CATALYST-CONTROLLED, SELECTIVE FUNCTIONALIZATION OF CONJUGATED DIENES WITH SULFUR IMIDE REAGENTS

APPROVED BY SUPERVISORY COMMITTEE

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DEDICATION

I dedicate my dissertation to my family, friends, and colleagues who have supported me over the last five and a half years. A special feeling of gratitude goes to my loving wife, Iris, whose words of encouragement and unwavering support have guided me in the most difficult times. Her extraordinary ability to listen compassionately has provided me with comfort and reassurance that my ambitions are not mine alone, but ours. I will forever be grateful for that. To my father, mother, and sister who constantly show me what it means to be family. I know that distance will never separate us. I am appreciative for endless hours of conversation through FaceTime and phone.

Moreover, to my many colleagues who I now delightfully call friends. In particular, I would like to acknowledge Dr. Aaron Nash. Aaron is an outstanding chemist. I admire him deeply for his dedication through life's challenges. He is the only graduate student (now alumnus) that I know would volunteer to help you fix equipment on the weekend then provide you a spot at the gym later that day. I trust him with the most dangerous of chemicals and know that if I needed help he would make it his priority to be there. I am thrilled to call him a friend and intend to remain connected. I would also like to thank Dr. Liela Bayeh Romero, her positive attitude is admirable. She welcomed me into the laboratory on my first day, sacrificing her fume hood space for my summer rotation. She will always be remembered as the second cleanliest person in the lab. Without hesitation, I would like to acknowledge Dr. Bin Xu. Bin's honesty and candidness are his greatest attributes. He has been my bench mate for the past four years. I would not trade him for any other chemist. He remains a source of inspiration. Although we were raised

thousands of miles apart, speaking a different first language, we often understand what one another is thinking. I appreciate that and it has led to many enjoyable conversations.

Finally, without added fuss, I would like to extend my deepest gratitude to my undergraduate mentor Professor Subash Jonnalagadda and graduate mentor Professor Uttam Tambar. Without their unrelenting support in the laboratory, classroom, and life, I would not be half the chemist that I am today. Their lessons will follow me for the rest of my existence and I know that they have prepared me well to ask questions surrounding 'why?' and seek answers. Both mentors have afforded me an opportunity to grow independently and as a team member. I will miss the opportunities to learn from them, but relish the prospects of being their alumnus, granted the honor of representing their laboratories. Having learned from them will also connect me to an ever-growing network of great scientists who continue to study under them and for that I am indebted.

CATALYST-CONTROLLED, SELECTIVE FUNCTIONALIZATION OF CONJUGATED DIENES WITH SULFUR IMIDE REAGENTS

by

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DISSERTATION

Presented to the Faculty of the Graduate School of Biomedical Sciences

The University of Texas Southwestern Medical Center

In Partial Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

The University of Texas Southwestern Medical Center

Dallas, Texas

May, 2019

CATALYST-CONTROLLED, SELECTIVE FUNCTIONALIZATION OF CONJUGATED DIENES WITH SULFUR IMIDE REAGENTS

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Organic transformations to install heteroatoms continue to be a thriving area of research for synthetic chemists. The synthesis of small, heteroatom-containing molecules from inexpensive and abundant starting materials, such as hydrocarbons, requires unique methods that provide activation of the hydrocarbon without affecting the substrate scope and/or disturbing the reactivity of the heteroatom source. Efforts to accomplish these tasks are discussed. Emphasis is placed on the hetero-Diels-Alder reaction of sulfur imide dienophiles.

Sulfur imide reagents are highly electrophilic sources of sulfur and nitrogen. Exploiting the distinctive properties of sulfur, together with the sulfur-nitrogen bond, a method to access 1,4-aminothiols has been developed. This difunctionalization strategy installs two diverse functional groups in a selective manner across 1,3-dienes. Whereas traditional methods to install a single heteroatomic functional group suffer from regiocontrol alone. The developed method for 1,4-aminothiolation must provide both regio- and diastereocontrol. Owing to the inclusion of a

concerted [4+2]-cycloaddition as the first step in a tandem process, the aminothiolation protocol established within is able to achieve complete regio- and diastereocontrol. This method represents the first concise, direct method to access aminothiol scaffolds from abundant 1,3-dienes. Additionally, the mechanistic investigation suggests the transformation proceeds through a highly reactive [10-S-4] sulfurane, generated via nucleophilic addition of a Grignard reagent. Notably, the second step of this tandem process is not able to provide the desired aminothiol functionality without the addition of Lewis acid.

Subsequent the presence of a copper catalyst in the tandem process to generate aminothiols from 1,3-dienes, the development of a chiral Lewis acid catalyst was studied. With the advent of a chiral Lewis acid catalyst, an asymmetric hetero-Diels-Alder reaction may be developed to provide enantioenriched [4+2] adducts. The utility of [4+2] adducts of sulfur imide reagents extends beyond the scope of the aminothiolation protocol. With proper selection of a sulfur imide reagent it may be possible to access products of aminothiolation, aminoarylation, amination, and others. In the presence of a chiral $SnCl_4$•(*R*)-SITCP catalyst, a homoallylic amination was achieved in up to 61% enantiomeric excess.

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LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
app.	apparent
aq.	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
BOX	bisoxazoline
i-Bu	*iso*-butyl
t-Bu	*tert*-butyl
ºC	degrees Celsius
calc'd	calculated
cat.	catalytic
Cbz	carboxybenzyl
conc.	concentrated
Cy	cyclohexyl
d	day(s) or doublet
DACH	diaminocyclohexane
dba	dibenzylideneacetone
DCM	methylene chloride
Dia	diameter
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMB	dimethoxybenzene
DME	dimethoxyethane
EDG	electron donating group
ee	enantiomeric excess
ent	enantiomer
equiv	equivalent(s)

er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
EWG	electron withdrawing group
FTIR	fourier transform infrared spectroscopy
g	gram(s)
GC-MS	gas chromatography-mass spectrometry
Δ	heat
h	hour(s)
HDA	hetero-Diels-Alder
hfc	heptafluoropropylhydroxymethylene
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IPA	isopropyl alcohol
IR	infrared
J	coupling constant
L	liter or ligand
LA	Lewis acid
LBA	Lewis acid-assisted Brønsted acid
LC-MS	liquid chromatography-mass spectrometry
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
m	multiplet
m	meta
M	molar or metal
Me	methyl
mg	milligram(s)
MHz	megahertz
MOM	methoxymethyl

μ	micro
min	minute(s)
mL	milliliter(s)
mmol	millimole
mol	mole
mol %	mole percentage
NMDPP	neomenthyldiphenylphosphine
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
p	pentet
p	para
Ph	phenyl
PhH	benzene
PhMe	toluene
pin	pinacol
ppm	parts per million
PyBOX	pyridylbisoxazoline
q	quartet
R_f	retention factor
rr	regiomeric ratio
rt	room temperature
s	second(s) or singlet
SEGPHOS	4,4'-bi-1,3-benzodioxole-5,5'diylbis(diphenylphosphane)
SITCP	5,6,10,11,12,13-hexahydro-5-phenyl-4H-diindeno[7,1-cd:1,7-ef]phosphocin
SPINOL	1,1'-spirobiindane-7,7'-diol
t	triplet
TADDOL	α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
tart	tartrate
TBS	*tert*-butyldimethylsilyl

Tf	triflyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	tosyl
TS	transition state
VANOL	3,3'-diphenyl-2,2'-bi-1-naphthol
ν	wave number (cm^{-1})

CHAPTER ONE

Copper-Catalyzed Aminothiolation of 1,3-Dienes via a Dihydrothiazine Intermediate

1.1 Background

1.1.1 Introduction

Heteroatom-containing molecules are of particular interest to medicinal chemists and materials scientists.[1-4] The selective introduction of heteroatoms into unsaturated hydrocarbons has emerged as a powerful synthetic strategy for the construction of these useful materials. Specifically, direct functionalization of inexpensive and abundant 1,3-dienes has gathered increasing attention.[5-7]

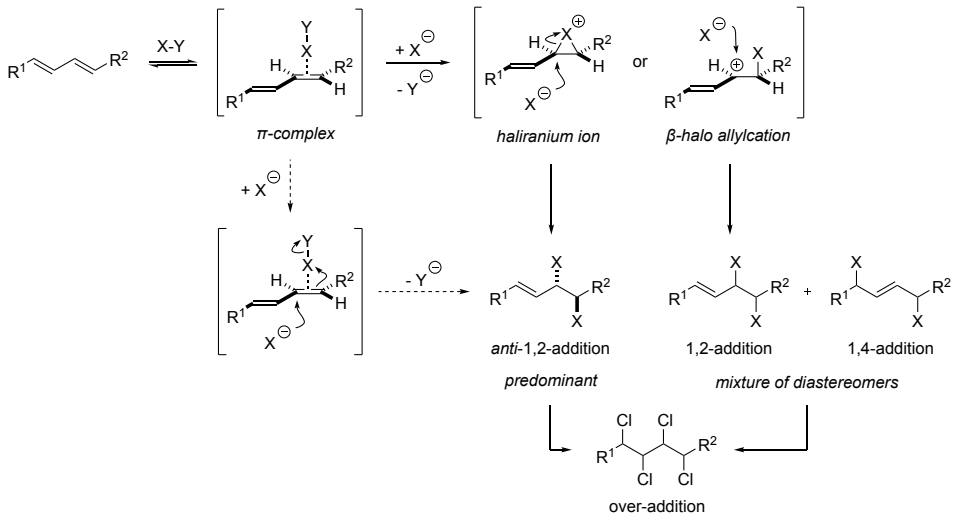
Although selective introduction of a single functional group retains its own set of challenges,[8-10] the ability to introduce two functional groups in a selective manner increases the complexity. This concept is further realized when attempting to install two distinct functional groups. Instead of accounting for predominantly regioselectivity, as is the case with single functional group installation, difunctionalization requires attention to both regio- and diastereoselectivity. This may be rationalized by the *syn*/*anti* relationship of the two newly installed groups.

To overcome these challenges, synthetic chemists have resorted to installing directing or activating functionality in the starting hydrocarbon.[11-13] The limitations of such strategies are seen in the substrate scope as well as the nature of functional group additions that may take place without affecting the previously installed directing or activating functionality. To date, limited examples exist for a highly selective difunctionalization of unactivated dienes with heteroatoms. This circumstance presents a pronounced need for transformations that may accomplish this task in a concise, direct manner.

1.1.2 Strategies for the Difunctionalization of 1,3-Dienes with Heteroatoms

The most fundamental method for functionalizing 1,3-dienes is based upon the concept of electrophilic addition. In some of the earliest reports, chemists communicate the addition of simple acids to olefins.[14] To expand upon this general concept and introduce two heteroatoms, chemists elected to explore the capabilities of molecular dihalides (X-Y, Scheme 1.1.1).[15-16] The benefit of a transformation of this type is availability of the halogen source and predominant selectivity for vicinal difunctionalization. However, to the dismay of many synthetic chemists, the transformation suffers in the number of drawbacks relative to its benefits. For example, molecular dihalides present toxicity and the ability to establish total control over regioselectivity or number of halide additions remains a challenge.

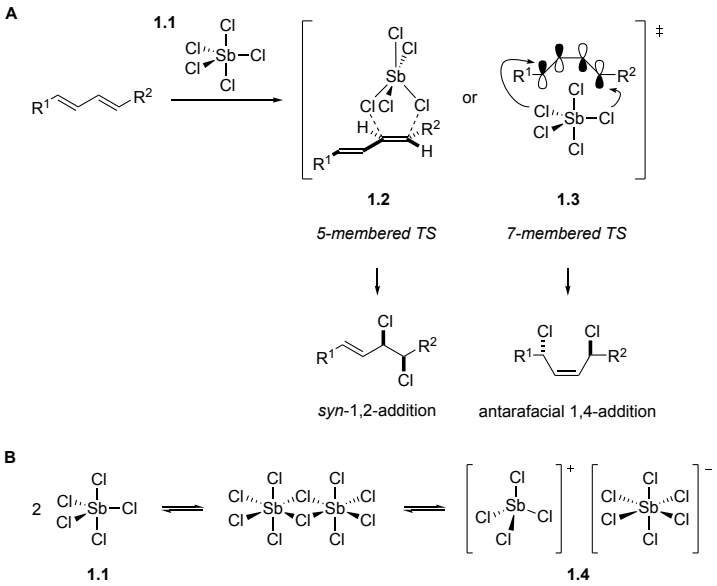
Scheme 1.1.1



In order to enable better control over diasteroselectivity, chemists opted to investigate metal halides as the halogen source. In the case of high-valent species such as antimony(V) pentachloride **1.1**, a concerted mechanism is suggested wherein the two halide atoms are added in a stereospecific fashion across the alkene substrate (Scheme 1.1.2A).[15,17-18] In regards to 1,2-dichlorination, this transformation is believed to be a result of group transfer from a 5-membered

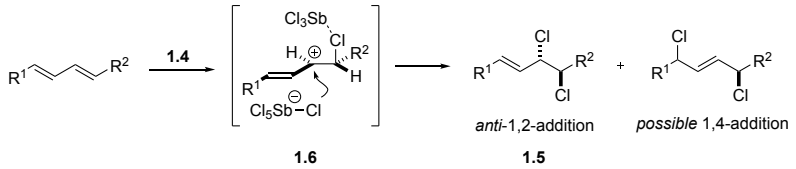
transition state **1.2** leading to a *syn*-specific dichlorination. 1,4-Dichlorination, on the other hand, is considered to be a result of concerted group transfer from a 7-membered transition state **1.3** leading to *anti*-specific addition of chlorine. Unfortunately, the transformation suffers from low selectivity between 1,2- and 1,4-addition. Additionally, in order to maintain high diastereocontrol proper selection of solvent, additives, and temperature are necessary; this is due to the ionization of antimony(V) pentachloride in solution to $[SbCl_4]^+[SbCl_6]^-$ **1.4** (Scheme 1.1.2B).[19-23]

Scheme 1.1.2



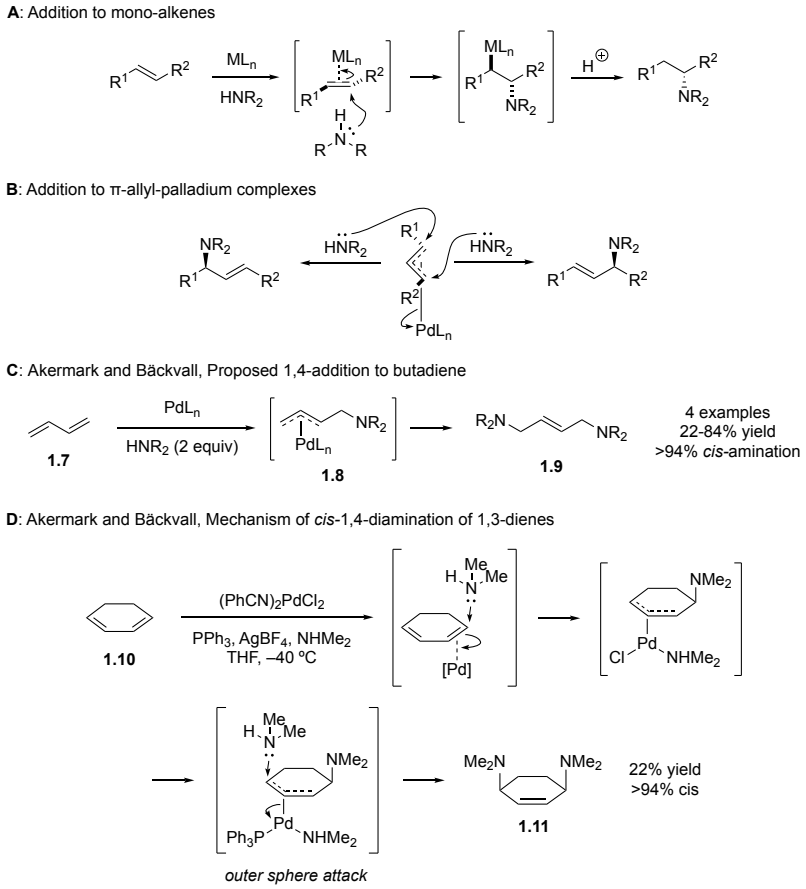
Under ionizing conditions, $[SbCl_4]^+[SbCl_6]^-$ **1.4** is believed to be responsible for formation of the *anti*-1,2-dichlorinated product **1.5** (Scheme 1.1.3).[17] Instead of a concerted mechanism, reactive chlorinating species **1.4** is thought to promote an ionic mechanism via β-chlorocarbenium ion intermediate **1.6**. The interaction of the initial chlorine atom with antimony is invoked as an explanation for preventing formation of a bridging chloriranium ion, thereby leading to measurable amounts of isomerization.[24-25] Higher *anti* selectivity is observed when using simple mono-olefins and phosphorus(V) pentachloride as a chlorinating reagent, however the mechanism remains ambiguous and the use of 1,3-dienes is yet to be investigated.[26]

Scheme 1.1.3



Following the use of metal halides, synthetic chemists questioned the electrophilic nature of metals themselves to facilitate functionalization of 1,3-dienes. In most cases, efforts have been placed upon the control of stereochemistry in nucleophilic additions to simple mono-alkenes and allyl hydrocarbons coordinated to late transition metals (Scheme 1.1.4A-B).[27-29] Meaningfully,

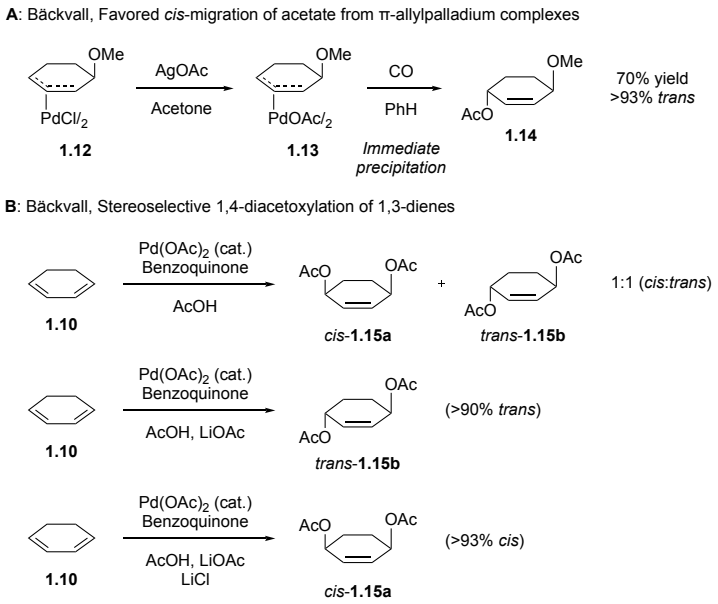
Scheme 1.1.4



the vast majority of the reports are devoted to nucleophilic additions of π-allylpalladium complexes and the applications of these reactions to the synthesis of synthetically useful materials.[30] In 1979, Akermark and Bäckvall identified that monoamination of butadiene **1.7** would provide an amino π-allylpalladium complex **1.8** that may react with a second molar equivalent of amine to yield diamine **1.9** (Scheme 1.1.4C).[31] Using 1,3-cyclohexadiene **1.10** as a substrate, the researchers were able to determine the overall steric course of the reaction (Scheme 1.1.4D). Notably, the two amino groups are added in a *cis*-fashion to the diene system. These results indicate that the second nucleophile (in this case a second molar equivalent of amine) substitutes palladium via an outer sphere mechanism, opposed to an inner sphere, or intramolecular, mechanism.

A year later, the Bäckvall group identified a method for controlling the stereochemistry of nucleophilic attack on π-allylpalladium complexes. The researchers discovered that the introduction of additives, such as carbon monoxide, may favor an intramolecular *cis* migration of acetate from palladium to carbon (Scheme 1.1.5A).[32] Immediately following the investigation, the Bäckvall group postulated that a similar outcome may be attained with 1,3-dienes. At the

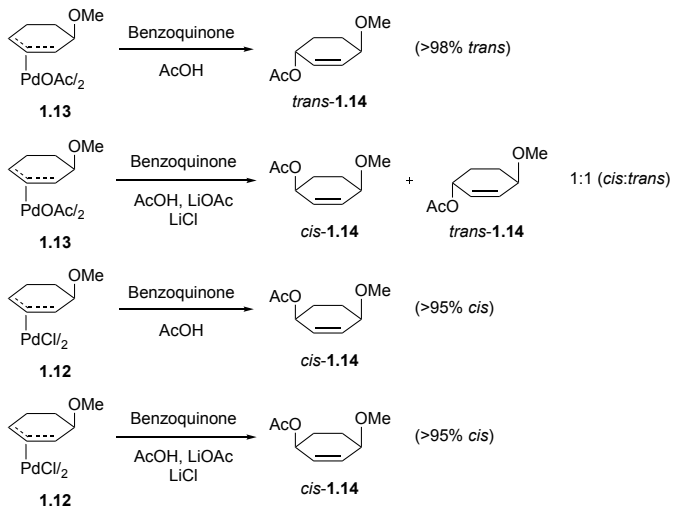
Scheme 1.1.5



time, it was known that palladium-catalyzed diacetoxylation of 1,3-dienes occurs in the presence of acetic acid, unfortunately the stereochemistry was undetermined.[33] The Bäckvall group studied the stereochemistry of the transformation and found that the presence of lithium chloride and/or lithium acetate has a profound effect on the stereochemical outcome.[34,35] Oxidation of 1,3-cyclohexadiene **1.10** using benzoquinone and catalytic amounts of palladium acetate in acetic acid afforded a 1:1 mixture of *cis*- and *trans*-1,4-diacetoxy-2-cyclohexene **1.15** (Scheme 1.1.5B). Under the same oxidation conditions with addition of lithium acetate, the main product observed was *trans*-1,4-diacetoxy-2-cyclohexene **1.15b** (>90% *trans*). Contrasting this result, in the presence of both lithium acetate and lithium chloride as additives, the main product observed was *cis*-1,4-diacetoxy-2-cyclohexene **1.15a** (>93% *cis*).

Later, the reaction to form *cis*-diacetate **1.15a** was found to be favorable using Li_2PdCl_4 as a catalyst and lithium acetate as an additive. This result was used to help explain the mode of acetate attack on the intermediate π-allylpalladium complex. Specifically, the π-allylpalladium intermediates from both catalyst systems were obtained and stoichiometric reactions carried out. Treament of the π-allylpalladium complex **1.13** containing acetate ligands with benzoquinone in acetic acid resulted in *cis* attack to afford the *trans* product **1.14** (Scheme 1.1.6). Under the same conditions, but with addition of lithium chloride and lithium acetate as additives, a 1:1 mixture of

Scheme 1.1.6



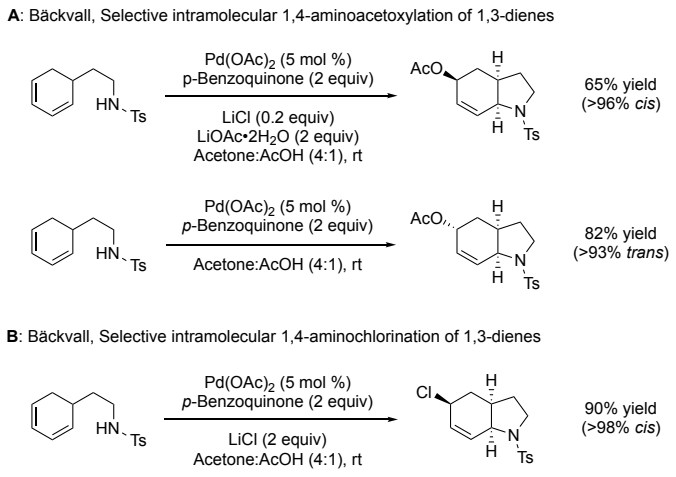
cis and *trans* products were obtained. Treatment of the π-allylpalladium complex **1.12** containing chloride ligands with benzoquinone in acetic acid, with and without lithium chloride and lithium acetate as additives, resulted in pure *cis* product; a result of *trans* attack.

The mechanism Bäckvall and coworkers propose supporting the results, is that chloride ligands block the coordination of acetate to palladium, thereby minimizing the inner sphere *cis*-migration pathway, instead favoring an outer sphere *trans* attack of acetate on the π-allylpalladium complex. In the absence of chloride ligands, both *cis* and *trans* attack may occur depending on the concentration of acetate ions.

Although the 1,4-diacetoxylation is highly regio- and diastereoselective, the transformation is limited in scope. Often cyclic dienes are required, providing yield between 21-57%. While acyclic dienes provide product, the yield is routinely low due to a competing Diels-Alder cycloaddition between the 1,3-diene and benzoquinone. Furthermore, the concentration of both benzoquinone and chloride ions have a direct affect on product formation. In the presence of higher chloride ion concentrations *cis*-1,4-acetoxychlorination will occur.[36]

Following the early reports by the Bäckvall group, the team extended their methodology to enable the use of intramolecular nucleophiles. Their first example was in 1990 on the difunctionalization of 1,3-dienes with nitrogen and oxygen.[37] In the article, the scientists exploit an intramolecular amide nucleophile to install nitrogen, succeeded by acetate substitution for palladium on the resulting α-amino-π-allylpalladium complex (Scheme 1.1.7A). The

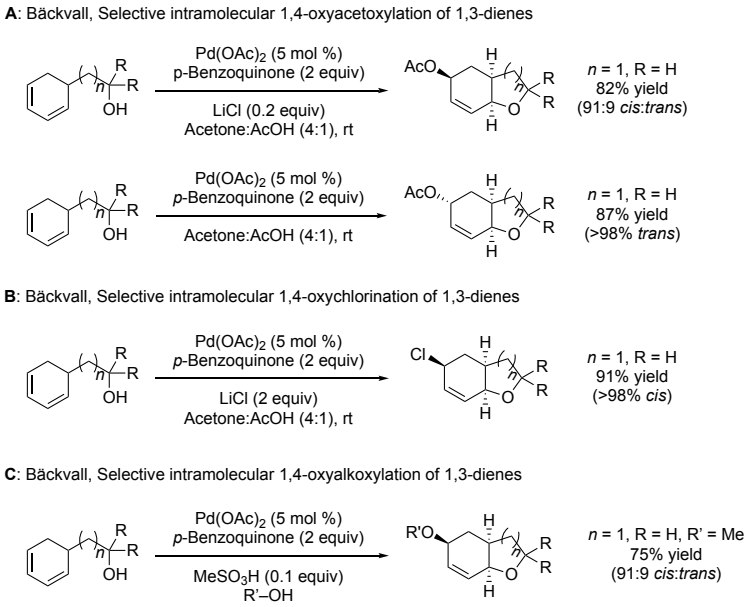
Scheme 1.1.7



transformation proceeds moderately well, affording yields between 65-92%, with excellent *cis*/*trans* selectivity (up to >98%). Moreover, the researchers include several examples of selective 1,4-aminochlorination (Scheme 1.1.7B); a process that follows suit to the 1,4-acetoxychlorination made possible with a high concentration of chloride ions. Attractively, the aminochlorination occurs with increased yield (86-97%) and solely *cis* selectivity.

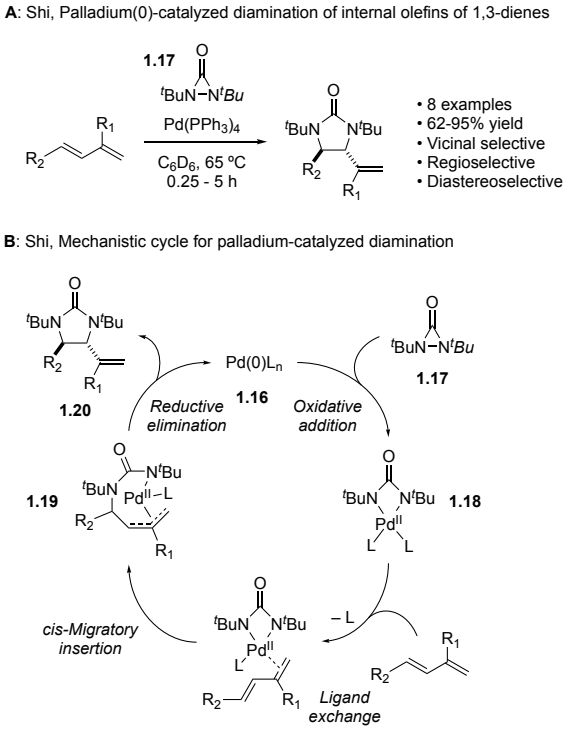
The Bäckvall group published a second report in 1992 exploring intramolecular nucleophiles. In this report, they use an intramolecular hydroxyl nucleophile to enable selective 1,4-oxyacetoxylation of 1,3-dienes (Scheme 1.1.8A).[38] The unique methodology enables the synthesis of fused tetrahydrofurans or tetrahydropyrans in good yield (65-90%) and selectivity (up to >98% *cis* or *trans*). Unsurprisingly, they extended this method to permit 1,4-oxychlorination comparable to their previous reports (Scheme 1.1.8B). Uniquely however, when an alcohol is employed as the reaction medium, the substitution for palladium is executed with the solvent, instead of acetate or chlorine, providing access to a 1,4-oxyalkoxylation product (Scheme 1.1.8C). Additionally, this transformation provides the product with excellent *cis* diastereoselectivity (90 to >98% *cis*).

Scheme 1.1.8



Over the past several decades, the Bäckvall group has played a pivotal role in discovering methods for the difunctionalization of 1,3-dienes with heteroatoms. Subsequent to those discoveries, the Shi group theorized that they could use a similar mode of activation to functionalize 1,3-dienes with palladium-activated diazridinones **1.18** (Scheme 1.1.9).[39] Taking advantage of the labile nitrogen-nitrogen bond in diaziridinone **1.17**, a palladium(0) catalyst could perform an oxidative addition into the weak bond producing a four-membered palladacycle with two nitrogen ligands. This activated complex could then mimic the palladium(II) catalysts seen in Bäckvall's chemistry. Ligand substitution on palladium with the desired 1,3-diene provides access to the necessary environment for migratory insertion of a single amido ligand to afford α-amido-π-allylpalladium complex **1.19**. Instead of traditional substitution, such as in Bäckvall's work, reductive elimination delivers diamination product **1.20** – regenerating the palladium(0) catalyst **1.16**. The advantage of this novel chemistry is the high selectivity for internal olefins, a result of preferential migration into higher substituted carbons, as well as the

Scheme 1.1.9



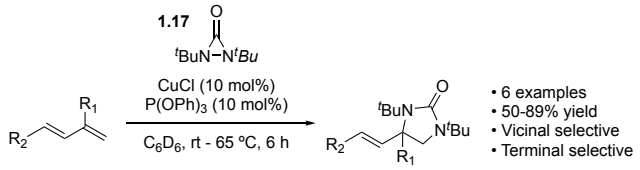
syn-relationship of the amines in the final product. Moreover, 1,2-diamination is preferred over 1,4-diamination due to the thermodynamic stability of 5-membered rings over 7-membered rings.

In the Shi group's attempt to discover complementary catalytic systems, they uncovered that copper(I) catalysts also engage diaziridinones to afford diamination products. In contrast to the palladium(0)-catalyzed process, the copper(I)-catalyzed diamination occurs mostly at the terminal double bond of 1,3-dienes. Their studies show that the terminal and internal diamination likely arise from two distinct and competing pathways. In particular, they believe that copper(II) and copper(III) species are existent in solution, and that these species have an ability to interconvert. It is proposed that the copper(II) species **1.21** is inherently favored upon addition of ligand such as PCy_3. The addition of the nitrogen radical to the terminal double bond of the diene leads to allyl radical **1.22**, which is converted to diamination product **1.23** along with regeneration of the copper(I) catalyst (Scheme 1.1.10). The steric hindrance and formation of a stable allyl radical are invoked as motives for the preferential addition of the nitrogen radical to the terminal double bond. Without addition of ligand, the internal diamination process is most likely to proceed, in a similar manner to the palladium(0)-catalyzed diamination. However, overall the regioselectivity is highly dependent on the counterion of the copper(I) catalyst and the nature of the diene.

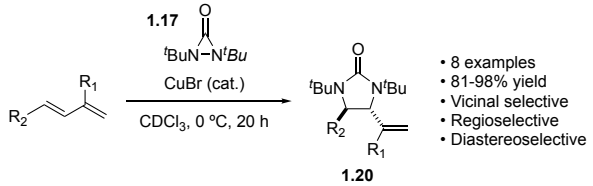
Around the same time as chemists were investigating the use of single metal species to activate mono olefins in conjugated diene systems, scholars were exploring opportunities to access dimetallated products. Specifically, the use of nickel catalysis provided the first example of this transformation. In 1972, Kumada and coworkers reported the nickel-catalyzed 1,4-disilylation of 1,3-dienes.[40] In the presence of $NiCl_2(PEt_3)_2$ and *sym*-tetramethyldisilane **1.24**, a small group of 1,3-dienes were transformed into 1,4-disilylated products **1.25** (Scheme 1.1.11). Later, Kumada and Tsuji developed palladium- and platinum-catalyzed variants of this process.[41,42] Although the disilylated products themselves are of insignificant synthetic value, the mechanistic discoveries presented by Kumada and others laid the groundwork for reactions such as silylboration and diboration of 1,3-dienes.[43-45]

Scheme 1.1.10

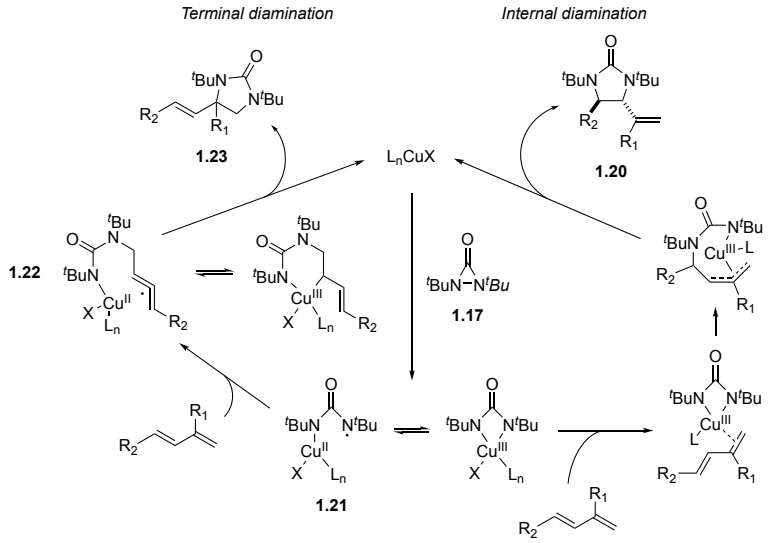
A: Shi, Copper(I)-catalyzed terminal diamination of 1,3-dienes



B: Shi, Copper(I)-catalyzed internal diamination of 1,3-dienes

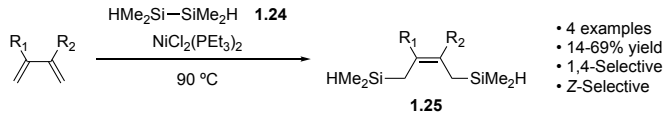


C: Shi, Mechanistic cycle for copper-catalyzed diamination of 1,3-dienes



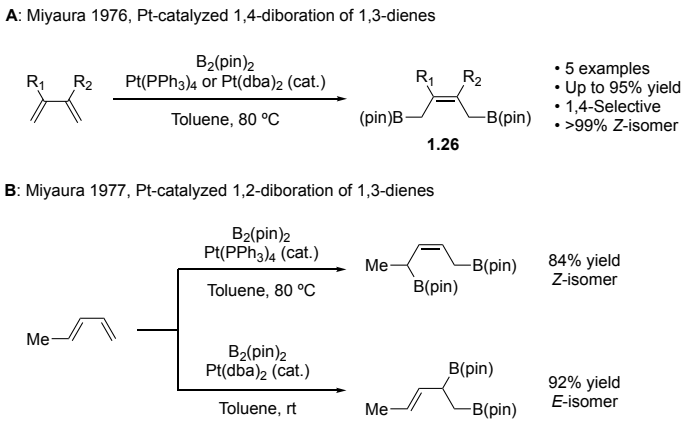
Scheme 1.1.11

Kumada, Nickel(II)-catalyzed 1,4-disilylation of 1,3-dienes



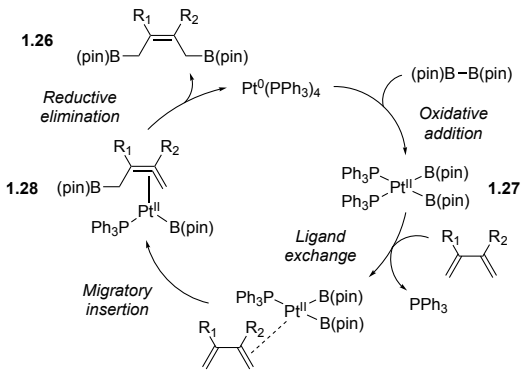
Particularly, the diboration of 1,3-dienes has attracted meaningful attention in recent years. Miyaura and coworkers first realized this transformation in 1996.[46] In the presence of catalytic $Pt(PPh_3)_4$, terminal 1,3-dienes undergo diboration to afford 1,4-diborylated products **1.26**, cleanly with extremely high *Z*-selectivity (>99% *Z*, Scheme 1.1.12A). When using $Pt(dba)_2$ as the catalyst, it is possible to form similar 1,4-diboration products. Unexpectedly, when 1,3-dienes containing an internal olefin, such as penta-1,3-diene, are employed then a change in selectivity is observed. Predominantly 1,2-diboration of the terminal olefin is obtained when $Pt(dba)_2$ is engaged as the catalyst in place of $Pt(PPh_3)_4$ (Scheme 1.1.12B).[47]

Scheme 1.1.12



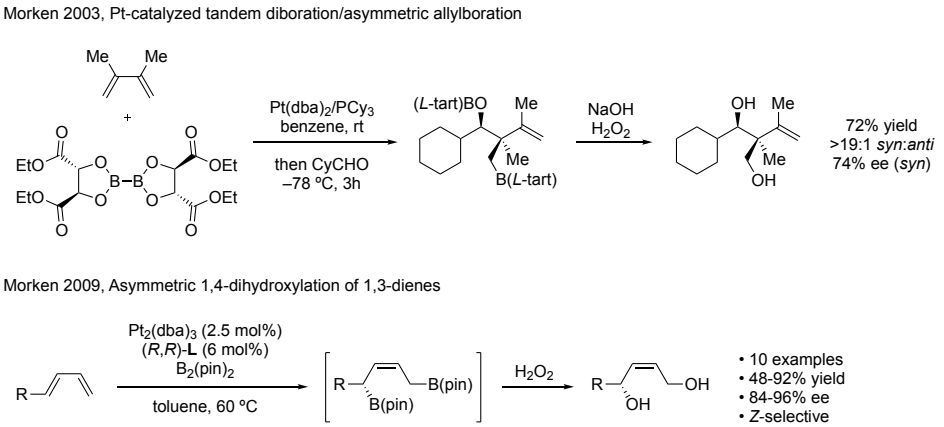
The mechanism proposed by Miyaura and others is widely accepted for all dimetallation reactions; this includes the nickel-catalyzed 1,4-disilylation of 1,3-dienes discovered by Kumada in 1972. The initial process within the catalytic cycle is oxidative addition of bis(pinacolato)diboron to $Pt(PPh_3)_4$, generating bis(boryl)platinum intermediate **1.27** (Scheme 1.1.13). Subsequent coordination and migratory insertion to the 1,3-diene generates π-allylplatinum complex **1.28**. This intermediate then undergoes reductive elimination to afford the desired (*Z*)-1,4-bis(boronate) **1.26**.

Scheme 1.1.13



A central drawback to this strategy of difunctionalization is the ability to control the reductive elimination. In the presence of $Pt(dba)_3$, which would normally be used to obtain the 1,2-diboration product, the researchers experience significant amounts of homodimerization of the π-allylplatinum intermediate. Furthermore, the inability to differentiate between both boron functional groups in the final product is a critical challenge that is necessary to render this synthetic process useful. Else, the scope of 1,3-dienes will be limited to symmetrical compounds. Nonetheless, the materials from this process are considerably more valuable than the 1,4-disilanes as they can be oxidized to afford 1,4-diols or used as allylboronate nucleophiles. Specifically work by Morken in the past 15 years has focused on developing asymmetric accounts of these methods (Scheme 1.1.14).[48-50] The addition of such findings also showcase the

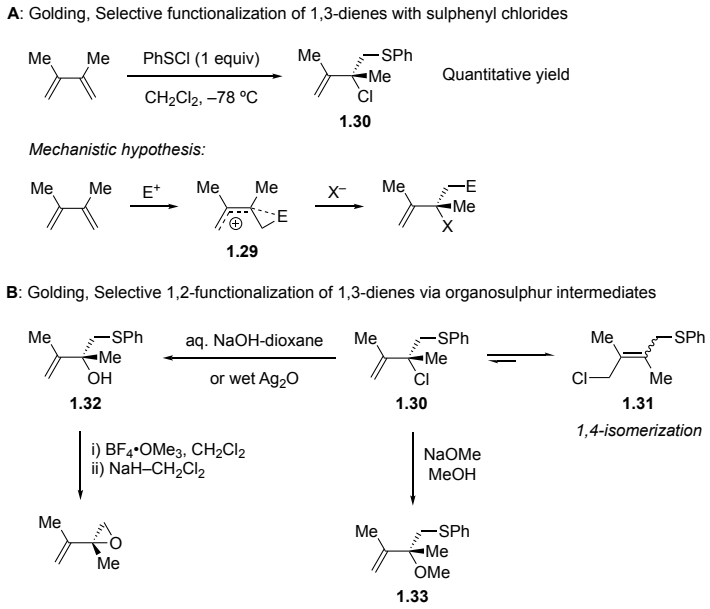
Scheme 1.1.14



potential for 1,4-diboration products as valuable intermediates in complex synthesis. Congruently, their group investigated a nickel-catalyzed method of 1,4-diboration, but they were unable to render the process enantioselective.[51]

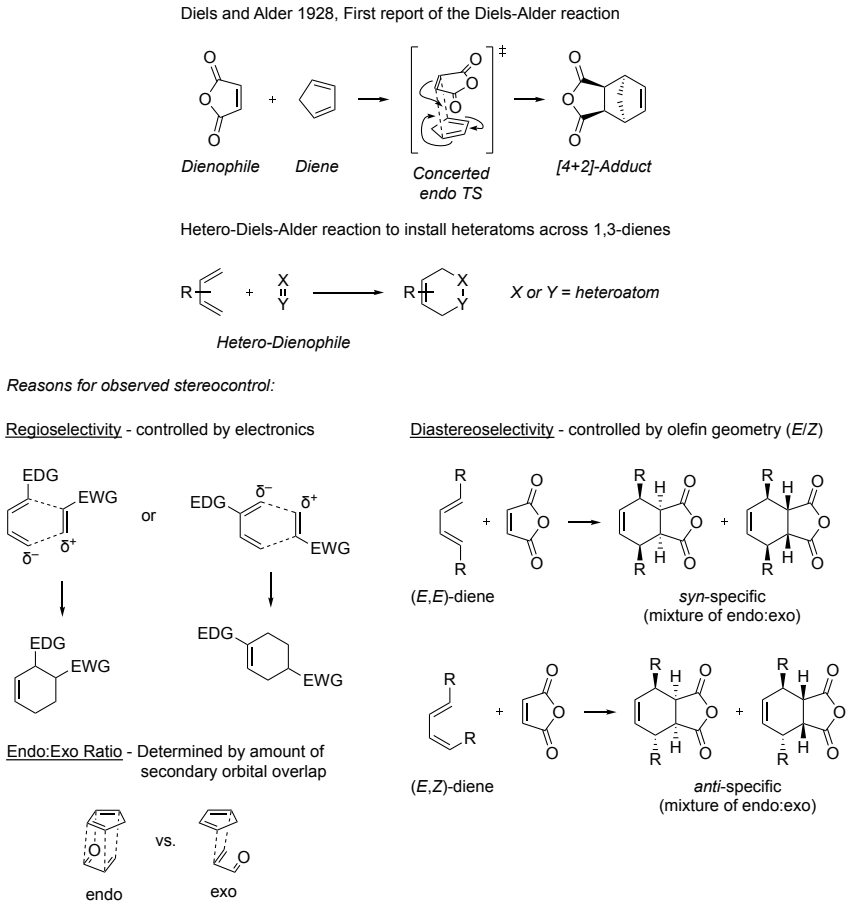
Branching away from the use of unfriendly, rare-earth metals there has been little investigation into the use of organic compounds to selectively functionalize 1,3-dienes with heteroatoms. Golding and colleagues developed an interesting method to selectively oxidize 1,3-dienes at the terminal position using sulphenyl chlorides.[52] The team hypothesized that a selective functionalization may be achieved if an electrophilic reagent, such as sulphenyl chloride, stabilizes a partially formed allyl cation transition state **1.29** *en route* to adduct **1.30** (Scheme 1.1.15A). It is known that benzenesulphenyl chloride reacts with 1,3-dienes to provide 1,2-adducts under kinetic conditions (rapid reaction at –78 ºC).[53-54] However, the adducts readily rearrange to thermodynamically stable 1,4-adducts **1.31** and they have rarely been utilized for synthetic purposes.[55] Golding and coworkers expanded the reach of these materials by developing methods to generate 1,2-oxysulphenylation **1.32** and 1,2-alkoxysulphenylation products **1.33** in good yield and regioselectivity (Scheme 1.1.15B).

Scheme 1.1.15



The final and most compelling method for functionalizing 1,3-dienes with heteroatoms is the Diels-Alder reaction. This [4+2]-cycloaddition reaction discovered by Otto Diels and Kurt Alder in 1928 has transformed the field of organic chemistry (Scheme 1.1.16).[56] The original report described by the scientists showcases a concerted cycloaddition between an all carbon diene and all carbon dieneophile. The advent of increased interest in the transformation led to multiple academic groups introducing heteroatoms in both the diene and dienophile.[57-58] These advancements provided the name of the transformation known today as the hetero-Diels-Alder reaction. The advantage of this reaction manifold is the ability to express extremely high regio- and diastereocontrol. The reason for this is the substrates themselves dictate the orientation of substituents and distribution of charge across the molecular orbital. The molecular orbitals are the main predictor of regioselectivity. Utilizing frontier molecular orbital theory, a chemist may

Scheme 1.1.16



develop predictions on which regioisomer will be predominant.[59] In a typical Diels-Alder reaction, the highest occupied molecular orbital (HOMO) of the diene reacts with the lowest unoccupied molecular orbital (LUMO) of the dienophile in a concerted fashion. Although stepwise mechanisms may also be possible in exceptional cases, a non-concerted mechanism is not considered a pericyclic reaction, thereby not a Diels-Alder reaction. When the dienophile itself is made up of two heteroatoms it provides a very secure route for installing functionality in a highly selective manner.

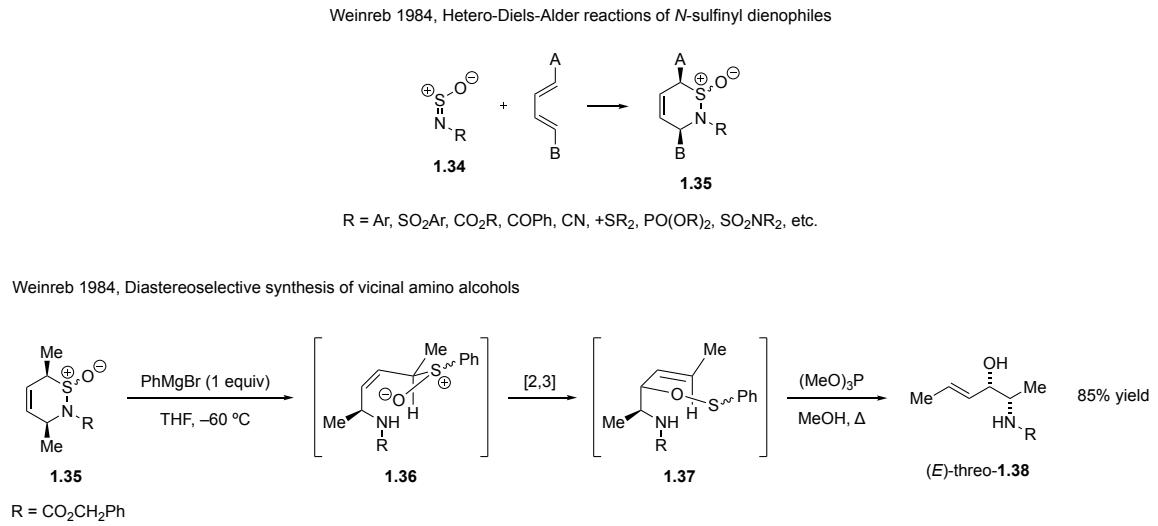
The drawbacks to the hetero-Diels-Alder reaction to install heteroatoms across 1,3-dienes are the need to use an often-contrived dienophile as well as the demand for meeting precise electronic requirements to deliver appropriate regioselection. Further, the product of the reaction is a 6-membered cycloadduct. These adducts are not (always) inherently useful and may need to be derivatized further to be of value. However, if these requirements are met the transformation benefits from remarkably high regio- and diastereocontrol contrasting countless other single-step procedures to install heteroatoms.

1.1.3 Weinreb Functionalizations

In 1984, Weinreb and colleagues reported the first diastereoselective synthesis of unsaturated vicinal amino alcohols and vicinal diamines from 1,3-dienes.[60-61] In the back-to-back studies they describe the use of sulfur imide derived dienophiles to functionalize 1,3-dienes via a hetero-Diels-Alder reaction. To obtain the vicinal amino alcohols, they employ *N*-sulfinyl dienophiles of type **1.34** reacting them with various dienes to provide dihydrothiazine oxide cycloadducts **1.35** (Scheme 1.1.17). These cycloadducts are highly electrophilic at sulfur owing to the extreme electron withdrawing capabilities of the *oxo*-group from dienophile **1.34**. Subjecting these unique adducts to one equivalent of phenylmagnesium bromide in THF at low temperature results in nucleophilic attack at sulfur with concomitant cleavage of the sulfur-nitrogen bond to access allylic sulfoxide **1.36**. Allylic sulfoxides are retrons of a Mislow-Evans-type rearrangement. Upon thermal [2,3]-rearrangement, this produces the vicinal amino alcohol functionality needed to reach the desired product. Final cleavage of the sulfur-oxygen bond in

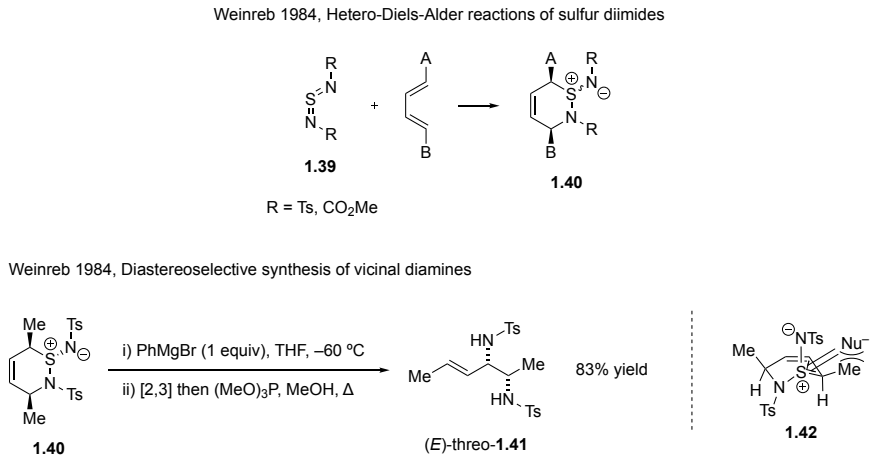
sulfenate ester **1.37** with trimethyl phosphite delivers the final product in 85% yield with (*E*)-*threo*-hydroxy carbamate **1.38** as the only detectable stereoisomer.

Scheme 1.1.17



Comparable to their synthesis of vicinal amino alcohols, Weinreb and colleagues employed sulfur diimide reagents **1.39** to access vicinal diamines (Scheme 1.1.18). The cycloadducts of diimide reagents are especially electrophilic due to the presence of two electron-

Scheme 1.1.18



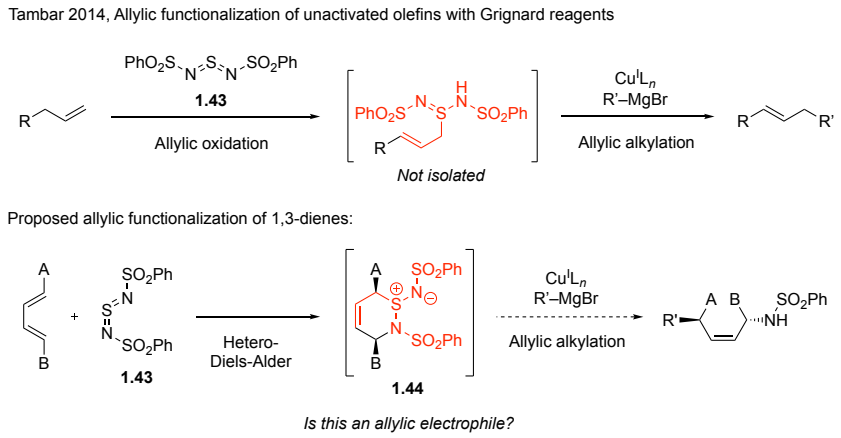
withdrawing functionalities. Subjecting 3,6-dihydrothiazine-1-imines **1.40** to one equivalent of Grignard reagent, followed by [2,3]-rearrangement, and treatment with trimethyl phosphite provides vicinal diamine **1.41**. Again, the (*E*)-threo configuration was obtained as a single stereoisomer in complete similarity to the vicinal amino alcohol protocol.

The advantage of both of these procedures is the high stereocontrol provided by the hetero-Diels-Alder reaction along with the concerted [2,3]-sigmatropic rearrangement. Fortunately, the presence of a sulfur stereocenter has no influence on the stereochemical outcome. However, it should be noted that the epimer of cycloadduct **1.40** was unable to provide product under nucleophilic Grignard conditions. Instead, it required the use of organolithium reagents, such as methyl lithium to overcome the presumed nucleophile-methyl torsional barrier in epimer **1.42**.

1.1.4 Tambar Aminoarylation

Our group became interested in the work completed by Weinreb during the course of our study on the allylic alkylation of unactivated olefins with sulfur diimide **1.43** (Scheme 1.1.19).[62] Specifically, we wanted to understand the reactivity of the sulfur diimide oxidant with other π-systems, such as 1,3-dienes. Based on the reports by Weinreb and others on the use of sulfur diimide reagents as dienophiles in hetero-Diels-Alder reactions,[60-61] we wondered if we could

Scheme 1.1.19

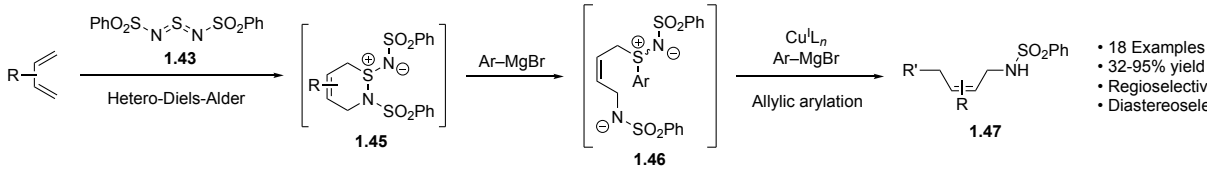


develop a concise, single-flask strategy to access new products beyond the scope of Weinreb's vicinal diamination procedure. In particular, we wanted to identify if the cycloadduct **1.44** is a potential source of an allylic electrophile. If so, one could envision a strategy that utilizes a copper-catalyzed allylic alkylation to generate a new carbon-carbon bond.

