Towards the Synthesis of Polysulfurous Molecules Found in Shiitake Mushrooms (*Lentinula Edodes*) and Optimizing the Synthesis of Allenyl Sulfoxides from Thiosuccinimides

by

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ABSTRACT

TOWARDS THE SYNTHESIS OF POLYSULFUROUS MOLECULES FOUND IN SHIITAKE MUSHROOMS (LENTINULA EDODES)

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Lentinic acid, the precursor to lenthionine (the primary aroma producing compound of shiitake mushrooms), represents a valuable synthesis target due its natural isomer being unknown and the lack of literature about the final non-enzymatic step of its conversion to lenthionine. The synthesis of lentinic acid provides an opportunity to explore novel organosulfur chemistry as it contains a previously unreported sulfur carbon. The primary focus of this research was to investigate the synthesis of lentinic acid via novel organosulfur methods. The first objective was the synthesis of β-sulfonyl sulfinate esters/sulfinamides from sulfones. The second objective was the investigation of the double deprotonation chemistry of β-bis-sulfoxides with the goal of reacting them with the β-sulfonyl sulfinate esters/sulfinamides to synthesize lentinic acid. The final objective was the synthesis of lentinic acid via an iterative sulfenate release. These objectives were unsuccessful and alternative methods should be investigated for the synthesis of lentinic acid.

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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	2,2′-azobis(2-methylpropionitrile)
Ar	aryl
Bn	benzyl
Boc	tert-butyloxycarbonyl
Bz	benzoyl
Cy	cyclohexyl
d.r.	diastereomeric ratio
DABSO	1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct
DAG or DAGOH	diacetone glucose
DCE	1,2-dichloroethane
DCM	dichloromethane
DIMSYL	dimethyl sulfoxide anion
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyl dioxirane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
$DMSO_2$	dimethyl sulfone
ee	enantiomeric excess
EI	electron impact
ESI	electrospray ionization
Et	ethyl
EtMgBr	ethyl magnesium bromide
Et_2O	diethyl ether
Et_3N	triethylamine
EWG	Electron withdrawing group
FTIR	Fourier transformed infrared
GC	gas chromatography
*i*Bu	isobutyl
Im	imidazole
*i*Pr	isopropyl
LDA	lithium diisopropylamine
LiHMDS	lithium hexamethyldisilazane
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeMgCl	methyl magnesium chloride
MeOH	methanol
M3MP	methyl 3-mercaptopropanoate
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
*n*Bu	normal butyl

NMR	nuclear magnetic resonance
Ph	phenyl
PhMe	toluene
p-tolyl	para tolyl functional group
PTSA	p-toluenesulfonic acid
r.t.	room temperature
SRG	sulfenate releasing group
TBAF	tetrabutylammonium fluoride
*t*Bu	tert-butyl
*t*BuMgCl	tert-butyl magnesium chloride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	N,N,N′,N′-tetramethylethylenediamine
TMS	trimethylsilane

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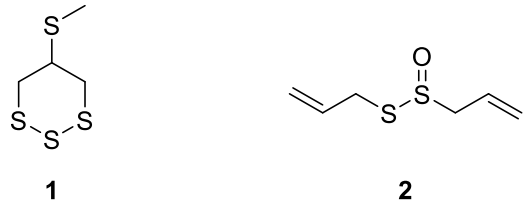
Part 1: Towards the Synthesis of Polysulfurous Molecules Found in Shiitake Mushrooms (*Lentinula Edodes*)

Chapter 1: Introduction

1.0 Introduction

The presence of sulfur-rich compounds in nature is very prevalent.[1–4] These compounds range from sulfur containing rings such as 5-methylthio-l,2,3-trithiane (**1**) which comes from the green alga *Chara globakiri* to thiosulfinates, such as allicin (**2**), which can be isolated from garlic bulbs.[3] These naturally-occurring sulfur-containing compounds are desired for their aromas as they are often similar to the smells of various foods such as garlic or mushrooms (***Figure 1***).[1] Many of these compounds have been isolated from the plant or fungi species previously, however, this does not produce enough of the desired compounds to meet demands and the process often involves destroying the plant from which the compound is being isolated.[5]

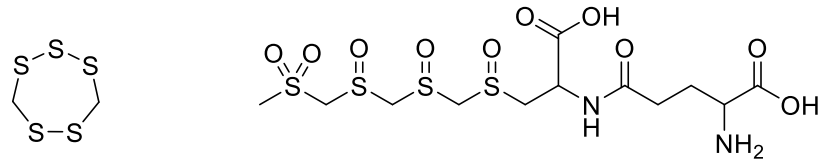


1 **2**

Figure 1: Sulfur containing natural products 5-methylthio-1,2,3-trithiane and allicin

One sulfur rich natural product that is difficult to isolate in appreciable amounts is a 7-membered sulfur-containing ring known as lenthionine (**3**) (1,2,3,5,6-pentathiepane), one of the principal aroma-producing compounds found in a shiitake mushroom (*Lentinula edodes*) (***Figure 2***).[1] In nature, this compound is produced via an enzymatic process that converts lentinic acid (**4**) to lenthionine. Lentinic acid contains a sulfur-carbon backbone which itself includes a terminal sulfone and three sulfoxides and the attempted synthesis of this backbone will be the basis of the work of this chapter. In the following sections, the process by which lentinic acid is converted to lenthionine will be discussed and chemistry that is potentially useful for synthesizing lentinic acid, such as oxidation of sulfur, sulfenate chemistry and sulfinate/sulfinamide chemistry will be introduced. The stereochemistry of the lentinic acid will also be investigated as the natural

configuration of the sulfoxides in lentinic acid has never been determined and it may play a factor in its ability to be converted to lenthionine via the enzymatic process.



3 **4**

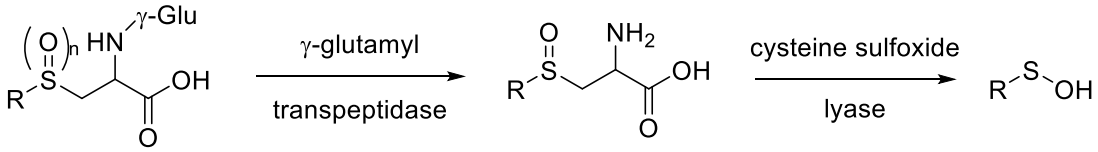
Figure 2: Sulfur rich aroma producing compounds found within the shiitake mushroom

1.1 Plants of the Genus *Allium* and Mushrooms of the Family *Tricholomataceae*

Plants of the genus *Allium*, such as garlic, onions, chives, and edible mushrooms of the family *Tricholomataceae* (shiitake mushrooms) or *Marasmius* all produce a strong aroma and flavour that likely serve to protect the species from predators when threatened.[6,7] However, it is often found that the aroma and flavour produced by these species provides them with the culinary value they possess today.[8,9] While all of these species have different compounds that are responsible for their pungent aroma, the process by which the aroma is produced and the starting compounds are very similar.[10–13] All of the aroma-producing compounds which are released from these species are derived from a group of γ-L-glutamyl-cysteine sulfoxide precursors (**5**).[10–13] These compounds subsequently undergo a two-step enzymatic process of which the first step involves the removal of the γ-L-glutamyl moiety either before or after a sulfur oxidation has occurred.[1] The family of enzymes which catalyse this step are known as γ-glutamyl transpeptidases.[1] This process produces L-cysteine sulfoxides (**6**) which are then acted upon by cysteine sulfoxide lyases (known as alliinases for plants of the genus *Allium*) which produces the corresponding sulfenic acids (**7**).[14,15] These sulfenic acids are highly reactive and it is from these compounds that the major aroma-producing compounds are formed.[1] The mechanism for the

formation of these compounds is largely unknown, although it is believed that the first step for most of these species is the sulfenic acid undergoing self-condensation to form a thiosulfinate species such as allicin (**2**).

A few examples of species which are known to undergo this process are *A. tuberosum* (Chinese chive), *A. sativum* (garlic), *A. cepa* (onion), *M. alliaceus* (garlic parachute mushroom), *and L. edodes* (shiitake mushroom).[1] A general visual example of the enzymatic process is shown in ***Scheme 1***. Some processes begin with sulfides as seen in ***Scheme 1*** but some of the compounds, such as lentinic acid, begin as sulfoxides before the removal of the γ-Glu group.[1]



4,5a-d **6** **7**

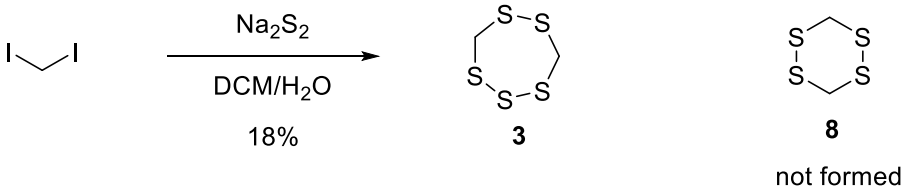
R: 4. $CH_3SO_2CH_2S(O)CH_2S(O)$-, Shiitake Mushroom; **5a)** CH_3-, Chinese Chive; **b)** CH_2=$CHCH_2$-, Garlic; **c)** CH_3CH=CH-, Onion; **d)** $CH_3S(O)CH_2$-, Garlic Parachute.
n = 0 or 1

Scheme 1: Enzymatic mechanism for the generation of sulfenic acids from compounds **4** and **5**

1.2 Lentinic acid and Lenthionine

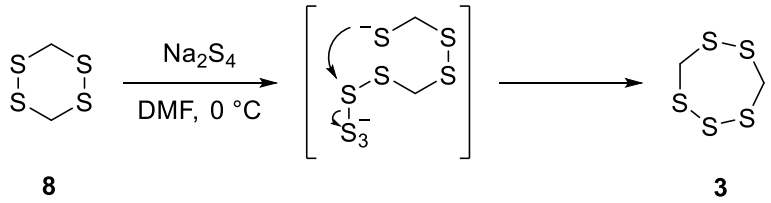
Previously, lenthionine has been synthesized via two methods. The first method was performed by Bannister and Rees and involves the reaction of diiodomethane with sodium disulfide in a dichloromethane/water mixture as seen in ***Scheme 2***.[16] This reaction resulted in a very low yield of 18% for the synthesis of lenthionine, yet the protocol is still superior to extracting the compound from shiitake mushrooms. [16] In this research, Bannister and Rees were attempting this reaction to synthesize 1,2,4,5-tetrathiane (**8**) in order to use these rings as precursors to 1,3,5,2,4-trithiadiazines but were unable to synthesize the tetrathiane ring via this method.[16] They

postulated that the 7 membered lenthionine is more thermodynamically stable than the 1,2,4,5-tetrathiane ring which speaks to the stability of lenthionine.[16]



Scheme 2: Synthesis of lenthionine performed by Bannister and Rees[16]

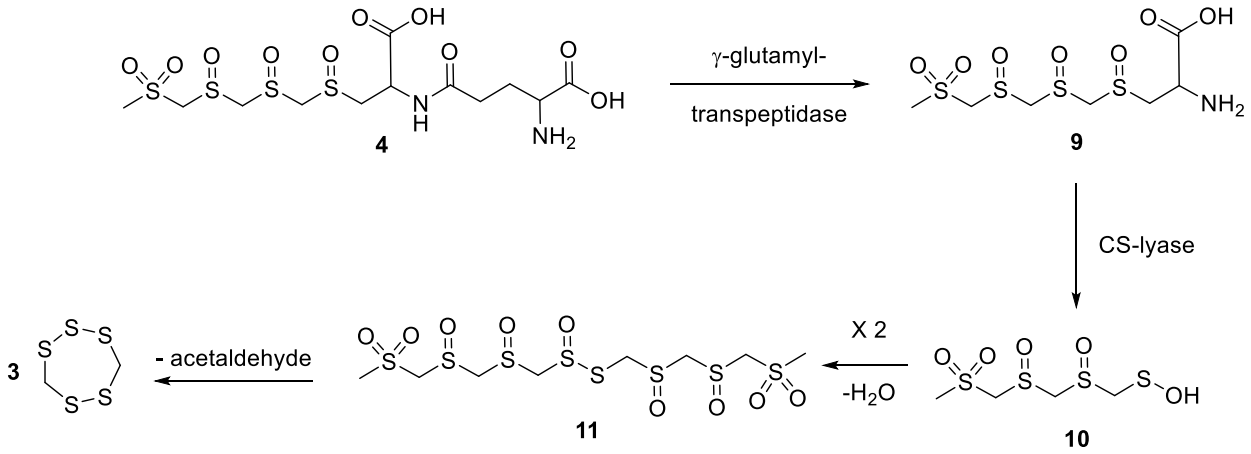
The other method by which lenthionine has been synthesized was performed by Takikawa and coworkers,[17] who achieved a 30% yield of lenthionine in their work. This synthesis involved first making the 1,2,4,5-tetrathiane (**8**) that Bannister and Rees were unable to produce by reacting 1,3,5-dithiazines with N-bromosuccinimide (NBS) in dichloromethane at -78 °C. [17] They went on to react **8** with 10 equivalents of sodium tetrasulfide in dimethylformamide (DMF) at 0 °C to yield **3**.[17] This reaction can be seen in ***Scheme 3*** along with a possible explanation of the mechanism of formation of lenthionine.



Scheme 3: Synthesis of lenthionine as performed by Takikawa and coworkers

Unlike lenthionine, lentinic acid (**4**) has not previously been synthesized. This compound is also very difficult to isolate as any perturbation of the mushroom causes the compound to rapidly be converted to lenthionine according to the enzymatic process outlined in ***Scheme 4***. This enzymatic process for lentinic acid is the same as described for the other similar plants and mushrooms until the thiosulfinate form (**11**) of the molecule. After the thiosulfinate is generated, however, the mechanism for formation of lenthionine is unknown.[15] What is known about the

formation of lenthionine from thiosulfinate **11** is that there is no enzyme involved in catalysing the conversion and that acetaldehyde is released.[15] The full enzymatic and non-enzymatic process to convert lentinic acid to lenthionine is presented in ***Scheme 4***.



Scheme 4: Natural enzymatic conversion of lentinic acid to lenthionine

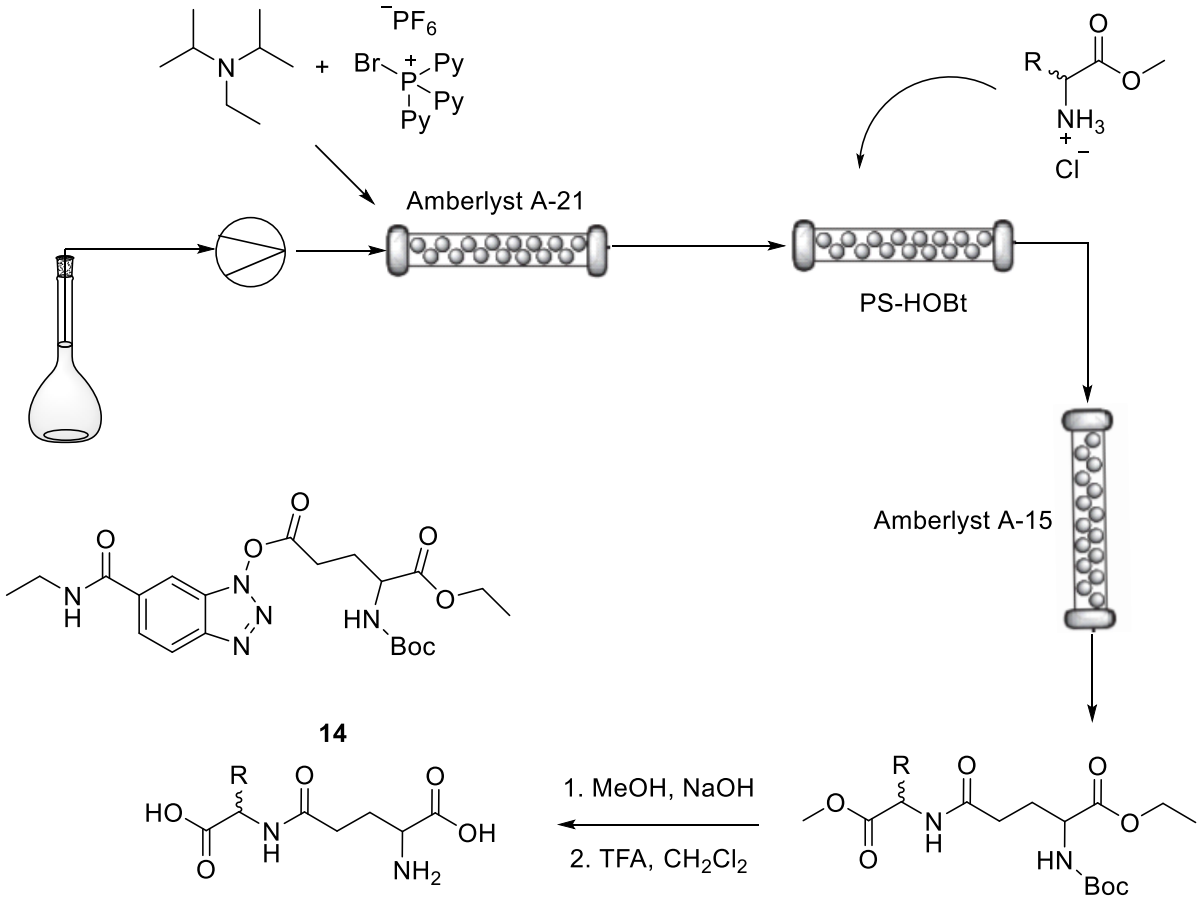
Scheme 4 illustrates the potential targets of this work as molecules **4**, **9**, and **10** in this diagram could possibly be synthesized and the remainder of the process could then be performed to obtain lenthionine.

1.3 Methods for Synthesizing Lentinic Acid

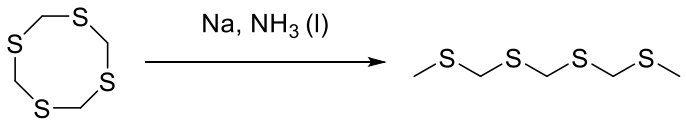
The molecule of lentinic acid contains two substructure sections with the first containing a carbon-sulfur backbone consisting of three sulfoxides and one terminal sulfone. The other section contains a dipeptide. The amino acid containing portion of the molecule has been synthesized recently by Tamborini and coworkers[18] and in this work, the researchers illustrated how it can be functionalized at a position useful for synthesis of lentinic acid. This work utilized a highly efficient flow process which involved the sequential addition of compounds that resulted in the formation of **14.**[18] Three columns were utilized as part of this flow process with Amberlyst A-21, PS-HOBT, and Amberlyst A-15 being utilized as the solid phases in that order.[18] The first step

was to combine a protected L-glutamine (**13**) with diisopropylethylamine (DIPEA) and bromo-tris-pyrrolidino phosphonium hexafluorophosphate (PyBroP, a phosphonium coupling agent) in DMF and this solution was then fluxed into the reactor.[18] Then a 0.2 M solution of an amino acid methyl ester hydrochloride (**12**) is fluxed into the reactor which couples the two amino acids together.[18] After deprotection of the coupled molecule, **14** was obtained in an 80% yield.[18] This process is illustrated in ***Scheme 5***. Other examples of the synthesis of **14** have been described in literature making this substructure of lentinic acid easier than the sulfur carbon backbone of lentinic acid to synthesize.[19]

Synthesis of carbon-sulfur backbone is therefore the more difficult substructure of **4** to synthesize and its synthesis has not been reported in the literature. Similar analogs have been prepared before although they all present challenges for the subsequent synthesis of lentinic acid such as sulfur being in the incorrect oxidation state or the molecule not possessing the functionalization required to combine with substructure **14.**[20,21] One such example of this involves work by Weissflog[20] which showed that it was possible to synthesize the carbon-sulfur backbone without any oxygens (**16**) through a ring opening reaction of 1,3,5,7-tetrathiacane (**15**) with metallic sodium in liquid ammonia. This method provides the correct backbone structure but the subsequent precision oxidation of the sulfurs to end up with a terminal sulfone and three sulfoxides of a single conformation would be nearly impossible. The research performed by Weissflog is illustrated in ***Scheme 6***.



Scheme 5: Synthesis of **14** utilizing a flow reactor that resulted in an 80% yield[19]



Scheme 6: Synthesis of **16** via a ring opening reaction of a 1,3,5,7-tetrathiacane

To synthesize lentinic acid or a similarly behaving analogue, the stereochemistry of the sulfoxide moieties must be considered if only one of the eight diastereomers of lentinic acid can form lenthionine via the processes described in *Section 1*. The methods that have previously been utilized for the synthesis of enantiopure sulfoxides include asymmetric oxidation of sulfides to sulfoxides, sulfinate chemistry and sulfenate chemistry.[22]

1.4 Sulfur Chemistry

Sulfur is an omnipresent element and has great value in nature as it is most frequently found within amino acids, sugars, vitamins, and various other building blocks of life. This shines a light on the importance of synthesizing sulfur-containing natural products as they have a variety of uses both inside and out of the human body. Sulfur, while being in the same group of the periodic table to oxygen, displays a variety of properties that are very different from oxygen. Additionally, sulfur is present in more oxidation states than oxygen (***Figure 3***). Due to lower electronegativity and more available lone pairs, a thiol is more nucleophilic than an alcohol. Thiols are also more acidic than alcohols with phenol having a pK_a of approximately 10 whereas the pK_a of thiophenol is approximately 7. In addition, peroxides are thought to be generally unstable and highly reactive whereas disulfides are very stable.[23]

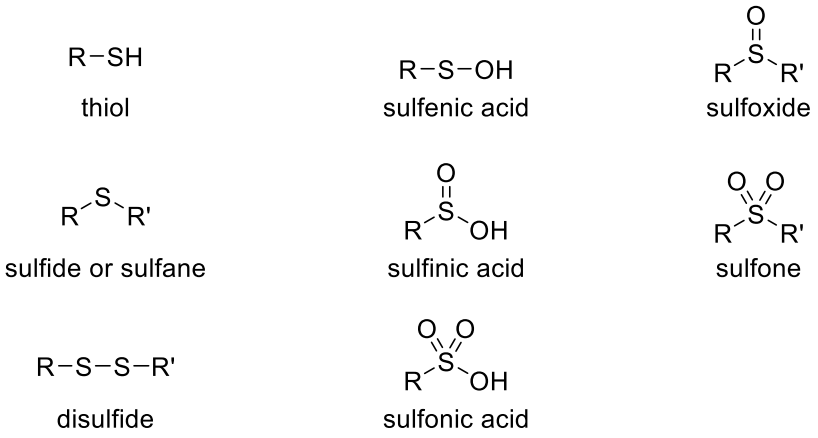
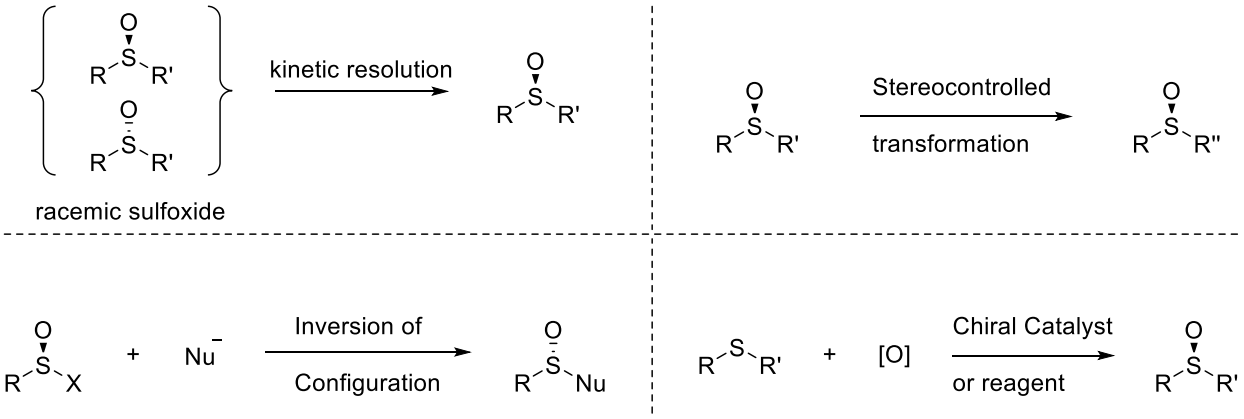


Figure 3: Various oxidation states and common sulfur containing functional groups

An important aspect of this research is the synthesis of chiral sulfoxides and there have been various routes since the initial preparation of chiral sulfoxides via kinetic resolution performed by Harrison and coworkers in 1926.[24] There have now been various methods developed which have proven effective at synthesizing chiral sulfoxides.[22] The first of these involved the transformation of diastereomerically pure sulfinate esters or sulfinamides to sulfoxides through

substitution.[22] Another method involves starting with a chiral sulfoxide and performing reactions that do not result in any loss in the stereochemistry of the sulfoxide. Finally, asymmetric oxidation reactions of sulfides that have the potential to be chiral via the addition of chiral reagents or oxidants has garnered recent interest. These four methods are outlined in ***Scheme 7***.

Of these four methods, the asymmetric oxidation of sulfides, kinetic or chemical resolution, and the inversion of configuration methods could prove useful in the synthesis of the sulfur-carbon backbone substructure of lentinic acid. Another method which has surfaced recently is sulfenate chemistry which could also prove useful in the synthesis of lentinic acid.

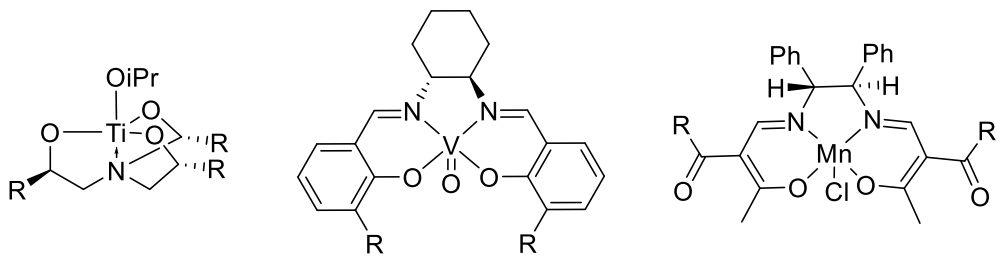


Scheme 7: The four known methods for the synthesis of chiral sulfoxides

1.4.1 Oxidation of Sulfides

The most common and direct route for the preparation of chiral sulfoxides has been through direct asymmetric oxidation.[22] Traditionally, the oxidation of sulfides was carried out utilizing various reagents, such as m-chloroperbenzoic acid, sodium metaperiodate, and hydrogen peroxide, and this would lead to an overall 50:50 enantiomeric ratio of the R and S isomers of the sulfoxide. However, recently there has been a variety of chiral catalysts or ligands developed that, when used in tandem with traditional oxidation reagents, can provide a direct asymmetric oxidation of sulfides

to sulfoxides.[22] Since this revelation in the 1980s,[25,26] many enzymatic,[27–32] metal catalysed,[33–40] and organocatalytic[41,42] methods have been developed that provide an enantiomeric excess of close to 100% for a particular sulfoxide configuration. The most commonly utilized complexes are derived from titanium, vanadium, and manganese, but metals such as molybdenum, iron, aluminum, copper, niobium, tungsten and osmium have also been utilized (some of these appear in **Figure 4**).[33,37,43–47] Oxidation, however, suffers from two potential issues. The first of these is that oxidation using the above methods is highly substrate dependent and no general asymmetric oxidation method has been created to date.[22] The second problem with oxidation is that there is potential for overoxidation to a sulfone which may increase the enantiomeric excess value for the reaction but decrease the yield.[22] The goal of this project is not only to synthesize lentinic acid or an equivalent to lentinic acid, but also to learn about the molecule. Sulfoxidation will therefore be deemed an ill fit to serve as a method for lentinic acid synthesis, as designing a catalyst to only work for this compound will be difficult due to the multiple sulfurs and not serve to advance the knowledge of the chemical society as much as other conceivable methods.



17
R = Me, t-Bu, Ph

18
R = OMe, OEt, t-Bu

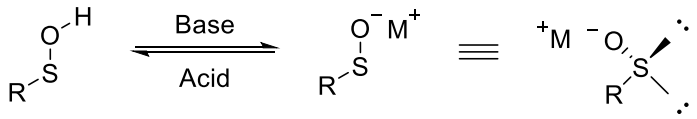
19
R = Mesityl

Figure 4: Some transition metal catalysts utilized for asymmetric sulfoxidation

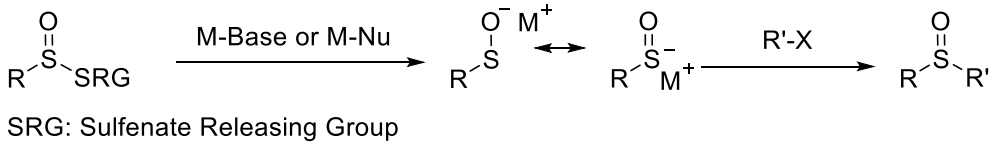
1.4.2 Sulfenate Chemistry

The chemical behaviour of sulfenate anions and sulfenic acids has garnered great interest recently in organosulfur and biochemical research. Sulfenic acids can be both electrophiles and nucleophiles as the oxidation state of sulfur is close to 0.[23] Sulfenate anions are the conjugate bases of sulfenic acids and have the potential to create chiral compounds (***Scheme 8***).[48] Both sulfenate anions and sulfenic acids are unstable. A sulfenate anion will be converted to the corresponding sulfinate when exposed to molecular oxygen and sulfenic acids are converted to the corresponding thiosulfinate ester.[23,49] Due to this instability, there exists only a few examples of the isolation of these compounds[50] and thus they need to be both generated and functionalized *in situ* (***Scheme 9***). The usefulness of this method compared to others is that the sulfenate precursor can be racemic, but it can also yield a chiral sulfoxide.

Due to the ambident nature of the sulfenate anion as a nucleophile,[51] the anion can be alkylated at both the sulfur and oxygen positions. According to a review done by O'Donnell and Schwan,[50] S-alkylation occurs via an S_N2 type mechanism when the electrophile is considered soft and O-alkylation occurs when the electrophile is considered hard. The next few sections will discuss methods for generation of sulfenate anions and a comprehensive review of the alkylation reactions which occur afterwards.



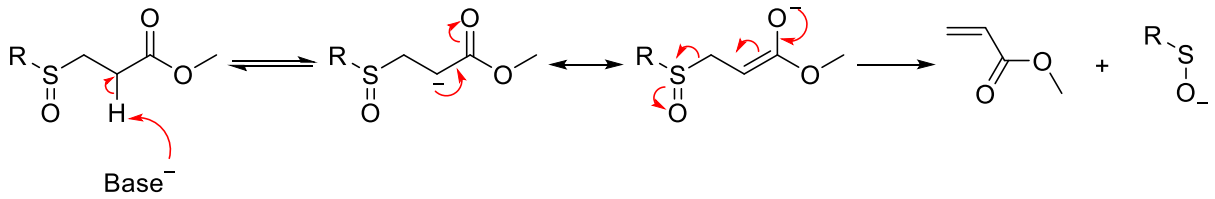
Scheme 8: Prochirality of sulfenate anions



Scheme 9: Generation and alkylation of sulfenate anions

1.4.2.1 Deprotonation of β-Sulfinylesters

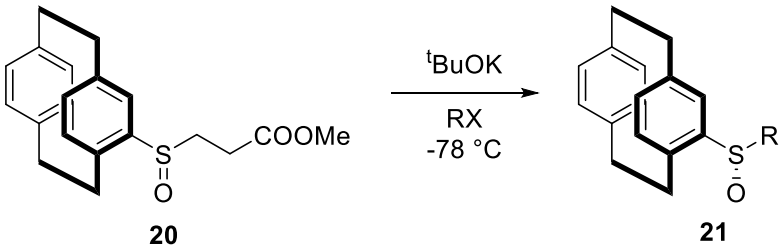
The release of a sulfenate anion through a base initiated retro-Michael fragmentation of β-sulfinylesters was first performed by Perrio and coworkers.[52] The mechanism for this generation involves first a deprotonation α to the carbonyl group which fragments to generate an acrylate molecule and a sulfenate anion (***Scheme 10***).[52] Perrio and coworkers[52] reported that the sulfenate generated was stable up to temperatures of 70 °C. The researchers reported yields of up to 95% when utilizing t-BuOK as the base and THF as the solvent.[52] In the same paper, the researchers attempted to utilize a base derived from a 1:1 mixture of (-)-sparteine and n-BuLi to induce asymmetry in the alkylation of the sulfenate with an enantioselective external ligand.[52] This unfortunately only led to ee's up to 23% but showed that the chirality of the base did not have a great effect on the asymmetry of the outcome.[52]



Scheme 10: Generation of Sulfenate anions from β-sulfinylesters

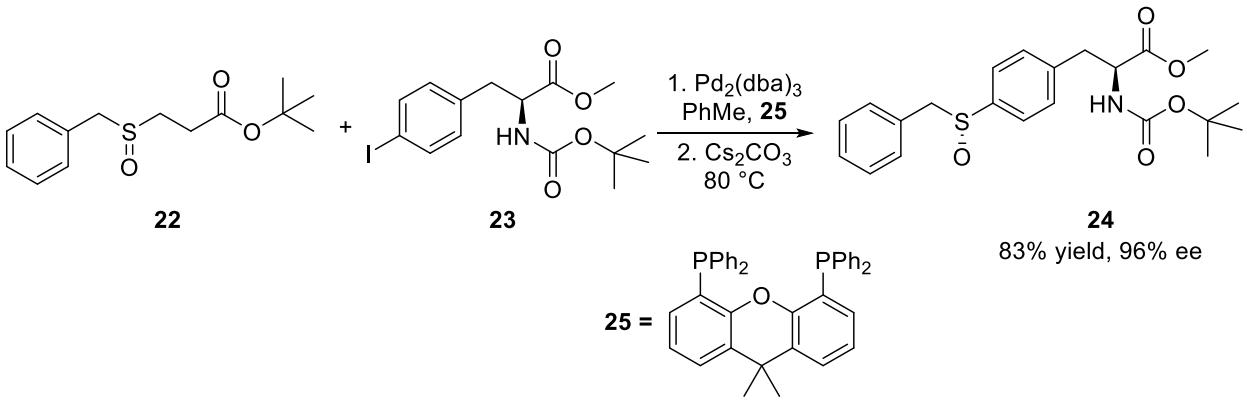
In 2008, Perrio and coworkers[53] demonstrated that sulfenate alkylation could produce sulfoxides with a 100% d.e. and illustrated this using paracyclophane sulfenates. The axial chirality of the paracyclophane ring had a great effect on the chiral induction ability of the sulfenate anion with the alkylation reaction leading to the formation of one diastereomer in great to excellent yields

(82 to 90% yields and 100% de) (***Scheme 11***).[53] The researchers explained the formation of a single diastereomer by stating that the sulfenate S-O bond had a preference for lying within the plane of the aromatic ring oriented towards the ortho arene hydrogen.[53]



Scheme 11: Sulfenate alkylation with axially chiral substituent on the sulfenate precursor sulfoxide

Söderman and Schwan[54] probed various methods for generating and quenching alkyl sulfenates with enantiopure electrophiles. They found that this method was best due to the thermal stability of the protocol.[52] The use of this method and LiHMDS led to the formation of alkyl sulfoxides with diastereomeric ratios up to 91:9.[54]



Scheme 12: Catalytic asymmetric arylation of sulfenates

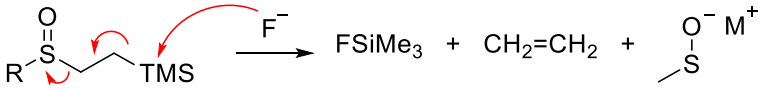
In 2018, Wang and coworkers[55] investigated palladium mediated catalytic asymmetric sulfenate arylation with the use of PC-Phos ligands. Before this work, the highest ee achieved for benzyl sulfenate alkylation was 47% and there remained no general process for the arylation of

alkyl and aryl sulfenate anions.[55] In this reaction, the palladium/PC-Phos complex is oxidatively added to the aryl iodide and then the sulfenate anion is subsequently generated, leading to the arylation of the sulfenate.[55] This led to aryl sulfoxides being produced in yields of 54 to 98% with ee's ranging from 88 to 98%. One example reaction is illustrated in **Scheme 12**.[55]

1.4.2.2 Desilylation

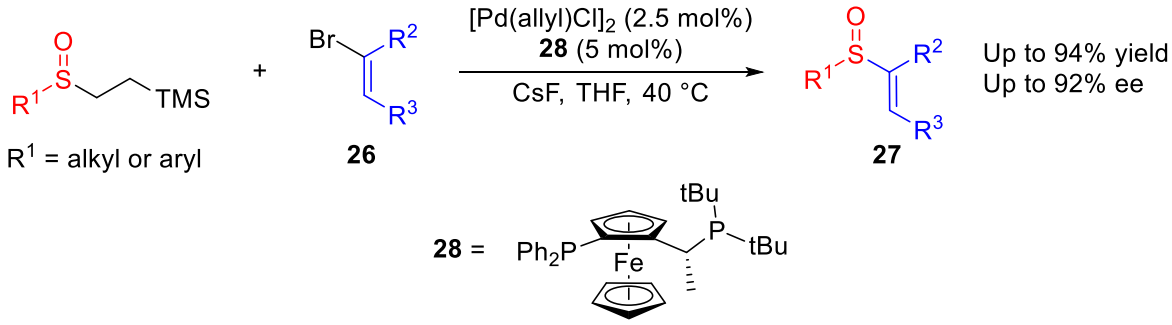
Fluoride induced fragmentation of 2(trimethylsilyl)ethyl sulfoxides was investigated by various groups for its ability to generate a sulfenate anion. Oida and coworkers[56] reported the generation of a sulfenate anion from the corresponding 2(trimethylsilyl)ethyl phenylsulfenate ester using TBAF and quenched with alkyl halides or acetylenic compounds to yield the corresponding sulfoxide in most cases.[56] This mechanism is believed to proceed via a fluoride attack at the TMS group causing the formation of ethene and a sulfenate anion. Side products of these reactions were believed to originate from the fluorine anion acting as a base and deprotonating α to the sulfenate ester oxygen.[50] In a follow up study, Oida and coworkers[50] utilized CaF_2 and KF instead of TBAF which increased the yields of the reaction and decreased production of the side products. An explanation for this trend involves the fluoride anion in CaF_2 and KF being less basic than the fluoride in TBAF.[50]

Subsequently, Perrio and coworkers[57] investigated whether the tautomeric sulfoxide to Oida's sulfenate ester would also generate a sulfenate anion (***Scheme 13***). In these investigations, generating p-toluenesulfenate anion from the corresponding sulfoxide was the goal.[57] Varying amounts of TBAF were introduced until the researchers found the optimal conditions to be a 1:3 ratio of sulfoxide to TBAF.[57] With this method, Perrio and coworkers were able to synthesize benzyl and p-tolyl sulfoxides in yields between 49% and 87% for 3,3-dimethylbut-1-yl benzyl and p-tolyl benzyl sulfoxide respectively.[57]



Scheme 13: Generation of sulfenate anions from 2(trimethylsilyl)ethyl sulfoxides

In 2019, Walsh and coworkers[58] reported the catalytic asymmetric synthesis of various vinyl and aryl sulfoxides utilizing the desilylation method of generating sulfenate anions. This work utilized a palladium catalyst made of $[Pd(allyl)Cl]_2$, and a phosphorus containing ferrocene derived ligand **33** present in 2.5 and 5 mol% respectively to activate the aryl and vinyl halides **34**.[58] The fluoride source for this reaction was CsF present in three equivalents. With these conditions, the researchers were able to synthesize aryl and vinyl sulfoxides **35** with good to great enantiopurity (ee ranging from 63 to 92%) and moderate to great yields according to ***Scheme 14***.[58] It was found that the addition of 15-crown-5 ether increased the yield of the reaction when the substrates were temperature sensitive.[58]

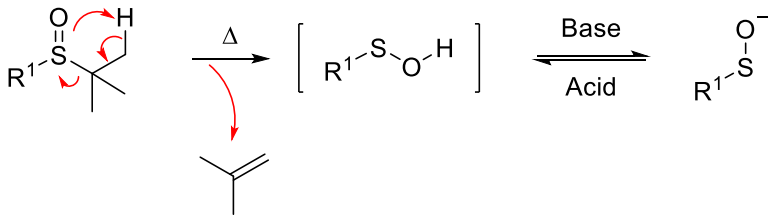


Scheme 14: Generation of aryl and vinyl sulfoxides via sulfenates generated by disilylation

1.4.2.3 Base Promoted Thermal Elimination of *tert*-Butyl Sulfoxides

Since 2015, two different publications have shown that it is possible to release a sulfenate anion through base promoted thermal decomposition of *tert*-butyl sulfoxides.[59,60] Walsh and coworkers[59] first reported the use of *tert*-butyl sulfoxides as precursors to sulfenate anions when

they utilized them as pre-catalysts in an attempt to synthesize trans-stilbenes. The researchers found that the optimal conditions for producing the sulfenate anion involved heating the *tert*-butyl sulfoxides to 110 °C in the presence of a base (^{t}BuOK).[59] Perrio and coworkers[60] also investigated *tert*-butyl sulfoxides for their ability to produce sulfenate anions. In their work, Perrio and coworkers[60] attempted to utilize *tert*-butyl sulfoxides as precursors to sulfenate anions that undergo cross coupling with aryl halides.[60] Their attempts were successful as they were able to synthesize aryl sulfoxides with yields up to 99% when the temperature was set at 100 °C and K_3PO_4 was utilized as the base.[60] The mechanism for this method involves the thermal decomposition of sulfoxides with β-hydrogens in which the sulfoxide oxygen abstracts a β-hydrogen from the *tert*-butyl group leading to the production of a sulfenic acid and isobutene.[60] This sulfenic acid can then be deprotonated to form the corresponding sulfenate anion (***Scheme 15***).[60]

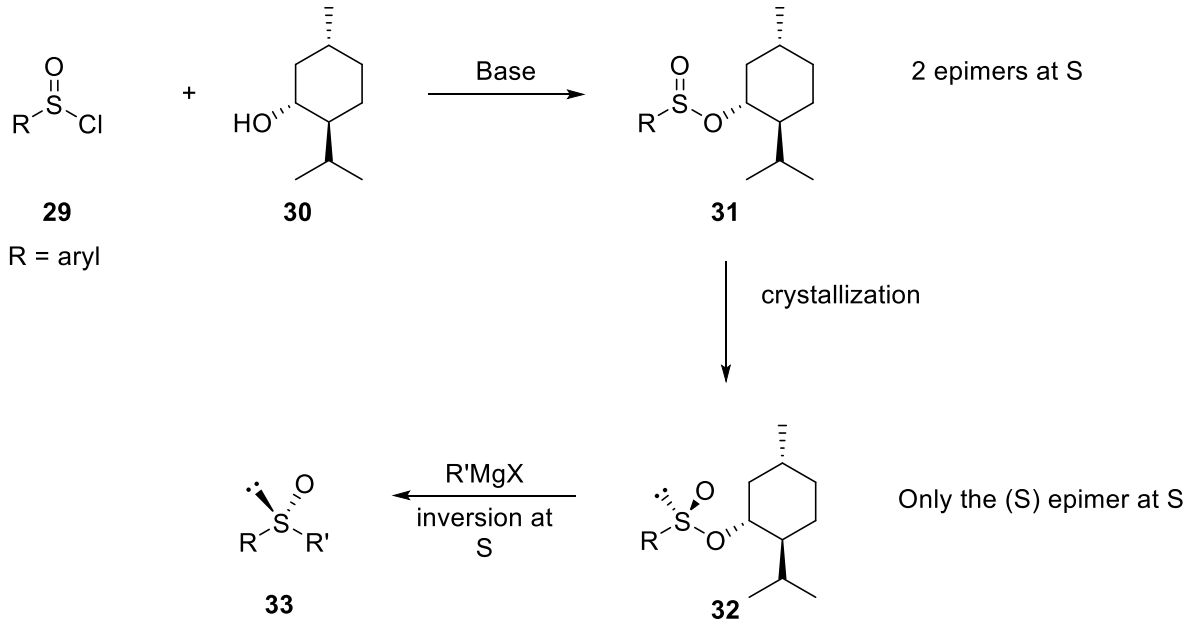


Scheme 15: Generation of sulfenate anions from tert-butyl sulfoxides

1.4.3 Sulfinate Chemistry

Sulfinate esters (or sulfinates), of the general structure of $R^1S(O)OR^2$, have been shown in literature to be an excellent precursor to the formation of chiral sulfoxides. The synthesis of chiral sulfoxides **33** from chiral sulfinates **32** was pioneered by Andersen in 1962 and involved a Grignard reaction on one diastereomer of p-tolylsulfinate prepared from (-)-menthol (***Scheme 16***).[61] For a chiral sulfoxide to be produced, there must be only one configuration of the proceeding sulfinate ester. If this is the case, the nucleophilic attack leads to a complete inversion of the

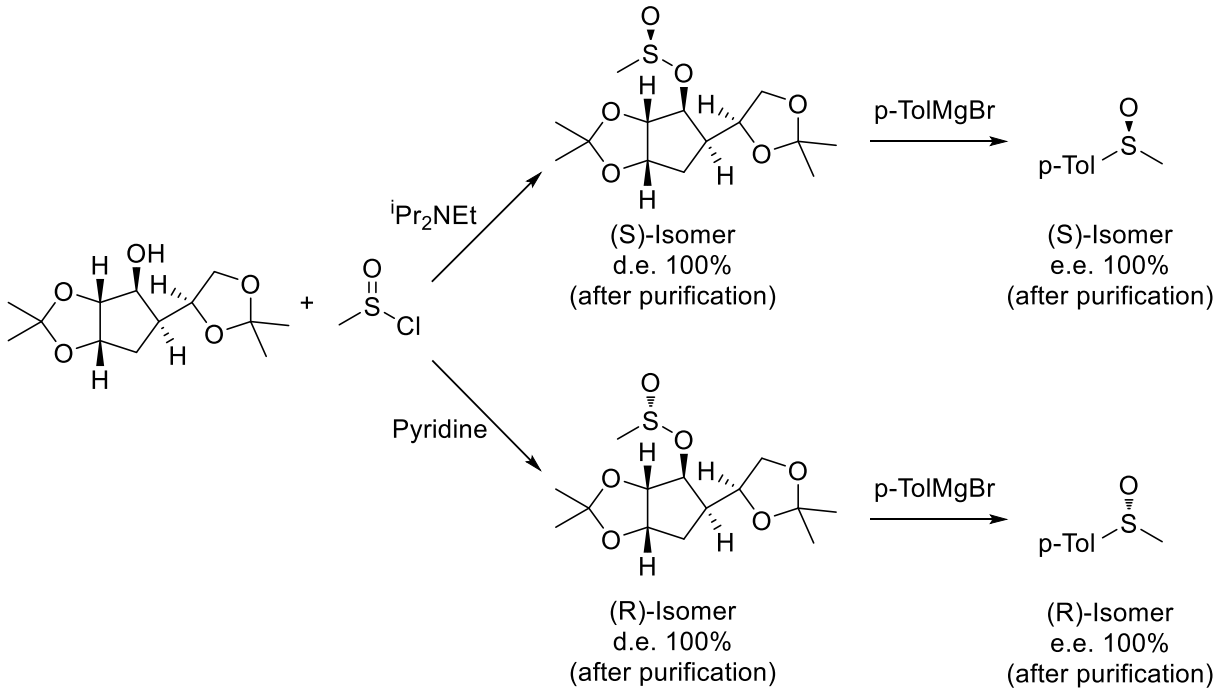
configuration at the sulfur and the synthesis of an enantiopure sulfoxide if the substituents are different.[62] This *Andersen method,* has become one of the most useful methods for the preparation of chiral sulfoxides, but the requirement of obtaining only one diastereomer of the sulfinate ester **31** has presented some challenges. Generally, sulfinates are prepared through a reaction between sulfinyl chlorides **29** and an alcohol (**30**) which produces both diastereomers of the sulfinate ester. For arylsulfinates prepared by the *Andersen method*, the S configuration is often crystalline whereas the R configuration is oily. The two can be separated by crystallization to afford a 100% ee of the S epimer.[61] It was also found that the addition of a catalytic amount of HCl to the recrystallization led to higher yields of the S isomer due to *in situ* epimerization.[63]



Scheme 16: Synthesis of chiral sulfoxides from sulfinates using the Andersen method

The Andersen method, however, is not suitable for menthyl alkanesulfinates (**31**, R is alkyl) as both epimers are generally oily and cannot be separated by crystallization.[22] To circumvent this issue, many new methods have been developed for the synthesis of chiral alkanesulfinate esters to move past this shortcoming of the Andersen method. Andersen and coworkers[64] developed a

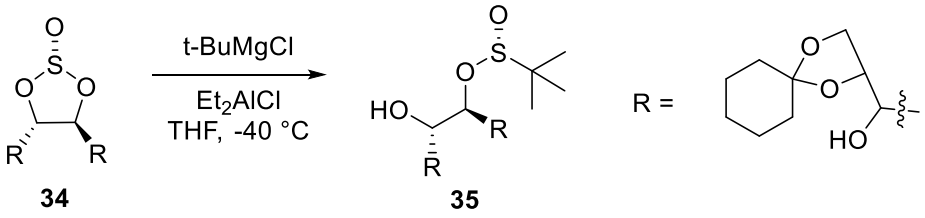
method in 1984 that involved the use of cholesterol instead of menthol and was able to synthesize cholesteryl methanesulfinate epimers that could be separated via crystallization and many chiral sulfoxides have been synthesized from the cholesteryl alkanesulfinates made by this method. L-N-Methylephedrine has also been utilized as an alcohol which gave diastereomerically pure sulfinates in poor yields.[22] Llera and coworkers[65] developed a technique which utilized diacetone-D-glucose (DAG) as the alcohol. This method was utilized to stereoselectively synthesize both (R)- and (S)-DAG methanesulfinates in 90% yields from the corresponding methylsulfinyl chloride. The researchers reported that when triethylamine or DIPEA is utilized, the (S)-configuration is obtained whereas when pyridine is utilized, the (R)-configuration is obtained (***Scheme 17***).[65]



Scheme 17: Synthesis of chiral sulfoxides using DAG technology

Chiral sulfinate esters have also been synthesized from dissymmetrical sulfites and subsequent attack of these esters has been utilized in the synthesis of chiral sulfoxides previously.

