Novel Preparations of Alkenyl and Allenyl Beta-Aminoalkyl Sulfur Derivatives for Probing Intramolecular Cyclizations

by

Monika Rose Kulak

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Guelph, Ontario, Canada

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ABSTRACT

NOVEL PREPARATIONS OF ALKENYL AND ALLENYL $\beta$-AMINOALKYL SULFUR DERIVATIVES FOR PROBING INTRAMOLECULAR CYCLIZATIONS

Monika Rose Kulak
University of Guelph, 2016

Advisor:
Professor A. L. Schwan

Research efforts focusing on organosulfur compounds have had wide implications in the understanding of organic synthetic reactions. Nevertheless, there are still many areas to be studied, such as the stereoselectivity of sulfur mediated cyclizations, particularly those pertaining to the cis forms of 1-alkenyl $\beta$-aminoalkyl sulfoxides and sulfones. The synthesis of this small family of compounds is proposed to take place through the manipulation of Boc-protected $L$-amino acids. Hence, the main goal of this study was to explore the intramolecular cyclizations of cis-1-alkenyl $\beta$-aminoalkyl sulfoxides and sulfones, and various strategies are provided here in order to accomplish their synthesis in the most cost and time efficient manner. To add, the allenyl sulfenate functional group is considered to be an unknown reactive species and its substitution chemistry remains unexplored. Therefore, a second goal of this study was to generate transient allenyl sulfenates that can be used in the preparation of allenyl sulfoxides and from there, a series of new 1, 4-thiazines. For now, the allenyl sulfoxides were formed and preliminary trials for the formation of allenyl sulfenates conducted. Some leeway has been developed into the conditions and reactivity patterns pertaining to the generation chemistry of allenyl sulfenates. Further investigations as well as detailed computational results are required. It was observed that the sulfones bearing a cis alkene demonstrate little selectivity during cyclization. Overall, this study contributes to a better understanding of the most appropriate environment to access selected cyclic organosulfur compounds, which will then direct their further application.
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ACN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>Ala</td>
<td>alanine</td>
</tr>
<tr>
<td>BDE</td>
<td>bond dissociation energy</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butylloxycarbonyl</td>
</tr>
<tr>
<td>Cbz</td>
<td>benzylxycarbonyl</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionization</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation Spectroscopy</td>
</tr>
<tr>
<td>CPME</td>
<td>cyclopentyl methyl ether</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIED</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DMAP</td>
<td>N,N-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>er</td>
<td>enantiomeric ratio</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Fmoc</td>
<td>fluorenlymethyloxycarbonyl</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>HFIP</td>
<td>hexafluoro-2-propanol</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond Correlation</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>high resolution liquid chromatography</td>
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<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>Heteronuclear Single Quantum Coherence</td>
</tr>
<tr>
<td>Pr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Form</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LCMS</td>
<td>liquid chromatography mass spectroscopy</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium hexamethyldisilazide</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>Ms</td>
<td>mesylate</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium hexamethyldisilazide</td>
</tr>
<tr>
<td>nBu</td>
<td>normal butyl</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>Phe</td>
<td>phenylalanine</td>
</tr>
<tr>
<td>RBR</td>
<td>Ramberg Bäcklung</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TFE</td>
<td>trifluoroethanol</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>tBu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TPP</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>TPPO</td>
<td>triphenylphosphine oxide</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>Val</td>
<td>valine</td>
</tr>
</tbody>
</table>
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For simplicity in this report, the common place S=O bond in a sulfoxide will be represented by a S-O, as this helps to further emphasize the stereocenter of the sulfoxide. Either sulfinyl configuration may arise with the synthesis of sulfoxides.

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Chapter 1: Introduction
1.0 Introduction

Organosulfur compounds are fundamental in organic synthesis and biological systems.\(^1\) Sulfur (S) containing mixtures occur in natural products like penicillin, they are responsible for the stench component in skunk smells, and are part of essential amino acids such as cysteine and methionine which participate in biochemical reactions.\(^2\) Many chemical reviews have been conducted with respect to sulfuric compounds and their derivatives, and the role of element 16 in living organisms is actively being investigated.\(^3,4\) Sulfone polymers are prominent in plastics engineering due to their strength and resistance under oxidative, corrosive, and high temperature environments.\(^5\) Appropriately, optically pure \(\alpha,\beta\)-unsaturated sulfoxides have been used abundantly in asymmetric synthesis as chiral auxiliaries because the sulfinyl moiety is a strong chiral influence. Opposingly, sulfenic acids and their anions are not as extensively studied,\(^6\) but are garnering interest in organic reaction pathways as well as biological processes, such as sulfenic acid modification with regard to reactive oxygen species-mediated cysteine.\(^7\) The stereochemical diversity provided by sulfoxides and sulfenic acids is of interest in the formation of the cyclic structures that are investigated herein.\(^8\) Aspects that can be used towards the synthesis of these alkenyl and allenyl sulfur compounds is represented here by providing a suitable literary background and review on techniques and methods that can be used towards the production of these constituents. This includes, but is not limited to, organosulfur compound characteristics and importance, Michael additions, sulfone and sulfoxide ring systems and general sulfenate chemistry.
1.1 Sulfur Compound Characteristics

Sulfoxides are generally represented with a structural formula where the sulfur is shown to contain three sigma bonds: two R-group bonds and a third one to an oxygen. The S–O interaction has an electrostatic feature, resulting in a noteworthy dipolar character involving a negative charge centered on the oxygen and the sulfur having a formal positive charge. A lone pair of electrons resides on the sulfur atom giving it a pyramidal-type geometry similar to that of an amine, as compared in Figure 1.

![Figure 1. Pyramidal structure similarities of amines to sulfoxides.](image)

Sulfoxides are an important S-functional group that can impart a stereochemical influence on chemical transformations. Unlike amines that comprise an average inversion barrier of 8-14 kcal/mol, sulfoxides have a stable configuration at room temperature, possessing a higher pyramidal inversion barrier of 35-43 kcal/mol. The sulfinyl (S-O) functional group found in sulfoxides comprises polar double bond features and dative bond components. Sulfoxides are conformationally stable at room temperature and therefore can be obtained as pure enantiomers. Additionally, the sulfinyl group is much less polarizable than the carbonyl group through comparing Hammett ρ-values done in a variety of studies. It is these properties that demonstrate the superiority of polysulfones in industry compared to polycarbonates, the only drawback being increased cost for the increased strength and durability. For sulfoxides, when the two organic bonds are dissimilar, the sulfur is a chiral center, such as in the case of common drugs such as omeprazole and armodafinil, as well as the naturally occurring molecule of alliin (Figure 2).
On the other hand, sulfones are tetra-coordinate sulfur molecules, with one sulfur bonded to two oxygens and two hydrocarbon substituents. They represent a large class of organosulfur compounds of interest in organic syntheses. Sulfones are typically stable and non-volatile, unlike their un-oxidized sulfide relatives. While there are a number of uses for sulfones, their importance for organic chemists lies in their versatility and functionality. Sulfones can participate in a large assortment of reactions, including a variety of Michael additions, alkylation, and acylation. The versatility and utility of the sulfone component makes it an important group in synthetic chemistry and it is typically obtained through sulfur oxidations as shown in Scheme 1.

Although sulfoxides and sulfones have a resemblance to the carbonyl group, there are several key differences. For the carbonyl group, the stabilizing effect of conjugation between C=C and C=O is maximized when π-orbitals are co-linear. This is not applicable to the C=C and S-O bonds of vinylic sulfoxides, since a π bond is virtually nonexistent between the S and O atoms. This concept can also be explained via parachor analysis, which takes into account the function of molecular weight, liquid density, vapour density and surface tension within bonds. The notion has been used to solve various structural problems, since it is approximately a sum of

**Figure 2. Examples of common chiral sulfoxide molecules.**

**Scheme 1. Oxidation schematic of organosulfur compounds.**
separate atoms and their linkages. For instance, double bonds on average have 21.3 parachor units each and triple bonds have 46.4 units. Atomic carbon has 4.8 and S has 48.2 units. The observed parachor values for sulfones are roughly equal or slightly less than the calculated parachor values if the S-O bonds were single bonds. This is a typical characteristic of semi-polar bonds. If the S-O bonds were double bonds, the observed parachor values would be higher than the calculated values.

Another semi-polar bond characteristic was observed when sulfone’s S-O bonds were studied using ultraviolet absorptions. Delocalization of the C=C π electrons into an S-O bond is possible when the S-O bond and C=C π system exist in a co-linear arrangement. When comparing UV-Vis spectra of the investigated C=O and S-O, a shift in wavelengths was experimentally observed by Podlech, indicating an increase in the orbital alignment, and by default also stability of the oxidized sulfur. Longer wavelength ultraviolet absorptions are generally observed with functional groups possessing double bonds, such as olefins, carbonyl, carboxyl, and nitro groups.

The stereochemistry of the sulfinyl group plays an important part in the reactivity of the sulfur material. This has been attributed to varying stereoelectronic effects between donor bonds and acceptor orbitals, which are most favorable when the corresponding groups adopt an antiperiplanar orientation due to favorable hyperconjugation, as shown in Scheme 2. These effects influence the stability, structure and reactivity of chemical compounds.
Scheme 2. Stereoelectronic effects of a nucleophilic addition to stationary vinylic sulfoxides.\textsuperscript{19,20}

Podlech also showed \textit{ab initio} calculations that quantified hyperconjugative interactions.\textsuperscript{19} A calculation of selected delocalization energies of 1 exhibited a significant stabilizing contribution from the \(\pi_{\text{c=c}}\) to the \(\sigma^*_{\text{s-o}}\) stereoelectronic state which was effectively non-existent in sulfoxide 2.\textsuperscript{9,14,15} Evidence for a related stabilizing interaction in 5 involving an antiperiplanar lone pair and S-O bond was obtained from differing diastereomeric ratios of conjugate additions of 1 or 2 with piperidine. Sulfoxide 1 produced amine 3 as the major diastereomer through intermediate 5.\textsuperscript{9,14,15} Here, an \(n_c\) to \(\sigma^*_{\text{s-o}}\) interaction is made possible by the antiperiplanar arrangement of the anionic lone pair and S-O bond, which creates stability. Competition experiments between 1 and 2 provided evidence that acceptor stabilization from the \(\sigma^*_{\text{s-o}}\) orbital of 1 is greater than from the \(\sigma^*_{\text{s-c}}\) orbital of 2.\textsuperscript{9,14,15}

Podlech expanded upon this investigation to include natural bond order analyses for the evaluation of the stereoelectronic effects in \(\alpha\)-carbanions of thiane derived sulfones and sulfoxides as depicted in Scheme 3. Sulfones 7 and 8 were found to have almost identical energies, which
means the $n_c \rightarrow \sigma^*_{s-o}$ interaction of 8 contributes significantly less to anion stabilization than in the case of a corresponding sulfoxide analog. This is because 7 possesses three major stabilizing effects including an $n_c \rightarrow \sigma^*_{s-c}$ hyperconjugation, a $\sigma_{c-H} \rightarrow \sigma^*_{s-o}$ interaction, and a synclinal $n_c \rightarrow \sigma^*_{s-o}$ interaction into the axial S-O bond following rehybridization of the lone pair to anion 9. Therefore, oxidized sulfur compounds can provide unique stereochemically dependent stability features, and new types of sulfur compounds should be pursued in order to fully understand such interactions.\textsuperscript{9,14,15}

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme3.png}
\end{center}

\textbf{Scheme 3. Evaluation of the stereo electronic effects in $\alpha$-carbanions of thiane derived sulfones.}

1.2 Michael Additions

The Michael conjugate addition reaction consists of adding various active methylene compounds (Michael donors) to electron deficient alkenes under basic conditions for the formation of carbon-carbon bonds.\textsuperscript{22} The reaction has been accomplished mostly with carbon nucleophiles, and it generally follows the reaction pattern demonstrated in Scheme 4. This reaction can occur with a variety of different functional groups ($Z^1$) that define the Michael donor, and various electron withdrawing groups that establish the Michael acceptors\textsuperscript{22,23} as shown in Figure 3. The
addition occurs when an EWG is attached to an alkene, thus activating it for nucleophilic attack as demonstrated in Scheme 4. The $Z^1$ component can also be electron withdrawing, a feature that helps to create the requisite anionic nucleophile. The same functional groups can serve to activate either the nucleophile or the electrophile, and a wide variety of functional pathways can be further elaborated experimentally.