Reacting benzenesulfonyl sulfur diimide **1.43** with 1,3-diene, a spontaneous cyclization occurs providing [4+2] adduct **1.45** (Scheme 1.1.20). We hypothesized that the resulting adduct **1.45** could be converted to ring-opened intermediate **1.46** by one equivalent of Grignard reagent. This belief is in alignment with Weinreb's reported mechanism for vicinal diamination. Following successful ring opening, we are provided with an allylic electrophile comparable to the allylic alkylation procedure developed previously by our lab. Conducting a copper-catalyzed allylic alkylation utilizing additional aryl Grignard reagent would provide aminoarylation product **1.48**. This concise, single-flask operation was determined to be effective providing a wide variety of aminoarylation products (18 examples) in 32-95% yield with good 1,4-regioslectivity and excellent *Z*-olefin specificity.[63]

Scheme 1.1.20

Tambar 2014, Regioselective and diastereoselective aminoarylation of 1,3-dienes



1.2 The Development of a Copper-Catalyzed Aminothiolation of 1,3-Dienes

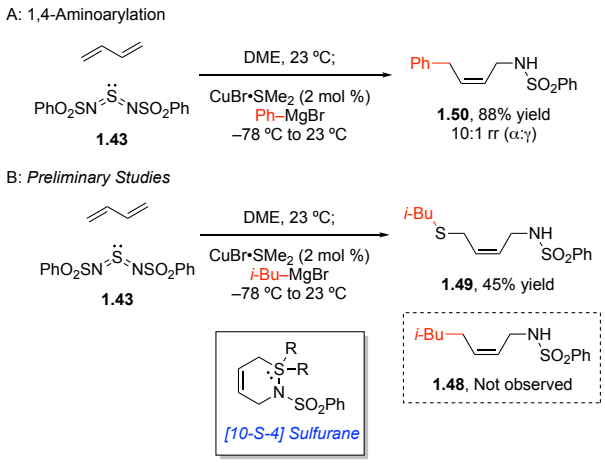
1.2.1 Preliminary Results

We were interested in developing efficient approaches to heteroatom-containing molecules by taking advantage of the unique reactivity of sulfur diimide reagents. Ideally, we wanted to generate these products from inexpensive and abundant starting materials, like 1,3-

dienes. In the course of examining the copper-catalyzed reaction between dienes, sulfur diimide **1.43**, and aryl Grignard reagents (Scheme 1.2.1A), we discovered an exciting product when we employed alkyl Grignard reagents (Scheme 1.2.1B).[4] Instead of generating the anticipated allylic sulfonamides **1.48**, we observed the formation of sulfur-containing allylic sulfonamides **1.49**.

In this chapter, we report the optimization of this process, an exploration of the substrate scope, and the examination of the unprecedented mechanism that proceeds through a reductive elimination from a [10-S-4] sulfurane intermediate.[64] This transformation represents the first example of generating aminothiols directly from dienes. It is also the first copper-catalyzed generation of a highly reactive [10-S-4] sulfurane; which provides a mild method for accessing multifunctional products that contain sulfur and nitrogen. By incorporating the unique reactivity of tetrasubstituted sulfuranes into a transition metal catalytic cycle, we anticipate future opportunities for exploring metal-mediated reactions that take advantage of sulfurane chemistry.

Scheme 1.2.1



In a preliminary investigation, we determined that our conditions for the metal-catalyzed 1,4-aminoarylation of 1,3-dienes with aryl Grignard reagents (Scheme 1.2.1A) does permit the aminothiolation of dienes with alkyl Grignard reagents; however, the yield of the desired product is modest. Nonetheless, through optimization of the appropriate reaction parameters we were able to develop a method to supply the desired aminothiolation product **1.49** in high-yield (94% isolated yield), under mild conditions via a single-flask operation (Table 1.2.1, entry 1). It should

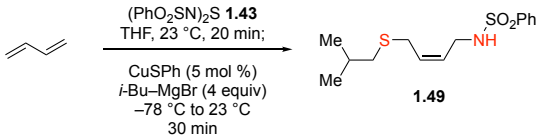
be noted, that the optimized conditions do not provide an observable quantity of the undesired aminoalkylation product **1.48**. This highlights a clear distinction between the aminoalkylation and aminothiolation processes; something that will be discussed in greater detail later in the chapter.

1.2.2 Optimization

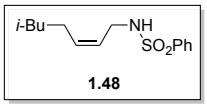
We began our optimization by identifying an efficient solvent for this process. The use of diethyl ether, an acyclic ethereal solvent, had a deleterious affect on the procedure (Table 1.2.1, entry 2). This may be attributed to the poor solubility of benzenesulfonyl sulfur diimide **1.43** in diethyl ether. Instead the use of 1,4-dioxane, a cyclic ethereal solvent, gave improved yet modest yield (entry 3). Less common solvents, still compatible with Grignard reagents, such as dichloromethane and toluene (entries 4-5) presented the desired product with only minor improvements over 1,4-dioxane. Surprisingly, tetrahydrofuran exhibited a unique affect, furnishing the desired aminothiolation product **1.49** in high yield and was therefore chosen as the optimal solvent. To verify the importance of copper(I) thiophenolate upon this process, a series of copper(I) and copper(II) sources were screened (entries 6-11). Neither oxidation state of copper appeared to have a significant effect on the yield of the reaction. Notably, a decreased catalyst loading from 5 mol % to 2 mol % of copper(I) thiophenolate was achieved – albeit with a minor sacrifice in yield (entry 12). To reaffirm the need for copper, a control reaction was implemented (entry 13). Remarkably, no aminothiolation product was observed without copper under the optimized conditions. Alternatively, no aminoalkylation product **1.48** was observed. Last but not least, an equivalents screen of isobutylmagnesium bromide was conducted. With only one equivalent of isobutylmagnesium bromide a trace amount of the desired aminothiolation product **1.49** was observed (entry 16). Instead, a majority of the intermediate [4+2] cycloadduct (prepared in the hetero-Diels-Alder/first step of the single-flask operation) was recovered. In addition, a newly observed intermediate **1.52** was isolated. Increasing to two equivalents of Grignard reagent revealed incomplete conversion as well (entry 15). With two equivalents of Grignard reagent, greater quantities of both the newly observed intermediate **1.52** and the desired aminothiolation product **1.49** were isolated. Three equivalents of Grignard

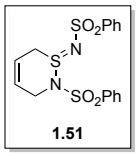
reagent enabled full conversion to the desired product, excluding the newly observed intermediate **1.52** (entry 14). This information further indicated compound **1.52** might be an intermediate of the reaction. Four equivalents of isobutylmagnesium bromide were settled on for the optimized conditions due to the greater efficiency of the reaction, providing much higher yield.

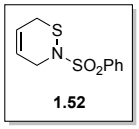
Table 1.2.1



Entry	Change from Standard Conditions	Yield (%)[a]
1	none	94
2	Et_2O instead of THF	53
3	1,4-Dioxane instead of THF	76
4	CH_2Cl_2 instead of THF	82
5	Toluene instead of THF	81
6	CuCN instead of CuSPh	77
7	CuBr instead of CuSPh	89
8	CuI instead of CuSPh	72
9	$CuBr_2$ instead of CuSPh	87
10	$Cu(OTf)_2$ instead of CuSPh	74
11	Li_2CuCl_4 instead of CuSPh	44
12	2 mol% CuSPh	85
13	No Cu	None
14	3 equiv of *i*-Bu-MgBr	80
15	2 equiv of *i*-Bu-MgBr	20[b]
16	1 equiv of *i*-Bu-MgBr	4[c]







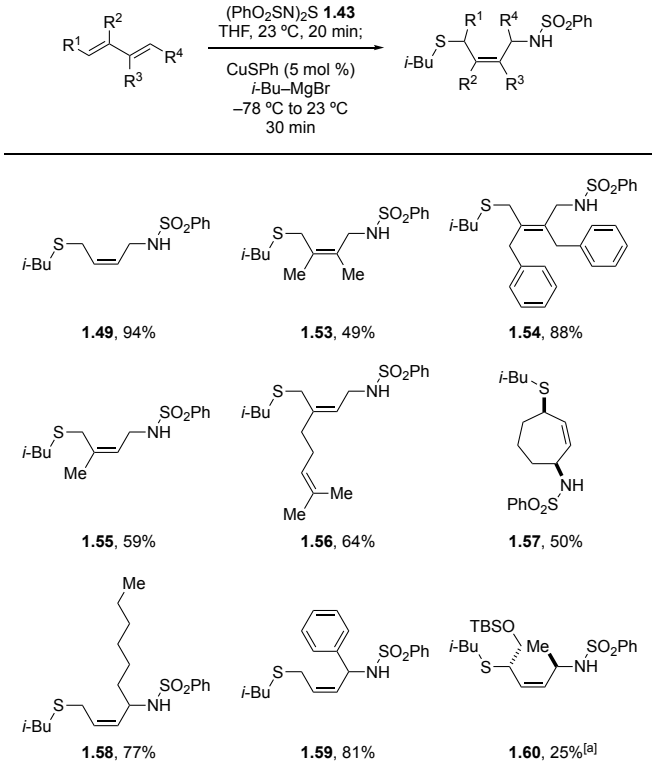
Reaction conditions. Sulfur diimide **1.43** (1 mmol, 1 equiv), THF (0.2 M), 1,3-butadiene (sparge for 10 min and then stir for 10 min at 23 ºC); CuSPh (5 mol %), cool to –78 ºC, *i*-Bu–MgBr (4 equiv), then 23 ºC for 30 min. [a] Isolated yield. [b] 40% yield of intermediate **1.52**. [c] 16% yield of intermediate **1.52** and 42% yield of recovered [4+2] adduct **1.51**.

1.2.3 Scope of the 1,4-Aminothiolation of 1,3-Dienes

With optimal reaction conditions in hand for the aminothiolation of 1,3-dienes with alkyl Grignard reagents, we explored the diene scope of this process (Scheme 1.2.2). As expected, the

di-functionalization of symmetrical olefins ran smoothly with no challenges in regioselectivity. Substitution in the 2,3-position of the diene was well tolerated leading to 2,3-dibenzyl aminothiolation product **1.54** in high yield and 2,3-dimethyl aminothiolation product **1.53** in moderate yield. Symmetrical cyclic olefins were also tolerated, such as 1,3-cycloheptadiene, affording aminothiolation product **1.57** in moderate yield. Unsymmetrical substrates were predicted to provide di-functionalization in a regioselective manner. Expressly owing to the first step of this single-flask operation, which incorporates a hetero-Diels-Alder reaction between the 1,3-diene and sulfur diimide **1.43**. The regioselectivity can be rationalized by frontier molecular orbital analysis of the concerted [4+2] cycloaddition.[59] Selective formation of a single regioisomer when utilizing 4-substituted dienes provided support for this argument. Examples of this include the *n*-hexyl and phenyl substituted aminothiolation products (**1.58** and **1.59**) formed in 77% and 81% yield, respectively. Unsymmetrical dienes with substitution at the 2-postion also

Scheme 1.2.2

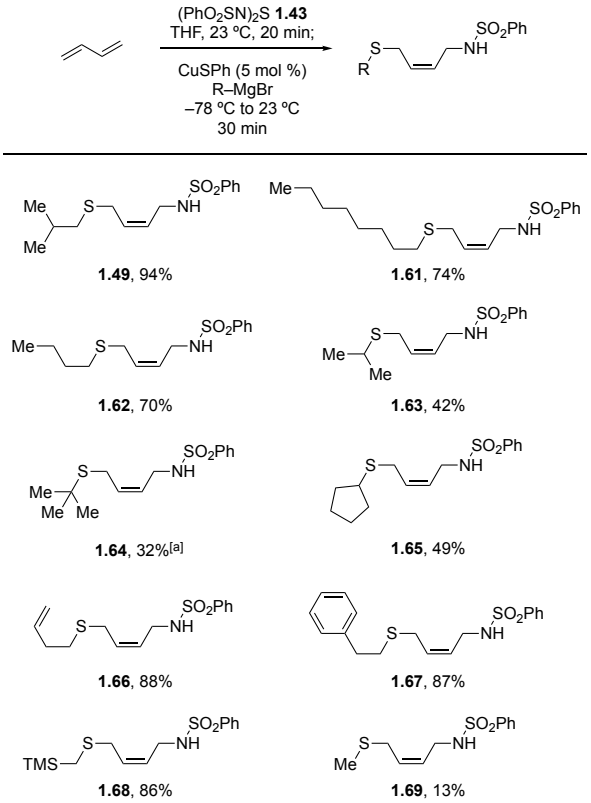


Reaction conditions: Sulfur diimide **1.43** (1 equiv), THF (0.2 M), 1,3-diene (1.5 equiv), 20 min at 23 ºC; CuSPh (5 mol %), cool to -78 ºC, *i*-Bu–MgBr (4 equiv), then 23 ºC for 30 min. Isolated yield. [a] Two-pot procedure. Isolated yield over 2 steps.

followed this logic, leading to corresponding 2-substituted aminothiolation products in good yield (**1.55** and **1.56**). Unfortunately, substitution at the 1-postion was not well tolerated. It is hypothesized that substitution at this position (α-carbon next to sulfur in the [4+2] adduct) increases steric bulk around sulfur making it difficult for the Grignard reagent to attack sulfur directly (refer to Scheme 1.2.4a). In spite of this, we were able to convert complex 1,3-diene, tertbutyldimethylsilyl protected sorbic alcohol **S1.4**, into the desired aminothiolation product **1.60** with acceptable yield and complete regio- and diasteroselectivity. We believe this showcases the potential utility of this transformation for late stage functionalization. Notably, the *Z*-olefin geometry and 1,4-diasteroselectivity in the aminothiolation products is retained upon opening the [4+2] cycloadduct with Grignard reagent.

Next, we examined the scope of alkyl Grignard reagents applicable to this highly efficient protocol for the aminothiolation of 1,3-dienes (Scheme 1.2.3). Primary alkyl Grignards are well

Scheme 1.2.3



Reaction conditions: Sulfur diimide **1.43** (1 equiv), THF (0.2 M), 1,3-butadiene (sparge for 10 min and then stir for 10 min at 23 ºC); CuSPh (5 mol %), cool to -78 ºC, Grignard reagent (4 equiv), then 23 ºC for 30 min. Isolated yield. [a] Two-pot procedure. Isolated yield over 2 steps.

suited for this process providing access to long chain octyl (**1.61**) and butyl (**1.62**) products with good yields. Fortuitously, primary alkyl Grignards with diverse, yet common, functional groups such as phenethyl (**1.67**), butenyl (**1.66**), and trimethylsilyl methyl (**1.68**) provided even higher yields of the desired aminothiolation products. Secondary alkyl Grignard reagents were also well tolerated in this process, such as isopropyl (**1.63**) and cyclic cyclopentyl (**1.65**). Unfortunately, sterically encumbered Grignard reagents such as tert-butyl Grignard (**1.64**) are not well suited for this transformation, providing only modest yield. We hypothesize that this phenomenon may be attributed to the challenge of sterically bulky Grignard reagents to generate a [10-S-4] sulfurane, such as **1.70** (Scheme 1.2.4A).

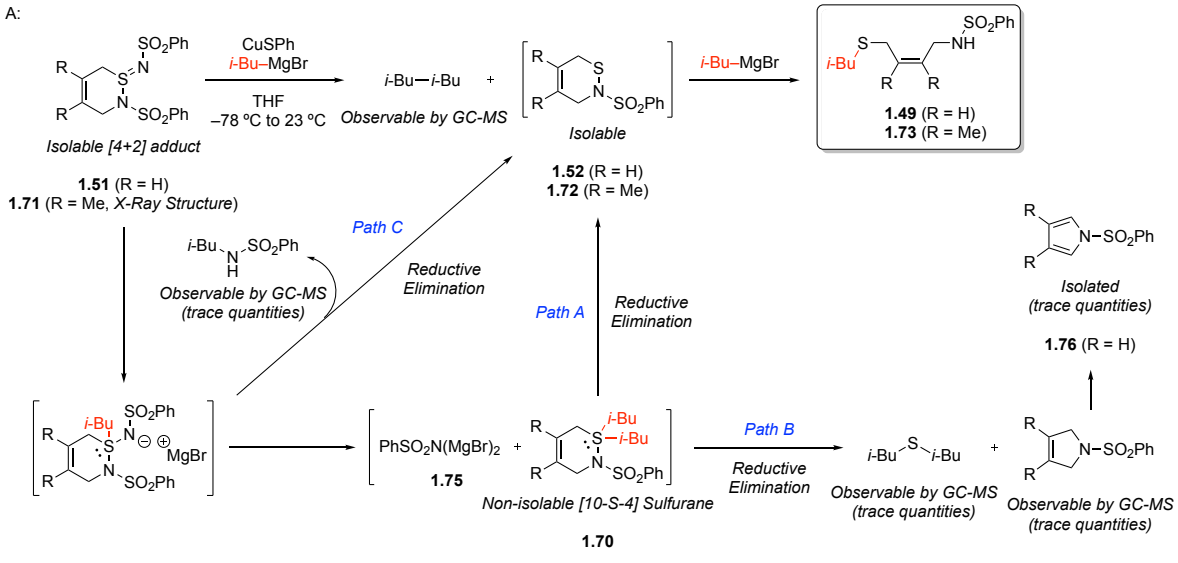
1.2.4 Mechanistic Investigation

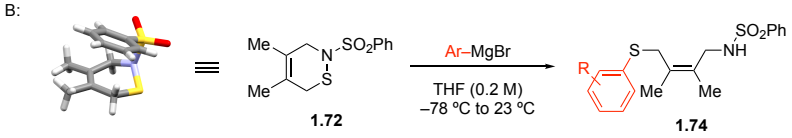
With respect to the mechanism of the aminothiolation of 1,3-dienes, we hypothesize that the reaction proceeds through the copper-catalyzed formation of a highly reactive [10-S-4] sulfurane (**1.70**, Scheme 1.2.4A). To provide support for our mechanistic proposal in Scheme 1.2.4A, we isolated the hetero-Diels-Alder [4+2] adducts **1.51** and **1.71**. Normally, these [4+2] cycloadducts are generated in-situ under the one-pot optimized conditions presented in Table 1.2.1, entry 1. However, isolation of these products permitted us to disregard any side products that may be produced in the first step of this overall process. Taking note of the control reaction (Table 1.2.1, entry 13), without copper-catalyst, no product **1.49** or intermediate **1.52** were observed. Subjecting [4+2] cycloadducts **1.51** and **1.71** to less than three equivalents of isobutylmagnesium bromide in the presence of catalytic copper(I) thiophenolate afforded a mixture of 2-benzenesulfonyl-3,6-dihydrothiazine intermediate (**1.52** or **1.72**) and aminothiolation product (**1.49** or **1.73**), similar to Table 1.2.1, entries 15 and 16. To provide evidence that dihydrothiazine **1.72** could be an intermediate in this aminothiolation procedure, it was isolated and resubjected to nucleophilic Grignard reagent conditions. After changing a series of reaction parameters, including catalyst addition/removal and equivalents of Grignard reagent, it was uncovered that the process to convert 2-benzenesulfonyl-3,6-dihydrothizaine **1.52** or **1.72** to the aminothiolation product requires exactly one equivalent of Grignard reagent. More intriguing, is that it does not require addition of catalyst. To confirm the exact structure of this

newly discovered product, a crystal structure was obtained utilizing the dimethyl compound **1.72**, which formed a nice solid as compared to compound **1.52**.

To take advantage of the nuanced reactivity of sulfur and nitrogen in this newly discovered intermediate, we designed a crossover experiment using aryl Grignard reagents, which previously were thought to provide aminoarylation products such as **1.50**, not aminothiolation products (Scheme 1.2.1A). Incredibly, one equivalent of an aryl Grignard in the absence of copper-catalyst converted dimethyl intermediate **1.72** to the desired aryl aminothiolation product **1.74** in near quantitative yield (98% isolated yield, Scheme 1.2.4B, entry 1). Moreover, the reaction was very tolerant to the addition of electron-donating (entry 2) and electron-withdrawing (entry 3) groups located on the aryl ring in the Grignard reagent providing similar yields of 96% and 99%, respectively.

Scheme 1.2.4





Entry	R	Yield (%)[a]
1	H	98
2	4-Methoxy	96
3	3,5-Bis(trifluoromethyl)	99

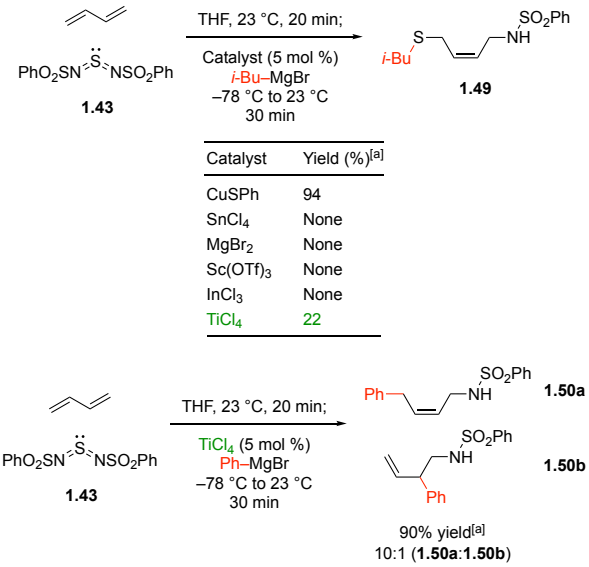
Reaction conditions: Dimethyl intermediate **1.72** (0.2 mmol, 1 equiv), THF (0.2 M), cool to -78 °C, Ar–MgBr (1 equiv), then 23 °C for 30 min. [a] Isolated yield.

Based off our early experience in optimization of the one-pot process for the aminothiolation of 1,3-dienes, we know that a minimum of three, full equivalents of Grignard reagent are required to reach complete conversion to the desired aminothiolation product (Table 1.2.1, entry 14). We also know that copper-catalyst is required to produce any amount of product, therefore we hypothesized that two equivalents of alkyl Grignard reagent in combination with copper catalyst are necessary to generate the dihydrothiazine intermediate **1.52** or **1.72**. This type of proposal led us to suggest a [10-S-4] sulfurane intermediate such as **1.70** (Scheme 1.2.4A). Work by Oae and others on the nucleophilic attack of Grignard reagents at sulfinyl centers to form metastable [10-S-4] σ-sulfuranes,[65-69] provides mechanistic support for the possibility of this unique, first of its kind tetrasubstitued [10-S-4] sulfurane with three σ S-C(sp^3) bonds and one σ S-N bond. To further validate our suspicions, we considered the evolution of by-products from a pathway converting sulfurane **1.70** to dihydrothiazine intermediate **1.52** or **1.72** (Path A, Scheme 1.2.4A) and attempted to detect these by-products using GC-MS. To our astonishment, our hypotheses were correct. The diisobutyl coupled by-product formed by reductive elimination of two Grignard equivalents off sulfurane intermediate **1.70** was detected in large quantities in the crude solution of the one-pot aminothiolation reaction. Additionally, by-products from alternate pathways of reductive elimination such as Path B or C were also detected, albeit in trace quantities. Attempts were made to observe the [10-S-4] sulfurane directly, but to no avail, owing in part to the instability of these complexes at temperatures greater than -45 ºC.[70-72]

A lasting piece of information that supports this mechanistic proposal is the isolation of benzenesulfonamide. One full equivalent of benzenesulfonamide is isolated after purification. This product is presumably generated upon workup of the di-anion **1.75** produced during the formation of sulfurane **1.70**. This enabled us to develop a final working hypothesis. Specifically, we needed to understand the role copper plays in constructing the [10-S-4] sulfurane **1.70**. To explain this phenomenon, we hypothesized that copper(I) thiophenolate acts as a Lewis acid, coordinating to the sulfilimine in the [4+2] cycloadduct increasing the leaving group ability of benzenesulfonamide as a di-anion. To test this hypothesis, we screened a series of Lewis acids incapable of participating in redox pathways and recorded their reactivity. It is also required that these metals do not form alkyl-metal species with the alkyl Grignard reagent (i.e. – alkylcuprates in the case of copper). Several Lewis acids, such as $SnCl_4$, $MgBr_2$, $Sc(OTf)_3$, $InCl_3$ were

screened for their ability to enhance product formation in place of a copper-catalyst (Scheme 1.2.5). None of these metals enabled measurable product formation. Interestingly, however, when titanium(IV) tetrachloride was employed, the reaction furnished approximately 22% isolated yield of the desired aminothiolation product exposing that this method may in fact be a Lewis acid assisted process. Moreover, when utilizing aryl Grignard reagents in the presence of catalytic titanium(IV) tetrachloride, exclusively the aminoarylation products **1.50a** and **1.50b** are obtained, with excellent yield (90% isolated yield) and high selectivity (10:1, linear:branched, σ:γ) analogous to our previous findings with copper catalysts. This supports the previous statement that both products are made through different mechanisms. However, it also suggests that both mechanisms may be Lewis acid assisted. We hypothesize that generation of the aminoarylation products is a result of aryl Grignard reagents displaying a partial preference for nucleophilic substitution (S_N1 or S_N2) at carbon instead of sulfur. The inverse may be said about alkyl Grignard reagents.

Scheme 1.2.5



Catalyst	Yield (%)[a]
CuSPh	94
$SnCl_4$	None
$MgBr_2$	None
$Sc(OTf)_3$	None
$InCl_3$	None
$TiCl_4$	22

Reaction conditions. Sulfur diimide **1.43** (1 mmol, 1 equiv), THF (0.2 M), 1,3-butadiene (sparge for 10 min and then stir for 10 min at 23 ºC); Catalyst (5 mol %), cool to -78 ºC, Grignard reagent (4 equiv), then 23 ºC for 30 min. [a] Isolated yield.

1.2.5 Conclusion

In conclusion, we have developed a concise, one-pot method for the aminothiolation of 1,3-dienes. This difunctionalization strategy installs remote sulfur and nitrogen functionality with extremely high regio- and diastereocontrol. Furthermore, the mild reaction conditions enable a broad use of alkyl Grignard reagents and substituted 1,3-dienes. Mechanistic investigation leads us to believe that this transformation proceeds through an unprecedented Lewis acid catalyzed generation of a [10-S-4] sulfurane. Taking advantage of the distinct ability of these tetrasubstituted [10-S-4] sulfuranes to reductively eliminate, we uncovered the formation of a unique, isolable dihydrothiazine intermediate, which may be converted to aminothiols in one step via nucleophilic addition of a Grignard reagent. To the best of our knowledge, this transformation represents two firsts: not only the first Lewis acid catalyzed generation of a [10-S-4] sulfurane, but also the first direct aminothiolation of 1,3-dienes.

1.3 Experimental Section

1.3.1 General Information

All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring unless otherwise indicated. Commercially obtained reagents were used as received. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. All reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). All flash chromatography purifications were performed on a Teledyne Isco CombiFlash® Rf unless otherwise indicated. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian Inova-400 and -500 spectrometers. Data for ^{1}H-NMR spectra are reported relative to chloroform as an internal standard (7.26 ppm) and are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C-NMR spectra are reported relative to chloroform as

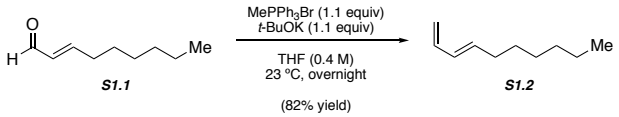
an internal standard (77.16 ppm) and are reported in terms of chemical shift (δ ppm). Infrared spectra were recorded on a Perkin-Elmer 1000 series FTIR. ESI-LRMS data were recorded on an AB Sciex QTRAP® 4500 LC-MS. HRMS data were obtained at the Scripps Center for Mass Spectrometry. X-ray diffraction data was obtained by Dr. Vincent Lynch at the X-ray Diffraction Lab at The University of Texas at Austin.

1.3.2 Grignard Reagents

All Grignard reagents were purchased from Sigma-Aldrich.

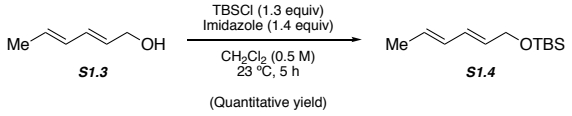
1.3.3 1,3-Dienes

Trans-1,3-decadiene **S1.2** and *tert*-butyldimethylsilyl protected sorbic alcohol **S1.4** were synthesized via the procedures below. All other 1,3-dienes in Table 2 were purchased from Sigma-Aldrich. Diene **S1.2** was synthesized via a reported procedure.[73] Spectroscopic data for diene **S1.2** was identical to the reported data in the literature.

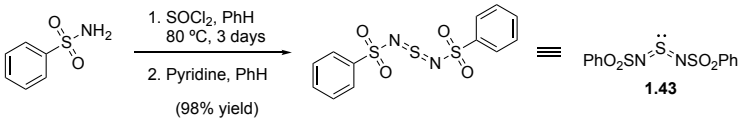


*Diene **S1.4** was synthesized by the following procedure:* A flame-dried 100 mL round bottom flask, under argon, was charged with *trans,trans*-2,4-hexadien-1-ol **S1.3** (1.0 g, 10.2 mmol, 1 equiv) and dichloromethane (20.4 mL, 0.5 M). The mixture stirred at 23 ºC until homogenous, then was treated with imidazole (971.2 mg, 14.3 mmol, 1.4 equiv) and TBSCl (2.0 g, 13.3 mmol, 1.3 equiv), respectively. The resulting mixture was stirred at 23 ºC for 5 h (monitor completion by TLC, 1:1 hexanes:ethyl acetate). Upon completion, the reaction was quenched by the addition of saturated aqueous NH_4Cl (8 mL). The aqueous layer was extracted three times with dichloromethane (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by

flash chromatography (gradient eluent hexanes:ethyl acetate) to afford the desired product, *tert*-butyldimethylsilyl protected sorbic alcohol **S1.4** as a clear, colorless oil (2.16 g, Quantitative yield). Spectroscopic data for diene **S1.4** was identical to the reported data in the literature.[74]



1.3.4 Synthesis of Benzenesulfonyl Sulfur Diimide

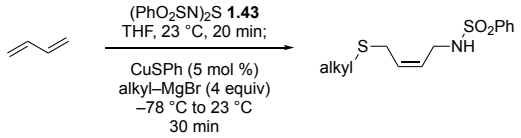


Our procedure was modified from a method reported in the literature for the synthesis of similar arylsulfonyl sulfur diimides[75]: A solution of benzenesulfonamide (50 g, 0.318 mol) and $SOCl_2$ (80 mL, 1.1 mol) in benzene (30 mL) was refluxed at 80 ºC for 3 days (over the course of the reaction, the mixture became a clear solution). When the starting material was consumed by ^{1}H-NMR analysis of an aliquot, the mixture was concentrated under vacuum to remove benzene and excess $SOCl_2$. Trace amounts of $SOCl_2$ were removed by dissolving the residue in toluene (50 mL), concentrating under reduced pressure, and storing under vacuum at 50 ºC for 6 h. The residue was then treated with benzene (70 mL) and heated slightly to ensure all material dissolved in the solvent. Once the solution was cooled to 23 ºC, pyridine (0.5 mL) was added, and the mixture was stirred. After 12 h, stirring was ceased, and a yellow precipitate crystallized slowly from the solution. The precipitate was separated by vacuum filtration and stored under vacuum at 50 ºC for 8 h. Benzenesulfonyl sulfur diimide **1.43** was obtained as a yellow solid (53.5 g, 98% yield). *Since benzenesulfonyl sulfur diimide **1.43** is sensitive to water, we store it in a glovebox inside a sealed flask that has been purged with argon.*

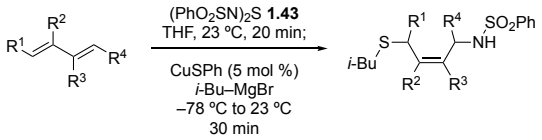
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.67 (t, *J* =8.0 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 137.9, 135.0, 129.6, 128.3. **IR (□ cm^{-1})** 3348, 3255, 1557, 1332, 1159.

*Although we continue to synthesize benzenesulfonyl sulfur diimide **1.43** in our lab, Sigma-Aldrich has decided to commercialize this reagent based on conversations with our group about its synthetic utility (Catalog #L511390, $25/gram).*

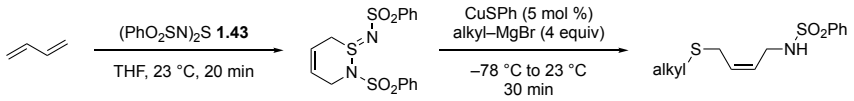
1.3.5 General Procedures for the Aminothiolation of Dienes



*One-pot procedure for the aminothiolation of 1,3-butadiene (**Method A**):* An oven-dried 25 mL reaction flask was charged with benzenesulfonyl sulfur diimide **1.43** (342.4 mg, 1 mmol, 1 equiv) within the glovebox. The flask was septa sealed, removed from the glovebox, and placed under a stream of argon. THF (5 mL, 0.2 M) was added to the flask and the mixture stirred at 23 ºC until the solid dissolved fully. Next, 1,3-butadiene was sparged into the solution at 23 ºC while venting directly to the atmosphere. The reaction mixture was sparged for 10 min. After, the sparging was ceased and the reaction mixture was placed back under a stream of argon. The mixture stirred for an additional 10 min at 23 ºC. CuSPh (8.6 mg, 0.05 mmol, 5 mol %) was added in one portion at 23 ºC. Immediately after addition of CuSPh, the reaction flask was cooled to -78 ºC. Grignard reagent (4 mmol, 4 equiv) was added in one portion, moderate-fast speed. Once addition was complete, the reaction flask was warmed to 23 ºC and stirred for 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (gradient eluent hexanes:ethyl acetate).



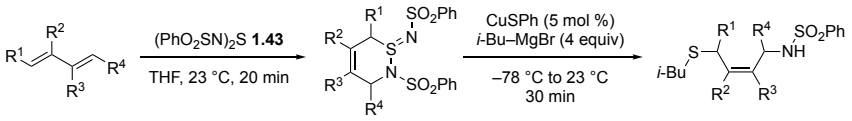
*One-pot procedure for the aminothiolation of substituted 1,3-dienes (**Method B**):* An oven-dried 25 mL reaction flask was charged with benzenesulfonyl sulfur diimide **1.43** (342.4 mg, 1 mmol, 1 equiv) within the glovebox. The flask was septa sealed, removed from the glovebox, and placed under a stream of argon. THF (5 mL, 0.2 M) was added to the flask and the mixture stirred at 23 ºC until the solid dissolved fully. Next, 1,3-diene (1.5 mmol, 1.5 equiv) was added in one portion at moderate-fast speed. The mixture stirred for 20 min at 23 ºC. After 20 min, CuSPh (8.6 mg, 0.05 mmol, 5 mol %) was added in one portion. Immediately after addition of CuSPh, the reaction flask was cooled to -78 ºC and isobutylmagnesium bromide (2.0 mL, 4 mmol, 4 equiv, 2.0 M in Et_2O) was added in one portion, moderate-fast speed. Once addition was complete, the reaction flask was warmed to 23 ºC and stirred for 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted three times with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (gradient eluent hexanes:ethyl acetate).



*Two-pot procedure for the aminothiolation of 1,3-butadiene (**Method C**):* An oven-dried 25 mL reaction flask was charged with benzenesulfonyl sulfur diimide **1.43** (342.4 mg, 1 mmol, 1 equiv) within the glovebox. The flask was septa sealed, removed from the glovebox, and placed under a stream of argon. Dichloromethane (5 mL, 0.2 M) was added to the flask and the mixture stirred at 23 ºC until the solid dissolved fully. Next, 1,3-butadiene was sparged into the solution at 23 ºC while venting directly to the atmosphere. The reaction mixture was sparged for 10 min. After, the sparging was ceased and the reaction mixture was placed back under a stream of argon. The mixture stirred for an additional 10 min at 23 ºC. The mixture was concentrated under reduced pressure and purified by flash chromatography (gradient eluent hexanes:ethyl acetate) to yield [4+2] adduct **1.51** as a white solid: **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.6, 2H), 5.95 – 5.89 (m, 1H), 5.81 – 5.76 (m, 1H), 4.14 – 4.08 (m, 1H), 4.00 – 3.94 (m, 1H), 3.76 – 3.69 (m, 1H), 3.35 – 3.28 (m, 1H). **^{13}C-NMR** (100 MHz,

$CDCl_3$) δ 143.46, 136.86, 134.65, 131.94, 129.79, 128.88, 128.28, 126.32, 124.25, 115.31, 47.72, 39.08. **LRMS (ESI) calcd for $[C_{16}H_{17}N_2O_4S_3]^+$ ($[M+H]^+$):** 396.03, found 397.00.

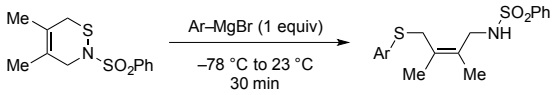
A septum sealed and flame-dried reaction flask, under argon, was charged with [4+2] adduct **1.51** (1 equiv), THF (0.2 M), and CuSPh (5 mol %) at 23 ºC. Next, the flask was cooled to -78 ºC and Grignard reagent (4 equiv) was added in one portion, moderate-fast speed. Once addition was complete, the reaction flask was warmed to 23 ºC and stirred for 30 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted three times with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (gradient eluent hexanes:ethyl acetate).



*Two-pot procedure for the aminothiolation of substituted 1,3-dienes (**Method D**):* An oven-dried 25 mL reaction flask was charged with benzenesulfonyl sulfur diimide **1.43** (1 equiv) within the glovebox. The flask was septa sealed, removed from the glovebox, and placed under a stream of argon. THF (0.2 M) was added to the flask and the mixture stirred at 23 ºC until the solid dissolved fully. Next, 1,3-diene (1.5 equiv) was added in one portion at moderate-fast speed. The mixture stirred for 20 min at 23 ºC to reach full conversion to [4+2] adduct, or until the reaction appeared to stall (monitored by TLC 1:1 hexanes:ethyl acetate). The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (gradient eluent hexanes:ethyl acetate) to yield the desired [4+2] adduct.

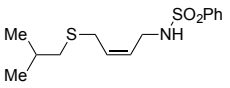
A septum sealed and flame-dried 25 mL reaction flask, under argon, was charged with [4+2] adduct (1 equiv), THF (0.2 M), and CuSPh (5 mol %) at 23 ºC. Next, the flask was cooled to -78 ºC and isobutylmagnesium bromide (4 equiv., 2.0 M in Et_2O) was added in one portion, moderate-fast speed. Once addition was complete, the reaction flask was warmed to 23 ºC and stirred for 30 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted three times with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced

pressure. The crude material was purified by flash chromatography (gradient eluent hexanes:ethyl acetate).



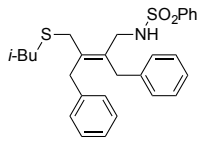
*General procedure for the aminothiolation of 2,3-dimethyl-1,3-butadiene with aryl Grignard reagents (**Method E**):* A flame-dried 4 mL reaction vial, under argon, was charged with dimethyl intermediate **1.72** (50 mg, 0.207 mmol, 1 equiv) and THF (1.04 mL, 0.2 M) at 23 ºC. The mixture stirred at 23 ºC until the solid dissolved fully. Then the vial was cooled to -78 ºC and aryl Grignard reagent (0.207 mmol, 1 equiv) was added in one portion, moderate-fast speed. Once addition was complete, the reaction vial was warmed to 23 ºC and stirred for 30 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (2 mL). The aqueous layer was extracted three times with ethyl acetate (3 x 4 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (gradient eluent hexanes:ethyl acetate).

1.3.6 Characterization Data for Aminothiolation Products

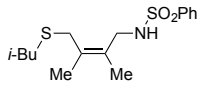


Scheme 1.2.2, Compound 1.49: Following the one-pot procedure for the aminothiolation of 1,3-butadiene (**Method A**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (280.6 mg, 94% yield). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 2H), 7.61 (dd, *J* = 8.4, 6.5 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 5.67 – 5.58 (m, 1H), 5.45 (m, 1H), 4.63 (s, 1H), 3.64 (t, *J* = 6.3 Hz, 2H), 3.03 (d, *J* = 8.0 Hz, 2H), 2.31 (d, *J* = 6.9 Hz, 2H), 1.73 (dp, *J* = 13.4, 6.7 Hz, 1H), 0.96 (d, *J* = 6.7 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 140.01, 133.01, 130.76, 129.38, 127.33, 126.59, 41.00, 40.05, 28.72, 28.63,

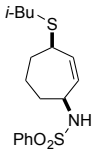
22.25. **IR (ν cm^{-1})** 3280, 3065, 3027, 2957, 1586, 1447, 1425, 1326, 1161, 1094, 900, 755, 720, 588. **HRMS (ESI) calcd for [$C_{14}H_{22}NO_2S_2$]$^+$([M+H]$^+$):** 300.1086, found 300.1089.



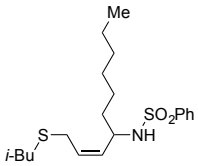
Scheme 1.2.2, Compound 1.54: Following the one-pot procedure for the aminothiolation of substituted 1,3-dienes (**Method B**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (419.7 mg, 88% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 2H), 7.62 – 7.56 (m, 1H), 7.53 – 7.47 (m, 2H), 7.31 – 7.18 (m, 7H), 7.16 – 7.12 (m, 2H), 7.07 – 7.03 (m, 2H), 4.88 (t, *J* = 6.0 Hz, 1H), 3.71 (s, 2H), 3.59 – 3.53 (m, 4H), 3.07 (s, 2H), 2.24 (d, *J* = 6.9 Hz, 2H), 1.72-1.60 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 6H) **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 138.94, 138.75, 136.19, 132.81, 132.75, 129.21, 128.75, 128.69, 128.67, 127.25, 126.55, 126.52, 43.56, 41.94, 37.42, 36.77, 33.57, 28.52, 22.10. **IR (ν cm^{-1})** 3271, 2955, 1324, 1162, 728. **LRMS (ESI) calcd for [$C_{28}H_{33}NO_2S_2Na$]$^+$([M+Na]$^+$):** 502.19, found 502.20.



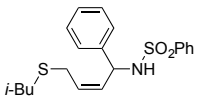
Scheme 1.2.2, Compound 1.53: Following the one-pot procedure for the aminothiolation of substituted 1,3-dienes (**Method B**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (160.2 mg, 49% yield): **^{1}H-NMR**: (400 MHz, $CDCl_3$) δ 7.89 – 7.85 (m, 2H), 7.60 – 7.55 (m, 1H), 7.54 – 7.48 (m, 2H), 4.86 (t, *J* = 6.0 Hz, 1H), 3.53 (d, *J* = 6.1 Hz, 2H), 3.01 (s, 2H), 2.23 (d, *J* = 6.9 Hz, 2H), 1.73 – 1.63 (m, 4H), 1.59 (s, 3H), 0.92 (d, *J* = 6.6 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.96, 132.68, 131.15, 129.11, 127.40, 127.18, 45.91, 41.61, 36.04, 28.58, 22.13, 19.14, 17.66. **IR (ν cm^{-1})** 3278, 2955, 1323, 1161, 690. **LRMS (ESI) calcd for [$C_{16}H_{25}NO_2S_2Na$]$^+$([M+Na]$^+$):** 350.12, found 350.16.



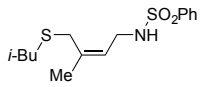
Scheme 1.2.2, Compound 1.57: Following the one-pot procedure for the aminothiolation of substituted 1,3-dienes (**Method B**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (170.8 mg, 50% yield): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.84 (m, 2H), 7.58 – 7.53 (m, 1H), 7.52 – 7.46 (m, 2H), 5.79 – 5.70 (m, 2H), 5.51 (dd, *J* = 11.6, 6.8 Hz, 1H), 4.03 (ddt, *J* = 9.3, 6.8, 3.4 Hz, 1H), 3.49 (td, *J* = 6.6, 2.6 Hz, 1H), 2.38 (dt, *J* = 8.0, 4.1 Hz, 2H), 2.06 (tdd, *J* =13.6, 6.8, 2.8 Hz, 1H), 1.88 – 1.46 (m, 7H), 1.00 (dd, *J* = 6.6, 1.2 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 141.70, 134.80, 133.66, 132.53, 129.12, 127.05, 52.18, 43.45, 40.25, 33.86, 31.68, 28.59, 22.30, 21.52. **IR (ν cm^{-1})** 3273, 2927, 1328, 1161, 1093. **LRMS (ESI) calcd for [$C_{17}H_{25}NO_2S_2Na]^+$([M+Na]$^+$):** 362.12, found 362.16.



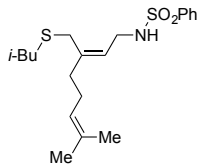
Scheme 1.2.2, Compound 1.58: Following the one-pot procedure for the aminothiolation of substituted 1,3-dienes (**Method B**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (294.8 mg, 77% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.83 (m, 2H), 7.59 – 7.52 (m, 1H), 7.52 – 7.45 (m, 2H), 5.42 – 5.33 (m, 1H), 5.17 – 5.08 (m, 1H), 4.64 (d, *J* = 7.0 Hz, 1H), 4.08 – 3.98 (m, 1H), 3.06 (ddd, *J* = 13.6, 8.6, 1.2 Hz, 1H), 2.83 (ddd, *J* = 13.6, 6.9, 1.3 Hz, 1H), 2.32 (d, *J* = 6.9 Hz, 2H), 1.81 – 1.68 (m, 1H), 1.64 – 1.11 (m, 10H), 0.97 (dd, *J* = 6.6, 2.2 Hz, 6H), 0.85 (t, *J* = 7.0 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 141.19, 132.64, 131.76, 129.04, 128.64, 127.26, 51.11, 41.24, 36.40, 31.74, 29.30, 29.02, 28.61, 25.44, 22.65, 22.14, 14.18. **IR (ν cm^{-1})** 3273, 2927, 1326, 1160, 689. **LRMS (ESI) calcd for [$C_{20}H_{33}NO_2S_2Na]^+$([M+Na]$^+$):** 406.19, found 406.20.



Scheme 1.2.2, Compound 1.59: Following the one-pot procedure for the aminothiolation of substituted 1,3-dienes (**Method B**), purification by flash chromatography afforded the desired aminothiolation product as a white solid (302.6 mg, 81% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.72 (m, 2H), 7.53 – 7.47 (m, 1H), 7.43 – 7.37 (m, 2H), 7.23 – 7.16 (m, 5H), 5.56 – 5.46 (m, 2H), 5.25 – 5.19 (m, 2H), 3.16 – 3.10 (m, 1H), 3.00 – 2.94 (m, 1H), 2.25 (d, *J* = 6.9 Hz, 2H), 1.75 – 1.65 (m, 1H), 0.91 (dd, *J* = 8.2, 6.6 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 140.73, 139.87, 132.60, 130.69, 129.24, 128.93, 128.81, 127.93, 127.28, 126.97, 54.65, 41.04, 29.14, 28.51, 22.12, 22.08. **IR (ν cm^{-1})** 3268, 2955, 1326, 1160, 688. **LRMS (ESI) calcd for [$C_{20}H_{25}NO_2S_2Na$]$^+$([M+Na]$^+$):** 398.12, found 398.15.

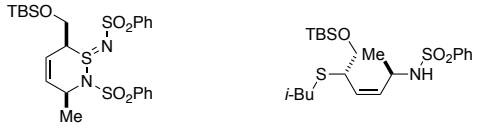


Scheme 1.2.2, Compound 1.55: Following the one-pot procedure for the aminothiolation of substituted 1,3-dienes (**Method B**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (183.4 mg, 59% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.89 – 7.85 (m, 2H), 7.61 – 7.56 (m, 1H), 7.54 – 7.48 (m, 2H), 5.20 (t, *J* = 7.3 Hz, 1H), 4.73 (t, *J* = 5.7 Hz, 1H), 3.56 (t, *J* = 6.5 Hz, 2H), 2.99 (s, 2H), 2.24 (d, *J* = 6.9 Hz, 2H), 1.75 – 1.65 (m, 4H), 0.93 (d, *J* = 6.6 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 140.00, 137.90, 132.78, 129.19, 127.23, 122.28, 41.28, 40.79, 33.34, 28.51, 23.12, 22.14. **IR (ν cm^{-1})** 3278, 2956, 1327, 1161, 689. **LRMS (ESI) calcd for [$C_{15}H_{23}NO_2S_2Na$]$^+$([M+Na]$^+$):** 336.11, found 336.15.



Scheme 1.2.2, Compound 1.56: Following the one-pot procedure for the aminothiolation of substituted 1,3-dienes (**Method B**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (242.5 mg, 64% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.84 (m, 2H), 7.61 – 7.55 (m, 1H), 7.55 – 7.48 (m, 2H), 5.21 (t, *J* = 7.3 Hz, 1H),

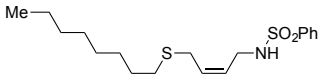
5.05 – 4.96 (m, 1H), 4.70 (t, J = 5.9 Hz, 1H), 3.60 (t, J = 6.6 Hz, 2H), 3.02 (s, 2H), 2.26 (d, J = 6.9 Hz, 2H), 2.10 – 1.93 (m, 4H), 1.76 – 1.63 (m, 4H), 1.56 (s, 3H), 0.94 (d, J = 6.6 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 141.58, 140.11, 132.77, 132.23, 129.21, 127.25, 123.49, 122.01, 41.60, 40.84, 36.35, 32.13, 28.52, 26.49, 25.79, 22.16, 17.86. **IR (ν cm^{-1})** 3278, 2958, 1446, 1327, 1162. **LRMS (ESI) calcd for [$C_{20}H_{31}NO_2S_2Na$]$^+$([M+Na]$^+$):** 404.17, found 404.21.



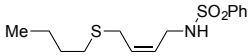
Scheme 1.2.2, Compound 1.60: Following the two-pot procedure for the aminothiolation of substituted 1,3-dienes (**Method D**), *tert*-butyldimethylsilyl protected sorbic alcohol **S1.4** (100 mg, 0.471 mmol, 1.5 equiv) was converted to the [4+2] adduct **S1.5**. Purification by flash chromatography afforded the desired [4+2] adduct as a white solid (115.7 mg, 66% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H), 7.96 – 7.91 (m, 2H), 7.67 – 7.61 (m, 1H), 7.58 – 7.40 (m, 5H), 5.86 (ddd, J = 10.8, 2.6, 0.9 Hz, 1H), 5.66 (ddd, J = 10.7, 5.5, 1.7 Hz, 1H), 4.32 – 4.23 (m, 1H), 3.85 (dd, J = 11.8, 4.4 Hz, 1H), 3.74 (dd, J = 11.7, 9.8 Hz, 1H), 3.61 (dt, J = 9.7, 4.4 Hz, 1H), 1.32 (d, J = 7.0 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 143.47, 139.57, 134.63, 134.10, 131.83, 129.57, 128.82, 128.10, 126.75, 116.42, 65.66, 61.91, 49.30, 25.83, 19.23, 18.24, -5.31. **IR (ν cm^{-1})** 2928, 2856, 1149, 836, 751. **LRMS (ESI) calcd for [$C_{24}H_{35}N_2O_5S_3Si$]$^+$([M+H]$^+$):** 555.15, found 555.13. **LRMS (ESI) calcd for [$C_{24}H_{34}N_2O_5S_3SiNa$]$^+$([M+Na]$^+$):** 577.13, found 577.10.

[4+2] adduct **S5** (330.0 mg, 0.595 mmol, 1 equiv) was converted to the desired aminothiolation product via the two-pot procedure (**Method D**). Purification by flash chromatography afforded the product as a clear, colorless oil (102.9 mg, 38% yield or 25% yield over 2 steps): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.92 – 7.88 (m, 2H), 7.59 – 7.53 (m, 1H), 7.53 – 7.47 (m, 2H), 5.31 (dd, J = 10.8, 8.7 Hz, 1H), 5.18 (t, J = 10.1 Hz, 1H), 4.73 (s, 1H), 4.29 – 4.17 (m, 1H), 3.74 – 3.67 (m, 1H), 3.55 – 3.43 (m, 2H), 2.41 (d, J = 6.7 Hz, 2H), 1.84 – 1.72 (m, 1H), 1.16 (d, J = 6.6 Hz, 3H), 0.99 (dd, J = 6.6, 1.7 Hz, 6H), 0.85 (s, 9H), 0.01 (d, J = 1.4 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 141.28, 132.92, 132.65, 131.11, 129.14, 127.23, 66.41, 47.81,

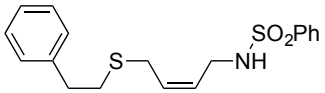
44.76, 39.83, 29.11, 26.07, 22.92, 22.25, 18.59, -5.17, -5.18. **IR (ν cm^{-1})** 3273, 2956, 1163, 1094, 837. **LRMS (ESI) calcd for [$C_{22}H_{39}NO_3S_2SiNa$]$^+$([M+Na]$^+$):** 480.20, found 480.20.



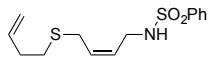
Scheme 1.2.3, Compound 1.61: Following the one-pot procedure for the aminothiolation of 1,3-butadiene (**Method A**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (264.0 mg, 74% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.80 (m, 2H), 7.66 – 7.55 (m, 1H), 7.51 (dd, *J* = 8.2, 6.8 Hz, 2H), 5.58 (m, 1H), 5.42 (m, 1H), 4.89 (s, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.02 (d, *J* = 7.9 Hz, 2H), 2.50 – 2.22 (m, 2H), 1.53 – 1.44 (m, 2H), 1.37 – 1.20 (m, 10H), 0.87 (t, *J* = 6.9, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.96, 132.92, 130.48, 129.31, 127.27, 126.57, 39.97, 31.96, 31.75, 29.55, 29.35, 29.05, 28.20, 25.90, 22.81, 14.27. **IR (ν cm^{-1})** 3281, 3066, 3027, 2925, 1586, 1447, 1327, 1161, 1094, 754, 689. **HRMS (ESI) calcd for [$C_{18}H_{30}NO_2S_2$]$^+$([M+H]$^+$):** 356.1712, found 356.1714.



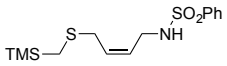
Scheme 1.2.3, Compound 1.62: Following the one-pot procedure for the aminothiolation of 1,3-butadiene (**Method A**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (209.3 mg, 70% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.85 (m, 2H), 7.62 – 7.56 (m, 1H), 7.55 – 7.49 (m, 2H), 5.65 – 5.56 (m, 1H), 5.43 (dt, *J* = 10.7, 7.1 Hz, 1H), 4.73 (t, *J* = 5.7 Hz, 1H), 3.66-3.59 (m, 2H), 3.03 (d, *J* = 7.9 Hz, 2H), 2.40 (t, *J* = 7.3 Hz, 2H), 1.54 – 1.44 (m, 2H), 1.41 – 1.30 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.88, 132.90, 130.52, 129.28, 127.23, 126.52,39.94, 31.58, 31.37, 28.13, 22.09, 13.81. **IR (ν cm^{-1})** 3281, 2956, 1326, 1161, 1094. **LRMS (ESI) calcd for [$C_{14}H_{21}NO_2S_2Na$]$^+$([M+Na]$^+$):** 322.09, found 322.13.