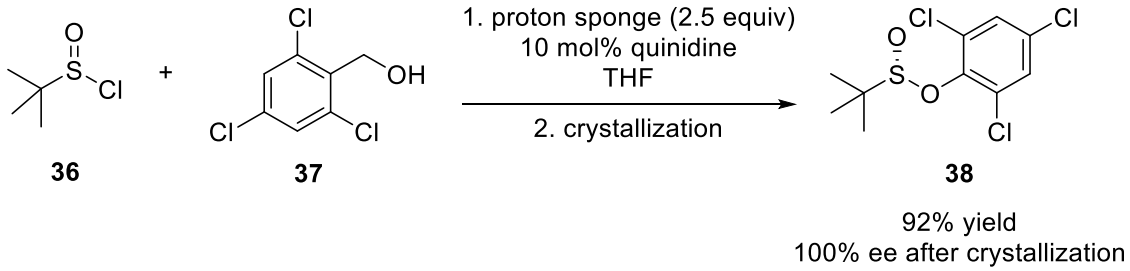
Vallée and coworkers[66] investigated the ability of cyclic sulfites (**34**) prepared from mannitol to generate one diastereomer of a sulfinate ester after subsequent attack from an organometallic compound. They found that they could prepare *tert*-butanesulfinates (**35**) with excellent stereoselectivity (up to 96% diastereomeric excess) through the attack of ^{t}BuMgCl onto a chiral sulfite when in the presence of diethyl aluminum chloride (***Scheme 18***).[66] Cyclic sulfates prepared from mannitol biscyclohexylidene gave better diastereoselectivities than the other mannitols that were investigated.[66]



Scheme 18: Formation of diastereomerically pure sulfinates from C_2-symmetric sulfites

The above examples all describe the synthesis of diastereomerically pure sulfinate esters. The synthesis of enantiomerically pure sulfinate esters has also been investigated and offers two key advantages. The first advantage is that the by-products of the reaction will be achiral in nature and thus do not have the potential to interfere with the optical purity and the second example is that the alcohols utilized can be made to be miscible in water which renders the by-products of subsequent reactions easily removed after a basic wash.[22] The disadvantage of this synthetic category is that the enantiomers are often impossible to separate. The first method attempted for this was performed by Sagramora and coworkers[67] in 1967 and involved the asymmetric oxidation of sulfenate esters. However, this method gave poor ee values (up to 36%). A more general method for the synthesis of enantiomerically pure sulfinate esters is based on the reaction of sulfinyl

chlorides (**36**) with achiral alcohols (**37**) in the presence of a base and catalytic amounts of optically active tertiary amines such as quinidine.[68] This method has been able to deliver alkanesulfinate esters and aryl sulfinate esters with ee's as high as 90% and 99% respectively.[22] Ellman and coworkers[68] utilized this procedure to synthesize 2,4,6-chlorobenzyl *tert*-butanesulfinate (**38**) in a 92% yield with a 90% ee when in the presence of 10 mol% quinidine and proton sponge as the base (***Scheme 19***). This sulfinate was recrystallized to give it a 100% ee and remains one of the few examples of an enantiopure sulfinate being formed.[68]

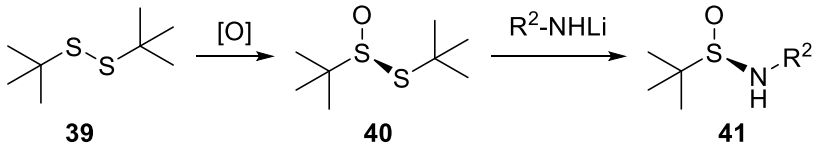


Scheme 19: Use of quinidine and proton sponge to synthesize enantiopure *tert*-butanesulfinates

1.4.4 Sulfinamide Chemistry

Sulfinamides have garnered great interest in recent years due to their widespread applications in the synthesis of various sulfur-containing compounds such as sulfoxides.[69] Enantiopure sulfinamides, such as those developed by Ellman and co-workers,[70] have been utilized as a chiral ammonia equivalent and subsequently Ellman's[70] sulfinamides have been used as chiral auxiliaries in asymmetric synthesis. Traditionally, enantiopure sulfinamides have been synthesized by the method developed by Ellman and co-workers[70] which involves first the catalytic asymmetric oxidation of tert-butyl disulfide (**39**) to tert-butyl tert-butanethiosulfinate (**40**) using vanadium-based catalysts. Thiosulfinate **40** is then converted into various sulfinamides (**41**) through the attack of a lithium amide (***Scheme 20***).[70] However, the issue with thiosulfinates for the synthesis

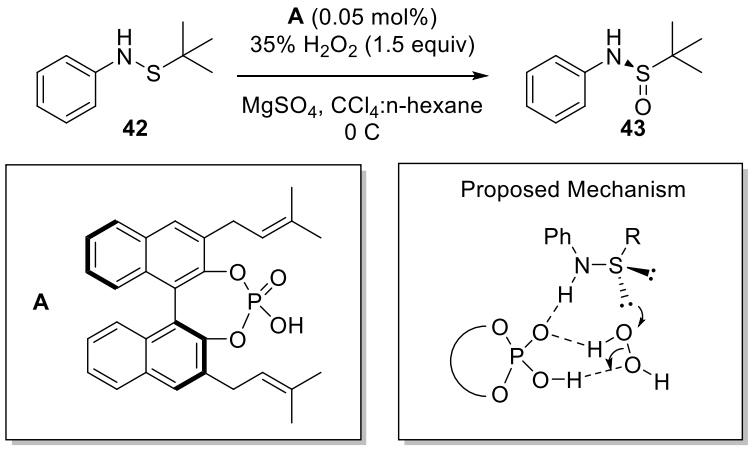
of sulfinamides is the production of a mercaptan by-product which goes against the principles of green chemistry.[69] Given the odorous by-product issue, alternative leaving groups have been explored for this method of synthesizing enantiopure sulfinamides such as DAG,[71] menthol,[61] and quinine[72] which were all able to synthesize enantiopure sulfinamides and from there, enantiopure sulfoxides.



Scheme 20: Synthesis of chiral sulfinamides from disulfides using catalytic asymmetric oxidation

Sulfinamides can also be synthesized through the oxidation of sulfenamides.[69] Sulfenamides, owing to their widespread applications, can be synthesized via various synthetic methods and many of them are commercially available, making this method intriguing for the facile synthesis of sulfinamides. Recently, Ma and coworkers[69] developed a method for the catalytic asymmetric oxidation of aryl tert-butanesulfenamides (**42**) to the corresponding sulfinamides (**43**) with the use of hydrogen peroxide and a chiral phosphoric acid catalyst. When performed in the presence of 0.05 mol% of a BINOL derived phosphoric acid catalyst, sulfenamides can be oxidized to the corresponding sulfinamides in yields up to 96% and an enantiomeric excess of 99% when the reaction is performed in a magnesium sulfate containing 3:1 mixture of CCl_4:n-hexane (***Scheme 21***) .[69] The purpose of the phosphoric acid catalyst is to activate oxidative capabilities of hydrogen peroxide through hydrogen bonding and the catalysts also acts as a chiral auxillary.[77] This reaction cannot be performed with doubly N-substituted sulfenamides as the N-H bond is required to help the catalyst reach the reaction site.[69]

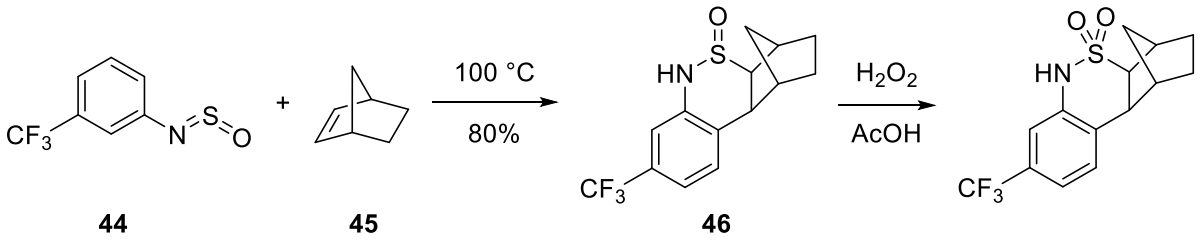
Another common method for the preparation of sulfinamides is achieved using N-sulfinylamines (R-NSO). N-Sulfinylamines were first discovered in 1890 by Michaelis and Herz[73] when they performed a reaction between aniline and thionyl chloride which yielded N-sulfinylaniline. These compounds are structurally related to isocyanates, ketenes and isothiocyanates and can react with organometallic compounds to form sulfinamides.[74] N-Sulfinylamines are traditionally synthesized by mixing together thionyl chloride with an amine in anhydrous benzene and refluxing the mixture for three hours, yielding the resulting N-sulfinyl amine as a bench stable compound.[74]



Scheme 21: Synthesis of sulfinamides through the oxidation of sulfenamides

Recently, N-sulfinylamines have been shown to be useful intermediates in the formation of cyclic sulfonamides, a useful pharmacophore, via a Diels-Alder reaction performed by Veremeichik and coworkers.[75] In their work, they reacted m-trifluoromethylphenyl N-sulfinylamines (**44**) with norbornene (**45**) (1:1.5 ratio) or norbornadiene in the absence of solvent at 100 °C for 8-10 hours achieving yields in excess of 80% (***Scheme 22***).[75] In this reaction, the N-sulfinylamine acts as the diene and the incorporation of the trifluoromethyl group into this pharmacophore is useful for the pharmaceutical industry as the trifluoromethyl group has been

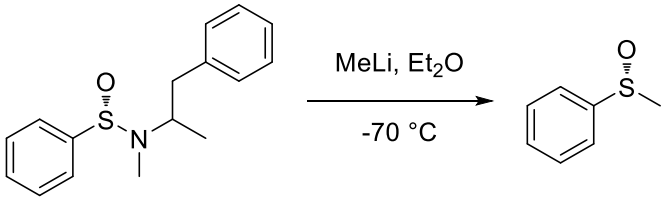
shown to have important properties of lipophilicity.[75] Veremeichik and coworkers[75] then oxidized the resulting cyclic sulfinamide (**46**) to the corresponding cyclic sulfonamide.



44 **45** **46**

Scheme 22: Synthesis of cyclic sulfinamides from a Diels-Alder reaction between norbornene and a N-sulfinylamine

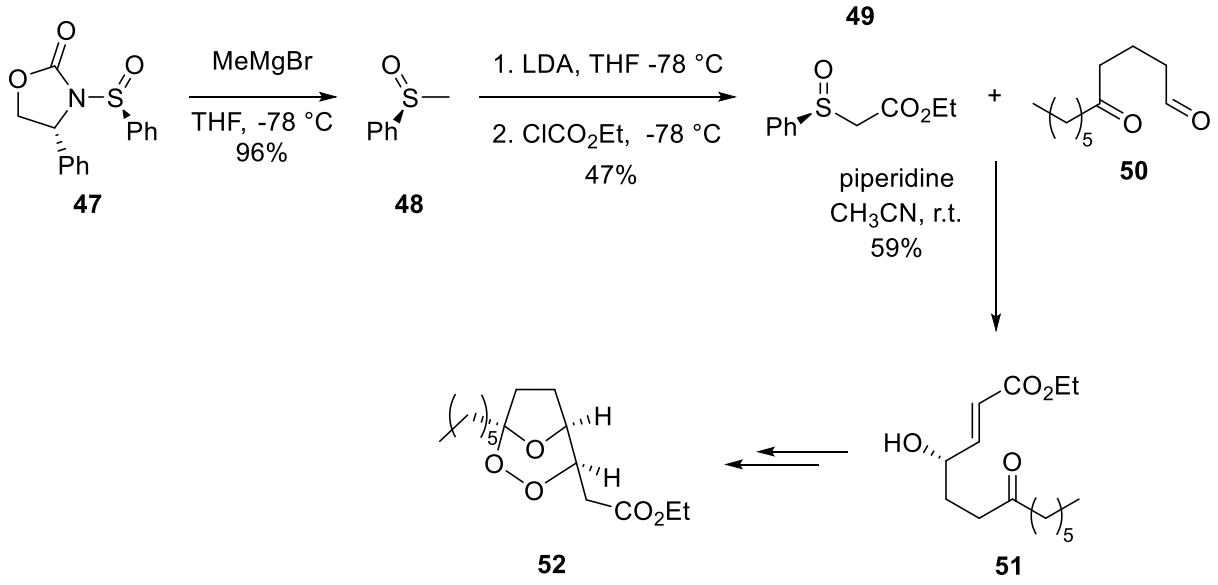
Synthesis of sulfoxides from sulfinamides has been extensively explored and through these investigations it has become clear, barring a few exceptions, that the nitrogen must be doubly substituted or protected in order for a nucleophile to break the S-N bond of a sulfinamide.[69] The first instance of sulfinamides being utilized for the synthesis of sulfoxides was performed by Jacobus and Mislow[76] in 1968 when they synthesized methyl phenyl sulfoxide with an optical purity of 90 to 92% by reacting diastereomerically pure N-methyl-N-(1-methyl-2-phenylethyl)benzenesulfinamide with methyl lithium in diethyl ether at -70 °C (***Scheme 23***).



Scheme 23: First use of sulfinamides for the synthesis of chiral sulfoxides

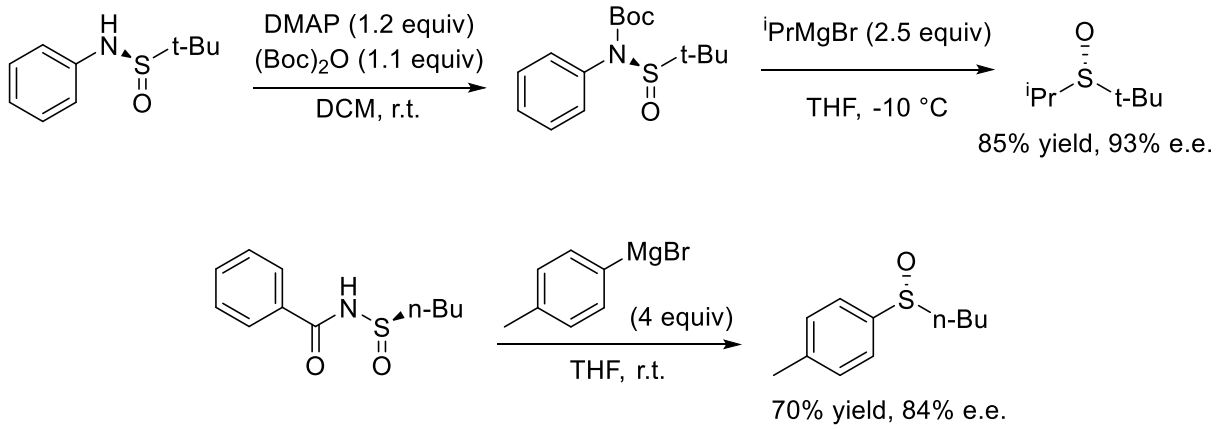
Since then, sulfinamides have been utilized for the synthesis of various sulfoxides. An important development for the synthesis of enantiopure sulfoxides from sulfinamides is the use of an oxazolidinone as the nitrogen portion of the sulfinamide. Research performed by Evans and coworkers[77] has shown that when lithiated oxazolidinone derivatives of either (4R,5S)-

norephedrine or (4S)-phenylalanine are reacted with aryl sulfinyl chlorides, diastereomerically pure sulfinamides can be synthesized after purification by recrystallization. The oxazolidinone derived sulfinamides were then utilized for the synthesis of enantiopure sulfoxides.[77] This technique was utilized further in the synthesis of bridged 1,2,4-trioxanes, the general structure of which have been utilized in the synthesis of pharmaceuticals such as the anti-malarial drug artemisinin.[78] In this work, performed by Zhang and Wu,[78] (R)-4-phenyl-oxazolidin-2-one (**47**) was reacted with methyl magnesium bromide to synthesize the (S)-isomer of methyl phenyl sulfoxide (**48**). Sulfoxide **48** was then treated with n-butyl lithium and ethyl chloroformate to synthesize β-sulfinyl ester **49**.[78] As the chirality of sulfoxide **48** was maintained, β-sulfinyl ester **49** was reacted with aldehyde **50** in the presence of piperidine to yield acrylate ester **51**. Ester **51** was utilized in the synthesis of a sought after bridged 1,2,4-trioxane **52** (***Scheme 24***).[78] The synthesis of **52** could not have been performed without the advancements made in chiral sulfinamide chemistry.



Scheme 24: Synthesis of a bridged 1,2,4-trioxane compound utilizing a chiral sulfinamide

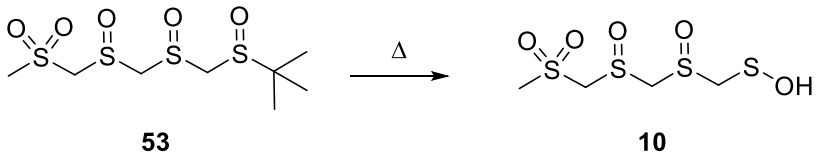
Another important advancement in the synthesis of sulfoxides from sulfinamides came when Ma and coworkers[69] showed that the nitrogen of a sulfinamide can be protected in order to make the sulfur more electrophilic. In their work, Ma and coworkers[69] synthesized various sulfinamides via catalytic asymmetric oxidation of sulfenamides and then they attempted various methods for synthesizing sulfoxides from these mono N-substituted sulfinamides. The researchers found that mono-substituted sulfinamides can be utilized to synthesize sulfoxides by two methods, the first of which involved protecting the nitrogen with a tert-butyloxycarbonyl group (in yields up to 99%) and then attacking with various Grignard reagents (***Scheme 25***).[69] Ma and coworkers[69] also found that when sulfinamides are prepared from benzamide, the use of four equivalents of Grignard reagent led to the synthesis of a sulfoxide without the need for further nitrogen protection (***Scheme 25***). This discovery made the synthesis of sulfoxides from sulfinamides much more accessible to a wide variety of researchers and the research conducted by Ma and coworkers[69] presents a shorter route for preparing of tert-butyl sulfoxides compared to the traditional tert-butanesulfinate methods.



Scheme 25: Synthesis of sulfoxides from mono N-substituted sulfinamides

1.5 Project Goals

The overall goals of this work are to synthesize a lentinic acid analog which can produce the corresponding sulfenic acid, and therefore lenthionine, without the need for rigorous and low yielding extraction procedures or expensive enzymes. As stated in *Section 1.4.2.4*, sulfenic acids can be generated through the thermal decomposition of *tert*-butyl sulfoxides. This would, in theory, provide a much simpler entry point to the formation of lenthionine as seen in ***Scheme 4*** as **10** could be generated through the thermal breakdown of the *tert*-butyl sulfoxide **53** (***Scheme 26***). If the corresponding sulfenic acid (**10**) is generated, it will react with a second sulfenic acid molecule to create thiosulfinate **11**, which will then form lenthionine via an unknown mechanism.

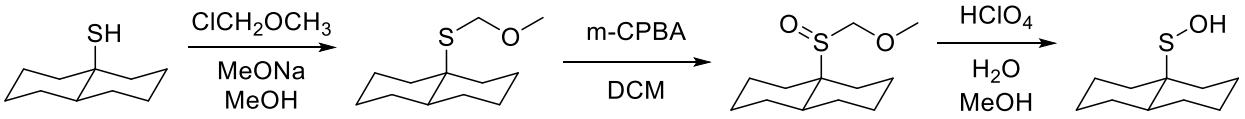


53 **10**

Scheme 26: Generation of sulfenic acid (**10**) from tert-butyl sulfoxide (**53**)

The generation of sulfenic acids has been performed from many different starting materials.[23] Of note to this research is the generation of sulfenic acids from sulfoxides that bear a strong electron donating group at the β-position from a sulfoxide.[23] That means that a structure such as **54** could generate **10** through thermal decomposition as well.[23] Sulfoxide **54** also resembles a sulfenate releasing group of the type described in *Section 1.4.2.1* which would correlate to sulfenate chemistry being an optimal method for synthesizing **54**. If either **53** or **54** are heat sensitive and do not generate the desired sulfenic acid (**10**), a sulfenic acid generation method that does not involve heat could be employed. In 1992, Yoshimura and coworkers.[79] described a method for the hydrolysis of methoxymethyl sulfoxides which produced the corresponding sulfenic acid (***Scheme 27***). The researchers utilized 7% perchloric acid in a methanol/water

mixture to perform the hydrolysis. Therefore, if **55** can be synthesized, this would provide another route to the formation of **10** and by extension, lenthionine.



Scheme 27: Generation of sulfenic acids from methoxymethyl sulfoxides

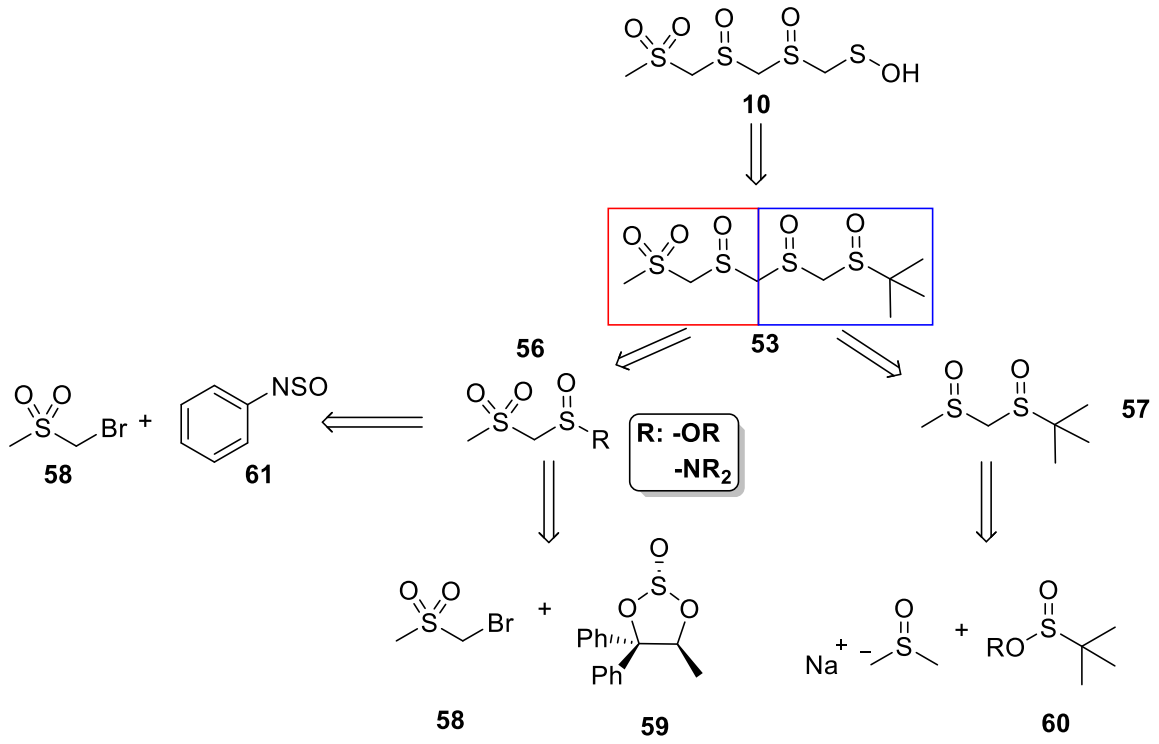
54 **55**

Figure 5: Other potential targets for this research

The syntheses of **53-55** have not been conducted before and neither has the synthesis of lentinic acid. Thus, it is unknown whether the stereochemistry of the sulfoxides in the backbone plays a factor in the formation of lenthionine. As such, the synthesis of **53-55** should be carried out with careful tracking of the stereochemistry at each sulfoxide position (***Figure 5***). To do this, the synthesis of these molecules will be carried out via sulfenate or sulfinate/sulfinamide chemistry as these methods traditionally provide easy access to sulfoxides. The following sections will present, in significant detail, the method that will be attempted for the synthesis of sulfoxides **53-55** with justifications for the synthetic choices for how to synthesize these compounds.

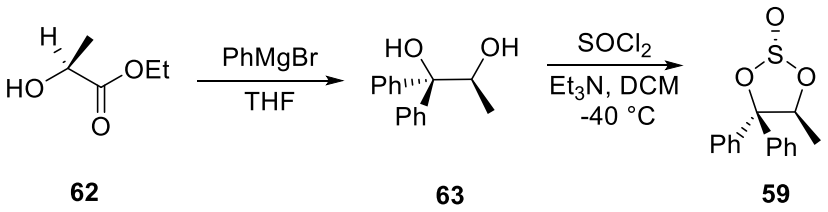
1.5.1 Sulfinate/Sulfinamide Chemistry

Compound **10** (***Scheme 4***) is the goal for this synthesis and therefore the sulfenic acid generation step will be generalized for the syntheses described. For this section, the synthesis of *tert*-butyl sulfoxide **53** will be described. A building block analysis of **53** is presented in ***Scheme 28*** and steps for the synthesis of each block, as well as the amalgamation of the blocks, will be described subsequently.



Scheme 28: Building block analysis of **53** using sulfinate/sulfinamide chemistry

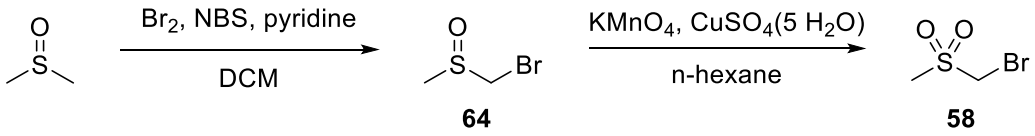
Compound **56** is a key component for the synthesis of **53**. The synthesis of **56** can be carried out through a nucleophilic attack by sulfone **58** at the sulfur in cyclic sulfite **59** or at the sulfur of N-sulfinylaniline (**61**). Sulfone **58** and cyclic sulfite **59** have been synthesized previously and N-sulfinylaniline (**61**) is commercially available.[80] The synthesis of **59** was carried out in a two-step process starting from (S)-ethyl lactate (**62**). Compound **62** was subject to an attack from phenylmagnesium bromide which gave diol **63**. The addition of thionyl chloride and triethylamine at -40 °C leads to the synthesis of building block **59** as illustrated in ***Scheme 29***. The sulfite produced from this is only present in the trans product.[80] This sulfite, when attacked by one nucleophile, exclusively gave sulfinates with an R configuration about the sulfur and when the produced sulfinate was attacked, this led to the synthesis of sulfoxides with 100% enantiomeric excesses.[80]



62 **63** **59**

Scheme 29: Synthesis of building block **59**

Synthesis of **58** can be carried out in a two-step process as well. The first step involves the alpha bromination of dimethyl sulfoxide with bromine and NBS in methylene chloride. The second step is an oxidation of the purified bromosulfoxide (**64**) to sulfone **58** using potassium permanganate in the presence of copper (II) sulfate.

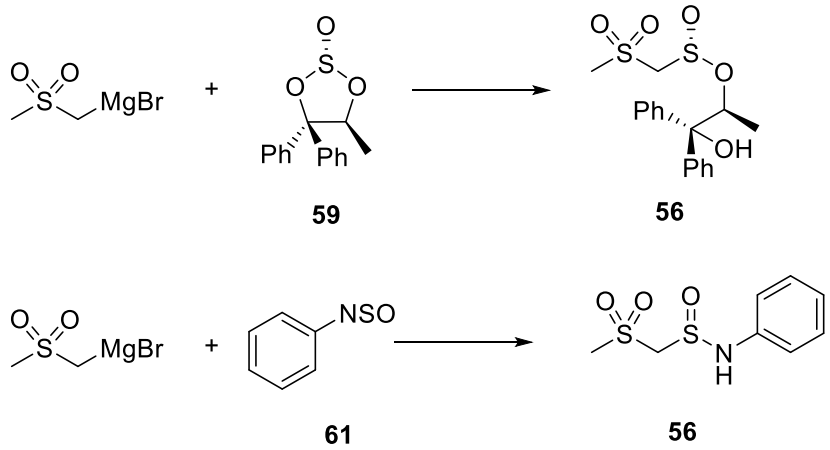


64 **58**

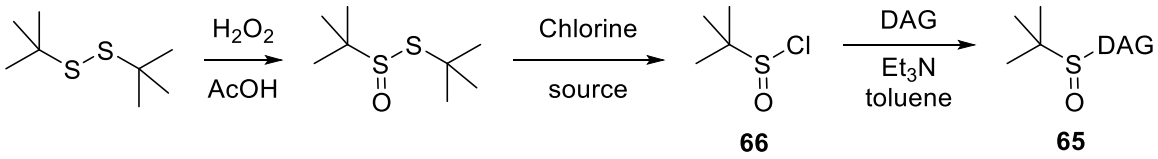
Scheme 30: Synthesis of building block **58**

The synthesis of building block **56** could then be performed through a Grignard reaction of **58** onto cyclic sulfite **59** or N-sulfinylaniline (**61**) (***Scheme 31***). The equivalent Grignard reagent form of **58** has not been synthesized previously and this poses a potential problem. If the Grignard reaction does not work, the synthesis of **56** could be carried out by deprotonating dimethyl sulfone instead.

The synthesis of **60** can be carried out in a variety of ways and many of these have been described in previous sections of this paper. The most effective method for synthesizing **60** has been to first generate the *tert*-butyl sulfinyl chloride (**66**) and then displace the chloride with an alcohol as seen in ***Scheme 32***. An optimal method of synthesizing *tert*-butyl sulfinyl chloride (**66**) is to oxidize *tert*-butyl disulfide and then add a chlorine source such as chlorine gas or sulfuryl chloride.[81] Subjecting **66** to DAG in the presence of an amine base (***Scheme 32***) provides easy access to **65** (**60** with R being DAG) with only one conformation about the sulfur.[81]

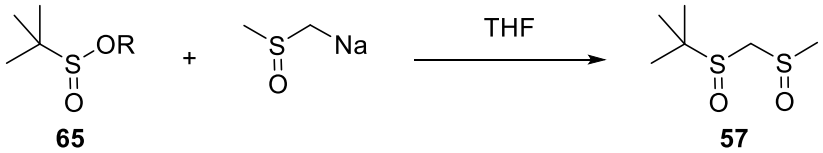


Scheme 31: Potential syntheses of building block **56** from sulfone **58**



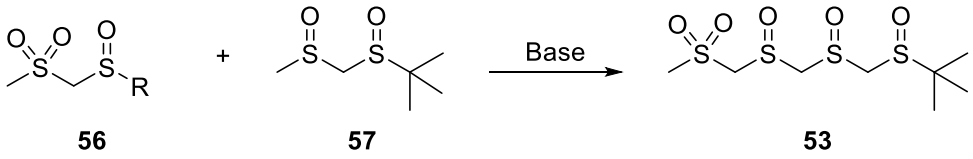
Scheme 32: Potential Synthesis of building block **65**

From **65**, the synthesis of **57** could be carried out through the addition of a dimsyl anion. A dimsyl anion is the sodium (or potassium) salt of DMSO and has been used broadly as a nucleophile since Corey and Chaykovsky first reported it in 1962.[82–84] It has also previously been utilized in the synthesis of optically active β-bis-sulfoxides.[85] In this research, Kunieda and coworkers[85] prepared optically active p-tolyl-bissulfoxides with diastereomeric ratios of up to 100:0 through the reaction of sodium dimsyl with p-toluenesulfinyl chlorides. This methodology will be employed for the synthesis of **57** (***Scheme 33***).



Scheme 33: Synthesis of building block **57**

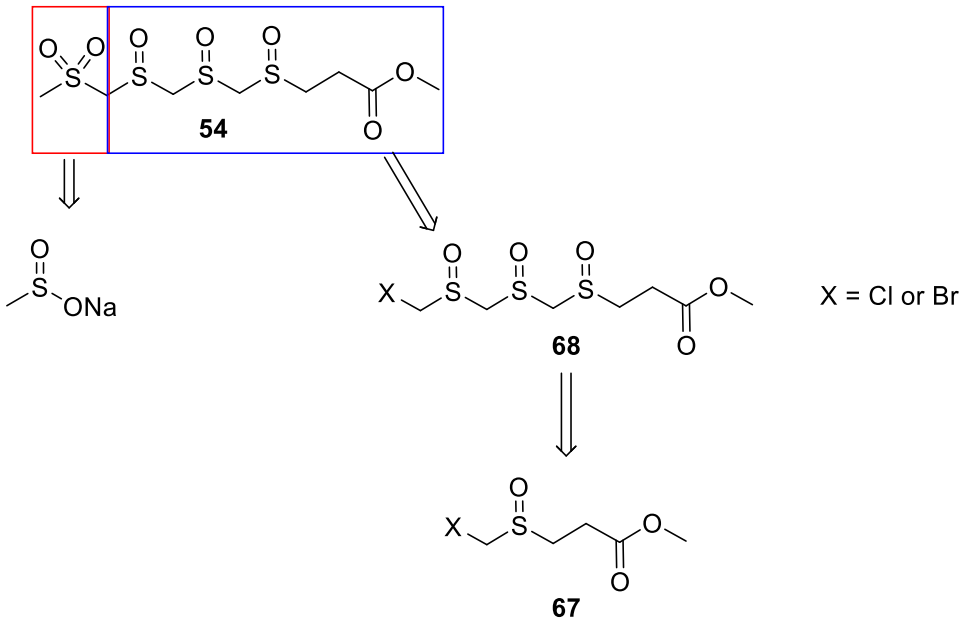
To synthesize **53** from building blocks **56** and **57**, a nucleophilic attack of **57** onto the sulfinate/sulfinamide centre of **56** must take place (***Scheme 34***). For this to occur for sulfinamide **56**, the nitrogen must first be protected with a tert-butyloxycarbonyl group. The reaction between **57** and **56** will be attempted through the deprotonation of an outer α-hydrogen on **57** and its subsequent nucleophilic attack. It is unlikely that the outer hydrogen will be deprotonated with one equivalent of base due to the pK_a of the inner hydrogens being ~18 compared to ~30 for the outer α-hydrogens. To achieve the outer deprotonation, at least two equivalents of base will be utilized as the outer carbanion would be less stable and thus more reactive. This chemistry has been utilized for biscarbonyl compounds previously.[86]



Scheme 34: Synthesis of lenthionine precursor **53** using sulfinate chemistry

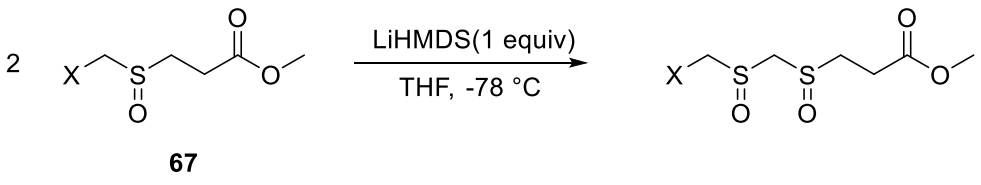
1.5.2 Sulfenate Chemistry

Like the sulfinate chemistry section, the goal of this section is to propose a synthesis of a potential precursor to sulfenic acid **10**. The target molecule in this section will be compound **54** as the EWG at the β position from the sulfoxide resembles the sulfenate-releasing groups that are described in *Section 1.4.2.1*. A building block analysis of **54** is illustrated in ***Scheme 35*** and steps toward the synthesis of the building blocks, as well as the eventual synthesis of **54**, will be described.



Scheme 35: Building block analysis of **54**

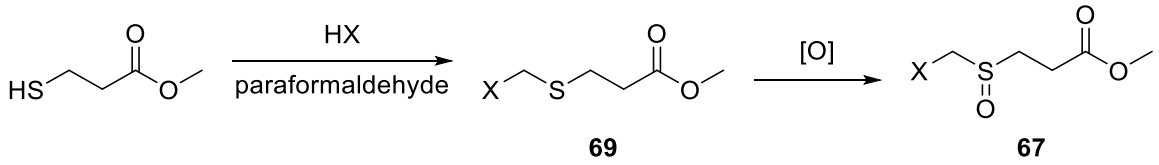
As seen in ***Scheme 35***, the route to the synthesis of **54** only involves three compounds. The center point of this synthesis is an iterative sulfenate-release reaction in which multiple molecules of **67** are reacted together to form poly-sulfoxide containing compounds. This would involve the synthesis of a sulfenate-precursor compound (**67**) containing a halogen atom at the α-position to the sulfoxide group. If two equivalents of **67** were utilized and only one equivalent of base was added, an α-halogenated sulfenate anion would proceed to attack the other molecule of **67**, displacing the halogen and forming a poly-sulfoxide structure. This reaction is illustrated in ***Scheme 36***.



Scheme 36: General structure of an iterative sulfenate release

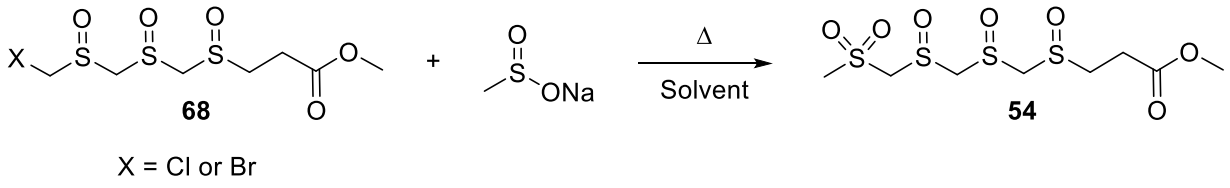
If controllable, this reaction could be a method for building the three sulfoxides in **54**. In order to test the controllability, sulfoxide **67** must be synthesized. One potential synthesis of **67**

would be to synthesize an α-halogenated sulfide such as **69** and then oxidize the compound. Using this mentality, **67** could be synthesized from methyl 3-mercaptopropanoate (M3MP) as seen in ***Scheme 37***. Oxidation of **69** by *m*-chlorobenzoic acid, sodium metaperiodate, or hydrogen peroxide could be tested for the synthesis of sulfoxide **67**. Two iterative sulfenate releases could then be utilized to synthesize building block **68**.



Scheme 37: Potential synthesis of building block **67**

After the synthesis of building block **68**, the only step remaining before the synthesis of **54** is the addition of a sulfone. In the literature, sodium methanesulfinate has been utilized as a source of sulfones through a nucleophilic substitution of a halide.[87,88] This has been useful as a method for the synthesis of various aryl and alkyl sulfones with good, to great, yields.[87,88] As such, the reaction of sodium methanesulfinate and **68** will be utilized in the synthesis of **54**. The temperature of the reaction needs to be carefully controlled in order to not form the sulfenic acid equivalent of **72**, which has been shown in literature to occur at temperatures of 110 °C and higher.[23]



Scheme 38: Synthesis of lentinic acid analog **54** from building block **68**

The purpose of this research is to synthesize a lentinic acid analog such as **53-55** and utilize these to synthesize lenthionine. As lenthionine is the principal aroma and taste producing compound found in shiitake mushrooms, this project has the potential to synthesize an artificial flavouring alternative to using the actual mushrooms. Aside from the value of producing an

artificial flavour, this project could be useful for determining the natural conformation of lentinic acid about the sulfoxides in the sulfur-carbon backbone. Another potential significance is the exploration of new uses for sulfenate (iterative sulfenate release) and sulfinate chemistry (deprotonation of the outer α-hydrogens in **57**) which could provide routes to other polysulfurous compounds.

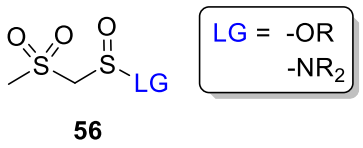
Chapter 2: Results and Discussion

2.0 Results and Discussion

2.1 Attempted Syntheses of Building Block 56

2.1.1 Pathways for the Synthesis of an α-Sulfonyl Carbanion

The initial focus of this research was to determine the optimal method for the synthesis of a compound with the structure of building block **56** (***Figure 6***). As the occurrence of compound **56** is rarely claimed in literature, with no actual synthesis verified and published, a variety of methods were attempted in order to form this thus far, elusive compound. The intuitive route for the synthesis of a compound in the class of building block **56** would be to utilize either sulfinate ester or sulfinamide chemistry for its synthesis.

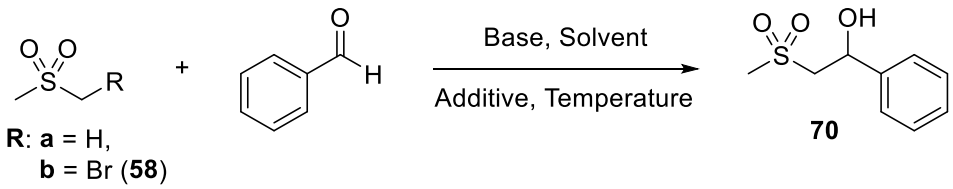


56

Figure 6: Building Block **56**

As the attack of an α-carbanion of a sulfide, sulfoxide, sulfone, or sulfinate ester on a sulfonic ester has never been reported in literature, but the attack of an α-sulfonyl carbanion onto a sulfinate ester has been reported in literature, the best course of action would be to utilize the sulfone as the nucleophile and determine the optimal electrophile for the synthesis of **56** via that method.[89,90] There have been many methods by which an α-sulfonyl carbanion has been synthesized and utilized to attack electrophiles, however the synthesis and use of the α-sulfonyl carbanion/Grignard reagent form of dimethyl sulfone has presented challenges to researchers in the past. Many methods have been attempted for this purpose however the yield for the resulting products, such as β-hydroxysulfones, of the reactions with various electrophiles have generally all been low.[91,92] It has been postulated that the reason for the yields being low is a poor solubility of the α-sulfonyl carbanion of dimethyl sulfone ($DMSO_2$) in certain solvents leading to the isolation

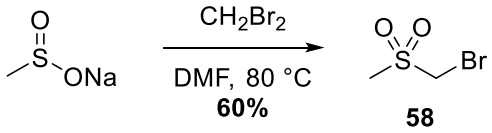
of dimethyl sulfone along with the product of the reaction.[93] In order to determine the best method for the formation of the α-sulfonyl carbanion of dimethyl sulfone various bases, solvents, temperatures and additives were investigated in the synthesis of β-hydroxysulfone **70** from dimethyl sulfone or bromo(methanesulfonyl)methane (**58**) and benzaldehyde (***Scheme 39***). The results are separated based on the counterion of the base that was utilized, and the effectiveness of the trial was evaluated based on the ratio of sulfone **58** to product **70** in the ^{1}H NMR.



Scheme 39: Synthesis of β-hydroxysulfone **70** utilizing the a-sulfonyl carbanion or Grignard reagent of dimethyl sulfone

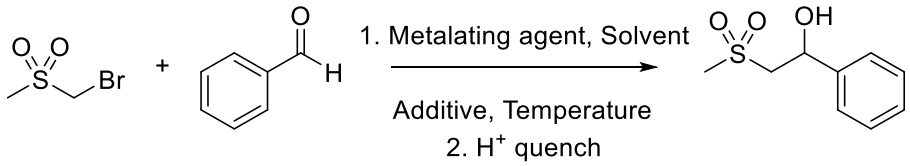
The initial efforts towards the synthesis of **70** involved the use of **58** and attempts to convert it to an organometallic compound. Sulfone **58** was synthesized by mixing sodium methanesulfinate with dibromomethane in DMF at 80 °C for 20 hours and this resulted in a 60% yield (***Scheme 40***). Once synthesized, **58** was subjected to the conditions outline in ***Table 1*** with the goal of synthesizing compound **70**. All attempts at synthesizing the Grignard reagent of **58** were unsuccessful and in no instance was there any noticeable product formation. This had previously been attempted on aryl sulfones by Field[94] and the same result was achieved. Thus, all attempts at Grignard reagent formation from **58** were abandoned. The use of samarium (II) iodide has previously been utilized to react bromomethyl phenyl sulfone with acetone and thus it was hypothesized that SmI_2 could be used to react **58** with benzaldehyde.[95] However, this was unsuccessful and the ^{1}H NMR spectrum showed evidence of the formation of benzyl alcohol and no product formation. As SmI_2 can reduce benzaldehyde and potentially other electrophiles, this

potentially explains why the reaction was unsuccessful. As there had been no positive results from these trials, all further attempts to form **70** from **58** were discontinued and instead deprotonation of dimethyl sulfone became the focus moving forward.



Scheme 40: Synthesis of bromo sulfone **58**

Table 1: Trials for the metalation of **58**



Reaction	Metalating Agent	Metal: Starting Material	Additive	Solvent	Reaction Temp.	Product
1	Mg	2.2:1	I_2	Et_2O	reflux	No
2	Mg	2.2:1	I_2	THF	reflux	No
3[1]	SmI_2	2.2:1	N/A	THF	25 °C	No
4[2]	SmI_2	2.2:1	N/A	THF	25 °C	No
5	Zn	2:1	TMSCl, Dibromoethane	THF	40 °C	No

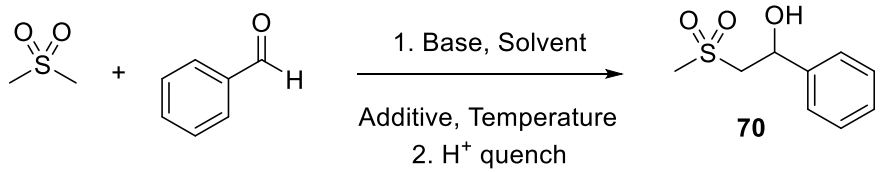
1: SmI_2 was added to both **75b** and benzaldehyde in THF
2: SmI_2 was added to a solution of **75b** in THF before benzaldehyde was added

The trials for the creation of an α-sulfonyl carbanion of dimethyl sulfone utilizing lithium bases are presented in ***Table 2***. The use of lithium bases and specifically n-butyl lithium (nBuLi) led to the production of β-hydroxysulfone **76** in the best ratios when compared to leftover starting material and overall isolated yields. The most successful result of these trials involved the addition of N, N, N', N'-tetraethylenediamine (TMEDA) in a 1:1 mole ratio to nBuLi and when TMEDA

and nBuLi were present in a 1.09: 1 mole ratio compared to $DMSO_2$ for 30 minutes at -78 °C before the addition of benzaldehyde. When this was done, the ^1H NMR spectrum of the crude reaction material (300 MHz, $CDCl_3$) showed a β-hydroxysulfone (**70**): $DMSO_2$ percent mole ratio of 95:5 and β-hydroxysulfone **70** could be isolated in a 67% yield. A possible reason for this trial yielding much better results than all other trials is that the TMEDA present could have complexed with the lithiated $DMSO_2$ making it more soluble in THF. To account for the increased reactivity when TMEDA is added, it has been shown that when in the presence of lithium chelating agents, such as TMEDA and HMPA, lithiated sulfones, which are normally contact ion pair species (CIPS) in THF, are converted to separated ion pair species (SIPS) which have increased reactivity compared to contact ion pair species.[96] These trials also exemplified that the deprotonation of $DMSO_2$ is best performed at cold, rather than warm, temperatures.

