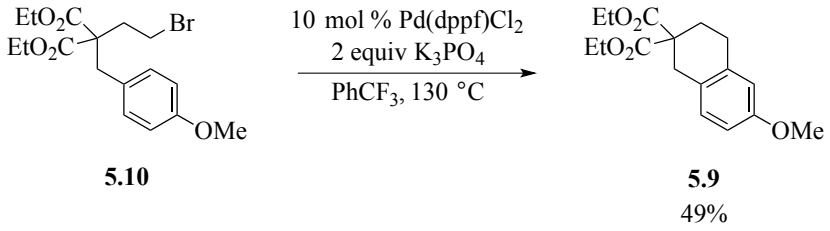
Table 5-2. Effect of Varying the Electronics of the Aromatic Ring in the Palladium-Catalyzed C-H Alkylation of Primary Alkyl Iodides[a]

Entry	Substrate	Product	%Yield[b]
1	 **5.1**	 **5.2**	67
2	 **5.4**	 **5.5**	29
3	 **5.6**	 **5.7**	25
4	 **5.8**	 **5.9**	46

[a]All reactions run 0.5 M in PhH at 130° C in a sealed tube in the presence of 10 mol % $Pd(PPh_3)_4$ and 2.0 equiv of K_3PO_4. [b]Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Interestingly, alkyl bromide **5.10** provided the C-H alkylation product in 49% yield (Scheme 5-7). This result was exciting as we were unsuccessful in employing alkyl bromides in any of our other transformations developed in our laboratory.[32,33] Reaction

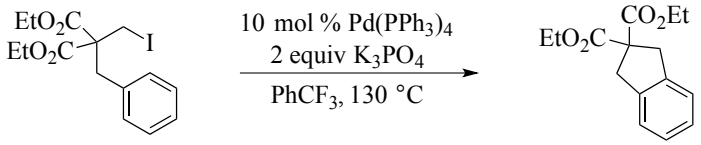
of the bromide was slower than reaction of the iodide, as 15% of the starting material remained after 24 hours. Additionally, reaction with $Pd(dppf)Cl_2$ instead of palladium-tetrakis was observed to minimize β-hydride elimination.



5.10 **5.9** 49%

Scheme 5-7. Palladium-Catalyzed C-H Alkylation of Alkyl Bromides

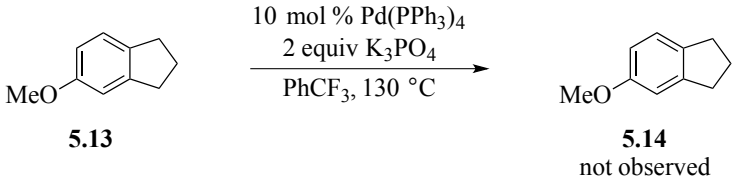
Indanes were also accessible via this method (Scheme 5-8). Higher conversions were noted in polar solvent. While very few side reactions were noted in the reaction of iodide **5.11**, conversion to indane **5.12** was sluggish. After 24 hours, 16% unreacted starting material still remained.



5.11 **5.12** 50%

Scheme 5-8. Formation of Indanes via Palladium-Catalyzed C-H Alkylation with Primary Alkyl Iodides

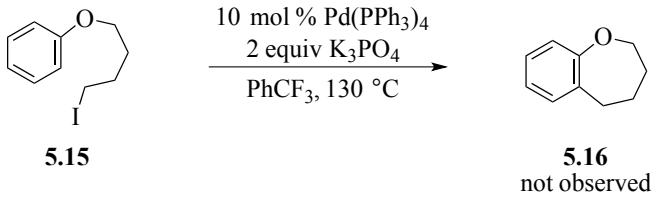
Furthermore, the presence of the diesters in the alkyl tether was critical to the success of the reaction, as exemplified by alkyl iodide **5.13** (Scheme 5-9). Upon reaction, none of the desired indane **5.14** was observed.



5.13 **5.14** not observed

Scheme 5-9. Attempted Formation of an Indane without Substitution on the Alkyl Tether

Additionally, attempts were made to synthesize cyclopentane **5.16** (Scheme 5-10); however, upon reaction of iodide substrate **5.15**, none of the desired C-H alkylation product was observed. Instead, several side reactions had taken place including β-hydride elimination and reduction of the alkyl iodide to the alkane. This indicates that the iodide was indeed activated, but the rate of cyclization to the 7-membered ring was slower than the rates of the aforementioned side reactions.



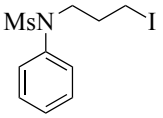
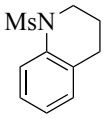
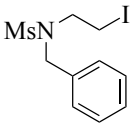
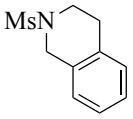
5.15 **5.16** not observed

Scheme 5-10. Attempted Cycloheptane Synthesis via Palladium-Catalyzed C-H Alkylation

Tetrahydroquinoline derivatives were also readily synthesized from sulfonamide precursors (Table 5-3). Alkyl iodide **5.17** proved that electronically-neutral aromatic systems could undergo C-H alkylation to provide tetrahydroquinoline derivative **5.18** in 31% yield (entry 1). The reaction did not prove sensitive to the position of the sulfonamide in the alkyl tether, as tetraisoquinoline derivative **5.20** was synthesized in a similar 30% yield (entry 2). The protecting group on nitrogen should be carefully

selected, though, to be electron-withdrawing enough not to promote the formation of mustard gases[36] or not to contain aromatic compounds that can undergo C-H alkylation as well (e.g. tosylates).

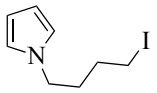
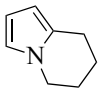
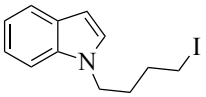
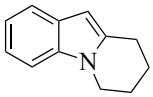
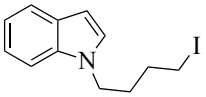
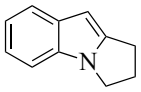
Table 5-3. Palladium-Catalyzed C-H Alkylation Reactions of Alkyl Iodides with a Sulfonamide Alkyl Tether[a]

Entry	Substrate	Product	%Yield[b]
1	 **5.17**	 **5.18**	31
2	 **5.19**	 **5.20**	30

[a]All reactions run 0.5 M in PhH at 130° C in a sealed tube in the presence of 10 mol % $Pd(PPh_3)_4$ and 2.0 equiv of K_3PO_4. [b]Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

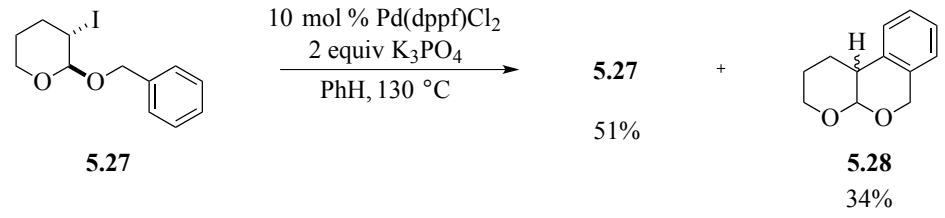
Heteroaromatic compounds were also studied (Table 5-4). Pyrrole **5.21** was readily cyclized to **5.22** under slightly different conditions. The use of dppp as a ligand significantly reduced the amount of β-hydride elimination, allowing for a more efficient process. There was a polar background reaction, and **5.22** was generated in 34% yield in the absence of palladium. Indoles were able to undergo C-H alkylation with tethered alkyl iodides to synthesize both cyclohexanes (**5.24**, entry 2) and cyclopentanes (**5.26**, entry 3).

Table 5-4. Palladium-Catalyzed C-H Alkylation of Heteroaromatic Compound with Primary Alkyl Iodides[a]

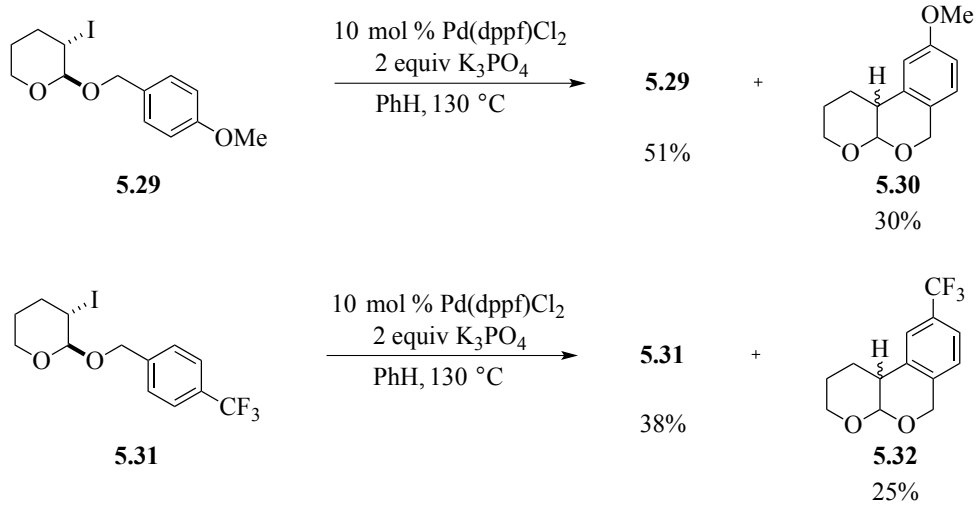
Entry	Substrate	Product	%Yield[b]
1	 **5.21**	 **5.22**	64[c]
2	 **5.23**	 **5.24**	43[d]
3	 **5.25**	 **5.26**	34

[a]Reaction run 0.5 M in PhH at 130° C in a sealed tube in the presence of 10 mol % $Pd(PPh_3)_4$ and 2.0 equiv of K_3PO_4 for 18 h. [b]Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene. [c]Reaction run with 5 mol % $[PdCl(allyl)]_2$ and 11 mol % dppp instead of $Pd(PPh_3)_4$. [d]Reaction run with PMP instead of K_3PO_4.

We also investigated the potential to employ secondary alkyl iodides in the cyclization reaction (Scheme 5-11); however, little conversion to the cyclized product **5.27** was observed. Optimization efforts studied the effect of catalyst systems, base, solvent, and reaction temperature on the success of the reaction. In all cases, further conversion to product **5.27** was not observed; instead, side reactions were promoted. The electronics of the aromatic ring were varied with hopes of promoting the reaction; although, no increase in yield was observed (Scheme 5-12). The low levels of cyclization could be attributed to increased stability of a secondary carbon-centered radical.



Scheme 5-11. Palladium-Catalyzed C-H Alkylation of Secondary Alkyl Iodides



Scheme 5-12. Varying the Electronics of the Aromatic System in the Reaction with Secondary Alkyl Iodides

5.4 Summary

In conclusion, preliminary results for the alkylation of inert C-H bonds of aromatic and heteroaromatic systems with unactivated alkyl halides have been described. Primrary and secondary alkyl iodides and bromides were shown to react with electron-rich and electron-poor aromatic components as well as electronically neutral phenyl rings. Promising preliminary data also includes the cyclopentane as well as cyclohexane synthesis. Future work will focus on further optimizing the reaction conditions to improve the yield as well as expanding the substrate scope to include different ring sizes

and substitution in the alkyl tether. Additionally, mechanistic studies will be undertaken to elucidate the mechanism of the reaction.

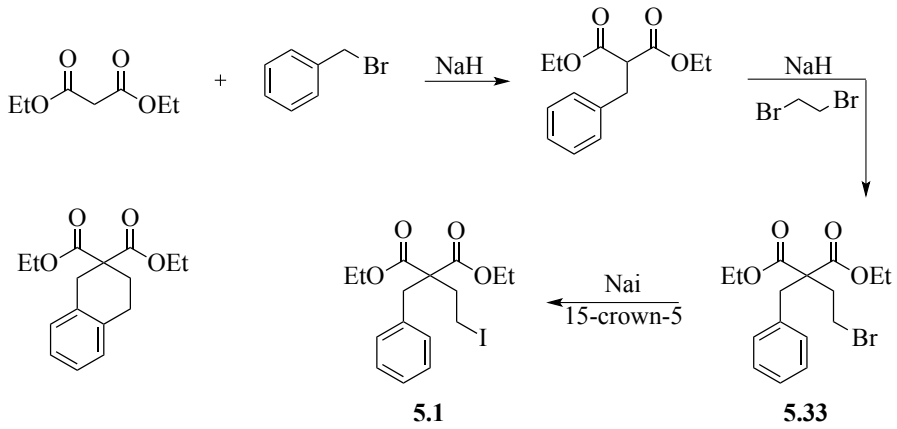
5.5 Experimental

5.5.1 General Methods

Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model AVANCE III 400 or 600 (^{1}H NMR at 400 MHz, or 600 MHz and ^{13}C NMR at 100 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.28 ppm, ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), coupling constants (Hz), and integration. Mass spectra were obtained using Micromass (now Waters Corporation, 34 Maple Street, Milford, MA 01757) Quattro-II, Triple Quadrupole Mass Spectrometer, with a Z-spray nano-Electrospray source design, in combination with a NanoMate (Advion, 19 Brown Road, Ithaca, NY 14850) chip based electrospray sample introduction system and nozzle. Visualization was accomplished with short wave UV light (254 nm), aqueous basic potassium permanganate solution, or ethanolic acidic *p*-anisaldehyde solution followed by heating. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63 μm) purchased from Silicycle. Tetrahydrofuran, diethyl ether, and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use. Acetone, 99.8%, Extra Dry was

purchased from Acros. Carbon Monoxide, Research Purity 99.998% was purchased from Matheson Tri-Gas. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted. The pressure reactors used were purchased from Parr Instrument Company that included a 4310 Gage Block Assembly and a GP VS 22 mL A SKT 316SS ST CLS reaction vessel.

5.5.2 Preparation of Alkyl Iodide and Bromide Substrates



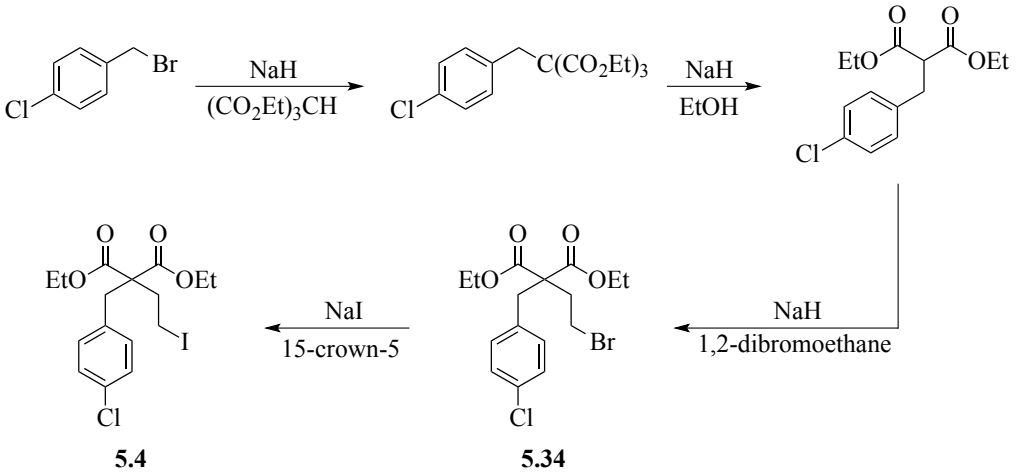
5.1 **5.33**

Diethyl 2-benzyl-2-(2-iodoethyl)malonate (5.1, Table 5-2, entry 1). The title compound was synthesized by an alkylation with benzyl bromide according to the literature procedure by Renaud *et. al*.[37] followed by alkylation with dibromoethane, and an iodination.[33]

Analytical data for **(5.33)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 3 H), 7.11 (d, *J* = 7.2 Hz, 2 H), 4.24 (m, 4 H), 3.41 (t, *J* = 8.4 Hz, 2 H), 3.28 (s, 2 H), 2.38 (t, *J* = 8.4 Hz, 2 H), 1.29 (t, *J* = 7.2 Hz, 6 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 170.2, 135.2, 129.8, 127.2, 61.66, 61.64, 58.88, 39.22, 36.06, 27.23, 13.99

Analytical data for **(5.1)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32-7.26 (m, 3 H), 7.10, (d, *J* = 7.2 Hz, 2 H), 4.23 (m, 4 H), 3.26 (s, 3 H), 3.15 (t, *J* = 8.4 Hz, 2 H), 2.41 (t, *J* = 8.4

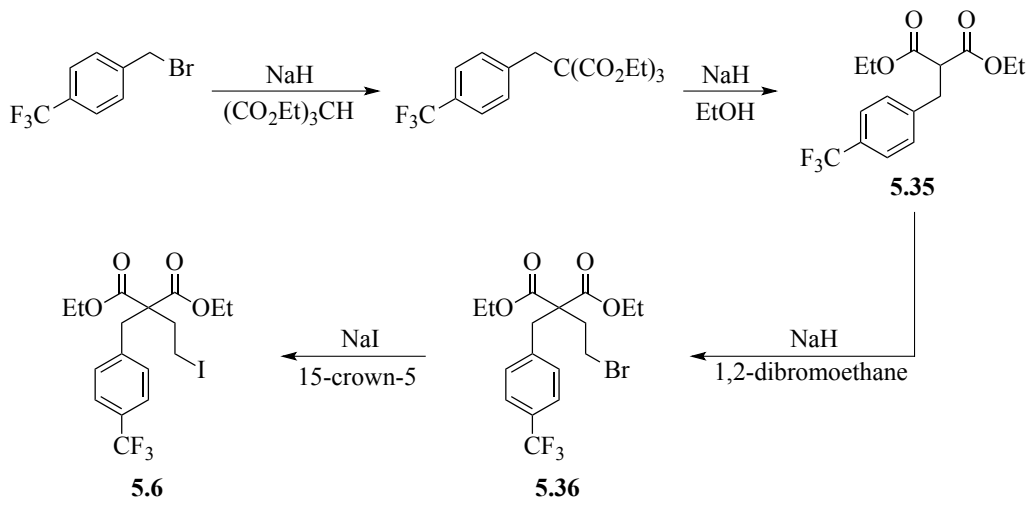
Hz, 2 H), 1.28 (t, *J* = 7.2 Hz, 6 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 170.1, 135.3, 129.8, 128.4, 127.2, 61.58, 60.48, 38.88, 37.56, 14.00, –2.39



Diethyl 2-(2-iodoethyl)-2-(4-chloro)benzyl)malonate (5.4, Table 5-2, entry 2). The title compound was synthesized by an alkylation followed by monodecarboxylation,[38,39] alkylation with dibromoethane, and an iodination.[33]

Analytical data for **(5.33)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 10.8 Hz, 2 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 4.22 (m, 4 H), 3.39 (t, *J* = 7.8 Hz, 2 H), 3.24 (s, 2 H), 2.35 (t, *J* = 7.8 Hz, 2 H), 1.28 (t, *J* = 7.2 Hz, 6 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 170.0, 133.8, 133.2, 131.2, 128.6, 61.76, 58.8, 38.70, 35.24, 26.99, 13.99.

Analytical data for **(5.4)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.03 (m, 2 H), 4.21 (m, 4 H), 3.21 (s, 2 H), 3.12 (m, 2 H), 2.39 (m, 2 H), 1.27 (t, *J* = 7.2 Hz); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 169.8, 133.8, 133.2, 131.1, 128.6, 61.71, 60.34, 38.28, 37.64, 14.00, -2.67.

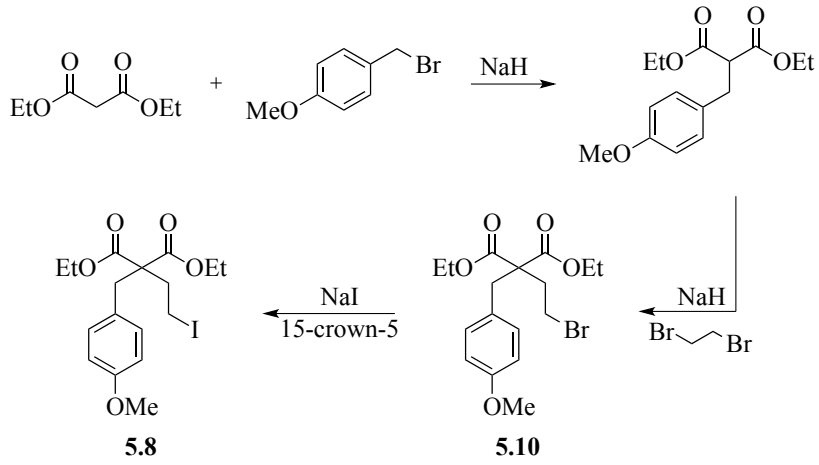


Diethyl 2-(2-iodoethyl)-2-(4-(trifluoromethyl)benzyl)malonate (5.6, Table 5-2, entry 3). The title compound was synthesized by an alkylation followed by a monodecarboxylation,[38] alkylation with dibromoethane, and an iodination.[33]

Analytical data for **(5.35)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 7.8 Hz, 2 H), 4.18 (m, 4 H), 3.66 (t, *J* = 7.8 Hz, 1 H), 3.28 (d, *J* = 7.8 Hz, 2 H), 1.22 (t, *J* = 7.2 Hz, 6 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 168.5, 126.8, 125.4 (q, *J* = 4.05), 124.1 (q, *J* = 270), 121.4, 61.64, 53.36, 34.32, 13.95.

Analytical data for **(5.36)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 4.22 (m, 4 H), 3.40 (t, *J* = 8.4 Hz, 2 H), 3.32 (s, 2 H), 2.37 (t, *J* = 8.4 Hz, 2 H), 1.27 (t, *J* = 7.2 Hz, 6H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 169.9, 139.6, 130.3, 129.5 (q, *J* = 32 Hz), 125.3 (q, *J* = 3.6 Hz), 61.85, 58.76, 39.14, 36.37, 26.83, 13.95.

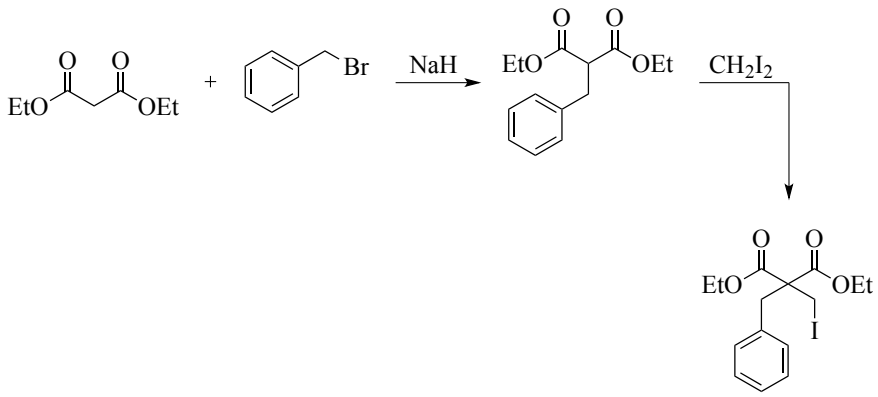
Analytical data for **(5.6)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2 H), 7.23 (d, *J* = 7.8 Hz, 2 H), 4.22 (m, 4 H), 3.29 (s, 2 H), 3.14 (m, 2 H), 2.32 (m, 2 H), 1.26 (t, *J* = 7.2 Hz, 6 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 169.7, 139.6, 130.2, 129.5 (q, J = 32 Hz), 125.3 (q, *J* = 3.3 Hz), 61.80, 60.31, 38.72, 37.79, 13.96, -2.92.



Diethyl 2-(2-iodoethyl)-2-(4-methoxybenzyl)malonate (5.8, Table 5-2, entry 4). The title compound was synthesized by an alkylation of diethyl malonate[38] followed by alkylation with dibromoethane, and an iodination.[33]

Analytical data for **(5.10)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 4.23 (m, 4 H), 3.80, (s, 3 H), 3.40 (m, 2 H), 3.21 (s, 2 H), 2.35 (m, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 170.3, 158.7, 130.8, 127.1, 113.8, 61.60, 58.98, 55.19, 55.16, 38.45, 36.07, 27.32, 14.01

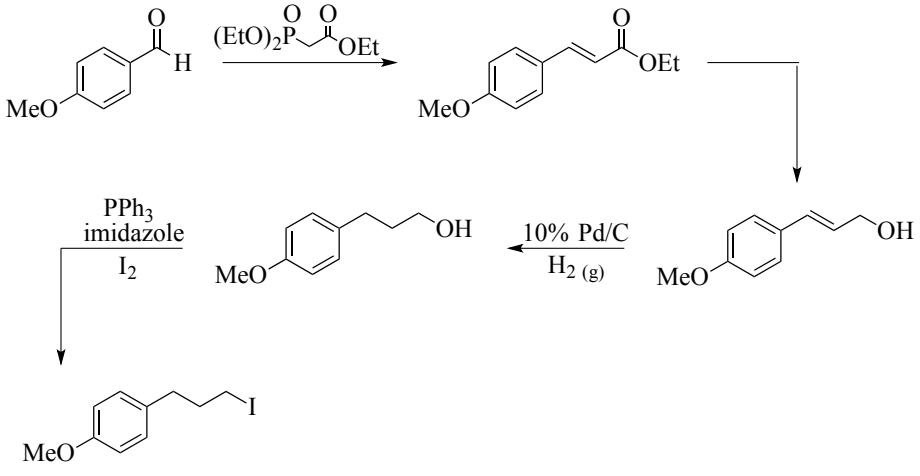
Analytical data for **(5.8)**: **IR** (thin film, cm^{-1}) ; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 9.0 Hz, 2 H), 6.83 (d, *J* = 9.0 Hz, 2 H), 4.22 (m, 4 H), 3.80 (s, 3 H), 3.19 (s, 2 H), 3.14 (m, 2 H), 2.40 (m, 2 H), 1.28 (t, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 170.2, 158., 130.8, 127.1, 113.8, 61.56, 60.54, 55.18, 38.04, 37.46, 14.04, –2.18.



5.12

Diethyl 2-benzyl-2-(iodomethyl)malonate (5.12, Scheme 5-8). The title compound was iodinated according to the literature procedure by List *et. al*.[41]

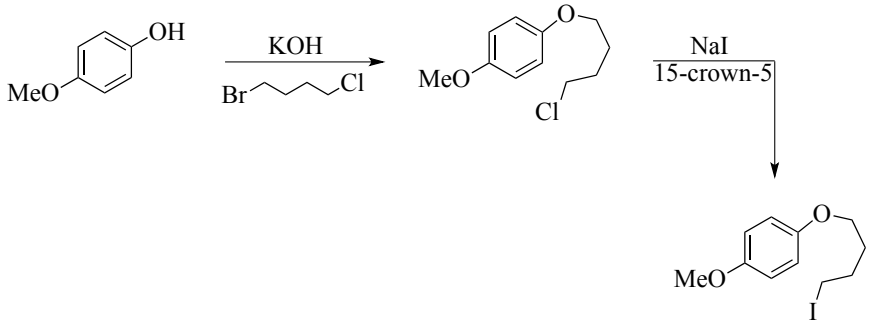
Analytical data for **(5.12)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28 m, 3 H), 7.20 (m, 2 H), 4.24 (m, 4 H), 3.47 (s, 2 H), 3.39 (s, 2 H), 1.28 (t, J = 7.2 Hz, 6 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 168.2, 135.2, 129.6, 128.5, 127.4, 62.06, 59.41, 37.97, 14.01, 7.08.



5.13

1-(3-iodopropyl)-4-methoxybenzene (5.13, Scheme 5-9). The title compound was synthesized by an HWE olefination,[42] reduction of the resulting ester,[43,44] reduction of the allylic alcohol,[45,46] and an iodination reaction.

Triphenylphosphine (1.77 g, 6.75 mmol), imidazole (460 mg, 6.75 mmol), and iodine (1.71 g, 6.75 mmol) in DCM (11.3 mL) were combined at 0 °C under Ar and stirred for 15 min. A solution of alcohol (750 mg, 4.50 mmol) in DCM (11.3 mL) was then added dropwise. The reaction mixture was stirred at 0 °C for 30 min. The reaction was then quenched with H_2O and extracted with DCM three times. The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (20:1 Hexanes/EtOAc) to provide **5.13** (967 mg, 3.50 mmol, 78%) as a pale yellow oil. Analytical data for **(5.13)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.14 (d, J = 8.4 Hz, 2 H), 6.86 (d, J = 8.4 Hz, 2 H), 3.82 (s, 3 H), 3.18 (t, J = 6.6 Hz, 2 H), 2.70 (t, J = 7.2 Hz, 2 H), 2.12 (p, J = 7.2 Hz, 2 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 158.0, 132.4, 129.4, 113.8, 55.23, 35.21, 35.04, 6.48.

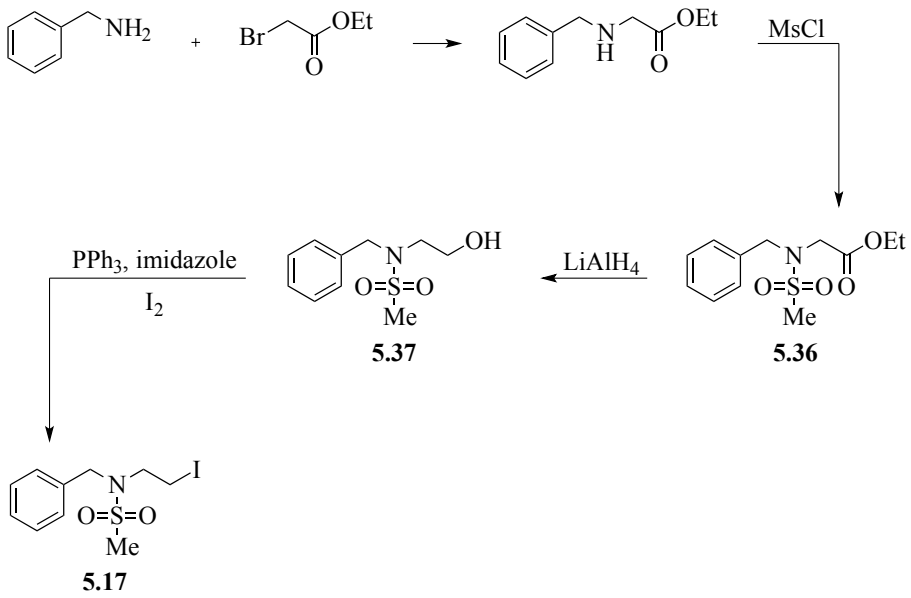


5.15

-(4-iodobutoxy)-4-methoxybenzene (5.15, Scheme 5-10). The title compound was synthesized via an alkylation[47] and an iodination.

To a solution of chloride (2.8 g, 13.0 mmol) in dried acetone (43 mL) was added NaI (5.85 g, 39.0 mmol) and 15-crown-5 (250 μL, 1.3 mmol) at room temperature under Ar. The reaction was then heated to a reflux and stirred overnight. The reaction was

cooled to room temperature and diluted with CH_2Cl_2. The reaction mixture was stirred for ~15 minutes. The organic layer was then washed with sat. aq. $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by column chromatography (80:5:2 Hex:EtOAc:DCM) to provide **5.15** (1.46 g, 4.77 mmol, 37% yield) as a white solid. Analytical data for **(5.15)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.85 (s, 4 H), 3.96 (t, *J* = 6.0 Hz, 2 H), 3.79 (s, 3 H), 3.28 (t, *J* = 6.6 Hz, 2 H), 2.05 (m, 2 H), 1.89 (m, 2 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 153.8, 152.9, 115.3, 114.6, 67.24, 55.73, 30.24, 30.18, 6.52.



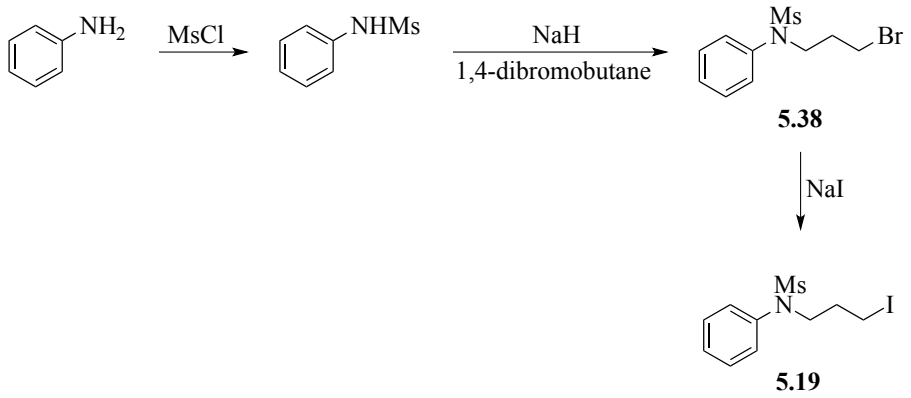
***N*-benzyl-*N*-(2-iodoethyl)methanesulfonamide (5.17, Table 5-3, entry 1).** The title compound was prepared by alkylation[48] followed by a standard mesylate protection of the amine, a standard LAH reduction of the ester moiety, and an iodination.

Analytical data for **(5.36)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 4.50 (s, 2 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 3.95 (s, 2 H), 3.12 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H); **^{13}C**

NMR (600 MHz, $CDCl_3$) δ 169.5, 134.9, 128.8, 128.4, 128.2, 61.44, 50.84, 46.76, 40.71, 14.07.

Analytical data for **(5.37)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36 (m, 5 H), 4.48 (s, 2 H), 3.66 (t, *J* = 5.4 Hz, 2 H), 3.38 (t, *J* = 5.4 Hz, 2 H), 2.96 (s, 3 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 135.8, 128.8, 128.3, 128.1, 60.26, 51.68, 49.43, 38.79.

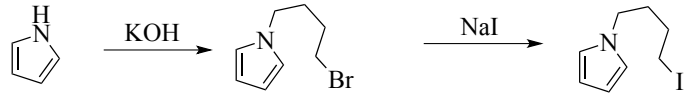
Analytical data for **(5.17)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 (m, 5 H), 4.45 (s, 2 H), 3.55 (t, *J* = 7.8 Hz, 2 H), 3.10 (t, *J* = 7.8 Hz, 2 H), 2.93 (s, 3 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 135.7, 129.0, 128.4, 128.4, 52.06, 50.39, 39.48, 1.69.



***N*-(3-iodopropyl)-*N*-phenylmethanesulfonamide (5.19, Table 5-3, entry 2). The** title compound was prepared mesyl protection of aniline[49] followed by alkylation,[50] and an iodination.

Analytical data for **(5.38)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 (m, 2 H), 7.38 (m, 3 H), 3.86 (t *J* = 7.2 Hz, 2 H), 3.45 (t, *J* = 6.6 Hz, 2 H), 2.91 (s, 3 H), 2.08 (p, *J* = 6.6 Hz, 2 H); **^{13}C NMR** (600 MHz, $CDCl_3$) d 139.0, 129.6, 128.3, 128.3, 49.23, 36.82, 31.79, 28.81.

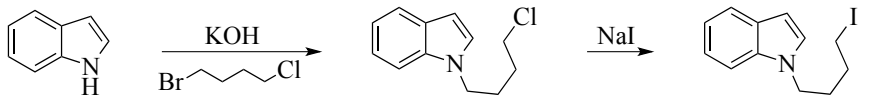
Analytical data for **(5.19)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 (m, 2 H), 7.38 (m, 3 H), 3.80 (t, *J* = 6.6 Hz, 2 H), 3.20 (t, *J* = 6.6 Hz, 2 H), 2.91 (s, 3 H), 2.04 (p, *J* = 6.6 Hz, 2 H); **^{13}C NMR** (600 MHz, $CDCl_3$) d 139.0, 129.7, 128.4, 128.3, 51.18, 36.86, 32.54, 1.72.



5.21

1-(4-iodobutyl)-1*H*-pyrrole (5.21, Table 5-4, entry 1). The title compound was synthesized by an alkylation of pyrrole[51] and an iodination.

Analytical data for **(5.21)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.66 (t, *J* = 1.8 Hz, 2 H), 6.17 (t, *J* = 1.8 Hz, 2 H), 3.93 (t, *J* = 6.6 Hz, 2 H), 3.17 (t, *J* = 6.6 Hz, 2 H), 1.91 (m, 2 H), 1.81 (m, 2 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 120.4, 108.1, 48.46, 32.30, 30.42, 5.85.

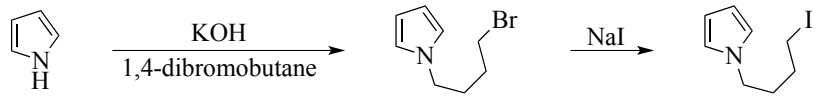


5.39 **5.23**

1-(4-iodobutyl)-1*H*-indole (5.23, Table 5-4, entry 2). The title compound was synthesized via an alkylation and an iodination.[52,53]

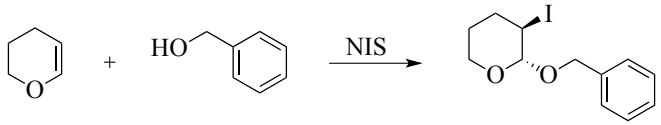
Analytical data for **(5.39)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 1 H, 7.24 (t, *J* = 7.2 Hz, 1 H), 7.14 (t, *J* = 7.2 Hz, 1 H), 7.12 (d, *J* = 3 Hz, 1 H), 6.53 (d, *J* = 3 Hz, 1 H), 4.20 (t, *J* = 6.6 Hz, 2 H), 3.54 (t, *J* = 6.6 Hz, 2 H),

2.04 (m, 2 H), 1.80 (m, 2 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 135.8, 128.5, 127.6, 121.5, 121.0, 119.3, 109.22, 101.2, 45.59, 44.44, 29.82, 27.58.



5.25

1-(3-iodopropyl)-1*H*-indole (5.25, Table 5-4, entry 3). The title compound was prepared by alkylation and iodination.[52] Physical data was in accordance with the literature for the chloride[54] and iodide.[55]



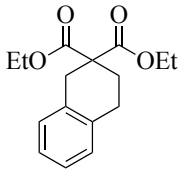
5.27

(*trans*)-2-(benzyloxy)-3-iodotetrahydro-2*H*-pyran (5.27, Scheme 5-11). The title compound was synthesized according to the literature procedure by Oshima *et. al*.[54] Analytical data for **(5.27)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.8 Hz, 2 H), 7.38 (t, *J* = 7.2 Hz, 2 H), 7.33 (m, 1 H), 4.83 (d, *J* = 11.4 Hz, 1 H), 4.76 (d, *J* = 5.4 Hz, 1 H), 4.59 (d, *J* = 12.0 Hz, 1 H), 4.17 (m, 1 H), 4.06 (m, 1 H), 3.64 (m, 1 H), 2.42, (m, 1 H), 2.04 (m, 1 H), 1.81 (m, 1 H), 1.62 (m, 1 H); **^{13}C NMR** (600 MHz, $CDCl_3$) δ 137.2, 128.4, 128.0, 127.8, 101.4, 69.79, 63.49, 32.54, 29.15, 25.43.

5.5.3 Results for the Palladium-Catalyzed C-H Alkylation of Alkyl Halides

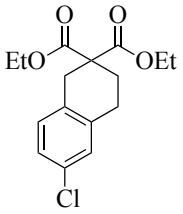
General Procedure for the Alkyl-Heck-Type Reaction: In a glovebox, the alkyl iodide (1.0 equiv), $Pd(PPh_3)_4$ (10 mol %), base (2.0 equiv), and solvent (0.5 M)

were combined in a sealed tube with a stir bar added. Upon removal from the glovebox, the sealed tube was placed into an oil bath at 130 °C. The reaction mixture was stirred for 24 h, after which it was cooled to room temperature and diluted with Et_2O. The reaction mixture was washed with 1 N HCl. The reaction was then extracted with Et_2O three times. The combined organic layers were dried ($MgSO_4$), and concentrated.



5.2

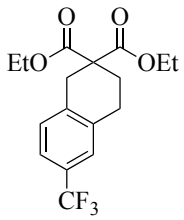
Diethyl 3,4-dihydronaphthalene-2,2(1*H*)-dicarboxylate (5.2, Table 5-2, entry 1). The title compound was synthesized from **5.1** (101 mg, 0.25 mmol) according to the general procedure to afford 67% **5.2** by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene. Analytical data for **(5.2)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 – 7.06 (m, 4 H), 7.05 (m, 1 H), 4.18 (q, *J* = 7.2 Hz, 4 H), 3.26 (s, 2 H), 2.84 (t, *J* = 6.6 Hz, 2 H), 2.32 (t, *J* = 7.2 Hz, 2 H), 1.22 (t, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (600 MHz, $CDCl_3$) d 171.3, 134.6, 133.6, 128.8, 128.6, 125.9, 61.38, 53.64, 34.66, 28.11, 14.00.



5.5

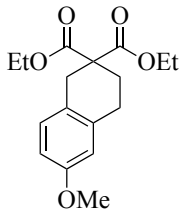
Diethyl 6-chloro-3,4-dihydronaphthalene-2,2(1*H*)-dicarboxylate (5.5, Table 5-2, entry 2). The title compound was synthesized from **5.4** (110 mg, 0.25 mmol)

according to the general procedure to afford 29% **5.5** by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene.



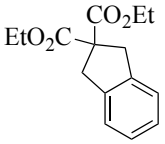
5.7

Diethyl 6-(trifluoromethyl)-3,4-dihydronaphthalene-2,2(1*H*)-dicarboxylate (5.7, Table 5-2, entry 3). The title compound was synthesized from **5.6** (118 mg, 0.25 mmol) according to the general procedure to afford 25% **5.5** by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene.



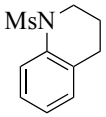
5.9

Diethyl 6-methoxy-3,4-dihydronaphthalene-2,2(1*H*)-dicarboxylate (5.9, Table 5-2, entry 4). The title compound was synthesized from **5.8** (109 mg, 0.25 mmol) according to the general procedure to afford 46% **5.9** by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene.



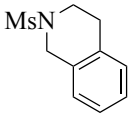
5.12

Diethyl 2-benzyl-2-(iodomethyl)malonate (5.12, Scheme 5-8). The title compound was synthesized from **5.11** (98 mg, 0.25 mmol) according to the general procedure except $PhCF_3$ was used as a solvent instead of benzene to afford 50% **5.12** by ^1H NMR analysis using 1,3,5-trimethoxybenzene. Physical and spectral data were in accordance with the literature data.[57]



5.18

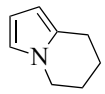
1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoline (5.19, Table 4-3, entry 1). The title compound was synthesized from **5.17** (85 mg, 0.25 mmol) according to the general procedure to afford 31% **5.18** by ^1H NMR analysis using 1,3,5-trimethoxybenzene. Physical and spectral data were in accordance with the literature data.[58]



5.20

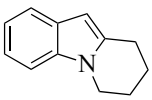
2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (5.20, Table 4-3, entry 2). The title compound was synthesized from **5.19** (85 mg, 0.25 mmol) according to the general procedure to afford 30% **5.20** by ^1H NMR analysis using 1,3,5-

trimethoxybenzene. Physical and spectral data were in accordance with the literature data.[59]



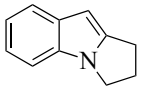
5.21

5,6,7,8-tetrahydroindolizine (5.21, Table 4-4, entry 1). The title compound was synthesized according to the general procedure using **5.20** (60 mg, 0.24 mmol) except 5 mol % $[Pd(allyl)Cl]_2$ with 11 mol % dppp in was utilized. A 64% yield of **5.21** was determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Physical and spectral data were in accordance with the literature data.[60]



5.23

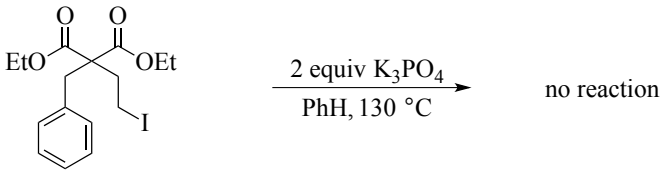
6,7,8,9-tetrahydropyrido[1,2-*a*]indole (5.23, Table 4-4, entry 2). The title compound was synthesized according to the general procedure using **5.22** (75 mg, 0.25 mmol), but PMP base was used instead of K_3PO_4. 5.23 was generated in 43% by ^1H NMR analysis using 1,3,5-trimethoxybenzene. Physical and spectral data were in accordance with the literature data.[61]



5.25

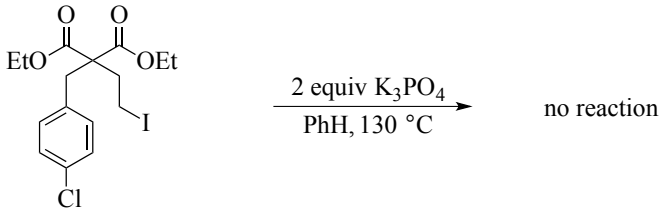
2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (5.25, Table 4-4, entry 3). The title compound was synthesized according to the general procedure using **5.24** (71 mg, 0.25 mmol) to afford 34% **5.25** by 1H NMR analysis using 1,3,5-trimethoxybenzene. Physical and spectral data were in accordance with the literature data.[61]

5.5.4 Additional Experiments



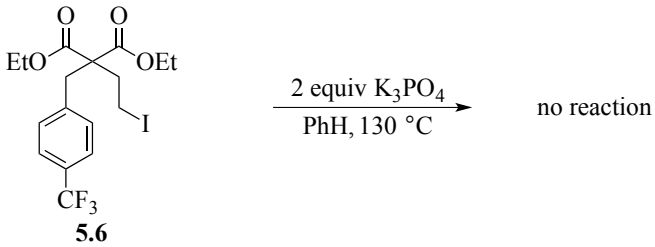
5.1

Control Experiment in the Absence of Pd Catalyst for 5.2 (Table 5-2, entry 1): 5.1 (101 mg, 0.25 mmol) was reacted according to the general procedure in the absence of $Pd(PPh_3)_4$. No product was observed by ^1H NMR analysis of the crude reaction mixture.



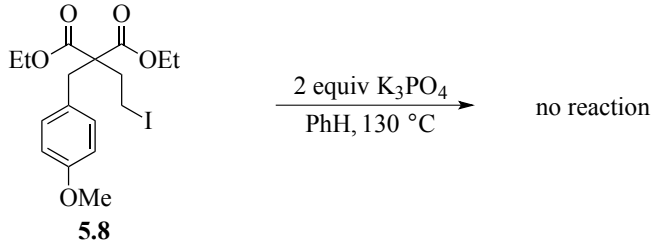
5.4

Control Experiment in the Absence of Pd Catalyst for 5.4 (Table 5-2, entry 1): 5.4 (110 mg, 0.25 mmol) was reacted according to the general procedure in the absence of $Pd(PPh_3)_4$. No product was observed by ^1H NMR analysis of the crude reaction mixture.



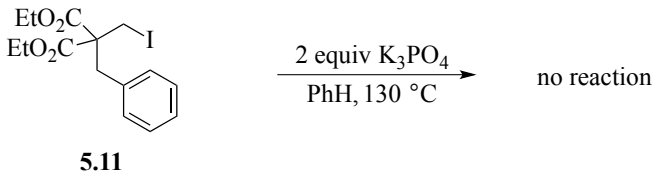
5.6

Control Experiment in the Absence of Pd Catalyst for 5.6 (Table 5-2, entry 3): 5.6 (118 mg, 0.25 mmol) was reacted according to the general procedure in the absence of $Pd(PPh_3)_4$. No product was observed by ^1H NMR analysis of the crude reaction mixture.



5.8

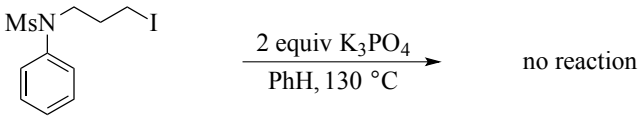
Control Experiment in the Absence of Pd Catalyst for 5.8 (Table 5-2, entry 4): 5.8 (109 mg, 0.25 mmol) was reacted according to the general procedure in the absence of $Pd(PPh_3)_4$. No product was observed by ^1H NMR analysis of the crude reaction mixture.



5.11

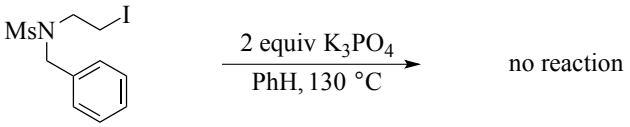
Control Experiment in the Absence of Pd Catalyst for 5.11 (Scheme 5-8): 5.11 (98 mg, 0.25 mmol) was reacted according to the general procedure in the absence

of $Pd(PPh_3)_4$. No product was observed by ^1H NMR analysis of the crude reaction mixture.



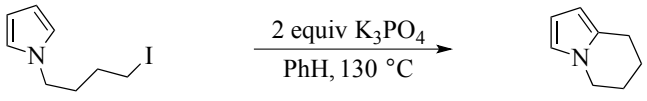
5.17

Control Experiment in the Absence of Pd Catalyst for 5.17 (Table 5-3, entry 1): 5.11 (85 mg, 0.25 mmol) was reacted according to the general procedure in the absence of $Pd(PPh_3)_4$. No product was observed by ^1H NMR analysis of the crude reaction mixture.



5.19

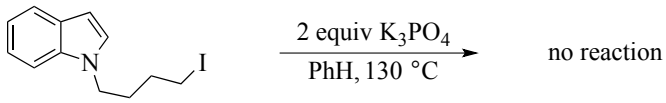
Control Experiment in the Absence of Pd Catalyst for 5.19 (Table 5-3, entry 2): 5.19 (85 mg, 0.25 mmol) was reacted according to the general procedure in the absence of $Pd(PPh_3)_4$. No product was observed by ^1H NMR analysis of the crude reaction mixture.



5.21 34%

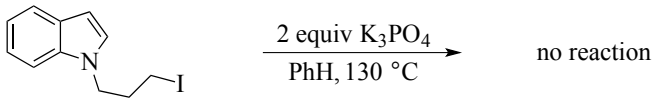
Control Experiment in the Absence of Pd Catalyst for 5.21 (Table 5-4, entry 1): 5.21 (62 mg, 0.25 mmol) was reacted according to the general procedure in the

absence of $Pd(PPh_3)_4$. 34% product **5.22** and 43% **5.21** were observed by ^1H NMR analysis using 1,3,5-trimethoxybenzene of the crude reaction mixture.



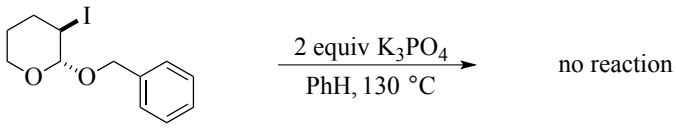
5.23

Control Experiment in the Absence of Pd Catalyst for 5.23 (Table 5-4, entry 2): 5.23 (75 mg, 0.25 mmol) was reacted according to the general procedure in the absence of $Pd(PPh_3)_4$. No product was observed by ^1H NMR analysis of the crude reaction mixture.



5.25

Control Experiment in the Absence of Pd Catalyst for 5.25 (Table 5-4, entry 3): 5.25 (71 mg, 0.25 mmol) was reacted according to the general procedure in the absence of $Pd(PPh_3)_4$. No product was observed by ^1H NMR analysis of the crude reaction mixture.

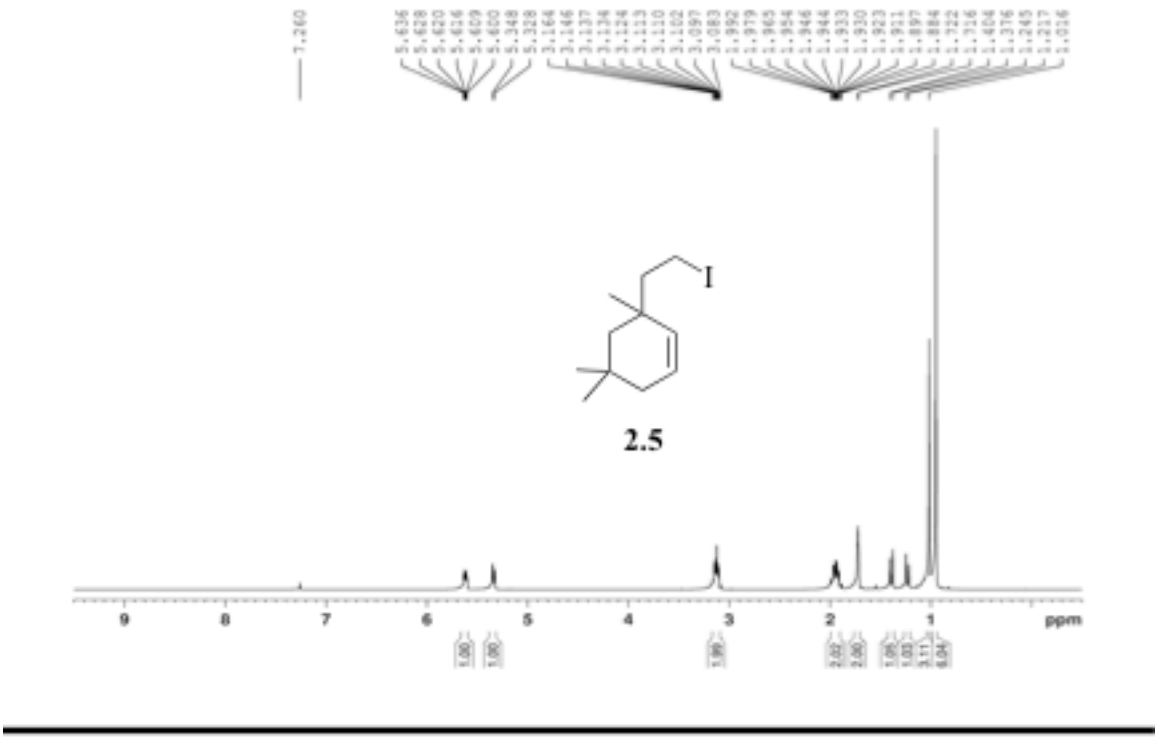


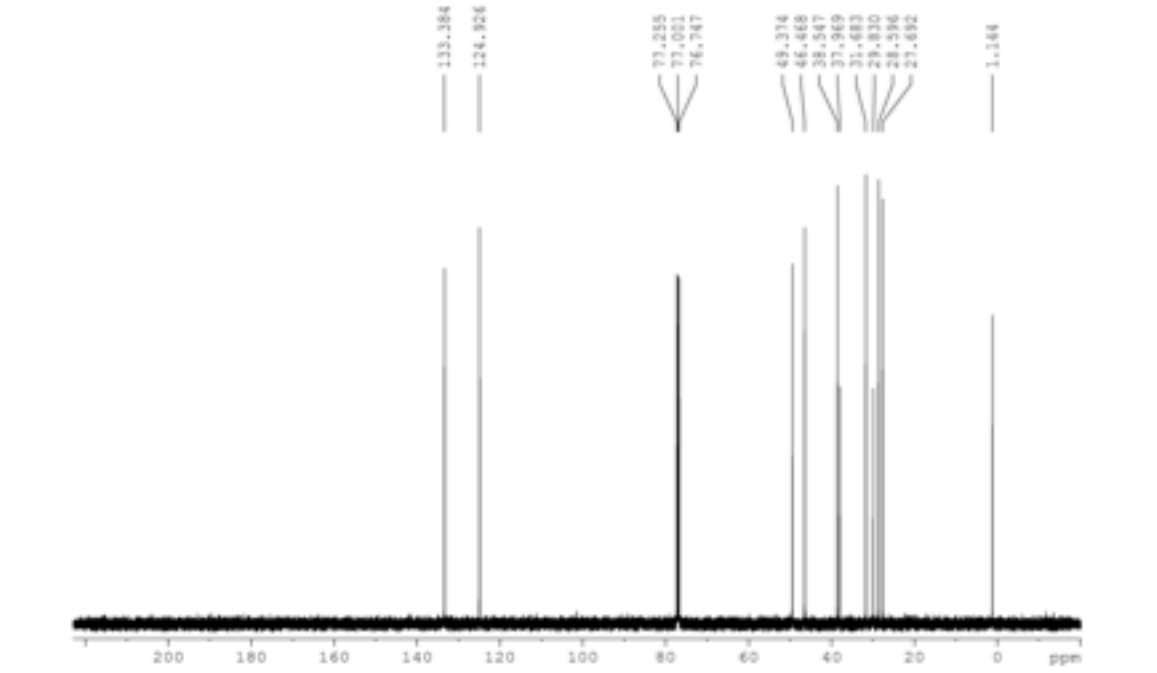
5.27

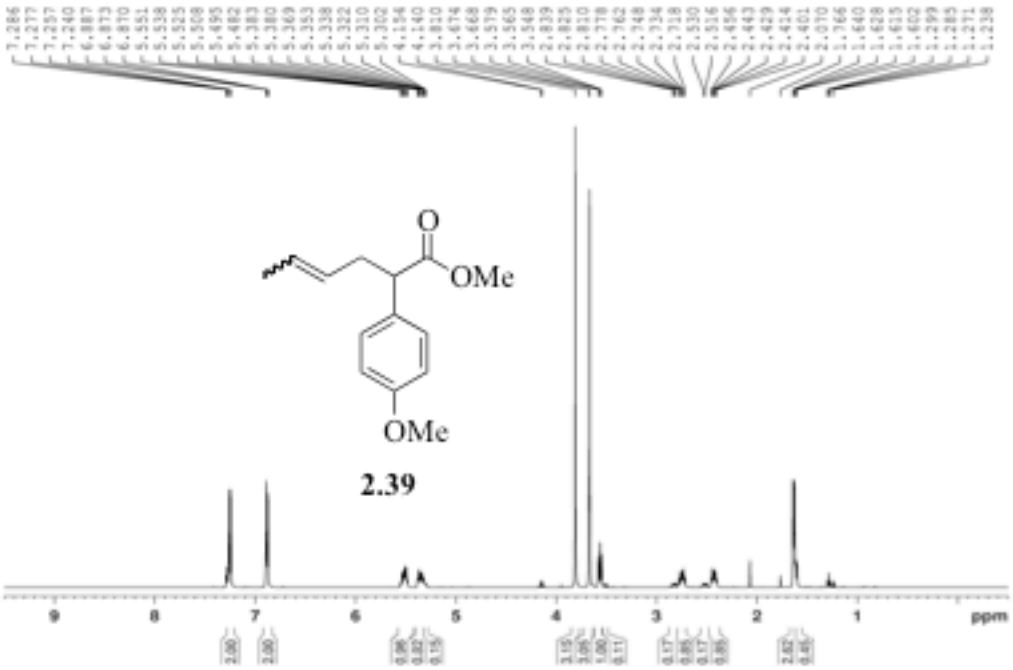
Control Experiment in the Absence of Pd Catalyst for 5.27 (Scheme 5-11): 5.27 (80 mg, 0.25 mmol) was reacted according to the general procedure in the absence

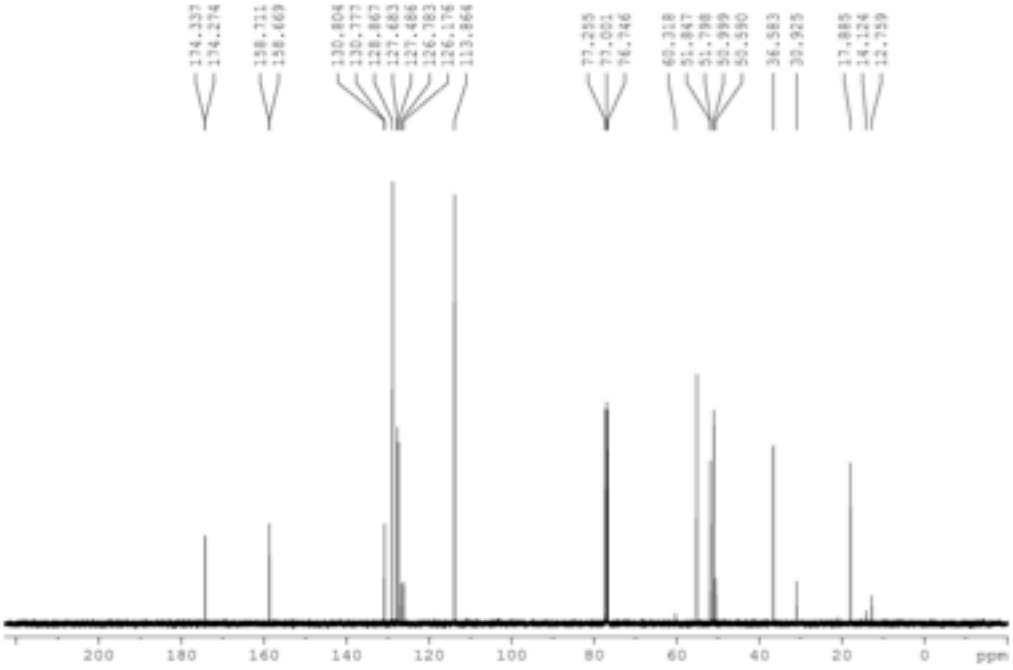
of $Pd(PPh_3)_4$. No product was observed by ^1H NMR analysis of the crude reaction mixture.