Scheme 1.2.3, Compound 1.67: Following the one-pot procedure for the aminothiolation of 1,3-butadiene (**Method A**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (303.5 mg, 87% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 2H), 7.61 – 7.55 (m, 1H), 7.54 – 7.47 (m, 2H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.25 – 7.13 (m, 3H), 5.64 – 5.55 (m, 1H), 5.44 (dt, *J* = 10.7, 7.1 Hz, 1H), 4.77 (t, *J* = 5.8 Hz, 1H), 3.62 (t, *J* = 6.1 Hz, 2H), 3.04 (d, *J* = 7.9 Hz, 2H), 2.86 – 2.79 (m, 2H), 2.71 – 2.64 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 140.32, 139.85, 132.89, 130.22, 129.27, 128.62, 128.56, 127.20, 126.80, 126.56, 39.92, 36.19, 33.12, 28.37. **IR (ν cm^{-1})** 3276, 1325, 1160, 754, 689. **LRMS (ESI) calcd for [$C_{18}H_{21}NO_2S_2Na]^+$([M+Na]$^+$):** 370.09, found 370.12.

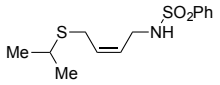


Scheme 1.2.3, Compound 1.66: Following the one-pot procedure for the aminothiolation of 1,3-butadiene (**Method A**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (262.9 mg, 88% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 2H), 7.63 – 7.55 (m, 1H), 7.55 – 7.48 (m, 2H), 5.77 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.64 – 5.54 (m, 1H), 5.44 (dt, *J* = 10.7, 7.1 Hz, 1H), 5.09 – 4.98 (m, 2H), 4.83 (t, *J* = 5.8 Hz, 1H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.05 (d, *J* = 7.9 Hz, 2H), 2.47 (t, *J* = 7.4 Hz, 2H), 2.26 (dt, *J* = 7.1, 6.8 Hz, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.84, 136.58, 132.90, 130.23, 129.28, 127.21, 126.72, 116.25, 39.91, 33.76, 30.87, 28.16. **IR (ν cm^{-1})** 3280, 1324, 1159, 1094, 689. **LRMS (ESI) calcd for [$C_{14}H_{19}NO_2S_2Na]^+$([M+Na]$^+$):** 320.08, found 320.12.

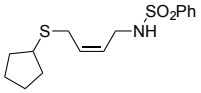


Scheme 1.2.3, Compound 1.68: Following the one-pot procedure for the aminothiolation of 1,3-butadiene (**Method A**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (284.2 mg, 86% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.85 (m, 2H), 7.63 – 7.56 (m, 1H), 7.55 – 7.48 (m, 2H), 5.62 – 5.53 (m, 1H), 5.46 (dt, *J* = 10.7, 7.0 Hz, 1H), 4.79 (t, *J* = 5.7 Hz, 1H), 3.63 (t, *J* = 6.5 Hz, 3H), 3.02 (d, *J* = 7.9 Hz, 2H), 1.64 (s, 2H), 0.06 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.91, 132.88, 130.13,

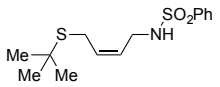
129.27, 127.21, 126.65, 39.98, 32.04, 17.89, -1.56. **IR (ν cm^{-1})** 3282, 2953, 1326, 1161, 845. **LRMS (ESI) calcd for [$C_{14}H_{23}NO_2S_2SiNa]^+$([M+Na]$^+$):** 352.08, found 352.12.



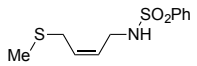
Scheme 1.2.3, Compound 1.63: Following the one-pot procedure for the aminothiolation of 1,3-butadiene (**Method A**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (121.0 mg, 42% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.85 (m, 2H), 7.62 – 7.55 (m, 1H), 7.55 – 7.48 (m, 2H), 5.62 (dtt, *J* = 10.5, 7.8, 1.3 Hz, 1H), 5.41 (dt, *J* = 10.7, 7.1 Hz, 1H), 4.81 (t, *J* = 5.7 Hz, 1H), 3.64 (dd, *J* = 7.1 Hz, 2H), 3.06 (d, *J* = 7.9 Hz, 2H), 2.81 (hept, *J* = 6.7 Hz, 1H), 1.20 (d, *J* = 6.7 Hz, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.86, 132.88, 130.58, 129.26, 127.22, 126.43, 39.94, 34.86, 26.96, 23.33. **IR (ν cm^{-1})** 3282, 2959, 1324, 1159, 1094. **LRMS (ESI) calcd for [$C_{13}H_{19}NO_2S_2Na]^+$([M+Na]$^+$):** 308.08, found 308.10.



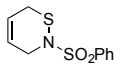
Scheme 1.2.3, Compound 1.65: Following the one-pot procedure for the aminothiolation of 1,3-butadiene (**Method A**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (152.3 mg, 49% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.85 (m, 2H), 7.61 – 7.55 (m, 1H), 7.55 – 7.48 (m, 2H), 5.62 (dtt, *J* = 10.5, 7.9, 1.3 Hz, 1H), 5.41 (dt, *J* = 10.7, 7.1 Hz, 1H), 4.87 (t, *J* = 5.7 Hz, 1H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.05 (d, *J* = 8.0 Hz, 2H), 2.97 (p, *J* = 6.9 Hz, 1H), 1.95 – 1.84 (m, 2H), 1.75 – 1.64 (m, 2H), 1.59 – 1.48 (m, 2H), 1.48 – 1.37 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.83, 132.85, 130.62, 129.24, 127.20, 126.27, 43.45, 39.92, 33.71, 28.22, 24.93. **IR (ν cm^{-1})** 3278, 2954, 1325, 1161, 1094. **LRMS (ESI) calcd for [$C_{15}H_{21}NO_2S_2Na]^+$([M+Na]$^+$):** 334.09, found 334.13.



Scheme 1.2.3, Compound 1.64: Following the two-pot procedure for the aminothiolation of 1,3-butadiene (**Method C**), [4+2] cycloadduct (100 mg, 0.252 mmol) was converted to the desired aminothiolation product. Purification by flash chromatography afforded the product as a clear, colorless oil (24 mg, 32% yield over 2 steps): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.92 – 7.86 (m, 2H), 7.63 – 7.56 (m, 1H), 7.56 – 7.49 (m, 2H), 5.72 – 5.61 (m, 1H), 5.42 (dt, *J* = 10.6, 7.2 Hz, 1H), 4.64 (t, *J* = 5.7 Hz, 1H), 3.66 (t, *J* = 6.1 Hz, 2H), 3.09 (d, *J* = 8.0 Hz, 2H), 1.28 (s, 9H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.96, 132.87, 130.36, 129.28, 127.28, 126.85, 42.99, 39.97, 30.89, 25.09. **IR (ν cm^{-1})** 3283, 2960, 1325, 1159, 689. **LRMS (ESI) calcd for [$C_{14}H_{21}NO_2S_2Na]^+$([M+Na]$^+$):** 322.09, found 322.12.

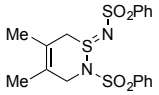


Scheme 1.2.3, Compound 1.69: Following the two-pot procedure for the aminothiolation of 1,3-butadiene (**Method C**), [4+2] cycloadduct (100 mg, 0.252 mmol) was converted to the desired aminothiolation product. Purification by flash chromatography afforded the product as a clear, colorless oil (14.6 mg, 23% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.85 (m, 2H), 7.63 – 7.56 (m, 1H), 7.56 – 7.49 (m, 2H), 5.59 (dtt, *J* = 10.1, 7.5, 1.1 Hz, 1H), 5.47 (dt, *J* = 10.7, 7.1 Hz, 1H), 4.75 (t, *J* = 5.4 Hz, 1H), 3.63 (t, *J* = 7.0 Hz, 2H), 3.01 (d, *J* = 7.9 Hz, 2H), 1.97 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.86, 132.94, 129.98, 129.30, 127.22, 126.78, 39.91, 29.97, 14.90. **IR (ν cm^{-1})** 3281, 2917, 1320, 1156, 688. **LRMS (ESI) calcd for [$C_{11}H_{15}NO_2S_2Na]^+$([M+Na]$^+$):** 280.04, found 280.10.

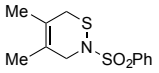


Scheme 1.2.4A, Compound 1.52: The compound was isolated as a by-product of the aminothiolation of 1,3-butadiene when using less than 4 equivalents of Grignard reagent (**Method A or C**). The compound was purified by flash chromatography (First run gradient eluent hexanes:ethyl acetate, then second run gradient eluent hexanes:dichloromethane): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.92 (m, 2H), 7.64 – 7.58 (m, 1H), 7.53 – 7.47 (m, 2H), 5.81

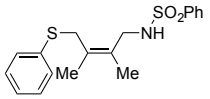
– 5.74 (m, 1H), 5.73 – 5.66 (m, 1H), 4.32 – 4.28 (m, 2H), 2.74 – 2.69 (m, 2H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.06, 133.39, 129.07, 128.30, 125.12, 123.05, 46.73, 27.54. **IR (ν cm^{-1})** 1351, 1167, 1091, 725, 630. **LRMS (ESI) calcd for [$C_{10}H_{11}NO_2S_2Na$]$^+$([M+Na]$^+$):** 264.01, found 264.06.



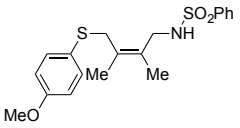
Scheme 1.2.4A, Compound 1.71: Following the two-pot procedure for the aminothiolation of substituted 1,3-dienes (**Method D**), 2,3-dimethyl-1,3-butadiene (169.7 µL, 1.5 mmol) was converted to the [4+2] adduct. Purification by flash chromatography afforded the desired [4+2] adduct as a white solid (308.5 mg, 73% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.98 – 7.92 (m, 2H), 7.81 – 7.74 (m, 2H), 7.70 – 7.64 (m, 1H), 7.60 – 7.53 (m, 2H), 7.50 – 7.44 (m, 1H), 7.43 – 7.36 (m, 2H), 3.92 (d, *J* = 16.2 Hz, 1H), 3.83 (d, *J* = 16.7 Hz, 1H), 3.62 (d, *J* = 16.5 Hz, 1H), 3.08 (d, *J* = 16.2 Hz, 1H), 1.71 (s, 3H), 1.67 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 143.52, 136.90, 134.53, 131.84, 129.70, 128.81, 128.27, 126.33, 124.06, 115.85, 51.64, 42.90, 19.45, 17.20. **IR (ν cm^{-1})** 1171, 1146, 1090, 1009, 751. **LRMS (ESI) calcd for [$C_{18}H_{20}N_2O_4S_3Na$]$^+$([M+Na]$^+$):** 447.05, found 447.06.



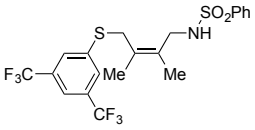
Scheme 1.2.4A, Compound 1.72: The compound was isolated as a by-product of the aminothiolation of 2,3-dimethyl-1,3-butadiene when using less than 4 equivalents of Grignard reagent (**Method B or D**). The compound was purified by flash chromatography (First run gradient eluent hexanes:ethyl acetate, then second run gradient eluent hexanes:dichloromethane): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.88 (m, 2H), 7.63 – 7.56 (m, 1H), 7.51 – 7.45 (m, 2H), 4.15 – 4.11 (m, 2H), 2.56 – 2.50 (m, 2H), 1.64 – 1.59 (m, 3H), 1.48 – 1.44 (m, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.15, 133.28, 128.91, 128.20, 123.75, 122.70, 51.36, 31.97, 19.44, 17.21. **IR (ν cm^{-1})** 2891, 1350, 1338, 1166, 727. **LRMS (ESI) calcd for [$C_{12}H_{15}NO_2S_2Na$]$^+$([M+Na]$^+$):** 292.04, found 292.08.



Scheme 1.2.4B, Compound 1.74, Entry 1: Following the general procedure for the aminothiolation of 2,3-dimethyl-1,3-butadiene with aryl Grignard reagents (**Method E**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (70.3 mg, 98% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.74 (m, 2H), 7.58 – 7.51 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.30 – 7.23 (m, *J* = 2.6 Hz, 5H), 3.97 (t, *J* = 6.1 Hz, 1H), 3.36 (s, 2H), 3.24 (d, *J* = 6.2 Hz, 2H), 1.75 (s, 3H), 1.59 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 139.81, 135.40, 132.67, 132.27, 129.61, 129.08, 129.04, 128.56, 127.59, 127.12, 45.53, 39.12, 18.86, 17.42. **IR (ν cm^{-1})** 3282, 1323, 1161, 751, 689. **LRMS (ESI) calcd for [$C_{18}H_{21}NO_2S_2Na$]$^+$([M+Na]$^+$):** 370.09, found 370.12.



Scheme 1.2.4B, Compound 1.74, Entry 2: Following the general procedure for the aminothiolation of 2,3-dimethyl-1,3-butadiene with aryl Grignard reagents (**Method E**), purification by flash chromatography afforded the desired aminothiolation product as a clear, colorless oil (74.7 mg, 96% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 2H), 7.59 – 7.53 (m, 1H), 7.52 – 7.45 (m, 2H), 7.25 – 7.19 (m, 2H), 6.84 – 6.78 (m, 2H), 3.84 (s, 3H), 3.65 (t, *J* = 6.4 Hz, 1H), 3.24 (s, 2H), 3.11 (d, *J* = 6.3 Hz, 2H), 1.74 (s, 3H), 1.56 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 159.98, 139.93, 136.12, 132.60, 129.88, 129.03, 128.02, 127.06, 124.99, 114.64, 55.50, 45.32, 40.66, 18.59, 17.25. **IR (ν cm^{-1})** 1493, 1324, 1246, 1160, 1030. **LRMS (ESI) calcd for [$C_{19}H_{23}NO_3S_2Na$]$^+$([M+Na]$^+$):** 400.10, found 400.12.



Scheme 1.2.4, Compound 1.74, Entry 3: Following the general procedure for the aminothiolation of 2,3-dimethyl-1,3-butadiene with aryl Grignard reagents (**Method E**), purification by flash chromatography afforded the desired aminothiolation product as a clear, light brown oil (99.1 mg, 99% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.84 – 7.79 (m, 2H), 7.67 (s, 1H), 7.58 (s, 2H), 7.54 – 7.47 (m, 1H), 7.47 – 7.40 (m, 2H), 4.62 (t, *J* = 5.8 Hz, 1H), 3.50 (s, 2H), 3.42 (d, *J* = 5.9 Hz, 2H), 1.75 (s, 3H), 1.62 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 140.34, 139.69, 132.84, 132.29, 131.96, 130.20, 129.12, 128.98, 128.18, 127.14, 124.46, 121.71, 119.96, 45.53, 37.72, 19.01, 17.62. **IR (ν cm^{-1})** 3274, 2919, 1353, 1278, 1136. **LRMS (ESI) calcd for [$C_{20}H_{19}F_6NO_2S_2Na$]$^+$([M+Na]$^+$):** 506.07, found 506.08.

1.3.7 Detection of By-Products

$PhSO_2NH_2$ was isolated and characterized by ^{1}H-NMR. The $PhSO_2NH_2$ generated from the aminothiolation reaction was spectroscopically identical to commercial $PhSO_2NH_2$ purchased from Sigma-Aldrich.

N-Benzenesulfonyl pyrrole **1.76** was isolated in trace quantities after flash chromatography. Spectroscopic data was identical to the reported data in the literature.[76]

The following compounds were detected by GC-MS of the crude solution:

Instrument: Agilent 7820A/5935 GC-MS
Column: HP-5ms, 0.25 micron (19091S-433)
Method: Initial temperature 40 ºC for 2 min, ramp 20 ºC/min until 250 ºC, hold at 250ºC for 4 min.

N-Isobutyl benzenesulfonamide
Retention time: 12.2 min (trace quantities; MS: 213.1, 170.1, 141.0, 77.1)

2,5-Dimethylhexane

Retention time: 2.6 min (*override solvent delay*, major quantities, MS: 114.1, 99.2, 71.1, 57.1)

Diisobutylsulfide

Retention time: 5.5 min (trace quantities; MS: 146.1, 103.1, 57.1)

N-Benzenesulfonyl-2,5-dihydropyrrole

Retention time: 14.8 min (trace quantities; MS: 209.1, 141.0, 85.1, 68.1)

Isobutanethiol **S1.6**

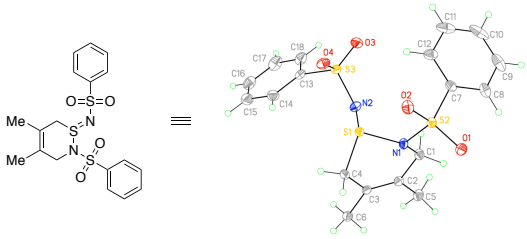
Retention time: 2.2 min (*override solvent delay*, trace quantities; MS: 90.1, 57.1, 56.1)

1.3.8 X-Ray Diffraction Data

We thank Dr. Vincent Lynch (Manager of the X-ray Diffraction Lab at The University of Texas at Austin) for all the X-ray structural analysis.

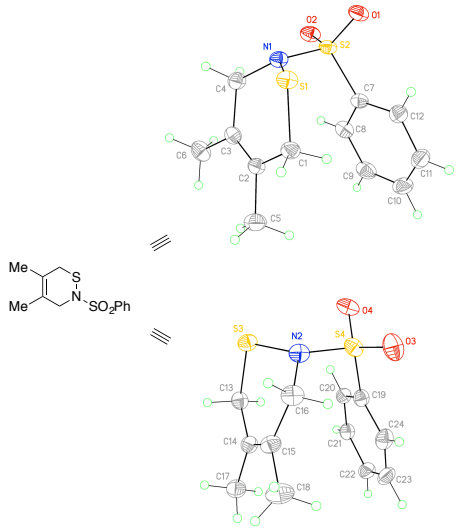
A sample of dimethyl [4+2] adduct **1.71** was recrystallized from dichloromethane and hexanes (slow diffusion). The resulting crystals were suitable for X-ray diffraction and the structure was solved. The CIF file is available as a separate file in the Supporting Information.

Figure 1.3.1



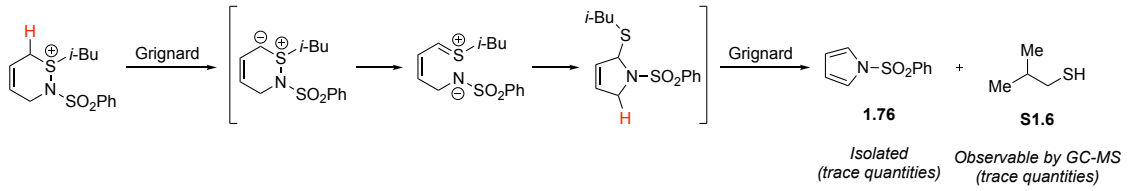
A sample of dimethyl intermediate **1.72** was recrystallized from diethyl ether and hexanes (slow diffusion). The resulting crystals were suitable for X-ray diffraction and the structure was solved. The CIF file is available as a separate file in the Supporting Information.

Figure 1.3.2



1.3.9 Mechanistic Details of Path D

Scheme 1.3.1



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APPENDIX ONE

Spectra Relevant to Chapter One: Copper-Catalyzed Aminothiolation of 1,3-Dienes via a Dihydrothiazine Intermediate

NMR Spectra

Figure A1.1, Compound 1.51

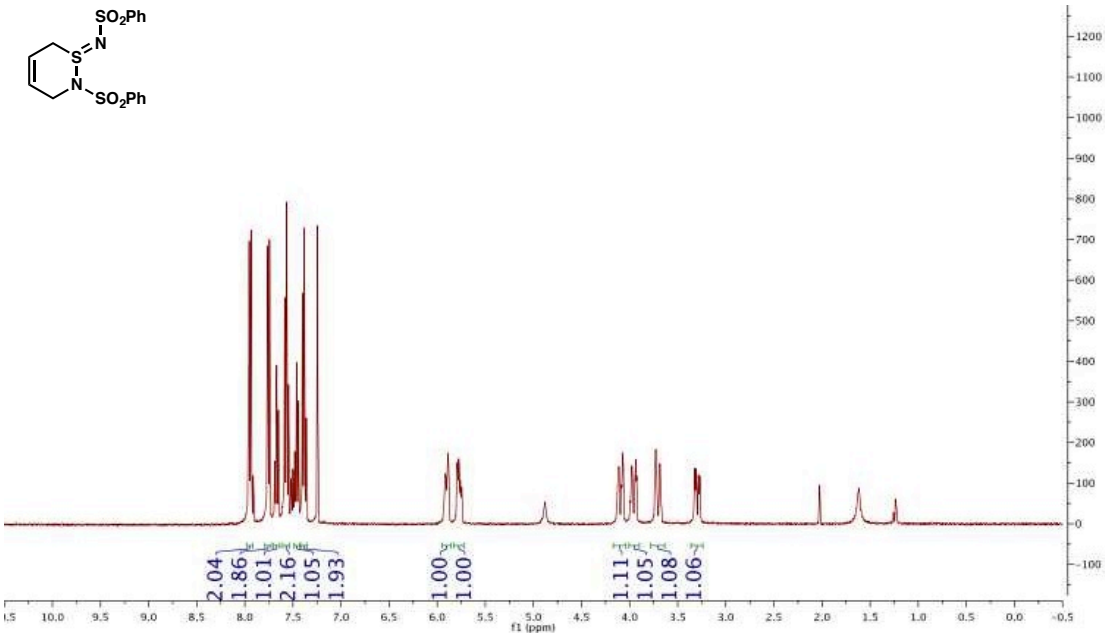


Figure A1.2, Compound 1.51

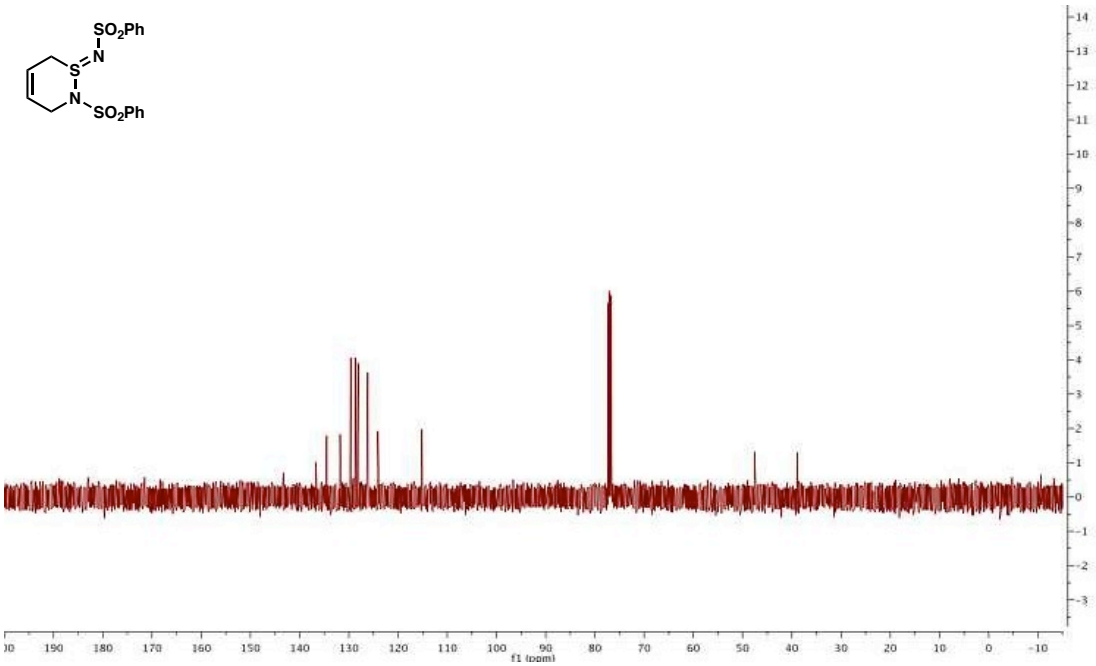
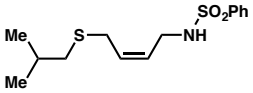


Figure A1.3, Compound 1.49



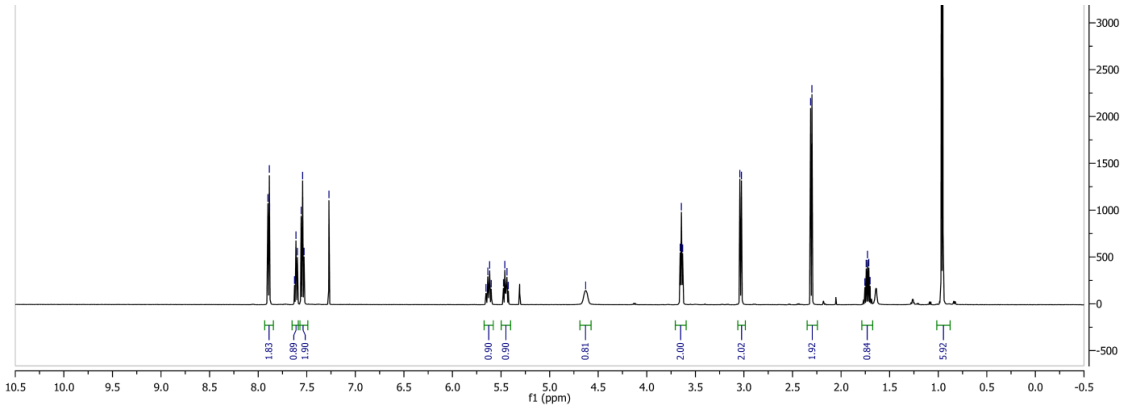
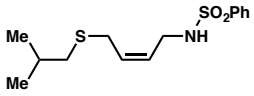


Figure A1.4, Compound 1.49



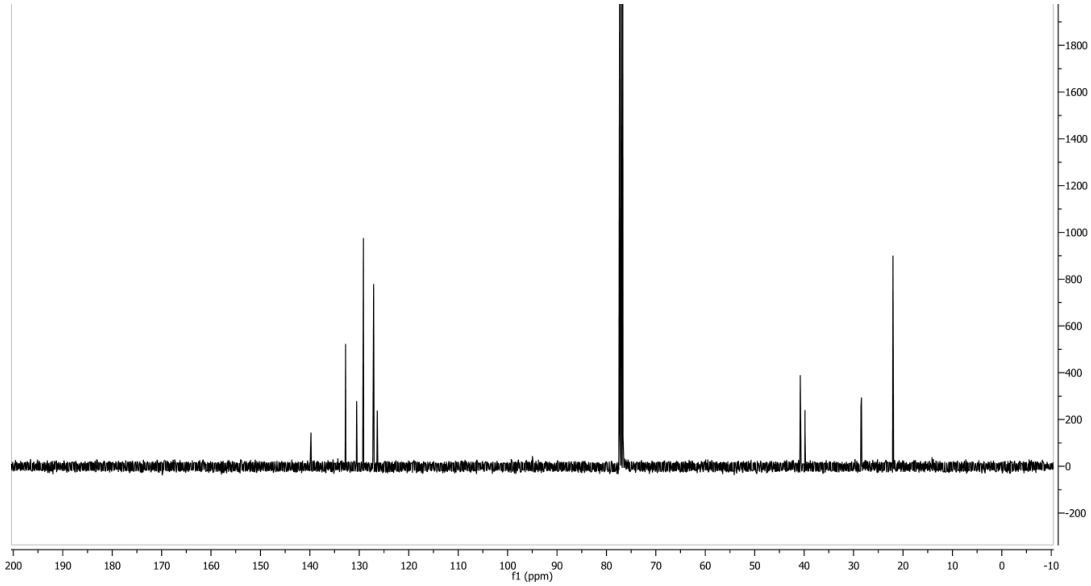


Figure A1.5, Compound 1.54

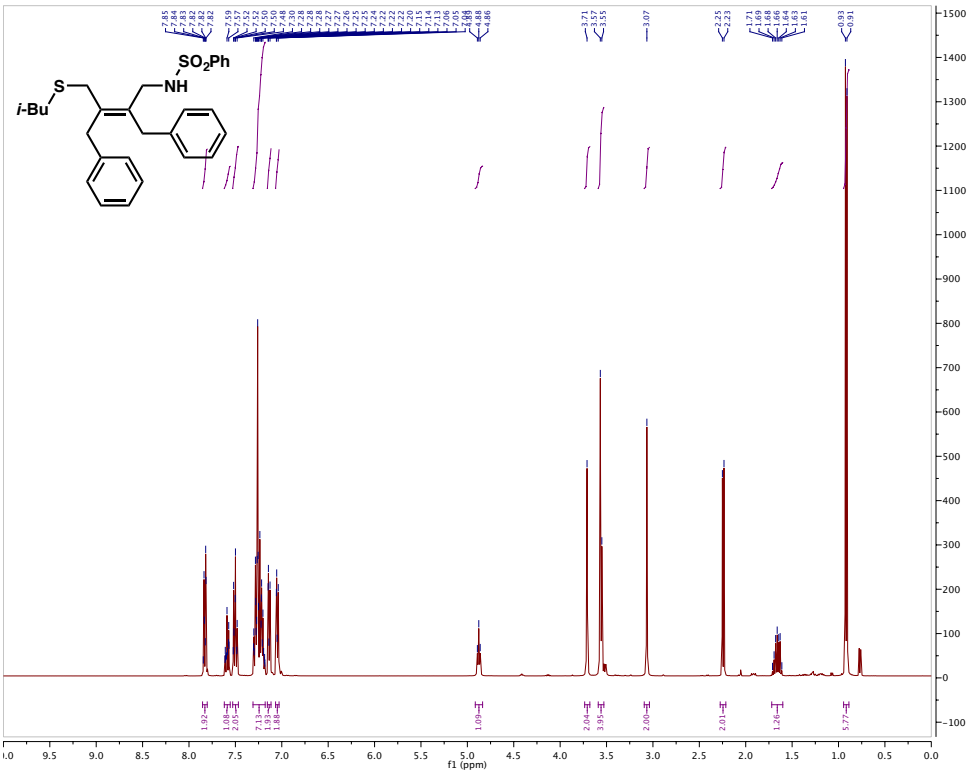


Figure A1.6, Compound 1.54

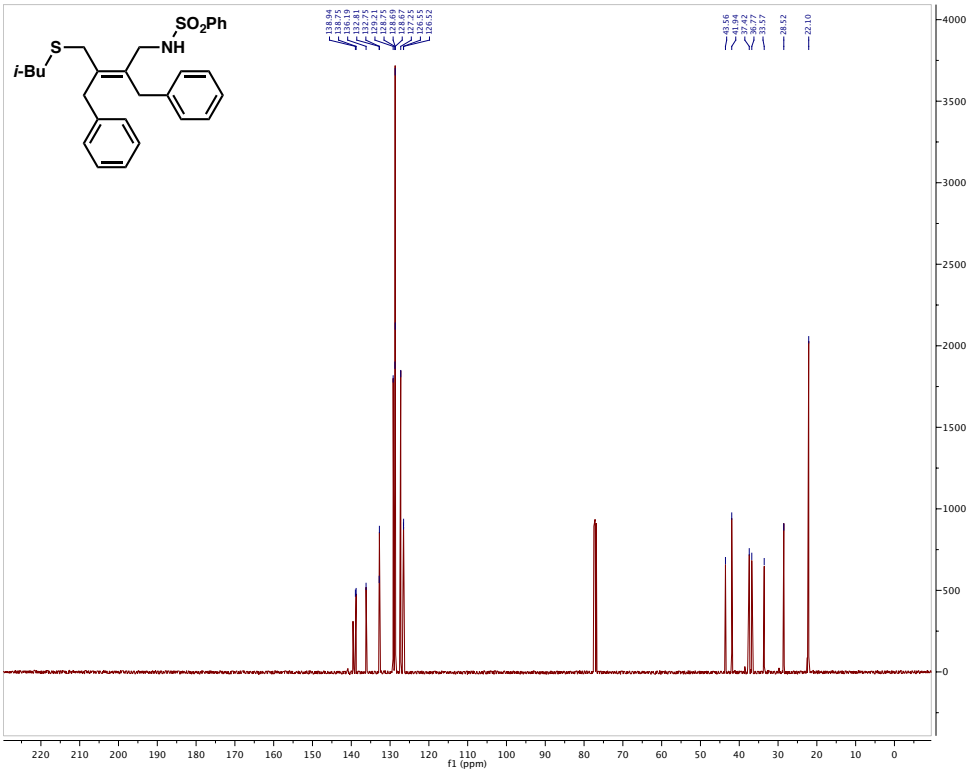


Figure A1.7, Compound 1.53

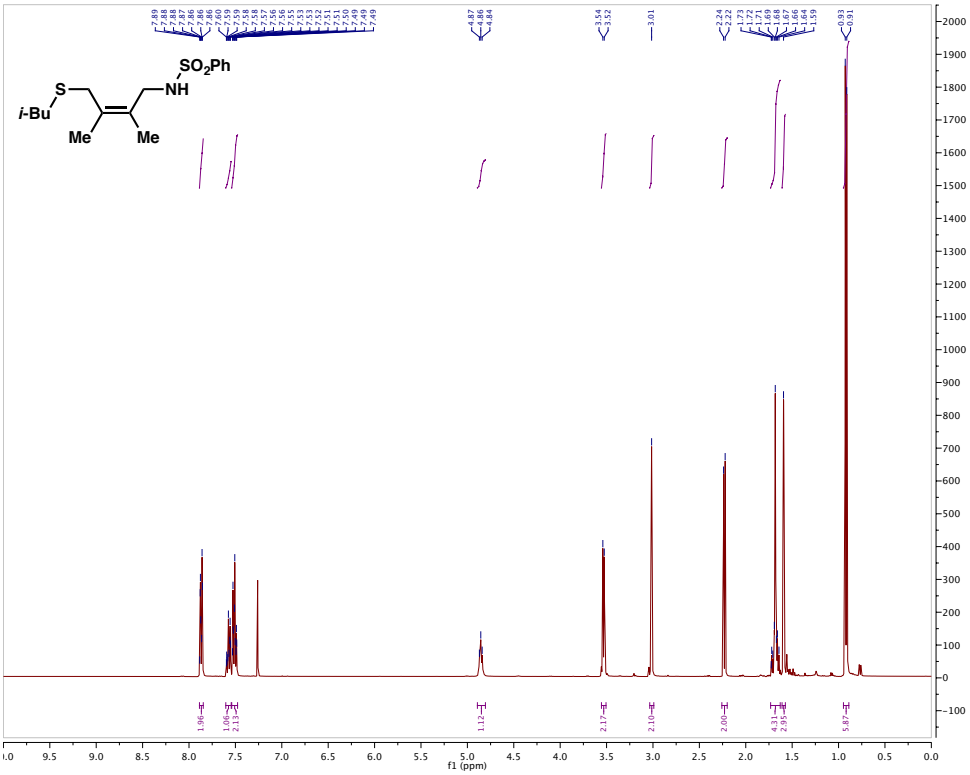


Figure A1.8, Compound 1.53

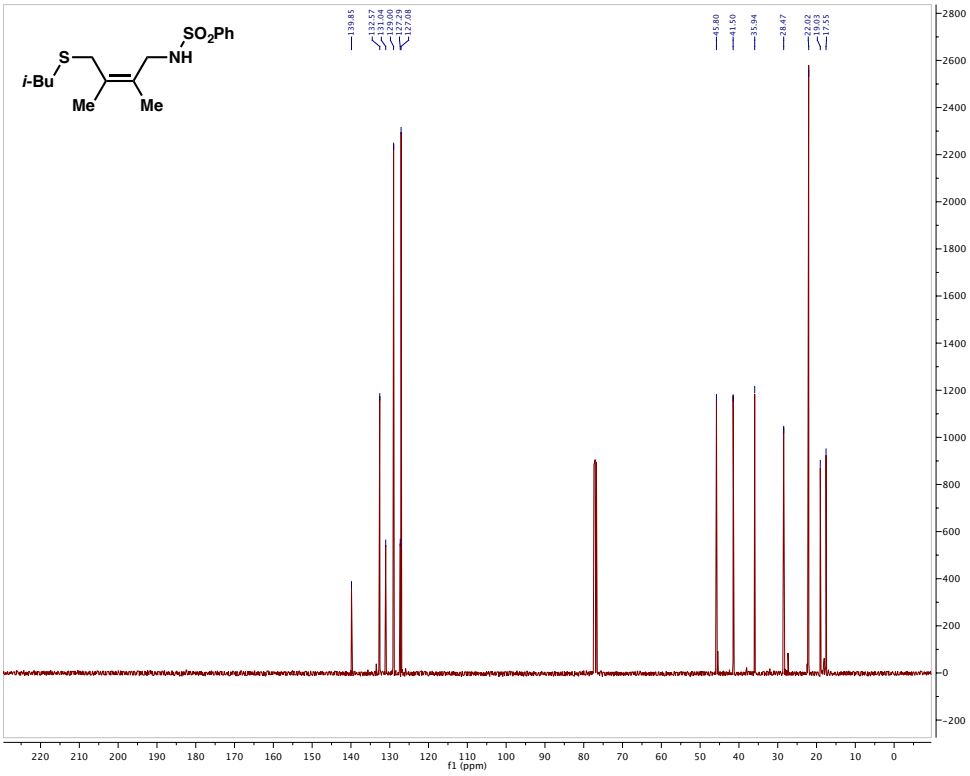
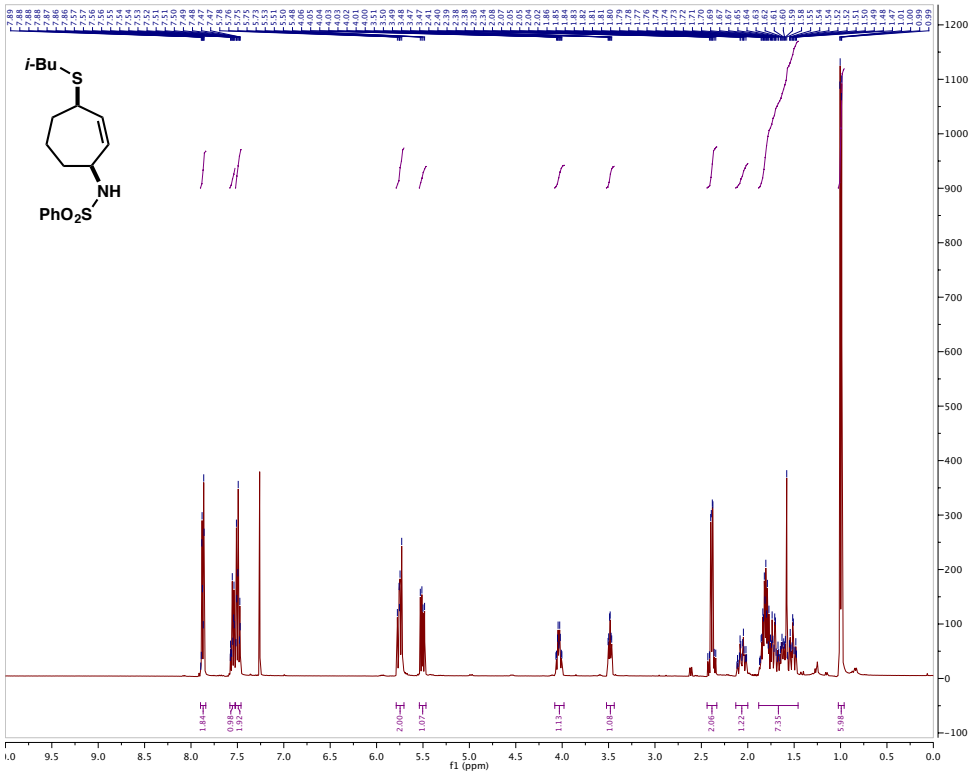


Figure A1.9, Compound 1.57



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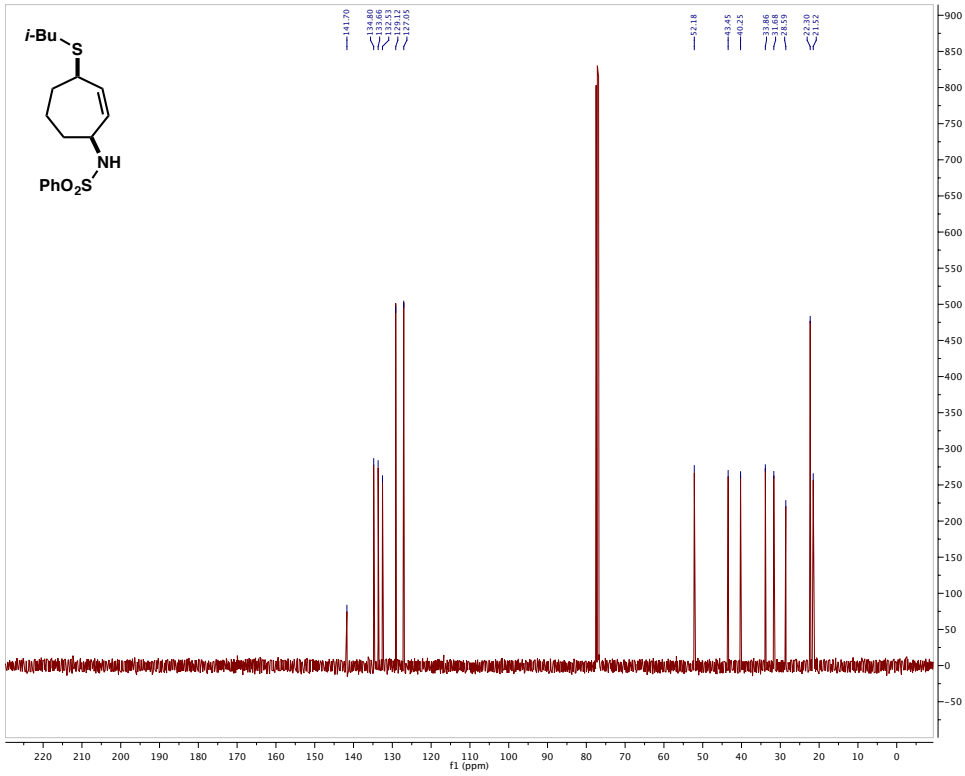
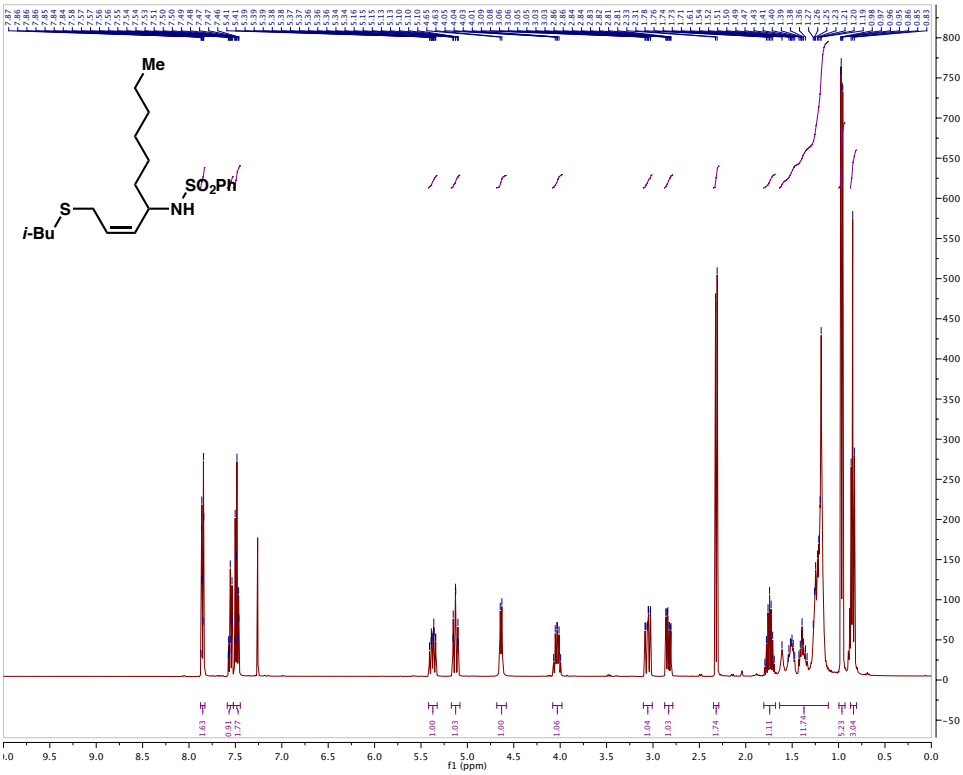


Figure A1.11, Compound 1.58



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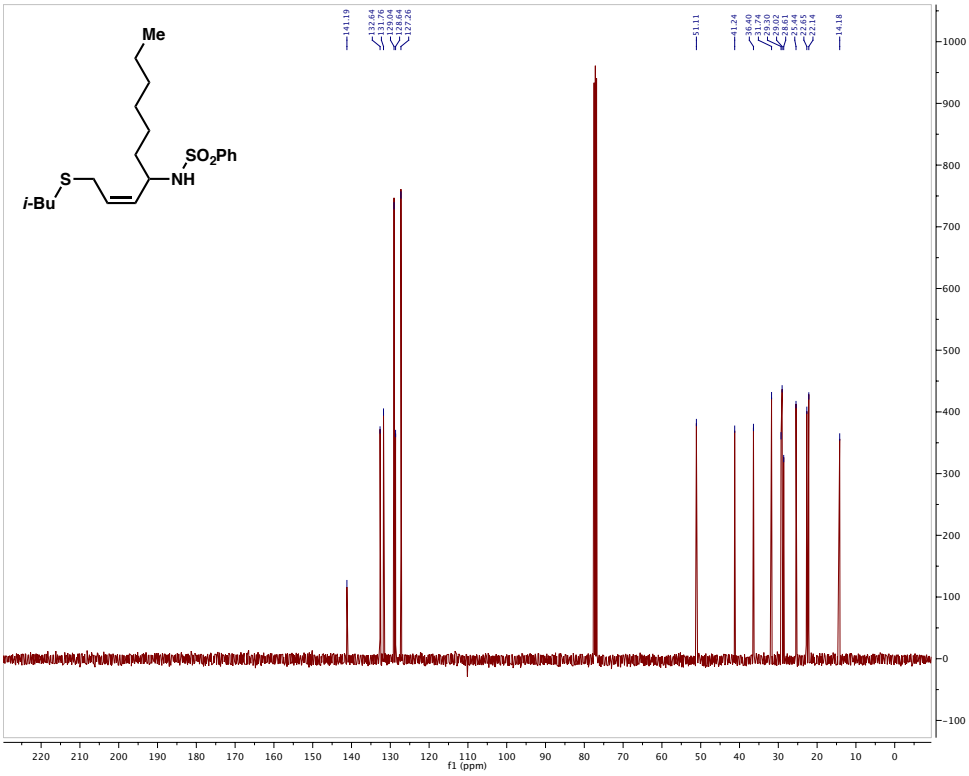

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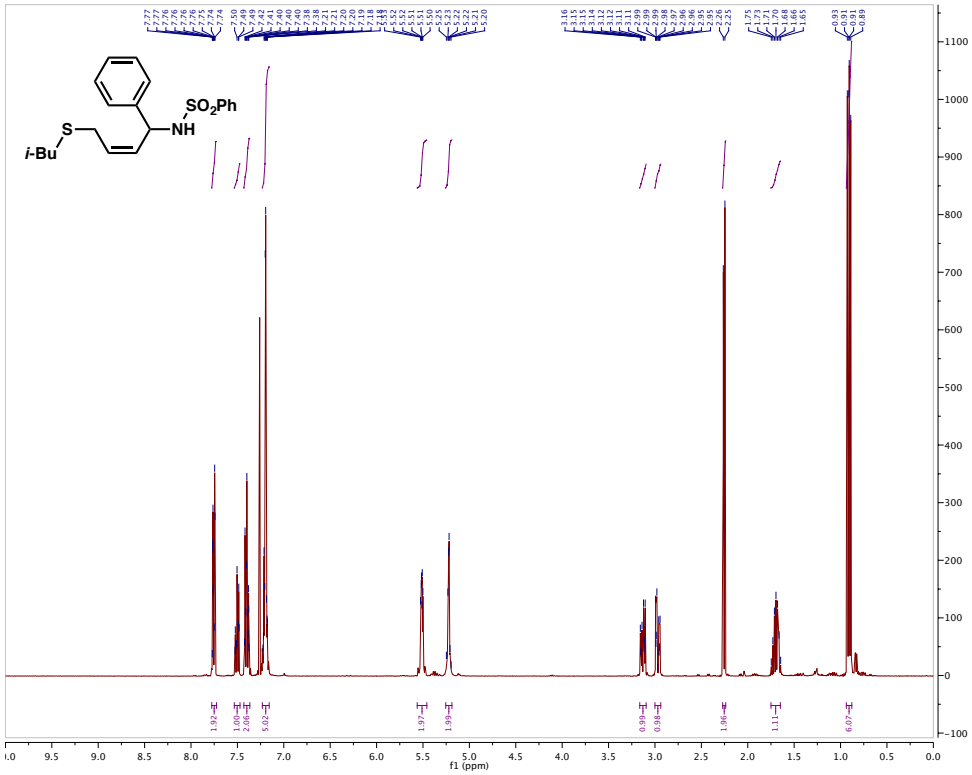


Figure A1.14, Compound 1.59

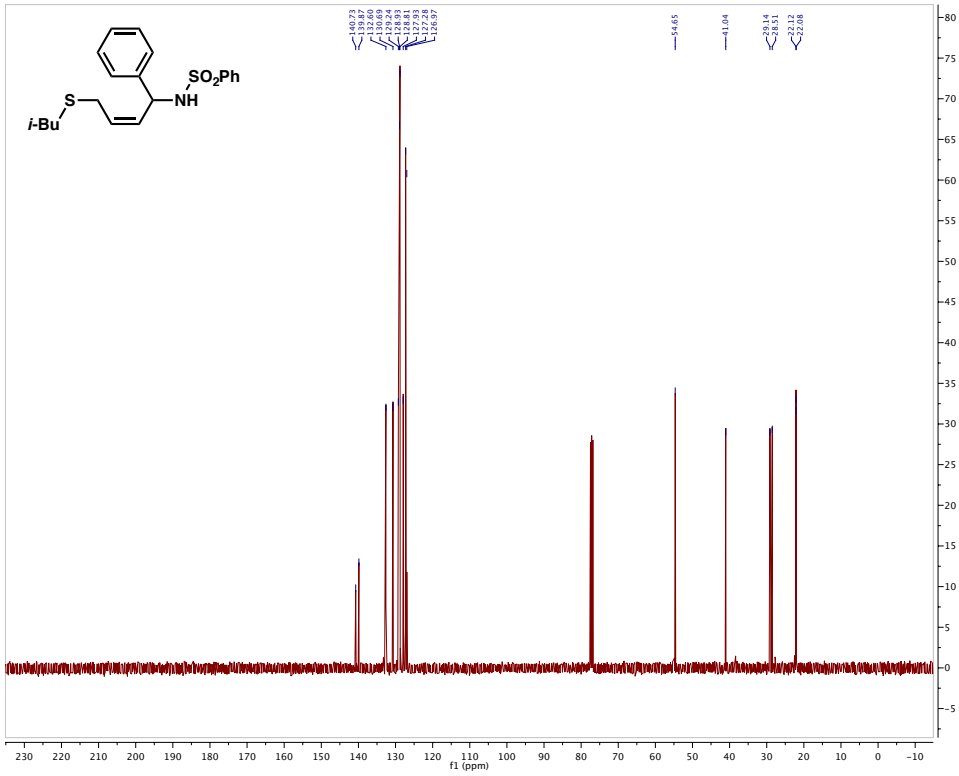


Figure A1.15, Compound 1.55

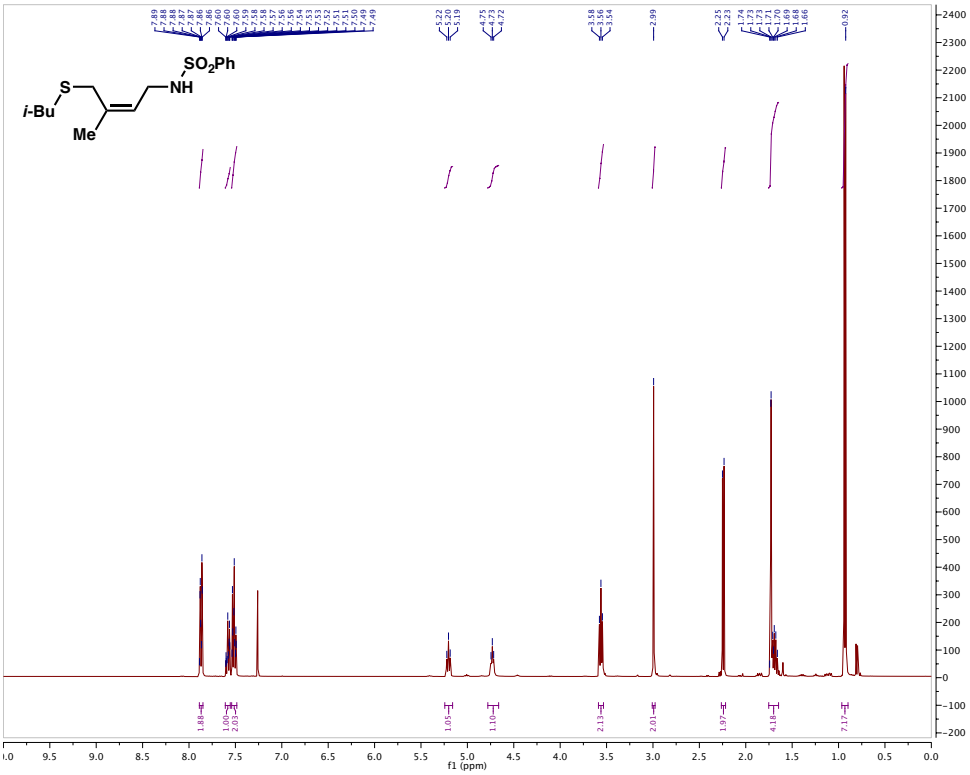
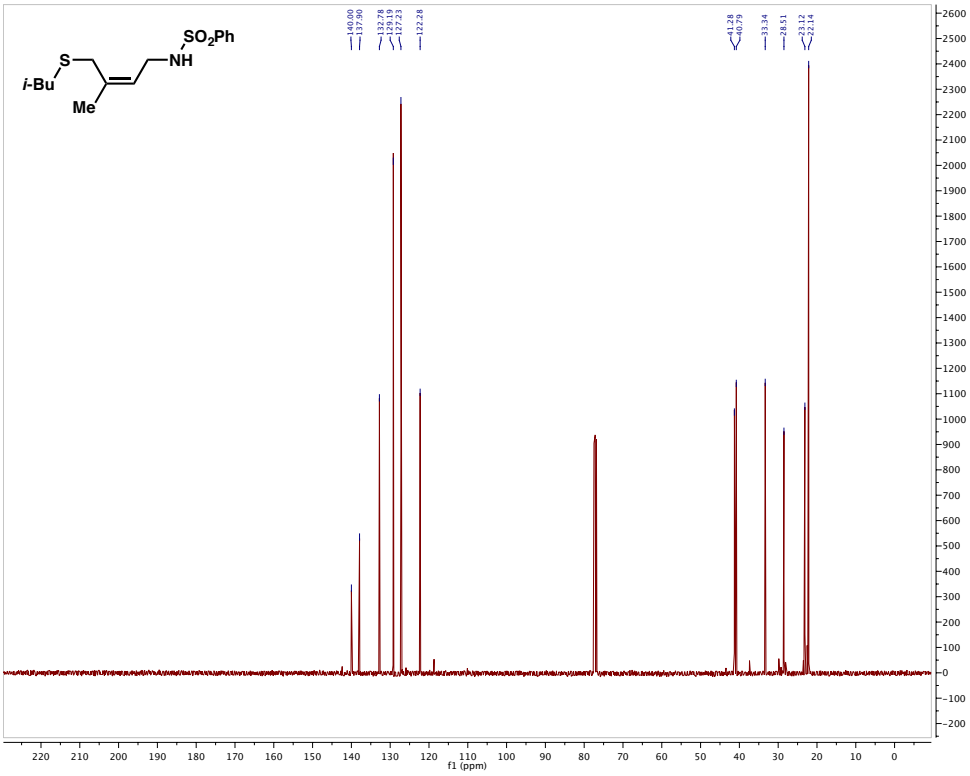


