PALLADIUM-CATALYZED CARBON-CARBON BOND-FORMING REACTIONS WITH UNACTIVATED ALKYL ELECTROPHILES

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A dissertation submitted to the faculty of the University of North Carolina in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry.

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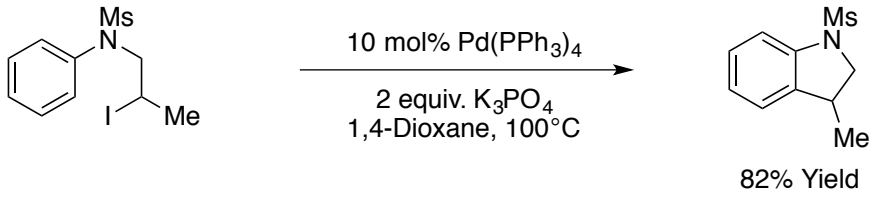
ABSTRACT

Alexander R.O. Venning: Palladium-Catalyzed Carbon-Carbon Bond-Forming Reactions with Unactivated Alkyl Electrophiles
(Under the direction of Erik J. Alexanian)

I. Cross-Coupling Reactions with Alkyl Electrophiles

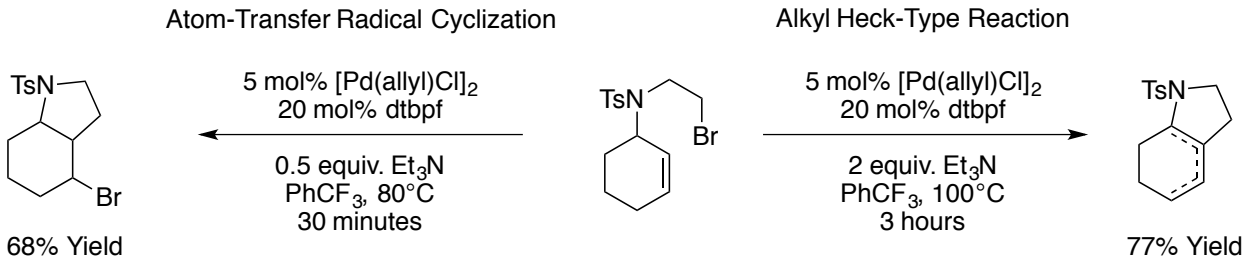
An overview of the application of alkyl electrophiles in cross-coupling reactions is presented, highlighting the importance of this reactivity and challenges associated therein. Recent advances in alkyl cross-coupling are discussed, from both a process development and mechanistic perspective, to describe the current state of the field. Advances in hybrid organometallic-radical reactivity are also considered, with particular focus on application in alkyl cross-coupling and perspective on mechanistic analysis.

II. Palladium-Catalyzed Ring-Forming Aromatic C-H Alkylation



A palladium-catalyzed, intramolecular aromatic C-H alkylation with unactivated alkyl halides is described. This process is successful with both iodides and bromides, including those with β-hydrogen atoms present. It tolerates both electron-rich and electron-poor aromatic rings, as well as heteroaromatic substrates. The mild, palladium-catalyzed approach displays compatibility with a diverse range of functional groups, including those which are base- or nucleophile-sensitive. A mechanistic investigation is also presented, suggesting the presence of radical intermediates.

III. A Versatile, Palladium-Catalyzed Approach to Alkene-Alkyl Halide Coupling



A method for the palladium-catalyzed coupling of alkyl halides with alkenes is presented. Reaction conditions determine whether the end product retains the alkyl halide moiety in an atom-transfer radical cyclization (ATRC) reaction, or if the alkene component is restored, affecting a formal Heck-type transformation. The manifold is capable of performing both transformations with unactivated alkyl bromides and a variety of terminal, di- and tri-substituted alkenes under argon atmosphere. It also enables formation of both 5- and 6-membered rings. A mechanistic investigation of this reaction is presented, which suggests the operation of a catalytic, hybrid organometallic-radical process.

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Finally, I owe my deepest gratitude to my wife, Sarah, who in so many ways has enabled me to complete my graduate studies. Her companionship, encouragement, and unwavering support have empowered me to continue in the face of frustration and failure. Her sense of adventure has gotten me out of lab on weekends to explore North Carolina, and my experience here has been richer for it. I cannot fully express the extent of her support over the last five years, but I am unendingly appreciative of it.

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LIST OF ABBREVIATIONS AND SYMBOLS

2D-NMR	two-dimensional nuclear magnetic resonance
acac	acetylacetone
Ad	1-adamantyl
AIBN	2,2'-azobis(2-methylpropionitrile)
AMBN	2,2'-azodi(2-methylbutyronitrile)
Ar	aryl
atm	atmospheres
ATRA	atom-transfer radical addition
ATRC	atom-transfer radical cyclization
ATRP	atom-transfer radical polymerization
BDFE	bond dissociation free energy
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bipy	2,2'-bipyridine
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bs	broad singlet
^{n}Bu	*n*-butyl
^{t}Bu	*tert*-butyl
^{n}BuOH	*n*-butanol
Bu_3SnH	tributyltin hydride
Bz	benzoyl
C	Celsius

CAN	ceric ammonium nitrate
C-C	carbon-carbon bond
C-H	carbon-hydrogen bond
C-M	carbon-metal bond
^{13}C NMR	carbon-13 nuclear magnetic resonance
COD	cyclooctadiene
C-X	carbon-halide bond
Cy	cyclohexyl
Cyp	cyclopentyl
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCA	dichloroacetic acid
DCE	1,2-dichloroethane
DCM	dichloromethane
dcypf	1,1'-bis(dicyclohexylphosphino)ferrocene
dd	doublet of doublets
DIAD	diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine
dippf	1,1'-bis(diisopropylphosphino)ferrocene
DLP	dilauroyl peroxide
DMA	dimethylacetamide
DMAP	4-*N*,*N*-dimethylaminopyridine

DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
dt	doublet of triplets
dtbdppf	1-diphenylphosphino-1'-(di-*tert*-butylphosphino)ferrocene
dtbpf	1,1'-bis(di-*tert*-butylphosphino)ferrocene
EDG	electron-donating group
ee	enantiomeric excess
equiv.	equivalents
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron-withdrawing group
g	gram
h	hour
HAS	homolytic aromatic substitution
^{1}H NMR	proton nuclear magnetic resonance

HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
JohnPhos	2-(di-*tert*-butylphosphino)biphenyl
kcal	kilocalorie
KOAc	potassium acetate
KO^{t}Bu	potassium *tert*-butoxide
L	ligand
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LED	light-emitting diode
LiHMDS	lithium bis(trimethylsilyl)amide
L_n	ligand sphere
LRMS	low-resolution mass spectrometry
M	molar or metal
m	multiplet
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
Me_4NF	tetramethylammonium fluoride
MeOH	methanol

Mes	mesityl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mmol	millimole
MS	molecular sieves
Ms	methanesulfonyl
n	number of atoms/iterations
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
$Ni(COD)_2$	bis(1,5-cyclooctadiene)nickel(0)
$Ni(PPh_3)_4$	tetrakis(triphenylphosphine)nickel(0)
NIS	*N*-iodosuccinimide
NMI	*N*-methylimidazole
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
Nu	nucleophile
OMTM	methylthiomethyl ether
$P(4\text{-}ClPh)_3$	tris(4-chlorophenyl)phosphine
PBI	perylene-3,4:9,10-tetracarboxylic acid bisimide
p-cymene	1-methyl-4-(propan-2-yl)benzene

$[Pd(allyl)Cl]_2$	allylpalladium(II) chloride dimer
Pd/C	palladium on carbon
$[Pd(cinnamyl)Cl]_2$	cinnamylpalladium(II) chloride dimer
$PdCl_2(PhCN)_2$	bis(benzonitrile)palladium(II) chloride
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$	dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)
$Pd(dtbpf)Cl_2$	dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II)
$Pd(OAc)_2$	palladium(II) acetate
$Pd(P^tBu_3)_2$	bis(tri-*tert*-butylphosphine)palladium(0)
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
Ph	phenyl
Ph^tBu	*tert*-butylbenzene
$PhCF_3$	*α*,*α*,*α*-trifluorotoluene
$PhCH_3$	toluene
PhH	benzene
PhI	iodobenzene
PMDETA	*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine
PMP	1,2,2,6,6-pentamethylpiperidine
ppm	parts per million
^iPr	isopropyl
Proton Sponge	1,8-bis(dimethylamino)naphthalene
$P(^tBu)_2Me$	di-*tert*-butylmethylphosphine
pyr	pyridine

q	quartet
Q-Phos	1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene
R	substituent
rac	racemic
R_f	retention factor
rr	regioisomeric ratio
rt	room temperature
s	singlet
S_EAr	electrophilic aromatic substitution
SET	single-electron transfer
SIMes	1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
S_N2	bimolecular nucleophilic substitution
S_NAr	nucleophilic aromatic substitution
T	temperature
t	triplet
TAA	2-methylbutan-2-ol
TBABr	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

THP	tetrahydropyran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
Tol	tolyl
Ts	*para*-toluenesulfonyl
UV	ultraviolet
X	halide
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
Å	angstrom
∂	chemical shift
µL	microliter
°	degree
□	vacant coordination site

Chapter I: Alkyl Electrophiles in Palladium-Catalyzed Cross-Coupling

1.1 Introduction

Alkyl halides are among the simplest and most useful organic building blocks available. Due to the high electronegativity of halogens as compared to carbon, they are widely applied as electrophiles in substitution and elimination reactions, and can contribute to the induction of electron density away from reactive moieties to further activate them towards reactivity. The utility of alkyl halides in synthesis is complemented by their low cost and ubiquitous availability from a variety of commercial sources. Additionally, they can be easily synthesized in one step from other, even more common functional groups, such as alcohols, alkenes, and carboxylic acids, when not commercially available.

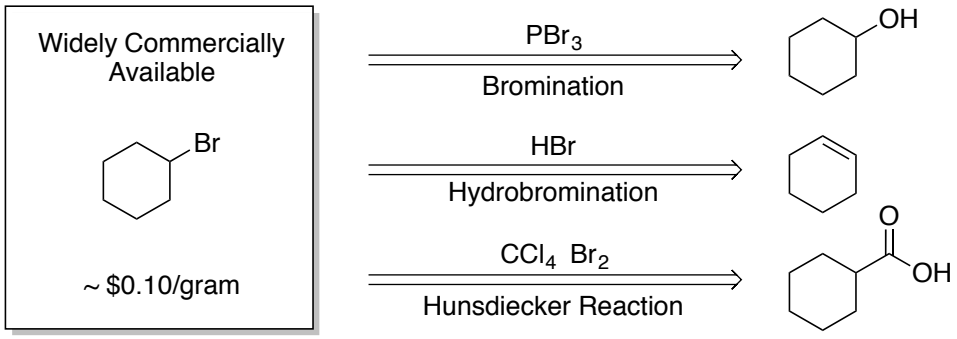

Figure 1-1: Availability of Alkyl Halides as Synthetic Organic Building Blocks

1.1.1 Obstacles of Metal-Catalyzed Alkyl Halide Reactions

While the use of alkyl halides is widespread in a variety of fundamental organic transformations, their scope of application is not universal. Transition-metal-catalyzed transformations have long made use of aryl and vinyl halides as electrophiles for oxidative

addition and subsequent transformations.[1-4] However, these reactions are far less common with alkyl halides as electrophiles.[5-8] This can be traced to two fundamental properties of interactions between alkyl halides and transition metals: poor oxidative addition of sp^3-hybridized C-X bonds,[9-11] and facile β-hydride elimination upon formation of an alkyl-metal intermediate.[12-14]

Oxidative addition of sp^2-hybridized aryl and vinyl halides normally occurs as a two-step process. First the metal center coordinates to the arene or alkene, followed by insertion of the metal into the C-X bond. This process is thought to be operant because aryl and vinyl halides cannot undergo S_N2-type activation and aryl halides are too electron-rich to undergo nucleophilic aromatic substitution.[15]

On the other hand, sp^3-hybridized alkyl halides are thought to operate via S_N2-type activation with the metal center in a two-step process.[16] This is substantiated by an acceleration of rate in polar solvents and the observation of stereochemical inversion at C-X stereocenters. A pair of electrons from the electron-rich metal center displaces the halide ion, forming a carbon-metal bond. The displaced halide then recombines with the now electron deficient metal center, resulting in a net two-electron oxidation of the metal. This process is substantially slower than sp^2-hybridized halide activation, as substitution into the electron-rich alkyl halide is less favorable than when the process is assisted by coordination to an arene or alkene, and the arene withdraws electron density from the C-X bond.

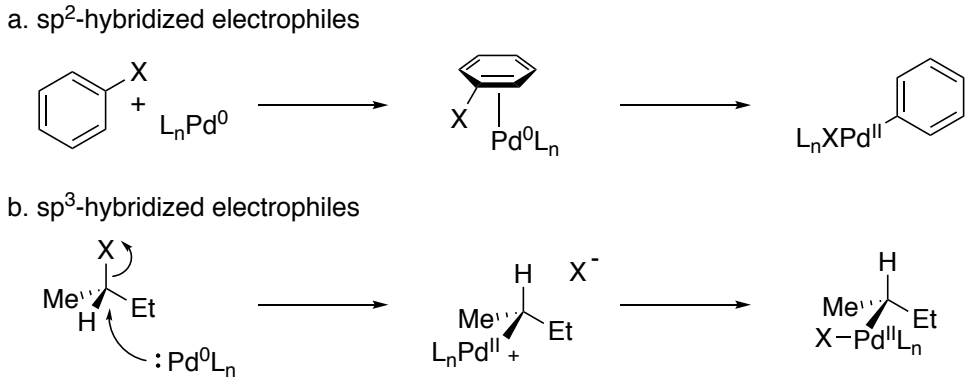

Figure 1-2: Differences in Oxidative Addition with Palladium Between sp^2- and sp^3-Hybridized Electrophiles

If oxidative addition with an alkyl electrophile is successful, the alkyl-metal intermediate formed is prone to undergo unproductive side reactions at a faster rate than the desired reactive pathway. The most prevalent such reaction is β-hydride elimination. This occurs when a vacant coordination site on the coordinatively unsaturated metal center is filled by an agostic interaction from a hydrogen atom in the β-position of the alkyl substituent. This restricts rotation, and locks the complex in a configuration in which the metal and the β-hydrogen are *syn* coplanar. When this conformation is achieved, rapid elimination occurs, forming a metal hydride species bound to the newly formed alkene in an η^2-fashion. This process is oxidation-state-neutral from the perspective of the metal. Aryl- and vinyl-metal species do not share this proclivity, as they are unable to achieve proper overlap between the metal and a β-hydrogen, and would form high-energy benzyne intermediates upon elimination.

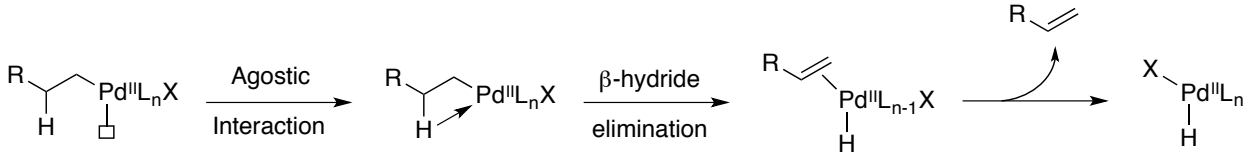

Figure 1-3: β-Hydride Elimination Mechanism for Alkyl-Palladium Intermediates

1.1.2 Privileged Alkyl Electrophiles

In order to employ sp^3-hybridized alkyl halides in transition-metal-catalyzed carbon-carbon bond-forming reactions, researchers have turned to substrate design to obviate the challenges associated with slow oxidative addition and facile β-hydride elimination. These "privileged" alkyl halide electrophiles generally fall into two categories: activated alkyl halides and those without accessible β-hydrogens. Examples of these two types are shown in Figure 1-4.

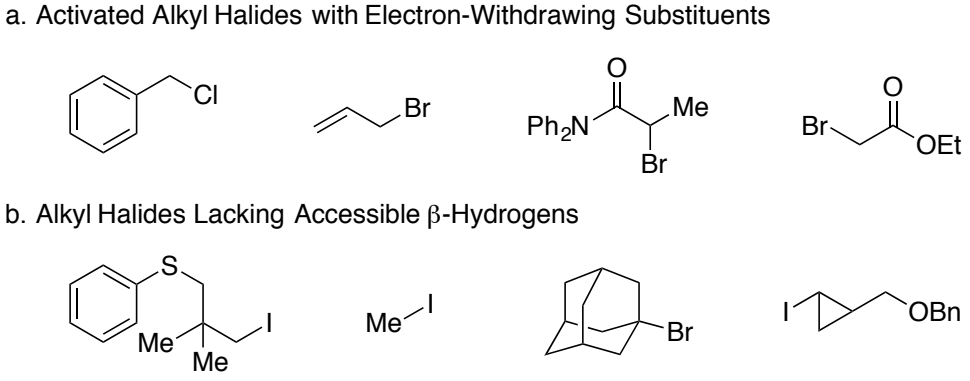

Figure 1-4: Privileged Alkyl Electrophiles Designed to Engage Transition-Metal Catalysts

The first category, activated alkyl halides, includes those which seek to mimic the advantages of sp^2-hybridized aryl and vinyl halides in order to facilitate more rapid oxidative addition (Figure 1-5a). This can take the form of benzylic[17] or allylic[18] halides, where the metal center is able to bind first to the arene or alkene before undergoing oxidative addition into the C-X bond. Additionally, α-halo carbonyl complexes serve as electron-withdrawing groups to decrease electron density in the C-X bond and make S_N2-type oxidative addition more facile.[19]

Another approach involves the preclusion of β-hydride elimination upon formation of an alkyl-metal intermediate (Figure 1-5b). This approach can also be achieved in two different ways. The alkyl halide may be designed without any β-hydrogens, such as a methyl[20] or neopentyl[21] halide and therefore would be unable to eliminate. Additionally, alkyl halides where

β-hydrogens are unable to properly align with palladium to allow elimination, or where elimination itself is geometrically forbidden (i.e., Bredt's Rule) have been successfully employed. Such categories include cyclopropyl[22] and adamantyl[23] halides.

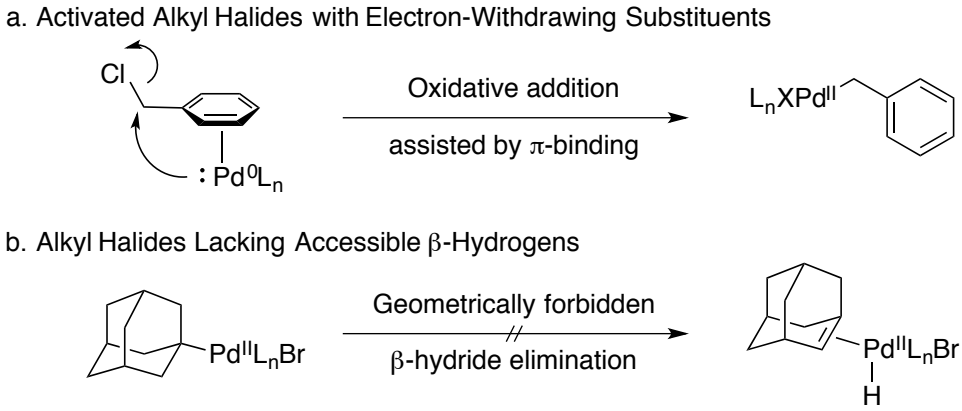

Figure 1-5: Mechanistic Justification for the Activity of Privileged Alkyl Electrophiles

1.2 Cross-Coupling Reactions with Alkyl Electrophiles

One of the principal methods for building molecular complexity through the use of carbon-halide bonds is through transition metal-catalyzed cross-coupling reactions. These reactions join two carbon fragments together through formation of a C-C bond through the use of a late transition metal catalyst, typically palladium, and are regularly used in the synthesis of medicinally and industrially valuable compounds. They are known for their efficiency (often requiring <5 mol% catalyst), selectivity, and mild reaction conditions, tolerating high molecular complexity and a wide variety of peripheral functional groups. The significant utility of these reactions was recognized by the awarding of the Nobel Prize in Chemistry jointly to Richard Heck, Ei-ichi Negishi, and Akira Suzuki in 2010 "for palladium-catalyzed cross-couplings in organic synthesis."[24] A number of different coupling reactions have been developed using different nucleophilic coupling partners, which generally complement each other to encompass a broad scope of reactivity.[25] A selection of cross-coupling reactions is described in Figure 1-6.

However, they all typically employ aryl and vinyl alkyl halides as electrophiles, due to the difficulties associated with alkyl halides discussed above.

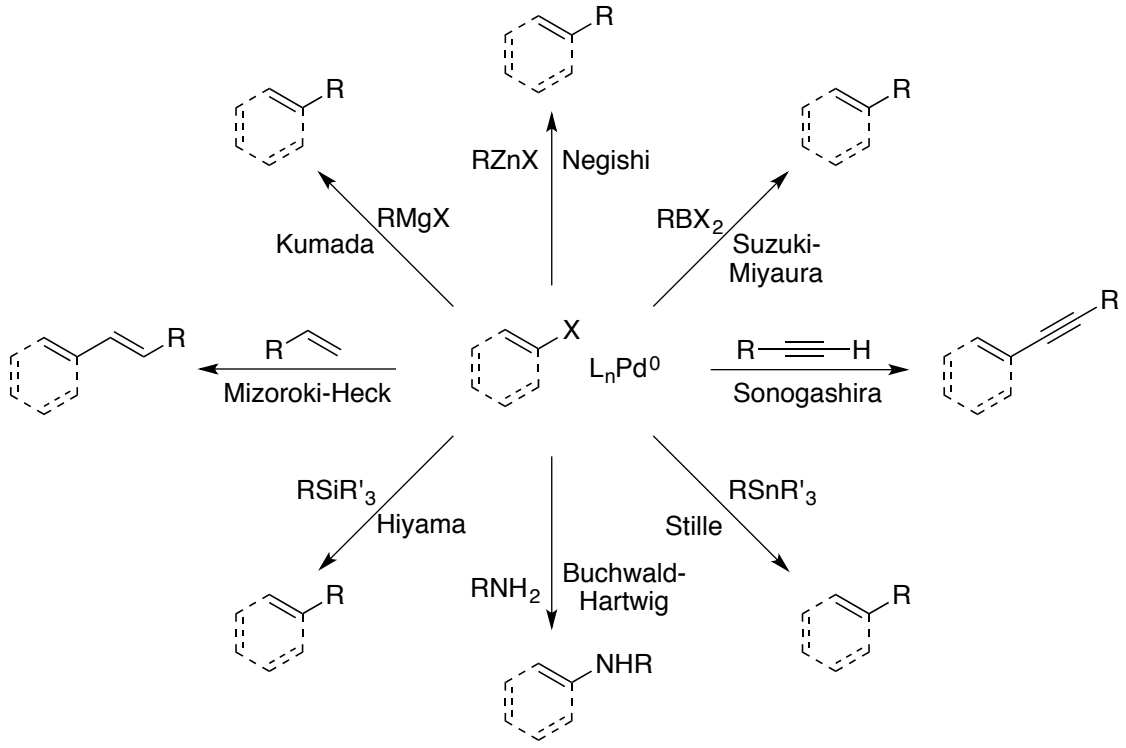

Figure 1-6: Palladium-Catalyzed Cross-Coupling Reactions

1.2.1 Cross-Coupling Reactions Involving Transmetallation

Over the past two decades, significant progress has been made to employ unactivated alkyl electrophiles in cross-coupling reactions. The first such reactions developed were those featuring transmetallation in the reaction mechanism. The seminal report of a cross-coupling reaction featuring an unactivated alkyl halide was made by Suzuki in 1992 (Figure 1-7).[26] This report described the palladium-catalyzed coupling of primary alkyl iodides with alkyl and aryl borane reagents. While these conditions suppressed β-hydride elimination enough to facilitate coupling in good yield, significant quantities of β-hydride elimination and byproduct were still observed.

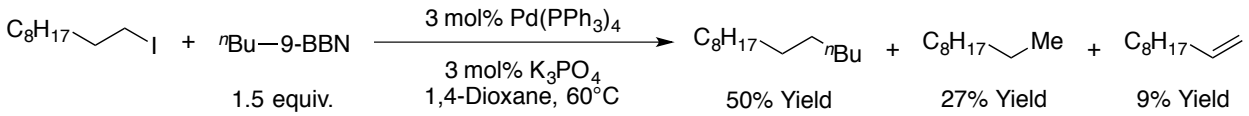

Figure 1-7: Seminal Report of Alkyl Halides in Transition Metal-Catalyzed Cross-Coupling

More recently, the Fu group has developed several examples of palladium-catalyzed cross-coupling reactions utilizing unactivated alkyl electrophiles. Early reports described Hiyama,[27] Negishi,[28-29] Stille,[30-31] and Suzuki[32-35] reactions, coupling unactivated alkyl halides with silanes, organozinc, organotin, and organoboron reagents respectively. These reports are summarized in Figure 1-8. In each report, bulky, electron-rich trialkylphosphine ligands were used to facilitate the reaction. These have a two-fold impact; first the ligands contributed electron density to the metal center, enabling more rapid oxidative addition with the unactivated alkyl electrophiles. These ligands also bind tightly to the metal and block access to coordination sites, preventing β-hydride elimination, which requires coordination of an agostic hydrogen to the metal before eliminating.

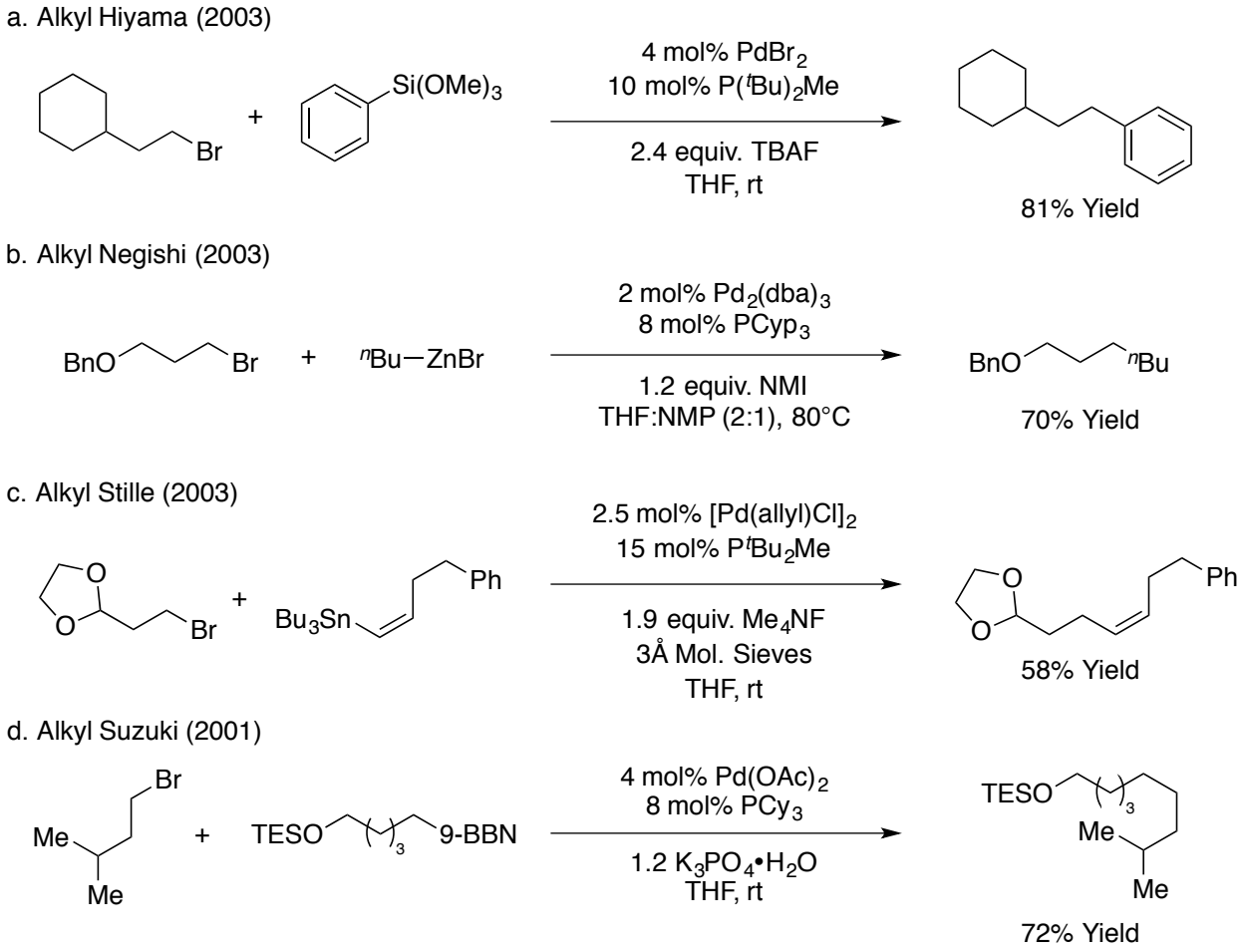

Figure 1-8: Examples of Palladium-Catalyzed Cross-Coupling Reactions of Alkyl Halides with Trialkyl Phosphine Ligands

Mechanistic inquiry into these reactions suggests that they proceed through a conventional organometallic cross-coupling mechanism, undergoing oxidative addition, transmetallation, and reductive elimination (Figure 1-9). This is substantiated by the isolation of alkyl palladium species following oxidative addition of alkyl halide with stoichiometric palladium complex.[35] Reaction rates were shown to accelerate in increasingly polar media, caused by decreased reaction barrier from stabilization of charged transition state. Additionally, stereochemical inversion is observed in reactions of stereoenriched primary deuterated tosylates.[34]

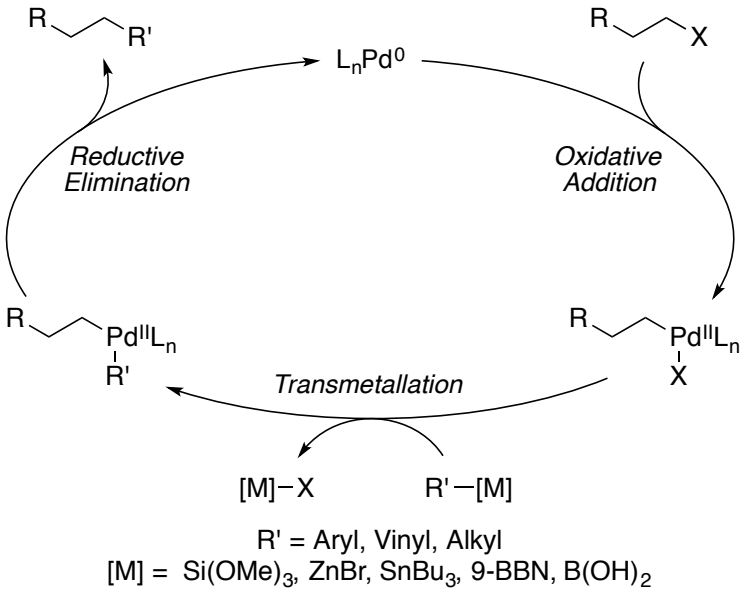

Figure 1-9: Proposed Mechanism for Palladium-Catalyzed Alkyl Cross-Coupling Reactions

Another cross-coupling reaction that has proved difficult to perform with unactivated alkyl halide electrophiles is the Kumada coupling. This transformation involves the coupling of a carbon electrophile with a Grignard reagent through transition metal catalyst. The Beller group was the first to report an alkyl Kumada coupling, joining aryl Grignard reagents and unactivated alkyl chlorides in good yields with palladium catalyst and bulky trialkylphosphine ligands.[36] The use of NMP was found to be crucial to the success of the reaction. It was proposed that NMP binds weakly to palladium to block vacant coordination sites, inhibiting β-hydride elimination enough to allow efficient coupling. Further investigation by the Kambe group extended this manifold to include coupling unactivated alkyl bromides and tosylates with Grignard reagents.[37]

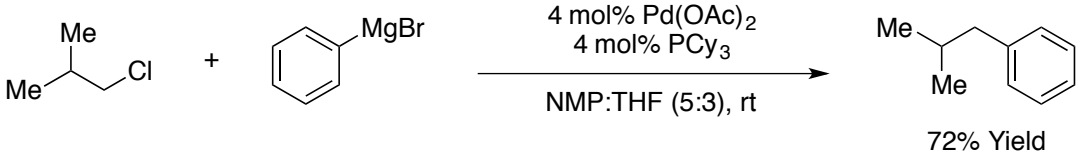

Figure 1-10: Palladium-Catalyzed Kumada Couplings with Unactivated Alkyl Chlorides

The Sonogashira cross-coupling involves the formation of a carbon-carbon bond between a carbon electrophile and an alkyne through tandem palladium/copper catalysis.[38] Copper first binds to the alkyne, forming a copper acetylide species *in situ*, which undergoes transmetallation with an arylpalladium (II) halide, followed by reductive elimination to form the target carbon-carbon bond. Because of the mechanism by which this transformation functions, it was expected that the use of palladium catalysts with bulky, electron-rich phosphine ligands could enable successful coupling with unactivated alkyl electrophiles. However, the Fu group attempted alkyl Sonogashira reactions with catalyst systems they had previously employed in alkyl Hiyama, Negishi, Stille, and Suzuki reactions, with each set of conditions proving unsuccessful.

In screening other highly donating ligands, the Fu group found NHC ligands to successfully affect the desired coupling.[39] Further screening found highly sterically demanding NHC ligands to be more successful than less bulky analogues, presumably due to their ability to block coordination sites on the metal, restricting β-hydride elimination. Settling on 1,3-bis(1-adamantyl)imidazolium tetrafluoroborate and allylpalladium chloride dimer as the catalyst system, they were able to couple a variety of primary bromides and terminal alkynes (Figure 1-11). Furthermore, mild reaction conditions and low catalyst loadings of both palladium and copper enable a broad functional group tolerance, including unprotected alcohols, nitriles, and alkyl chlorides.

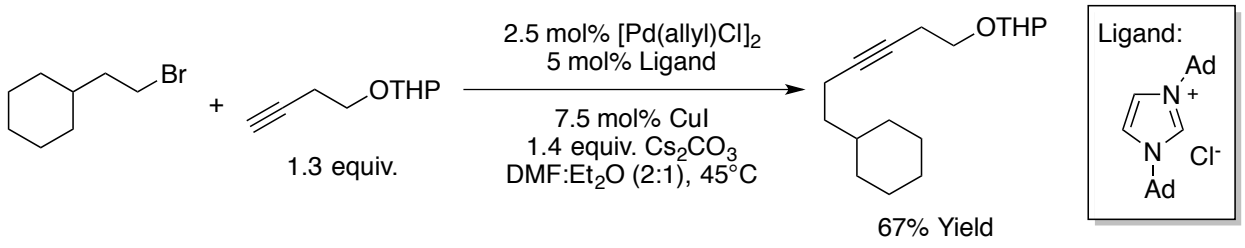

Figure 1-11: Palladium-Catalyzed Sonogashira Couplings with Unactivated Alkyl Halides Using NHC Ligands

In 2006, the Glorius group was able to expand upon the work of the Fu group to employ secondary alkyl bromides in a Sonogashira coupling reaction (Figure 1-12).[40] This report describes the use of a palladium catalyst with a bioxazoline-derived NHC ligand. This class of ligands is highly electron-rich and features significant steric demand. Additionally, higher reaction temperatures and more polar solvent systems were required. These more forcing conditions are required to facilitate oxidative addition with more reticent secondary alkyl electrophiles. However, they did not diminish from the broad functional group tolerance featured, as alkenes, epoxides, and alkyl chlorides are well tolerated.

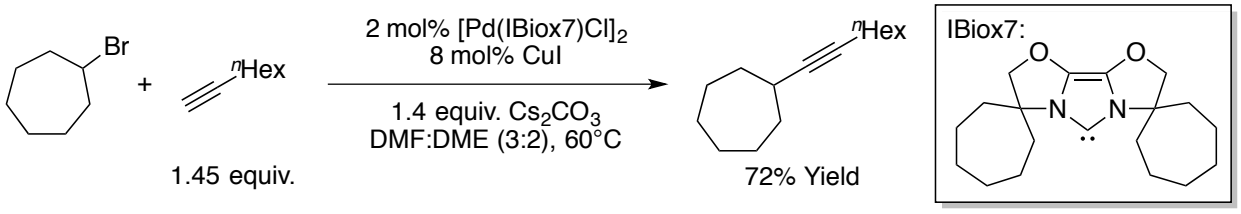

Figure 1-12: Palladium-Catalyzed Sonogashira Couplings with Secondary Alkyl Bromides

1.2.2 Alkyl Heck Reactions

Unlike the cross-coupling reactions discussed herein, the Heck reaction does not bind the coupling partner to palladium through a concerted transmetallation step.[41-43] Instead, an open site is required on palladium where the alkene can bind in an η^2 fashion before the target carbon-carbon bond is formed through carbopalladation. While this mode of incorporation allows the reaction to work with simple alkenes rather than prefunctionalized coupling partners, the open site on palladium can facilitate premature β-hydride elimination, furnishing dehydrohalogenation byproducts (Figure 1-13).

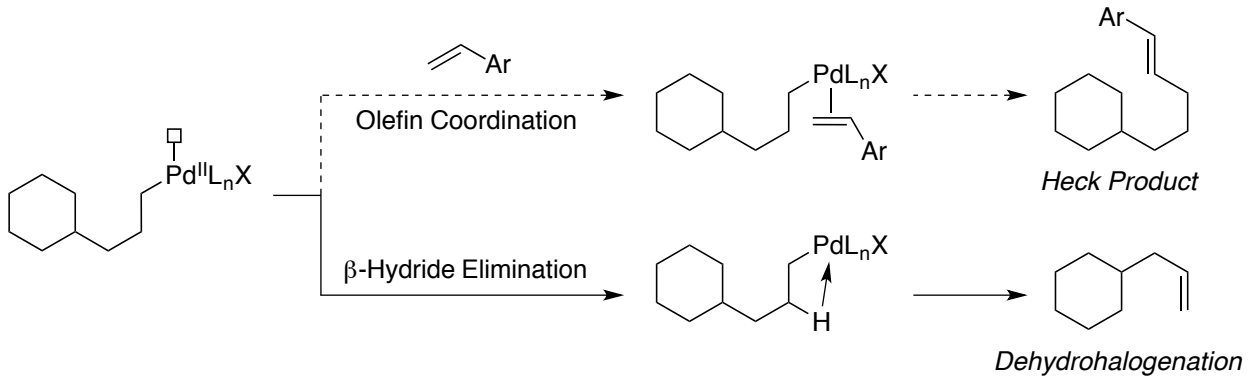

Figure 1-13: Possible Reaction Pathways for Organopalladium Intermediates in Alkyl Heck Reactions

However, β-hydride elimination cannot be restricted outright, as it is necessary for the success of a Heck-type reaction. Premature β-hydride elimination affects the dehydrohalogenation of the alkyl halide electrophile, but β-hydride elimination following carbopalladation affects the successful Heck coupling (Figure 1-14). Failure to enable β-hydride elimination following carbopalladation can allow further carbopalladation, leading to polymer or oligomer formation. This balance between carbopalladation and β-hydride elimination is at the heart of developing a palladium-catalyzed alkyl Heck reaction which proceeds through organometallic intermediates. The traditional Heck transformation with aryl or vinyl halides does not face this particular challenge, since β-hydride elimination of aryl and vinyl halides before carbopalladation is geometrically restricted. Therefore, as long as β-hydride elimination is rapid as soon as it is geometrically allowed (i.e. after carbopalladation), the coupling is successful.

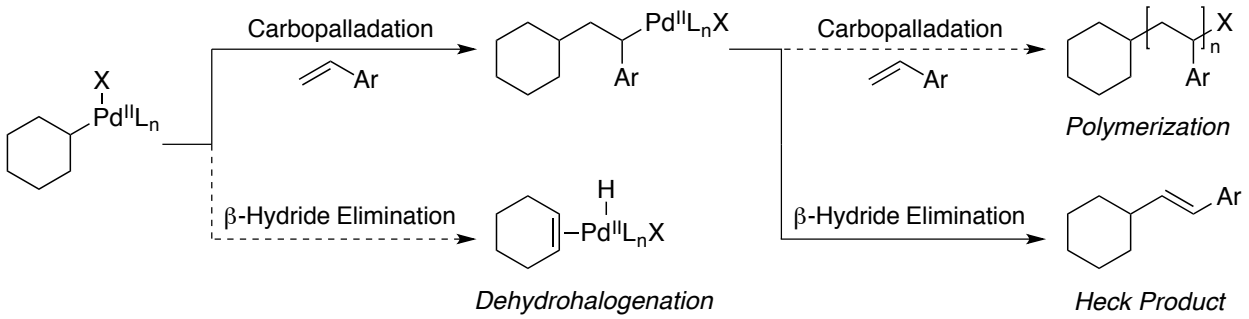

Figure 1-14: Roles of Carbopalladation and β-Hydride Elimination in a Palladium-Catalyzed Alkyl Heck Reaction

This particular challenge causes the Heck reaction to be more difficult to adapt to the use of alkyl halide electrophiles. For this reason, the initial report of an alkyl Heck reaction was made somewhat later than other cross-coupling reactions which utilize organometallic coupling partners. Recently, however, there have been a few reports engaging alkyl halides in Heck-type reactions. In 2007, the Fu group reported the first such example, demonstrating intramolecular Heck-type cyclizations with alkyl halides and alkenes (Figure 1-15).[44] While this report described the coupling of bromides and chlorides through the use of a palladium/NHC catalyst, it was limited to the formation of methylenecyclopentene rings through 5-exo cyclization with primary alkyl halides and terminal alkenes. To date this is the only example of an alkyl Heck reaction proposed to function through an entirely organometallic mechanism.

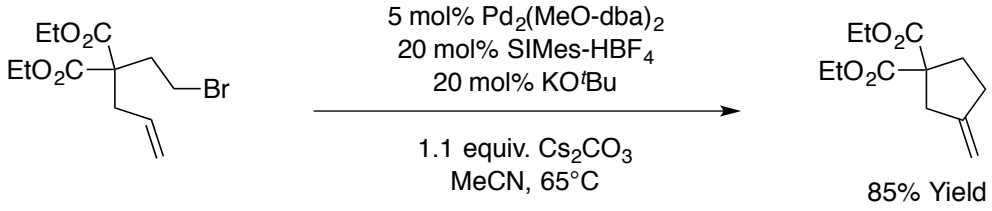

Figure 1-15: Seminal Report of Palladium-Catalyzed Alkyl Heck Cyclizations

1.3 Single Electron Activation of Alkyl Electrophiles

The difficulties associated with the activation of alkyl halides by transition metal catalysts typically apply to oxidative addition which occurs through a two-electron process. Alternatively, alkyl halides may be activated through radical intermediates, which obviate these disadvantages by avoiding alkylmetal species. The most common way to activate alkyl halides towards a carbon-centered radical is through the use of radical initiators such as AIBN or DLP.[45-47] While these reagents can achieve important transformations without the drawbacks of two-electron transition metal catalysis, radical intermediates are highly reactive and can suffer promiscuous reactivity, often leading to unproductive byproducts.

A means to reining in the reactivity of radical intermediates is the use of hybrid organometallic radical processes, using transition metal catalysts to activate alkyl halides through radical intermediates.[48] This type of activation can occur through one of two ways, shown in Figure 1-16 compared to purely organometallic activation and radical initiation.[49] The first method involves the direct abstraction of the halide by the metal, forming a carbon-centered radical and a metal-halide species. Alternatively, the metal may engage in single-electron transfer with the halide, forming an alkyl halide radical anion, which can then disproportionate with the metal(m+1) species to form the alkyl radical intermediate. As with all radical-mediated processes, mechanisms which proceed via radical abstraction or single-electron transfer will result in stereoablative activation of a stereoenriched alkyl halide.

The means by which activation of an alkyl halide to a carbon-centered radical is achieved largely depends on the reduction potential of the metal and the homolytic bond dissociation free energy (BDFE) of the target halide. Secondary halides have lower barriers to single-electron reduction than do primary halides, while iodides have lower barriers than similar bromides.[50] As

such, substrates bearing these moieties are more likely to undergo activation by single electron transfer. Electrophiles with higher single-electron reduction potentials but still fairly modest BDFEs (i.e., primary halides) can be more likely to undergo direct abstraction.

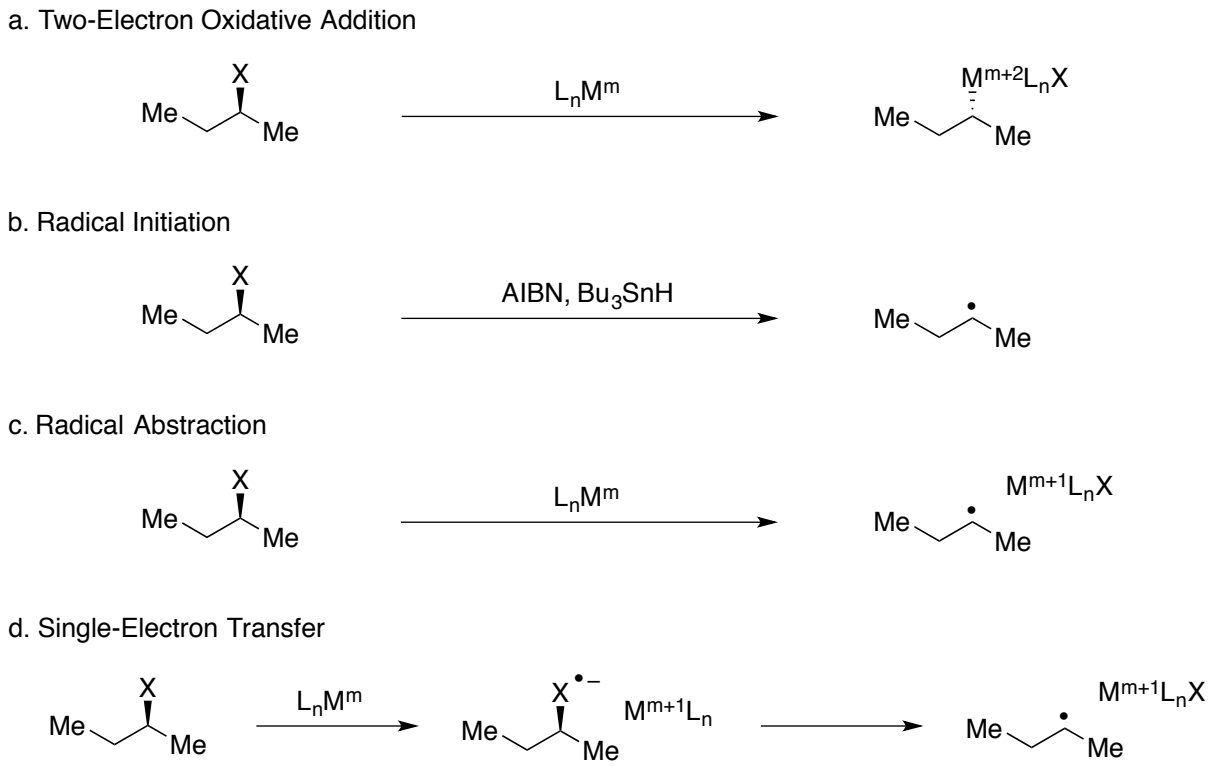

Figure 1-16: Comparison of Oxidative Addition to Radical-Mediated Carbon-Halide Activation

1.3.1 Initiation and Catalysis of Radical Reactions

The use of transition metals to facilitate organic reactions is typically thought of in terms of catalysis, with catalytic cycles being drawn to describe the formation of product and the regeneration of the active transition metal reagent. However, simpler reaction diagrams can be considered when metal complexes activate C-X bonds through radical intermediates. While the catalytic model involves the turnover of catalyst for each molecule of product made, if the turnover step is favorable enough to proceed through radical propagation without intervention by the transition metal reagent, the metal reagent may primarily serve as a radical initiator.

The primary determinant between metal-catalyzed reactions involving radical intermediates and transition-metal-initiated radical chain reactions is the rate of the radical propagation steps involved in the reaction.[51-52] If all propagation steps are fast, the radical chain will outcompete catalysis and off-chain side reactions, and be the predominant mechanism of the reaction. If however, there are one or more slow steps, radical-radical termination can outcompete propagation, and the chain will not be efficient. In cases where radical chains do not turn over efficiently, the metal may be reintroduced after initial activation to complete the cycle in place of slow propagation steps.

In Figure 1-17 is shown an atom-transfer radical addition reaction and the two mechanisms by which it may operate.[53] In both mechanisms, a malonate radical undergoes addition into the alkene to form a secondary carbon-centered radical. This step is driven by the formation of a new carbon-carbon bond at the expense of an existing π bond. In part a, the product is formed and a new equivalent of substrate is activated through radical abstraction of the tertiary halide. This step is thermodynamically favorable due to the formation of a more stable tertiary radical from a less stable intermediate. If however, this transfer is kinetically disfavored, the chain is inoperative. In this case, the radical intermediate may transfer its electron back to palladium, recombining with the halide and regenerating the original palladium(0) species. This palladium(0) reagent may then activate another molecule of starting material by abstraction or single electron transfer and in doing so complete the catalytic cycle.

Since the kinetic properties of the radical propagation steps determine which mechanism will be operant, changing the physical properties of these substrates can determine the character of the mechanism. Because it was determined for the atom-transfer radical addition reaction described in Figure 1-17 that exchanging iodide for bromide decreases the rate of radical

propagation through halide abstraction by a factor of 10^3, it is possible that modifying the halide could alter the rates of radical propagation steps enough to change the type of mechanism that is operant.

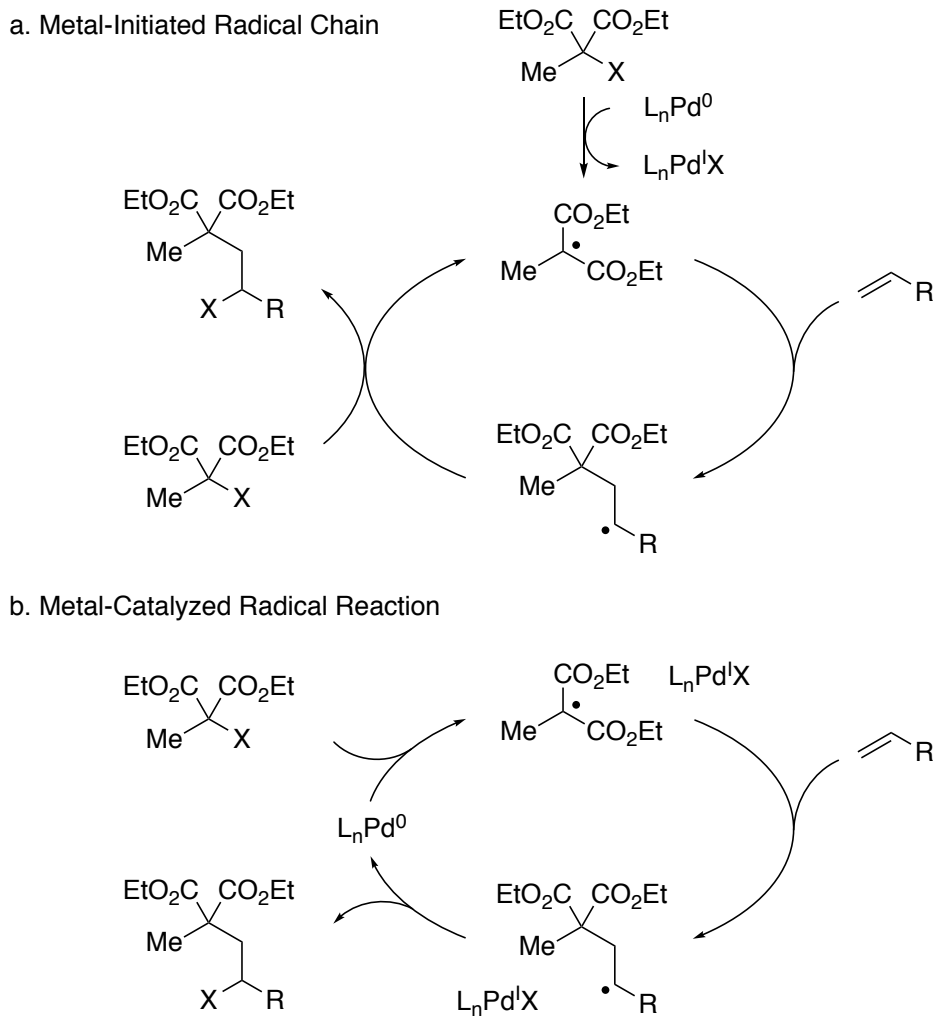

Figure 1-17: Mechanistic Distinctions Between Metal-Catalyzed and Metal-Initiated Radical Reactions.

1.3.2 Atom-Transfer Radical Polymerization

The use of hybrid organometallic-radical reactivity has the potential to capitalize on the most advantageous aspects of each method. Highly reactive radical intermediates can accelerate reaction rates or enable reactions not otherwise possible, while the presence of transition metal

catalysts can stabilize these intermediates and reduce the issues of promiscuous reactivity. A reaction that demonstrates this ability to great effect is atom-transfer radical polymerization (ATRC). As depicted in Figure 1-18, this process begins by the activation of an alkyl halide through abstraction by a copper(I) catalyst, forming an alkyl radical and a copper(II) intermediate.[54] Radical addition to one equivalent of styrene leads to the formation of a benzylic radical intermediate. This intermediate can continue to react with additional equivalents of styrene. However, the benzylic intermediate can also undergo ligand transfer with the copper(II) intermediate to form a more stable benzyl bromide and reform the copper(I) catalyst. This ligand transfer is reversible, but the equilibrium lies towards the alkyl bromide. This keeps the effective concentration of the radical intermediate low, limiting deleterious side reactivity and funneling the reactive intermediates towards the desired polymerization.

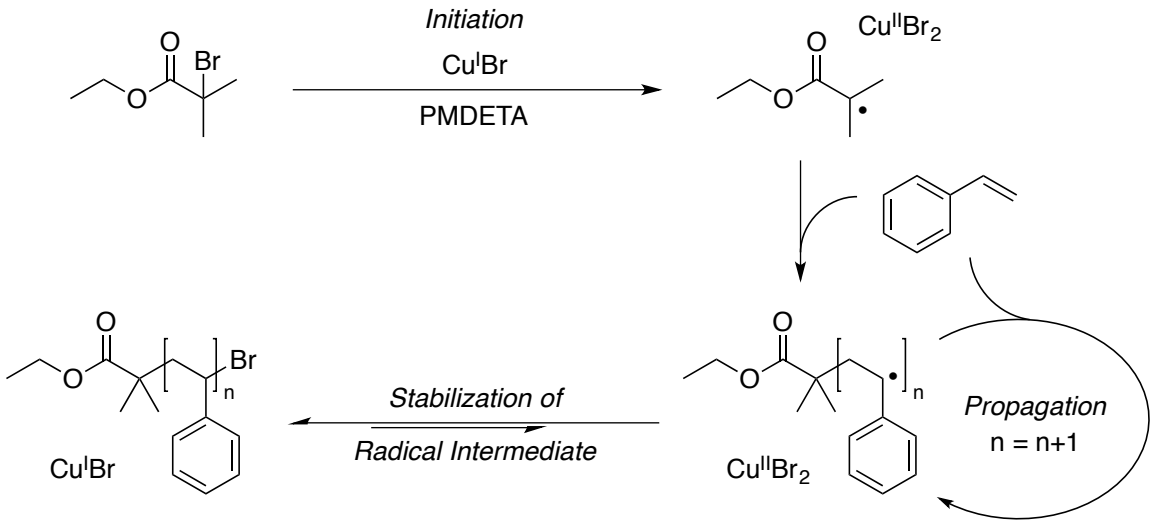

Figure 1-18: Mechanism of Atom-Transfer Radical Polymerization

1.3.3 Radical-Mediated Cross-Coupling Reactions

The characteristics of hybrid organometallic-radical reactivity that prove so advantageous for ATRC can also facilitate carbon-carbon bond formation in cross-coupling reactions. One of

the best-known transition-metal-catalyzed hybrid organometallic-radical cross-coupling reactions is the Kharasch addition, which can be seen as a discrete variant of ATRP (Figure 1-19).[55] In the Kharasch addition, a perfluoroalkyl halide is activated by a palladium catalyst through radical intermediates to add across an alkene, followed by recombination of the alkyl radical intermediate with the transition metal halide species. As with ATRP, this process limits the promiscuity of radical intermediates and funnels the reaction towards successful coupling.

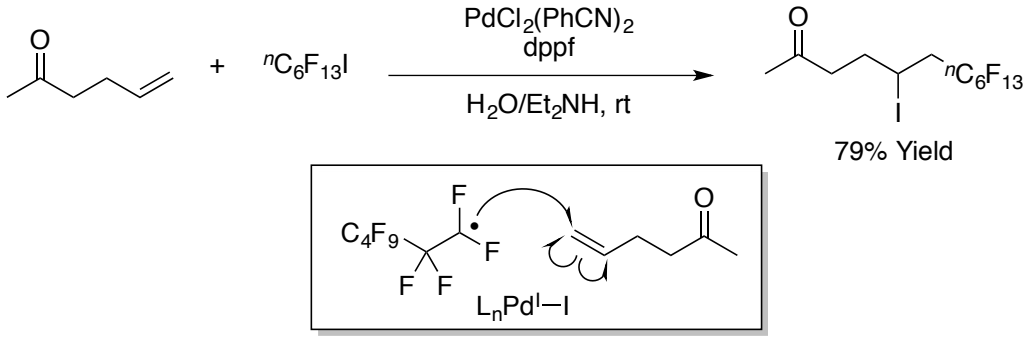

Figure 1-19: Palladium-Catalyzed Kharasch Addition of Perfluoroalkyl Iodides

In contrast to the palladium-catalyzed cross-couplings shown in Figures 1-8 and 1-10, which are thought to proceed through a two-electron pathway, Fu has reported nickel-catalyzed cross-couplings with unactivated alkyl electrophiles, which are proposed to involve radical intermediates.[56-58] One such reaction, a Suzuki coupling of unactivated alkyl bromides with arylboronic acids, involves a carbon-centered radical which undergoes cyclization onto a pendant olefin before intermolecular carbon-carbon bond formation with the organometallic coupling partner (Figure 1-20).[59] Stereochemical outcomes are found to be identical to radical chain reactions initiated by radical initiators such as AIBN and tributyltin hydride.

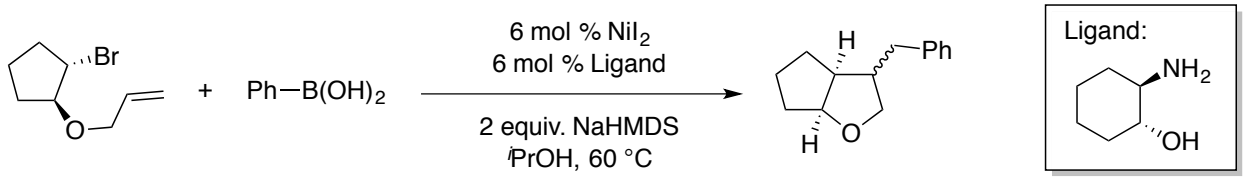

Figure 1-20: Nickel-Catalyzed Suzuki Cross-Couplings with Unactivated Alkyl Electrophiles

Our laboratory has developed two examples of Heck reactions using palladium catalysis and unactivated alkyl electrophiles (Figure 1-21). Both of these reactions were proposed to function through radical intermediates rather than by traditional organometallic means. The first report described palladium-catalyzed alkyl Heck-type cyclizations under CO atmosphere.[60] This manifold enables the use of both primary and secondary alkyl iodides, and a variety of substituted alkenes to form both 5- and 6-membered rings. Subsequently, we reported the first example of a palladium-catalyzed intermolecular alkyl Heck reaction, coupling primary and secondary iodides with a variety of activated alkenes.[61]

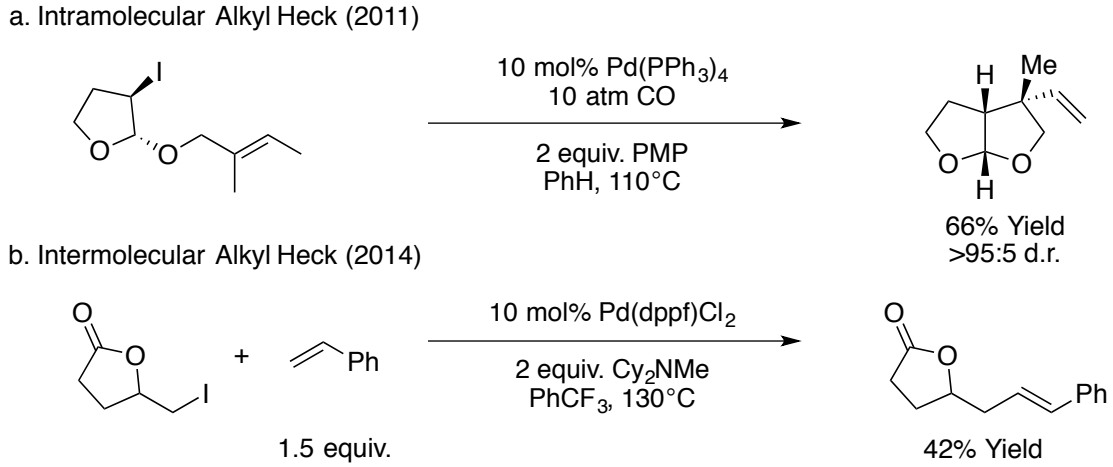

Table 1-21: Palladium-Catalyzed Heck Reactions with Unactivated Alkyl Iodides

1.4 Summary and Outlook

The use of alkyl electrophiles in transition-metal-metal catalyzed cross-coupling reactions has long posed a significant challenge due to their reluctance towards engaging in

oxidative addition with transition metal catalysts and the proclivity of alkyl-metal intermediates to engage in undesired reaction pathways. Despite these challenges, Fu and others have been able to engage alkyl electrophiles in organometallic cross-couplings through the use of bulky, electron-rich trialkylphosphine ligands to block up empty coordination sites on the metal. Alternatively, the use of hybrid organometallic-radical reactivity has been shown to enhance the ability to engage alkyl electrophiles in transition metal-catalyzed cross-coupling reactions without the drawback of alkylmetal intermediates.

While alkyl electrophiles have been employed in a few seminal examples of cross-coupling reactions requiring π-coordination of the nucleophilic coupling partner (alkene, alkyne, or arene), these manifolds are either severely limited in scope, as with Fu's alkyl Heck reaction, or require harsh or toxic reaction conditions. There remains a need for a mild, palladium-catalyzed manifold for the cross-coupling of unactivated alkyl-electrophiles with coupling partners that require π-coordination to a vacant coordination site on palladium. Herein are described efforts to engage arenes and heteroarenes (Chapter II) and alkenes (Chapter III) in cross couplings with unactivated alkyl electrophiles to affect C-H alkylation and Heck reactions respectively.

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Chapter II: Palladium-Catalyzed Ring-Forming Aromatic C-H Alkylation

2.1 Introduction

The construction of aryl and heteroaryl C(sp2)-C(sp3) bonds is of great importance in the synthesis of bioactive small molecules containing polycyclic cores.[1-3] This transformation is typically achieved through one of three methods: the Friedel-Crafts reaction,[4,5] homolytic aromatic substitution (HAS),[6-8] or a condensation such as the Pictet-Spengler reaction.[9,10] These are all highly synthetically useful reactions, and all have long histories in the synthesis of pharmaceutical targets, but each has significant limitations, and none can be considered a general method for the synthesis of the target carbon-carbon bonds.

2.1.1 Friedel-Crafts Reaction

The Friedel-Crafts Reaction is achieved through the treatment of an alkyl halide with a strong Lewis acid such as $AlCl_3$, inducing electrophilic aromatic attack at the activated halide. While this has been applied to great effect in complex chemical synthesis, such as the formation the dihydroquinolone core of the antipsychotic aripiprazole as shown in Figure 2-1,[11] the more widespread use of this method is hindered by its limitations in reactivity. It requires superstoichiometric strong Lewis acid and high temperatures, and is limited to the use of highly electron-rich arenes and heteroarenes such as anisole or aniline derivatives. Additionally, as arenes become increasingly electron-rich as they are alkylated, substrates can be polyalkylated unless run with great excess of the arene component or in an intramolecular fashion.[12] This limits the application of the Friedel-Crafts reaction in complex and late-stage synthesis when arene components are costly, and the use of excess reagent is undesirable.

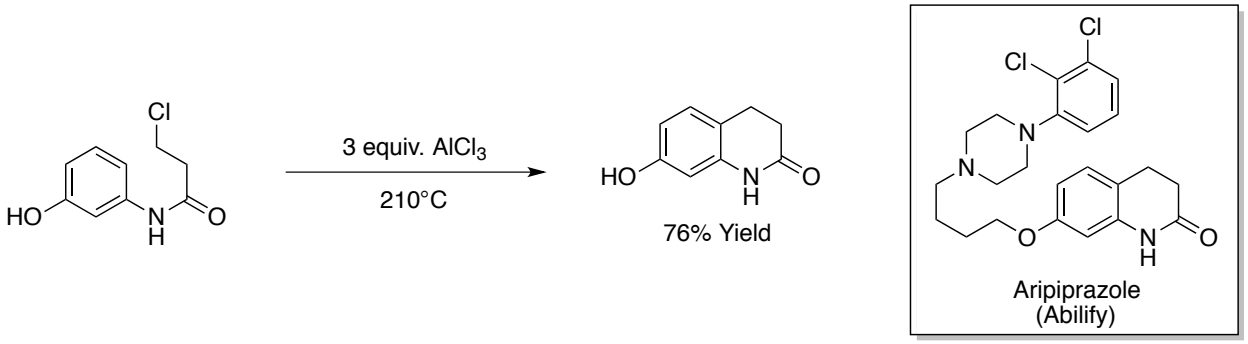


Figure 2-1: Use of Friedel-Crafts Reaction in the Synthesis of Antipsychotic Aripiprazole

More recently, advances have been made to expand the scope of this manifold, using transition metal catalysts instead of strong Lewis acids and alcohols instead of alkyl halides. For instance, in 2008, the Chan group reported the C-H alkylation of arenes and heteroarenes with allylic alcohols using gold(III) chloride in catalytic amounts (Figure 2-2).[13] While an improvement on the original Friedel-Crafts reaction, it is still quite limited to highly electron rich (hetero)arenes and activated allylic alcohols.

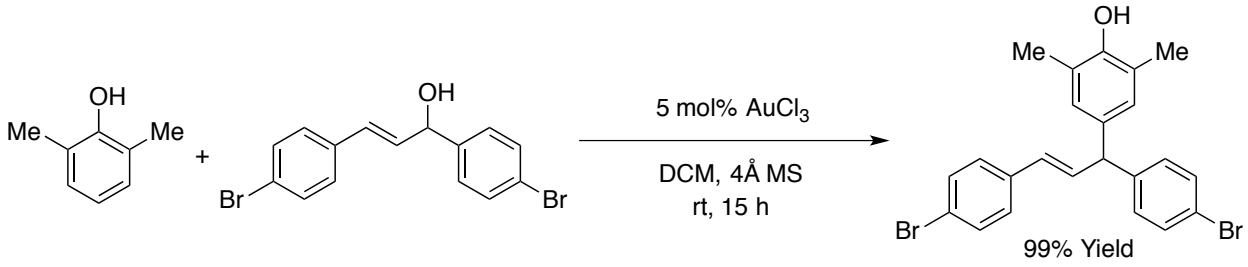


Figure 2-2: Gold-Catalyzed Friedel-Crafts Reaction with Allylic Alcohols and Heteroarenes

The Ackerman group reported the use of a 2-pyridyl substituent as a directing group in the intermolecular *meta*-selective C-H alkylation of arenes using unactivated, secondary alkyl bromides through a Friedel-Crafts-type mechanism (Figure 2-3).[14] This reaction is catalyzed by ruthenium(II) biscarboxylate catalysts, and proceeds via binding of the pyridyl nitrogen to ruthenium, followed by the reversible formation of a ruthenacycle through C-H activation. The

strong directing group effect of the ruthenium-carbon bond primes the complex for electrophilic aromatic substitution with the alkyl halide electrophile *para* to ruthenium. While the transient nature of the ruthenium catalyst activates the aromatic ring temporarily and in doing so reduces the need for permanent electron-donating substituents, the pyridyl directing group requires pre-installation and is difficult to remove after alkylation.

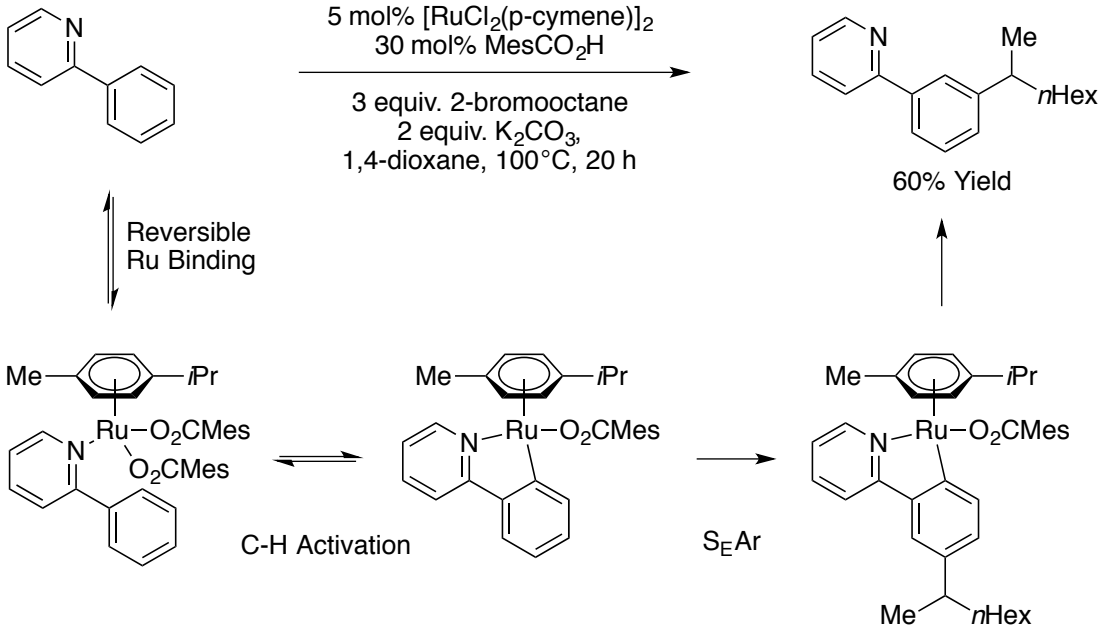


Figure 2-3: Ruthenium-Catalyzed 2-Pyridyl-Directed *meta*-Selective C-H Alkylation

2.1.2 Homolytic Aromatic Substitution

Homolytic aromatic substitution is achieved by treating an alkyl halide with a radical initiator, such as AIBN, cleaving the C-X bond to form a nucleophilic alkyl radical. This nucleophilic radical can then attack an arene or heteroarene to form the target aryl $C(sp^2)$-$C(sp^3)$ bond. Similarly to the Friedel-Crafts reaction, HAS has been widely used in the synthesis of small heterocyclic compounds of medicinal value. One such example is the formation of the pyrroloquinoline core of topoisomerase inhibitor camptothecin through a radical domino cyclization featuring radical cyclization with a highly reactive vinyl radical (Figure 2-4).[15]

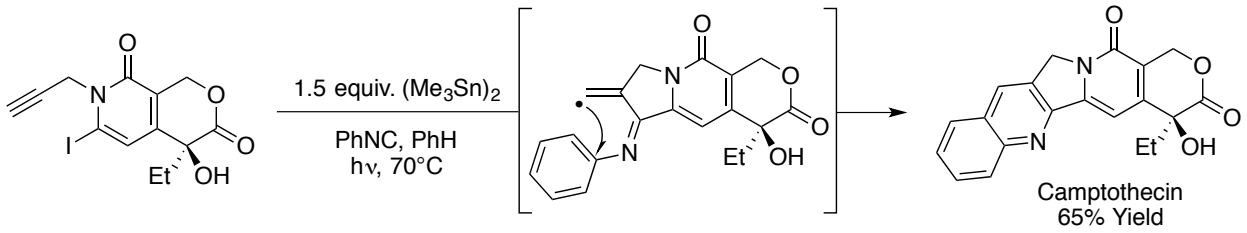


Figure 2-4: Tin-Initiated Radical Domino Reaction Featuring Homolytic Aromatic Substitution in Camptothecin Synthesis

HAS is also, however, subject to mechanistic weaknesses that limit its more general use. The use of superstoichiometric radical initiators and radical propagation reagents limit its application.[16] Additionally, radical promoting reagents are often highly toxic, either through the initiation of highly destructive radical chains, or by the presence of toxic metals such as tin.[17] Additionally, in contrast to the Friedel-Crafts reaction, HAS requires quite electron-poor arenes or heteroarenes with low aromatic stabilization energies and electron-rich carbon-centered radicals to facilitate nucleophilic aromatic attack.

These weaknesses have to some degree been addressed by more recent progress in the field. The Charette group was able to use nickel catalysis to avoid the necessity of highly electron-poor arenes in C-H alkylations, employing tetrakis(triphenylphosphine)nickel and sodium hexamethyldisilazane to perform an intramolecular C-H alkylation with primary alkyl iodides towards the synthesis of tetrahydronaphthalene and thiochroman ring systems (Figure 2-5).[18] However, the presence of the strong base necessitates geminal dimethyl groups *beta* to the iodide to prevent E2 elimination to form the terminal alkene and prevent successful cyclization.

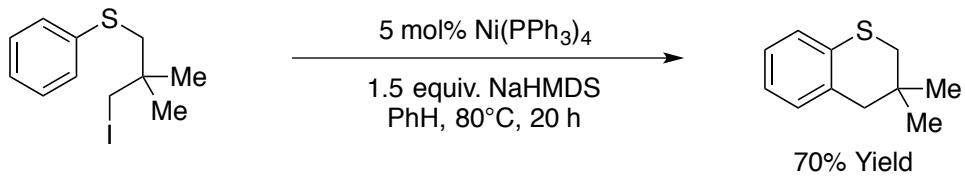


Figure 2-5: Nickel-Catalyzed Homolytic Aromatic Substitution with Neopentyl Halides

Furthermore, the application of iridium-catalyzed photoredox chemistry to HAS continues to improve the capabilities and conditions of these reactions. The Li group reported a C-H arylation which proceeds via an HAS-type mechanism to provide a wide variety of biaryl compounds (Figure 2-6).[19] The use of photocatalysis in this reaction enables the use of mild reaction conditions in the absence of traditional radial initiators or propagation reagents. However, the reaction does require complementary electron-rich nucleophile and electron-poor elecrophile to facilitate efficient coupling, and the arene coupling partner must be used in solvent quantities. Furthermore, no comparable C-H alkylation has yet been developed, limiting its use to the synthesis of biaryl species.

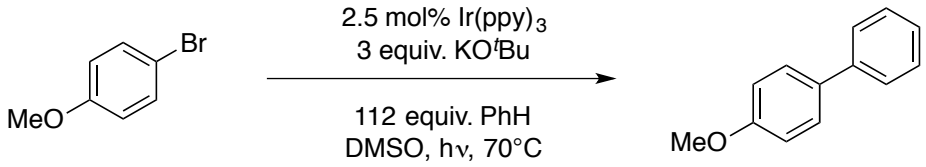


Figure 2-6: Iridium-Catalyzed C-H Arylation via Photoredox Homolytic Aromatic Substitution

2.1.3 Pictet-Spengler Reaction

The Pictet-Spengler reaction is yet another common method for the synthesis of aryl-fused heterocycles, operating through the condensation of an aryl-tethered amine onto an aldehyde, followed by the induction of electrophilic aromatic substitution into the activated iminium intermediate. The reaction conditions can range from quite mild with highly electron-rich arenes such as indoles, to necessitating strong acids or superacids with more electron-neutral aromatic systems.[20] A number of similar reactions, such as the Bischler-Napieralski reaction, enable cyclization with other nitrogen-based electrophiles, such as amides. While the Pictet-Spengler reaction has been utilized to great effect in the synthesis of medicinally valuable compounds, forming the pyridoindole core of anti-tumor agent eudistomin C (Figure 2-7),[21] the

necessity of the electrophilic iminium intermediate limits the scope exclusively to fused aryl piperidines.

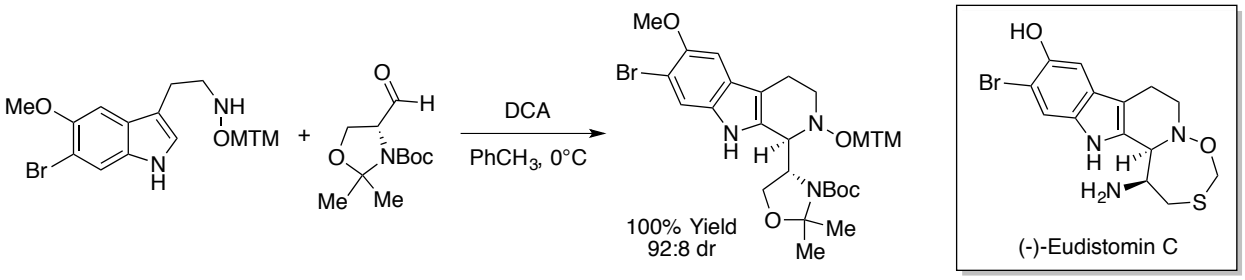


Figure 2-7: Use of Pictet-Spengler Reaction in the Synthesis of Anti-Tumor Agent (-)-Eudistomin C

These examples of aryl $C(sp^2)$-$C(sp^3)$ bond-forming reactions have long been the preeminent means of forming aryl fused heterocycles in complex synthesis. However, they face numerous disadvantages that limit application more broadly as a general method. Our goal was to develop a platform for the application of hybrid organometallic-radical palladium catalysis to facilitate efficient coupling of arenes with unactivated alkyl halides under mild conditions.

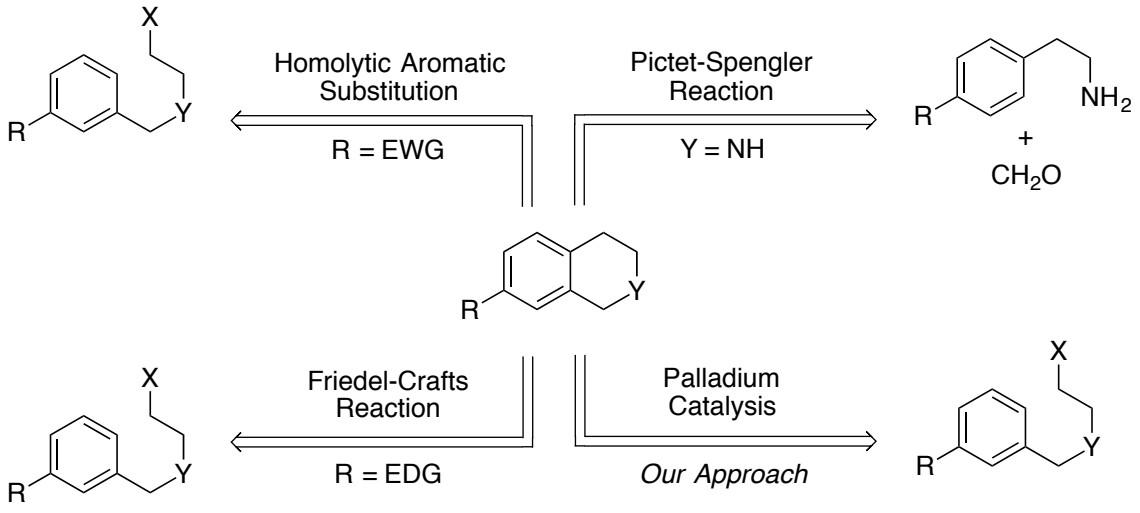


Figure 2-8: General Strategies for C-H Alkylation of Arenes and Heteroarenes

2.2 Background

Transition-metal-catalyzed C-H alkylation of aromatic compounds with sp^2-hybridized electrophiles is a well-explored field, with numerous examples from which to draw.[22] However, examples utilizing sp^3-hybridized electrophiles are far less common. This can be attributed to the general difficulties associated with the use of transition-metal catalysis with alkyl electrophiles, most notably palladium catalysts (Figure 2-9). Electron-rich alkyl C-X bonds are considerably less able to engage in oxidative addition with electron-rich palladium(0) catalysts than relatively electron-poor aryl or vinyl C-X bonds.[23-24] Additionally, sp^3 alkyl-palladium species are prone to undergo rapid β-hydride elimination, resulting in a formal dehydrohalogenation to provide an alkene and palladium hydride species, preventing the formation of the desired carbon-carbon bond.[25-26]

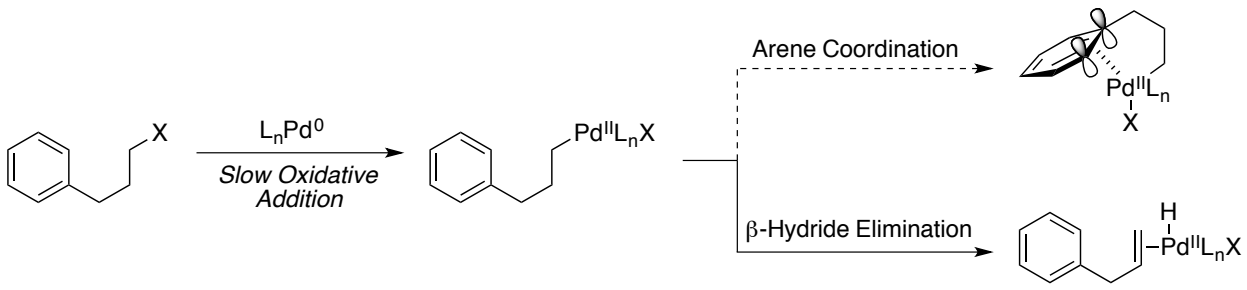


Figure 2-9: Difficulties Involved in Employing Alkyl Halides towards Aromatic C-H Alkylation

Several strategies have emerged to avoid these difficulties and engage sp^3-hybridized alkyl electrophiles in transition-metal-catalyzed C-H alkylation. These strategies generally fall into one of a few categories. One such category is the limitation of access to β-hydrogen atoms. This can be done either by the omission of β-hydrogens altogether, such as neopentyl or methyl bromide,[27] or constraining access to β-hydrogens by geometric restrictions (i.e. Bredt's Rule) as with adamantyl bromide.[28] Furthermore, halides can be activated through electron-withdrawing groups near the target C-X bond to decrease its electron density and encourage activation by

oxidative addition with the electron rich palladium(0) catalyst. Directing groups, both permanent and temporary, can be used to align the metal catalyst at the target site on the arene to facilitate rapid activation so the formation of the target C-C bond is faster than β-hydride elimination or elimination is untenable from insufficient coordination sites on the metal.[29] Finally, there have also been reports of coupling highly activated heteroarenes with unactivated alkyl halides with good results.

2.2.1 Restricted β-Hydride Elimination

Recently, there have been several reports of successful aromatic C-H alkylation using unactivated sp^3-hybridized alkyl halides that lack accessible β-hydrogens. For example, the Sanford group reported a palladium-catalyzed intermolecular perfluoroalkylation of arenes and heteroarenes using perfluoroalkyl iodides (Figure 2-10).[30] Mechanistic investigations provided evidence that this reaction does not proceed via a radical pathway, suggesting a two-electron mechanism, wherein the perfluoroalkyl iodide undergoes oxidative addition, followed by arene activation and reductive elimination of the perfluoroalkyl arene product (Figure 2-11).

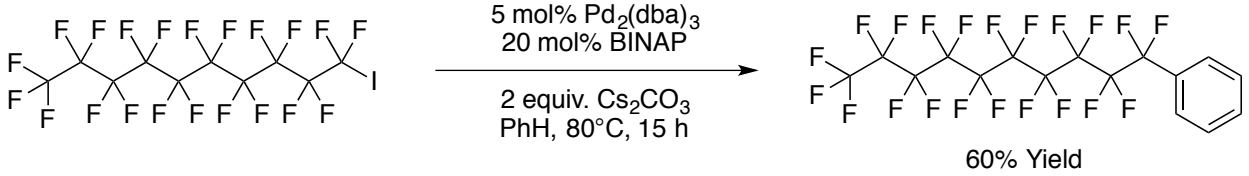


Figure 2-10: Palladium-Catalyzed Perfluoroalkylation of Arenes and Heteroarenes

A notable aspect of this reaction is that the use of fluoride achieves dual functions. The inductive effect of the fluoride decreases the electron-density of the carbon-iodide bond, facilitating oxidative addition. Upon formation of the putative alkyl-palladium intermediate, β-elimination is disfavored because of the strong carbon-fluoride bond. The impact of this reaction is limited by the restriction of scope to perfluoroalkyl halides and the use of the arene as solvent.

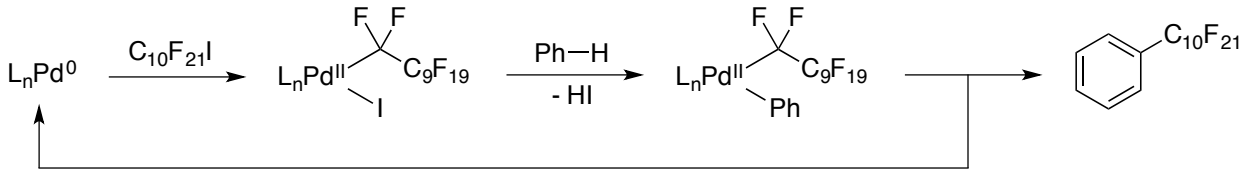


Figure 2-11: Proposed Mechanism for Palladium-Catalyzed Aryl C-H Perfluoroalkylation

Capitalizing on a similar mode of substrate design, the Wang group reported an aryldifluoromethylation of enamides with difluoromethylating reagent iododifluoromethyl phenyl sulfone, affecting the synthesis of 2-indolones (Figure 2-12).[31] Unlike Sanford's perfluoroalkylation, this reaction is proposed to occur via a single-electron pathway, whereby the difluoroalkyl iodide is activated to form a radical, which attacks the electron poor enamide, forming a tertiary radical. This radical then adds into the arene, forming the second carbon-carbon bond. As with the perfluoroalkylation, elimination is prevented by the lack of both α- and β-hydrogens. Upon formation of the tertiary radical intermediate, recombination with palladium is sterically hindered, while cyclization is much faster, discouraging β-hydride elimination.

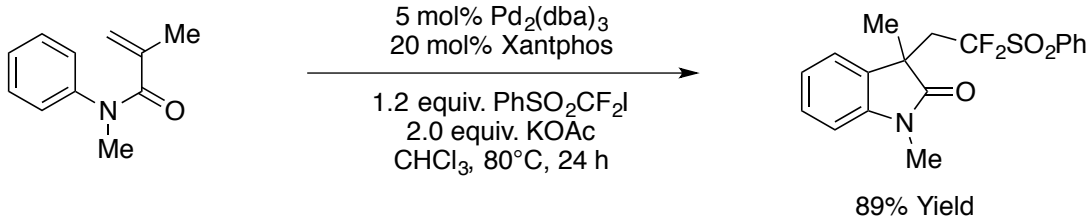


Figure 2-12: Palladium-Catalyzed Aryldifluoroalkylation of *N*-Aryl Enamides

2.2.2 Electronically Activated Alkyl Halides

In addition to reducing elimination through blocking access to β-hydrogens, there have been examples of the use of activated alkyl halides to encourage faster functionalization. Buchwald and coworkers utilized this strategy in the synthesis of oxindoles through intramolecular, ring-forming C-H alkylation of chloroacetanilides (Figure 2-13).[32] Preliminary

mechanistic studies suggest this transformation follows a traditional, two-electron, organometallic pathway. The proximity of the halide to the amide both provides a π-system which palladium binds before oxidative addition and reduces electron density of the C-X bond, facilitating rapid addition. Furthermore, the presence of the carbonyl stabilizes the alkyl palladium species upon formation, and the lack of β-hydrogens prevents elimination. The alkyl palladium species then undergoes cyclization, either through σ-bond metathesis followed by reductive elimination or carbopalladation and β-hydride elimination. While a significant achievement, limitation in scope to primary chloroacetanilides for oxindole synthesis reduces its impact.

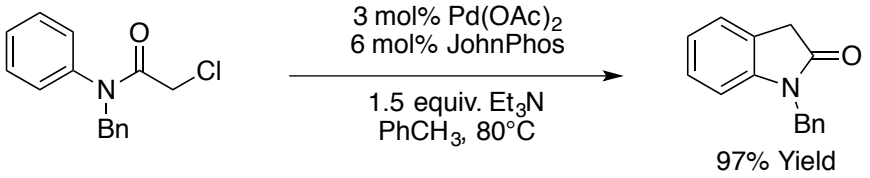


Figure 2-13: Oxindole Synthesis via Palladium-Catalyzed C-H Alkylation of Chloroacetanilides

Recently, the Lei group reported an intramolecular C-H alkylation of arenes with α-haloacetamides to synthesize oxindoles (Figure 2-14).[33] Unlike the precedent from the Buchwald lab (Figure 2-12), this transformation is thought to occur through single electron transfer to form the tertiary alkyl radical, which then reacts with the arene to form the desired heterocycle. The presence of the amide is required to stabilize the alkyl radical. Only tertiary and secondary halides are able to complete this transformation, though yields suffer with secondary substrates, relating to the relative stability of the radical intermediate. While this reaction is significant as one of the few examples of C-H alkylation with an alkyl halide capable of β-hydride elimination, and complements the similar work from the Buchwald group, it is limited by the restriction to the use of secondary and tertiary α-haloamides due to radical stability. This manifold is unlikely to

translate to unactivated alkyl halides, since the single-electron reduction potential of activated alkyl halides are 1-1.5 V more favorable than unactivated halides.[34]

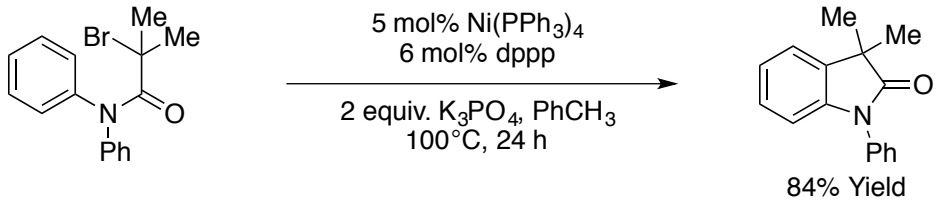


Figure 2-14: Nickel-Catalyzed Aryl C-H Alkylation with Activated Secondary and Tertiary α-Haloamides

2.2.3 Directing-Group-Assisted C-H Alkylations

In addition to the manipulation of the alkyl halide electrophile to facilitate efficient C-H alkylation, the aromatic system can be altered to make the desired reaction more favorable. The primary means to achieve this is the installation of directing groups proximal to the arene. The presence of a heteroatom directing group can reversibly bind a metal catalyst and hold it in the right configuration to facilitate insertion into an aromatic C-H bond. With this C-M bond established, upon oxidative addition of an alkyl halide, reductive elimination to form the desired C-C bond will then be fast.

The Yu group achieved C-H alkylation of benzoic acids with dihaloalkanes to synthesize benzo-fused gamma- and delta-lactones (Figure 2-15).[35] While the reactivity is quite robust, and the reaction can be run under air atmosphere, the dihaloalkane electrophile must be used in solvent quantities to achieve efficient reactivity.

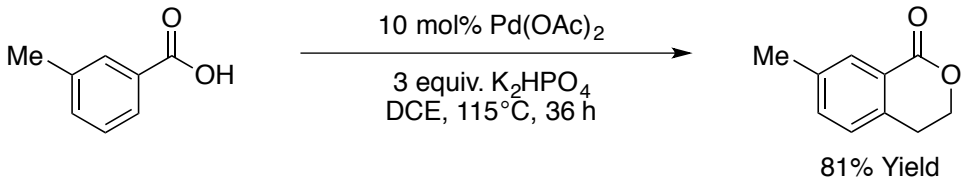


Figure 2-15: Palladium-Catalyzed *ortho* C-H Alkylation/Lactonization of Benzoic Acids with Dihaloalkanes

Following this report, the Cook group disclosed a directing-group-assisted C-H alkylation of arenes and heteroarenes without cyclization onto the directing group heteroatom (Figure 2-16).[36] They found that 8-aminoquinoline was ideally suited for the direction of an iron catalyst towards *ortho*-functionalization before incorporation of the alkyl halide electrophile. While this achieves a useful *ortho*-C-H-alkylation using cheap and environmentally benign iron catalysts, it has poor atom and step economy due to the installation and removal of the aminoquinoline amide, and the use of superstoichiometric Grignard reagent may limit the scope of application.

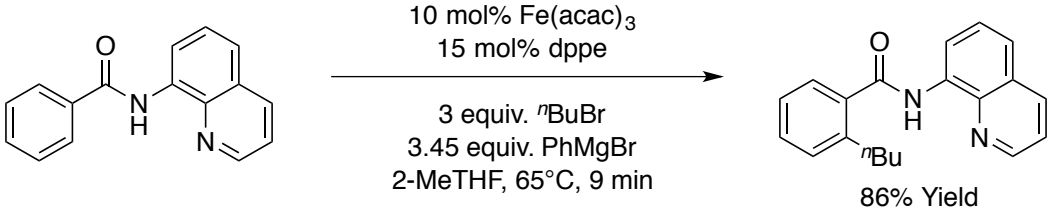


Figure 2-16: Iron-Catalyzed Aminoquinoline-Directed *ortho* C-H Alkylation with Unactivated Alkyl Halides

2.2.4 Transient Directing Groups

An alternative strategy to a permanent or pre-installed directing group is the use of norbornene as a transient directing group to prevent unproductive side reactions and facilitate the desired reactive pathway. Upon formation of an alkyl- or aryl-palladium species, norbornene undergoes rapid carbometallation, driven by the relief of ring strain.[37] The resulting norbornyl palladium species is unable to undergo β-hydride elimination due to geometric constraints, and can be induced into C-H activation by σ-bond metathesis. This strategy was pioneered by Marta Catellani to enable *ortho*-selective difunctionalization of aryl halides through a variety of cross-coupling manifolds. Figure 2-17 depicts its use in the difunctionalization of iodothiophene with bromopyridine and methyl acrylate.[38]

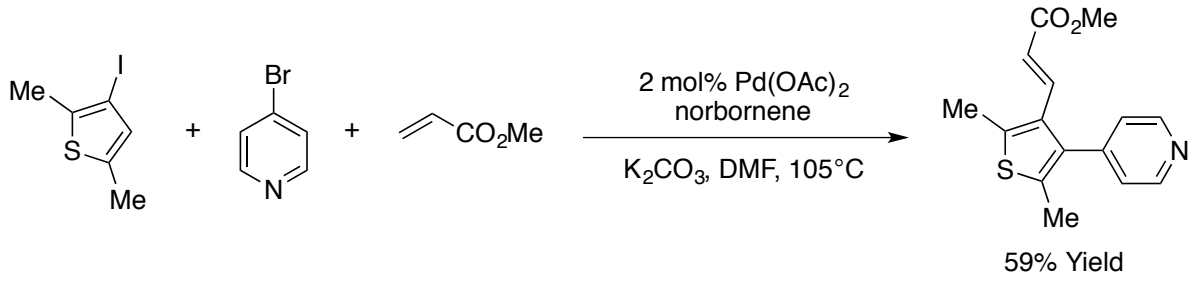


Figure 2-17: Palladium-Catalyzed Norbornene-Enabled Catellani Reaction with Unsymmetrical Aryl Iodides

The norbornene-mediated Catellani reaction can also be utilized in intramolecular, ring-forming couplings and can be applied to unactivated alkyl halide electrophiles. A report from the Lautens group uses this strategy to enact an intramolecular C-H functionalization followed by a Heck cross-coupling (Figure 2-18).[39] While the use of norbornene can be a very powerful strategy for C-H activation of arenes, it requires the initial formation of a carbon-metal bond into which norbornene can insert. In the example of indole alkylation, this is achieved by the low energy of aromaticity and the nucleophilicity of the heterocycle. The domino reaction developed by the Lautens group requires an aryl iodide to facilitate oxidative addition, forming the carbon-palladium bond before carbopalladation and C-H activation.

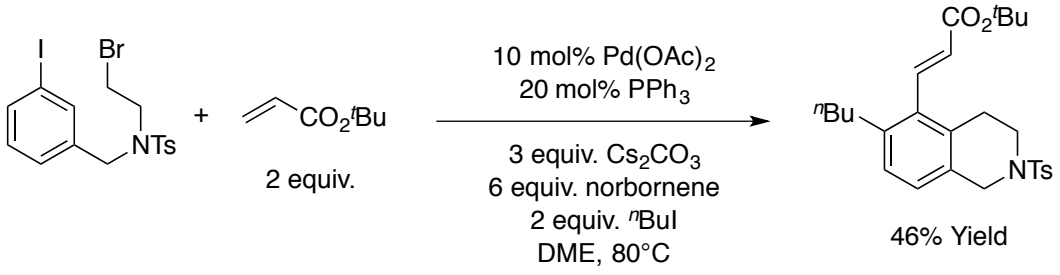


Figure 2-18: Palladium-Catalyzed Tandem C-H Alkylation-Heck Reaction Facilitated by Norbornene

Norbornene has also been used to great effect in the selective alkylation of indoles at the 2-position as shown in Figure 2-19.[40,41] Upon carbopalladation, since the alkyl palladium species

is unable to eliminate, it is forced to undergo C-H activation at the 2-position, *ortho* to the original site of palladation. At this point, palladium activates the alkyl electrophile via oxidative addition, and quickly undergoes reductive elimination to form the target carbon-carbon bond. β-Hydride elimination following activation is unfavorable, as it requires an open coordination site on palladium**.** Reversal of the initial two steps generates the product and turns over the catalyst.

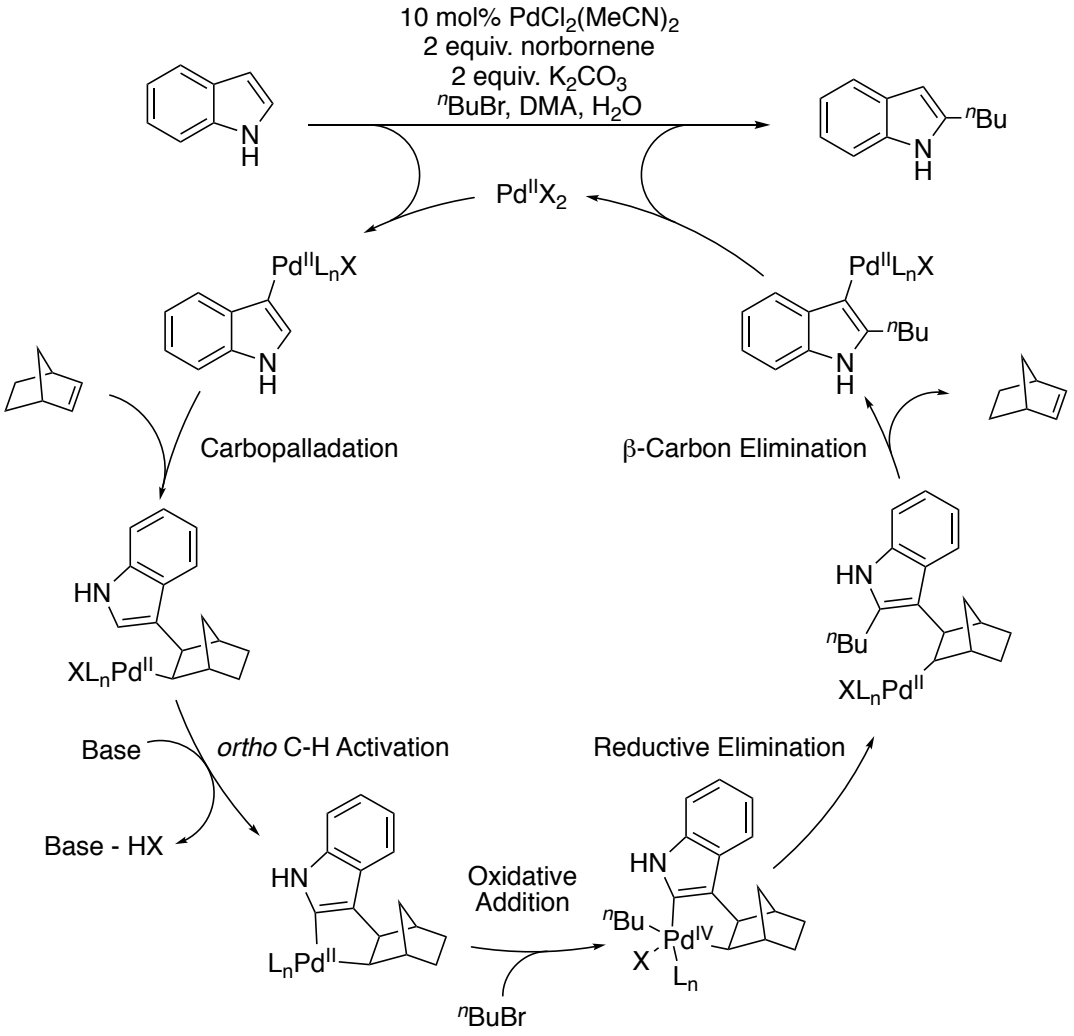


Figure 2-19: Palladium-Catalyzed Norbornene-Mediated C-H Alkylation of Indoles

2.2.5 Activated Aromatic Systems

Finally, there have been few reports of non-directed C-H alkylation of aromatic systems using unactivated alkyl halides as electrophilic coupling partners. These examples all utilize highly specific and activated aromatic systems to facilitate the desired C-C bond formation. For example, Wang and coworkers report a palladium-catalyzed selective C-H alkylation of perylene-3,4:9,10-tetracarboxylic acid bisimides (PBIs) with simple primary alkyl halides (Figure 2-20).[42] Palladium participates in the carbonate-assisted C-H activation of the PBI, which acts selectively at the site of the weakest C-H bond. However, the authors note that upon oxidative addition of the alkyl halide, the alkyl palladium intermediate is prone to β-hydride elimination. Therefore both alkyl halide and base must be used in excess to achieve efficient coupling. This limitation makes this method untenable for efficient intramolecular C-H functionalization.

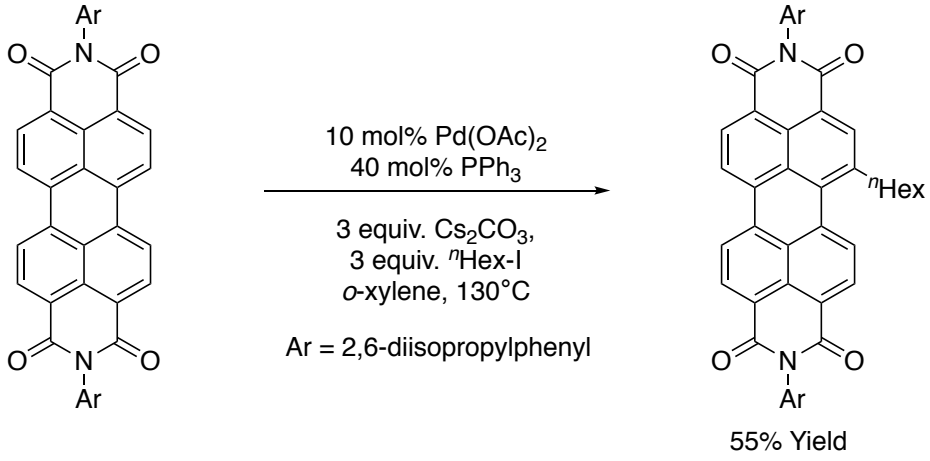


Figure 2-20: Palladium-Catalyzed *meta*-Selective C-H Alkylation of PBIs

An additional strategy to alkylate activated heteroaromatic systems is through the use alkyl radical intermediates. The reduction of alkyl halides to alkyl radicals avoids the difficulties commonly associated with alkyl palladium species such as β-hydride elimination. After

formation, the radical intermediate attacks the heteroarene, similarly to the mechanism involved in homolytic aromatic substitution. The difference between these methods and HAS is that the palladium catalyst is turned over after each activation of alkyl halide, whereas HAS typically uses radical initiators, such as AIBN. These initiators are either used stoichiometrically or in substoichiometric quantities to initiate chain reactions, which propagate the radical rather than needing activation of every individual substrate.

The use of metal catalysts in radical-mediated C-H alkylation has an advantage over HAS reactions in that metal catalysts can stabilize and control reactivity of radical intermediates.[43] Similar effects are seen in atom-transfer radical polymerization (ATRP) reactions.[44] HAS reactions, on the other hand, operate via free radical intermediates, which often suffer higher rates of unproductive side reactions.[45]

Two recent examples of this method are shown in Figure 2-21, and include the C-H alkylation of pyridine N-oxides by the Fu group[46] and of benzoxazoles from the Zhou lab.[47] Similarly to HAS reactivity, the electron density and aromatic nature of the arene component is highly important to the success of the reaction. As such, these reactions are highly specific to each respective arene due to their electron-poor nature and the low aromatic stabilization energies.

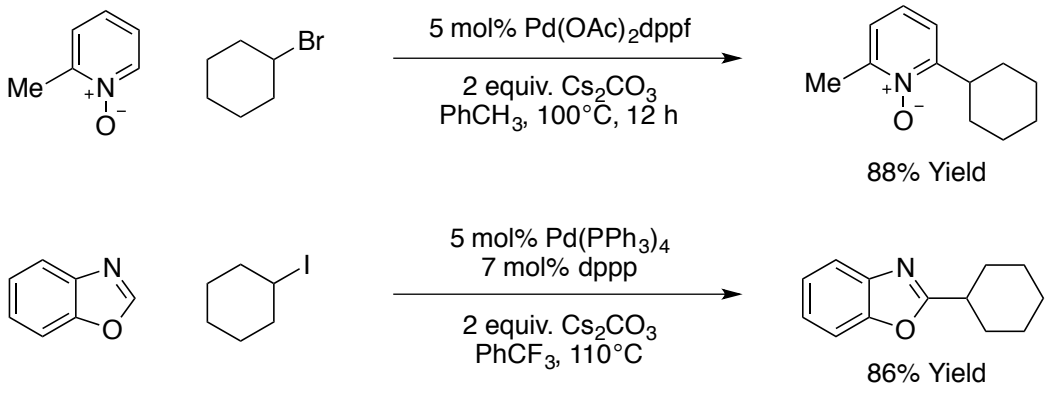


Figure 2-21: Palladium-Catalyzed C-H Alkylation of Activated Heteroaromatic Systems

While all of the reports described herein represent contributions towards the understanding and implementation of methods for the C-H alkylation of aromatic systems with alkyl halide electrophiles, none can be considered a general method to achieve this transformation, and each method is subject to limitations in the breadth and effectiveness of its application.

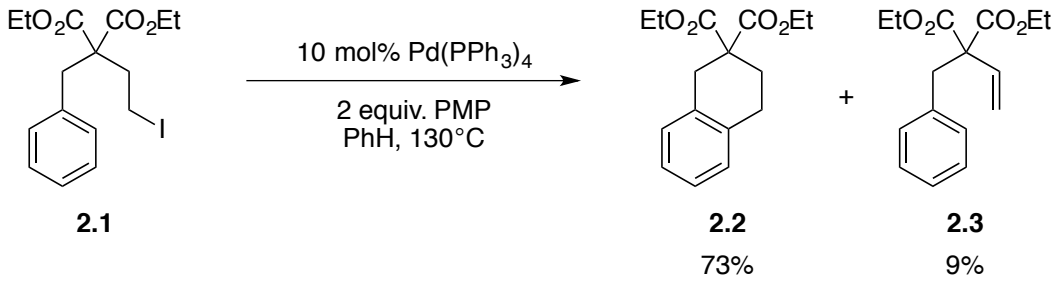
2.3 Results and Discussion

In our laboratory, having previously demonstrated methods to utilize unactivated alkyl halides in carbon-carbon bond-forming reactions under mild palladium-catalyzed conditions,[48-50] we sought to extend this effort towards C-H alkylation. In doing so, we applied palladium-catalyzed sp^3 C-X bond activation through a hybrid organometallic radical manifold towards the formation of sp^2-sp^3 carbon-carbon bonds with a wide variety of arene electronic states.[51] This method could be used in the efficient synthesis of countless bioactive small molecules and pharmaceuticals which feature aromatic and heteroaromatic cores.

2.3.1 Reaction Development

This effort began with the design of a substrate that would achieve the primary goals of this effort. We chose primary alkyl iodide **2.1** with an electronically neutral and sterically unencumbered arene, tethered with a geminal diester group to encourage cyclization through the Thorpe-Ingold effect.[52] Reaction development began with the use of conditions employed by our laboratory's previous report of intramolecular alkyl-Heck couplings featuring a palladium(0) catalyst and an organic amine base in aromatic solvent (Figure 2-22).[49] Gratifyingly, these conditions were successful in providing tetrahydronaphthalene product **2.2** in 73% yield. Unlike our previous efforts using these conditions to activate alkyl halides, however, significant quantities of dehydrohalogenation byproduct **2.3** are observed. This can presumably be attributed

to the 6-exo cyclization into an aromatic ring being slower than a 5-exo radical cyclization into an alkene, which is known to be very fast.[53] As a result, the substrate may have more time to participate in undesired side pathways such as β-hydride elimination.

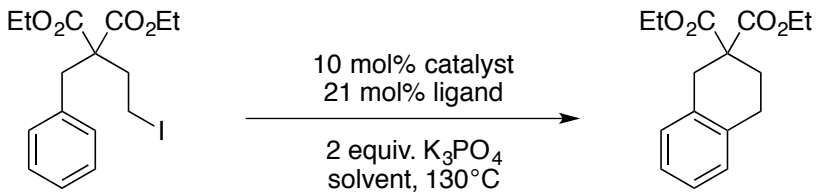


2.1 **2.2** 73% **2.3** 9%

Figure 2-22: Preliminary Result for the Aromatic C-H Alkylation with Unactivated Alkyl Iodide

In addition to using our previously developed palladium-catalysis conditions for the activation of alkyl halides, we explored the use of catalysts which have been previously employed to activate alkyl halides in atom-transfer radical polymerization (ATRP).[44] The results of this investigation are summarized in Table 2-1. Copper catalysts are perhaps the most widely used for ATRP, but were unsuccessful in promoting the desired reaction (Entries 1-4). Changing the solvent with the intent of greater stabilization of radical intermediates was also unsuccessful. Iron/phosphine catalytic systems, which have been demonstrate to activate primary alkyl halides to form carbon-centered radicals also failed to return appreciable reactivity (Entries 5-6). Wilkinson's catalyst was able to perform the desired cyclization, but in quite low yield (Entries 7-8). Changing the solvent to a more polar aromatic solvent failed to improve its performance.

Table 2-1: Transition Metal Screen for Intramolecular Aromatic C-H Alkylation with Unactivated Primary Alkyl Iodide



2.1 **2.2**

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

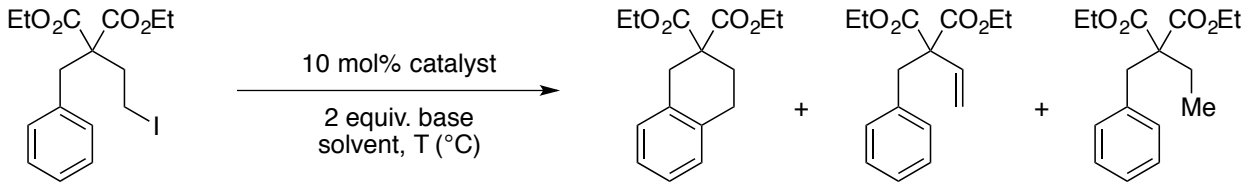
[a] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Having screened other metal sources as potential catalysts in this reaction with no success, we sought to optimize the initial palladium-catalyzed conditions. The results of this optimization effort are summarized in Table 2-2. Decreasing the temperature and changing the solvent to 1,4-dioxane, which enabled reactions to be run in vials rather then sealed reaction vessels, caused an increase in yield (Entry 2). Changing the base caused only marginal differences in yield, even between inorganic and organic amine bases (Entries 3-4). The use of K_3PO_4, however, minimized the amount of β-hydride elimination that was observed.

Introducing xylenes as a higher-boiling aromatic solvent caused a sharp decline in yield, coupled with a sizeable yield of reductive dehalogenation byproduct **2.4** (Entry 5). This was attributed to the presence of abstractable benzylic hydrogen atoms on the solvent, which

presumably interrupts the desired reaction, leading instead to unproductive reduction of the halide. In an attempt to reduce β-hydride elimination, $Pd(dppf)Cl_2$ was used (Entry 6). Bidentate ligands are known to bind more tightly to their metal center, and it was thought that their use would minimize the presence of open coordination sites on palladium, which are required for β-hydride elimination to proceed.[54] While this did reduce the presence of β-hydride elimination, it also greatly reduced the conversion of the reaction, with 47% starting material remaining. Finally, omission of the palladium catalyst resulted in no conversion (Entry 7).

Table 2-2: Reaction Condition Optimization for Intramolecular Aromatic C-H Alkylation with Unactivated Primary Alkyl Iodide[a]



2.1 **2.2** **2.3** **2.4**

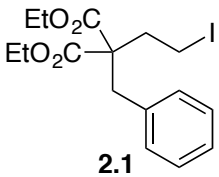
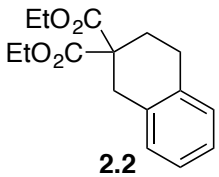
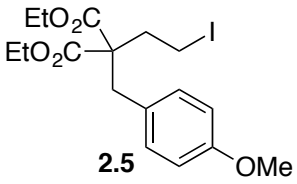
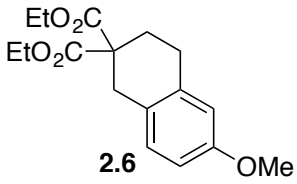
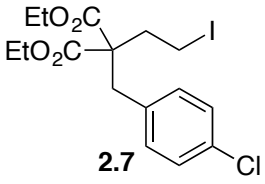
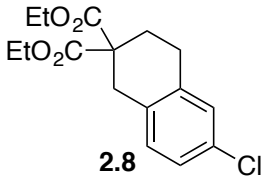
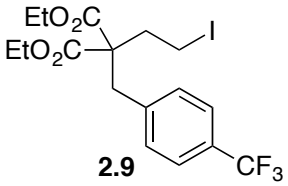
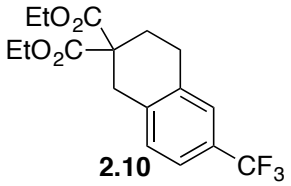
Entry	Catalyst	Base	Solvent	Temperature (°C)	**2.2** (%)	**2.3** (%)	**2.4** (%)
1	$Pd(PPh_3)_4$	PMP	PhH	130	73	9	0
2	$Pd(PPh_3)_4$	PMP	1,4-Dioxane	100	87	3	0
3	$Pd(PPh_3)_4$	K_3PO_4	1,4-Dioxane	100	85	2	0
4	$Pd(PPh_3)_4$	Cs_2CO_3	1,4-Dioxane	100	73	6	0
5	$Pd(PPh_3)_4$	K_3PO_4	Xylenes	130	22	<2	49
6	$Pd(dppf)Cl_2$	K_3PO_4	1,4-Dioxane	100	20[b]	0	0
7	--	K_3PO_4	1,4-Dioxane	100	0	0	0

[a] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [b] 47% starting material **2.1** observed.

2.3.2 Reaction Scope

With optimized conditions in hand for this transformation (Table 2-2, Entry 3), we sought to explore the scope of the reaction. Since the use of a wide variety of aromatic systems in this reaction was a primary goal of this effort, we began by altering the electronic state of the arene in the diester-tethered primary iodide substrate **2.1**. As shown in Table 2-3, this mode of reactivity is highly amenable to these changes in arene electronics. While the yield decreased slightly with electron-donating and electron-withdrawing substituents, it remained quite high throughout the spectrum of electron density.

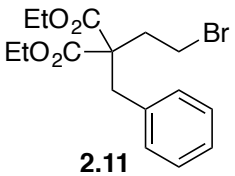
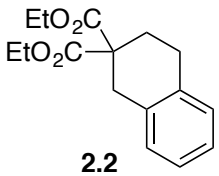
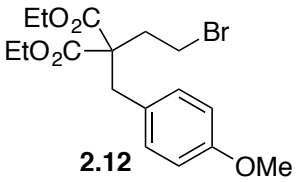
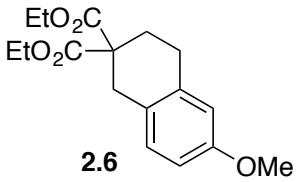
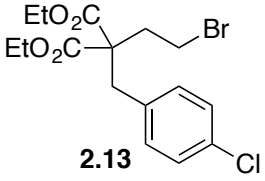
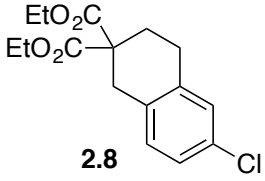
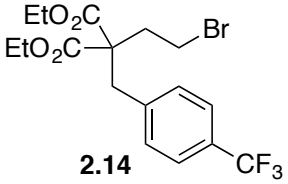
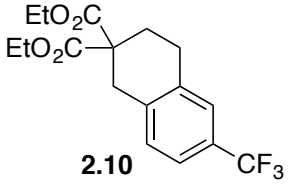
Table 2-3: Effects of Altering Electronic Character of Aromatic System in C-H Alkylation with Primary Alkyl Iodides[a]

Entry	Substrate	Product	Yield (%)[b]
1	 **2.1**	 **2.2**	85
2	 **2.5**	 **2.6**	66
3	 **2.7**	 **2.8**	59
4	 **2.9**	 **2.10**	68

[a] Reactions performed with $[substrate]_0$ = 0.5 M in 1,4-dioxane in the presence of 10 mol% $Pd(PPh_3)_4$ and 2 equiv. K_3PO_4 at 100°C. [b] Isolated yield.

In addition to employing primary iodides in this transformation, we were also able to effect this C-H alkylation using primary alkyl bromides, as depicted in Table 2-4. This result was unexpected, as previous reports from our laboratory using palladium catalysis to activate alkyl halides were limited to alkyl iodides. Similarly to the results observed with iodides, these bromide substrates achieved good to excellent yields with a variety of arene electronic states. However, higher temperatures (130°C) and longer reaction times were required to achieve good conversion.

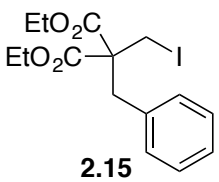
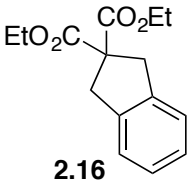
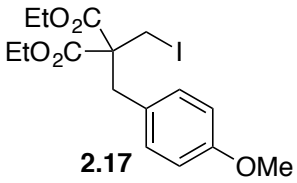
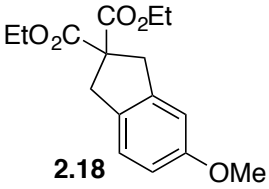
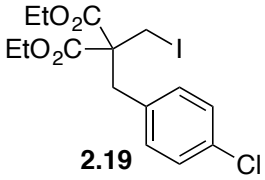
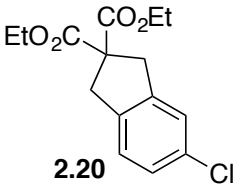
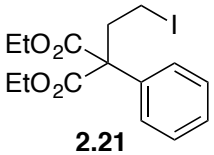
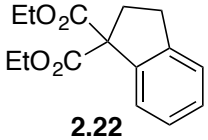
Table 2-4: Palladium-Catalyzed Aromatic C-H Alkylation with Primary Alkyl Bromides[a]

Entry	Substrate	Product	Yield (%)[b]
1	 **2.11**	 **2.2**	91
2	 **2.12**	 **2.6**	78
3	 **2.13**	 **2.8**	75
4	 **2.14**	 **2.10**	92

[a] Reactions performed with $[substrate]_0$ = 0.5 M in Ph^{t}Bu in the presence of 10 mol% $Pd(PPh_3)_4$ and 2 equiv. PMP at 130°C. [b] Isolated yield.

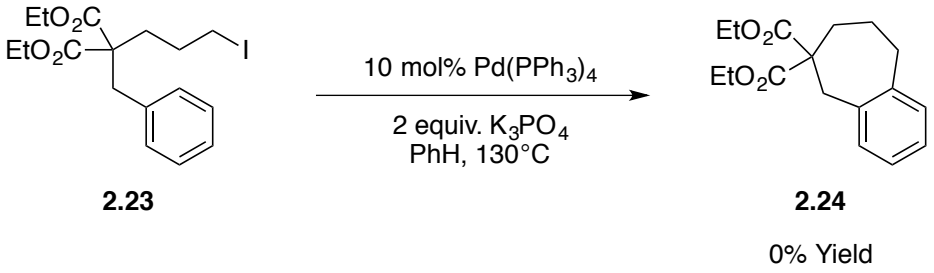
After employing these conditions to form tetrahydronaphthalene products through 6-exo cyclizations, we turned our attention to the formation of indane products through 5-exo cyclizations. These reactions were successful in modest to good yield with a variety of arene electronic states. Additionally, moving the diester moiety along the tether was also accommodated with only modest decline in yield.