\[
\begin{align*}
R^1 & \quad Z^1 \quad + \\
 & \quad R^2 \quad \text{EWG} \\
\rightarrow & \\
& \quad Z^1 \quad \text{EWG}
\end{align*}
\]

**Scheme 4.** General conjugate addition through an alkene.

![Possible Michael reaction functional groups](image)

**Figure 3.** Possible Michael reaction functional groups.

The nucleophilic addition may take place in an enantioselective or a non-enantioselective manner. Currently, there is a high demand for optically active compounds, which has driven many studies of asymmetric versions of the Michael addition in order to provide compounds with a high enantiomeric purity. The asymmetric Michael reaction has been categorized into two groups depicted in Scheme 5. The first consists of an enantioselective addition of prochiral enolates, meaning a Michael donor to an acceptor, and the second describes an enantioselective addition of enolates to a prochiral Michael acceptor.
Scheme 5. Schematic of prochiral donors and acceptors for asymmetric Michael addition.\textsuperscript{25,26}

In Scheme 5a), the enantiomeric face of the prochiral Michael donor is depicted in the formation of the asymmetric centers. In reaction Scheme 5b), the enantiomeric face of the prochiral Michael acceptor and the resulting asymmetric centers are formed on the Michael acceptor.\textsuperscript{25} There are many chiral additives that have been used for promoting the enantioselective C-C bonds, such as chiral alkaloids, chiral alkoxides and chiral amino acid complexes.\textsuperscript{25} For instance, in Scheme 6, an addition of the chiral Michael donor to achiral Michael acceptor occurs. Here, the source of chirality is present in the Michael donor, which controls the formation of the new stereogenic center in the product.\textsuperscript{25}

Scheme 6. Sulfoxide Michael donor forming a chiral center.\textsuperscript{25}

The use of various other nucleophiles such as N (aza-Michael) and S (thia-Michael) to create carbon-nitrogen and carbon-sulfur bonds are also of interest.\textsuperscript{28,29} The role of the aza-
Michael reaction in the synthesis of pharmacologically important $\beta$-amino carbonyl compounds and its derivatives is well documented in the literature. Over the last few years, there has been increasing interest in the synthesis of such pharmacologically important compounds by reaction of a variety of nitrogen nucleophiles with a range of Michael acceptors being employed in catalytic systems. A standard aza-Michael reaction is represented in Scheme 7, where in this case a chiral amine compound is formed.

![Scheme 7. Outline for a typical aza-Michael reaction.](image)

Aza-Michael additions can be stimulated by the incorporation of various Bronsted acid that demonstrate catalytic activity with secondary amines or primary aliphatic amines, which allows reaction proliferation. In order for the reaction to proceed, the acid catalyst must be sufficiently nucleophilic as well as be able to create an aza-Michael addition product consisting of weakly nucleophilic amine. In addition, Amore et al. have developed an acetic acid mediated microwave assisted protocol to promote addition of weakly nucleophilic aromatic amines to a range of conjugated alkenes, in Scheme 8.

![Scheme 8. Example of an aza-Michael addition where the nucleophile is an amino group.](image)

Many strategies for aza-Michael reactions have also proved useful in the synthesis of core intermediates of many natural products. A wide variety of nitrogen nucleophiles can be employed to react with a suitable acceptor. Aza-Michael additions have great potential in organic synthesis,
primarily because of the abundance of β-amino acids or alcohols in many natural products.\textsuperscript{32,33} The β-amino carbonyl compounds have been considered not only as building units of biologically important natural products including β–lactams, but also as versatile nitrogen-containing intermediates such as β-amino alcohols, β-amino acids and thiazines.\textsuperscript{9}

Recently, a 9-amino substituted cinchona alkaloid, in combination with various acids, has been shown to provide an effective catalysis for the activation of enones in various asymmetric conjugate addition reactions (Scheme 9).\textsuperscript{9} This represents a highly enantioselective aza-Michael reaction of a generic α,β-unsaturated ketone with an organic catalyst.\textsuperscript{9} It is particularly noteworthy that this catalytic asymmetric aza-Michael reaction is effective for a broad range of alkyl vinyl ketones bearing both aryl and alkyl β-substituents.\textsuperscript{9} By utilizing commercially available nitrogen nucleophiles and readily available chiral catalysts, this asymmetric aza-Michael reaction provides a highly promising method for the asymmetric synthesis of a wide range of optically active chiral amines.

\begin{align*}
\text{Ph} & \text{CH} = \text{C} & \text{H} & \text{N} \quad \text{cat. alkaloid} \quad 0.4 \text{ equiv TFA, DCM, rt} \quad \text{Ph} & \text{CH} = \text{C} \quad \text{H} & \text{N} \\
\text{Ph} & \text{CH} = \text{C} & \text{H} & \text{N} \quad \text{cat. alkaloid} \quad 0.4 \text{ equiv TFA, DCM, rt} \quad \text{Ph} & \text{CH} = \text{C} \quad \text{H} & \text{N}
\end{align*}

\textbf{Scheme 9.} Asymmetric conjugate aza-Michael reaction utilizing a 9-amino cinchona alkaloid in acid.\textsuperscript{9}

Symmetric aza-Michael reactions have been shown to form thiazine compounds, such as product 11 in Scheme 10.\textsuperscript{34} Thiazines constitute an important class of molecules possessing diverse biological activities such as antibacterial, insecticidal, fungicidal, antitumor, antioxidant, antipyretic, and calcium channel modulator.\textsuperscript{34} More recently, Knoevenagel condensation followed by hetero-Michael addition has considerably attracted attention as a versatile, and cost-effective strategy for synthesis of these 1,3-thiazine molecules for drug discovery process.\textsuperscript{35}
Scheme 10. Formation of thiazine 11 via Michael addition through the use of methylamine 10.

The most direct route to obtain enantiomerically enriched sulfoxides involves preparation and substitution of a pure diastereomer using a chiral reagent. An unsaturated sulfoxide or sulfone which could undergo an intramolecular aza-Michael addition in order to form thiazine based compounds, as represented in Scheme 11. The stereoselectivity of cis- and trans- $\alpha,\beta$-unsaturated sulfoxides and sulfones towards optimized cyclization conditions in order to form various derivatives of 13 is an interesting pursuit for investigation.

Scheme 11. The aza-Michael addition for the possible creation of cycloalliin, and other thiazine derivative compounds that can be investigated.

1.3 Sulfur Michael Acceptors

Optically pure $\alpha,\beta$-unsaturated sulfoxides have been used abundantly in asymmetric synthesis as chiral precursors due to the fact that the sulfinyl component is a strong chiral influence as discussed in section 1.1. Asymmetric Michael additions of nucleophiles to $\alpha,\beta$-unsaturated sulfoxides is an approach that has been used to create optically pure natural products and biologically active compounds. Two examples of such compounds are shown in Figure 4, and the bond that is generated through the asymmetric addition to the chiral $\alpha,\beta$-unsaturated sulfoxide is indicated by the arrow.
Figure 4. Examples of optically active natural products that can be synthesized through a Michael addition to an α,β-unsaturated sulfoxide.⁶

The configuration of the α,β-unsaturated sulfoxide has an effect on the overall chirality of the compound, as evidenced by desirable stereochemical outcomes during the formation of alkyl bonds.³⁸ The Posner group achieved the asymmetric addition of a methyl Grignard reagent to chiral sulfinyl cyclopentenone to give cyclopentanone 16 (Scheme 12).³⁹ The sulfinyl component of the product was removed by reduction to form a methylcyclopentanone in a good yield.³⁹ The stereoselection is suggested to involve nucleophilic attack of the organometallic agent to the less hindered face of the magnesium complex, as shown in Scheme 12 below.

Scheme 12. Stereoselective synthesis of (R)-(+) 3-methylcyclopentanone through nucleophilic attack to an alkene.³⁹

To expand on this category, α-sulfonyl anions can also be used as nucleophiles in Michael-type additions. Enantioselectivity can be achieved through various modifications of reaction conditions. For instance, through the use of primary amine catalysts, enantioselective Michael
reactions of sulfonyl anions to \(\alpha-\beta\)-unsaturated aldehydes have been reported by several groups. Unsaturated sulfones can also act as Michael acceptors as depicted in Scheme 13. This class of \(\alpha,\beta\)-unsaturated sulfones can participate in Michael type additions due to their strong electron withdrawing influence. Steert and co-workers used a Michael addition reaction in their synthesis to make a series of cysteine proteases. Thiol 19 undergoes a conjugate attack on vinyl phenyl sulfone 20.\(^{40}\)

![Scheme 13. Addition of phenethyl mercaptan to an unsaturated sulfone Michael acceptor.](image)

1.4 Formation of Sulfoxide and Sulfone Heterocycles

In the 1950’s, Virtanen was the first to report the cyclization of the amino acid isoalliin to cycloalliin (Figure 5), a reaction that was thought to occur in onions.\(^{41}\) The reaction was experimentally shown to occur in an aqueous ammonium hydroxide solution, with workup involving the addition of acid.\(^{41}\)

![Figure 5. Structure of cycloalliin.](image)
The success of Virtanen’s biosynthesis drove chemists to further study the cyclization properties of a new family of molecules known as 1,4-thiazines.\textsuperscript{41,42} Attempts were made to define the stereoselectivity of thiazine formation through the cyclization of cis- and trans-1-alkenyl β-aminoalkyl sulfoxides, but these trials were deemed unsuccessful as firm conclusions could not be established.\textsuperscript{41,42} This was because the experiments had a starting material that was a diastereomeric mixture, which caused problems in identifying the origin of the sulfinyl configuration produced with the corresponding cis or trans cyclized product. As such, no conclusive data or interpretations could be effectively made on the stereoselectivity of these cyclizations.\textsuperscript{41,42} Correspondingly, the experiments completed in an aqueous medium were time consuming and also produced a mixture of diastereomers, as demonstrated in Scheme 14. Specifically, sulfoxides 21 and 24 had to be reacted for several days in ammonium hydroxide and did not form a single high-yielding product. Rather, a mixture of diastereomers (22, 23, 25 and 26) was created, and these proved to be difficult to separate.\textsuperscript{41,42}

\textbf{Scheme 14.} The cyclization of trans and cis 1-propenyl β-aminoalkyl sulfoxides.
Moving forward, Carson further conducted intramolecular cyclizations utilizing sulfones and sulfoxides based on Virtanen’s work. Isomers of the corresponding alkenyl sulfoxides where prepared and cyclized. An isomer of chondrine with the sulfoxide in the opposite configuration has been synthesized. Nuclear magnetic resonance and infrared spectra of the isomers were found to be consistent with an equatorial sulfoxide, but unusually high gauche coupling constants for equatorial sulfoxides were also uncovered. This indicated that a highly sterically hindered chair form for these compounds must be involved.

The stereoselectivities of the cyclizations of trans-1-alkenyl β-aminoalkyl sulfoxides and sulfones unrelated to onion constituents has since been recently pursued. Utilizing sulfenate alkylation, diastereomerically pure 1-alkenyl β-aminoalkyl sulfoxides of the trans stereochemistry were effectively produced and properly characterized by Söderman and Schwan. The pure starting material was the key to this experiment, which gave conclusive results that trans alkenes give trans cyclic stereoisomers as shown in the scheme below. In Scheme 15, the optimized synthesis for trans-1-alkenyl β-aminoalkyl sulfoxides from thiirane S-oxides is drawn. These pure chiral E-vinylic β-amino sulfoxides as starting materials were intriguing results to the exploration of sulfenate chemistry and were valuable for the analysis of intramolecular cyclization reactivity. It is the unique chemistry of the sulfenate which allows for variation at the R and R’ positions to explore trends in cyclization selectivity and reactivity.