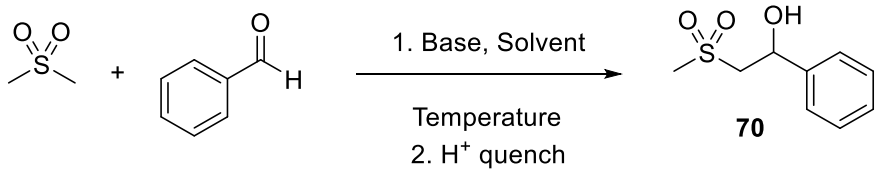
Various Grignard reagents/magnesium bases were also utilized in the attempt to form an α-sulfonyl carbanion of $DMSO_2$ and the results of these trials are illustrated in ***Table 3***. These trials illustrated that the formation of an α-sulfonyl carbanion of $DMSO_2$ using a Grignard reagent is best performed at room temperature for 2.5 hours utilizing ethyl magnesium bromide (EtMgBr). This led to a product: $DMSO_2$ percent mole ratio of 72:28 and the β-hydroxysulfone product was able to be isolated in a 51% yield. It is important to have a magnesium derivative of the α-sulfonyl carbanion of $DMSO_2$ as it has been shown that some lithiated species are more reactive than Grignard reagents in reactions with sulfites, such as **59**, leading to a double attack of the sulfur substrate which is not desired for this research.[80]

Table 2: Trials for the synthesis of **70** from dimethyl sulfone using lithium bases



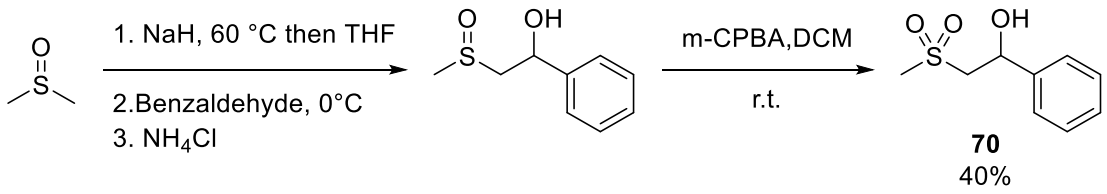
Reaction	Base (equiv.)	Additive (equiv.)	Solvent	Metalation Temp.	Metalation Time	Reaction Time	Reaction Temp.	Product: $DMSO_2$	Yield
1	nBuLi (1.0)	N/A	Benzene	80 °C	2.5 hr	20 hr	0 °C	No product	N/A
2	nBuLi (1.0)	N/A	THF	-78 °C	0.5 hr	20 hr	-78 °C	81:19	N/A
3	nBuLi (1.2)	N/A	THF	-78 °C	1 hr	20 hr	-78 °C	74:26	N/A
4	nBuLi (1.0)	N/A	THF	-78 °C to -30 °C	0.5 hr	20 hr	25 °C	62:38	N/A
5	nBuLi (1.2)	TMEDA (1.2)	THF	-78 °C	0.5 hr	2 hr	-78 °C	95:5	67%
6	nBuLi (1.2)	TMEDA (1.2)	THF	-78 °C	1 hr	2.5 hr	-78 °C	87:13	51%

Table 3: Trials for the synthesis of **70** from dimethyl sulfone using magnesium bases



Reaction	Base (equiv.)	Solvent	Metalation Temp.	Metalation Time	Reaction Time	Reaction Temp.	Product: $DMSO_2$	Yield
1	MeMgCl (1.25)	THF	0 °C - 25 °C	0.5 hr	24 hr	0 °C - reflux	No product	N/A
2	EtMgBr (1.20)	THF	25 °C	0.5 hr	18 hr	25 °C	51:49	N/A
3	EtMgBr (1.20)	anisole	100 °C	3 hr	18 hr	25 °C	12:88	N/A
4	EtMgBr (1.20)	THF	reflux	1 hr	20 hr	25 °C - reflux	60:40	N/A
5	EtMgBr (1.20)	THF	25 °C	2.5 hr	20 hr	25 °C	72:28	51%
6	EtMgBr (1.20)	THF	25 °C	5 hr	20 hr	25 °C	58:42	N/A

Due to the increased stabilization from the two oxygens of a sulfone, a sulfone-stabilized carbanion can be a weaker nucleophile than analogs based on a sulfoxide or a sulfide.[97] As such, in the case that an α-sulfonyl carbanion would not be a strong enough nucleophile to attack a sulfite, a method for the use of sulfoxides was also developed. The method, illustrated in ***Scheme 41***, involves synthesizing the sodium salt of DMSO by reacting DMSO with sodium hydride (NaH) at 60 °C for 45 minutes before cooling it to 0 °C and dissolving it in THF before the addition of benzaldehyde. After a workup, the resulting compound was immediately oxidized utilizing *m*-CPBA to form β-hydroxysulfone **70** in a 40% overall yield compared to benzaldehyde. As neither a β-sulfonyl- nor β-sulfinyl- sulfinate ester has been synthesized before, it is currently unknown whether the sulfoxide or the sulfinate ester will be oxidized selectively to the sulfone or sulfonate ester respectively. However, if the sulfone is not a good enough nucleophile to attack a sulfite, this is another method by which building block **56** can be synthesized.

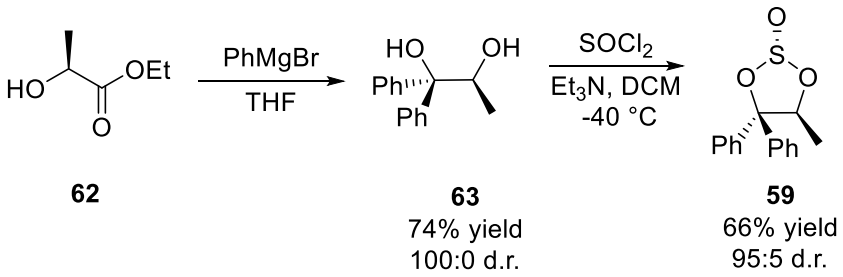


Scheme 41: Synthesis of **70** from the DIMSYL anion

From the trials detailed in ***Table 1-Table 3***, there are three clear methods by which an α-carbanion of $DMSO_2$ or DMSO can be utilized to synthesize building block **56**. The following sections will detail the attempts made to synthesize building block **56** from $DMSO_2$ and DMSO utilizing sulfinate and sulfinamide chemistry. This section also illustrates the best synthetic methods for synthesizing an α-sulfonyl carbanion from $DMSO_2$ and presents reasons for why α-sulfonyl carbanions of $DMSO_2$ cannot be generated from α-halo sulfones.

2.1.2 Attack of α-Sulfonyl/α-Sulfinyl Carbanions on Unsymmetrical Sulfites

Utilizing a method adapted from Rebiere and coworkers[80] unsymmetrical sulfite **59** was synthesizied in a two-step process outlined in ***Scheme 42***. The first step involves the attack of 3.75 equivalents of freshly synthesized phenylmagnesium bromide onto (S)-ethyl lactate which results in a 74% yield of chiral diol **63**. The second step involves cooling a solution of diol **63** in DCM to -40 °C before succesively adding a solution of thionyl chloride (2.74 M in DCM) and a solution of Et_3N (0.876 M in DCM). This results in the synthesis of sulfite **59** in a 66% yield after purification by recrystallization from a 1:1 solution of hexane and cyclohexane.



62

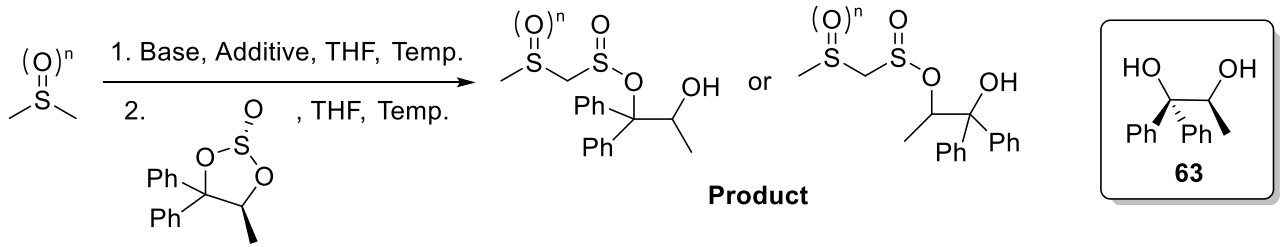
63
74% yield
100:0 d.r.

59
66% yield
95:5 d.r.

Scheme 42: Synthesis of sulfite **59** from (S)-ethyl lactate

Now that the sulfite had been synthesized, the next step would be to attack it with an α-sulfonyl or α-sulfinyl carbanion to synthesize the desired α-sulfonyl sulfinate ester form of building block **56**. As the attack of **59** with an α-sulfonyl or α-sulfinyl carbanion constitutes novel chemistry, a few variables were investigated to determine the best method for the synthesis of **56**. The variables investigated were the temperature of the reaction, the number of equivalents of the α-sulfonyl or α-sulfinyl carbanion, how the carbanion and sulfite are combined, and the counterion of the α-sulfonyl or α-sulfinyl carbanion. The results of the investigations into the attempted synthesis of **56** from sulfite **59** and the α-carbanion of DMSO and $DMSO_2$ are illustrated in ***Table 4***. The regioselectivity of the sulfur nucleophiles is unknown and thus the reaction could produce either of the potential sulfinate esters or attack the sulfite sulfur twice yielding diol **63** (***Table 4***). The effect that the order of addition of compounds had is unknown and thus this was also investigated. Method A involves the addition of the sulfite to the nucleophile and method B involves the addition of the nucleophile to the sulfite in solution. All the molar equivalent values in ***Table 4*** are compared to the moles present of sulfite **59**.

Table 4: Trials for the synthesis of building block **56** from DMSO/$DMSO_2$ and cyclic sulfite **59**



Reaction	DMSO or $DMSO_2$ (equiv.)	Base (equiv.)	Additive	Metalation Temp.	Metalation Time	Order of Addition	Reaction Temp.	Reaction Time	Sulfite remains?	Product?
1	DMSO (17)	NaH (2.1)	N/A	60 °C	0.75 hr	A	0 °C	4 hr	No	No
2	DMSO (2.1)	LDA (2.1)	N/A	0 °C	0.5 hr	A	0 °C to 25 °C	20 hr	Yes	No
3	DMSO (17)	NaH (1.1)	N/A	60 °C	0.75 hr	A	0 °C	20 hr	Yes	No
4	$DMSO_2$ (1.1)	nBuLi (1.2),	TMEDA (1.2)	-78 °C	0.5 hr	A	50 °C	20 hr	Yes	No
5	$DMSO_2$ (2.1)	nBuLi (2.2),	TMEDA (2.2)	-78 °C	0.5 hr	A	50 °C	20 hr	Yes	No
6	$DMSO_2$ (1.1)	nBuLi (1.2),	$MgBr_2$ (0.50)	-78 °C	0.5 hr	A	25 °C	20 hr	Yes	No
7	$DMSO_2$ (1.2)	EtMgBr (1.45)	N/A	25 °C	2.5 hr	A	25 °C	20 hr	Yes	No
8	$DMSO_2$ (1.8)	EtMgBr (2.2)	N/A	25 °C	2.5 hr	B	25 °C	18 hr	Yes	No
9	$DMSO_2$ (1.8)	EtMgBr (2.2)	N/A	25 °C	2.5 hr	B	-78 °C	20 hr	Yes	No
10	$DMSO_2$ (1.1)	nBuLi (1.2),	TMEDA (1.2)	-78 °C	0.5 hr	B	-78 °C	20 hr	Yes	No

As illustrated in ***Table 4***, none of the conditions attempted were able to afford a mono attack of an α-sulfinyl or α-sulfonyl carbanion on cyclic sulfite **59** to synthesize a sulfenic acid form of building block **56**. All the attempted reaction conditions produced chiral diol **63** regardless of whether the sulfite starting material had been completely consumed. The number of equivalents of the α-carbanion of DMSO or $DMSO_2$ and the temperature of the reaction did not change how the α-carbanion of DMSO or $DMSO_2$ reacted with sulfite **65**. The synthesis of building block **56** via the attack of an α-carbanion of DMSO or $DMSO_2$ was therefore discontinued.

When the reaction between the α-carbanion of $DMSO_2$ and sulfite **59** was subjected to aqueous workup conditions, diol **63** was isolated without the presence of the corresponding α,α'-bissulfonylsulfoxide. However, when the reaction is quenched with a minimal amount of a saturated aqueous NH_4Cl solution and then dried and evaporated, the ^1H NMR of crude material displayed the presence of α,α'-bissulfonylsulfoxide **71**. The NMR spectra shown in ***Figure 7*** display that the peaks at 4.41 ppm and 2.57 ppm (blue) are unaccounted for when compared to the ^1H NMR spectrum after aqueous workup (red). While there is evidence of the formation of an α,α'-bissulfonylsulfoxide via ^1H NMR, all attempts to isolate **71** were unsuccessful.

There are, however, some important results that can be identified from the outcome of the reactions in ***Table 4***. The attack of a chiral sulfite with the α-carbanion of DMSO or $DMSO_2$ could potentially be useful for the synthesis of chiral vicinal diols from the corresponding racemic vicinal diols via a two-step reaction. Attacking of chiral sulfite **59** with the α-carbanion of DMSO or $DMSO_2$ led to the synthesis of diol **63** in a diastereomeric ratio that was the same as the chiral sulfite. As such, a racemic diol can be converted into a chiral sulfite by reacting the diol with thionyl chloride, separation of the sulfite diastereomers and the attack of an α-carbanion of DMSO

or $DMSO_2$ to synthesize the corresponding chiral diol (***Scheme 43***). The synthetic utility of using the α-carbanions of DMSO or $DMSO_2$ for synthesizing diols is being investigated.

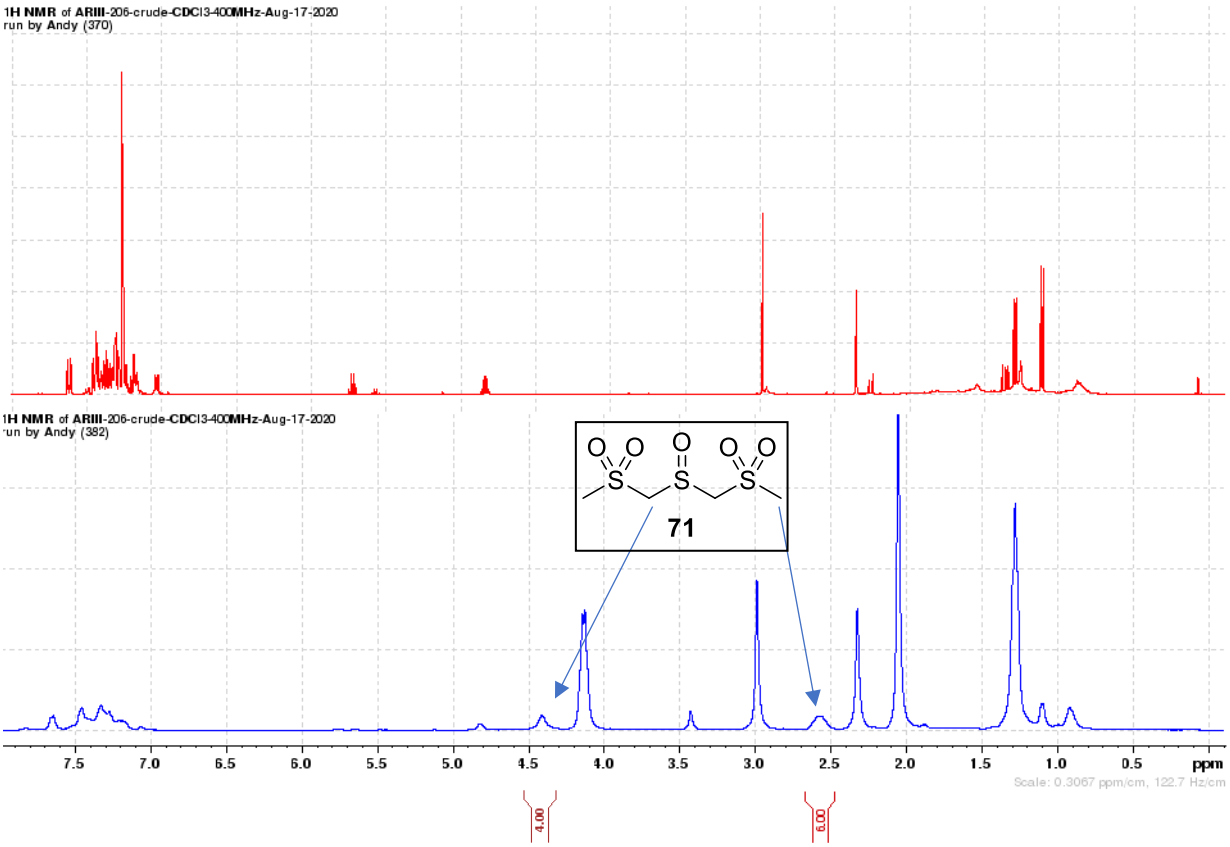
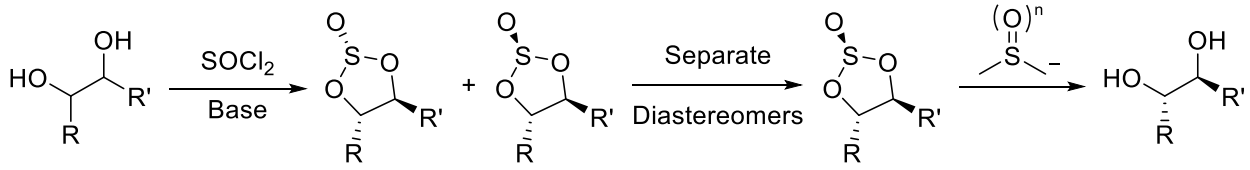


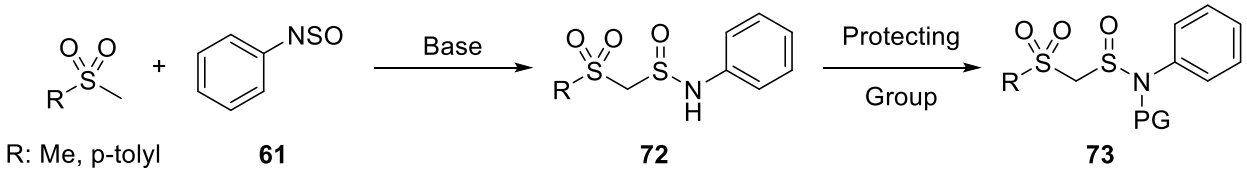
Figure 7: ^{1}H NMR spectral (400 MHz, $CDCl_3$) evidence of the formation o f α,α'-bissulfonylsulfoxide **71**



Scheme 43: Synthesis of chiral vicinal diols from vicinal diols using α-carbanions of DMSO or $DMSO_2$

2.1.3 Attack of α-Sulfonyl Carbanions on N-Sulfinylamines

As the formation of the sulfinate ester form of building block **56** via the attack of α-carbanions of DMSO or $DMSO_2$ on sulfite **59** was unsuccessful, alternative routes to the synthesis of building block **56** were attempted. The goal of this research shifted towards the synthesis of a sulfinamide form of building block **56.** Previously, a series of aryl sulfinamoyl sulfones were synthesized via the attack on N-sulfinylaniline (**61**) by a series of aryl sulfonyl carbanions.[98] As such, the next attempt at the synthesis of building block **56** involves a two-step process consisting first of the attack of the α-carbanion of $DMSO_2$ onto an *in situ* generated N-sulfinylaniline (**61**) to yield sulfinamoyl sulfone **72**. The second step then involves the protection of sulfinamoyl sulfone **72** to form sulfinamide **73** which can act as building block **56** in the attempted synthesis of lentinic acid analog **53** (***Scheme 44***).

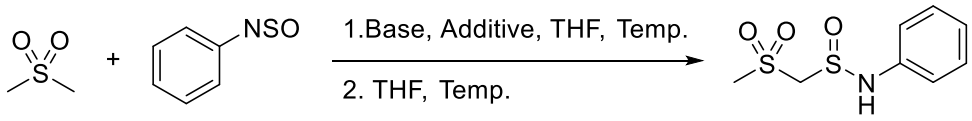


Scheme 44: Synthesis of sulfinamide **73** from dimethyl sulfone and N-sulfinylaniline

The first step is to synthesize sulfinamoyl sulfone **72** (R = Me) from dimethyl sulfone and the trials for the attempted synthesis of compound **72** (R = Me) are illustrated in ***Table 5*** with the molar equivalents described being compared to the starting molar value of aniline present. These reactions proceed by generating N-sulfinylaniline through the reaction between aniline and thionyl chloride (1.3 equivalents) in toluene at reflux for 2.5 hours followed by concentrating the mixture under reduced pressure and dissolving it in dry THF. The carbanion of $DMSO_2$ and **61** are then combined at 0 °C or -78 °C depending on the counterion of the α-carbanion of $DMSO_2$ and the reaction is stirred overnight. In these trials, the $DMSO_2$ counterion and the order of addition of the

substrates was varied. The addition of compound **61** to a solution containing the α-carbanion of $DMSO_2$ was designated method A and the addition of a solution containing the α-carbanion of $DMSO_2$ to compound **61** was designated method B.

Table 5: Trials for the attempted synthesis of sulfinamoyl sulfone **72**

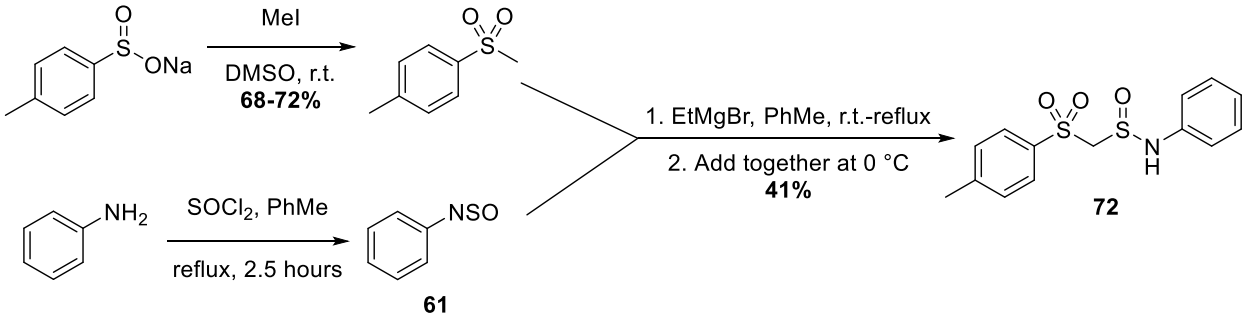


61 **72**

Reaction	$DMSO_2$: Aniline	Base (equiv.)	Additive (equiv.)	Metalation Temp.	Metalation Time	Addition Method	Reaction Temp.	Product?
1	1.5:1.0	nBuLi (1.7)	TMEDA (1.7)	-78 °C	0.5 hr	A	-78 °C	No product
2	1.5:1.0	EtMgBr (1.8)	N/A	25 °C	2.5 hr	A	0 °C	No product
3	1.0:1.0	nBuLi (1.2)	TMEDA (1.2)	-78 °C	0.5 hr	B	-78 °C	No product
4	1.5:1.0	EtMgBr (1.8)	N/A	25 °C	2.5 hr	B	0 °C	No product

As can be seen in ***Table 5***, all attempts to synthesize sulfinamide **72** (R = Me) from dimethyl sulfone and N-sulfinylylaniline **61** proved to be unsuccessful. In every reaction, the two main products were dimethyl sulfone and aniline. This is a clear indication that the sulfonyl carbanion failed to attack compound **61**, leading to no reaction. As such, when the reaction was quenched with water, the sulfonyl carbanion was protonated reforming dimethyl sulfone. It has been shown in literature that when N-sulfinylaniline **61** is reacted with water, it produces aniline.[99] It appears that the α-carbanion of dimethyl sulfone is not sufficiently nucleophilic to react with N-sulfinylamines.

However, as aryl methyl sulfones have been shown to attack N-sulfinylaniline **61** previously, the next goal of this research was the synthesis of sulfinamide **73** (R = p-tolyl) in order to examine the protection step in ***Scheme 45***. To examine the protection chemistry, sulfinamoyl sulfone **72** (R = p-tolyl) must be synthesized from methyl p-tolyl sulfone and N-sulfinylaniline **61**. Sulfinamoyl sulfone **72** (R = p-tolyl) was synthesized in a two-step process; the first of which involved reacting sodium p-toluene sulfinate with methyl iodide in DMSO at 25 °C for 20 hours which yields methyl p-tolyl sulfone in a 68 to 72% yield. Methyl p-tolyl sulfone is then deprotonated with EtMgBr and reacted with compound **61** to synthesize sulfinamoyl sulfone **72** (R = p-tolyl) in a 41% yield via a method adopted from Baltas and coworkers (***Scheme 45***).[98]

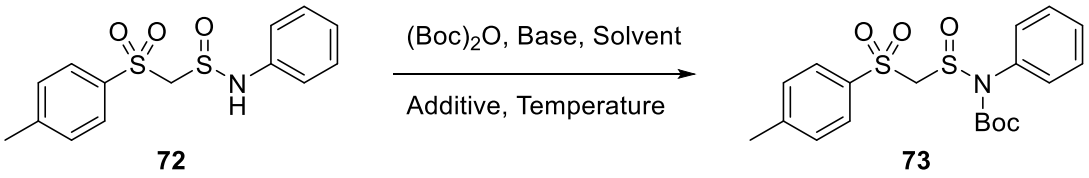


Scheme 45: Synthesis of 1-(4-methylbenzenesulfonyl)-N-phenylmethanesulfinamide **72**

With sulfinamoyl sulfone **72** (R = p-tolyl) synthesized, the next step in the synthesis of sulfinamide **73** (R = p-tolyl) is the protection of the nitrogen in compound **72**. The most efficient method for protecting the nitrogen on sulfinamides has been to utilize the tert-butyloxycarbonyl group as outlined in research performed by Ma and coworkers[69] and this strategy was attempted here for the synthesis of sulfinamide **73** (R = p-tolyl). An issue with this chemistry is that the pK_a's of the protons found on the nitrogen and carbon between the two sulfur functional groups are unknown and therefore it is uncertain whether the nitrogen can be selectively protected. Various

basic conditions were attempted to achieve the protection of compound **72** and these conditions, along with the results of these attempts, are outlined in ***Table 6***.

Table 6: Trials towards the synthesis of compound **73**



72 **73**

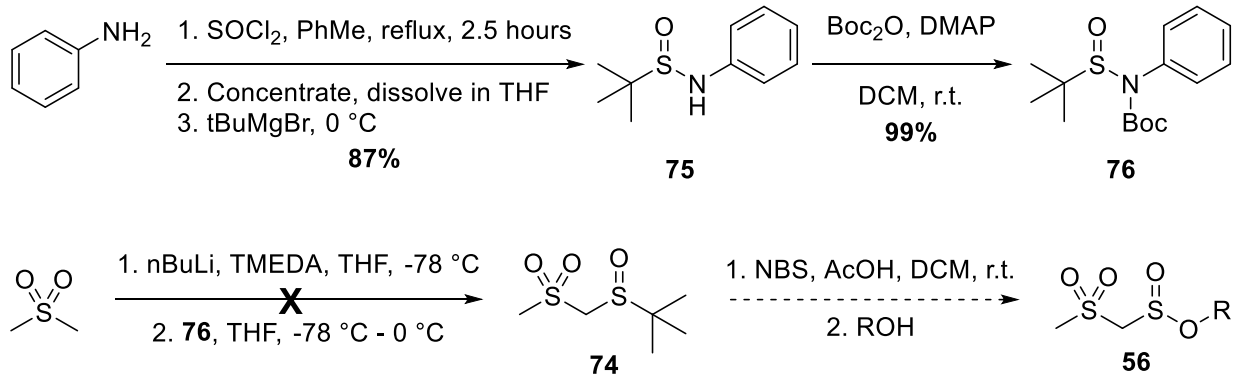
Reaction	$(Boc)_2O$: 78	Base (equiv.)	Additive (equiv.)	Solvent	Reaction Time	Reaction Temp.	Product?
1	0.75:1	Et_3N (1.5)	DMAP (0.1)	DCM	2 hr	0 °C	No product
2	1.4:1	Cs_2CO_3 (1.5)	N/A	DMF	Overnight	0 °C	No product
3	1.4:1	Cs_2CO_3 (1.5)	N/A	THF	Overnight	-78 °C to -40 °C	No product

Table 6 illustrates that all attempts to protect sulfinamoyl sulfone **72** (R = p-tolyl) with a tert-butyloxycarbonyl group to form sulfinamide **73** were unsuccessful. In every reaction, the main product found in the ^{1}H NMR spectrum of the crude reaction material was aniline. Sulfinamoyl sulfones are known to undergo a base catalyzed scission of the N-S bond to produce the corresponding amine and a sulfine which is susceptible to further attack.[98] The sulfine produced in the scission of the N-S bond can go on to produce various water soluble thioureas which explains its absence in the ^{1}H NMR spectrum of the crude reaction material.[98] Due to the lack of success in protecting compound **72**, the use of sulfinamides for the synthesis of building block **56** was discontinued in favour of attempting other methods.

2.1.4 Other Attempts Towards the Synthesis of Building Block 56

Given that all previous attempts to synthesize building block **56** did not produce the compound, other methods for the synthesis of building block **56** were attempted to ensure exhaustive assessment was undertaken.

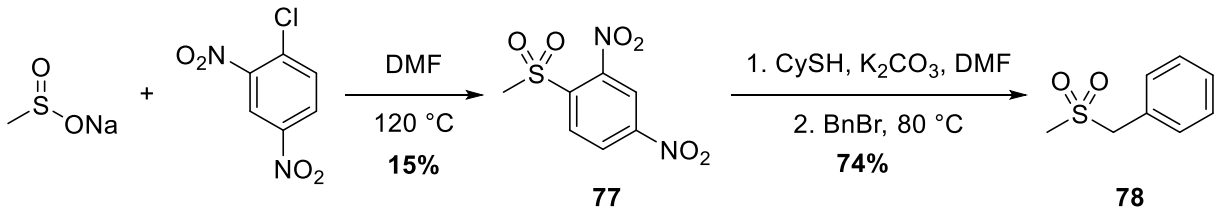
As illustrated in *Section 2.1.2*, the attack of an α-sulfonyl carbanion onto a sulfite results in a double attack at the sulfur centre and the synthesis of a diol and an α,α'-bissulfonylsulfoxide (***Table 4***). As such, the attack of an α-sulfonyl carbanion on a sulfur functionality that can later be converted into a sulfinate ester would be a way to circumvent that issue. Recently, Wei and Sun[100] reported a method by which tert-butyl sulfoxides can be converted into sulfinate esters by reacting them with N-bromosuccinimide and acetic acid in DCM followed by the addition of an alcohol (***Scheme 46***). Accordingly, if β-sulfinyl sulfone **74** can be synthesized, the method developed by Wei and Sun[100] could be utilized for the synthesis of a sulfinate ester equivalent of building block **56**. To synthesize compound **74**, first a tert-butyl sulfinamide or sulfinate ester must be synthesized. Traditionally, a tert-butyl sulfinate ester is synthesized in a 3-step process from tert-butyl disulfide, but a tert-butyl sulfinamide can be synthesized in a higher yield by employing N-sulfinylamines. When N-sulfinylaniline **61** is subject to nucleophilic attack by tert-butyl magnesium chloride (tBuMgBr) at 0 °C in THF, tert-butyl sulfinamide **75** is synthesized in 87% yield. The subsequent protection of compound **75** with Boc_2O and DMAP in THF at room temperature yields sulfinamide **76** in a 99% yield. However, when sulfinamide **76** is subject to an attack by an α-sulfonyl carbanion, no product was detected despite complete consumption of the starting material by ^1H NMR spectrum (***Scheme 46***).



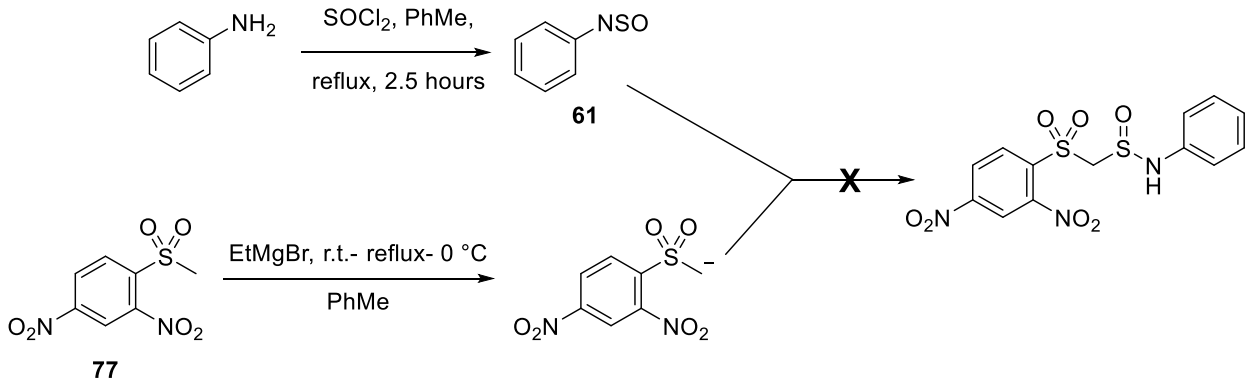
Scheme 46: Attempted synthesis of building block **56** through the attack of an α-sulfonyl carbanion on a tert-butyl sulfinamide

The synthesis of compound **72** demonstrated (***Scheme 45***) that aryl methyl sulfones can attack N-sulfinylamines to produce the corresponding β-sulfonyl sulfinamides. Failures in the synthesis of building block **56** via sulfinate and sulfinamide chemistry however showed that the α-carbanions of dialkyl sulfones such as $DMSO_2$ lack the nucleophilicity to attack an N-sulfinylamine in the same way that aryl methyl sulfones can. To circumvent this issue, a method by which an aryl methyl sulfone can be converted to dialkyl sulfone after it has attacked another compound, such as an N-sulfinylamine, was envisioned. If the aryl methyl sulfone that is utilized has a nitro group at the para position (or para and ortho positions) to the sulfone, it has been shown that a nucleophile can attack the benzene ring para to the nitro group and displace a sulfinic acid derivative.[101] Work by Thompson and coworkers[101] illustrated that the attack of a o,p-dinitrophenyl sulfone with a thiol in the presence of K_2CO_3 in DMF yielded the corresponding o,p-dinitrophenyl sulfide within 5 minutes. However, Thompson and coworkers[101] did not confirm the potassium sulfinate salt coproduct. Nonetheless, this method was pursued for the production of dialkyl sulfones from a o,p-dinitrophenyl methyl sulfone. The synthesis of o,p-dinitrophenyl methyl sulfone was carried out by reacting sodium methanesulfinate with 2,4-dinitrochlorobenzene in DMF at 120 °C for 20 hours and this led to a 15% yield of sulfone **77**. In order to test the feasibility of this synthetic pursuit, sulfone **77** was then dissolved in dry DMF and

reacted with cyclohexyl thiol and potassium carbonate for 10 minutes before the addition of benzyl bromide and increasing the reaction temperature to 80 °C overnight. This method yielded benzyl methyl sulfone (**78**) in a 74% yield (***Scheme 47***). As that was a success, sulfone **77** was then subjected to the same conditions utilized for the synthesis of sulfinamide **72**, but this was unsuccessful (***Scheme 48***). Due to the low yield of the reaction producing sulfone **77**, this synthetic investigation was terminated, but this work has provided a method for the protection and deprotection of methanesulfinate salts and should be investigated further to determine the applicability of this chemistry.



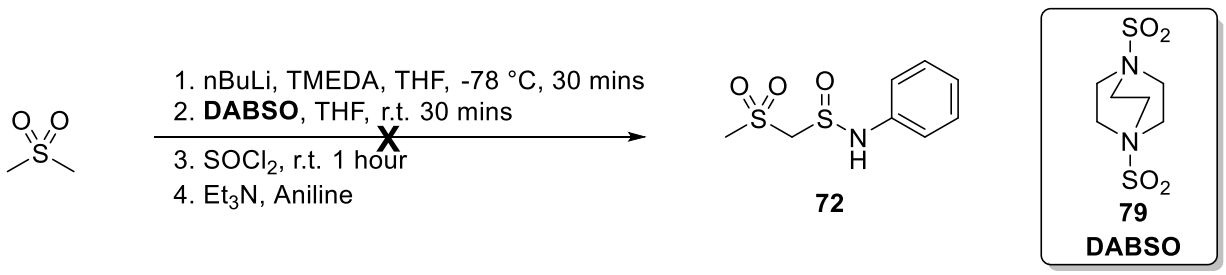
Scheme 47: Synthesis of sulfone **77** and subsequent synthesis of benzyl methyl sulfone **78** from sulfone **77**



Scheme 48: Attempted synthesis of building block **56** from o,p-dintrophenyl methyl sulfone **77**

Analogous to the use of carbon dioxide, sulfur dioxide has been utilized throughout literature for the synthesis of sulfinic acids from Grignard reagents.[102–104] The sulfinic acids formed from sulfur dioxide can then be functionalized in many ways, with a common reaction being the conversion of sulfinyl chlorides for further functionalization.[105] However, due to the issues

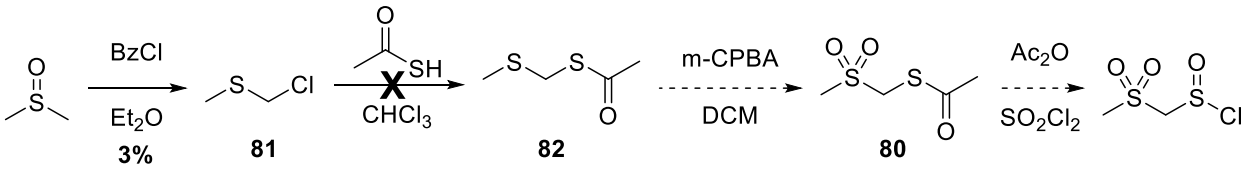
associated with sulfur dioxide, researchers have made a new molecule that can replace sulfur dioxide, 1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct **79** (DABSO).[106] The invention of DABSO gives researchers a safer way of utilizing sulfur dioxide and recently, DABSO has been utilized for an efficient multiple step, one-pot synthesis of sulfinamides.[105] This method, developed by Lo and coworkers,[105] involves the attack of an organometallic reagent onto DABSO which is then allowed to react for 30 minutes before the addition of thionyl chloride to the *in situ* formed sulfinic acid to convert it to the corresponding sulfinyl chloride. This sulfinyl chloride is then converted to a sulfinamide by reacting the sulfinyl chloride with an amine (primary or secondary) and triethylamine.[105] As such, this method was attempted for the formation of building block **56**. In this reaction, 1.6 equivalents of $DMSO_2$ were deprotonated with nBuLi and TMEDA before being reacted with DABSO for 30 minutes at room temperature. Thionyl chloride was added, and the solution was reacted for 1 hour before the addition of aniline and triethylamine (***Scheme 49***). This reaction yielded no product according to the ^1H NMR of the crude reaction material and closer examination of this NMR showed that it consisted of mostly aniline and $DMSO_2$, thus illustrating that there was no reaction between DABSO and $DMSO_2$.



Scheme 49: Attempted synthesis of sulfinamoyl sulfone **72** (R = Me) from $DMSO_2$ and DABSO (**79**)

The final method attempted for the synthesis of building block **56** was based on the synthesis of β-sulfonyl thiolacetate **80** performed by Ahern and coworkers.[107] In their work, they synthesized sulfone **80** by reacting α-chlorosulfide **81** with thiolacetic acid in carbon tetrachloride

in the presence of pyridine. The corresponding compound **82** was then oxidized with *m*-CPBA to form β-sulfonyl thiolacetate **80**.[107] In literature, it has been shown that thiolacetates can be converted to sulfinyl chlorides through a reaction with acetic anhydride and sulfuryl chloride and from there, sulfinyl chlorides can be functionalized into sulfinate esters.[108] As such, it became the goal of this research to synthesize β-sulfonyl thiolacetate **80** and determine if it can be converted to building block **56**. The initial step of this synthetic pathway involves the synthesis of α-chlorosulfide **81**. The chosen method was a Pummerer reaction between DMSO and benzoyl chloride in ether, which needs to be purified by distillation. However, the purification of this compound proved to be difficult and compound **81** was only able to be purified in a 3% yield due to its volatile nature (***Scheme 50***). Despite the low yield of compound **81**, there was still enough material to continue. Compound **81** was then subjected to a reaction with thiolacetic acid and pyridine in dry chloroform, however, the ^{1}H NMR spectrum of the crude reaction material showed that no product had formed. Perhaps a solvent change from carbon tetrachloride as originally performed by Ahern and coworkers[107] prevented the reaction from taking place. Due to the low yield and not being able to synthesize compound **82**, this method was abandoned in pursuit of better methods.

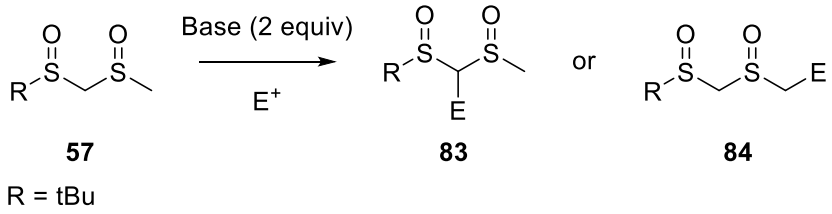


Scheme 50: Attempted synthesis of building block **56** from α-chlorosulfide **81**

2.2 Synthesis and Nucleophilicity of Building Block 57

Despite being unsuccessful in the synthesis of building block **56**, examining the synthesis and nucleophilicity of β-sulfinyl sulfoxides such as building block **57** still possess immense value.

While the synthesis of compound **57** is essential, the more important element to this research is the examination of the nucleophilicity of β-sulfinyl sulfoxides bearing a terminal methyl group. As such, this section will provide an in-depth analysis of the outcomes of deprotonating β-sulfinyl sulfoxides bearing a terminal methyl group with varying amounts of base and examining the results after quenching with a nucleophile. This chemistry has never been attempted previously and thus, the order that the protons will be deprotonated is currently unknown. In β-sulfinyl ketones and biscarbonyl compounds, only two equivalents of base are required for the α'-protons to be deprotonated but in β-sulfonyl sulfones, it takes three equivalents of a strong base to achieve the same α'-proton deprotonation.[86,109–111] However, for the β-sulfonyl sulfones, the selective alkylation of the α'-carbon proved difficult with the isolation of α,α'-alkylation being common.[110] As α'-functionalization (**84**) is the goal, both triple and double deprotonation will be attempted in order to meet this goal.



57 **83** **84**

Scheme 51: Theoretical deprotonation chemistry of β-sulfinyl sulfoxide bearing a terminal methyl group

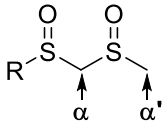
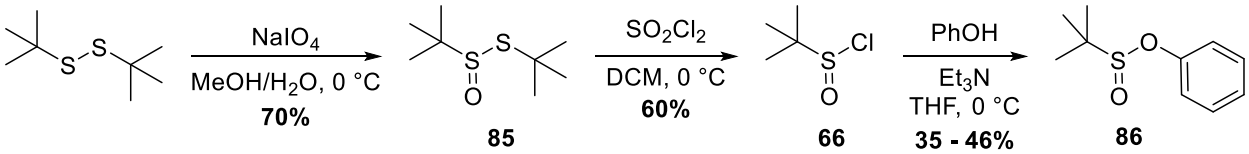


Figure 8: Identification of α and α' carbons of β-sulfinyl sulfoxides bearing a terminal methyl group

2.2.1 Synthesis of β-Sulfinyl Sulfoxides Bearing a Terminal Methyl Group

Investigations of the deprotonation chemistry of β-sulfinyl sulfoxides/ bissulfoxides began with the synthesis of building block **57**. The method was based on research performed by Kunieda and coworkers[85] in which they synthesized various β-bissulfoxides from dimsyl anions and sulfinate esters. In this research, Kunieda and coworkers[85] formed the dimsyl anions by reacting sodium hydride with DMSO at 60 °C for 45 minutes and then dissolving this solution in THF before cooling it to 0 °C and adding in a sulfinate ester. It was important to this chemistry that at least 2.1 equivalents of sodium hydride, and therefore dimsyl anion, were utilized as the purified yield with less than two equivalents was very poor.[85] This method was therefore adapted for the synthesis of building block **57** by first synthesizing a tert-butanesulfinate ester and then attacking it with a dimsyl anion.

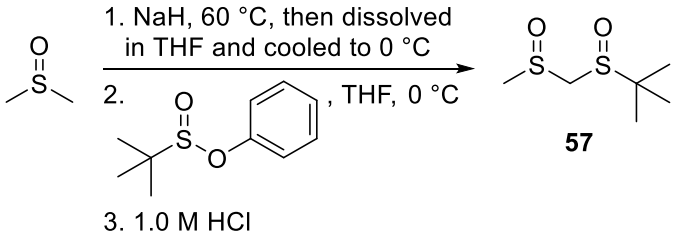


Scheme 52: Synthesis of tert-butanesulfinate **86** from tert-butyl disulfide

Phenyl tert-butanesulfinate **86** was synthesized in a three-step process starting with the oxidation of tert-butyl disulfide to tert-butyl tert-butanethiosulfinate **85**. This was performed by dissolving the disulfide in methanol, cooling the solution to 0 °C and adding an aqueous solution of sodium meta-periodate which yields thiosulfinate **85** in a 70% yield. Thiosulfinate **85** is then reacted with sulfuryl chloride in anhydrous DCM at 0 °C to yield tert-butyl sulfinyl chloride **66** in a 60% yield without the need for purification. Sulfinyl chloride **66** was then dissolved in THF and cooled to 0 °C before the addition of phenol and triethylamine which mixed overnight and yielded sulfinate **86** in a 35 to 46% yield (***Scheme 52***).

With sulfinate **86** synthesized, the focus turned to the synthesis of building block **57**. Due to the labile nature of tert-butyl functional groups and tert-butyl sulfoxides particularly, a variety of methods were attempted for the formation of building block **57** from sulfinate **86** all based on the method developed by Kunieda and coworkers.[85] The temperature and the equivalents of base were varied in order to effect the synthesis of building block **57**. The results of these experiments are summarized in ***Table 7***.

Table 7: Trials of the attempted synthesis of building block **57**



Reaction	DMSO (equiv.)	NaH (equiv.)	Reaction Temp.	Reaction Time	Product?
1	17	2.1	0 °C	1.5 hr	Trace
2	17	2.1	-30 °C	20 hr	No product
3	17	1.1	0 °C	SM not fully consumed	No product

As outlined in ***Table 7***, the synthesis of building block **57** was largely unsuccessful. The first reaction conditions produced a small amount of product (as confirmed by the ^{1}H NMR spectrum of the crude reaction material), however, the ^{1}H NMR spectrum should indicate a 1:1 ratio of the by-product phenol to building block **57** and this is not the case (***Figure 9***). Instead, there was substantially more phenol than product in the ^{1}H NMR spectra of all trials, leading to the theory that the product is destroyed after it is formed. As there are two equivalents of base in the first reaction, it is possible that the second equivalent of dimsyl anion attacks the tert-butyl

group causing the formation of the corresponding sulfenic acid which could react to form a material that was lost in the aqueous workup stage of the reaction (***Scheme 53***). Since it was not possible to isolate the product that was made, the goal of this research turned to investigating the deprotonation chemistry of β-bissulfoxides with another substrate.

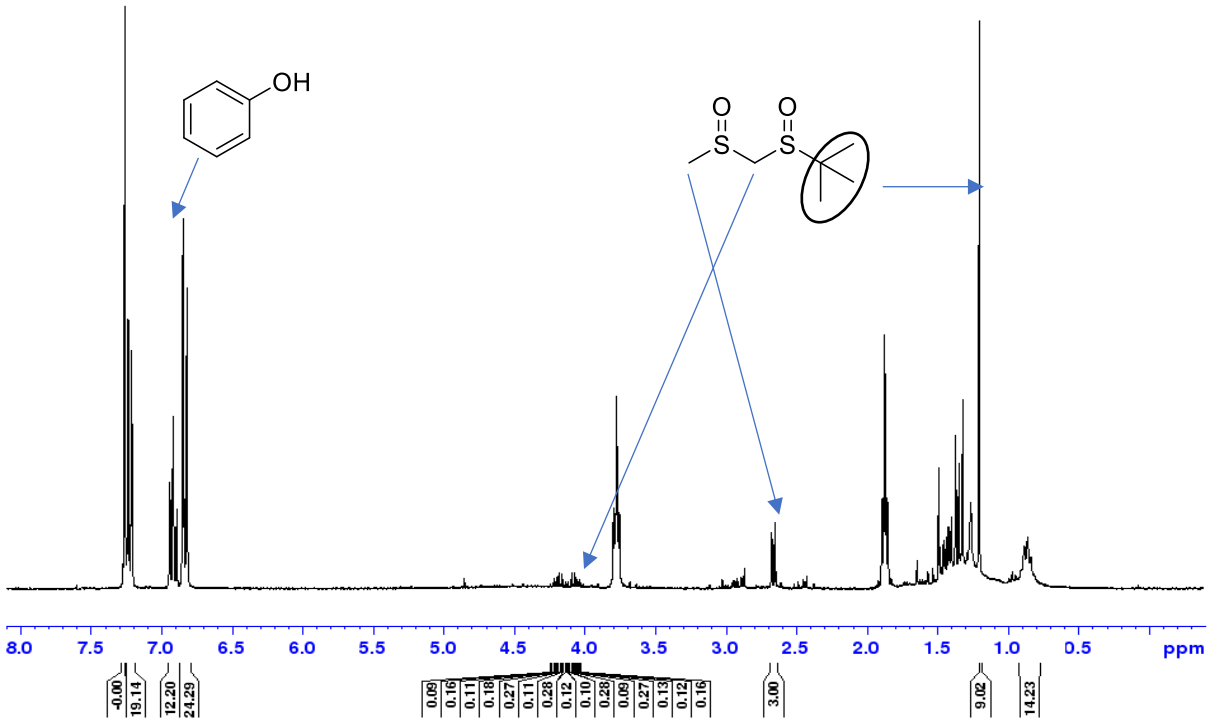
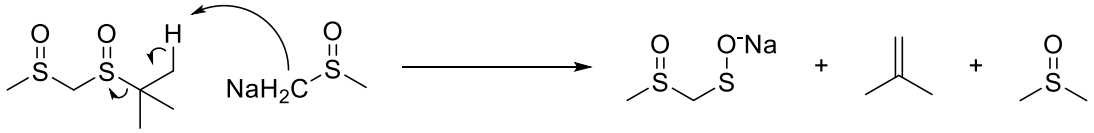


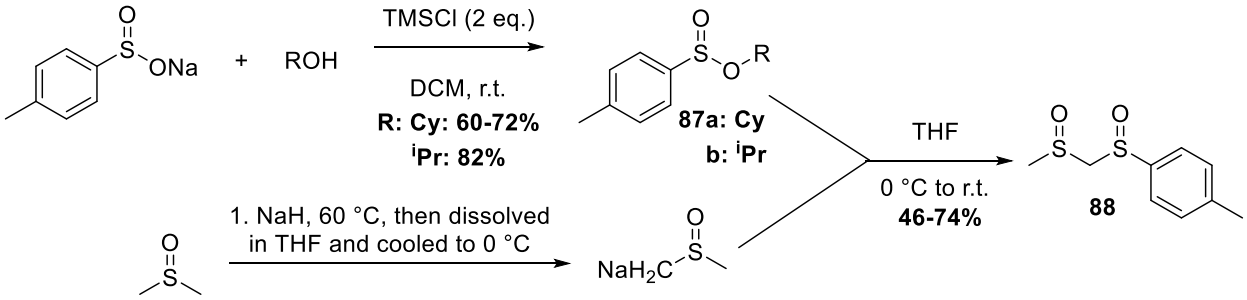
Figure 9: ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the crude reaction material of trial 1 towards the synthesis of building block **57**



Scheme 53: Proposed mechanism for the loss of building block **57** from the reaction mixture

As the synthesis of building block **57** was unsuccessful, the synthesis of p-tolyl β-bissulfoxide **88** was performed to investigate the deprotonation chemistry of such molecules. The synthesis of compound **88** was carried out in a two-step synthesis starting from sodium p-toluenesulfinate. In the first step, adapted from Yuan-Zhao and coworkers,[112] sodium p-

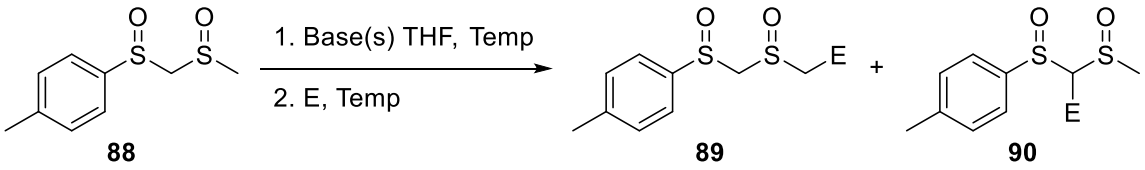
toluenesulfinate was dissolved in dry DCM and to this solution was added two equivalents of both trimethylsilyl chloride and an alcohol. This produced p-toluenesulfinate **87** in a 60 to 82% yield. Sulfinate **87** was then reacted with 2.1 equivalents of dimsyl anion (prepared according to the method utilized by Kunieda and coworkers[85]) to produce p-tolyl β-bissulfoxide **87** in a 46 to 74% yield (***Scheme 54***).