Table 2-5: Palladium-Catalyzed Indane Synthesis via Intramolecular C-H Alkylation[a]

Entry	Substrate	Product	Yield (%)[b]
1	 **2.15**	 **2.16**	88
2	 **2.17**	 **2.18**	66
3	 **2.19**	 **2.20**	59
4	 **2.21**	 **2.22**	68

[a] Reactions performed with $[substrate]_0$ = 0.5 M in 1,4-dioxane in the presence of 10 mol% $Pd(PPh_3)_4$ and 2 equiv. K_3PO_4 at 100°C. [b] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Efforts to expand this manifold to the formation of medium-sized rings were unsuccessful (Figure 2-23). Application of the optimized reaction conditions to iodide **2.23** failed to produce the desired benzocycloheptane product **2.24**. It did, however, produce a mixture of starting material with reaction byproducts β-hydride elimination and reductive dehalogenation. This suggests activation of the alkyl iodide occurred, but the 7-exo cyclization was adequately slow or disfavored that no appreciable quantity of product was formed.



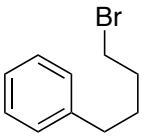
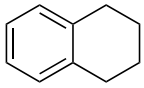
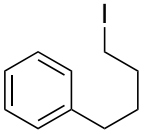
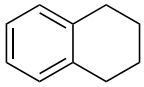
2.23 **2.24**

0% Yield

Figure 2-23: Attempted Formation of Medium-Sized Rings via Intramolecular C-H Alkylation

We also investigated the ability to remove the diester moiety from the tether, forming unsubstituted tetrahydronaphthelene products without influence from the Thorpe-Ingold Effect. It was determined that the diester was not necessary to encourage cyclization, and tetrahydronaphthalene was formed in good yield from both the bromide and the iodide. Due to product volatility, yields were determined by gas chromatography.

Table 2-6: Formation of Tetrahydronaphthalene through C-H Alkylation of Primary Halides[a]

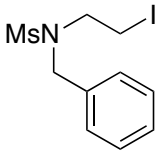
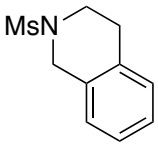
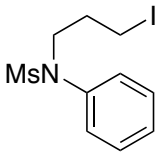
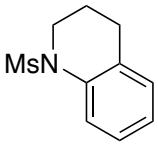
Entry	Substrate	Product	Yield (%)[b]
1	 **2.25**	 **2.26**	85[c]
2	 **2.27**	 **2.26**	66[d]

[a] Reactions performed with $[substrate]_0$ = 0.5 M in solvent in the presence of 10 mol% $Pd(PPh_3)_4$ and 2 equiv. base. [b] Yield determined by gas chromatography. [c] PMP, Ph^{t}Bu, 130°C. [d] K_3PO_4, 1,4-dioxane, 100°C

In addition to the synthesis of carbocycles, this means of cyclization could be applied to another highly important class of small molecules, benzo-fused heterocycles. We began this effort with the formation of tetrahydroquinoline derivatives **2.29** and **2.31** (Table 2-7). While cyclization proved successful, further optimization of reaction conditions failed to increase yields past 31%, while byproducts resulting from β-hydride elimination and reductive dehalogenation were formed in significant quantities.

The scope of protecting groups available for use in this cyclization is quite narrow. An effective protecting group must be sufficiently electron withdrawing so as to prevent formation of mustard agents through amine displacement of the halide. It must not be a nucleophilic group, such as an acetyl group, as this can displace the halide forming a larger heterocycle in an unproductive side reaction. Finally, protecting groups that include arene moieties, such as toluenesulfonamide, are not preferred, as they can cause chemoselectivity difficulties between the two arenes in the molecule.

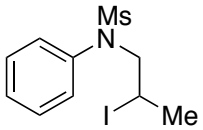
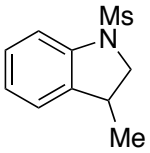
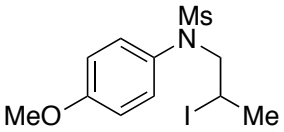
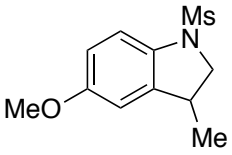
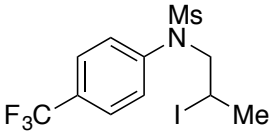
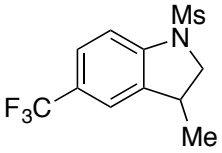
Table 2-7: Palladium-Catalyzed Tetrahydroquinoline Synthesis via C-H Alkylation of Primary Iodides[a]

Entry	Substrate	Product	Yield (%)[b]
1	 **2.28**	 **2.29**	30
2	 **2.30**	 **2.31**	31

[a] Reactions performed with $[substrate]_0$ = 0.5 M in Ph^{t}Bu in the presence of 10 mol% $Pd(PPh_3)_4$ and 2 equiv. K_3PO_4 at 130°C. [b] Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Use of secondary iodides instead of primary iodides in this reaction caused a significant increase in observed yield and a decrease in the amount of unproductive byproducts such as β-hydride elimination and reductive dehalogenation. As depicted in Table 2-8, indoline products were formed in good yields with similar tolerance of arene electronics as seen in tetrahydronaphthalene formation.

Table 2-8: Palladium-Catalyzed Indoline Synthesis via C-H Alkylation with Secondary Alkyl Iodides[a]

Entry	Substrate	Product	Yield (%)[b]
1	 **2.32**	 **2.33**	82
2	 **2.34**	 **2.35**	66
3	 **2.36**	 **2.37**	70

[a] Reactions performed with $[substrate]_0$ = 0.5 M in 1,4-dioxane in the presence of 10 mol% $Pd(PPh_3)_4$ and 2 equiv. K_3PO_4 at 100°C. [b] Isolated yield.

In addition to secondary iodides, an analogous secondary bromide was submitted to the same reaction conditions, forming the indoline product with only moderate erosion of yield from the iodide (Figure 2-24). Interestingly, while this reaction did require extended reaction time as compared to the iodide, it achieved full conversion at 100°C and did not require increasing the temperature from the secondary iodide conditions.

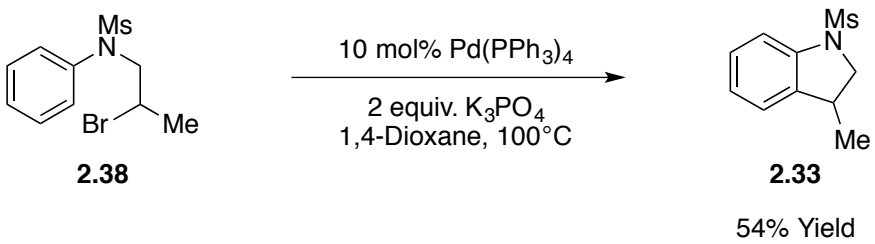
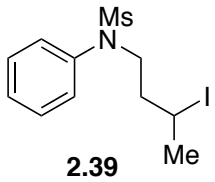
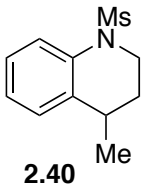
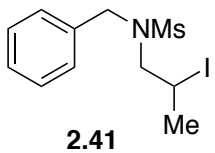
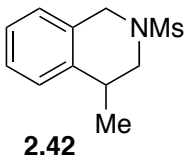


Figure 2-24: Palladium-Catalyzed Indoline Synthesis via C-H Alkylation with a Secondary Alkyl Bromide

Expansion of the sulfonamide tether by one methylene group to affect the formation of tetrahydroquinoline derivatives via 6-exo cyclization was also successful in modest yields (Table 2-9). It was determined that the location of the sulfonamide on the alkyl tether was not significant, as both aniline and benzylamine derivatives reacted in similar yields. The decrease in yield from the analogous 5-membered ring formations in Table 2-8 can be attributed to the generally slower nature of a 6-exo cyclization compared a 5-exo cyclization. Slower cyclizations allow more time for unproductive side reactions which decrease the yield of the desired product.

Table 2-9: Palladium-Catalyzed Tetrahydroquinoline Synthesis via C-H Alkylation of Secondary Iodides[a]

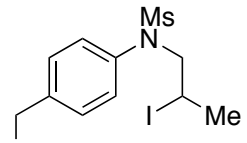
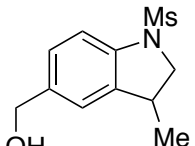
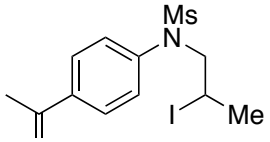
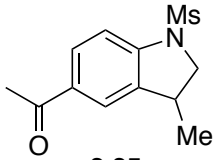
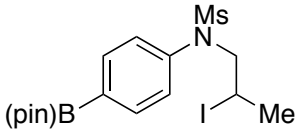
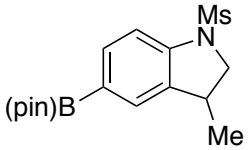
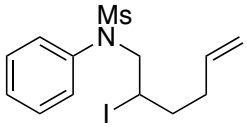
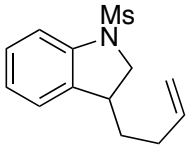
Entry	Substrate	Product	Yield (%)[b]
1	 **2.39**	 **2.40**	57
2	 **2.41**	 **2.42**	61

[a] Reactions performed with $[substrate]_0$ = 0.5 M in 1,4-dioxane in the presence of 10 mol% $Pd(PPh_3)_4$ and 2 equiv. K_3PO_4 at 100°C. [b] Isolated yield

In addition to substituent groups modifying the electronic nature of the arene component, we investigated the scope of functional groups compatible with the developed reactivity, the results of which are shown in Table 2-10. We found the reaction conditions to be quite mild and accommodating of unprotected functional groups, achieving modest to good yield with an unprotected primary alcohol (Entry 1) and ketone (Entry 2). Additionally, the secondary iodide featuring a pinacolato boronate ester (Entry 3) provided good yield, and did not produce any

measurable amount of Suzuki cross-coupling between iodide and boronate ester. Entry 4 featuring a terminal alkene also achieved good yield. The substrate was designed such that 5-exo cyclization into the arene was more favorable than 4-exo cyclization into the alkene.

Table 2-10: Functional Group Compatibility of the Palladium-Catalyzed Aromatic C-H Functionalization with Secondary Alkyl Iodides[a]

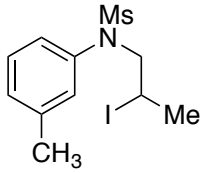
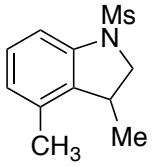
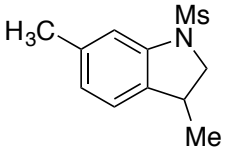
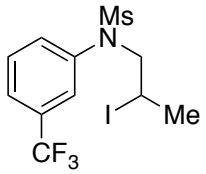
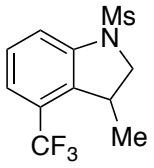
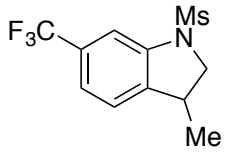
Entry	Substrate	Product	Yield (%)[b]
1	 **2.32**	 **2.33**	57
2	 **2.34**	 **2.35**	77
3	 **2.36**	 **2.37**	72
4	 **2.36**	 **2.37**	80

[a] Reactions performed with $[substrate]_0$ = 0.5 M in 1,4-dioxane in the presence of 10 mol% $Pd(PPh_3)_4$ and 2 equiv. K_3PO_4 at 100°C. [b] Isolated yield.

In addition to *para*-substitution of the arene, the reaction also tolerated *meta*-substitution (Table 2-11). Both methyl and trifluoromethyl substitution resulted in good to excellent yield. However, the reaction occurred with only modest regioselectivity, favoring cyclization *ortho* to

the substituent over *para* cyclization by a roughly 2:1 margin. There appears to be minimal electronic bias associated with this selectivity, as electron-donating methyl substituent and electron-withdrawing trifluoromethyl group resulted in comparable product ratios.

Table 2-11: Regioselectivity of Palladium-Catalyzed C-H Alkylation with *meta*-Substituted Arenes[a]

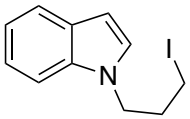
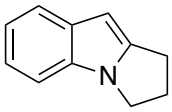
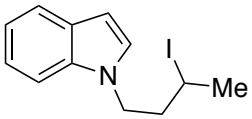
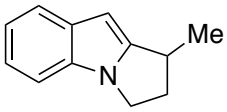
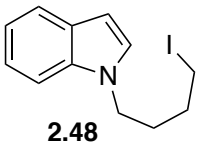
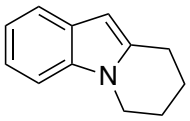
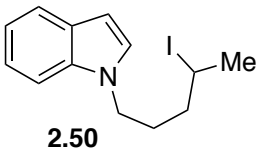
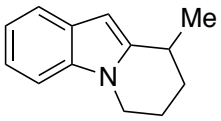
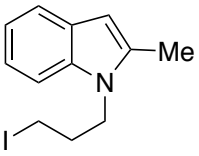
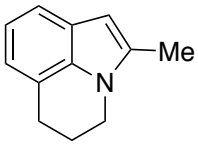
Entry	Substrate	Products		Yield[b]
1	 **2.38**	 **2.39**	 **2.40**	91 (2.0:1 rr)
2	 **2.41**	 **2.42**	 **2.43**	81 (2.4:1 rr)

[a] Reactions performed with $[substrate]_0$ = 0.5 M in 1,4-dioxane in the presence of 10 mol% $Pd(PPh_3)_4$ and 2 equiv. K_3PO_4 at 100°C. [b] Isolated yield.

The C-H alkylation of heteroaromatic compounds was also investigated. Since indole has often been used as a C-H alkylation substrate in previous reports,[55] we began our efforts with *N*-iodoalkyl indoles (Table 2-12). These substrates were found to readily form 5- and 6-membered rings with both primary and secondary iodides. Similarly to our studies towards the synthesis of indoline and tetrahydroquinoline products, secondary iodides provided higher yields with both 5- and 6-membered rings. Alkylation of indole was limited to the 2-position, however, as substrate **2.52** was unsuccessful in forming 6-exo product **2.53** (Entry 5). This can be attributed to the lower energy associated with breaking aromaticity of the pyrrole ring than of breaking the benzene portion of the bicyclic heterocycle. Additionally, the substrate may be geometrically

restrained, and the tether may be unable to achieve proper alignment for cyclization at the desired position.

Table 2-12: Palladium-Catalyzed C-H Alkylation of Indoles[a]

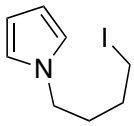
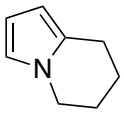
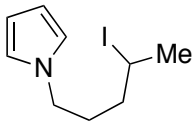
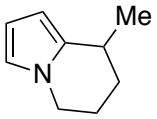
Entry	Substrate	Product	Yield (%)[b]
1	 **2.44**	 **2.45**	51
2	 **2.46**	 **2.47**	71
3	 **2.48**	 **2.49**	70
4	 **2.50**	 **2.51**	90
5	 **2.52**	 **2.53**	0

[a] Reactions performed with $[substrate]_0$ = 0.5 M in 1,4-dioxane in the presence of 10 mol% $Pd(PPh_3)_4$ and 2 equiv. K_3PO_4 at 100°C. [b] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

In addition to indoles, *N*-iodoalkyl pyrroles were found to readily form indolizine derivatives with the developed palladium-catalyzed conditions (Table 2-13). These reactions

should be considered an improvement on HAS conditions previously developed. For example, in order for iodide **2.54** to undergo cyclization under HAS conditions, electron withdrawing groups must be applied to the pyrrole ring.[56] However, it should be noted that a background reaction was observed in the absence of palladium, with tetrahydrodindolizine **2.55** formed in 34% yield.

Table 2-13: Palladium-Catalyzed C-H Alkylation of Pyrroles[a]

Entry	Substrate	Product	Yield (%)[b]
1	 **2.54**	 **2.55**	64
2	 **2.56**	 **2.57**	95

[a] Reactions performed with $[substrate]_0$ = 0.5 M in 1,4-dioxane in the presence of 10 mol% $Pd(PPh_3)_4$ and 2 equiv. K_3PO_4 at 100°C. [b] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

2.3.3 Mechanistic Investigation

Because the reactive manifold presented herein defies conventional trends traditionally associated with the C-H alkylation of arenes, nominally the use of unactivated sp^3-hybridized alkyl halides as electrophiles and the ability to alkylate arenes with a wide variety of electronic properties, we sought to investigate the mechanism of the reaction. Building upon previous mechanistic studies performed by our group, we hypothesized that the reaction followed a radical-type pathway.

In order to test for the presence of alkyl radical intermediates, initial studies involved performing the reaction in the presence of radical trap TEMPO. When secondary iodide **2.32** is

subjected to normal reaction conditions with the addition of one equivalent of TEMPO, no indoline product was observed (Figure 2-25). However, TEMPO adduct **2.58** was returned in 60% yield, along with 35% starting material **2.32**. This observation is consistent with the existence of a carbon-centered radical intermediate in the reaction mechanism.[57]

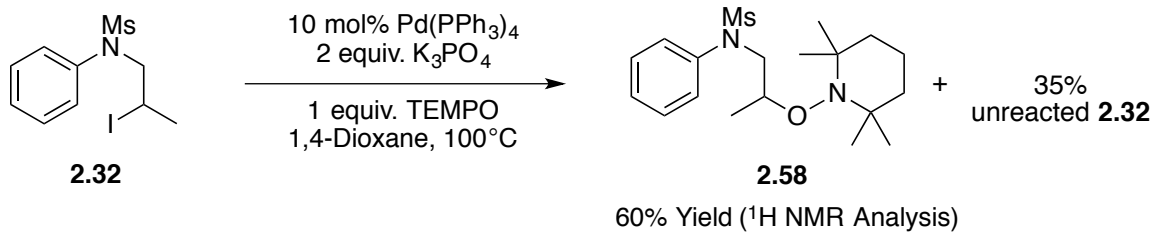


Figure 2-25: Palladium-Catalyzed Aromatic C-H Alkylation in the Presence of TEMPO

Further investigation focused on the stereochemical implications of the reaction mechanism. Were the mechanism to proceed via a traditional organometallic pathway through S_N2-type oxidative addition with palladium, it would be expected that the stereocenter at the C-X bond would be preserved and inverted.[58] On the other hand, if the mechanism operates through a radical-type pathway, it would be expected that the stereocenter would be racemized upon activation to the alkyl radical.[59] To further distinguish between these two general pathways, we subjected stereoenriched secondary iodide **(*R*)-2.32** to the normal reaction conditions (Figure 2-26). Quenching the reaction before it achieved full conversion, we isolated both product **2.33** and unreacted starting material. We found that both the product of the reaction as well as the recovered starting material were racemic. Not only does this further suggest a radical-type process is involved due to racemization of the stereocenter, but it also indicates that the activation of the iodide is reversible, facilitating the return of racemic starting material.

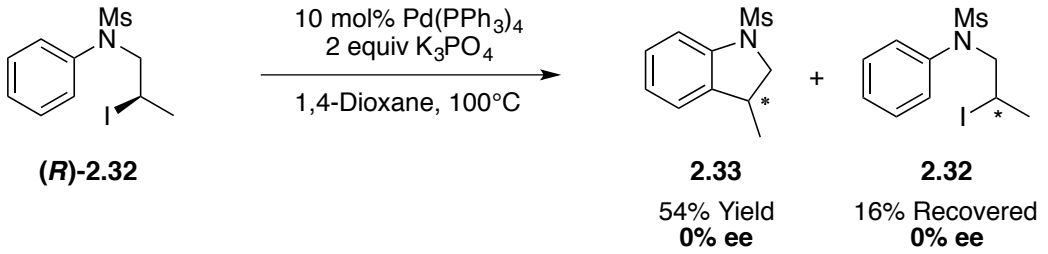


Figure 2-26: Stereochemical Outcome of Palladium-Catalyzed C-H Alkylation with Stereoenriched Alkyl Iodide

We then performed a kinetic isotope study, synthesizing perdeuteroaryl alkyl iodide **2.59**. We ran a reaction with iodides **2.32** and **2.59** in equal quantities and again quenched it before reaching full conversion (Figure 2-27). Both products **2.33** and **2.60** were formed in equal measure, amounting to a KIE of 1. This result indicates that C-H cleavage is not involved in the rate-determining step of the reaction.[60]

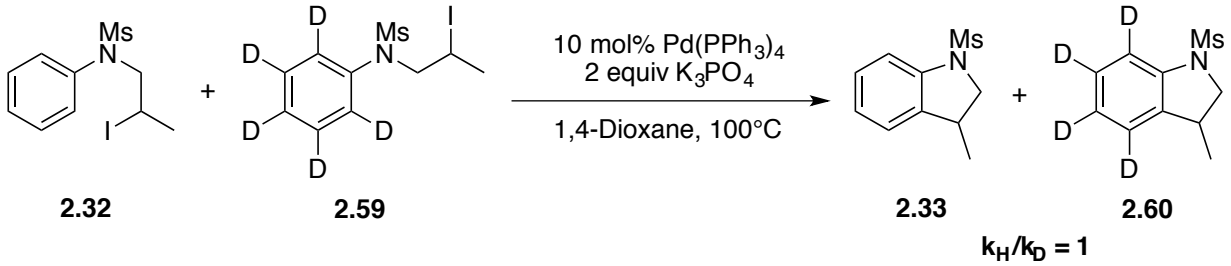


Figure 2-27: Kinetic Isotope Effect Experiment for Palladium-Catalyzed C-H Alkylation

Finally, primary iodide **2.61** with *ortho* methyl substitution was run under standard reaction conditions (Figure 2-28). Surprisingly, in addition to expected tetrahydronaphthalene product **2.62**, product **2.63** was also formed in equal measure. This result indicates that the ring-forming step does not differentiate between the methyl-substituted carbon and the unsubstituted carbon when forming the target carbon-carbon bond. Additionally, when cyclization occurs onto the methyl-substituted carbon, a methyl shift is required to relieve the quaternary carbon and

allow rearomatization to occur. Since 1,2-methyl shifts are not favorable in radical species,[53] the presence of a carbocation vicinal to the quaternary center is likely.

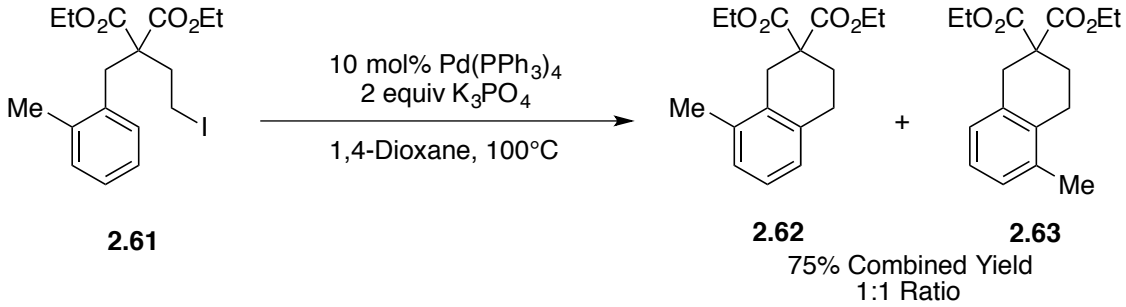


Figure 2-28: Palladium-Catalyzed C-H Alkylation with *ortho*-Substituted Arene

Based on the trends observed in the development of this manifold, as well as the mechanistic experiments performed, we postulate that the reaction proceeds through the mechanism described in Figure 2-29. The reaction begins through the reversible abstraction of the alkyl iodide, forming carbon-centered radical intermediate **2.64**. Fast 5-exo cyclization into the arene follows, forming cyclohexadienyl radical intermediate **2.65**. Single electron transfer then oxidizes this radical to cyclohexadienyl cation **2.66**, before undergoing elimination with base to form product and regenerate the active catalyst.

An alternative pathway can also be imagined for this transformation, involving the formation of a spirocyclic intermediate through cyclization at the *ipso* position, followed by ring expansion. However, if this were occurring, we would also expect to see it with substrates bearing substituents in the *meta* and *para* positions as well. The absence of such rearrangement with other substrates underscores the unlikeliness that it is occurring in this case, and points to the presence of carbocationic intermediates.

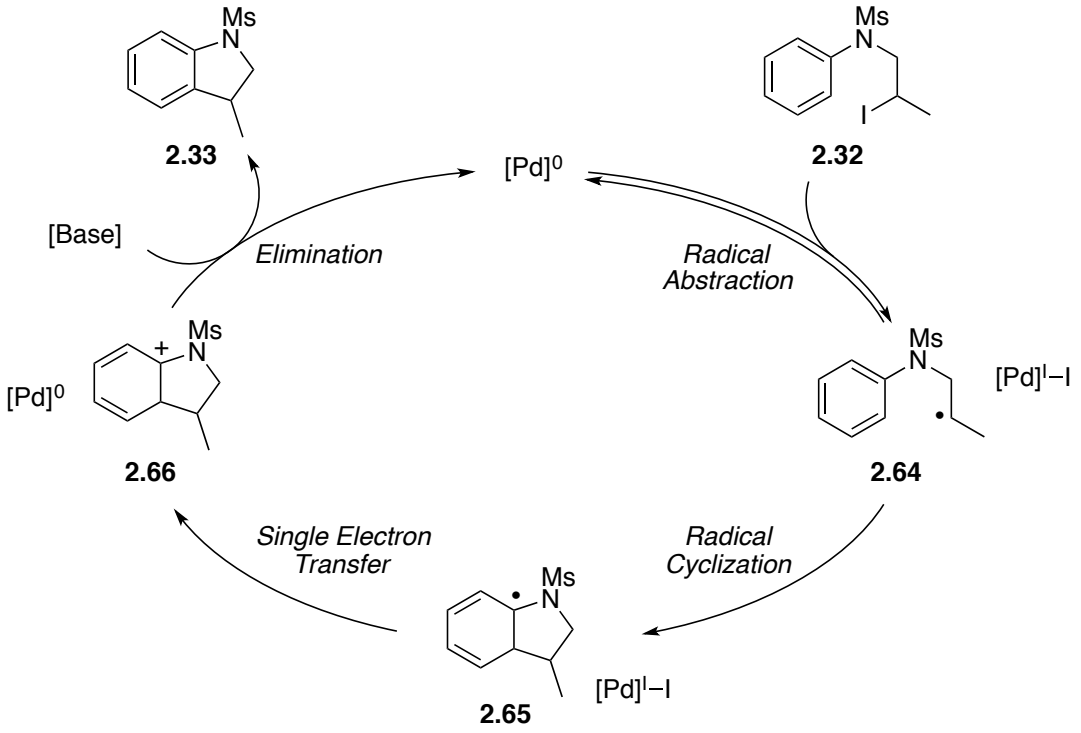


Figure 2-29: Proposed Mechanism for the Palladium-Catalyzed Aromatic C-H Alkylation with Unactivated Alkyl Halides

2.3.4 Summary

In conclusion, we have developed an intramolecular palladium-catalyzed aromatic C-H alkylation with unactivated halides. This reaction is capable of achieving cyclization with a wide range of substrates, and is applicable towards the synthesis of a variety of medicinally important benzo-fused small molecules. Of particular note, primary and secondary halides, including iodides and bromides are utilized successfully. Additionally, a wide variety of arenes and heteroarenes, including both electron-poor and electron-rich ring systems react efficiently. Mild reaction conditions allow for broad functional group compatibility, broadening its utility in the synthesis of complex targets. The breadth of scope available is proposed to be due to the hybrid organometallic-radical nature of the reaction mechanism, particularly the reversible activation of

the alkyl halide, as this minimizes the prominence of deleterious side reactions common to palladium-catalyzed reactions involving unactivated alkyl electrophiles.

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Chapter III: A Versatile, Palladium-Catalyzed Approach to Alkene-Alkyl Halide Coupling

3.1 Introduction

Alkyl halides and alkenes are two of the most fundamental building blocks available for organic synthesis. Their ubiquity, price, and broad reactivity make them ideal reagents for a wide range of transformations. As such, the direct coupling of these two components is a particularly attractive route for the formation of carbon-carbon bonds with the preservation of one of the two reactive handles. However, their application to certain reactive manifolds remains challenging. Herein are described two such coupling methods, the Mizoroki-Heck reaction and transition metal-catalyzed carbohalogenation, and the advantages and challenges associated with the application of each. These coupling reactions feature two notable differences from other transition metal-catalyzed cross-couplings such as Suzuki and Negishi reactions. One such advantage is that they do not require prefunctionalized organometallic coupling partners such as boronate or alkyl zinc moieties. Additionally, one of the two functional handles (alkene and halide) from the starting materials is restored in the product, providing a basis for further reactivity.

3.1.1 Mizoroki-Heck Reaction

Since its development in the 1970s, the Mizoroki-Heck reaction has become an important method for transition metal-catalyzed carbon-carbon bond-forming transformations in organic chemistry.[1-4] The utility of this reaction has been well demonstrated in complex synthesis, and was recognized with the Nobel Prize in 2010.[5] It affects the direct coupling of aryl or vinyl halides and sulfonates with alkenes, without requiring pre-installation of an organometallic

coupling partner. Furthermore, it regenerates the alkene in the product, allowing further functionalization in subsequent steps.

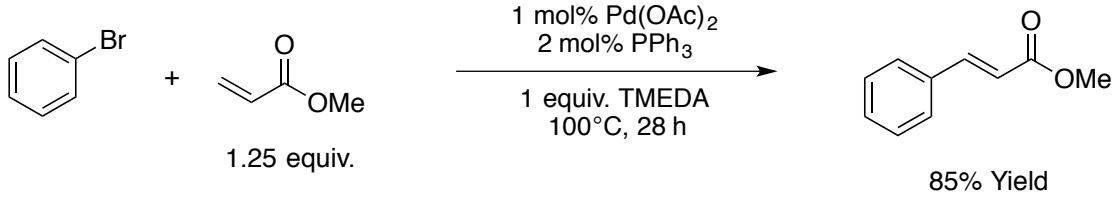


Figure 3-1: Early Report of Palladium-Catalyzed Heck Cross-Coupling of an Aryl Halide with Methyl Acrylate

In the 45 years since its discovery, the Heck reaction has been used in the total synthesis of countless natural product targets.[6] The versatility of this reaction allows its application towards a number of synthetic functions, including C-C coupling of complex fragments, attachment of small fragments, poly-ene core synthesis, and ring-closure of cyclic and polycyclic targets. Its mild reaction conditions and wide functional group tolerance make it ideal for late stage transformations. This is exhibited in the formation of the central 8-membered ring in Danishefsky's 1995 synthesis of chemotherapeutic agent paclitaxel via intramolecular Heck-type cyclization (Figure 3-2).[7]

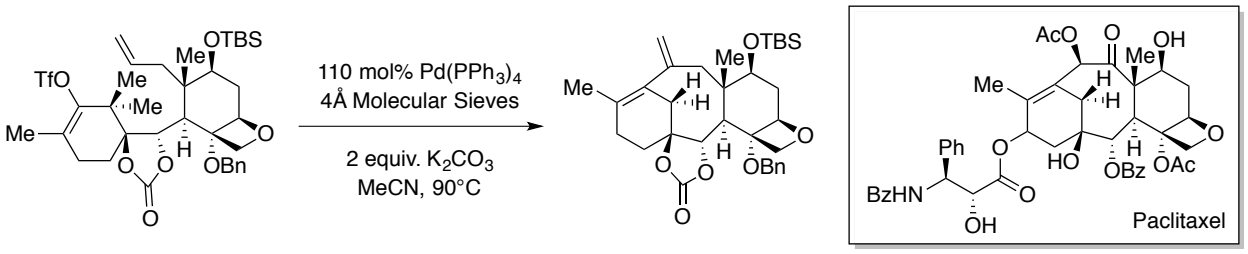


Figure 3-2: Palladium-Catalyzed Heck-Type Cyclization *En Route* to Paclitaxel

A significant challenge facing efforts to further develop this reaction is in its application towards alkyl halide electrophiles. As with most other palladium-catalyzed cross-coupling reactions, unactivated sp^3-hybridized halides suffer from slow oxidative addition due to the

electron-rich nature of the C-X bond,[8,9] and rapid β-hydride elimination with accessible β-hydrogens (Figure 3-3).[10,11] Furthermore, unlike cross-coupling reactions, which proceed via transmetallation, the Mizoroki-Heck reaction requires an open coordination site on palladium to which the alkene binds. However, this open coordination site also facilitates β-hydride elimination, making application of unactivated alkyl halides towards Mizoroki-Heck reactivity a particularly challenging venture.

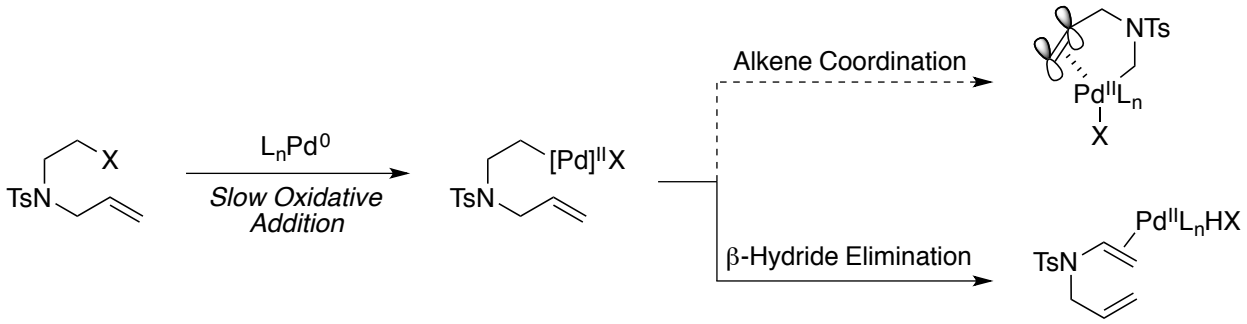


Figure 3-3: Challenges Associated with Developing Palladium-Catalyzed Alkyl Heck Reactions

3.1.2 Carbohalogenation Reactions

An alternative method for the coupling of C-X bonds with alkenes to form new carbon-carbon bonds is the transition-metal-catalyzed carbohalogenation of alkenes.[12,13] After formation of the target carbon-carbon bond, carbohalogenation reactions create a new carbon-halide bond, rather than restoring the alkene. This halide may be the same halide removed and transferred from the alkyl halide substrate, or a new halide may be introduced.[14,15] There are generally two categories within carbohalogenation reactions, namely Kharasch reactions and atom-transfer radical cyclization (ATRC). As indicated by the name ATRC, these reactions typically proceed via radical intermediates.

The Kharasch reaction involves the anti-Markovnikov addition of 1,1,1-trichloroalkanes across an alkene, forming a new C-C bond on one side of the alkene, and a C-X bond on the

other.[16] This reaction is widely used in the synthesis of aromatic carbocycles and heterocycles, where the introduction of chlorinated carbon is advantageous for their ability to eliminate to establish aromaticity (Figure 3-4).[17] Outside of this capacity, however, its broader use in complex synthesis has been curtailed by the requirement of trichloromethyl-substituted starting materials, and its general limitation to terminal alkenes. Additionally, harsh reaction conditions, including high temperatures and long reaction times, are often required for efficient coupling.

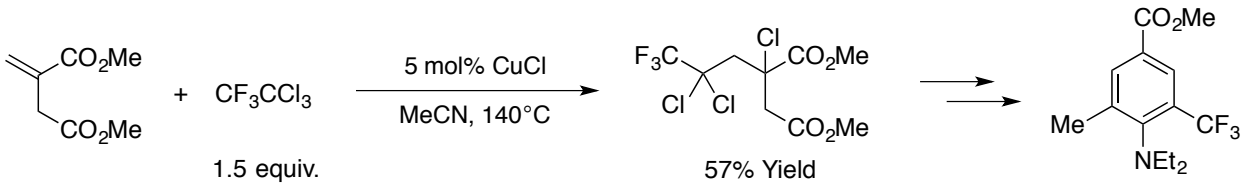


Figure 3-4: Transition Metal-Catalyzed Kharasch Addition in Synthesis of Substituted Arenes

Atom-transfer radical cyclization reactions are another form of carbohalogenation which enable the intramolecular transfer of a C-X bond across an alkene, for the formation of a new C-C bond and restoration of the C-X bond. These reactions can be divided roughly into two sets. One is an intramolecular subset of Kharasch reactions, facilitating chloride atom transfer from a trichloromethyl group or otherwise highly electron-withdrawn C-Cl bond across an alkene within the same molecule (Figure 3-5).[18] These intramolecular variants, unlike traditional intermolecular Kharasch reactions, tolerate α-chloro-esters and disubstituted alkenes.

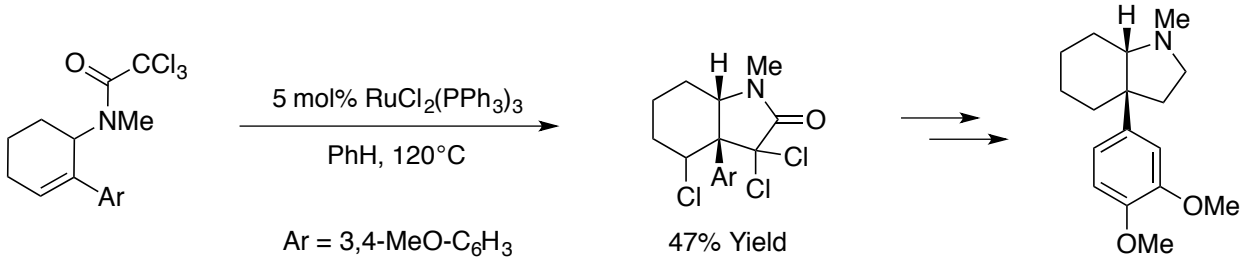


Figure 3-5: Ruthenium-Catalyzed Intramolecular Kharasch-Type Atom-Transfer Radical Cyclization in Synthesis of (±)-Mesembrane

ATRC reactions can also take quite a different form, enabling the use of aryl, vinyl, and even sp^3-hybridized alkyl iodides in intramolecular carbohalogenations. The ability to facilitate reactivity without the need for highly activated C-X bonds as with the reactions described above represents a significant increase in the scope of transformations accessible via this pathway. However, these reactions are also not without their limitations. Aryl and vinyl halides, similarly to other forms of transition-metal catalysis, undergo activation and coupling readily (Figure 3-6).[19] Sp^3-hybridized alkyl halides, however, are more reticent electrophilic partners, as the electron-rich C-X bond resists activation and the presence of β-hydrogens allows for facile elimination. In addition to challenges stemming from the use of alkyl halides, carbohalogenation reactions are also quite sensitive to the nature of the alkene component and are typically limited to terminal alkenes.

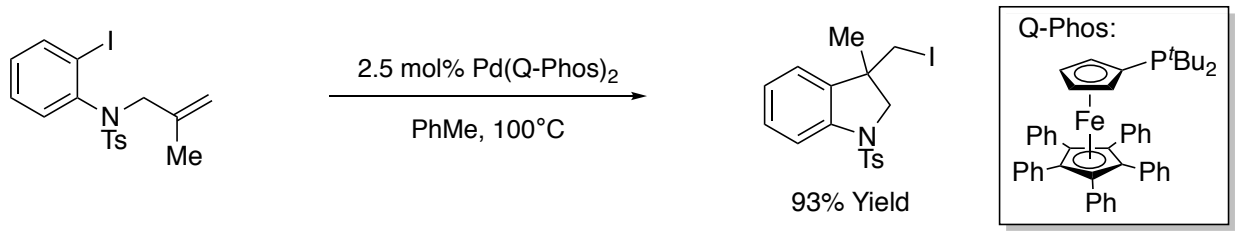


Figure 3-6: Palladium-Catalyzed Atom-Transfer Radical Cyclization with Aryl Iodides

While advances have been made to employ unactivated alkyl halides and a variety of alkenes in both the Mizoroki-Heck Reaction and transition-metal-catalyzed carbohalogenation, there remain vast areas of undeveloped chemical space therein. Improvement in these fields to address these difficulties could vastly broaden the scope of application of these reactions in key areas such as pharmaceutical synthesis.

3.2 Background

The Mizoroki-Heck reaction has been instrumental in the advancement of organic synthesis through enabling the coupling of aryl and vinyl halides with alkene coupling partners. Likewise, transition metal-catalyzed carbohalogenation reactions such as the Kharasch reaction and atom-transfer radical cyclization have greatly contributed in terms of versatility offered for coupling these types of fragments. However, both reaction categories are limited in terms of affecting reactivity with unactivated alkyl halide substrates. This can be attributed to the general difficulties associated with palladium catalysis and alkyl electrophiles.

A number of strategies have emerged to combat the challenges associated with engaging alkyl halide electrophiles in both Heck-type and carbohalogenation reactions. Among Heck reactions, while palladium is the metal traditionally used for this transformation, alternative metal catalysts have been employed to obviate the difficulties associated with palladium reactivity. More recently, however, palladium-catalysts have been employed successfully to facilitate a number of alkyl Heck reactions. With regard to carbohalogenation reactions, on the other hand, the use of alkyl halide electrophiles is not new. However, the challenge therein is in decreasing the degree of activation of the halide and the severity of the conditions required to affect the desired transformation.

3.2.1 Alternative Transition Metals in Alkyl Heck Reactions

Among the available alternative transition metal catalysts available to employ towards alkyl Heck reactivity, cobalt, copper, and titanium have emerged as promising options.[20] Nickel has also been thoroughly investigated as a catalyst due to its similarity to palladium and its history of use in conventional Heck reactions.[21,22] Each of these metals is several orders of magnitude more earth-abundant than palladium, and is correspondingly cheaper. In one of the

earliest such reports, the Beletskaya group found nickel capable of catalyzing a Heck-type reaction of unactivated alkyl bromides with styrenes or methyl acrylate (Figure 3-7).[23] However, the scope of substrates made accessible by this manifold is quite small, and stoichiometric zinc powder is required to turn over the catalyst.

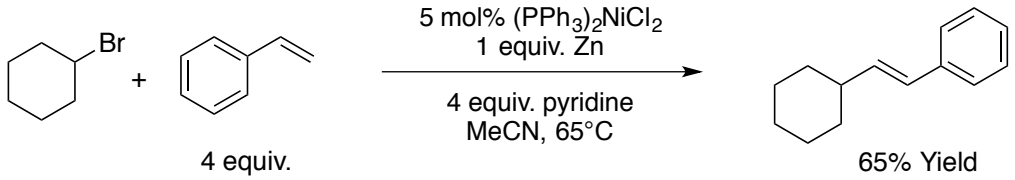


Figure 3-7: Nickel-Catalyzed Intermolecular Alkyl-Heck Reaction

More recently, the Jarvo group expanded the scope of alkyl electrophile capable of activation by nickel catalysis (Figure 3-8).[24] They demonstrated the ability to engage benzylic methyl ethers in nickel-catalyzed Heck-type reactions. Furthermore, application to enantioenriched benzylic ethers affects an enantiospecific cross-coupling, suggesting a two-electron pathway. However, superstoichiometric Grignard reagent is required to activate the ether towards formation of the alkyl-metal intermediate.

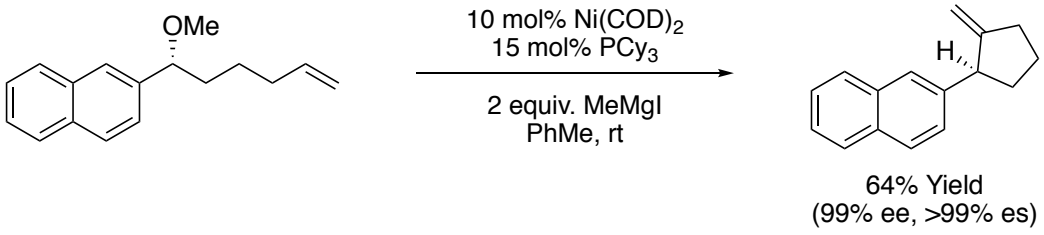


Figure 3-8: Enantiospecific, Nickel-Catalyzed, Intramolecular Alkyl Heck Reaction utilizing Methyl Ether Electrophiles with Superstoichiometric Alkylmagnesium Base

Kambe and coworkers have demonstrated the use of titanocene catalysts to enable similar reactions, coupling primary and secondary alkyl bromides with styrene coupling partners (Figure 3-9).[25] Additionally, secondary alkyl chlorides were also found to be effective electrophiles. It

should also be noted that this reaction is proposed to function via radical intermediates. While it is a significant achievement to engage unactivated alkyl bromides and chlorides in an alkyl Heck reaction, stoichiometric, highly reactive Grignard reagent is required, which limits the substrate scope available.

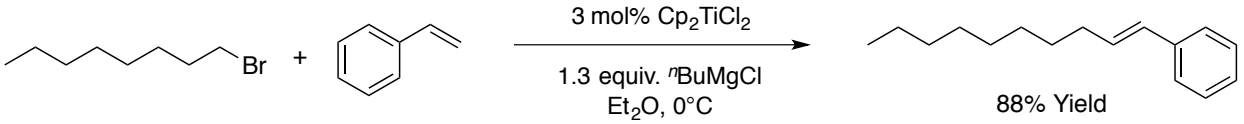


Table 3-9: Titanocene-Catalyzed Intermolecular Alkyl Heck Reaction with Alkylmagnesium Reagents

Nishikata and coworkers reported the copper-catalyzed Heck-type cross coupling of tertiary alkyl bromides with styrenes, facilitating the construction of challenging quaternary carbon centers (Figure 3-10).[26] This method is proposed to function through radical intermediates. While this reaction is significant in enabling cross coupling under quite mild conditions, the scope is limited to tertiary α-halo esters and styrene substrates due to their ability to stabilize radical intermediates.

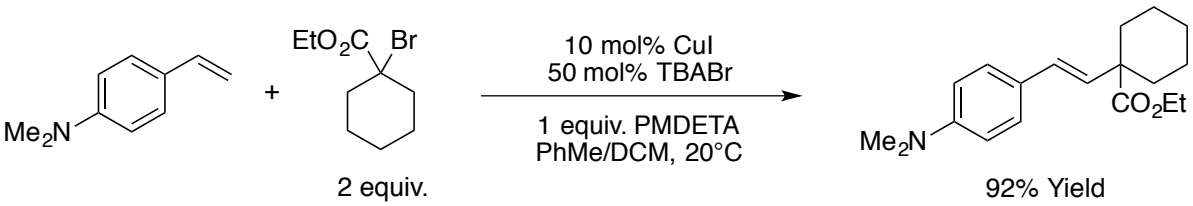


Table 3-10: Copper-Catalyzed Intermolecular Heck Reaction with Tertiary Alkyl Bromides

Cobalt was also found to be adept at enabling Heck-type transformations of alkyl halides. In 2002, the Oshima group disclosed a cobalt-catalyzed intermolecular cross coupling of unactivated alkyl iodides, bromides, and chlorides with styrene coupling partners with only slight excess of the alkyl halide component (Figure 3-11).[27] However, like the nickel- and titanium-

catalyzed alkyl-Heck-type couplings reported by Jarvo and Kambe respectively, superstoichiometric alkyl Grignard reagent is required to achieve the desired reactivity, eroding the substrate scope achievable by this manifold.

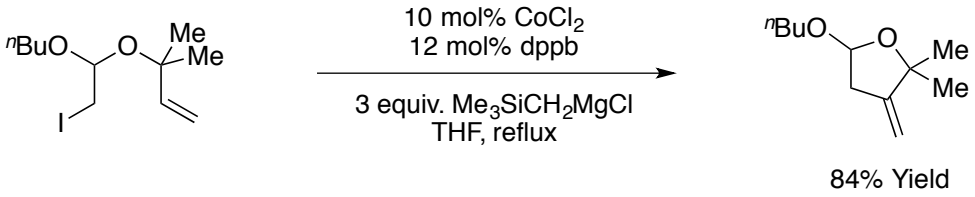


Table 3-11: Cobalt-Catalyzed Intramolecular Alkyl Heck Cyclization with Alkylmagnesium Reagents

More recently, Carreira and coworkers reported an intramolecular alkyl Heck-type coupling with unactivated alkyl iodides and a variety of alkenes without requiring the presence of Grignard reagent (Figure 3-12).[28] They achieved this transformation with a cobaloxime catalyst, running reactions under blue LED irradiation at room temperature to achieve alkyl iodide activation to form alkyl radical intermediates. While this reaction is notable for requiring no activation of either iodide or alkene, the requirement of triphenyltin in the catalyst is undesirable from a toxicity perspective, and makes scale-up challenging.

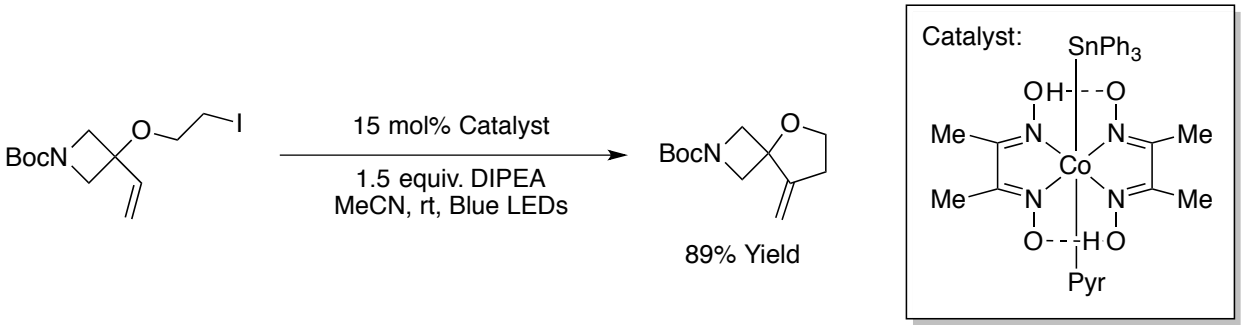


Table 3-12: Cobaloxime-Catalyzed Intramolecular Heck Reaction under Blue LED Irradiation

In contrast to the reports of first-row transition metal-catalyzed alkyl Heck-type reactions, the Hashmi group reported an intermolecular Heck-type cross-coupling reaction with unactivated alkyl bromides and styrenyl olefins, using a dinuclear gold photocatalyst (Figure 3-13).[29] The reaction is capable of activating primary, secondary, and tertiary alkyl bromides, and is proposed to function through radical intermediates. While this reaction represents promising advancement in the field of alkyl cross-couplings, it is limited by the requirement of UVA irradiation and the restriction to highly activated styrenyl coupling partners. Additionally, gold does not feature the same earth abundance and cost advantages as the first-row transition metals discussed herein.

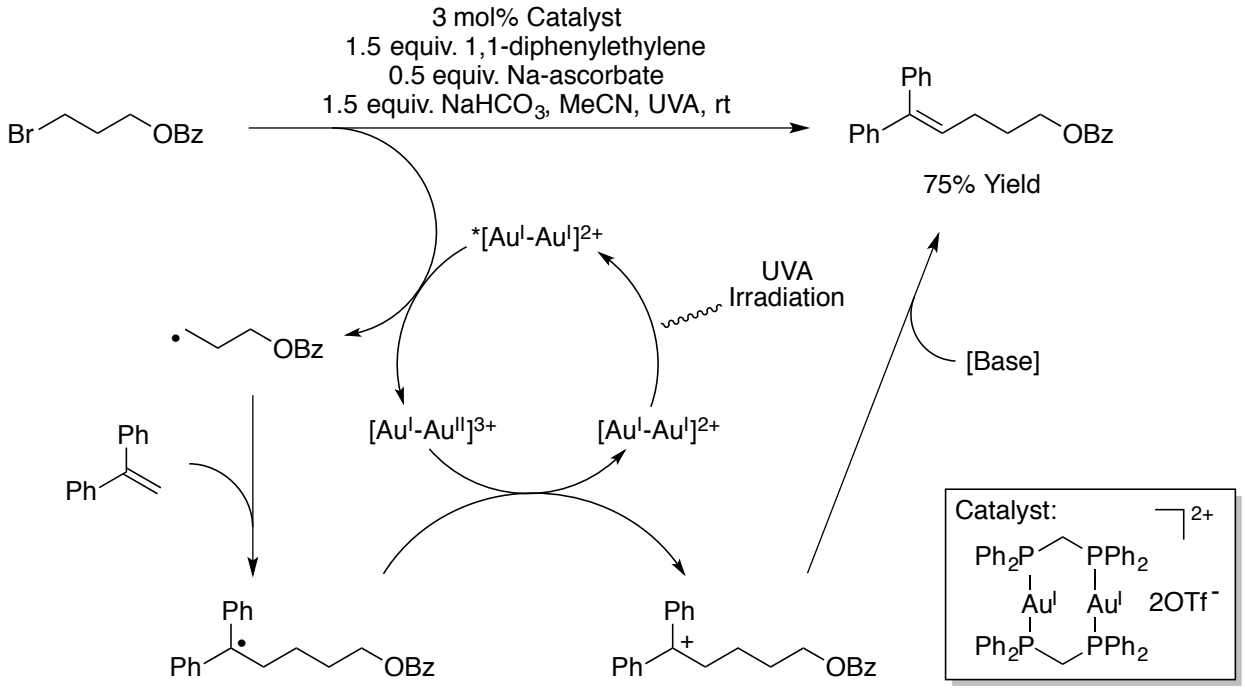


Figure 3-13: Gold-Catalyzed Photoredox Intermolecular Alkyl Heck-Type Coupling of Alkyl Bromides and Styrenes

3.2.2 Palladium-Catalyzed Alkyl Heck Reactions

While efforts to employ other transition metal catalysts to facilitate alkyl-Heck-type cross coupling reactions achieved promising results, no such manifold has yet achieved a broad range of reactivity under the mild reaction conditions often enabled by palladium catalysis. As with

palladium-catalyzed C-H alkylation reactions, methods to employ alkyl halide electrophiles include the use of privileged alkyl halides. These privileged electrophiles include activated benzylic[30] and allylic[31] halides as well as α-halo carbonyl reagents[32,33] to facilitate oxidative addition, and perfluoroalkyl[34,35] or adamantyl[36] halides to prohibit β-hydride elimination.

The first palladium-catalyzed alkyl Heck reaction with unactivated alkyl halides was reported by the Fu group in 2007.[37] They used a palladium/NHC complex to enable the intramolecular coupling of alkyl iodides, bromides, and chlorides with unactivated alkenes (Figure 3-14).

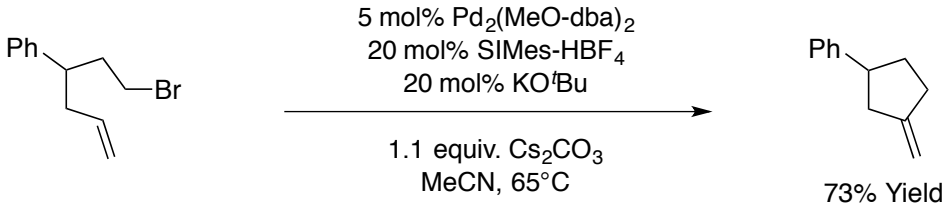


Figure 3-14: Palladium-Catalyzed Intramolecular Alkyl Heck Reaction with Unactivated Primary Halides and Terminal Alkenes

This reaction is proposed to proceed via two-electron oxidative addition, following a traditional Heck-type mechanism. Mechanistic investigations included subjecting a *cis*-di-deuterated alkyl bromide to standard reaction conditions (Figure 3-15). The methyleneindane product was formed in one diastereomer, with complete inversion of the stereocenter at the alkyl bromide carbon. This is consistent with the hypothesized organometallic reaction mechanism. While this reaction is notable as the first such report, it is quite limited in that only primary halides and terminal alkenes facilitate reactivity, exclusively forming 5-membered methylenecyclopentane rings.

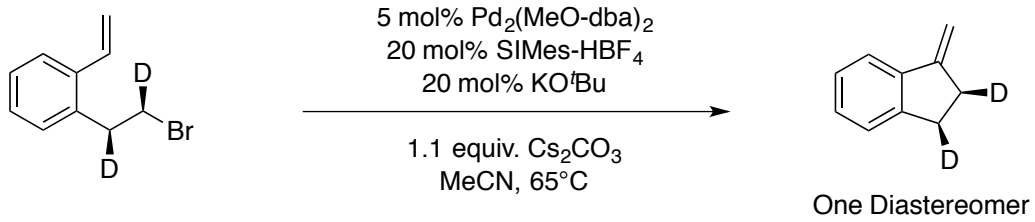


Figure 3-15: Mechanistic Investigation of Palladium-Catalyzed Alkyl Heck Reaction

Following this report, our laboratory found that employing palladium catalysis under CO atmosphere could achieve similar intramolecular alkyl Heck-type reactions with alkyl iodides (Figure 3-16).[38] However, this manifold expanded the accessible scope to include both primary and secondary halides, as well as a variety of alkene substitution patterns. Furthermore, 6-membered rings were found to be accessible through this reaction. While this report complements the existing literature and expands the scope of achievable transformations, the presence of CO in a reaction where it is not incorporated into the product is detrimental.

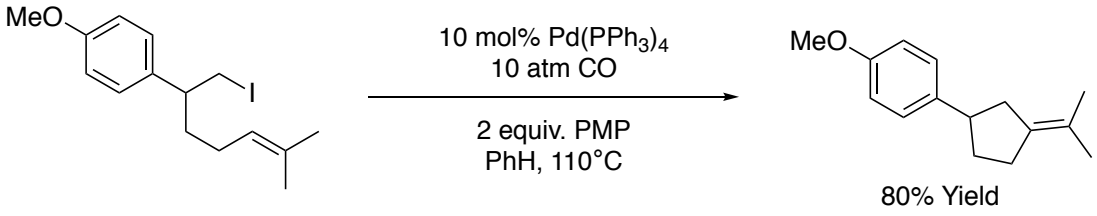


Figure 3-16: Palladium-Catalyzed, Intramolecular Heck Reaction under CO Atmosphere

Preliminary mechanistic investigations suggest the reaction functions through single-electron activation of the alkyl iodide, forming an alkyl radical, followed by radical cyclization into the alkene. Mechanistic studies included performing the reaction in the presence of TEMPO radical trap (Figure 3-17). While it was determined that 5-exo cyclization occurred too rapidly to be interrupted by TEMPO, the use of a 6-exo cyclization substrate in the presence of TEMPO resulted in the formation of the TEMPO adduct, supporting the hypothesized radical mechanism.

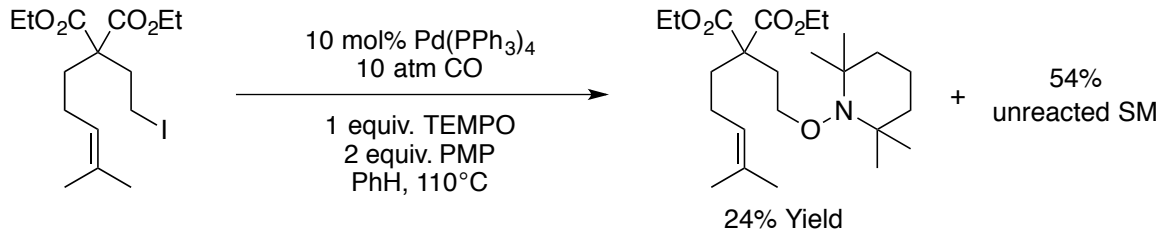


Figure 3-17: Formation of TEMPO Adduct in Palladium-Catalyzed Alkyl Heck Reaction

Our group then expanded this manifold to include intermolecular couplings of unactivated alkyl iodides and activated alkenes (Figure 3-17).[39] This reaction was also able to facilitate the reaction of both primary and secondary alkyl iodides. Similarly to the intramolecular report, the reaction was proposed to function via radical intermediates. However, it did not require CO to facilitate the reaction.

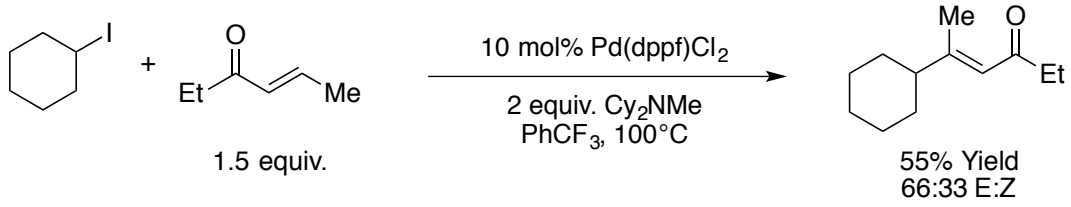


Figure 3-18: Palladium-Catalyzed Intermolecular Alkyl Heck Reaction with Unactivated Alkyl Iodides

Concurrently with this report, the Zhou group also disclosed an intermolecular Heck reaction with unactivated alkyl iodides and styrenes (Figure 3-19).[40] This report employed remarkably similar conditions to the reaction developed by our laboratory, and was also proposed to function through a hybrid organometallic-radical process. Notably, they report significant amounts of carbovinylation byproduct arising from a second addition of styrene onto the radical formed after the first styrene addition. This highlights one of the key challenges associated with developing an alkyl Heck reaction, where balance between addition of alkene

units and elimination of alkyl palladium intermediates is crucial. Improper balance can cause increased dehydrohalogenation of starting material or, in this case, di-addition of alkene.

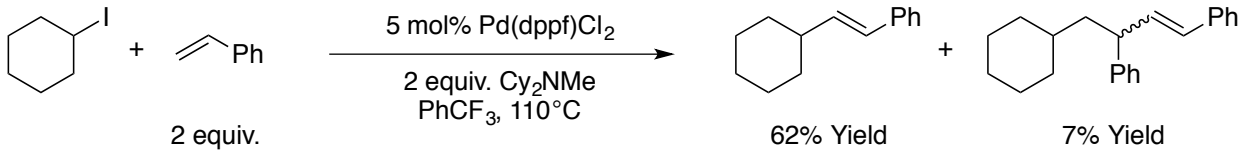


Figure 3-19: Palladium-Catalyzed Intermolecular Heck Reaction of Alkyl Halides with Styrene

More recently, the Gevorgyan group reported an intramolecular alkyl Heck reaction with iodomethyl silyl ethers and styrenes (Figure 3-20).[41] This reaction is endo-selective, forming 7-, 8- and 9-membered rings in good yields. It utilizes the mixed phosphinoferrocene ligand 1-diphenylphosphino-1'-(di-*tert*-butylphosphino)ferrocene (dtbdppf) which is believed to activate the alkyl iodide via single electron transfer to access radical intermediates. The influence of the silyl ether and the stability of a benzylic radical intermediate are thought to control the regioselectivity of the cyclization.

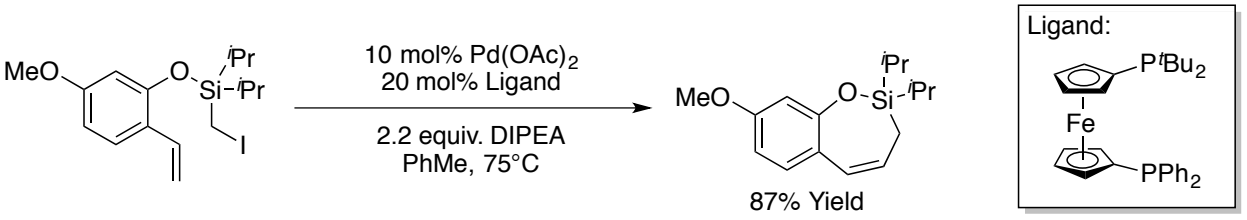


Figure 3-20: Palladium-Catalyzed, Endo-Selective Silyl-Methyl Heck Cyclization

The Liu group expanded upon this concept by reporting an endo-selective Heck cyclization of unactivated alkyl iodides with styrenyl olefins without the influence of silane in the substrate tether (Figure 3-21).[42] Similarly to previous reports, this reaction is proposed to utilize radical intermediates en route to forming 5-phenyl-1,2,3,6-tetrahydropyridine derivatives in good yield. Upon formation of a primary radical intermediate, cyclization into the styrene occurs exclusively

in an endo-fashion due to the stability of the resulting tertiary benzylic radical. As these particular characteristics of substrate design are crucial to achieving proper cyclization, the scope of this reaction is quite narrow.

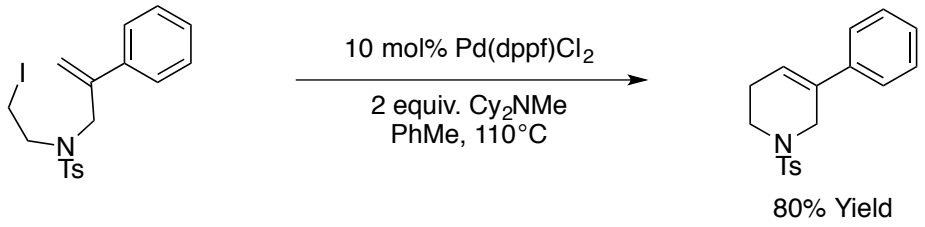


Figure 3-21: Palladium-Catalyzed Endo-Selective Heck-Type Cyclizations with Unactivated Alkyl Iodides and Styrene

3.2.3 Atom-Transfer Radical Cyclization

Similarly to Heck reactions, palladium-catalyzed atom-transfer radical cyclization reactions are difficult to achieve with alkyl halide electrophiles due to poor activation of an electron-rich C-X bond. As such, much of the literature on ATRC reactions is confined to aryl,[14,19,43-45] vinyl,[46,47], or activated alkyl[16] halides. The Ban group has published two reports in the 1980s utilizing alkyl iodides in ATRC reactions towards the synthesis of pyrrolidine and pyrrolidinone ring structures (Figure 3-22).[48,49] While these transformations are significant, they require activated α-halo carbonyls to react, and are limited to iodides and terminal alkenes in their scope, restricting the variety of rings the reaction is capable of producing.

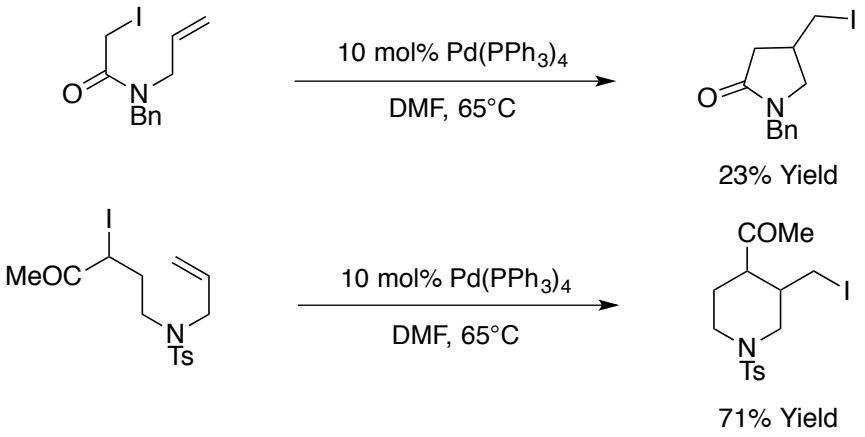


Figure 3-22: Palladium-Catalyzed Atom-Transfer Radical Cyclization with Activated Alkyl Iodides

More recently, the Cook group published an atom-transfer radical cyclization utilizing unactivated alkyl iodides in a domino cyclization reaction to form diquinane derivatives (Figure 3-23).[50] While the reaction is proposed to function through radical intermediates, they found that variation of the ligand on the palladium catalyst had noticeable effects on the ratios of diastereomers observed in the product. Because of this observation, it was postulated that palladium was involved in the cyclization step, and not merely as a radical initiator and/or propagation agent. While the use of unactivated alkyl halides is significant, the use of highly active alkynes to trap and relay the radical intermediate before cyclization into the alkene is limiting in the scope achievable. Additionally, the reaction is limited to alkyl iodides and terminal alkenes.

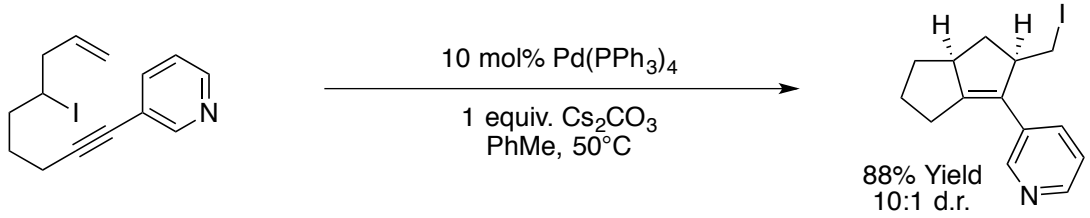


Figure 3-23: Palladium-Catalyzed Tandem Atom-Transfer Radical Cyclization with Unactivated Alkyl Iodides

The first example of an ATRC reaction coupling unactivated alkyl halides with alkenes was reported by the Jiang group. Using a palladium/bisphosphinoferrocene catalytic system, they enabled the formation of 3-(iodomethyl)pyrrolidine ring structures in modest to good yield (Figure 3-24).[51] Furthermore, introduction of a chiral substituent at the β-position relative to the iodide experienced complete retention of stereochemistry in the product, indicating negligible amounts of β-hydride elimination and reinsertion in the reaction mechanism. This manifold is, however limited to the use of iodides and 1,1-disubstituted alkenes. This substitution pattern forms a quaternary center upon cyclization, restricting elimination and formation of a Heck-type product.

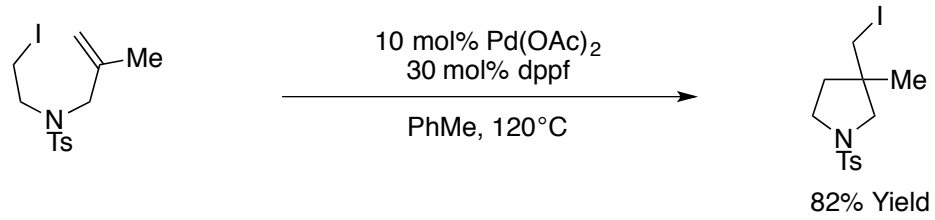


Figure 3-24: Palladium-Catalyzed Atom-Transfer Radical Cyclization of Unactivated Alkyl Iodides

3.3 Results and Discussion

In our laboratory, having previously demonstrated the ability to employ palladium catalysis to affect the Heck-type cross coupling of unactivated alkyl iodides,[38] we sought to greatly improve the scope, conditions, accessibility, and versatility of this reaction. While our previous reports have been limited to iodides, we hoped to expand this to include the use of alkyl bromides. Additionally, this previous report had the disadvantage of requiring CO atmosphere, despite CO not being incorporated into the product. This particular drawback significantly limits the potential use of this reaction in large-scale synthesis such as industrial or medicinal chemical applications. Finally, while the Heck reaction couples iodides with alkenes and restores the

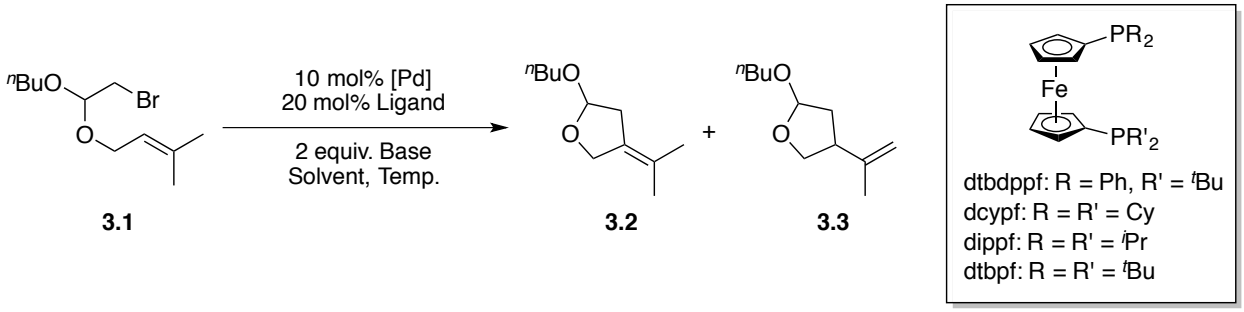
alkene in the product, the ability to adjust reaction conditions to choose which functional group is restored in the product would be a significant improvement in the versatility of this manifold.

3.3.1 Reaction Development

We began this effort focusing on improving upon the previously reported alkyl Heck-type reaction. As such, in our early efforts we sought a substrate similar to those used in that report. We chose a bromide which could be made rapidly and on scale to aid in the development of this reaction. Settling on bromide **3.1**, we began screening conditions known to activate primary or secondary alkyl bromides in single-electron processes or to do so with iodides in the absence of CO (Table 3-1).[52] A palladium/NHC complex shown to activate alkyl bromides for low-pressure carbonylation was unsuccessful (Entry 1),[53] as were catalyst systems used in the aromatic C-H alkylation of bromides (Entry 2),[54] and in the intermolecular alkyl Heck-type coupling of alkyl iodides run in the absence of CO (Entry 3).[39] However, employing palladium(II) acetate with 1-diphenylphosphino-1'-(di-*tert*-butylphosphino)ferrocene (dtbdppf) as a ligand under conditions developed by Gevorgyan and coworkers for the intramolecular endo-selective silyl methyl Heck reaction was able to generate the desired product, albeit in quite low yield (Entry 4).[41]

Further screening of alkyl phosphinoferrocene ligands (Entries 5-7) found the use of 1,1'-bis(di-*tert*-butylphosphino)ferrocene (dtbpf) to generate modest yields of the desired product (Entry 7). Changing the palladium(II) precatalyst from palladium(II) acetate to one which is designed to rapidly eliminate *in situ* to form an active palladium(0) catalyst, allylpalladium chloride dimer, increased yield significantly (Entry 8). Changing the base to triethylamine improved the ratio of products observed (Entry 9), and exchanging toluene for trifluorotoluene modestly improved the yield further (Entry 10). Interestingly, the premade palladium(II) catalyst $Pd(dtbpf)Cl_2$ did not perform as well as the precatalyst/ligand mixture (Entry 11).

Table 3-1: Reaction Condition Optimization for Intramolecular Aromatic C-H Alkylation with Unactivated Primary Alkyl Bromides



3.1 **3.2** **3.3**

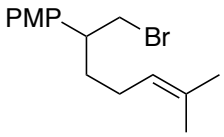
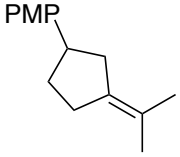
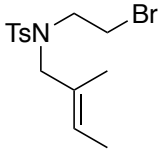
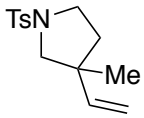
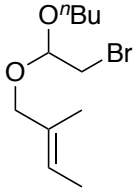
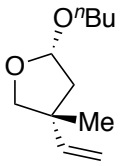
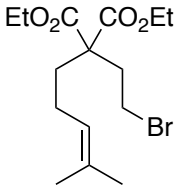
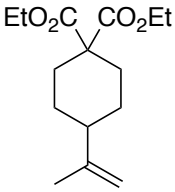
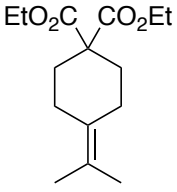
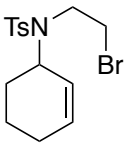
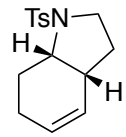
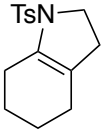
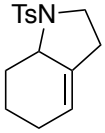
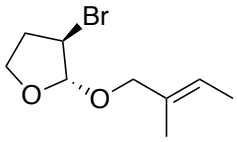
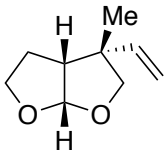
Entry	Catalyst	Ligand	Base	Solvent	Temperature (°C)	**3.2** (%)[a]	**3.3** (%)
1	$[Pd(allyl)Cl]_2$	IMes	DIPEA	$PhCH_3$	100	0	0
2	$Pd(PPh_3)_4$	--	PMP	Ph^tBu	130	0	0
3	$Pd(dppf)Cl_2$	--	Cy_2NMe	$PhCF_3$	100	0	0
4	$Pd(OAc)_2$	dtbdppf	DIPEA	$PhCH_3$	100	5	1
5	$Pd(OAc)_2$	dcypf	DIPEA	$PhCH_3$	100	0	0
6	$Pd(OAc)_2$	dippf	DIPEA	$PhCH_3$	100	0	0
7	$Pd(OAc)_2$	dtbpf	DIPEA	$PhCH_3$	100	30	3
8	$[Pd(allyl)Cl]_2$	dtbpf	DIPEA	$PhCH_3$	100	65	12
9	$[Pd(allyl)Cl]_2$	dtbpf	Et_3N	$PhCH_3$	100	73	5
10	$[Pd(allyl)Cl]_2$	dtbpf	Et_3N	$PhCF_3$	100	85	5
11	$Pd(dtbpf)Cl_2$	--	Et_3N	$PhCF_3$	100	14	2

[a] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

3.3.2 Reaction Scope

With optimized conditions in hand for this transformation (Table 3-1, Entry 10), we sought to explore the scope of substrates available for cyclization. We began with a selection of bromides analogous to the iodides used in our alkyl Heck previous report. We found these conditions to successfully catalyze the Heck-type cyclization of these substrates in comparable yields to the previous report, but in the absence of CO and as bromide as the alkyl electrophile. This method is tolerant of both primary and secondary bromides, can enable cyclization onto a variety of alkenes, and forms both 5- and 6-membered rings.

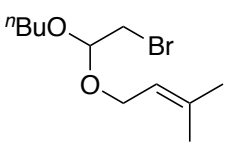
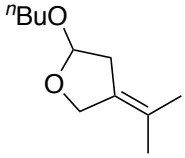
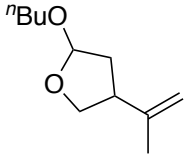
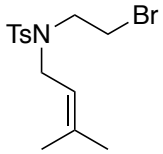
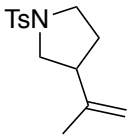
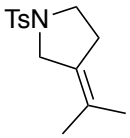
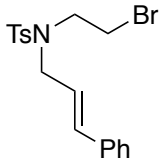
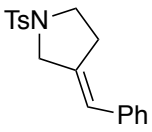
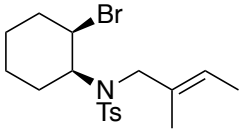
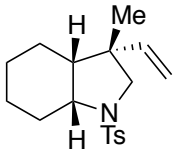
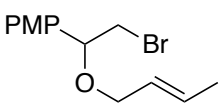
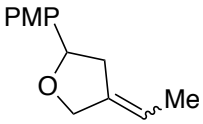
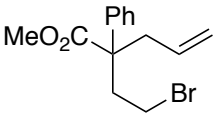
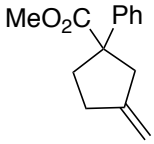
Table 3-2: Palladium-Catalyzed Heck-Type Cyclizations with Unactivated Alkyl Bromides[a]

Entry	Substrate	Product(s)	Yield (%)[b]
1	 **3.4**	 **3.5**	90
2	 **3.6**	 **3.7**	80
3	 **3.8**	 **3.9**	73 (89:11 dr)
4	 **3.10**	 **3.11**  **3.12**	82 (4:1 rr)
5	 **3.13**	 **3.14**  **3.15**  **3.16**	77 (7.2:3:1 rr)
6	 **3.17**	 **3.18**	93 (>95:5 dr)

[a] Reactions performed with [substrate]$_0$ = 0.25 M in $PhCF_3$ in the presence of 5 mol% $[Pd(allyl)Cl]_2$, 20 mol% dtbpf and 2 equiv. Et_3N at 100°C. [b] Isolated Yield.

After applying the new conditions developed for Heck-type cyclization of alkyl bromides to substrates used in our laboratory's previous report of alkyl Heck reactivity, we sought to expand the scope of what this manifold is capable of performing. The results of this effort are described in Table 3-3. Cyclization into styrenyl alkenes was successful in modest yield, but required longer reaction times than unactivated alkenes (Entry 2). Previously employed secondary alkenes all utilized an acetal tether. However, this ring system can be distorted due to anomeric effects. As such, we sought to engage a secondary alkyl bromide in a Heck-type cyclization without influence from an acetal tether. The target secondary bromide (Entry 3) reacted in good yield to form the octahydroindole product. Substrates with ether tethers were found to undergo efficient cyclization, forming substituted tetrahydrofuran rings in good yield (Entry 4). Sterically demanding, geometrically restricted alkenes were found to be willing coupling partners (Entry 5). Additionally, cyclization onto terminal alkenes was successful in good yield, but required the use of DBU as base to enable cyclization (Entry 6).

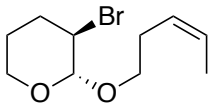
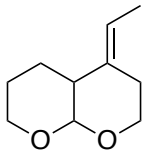
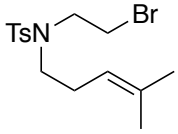
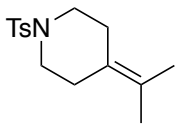
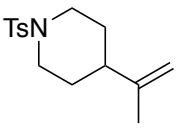
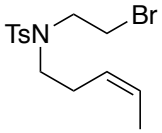
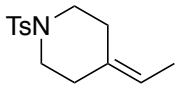
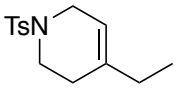
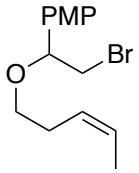
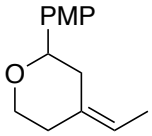
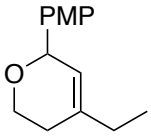
Table 3-3: Palladium-Catalyzed Alkyl Heck-Type Reactions via 5-Exo Cyclization[a]

Entry	Substrate	Product(s)	Yield (%)[b]
1	 **3.1**	 **3.2**  **3.3**	86 (17:1 rr)
2	 **3.19**	 **3.20**  **3.21**	81 (6:1 rr)
3	 **3.22**	 **3.23**	59[c]
4	 **3.24**	 **3.25**	63 (>95:5 dr)
5	 **3.26**	 **3.27**	71 (1:1 E:Z)
6	 **3.28**	 **3.29**	65

[a] Reactions performed with $[substrate]_0 = 0.25$ M in $PhCF_3$ in the presence of 5 mol% $[Pd(allyl)Cl]_2$, 20 mol% dtbpf and 2 equiv. Et_3N at 100°C. [b] Isolated Yield. [c] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

After exploring the scope of 5-membered rings accessible through this reaction, we sought to expand access to a number of 6-membered rings through 6-exo Heck-type cyclizations. Substrates bearing acetal (Entry 1), sulfonamide (Entries 2-3), and ether (Entry 4) moieties in the tether were found to undergo cyclization in modest to excellent yields.

Table 3-4: 6-Membered Ring Formation via Palladium-Catalyzed Alkyl Heck-Type Reactions[a]

Entry	Substrate	Product(s)	Yield (%)[b]
1	 **3.30**	 **3.31**	69[c]
2	 **3.32**	 **3.33**  **3.34**	92 (2:1 rr)
3	 **3.35**	 **3.36**  **3.37**	70 (3:1 rr)
4	 **3.38**	 **3.39**  **3.40**	41 (7:1 rr)

[a] Reactions performed with $[substrate]_0 = 0.33$ M in $PhCF_3$ in the presence of 5 mol% $[Pd(allyl)Cl]_2$, 20 mol% dtbpf and 2 equiv. Cy_2NMe at 120°C. [b] Isolated Yield. [c] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

When optimizing conditions for the formation of 5-membered rings, under certain conditions with brief reaction times we observed the formation of an intermediate, which was

determined to be the product of atom-transfer radical cyclization, in addition to the alkyl Heck product (Figure 3-25).

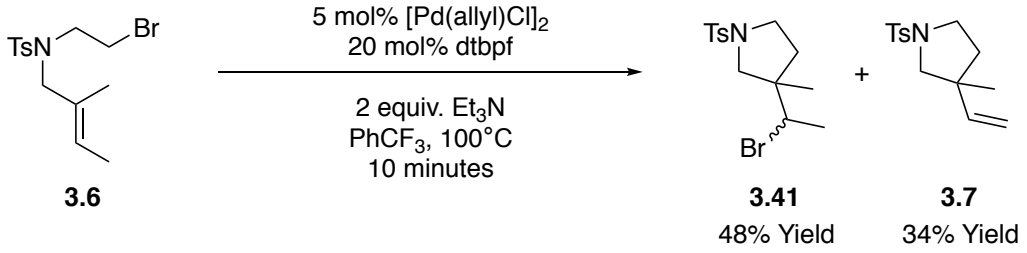
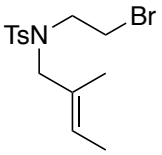
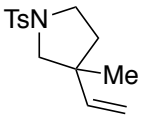
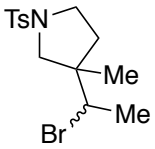
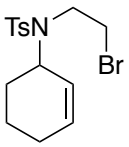
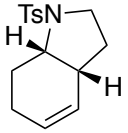
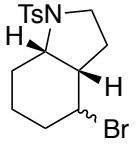
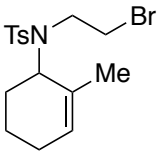
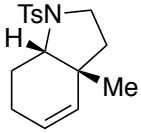
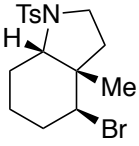
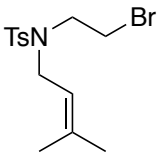
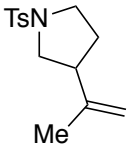
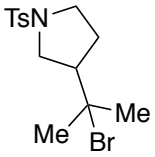


Figure 3-25: Observation of Atom-Transfer Radical Cyclization Product

Further investigation focused on the reoptimization of reaction conditions to maximize the yield of this product. We hypothesized that the reaction formed this ATRC product as an intermediate en route to the Heck product. Therefore, we expected that lowering the reaction temperatures and decreasing the amount of base added would slow the rate of elimination of the carbohalogenation product. This would increase the ratio of ATRC to Heck product. Application of these revised conditions to (primary and secondary) alkyl bromides yielded secondary and tertiary bromide products in modest to good yield (Figure 3-5).

While these conditions form ATRC products in modest yields and ratios to alkyl Heck products, the results serve as a proof of concept, demonstrating the ability to alter conditions to select for the functional handle to be restored in the product. Additionally, these results represent the first examples of ATRC reactions with unactivated alkyl bromides and alkenes with a variety of substitution patterns. While the ATRC product was observed with a wide variety of substrates by NMR of crude reaction mixtures, the isolation and characterization of some of these products proved challenging due to the presence and similar polarity of ATRC product, Heck product, and unreacted starting material.

Table 3-5: Palladium-Catalyzed Atom-Transfer Radical Cyclization of Unactivated Alkyl Bromides[a]

Entry	Substrate	Product(s)		Heck (%)[b]	ATRC (%)[c]
1	 **3.6**	 **3.7**	 **3.41**	11	49 (1:1 dr)
2	 **3.13**	 **3.14**	 **3.42**	16	68 (1:1 dr)
3	 **3.43**	 **3.44**	 **3.45**	6	84 (1.5:1 dr)
4	 **3.19**	 **3.20**	 **3.46**	40	26

[a] Reactions performed with $[substrate]_0$ = 0.25 M in $PhCF_3$ in the presence of 5 mol% $[Pd(allyl)Cl]_2$, 20 mol% dtbpf and 0.5 equiv. Et_3N at 80°C. [b] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated Yield.

In addition to our studies developing intramolecular Heck-type cyclizations, we also found this manifold capable of successfully coupling unactivated alkyl bromides and styrene in intermolecular alkyl Heck reactions (Figure 3-26). While this coupling formed the desired carbon-carbon bond in modest yield with unoptimized conditions, it serves as proof of concept for expanding the range of synthetic targets accessible by the developed reactive manifold.

Additionally, this result represents the first example of a palladium-catalyzed intermolecular Heck-type reaction with unactivated alkyl bromides.

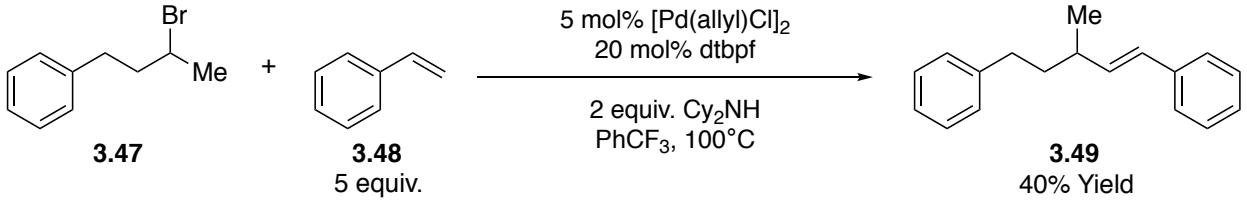


Figure 2-26: Palladium-Catalyzed Intermolecular Heck Coupling with Unactivated Alkyl Bromides

3.3.3 Mechanistic Investigation

Having investigated the reactive scope and weaknesses involved in achieving both transformations, we turned our attention towards gaining a greater understanding of the mechanism by which this reaction proceeds. Based on our previous report describing Heck-type reactions with alkyl electrophiles, and precedents describing atom-transfer cyclization reactions, we began with the premise that this reaction likely operates through radical intermediates. From here, the mechanism can take one of two forms (Figure 3-27).[55] The reaction may proceed by palladium catalysis, whereby the active palladium(0) catalyst is turned over for each molecule of product it makes, and is involved in activating each molecule of substrate to the radical intermediate. Alternatively, an "innate" chain may be at work, wherein palladium acts only as an initiator, activating one equivalent of substrate to the active radical species, which, through propagation, can facilitate the desired reaction faster than the catalyst can catalyze it.

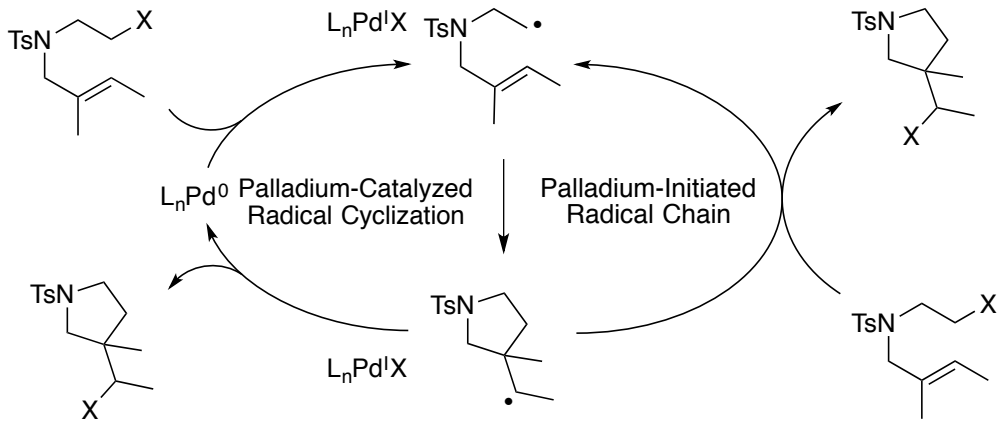


Figure 3-27: Possible Mechanisms for Palladium-Catalyzed and Palladium-Initiated Radical Processes

Innate radical chains are operant only when all propagation steps are fast enough to outcompete recombination with the palladium species or inhibition by solvent or base. If one step of this chain is slow, typically halide abstraction from a new molecule of starting material, then the chain becomes inefficient, and proceeds only in short chains or not at all. In the case of this reaction, the cyclization step should be quite fast. Formation of a new carbon-carbon bond at the expense of a π bond is a favorable process, and in many substrates a more stable radical is produced in this step. Therefore, halide abstraction is the step that likely defines the character of this mechanism. If this step is fast, a chain reaction is likely operant; however, if this step is slow, then palladium catalysis is most likely necessary to facilitate efficient cyclization.

Experiments in the absence of palladium began to eleucidate this reaction. We found that traditional radical initiator AIBN was able to facilitate the cyclization of primary iodide **3.50** in good yield, albeit with incomplete conversion (Figure 3-28). However, these same conditions were unsuccessful at initiating an efficient radical chain with bromide **3.1**, forming only minor amounts of product allowing most of the starting material to be recovered. This result can begin to shed some light on the nature of the mechanism at work with each halide. We can ignore the

radical cyclization step since it is the same in both reactions. The halide abstraction step is likely fast with iodides, leading to efficient radical cycles and efficient cyclization in the absence of palladium. With bromides, however, halide abstraction may be slow. While cyclization does occur with AIBN as initiator, it is likely that only short chains are operant, leading to poor yield and conversion. We hypothesize that under normal palladium-involved conditions, bromide reactions are likely catalytic in palladium, while iodide reactions are palladium-initiated radical chains.

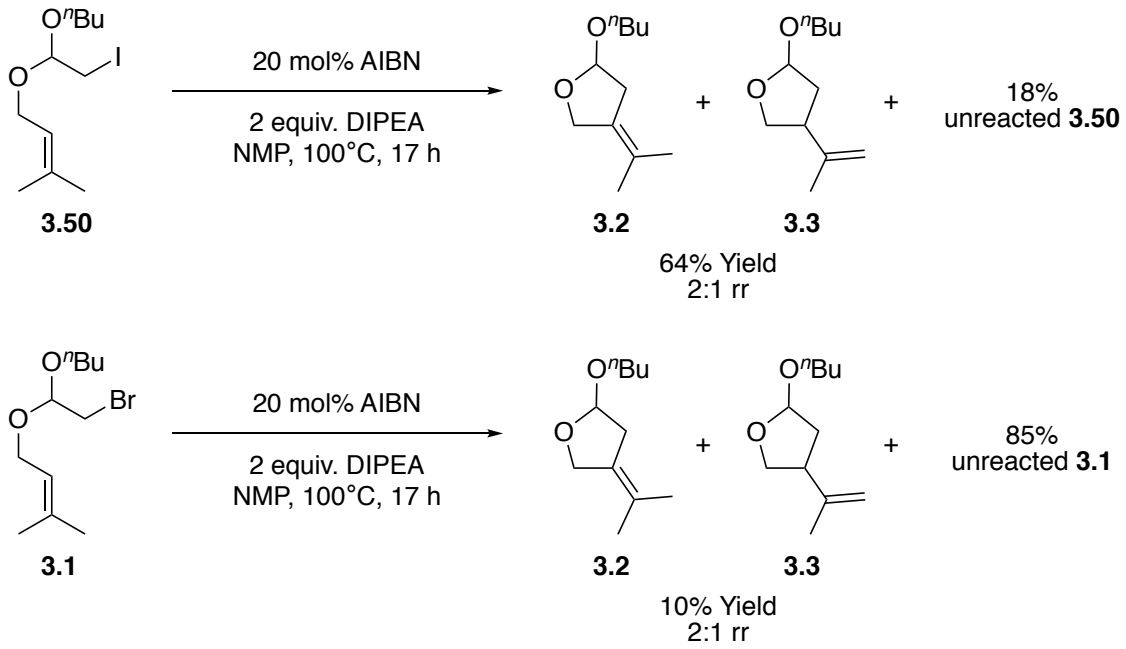
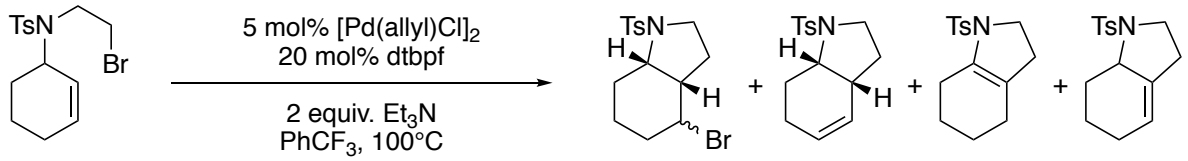


Figure 3-28: Radical Chain Cyclizations of Alkyl Halides in the Absence of Palladium

We continued our mechanistic study with the application of alkyl iodide and bromide substrates to standard Heck reaction conditions in the presence of radical inhibitors (Table 3-6). Reaction of alkyl bromide **3.13** in the presence of single electron transfer inhibitor 1,4-dinitrobenzene resulted in complete return of starting material. Radical inhibitor galvinoxyl prevented formation of the Heck product, while carbohalogenation product was observed in trace amounts. The addition of radical trap TEMPO halted formation of both carbohalogenation and

Heck products, though no TEMPO adduct was observed. While it is possible for TEMPO to inhibit radical reactions without forming adduct, it should be noted that TEMPO can also react with palladium hydride intermediates, inhibiting a reaction in the absence of radical intermediates.[56] For this reason multiple radical and single-electron transfer inhibitors were used and their results compiled.

Table 3-6: Effect of Radical Inhibitors on Palladium-Catalyzed Cyclization of Alkyl Bromides



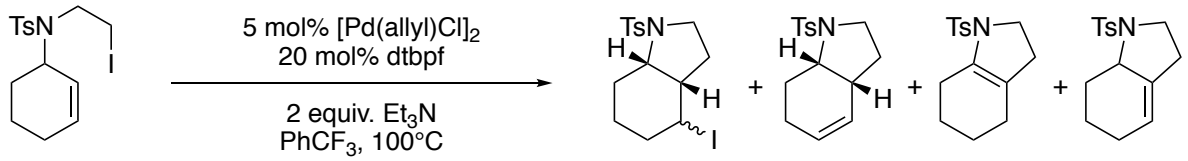
3.13 **3.51** **3.14** **3.15** **3.16**

Entry	Changes to Above Conditions	**3.13** (%)	**3.51** (%)	Heck Yield (%)[a] (**3.14**:**3.15**:**3.16**)
1	none	0	0	77 (7.2:3:1)
2	with 10 mol% 1,4-dinitrobenzene	99	0	0
3	with 1 equiv. galvinoxyl	42	5	0
4	with 1 equiv. TEMPO	69	0	0

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

Conversely, when each radical inhibitor was applied to reactions of the corresponding iodide **3.52** (Table 3-7), full conversion was achieved, with no unreacted starting material or carbohalogenation product remaining. These results are consistent with radical initiation, followed by a fast radical chain reaction that outcompetes inhibition by the radical inhibitors. The successful inhibition of bromide reactions, on the other hand, is consistent with an inefficient chain unable to outcompete inhibition, and, correspondingly, with a palladium-catalyzed reaction pathway.

Table 3-7: Effect of Radical Inhibitors on Palladium-Catalyzed Cyclization of Alkyl Iodides



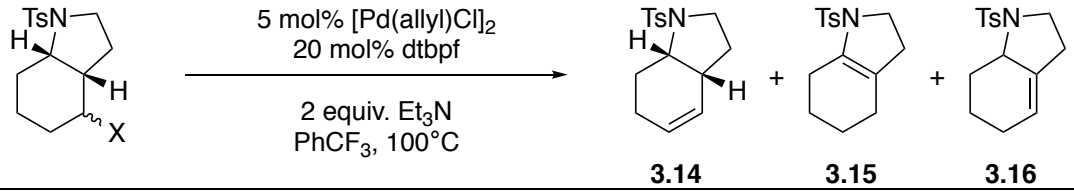
3.52 **3.53** **3.14** **3.15** **3.16**

Entry	Changes to Above Conditions	**3.52** (%)	**3.53** (%)	Heck Yield (%)[a] (**3.14**:**3.15**:**3.16**)
1	none	0	0	48 (2.7:1:1.1)
2	with 10 mol% 1,4-dinitrobenzene	0	0	78 (1:0:1.4)
3	with 1 equiv. galvinoxyl	0	0	23 (1:0.1:1.2)
4	with 1 equiv. TEMPO	0	0	55 (7.8:1:5)

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

We then isolated ATRC products **3.51** and **3.53** and resubjected them to the same reaction conditions. Under normal conditions, both iodide and bromide reacted in roughly quantitative yield to form alkyl Heck product (Entries 1,4). The addition of single electron transfer inhibitor 1,4-dinitrobenzene caused an abrupt decrease in conversion with the bromide, bringing the yield of Heck product down to 9%, but had no effect on the reactivity of the iodide (Entries 2,5). Furthermore, omission of the palladium catalyst resulted in the complete recovery of starting material. The results observed with the bromide indicate the operation of a palladium-mediated elimination pathway operating through radical intermediates. Conversely, the iodide pathway may be at least partially driven by base-induced E2 elimination.

Table 3-8: Examination of Dehydrohalogenation of Atom-Transfer Radical Cyclization Products



3.14 **3.15** **3.16**

Entry	Changes to Above Conditions	X	SM	Recovered SM (%)	Heck Yield (%)[a] (**3.14:3.15:3.16**)
1	none	Br	**3.51**	0	100 (2:1:0.1)
2	with 10 mol% 1,4-dinitrobenzene	Br	**3.51**	78	9
3	no $[Pd(allyl)Cl]_2$ or dtbpf	Br	**3.51**	100	0
4	none	I	**3.53**	0	97 (1:1:0.7)
5	with 10 mol% 1,4-dinitrobenzene	I	**3.53**	0	100 (1:1:1.3)
6	no $[Pd(allyl)Cl]_2$ or dtbpf	I	**3.53**	44	37 (2:2:1)

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

Based on the data presented, we propose the following as a plausible mechanism for the palladium-catalyzed cyclization of unactivated alkyl bromides (Figure 3-29). The active palladium(0) catalyst abstracts the alkyl bromide, forming alkyl radical intermediate **3.54** and a putative palladium(I) bromide species. Rapid 5-exo radical cyclization forms the target carbon-carbon bond and generates secondary (or tertiary) alkyl radical **3.55**. The bromide then recombines with this new radical, forming the atom-transfer radical cyclization product **3.41** and regenerating the active palladium(0) catalyst. This palladium catalyst can then reengage alkyl bromide **3.41**, regenerating alkyl radical **3.55**. Recombination with the palladium(I) bromide species forms alkylpalladium **3.56**, which can undergo β-hydride elimination to form the product and regenerate the active catalyst.

It is possible that alkyl radical **3.55** proceeds to form alkylpalladium species **3.56** without first recombining with the halide to form ATRC **3.41**. However, based on the rate and order of appearance of the two products and the isolation of ATRC product in good to high yield, it is

likely that recombination with the halide is much more kinetically favorable than recombination with palladium. Therefore, we propose that the predominant reaction pathway does involve carbohalogenation *en route* to Heck product, rather than proceeding directly to the alkylmetal species.

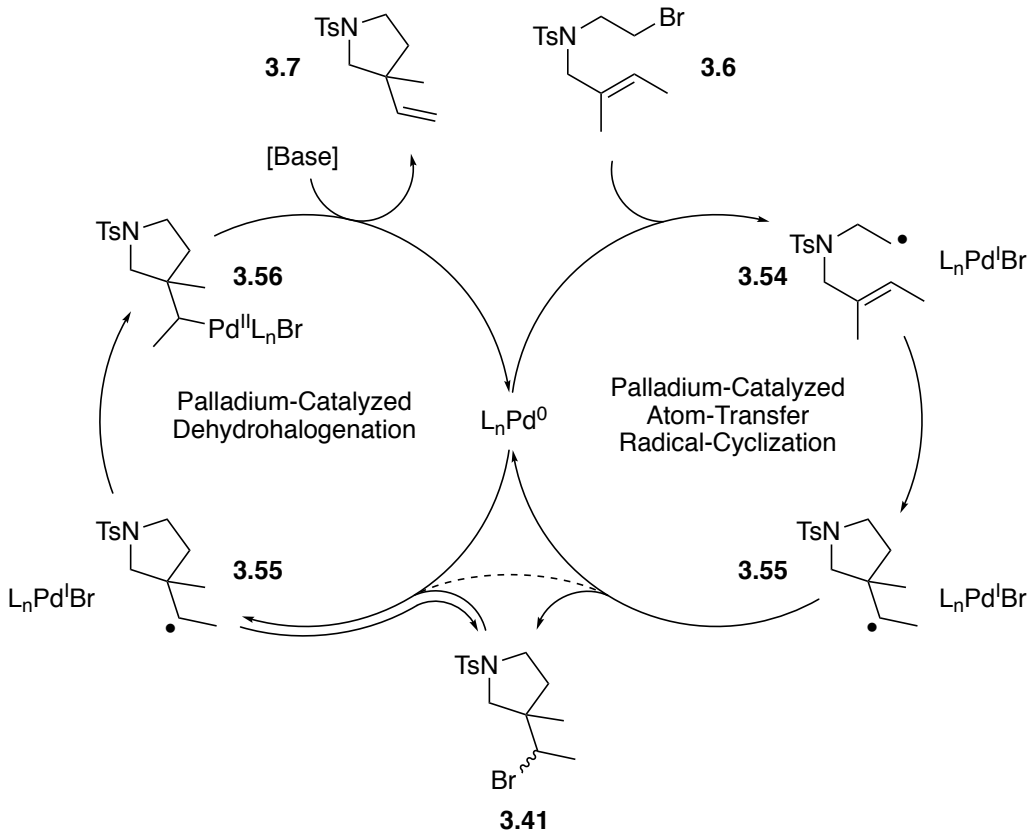


Figure 3-29: Plausible Mechanism for the Palladium-Catalyzed Alkyl Halide-Olefin Cross-Coupling

Additionally, it is possible that substrates featuring 1,2,2-trisubstituted alkenes, which form tertiary alkyl radicals upon cyclization, could operate through a slightly different mechanism. Since recombination of a bulky palladium complex with a tertiary radical is sterically disfavored, and tertiary carbocations are highly stable, these substrates may, after re-activation of the atom transfer intermediate, undergo single electron transfer with palladium to

regenerate the palladium(0) species and form a tertiary cation. This intermediate can then be deprotonated to generate the alkene product.

3.3.4 Summary

In conclusion, we have demonstrated a versatile method for the coupling of alkenes and alkyl bromides with the restoration of one of the functional groups in the product. Tailoring of the reaction conditions allows for the choice of which functional group is restored. The mild, palladium-catalyzed conditions engage a wide variety of substrates, forming 5- and 6-membered rings with primary and secondary bromides and a variety of alkenes. We have proposed the reaction to proceed via radical intermediates in a dual-catalytic cycle, first forming the ATRC product via radical cyclization and recombination with the bromide, followed by palladium-catalyzed, radical-mediated dehydrohalogenation. While reaction with alkyl iodides under the same reaction conditions is also successful, it is believed that this reaction undergoes initiation by palladium, but functions through an innate radical chain, rather than palladium catalysis. These developments represent a major advancement with regard to both transformations (alkyl Heck and ATRC), enabling the first palladium-catalyzed alkyl Heck reaction using secondary alkyl bromides, and facilitating the first report of atom-transfer radical cyclization with unactivated alkyl bromides and non-terminal alkenes.

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Chapter IV: Experimental Section

4.1 General Experimental Details

Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were obtained using 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 internal reference (^{1}H NMR: $CDCl_3$ at 7.28 ppm, ^{13}C NMR: $CDCl_3$ at 77.00 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet), coupling constants (Hz), and integration. Mass spectra were obtained using a Micromass (now Waters Corporation) Quattro-II, Triple Quadrupole Mass Spectrometer, with a Z-spray nano-Electrospray source design, in combination with an Advion NanoMate chip-based electrospray sample introduction system or a Perkin Elmer Flexar SQ300 MS LC Detector.

Optical rotation measurements were obtained using a Jasco DIP-1000 Digital Polarimeter. Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. HPLC spectra were obtained using an Agilent 1200 series HPLC with detection at 210, 230, 250 and 254 nm using a Chiralpak IA & IC columns using a flow rate of 1 mL per minute. The solvent system used for HPLC resolution of enantiomers was hexanes (A1) and isopropanol (B2). Flash chromatography was performed using SiliaFlash P60 silica gel (40-63μm) purchased from Silicycle. Visualization was achieved using a short wave UV light (254 nm) and aqueous basic potassium permanganate solution. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (DCM), toluene, acetonitrile (MeCN), and dimethylformamide (DMF) were dried by passage through a column of neutral alumina under nitrogen prior to use. Acetone,

1,4-dioxane, *tert*-butylbenzene, and α,α,α-trifluorotoluene were dried over 3Å molecular sieves and degassed with argon prior to use. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted.

4.2 Experimental Section for Chapter II

4.2.1 General Synthetic Methods

General Procedure A: Sulfonylation of Anilines[1].

To a 0°C solution of aniline (1 equiv.) and pyridine (1.1 equiv.) in CH_2Cl_2 (0.35 M) was added methanesulfonyl chloride (1 equiv.). The reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The reaction was quenched with 3N NaOH and the aqueous layer was extracted with CH_2Cl_2 (3x). The aqueous layer was acidified with conc. HCl and filtered through a fritted funnel. The recovered white precipitate was dried under vacuum.

General Procedure B: Alkylation of Methanesulfonamides.[2]

To a solution of methanesulfonamide (1 equiv.) in acetonitrile (0.15 M) was added K_2CO_3 (3 equiv.) and alkyl halide (8 equiv.). The reaction mixture was heated to reflux and stirred for 20 hours before being quenched with H_2O and extracted with Et_2O (3x). The organic layers were combined and dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography.

General Procedure C. Epoxidation of Terminal Alkenes.

To a room temperature solution of alkene (1 equiv.) in DCM (0.3 M) was added mCPBA (70%, 2 equiv.) portionwise. The reaction mixture was stirred at room temperature for 48 hours, and was quenched with saturated $NaHSO_3$ solution. The aqueous layer was extracted with DCM (3x) and the combined organic layers were washed with saturated $NaHCO_3$ and H_2O, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

General Procedure D: Opening of Terminal Epoxides with Super Hydride.

To a solution of epoxide (1 equiv.) in THF (0.15 M) at -78°C was added Super-Hydride solution by syringe pump over 30 minutes (1M in THF, 1.2 equiv.). The reaction mixture was stirred, warming to room temperature for 1 hour. The solution was quenched with saturated NH_4Cl and extracted with Et_2O (3x). The organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

General Procedure E: Iodination of Primary and Secondary Alcohols.

To a solution of triphenylphosphine (1.05 equiv.) and imidazole (1.05 equiv.) in toluene (0.2 M) was added iodine (1.05 M) and stirred for 30 minutes at room temperature. The alcohol (1 equiv.) was then added, and the reaction mixture was heated to 80°C and stirred for 16 hours. The solution was then quenched with H_2O, extracted with Et_2O (3x), and washed with saturated $Na_2S_2O_3$. The organic extracts were then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography. As a precaution, alkyl iodide products were stored in the dark, under inert atmosphere, at -40°C upon purification.

General Procedure F: Bromination of Primary and Secondary Alcohols.

To a 0°C solution of secondary alcohol (1 equiv.) in Et_2O (1.0 M) was added phosphorus tribromide (0.5 equiv.) dropwise. The reaction mixture was stirred at room temperature for 1 hour, and was then quenched with H_2O. The aqueous layer was back extracted with Et_2O (3x) and the combined organic layers were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

General Procedure G: Alkylation of Triethyl Methanetricarboxylate.

To a solution of sodium hydride (60 %, 1.02 equiv.) in 1:1 DMF:toluene (0.3 M) was added triethyl methanetricarboxylate (1 equiv.). The solution was stirred for 30 minutes at room temperature before the addition of benzyl bromide (1.02 equiv.). The reaction mixture was heated to reflux and stirred for 20 hours. The reaction was quenched with H_2O, extracted with EtOAc (5x) and washed with H_2O, saturated $NaHCO_3$, and brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated.

General Procedure H: Decarboxylation of Benzyl Triesters.

To a solution of sodium hydride (60%, 1.1 equiv.) in THF (0.4 M) was added ethanol (1.2 equiv.) and stirred for 30 minutes at room temperature. Benzyl triester (1 equiv.) was then added, and the solution was heated to reflux and stirred for 16 hours. The reaction mixture was quenched with 1N HCl, extracted with Et_2O, and washed with H_2O, saturated $NaHCO_3$, and brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

General Procedure I: Alkylation of Diethyl Benzylmalonates.

To a solution of sodium hydride (60%, 1.3 equiv.) in THF (0.3 M) was added diethyl benzylmalonate (1 equiv.). The solution was stirred for 30 minutes at room temperature and 1,2-dibromoethane (10 equiv.) was then added. The reaction mixture was heated to reflux, stirred for 24 hours. The reaction was quenched with H_2O, extracted with Et_2O (3x), washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

General Procedure J: Iodination of Primary Bromides and Chlorides.

To a solution of primary halide (1 equiv.) in acetone (0.3 M) was added NaI (3 equiv.) and 15-crown-5 (10 mol %). The solution was heated to reflux and stirred for 20 hours. The reaction mixture was quenched with H_2O, extracted with DCM (3x), and washed with saturated $Na_2S_2O_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography. As a precaution, alkyl iodide products were stored in the dark, under inert atmosphere, at -40°C upon purification.

General Procedure K: Iodoalkylation of Diethylbenzylmalonates.

To a solution of sodium hydride (60%, 1.1 equiv.) in THF (0.2 M) was added diethyl benzylmalonate (1 equiv.). The solution was stirred for 30 minutes at room temperature before the addition of diiodomethane (2 equiv.). The reaction mixture was heated to reflux and stirred for 20 hours. The reaction was quenched with H_2O, extracted with Et_2O, and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography. As a precaution, alkyl iodide products were stored in the dark, under inert atmosphere, at -40°C upon purification.

General Procedure L: Epoxylkylation or Alkylation of Indoles and Pyrroles.

To a solution of indole or pyrrole (1 equiv.) in DMF (0.3 M) was added KOH (1.1 equiv.). The solution was stirred for 15 minutes at room temperature before the addition of alkyl halide (1.1 equiv.). The reaction mixture was heated to 80°C and stirred for 16 hours, before being quenched with H_2O, extracted with Et_2O (3x), and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

General Procedure M: Alkylation of Indoles and Pyrroles with Dihaloalkanes.

To a solution of indole or pyrrole (1 equiv.) in DMSO (0.5 M) was added KOH (1.3 equiv.). The solution was sonicated for 10 minutes before the addition of alkyl bromide (3 equiv.). The reaction mixture was stirred for 20 hours at room temperature, and was then quenched with H_2O, extracted with Et_2O (3x), and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

General Procedure N: Iodination of Primary Alkyl Chlorides.

To a solution of primary halide (1 equiv.) in acetonitrile (0.15 M) was added NaI (4.5 equiv.). The solution was heated to reflux and stirred for 16 hours. The reaction mixture was quenched with H_2O, extracted with Et_2O (3x), and washed with saturated $Na_2S_2O_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography. As a precaution, alkyl iodide products were stored in the dark, under inert atmosphere, at -40°C upon purification.

C-H Alkylation Procedure A:

To a one-dram vial in a glove box under argon atmosphere was added primary or secondary iodide (0.25 mmol, 1 equiv.) dissolved in 1,4-dioxane (0.5 M). $Pd(PPh_3)_4$ (10 mol%) and K_3PO_4 (2 equiv.) were then added. The reaction vial was removed from the glove box and heated to 100°C, stirring for 6-24 hours. The reaction mixture was allowed to cool to ambient temperature, was quenched with 1N HCl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

C-H Alkylation Procedure B:

To a one-dram vial in a glove box was added primary iodide (0.25 mmol, 1 equiv.) dissolved in *tert*-butylbenzene (0.5 M). $Pd(PPh_3)_4$ (10 mol%) and K_3PO_4 (2 equiv.) were then added. The reaction vial was removed from the glove box and heated to 100°C, stirring for 24 hours. The reaction mixture was allowed to cool to ambient temperature, was quenched with 1N HCl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

C-H Alkylation Procedure C:

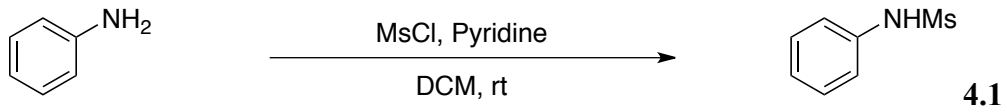
To a one-dram vial in a glove box was added primary bromide (0.25 mmol, 1 equiv.) dissolved in *tert*-butylbenzene (0.5 M). $Pd(PPh_3)_4$ (10 mol%) and 1,2,2,6,6-pentamethylpiperidine (2 equiv.) were then added. The reaction vial was removed from the glove box and heated to 130°C, stirring for 48 hours. The reaction mixture was allowed to cool to ambient temperature, was quenched with 1N HCl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

C-H Alkylation Procedure D:

To a one-dram vial in a glove box was added primary or secondary bromide (0.25 mmol, 1 equiv.) dissolved in *tert*-butylbenzene (0.5 M). $Pd(PPh_3)_4$ (10 mol%) and K_3PO_4 (2 equiv.) were then added. The reaction vial was removed from the glove box and heated to 130°C, stirring for 48 hours. The reaction mixture was allowed to cool to ambient temperature, was quenched with 1N HCl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were

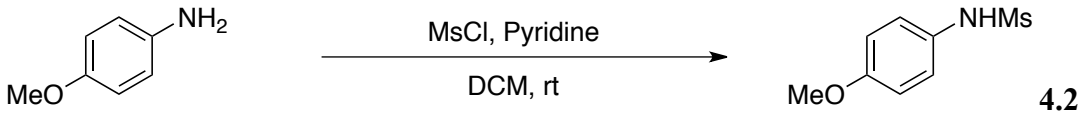
dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

4.2.2 Experimental Data



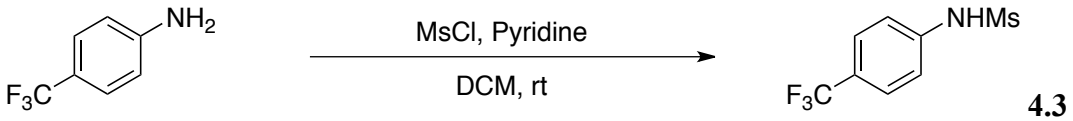
4.1

(4.1): ***N*-Phenylmethanesulfonamide.** Aniline (4.2 g, 45 mmol) was sulfonylated with methanesulfonyl chloride (5.2 g, 45 mmol) according to General Procedure A. The crude product was isolated as a white solid (90% Yield). All physical and spectroscopic data were in accordance with literature data. [3]



4.2

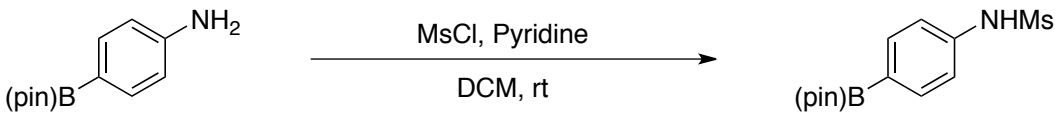
(4.2): ***N*-(4-Methoxyphenyl)methanesulfonamide.** *p*-Anisidine (5.0 g, 40.5 mmol) was sulfonylated with methanesulfonyl chloride (4.6 g, 40.5 mmol) according to General Procedure A. The crude product was isolated as a white solid (83% Yield). All physical and spectroscopic data were in accordance with literature data. [3]



4.3

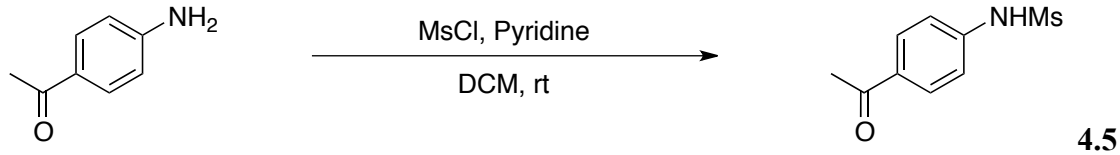
(4.3): ***N*-(4-Trifluoromethylphenyl)methanesulfonamide.** *p*-Trifluoromethylaniline (10.0 g, 62 mmol) was sulfonylated with methanesulfonyl chloride (7.1 g, 62 mmol) according to

General Procedure A. The crude product was isolated as a white solid (82% Yield). All physical and spectroscopic data were in accordance with literature data.[4]



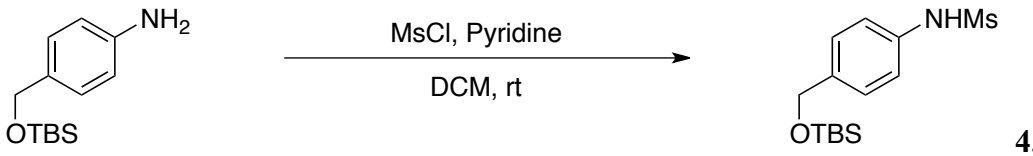
4.4

(4.4): *N*-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanesulfonamide. *p*-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (5.0 g, 23 mmol) was sulfonylated with methanesulfonyl chloride (2.6 g, 23 mmol) according to General Procedure A. The crude product was isolated as a white solid (91% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.82 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 3.05 (s, 3H), 1.37 (s, 12H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 139.40, 136.46, 118.57, 83.95, 39.52, 24.86. **IR** (Thin Film, cm^{-1}): 3253, 2979, 1608, 1361, 1332, 1143, 967, 857. **LRMS** (ESI): Calculated for $[C_{13}H_{20}BNO_4SNa]^+$ 320.17, found 320.31.