**Scheme 15.** Forming stereoselective β-amino sulfoxides utilizing lithium sulfenate anions.
Boc-deprotection occurred via the formation of a TFA salt, which then resulted in the amine through a base quench. The efficiency of this cyclization was drastically improved in both time and yield by using triethylamine in methanol as reaction conditions illustrated in Scheme 16.38

![Scheme 16. Amine deprotection and subsequent cyclization protocol.](image)

Expanding on this knowledge and investigations with other derivatives, three key concepts where then developed on the cyclization of trans-1-alkenyl β-aminoalkyl sulfoxides as demonstrated in Scheme 17 and the corresponding sulfone synthesis in Scheme 18.38 Here, the anti and syn designations are assigned as structural labels with respect to the stereochemistries of the S-O bond and β-substituent in compounds 29 and 31, respectively. The subsequent cyclization of the syn-β-amino sulfoxides 31 led to trans substituted heterocycles 32 (trans selectivity), while the cyclization of the minor anti-diastereomer 29 gave the complementary cis-heterocycle 30 (cis selectivity). Conversion of the sulfoxides to the sulfones can occur to form the enantiomerically pure trans-1-alkenyl 2-aminoalkyl sulfones, which by contrast, undergo cyclization to give the complementary cis-3, 5-disubstituted thiomorpholine S,S-dioxides. The importance of these specific cyclization outcomes is underscored by their application to the stereodivergent synthesis of cis and trans ant venom alkaloids.38 Ant venom alkaloids have shown a high biological activity, and their study can be used for the development of new types of therapeutic agents.44 Therefore, the greater availability of chiral sulfoxides spurs further inquiries into their utility. The expansion of Söderman’s work is to synthesize cis-1-alkenyl β-aminoalkyl
sulfoxides and sulfones exposed to the same cyclization conditions in order to give a complete characterization of the stereospecific process of this class of compounds.

Scheme 17. Anti and syn selectivity's contracted for the 1-alkenyl β-aminoalkyl sulfur compounds as discovered by Söderman.

Scheme 18. Sulfone stereoselectivity of trans-1-alkenyl β-aminoalkyl sulfones

1.5 Sulfenate Chemistry

Sulfenates are the conjugate bases of sulfenic acids. When a sulfenate group is deprotonated, the corresponding sulfenate anion is formed as shown in Scheme 19. Sulfenate anions are an interesting family of organosulfur compounds that have garnered increasing attention in synthetic organic chemistry. Attention to these reactive species has increased due to the newly realized existence and importance of sulfenate anions as intermediates in biological systems. Recently, several synthetic research groups have also made developments in the study of these
reactive intermediates. Sulfenates are relatively unstable, even to molecular oxygen; they are converted to the corresponding sulfinates upon exposure to air as detailed in Scheme 19.\textsuperscript{49}

\[ R^-S-O^- + O_2 \rightarrow [O \begin{array}{c} O \\ R^-S-O^- \\ O^- \end{array}] \rightarrow R^-S-O^- \rightarrow R^-S-O^- \]

Scheme 19. Sulfenate anions representation in acid.

The formal oxidation state of sulfur in sulfenic acid (RSOH) is 0 which results in its unique ability to function as both a nucleophile and an electrophile.\textsuperscript{50} Although the nucleophilic character of sulfenic acids is not very strong, it can still play a prominent role where the possibility of the formation of intermolecular hydrogen bonding is present.\textsuperscript{50} This dual nature is most clearly illustrated in allicin (a derivative of alliin that was depicted in Figure 2) chemistry which is propagated primarily by the formation of a hydrogen-bonded sulfenic acid dimer. The condensation of two sulfenic acids results in the formation of thiosulfinates. This is a unique feature among organic acids, in that favorable formation of thiosulfinate means that aqueous equilibrium favors the anhydride form of sulfenic acid. As a direct result of this feature, less is known about sulfenic acids than about corresponding higher sulfur oxyacids.\textsuperscript{51} The prevalence of thiosulfinates in biology is largely unknown; however, it must be acknowledged that due to the low abundance of cellular thiols the interfacing of two sulfenic acids is likely to be a rare event.\textsuperscript{51} Isolation of a few stable sulfenic acid compounds have been observed from plants of the \textit{Allium} genus, indicating that sulfenic acids and their derivatives play a role in the chemistry of garden vegetables such as onions and garlic.\textsuperscript{51,52}
Regardless of the instability of sulfenate anions, some research groups have managed to isolate examples for characterization. The sodium salt of 2-pyridinesulfenate (35 in Figure 6) in an oxygen free environment was isolated some time ago and an IR analysis was conducted to observe any characteristic absorptions. The S-O stretch of 870 cm\(^{-1}\) was detected, whereas the S-O stretch of an azetidinone sulfenic acid is observed at 770 cm\(^{-1}\). A higher stretching frequency for a sulfenate anion compared to its conjugate acid is consistent with an increase in multiple bond character in the S-O bond of the sulfenate.\(^{9,49}\) The IR stretching frequency (\(\nu_{SO}\)) for methanesulfenate was calculated to be 836 cm\(^{-1}\) using B3LYP/6-31(d,p) while its sulfenic acid counterpart was calculated to have an S-O stretching frequency of 756 cm\(^{-1}\).\(^{54}\) Thus the changes from sulfenic acid to its conjugate anion (sulfenate) are consistent as a corroboration of measurements.

Schwan has reported the \(^1\)H NMR spectrum of labile lithium sulfenate 35 through its creation in THF-d\(_8\).\(^{55}\) A solution of sulfenate 35 at -78 °C was prepared via treatment of anti-n-butythiirane S-oxide with solid LiHMDS∙Et\(_2\)O and the formation of the lithium sulfenate observed.\(^{55}\) The resonances for the vinylic component were measured at 6.2 (d) and 5.0 ppm (dt) for the \(\alpha\) and \(\beta\) hydrogens, respectively.\(^{55}\) Correspondingly, the divalent sulfur of a typical butenyl thioether such as benzyl 1-hexenyl sulfide shows vinylic proton resonances to be at 5.9 (d) and 5.7 (dt) ppm.\(^{56}\) This difference in chemical shifts implies that the sulfenate exhibits a stronger electron donor than its divalent congener.\(^{55,56}\)

Figure 6. Molecules of sulfenate anions.
Downard has dedicated much effort into both experimental and computational studies on the gas-phase deprotonation of methanesulfenic acid by $^-\text{OH}$, creating 37. The collisional activation mass spectrum ($\text{M}^+ : m/z = 63$) showed the anticipated loss of $^\cdot\text{CH}_3$ and loss of $\text{H}_2\text{O}$, which was interpreted as being an artifact of decomposition of the sulfenic acid isomer.\textsuperscript{57}\textit{Ab initio} calculations using MP2/6-31+G/HF/6-31+G(d) indicated that the $\alpha$-sulfur anion 38 has a higher energy tautomer than that of a typical sulfenic acid salt. The sulfenate in 37 was found to obtain a bond length of 1.580 Å – a bond length equivalent to something between an S-O single bond (~1.66 Å) and the “S=O” bond of a typical sulfoxide (1.490 Å). Additional characteristic data is shown in Table 1 as determined by Hartree Fock computation. The ion molecule chemistry in methanesulfinenate reveals that it is an oxidizing agent with reactivity between that of $\text{HO}_2^-$ and $\text{HCO}_3^-$. Although slow, sulfenate 37 is capable of undergoing reactions with $\text{CS}_2$ and COS, and while the electron transfer with sulfur dioxide is surprisingly fast, a minor oxidation reaction is observed.\textsuperscript{58}

Generation of ethanesulfinenate anions through rearrangement chemistry of deprotonated thirane S-oxides has been extensively studied by Merrill and coworkers. The Maccagnani research group also contributed to the information. The theoretical analysis of the rearrangement is shown in Table 2, where the cisoid and transoid ethanesulfenate anions is shown. The results demonstrate that the transoid conformation is less stable than the cisoid, but the bond length and angle calculations do not depict a strict analysis of sulfenate structure. The C=C bond length shown in 39 has the possibility to extend more than the normal alkene length of 1.34 Å, a notion which is consistent with some of the sulfur to alkene conjugation.\textsuperscript{59-62} The HOMO of ethanesulfenate has electronegative components at O, S and the $\beta$-carbon,\textsuperscript{63} and the S-C bond length is very much shorter than that found for methanesulfenate (Table 1).
The broadening of the <CSO also corresponds to the electron donation to the alkene. The approaches involved for the generation of sulfenate anions include transformations of sulfenate esters, sulfines and sulfoxides using addition-elimination reactions, ring manipulation, sigmatropic rearrangements and metal insertions.

**Table 1:** Computational (HF/6-31 +G(d)) calculation of the gas-phase methanesulfenate anion 37.

<table>
<thead>
<tr>
<th>Bond Length (Å)</th>
<th>Bond Angle (°)</th>
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</thead>
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<tr>
<td>HₐC</td>
<td>1.092</td>
</tr>
<tr>
<td>HₐC</td>
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<tr>
<td>CS</td>
<td>1.812</td>
</tr>
<tr>
<td>SO</td>
<td>1.580</td>
</tr>
<tr>
<td>SO</td>
<td>-60.0</td>
</tr>
</tbody>
</table>

37
Table 2: Calculated relative energies using varied Gaussian computational methods for transoid (39a) and cisoid (39b) isomers.\textsuperscript{63,64}

<table>
<thead>
<tr>
<th>Calculated Parameter</th>
<th>Method</th>
<th>Conformation</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Energies</td>
<td>RHF/STO-3G*</td>
<td>39a -19.8</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>RHF/3-21+G*</td>
<td>39b -17.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MP2/3-21+G*</td>
<td>39a -56.6</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39b -56.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G2+</td>
<td>39a -48.9</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39b -52.0</td>
<td></td>
</tr>
<tr>
<td>&lt;CSO</td>
<td>3-21+G*</td>
<td>39a -40.0</td>
<td>64</td>
</tr>
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<td></td>
<td>STO-3G*</td>
<td>39b -32.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MP2(fc)/6-31+G(d,p)</td>
<td>39a 104.3</td>
<td>63</td>
</tr>
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<td></td>
<td></td>
<td>39b 110.2</td>
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<td></td>
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<td>39b 112.4</td>
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<td>39b 107.5</td>
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</tr>
<tr>
<td></td>
<td>3-21+G*</td>
<td>39a 106.5</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>STO-3G*</td>
<td>39b 107.5</td>
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</tr>
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<td></td>
<td>MP2(fc)/6-31+G(d,p)</td>
<td>39a 106.5</td>
<td>64</td>
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<td></td>
<td></td>
<td>39b 107.5</td>
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<td>R(C=)(Å)</td>
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<td>39b 1.362</td>
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<td>R(S-C) (Å)</td>
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<td>63</td>
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<td>STO-3G*</td>
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<td></td>
<td>MP2(fc)/6-31+G(d,p)</td>
<td>39a 1.716</td>
<td>63</td>
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<td></td>
<td></td>
<td>39b 1.708</td>
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<td></td>
<td></td>
<td>39a 1.733</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>39b 1.725</td>
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</tr>
<tr>
<td>R(S-O) (Å)</td>
<td>3-21+G*</td>
<td>39a 1.623</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>STO-3G*</td>
<td>39b 1.607</td>
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</tr>
<tr>
<td></td>
<td>MP2(fc)/6-31+G(d,p)</td>
<td>39a 1.531</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39b 1.526</td>
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</tr>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>39b 1.587</td>
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</tr>
</tbody>
</table>

The preparation and exploratory generation of simple arene- and alkanesulfenate anions was conducted by O’Donnell for a large family of both alkane- and arenesulfenate anions, including the first bis alkanesulfenate to be liberated from a sulfoxide.\textsuperscript{65} Other objectives of the
work involved determining the addition or elimination reaction pathway for sulfonate anion release. It was shown that the arene compounds studied by O’Donnell are very efficient in capturing the sulfonate anions with good yields (>75%), an example of which is shown in Scheme 20. Here, no elimination pathway by product was observed in the $^1$H NMR spectrum of the crude reaction mixture. This indicates that under these experimental conditions, competitive elimination of the quenching agent is not a factor.

Scheme 20. Arene reaction used for the study of equivalent effects on sulfenate capture.