Scheme 54: Synthesis of p-tolyl β-bissulfoxide **88** from sodium p-toluenesulfinate

As compound **88** had been successfully synthesized, the deprotonation chemistry of the compound could then be analyzed. This was carried out by reacting β-bissulfoxide **88** with an excess of an electrophile (methyl iodide or benzaldehyde), varying the amount of base and analyzing the outcome of the reactions. The eventual goal of this research is to affect an α' deprotonation (***Figure 8***) such that it will react with building block **56**, forming a compound similar to sulfoxide **53**. Therefore, two or more equivalents of base were utilized as the pK_a gap between the α and α' protons is too wide to permit initial deprotonation of an α' proton. In the literature, the bases that are commonly used for this purpose are nBuLi (two or more equivalents), lithium diisopropylamine (LDA) and a combination of sodium hydride and nBuLi. [86,109–111] As such, these will be the bases utilized for this chemistry. The results of the trials which examined the deprotonation chemistry of β-bissulfoxide **88** with the goal of synthesizing sulfoxide **89** are illustrated in ***Table 8***.

Table 8: Trials towards the synthesis of sulfoxide **89**



88 **89** **90**

Reaction	Base(s) (equiv.)	Deprotonation Duration, Temp.	Electrophile (equiv.)	Reaction Temp.	Reaction Time	Compound 89 Formed?	Compound 90 Formed?
1	NaH (1.1), nBuLi (1.1)	1 hr, 0 °C	MeI (1.1)	0 °C	3 hr	No	Trace
2	LDA (2.1)	0.5 hr, -78 °C; 1 hr, 25 °C	Benzaldehyde (1.5)	-78 °C	10 hr	No	No
3	nBuLi (3.0)	1 hr, 25 °C	Benzaldehyde (0.5)	25 °C	23 hr	No	No
4	nBuLi (2.05)	0.5 hr, -78 °C	MeI (8.0)	-78 °C	22 hr	No	Trace
5	nBuLi (2.37)	0.5 hr, -78 °C	MeI (10.0)	-78 °C	21 hr	No	Trace
7	nBuLi (3.1)	1 hr, -78 °C	MeI (10.0)	-78 °C to -40 °C	16 hr	No	Trace
8	NaH (2.1), nBuLi (1.0)	1 hr, 0 °C	MeI (10)	0 °C	16 hr	No	Trace

As seen in ***Table 8***, all attempts to synthesize any form of bissulfoxide **89** from bissulfoxide **88** were unsuccessful. In all cases, the major product was recovered starting material after the times indicated in ***Table 8*** and no further progress of the reaction was observed by TLC. The only minor product detected was the monomethylated bissulfoxide **90** and it could not be isolated. As bissulfoxide **88** was a mixture of diastereomers, monomethylated bissulfoxide **90** was also always present in a mixture of multiple diastereomers which made the ^{1}H NMR spectrum more complicated to interpret but a series of equally convoluted doublets at 1.50-1.30 ppm and quartets at 3.93-3.64 ppm illustrate the formation of only the monomethylated product (***Figure 10***).

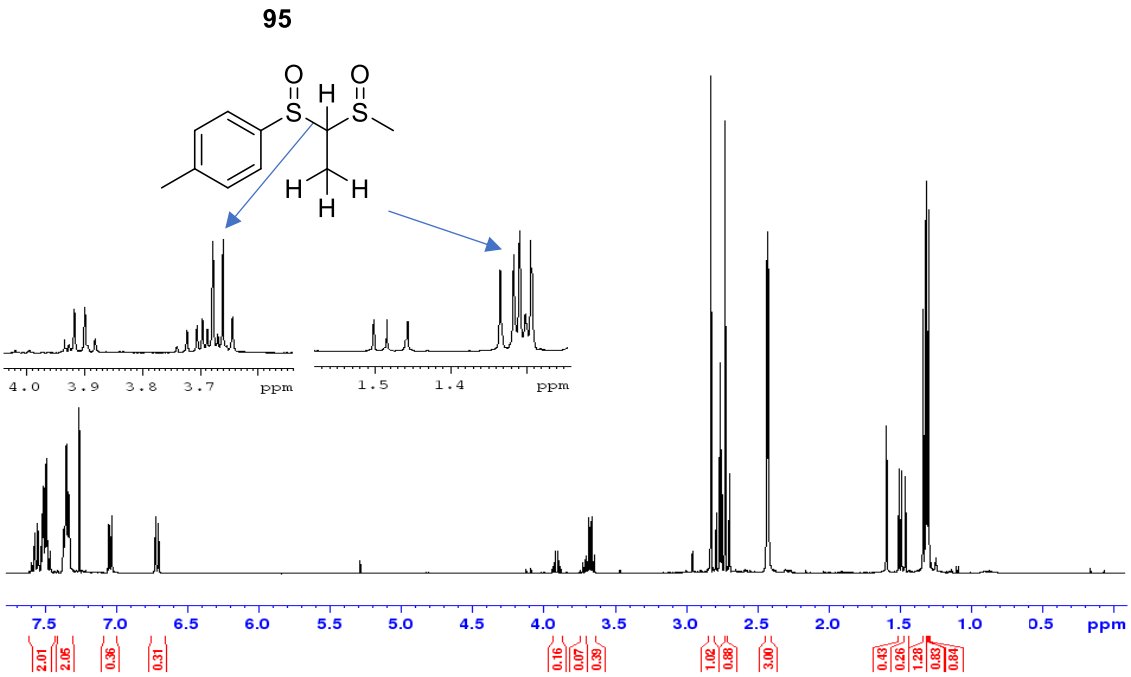
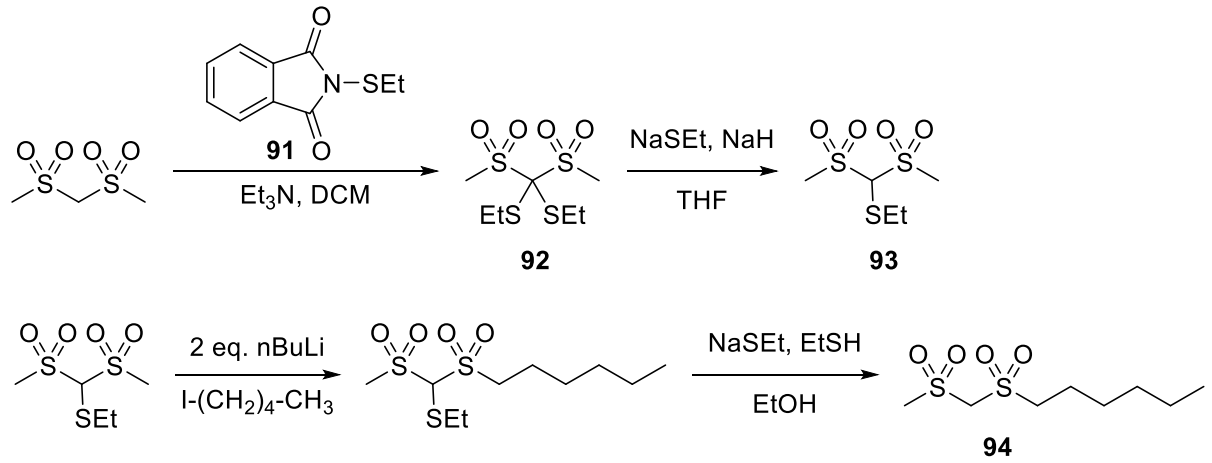


Figure 10: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of a mixture of compounds containing monomethylated bissulfoxide **90**

As this is novel chemistry, the true reason for why so little of bis-sulfoxide **88** was able to react or why, in the presence of up to 3.1 equivalents of strong base and excess methyl iodide, the only product detected was the monomethylated compound **90** and not a doubly or triply methylated bissulfoxide is unknown. However, previous studies on the functionalization of bis-sulfoxides, such as bis-p-tolylsulfinyl methane, have also encountered the issue of exclusive monofunctionalization at the central carbon despite multiple equivalents of base and electrophile being present.[113,114] One possible explanation for this would be the coordination of the lithium and sodium of the bases to the sulfoxides in bissulfoxide **90** preventing the base from acting upon the acidic protons in the molecule.[115,116] The focus of this project shifted from this to the protection of the middle carbon of bissulfoxide **88** in order to induce α'-methylation. The attempted protection chemistry is detailed in the next section.

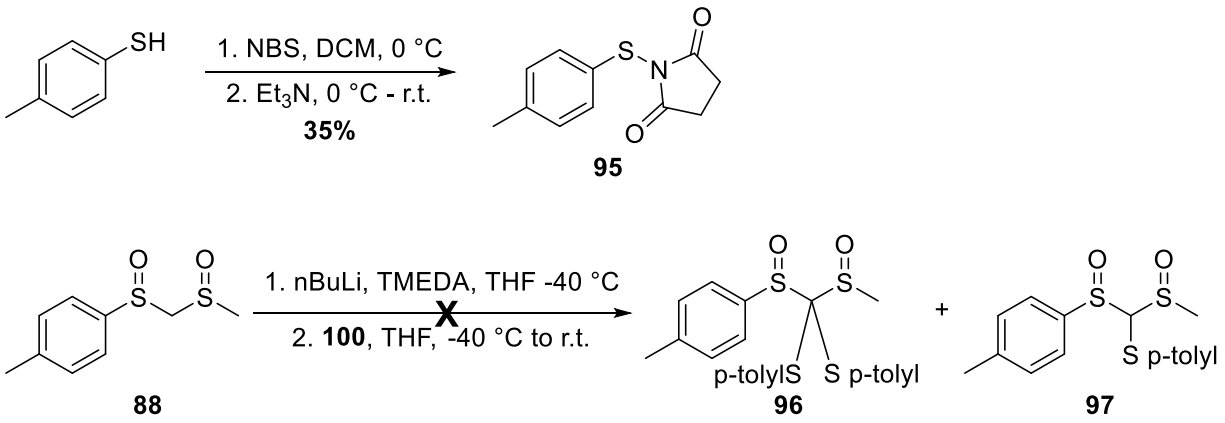
2.2.2 Protection of β-Bissulfoxides

As previously stated, the addition of multiple equivalents of base to β-bissulfoxide **88** was only able to afford the synthesis of the mono α-substituted product (**90**). However, when a similar problem was encountered while investigating the deprotonation chemistry of β-sulfonyl sulfones, Zhu and Drueckhammer[117] proposed a method for the protection of the α-carbon such that the α'-carbon could be deprotonated more easily.



Scheme 55: Protection of the α-carbon of β-sulfonyl sulfones in order to achieve a clean α'-alkylation

The research performed by Zhu and Drueckhammer[117] showed that reacting a β-sulfonyl sulfone with two equivalents of ethylthio phthalimide **91** led to the synthesis of thioketal **92** which was then reduced to thioether **93**. Compound **93** could then be subject to two equivalents of base and an alkyl halide to afford α'-alkylation before the ethylthio group was removed via a reaction with ethanethiol, ethanethiolate, and ethanol to afford β-sulfonyl sulfone **94**.[117] Due to the similarities between the β-bissulfoxide and β-sulfonyl sulfone deprotonation chemistry, there was value in investigating the synthetic utility of this method for protecting the α-carbon of β-bissulfoxide **88**.



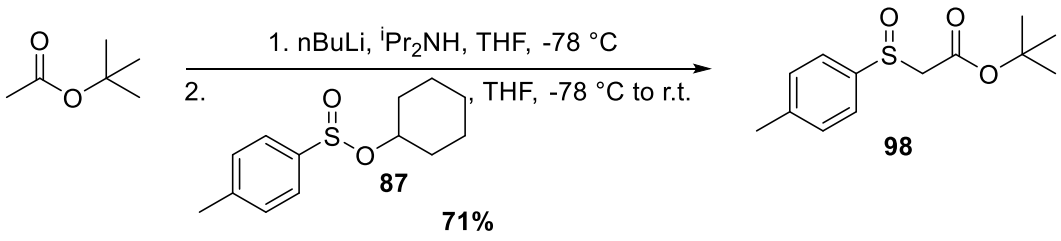
Scheme 56: Synthesis of p-tolylthio succinimide **95** and attempted protection of β-bissulfoxide **88**

Replacing ethylthio phthalimide for the attempted protection of β-bissulfoxide **88** was p-tolylthio succinimide **95** which was synthesized in a 35% yield by reacting p-toluenethiol with N-bromo succinimide and triethyl amine in DCM (***Scheme 56***). β-bissulfoxide **88** was then subjected to two equivalents of nBuLi and TMEDA for 1 hour at -40 °C before the addition of two equivalents of thiosuccinimide **95** (***Scheme 56***). Despite the disappearance of the β-bissulfoxide **88** starting material, it was unclear by the ^{1}H NMR spectrum of the crude reaction material, post quench with water, if either thioketal (**96**) or thioether (**97**) had formed. All attempts to purify the mixture were unsuccessful and therefore this protection pathway was abandoned. Future attempts could investigate using a small protecting group, such as the ethylthio group, to achieve this chemistry.

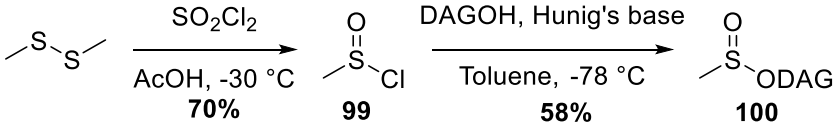
Another method attempted for the protection of the α-carbon of β-bissulfoxide **88** involved the use of the common tert-butyloxycarbonyl (Boc) group. The Boc group has been utilized extensively to protect amines and has been shown to be easily removed from the α-carbon of biscarbonyl compounds.[118,119] It is unknown if the Boc group aids with the deprotonation of the α'-carbon, but the ease of removal of the group provided the value of performing this research.

Due to the failures of installing the thioether groups onto compound **88** (*Scheme 56*), reacting it with tert-butyl bromoacetate was not attempted and instead, the synthesis of β-sulfinyl ester **98** was the initial goal of this research. This synthesis of β-sulfinyl ester **98** was achieved via a reaction, adapted from Rivero and coworkers,[120] between tert-butyl acetate and sulfinate **87a** at -78 °C. This yielded β-sulfinyl ester **98** in a 71% yield after purification by column chromatography (*Scheme 57*).

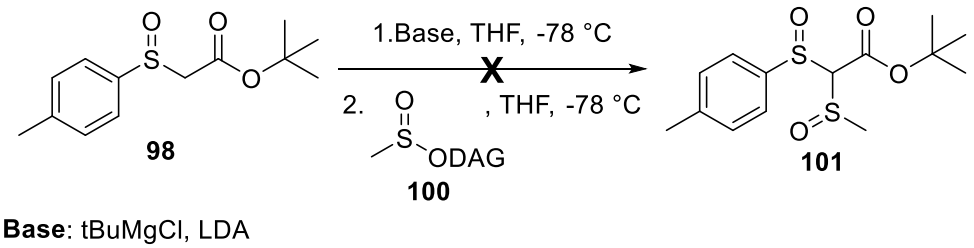
The next step in this synthesis involves the deprotonation of β-sulfinyl ester **98** before the addition of an electrophilic source of a methyl sulfoxide. The chosen electrophile was the methanesulfinate ester of diacetone glucose **100**. Sulfinate ester **100** was synthesized by first treating dimethyl disulfide with sulfuryl chloride and acetic acid to produce methanesulfinyl chloride (**99**) in a 70% yield (*Scheme 58*). Sulfinyl chloride **99** was then treated with Hunig's base and diacetone glucose (DAG) in toluene at -78 °C to yield sulfinate ester **100** in a 58% yield (*Scheme 58*).



Scheme 57: Synthesis of β-sulfinyl ester **98**



Scheme 58: Synthesis of sulfinate **99** from dimethyl disulfide



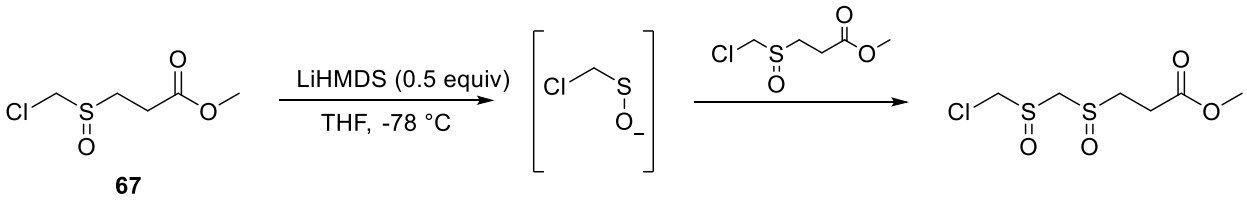
Scheme 59: Attempted syntheses of protected β-bissulfoxide **106**

A number of conditions were tested for their potential in synthesizing tert-butyl 2-methanesulfinyl-2-(4-methylbenzenesulfinyl)acetate (**106**) from β-sulfinyl ester **98** (***Scheme 59***). Sulfinate **99** was utilized as the source of the second sulfinyl group in compound **101**. Tert-butyl magnesium chloride was utilized as a base due to its past use to deprotonate and functionalize compound **98** at the central carbon.[121] Unfortunately all methods attempted were unable to synthesize compound **101**, and thus this protection method was discontinued. Future efforts for the synthesis of compound **101** should investigate the use of a smaller electrophilic sulfur source, such as sulfinyl chloride **100**, as the bulky nature of sulfinate **99** could have prevented a reaction from taking place.

2.3 Synthesis of Building Block 67 and the Iterative Sulfenate Release

So far, no viable means of preparing lentinic acid analog **53** have been discovered as the synthesis of building block **56** and **57** proved unsuccessful. Investigations into the deprotonation chemistry of β-bissulfoxides yielded unfavourable results as no attempt successfully rendered the α'-carbon of a β-bissulfoxide to be deprotonated and therefore nucleophilic. As such, another method to access a lentinic acid analog had to be explored. Since previous attempts to form the target were grounded in sulfinate and sulfinamide chemistry, sulfenate chemistry was chosen to be the next method as it has been a focus of the Schwan group for many years. Also, the

development of new techniques pertaining to sulfenate chemistry would be beneficial for the Schwan group.



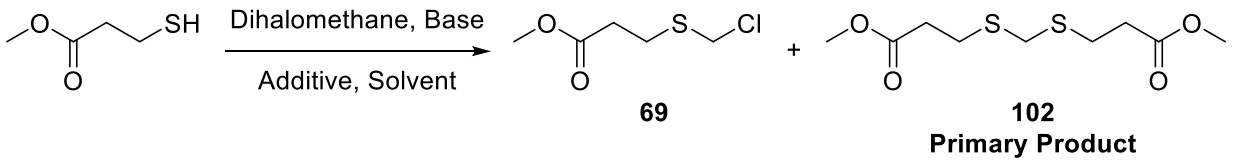
Scheme 60: Iterative sulfenate release

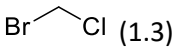
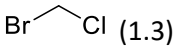
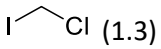
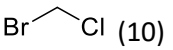
The initial goal of this research is the synthesis of α-chloro sulfoxide **67** such that an iterative sulfenate release can be attempted (***Scheme 60***). If successful, an iterative sulfenate release can be utilized to synthesize the sulfoxide chain in lentinic acid **4** with the ability to functionalize both sides for building larger molecules. To achieve an iterative sulfenate release, compound **67** will be subject to half an equivalent of base to release half an equivalent of an α-chloro sulfenate anion which will attack the remaining compound **67** in solution (***Scheme 60***).

2.3.1 Synthesis of Building Block 67

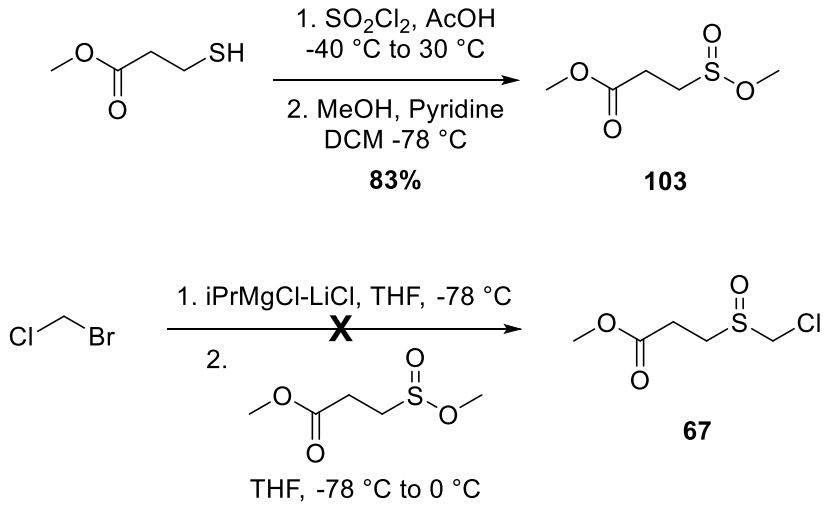
The synthesis of building block **67** was attempted via various methods with varying degrees of success. Access to starting materials centered around the synthesis of α-chlorosulfide **69** by reacting methyl 3-mercaptopropionate with dihalomethanes in the presence of a base. The outcomes of these trials are displayed in ***Table 9***. Every one of these methods resulted in the formation of bissulfide **102** despite the large excess of the dihalomethane compared to thiol in the reaction. Trial 1 did produce some product; however, it could not be purified by column chromatography and was likely hydrolyzed by the silica gel. This strategy for synthesizing building block **67** was quickly discarded.

Table 9: Initial trials towards the synthesis of compound **67** from methyl 3-mercaptopropionate and dihalomethanes



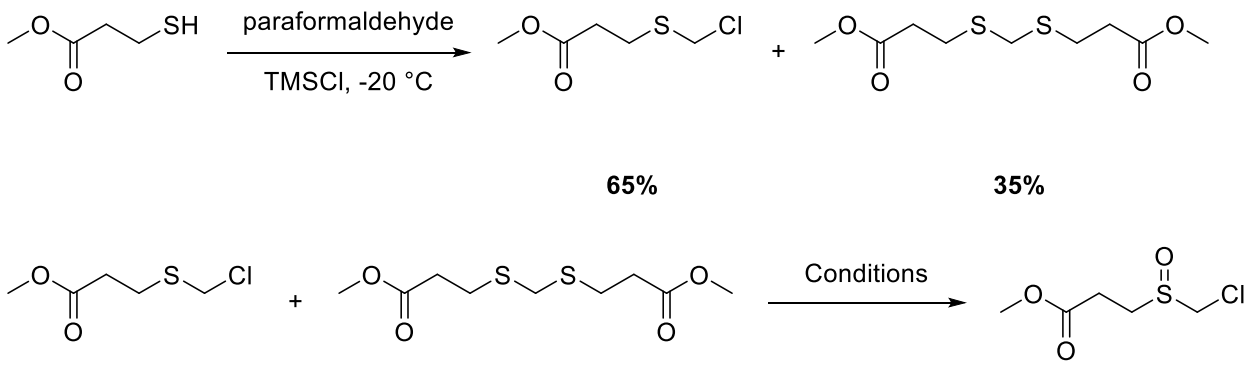
Reaction	Dihalomethane (equiv.)	Base (equiv.)	Additive (equiv.)	Solvent	Reaction Time	Product?
1	 (1.3)	KOH (1.4)	TEBAC (0.4)	DCM	0.5 hr	Trace
2	 (1.3)	KOH (1.4)	TEBAC (0.4)	Dry DCM	2 hr	No product
3	 (1.3)	KOH (1.4)	TEBAC (0.4)	Dry DCM	48 hr	No product
4	 (10)	DBU (1.2)	N/A	CH_3CN	72 hr	No product

The next technique attempted for the synthesis of building block **67** was to utilize sulfinate and Grignard chemistry. A Grignard reaction between methyl 3-(methoxysulfinyl)propanoate **103** and the Grignard reagent of a dihalomethane was attempted in order to synthesize building block **67**. Methyl 3-mercaptopropionate was first treated with sulfuryl chloride and acetic acid to convert the thiol into the corresponding sulfinyl chloride.[122] Methanol and pyridine were mixed together in DCM, and then the sulfinyl chloride mixture was added to the methanol mixture, forming sulfinate ester **103** in a one-pot synthesis.[123] The Grignard reaction began with mixing bromochloromethane and an isopropylmagnesium chloride lithium chloride complex solution at -78 °C for 20 minutes before the addition of compound **103**. Unfortunately, the substitution of the Grignard reagent was unsuccessful and building block **67** could not be formed by this method (***Scheme 61***).



Scheme 61: Attempted synthesis of building block **67** via sulfinate and Grignard chemistry

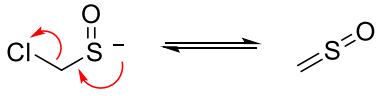
As the sulfinate and Grignard chemistry was unsuccessful, the final method attempted involved a chloromethylation of methyl 3-mercaptopropionate adapted from Turchaninova and coworkers.[124] It involves the reaction of methyl 3-mercaptopropionate with paraformaldehyde and trimethylsilyl chloride in order to synthesize chloromethyl sulfide **69**. This reaction led to the synthesis of a 65: 35 mol% ratio of sulfide **69** to bissulfide **102** (***Scheme 62***). Due to difficulties purifying sulfide **69**, this mixture was oxidized via two different methods in order to synthesize sulfoxide **67**, as similar chloromethyl sulfoxides have been isolated by column chromatography previously.[125] To oxidized this mixture two different methods were attempted; both having the moles of the oxidant match the number of moles of sulfur present in the reaction. The first method utilized *m*-CPBA as the oxidant and this did not produce building block **67** from the mixture. The second method attempted utilized sulfuryl chloride, silica gel, and water in DCM at room temperature to oxidize sulfide **69**. This resulted in an isolated yield of sulfoxide **67** of 1% compared to the initial amount of TMSCl (***Scheme 62***). While this provided enough material to attempt subsequent reactions, purification of sulfide **69** by vacuum distillation prior to the oxidation would likely lead to higher yield of sulfoxide **67** in the future.



Scheme 62: Synthesis of methyl 3-chloromethanesulfinylpropanoate **67**

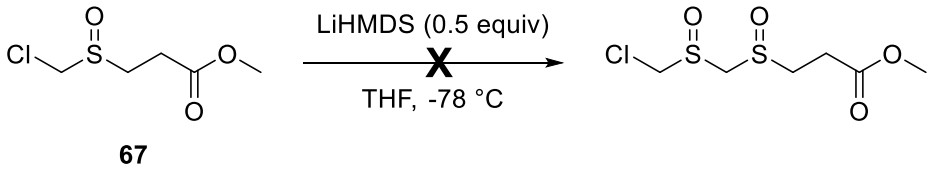
2.3.2 Iterative Sulfenate Release

With α-chlorosulfoxide **67** synthesized, the goal of this research turned to attempting to release the sulfenate anion of compound **67** and have this sulfenate anion attack another molecule of compound **67**. As compound **67** is a Perrio-type sulfenate precursor, meaning that it is a β-sulfinyl ester, the method for the release of the sulfenate in this case is to induce a base mediated retro-fragmentation of the sulfoxide.[126] Previous research in the Schwan group has shown that the optimal base for sulfenate anion release in this chemistry is lithium bis(trimethylsilyl)amide (LiHMDS). The issue with this reaction would be the stability of the sulfenate anion which is released. The concern stems from the potential of the sulfenate anion to form a sulfine which would not have the same reactivity as the equivalent sulfenate anion (***Scheme 63***). As such, the reaction will be kept at -78 °C to prevent the formation of a sulfine.



Scheme 63: Sulfine formation from an α-chloro sulfenate anion

An attempted iterative sulfenate release was carried out by first cooling a THF solution of sulfoxide **67** to -78 °C before the addition of half an equivalent of LiHMDS (***Scheme 64***). The reaction was left to mix for 1 hour at -78 °C before allowing the reaction to warm to -35 °C overnight. A ^{1}H NMR spectrum of the crude reaction material, post quench with a saturated NH_4Cl solution, showed no product formation and that only starting material remained. As the mass of the crude material was about half of the original starting material, a possible conclusion is that the sulfenate anion was formed, but quickly converted into a sulfine before it was able to react with the remaining amount of compound **67**. Due to sulfine formation at -78 °C, this method of synthesizing a lentinic acid analog was discontinued.

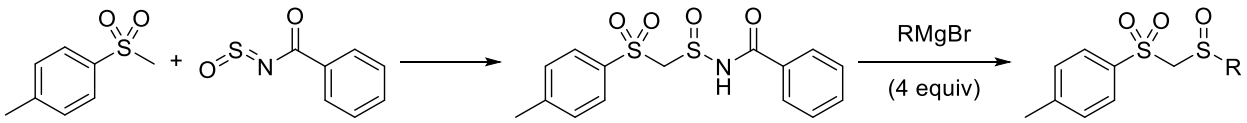


Scheme 64: Attempted iterative sulfenate release of sulfoxide **67**

2.4 Conclusions and Future Work

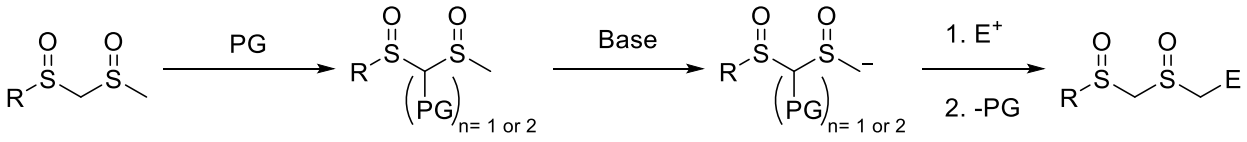
In conclusion, the synthesis of a lentinic acid analog utilizing the methods outlined in ***Scheme 28*** and ***Scheme 35*** was unsuccessful. The synthesis of building block **56** was not achieved as dimethyl sulfone proved to possess unpredictable reactivity with all substrates attempted. The methods which did not involve dimethyl sulfone led to some success in the way of the synthesis of sulfinamoyl sulfone **72** but the inability to protect the nitrogen of compound **72** prevented the synthesis of compound **56** by this method. Future work could examine different protection methods of compound **72** or the use of N-sulfinylbenzamide instead of N-sulfinylaniline as

sulfinamides that possess benzamide have been shown to react with organometallic nucleophiles to create sulfoxides without the need for further protection (***Scheme 65***).[69]



Scheme 65: Synthesis and subsequent functionalization of the N-benzamide form of building block **56**

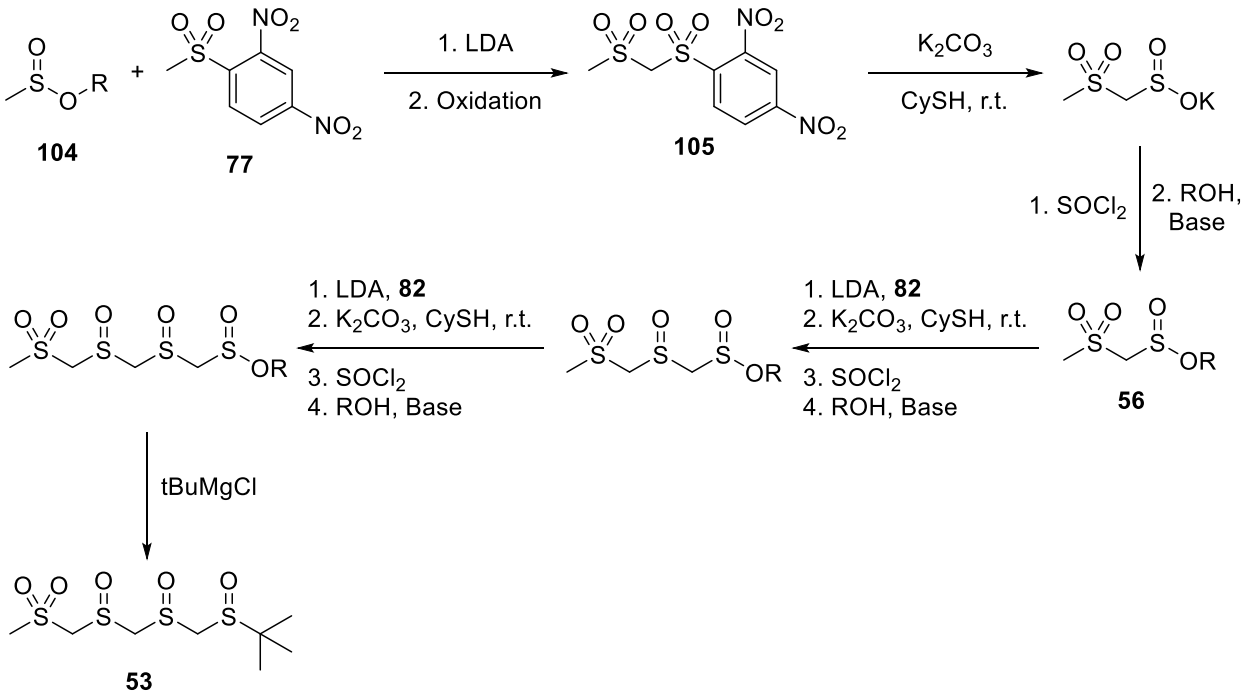
The synthesis of building block **57** was also unsuccessful due to the reactive nature of the tert-butyl group. However, a p-tolyl β-bissulfoxide (**88**) was synthesized from a dimsyl anion and a p-tolyl sulfinate ester. The deprotonation chemistry of **88** was analyzed by reacting it with various equivalents of base and in the presence of an excess of electrophilic species to determine if the α'-carbon could be made more nucleophilic than the α-carbon (***Figure 8***). It was found that no matter the amount of base added, a single α-carbon (***Figure 8***) alkylation was always the outcome. As such, the use of Boc and thioethers to protect the α-carbon were attempted to affect an α'-carbon alkylation but the synthesis of the α-protected β-bissulfoxides were unsuccessful. Subsequent work in this chemistry could involve use of a different α-protecting group such that the α'-carbon alkylation of β-bissulfoxides can be achieved (***Scheme 66***).



Scheme 66: Protection of the α-carbon of β-bissulfoxides for the a'-functionalization of β-bissulfoxides

As the synthesis of tert-butyl sulfoxide **53** (lentinic acid analog) could not be achieved through the use of building blocks **56** and **57** and the method outlined in ***Scheme 28***, the goal of the research moved to the synthesis of compound **54** via an iterative sulfenate release. Iterative

sulfenate precursor molecule **67** was synthesized from methyl 3-mercaptopropionate in a two-step process before the iterative sulfenate release was attempted. However, the instability of the α-chloro methanesulfenate anion, leading to the formation of a sulfine (***Scheme 63***) led to the iterative sulfenate release being unsuccessful.



Scheme 67: Proposed future synthesis of lentinic acid analog **53**

Future work in this project could investigate the use of a 2,4-dinitrophenyl or 4-nitrophenyl methyl sulfone for the synthesis of a lentinic acid analog. In *Section 2.1.4,* it was shown that 2,4-dinitrophenyl methyl sulfone (**77**) can be converted into a potassium methanesulfinate salt *in situ* through a reaction with cyclohexyl thiol and potassium carbonate. If compound **77** can be added to a methylsulfinate ester (**104**), this would synthesize β-bissulfone **105** after an oxidation, which can then be converted into building block **56**. The reaction between compound **105** with cyclohexyl thiol and potassium carbonate would synthesize the corresponding potassium sulfinate salt, which

can then be reacted with thionyl chloride to synthesize the corresponding sulfinyl chloride. A subsequent reaction of the sulfinyl chloride with an alcohol is anticipated to produce building block **56** (*Scheme 67*). Repeating the sulfone attack and conversion to sulfinate ester two more times would deliver a compound that can be transformed into compound **53** by the attack of tert-butyl Grignard. This synthetic pathway should be investigated for the potential to synthesize a lentinic acid analog as the other methods described in this section have been unsuccessful.

If future work can synthesize a lentinic analog, the subsequent steps would first involve the development of a method for synthesizing lenthionine from that lentinic acid analog. Once that has been performed, the next step would involve investigating if the stereochemistry of the sulfoxides in the lentinic acid analog affect the synthesis of lenthionine and tracking the conversion of the lentinic acid analog to lenthionine to gain insight into the mechanism for conversion. The lentinic acid analog should also be utilized for the synthesis of lentinic acid **4** such that the natural configurations of the sulfoxides can be identified.

Part 2: Optimizing the Synthesis of Allenyl Sulfoxides from Thiosuccinimides

ABSTRACT

OPTIMIZING THE SYNTHESIS OF ALLENYL SULFOXIDES FROM THIOSUCCINIMIDES

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University of Guelph, 2021

Advisor:
Professor A. L. Schwan

Due to their value in natural product synthesis and potential in stereoselective reactions, allenes are of great interest. Investigation in the Schwan group has focused on the synthesis of allenyl sulfoxides, but no universally optimized method for this purpose had been found. The focus of this research was the optimization of work performed by previous Schwan group members for the synthesis of allenyl sulfoxides from thiosuccinimides via a [2,3]-sigmatropic rearrangement. The primary objective was optimizing the yields of various allenyl sulfoxides by varying the reaction temperature and basic conditions of the reaction between thiosuccinimides and propargyl alcohols. The secondary objective was the synthesis of various allenyl sulfoxides utilizing the optimized conditions. The use of chloroform and K_2CO_3 at 50 °C was determined to be the optimal conditions for the synthesis of most allenyl sulfoxides and these conditions were utilized for the synthesis of 20 allenyl sulfoxides from thiosuccinimides.

Chapter 3: Introduction

3.0 Introduction

Allenyl sulfoxides have been a topic of great interest due to their potential for stereoselective reactions, use in the pharmaceutical industry as well as their value in natural product synthesis as cyclizable intermediates.[127–129] Initial studies in the Schwan group attempted to synthesize allenyl sulfoxides through the standard reaction of sulfenyl chlorides with propargyl alcohols, which is typically followed by a [2,3]-sigmatropic rearrangement, for the purposes of exploring their utility in sulfenate alkylation chemistry.[50] This approach was marginally successful using specific substrates which were sought for further studies in sulfenate chemistry. To optimize the process, finding a replacement for the sulfenyl chlorides became a primary interest as the instability of aliphatic sulfenyl chlorides has been illustrated as problematic in the past.[130] A preliminary study showed that sulfenamides, thiosuccinimides in particular, were the most successful for forming the sulfenic esters that would undergo a [2,3]-sigmatropic rearrangement to form the desired allenyl sulfoxides.[131] In the following sections will discuss the allene functionality, synthesis of allenes by [2,3]-sigmatropic rearrangement and the synthetic utility of thiosuccinimides as electrophilic sulfenylating reagents.

3.1 The Allene Functionality

An allene is a functional group with 2 orthogonal π-bonds on a single carbon. This orthogonality causes an allene to be an axially chiral functional group (***Figure 11***). As there are a variety of reactive modes of allenes as well as many methods for synthesizing allenes, especially with stereoselectivity, they have become very useful in organic synthesis. Typical methods for the formation of allenes include treatment with aluminum hydride reagents, skeletal rearrangements, direct homologations, β-eliminations, and transition metal catalyzed reactions.[132] As the

numerous methods for formation indicate, allenes can be synthesized from many sources such as alkynes, cyclopropanes, alkenes, conjugated enynes and other allenes.[128]

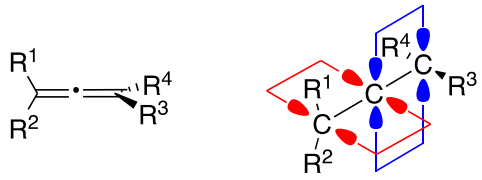
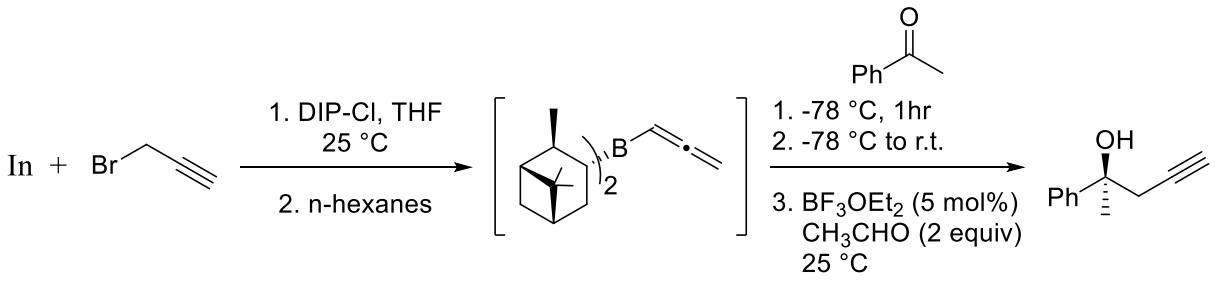


Figure 11: Orthogonal π-systems of an allene

3.1.1 Reactivity of Allenes

Allenes can undergo several transformations including cycloadditions, epoxidations, cyclizations, and allenylmetal reactions with carbonyl compounds and their derivatives. Recently, the use of allenylindium reagents in reactions with carbonyl compounds for the formation of homopropargyl alcohols has become a great interest due to the aqueous stability of organoindium reagents.[133] Allenylindium reagents are formed by reacting propargyl halides with indium metal which proceed to isomerize to the corresponding allenylindium reagent if the substituent on the initial propargyl bromide is not bulky (methyl or hydrogen substituents only).[133] Recently, allenylindium reagents have also been used in the synthesis of *β*-substituted diisopinocampheylborane compounds as these are excellent reagents for the synthesis of enantiomerically enriched products.[134] In this work, performed by Hirayama and coworkers, [134] they synthesized *β*-substituted allenyldiisopinocampheylborane utilizing Barbier-type conditions from *β*-chlorodiisopinocampheylborane and reacted it with acetophenone in order to assess the enantiomeric excess (ee) of the homopropargyl alcohol (***Scheme 68***). [134] They found this method produced the homopropargyl alcohols in yields up to 97% and ee up to 41%.[134]

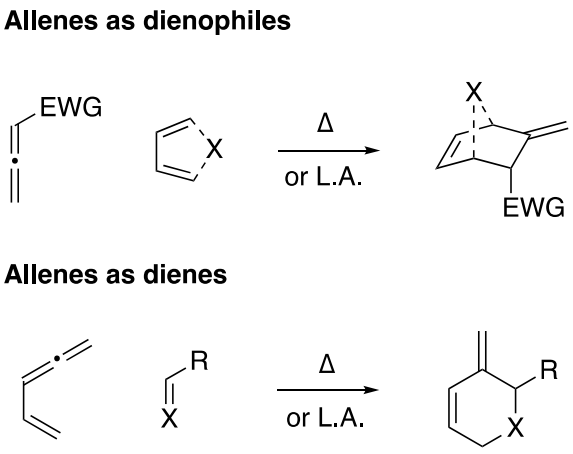


Scheme 68: Synthesis of homopropargyl alcohols with allenylindium and allenylborane reagents

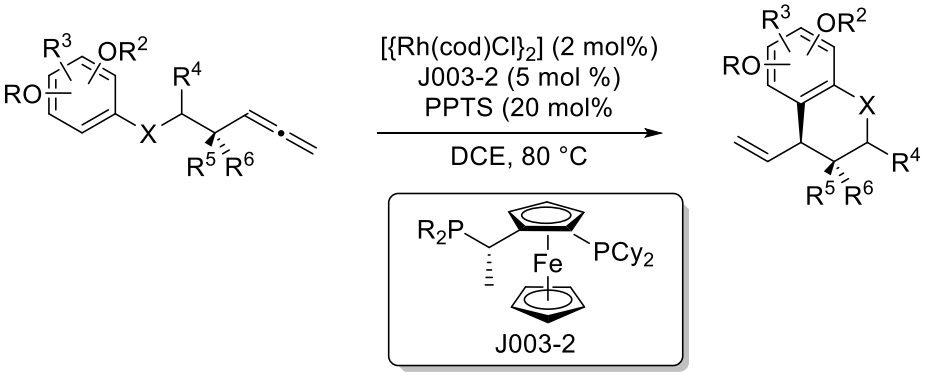
Allenes are also able to undergo cycloadditions mostly as part of [2+2] and [4+2] cycloadditions. The formation of a four-membered ring can be carried out through a [2+2] cycloaddition between an allene and α,β-unsaturated ketone. This forms a functionalized four-membered ring that has value on its own, but this ring can also succumb to further transformations into polycyclic compounds or other functionalized cyclobutanes. Additionally, the cyclobutanes can undergo ring expansions or ring openings via electrophilic attacks. Allenes can also undergo [4+2] cycloadditions such as the Diels-Alder and hetero Diels-Alder reactions. In these reactions, an allene can act as both the diene and dienophile, but it is important to note that when using a vinylic allene only one of the carbon-carbon double bonds in the allene is participating in the reaction. The use of Lewis acid conditions, rather than thermal conditions, has shown to improve regioselectivity as well as overall reaction time. The regio- and stereoselectivity of the products of the Diels-Alder reactions with allenes can be determined by examining the secondary orbital interactions, steric effects and electronic effects of the substituents on the starting compounds.[135]

Along with cycloadditions, cyclization reactions of allenes are very well known and have interest surrounding them as they are a series of reactions that have the ability to synthesize medium-sized functionalized ring systems. A recent example of allenes being utilized for the synthesis of medium-sized functionalized ring systems is illustrated in the work of Berthold and coworkers.[136] The researchers attempted to access functionalized benzocycles through

intramolecular hydroarylation of allenes. Prior to their work, these α-chiral benzocycles were synthesized through an intramolecular cyclization involving the attack on a functionalized allylic system which violates atom economy principles. [136] To get around this, Berthold and coworkers[136] proposed a set of conditions that would lead to an asymmetric cyclization of allenylarenes producing the desired benzocycles while following the rules of atom economy. The conditions consisted of the use of a rhodium catalyst with a ferrocene-based phosphine ligand and pyridinium p-toluene sulfonate and this led to yields of up to 99% and ee up to 99% (***Scheme 70***).[136]

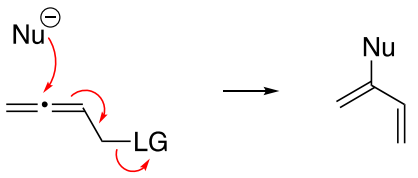


Scheme 69: Participation of allenes as both dienes and dienophiles in Diels-Alder reactions

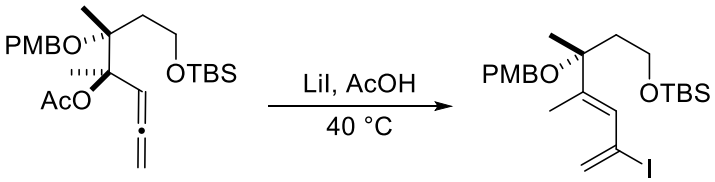


Scheme 70: A rhodium-catalyzed intramolecular asymmetric cyclization of allenyl arenes

Furthermore, allenes containing a good leaving group at the α-position can undergo isomerization to synthesize 1,3-conjugated dienes upon the attack of a nucleophile at the center carbon of the allene (***Scheme 71***). This chemistry has been utilized in the synthesis of various natural products including when it was utilized by Mandal and coworkers[137] in the synthesis of a diene-containing fragment of Amphidinolide B1. This was realized by first forming an allenyl acetate through an attack of ethynyl magnesiumbromide on a ketone, followed by a homologation and acetylation. [137] The diene was then formed by the addition of lithium iodide which displaced the acetyl group and formed the functionalized 1,3-conjugated diene (***Scheme 72***). [137]



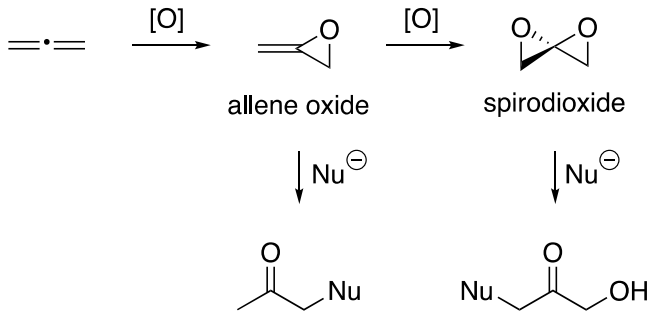
Scheme 71: Addition/elimination mechanism of allenes bearing a good leaving group at the α-position



Scheme 72: Synthesis of a conjugated diene containing fragment of Amphidinolide B1

Another functional group that can be synthesized starting from an allene is an α-functionalized acyclic ketone and which proceeds through the epoxidation of an allene. The first step is the epoxidation of the allene using an oxidant such as dimethyldioxirane (DMDO) which forms the allene oxide and further oxidation can lead to the formation of a spirodioxide.[135] Both of these compounds are susceptible to nucleophilic attack which can lead to the formation of an α-substituted ketone and α-substituted α-hydroxy ketone respectively (***Scheme 73***). [135] The

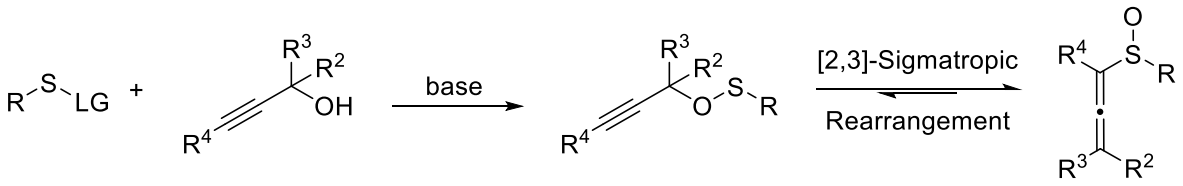
regiochemistry of the initial oxidation to the allene oxide is important as the most electron-rich double bond will be oxidized and it will always give the less hindered product. [135]



Scheme 73: Oxidation of subsequent nucleophilic attack of allenes

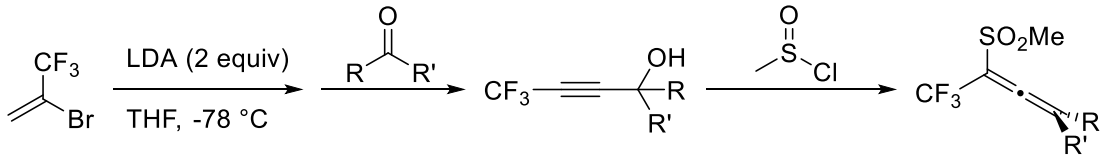
3.1.2 Synthesis of Allenes utilizing a [2,3]-Sigmatropic Rearrangement

This research is focused on the synthesis of allenyl sulfoxides and thus, the methods of preparing allenyl sulfones are important as they can serve as a model for how the allenyl sulfoxides should be synthesized. Allenyl sulfones can be synthesized by isomerisation of propargylic or alkynyl sulfones, α-functionalization of pre-existing allenyl sulfone, oxidation of allenyl thioethers, and [2,3]-sigmatropic rearrangement of propargylic sulfinates/ sulfinate esters.[138] Preliminary studies by the Schwan group illustrated that the [2,3]-sigmatropic rearrangement method would be the best for the synthesis of various allenyl sulfoxides.[131,139] This is a common method for synthesizing functionalized allenes so this method was adopted for investigation. To access allenyl sulfoxides using the [2,3]-sigmatropic rearrangement, a propargyl alcohol must act as a nucleophile on a sulfenyl group bearing a good leaving group creating a sulfenate ester which would rearrange to form the allenyl sulfoxide (***Scheme 74***).