Figure A1.16, Compound 1.55



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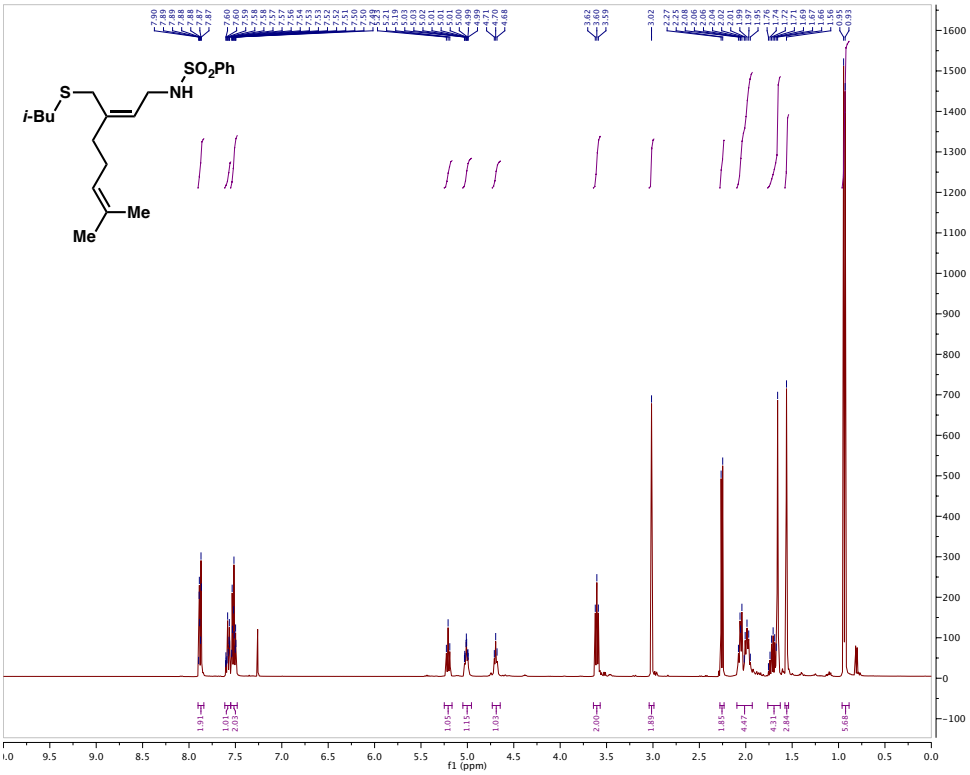

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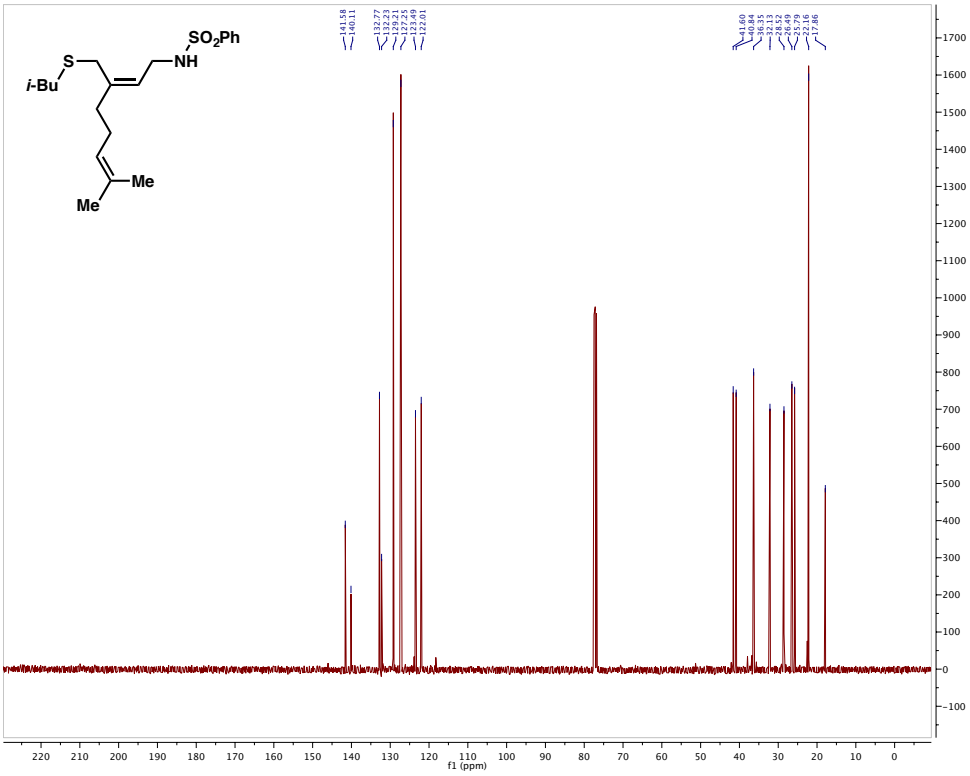

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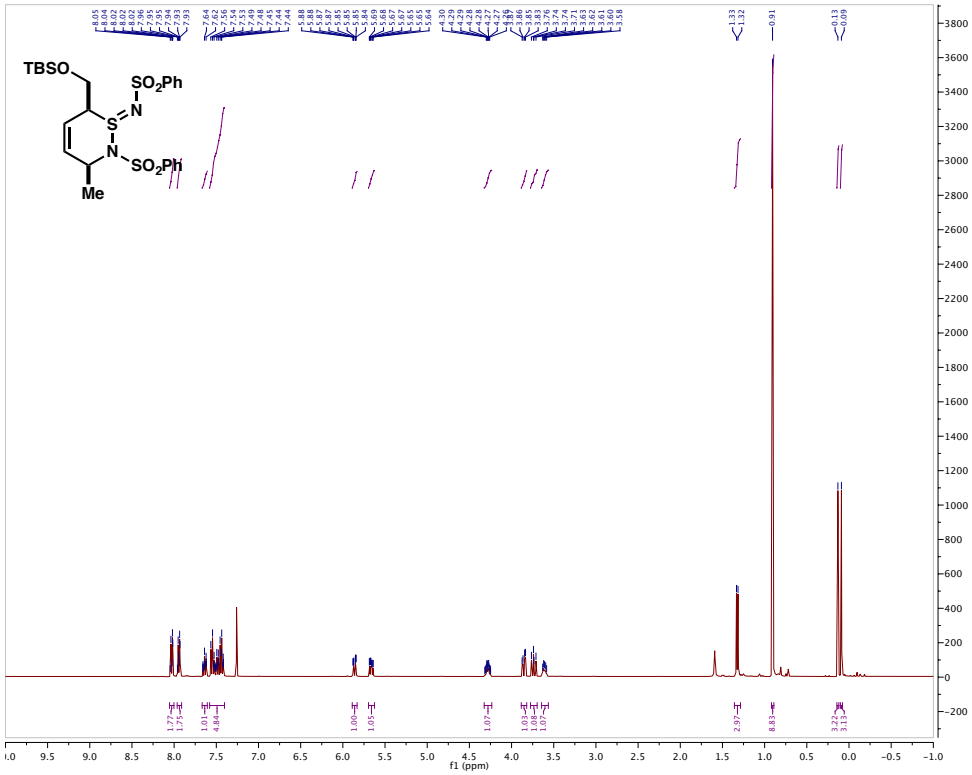

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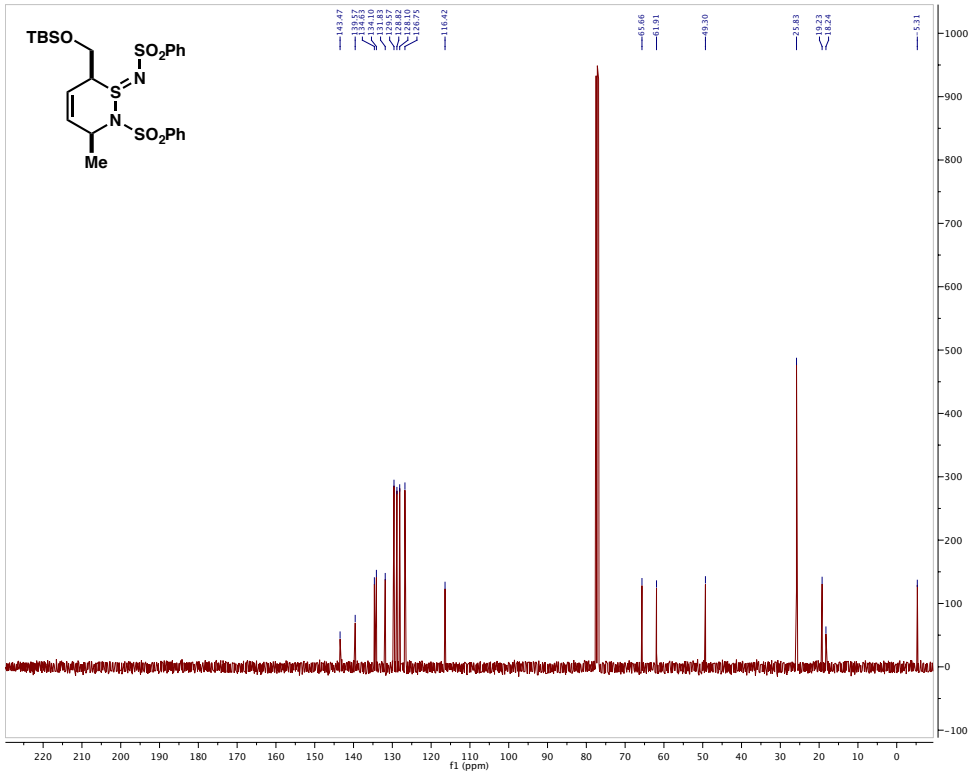

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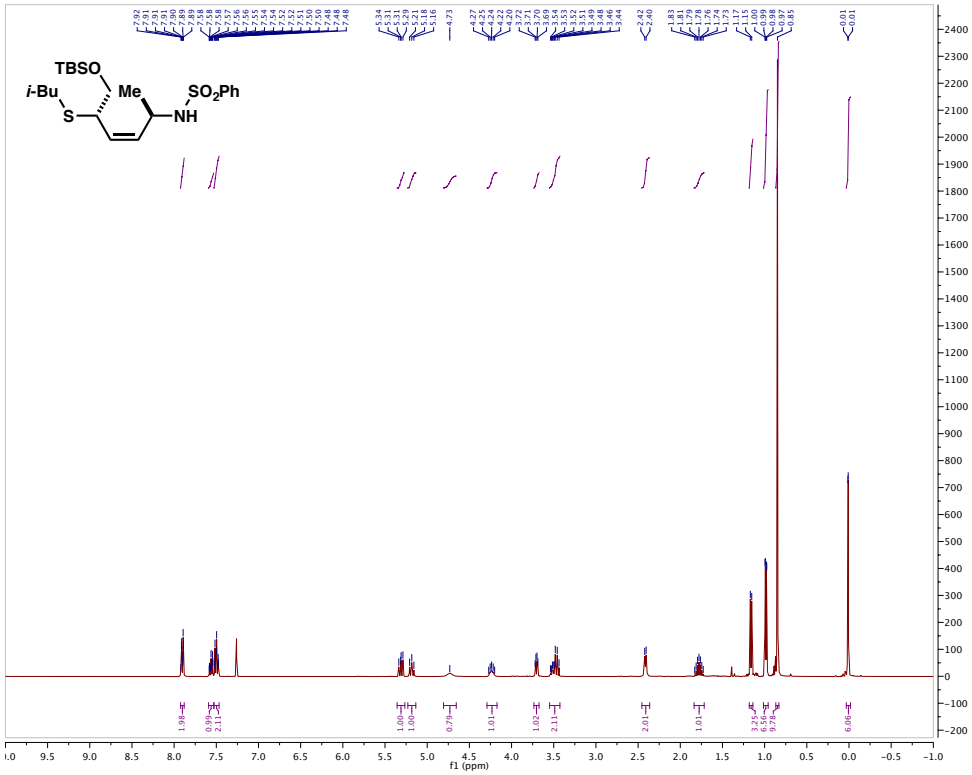

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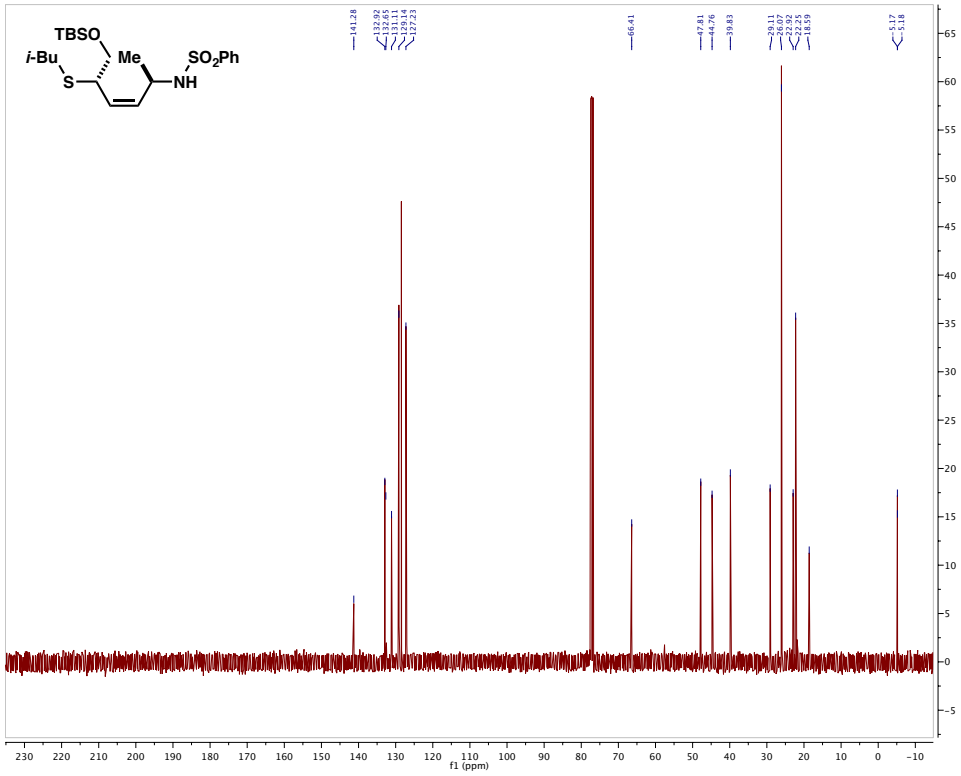

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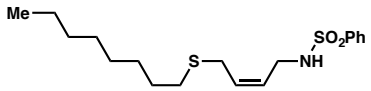

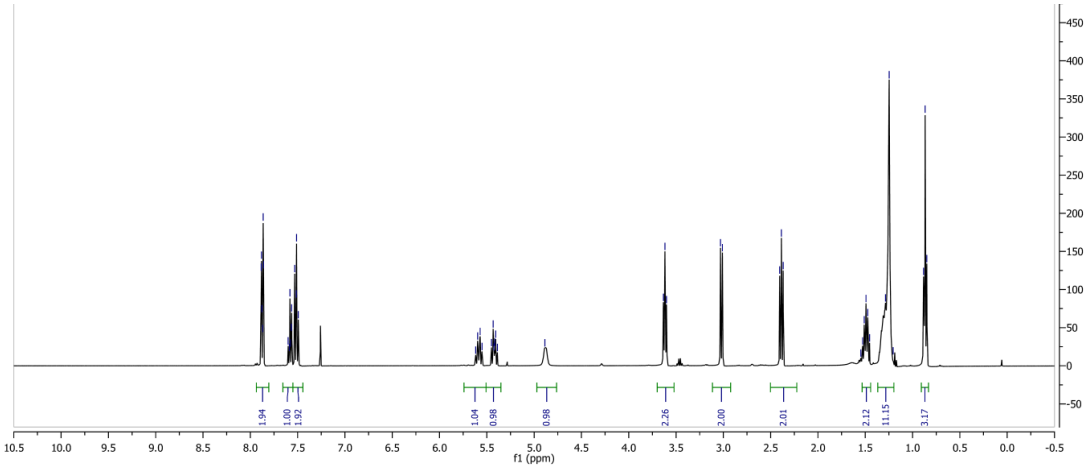

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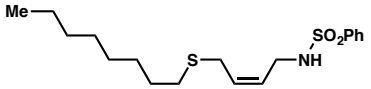

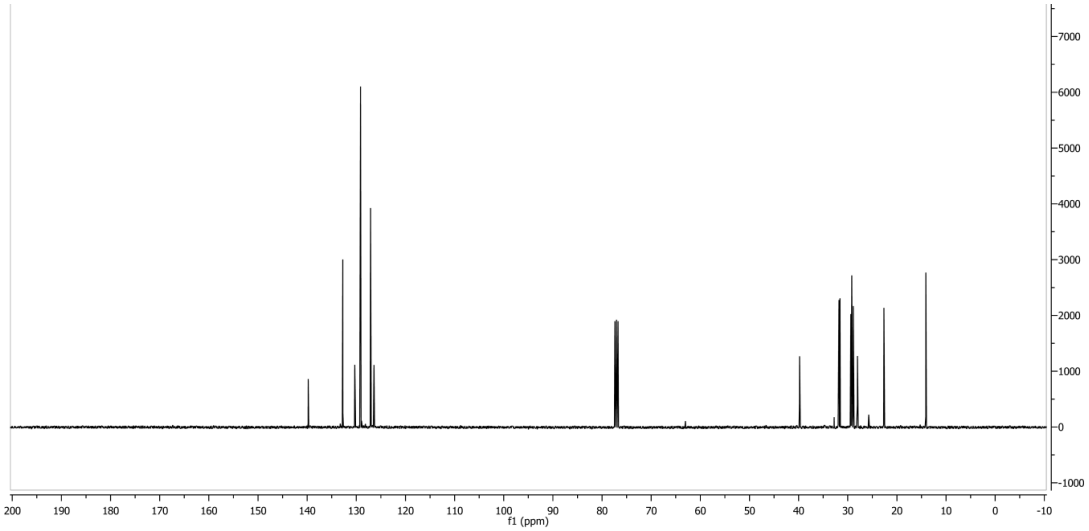

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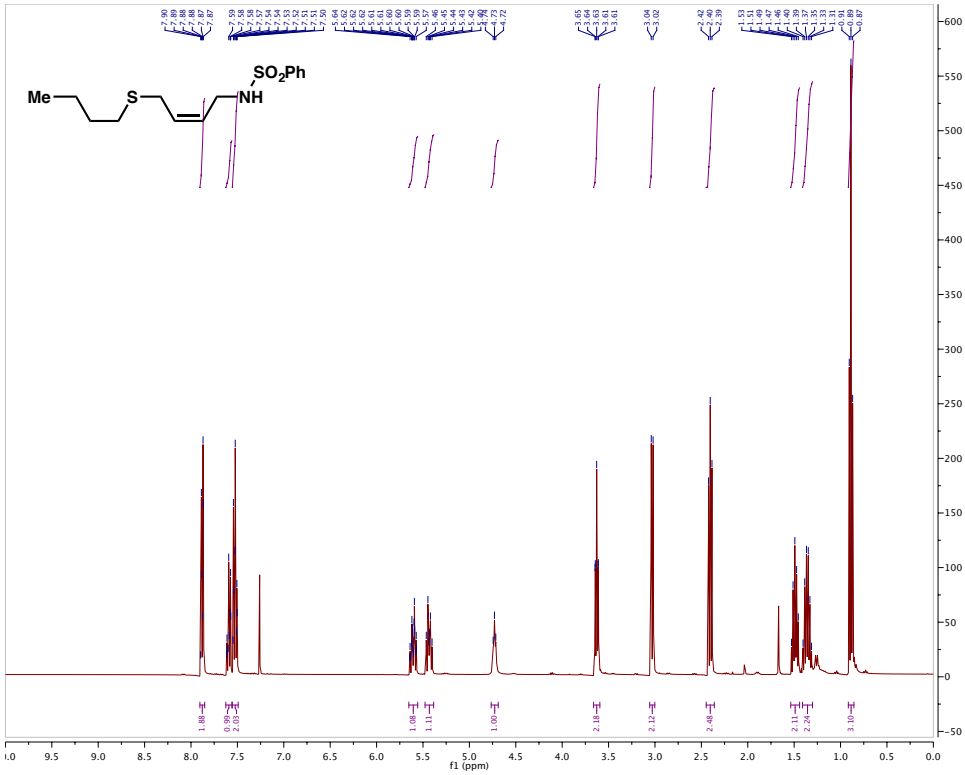

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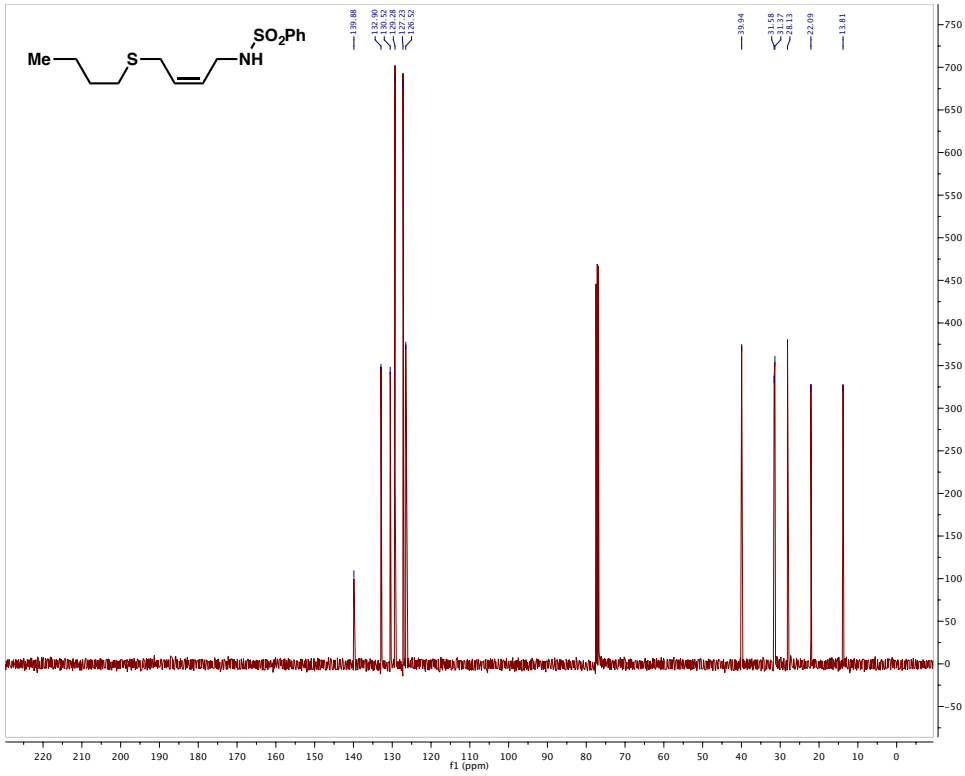
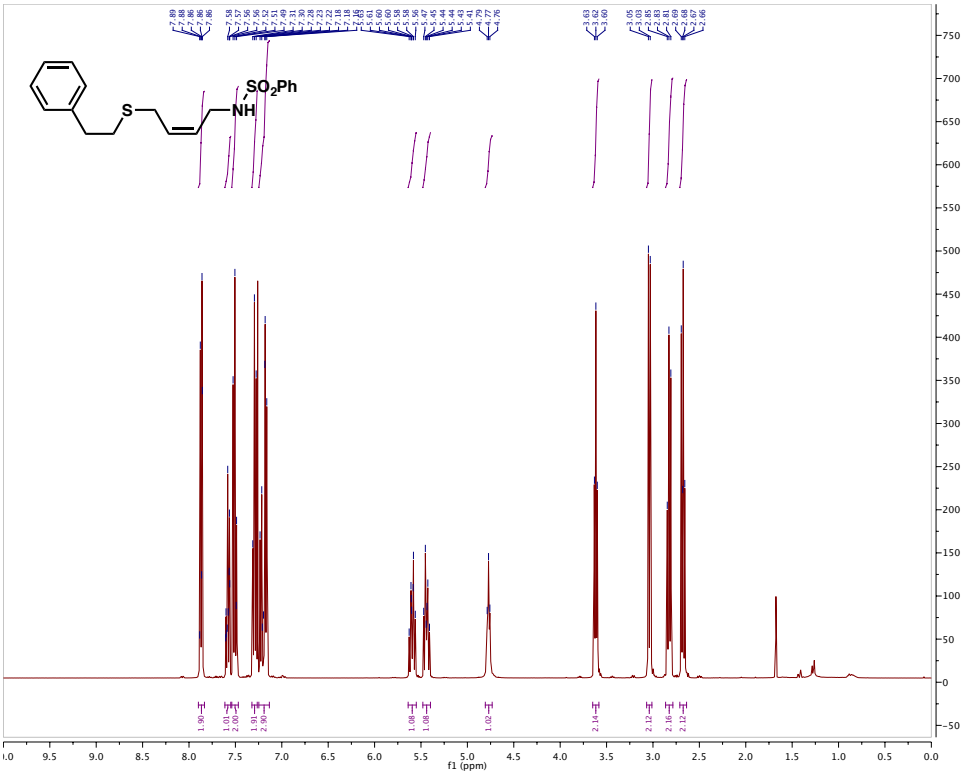


Figure A1.27, Compound 1.67



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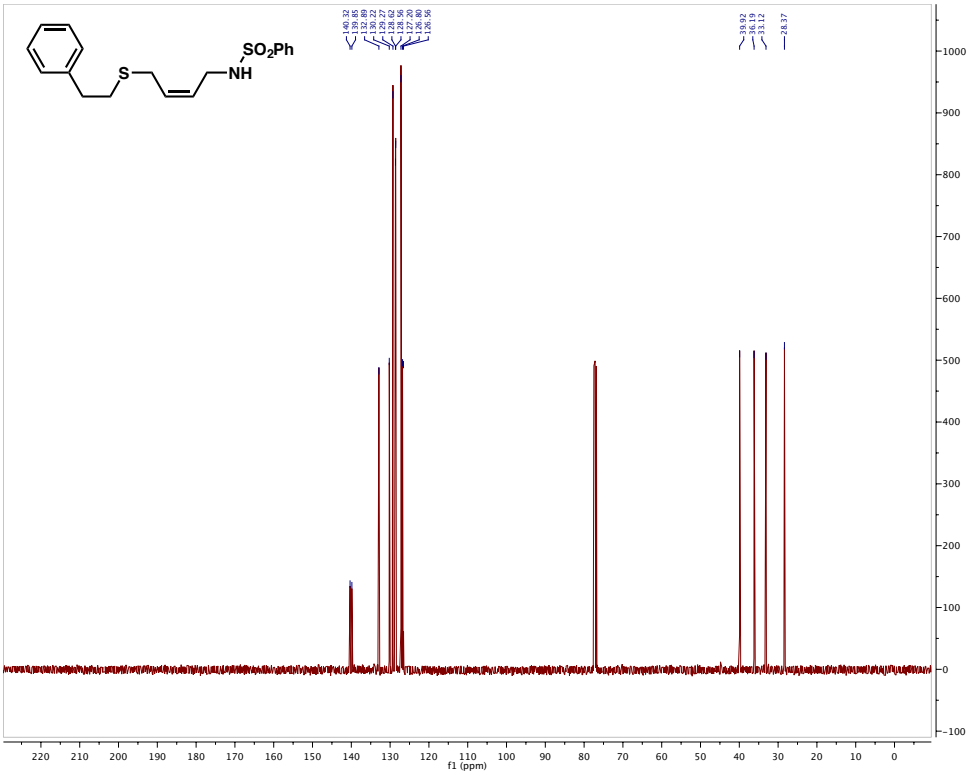

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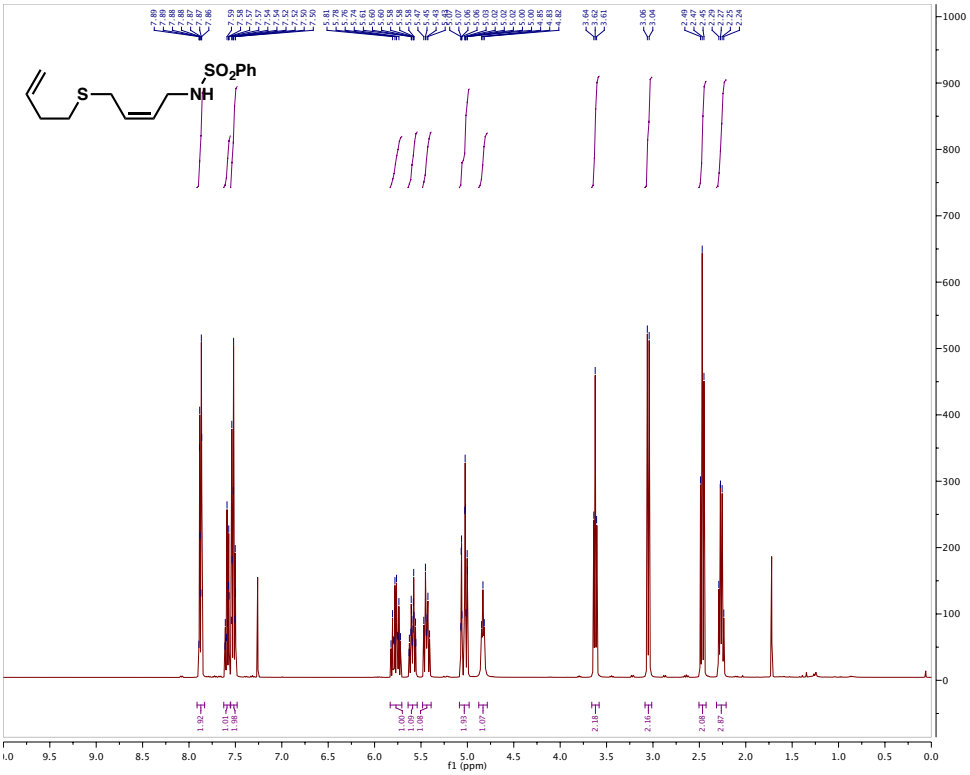

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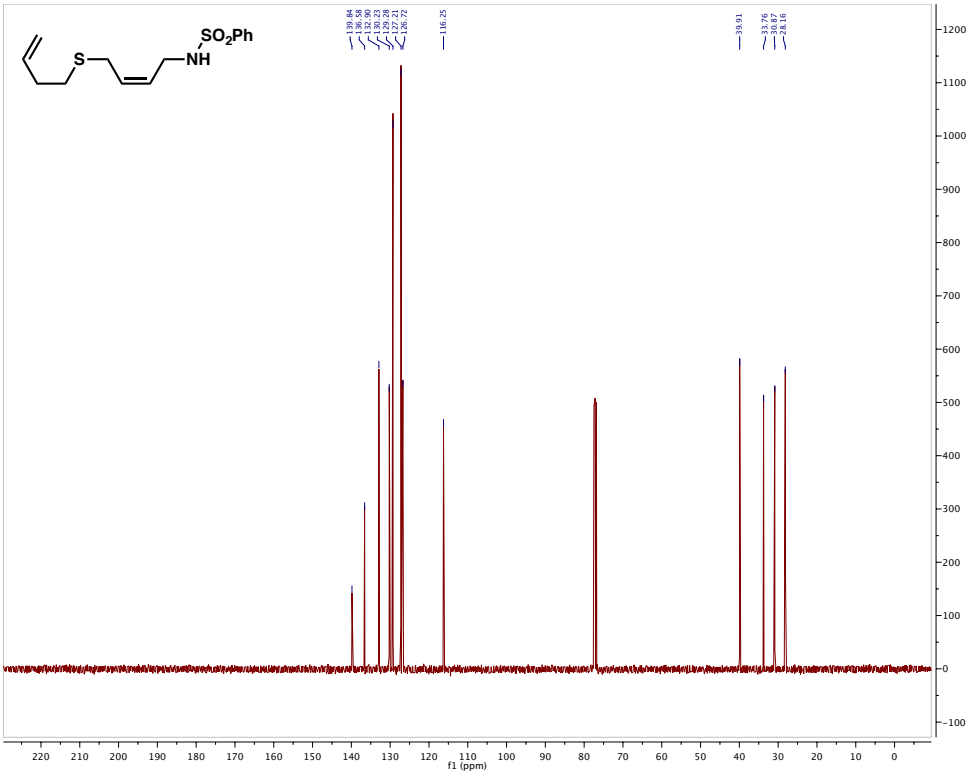
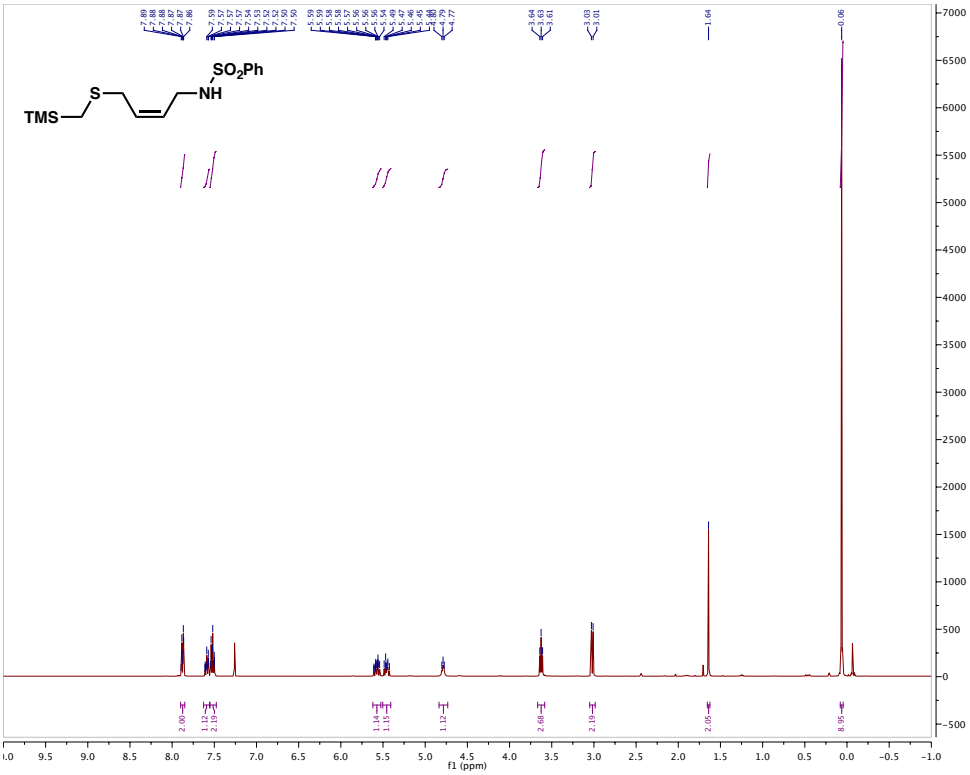


Figure A1.31, Compound 1.68



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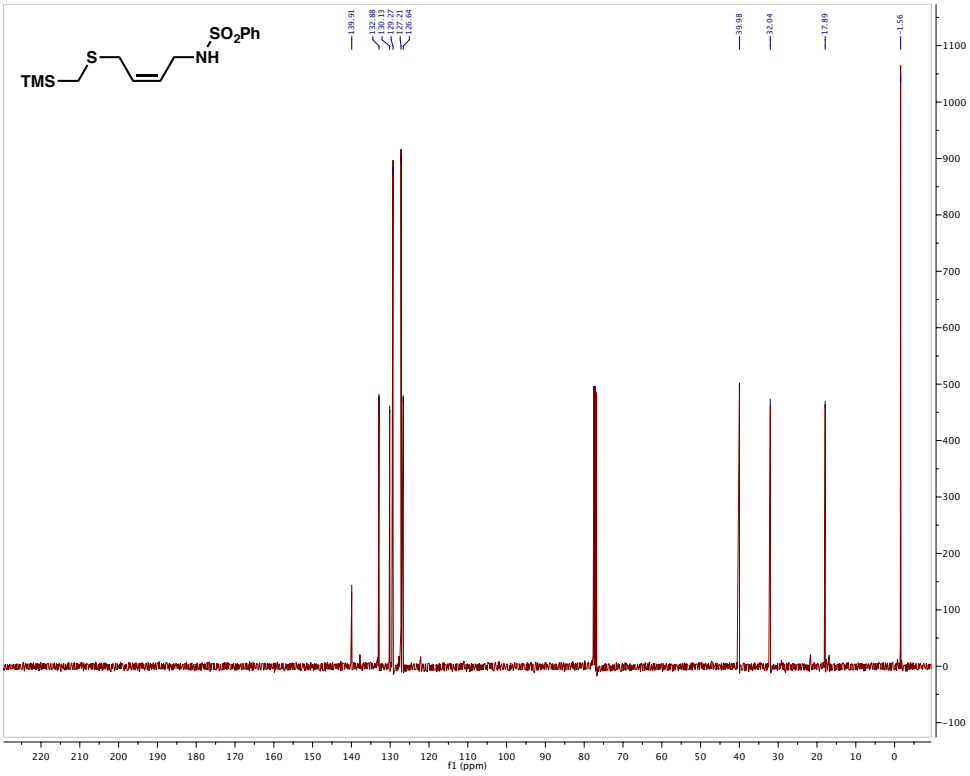

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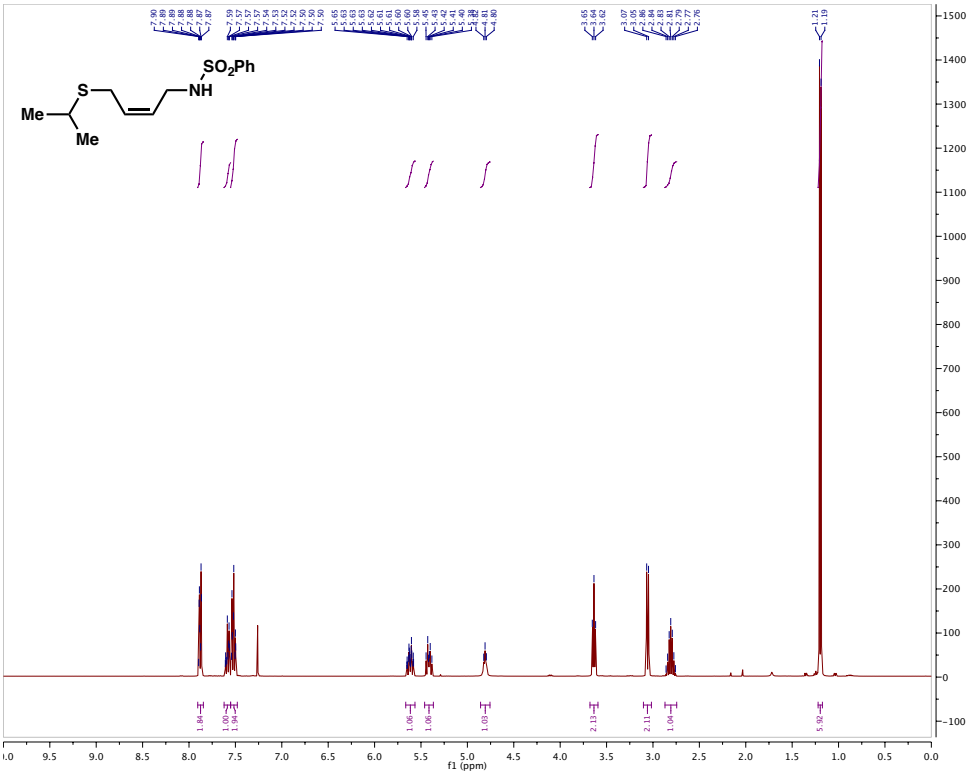

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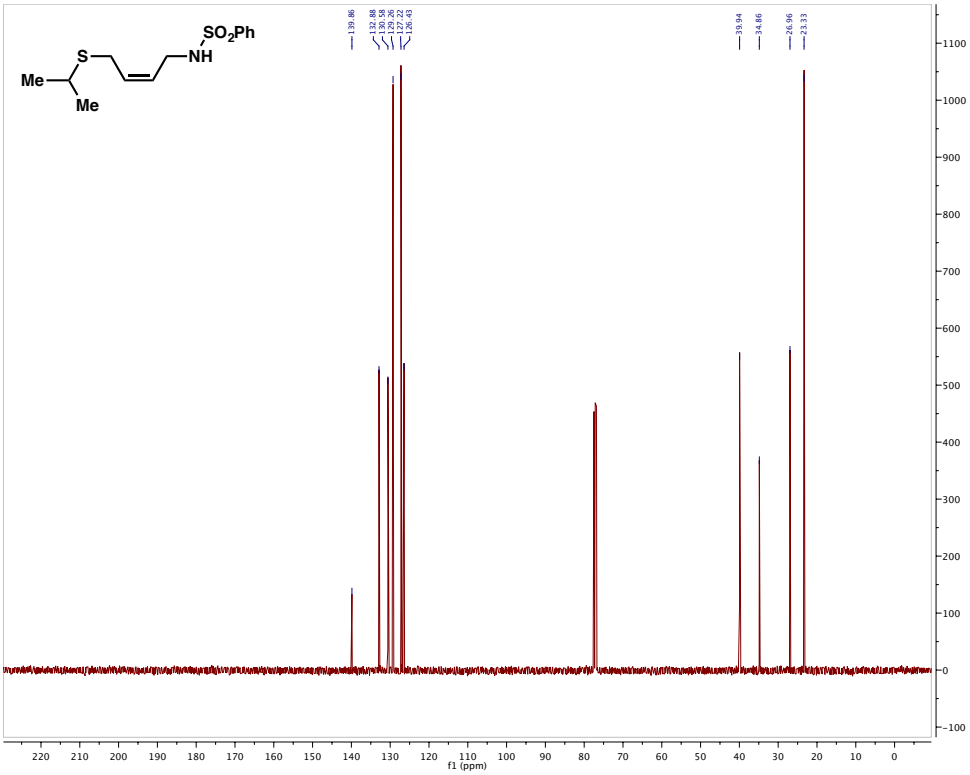

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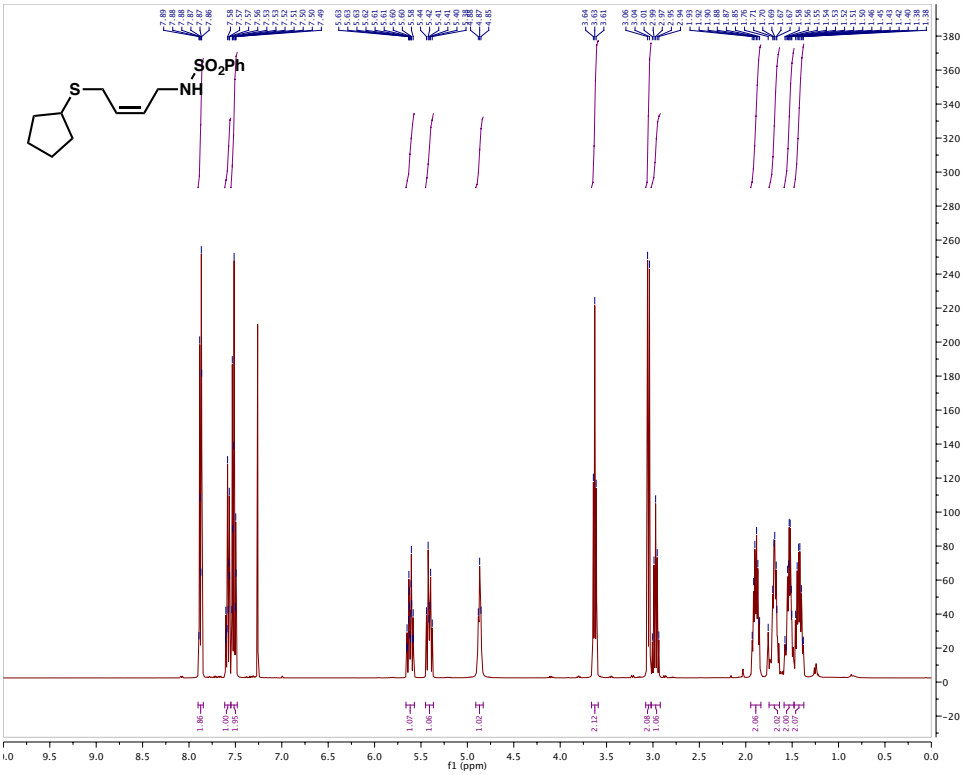

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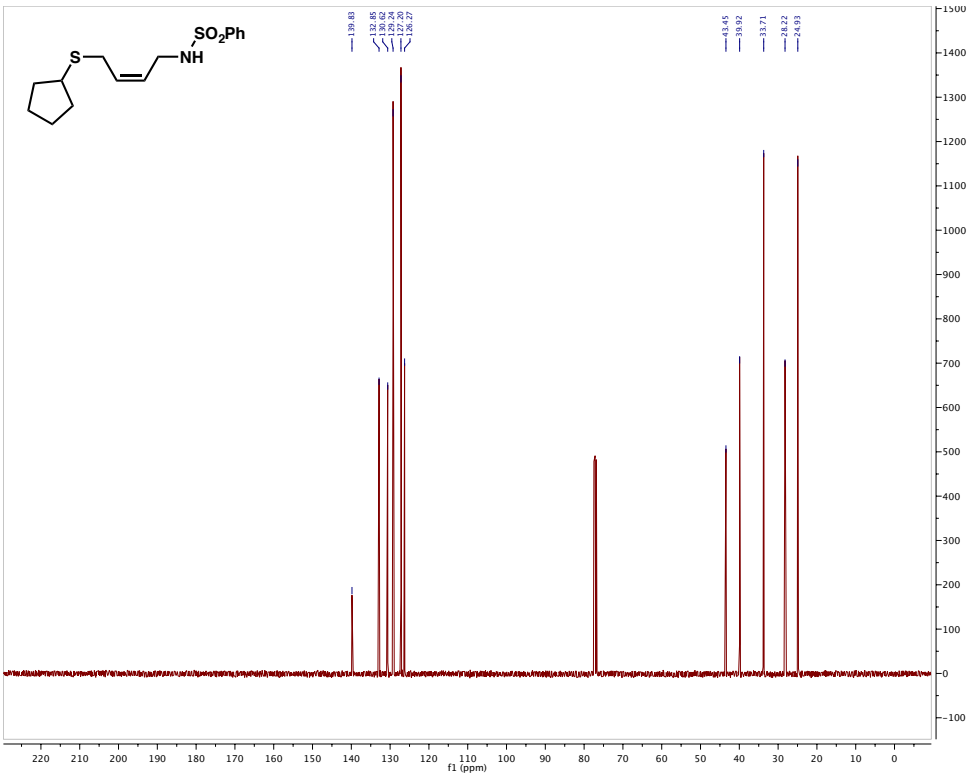


Figure A1.37, Compound 1.64

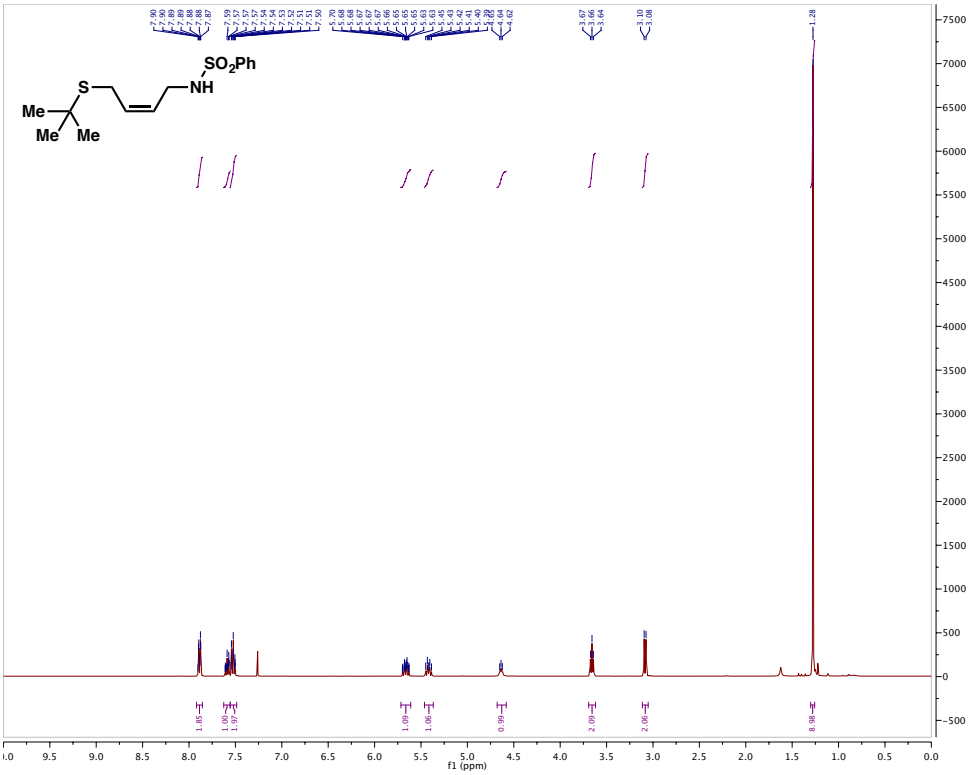
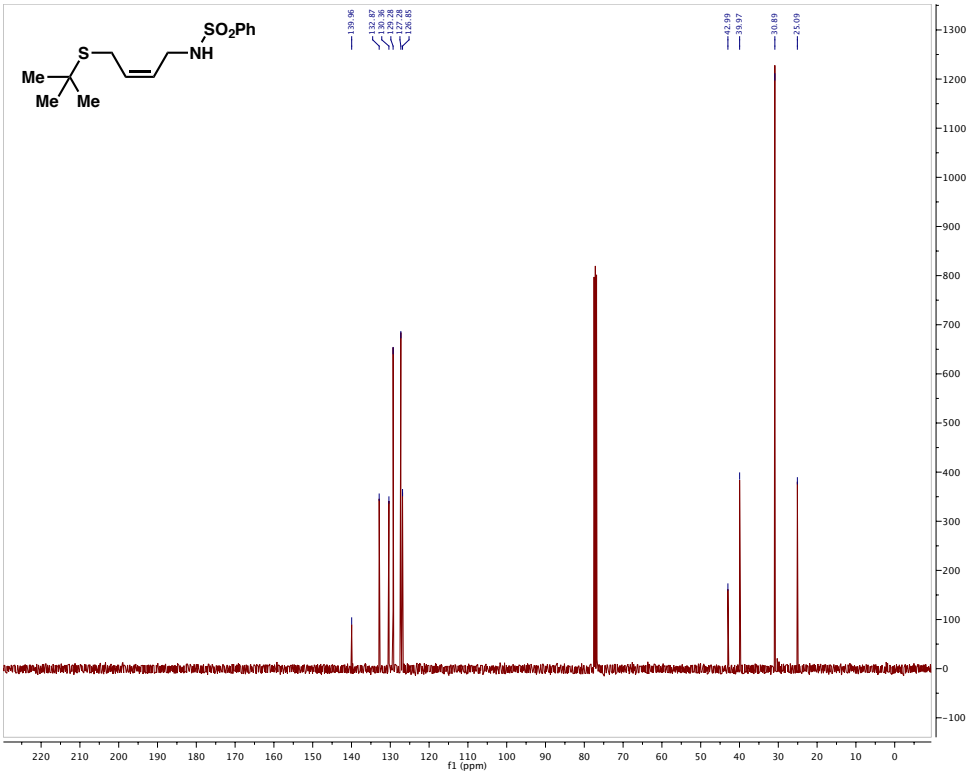


Figure A1.38, Compound 1.64



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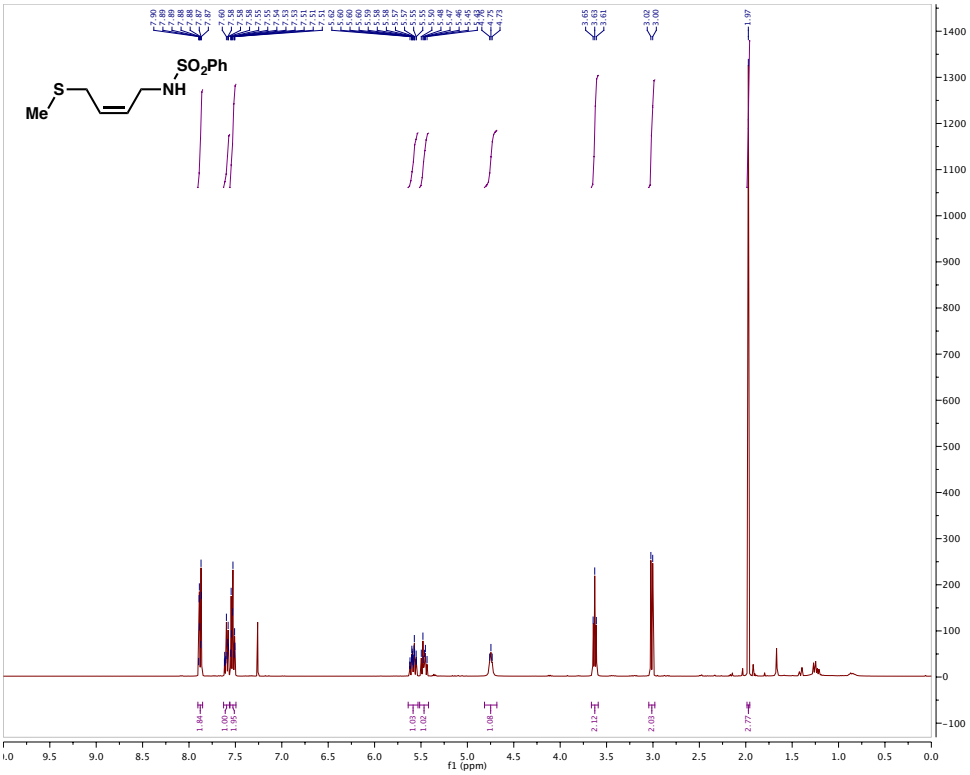