O’Donnell also noted that the chain electrophile impedes efficient alkylation of the sulfenate given that 4 equiv. causes a decrease in the isolated yield of the sulfoxide. However, the reasoning for highest sulfoxide formation with the least amount of electrophile is still unclear. The E/Z isomers obtained of 42 in Scheme 21 were separated and individually subjected to the reaction sequence to liberate $p$-toluenesulfenate. The highest yield was obtained for the Z-isomer, yet individual isomers gave varying yields. This is related to the ease in which the sulfenate can be eliminated in order to create 43. Through an addition/elimination pathway, addition of the nucleophile is kinetically simpler for the cis system due to its steric features.

Scheme 21. Reaction used for the effect on the yield with separation of E/Z isomers.

The elimination sequence is speculated to be easier due to the anti-periplanar arrangement that is achieved after a 60° rotation as shown in Scheme 22. Also using steric arguments, addition may be more difficult for the trans system depending on the bulkiness of the nucleophile and the
orientation of the sulfinyl oxygen. Due to the sp² hybridization on the carbon, pyramidal inversion should occur before displacing the sulfenate moiety. It is shown in Scheme 22 that both cis and trans systems exhibit eclipsing substituents to induce the liberation of the sulfenate. An alternative though, is that syn-elimination of the sulfenates is occurring in a method similar to that observed for previous systems of β-protiosulfoxides in the alkene and sulfenic acid generations.

A syn ring opening has also been observed in the formation of 1-alkenesulfenate anions. If intermediate A were to succumb to syn-elimination, Z-45 would result. Likewise, if intermediate B were to undergo syn-elimination, E-45 would be produced. This indicates that sulfoxide E-44 is part of the addition/elimination sequence while Z-44 is prone towards an E2 mechanism.

The cis isomer in Scheme 22 is not sterically hindered and the base-induced proton abstraction can occur quickly. This would be followed by fast release of the sulfenate due to the anti-periplanar arrangements of the substituents. For the trans isomer, the anion must first overcome the inversion barrier to adopt the anti-periplanar arrangement before any elimination may occur. The anti-periplanar elimination of the sulfenate is supported experimentally by the sole formation of the E-vinylic by-product. These results were pursued further and were utilized for the formation of cysteinesulfenate anions. One of the surprising outcomes with the homocysteine derivatives was that in all circumstances, the vinylic sulfides by-product could be isolated in both the E and Z isomers, something which was not observed for Z-45 in Scheme 22, even when the starting sulfoxide had the cis double bond in place. This evidence suggests and supports the possibility in Scheme 22 of the syn elimination. The homocysteine derivatives provide a long enough tether and the appropriate sites for coordination to the lithium counterion to effect the syn elimination as per Scheme 23.
Scheme 22. Addition/elimination pathway for E/Z isomers in O'Donnell’s work. Newman projections represent the olefin as the proximal and distal carbons.
Scheme 23. Diastereoselective alkylation of homocysteinesulfenates.

To further describe sulfenate anions as nucleophiles, it is known that alkylation can take place at either the sulfur or oxygen atom depending on the identity of the electrophile. These anions are interestingly not chiral due to their plane of symmetry, yet represent significant prochiral components for a molecular construction through S-alkylation processes. Soft electrophiles, like reactive alkyl halides, will alkylate at the softer sulfur atom, while hard electrophiles such as dimethyl sulfate alkylate the oxygen atom of the sulfenates demonstrated in Scheme 24.

Scheme 24. Hard and soft alkylations of acidic sulfenate anions.

Metzner et al. developed a convenient method to release sulfenates through the formation of 2-(trimethylsilyl)ethyl sulfoxides 51 using a fluoride ion source. Optimal conditions included using tetrabutylammonium fluoride (2 equiv.) in THF in the presence of 1.1 equiv. of benzyl bromide as shown in Scheme 25. Several aromatic sulfenates with different substituents were tolerated and the reaction sequence provided benzyl sulfoxides in good yields.

Scheme 25. Sulfoxide formation utilizing fluoride ions in hot temperatures.
Starting from the (trimethylsilyl)ethyl sulfoxides, a 2-pyridinesulfenate was alkylated cleanly with BnBr without any detection of pyridinium salt from the competing nitrogen alkylation.\textsuperscript{68} Both alkenyl and alkynyl sulfenates were alkylated and the alkenyl sulfenate gave the corresponding sulfoxide with clean retention of the olefin geometry.\textsuperscript{68} Sulfenate release was attempted on a t-butyl derivative, yet here, the starting material remained unaffected by TBAF. The robustness of this substrate was attributed to the lack of resonance stabilization from the aliphatic 'Bu group necessary to delocalize negative charge build up during fragmentation.\textsuperscript{68} This theory on the 'Bu group has now been overturned as there is now evidence showing that t-butyl sulfoxides can generate sulfenates, albeit under different conditions.\textsuperscript{69} Walsh \textit{et al.} shows the formation of stilbene derivatives \textbf{52} from benzyl halides that can be catalyzed by sulfenate anions using 'Bu derivatives,\textsuperscript{69} as in Scheme 26.

\textbf{Scheme 26.} Sulfenate anion catalyzed stilbene formation from benzyl halides in base and CPME.

The proposed mechanism for the sulfenate anion-catalyzed coupling of benzyl halides is illustrated in Scheme 27. Beginning with benzyl phenyl sulfoxide, deprotonation by KO'Bu generates the anion, which was demonstrated to be the catalyst resting state. The anion undergoes nucleophilic substitution with benzyl halide to form the sulfoxide.\textsuperscript{69} Deprotonation at the β-position of the sulfoxide is followed by elimination to generate the sulfenate anion and the double bond with very high trans selectivity.\textsuperscript{69} It is reported that a second-generation sulfenate anion catalyst that avoids contamination in the first cycle. The precatalyst, 'Bu-phenyl sulfoxide, undergoes base promoted elimination to generate phenyl sulfenate anion and isobutylene as a gaseous byproduct.\textsuperscript{69} The group has since reported in 2016 a palladium-catalyzed arylation of aryl
sulfenate anions generated from aryl 2-(trimethylsilyl)ethyl sulfoxides and CsF. This protocol is effective for the synthesis of diaryl sulfoxides and heteroaryl aryl sulfoxides under mild conditions employing aryl bromides.

**Scheme 27.** Proposed mechanism for sulfenate anion catalyzed trans-Stilbene formation from benzyl halides.

The conversion of allyl sulfoxides to allyl sulfenates with respect to the generation of sulfenate anions has also been explored. Here, sulfenates were formed from allyl sulfoxides by treatment with catalytic amounts of a Pd(0) complex and an appropriate nucleophilic species. With Pd(0) and an aryl sulfenate available in one-pot, Ar-I coupling reactions successfully created diaryl sulfoxides (Scheme 28). To add, t-butyl sulfoxides have also been shown to act as key precursors for palladium-catalyzed arylation of sulfenate salts through a generalized cross-coupling procedure developed by Perrio.
Fluoride ion mediated sulfenate release has also been applied in the investigation of a proposed sulfenate intermediate in the leinamycin rearrangement presented in Scheme 29. Treatment of leinamycin analog 53 with TBAF causes the liberation of a sulfenate intermediate. The sulfenate attacks the proximal thiolester moiety via the sulfenate oxygen anion to produce a short-lived carboxylic acid derivative. Then, a cyclization involving the pendant olefin moiety generates an episulfonium ion, which is believed to be analogous to the leinamycin intermediate that alkylates DNA. Attack by the excess fluoride anion and methylation by diazomethane gave heterocycle 54. 

Perrio was able to achieve a modest asymmetric sulfenate alkylation using a β-sulfinyl ester substrate for sulfenate release as shown in Scheme 30. Treatment of 55 with 8BuLi/(L)-sparteine
in toluene followed by the addition of methyl iodide at 45 °C gave sulfoxide 56 (29% ee).\textsuperscript{76} The alkaloid (L)-sparteine was the only chiral bidentate ligand evaluated. The temperature of -45 °C was optimal for achieving the highest ee. Lower temperatures (-78 °C) actually decreased the ee of the product. This effort was the first external ligand-controlled enantioselective alkylation of a sulfenate.\textsuperscript{76} This follows recent work that demonstrates halogenated pentanidiums can greatly improve the enantioselectivity of sulfoxides (up to 99\%) when alkylating sulenate anions.\textsuperscript{77,78} The cyclized sulfoxides could potentially be adapted as chiral ligands or form bioactive molecules.

Scheme 30. Example of an asymmetric sulfenate alkylation.\textsuperscript{76}

Sulfenate chemistry allows variation at both R-group positions in order to explore trends in cyclization selectivity and reactivity previously depicted in Scheme 15.\textsuperscript{73} The relative reactivity of different electrophiles towards a selection of lithium sulenate anions was also evaluated by performing competition experiments by Söderman.\textsuperscript{7} This asymmetric sulfenate alkylation chemistry provides access to chiral vinylic β-amino sulfoxides as starting materials to explore subsequent cyclization reactivity.\textsuperscript{7}

Kinetically, many sulfenate esters are converted to their rearranged allyl sulfoxides,\textsuperscript{78} and it is likely that the allenyl sulfenate anions propagate toward kinetic rearrangement also. Though much progress in the last decade has been accomplished in sulfenate chemistry, it is the allenyl sulfenate systems which merit further investigation.
1.6 Project Goals

Our group felt we could make a contribution to the general heterocycle chemistry, with the goals of creating additional examples for cyclization chemistry, particularly for the cis β-amino sulfur compounds. In this way, it was felt that higher yields of oxygenated 1,4-thiazone could be obtained, particularly in the sulfoxide manifold. A practical and relatively simple procedure for the generation of allenyl sulfinates is also desired, something of which currently garners a small amount of literary interest. Exploration into the reactive nature of sulfinates and to establish some comprehension with regards to their prochiral behavior from a synthetic point of view is pursued. As a possible long-term goal for the research group, this can be attempted through cyclization of the allenyl sulfinate utilizing the previously described NEt₃/MeOH treatment as shown in Scheme 31. At the core of all of this work is the relative stereochemistry of the β-amino sulfoxides obtained from the sulfinate alkylation chemistry.

*Scheme 31.* Possible exploratory cyclization chemistry incorporating the allenyl sulfinate.
Chapter 2: Results and Discussion
2.1 Cyclization Results and Discussion

2.1.1. Background Information and Theory

The stereoselective cyclization patterns of trans-1-alkenyl β-aminoalkyl sulfoxides and sulfones have been uncovered through the work of Söderman via his exploration of an aza-Michael addition. In combination with the Ramburg-Backlung chemistry, he showed that the cyclization chemistry of these compounds is useful for the diastereoselective synthesis of two ant venom alkaloids. Here, investigation of the cyclization of the corresponding cis-1-alkenyl β-aminoalkyl sulfoxides and sulfones in order to establish their stereochemical results is presented. The outcomes achieved can be compared to the cyclization models forwarded by Söderman.

Due to the promising nature of this reaction, the initial aim of this M.Sc. project is to further explore the synthetic scope and mechanistic details of the induced cyclization reaction using 1-alkenyl β-aminoalkyl sulfoxides and sulfones. Specifically, the objective of this master’s thesis includes: (1) thorough optimization for the formation of cis sulfoxides, (2) establish and study relative reaction rates and mechanism parameters, which include (3) to probe and establish stereoselectivity of cyclization, and (4) expand the synthetic scope of the reaction by varying the side chain of the starting amino acid. This chapter will begin by describing the synthesis of starting materials, adapted from methods initiated by previous group members.