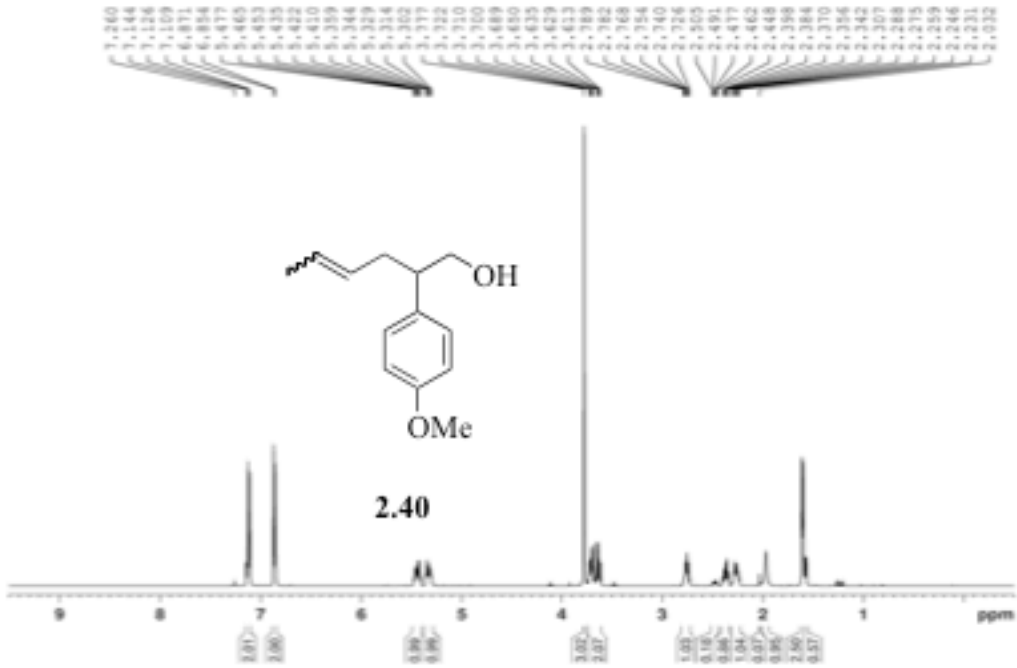
Appendix A: Spectral Data for Chapter 2






O
OMe
OMe
2.39
ppm


ppm


OH
OMe
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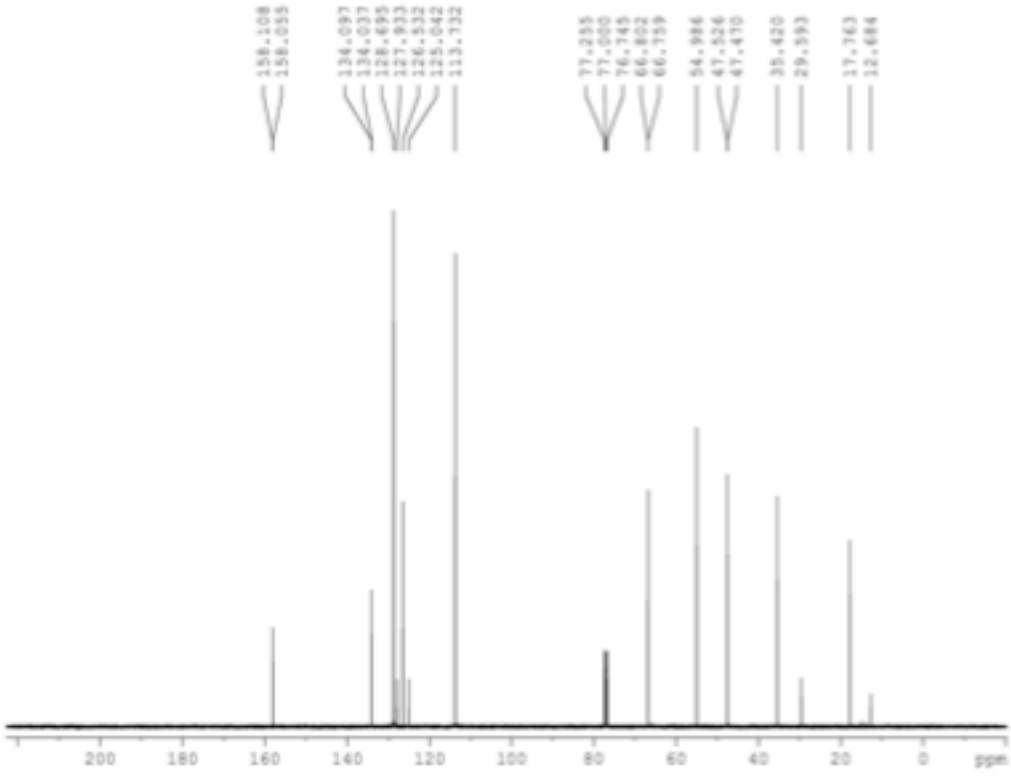
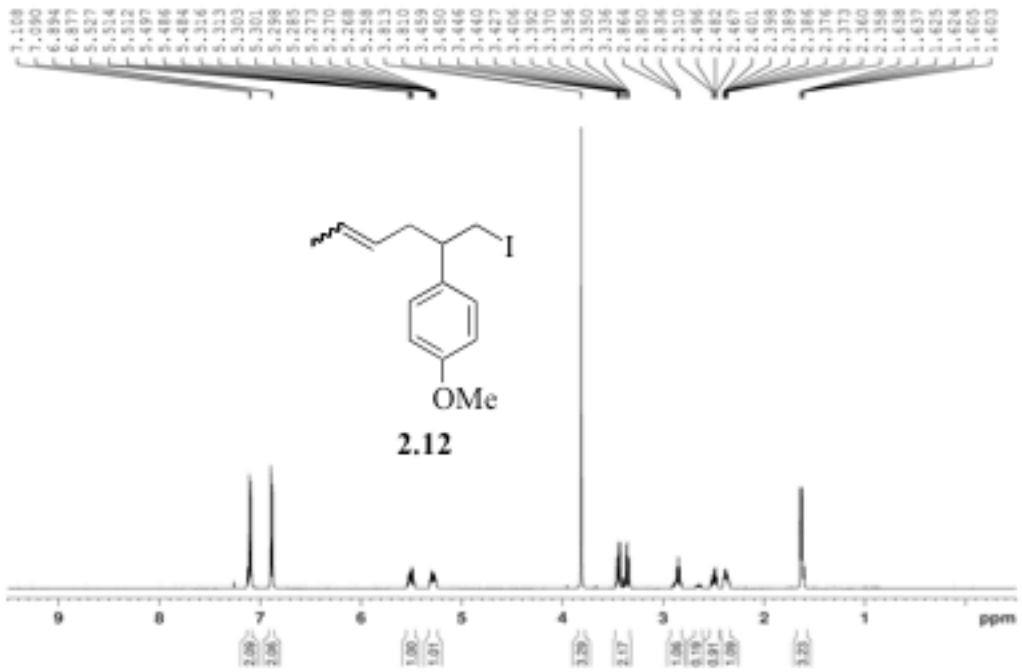
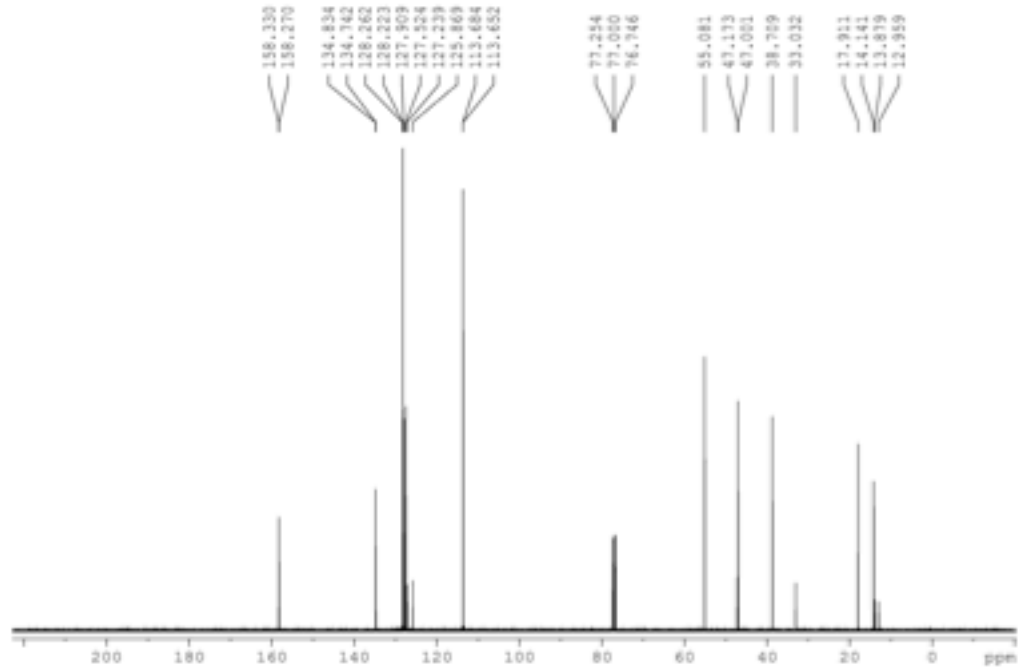
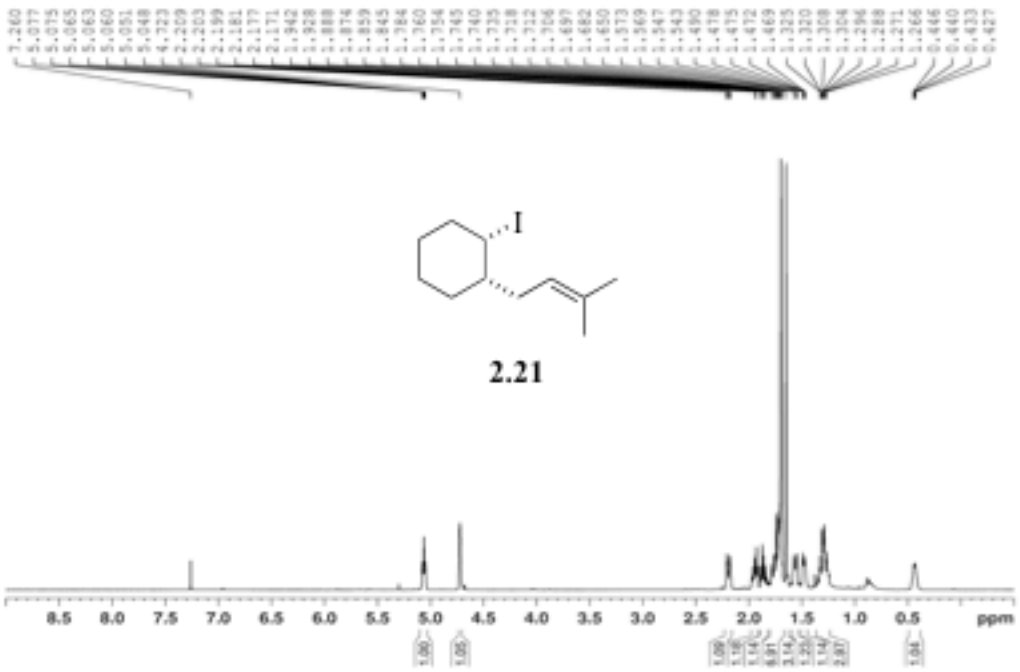
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

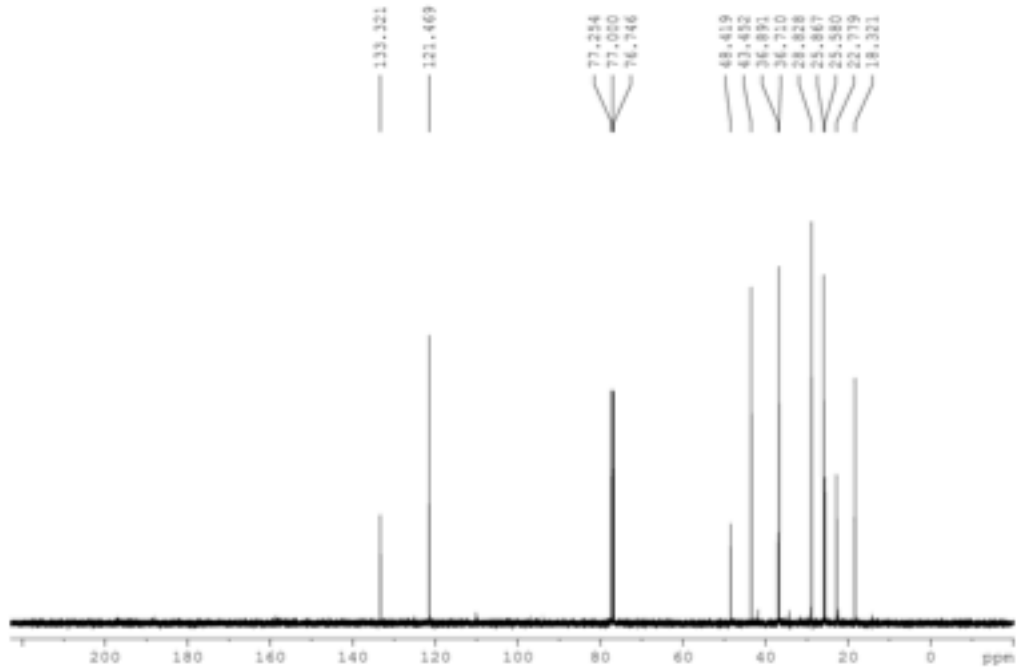


2.12



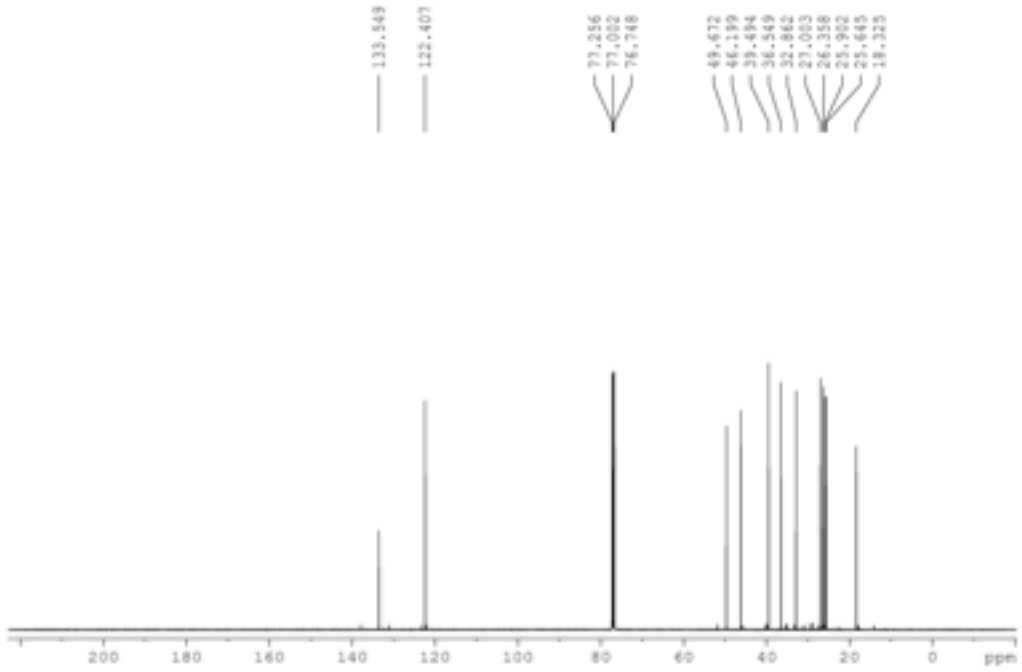

I
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

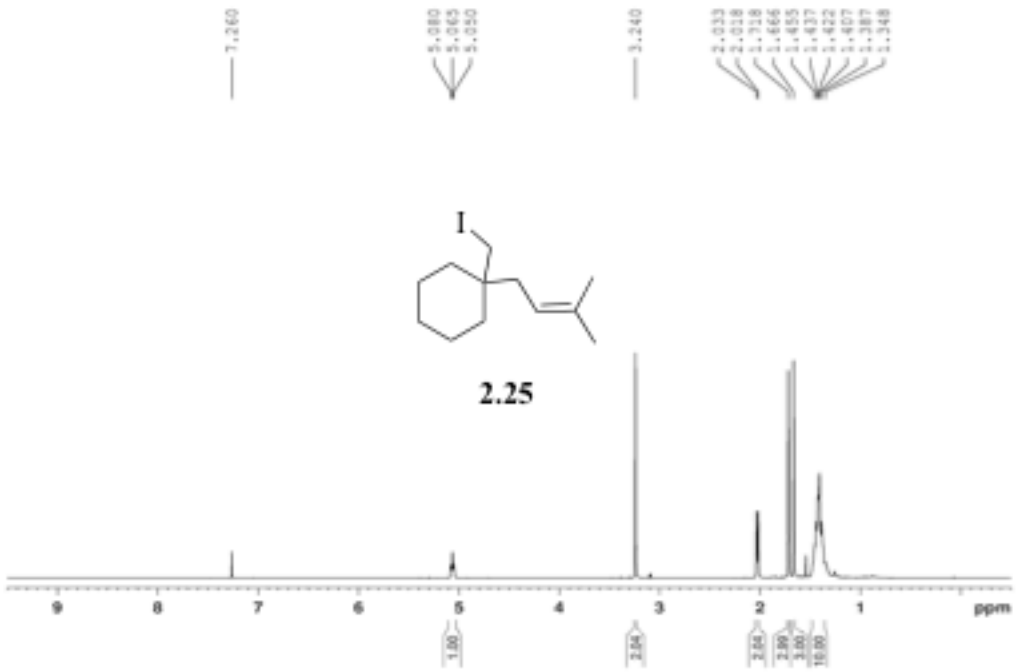
2.21


133.321
121.469
77.254
77.000
76.746
48.419
43.402
36.891
34.710
28.828
25.867
25.580
22.719
18.321
200
180
160
140
120
100
80
60
40
20
0
ppm


7.260
5.057
5.044
5.029
4.709
4.704
4.698
2.293
2.283
2.274
2.264
2.254
2.245
2.010
1.995
1.981
1.966
1.951
1.933
1.920
1.906
1.888
1.880
1.873
1.867
1.857
1.851
1.839
1.828
1.822
1.702
1.667
1.611
1.597
1.575
1.562
1.552
1.537
I
9
8
7
6
5
4
3
2
1
ppm
1.00
1.00
1.02
3.08
7.04
3.07
3.07
1.07
1.01

2.23


133.549
122.407
77.256
77.002
76.748
49.672
46.199
39.494
36.549
32.862
27.003
26.398
25.992
25.645
18.325
200
180
160
140
120
100
80
60
40
20
0
ppm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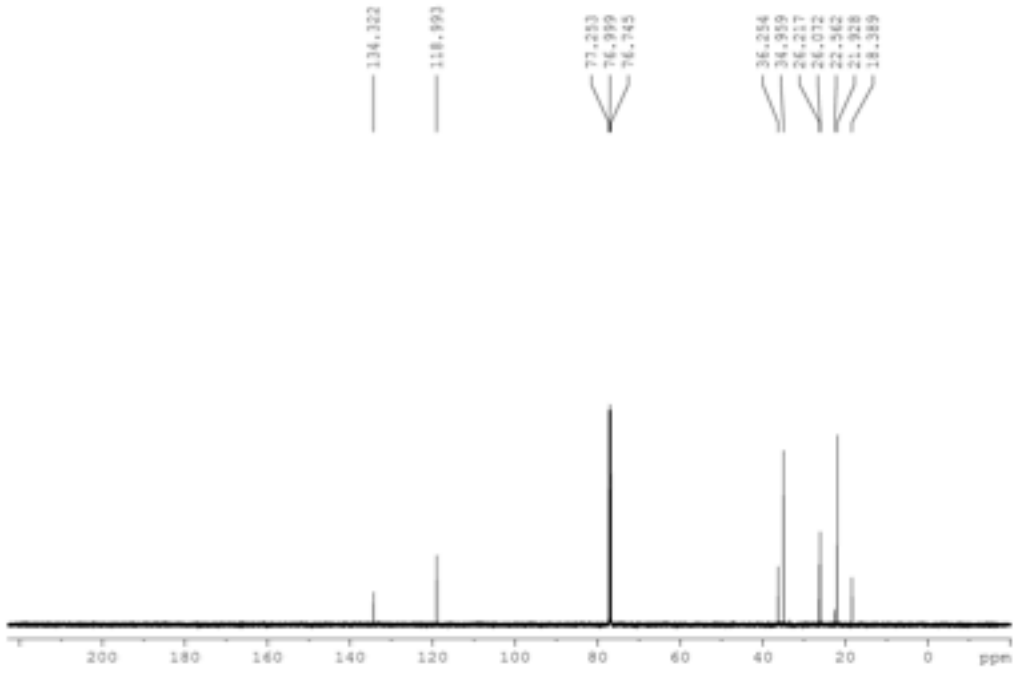
5.080
5.065
5.050
3.240
2.033
2.018
1.718
1.666
1.455
1.437
1.422
1.407
1.387
1.348
I
2.25
9
8
7
6
5
4
3
2
1
ppm
1.00
2.84
2.84
2.89
3.00
16.00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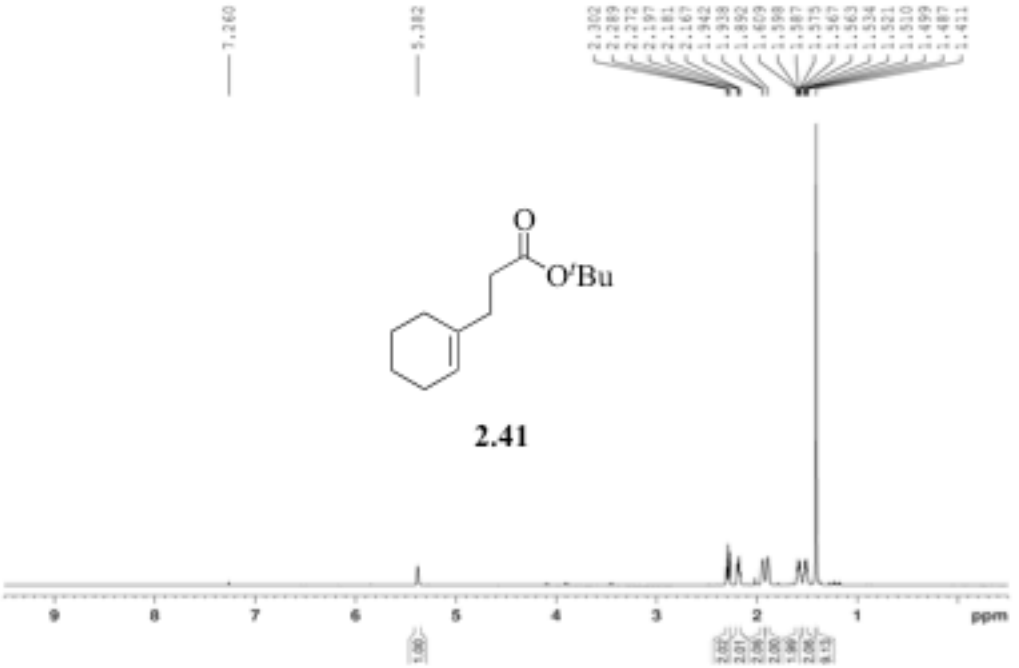
118.893
77.253
76.999
76.745
36.254
34.959
26.217
26.072
22.562
21.928
18.389
200
180
160
140
120
100
80
60
40
20
0
ppm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5.382
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2.289
2.272
2.197
2.181
2.167
1.942
1.938
1.892
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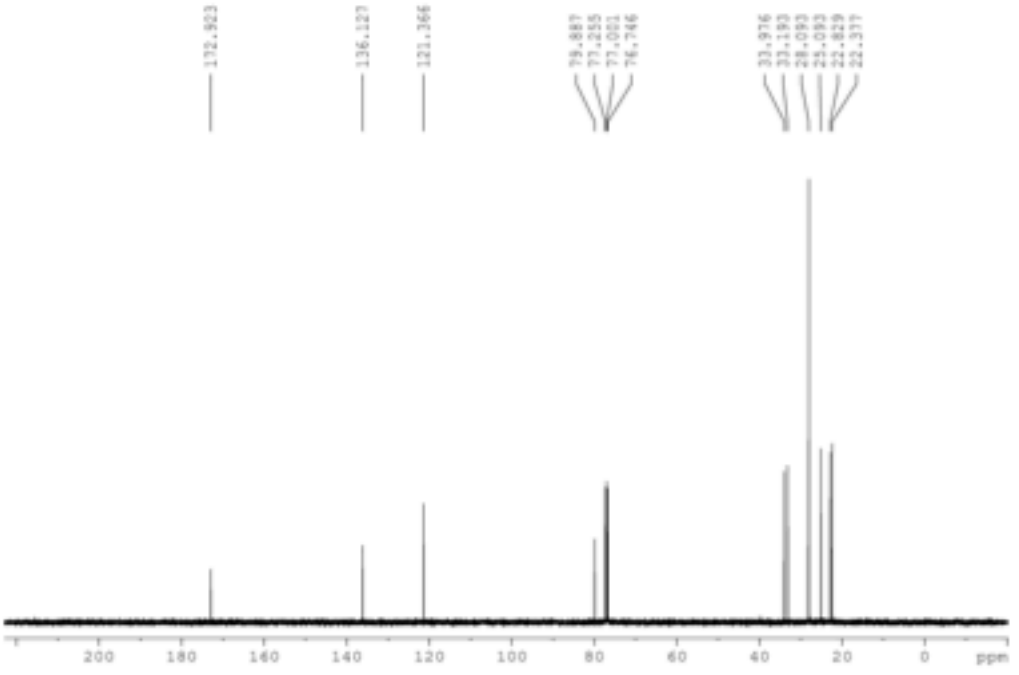
1.598
1.587
1.575
1.567
1.563
1.534
1.521
1.510
1.499
1.487
1.411
O
O^{t}Bu
9
8
7
6
5
4
3
2
1
ppm

2.41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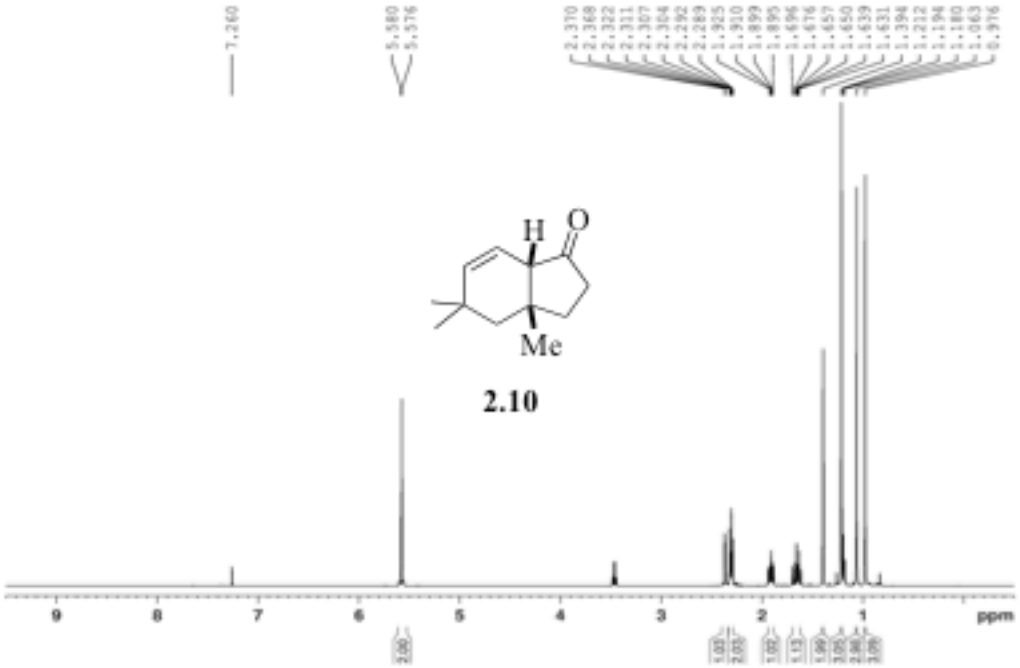
136.127
121.366
79.887
77.255
77.001
76.746
33.976
33.193
28.093
25.093
22.829
22.377
200
180
160
140
120
100
80
60
40
20
0
ppm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5.576
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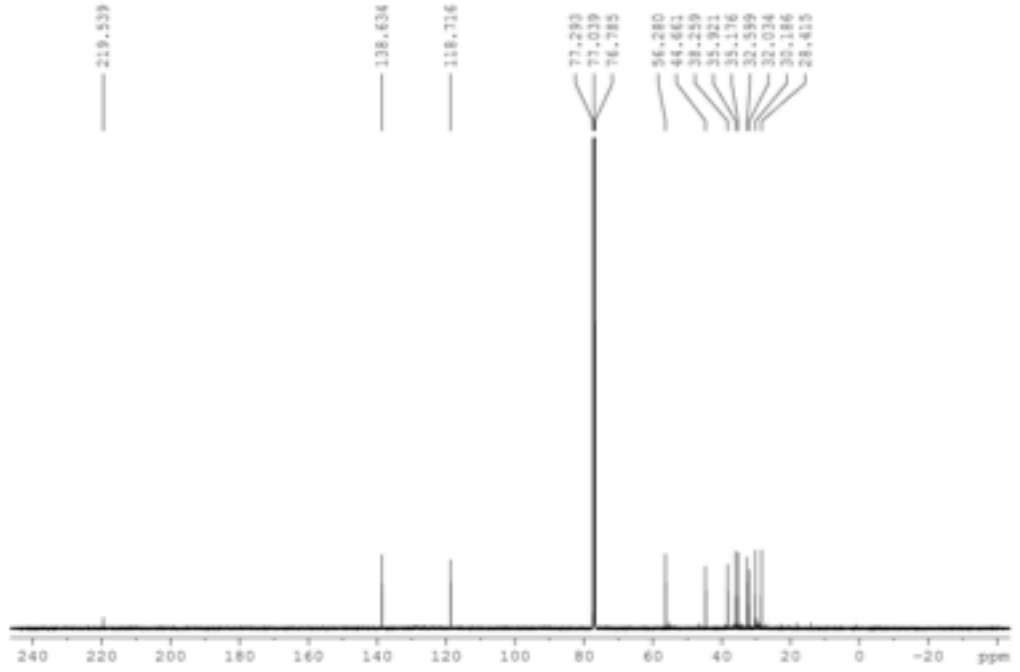
2.322
2.311
2.307
2.304
2.292
2.289
1.925
1.910
1.899
1.895
1.696
1.676
1.657
1.650
1.639
1.631
1.394
1.212
1.194
1.180
1.063
0.976
H
O
Me
9
8
7
6
5
4
3
2
1
ppm

2.10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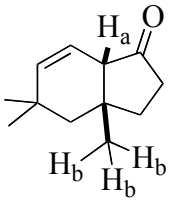
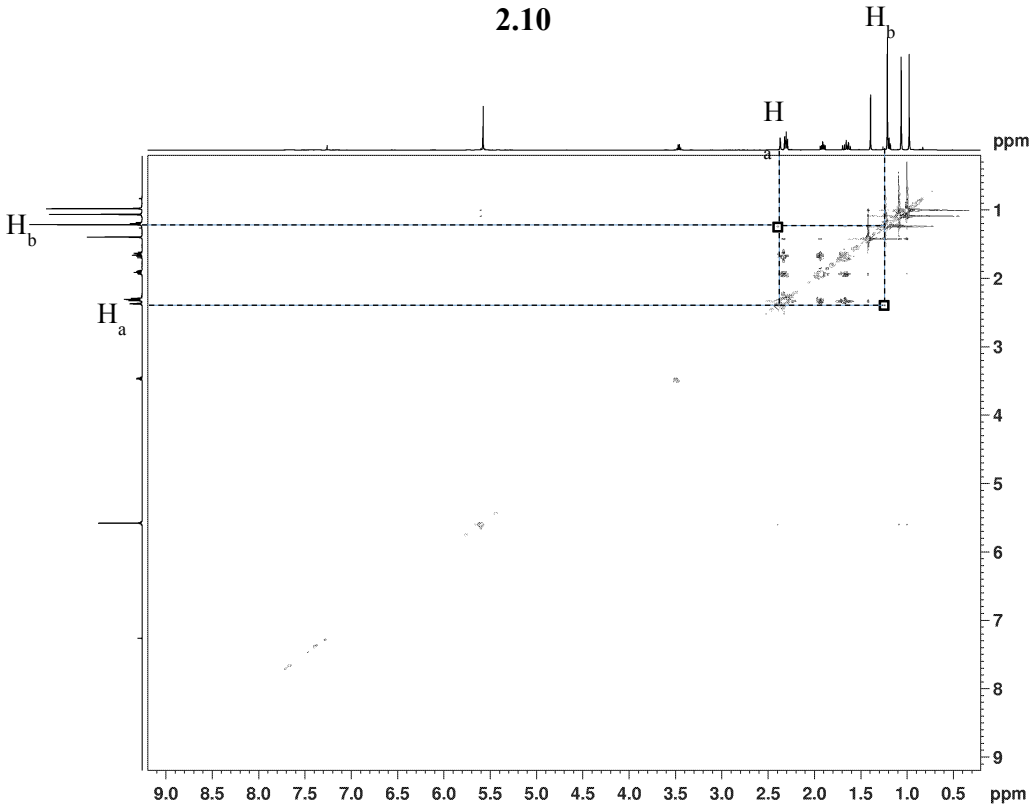
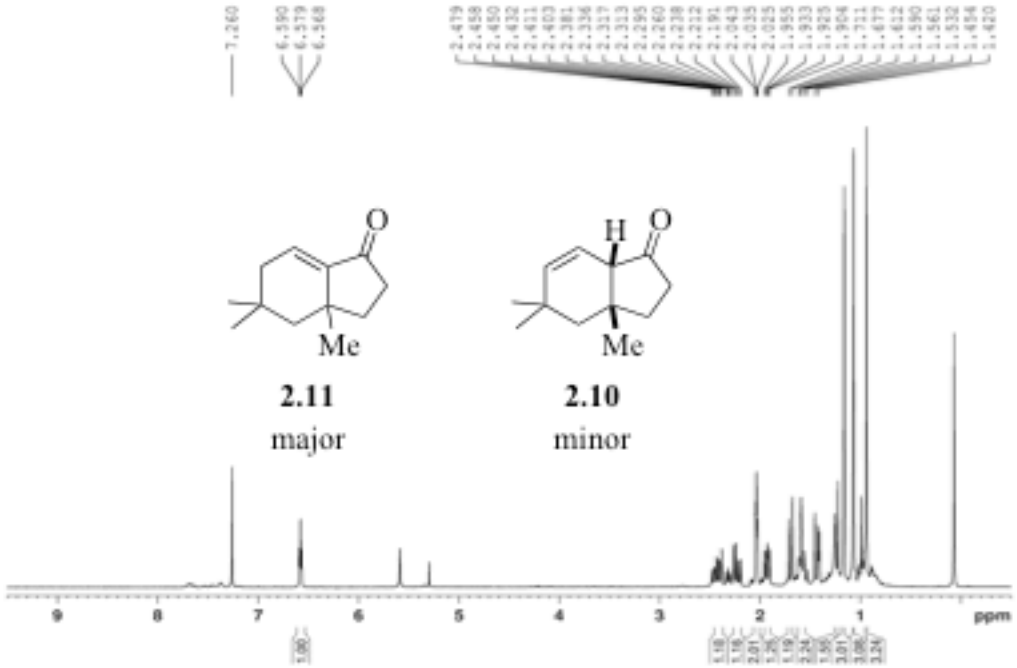
138.634
118.716
77.293
77.039
76.785
56.280
44.661
38.259
35.921
35.176
32.599
32.034
20.186
28.415
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

2-D NOESY:


Ha
O
Hb
Hb
Hb

2.10


Hb
H
a
ppm
Hb
Ha
1
2
3
4
5
6
7
8
9
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm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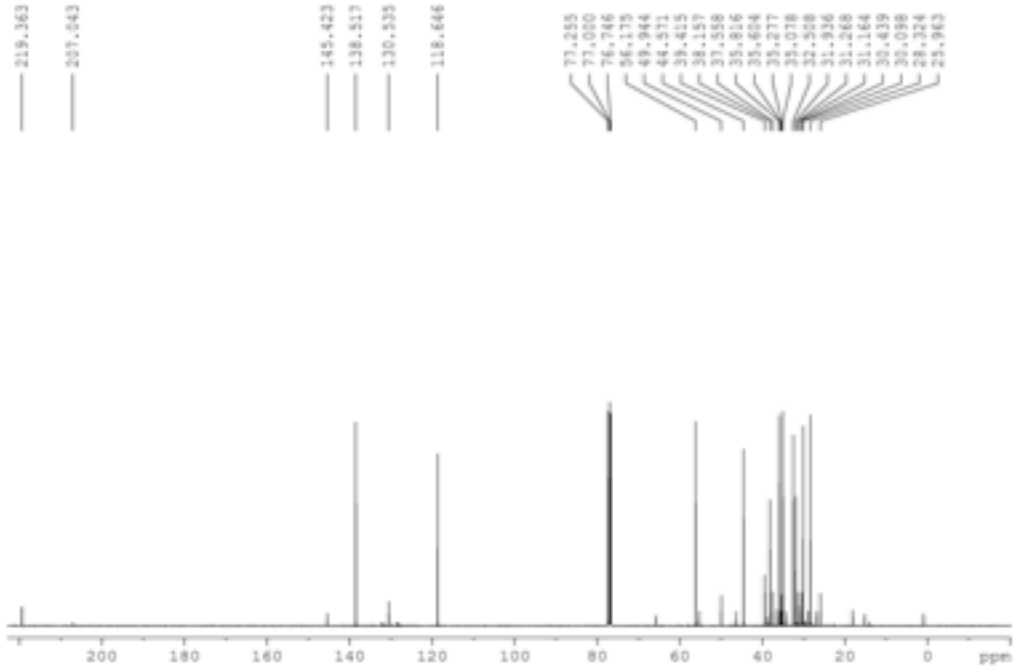
6.579
6.568
2.479
2.458
2.450
2.432
2.411
2.403
2.381
2.336
2.317
2.313
2.295
2.260
2.238
2.212
2.191
2.043
2.035
2.025
1.955
1.933
1.925
1.904
1.711
1.677
1.612
1.590
1.561
1.532
1.454
1.420
O
Me
2.11
major
H
O
Me
2.10
minor
9
8
7
6
5
4
3
2
1
ppm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118.646
77.255
77.000
76.746
56.175
49.944
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38.157
37.558
35.816
35.604
35.277
35.078
32.508
31.936
31.268
31.164
30.439
30.098
28.324
25.963
200
180
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120
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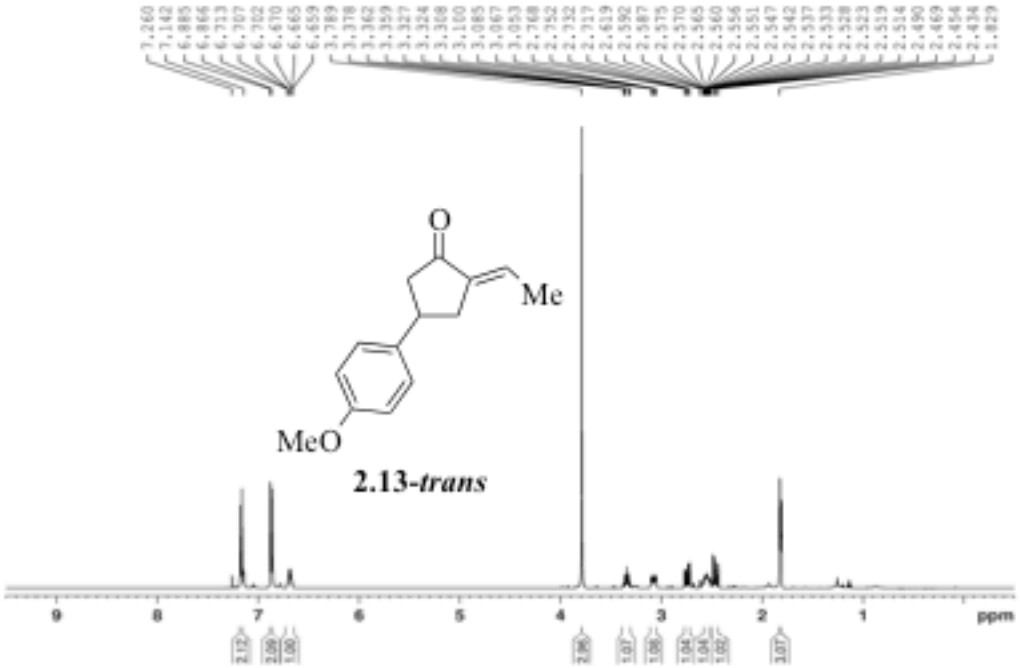
80
60
40
20
0
ppm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7.142
6.885
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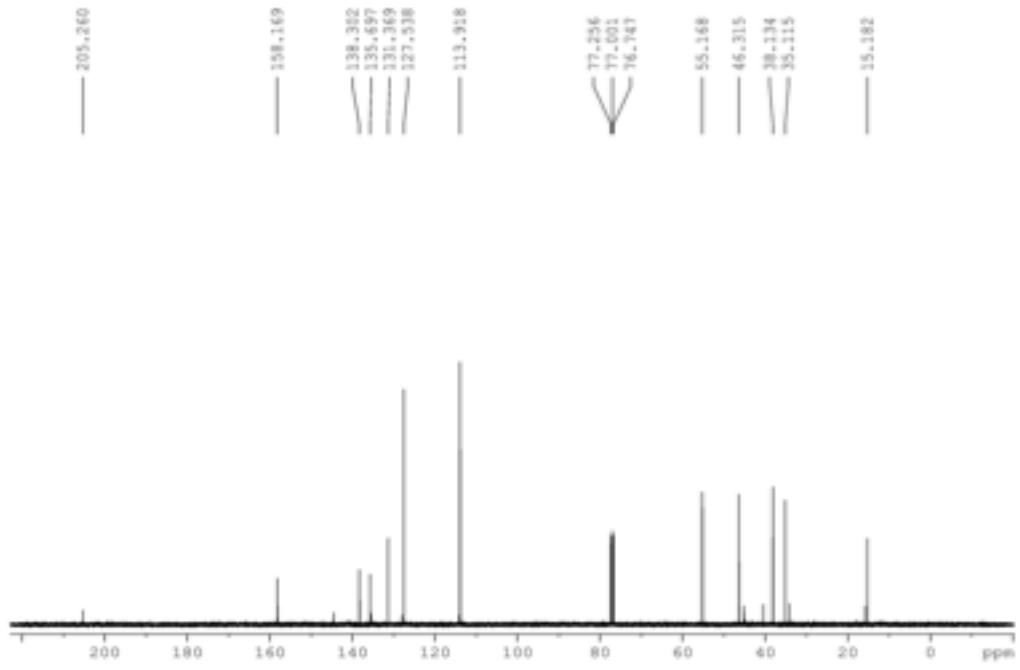
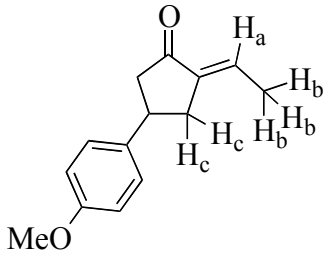
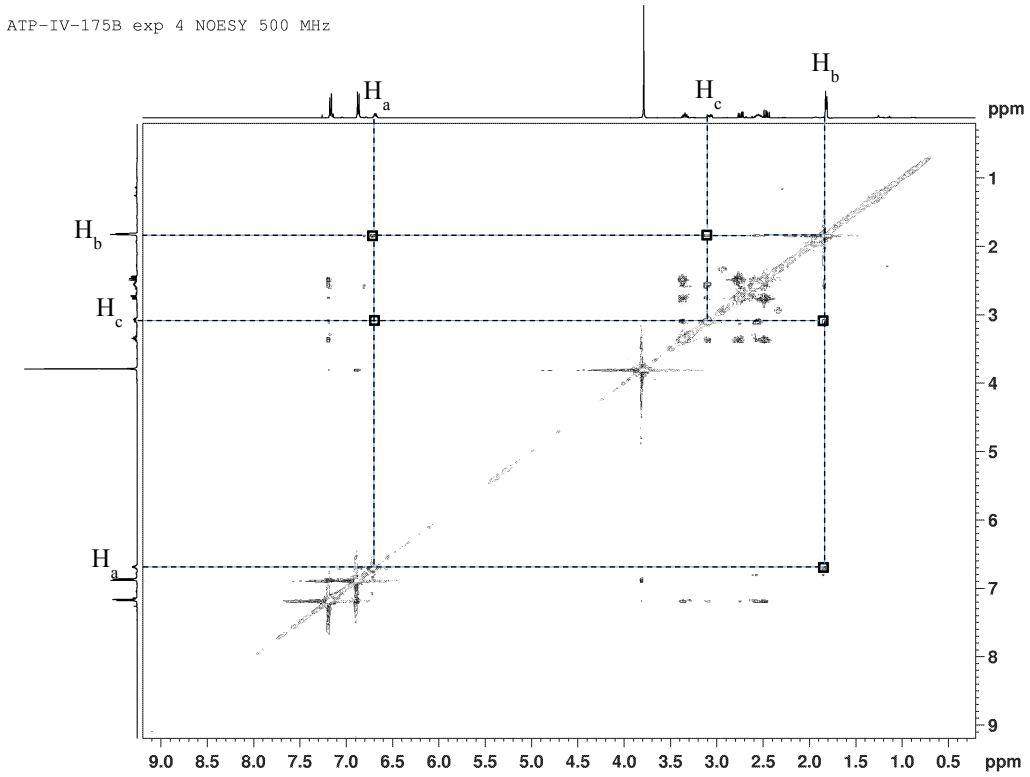
6.713
6.707
6.702
6.670
6.665
6.659
3.789
3.378
3.362
3.359
3.327
3.324
3.308
3.100
3.085
3.067
3.053
2.768
2.752
2.732
2.717
2.619
2.592
2.587
2.575
2.570
2.565
2.560
2.556
2.551
2.547
2.542
2.537
2.533
2.528
2.523
2.519
2.514
2.490
2.469
2.454
2.434
1.829
O
Me
MeO
2.13-trans
9
8
7
6
5
4
3
2
1
ppm
2.12
2.09
1.00
2.86
1.07
1.08
1.04
1.04
1.02
3.07

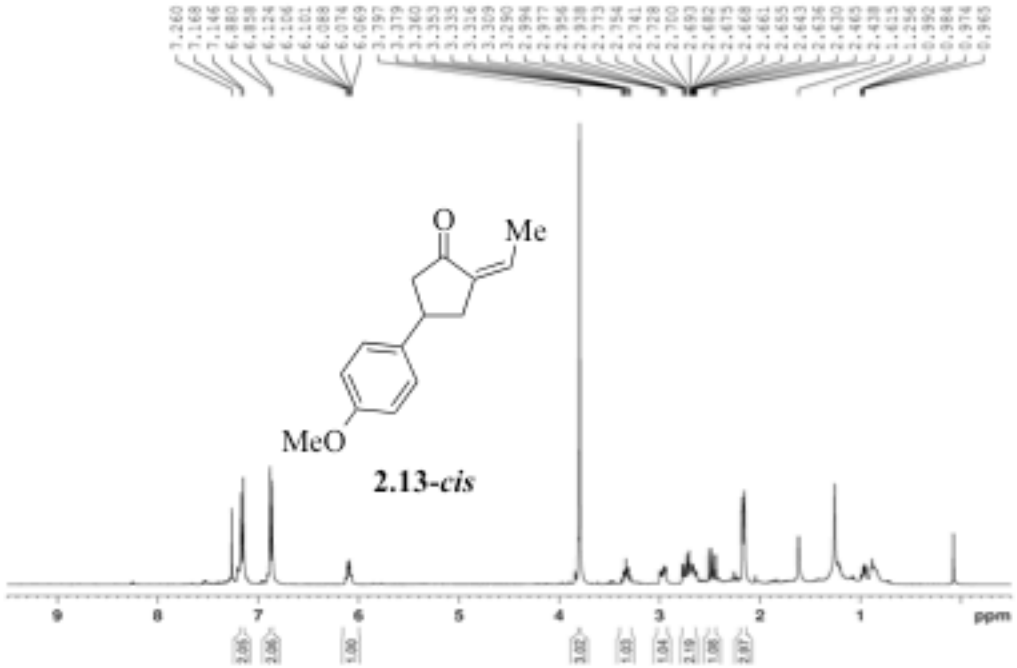

205.260
158.169
138.302
135.697
131.369
127.538
113.918
77.256
77.001
76.747
55.168
46.315
38.134
35.115
15.182
200
180
160
140
120
100
80
60
40
20
0
ppm

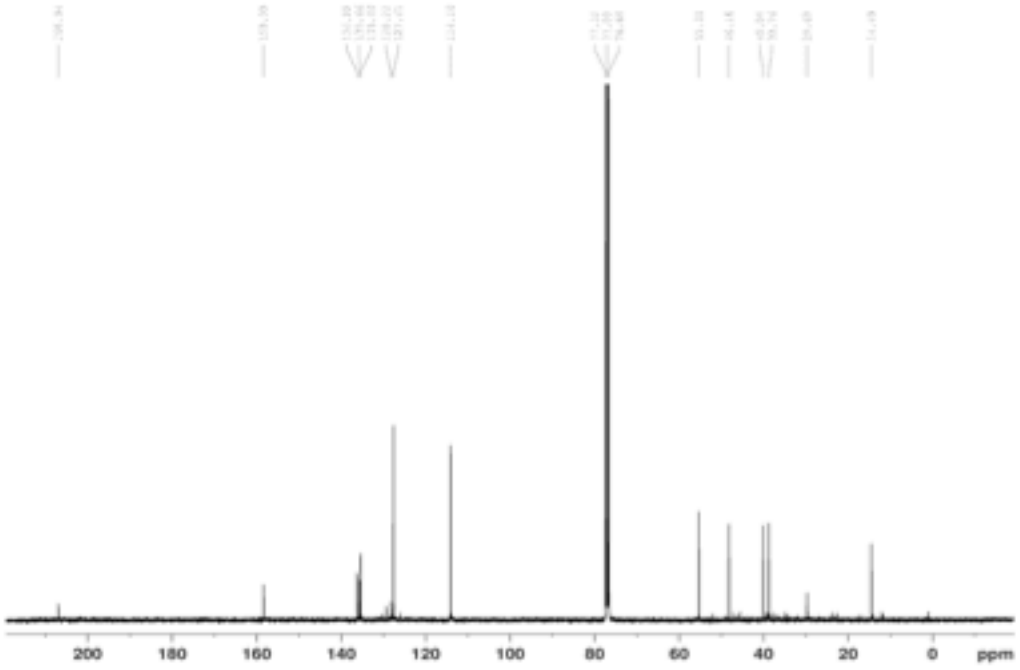
2-D NOESY:



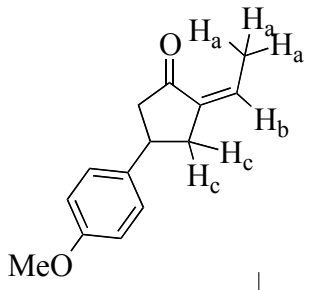
2.13-*trans*



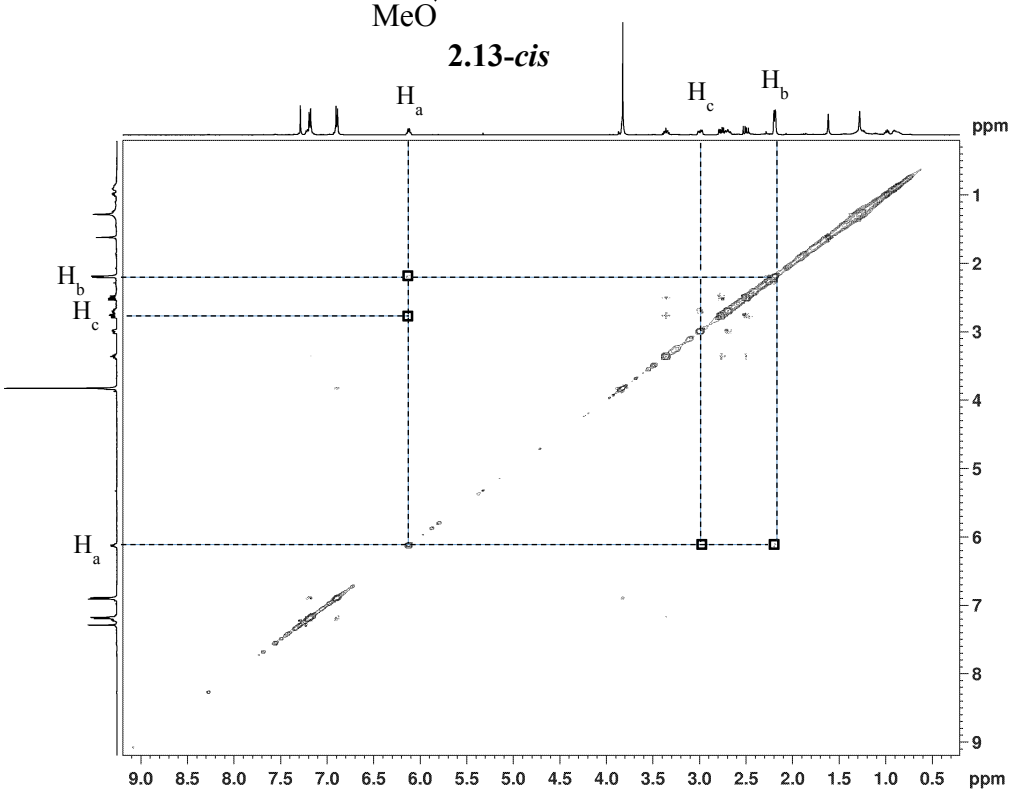

O
Me
MeO
2.13-*cis*
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

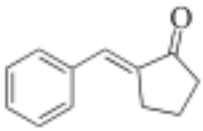
2-D NOESY:



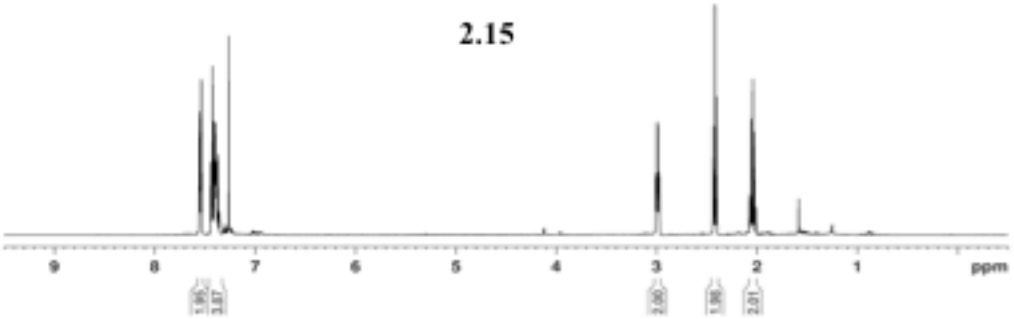
2.13-*cis*

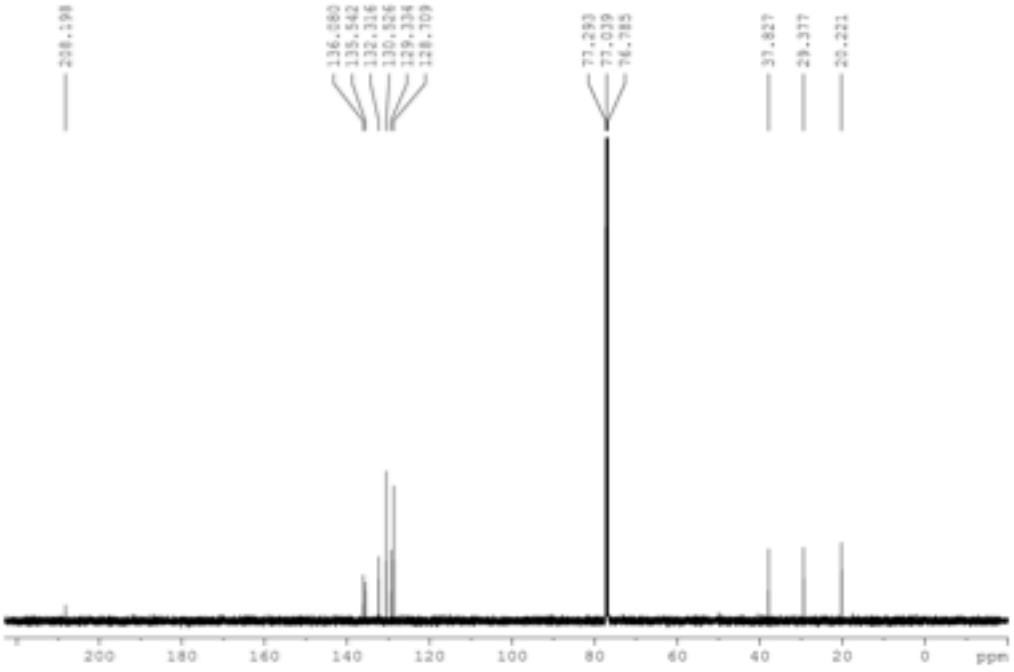


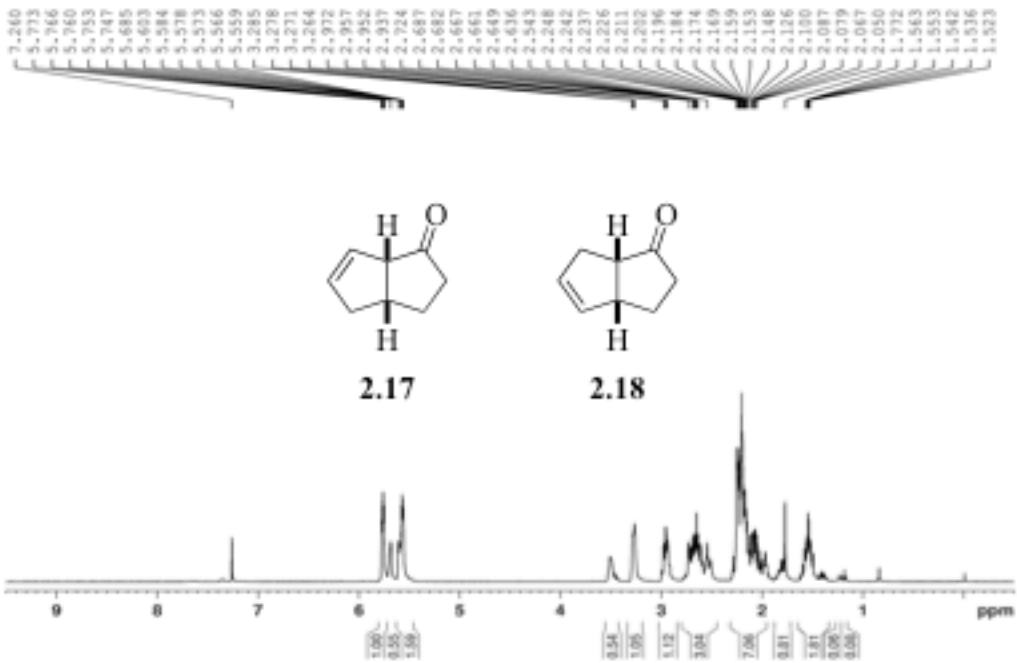

7.549
7.534
7.438
7.436
7.433
7.422
7.419
7.407
7.402
7.396
7.391
7.385
7.383
7.373
7.369
7.364
7.354
7.260
3.008
3.002
2.993
2.988
2.979
2.974
2.434
2.418
2.402
2.072
2.057
2.041
2.026
2.011

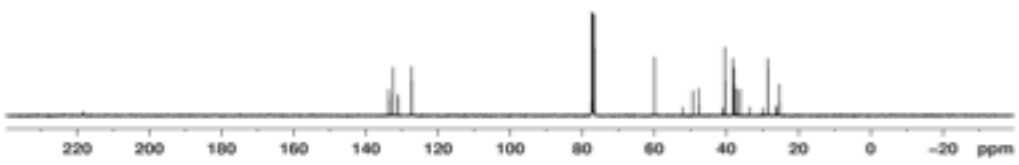

O

2.15


9
8
7
6
5
4
3
2
1
ppm
5.95
3.87
2.00
1.96
2.01

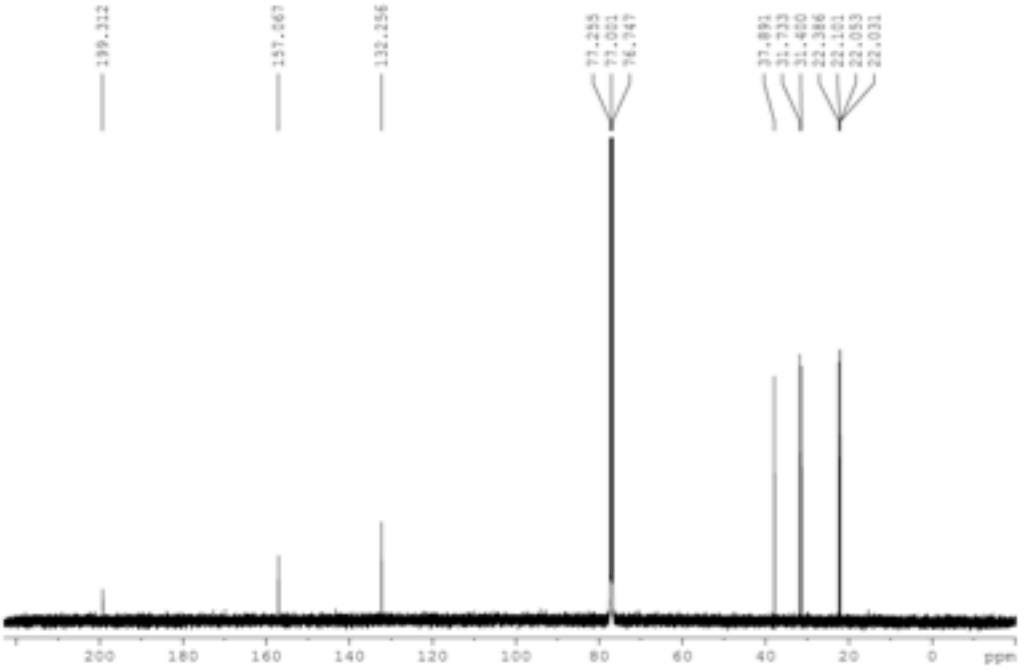

208.198
136.080
135.542
132.316
130.526
129.334
128.709
77.293
77.039
76.785
31.827
29.377
20.221
200
180
160
140
120
100
80
60
40
20
0
ppm

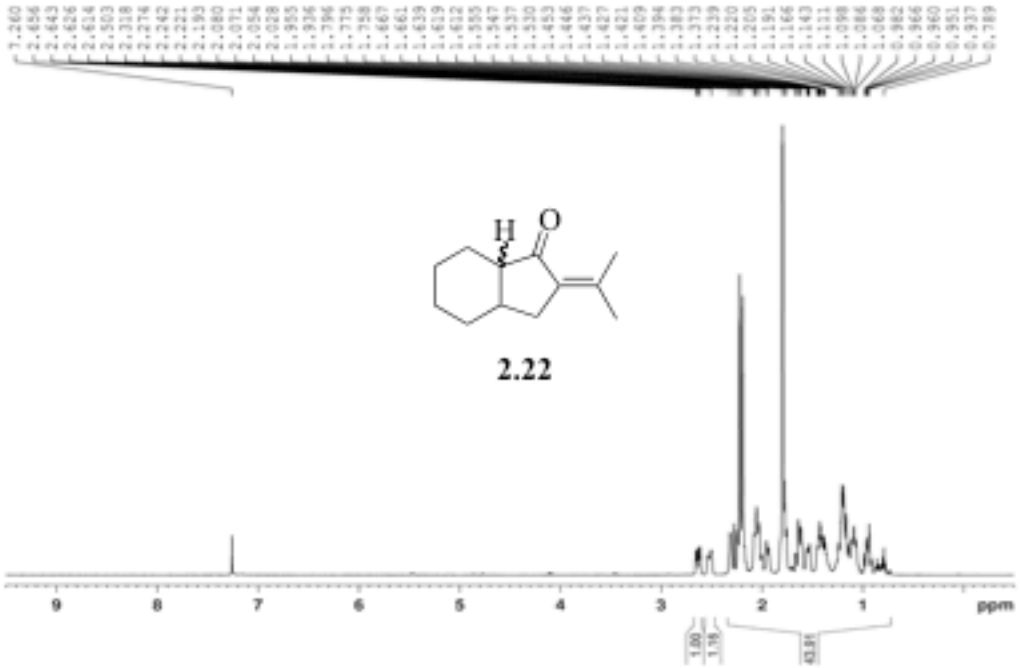

7.260
5.773
5.766
5.760
5.753
5.747
5.685
5.603
5.584
5.578
5.573
5.566
5.559
3.285
3.278
3.271
3.264
2.972
2.957
2.952
2.937
2.724
2.687
2.682
2.667
2.661
2.649
2.636
2.543
2.248
2.242
2.237
2.226
2.211
2.202
2.196
2.184
2.174
2.169
2.159
2.153
2.148
2.126
2.100
2.087
2.079
2.067
2.050
1.772
1.563
1.553
1.542
1.536
1.523
H
O
H
H
O
H
2.17
2.18
9
8
7
6
5
4
3
2
1
ppm


220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

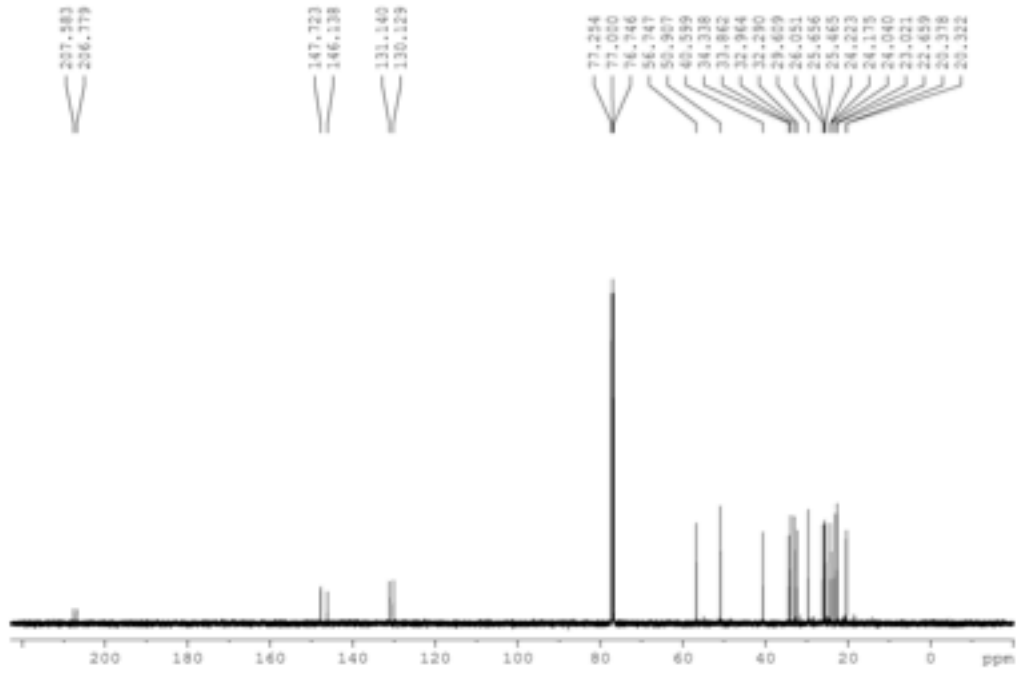

7.260
2.405
2.392
2.378
2.237
2.226
2.191
2.177
1.967
1.955
1.942
1.929
1.614
1.610
1.603
1.595
O
9
8
7
6
5
4
3
2
1
ppm
2.00
2.02
4.00
2.01
3.05

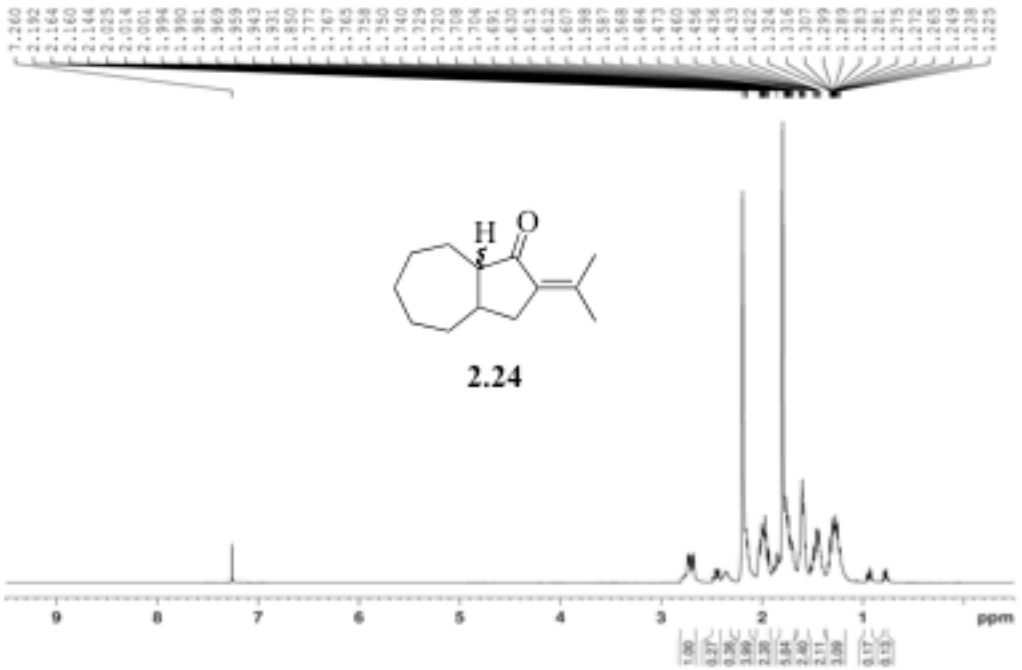
2.20


199.312
157.867
132.256
77.255
77.001
76.747
37.891
31.733
31.400
22.386
22.101
22.053
22.031
200
180
160
140
120
100
80
60
40
20
0
ppm

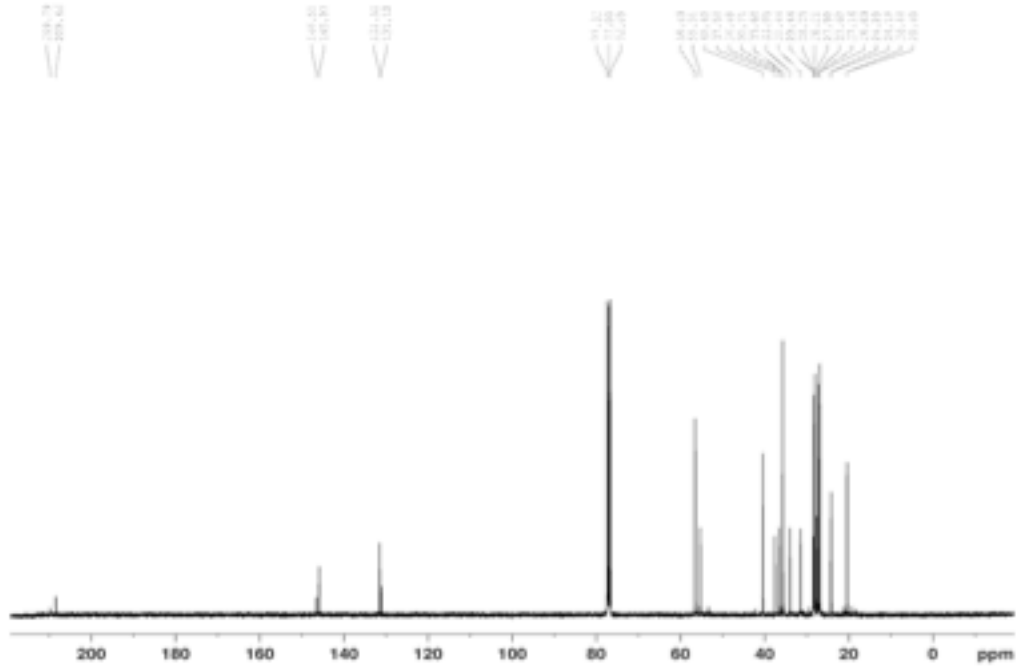


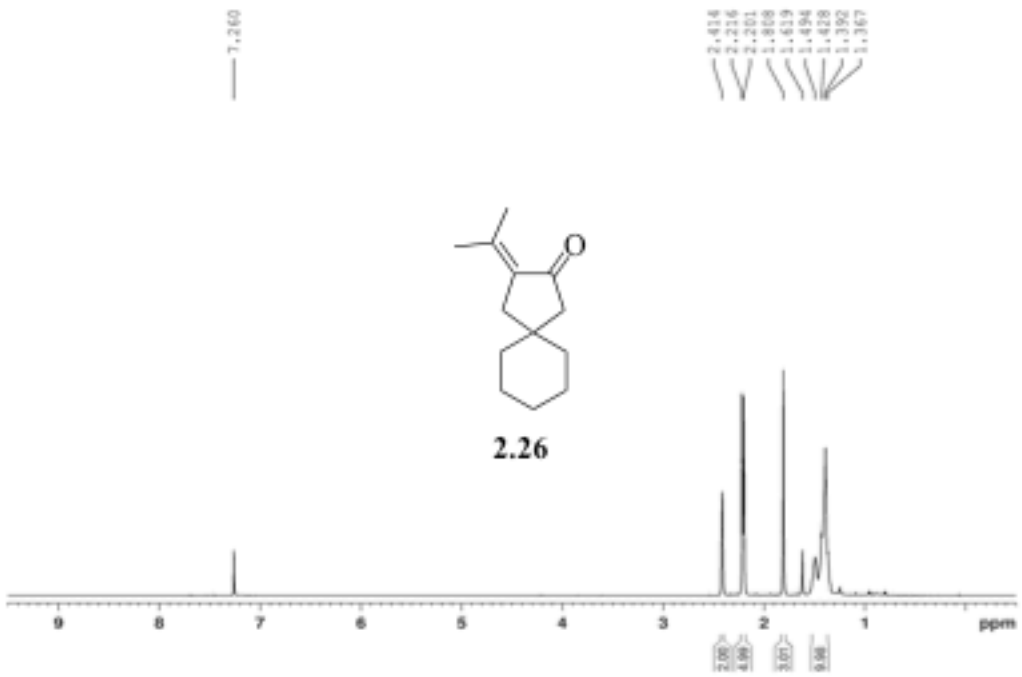
2.22





2.24

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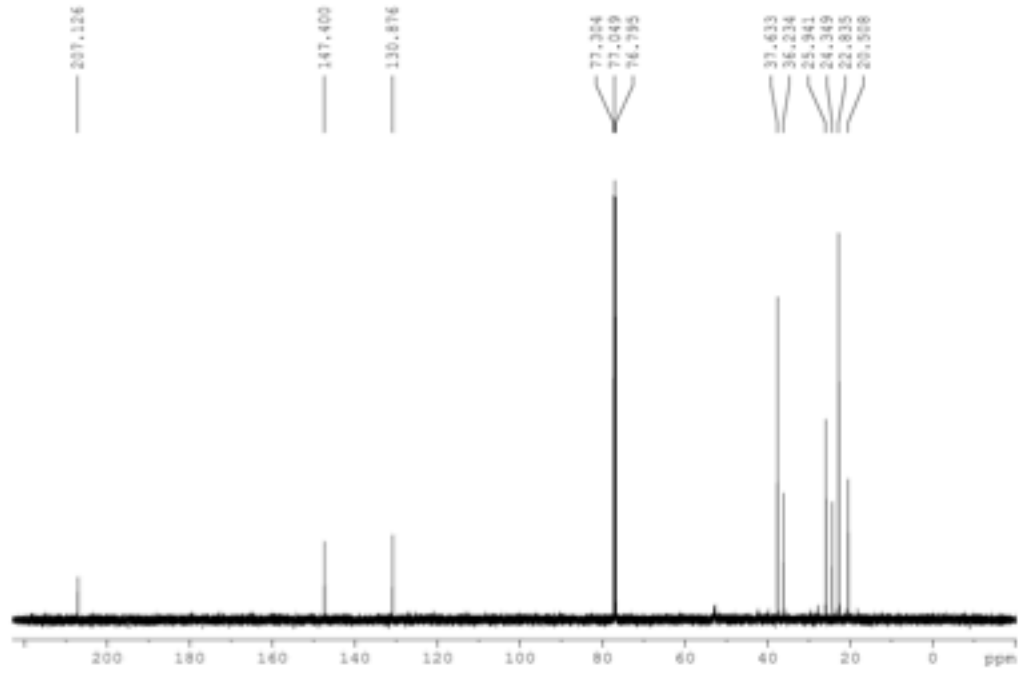
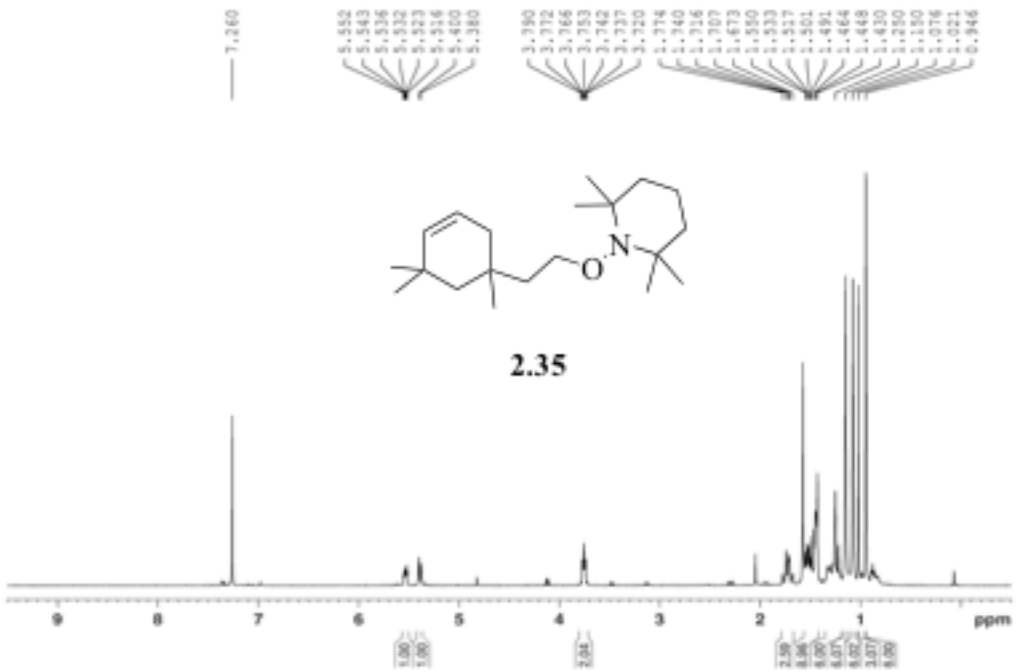
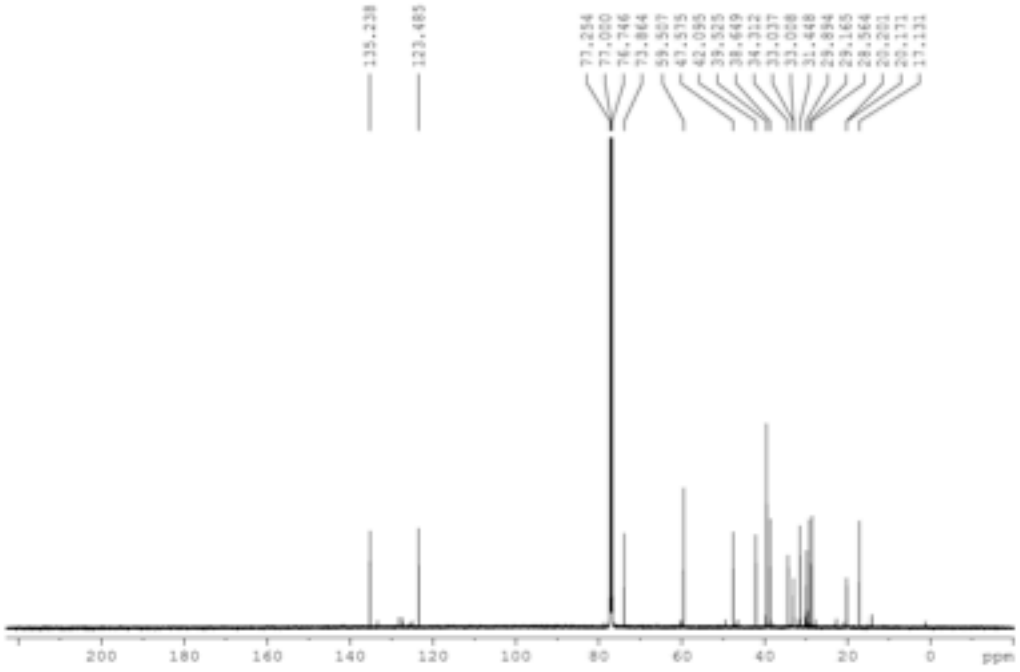
2.414
2.214
2.201
1.809
1.619
1.494
1.428
1.392
1.367
O
9
8
7
6
5
4
3
2
1
ppm
2.00
4.99
3.05
9.98

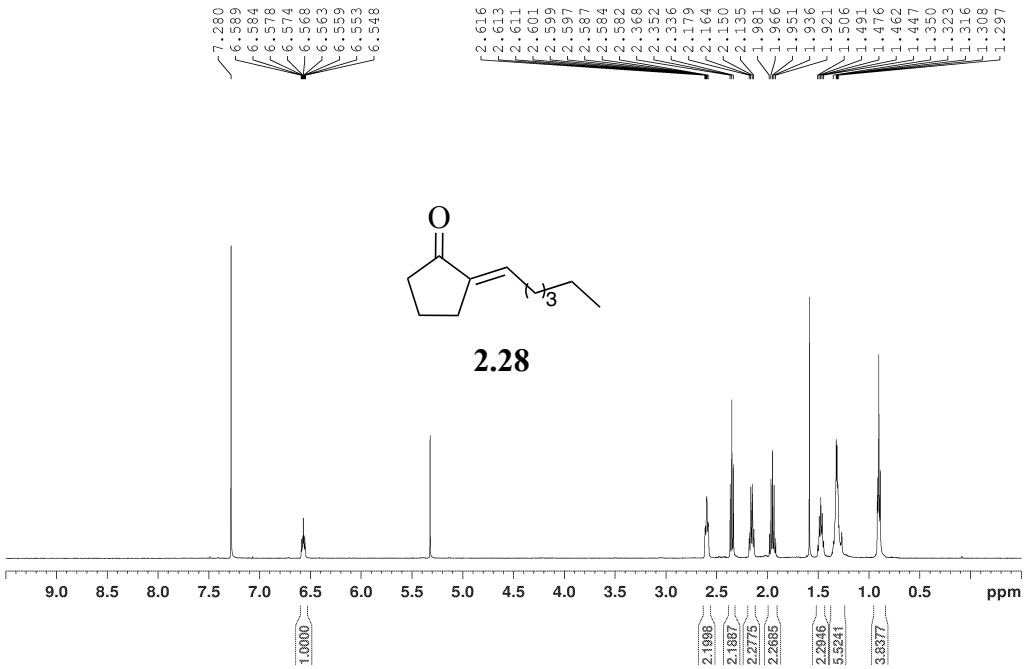
2.26


207.126
147.400
130.876
77.304
77.049
76.795
37.633
36.234
25.941
24.349
22.835
20.508
200
180
160
140
120
100
80
60
40
20
0
ppm

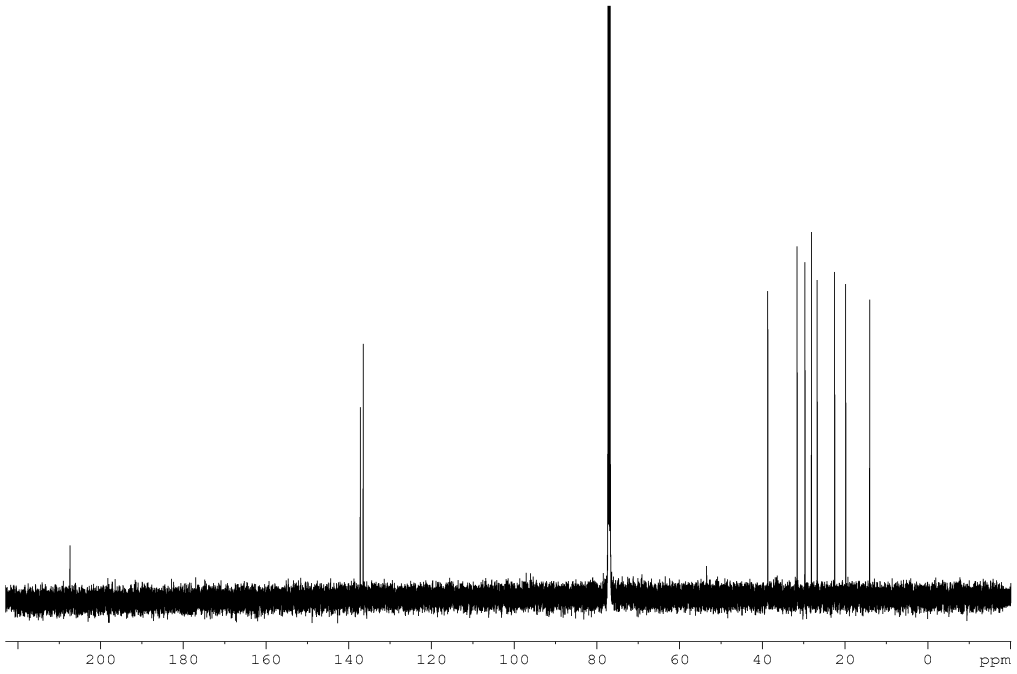

7.260
5.552
5.543
5.536
5.532
5.523
5.516
5.400
5.380
3.390
3.372
3.366
3.353
3.342
3.337
3.320
1.774
1.740
1.716
1.707
1.673
1.590
1.533
1.517
1.501
1.491
1.464
1.449
1.430
1.250
1.150
1.076
1.021
0.946
O
N
ppm

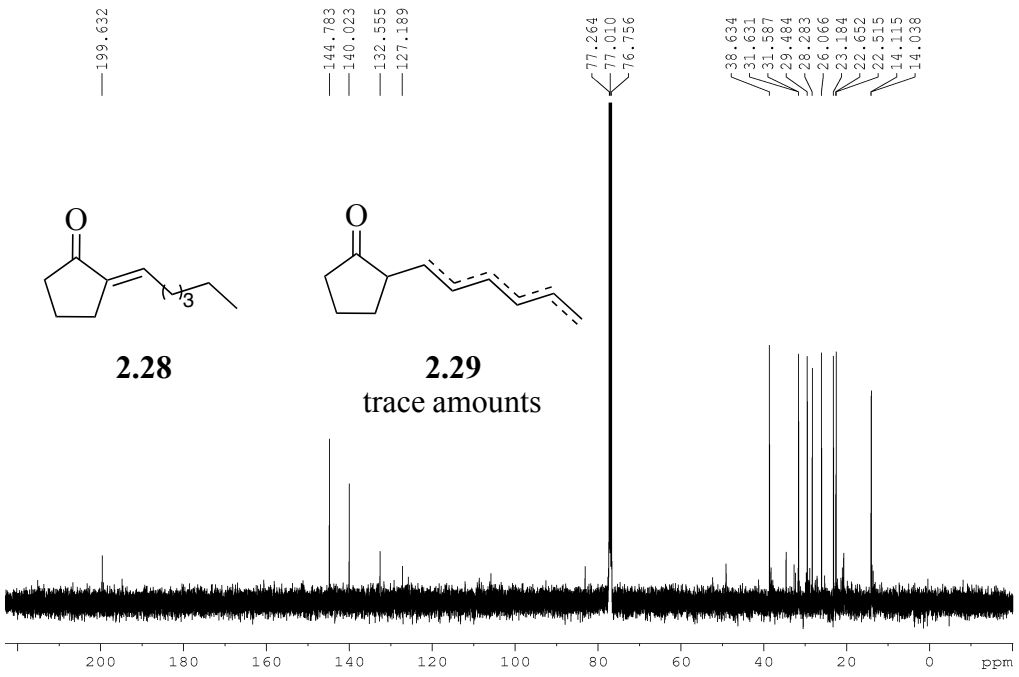
2.35


135.239
123.485
77.254
77.000
76.746
73.864
59.507
47.575
42.095
39.525
38.649
34.312
33.037
33.008
31.448
29.894
29.165
28.564
20.201
20.171
17.131
ppm

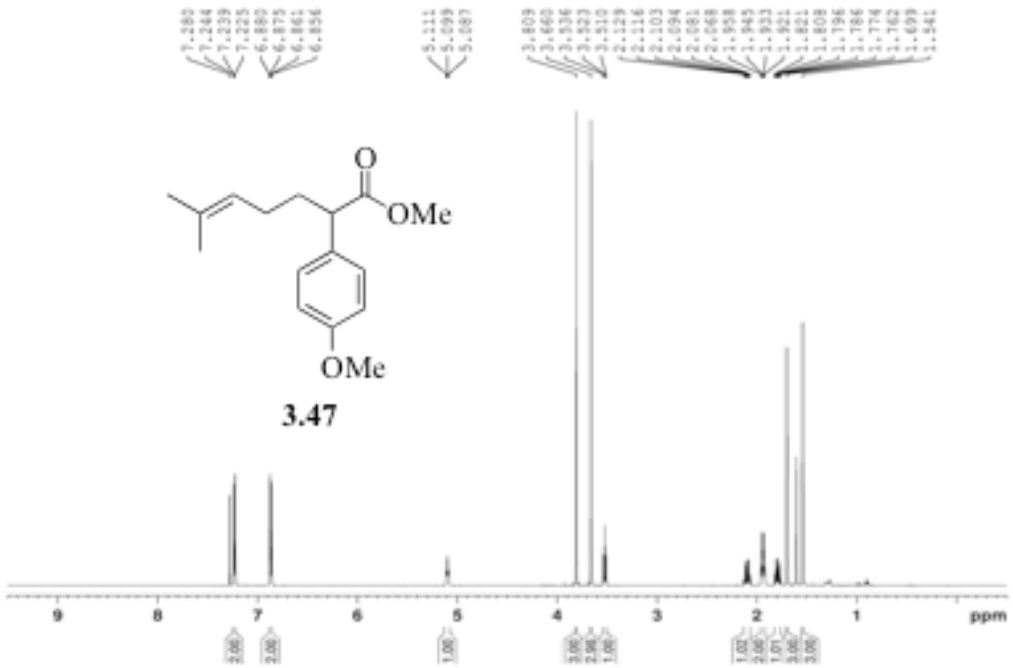

7.280
6.589
6.584
6.578
6.574
6.568
6.563
6.559
6.553
6.548
2.616
2.613
2.611
2.601
2.599
2.597
2.587
2.584
2.582
2.368
2.352
2.336
2.179
2.164
2.150
2.135
1.981
1.966
1.951
1.936
1.921
1.506
1.491
1.476
1.462
1.447
1.350
1.323
1.316
1.308
1.297
O
3
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0000
2.1998
2.1887
2.2775
2.2685
2.2946
5.5241
3.8377

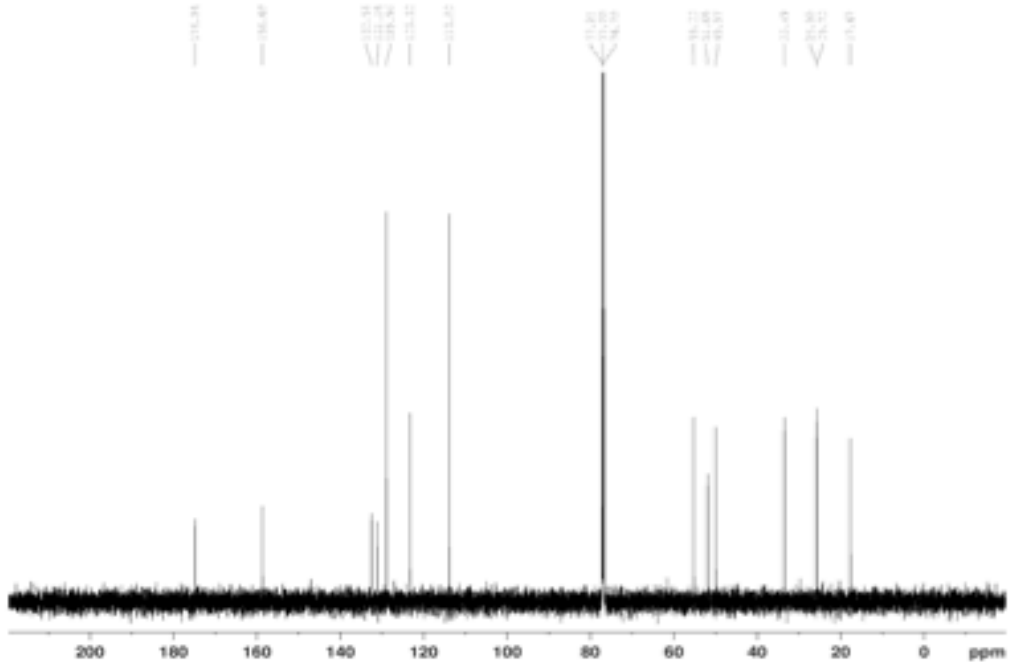
2.28

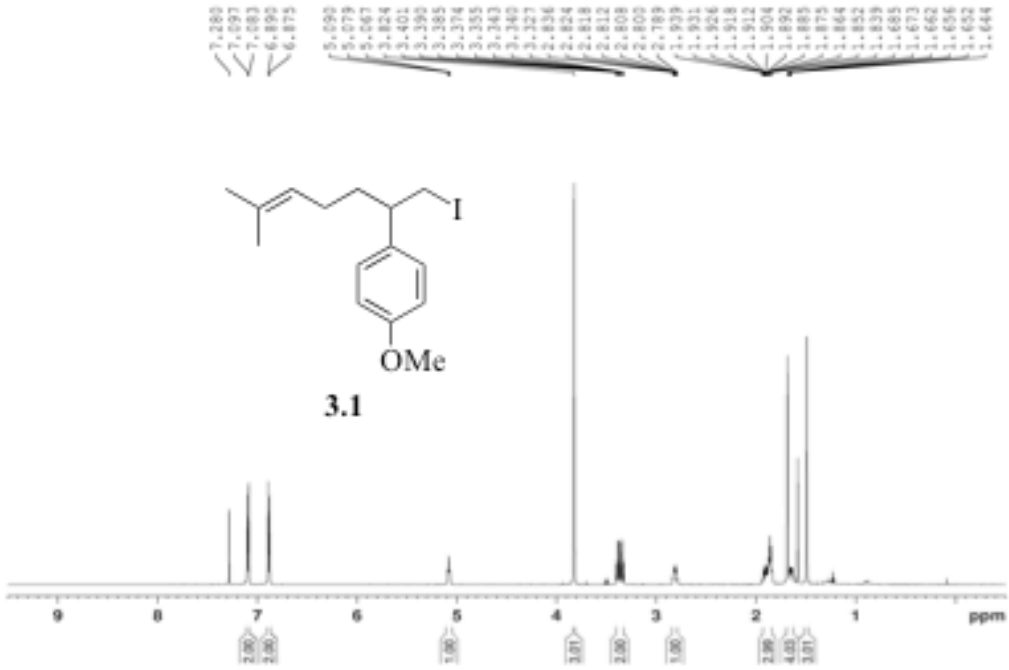

200 180 160 140 120 100 80 60 40 20 0 ppm

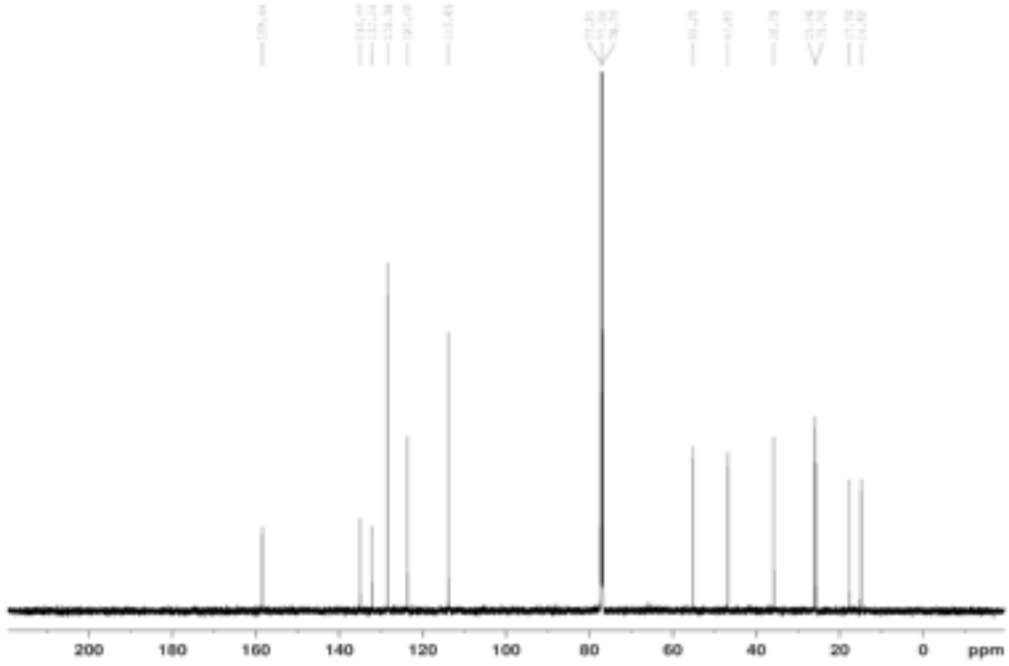

199.632
144.783
140.023
132.555
127.189
77.264
77.010
76.756
38.634
31.631
31.587
29.484
28.283
26.066
23.184
22.652
22.515
14.115
14.038
O
3
O
2.28
2.29
trace amounts
200
180
160
140
120
100
80
60
40
20
0
ppm

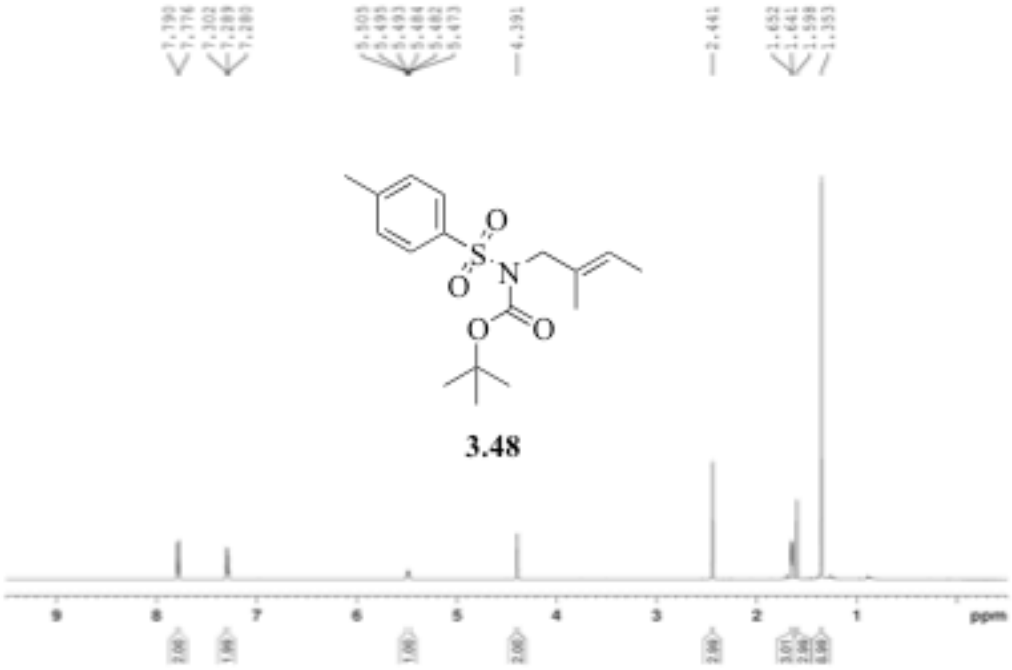
Appendix B: Spectral Data for Chapter 3



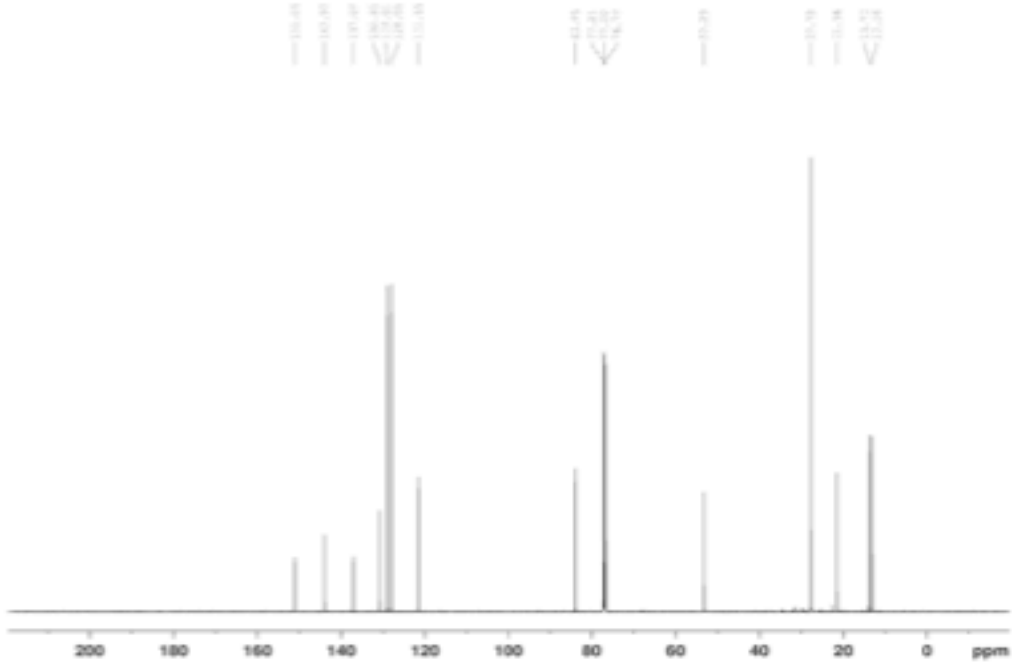


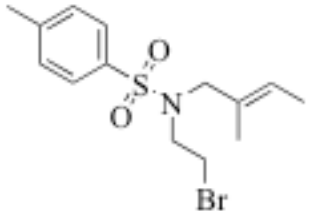

I
OMe
3.1
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

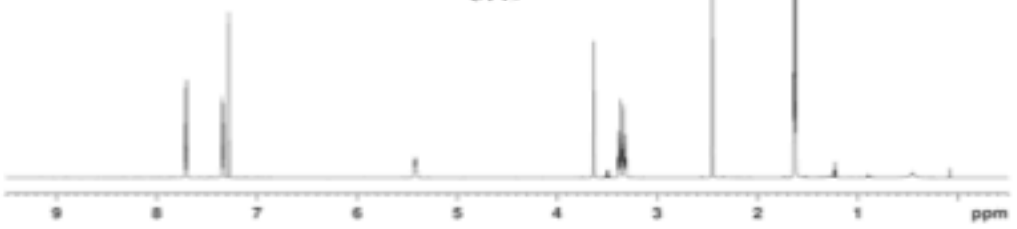

7.790
7.776
7.302
7.289
7.283
5.505
5.495
5.493
5.484
5.482
5.473
4.391
2.441
1.652
1.641
1.598
1.353
9
8
7
6
5
4
3
2
1
ppm