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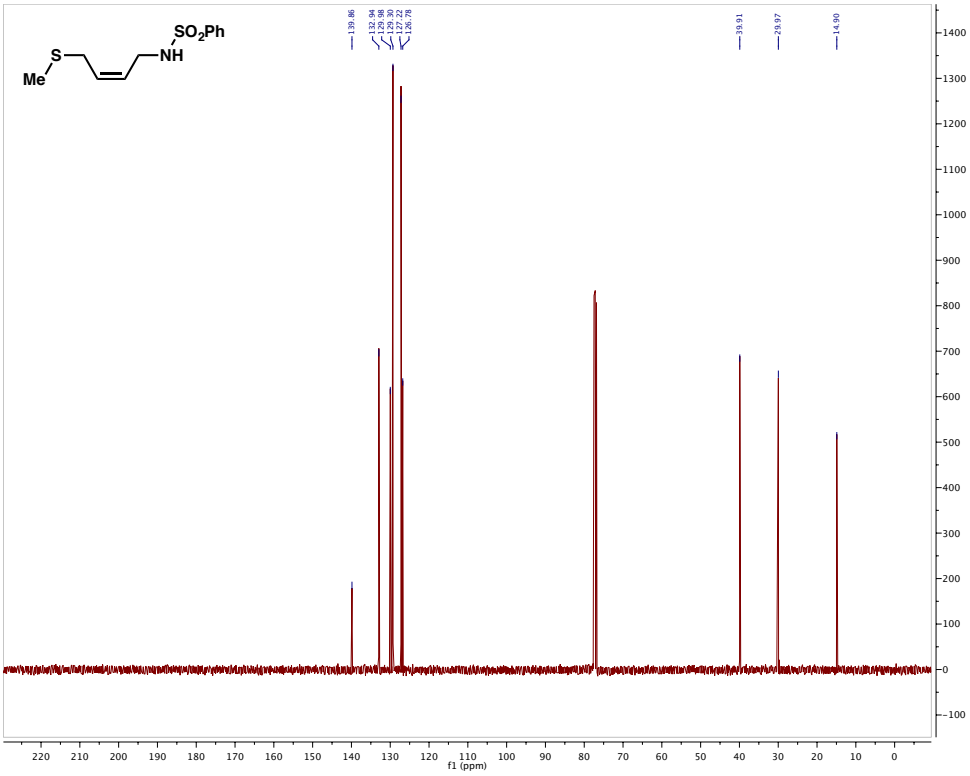
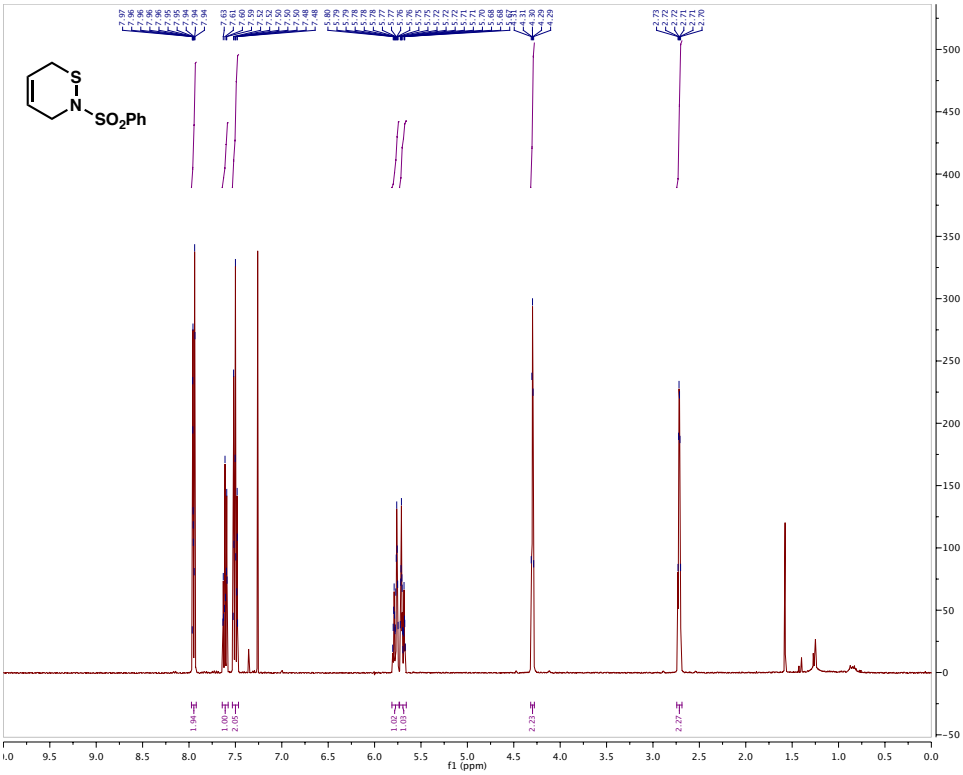


Figure A1.41, Compound 1.52



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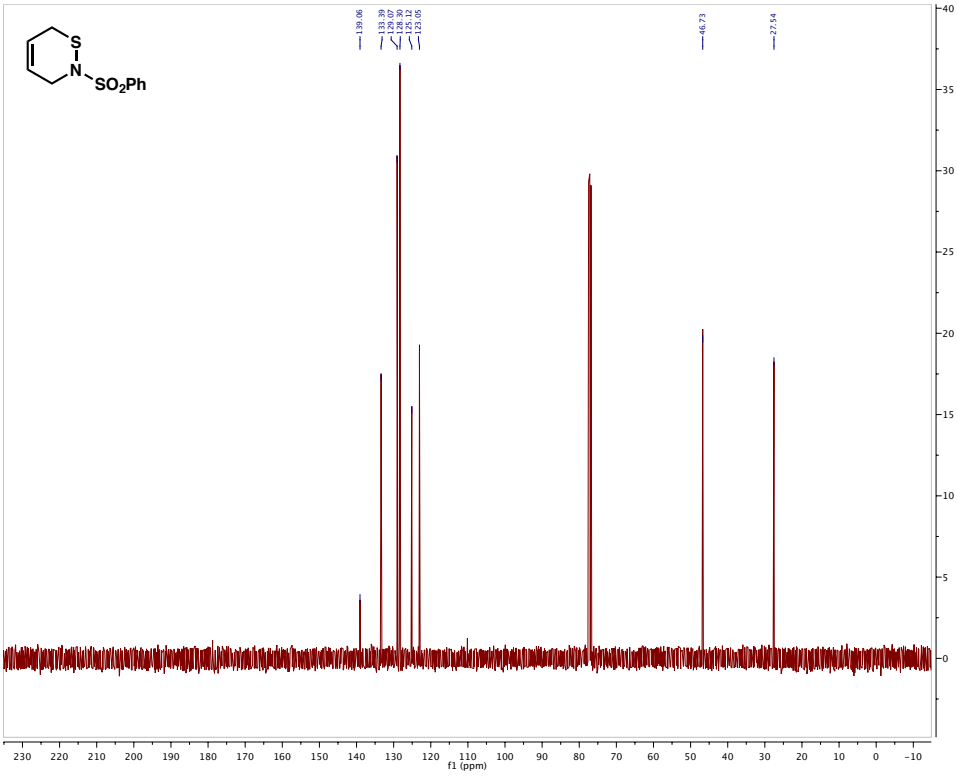
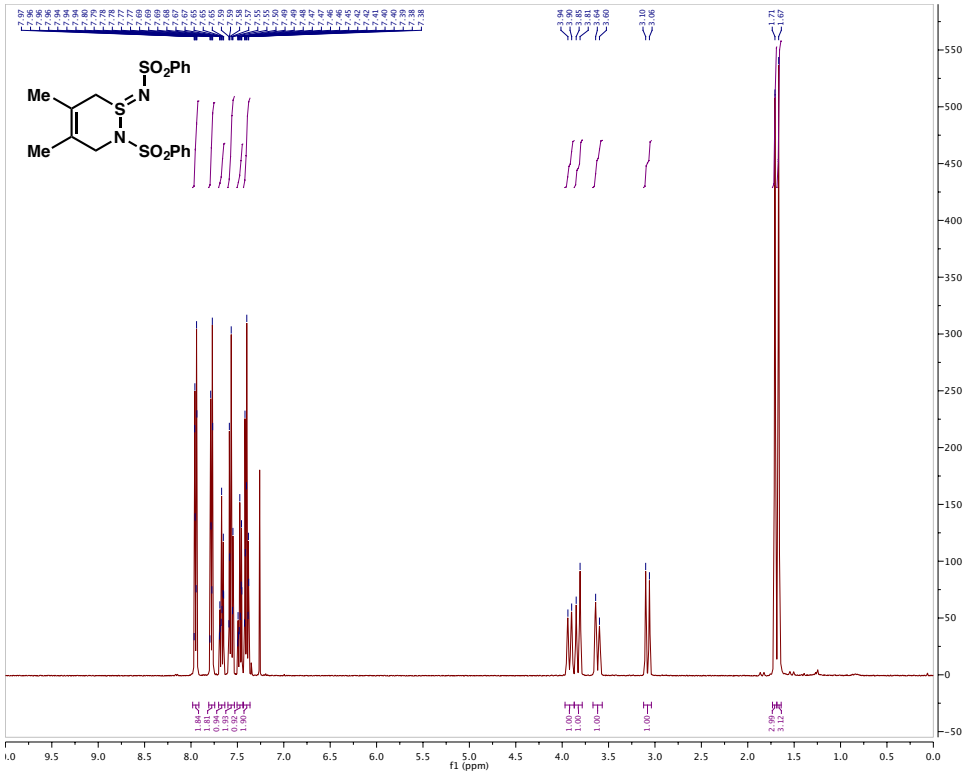


Figure A1.43, Compound 1.71



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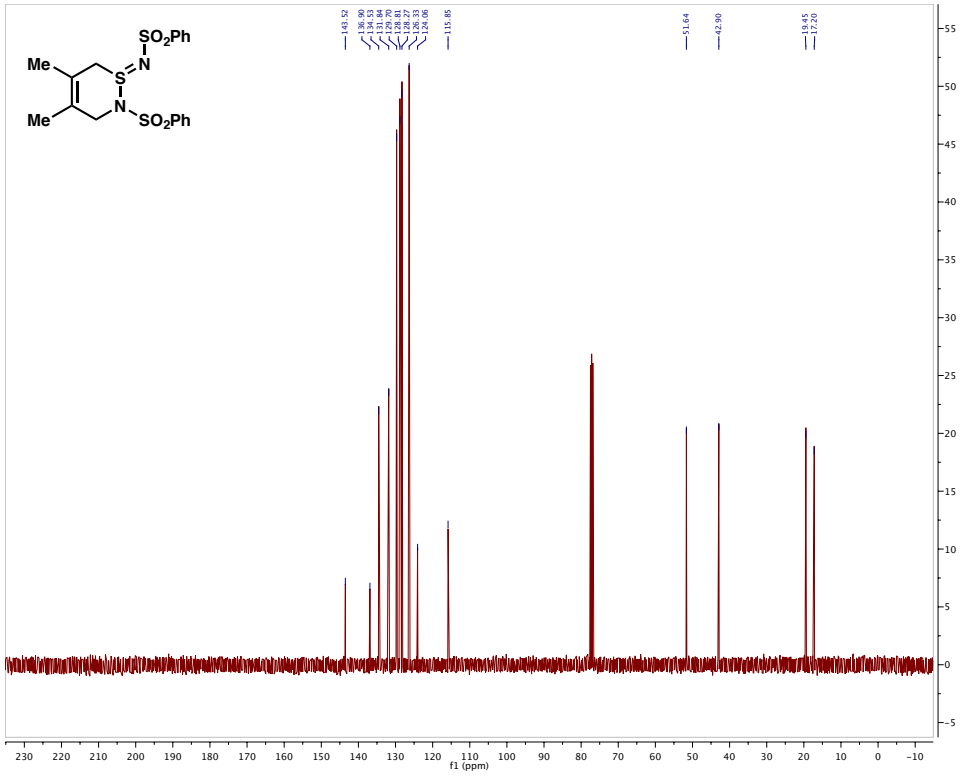

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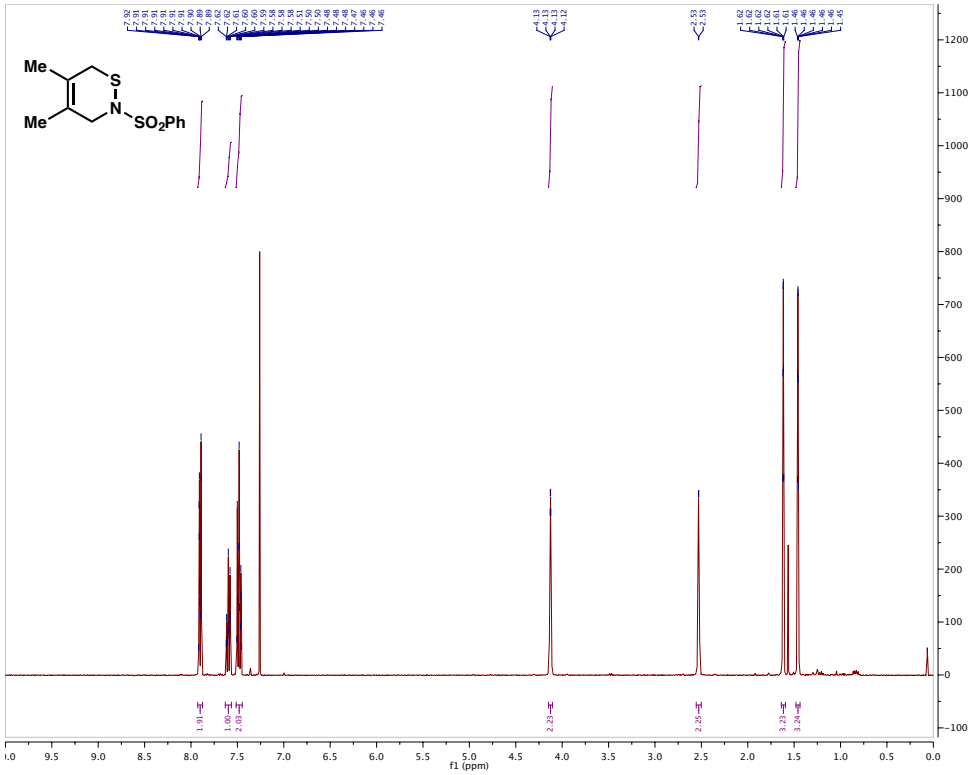

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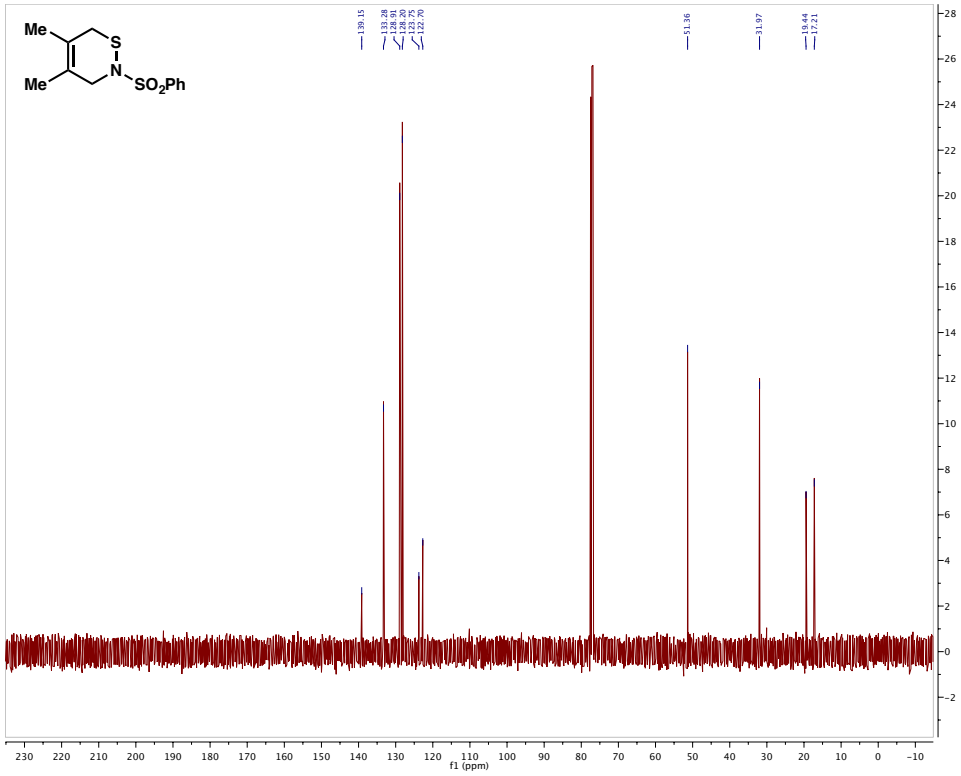


Figure A1.47, Compound 1.74, Entry 1

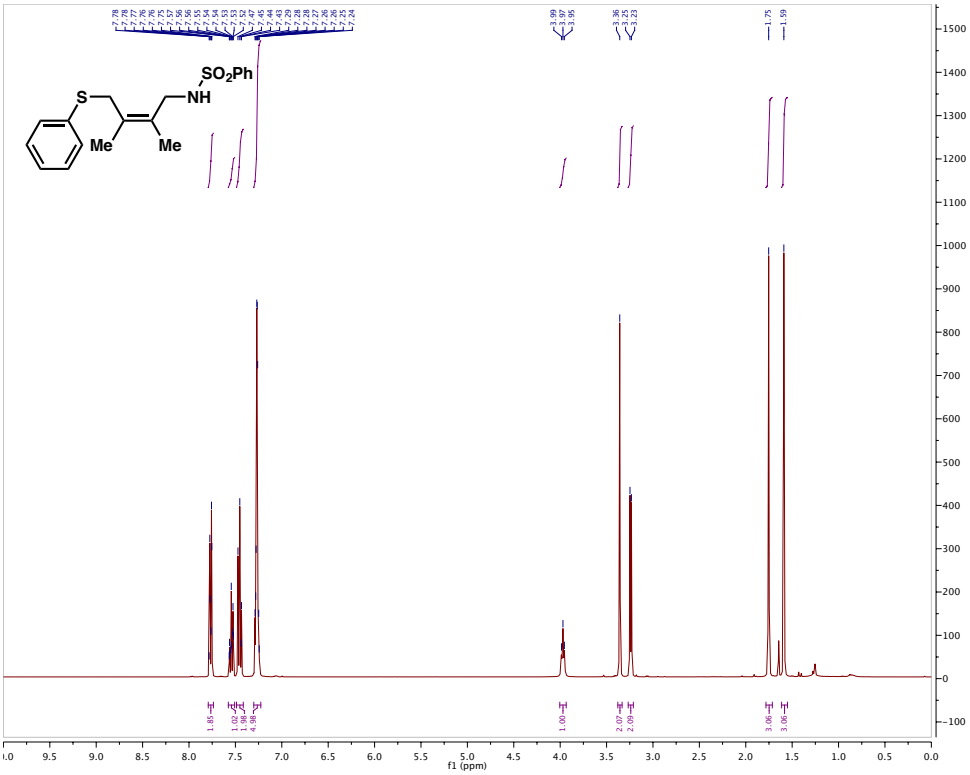


Figure A1.48, Compound 1.74, Entry 1

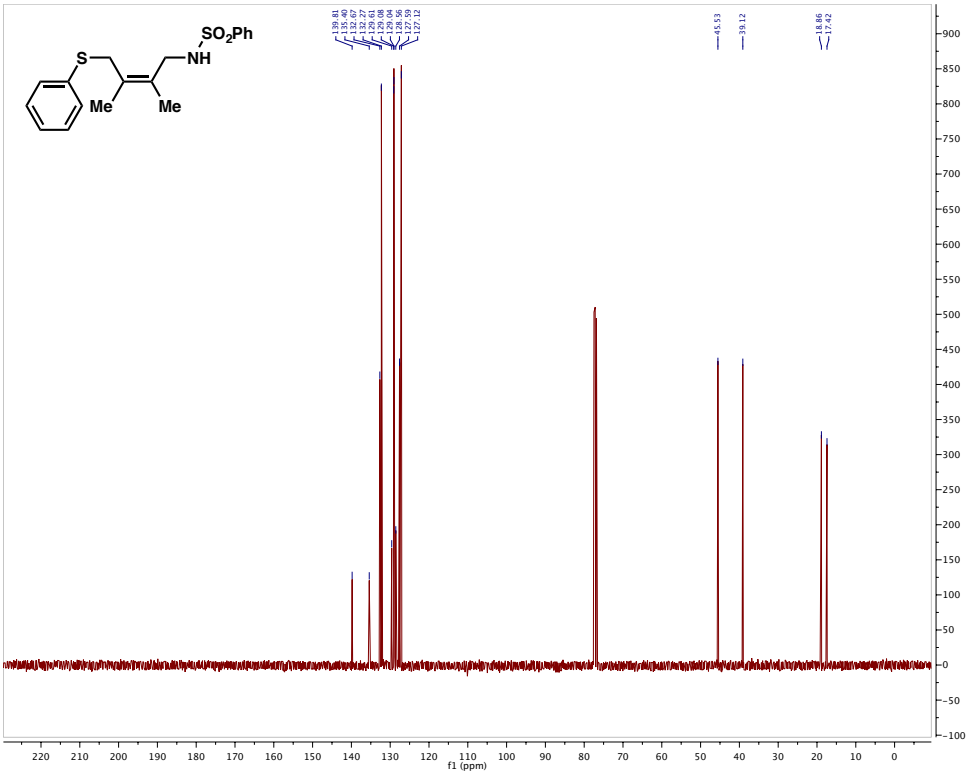


Figure A1.49, Compound 1.74, Entry 2

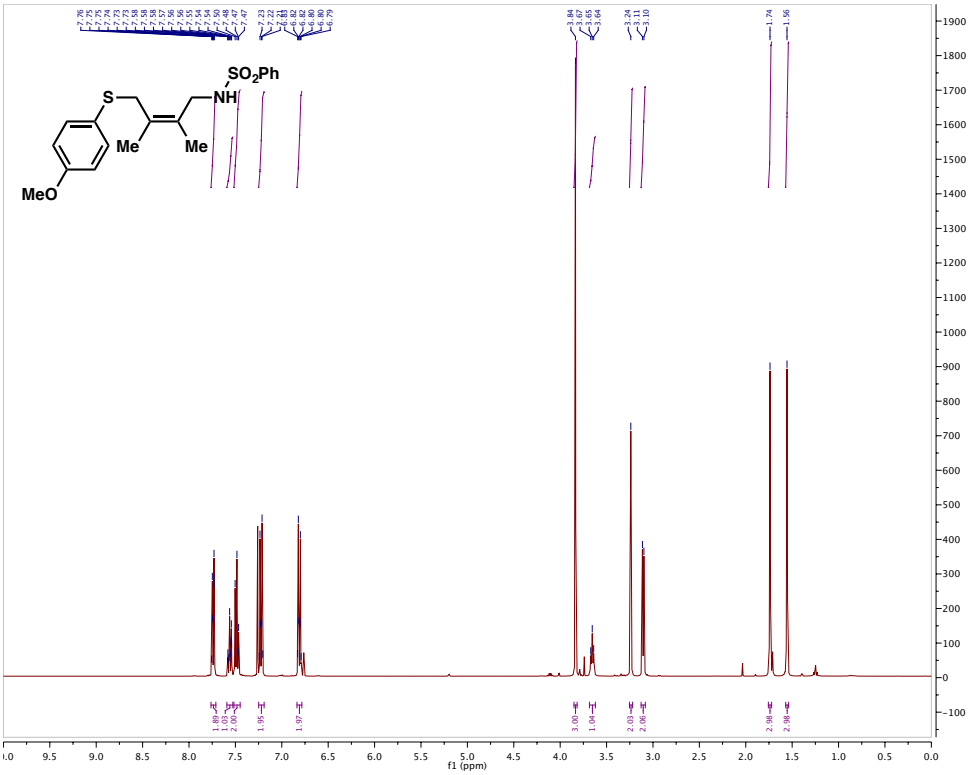


Figure A1.50, Compound 1.74, Entry 2

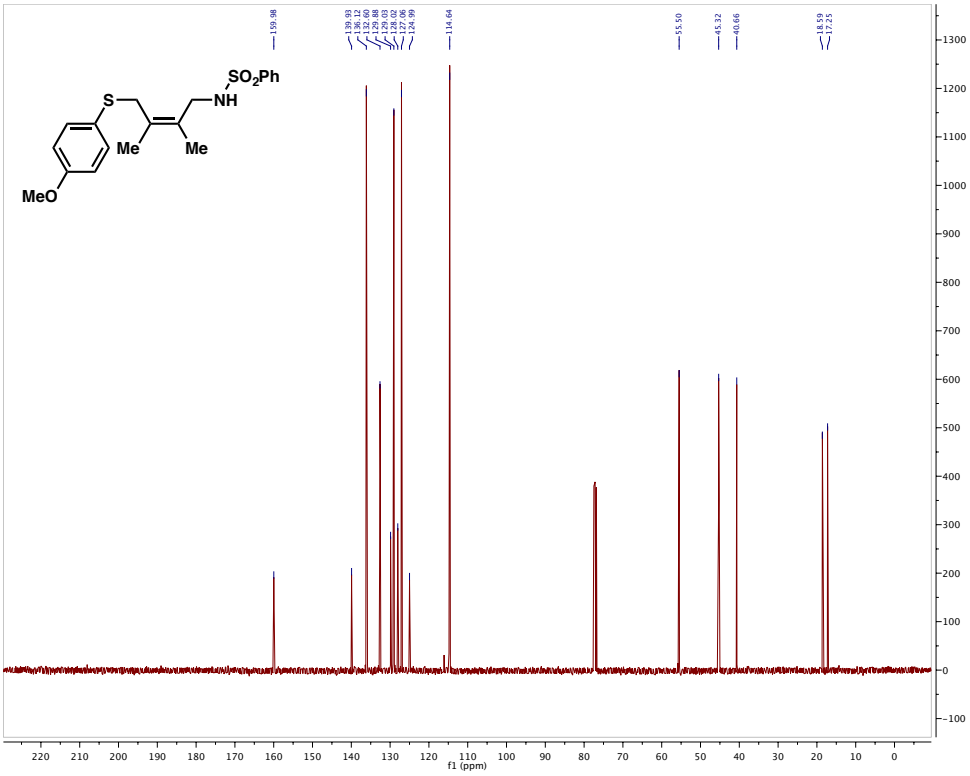


Figure A1.51, Compound 1.74, Entry 3

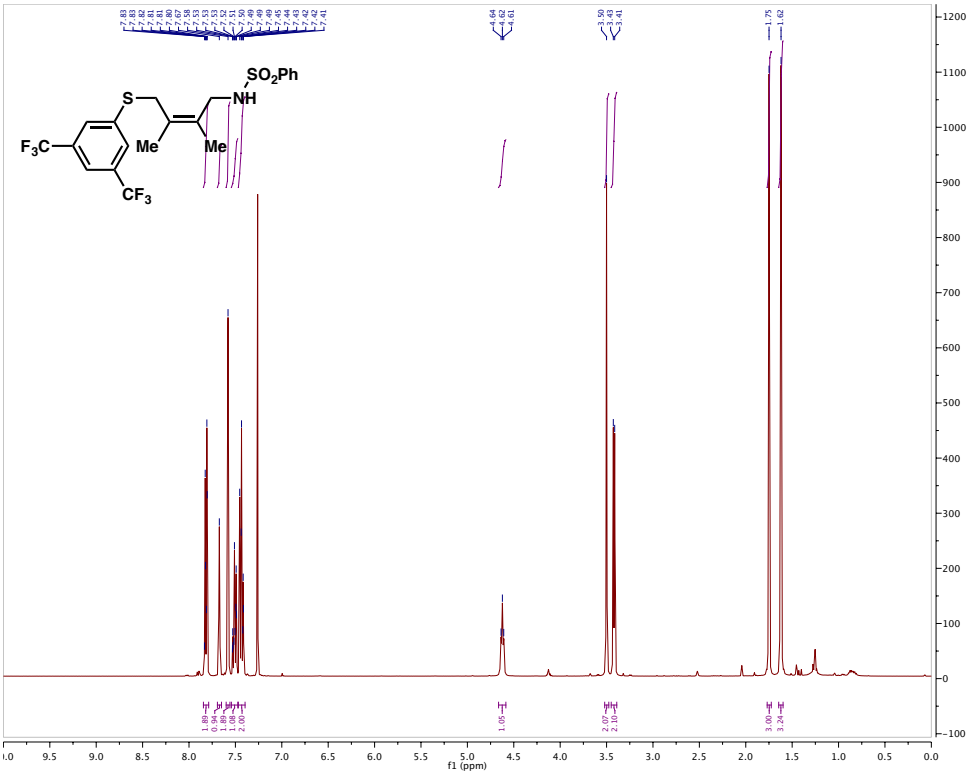
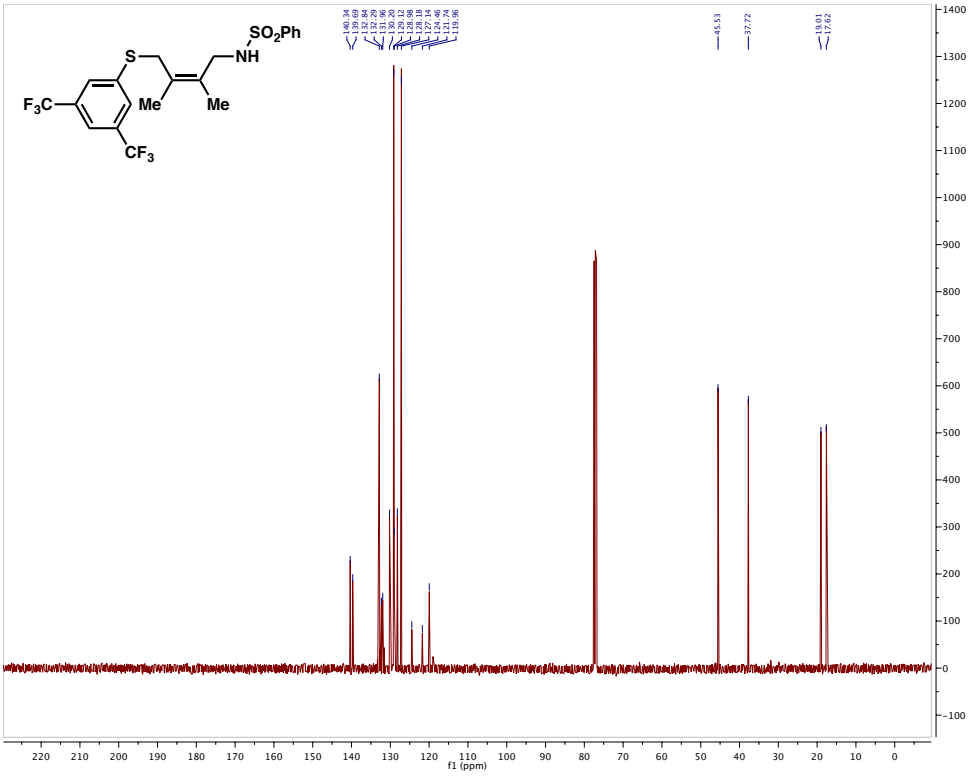


Figure A1.52, Compound 1.74, Entry 3



CHAPTER TWO

The Development of a Catalyst-Controlled, Enantioselective Hetero-Diels-Alder Reaction of Sulfur Imide Dienophiles

2.1 Background

2.1.1 Introduction

The Diels-Alder reaction continues to provide significant inspiration for synthetic organic chemists. The transformation's ability to selectively combine two complex stereochemical fragments with ease is difficult to match. Moreover, the full potential of the reaction is yet to be realized. The general Diels-Alder reaction combines a four-membered, carbon-based 1,3-diene with a two-membered, carbon-based dienophile.[1] The product of the transformation is an all-carbon cyclohexene. Although the transformation appears simple on the surface, one can exert a substantial amount of control over the regio- and stereoselectivity of the product by altering the electronics, geometry, and steric hinderance of the diene and/or dienophile. The reaction is further complicated when introducing one or more heteroatoms into the diene and/or dienophile. The introduction of heteroatoms into the reacting functional groups (diene and/or dienophile) is known as the hetero-Diels-Alder reaction.[2-3]

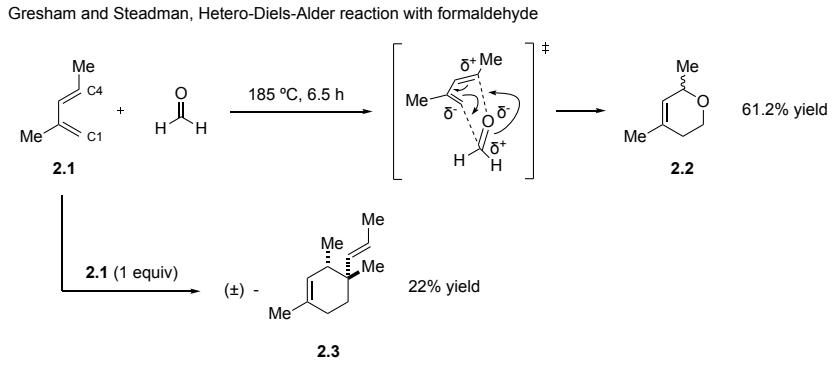
The selective introduction of heteroatoms continues to be an exciting area of research, with many high-impact discoveries made over the past several decades.[4-7] Utilizing the hetero-Diels-Alder reaction one can introduce a series of heteroatoms with high regio- and diastereoselectivity, however enantioselectivity remains to be a challenge. Specifically, a method to insert both sulfur and nitrogen into the product with high enantioselectivity is difficult to accomplish. If one were to produce a method delivering sulfur and nitrogen into the cycloadduct with high enantioselectivity, it would provide a favorable method to access valuable products for medicine and materials science.

Notably, with the advent of possible secondary transformations it would be plausible to reach products beyond the scope of the Diels-Alder transformation. Specifically, one could envision a selective aminothiolation of 1,3-dienes if sulfur and nitrogen were components of the dienophile.[8] The development of a catalyst-controlled method to reach the desired enantiomer of the cycloadduct would further benefit the utility of such an approach. Amid proper selection of a catalyst, the scope of the diene may potentially have fewer limitations.

2.1.2 Hetero-Diels-Alder Reaction

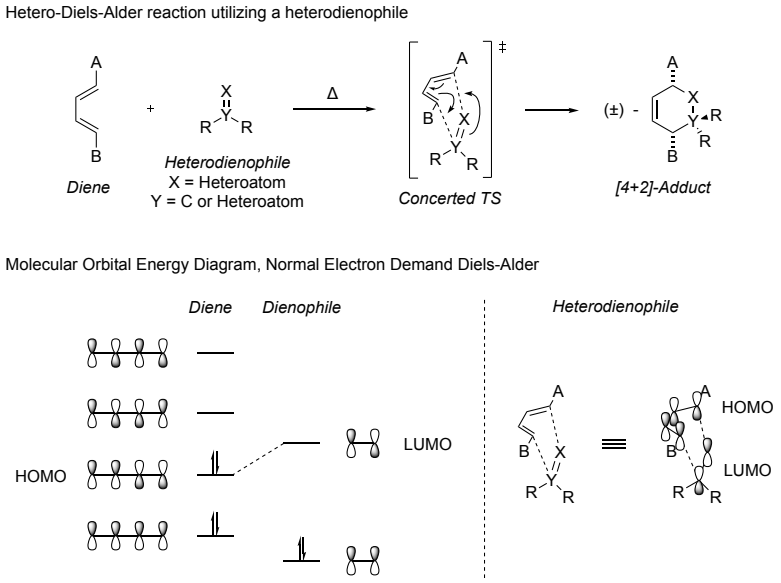
The first example of a hetero-Diels-Alder reaction was reported by Gresham and Steadman in 1949, approximately 21 years after the initial discovery of the Diels-Alder reaction by Otto Diels and Kurt Alder.[9-10] The pair report an unusual example in which formaldehyde serves as the dienophile, reacting with 2-methylpenta-1,3-diene **2.1** to yield 2,4-dimethyl-5,6-dihydro-1,2-pyran **2.2** (Scheme 2.1.1). The reaction displayed high regioselectivity, a result of the electron-donating nature of the methyl substituents on 1,3-diene **2.1** and the dipole of the carbon-oxygen bond in formaldehyde. However, the yield of the reaction is unimpressive due to the competing Diels-Alder reaction between 1,3-diene **2.1** and a second equivalent of itself, forming homo-dimer **2.3**.

Scheme 2.1.1



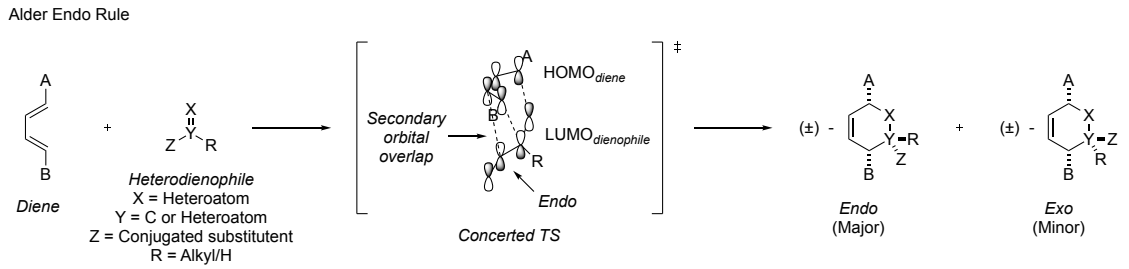
Following the innovation by Gresham and Steadman, researchers from around the world were inspired to examine the inclusion of heteroatoms in the Diels-Alder reaction. In turn, it was uncovered that heteroatoms may be incorporated into both the 1,3-diene and dienophile. For the purposes of this mini-review, it will focus on the incorporation of heteroatoms into the dienophile. A special advantage of heteroatoms residing within the dienophile, is that many 2-membered, heteroatom-containing functional groups exist that are linked by a double bond. Further, the heteroatom-containing dienophiles are easily accessible compared to their 1,3-diene counterparts. The general scheme for the reaction between a heterodienophile and carbon-based 1,3-diene is pictured below in Scheme 2.1.2. The reaction proceeds under thermal conditions, and advances via a concerted 6-membered transition state. The concerted nature of the transformation qualifies it as a pericyclic reaction. The step-wise transformation is not considered pericyclic; however, it does provide a formal hetero-Diels-Alder product. The benefit of a concerted mechanism is added stereocontrol, contrasting the step-wise mechanism which may lead to isomerization or rearrangement of intermediates. To promote a concerted mechanism, the energy gap between the diene's HOMO and dienophile's LUMO must be relatively small (Scheme 2.1.2).[11]

Scheme 2.1.2



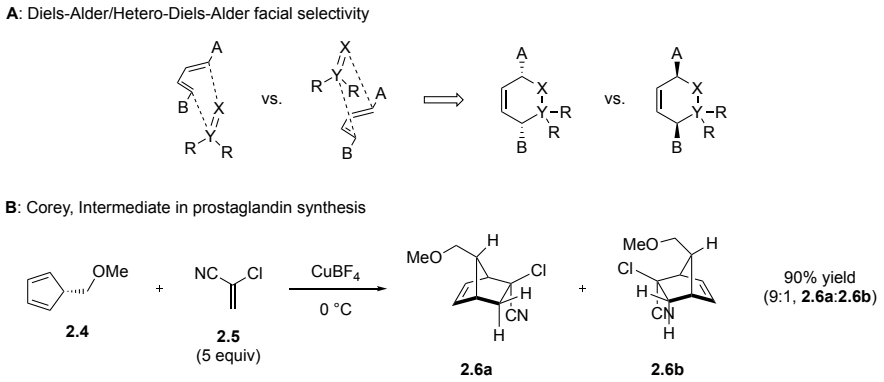
Changing substituents on both the diene and dienophile may exhibit a dramatic effect on the regio- and diastereoselectivity of the transformation. The reaction itself proceeds via matching of molecular charge for the diene and dienophile. For example, in 2-methylpenta-1,3-diene **2.1**, the electron-donating nature of the methyl substituents leads to a buildup of negative charge on C1 (Scheme 2.1.1). The dipole of formaldehyde creates a net positive charge on the carbonyl carbon. The development of these charge distributions leads to matching and coordination of the reactants. Following the overlap of the HOMO-LUMO orbitals, the reaction is initiated. If the dienophile contains a substituent that has the ability to contribute secondary molecular orbital overlap with the 1,3-diene then it will lead to diastereoselection of substituents in the product; this observation is known as the Alder endo rule (Scheme 2.1.3).[12] The endo:exo ratio may be controlled under thermodynamic and/or kinetic conditions.

Scheme 2.1.3



The final means that may exert control over selectivity in the product is the face from which the dienophile approaches the diene, this decision will affect the enantioselectivity (Scheme 2.1.4A). Markedly, if the diene or dienophile does not possess planar symmetry then facial selectivity may be observed. For example, in Scheme 2.1.4B 5-methoxymethyl-cyclopenta-1,3-diene **2.4** does not possess planar symmetry.[13] As a result, one enantiomer of the endo product is preferred over the other. Combinations of steric and electronic effects are responsible for this outcome. In the case of planar-symmetrical reactants, one would have to introduce a catalyst to control the facial selectivity.

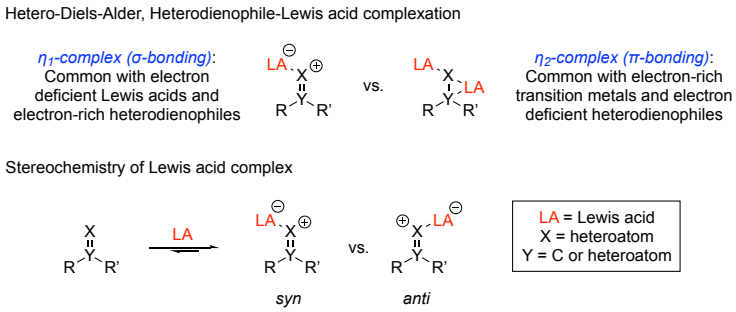
Scheme 2.1.4



2.1.3 Hetero-Diels-Alder Catalysis

In recent years, countless developments have been made in the area of catalysis. Particularly, asymmetric catalysis has dominated the field due to the pharmaceutical industry's demand for efficient methods to access single enantiomers of many biologically active small molecules.[14] Appropriately, a sizeable number of new chiral catalysts have been reported. Similarly, the number of catalytic enantioselective hetero-Diels-Alder reactions has realized an increase.[15] A central requirement for the design of an enantioselective hetero-Diels-Alder transformation is the promotion of catalyst-substrate binding. The most common strategy seen is complexation of a heterodienophile with a chiral Lewis acid catalyst (Scheme 2.1.5).[16-17] The

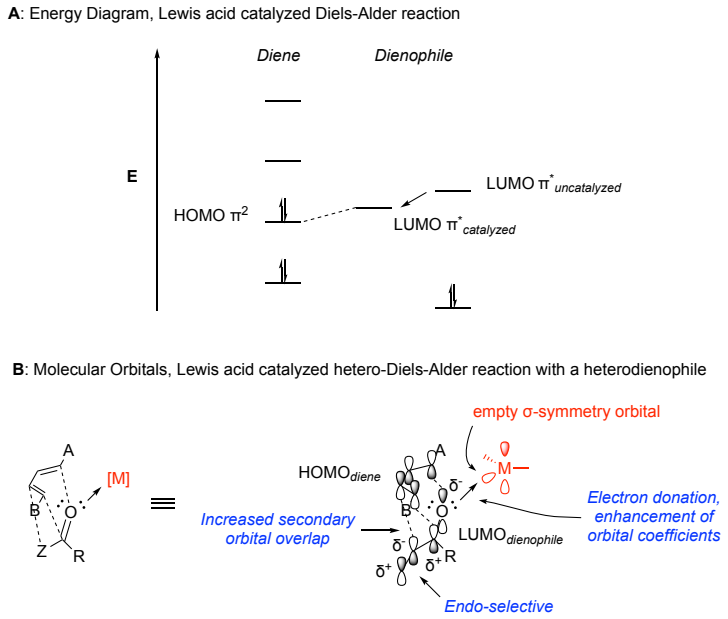
Scheme 2.1.5



reason for this is the simplicity of a dienophile compared to a 1,3-diene (ignoring substituents); The dienophile contains a single π-bond, inherently limiting the number of potential reactant-catalyst complexes formed in solution. Additionally, the electronics of the system based-off size and number of substituents are often less complicated. To accomplish noteworthy control over enantioselectivity, knowledge of the chiral environment and concentration of each reactant-catalyst complex present in equilibrium is required.

Depending on the nature of the dienophile and mode of catalyst binding, the selection of a proper catalyst system may become extraordinarily complicated. To generate catalyst control, the catalyst must be an intermediary in the transition state of the reaction. Given the normal demand hetero-Diels-Alder reaction is a concerted reaction between the HOMO of the 1,3-diene and LUMO of the dienophile, the catalyst must interact with one of the reactants (i.e. the heterodienophile) to decrease the activation energy/HOMO-LUMO energy gap (Scheme 2.1.6A).[18-21] In order to be considered practical and efficient by the synthetic community, the decrease in energy must be significant enough to greatly out-perform the uncatalyzed transformation. Furthermore, the catalyst must have sufficient orbital overlap with the reactant in a reversible manner with respect to the cycloadduct. A frequently observed benefit of catalyst-dienophile complexation is the enhancement of regioselectivity and *endo*-selectivity due to

Scheme 2.1.6

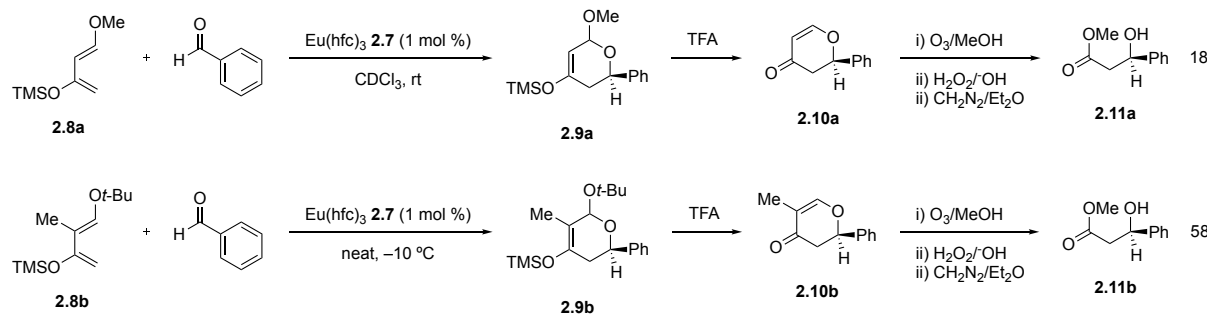


increases in the magnitude of coefficients for not only the two dienophile components but also substituents that may participate in secondary orbital overlap (Scheme 2.1.6B).[20-22]

Following Gresham and Steadman's report on the hetero-Diels-Alder reaction of formaldehyde with a conjugated diene (Scheme 2.1.1), aldehydes presented themselves as a logical selection for the development of an asymmetric hetero-Diels-Alder reaction utilizing a heterodienophile.[9] In 1983, Danishefsky and coworkers identified that tris-[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium(III) **2.7** may catalyze the hetero-Diels-Alder reaction of Danishefsky's diene **2.8a** with benzaldehyde to afford dihydropyran **2.9a** (Scheme 2.1.7).[23] The reaction proceeded with modest enantioselectivity (18% ee). The selectivity was measured following subsequent conversion of the cycloadduct to dihydropyrone **2.10a**, trailed by oxidative cleavage of the ring's unsaturation to provide ester **2.11a**. Attempts to increase the selectivity resulted in modification of the 1,3-diene to include 1-*tert*-butoxy and 2-methyl substituents, alongside removal of the solvent and reduction of the reaction temperature. Formulating these changes afforded the expected product, methyl ester **2.11b**, in 58% ee. Since the discovery, an extensive variety of chiral ligand-Lewis acid complexes were found to catalyze this transformation. For example, rhodium(II), vanadium(IV), boron(III), aluminum(III), ytterbium(III), chromium(III), manganese(IV), titanium(IV), cobalt(II), and copper(II) bound to numerous asymmetrical ligand classes, such as carboxamidate, *N*-tosyltryptophan, BINOL, triflylamide, salen, bisoxazoline, and/or BINAP, have revealed effective catalysis.[24-25]

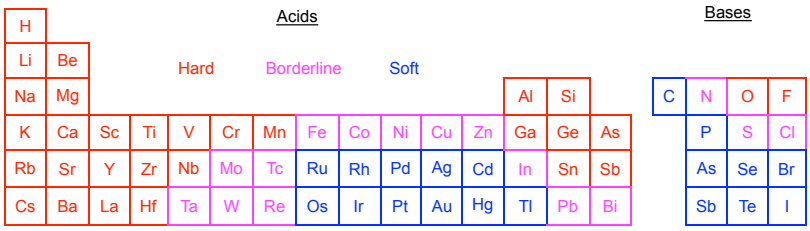
Scheme 2.1.7

Danishefsky, Lewis acid catalyzed enantioselective cyclocondensation



In order to effect catalysis, the Lewis acid must be a strong σ-acceptor of the lone-pairs on oxygen. A common method used for predicting the acceptor ability of the Lewis acid coupled to a Lewis base pair is hard-soft acid base theory. First proposed by Ralph Pearson in the early 1960's, hard-soft acid base theory states that "hard" acids react faster with "hard" bases, promoting greater orbital overlap, comparatively "soft" acids react faster with "soft" bases to achieve a similar function.[26] Like-pairings are preferential, or faster, compared to a mixed hard-soft pairing. "Hard" chemical species may be characterized as small, with high charge states, and weakly polarizable. "Soft", on the other hand, is a characteristic of chemical species that are large, with low charge states, and high polarizability.[27] The trend of hard-soft characteristics may be visualized in the periodic table, below (Scheme 2.1.8). Since oxygen is highly electronegative with a low energy valence shell, it is frequently considered to be a strong Lewis base. Appropriately, an aldehyde dienophile pairs well with many hard Lewis acids; this actuality is evident by the metal catalysts mentioned previously.

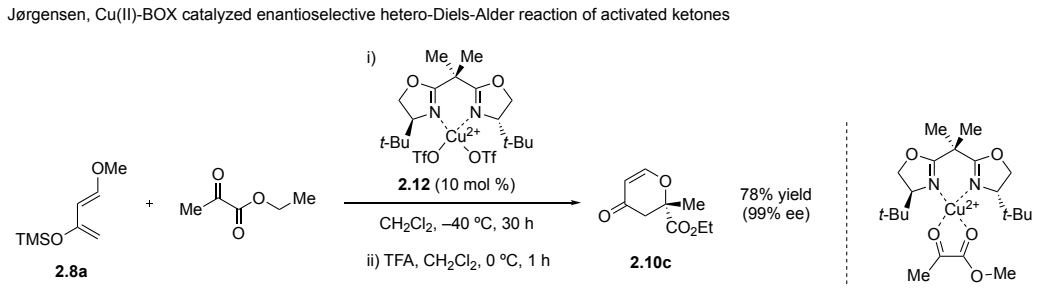
Scheme 2.1.8



The majority of work following the development of the asymmetric hetero-Diels-Alder reaction of aldehydes is the reaction of ketone dienophiles.[28] Due to the higher energy LUMO in ketones, activating groups such as an ester are introduced to attain reactivity. Although the presence of an activating group creates a set of limitations in the substrate scope, it does provide a substantial benefit for development of a Lewis acid-catalyzed enantioselective transformation. Specifically, an α-keto ester provides bidentate coordination to a chiral Lewis acid. This occurrence promotes the discrimination of one face of the dienophile for approach by the 1,3-diene. In 1997, Jørgensen and colleagues reported the first catalytic enantioselective hetero-Diels-Alder reaction of activated ketones using a copper(II)-bisoxazoline catalyst **2.12** (Scheme

2.1.9).[29] The catalyst is reported to be C_2-symmetrical, binding selectively to both carbonyl oxygen atoms. This provides excellent facial selection for the reaction of ethyl pyruvate with Danishefsky's diene **2.8a** to afford dihydropyrone **2.10c** in 78% yield and 99% ee. The unique feature of this transformation is the formation of a quaternary carbon stereocenter, something which is attainable by the use of ketones, unlike aldehydes. Further, the recorded potential for low catalyst loading, down to 0.05 mol %, is quite impressive.

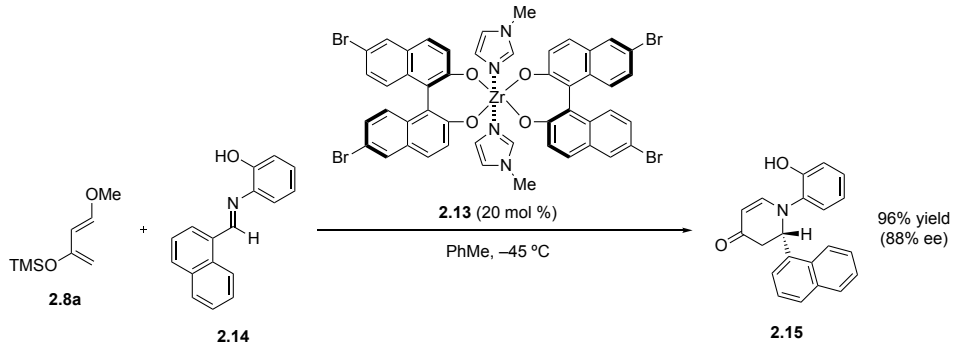
Scheme 2.1.9



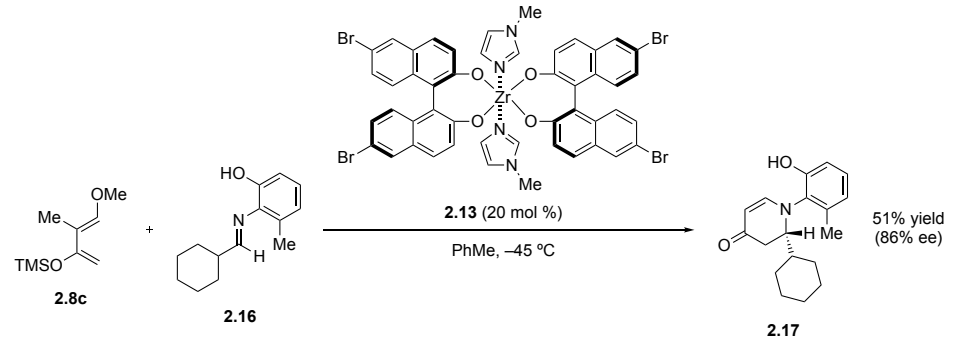
The synthetic community did not want to limit the scope of hetero-Diels-Alder reactions to simply oxo-dienophiles, consequently several laboratories elected to experiment with aza-dienophiles.[30] The first development of a catalytic asymmetric aza-Diels-Alder cycloaddition employing an imine dienophile was established in 1998, one year after the development of the enantioselective hetero-Diels-Alder cycloaddition with a ketone dienophile.[31] In the report, Kobayashi and coworkers utilize a chiral BINOL-zirconium(IV) catalyst **2.13** to mediate the reaction of *N*-(2'-hydroxyphenyl)-naphthaldimine **2.14** with Danishefsky's diene **2.8a** (Scheme 2.1.10A). The product, 2,3-dihydro-4-pyridone **2.15**, is produced in 96% yield and 88% ee. A notable accomplishment is obtaining high selectivity through reaction of cyclohexyl-substituted aldimine **2.16** with 2-methyl-substituted Danishefsky's diene **2.8c** (Scheme 2.1.10B). Under standard conditions, without the methyl substituent, enantioselectivity is described as low. The authors attribute this to the *cis*/*trans* isomerization of aliphatic aldimines. However, upon introduction of a methyl substituent on aldimine **2.16**, the enantioselectivity of product **2.17** is improved to 86% ee.