The cyclization of the syn-β-amino sulfoxides uncovered by Söderman led to trans substituted heterocycles, while the cyclization of the minor anti-diastereomer gave the complementary cis-heterocycle (See Chapter 1.4). Furthermore, by oxidation of the sulfur atom of the syn-β-amino sulfoxides prior to cyclization, the cis-heterocycles can be accessed (Scheme 32). This led to the development of new and more economical conditions for the RBR method, which gave way to the synthesis of alkaloids 68 and 71. The utility of this chemistry provides a method
for the stereodivergent distereoselective synthesis of two isomeric ant venom alkaloids from identical starting material 58, which upon oxidation/deprotection, gave material 60 which required no further nitrogen protecting group. However, cyclization of the sulfoxide (58 → 61; Scheme 32) required addition of a carboxybenzyl group before further oxidation. The cis stereochemistry remained throughout. Sulfones 66 and 69 were subjected to Ramberg-Backlund conditions to afford pyrrolidines 67 and 70, which were then hydrogenated without significant loss of stereochemical integrity. In nature, alkaloids 68 and 71 are sprayed from a venom gland of Myrmicaria melanogaster to ward off predators and structurally similar 2,5-substituted pyrrolidine natural products have shown potent insecticidal activity towards arthropods.\(^{79-81}\) Also, the biological study of insect venoms has led to the discovery of new therapeutic agents.\(^{79}\)

![Scheme 32](image)

**Scheme 32.** Formation of the *trans*-1-alkenyl β-aminoalkyl sulfoxides (58) and sulfone (59/60).
Scheme 33. Formation of sulfones rings followed by RBR for the formation of a 5 membered ring.

Scheme 34. Final reaction steps to obtain trans and cis ant venom alkaloids.

To obtain the cis starting materials for stereochemical studies and to possibly form 1,4-thiazanes such as 66 and 61, various retrosynthetic approaches were taken into consideration. A model synthetic protocol is outlined in Scheme 35 with protected amino acids and alkyl halide starting materials. Once compounds 72 and 73 are obtained, they will be subjected to deprotection to form the free base or TFA salt, followed by cyclization much like compounds 58 and 60. Oxidation precedes the nitrogen deprotection, as a free amine introduces problems associated with chemoselection of the oxidizing agent that can be associated with 74. This also allows for easier purification without the need of specialized HPLC.82 In what is expected to be the most challenging
aspect of the synthetic protocol, different isomerization conditions can be investigated in order to form the cis alkene from a terminal alkene such as 75. The 3-carbon alkene component may be introduced through nucleophilic substitution with a sulfur nucleophile. This would mean having a sulfur substituent already on the molecule. The sulfur component (-SY) in 76 should be something easily manageable with minimum odor, such as a thiolester, though thiols (-SH) have been used for such conversions.\textsuperscript{82} Compound 76 can be obtained through a nucleophilic addition with β-amino alkyl halide (77) formed from a β-amino alcohol that would correspond to the given starting amino acid. Amino acids are cheap and have set stereochemistry, and therefore a good starting point for synthesis.

\begin{center}
\includegraphics[width=\textwidth]{scheme35.png}
\end{center}

\textbf{Scheme 35.} Retrosynthetic scope for the formation of cis-1-alkenyl sulfur derivatives.

\subsection*{2.1.2. Pursuit of the \textit{cis}-Isomer}

Experiments for obtaining the \textit{cis}-1-alkenyl β-aminoalkyl sulfoxides and sulfones were primarily conducted with \textit{L}-phenylalanine, and then expanded to other amino acids once the chemistry was optimized. The protecting group for the amino is \textit{t}-butyloxycarbonyl as it has shown simple removal with the addition of 2 equiv. TFA as previously performed,\textsuperscript{38,83} or through the use of another base as is shown in other literature.\textsuperscript{84-86} Boc protected amino acids are also readily available, eliminating the supplementary step of having to add the Boc group, although it has been
successfully achieved in the lab group. There are various methods of placing a Boc protecting group onto an amine.\(^87\)\(^-\)\(^91\)

Addition of the protecting group may occur as the first reaction inflicted to the amino acid (Method A, Scheme 36), or it can occur after reduction of the carboxylic acid (Method B, Scheme 36) in order to form the \(\beta\)-amino alcohol (78).\(^92\)\(^,\)\(^93\) Both methodologies, along with simply purchasing the protected amino acids have been accomplished in the Schwan lab. Purification was done easily through recrystallization regardless of whether Method A or B was adopted. The Boc protected amino acids that were purchased were subjected to steps 2 and 3 of Method B, with yields that ranged from 70-85% after recrystallization. The yields obtained may have been affected in part by the use of ethyl chloroformate that was old and did not have a Sure-Seal\(^\circledR\), indicating some exposure to moisture in step 2 which can decrease the amount of alcohol obtained.

![Scheme 36](image)

**Scheme 36.** Methods explored for obtaining \(\beta\)-amino alcohols.

Following this, the displacement of the alcohol with a halide was attempted. Hydroxyl to iodide conversions are common, and have been used in the synthesis for the trans compounds that exhibited \(E\)-selectivity in Scheme 32, so this approach was chosen as the starting point. The reaction was completed through a Mitsunobu-like reaction in \(\text{PPh}_3\), iodine, and imidazole (Scheme 37). The triphenylphosphine becomes triphenylphosphine oxide permitting pure iodide to be tritutrated out of the crude mixture via addition of petroleum ether as a white solid.\(^{94}\) The remaining crude mixture is put through a flash column to obtain an average yield of 70%. It was attempted to improve this, as there are still many steps remaining in the synthetic procedure. A
mesylate is also a very good leaving group and a good alternative to iodide in this case.\textsuperscript{95-100} This gave a $>90\%$ yield the majority of the time without the need for purification, as was indicated by $^1$H and $^{13}$C NMR analysis. This method also avoids any TPPO purification protocols.

The reaction typically takes about 4-6 hours to complete, which is much more time efficient than the formation of compound 79, which took 10-16 hrs and also required further purification. The mesylate was immediately (same day) converted into the corresponding thiolester. If the derivatives of compound 80 were left at room temperature for more than a day and not reacted further, spontaneous cyclization of the compound occurred due to the mesylate’s high propensity to act as a leaving group, and the inherent nucleophilicity of the Boc group. This problem occurred when $R=\text{CH}_3$ or $^2\text{Pr}$. When $R=\text{Bn}$, no cyclization issues occurred within 2 days. It was very easy then, to mix in potassium thioacetate and 80 in anhydrous CH$_3$CN at room temperature overnight in order to form the corresponding thiolester 81, where the thiolester is representative of a Y-S-R group as in compound 76. The literature has previously demonstrated this reaction with C$_3$H$_7$NO as solvent,\textsuperscript{101,102} but the corresponding workups for the reaction in Scheme 39 were much easier with acetonitrile and the yield improved from 70\% to 82\%. Procedures were then investigated that could take a $\beta$-amino alcohol and directly convert it into the corresponding thiolester, particularly for valinol and alaninol.

![Scheme 37. Mitsunobu-like reaction of a hydroxyl to iodide.](image-url)
Scheme 38. Testing the conversion of amino alcohol into mesylate.

\[
\begin{align*}
\text{HO} & \quad \text{1. MsCl, CH}_2\text{Cl}_2, 0^\circ\text{C} \\
\text{NH}_{\text{Boc}} & \quad \text{2. Et}_3\text{N} \\
\text{78} & \quad \text{MsO} \\
\text{R} & \quad \text{R} \\
\to & \quad \to \\
\text{100%} & \quad \text{80a} \\
\end{align*}
\]

Scheme 39. Mild conditions used for the conversion of a mesylate to a thiolacetate group.

It was reported in 1981 that various alcohols can be converted into their corresponding thiolacetates by treatment with PPh\textsubscript{3} and C\textsubscript{8}H\textsubscript{14}N\textsubscript{2}O\textsubscript{4}, in the presence of thiolacetic acid in a stereoselective and highly efficient manner.\textsuperscript{103} It is noted that either DIAD or DEAD could work in the reaction to form 81 in Scheme 40.

\[
\begin{align*}
\text{MsO} & \quad \text{AcS}^-\text{K}^+, \text{CH}_3\text{CN, rt} \\
\text{NH}_{\text{Boc}} & \quad \text{O} \\
\text{Bn} & \quad \text{Bn} \\
\text{80a} & \quad \text{80%} \\
\end{align*}
\]

Scheme 40. Direct formation of thiolester from β-amino alcohol.

Once the β-amino thiolester 81 is formed, it can be subjected to methonolysis under basic conditions in order to obtain a 2-alkenyl β-aminoalkyl sulfide derivative as in Scheme 41. This is accomplished via the base mediated removal of the acetate, followed by the nucleophilic attack of the resulting anionic sulfur species on an allyl halide. This reaction was pursued with allyl bromide,\textsuperscript{104} although other allyl iodides have been shown to also be effective.\textsuperscript{105,106} Upon addition of saturated aq. NH\textsubscript{4}Cl to the reaction mixture, the product precipitated as a white solid from the acidified aq. methanol solution. Yields for the formation of 82 are in the 75-95% range and
purification was simple through the use of flash chromatography, therefore the 2-step alcoholysis and substitution procedure is highly efficient.

**Scheme 41.** Methanolysis for the formation of 2-alkenyl β-aminoalkyl sulfides.

Upon formation of 82, the next step was to conduct trials to create the desired cis-isomer, as in Scheme 42. Many methods to make the conversion were possible, but it was vital to minimize formation of the trans isomer. The migration of the double bond to the 1-alkenyl position was investigated by using a strong base in dry DMSO through a deprotonation/protonation sequence, much like the protocol of Carson and Boggs. The selectivity for the cis double bond was produced by a method that shows promise, with no trans isomer formation, but had to be optimized. It is possible to distinguish the cis alkene from the trans by the J-coupling constant of 9.3 Hz in the 1H NMR between the alkenyl peaks, which is consistent with cis double bond coupling. As well, comparing the integrations of the propenyl protons, the 2-propenyl compound represented 3 protons whereas the 1-propenyl compound only represented 2 protons.

**Scheme 42.** Process to convert the 2-alkenyl β-aminoalkyl sulfides into cis-1-alkenyl β-aminoalkyl sulfide.

When the reactions were first attempted, loss of the Boc group occurred. This was observed by a significant decrease in intensity of the Boc peak on the 1H NMR spectrum, as well as the gradual upfield peak shift of the N-C-H proton near the Boc group. Under literature protocol, 18
hours was the time used to stir the reaction; however, almost 100% of the Boc group was shown to be removed. Several reaction conditions were tested, as seen in Table 3, to determine the optimal conditions which allowed cis isomerization with minimal Boc deprotection. The results showed that isomerization to cis-alkene had occurred with less than 10% of Boc removal in 45 minutes using 0.75 equivalents of base. If the reaction proceeded longer or was heated, some of the thermodynamic trans compound would also appear. The reaction is optimal if there is no heating, and the temperature should be in the range of 18-20 °C for completion of the synthesis of cis-1-alkenyl β-aminoalkyl sulfide (Scheme 43). The success of the reaction is further evidenced by examining several aspects of the respective spectra presented in Figures 7 (allyl) and 8 (cis-1-propenyl). The first piece of evidence is the downfield shift from the 2-alkenyl proton peaks to the newly formed 1-alkenyl proton peaks, in part due to the closer vicinity of the electronegative sulfur atom. It is important to note the appearance of a new methyl doublet, a doublet of quartets with J_{cis} coupling and the loss of the allyl methylene. Hence, there is evidence of the isomerization of double bond to produce the cis isomer (83).

Scheme 43. Synthesis of cis-1- alkenyl β-aminoalkyl sulfide.
Figure 7. $^1$H NMR (300 MHz, CDCl$_3$) of $^1$Bu 2-allyl-1-benzyethyl carbamate.

Figure 8. $^1$H NMR (300 MHz, CDCl$_3$) of cis-1-propenyl β-N-Boc-aminobenzylethyl sulfide.
Table 3: Optimization of allyl 82a to cis-1-propenyl isomerization 83a.