Scheme 74: Proposed synthesis for allenyl sulfoxides via [2,3]-sigmatropic rearrangement

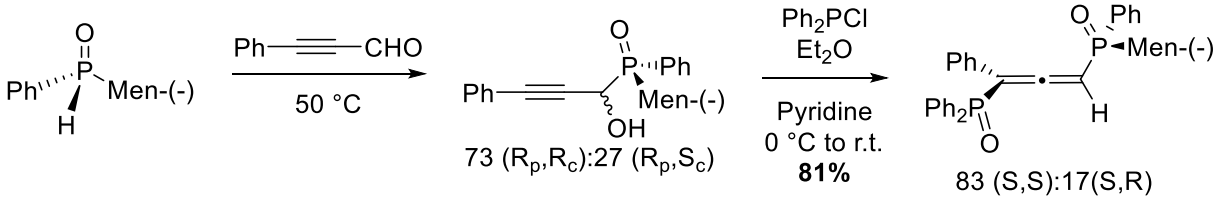
As previously outlined, the [2,3]-sigmatropic rearrangement is useful for the synthesis of allenyl sulfones. This process often involves a nucleophilic substitution of a propargyl alcohol onto a sulfinyl halide or sulfinate ester creating a propargyl sulfinate ester which then undergoes the sigmatropic rearrangement to form the corresponding allenyl sulfone. This method for synthesizing allenyl sulfones was utilized recently by Li and coworkers[140] in 2017 for the synthesis of the highly functionalized 1-sulfonyl-1-triflurormethyl allenes (***Scheme 75***). The trifluoromethyl functional group has various uses in the medicinal chemistry industry as its lipophilicity properties are useful for fine-tuning properties such as water-solubility in medicinal compounds.[138]



Scheme 75: Synthesis of 1-sulfonyl-1-trifluoromethyl allenes by [2,3]-sigmatropic rearrangement

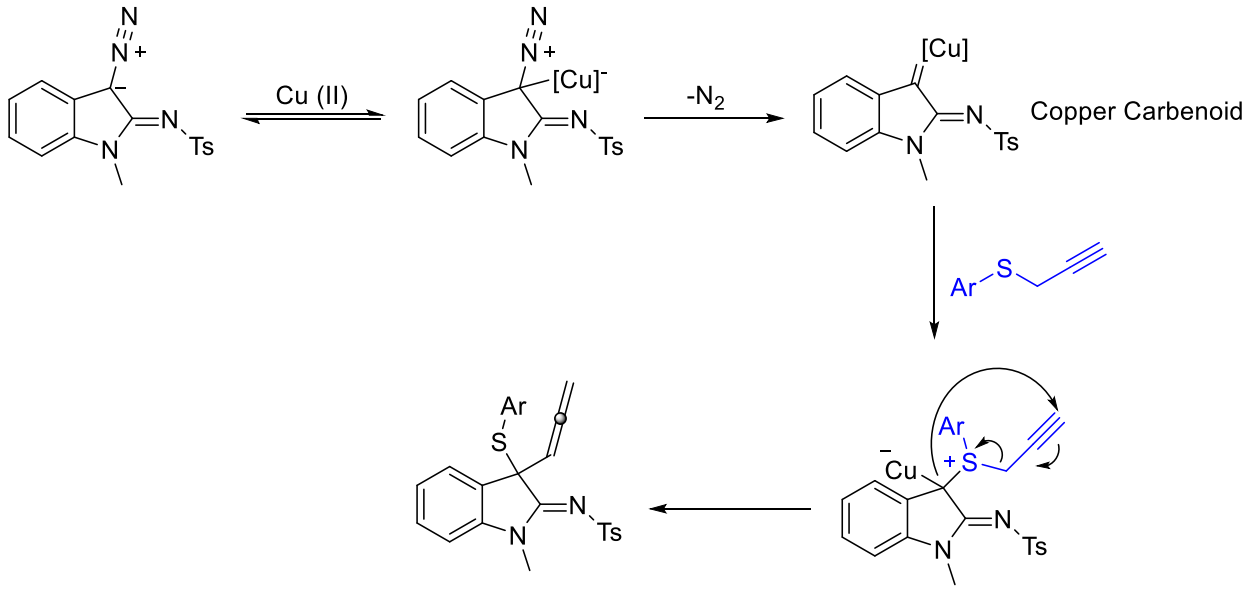
The [2,3]-sigmatropic rearrangement has also been useful in the synthesis of various chiral ligands and catalysts that contain an allenic component. Recently, Qui and coworkers[141] investigated the synthesis of chiral tertiary phosphines containing an allene functional group for use in asymmetric catalysis. The authors planned to synthesize these compounds by reacting chiral α-phosphoryl propargyl alcohols with chlorodiphenylphosphine followed by a [2,3]-sigmatropic rearrangement to afford chiral allenyl 1,3-bisphosphine oxide (***Scheme 76***). [141] This example of

the [2,3]-sigmatropic rearrangement illustrates its ability to transfer chirality from the starting material as the d.r. of the products were as high as 99:1 for many examples.[141]



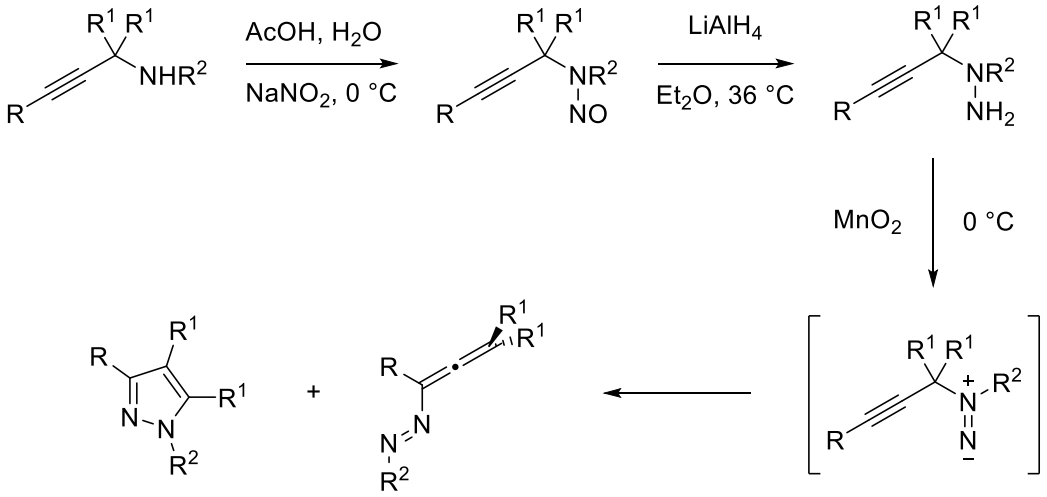
Scheme 76: Synthesis of chiral allenyl 1,3-bisphosphine oxides via [2,3]-sigmatropic rearrangement

Unlike the previous two examples, the [2,3]-sigmatropic rearrangement can be initiated via various processes not involving propargyl alcohols and can be initiated through the formation of a sulfonium ylide produced from a copper carbenoid.[142] Recently, Wu and coworkers[142] explored the synthesis of 3,3-disubstituted indolines as they are found in various natural products and pharmaceutical targets. In their research, they explained that the Doyle-Kirmse reaction, which is essentially a [2,3]-sigmatropic rearrangement of a sulfonium ylide generated from a metal carbene and sulfide, could be useful for the installation of allylic and allenic systems onto indolines at the position number three. [142] A side benefit of this process is that an aryl sulfide would be installed at the other '3' position and these have wide uses as good leaving groups. [142] Wu and coworkers[142] synthesized these 3,3-disubstituted indolines by reacting 3-diazoindolin2-imines with allenyl(aryl)sulfides in the presence of 5 mol% of $Cu(OTf)_2$ at 50 °C for 3 hours. This led to yields of the corresponding 3-allenyl-3-arylthioindolin-2-imines up to 84%.[142] The researchers proposed a mechanism for the initiation of this reaction and this mechanism is shown in ***Scheme 77***. [142]



Scheme 77: Synthesis of 3 allenyl-3-arylthioindolin-2-imines utilizing the Doyle-Kirmse reaction

Another class of compounds that has previously been accessed by the [2,3]-sigmatropic rearrangement are the highly reactive and useful allenyl azo compounds. The first synthesis of these compounds came when Banert and coworkers[143] were exploring the rearrangement chemistry of short-lived allylic 1,1-diazenes and realized they could modify the chemistry to start with allenic 1,1-diazenes to produce the corresponding allenyl azo compounds. To synthesize these compounds, the researchers first performed a nitrosation on propargyl amines and then reduced the products to form propargyl hydrazines.[143] These hydrazines were then oxidized with manganese dioxide to produce the corresponding allenes and pyrazoles as an unwanted by-product (***Scheme 78***).[143] These highly reactive species can then undergo further reactions with nucleophiles to form substituted ring closure products and base initiated prototropic rearrangements to form α-alkynyl hydrazones.[143]



Scheme 78: Synthesis of allenyl azo compounds

3.2 Sulfenamides as Electrophilic Sulfur Sources

Sulfenamides are a group of compounds that contain a polar S-N bond, which due to the atoms' relative electronegativities, exhibits a partial positive charge existing on the sulfur and a partial negative charge on the nitrogen (***Figure 12***). The partial positive charge on the sulfur makes sulfenamides an excellent source of electrophilic sulfur and susceptible to nucleophilic attack at the sulfur. This makes sulfenamides a valuable source for installing various sulfur containing functionalities into various organic molecules. Thioimides, of which thiosuccinimides are classified, are specific sulfenamides that contain two carbonyl groups at the α-position to the nitrogen. The presence of these carbonyl groups stabilizes the nitrogen lone pair through resonance, resulting in the sulfur in thioimides being more electrophilic than normal sulfenamides. Therefore, thiosuccinimides are sources of electrophilic sulfur with a stabilized leaving group. Thiosuccinimides have been useful for the installation of various sulfur functionalities into various natural products and have general use in synthetic organic chemistry.

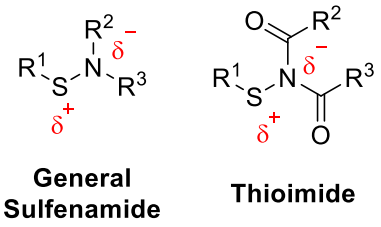
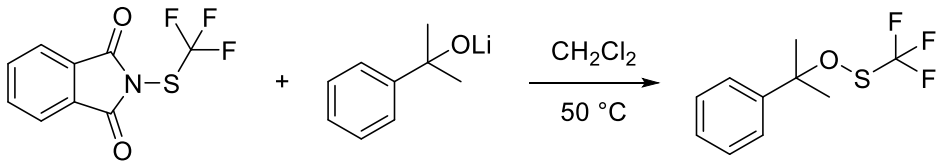


Figure 12: Sulfenamide and thioimide structure

In the past, thioimides have been useful for the preparation of unsymmetrical sulfides and disulfides in reactions with organometallic compounds and thiols respectively. Furukawa and coworkers[144] were able to synthesize unsymmetrical sulfides by reacting organometallic compounds with aryl thiosuccinimides and thiophthalimides. The reaction was successful when using both aryl and alkyl organometallic compounds but only when aryl thiosuccinimides and thiophthalimides were utilized.[144] Unsymmetrical disulfides were synthesized by Boustany and Sullivan[145] by reacting various thiols with thioimides. They were able to use by aryl and alkyl thioimides and thiols for the formation of the unsymmetrical disulfides.[145]

Sulfenate esters have also been synthesized with the use of thioimides. In 2015, Shao and coworkers[146] were investigating the structure-reactivity relationship of trifluoromethanesulfenate esters and the method used for synthesizing the aforementioned compounds were to use trifluoromethyl thiophthalimides (***Scheme 79***). [146] The researchers trifluorosulfenylated a wide range of nucleophiles such as aryl Grignard reagents, arylboronic acids, terminal alkynes, indoles, cyclic β-ketoesters, oxindoles, and sodium sulfinates chemoselectively.[146] They found that the substituents on the nucleophile influenced the trifluorosulfenylation greatly and that the trifluoromethyl thiophthalimides were able to be attacked under mild conditions.[146]

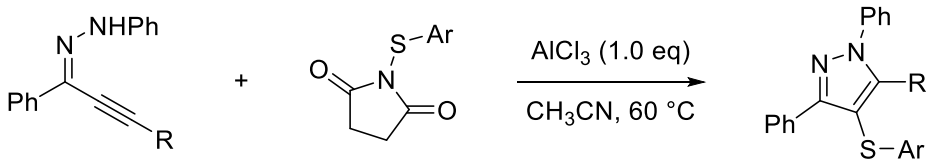


Scheme 79: Formation of trifluoromethylsulfenate esters from thioimides

Other literature examples of the uses of thioimides include access to alkenesulfonamides,[147] thiocyanations and asymmetric sulfenylations of organic compounds of which the latter will be discussed in detail in the upcoming section.

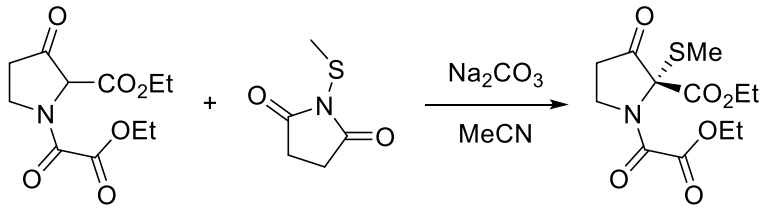
3.2.1 Recent Access to Alkyl- and Arylthiol Compounds from Sulfenamides

Pyrazoles have attracted significant recent attention in synthetic organic chemistry recently due to their recurring presence in pharmaceuticals and agrochemicals, as well as their utility to construct biologically active compounds.[148] Recently, Yu and coworkers[148] synthesized a series of 4-sulfenyl pyrazoles through the electrophilic cyclization α,β-alkynyl hydrazones. In this work, various thiosuccinimides were utilized as the sulfur electrophile in the cyclization. [148] The reaction involved mixing the thiosuccinimides with the α,β-alkynic hydrazone in the presence of aluminum chloride (one equivalent) in acetonitrile (***Scheme 80***).[148] This method was able to produce 4-sulfenyl pyrazoles in yields up to 98% but had issues with aliphatic thiosuccinimides, which was explained by Yu and coworkers[148] as being the result of the lower stability of the aliphatic sulfenyl cation. Due to the air and moisture sensitivity of sulfenyl chlorides, thiosuccinimides were used instead to optimize the reaction. In order to test this hypothesis, the use of sulfenyl chlorides and thiosuccinimides were compared with only the leaving group on the sulfur being changed.[148] The researchers found that thiosuccinimides gave better yields than sulfenyl chlorides for the one α,β-alkynyl hydrazone substrate that was tested.[148]



Scheme 80: Synthesis of 4-sulfenyl pyrazoles from thiosuccinimides

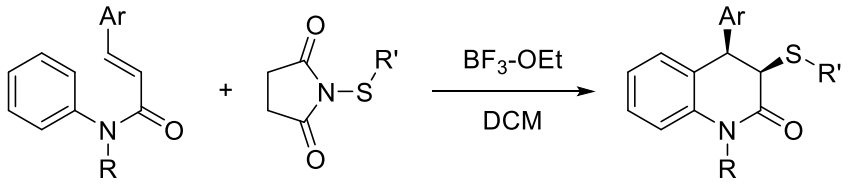
In a 2016 publication, Dong and coworkers[149] detailed their investigation of methods for the synthesis of the fungal metabolites MPC1001, MPC1001B-H and emestrin, compounds known for their usefulness as antifungal agents and as potential treatments of prostate cancer. One of the structures, MPC1001F, contains an alkyl sulfenyl chain (-SMe) and the researchers planned to add this functionality to the existing ring section of a segment of the fungal metabolite using an electrophilic sulfur source.[149] Three different sulfur sources were tested for this purpose, a thiotosylate, sulfenyl chloride, and a thiosuccinimide compound.[149] The thiotosylate and the sulfenyl chloride both produced the product but low yields were observed.[149] The thiosuccinimide was more promising and after some optimization of the base utilized, 1-(methylthio)- pyrrolidine-2,5-dione and sodium carbonate as base in acetonitrile at room temperature led to the best sulfenylation results (***Scheme 81***).[149] This method enabled sulfenylation of the existing ring section of a segment of the fungal metabolite in a 63% yield.[149]



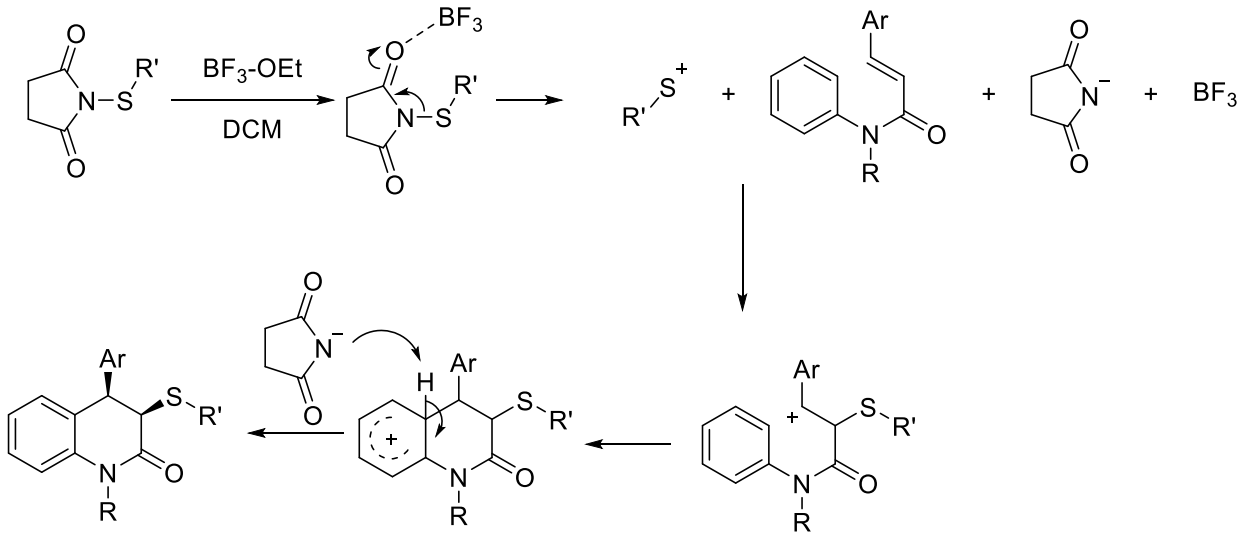
Scheme 81: Synthesis of a fragment of MPC1001F using thiosuccinimides

The synthesis of the 3,4-dihydroquinolin-2(1H)-one structural moiety has been of great interest recently as many compounds containing these ring systems have been linked to useful pharmaceutical and biological functions.[150] Recently, the synthesis of various 4-aryl-3-arylthio-

3,4-dihydroquinolin-2(1H)-ones was carried out by Ren and coworkers[150] in a reaction between N-arylcinnamamides and thiosuccinimides. This reaction had previously been carried out using sulfonyl hydrazines, however, there was a very limited substrate scope utilized for this preparation.[150] Owing to the fact that thiosuccinimides have been utilized in the asymmetric thiofunctionalization of unactivated alkenes and intramolecular carbosulfenylation of olefins, these compounds were chosen to see if the substrate scope could be expanded with a different sulfur source.[150–152] These reaction conditions involve the use of BF_3-OEt as a Lewis acid and DCM as the solvent. [150] The researchers proposed an electrophilic cyclization mechanism to explain this reaction (***Scheme 82***). [150]

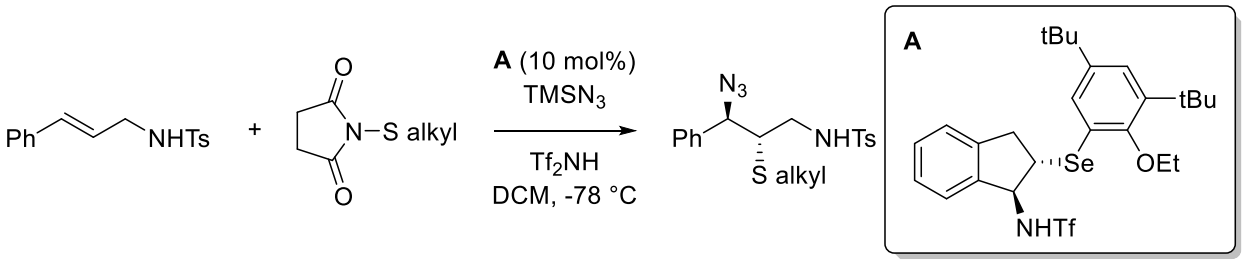


Proposed mechanism



Scheme 82: Mechanism for the formation of 4-aryl-3-arylthio-3,4-dihydroquinolin-2(1H)-ones from thiosuccinimides and N-arylcinnamamides

Most standard methods involving electrophilic sulfenation suffer from the inability to perform equally well when utilizing electrophilic alkyl sulfenating agents. Until recently, most protocols focused on arylthio and strong electron withdrawing groups such as the trifluoromethylthio groups.[153] Therefore, methods that can utilize electrophilic alkyl sulfenating groups and still yield a product with chirality, like that of Liang and Zhao,[153] are notable. Liang and Zhao[153] investigated the synthesis of chiral sulfides with the purpose of providing a new method that can be utilized in the synthesis of chiral organosulfur pharmaceuticals. Their synthetic protocol involved mixing a thiosuccinimide with N-allylsulfonamides in the presence of a nucleophile (normally an azide or alkoxide), selenium-based Lewis base catalyst and Tf_2NH at -78 °C (***Scheme 83***).[153] With this method, the researchers were able to synthesize various chiral alkyl sulfides with yields up to 92% and ee up to 96%. The mechanism for this reaction is thought to go through a thiiranium ion complexed with the selenium catalyst which is then attacked by the nucleophile that is present.[153]

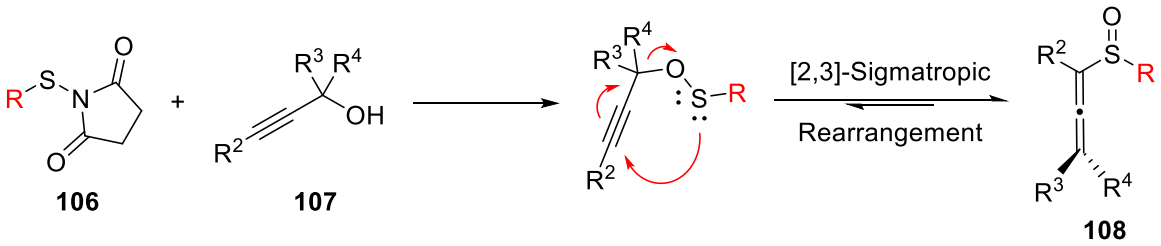


Scheme 83: Synthesis of chiral sulfides with the use of a selenium-based Lewis base catalyst

3.3 Allenyl Sulfoxides

Despite the growing interest in the installation of chiral sulfur entities into larger molecules for pharmaceutical purposes, a relatively unexplored region of sulfur chemistry has been the generation and installation of allenyl sulfoxides into larger molecules. This likely stems from inefficient methods by which allenyl sulfoxides can be synthesized. The Schwan group has been

investigating the synthesis of allenyl sulfoxides for the long-term goal of the generation of allenyl sulfenate anions. Previous work in the Schwan group has shown that reacting an electrophilic sulfur source with a propargyl alcohol (**107**) under basic conditions synthesized a sulfenate ester which underwent a [2,3]-sigmatropic rearrangement to form the corresponding allenyl sulfoxide (***Scheme 84***). Investigations into the optimal electrophilic sulfur source were performed and the use of thiosuccinimides (**106**) produced allenyl sulfoxides (**108**) in the best yields. However, the use of thiosuccinimides occasionally led to the synthesis of an alkyne by-product and poor yields during the aforementioned investigations (***Scheme 84***). Given the alkyne and yield issues, the initial goals for this research were to optimize the method by which allenyl sulfoxides were synthesized from thiosuccinimide. The effect that solvent and base had on the synthesis of allenyl sulfoxides will be discussed. Subsequently, the optimal conditions will be utilized for the synthesis of various allenyl sulfoxides in order to test the synthetic applications of synthesizing allenyl sulfoxides from thiosuccinimides. Aside from the value of pursuing new synthetic methods, the synthesis of allenyl sulfoxides provides access to the installation of two chiral centers into a larger molecule which will prove useful in the synthesis of natural products that contain a sulfoxide moiety.

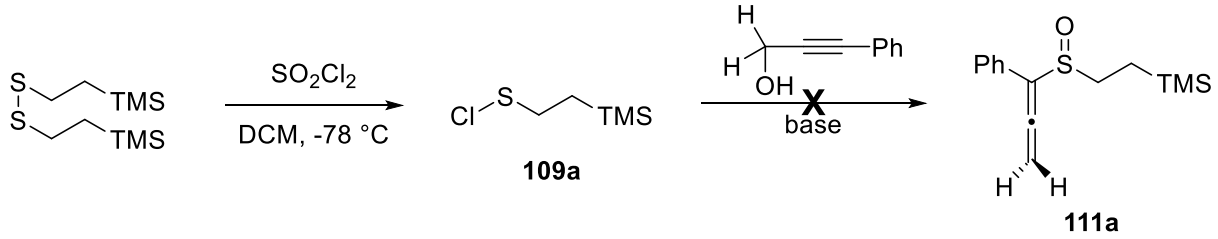


Scheme 84: Synthesis of allenyl sulfoxides from thiosuccinimides utilizing the [2,3]-sigmatropic rearrangement

Chapter 4: Results and Discussion

4.0 Results and Discussion

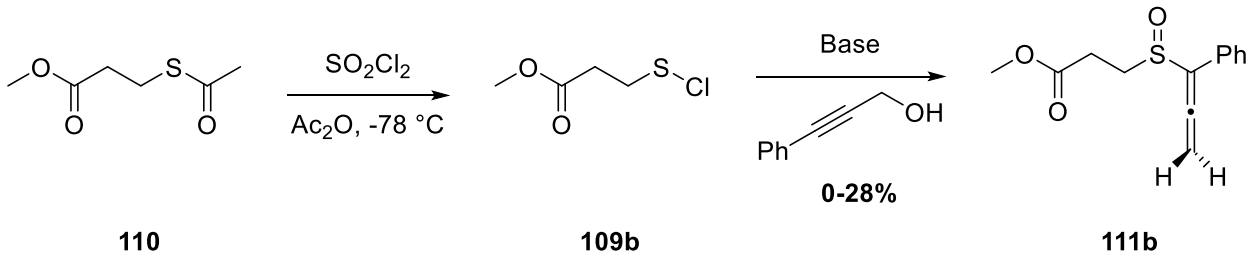
The efforts of the Schwan group toward successfully synthesizing allenyl sulfoxides were started by previous M.Sc. student Monika Kulak.[139] The functional groups that were targeted by Kulak included the 2-trimethylsilylethyl and 2-alkoxycarbonylethyl groups as they have been identified as valuable sulfenate releasing groups (SRG).[139] Her approach to the synthesis of 2-trimethylsilylethyl and 2-alkoxycarbonylethyl allenyl sulfoxides involved the generation of the corresponding sulfenyl chlorides followed by an attack of a propargyl alcohol.[139] The sulfenate ester that formed would then undergo a [2,3]-sigmatropic rearrangement to form an allenyl sulfoxide. 2-Trimethylsilylethanesulfenyl chloride (**109a**) is a known compound which has been prepared previously by reacting the corresponding disulfide with sulfuryl chloride at -78 °C in dichloromethane (DCM).[154] However, several attempts to synthesize allenyl sulfoxide **111a** from 2-trimethylsilylethanesulfenyl chloride (**109a**) proved futile (***Scheme 85***).[139]



Scheme 85: Attempted synthesis of sulfoxide **111a** from sulfenyl chloride **109a**

The use of 2-methoxycarbonylethanesulfenyl chloride (**109b**), which had not been reported previously, became Kulak's subsequent synthetic target. Generation of the sulfenyl chloride can be achieved from the corresponding thiolacetate (**110**) by an established protocol using sulfuryl chloride and acetic anhydride at -78 °C (***Scheme 86***).[155] A series of trials reacting sulfenyl chloride with 3-phenyl-2-propyn-1-ol led to a maximum yield of 28% of 1-phenyl allenyl sulfoxide (**111b**).

As a result of this poor yield, the use of sulfenyl chlorides was deemed an inefficient method for the synthesis of allenyl sulfoxides.



110 **109b** **111b**

Scheme 86: Attempted synthesis of sulfoxide **111b** from sulfenyl chloride **109b**

Research into the synthesis of allenyl sulfoxides was continued by previous B.Sc. student Mark Hirst. His work involved a new approach focused on the synthesis of allenyl sulfoxides containing the 2-alkoxycarbonylethenyl SRG from the corresponding allenyl sulfide as this group has also been identified as a valuable sulfenate releasing group. To synthesize these sulfoxides, the alkynylation of thiolate anions, making 2-alkynyl sulfides, followed by a π-bond isomerization protocol was attempted. However, the isomerization protocol only produces a mixture of allenyl sulfide product and starting material. This mixture is difficult to purify due to their similar elution patterns in various column chromatography conditions and thus, oxidation of the sulfide to the corresponding sulfoxide was attempted to improve separability. Unfortunately, the oxidation did not assist with the separation and as the product of interest was not synthesized methodology was discontinued for the synthesis of allenyl sulfoxides.

After the work performed by Kulak[139] and Hirst, previous M.Sc. student Michelle Michalski[131] continued the investigation of the Schwan group towards an efficient method for synthesizing allenyl sulfoxides. Her research explored the optimal choice for an electrophilic sulfur source to replace sulfenyl chlorides for the synthesis of allenyl sulfoxides. She investigated the synthesis of 2-trimethylsilylethyl and 2-alkoxycarbonylethyl thioimides and was able to

synthesize 2-trimethylsilylethyl and 2-alkoxycarbonylethyl variants of thiosuccinimides **112a-b**, thiophthalimides **113a-b**, and thiosaccharins **114a-b** from the corresponding disulfides (***Figure 13***).[131]

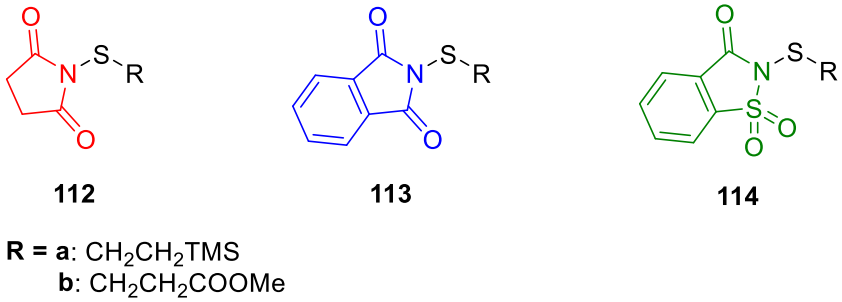
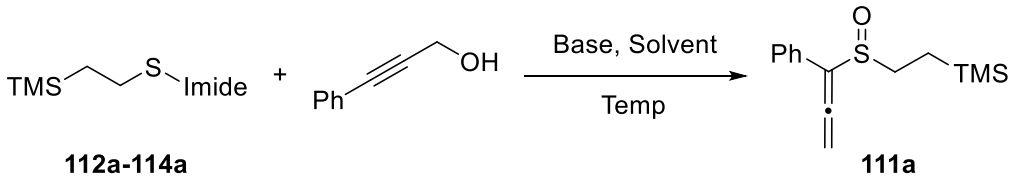


Figure 13: Thioimides utilized in the attempted synthesis of allenyl sulfoxides **111a** and **111b**

Table 10: Synthesis of allenyl sulfoxides from various thioimides

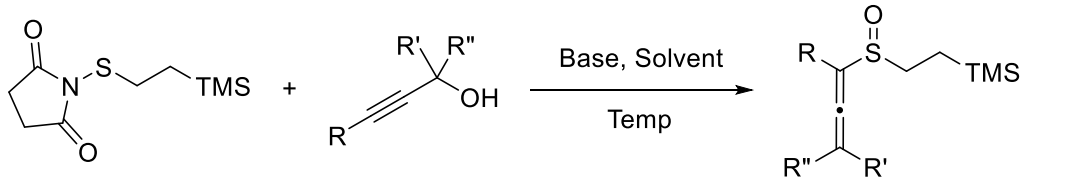


Imide	Base (equiv.)	Solvent	Reaction Temp.	Reaction Time	Yield
Succinimide	K_2CO_3 (3.0)	DCM	50 °C	3 days	43%
Phthalimide	Et_3N (2.0)	DCM	50 °C	7 days	43%
Saccharin	nBuLi (1.2)	THF	-78 °C to 5 °C	4 hr	28%

Michalski[131] then probed the synthesis of allenyl sulfoxides **111a** and **111b** from thioimides **112-114** and was able to synthesize allenyl sulfoxide **111a** in a 43% yield when using thiosuccinimide **112a** or thiophthalimide **113a** but only achieved a 28% from thiosaccharin **114a** (***Table 10***). Due to the ease in purifying allenyl sulfoxide **111a** produced by the thiosuccinimide (succinimide is water soluble and phthalimide is not), thiosuccinimides were determined to be the optimal electrophilic sulfur source for synthesizing allenyl sulfoxides via a [2,3]-sigmatropic rearrangement.[131] Michalski[131] then reacted propargyl alcohol, 3-butyn-2-ol and 2-butyn-1,4-diol

with thiosuccinimide **112a** to synthesize allenyl sulfoxides **115-117** using the conditions illustrated in ***Table 11***.

Table 11: Conditions for the synthesis of allenyl sulfoxides **115-117**



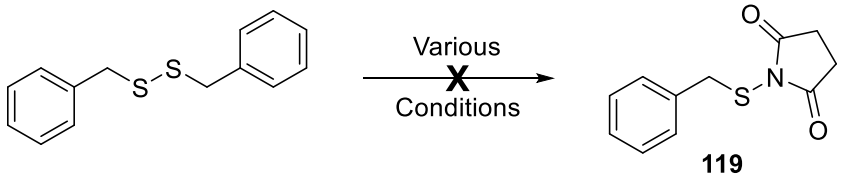
115: R=H, R'=H, R"=H
116: R=H, R'=Me, R"=H
117: R=CH_2OH, R'=H, R"=H

R	R'	R''	Base (equiv.)	Solvent	Reaction Temp.	Reaction Time	Product (Yield)
H	H	H	Et_3N (1.0)	DCM	25 °C	72 hr	**115** (65%)
H	Me	H	Et_3N (1.0)	DCM	50 °C	72 hr	**116** (59%)
CH_2OH	H	H	Et_3N (1.0)	THF	25 °C	72 hr	**117** (71%)

The purpose of the current research in this project is to improve upon the synthesis of allenyl sulfoxides carried out by Kulak,[139] Hirst, and Michalski.[131] The scope of the synthesis of allenyl sulfoxides will be broadened to include other thiosuccinimides and propargyl alcohols in order to test the robustness of synthesizing allenyl sulfoxides with thiosuccinimides. In addition, the synthesis of allenyl sulfoxides from thiosuccinimides will be optimized by examining the effects that different solvents and bases have on the yields of the allenyl sulfoxides. These effects will be probed by synthesizing various thiosuccinimides and then reacting them with a variety of propargyl alcohols in order to determine the optimal method for the universal synthesis of allenyl sulfoxides.

4.1 Synthesis of Thiosuccinimides

To exemplify the utility of employing thiosuccinimides to synthesize allenyl sulfoxides, various thiosuccinimides were synthesized and reacted with several propargyl alcohols. The thiosuccinimides that are evaluated in this section are N-(cyclohexylthio)succinimide (**118**), N-(benzylthio)succinimide (**119**), N-(trimethysilylethylthio)succinimide (**112a**), N-(methoxycarbonylethylthio)succinimide (**112b**) and N-(hexadecanylthio)succinimide (**120**). The synthesis of N-(benzylthio)succinimide (**119**) was attempted via various methods starting from dibenzyl disulfide, benzyl bromide and benzyl thiol. Two reaction conditions were attempted to synthesize N-(benzylthio)succinimide (**119**) from dibenzyl disulfide. The first involved mixing dibenzyl disulfide with sulfuryl chloride at -78 °C for 10 minutes before the addition of a 2.5 times excess of succinimide and triethylamine.[156] The other method for synthesizing N-(benzylthio)succinimide (**119**) from dibenzyl disulfide involved mixing dibenzyl disulfide with N-chlorosuccinimide or N-bromosuccinimide in acetonitrile or toluene respectively at reflux (***Scheme 87***). Unfortunately, neither of these methods produced thiosuccinimide **119**.

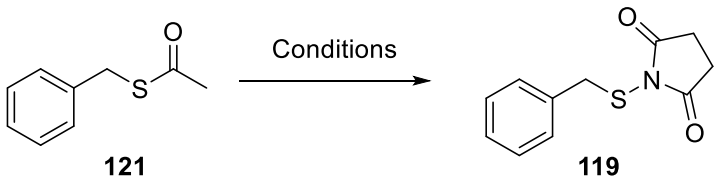


Scheme 87: Attempted synthesis of thiosuccinimide **119** from dibenzyl disulfide

The next method attempted for producing N-(benzylthio)succinimide (**119**) involved a two-step process starting from benzyl bromide. The first step involved reacting benzyl bromide with potassium thioacetate in dimethyl formamide (DMF) to synthesize benzyl thiolacetate (**121**).[157] The next step involved an oxidative deacetylation of thiolacetate **121** which was attempted by various methods that are outlined in ***Table 12***. These methods were able to deliver

thiosuccinimide **119** in yields up to 19%. Due to the poor yield, an alternative preparation of thiosuccinimide **119** was investigated.

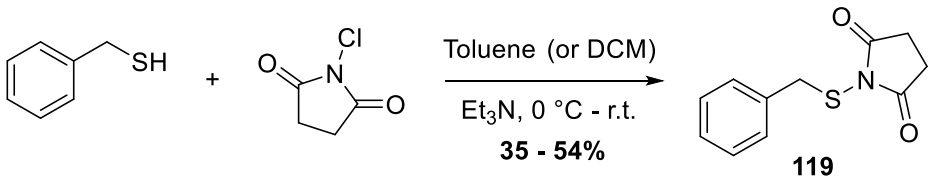
Table 12: Trials towards the synthesis of thiosuccinimide **119** from benzyl thiolacetate **121**



121 **119**

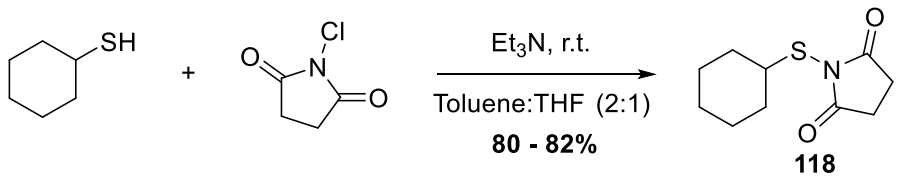
Reaction	Deacetylating Conditions (equiv.)	Succinimide Source (equiv.)	Base (equiv.)	Reaction Time, Temp.	Product?
1	SO_2Cl_2 (1.1), DCM, -78 °C, 10 minutes	Succinimide (2.4)	Et_3N (2.2)	0.5 hr, 25 °C	Yes
2	SO_2Cl_2 (1.1), DCM, -78 °C, 10 minutes	Succinimide (2.4)	Et_3N (2.2)	1 hr, 25 °C	Yes, 19%
3	MeOH, K_2CO_3 (2.0), 25 °C, 1 hour	NCS (1.2)	N/A	72 hr, 25 °C	No product
4	MeOH, K_2CO_3 (2.0), 25 °C, 1 hour	NCS (1.0), Succinimide (3.0)	N/A	72 hr, 25 °C	No product

The final method attempted for the synthesis of thiosuccinimide **119** involved starting from benzyl thiol. When benzyl thiol was reacted with N-chlorosuccinimide in the presence of triethyl amine in either toluene or DCM, thiosuccinimide **119** was formed in a 35 to 54% yield depending on the purification method (***Scheme 88***).[158] If purified by column chromatography, the product would crystallize in the column and thus decrease the yield to 35%. However, if the crude reaction material is triturated with pentane and then recrystallized from hexanes, a yield of up to 54% was achieved.



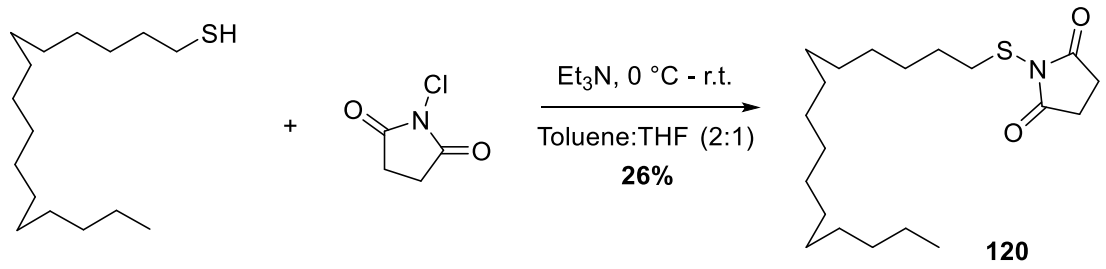
Scheme 88: Synthesis of thiosuccinimide **119** from benzyl thiol

N-(Cyclohexylthio)succinimide (**118**) was synthesized in a 80 to 82% yield by mixing N-chlorosuccinimide with cyclohexyl mercaptan followed by the dropwise addition of triethylamine in a 2:1 toluene to THF solvent at room temperature (***Scheme 89***).[158]



Scheme 89: Synthesis of 1-(cyclohexylsulfanyl)pyrrolidine-2,5-dione (**118**)

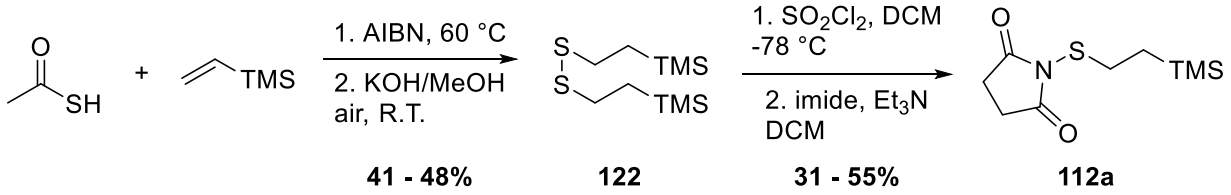
A similar procedure was utilized to synthesize N-(hexadecanylthio)succinimide (**120**) from hexadecane thiol in a 26% yield when the reaction is performed at 0 °C (***Scheme 90***).



Scheme 90: Synthesis of 1-(hexadecylsulfanyl)pyrrolidine-2,5-dione (**120**)

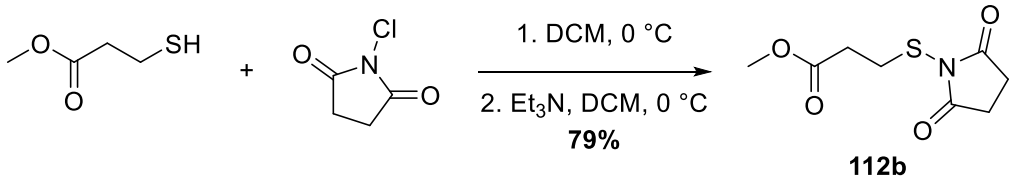
Following a method developed by Michalski,[131] N-(trimethysilylethylthio)succinimide (**112a**) was synthesized by in a two-step process from vinyl trimethylsilane (vinyl TMS). First, vinyl TMS and thiolacetic acid were mixed with AIBN at 60 °C for four hours before the addition of methanol and potassium carbonate. This solution was mixed for 7 days before it was distilled

yielding disulfide **122** in a 41 to 48% yield. This disulfide was then dissolved in DCM and reacted with sulfuryl chloride for 10 minutes at -78 °C before the addition of succinimide and triethylamine. This synthesized thiosuccinimide **112a** in a 31 to 95% yield (***Scheme 91***).



Scheme 91: Synthesis of {[2-(trimethylsilyl)ethyl]sulfanyl}pyrrolidine-2,5-dione (**112a**)

N-(Methoxycarbonylethylthio)succinimide **112b** was synthesized in a 79% yield by mixing N-chlorosuccinimide with methyl 3-mercaptopropanoate at 0 °C for 30 minutes followed by the addition of a triethylamine solution (1.34 M in DCM) at 0 °C (***Scheme 92***)



Scheme 92: Synthesis of methyl 3-[(2,5-dioxopyrrolidin-1-yl)sulfanyl]propanoate (**112b**)

These thiosuccinimides were then mixed with propargyl alcohol (**123**), 3-butyn-2-ol (**124**), 2-methyl-3-butyn-2-ol (**125**), 2-butyn-1,4-diol (**126**) and 3-phenyl-2-propyn-1-ol (**127**), 2-pentyn-1-ol (**145**) to illustrate the utility of synthesizing allenyl sulfoxides from thiosuccinimides.