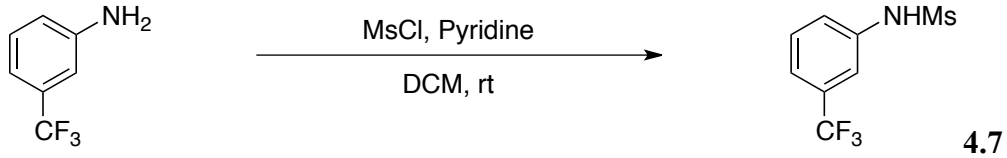
4.5

(4.5): *N*-(4-Acetylphenyl)methanesulfonamide. 4'-Aminoacetophenone (9.0 g, 66.5 mmol) was sulfonylated with methanesulfonyl chloride (7.6 g, 66.5 mmol) according to General Procedure A. The crude product was isolated as a white solid (85% Yield). All physical and spectroscopic data were in accordance with literature data.[5]



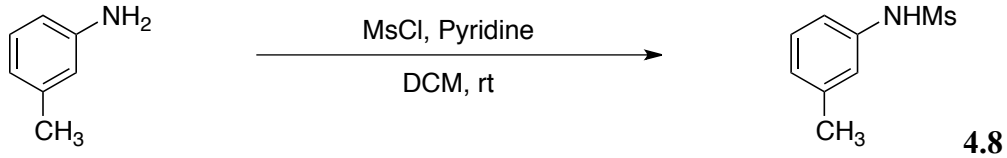
4.6

(4.6): *N*-(4-((*tert*-Butyldimethylsilyloxy)methyl)phenyl)methanesulfonamide. 4-((*tert*-Butyldimethylsilyloxy)methyl)aniline (10 g, 42.2 mmol) was sulfonylated with methanesulfonyl chloride (4.8 g, 42.2 mmol) according to General Procedure A. The crude product was isolated as a white solid (88% Yield). **^{1}H-NMR** (600 MHz, D_2O): δ 7.13 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 2.76 (s, 3H), 0.80 (s, 9H), 0.02 (s, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 145.80, 132.22, 128.41, 121.97, 65.27, 38.43, 25.24, 17.74, -6.04. **IR** (Thin Film, cm^{-1}): 2930, 1505, 1256, 1197, 1092, 999, 837, 775. **LRMS** (ESI): Calculated for $[C_{14}H_{25}NO_3SSiNa]^+$ 338.49, found 338.38.



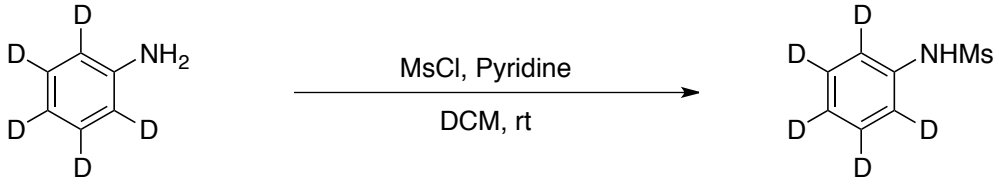
4.7

(4.7): *N*-(3-Trifluoromethylphenyl)methanesulfonamide. *m*-Trifluoromethylaniline (7.3 g, 45 mmol) was sulfonylated with methanesulfonyl chloride (5.2 g, 45 mmol) according to General Procedure A. The crude product was isolated as a white solid (52% Yield). All physical and spectroscopic data were in accordance with literature data.[3]



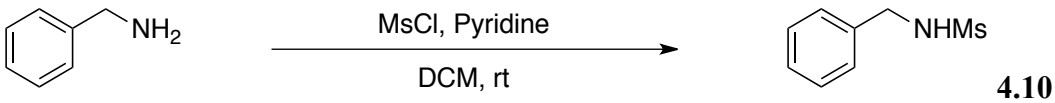
4.8

(4.8): *N*-(3-Tolyl)methanesulfonamide. *m*-Toluidine (4.8 g, 45 mmol) was sulfonylated with methanesulfonyl chloride (5.2 g, 45 mmol) according to General Procedure A. The crude product was isolated as a white solid (98% Yield). All physical and spectroscopic data were in accordance with literature data.[3]



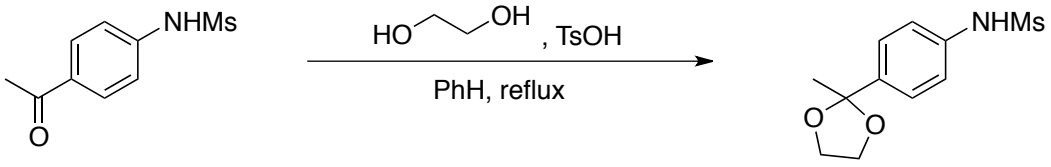
4.9

(4.9): *N*-(d_5-Phenyl)methanesulfonamide. Aniline-2,3,4,5,6-d_5 (2.0 g, 20. mmol) was sulfonylated with methanesulfonyl chloride (2.3 g, 20 mmol) according to General Procedure A. The crude product was isolated as a white solid (94% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 6.33 (bs, 1H) 3.04 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 136.51, 126.39, 129.23, 129.06, 124.95, 120.48, 120.31, 120.15, 39.30. **IR** (Thin Film, cm^{-1}): 3263, 1565, 1381, 1308, 1149, 911, 770, 555, 512. **LRMS** (ESI): Calculated for $[C_7H_4D_5NO_2SH]^+$ 177.07, found 177.08.



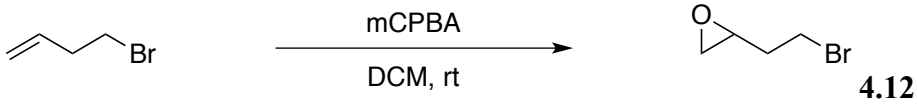
4.10

(4.10): *N*-Benzylmethanesulfonamide. Benzylamine (7.1 g, 66. mmol) was sulfonylated with methanesulfonyl chloride (7.2 g, 66 mmol) according to General Procedure A. The crude product was isolated as a white solid (99% Yield). All physical and spectroscopic data were in accordance with literature data.[6]



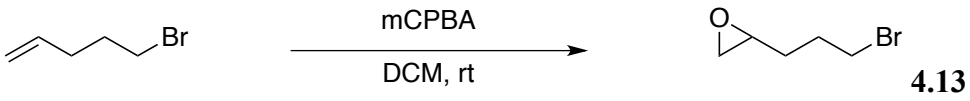
4.11

(4.11): *N*-(4-(2-Methyl-1,3-dioxolan-2-yl)phenyl)methanesulfonamide. To a solution of sulfonamide **4.5** (10.0 g, 46.9 mmol, 1 equiv.) in benzene (50 mL, 1.0 M) was added p-toluenesulfonic acid monohydrate (0.89 g, 2.7 mmol, 10 mol%) and ethylene glycol (3.5 g, 56.3 mmol, 1.2 equiv.). The reaction mixture was heated to reflux using a Dean-Stark apparatus and reflux condenser and stirred for 18 hours before being quenched with saturated $NaHCO_3$. The aqueous layer was extracted with DCM and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide epoxide **4.11** as a white solid (56% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.47 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 4.04 (m, 2H), 3.78 (m, 2H), 3.03 (s, 3H), 1.64 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.17, 130.83, 127.26, 120.89, 108.94, 64.99, 40.01, 28.01. **IR** (Thin Film, cm^{-1}): 3251, 1673, 1603, 1329, 1153, 1037, 970. **LRMS** (ESI): Calculated for $[C_{11}H_{15}NO_4SNa]^+$ 280.30, found 280.31.



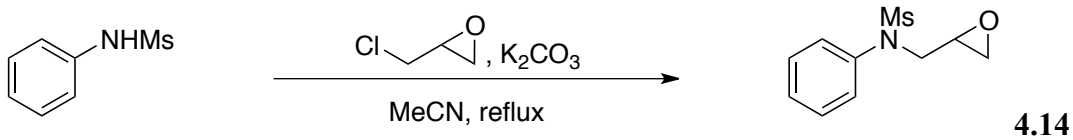
4.12

(4.12): (2-Bromoethyl)oxirane. Following General Procedure C, 4-bromo-1-butene (8.0 g, 59.3 mmol) was epoxidized with *m*CPBA (75%, 20 g, 88.9 mmol). The crude product was isolated as a clear oil (89% Yield). All physical and spectroscopic data were in accordance with literature data.[7]



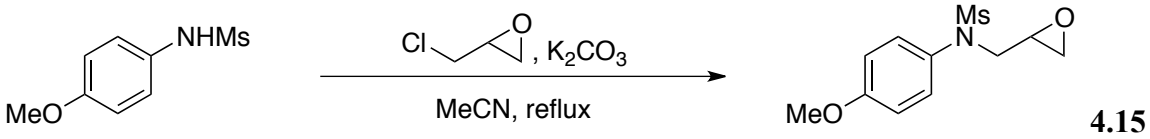
4.13

(4.13): (2-Bromoethyl)oxirane. Following General Procedure C, 5-bromo-1-pentene (6.0 g, 40 mmol) was epoxidized with *m*CPBA (75%, 15 g, 60 mmol). The crude product was isolated as a pure clear oil (97% Yield). All physical and spectroscopic data were in accordance with literature data.[8]



4.14

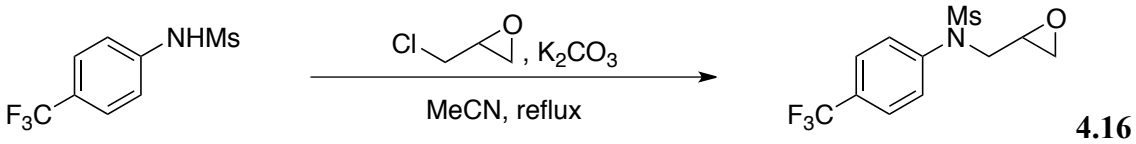
(4.14): *N*-(2,3-Epoxypropyl)-*N*-phenylmethanesulfonamide. Following General Procedure B, methanesulfonamide **4.1** (8.6 g, 50 mmol) was alkylated with epichlorohydrin (18.5 g, 200 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide epoxide **4.14** as a white solid (70% Yield). All physical and spectroscopic data were in accordance with literature data.[9]



4.15

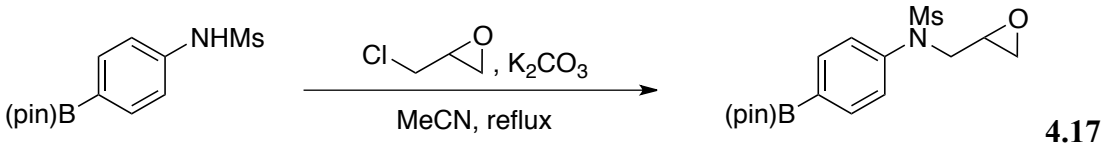
(4.15): *N*-(4-Anisyl)-*N*-(2,3-epoxypropyl)methanesulfonamide. Following General Procedure B, methanesulfonamide **4.2** (3.2 g, 15.9 mmol) was alkylated with epichlorohydrin (11.7 g, 127 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate

(3:1) to provide epoxide **4.15** as a white solid (53% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.34 (m, 2H), 6.95 (m, 2H), 3.84 (s, 3H), 3.83 (dd, *J* = 15.0 Hz, 4.2 Hz, 1H), 3.73 (dd, *J* = 15.0 Hz, 6.0 Hz, 1H), 3.19 (m, 1H), 2.98 (s, 3H), 2.79 (t, *J* = 4.8 Hz, 1H), 2.54 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 159.51, 131.96, 130.30, 114.82, 55.47, 54.00, 50.30, 45.90, 38.19. **IR** (Thin Film, cm^{-1}): 2933, 1509, 1336, 1251, 1152, 1029, 960, 842. **LRMS** (ESI): Calculated for $[C_{11}H_{15}NO_4SH]^+$ 258.08, found 258.00.



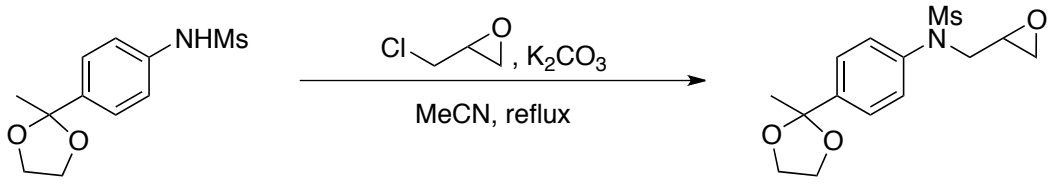
4.16

(4.16): *N*-(2,3-Epoxypropyl)-*N*-(4-trifluoromethylphenyl)methanesulfonamide. Following General Procedure B, methanesulfonamide **4.3** (6.0 g, 25.0 mmol) was alkylated with epichlorohydrin (18.6 g, 200 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide epoxide **4.16** as a white solid (77% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 4.07 (dd, *J* = 15.2 Hz, 3.6 Hz, 1H) 3.70 (dd, *J* = 15.2 Hz, 6.8 Hz, 1H) 3.27 (m, 1H), 3.01 (s, 3H), 2.72 (dd, *J* = 4.8 Hz, 2.4 Hz, 1H), 2.60 (dd, *J* = 4.8 Hz, 2.4 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 128.34, 126.79, 126.77, 53.61, 50.27, 45.75, 38.71. **IR** (Thin Film, cm^{-1}): 2365, 1616, 1325, 1185, 1121, 1069, 511. **LRMS** (ESI): Calculated for $[C_{11}H_{12}F_3NO_3SH]^+$ 296.06, found 296.06.



4.17

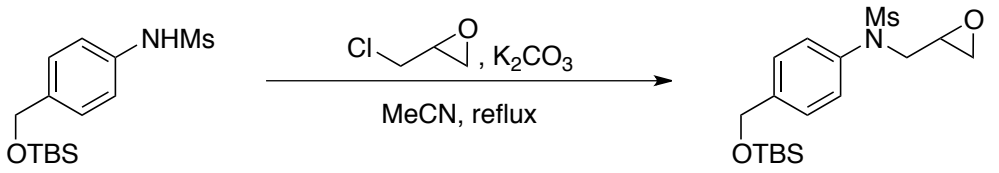
(4.17): *N*-(2,3-Epoxypropyl)-*N*-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) methanesulfonamide. Following General Procedure B, methanesulfonamide **4.4** (6.0 g, 20.2 mmol) was alkylated with epichlorohydrin (14.9 g, 162 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (2:1) to provide epoxide **4.17** as a white solid (47% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.89 (dd, *J* = 15 Hz, 6.0 Hz, 1H), 3.83 (dd, *J* = 15, 6.0 Hz, 1H), 3.19 (m, 1H), 2.98 (s, 3H), 2.78 (m, 1H), 2.54 (m, 1H), 1.37 (s, 12H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 142.19, 136.17, 127.49, 84.10, 75.03, 53.54, 50.27, 45.99, 38.39, 24.86. **IR** (Thin Film, cm^{-1}): 3528, 2980, 1605, 1361, 1148, 1093, 961, 857, 658, 550. **LRMS** (ESI): Calculated for $[C_{16}H_{24}BNO_5SNa]^+$ 376.23, found 376.34.



4.18

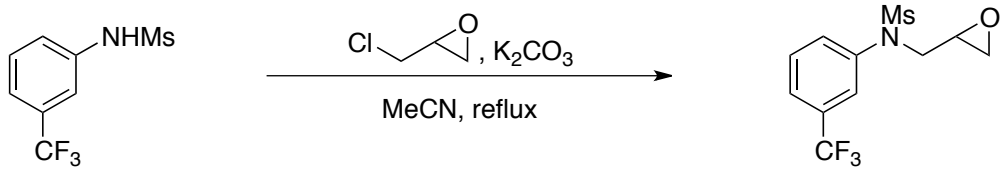
(4.18): *N*-(2,3-Epoxypropyl)-*N*-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)methanesulfonamide. Following General Procedure B, methanesulfonamide **4.11** (6.0 g, 23.3 mmol) was alkylated with epichlorohydrin (17.2 g, 186 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide epoxide **4.18** as a white solid (56% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4, 2H), 4.05 (m, 2H), 3.87 (dd, *J* = 14.4 Hz, 3.6 Hz, 1H), 3.80 (m, 2H), 3.73 (dd, *J* = 15.0 Hz, 6.6 Hz, 1H), 3.18 (m, 1H), 2.98 (s, 3H), 2.79 (t, *J* = 4.2 Hz, 1H), 2.59 (m, 1H), 1.65 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 144.27, 139.67, 128.89, 127.17, 108.93, 65.05, 54.34, 50.80, 46.45, 38.89, 28.07. **IR**

(Thin Film, cm^{-1}): 2989, 1506, 1340, 1155, 1037, 956, 872. **LRMS** (ESI): Calculated for $[C_{14}H_{19}NO_5SNa]^+$ 336.36, found 336.29.



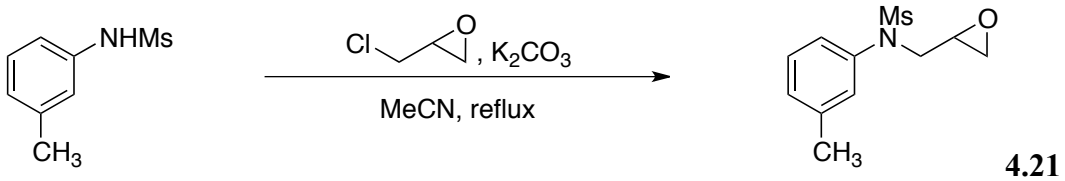
4.19

(4.19): *N*-(2,3-Epoxypropyl)-*N*-(4-(*tert*-butyldimethylsilyloxylmethyl)phenyl)methane sulfonamide. Following General Procedure B, methanesulfonamide **4.6** (7.0 g, 22.2 mmol) was alkylated with epichlorohydrin (16.5 g, 178 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide epoxide **4.19** as a white solid (59% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.40 (m, 4H), 4.78 (s, 2H), 3.86 (dd, *J* = 15.0 Hz, 4.2 Hz, 1H), 3.79 (dd, *J* = 14.4 Hz, 6.0 Hz, 1H), 3.20 (m, 1H), 2.99 (s, 3H), 2.80 (t, *J* = 4.2 Hz, 1H), 2.55 (m, 1H), 0.98 (s, 9H), 0.14 (s, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 142.03, 138.16, 128.55, 127.08, 64.26, 53.87, 50.30, 46.01, 38.30, 25.94, 18.41, -5.29. **IR** (Thin Film, cm^{-1}): 2931, 1509, 1342, 1255, 1155, 1089, 840, 777. **LRMS** (ESI): Calculated for $[C_{17}H_{29}NO_4SSiNa]^+$ 394.56, found 394.39.



4.20

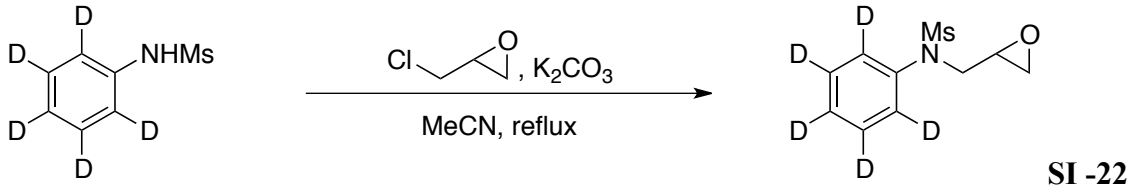
(4.20): *N*-(2,3-epoxypropyl)-*N*-(3-trifluoromethylphenyl)methanesulfonamide. Following General Procedure B, methanesulfonamide **4.7** (4.0 g, 16.7.0 mmol) was alkylated with epichlorohydrin (12.4 g, 134 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide epoxide **4.20** as a white solid (51 % Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.70-7.64 (m, 3H), 7.59 (t, *J* = 7.6 Hz, 1H), 4.03 (dd, *J* = 14.4 Hz, 2.4 Hz, 1H), 3.71 (dd, *J* = 15.2 Hz, 6.0 Hz, 1H), 3.22 (m, 1H), 3.02 (s, 3H), 2.83 (dd, *J* = 4.0 Hz, 4.0 Hz, 1H), 2.59 (dd, *J* = 2.4 Hz, 2.4 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 140.37, 132.19, 132.08, 131.97, 130.23, 125.15, 125.13, 125.08, 125.05, 124.28, 122.47, 53.77, 50.77, 50.18, 45.70, 38.60. **IR** (Thin Film, cm^{-1}): 3068, 3010, 2934, 1593, 1491, 1445, 1331, 1158, 919, 809, 757, 700, 539. **LRMS** (ESI): Calculated for $[C_{11}H_{12}F_3NO_3SH]^+$ 296.06, found 295.99.



4.21

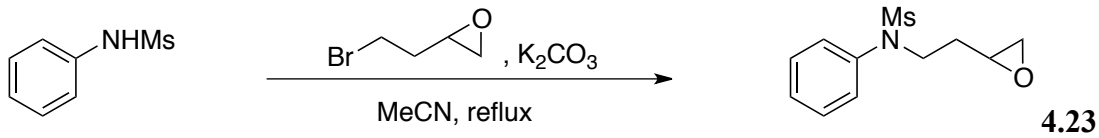
(4.21): *N*-(2,3-Epoxypropyl)-*N*-(3-tolyl)methanesulfonamide. Following General Procedure B, methanesulfonamide **4.8** (5.0 g, 27.0 mmol) was alkylated with epichlorohydrin (19.9 g, 216 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide epoxide **4.21** as a white solid (69% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.33 (t, *J* = 8.4 Hz, 1H) 7.25-7.18 (m, 3H) 3.86 (dd, *J* = 14.8 Hz, 4.0 Hz, 1H), 3.77 (dd, *J* = 14.8 Hz, 6.0 Hz, 1H) 3.20 (m, 1H), 3.00 (s, 3H), 2.79 (dd, *J* = 4.0 Hz, 4.0 Hz, 1H) 2.56 (dd, *J* = 2.4 Hz, 2.4 Hz, 1H), 2.40 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 139.72, 139.48, 129.43, 129.35, 129.27, 125.42, 53.80, 50.27, 45.93, 38.32, 21.30. **IR** (Thin Film, cm^{-1}): 3005, 2929, 1605, 1487,

1337, 1155, 1074, 961, 825, 706, 612, 516. **LRMS** (ESI): Calculated for $[C_{11}H_{15}NO_3SH]^+$ 242.08, found 242.12.



SI -22

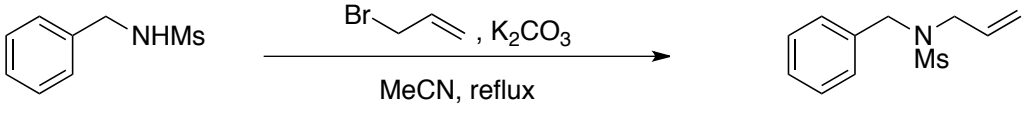
(4.22): *N*-(2,3-Epoxypropyl)-*N*-(perdeuterophenyl)methanesulfonamide. Following General Procedure B, methanesulfonamide **4.9** (2.5 g, 14.2 mmol) was alkylated with epichlorohydrin (10.5 g, 113 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide epoxide **4.22** as a white solid (61% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 3.90 (dd, *J* = 14.8 Hz, 4.4 Hz, 1H), 3.79 (dd, *J* = 14.8 Hz, 6.0 Hz, 1H), 3.21 (m, 1H), 3.00 (s, 3H), 2.80 (dd, *J* = 4.4 Hz, 4.4 Hz, 1H), 2.56 (dd, *J* = 4.8 Hz, 2.4 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 53.82, 50.29, 45.94, 38.34. **IR** (Thin Film, cm^{-1}): 1382, 1336, 1152, 958, 815, 525. **LRMS** (ESI): Calculated for $[C_{10}H_8D_5NO_3SH]^+$ 233.10, found 233.11.



4.23

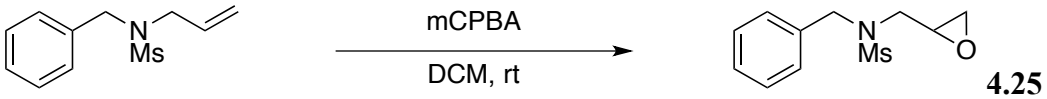
(4.23): *N*-(3,4-Epoxybutyl)-*N*-phenylmethanesulfonamide. Following General Procedure B, methanesulfonamide **4.1** (2.3 g, 13.3 mmol) was alkylated with (2-bromoethyl)oxirane (3.0 g, 19.9 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide epoxide **4.23** as a white solid (62% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$):

δ 7.50-7.33 (m, 5H), 3.89 (td, *J* = 7.2 Hz, 2.4 Hz, 2H), 2.99 (m, 1H), 2.93 (s, 3H) 2.78 (dd, *J* = 4.8 Hz, 4.4 Hz, 1H), 2.48 (dd, *J* = 4.8 Hz, 2.4 Hz, 1H) 1.87 (m, 1H), 1.69 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 138.99, 129.61, 128.50, 128.28, 49.80, 48.02, 46.90, 37.03, 32.01. **IR** (Thin Film, cm^{-1}): 2930, 1491, 1336, 1153, 1074, 961, 769, 700, 543, 521. **LRMS** (ESI): Calculated for $[C_{11}H_{15}NO_3SH]^+$ 242.08, found 242.12.



4.24

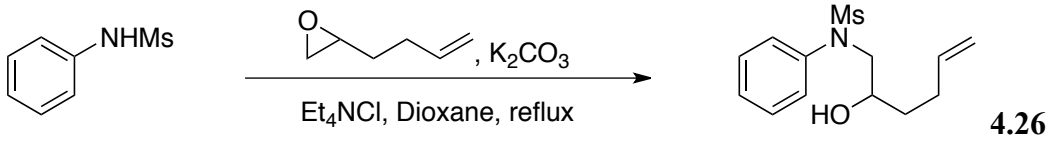
(4.24): ***N*-Allyl-*N*-benzylmethanesulfonamide.** Following General Procedure B, methanesulfonamide **4.10** (5.0 g, 27.0 mmol) was alkylated with allyl bromide (3.4 g, 28.3 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (6:1) to provide alkene **4.24** as a clear oil (75% Yield). All physical and spectroscopic data were in accordance with literature data.[6]



4.25

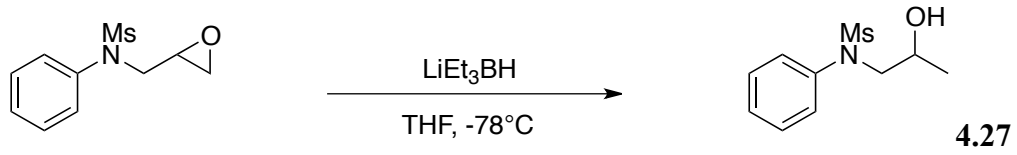
(4.25): ***N*-Benzyl-*N*-(2,3-epoxypropyl)methanesulfonamide.** Following General Procedure C, methanesulfonamide **4.24** (2.5 g, 11.1 mmol) was epoxidized with *m*CPBA (75%, 5.5 g, 22.2 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide epoxide **4.25** as a white solid (56% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.47-7.29 (m, 5H), 4.56 (d, *J* = 3.2 Hz, 2H), 3.54 (dd, *J* = 14.8 Hz, 2.8 Hz, 1H), 3.16 (dd, *J* = 21.6 Hz,

6.8 Hz, 1H), 3.11 (m, 1H), 2.96 (s, 3H), 2.77 (dd, *J* = 4.4 Hz, 4.4 Hz, 1H), 2.48 (dd, *J* = 4.8 Hz, 2.4 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 135.64, 128.79, 128.59, 128.16, 51.63, 50.08, 49.21, 45.39, 39.59. **IR** (Thin Film, cm^{-1}): 3007, 2929, 1722, 1329, 1255, 1149, 1027, 965, 935, 792, 700, 515. **LRMS** (ESI): Calculated for $[C_{11}H_{15}NO_3SH]^+$ 242.08, found 242.12.



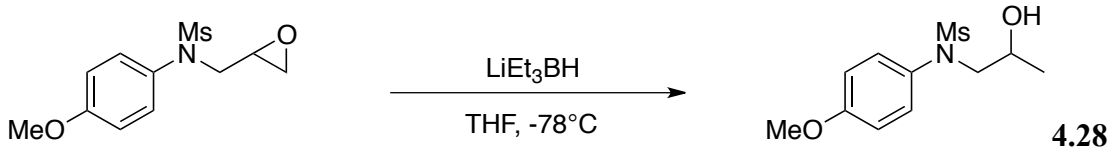
4.26

(4.26): *N*-(2-Hydroxyhex-5-enyl)-*N*-phenylmethanesulfonamide. To a solution of sulfonamide **4.1** (4.0 g, 23.4 mmol, 1 equiv.) in 1,4-dioxane (120 mL, 0.2 M) was added K_2CO_3 (3.2 g, 23.4 mmol, 1 equiv.) and Et_4NCl (3.9 g, 23.4 mmol, 1 equiv.) and stirred for 10 minutes at room temperature. 1,2-epoxy-5-hexene (2.3 g, 23.4 mmol, 1 equiv.) was then added, and the solution was heated to reflux and stirred for 24 hours before being quenched with water. The aqueous layer was extracted with Et_2O (3x), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide epoxide **4.26** as a white solid (32% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.43 (m, 2H), 7.37 (m, 3H), 5.75 (m, 1H), 4.98 (dd, *J* = 25.8 Hz, 10.2 Hz, 2H), 3.77 (dd, *J* = 13.8 Hz, 8.4 Hz, 1H), 3.70 (m, 1H), 3.61 (dd, *J* = 13.8 Hz, 3.0 Hz, 1H), 2.94 (s, 3H), 2.18 (m, 1H), 2.16 (m, 1H), 2.08 (m, 1H), 1.53 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 140.24, 138.43, 130.22, 129.09, 128.92, 115.62, 69.76, 57.80, 37.86, 33.96, 30.15. **IR** (Thin Film, cm^{-1}): 3514, 2930, 1492, 1336, 1153, 965, 777, 698, 544. **LRMS** (ESI): Calculated for $[C_{13}H_{19}NO_3SNa]^+$ 292.35, found 292.38.



4.27

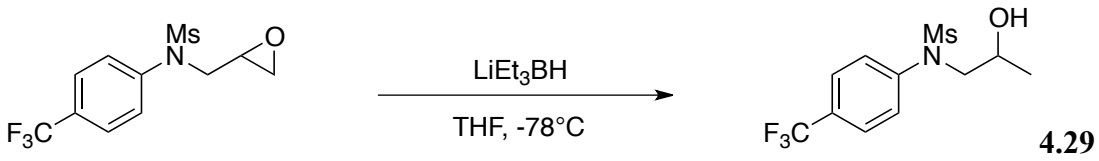
(4.27): *N*-(2-Hydroxypropyl)-*N*-phenylmethanesulfonamide. Following General Procedure D, epoxide **4.14** (3.5 g, 15.3 mmol) was reduced with super hydride (1M in THF, 18.4 mL, 18.4 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide secondary alcohol **4.27** as a white solid (83% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.45 (m, 2H), 7.39 (m, 3H), 3.88 (m, 1H), 3.77 (dd, *J* = 8.4 Hz, 7.8 Hz, 1H), 3.57 (dd, *J* = 14.4 Hz, 3.6 Hz, 1H), 2.97 (s, 3H), 1.19 (d, *J* = 6.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 139.72, 129.71, 128.62, 128.42 65.80, 58.53, 37.37, 20.37. **IR** (Thin Film, cm^{-1}): 3511, 2974, 2931, 1491, 1333, 1152, 1070, 968, 866, 778, 698, 544. **LRMS** (ESI): Calculated for $[C_{10}H_{15}NO_3SH]^+$ 230.08, found 230.09.



4.28

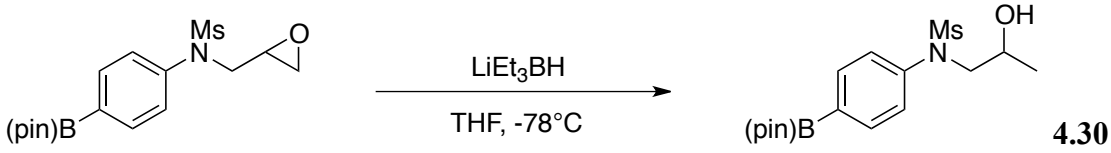
(4.28): *N*-(2-Hydroxypropyl)-*N*-(4-methoxyphenyl)methanesulfonamide. Following General Procedure D, epoxide **4.15** (2.4 g, 9.1 mmol) was reduced with super hydride (1M in THF, 10.9 mL, 10.9 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide secondary alcohol **4.28** as a white solid (73% Yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.22 (m, 2H), 6.85 (m, 2H), 3.79 (m, 1H), 3.77 (m, 3H), 3.64 (dd, *J* = 14.4 Hz,

8.4 Hz, 1H), 3.42 (dd, *J* = 14.4 Hz, 3.6 Hz, 1H), 2.87 (s, 3H), 2.14 (m, 1H), 1.10 (d, *J* = 6.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 159.38, 132.02, 129.91, 114.80, 65.63, 58.63, 55.43, 387.20, 20.29. **IR** (Thin Film, cm^{-1}): 3515, 2932, 1509, 1330, 1250, 1151, 1029, 970, 837. **LRMS** (ESI): Calculated for $[C_{11}H_{17}NO_4SH]^+$ 260.10, found 260.17.



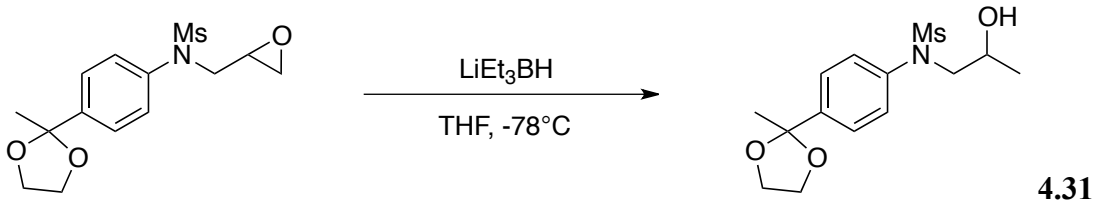
4.29

(4.29): *N*-(2-Hydroxypropyl)-*N*-(4-trifluoromethylphenyl)methanesulfonamide. Following General Procedure D, epoxide **4.16** (4.0 g, 13.6 mmol) was reduced with super hydride (1M in THF, 16.3 mL, 16.3 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide secondary alcohol **4.29** as a white solid (55% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 3.91 (m, 1H), 3.79 (dd, *J* = 14.4 Hz, 8.4 Hz, 1H), 3.65 (dd, *J* = 14.4 Hz, 3.6 Hz, 1H), 3.00 (s, 3H), 1.98 (bs, 1H), 1.22 (d, *J* = 6.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.14, 128.61, 126.84, 126.82, 126.80, 65.95, 58.21, 37.92, 20.63. **IR** (Thin Film, cm^{-1}): 3505, 1615, 1325, 1159, 1126, 1070, 1017, 970, 873, 788, 525. **LRMS** (ESI): Calculated for $[C_{11}H_{14}F_3NO_3SH]^+$ 298.07, found 298.09.



4.30

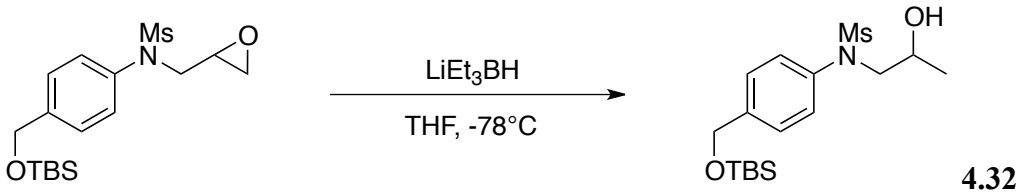
(4.30): *N*-(2-Hydroxypropyl)-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl)methanesulfonamide. Following General Procedure D, epoxide **4.17** (1.5 g, 4.2 mmol) was reduced with super hydride (1M in THF, 5.1 mL, 5.1 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide secondary alcohol **4.30** as a white solid (60% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 3.88 (m, 1H), 3.79 (dd, *J* = 14.4 Hz, 8.4 Hz, 1H), 3.62 (dd, *J* = 14.4, 3.6 Hz, 1H), 2.96 (s, 3H), 1.37 (s, 12H), 1.19 (d, *J* = 6.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.71, 137.66, 129.01, 90.06, 85.56, 67.35, 59.77, 54.98, 38.85, 26.29, 26.26, 21.82. **IR** (Thin Film, cm^{-1}): 3504, 2978, 1605, 1361, 1146, 1092, 966, 857, 657. **LRMS** (ESI): Calculated for $[C_{16}H_{26}BNO_5SNa]^+$ 378.25, found 378.36.



4.31

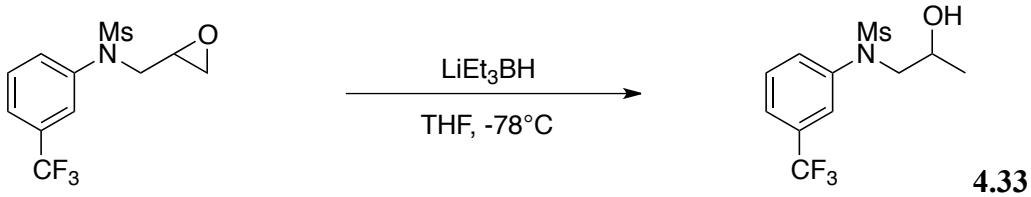
4.31): *N*-(2-Hydroxypropyl)-*N*-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)methane sulfonamide. Following General Procedure D, epoxide **4.18** (2.5 g, 8.0 mmol) was reduced with super hydride (1M in THF, 9.6 mL, 9.6 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide secondary alcohol **4.31** as a white solid (70% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.05 (m, 2H), 3.85 (m, 1H), 3.79 (m, 2H), 3.73 (dd, *J* = 14.4 Hz, 6.0 Hz, 1H), 3.55 (dd, *J* = 14.4 Hz, 3.6 Hz, 1H), 2.92 (s, 3H), 2.08 (bs, 1H), 1.64 (s, 3H), 1.17 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 144.29, 139.71, 128.83, 127.20, 108.91, 66.31, 65.05, 59.07, 37.87, 28.06, 20.84. **IR**

(Thin Film, cm^{-1}): 3504, 2981, 1506, 1336, 1155, 1037, 969, 871. **LRMS** (ESI): Calculated for $[C_{14}H_{21}NO_5SNa]^+$ 338.37, found 338.32.



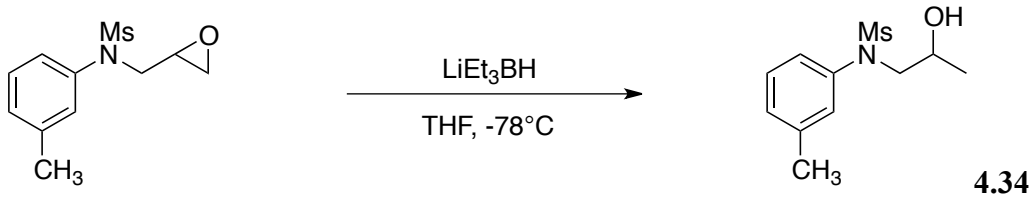
4.32

4.32): *N*-(2-Hydroxypropyl)-*N*-(4-(*tert*-butyldimethylsilyloxylmethyl)phenyl)methane sulfonamide. Following General Procedure D, epoxide **4.19** (4.2 g, 11.3 mmol) was reduced with super hydride (1M in THF, 13.6 mL, 13.6 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide secondary alcohol **4.32** as a white solid (69% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 4.78 (s, 2H), 3.87 (m, 1H), 3.77 (dd, *J* = 14.4 Hz, 8.4 Hz, 1H), 3.57 (dd, *J* = 14.4 Hz, 3.0 Hz, 1H), 2.97 (s, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 0.98 (s, 9H), 0.14 (s, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 142.00, 138.26, 128.44, 127.14, 65.83, 64.24, 58.60, 37.32, 25.94, 20.38, 18.42, -5.29. **IR** (Thin Film, cm^{-1}): 3515, 2931, 1509, 1338, 1255, 1155, 1090, 969, 839, 778. **LRMS** (ESI): Calculated for $[C_{17}H_{31}NO_4SSiNa]^+$ 396.57, found 396.43.



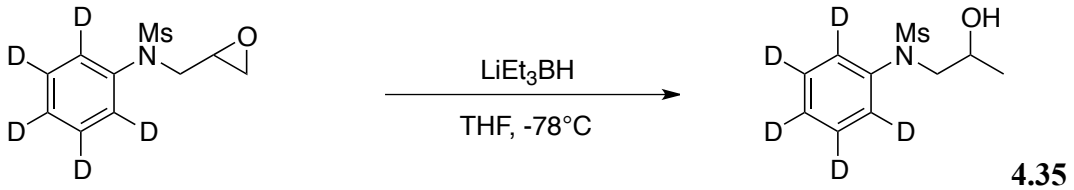
4.33

(4.33): *N*-(2-Hydroxypropyl)-*N*-(3-trifluoromethylphenyl)methanesulfonamide. Following General Procedure D, epoxide **4.20** (1.9 g, 6.3 mmol) was reduced with super hydride (1M in THF, 7.5 mL, 7.5 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (2:1) to provide secondary alcohol **4.33** as a white solid (62% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.64 (m, 4H), 3.92 (m, 1H), 3.79 (dd, *J* = 14.0 Hz, 6.6 Hz, 1H), 3.63 (dd, *J* = 14.0 Hz, 3.6 Hz, 1H), 3.00 (s, 3H), 1.97 (d, *J* = 4.4 Hz, 1H), 1.22 (d, *J* = 6.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 171.05, 139.66, 139.51, 129.40, 129.24, 129.00, 125.44, 65.42, 60.28, 37.35, 20.86. **IR** (Thin Film, cm^{-1}): 3502, 2930, 1333, 1153, 1074, 970, 757, 514. **LRMS** (ESI): Calculated for $[C_{11}H_{14}F_3NO_3SH]^+$ 298.07, found 298.06.



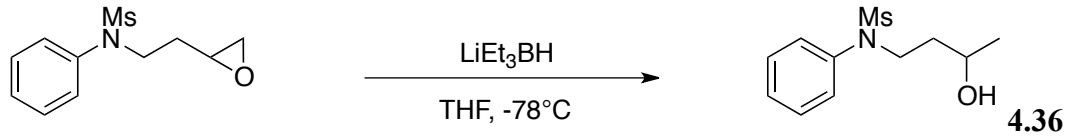
4.34

(4.34): *N*-(2-Hydroxypropyl)-*N*-(3-tolyl)methanesulfonamide. Following General Procedure D, epoxide **4.21** (2.5 g, 10.4 mmol) was reduced with super hydride (1M in THF, 12.4 mL, 12.4 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (2:1) to provide secondary alcohol **4.34** as a white solid (58% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.31 (m, 1H), 7.20 (m, 2H), 3.87 (m, 1H), 3.76 (dd, *J* = 13.8 Hz, 8.4 Hz, 1H), 3.57 (dd, *J* = 13.8 Hz, 3.6 Hz, 1H), 2.97 (s, 3H), 2.40 (s, 3H), 1.20 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 139.86, 139.60, 129.46, 129.42, 129.30, 125.32, 65.81, 58.59, 37.36. **IR** (Thin Film, cm^{-1}): 3507, 2973, 2929, 2360, 1605, 1333, 1154, 1074, 970, 709, 515. **LRMS** (ESI): Calculated for $[C_{11}H_{17}NO_3SH]^+$ 244.10, found 244.11.



4.35

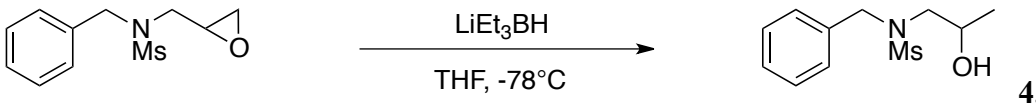
(4.35): *N*-(2-Hydroxypropyl)-*N*-(perdeuterophenyl)methanesulfonamide. Following General Procedure D, epoxide **4.22** (1.8 g, 7.5 mmol) was reduced with super hydride (1M in THF, 9.0 mL, 9.0 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (2:1) to provide secondary alcohol **4.35** as a white solid (57% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 3.87 (m, 1H), 3.77 (dd, *J* = 14.4 Hz, 8.4 Hz, 1H), 3.58 (dd, *J* = 14.4 Hz, 3.6 Hz, 1H), 2.97 (s, 3H), 2.19 (d, *J* = 4.2 Hz, 1H), 1.19 (d, *J* = 6.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 139.58, 129.37, 129.21, 129.05, 128.34, 128.18, 128.02, 65.79, 58.49, 37.34, 20.35. **IR** (Thin Film, cm^{-1}): 3509, 2973, 2932, 1563, 1378, 1329, 1153, 1059, 971, 814, 763. **LRMS** (ESI): Calculated for $[C_{10}H_{10}D_5NO_3SH]^+$ 235.12, found 235.08.



4.36

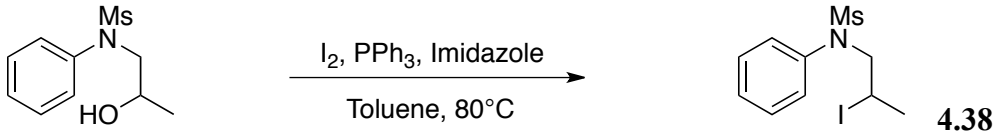
(4.36): *N*-(3-Hydroxybutyl)-*N*-phenylmethanesulfonamide. Following General Procedure D, epoxide **4.23** (2.0 g, 8.3 mmol) was reduced with super hydride (1M in THF, 9.9 mL, 9.9 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide secondary alcohol **4.36** as a white solid (53% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.44 (m, 2H), 7.37 (m, 3H), 4.05 (m, 1H), 4.02-3.97 (m, 1H), 3.73-3.69 (m, 1H), 2.93 (s, 3H), 2.27 (d, *J* = 4.2 Hz, 1H), 1.63-1.59 (m, 1H), 1.54-1.52 (m, 1H), 1.22 (d, *J* = 6.0 Hz, 3H). **^{13}C-**

NMR (100 MHz, $CDCl_3$): δ 138.87, 129.60, 128.57, 128.28, 64.15, 47.80, 37.44, 36.91, 23.20. **IR** (Thin Film, cm^{-1}): 3506, 2930, 1492, 1332, 1153, 1075, 959, 775, 699, 543. **LRMS** (ESI): Calculated for $[C_{11}H_{17}NO_3SH]^+$ 244.10, found 244.16.



4.37

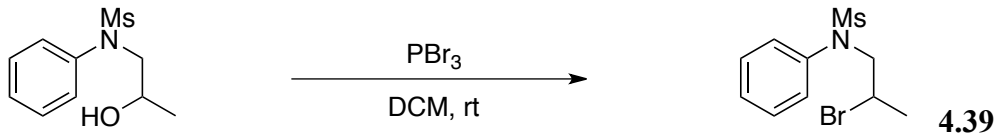
(4.37): *N*-Benzyl-*N*-(2-hydroxypropyl)methanesulfonamide. Following General Procedure D, epoxide **4.25** (1.0 g, 4.1 mmol) was reduced with super hydride (1M in THF, 4.9 mL, 4.9 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide secondary alcohol **4.37** as a white solid (76% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.40 (m, 3H), 7.35 (m, 1H), 4.55 (d, J = 15.00 Hz, 1H), 4.45 (d, J = 15.0 Hz, 1H), 3.27 (dd, J = 15.0 Hz, 9.0 Hz, 1H), 3.12 (dd, J = 15.0 Hz, 2.4 Hz, 1H), 2.93 (s, 3H), 1.12 (d, J = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 135.89, 128.90, 128.49, 128.22, 65.74, 54.88, 52.39, 38.81, 20.80. **IR** (Thin Film, cm^{-1}): 3504, 2930, 1321, 1145, 1022, 958, 795, 700, 518. **LRMS** (ESI): Calculated for $[C_{11}H_{17}NO_3SH]^+$ 244.10, found 244.09.



4.38

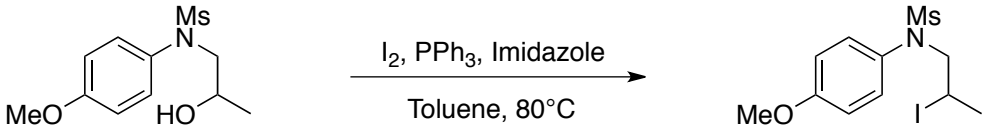
(4.38): *N*-(2-Iodopropyl)-*N*-phenylmethanesulfonamide. Secondary alcohol **4.27** (1.0 g, 4.3 mmol) was iodinated with molecular iodine (1.2 g, 4.6 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (7:1) to

provide secondary iodide **4.38** as a white solid (62% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.47-7.44 (m, 2H), 7.41-7.38 (m, 3H), 4.13 (dd, *J* = 13.8 Hz, 6.6 Hz, 1H), 4.02 (m, 1H), 3.90 (dd, *J* = 13.8 Hz, 8.4 Hz, 1H), 2.94 (s, 3H), 1.93 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 138.93, 129.80, 128.59, 128.55, 60.29, 37.56, 24.93, 23.14. **IR** (Thin Film, cm^{-1}): 2925, 1593, 1491, 1341, 1153, 1059, 964, 843, 776, 697, 541. **LRMS** (ESI): Calculated for $[C_{10}H_{14}INO_2SH]^+$ 339.99, found 339.91.



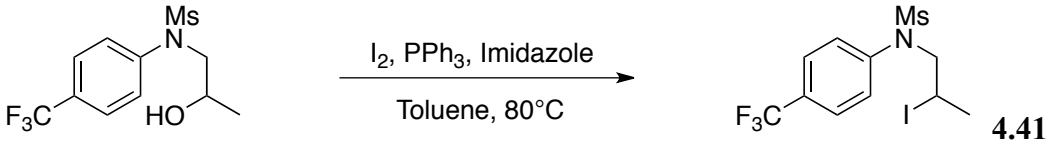
4.39

(4.39): *N*-(2-Bromopropyl)-*N*-phenylmethanesulfonamide. Secondary alcohol **4.28** (1.5 g, 6.3 mmol) was brominated with phosphorus tribromide (0.3 mL, 3.2 mmol) following General Procedure F. The crude product was purified by flash chromatography using hexanes/ethyl acetate (7:1) to provide secondary bromide **4.39** as a white solid (46% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.47-7.44 (m, 2H), 7.42-7.38 (m, 3H), 4.07 (dd, *J* = 13.2 Hz, 6.6 Hz, 1H), 4.02 (m, 1H), 3.90 (dd, *J* = 13.8 Hz, 7.2 Hz, 1H), 2.96 (s, 3H), 1.73 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 139.08, 129.78, 128.66, 128.60, 58.70, 46.05, 37.77, 22.91. **IR** (Thin Film, cm^{-1}): 2981, 2929, 2360, 1593, 1492, 1341, 1156, 1067, 965, 849, 777, 698, 542. **LRMS** (ESI): Calculated for $[C_{10}H_{14}BrNO_2SH]^+$ 292.00, found 291.98.



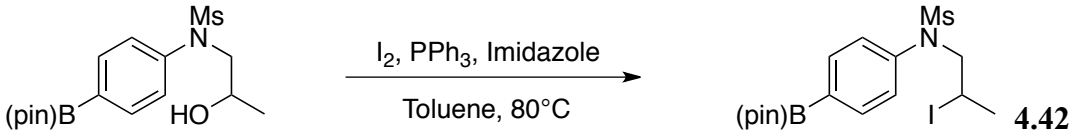
4.40

(4.40): *N*-(2-Iodopropyl)-*N*-(4-methoxyphenyl)methanesulfonamide. Secondary alcohol **4.29** (1.6 g, 6.2 mmol) was iodinated with molecular iodine (1.7 g, 6.5 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (4:1) to provide secondary iodide **4.40** as a white solid (72% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 3.32 (m, 2H), 6.95 (m, 2H), 4.07 (dd, *J* = 13.8 Hz, 6.6 Hz, 1H), 4.00 (m, 1H), 3.84 (s, 3H), 3.82 (dd, *J* = 13.8 Hz, 8.4 Hz, 1H), 2.93 (s, 3H), 1.93 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 159.54, 131.21, 129.90, 114.93, 60.45, 55.50, 37.47, 24.91, 23.34. **IR** (Thin Film, cm^{-1}): 2929, 2838, 1606, 1509, 1448, 1339, 1251, 1153, 966, 843, 759, 545. **LRMS** (ESI): Calculated for $[C_{11}H_{16}INO_3SH]^+$ 370.00, found 369.95.



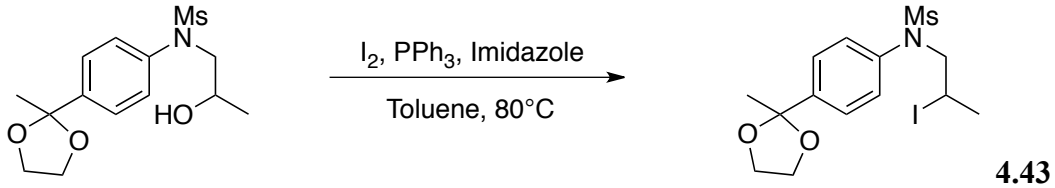
4.41

(4.41): *N*-(2-Iodopropyl)-*N*-(4-trifluoromethylphenyl)methanesulfonamide. Secondary alcohol **4.30** (1.4 g, 4.7 mmol) was iodinated with molecular iodine (1.3 g, 5.0 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (4:1) to provide secondary iodide **4.41** as a white solid (64% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 4.14 (dd, *J* = 13.8 Hz, 6.6 Hz, 1H), 4.01 (m, 1H), 3.93 (dd, *J* = 13.8 Hz, 7.8 Hz, 1H), 2.96 (s, 3H), 1.92 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 142.28, 128.56, 126.94, 126.92, 126.89, 60.03, 37.92, 24.94, 22.50. **IR** (Thin Film, cm^{-1}): 2928, 1615, 1325, 1158, 1068, 965, 853, 785, 602, 522. **LRMS** (ESI): Calculated for $[C_{11}H_{13}F_3INO_2SH]^+$ 407.97, found 408.02.



4.42

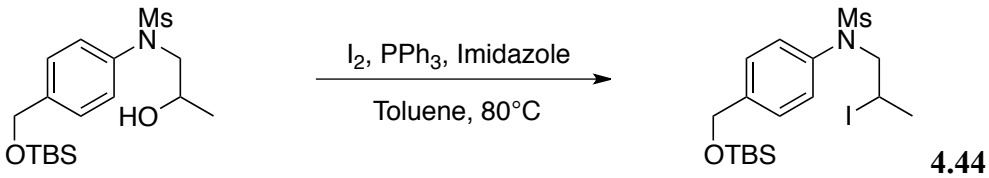
(4.42): *N*-(2-Iodopropyl)-*N*-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) methanesulfonamide. Secondary alcohol **4.31** (0.7 g, 2.0 mmol) was iodinated with molecular iodine (0.53 g, 2.1 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (5:1) to provide secondary iodide **4.42** as a white solid (56% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 4.15 (dd, *J* = 13.8, 6.6 Hz, 1H), 4.01 (m, 1H), 3.92 (dd, *J* = 13.8, 9.0 Hz, 1H), 2.93 (s, 3H), 1.92 (d, *J* = 7.2 Hz, 3H), 1.37 (s, 12H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.50, 136.25, 127.47, 84.15, 60.11, 37.59, 24.96, 24.86, 24.85, 22.99. **IR** (Thin Film, cm^{-1}): 2978, 2360, 1605, 1359, 1150, 1093, 963, 856, 657. **LRMS** (ESI): Calculated for $[C_{16}H_{25}BINO_4SNa]^+$ 488.14, found 488.32.



4.43

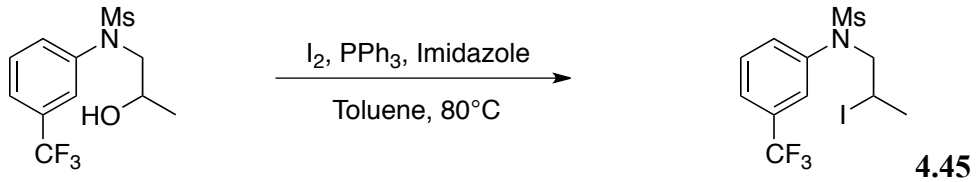
(4.43): *N*-(2-Iodopropyl)-*N*-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)methane sulfonamide. Secondary alcohol **4.32** (1.5 g, 4.8 mmol) was iodinated with molecular iodine (1.3 g, 5.0 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (5:1) to provide secondary iodide **4.43** as a white solid (64% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.09 (dd, *J* = 13.8

Hz, 6.6 Hz, 1H), 4.06 (m, 2H), 3.98 (m, 1H), 3.87 (dd, *J* = 13.8 Hz, 8.4 Hz, 1H), 3.81 (m, 2H), 2.93 (s, 3H), 1.92 (d, *J* = 7.2 Hz 3H), 1.65 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 138.87, 128.79, 127.29, 125.62, 108.91, 65.10, 60.79, 38.08, 28.06, 25.38, 23.57. **IR** (Thin Film, cm^{-1}): 2985, 1505, 1341, 1154, 1038, 966, 872, 731. **LRMS** (ESI): Calculated for $[C_{14}H_{20}INO_4SNa]^+$ 448.27, found 448.25.



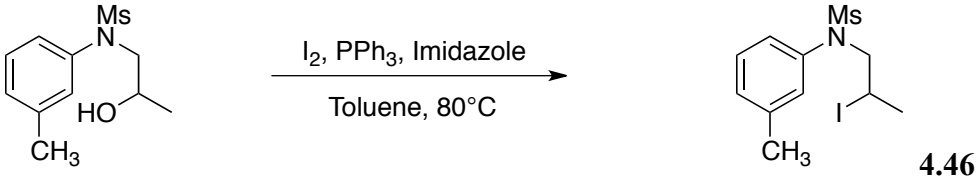
4.44

(4.44): *N*-(2-Iodopropyl)-*N*-(4-(*tert*-butyldimethylsilyloxymethyl)phenyl)methane sulfonamide. Secondary alcohol **4.33** (2.0 g, 5.4 mmol) was iodinated with molecular iodine (1.5 g, 5.7 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (5:1) to provide secondary iodide **4.44** as a white solid (65% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 4.78 (s, 2H), 4.12 (dd, *J* = 13.8 Hz, 6.0 Hz, 1H), 4.01 (m, 1H), 3.89 (dd, *J* = 14.4 Hz, 8.4 Hz, 1H), 2.95 (s, 3H), 1.94 (d, *J* = 6.6 Hz, 3H), 0.99 (s, 9H), 0.15 (s, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 142.17, 137.44, 128.38, 127.17, 64.22, 60.35, 37.53, 25.95, 24.95, 23.21, 18.43, -5.29. **IR** (Thin Film, cm^{-1}): 2929, 1509, 1343, 1254, 1155, 1091, 966, 839, 777. **LRMS** (ESI): Calculated for $[C_{17}H_{30}INO_3SSiNa]^+$ 506.47, found 506.38.



4.45

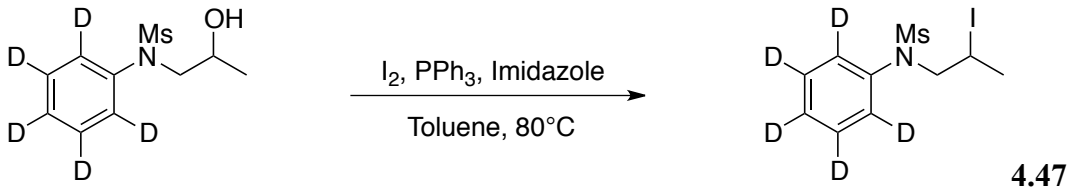
(4.45): ***N*-(2-Iodopropyl)-*N*-(3-trifluoromethylphenyl)methanesulfonamide.** Secondary alcohol **4.34** (0.4 g, 1.3 mmol) was iodinated with molecular iodine (0.4 g, 1.4 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (7:1) to provide secondary iodide **4.45** as a white solid (77% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.68-7.58 (m, 4H), 4.12 (dd, *J* = 13.8 Hz, 6.6 Hz, 1H), 4.02 (m, 1H), 3.91 (dd, *J* = 13.8 Hz, 7.8 Hz, 1H), 2.97 (s, 3H), 1.93 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 139.80, 132.20, 130.42, 125.37, 125.08, 60.26, 37.90, 24.97, 22.63. **IR** (Thin Film, cm^{-1}): 2927, 1593, 1491, 1447, 1328, 1156, 1069, 966, 810, 700, 539. **LRMS** (ESI): Calculated for $[C_{11}H_{13}F_3INO_2SH]^+$ 407.97, found 407.95.



4.46

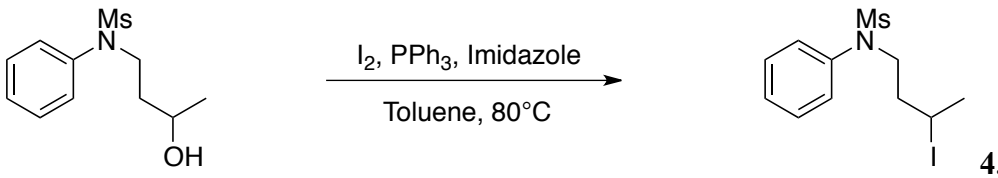
(4.46): ***N*-(2-Iodopropyl)-*N*-(3-tolyl)methanesulfonamide.** Secondary alcohol **4.35** (0.5 g, 2.1 mmol) was iodinated with molecular iodine (0.6 g, 2.2 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (7:1) to provide secondary iodide **4.46** as a white solid (54% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.8 Hz, 1H), 7.21-7.17 (m, 3H), 4.11 (dd, *J* = 13.8 Hz, 6.6 Hz, 1H), 4.02 (m, 1H), 3.88

(dd, J = 13.8 Hz, 8.4 Hz, 1H), 2.94 (s, 3H), 2.41 (s, 3H), 1.94 (d, J = 7.2 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 139.91, 138.82, 129.50, 129.43, 129.29, 125.28, 60.33, 37.58, 24.94, 23.26, 21.35. **IR** (Thin Film, cm^{-1}): 2923, 1604, 1486, 1340, 1153, 1065, 966, 808, 690. **LRMS** (ESI): Calculated for $[C_{11}H_{16}INO_2SH]^+$ 354.00, found 354.07.



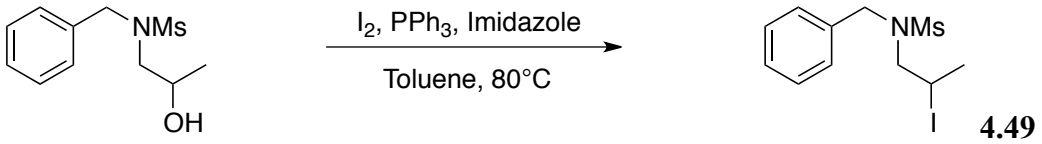
4.47

(4.47): *N*-(2-Iodopropyl)-*N*-(perdeuterophenyl)methanesulfonamide. Secondary alcohol **4.36** (1.0 g, 4.3 mmol) was iodinated with molecular iodine (1.1 g, 4.5 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (7:1) to provide secondary iodide **4.47** as a white solid (51% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 4.13 (dd, J = 13.8 Hz, 6.6 Hz, 1H), 4.02 (m, 1H), 3.90 (dd, J = 13.8 Hz, 8.4 Hz, 1H), 2.94 (s, 3H), 1.93 (d, J = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 138.80, 129.46, 129.30, 129.13, 128.27, 128.11, 127.95, 60.28, 37.53, 24.92, 23.14. **IR** (Thin Film, cm^{-1}): 2925, 2360, 1562, 1339, 1153, 1053, 968, 812, 762, 520. **LRMS** (ESI): Calculated for $[C_{10}H_9D_5INO_2SH]^+$ 345.02, found 344.97.



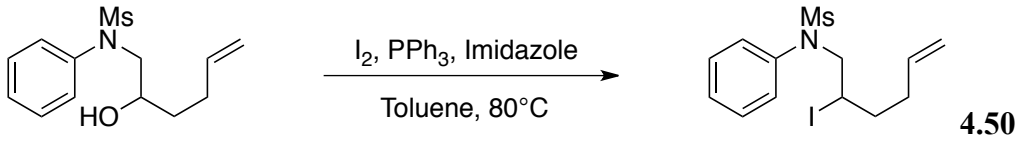
4.48

(4.48): *N*-(3-Iodobutyl)-*N*-phenylmethanesulfonamide. Secondary alcohol **4.37** (1.0 g, 4.1 mmol) was iodinated with molecular iodine (1.1 g, 4.3 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide secondary iodide **4.48** as a white solid (64% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.45 (t, *J* = 7.2 Hz, 2H), 7.38 (m, 3H), 4.19 (m, 1H), 3.88 (m, 1H), 3.79 (m, 1H), 2.91 (s, 3H), 2.04 (m, 1H), 1.93 (d, *J* = 6.6 Hz, 3H), 1.89 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 139.08, 129.63, 128.32, 128.29, 51.09, 41.63, 36.83, 28.80, 24.53. **IR** (Thin Film, cm^{-1}): 2922, 1491, 1339, 1151, 1078, 958, 766, 698, 542, 520. **LRMS** (ESI): Calculated for $[C_{11}H_{16}INO_2SH]^+$ 354.00, found 354.06.



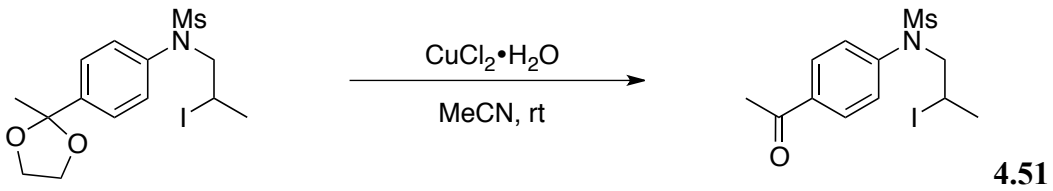
4.49

(4.49): *N*-Benzyl-*N*-(2-iodopropyl)methanesulfonamide. Secondary alcohol **4.38** (0.75 g, 3.1 mmol) was iodinated with molecular iodine (0.79 g, 3.2 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (7:1) to provide secondary iodide **4.49** as a white solid (84% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.42-7.35 (m, 4H), 4.60 (d, *J* = 15.0 Hz, 1H), 4.36 (d, *J* = 15.0 Hz, 1H), 4.11 (m, 1H), 3.57 (dd, *J* = 15.0 Hz, 7.2 Hz, 1H), 3.49 (dd, *J* = 14.4 Hz, 7.8 Hz, 1H), 2.91 (s, 3H), 1.81 (d, *J* = 6.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 135.40, 128.94, 128.69, 128.40, 57.48, 52.69, 39.55, 25.18, 23.73. **IR** (Thin Film, cm^{-1}): 2923, 1451, 1329, 1147, 1023, 962, 790, 700. **LRMS** (ESI): Calculated for $[C_{11}H_{16}INO_2SH]^+$ 354.00, found 354.07.



4.50

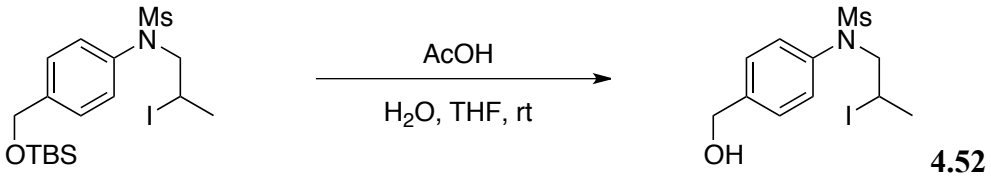
(4.50): *N*-(2-Iodohex-5-enyl)-*N*-phenylmethanesulfonamide. Secondary alcohol **4.26** (1.0 g, 3.7 mmol) was iodinated with molecular iodine (1.0 g, 3.9 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide secondary iodide **4.50** as a white solid (57% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.45 (m, 2H), 7.40 (m, 3H), 5.71 (m, 1H), 5.04 (m, 2H), 4.17 (dd, *J* = 13.8 Hz, 6.0 Hz, 1H), 4.04 (dd, *J* = 13.8 Hz, 8.4 Hz, 1H), 3.97 (m, 1H), 2.94 (s, 3H), 2.31 (m, 1H), 2.12 (m, 1H), 2.01 (m, 1H), 1.84 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 138.83, 136.38, 129.78, 128.61, 128.50, 115.94, 58.68, 37.40, 35.11, 33.13, 32.28. **IR** (Thin Film, cm^{-1}): 2927, 1593, 1491, 1342, 1154, 962, 775, 697, 542. **LRMS** (ESI): Calculated for $[C_{13}H_{18}INO_2SNa]^+$ 402.25, found 402.23.



4.51

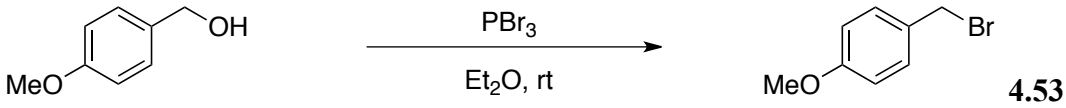
(4.51): *N*-(4-Acetylphenyl)-*N*-(2-iodopropyl)methanesulfonamide. To a solution of acetal **4.43** (1.2 g, 2.8 mmol) in acetonitrile (50 ml, 0.05 M) was added copper (II) chloride (0.97 g, 5.6 mmol). The reaction solution was stirred for 3 hours at room temperature before being quenched with water. The aqueous layer was extracted with Et_2O (3x), and the combined aqueous layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide secondary iodide

4.51 as a white solid (89% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 4.13 (dd, *J* = 14.4 Hz, 6.6 Hz, 1H), 4.00 (m, 1H), 3.91 (dd, *J* = 14.4, 7.8 Hz, 1H), 2.93 (s, 3H), 2.61 (s, 3H), 1.89 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 197.32, 143.69, 137.04, 130.31, 128.58, 60.39, 38.40, 27.19, 25.47, 23.12. **IR** (Thin Film, cm^{-1}): 2925, 1683, 1600, 1343, 1266, 1155, 963, 732, 599. **LRMS** (ESI): Calculated for $[C_{12}H_{16}INO_3SNa]^+$ 404.22, found 404.23.



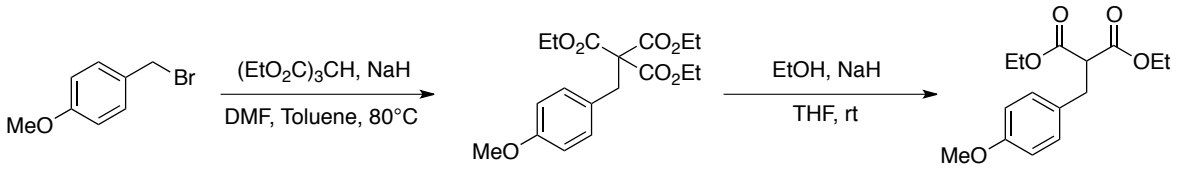
4.52

(4.52): *N*-(4-(Hydroxymethyl)phenyl)-*N*-(2-iodopropyl)methanesulfonamide. To a solution of acetic acid, water, and THF (3:1:1, 50 mL, 0.03 M) was added silyl ether **4.44** (0.75g, 1.5 mmol). The reaction mixture was stirred at room temperature for 15 hours before being quenched with $NaHCO_3$. The aqueous layer was extracted with Et_2O (3x), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide secondary iodide **4.52** as a white solid (72% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 4.76 (s, 2H), 4.12 (dd, *J* = 13.8 Hz, 6.6 Hz, 1H), 4.02 (m, 1H), 3.88 (dd, *J* = 13.8 Hz, 8.4 Hz, 1H), 2.95 (s, 3H), 1.94 (d, *J* = 6.6 Hz, 3H), 1.75 (bs, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.37, 138.17, 128.65, 128.18, 64.54, 60.29, 37.58, 24.93, 23.04. **IR** (Thin Film, cm^{-1}): 3516, 2924, 1509, 1336, 1152, 1056, 966, 731. **LRMS** (ESI): Calculated for $[C_{11}H_{16}INO_3SNa]^+$ 392.21, found 392.29.



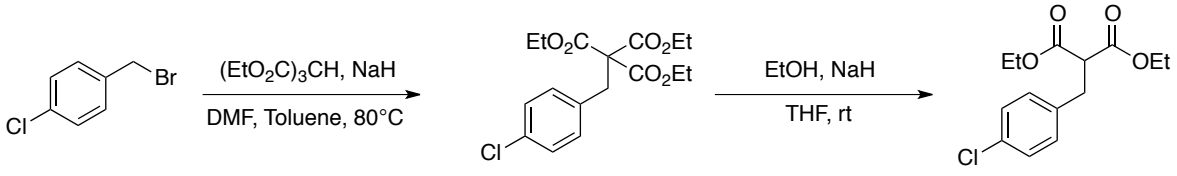
4.53

(4.53): 4-Methoxybenzyl bromide. 4-Methoxybenzyl alcohol (10.0 g, 72.4 mmol) was brominated with phosphorus tribromide (3.6 mL, 38.1 mmol) following General Procedure F. The crude product was purified by flash chromatography using hexanes/ethyl acetate (19:1) to provide benzyl bromide 4.53 as a clear oil (88% Yield). All physical and spectroscopic data were in accordance with literature data.



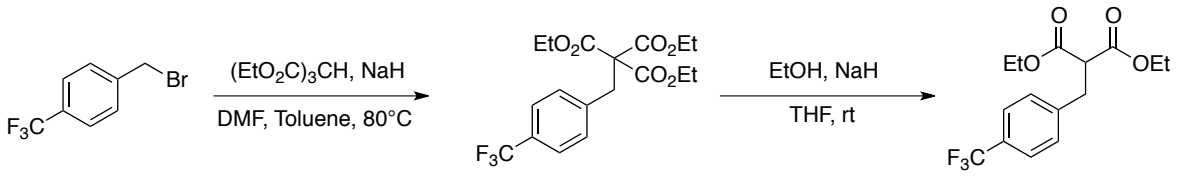
4.54

(4.54): Diethyl (4-methoxybenzyl)malonate. Triethyl methanetricarboxylate (6.8 g, 29.4 mmol) was alkylated with (4-methoxybenzyl) bromide (6.0 g, 30.0 mmol) following General Procedure G. The crude intermediate was then decarboxylated without further purification following General Procedure H. The crude malonate product was purified by flash chromatography using hexanes/ethyl acetate (7:1) to provide diethyl benzylmalonate **4.54** as a pale yellow oil (81% yield). All physical and spectroscopic data were in accordance with literature data.[10]



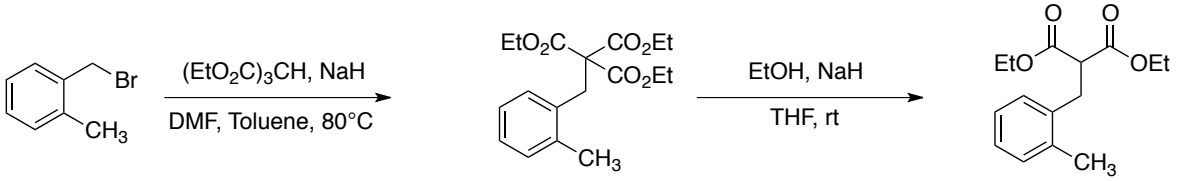
4.55

(4.55): Diethyl (4-chlorobenzyl)malonate. Triethyl methanetricarboxylate (7.5 g, 32.2 mmol) was alkylated with 4-chlorobenzyl bromide (6.7 g, 32.8 mmol) following General Procedure G. The crude intermediate was then decarboxylated without further purification following General Procedure H. The crude malonate product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide diethyl benzylmalonate **4.55** as a pale yellow oil (71% yield). All physical and spectroscopic data were in accordance with literature data.[11]



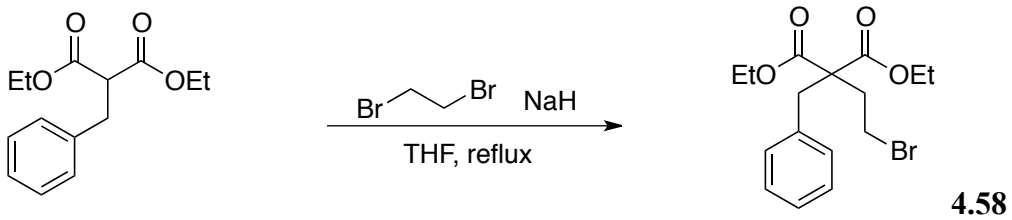
4.56

(4.56): Diethyl (4-trifluoromethylbenzyl)malonate. Triethyl methanetricarboxylate (5.3 g, 22.7 mmol) was alkylated with 4-trifluoromethylbenzyl bromide (5.5 g, 23.2 mmol) following General Procedure G. The crude intermediate was then decarboxylated without further purification following General Procedure H. The crude malonate product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide diethyl benzylmalonate **4.56** as a pale yellow oil (80% yield). All physical and spectroscopic data were in accordance with literature data.[10]



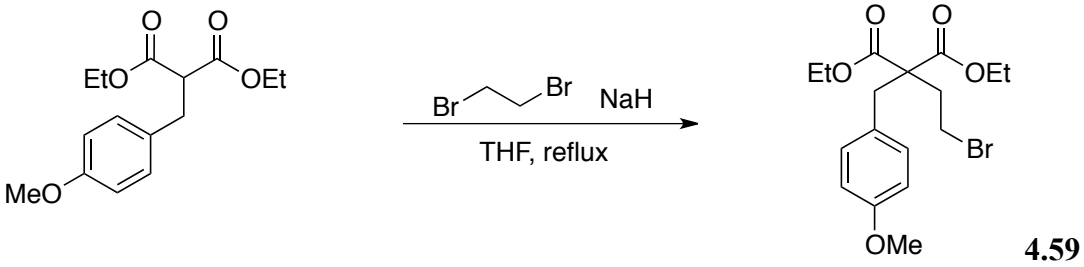
4.57

(4.57): Diethyl (2-methylbenzyl)malonate. Triethyl methanetricarboxylate (8.6 g, 37.1 mmol) was alkylated with 2-methylbenzyl bromide (7.0 g, 37.8 mmol) following General Procedure G. The crude intermediate was then decarboxylated without further purification following General Procedure H. The crude malonate product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide diethyl benzylmalonate **4.57** as a pale yellow oil (78% yield). All physical and spectroscopic data were in accordance with literature data.[12]



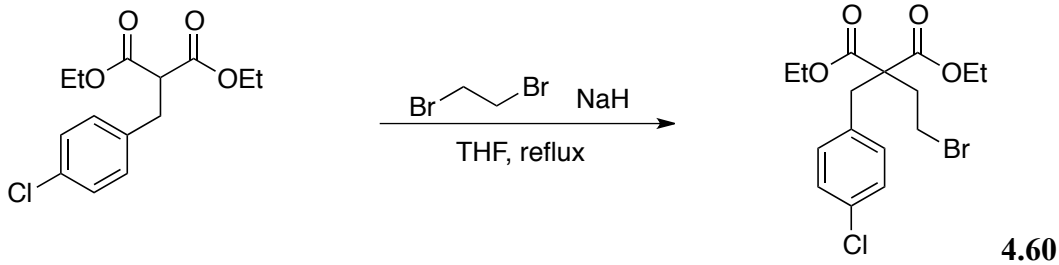
4.58

(4.58): Diethyl benzyl(2-bromoethyl)malonate. Diethyl benzylmalonate (5.1 g, 20.4 mmol) was alkylated with dibromoethane (38.3 g, 204 mmol) following General Procedure I. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide bromide **4.58** as a clear oil (64% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.32-7.26 (m, 3H), 7.11 (d, J = 7.2 Hz, 2H), 4.24 (m, 4H), 3.41 (dd, J = 8.4 Hz, 8.4 Hz, 2H), 3.28 (s, 2H), 2.38 (dd, J = 8.4 Hz, 8.4 Hz, 2H), 1.29 (t, J = 7.1 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 170.24, 135.27, 129.83, 128.45, 127.23, 61.66, 61.64, 58.88, 39.22, 36.06, 27.23, 13.99. **IR** (Thin Film, cm^{-1}): 2980, 1729, 1449, 1261, 1186, 1094, 1035, 861, 701. **LRMS** (ESI): Calculated for $[C_{16}H_{21}BrO_4H]^+$ 357.07, found 357.15.



4.59

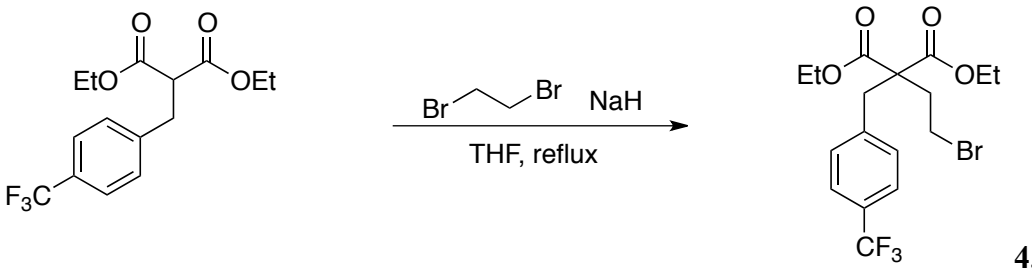
(4.59): Diethyl (2-bromoethyl)(4-methoxybenzyl)malonate. Diethyl benzylmalonate **4.54** (6.1 g, 21.8 mmol) was alkylated with dibromoethane (40.9 g, 218 mmol) following General Procedure I. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide bromide **4.59** as a clear oil (52% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.23 (m, 4H), 3.80 (s, 3H), 3.40 (dd, *J* = 7.8 Hz, 7.2 Hz, 2H), 3.21 (s, 2H), 3.36 (dd, *J* = 7.8 Hz, 7.2 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 170.32, 158.71, 130.84, 127.14, 113.84, 61.60, 58.98, 55.19, 55.16, 38.45, 36.07, 27.32, 14.01. **IR** (Thin Film, cm^{-1}): 2979, 1729, 1612, 1512, 1445, 1248, 1181, 1033, 845. **LRMS** (ESI): Calculated for $[C_{17}H_{23}BrO_4H]^+$ 387.08, found 387.01.



4.60

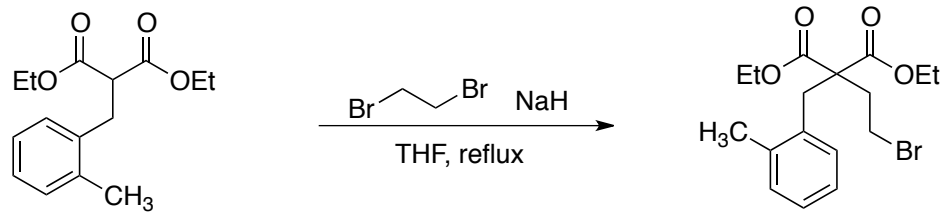
(4.60): Diethyl (2-bromoethyl)(4-chlorobenzyl)malonate. Diethyl benzylmalonate **4.55** (2.5 g, 8.8 mmol) was alkylated with dibromoethane (16.5 g, 88 mmol) following General Procedure I. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to

provide bromide **4.60** as a clear oil (48% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 4.23 (m, 4H), 3.39 (dd, *J* = 7.8 Hz, 7.8 Hz, 2H), 3.24 (s, 2H), 2.36 (dd, *J* = 7.8 Hz, 7.8 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 170.03, 133.81, 133.21, 131.20, 128.62, 61.76, 58.80, 38.70, 36.24, 26.99, 13.99. **IR** (Thin Film, cm^{-1}): 2981, 1729, 1491, 1446, 1261, 1186, 1095, 1015, 861. **LRMS** (ESI): Calculated for $[C_{16}H_{20}BrClO_4H]^+$ 391.03, found 391.15.



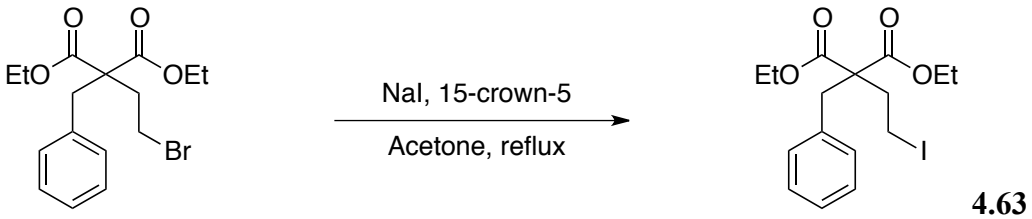
4.61

(4.61): Diethyl (2-bromoethyl)(4-trifluoromethylbenzyl)malonate. Diethyl benzylmalonate **4.56** (1.5 g, 3.5 mmol) was alkylated with dibromoethane (1.6 g, 10.6 mmol) following General Procedure I. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide bromide **4.61** as a clear oil (62% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz), 4.22 (m, 4H), 3.40 (m, 2H), 3.32 (s, 2H), 2.37 (m, 2H), 1.27 (t, 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.90, 139.58, 130.26, 125.36, 125.33, 61.85, 58.76, 39.14, 36.37, 26.83, 13.95. **IR** (Thin Film, cm^{-1}): 2983, 1730, 1619, 1448, 1326, 1165, 1120, 1019, 857. **LRMS** (ESI): Calculated for $[C_{17}H_{20}BrF_3O_4H]^+$ 425.06, found 425.14.



4.62

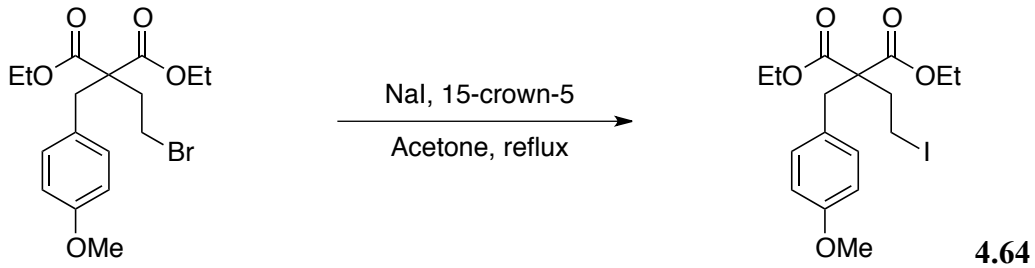
(4.62): Diethyl (2-bromoethyl)(2-methylbenzyl)malonate. Diethyl benzylmalonate **4.57** (4.0 g, 15.1 mmol) was alkylated with dibromoethane (28.4 g, 151 mmol) following General Procedure I. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide bromide **4.62** as a clear oil (73% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.14 (m, 3H), 7.06 (d, *J* = 7.8 Hz, 1H), 4.21 (m, 4H), 3.39 (m, 2H), 3.35 (s, 2H), 2.42 (m, 2H), 2.34 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 170.57, 137.12, 134.03, 130.74, 129.82, 127.06, 125.90, 61.65, 58.98, 36.78, 35.64, 27.52, 19.97, 13.92. **IR** (Thin Film, cm^{-1}): 2980, 1729, 1447, 1245, 1217, 1159, 1054, 862, 742. **LRMS** (ESI): Calculated for $[C_{17}H_{23}BrO_4H]^+$ 371.09, found 371.12.



4.63

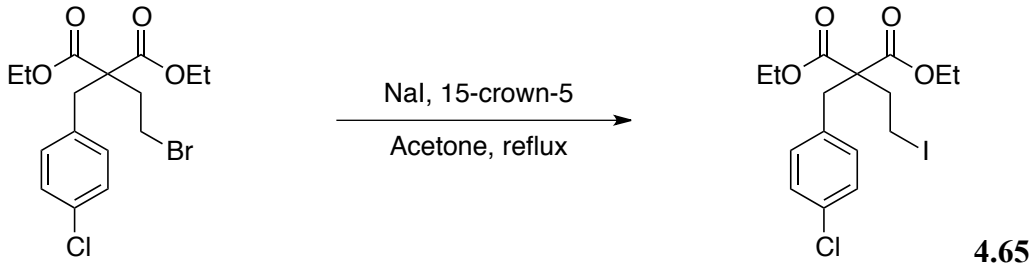
(4.63): Diethyl benzyl(2-iodoethyl)malonate. Primary bromide **4.58** (3.0 g, 8.4 mmol) was iodinated with sodium iodide (3.8 g, 25.2 mmol) following General Procedure J. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide iodide **4.63** as a clear oil (85% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.29 (m, 3H), 7.10 (d, *J* = 6.6 Hz,

2H), 4.32 (m, 4H), 3.26 (s, 2H), 3.15 (m, 2H), 2.42 (m, 2H), 1.29 (t, J = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 170.10, 135.31, 129.78, 128.47, 127.23, 61.62, 60.46, 38.82, 37.46, 14.02, -2.32. **IR** (Thin Film, cm^{-1}): 2980, 1728, 1611, 1512, 1248, 1181, 1030, 842. **LRMS** (ESI): Calculated for $[C_{16}H_{21}IO_4H]^+$ 405.06, found 405.20.



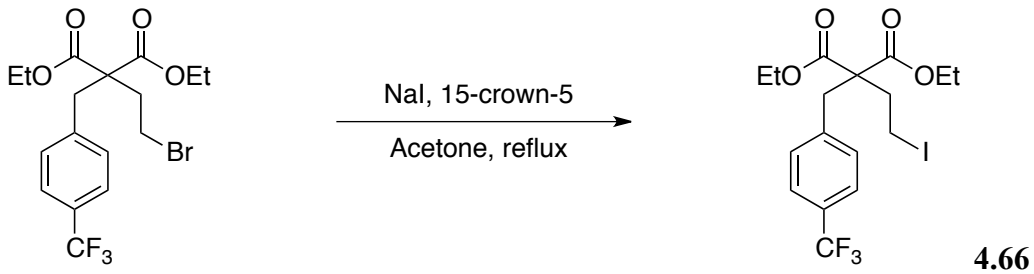
4.64

(4.64): Diethyl (2-iodoethyl)(4-methoxybenzyl)malonate. Primary bromide **4.59** (1.8 g, 4.7 mmol) was iodinated with sodium iodide (2.1 g, 14.1 mmol) following General Procedure J. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide iodide **4.64** as a clear oil (45% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.00 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 4.22 (m, 4H), 3.80 (s, 3H), 3.19 (s, 2H), 3.14 (m, 2H), 2.40 (m, 2H), 1.28 (t, J = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 170.17, 158.70, 130.78, 127.16, 113.85, 61.56, 60.54, 55.18, 38.04, 37.46, 14.04, -2.18. **IR** (Thin Film, cm^{-1}): 2980, 1769, 1728, 1611, 1512, 1445, 1248, 1180, 1029, 839. **LRMS** (ESI): Calculated for $[C_{17}H_{23}IO_5H]^+$ 435.07, found 435.07.



4.65

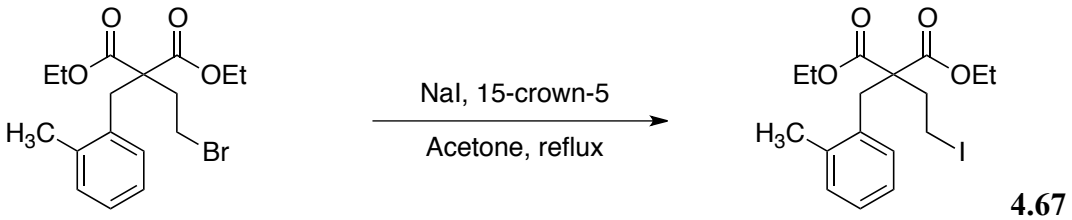
(4.65): Diethyl (4-chlorobenzyl)(2-iodoethyl)malonate. Primary bromide **4.60** (1.0 g, 2.6 mmol) was iodinated with sodium iodide (1.2 g, 7.7 mmol) following General Procedure J. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide iodide **4.65** as a clear oil (58% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.26 (d, *J* = 6.0 Hz, 2H), 7.03 (d, *J* = 6.0 Hz, 2H), 4.21 (m, 4H), 3.21 (s, 2H), 3.12 (m, 2H), 2.39 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.85, 133.82, 133.17, 131.12, 128.60, 61.71, 60.34, 38.28, 37.64, 14.00, -2.67. **IR** (Thin Film, cm^{-1}): 2981, 1773, 1728, 1491, 1186, 1094, 1028, 859. **LRMS** (ESI): Calculated for $[C_{16}H_{20}ClIO_4H]^+$ 439.02, found 438.96.



4.66

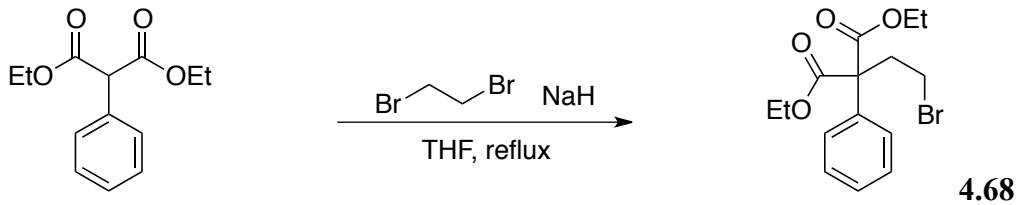
(4.66): Diethyl (2-iodoethyl)(4-trifluoromethylbenzyl)malonate. Primary bromide **4.61** (1.5 g, 3.5 mmol) was iodinated with sodium iodide (1.6 g, 10.6 mmol) following General Procedure J. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide iodide **4.66** as a clear oil (62% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.4

Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 4.22 (m, 4H), 3.30 (s, 2H), 3.13 (m, 2H), 2.41 (m, 2H), 1.26 (t, J = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.73, 139.60, 130.20, 125.35, 125.32, 61.80, 60.31, 38.72, 37.79, 13.96, -2.92. **IR** (Thin Film, cm^{-1}): 3468, 2983, 1729, 1619, 1447, 1326, 1263, 1165, 1119, 1067, 1021, 858. **LRMS** (ESI): Calculated for $[C_{17}H_{20}F_3IO_4H]^+$ 473.05, found 473.17.



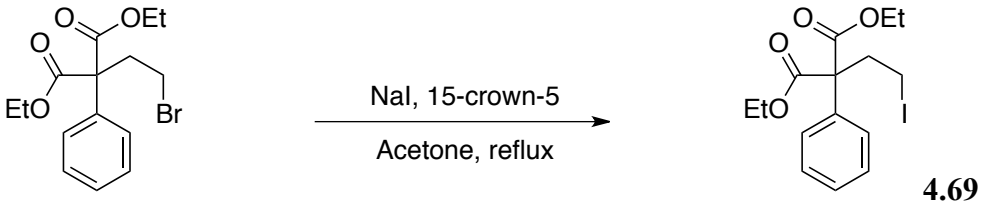
4.67

(4.67): Diethyl (2-iodoethyl)(2-methylbenzyl)malonate. Primary bromide **4.62** (3.0 g, 8.1 mmol) was iodinated with sodium iodide (3.6 g, 24.2 mmol) following General Procedure J. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide iodide **4.67** as a clear oil (74% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.13 (m, 3H), 7.05 (d, J = 7.2 Hz, 1H), 4.21 (m, 4H), 3.33 (s, 2H), 3.14 (m, 2H), 2.47 (m, 2H), 2.33 (s, 3H), 1.25 (t, J = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 170.41, 137.08, 134.04, 130.72, 129.84, 127.04, 125.88, 61.59, 60.42, 38.23, 35.29, 19.89, 13.92, -1.82. **IR** (Thin Film, cm^{-1}): 2979, 1729, 1447, 1237, 1194, 1035, 862, 747. **LRMS** (ESI): Calculated for $[C_{17}H_{23}IO_4H]^+$ 419.07, found 419.18.



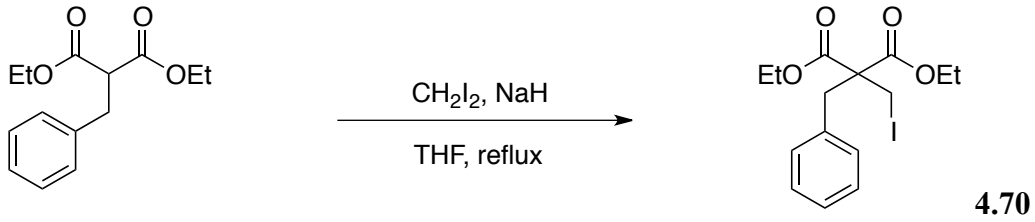
4.68

(4.68): Diethyl (2-bromoethyl)phenylmalonate. Diethyl phenylmalonate (5.9 g, 25.0 mmol) was alkylated with dibromoethane (47.0 g, 250 mmol) following General Procedure I. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide bromide **4.68** as a clear oil (59% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.37 (m, 5H), 4.28 (m, 4H), 3.30 (m, 2H), 2.87 (m, 2H), 1.28 (t, *J* = 6.6 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.83, 135.87, 128.49, 127.90, 127.70, 62.96, 61.99, 39.54, 27.66, 13.96. **IR** (Thin Film, cm^{-1}): 2982, 1732, 1447, 1252, 1094, 1026, 860, 698. **LRMS** (ESI): Calculated for $[C_{15}H_{19}BrO_4H]^+$ 343.06, found 343.09.



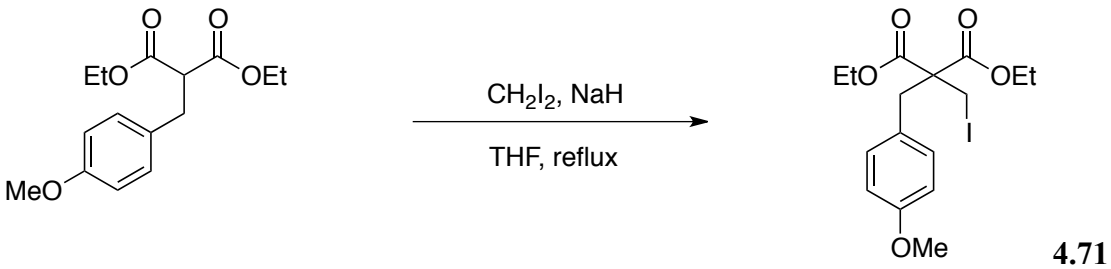
4.69

(4.69): Diethyl (2-iodoethyl)phenylmalonate. Primary bromide **4.68** (3.0 g, 8.7 mmol) was iodinated with sodium iodide (3.9 g, 26.1 mmol) following General Procedure J. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide iodide **4.69** as a clear oil (65% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.35 (m, 5H), 4.27 (m, 4H), 3.07 (m, 2H), 2.90 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.67, 135.74, 128.45, 127.83, 127.71, 64.37, 61.92, 41.05, 13.94, -1.44. **IR** (Thin Film, cm^{-1}): 2979, 1775, 1727, 1448, 1371, 1214, 1162, 1024, 698. **LRMS** (ESI): Calculated for $[C_{15}H_{19}IO_4H]^+$ 391.04, found 391.07.



4.70

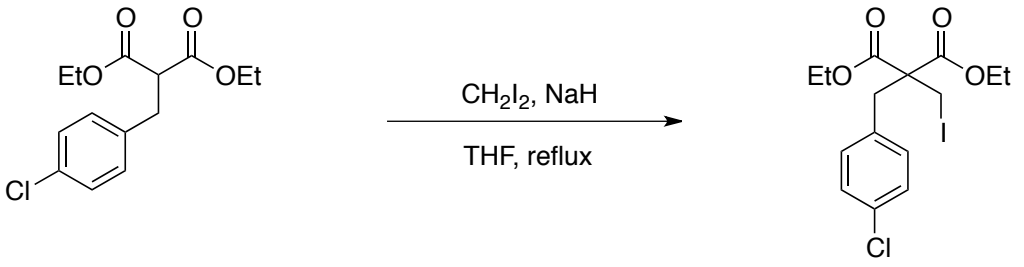
(4.70): Diethyl benzyl(iodomethyl)malonate. Diethyl benzylmalonate (1.5 g, 5.8 mmol) was alkylated with diiodomethane (3.1 g, 11.6 mmol) following General Procedure K. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide iodide **4.70** as a clear oil (68% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.28 (m, 3H), 7.20 (m, 2H), 4.24 (m, 4H), 3.47 (s, 2H), 3.39 (s, 2H), 1.28 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 168.20, 135.18, 129.58, 128.50, 127.38, 62.06, 59.41, 37.97, 14.01, 7.08. **IR** (Thin Film, cm^{-1}): 2981, 1734, 1443, 1271, 1183, 1032, 862, 741, 702. **LRMS** (ESI): Calculated for $[C_{15}H_{19}IO_4H]^+$ 391.04, found 391.15.



4.71

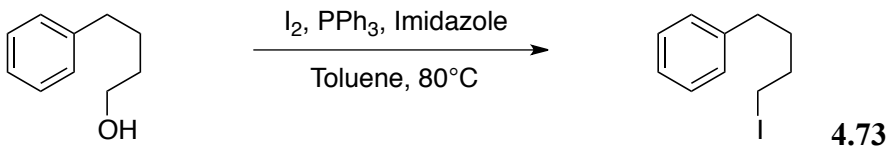
(4.71): Diethyl (iodomethyl)(4-methoxybenzyl)malonate. Diethyl benzylmalonate **4.54** (4.5 g, 16.2 mmol) was alkylated with diiodomethane (8.6 g, 32.3 mmol) following General Procedure K. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide iodide **4.71** as a clear oil (60% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.12 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 4.23 (m, 4H), 3.79 (s, 3H), 3.47 (s, 2H), 3.34 (s, 2H), 1.29 (t, *J*

= 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 168.25, 158.85, 130.58, 127.01, 113.87, 61.98, 59.41, 55.13, 37.17, 14.01, 7.16. **IR** (Thin Film, cm^{-1}): 2981, 2835, 1732, 1612, 1512, 1453, 1249, 1182, 1104, 1032, 948, 575. **LRMS** (ESI): Calculated for $[C_{16}H_{21}IO_5H]^+$ 421.05, found 421.09.



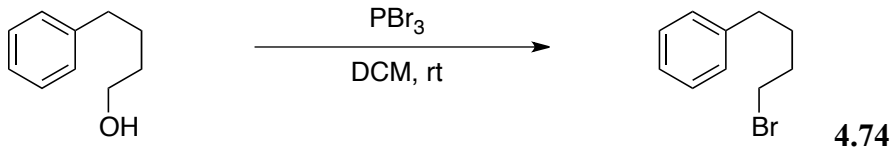
4.72

(4.72): Diethyl (4-chlorobenzyl)(iodomethyl)malonate. Diethyl benzylmalonate **4.55** (2.0 g, 7.0 mmol) was alkylated with diiodomethane (3.5 g, 14.0 mmol) following General Procedure K. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide iodide **4.72** as a clear oil (85% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.27 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 4.27 (m, 4H), 3.45 (s, 2H), 3.37 (s, 2H), 1.29 (t, J = 7.2 Hz). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 168.01, 133.71, 133.37, 130.96, 128.69, 62.19, 59.31, 37.45, 14.02, 6.81. **IR** (Thin Film, cm^{-1}): 2981, 1732, 1491, 1267, 1182, 1096, 1033, 851, 828, 576. **LRMS** (ESI): Calculated for $[C_{15}H_{18}ClIO_4H]^+$ 425.00, found 425.06.



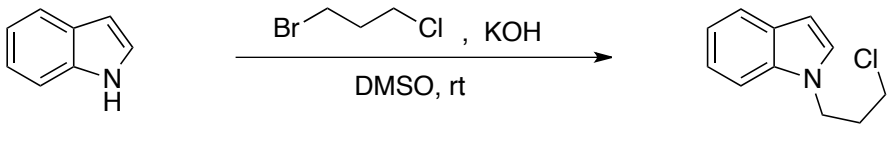
4.73

(4.73): (4-Iodobutyl)benzene. 4-Phenyl-1-butanol (2.0 g, 13.3 mmol) was iodinated with molecular iodine (3.6 g, 14.0 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide primary iodide **4.73** as a clear oil (52% Yield). All physical and spectroscopic data were in accordance with literature data.[13]



4.74

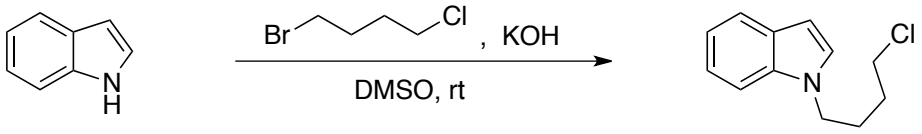
(4.74): (4-Bromobutyl)benzene. 4-Phenyl-1-Butanol (2.0 g, 13.3 mmol) was brominated with phosphorus tribromide (0.7 mL, 6.7 mmol) following General Procedure F. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide primary bromide **4.74** as a clear oil (57% Yield). All physical and spectroscopic data were in accordance with literature data.[14]



4.75

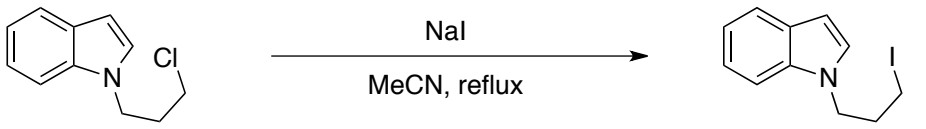
(4.75): *N*-(3-Chloropropyl)indole. Indole (3.0 g, 25.6 mmol) was alkylated with 1-bromo-3-chloropropane (12.1 g, 76.8 mmol) following General Procedure M. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide chloride **4.75** as a clear oil (72% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 8.4

Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.15 (m, 2H), 6.53 (d, *J* = 3.0 Hz, 1H), 4.38 (t, *J* = 6.6 Hz, 2H), 3.48 (t, *J* = 6.0 Hz, 2H), 2.30 (t, *J* = 6.6 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 128.68, 128.03, 121.62, 121.07, 119.47, 109.22, 101.48, 42.83, 41.86, 32.59. **IR** (Thin Film, cm^{-1}): 2943, 1711, 1610, 1463, 1362, 1239, 1161, 740, 651. **LRMS** (ESI): Calculated for $[C_{11}H_{12}ClNH]^+$ 196.08, found 196.11.



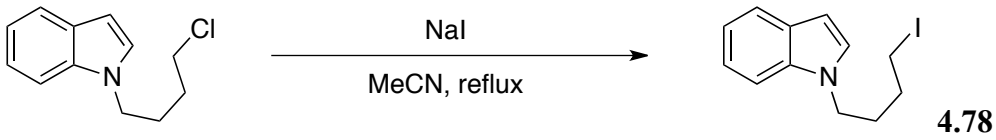
4.76

(4.76): *N*-(4-Chlorobutyl)indole. Indole (3.0 g, 25.6 mmol) was alkylated with 1-bromo-4-chlorobutane (13.3 g, 76.8 mmol) following General Procedure M. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide chloride **4.76** as a clear oil (61% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.13 (m, 2H), 6.53 (d, *J* = 3.0 Hz, 1H), 4.20 (t, *J* = 6.6 Hz, 2H), 3.54 (t, *J* = 6.0 Hz, 2H), 2.05 (m, 2H), 1.80 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 135.88, 128.60, 127.59, 121.50, 121.04, 119.33, 109.22, 101.28, 45.61, 44.43, 29.84, 27.60. **IR** (Thin Film, cm^{-1}): 3420, 2955, 2360, 1637, 1462, 1314, 781, 739. **LRMS** (ESI): Calculated for $[C_{12}H_{14}ClNH]^+$ 208.09, found 208.14.



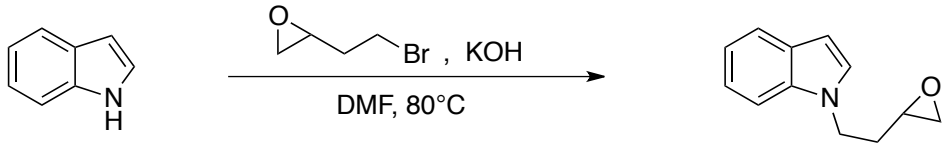
4.77

(4.77): *N*-(3-Iodopropyl)indole. Primary chloride **4.75** (2.5 g, 12.9 mmol) was iodinated with sodium iodide (8.7 g, 58.1 mmol) following General Procedure M. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide iodide **4.77** as a white powder (59% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.27 (m, 1H), 7.17 (m, 1H), 6.55 (d, *J* = 3.0 Hz, 1H), 4.31 (t, *J* = 6.0 Hz, 2H), 3.10 (t, *J* = 6.0 Hz, 2H), 2.34 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 135.84, 128.75, 128.00, 121.68, 121.14, 119.55, 109.34, 101.59, 46.10, 33.42, 3.24. **IR** (Thin Film, cm^{-1}): 3049, 2935, 1510, 1461, 1314, 1209, 1166, 745. **LRMS** (ESI): Calculated for $[C_{11}H_{12}INH]^+$ 286.01, found 286.09.



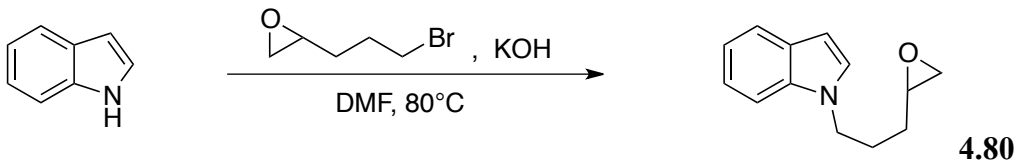
4.78

(4.78): *N*-(4-Iodobutyl)indole. Primary chloride **4.76** (2.5 g, 12.0 mmol) was iodinated with sodium iodide (8.1 g, 54.2 mmol) following General Procedure M. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide iodide **4.78** as a clear oil (66% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.25 (t, *J* = 8.4 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 3.0 Hz, 1H), 6.54 (t, *J* = 3.0 Hz, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 135.83, 128.57, 127.56, 121.49, 121.02, 119.32, 109.21, 101.29, 45.25, 31.08, 30.62, 5.76. **IR** (Thin Film, cm^{-1}): 3049, 2935, 1509, 1462, 1315, 1237, 1203, 1167, 741. **LRMS** (ESI): Calculated for $[C_{12}H_{14}INH]^+$ 300.03, found 300.11.



4.79

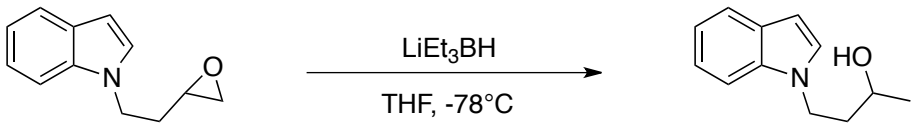
(4.79): *N*-(3,4-Epoxybutyl)indole. Indole (6.0 g, 51 mmol) was alkylated with (2-bromoethyl)oxirane (5.2 g, 56 mmol) following General Procedure L. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide epoxide **4.79** as a clear oil (45% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.15 (m, 2H), 6.54 (d, *J* = 3.2 Hz, 1H), 3.45 (m, 2H), 2.90 (m, 1H), 2.76 (m, 1H), 2.42 (m, 1H), 2.22 (m, 1H), 1.92 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 136.35, 128.58, 128.25, 121.81, 119.66, 109.27, 101.94. **IR** (Thin Film, cm^{-1}): 3053, 2924, 1511, 1462, 1316, 1255, 1201, 909, 850, 743. **LRMS** (ESI): Calculated for $[C_{12}H_{13}NOH]^+$ 174.13, found 174.03.



4.80

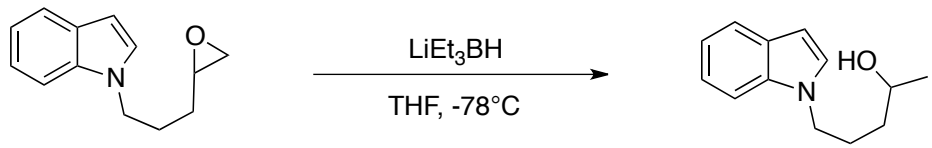
(4.80): *N*-(4,5-Epoxypentyl)indole. Indole (2.3 g, 20.0 mmol) was alkylated with (4-bromopropyl)oxirane (3.6 g, 22.0 mmol) following General Procedure L. The crude product was purified by flash chromatography using hexanes/ethyl acetate (7:1) to provide epoxide **4.80** as a clear oil (52% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 6.6 Hz, 1H), 7.13 (m, 2H), 6.52 (d, *J* = 3.0 Hz, 1H), 4.23 (m, 2H), 2.93 (m, 1H), 2.76 (m, 1H), 2.48 (m, 1H), 2.06-2.02 (m, 2H), 1.75-1.68 (m, 1H), 1.52-1.46 (m, 1H). **^{13}C-**

NMR (100 MHz, $CDCl_3$): δ 135.87, 128.59, 127.74, 121.43, 120.99, 119.27, 109.27, 101.14, 51.77, 46.77, 45.88, 29.67, 26.80. **IR** (Thin Film, cm^{-1}): 2938, 1509, 1462, 1315, 1183, 918, 837, 741. **LRMS** (ESI): Calculated for $[C_{13}H_{15}NOH]^+$ 202.13, found 202.12.



4.81

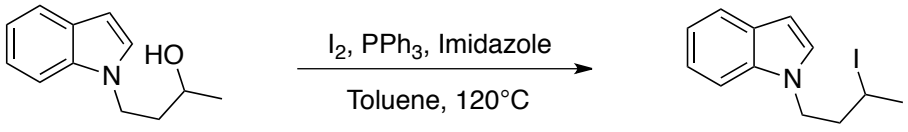
(4.81): *N*-(3-Hydroxybutyl)indole. Following General Procedure D, epoxide **4.79** (1.6 g, 8.9 mmol) was reduced with super hydride (1M in THF, 10.7 mL, 10.7 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (5:1) to provide secondary alcohol **4.81** as a clear oil (79% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.64 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 4.19 (m, 2H), 3.82 (m, 1H), 2.01 (m, 1H), 1.93 (m, 1H), 1.19 (d, J = 6.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 136.26, 128.61, 128.48, 121.64, 121.00, 119.51, 109.47, 101.56, 67.25, 60.38, 53.79, 20.44. **IR** (Thin Film, cm^{-1}): 3381, 2970, 1511, 1461, 1314, 1206, 1081, 938, 837, 741. **LRMS** (ESI): Calculated for $[C_{12}H_{15}NOH]^+$ 189.12, found 189.05.



4.82

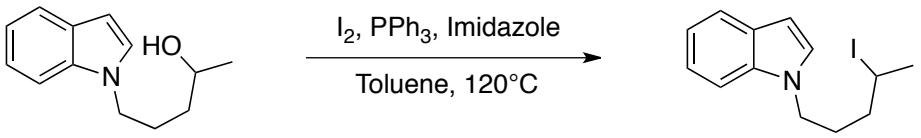
(4.82): *N*-(4-Hydroxypentyl)indole. Following General Procedure D, epoxide **4.80** (2.0 g, 9.9 mmol) was reduced with super hydride (1M in THF, 11.9 mL, 11.9 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide secondary

alcohol **4.82** as a clear oil (70% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 6.6 Hz, 1H), 7.13 (m, 2H), 6.51 (d, *J* = 3.0 Hz, 1H), 4.19 (m, 2H), 3.82 (m, 1H), 2.01 (m, 1H), 1.92 (m, 1H), 1.19 (d, *J* = 6.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.12, 135.80, 128.63, 127.69, 121.23, 119.00, 109.07, 101.03, 67.75, 67.02, 46.10, 23.73. **IR** (Thin Film, cm^{-1}): 3388, 2965, 1702, 1464, 1368, 1133, 741. **LRMS** (ESI): Calculated for $[C_{13}H_{17}NOH]^+$ 204.14, found 204.23.



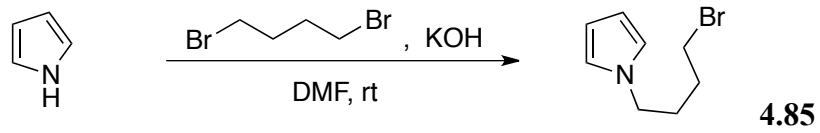
4.83

(4.83): *N*-(3-Iodobutyl)indole. Secondary alcohol **4.81** (1.21 g, 6.9 mmol) was iodinated with molecular iodine (1.84 g, 7.2 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide secondary iodide **4.83** as a clear oil (89% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.14 (m, 2H), 6.52 (d, *J* = 3.0 Hz, 1H), 4.40 (m, 1H), 4.29 (m, 1H), 3.97 (m, 1H), 2.24 (m, 1H), 2.14 (m, 1H), 1.95 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 132.15, 132.09, 127.94, 121.63, 121.10, 119.49, 109.35, 101.47, 46.61, 42.61, 29.10, 26.28. **IR** (Thin Film, cm^{-1}): 3051, 2921, 1460, 1315, 1192, 1116, 741. **LRMS** (ESI): Calculated for $[C_{12}H_{14}INH]^+$ 300.03, found 300.05.



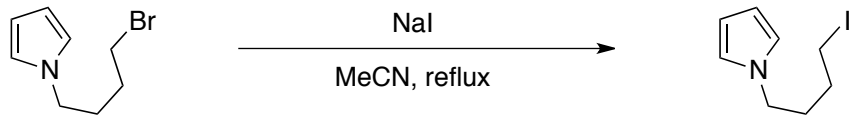
4.84

(4.84): *N*-(4-Iodopentyl)indole. Secondary alcohol **4.82** (1.0 g, 4.9 mmol) was iodinated with molecular iodine (1.3 g, 5.2 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide secondary iodide **4.84** as a clear oil (45% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.25 (t, *J* = 8.4 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 3.0 Hz, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 4.17 (m, 2H), 4.15 (m, 1H), 2.11 (m, 1H), 1.99 (m, 1H), 1.91 (d, *J* = 7.2 Hz, 3H), 1.84 (m, 1H), 1.63 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 135.87, 128.57, 127.56, 121.49, 121.01, 119.31, 109.24, 101.26, 45.40, 39.86, 30.54, 28.98, 28.92. **IR** (Thin Film, cm^{-1}): 3048, 2934, 1611, 1461, 1373, 1232, 1155, 1012, 742. **LRMS** (ESI): Calculated for $[C_{13}H_{16}INH]^+$ 314.04, found 314.14.



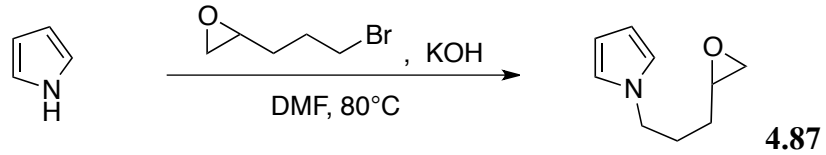
4.85

(4.85): *N*-(4-Bromobutyl)pyrrole. Pyrrole (3.0 g, 44.7 mmol) was alkylated with 1,4-dibromobutane (28.9 g, 134 mmol) following General Procedure M. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide bromide **4.85** as a clear oil (45% yield). All physical and spectroscopic data were in accordance with literature data.[15]



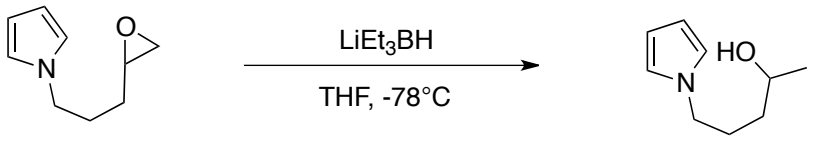
4.86

(4.86): *N*-(4-Iodobutyl)pyrrole. Primary chloride **4.85** (2.0 g, 9.9 mmol) was iodinated with sodium iodide (6.7 g, 44.6 mmol) following General Procedure M. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide iodide **4.86** as a clear oil (50% yield). All physical and spectroscopic data were in accordance with literature data.[16]



4.87

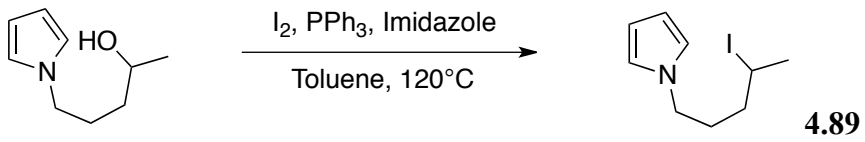
(4.87): *N*-(4,5-Epoxypentyl)pyrrole. Pyrrole (1.3 g, 20 mmol) was alkylated with (4-bromopropyl)oxirane (3.6 g, 22 mmol) following General Procedure L. The crude product was purified by flash chromatography using hexanes/ethyl acetate (7:1) to provide epoxide **4.87** as a clear oil (58% yield). All physical and spectroscopic data were in accordance with literature data.[17]



4.88

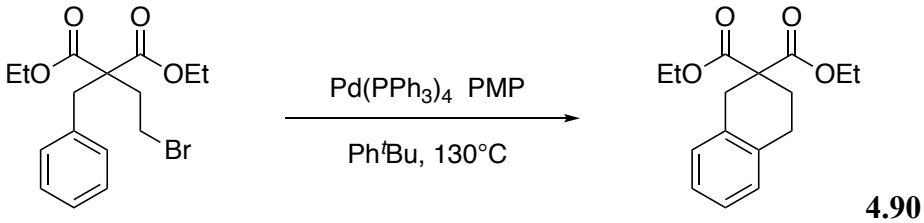
(4.88): *N*-(4-Hydroxypentyl)pyrrole. Following General Procedure D, epoxide **4.87** (0.6 g, 4.0 mmol) was reduced with super hydride (1M in THF, 4.8 mL, 4.8 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide secondary alcohol **4.88** as a clear oil (70% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 6.68 (m, 2H), 6.16 (m, 2H), 3.93

(m, 2H), 3.82 (m, 1H), 1.96-1.91 (m, 1H), 1.86-1.82 (m, 1H), 1.45 (m, 2H), 1.21 (d, J = 6.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 120.44, 107.92, 67.69, 49.53, 36.17, 27.81, 23.69. **IR** (Thin Film, cm^{-1}): 3372, 2928, 1673, 1501, 1375, 1281, 1089, 725. **LRMS** (ESI): Calculated for $[C_9H_{15}NOH]^+$ 154.13, found 154.19.