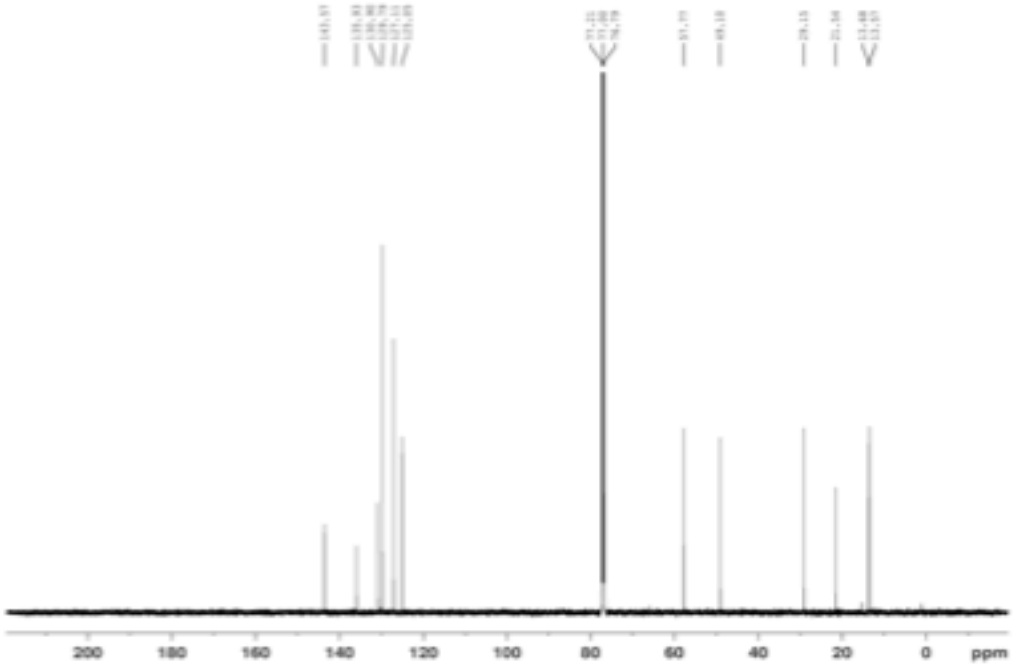
3.48

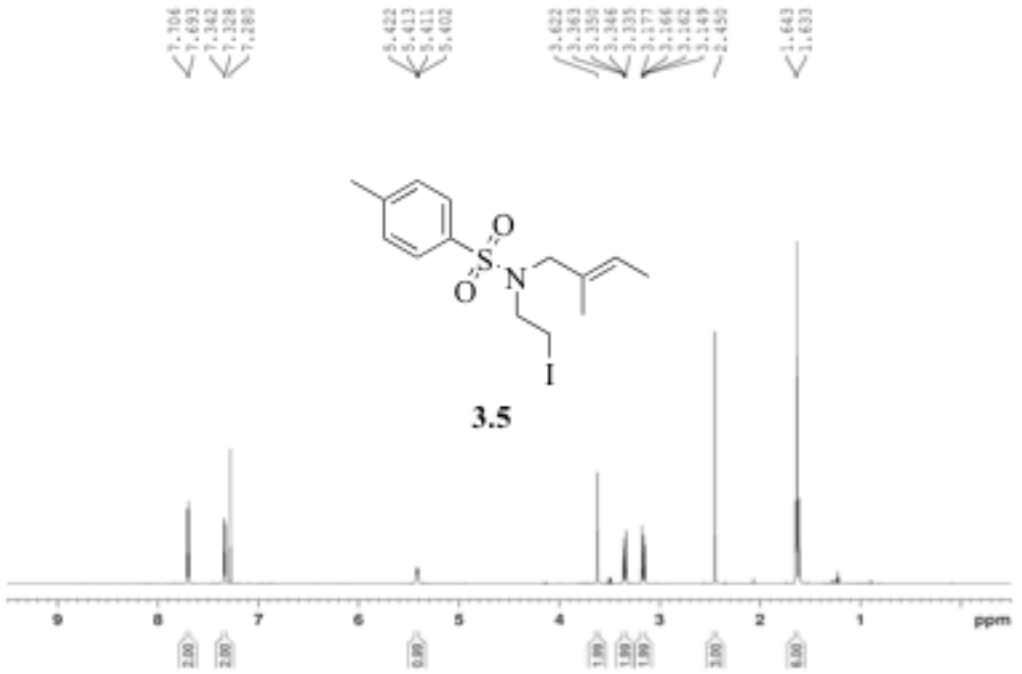

200
180
160
140
120
100
80
60
40
20
0
ppm

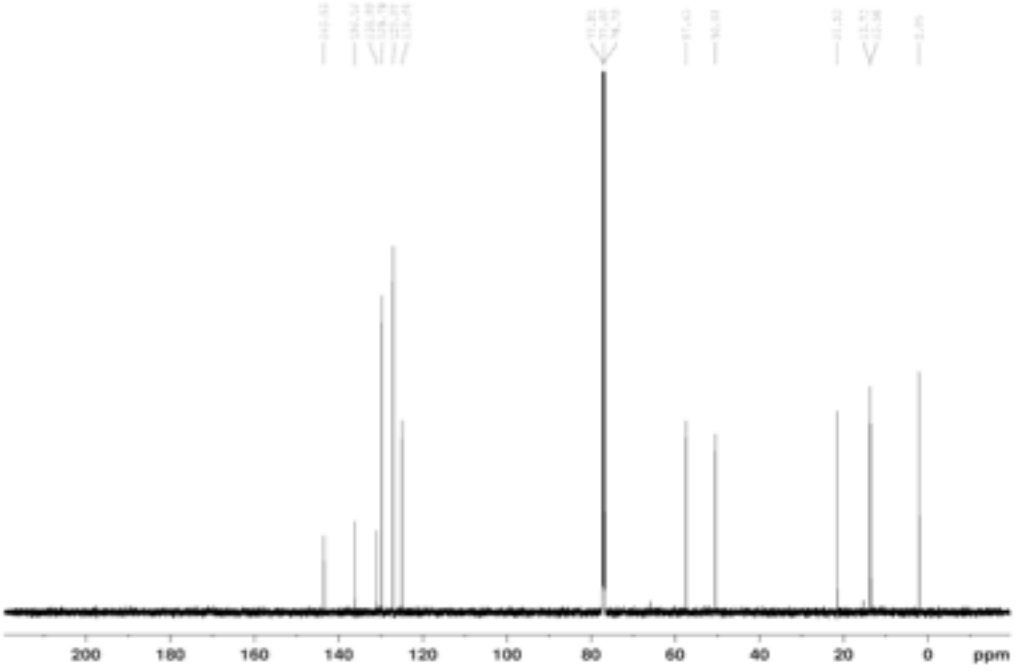


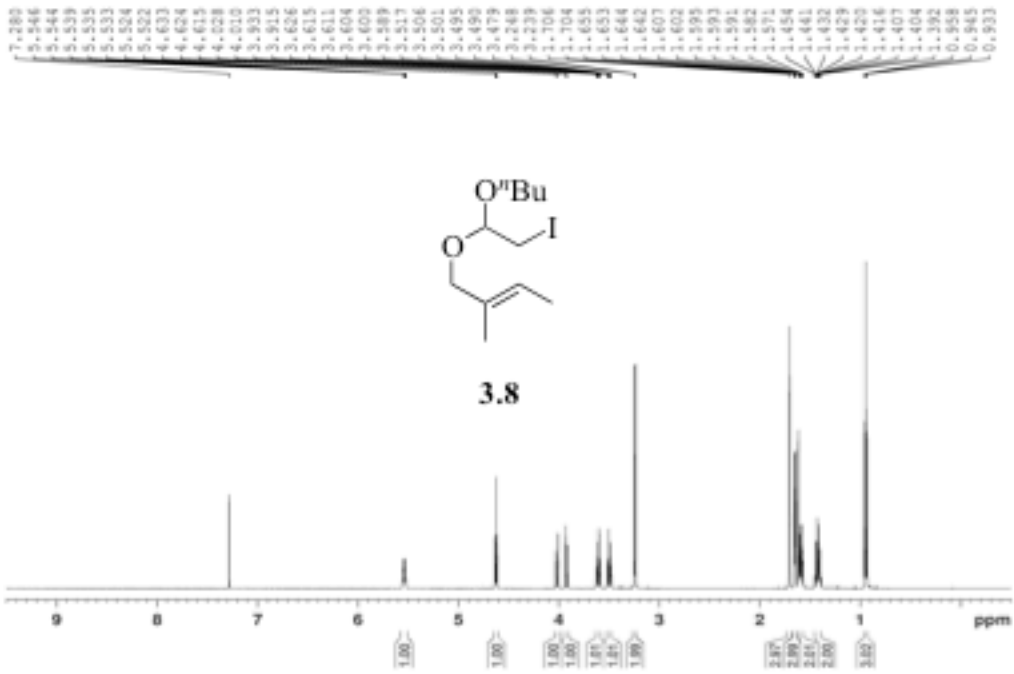
3.49

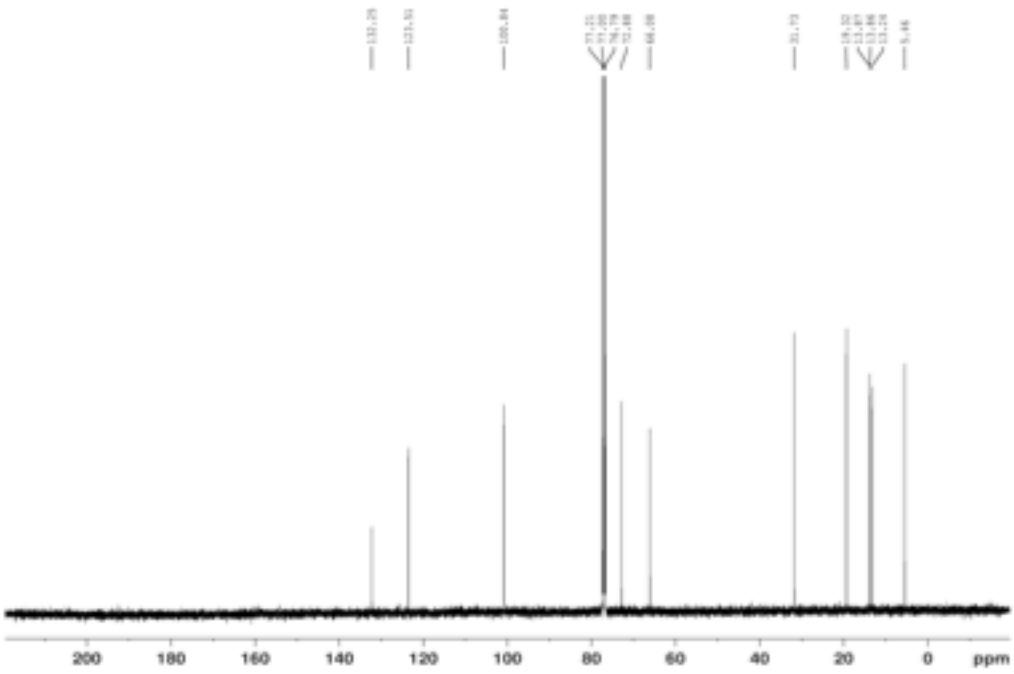


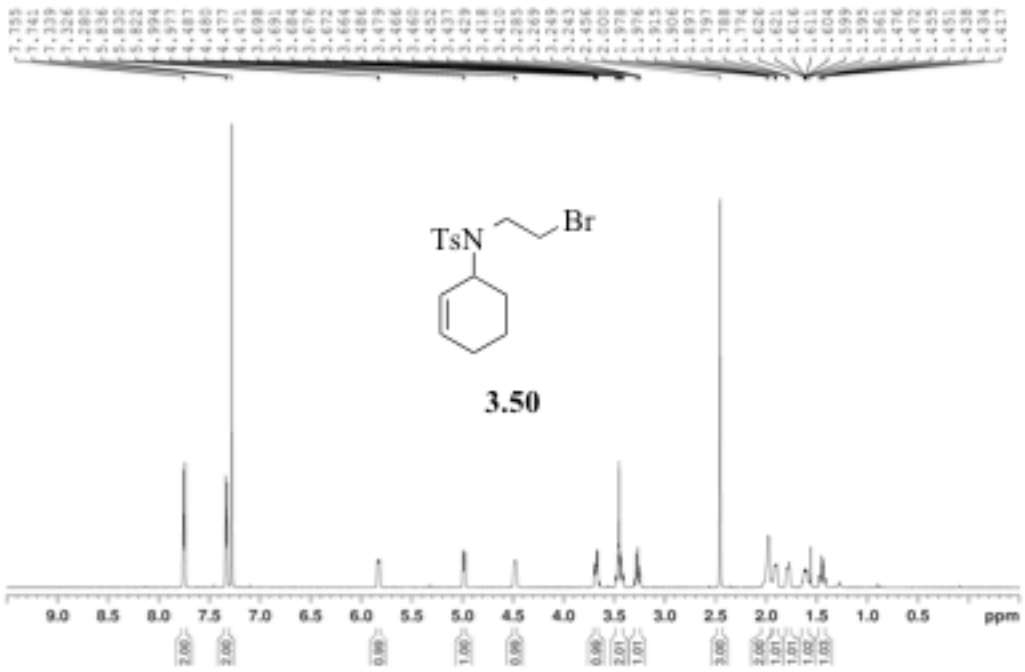


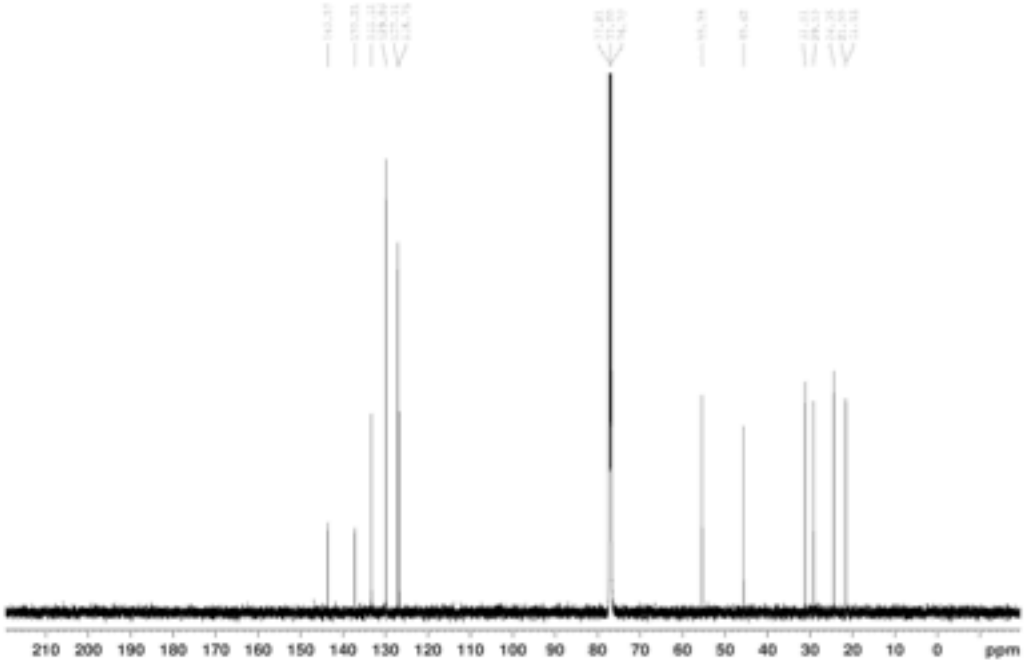

7.706
7.693
7.342
7.328
7.280
5.422
5.413
5.411
5.402
3.622
3.363
3.350
3.346
3.335
3.177
3.166
3.162
3.149
2.450
1.643
1.633
O
S
O
N
I
3.5
9
8
7
6
5
4
3
2
1
ppm
2.00
2.00
0.98
1.99
1.99
1.99
3.00
6.00

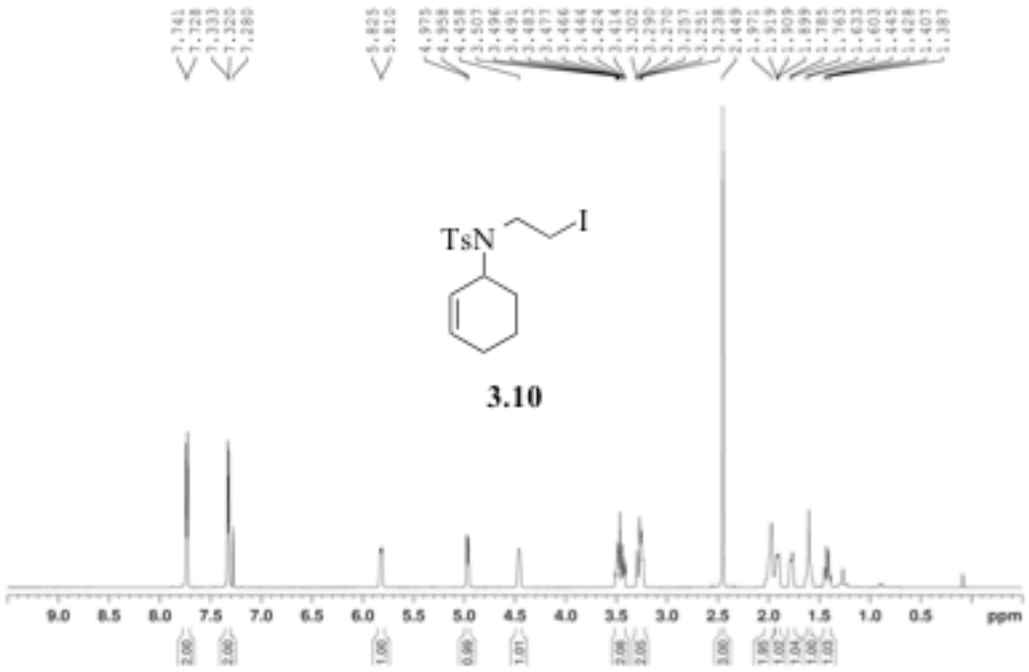

200
180
160
140
120
100
80
60
40
20
0
ppm

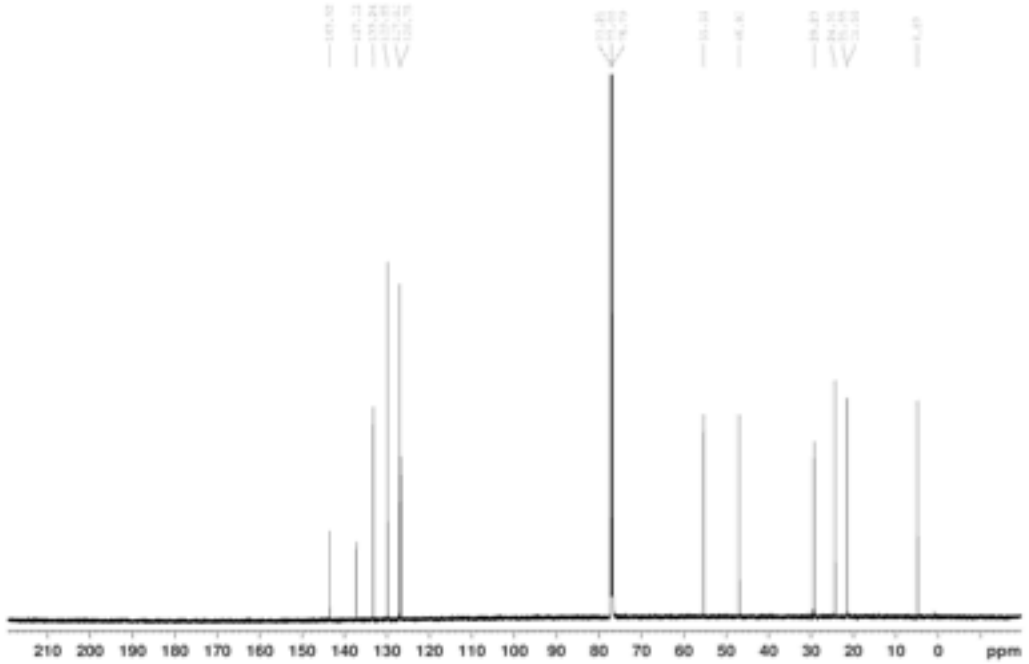

O^{n}Bu
I
O
3.8
9
8
7
6
5
4
3
2
1
ppm

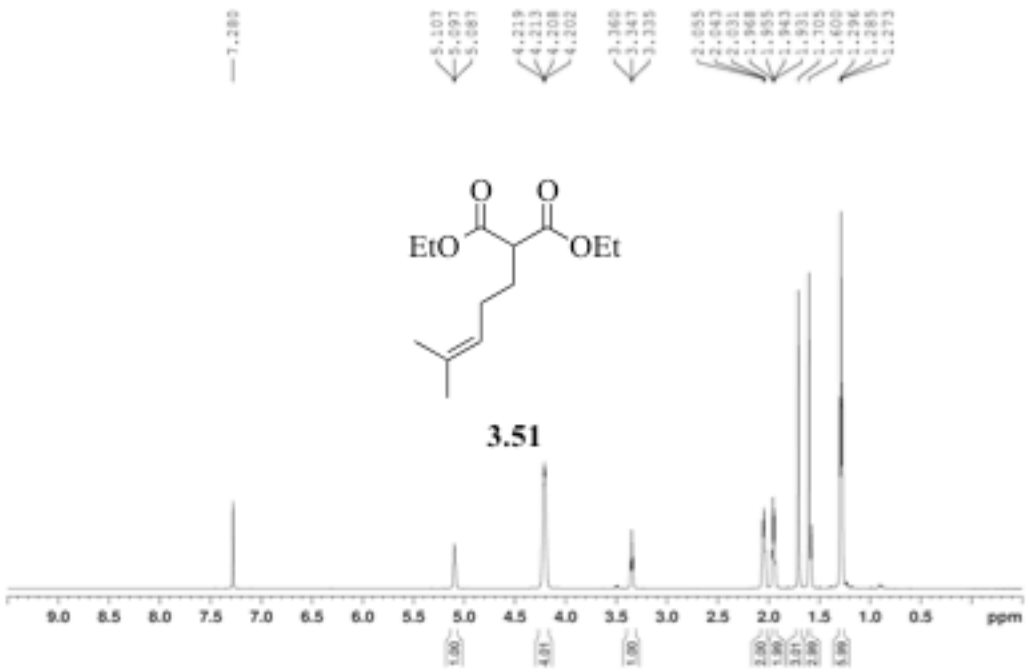

200
180
160
140
120
100
80
60
40
20
0
ppm

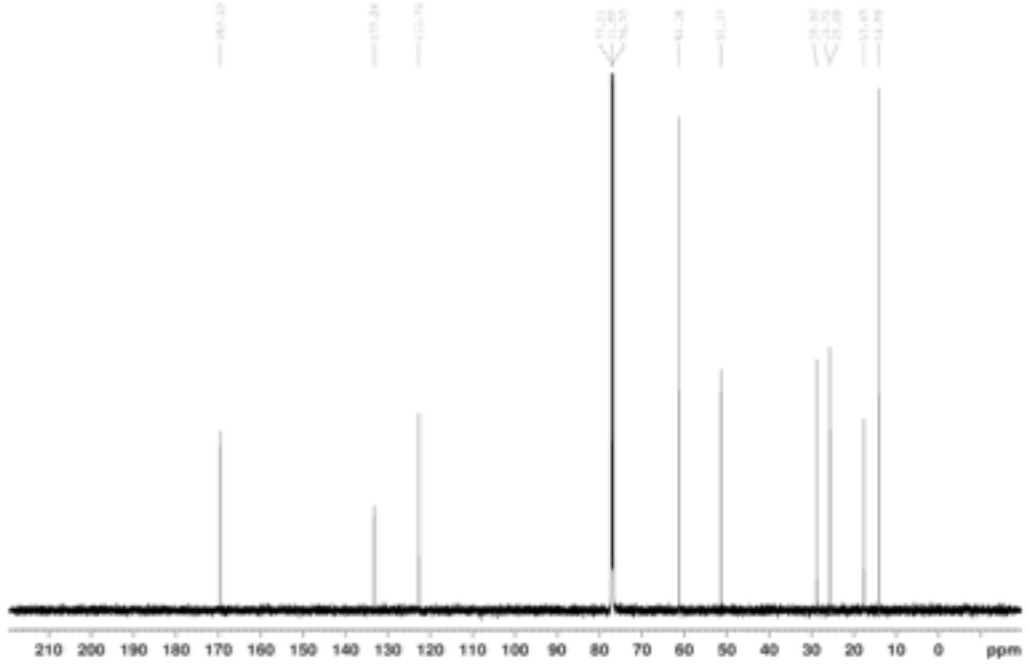

TsN
Br
3.50
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

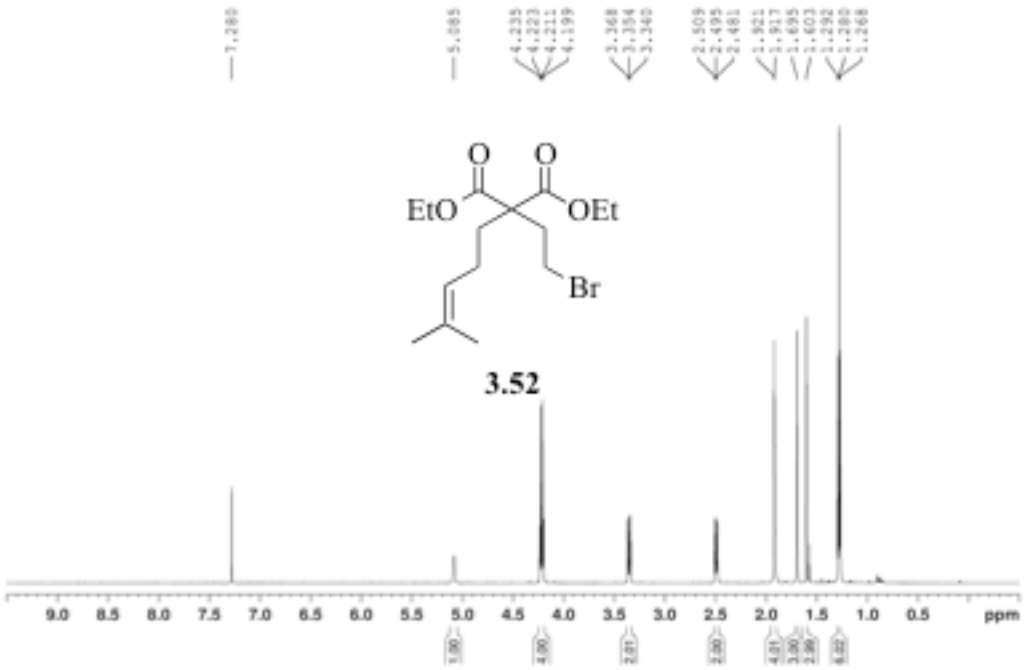

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

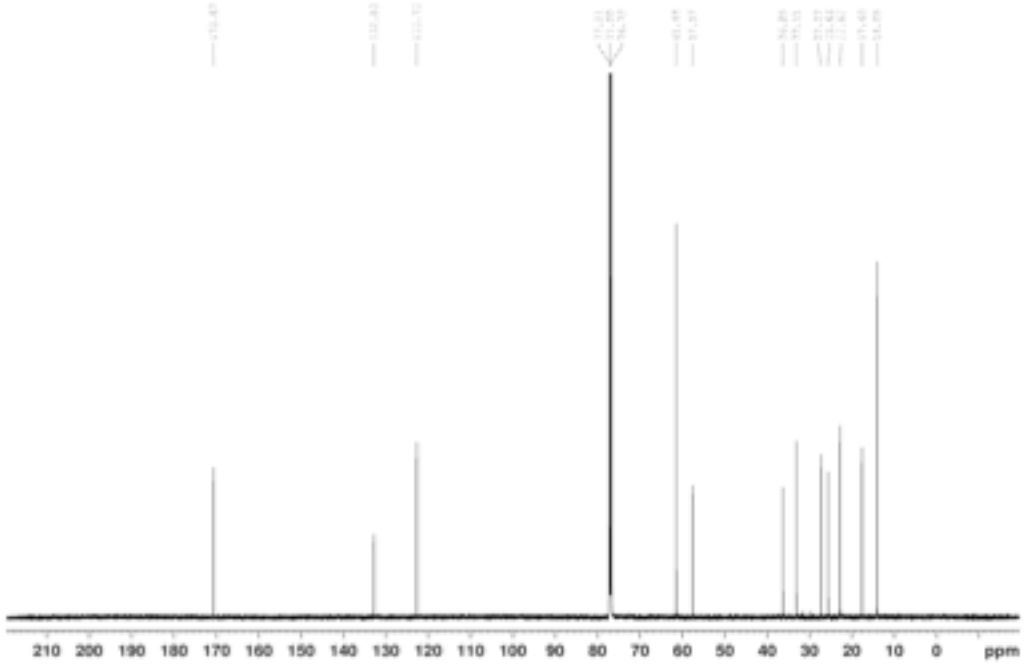

TsN
I
3.10
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

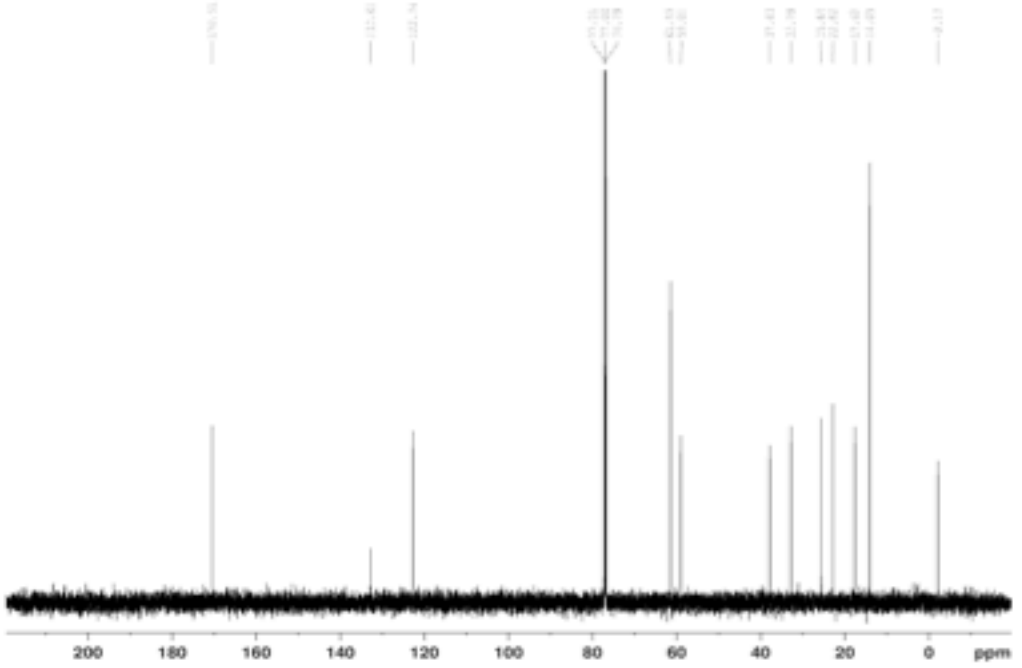

7.280
5.107
5.097
5.087
4.219
4.213
4.208
4.202
3.360
3.347
3.335
2.055
2.043
2.031
1.968
1.955
1.943
1.931
1.705
1.600
1.296
1.285
1.273
O
O
EtO
OEt
3.51
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
4.01
1.00
2.00
1.98
3.01
2.00
3.00

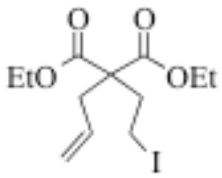

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


EtO
OEt
Br
3.52
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

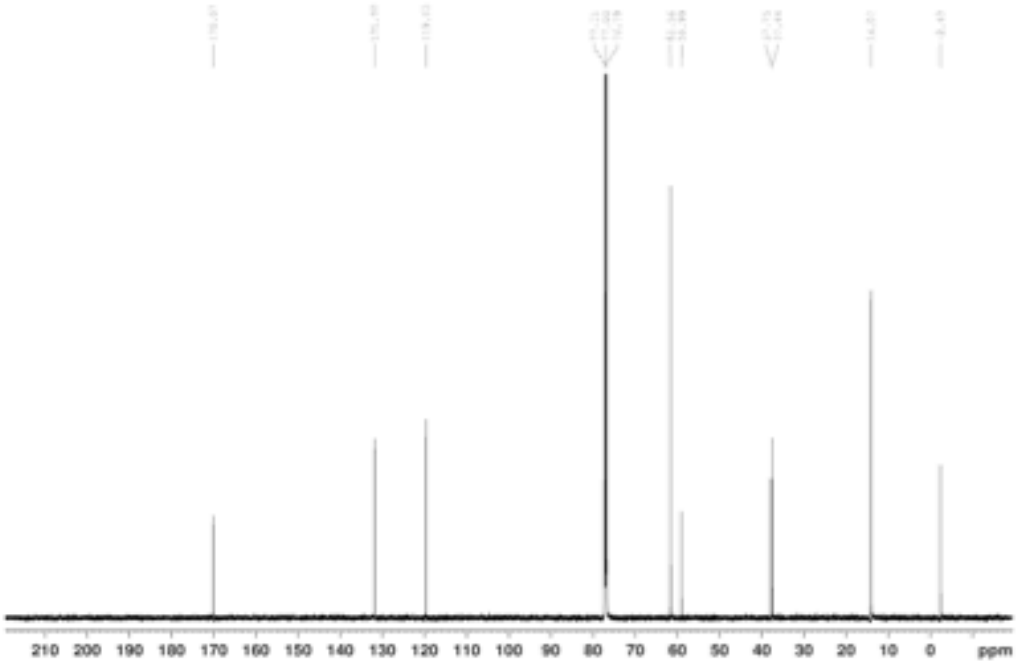

EtO
OEt
I
3.14
9
8
7
6
5
4
3
2
1
ppm

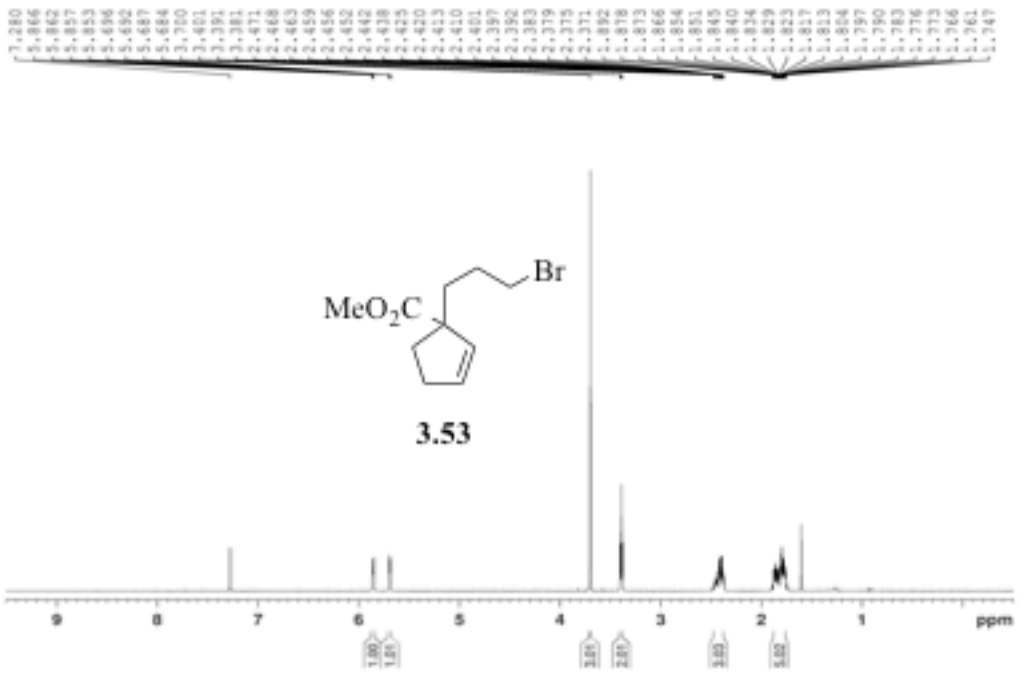

200
180
160
140
120
100
80
60
40
20
0
ppm

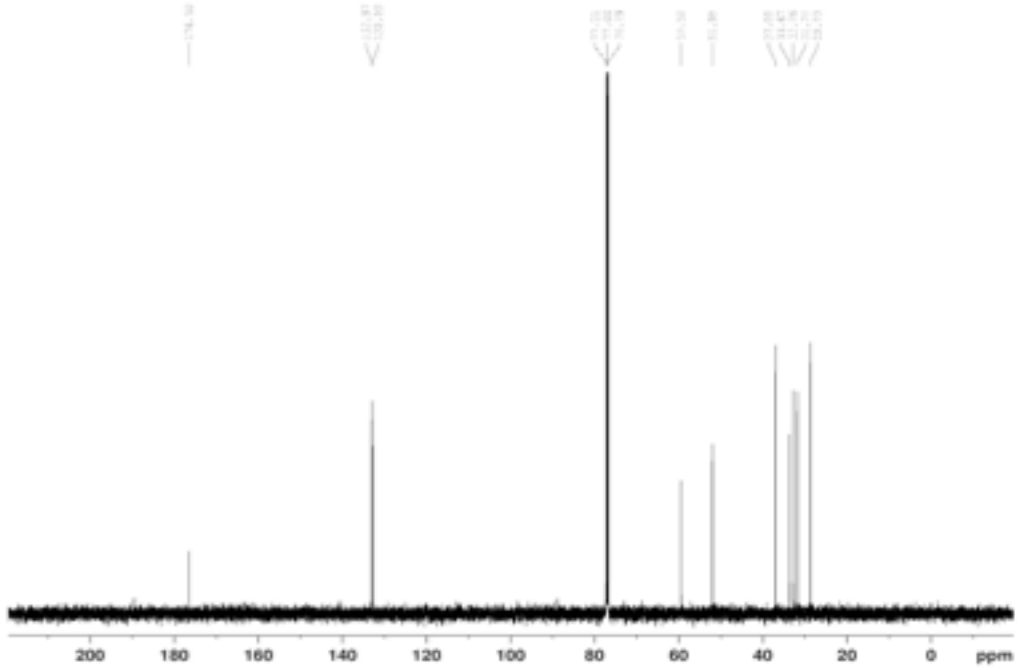

O
O
EtO
OEt
I

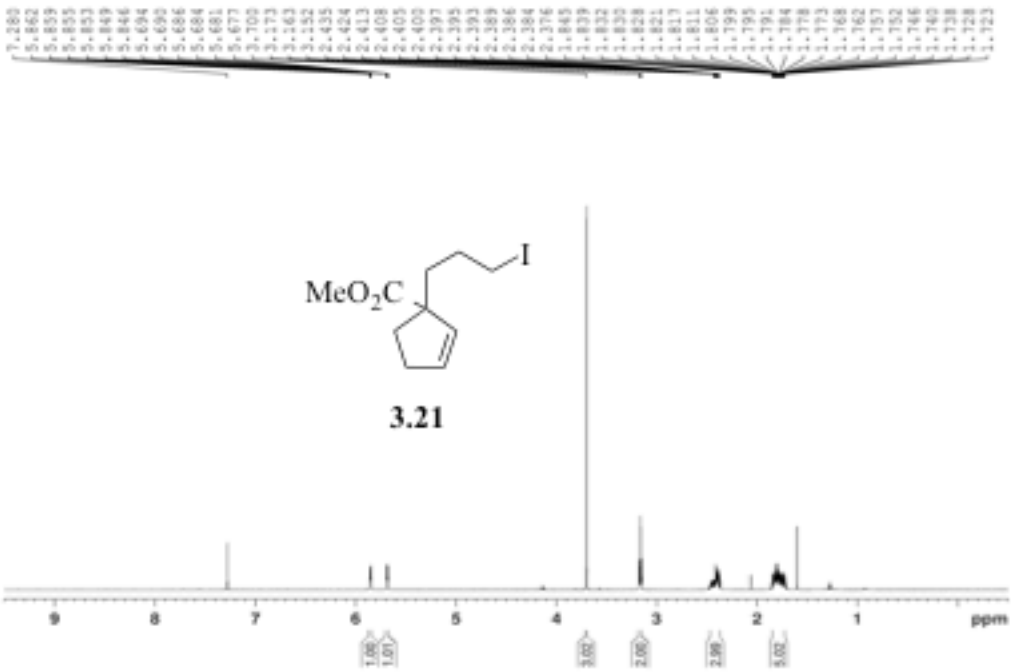
3.17

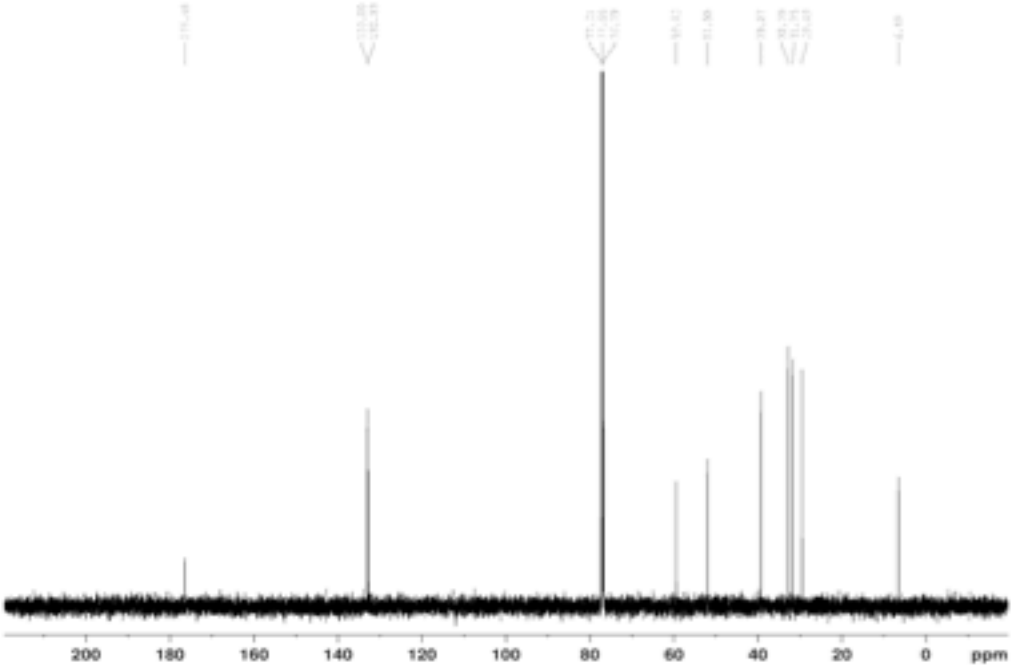
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.01
3.99
1.98
2.01
2.01
5.99