Scheme 2.1.10

A: Kobayashi, Zr(IV)-BINOL catalyzed enantioselective hetero-Diels-Alder reaction of imino dienophiles



B: Kobayashi, Asymmetric hetero-Diels-Alder reaction with aliphatic imino dienophile

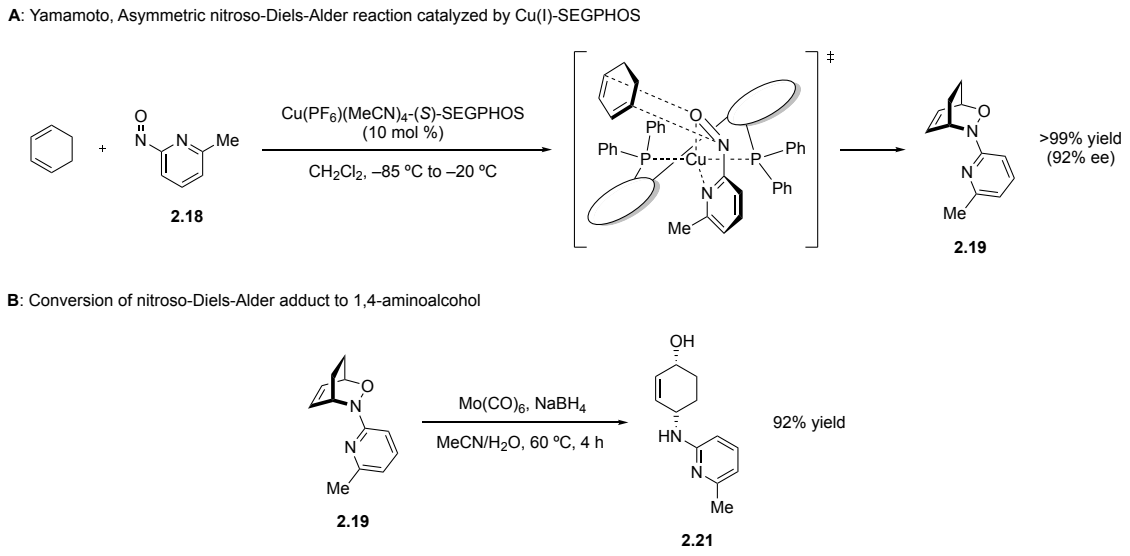


The ability of imines to produce nitrogen containing heterocycles is important to the synthesis of innumerable complex alkaloids and their unnatural analogues. Unfortunately, imine dienophiles suffer many drawbacks which make them extremely challenging to use in various synthetic transformations. For example, the nitrogen atom of an imine is known to be more Lewis basic than the oxygen atom of aldehydes and/or ketones. The high Lewis basicity leads to coordination and shutdown of catalyst activity. The reason is the Lewis basic nitrogen will coordinate strongly to the acid in a manner which is irreversible, eliminating catalyst turnover. To overcome this aspect, synthetic chemists rely on introduction of stoichiometric amounts of Lewis acid. The downside, however, is that an enantioselective transformation may require a chiral ligand, which would be inefficient to introduce in stoichiometric quantities. Further, imines routinely have low reactivity and are poor electron acceptors. This is because the C=N dipole is lower in energy compared to C=O, which is a good electron acceptor. Lastly, the alpha-

acidity is high, forming enolates in solution; a characteristic that is a contributing factor to the *cis*/*trans* isomerization of imines.

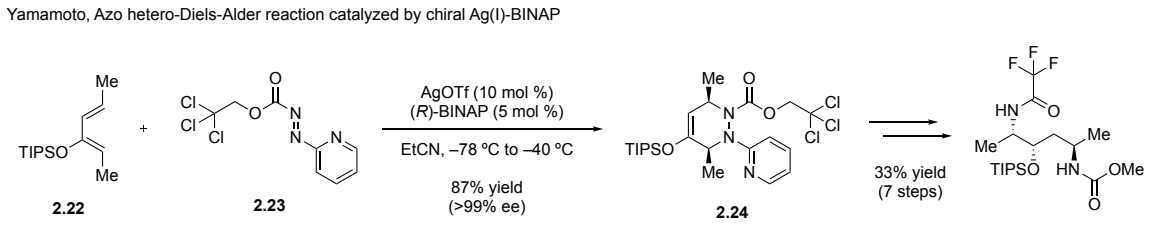
These advancements in the hetero-Diels-Alder reaction guided researchers to investigate access of two heteroatoms, i.e. nitrogen and oxygen, into the dienophile. The nitroso functional group adhered to these guidelines, and the first catalytic asymmetric nitroso-Diels-Alder reaction was reported in 2004 by Yamamoto and Yamamoto.[32] In their communication, the investigators identified a Cu(I)-SEGPHOS catalyst capable of chelating the nitroso oxygen and pyridyl nitrogen on nitrosopyridine **2.18** (Scheme 2.1.11A). Following reaction with 1,3-cyclohexadiene, cycloadduct **2.19** is obtained in >99% yield and 92% ee. The dual chelation capability of nitroso dienophile **2.18** is valuable for providing high stereocontrol. The metal chelation locks the dienophile in a planar confirmation, allowing the SEGPHOS ligand to have total control over facial selectivity. The nitroso-Diels-Alder reaction, is a significant enhancement to the repertoire of synthetic strategies available to chemists. Cycloadduct **2.19** may be converted to 1,4-aminoalcohol **2.20** in a single step (Scheme 2.1.11B), granting access to a product that may be time consuming to synthesize through other methods.

Scheme 2.1.11



Two nitrogen atoms are a second possibility for incorporation into the dienophile. The development of a specialized azo hetero-Diels-Alder reaction was detailed by Kawasaki and Yamamoto in 2006.[33] The cyclization between silyloxydiene **2.22** and 2-azopyridine **2.23** in the presence of a silver(I)-BINAP catalyst afforded adduct **2.24** in 87% yield and >99% ee (Scheme 2.1.12). The catalytic process supplies an operational route to chiral 1,4-diamines, a structural motif that is beneficial for the design of pharmaceutically-relevant small molecules.[34]

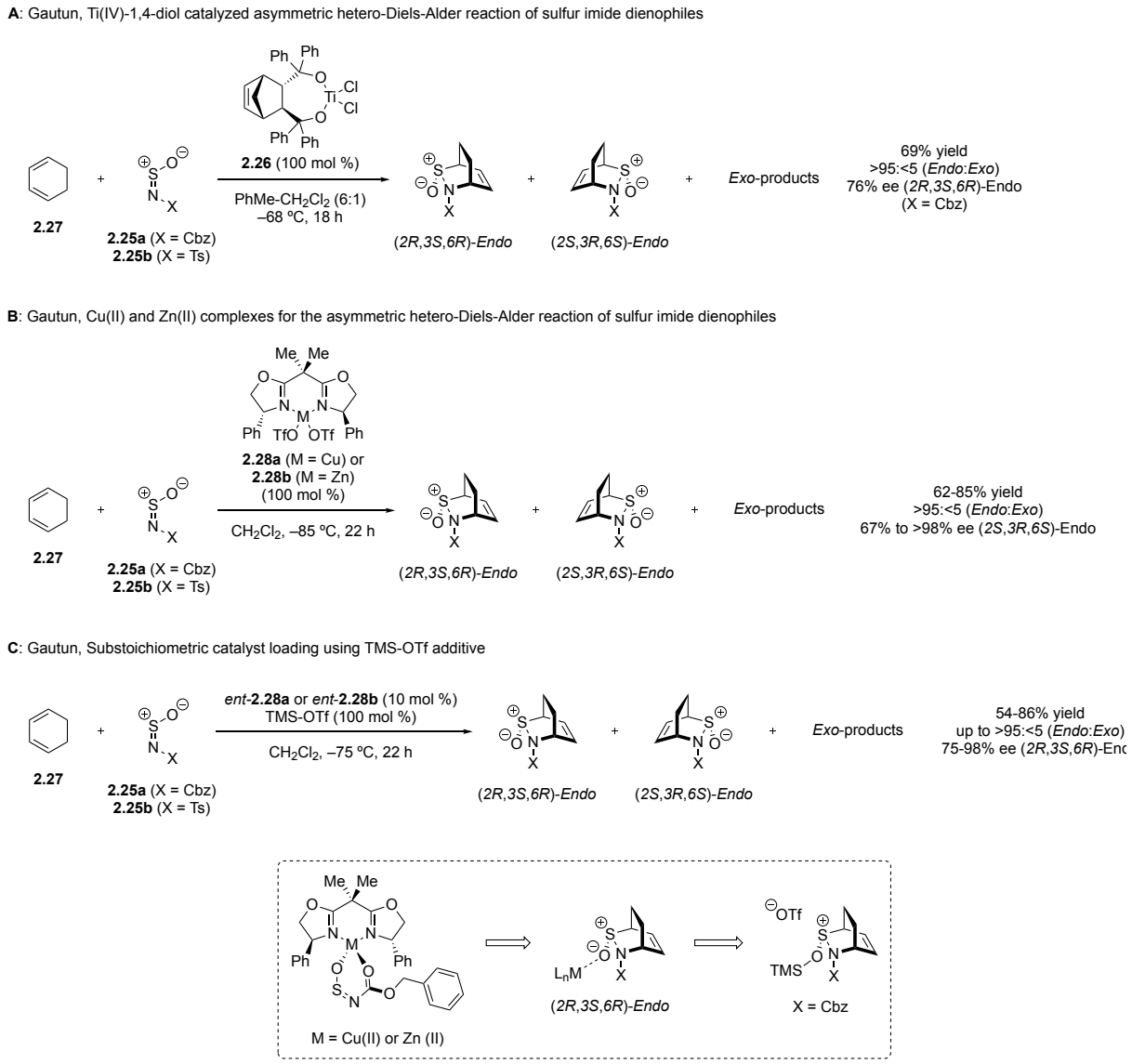
Scheme 2.1.12



While researchers continued to investigate numerous heteroatoms, the use of sulfur and nitrogen dienophiles surpassed many expectations and materialized as attractive molecules.[35] It is often difficult to incorporate both nitrogen and sulfur into a reaction due to the diverse and conflicting reactivity of their respective functional groups.[36] Expressly, the ability of nitrogen and sulfur to coordinate a catalyst and destroy its reactivity presented a challenge that remains to this day.[37-46] By joining nitrogen and sulfur in a simplified dienophile, one can circumvent a few of the usual complexities of sulfur/nitrogen reactivity.[47-48] This is confirmed in the discovery by Gautun and coworkers of an enantioselective hetero-Diels-Alder reaction of sulfur imides **2.25a-b** in the presence of a titanium(IV)-1,4-diol catalyst **2.26** (Scheme 2.1.13A).[49] Although the reaction displays moderate yield and selectivity (69% yield and 76% ee, X = Cbz), it suffers from an extraordinarily limited substrate scope. The only reported diene is 1,3-cyclohexadiene **2.27**. Additionally, the reproducibility of this cycloaddition is modest; the researchers admit this judgement in numerous follow-up publications.[50-51] One year later, Gautun and coworkers identified chiral bisoxazoline-copper(II) and zinc(II) complexes **2.28a-b** that accomplished this transformation with improved selectivities (67% to >98% ee) and yields (62-85%, Scheme 2.1.13B).[52] Unfortunately, the upgraded systems also provide a limited substrate scope and have

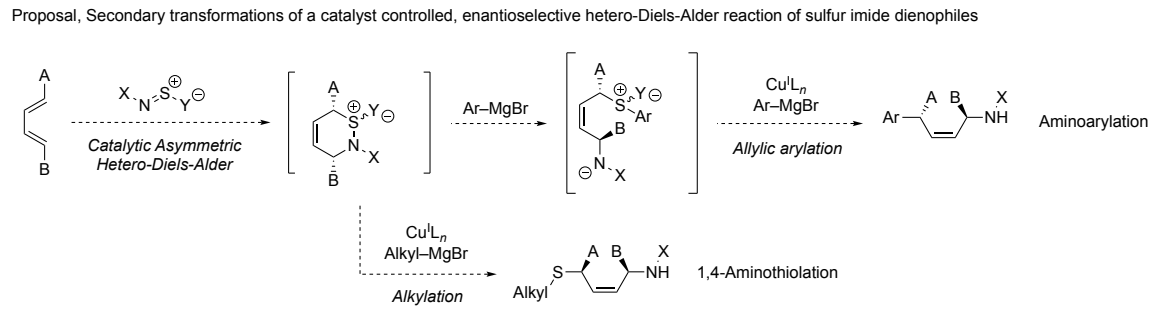
some issues with reproducibility.[51,53-55] A likely contributor to these shortcomings is catalyst preparation and low catalyst turnover, commonly requiring stoichiometric quantities of catalyst to afford product selectivity. To enable the use of substoichiometric metal, TMS-OTf was employed as an additive to release the metal from the metal-adduct complex facilitating catalyst turnover (Scheme 2.1.13C).[51,53-56]

Scheme 2.1.13



If one could generate methods to increase substrate scope and take advantage of these unique cycloadducts containing multiple heteroatoms, it would have a substantial impact on the fields of medicine, agriculture, and materials science. The reason is protocols, such as aminoarylation and aminothiolation of 1,3-dienes, may reach valuable, complex asymmetric products that are challenging to obtain through other methods (Scheme 2.1.14).[8,57]

Scheme 2.1.14



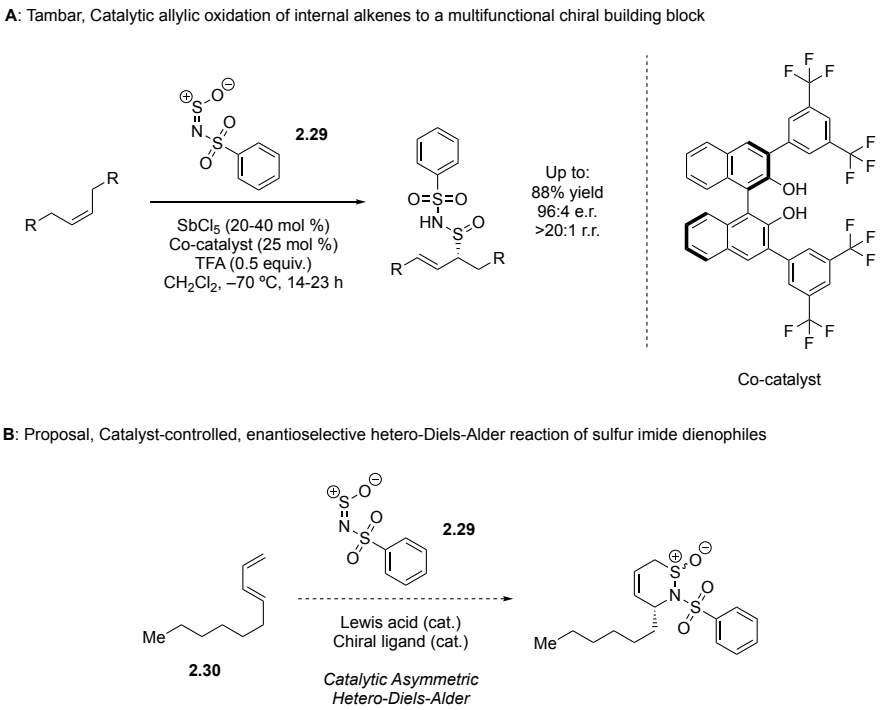
2.2 The Development of a Catalyst Controlled, Enantioselective Hetero-Diels-Alder Reaction of Sulfur Imide Dieneophiles

2.2.1 Diene Selection

We became interested in expanding the number of approaches to chiral heteroatom-containing molecules after our laboratory published two landmark reports on the aminoarylation and 1,4-aminothiolation of 1,3-dienes with sulfur imide reagents.[8,57] Following additional development of an asymmetric allylic functionalization of alkenes with *N*-(benzenesulfonyl)sulfur imide **2.29** (Scheme 2.2.1A),[58] we envisioned developing a strategy to reach chiral products of 1,3-dienes. This strategy would take advantage of the Lewis acids' capability to coordinate sulfur imide reagents enabling the production of a catalytic method to reach asymmetrical adducts of a hetero-Diels-Alder reaction. Although attempts to reach chiral

cycloadducts have been made by Gautun and coworkers, the reproducibility and scope of 1,3-dienes for the reaction are decidedly limiting to its use.[49-54] In order to overcome these challenges, we first needed to identify a 1,3-diene that may lead to a more general method. Consequently, we decided on *trans*-1,3-decadiene **2.30** (Scheme 2.2.1B). The reason is three-fold. First, *trans*-1,3-decadiene **2.30** is an acyclic terminal 1,3-diene, which may be easier to produce in complex molecule synthesis with high selectivity. Second, the hexyl side chain is substantial in size to allow recognition by a ligand. Lastly, the chain may mimic a more complex, or lengthy, component without introducing extraordinary complexity.

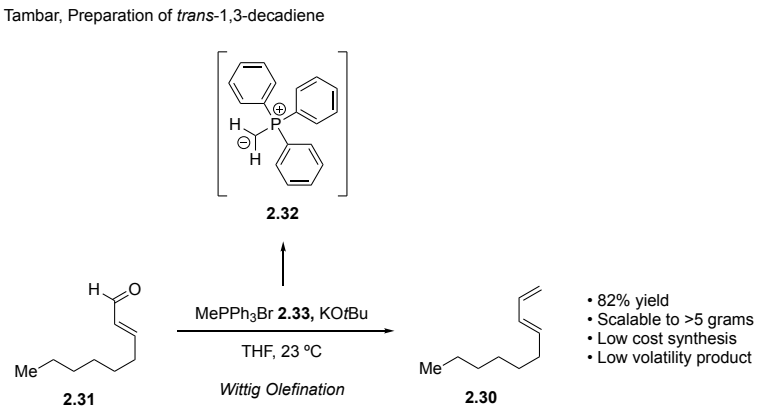
Scheme 2.2.1



Although *trans*-1,3-decadiene **2.30** is not commercially available, it is easily synthesized by reacting *trans*-2-nonenal **2.31** with phosphonium ylide **2.32**, prepared by reaction of phosphonium bromide **2.33** with potassium *tert*-butoxide (Scheme 2.2.2).[8] The value in this material is in the production of *trans*-1,3-decadiene **2.30**; it is in fact lower cost to produce diene **2.30** than the price to purchase many commercially available 1,3-dienes. This allows for production of higher quantities of the material which are needed to complete reaction

optimization. Further, the weight of the final molecule decreases its volatility, something that is experienced with lighter molecules such as *trans*-1,3-pentene.

Scheme 2.2.2



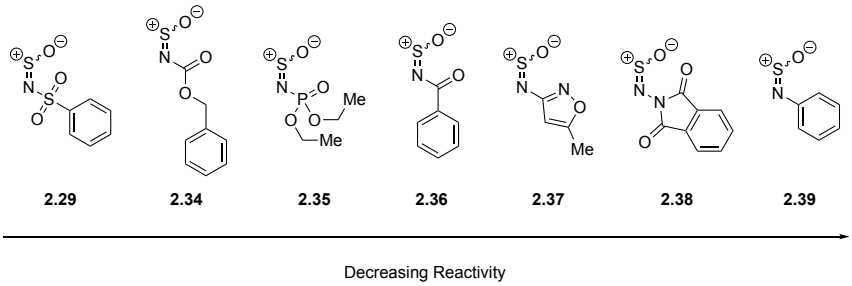
2.2.2 Dienophile Selection

With a desirable conjugated diene in hand, proper selection of a sulfur imide dienophile becomes imperative. To accomplish this, one must choose a dienophile that predominantly affords the hetero-Diels-Alder adduct as opposed to an Alder-ene adduct. Equally, the hetero-Diels-Alder reaction must be temperature dependent, so that the uncatalyzed thermal reaction may be suppressed. Final requirements are the ability of the sulfur imide dienophile to engage in bidentate coordination to a chiral Lewis acid, restricting the conformational freedom of the system enabling the chiral ligand to promote enantioselectivity. Lastly, the bidentate moiety must readily release the Lewis acid catalyst upon immediate formation of the hetero-Diels-Alder adduct.[51] Doing so will permit the catalyst to turnover, supporting the use of substoichiometric quantities of chiral ligand-Lewis acid complex.

To fulfill these many requirements, a series of sulfur imide dienophiles containing electron withdrawing substituents (**2.29**, **2.34**-**2.38**) were identified (Scheme 2.2.3). The reason sulfur imide reagents with electron withdrawing substituents were chosen is because they are highly electropositive at sulfur, making the sulfur imide susceptible to attack by electron

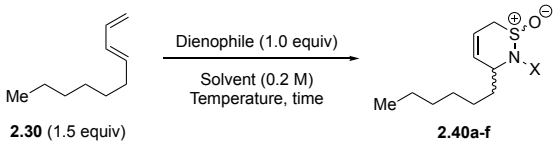
abundant 1,3-dienes compared to allylic-ene functionality. Additionally, electron withdrawing substituents may be tailored to provide a secondary chelating moiety complementing the bidentate capability of the dienophile. *N*-benzenesulfur imide **2.39**, was selected due to its limited reactivity. The thermal reaction of *N*-benzenesulfur imide **2.39** with 2,3-dimethyl-1,3-butadiene is reported to take place at >80 ºC.[59,60] Unlike, imide **2.39**, dienophiles **2.29**, **2.34-2.38** undergo thermal reaction at or below room temperature with most 1,3-dienes.[51] This means an opportunity may exist for a catalyst to reduce the activation energy barrier of the hetero-Diels-Alder reaction with *N*-benzenesulfur imide **2.39** providing high selectivity at common laboratory temperatures. The absence of a secondary chelating group, however, on dienophile **2.39** is troubling. Adding a resonance capable electron-donating or -withdrawing substituent, such as methoxy or nitro, across the phenyl ring negatively effects product selectivity; such substituents are known to manipulate the nature of the transition state, making the step-wise mechanism predominant.[59]

Scheme 2.2.3



To assess the product profiles and gain a better understanding of how rapid the competitive, thermal background reaction is for each dienophile, sulfur imides **2.29**, **2.34-2.39** were subjected to uncatalyzed conditions in several solvents at varying temperatures (Table 2.2.1). The goal was to identify a temperature at which the uncatalyzed reaction is completely suppressed. The resultant value is the temperature at which Lewis acids and/or ligands should be screened to obtain non-background-competitive results. Key requirements for the solvent are that it has a low melting point and is neither protic or nucleophilic.

Table 2.2.1



Entry	Dienophile	Solvent	Temperature (ºC)	time (h)	Product	Isolated Yield (%)
1	**2.29**	CH_2Cl_2	–75	20	**2.40a**	99
2	**2.29**	CH_2Cl_2	–75	5	**2.40a**	48
3	**2.29**	THF	–45	20	**2.40a**	36
4	**2.29**	THF	–60	20	**2.40a**	None
5	**2.29**	PhMe	–60	20	**2.40a**	Trace
6	**2.34**	CH_2Cl_2	23	0.5	**2.40b**	67
7	**2.34**	CH_2Cl_2	–78 to –60	22	**2.40b**	33
8	**2.34**	PhMe	23	20	**2.40b**	56
9	**2.34**	PhMe	–45	20	**2.40b**	4
10	**2.34**	PhMe	–78 to –60	22	**2.40b**	None
11	**2.36**	CH_2Cl_2	23	20	**2.40c**	86
12	**2.36**	CH_2Cl_2	–78	20	**2.40c**	11
13	**2.36**	PhMe	23	20	**2.40c**	88
14	**2.36**	PhMe	–78	20	**2.40c**	None
15	**2.37**	CH_2Cl_2	23	20	**2.40d**	65[a]
16	**2.37**	CH_2Cl_2	–45	20	**2.40d**	1[a]
17	**2.38**	CH_2Cl_2	40	20	**2.40e**	22[a,b]
18	**2.38**	PhMe	80	20	**2.40e**	15[a,b]
19	**2.39**	CH_2Cl_2	40	20	**2.40f**	None
20	**2.39**	PhMe	80	20	**2.40f**	None

Reaction conditions: Dienophile (1 equiv), Solvent (0.2 M), 1,3-diene **2.30** (1.5 equiv), at Temperature for time. Isolated yield. [a] NMR yield, calculated using 1,4-DMB as an internal standard. [b] Messy mixture of recovered phthalamide and endo/exo product

To begin our studies, *N*-benzenesulfonylsulfur imide **2.29**, a dienophile that is interrelated with our laboratory, was mixed with the selected diene, *trans*-1,3-decadiene **2.30**, in methylene chloride at –75 ºC. To no surprise, the hetero-Diels-Alder reaction afforded the desired cycloadduct in 99% yield after 20 h (entry 1, Table 2.2.1). Shortening the reaction time to 5 h did not generate a drastic effect on the yield which would enable the use of a Lewis acid catalyst that could outcompete the uncatalyzed reaction in a brief time frame. The reaction in methylene chloride for 5 h provided 48% yield (entry 2). It should be noted that the reaction with dienophile **2.29** is highly, energetically favored, producing the endo adduct as the primary observable stereoisomer. Switching the reaction solvent to tetrahydrofuran decreased the reactivity. This

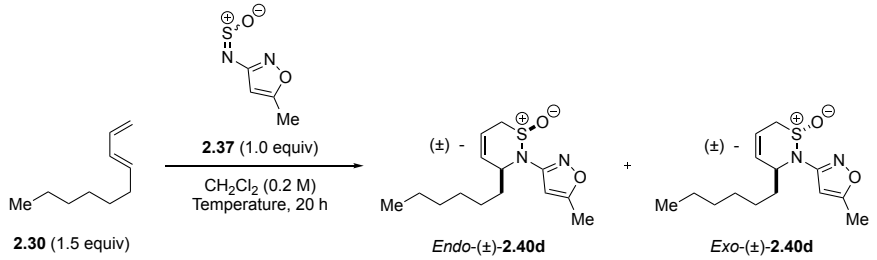
result is likely correlated to the polarity of the solvent. In tetrahydrofuran at –45 ºC, the reaction of *N*-benzenesulfonylsulfur imide **2.29** with *trans*-1,3-decadiene **2.30** afforded the adduct in 36% yield (entry 3). Decreasing the temperature to –60 ºC completely suppressed its reactivity (entry 4). This suggested that tetrahydrofuran at –60 ºC was a starting point for Lewis acid screening as it would allow us to accurately measure the catalyst reactivity without observable uncatalyzed reaction of imide **2.29** with diene **2.30**. Similarly, in toluene the reactivity was suppressed at –60 ºC providing trace product by NMR (entry 5).

Dienophile **2.34**, containing a carboxybenzyl moiety, was used extensively in Gautun and coworker's reports.[52-54] As a result, we found it necessary to investigate the imide's reactivity to record how it correlates with reported and newly discovered catalyst systems. Subjecting dienophile **2.34** to the hetero-Diels-Alder reaction with diene **2.30** produced the cycloadduct in 67% yield in methylene chloride at room temperature (23 ºC, entry 6). The reaction of *N*-carboxybenzylsulfur imide **2.34** is extremely facile. Decreasing the reaction temperature had little effect on suppressing the dienophile's high rate of reaction (entry 7). Swapping the solvent for toluene provided a positive result as the reaction was suppressed at lower temperatures (entries 8-10).

Reacting dienophile **2.35**, a unique dienophile prepared from diethyl phosphoramidate, provided no product in any of the solvents and at any temperature. The reason for this is believed to be the instability of phosphorus-related dienophiles.[61-63] Phosphorus is highly oxophilic and the resonating charge on the sulfinyl group may cause undesired aggregation inhibiting further reactivity. Benzoylsulfur imide **2.36**, on the other hand, containing a keto- electron withdrawing group is less-reactive compared to the ester functional groups in imides such as *N*-benzenesulfonylsulfur imide **2.29**, *N*-carboxybenzylsulfur imide **2.34**, and diethyl phosphonosulfur imide **2.35**. The greater electron withdrawing capability of an ester compared to (C=O)-R produces a greater positive coefficient on the central atom, in turn increasing the bond order between sulfur and nitrogen. When the sulfur-nitrogen bond order is closer to 2, the Diels-Alder reaction is accelerated. Consequently, benzoylsulfur imide **2.36** provides lower reactivity, affording the desired cycloadduct in 11% yield at –78 ºC in methylene chloride (entry 12). Gratifyingly, toluene at –78 ºC is able to suppress the dienophile's reactivity (entry 14). Although, recognizably the reproducibility with the dienophile suffers, eliminating the potential to carry the dienophile forward for further optimization.

The Diels-Alder reaction of *N*-(5-methyl-3-isoxazolyl)sulfur imide **2.37** with *trans*-1,3-decadiene **2.30** is able to be suppressed at –45 ºC in methylene chloride (entry 16). This is the first molecule from the selected series of sulfur imide dienophiles that exhibits suppression in methylene chloride. However, the reaction of *N*-(5-methyl-3-isoxazolyl)sulfur imide **2.37** displays intriguing diastereoselectivity. Opposed to the previous dienophiles that provide a single endo isomer, there is an observable switch in the endo:exo ratio for sulfur imide **2.37** that is temperature dependent. At 40 ºC in methylene chloride the endo:exo ratio is 61:26 (entry 1, Table 2.2.2). Decreasing the temperature to 4 ºC displays a minor shift in the ratio, affording 6% endo and 16% exo adduct. At –45 ºC trace amounts of the exo adduct **2.40d** are observed, providing an optimal temperature to carry out Lewis acid catalyzed transformations (entry 5).

Table 2.2.2



Entry	Temperature (ºC)	NMR yield Endo (%)	NMR yield Exo (%)
1	40	61	26
2	23	43	22
3	4	6	16
4	–20	1	11
5	–45	None	1

Reaction conditions: Dienophile **2.37** (1.0 equiv), CH_2Cl_2 (0.2 M), 1,3-diene **2.30** (1.5 equiv), at Temperature for 20 h. NMR yield calculated using 1,4-DMB as an internal standard.

Phthalamide dienophile **2.38** is the final electron withdrawing sulfur imide selected in this series (Scheme 2.2.3). Unfortunately, its reactivity is lower compared to the previous dienophiles since its amide nitrogen is able to donate a small degree via its electron pair. This effect also reduces the bond order of the sulfur-nitrogen bond. At reflux (40 ºC) in methylene chloride a minor amount of adduct is observed (22%, entry 17, Table 2.2.1). However, more concerning is that the product is not easily isolated, forming messy mixtures of materials, which

often overlap in liquid chromatography; most often the adduct overlaps with phthalimide that is released from the hydrolyzed sulfur imide in solution and upon workup. Attempts were made to remove phthalimide via acid-base chemistry, however the hetero-Diels-Alder adduct was also affected. In toluene at 80 ºC the transformation yields similar results (entry 18, Table 2.2.1).

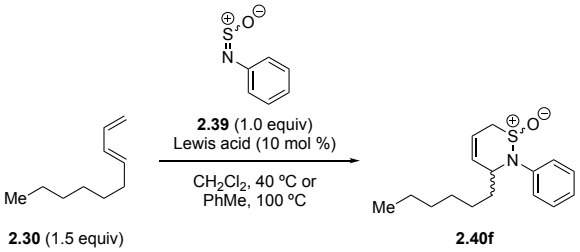
The last sulfur imide that was investigated is *N*-benzenesulfur imide **2.39** (Scheme 2.2.3). Discussed earlier in this section, *N*-benzenesulfur imide **2.39** is known to be one of the least reactive sulfur imide dienophiles. Subjecting *N*-benzenesulfur imide dienophile **2.39** to the hetero-Diels-Alder reaction with *trans*-1,3-decadiene **2.30** does not provide any observable product in both methylene chloride and toluene at elevated temperatures (entries 19-20, Table 2.2.1). To confirm the capability of the dienophile, the reaction with 2,3-dimethyl-1,3-butadiene reported in literature was reproduced successfully.[59]

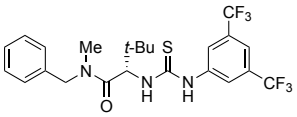
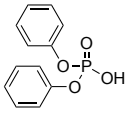
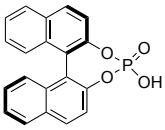
2.2.3 Lewis Acid Screen

Following the identification of several dienophiles (**2.29**, **2.34**, **2.37**, **2.39**) that have suppressible, uncatalyzed hetero-Diels-Alder reactions, we must pinpoint Lewis acids that are proficient in catalyzing the transformation. It is required that the Lewis acid strongly coordinates the innate dienophile and is readily released from the hetero-Diels-Alder adduct. This is necessary to achieve catalyst turnover. Another requirement is the ability to conduct bidentate chelation with the dienophile in addition to chelation with a chiral ligand. The presence of a chiral ligand will be necessary to afford facial selectivity, leading to enantiomeric excess in the adduct. Initially, identification of a Lewis acid capable of decreasing the activation energy barrier is not only proof of concept but also an informative lead for the exploration of active chiral ligand-Lewis acid complexes.

Luckily, *N*-benzenesulfur imide dienophile **2.39** was quickly identified as a poor choice for further optimization. Mostly due to its low reactivity with *trans*-1,3-decadiene **2.30**. In the presence of assorted Lewis acids, such as titanium(IV) tetrachloride, boron trifluoride etherate, Jacobsen's thiourea, and varying phosphoric acids no product was observed (entries 1-5, Table 2.2.3). This consequence was realized at elevated temperatures in both methylene chloride and toluene.

Table 2.2.3



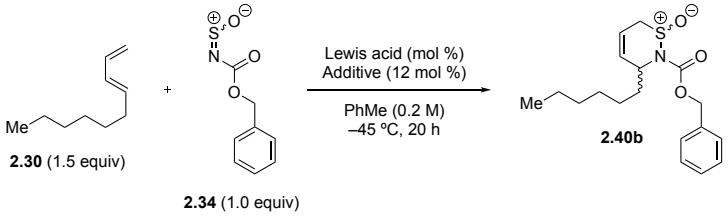
Entry	Lewis acid	NMR yield (%)
1	$TiCl_4$	None
2	$BF_3{\cdot}Et_2O$	None
3		None
4		None
5	(R) - 	None

Reaction conditions: Dienophile **2.39** (1.0 equiv), Solvent (0.2 M), Lewis acid (10 mol %), 30 min., 23 ºC, then 1,3-diene **2.30** (1.5 equiv), raise to Temperature, 20 h. NMR yield calculated using 1,4-DMB as an internal standard.

N-Carboxybenzylsulfur imide **2.34** was also recognized as a meager selection for further optimization. Dienophile **2.34** was mixed with Lewis acid, followed by *trans*-1,3-decadiene **2.30**, then screened for catalytic activity after stirring at –45 ºC for 20 h (Table 2.2.4). The uncatalyzed background reaction with diene **2.30** affords carboxybenzyl adduct **2.40b** in approximately 4% yield (entry 1). Addition of hard Lewis acids such as titanium(IV) tetrachloride and tin(IV) tetrachloride, common oxygen chelators that may participate in dual binding, imparted a minor effect on yield when introduced at 10 mol % loading (entries 2-3). Attempts to increase the yield by inflating the mole percentage of catalyst to 50 mol % heightened the degree of decomposition leading to no observable product (entries 4-5). In suit of discoveries made by Gautun and coworkers in the past decade, the reaction system was subjected to copper(II) triflate and zinc(II) triflate at molar equivalent loadings.[52-53] The results of the additions were incongruent with those reported by the researchers and did not fare well to enhance the uncatalyzed reaction (entries 6-

7). Lastly, antimony(V) pentachloride was introduced as a traditional Lewis acid in 10 mol % (entry 8). The results of the reaction suggested no improvement over the background reaction. Following the final traditional Lewis acid screen, (*R*)-1,1'-bi-2-naphthol, abbr. (*R*)-BINOL, was added as an additive to generate a Lewis acid-assisted Brønsted acid (LBA) recently reported by our laboratory to catalyze the Alder-ene reaction of *N*-benzenesulfonylsulfur imide **2.29**, a similar sulfur imide to *N*-carboxybenzylsulfur imide **2.34**.[58] Unfortunately, no improvement in the yield was observed (entry 9). Likewise, titanium(IV) tetrachloride and tin(IV) tetrachloride were unable to assist the Brønsted acidity of binaphthol – providing no enhancement over the uncatalyzed, background hetero-Diels-Alder reaction (entries 10-11).

Table 2.2.4



Entry	Lewis acid (mol %)	Additive	NMR yield (%)
1	None	None	4
2	$TiCl_4$ (10 mol %)	None	6
3	$SnCl_4$ (10 mol %)	None	7
4	$TiCl_4$ (50 mol %)	None	None
5	$SnCl_4$ (50 mol %)	None	None
6	$Cu(OTf)_2$ (100 mol %)	None	6
7	$Zn(OTf)_2$ (100 mol %)	None	1
8	$SbCl_5$ (10 mol %)	None	4
9	$SbCl_5$ (10 mol %)	(*R*)-BINOL	3
10	$TiCl_4$ (10 mol %)	(*R*)-BINOL	4
11	$SnCl_4$ (10 mol %)	(*R*)-BINOL	4

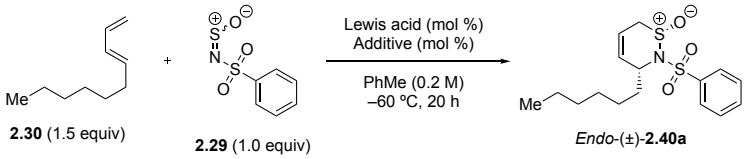
Reaction conditions: Lewis acid (mol %), Additive (12 mol %), PhMe (0.2 M), 23 ºC, 0.25 h, then –78 ºC, Dienophile **2.34** (1.0 equiv), warm to 23 ºC, 0.5 h, then –78 ºC, 1,3-diene **2.30** (1.5 equiv), 0.5 h, warm to –45 ºC, 20 h. NMR yield calculated using 1,4-DMB as an internal standard.

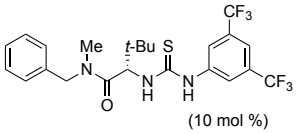
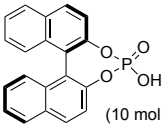
To our satisfaction, *N*-benzenesulfonylsulfur imide **2.29** presented promise as a sulfur imide dienophile for the Lewis acid catalyzed hetero-Diels-Alder reaction with *trans*-1,3-decadiene **2.30**. Utilizing copper(II) triflate at 10 mol % loading in toluene the desired adduct

2.40a was procured in 13% yield (entry 1, Table 2.2.5). Notably, toluene materialized as an effective solvent for this transformation providing the desired cycloadduct **2.40a** in 32% yield when using titanium(IV) tetrachloride at 10 mol % loading (entry 2). Contrasting these results, when tetrahydrofuran is employed as the reaction medium the mixture is unable to afford the desired cycloadduct **2.40a** (entries 3-4). Increasing the mole percentage loading for titanium(IV) tetrachloride had a deleterious effect on the reaction efficiency and led to greater observed decomposition (entry 5). To combat this circumstance, trimethylsilyl triflate was exercised as an additive (entries 6-7). The role of trimethylsilyl triflate is to act as a substitute for the Lewis acid upon formation of the cycloadduct **2.40a**. This will enable release of the adduct **2.40a** from its coordination with the Lewis acid, in turn allowing for greater catalyst turnover and a potentially decreased amount of decomposition. Precedence for the use of trimethylsilyl triflate as a substitute for Lewis acids is reported by Gautun and Evans.[53-54,56] In his report, Gautun claims trimethylsilyl triflate is a necessity to achieve reliable turnover and that the substance behaves as a proton mimic.

Trailing the identification of two Lewis acids capable of catalyzing the hetero-Diels-Alder reaction of dienophile **2.29** and 1,3-diene **2.30**, we assessed a laundry list of other hard and soft Lewis acids to ascertain a trend in reactivity. Subjecting the reaction mixture to catalysis by zinc(II) triflate at 10 mol % loading afforded the desired adduct **2.40a** in 7% yield (entry 8). Magnesium(II) bromide did not fare meaningfully better, yielding the adduct in 8% yield, only a one percent improvement over zinc(II) triflate (entry 9). A hard, oxophilic Lewis acid, boron trifluoride etherate, provided greater yield (18%) when compared to copper(II) triflate, but was unable to improve upon the 32% yield afforded by titanium(IV) tetrachloride (entry 10). Tin(IV) tetrachloride, on the other hand, provided the desired adduct **2.40a** in 38% yield with an analogous 10 mol % loading (entry 11). Comparable to magnesium(II) bromide, trimethyl aluminum yielded 8% of adduct **2.40a** (entry 12). Scandium(III) triflate, indium(III) tribromide, iron(III) tribromide, and antimony(V) pentachloride all yielded mediocre results with yields ranging from 4-11% (entries 13-16). Though, unlike *N*-carboxybenzylsulfur imide **2.34**, *N*-benzenesulfonylsulfur imide **2.29** was activated by the Lewis acid-assisted Brønsted acid (LBA) complex composed of antimony(V) pentachloride and (*R*)-1,1'-bi-2-naphthol (entry 17). The $SbCl_5$•(*R*)-BINOL complex afforded the hetero-Diels-Alder adduct **2.40a** in 38% yield, matching the current best result observed by tin(IV) tetrachloride. In fact, titanium(IV) tetrachloride and

Table 2.2.5



Entry	Lewis acid (mol %)	Additive (mol %)	NMR yield (%)
1	$Cu(OTf)_2$ (10 mol %)	None	13[a]
2	$TiCl_4$ (10 mol %)	None	32
3	$Cu(OTf)_2$ (10 mol %)	None	None[a,b]
4	$TiCl_4$ (10 mol %)	None	None[a,b]
5	$TiCl_4$ (100 mol %)	None	Trace
6	$TiCl_4$ (10 mol %)	TMS-OTf (100 mol %)	36
7	$Cu(OTf)_2$ (10 mol %)	TMS-OTf (100 mol %)	27
8	$Zn(OTf)_2$ (10 mol %)	None	7
9	$MgBr_2$ (10 mol %)	None	8
10	BF_3•Et_2O (10 mol %)	None	18
11	$SnCl_4$ (10 mol %)	None	38
12	$AlMe_3$ (10 mol %)	None	8
13	$Sc(OTf)_3$ (10 mol %)	None	11
14	$InBr_3$ (10 mol %)	None	10
15	$FeBr_3$ (10 mol %)	None	4
16	$SbCl_5$ (10 mol %)	None	10
17	$SbCl_5$ (10 mol %)	(*R*)-BINOL (12 mol %)	38
18	$TiCl_4$ (10 mol %)	(*R*)-BINOL (12 mol %)	27
19	$SnCl_4$ (10 mol %)	(*R*)-BINOL (12 mol %)	44
20	 (10 mol %)	None	21
21	(R) -  (10 mol %)	None	12

Reaction conditions: Lewis acid (mol %), Additive (mol %), PhMe (0.2 M), 23 ºC, 0.25 h, then –78 ºC, Dienophile **2.29** (1.0 equiv), warm to 23 ºC, 0.5 h, then –78 ºC, 1,3-diene **2.30** (1.5 equiv), 0.5 h, warm to –60 ºC, 20 h. NMR yield calculated using 1,4-DMB as an internal standard. [a] –78 ºC, 2 h before warming to –60 ºC, 20 h. [b] THF substituted for PhMe.

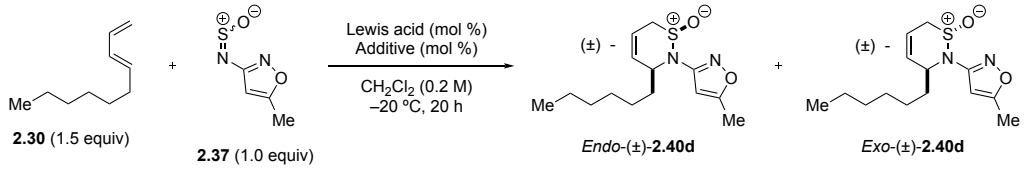
tin(IV) tetrachloride similarly initiated the hetero-Diels-Alder reaction following formation of the LBA catalyst system with (*R*)-BINOL (entries 18-19). The resultant yields were 27% and 44%, respectively. To finish the screen, Jacobsen's thiourea and (*R*)-BINOL phosphoric acid were examined, providing 21% and 12% yield, individually (entries 20-21). These examples

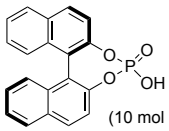
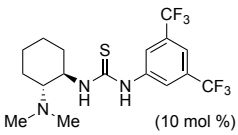
indicate that it is possible for Brønsted-Lowry acids, a subset of Lewis acids, to catalyze the hetero-Diels-Alder reaction between *N*-benzenesulfonylsulfur imide **2.29** and *trans*-1,3-decadiene **2.30**.

The findings from this initial Lewis acid screen for dienophile **2.29** conclude that hard Lewis acids, such as titanium(IV) tetrachloride and tin(IV) tetrachloride match best with the chelating ability of the sulfinyl and sulfonate ester groups. Furthermore, the LBA catalyst system of tin(IV)-tetrachloride with (*R*)-BINOL matches well with the dienophile. However, it should be noted that this screen is not exhaustive, nor is it a perfect representation of activity that may be observed following introduction of a chiral ligand. The reason is once a chiral ligand binds to a metal-based Lewis acid it will alter the electronic properties of the metal center, as one or more of the original ligands surrounding the metal center are replaced by the new moiety. Additionally, the behavior of the Lewis acid complex may be dissimilar after mixing with dienophile **2.29,** as the dienophile may substitute the chiral ligand instead of the original ligands when binding to the metal center. This is our first example and a proof of concept for the Lewis acid catalyzed activation of sulfur imide dienophiles for the hetero-Diels-Alder reaction, showcasing that the strategy is indeed viable. Each of these Lewis acid types will be investigated further in the following section encompassing a ligand screen.

Under uncatalyzed conditions at –20 ºC in methylene chloride, the reaction of *N*-(5-methyl-3-isoxazolyl)sulfur imide **2.37** and *trans*-1,3-decadiene **2.30** provides a combination of endo and exo adduct (entry 1, Table 2.2.6). Specifically, the reaction mixture delivers 1% endo and 11% exo adduct **2.40d**. Introducing titanium(IV) tetrachloride, a catalyst that worked well for activating the cycloaddition of *N*-benzenesulfonylsulfur imide **2.29** with diene **2.30** (entry 2, Table 2.2.5), at 10 mol % loading afforded the desired 5-methyl-3-isoxazolyl adduct **2.40d** in 11% combined yield (entry 2, Table 2.2.6). What piqued our interest was the unique flip in endo:exo ratio. The titanium(IV) tetrachloride mixture provided 9% endo and 2% exo adduct **2.40d**. Increasing the mole percentage loading to 50 mol % enhanced the endo selectivity affording the desired cycloadduct **2.40d** in 38% combined yield (2.8:1 endo:exo, entry 3). Unfortunately, 1.0 equivalent of Lewis acid did not increase the yield and led to greater decomposition, providing only 3% combined yield of adduct **2.40d** (2:1 endo:exo, entry 4). Switching the Lewis acid to tin(IV) tetrachloride, provided a similar result; the endo:exo ratio was flipped. At 10 mol % loading for tin(IV) tetrachloride the reaction delivered 15% combined

Table 2.2.6



Entry	Lewis acid (mol %)	Additive (mol %)	NMR yield Endo (%)	NMR yield Exo (%)
1	None	None	1	11
2	$TiCl_4$ (10 mol %)	None	9	2
3	$TiCl_4$ (50 mol %)	None	28	10
4	$TiCl_4$ (100 mol %)	None	2	1
5	$SnCl_4$ (10 mol %)	None	11	4
6	$SnCl_4$ (25 mol %)	None	35	7
7	$SnCl_4$ (50 mol %)	None	61	15
8	$SnCl_4$ (100 mol %)	None	70	14
9	$SnCl_4$ (100 mol %)	(*R*)-BINOL (105 mol %)	29	1
10	$Sn(OTf)_2$ (50 mol %)	None	5	Trace
11	$Sn(OTf)_2$ (100 mol %)	None	4	None
12	$AlCl_3$ (50 mol %)	None	47	14
13	$EtAlCl_2$ (50 mol %)	None	Trace	4
14	Et_2AlCl (50 mol %)	None	None	None
15	BCl_3 (50 mol %)	None	3	Trace
16	$ZrCl_4$ (50 mol %)	None	Trace	Trace
17	$Cu(OTf)_2$ (10 mol %)	None	None	2
18	$Zn(OTf)_2$ (10 mol %)	None	None	Trace
19	$SbCl_5$ (10 mol %)	None	Trace	Trace
20	$SbCl_5$ (10 mol %)	(*R*)-BINOL (12 mol %)	4	Trace
21	(R) -  (10 mol %)	None	1	1
22	 (10 mol %)	None	None	2

Reaction conditions: Lewis acid (mol %), Additive (mol %), CH_2Cl_2 (0.2 M), 23 ºC, 0.25 h, then –78 ºC, Dienophile **2.37** (1.0 equiv), warm to 23 ºC, 0.5 h, then –78 ºC, 1,3-diene **2.30** (1.5 equiv), 0.5 h, warm to –20 ºC, 20 h. NMR yield calculated using 1,4-DMB as an internal standard.

yield, composed of 11% endo and 4% exo adduct **2.40d** (entry 5). Luckily, increasing the catalyst loading did not have a deleterious effect on the reaction efficiency. In fact, 25, 50, and 100 mol % loadings provided the desired adduct **2.40d** in 42%, 76%, and 84% combined yields,

respectively (entries 6-8). In general, the endo:exo ratio for the transformation was between 4:1 and 5:1 (endo:exo).

Inspired by the recent results, we elected to examine other Lewis acids to see if they could similarly activate this transformation. Formation of the LBA catalyst system with tin(IV) tetrachloride and (*R*)-1,1'-bi-2-naphthol, followed by reaction at –20 ºC in methylene chloride afforded the endo adduct **2.40d** in 29% yield and the exo adduct **2.40d** in 1% yield (entry 9). This is an exciting result, but does not match the results obtained by metal-based Lewis acids alone. Testing an additional source of tin, tin(II) triflate, which is used to generate several chiral tin complexes did not provide the desired product in considerable yield (4-5% endo, trace exo, entries 10-11). Applying aluminum(III) trichloride we were able to obtain the desired adduct **2.40d** in moderate yield and selectivity, 47% yield endo and 14% exo adduct **2.40d** (entry 12). Though, modification of the aluminum-based Lewis acid to other sources which may be used synthetically to obtain chiral aluminum complexes did not provide promising results (entries 13-14). Inspection of supplementary hard Lewis acids, such as boron trichloride and zirconium(IV) tetrachloride, as well as previously surveyed acids, like copper(II) triflate, zinc(II) triflate, antimony(V) pentachloride, $SbCl_5$•(*R*)-BINOL, (*R*)-BINOL phosphoric acid, and thiourea, also yielded poor results (entries 15-16).

In summary, the activity of tin(IV) tetrachloride emerged as the most encouraging outcome for catalyzing the hetero-Diels-Alder reaction of *N*-(5-methyl-3-isoxazolyl)sulfur imide **2.37** with *trans*-1,3-decadiene **2.30**. The catalytic capability of tin(IV) tetrachloride presented an opening for continuing studies with chiral ligands. However, it should be noted, that like the reaction of *N*-benzenesulfonylsulfur imide **2.29** with diene **2.30**, the reactivity of tin(IV) may change in the presence of chiral ligands. Nonetheless, the identification and unearthing of reactivity trends leaning toward hard Lewis acids, suggests tin(IV), aluminum(III), titanium(IV), and others shall be the starting point for those investigations.

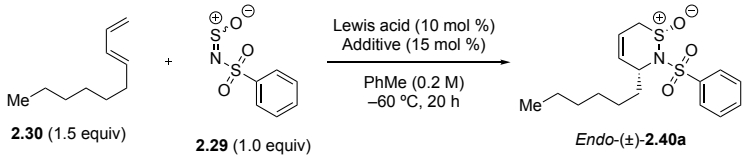
2.2.4 Ligand Screen

Following an extensive study on Lewis acids that may catalyze the hetero-Diels-Alder reaction of sulfur imide dienophiles (**2.29**, **2.37**) with *trans*-1,3-decadiene **2.30**, we must discover

chiral ligands that can work in conjunction with the acid to provide facial selectivity surrounding the dienophile leading to enantiomeric excess in the adduct. The requirements for the ligand are that it complements the binding ability of the Lewis acid, replacing the original ligands, and that it is structurally large enough to impose geometric restrictions on the pericyclic transition state. Meeting the latter requirement will force the 1,3-diene to approach the dienophile from a single face. The challenge associated with this investigation is the capability of knowing the exact structure of the chiral ligand-Lewis acid-dienophile complex in solution. Some assumptions and/or predictions may be made based off trends in selectivity. Ultimately, screening a series of chiral ligands in combination with the best-fit Lewis acid(s) should afford a reasonable opportunity to discover chiral ligand-Lewis acid complexes that provide excellent selectivity.

To accomplish the described task, titanium(IV) tetrachloride, tin(IV) tetrachloride, and antimony(V) pentachloride were selected as Lewis acids to investigate ligand selectivity in the reaction of *N*-benzenesulfonylsulfur imide **2.29** with *trans*-1,3-decadiene **2.30**. At –60 ºC in toluene, the reaction of titanium(IV) tetrachloride in the absence of additive or ligand provides 32% yield of adduct **2.40a** (entry 1, Table 2.2.7). Similar reactions with tin(IV) tetrachloride and antimony(V) pentachloride provide 38% and 10% yield adduct **2.40a**, respectively (entries 2-3). Introduction of (*R*)-BINOL **2.41** (Scheme 2.2.4) as an additive to generate the Lewis acid-assisted Brønsted acid (LBA) system afforded 27%, 44%, and 38% yield of adduct **2.40a** independently for titanium(IV) tetrachloride, tin(IV) tetrachloride, and antimony(V) pentachloride (entries 4-6). Since (*R*)-BINOL is acting as a chiral Brønsted acid in this system, introduction of additional ligand is unnecessary. In turn, the enantiomeric excess (ee) of adduct **2.40a** may be determined. The excess was measured by high pressure liquid chromatography through a Chiracel AD-H column eluted with 1:9 isopropyl alcohol:hexanes at 0.6 mL/min. The enantiomeric excess for entries 4, 5, and 6 were determined to be 7%, 3%, and 1% ee. Although the LBA catalyst system provides higher yield compared to traditional metal-based Lewis acids (determined by the Lewis acid screen in the previous section, Table 2.2.5), the enantioselectivity is low and insufficient. In accordance with the results, TADDOL **2.42**, another 1,4-diol was employed as an additive to generate a Lewis acid-assisted Brønsted acid (entries 7-9). Unfortunately, the catalyst was unable to achieve similar yields with titanium(IV) tetrachloride, tin(IV) tetrachloride, and antimony(V) pentachloride as assistants. However, there is a minor observed boost in enantioselectivity to 11%, 12%, and 6% ee, respectively.