4.89

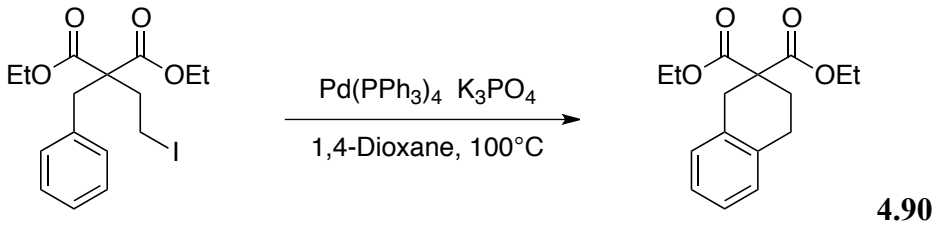
(4.89): *N*-(4-Iodopentyl)pyrrole. Secondary alcohol **4.88** (0.5 g, 3.2 mmol) was iodinated with molecular iodine (0.86 g, 3.4 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (7:1) to provide secondary iodide **4.89** as a clear oil (57% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 6.67 (m, 2H), 6.17 (m, 2H), 4.15 (m, 1H), 3.94 (t, J = 7.2 Hz, 2H), 2.02 (m, 1H), 1.93 (d, J = 6.6 Hz, 3H), 1.89 (m, 1H), 1.79 (m, 1H), 1.61 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 120.41, 108.12, 48.61, 39.68, 31.75, 29.02, 28.94. **IR** (Thin Film, cm^{-1}): 2924, 1500, 1444, 1375, 1280, 1141, 1088, 723, 617.



4.90

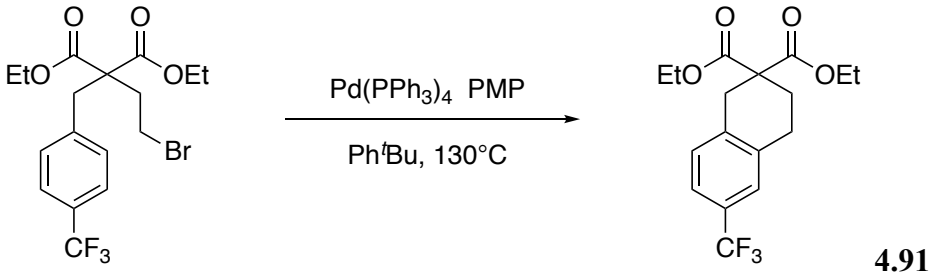
Diethyl benzyl(2-bromoethyl)malonate. Primary bromide **4.58** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure C. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide tetrahydronaphthalene product

4.90 as a clear oil (62.6 mg, 91% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.13 (m, 3H), 7.07 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 4H), 3.29 (s, 2H), 2.86 (t, *J* = 6.6 Hz, 2H), 2.35 (t, *J* = 6.6 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 171.34, 134.63, 133.59, 128.80, 128.57, 126.02, 125.93, 61.38, 53.61, 34.64, 28.08, 25.92, 13.99. **IR** (Thin Film, cm^{-1}): 2980, 1732, 1451, 1226, 1175, 1083, 861, 745. **LRMS** (ESI): Calculated for $[C_{16}H_{20}O_4H]^+$ 277.15, found 277.06.



4.90

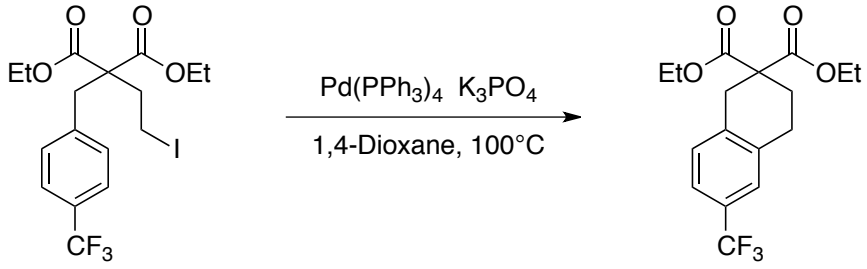
Diethyl benzyl(2-iodoethyl)malonate. Primary iodide **4.63** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide tetrahydronaphthalene product **4.90** as a clear oil (58.7 mg, 85% Yield).



4.91

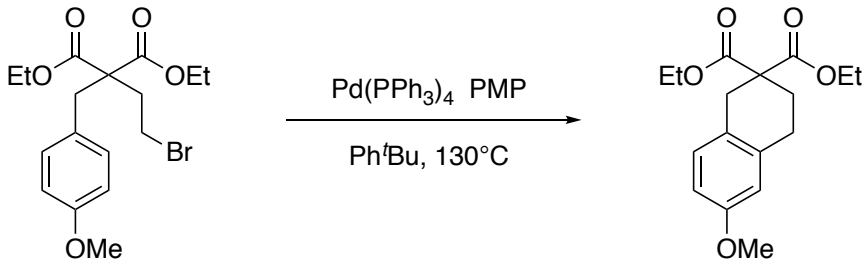
Diethyl (2-bromoethyl)(4-trifluoromethylbenzyl)malonate. Primary bromide **4.61** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure C. The crude product was purified

by flash chromatography using hexanes/ethyl acetate (40:1) to provide tetrahydronaphthalene product **4.91** as a clear oil (79.4 mg, 92% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.39 (m, 1H), 7.28 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 4H), 3.32 (s, 2H), 2.90 (t, *J* = 6.6 Hz, 2H), 2.37 (t, *J* = 6.6 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 170.99, 137.82, 135.35, 129.23, 129.04, 128.27, 125.50, 125.47, 125.45, 125.12, 123.32, 122.74, 122.71, 61.61, 53.36, 34.60, 27.78, 25.94, 13.99. **IR** (Thin Film, cm^{-1}): 2983, 1733, 1443, 1330, 1267, 1163, 1124, 1020, 859, 824. **LRMS** (ESI): Calculated for $[C_{17}H_{19}F_3O_4H]^+$ 345.33, found 345.19.



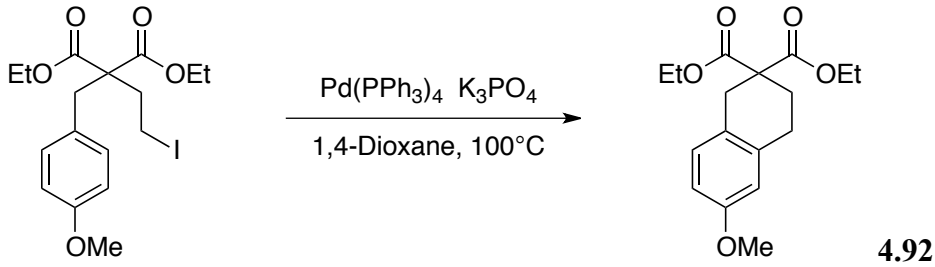
4.91

Diethyl (2-iodoethyl)(4-trifluoromethylbenzyl)malonate. Primary iodide **4.66** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide tetrahydronaphthalene product **4.91** as a clear oil (58.5 mg, 68% Yield).



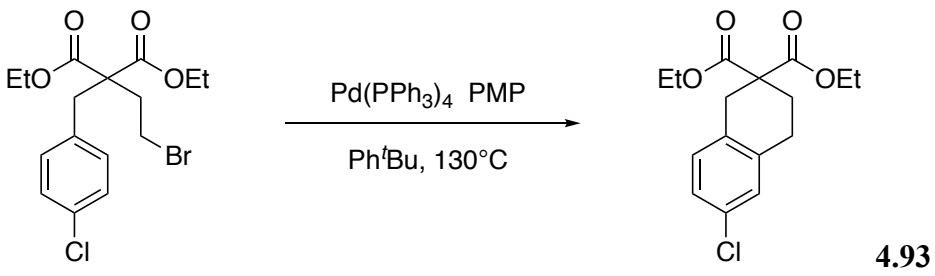
4.92

Diethyl (2-bromoethyl)(4-methoxybenzyl)malonate. Primary bromide **4.59** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure C. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide tetrahydronaphthalene product **4.92** as a clear oil (59.8 mg, 78% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.4 Hz, 1H), 6.72 (m, 1H), 6.61 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 4H), 3.78 (s, 3H), 3.22 (s, 2H), 2.84 (s, *J* = 7.0 Hz, 2H), 2.32 (t, *J* = 7.0 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 171.38, 157.80, 135.73, 129.69, 125.69, 113.11, 112.41, 61.37, 55.17, 53.77, 33.95, 28.03, 26.25, 14.02. **IR** (Thin Film, cm^{-1}): 2980, 1732, 1612, 1504, 1445, 1225, 1051, 858, 808. **LRMS** (ESI): Calculated for $[C_{17}H_{22}O_5H]^+$ 307.16, found 307.22.



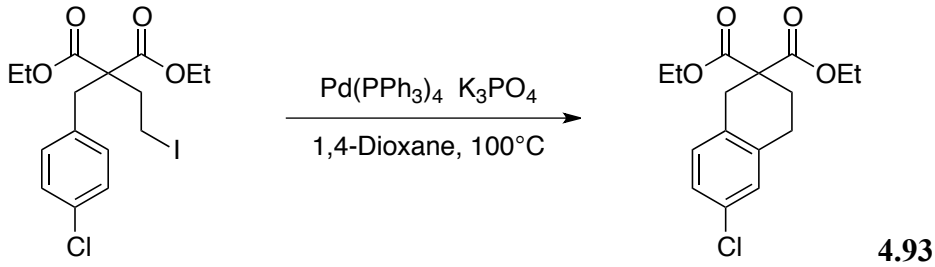
4.92

Diethyl (2-iodoethyl)(4-methoxybenzyl)malonate. Primary iodide **4.64** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide tetrahydronaphthalene product **4.92** as a clear oil (50.6 mg, 66% Yield).



4.93

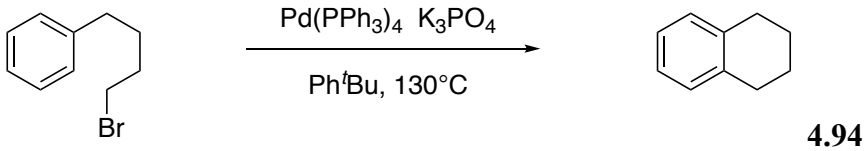
Diethyl (2-bromoethyl)(4-chlorobenzyl)malonate. Primary bromide **4.60** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure C. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide tetrahydronaphthalene product **4.93** as a clear oil (58.4 mg, 75% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.10 (m, 1H), 7.06 (m, 2H), 4.20 (q, *J* = 7.2 Hz, 4H), 3.23 (s, 2H), 2.83 (t, *J* = 6.6 Hz, 2H), 2.32 (t, *J* = 6.6 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 171.08, 136.47, 132.12, 131.55, 130.08, 128.38, 126.17, 61.52, 53.46, 34.15, 27.73, 25.84, 14.00, 13.97. **IR** (Thin Film, cm^{-1}): 2981, 1732, 1486, 1263, 1180, 1087, 1019, 858, 809. **LRMS** (ESI): Calculated for $[C_{16}H_{19}ClO_4H]^+$ 311.11, found 311.08.



4.93

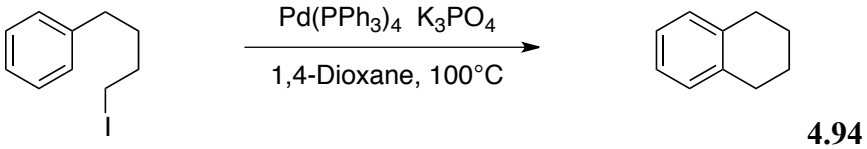
Diethyl (4-chlorobenzyl)(2-iodoethyl)malonate. Primary iodide **4.65** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash

chromatography using hexanes/ethyl acetate (40:1) to provide tetrahydronaphthalene product **4.93** as a clear oil (45.8 mg, 59% Yield).



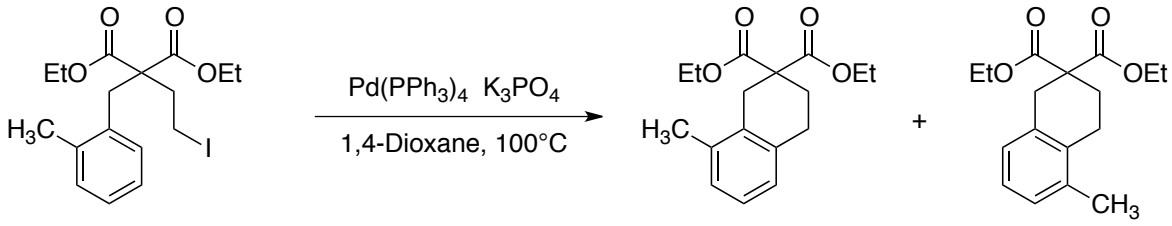
4.94

(4-Bromobutyl)benzene. Primary bromide **4.74** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure D. The yield of the crude product was determined via gas chromatography using cyclooctane as internal standard (89% Yield). All physical and spectroscopic data were in accordance with literature data.



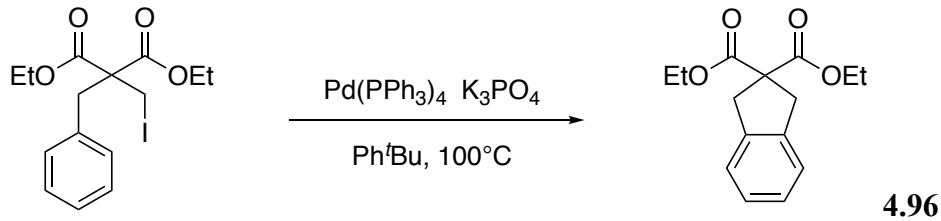
4.94

(4-Iodobutyl)benzene. Primary iodide **4.73** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The yield of the crude product was determined via gas chromatography using cyclooctane as internal standard (51% Yield). All physical and spectroscopic data were in accordance with literature data.



4.95A **4.95B**

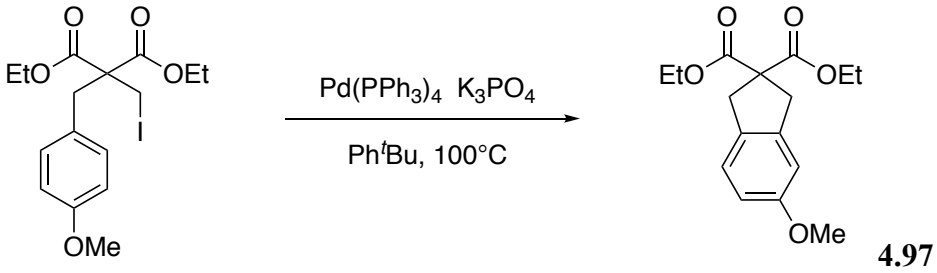
Diethyl (2-iodoethyl)(2-methylbenzyl)malonate. Primary iodide **4.67** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide a 50:50 mixture of tetrahydronaphthalene products **4.95A** and **4.95B** as a clear oil (54.4 mg, 75% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.04 (m, 2H), 7.01 (m, 3H), 6.94 (m, 1H), 4.20 (m, 8H), 3.29 (s, 2H), 3.15 (s, 2H), 2.83 (t, J = 6.6 Hz, 2H), 2.73 (t, J = 6.6 Hz, 2H), 2.37 (t, J = 6.6 Hz, 2H), 2.32 (t, J = 6.6 Hz, 2H), 2.30 (s, 3H), 2.21 (s, 3H), 1.25 (m, 12H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 171.58, 171.36, 136.28, 136.13, 134.62, 133.38, 133.06, 132.16, 127.60, 127.51, 126.64, 126.36, 125.65, 125.61, 61.43, 61.36, 53.87, 53.27, 35.18, 31.89, 28.18, 27.70, 26.32, 23.69, 19.59, 19.41, 14.00. **IR** (Thin Film, cm^{-1}): 2978, 2935, 1733, 1463, 1257, 1176, 1090, 1024, 862, 767. **LRMS** (ESI): Calculated for $[C_{17}H_{22}O_4H]^+$ 291.16, found 291.05.



4.96

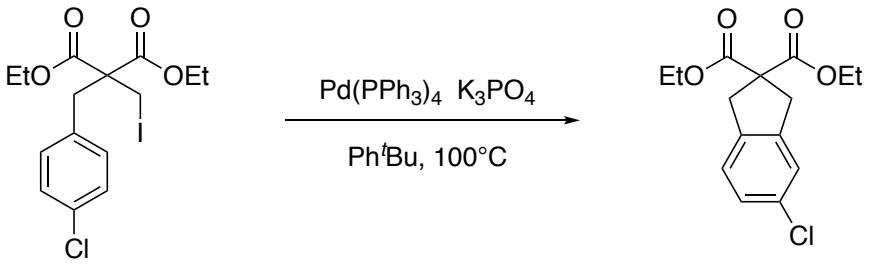
Diethyl benzyl(iodomethyl)malonate. Primary iodide **4.70** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure B. The yield of the crude product was determined by NMR

spectroscopy using 1,3,5-trimethoxybenzene as internal standard (88% Yield). The crude product was then purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide indane product **4.96** as a clear oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.21 (m, 2H), 7.18 (m, 2H), 4.23 (q, J = 6.6 Hz, 4H), 3.62 (s, 4H), 1.28 (t, J = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 171.67, 139.98, 126.87, 124.18, 61.68, 60.30, 40.47, 14.02. **IR** (Thin Film, cm^{-1}): 2980, 2929, 1732, 1461, 1280, 1246, 1188, 1068, 861, 740. **LRMS** (ESI): Calculated for $[C_{15}H_{18}O_4H]^+$ 263.13, found 263.16.



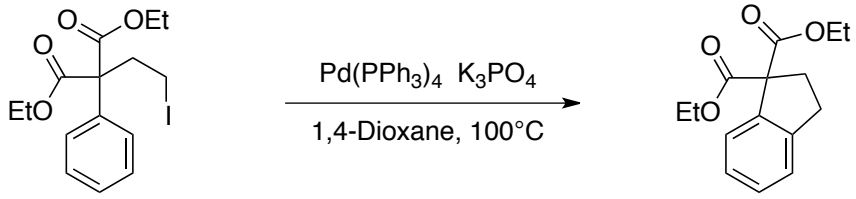
4.97

Diethyl (iodomethyl)(4-methoxybenzyl)malonate. Primary iodide **4.71** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure B. The yield of the crude product was determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (66% Yield). The crude product was then purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide indane product **4.97** as a clear oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.10 (d, J = 7.8 Hz, 1H), 6.76 (s, 1H), 6.74 (m, 1H), 4.22 (q, J = 7.2 Hz, 4H), 3.79 (s, 3H), 3.58 (s, 2H), 3.54 (s, 2H), 1.28 (t, J = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 171.67, 159.12, 141.47, 131.90, 124.74, 113.01, 109.50, 61.66, 60.79, 55.38, 40.61, 39.66, 14.02. **IR** (Thin Film, cm^{-1}): 3231, 3019, 1455, 1302, 1135, 1061, 972, 737, 700, 524. **LRMS** (ESI): Calculated for $[C_{16}H_{20}O_5H]^+$ 293.14, found 293.23.



4.98

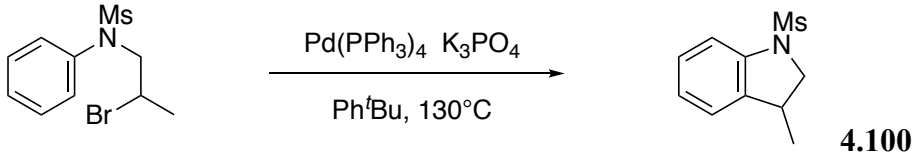
Diethyl (4-chlorobenzyl)(iodomethyl)malonate. Primary iodide **4.72** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure B. The yield of the crude product was determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (74% Yield). The crude product was then purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide indane product **4.98** as a clear oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.19 (s, 1H), 7.14 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 4H), 3.58 (s, 2H), 3.56 (s, 2H), 1.28 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 171.28, 141.97, 138.47, 132.60, 127.10, 125.24, 124.43, 61.82, 40.22, 39.85, 13.99. **IR** (Thin Film, cm^{-1}): 2982, 1732, 1473, 1274, 1245, 1189, 1069, 962. **LRMS** (ESI): Calculated for $[C_{15}H_{17}ClO_4H]^+$ 297.09, found 297.13.



4.99

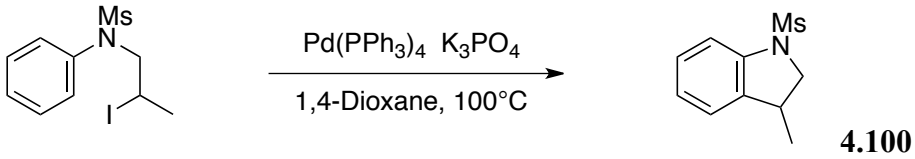
Diethyl (2-iodoethyl)phenylmalonate. Primary iodide **4.69** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide indane product **4.99** as a clear oil (54.7 mg, 83% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.2 Hz, 1H), 7.25 (m, 2H), 4.23 (m, 4H),

3.05 (t, J = 7.2 Hz, 2H), 2.72 (t, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 170.77, 136.92, 128.13, 128.06, 127.38, 63.10, 61.40, 31.39, 28.85, 14.00, 13.95, 9.29. **IR** (Thin Film, cm^{-1}): 2980, 1731, 1238, 1025, 698, 509. **LRMS** (ESI): Calculated for $[C_{15}H_{18}O_4H]^+$ 263.13, found 263.17.



4.100

***N*-(2-Bromopropyl)-*N*-phenylmethanesulfonamide.** Secondary bromide **4.39** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure D. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide indoline product **4.100** as a pale orange solid (28.5 mg, 54% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.42 (d, J = 7.8 Hz, 1H), 7.22 (m, 2H), 7.08 (t, J = 7.2 Hz, 2H), 4.16 (m, 1H), 3.50 (m, 2H), 2.90 (s, 3H), 1.38 (d, J = 6.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.47, 136.26, 128.14, 124.21, 123.75, 113.50, 58.03, 34.74, 34.27, 19.47. **IR** (Thin Film, cm^{-1}): 3249, 1617, 1520, 1479, 1327, 1147, 979, 916, 844. **LRMS** (ESI): Calculated for $[C_{10}H_{13}NO_2SH]^+$ 212.08, found 212.07.

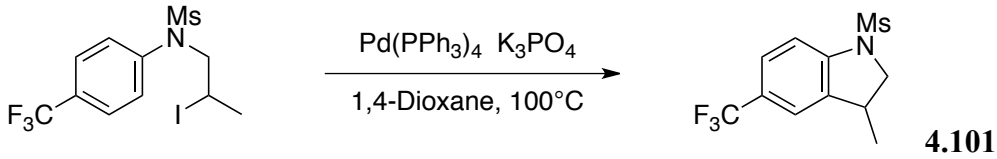


4.100

***N*-(2-Iodopropyl)-*N*-phenylmethanesulfonamide.** Secondary iodide **4.38** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash

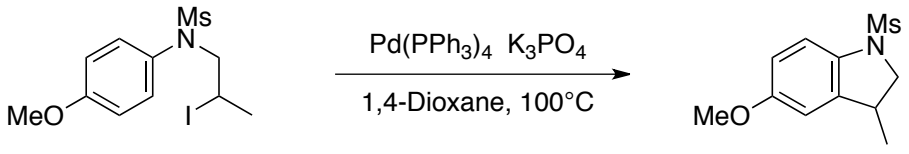
chromatography using hexanes/ethyl acetate (20:1) to provide indoline product **4.100** as a pale orange solid (43.5 mg, 82% Yield).

Large-scale (1 mmol) reaction. Iodide **4.38** (338 mg, 1.0 mmol) was set up to react with $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) and K_3PO_4 (424 mg, 2.0 mmol) in 1,4-dioxane (2.0 mL 0.5 M) following C-H Alklation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (10:1) to provide indoline product **4.100** as a pale orange solid (177 mg, 84% Yield).



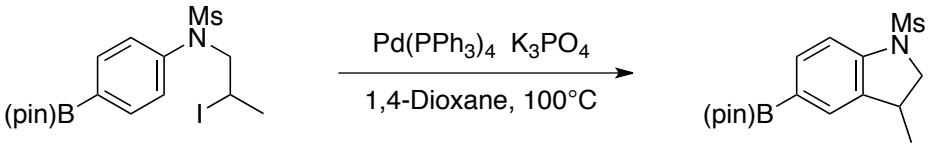
4.101

***N*-(2-Iodopropyl)-*N*-(4-trifluoromethylphenyl)methanesulfonamide.** Secondary iodide **4.41** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide indoline product **4.101** as a pale orange solid (48.8 mg, 70% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.50 (m, 2H), 7.44 (s, 1H), 4.23 (m, 1H), 3.59 (m, 1H), 3.54 (m, 1H), 2.95 (s, 3H), 1.42 (s, J = 7.2 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 144.43, 136.87, 126.01, 125.90, 125.87, 125.80, 125.07, 123.27, 121.45, 121.43, 112.98, 58.16, 35.08, 34.51, 19.43. **IR** (Thin Film, cm^{-1}): 2931, 1617, 1492, 1338, 1161, 1119, 985, 833, 770, 551. **LRMS** (ESI): Calculated for $[C_{11}H_{12}F_3NO_2SH]^+$ 280.06, found 280.11.



4.102

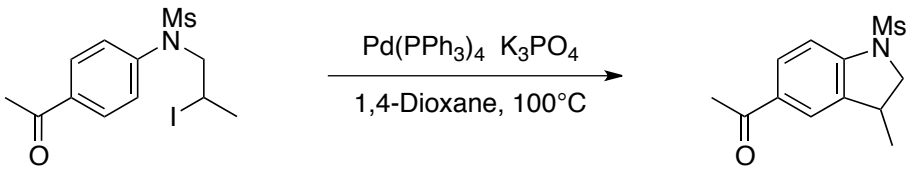
***N*-(2-Iodopropyl)-*N*-(4-methoxyphenyl)methanesulfonamide.** Secondary iodide **4.40** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide indoline product **4.85** as a pale orange solid (39.6 mg, 66% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.4 Hz, 1H), 6.78 (s, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 4.17 (m, 1H), 3.82 (s, 3H), 3.49 (m, 2H), 2.85 (s, 3H), 1.38 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 156.90, 138.10, 134.97, 114.77, 112.70, 110.54, 58.38, 55.71, 35.04, 33.76, 19.27. **IR** (Thin Film, cm^{-1}): 2964, 1596, 1485, 1344, 1232, 1159, 1032, 1159, 1032, 982, 850, 770. **LRMS** (ESI): Calculated for $[C_{11}H_{15}NO_3SH]^+$ 242.09, found 242.02.



4.103

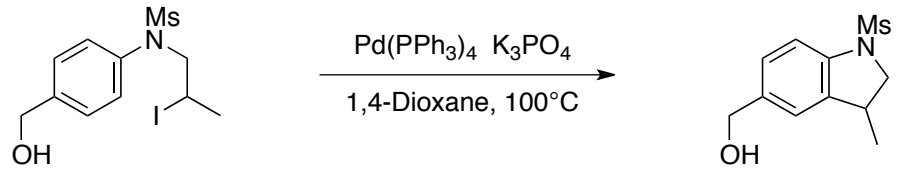
***N*-(2-Iodopropyl)-*N*-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) methanesulfonamide.** Secondary iodide **4.42** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide indoline product **4.85** as a pale orange solid (60.4 mg, 72% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.8 Hz, 1H), 7.68 (s, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 4.17 (dd, *J* = 9.6 Hz, 9.0 Hz, 1H), 3.51 (m, 2H), 2.90 (s, 3H), 1.40 (d, *J* = 6.6 Hz,

3H), 1.37 (s, 12H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 135.56, 135.42, 130.54, 112.59, 83.81, 58.15, 34.53, 34.48, 24.89, 24.79, 19.53. **IR** (Thin Film, cm^{-1}): 2976, 1608, 1351, 1161, 1122, 963, 861, 772. **LRMS** (ESI): Calculated for $[C_{16}H_{24}BNO_4SNa]^+$ 360.23, found 360.44.



4.104

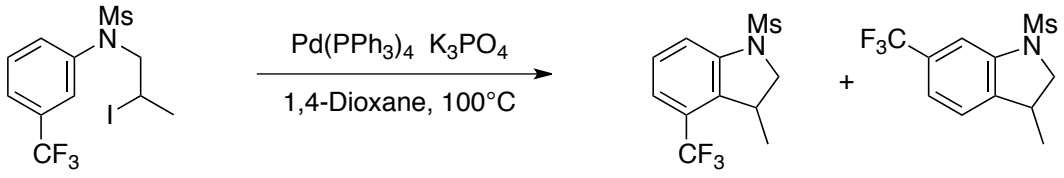
***N*-(4-Acetylphenyl)-*N*-(2-iodopropyl)methanesulfonamide.** Secondary iodide **4.51** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide indoline product **4.104** as a pale orange solid (48.5 mg, 77% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.86 (d, J = 8.4 Hz, 1H), 7.84 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 4.23 (t, J = 9.0 Hz, 1H), 3.58 (dd, J = 9.6 Hz, 7.2 Hz, 1H), 3.52 (m, 1H), 2.96 (s, 3H), 2.59 (s, 3H), 1.42 (d, J = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 196.65, 145.61, 136.71, 133.00, 129.93, 124.31, 112.31, 58.26, 35.27, 34.29, 26.49, 19.52. **IR** (Thin Film, cm^{-1}): 2965, 1675, 1604, 1483, 1351, 1258, 1161, 985, 771. **LRMS** (ESI): Calculated for $[C_{12}H_{15}NO_3SNa]^+$ 276.31, found 276.30.



4.105

***N*-(4-(Hydroxymethyl)phenyl)-*N*-(2-iodopropyl)methanesulfonamide.** Secondary iodide **4.52** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was

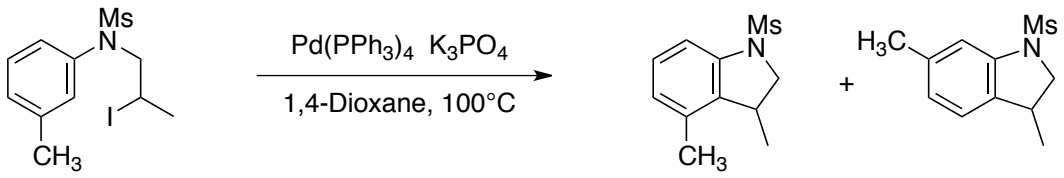
purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide indoline product **4.105** as a pale orange solid (34.5 mg, 57% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.4 Hz, 1H), 7.25 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 4.68 (s, 2H), 4.18 (t, *J* = 8.4 Hz, 1H), 3.51 (m, 2H), 2.89 (s, 3H), 1.68 (bs, 1H), 1.38 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.10, 136.79, 128.62, 127.21, 123.27, 113.48, 65.02, 58.24, 34.71, 34.23, 19.43. **IR** (Thin Film, cm^{-1}): 3522, 2928, 1485, 1343, 1159, 985, 771, 557. **LRMS** (ESI): Calculated for $[C_{11}H_{15}NO_3SNa]^+$ 264.80, found 264.35.



4.106a **4.106b**

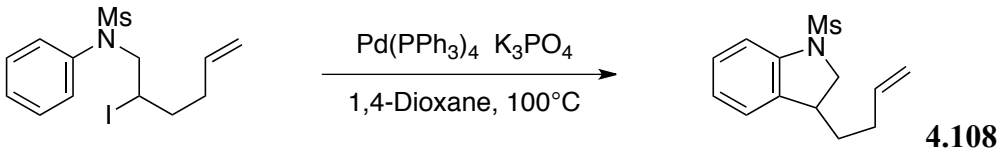
***N*-(2-Iodopropyl)-*N*-(3-trifluoromethylphenyl)methanesulfonamide.** Secondary iodide **4.45** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide indoline products **4.106a** and **4.106b** as pale orange solids (56.7 mg, 81% Yield, 2.4:1 A:B). **4.106a: ^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 7.8 Hz), 7.31 (d, *J* = 7.2 Hz), 3.94 (dd, *J* = 10.2 Hz, 8.4 Hz, 1H), 3.84 (dd, *J* = 9.6 Hz, 1.8 Hz, 1H), 3.68 (m, 1H), 2.94 (s, 3H), 1.36 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 142.54, 134.38, 128.90, 127.36, 127.15, 124.87, 123.06, 120.81, 120.78, 120.75, 120.72, 116.49, 58.31, 34.72, 34.31, 21.09. **IR** (Thin Film, cm^{-1}): 2934, 1596, 1453, 1353, 1318, 1252, 1162, 1122, 997, 801, 549. **LRMS** (ESI): Calculated for $[C_{11}H_{12}F_3NO_2SH]^+$ 280.06, found 280.10. **4.106b: ^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 4.22 (m, 1H), 3.58 (m, 1H), 3.54 (m, 1H), 2.95

(s, 3H), 1.41 (d, J = 7.2 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 142.04, 124.55, 120.85, 110.18, 58.04, 34.96, 34.69, 19.38. **IR** (Thin Film, cm^{-1}): 2933, 1432, 1351, 1321, 1276, 1162, 1123, 991, 824, 551. **LRMS** (ESI): Calculated for $[C_{11}H_{12}F_3NO_2SH]^+$ 280.06, found 280.11.



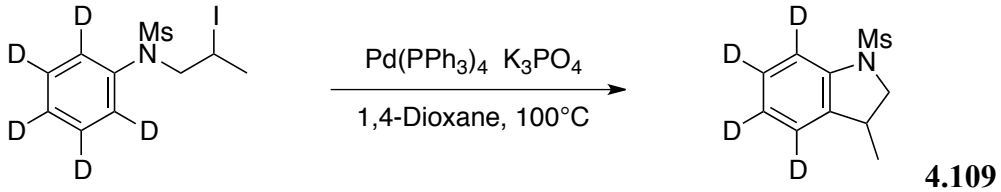
4.107a **4.107b**

***N*-(2-Iodopropyl)-*N*-(3-tolyl)methanesulfonamide.** Secondary iodide **4.46** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The yield of the crude product was determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (91% Yield, 2.0:1 A:B). The crude product was then purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide a mixture of indoline products **4.107a** and **4.107b** as a pale orange solid**. ^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.24 (s, 2H), 7.13 (t, J = 9.2 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.87 (t, J = 7.6 Hz, 2H), 4.15 (m, 1H), 3.92 (m, 1H), 3.74 (m, 1H), 3.47 (m, 3H), 2.89 (s, 3H), 2.88 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H), 1.34 (d, J = 6.4 Hz, 3H), 1.30 (d, J = 6.4 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 138.31, 134.68, 133.43, 128.25, 125.23, 124.46, 123.86, 114.19, 110.85, 58.36, 57.99, 34.42, 34.08, 21.57, 19.76, 19.59, 18.20. **IR** (Thin Film, cm^{-1}): 2964, 2927, 1610, 1455, 1346, 1246, 1159, 1077, 956, 771, 550. **LRMS** (ESI): Calculated for $[C_{11}H_{15}NO_2SH]^+$ 226.09, found 226.00.



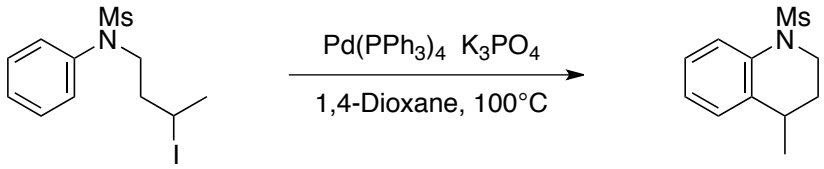
4.108

***N*-(2-Iodohex-5-enyl)-*N*-phenylmethanesulfonamide.** Secondary iodide **4.50** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (10:1) to provide indoline product **4.108** as a pale orange solid (50.1 mg, 80% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 1H), 7.23 (m, 2H), 7.08 (t, *J* = 7.2 Hz, 1H), 5.85 (m, 1H), 5.09 (dd, *J* = 26.4 Hz, 10.2 Hz, 2H), 4.10 (t, *J* = 9.6 Hz, 1H), 3.65 (m, 1H), 3.41 (m, 1H), 2.90 (s, 3H), 2.20 (m, 2H), 1.96 (m, 1H), 1.69 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.63, 137.40, 134.88, 128.28, 124.63, 123.60, 115.61, 113.41, 56.18, 39.35, 34.23, 33.91, 31.13. **IR** (Thin Film, cm^{-1}): 2927, 1593, 1491, 1342, 1154, 962, 775, 697, 542. **LRMS** (ESI): Calculated for $[C_{13}H_{17}NO_2SNa]^+$ 274.33, found 274.38.



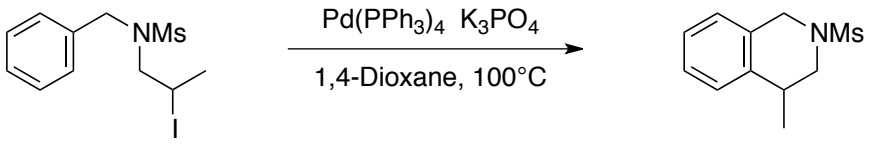
4.109

***N*-(2-Iodopropyl)-*N*-(perdeuterophenyl)methanesulfonamide.** Secondary iodide **4.47** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was then purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide indoline product **4.109** as a pale orange solid**. ^{1}H-NMR** (600 MHz, $CDCl_3$): δ 4.16 (m, 1H), 3.50 (m, 2H), 2.89 (s, 3H), 1.38 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.40, 136.16, 127.79, 127.63, 127.47, 123.97, 123.81, 123.65, 123.41, 123.25, 123.09, 113.30, 113.13, 112.97, 58.04, 34.72, 34.23, 19.46. **IR** (Thin Film, cm^{-1}): 2965, 2874, 2283, 1582, 1454, 1399, 1346, 1228, 1159, 1078, 975, 768. **LRMS** (ESI): Calculated for $[C_{10}H_9D_4NO_2SH]^+$ 216.10, found 216.16.



4.110

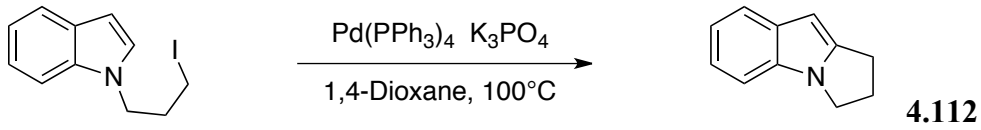
***N*-(3-Iodobutyl)-*N*-phenylmethanesulfonamide.** Secondary iodide **4.48** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide tetrahydroquinoline product **4.110** as a pale orange solid (32.0 mg, 57% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.73 (m, 1H), 7.27 (m, 1H), 7.21 (m, 1H), 7.14 (m, 1H), 3.85 (m, 2H), 3.00 (m, 1H), 2.93 (s, 3H), 2.12 (m, 1H), 1.39 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 136.28, 134.16, 128.53, 126.86, 124.59, 122.49, 44.16, 38.69, 30.69, 30.29, 22.23. **IR** (Thin Film, cm^{-1}): 2931, 2360, 1487, 1339, 1156, 957, 839, 773 **LRMS** (ESI): Calculated for $[C_{11}H_{15}NO_2SH]^+$ 226.09, found 226.09.



4.111

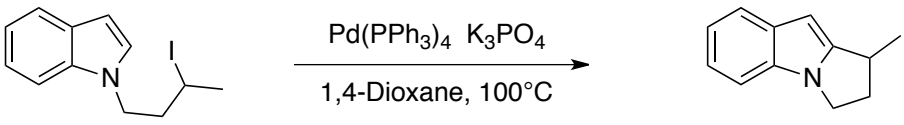
***N*-Benzyl-*N*-(2-iodopropyl)methanesulfonamide.** Secondary iodide **4.49** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide tetrahydroisoquinoline product **4.111** as a pale orange solid (34.2 mg, 61% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.28-7.22 (m, 3H), 7.11 (d, *J* = 7.2 Hz, 1H), 4.55 (d, *J* = 15.0 Hz, 1H), 4.38 (d, *J* = 15.0 Hz, 1H), 3.50 (m, 1H), 3.56 (m, 1H), 3.14 (m, 1H), 3.87 (s, 3H), 1.39 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 138.60, 131.09, 127.92, 127.15, 126.46, 126.24, 49.72, 47.62, 35.25, 32.93, 20.14. **IR** (Thin

Film, cm^{-1}): 2965, 2928, 1454, 1329, 1156, 1037, 961, 808, 754, 519. **LRMS** (ESI): Calculated for $[C_{11}H_{15}NO_2SH]^+$ 226.09, found 226.09.



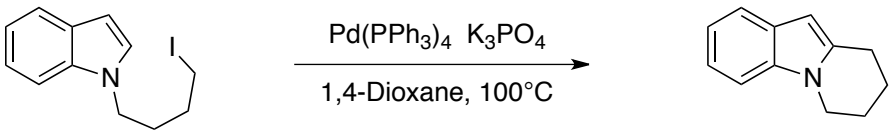
4.112

***N*-(3-Iodopropyl)indole.** Primary iodide **4.77** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The yield of the crude product was determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (51% Yield). All physical and spectroscopic data were in accordance with literature data.[18]



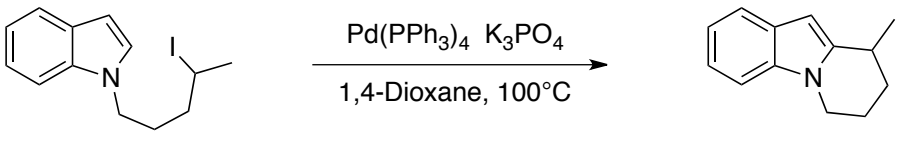
4.113

***N*-(3-Iodobutyl)indane.** Secondary iodide **4.83** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The yield of the crude product was determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (71% Yield). All physical and spectroscopic data were in accordance with literature data.[19]



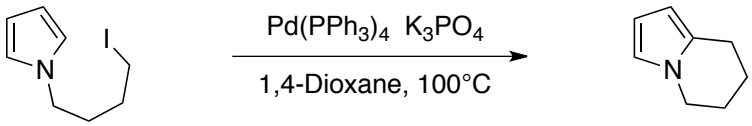
4.114

***N*-(4-Iodobutyl)indane.** Primary iodide **4.78** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The yield of the crude product was determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (70% Yield). All physical and spectroscopic data were in accordance with literature data.[20]



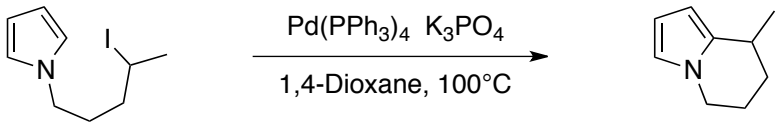
4.115

***N*-(4-Iodopentyl)indane.** Secondary iodide **4.84** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The yield of the crude product was determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (90% Yield). All physical and spectroscopic data were in accordance with literature data.[19]



4.116

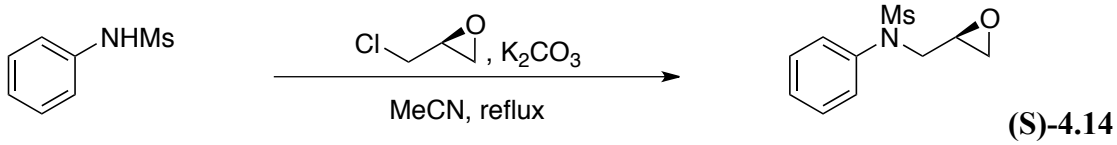
***N*-(4-Iodobutyl)pyrrole.** Primary iodide **4.86** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The yield of the crude product was determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (64% Yield). All physical and spectroscopic data were in accordance with literature data.[21]



4.117

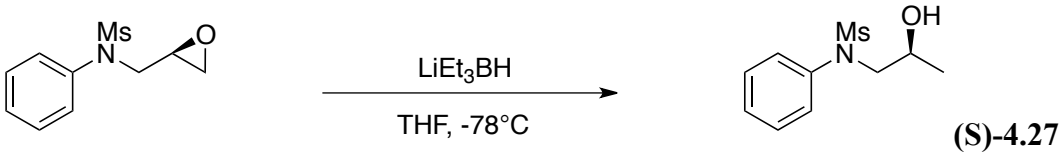
***N*-(4-Iodopentyl)pyrrole.** Secondary iodide **4.89** was made to react with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The yield of the crude product was determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (95% Yield). All physical and spectroscopic data were in accordance with literature data.[16]

4.2.3 Stereochemical Experiments



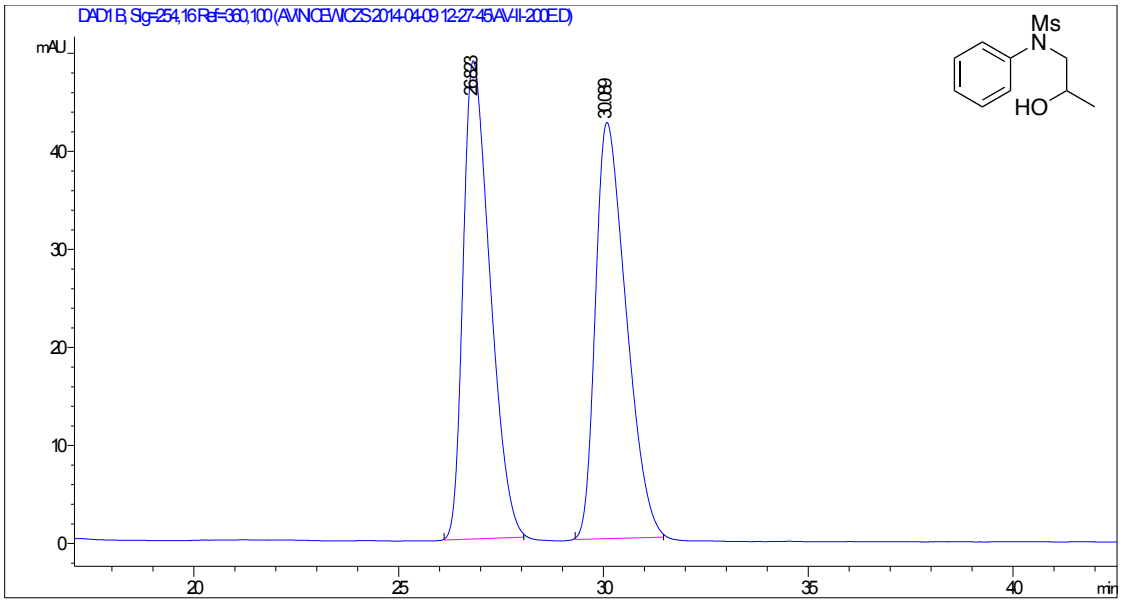
(S)-4.14

((S)-4.14): *N*-((S)-2,3-Epoxypropyl)-*N*-phenylmethanesulfonamide. Following General Procedure B, methanesulfonamide **4.1** (3.0 g, 17.5 mmol) was alkylated with S-(+)-epichlorohydrin (6.5 g, 70 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide epoxide **(S)-4.14** as a white solid (61% Yield). All physical and spectroscopic data were in accordance with racemate **4.14**.

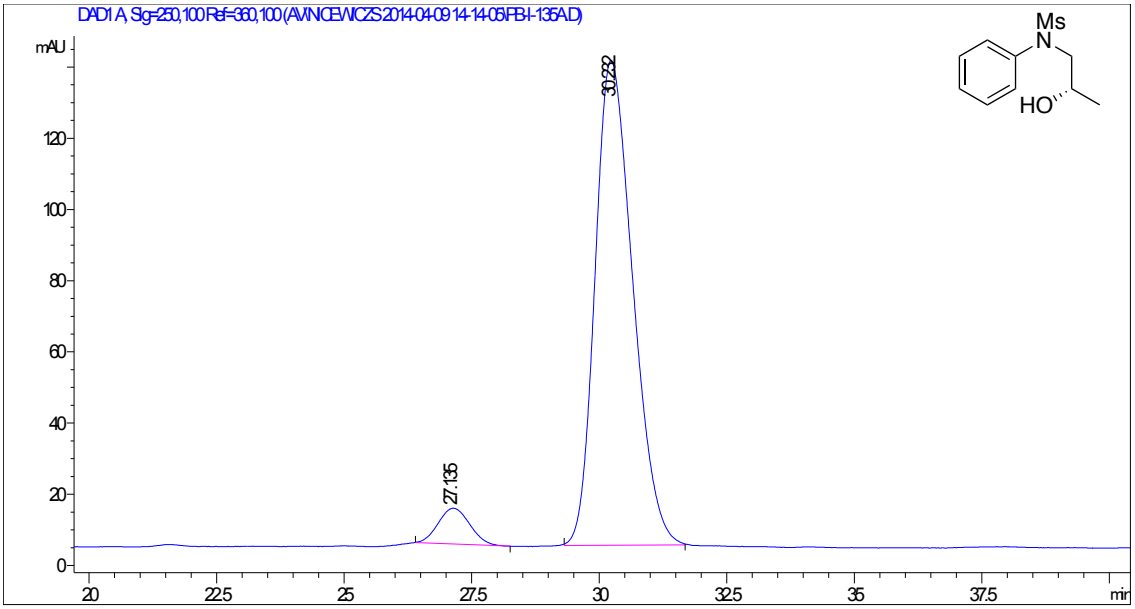


(S)-4.27

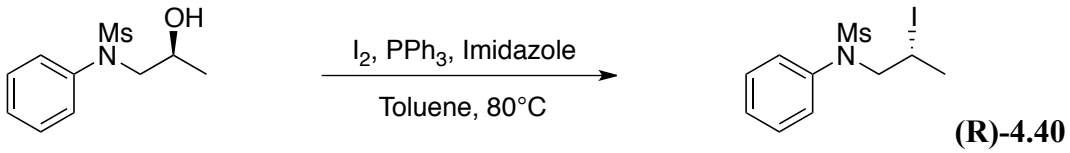
((S)-4.27): *N*-((S)-2-Hydroxypropyl)-*N*-phenylmethanesulfonamide. Following General Procedure D, epoxide **(S)-4.14** (2.45 g, 10.7 mmol) was reduced with super hydride (1M in THF, 12.9 mL, 12.9 mmol). The crude product was purified by flash chromatography using hexanes/ethyl acetate (1:1) to provide secondary alcohol **(S)-4.27** as a white solid (58% Yield). All physical and spectroscopic data were in accordance with racemate **4.27**. **Chiral HPLC** (Column IC, 75:25 A1:B2)**:** ee = 88.3%.



#	Time	Area	Height	Width	Area %	Symmetry
1	26.823	2223.8	48.8	0.6977	50.13	0.567
2	30.089	2212.3	42.5	0.7798	49.87	0.572

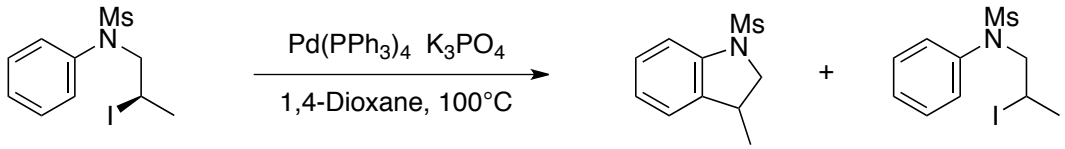


#	Time	Area	Height	Width	Area %	Symmetry
1	27.135	433.5	10.1	0.5826	5.849	0.858
2	30.232	6979.2	136.2	0.7858	94.151	0.701



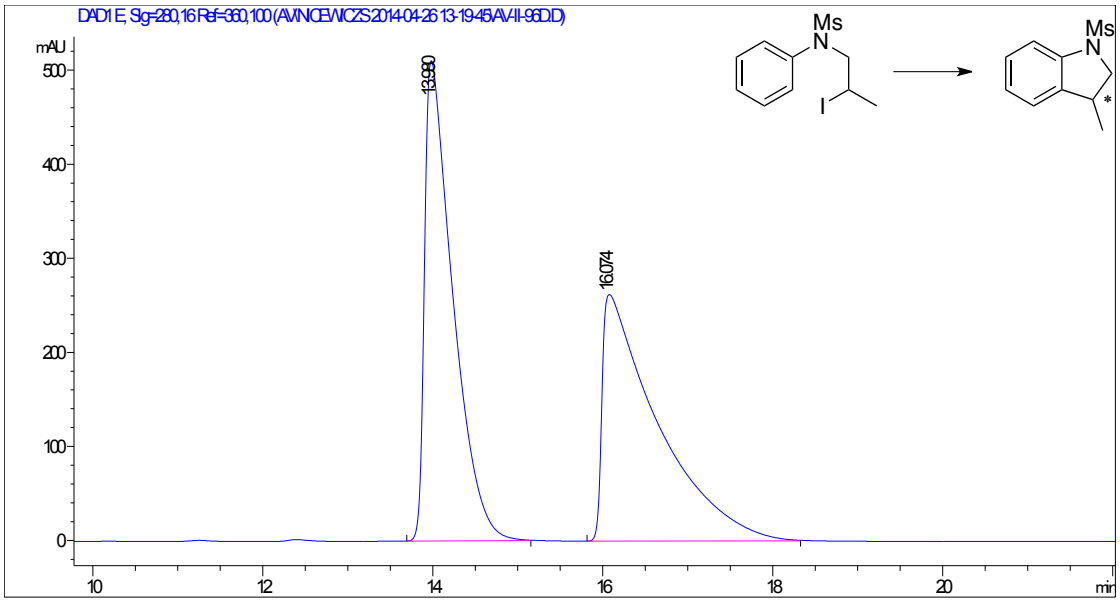
(R)-4.40

((R)-4.40): *N*-((R)-2-Iodopropyl)-*N*-phenylmethanesulfonamide. Secondary alcohol **(S)-4.27** (1.4 g, 6.2 mmol) was iodinated with molecular iodine (1.7 g, 6.5 mmol) following General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide secondary iodide **(R)-4.40** as a white solid (52% Yield). All physical and spectroscopic data were in accordance with racemate **4.40**. **Optical Rotation:** $[\alpha]_D^{20} = + 0.420$.

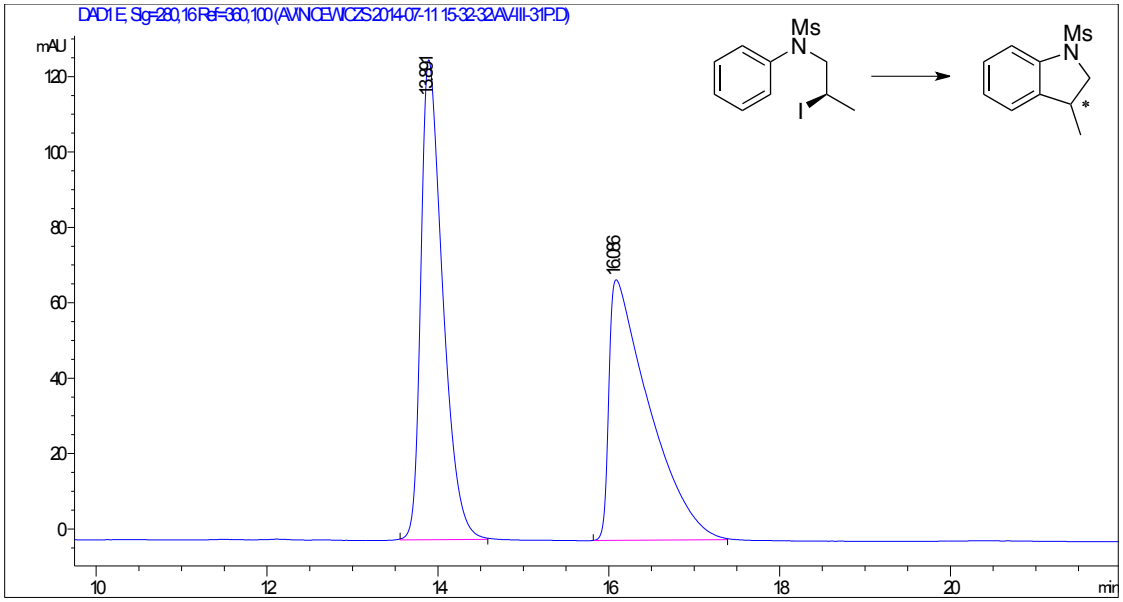


$\alpha_D^{20} = + 0.420$ ee = 0% $\alpha_D^{20} = - 0.005$

Secondary iodide (**R)-4.40** was made to react incompletely with $Pd(PPh_3)_4$ following C-H Alkylation Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide indoline cyclization product and unreacted starting material. The enantiomeric excess of the indoline product was determined to be 0% by chiral HPLC analysis using 90:10 A1:B2 mobile phase and column IA. The recovered starting material was also determined to have racemized by measurement of its optical rotation ($[\alpha]_D^{20} = - 0.005$). By contrast, stereochemistry of the starting material was retained when iodide (**R)-4.40** was treated with potassium iodide in the absence of palladium ($[\alpha]_D^{20} = + 0.423$).

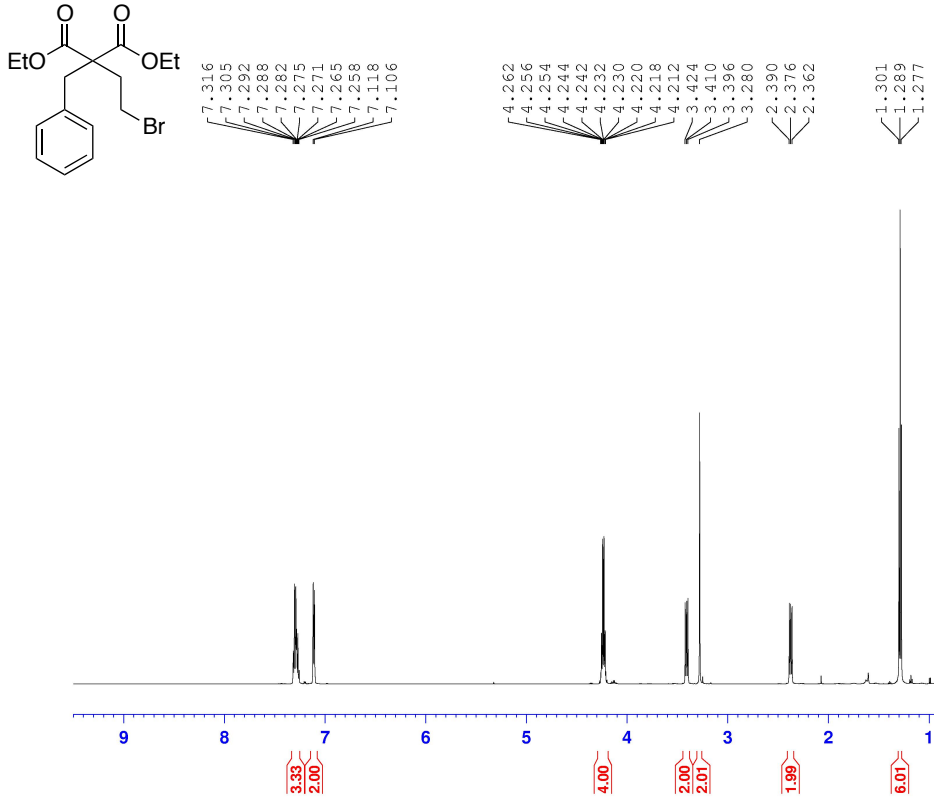


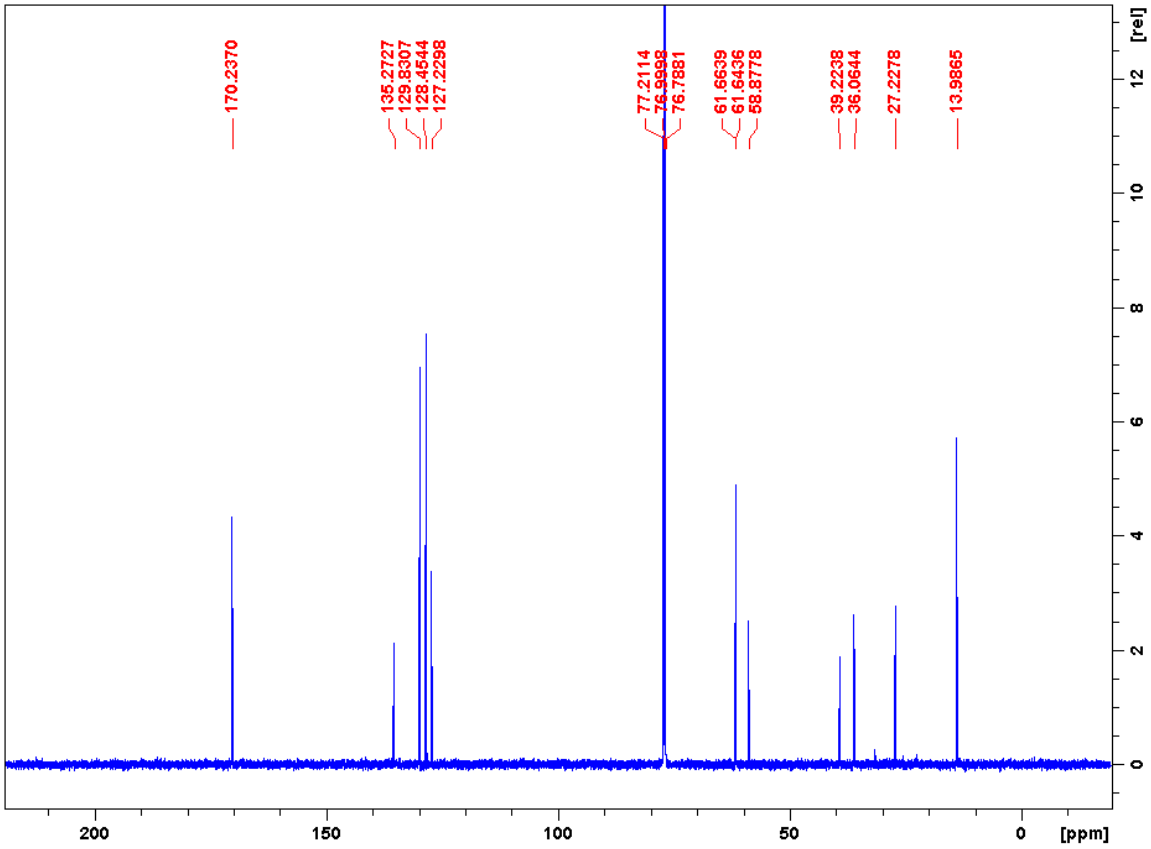
#	Time	Area	Height	Width	Area %	Symmetry
1	13.98	11846	510.7	0.3386	50.014	0.295
2	16.074	11839.4	262.2	0.6029	49.986	0.133

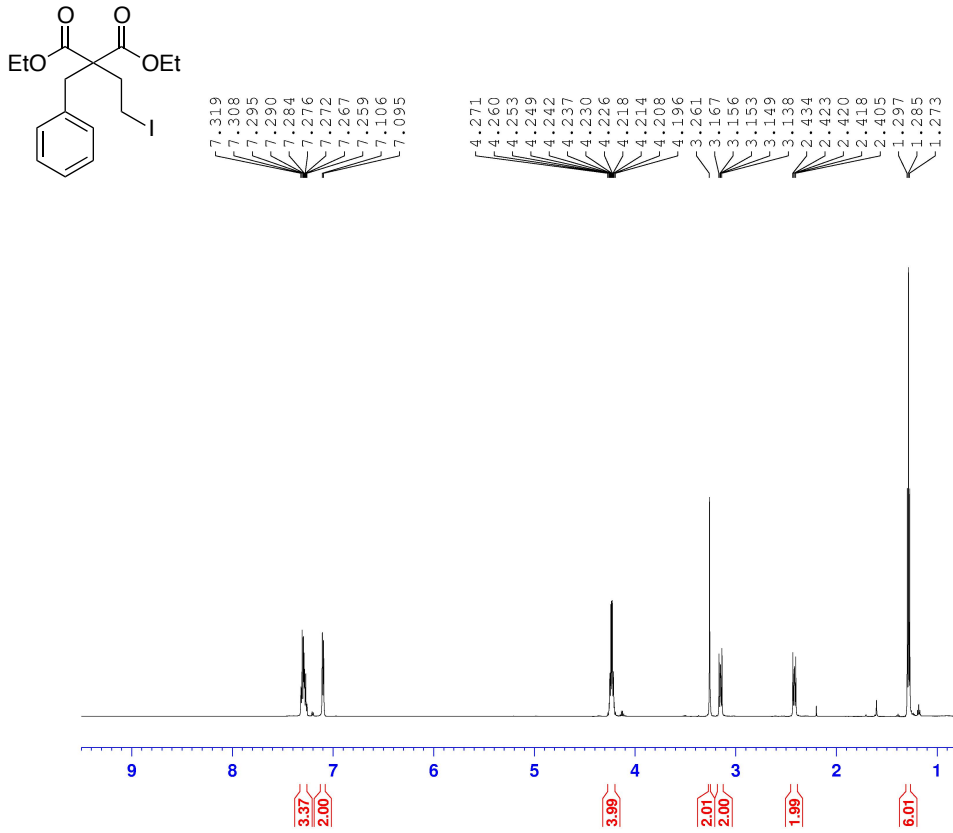


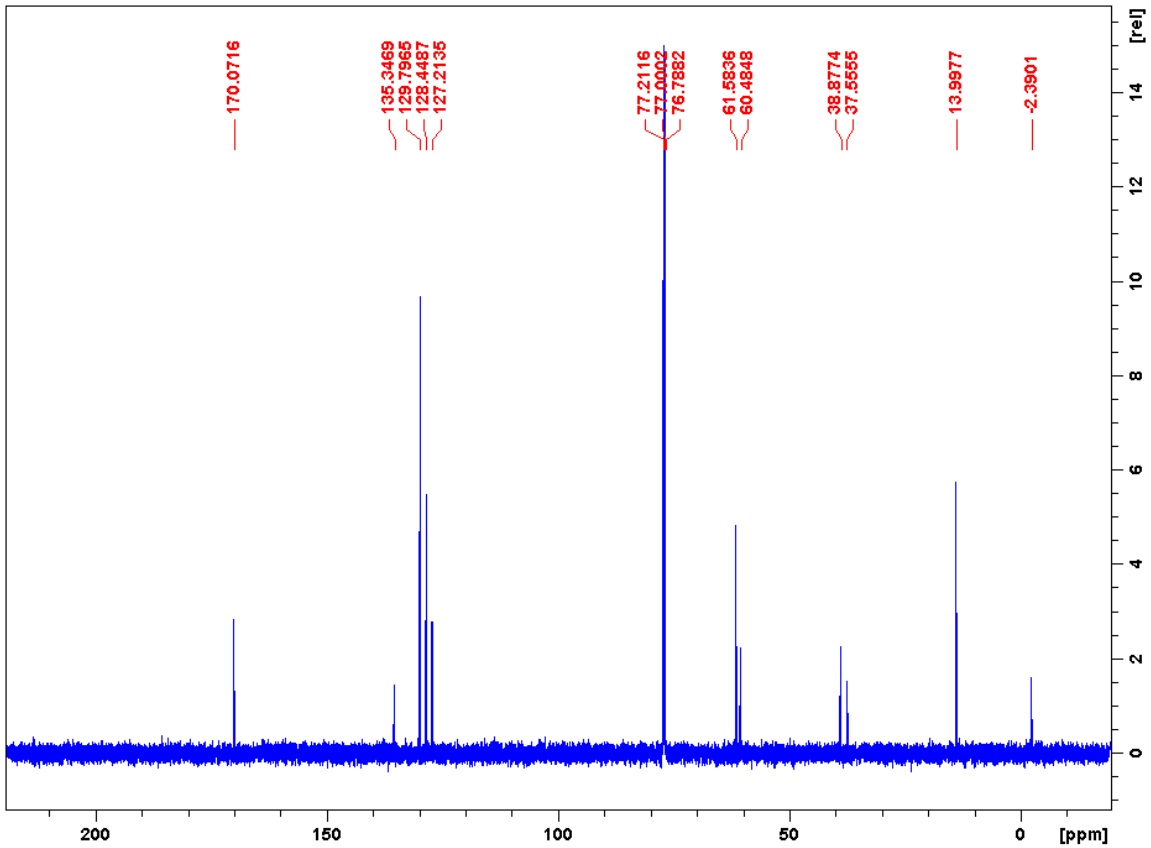
#	Time	Area	Height	Width	Area %	Symmetry
1	13.891	2270.8	127.4	0.27	50.05	0.535
2	16.086	2266.3	69.2	0.4483	49.95	0.2

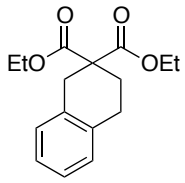
4.2.4 NMR Spectra

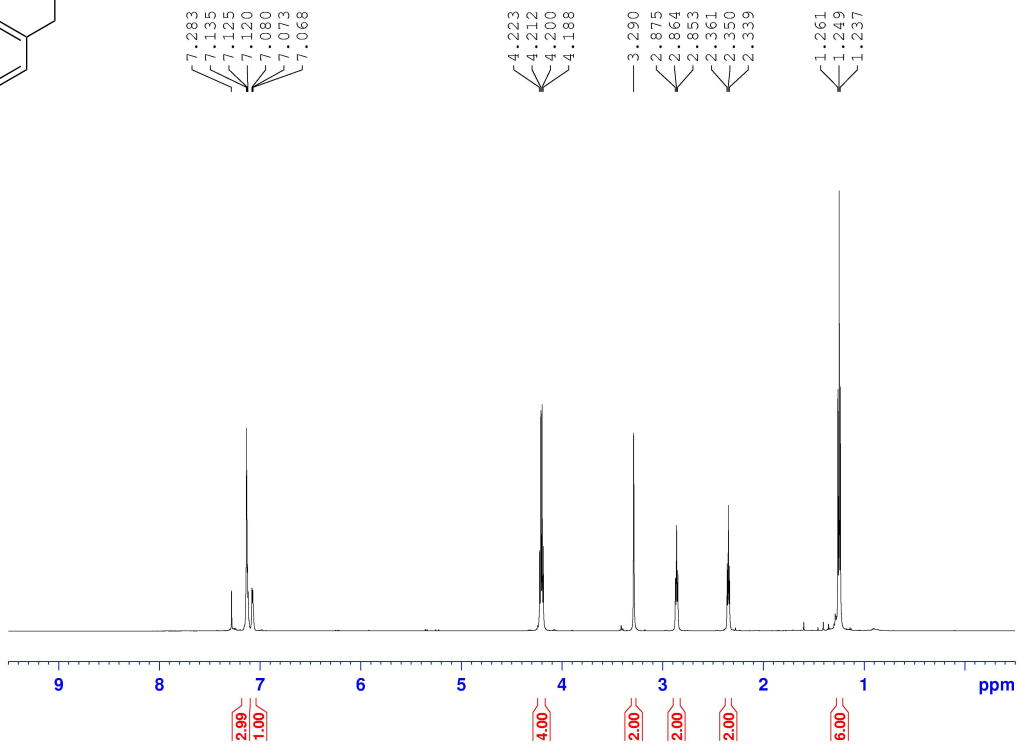





EtO
OEt
I
7.319
7.308
7.295
7.290
7.284
7.276
7.272
7.267
7.259
7.106
7.095
4.271
4.260
4.253
4.249
4.242
4.237
4.230
4.226
4.218
4.214
4.208
4.196
3.261
3.167
3.156
3.153
3.149
3.138
2.434
2.423
2.420
2.418
2.405
1.297
1.285
1.273
9
8
7
6
5
4
3
2
1
ppm
3.37
2.00
3.99
2.01
2.00
1.99
6.01


170.0716
135.3469
129.7965
128.4487
127.2135
77.2116
77.0002
76.7882
61.5836
60.4848
38.8774
37.5555
13.9977
-2.3901
[rel]
200
150
100
50
0
[ppm]


O
O
EtO
OEt


7.283
7.135
7.125
7.120
7.080
7.073
7.068
4.223
4.212
4.200
4.188
3.290
2.875
2.864
2.853
2.361
2.350
2.339
1.261
1.249
1.237
9
8
7
6
5
4
3
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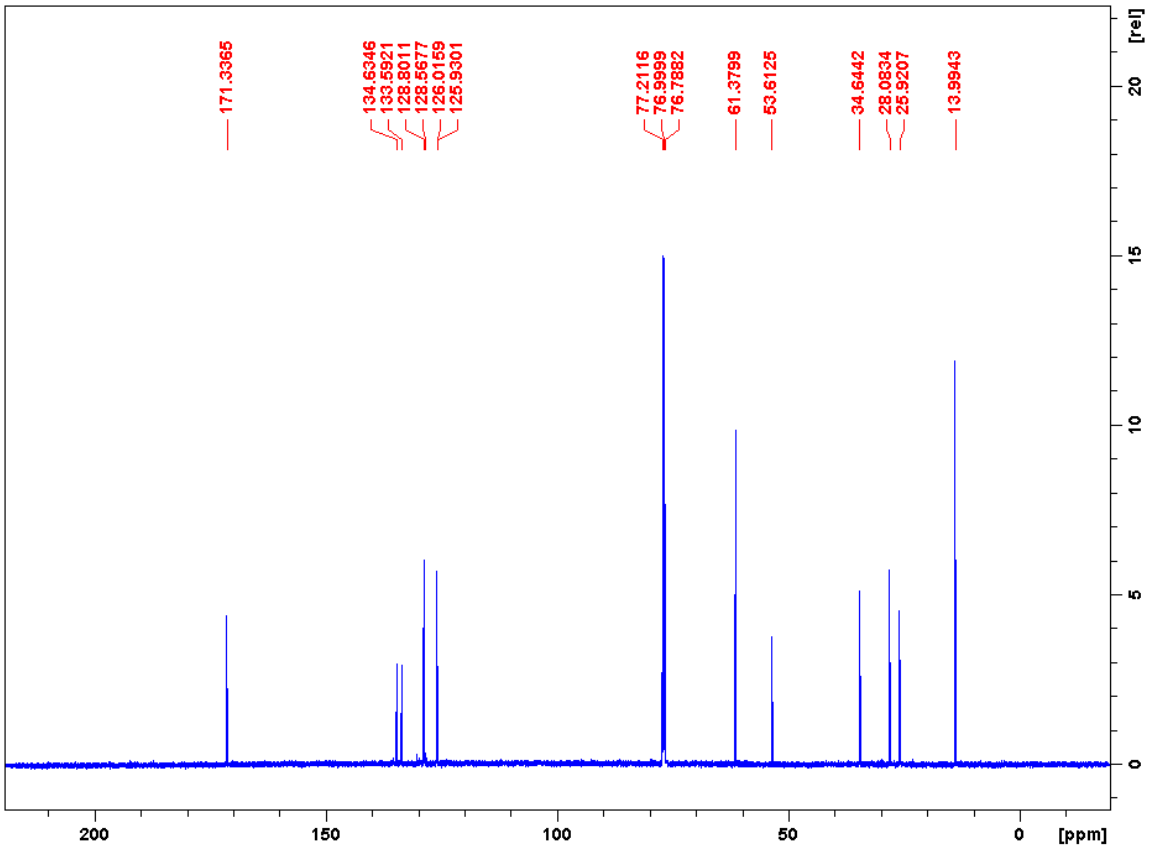
1.00
4.00
2.00
2.00
2.00
6.00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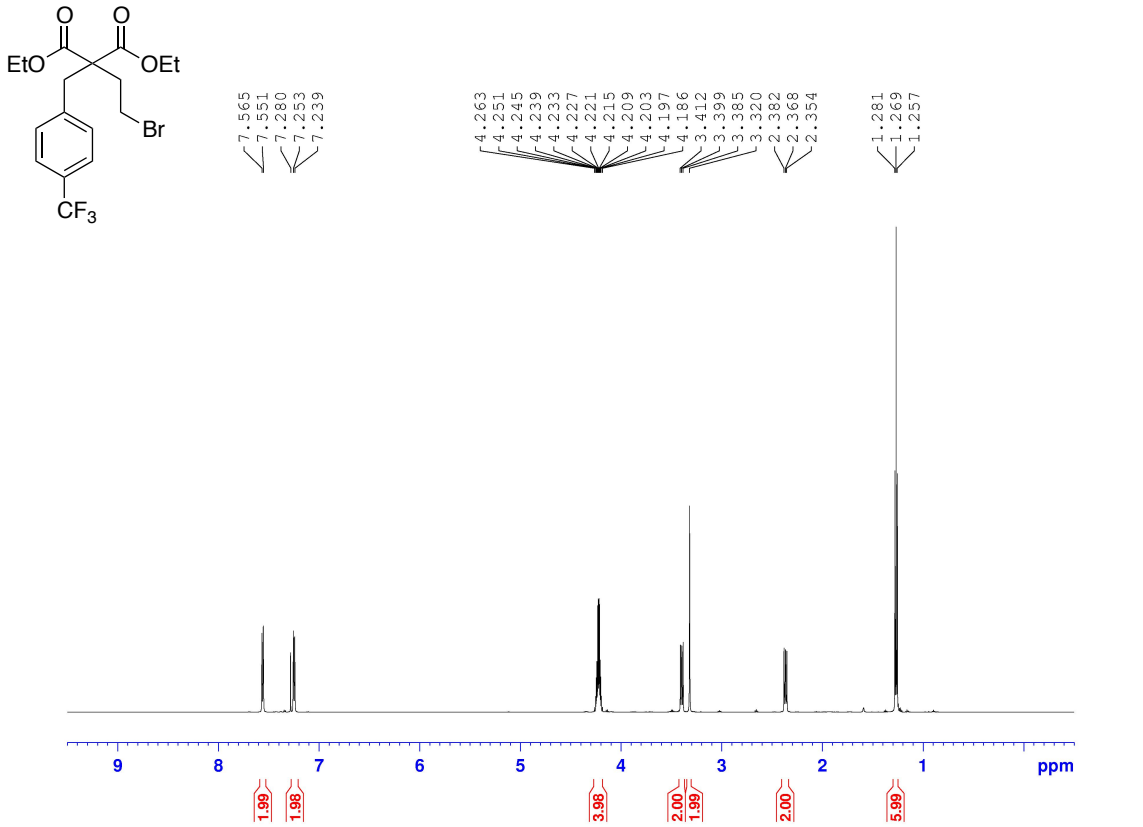
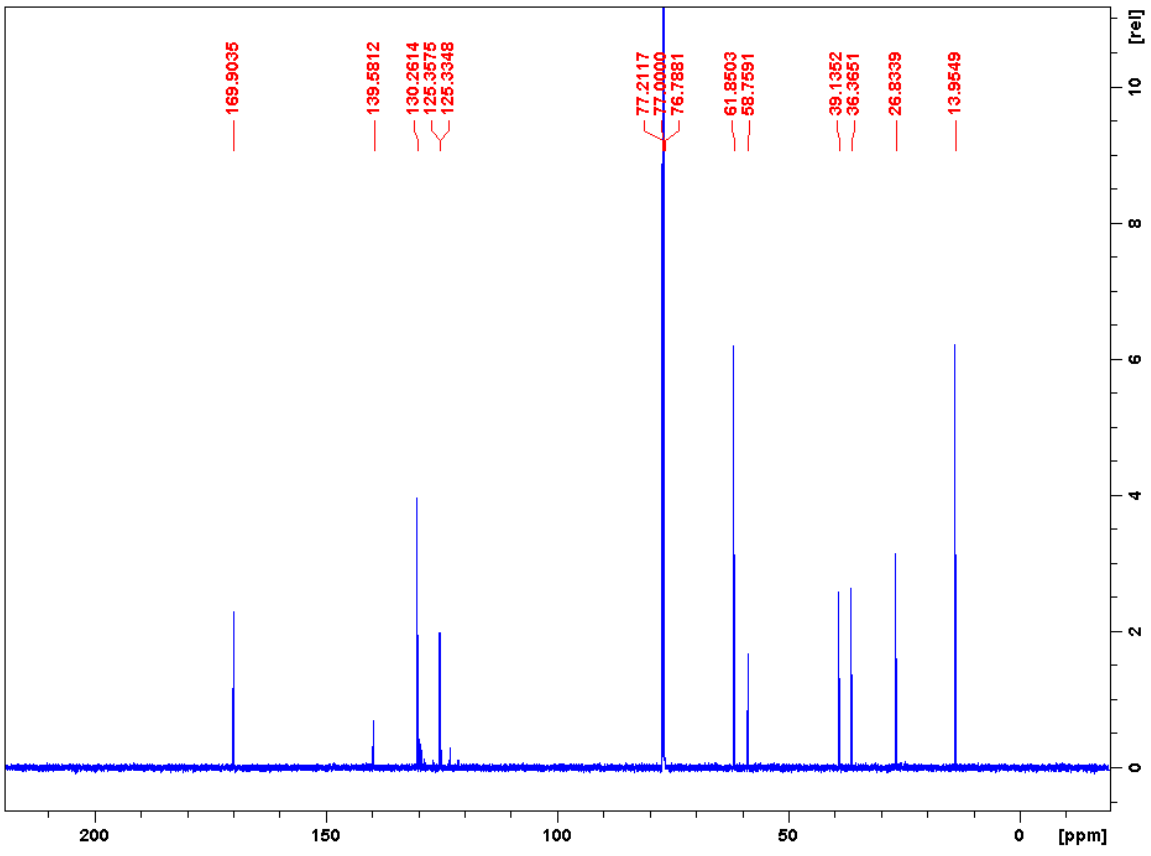
133.5921
128.8011
128.5677
126.0159
125.9301
77.2116
76.9999
76.7882
61.3799
53.6125
34.6442
28.0834
25.9207
13.9943
[rel]
20
15
10
5
0
200
150
100
50
0
[ppm]


EtO
O
O
OEt
Br
CF3
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
9
8
7
6
5
4
3
2
1
ppm
1.99
1.98
3.98
2.00
1.99
2.00
5.99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139.5812
130.2614
125.3575
125.3348
77.2117
77.0000
76.7881
61.8503
58.7591
39.1352
36.3651
26.8339
13.9549
[rel]
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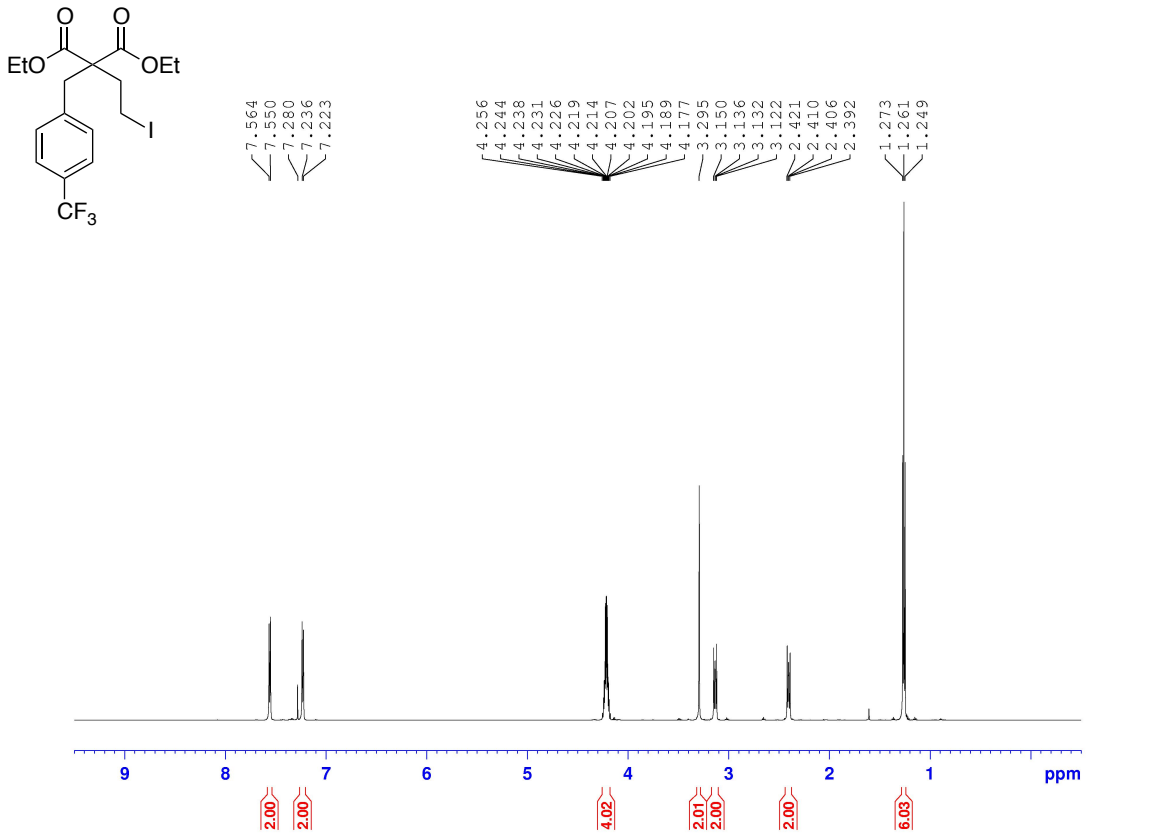
150
100
50
0
[ppm]


EtO
O
O
OEt
I
CF3
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
9
8
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3
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ppm
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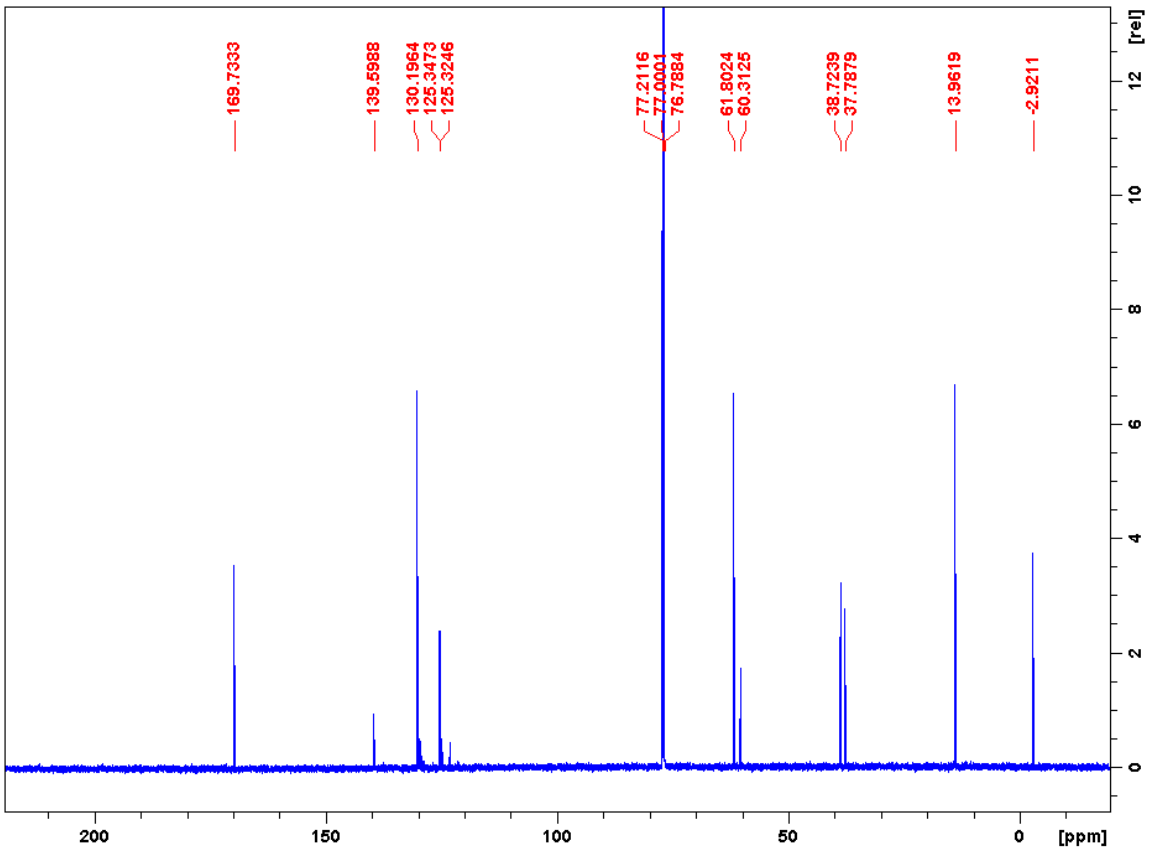
2.00
4.02
2.01
2.00
2.00
6.03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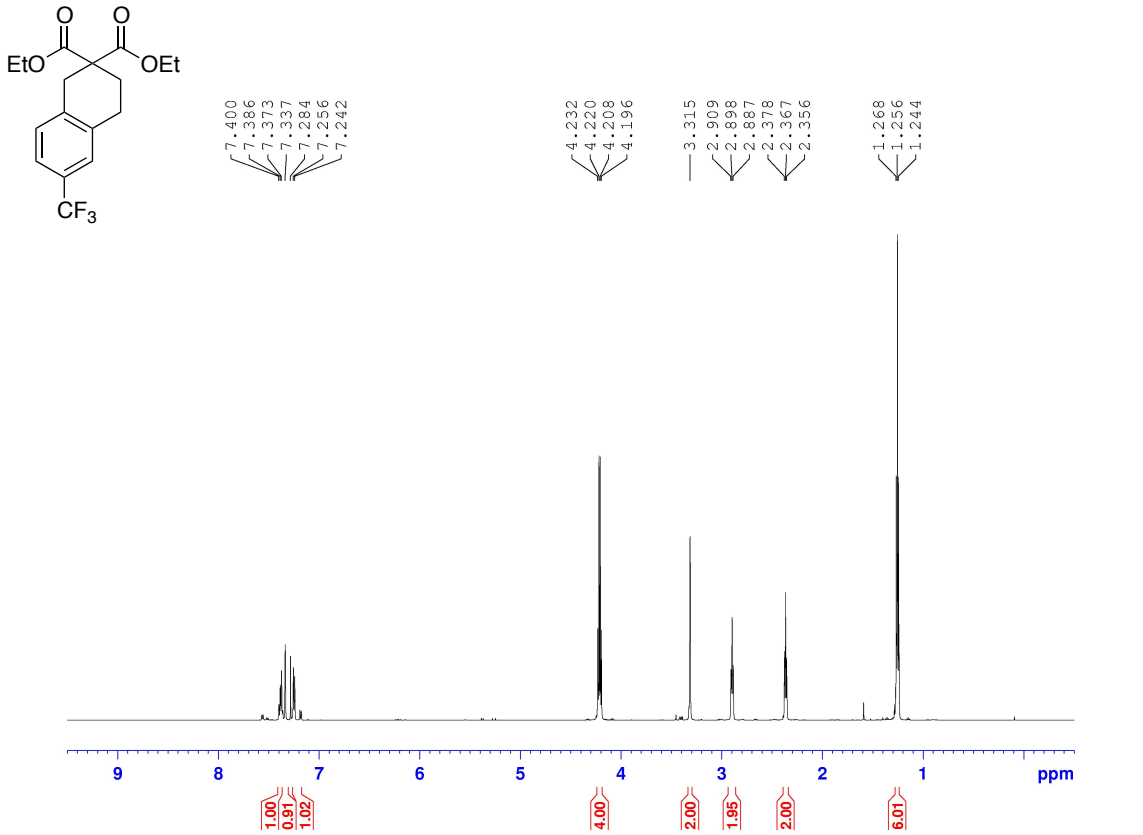
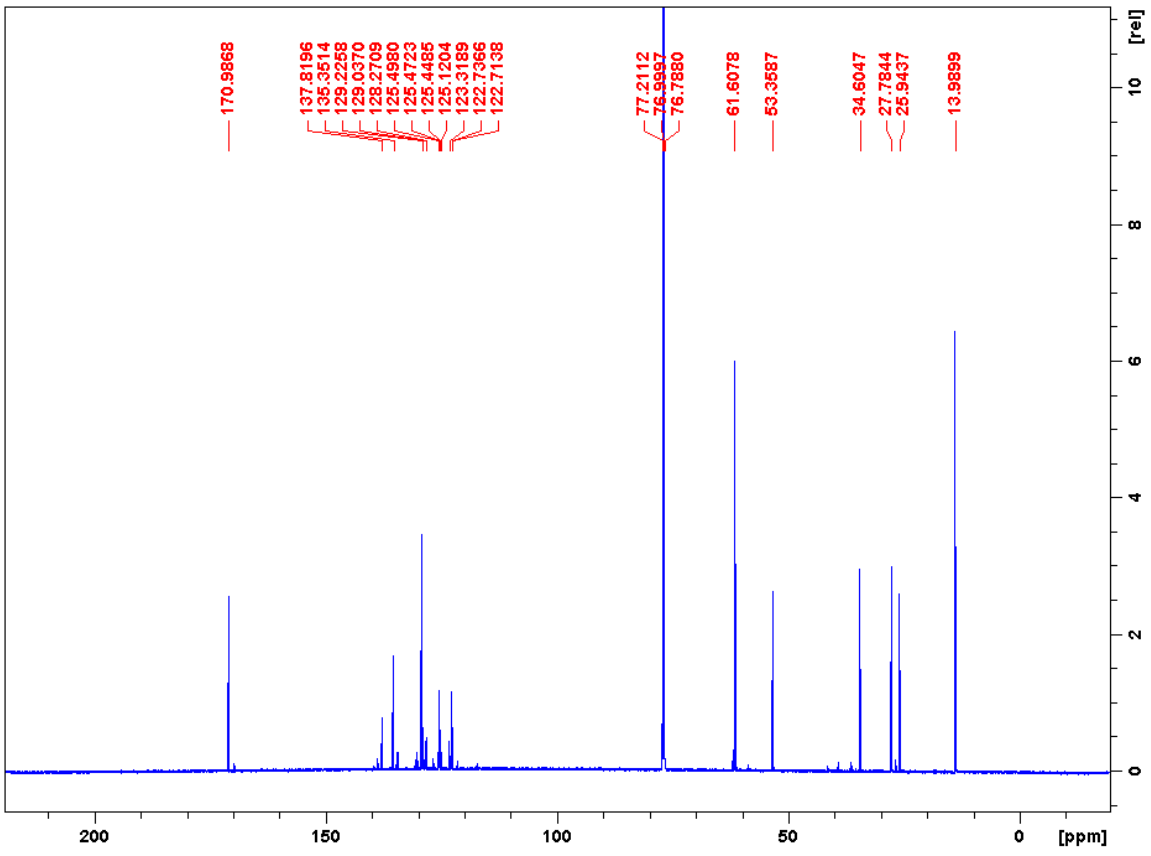
130.1964
125.3473
125.3246
77.2116
77.0001
76.7884
61.8024
60.3125
38.7239
37.7879
13.9619
-2.9211
200
150
100
50
0
[ppm]
0
2
4
6
8
10
12
[rel]


EtO
O
O
OEt
CF3
7.400
7.386
7.373
7.337
7.284
7.256
7.242
4.232
4.220
4.208
4.196
3.315
2.909
2.898
2.887
2.378
2.367
2.356
1.268
1.256
1.244
9
8
7
6
5
4
3
2
1
ppm
1.00
0.91
1.02
4.00
2.00
1.95
2.00
6.01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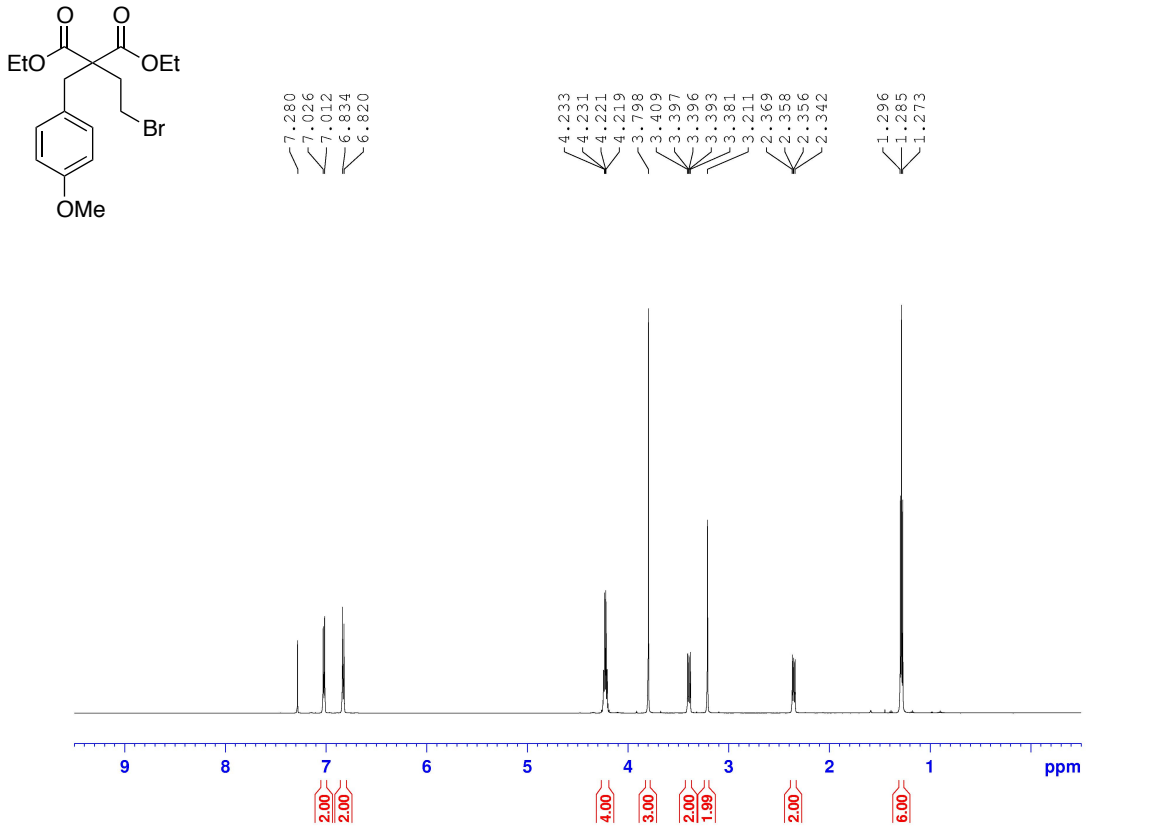
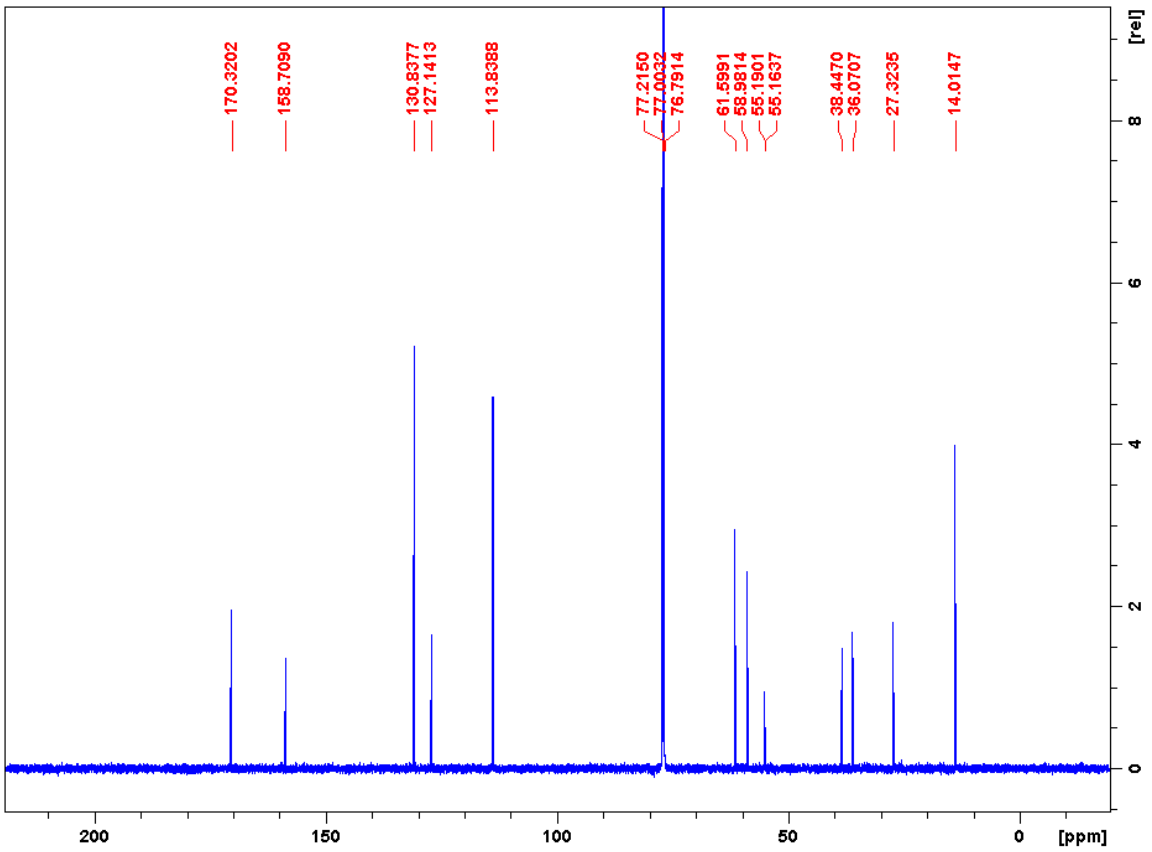
135.3514
129.2258
129.0370
128.2709
125.4980
125.4723
125.4485
125.1204
123.3189
122.7366
122.7138
77.2112
76.9937
76.7880
61.6078
53.3587
34.6047
27.7844
25.9437
13.9899
200
150
100
50
0
[ppm]
0
2
4
6
8
10
[rel]


EtO
O
O
OEt
Br
OMe
7.280
7.026
7.012
6.834
6.820
4.233
4.231
4.221
4.219
3.798
3.409
3.397
3.396
3.393
3.381
3.211
2.369
2.358
2.356
2.342
1.296
1.285
1.273
9
8
7
6
5
4
3
2
1
ppm
2.00
2.00
4.00
3.00
2.00
1.99
2.00
6.00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130.8377
127.1413
113.8388
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77.0032
76.7914
61.5991
58.9814
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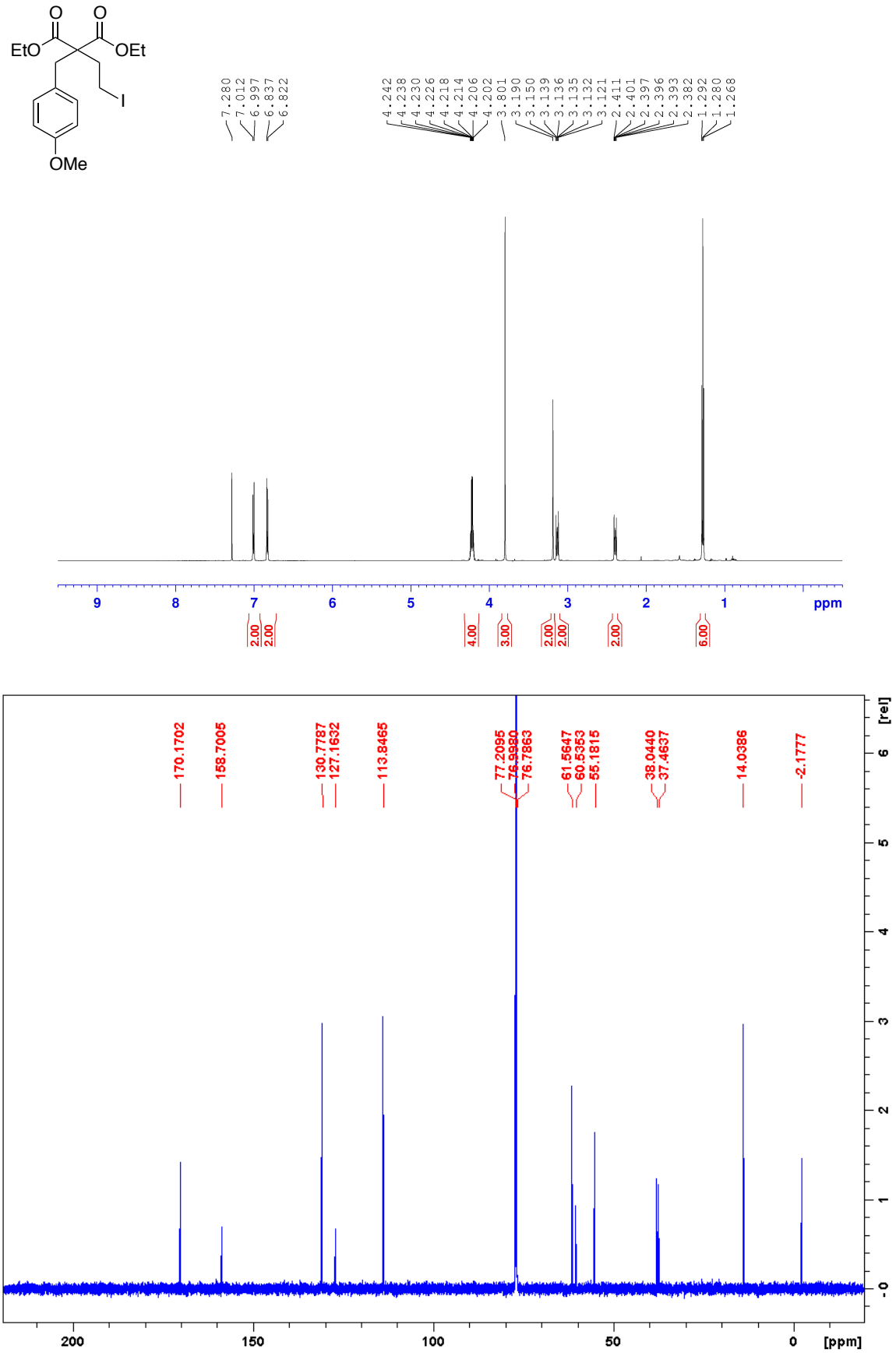
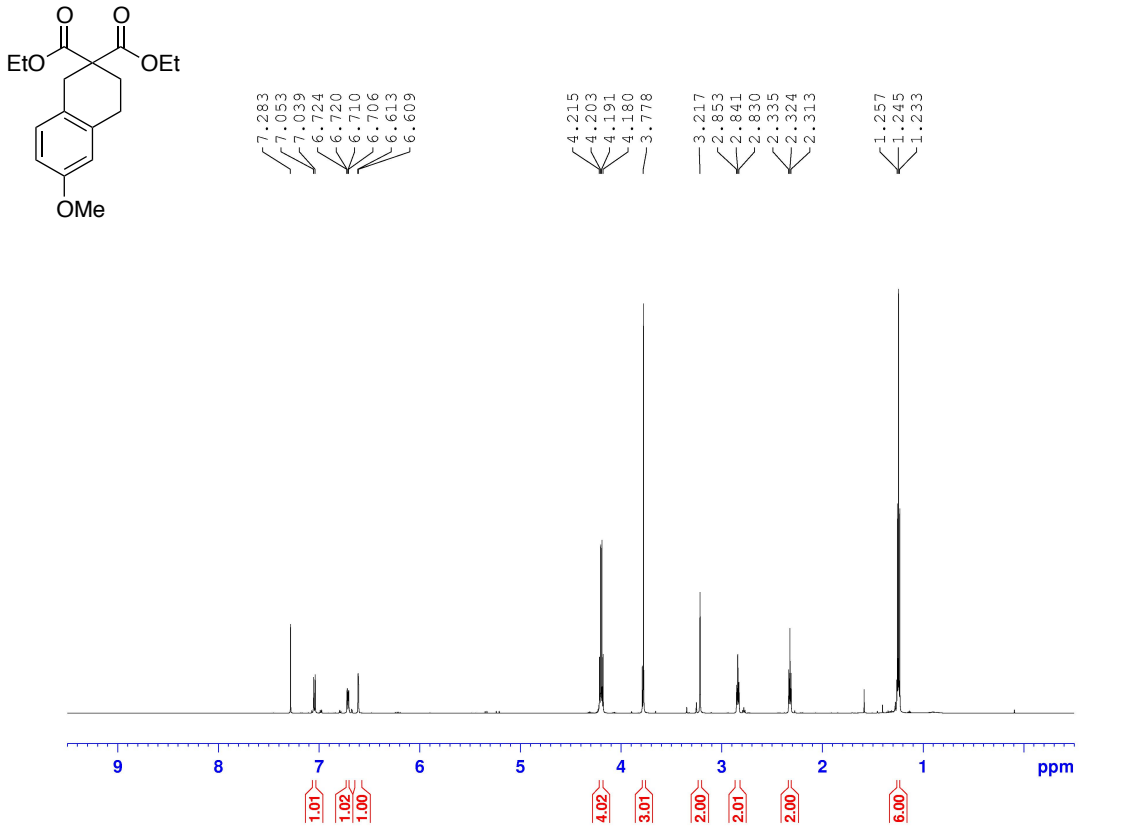
55.1637
38.4470
36.0707
27.3235
14.0147
[rel]
200
150
100
50
0
[ppm]


EtO
O
O
OEt
I
OMe
7.280
7.012
6.997
6.837
6.822
4.242
4.238
4.230
4.226
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
9
8
7
6
5
4
3
2
1
ppm
2.00
2.00
4.00
3.00
2.00
2.00
2.00
6.00
170.1702
158.7005
130.7787
127.1632
113.8465
77.2095
76.9380
76.7863
61.5647
60.5353
55.1815
38.0440
37.4637
14.0386
-2.1777
[rel]
200
150
100
50
0
[ppm]


EtO
OEt
OMe
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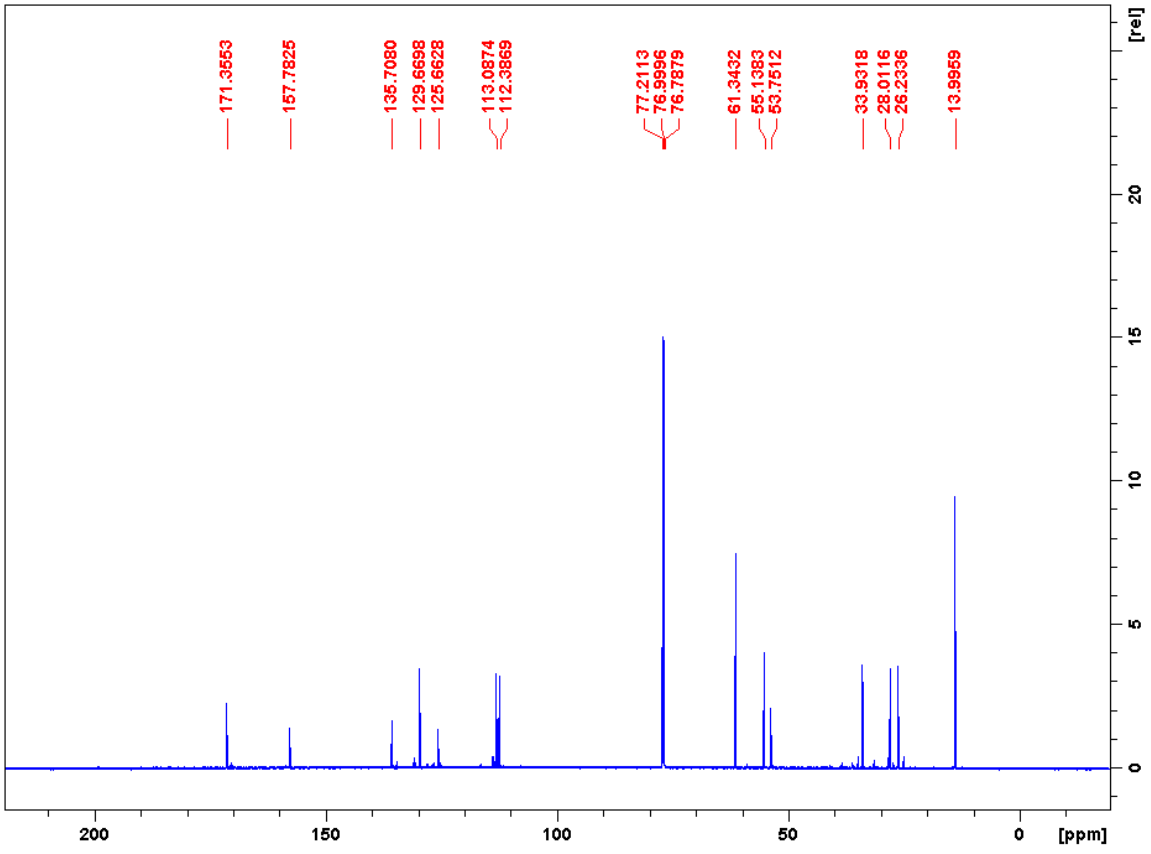
7.053
7.039
6.724
6.720
6.710
6.706
6.613
6.609
4.215
4.203
4.191
4.180
3.778
3.217
2.853
2.841
2.830
2.335
2.324
2.313
1.257
1.245
1.233
ppm
1.01
1.02
1.00
4.02
3.01
2.00
2.01
2.00
6.00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135.7080
129.6698
125.6628
113.0874
112.3869
77.2113
76.9996
76.7879
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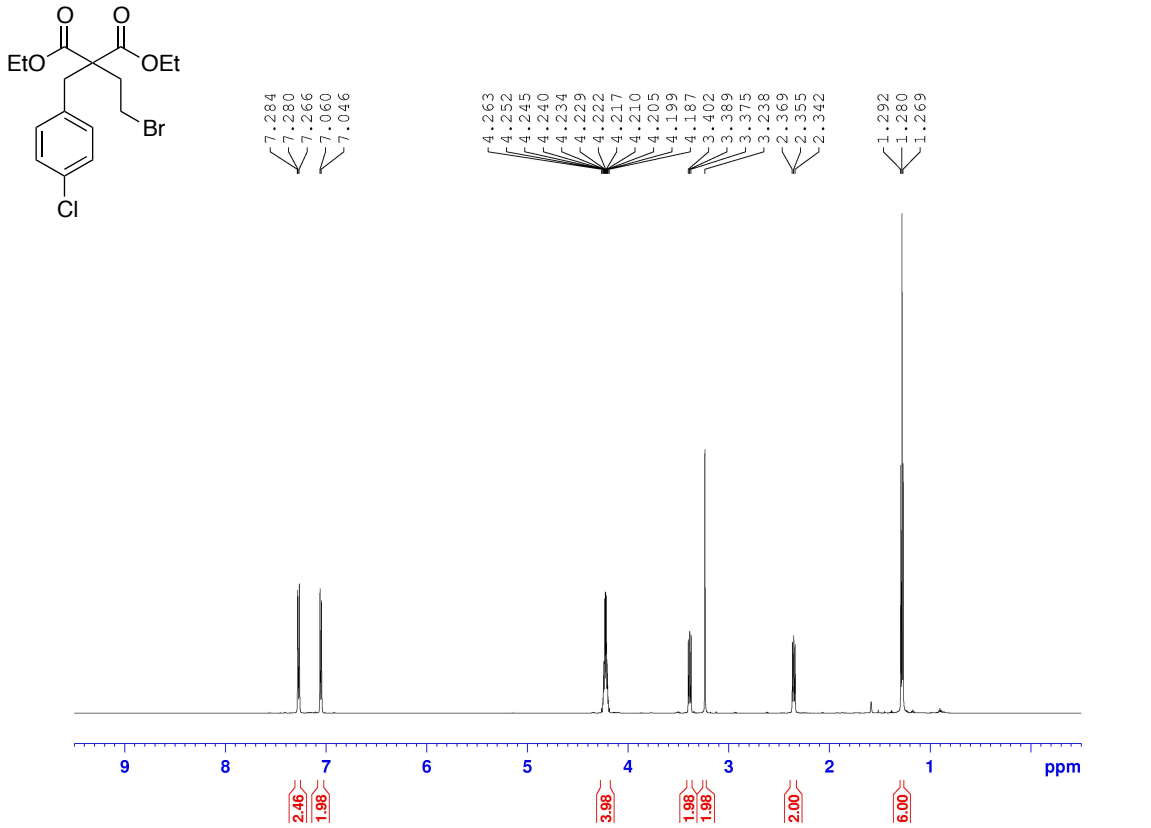
55.1383
53.7512
33.9318
28.0116
26.2336
13.9959
[rel]
[ppm]


EtO
O
O
OEt
Br
Cl
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
9
8
7
6
5
4
3
2
1
ppm
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3.98
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1.98
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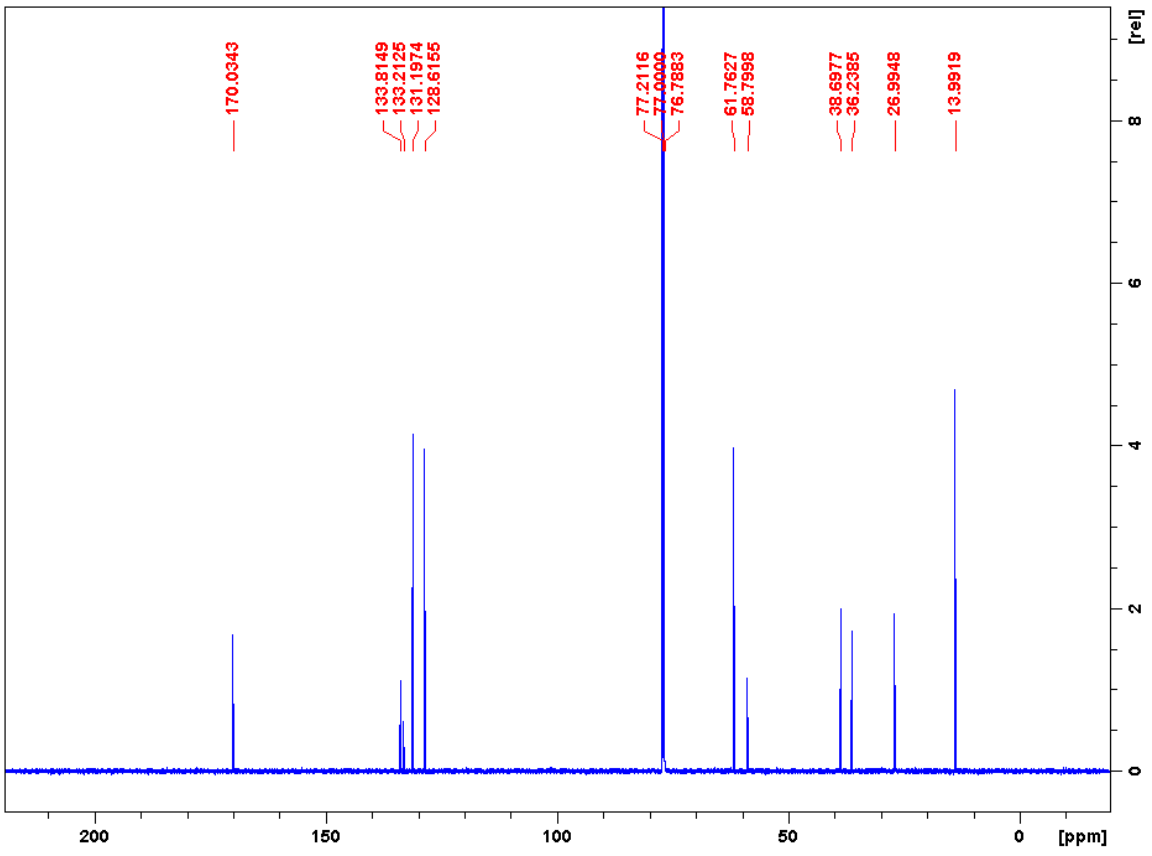
6.00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133.2125
131.1974
128.6155
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77.0000
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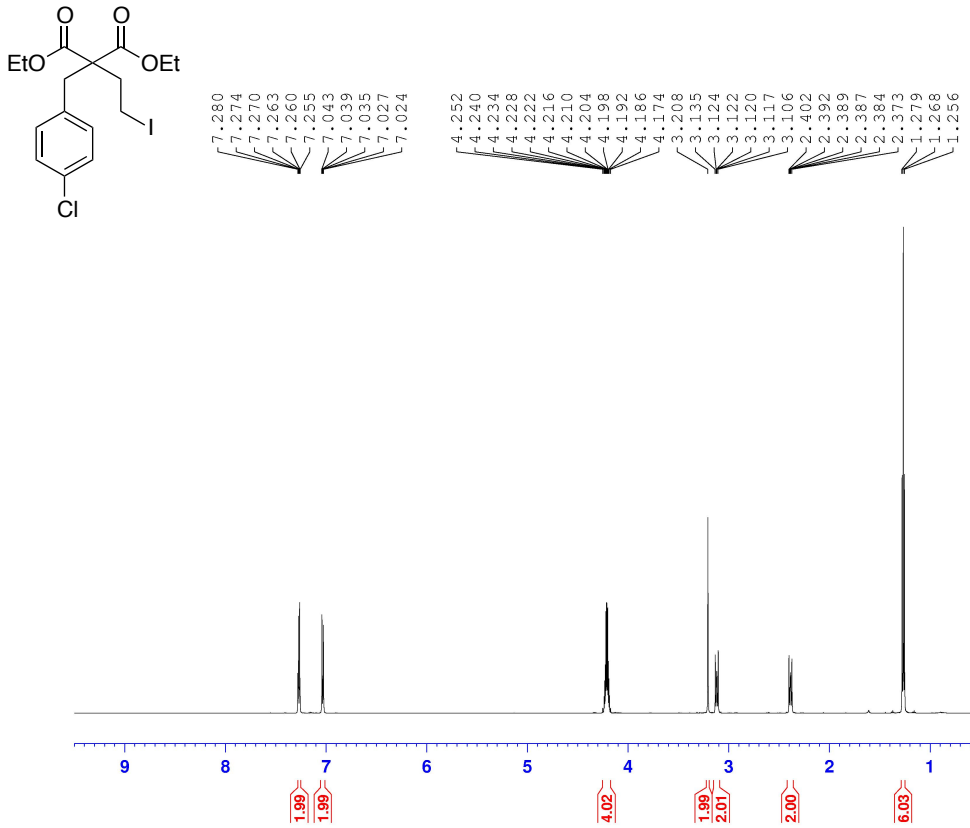
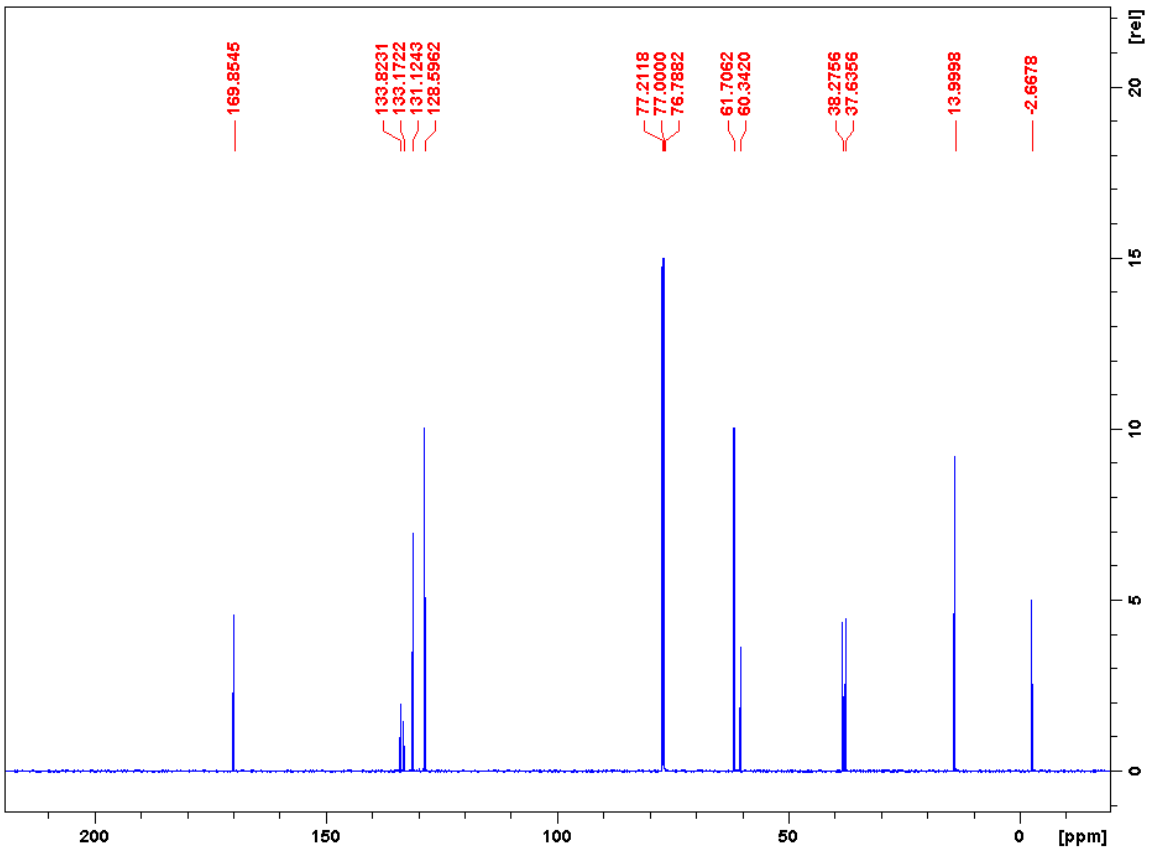
38.6977
36.2385
26.9948
13.9919
[rel]
200
150
100
50
0
[ppm]