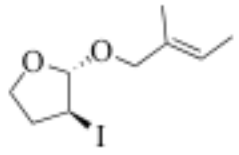

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


Br
MeO2C
3.53
9
8
7
6
5
4
3
2
1
ppm

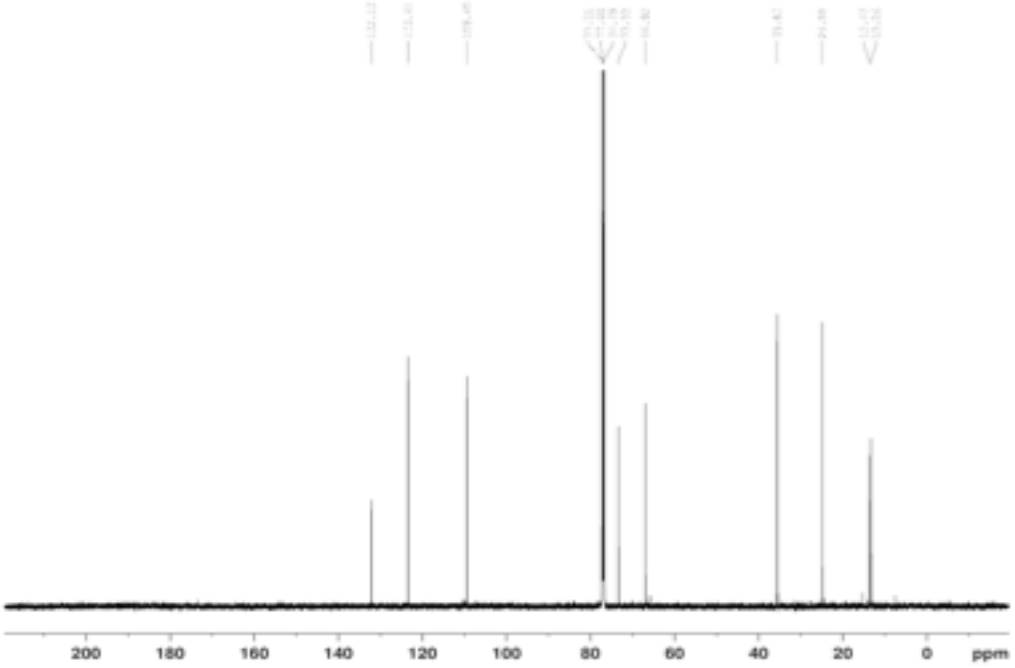

200
180
160
140
120
100
80
60
40
20
0
ppm

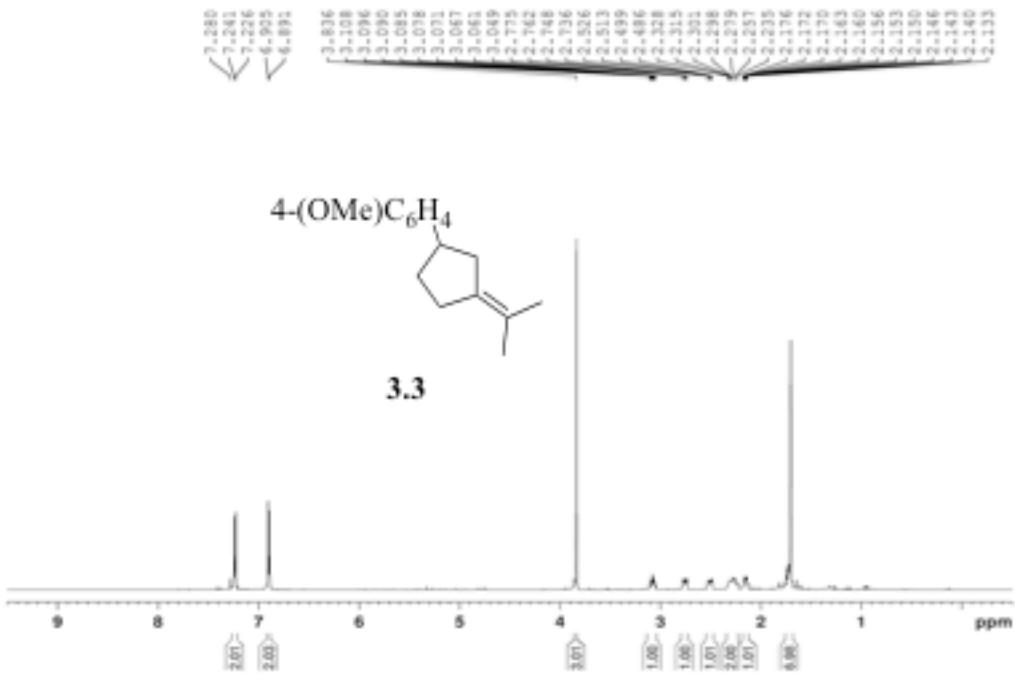

I
MeO2C
3.21
9
8
7
6
5
4
3
2
1
ppm
1.00
1.07
5.02
2.00
2.90
5.02

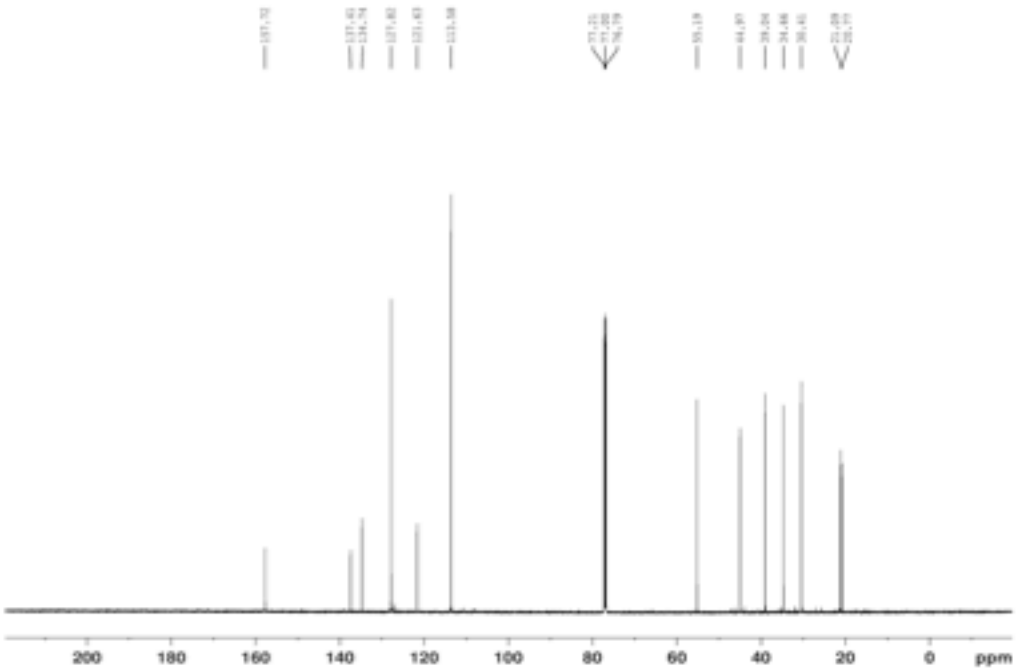

200
180
160
140
120
100
80
60
40
20
0
ppm

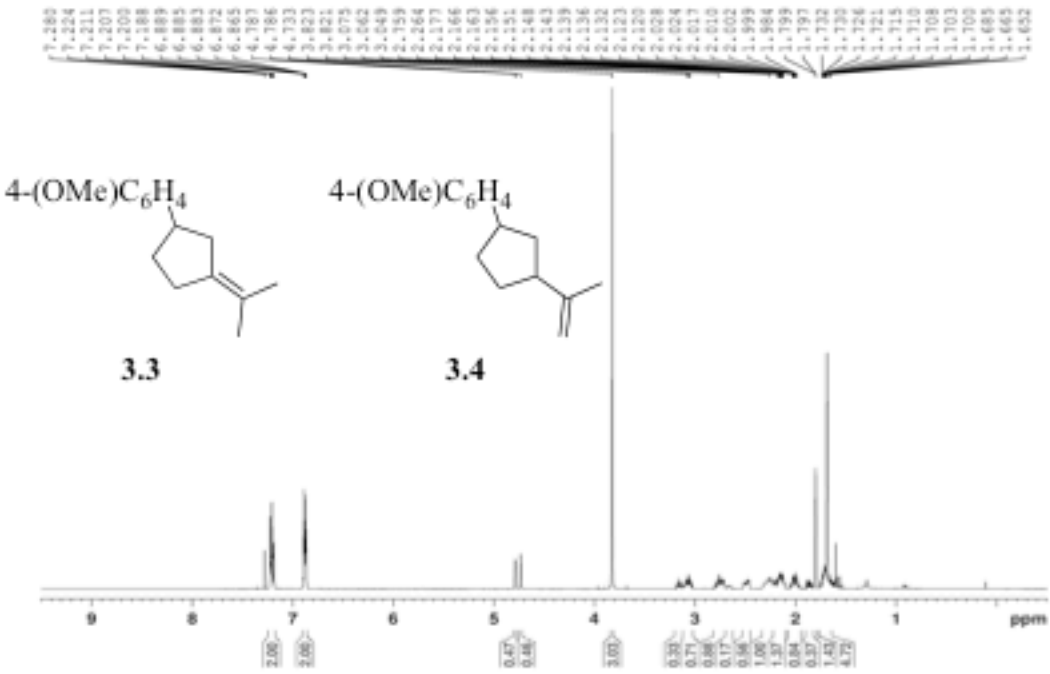


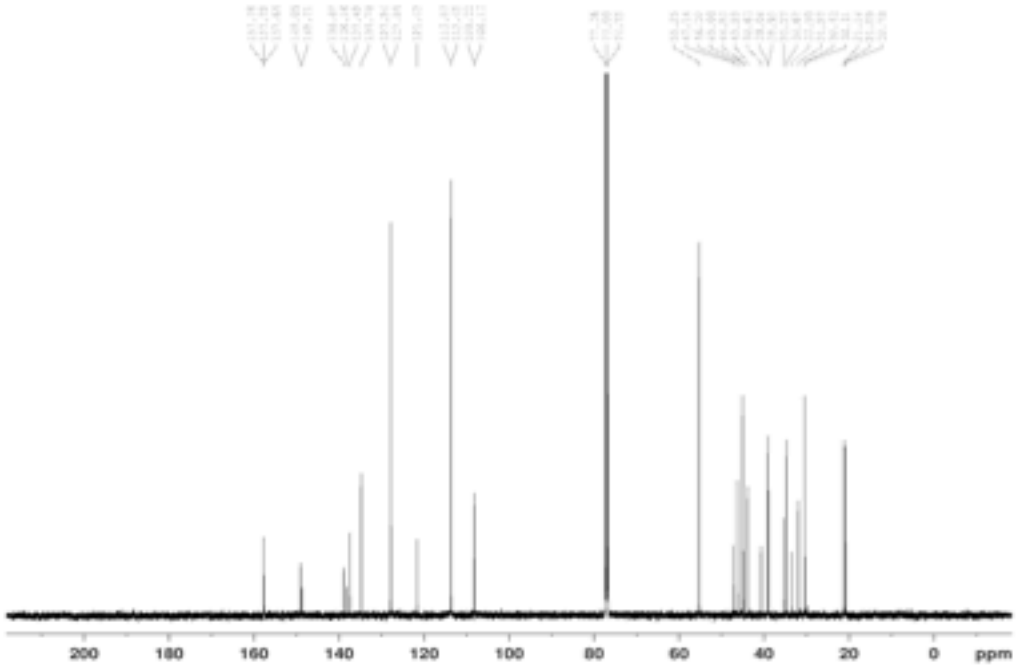
3.29

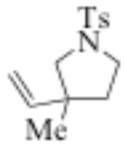



4-(OMe)C6H4
3.3
9
8
7
6
5
4
3
2
1
ppm

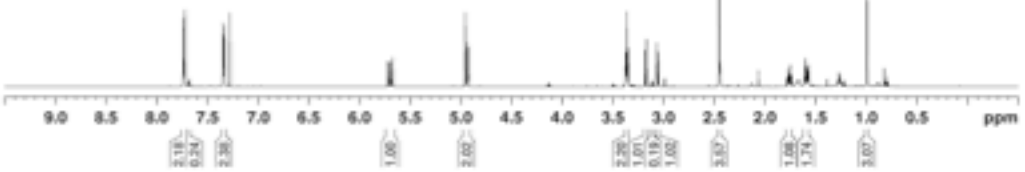

200
180
160
140
120
100
80
60
40
20
0
ppm

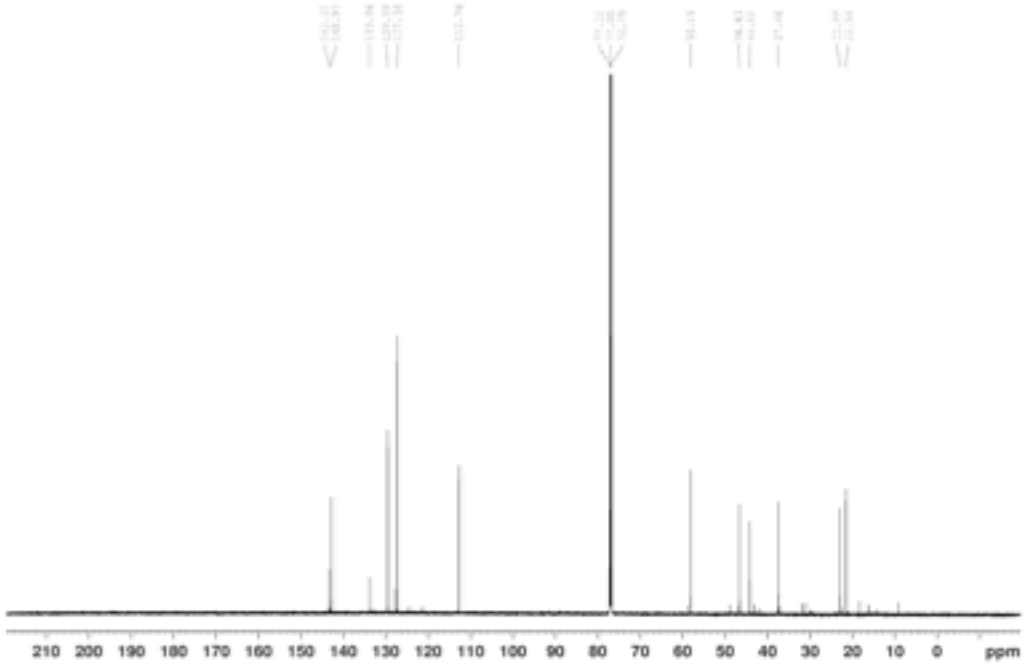

4-(OMe)C6H4
4-(OMe)C6H4
3.3
3.4
9
8
7
6
5
4
3
2
1
ppm

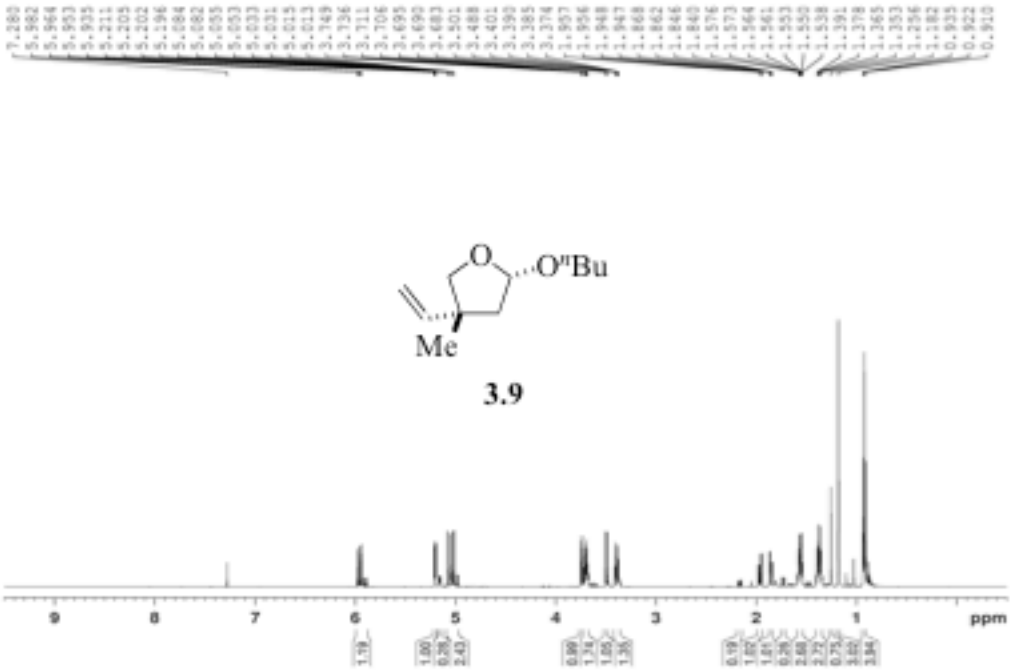

200
180
160
140
120
100
80
60
40
20
0
ppm


Ts
N
Me

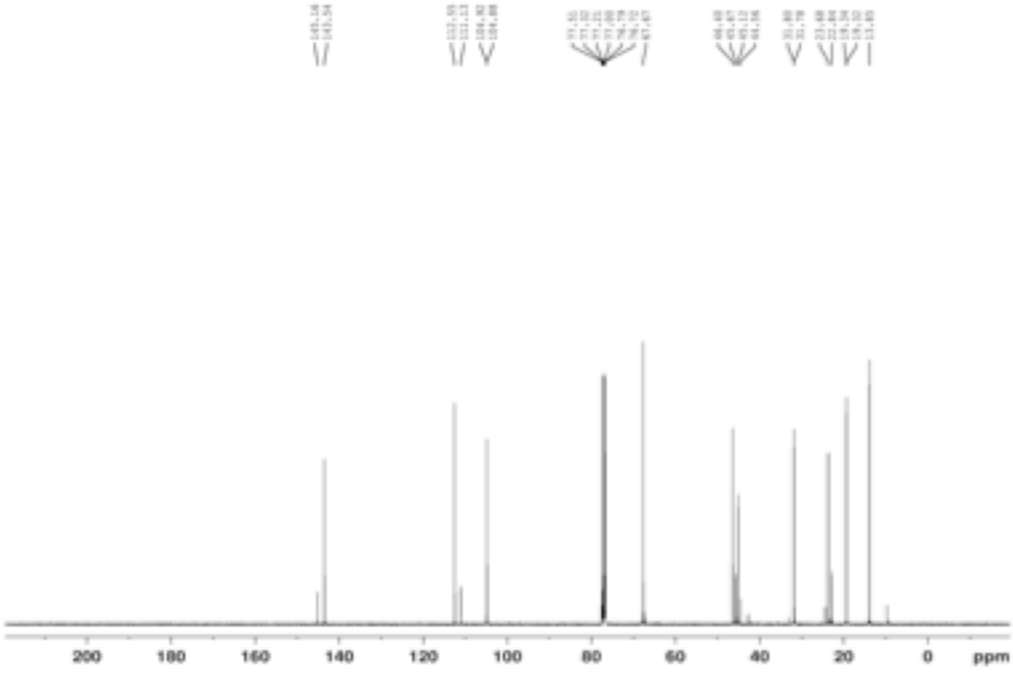
3.6

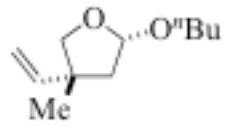

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

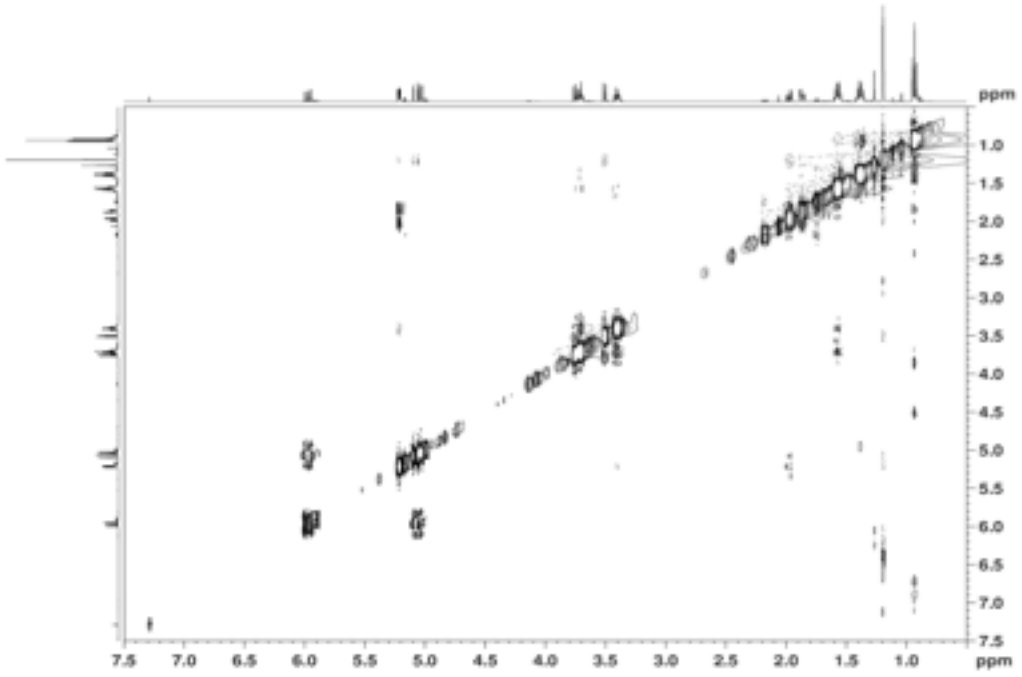


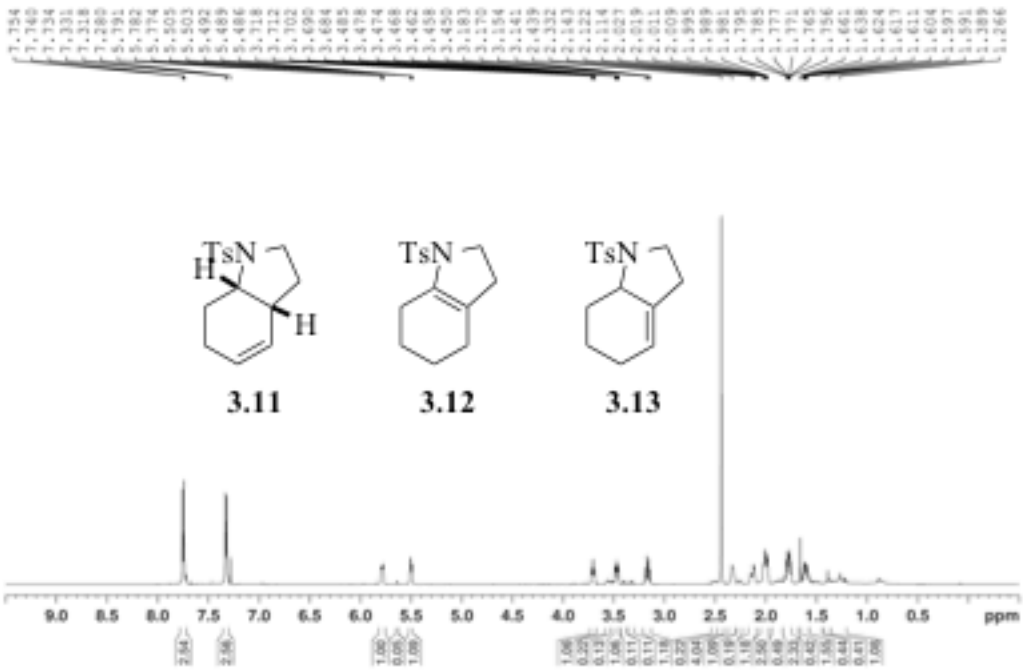
3.9

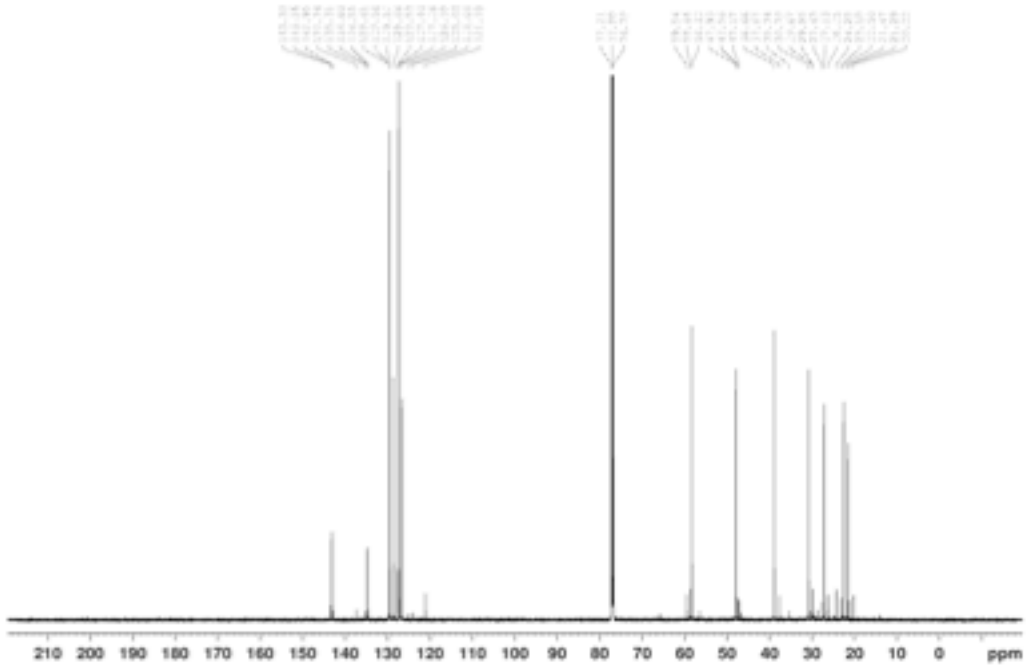


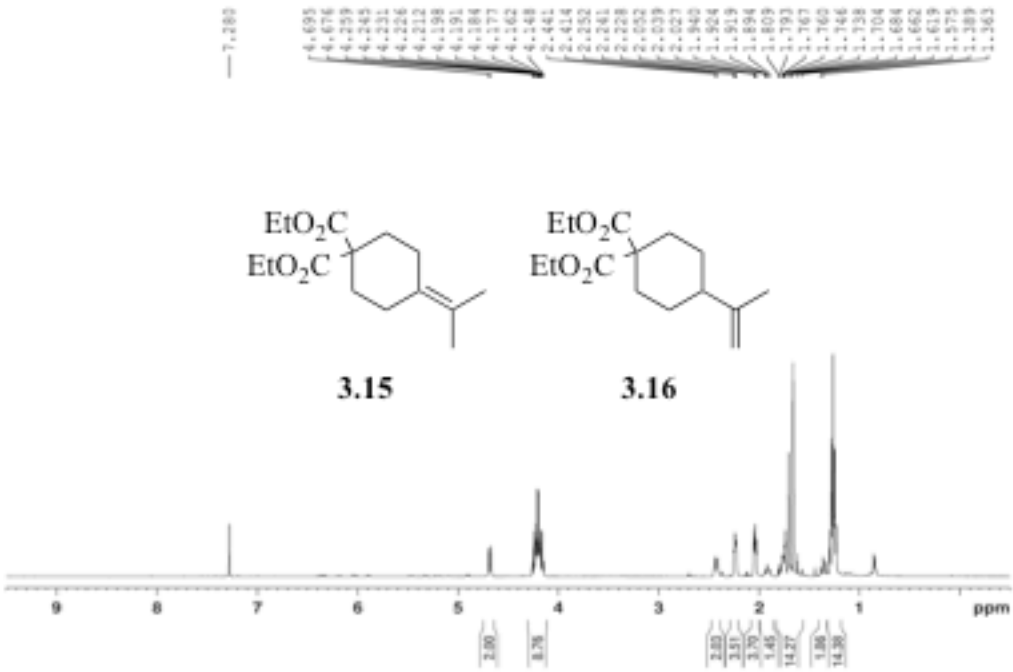

O
O^{n}Bu
Me

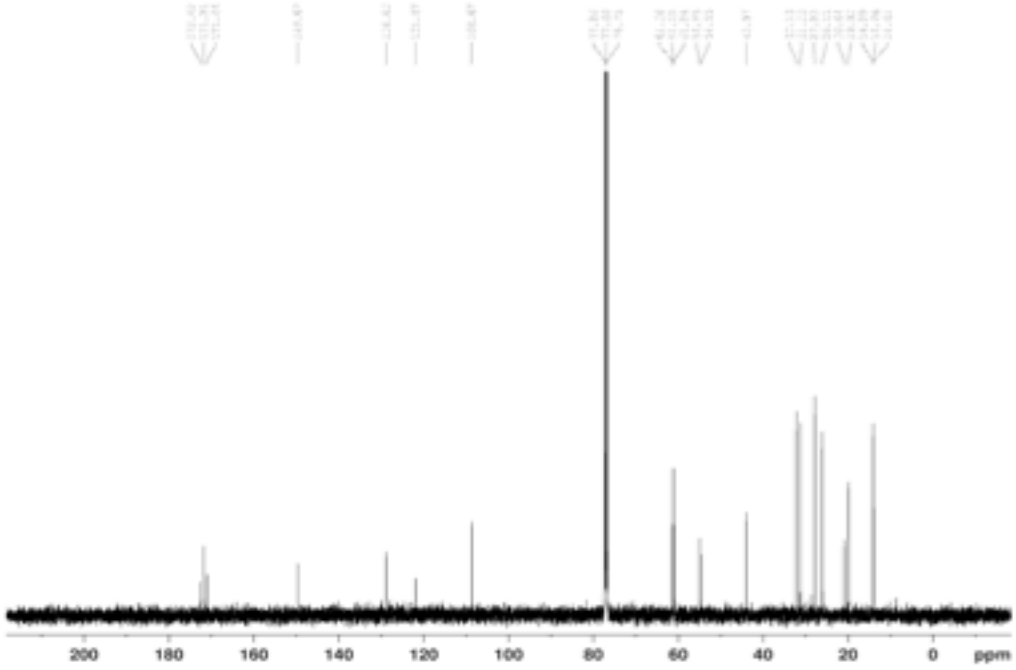
3.9

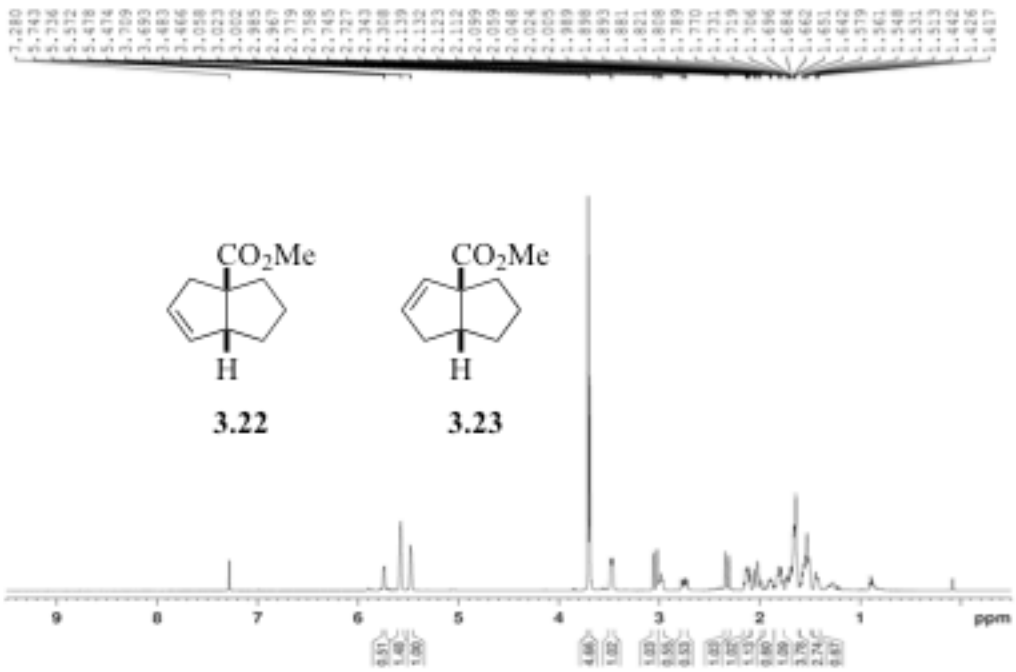

ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

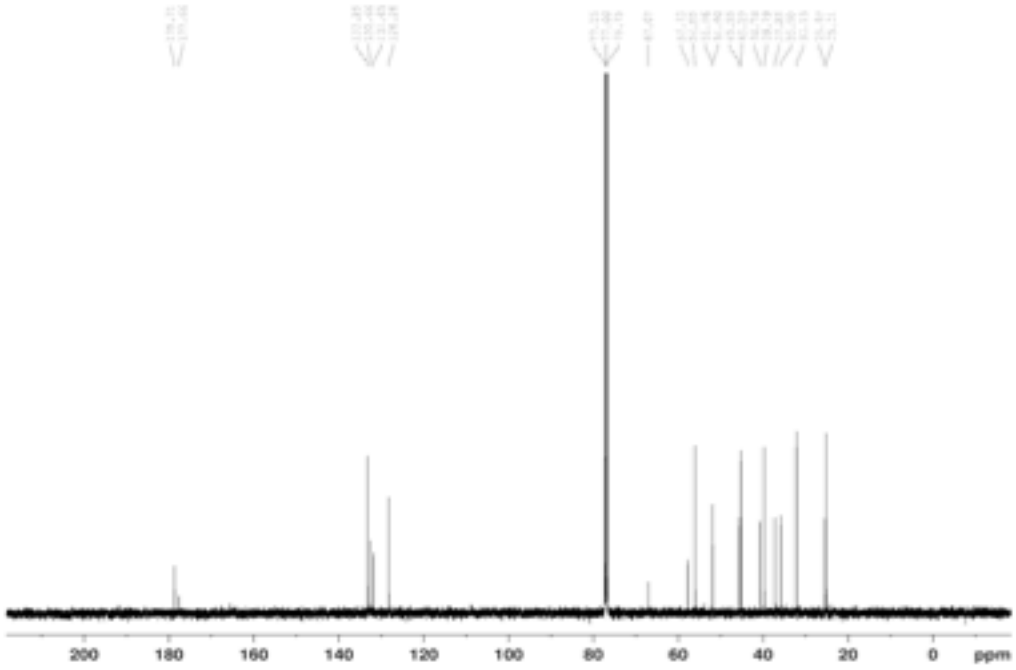

TsN
H
H
TsN
TsN
3.11
3.12
3.13
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

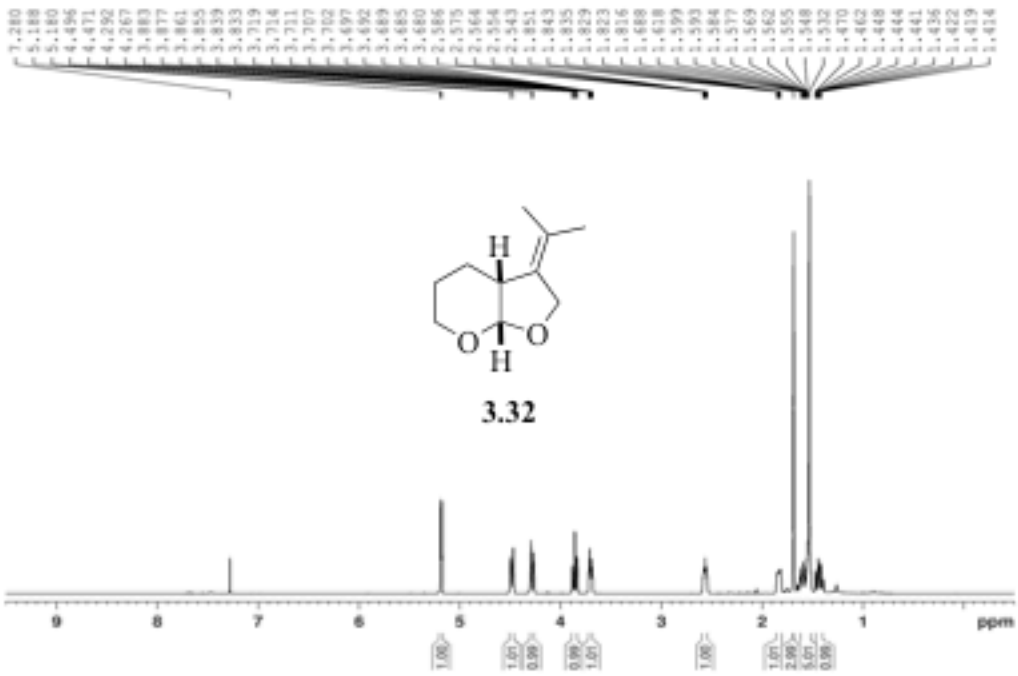

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


EtO2C
EtO2C
EtO2C
EtO2C
3.15
3.16
9
8
7
6
5
4
3
2
1
ppm

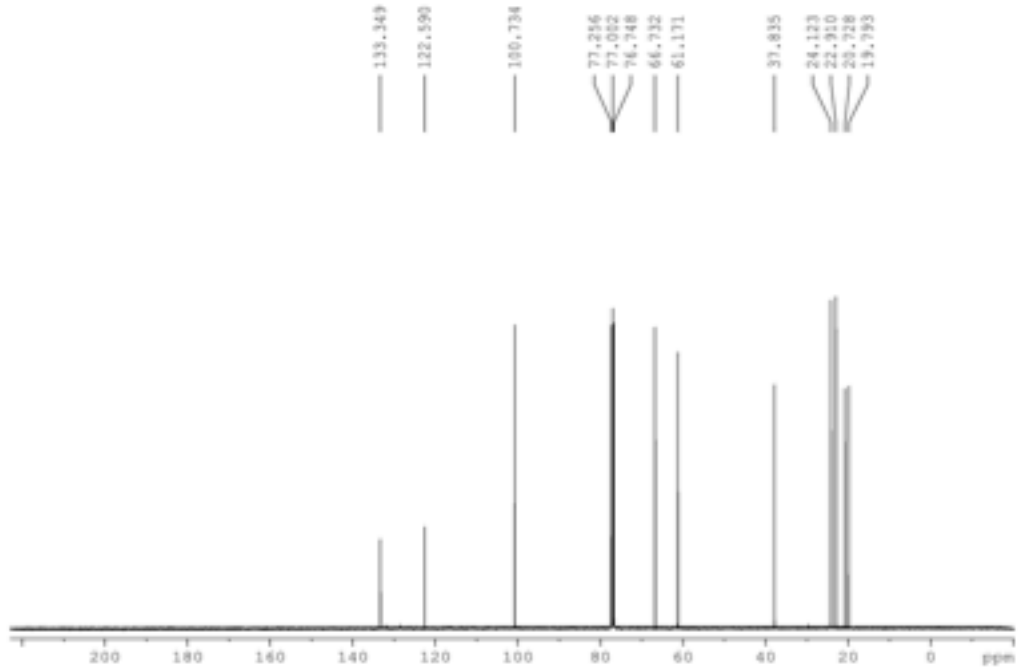

200
180
160
140
120
100
80
60
40
20
0
ppm

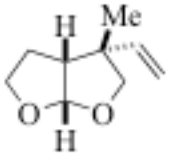

CO2Me
H
3.22
CO2Me
H
3.23
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

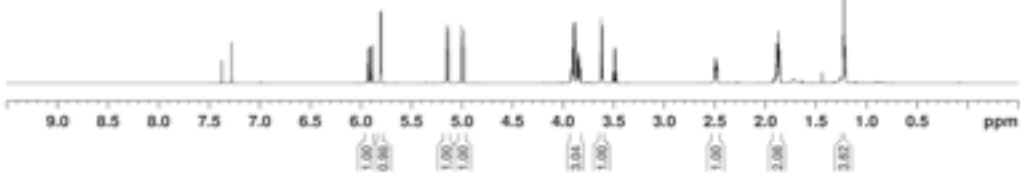

7.280
5.188
5.180
4.496
4.471
4.292
4.267
3.883
3.877
3.861
3.855
3.839
3.833
3.719
3.714
3.711
3.707
3.702
3.697
3.692
3.689
3.685
3.680
2.586
2.575
2.564
2.554
2.543
1.851
1.843
1.835
1.829
1.823
1.816
1.688
1.618
1.599
1.593
1.584
1.577
1.569
1.562
1.555
1.548
1.532
1.470
1.462
1.448
1.444
1.441
1.436
1.422
1.419
1.414
H
O
O
H
9
8
7
6
5
4
3
2
1
ppm
1.00
1.01
0.99
0.99
1.01
1.00
1.01
2.99
5.01
0.98

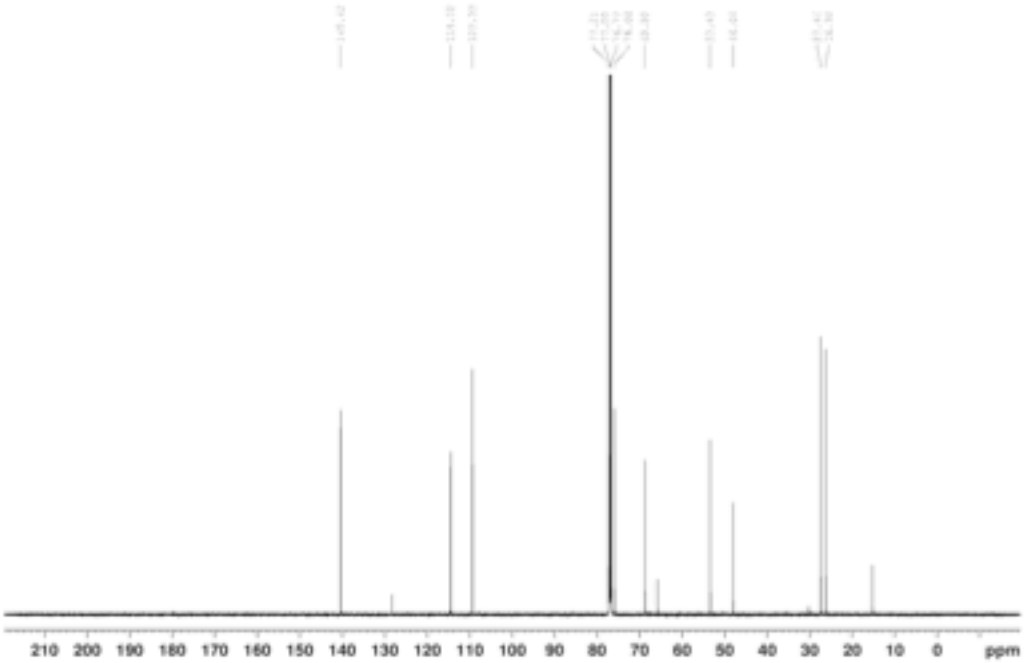
3.32

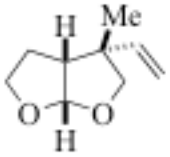

133.349
122.590
100.734
77.256
77.062
76.748
66.732
61.171
37.835
24.123
22.910
20.728
19.793
200
180
160
140
120
100
80
60
40
20
0
ppm


H
Me
O
O
H

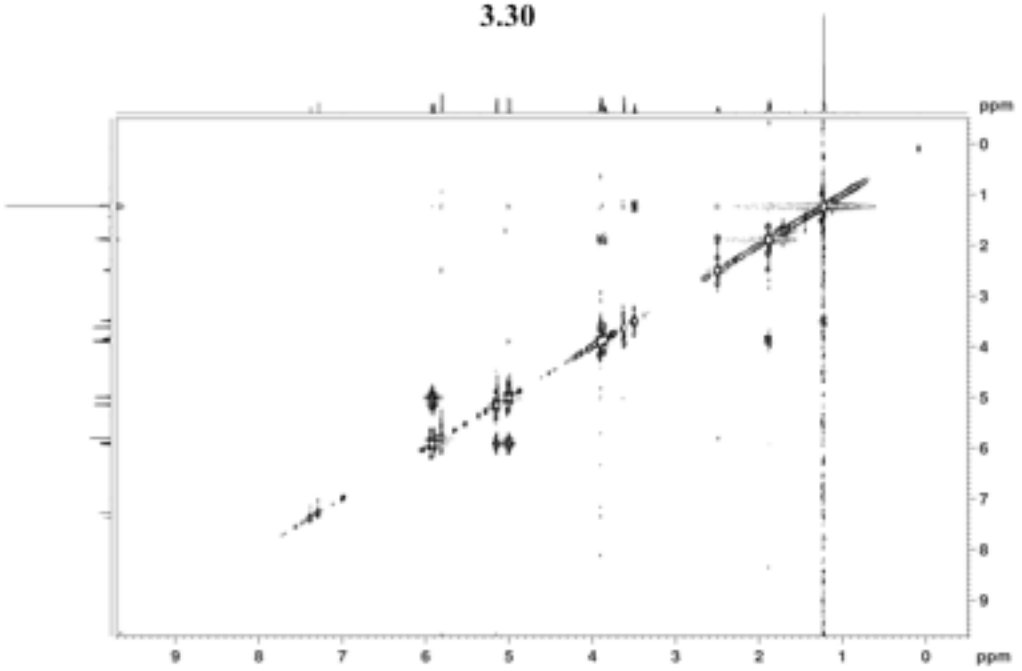
3.30

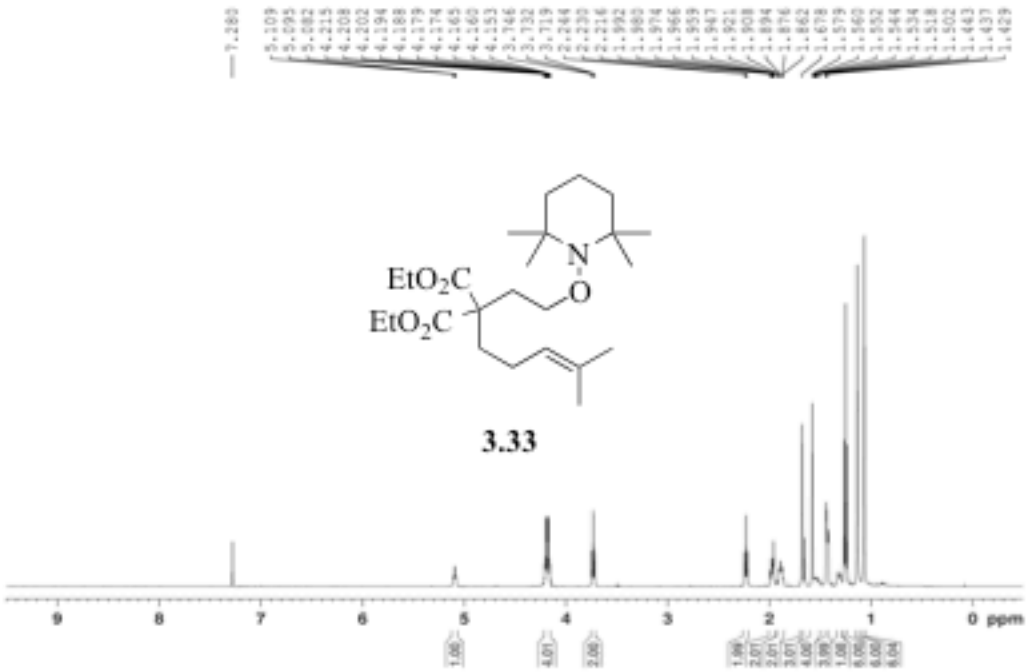

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

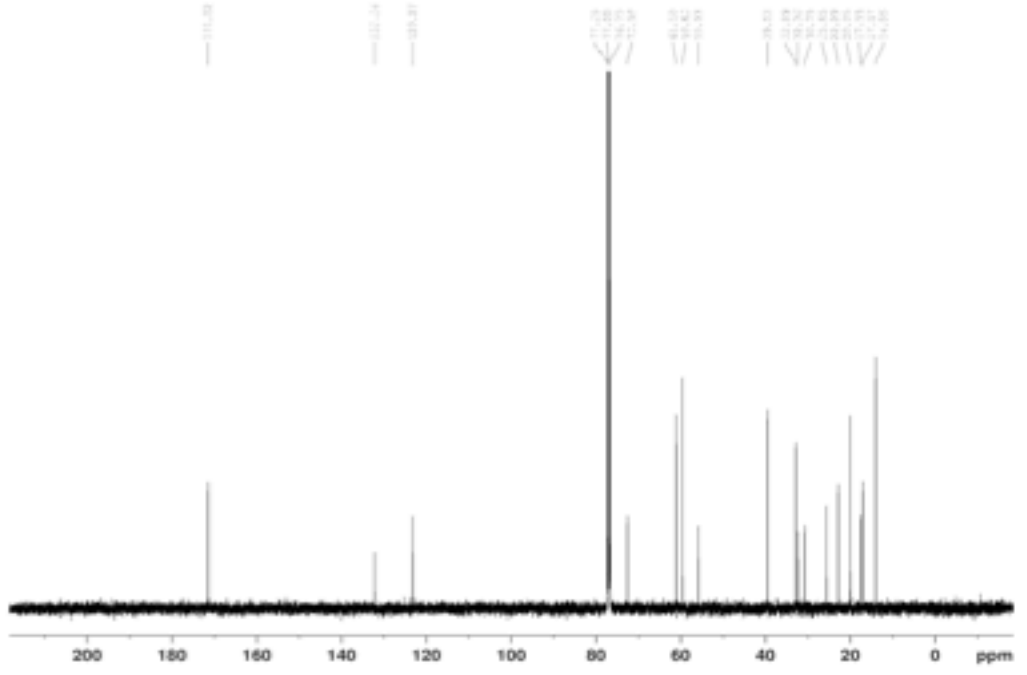

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



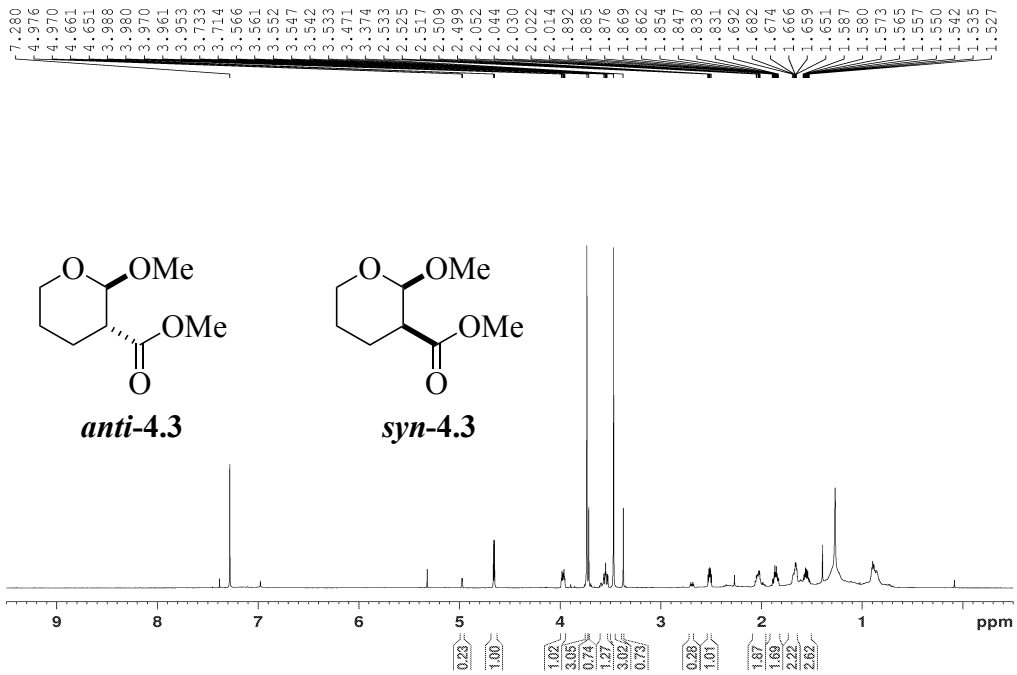
3.30

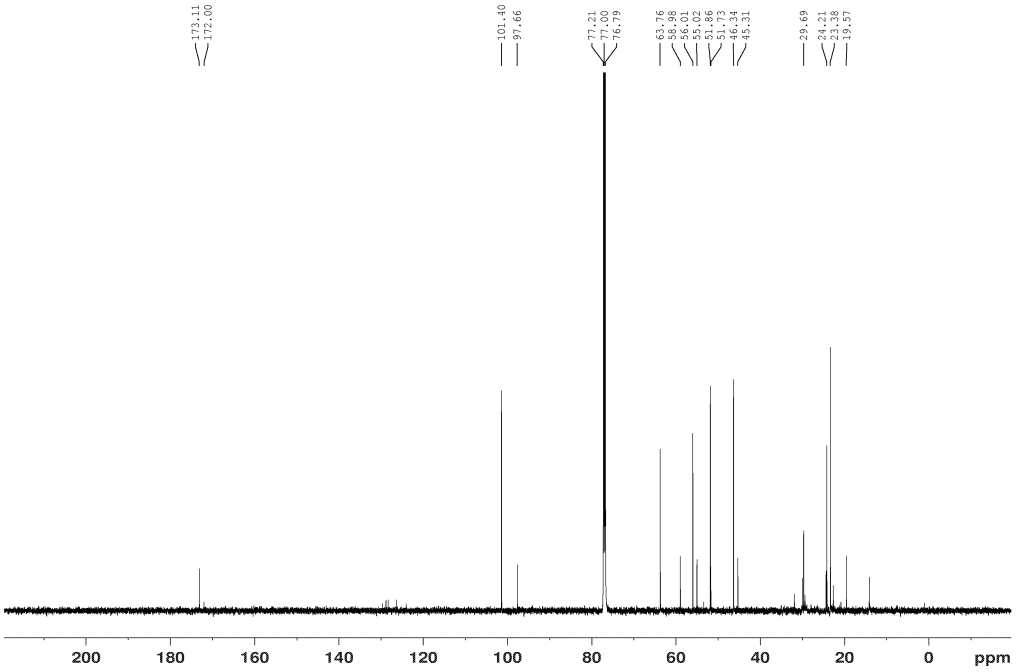



EtO2C
EtO2C
N
O
3.33
9
8
7
6
5
4
3
2
1
0 ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

Appendix C: Spectral Data for Chapter 4





Appendix D: GC & HPLC Trace Data for Chapter 4

```
Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-13 13-58-01\KSB-VI-139-120ISO60.D
Sample Name: KSB-VI-139-120ISO60

    ======================================================================
    Acq. Operator    : KSB                              Seq. Line :   2
    Acq. Instrument : 6850GC                             Location : Vial 10
    Injection Date  : 13-Sep-12, 14:13:23                    Inj :   1
                                                       Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-13 13-58-01\120ISO60.M
    Last changed    : 9/7/2012 4:26:46 PM by KSB
    Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
    Last changed    : 12/17/2012 5:48:10 PM by KSB
                      (modified after loading)
```

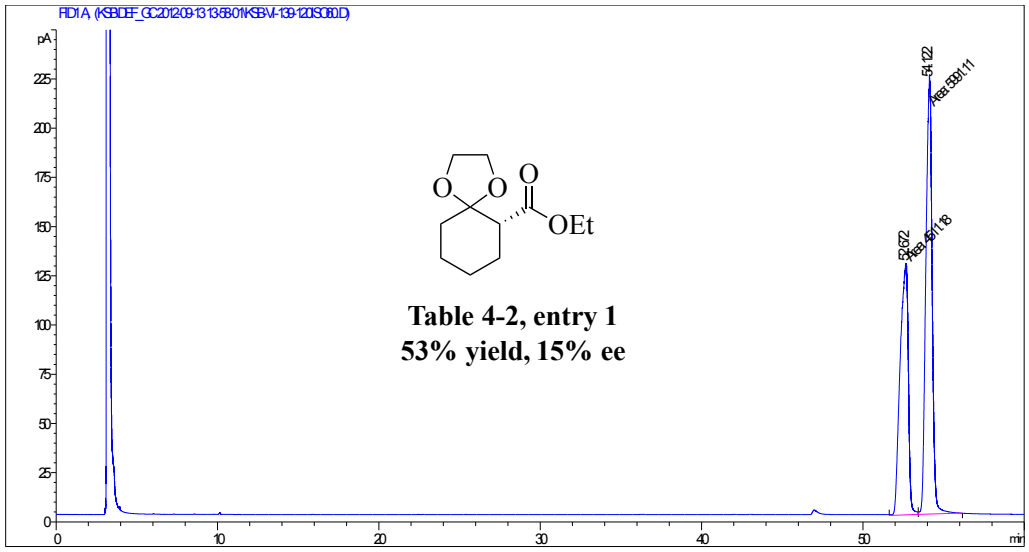


Table 4-2, entry 1
53% yield, 15% ee

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1  52.672 MF    0.5881 4511.18164  127.84280 42.95425
       2  54.122 FM    0.4474 5991.11279  223.19855 57.04575

    Totals :                  1.05023e4   351.04134

    ======================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-18 14-50-58\KSB-VI-149-120ISO60.D
Sample Name: KSB-VI-149-120ISO60

```
==========================================================================
Acq. Operator   : KSB                              Seq. Line :   4
Acq. Instrument : 6850GC                          Location : Vial 9
Injection Date  : 18-Sep-12, 16:44:56                  Inj :   1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-18 14-50-58\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/21/2012 10:03:40 AM by KSB
                  (modified after loading)
```

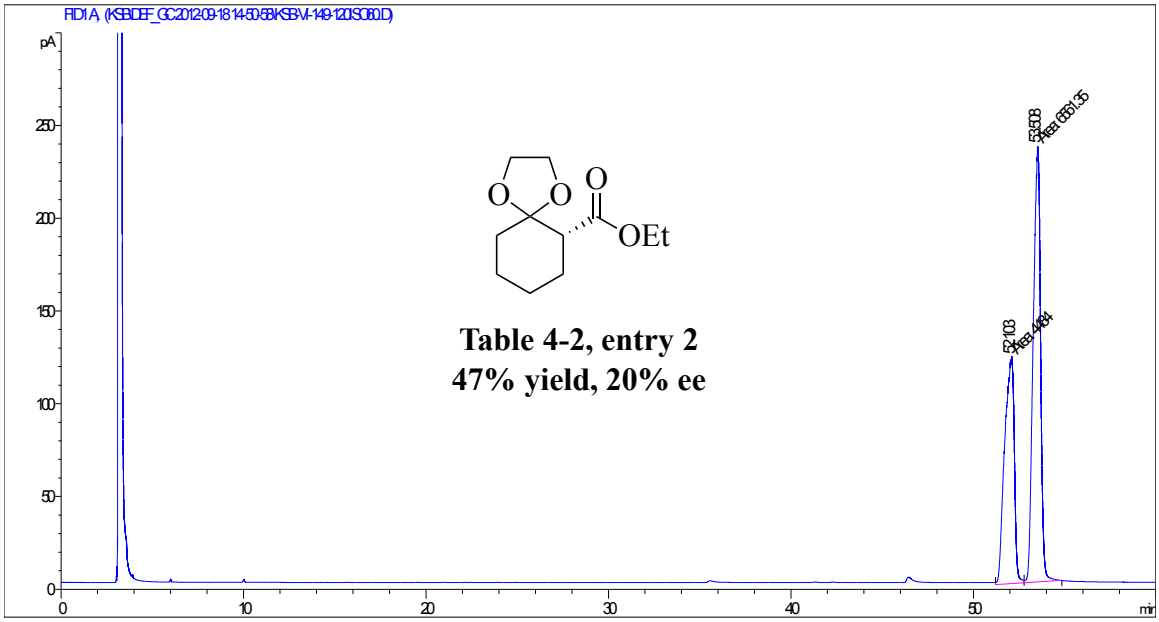


Table 4-2, entry 2
47% yield, 20% ee

```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  52.103 MF    0.6111 4484.00293  122.30215 40.59629
   2  53.508 FM    0.4648 6561.34863  235.27882 59.40371

Totals :                  1.10454e4   357.58097

==========================================================================
```

```
Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-18 14-50-58\KSB-VI-147-120ISO60.D
Sample Name: KSB-VI-147-120ISO60

    ======================================================================
    Acq. Operator    : KSB                              Seq. Line :   6
    Acq. Instrument : 6850GC                             Location : Vial 10
    Injection Date  : 18-Sep-12, 18:23:40                     Inj :   1
                                                        Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-18 14-50-58\120ISO60.M
    Last changed    : 9/7/2012 4:26:46 PM by KSB
    Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
    Last changed    : 12/21/2012 10:00:16 AM by KSB
                      (modified after loading)
```

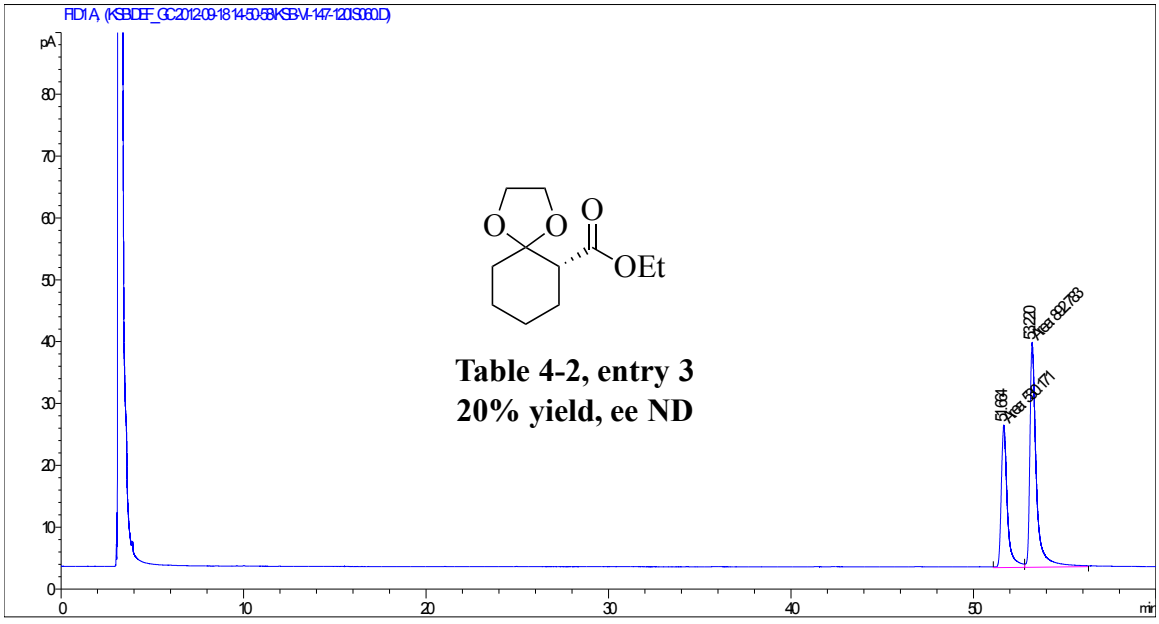


Table 4-2, entry 3
20% yield, ee ND

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]       [min]   [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1  51.664 MF    0.3835  530.17065   23.03972 37.25846
       2  53.220 FM    0.4098  892.78326   36.31116 62.74154

    Totals :                  1422.95392   59.35088

    ======================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-15 16-32-28\KSB-VI-141-120ISO60.D
Sample Name: KSB-VI-141-120ISO60

```
==========================================================================
Acq. Operator   : KSB                              Seq. Line :   6
Acq. Instrument : 6850GC                          Location : Vial 10
Injection Date  : 15-Sep-12, 20:05:15                  Inj :   1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-15 16-32-28\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/18/2012 5:26:21 PM by KSB
                  (modified after loading)
```

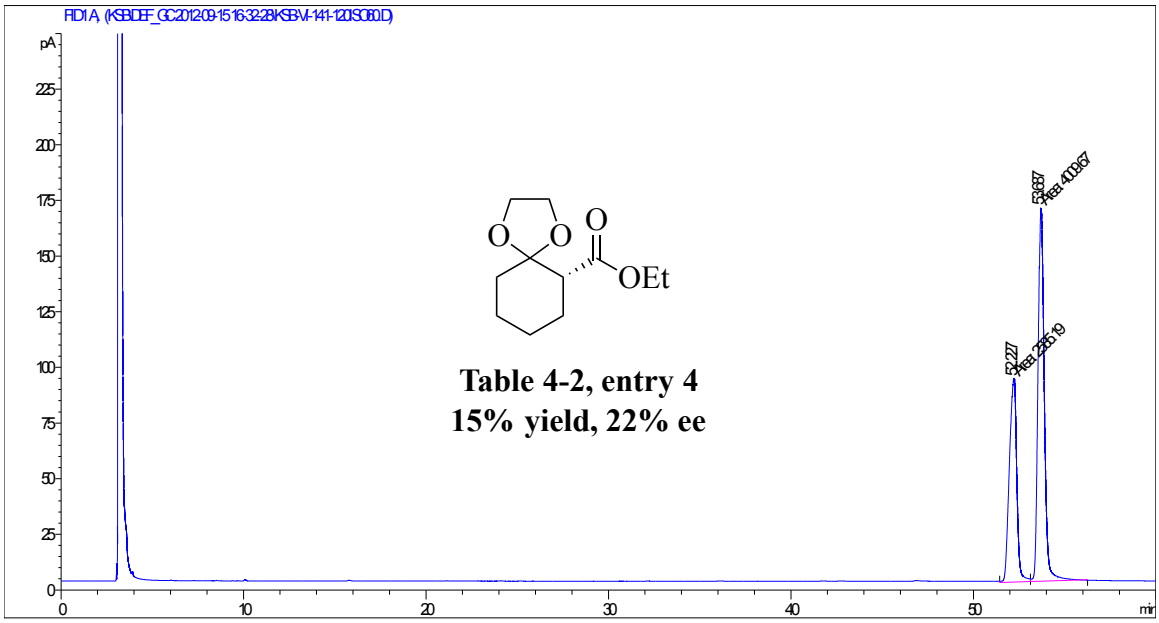
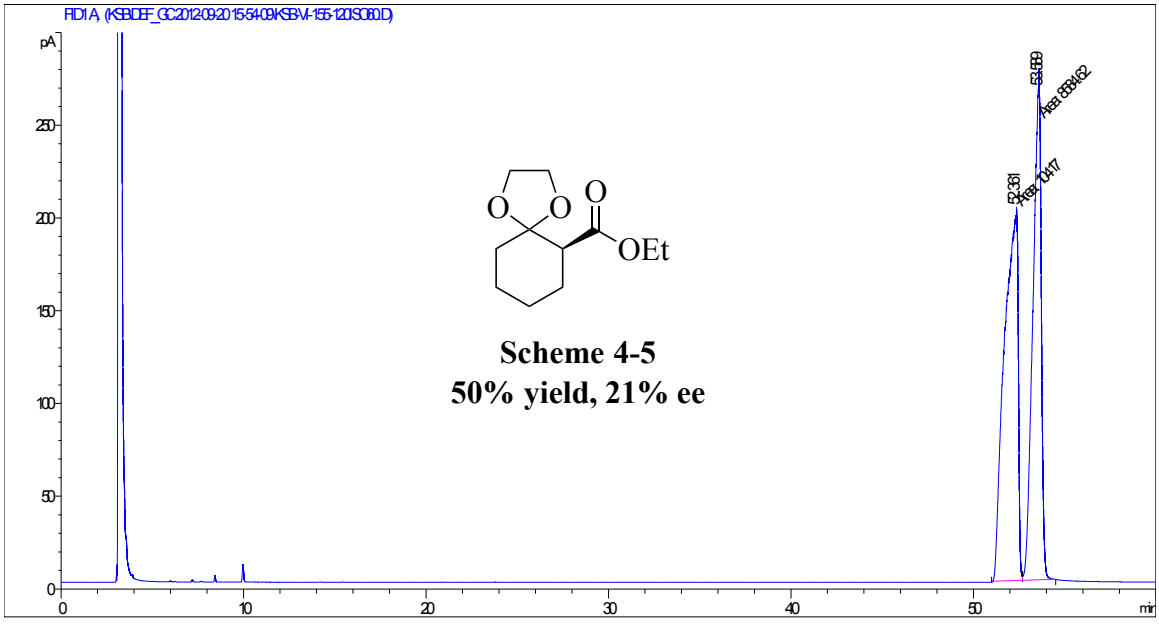


Table 4-2, entry 4
15% yield, 22% ee

```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  52.227 MF    0.4707 2585.18921   91.54167 39.20005
   2  53.687 FM    0.3982 4009.67212  167.80476 60.79995

Totals :                  6594.86133  259.34644

==========================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-20 15-54-09\KSB-VI-155-120ISO60.D
Sample Name: KSB-VI-155-120ISO60

```
==========================================================================
Acq. Operator    : KSB                              Seq. Line :   4
Acq. Instrument : 6850GC                             Location : Vial 10
Injection Date  : 20-Sep-12, 17:48:13                     Inj :   1
                                                   Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-20 15-54-09\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/21/2012 10:14:27 AM by KSB
                  (modified after loading)
```



Scheme 4-5
50% yield, 21% ee

```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [pA*s]      [pA]        %
----|-------|----|-------|---------|----------|--------|
   1  52.361 MF    0.8651 1.04170e4   200.68242 54.82164
   2  53.589 FM    0.5190 8584.61621  275.69913 45.17836

Totals :                  1.90016e4   476.38155

==========================================================================
```

```
Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-23 14-24-43\KSB-VI-154-120ISO60.D
Sample Name: KSB-VI-154-120ISO60

    ======================================================================
    Acq. Operator   : KSB                              Seq. Line :   2
    Acq. Instrument : 6850GC                          Location : Vial 11
    Injection Date  : 23-Sep-12, 14:40:06                  Inj :   1
                                                     Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-23 14-24-43\120ISO60.M
    Last changed    : 9/7/2012 4:26:46 PM by KSB
    Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
    Last changed    : 12/21/2012 12:48:27 PM by KSB
                      (modified after loading)
```

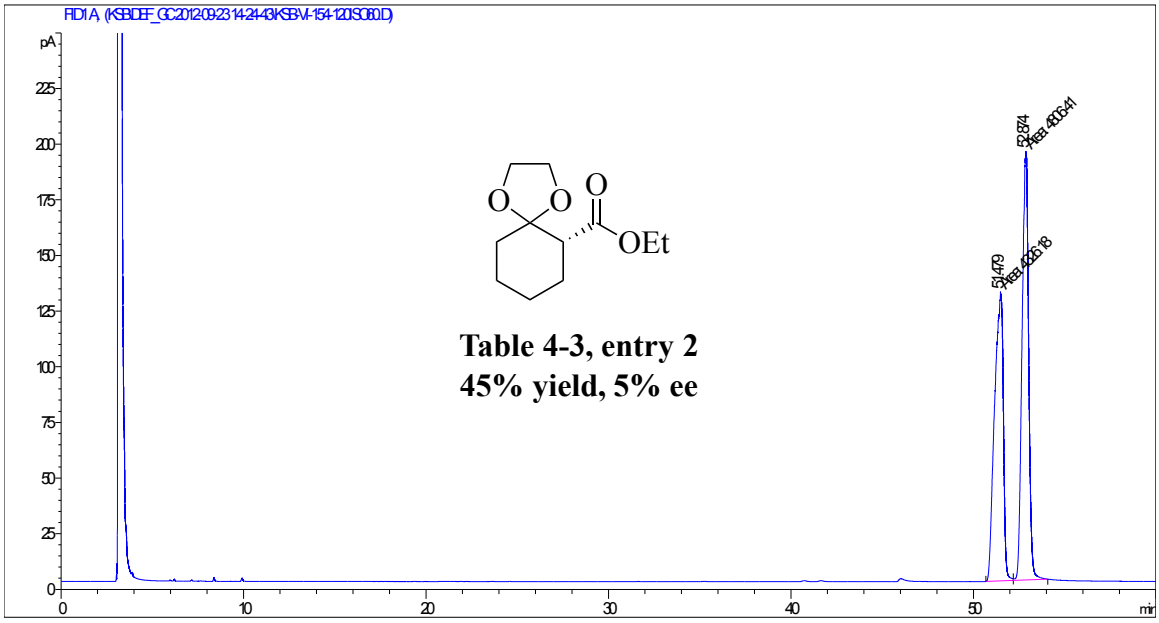


Table 4-3, entry 2
45% yield, 5% ee

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1  51.479 MF    0.5553 4326.17773  129.84593 47.37078
       2  52.874 FM    0.4159 4806.40869  192.63336 52.62922

    Totals :                  9132.58643  322.47929

    ======================================================================
```

```
Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-18 14-50-58\KSB-VI-150-120ISO60.D
Sample Name: KSB-VI-150-120ISO60

    ======================================================================
    Acq. Operator   : KSB                              Seq. Line :   2
    Acq. Instrument : 6850GC                          Location : Vial 8
    Injection Date  : 18-Sep-12, 15:06:16                   Inj :   1
                                                     Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-18 14-50-58\120ISO60.M
    Last changed    : 9/7/2012 4:26:46 PM by KSB
    Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
    Last changed    : 12/21/2012 10:06:25 AM by KSB
                      (modified after loading)
```

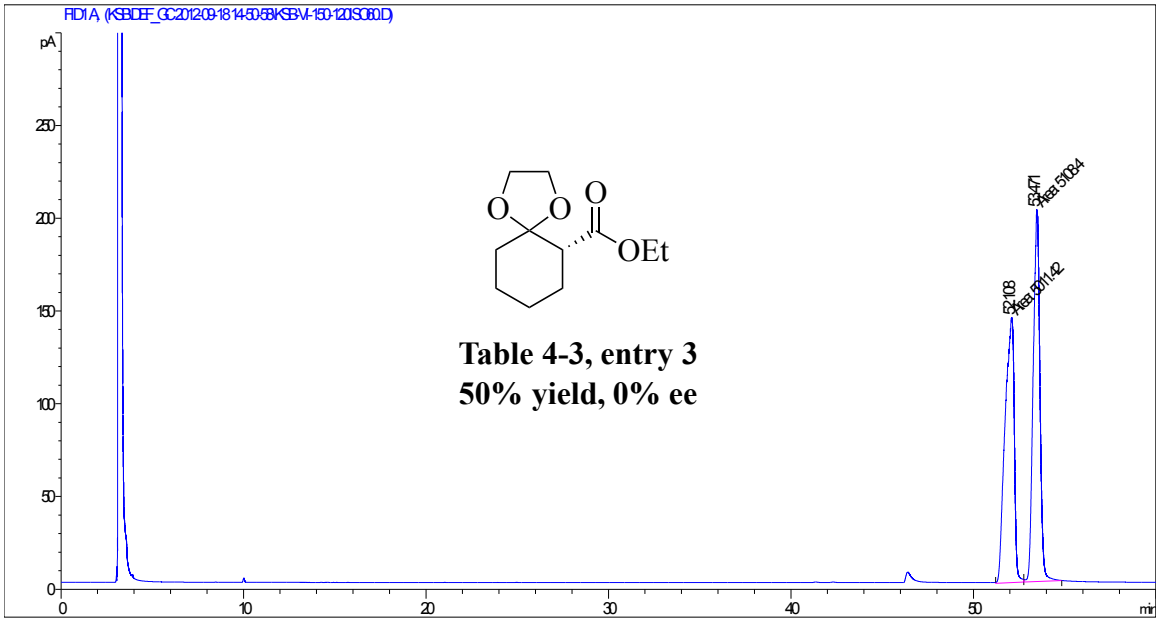


Table 4-3, entry 3
50% yield, 0% ee

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1  52.108 MF    0.5844 5011.41797  142.91930 49.52083
       2  53.471 FM    0.4252 5108.39990  200.25706 50.47917