Table 2.2.7

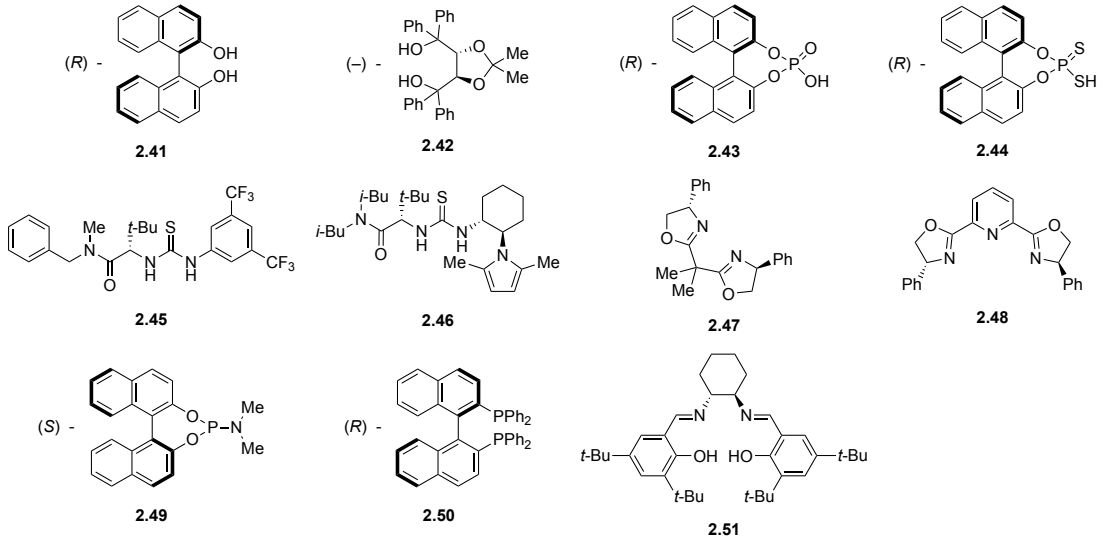


2.30 (1.5 equiv) **2.29** (1.0 equiv) *Endo*-(±)-**2.40a**

Entry	Lewis acid	Additive or Ligand	NMR yield (%)	ee (%)
1	$TiCl_4$	None	32	N/A
2	$SnCl_4$	None	38	N/A
3	$SbCl_5$	None	10	N/A
4	$TiCl_4$	**2.41**[a]	27	7
5	$SnCl_4$	**2.41**[a]	44	3
6	$SbCl_5$	**2.41**[a]	38	1
7	$TiCl_4$	**2.42**	13	11
8	$SnCl_4$	**2.42**	8	12
9	$SbCl_5$	**2.42**	30	6
10	**2.42**	None	8	10
11	**2.43**[b]	None	12	0
12	**2.44**[b]	None	18	2
13	**2.45**	None	21	12
14[c]	**2.45**	None	26	12
15	**2.46**	None	20	1
16	$TiCl_4$	**2.47**	12	1
17	$SnCl_4$	**2.47**	20	1
18	$SbCl_5$	**2.47**	28	1
19	$TiCl_4$	**2.48**	21	0
20	$SnCl_4$	**2.48**	30	0
21	$SbCl_5$	**2.48**	12	0
22	$TiCl_4$	**2.49**	22	2
23	$SnCl_4$	**2.49**	20	5
24	$SbCl_5$	**2.49**	20	0
25	$TiCl_4$	**2.50**	22	1
26	$SnCl_4$	**2.50**	32	1
27	$SbCl_5$	**2.50**	23	1
28	$TiCl_4$	**2.51**	15	0
29	$SnCl_4$	**2.51**	15	1
30	$SbCl_5$	**2.51**	24	0

Reaction conditions: Lewis acid (10 mol %), Additive/Ligand (15 mol %), PhMe (0.2 M), 23 ºC, 1 h, then –78 ºC, Dienophile **2.29** (1.0 equiv), warm to 23 ºC, 0.5 h, then –78 ºC, 1,3-diene **2.30** (1.5 equiv), 0.5 h, warm to –60 ºC, 20 h. NMR yield calculated using 1,4-DMB as an internal standard. Racemic assay: HPLC, AD-H, 1:9 IPA:Hexanes, 0.6 mL/min. [a] Additive (12 mol %). [b] Lewis acid (15 mol %). [c] Stir at –60 ºC for 3 d.

Scheme 2.2.4



As a control, TADDOL **2.42** was examined independently as a Lewis acid. The yield was markedly decreased providing 8% adduct **2.40a** (entry 10). In contrast, the enantiomeric excess was similar, 10% ee. This suggests that TADDOL **2.42** is able to stipulate a small degree of facial selectivity for dienophile **2.29**, but diol **2.42** is not a strong enough acid. This is logical, since (*R*)-BINOL **2.41** contains aryl alcohols and TADDOL **2.42** is comprised of tertiary alcohols. The addition of titanium(IV), tin(IV), and antimony(V) increase the acidity of TADDOL's protons.

To follow up some of these intriguing results, a series of chiral Brønsted acids were investigated. (*R*)-BINOL phosphoric acid **2.43** afforded the desired adduct **2.40a** in 12% yield, 0% ee (entry 11). To increase the acidity of phosphoric acid **2.43**, dithioic acid **2.44** was studied, delivering the desired adduct **2.40a** in greater yield (18%, entry 12). Although, it offered an insignificant improvement in selectivity of only 2% ee. Jacobsen's thiourea **2.45** provided the desired adduct **2.40a** in 21% yield, 12% ee (entry 13). The enantiomeric excess is similar to that of tin(IV) tetrachloride and TADDOL **2.42** (entry 8), with three-times the yield. Allowing the reaction to advance for an extended period of time, 3 days, had little effect on the yield and selectivity (26% yield, 12% ee, entry 14). Employing a related thiourea catalyst, thiourea **2.46**, had inferior results (20% yield, 1% ee, entry 15).

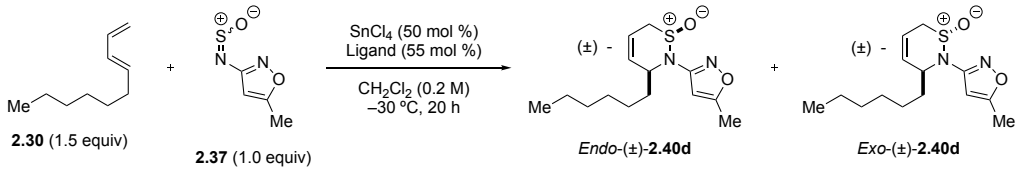
Without momentous results from a Brønsted acid screen, we decided to reinvestigate metal-based Lewis acids with a diversity of chiral ligand classes. Two nitrogen-based ligands, BOX **2.47** and PyBOX **2.48**, commonly used in asymmetric synthesis, were surveyed providing 12-30% yield with ≤1% ee when used in combination with titanium(IV) tetrachloride, tin(IV) tetrachloride, and/or antimony(V) pentachloride (entries 16-21). Using the same metal-based Lewis acids with a monodentate phosphoramidite ligand **2.49** the desired adduct **2.40a** was afforded in 20-22% yield, with up to 5% ee (entries 22-24). Switching to a bidentate phosphorus ligand, (*R*)-BINAP **2.50**, delivered the desired adduct **2.40a** in 22-32% yield, 1% ee (entries 25-27). Rounding out the investigation, a final Jacobsen, salen-type ligand **2.51** was explored. The salen-type ligand **2.51** provided 15-24% yield and ≤1% ee (entries 28-30).

In summary thus far, Jacobsen's thiourea **2.45** (entries 13-14) is the best performing chiral catalyst for the hetero-Diels-Alder reaction of *N*-benzenesulfonylsulfur imide **2.29** with *trans*-1,3-decadiene **2.30**. Among the list of chiral complexes examined, thiourea **2.45** provided the highest degree of facial selectivity, 12% ee. Unfortunately, the selectivity is still meager and the catalytic conditions do not provide substantial yield (26%). Moving forward, it would be valuable to investigate catalyst turnover taking advantage of additives such as trimethylsilyl triflate, trifluoroacetic acid, and/or triflic anhydride. Additionally, a greater number of LBA and Brønsted acid catalysts could be tested.

In light of the feeble results obtained exploiting *N*-benzenesulfonylsulfur imide **2.29** as a dienophile for the asymmetric transformation, *N*-(5-methyl-3-isoxazolyl)sulfur imide **2.37** was probed for its ability to affect the catalytic reaction. During the course of the Lewis acid screen, a flip in the endo:exo ratio of isoxazolyl adduct **2.40d** was observed (Table 2.2.6). The initial screening was conducted at –20 ºC in methylene chloride where the uncatalyzed transformation afforded the desired adduct **2.40d** in 12% combined yield (1% endo, 11% exo, entry 1, Table 2.2.6). At the time, catalytic activity was studied at –20 ºC to discern the extent at which the Lewis acid reversed the endo:exo ratio. In order to rationalize the catalytic activity of a chiral ligand-Lewis acid complex effectively, it requires that the yield and enantioselectivity be independent of outside influence stemming from the uncatalyzed, thermal reaction. Therefore, the following studies were conducted at –30 ºC in methylene chloride; the temperature at which the uncatalyzed reaction is fully suppressed (entry 1, Table 2.2.8).

To begin the studies of chiral ligand-Lewis acid complexes with dienophile **2.37**, we selected tin(IV) tetrachloride as a Lewis acid to be paired with a diverse set of ligand classes. Tin(IV) tetrachloride provided the greatest yield at –20 ºC in methylene chloride with 50 mol % loading (entry 2, Table 2.2.6). At –30 ºC in methylene chloride, tin(IV) tetrachloride catalyzes the hetero-Diels-Alder reaction of *N*-(5-methyl-3-isoxazolyl)sulfur imide **2.37** with *trans*-1,3-decadiene **2.30** to afford the desired cycloadduct **2.40d** in 74% combined yield, 65% endo and 9% exo (entry 2, Table 2.2.8). Introducing an oxygen-based ligand, (*S*)-VANOL **2.52** (Scheme 2.2.5), provided the desired adduct **2.40d** in 20% combined yield (18% endo, 2% exo) with 4% ee (entry 3). Switching to commonly used nitrogen-based ligands, the yield went up drastically.

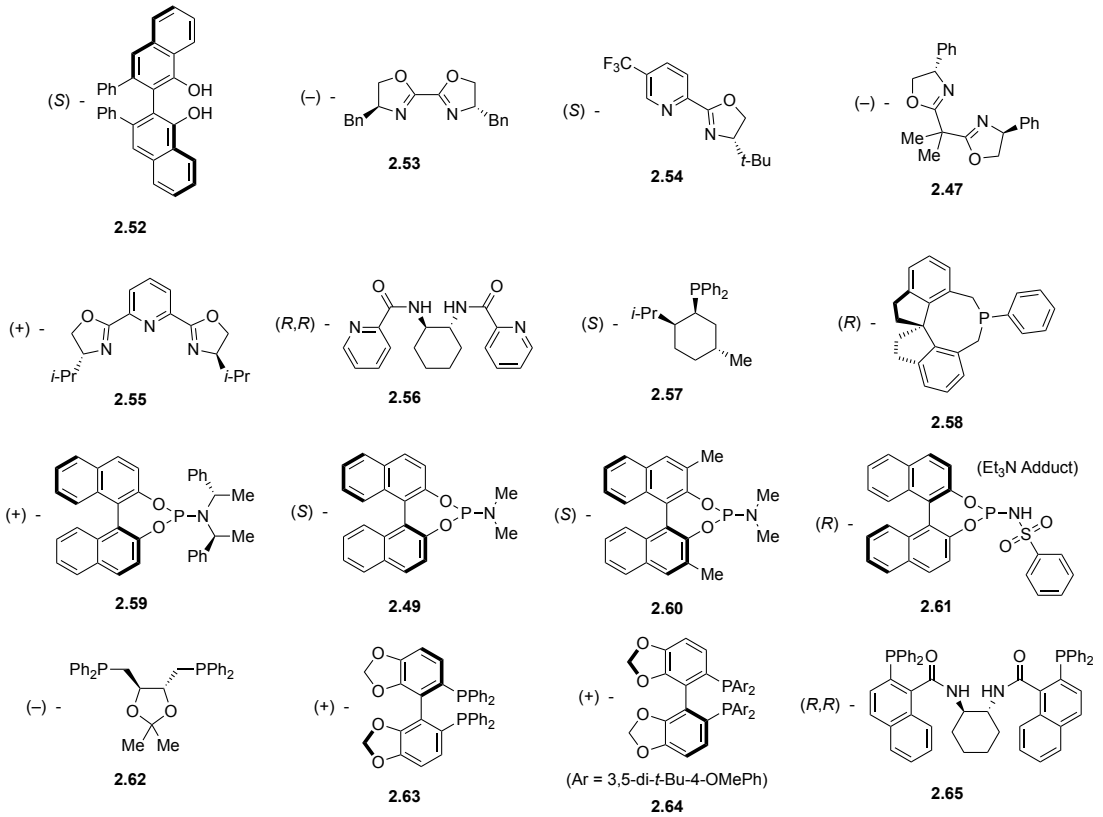
Table 2.2.8



Entry	Additive or Ligand	NMR yield Endo (%)	NMR yield Exo (%)	ee[a] (%)
1[b]	None	None	None	N/A
2	None	65	9	N/A
3	**2.52**	18	2	4
4	**2.53**	90	9	0
5	**2.54**	86	12	0
6	**2.47**	77	9	0
7	**2.55**	51	6	1
8	**2.56**	21	1	1
9	**2.57**	42	1	0
10	**2.58**	13	1	61
11	**2.59**	33	3	2
12	**2.49**	35	3	0
13	**2.60**	42	3	2
14	**2.61**	46	3	0
15	**2.62**	78	6	2
16	**2.63**	56	25	2
17	**2.64**	40	25	2
18	**2.65**	33	0	0

Reaction conditions: $SnCl_4$ (50 mol %), Ligand (55 mol %), CH_2Cl_2 (0.2 M), 23 ºC, 1 h, then –78 ºC, Dienophile **2.37** (1.0 equiv), warm to 23 ºC, 0.5 h, then –78 ºC, 1,3-diene **2.30** (1.5 equiv), 0.5 h, warm to –30 ºC, 20 h. NMR yield calculated using 1,4-DMB as an internal standard. Racemic assay: HPLC, AD-H, 2.5:97.5 IPA:Hexanes, 0.5 mL/min. [a] ee was determined by converting the crude adduct **2.40d** to homoallylic amine **2.80**. [b] No $SnCl_4$ was added.

Scheme 2.2.5



Specifically, when employing BOX ligand **2.53** the yield increased dramatically delivering adduct **2.40d** in 99% combined yield (90% exo, 9% endo, entry 4). Unfortunately, the ligand provided a racemic mixture of adduct. Utilizing (*S*)-PyrOX **2.54**, encompassing a similar zero atom spacer, provided comparable results, 98% combined yield (86% endo, 12% exo), with zero impact on enantioselectivity (entry 5). Changing to traditional BOX ligand **2.47**, with a single atom spacer, affords the desired cycloadduct **2.40d** in 86% combined yield, slightly lower than the previous entries (entry 6). This ligand also provided zero influence on the facial selectivity for dienophile **2.37**. (+)-PyBOX ligand **2.55** diminished the yield further, generating the cycloadduct in 57% combined yield (51% exo, 6% endo) with 1% ee (entry 7). A final bidentate nitrogen ligand was examined, (*R*,*R*)-DACH-pyridyl Trost ligand **2.56** providing the isoxazolyl adduct **2.40d** in 21% yield endo, 1% yield exo, and 1% ee (entry 8).

Next, we moved on to screening a series of phosphorus ligands. Employing tin(IV) tetrachloride in combination with monodentate (*S*)-NMDPP **2.57** at –30 ºC in methylene chloride affords the desired adduct **2.40d** in 43% combined yield (entry 9). A meaningful outcome of the transformation was the high endo selectivity with only 1% exo adduct **2.40d** observed. Unfortunately, there was no enantioselectivity imparted on the product. Supplying (*R*)-SITCP **2.58** as the ligand afforded the desired adduct **2.40d** in 14% combined yield (13% endo, 1% exo, entry 10). However, to our satisfaction, we obtained 61% enantiomeric excess (entry 10). This was a marvelous development for achieving facial selectivity. We hoped to obtain similar results with other monodentate phosphine ligands but were unsuccessful. Utilizing various phosphoramidite ligands, **2.49**, **2.59-2.61**, provided 36%-49% combined yield with ≤2% ee (entries 11-14). The final ligand class we were interested in studying was bidentate phosphorus ligands. Implementing (–)-DIOP **2.62** in combination with tin(IV) tetrachloride afforded adduct **2.40d** in 84% combined yield (78% endo, 6% exo) with 2% ee (entry 15). Two (+)-SEGPHOS ligands, **2.63** and **2.64,** were tested but provided poor diastereoselectivity and only 2% ee (entries 16-17). (*R*,*R*)-DACH-naphthyl Trost ligand **2.65**, on the other hand, delivered adduct **2.40d** in a modest 33% yield and 0% ee (entry 18). To our astonishment, the modest yield was entirely diastereoselective, affording a single diastereomer, the endo adduct **2.40d**.

In conclusion, the ligand screening for *N*-(5-methyl-3-isoxazolyl)sulfur imide **2.37** provided the greatest achievement for facial selectivity amongst the sulfur imide dienophiles examined in our laboratory. Although the reaction provided moderate enantioselectivity of 61% ee with minimal optimization, it requires further enhancement to be viable as a general method. Additionally, the ability of the catalyst system to turnover and provide greater yield is a must. To tackle these challenges, we must exploit the use of additives, similar to the case presented for *N*-benzenesulfonylsulfur imide **2.29**. Proportionately, the SITCP ligand should also be modified to furnish enhanced facial selectivity; an objective that is currently being pursued in our laboratory and described in the following section. In general, the reactivity revealed by this screening suggests that a general method is reasonable, following necessary optimization.

2.2.5 Preparation of SITCP Analogs

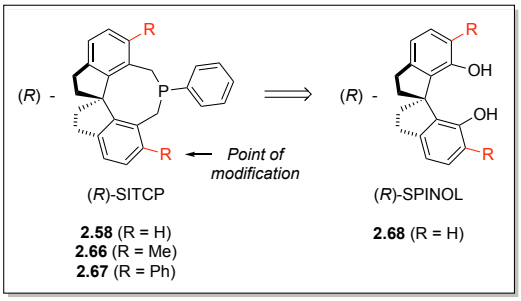
The hetero-Diels-Alder reaction of *N*-(5-methyl-3-isoxazolyl)sulfur imide **2.37** with *trans*-1,3-decadiene **2.30** may be catalyzed at –30 ºC in methylene chloride. Formation of a tin(IV) tetrachloride•(*R*)-SITCP complex, prepared *in situ*, enables this transformation; providing 14% combined yield (13% endo, 1% exo) of adduct **2.40d** with a remarkable 61% enantiomeric excess (entry 10, Table 2.2.8). While ligand **2.58** (Scheme 2.2.5) conveys good selectivity, preparation of numerous analogs of the SITCP scaffold may deliver more desirable results. Additionally, other variants of the scaffold may aide in optimization of the reaction yield something which is necessary to support a general method.

To accomplish this task, a general strategy for derivatization of the spirocyclic backbone was prepared. An initial target was modification at the ortho-position of the indane cycle in (*R*)-SITCP **2.58** (Scheme 2.2.6). Modification at this position would allow the generation of bulkier ligands that may enhance the enantioselectivity, hopefully by 30% ee or more. The primary targets were *o*-methyl-SITCP **2.66** and *o*-phenyl-SITCP **2.67**. Beginning from (*R*)-SPINOL **2.68**, the SITCP ligand **2.58** (R = H) is synthesized. The only reported procedure for preparation of this ligand is the report by Zhou and coworkers in 2005.[64] In their report, the researchers describe taking (*R*)-SPINOL **2.68** and reacting with triflic anhydride to access (*R*)-SPINOL triflate **2.69**. Following, they subject triflate **2.69** to palladium catalyzed cyanation to afford cyano-spirocycle **2.70**. Acid catalyzed hydrolysis provides the di-carboxylic acid **2.71**. Reduction of acid **2.71** with lithium aluminum hydride grants access to benzyl alcohol **2.72** which may be further converted to benzyl chloride **2.73** upon substitution with a chloride ion from thionyl chloride. The final step in the preparation of the SITCP scaffold is the reaction of benzyl chloride **2.73** with a monophosphine. The benefit of this strategy is the ability to modify the aryl ring on the monophosphine without affecting the preceding steps related to modification of the SPINOL backbone.

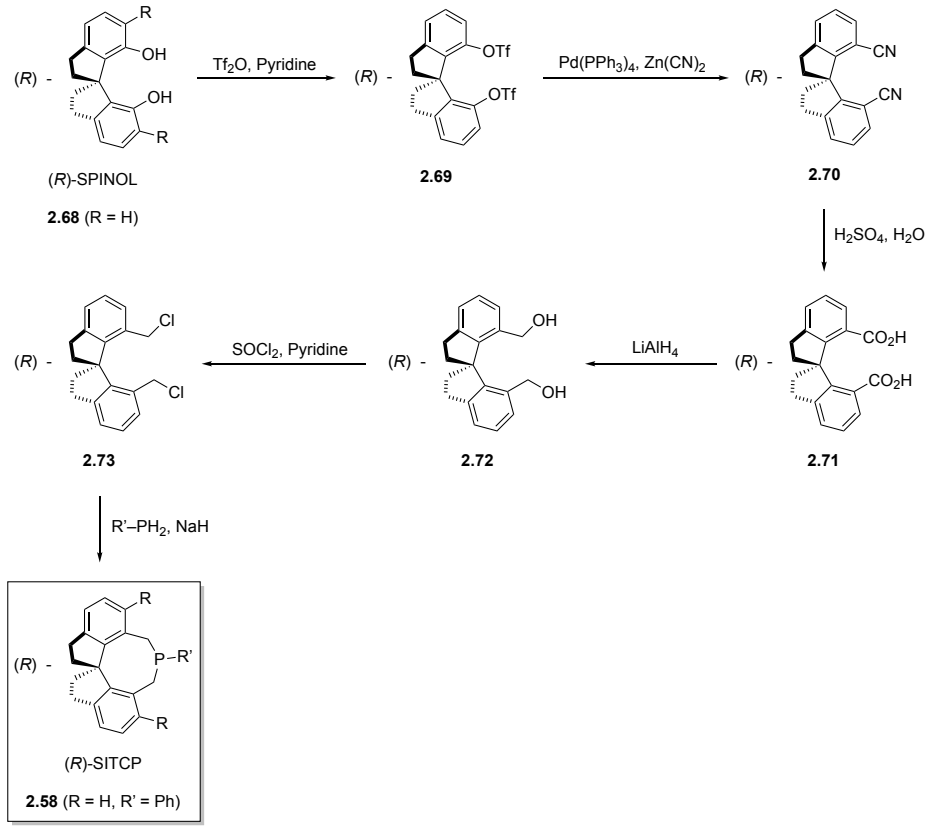
We set out to prepare *o*-methyl-SITCP **2.66** and *o*-phenyl-SITCP **2.67** by synthesizing two modified SPINOLs, **2.74** and **2.75** (Scheme 2.2.7), that may potentially be used in the route reported by Zhou. To generate these compounds, we devised a strategy that begins from (*R*)-SPINOL **2.68** and installs ortho-substitution without the need to create the spirocyclic core from scratch. The protection of (*R*)-SPINOL **2.68** with chloromethyl methyl ether provided methoxy

methyl ether **2.77** in 90% yield. Directed ortho-lithiation of (*R*)-SPINOL ether **2.76** permitted us to install both methyl and phenyl substituents with ease.[65] Quenching of the ortho-lithiation reaction with methyl iodide generated *o*-methyl-SPINOL ether **2.77** in 99% yield. Whereas, synthesis of the *o*-phenyl-substituted SPINOL **2.75** required that we perform a lithium-halogen exchange reaction with iodine. Ensuing formation of iodo ether **2.78** (75% yield), we implemented a Suzuki cross-coupling reaction with phenyl boronic acid, providing the desired *o*-phenyl-SPINOL ether **2.79** in 98% yield. Deprotection of both SPINOL ethers via stirring with concentrated hydrochloric acid delivered the desired ortho-substituted SPINOLs, *o*-methyl-SPINOL **2.74** and *o*-phenyl-SPINOL **2.75** in 91% and >99% yield, respectively. Following these steps, we are impelled to follow the SITCP synthesis reported by Zhou, shown in Scheme 2.2.6. Triflate protection is uncomplicated, however the zinc cyanide cross-coupling conditions provided by Zhou are problematic and currently under investigation by our lab. Unfortunately, Zhou and coworkers do not report synthesizing ortho-substituted SITCP ligands and we believe that the bulky nature of the ortho substituents in our compounds may be prohibiting the palladium-catalyzed cyanation reaction from taking place.

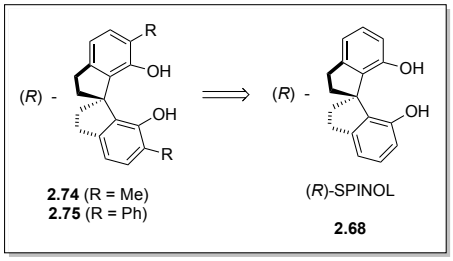
Scheme 2.2.6



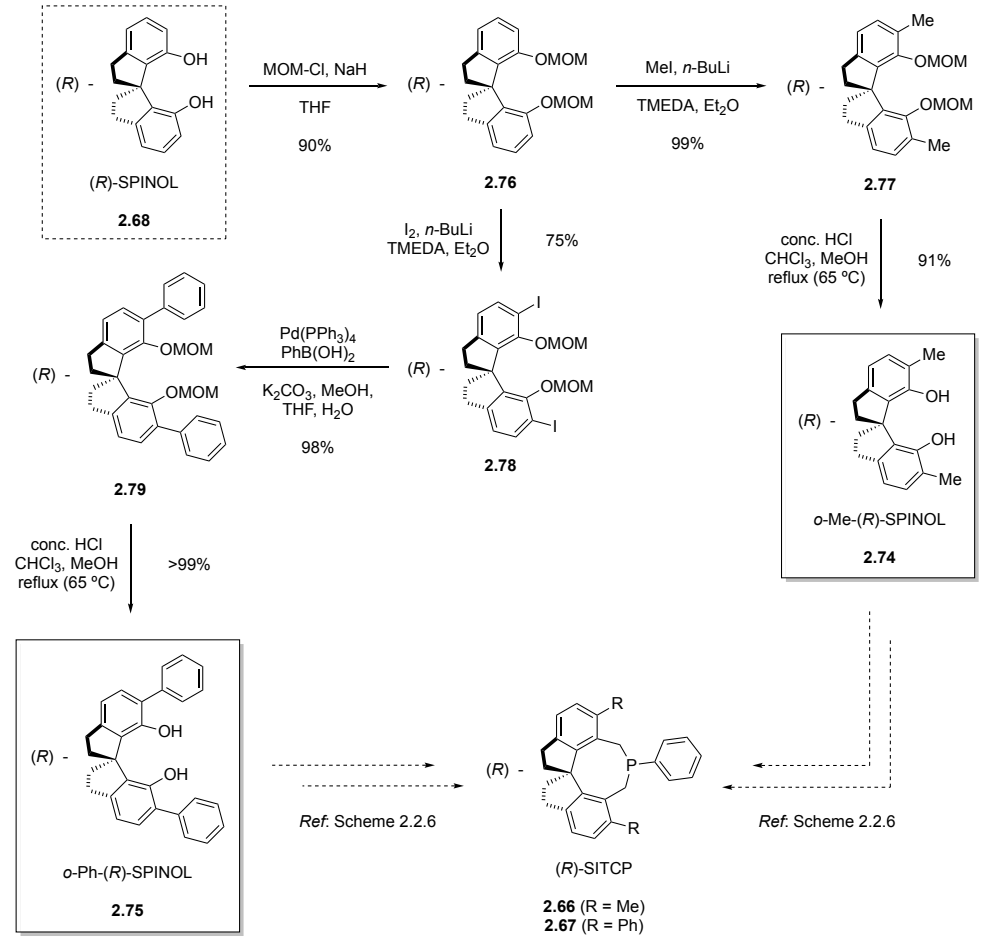
Zhuo, Synthesis of (*R*)-SITCP from (*R*)-SPINOL



Scheme 2.2.7



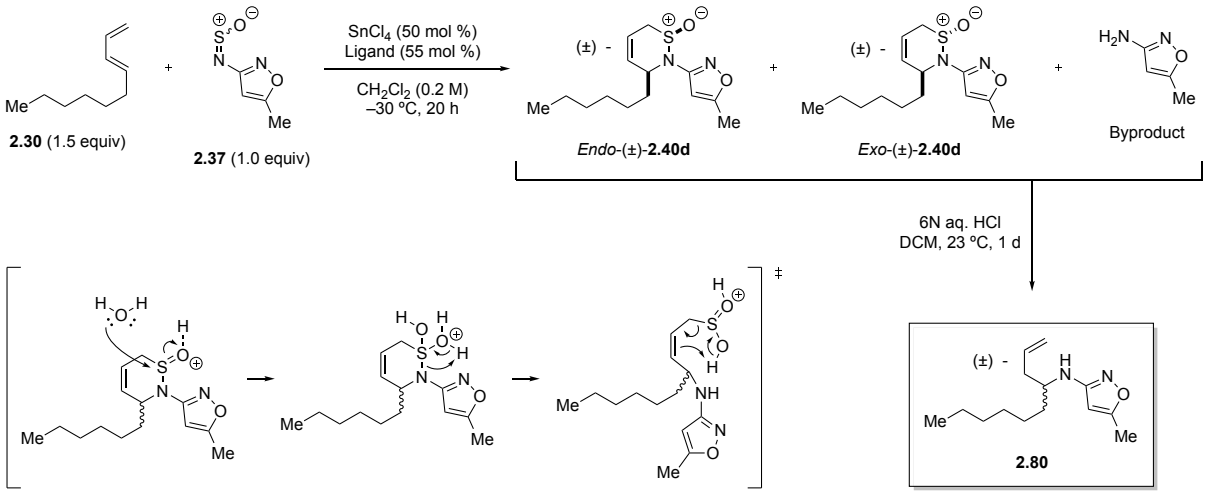
Synthesis of ortho-substituted (*R*)-SPINOLs



2.2.6 Secondary Transformation to Determine Enantioselectivity

To measure the enantiomeric excess for the catalytic hetero-Diels-Alder reactions of *N*-(5-methyl-3-isoxazolyl)sulfur imide **2.37** with *trans*-1,3-decadiene **2.30** it required a secondary transformation that eliminated the complexity associated with mixtures of diastereomers and the high presence of 5-methyl-3-aminoisoxazole. Inopportunely, the catalytic reactions provided mixtures of endo and exo adduct **2.40d** and while attempting to attain a racemic assay via high pressure liquid chromatography, aminoisoxazole, produced upon workup of the remaining imide **2.37**, would elute at the same time as the desired adducts. To adjust the polarity of the adducts and/or amine byproduct, a series of reaction conditions were examined. However, traditional acid-base chemistry worked to our advantage. It was discovered that in the presence of aqueous 6N HCl, not only would the amine crash out as a salt, but the hetero-Diels-Alder adduct **2.40d** would be converted to homoallylic amine **2.80** (Scheme 2.2.8). The mechanism of this transformation is quite unique. It is postulated that under acidic conditions, the sulfinyl group of adduct **2.40d** is activated and that a single molecule of water attacks at the electron deficient sulfur atom.[66-67] Following attack, the nitrogen from the aminoisoxazole moiety acts a good leaving group and is eliminated. The SO_2H functionality then undergoes a retro-ene reaction to afford homoallylic amine **2.80**. The benefit of this transformation-type is that it eliminates the sulfinyl stereocenter, eradicating the diastereomer complexity leaving us with a single carbon

Scheme 2.2.8



stereocenter. Furthermore, the chiral homoallylic amine product **2.80** is synthetically useful and would grant this transformation greater value in the field of medicine and materials science.

Note: The secondary transformation to homoallylic amine **2.80** may be made on the crude reaction mixture after obtaining the diastereomeric ratio by NMR. This permits high throughput optimization of the catalytic hetero-Diels-Alder reaction of *N*-(5-methyl-3-isoxazolyl)sulfur imide **2.37** and provides a synthetically useful process for tandem reactions.

2.2.7 Conclusion

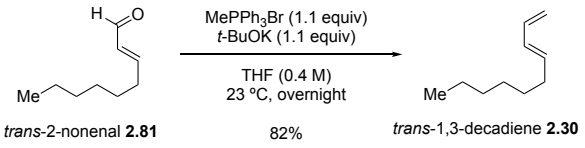
In conclusion, we have explored the development of a catalyst-controlled, enantioselective hetero-Diels-Alder reaction of sulfur imide dienophiles. Among a diverse subset of sulfur imide reagents with cleavable electron-withdrawing functionality, *N*-(5-methyl-3-isoxazolyl)sulfur imide was found to be most amenable to catalyst control. To date, we have been able to achieve up to 61% enantiomeric excess for the [4+2] adduct. This result was realized using tin(IV) tetrachloride in combination with a chiral SITCP ligand. While this is a promising result, the reaction requires additional optimization. Future directions of the study include investigating the use of additives to increase catalyst turnover and the synthesis of SITCP derivatives that may afford enhanced facial selectivity. Nevertheless, the product of the hetero-Diels-Alder reaction is demonstrated to be quite versatile. This versatility was showcased through the elaboration of an acid catalyzed ring opening–retro-ene reaction to reach chiral homoallylic amines used for the determination of enantiomeric excess. We believe this adduct will be agreeable to other valuable transformations, something which we anticipate to report in future studies.

2.3 Experimental Section

2.3.1 General Information

All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring unless otherwise indicated. Commercially obtained reagents were used as received. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. Reactions at low temperature for extended periods were cooled using a Thermo Scientific Neslab CB-80 Chiller equipped with magnetic stirring. All reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). All flash chromatography purifications were performed on a Teledyne Isco CombiFlash® Rf unless otherwise indicated. Distillations were conducted using a Buchi Glass Oven B-585 Kugelrohr unless otherwise indicated. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian Inova-400 and -500 spectrometers. Data for ^{1}H-NMR spectra are reported relative to chloroform as an internal standard (7.26 ppm) and are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C-NMR spectra are reported relative to chloroform as an internal standard (77.16 ppm) and are reported in terms of chemical shift (δ ppm). Infrared spectra were recorded on a Perkin-Elmer 1000 series FTIR. ESI-LRMS data were recorded on an AB Sciex QTRAP® 4500 LC-MS. HPLC data were recorded on an Agilent 1200 series system equipped with chiral columns.

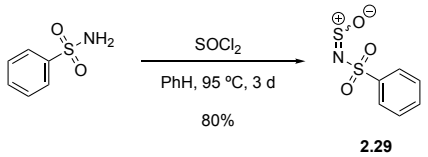
2.3.2 Diene



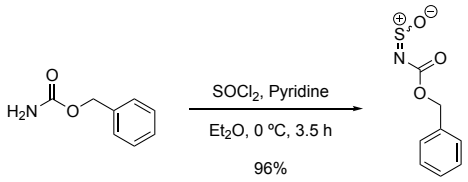
*Diene **2.30** was synthesized by the following procedure*: A flame-dried 100 mL round bottomed flask, under argon, was charged with $MePPh_3Br$ (3.87 g, 10.8 mmol, 1.1 equiv) and tetrahydrofuran (25 mL, 0.432 M). To this suspension, was added *t*-BuOK (1.21 g, 10.8 mmol,

1.1 equiv) in a single portion. The mixture stirred at 23 ºC for 1 h, then was treated with *trans*-2-nonenal **2.81** (1.0 g, 10.2 mmol, 1 equiv). The new mixture was stirred at 23 ºC, overnight (monitor completion by TLC, 10:1 hexanes:ethyl acetate). Upon completion, the reaction was diluted with pentane (20 mL) and filtered through a plug of celite. The celite plug was eluted with additional pentane (20 mL). The filtrate was filtered through a plug of silica, eluting with additional pentane (2 x 20 mL). The resulting filtrate was concentrated in vacuo. The crude material was purified by flash chromatography (100% pentane) to afford the desired product, *trans*-1,3-decadiene **2.30** as a clear, colorless oil (1.03 g, 82% yield). Spectroscopic data for diene **2.30** was identical to the reported data in the literature.[68]

2.3.3 Dienophiles

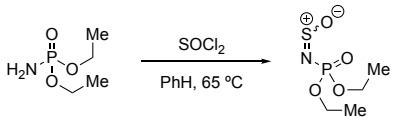


*Our procedure to prepare N-benzenesulfonylsulfur imide **2.29** (Scheme 2.3.2) was modified from a method reported in the literature for the synthesis of similar arylsulfonyl sulfur imides*:[69] A solution of benzenesulfonamide (14.55 g, 92.5 mmol) and $SOCl_2$ (20 mL, 0.275 mol) in benzene (20 mL) was refluxed at 95 ºC for 3 days (over the course of the reaction, the mixture became a clear solution). When the starting material was consumed by ^{1}H-NMR analysis of an aliquot, the mixture was concentrated under vacuum to remove benzene and excess $SOCl_2$. Trace amounts of $SOCl_2$ were removed by dissolving the residue in toluene (20 mL) and concentrating under reduced pressure. The residue was redissolved in toluene (8 mL) and stored at 0 ºC until a yellow precipitate crystallized slowly from the solution. The precipitate was separated by vacuum filtration under an argon atmosphere, washed with cold toluene (3 x 5 mL) and stored under vacuum until dry. *N*-benzenesulfonylsulfur imide **2.29** was obtained as a pale, yellow solid (15 g, 80% yield). ^{1}H-NMR and ^{13}C-NMR spectra were consistent with those reported in literature. *Since N-benzenesulfonylsulfur imide **2.29** is sensitive to water, we store it in a vacuum desiccator within a sealed flask that has been purged with argon.*



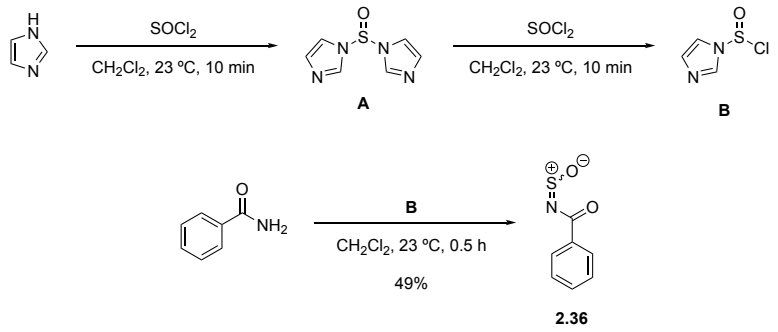
2.34

N-Carboxybenzylsulfur imide ***2.34*** *was synthesized by the following reported procedure*:[70] A flame-dried 250 mL round bottomed flask, under argon, was charged with benzyl carbamate (5.14 g, 34 mmol, 1.0 equiv) and diethyl ether (80 mL, 0.425 M). The suspension was cooled to 0 ºC in an ice bath and $SOCl_2$ (2.5 mL, 34 mmol, 1.0 equiv) was added in a single portion. To the reaction mixture was added anhydrous pyridine (5.4 mL, 2.0 equiv) via syringe pump (14 mm Dia, 3.6 mL/h) over a period of 1.5 h. The reaction mixture was stirred at 0 ºC for an additional 2 h. After, the reaction mixture was filtered through a fritted funnel into an oven-dried 500 mL round bottomed flask to remove the precipitated pyridinium hydrochloride. The reaction flask and salt were rinsed with additional anhydrous diethyl ether. The resulting filtrate was concentrated in vacuo. The crude material was purified by Kugelrohr distillation to afford the desired product, *N*-carboxybenzylsulfur imide **2.34** as a pale, yellow oil (6.44 g, 96% yield). Spectroscopic data for imide **2.34** was identical to the reported data in the literature. *Since N-carboxybenzylsulfur imide* ***2.34*** *is sensitive to water, we store it in a vacuum desiccator within a sealed flask that has been purged with argon.*



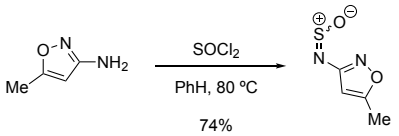
2.35

N-Sulfinyl diethyl phosphoramidate ***2.35*** *was prepared via a reported procedure.*[61] Unfortunately, the crude material decomposed during purification by Kugelrohr distillation at higher temperatures. To circumvent this problem, the crude material was used neat for the reactions of imide **2.35**. Spectroscopic data for imide **2.35** was identical to the reported data in the literature. *Since N-sulfinyl diethyl phosphoramidate* ***2.35*** *is sensitive to water, we store it in a vacuum desiccator within a sealed flask that has been purged with argon.*



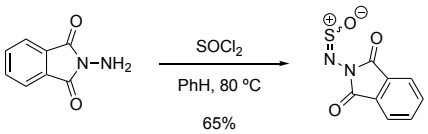
N-Benzoylsulfur imide ***2.36*** *was synthesized by the following reported procedure*:[71] A flame-dried 25 mL round bottomed flask, under argon, was charged with imidazole (1.36 g, 20 mmol, 4.0 equiv) and methylene chloride (20 mL). The solution stirred until imidazole dissolved fully, then was cooled to –10 ºC in an ethylene glycol/dry ice bath. $SOCl_2$ (0.368 mL, 5 mmol, 1.0 equiv) was added dropwise. Once addition was completed, the reaction mixture was warmed to 23 ºC and stirred for 10 min. *Note*: A white precipitate, imidazolium chloride, began to form. After 10 min at 23 ºC, the mixture was filtered through a fritted funnel into an oven-dried 100 mL round bottomed flask. The flask containing filtrate (**A**) was sealed with a septum and cooled to –10 ºC. $SOCl_2$ (0.368 mL, 5 mmol, 1.0 equiv) was added dropwise. Following complete addition, the reaction mixture was warmed to 23 ºC and stirred for an additional 10 min. *Note*: the clear, colorless solution (**A**) was converted to a pale, yellow solution (**B**). The solution (**B**) was used in the following step without workup or purification.

A separate flame-dried 100 mL pear shaped flask, under argon, was charged with benzamide (1.21 g, 10 mmol, 2.0 equiv) and methylene chloride (10 mL). The suspension stirred until homogeneous, then was cooled to –40 ºC in an acetonitrile/dry ice bath. The imidazole solution (**B**) was added, slowly. Once addition was completed, the reaction mixture was warmed to 23 ºC and stirred for 0.5 h. Then, the mixture was filtered through a fritted funnel and the filtrate was concentrated in vacuo. The crude material was purified by Kugelrohr distillation to afford the desired product, *N*-benzoylsulfur imide **2.36** as a yellow oil (823 mg, % yield). Spectroscopic data for imide **2.36** was identical to the reported data in the literature. *Since N-benzoylsulfur imide* ***2.36*** *is sensitive to water, we store it in a vacuum desiccator within a sealed flask that has been purged with argon.*



2.37

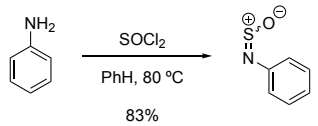
*N-(5-methyl-3-isoxazolyl)sulfur imide **2.37** was synthesized by the following reported procedure*:[59] A flame-dried 250 mL round bottomed flask, under argon, outfitted with a condenser was charged with 3-amino-5-methylisoxazole (4.00 g, 40.8 mmol, 1.0 equiv) and anhydrous benzene (40 mL). To the suspension, $SOCl_2$ (9.2 mL, 126.4 mmol, 3.1 equiv) was added dropwise at 23 ºC. Once addition was completed, the reaction mixture was heated at 80 ºC (monitor completion by ^{1}H-NMR, $CDCl_3$). Following completion, the reaction mixture was cooled to 23 ºC and concentrated in vacuo. The resulting residue was dried under high vacuum for 1 h to afford the desired product, *N*-(5-methyl-3-isoxazolyl)sulfur imide **2.37** as dark, brown-orange needles (4.35 g, 74% yield). Spectroscopic data for imide **2.37** was identical to the reported data in the literature. *Since N-(5-methyl-3-isoxazolyl)sulfur imide **2.37** is sensitive to water, we store it in a vacuum desiccator within a sealed flask that has been purged with argon.*



2.38

*N-sulfinyl-N-aminophthalimide **2.38** was synthesized by the following reported procedure*:[51] A flame-dried 100 mL round bottomed flask, under argon, outfitted with a condenser was charged with *N*-aminophthalimide (3.3 g, 20.4 mmol, 1.0 equiv) and anhydrous benzene (40 mL, 0.5 M). The reaction mixture was heated at 40 ºC for 10 min. Following, $SOCl_2$ (4.6 mL, 63.2 mmol, 3.1 equiv) was added at medium speed in one portion at 40 ºC. Once addition was completed, the mixture was heated to 80 ºC and stirred overnight (monitor completion by ^{1}H-NMR, $CDCl_3$). After, the reaction was cooled to 23 ºC. Upon reaching 23 ºC, a solid precipitated from solution. The mixture was filtered through a fritted funnel. The yellow solid was rapidly collected to afford the desired product, *N*-sulfinyl-*N*-aminophthalimide **2.38** (2.74 g, 65% yield). Spectroscopic data for imide **2.38** was identical to the reported data in the

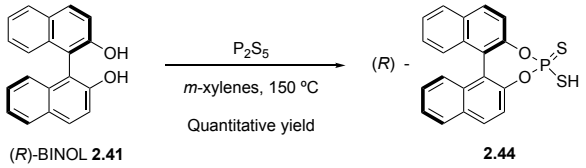
literature. *Since N-sulfinyl-N-aminophthalamide **2.37** is sensitive to water, we store it in a vacuum desiccator within a sealed flask that has been purged with argon.*



*N-benzenesulfur imide **2.39** was synthesized by the following reported procedure*:[47] A flame-dried 250 mL round bottomed flask, under argon, outfitted with a condenser was charged with redistilled aniline (7.5 mL, 82.5 mmol, 1.0 equiv) and anhydrous benzene (37.5 mL, 2.2 M). $SOCl_2$ (4.6 mL, 63.2 mmol, 3.1 equiv) was added dropwise. *Note*: The reaction mixture appeared yellow in color and a yellow-white solid precipitated upon addition of $SOCl_2$. Once addition was completed, the mixture was heated to 80 ºC and stirred overnight (monitor completion by ^{1}H-NMR, $CDCl_3$). Following completion, the reaction mixture was cooled to 23 ºC and concentrated in vacuo. The crude material was purified by Kugelrohr distillation to afford the desired product, *N*-benzenesulfur imide **2.39** as an amber oil (9.52 g, 83% yield). Spectroscopic data for imide **2.39** was identical to the reported data in the literature. *Since N-benzenesulfur imide **2.39** is sensitive to water, we store it in a vacuum desiccator within a sealed flask that has been purged with argon.*

2.3.4 Lewis Acids

All Lewis acids, except for dithioic acid **2.44**, were obtained commercially and used as received. The procedure to prepare dithioic acid **2.44** is provided below.

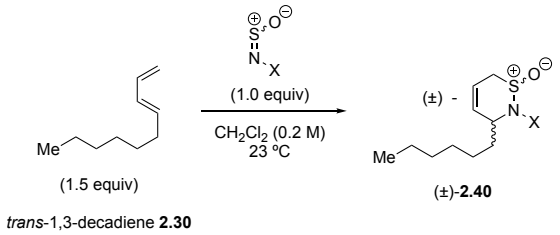


(R)-1,1'-bis-2-naphthoxyphosphinodithioic acid ***2.44*** *was synthesized by the following procedure*: An oven-dried crimp top vial was charged with (*R*)-BINOL **2.41** (115 mg, 0.40 mmol, 1.0 equiv) and P_2S_5 (88.9 mg, 0.20 mmol, 0.50 equiv). The cap was crimped to the top of the vial and the solids were dissolved in anhydrous *m*-xylenes (5.4 mL, 0.074 M) at 23 ºC. *Note*: The solids do not dissolve in their entirety. The reaction mixture was stirred at 150 ºC for 2 h (monitor reaction completion by ^{1}H and ^{31}P-NMR, $CDCl_3$). Following completion, the reaction mixture was cooled to 23 ºC and the solvent was decanted into an oven-dried 50 mL round bottomed flask. The solution was concentrated in vacuo at 70 ºC. The resulting yellow solid was dissolved in methylene chloride (3.5 mL). *Note*: Pale yellow precipitant remained. After, anhydrous hexanes (35 mL) was added. The solution was concentrated in vacuo to approximately 3-5 mL. *Note*: A white solid precipitated from solution. The reduced mixture was filtered through a fritted funnel, rinsing with anhydrous hexanes (5 mL). The solid was collected to afford the desired product, (*R*)-1,1'-bis-2-napthoxyphosphinodithioic acid **2.44** as a white solid (153.9 mg, quantitative yield). Spectroscopic data for dithioic acid **2.44** was identical to the reported data in the literature.[72-73]

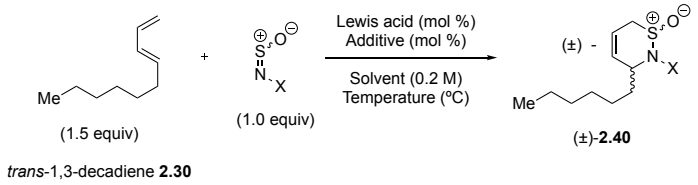
2.3.5 Ligands

All chiral ligands tested were obtained commercially and used as received. Procedures to prepare (*R*)-SPINOL derivatives, such as *o*-Me-(*R*)-SPINOL **2.74** and *o*-Ph-(*R*)-SPINOL **2.75** were reported by Zhou and coworkers.[74] Yields were recorded following the literature procedures. Spectroscopic data for *o*-Me-(*R*)-SPINOL **2.74**, *o*-Ph-(*R*)-SPINOL **2.75** and their corresponding intermediates are identical to the reported data in the literature.

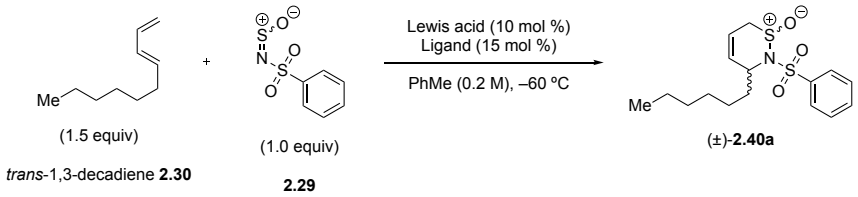
2.3.6 General and Representative Procedures for the Hetero-Diels-Alder Reactions of Sulfur Imide Dienophiles



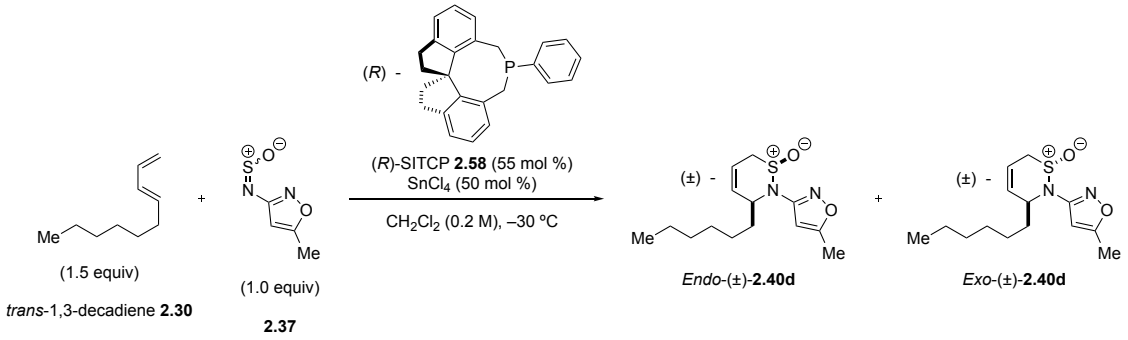
*General procedure for the thermal hetero-Diels-Alder reactions of sulfur imide dienophiles (**Method A**)*: A flame-dried 10 mL round bottomed flask, under argon, was charged with sulfur imide (1.0 equiv) and methylene chloride (0.2 M). The reaction mixture stirred until the solid dissolved fully. Then, *trans*-1,3-decadiene **2.30** (1.5 equiv) was added in a single portion. The mixture stirred at 23 ºC (monitor completion by TLC, hexanes:ethyl acetate). Upon completion, the reaction mixture was concentrated under reduced pressure. The crude material was purified by flash chromatography (hexanes:ethyl acetate) to afford the desired product, cycloadduct **2.40**.



*General procedure for the Lewis acid-catalyzed hetero-Diels-Alder reaction of sulfur imide dienophiles (**Method B**)*: A flame-dried round bottomed flask, under Argon, was charged with Lewis acid (mol %), Additive (mol %) and Solvent (0.2 M) at 23 ºC. The reaction mixture stirred at 23 ºC for 0.5 h. Then, the solution was cooled to –78 ºC and *trans*-1,3-decadiene **2.30** (1.5 equiv) was added in a single portion. The reaction mixture stirred at –78 ºC for 0.5 h. Following, the reaction mixture was warmed to Temperature (ºC) and stirred (monitor completion by TLC). Once completed, the reaction was quenched by the addition of H_2O (1.0 mL) at Temperature (ºC). The aqueous layer was extracted three times with methylene chloride (3 x 4.0 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The yield was determined by ^{1}H-NMR adding 1,4-dimethoxybenzene as an internal standard ($CDCl_3$).

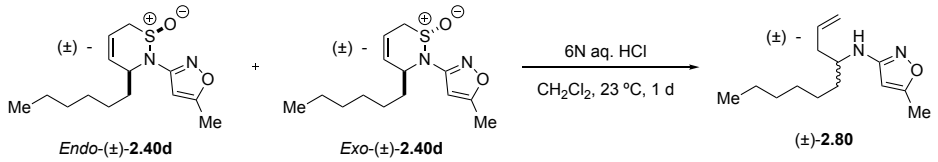


General procedure for the catalyst-controlled, asymmetric synthesis of 3-hexyl-N-benzensulfonyl-3,6-dihydrothiazine S-oxide ***2.40a (Method C)***: A flame-dried 5 mL round bottomed flask, under argon, was charged with *N*-benzenesulfonylsulfur imide **2.29** (40.6 mg, 0.20 mmol, 1.0 equiv) and chiral ligand (0.030 mmol, 15 mol %). The reaction flask was sealed with a septum and taped shut with electrical tape. Toluene (1.0 mL, 0.20 M) was added and the reaction mixture was cooled to –78 ºC. Then, Lewis acid (0.020 mmol, 10 mol %) was added and the reaction mixture stirred at –78 ºC for 0.25 h. Following, *trans*-1,3-decadiene **2.30** (41.5 mg, 0.30 mmol, 1.5 equiv) was added in a single portion. Once addition was completed, the reaction mixture stirred at –78 ºC for 0.5 h. After, the reaction mixture was warmed to –60 ºC and stirred, overnight (monitor completion by TLC, 20:1 methylene chloride:ethyl acetate, stained with $KMnO_4$). Once completed, the reaction was quenched by the addition of H_2O (1.0 mL) at –60 ºC. The aqueous layer was extracted three times with methylene chloride (3 x 4.0 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The yield was determined by ^{1}H-NMR adding 1,4-dimethoxybenzene as an internal standard ($CDCl_3$).