O
O
EtO
OEt
I
Cl
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
9
8
7
6
5
4
3
2
1
ppm
1.99
1.99
4.02
1.99
2.01
2.00
6.03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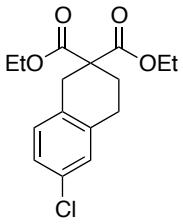
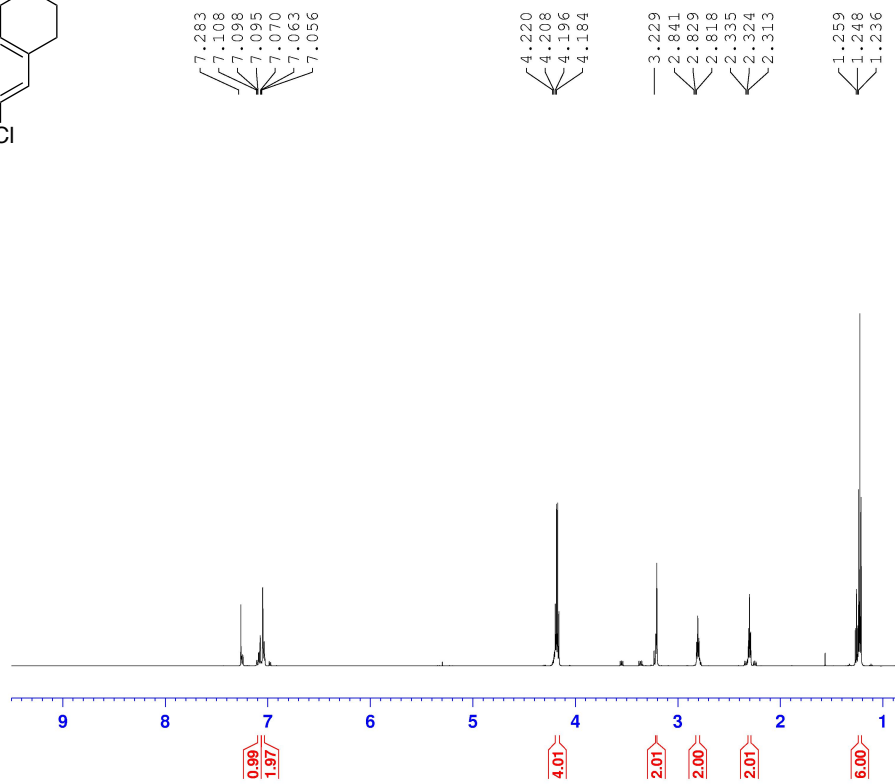
131.1243
128.5962
77.2118
77.0000
76.7882
61.7062
60.3420
38.2756
37.6356
13.9998
-2.6678
[rel]
20
15
10
5
0
200
150
100
50
0
[ppm]


O
O
EtO
OEt
Cl


7.283
7.108
7.098
7.095
7.070
7.063
7.056
4.220
4.208
4.196
4.184
3.229
2.841
2.829
2.818
2.335
2.324
2.313
1.259
1.248
1.236
9
8
7
6
5
4
3
2
1
ppm
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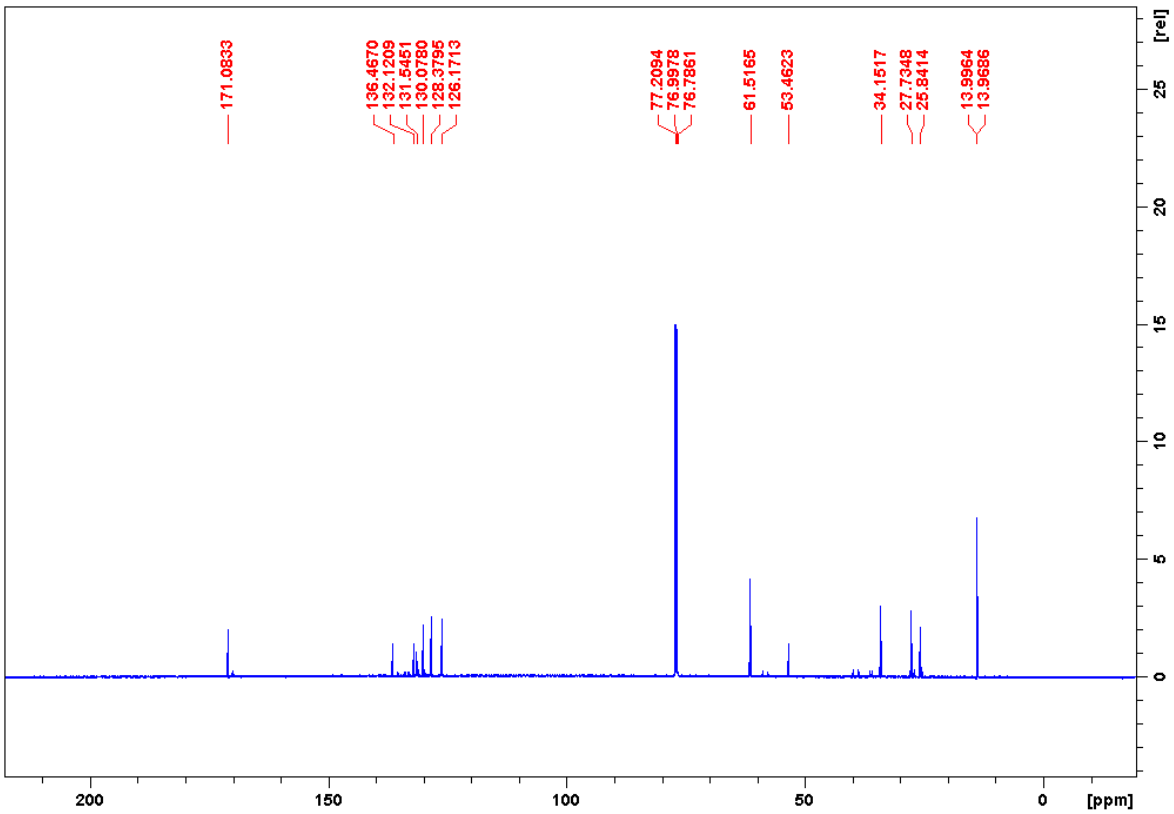
1.97
4.01
2.01
2.00
2.01
6.00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131.5451
130.0780
128.3795
126.1713
77.2094
76.9978
76.7861
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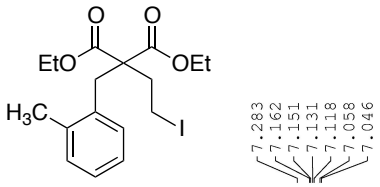
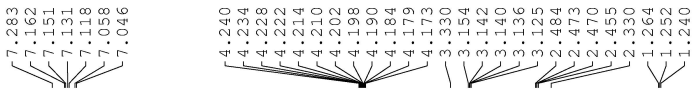
27.7348
25.8414
13.9964
13.9686
[rel]
25
20
15
10
5
0
200
150
100
50
0
[ppm]


O
O
EtO
OEt
H3C
I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4.210
4.202
4.198
4.190
4.184
4.179
4.173
3.330
3.154
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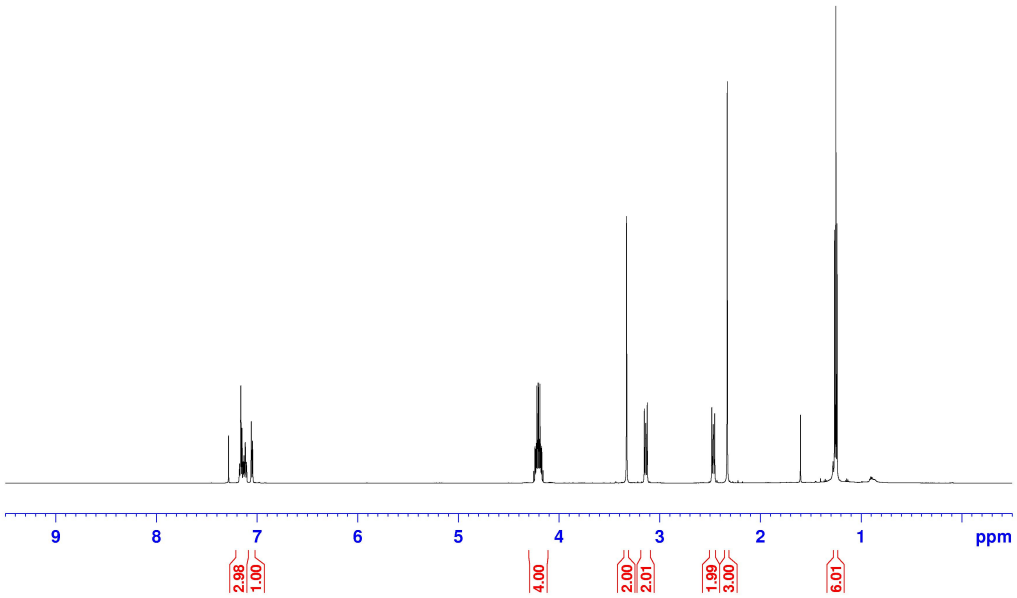
1.252
1.240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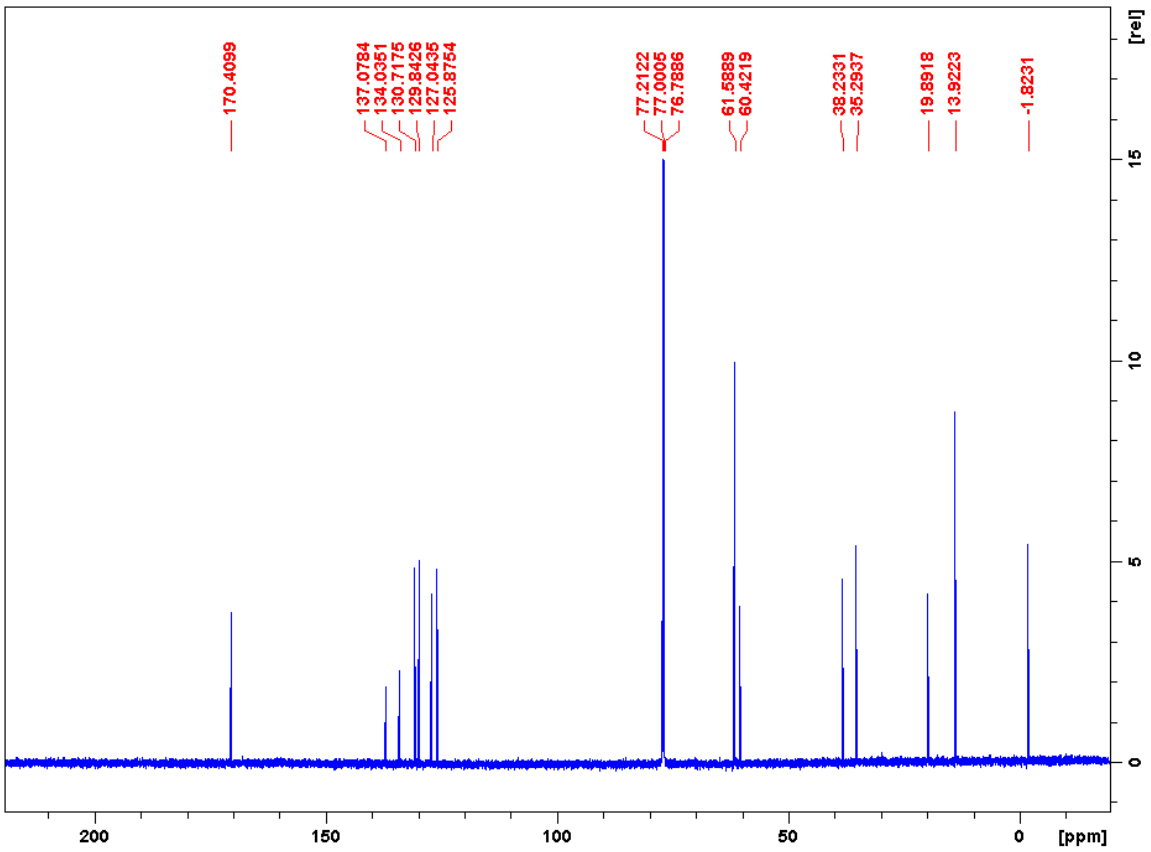
6.01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38.2331
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-1.8231
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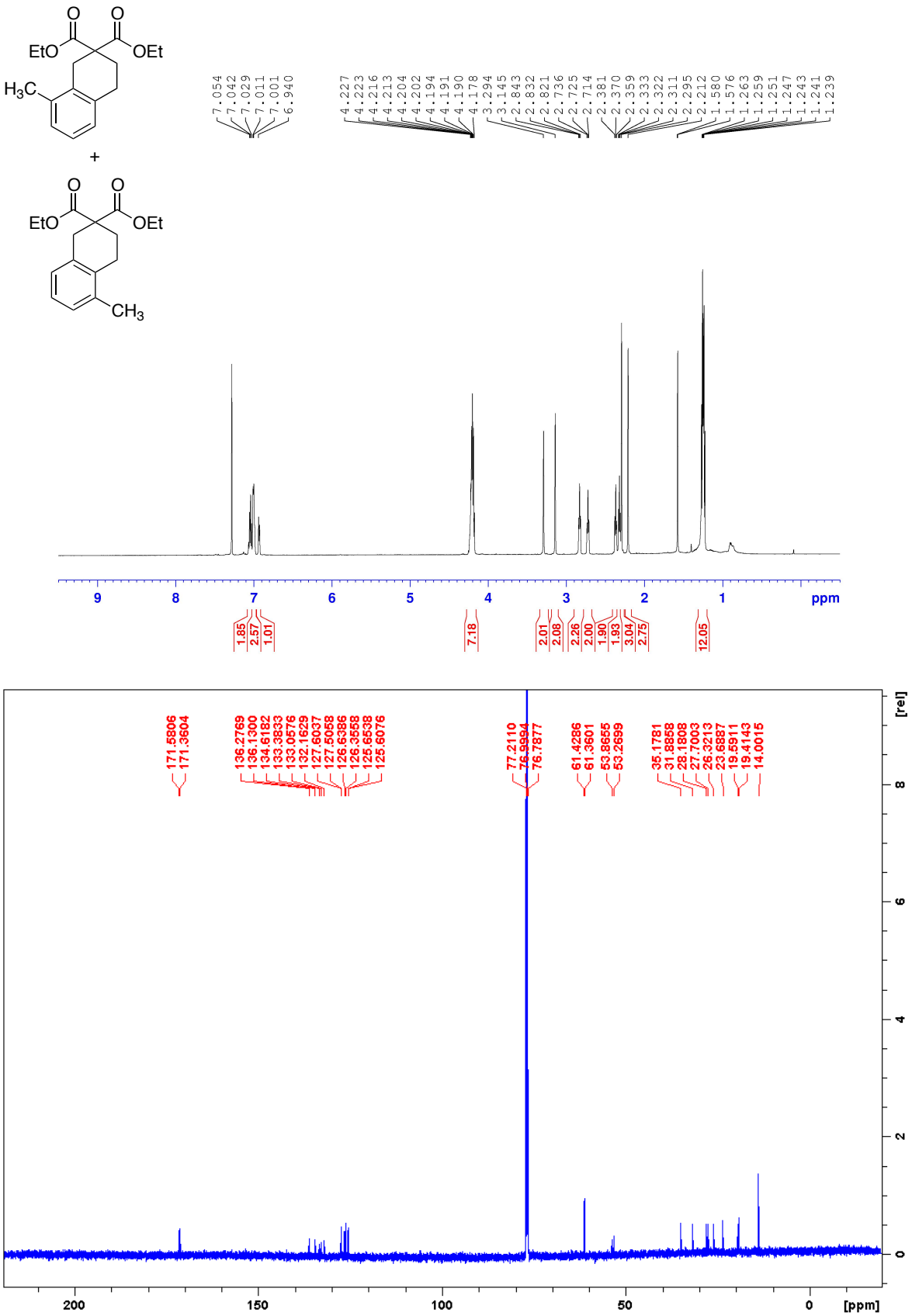
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OEt
O
O
H3C
+
CH3
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7.001
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4.223
4.216
4.213
4.204
4.202
4.194
4.191
4.190
4.178
3.294
3.145
2.843
2.832
2.821
2.736
2.725
2.714
2.381
2.370
2.359
2.333
2.322
2.311
2.295
2.212
1.580
1.576
1.263
1.259
1.251
1.247
1.243
1.241
1.239
9
8
7
6
5
4
3
2
1
ppm
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2.01
2.08
2.26
2.00
1.90
1.93
3.04
2.75
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127.5058
126.6386
126.3558
125.6538
125.6076
77.2110
76.9994
76.7877
61.4286
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53.8655
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31.8858
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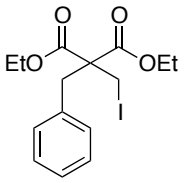
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EtO
OEt
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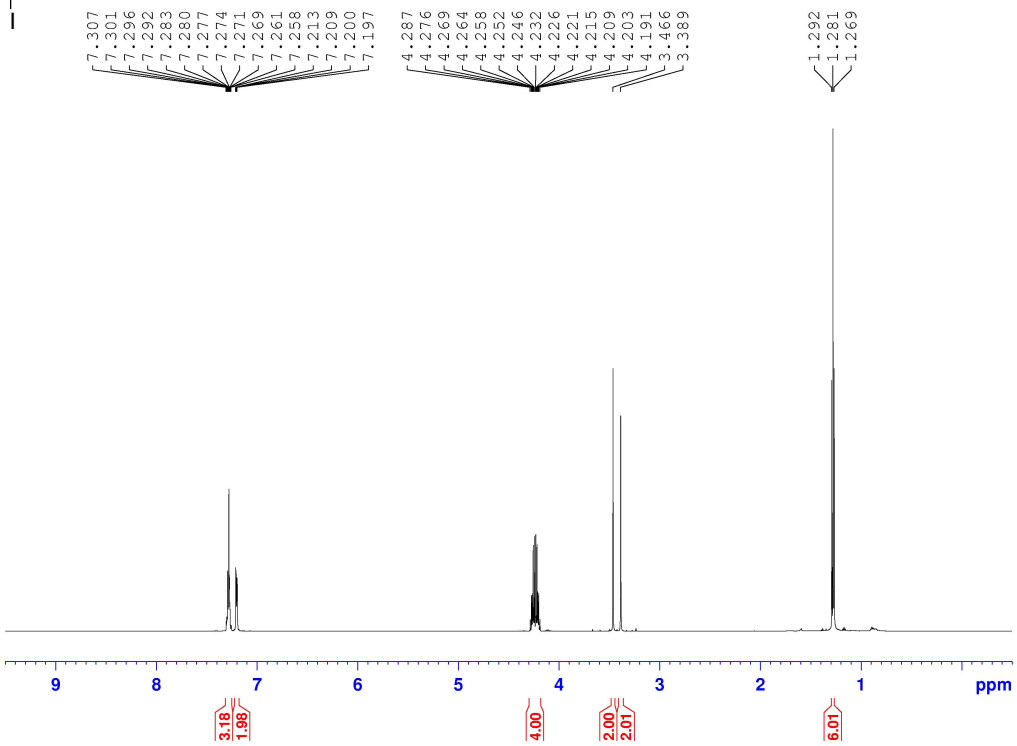
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7.277
7.274
7.271
7.269
7.261
7.258
7.213
7.209
7.200
7.197
4.287
4.276
4.269
4.264
4.258
4.252
4.246
4.232
4.226
4.221
4.215
4.209
4.203
4.191
3.466
3.389
1.292
1.281
1.269
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8
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6
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4
3
2
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ppm
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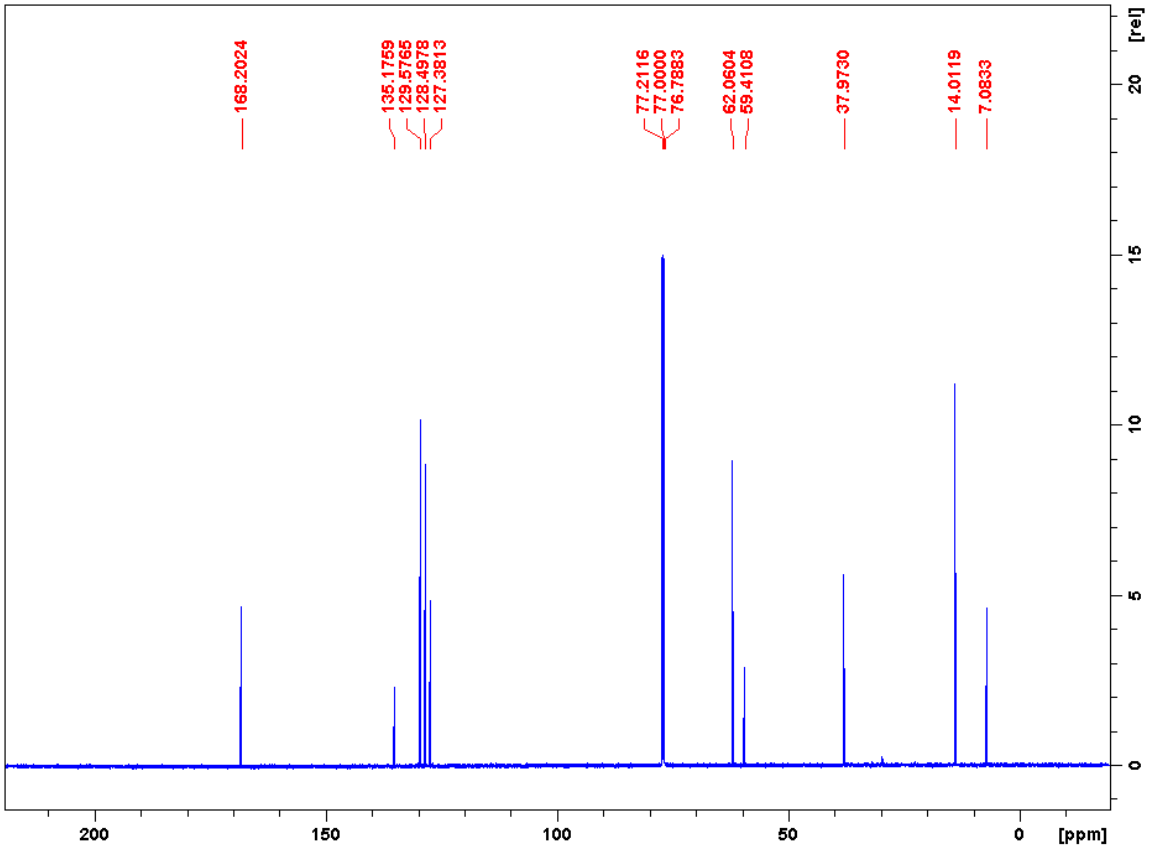
2.00
2.01
6.01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7.0833
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50
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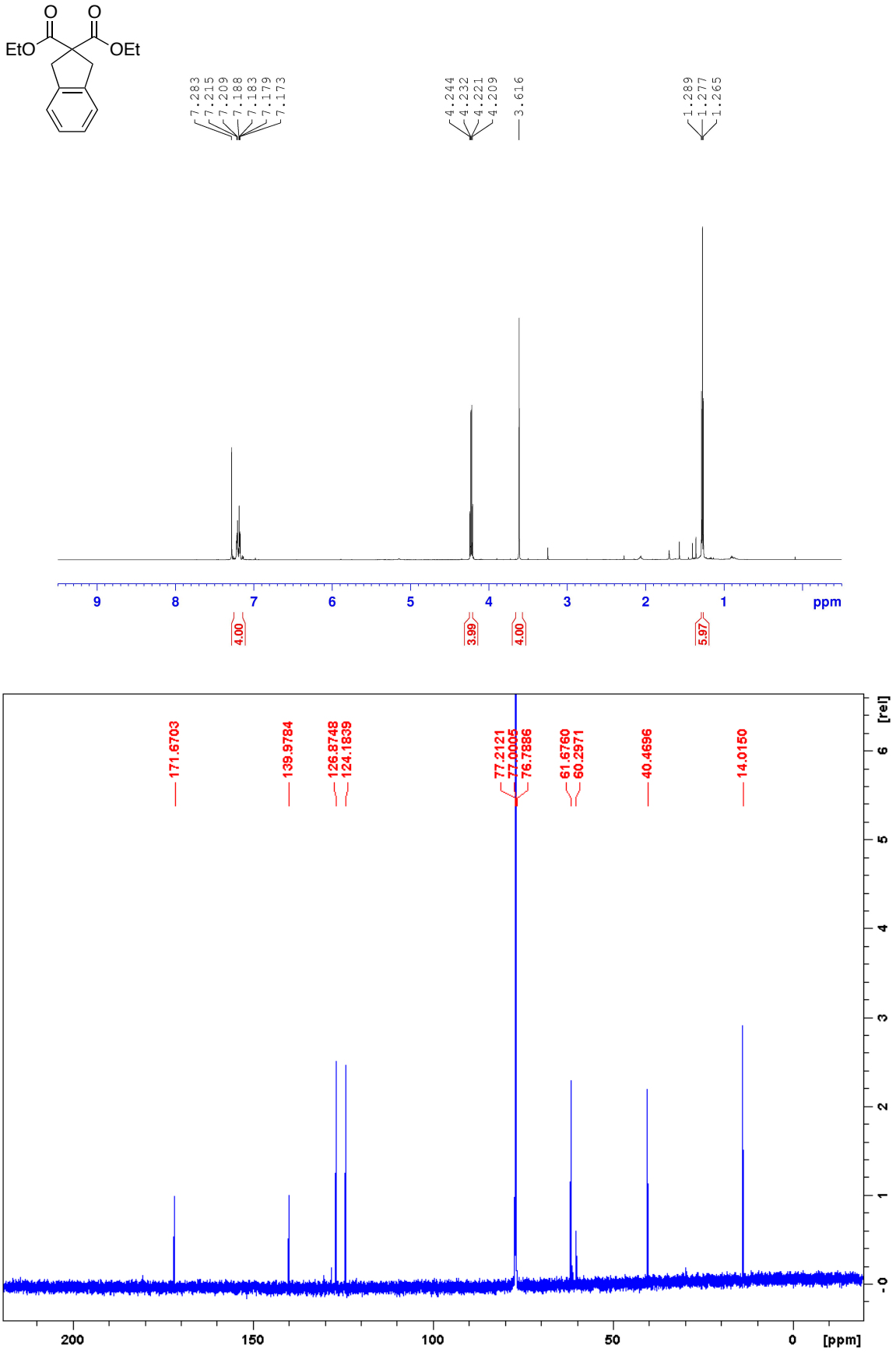
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O
EtO
OEt
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7.209
7.188
7.183
7.179
7.173
4.244
4.232
4.221
4.209
3.616
1.289
1.277
1.265
9
8
7
6
5
4
3
2
1
ppm
4.00
3.99
4.00
5.97
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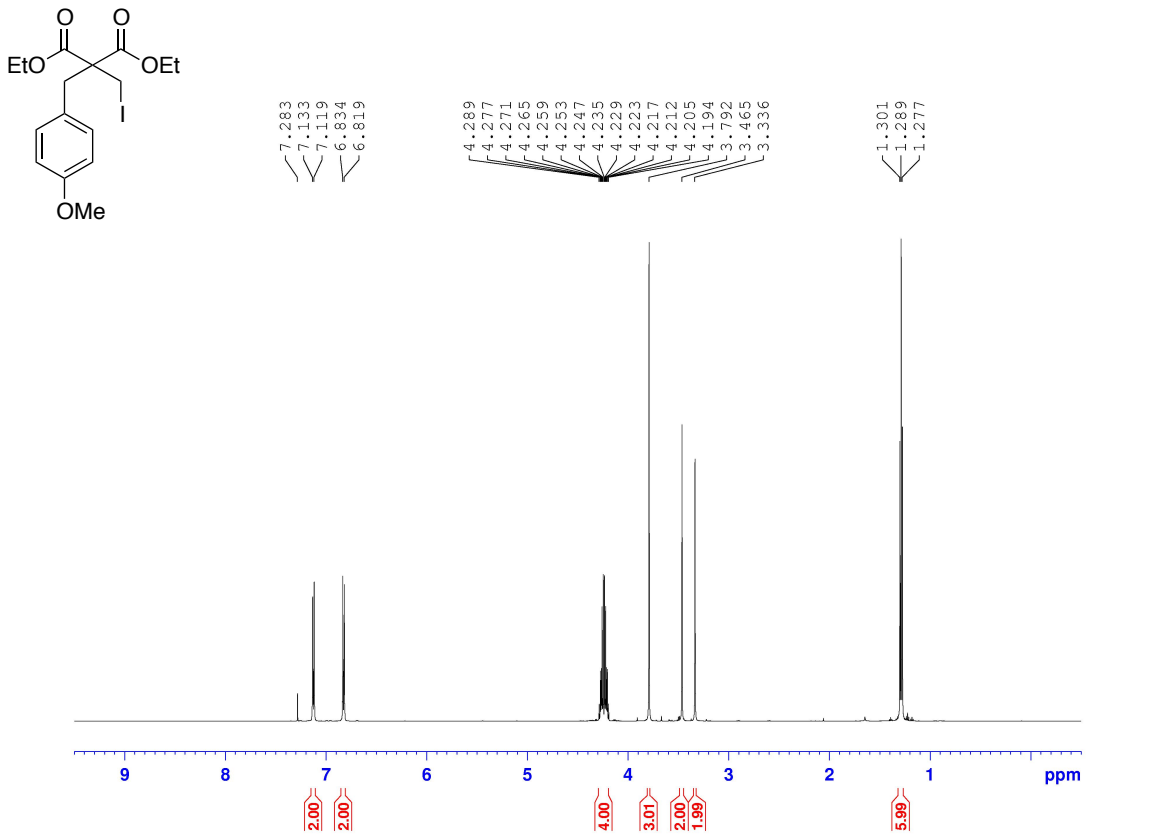
O
O
EtO
OEt
I
OMe
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7.133
7.119
6.834
6.819
4.289
4.277
4.271
4.265
4.259
4.253
4.247
4.235
4.229
4.223
4.217
4.212
4.205
4.194
3.792
3.465
3.336
1.301
1.289
1.277
9
8
7
6
5
4
3
2
1
ppm
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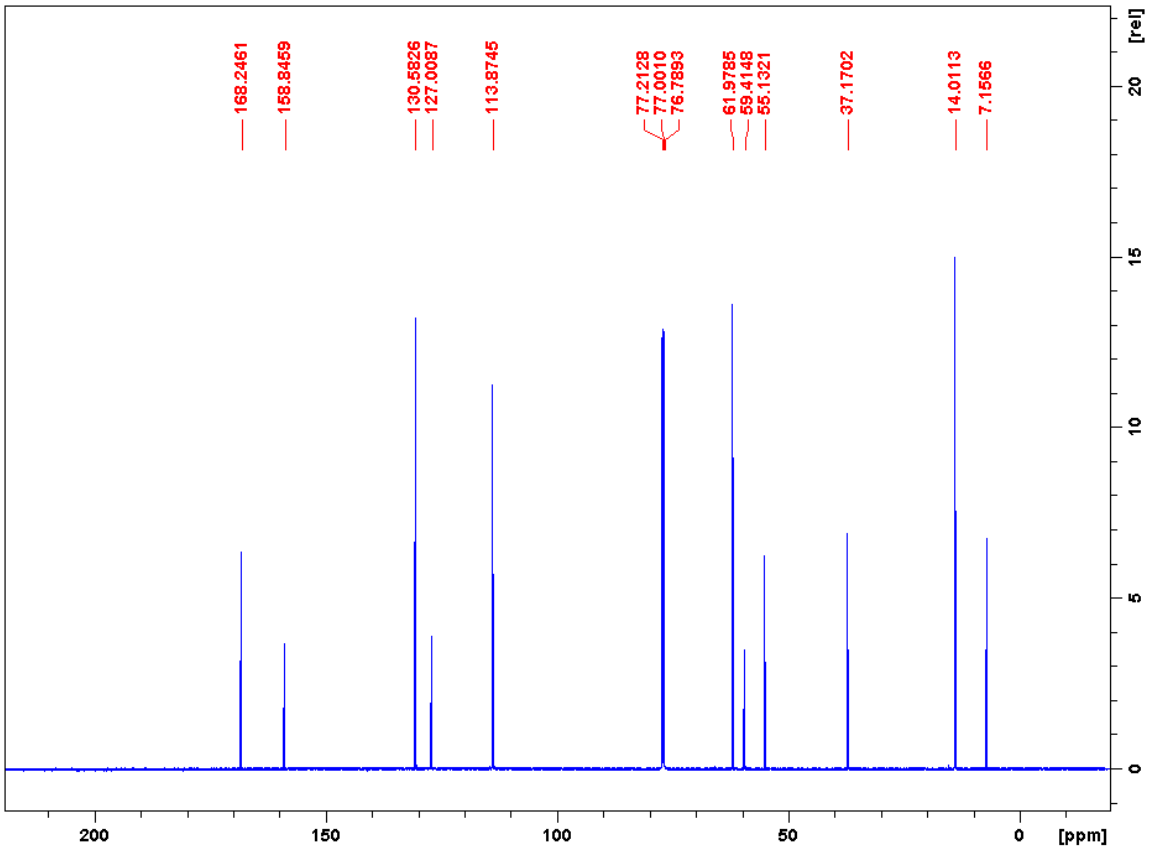
2.00
4.00
3.01
2.00
1.99
5.99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113.8745
77.2128
77.0010
76.7893
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59.4148
55.1321
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7.1566
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5
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100
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0
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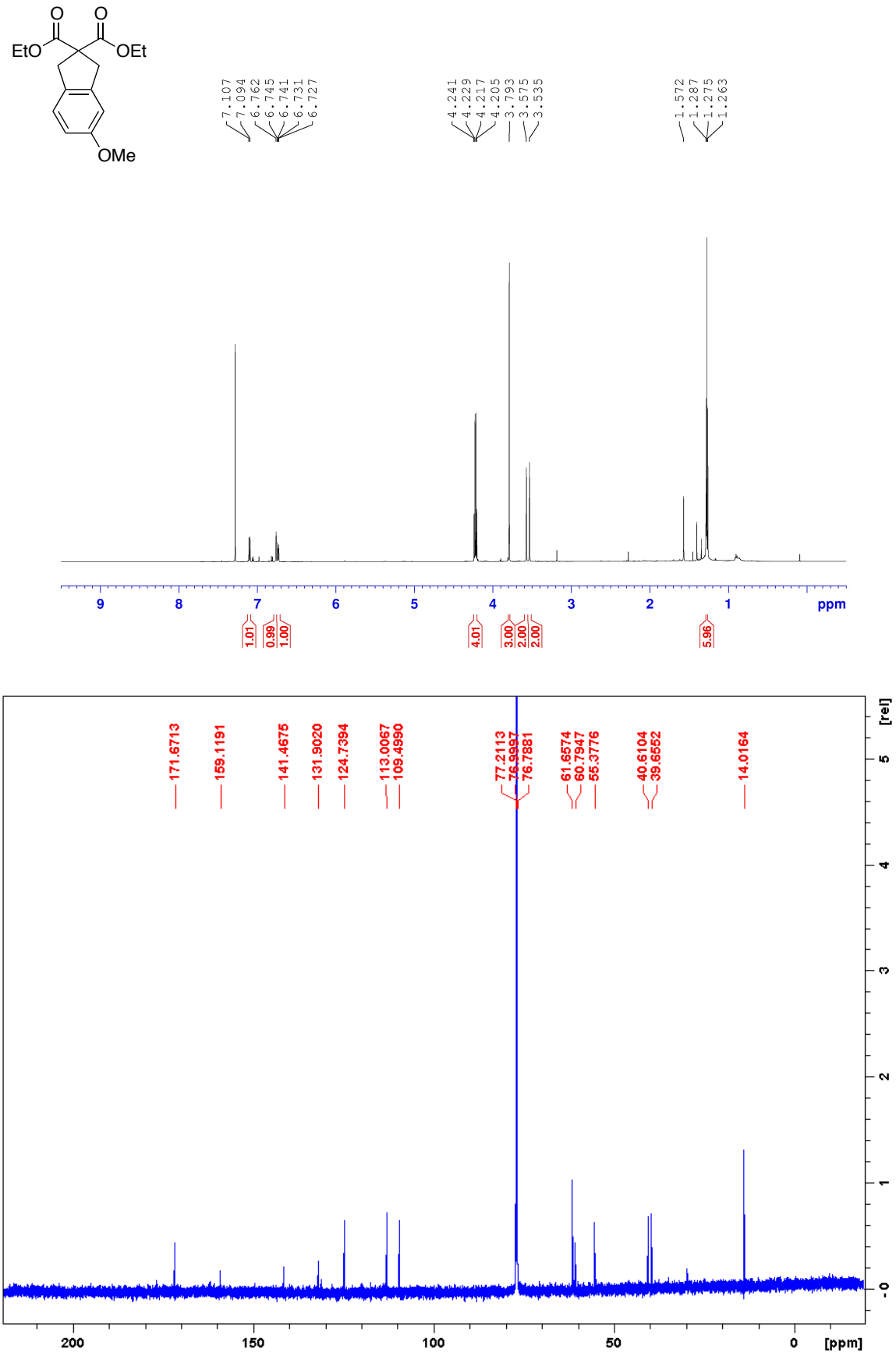
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OEt
OMe
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6.745
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6.731
6.727
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4.217
4.205
3.793
3.575
3.535
1.572
1.287
1.275
1.263
ppm
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0.99
1.00
4.01
3.00
2.00
2.00
5.96
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141.4675
131.9020
124.7394
113.0067
109.4990
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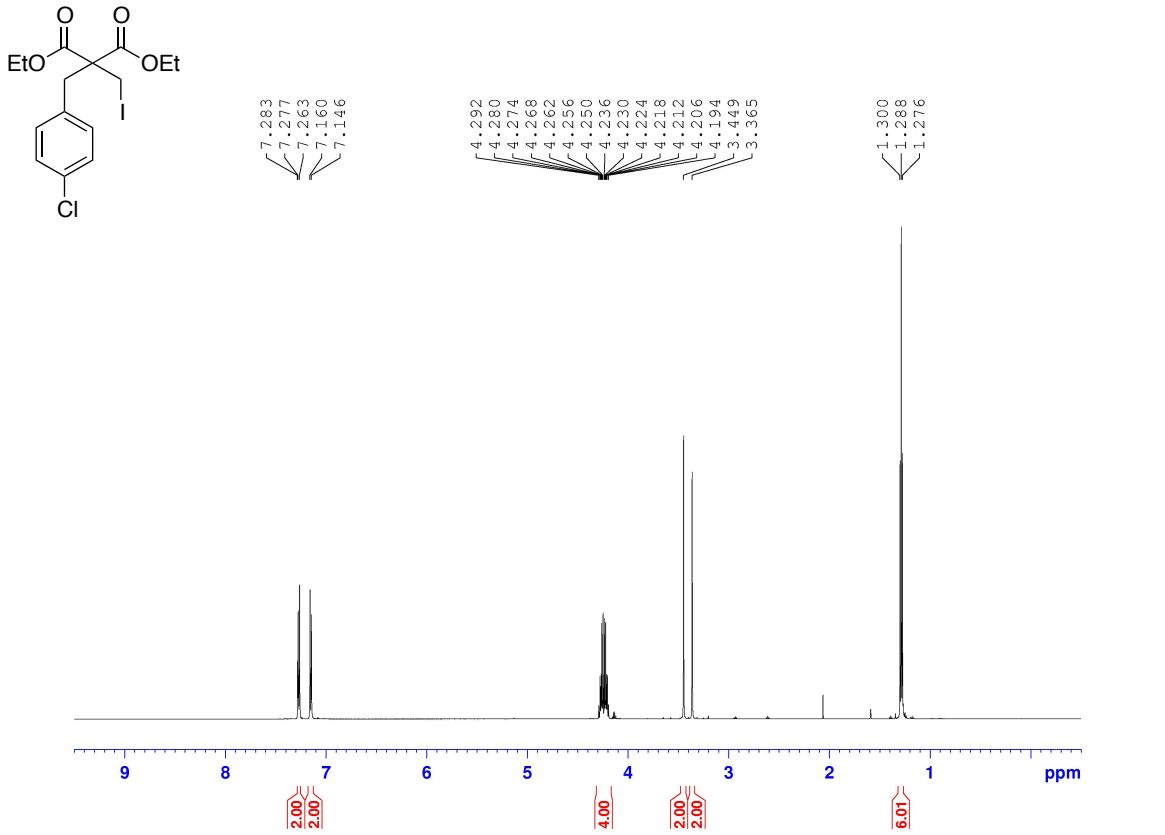
O
O
EtO
OEt
I
Cl
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7.277
7.263
7.160
7.146
4.292
4.280
4.274
4.268
4.262
4.256
4.250
4.236
4.230
4.224
4.218
4.212
4.206
4.194
3.449
3.365
1.300
1.288
1.276
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8
7
6
5
4
3
2
1
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2.00
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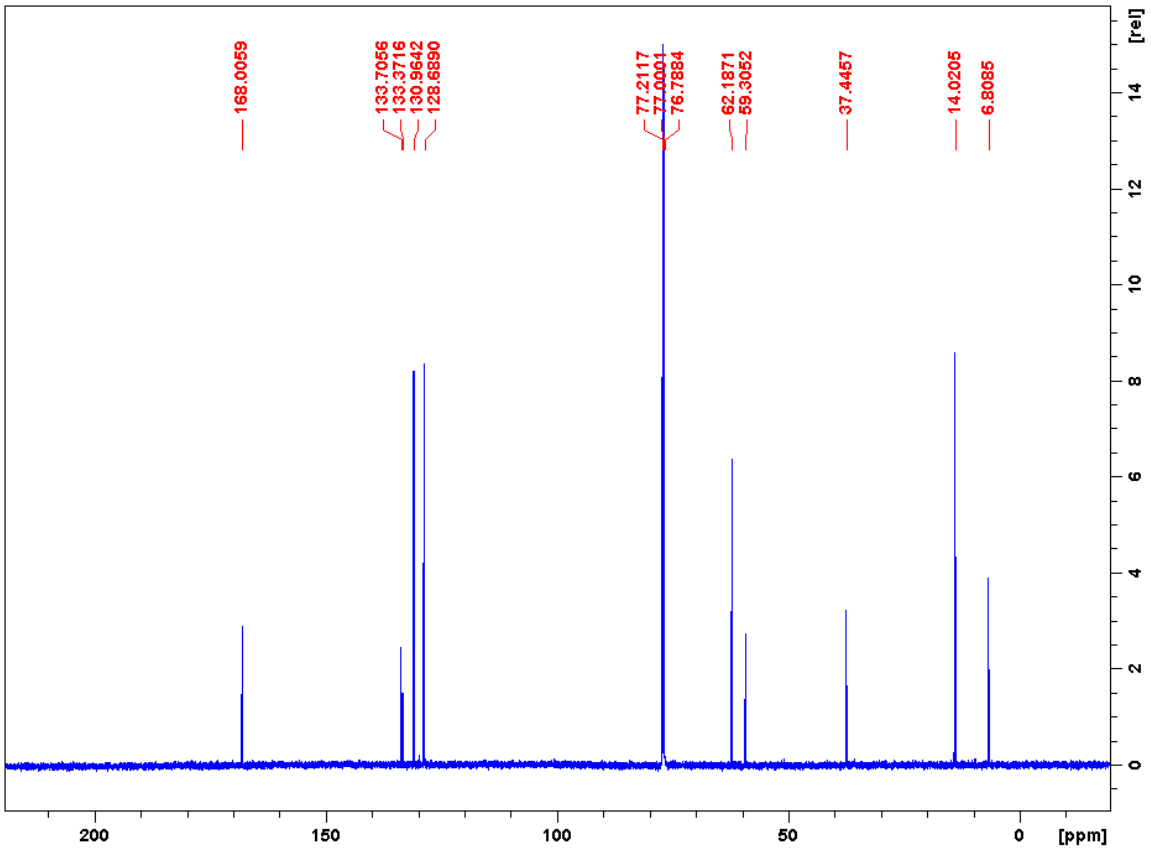
2.00
2.00
6.01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10
8
6
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2
0
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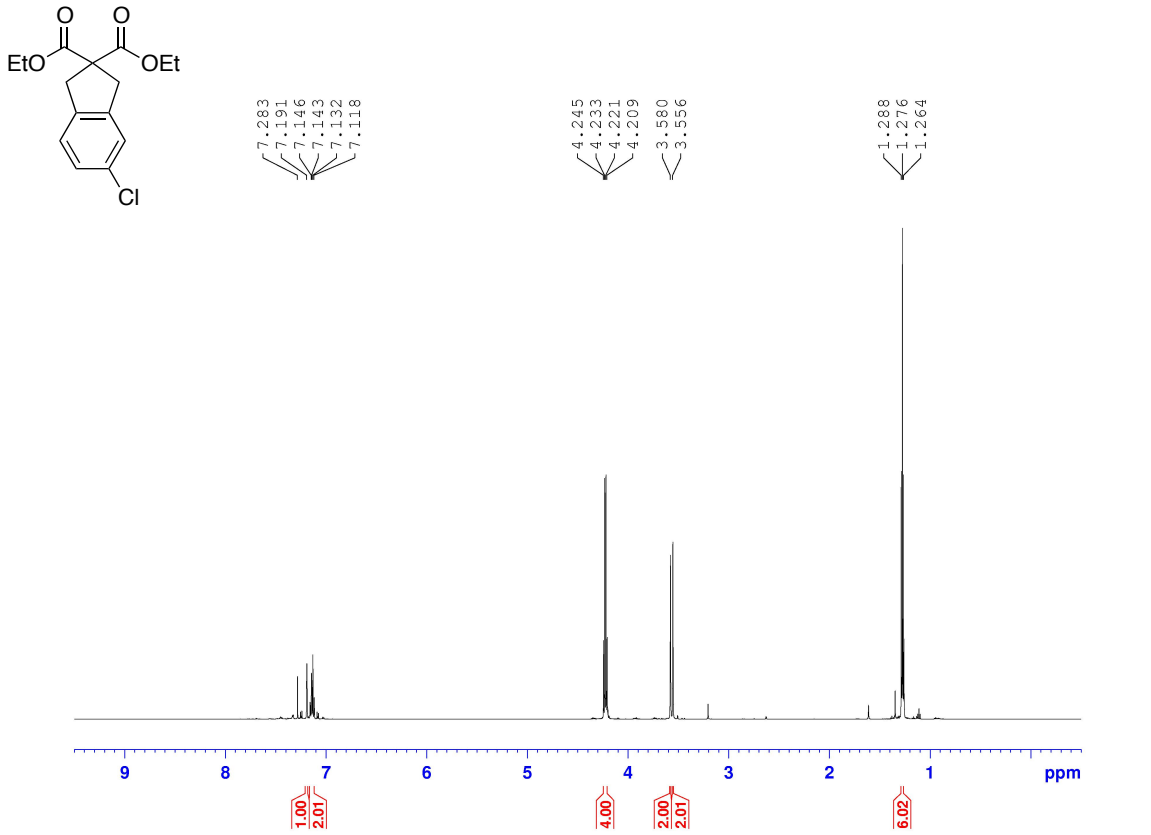
100
50
0
[ppm]


O
O
EtO
OEt
Cl
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7.191
7.146
7.143
7.132
7.118
4.245
4.233
4.221
4.209
3.580
3.556
1.288
1.276
1.264
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8
7
6
5
4
3
2
1
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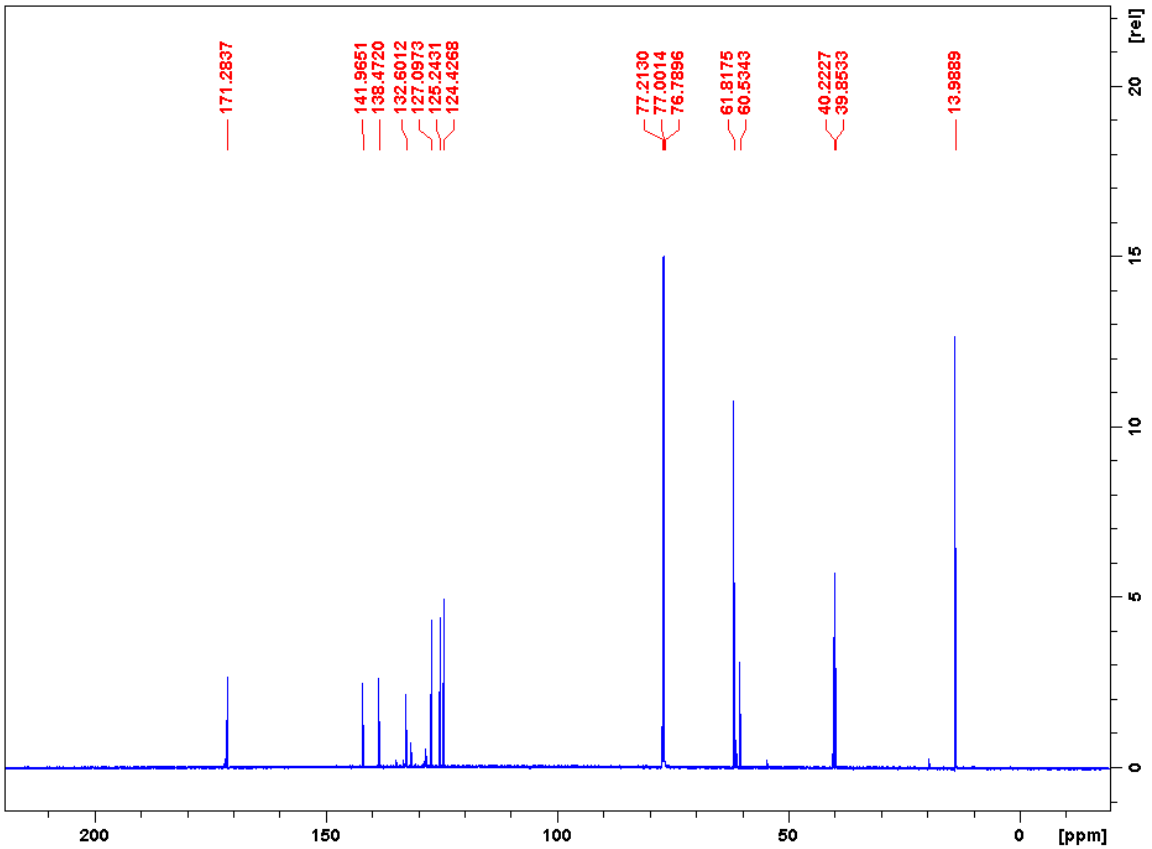
2.00
2.01
6.02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124.4268
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77.0014
76.7896
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13.9889
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5
0
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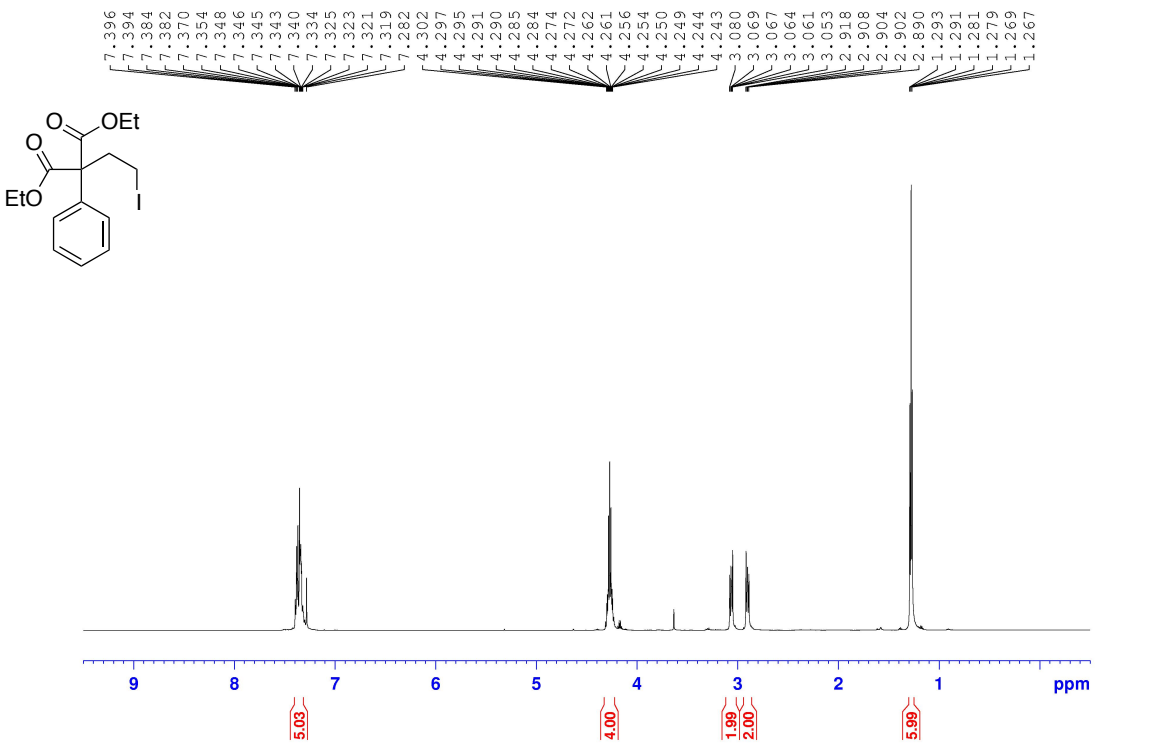
150
100
50
0
[ppm]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7.340
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7.325
7.323
7.321
7.319
7.282
4.302
4.297
4.295
4.291
4.290
4.285
4.284
4.274
4.272
4.262
4.261
4.256
4.254
4.250
4.249
4.244
4.243
3.080
3.069
3.067
3.064
3.061
3.053
2.918
2.908
2.904
2.902
2.890
1.293
1.291
1.281
1.279
1.269
1.267
O
OEt
O
EtO
I
9
8
7
6
5
4
3
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ppm
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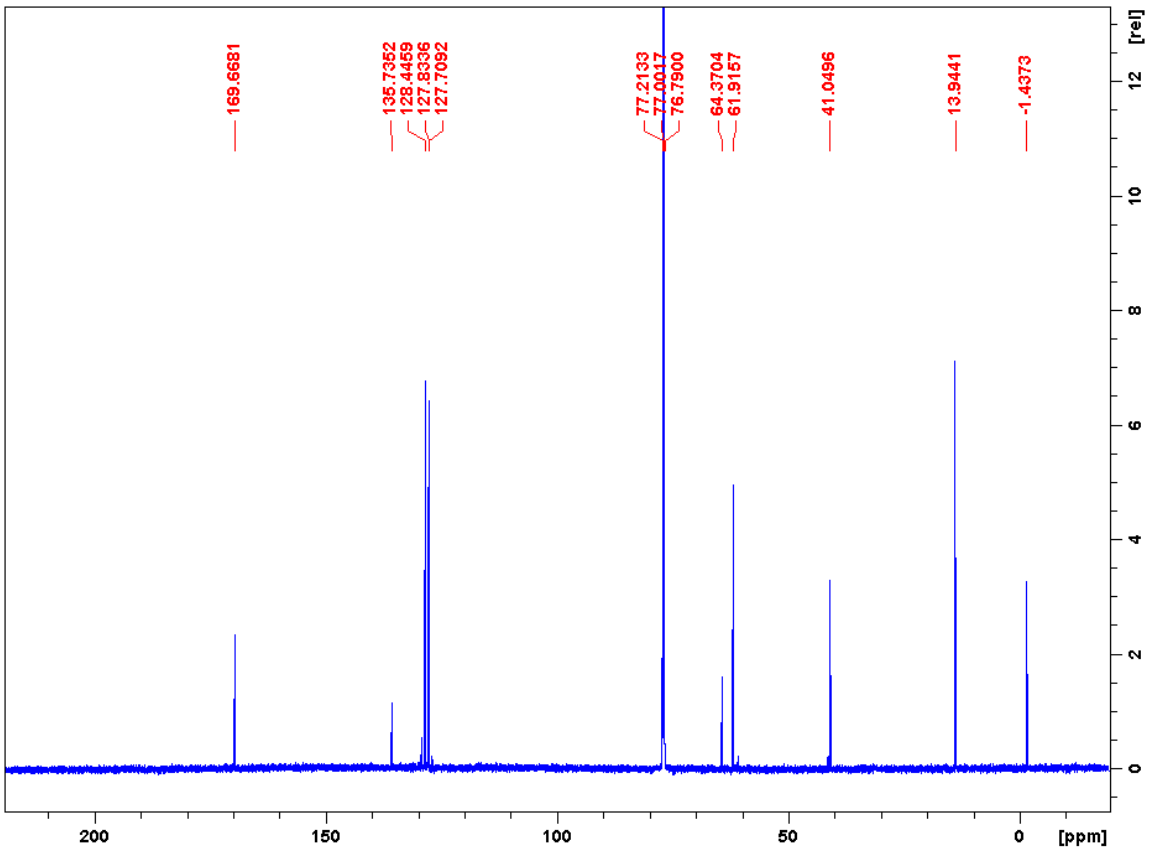
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[rel]
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8
6
4
2
0
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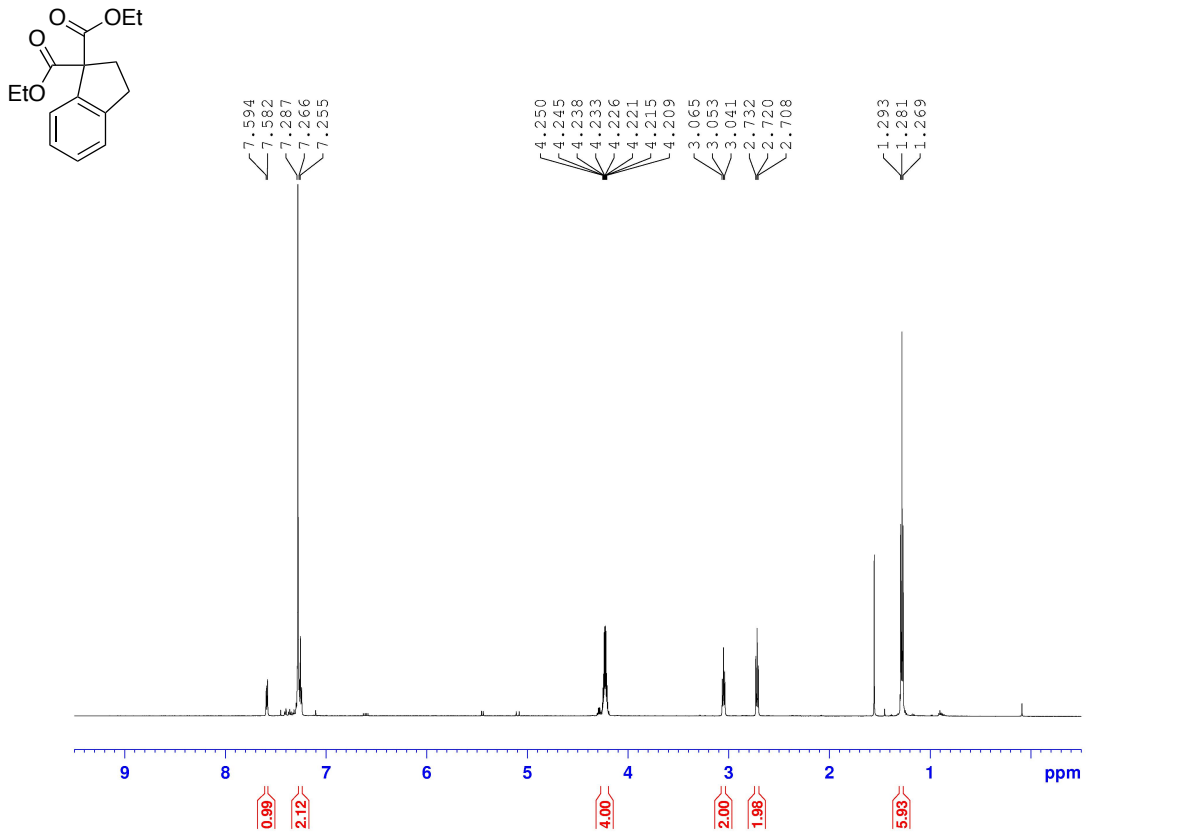
150
100
50
0
[ppm]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OEt
O
EtO
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7.266
7.255
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4.245
4.238
4.233
4.226
4.221
4.215
4.209
3.065
3.053
3.041
2.732
2.720
2.708
1.293
1.281
1.269
9
8
7
6
5
4
3
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1
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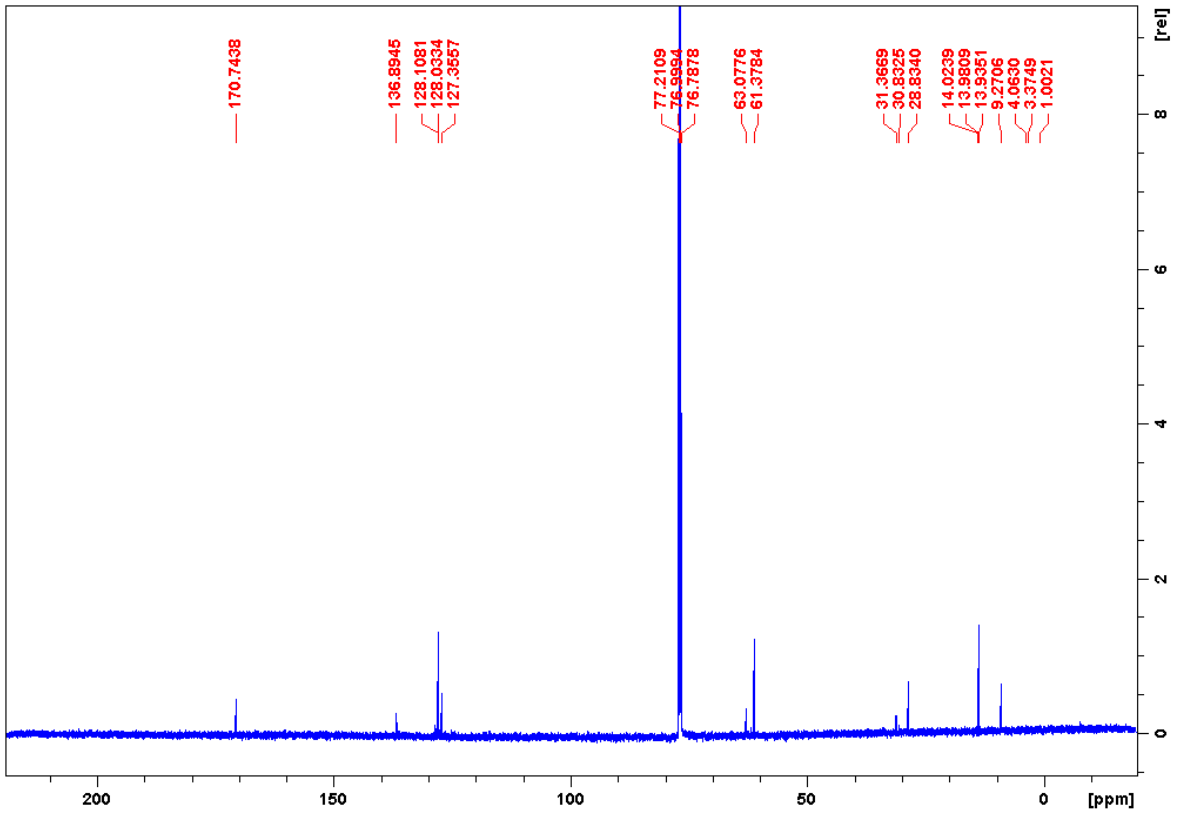
5.93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128.0334
127.3557
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76.9994
76.7878
63.0776
61.3784
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14.0239
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1.0021
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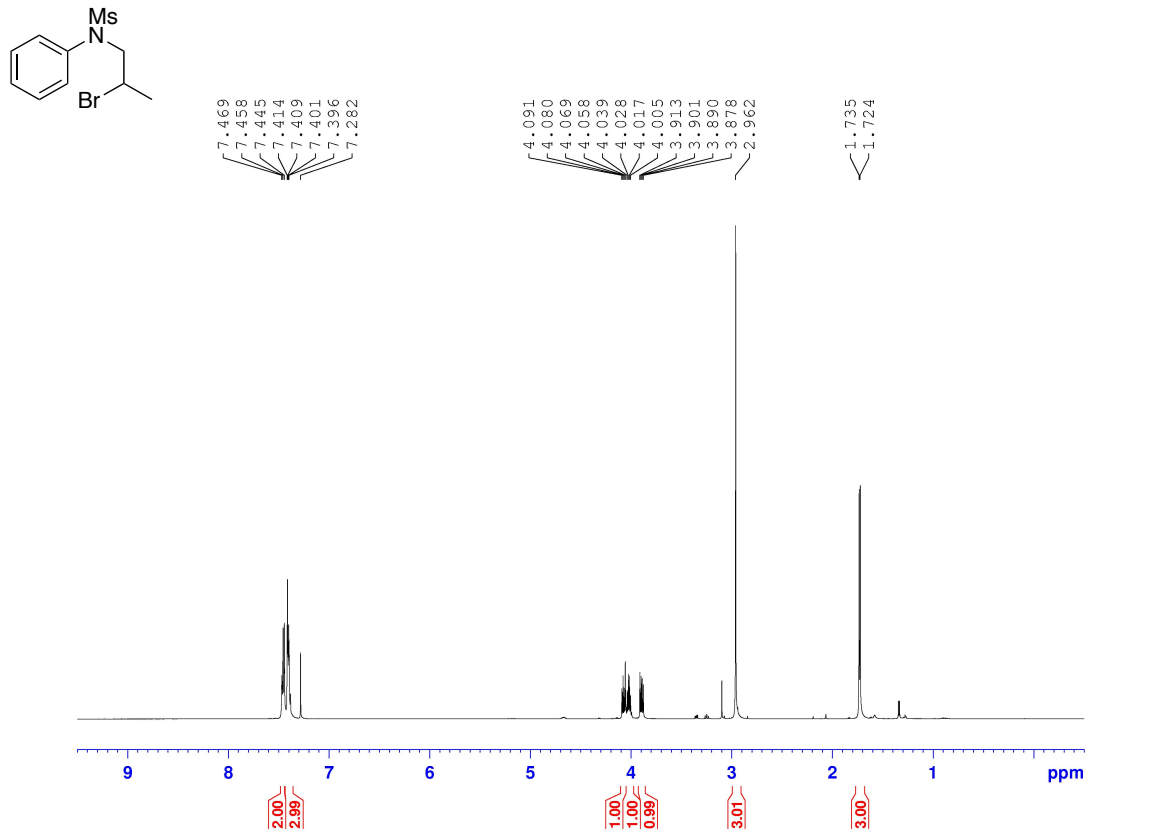
100
50
0
[ppm]


Ms
N
Br
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7.409
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7.282
4.091
4.080
4.069
4.058
4.039
4.028
4.017
4.005
3.913
3.901
3.890
3.878
2.962
1.735
1.724
9
8
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6
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3
2
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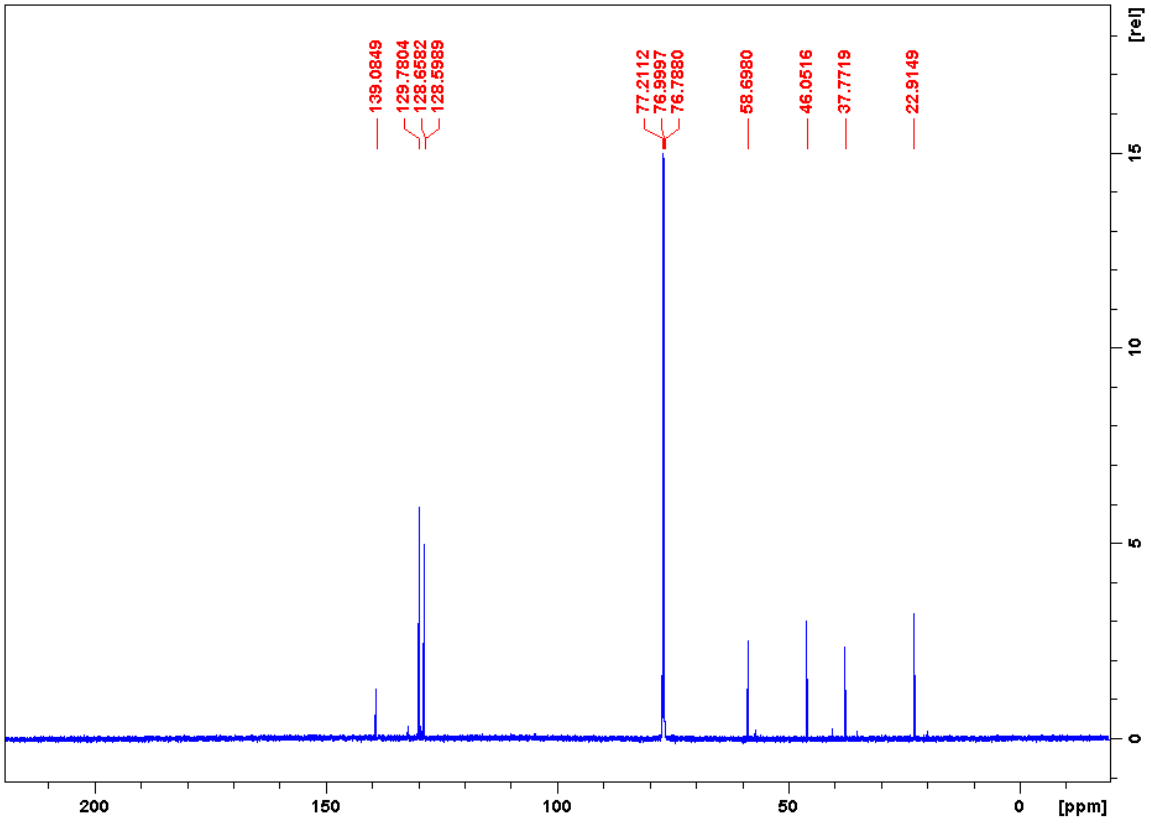
3.00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76.7880
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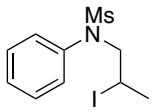
37.7719
22.9149
[rel]
15
10
5
0
200
150
100
50
0
[ppm]


Ms
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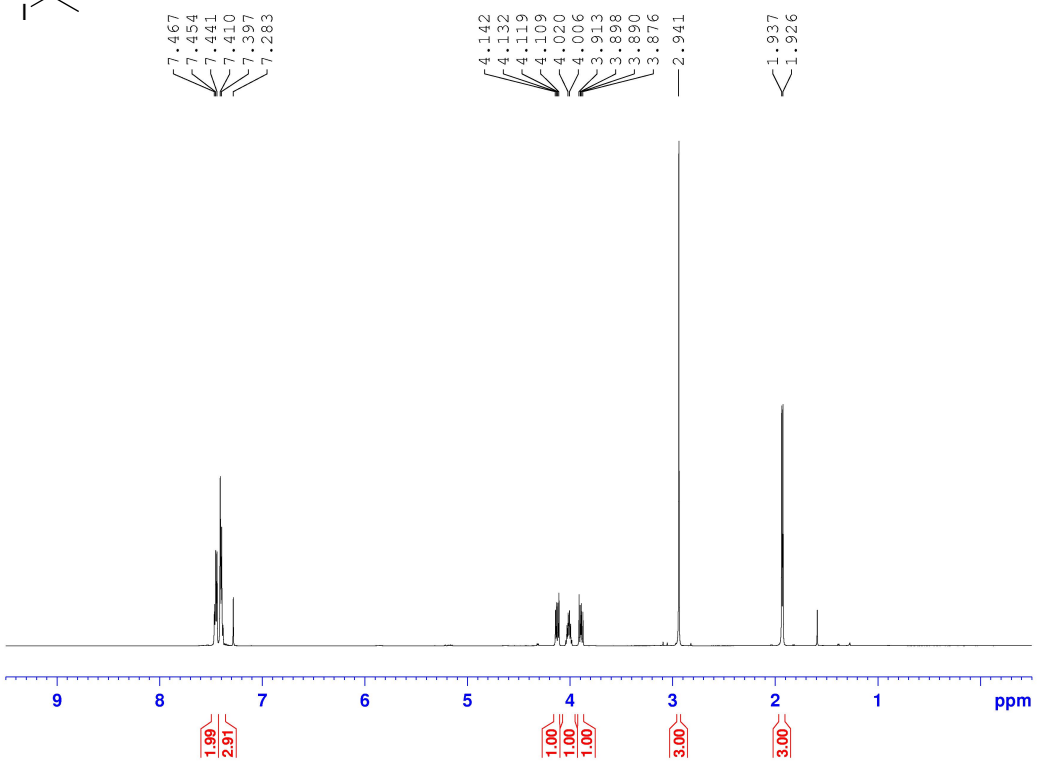
I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4.109
4.020
4.006
3.913
3.898
3.890
3.876
2.941
1.937
1.926
9
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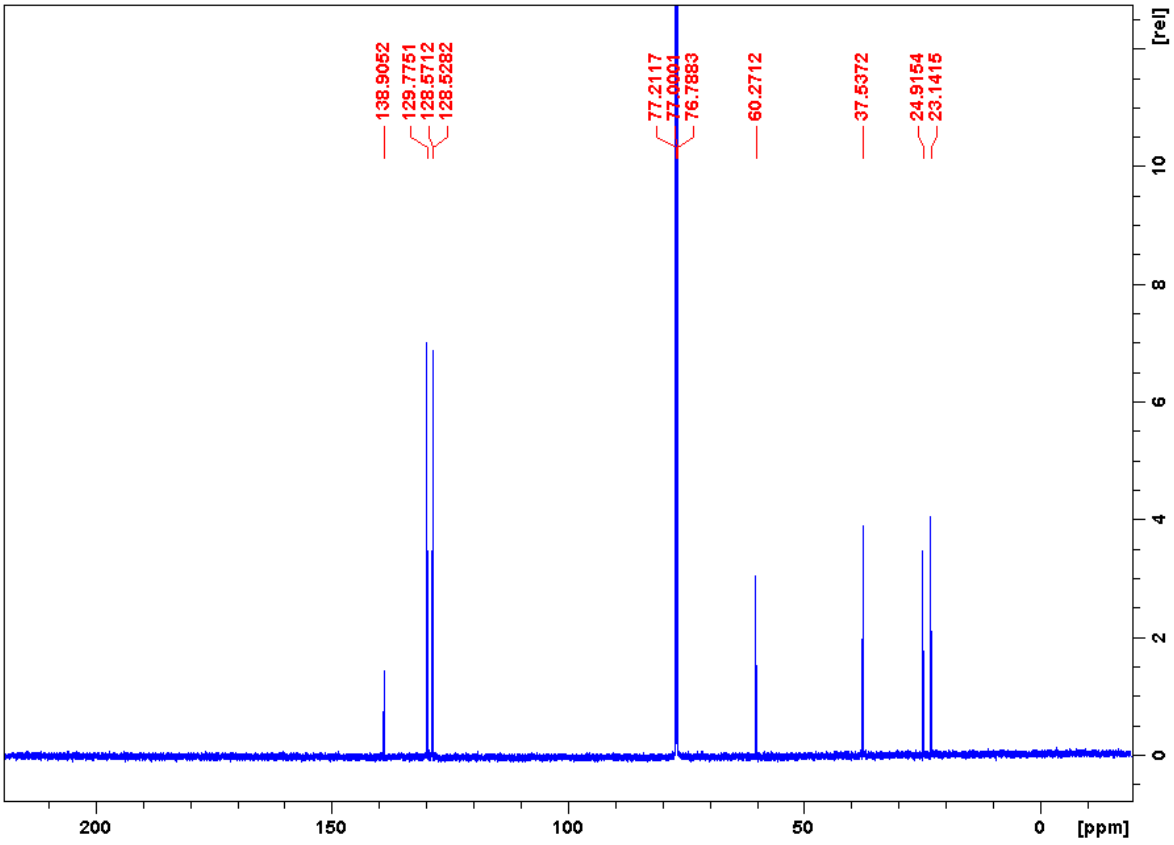
3.00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37.5372
24.9154
23.1415
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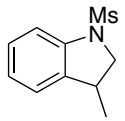
Ms
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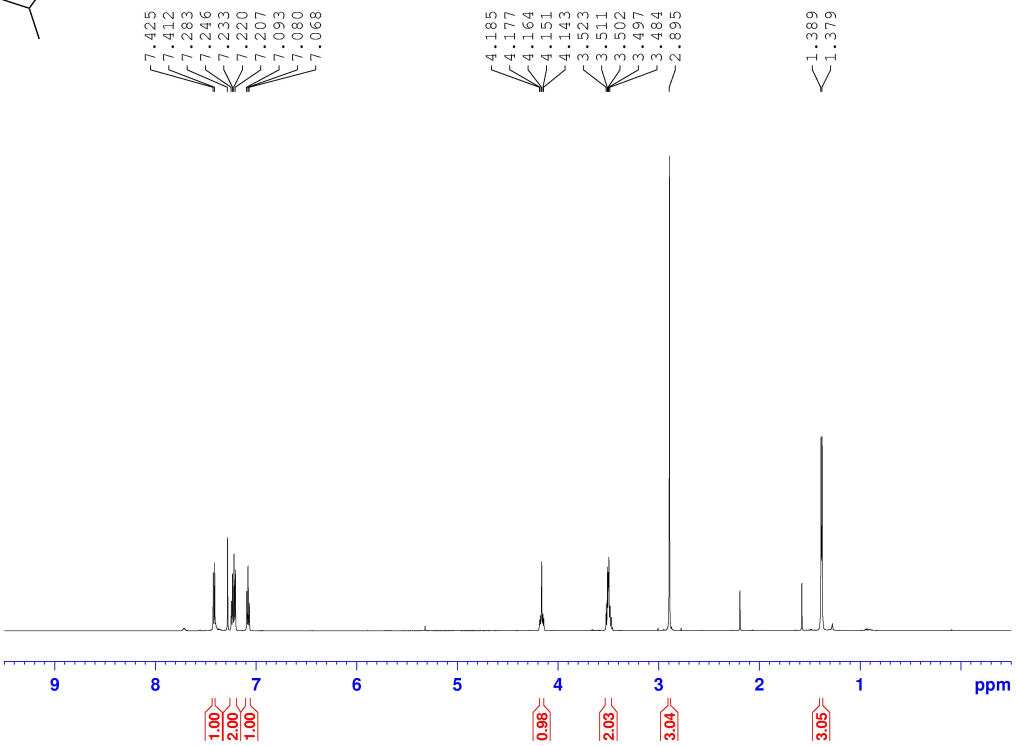
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7.246
7.233
7.220
7.207
7.093
7.080
7.068
4.185
4.177
4.164
4.151
4.143
3.523
3.511
3.502
3.497
3.484
2.895
1.389
1.379
9
8
7
6
5
4
3
2
1
ppm
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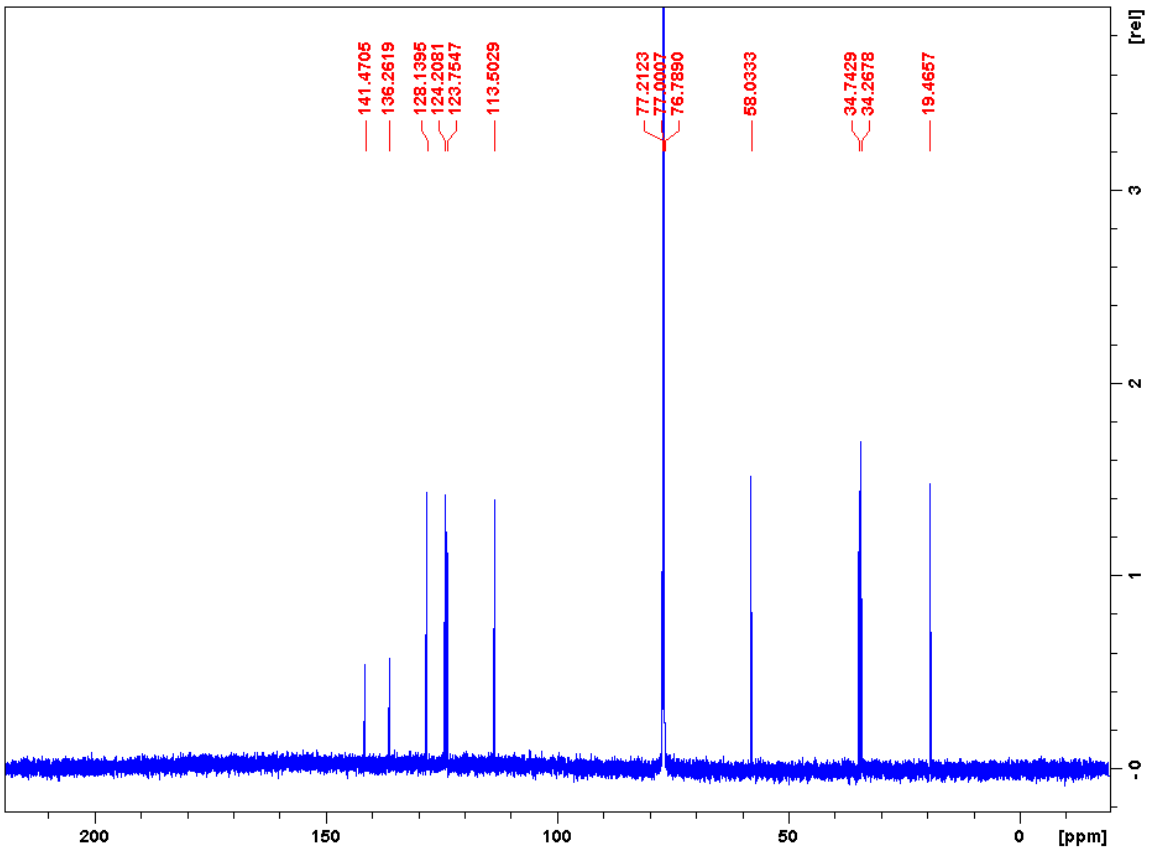
2.00
1.00
0.98
2.03
3.04
3.05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136.2619
128.1395
124.2081
123.7547
113.5029
77.2123
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76.7890
58.0333
34.7429
34.2678
19.4657
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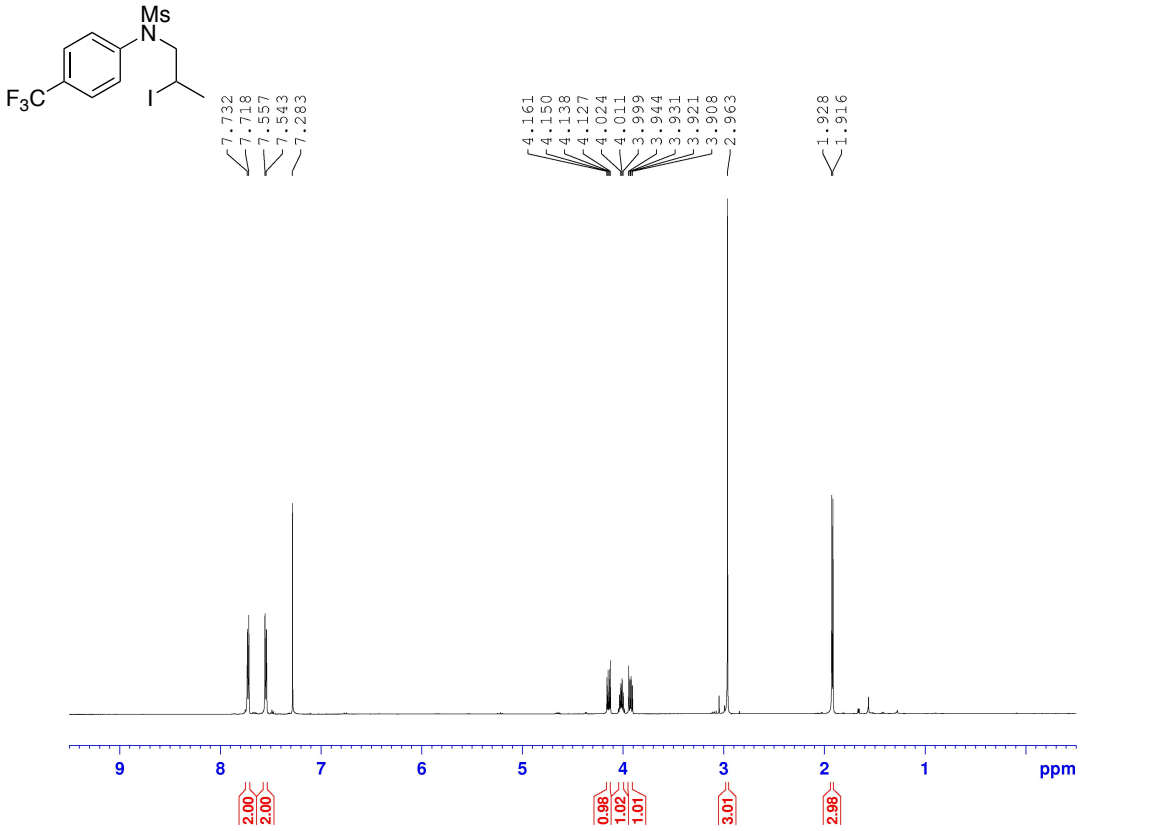
200
150
100
50
0
[ppm]


Ms
N
I
F3C
7.732
7.718
7.557
7.543
7.283
4.161
4.150
4.138
4.127
4.024
4.011
3.999
3.944
3.931
3.921
3.908
2.963
1.928
1.916
9
8
7
6
5
4
3
2
1
ppm
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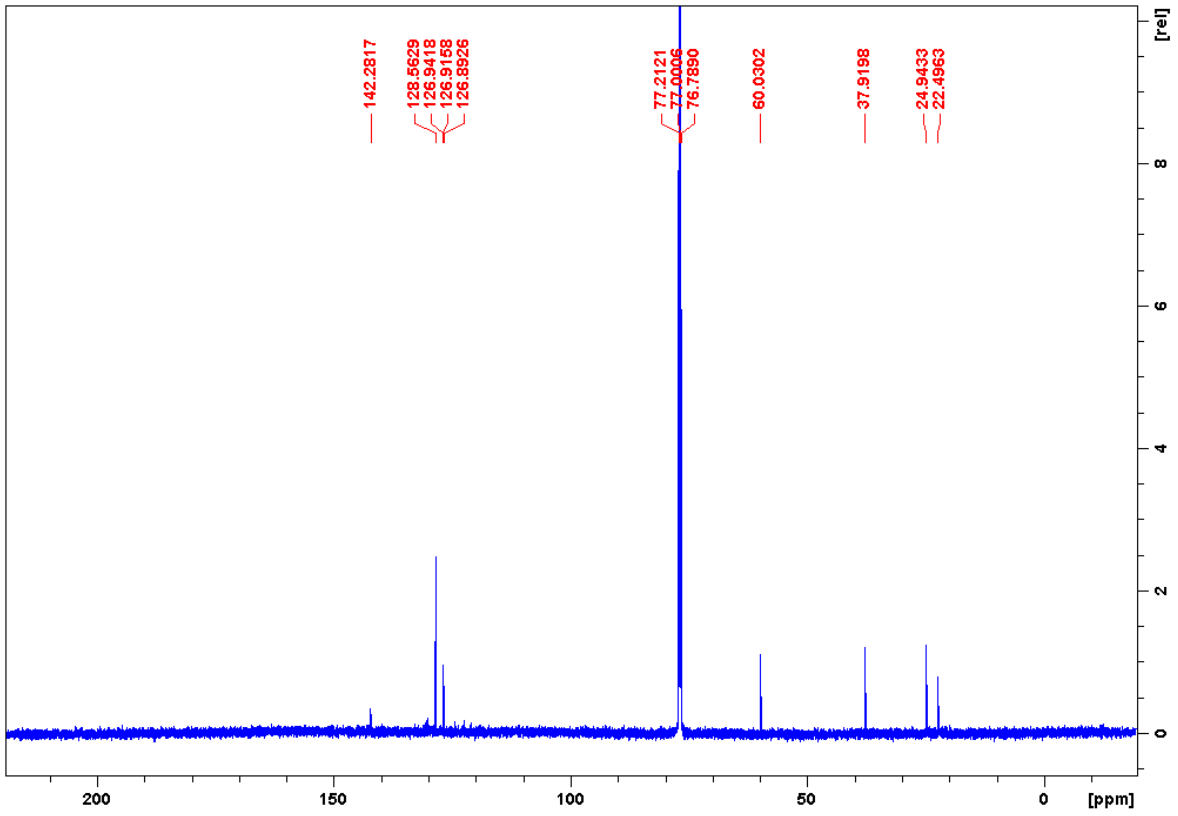
2.00
0.98
1.02
1.01
3.01
2.98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128.5629
126.9418
126.9158
126.8926
77.2121
77.0006
76.7890
60.0302
37.9198
24.9433
22.4963
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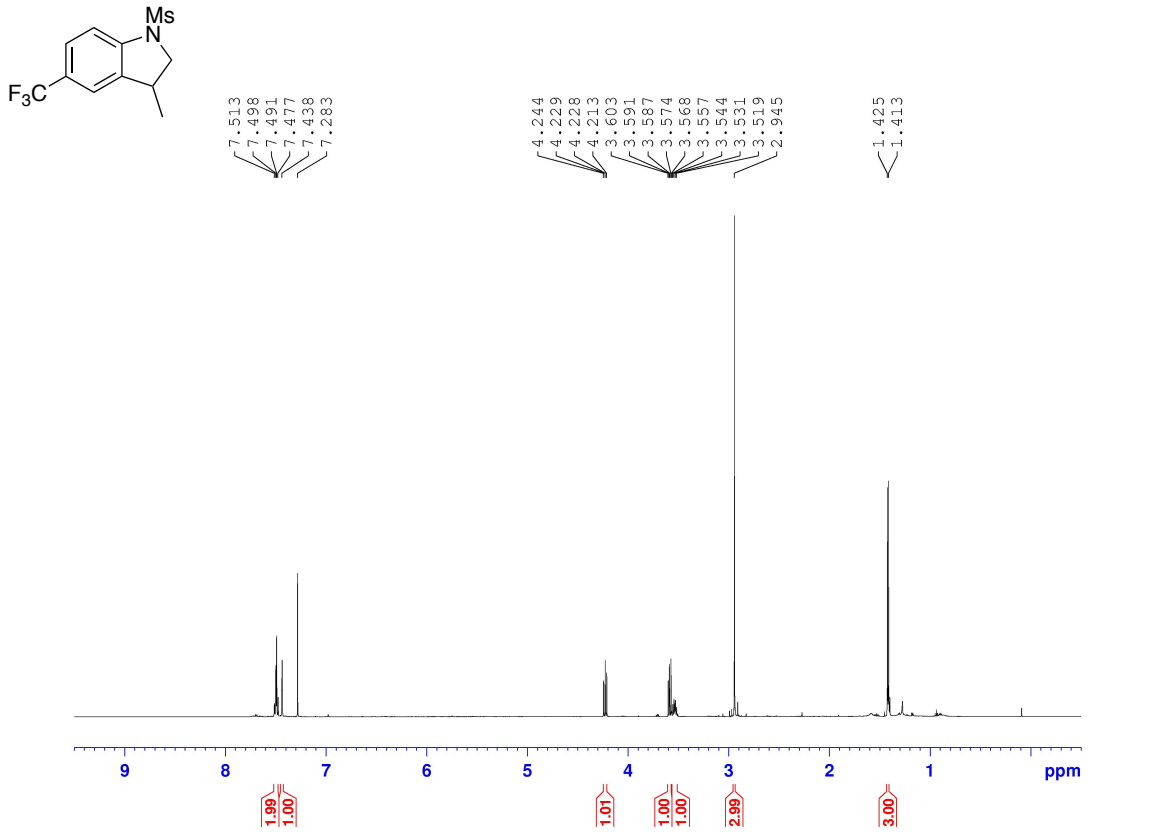
100
50
0
[ppm]


Ms
N
F3C
7.513
7.498
7.491
7.477
7.438
7.283
4.244
4.229
4.228
4.213
3.603
3.591
3.587
3.574
3.568
3.557
3.544
3.531
3.519
2.945
1.425
1.413
9
8
7
6
5
4
3
2
1
ppm
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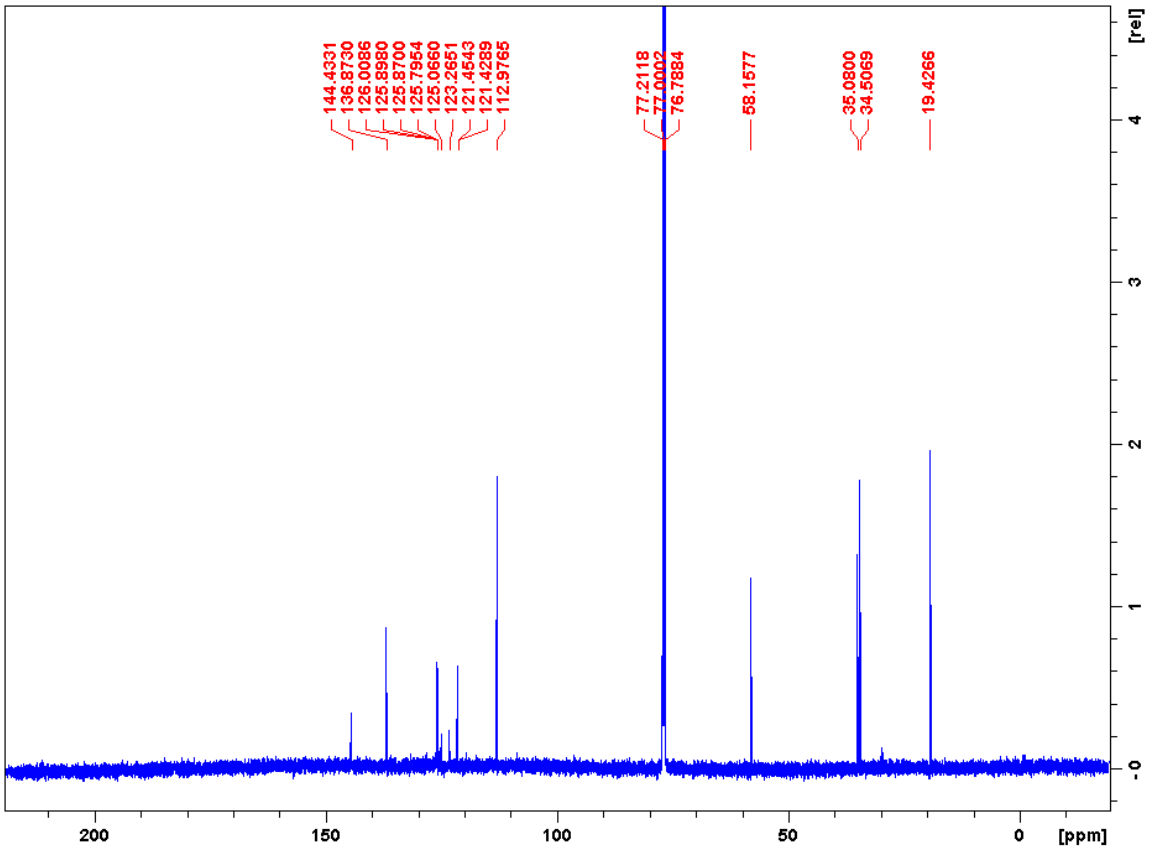
1.00
1.01
1.00
1.00
2.99
3.00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136.8730
126.0086
125.8980
125.8700
125.7954
125.0660
123.2651
121.4543
121.4289
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77.2118
77.0002
76.7884
58.1577
35.0800
34.5069
19.4266
[rel]
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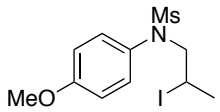
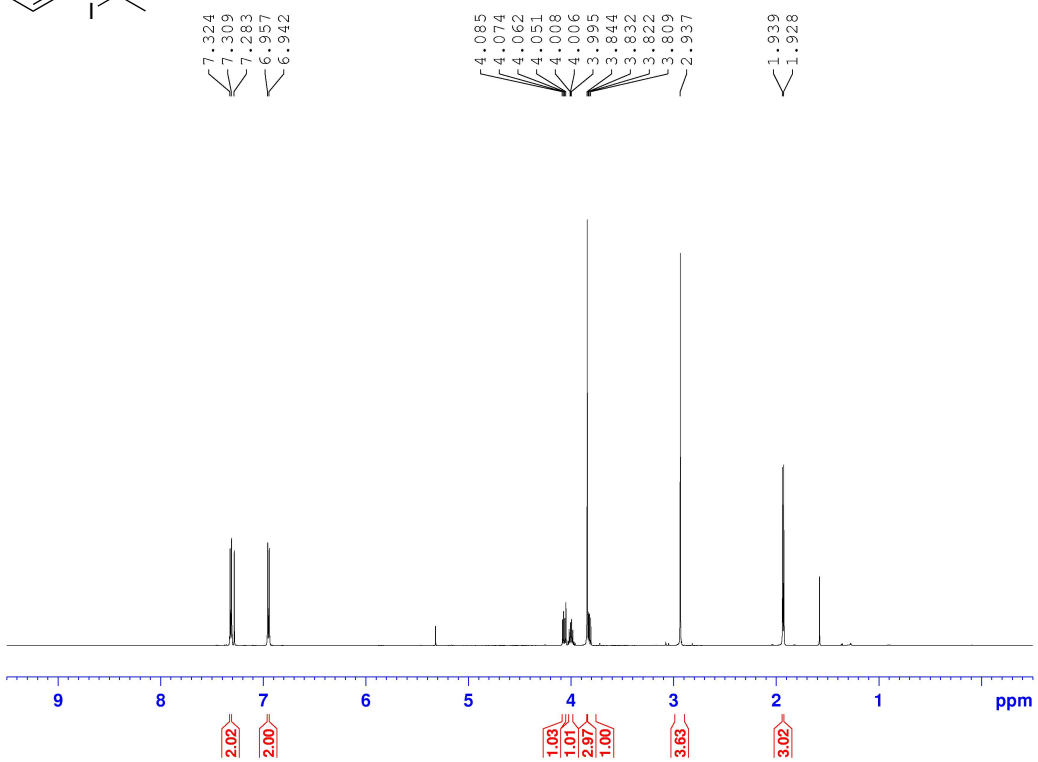
150
100
50
0
[ppm]


Ms
N
MeO
I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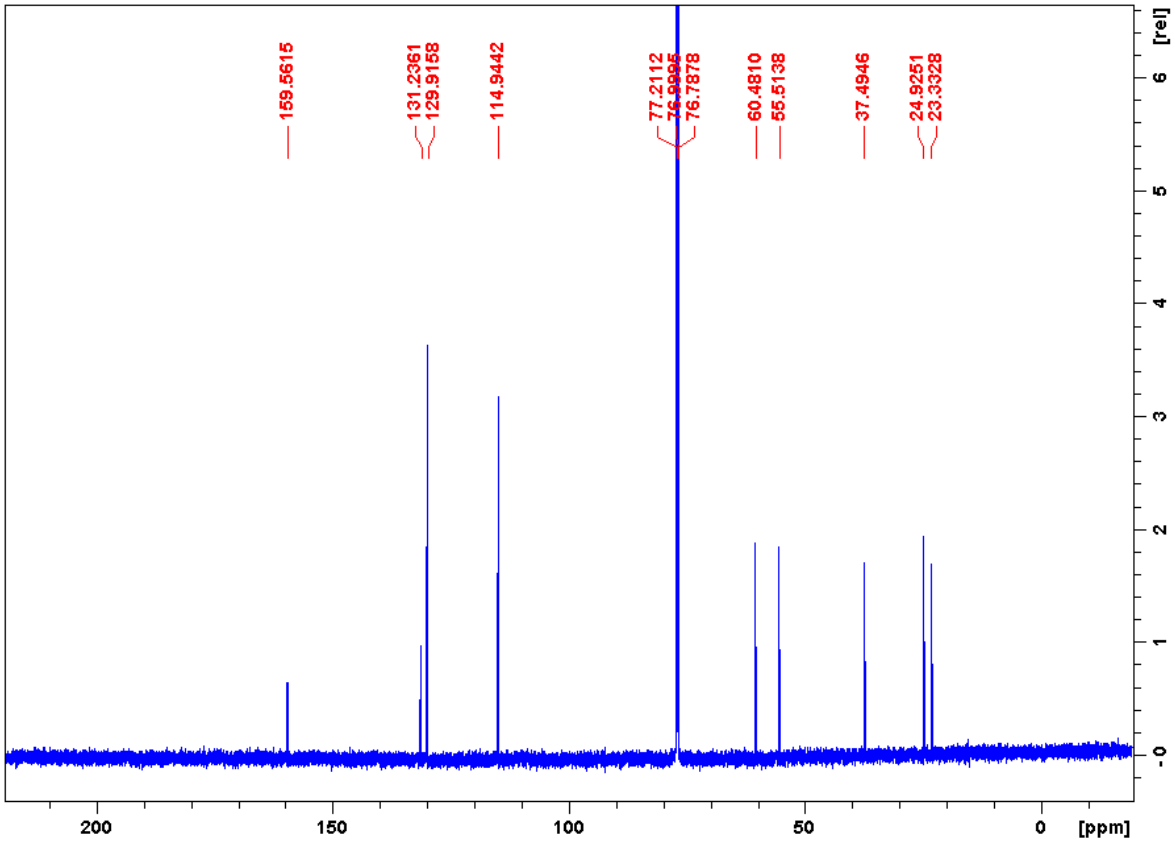
7.309
7.283
6.957
6.942
4.085
4.074
4.062
4.051
4.008
4.006
3.995
3.844
3.832
3.822
3.809
2.937
1.939
1.928
9
8
7
6
5
4
3
2
1
ppm
2.02
2.00
1.03
1.01
2.97
1.00
3.63
3.02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131.2361
129.9158
114.9442
77.2112
76.7878
60.4810
55.5138
37.4946
24.9251
23.3328
200
150
100
50
0
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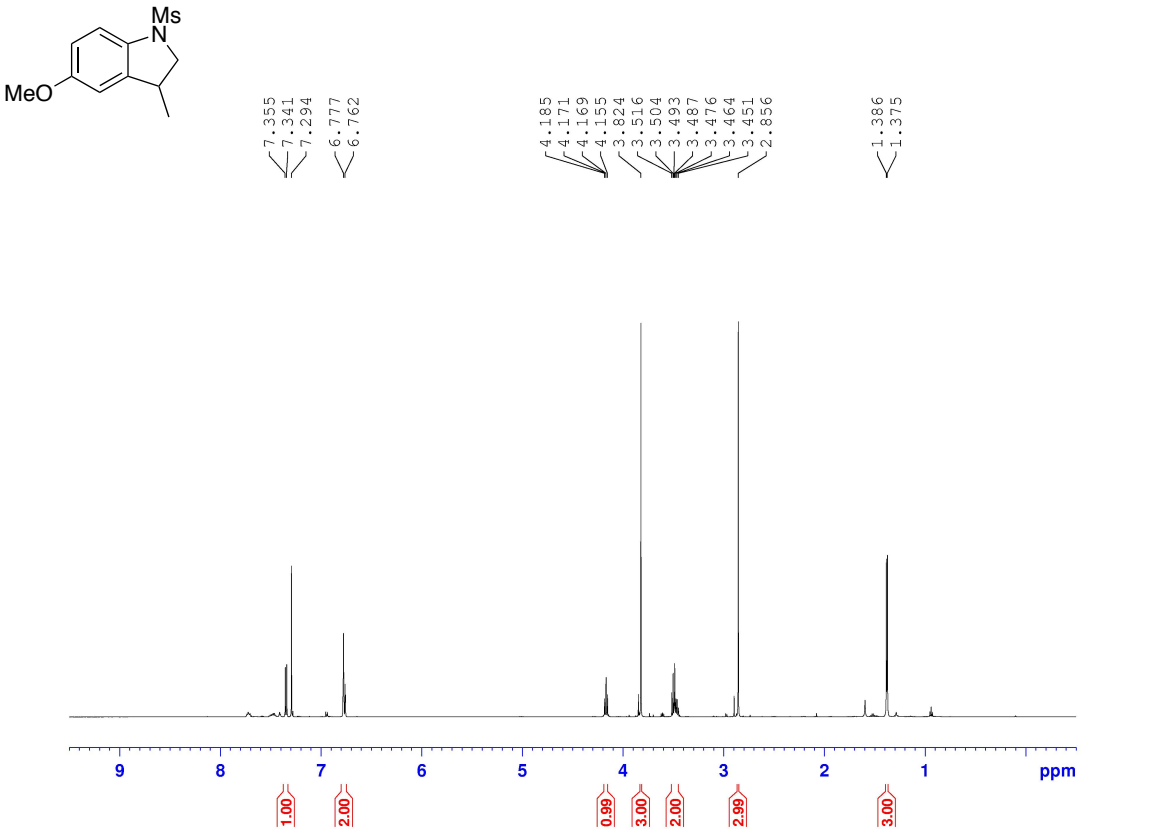
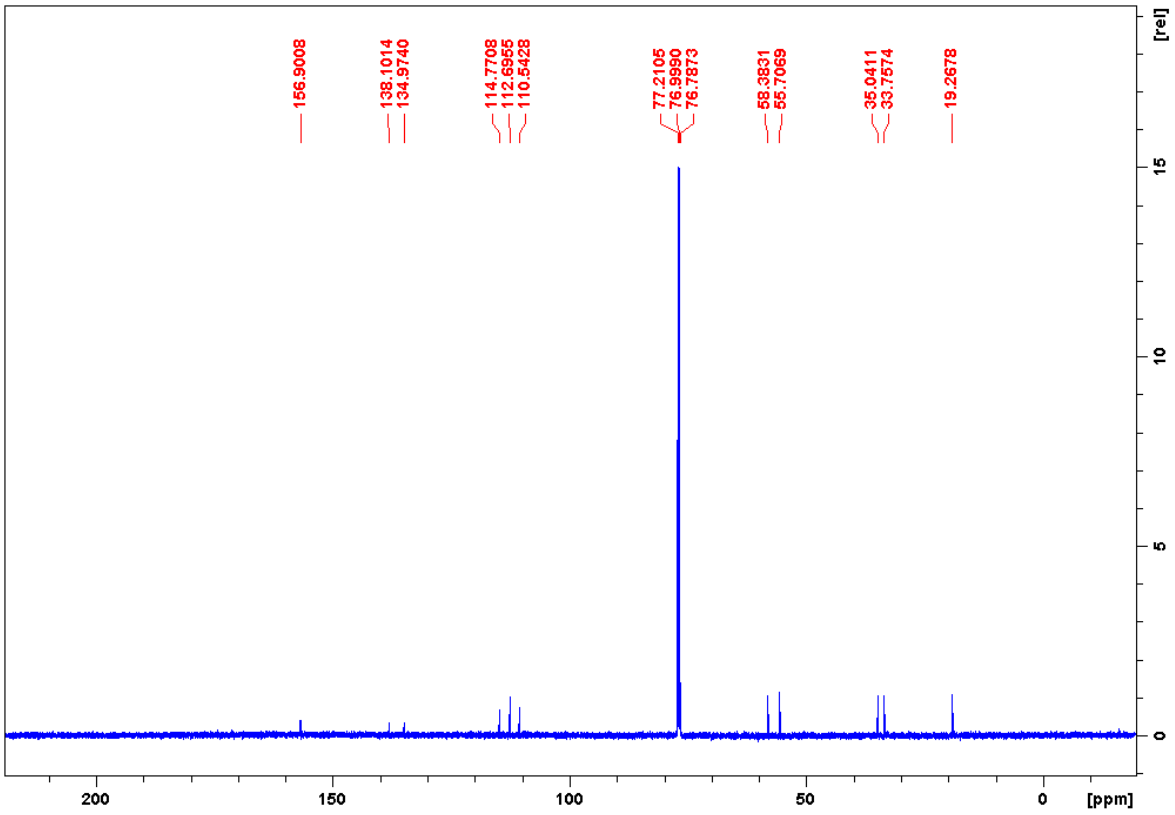
[rel]


Ms
N
MeO
7.355
7.341
7.294
6.777
6.762
4.185
4.171
4.169
4.155
3.824
3.516
3.504
3.493
3.487
3.476
3.464
3.451
2.856
1.386
1.375
9
8
7
6
5
4
3
2
1
ppm
1.00
2.00
0.99
3.00
2.00
2.99
3.00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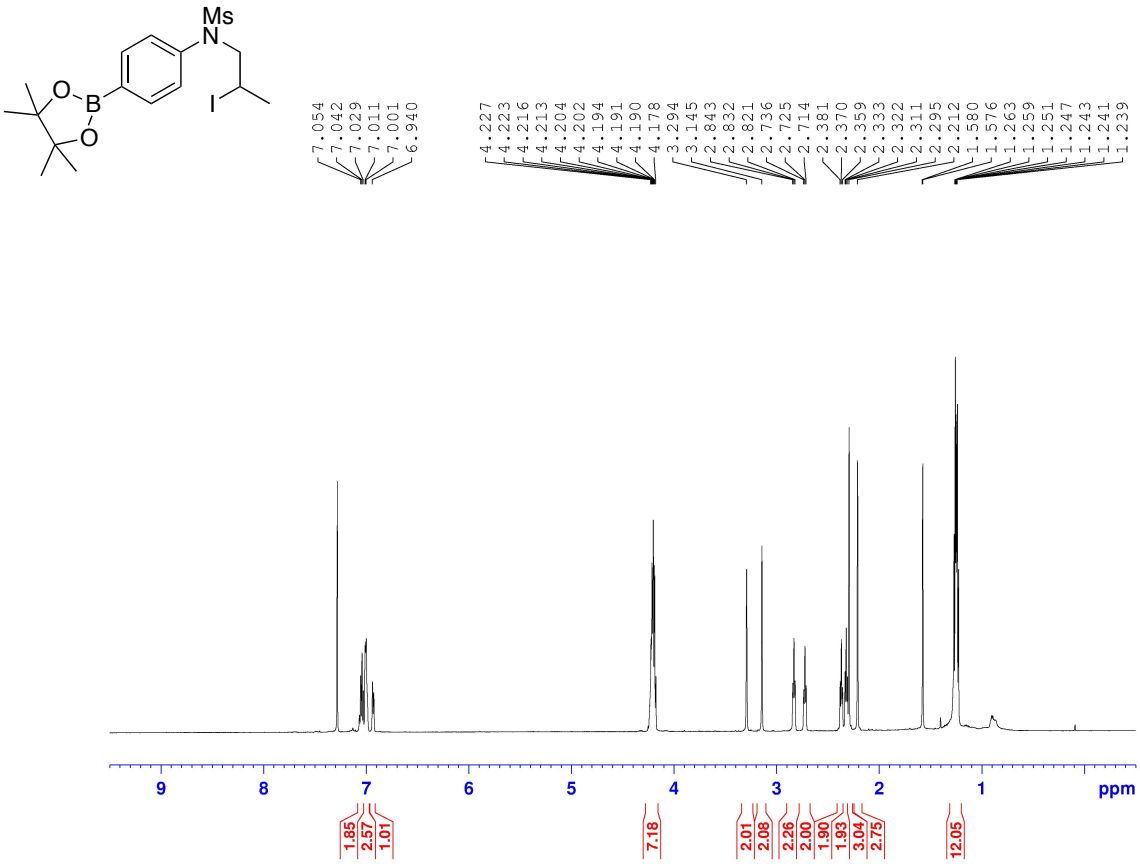
138.1014
134.9740
114.7708
112.6955
110.5428
77.2105
76.9990
76.7873
58.3831
55.7069
35.0411
33.7574
19.2678
[rel]
15
10
5
0
200
150
100
50
0
[ppm]


Ms
N
O
B
O
I
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7.042
7.029
7.011
7.001
6.940
4.227
4.223
4.216
4.213
4.204
4.202
4.194
4.191
4.190
4.178
3.294
3.145
2.843
2.832
2.821
2.736
2.725
2.714
2.381
2.370
2.359
2.333
2.322
2.311
2.295
2.212
1.580
1.576
1.263
1.259
1.251
1.247
1.243
1.241
1.239
9
8
7
6
5
4
3
2
1
ppm
1.85
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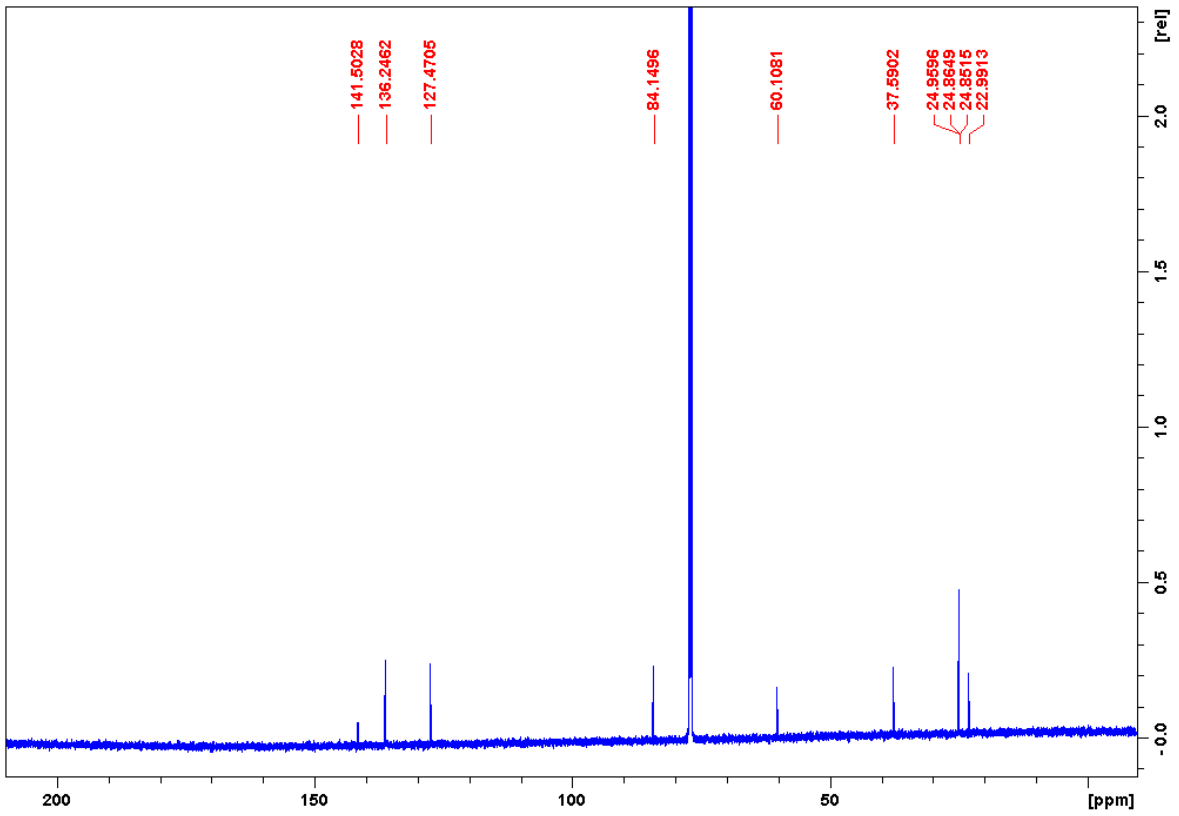
7.18
2.01
2.08
2.26
2.00
1.90
1.93
3.04
2.75
12.05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127.4705
84.1496
60.1081
37.5902
24.9596
24.8649
24.8515
22.9913
[rel]
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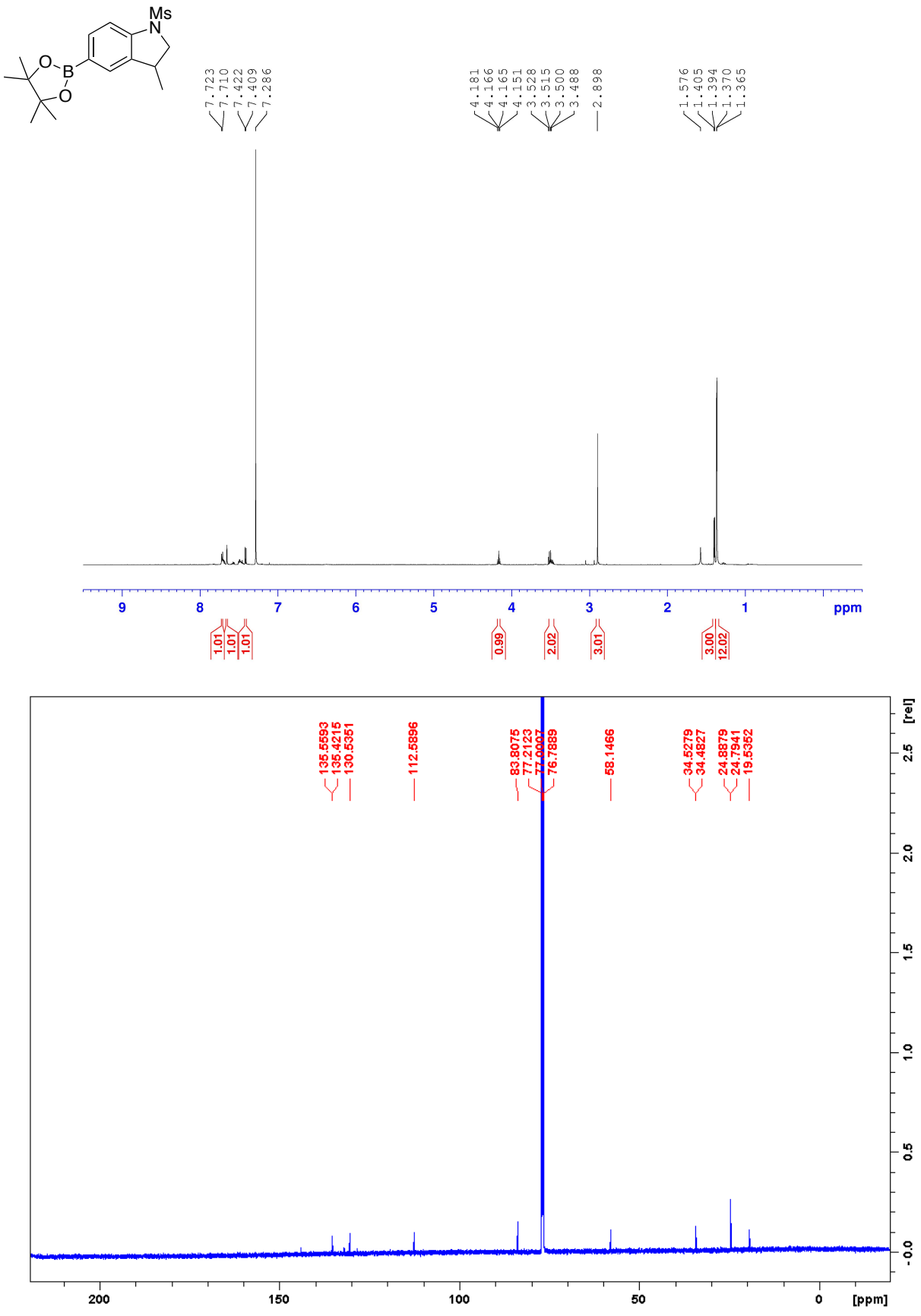
1.5
1.0
0.5
-0.0
200
150
100
50
[ppm]