    Totals :                  1.01198e4   343.17636

    ======================================================================
```

```
Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-23 14-24-43\KSB-VI-157-120ISO60.D
Sample Name: KSB-VI-157-120ISO60

    ======================================================================
    Acq. Operator   : KSB                              Seq. Line :   4
    Acq. Instrument : 6850GC                          Location : Vial 12
    Injection Date  : 23-Sep-12, 16:18:50                  Inj :   1
                                                     Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-23 14-24-43\120ISO60.M
    Last changed    : 9/7/2012 4:26:46 PM by KSB
    Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
    Last changed    : 12/21/2012 12:51:40 PM by KSB
                      (modified after loading)
```

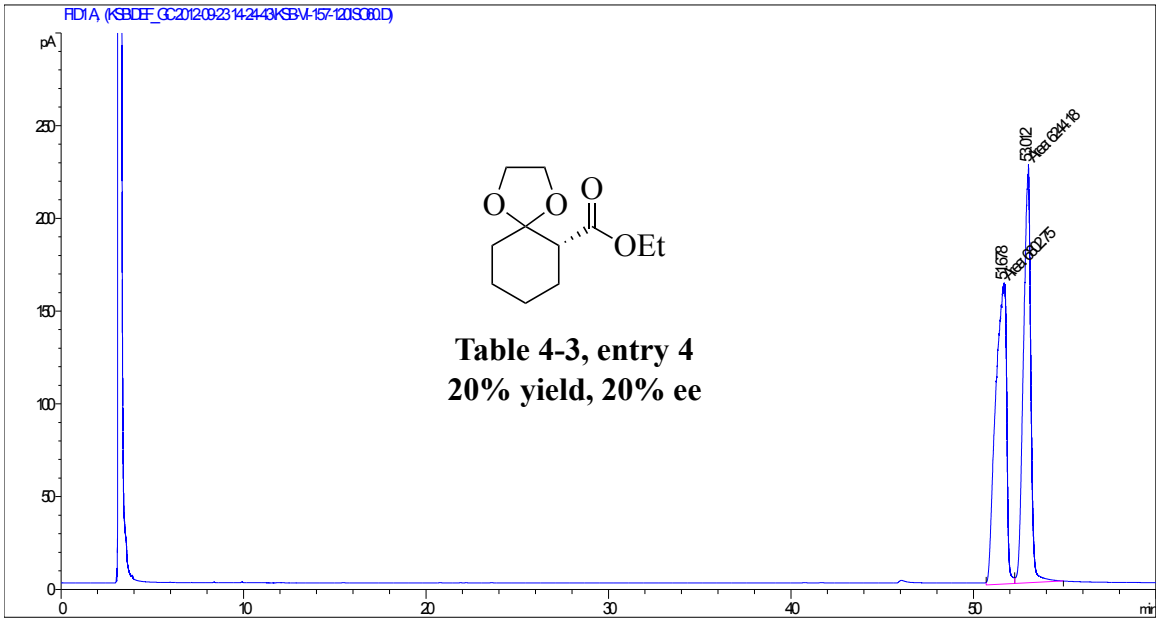


Table 4-3, entry 4
20% yield, 20% ee

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1  51.678 MF    0.6983 6802.75244  162.35379 52.14061
       2  53.012 FM    0.4614 6244.18359  225.54286 47.85939

    Totals :                  1.30469e4   387.89665

    ======================================================================
```

```
Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-15 16-32-28\KSB-VI-143-120ISO60.D
Sample Name: KSB-VI-143-120ISO60

    ======================================================================
    Acq. Operator    : KSB                              Seq. Line :   4
    Acq. Instrument : 6850GC                             Location : Vial 9
    Injection Date  : 15-Sep-12, 18:26:30                     Inj :   1
                                                        Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-15 16-32-28\120ISO60.M
    Last changed    : 9/7/2012 4:26:46 PM by KSB
    Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
    Last changed    : 12/18/2012 5:30:11 PM by KSB
                      (modified after loading)
```

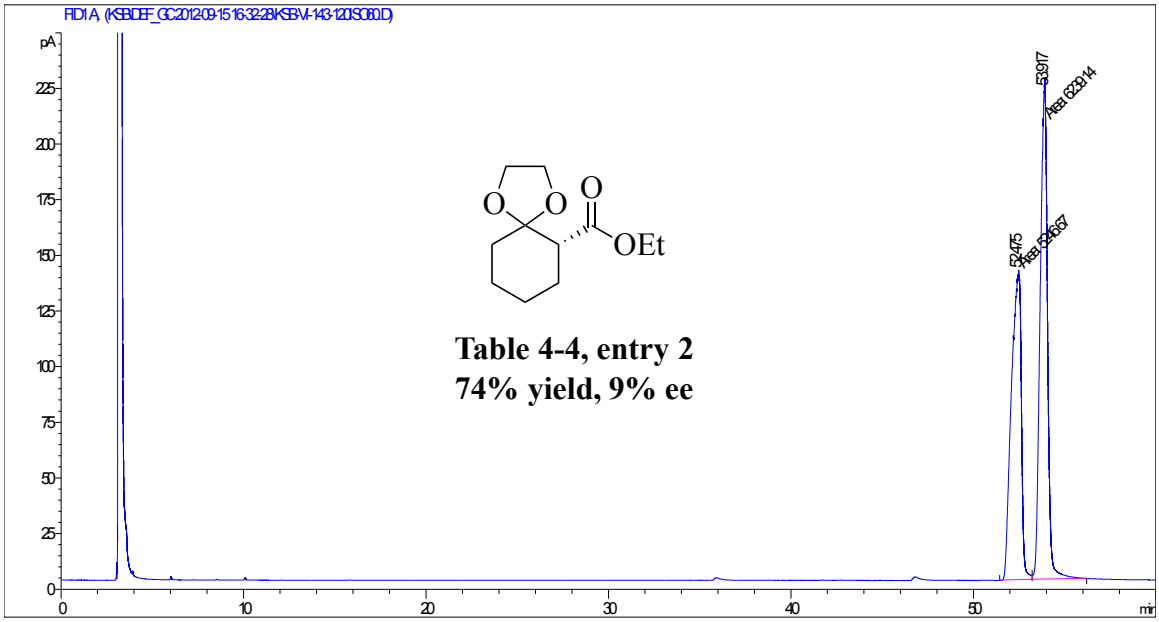


Table 4-4, entry 2
74% yield, 9% ee

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]       [min]   [pA*s]      [pA]         %
    ----|-------|----|-------|----------|----------|--------|
       1  52.475 MF    0.6304 5246.67285  138.70439 45.67959
       2  53.917 FM    0.4611 6239.14063  225.50307 54.32041

    Totals :                  1.14858e4   364.20746

    ======================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-24 14-23-22\KSB-VI-159-120ISO60.D
Sample Name: KSB-VI-159-120ISO60

```
==========================================================================
Acq. Operator   : KSB                              Seq. Line :   4
Acq. Instrument : 6850GC                          Location : Vial 8
Injection Date  : 24-Sep-12, 16:17:18                  Inj :   1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-24 14-23-22\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/21/2012 12:57:30 PM by KSB
                  (modified after loading)
```

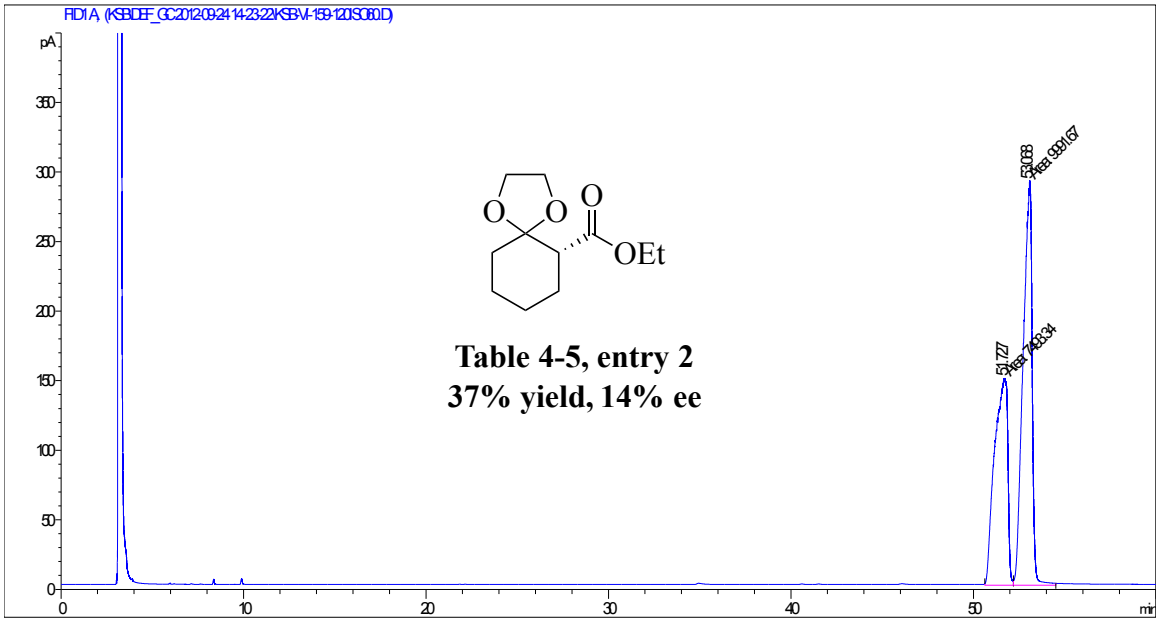


Table 4-5, entry 2
37% yield, 14% ee

```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  51.727 MF    0.8400 7493.34473  148.67274 42.85580
   2  53.068 FM    0.5738 9991.67480  290.22382 57.14420

Totals :                  1.74850e4   438.89656

==========================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-24 18-26-43\KSB-VI-160-120ISO60.D
Sample Name: KSB-VI-160-120ISO60

```
==========================================================================
Acq. Operator   : KSB                              Seq. Line :   2
Acq. Instrument : 6850GC                            Location : Vial 9
Injection Date  : 24-Sep-12, 18:41:57                    Inj :   1
                                                   Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-24 18-26-43\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/21/2012 1:00:04 PM by KSB
                  (modified after loading)
```

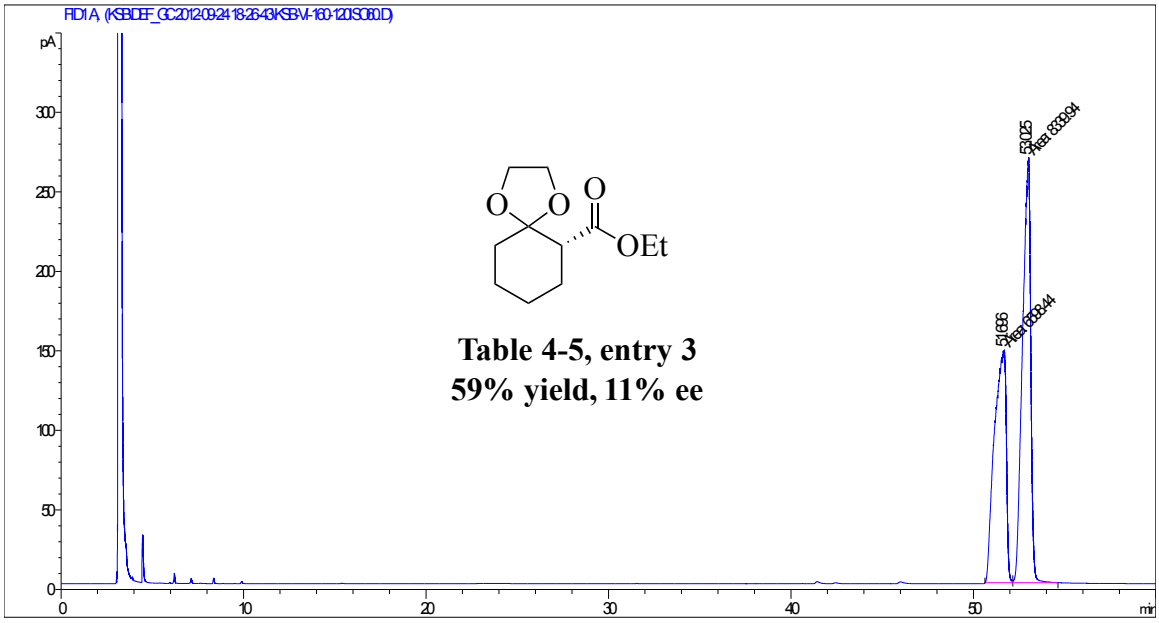


Table 4-5, entry 3
59% yield, 11% ee

```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  51.696 MF    0.7511 6598.44385  146.41844 44.17106
   2  53.025 FM    0.5202 8339.94336  267.18445 55.82894

Totals :                  1.49384e4   413.60289

==========================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-27 16-34-54\KSB-VI-169-120ISO60.D
Sample Name: KSB-VI-169-120ISO60

```
==========================================================================
Acq. Operator   : KSB                              Seq. Line :   2
Acq. Instrument : 6850GC                          Location : Vial 7
Injection Date  : 27-Sep-12, 16:50:18                  Inj :   1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-27 16-34-54\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/21/2012 1:17:20 PM by KSB
                  (modified after loading)
```

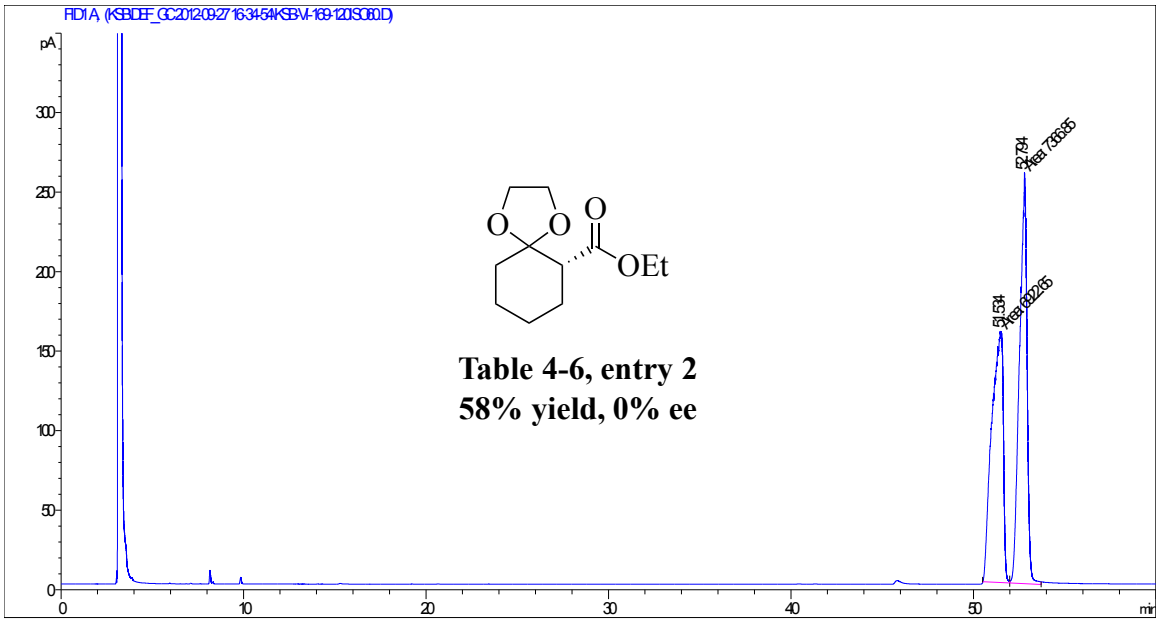


Table 4-6, entry 2
58% yield, 0% ee

```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  51.534 MF    0.7294 6922.65234  158.19110 48.44571
   2  52.794 FM    0.4756 7366.85449  258.18121 51.55429

Totals :                  1.42895e4   416.37231

==========================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-20 15-54-09\KSB-VI-156-120ISO60.D
Sample Name: KSB-VI-156-120ISO60

```
==========================================================================
Acq. Operator   : KSB                              Seq. Line :   2
Acq. Instrument : 6850GC                            Location : Vial 9
Injection Date  : 20-Sep-12, 16:09:32                    Inj :   1
                                                   Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-20 15-54-09\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/21/2012 10:17:39 AM by KSB
                  (modified after loading)
```

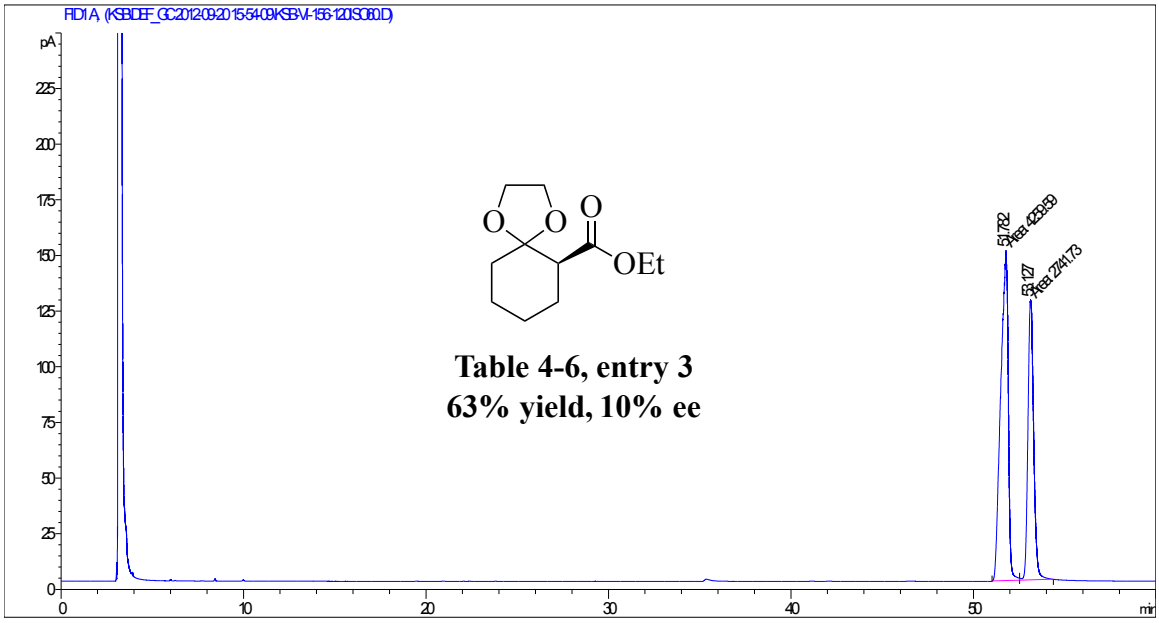


Table 4-6, entry 3
63% yield, 10% ee

```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  51.782 MF    0.4775 4259.59229  148.67659 60.83982
   2  53.127 FM    0.3634 2741.73047  125.74683 39.16018

Totals :                  7001.32275  274.42342


==========================================================================
```

```
Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-12 15-29-08\KSB-VI-138-120ISO60.D
Sample Name: KSB-VI-138-120ISO60

    ======================================================================
    Acq. Operator    : KSB                              Seq. Line :   4
    Acq. Instrument : 6850GC                             Location : Vial 9
    Injection Date  : 12-Sep-12, 17:23:03                     Inj :   1
                                                       Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-12 15-29-08\120ISO60.M
    Last changed    : 9/7/2012 4:26:46 PM by KSB
    Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
    Last changed    : 12/21/2012 1:41:25 PM by KSB
                      (modified after loading)
```

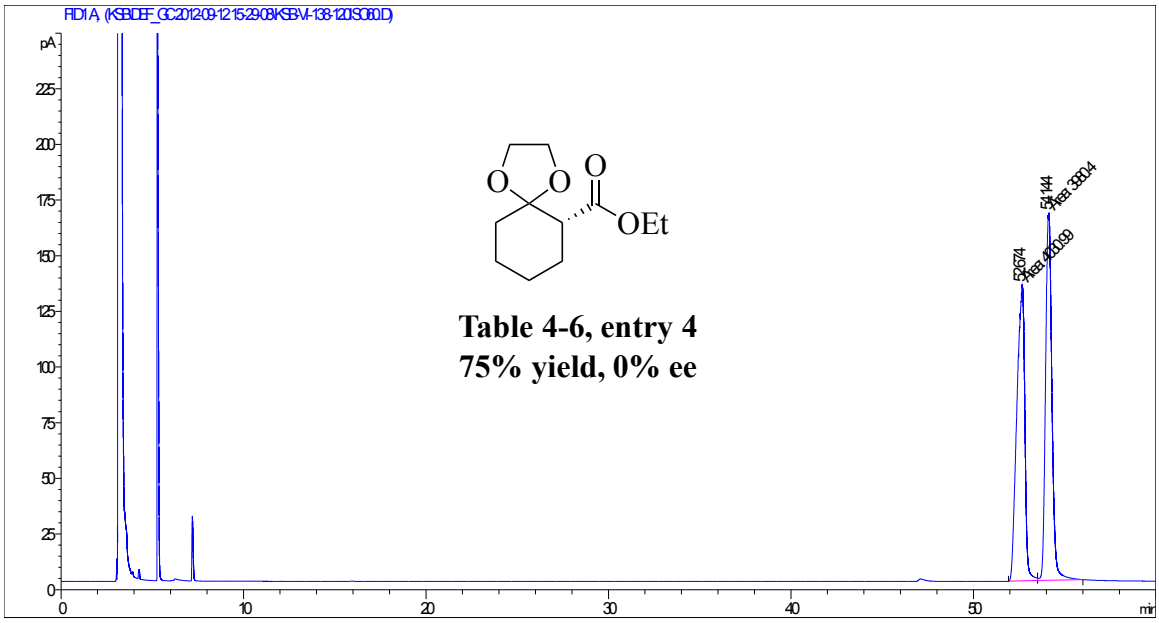


Table 4-6, entry 4
75% yield, 0% ee

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [pA*s]      [pA]         %
    ----|-------|----|-------|----------|----------|--------|
       1  52.674 MF    0.5051 4030.98950  133.01140 50.31572
       2  54.144 FM    0.4019 3980.40210  165.06123 49.68428

    Totals :                  8011.39160  298.07263

    ======================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-13 13-58-01\KSB-VI-140-120ISO60.D
Sample Name: KSB-VI-140-120ISO60

```
==========================================================================
Acq. Operator   : KSB                          Seq. Line :   4
Acq. Instrument : 6850GC                        Location : Vial 11
Injection Date  : 13-Sep-12, 15:52:18              Inj :   1
                                                Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-13 13-58-01\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/17/2012 5:00:04 PM by KSB
                  (modified after loading)
```

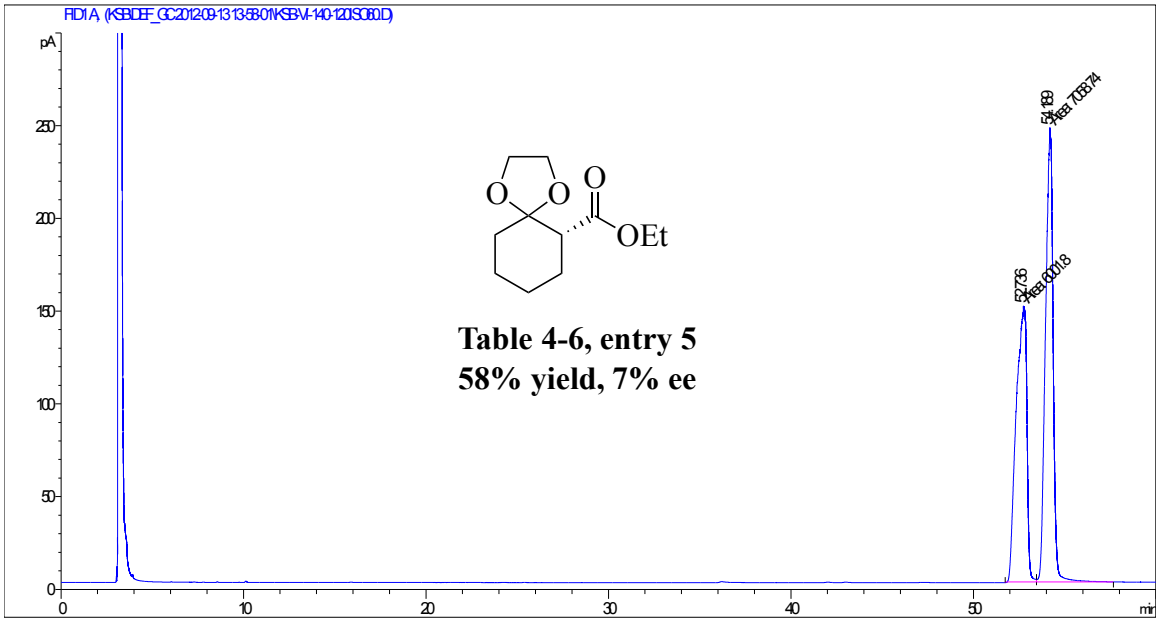


Table 4-6, entry 5
58% yield, 7% ee

```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  52.736 MF    0.6718 6001.79639  148.88988 45.95369
   2  54.189 FM    0.4803 7058.73584  244.92209 54.04631

Totals :                  1.30605e4   393.81197

==========================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-24 18-26-43\KSB-VI-161-120ISO60.D
Sample Name: KSB-VI-161-120ISO60

```
==========================================================================
Acq. Operator   : KSB                              Seq. Line :   4
Acq. Instrument : 6850GC                          Location : Vial 10
Injection Date  : 24-Sep-12, 20:20:47                  Inj :   1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-24 18-26-43\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/21/2012 1:02:53 PM by KSB
                  (modified after loading)
```

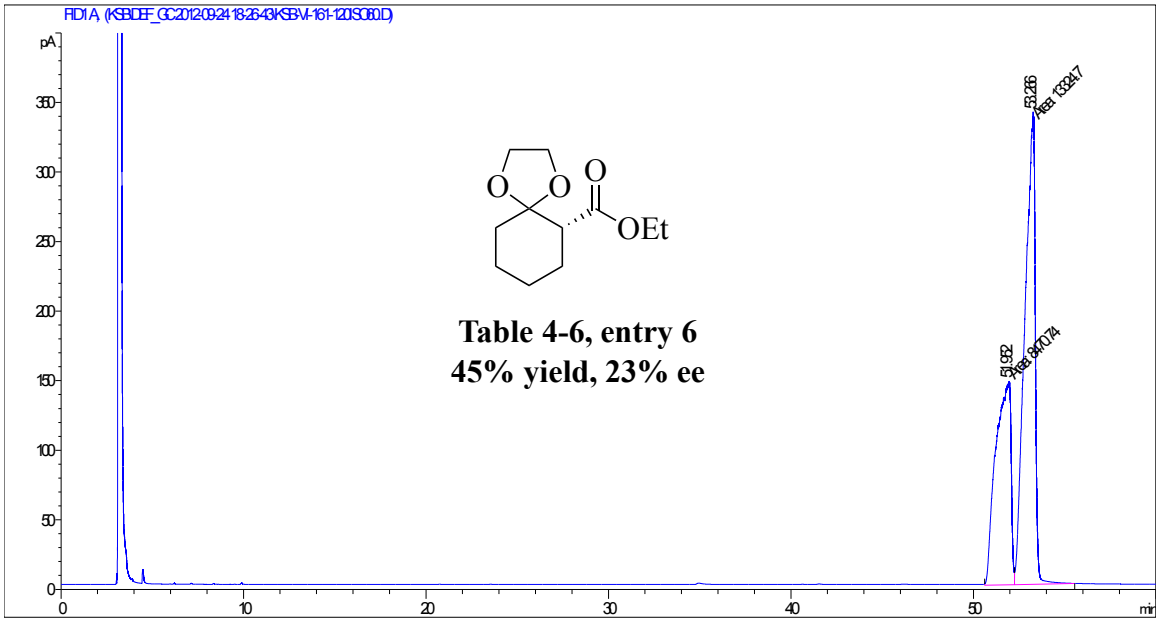


Table 4-6, entry 6
45% yield, 23% ee

```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  51.952 MF    0.9652 8470.74023  146.27652 38.86480
   2  53.266 FM    0.6543 1.33247e4   339.43405 61.13520

Totals :                  2.17954e4   485.71057

==========================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-19 18-06-26\KSB-VI-152-120ISO60.D
Sample Name: KSB-VI-152-120ISO60

```
==========================================================================
Acq. Operator    : KSB                              Seq. Line :    4
Acq. Instrument : 6850GC                             Location : Vial 8
Injection Date  : 19-Sep-12, 20:00:30                     Inj :    1
                                                   Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-19 18-06-26\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/21/2012 10:09:05 AM by KSB
                  (modified after loading)
```

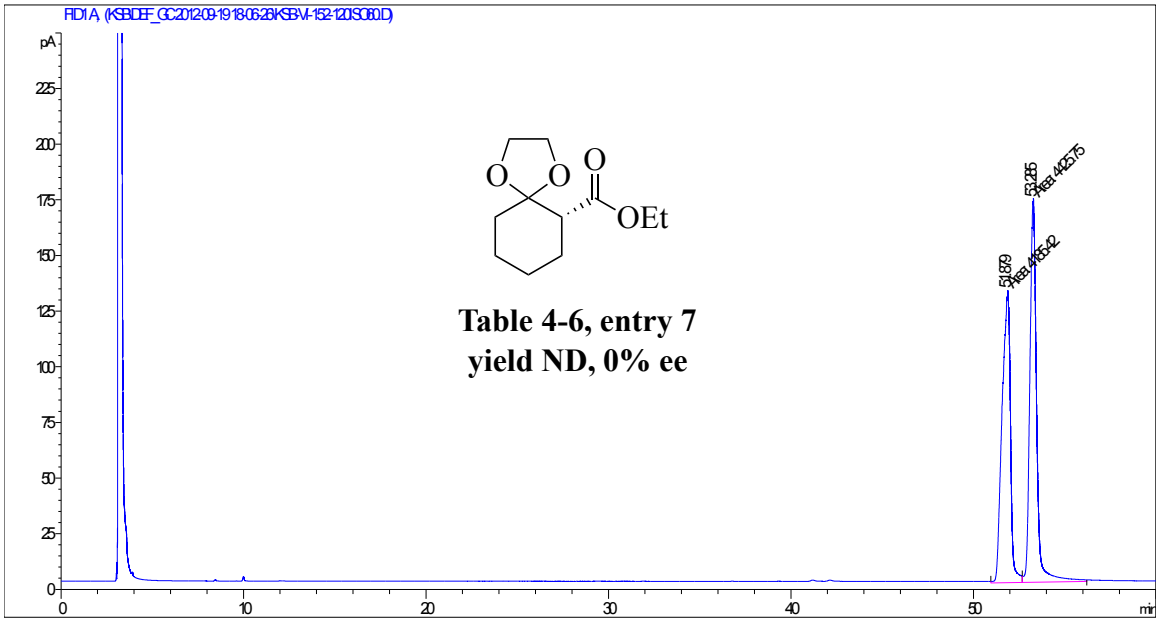


Table 4-6, entry 7
yield ND, 0% ee

```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1  51.879 MF    0.5322 4185.42432  131.06645 48.60455
   2  53.285 FM    0.4290 4425.75342  171.92226 51.39545

Totals :                  8611.17773  302.98871

==========================================================================
```

```
Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-19 18-06-26\KSB-VI-153-120ISO60.D
Sample Name: KSB-VI-153-120ISO60

    ========================================================================
    Acq. Operator    : KSB                              Seq. Line :   2
    Acq. Instrument : 6850GC                             Location : Vial 7
    Injection Date  : 19-Sep-12, 18:21:47                     Inj :   1
                                                       Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-19 18-06-26\120ISO60.M
    Last changed    : 9/7/2012 4:26:46 PM by KSB
    Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
    Last changed    : 12/21/2012 10:12:06 AM by KSB
                      (modified after loading)
```

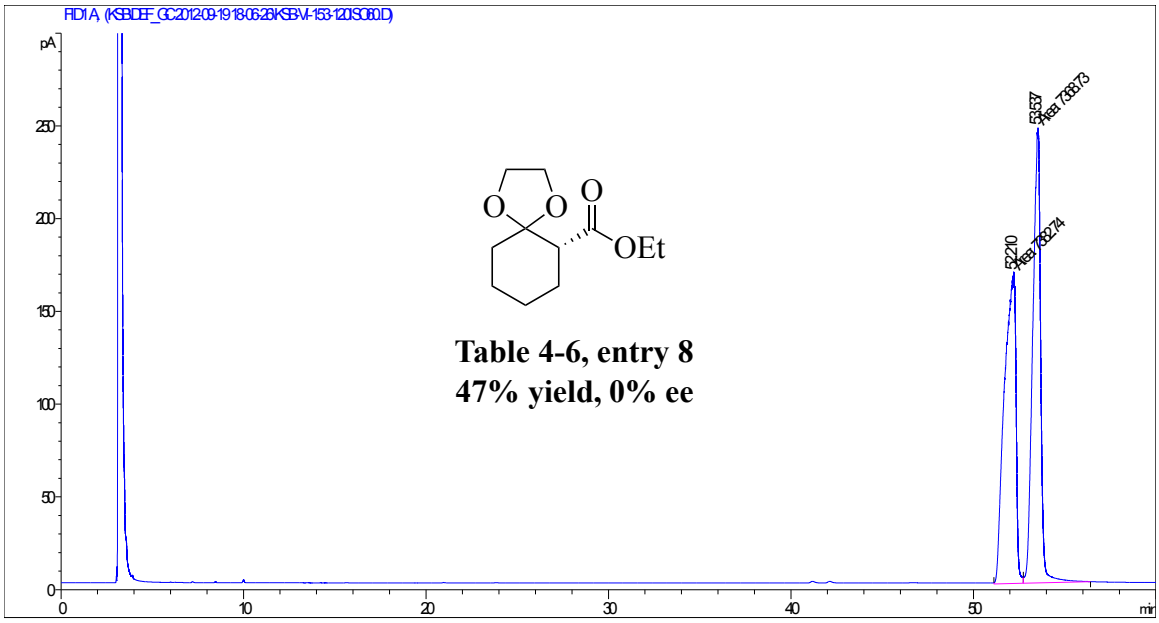


Table 4-6, entry 8
47% yield, 0% ee

```
    ========================================================================
                            Area Percent Report
    ========================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1  52.210 MF    0.7346 7382.74072  167.50327 50.04747
       2  53.537 FM    0.5008 7368.73438  245.24182 49.95253

    Totals :                  1.47515e4   412.74509

    ========================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-17 14-11-42\KSB-VI-145-120ISO60.D
Sample Name: KSB-VI-145-120ISO60

```
==========================================================================
Acq. Operator   : KSB                              Seq. Line :   2
Acq. Instrument : 6850GC                          Location : Vial 11
Injection Date  : 17-Sep-12, 14:27:07                  Inj :   1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-17 14-11-42\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/18/2012 5:37:41 PM by KSB
                  (modified after loading)
```

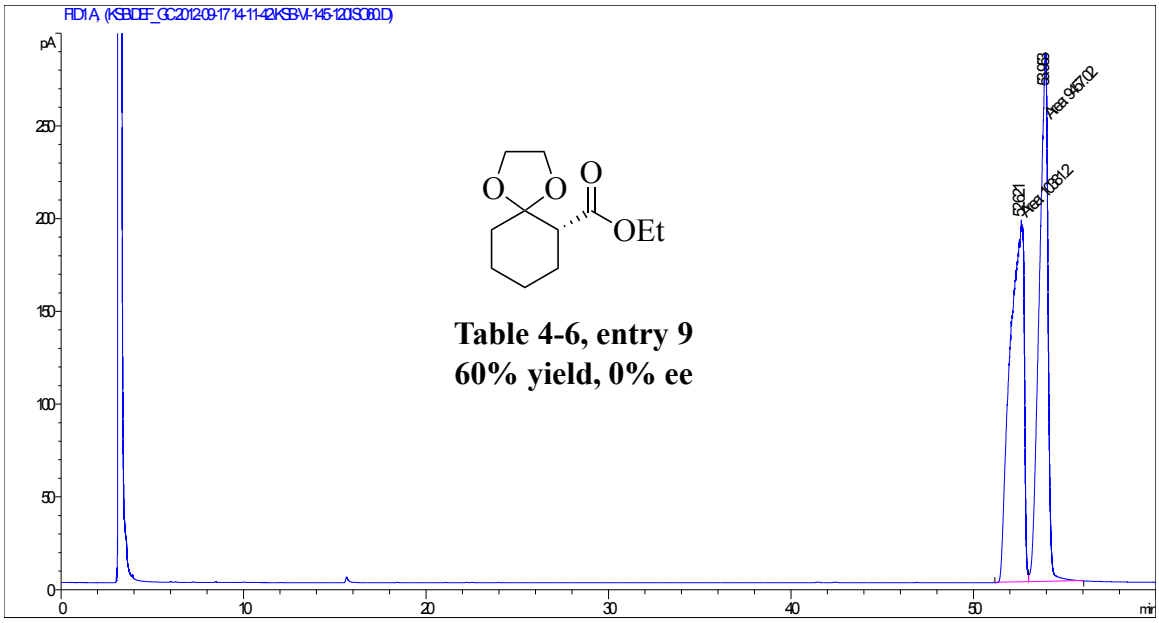


Table 4-6, entry 9
60% yield, 0% ee

```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [pA*s]       [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  52.621 MF    0.8864 1.03812e4   195.18536 52.32922
   2  53.953 FM    0.5541 9457.01563  284.47778 47.67078

Totals :                  1.98382e4   479.66315

==========================================================================
```

```
Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-17 14-11-42\KSB-VI-146-120ISO60.D
Sample Name: KSB-VI-146-120ISO60

    ======================================================================
    Acq. Operator   : KSB                              Seq. Line :   4
    Acq. Instrument : 6850GC                          Location : Vial 12
    Injection Date  : 17-Sep-12, 16:05:51                  Inj :   1
                                                     Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-17 14-11-42\120ISO60.M
    Last changed    : 9/7/2012 4:26:46 PM by KSB
    Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
    Last changed    : 12/18/2012 5:40:43 PM by KSB
                      (modified after loading)
```

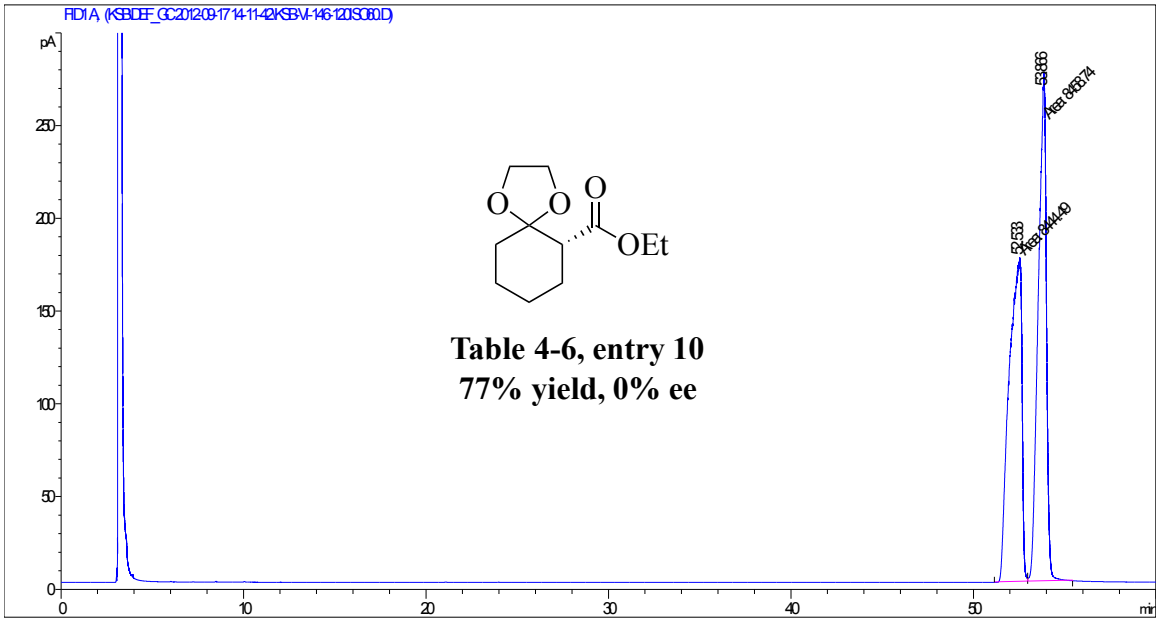


Table 4-6, entry 10
77% yield, 0% ee

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1  52.533 MF    0.8072 8444.48535  174.34886 49.95782
       2  53.866 FM    0.5142 8458.74414  274.18054 50.04218

    Totals :                  1.69032e4   448.52940

    ======================================================================
```

```
Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-26 18-57-10\KSB-VI-164-120ISO60.D
Sample Name: KSB-VI-164-120ISO60

    ======================================================================
    Acq. Operator    : KSB                              Seq. Line :   2
    Acq. Instrument : 6850GC                             Location : Vial 13
    Injection Date  : 26-Sep-12, 19:12:33                     Inj :   1
                                                       Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-26 18-57-10\120ISO60.M
    Last changed    : 9/7/2012 4:26:46 PM by KSB
    Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
    Last changed    : 12/21/2012 1:11:56 PM by KSB
                      (modified after loading)
```

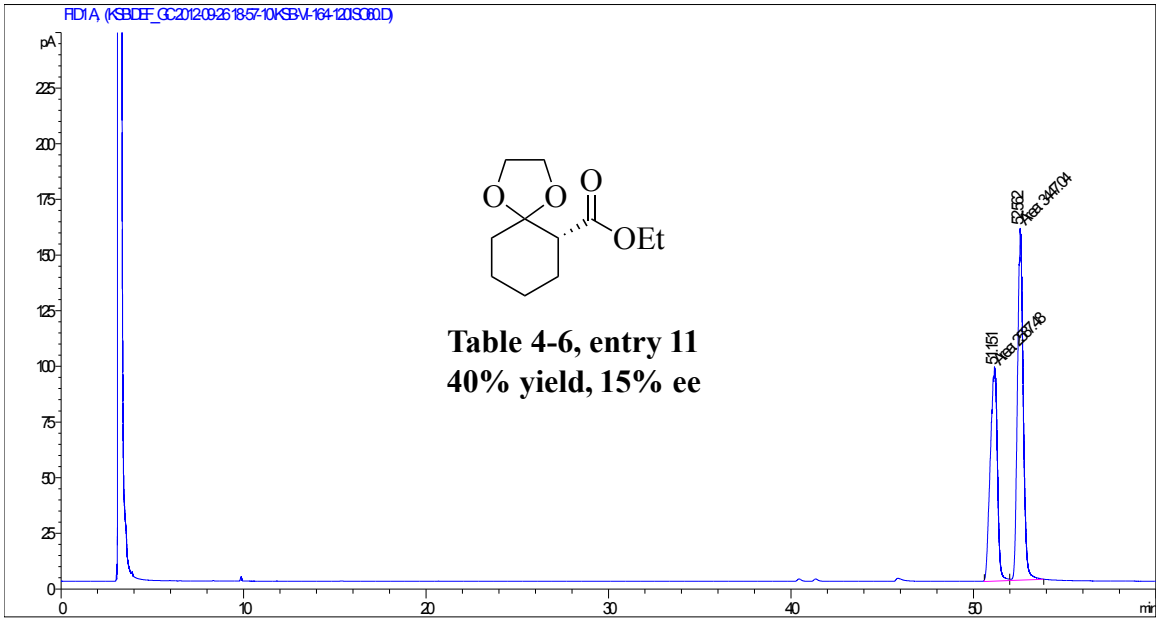


Table 4-6, entry 11
40% yield, 15% ee

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]       [min]   [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1  51.151 MF    0.4494 2587.48389   95.95895 42.87801
       2  52.562 FM    0.3632 3447.03979  158.17490 57.12199

    Totals :                  6034.52368  254.13385

    ======================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-10-01 16-17-14\KSB-VI-171-120ISO60.D
Sample Name: KSB-VI-171-120ISO60

```
==========================================================================
Acq. Operator   : KSB                              Seq. Line :   2
Acq. Instrument : 6850GC                          Location : Vial 10
Injection Date  : 01-Oct-12, 16:33:01                  Inj :   1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-10-01 16-17-14\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/21/2012 1:23:09 PM by KSB
                  (modified after loading)
```

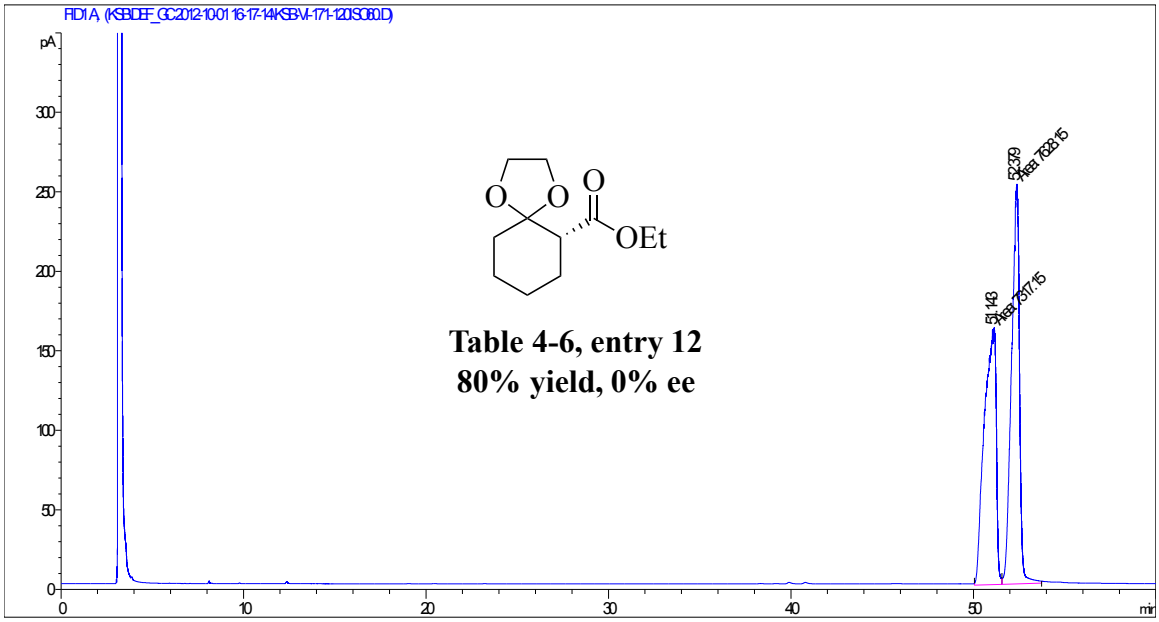


Table 4-6, entry 12
80% yield, 0% ee

```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  51.143 MF    0.7558 7317.14844  161.34979 48.95954
   2  52.379 FM    0.5056 7628.14844  251.47435 51.04046

Totals :                  1.49453e4   412.82414

==========================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-12-06 14-58-00\KSB-VI-222-120ISO60.D
Sample Name: KSB-VI-222-120ISO60

```
==========================================================================
Acq. Operator   : KSB                              Seq. Line :   4
Acq. Instrument : 6850GC                            Location : Vial 2
Injection Date  : 06-Dec-12, 17:15:30                    Inj :   1
                                                   Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-12-06 14-58-00\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/21/2012 1:28:09 PM by KSB
                  (modified after loading)
```

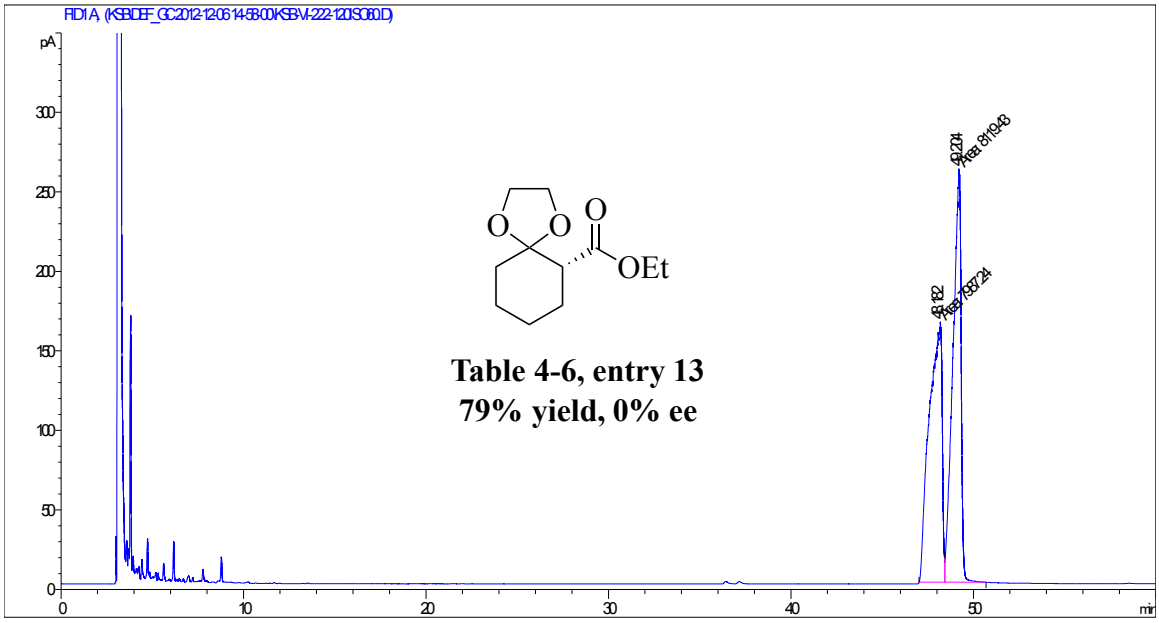


Table 4-6, entry 13
79% yield, 0% ee

```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  48.182 MF    0.8137 7987.23584  163.60860 49.58964
   2  49.204 FM    0.5210 8119.42529  259.74753 50.41036

Totals :                  1.61067e4   423.35612

==========================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-12-10 12-16-46\KSB-IV-226-120ISO60.D
Sample Name: KSB-IV-226-120ISO60

```
==========================================================================
Acq. Operator   : KSB                              Seq. Line :   2
Acq. Instrument : 6850GC                          Location : Vial 3
Injection Date  : 10-Dec-12, 12:35:25                   Inj :   1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-12-10 12-16-46\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/21/2012 1:31:35 PM by KSB
                  (modified after loading)
```

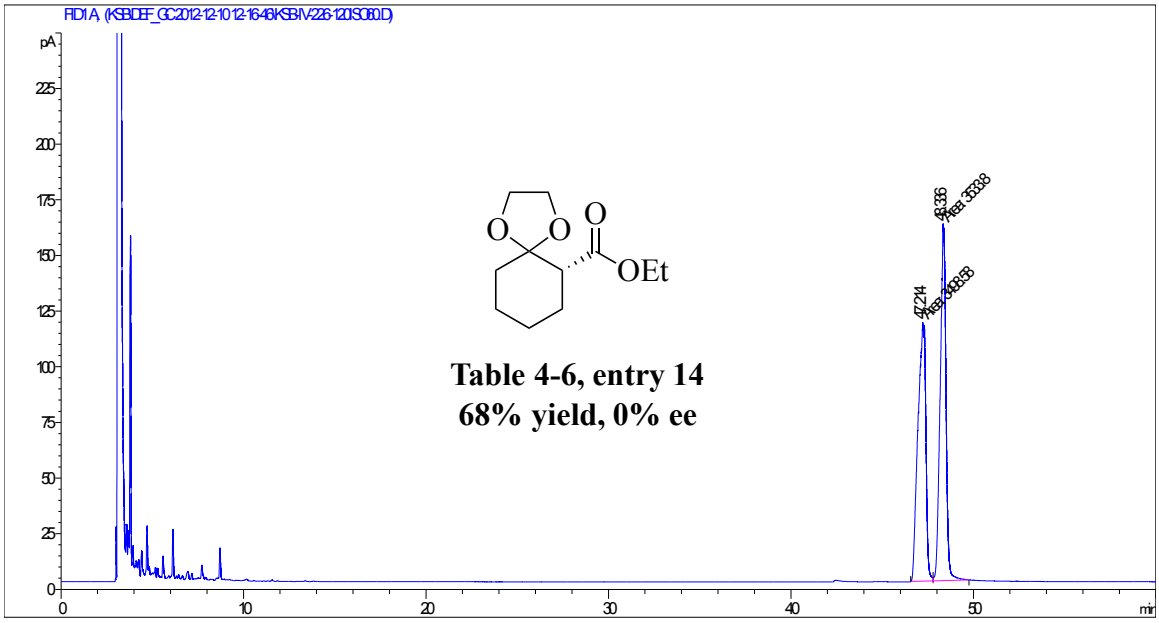


Table 4-6, entry 14
68% yield, 0% ee

```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  47.214 MF    0.5008 3498.57642  116.42377 49.74959
   2  48.336 FM    0.3678 3533.79614  160.14668 50.25041

Totals :                  7032.37256  276.57046

==========================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-26 18-57-10\KSB-VI-165-120ISO60.D
Sample Name: KSB-VI-165-120ISO60

```
    ======================================================================
    Acq. Operator    : KSB                              Seq. Line :   4
    Acq. Instrument  : 6850GC                            Location : Vial 14
    Injection Date   : 26-Sep-12, 20:51:24                    Inj :   1
                                                       Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method      : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-09-26 18-57-10\120ISO60.M
    Last changed     : 9/7/2012 4:26:46 PM by KSB
    Analysis Method  : C:\CHEM32\1\METHODS\BAKE10.M
    Last changed     : 12/21/2012 1:14:15 PM by KSB
                       (modified after loading)
```

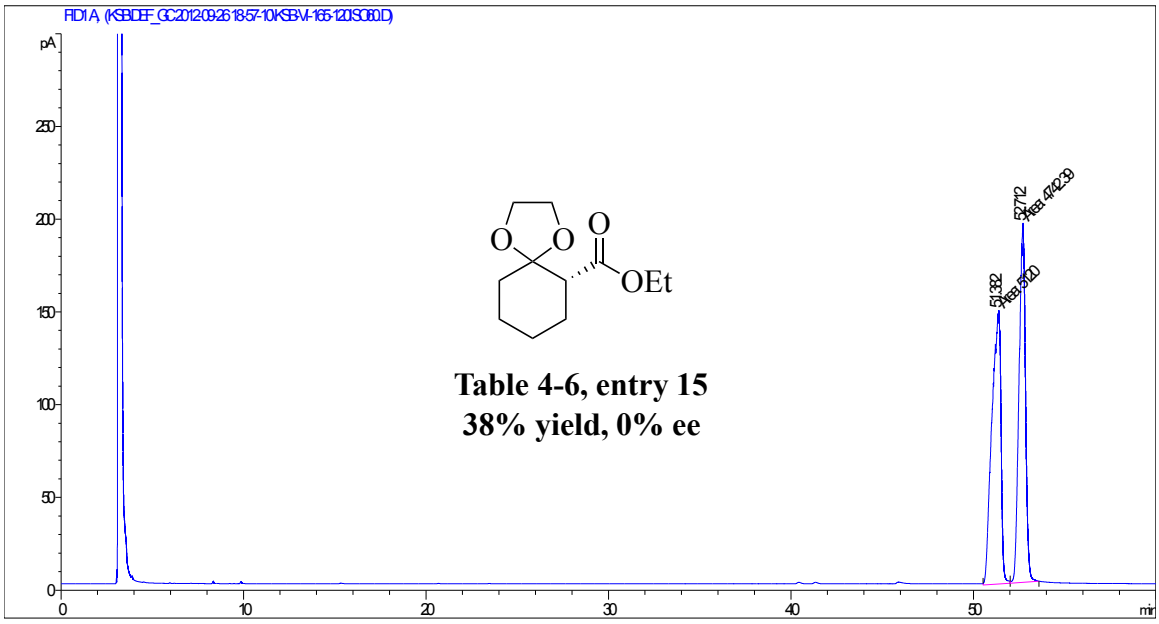


Table 4-6, entry 15
38% yield, 0% ee

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]       [min]   [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1  51.382 MF    0.5790 5120.00293  147.38757 51.91441
       2  52.712 FM    0.4090 4742.38916  193.25851 48.08559