Representative procedure for the catalyst-controlled, asymmetric synthesis of 3-hexyl-N-(5-methyl-3-isoxazolyl)-3,6-dihydrothiazine S-oxide ***2.40d (Method D)***: A flame-dried vial,

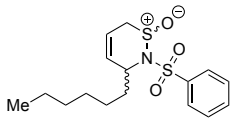
under argon, was charged with (*R*)-SITCP **2.58** (34.1 mg, 0.0963 mmol, 55 mol %) and methylene chloride (0.438 mL, 0.4 M). $SnCl_4$ (10.2 µL, 22.8 mg, 0.0875 mmol, 50 mol %) was added and the mixture stirred at 23 ºC for 1 h. A separate flame-dried 5 mL round bottomed flask, under argon, sealed with a septum was charged with *N*-(5-methyl-3-isoxazolyl)sulfur imide **2.37** (25.0 mg, 0.175 mmol, 1.0 equiv) and methylene chloride (0.438 mL, 0.4 M). The mixture stirred for 5 min at 23 ºC to dissolve the solid, then was cooled to –78 ºC. The (*R*)-SITCP•$SnCl_4$ solution was transferred to the round bottomed flask containing imide **2.37**, dropwise. Upon completed addition, the reaction mixture stirred at –78 ºC for 0.25 h. After, *trans*-1,3-decadiene **2.30** was added dropwise. Immediately following, the septum was sealed with electrical tape and the flask was transferred to the cryocool and stirred at –30 ºC, overnight (monitored completion by TLC 10:1 hexanes:ethyl acetate). The reaction mixture was quenched by the addition of H_2O (1.0 mL) at –30 ºC. The aqueous layer was extracted three times with methylene chloride (3 x 4.0 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The yield and/or endo:exo ratio were determined by ^{1}H-NMR adding 1,4-dimethoxybenzene as an internal standard (13% yield endo, 1% yield exo, $CDCl_3$). The product may be purified by preparative TLC (refer to thermal procedure, above).



*General procedure for the conversion of crude adduct **2.40d** to homoallylic amine **2.80** allowing for the determination of enantiomeric excess*: The crude material was dissolved in methylene chloride (4.0 mL) A 2.0 mL portion of the crude mixture was removed and transferred to a 20 mL scintillation vial equipped with a magnetic stirring bar. 6N HCl (2.0 mL) was added, the vial was capped, and the reaction mixture stirred, vigorously, at 23 ºC for 1 d. After, the reaction mixture was transferred to a separatory funnel, rinsing with additional methylene chloride (2 x 2.0 mL). H_2O (2.0 mL) was added and the aqueous layer was extracted three times with methylene chloride (3 x 2.0 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by preparative

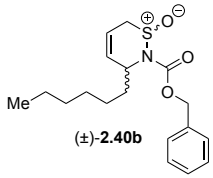
TLC (1:1 hexanes:ethyl acetate, R_f = 0.75) to afford the desired product, homoallylic amine **2.80** as a clean product for HPLC analysis.

2.3.7 Characterization Data for the [4+2]-Adducts



(±)-**2.40a**

Table 2.2.1, Compound (±)-2.40a: Following the general procedure for the thermal hetero-Diels-Alder reactions of sulfur imide dienophiles (**Method A**), *N*-benzenesulfonylsulfur imide **2.29** (101.6 mg, 0.50 mmol) was converted to the [4+2] adduct **2.40a**. Purification by flash chromatography afforded the desired [4+2] adduct **2.40a** as a white solid (161.9 mg, 99% yield): **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.92 – 7.90 (m, 2H), 7.63 (tt, *J* = 7.5, 1.1 Hz, 1H), 7.57 – 7.54 (m, 2H), 6.11 (dt, *J* = 11.1, 3.0 Hz, 1H), 5.71 (ddt, *J* = 11.1, 6.5, 2.6 Hz, 1H), 4.52 – 4.47 (m, 1H), 3.41 (dd, *J* = 16.5, 6.5 Hz, 1H), 3.31 (ddd, *J* = 16.5, 6.0, 2.6 Hz, 1H), 1.85 – 1.77 (m, 1H), 1.73 – 1.65 (m, 1H), 1.34 – 1.14 (m, 8H), 0.85 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 140.61, 133.72, 129.61, 128.76, 127.13, 113.38, 55.39, 49.43, 36.51, 31.66, 29.84, 28.91, 26.50, 22.65, 14.28, 14.19. **IR (ν cm^{-1})** 2927.62, 2856.81, 2345.73, 1167.62, 1090.95. **LRMS (ESI) calcd for [$C_{16}H_{24}NO_3S_2$]$^+$([M+H]$^+$):** 342.11, found 342.2.



(±)-**2.40b**

Table 2.2.1, Compound (±)-2.40b: Following the general procedure for the thermal hetero-Diels-Alder reactions of sulfur imide dienophiles (**Method A**), *N*-carboxybenzylsulfur imide **2.34** (98.6 mg, 0.50 mmol) was converted to the [4+2] adduct **2.40b**. Purification by flash chromatography afforded the desired [4+2] adduct **2.40b** as a clear, colorless oil (112.9 mg, 67%

yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 5H), 6.46 – 6.38 (m, 1H), 5.96 – 5.88 (m, 1H), 5.28 (dt, *J* = 12.5, 10.5 Hz, 2H), 4.60 – 4.52 (m, 1H), 3.53 (dd, *J* = 15.2, 7.7 Hz, 1H), 3.38 (d, *J* = 15.2 Hz, 1H), 1.92 – 1.80 (m, 1H), 1.70 – 1.56 (m, 1H), 1.37 – 1.17 (m, 8H), 0.87 (t, *J* = 6.3 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 154.84, 135.33, 133.44, 128.75, 128.56, 128.17, 115.32, 69.04, 54.40, 47.56, 34.88, 31.81, 29.20, 25.70, 22.66, 14.18. **IR (ν cm^{-1})** 2955.10, 2927.30, 2857.67, 1721.49, 1283.95. **LRMS (ESI) calcd for [$C_{18}H_{26}NO_3S$]$^+$([M+H]$^+$):** 336.17, found 336.2.

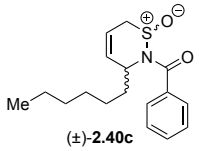
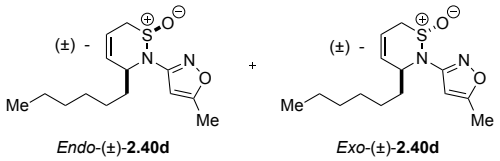


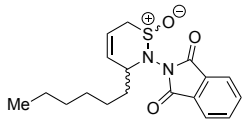
Table 2.2.1, Compound (±)-2.40c: Following the general procedure for the thermal hetero-Diels-Alder reactions of sulfur imide dienophiles (**Method A**), *N*-benzoylsulfur imide **2.36** (50.0 mg, 0.30 mmol) was converted to the [4+2] adduct **2.40c**. Purification by flash chromatography afforded the desired [4+2] adduct **2.40c** as an off-white solid (78.4 mg, 86% yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.48 (m, 3H), 7.43 (dd, *J* = 7.6, 7.3 Hz, 2H), 6.42 (ddd, *J* = 10.3, 5.0, 2.8 Hz, 1H), 5.88 (ddd, *J* = 10.3, 7.3, 2.8 Hz, 1H), 4.87 (d, *J* = 5.0 Hz, 1H), 3.62 – 3.54 (m, 1H), 3.50 (dd, *J* = 15.3, 7.3 Hz, 1H), 1.94 – 1.84 (m, 2H), 1.47 – 1.20 (m, 8H), 0.87 (t, *J* = 6.5 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 173.30, 134.74, 133.46, 131.74, 129.03, 128.48, 114.12, 52.42, 48.61, 33.44, 31.86, 29.27, 25.03, 22.70, 14.19. **IR (ν cm^{-1})** 2955.14, 2926.95, 2857.49, 1677.62, 1289.58. **LRMS (ESI) calcd for [$C_{17}H_{24}NO_2S$]$^+$([M+H]$^+$):** 306.15, found 306.2.



Endo-(±)-**2.40d** *Exo*-(±)-**2.40d**

Table 2.2.1, Compound (±)-2.40d: Following the general procedure for the thermal hetero-Diels-Alder reactions of sulfur imide dienophiles (**Method A**), *N*-(5-methyl-3-isoxazolyl)sulfur imide **2.37** (50.0 mg, 0.35 mmol) was converted to the [4+2] adduct (±)-**2.40d**

(46% NMR yield endo-(±)-**2.40d**, 19% NMR yield exo-(±)-**2.40d**, 1,4-dimethoxybenzene as an internal standard). Purification by flash chromatography (hexanes:ethyl acetate) afforded the desired adduct as an inseparable mixture of diastereomers appearing as a light-brown semisolid (10:1 endo:exo). The diastereomers were identified following the transformation of the crude endo-exo-amine mixture to homoallylic amine **2.80**, delivering quantitative yield relative to the sum of endo- and exo-(±)-**2.40d** measured by crude ^{1}H-NMR (See: Section 2.3.8). *Note: A greater quantity of exo-(±)-**2.40d** is present in the crude material. Upon purification, the endo and/or exo adduct have minor separation from 3-amino-5-methylisoxazole. In a separate fraction, 3-amino-5-methylisoxazole remains mixed with exo-(±)-**2.40d** (See: Appendix 2 for NMR spectra).* **^{1}H-NMR** Endo-(±)-**2.40d** (500 MHz, $CDCl_3$) δ 6.24 – 6.19 (m, 1H), 6.00 (q, *J* = 0.8 Hz, 1H), 5.83 – 5.77 (m, 1H), 4.50- 4.44 (m, 1H), 3.54 – 3.48 (m, 1H), 3.44 (dd, *J* = 16.3, 6.4 Hz, 1H), 2.36 (d, *J* = 0.8 Hz, 3H), 2.05 – 1.95 (m, 1H), 1.93 – 1.83 (m, 1H), 1.49 – 1.20 (m, 8H), 0.85 (t, *J* = 0.85 Hz, 3H). **^{1}H-NMR** Exo-(±)-**2.40d** (500 MHz, $CDCl_3$) δ 6.26 – 6.21 (ddd, *J* = 10.6, 4.4, 2.6 Hz, 1H), 6.03 (q, *J* = 0.8 Hz, 1H), 5.86 (ddd, *J* = 6.9, 3.0, 0.8 Hz, 1H), 4.59 – 4.53 (m, 1H), 3.56 – 3.51 (m, 1H), 3.51 – 3.46 (m, 1H), 2.38 (d, *J* = 0.8 Hz, 3H), 1.93 – 1.76 (m, 2H), 1.35 – 1.16 (m, 8H), 0.84 (t, *J* = 6.9, 3H).

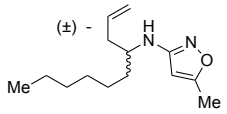


(±)-**2.40e**

Table 2.2.1, Compound (±)-2.40e: Following the general procedure for the thermal hetero-Diels-Alder reactions of sulfur imide dienophiles (**Method A**) at 40 ºC, *N*-sulfinyl-*N*-aminophthalamide **2.38** (50.0 mg, 0.24 mmol) was converted to the [4+2] adduct **2.40e** (22% NMR yield). Purification by preparatory TLC (1:2 hexanes:diethyl ether) afforded the desired [4+2] adduct **2.40e** as a white solid: **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H), 5.88 (dddd, *J* = 17.0, 10.2, 8.1, 5.9 Hz, 1H), 5.19 – 5.13 (m, 1H), 5.12 – 5.08 (m, 1H), 4.55 (s, 1H), 3.29 – 3.20 (m, 1H), 2.36 – 2.29 (m, 1H), 2.24 – 2.16 (m, 1H), 1.51 – 1.20 (m, 8H), 0.86 (t, *J* = 6.7 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 167.36, 134.90, 134.37, 130.37, 123.55, 118.06, 58.78, 37.20, 32.60, 31.89, 29.56, 25.54, 22.73, 14.21.

IR (ν cm^{-1}) 2928.53, 2856.95, 1786.47, 1726.35, 1381.68. **LRMS (ESI) calcd for [$C_{18}H_{23}N_2O_3S$]$^+$([M+H]$^+$):** 347.15, found 347.2.

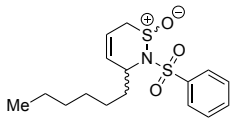
2.3.8 Characterization Data for Homoallylic Amine



(±)-**2.80**

Scheme 2.2.8, Compound 2.80: Following the general procedure for the conversion of crude adduct **2.40d** to an homoallylic amine, the crude mixture was converted to homoallylic amine **2.80**. Purification by preparative TLC afforded the desired product, homoallylic amine **2.80** as a white solid (53.2 mg, quantitative yield): **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.85 – 5.74 (m, 1H), 5.45 (s, 1H), 5.11 – 5.04 (m, 2H), 3.45 (apparent quintet, *J* = 6.0 Hz, 1H), 3.27 – 2.23 (m, 2H), 2.27 (s, 3H), 1.57 – 1.19 (m, 10H), 0.86 (t, *J* = 6.9 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 168.59, 164.59, 134.71, 117.91, 93.34, 53.51, 38.96, 34.66, 31.93, 29.43, 26.01, 22.75, 14.23, 12.67. **IR (ν cm^{-1})** 3298.36, 2928.13, 2856.84, 1629.06, 1549.00. **LRMS (ESI) calcd for [$C_{14}H_{25}N_2O$]$^+$([M+H]$^+$):** 237.20, found 237.2.

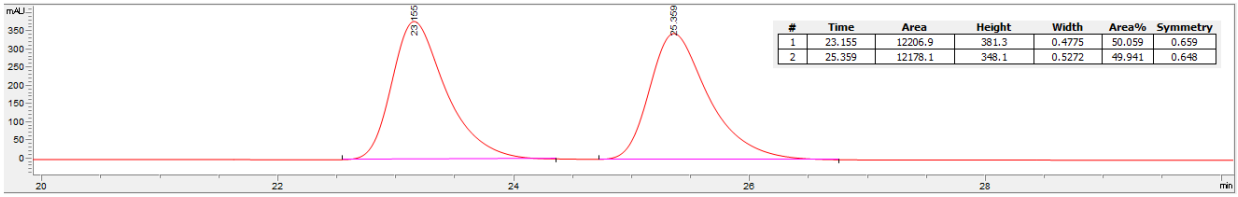
2.3.9 HPLC Data for the Asymmetric Hetero-Diels-Alder Reaction



(±)-**2.40a**

Figure 2.3.1

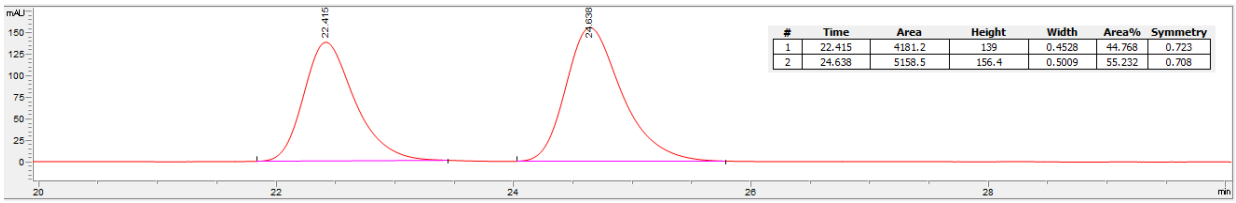
(±)-2.40a Racemic assay: Chiracel AD-H, 90:10 Hexanes:Isopropyl alcohol, 0.6 mL/min.



#	Time	Area	Height	Width	Area%	Symmetry
1	23.155	12206.9	381.3	0.4775	50.059	0.659
2	25.359	12178.1	348.1	0.5272	49.941	0.648

Figure 2.3.2

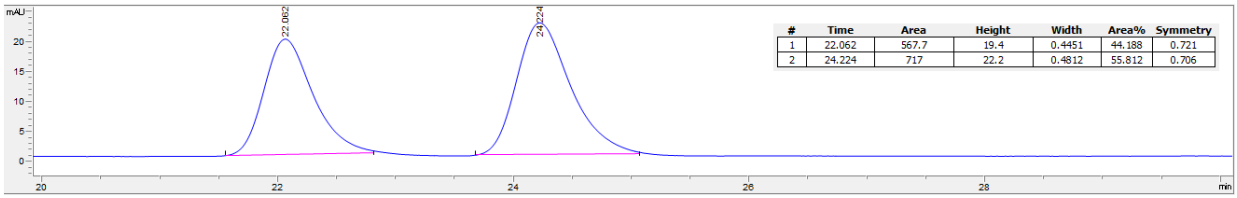
Table 2.2.7, entry 13: Chiracel AD-H, 90:10 Hexanes:Isopropyl alcohol, 0.6 mL/min.



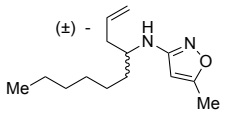
#	Time	Area	Height	Width	Area%	Symmetry
1	22.415	4181.2	139	0.4528	44.768	0.723
2	24.638	5158.5	156.4	0.5009	55.232	0.708

Figure 2.3.3

Table 2.2.7, entry 14: Chiracel AD-H, 90:10 Hexanes:Isopropyl alcohol, 0.6 mL/min.



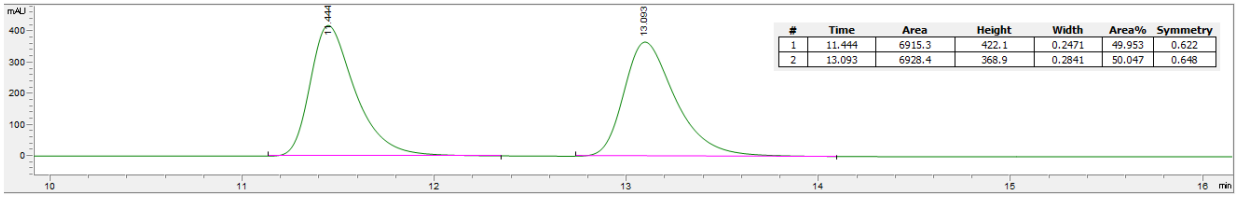
#	Time	Area	Height	Width	Area%	Symmetry
1	22.062	567.7	19.4	0.4451	44.188	0.721
2	24.224	717	22.2	0.4812	55.812	0.706



(±)-**2.80**

Figure 2.3.4

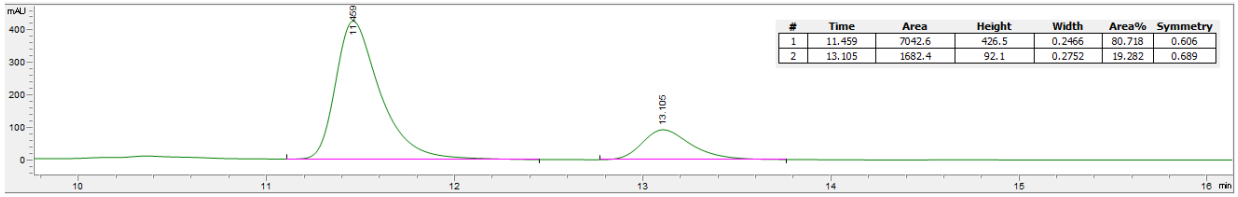
(±)-2.80 Racemic assay: Chiracel OD-H, 95:5 Hexanes:Isopropyl alcohol, 0.5 mL/min.



#	Time	Area	Height	Width	Area%	Symmetry
1	11.444	6915.3	422.1	0.2471	49.953	0.622
2	13.093	6928.4	368.9	0.2841	50.047	0.648

Figure 2.3.5

Table 2.2.8, entry 10: Chiracel OD-H, 95:5 Hexanes:Isopropyl alcohol, 0.5 mL/min.



#	Time	Area	Height	Width	Area%	Symmetry
1	11.459	7042.6	426.5	0.2466	80.718	0.606
2	13.105	1682.4	92.1	0.2752	19.282	0.689

2.4 References

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APPENDIX TWO

Spectra Relevant to Chapter Two:
The Development of a Catalyst-Controlled, Enantioselective Hetero-Diels-Alder Reaction of Sulfur Imide Dienophiles

NMR Spectra

Figure A2.1, Compound (±)-2.40a

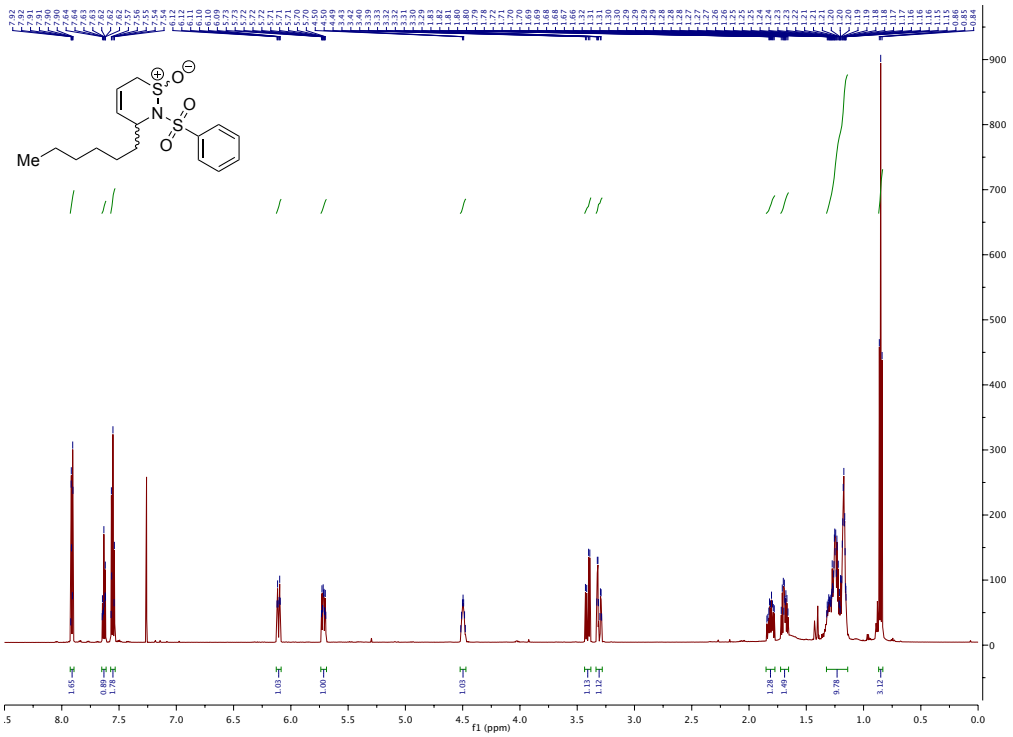


Figure A2.2, Compound (±)-2.40a

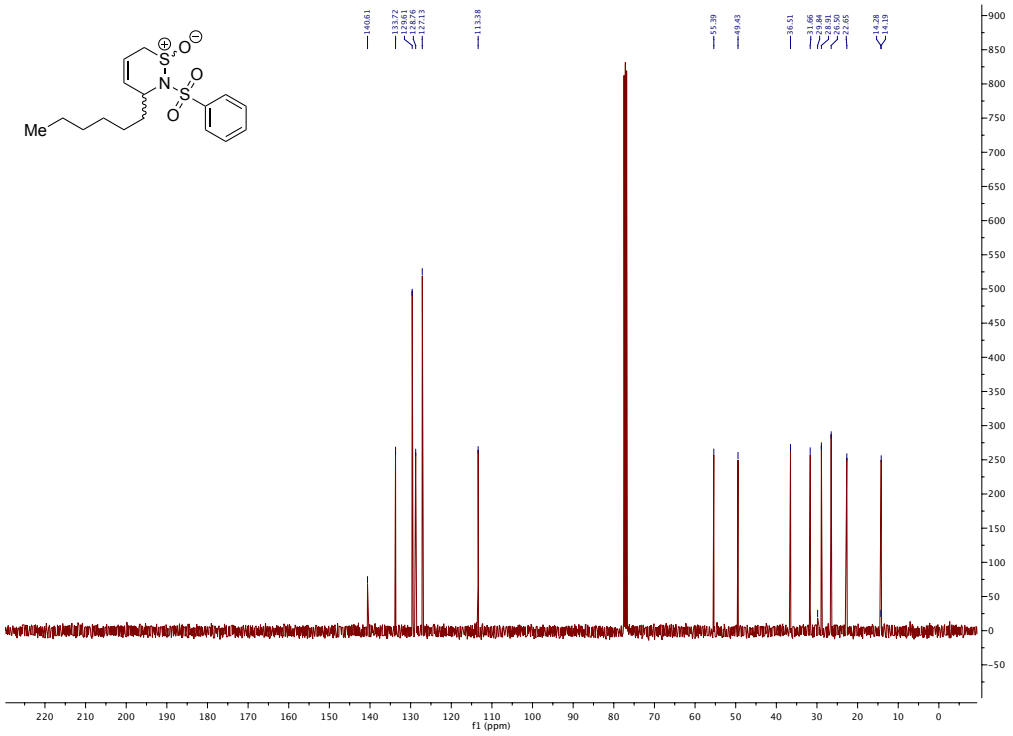


Figure A2.3, Compound (±)-2.40b

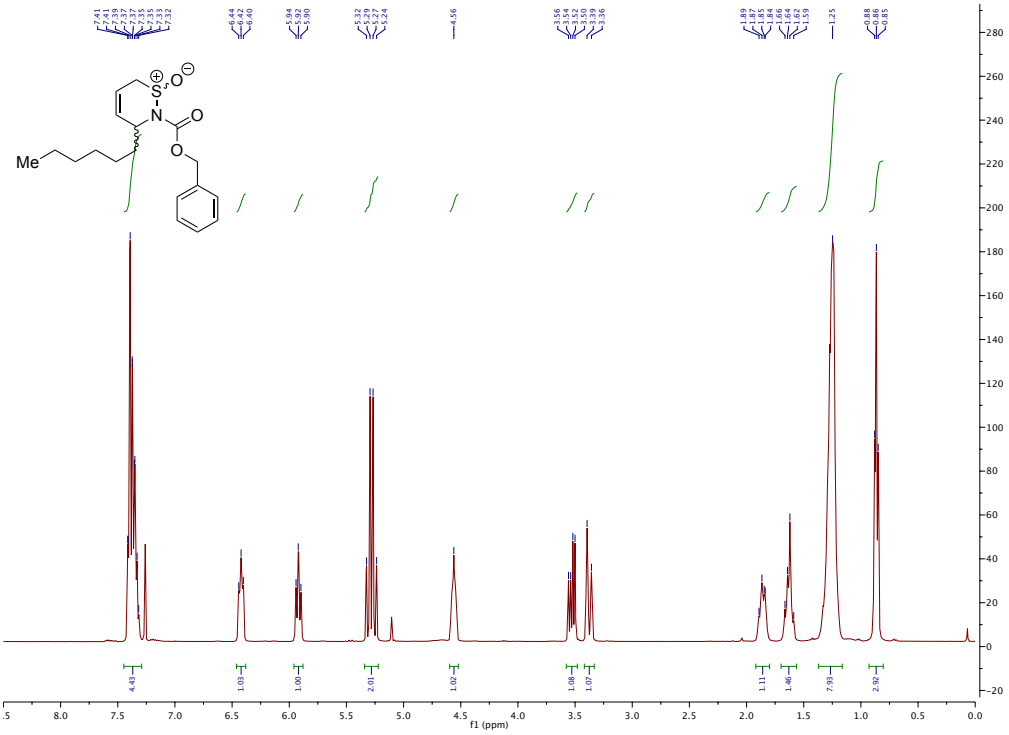


Figure A2.4, Compound (±)-2.40b

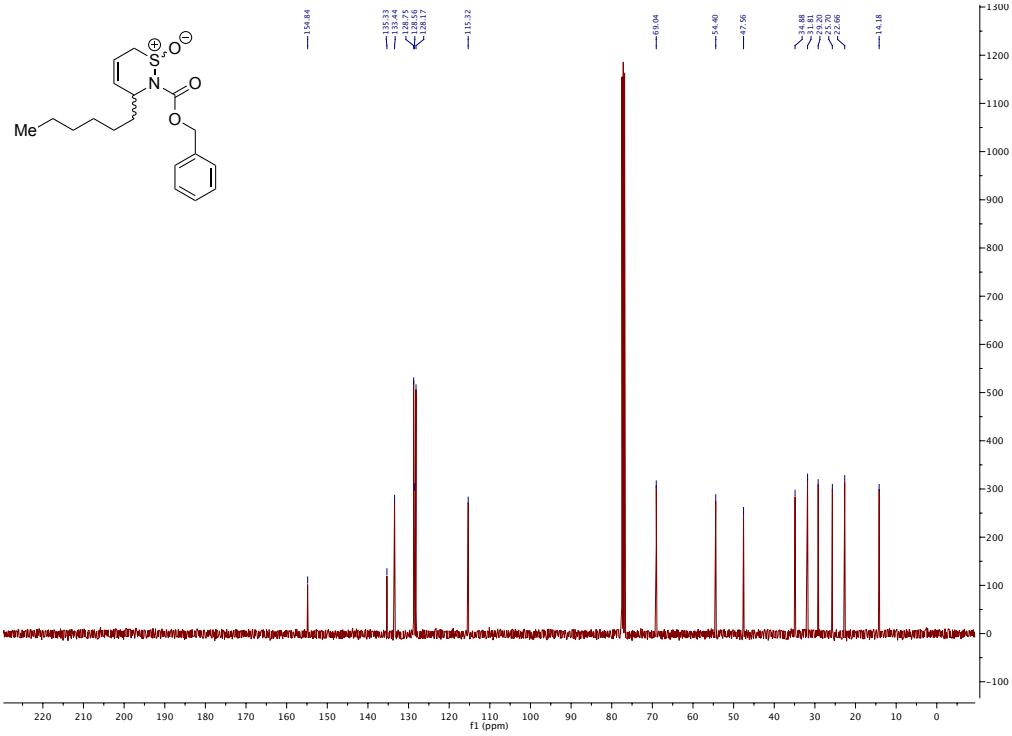


Figure A2.5, Compound (±)-2.40c

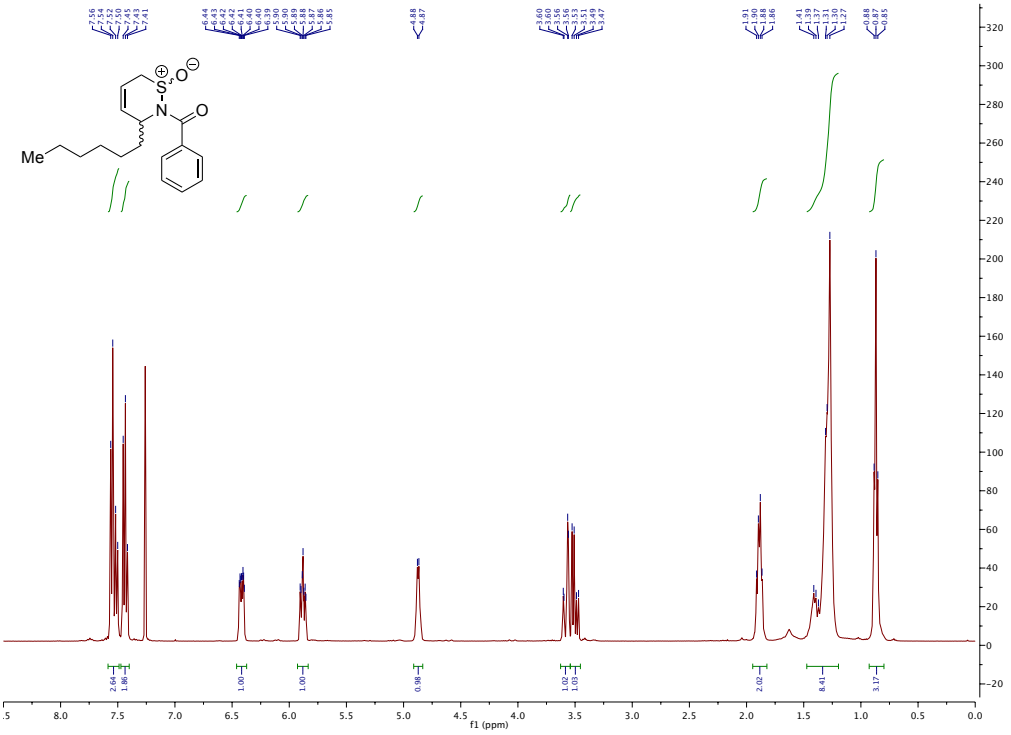


Figure A2.6, Compound (±)-2.40c

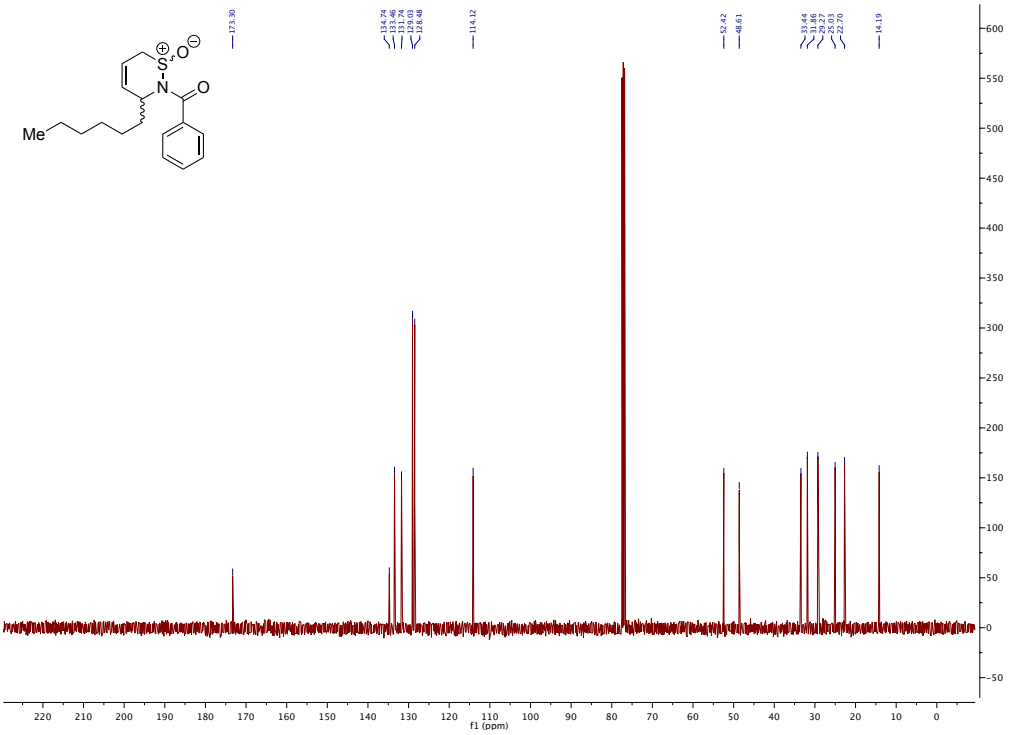


Figure A2.7, Compound (±)-2.40d

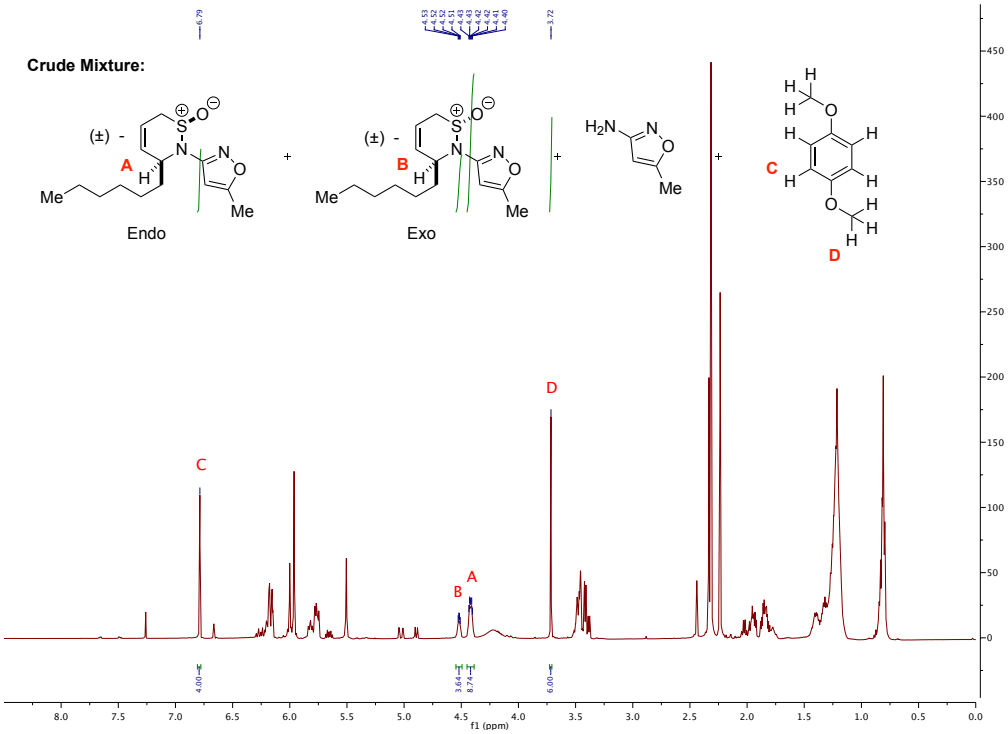
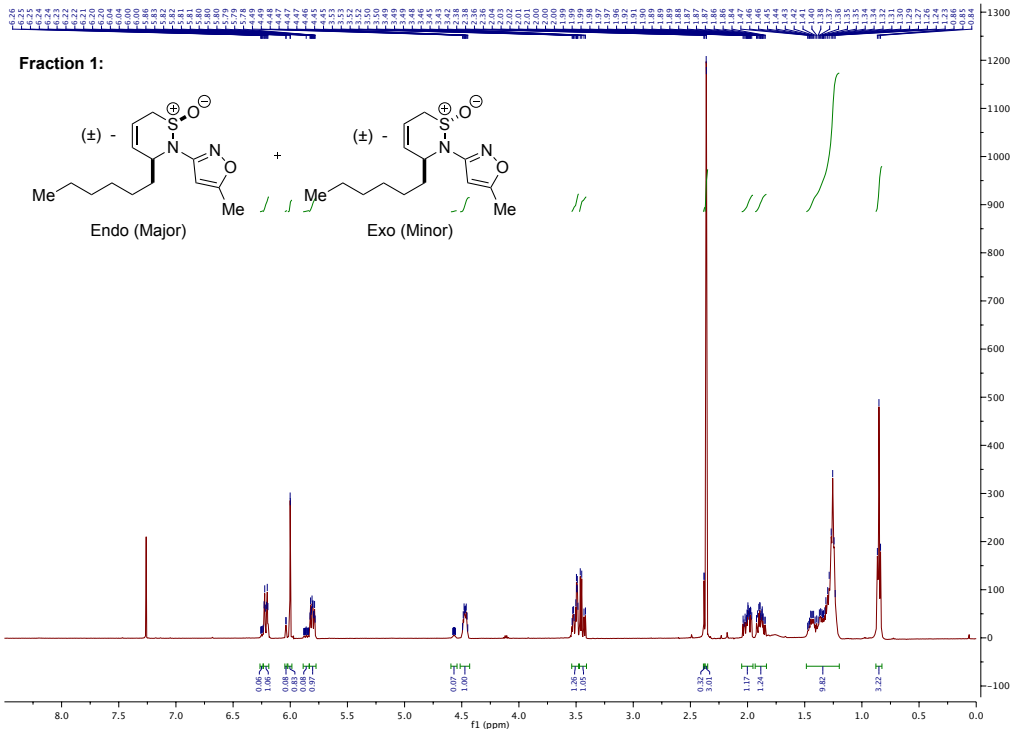


Figure A2.8, Compound (±)-2.40d



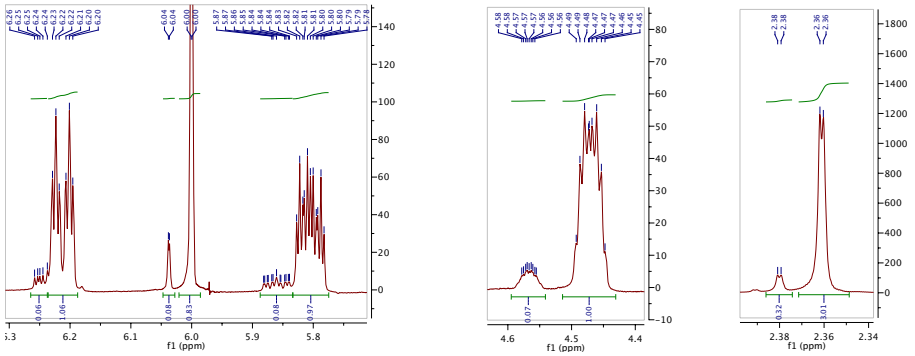


Figure A2.9, Compound (±)-2.40d

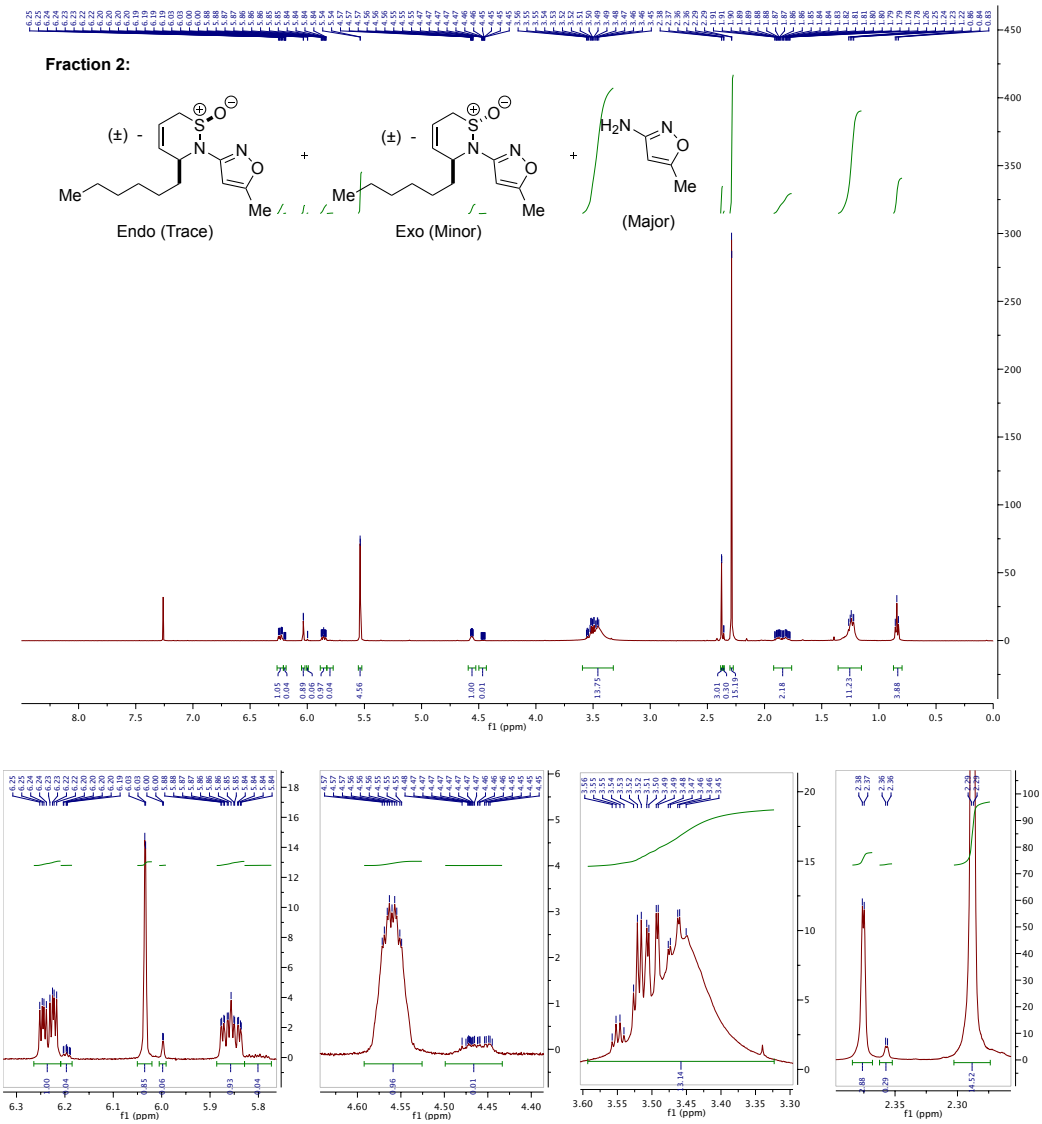


Figure A2.10

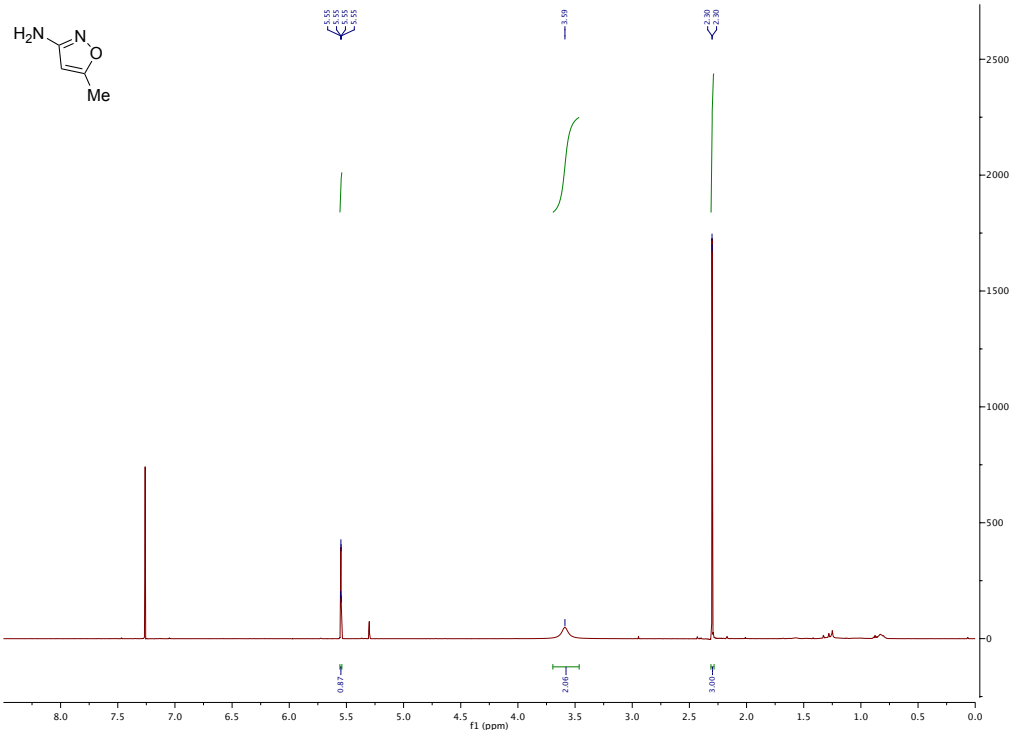

H2N
N
O
Me
5.55
5.55
5.55
5.55
5.55
3.59
2.30
2.30
2500
2000
1500
1000
500
0
0.87
2.06
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

Figure A2.11, Compound (±)-2.80

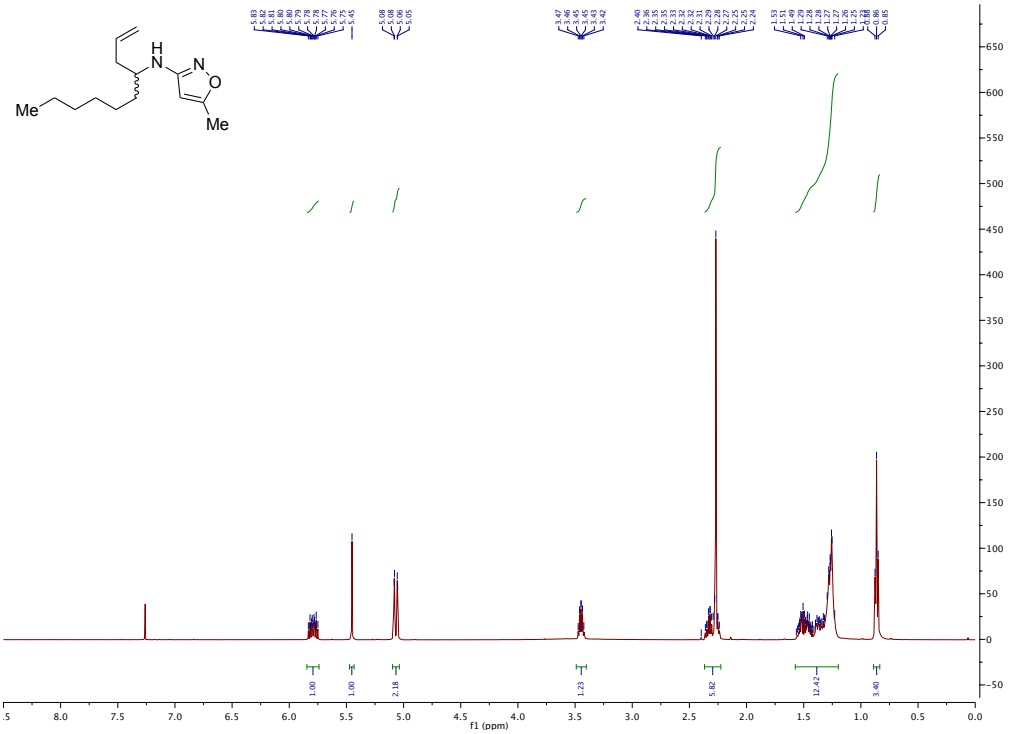


Figure A2.12, Compound (±)-2.80

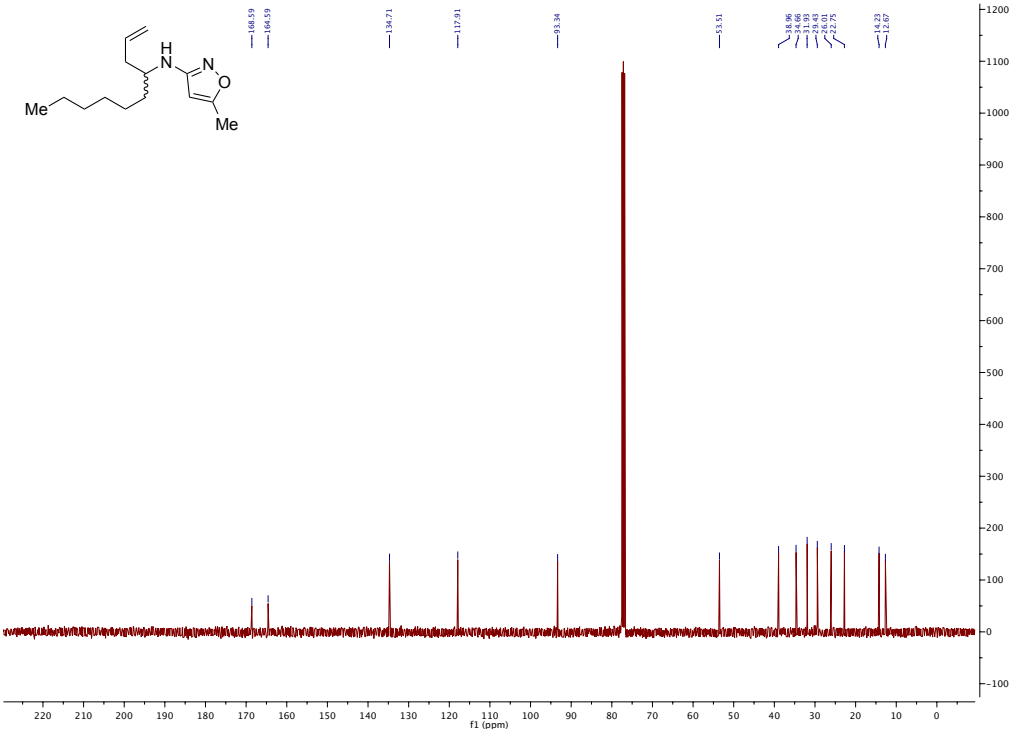


Figure A2.13, Compound (±)-2.40e

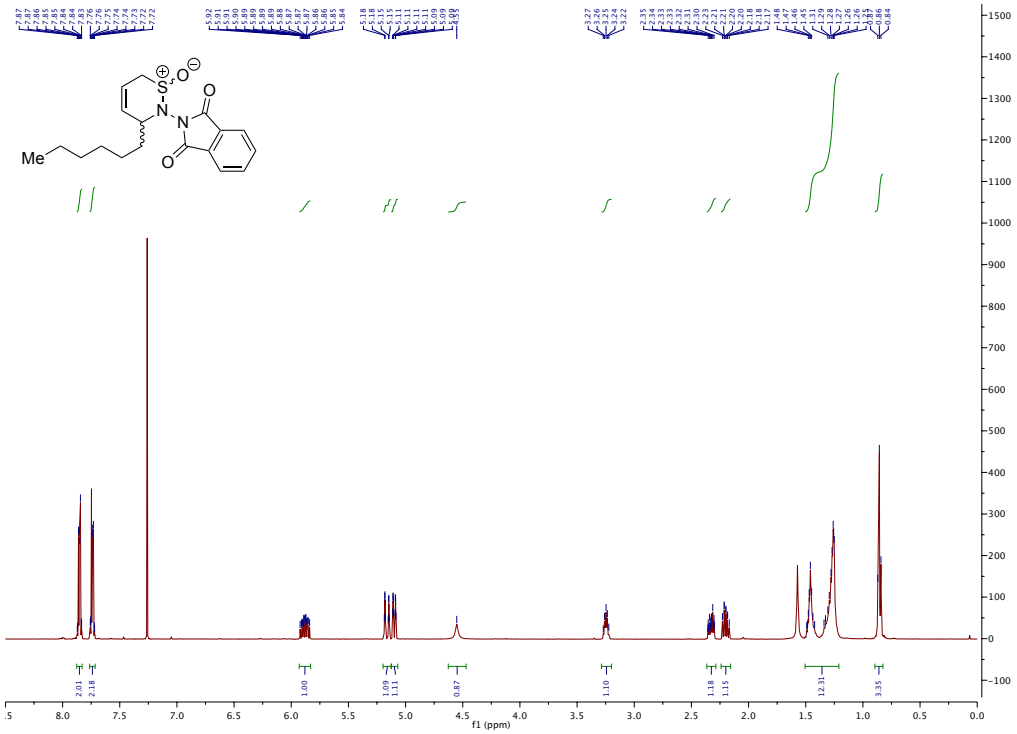


Figure A2.14, Compound (±)-2.40e