4.2 Synthesis of Allenyl Sulfoxides from Propargyl Alcohols

4.2.1 Towards the Synthesis of Unsubstituted Allenyl Sulfoxides

The synthesis of unsubstituted allenyl sulfoxides was chosen for optimization of the synthesis of allenyl sulfoxides from thiosuccinimides. Initial investigations illustrated that while phenyl allenyl sulfoxides, like **111a**, can be synthesized in good yields from thiosuccinimides, they

can be difficult to purify from the initial thiosuccinimide due to similar elution patterns across many solvent systems in column chromatography.[131] Despite the synthesis of phenyl allenyl sulfoxides being previously utilized to optimize the synthesis of allenyl sulfoxides from thiosuccinimides, the synthesis of unsubstituted allenyl sulfoxides will be utilized in this work due to the ease of purification from any remaining starting material. The unsubstituted allenyl sulfoxide was also chosen as it was discovered, during the work of Michalski,[131] that a significant amount of the unsubstituted allenyl sulfoxide rearranges to form the corresponding alkyne if exposed to high temperatures over a long period of time. As such, this optimization will also strive to limit the amount of alkyne produced. The factors that will be optimized are the base and solvent utilized in the reaction.

The reaction chosen to optimize the formation of unsubstituted allenyl sulfoxides was the reaction between N-(cyclohexylthio)succinimide **118** and propargyl alcohol in the presence of a base in the indicated solvent, at 50 °C. In order to determine the ratio of the unsubstituted allenyl sulfoxide product (**128)** to the rearranged alkyne product (**129**), the ^{1}H NMR spectrum of the purified product or of the crude reaction material was examined (***Figure 14***). Careful inspection of the ^{1}H NMR spectrum of a purified mixture of sulfoxide **128** and alkyne **129** illustrates peaks that can be utilized to differentiate the two. There is an apparent triplet at 5.83 ppm with J = 6.4 Hz which corresponds to H_m of the allene due to the splitting from both H_A and H_B. Although protons A and B exist in different chemical environments, their coupling influences on H_m are comparable, revealing an apparent triplet rather than a doublet of doublets. There is also a peak at 5.15 ppm which corresponds to both H_A and H_B of the allene with $J_{AM} = J_{BM} = 13.6$ Hz and $J_{AB} = 6.4$ Hz the pattern of which arises from the near overlap of two doublet of doublets (one of H_A and one of H_B) in an ABM environment. The peaks at 3.45 ppm and 2.36 ppm correspond to the alkyne

impurity. Using the integrations of these peaks, the mole ratios of the allene to the alkyne product can be determined.

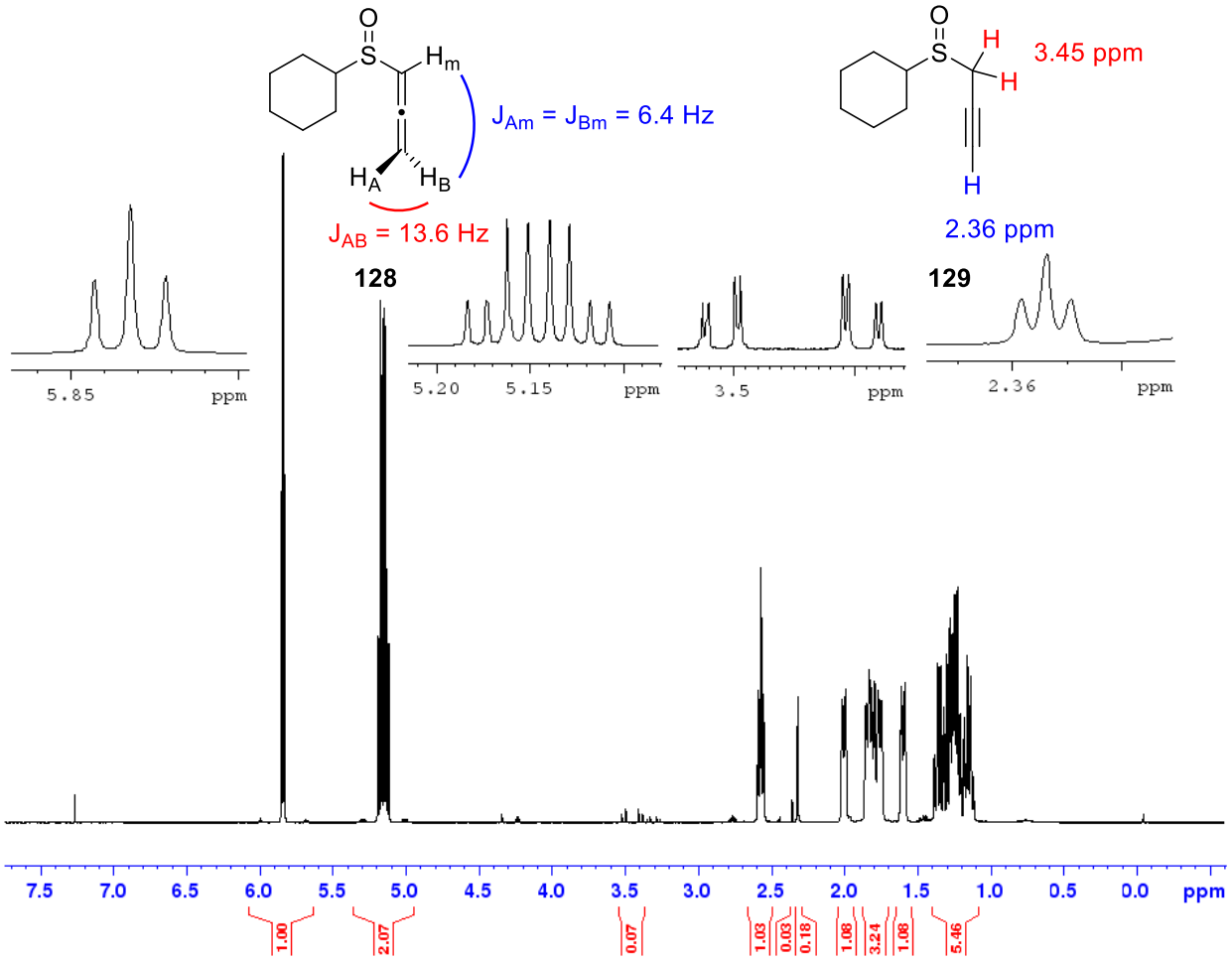
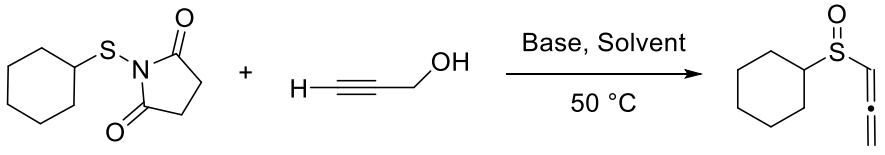


Figure 14: ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of (propa-1,2-diene-1-sulfinyl)cyclohexane (**128**)

The first parameter that was optimized was the base utilized in the reaction. Michalski[131] had shown previously that the most useful bases for the synthesis of allenyl sulfoxides from thiosuccinimides were triethylamine and potassium carbonate. However, a direct comparison between the two bases had yet to be performed. As such, one equivalent of propargyl alcohol **123** and thiosuccinimide **118** were mixed together in DCM with three equivalents of either triethylamine or potassium carbonate. The reactions were stopped after 16 hours, despite not being

completed in order to assess the amount of starting material remaining in the reaction mixture and thus illustrating the effectiveness of the base. The results are outlined in ***Table 13***. The potassium carbonate reaction was able to produce more product than triethylamine in the same amount of time and therefore potassium carbonate is the optimal base for allenyl sulfoxide formation from thiosuccinimides.

Table 13: Trials for the determination of the optimal base for synthesizing allenyl sulfoxides from thiosuccinimides



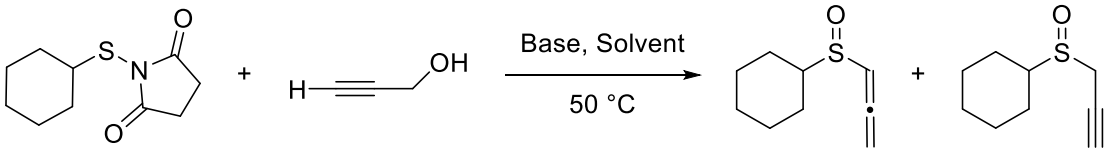
118 **123** **128**

Reaction	Base	Base: Alcohol: Thiosuccinimide	Solvent	Reaction Time	Yield
1	K_2CO_3	3.0 : 1.0 : 1.0	DCM	16 hr	Not isolated, Starting material to product ratio of 2.4 : 1.0
2	Et_3N	3.0 : 1.0 : 1.0	DCM	16 hr	Not isolated, Starting material to product ratio of 4.0 : 1.0

Furthermore, an analysis into the optimal solvent had not previously been performed. Michalski[131] had previously synthesized allenyl sulfoxides in DCM and THF at 50 °C with DCM being the favoured solvent. The boiling point of DCM is below 50 °C and therefore those reactions needed to be performed in a sealed pressure vessel. This made it difficult to assess to progress of the reaction as the pressure vessel would need to cool fully before a TLC could be performed on the reaction mixture. In addition to this, the inability to check the progress often decreased the purity of the reaction as the longer the reaction was left at 50 °C, the more rearranged alkyne product would be produced.[131] Therefore, an alternative solvent to DCM was sought and the trials

for different solvents are depicted in ***Table 14***. As seen in ***Table 14***, chloroform was the optimal solvent for the synthesis of allenyl sulfoxides due to the higher yield, decreased reaction time and smallest amount of rearranged alkyne product being formed. The chloroform utilized also has 0.75% v/v of ethanol and thus 0.75% v/v was added to a DCM reaction to understand the effects that it might have. That the DCM/EtOH trial was completed in the same time as the chloroform trial shows that the ethanol likely acts to increase the rate of the reaction. The higher yield of the chloroform trial could also be explained by the by-product of the reaction, succinimide, being insoluble in chloroform and thus driving the reaction more towards the products, should the reaction mechanism involve reversibility. To further test this, subsequent reactions were performed in both DCM and chloroform in order to ensure this was not an isolated occurrence.

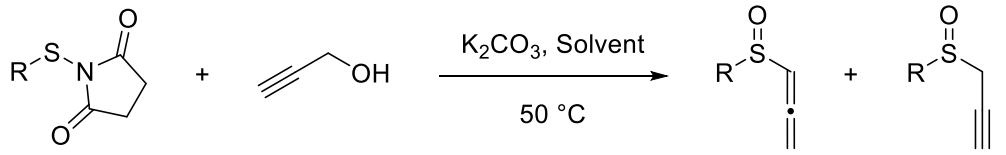
Table 14: Trials analyzing the effects of solvents on the synthesis of allenyl sulfoxide **128**



118 **123** **128** **129**

Reaction	Base	Base: Alcohol: Thiosuccinimide	Solvent	Reaction Time	128(%): 129(%)	Yield
1	K_2CO_3	4.0 : 3.0 : 1.0	DCM	16 hr	96 : 4	43%
2	K_2CO_3	4.0 : 3.0 : 1.0	THF	16 hr	88 : 12	46%
3	K_2CO_3	4.0 : 3.0 : 1.0	DCM + 0.75% EtOH	6 hr	93 : 7	43%
4	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	6 hr	97 : 3	63%

Table 15: Synthesis of unsubstituted allenyl sulfoxides **128, 130-132a-b** from thiosuccinimides



112a, 118-120 | **123**

R: 128: Cyclohexyl **130:** Benzyl
131: Hexadecanyl **132a:** TMS ethyl
132b: Methoxycarbonyl ethyl

Thiosuccinimide	Base	Base: Alcohol: Thiosuccinimide	Solvent	Reaction Time	Product (%): Alkyne (%)	Yield
Cyclohexyl (**118**)	K_2CO_3	4.0 : 3.0 : 1.0	DCM	16 hr	96 : 4	43%
Cyclohexyl (**118**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	6 hr	97 : 3	63%
Benzyl (**119**)	K_2CO_3	4.0 : 3.0 : 1.0	DCM	16 hr	92 : 8	36%
Benzyl (**119**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	2.5 hr	98 : 2	67%
Hexadecanyl (**120**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	3 hr	97 : 3	64%
TMS ethyl (**112a**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	2 hr	96 : 4	72%
Methoxycarbonyl ethyl (**112b**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	1.5 hr	98 : 2	52%

The optimization trials illustrated that potassium carbonate was the optimal base for the synthesis of allenyl sulfoxides and that chloroform was the optimal solvent. Therefore, potassium carbonate and chloroform defined the conditions utilized for the synthesis of various allenyl sulfoxides from thiosuccinimides in the molar ratio stated in ***Table 14***.

Using the conditions illustrated in ***Table 15***, allenyl sulfoxides **128, 130-132a-b** can be synthesized in yields ranging from 36 to 72%. ***Table 15*** also depicts that the use of chloroform, rather than DCM, can improve the yields of thiosuccinimides by up to 20%. When chloroform and

DCM are utilized for the same substrates, the chloroform reaction led to a decreased amount of alkyne by-product and thus higher purity of the allenyl sulfoxide product. Whether this is from the ability to assess the completeness of the reaction more easily or due to mechanistic reasons is unknown, however it is an improvement over the use of DCM regardless.

4.2.2 Towards the Synthesis of Methyl Allenyl Sulfoxides

The synthesis of various methyl-substituted allenyl sulfoxides (**133-135a-b**) can also be performed utilizing thiosuccinimides as the starting material by reacting them with 3-butyn-2-ol (**124**). Sulfoxides **133-135a-b** can be synthesized in yields ranging from 38 to 65% as illustrated in ***Table 16***. Chloroform also has a positive effect on the synthesis of the methyl substituted allenyl sulfoxides with yields increasing by up to 18% over the use of DCM as the solvent. Notably, the synthesis of allenyl sulfoxides (**133-135a-b**) generally required more time than the unsubstituted allenyl sulfoxides due to the steric hindrance of the methyl group at the α-position of alkynol (**124**).

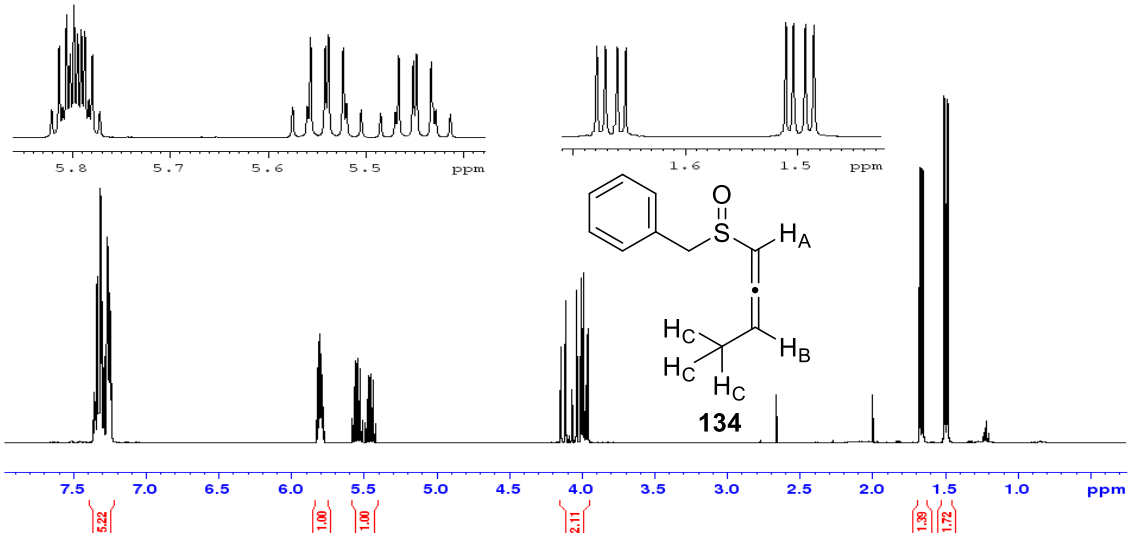
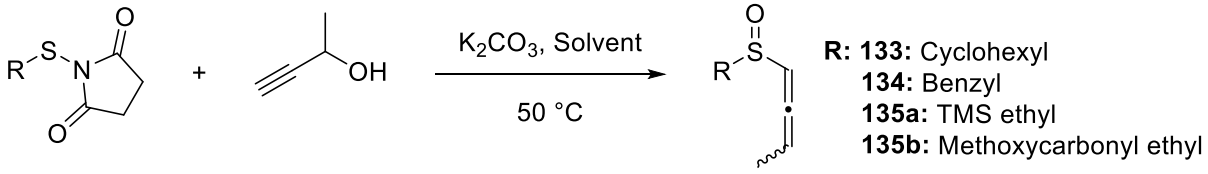


Figure 15: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (buta-1,2-diene-1-sulfinyl)cyclohexane

The ^{1}H NMR spectrum of the methyl substituted allenyl sulfoxide **134** is shown in ***Figure 15***. The two allenyl protons H_A and H_B are seen at 5.80 and 5.49 ppm as multiplets. The H_C protons are at 1.67 and 1.50 ppm. As methyl substituted allenes are axially chiral and the sulfoxide is a stereogenic center, there are two isomers present resulting in the two doublet of doublet patterns for H_C with J = 3.1 and 7.4 Hz.

Table 16: Synthesis of methyl substituted allenyl sulfoxides **133-135a-b** from thiosuccinimides



112a-b, 118, 119 **124**

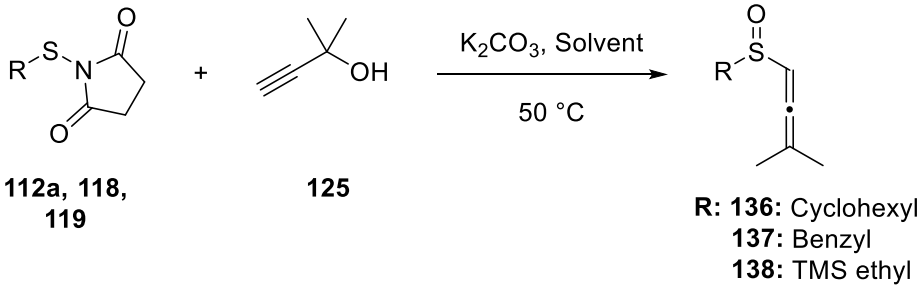
Thiosuccinimide	Base	Base: Alcohol: Thiosuccinimide	Solvent	Reaction Time	Yield
Cyclohexyl (**118**)	K_2CO_3	3.0 : 2.0 : 1.0	DCM	36 hr	47% (55:45 d.r.)
Cyclohexyl (**118**)	K_2CO_3	3.0 : 2.0 : 1.0	Chloroform	30 hr	65% (53:47 d.r.)
Benzyl (**119**)	K_2CO_3	4.0 : 2.5 : 1.0	DCM	16 hr	38% (55:45 d.r.)
Benzyl (**119**)	K_2CO_3	3.0 : 2.0 : 1.0	Chloroform	11 hr	56% (55:45 d.r.)
TMS ethyl (**112a**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	2.5 hr	59% (56:44 d.r.)
Methoxycarbonyl ethyl (**112b**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	1.75 hr	47% (54:46 d.r.)

4.2.3 Towards the Synthesis of Dimethyl Allenyl Sulfoxides

The synthesis of dimethyl substituted allenyl sulfoxides **136-138** can also be performed from the corresponding thiosuccinimides. According to ***Table 17***, the yields for these sulfoxides

are drastically lower than that of the two proceeding allenyl sulfoxides, with yields ranging from trace amounts to 41%. It is hypothesized that the two methyl groups at the α-position of alkynol **125** cause too much steric hindrance for the alcohol to be in the proper position to perform a nucleophilic attack at the sulfur of the thioimides. This steric hindrance also led to increased reaction times, no matter the solvent, for the synthesis of the dimethyl allenyl sulfoxides compared to the unsubstituted and methyl substituted allenyl sulfoxides. The reaction between thiosuccinimide **119** and alkynol **125** in DCM led to a higher yield of allenyl sulfoxide **137** than in chloroform, however the chloroform reaction produced a purer version of allenyl sulfoxide **137** which is confirmed by the ^{1}H NMR spectrum.

Table 17: Synthesis of dimethyl substituted allenyl sulfoxides **136-138** from thiosuccinimides



112a, 118, 119 **125**

R: 136: Cyclohexyl
137: Benzyl
138: TMS ethyl

Thiosuccinimide	Base	Base: Alcohol: Thiosuccinimide	Solvent	Reaction Time	Yield
Cyclohexyl (**118**)	K_2CO_3	4.0 : 3.0 : 1.0	DCM	72 hr	9%
Cyclohexyl (**118**)	K_2CO_3	3.0 : 2.0 : 1.0	Chloroform	36 hr	37%
Benzyl (**119**)	K_2CO_3	4.0 : 3.0 : 1.0	DCM	48 hr	28%
Benzyl (**119**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	23 hr	23%
TMS ethyl (**112a**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	21 hr	41%

The ^{1}H NMR spectrum of dimethyl substituted allenyl sulfoxide **137** is depicted in ***Figure 16***. The allenyl proton H_A is seen at 5.71 ppm as an apparent septet with J = 2.8 Hz. The splitting

arises from coupling with the H_B and H_c methyl protons. As the H_B and H_c methyl protons exert the same coupling influence on H_A, their splitting of H_A overlaps and forms an apparent septet rather than the expected quartet of quartets. The H_B and H_c methyl protons are represented by the peaks at 1.62 ppm. These protons are doublets with a J = 2.8 Hz corresponding to the coupling of H_B with the allenyl H_A proton.

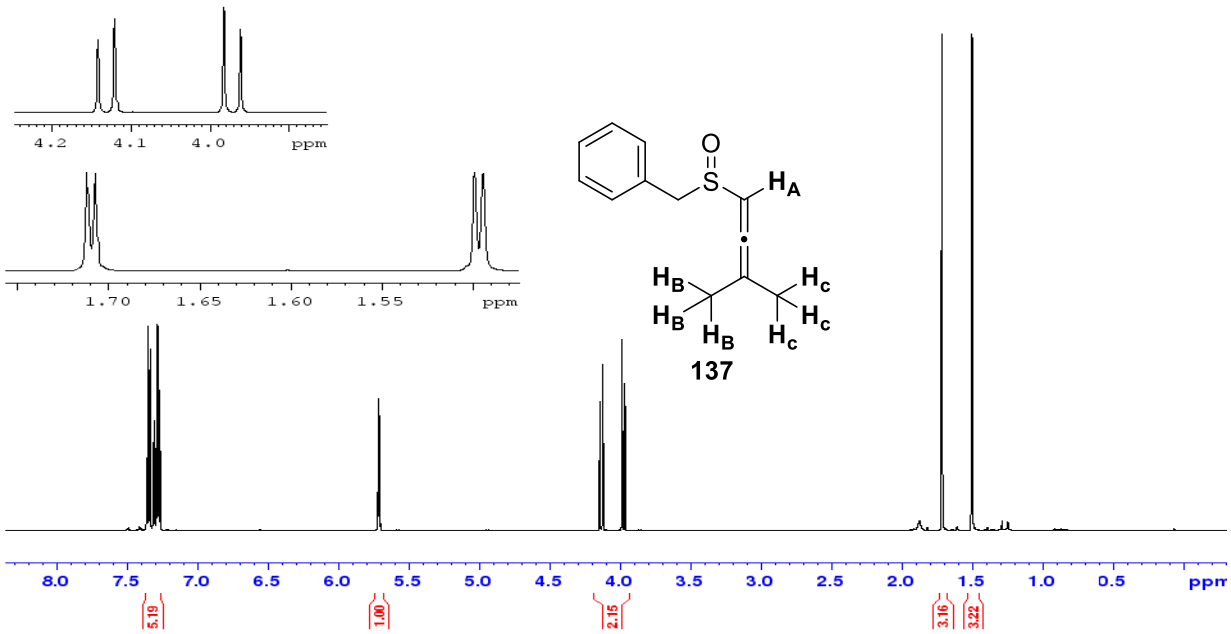


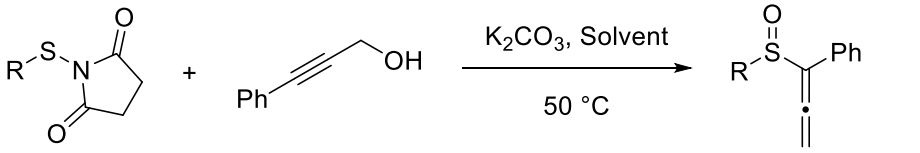
Figure 16: ^1H NMR spectrum (600 MHz, $CDCl_3$) of (3-methylbuta-1,2-diene-1-sulfinyl)cyclohexane (**137**)

4.2.4 Towards the Synthesis of Phenyl Allenyl Sulfoxides

The synthesis of 1-phenylallenyl sulfoxides, **111a, 139-140**, from thiosuccinimides was also investigated. When utilizing propargyl alcohol **127**, these allenyl sulfoxides can be synthesized in yields ranging from 38 to 53% using the conditions detailed in ***Table 18***. Worth mentioning is that there were purification issues which were experienced for the phenyl allenyl sulfoxides (**111a, 139-140**) and complete purification required multiple instances of column chromatography, due to the poor separability of the allenyl sulfoxide and the starting

thiosuccinimide. Conditions had to be altered in order for there to be complete consumption of the starting material such that the phenyl allenyl sulfoxides could be purified but this could only be done when chloroform was the reaction solvent. Moreover, the reaction between alkynol **127** and benzyl thiosuccinimide **119** in DCM did not yield any product but did produce allenyl sulfoxide **140** when the reaction was performed in chloroform. This is another illustration of the utility of chloroform in the synthesis of allenyl sulfoxides from thiosuccinimides.

Table 18: Synthesis of phenyl substituted allenyl sulfoxide **139-141** from thiosuccinimides



112a, 118, 119 **127**

R: 139: Cyclohexyl
140: Benzyl
111a: TMS ethyl

Thiosuccinimide	Base	Base: Alcohol: Thiosuccinimide	Solvent	Reaction Time	Yield
Cyclohexyl (**118**)	K_2CO_3	3.0 : 1.5 : 1.0	DCM	10 hr	52% by ^{1}H NMR (73:27 mix of product to SM)
Cyclohexyl (**118**)	K_2CO_3	3.0 : 2.0 : 1.0	Chloroform	36 hr	53% (no SM)
Benzyl (**119**)	K_2CO_3	3.0 : 1.5 : 1.0	DCM	48 hr	0%
Benzyl (**119**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	7 hr	29%
TMS ethyl (**112a**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	6 hr	49%

The ^{1}H NMR spectrum of [(1-phenylpropa-1,2-diene-1-sulfinyl)methyl]benzene (**140**) is illustrated in ***Figure 17***. The identifying feature of this spectrum (most diagnostic peaks) are the

two doublets which form an AB quartet pattern at 5.25 ppm. This AB pattern with a coupling of 13.3 Hz corresponds to the allenyl protons H_A and H_B. These protons are rendered diastereotopic by the asymmetry of the molecule that originates at the sulfoxide. This asymmetry is also exhibited by the proton peaks at 4.13 ppm and 3.84 ppm, with each being a doublet as part of an AB quartet pattern with a coupling constant of 13.0 Hz.

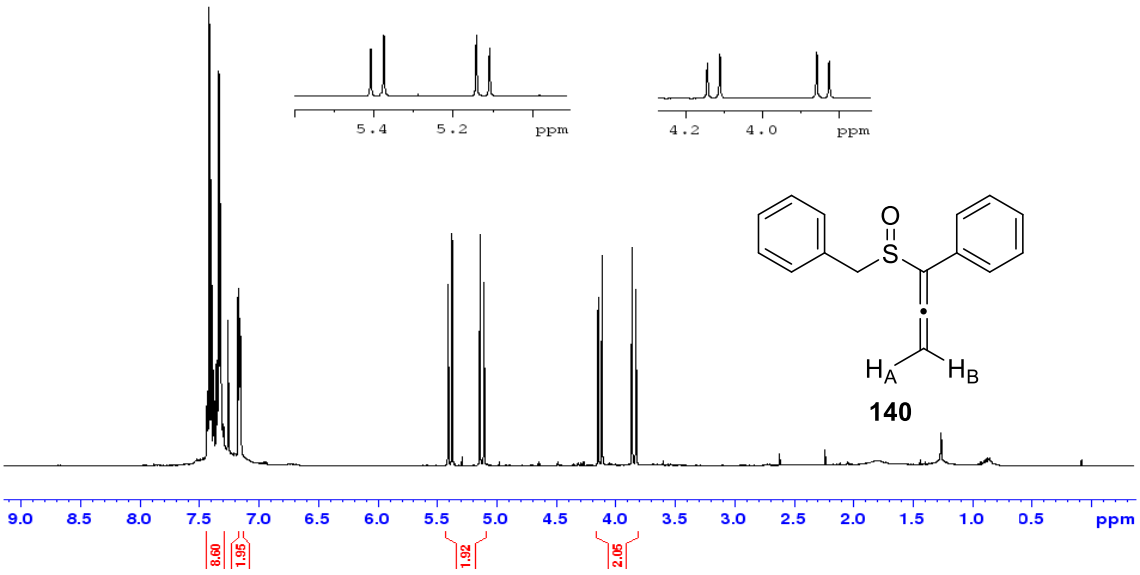


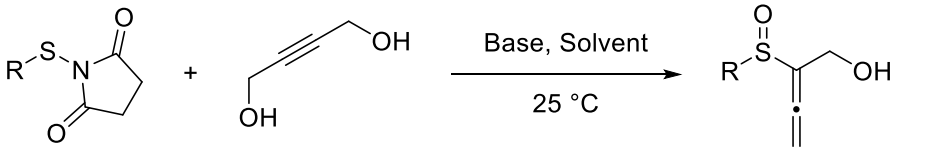
Figure 17: 1H NMR spectrum (400 MHz, $CDCl_3$) of [(1-phenylpropa-1,2-diene-1-sulfinyl)methyl]benzene (**140**)

4.2.5 Towards the Synthesis of Hydroxymethyl Allenyl Sulfoxides

A rather fascinating propargyl alcohol that can be used in the synthesis of an allenyl sulfoxides is 2-butyne-1,4-diol (**126**), an important polyester and polyurethane precursor produced on an industrial scale by a Reppe synthesis. The second hydroxyl group provides synthetic value in future functionalization chemistry of the allenyl sulfoxide. The synthesis of the hydroxymethyl allenyl sulfoxides (**141** and **142**) was carried out by mixing thiosuccinimides **118** and **119** with

diol **126**. The results of these reactions are depicted in ***Table 19***. Diol **126** is barely soluble in either DCM or chloroform and therefore these reactions were performed in THF as diol **126** dissolved better in THF. Moreover, triethylamine was utilized as the base for these trials as Michalski[131] had shown it to be superior to potassium carbonate for the synthesis of hydroxymethyl allenyl sulfoxides.

Table 19: Synthesis of hydroxymethyl substituted allenyl sulfoxides (**142** and **143**) from thiosuccinimides



118, 119 **126**

R: 141: Cyclohexyl
142: Benzyl

Thiosuccinimide	Base	Base: Alcohol: Thiosuccinimide	Solvent	Reaction Time	Yield
Cyclohexyl (**118**)	Et_3N	1.0 : 5.0 : 1.0	THF	10 hr	23%
Benzyl (**119**)	Et_3N	1.0 : 5.0 : 1.0	THF	48 hr	26%

The ^1H NMR spectrum of 2-(cyclohexylsulfinyl)buta-2,3-dien-1-ol (**141**) is illustrated in ***Figure 18*** and the diagnostic peaks of this spectrum are at 5.22, 4.51 and 3.47 ppm. The two allenyl protons (H_A and H_B) couple with each other and the hydroxymethyl protons (H_X and H_Y) leading to the formation of an ABXY pattern which appears as a triplet of an AB quartet at 5.22 ppm with J = 12.7 Hz and 1.9 Hz. The AB quartet pattern results from the allenyl protons coupling with one another and the triplet arises from the coupling of the allenyl protons with the hydroxymethyl protons. The hydroxymethyl protons (H_X and H_Y) appear as a doublet of triplets at 4.51 ppm with J = 6.2 and 1.8 Hz. The doublet arises from coupling with the hydroxy proton and the triplet arises

from the allenyl protons. Although protons A and B exist in different chemical environments, their coupling influences on H_X and H_Y are comparable revealing an apparent triplet rather than a doublet of doublets. The hydroxy proton is at 3.47 ppm and appears as a triplet (J = 6.3 Hz) due to the splitting from the hydroxymethyl protons.

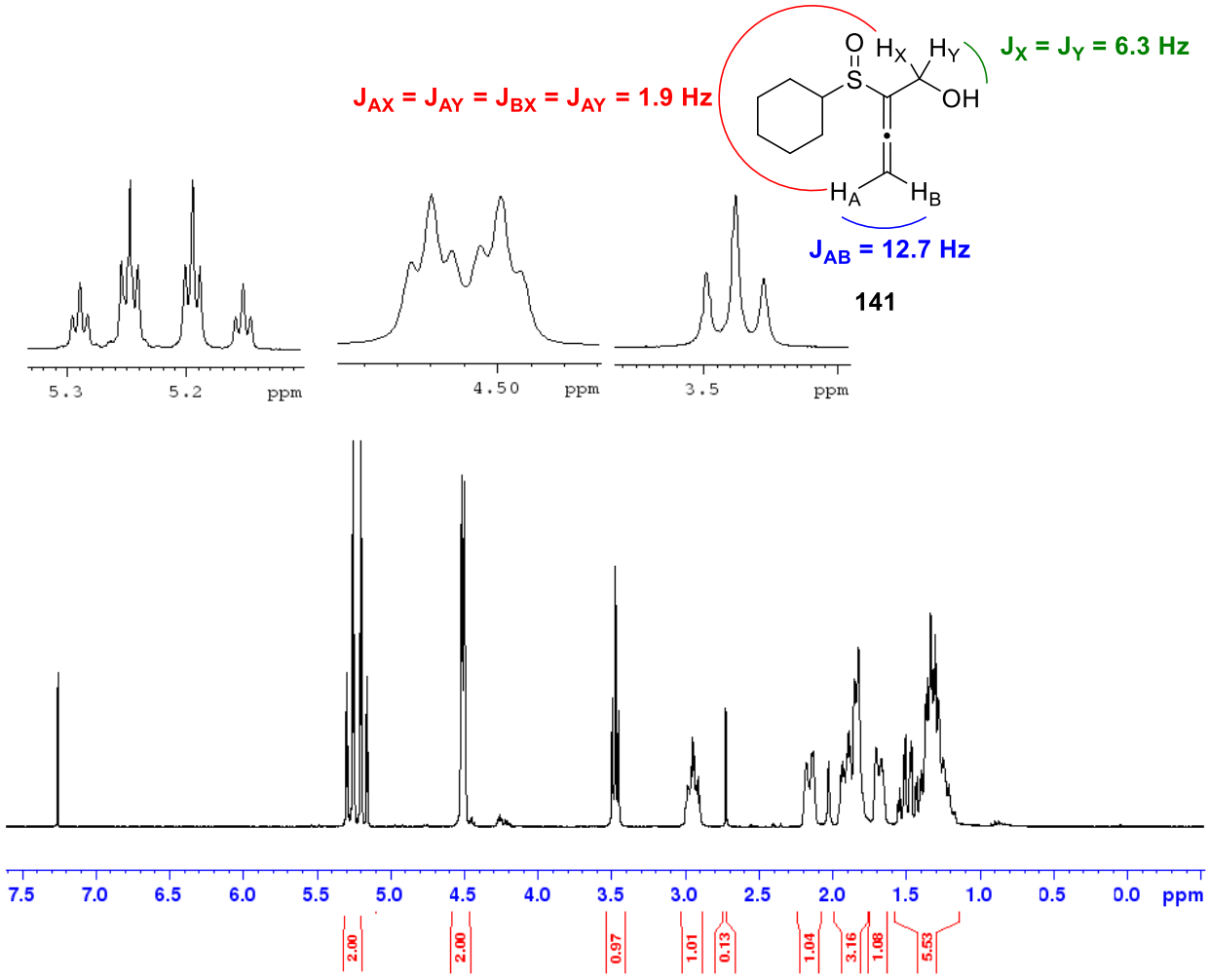
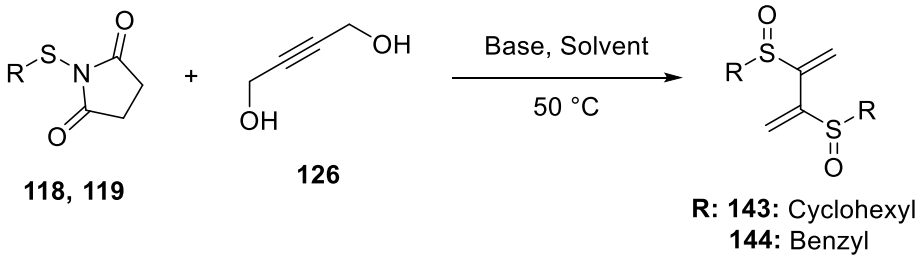


Figure 18: ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of 2-(cyclohexylsulfinyl)buta-2,3-dien-1-ol (**142**)

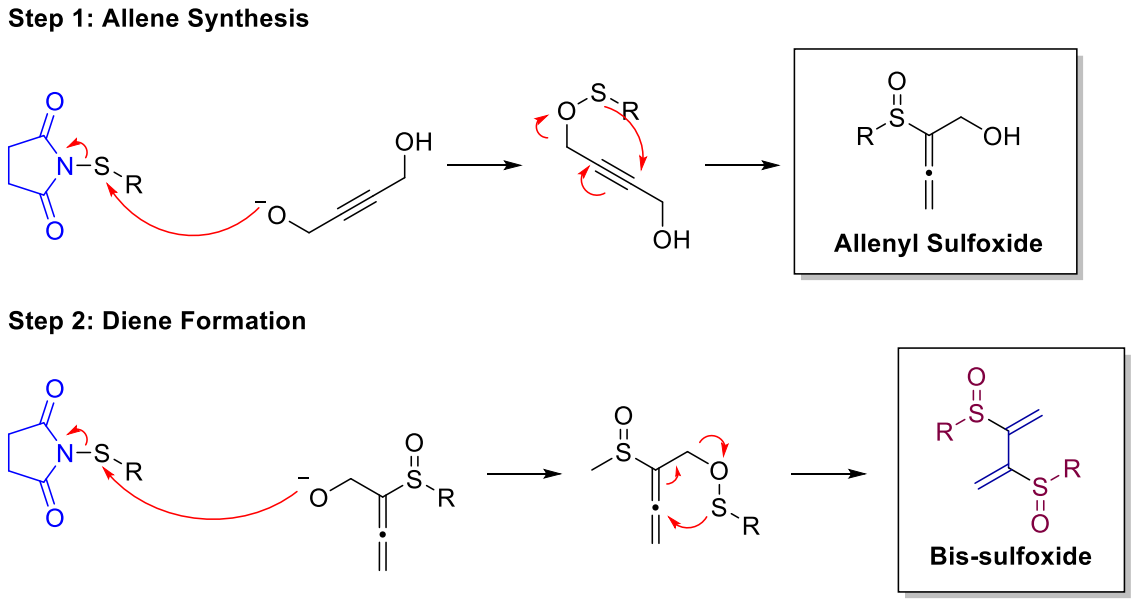
Interestingly, when thiosuccinimides **118** and **119** are reacted with diol **126** in chloroform a bis-sulfoxide (**143** and **144**) product forms. This likely arises from the poor solubility of diol **126** in chloroform as there would always be more thiosuccinimide than diol in solution leading to the

reaction of the hydroxymethyl group on allenyl sulfoxides **141** and **142** with another thiosuccinimide molecule. The conditions of these experiments are detailed in ***Table 20***.

Table 20: Synthesis of bis-sulfoxides **143** and **144** from thiosuccinimides



Thiosuccinimide	Base	Base: Alcohol: Thiosuccinimide	Solvent	Reaction Time	Percent Yield
Cyclohexyl (**118**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	7 hr	8%
Benzyl (**119**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	4 hr	25%



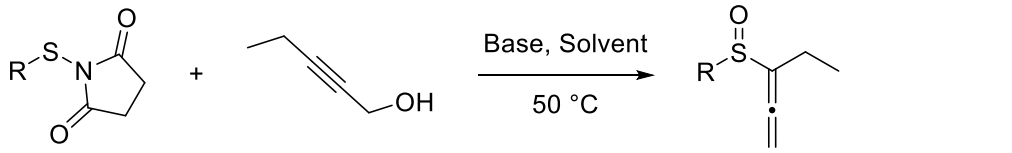
Scheme 93: Mechanism for the formation of hydroxymethyl allenyl sulfoxides and bis sulfoxides similar to **143** and **144**

The formation of bis-sulfoxides **143** and **144** can be explained by the mechanism shown in ***Scheme 93***. After the initial formation of the allenyl sulfoxide, another equivalent of base deprotonates the hydroxy group and this deprotonated oxygen attacks another thiosuccinimide molecule to create a sulfenate ester. Another [2,3]-sigmatropic rearrangement leads to bis-sulfoxides **143** or **144**. Bis-sulfoxides **143** and **144** have the potential for extensive synthetic utility as they possess a 1,3-diene functional group (shown in dark blue) which could prove useful in Diels-Alder reactions and also have two sites that could produce a sulfenate anion (shown in burgundy) if thiosuccinimide **112a** was utilized (***Scheme 93***).

4.2.6 Towards the Synthesis of Ethyl Allenyl Sulfoxides

The synthesis of various ethyl-substituted allenyl sulfoxides (**146-147**) can also be performed utilizing thiosuccinimides as the starting material and reacting them with 2-pentyn-1-ol (**145**). Sulfoxides **146-147** can be synthesized in yields ranging from 21 to 53% as illustrated in ***Table 21***. Both reactions were performed at 50 °C in chloroform and had similar reaction times to the phenyl allenyl sulfoxide reactions.

Table 21: Synthesis of ethyl substituted allenyl sulfoxides (**146** and **147**) from thiosuccinimides



112b, 118 **145**

R: 146: Cyclohexyl
147: Methoxylcarbonyl ethyl

Thiosuccinimide	Base	Base: Alcohol: Thiosuccinimide	Solvent	Reaction Time	Yield
Cyclohexyl (**118**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	4 hr	53%
Methoxycarbonyl ester (**112b**)	K_2CO_3	4.0 : 3.0 : 1.0	Chloroform	8 hr	21%

The ^{1}H NMR spectrum of methyl 3-(penta-1,2-diene-3-sulfinyl)propanoate (**147**) is illustrated in ***Figure 19*** and the diagnostic peaks are at 5.25, 2.24 and 1.13 ppm. The two allenyl protons (H_A and H_B) couple with each other and the methylene protons (H_X and H_Y) leading to the formation of an multiplet at 5.22 ppm and not the expected triplet of AB quartet pattern. The ^{1}H NMR spectrum of (penta-1,2-diene-3-sulfinyl)cyclohexane (**146**) in ***Figure 20*** illustrates the expected triplet of AB quartet pattern at 5.13 ppm with J = 11.9 Hz and 3.8 Hz. The two methylene protons (H_X and H_Y) couple the two allenyl protons (H_A and H_B) and the terminal methyl protons (H_T) leading to the formation of a multiplet with an AB type structure at 2.24 ppm. The terminal methyl protons (H_T) couple with the two methylene protons (H_X and H_Y) to produce a triplet at 1.13 ppm with J = 7.4 Hz.

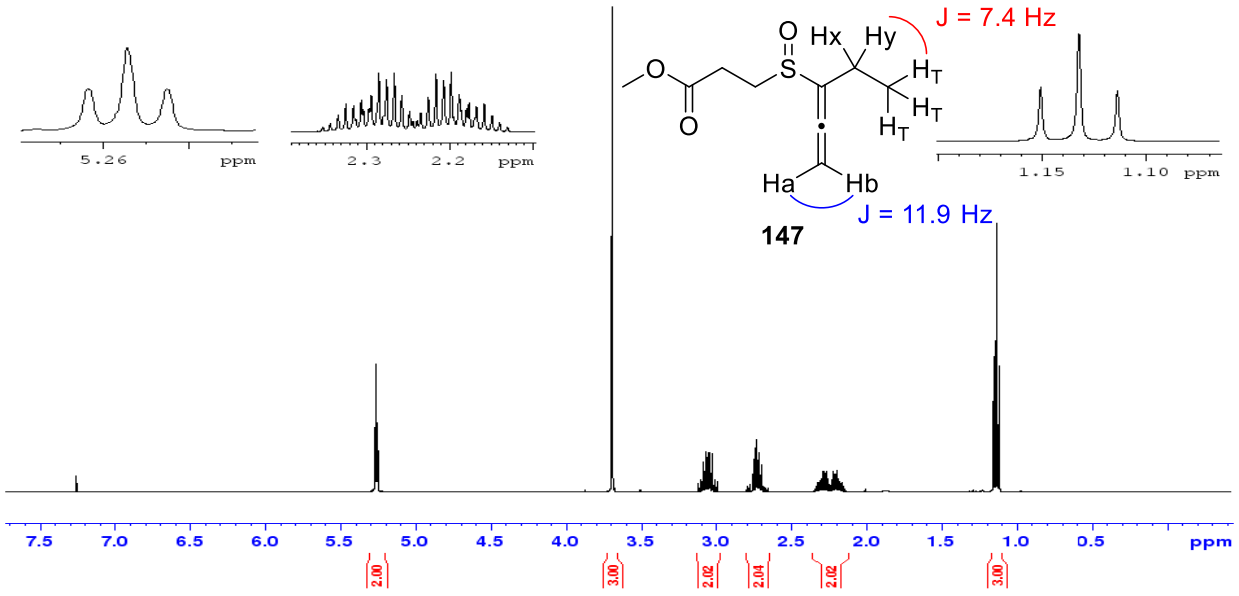


Figure 19: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of methyl 3-(penta-1,2-diene-3-sulfinyl)propanoate (**147**)

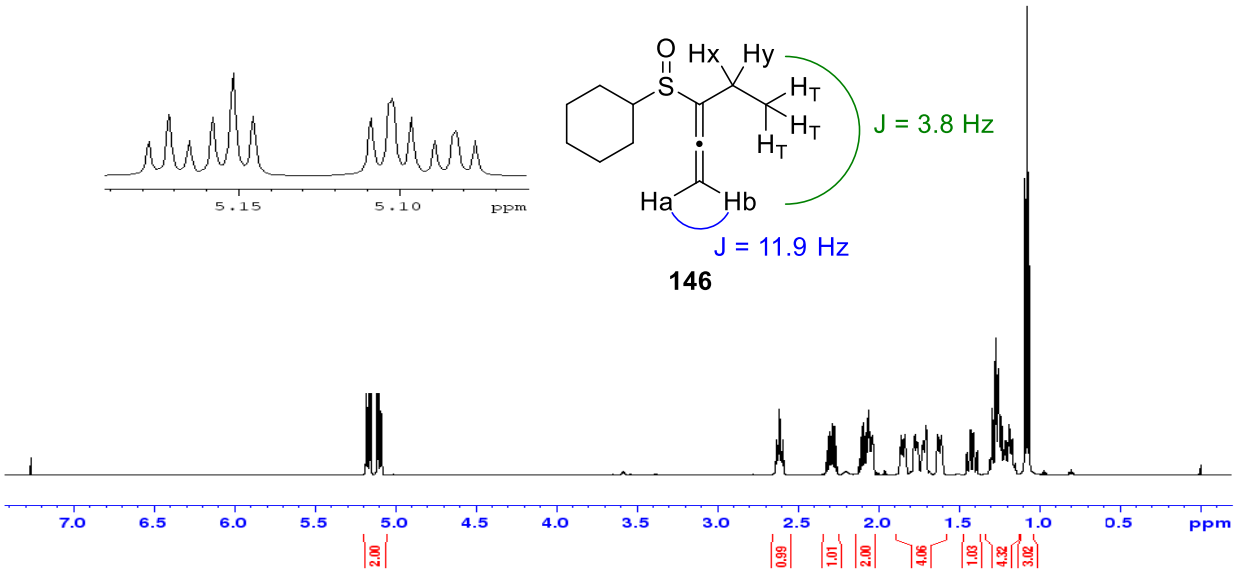
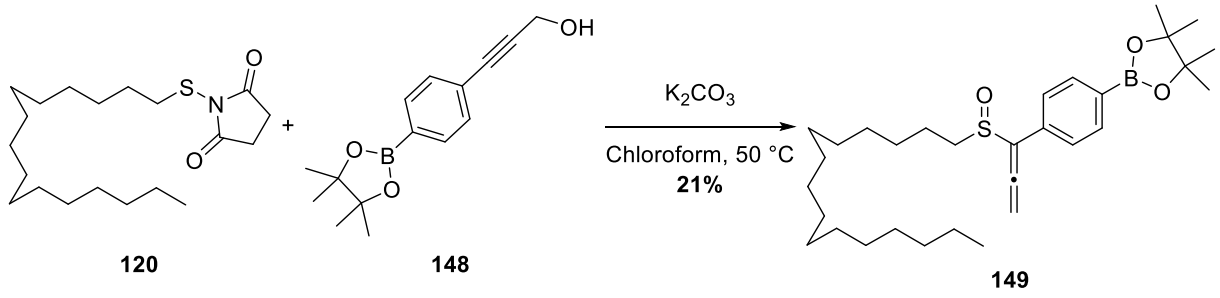


Figure 20: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (penta-1,2-diene-3-sulfinyl)cyclohexane (**146**)

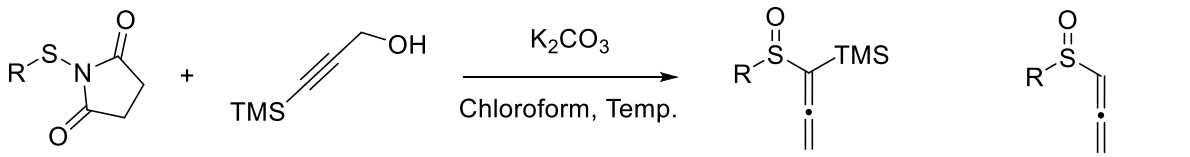
4.2.7 Towards the Synthesis of Other Allenyl Sulfoxides

To test the use of thiosuccinimides in the synthesis of more complex allenyl sulfoxides, more unique propargyl alcohols had to be utilized in the synthesis of allenyl sulfoxides. The first unique propargyl alcohol that was utilized was 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propyn-1-ol (**148**). Propargyl alcohol **148** contains a pinacol boronate ester (BPin) functional group which has been useful for cross-coupling reactions such as the Nobel Prize winning Suzuki-Miyaura coupling reaction.[159] The BPin group can therefore lead to further functionalization of the product allenyl sulfoxide in cross-coupling type and other borate ester related reactions. Allenyl sulfoxide **149** was synthesized by mixing thiosuccinimide **120** with two equivalents of propargyl alcohol **148** and three equivalents of potassium carbonate in chloroform at 50 °C for 5 days (***Scheme 94***). This procedure synthesized allenyl sulfoxide **149** in a 21% yield and illustrates that synthesizing allenyl sulfoxides from thiosuccinimides can be performed with large and complex propargyl alcohols.