    Totals :                  9862.39209  340.64609

    ======================================================================
```

```
Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-12-06 14-58-00\KSB-VI-221-120ISO60.D
Sample Name: KSB-VI-221-120ISO60

    ======================================================================
    Acq. Operator    : KSB                              Seq. Line :   2
    Acq. Instrument : 6850GC                             Location : Vial 1
    Injection Date  : 06-Dec-12, 15:36:46                     Inj :   1
                                                       Inj Volume : 1 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
    Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-12-06 14-58-00\120ISO60.M
    Last changed    : 9/7/2012 4:26:46 PM by KSB
    Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
    Last changed    : 12/21/2012 1:25:52 PM by KSB
                      (modified after loading)
```

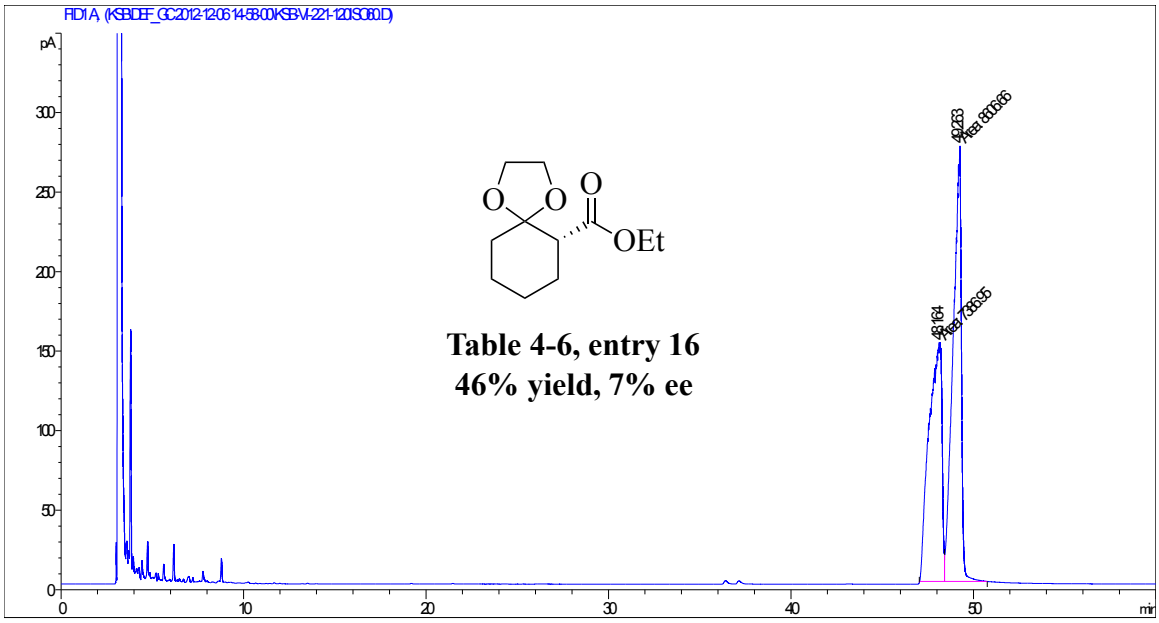


Table 4-6, entry 16
46% yield, 7% ee

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: FID1 A,

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [pA*s]      [pA]        %
    ----|-------|----|-------|----------|----------|--------|
       1  48.164 MF    0.8204 7386.94824  150.07468 46.18689
       2  49.263 FM    0.5235 8606.65625  274.01944 53.81311

    Totals :                  1.59936e4   424.09412

    ======================================================================
```

Data File C:\CHEM32\1\DATA\KSB\DEF_GC 2012-12-10 12-16-46\KSB-VI-227-120ISO60.D
Sample Name: KSB-VI-227-120ISO60

```
==========================================================================
Acq. Operator   : KSB                              Seq. Line :   4
Acq. Instrument : 6850GC                          Location : Vial 4
Injection Date  : 10-Dec-12, 14:14:10                  Inj :   1
                                                  Inj Volume : 1 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5 µl
Acq. Method     : C:\CHEM32\1\DATA\KSB\DEF_GC 2012-12-10 12-16-46\120ISO60.M
Last changed    : 9/7/2012 4:26:46 PM by KSB
Analysis Method : C:\CHEM32\1\METHODS\BAKE10.M
Last changed    : 12/21/2012 1:33:29 PM by KSB
                  (modified after loading)
```

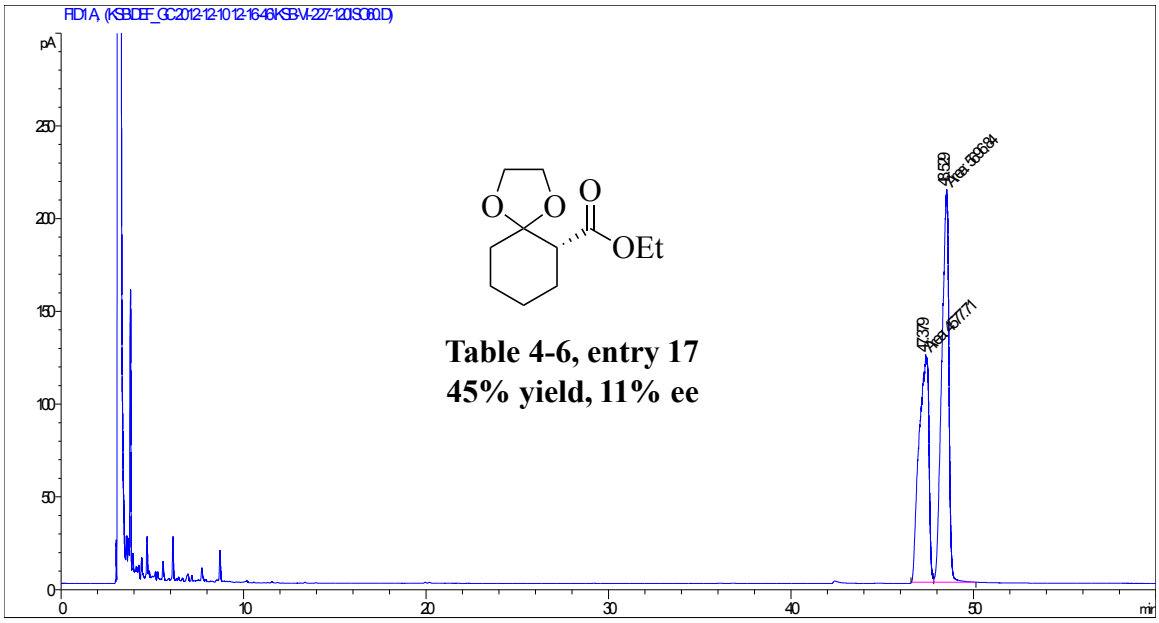
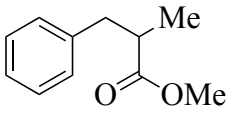


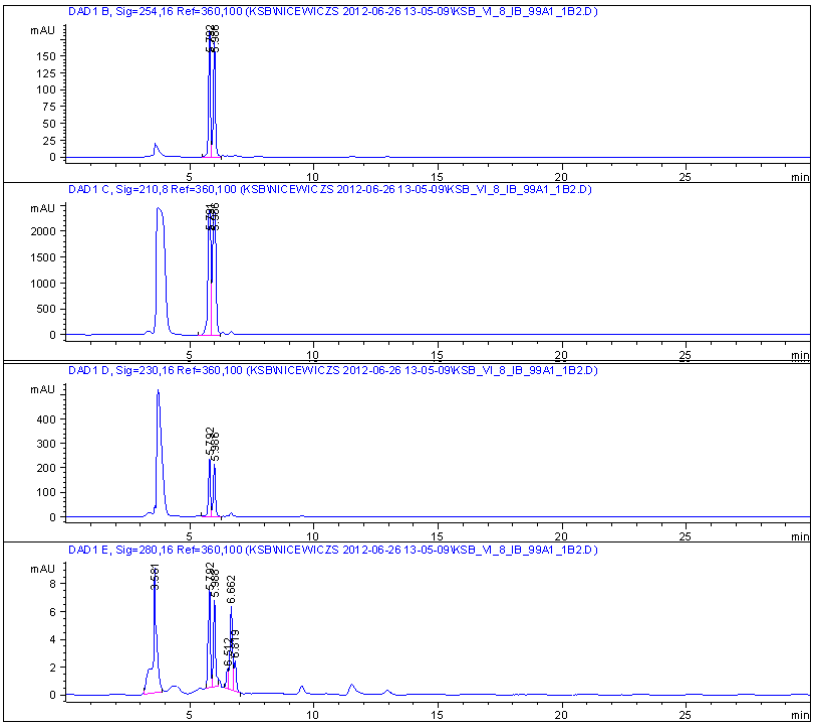
Table 4-6, entry 17
45% yield, 11% ee

```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  47.379 MF    0.6225 4577.70605  122.56359 44.55387
   2  48.529 FM    0.4481 5696.83643  211.87622 55.44613

Totals :                  1.02745e4   334.43981

==========================================================================
```



4.9, Scheme 4-6
73% yield, 0% ee

```
Data File C:\CHEM32\2\DATA\KSB\NICEWICZS 2012-06-26 13-05-09\KSB_VI_8_IB_99A1_1B2.D
Sample Name: KSB_VI_8_IB_99A1_1B2

    ================================================================
    Acq. Operator   : BLOOME                       Seq. Line :   3
    Acq. Instrument : 1200LC                       Location : Vial 12
    Injection Date  : 6/26/2012 1:47:20 PM             Inj :   1
                                                   Inj Volume : 5.0 µl
    Acq. Method     : C:\CHEM32\2\DATA\KSB\NICEWICZS 2012-06-26 13-05-09\IB_99A1_1B2_30.M
    Last changed    : 3/19/2011 2:31:09 PM by GRANDJEAN
    Analysis Method : C:\CHEM32\2\METHODS\IC_99,5A2_0,5B2_30.M
    Method Info     : Short Method
```



Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.792	BV	0.0785	979.32867	188.76982	49.6177
2	5.986	VV	0.0884	994.42169	169.68642	50.3823
Totals :				1973.75037	358.45624	

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.792	BV	0.0785	979.32867	188.76982	49.6177
2	5.986	VV	0.0884	994.42169	169.68642	50.3823
Totals :				1973.75037	358.45624	

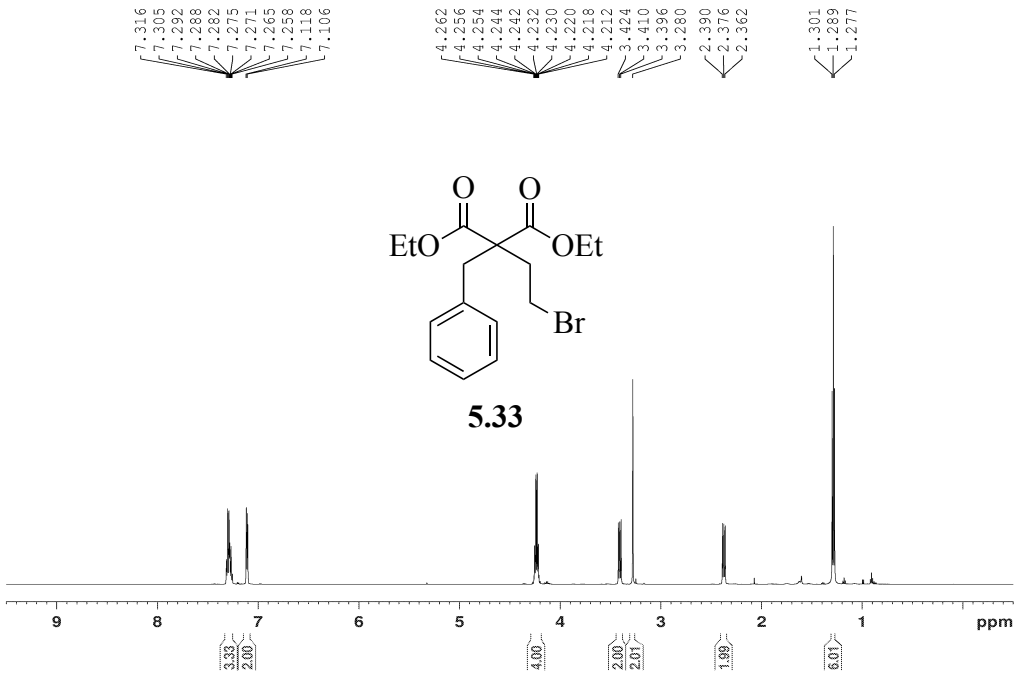
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.791	BV	0.1424	2.15044e4	2402.22656	47.5673
2	5.986	VV	0.1577	2.37039e4	2390.48145	52.4327
Totals :				4.52083e4	4792.70801	

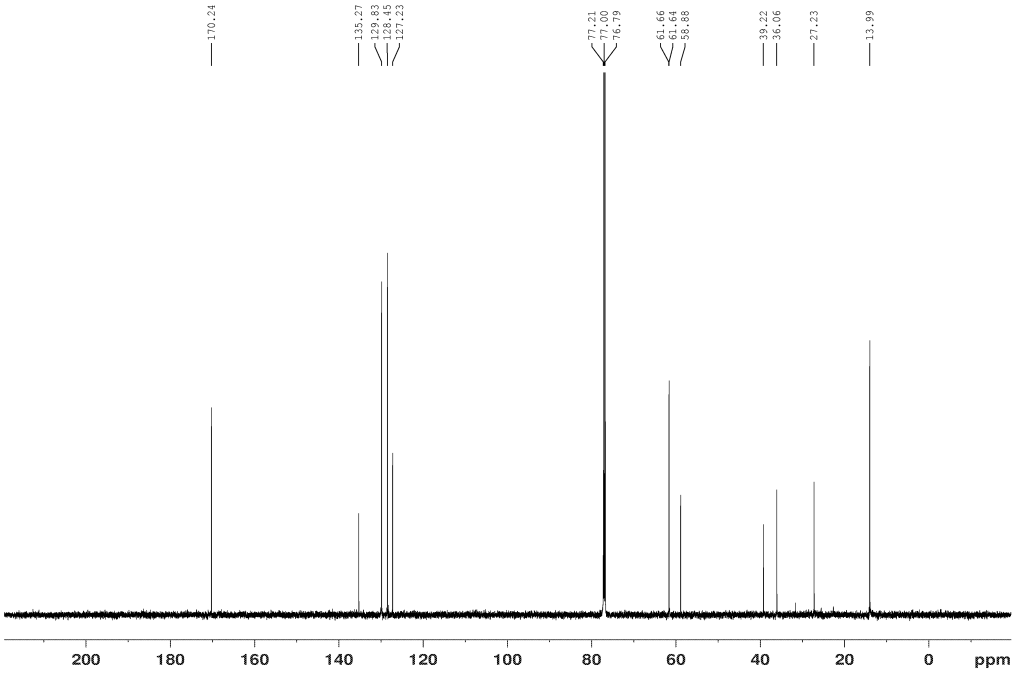
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

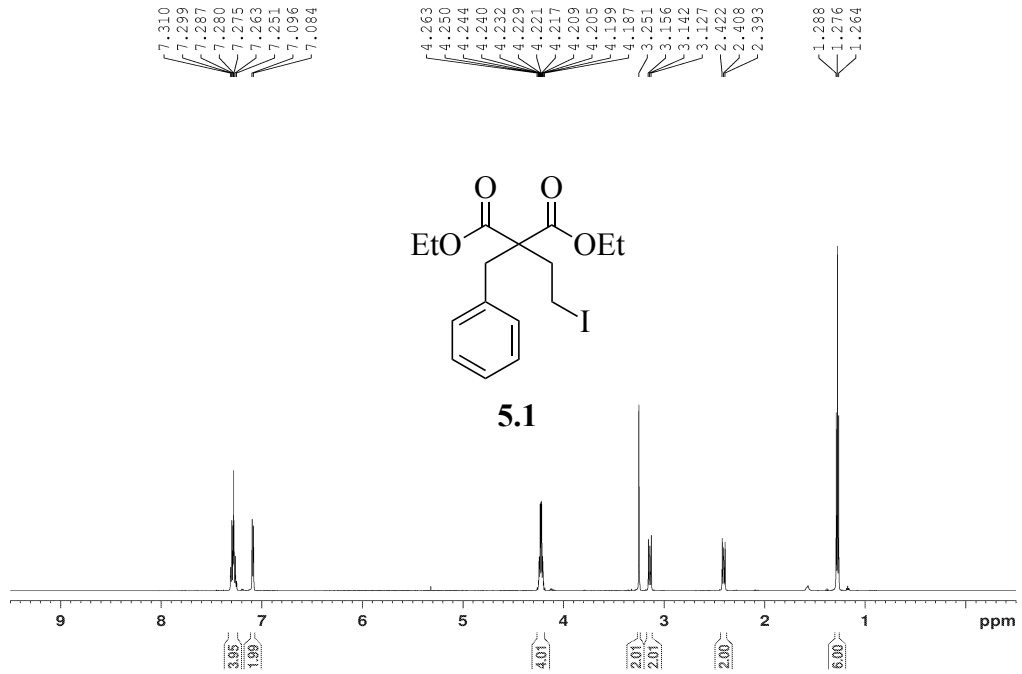
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.791	BV	0.1424	2.15044e4	2402.22656	47.5673
2	5.986	VV	0.1577	2.37039e4	2390.48145	52.4327
Totals :				4.52083e4	4792.70801	

Appendix E: Spectral Data for Chapter 5

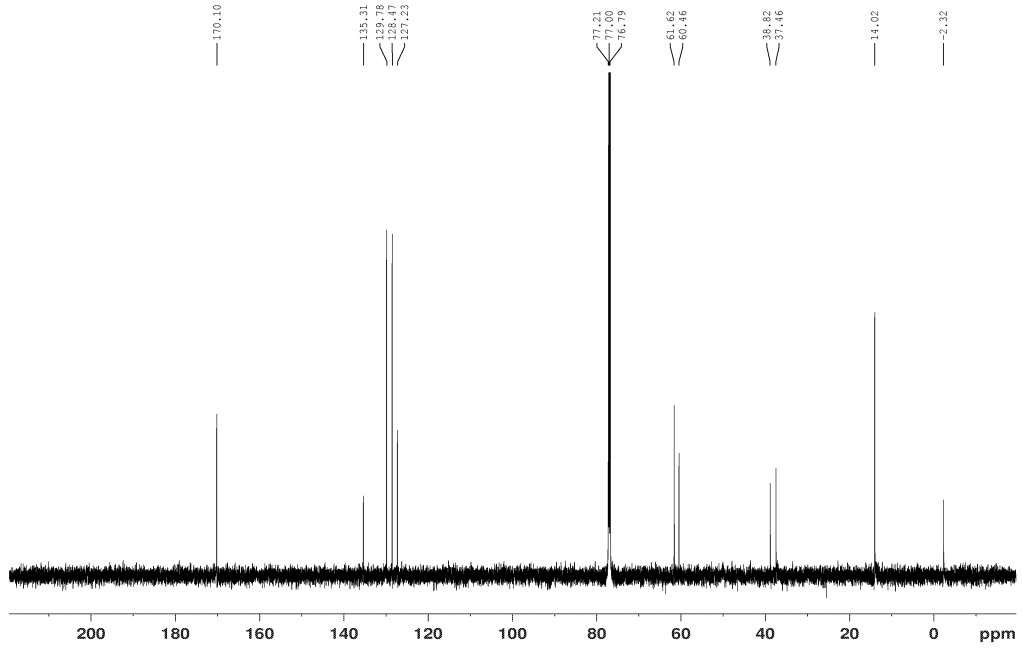


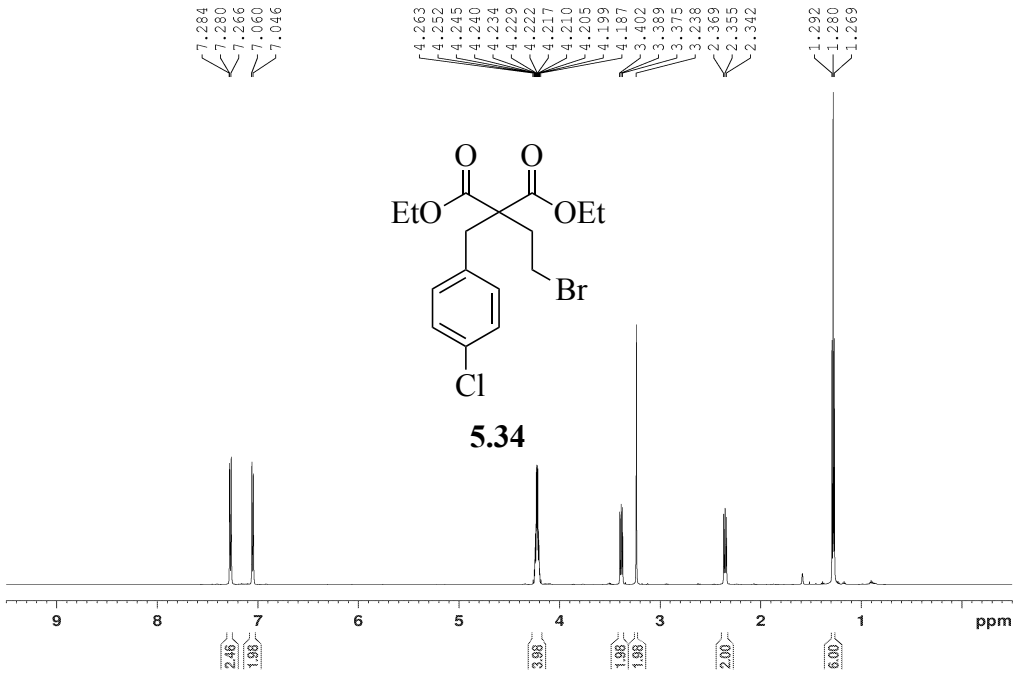
5.33



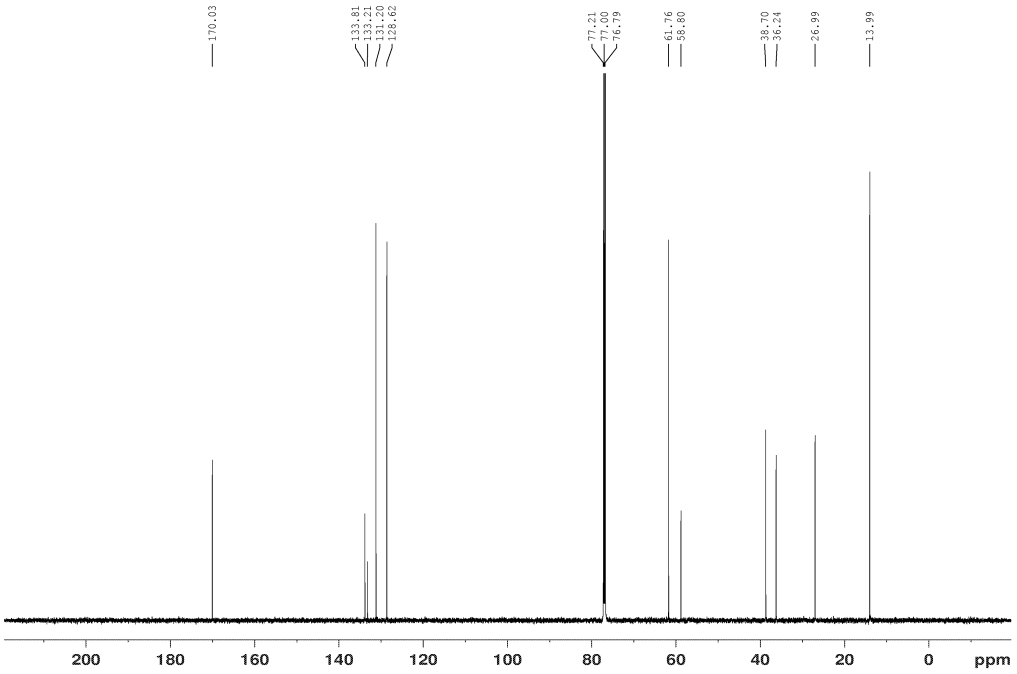

7.310
7.299
7.287
7.280
7.275
7.263
7.251
7.096
7.084
4.263
4.250
4.244
4.240
4.232
4.229
4.221
4.217
4.209
4.205
4.199
4.187
3.251
3.156
3.142
3.127
2.422
2.408
2.393
1.288
1.276
1.264
O
O
EtO
OEt
I
9
8
7
6
5
4
3
2
1
ppm
3.95
1.99
4.01
2.01
2.01
2.00
6.00

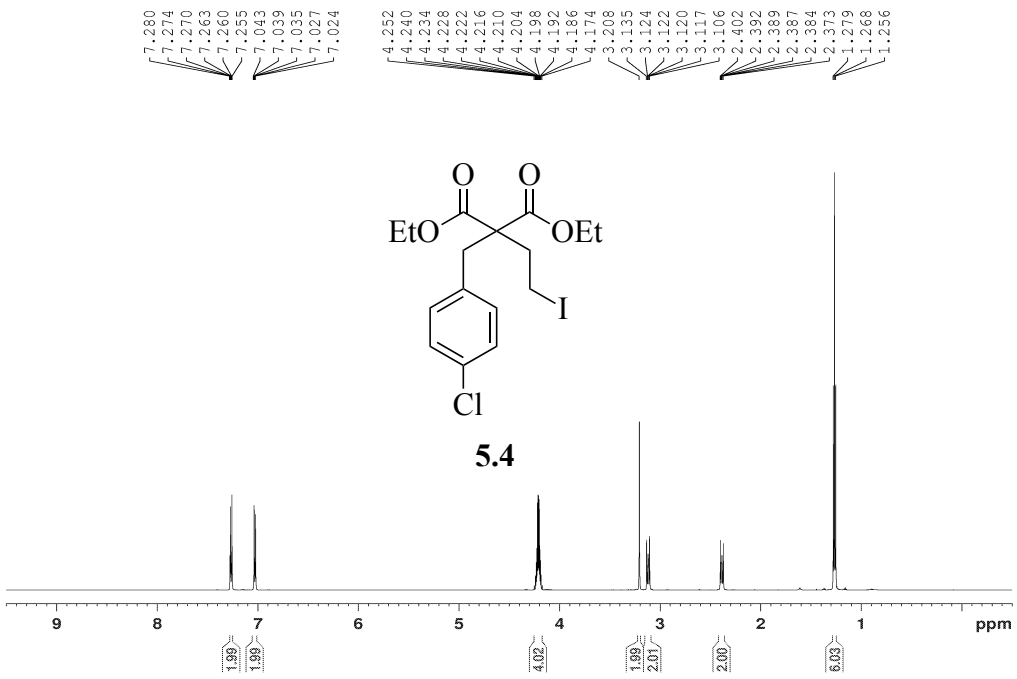
5.1

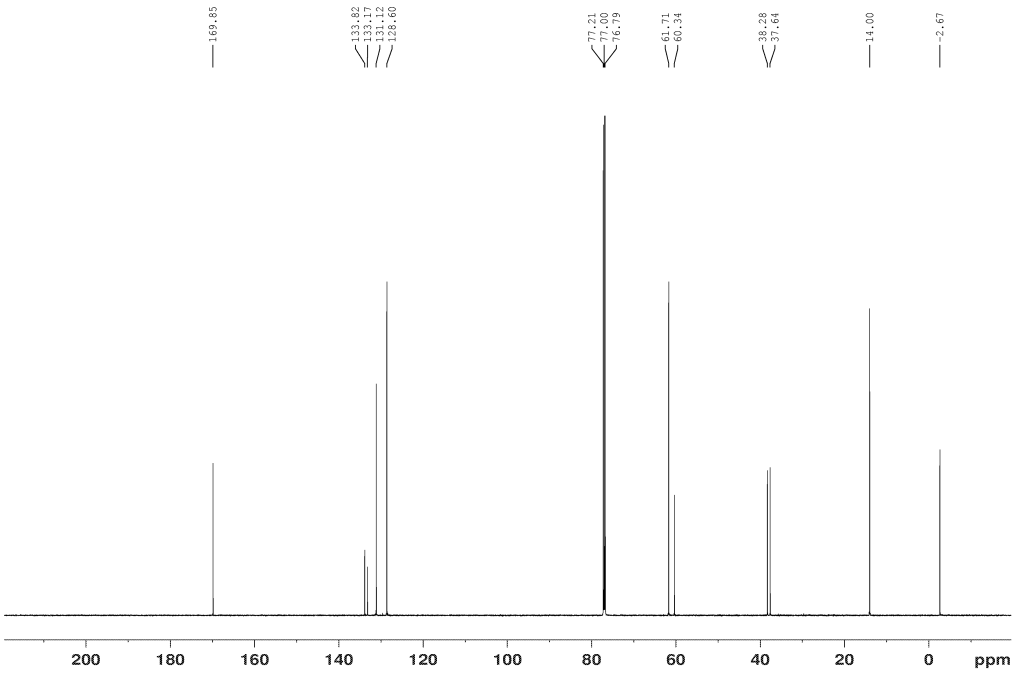

170.10
135.31
129.78
128.47
127.23
77.21
77.00
76.79
61.62
60.46
38.82
37.46
14.02
-2.32
200
180
160
140
120
100
80
60
40
20
0
ppm

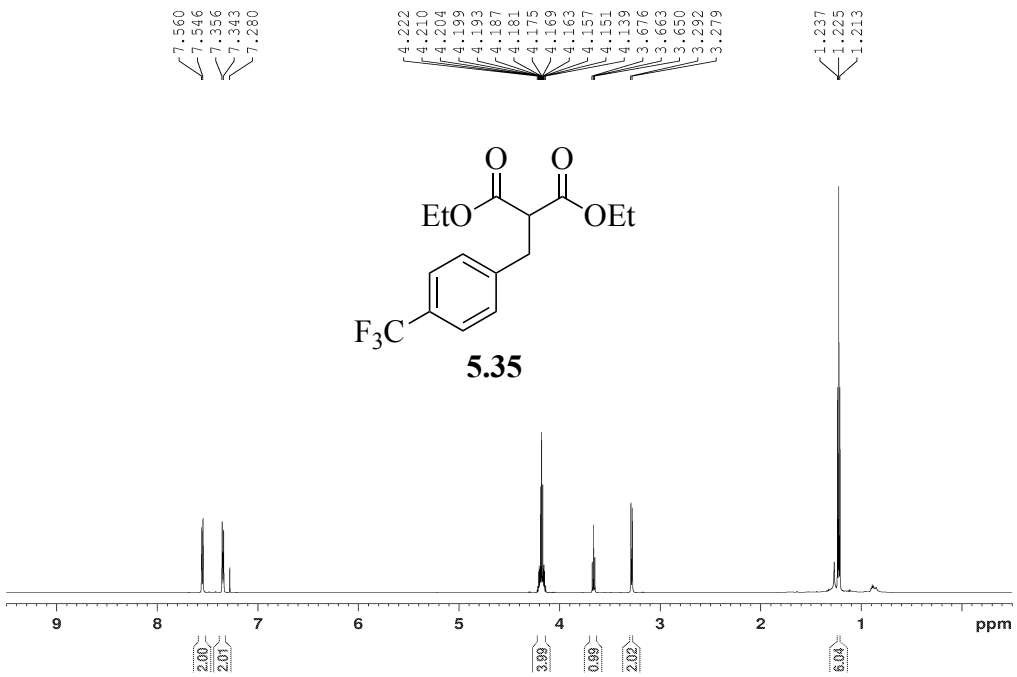

7.284
7.280
7.266
7.060
7.046
4.263
4.252
4.245
4.240
4.234
4.229
4.222
4.217
4.210
4.205
4.199
4.187
3.402
3.389
3.375
3.238
2.369
2.355
2.342
1.292
1.280
1.269
O
O
EtO
OEt
Br
Cl
9
8
7
6
5
4
3
2
1
ppm
2.46
1.98
3.98
1.98
1.98
2.00
6.00

5.34

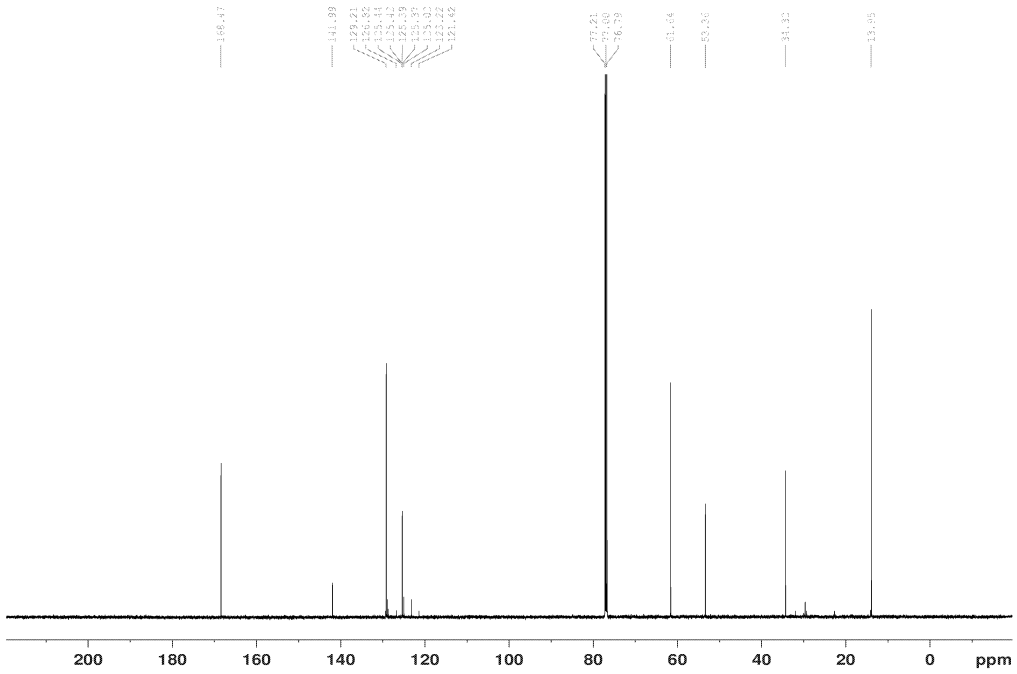

170.03
133.81
133.21
131.20
128.62
77.21
77.00
76.79
61.76
58.80
38.70
36.24
26.99
13.99
200
180
160
140
120
100
80
60
40
20
0
ppm

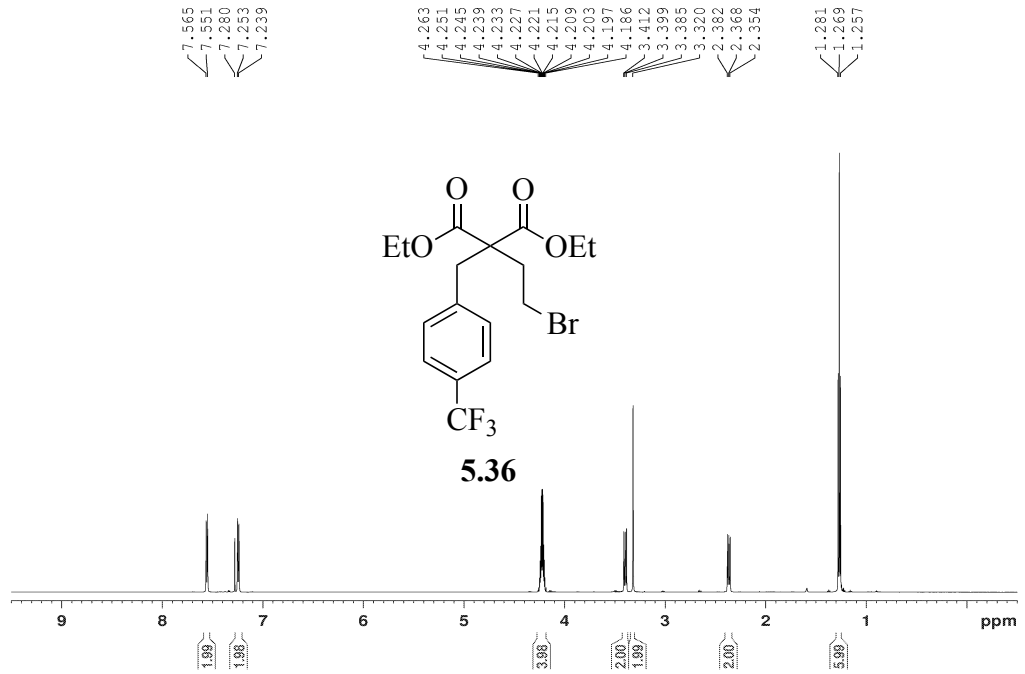

7.280
7.274
7.270
7.263
7.260
7.255
7.043
7.039
7.035
7.027
7.024
4.252
4.240
4.234
4.228
4.222
4.216
4.210
4.204
4.198
4.192
4.186
4.174
3.208
3.135
3.124
3.122
3.120
3.117
3.106
2.402
2.392
2.389
2.387
2.384
2.373
1.279
1.268
1.256
O
O
EtO
OEt
I
Cl
5.4
9
8
7
6
5
4
3
2
1
ppm
1.99
1.99
4.02
1.99
2.01
2.00
6.03

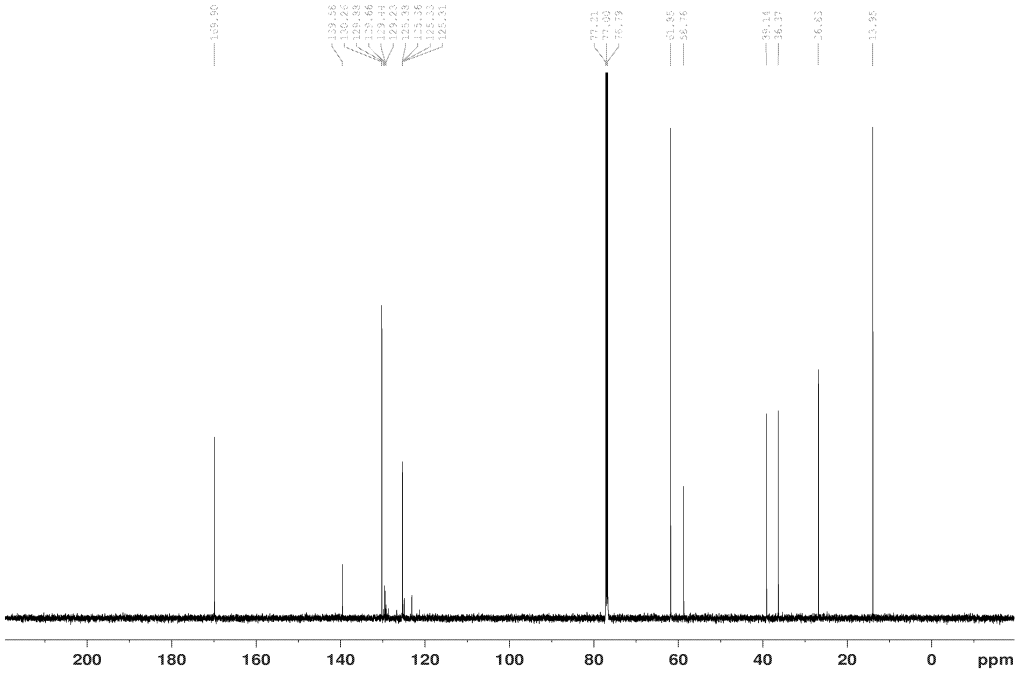

169.85
133.82
133.17
131.12
128.60
77.21
77.00
76.79
61.71
60.34
38.28
37.64
14.00
-2.67
200
180
160
140
120
100
80
60
40
20
0
ppm

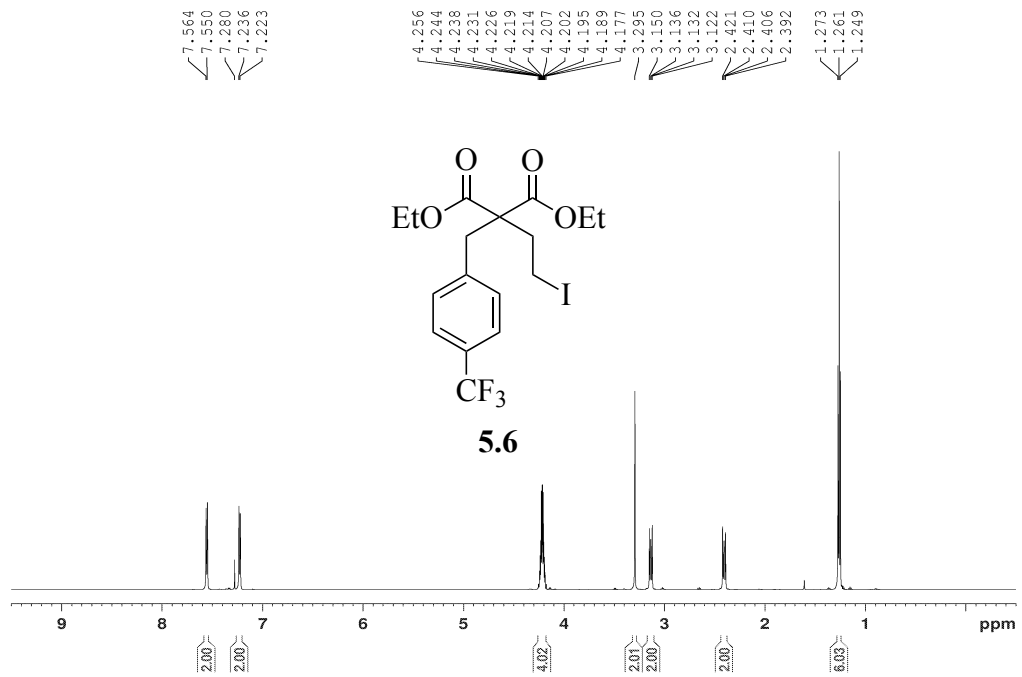

7.560
7.546
7.356
7.343
7.280
4.222
4.210
4.204
4.199
4.193
4.187
4.181
4.175
4.169
4.163
4.157
4.151
4.139
3.676
3.663
3.650
3.292
3.279
1.237
1.225
1.213
O
O
EtO
OEt
F3C
9
8
7
6
5
4
3
2
1
ppm
2.00
2.01
3.99
0.99
2.02
6.04

5.35


166.47
141.99
129.21
128.92
128.61
125.41
125.39
125.33
123.03
123.22
121.42
77.21
77.00
76.79
61.64
53.36
34.83
13.95
200
180
160
140
120
100
80
60
40
20
0
ppm


7.565
7.551
7.280
7.253
7.239
4.263
4.251
4.245
4.239
4.233
4.227
4.221
4.215
4.209
4.203
4.197
4.186
3.412
3.399
3.385
3.320
2.382
2.368
2.354
1.281
1.269
1.257
O
O
EtO
OEt
Br
CF3
5.36
9
8
7
6
5
4
3
2
1
ppm
1.99
1.98
3.98
2.00
1.99
2.00
5.99


169.90
139.58
130.26
129.88
129.66
129.44
129.22
125.34
125.36
125.33
125.31
77.31
77.00
76.79
61.45
58.76
39.14
36.37
26.83
13.95
200
180
160
140
120
100
80
60
40
20
0
ppm


7.564
7.550
7.280
7.236
7.223
4.256
4.244
4.238
4.231
4.226
4.219
4.214
4.207
4.202
4.195
4.189
4.177
3.295
3.150
3.136
3.132
3.122
2.421
2.410
2.406
2.392
1.273
1.261
1.249
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O
EtO
OEt
I
CF3
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8
7
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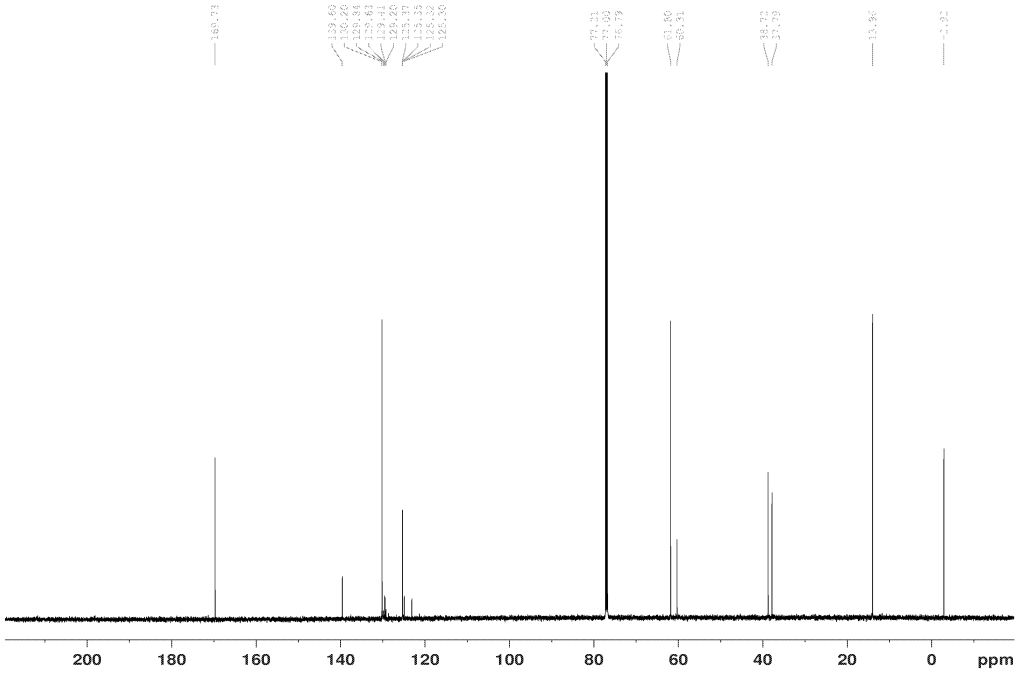
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77.00
76.79
61.46
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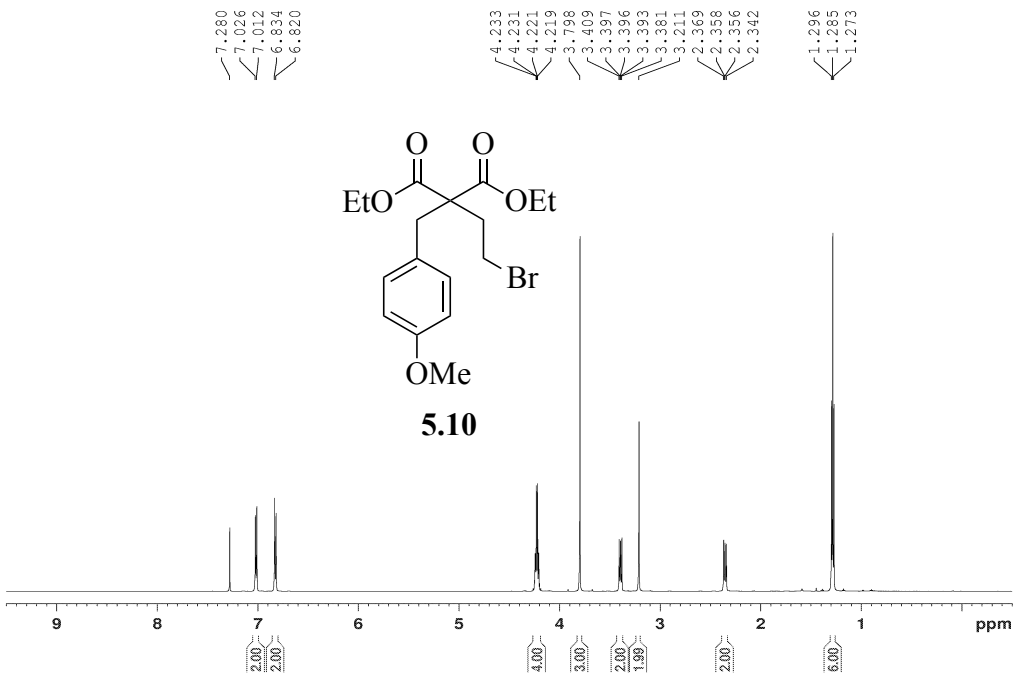
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3.393
3.381
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2.356
2.342
1.296
1.285
1.273
O
O
EtO
OEt
Br
OMe
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9
8
7
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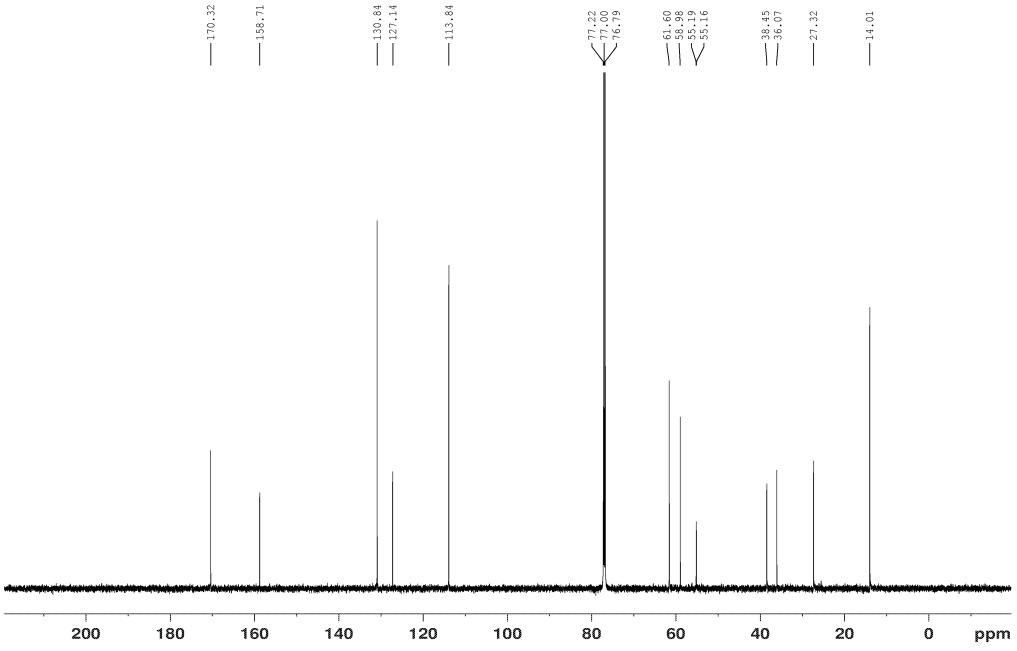
6.00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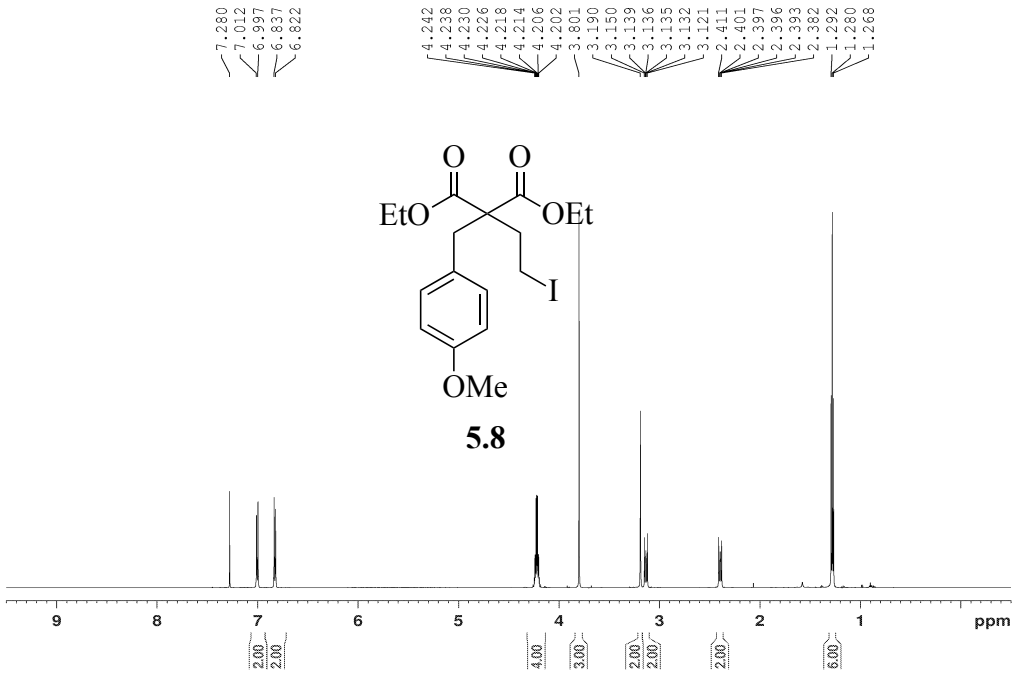
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4.218
4.214
4.206
4.202
3.801
3.190
3.150
3.139
3.136
3.135
3.132
3.121
2.411
2.401
2.397
2.396
2.393
2.382
1.292
1.280
1.268
O
O
EtO
OEt
I
OMe
5.8
9
8
7
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ppm
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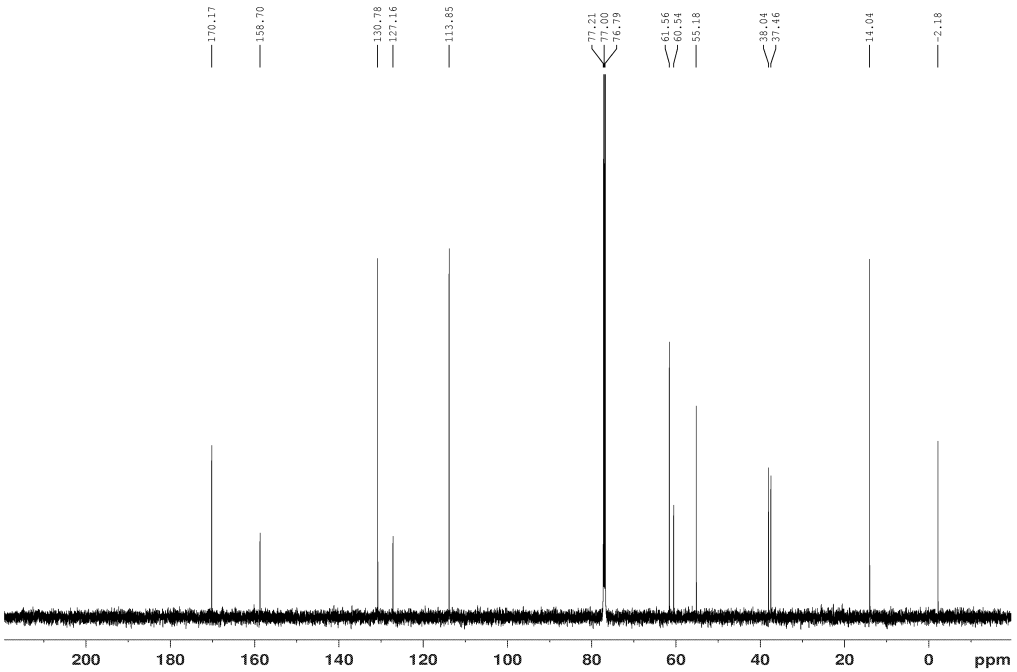
2.00
4.00
3.00
2.00
2.00
2.00
6.00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60.54
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120
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40
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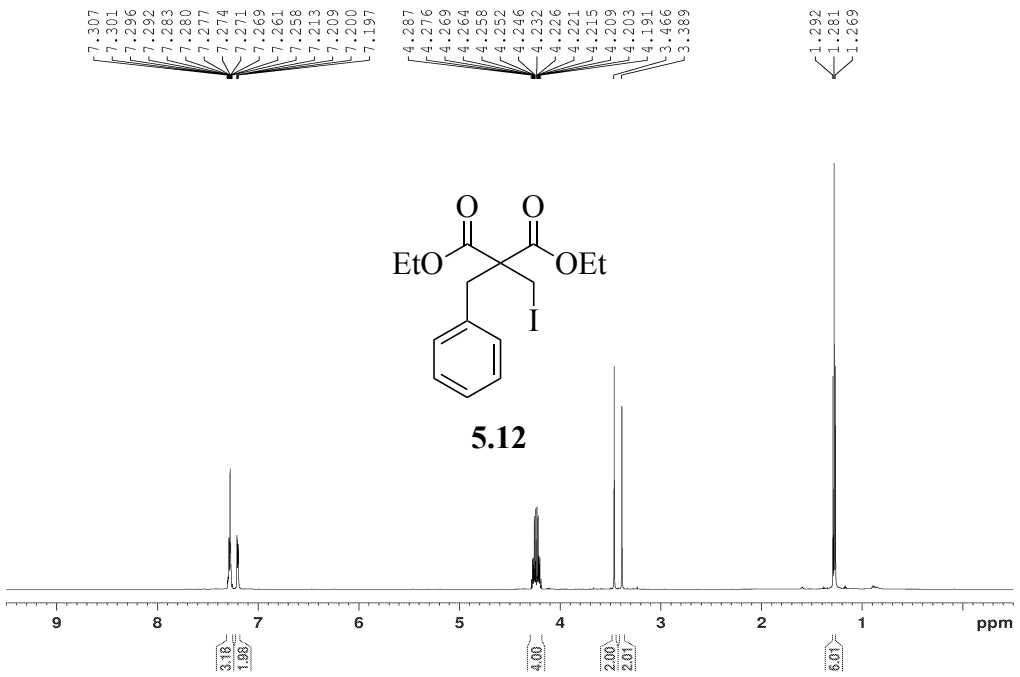
0
ppm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7.274
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7.269
7.261
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7.213
7.209
7.200
7.197
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4.276
4.269
4.264
4.258
4.252
4.246
4.232
4.226
4.221
4.215
4.209
4.203
4.191
3.466
3.389
1.292
1.281
1.269
O
O
EtO
OEt
I
5.12
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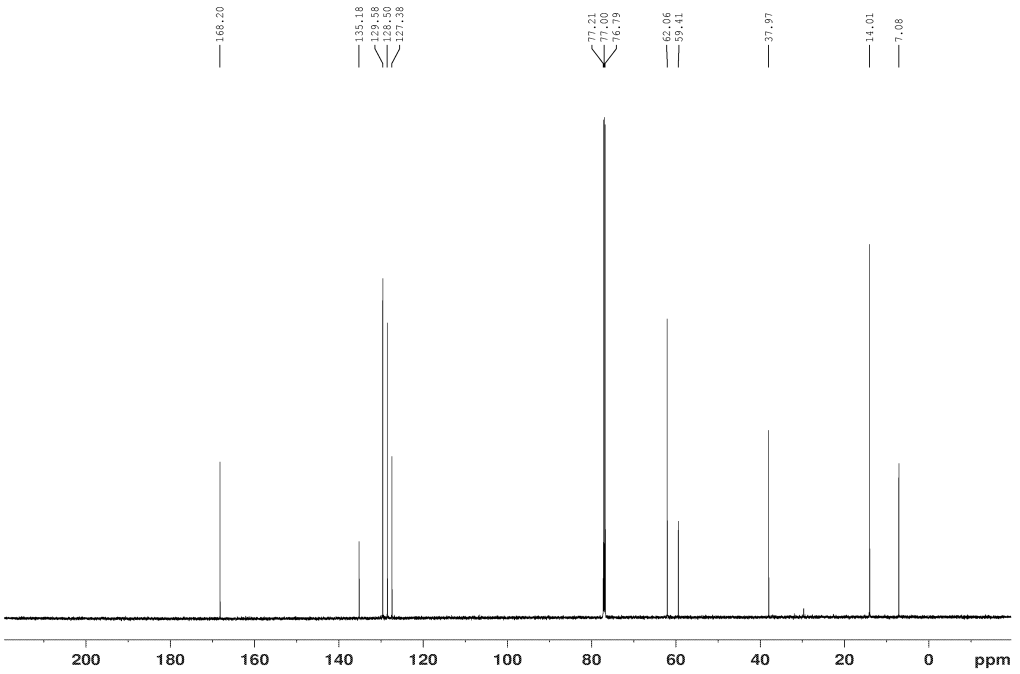
6.01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128.50
127.38
77.21
77.00
76.79
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59.41
37.97
14.01
7.08
200
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120
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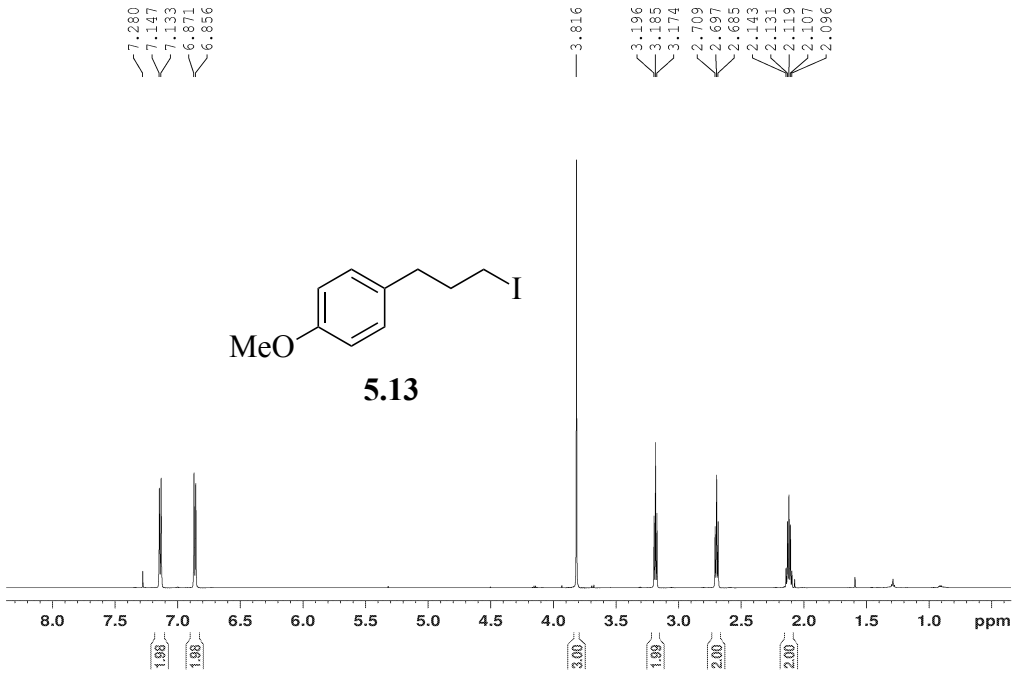
60
40
20
0
ppm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3.185
3.174
2.709
2.697
2.685
2.143
2.131
2.119
2.107
2.096
I
MeO
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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1.98
3.00
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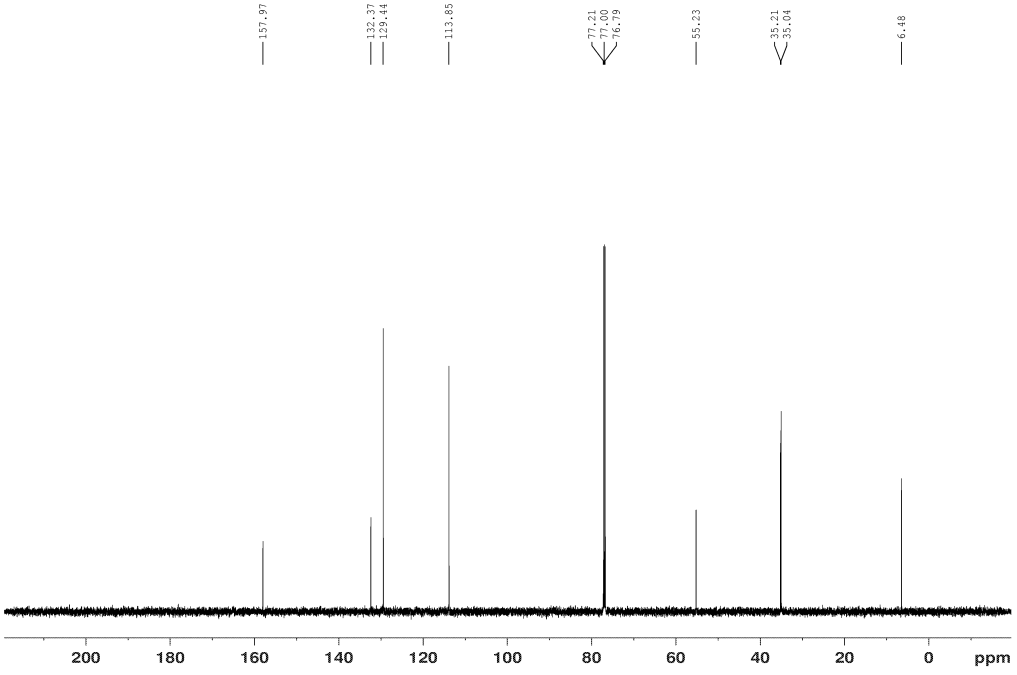
2.00
2.00