Ms
N
O
B
O
7.723
7.710
7.422
7.409
7.286
4.181
4.166
4.165
4.151
3.528
3.515
3.500
3.488
2.898
1.576
1.405
1.394
1.370
1.365
9
8
7
6
5
4
3
2
1
ppm
1.01
1.01
1.01
0.99
2.02
3.01
3.00
12.02
135.5593
135.4215
130.5351
112.5896
83.8075
77.2123
77.0007
76.7889
58.1466
34.5279
34.4827
24.8879
24.7941
19.5362
[rel]
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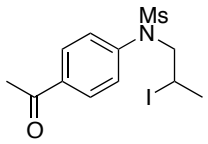
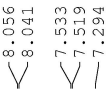
2.0
1.5
1.0
0.5
-0.0
200
150
100
50
0
[ppm]


Ms
N
I
O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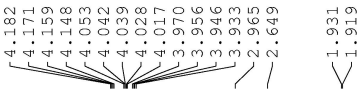
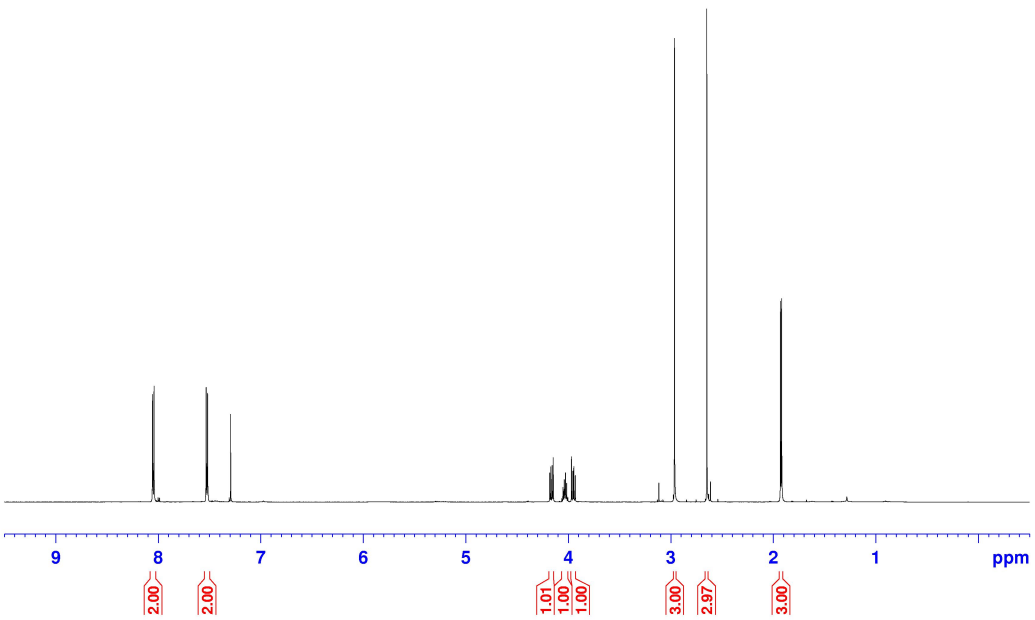
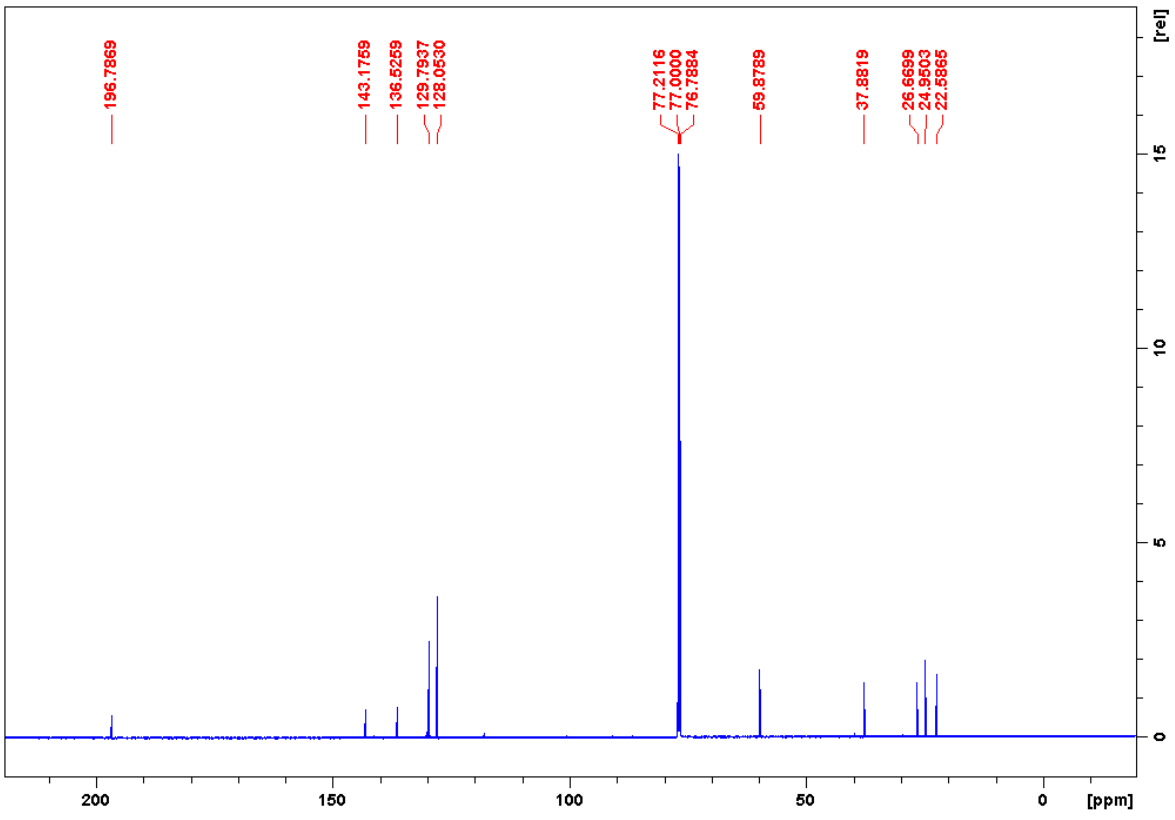
8.041
7.533
7.519
7.294


4.182
4.171
4.159
4.148
4.053
4.042
4.039
4.028
4.017
3.970
3.956
3.946
3.933
2.965
2.649
1.931
1.919


9
8
7
6
5
4
3
2
1
ppm
2.00
2.00
1.01
1.00
1.00
3.00
2.97
3.00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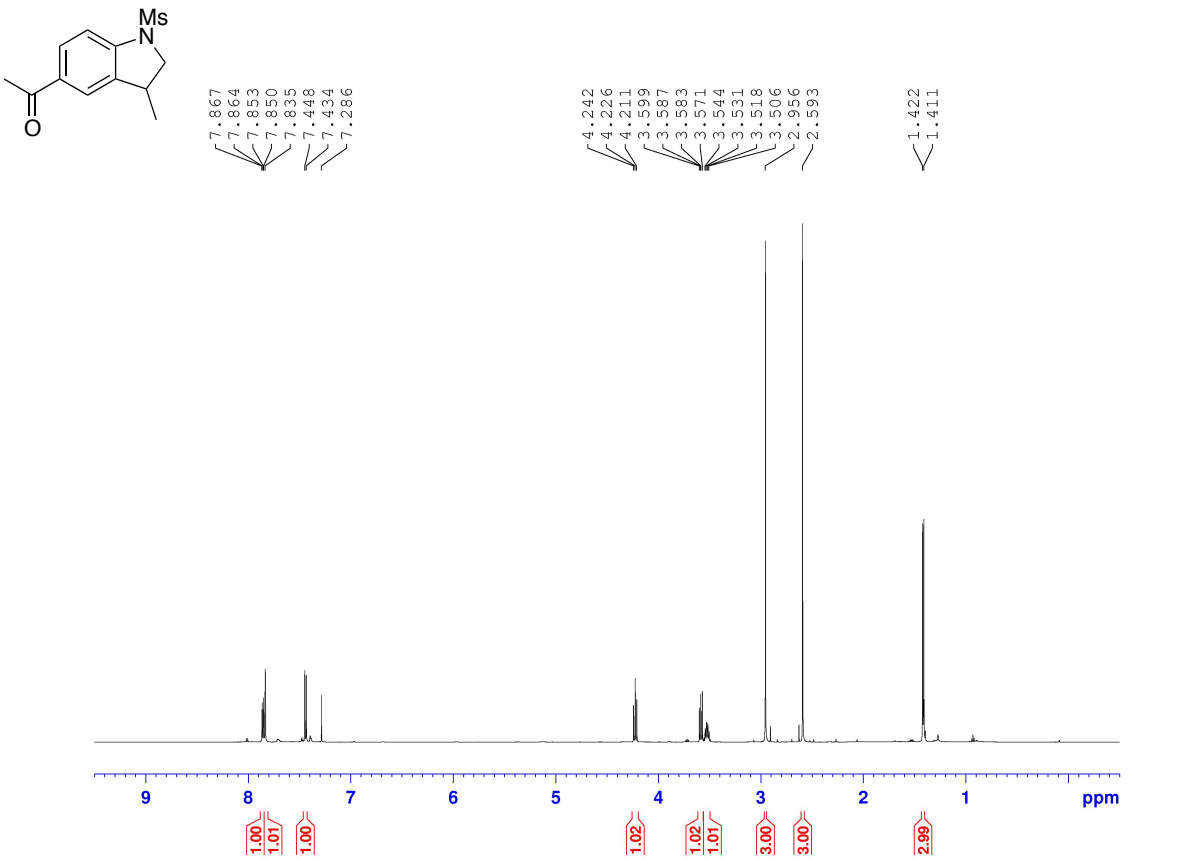
143.1759
136.5259
129.7937
128.0530
77.2116
77.0000
76.7884
59.8789
37.8819
26.6699
24.9503
22.5865
[rel]
15
10
5
0
200
150
100
50
0
[ppm]


Ms
N
O
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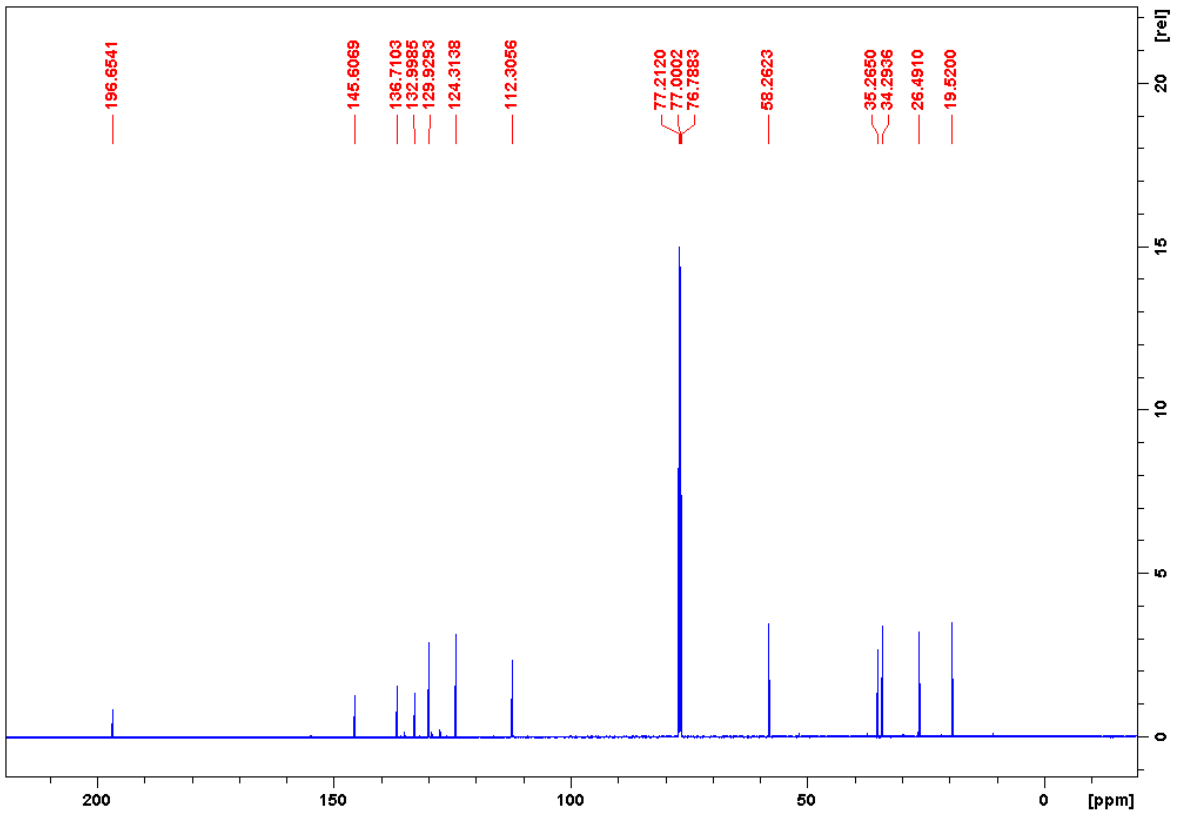
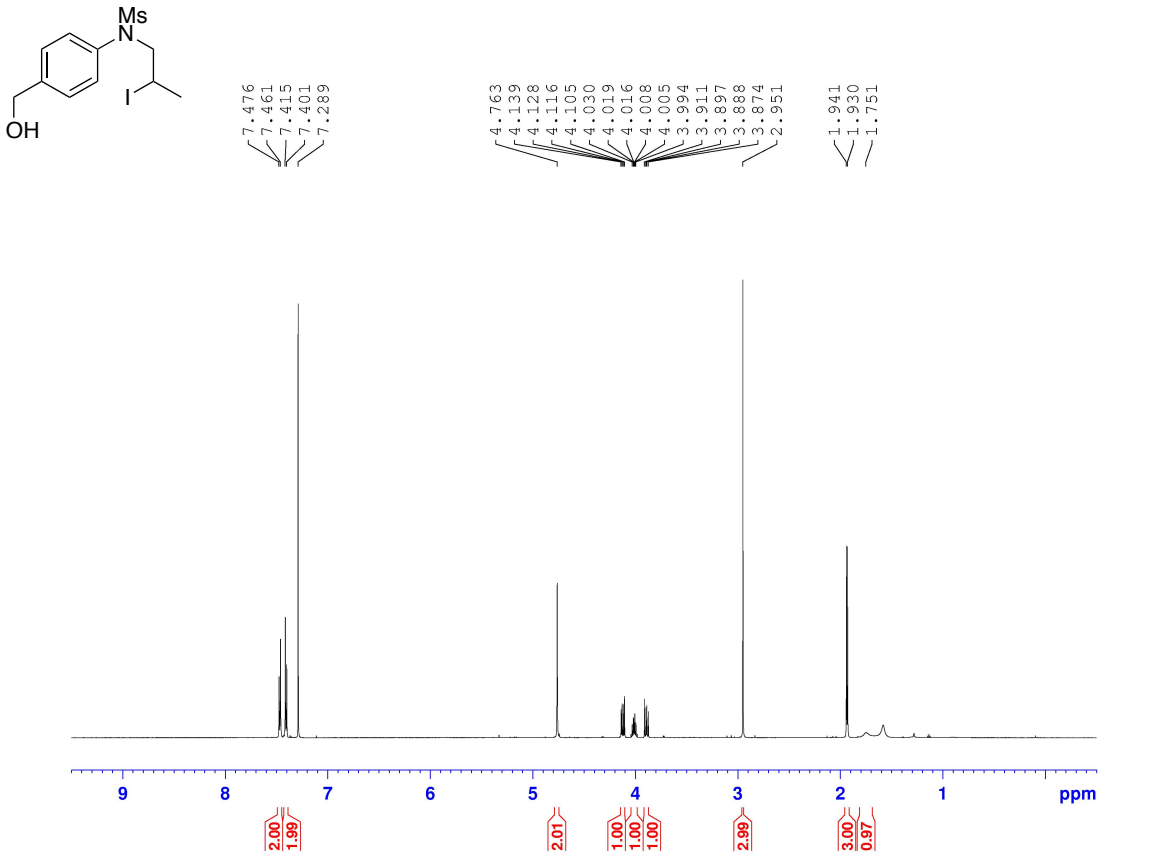
7.853
7.850
7.835
7.448
7.434
7.286
4.242
4.226
4.211
3.599
3.587
3.583
3.571
3.544
3.531
3.518
3.506
2.956
2.593
1.422
1.411
9
8
7
6
5
4
3
2
1
ppm
1.00
1.01
1.00
1.02
1.02
1.01
3.00
3.00
2.99


196.6541
145.6069
136.7103
132.9985
129.9293
124.3138
112.3056
77.2120
77.0002
76.7883
58.2623
35.2650
34.2936
26.4910
19.5200
[rel]
20
15
10
5
0
200
150
100
50
0
[ppm]


Ms
N
I
OH
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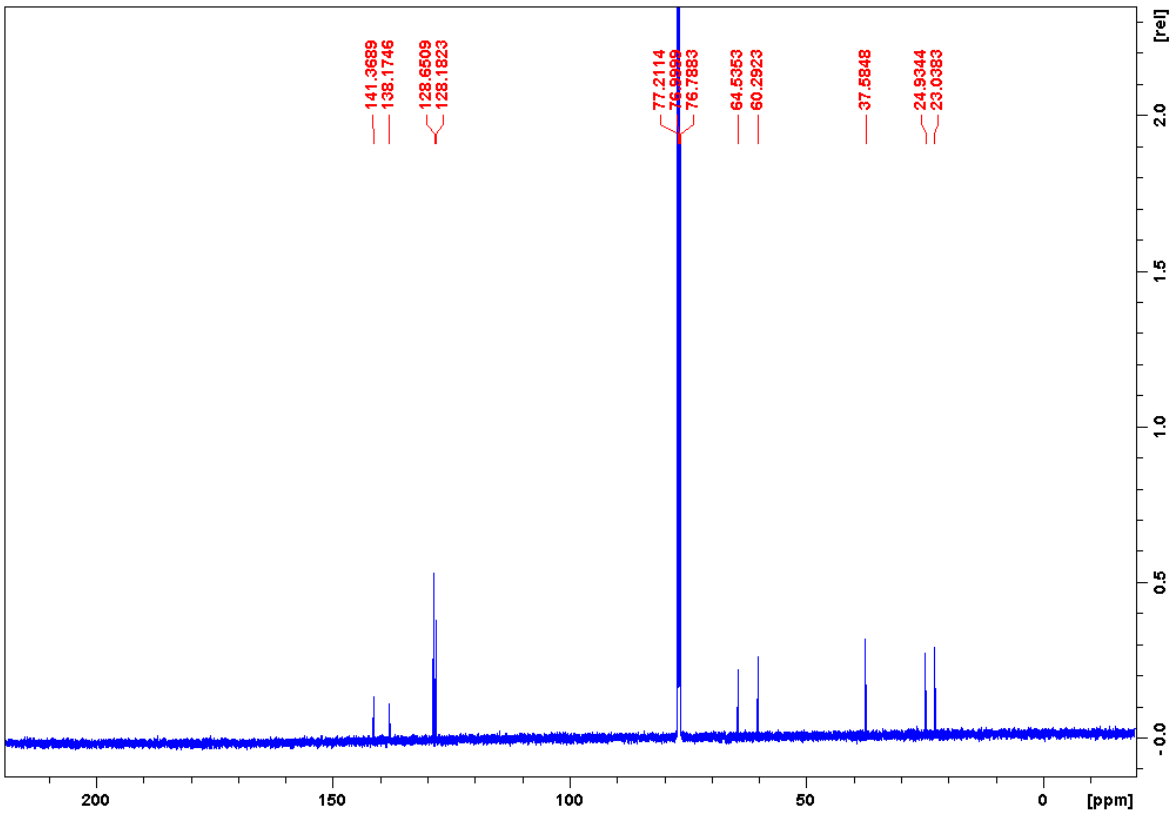
7.415
7.401
7.289
4.763
4.139
4.128
4.116
4.105
4.030
4.019
4.016
4.008
4.005
3.994
3.911
3.897
3.888
3.874
2.951
1.941
1.930
1.751
9
8
7
6
5
4
3
2
1
ppm
2.00
1.99
2.01
1.00
1.00
1.00
2.99
3.00
0.97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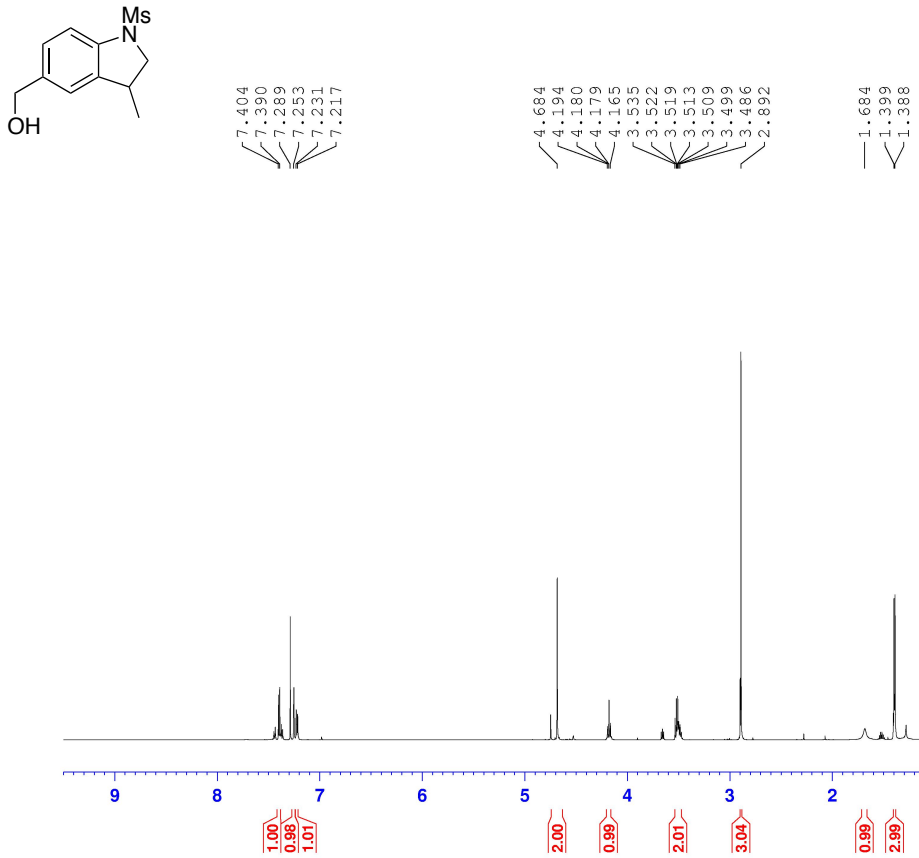
128.1823
77.2114
76.7883
64.5353
60.2923
37.5848
24.9344
23.0383
200
150
100
50
0
[ppm]
[rel]
2.0
1.5
1.0
0.5
-0.0


Ms
N
OH
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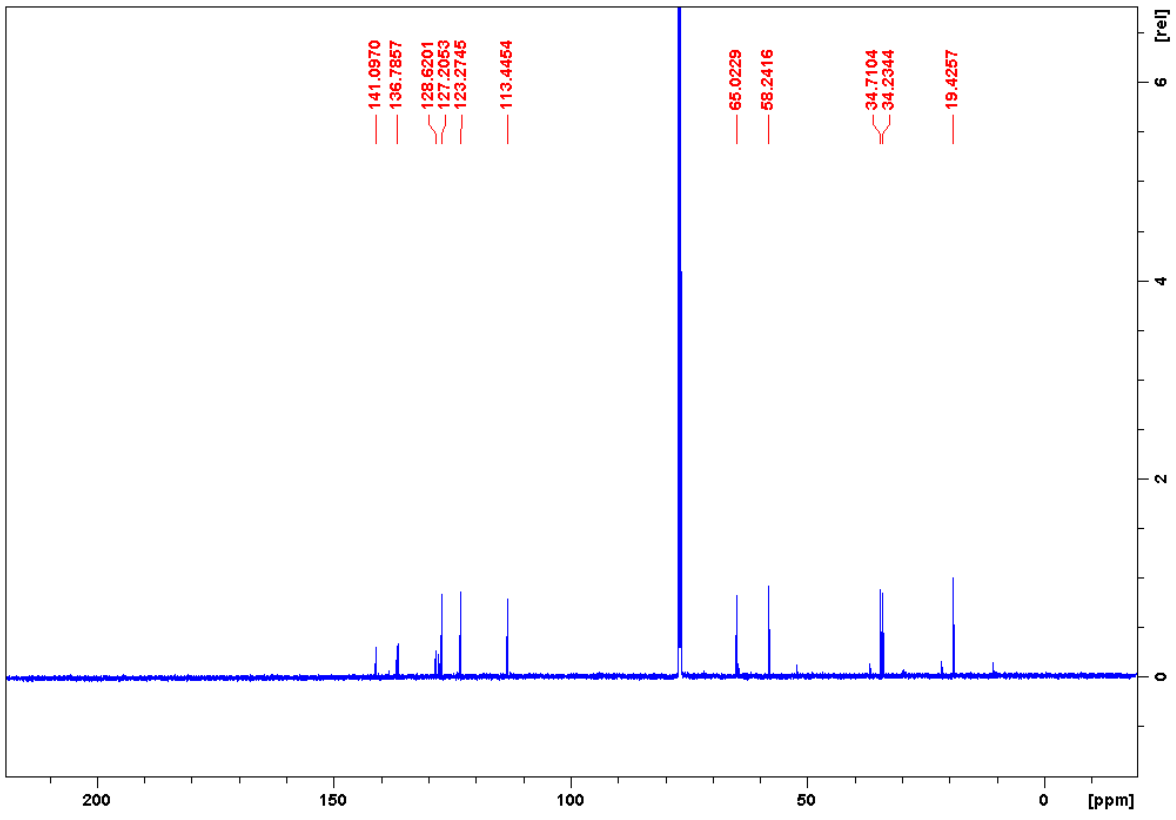
7.289
7.253
7.231
7.217
4.684
4.194
4.180
4.179
4.165
3.535
3.522
3.519
3.513
3.509
3.499
3.486
2.892
1.684
1.399
1.388
9
8
7
6
5
4
3
2
1
ppm
1.00
0.98
1.01
2.00
0.99
2.01
3.04
0.99
2.99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127.2053
123.2745
113.4454
65.0229
58.2416
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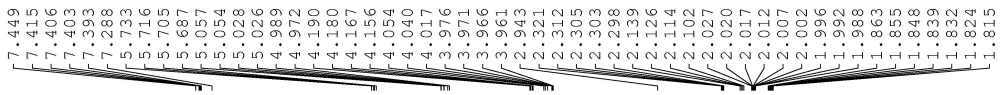
34.2344
19.4257
[rel]
6
4
2
0
200
150
100
50
0
[ppm]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7.415
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7.403
7.393
7.288
5.733
5.716
5.705
5.687
5.057
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5.028
5.026
4.989
4.972
4.190
4.180
4.167
4.156
4.054
4.040
4.017
3.976
3.971
3.966
3.961
3.943
2.321
2.312
2.305
2.303
2.298
2.139
2.126
2.114
2.102
2.027
2.020
2.017
2.012
2.007
2.002
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1.992
1.988
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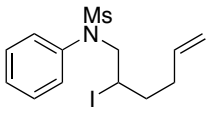
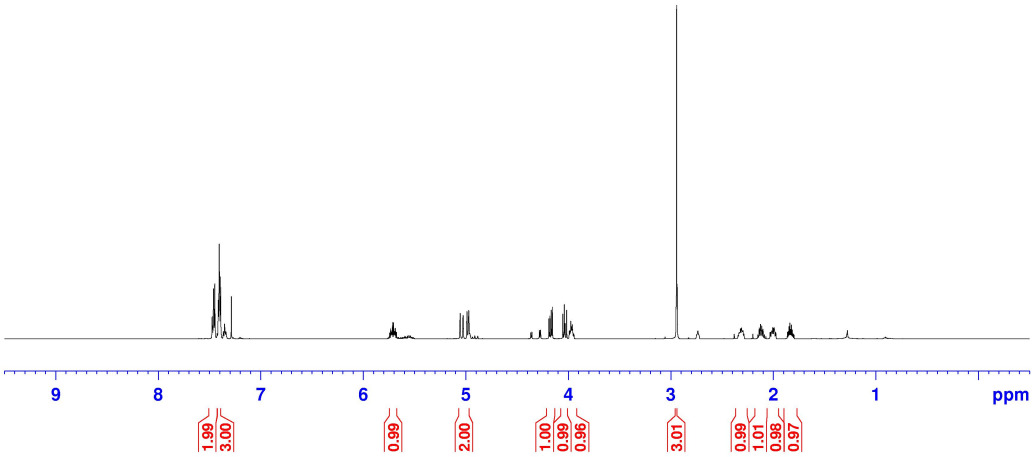
1.839
1.832
1.824
1.815


Ms
N
I


9
8
7
6
5
4
3
2
1
ppm
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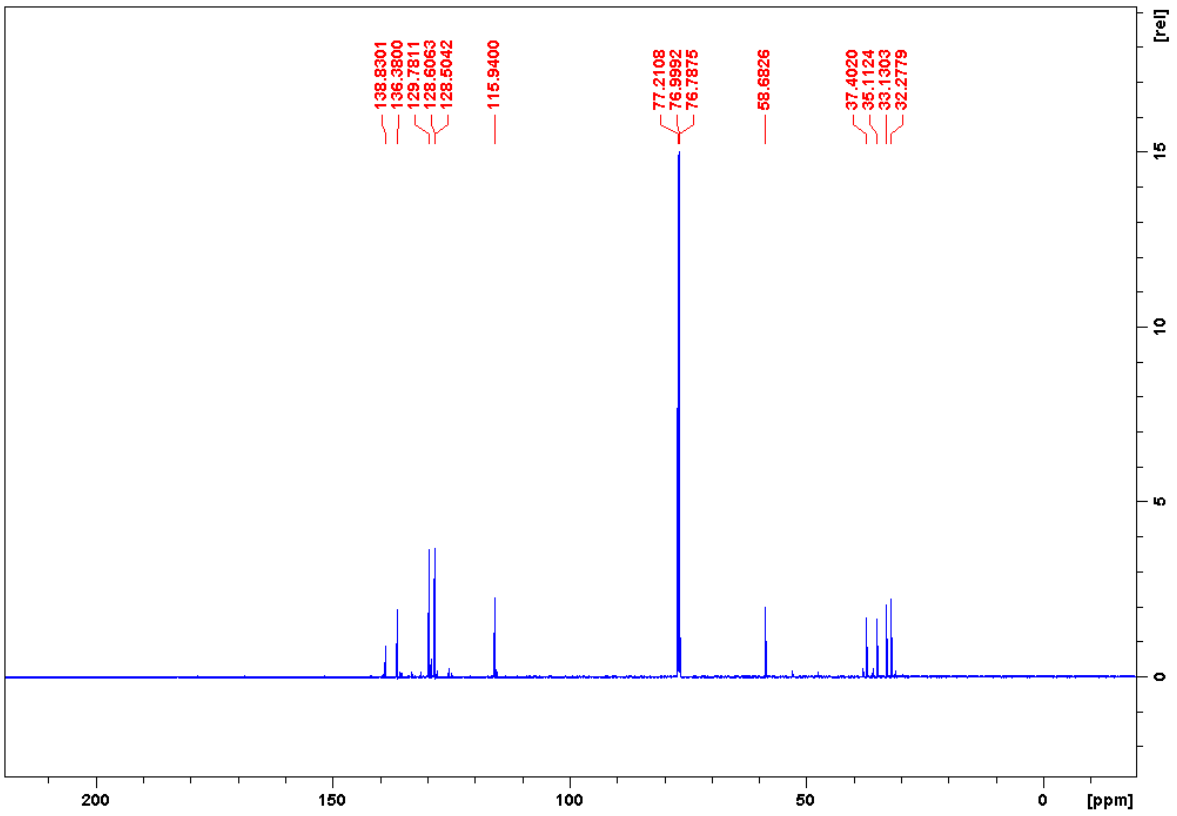
3.00
0.99
2.00
1.00
0.99
0.96
3.01
0.99
1.01
0.98
0.97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136.3800
129.7811
128.6063
128.5042
115.9400
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76.9992
76.7875
58.6826
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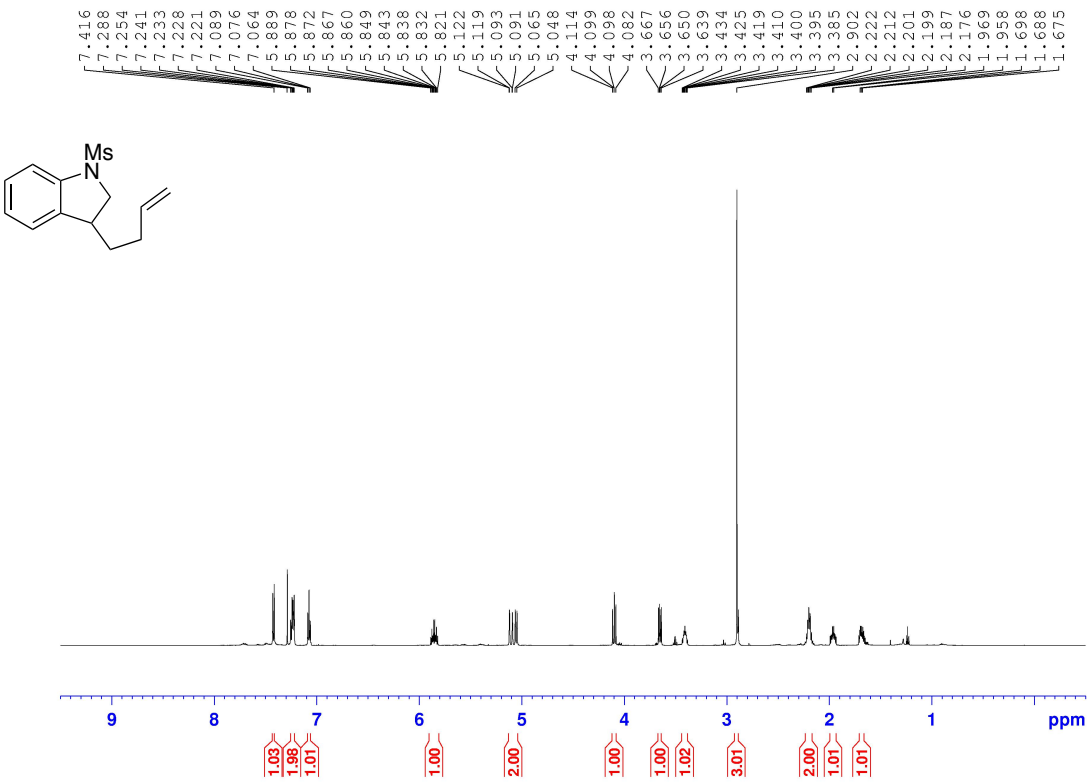
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7.089
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7.064
5.889
5.878
5.872
5.867
5.860
5.849
5.843
5.838
5.832
5.821
5.122
5.119
5.093
5.091
5.065
5.048
4.114
4.099
4.098
4.082
3.667
3.656
3.650
3.639
3.434
3.425
3.419
3.410
3.400
3.395
3.385
2.902
2.222
2.212
2.201
2.199
2.187
2.176
1.969
1.958
1.698
1.688
1.675
Ms
N
9
8
7
6
5
4
3
2
1
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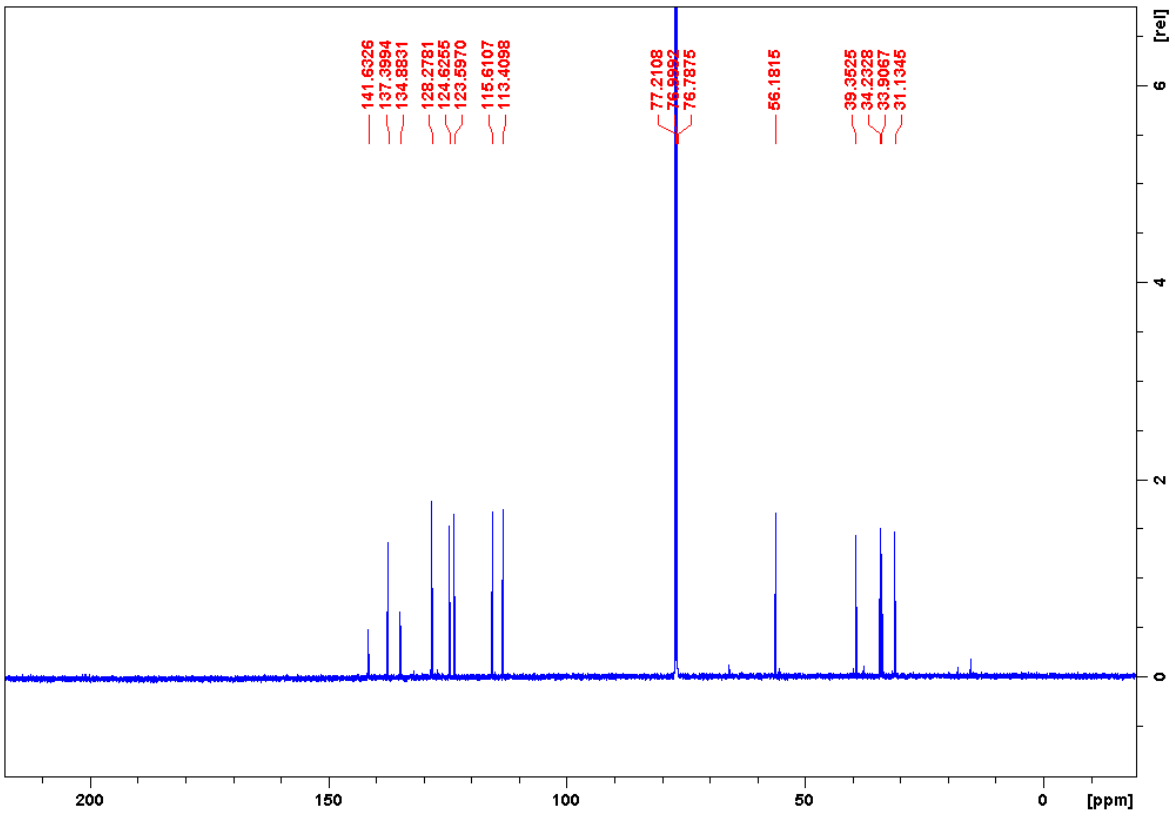
1.01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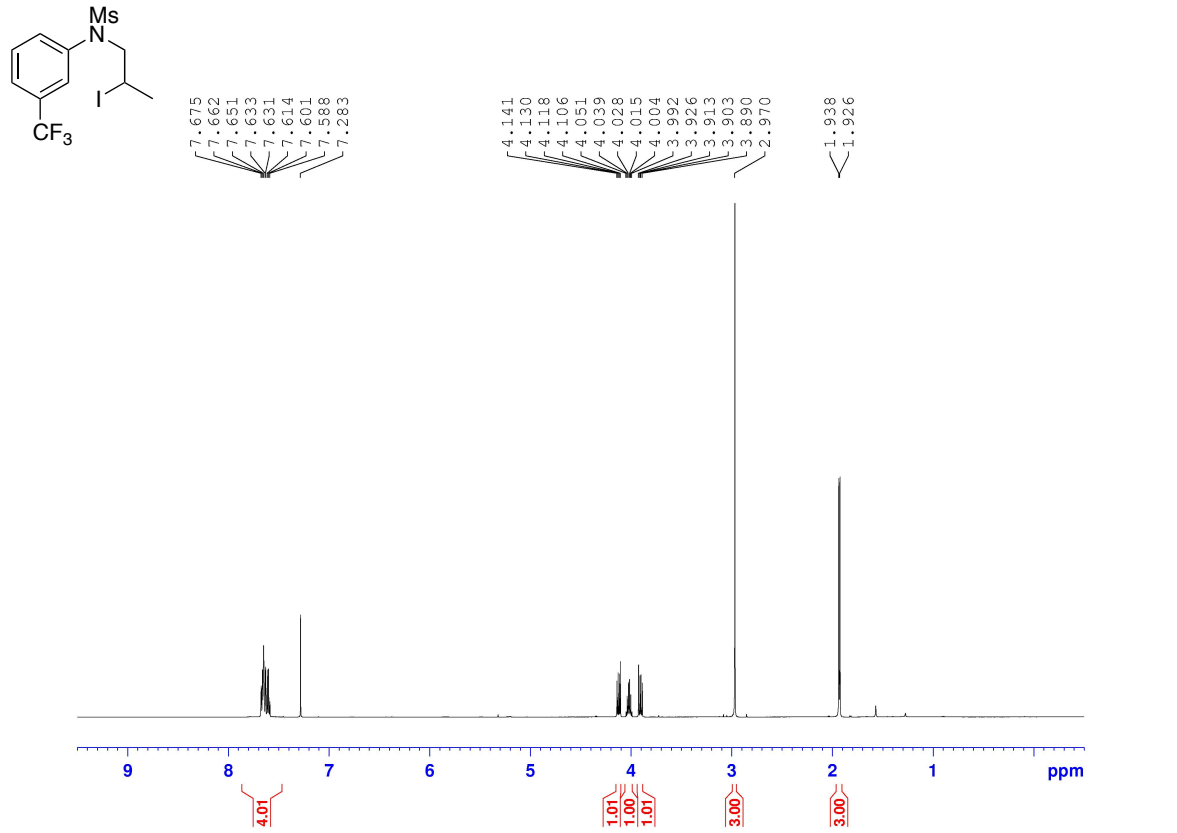
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I
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7.631
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7.601
7.588
7.283
4.141
4.130
4.118
4.106
4.051
4.039
4.028
4.015
4.004
3.992
3.926
3.913
3.903
3.890
2.970
1.938
1.926
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4
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1.01
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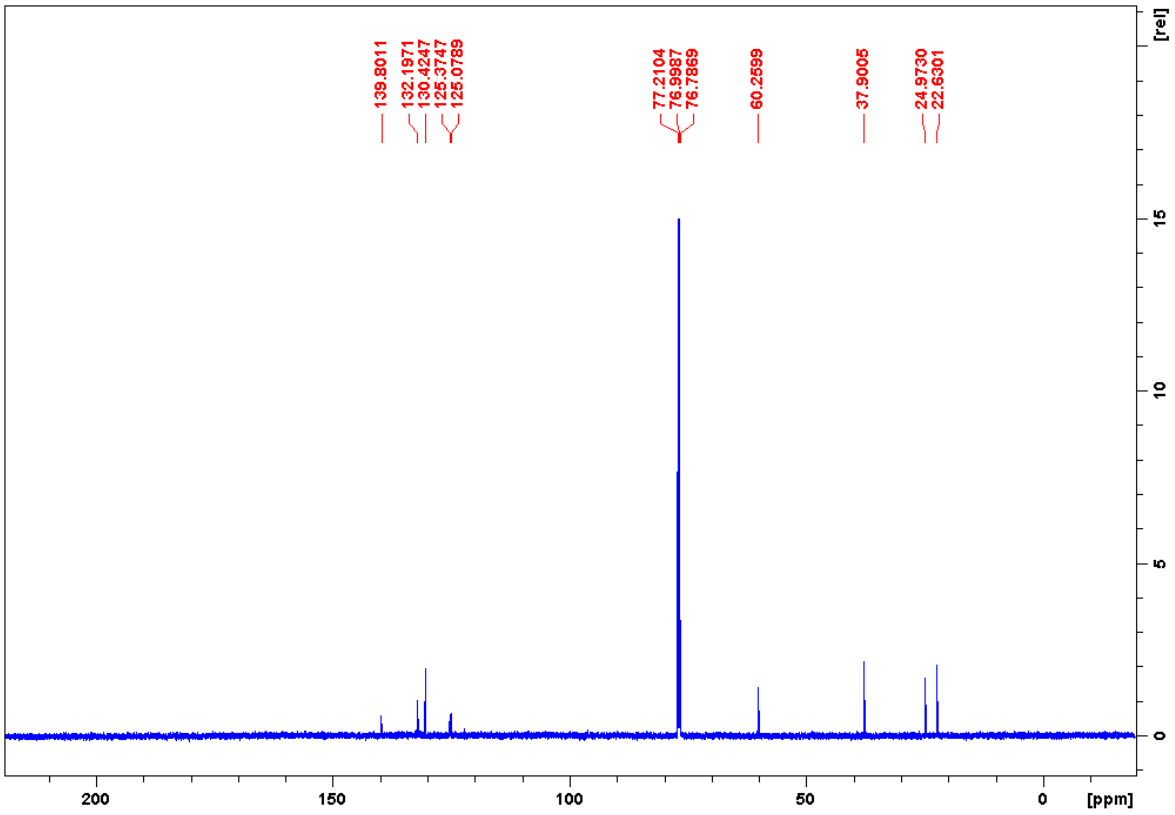
1.01
3.00
3.00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24.9730
22.6301
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100
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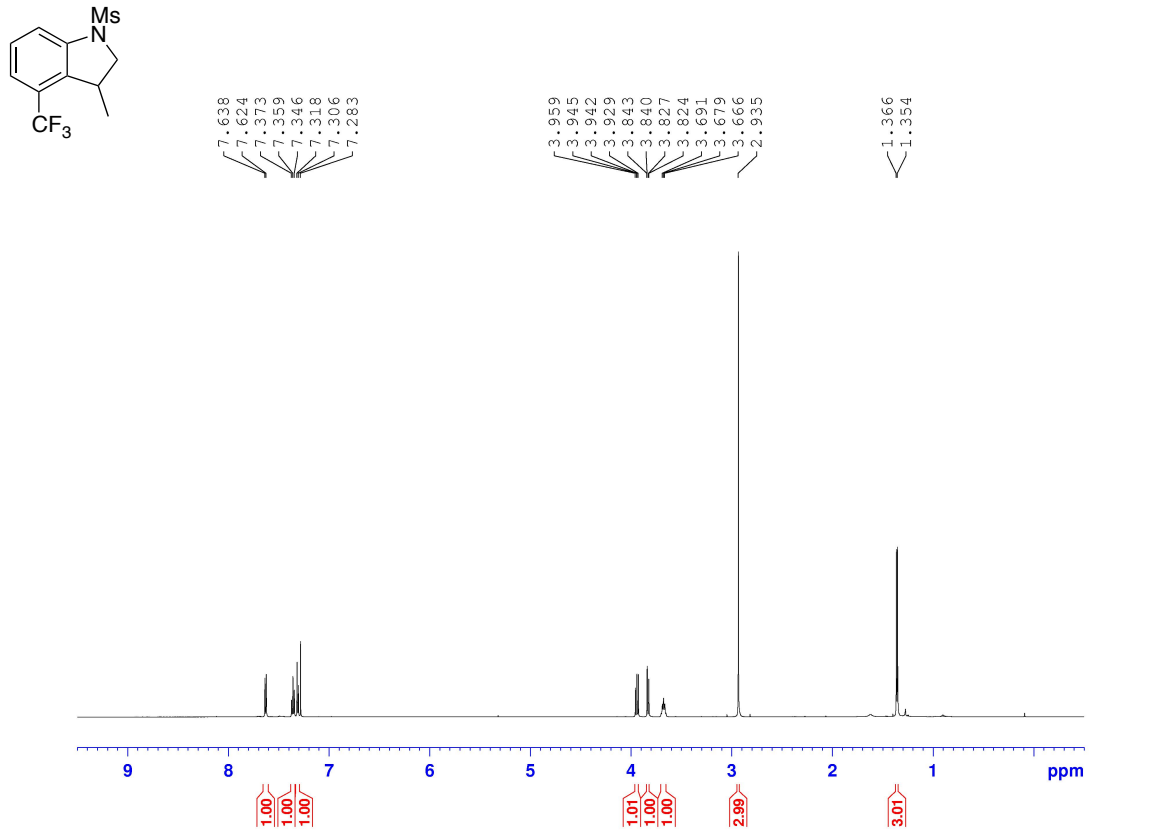
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7.318
7.306
7.283
3.959
3.945
3.942
3.929
3.843
3.840
3.827
3.824
3.691
3.679
3.666
2.935
1.366
1.354
9
8
7
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2
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1.00
1.01
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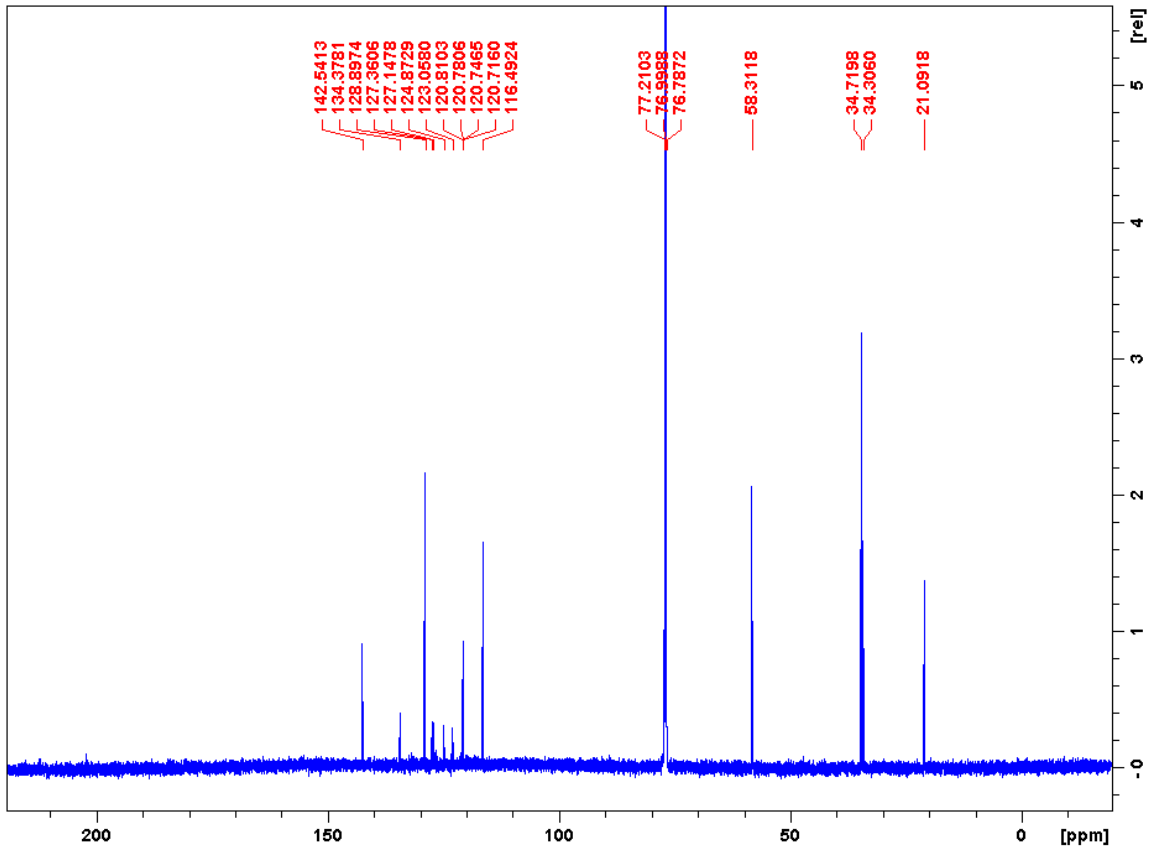
3.01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116.4924
77.2103
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150
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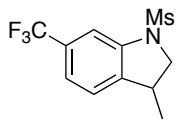
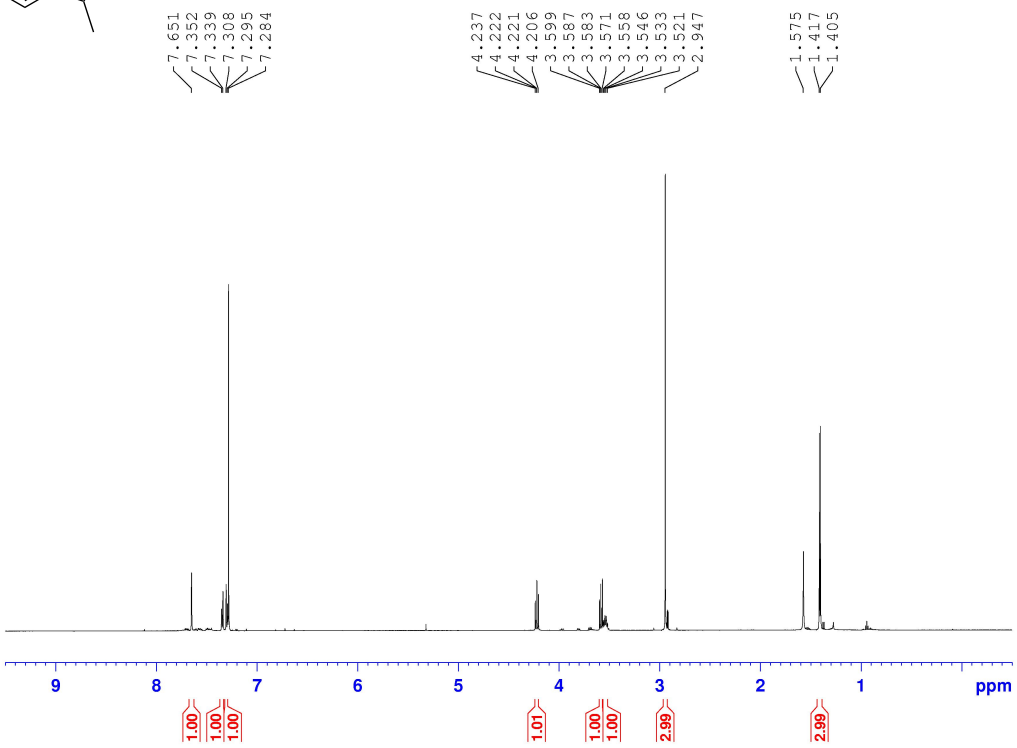

F3C
Ms
N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7.339
7.308
7.295
7.284
4.237
4.222
4.221
4.206
3.599
3.587
3.583
3.571
3.558
3.546
3.533
3.521
2.947
1.575
1.417
1.405
9
8
7
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2
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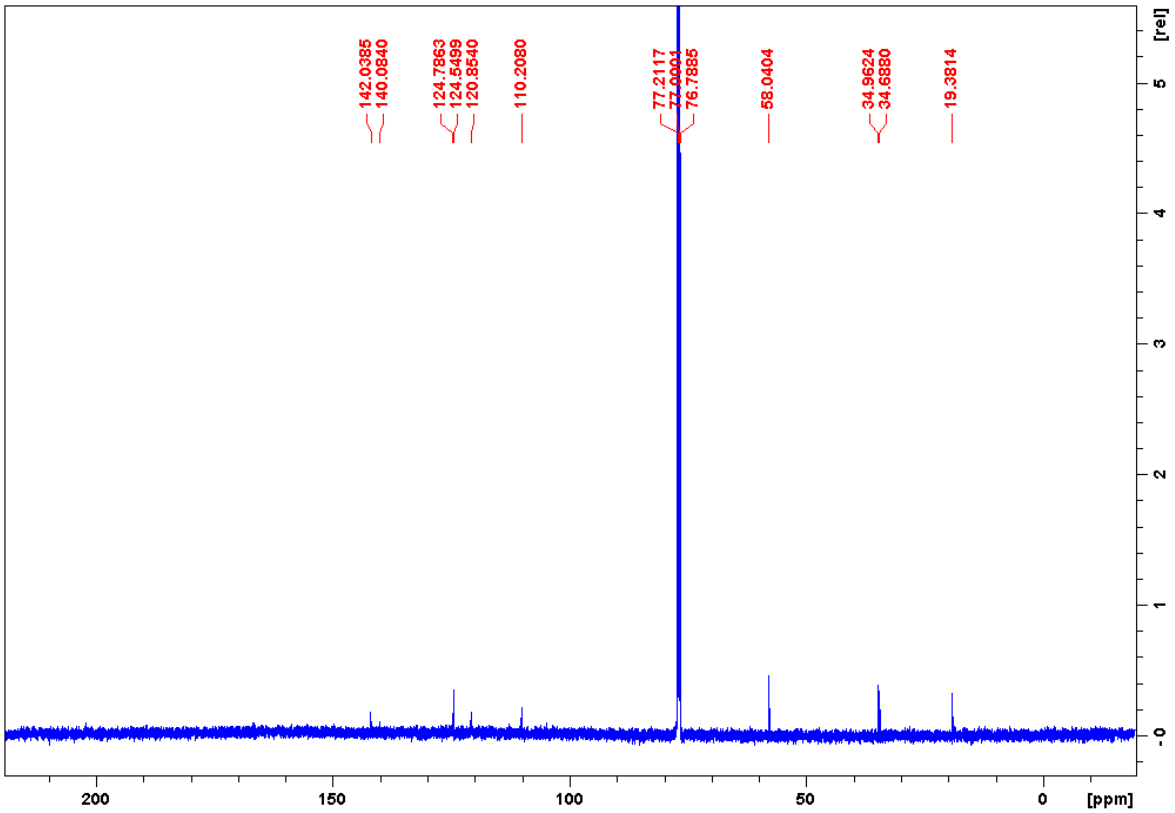
1.00
1.01
1.00
1.00
2.99
2.99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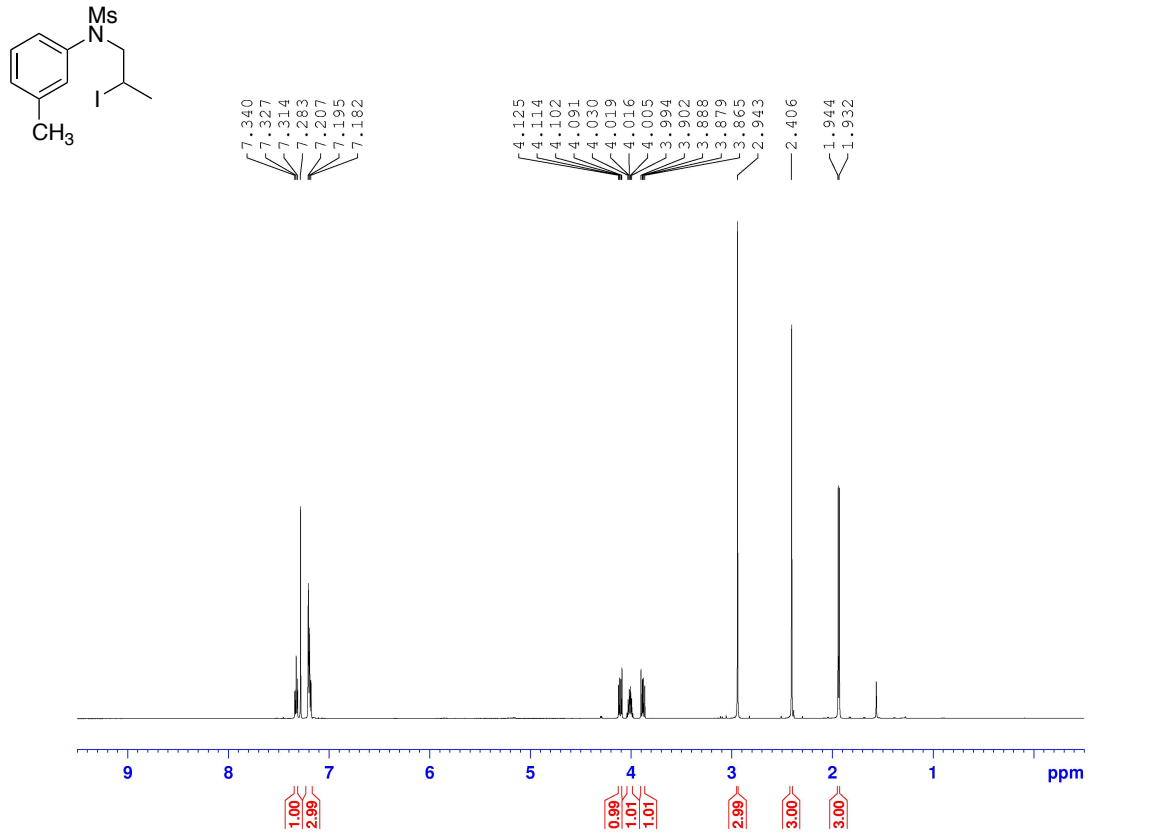
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I
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7.314
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7.207
7.195
7.182
4.125
4.114
4.102
4.091
4.030
4.019
4.016
4.005
3.994
3.902
3.888
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2.406
1.944
1.932
9
8
7
6
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2
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ppm
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1.01
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2.99
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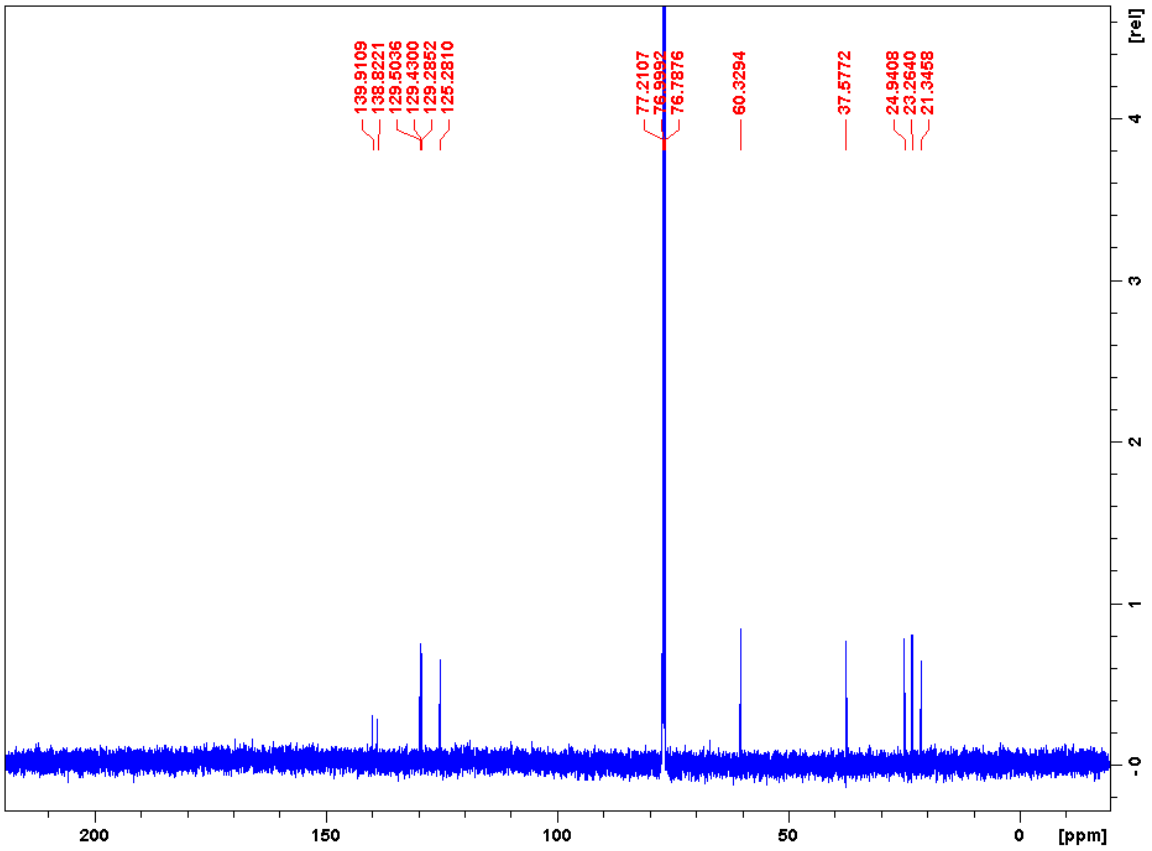
3.00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21.3458
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-0
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150
100
50
0
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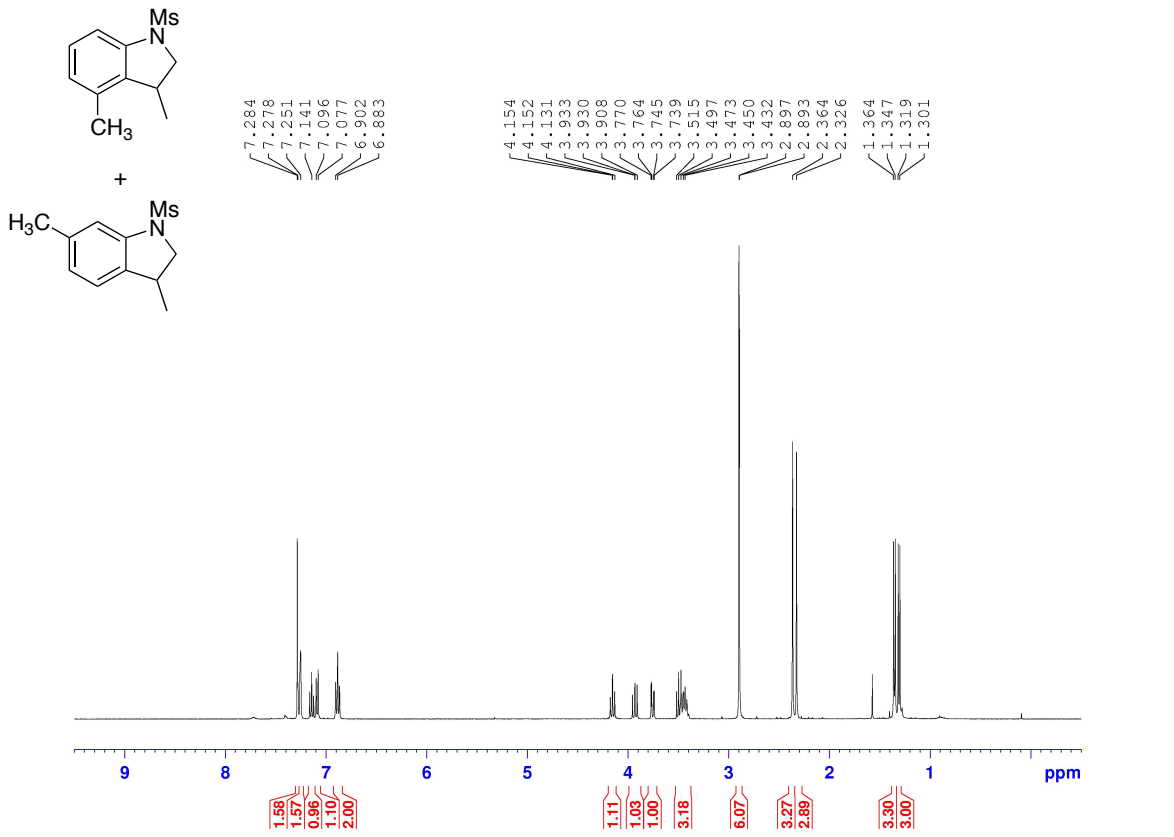
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N
CH3
+
H3C
Ms
N
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7.251
7.141
7.096
7.077
6.902
6.883
4.154
4.152
4.131
3.933
3.930
3.908
3.770
3.764
3.745
3.739
3.515
3.497
3.473
3.450
3.432
2.897
2.893
2.364
2.326
1.364
1.347
1.319
1.301
9
8
7
6
5
4
3
2
1
ppm
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1.57
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1.00
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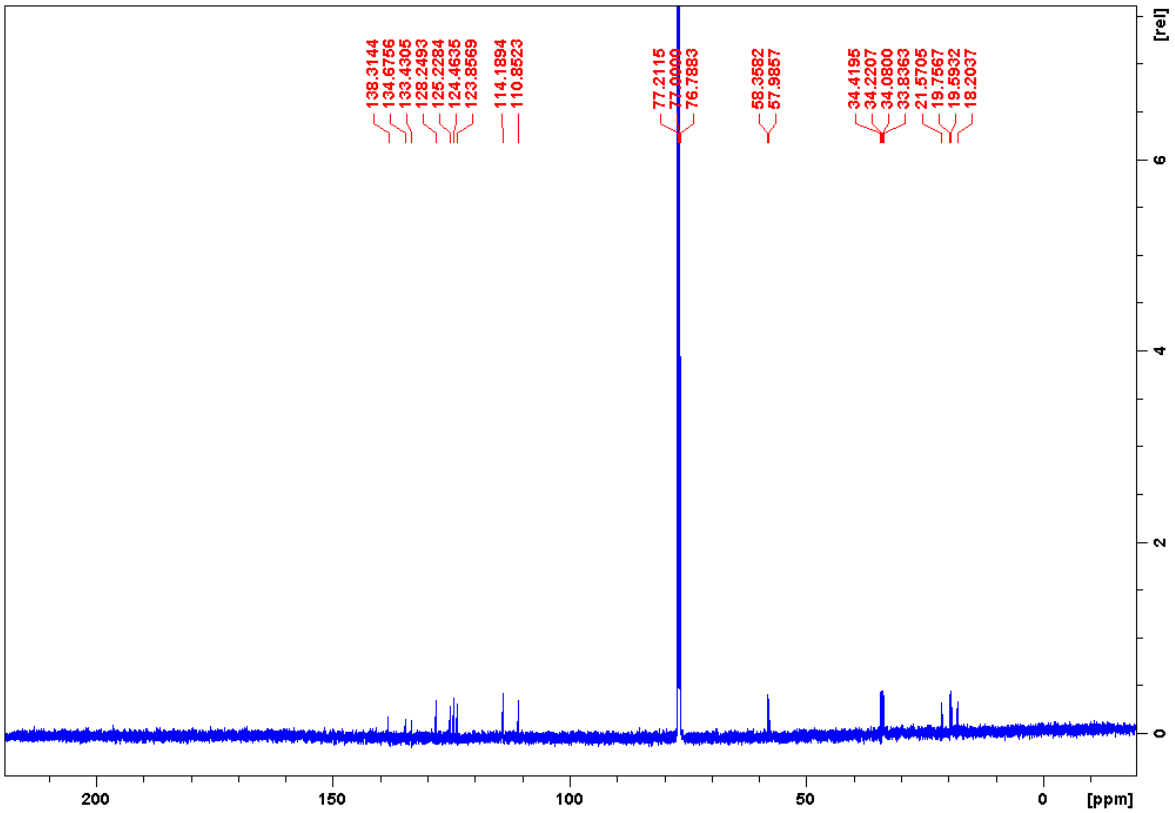
3.00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76.7883
58.3582
57.9857
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33.8363
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19.5932
18.2037
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4
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0
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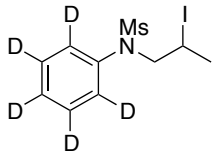
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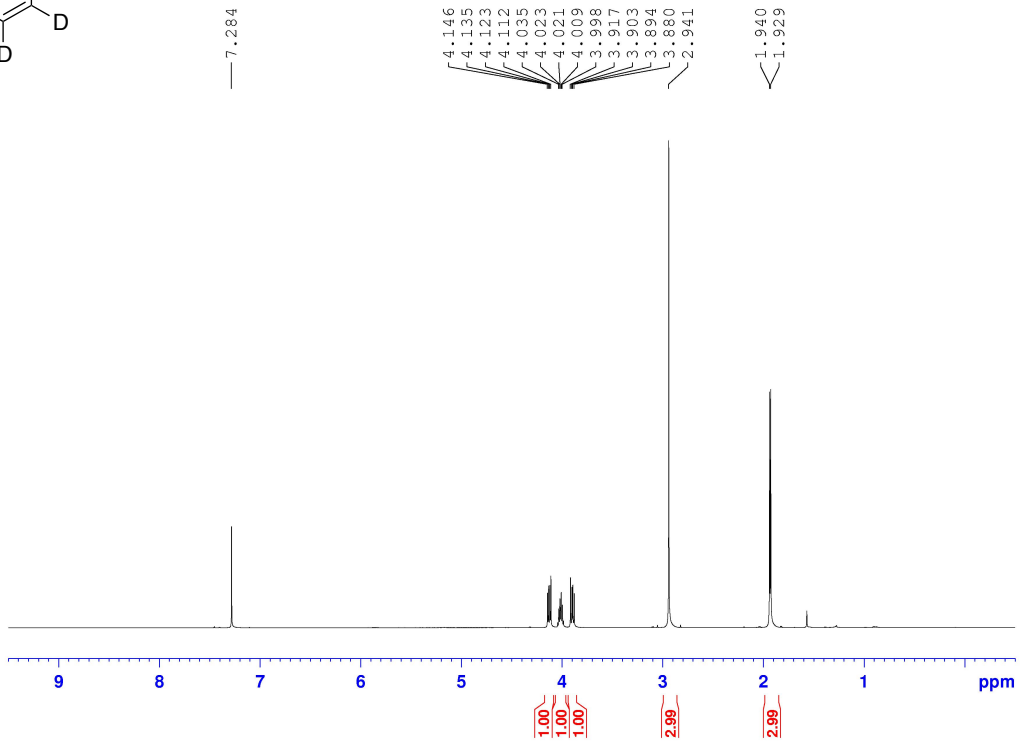
Ms
I
D
N
D
D
D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4.023
4.021
4.009
3.998
3.917
3.903
3.894
3.880
2.941
1.940
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7
6
5
4
3
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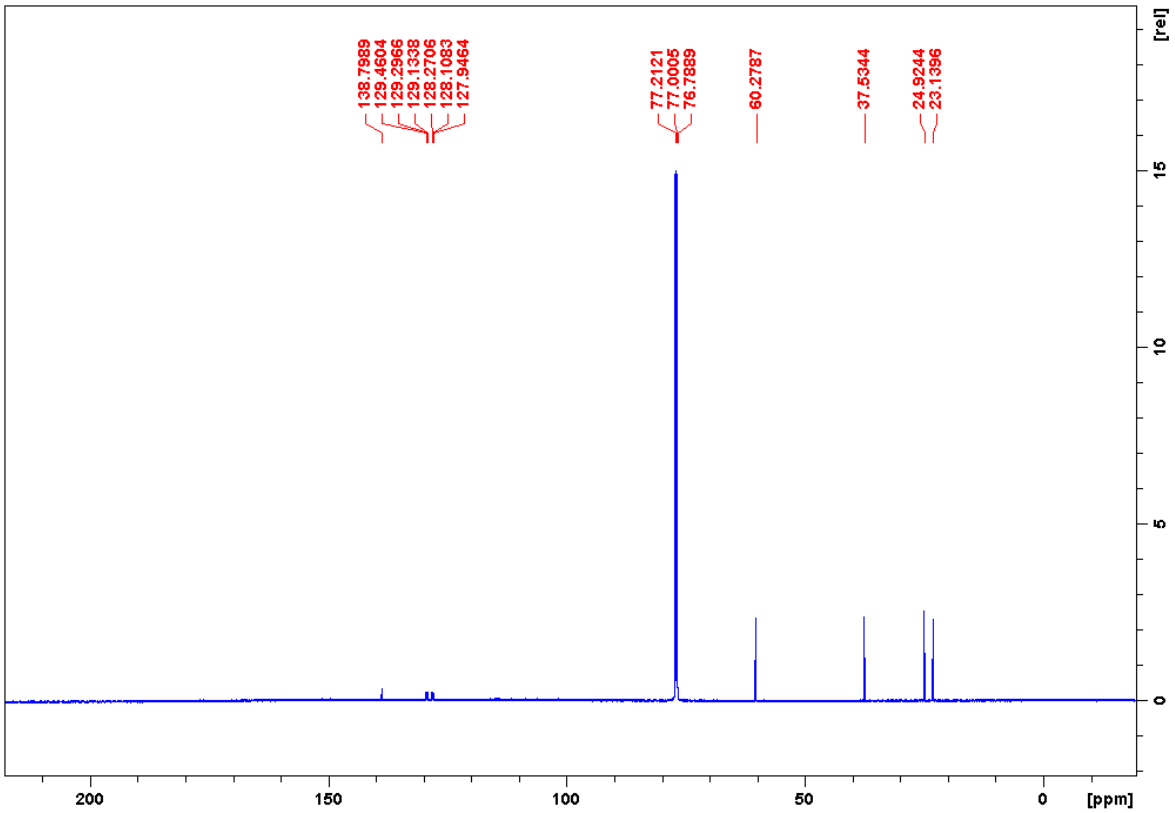
1.00
2.99
2.99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77.0005
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24.9244
23.1396
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150
100
50
0
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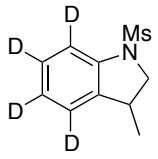
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D
Ms
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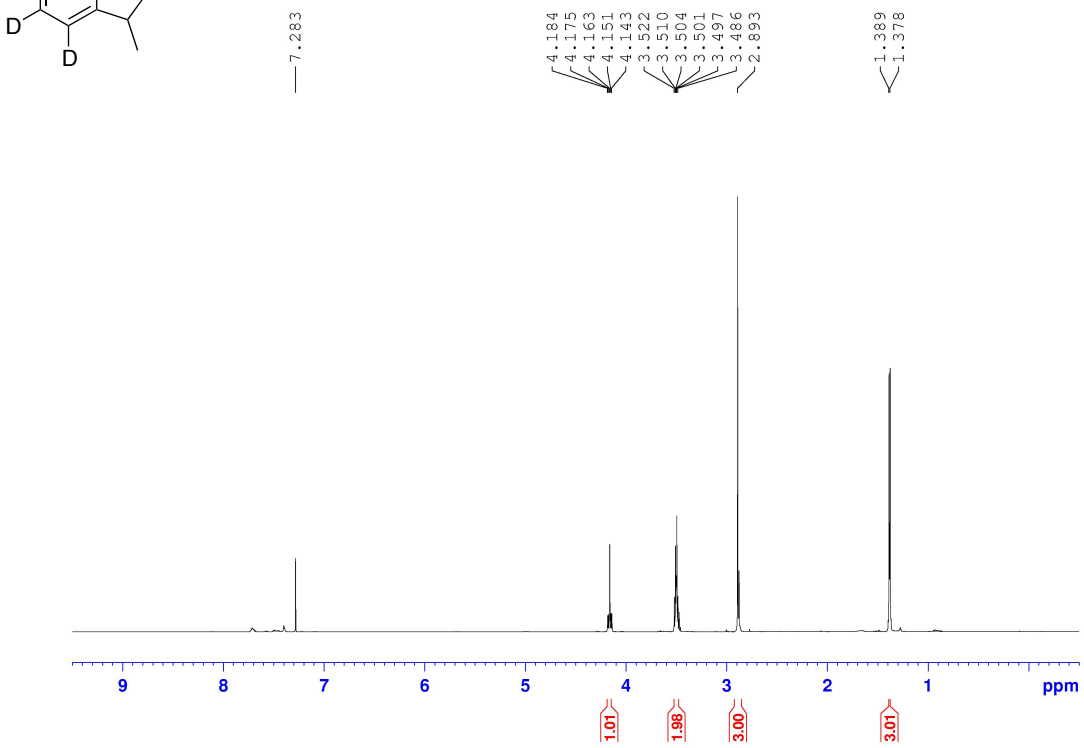
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3.510
3.504
3.501
3.497
3.486
2.893
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8
7
6
5
4
3
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ppm
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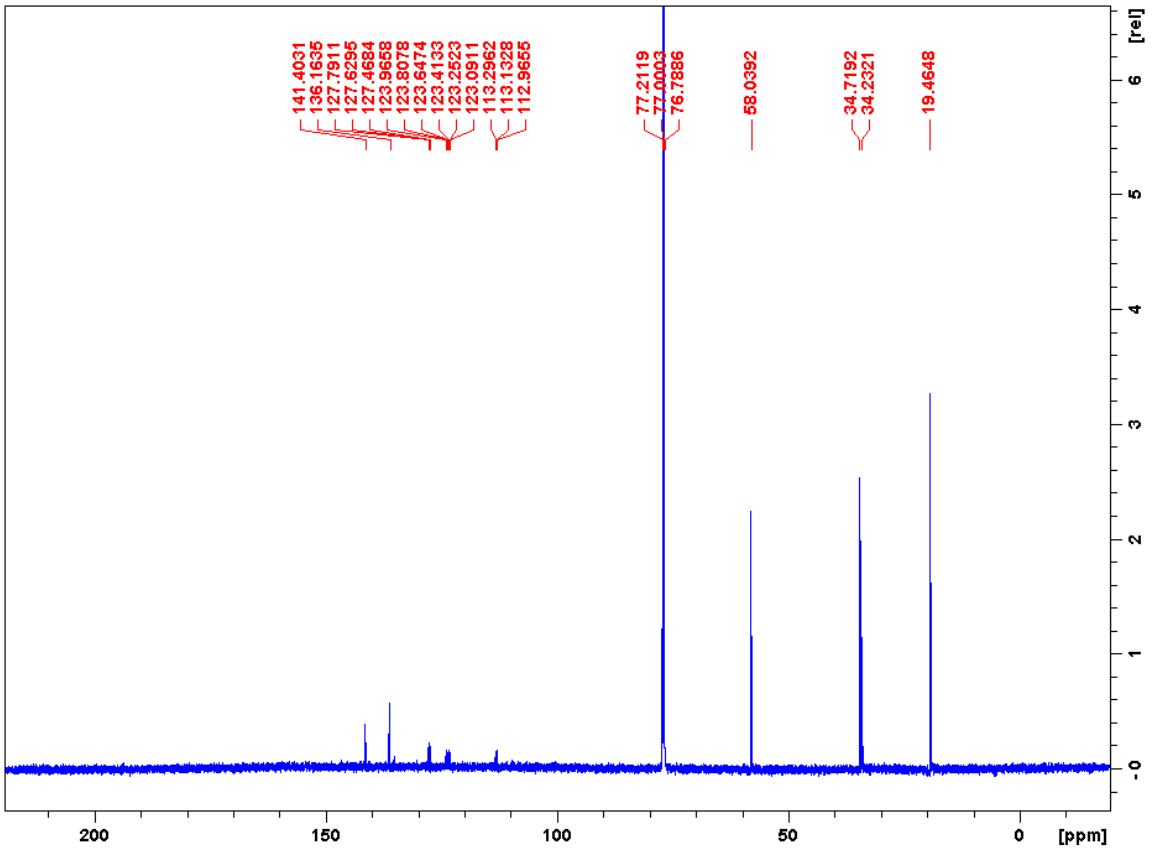
3.01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113.1328
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19.4648
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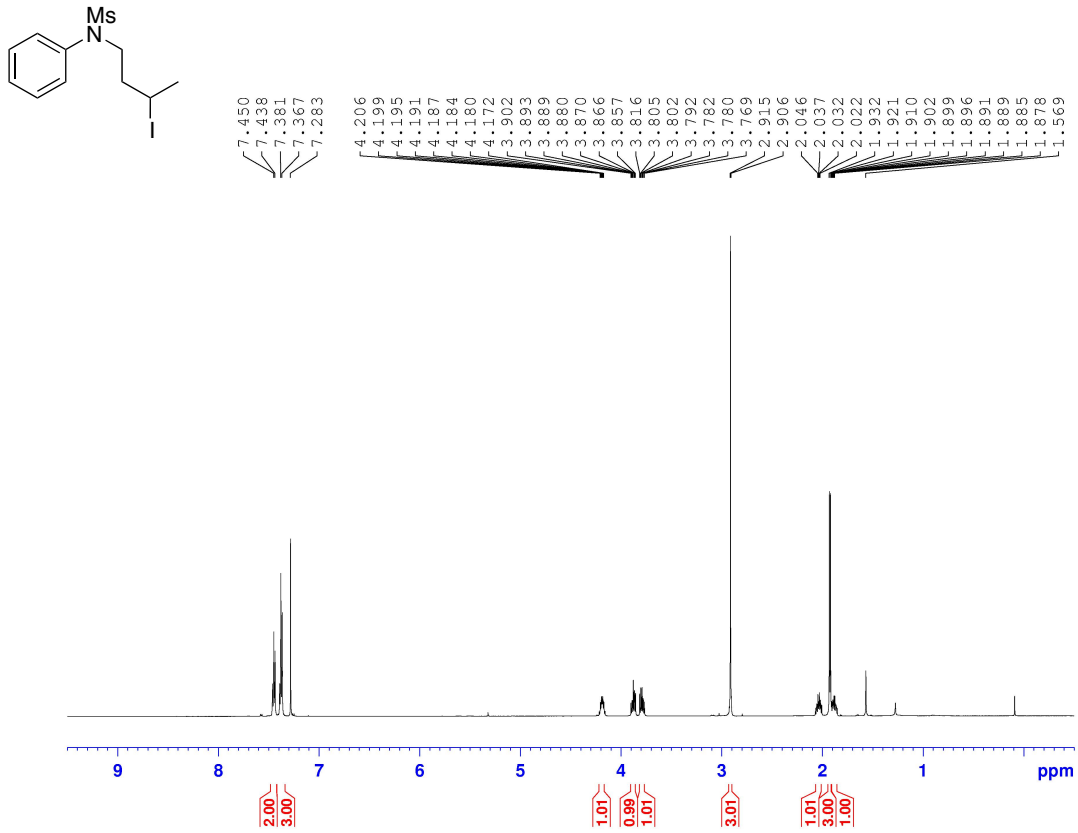
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4.180
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3.902
3.893
3.889
3.880
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3.816
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3.780
3.769
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2.037
2.032
2.022
1.932
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1.910
1.902
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1.885
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1.569
9
8
7
6
5
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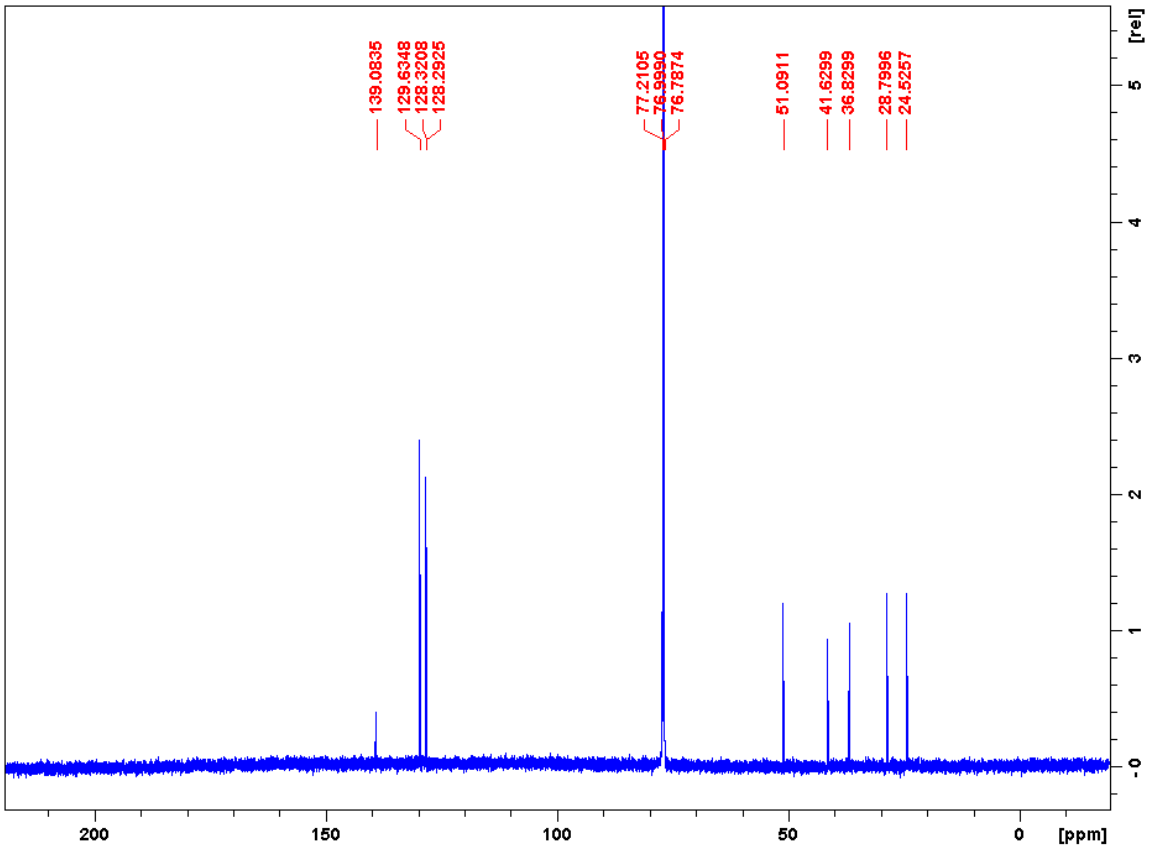
1.00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28.7996
24.5257
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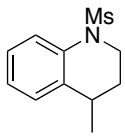
[rel]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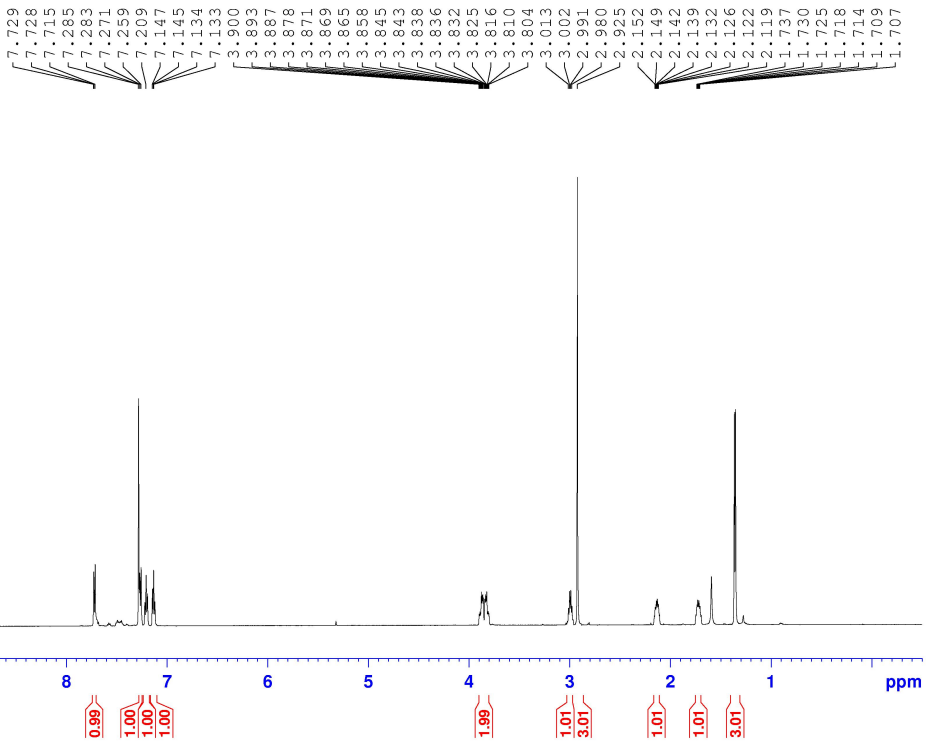
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7.133
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3.825
3.816
3.810
3.804
3.013
3.002
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2.980
2.925
2.152
2.149
2.142
2.139
2.132
2.126
2.122
2.119
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1.730
1.725
1.718
1.714
1.709
1.707
9
8
7
6
5
4
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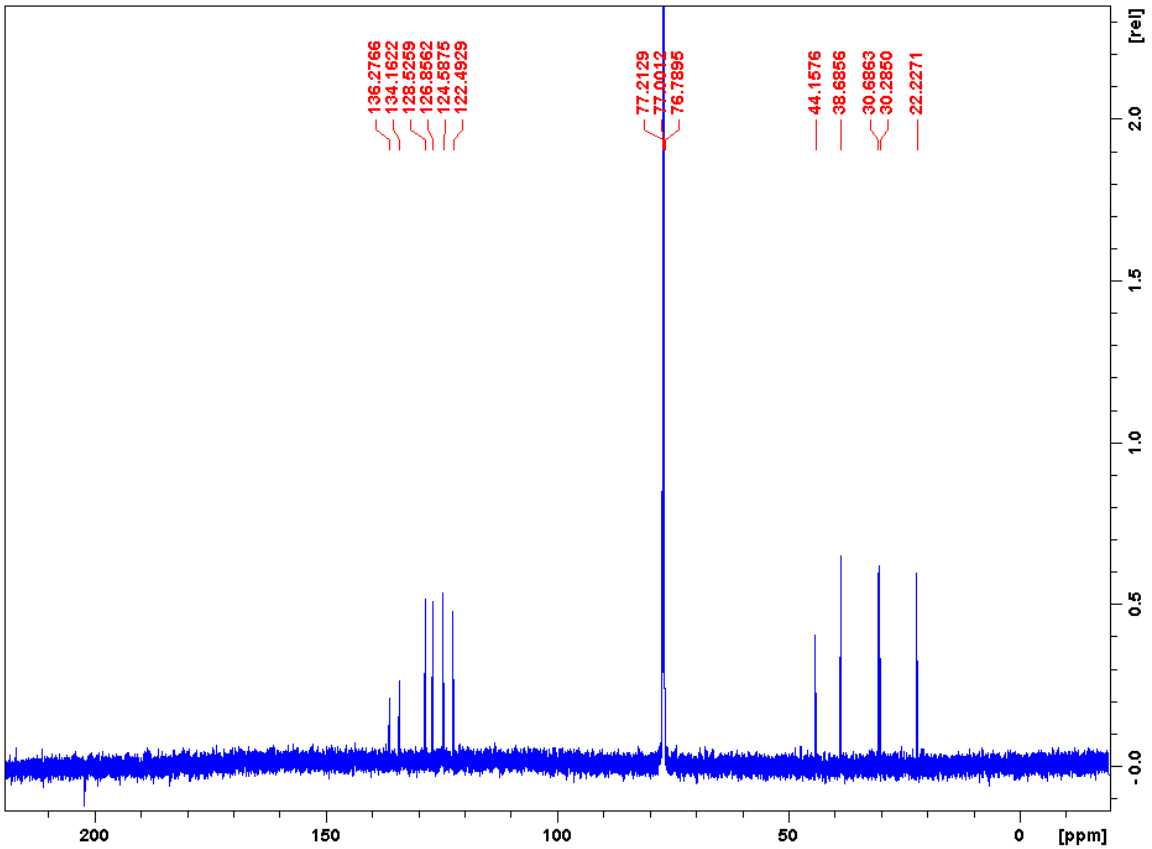
3.01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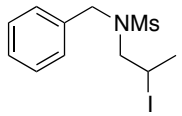
NMs
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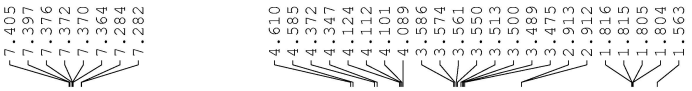
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4.124
4.112
4.101
4.089
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3.561
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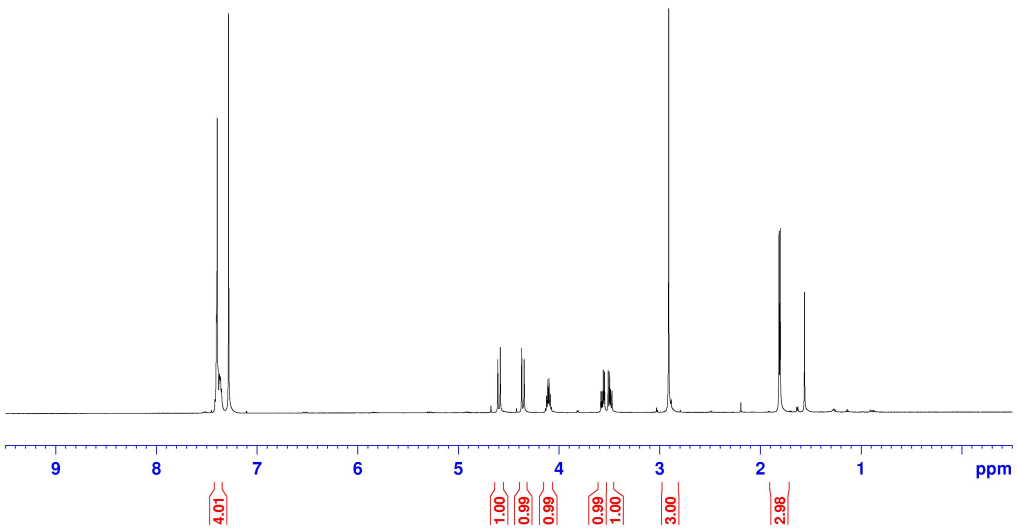
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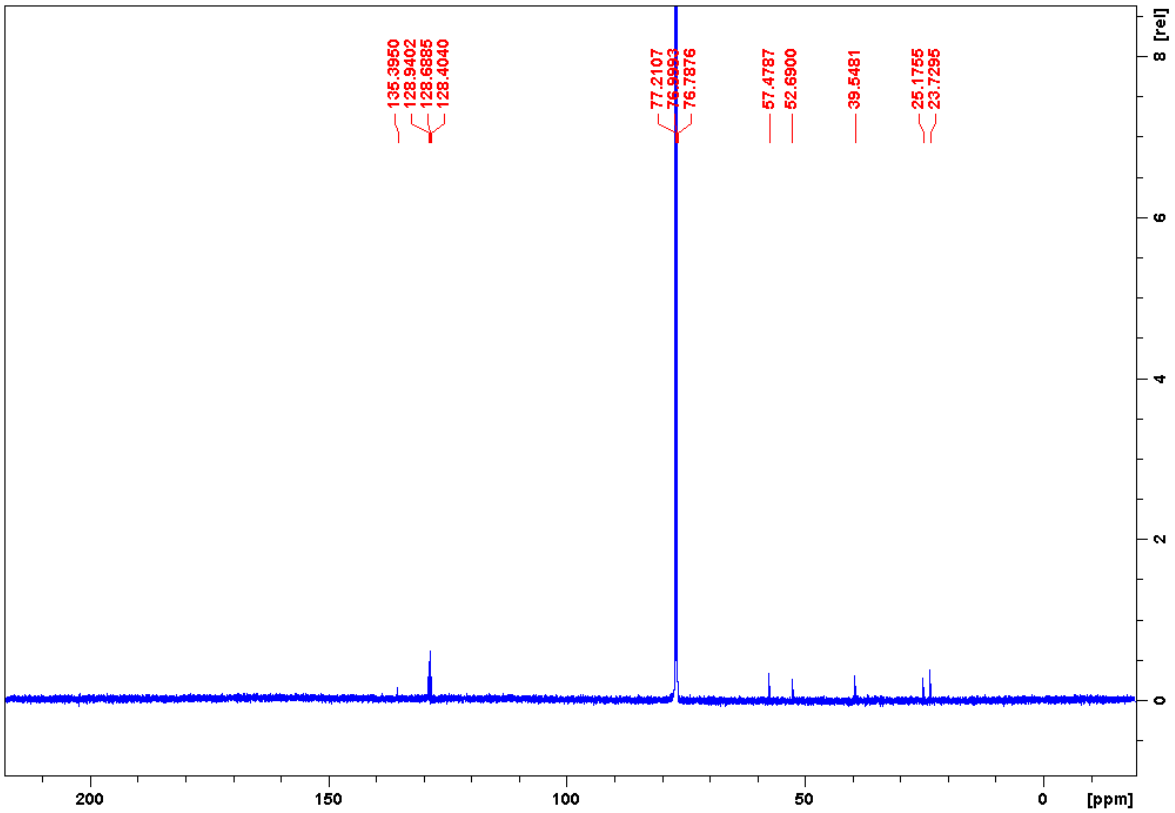
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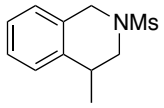
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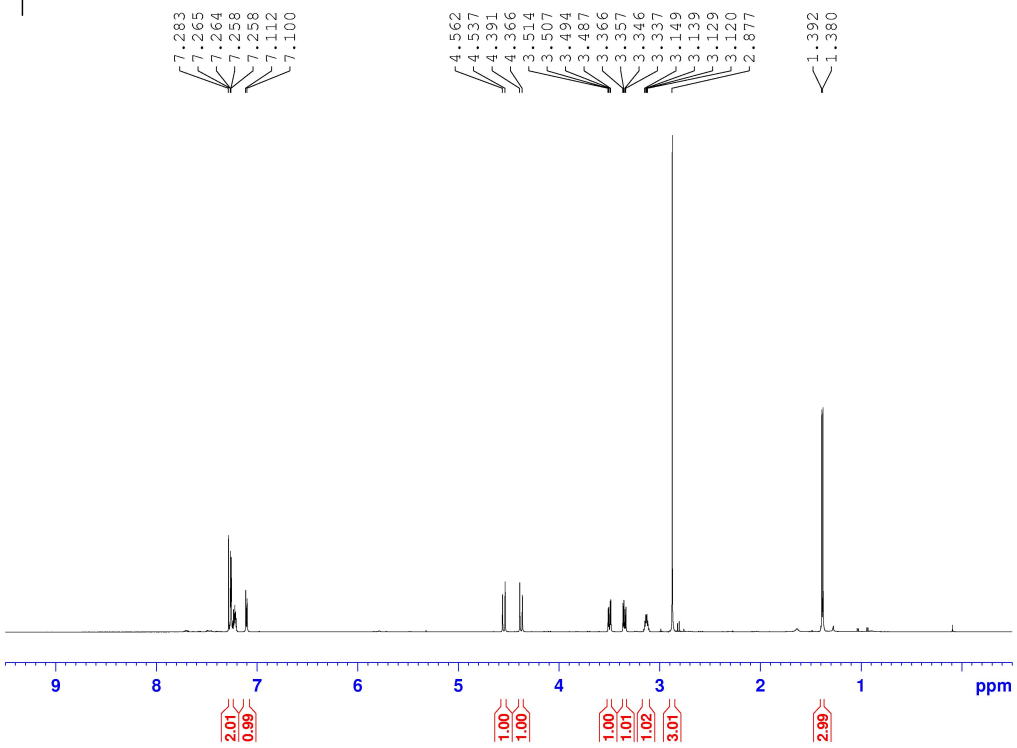
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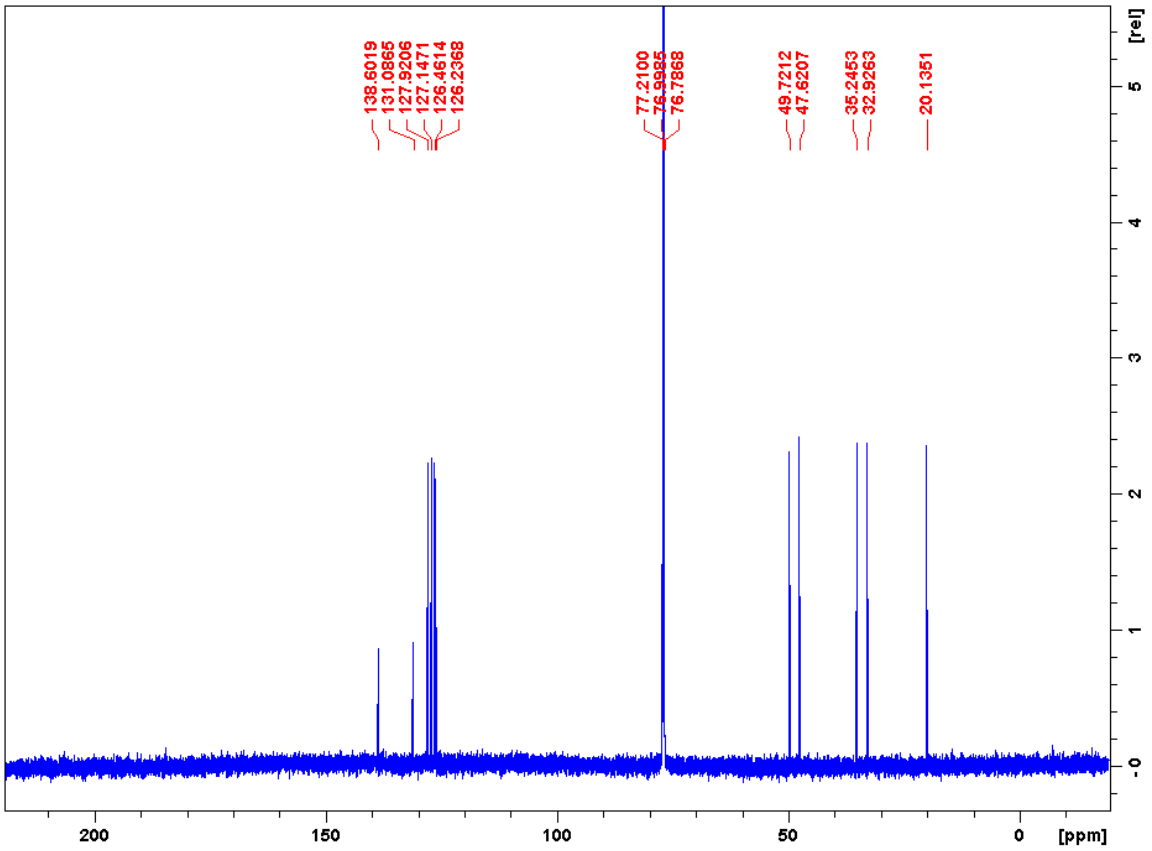
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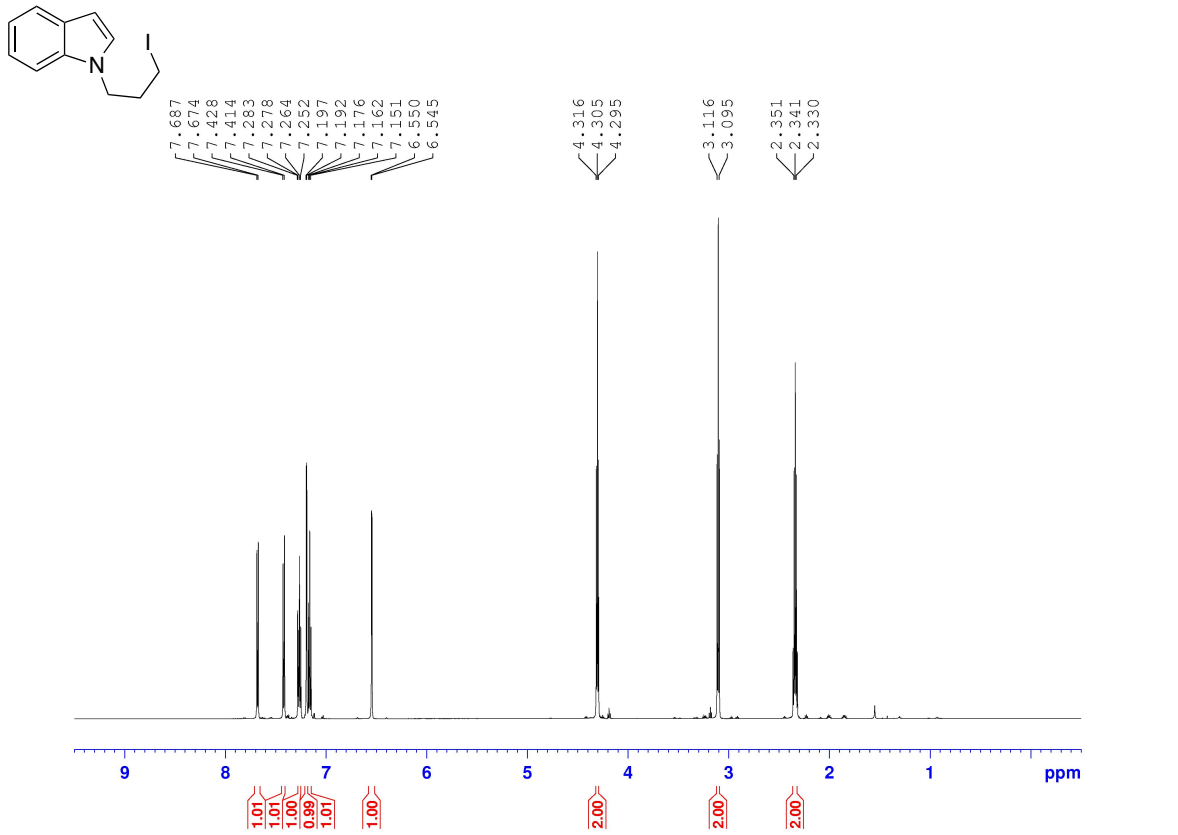
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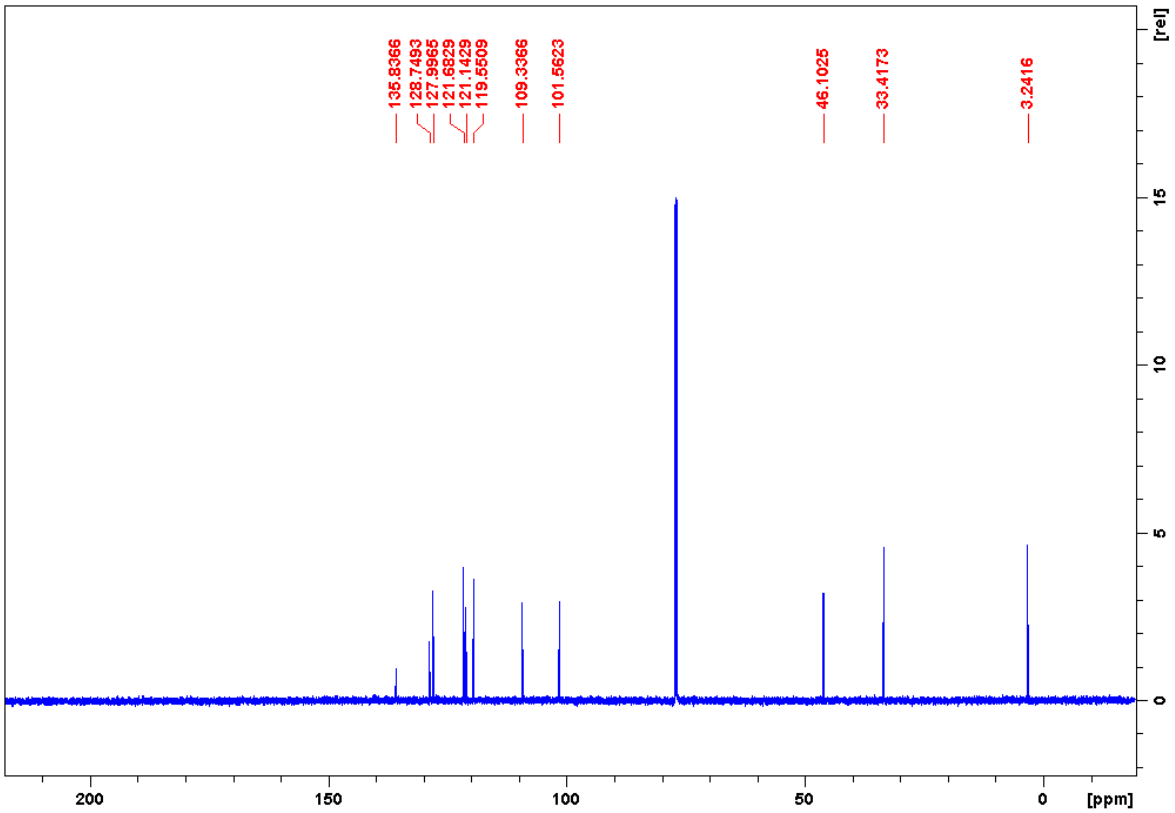
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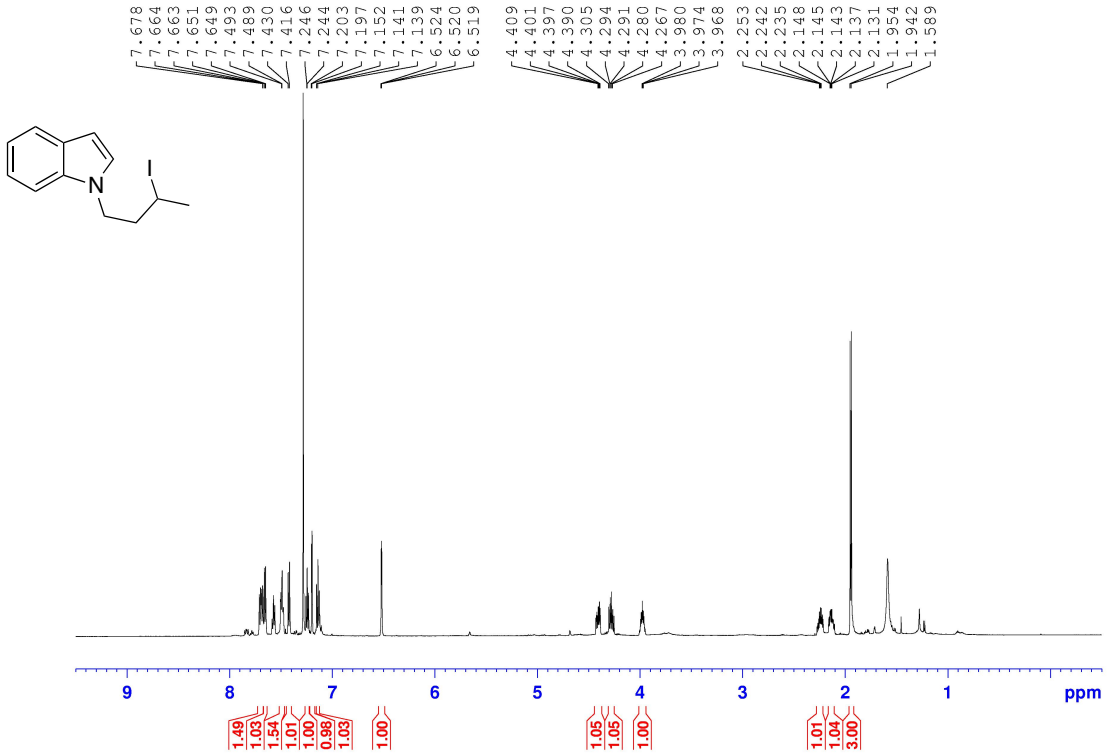
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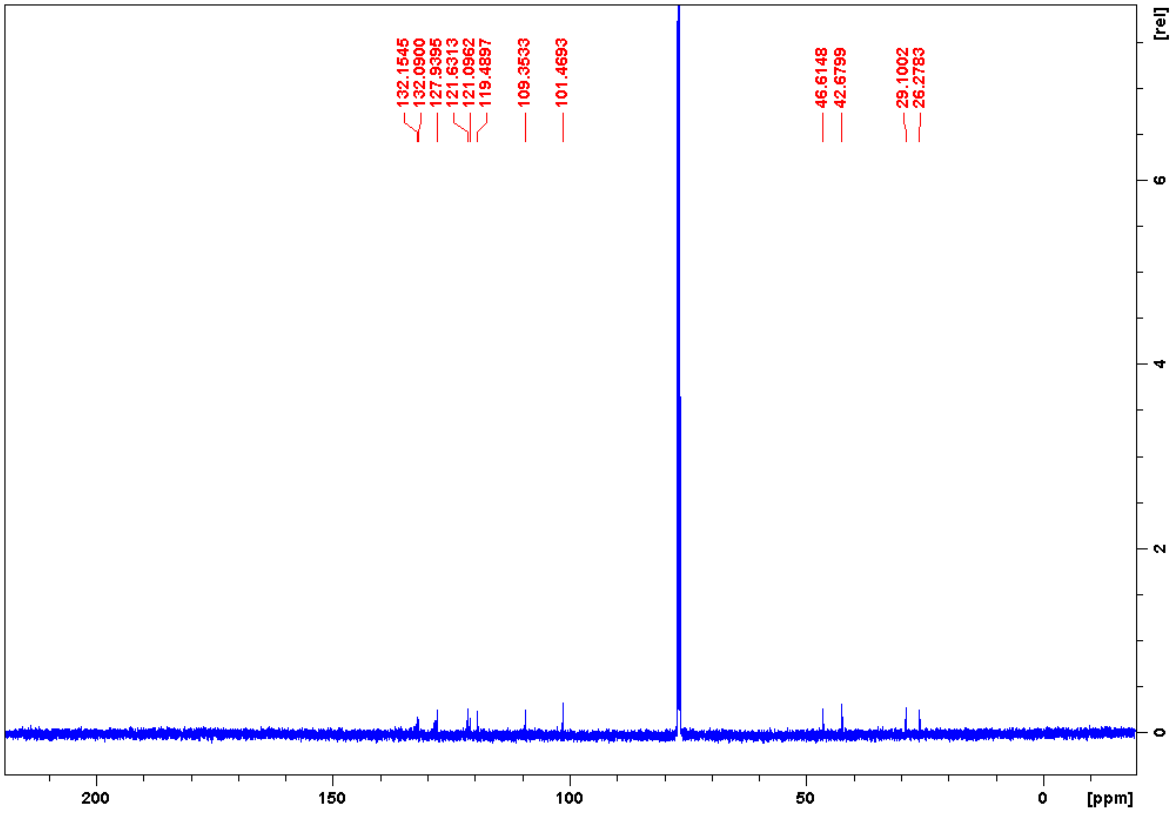
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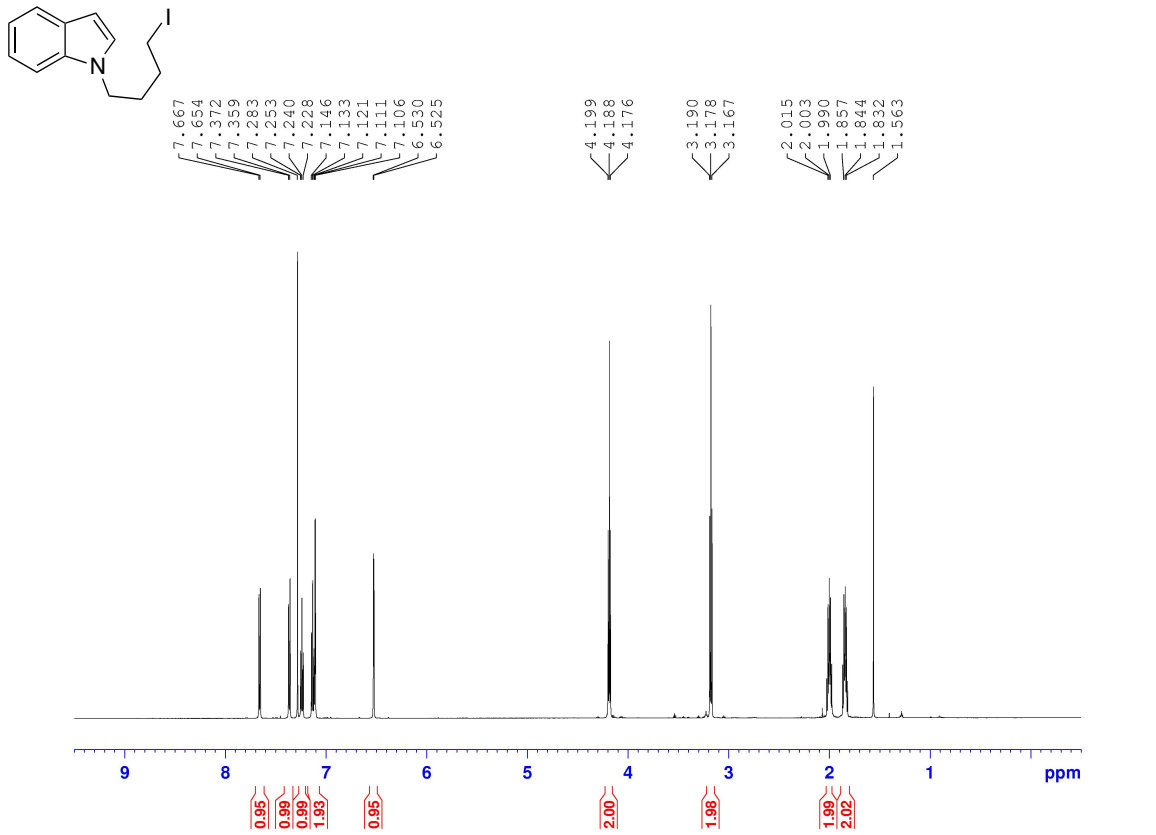
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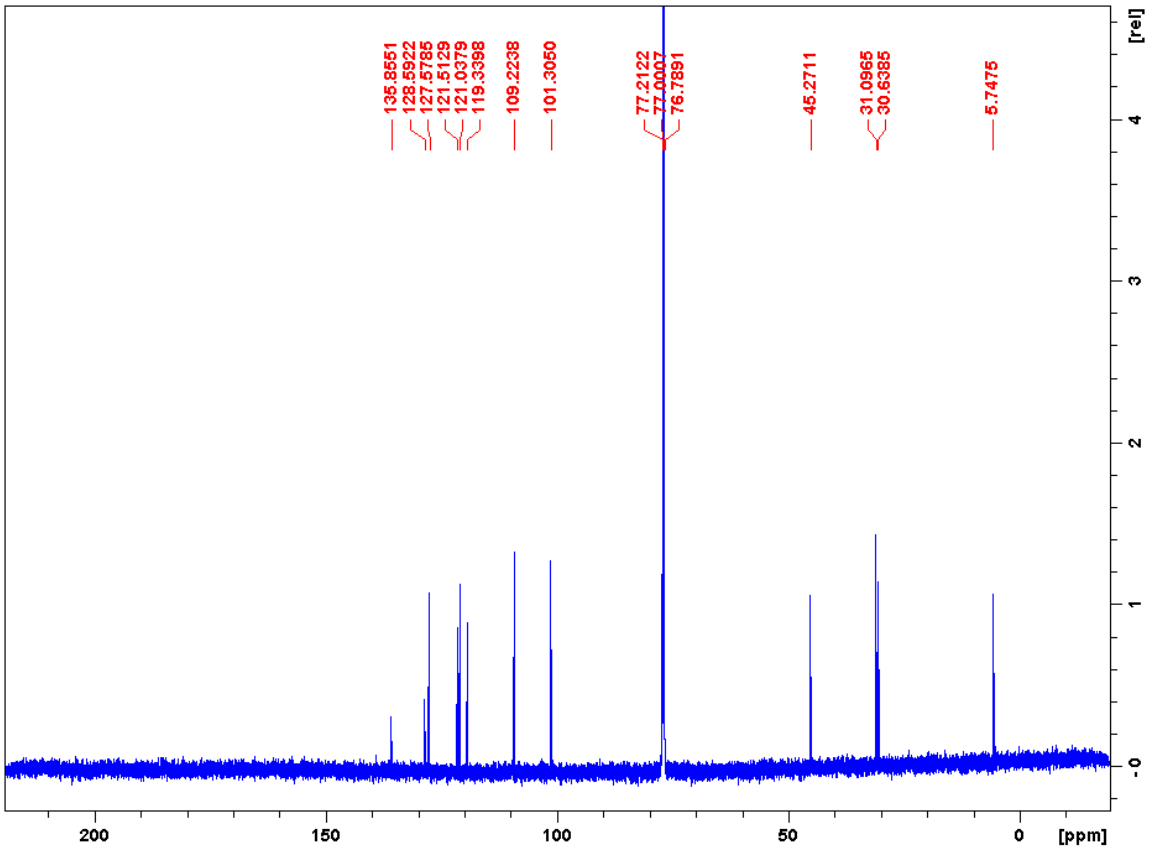
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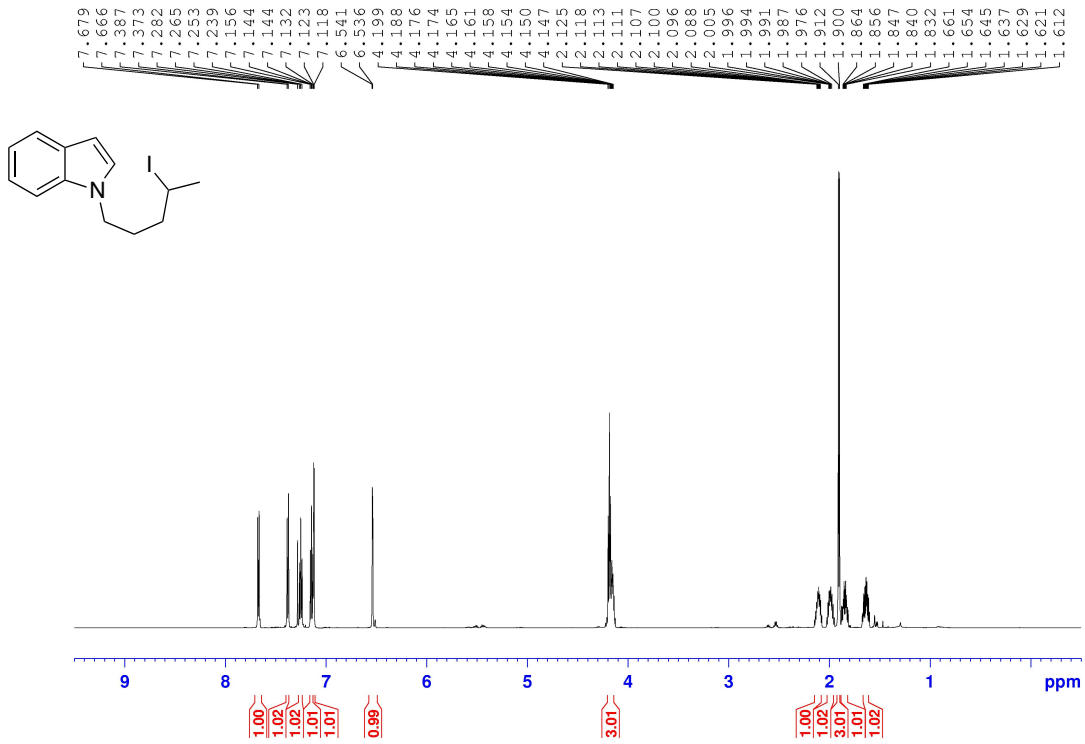
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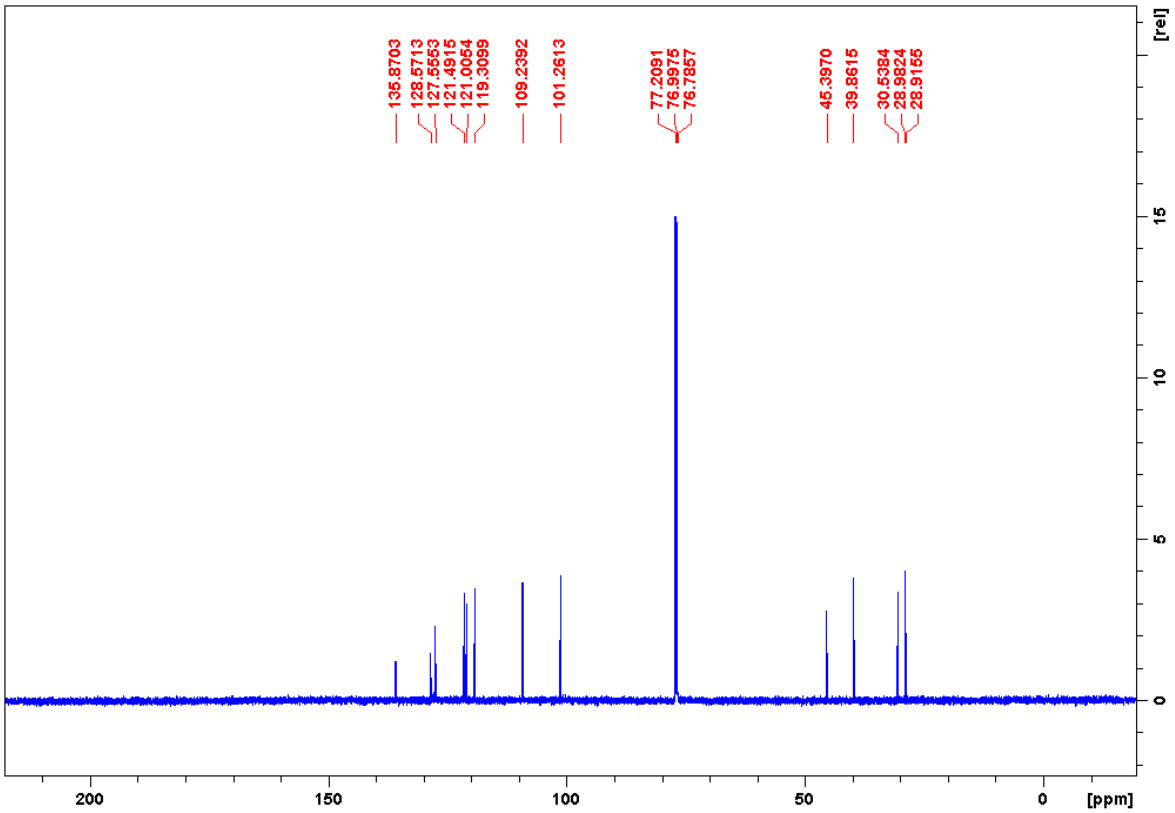
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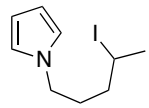

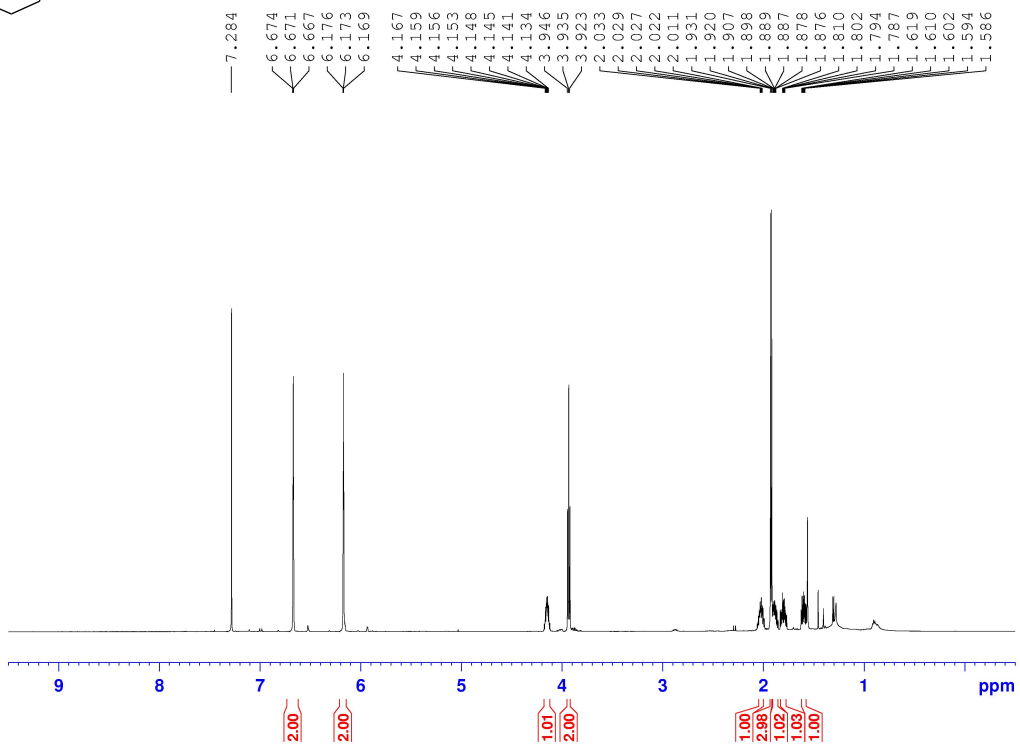
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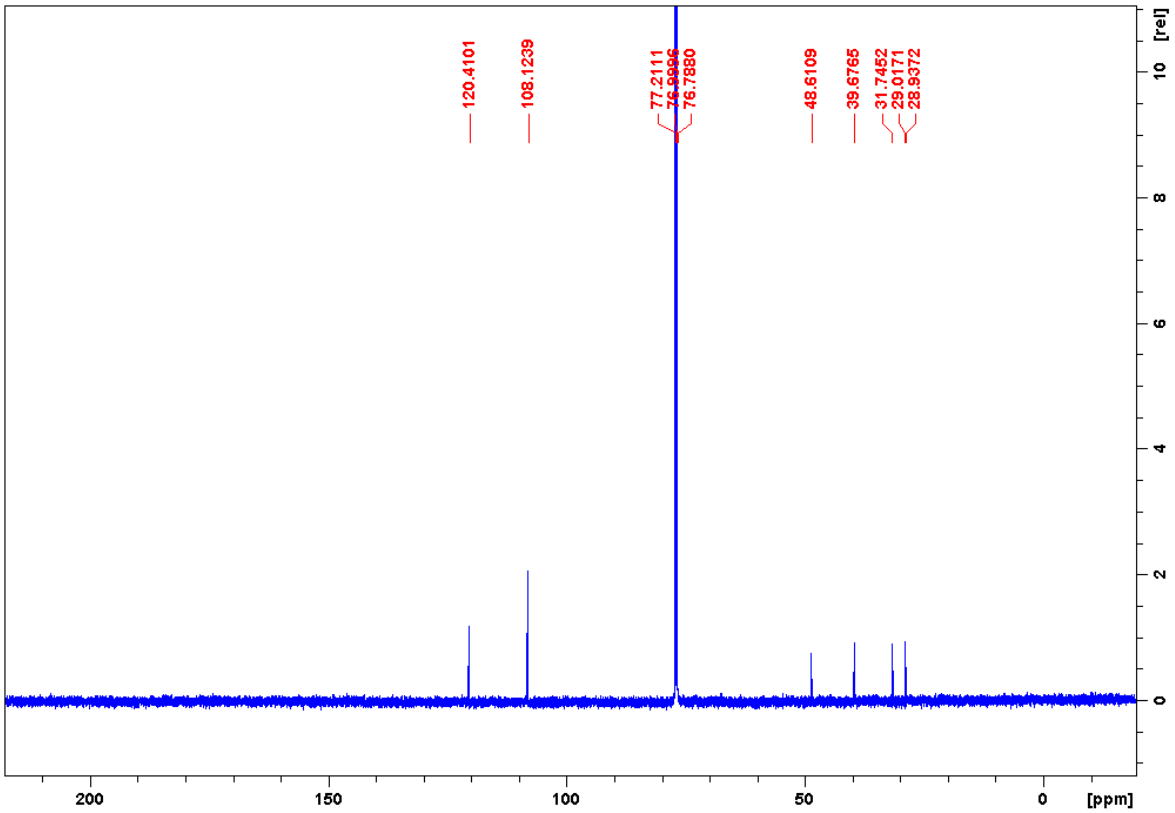
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4.3 Experimental Section for Chapter III

4.3.1 General Synthetic Methods

General Procedure A: Reduction of Esters and Carboxylic Acids.