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{Time of Reaction (h)} & \text{[Base] (mol/L)} & \% \text{Boc Removal} & \text{Temperature (°C)} & \text{Cis Isomerization?} \\
\hline
18 & 0.096 & 97 & 15-35 & Yes* \\
6 & 0.098 & 90 & 15-35 & Yes* \\
3 & 0.098 & 76 & 15-35 & Yes* \\
4 & 0.040 & 83 & 15-35 & Yes* \\
2 & 0.040 & 57 & 15-35 & Yes* \\
0.75 & 0.023 & < 10 & 15-35 & Yes* \\
1.5 & 0.023 & < 10 & 22-23 & Yes \\
1.5 & 0.023 & < 5 & 14-24 & Yes \\
1.5 & 0.023 & None & 18-20 & Yes \\
\hline
\end{array}
\]

* Performed by Tyler Mook, Undergraduate Fourth Year Project Student 2014

Once the cis isomer was obtained, oxidation of the sulfides into sulfoxides and sulfones was pursued. The 2-propenyl to cis-1-propenyl isomerization developed herein is a unique transformation, with only one other specialized example noted in the literature. Given that the cis isomer is the kinetic product during the isomerization and the important occurrence of the cis-propenyl unit in certain allium vegetables, attempts to generalize the isomerization process were undertaken. It was felt that selective formation of only the cis-1-propenyl unit on other substrates would prove useful. The first attempt is shown in Scheme 44, where trityl thiol 84 underwent nucleophilic substitution with allyl bromide in order to form 85 in a 77% yield. However, when exposed to tBuOK/DMSO the reaction did not occur to form the desired 86 and the 1H NMR spectrum exhibited with many peaks that did not correspond the desired cis isomer.
Unsuccessful attempt towards expanding the cis isomerization onto trityl sulfides.

The attempts with pyridine-2-thiol proceeded in a similar manner. Here (Scheme 45) the allyl bromide was used as the electrophile and the thiol component as a different form of sulfur nucleophile. This resulted in a 90% yield of 87, and gave way to both cis and trans isomers of 88 after a 4 hour isomerization period. This procedure also tests the ability of the nitrogen to participate in the kinetic isomerization process. However, due to the presence of both isomers, it appears the conditions for the allyl to cis-1-propenyl isomerization requires the rather specialized features of compounds such as 82.

Failed attempts of cis-isomerization onto pyridine sulfide systems.

Notwithstanding the unsuccessful allyl isomerization on the tritylthio group, attempts to add substitution of the parent allyl group were undertaken. The first alternative to allyl bromide examined was 1-bromo-3-methyl-2-butene (Scheme 46) and compound 89 was obtained using the established protocol, which was then subjected to isomerization conditions in order to obtain 90. Not many changes to the reaction mixture were observed with $^1$H NMR for the first 5 hours, however, formation of the cis molecule in 90 was present in the mixture 7 hours after addition of the base judging by the vinylic hydrogen splitting pattern in the 6-7 ppm peak region. The reaction was run for 24 hours total to test the limits of isomerization for this compound, and it was shown
in the NMR that the mixture cyclized, and that the Boc group was no longer part of the system. The isomerization towards 90 therefore, did not eventually work.

![Scheme 46](image)

**Scheme 46.** Isomerization attempt of the 3-methyl-2-Butene side chain compound.

The breadth of the thiolate alkylation protocol was further tested through a reaction with cinnamyl chloride. The reaction proceeded relatively well (77% yield) to form 91 with the chloride leaving group (Scheme 47). When the double bond migration was attempted for 92, a mixture of both cis/trans isomers formed over the course of 24 hours. The reaction was not yet complete after all this time as 55% of starting material was still present (based on peak intensities in the $^1$H NMR spectrum). Further exposure of base to this mixture suggested the outcome was a thermodynamic mixture and any further isomerization would not be forthcoming.

![Scheme 47](image)

**Scheme 47.** Cinnamyl chloride for the formation of a different side chain in 81a in order to identify propensity for the compound to cis cyclize.

It is probable to speculate why the isomerizations were effective for Carson’s compounds and the allyl β-aminoalkyl sulfides into a cis-1-alkenyl β-aminoalkyl sulfide yet does not work for the other systems. It is viable that the allylic strain present in the olefin (Figure 9) in the other systems such as trityl favors the formation of the thermodynamic trans product even under the kinetic conditions. There is perhaps a partial π-bond barrier that is formed which retards and halts
the formation if the cis-isomer. The strength of allylic strain increases as the size of the interacting
substituents increases, and could be an influencing factor as to why other systems do not show
favorable cis-isomerization under the optimized conditions. The rotational energies in order to
create the cis-conformer are probably greater for the supplementary systems attempted with the
bigger side groups, hence increasing the equilibrium enthalpies between compounds.\textsuperscript{108}

![Figure 9. Olefin demonstrating an A 1,3-strain.](image)

### 2.1.3. Oxidation and Deprotection

The formation of sulfone from the cis compound of 83 is quite straightforward. For the
oxidation process, 3 equiv. of mCPBA (90\%) were employed, beginning in an ice bath that was
gradually warmed to room temperature in order to obtain compound 93. Once characterization of
cis-sulfone 93 was completed, the protecting group was removed. This occurred through the use
of TFA/DCM in a 1:1 mixture under cold conditions that was gradually warmed to room
temperature. The pathway for direct sulfone heterocycle formation is shown in Scheme 48. The
scheme summarizes some of the reaction methods utilized for the formation of the sulfones 95.
Scheme 48. Conversion of cis-1-propenyl sulfides to 1,4-thiazane dioxides.

Oxidation to form the sulfoxides was indeed more complicated than with the formation of the sulfone, as the S-O bond can be either syn or anti to the given R group forming a mixture of two compounds. A few oxidation protocols (outlined in Table 4) were investigated in order to determine which would give preference for a single or major diastereomer.

**Table 4. Synthetic attempts to oxidize and obtain sulfoxides, conducted with R=Bn.**

<table>
<thead>
<tr>
<th>Oxidizing Agent (1 equiv.)</th>
<th>% Yield</th>
<th>TLC Analysis</th>
<th>Temp. (°C)</th>
<th>Time (mins)</th>
<th>dr (syn:anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$O$_2$ in HFIP</td>
<td>90</td>
<td>2 spots, UV active &amp; charring</td>
<td>rt</td>
<td>5</td>
<td>50:50</td>
</tr>
<tr>
<td>H$_2$O$_2$ in TFE</td>
<td>84</td>
<td>Multiple spots, UV active &amp; charring</td>
<td>rt-45</td>
<td>overnight</td>
<td>45:55</td>
</tr>
<tr>
<td>mCPBA 1</td>
<td>75</td>
<td>Multiple spots, UV active &amp; charring</td>
<td>0 °C</td>
<td>30</td>
<td>50:50</td>
</tr>
<tr>
<td>mCPBA 2</td>
<td>76</td>
<td>Multiple spots, UV active &amp; charring</td>
<td>-78 °C</td>
<td>105</td>
<td>50:50</td>
</tr>
</tbody>
</table>
Unfortunately, all the procedures attempted gave a mix of the two possible sulfoxide isomers (syn and anti to the R group – shown in Scheme 49, dr 50:50). This selectivity followed even when for R = Me, iPr. The protocol to be most efficient was utilizing hydrogen peroxide with HFIP solvent where the reaction proceeded very quickly (approx. 5 minutes). Purification with flash chromatography was relatively straightforward as there were only 2 spots to separate to obtain an NMR spectrum depicting solely 2 sulfoxide isomers. Purification to separate the diastereomeric mixture was attempted in various ways, the best outcome occurred in 2% MeOH/CHCl₃ in a deactivated silica column though even still, the fractions collected would overlap the two isomers. Due to the somewhat frustrating isomer separation, experimental trials were conducted with the isomer mixture of sulfoxides. Figure 10 shows the purified mixture of the two sulfoxide diastereomers for R=Bn, though it is interesting to note that R=Me, iPr followed the same splitting pattern and intensities in the 6-7 ppm region.

Scheme 49. Oxidation for the production of cis-1- alkenyl β-aminoalkyl sulfoxides with both syn and anti conformation (dr approx. 50:50 for R=Bn, iPr, Me).
Figure 10. $^1$H NMR (600 MHz, CDCl$_3$) of a mixture of cis-1-propenyl β-N-Boc-aminobenzylethyl sulfoxide (syn and anti to R=Bn).

Deprotection of the amino group in 2 equiv. of TFA in a 1:1 ratio with DCM solvent formed 98. Attempts to isolate the free amine forms of these compounds is still to be developed. After deprotection, the samples were only characterized ($^1$H, $^{13}$C NMR and IR) to confirm the transformation, and then were subjected to cyclization.

Scheme 50. Protocol for TFA salt formation of the sulfoxides, further subjected to cyclization conditions.

As part of the oxidation studies, the conversion of compound 91 (previously in 2.1.2) to its sulfone and the subsequent double bond isomerization were also investigated. However, under these circumstances, it was proposed that once isomerization occurred, then the compound would
be in a position to succumb to cyclization, given the double bond would be conjugated to the sulfone. In the experiment, 91 was oxidized using mCPBA (3 equiv.) and the amine was deprotected as per the developed protocol. Conditions for cyclization included a 24 hr reflux at 70 °C once it was established that compound 99 was recovered after the initial cyclization was attempted at room temperature.

The result of the 24 hour treatment is surprising as a mixture of compounds 101 is obtained as detailed in Scheme 51. This is not an isomeric heterocycle mixture; it is a combination of cis and trans isomers in which a shift in the double bond occurred. This observation is based on the change in chemical shift of the olefin peaks as well as the difference in splitting patterns from the starting materials, different from that of compound 92 (Section 2.1.2). It is also interesting that the intensity of the trans hydrogen peak is greater than that of the cis, indicating a greater percentage of the trans conformer of 101.

![Scheme 51. Cyclization attempt of the cinnamyl sulfone side chain compound.](image)

It was thought that deprotection prior to the oxidation would comprise a unique set of conditions, perhaps suitable to obtain only one sulfoxide diastereomer. The cis sulfide with R=Bn (83a) was treated TFA:DCM in order to obtain a salt. Deprotection of the amino group was
achieved however, the result was accompanied by the formation of two 1,3-thiazolidine diastereomers with respect to the orientation of the ethyl group (Scheme 52). The assigned structure is consistent with the $^1$H NMR (Figure 11) and $^{13}$C NMR spectra. Compounds similar to 102 have been previously, though not extensively investigated.$^{109}$ Thiazolidine components are found in a variety of drugs such as penicillin and pioglitazone.$^{110,111}$ This cyclization was not investigated further.

Scheme 52. Attempts to form a thiazine prior to sulfoxidation resulted in formation of cyclic system.

Figure 11. $^1$H NMR (600 MHz, CDCl$_3$) of two thiazolidine isomers.
2.1.4. Compound Cyclization and Theory

The deprotection of sulfoxide 96/97 occurred by utilizing cool temperatures (approx. 0 °C) in TFA as shown in Scheme 50. After deprotection, isomers of 98 were subjected to the reaction conditions suggested by Söderman. The treatment of triethylamine and methanol for a 72hr reflux formed compound 103 as one heterocycle along with the recovery of a sulfoxide starting material as its free amine (104). The formed sulfoxide heterocycle (103) contains a new stereocenter that is formed based on the position of the methyl group, adding into the already present sulfoxide and carbon stereocenters. The two compounds were separated by flash chromatography. Because of the evidence that one isomer cyclizes and not the other one, it is possible to conclude in Scheme 53 the proper orientation of the equatorial sulfoxide ring and the positioning of the sulfoxide in the unprotected cis-1- alkenyl β-aminoalkyl compound.

Scheme 53. Oxidation of cyclized sulfoxide to form the cyclized sulfone compound.

The configuration of compounds 103 and 104 can be ascertained through 2D NMR such as NOESY, HSQC, HMBC and COSY. With respect to the heterocycle, the COSY is shown in Figure 12. This aids in confirming which hydrogens are in splitting eachother, particularly useful when comparing the CH-Me vs CH-Bn protons. A 1D NOE with respect to irradiating the methyl group was also run in order to confirm if the methyl group was syn (down & equatorial) with the
benzyl group. In the 2D NOESY, the CH₂-Ph and the methyl protons correlate with each other, this indicates that they are in the same proximity of space, hence sharing the same directional geometry.