5.13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77.21
77.00
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35.04
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200
180
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120
100
80
60
40
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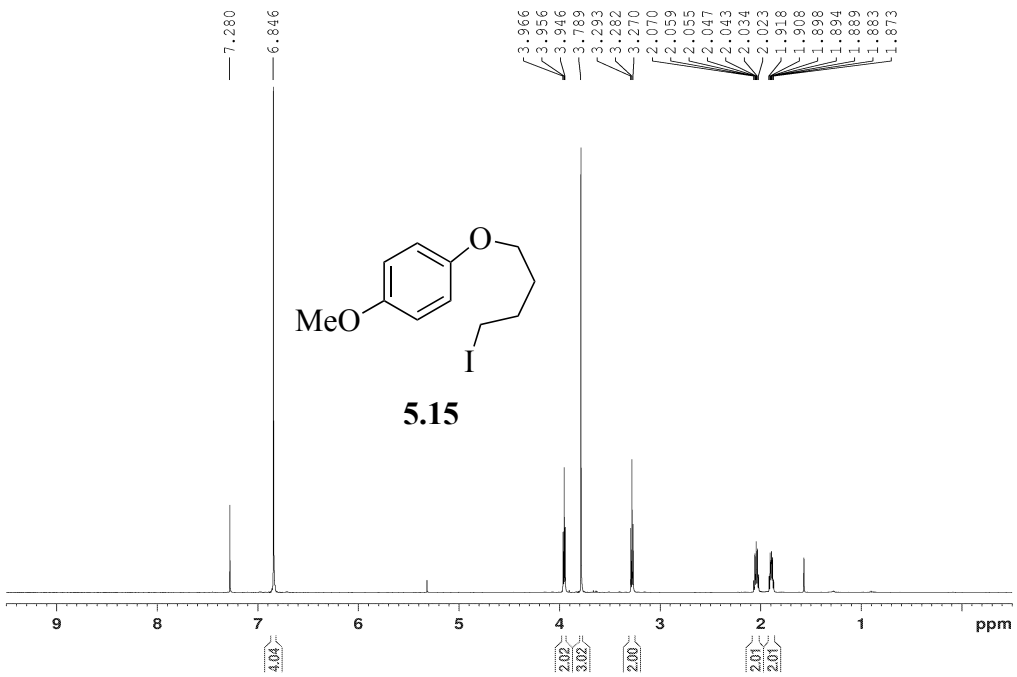
0
ppm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3.956
3.946
3.789
3.293
3.282
3.270
2.070
2.059
2.055
2.047
2.043
2.034
2.023
1.918
1.908
1.898
1.894
1.889
1.883
1.873
O
MeO
I
9
8
7
6
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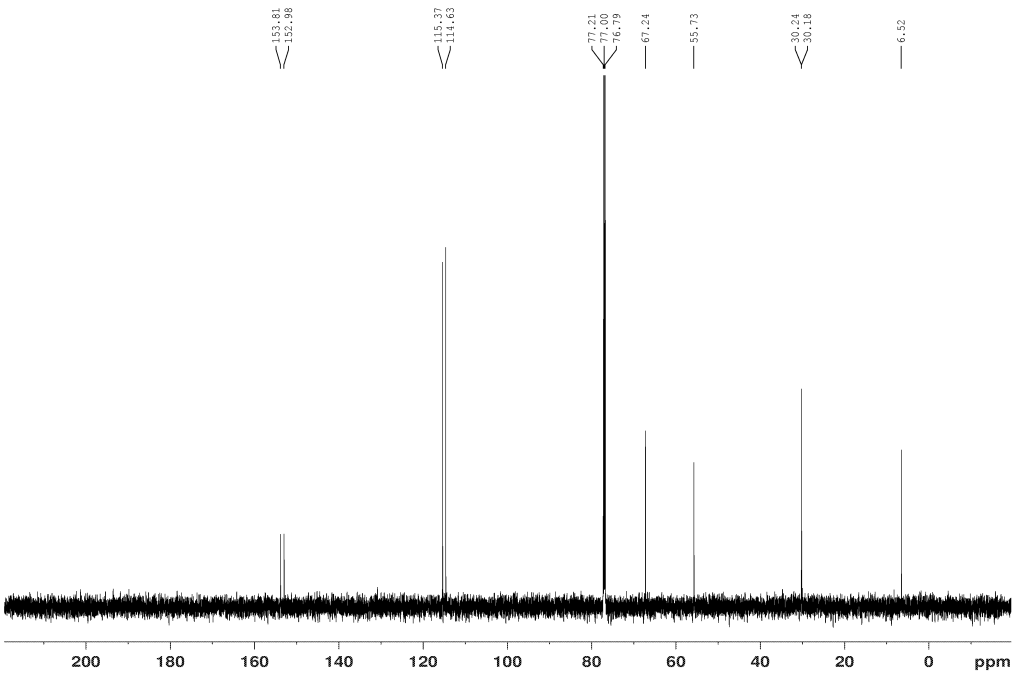
4
3
2
1
ppm
4.04
2.02
3.02
2.00
2.01
2.01

5.15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152.98
115.37
114.63
77.21
77.00
76.79
67.24
55.73
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30.18
6.52
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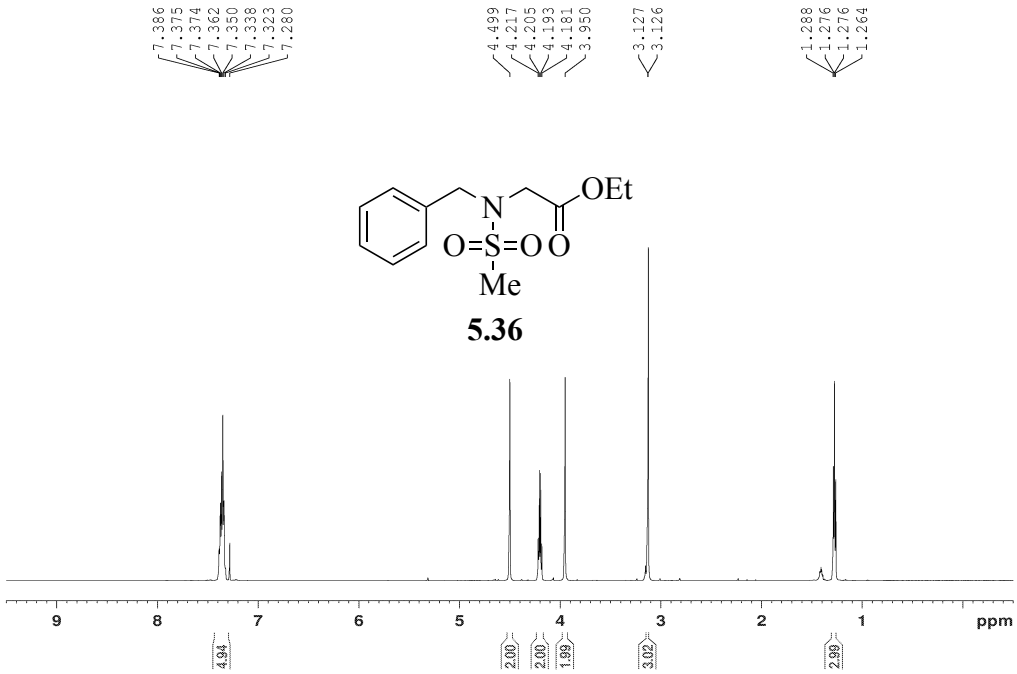
140
120
100
80
60
40
20
0
ppm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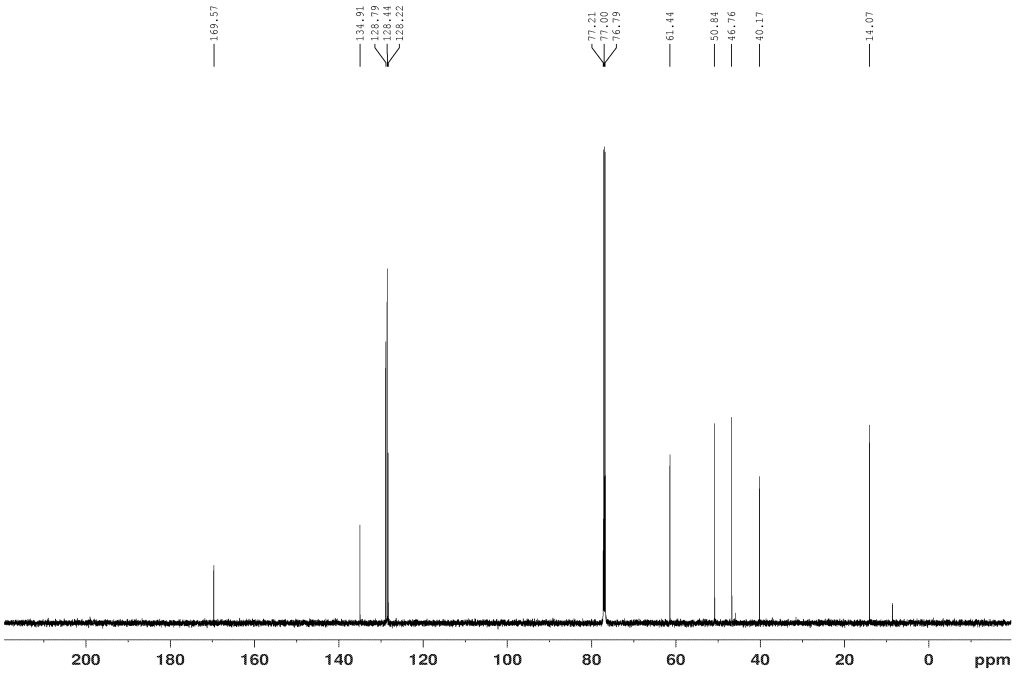
7.375
7.374
7.362
7.350
7.338
7.323
7.280
4.499
4.217
4.205
4.193
4.181
3.950
3.127
3.126
1.288
1.276
1.276
1.264
OEt
N
O=S=O O
Me
5.36
9
8
7
6
5
4
3
2
1
ppm
4.94
2.00
2.00
1.99
3.02
2.99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128.22
77.21
77.00
76.79
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46.76
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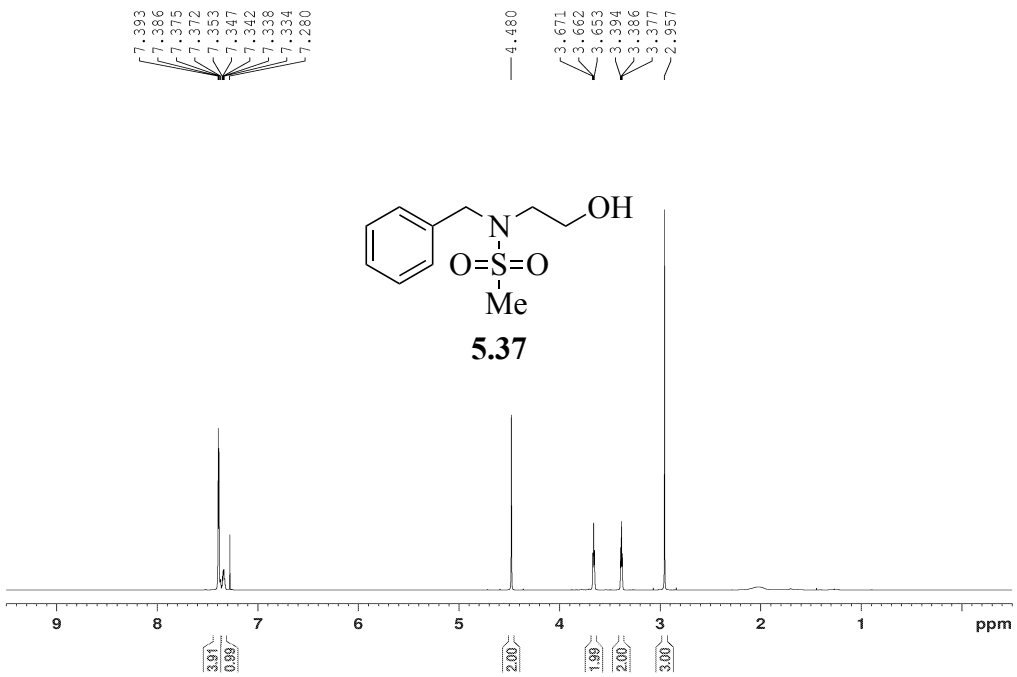
14.07
200
180
160
140
120
100
80
60
40
20
0
ppm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7.338
7.334
7.280
4.480
3.671
3.662
3.653
3.394
3.386
3.377
2.957
OH
N
O=S=O
Me
9
8
7
6
5
4
3
2
1
ppm
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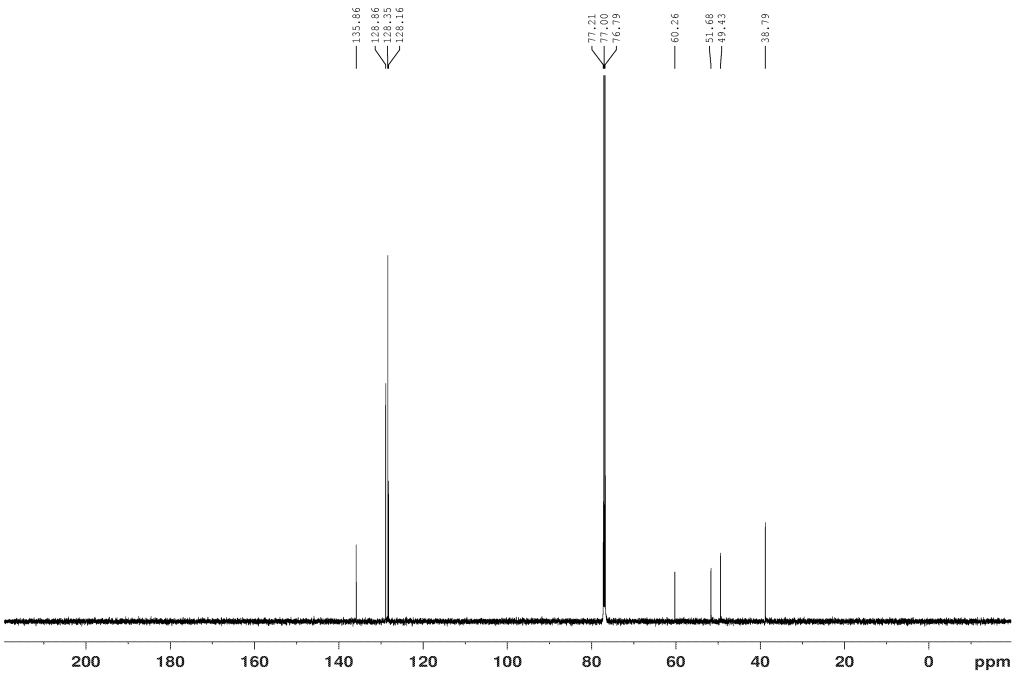
2.00
1.99
2.00
3.00

5.37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200
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140
120
100
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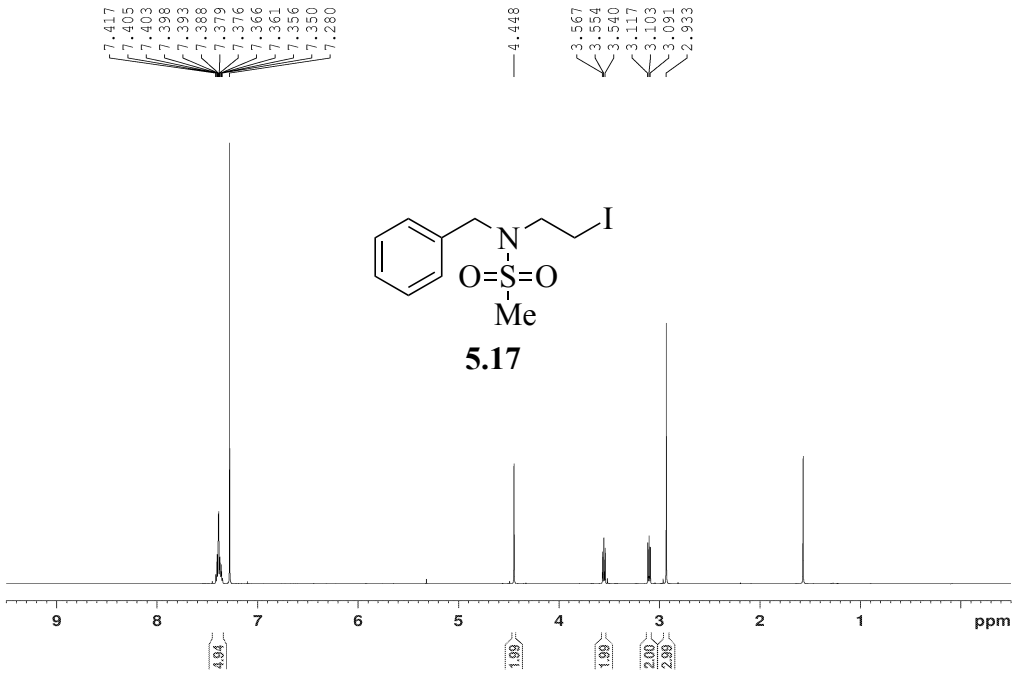
60
40
20
0
ppm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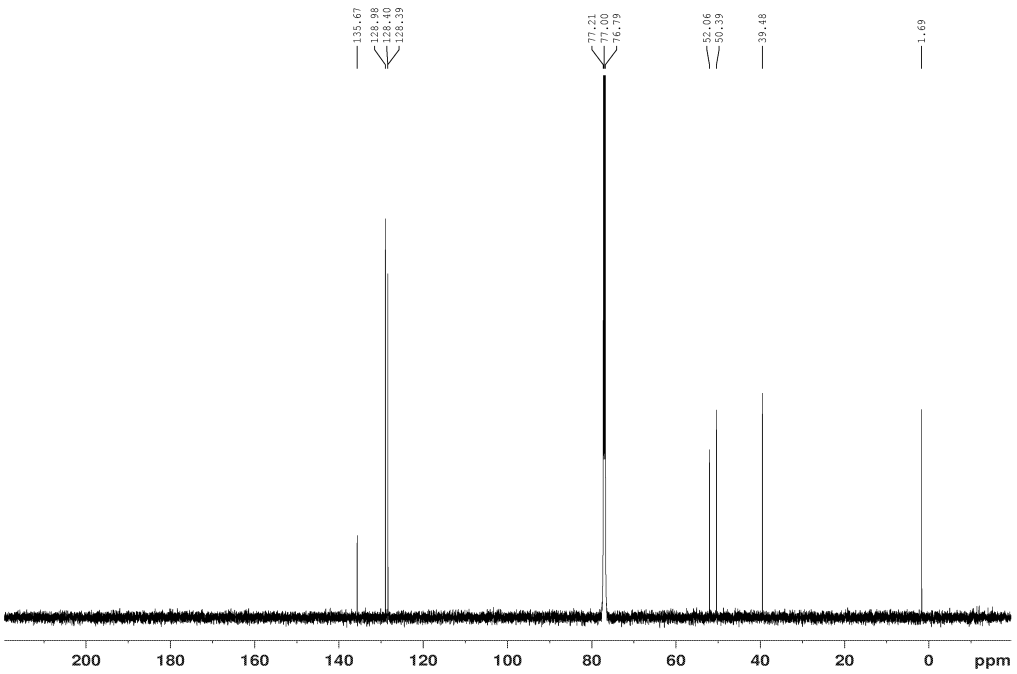
7.361
7.356
7.350
7.280
4.448
3.567
3.554
3.540
3.117
3.103
3.091
2.933
N
O=S=O
Me
I
9
8
7
6
5
4
3
2
1
ppm
4.94
1.99
1.99
2.00
2.99

5.17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20
0
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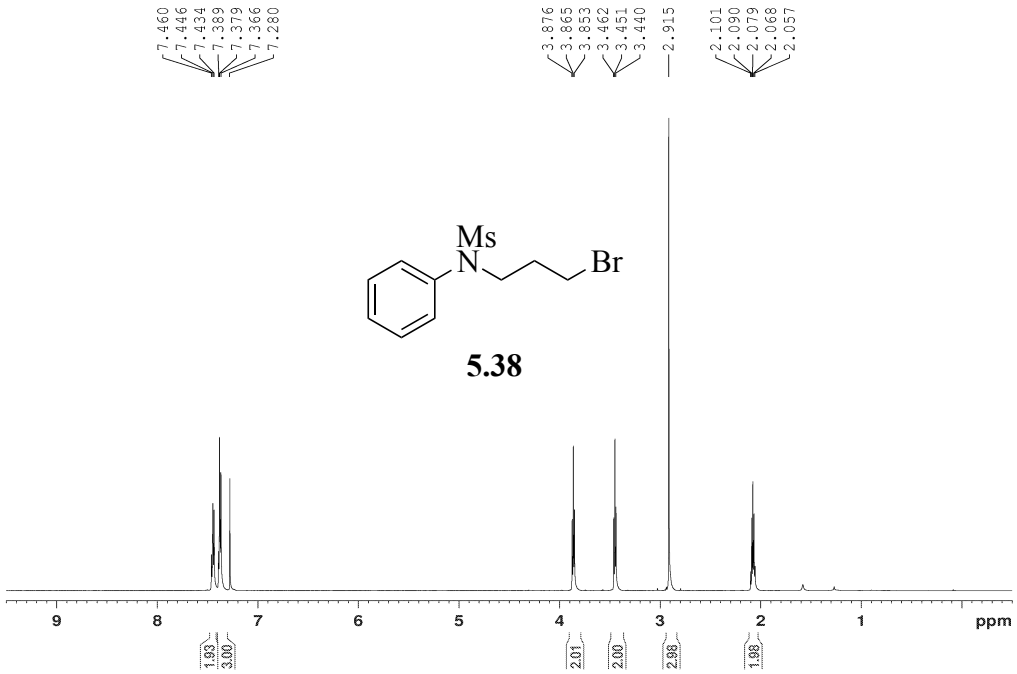
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3.440
2.915
2.101
2.090
2.079
2.068
2.057
Ms
N
Br
5.38
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8
7
6
5
4
3
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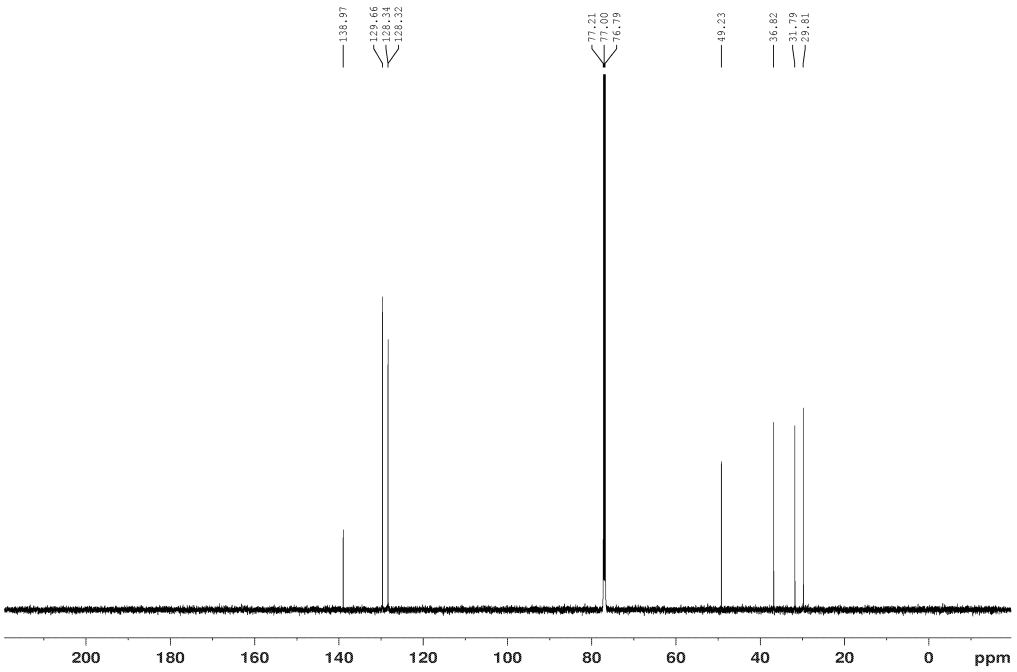
2.00
2.98
1.98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31.79
29.81
200
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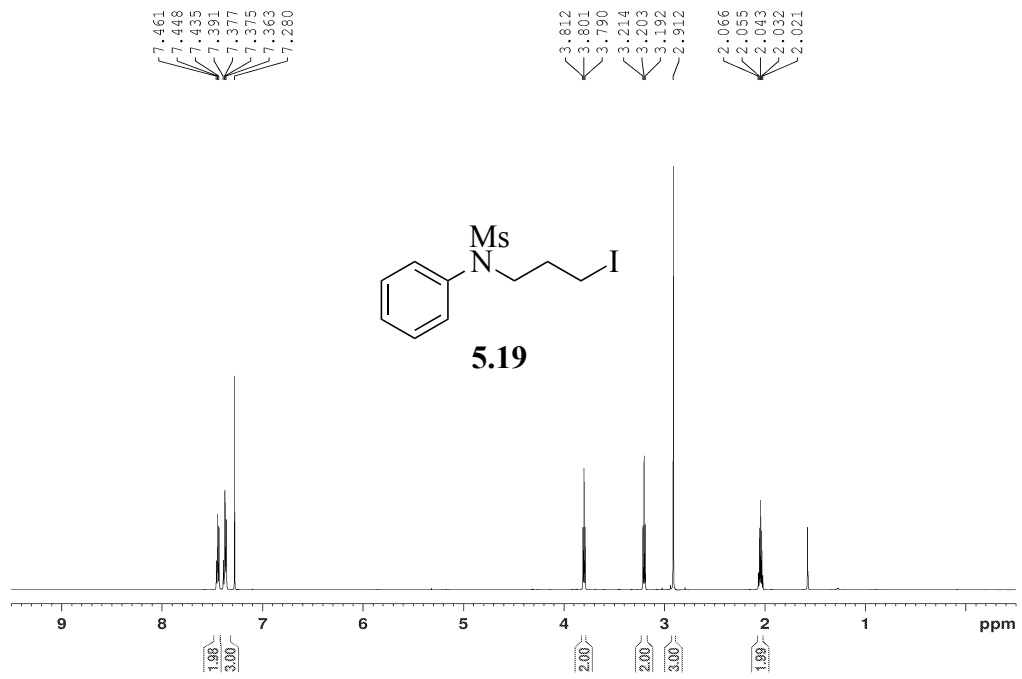
120
100
80
60
40
20
0
ppm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7.280
3.812
3.801
3.790
3.214
3.203
3.192
2.912
2.066
2.055
2.043
2.032
2.021
Ms
N
I
5.19
9
8
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5
4
3
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ppm
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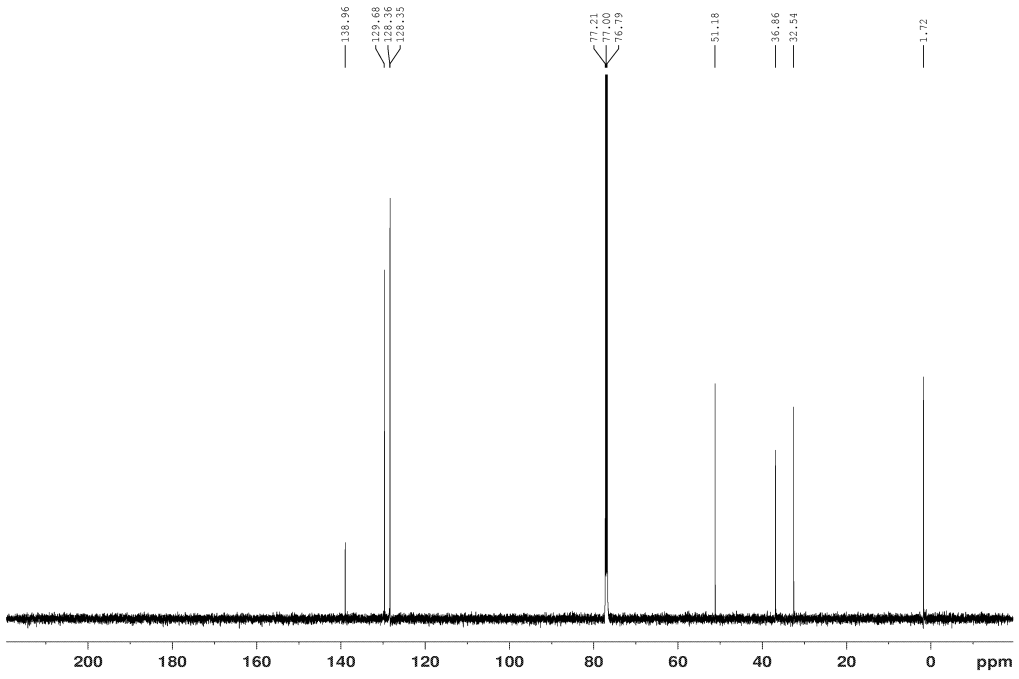
3.00
2.00
2.00
3.00
1.99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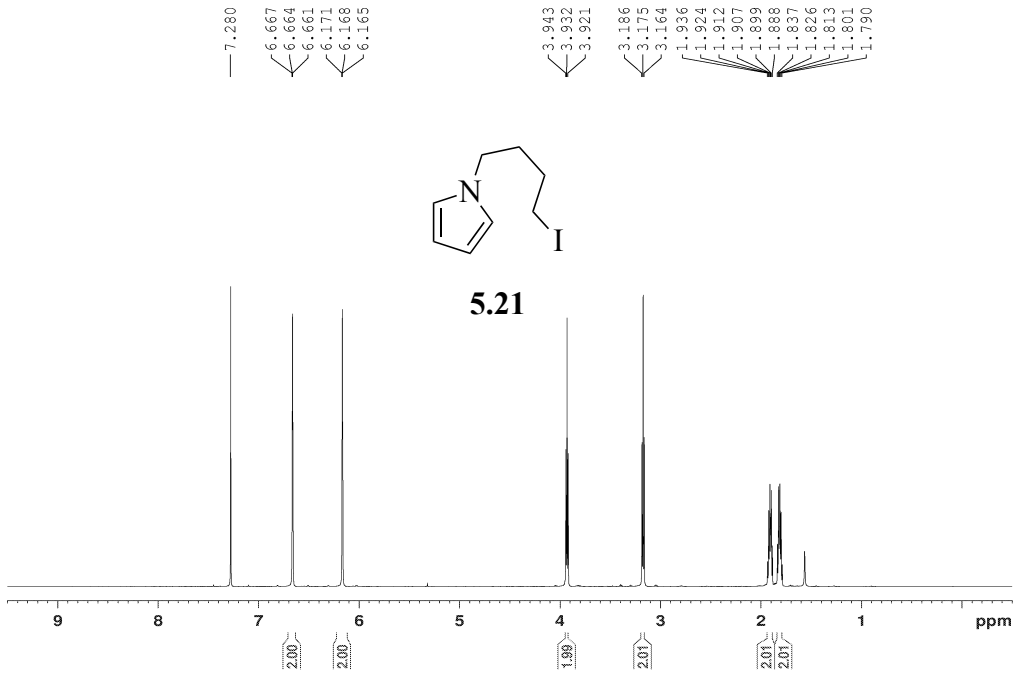
120
100
80
60
40
20
0
ppm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3.164
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1.924
1.912
1.907
1.899
1.888
1.837
1.826
1.813
1.801
1.790
N
I
9
8
7
6
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4
3
2
1
ppm
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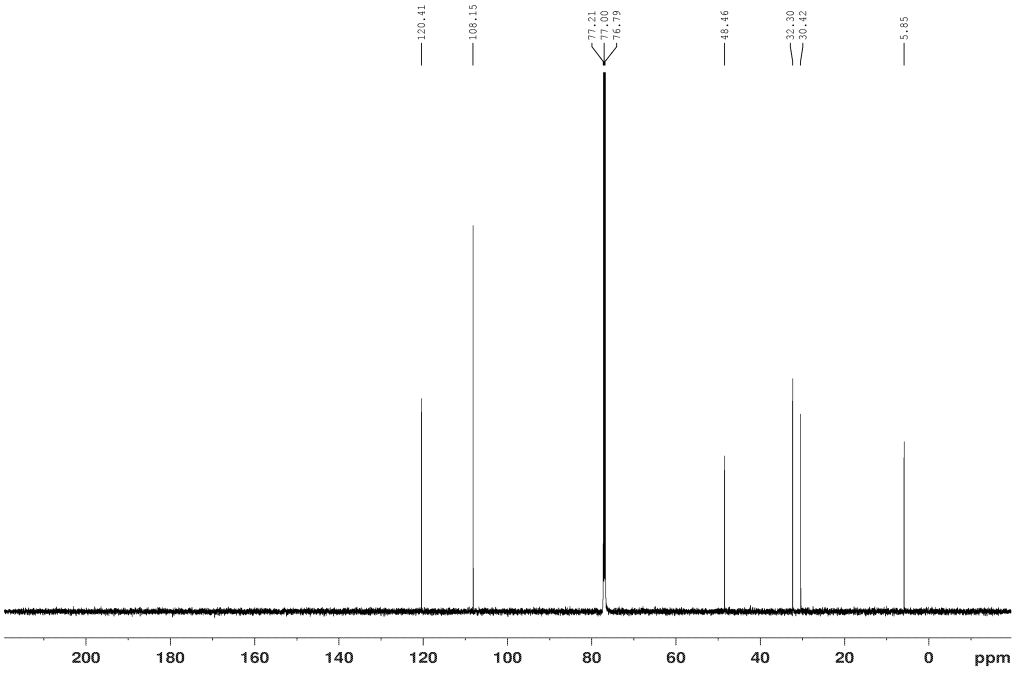
2.00
1.99
2.01
2.01
2.01

5.21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120
100
80
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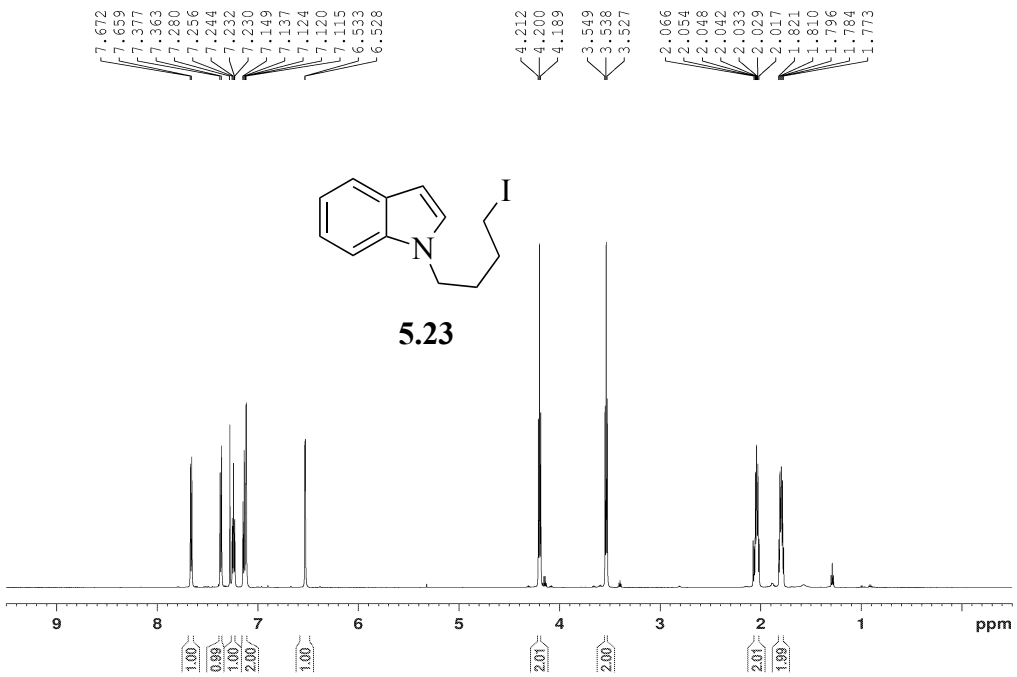
40
20
0
ppm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7.230
7.149
7.137
7.124
7.120
7.115
6.533
6.528
4.212
4.200
4.189
3.549
3.538
3.527
2.066
2.054
2.048
2.042
2.033
2.029
2.017
1.821
1.810
1.796
1.784
1.773
I
N
5.23
9
8
7
6
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3
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ppm
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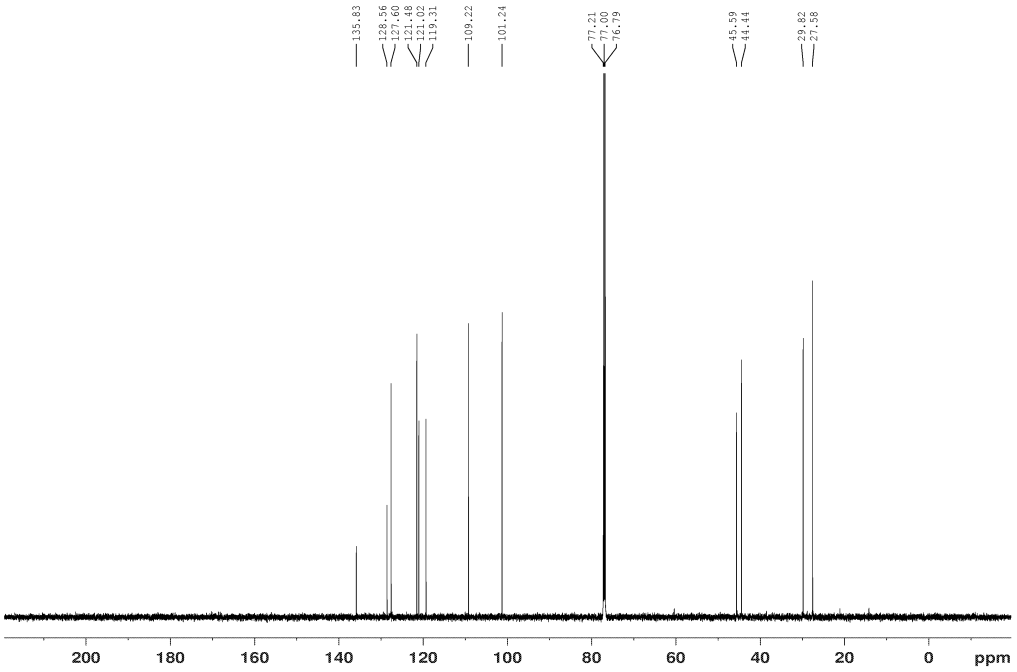
1.00
2.00
1.00
2.01
2.00
2.01
1.99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101.24
77.21
77.00
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29.82
27.58
200
180
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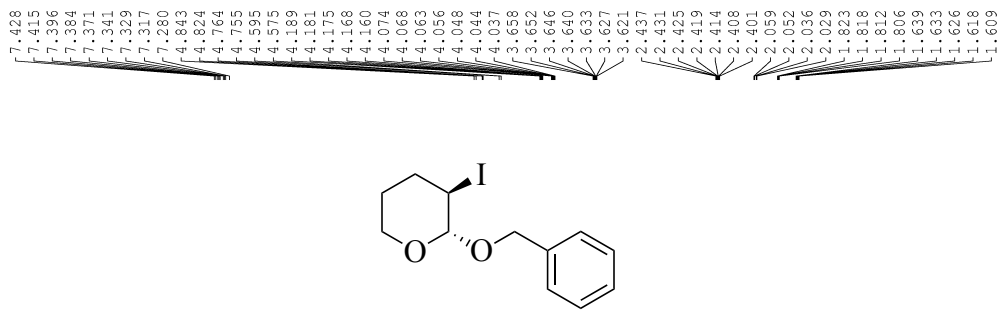
140
120
100
80
60
40
20
0
ppm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4.755
4.595
4.575
4.189
4.181
4.175
4.168
4.160
4.074
4.068
4.063
4.056
4.048
4.044
4.037
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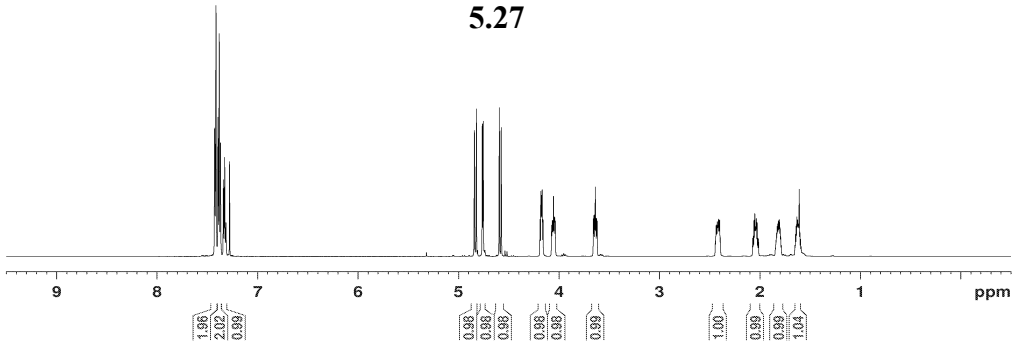
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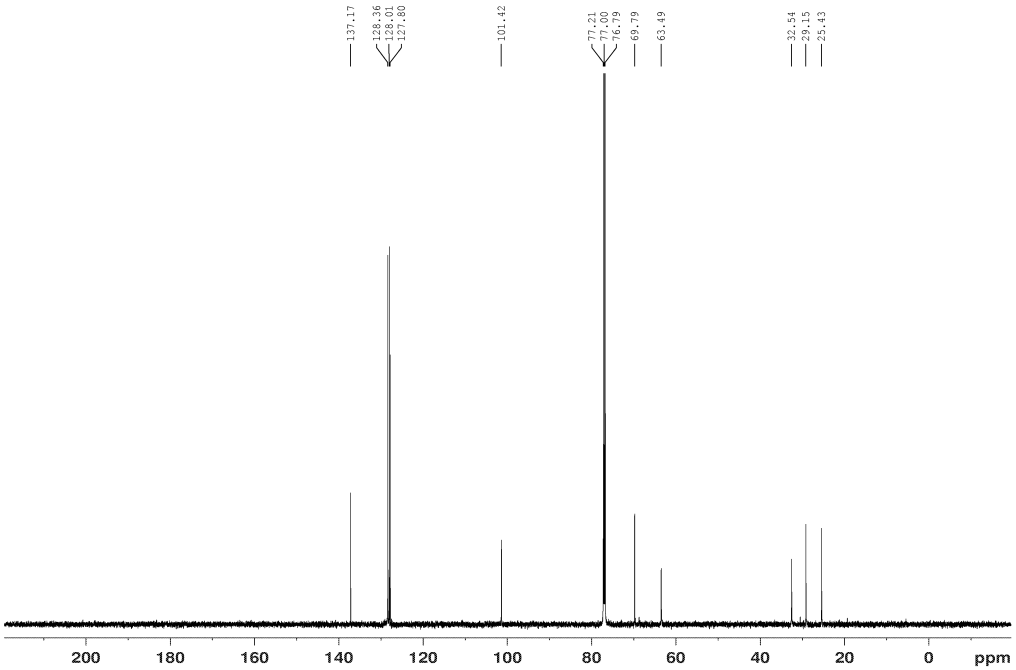
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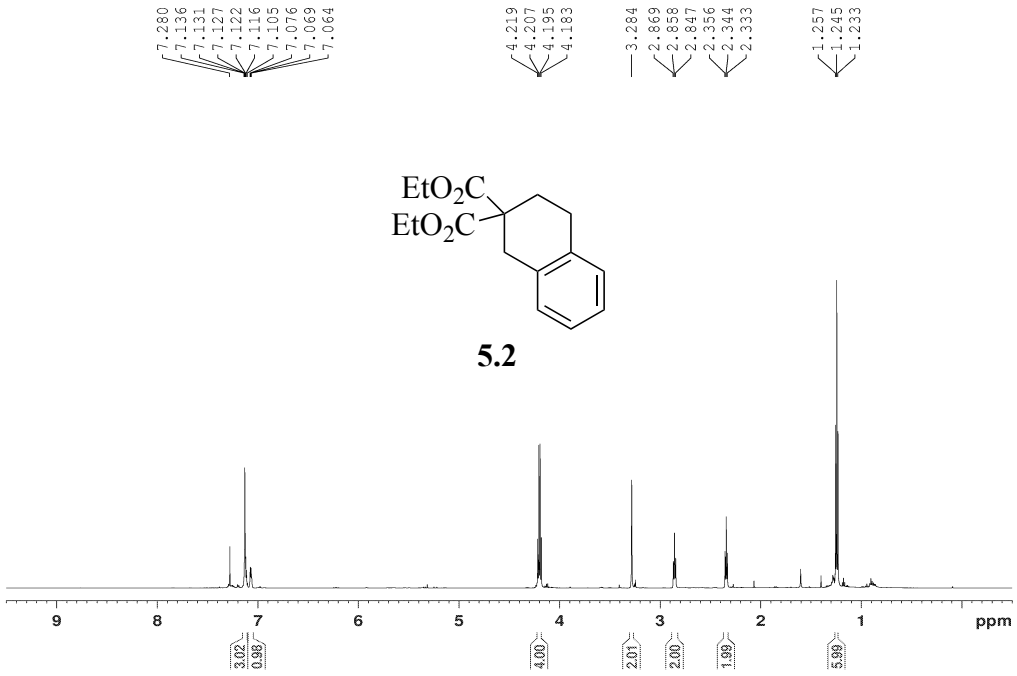
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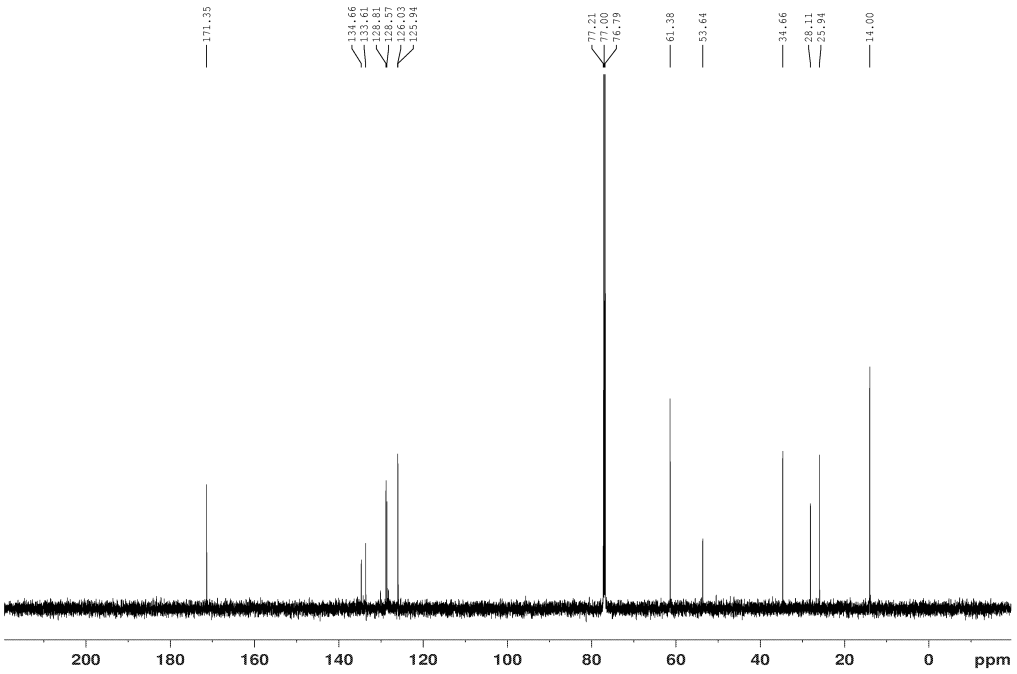
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