To a 0°C solution of ester or carboxylic acid (1 equiv.) in THF (0.5 M) was added $LiAlH_4$ (1 equiv.). The reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The reaction was cooled to 0°C and diluted with Et_2O. This mixture was quenched successively with H_2O (1 mL/g $LiAlH_4$), 15% aqueous NaOH (2 mL/g $LiAlH_4$), and H_2O (3 mL/g $LiAlH_4$). The quenched reaction mixture was allowed to warm to ambient temperature and was stirred for 30 minutes. $MgSO_4$ was added and the reaction was stirred for 30 more minutes. Aluminum and magnesium solids were removed by filtration and the crude product was concentrated under reduced pressure. The crude product was purified by flash chromatography or distillation.

General Procedure B: Bromoetherification of Enol Ethers.

To a 0°C solution of alcohol (1 equiv.) and enol ether (1.2 equiv.) in CH_2Cl_2 (1.0 M) was added N-bromosuccinimide (1 equiv). The reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The reaction was quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

General Procedure C: Bromoetherification of Methoxystyrene.

To a -78°C solution of styrene (1 equiv.) and alcohol (2 equiv.) in CH_2Cl_2 (0.25 M) was added N-bromosuccinimide (1.5 equiv). The reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The reaction was quenched with saturated $Na_2S_2O_4$ and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

General Procedure D: Bromination of Allylic and Homoallylic Alcohols.

To a 0°C solution of secondary alcohol (1 equiv.) in CH_2Cl_2 (1.0 M) was added phosphorus tribromide (0.5 equiv.) dropwise. The reaction mixture was stirred at room temperature for 1 hour, and was then quenched with H_2O. The aqueous layer was back extracted with CH_2Cl_2 (3x) and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography or distillation.

General Procedure E: Alkylation of Alkyl Sulfonamides.

To a solution of sulfonamide (1 equiv.) in acetone (0.5 M) was added allylic or homoallylic bromide (1.5 equiv.), K_2CO_3 (1.5 equiv.), and KI (0.1 equiv.). The reaction mixture was heated to reflux and stirred for 16 hours. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

General Procedure F: Bromination of Primary and Secondary Alcohols.

To a 0°C solution of triphenylphosphine (3 equiv.) in THF (0.25 M) was added CBr_4 (3 equiv.). This solution was stirred at 0°C for 5 minutes the solution turned bright yellow. Alcohol (1 equiv.) was then added dropwise, and the reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

General Procedure G: Alkylation of Allylic and Homoallylic Sulfonamides.

To a solution of allylic or homoallylic sulfonamide (1 equiv.) in MeCN (0.5 M) was added alkyl bromide (10 equiv.), and Cs_2CO_3 (1.5 equiv.). The reaction mixture was heated to reflux and stirred for 72 hours. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

General Procedure H: Alkylation of α-Aryl Acetates.

To a 0°C solution of $^{i}Pr_2NH$ (1.1 equiv.) in THF (0.25 M) was added $^{n}BuLi$ (1.1 equiv.). This solution was stirred for 15 minutes and then cooled to -78°C. α-Aryl acetate (1 equiv.) was then added dropwise, and the reaction mixture was stirred 30 minutes at -78°C. Alkyl bromide (1.2 equiv.) and HMPA (0.6 equiv.) were then added and the reaction was allowed to warm to room temperature and stirred for 16 hours. The reaction was quenched with saturated NH_4Cl and the aqueous layer was extracted with 1:1 hexanes : ethyl acetate (3x). The combined organic layers

were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

General Procedure I: Alternative Bromination Method for Primary Alcohols.

To a 0°C solution of triphenylphosphine (1.6 equiv.) and imidazole (1.5 equiv.) in DCM (0.5 M) was added Br_2 (1.5 equiv.). This solution was stirred at 0°C for 5 minutes until a color change had occurred. Alcohol (1 equiv.) was then added dropwise, and the reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with saturated $Na_2S_2O_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

Cross-Coupling Procedure A: 5-Membered Ring Formation

To a one-dram vial in a glove box under argon atmosphere was added primary or secondary iodide (1.0 mmol, 1 equiv) dissolved in $PhCF_3$ (0.25 M). $[Pd(allyl)Cl]_2$ (5 mol%), dtbpf (20 mol%), and Et_3N (2 equiv.) were then added. The reaction vial was removed from the glove box and heated to 100°C, stirring for 3-24 hours. The reaction mixture was allowed to cool to ambient temperature, was quenched with 1N HCl and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

Cross-Coupling Procedure B: Reaction with Terminal Alkenes

To a one-dram vial in a glove box under argon atmosphere was added primary or secondary iodide (1.0 mmol, 1 equiv) dissolved in $PhCF_3$ (0.25 M). $[Pd(allyl)Cl]_2$ (5 mol%), dtbpf (20 mol%), and DBU (2 equiv.) were then added. The reaction vial was removed from the glove box and heated to 100°C, stirring for 16 hours. The reaction mixture was allowed to cool to ambient temperature, was quenched with 1N HCl and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

Cross-Coupling Procedure C: 6-Membered Ring Formation

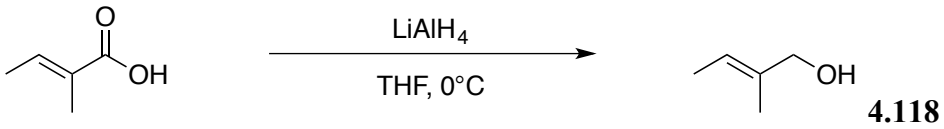
To a one-dram vial in a glove box under argon atmosphere was added primary or secondary iodide (1.0 mmol, 1 equiv) dissolved in $PhCF_3$ (0.25 M). $[Pd(allyl)Cl]_2$ (5 mol%), dtbpf (20 mol%), and Cy_2NMe (2 equiv.) were then added. The reaction vial was removed from the glove box and heated to 130°C, stirring for 16-48 hours. The reaction mixture was allowed to cool to ambient temperature, was quenched with 1N HCl and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

Cross-Coupling Procedure D: Atom-Transfer Radical Cyclization

To a one-dram vial in a glove box under argon atmosphere was added primary or secondary iodide (0.25 mmol, 1 equiv) dissolved in $PhCF_3$ (0.25 M). $[Pd(allyl)Cl]_2$ (5 mol%), dtbpf (20 mol%), and Et_3N (0.5 equiv.) were then added. The reaction vial was removed from the glove box and heated to 80°C, stirring for 30 minutes. The reaction mixture was allowed to cool to

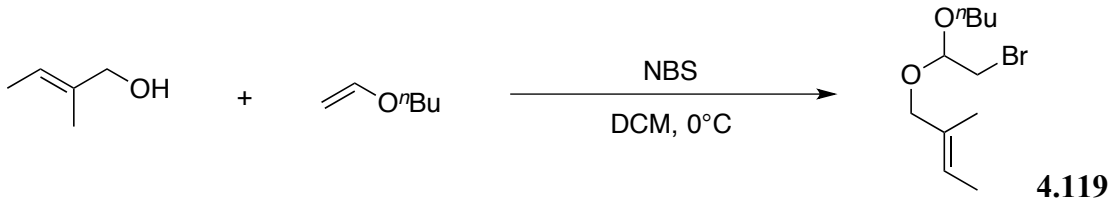
ambient temperature, was quenched with 1N HCl and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

4.3.2 Experimental Data



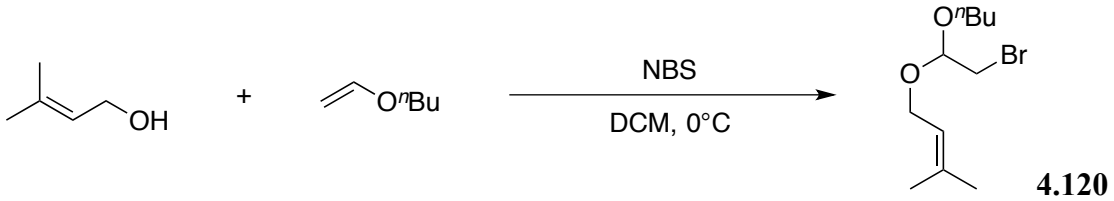
4.118

(4.118): *trans*-2-Methyl-2-buten-1-ol. *trans*-2-Methyl-2-butenoic acid (20 g, 200 mmol) was reduced by $LiAlH_4$ (7.6 g, 200 mmol) according to General Procedure A. The crude product was purified by distillation to provide alcohol **4.118** as a clear oil (7.5g, 46% Yield). All physical and spectroscopic data were in accordance with literature data.[22]



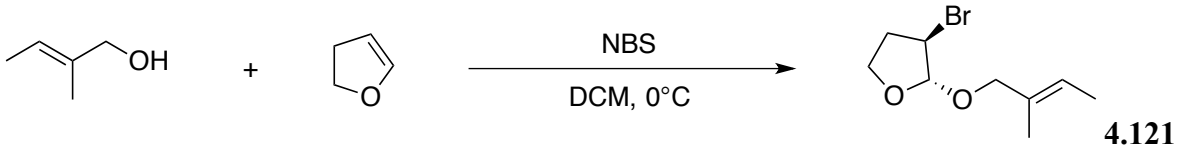
4.119

(4.119): 2-Bromoethanal butyl tiglic acetal. *n*-Butyl vinyl ether (2.8 g, 27.9 mmol) was bromoetherified by alcohol **4.118** (2.0 g, 23.2 mmol) according to General Procedure B. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide bromide **4.119** as a clear oil (4.4 g, 72% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 5.54 (m, 1H), 4.68 (t, *J* = 5.4 Hz, 1H), 4.04 (d, *J* = 11.4 Hz, 1H), 3.95 (d, *J* = 11.4 Hz, 1H), 3.62 (m, 1H), 3.52 (m, 1H), 3.39 (m, 2H), 1.70 (s, 3H), 1.65 (m, 3H), 1.60 (m, 2H), 1.41 (m, 2H), 1.94 (t, *J* = 7.8 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 132.21, 123.57, 100.54, 73.07, 66.37, 31.78, 31.77, 19.29, 13.85, 13.76, 13.24. **HRMS** (ESI): Calculated for $[C_{11}H_{21}BrO_2H]^+$ 266.0837, found 266.1209.



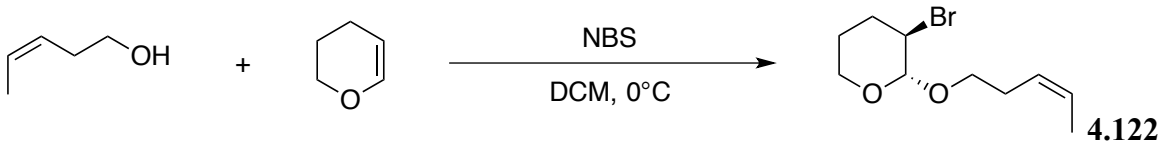
4.120

(4.120): 2-Bromoethanal butyl prenyl acetal. *n*-Butyl vinyl ether (2.3 g, 23.2 mmol) was bromoetherified by 3-methyl-2-buten-1-ol (2.4 g, 27.8 mmol) according to General Procedure B. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide bromide **4.120** as a clear oil (5.0 g, 81% Yield). All physical and spectroscopic data were in accordance with literature data.[23]



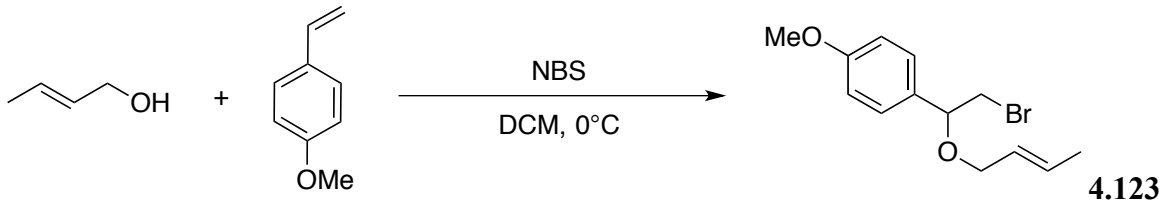
4.121

(4.121): *trans*-3-Bromo-2-(((E)-2-methylbut-2-en-1-yl)oxy)tetrahydrofuran. Dihydrofuran (3.9 g, 55.7 mmol) was bromoetherified by alcohol **4.118** (4.0 g, 46.5 mmol) according to General Procedure B. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide bromide **4.121** as a clear oil (4.3 g, 40% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 5.51 (m, 1H), 5.20 (s, 1H), 4.23 (dd, *J* = 6.0 Hz, 1.2 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 1H), 4.06 (td, *J* = 8.4 Hz, 3.6 Hz, 1H), 4.02 (d, *J* = 10.8 Hz, 1H), 3.85 (d, *J* = 10.8 Hz, 1H), 2.64 (m, 1H), 2.20 (m, 1H), 1.63 (s, 3H), 1.62 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 131.95, 123.26, 107.37, 73.15, 66.50, 50.09, 33.85, 33.85, 13.55, 13.14.



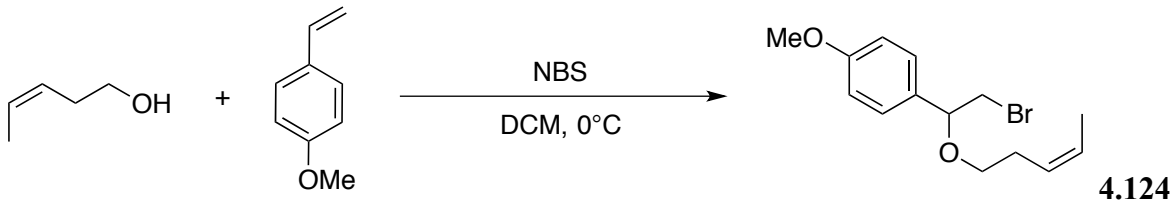
4.122

(4.122): *trans*-3-Bromo-2-((Z)-3-pentene-1-yloxy)tetrahydropyran. Dihydropyran (3.5 g, 41.8 mmol) was bromoetherified by *cis*-3-penten-1-ol (3.0 g, 34.8 mmol) according to General Procedure B. The crude product was purified by flash chromatography using hexanes/ethyl acetate (10:1) to provide bromide **4.122** as a clear oil (6.9 g, 80% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 5.57 (m, 1H), 5.44 (m, 1H), 4.63 (d, J = 4.8 Hz, 1H), 3.99 (m, 1H), 3.94 (m, 1H), 3.78 (m, 1H), 3.59 (m, 1H), 3.51 (m, 1H), 2.39 (m, 3H), 1.94 (m, 2H), 1.65 (d, J = 7.2 Hz, 3H), 1.56 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 126.08, 126.06, 101.09, 67.90, 62.59, 49.51, 30.19, 27.37, 23.38, 12.90.



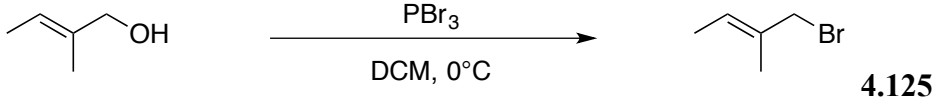
4.123

(4.123): 1-(But-2-enyl)oxy-2-bromo-1-(4-methoxyphenyl)ethane. *para*-Methoxystyrene (2.0 g, 14.9 mmol) was bromoetherified by *trans*-2-buten-1-ol (2.2 g, 29.8 mmol) according to General Procedure C. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide bromide **4.123** as a clear oil (1.0 g, 25% Yield).



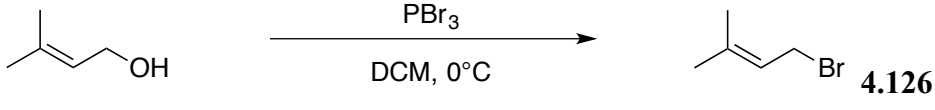
4.124

(4.124): 1-(Pent-3-enyl)oxy-2-bromo-1-(4-methoxyphenyl)ethane. *para*-Methoxystyrene (1.6 mL, 12 mmol) was bromoetherified by *cis*-3-penten-1-ol (2.5 mL, 24 mmol) according to General Procedure C. The crude product was purified by flash chromatography using hexanes/ethyl acetate (30:1) to provide bromide **4.124** as a clear oil (1.4 g, 39% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 5.57 (m, 1H), 5.22 (m, 1H), 4.65 (m, 1H), 2.98 (q, *J* = 6.6 Hz, 2H), 2.44 (s, 3H), 2.22 (q, *J* = 7.2 Hz, 2H), 1.57 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.34, 136.79, 129.65, 127.67, 127.06, 125.52, 42.60, 26.93, 21.48, 12.87.



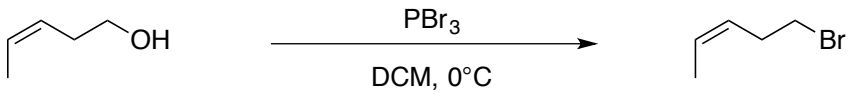
4.125

(4.125): *trans*-1-Bromo-2-methyl-2-butene. Alcohol **4.118** (22 g, 256 mmol) was brominated with PBr_3 (34.6 g, 128 mmol) according to General Procedure D. The crude product was purified by distillation to provide bromide **4.125** as a clear oil (26.3 g, 69% Yield). All physical and spectroscopic data were in accordance with literature data.[24]



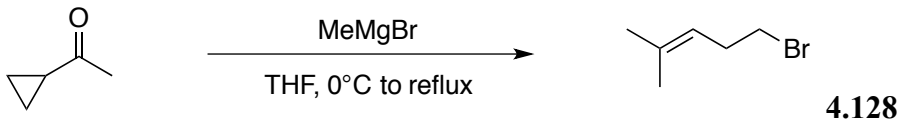
4.126

(4.126): 1-Bromo-3-methyl-2-butene. 3-methyl-2-buten-1-ol (21.5 g, 250 mmol) was brominated with PBr_3 (33.8 g, 125 mmol) according to General Procedure D. The crude product was purified by distillation to provide bromide **4.126** as a clear oil (23.1 g, 62% Yield). All physical and spectroscopic data were in accordance with literature data.



4.127

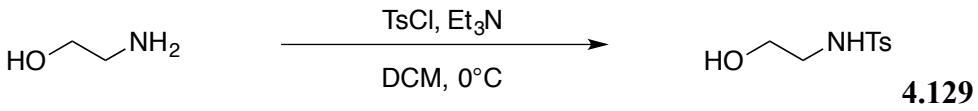
(4.127): *cis*-1-Bromo-3-pentene. *cis*-3-penten-1-ol (10.0 g, 116 mmol) was brominated with PBr_3 (15.7 g, 58.1 mmol) according to General Procedure D. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide bromide **4.127** as a clear oil (10.1 g, 59% Yield). All physical and spectroscopic data were in accordance with literature data.[25]



4.128

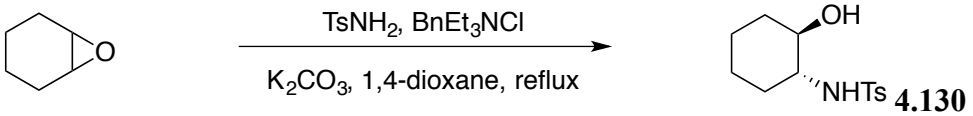
(4.128): 1-Bromo-4-methylpent-3-ene. To a 0°C solution of cyclopropyl methyl ketone (16.8 g, 200 mmol, 1 equiv.) in THF (2.0 M) was added MeMgBr (80 mL, 3.0 M in THF, 1.2 equiv.). The reaction mixture was heated to reflux stirred for 20 minutes. The reaction was cooled to 0°C and 2:1 H_2O:H_2SO_4 was added and stirred, warming to room temperature, for 16 hours. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$,

filtered, and concentrated. The crude product was purified by distillation to provide bromide **4.128** as a clear oil (10.4g, 33% Yield) All physical and spectroscopic data were in accordance with literature data.[26]



4.129

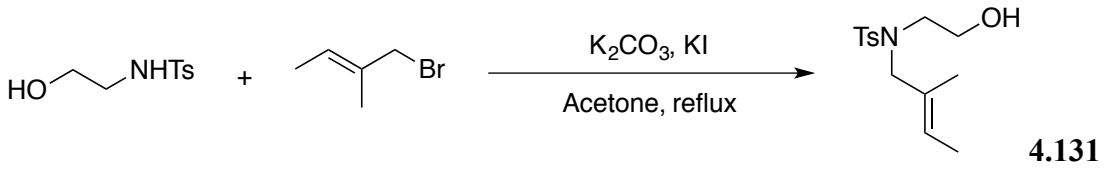
(4.129): *N*-(2-Hydroxyethyl)-4-toluenesulfonamide. To a solution of ethanolamine (5.0 g, 82 mmol, 1 equiv.) and toluenesulfonyl chloride (17.2 g, 90.2 mmol, 1.1 equiv.) in CH_2Cl_2 (180 mL, 0.45 M) was added triethylamine (12.6 mL, 90.2 mmol, 1.1 equiv.). The reaction mixture was allowed to warm to ambient temperature and was stirred for 24 hours. The reaction was quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product, sulfonamide **4.129** (17.6 g, 99% Yield), was carried on without further purification. All physical and spectroscopic data were in accordance with literature data.[27]



4.130

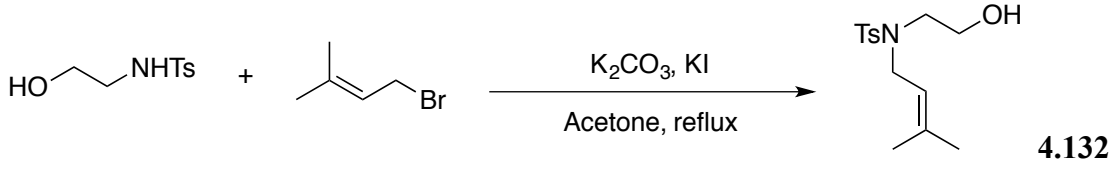
(4.130): *N*-(2-Hydroxycyclohexyl)-4-toluenesulfonamide. To a 0°C solution of cyclohexene oxide (8.0 g, 81.5 mmol, 1 equiv.) in 1,4-dioxane (50 mL, 1.6 M) was added toluenesulfonamide (16.8 g, 97.9 mmol, 1.2 equiv.), K_2CO_3 (1.1 g, 8.2 mmol, 0.1 equiv.), and $BnEt_3NCl$ (1.9 g, 8.2 mmol, 0.1 equiv.). The reaction mixture was heated to reflux and stirred at 96 hours. The

reaction was quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide sulfonamide **4.130** as a clear oil (9.1 g, 42% Yield). All physical and spectroscopic data were in accordance with literature data.[28]



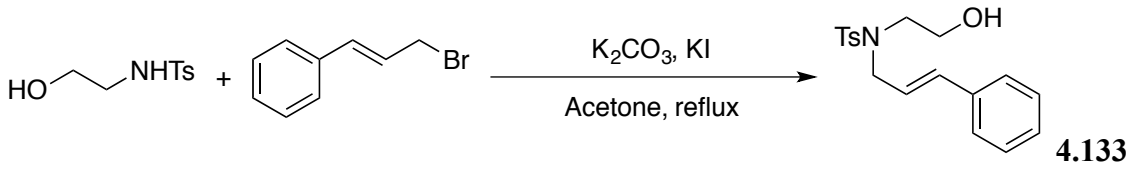
4.131

(4.131): *N*-(2-Hydroxyethyl)-4-methyl-*N*-((E)-2-methylbut-2-en-1-yl)benzene sulfonamide. Sulfonamide **4.129** (20 g, 92.9 mmol) was alkylated with bromide **4.125** (20.8 g, 139 mmol) according to General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide alcohol **4.131** as a white solid (19.2 g, 73% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.71 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 5.39 (m, 1H), 3.67 (s, 2H), 3.64 (t, J = 5.4 Hz, 2H), 3.15 (t, J = 5.4 Hz, 2H), 2.44 (s, 3H), 1.63 (s, 3H), 1.61 (d, J = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.46, 135.76, 131.11, 129.69, 127.22, 124.52, 61.16, 58.17, 50.02, 21.48, 13.67, 13.43. **HRMS** (ESI): Calculated for $[C_{14}H_{21}NO_3SNa]^+$ 306.1140, found 306.1136.



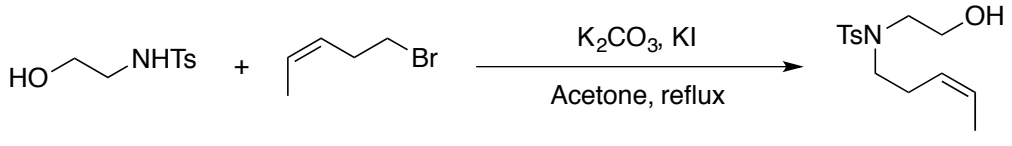
4.132

(4.132): *N*-(2-Hydroxyethyl)-4-methyl-*N*-(3-methylbut-2-en-1-yl)benzenesulfonamide. Sulfonamide **4.129** (15 g, 70 mmol) was alkylated with bromide **4.126** (15.6 g, 105 mmol) according to General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide alcohol **4.312** as a white solid (12.3 g, 62% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 7.8 Hz), 5.03 (m, 1H), 3.84 (d, *J* = 7.2 Hz, 2H), 3.73 (m, 2H), 3.21 (t, *J* = 4.8 Hz, 2H), 2.44 (s, 3H), 2.41 (m, 1H), 1.68 (s, 3H), 1.63 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.39, 137.55, 136.22, 129.65, 127.24, 118.71, 61.17, 49.63, 46.92, 25.74, 21.48, 17.77. **HRMS** (ESI): Calculated for $[C_{14}H_{21}NO_3SH]^+$ 284.1321, found 284.1314.



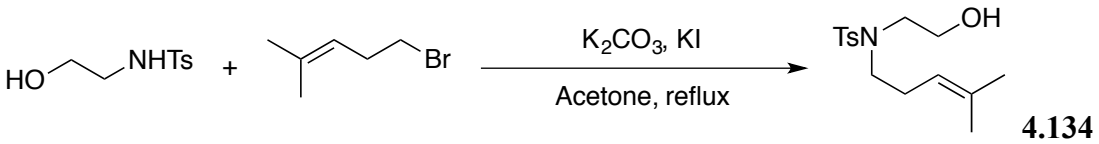
4.133

(4.133): *N*-Cinnamyl-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide. Sulfonamide **4.129** (6.0 g, 27.9 mmol) was alkylated with cinnamyl bromide (8.2 g, 41.8 mmol) according to General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide alcohol **4.133** as a thick brown sludge (5.8 g, 63% Yield). All physical and spectroscopic data were in accordance with literature data.[29]



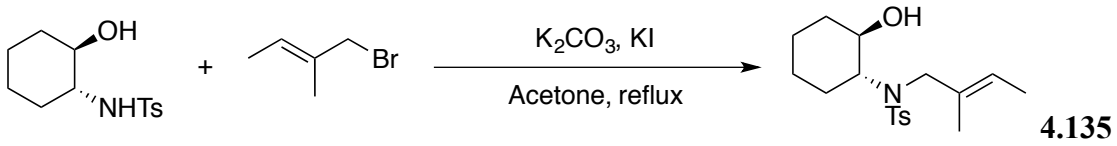
4.133

(4.133): *N*-(2-Hydroxyethyl)-4-methyl-*N*-((Z)-pent-3-en-1-yl)benzenesulfonamide. Sulfonamide **4.129** (1.7 g, 8.0 mmol) was alkylated with bromide **4.127** (2.0 g, 13 mmol) according to General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide alcohol **4.133** as a white solid (1.2 g, 53% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 5.56 (m, 1H), 5.32 (m, 1H), 3.77 (t, *J* = 5.4 Hz, 2H), 3.25 (m, 2H), 3.17 (m, 2H), 2.57 (bs, 1H), 2.43 (s, 3H), 2.32 (q, *J* = 7.8 Hz, 2H), 1.60 (dd, *J* = 7.2 Hz, 1.2 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.47, 135.85, 129.70, 127.17, 126.88, 125.73, 61.24, 50.98, 49.37, 37.61, 26.59, 21.44, 12.87.



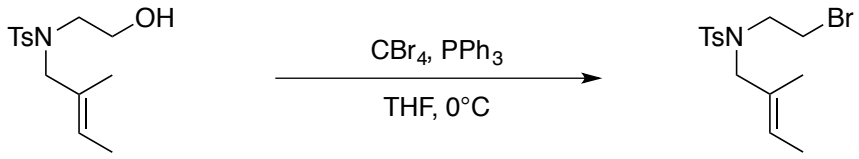
4.134

(4.134): *N*-(2-Hydroxyethyl)-4-methyl-*N*-(4-methylpent-3-en-1-yl)benzenesulfonamide. Sulfonamide **4.129** (5.4 g, 25 mmol) was alkylated with bromide **4.128** (6.0 g, 37 mmol) according to General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide alcohol **4.134** as a white solid (5.1 g, 68% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.04 (m, 1H), 3.77 (m, 2H), 3.26 (t, *J* = 5.4 Hz, 2H), 3.15 (m, 2H), 2.44 (s, 3H), 2.26 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.44, 135.94, 134.78, 129.71, 127.22, 119.80, 61.30, 50.97, 49.64, 27.75, 25.65, 21.47, 17.80. **HRMS** (ESI): Calculated for $[C_{15}H_{22}NO_3SNa]^+$ 320.1297, found 320.1289.



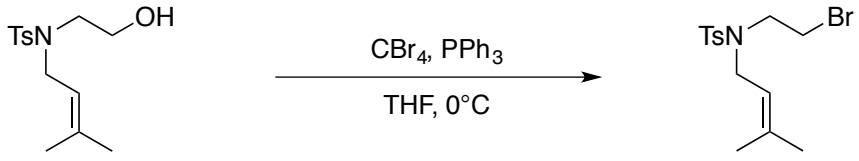
4.135

(4.135): *N*-(2-Hydroxycyclohexyl)-4-methyl-*N*-((E)-2-methylbut-2-en-1-yl)benzene sulfonamide. Sulfonamide **4.130** (6.0 g, 22.4 mmol) was alkylated with bromide **4.125** (5.0 g, 33.6 mmol) according to General Procedure E. The crude product was purified by flash chromatography using hexanes/ethyl acetate/methylene chloride (4:2:1) to provide alcohol **4.135** as a pale yellow oil (4.8 g, 64% Yield).



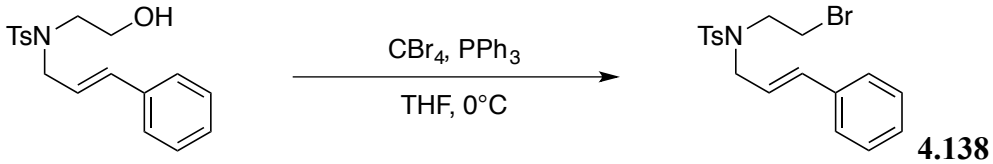
4.136

(4.136): (E)-*N*-(2-Bromoethyl)-4-methyl-*N*-((E)-2-methylbut-2-en-1-yl)benzenesulfonamide. Alcohol **4.131** (7.5 g, 26.5 mmol) was brominated with CBr_4 (26.3 g, 79.4 mmol) according to General Procedure F. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide bromide **4.136** as a white solid (6.4 g, 70% Yield). All physical and spectroscopic data were in accordance with literature data.[30]



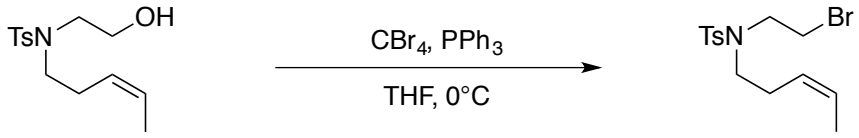
4.137

(4.137): *N*-(2-Bromoethyl)-4-methyl-*N*-(3-methylbut-2-en-1-yl)benzenesulfonamide. Alcohol **4.132** (2.5 g, 8.8 mmol) was brominated with CBr_4 (8.8 g, 26.5 mmol) according to General Procedure F. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide bromide **4.137** as a white solid (2.1 g, 69% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.33, (d, *J* = 7.8 Hz, 2H), 5.03 (m, 1H), 3.82 (d, *J* = 6.6 Hz, 2H), 3.46 (m, 2H), 3.39 (m, 2H), 2.45 (s, 3H), 1.71 (s, 3H), 1.65 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.49, 138.07, 136.37, 129.73, 127.16, 118.59, 48.81, 46.67, 29.61, 25.80, 21.52, 17.78. **HRMS** (ESI): Calculated for $[C_{14}H_{20}BrNO_2SH]^+$ 346.0477, found 346.0470.



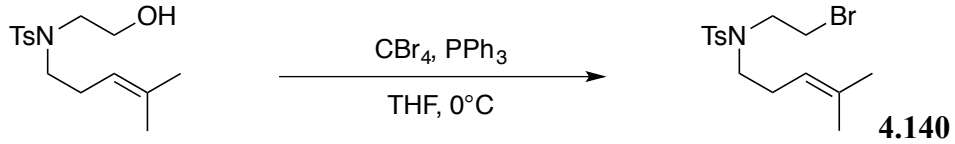
4.138

(4.138): *N*-Cinnamyl-*N*-(2-bromoethyl)-4-methylbenzenesulfonamide. Alcohol **4.133** (3.0 g, 9.1 mmol) was brominated with CBr_4 (9.0 g, 27.2 mmol) according to General Procedure F. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide bromide **4.138** as a white solid (2.6 g, 72% Yield). All physical and spectroscopic data were in accordance with literature data.[31]



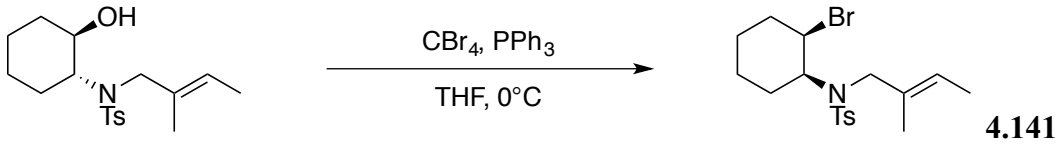
4.139

(4.139): *N*-(2-Bromoethyl)-4-methyl-*N*-((Z)-pent-3-en-1-yl)benzenesulfonamide. Alcohol **4.133** (0.9 g, 3.0 mmol) was brominated with Br_2 (0.23 mL, 4.5 mmol) according to General Procedure I. The crude product was purified by flash chromatography using hexanes/ethyl acetate (10:1) to provide bromide **4.139** as a white solid (0.53 g, 50% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 5.58 (m, 1H), 5.31 (m, 1H), 3.49 (m, 4H), 3.18 (m, 2H), 2.46 (s, 3H), 2.33 (q, *J* = 7.2 Hz, 2H), 1.63 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.62, 136.17, 129.82, 129.79, 127.14, 127.04, 125.49, 50.15, 49.15, 29.45, 26.83, 21.53, 12.96.



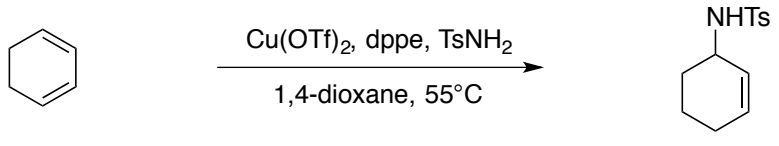
4.140

(4.140): *N*-(2-Bromoethyl)-4-methyl-*N*-(4-methylpent-3-en-1-yl)benzenesulfonamide. Alcohol **4.134** (1.5 g, 5 mmol) was brominated with Br_2 (0.38 mL, 7.5 mmol) according to General Procedure I. The crude product was purified by flash chromatography using hexanes/ethyl acetate (6:1) to provide bromide **4.140** as a white solid (1.1 g, 61% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.01 (m, 1H), 3.48 (m, 2H), 3.48 (m, 2H), 3.14 (t, *J* = 7.8 Hz, 2H), 2.45 (s, 3H), 2.25 (q, *J* = 7.8 Hz, 2H), 1.69 (s, 3H), 1.61 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.54, 136.22, 134.85, 129.78, 127.13, 119.59, 50.07, 49.33, 29.45, 27.95, 25.69, 21.52, 17.86. **HRMS** (ESI): Calculated for $[C_{15}H_{22}BrNO_2SH]^+$ 360.0633, found 360.0630.



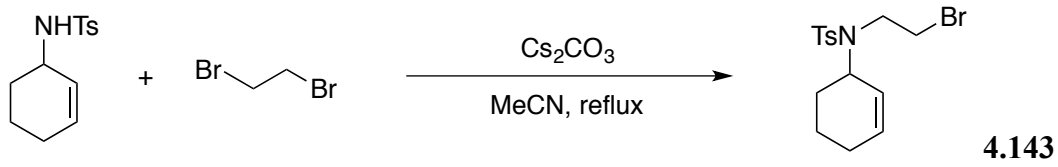
4.141

(4.141): *N*-(2-Bromocyclohexyl)-4-methyl-*N*-(2-methylbut-2-en-1-yl)benzenesulfonamide. Alcohol **4.135** (2.5 g, 7.4 mmol) was brominated with CBr_4 (7.4 g, 22.2 mmol) according to General Procedure F. The crude product was purified by flash chromatography using hexanes/ethyl acetate/methylene chloride (8:4:1) to provide bromide **4.141** as a thick orange oil (2.4 g, 82% Yield).



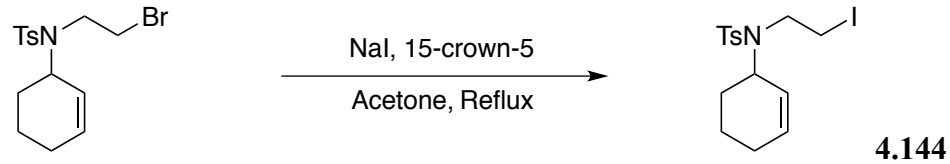
4.142

(4.142): *N*-Cyclohex-2-enyl-4-methyl-benzenesulfonamide. To a solution of $Cu(OTf)_2$ (1.1 g, 3.1 mmol, 5 mol %) in 1,4-dioxane (100 mL, 0.6 M) was added dppe (1.2 g, 3.1 mmol, 5 mol %). The reaction mixture was allowed to stir for 10 minutes at room temperature. Cyclohexadiene (5.0 g, 62 mmol) and toluenesulfonamide (16.1 g, 94 mmol) were then added, and the reaction mixture was heated to 55°C and stirred at 16 hours. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using hexanes/ethyl acetate (4:1) to provide sulfonamide **4.142** as white solid (5.8 g, 37% Yield). All physical and spectroscopic data were in accordance with literature data.[30]



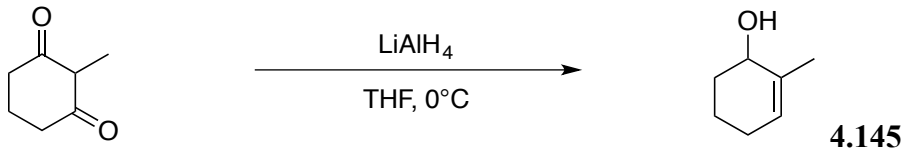
4.143

(4.143): *N*-(2-Bromoethyl)-*N*-(cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide. Sulfonamide **4.142** (3.0 g, 11.9 mmol) was alkylated with 1,2-dibromoethane (22.6 g, 119 mmol) according to General Procedure G. The crude product was purified by flash chromatography using hexanes/ethyl acetate (6:1) to provide bromide **4.143** as a white solid (1.5 g, 35% Yield). All physical and spectroscopic data were in accordance with literature data.[30]



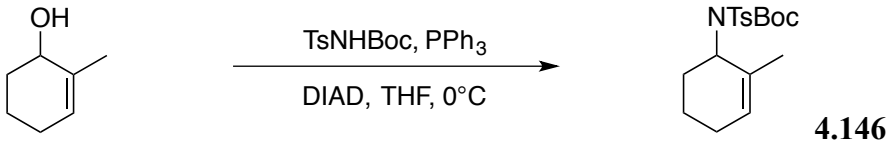
4.144

(4.144): *N*-(2-Iodoethyl)-*N*-(cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide. To a solution of bromide **4.143** (5.0 g, 14.0 mmol, 1 equiv.) in actone (60 mL, 0.3 M) was added NaI (6.3 g, 41.9 mmol, 3 equiv.) and 15-crown-5 (310 mg, 1.4 mmol, 0.1 equiv.). The reaction mixture was heated to reflux and stirred at 42 hours. The reaction was quenched with H_2O and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with saturated $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide sulfonamide **4.145** as white solid (4.2 g, 74% Yield). All physical and spectroscopic data were in accordance with literature data.[30]



4.145

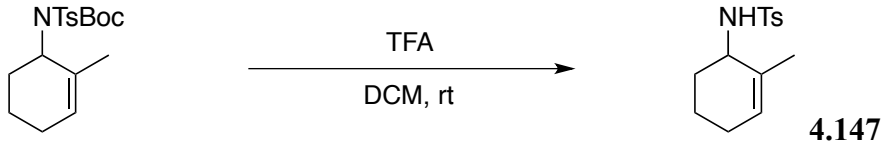
(4.145): 2-Methylcyclohex-2-en-1-ol. To a 0°C solution of 2-methyl-1,3-cyclohexadione (15.1 g, 120 mmol, 1 equiv.) in Et_2O (0.5 M) was added $LiAlH_4$ (11.4 g, 300 mmol, 2.5 equiv.). The reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The reaction was cooled to 0°C and diluted with Et_2O. This mixture was quenched successively with H_2O (12 mL), 15% aqueous NaOH (24 mL), and H_2O (36 mL). The quenched reaction mixture was allowed to warm to ambient temperature and was stirred for 30 minutes. $MgSO_4$ was added to this crude mixture, it was stirred for 30 more minutes. Aluminum and magnesium solids were removed by filtration and the crude product was concentrated under reduced pressure. The crude product was purified by distillation to provide enol **4.145** as a clear oil (10.1 g, 75% Yield). All physical and spectroscopic data were in accordance with literature data.[32]



4.146

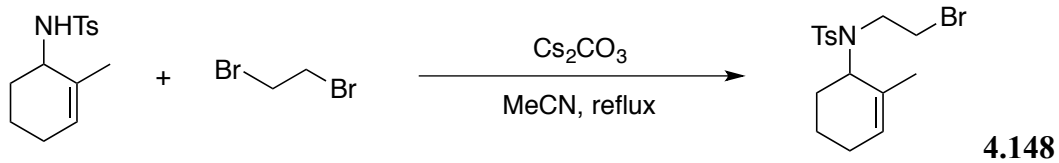
(4.146): *tert*-Butyl *N*-(4-methylbenzenesulfonyl)-*N*-(2-methylcyclohex-2-en-1-yl)carbamate. To a 0°C solution of enol **4.145** (8.4 g, 75 mmol, 2 equiv.), TsNHBoc (10.2 g, 37 mmol, 1 equiv.), and PPh_3 (29.5 g, 112.5 mmol, 3 equiv.) in THF (200 mL, 0.2 M) was added DIAD (19.7 g, 97.5 mmol, 2.6 equiv.). The reaction mixture was allowed to warm to ambient

temperature and was stirred for 24 hours. The reaction was concentrated under reduced pressure and filtered through silica. The silica plug was flushed with Et_2O (2x) and the combined organics were concentrated. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide sulfonamide **4.146** as a white solid (12.4 g, 90% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.54 (m, 1H), 4.99 (m, 1H), 2.46 (s, 3H), 2.16 (m, 1H), 2.07 (m, 2H), 1.99 (m, 1H), 1.86 (m, 1H), 1.67 (m, 1H), 1.56 (bs, 3H), 1.38 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 150.36, 143.91, 137.36, 132.94, 129.14, 128.07, 124.69, 83.83, 59.28, 29.06, 27.84, 24.79, 22.77, 21.61, 20.33.



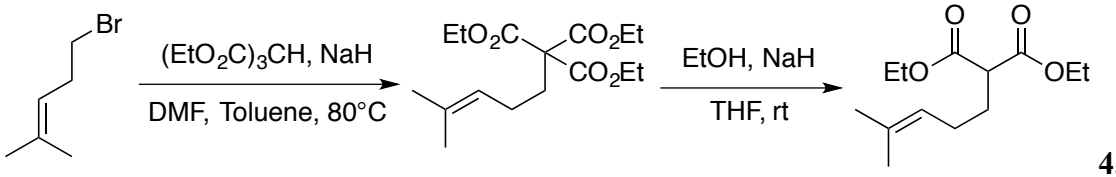
4.147

(4.147): 4-Methyl-*N*-(2-methyl-2-cyclohexen-1-yl)benzenesulfonamide. To a solution of sulfonamide **4.146** (10 g, 27.4 mmol, 1 equiv.) in DCM (70 mL, 0.4 M) was added TFA (15.6 g, 137 mmol, 5 equiv.). The reaction mixture stirred for 16 hours at room temperature. The reaction was quenched with saturated $NaHCO_3$ and the aqueous layer was extracted with DCM (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide sulfonamide **4.147** as a white solid (7.1 g, 98% Yield). All physical and spectroscopic data were in accordance with literature data.[33]



4.148

(4.148): ***N*-(2-Bromoethyl)-*N*-(2-methylcyclohex-2-en-1-yl)-4-methylbenzenesulfonamide.** Sulfonamide **4.147** (1.7 g, 6.4 mmol) was alkylated with 1,2-dibromoethane (12 g, 64 mmol) according to General Procedure G. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide bromide **4.148** as a white solid (1.1 g, 46% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 5.71 (m, 1H), 4.27 (m, 1H), 3.71 (m, 1H), 3.55 (m, 1H), 3.48 (m, 1H), 3.22 (m, 1H), 2.45 (s, 3H), 2.01 (m, 1H), 1.94 (m, 1H), 1.84 (m, 1H), 1.65-1.52 (m, 3H), 1.28 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.46, 137.51, 131.64, 129.94, 129.71, 127.06, 57.70, 45.89, 30.57, 30.09, 24.94, 21.54, 20.91, 20.60. **HRMS** (ESI): Calculated for $[C_{16}H_{22}BrNO_2SNa]^+$ 395.0531, found 395.0487.

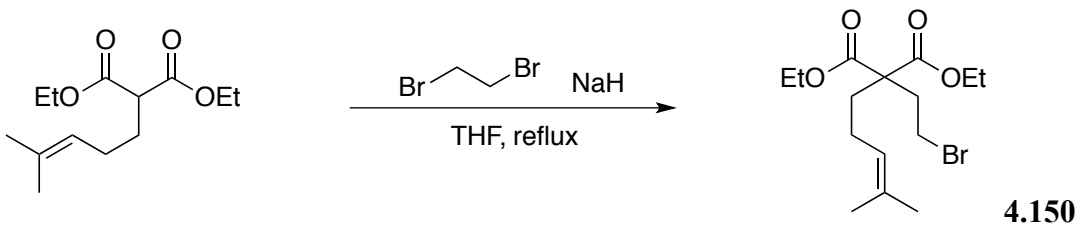


4.149

(4.149): Diethyl 2-(4-methylpent-3-en-1-yl)malonate. To a suspension of sodium hydride (0.74 g, 60 %, 18.4 mmol, 1.02 equiv) in 1:1 DMF:Toluene (60 mL, 0.3 M) was added triethyl methanetricarboxylate (4.2 g, 18.0 mmol, 1 equiv.). The solution was stirred for 30 minutes at room temperature before the addition of bromide **4.128** (3.0 g, 18.4 mmol, 1.02 equiv). The reaction mixture was heated to reflux and stirred for 20 hours. The reaction was quenched with H_2O, extracted with EtOAc (5x) and washed with H_2O, saturated $NaHCO_3$, and brine. The

organic layer was then dried over $MgSO_4$, filtered, and concentrated. The crude product was then decarboxylated without further purification.

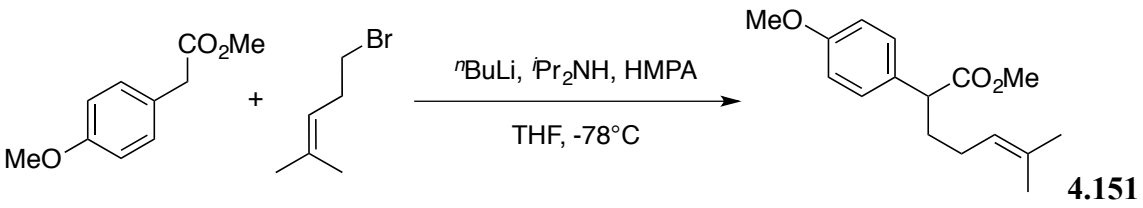
To a suspension of sodium hydride (0.81 g, 60%, 20.2 mmol, 1.1 equiv) in THF (50 mL, 0.4 M) was added ethanol (1.0 g, 22.1 mmol, 1.2 equiv) and stirred for 30 minutes at room temperature. Alkyl triester (6.0 g, 18.4 mmol, 1 equiv) was then added, and the solution was heated to reflux and stirred for 16 hours. The reaction mixture was quenched with 1N HCl, extracted with Et_2O, and washed with H_2O, saturated $NaHCO_3$, and brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide alkylmalonate **1.149** as a clear oil (2.8 g, 63% Yield). All physical and spectroscopic data were in accordance with literature data.[30]



4.150

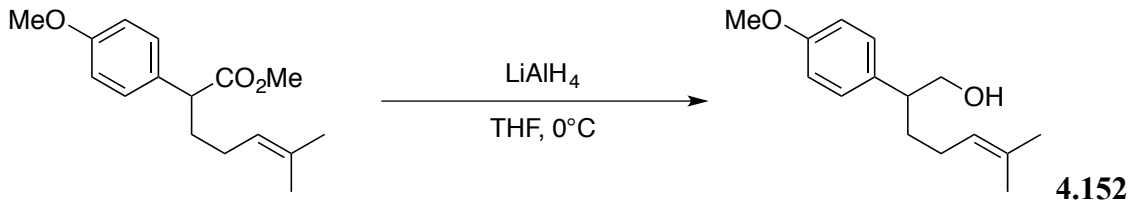
(4.150): Diethyl 2-(2-bromoethyl)-2-(4-methylpent-3-en-1-yl)malonate. To a suspension of sodium hydride (0.58 g, 60%, 14.5 mmol, 1.3 equiv) in THF (40 mL, 0.3 M) was added diethyl alkylmalonate **4.149** (2.7 g, 11.1 mmol, 1 equiv). The solution was stirred for 30 minutes at room temperature and 1,2-dibromoethane (20.9 g, 111 mmol, 10 equiv) was then added. The reaction mixture was heated to reflux, stirred for 24 hours. The reaction was quenched with H_2O, extracted with Et_2O (3x), washed with brine, Dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to

provide bromide **4.150** as a clear oil (1.8 g, 46% Yield). All physical and spectroscopic data were in accordance with literature data.[30]



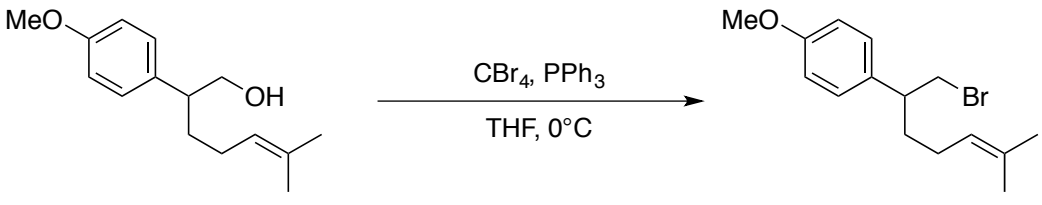
4.151

(4.151): Methyl 2-(4-methoxyphenyl)-6-methylhept-5-enoate. Methyl 4-methoxyphenyl acetate (4.0 g, 22.4 mmol) was alkylated with bromide **4.128** (4.0 g, 26.8 mmol) according to General Procedure F. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide methyl ester **4.151** as a clear oil (5.1 g, 91% Yield). All physical and spectroscopic data were in accordance with literature data.[30]



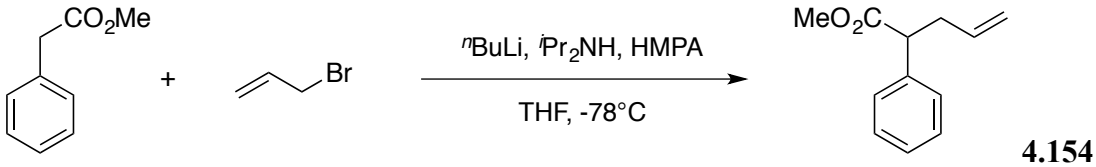
4.152

(4.152): 2-(4-Methoxyphenyl)-6-methylhept-5-enol. Methyl ester **4.151** (5.0 g, 20.1 mmol) was reduced by $LiAlH_4$ (1.5 g, 40.2 mmol) according to General Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (3:1) to provide alcohol **4.152** as a clear oil (2.2 g, 50% Yield). All physical and spectroscopic data were in accordance with literature data.[30]



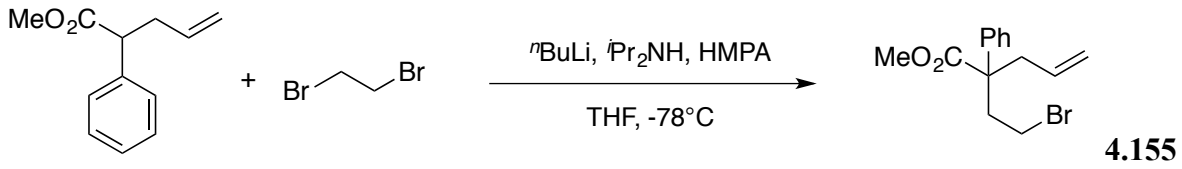
5.153

(4.153): 1-(1-Bromo-6-methylhept-5-en-2-yl)-4-methoxybenzene. Alcohol **4.152** (1.5 g, 6.4 mmol) was brominated with CBr_3 (6.4 g, 19.2 mmol) according to General Procedure F. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide bromide **4.153** as a clear oil (1.6 g, 84% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.12 (d, *J* = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 5.09 (m, 1H), 3.82 (s, 3H), 3.54 (d, *J* = 7.2 Hz, 2H), 2.92 (m, 1H), 1.94 (m, 1H), 1.87 (m, 2H), 1.69 (s, 3H), 1.65 (m, 1H), 1.49 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 158.44, 134.18, 132.15, 128.63, 123.66, 113.84, 55.19, 46.62, 39.48, 34.18, 25.71, 25.69, 17.70. **HRMS** (ESI): Calculated for $[C_{15}H_{21}BrOH]^+$ 297.0854, found 297.0672.



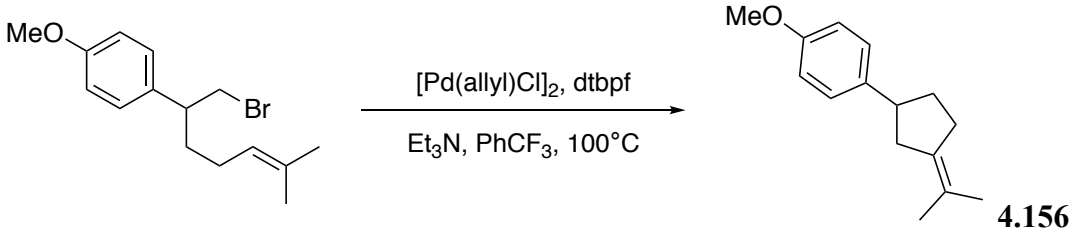
4.154

(4.154): Methyl allylphenylacetate. Methyl phenylacetate (3.8 g, 25.5 mmol) was alkylated with allyl bromide (3.7 g, 30.7 mmol) according to General Procedure F. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide methyl ester **4.154** as a clear oil (4.1 g, 85% Yield). All physical and spectroscopic data were in accordance with literature data.[34]



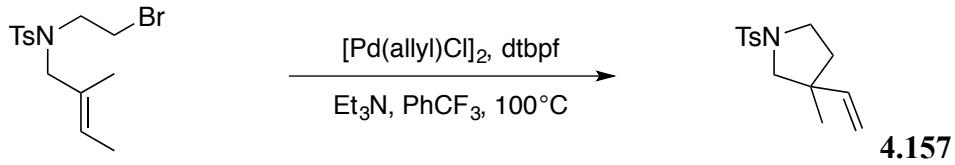
4.155

(4.155): Methyl allyl(2-bromoethyl)phenylacetate. Methyl ester **4.154** (3.8 g, 20 mmol) was alkylated with dibromoethane (4.5 g, 24 mmol) according to General Procedure F. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide bromide **4.155** as a clear oil (3.7 g, 62% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.37 (t, *J* = 7.8 Hz, 2H), 7.30 (m, 1H), 7.25 (d, *J* = 7.2 Hz, 2H), 5.61 (m, 1H), 5.15 (m, 2H), 3.71 (s, 3H), 3.24 (m, 1H), 3.14 (m, 1H), 2.88 (m, 1H), 2.75 (m, 1H), 2.65 (m, 1H), 2.54 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 174.67, 140.51, 132.78, 128.70, 127.29, 126.16, 119.17, 54.50, 52.29, 39.98, 38.83, 27.86. **HRMS** (ESI): Calculated for $[C_{14}H_{17}BrO_2H]^+$ 297.0490, found 297.1085.



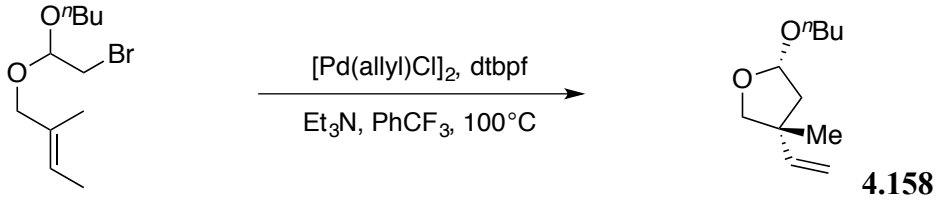
4.156

1-(1-Bromo-6-methylhept-5-en-2-yl)-4-methoxybenzene. Primary bromide **4.153** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide Heck product **4.156** as a yellow oil (195.3 mg, 90% Yield). All physical and spectroscopic data were in accordance with literature data.[30]



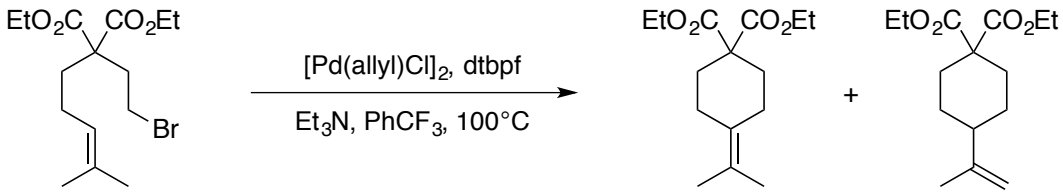
4.157

(E)-*N*-(2-Bromoethyl)-4-methyl-*N*-(2-methylbut-2-en-1-yl)benzene sulfonamide. Primary bromide **4.136** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide Heck product **4.157** as a yellow solid (213.6 mg, 80% Yield). All physical and spectroscopic data were in accordance with literature data.[30]



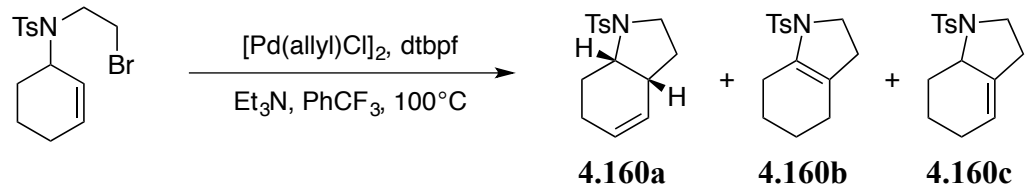
4.158

2-Bromoethanal butyl tiglic acetal. Primary bromide **4.119** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide Heck product **4.158** as a yellow oil (134.4 mg, 73% Yield, 9:1 dr). All physical and spectroscopic data were in accordance with literature data.[30]



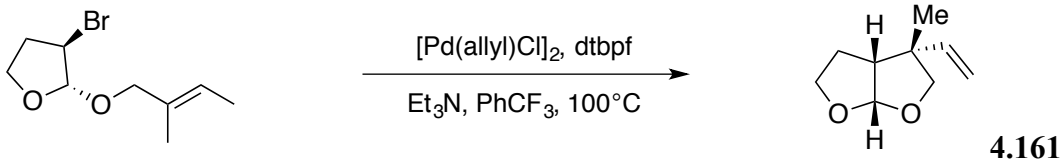
4.159a **4.159b**

Diethyl 2-(2-bromoethyl)-2-(4-methylpent-3-en-1-yl)malonate. Primary bromide **4.150** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide Heck products **4.159a** and **4.159b** as a yellow oil (221.1 mg, 82% Yield, 4:1 rr). All physical and spectroscopic data were in accordance with literature data.[30]



4.160a **4.160b** **4.160c**

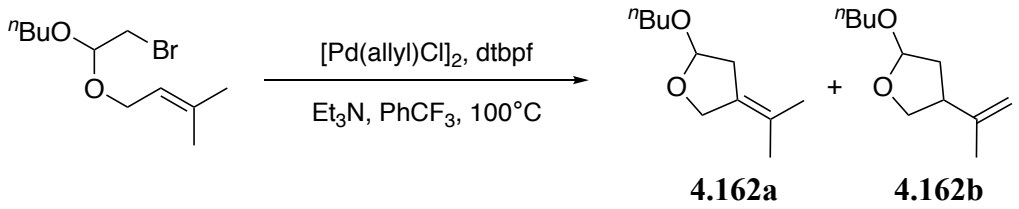
***N*-(2-Bromoethyl)-*N*-(cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide.** Primary bromide **4.143** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide Heck products **4.160a**, **4.160b,** and **4.160c** as a yellow solid (214.5 mg, 77% Yield). All physical and spectroscopic data were in accordance with literature data.[30]



4.161

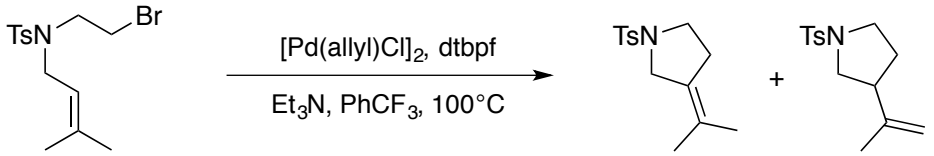
***trans*-3-Bromo-2-(((E)-2-methylbut-2-en-1-yl)oxy)tetrahydrofuran.** Secondary bromide **4.121** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure A. The product was found to decompose after prolonged contact with silica. The crude reaction mixture was dissolved in Et_2O and flushed multiple times through silica gel until no residue or

color remained in the silica, providing Heck product **4.161** as a red oil (143.6 mg, 93% Yield). All physical and spectroscopic data were in accordance with literature data.[30]



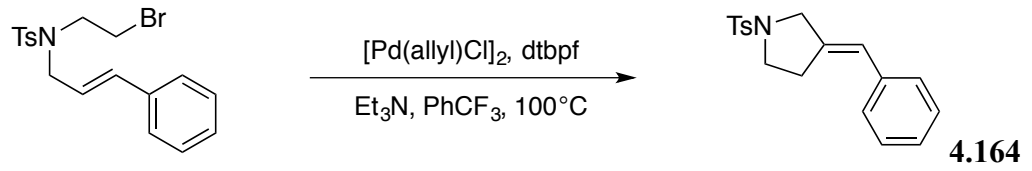
4.162a **4.162b**

2-Bromoethanal butyl prenyl acetal. Primary bromide **4.120** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (40:1) to provide Heck products **4.162a** and **4.162b** as a yellow oil (158.3 mg, 86% Yield, 17:1 rr). All physical and spectroscopic data were in accordance with literature data.[23,35]



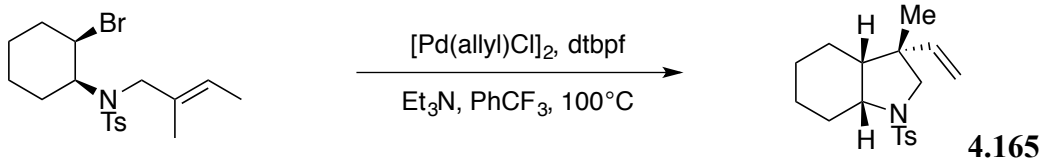
4.163a **4.163b**

***N*-(2-Bromoethyl)-4-methyl-*N*-(3-methylbut-2-en-1-yl)benzenesulfonamide.** Primary bromide **4.137** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide Heck products **4.163a** and **4.163b** as a yellow oil (214.1 mg, 81% Yield). All physical and spectroscopic data were in accordance with literature data.[36]



4.164

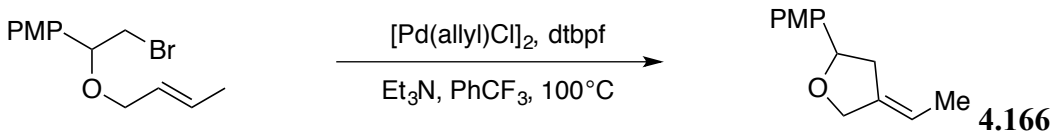
***N*-Cinnamyl-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide.** Primary bromide **4.138** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure A. The yield of the crude product was determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (59% Yield). All physical and spectroscopic data were in accordance with literature data.[37]



4.165

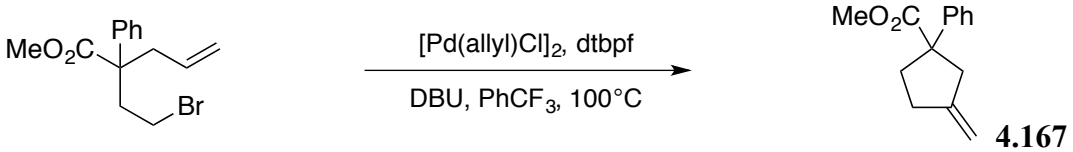
***N*-(2-Bromocyclohexyl)-4-methyl-*N*-(2-methylbut-2-en-1-yl)benzenesulfonamide.** Secondary bromide **4.141** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide Heck product **4.165** as a yellow solid (191.1 mg, 60% Yield, >95:5 dr). The major diastereomer was determined by 2D NMR analysis. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 5.80 (dd, *J* = 17.4 Hz, 10.8 Hz, 1H), 5.04 (d, *J* = 10.8 Hz, 1H), 4.94 (d, *J* = 17.4 Hz, 1H), 3.67 (d, *J* = 10.8 Hz, 1H), 3.60 (m, 1H), 3.12 (d, *J* = 10.8 Hz, 1H), 2.51 (m, 1H), 2.45 (s, 3H), 1.67-1.48 (m, 8H), 0.56 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.24, 141.43, 134.05, 129.49, 127.51, 113.56, 58.62, 57.50, 48.04, 45.07, 28.84,

25.17, 24.13, 23.93, 21.54, 20.37. **HRMS** (ESI): Calculated for $[C_{18}H_{25}NO_2SNa]^+$ 342.1504, found 342.1496.



4.166

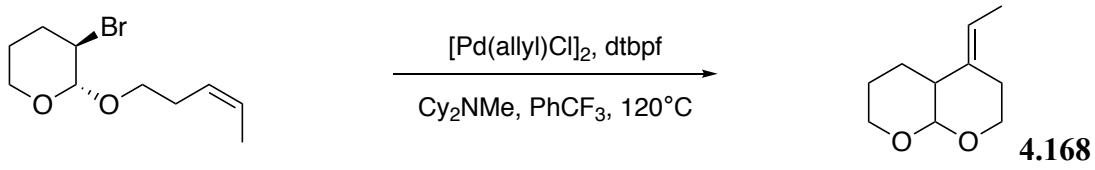
1-(But-2-enyl)oxy-2-bromo-1-(4-methoxyphenyl)ethane. Primary bromide **4.123** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure A. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide Heck product **4.166** as a light yellow oil (144.2 mg, 71% Yield, 1:1 E:Z). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.33 (m, 2H), 6.91 (m, 2H), 5.43 (m, 1H), 4.89 (m, 1H), 4.60 (m, 1H), 4.39 (m, 1H), 3.83 (s, 3H), 2.88 (m, 1H), 2.58-2.39 (m, 1H), 1.65 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 159.00, 139.29, 134.08, 133.79, 127.28, 127.26, 114.48, 113.70, 1113.67, 55.22, 40.89, 37.38, 15.07, 14.54. **HRMS** (ESI): Calculated for $[C_{13}H_{16}O_2Na]^+$ 227.1048, found 227.1562.



4.167

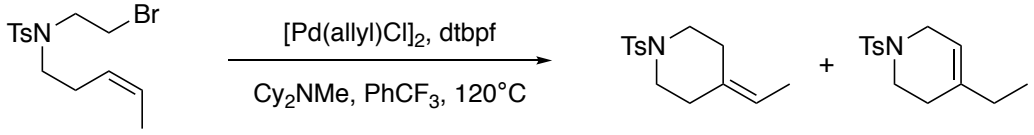
Methyl allyl(2-bromoethyl)phenylacetate. Primary bromide **4.155** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure B. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide Heck product **4.167** as a yellow oil (140.0 mg, 65% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.41 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.2 Hz, 2H), 7.28 (m, 1H), 5.03 (s, 1H), 4.93 (s, 1H), 3.65 (s, 3H), 3.35 (d, J = 15.6 Hz,

1H), 2.79 (m, 2H), 2.46 (m, 2H), 3.07 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 175.65, 149.08, 142.26, 128.33, 126.93, 126.59, 106.75, 58.05, 52.40, 43.09, 35.80, 30.53.



4.168

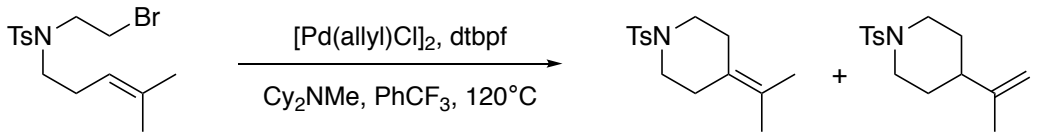
***trans*-3-Bromo-2-((Z)-3-pentene-1-yloxy)tetrahydropyran.** Secondary bromide **4.122** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure C. The yield of the crude product was determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (69% Yield).



4.169a **4.169b**

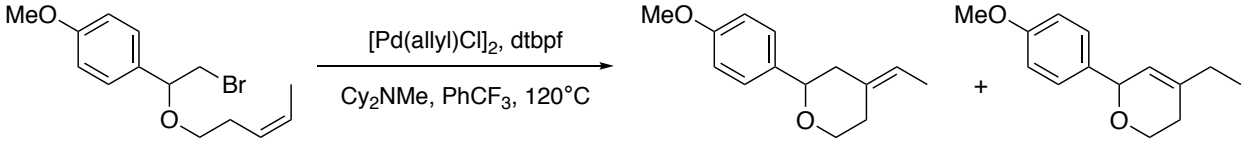
***N*-(2-Bromoethyl)-4-methyl-*N*-(pent-3-en-1-yl)benzenesulfonamide.** Primary bromide **4.139** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure C. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide Heck products **4.169a** and **4.169b** as a yellow solid (187.6 mg, 71% Yield, 3:1 rr). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.68 (d, J = 8.4 Hz, 0.6H), 7.64 (d, J = 8.4 Hz, 2H), 7.32 (m, 2.6H), 5.29 (m, 0.3H), 5.22 (m, 1H), 3.55 (m, 0.6H), 3.16 (t, J = 6.0 Hz, 0.6H), 3.00 (m, 4H), 2.43 (s, 3.9H), 2.32 (m, 2H), 2.25 (m, 2H), 2.13 (m, 0.6H), 1.95 (m, 0.6H), 1.52 (d, J = 6.6 Hz, 3H), 0.95 (t, J = 7.8 Hz, 0.9H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.39, 143.36, 138.07, 133.53, 133.10, 129.57,

129.57, 129.54, 129.51, 127.68, 127.61, 118.74, 114.80, 47.93, 47.08, 44.80, 42.90, 35.10, 29.53, 28.26, 27.07, 21.47, 12.57, 11.79. **HRMS** (APPI): Calculated for $[C_{14}H_{18}O_2H]^+$ 288.1029, found 288.1028.



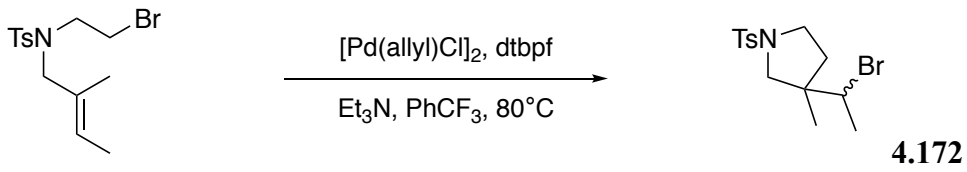
4.170a **4.170b**

***N*-(2-Bromoethyl)-4-methyl-*N*-(4-methylpent-3-en-1-yl)benzenesulfonamide.** Primary bromide **4.140** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure C. The crude product was purified by flash chromatography using hexanes/ethyl acetate (9:1) to provide Heck products **4.170a** and **4.170b** as a yellow solid (255.7 mg, 92% Yield, 2:1 rr). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 4.71 (s, 0.5H), 4.65 (s, 0.5H), 3.84 (m, 1H), 3.85 (t, *J* = 6.0 Hz, 4H), 2.43 (s, 1.5H), 2.41 (s, 3H), 2.36 (t, *J* = 5.4 Hz, 4H), 2.24 (m, 1H), 1.75 (m, 1H), 1.67 (s, 1.5H), 1.59 (s, 6H), 1.55 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 147.95, 143.33, 143.26, 132.83, 129.46, 129.44, 127.58, 127.56, 125.43, 124.13, 109.40, 47.24, 46.51, 42.41, 29.97, 28.74, 21.39, 20.56, 19.74. **HRMS** (APPI): Calculated for $[C_{15}H_{21}NO_2SNa]^+$ 302.1186, found 302.1185.



4.171a **4.171b**

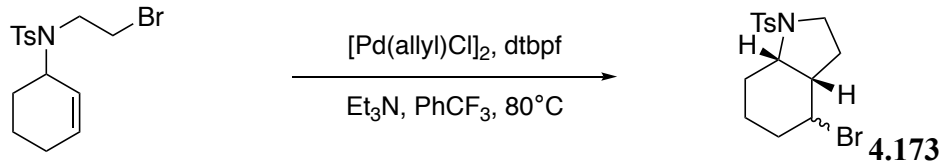
1-(Pent-3-enyl)oxy-2-bromo-1-(4-methoxyphenyl)ethane. Primary bromide **4.124** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure C. The crude product was purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide Heck products **4.171a** and **4.171b** as a yellow solid (90.3 mg, 41% Yield, 7:1 rr, 1:1 E:Z). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 6.93 (m, 2H), 5.53 (m, 0.15H), 5.38 (m, 1H), 4.53 (d, *J* = 7.8 Hz, 0.15H), 4.38 (s, 0.3H), 4.27 (m, 2H), 3.84 (s, 3.45H), 3.54 (m. 1H), 2.77 (d, J = 7.8 Hz, 0.5H), 2.56 (d, *J* = 7.8 Hz, 0.5H), 2.46 (m, 0.45H), 2.36 (m, 1H), 2.15 (m, 2H), 1.68 (m, 3H), 1.10 (t, *J* = 5.4 Hz, 0.45H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 158.90, 158.83, 134.80, 134.75, 134.71, 134.68, 127.15, 127.08, 127.02, 127.00, 117.98, 117.61, 117.55, 113.59, 113.55, 80.62, 79.70, 75.33, 69.28, 68.40, 66.45, 55.10, 55.08, 44.25, 36.49, 36.15, 36.04, 29.51, 28.58, 12.53, 12.40, 11.63. **HRMS** (APPI): Calculated for $[C_{14}H_{18}O_2H]^+$ 219.1380, found 219.1379.



4.172

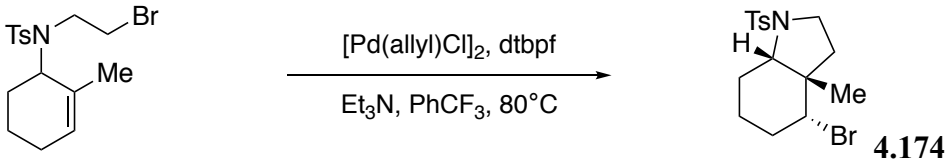
(E)-*N*-(2-Bromoethyl)-4-methyl-*N*-(2-methylbut-2-en-1-yl)benzene sulfonamide. Primary bromide **4.136** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure D. The crude product was purified by flash chromatography using hexanes/ethyl acetate (10:1) to provide ATRC product **4.172** as a yellow solid (19.6 mg, 45% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 4.01 (q, *J* = 6.6 Hz, 1H), 3.47 (m, 1H), 3.37 (m, 1H), 3.21 (d, *J* = 10.2 Hz, 1H), 3.12 (d, *J* = 10.2 Hz, 1H), 2.46 (s, 3H), 1.70 (m, 2H), 1.67 (d, *J* = 6.6 Hz, 3H), 0.99 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.56,

133.53, 129.72, 127.53, 60.36, 57.99, 47.59, 47.56, 36.01, 21.92, 21.60, 18.78. **HRMS** (ESI): Calculated for $[C_{14}H_{20}BrNO_2SH]^+$ 346.0477, found 346.0468.



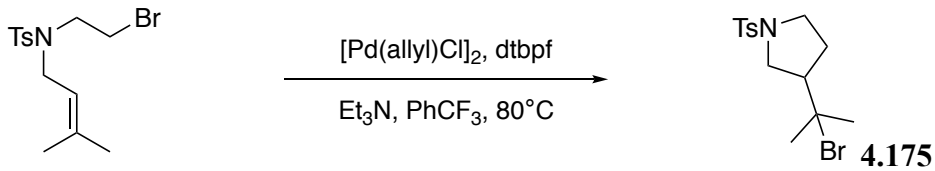
4.173

***N*-(2-Bromoethyl)-*N*-(cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide.** Primary bromide **4.143** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure D. The crude product was purified by flash chromatography using hexanes/ethyl acetate (10:1) to provide ATRC product **4.173** as a yellow solid (26.7 mg, 60% Yield, 1:1 dr). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 4.22 (m, 1H), 4.20 (m, 1H), 3.74 (m, 1H), 3.69 (m, 1H), 3.60 (m, 1H), 3.57 (m, 1H), 3.29 (m, 1H), 3.16 (m, 1H), 2.46 (s, 3H), 2.45 (s, 3H), 2.22 (m, 1H), 2.16 (m, 1H), 2.07 (m, 2H), 2.06 (m, 4H), 1.93 (m, 1H), 1.85 (m, 2H), 1.77 (m, 2H), 1.74 (m, 1H), 1.46 (m, 2H), 1.39 (m, 1H), 1.26 (m, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.55, 143.46, 135.18, 134.06, 129.83, 129.77, 127.47, 127.20, 59.79, 59.01, 52.92, 50.09, 48.06, 47.19, 46.04, 45.35, 33.15, 31.85, 29.06, 28.58, 27.73, 27.01, 25.78, 24.23, 21.58, 20.32. **HRMS** (ESI): Calculated for $[C_{15}H_{20}BrNO_2SH]^+$ 358.0477, found 358.0472.



4.174

***N*-(2-Bromoethyl)-*N*-(2-methylcyclohex-2-en-1-yl)-4-methylbenzenesulfonamide.** Primary bromide **4.148** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling Procedure D. The yield of the crude product was determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (84% Yield, 1.5:1 dr). The crude product was then purified by flash chromatography using hexanes/ethyl acetate (20:1) to provide bromide **4.174** as a white solid. The major diastereomer was determined by 2D NMR analysis. **Major Diastereomer:** ^{1}**H-NMR** (600 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 3.97 (dd, *J* = 12.6, 4.8 Hz, 1H), 3.53 (m, 1H), 3.42 (m, 1H), 3.21 (m, 1H), 2.45 (s, 3H), 2.17 (m, 3H), 1.87 (m, 1H), 1.69 (m, 2H), 1.40 (m, 1H), 1.25 (m, 1H), 0.72 (s, 3H). ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 143.28, 135.82, 129.64, 127.12, 65.38, 60.02, 47.02, 43.99, 33.75, 31.69, 31.14, 25.46, 24.16, 21.58. **HRMS** (ESI): Calculated for $[C_{16}H_{22}BrNO_2SH]^+$ 372.0633, found 372.0629. **Minor Diastereomer:** ^{1}**H-NMR** (600 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 4.30 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.57 (m, 1H), 3.39 (m, 1H), 3.01 (m, 1H), 2.47 (s, 3H), 2.17 (m, 1H), 2.07 (m, 1H), 1.95 (m, 1H), 1.79 (m, 1H), 1.64 (m, 2H), 1.12 (m, 1H), 1.09 (s, 3H). ^{13}**C-NMR** (100 MHz, $CDCl_3$): δ 143.62, 133.27, 129.75, 127.60, 66.27, 58.55, 46.81, 46.66, 34.95, 33.30, 24.85, 21.81, 21.61, 20.13. **HRMS** (ESI): Calculated for $[C_{16}H_{22}BrNO_2SH]^+$ 372.0633, found 372.0629.

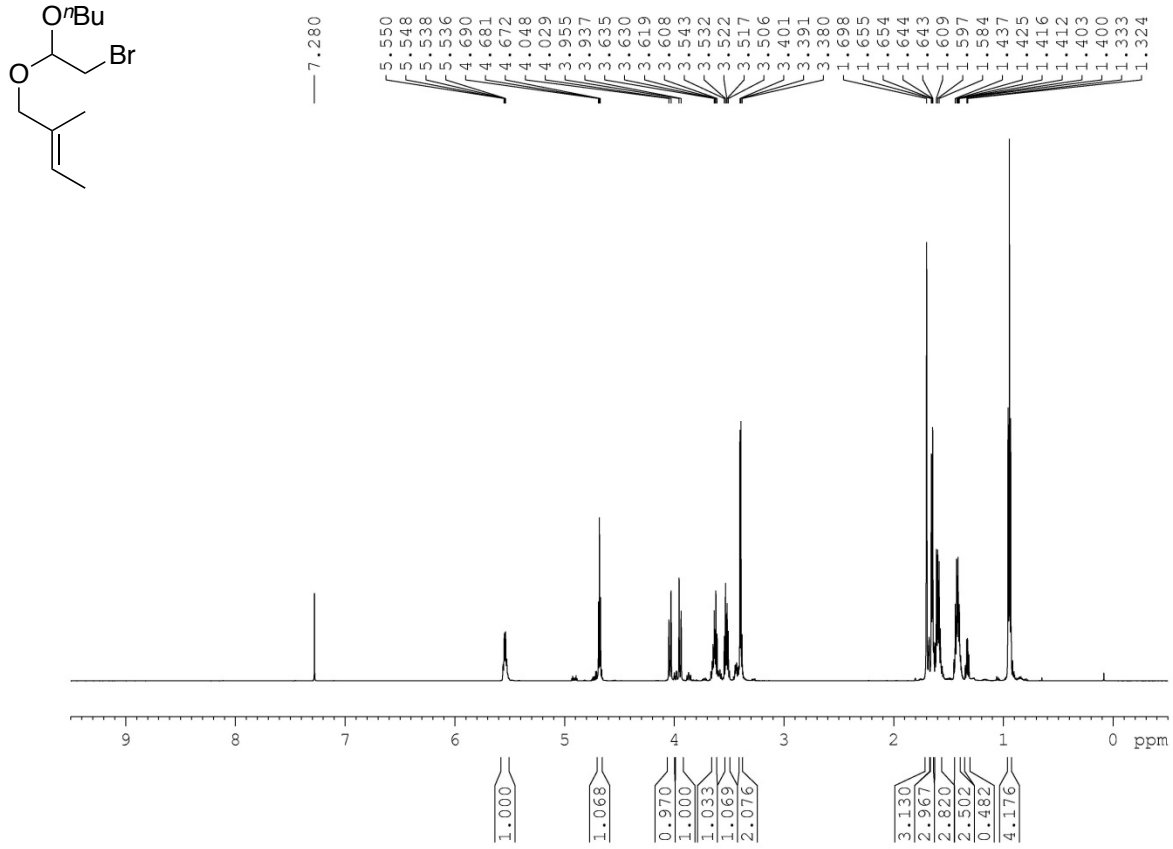


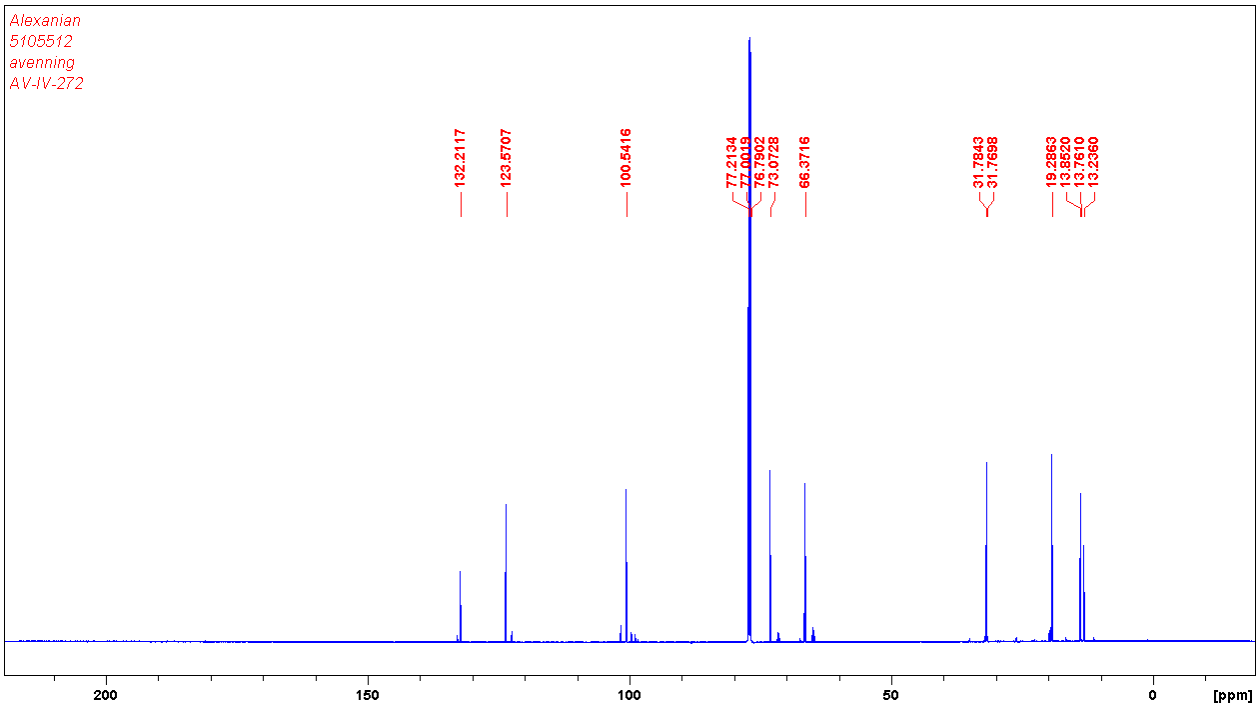
4.175

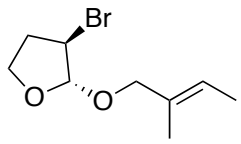
***N*-(2-Bromoethyl)-4-methyl-*N*-(3-methylbut-2-en-1-yl)benzenesulfonamide.** Primary bromide **4.137** was made to react with $[Pd(allyl)Cl]_2$ and dtbpf following Cross-Coupling

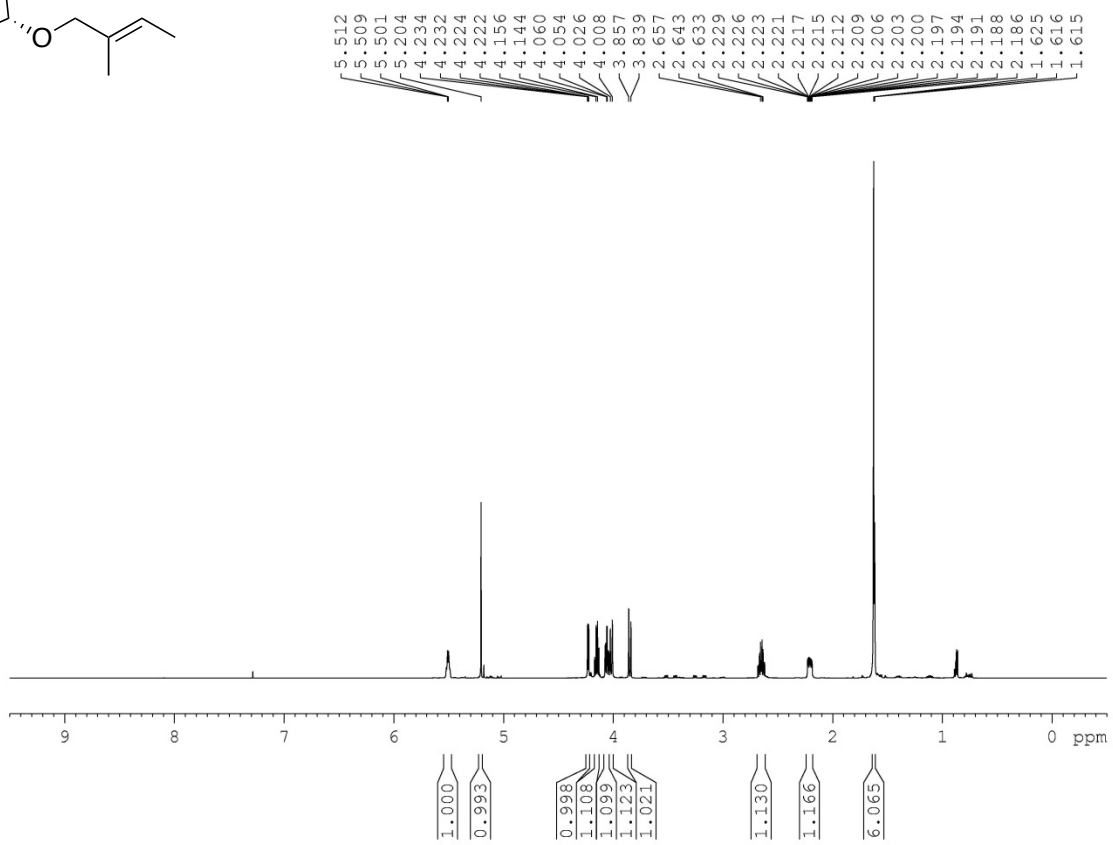
Procedure D. The crude product was purified by flash chromatography using hexanes/ethyl acetate (10:1) to provide ATRC product **4.175** as a yellow solid (11.3 mg, 26% Yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 3.49 (m, 1H), 3.41 (m, 1H), 3.24 (m, 1H), 3.16 (m, 1H), 2.46 (s, 3H), 2.34 (m, 0.5H), 2.17 (m, 0.5H), 1.97 (m, 1H), 1.79 (m, 1H), 1.75 (s, 3H), 1.52 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 143.59, 143.57, 133.31, 133.28, 129.73, 129.72, 127.70, 127.67, 70.56, 67.82, 51.81, 50.84, 50.60, 49.44, 47.96, 47.94, 33.20, 32.66, 31.54, 31.04, 29.73, 28.50, 27.29, 21.60. **HRMS** (ESI): Calculated for $[C_{14}H_{20}BrNO_2SH]^+$ 346.0477, found 346.0470.