The orientation of the S-O bond (axial vs equatorial) can be determined through the chemical shifts and coupling patterns exhibited in the proton NMR (Figure 13). From the literature, it is shown that the difference between the α and β hydrogen chemical shifts is greater when the oxygen is equatorial in the system.¹¹² This indicates the positioning of the S-O bond in the heterocycle is not in the axial position, as the chemical shifts would be closer.¹¹² It has also been demonstrated that the two germinal α protons will have at least a 1 ppm chemical shift difference between them when the sulfoxide is equatorial¹¹³ which is apparent in Figure 12 and 13. This big difference between the two α germinal hydrogens is due to the diamagnetic anisotropy present from the sulfoxide in the ring system.¹¹⁴

**Figure 12.** COSY(600 MHz, CDCl₃, 4-0ppm region) of sulfoxide cyclized product 103 to ascertain hydrogen position on ring and coupling.
It is now possible to suggest based on this information a transition state for the sulfoxide cyclization for the cis-1-alkenyl β-aminoalkyl sulfoxides by comparing the obtained $^1$H NMR spectrum with that of Söderman’s sulfoxide cyclized products (61). The $^1$H NMR of Söderman’s cis cyclized sulfoxide appeared to be most disimilar, as the peaks present in the region from 3-4 ppm were not the same. It is proposed in Scheme 54 that hydrogen bonding plays a key role in the formation of the thiazine ring through the O-H-N bonding interaction. Both trans-1-alkenyl β-aminoalkyl sulfoxides undergo cyclization but the cis counterparts only display cyclization of the syn isomer, whereas the anti-cis diastereomer remains uncyclized (104). This is likely due to a H-bonding arrangement that causes a greater energy barrier towards the cyclization process, as represented in scheme 54 for the anti-isomer. For the modes of reactivity uncovered herein, DFT calculations can be used to follow up this experimental information.
It is also interesting to denote how this information relates to that of Carson.\textsuperscript{43,107} When cyclization was performed for formation of 1,4-thiazane-3-carboxylic acid 1-oxide in aqueous base (Ba(OH)\textsubscript{2} or Na\textsubscript{2}CO\textsubscript{3}), no thiazane derivative could be detected and the major product was 2-hydroxyethyl cysteine.\textsuperscript{115,116} It was also reported in 1966 that trans-S-(1-propenyl)cysteine sulfoxide cyclizes in high yield to cycloalliin (3-carboxy-5-methyl-1,4-thiazane S-oxide), yet the analogous (+)- and (-)-cis sulfoxides yield cycloalliin and a stereoisomer in dilute NH\textsubscript{4}OH. Under comparable conditions, the S-vinyl-L-cysteine sulfoxide also yields L-carboxy-1,4-thiazane S-oxide. The styrylcysteine sulfoxides that underwent cyclization were inert to dilute NH\textsubscript{4}OH at room temperature. Neither cyclization nor epimerization of the sulfoxide occurred and starting material was recovered.\textsuperscript{43,107} Overall, the Carson cyclization work did not uncover a kinetic resolution phenomenon comparable to that discovered here for sulfoxides 98.

Scheme 54. The pseudo-twist boat transition state of the cis cyclized product that leads to the obtained cyclized product (Top: equatorial sulfoxide; Bottom: axial sulfoxide).

For the formation of the corresponding sulfone ring, the process is simplified due to the presence of one less stereocenter. Deprotection occurs with TFA:DCM, however the cyclization can proceed at room temperature within a few hours. When the starting amino acid is L-phenylalanine or L-valine, the final sulfone heterocycles exhibit a slight preference for one major isomer (95a, Scheme 55). The mild diastereoselection of the chemistry for the two examples is
shown in Scheme 56. The minor isomer corresponds with data of the same compound found in literature. Correspondingly, the structural assignment can be made for 95a as the NMR information does not match with any of Söderman’s isomers and is the only other possible structure. The general pattern of the results indicate that cis-1-alkenyl β-aminoalkyl sulfones do not exhibit stereoselectivity when cyclized, whereas trans-1-alkenyl β-aminoalkyl sulfones exhibit a high preference for one conformation over the other as introduced by Söderman (see compound 66 Scheme 33).

\[
\text{Scheme 55. The cyclization of sulfone 94 to create thiazine derivatives.}
\]

\[
\text{Scheme 56. Cyclizations of cis-1-alkenyl β-aminoalkyl sulfones.}
\]

These results infer that the more favored path of the trans-1-alkenyl β-aminoalkyl sulfones as proposed by Söderman⁶ - where both R groups are equatorial - is not readily applicable to the cis counterparts (Scheme 57). Because the preference towards the trans heterocycle over cis is only slight, the cis-1-alkenyl β-aminoalkyl sulfones do not exhibit a tendency for a single cyclization transition state. It is proposed that two transition states are almost equally likely for the cis sulfones,
and since the product ratios are nearly equal, the transition state energies must be comparable. The reactions proceed faster than with the sulfoxides with little preference for a cis or trans isomer. This is likely due to transition states that occur with no diaxial interactions present in the system. Based on the observations, it is probable that a pseudo-twist boat T.S. occurs to form the cis ring, as a chair conformation is unlikely as shown in Scheme 58. The chair T.S. does however work as a probable means to the formation of the trans ring. Both rings with similar drs appear in the two different R-groups attempted. Nevertheless, results remain inconclusive.

Scheme 57. Proposed transition states for the trans-1-alkenyl β-aminoalkyl sulfones.
2.2 Towards an Allenesulfenate Anion

As part of the investigations towards sulfoxide stereogenicity, the expansion led to research concerning the formation of allenyl sulfenates. These entities exhibit prochiral characteristics and are anticipated to form heterocycles. As discussed in Section 1.5, sulfenates are generally not isolated and must be generated as well as functionalized in solution. The synthetic methodology involving sulfenate anions has been an integral part of the Schwan research group for over 20 years, and the study of sulfenate reactivity continues to be an important component. A summary of the group’s contributions in the field is provided in Scheme 59 and the reactions indicate the breadth of sulfenate chemistry as demonstrated with lithium (E)-alkenesulfenates.

Scheme 58. Likely transition states for the cis-1-alkenyl β-aminoalkyl sulfones.
Scheme 59. Summary of sulfenate chemistry with key intermediates all accomplished in the Schwan lab.

While previous work by Schwan and others has unveiled methods to produce aryl-, alkenyl- and alkyl- sulfenate anions; allenyl sulfenates remain unknown. They represent an intriguing pursuit, as they can carry an additional element of chirality. When allenes bear 1,3-substituents, they possess a type of axial chirality. As such, the allenyl sulfenate species and their substitution chemistry require investigation with regards to their stereoselectivity in addition to fundamental reactivity. The allenyl sulfenate can be generated, and alkylated to afford various sulfoxides or sulfones through oxidation chemistry. Scheme 60 shows the allenyl sulfenate species is intended to be synthesized and used to create either allenyl sulfoxides or sulfones, which can later proceed to become thiazine derivatives, as one possible mode of further derivatization.
The axial chirality in the allenyl sulfur derivatives arises from the fact the π-bonds from both alkenes do not overlap (Figure 14) and there is no free rotation in the allenyl group, thus the substituents are fixed. Given this feature and the anticipated Michael accepting nature of allenyl sulfoxides and sulfones, it is predicted that selected products from certain allenyl sulenate alkylations can be cyclized to create thiazines with different stereochemical elements.

![Figure 14](image_url)

**Figure 14.** Allenyl sulenate π-bonds are perpendicular to each other (pink perpendicular to blue lobes), which give this functional group its prochiral component.

In terms of creating these allenyl sulfenates, one logical approach involves the intermediacy of sulphenyl chlorides\(^{67,68,119}\) which can lead to sulfoxides - the sulenate precursors - in a single reaction pot. Different synthetic pathways have been attempted in the literature, those of which are summarized here in Scheme 61.
Scheme 61. Perrio (top, bottom) and Söderman (right) can be exposed to sulfuryl chloride to create the sulfenyl chloride precursors.\textsuperscript{67,68,119}

The sulfenyl chlorides will serve as precursors to the allenyl sulenate and can be created through the use of a thiolacetate with an EWG in the presence of sulfuryl chloride.\textsuperscript{29} Both types of methodologies by Söderman or Perrio should be pursued in order to create the desired starting materials for the allenyl sulfenate.

The overall generation of the allenyl sulfoxide compounds that will serve as sulenate sources is proposed to occur through a sigmatropic rearrangement.\textsuperscript{67,68,119} The required conditions can be met by reacting a propargyl alcohol and a sulfenyl chloride to deliver a propargyl sulenate ester. This in turn succumbs to an Evans-Breslow [2,3]-sigmatropic rearrangement at ambient temperatures (Scheme 62).

Scheme 62. Proposed synthetic pathway for creating allenyl sulfenate.

Compound 105 was first identified as a suitable sulfenyl chloride precursor and was prepared through a solvent-free Michael addition (Scheme 63).\textsuperscript{120} The compound can be purified through flash column chromatography or distillation, or be used as crude if the \textsuperscript{1}H NMR spectrum dictates the compound contains no unknown peaks. Instead of a methyl ester (105) it is also
possible to perform reactions with the corresponding ethyl ester. The process can then proceed to expose these thiolated propanoic acids to sulfuryl chloride for the formation of sulfenyl chlorides (106) which cannot be isolated, though it is possible obtain a $^1$H and $^{13}$C NMR spectra to verify the disappearance of the thiolacetate group in 105. A base is added to propagate the deprotonation of the acid proton and a selected 2-alkynyl alcohol is added to promote the formation of 107. Various methods and outcomes for the reaction in Scheme 64 were attempted as shown in Table 5, in order to obtain the allenyl sulfoxide starting material.  

![Scheme 63. Formation of 3-(acetylthio)methyl ester propanoic acid](image)

**Scheme 64. Method explored for formation of allenyl sulenate precursor.**

Different ways of mixing base, alcohol and sulfuryl chloride were attempted. In Method A, to a solution of 105 in DCM at -78°C, a mixture of trimethylamine and alcohol in anhydrous DCM is added dropwise over 15 minutes. For Method B, the solvent holding 106 and the byproduct acetyl chloride along with excess sulfuryl chloride, are removed under vacuum (dry ice trap), leaving pure sulfenyl chloride.  

A solution of base and alcohol in DCM is prepared in a separate flask and added via cannula to the sulfenyl chloride (106). In Method C, two solutions were prepared: a mixture of compound 105 and SO$_2$Cl$_2$ and a mixture of base and alcohol. The solution of 106 is formed and transferred via cannula to the mixture of base and alcohol at -78°C. In all
cases, the reaction is allowed to warm and to stir at room temperature. The sulfuryl chloride used is straight out of the bottle in neat form. From Table 5, through many attempts, Method B, which involves obtaining pure sulfenyl chloride under vacuum, gives the highest chance of success of this reaction. So far, only a low yield of 107a has been obtained but it must be noted that the allenyl sulfoxide has been formed and characterized through spectroscopy (Figure 15). The two roofing doublets at 5.6-5.7 ppm that form an AB pattern are indicative of the two terminal hydrogens of the allenyl system. All the H’s in the molecule are diastereotopic due to the asymmetry present in the compound, hence unique alkyl peaks (2.5-3.5 ppm) all significantly splitting one another.

Table 5: Trials towards the formation of the allenyl sulfoxide.