Scheme 94: Synthesis of 2-{4-[1-(hexadecane-1-sulfinyl)propa-1,2-dien-1-yl]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**149**)

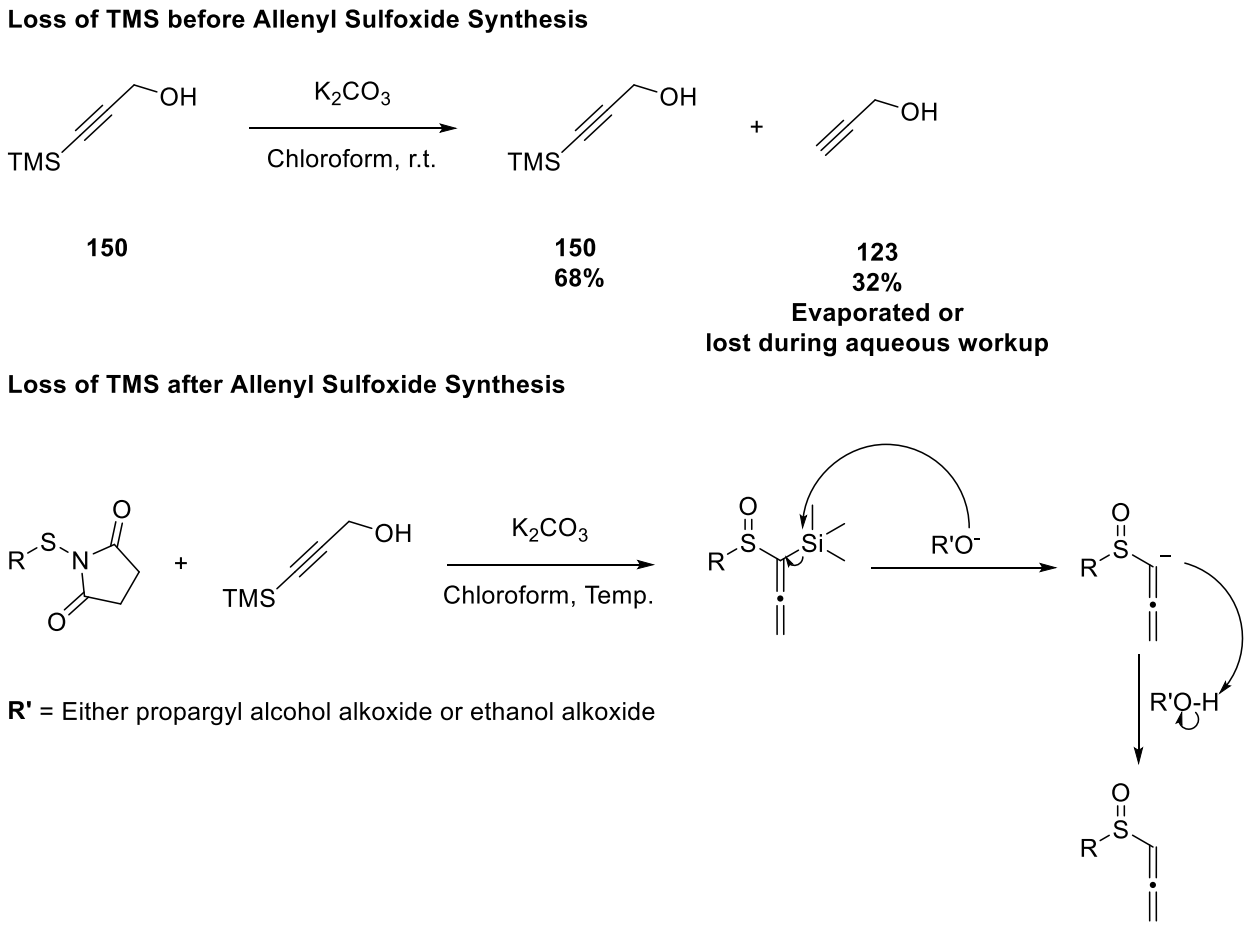
Table 22: Trials towards the synthesis of allenyl sulfoxide **151** from thiosuccinimides



Thiosuccinimide	Base	Base: Alcohol: Thiosuccinimide	Solvent	Reaction Time	Reaction Temp.	Product?
Benzyl (**119**)	K_2CO_3	3.0 : 2.0 : 1.0	Chloroform	12 hr	50 °C	No, **130** isolated in a 13% yield
Benzyl (**119**)	K_2CO_3	3.0 : 2.0 : 1.0	Chloroform	4 hr	25 °C	No, **130** formed
Cyclohexyl (**118**)	K_2CO_3	3.0 : 2.0 : 1.0	Chloroform	38 hr	25 °C	No, **128** formed

Another propargyl alcohol that was attempted is 3-(trimethylsilyl)-2-propyn-1-ol (**150**). The terminal trimethyl silyl group of propargyl alcohol **150** would also provide a method for further functionalizing the synthesized allenyl sulfoxides produced like propargyl alcohol **148**. The trials for the synthesis of allenyl sulfoxide **151** from various thiosuccinimides and propargyl alcohol **147** are illustrated in ***Table 22***, which indicates that allenyl sulfoxide **151** was not formed

from this reaction despite the different conditions attempted and instead, the reaction produced unsubstituted allenyl sulfoxide (**128** or **130**).



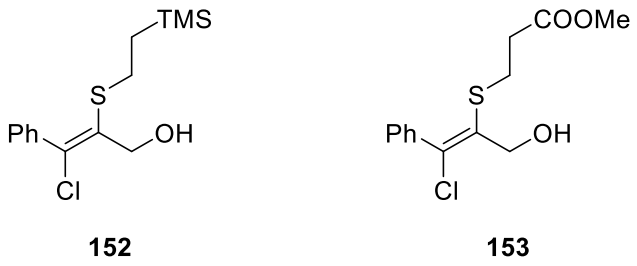
Scheme 95: Loss of the trimethyl silyl group and formation of unsubstituted allenyl sulfoxides

As the ^{1}H NMR spectrum of the crude reaction material for each of the trials illustrated in ***Table 22*** consistently indicated a loss of the trimethyl-silyl group from the alcohol, it was concluded that the trimethyl silyl group is lost during the reaction. However, it is unknown at which stage of the reaction, before or after the formation of the allenyl sulfoxide, the trimethyl silyl group is lost. To determine this, propargyl alcohol **150** was subjected to the reaction conditions depicted in trial 3 of ***Table 22*** without thiosuccinimide **119**. After 7 days, this experiment was analyzed and it was found that 68% of the original propargyl alcohol remained,

meaning that for 32% of the original propargyl alcohol it is likely that the TMS group was removed and the remaining propargyl alcohol (**123**) was lost in the concentration or workup of the sample. However, as allenyl sulfoxide **151** was not recovered, it is also likely that the trimethyl silyl group was removed after the formation of the allenyl sulfoxide. As basic conditions have been shown to remove a trimethyl silyl group from an allene previously, it is likely that the TMS group is removed both before, and after, the formation of allenyl sulfoxide **151** (*Scheme 95*).[160]

4.3 Attempted Synthesis of Allenyl Sulfoxides from Sulfenyl Chlorides

Previous Schwan group M.Sc. Students Michelle Michalski[131] and Monika Kulak[139] both attempted to synthesize allenyl sulfoxides directly from sulfenyl chlorides **109a,b**. However their attempts were unsuccessful and instead they both detected the synthesis of an alkene that corresponds to the addition of the sulfenyl chlorides **109a,b** across the triple bond of propargyl alcohol **127**.[131,139] As neither of these alkenes were properly characterized, the goal of this part of my research became the isolation and characterization of alkene **152** and **153** (*Figure 21*).

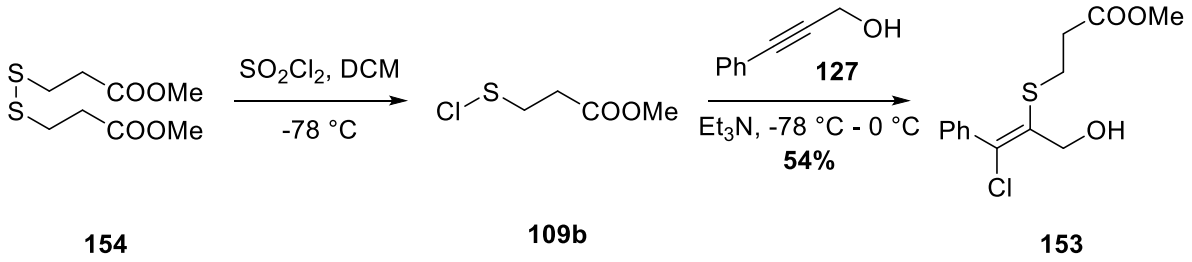


152 **153**

Figure 21: Proposed structures for the alkenes formed from the addition of sulfenyl chlorides **109a** and **109b** across the triple bond of propargyl alcohol **127**

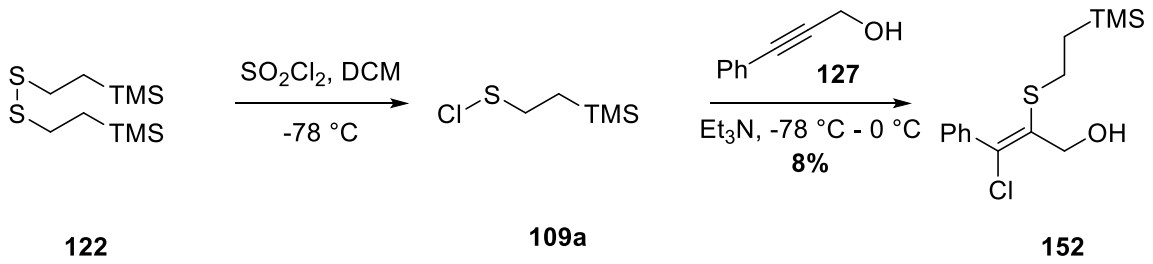
2-Methoxycarbonylethanesulfenyl chloride (**109b**) has been synthesized and characterized by Kulak[139] previously. Generation of the sulfenyl chloride (**109b**) can be achieved from the corresponding disulfide (**154**) via an established protocol using sulfuryl chloride in DCM at -78 °C.[131] After this, it was reacted with two equivalents of propargyl alcohol **127** and four equivalents

of triethylamine in an attempt to simulate the conditions that would be useful for the formation of the corresponding allenyl sulfoxide. These conditions produced alkene **153** in a 54% yield after purification by column chromatography (***Scheme 96***).



Scheme 96: Synthesis of methyl 3-{[(1E)-1-chloro-3-hydroxy-1-phenylprop-1-en-2-yl]sulfanyl}propanoate (**153**) from disulfide **154**.

Unlike sulfenyl chloride **109b**, 2-trimethylsilylethanesulfenyl chloride (**109a**) is a known compound which has been prepared previously by reacting the corresponding disulfide with sulfuryl chloride at -78 °C in DCM.[154] Several attempts to react compound **109a** with propargyl alcohol **127** in the attempt to form allenyl sulfoxide **111a**, in a similar manner to those utilized to form alkene **153** (***Scheme 96***) were carried out by Michalski[131] and Kulak[139] but none of these attempts were successful. However, the formation of alkene **152** was given as the reason for not forming the corresponding allenyl sulfoxide despite alkene **152** never being detected. The current work attempted to prove the synthesis of alkene **152** by generating sulfenyl chloride **109a** disulfide (**122**) by reacting the disulfide with sulfuryl chloride in DCM at -78 °C before the addition of propargyl alcohol **127** and triethylamine. This led to the synthesis of alkene **152** in an 8% yield with no other major products collected during purification of the crude reaction material (***Scheme 97***). This serves as an indication that sulfenyl chloride **109a** prefers to form alkene **152** instead of the corresponding allenyl sulfoxide when exposed to these conditions.



122 **109a** **152**

Scheme 97: Synthesis of (2E)-3-chloro-3-phenyl-2-{[2-(trimethylsilyl)ethyl]sulfanyl}prop-2-en-1-ol (**151**)

The successful synthesis of alkene **152** and **153** demonstrates the preferred outcome of the reaction between sulfenyl chlorides **109a-b** and phenyl propargyl alcohol **127**. Despite being in conditions favourable for the formation of allenyl sulfoxides (i.e. basic conditions), the sulfenyl chlorides preferred to add across the triple bond of alcohol **127** rather than acting as electrophilic sulfenylating agents for reaction with the alcohol functionality. The formation of alkenes **152** and **153** further demonstrates that sulfenyl chlorides are not the optimal electrophilic sulfur source for the formation of allenyl sulfoxides.

4.4 Conclusions and Future Work

In conclusion, twenty allenyl sulfoxides were synthesized by way of a [2,3]-sigmatropic rearrangement of sulfenate esters formed by reacting propargyl alcohols and thiosuccinimides (*Figure 22*). The synthesis of thiosuccinimides **112a-b,118-120** are detailed and the reactions between these thiosuccinimides and propargyl alcohols **123-127, 145** and **148** are illustrated in detail in the preceding sections. The effects of different solvents and bases on the synthesis of allenyl sulfoxides from thiosuccinimides and propargyl alcohols were investigated and led to the discovery that chloroform and potassium carbonate are the optimal solvent and base pair for the synthesis of allenyl sulfoxides.

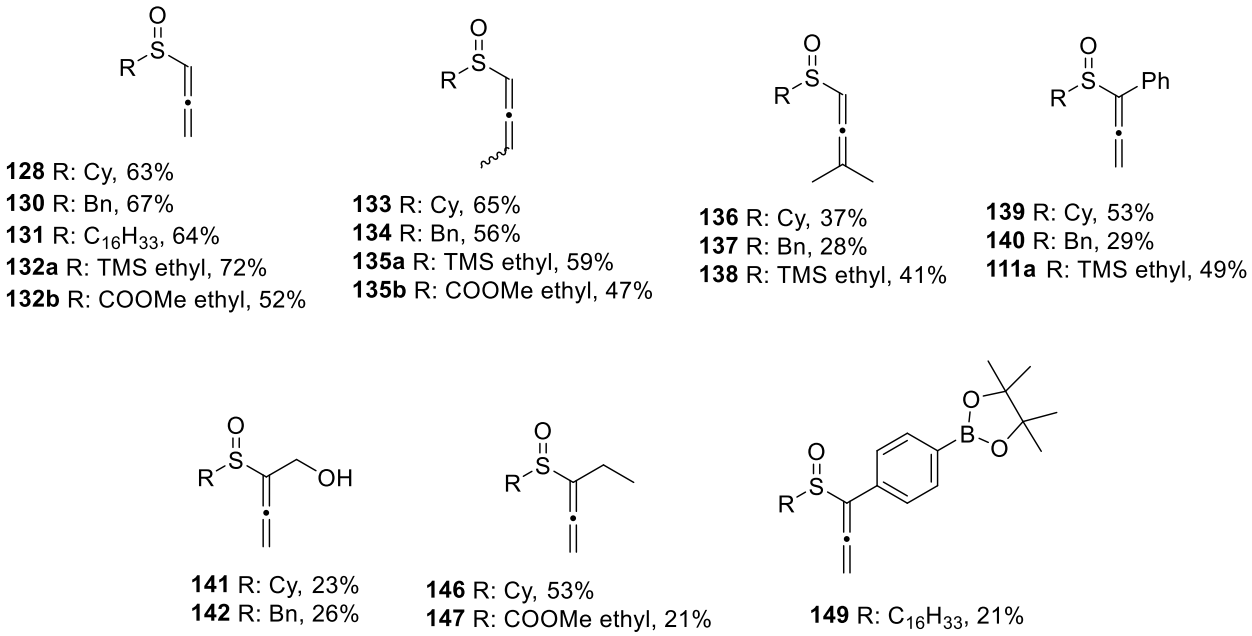
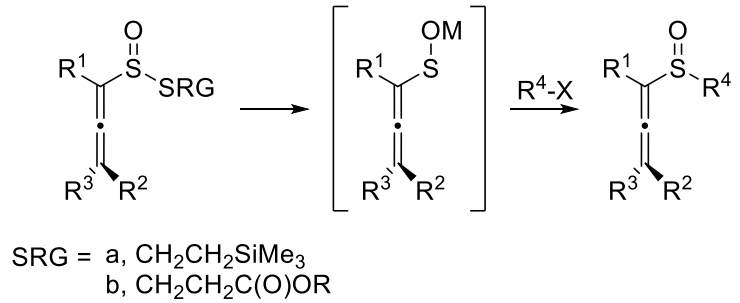


Figure 22: Allenyl sulfoxide synthesis summary

In order to illustrate that sulfenyl chlorides are suboptimal choices for the electrophilic sulfur source in the formation of allenyl sulfoxides, sulfenyl chlorides **109a-b** were subject to conditions that would be conducive to the formation of allenyl sulfoxides. From these reactions, alkenes **152** and **153** (***Figure 21***) were isolated which illustrated that sulfenyl chlorides would rather add across the triple bond of phenyl propargyl alcohol **127** than form the corresponding allenyl sulfoxides.

Future work on this project would involve investigations into the sulfenate chemistry of allenyl sulfoxides **111a**, **132b**, **135b**, **138**, and **147** as the utility of these compounds in the sulfenate alkylation reaction has not been probed. The sulfenate chemistry investigations would revolve around assessing the reactivity of these compounds when treated with the corresponding sulfenate releasing agent and the quenching of the corresponding allenyl sulfenates with various electrophiles (***Scheme 98***).



Scheme 98: The release and alkylation of an allenyl sulfenate anion

In addition to the investigations into sulfenate chemistry, the synthesis of allenyl sulfoxides from thiosuccinimides and a [2,3]-sigmatropic rearrangement should be probed for its utility in the synthesis of larger sulfoxide-containing natural products. The use of larger and more complex thiosuccinimides or propargyl alcohols could reveal new aspects about this chemistry that have yet to make themselves known. The effects of chiral thiosuccinimides and propargyl alcohols on the stereochemistry of the produced allenyl sulfoxides has yet to be examined and could also produce novel and interesting results in this field.

Chapter 5: Experimental

5.0 EXPERIMENTAL

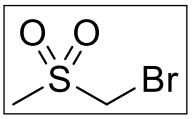
General Methods and Instrumentation

All reactions were performed in flame-dried glassware under argon unless specified otherwise. Pressure vessel reactions were carried out in heavy-walled cylindrical vessels with an internal thread and a 15 mm Teflon ® o-ring as a pressure seal. Dry solvents were obtained from a LC-SPS solvent purification system. TLC analysis with Silica Gel 60 pre-coated on glass plates with fluorescent indicator and visualized using UV, iodine, and/or *p*-anisaldehyde stain. Flash column chromatography was performed with silica supplied by Silicycle ® with particle size 30 – 60 (mesh 230 – 400).

^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker Avance 300 (300 MHz ^{1}H, 75 MHz ^{13}C), a Bruker Avance 400 (400 MHz ^{1}H, 100.6 MHz ^{13}C), or a Bruker Avance 600 (600 MHz ^{1}H, 150.9 MHz ^{13}C). Chemical shifts (ppm) and coupling constants (J, Hz) were determined from first order analysis of one-dimensional spectra. The proton spectra are reported as δ (multiplicity, coupling constant J, number of protons). ^{1}H NMR data is reported using standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublet (dd), and multiplet (m). ^{1}H NMR and ^{13}C NMR chemical shifts are referenced to $CHCl_3$ and $CDCl_3$ respectively. Melting points were determined using a MEL-TEMP melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Bruker FT-IR spectrometer as a neat film on KBr plates. EI and ESI HRMS was performed by the Mass Spectrometry Facility at Queens University, Kingston, ON or the McMaster Regional Centre for Mass Spectrometry at McMaster University, Hamilton, ON.

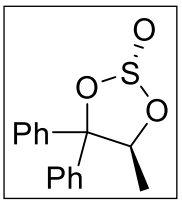
5.1 Shiitake Mushroom Project

Synthesis of bromo(methanesulfonyl)methane 58



To an oven dried and argon purged flask was added a solution of sodium methanesulfinate (2.00 g, 19.6 mmol) in dry dimethyl formamide (20 mL). Dibromomethane (1.65 mL, 23.5 mmol) was added dropwise to the solution. The reaction was heated to 80 °C and stirred for 20 hours. The reaction was allowed to return to room temperature and was quenched with water (100 mL). The mixture was extracted with ethyl acetate (5×) and the combined organic layers were washed with saturated sodium thiosulfate (1×) and brine (1×). The organic layer was dried over $MgSO_4$. The solids were filtered, and the solution was concentrated under reduced pressure. The crude product was purified by flash column chromatography (60:40 hexanes: ethyl acetate) to yield compound **75b**. The product was a white solid, 1.61 g, 59% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (q, J = 0.7 Hz, 2H), 3.11 (t, J = 0.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 42.63, 38.20. FTIR (cm^{-1}): 3018, 2946, 2931, 1298, 1132, 648.

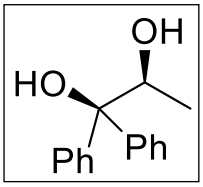
Synthesis of (2R,5S)- 1,3,2-Dioxathiolane, 5-methyl-4,4-diphenyl-, 2-oxide 59[80]



In a flame dried and argon purged flask, diol **69** (4.00 g, 17.5 mmol) was dissolved in dry DCM (30.0 mL) and cooled to -40 °C. Thionyl chloride (2.60 ml, 35.6 mmol) was dissolved in dry DCM (13.0 mL) and added to the solution. Triethylamine (6.10 ml, 43.8 mmol) was dissolved in dry DCM (50.0 mL) and added dropwise to the solution. Reaction was allowed to warm to -20 °C and was mixed for 1 hour. The reaction was quenched with water (150 mL) and the layers were separated. The aqueous layer was extracted with DCM (3×) and the combined organic layer was then washed with water (2×) and brine (1×). The organic solution was then dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The resulting crude solid was recrystallized from a

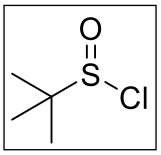
hexanes: cyclohexane solution (1:1) to afford compound **65**. The product consisted of pale orange crystals, 3.17 g, 66% yield with a 95:5 dr between the trans and cis products. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 8H), 7.03 (m, 2H), 5.72 (q, J = 6.4 Hz, 1H), 1.30 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.31, 138.36, 128.74, 128.55, 128.33, 128.06, 127.56, 126.74, 96.01, 80.42, 16.51. FTIR (cm^{-1}): 3062, 3036, 2990, 2938, 1496, 1228, 1386, 1350, 1214, 1159, 1138, 1097, 1083, 1054, 1033, 1002, 979, 946, 921, 896, 865. $[\alpha]_D^{25}$= -236 (c = 1 in chloroform).

Synthesis of 1,1-diphenylpropane-1,2-diol 63[80]



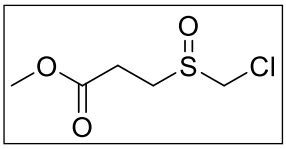
In a flame dried and argon purged flask, Mg turnings (0.800 g, 32.9 mmol) and 5 crystals of iodine were combined in dry Et_2O (15.0 mL). This mixture was stirred for 15 minutes at room temperature. Bromobenzene (3.50 mL, 33.2 mmol) was added and the mixture was heated to reflux for 1.5 hours. (S)-ethyl lactate (1.00 mL, 8.75 mmol) was dissolved in dry Et_2O (1.00 mL) and added dropwise. Reaction was refluxed for another 2 hours before being cooled to room temperature for 20 hours. A saturated ammonium chloride solution (30.0 mL) was added and the resulting mixture was extracted with Et_2O (3×). The combined organic layer was washed with water (2×), brine (1×) and dried over $MgSO_4$. The mixture was filtered and concentrated under reduced pressure and the resultant solid was recrystallized in hexanes. The product was a yellow-white crystalline solid, 1.48 g, 74% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.16 (m, 10H), 4.83 (q, J = 6.3 Hz, 1H), 1.12 (d, J = 6.2 Hz, 3H). 13C NMR (101 MHz, $CDCl_3$) δ 145.63, 128.61, 127.32, 126.85, 126.23, 125.55, 79.97, 71.67, 16.61. FTIR (cm^{-1}): 3449, 3059, 1492, 1449, 1374, 1173, 1066, 996, 881. $[\alpha]_D^{25}$= -94.6 (c = 1.6 in chloroform).

Synthesis of 2-methylpropane-2-sulfinyl chloride 66[81]



Thiosulfinate **91** (4.00 g, 22.4 mmol) was dissolved in dry DCM (30.0 mL) and the solution was cooled to 0 °C. A solution of sulfuryl chloride (1.90 ml, 23.4 mmol) in Dry DCM (30.0 mL) was added dropwise. After the addition was complete, the reaction mixture was stirred for 1 h, during which time the temperature was allowed to rise slowly to room temperature. The volatiles were removed under reduced pressure without heating to give compound **71** as a yellow liquid that did not require further purification. 3.76 g, 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s). ^{13}C NMR (75 MHz, CDCl3) δ 64.48, 22.61. FTIR (cm^{-1}): 2965, 2924, 2853, 1456, 1365, 1310, 1214, 1181, 1160, 1110, 1059, 1017, 752.

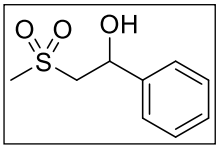
Synthesis of methyl 3-chloromethanesulfinylpropanoate 67



Paraformaldehyde (0.789 g, 26.2 mmol) and trimethylsilyl chloride (4.00 mL, 31.5 mmol) were combined and cooled to -20 °C. Methyl 3-mercaptopropanoate (2.90 mL, 26.2 mmol) was added dropwise and the resulting solution mixed at -20 °C for 1 hour and 0 °C for 1 hour. The solids were separated by vacuum filtration and the resulting organic solution was concentrated under reduced pressure. A solution of SiO_2 (1.08 g) and water (1.08 g) was added dropwise to a solution of the crude reaction material dissolved in DCM (10.8 mL). To the resulting solution was added dropwise a solution of sulfuryl chloride (1.23 ml, 15.2 mmol) in DCM (10.8 mL). The solution was mixed at room temperature for 2.5 hours before being quenched with water (20 mL). The layers were separated, and the aqueous layer was extracted with DCM (2×). The combined organic layer was washed with brine (1×) and dried over $MgSO_4$. The solids were filtered, and the remaining organic layer was concentrated under reduced pressure. The crude reaction material was purified by flash column chromatography (50:50 to 100:0 EtOAc: hexanes). The product was a clear and colourless oil, 0.0505 g, 1%. ^{1}H NMR (400

MHz, $CDCl_3$) δ 4.42 (ABq, *J* = 11.0 Hz, 2H), 3.72 (s, 3H), 3.14 (m, 2H), 2.84 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.54, 56.30, 52.43, 44.74, 26.35. FTIR (cm^{-1}): 3007, 2954, 1735, 1438, 1365, 1291, 1241, 1198, 1179, 1052, 979, 851. HRMS(ESI): Calc'd for $C_{14}H_{15}NO_3S_2$ $[M+H]^+$ 185.0034. Found: 185.0028.

Synthesis of 2-methanesulfonyl-1-phenylethan-1-ol 70



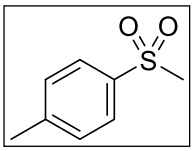
With nBuLi: Dimethyl sulfone (0.250 g, 2.66 mmol) was dissolved in dry THF (25.0 mL) and cooled to -78 C. A solution of nBuLi (1.6 M, 1.99 mL, 3.18 mmol) and TMEDA (0.480 mL, 3.20 mmol) were added. The solution was stirred for 30 minutes at -78 °C. Benzaldehyde (0.250 mL, 2.46 mmol) was added and the solution was allowed to warm to 25 °C for 2 hours. The solution was quenched with saturated NH_4Cl (25.0 mL) and the layers were separated. The organic layer was diluted with EtOAc before it was washed with water (2×) and brine (1×). The solution was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (50:50 hexanes: EtOAc). The product was a white solid. 0.324 g, 67% yield.

With EtMgBr: Dimethyl sulfone (0.250 g, 2.66 mmol) was dissolved in dry THF (25.0 mL). A solution of EtMgBr (3.0 M in THF, 1.08 ml, 3.24 mmol) was added dropwise over a 30-minute period. The solution was mixed at 25 °C for 2.5 hours before the addition of benzaldehyde (0.225 mL, 2.21 mmol). The cloudy mixture was stirred for 20 hours before being quenched with a solution of saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with water (2×) and brine (1×) and dried over $MgSO_4$. The solids were filtered, and the organic solution was concentrated under reduced pressure. The crude product was purified by flash column chromatography (50:50 hexanes: EtOAc). The product was a white solid. 0.225, 51% yield.

From dimethyl sulfoxide: NaH (60% dispersion in mineral oil, 0.590 g, 14.8 mmol) was added to dry DMSO (12.0 mL, 169 mmol) and heated to 60 °C. The solution was mixed for 45 minutes before being cooled to room temperature, diluted with dry THF (5.41 mL) and cooled to 0 °C. Benzaldehyde (1.00 mL, 9.84 mmol) was dissolved in dry THF (4.60 mL) and added dropwise. The solution mixed for 4 hours at 0 °C before being quenched with a saturated aqueous solution of NH_4Cl. The mixture was extracted with chloroform (3×) and the combined organic layer was washed with water (5×) and brine (1×) before being dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. This crude reaction mixture was then dissolved in DCM (20.0 mL). *m*-CPBA (59.7%, 6.26 g, 21.7 mmol) was dissolved in DCM (200 mL) and added dropwise over the period of 1 hour. The resulting solution mixed at room temperature for 17 hours before being washed with saturated $Na_2S_2O_3$ (1× 200 mL), sat. $NaHCO_3$ (1× 200 mL), water (3× 100 mL) and brine (1× 200 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude reaction material was purified by flash column chromatography (50:50 hexanes: EtOAc). The product was a white solid, 0.787 g, 40% yield.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41−7.30 (m, 5H), 5.32 (ddd, J = 10.3, 3.0, 2.1 Hz, 1H), 3.44 (ddd, J = 14.8, 10.3, 0.4 Hz, 1H), 3.14 (m, 1H), 3.07 (dd, J = 3.0, 1.2 Hz, 1H), 3.03 (br s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 141.22, 129.14, 128.71, 125.86, 69.47, 62.53, 43.01. FTIR (cm^{-1}): 3431, 1601, 1494, 1457, 1390, 1359, 1309, 1274, 1233, 1161, 1121, 1080, 1060, 1027, 1001.

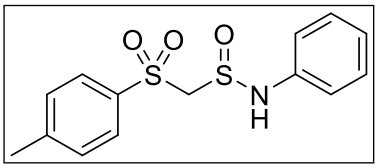
Synthesis of 1-methanesulfonyl-4-methylbenzene[161]



Sodium p-toluenesulfinate (5.00 g, 28.1 mmol) and iodomethane (2.10 mL, 33.7 mmol) were combined in dry DMSO (40.0 mL). The cloudy mixture was stirred at 25 °C for 20 hours during which time the solution became clear. The reaction was quenched

with water (50.0 mL) and the resulting solution was extracted with EtOAc (5×). The combined organic layer was washed with water (2×) and brine (1×) before being dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was recrystallized from a 1:1 solution of hexanes and EtOAc to afford the product. The product was a white crystalline solid, 3.44 g, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 2H), 7.36 (m, 2H), 3.03 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.83, 137.91, 130.14, 127.52, 44.73, 21.72. FTIR (cm^{-1}): 3010, 2926, 1320, 1301, 1290, 1148.

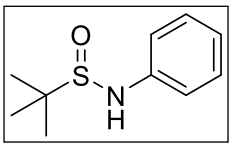
Synthesis of 1-(4-methylbenzenesulfonyl)-N-phenylmethanesulfinamide 72



To a solution consisting of aniline (0.538 mL, 5.90 mmol) in dry toluene (2.50 mL) was added a solution of thionyl chloride (0.560 ml, 7.68 mmol) in dry toluene (2.50 mL). The resulting mixture was heated to reflux for 2.5 hours before being concentrated under reduced pressure, dissolved in toluene (5.00 mL) and cooled to 0 °C. In a separate flame-dried round bottom flask, 1-methanesulfonyl-4-methylbenzene (1.01 g, 5.93 mmol) was dissolved in dry toluene (25.0 mL). To this solution was added EtMgBr (3.0 M in THF, 2.38 mL, 7.14 mmol) and then the mixture was stirred for 20 minutes at room temperature followed by 5 minutes at reflux. The sulfone solution was added dropwise to the N-thionyl aniline solution at 0 °C and this mixture was allowed to return to room temperature overnight before being quenched with water. The layers were separated, and the aqueous layer was then extracted with EtOAc (3×). The combined organic layers were washed with brine (1×) and dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was purified by flash column chromatography (70:30 EtOAc: hexanes). The product **78** was a pale orange flaky solid, 0.745 g, 41% yield. MP: 126-128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.35 (m, 2H),

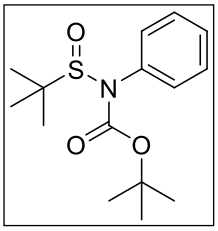
7.29 (m, 2H), 7.21 (br, s, 1H), 7.11 (tt, J = 7.4, 1.1 Hz, 1H), 7.04 (m, 2H), 4.51 (ABq, J = 13.9 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.14, 139.47, 136.55, 130.23, 129.78, 128.63, 124.68, 120.09, 73.14, 21.89. FTIR (cm^{-1}): 3201, 2917, 1599, 1497, 1410, 1352, 1305, 1293, 1234, 1186, 1149, 1121, 1087, 1063. HRMS(ESI): Calc'd for $C_{14}H_{15}NO_3S_2$ $[M+H]^+$ 310.0566. Found: 310.0581.

Synthesis of 2-methyl-N-phenylpropane-2-sulfinamide 75[162]



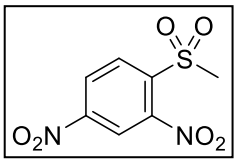
To a solution consisting of aniline (1.00 mL, 11.0 mmol) in dry toluene (5.00 mL) was added a solution of thionyl chloride (1.07 ml, 14.7 mmol) in dry toluene (5.00 mL). The resulting mixture was heated to reflux for 2.5 hours before being concentrated under reduced pressure, dissolved in toluene (5.00 mL) and cooled to 0 °C. A 1.0 M solution of tBuMgCl in THF (16.5 mL, 16.5 mmol) was added dropwise and the resulting solution was mixed for 1 hour at 0 °C followed by 2 hours at room temperature. The reaction was quenched with a saturated NH_4Cl solution (15.0 mL) and then extracted with EtOAc (3× 30 mL). The combined organic layers were washed with water (2×) and brine (1×) and then dried over Na_2SO_4. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was purified by flash column chromatography (75:25 hexanes: EtOAc). Compound **75** was a white solid, 1.88 g, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.01 (m, 3H), 5.45 (s, 1H), 1.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.01, 129.38, 122.92, 118.34, 56.43, 22.40. FTIR (cm^{-1}): 3188, 3080, 30456, 2960, 2869, 1600, 1497, 1475, 1390, 1364, 1282, 1235, 1178, 1060, 879.

Synthesis of tert-butyl N-(2-methylpropane-2-sulfinyl)-N-phenylcarbamate 76[69]



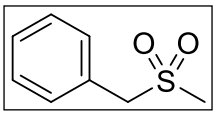
2-Methyl-N-phenylpropane-2-sulfinamide **80** (1.20 g, 6.08 mmol) and DMAP (0.819 g, 6.70 mmol) were dissolved in dry THF and cooled to 0 °C. $(Boc)_2O$ (1.54 mL, 6.70 mmol) was added and the reaction was allowed to return to room temperature to mix for 3 hours. The solution was concentrated under reduced pressure and the crude reaction material was purified by flash column chromatography (75:25 hexanes: EtOAc). The product was an off-white solid, 1.80 g, 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 1.46 (s, 9H), 1.10 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.62, 134.95, 130.31, 128.42, 128.02, 82.96, 59.75, 27.96, 22.98. FTIR (cm^{-1}): 2977, 1719, 1594, 1492, 1393, 1368, 1302, 1155, 1101, 955, 840.

Synthesis of 1-methanesulfonyl-2,4-dinitrobenzene 77



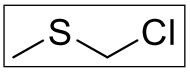
Sodium methanesulfinate (85%, 1.30 g, 10.8 mmol) and 2,4-dinitrochlorobenzene (2.01 g, 9.92 mmol) were dissolved in dry DMF (10.0 mL). The mixture was heated to 120 °C for 20 hours and was quenched with water. The solid precipitate was filtered by vacuum filtration and the remaining aqueous solution was extracted with EtOAc (3×). The combined organic layers were washed with water (2×) and brine (1×) and dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was purified by flash column chromatography (50:50 hexanes: EtOAc). The product was a yellow solid, 0.352 g, 15%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (d, J = 2.2 Hz, 1H), 8.62 (dd, J = 2.2, 8.6 Hz, 1H), 8.46 (d, J = 8.5 Hz, 1H), 3.49 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.14, 133.40, 127.80, 124.22, 120.40, 116.60, 42.43. FTIR (cm^{-1}): 3095, 1605, 1542, 1464, 1406, 1350, 1322, 1275, 1218, 1145, 1081, 1050, 957, 906.

Synthesis of Benzyl methyl sulfone 78



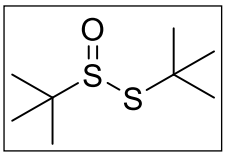
Cyclohexyl mercaptan (0.0300 mL, 0.245 mmol) and potassium carbonate (0.0880 g, 0.637 mmol) were combined in dry DMF (5.00 mL). Sulfone **77** (0.0503 g, 0.204 mmol) was added and the solution mixed for 10 minutes at room temperature. Benzyl bromide (0.0300 mL, 0.252 mmol) was added and the solution was mixed for 18 hours after being heated to 80 °C. The solution was quenched with water and extracted with EtOAc (3×). The combined organic layer was washed with water (6×) and brine (1×) before being dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was purified by flash column chromatography (50:50 hexanes: EtOAc). The product was a yellow solid, 0.0255 g, 74%. Mp: 124-126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 5H), 4.25 (s, 2H), 2.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 130.64, 128.57, 129.38, 130.62, 61.52, 39.15. FTIR (cm^{-1}): 3012, 2976, 2930, 1496, 1460, 1416, 1302, 1116.

Synthesis of chloro(methylsulfanyl)methane 81[163]



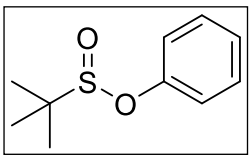
DMSO (5.00 mL, 70.4 mmol) was combined with ether (25.0 mL). The solution was cooled to 0 °C and benzoyl chloride (9.85 mL, 84.9 mmol) was added dropwise. The solution was stirred for three hours at room temperature. The ether was distilled off at atmospheric pressure and the crude reaction mixture was purified by vacuum fractional distillation. The product was a yellow and clear oil, 0.177 g, 3% yield. BP: 38-39 °C (80 mm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (s, 2H), 2.30 (s, 3H).

Synthesis of 2-methyl-2-[(2-methylpropane-2-sulfinyl)sulfanyl]propane 85[81]



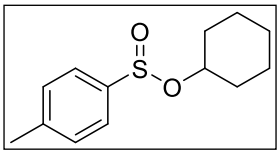
Di-tert-butyldisulfide (7.00 mL, 36.2 mmol) was dissolved in MeOH (180 mL) and cooled to 0 °C. A solution of $NaIO_4$ (7.75 g, 36.2 mmol) in water (125 mL) was added dropwise. The reaction mixture was stirred overnight allowing the cold bath to warm slowly to room temperature. The liberated sodium iodate was vacuum filtered, and the methanol was removed under reduced pressure. The remaining aqueous solution was extracted with DCM (2×). The combined organic layers were washed with brine (1×) and dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was then purified by flash column chromatography (90:10 hexanes: EtOAc). Thiosulfinate **91** was a colourless oil, 4.95 g, 70% yield. ^{1}H NMR (400 MHz, CDCl3): δ 1.55 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, CDCl3): δ 59.52, 48.68, 32.49, 24.43. FTIR (cm^{-1}): 2962, 1457, 1365, 1163, 1071.

Synthesis of phenyl 2-methylpropane-2-sulfinate 86[164]



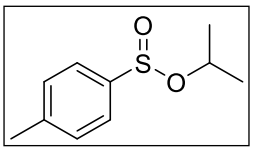
To a solution of phenol (2.04 g, 21.7 mmol) in dry THF (30.0 mL) at 0 °C was added sulfinyl chloride **71** (3.00 g, 21.3 mmol). Triethylamine (3.60 mL, 25.8 mmol) was added dropwise and the solution was stirred overnight while slowly returning to room temperature. The solution was diluted with EtOAc (70.0 mL) and washed with a saturated $NaHCO_3$ solution (5× 100 mL), water (2×) and brine (1×) before being dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was purified by flash column chromatography (90:10 hexanes: EtOAc). The product was a yellow oil, 1.94 g, 46% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.18 (m, 3H), 1.35 (s, 9H). ^{13}C NMR (101 MHz) δ 154.62, 129.80, 125.22, 120.26, 58.57, 21.07.

Synthesis of cyclohexyl 4-methylbenzene-1-sulfinate 87a[112]



Sodium p-toluenesulfinate (4.00 g, 22.4 mmol), TMSCl (5.69 mL, 44.8 mmol) and cyclohexanol (4.52 g, 45.1 mmol) were combined in dry DCM (60.0 mL). The solution was mixed for 1.5 hours and quenched with water (100 mL). The layers were separated, and the aqueous layer was extracted with DCM (4×). The combined organic layer was washed with water (2×), brine (1×) and a saturated solution of $NaHCO_3$ (1×) before being dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was purified by flash column chromatography (90:10 hexanes: EtOAc). The product was a clear oil, 3.83 g, 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.29 (m, 2H), 4.30 (m, 1H), 2.39 (s, 3H), 1.99 (m, 1H), 1.73 (m, 3H), 1.51 (m, 3H), 1.28 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.78, 142.26, 129.46, 124.92, 33.51, 25.02, 23.71, 21.37. FTIR (cm^{-1}): 2934, 2857, 1596, 1493, 1449, 1400, 1135, 1083, 941, 800, 756.

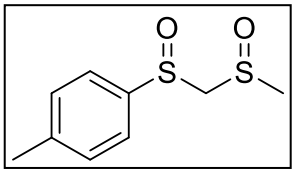
Synthesis of isopropyl 4-methylbenzene-1-sulfinate 87b[112]



Sodium p-toluenesulfinate (2.01 g, 11.3 mmol), TMSCl (2.85 mL, 22.4 mmol) and isopropanol (1.73 ml, 22.6 mmol) were combined in dry DCM (30.0 mL). The solution was mixed for 3.5 hours and quenched with water (50 mL). The layers were separated, and the aqueous layer was extracted with DCM (3×). The combined organic layers were washed with water (2×) and a saturated solution of $NaHCO_3$ (1×) before being dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure to yield the title compound without any need for further purification. The product was a clear and colourless oil, 1.82 g, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.32 (m, 2H), 4.60 (sept, J = 6.2 Hz, 1H), 2.42 (s, 3H), 1.38 (d, J = 6.2 Hz, 3H), 1.24 (d, J = 6.3 Hz,

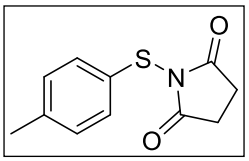
3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 142.58, 142.31, 129.49, 124.93, 72.54, 23.77, 23.56, 21.34. FTIR (cm^{-1}): 2977, 2924, 1597, 1452, 1384, 1373, 1142, 1103, 1083, 917, 841, 812, 743, 637.

Synthesis of 1-methanesulfinylmethanesulfinyl-4-methylbenzene 88[85]



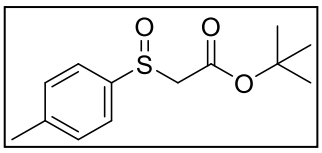
NaH (60% dispersion in mineral oil, 0.634 g, 15.9 mmol) was added to dry DMSO (9.00 mL) and heated to 60 °C. The solution was mixed for 45 minutes before being cooled to room temperature, diluted with dry THF (6.00 mL) and cooled to 0 °C. Sulfinate **87b** (1.50 g, 7.57 mmol) was dissolved in dry THF (4.00 mL) and added to the DMSO solution dropwise over 5 minutes. The resulting solution was mixed for 1 hour at 0 °C before being quenched with a saturated solution of NH_4Cl. The reaction mixture was extracted with chloroform (3×) and the combined organic layer was washed with saturated $NaHCO_3$ (1×), water (3×) and brine (1×). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting mixture was suitably pure, and no further purification was required. The product was a yellow solid, 1.28 g, 78% yield as a 50:50 mixture of diastereomers. Isomer 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.38 (m, 2H), 4.12 – 3.88 (ABq, J = 13.1 Hz, 2H), 2.96 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.95, 139.53, 130.62, 124.21, 80.16, 41.02, 21.61. Isomer 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.38 (m, 2H), 4.04 – 3.96 (ABq, J = 12.3 Hz, 2H), 2.81 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.73, 138.57, 130.48, 124.00, 73.95, 40.55, 21.60. FTIR (as a mixture of diastereomers, cm^{-1}): 3472, 2956, 2922, 2855, 1651, 1595, 1494, 1455, 1404, 1378, 1304, 1209, 1180, 1082, 1042, 963, 812.

Synthesis of [(4-methylphenyl)sulfanyl]pyrrolidine-2,5-dione 95[165]



4-Methylphenyl thiol (1.11 g, 8.94 mmol) was dissolved in dry DCM (40.0 mL) and cooled to 0 °C. To this was added N-bromosuccinimide (1.78 g, 10.0 mmol) in portions over a 5-minute period. The resulting solution was mixed for 5 minutes before a solution of triethylamine (1.90 mL, 13.6 mmol) in dry DCM (20.0 mL) was added dropwise. The resulting solution was mixed for 1.25 hours and quenched with water (60.0 mL). The layers were separated, and the aqueous layer was extracted with DCM (3×). The combined organic layer was washed with water (2×) and brine (1×) before being dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was then triturated with pentane (2× 40 mL) and the solvent (pentane) and its contents were discarded. The resultant orange powder was recrystallized from hexanes to yield compound **100** as white crystals, 0.688 g, 35% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.15 (m, 2H), 2.79 (s, 4H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.42, 140.89, 133.71, 130.38, 130.13, 28.64, 21.27. FTIR (cm^{-1}): 3060, 2941, 2922, 1712, 1596, 1488, 1428, 1405, 1296, 1240, 1143, 1007.

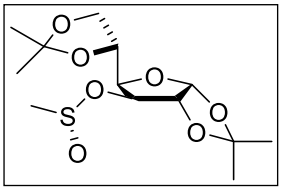
Synthesis of tert-butyl 2-(4-methylbenzenesulfinyl)acetate 98[120]



Diisopropylamine (1.72 mL, 12.3 mmol) was dissolved in dry THF (30.0 mL) and cooled to -78 °C. To this was added nBuLi (1.6 M in THF, 7.28 mL, 11.6 mmol) dropwise followed by tert-butyl acetate (1.49 mL, 11.1 mmol). The resulting solution was stirred at -78 °C for 30 minutes before a solution of sulfinate **87a** (1.20 g, 5.55 mmol) in dry THF (5.00 mL) was added. This mixture was allowed to return to room temperature for 4 hours before being quenched with saturated NH_4Cl (40.0 mL). The resulting solution was extracted with EtOAc (3× 50 mL) and the combined organic layer was washed with

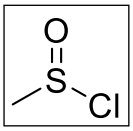
brine (1×) and dried over Na_2SO_4. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was purified by flash column chromatography (65:35 hexanes: EtOAc). The product was a yellow oil, 1.00 g, 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.32 (m, 2H), 3.67 (ABq, *J* = 13.6 Hz, 2H), 2.40 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.80, 142.18, 140.03, 129.92, 124.41, 83.08, 62.65, 27.84, 21.40.