4.3.3 NMR Spectra






Br
O
O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4.232
4.224
4.222
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4.054
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4.008
3.857
3.839
2.657
2.643
2.633
2.229
2.226
2.223
2.221
2.217
2.215
2.212
2.209
2.206
2.203
2.200
2.197
2.194
2.191
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1.615
9
8
7
6
5
4
3
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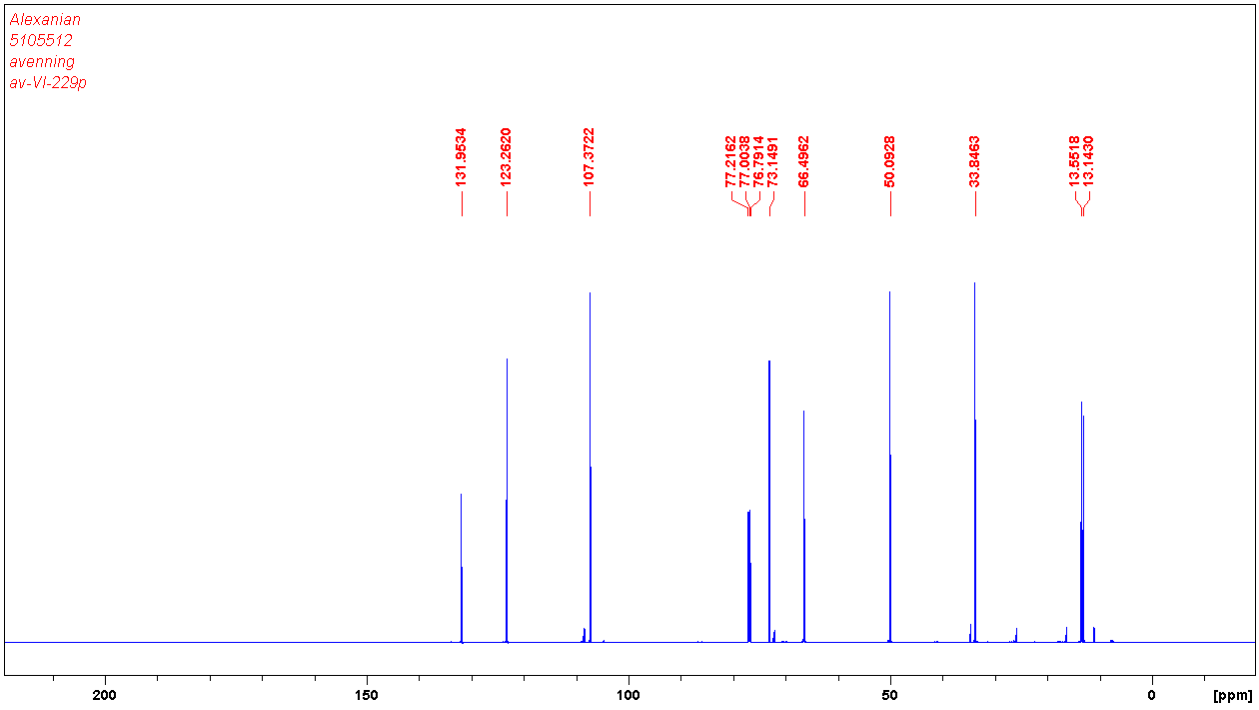
6.065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avenning
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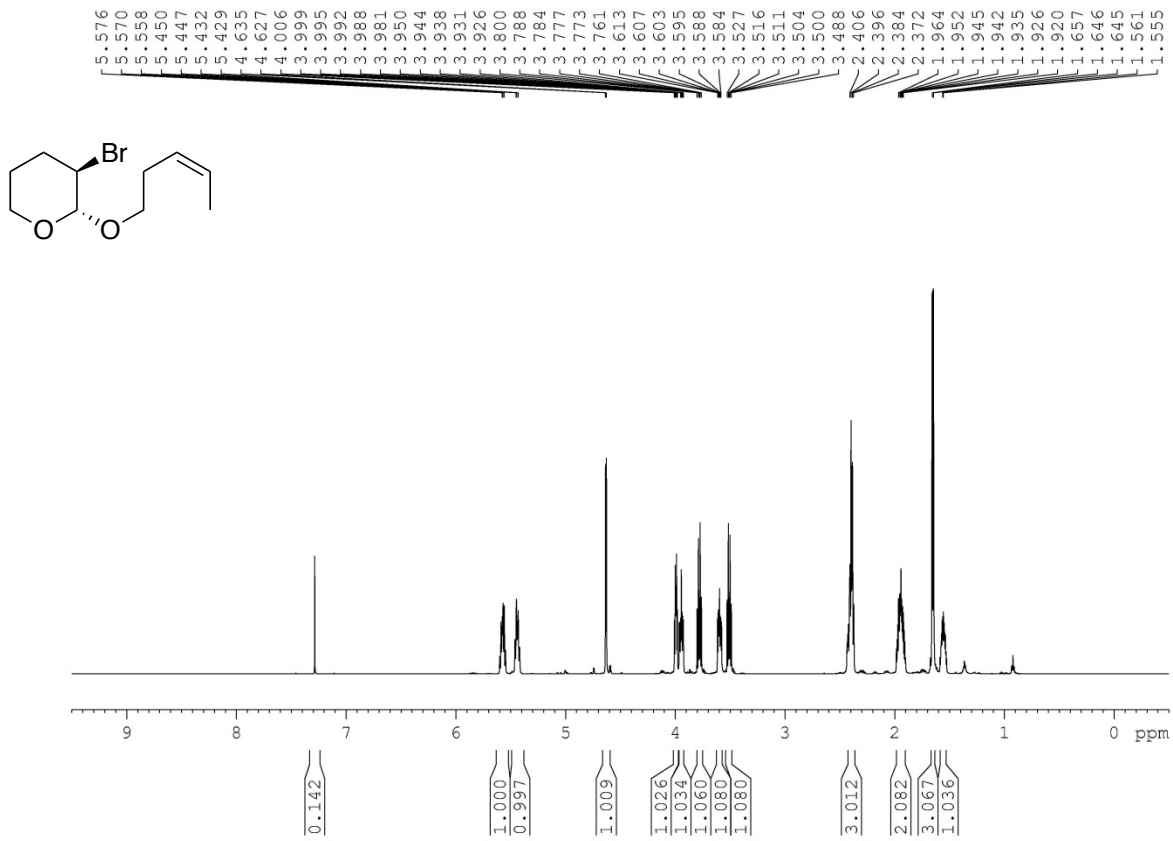
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3.992
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3.981
3.950
3.944
3.938
3.931
3.926
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3.788
3.784
3.777
3.773
3.761
3.613
3.607
3.603
3.595
3.588
3.584
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3.516
3.511
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3.500
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1.657
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1.555
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O
O
9
8
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6
5
4
3
2
1
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ppm
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1.080
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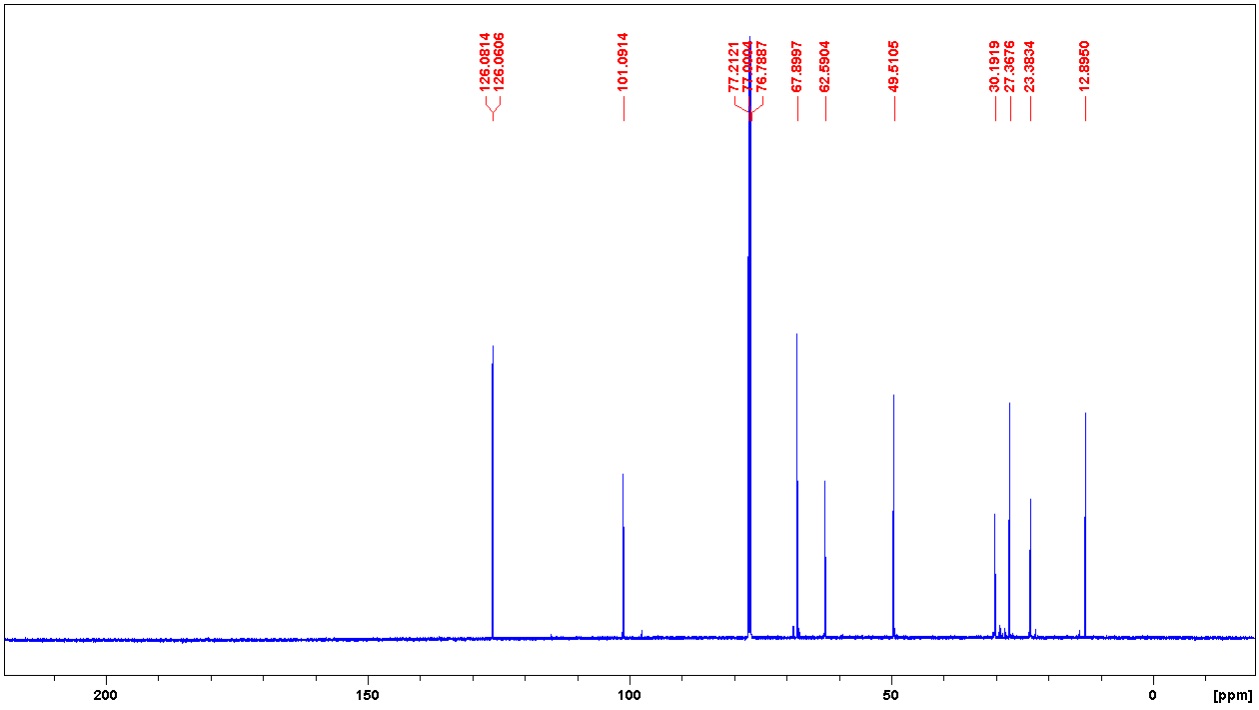
1.036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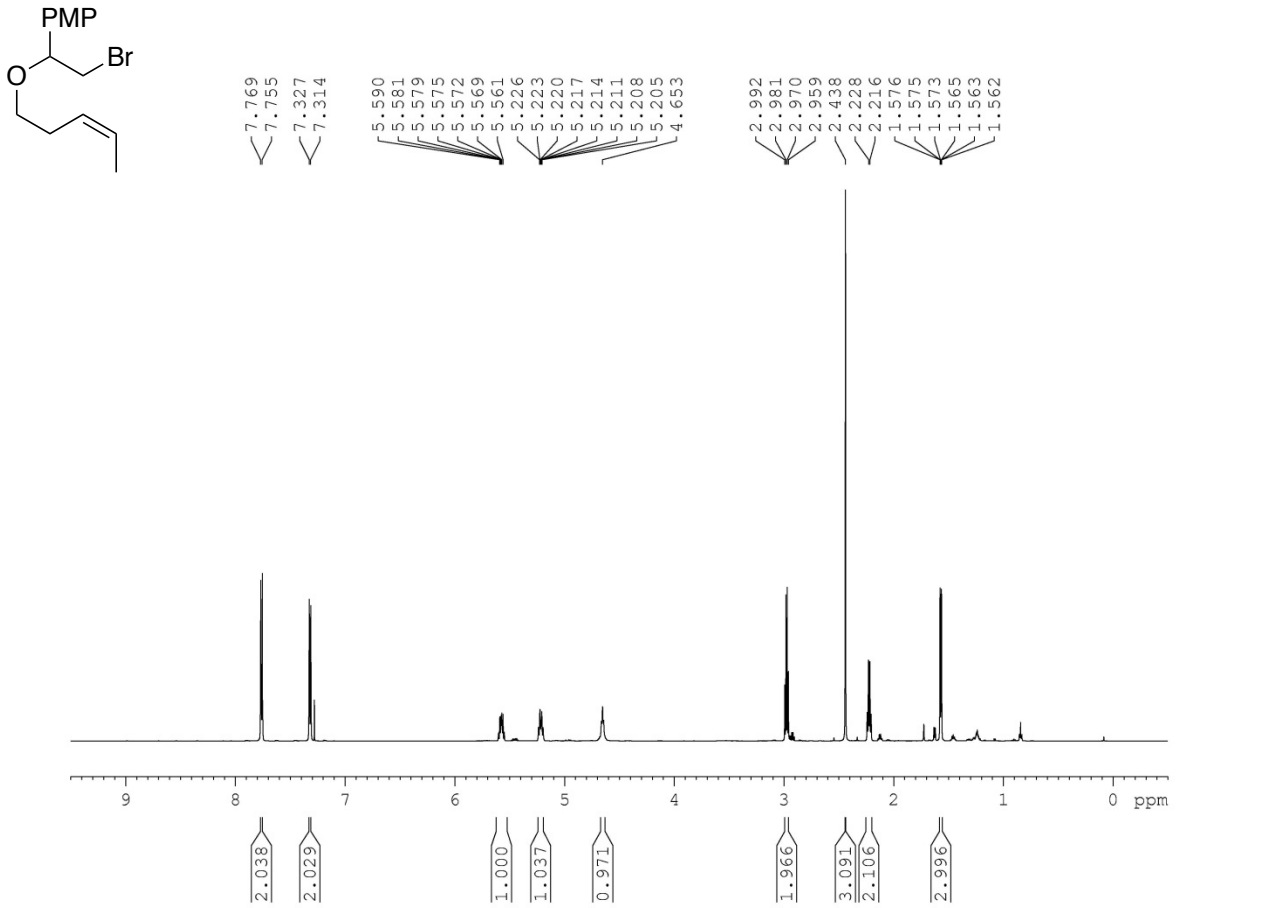
[ppm]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5.569
5.561
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5.223
5.220
5.217
5.214
5.211
5.208
5.205
4.653
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2.981
2.970
2.959
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2.228
2.216
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1.575
1.573
1.565
1.563
1.562
9
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7
6
5
4
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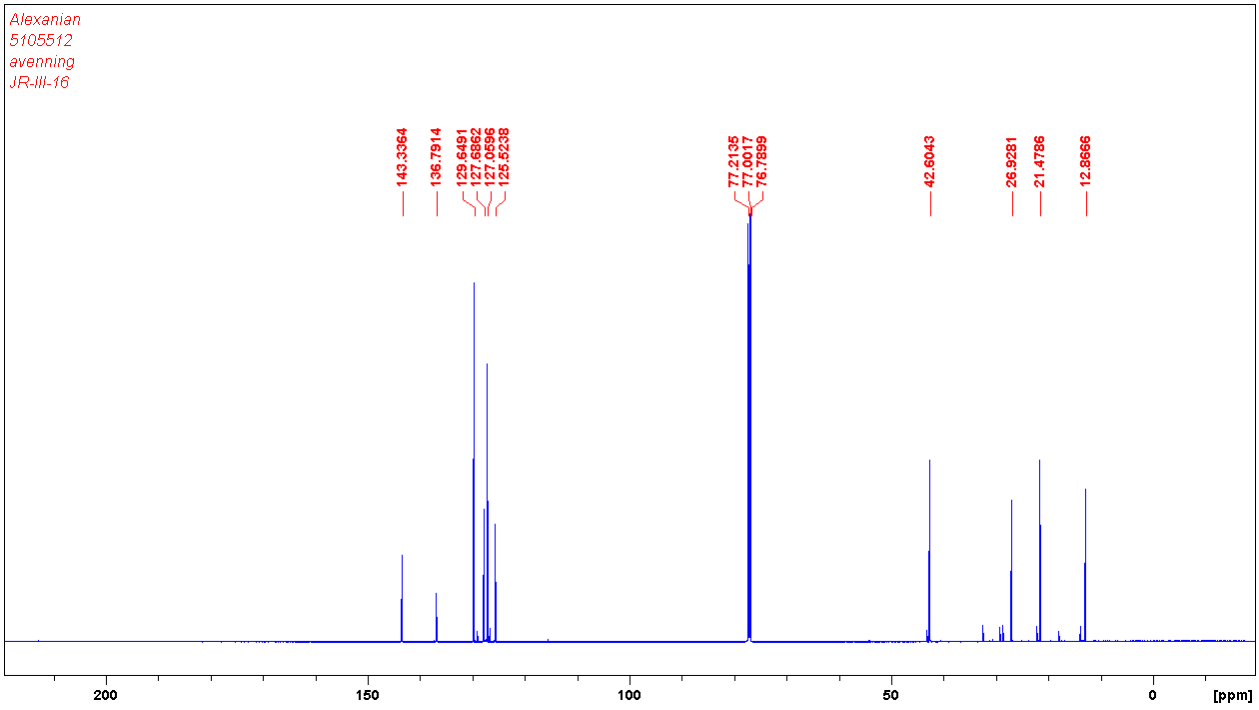
2.996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5105512
avenning
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127.0596
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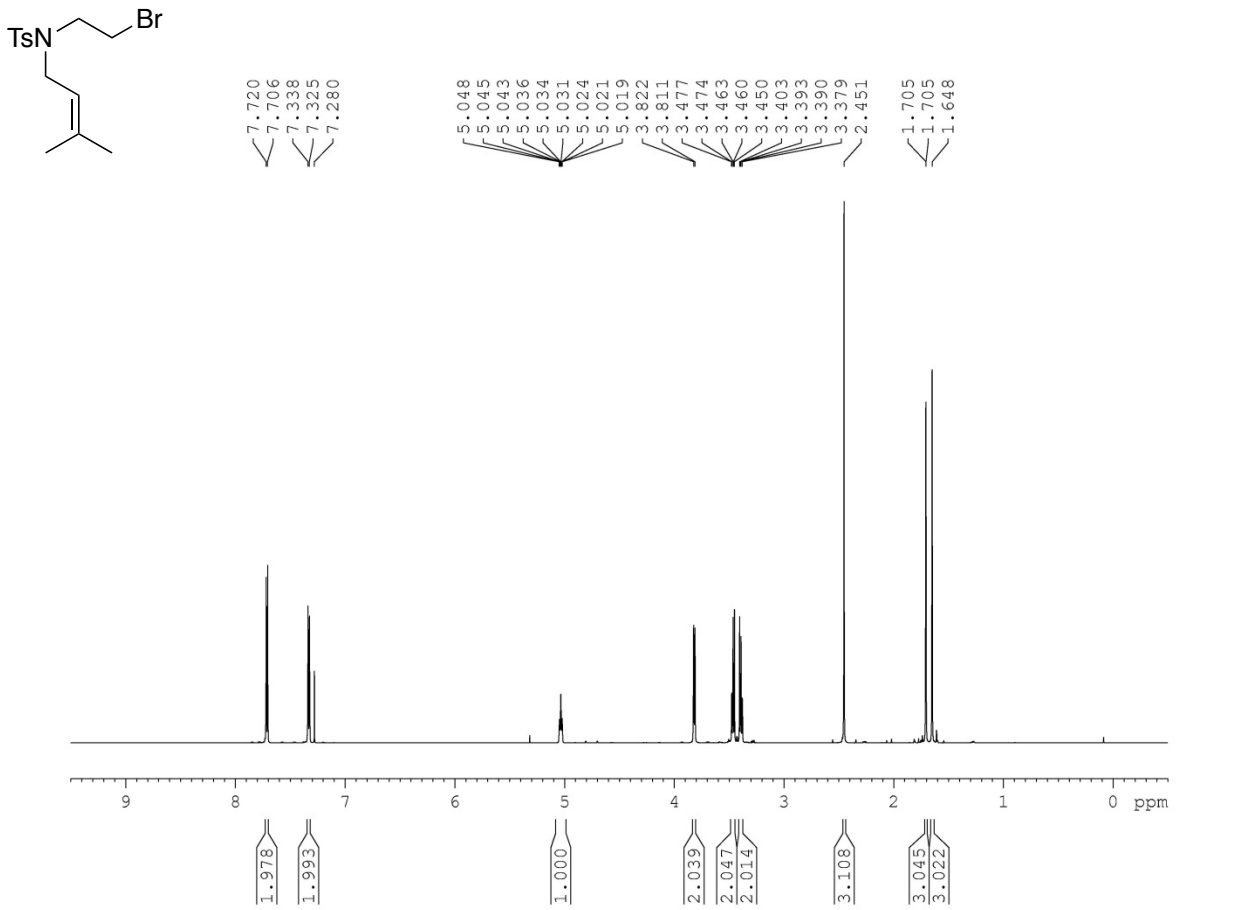
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5.045
5.043
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5.024
5.021
5.019
3.822
3.811
3.477
3.474
3.463
3.460
3.450
3.403
3.393
3.390
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1.705
1.648
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8
7
6
5
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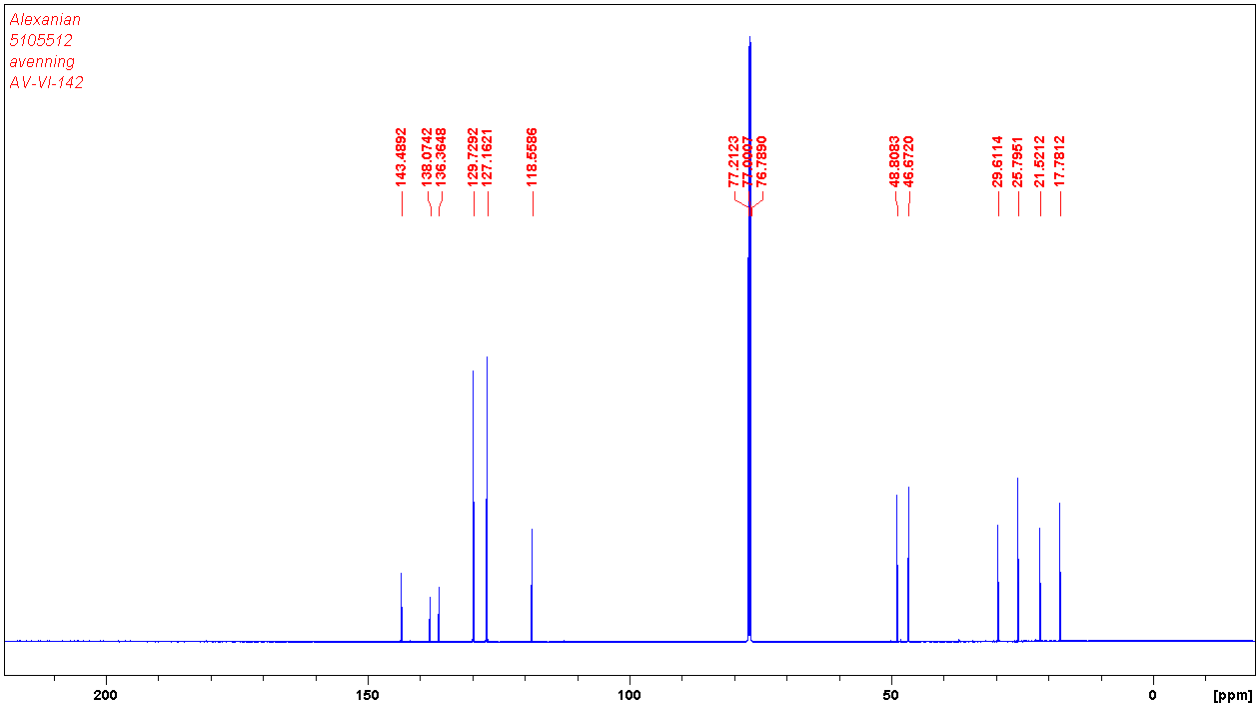
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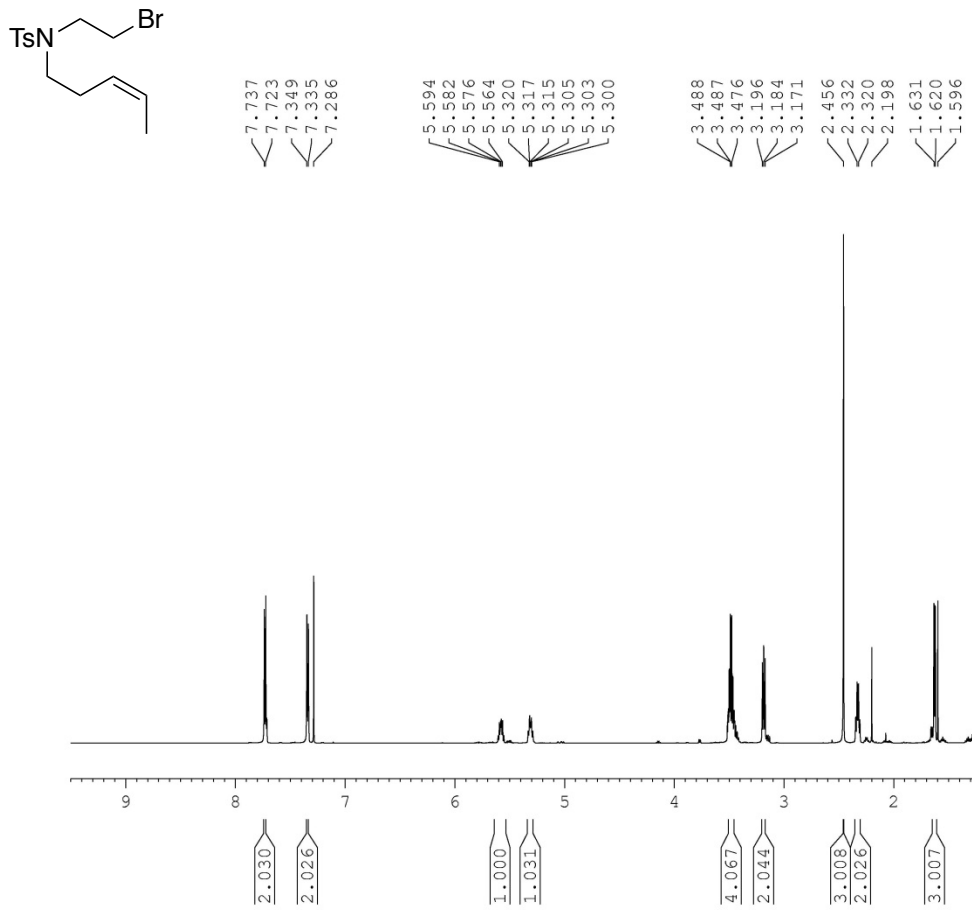
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5.315
5.305
5.303
5.300
3.488
3.487
3.476
3.196
3.184
3.171
2.456
2.332
2.320
2.198
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1.620
1.596
9
8
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6
5
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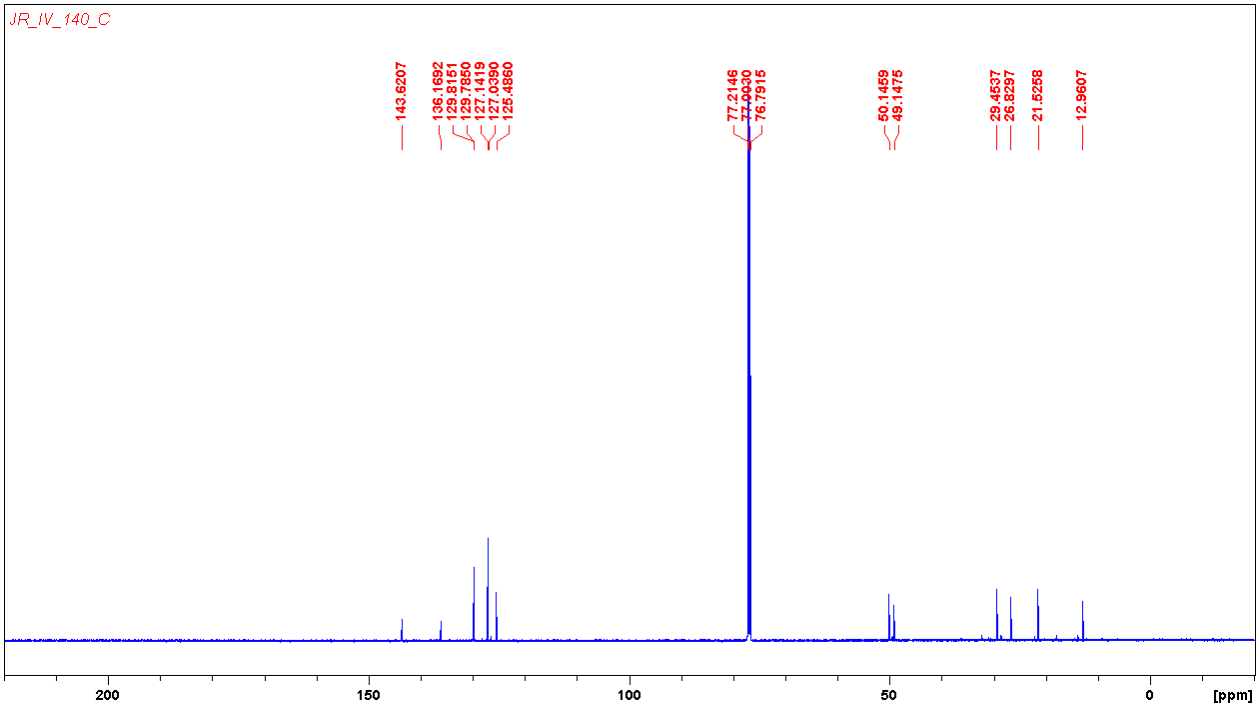
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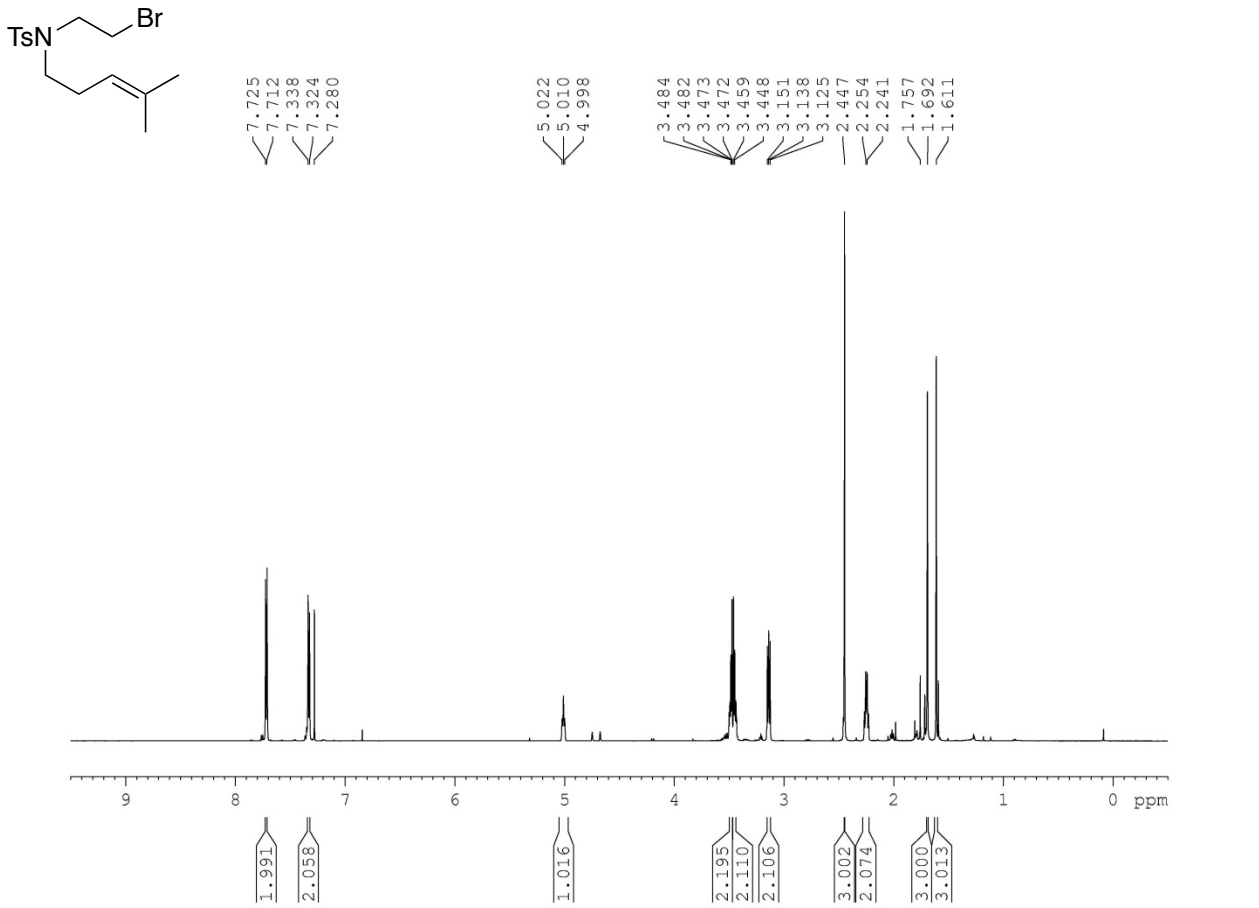
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3.472
3.459
3.448
3.151
3.138
3.125
2.447
2.254
2.241
1.757
1.692
1.611
9
8
7
6
5
4
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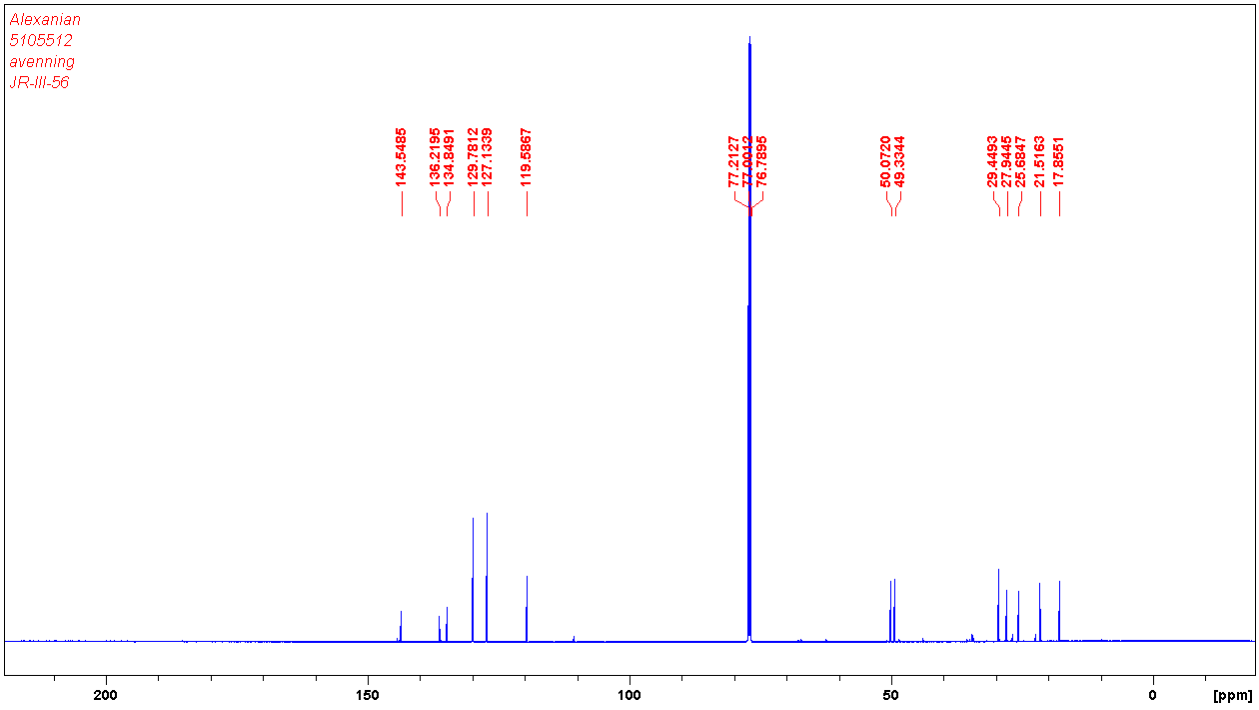
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5105512
avenning
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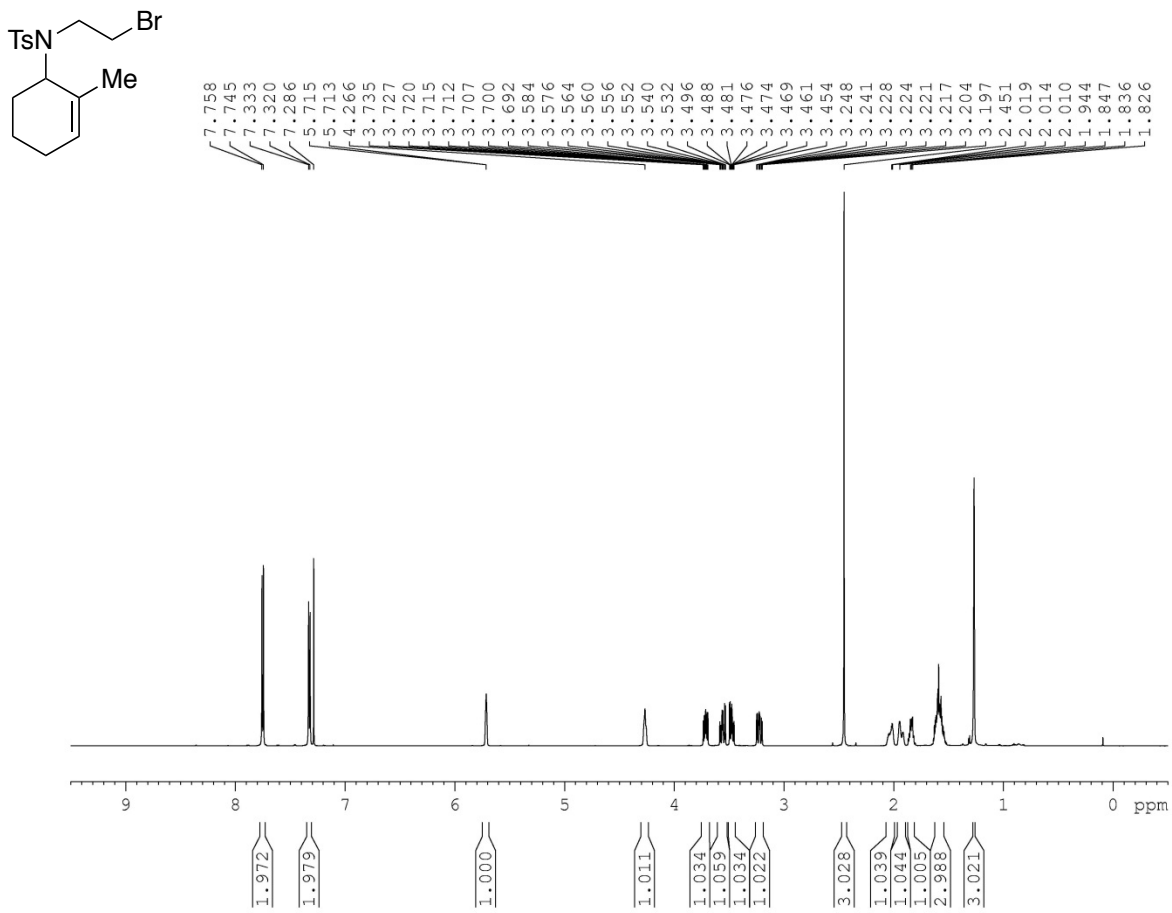
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3.715
3.712
3.707
3.700
3.692
3.584
3.576
3.564
3.560
3.556
3.552
3.540
3.532
3.496
3.488
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3.474
3.469
3.461
3.454
3.248
3.241
3.228
3.224
3.221
3.217
3.204
3.197
2.451
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1.826
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8
7
6
5
4
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0 ppm
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1.022
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1.039
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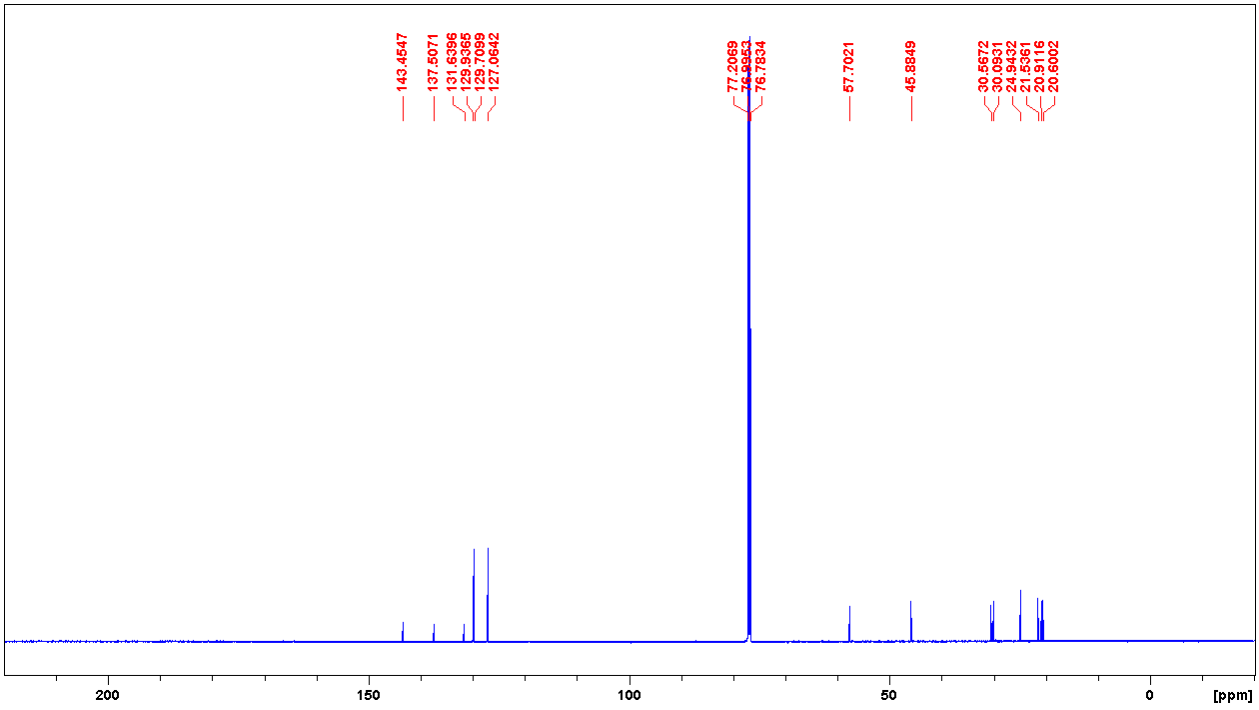
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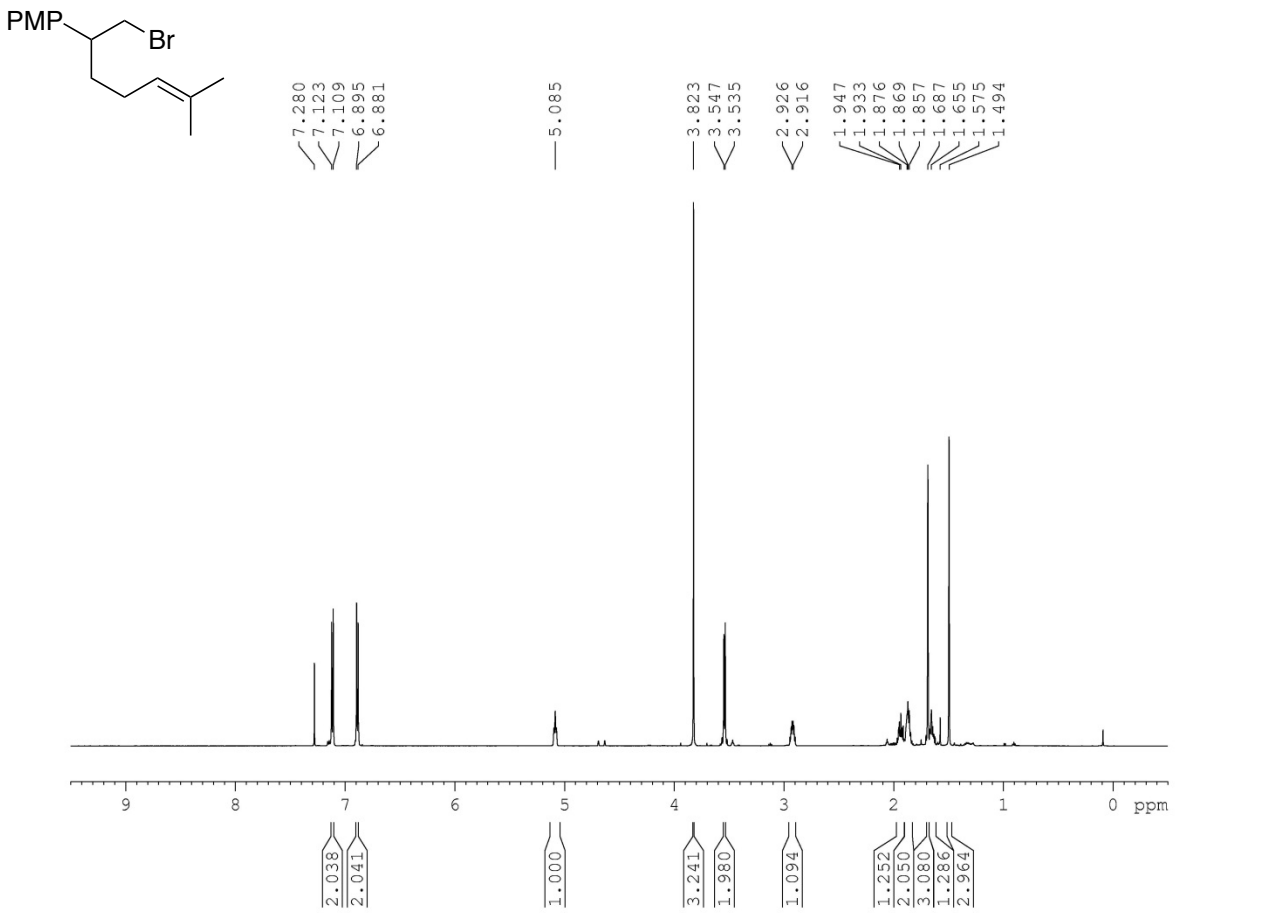
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2.916
1.947
1.933
1.876
1.869
1.857
1.687
1.655
1.575
1.494
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8
7
6
5
4
3
2
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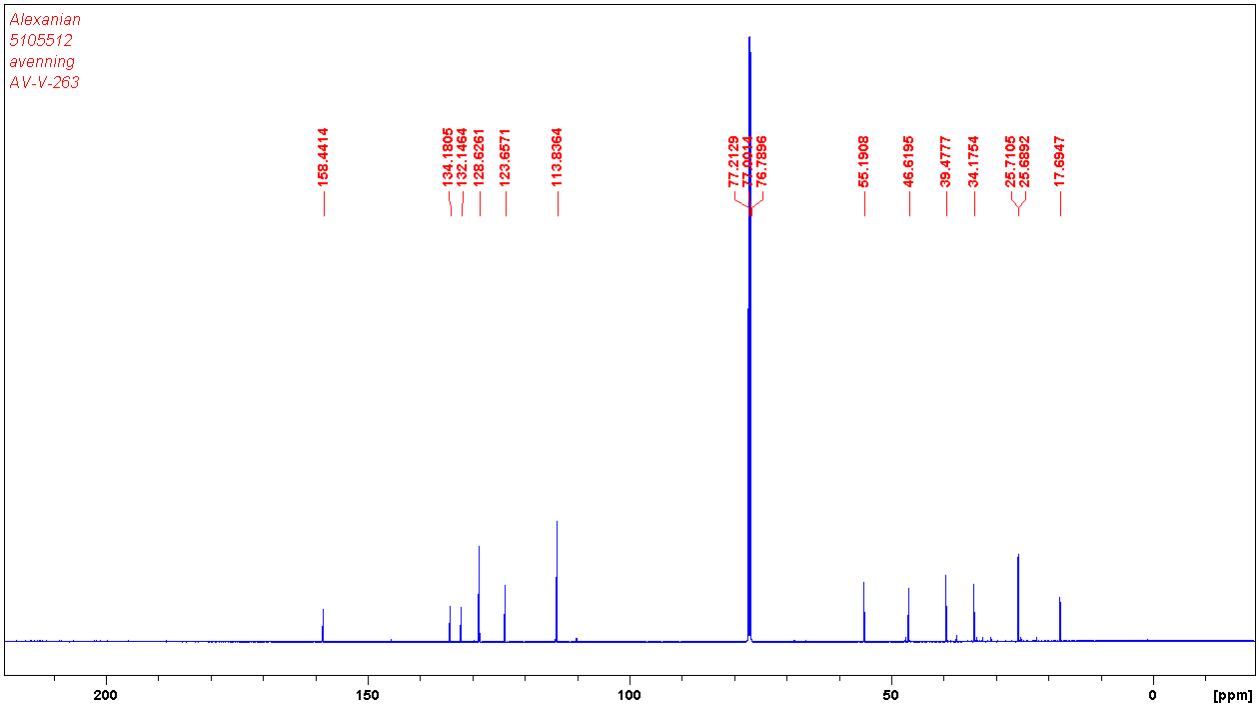
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5105512
avenning
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123.6571
113.8364
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50
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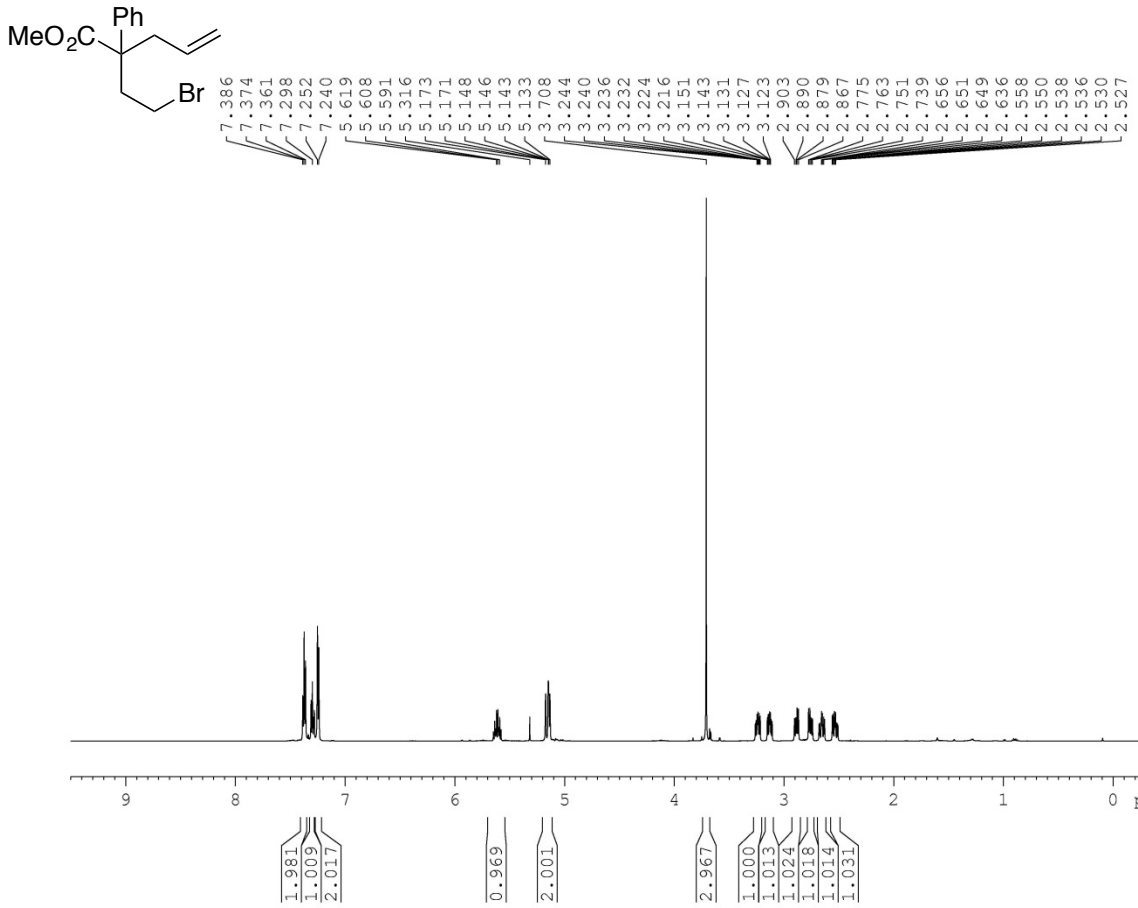
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5.143
5.133
3.708
3.244
3.240
3.236
3.232
3.224
3.216
3.151
3.143
3.131
3.127
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2.890
2.879
2.867
2.775
2.763
2.751
2.739
2.656
2.651
2.649
2.636
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2.538
2.536
2.530
2.527
9
8
7
6
5
4
3
2
1
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2.017
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2.967
1.000
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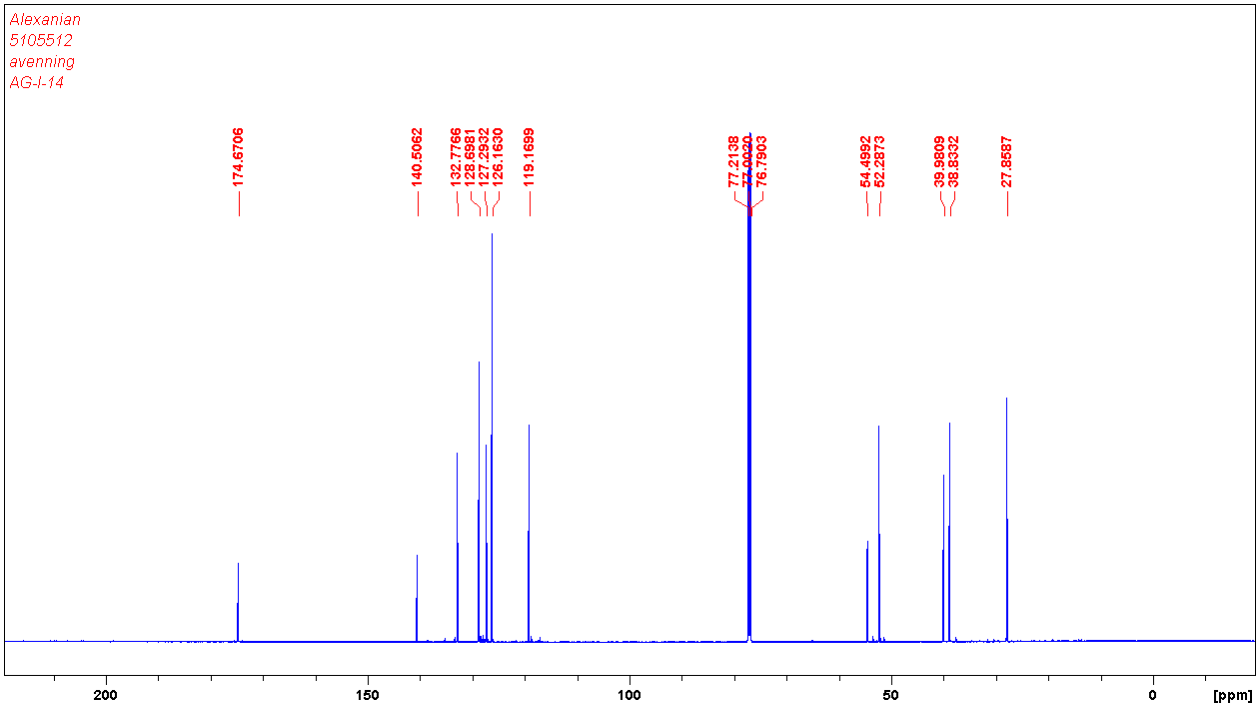
1.014
1.031


Alexanian
5105512
avenning
AG-I-14
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132.7766
128.6981
127.2932
126.1630
119.1699
77.2138
77.0020
76.7903
54.4992
52.2873
39.9809
38.8332
27.8587
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150
100
50
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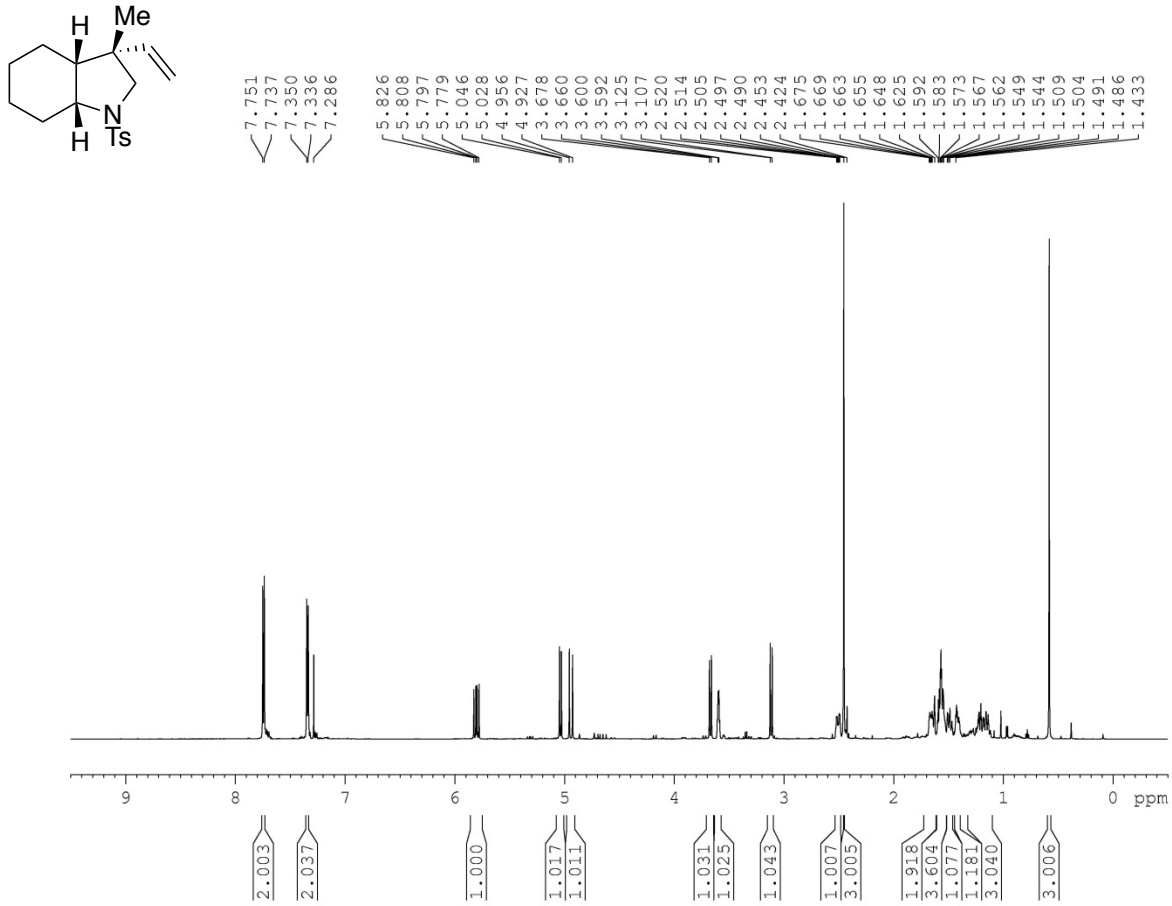
H
Me
N
Ts
H
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7.350
7.336
7.286
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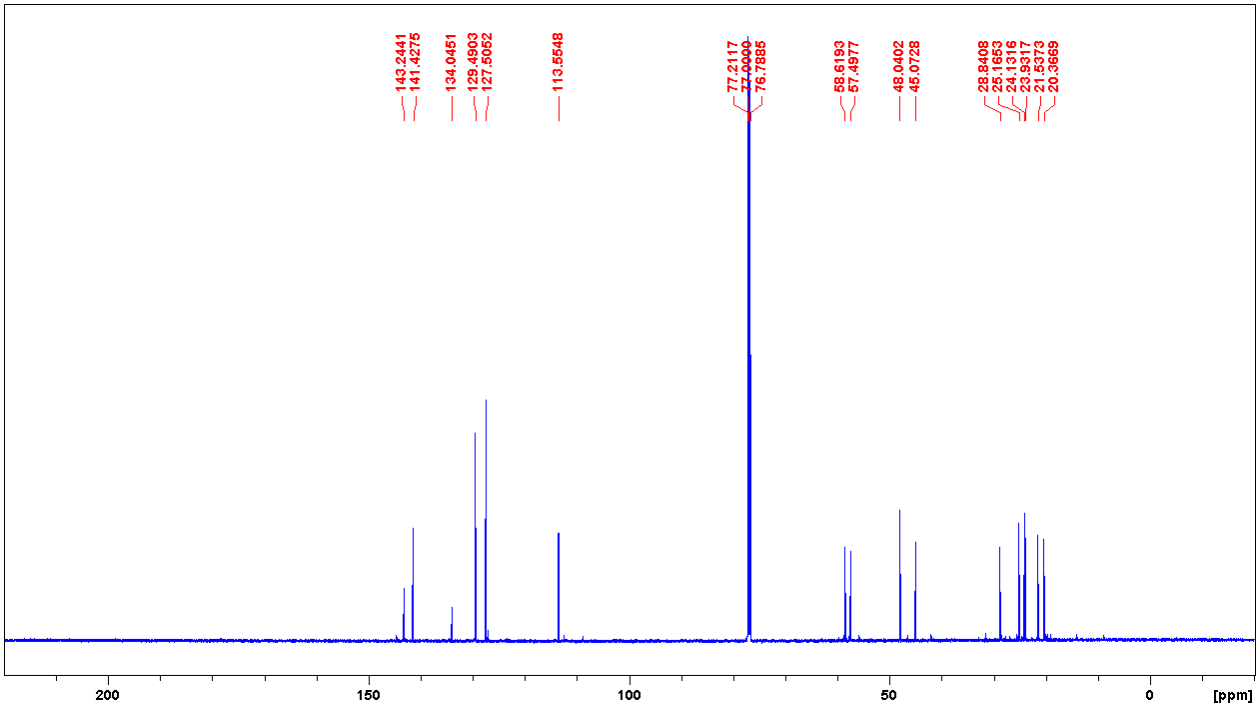
5.797
5.779
5.046
5.028
4.956
4.927
3.678
3.660
3.600
3.592
3.125
3.107
2.520
2.514
2.505
2.497
2.490
2.453
2.424
1.675
1.669
1.663
1.655
1.648
1.625
1.592
1.583
1.573
1.567
1.562
1.549
1.544
1.509
1.504
1.491
1.486
1.433
9
8
7
6
5
4
3
2
1
0 ppm
2.003
2.037
1.000
1.017
1.011
1.031
1.025
1.043
1.007
3.005
1.918
3.604
1.077
1.181
3.040
3.006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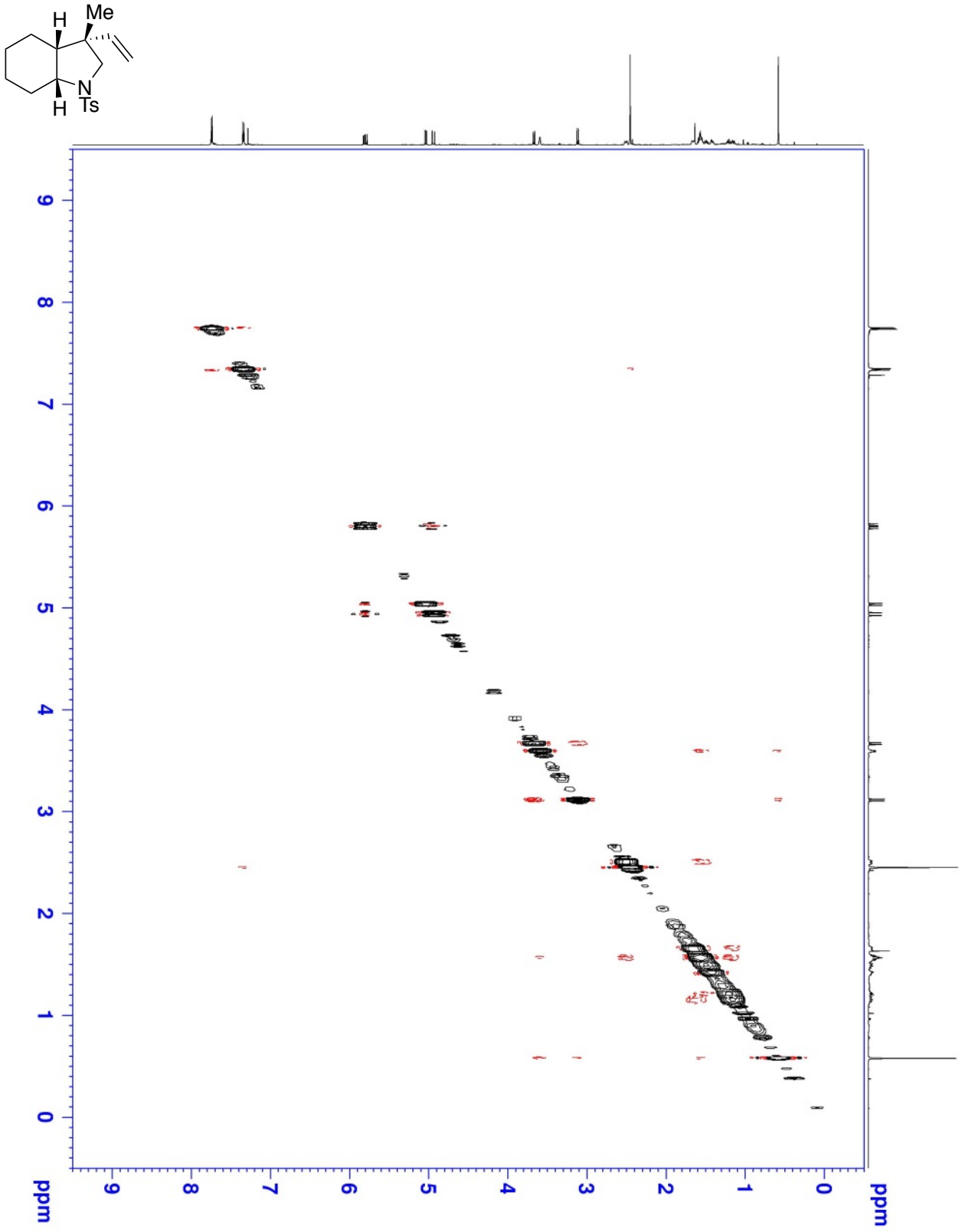
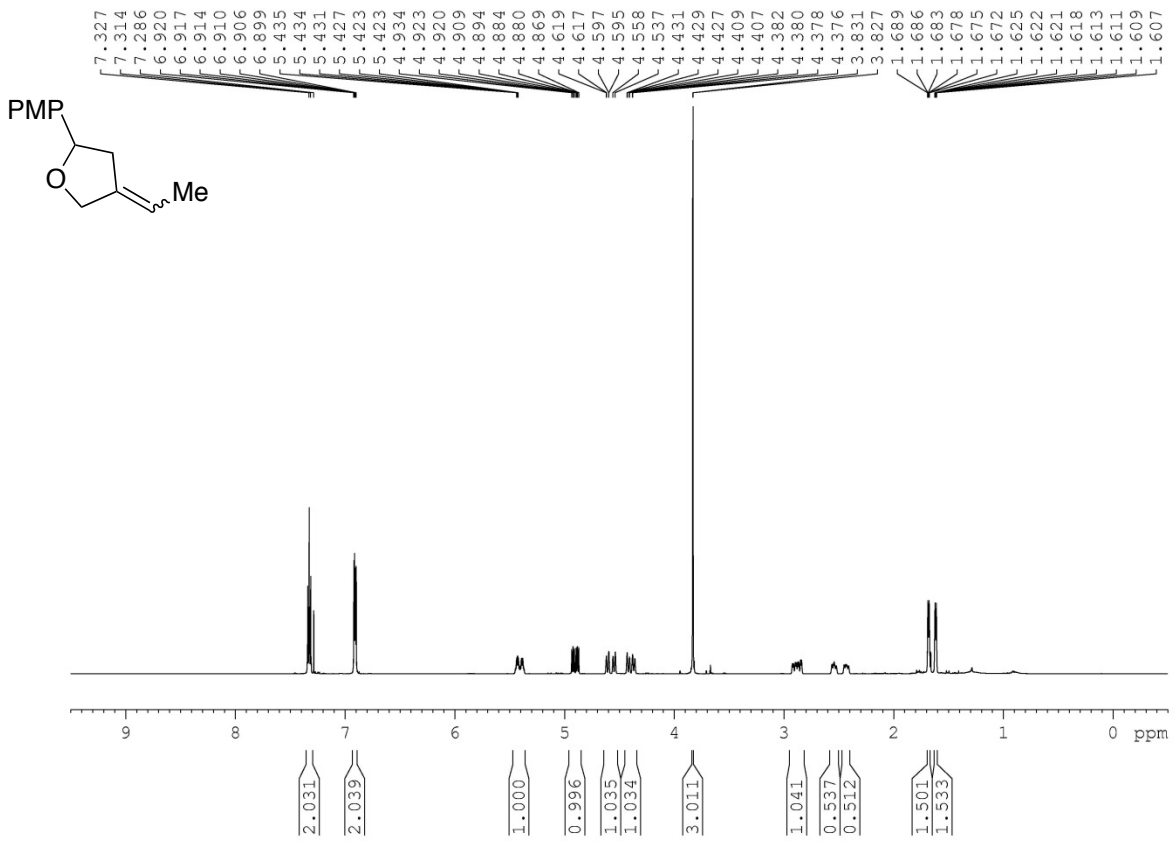
141.4275
134.0451
129.4903
127.5052
113.5548
77.2117
77.0000
76.7885
58.6193
57.4977
48.0402
45.0728
28.8408
25.1653
24.1316
23.9317
21.5373
20.3669
200
150
100
50
0
[ppm]


H
Me
N
Ts
H
ppm
ppm


7.327
7.314
7.286
6.920
6.917
6.914
6.910
6.906
6.899
5.435
5.434
5.431
5.427
5.423
5.423
4.934
4.923
4.920
4.909
4.894
4.884
4.880
4.869
4.619
4.617
4.597
4.595
4.558
4.537
4.431
4.429
4.427
4.409
4.407
4.382
4.380
4.378
4.376
3.831
3.827
1.689
1.686
1.683
1.678
1.675
1.672
1.625
1.622
1.621
1.618
1.613
1.611
1.609
1.607
PMP
O
Me
9
8
7
6
5
4
3
2
1
0
ppm
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2.039
1.000
0.996
1.035
1.034
3.011
1.041
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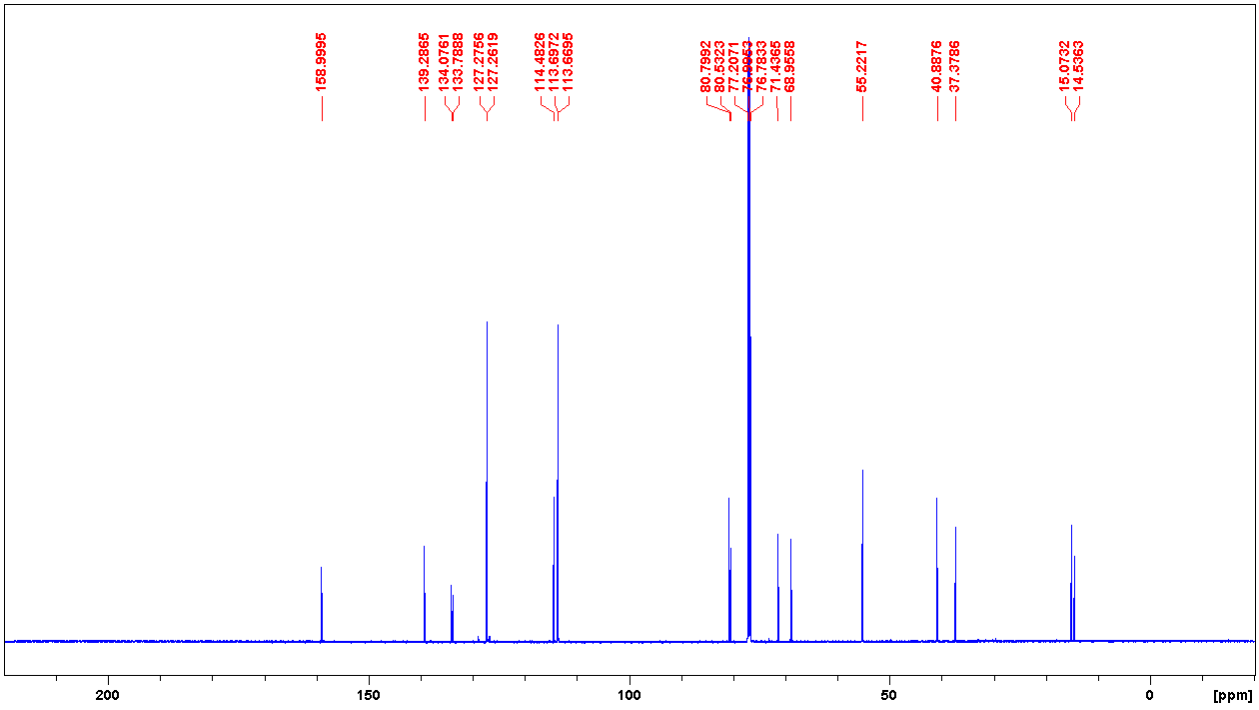
1.533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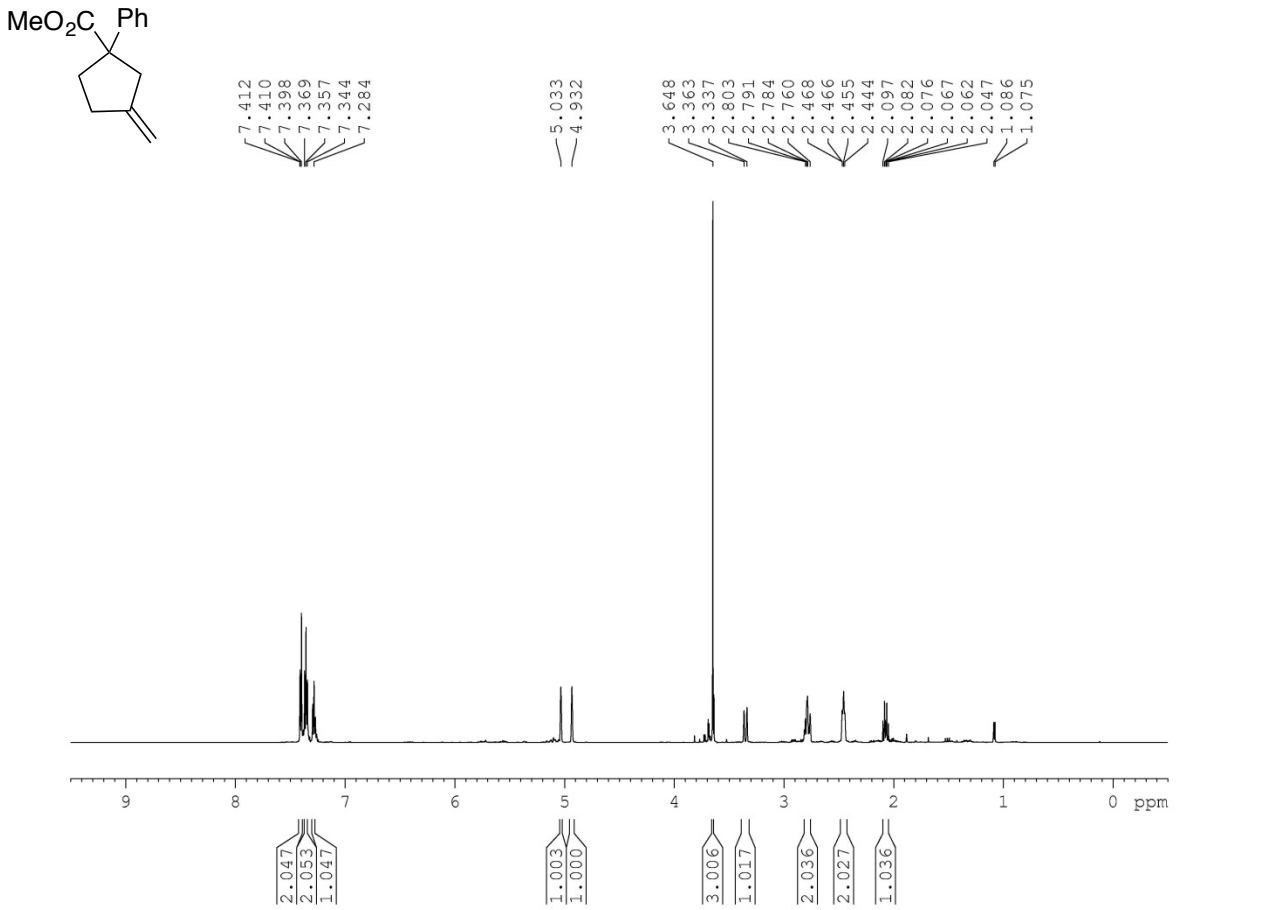
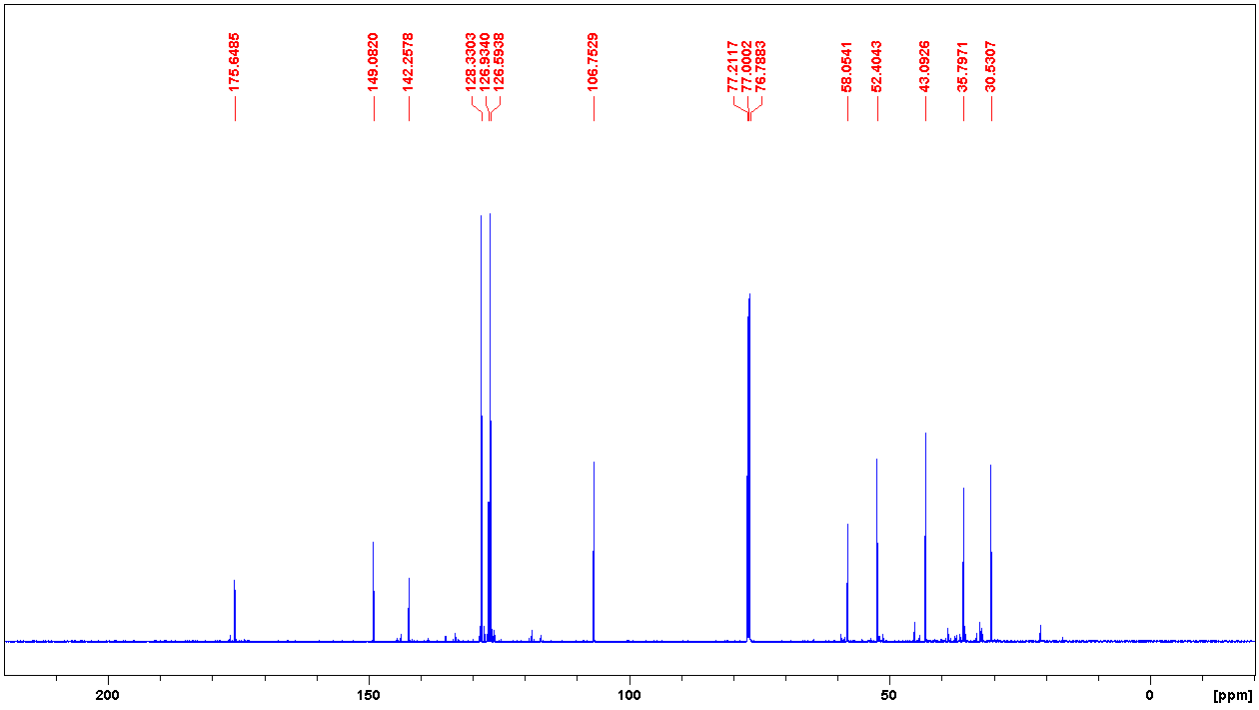
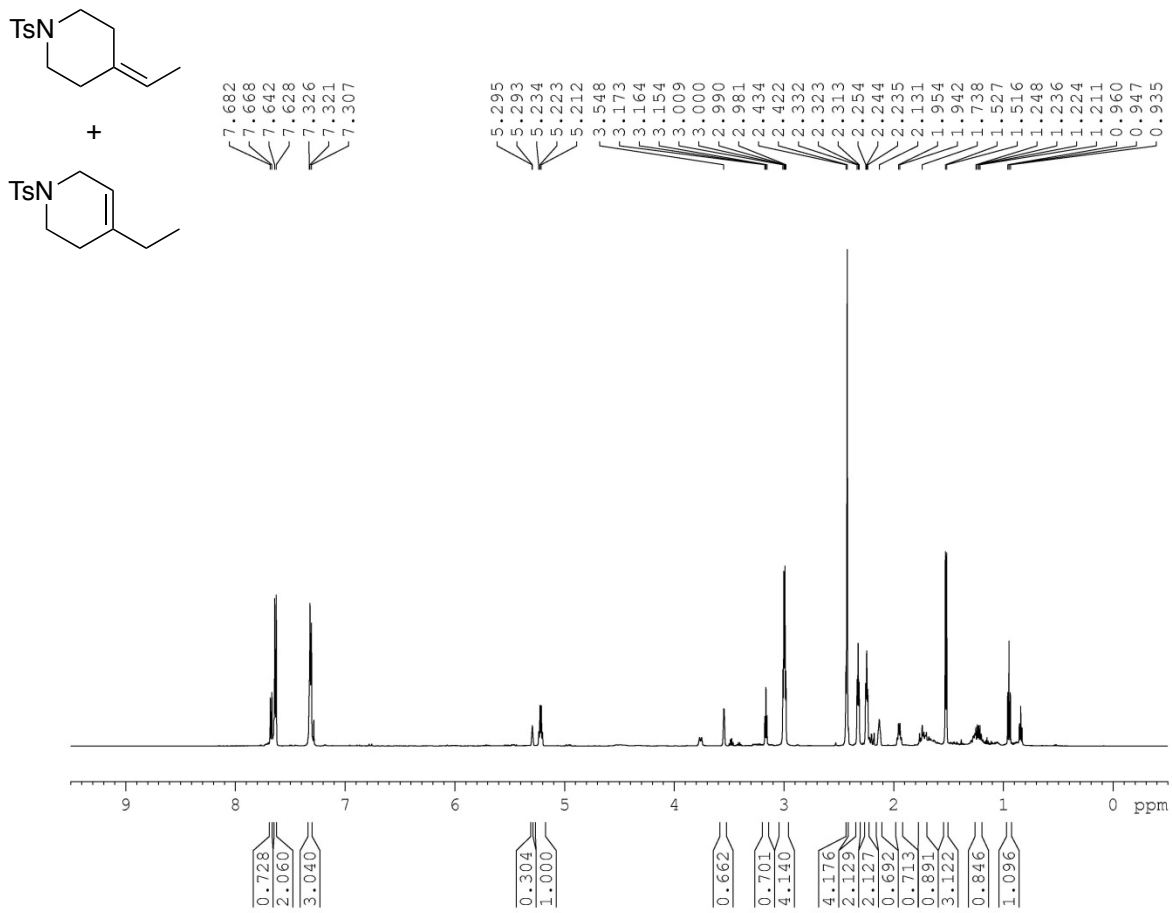
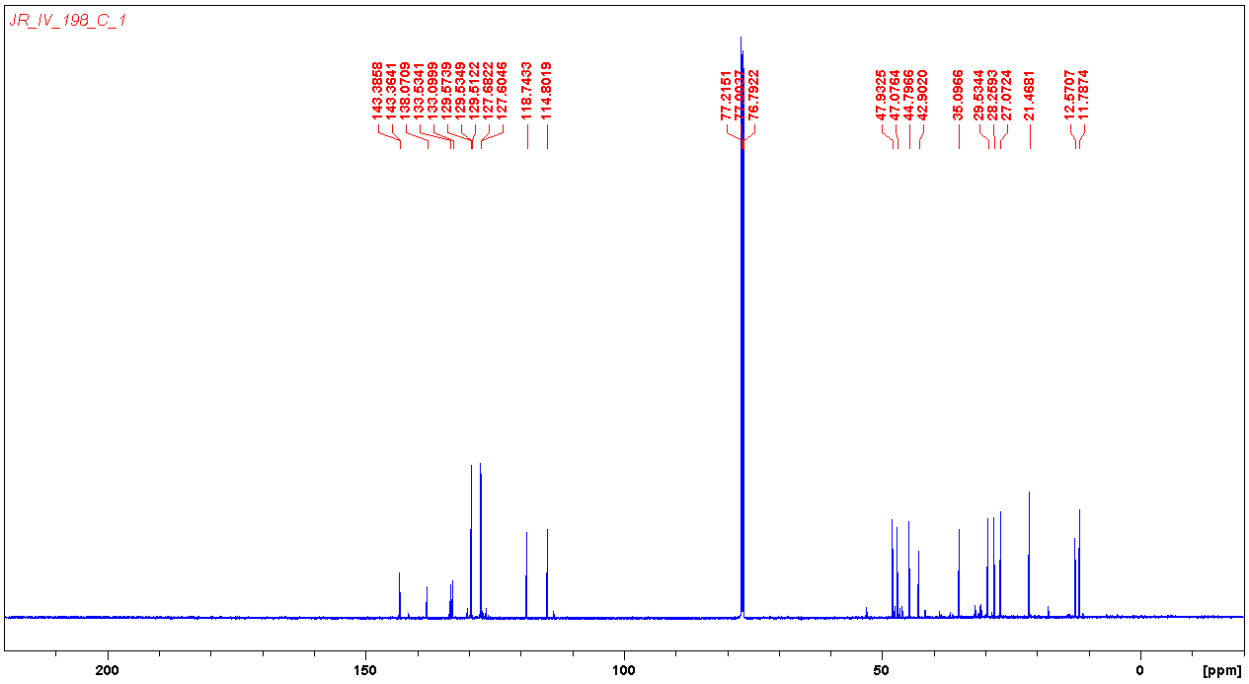
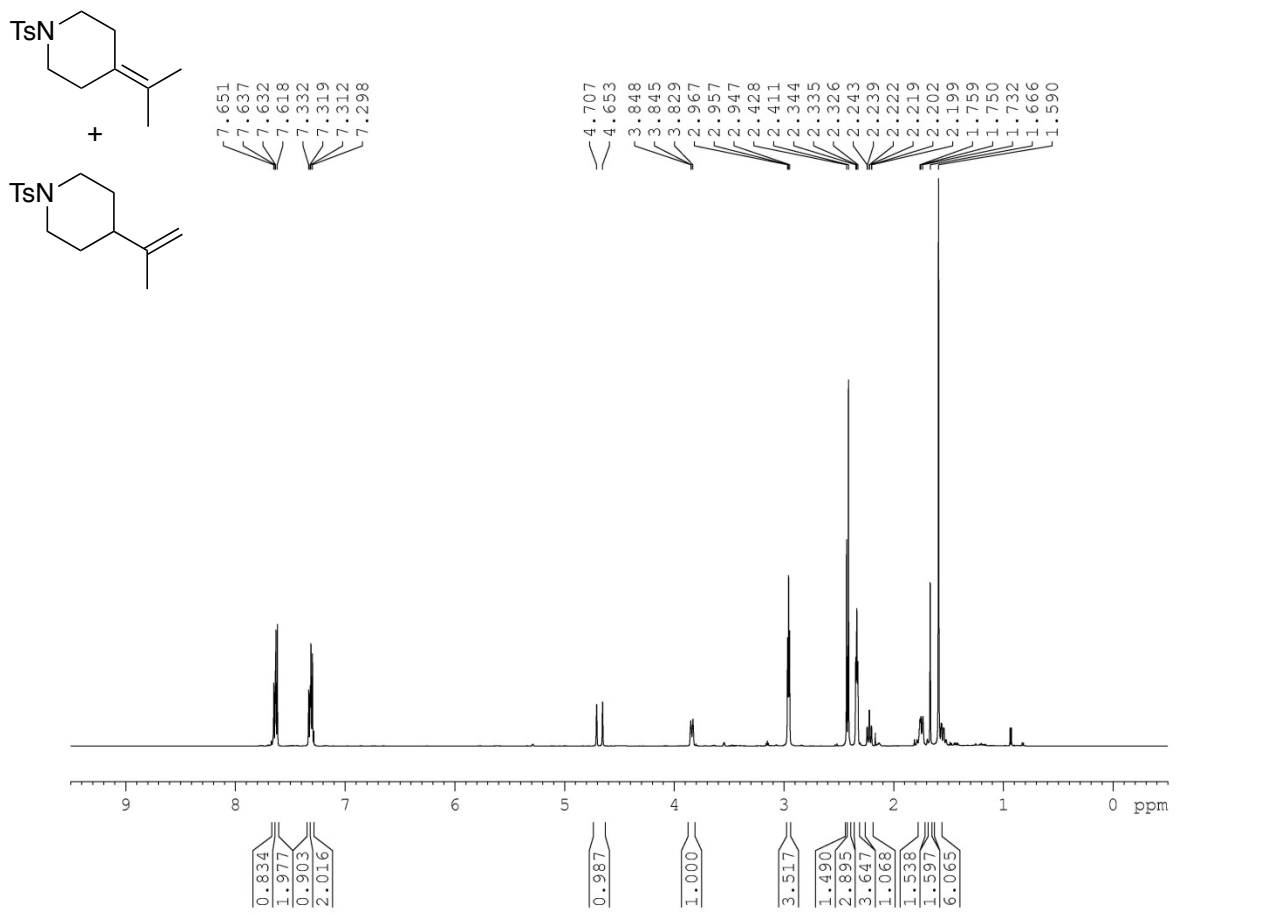
134.0761
133.7888
127.2756
127.2619
114.4826
113.6972
113.6695
80.7992
80.5323
77.2071
76.7833
71.4365
68.9558
55.2217
40.8876
37.3786
15.0732
14.5363
200
150
100
50
0
[ppm]

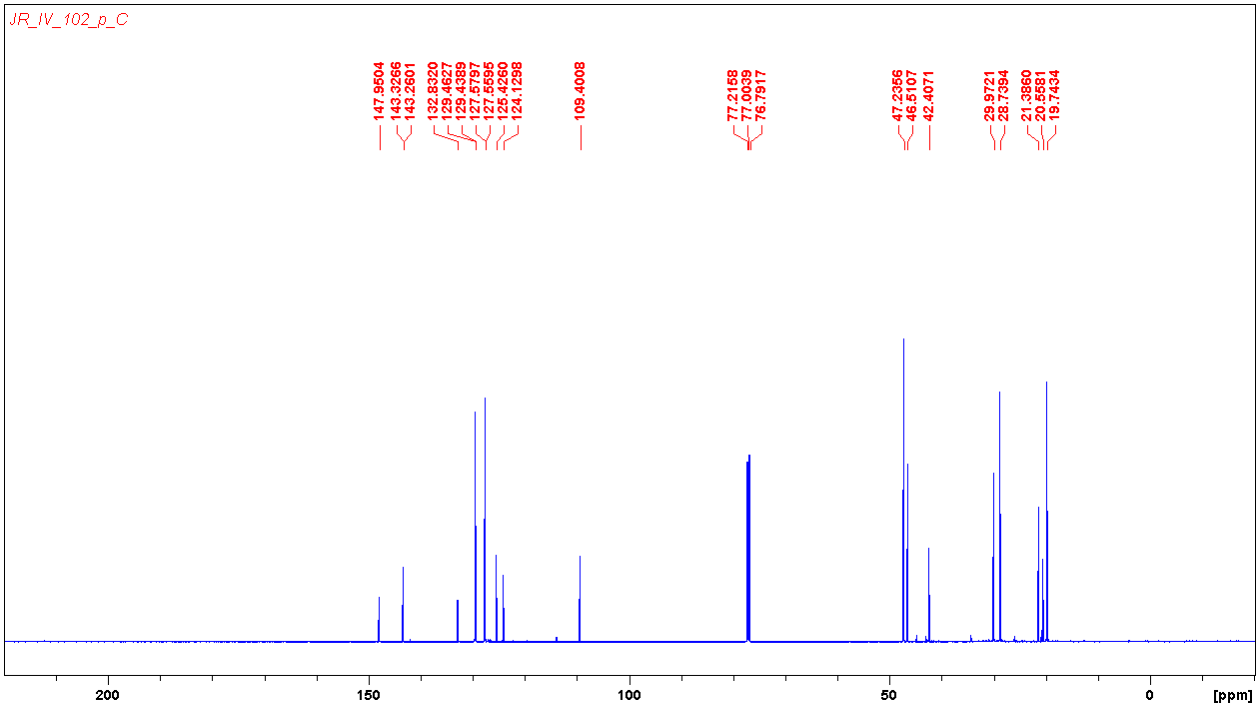

MeO2C
Ph
7.412
7.410
7.398
7.369
7.357
7.344
7.284
5.033
4.932
3.648
3.363
3.337
2.803
2.791
2.784
2.760
2.468
2.466
2.455
2.444
2.097
2.082
2.076
2.067
2.062
2.047
1.086
1.075
9
8
7
6
5
4
3
2
1
0 ppm
2.047
2.053
1.047
1.003
1.000
3.006
1.017
2.036
2.027
1.036

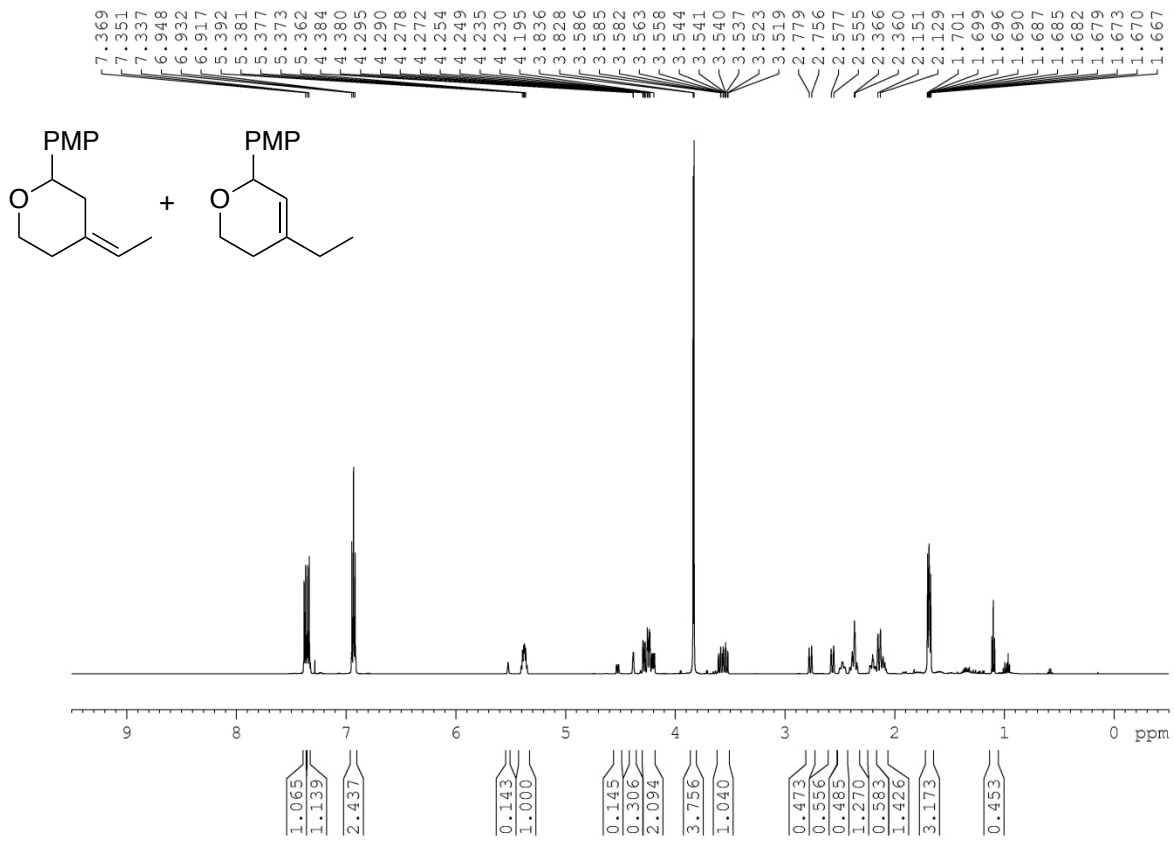

175.6485
149.0820
142.2578
128.3303
126.9340
126.5938
106.7529
77.2117
77.0002
76.7883
58.0541
52.4043
43.0926
35.7971
30.5307
200
150
100
50
0
[ppm]

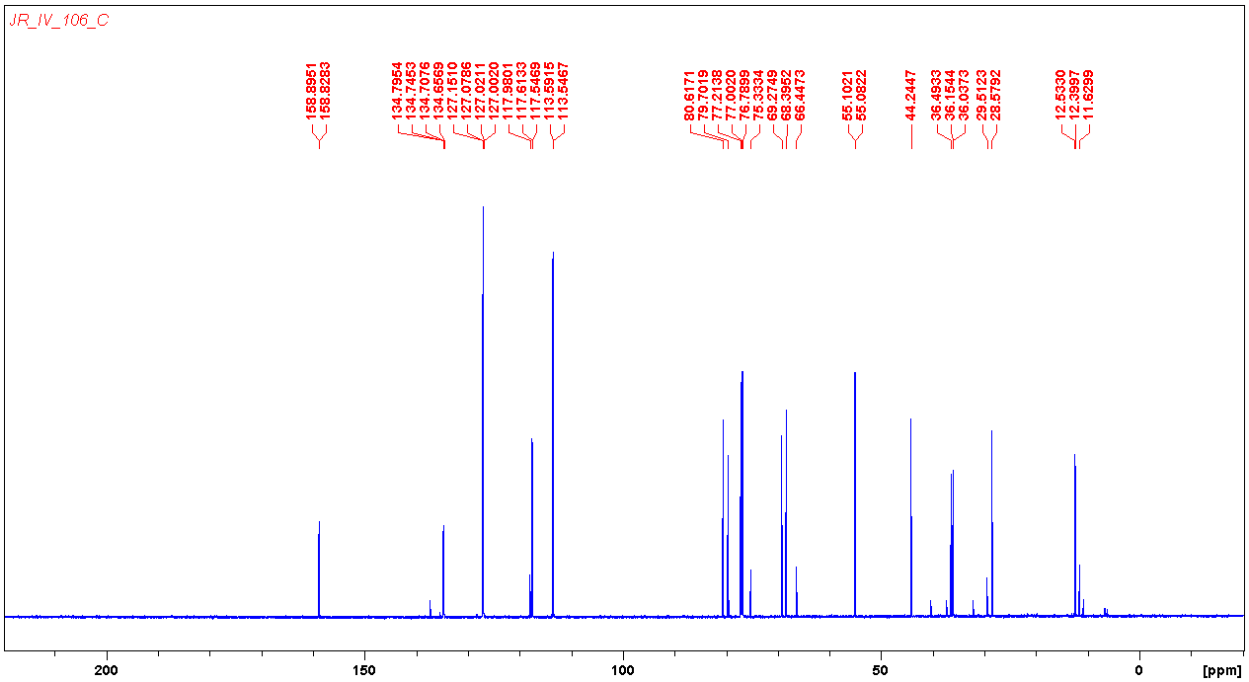

TsN
+
TsN
7.682
7.668
7.642
7.628
7.326
7.321
7.307
5.295
5.293
5.234
5.223
5.212
3.548
3.173
3.164
3.154
3.009
3.000
2.990
2.981
2.434
2.422
2.332
2.323
2.313
2.254
2.244
2.235
2.131
1.954
1.942
1.738
1.527
1.516
1.248
1.236
1.224
1.211
0.960
0.947
0.935
9
8
7
6
5
4
3
2
1
0 ppm
0.728
2.060
3.040
0.304
1.000
0.662
0.701
4.140
4.176
2.129
2.127
0.692
0.713
0.891
3.122
0.846
1.096


JR_IV_198_C_1
143.3858
143.3641
138.0709
133.5341
133.0999
129.5739
129.5349
129.5122
127.6822
127.6046
118.7433
114.8019
77.2151
77.0037
76.7922
47.9325
47.0764
44.7966
42.9020
35.0966
29.5344
28.2593
27.0724
21.4681
12.5707
11.7874
200
150
100
50
0
[ppm]


TsN
+
TsN
7.651
7.637
7.632
7.618
7.332
7.319
7.312
7.298
4.707
4.653
3.848
3.845
3.829
2.967
2.957
2.947
2.428
2.411
2.344
2.335
2.326
2.243
2.239
2.222
2.219
2.202
2.199
1.759
1.750
1.732
1.666
1.590
9
8
7
6
5
4
3
2
1
0 ppm
0.834
1.977
0.903
2.016
0.987
1.000
3.517
1.490
2.895
3.647
1.068
1.538
1.597
6.065


JR_IV_102_p_C
147.9504
143.3266
143.2601
132.8320
129.4627
129.4389
127.5797
127.5595
125.4260
124.1298
109.4008
77.2158
77.0039
76.7917
47.2356
46.5107
42.4071
29.9721
28.7394
21.3860
20.5581
19.7434
200
150
100
50
0
[ppm]


7.369
7.351
7.337
6.948
6.932
6.917
5.392
5.381
5.377
5.373
5.362
4.384
4.380
4.295
4.290
4.278
4.272
4.254
4.249
4.235
4.230
4.195
3.836
3.828
3.586
3.585
3.582
3.563
3.558
3.544
3.541
3.540
3.537
3.523
3.519
2.779
2.756
2.577
2.555
2.366
2.360
2.151
2.129
1.701
1.699
1.696
1.690
1.687
1.685
1.682
1.679
1.673
1.670
1.667
PMP
O
+
PMP
O
9
8
7
6
5
4
3
2
1
0
ppm
1.065
1.139
2.437
0.143
1.000
0.145
0.306
2.094
3.756
1.040
0.473
0.556
0.485
1.270
0.583
1.426
3.173
0.453


JR_IV_106_C
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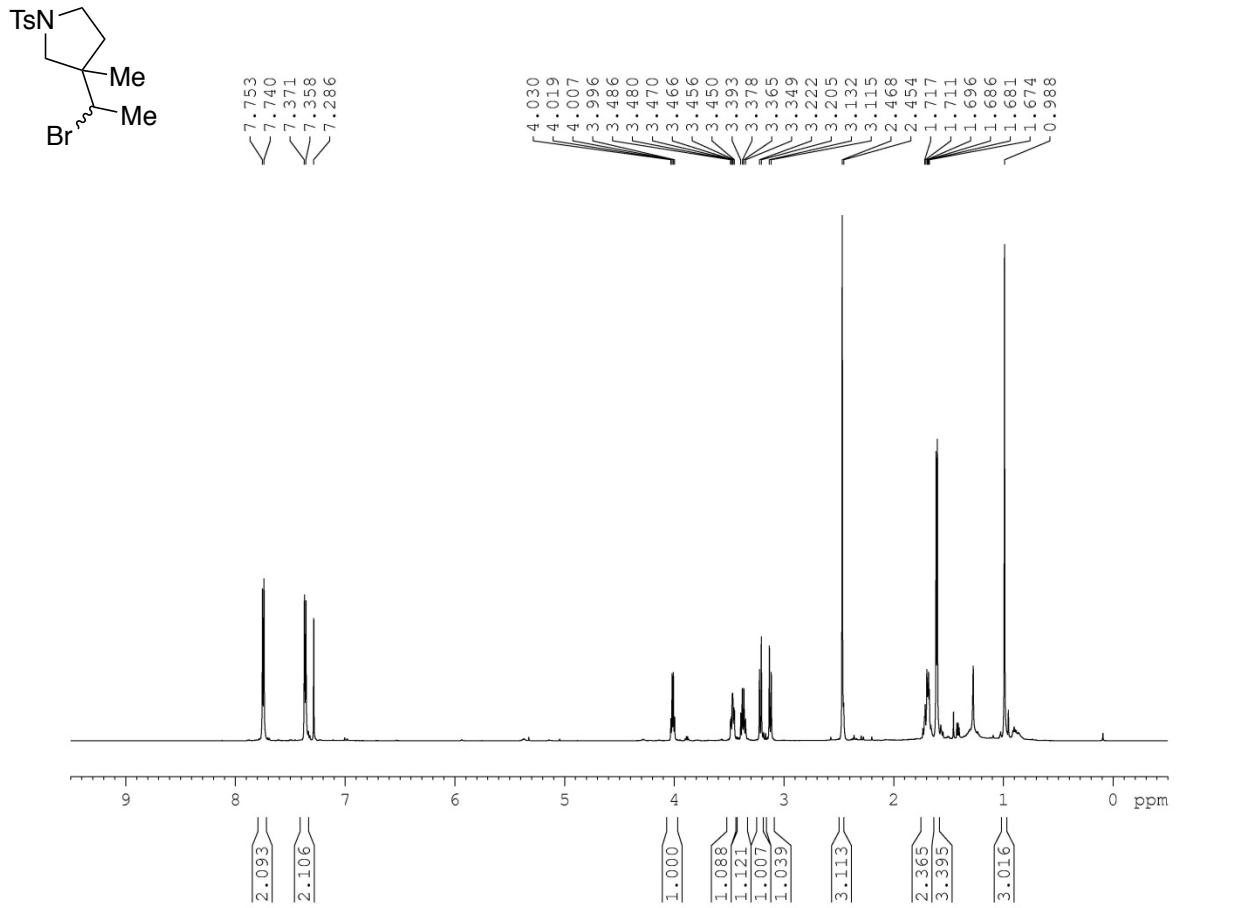
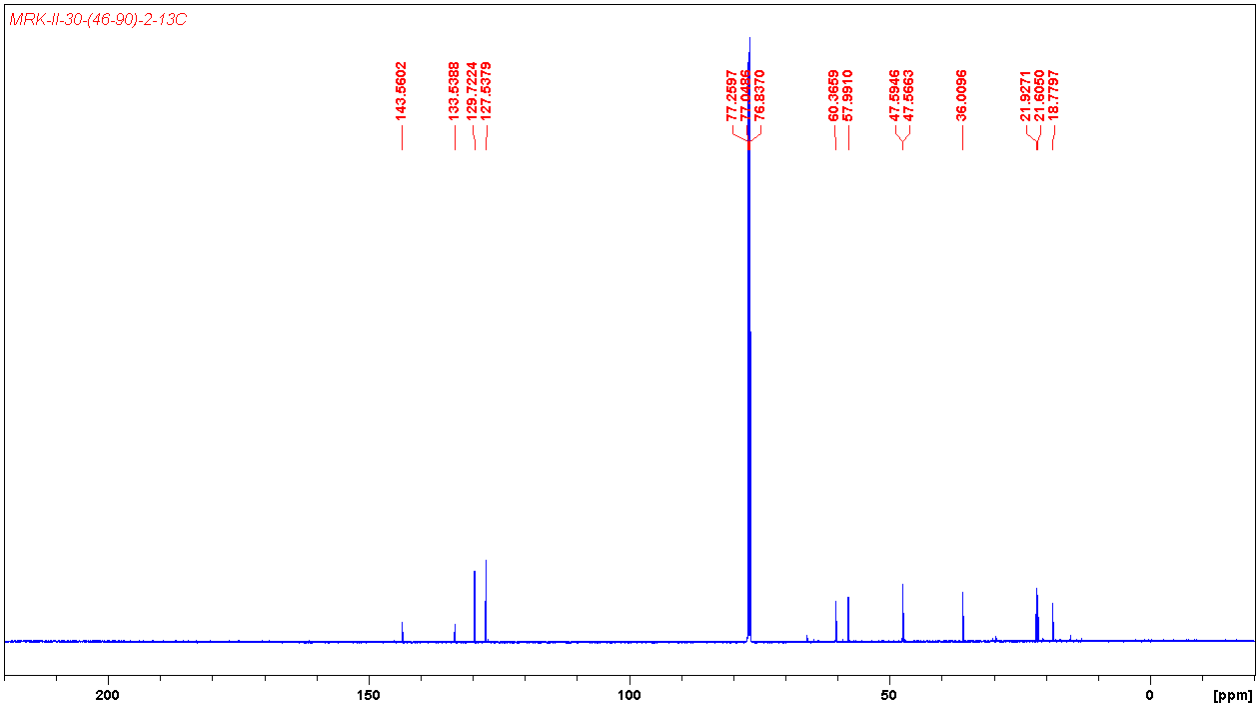
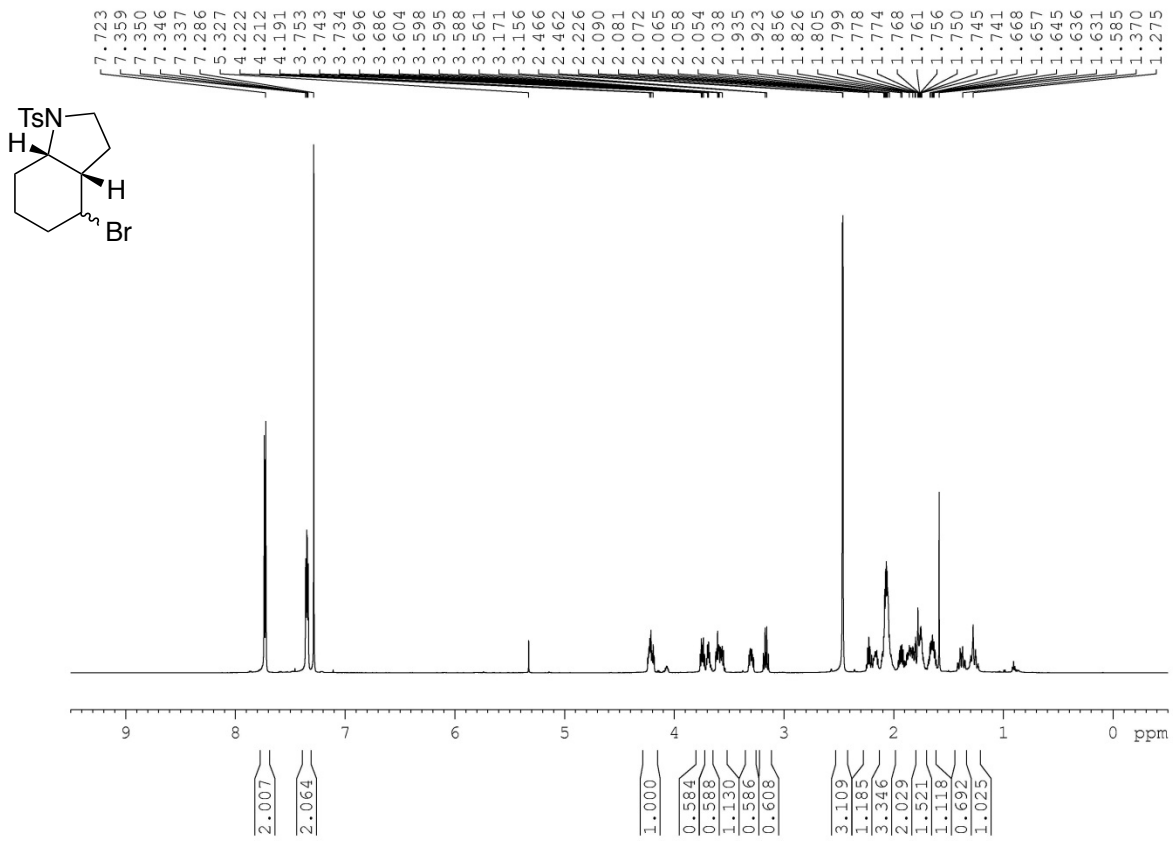
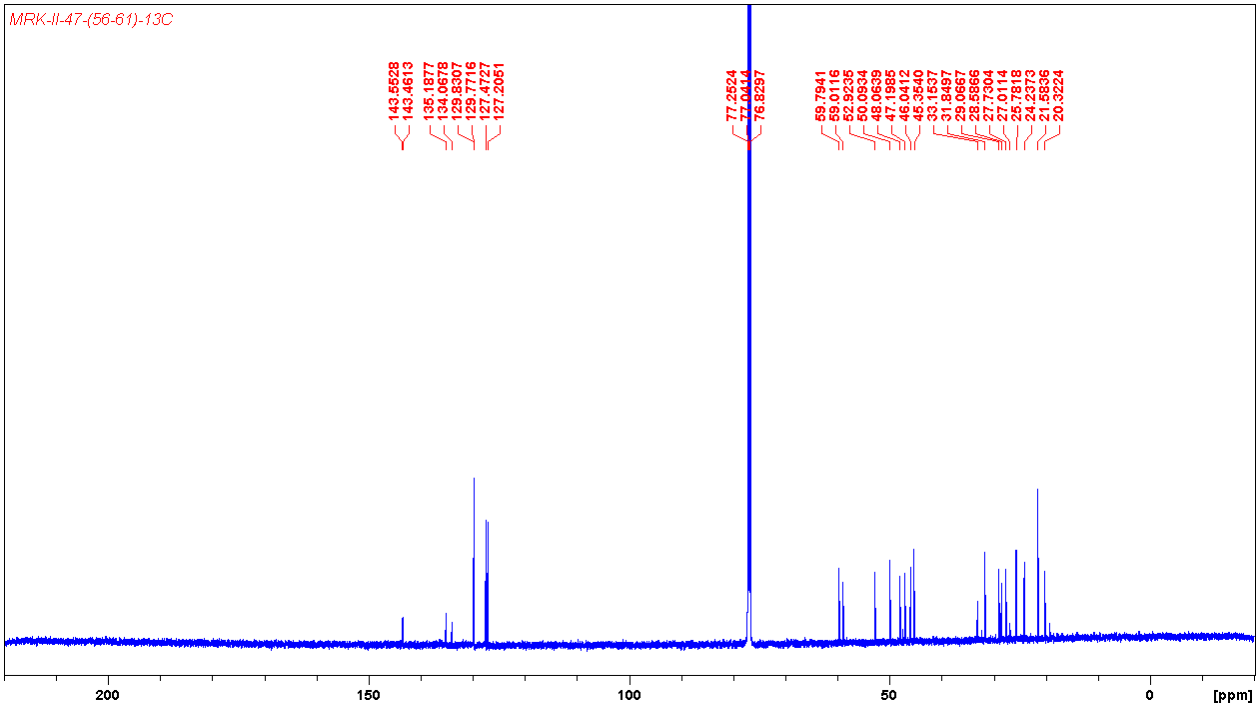
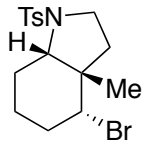
158.8283
134.7954
134.7463
134.7076
134.6568
127.1510
127.0786
127.0211
127.0020
117.9801
117.6133
117.5469
113.5915
113.5467
80.6171
79.7019
77.2138
77.0020
76.7899
75.3334
69.2749
68.3952
66.4473
55.1021
55.0822
44.2447
36.4933
36.1544
36.0373
29.5123
28.5792
12.5330
12.3997
11.6299
200
150
100
50
0
[ppm]


TsN
Me
Me
Br
7.753
7.740
7.371
7.358
7.286
4.030
4.019
4.007
3.996
3.486
3.480
3.470
3.466
3.456
3.450
3.393
3.378
3.365
3.349
3.222
3.205
3.132
3.115
2.468
2.454
1.717
1.711
1.696
1.686
1.681
1.674
0.988
9
8
7
6
5
4
3
2
1
0
ppm
2.093
2.106
1.000
1.088
1.121
1.007
1.039
3.113
2.365
3.395
3.016

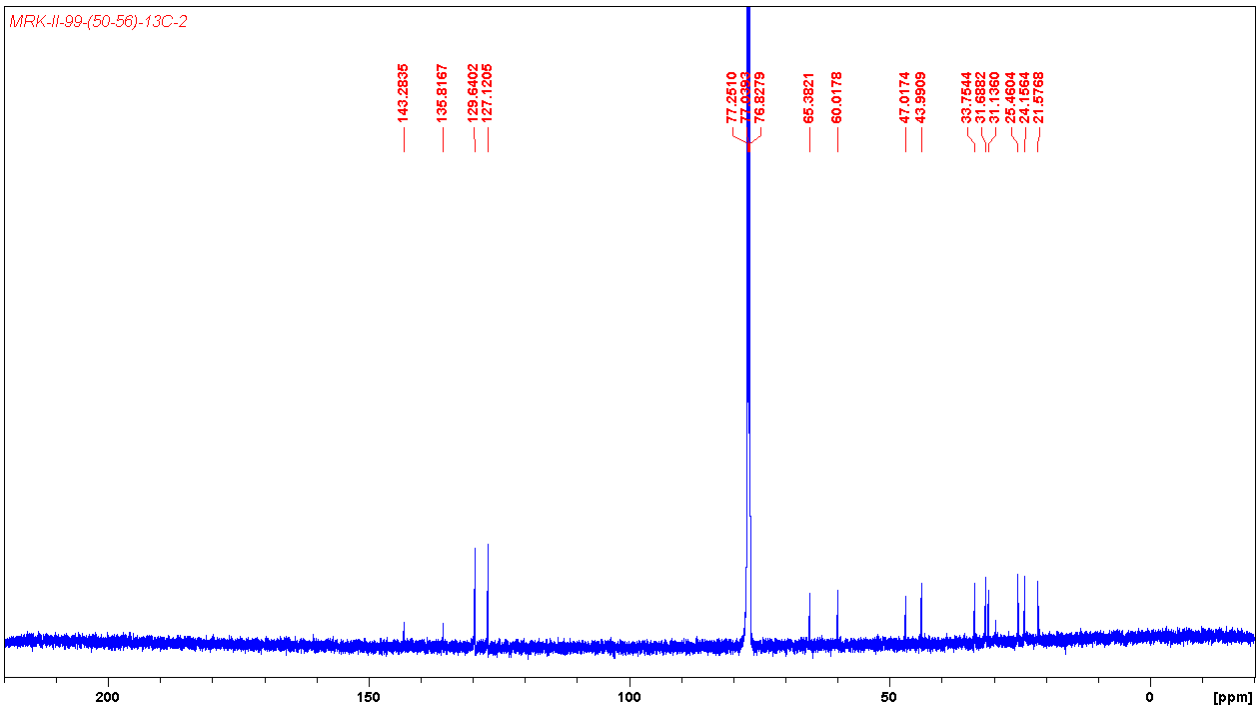

MRK-II-30-(46-90)-2-13C
143.5602
133.5388
129.7224
127.5379
77.2597
77.0486
76.8370
60.3659
57.9910
47.5946
47.5663
36.0096
21.9271
21.6050
18.7797
200
150
100
50
0
[ppm]

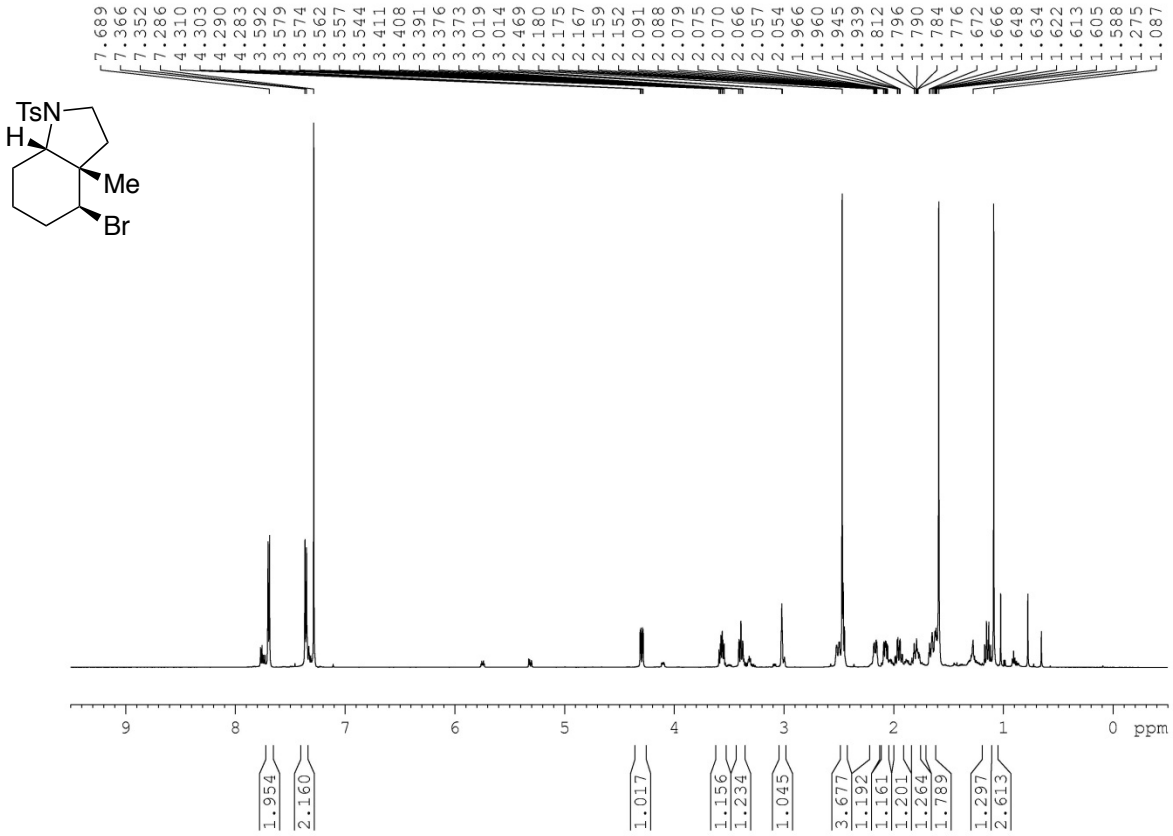

7.723
7.359
7.350
7.346
7.337
7.286
5.327
4.222
4.212
4.191
3.753
3.743
3.734
3.696
3.686
3.604
3.598
3.595
3.588
3.561
3.171
3.156
2.466
2.462
2.226
2.090
2.081
2.072
2.065
2.058
2.054
2.038
1.935
1.923
1.856
1.826
1.805
1.799
1.778
1.774
1.768
1.761
1.756
1.750
1.745
1.741
1.668
1.657
1.645
1.636
1.631
1.585
1.370
1.275
TsN
H
H
Br
9
8
7
6
5
4
3
2
1
0 ppm
2.007
2.064
1.000
0.584
0.588
1.130
0.586
0.608
3.109
1.185
3.346
2.029
1.521
1.118
0.692
1.025


MRK-II-47-(56-61)-13C
143.5528
143.4613
135.1877
134.0678
129.8307
129.7716
127.4727
127.2061
77.2524
77.0414
76.8297
59.7941
59.0116
52.9235
50.0934
48.0639
47.1985
46.0412
45.3540
33.1537
31.8497
29.0667
28.5866
27.7304
27.0114
25.7818
24.2373
21.5836
20.3224
200
150
100
50
0
[ppm]


TsN
H
Me
Br

7.750
7.736
7.333
7.319
7.285
3.981
3.973
3.960
3.952
3.544
3.528
3.512
3.436
3.426
3.417
3.407
3.233
3.220
3.216
3.203
3.187
2.450
2.195
2.174
2.165
2.159
1.887
1.881
1.865
1.860
1.718
1.701
1.695
1.677
1.665
1.656
1.588
1.423
1.405
1.400
1.394
1.382
9
8
7
6
5
4
3
2
1
0 ppm
1.935
1.917
1.000
1.093
1.023
1.091
3.076
2.939
1.029
2.280
1.197
1.575
2.912


MRK-II-99-(50-56)-13C-2
143.2835
135.8167
129.6402
127.1205
77.2510
77.0393
76.8279
65.3821
60.0178
47.0174
43.9909
33.7544
31.6882
31.1360
25.4604
24.1564
21.5768
200
150
100
50
0
[ppm]


7.689
7.366
7.352
7.286
4.310
4.303
4.290
4.283
3.592
3.579
3.574
3.562
3.557
3.544
3.411
3.408
3.391
3.376
3.373
3.019
3.014
2.469
2.180
2.175
2.167
2.159
2.152
2.091
2.088
2.079
2.075
2.070
2.066
2.057
2.054
1.966
1.960
1.945
1.939
1.812
1.796
1.790
1.784
1.776
1.672
1.666
1.648
1.634
1.622
1.613
1.605
1.588
1.275
1.087
TsN
H
Me
Br
9
8
7
6
5
4
3
2
1
0 ppm
1.954
2.160
1.017
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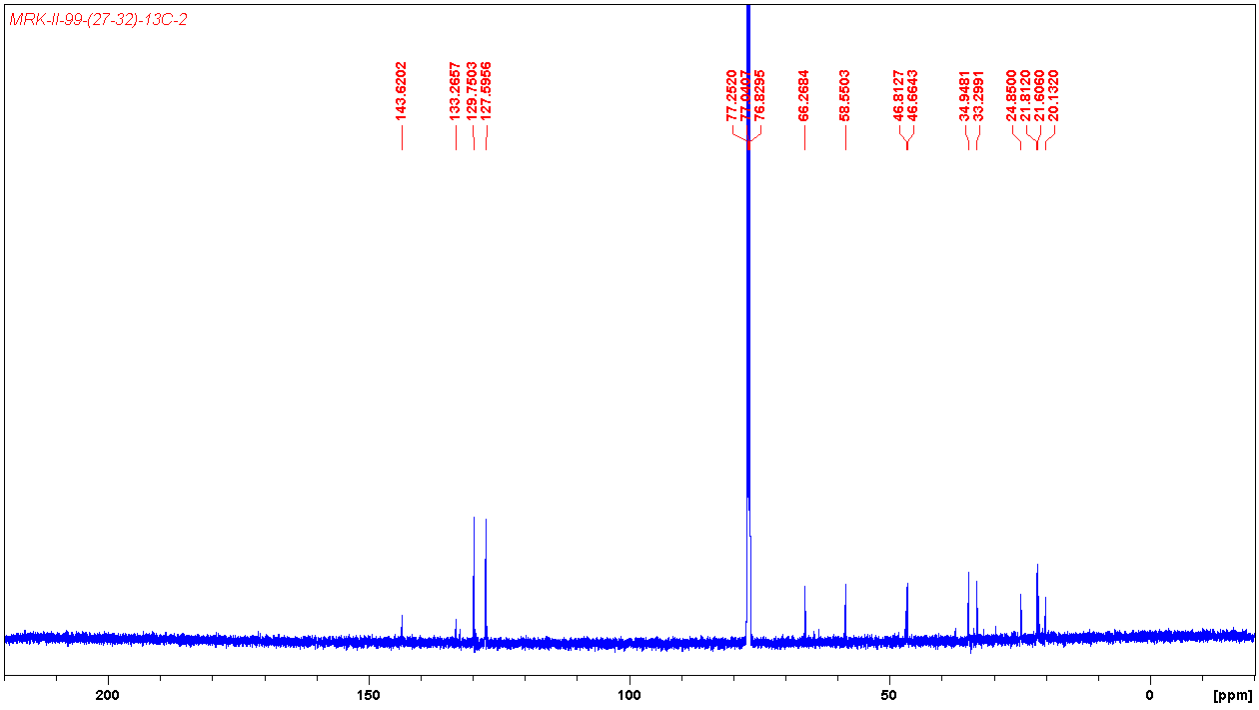
1.234
1.045
3.677
1.192
1.161
1.201
1.264
1.789
1.297
2.613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129.7503
127.5956
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66.2684
58.5503
46.8127
46.6643
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33.2991
24.8500
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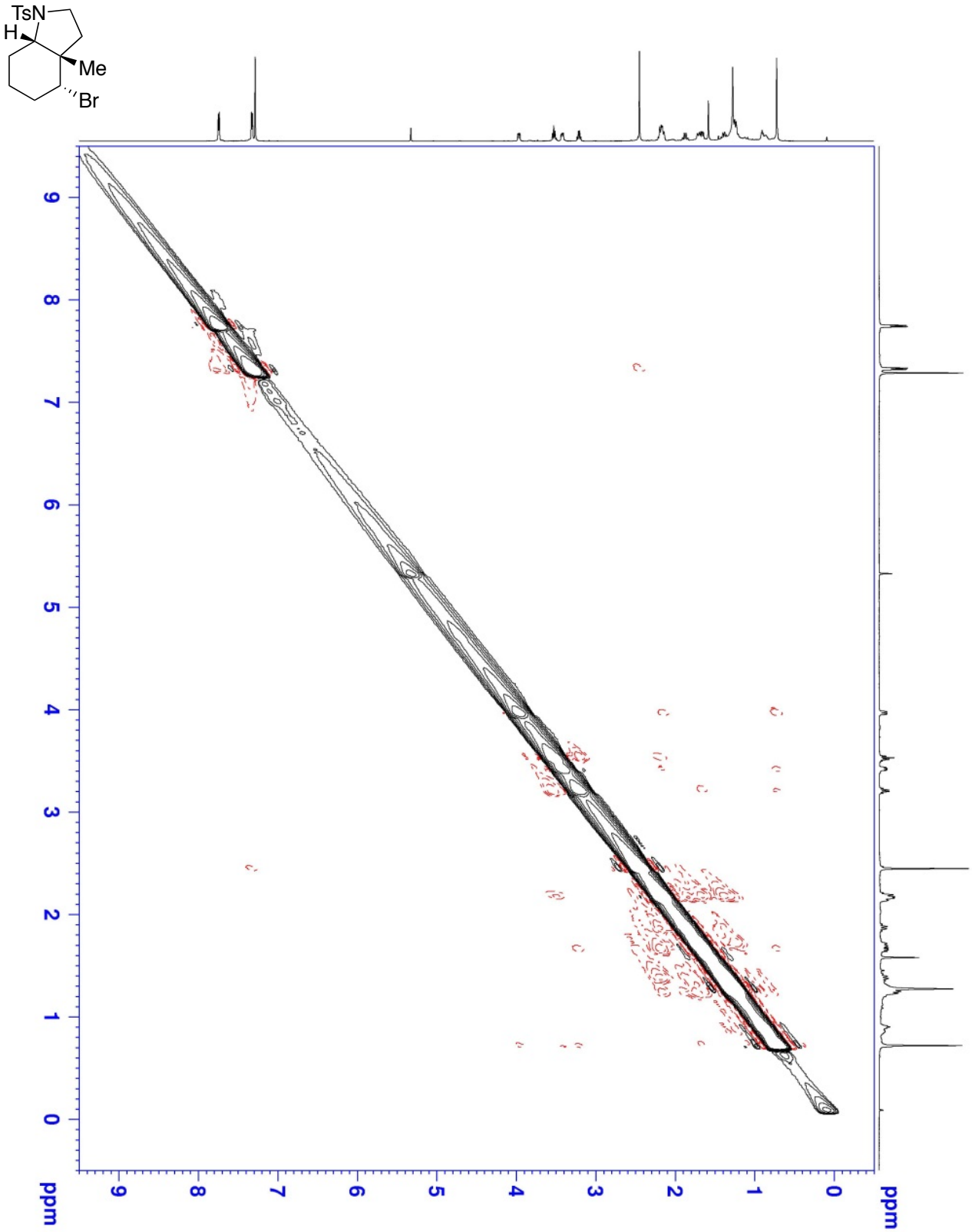
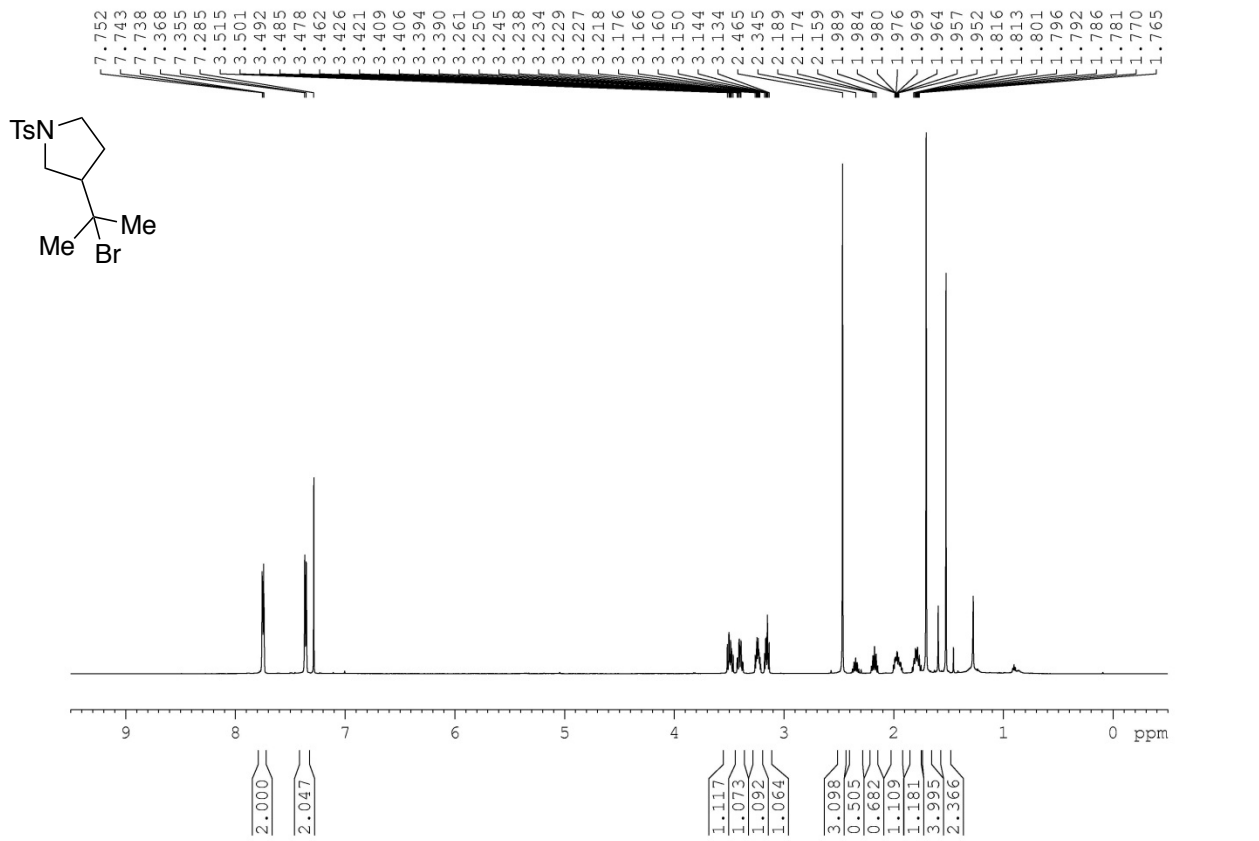
21.6060
20.1320
200
150
100
50
0
[ppm]


TsN
H
Me
Br
ppm
ppm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7.743
7.738
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7.355
7.285
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3.485
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3.426
3.421
3.409
3.406
3.394
3.390
3.261
3.250
3.245
3.238
3.234
3.229
3.227
3.218
3.176
3.166
3.160
3.150
3.144
3.134
2.465
2.345
2.189
2.174
2.159
1.989
1.984
1.980
1.976
1.969
1.964
1.957
1.952
1.816
1.813
1.801
1.796
1.792
1.786
1.781
1.770
1.765
TsN
Me
Me
Br
9
8
7
6
5
4
3
2
1
0
ppm
2.000
2.047
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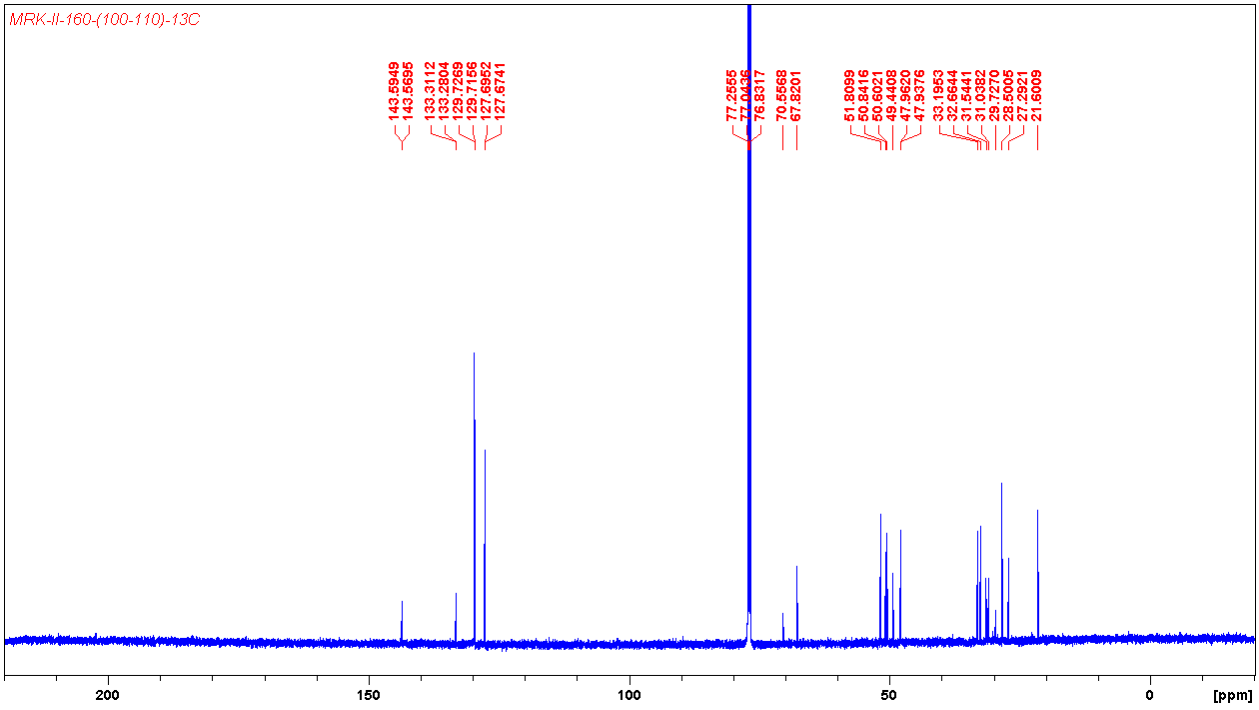
1.181
3.995
2.366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77.0436
76.8317
70.5568
67.8201
51.8099
50.8416
50.6021
49.4408
47.9620
47.9376
33.1953
32.6644
31.5441
31.0382
29.7270
28.5005
27.2921
21.6009
200
150
100
50
0
[ppm]

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