Synthesis of (SS)-1,2:5,6-Di-O-isopropylidene-α-D-glucofuranosyl methanesulfinate 99[65]



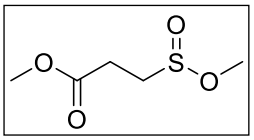
To a solution of diacetone glucose (1.25 g, 4.81 mmol) and DIPEA (1.10 mL, 6.32 mmol) in dry toluene (100 mL) at -78 °C was added methanesulfinyl chloride (0.615 g, 6.24 mmol) dropwise. After being stirred for 6 hours at -78 °C, the reaction mixture was quenched with water and diluted with DCM. The layers were separated, and the aqueous layer was extracted with DCM (3× 60 mL). The combined organic layers were washed with saturated NH_4Cl (1×), saturated $NaHCO_3$ (1×), and brine (1×) before being dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was purified via recrystallization from hexanes. The product was a white solid, 0.897 g, 58% yield. $[\alpha]_D^{25}$= -200.0 (c = 1.0 in acetone). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (d, *J* = 3.6 Hz, 1H), 4.78 (d, *J* = 2.3 Hz, 1H), 4.61 (d, *J* = 3.6 Hz, 1H), 4.27 (m, 2H), 4.11 (m, 1H), 4.02 (m, 1H), 2.70 (s, 3H), 1.51 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 112.58, 109.40, 105.19, 83.95, 80.42, 78.36, 72.46, 67.01, 44.45, 26.94, 26.85, 26.40, 25.36. FTIR (cm^{-1}): 2990, 2955, 2900, 1377, 1217, 1143, 1073, 1022, 939, 837.

Synthesis of methanesulfinyl chloride 100[166]



Dimethyl disulfide (2.00 mL, 22.2 mmol) was dissolved in acetic acid (2.54 ml, 44.4 mmol) and cooled to -30 °C. Sulfuryl chloride (5.58 ml, 68.8 mmol) was added dropwise over a period of 35 minutes before the reaction was allowed to warm to -20 °C and stirred for 5 hours. The crude reaction mixture was purified by fractional vacuum distillation to yield the title compound as a yellow oil, 3.08 g, 70% yield. BP: 83 – 84 °C (103 mm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 52.28. FTIR (cm^{-1}): 2924, 2533, 1651, 1404, 1304, 1214, 1132, 1046, 953, 813, 747, 703.

Synthesis of methyl 3-(methoxysulfinyl)propanoate 103[131]

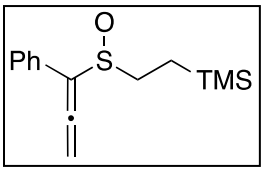


In one round bottom flask equipped with an argon balloon: methyl 3-mercaptopropionate (4.61 mL, 41.6 mmol) and acetic acid (2.38 mL, 41.6 mmol) were combined and cooled to -40 °C. Neat sulfuryl chloride (7.08 mL, 87.4 mmol) was added dropwise. The mixture was warmed slowly and stirred at room temperature for 4 hours, then diluted with DCM (25 mL). In a second round bottom flask equipped with an argon balloon, methanol (4.21 mL, 104 mmol) and DCM (50 mL) were combined and cooled to -78 °C. Pyridine (11.1 mL, 137 mmol) was added dropwise and the mixture was stirred for 30 minutes. The contents from flask 1 were added to flask 2 dropwise. After 1 hour at -78 °C, the reaction mixture was warmed slowly to room temperature. After 30 hours, the mixture was quenched with water (100 mL), extracted with DCM (3× 50 mL). The organic layers were combined and washed with water (1× 100 mL) and brine (1× 100 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated. The crude product was used without further purification as a clear oil 5.75 g, 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.70 (s, 3H), 3.00 (m, 2H), 2.75 (m, 2H). ^{13}C

NMR (101 MHz, $CDCl_3$) δ 171.49, 54.36, 51.85, 51.02, 25.36. FTIR (cm^{-1}): 2997, 2954, 2836, 1737, 1439, 1364, 1225-1121, 1043, 997, 832, 759, 701.

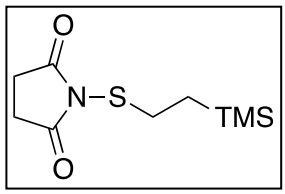
5.2 Allenyl Sulfoxide Project

Synthesis of 1-phenyl-1,2-propadien-1-yl 2-trimethylsilylethyl sulfoxide 111a



N-(Trimethylsilylethyl)succinimide (0.249 g, 1.08 mmol), 3-phenyl-2-propyn-1-ol (0.404 mL, 3.24 mmol) and potassium carbonate (0.600 g, 0.434 mmol) were combined in chloroform (5.00 mL).The reaction was heated to 50 °C and stirred for 6 hours. The solids were filtered and then the solution was washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (40:60 diethyl ether: hexanes). The product **4a** was a yellow oil, 0.139 g, 49% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.30 (m, 5H), 5.58 (AB q, J = 13.3 Hz, 2H), 2.81 (app. dt, J = 5.3, 13.0 Hz, 1H), 2.61 (app. dt, J = 5.3, 13.1 Hz, 1H), 0.85 (m, 2H), -0.04 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.28, 130.50, 129.04, 128.63, 127.23, 113.06, 84.85, 47.84, 7.82, -1.88. FTIR (cm^{-1}): 3056, 2952, 2924, 2897, 2855, 1933, 1597, 1493, 1446, 1416, 1248, 1157, 1094, 1048, 836, 757. HRMS(ESI): Calc'd for $C_{14}H_{21}OSSi$ $[M+H]^+$ 265.10769. Found: 265.10660.

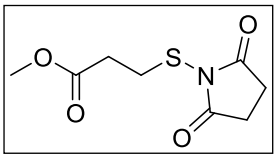
Synthesis of 1-[[2-(trimethylsilyl)ethyl]thio]-2,5-pyrrolidinedione 112a[131]



Bis[2-(trimethylsilyl)ethyl] disulfide **7** (1.48 g, 5.56 mmol) was dissolved in DCM (55 mL) and cooled to -78 °C. Sulfuryl chloride (0.826 g, 6.12 mmol) was added dropwise and stirring was continued for 8 minutes. Succinimide (1.32 g, 13.4 mmol) was added to the mixture at once followed by dropwise addition of triethylamine (1.24 g, 12.2 mmol). The mixture was kept in the cold bath for 10 more minutes,

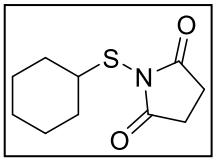
then moved to an ice-water bath. After 45 minutes the mixture was washed with water (3× 50 mL) and brine (1× 50 mL). The organic layer was dried with $MgSO_4$, filtered, concentrated, and dried on a vacuum pump. The resulting crude product was then purified using flash column chromatography (25:75 EtOAc: hexanes). The final product was a yellow oil (2.43 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (m, 2H), 2.84 (s, 4H), 0.76 (m, 2H), 0.01 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.18, 33.02, 28.62, 14.08, -1.84. FTIR (cm^{-1}): 2953, 2896, 1725, 1429, 1306, 1247, 1148, 1008, 859-841, 757.

Synthesis of methyl 3-[(2,5-dioxo-1-pyrrolidinyl)thio] propanoate 112b



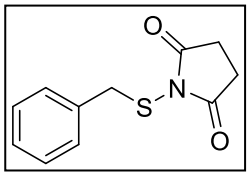
N-Chlorosuccinimide (1.33g, 9.96 mmol) was dissolved in DCM (32.0 mL) and cooled to 0 °C. Methyl 3-mercaptopropanoate (1.00 mL, 9.03 mmol) was dissolved in DCM (8.00 mL) and added dropwise to the NCS solution. The resulting solution was stirred at 0 °C for 30 minutes. Triethylamine (1.50 mL, 10.8 mmol) was dissolved in DCM and added dropwise. The resulting solution mixed for 3.5 hours at 0 °C and was then quenched with water (50 mL). The layers were separated, and the aqueous layer was extracted with DCM (3× 50 mL). The combined organic layer was washed with brine (1×) and dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction mixture was triturated with pentane (3× 40 mL) and once the solvent was discarded, purified compound **112b** remained. The product was a white solid, 1.54 g, 79% yield. MP: 72-75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.08 (t, J = 6.7 Hz, 2H), 2.83 (s, 4H), 2.74 (t, J = 6.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.23, 172.01, 52.01, 34.63, 32.71, 28.62. FTIR (cm^{-1}): 2953, 1722, 1437, 1363, 1308, 1245, 1146, 1008, 978, 819. HRMS(ESI): Calc'd for $C_8H_{12}NO_4S$ $[M+H]^+$ 218.04816. Found: 218.04798.

Synthesis of N-(cyclohexylthio)succinimide 118[158]



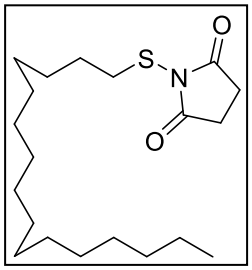
NCS (6.56 g, 49.1 mmol) was dissolved in dry toluene (130.0 mL). Cyclohexyl mercaptan (5.00 mL, 40.9 mmol) was added and the reaction was mixed for 45 minutes. Triethylamine (6.88 mL, 49.4 mmol) was dissolved in dry THF (60.0 mL) and added dropwise to the solution. The reaction was stirred overnight. Diethyl ether (400 mL) was added and the resulting precipitate was filtered off. The solution was concentrated under reduced pressure and the crude material was purified by flash column chromatography (50:50 EtOAc: hexanes). The product was an off-white flakey solid, 7.16 g, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (m, 1H), 2.85 (s, 4H), 1.82 (m, 4H), 1.62 (m, 1H), 1.29 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.52, 48.52, 30.99, 28.61, 25.49, 25.47. FTIR (cm^{-1}): 3006, 2990, 2931, 2854, 1724, 1300, 1276, 1261, 1145.

Synthesis of N-(benzylthio)succinimide 119[158]



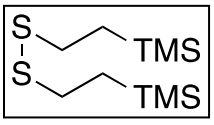
Benzyl thiol (2.00 mL, 17.04 mmol) and NCS (2.73 g, 20.4 mmol, 1.2 equiv) were combined in DCM (35.0 mL) and cooled to 0 °C. Triethylamine (2.85 mL, 20.4 mmol, 1.2 equiv) was added dropwise. The reaction was allowed to return to room temperature overnight. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. Triturated with pentane (2× 40 mL). Remaining residue was dissolved in DCM (40 mL) and was washed with NH_4Cl (3×), water (3×), brine (1×) and the organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure to give the orange powder, 2.05 g, 54% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H), 4.10 (s, 2H), 2.63 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.67, 134.01, 129.75, 128.72, 128.18, 41.10, 28.51. FTIR (cm^{-1}): 3062, 3033, 2945, 1720, 1527, 1493, 1454, 1421, 1309, 1247, 1149, 1028, 1009, 820.

Synthesis of N-(hexadecylthio)succinimide 120



Hexadecanethiol (1.11 g, 4.29 mmol) was dissolved in DCM (20.0 mL) and cooled to 0 °C. Et_3N (0.670 mL, 4.81 mmol) was added dropwise and NBS (0.827 g, 4.65 mmol) was added portionwise. The reaction was allowed to warm to room temperature overnight. The solution was washed with sat. NH_4Cl (2×), water (1×), $NaHCO_3$ (1×), water (1×) and brine (1×). The organic solution was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (80:20 hexanes: EtOAc). The product was a white solid, 0.359 g, 26% yield. MP: 70-71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (t, J = 7.4 Hz, 2H), 2.82 (s, 4H), 1.52 (m, J = 7.5 Hz, 2H), 1.37 (t, J = 7.0 Hz, 2H), 1.23 (s, 24H), 0.86 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.28, 37.73, 32.03, 29.79, 29.76, 29.73, 29.66, 29.53, 29.47, 29.22, 28.71, 28.56, 28.05, 22.80, 14.23. FTIR (cm^{-1}): 2957, 2920, 2850, 1718, 1473, 1463, 1317, 1276, 1261, 1247, 1154, 1006, 820. HRMS(EI): Calc'd for $C_{20}H_{37}NO_2S$ $[M+H]^+$ 356.2545. Found: 356.2618.

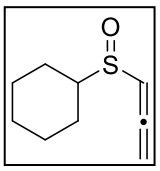
Synthesis of bis[2-(trimethylsilyl)ethyl] disulfide 122[131]



Thiolacetic acid (14.9 g, 0.195 mol), vinyltrimethylsilane (23.5 g, 0.235 mol) and AIBN (0.417 g, 0.00254 mol) were combined and refluxed at 60 °C for 4 hours with an argon balloon attached to the condenser. The heat was taken away from the mixture and 300 mL MeOH and KOH (85%, 20.2 g, 0.313 mol) was added. The mixture was left to stir at room temperature in open air for 5 days. The mixture was diluted with water (approx. 300 mL) and extracted with pentane (3× 300 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The resulting product was a pale-yellow oil, 16.5 g. It was purified by vacuum distillation to give a colourless oil, 12.2 g, 47% yield. BP: 90-92 °C (0.40 mm). ^{1}H NMR

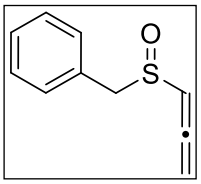
(400 MHz, $CDCl_3$) δ 2.74 (m, 2H), 0.93 (m, 2H), 0.03 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 34.81, 17.18, -1.73. FTIR (cm^{-1}): 2953, 2899, 2804, 1415, 1368, 1249, 1157, 1095, 1044, 1013, 882-839, 752, 717.

Synthesis of (Propa-1,2-diene-1-sulfinyl)cyclohexane 128



N-(Cyclohexylthio)succinimide (0.252 g, 1.18 mmol), propargyl alcohol (0.205 mL, 3.52 mmol) and potassium carbonate (0.648 g, 4.69 mmol) were combined in chloroform (5.00 mL). The reaction was heated to 50 °C and stirred for 16 hours. The solids were filtered and then washed with water (3×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (50:50 EtOAc: hexanes). The product was a yellow oil, 0.125 g, 63% yield. ^1H NMR (600 MHz, $CDCl_3$) δ 5.83 (t, J = 6.4 Hz, 1H), 5.18-5.10 (ABM, J_{AM}= J_{BM}= 6.5 Hz, J_{AB}= 13.8 Hz, 2H), 2.57 (m, 1H), 2.03-1.97 (m, 1H), 1.87-1.72 (m, 3H), 1.63-1.56 (m, 1H), 1.40-1.10 (m, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.86, 96.69, 81.28, 61.51, 25.61, 25.41, 25.21, 25.04, 24.94. FTIR (cm^{-1}): 3060, 2932, 2855, 1940, 1451, 1266, 1036, 997, 891, 849.

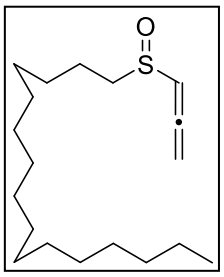
Synthesis of [(Propa-1,2-diene-1-sulfinyl)methyl]benzene 130



N-(Benzylthio)succinimide (0.252 g, 1.14 mmol), propargyl alcohol (0.200 mL, 3.44 mmol) and potassium carbonate (0.626 g, 4.53 mmol) were combined in chloroform (5.00 mL). The reaction was heated to 50 °C and stirred for 2.5 hours. The solids were filtered and the solution was diluted with DCM. Then, the solution was washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (40:60 EtOAc: hexanes). The product was a yellow oil, 0.133 g, 67% yield. ^1H

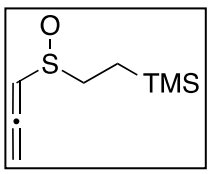
NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 5.87 (app. t, J = 6.4 Hz, 1H), 5.08 (ABM, J_{AM}= J_{BM}= 6.4 Hz, J_{AB}= 13.1 Hz, 2H), 4.04 (ABq, J = 12.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.89, 130.33, 129.30, 128.65, 128.29, 98.00, 81.85, 60.89. FTIR (cm^{-1}): 3062, 3030, 2985, 2922, 1939, 1634, 1495, 1455, 1415, 1074, 1040, 919, 857, 823. HRMS(ESI): Calc'd for $C_{10}H_{11}OS$ $[M+H]^+$ 179.0525. Found: 179.0518.

Synthesis of 1-(Propa-1,2-diene-1-sulfinyl)hexadecane 131



N-(Hexadecanylthio)succinimide (0.0990 g, 0.278 mmol), propargyl alcohol (0.0500 mL, 0.859 mmol) and potassium carbonate (0.156 g, 1.13 mmol) were combined in chloroform (2.20 mL).The reaction was heated to 50 °C and stirred for 3 hours. The solids were filtered, and the solution was diluted with DCM. Then, the solution was washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (80:20 hexanes: EtOAc). The product was a white solid, 0.0553 g, 64% yield. MP: 50-52 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (app. t, J = 6.4 Hz, 1H), 5.26 (ABM, J_{AM}= J_{BM}= 6.4 Hz, J_{AB}= 13.1 Hz, 2H), 2.81 (m, 2H), 1.73 (app. quintet, J = 7.6 Hz, 2H), 1.42 (m, 2H), 1.29 (m, 24H), 0.86 (app. t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.30, 99.04, 82.03, 54.92, 32.02, 29.78, 29.77, 29.75, 29.70, 29.62, 29.45, 29.44, 29.32, 28.83. FTIR (cm^{-1}): 2997, 2954, 2917, 2849, 1945, 1463, 1081, 1047, 1037, 856, 844. HRMS(ESI): Calc'd for $C_{19}H_{37}OS$ $[M+H]^+$ 313.2560. Found: 313.2553.

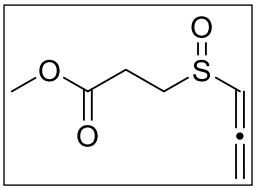
Synthesis of 1-propa-1,2-dien-1-yl 2-trimethylsilylethyl sulfoxide 132a



N-(Trimethylsilylthio)succinimide (0.100 g, 0.432 mmol), propargyl alcohol (0.0760 mL, 1.31 mmol) and potassium carbonate (0.240 g, 1.74 mmol) were combined in chloroform (2.00 mL).The reaction was heated to 50 °C and stirred

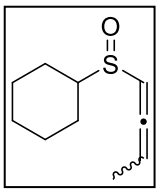
for 2 hours. The solids were filtered, and the solution was washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (50:50 EtOAc: hexanes). The product was a yellow oil, 0.0586 g, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (app. t, J = 6.4 Hz, 1H), 5.28 (ABM, $J_{AM} = J_{BM} = 6.7$ Hz, $J_{AB} = 13.3$ Hz, 2H), 2.80 (m, 2H), 0.90 (m, 2H), 0.07 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.51, 98.44, 81.81, 50.43, 8.46, -1.85. FTIR (cm^{-1}): 3060, 2953, 2898, 1941, 1416, 1249, 1158, 1096, 1043, 888-757. HRMS(EI): Calc'd for $C_8H_{16}OSSi$ $[M+H]^+$ 188.0691. Found: 188.0699.

Synthesis of methyl 3-(propa-1,2-diene-1-sulfinyl)propanoate 132b



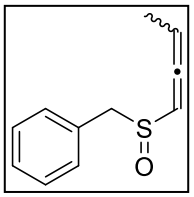
N-(Methoxycarbonylethylthio)succinimide (0.251 g, 1.16 mmol), propargyl alcohol (0.201 mL, 3.45 mmol) and potassium carbonate (0.637 g, 4.61 mmol) were combined in chloroform (5.00 mL). The reaction was heated to 50 °C and stirred for 1.5 hours. The solids were filtered and then washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was purified by flash column chromatography (70:30 EtOAc: hexanes). The product was a yellow oil, 0.104 g, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (app. t, *J* = 6.3 Hz, 1H), 5.29 (m, 2H), 3.69 (s, 3H), 3.09 (m, 2H), 2.77 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.17, 171.68, 98.60, 82.74, 52.27, 48.73, 26.32. FTIR (cm^{-1}) 2955, 1941, 1735, 1438, 1362, 1243, 1041. HRMS(EI): Calc'd for $C_7H_{10}O_3S$ $[M+H]^+$ 175.0423. Found: 175.042.

Synthesis of (Buta-1,2-diene-1-sulfinyl)cyclohexane 133



N-(Cyclohexylthio)succinimide (0.250 g, 1.17 mmol), 3-butyn-2-ol (0.185 mL, 2.36 mmol) and potassium carbonate (0.487 g, 3.52 mmol) were combined in chloroform (5.00 mL).The reaction was heated to 50 °C and stirred for 30 hours. The solids were filtered and then washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (50:50 EtOAc: hexanes). The product was a yellow oil, 0.136 g, 65% yield, 53:47 diastereomeric ratio. Diastereomer 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.63 (m, 1H), 2.62 (tt, J = 3.7, 11.7 Hz, 1H), 2.11 (m, 1H), 1.90 (m, 3H), 1.80 (dd, J = 3.1, 7.4 Hz, 3H), 1.69 (m, 1H), 1.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.24, 96.72, 93.13, 61.53, 25.79, 25.63, 25.43, 25.27, 25.13, 13.47. Diastereomer 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.63 (m, 1H), 2.62 (tt, J = 3.7, 17.1 Hz, 1H), 2.11 (m, 1H), 1.90 (m, 3H), 1.76 (dd, J = 3.1, 7.3 Hz, 3H), 1.69 (m, 1H), 1.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.17, 96.77, 92.98, 61.42, 25.77, 25.63, 25.43, 25.27, 25.13, 13.66. As a mixture of diastereomers: FTIR (cm^{-1}): 2930, 2855, 1949, 1450, 1033, 849. HRMS(ESI): Calc'd for $C_{10}H_{17}OS$ $[M+H]^+$ 185.09946. Found: 185.09923.

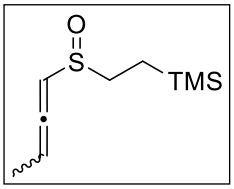
Synthesis of [(Buta-1,2-diene-1-sulfinyl)methyl]benzene 134



N-(Benzylthio)succinimide (0.251 g, 1.13 mmol), 3-butyn-2-ol (0.180 mL, 2.30 mmol) and K_2CO_3 (0.469 g, 3.39 mmol) were combined in chloroform (5.00 mL). The reaction was heated to 50 °C for 11 hours. The solution was filtered and diluted with DCM. The solution was washed with water (3×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (50:50 EtOAc: hexanes). The product

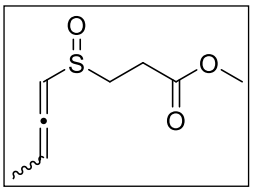
was a yellow oil, 0.122 g, 56% yield, 55:45 diastereomeric ratio. Diastereomer 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H), 5.80 (m, 1H), 5.54 (m, 1H), 4.05 (ABq, J = 12.6 Hz, 2H), 1.50 (dd, J = 3.1, 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.58, 130.40, 129.69, 128.79, 128.31, 98.01, 93.69, 61.23, 13.24. Diastereomer 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H), 5.80 (m, 1H), 5.45 (m, 1H), 4.02 (ABq, J = 12.7, 2H), 1.67 (dd, J = 3.1, 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.26, 130.49, 129.61, 128.70, 128.30, 97.98, 93.87, 60.94, 13.31. As a mixture of diastereomers: FTIR (cm^{-1}): 3062, 3030, 2978, 2923, 1949, 1633, 1496, 1455, 1439, 1366, 1190, 1072, 1040, 849. HRMS(ESI): Calc'd for $C_{11}H_{13}OS$ $[M+H]^+$ 193.06816. Found: 193.06765.

Synthesis of 2-buta-1,2-dienyl-1-yl 2-trimethylsilyethyl sulfoxide 135a



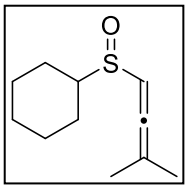
N-(Trimethylsilylethylthio)succinimide (0.203 g, 0.878 mmol), 3-butyn-2-ol (0.205 mL, 2.61 mmol) and potassium carbonate (0.477 g, 3.45 mmol) were combined in chloroform (4.50 mL). The reaction was heated to 50 °C and stirred for 2.5 hours. The solids were filtered and then washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (25:75 EtOAc: hexanes). The product was a yellow oil, 0.103 g, 59% yield, 56:44 diastereomeric ratio. Diastereomer 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.66 (m, 1H), 2.76 (m, 2H), 1.82 (dd, J = 3.1, 7.3 Hz, 3H), 0.88 (m, 2H), 0.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.60, 97.92, 93.54, 50.03, 13.62, 8.44, -1.83. Diastereomer 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.66 (m, 1H), 2.76 (m, 2H), 1.78 (dd, J = 3.1, 7.4 Hz, 3H), 0.88 (m, 2H), 0.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.82, 97.87, 93.53, 50.10, 13.45, 8.42, -1.82. As a mixture of diastereomers: FTIR (cm^{-1}): 2953, 2924, 2898, 1949, 1439, 1415, 1366, 1249, 1158, 1094, 1045, 888-841, 757. HRMS(ESI): Calc'd for $C_9H_{19}OSSi$ $[M+H]^+$ 203.09204. Found: 203.09248.

Synthesis of methyl 3-(buta-1,2-diene-1-sulfinyl)propanoate 135b



N-(Methoxycarbonylethylthio)succinimide (0.250 g, 1.15 mmol), 3-butyn-2-ol (0.272 mL, 3.47 mmol) and potassium carbonate (0.635 g, 4.59 mmol) were combined in chloroform (5.00 mL). The reaction was heated to 50 °C and stirred for 1.75 hours. The solids were filtered and then washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was purified by flash column chromatography (70:30 EtOAc: hexanes). The product was a yellow oil, 0.102 g, 47% yield, 54:46 diastereomeric ratio. Diastereomer 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.67 (m, 1H), 3.66 (s, 3H), 3.04 (m, 2H), 2.74 (m, 2H), 1.77 (dd, *J* = 3.1, 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.06, 171.52, 98.19, 94.32, 52.00, 48.38, 26.18, 13.41. Diastereomer 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.67 (m, 1H), 3.66 (s, 3H), 3.04 (m, 2H), 2.74 (m, 2H), 1.74 (dd, *J* = 3.1, 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.08, 171.53, 98.13, 94.38, 52.00, 48.31, 26.06, 13.33. As a mixture of diastereomers: FTIR (cm^{-1}): 2982, 2955, 2928, 1949, 1736, 1438, 1362, 1242, 1177, 1039, 978, 934, 853. HRMS(ESI): Calc'd for $C_8H_{12}O_3S$ $[M+H]^+$ 189.0580. Found: 189.0574.

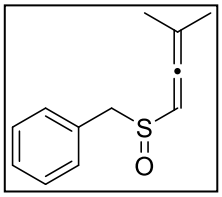
Synthesis of (3-Methylbuta-1,2-diene-1-sulfinyl)cyclohexane 136



N-(Cyclohexylthio)succinimide (0.250 g, 1.17 mmol), 2-methyl-3-butyn-2-ol (0.230 mL, 2.37 mmol) and potassium carbonate (0.486 g, 3.52 mmol) were combined in chloroform (5.00 mL). The reaction was heated to 50 °C and stirred for 36 hours. The solids were filtered, and the filtrate washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (50:50 EtOAc:

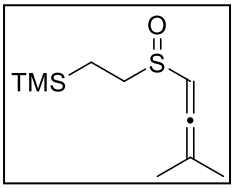
hexanes). The product was a yellow oil, 0.0860 g, 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (app. sept, J = 2.8 1H), 2.61 (m, 1H), 2.13 (m, 1H), 1.90 (m, 3H), 1.83 (d, J = 2.8 Hz, 3H), 1.78 (d, J = 2.8 Hz, 3H), 1.69 (m, 1H), 1.35 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.95, 103.53, 95.37, 61.48, 25.89, 25.80, 25.58, 25.49, 25.42, 20.30, 19.97. FTIR (cm^{-1}): 2930, 2855, 1957, 1450, 1346, 1262, 1036, 919, 891, 849. HRMS(ESI): Calc'd for $C_{11}H_{19}OS$ $[M+H]^+$ 199.11511. Found: 199.11411.

Synthesis of [(3-Methylbuta-1,2-diene-1-sulfinyl)methyl]benzene 137



N-(Benzylthio)succinimide (0.250 g, 1.13 mmol), 2-methyl-3-butyn-2-ol (0.330 mL, 3.41 mmol) and K_2CO_3 (0.624 g, 4.51 mmol) were combined in chloroform (5.00 mL). The reaction was heated to 50 °C and stirred for 23 hours. The solids were filtered, and the solution was diluted with DCM. Then, the solution was washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (50:50 EtOAc: hexanes). The product was a yellow oil, 0.0664 g, 28%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.71 (app. sept, J = 2.8 Hz, 1H), 4.05 (AB q, J = 12.6, 2H), 1.71 (d, J = 2.7 Hz, 3H), 1.50 (d, J = 2.7 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.37, 130.49, 129.95, 128.80, 128.28, 104.41, 96.53, 61.21, 19.80, 19.77. FTIR (cm^{-1}): 3062, 3030, 2983, 2943, 2918, 2856, 1957, 1603, 1495, 1454, 1377, 1364, 1347, 1192, 1165, 1072, 1039, 918, 888. HRMS(ESI): Calc'd for $C_{12}H_{15}OS$ $[M+H]^+$ 207.0838. Found: 207.0836.

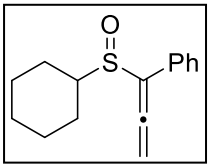
Synthesis of Trimethyl[2-(3-methylbuta-1,2-diene-1-sulfinyl)ethyl]silane 138



N-(Trimethylsilylethylthio)succinimide (0.201 g, 0.869 mmol), 2-methyl-3-butyn-2-ol (0.250 mL, 2.58 mmol) and potassium carbonate (0.479 g, 3.57 mmol) were combined in chloroform (4.50 mL).The reaction was heated to

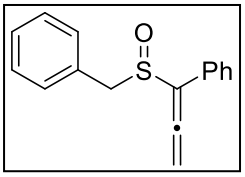
50 °C and stirred for 21 hours. The solids were filtered and then washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (50:50 EtOAc: hexanes). The product was a yellow oil, 0.0774 g, 41% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.75 (app. sept, J = 2.8 Hz, 1H), 2.73 (m, 2H), 1.81 (d, J = 2.7 Hz, 3H), 1.77 (d, J = 2.7 Hz, 3H), 0.84 (m, 2H), 0.03 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.28, 104.07, 96.70, 50.19, 20.28, 20.02, 8.59, -1.80. FTIR (cm^{-1}): 2952, 2917, 1957, 1448, 1416, 1376, 1363, 1348, 1250, 1192, 1160, 1095, 1026, 889, 860, 840. HRMS(ESI): Calc'd for $C_{10}H_{20}OSSiNa$ $[M+Na]^+$ 239.0896. Found: 239.0897.

Synthesis of [1-(Cyclohexanesulfinyl)propa-1,2-dien-1-yl]benzene 139



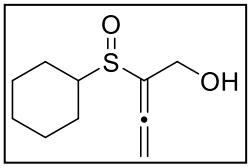
N-(Cyclohexylthio)succinimide (0.0335 g, 0.157 mmol), 3-phenyl-2-propyn-1-ol (0.0600 mL, 481 mmol) and potassium carbonate (0.0870 g, 0.629 mmol) were combined in chloroform (1.50 mL). The reaction was heated to 50 °C and stirred for 17 hours. The solids were filtered and the solution was diluted with DCM. Then, the solution was washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (60:40 hexanes: diethyl ether). The product was a yellow oil, 0.0205 g, 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 5H), 5.57 (AB q, J = 13.4 Hz, 2H), 2.59 (tt, J = 3.6, 11.7 Hz, 1H), 2.01 (m, 1H), 1.82 (m, 3H), 1.48 (m, 1H), 1.23 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.87, 131.07, 129.13, 128.62, 127.37, 112.06, 84.76, 59.44, 27.07, 25.69, 25.55, 25.33, 24.16. FTIR (cm^{-1}): 3093, 2931, 2854, 1933, 1492, 1448, 1146, 1043, 856. HRMS(ESI): Calc'd for $C_{15}H_{19}OS$ $[M+H]^+$ 247.1151. Found: 247.1149.

Synthesis of [(1-Phenylpropa-1,2-diene-1-sulfinyl)methyl]benzene 140



N-(Benzylthio)succinimide (0.202 g, 0.913 mmol), 3-phenyl-2-propyn-1-ol (0.340 mL, 2.73 mmol) and potassium carbonate (0.499 g, 3.61 mmol) were combined in chloroform (4.50 mL). The reaction was heated to 50 °C and stirred for 7 hours. The solids were filtered, and the solution was diluted with DCM. Then, the solution was washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (60:40 hexanes: diethyl ether). The product was a white solid, 0.0669 g, 29% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 8H), 7.15 (m, 2H), 5.26 (ABq, J = 13.3 Hz, 2H), 3.99 (ABq, J = 13.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.19, 130.68, 130.43, 129.39, 129.23, 128.72, 128.46, 128.35, 127.22, 112.59, 85.07, 58.16. FTIR (cm^{-1}): 3058, 3030, 2967, 2922, 1932, 1599, 1494, 1457, 1417, 1185, 1158, 1129, 1074, 1053, 1001, 915, 862. HRMS(ESI): Calc'd for $C_{16}H_{15}OS$ $[M+H]^+$ 277.0658. Found: 277.0659.

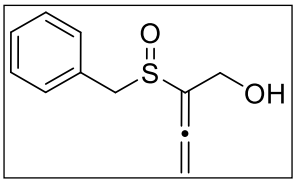
Synthesis of 2-(Cyclohexanesulfinyl)buta-2,3-dien-1-ol 141



N-(Cyclohexylthio)succinimide (0.252 g, 1.18 mmol), 2-butyn-1,4-diol (0.509 g, 5.91 mmol) and triethylamine (0.170 mL, 1.22 mmol) were combined in THF (5.00 mL). The reaction was stirred for 4 days at 25 °C. The solution was concentrated under reduced pressure and the remaining residue was dissolved in DCM. The solution was washed with water (3×) and brine (1×) and the organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (50:50 EtOAc: hexanes). The product was a yellow oil, 0.0537 g, 23% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22 (ABXY, J_{AX} = J_{BX}= J_{AY}= J_{BY}= 1.9 Hz, J_{AB}= 12.9 Hz, 2H), 4.51 (m, 2H), 3.48 (t, J = 6.3 Hz, 1H), 2.95 (m, 1H), 2.16 (m, 1H),

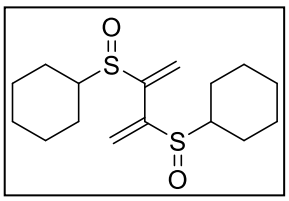
1.89 (m, 3H), 1.68 (m, 1H), 1.36 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.34, 106.18, 81.60, 60.59, 59.27, 26.31, 25.50, 25.45, 25.29, 25.14. FTIR (cm^{-1}): 2931, 2855, 1942, 1450, 1019, 862. HRMS(ESI): Calc'd for $C_{10}H_{17}O_2S$ $[M+H]^+$ 201.09438. Found: 201.09343.

Synthesis of 2-Phenylmethanesulfinylbuta-2,3-dien-1-ol 142



N-(Benzylthio)succinimide (0.250 g, 1.13 mmol), 2-butyn-1,4-diol (0.486 g, 5.65 mmol) and triethylamine (0.170 mL, 1.22 mmol) were combined in THF (5.00 mL). The reaction was stirred for 3 days at 25 °C. The solution was concentrated under reduced pressure and the remaining residue was dissolved in DCM. The solution was washed with water (3×) and brine (1×) and the organic layer was dried over MgSO4. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (50:50 EtOAc: hexanes). The product was a yellow oil, 0.0612 g, 26% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.90 (ABXY, J_{AX} = J_{BX}= J_{AY}= J_{BY}= 1.9 Hz, J_{AB}= 12.7 Hz, 2H), 4.49 (ABXY, J_{AX} = J_{BX}= J_{AY}= J_{BY}= 1.9 Hz, J_{AB}= 12.7 Hz, 2H), 4.27 (ABq, J = 12.6 Hz, 2H), 3.62 (s, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.52, 130.80, 129.76, 128.75, 128.42, 106.47, 81.69, 60.37, 58.59. FTIR (cm^{-1}): 3063, 2924, 1941, 1495, 1454, 1072, 1026, 862. HRMS(ESI): Calc'd for $C_{11}H_{13}O_2S$ [M+H]+ 209.06308. Found: 209.06206.

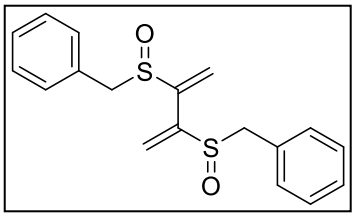
Synthesis of [3-(cyclohexanesulfinyl)buta-1,3-diene-2-sulfinyl]cyclohexane 143



N-(Cyclohexylthio)succinimide (0.151 g, 0.708 mmol), 2-butyne-1,4-diol (0.182 g, 2.11 mmol) and potassium carbonate (0.388 g, 2.81 mmol) were combined in chloroform (3.50 mL).The reaction was heated to 50 °C and stirred for 7 hours. The solids were filtered, and the solution was diluted with DCM. Then, the solution was washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$.

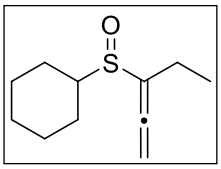
The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (40:60 EtOAc: hexanes). The product was a yellow solid, 0.0085 g, 8% yield. MP: 134-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 1H), 6.05 (s, 1H), 6.00 (s, 1H), 5.98 (s, 1H), 2.67 (tt, J = 3.7, 11.7 Hz, 1H), 2.57 (m, 1H), 1.66 (m, 20H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.16, 144.57, 121.83, 119.62, 57.88, 57.11, 28.16, 27.83, 26.18, 26.03, 25.45, 25.36, 25.34, 25.28, 22.18, 21.05. FTIR (cm^{-1}): 3084, 2931, 2855, 1575, 1451, 1358, 1296, 1264, 1180, 1120, 1045, 993, 925, 892, 848. HRMS(ESI): Calc'd for $C_{16}H_{27}O_2S_2$ [M+H]+ 315.1447. Found: 315.1438.

Synthesis of [(3-phenylmethanesulfinylbuta-1,3-diene-2-sulfinyl)methyl]benzene 144



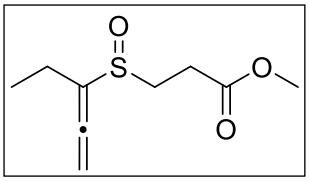
N-(Benzylthio)succinimide (0.200 g, 0.904 mmol), 2-butyne-1,4-diol (0.233 g, 2.71 mmol) and potassium carbonate (0.501 g, 3.62 mmol) were combined in chloroform (4.00 mL). The reaction was heated to 50 °C and stirred for 4 hours. The solids were filtered, and the solution was diluted with DCM. Then, the solution was washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (40:60 EtOAc: hexanes). The product was a white solid, 0.0372 g, 25% yield. MP: 141-143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 10H), 6.02 (s, 1H), 6.01 (s, 1H), 5.90 (s, 1H), 5.83 (s, 1H), 4.06 (ABq, *J* = 13.1 Hz, 2H), 4.01 (ABq, *J* = 13.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.53, 145.60, 130.48, 130.35, 129.52, 128.98, 128.87, 128.83, 128.73, 120.57, 119.79, 59.74, 59.41. FTIR (cm^{-1}): 3061, 3028, 2964, 2917, 1635, 1493, 1454, 1357, 1086, 1072, 1040, 922. HRMS(ESI): Calc'd for $C_{18}H_{19}O_2S_2$ [M+H]+ 331.0821. Found: 331.0816.

Synthesis of (penta-1,2-diene-3-sulfinyl)cyclohexane 146



N-(Cyclohexylthio)succinimide (0.250 g, 1.17 mmol), 2-pentyn-1-ol (0.330 mL, 3.41 mmol) and K_2CO_3 (0.648 g, 4.69 mmol) were combined in chloroform (5.00 mL). The reaction was heated to 50 °C and stirred for 30 hours. The solids were filtered, and the solution was diluted with DCM. Then, the solution was washed with water (2×) and brine (1×) and the organic layer was dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude product was purified by flash column chromatography (50:50 EtOAc: hexanes). The product was a yellow oil, 0.122 g, 53%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.13 (ABXY, J_{AX} = J_{BX}= J_{AY}= J_{BY}= 3.8 Hz, J_{AB}= 11.9 Hz, 2H), 2.62 (m, 1H), 2.29 (m, 1H), 2.08 (m, 2H), 1.73 (m, 4H), 1.41 (app. dq, *J* = 3.7, 11.8 Hz, 1H), 1.23 (m, 4H), 1.08 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 204.44, 109.78, 81.95, 59.01, 26.24, 25.34, 25.22, 25.02, 16.69, 11.88. FTIR (cm^{-1}): 3052, 2969, 2932, 2855, 1946, 1451, 1427, 1265, 1041, 995, 922, 890, 850. HRMS(ESI): Calc'd for $C_{11}H_{18}OS$ $[M+H]^+$ 199.1151. Found: 199.1151.

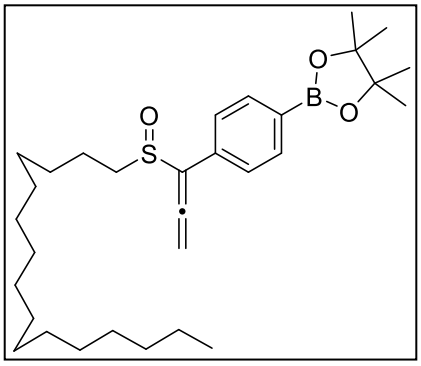
Synthesis of methyl 3-(penta-1,2-diene-3-sulfinyl)propanoate 147



N-(Methoxycarbonylethylthio)succinimide (0.250 g, 1.15 mmol), 2-pentyn-1-ol (0.320 mL, 3.46 mmol) and potassium carbonate (0.637 g, 4.61 mmol) were combined in chloroform (5.00 mL). The reaction was heated to 50 °C and stirred for 8 hours. The solids were filtered and then washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solids were filtered, and the remaining organic solution was concentrated under reduced pressure. The crude reaction material was purified by flash column chromatography (70:30 EtOAc: hexanes). The product was a yellow oil, 0.0482 g, 21% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (m, 2H), 3.69 (s, 3H), 3.05 (m, 2H),

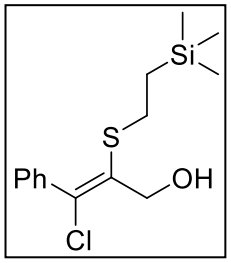
2.72 (m, 2H), 2.24 (m, 2H), 1.13 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.06, 171.60, 111.88, 83.62, 52.08, 46.57, 26.55, 17.59, 12.05. FTIR (cm^{-1}): 2973, 2936, 1946, 1737, 1437, 1360, 1276, 1234, 1176, 1139, 1046, 976, 865, 830. HRMS(ESI): Calc'd for $C_9H_{14}O_3S$ $[M+H]^+$ 203.0736. Found: 203.0730.

Synthesis of 2-{4-[1-(hexadecane-1-sulfinyl)propa-1,2-dien-1-yl]phenyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 149



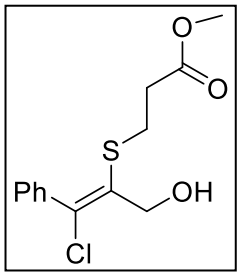
N-(Hexadecanylthio)succinimide (0.0992 g, 0.279 mmol), 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propyn-1-ol (0.454 g, 1.76 mmol) and potassium carbonate (0.486 g, 3.52 mmol) were combined in chloroform (5.00 mL). The reaction was heated to 50 °C and stirred for 5 days. The solids were filtered, and the solution was diluted with DCM. Then, the solution was washed with water (2×) and brine (1×). The organic layer was dried over $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (30:70 diethyl ether: hexanes). The product was a yellow oil, 0.0306 g, 21% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 5.62 (AB q, J = 13.5, 2H), 2.77 (m, 2H), 1.71 (m, 2H), 1.34 (s, 12H), 1.24 (m, 24H), 0.87 (app. t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.06, 135.51, 133.41, 126.41, 114.37, 85.63, 84.14, 53.02, 32.06, 29.82, 29.80, 29.79, 29.73, 29.64, 29.49, 29.46, 29.32, 28.80, 24.99, 22.83, 22.41. FTIR (cm^{-1}): 2924, 2853, 1931, 1608, 1466, 1398, 1361, 1325, 1145, 1087, 1020, 963, 858, 836. HRMS(ESI): Calc'd for $C_{31}H_{52}BO_3S$ [M+H]+ 515.3730. Found: 515.3723.

Synthesis of (2E)-3-chloro-3-phenyl-2-{[2-(trimethylsilyl)ethyl]sulfanyl}prop-2-en-1-ol 152



Bis[2-(trimethylsilyl)ethyl] disulfide (0.250 g, 0.938 mmol) was dissolved in DCM (10 mL) and cooled to -78 °C. Sulfuryl chloride (0.0840 mL, 1.036 mmol) was added dropwise and stirring was continued for approx. 8 minutes. 3-phenyl-2-propyn-1-ol (0.250 ml, 2.01 mmol) was added to the mixture at once followed by dropwise addition of triethylamine (0.290 mL, 2.08 mmol). The mixture was kept in the cold bath for 10 more minutes, then moved to an ice-water bath. After 2 hours the mixture was washed with water (3× 10 mL) and brine (1× 10 mL). The organic layer was dried with $MgSO_4$, filtered, concentrated, and dried on a vacuum pump. The resulting crude product was then purified using flash column chromatography (7.5:92.5 EtOAc: hexanes). The product was a yellow oil, 0.0402 g, 8% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.33 (m, 3H), 4.87 (ABq, J = 15.9 Hz, 2H), 2.77 (m, 2H), 0.92 (m, 2H), 0.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.03, 129.10, 128.49, 122.06, 88.14, 83.28, 55.98, 53.14, 7.38, -1.78. FTIR (cm^{-1}): 3451, 3060, 2956, 1611, 1591, 1441, 1357, 1286, 1149, 1105, 1067, 1023, 977, 884, 828.

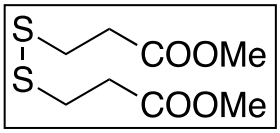
Synthesis of (E)-methyl 3-((1-chloro-3-hydroxy-1-phenylprop-1-en-2-yl)thio)propanoate 153



Methyl 3-[(3-methoxy-3-oxopropyl)disulfanyl]propanoate (0.250 g, 1.05 mmol) was dissolved in DCM (8.00 mL) and cooled to -78 °C. Sulfuryl chloride (0.0950 mL, 1.17 mmol) was added dropwise and stirring was continued for 8 minutes. 3-Phenyl-2-propyn-1-ol (0.260 ml, 2.08 mmol) was added to the mixture at once followed by dropwise addition of triethylamine (0.585 mL, 4.20 mmol). The mixture was kept in the cold bath for 10 more minutes, then moved to an ice-water bath. After 4 hours the mixture was washed with water (3× 10 mL) and brine (1× 10 mL). The organic layer was dried with $MgSO_4$, filtered, concentrated, and dried on a vacuum pump. The

resulting crude product was then purified using flash column chromatography (75:25 hexanes: EtOAc). The product was a yellow oil, 0.326 g, 54%. yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 4.59 (s, 2H), 3.62 (s, 3H), 2.84 (t, J = 7.1 Hz, 2H), 2.64 (br, s, 1H), 2.48 (t, J = 7.1 Hz 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.20, 138.18, 134.68, 131.49, 129.27, 129.05, 128.16, 62.93, 51.97, 34.29, 28.33. FTIR (cm^{-1}): 3057, 2951, 1736, 1590, 1488, 1441, 1360, 1245, 1199, 1177, 1149, 1108, 1072, 1019, 977, 884, 827. HRMS (ESI) calculated for $C_{13}H_{15}{}^{35}ClO_3SNa$ $[M+Na]^+$ 309.0323. Found: 309.0312.

Synthesis of bis(2-methoxycarbonylethyl) disulfide 154[131]



Methyl 3-mercaptopropionate (9.22 mL, 83.2 mmol) was dissolved in DCM (150 mL) and cooled to 0 °C. Sulfuryl chloride (6.75 mL, 83.2 mmol) dissolved in DCM (5.00 mL) added to the thiol mixture dropwise. The mixture was warmed slowly to room temperature. After 5 hours, the mixture was washed with water (3× 50 mL) and with brine (1× 50 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (20:80 EtOAc: hexanes) to yield a colourless oil, 7.32 g (74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 2.93 (t, J = 7.0 Hz, 2H), 2.74 (t, J = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.73, 51.57, 33.62, 32.91. FTIR (cm^{-1}): 2998, 2952, 2845, 1738, 1437, 1357, 1276-1142, 1048, 1017, 979, 936, 917, 893, 850, 823, 767.

Chapter 6: References

6.0 References

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