<table>
<thead>
<tr>
<th>Equiv. 105</th>
<th>Equiv. SO₂Cl₂</th>
<th>Base (Equiv)</th>
<th>R=CH₂OH</th>
<th>Mixing of Base with 106</th>
<th>Stir time</th>
<th>107 obtained?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>1.10</td>
<td>NEt₃, 1.10</td>
<td>R=H, 1.10</td>
<td>Method A</td>
<td>2 hrs</td>
<td>No</td>
</tr>
<tr>
<td>1.00</td>
<td>1.10</td>
<td>NEt₃, 1.10</td>
<td>R=Ph, 1.10</td>
<td>Method A</td>
<td>12 hrs</td>
<td>No</td>
</tr>
<tr>
<td>1.00</td>
<td>1.10</td>
<td>tBuLi, 1.00</td>
<td>R=Ph, 1.00</td>
<td>Method C</td>
<td>16 hrs</td>
<td>Trace</td>
</tr>
<tr>
<td>1.05</td>
<td>1.05</td>
<td>tBuLi, 1.00</td>
<td>R=Ph, 1.00</td>
<td>Method C</td>
<td>16 hrs</td>
<td>Trace</td>
</tr>
<tr>
<td>1.00</td>
<td>1.05</td>
<td>NEt₃, 1.05</td>
<td>R=Ph, 1.00</td>
<td>Method A</td>
<td>12 hrs</td>
<td>Trace</td>
</tr>
<tr>
<td>1.10</td>
<td>1.10</td>
<td>tBuLi, 1.00</td>
<td>R=Ph, 1.00</td>
<td>Method C</td>
<td>12 hrs</td>
<td>Trace</td>
</tr>
<tr>
<td>1.00</td>
<td>1.00</td>
<td>NEt₃, 5.00</td>
<td>R=Ph, 2.00</td>
<td>Method B</td>
<td>12 hrs</td>
<td>Yes, 15%</td>
</tr>
<tr>
<td>1.00</td>
<td>1.00</td>
<td>tBuLi, 1.00</td>
<td>R=Ph, 1.00</td>
<td>Method B</td>
<td>12 hrs</td>
<td>Yes, 15%</td>
</tr>
<tr>
<td>1.00</td>
<td>1.00</td>
<td>NEt₃, 1.00</td>
<td>R=Ph, 1.00</td>
<td>Method B</td>
<td>12 hrs</td>
<td>Yes, 28%</td>
</tr>
</tbody>
</table>
Purification of the compound 107a occurred through flash column chromatography, and one of the UV active fractions collected was shown to be side product 108 (Figure 16). This molecule appears in majority when base and alcohol are added as described in Method C.

Other methods for formation of the allenyl sulenate include the use of a disulfide (110). This disulfide has been prepared previously in the Schwan lab, and that protocol was repeated as shown in Scheme 65. Once 110 is purified via distillation it is proceed to react with sulfuryl chloride in anhydrous DCM at -78°C for 5-15 minutes. Base is added along with alcohol, similar
to Method A described beforehand with respect to the formation of 107. This process (shown in Scheme 66) gives trace amounts of product 111. This has so far only been attempted with propargyl alcohol so perhaps the phenyl counterpart will provide more reactivity. The process has also been attempted with K$_2$CO$_3$ and trimethylamine as the base, which likewise resulted in trace amounts of compound 111. The process can however be adapted to similar conditions found in Method B where some of 107a was obtained. The results presented herein consist of only the preliminary steps towards the formation of the allenyl sulfoxide precursor of the allenyl sulfenate.

\[
\begin{align*}
\text{O} & \quad + \quad \text{O} \\
\text{SH} & \quad \text{TMS} \\
\text{AIBN} & \quad 60^\circ\text{C} \\
\text{S} & \quad \text{TMS} \\
\text{KOH, air} & \quad \text{S} \quad \text{TMS} \\
107 & \quad 111 \quad 90\%
\end{align*}
\]

**Scheme 65.** Formation of a disulfide precursor to the allenyl sulfenate.

Once an optimized method for the requisite sulfenate precursors is established, the generation of the allenyl sulfenate can then be advanced. Here, a proven set of nucleophiles may be employed to prove the formation of derivatives of 112. An unsaturated ester can be used as the EWG (Scheme 67), but other possibilities include a saturated ester or a 2-(trimethylsilyl)ethyl group. As Metzner and Perrio indicated, those groups can generate sulfenates through retro-Michael chemistry and fluorodesilylation chemistry, respectively. Another method would be to have a nitrogen nucleophile perform a Michael addition to release the sulfenate.

\[
\begin{align*}
\text{S} & \quad \text{TMS} \\
\text{S} & \quad \text{TMS} \\
110 & \quad \text{1. SO}_2\text{Cl}_2, \text{DCM, } -78^\circ\text{C} \\
& \quad \text{2. NEt}_3, \text{HC}≡\text{CCH}_2\text{OH} \\
& \quad \text{H} \quad \text{H} \\
& \quad \text{H} \quad \text{H}
\end{align*}
\]

**Scheme 66.** Reaction sequence for the production of the allenyl sulfenate from a disulfide.
A nucleophilic addition reaction is proposed to release the allenyl sulfonate for an unsaturated system.

Simple alkylation with benzyl bromide and sulfoxide isolation can confirm the intermediacy of the sulfenate. It was attempted to prepare allenyl sulfenate anions through mild conditions with stoichiometric amounts of base (tBuOK, NaHMDS and nBuLi). The desired product did not result as shown in Scheme 68, indicating some re-arrangement from the allenyl sulfenate group that remains to be properly characterized. Though it appears promising, much work is still to be done in order to optimize the reaction pathway.

Overall, reaction treatments have more focus on exploring these compounds for their use in intramolecular cyclizations with respect to the aza-Michael addition onto an allene. Compounds with a high enantiomeric purity will hopefully be successful when someone else takes over the project, and when that happens, then a proper demonstration of stereoselective control of these reagents for forming thiazine-like rings can be possible. This can prove to be a feature that is very useful in the pharmacological and medicinal chemistry field.
2.3 Applications

The heterocyclic compounds which contain nitrogen and sulfur possess a large significance in the field of medicinal chemistry.\textsuperscript{124} The thiazine heterocycles and their derivatives are involved in the synthesis of biological molecules. A large number of thiazine derivatives also exhibit various biological activities such as antimicrobial, antioxidant and antitumor (Figure 17).\textsuperscript{124} For example, 1,4-thiazinane-2-carboxylates derivatives have been employed in studies for their antimicrobial potential against tuberculosis, a disease caused by bacteria.\textsuperscript{43} The thiazine skeleton is versatile, and it has a relative chemical simplicity and accessibility.\textsuperscript{125}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{sample_thiazine_structures.png}
\caption{Sample thiazine structures with beneficial properties.}
\end{figure}

The synthesis of new pharmacological agents to help in the battle against pathogenic microorganisms can be greatly aided by advancements in organosulfur cyclizations with a high stereoselective control, as this makes thiazine derivatives more readily available. The leading methods for the asymmetric synthesis of sulfoxide compounds have been presented and a number of applications have been detailed. The development of enantioselective Michael-addition reactions and their progress in organosulfur chemistry is currently underway. During the last five years, asymmetric aza-Michael additions have been a very active field of research and are very useful for the formation of thiazines when reacted with sulfur containing Michael acceptors. It is desired to pursue further investigations with these reactions with respect to sulfones and sulfoxides for their distinct chirality in intramolecular cyclizations.
Additionally, sulphenates are slowly garnering recognition as synthetically useful species in organosulfur chemistry and have a great synthetic potential as precursors to pharmacological substances. If successful, this type of stereoselective control on six-membered intramolecular cyclized rings could generate stable compounds that can have an impact on medicinal and drug chemistry.
Chapter 3: Experimental
3.0 Experimental

3.1 General Methods and Instrumentation

All reactions were carried out in flame-dried glassware under argon unless otherwise noted. TLC analysis was performed on glass plates pre-coated with Silica Gel 60 (250 µm) containing a fluorescent indicator. To visualize compounds, the plates were placed under a UV lamp and/or charred with a p-anisaldehyde solution. Flash column chromatography was performed with silica gel particle size 30–63 (mesh 230–400) supplied by Silicycle®. Anhydrous solvents were obtained from an air-free solvent dispensing system. Organic solutions were dried over MgSO₄ and concentrated under reduced pressure at 20-45 °C. Starting materials and reagents were provided by Sigma-Aldrich unless otherwise noted.

¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 300 (300 MHz ¹H), a Bruker Avance 400 (400 MHz ¹H, 100.6 MHz ¹³C) or a Bruker Avance 600 (600 MHz ¹H, 150.9 MHz ¹³C). Chemical shifts (ppm) and coupling constants (J, Hz) were obtained from a first-order analysis of one-dimensional spectra and assignments. The proton spectra are reported as δ (multiplicity, coupling constant J, number of protons). ¹H NMR data is reported using standard abbreviations: singlet (s), doublet (d), triplet (t), doublet of doublet (dd), quartet (q), and multiplet (m). 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. Optical rotations were measured by a Rudolph Research Autopol IV automatic polarimeter in 1 or 0.5 dm tubes where the samples were dissolved in ethanol. Elemental analysis was performed by MHW Laboratories of Phoenix, AZ. ESI HRMS was performed by the Mass Spectrometry Facility at the University of Waterloo, ON and Queens University, Kingston, ON.
3.2 Synthesis of Compounds and Characterization

**General protocol for the reduction of Boc-protected amino acids 78**

Boc-L amino acids were obtained from Sigma-Aldrich as white solids. Following protocols set by Liskamp, the amino acid was placed in an oven dried RBF at -10 °C under an inert atmosphere, where THF was added via cannula and stirred. The solution was treated with triethylamine and let stir for 10 minutes. Neat ethyl chloroformate was then added dropwise over 15 minutes, and a white solid began to appear. The reaction was left to stir for approximately 2 hours until the mixture showed completion via TLC analysis. A suction filtration was performed; the filtrate was collected and white precipitate was discarded. The obtained filtrate was added to a 0 °C solution of water and NaBH₄ and let to gradually warm to room temperature over the course of 5 hours. The solution was quenched with 1M HCl. The organic layer was washed with water and brine, dried over magnesium sulfate, and filtered. Solvent was removed *in vacuo* to obtain crude product.

**Synthesis of Boc-L-phenylalaninol 78a (Scheme 36)**

Upon treatment of the crude, clear oil with petroleum ether, white crystals of pure compound appeared over the course of 4 hours at room temperature (78%). Mp = 95-96 °C, Lit.¹²⁷; 97 °C. ¹H NMR (CDCl₃, 400 MHz, ppm): δ = 7.29 – 7.24 (m, 5H), 4.87 (br s, 1H), 3.89 (br s, 1H), 3.65 (m, 1H), 3.55 (dd, J = 10.1 & 7.2 Hz, 1H), 3.16 (dd, J = 10.2 & 6.8 Hz, 1H), 2.86 (d, J = 7.2 Hz, 2H), 1.34 (s, 9H). ¹³C NMR (CDCl₃, 400 MHz, ppm): δ = 156.2, 137.8, 129.3, 128.6, 126.5, 79.7, 64.3, 53.7, 37.4, 28.3. [α]ᵢ²⁻: -26 (c = 1.00). FTIR (cm⁻¹): 3470, 3436, 3150, 2980-2928, 1707.
Synthesis of Boc-L-Valinol 78b (Scheme 36)

The pure clear liquid of (S)-tert-butyl 1-hydroxyl-3-methylbutan-2-ylcarbamate was obtained through flash column chromatography (15%EtOAc/Hex)(82%).

$^1$H NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 4.80$ (br s, 1H), 4.05 (br s, 1H), 3.62 (dd, $J = 12.4$ & 7.2 Hz, 1H), 3.16 (dd, $J = 12.4$ & 7.3 Hz, 1H), 3.10 (m, 1H), 1.74 (m, 1H), 1.37 (s, 9H), 0.82 (d, $J = 6.6$ Hz, 3H), 0.78 (d, $J = 6.9$ Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 156.5, 79.4, 64.3, 53.7, 31.3, 29.3, 28.9, 19.8$.

$[\alpha]_{D}^{22}: -16$ (c = 1.00). FTIR (cm$^{-1}$): 3416, 3250, 2980-2910, 1710.

Synthesis of Boc-L-Alaninol 78c (Scheme 36)

Pure white solid of (S)-N-Boc-2-aminopropan-1-ol was obtained through flash column (15%EtOAc/Hex)(75%). Mp: 56-58 °C, Lit.$^{12}$: 58 °C.

$^1$H NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 4.76$ (br s, 1H), 3.49(m, 1H), 3.55 (dd, $J = 13.4$ & 6.8 Hz, 1H), 3.12 (dd, $J = 13.7$ & 6.8 Hz, 1H), 2.66 (br s, 1H), 1.45(s, 9H), 1.15 (d, $J = 6.5$ Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 155.7, 80.3, 63.2, 50.8, 29.6, 18.3$.

$[\alpha]_{D}^{22}: -5.9$ (c = 1.00). FTIR(cm$^{-1}$): 3410, 3250, 2980-2910, 1710.

Synthesis of $N$-[(1S)-1-(iodomethyl)-2-phenylethyl]-1,1-dimethylethyl ester carbamic acid 79 (Scheme 37)

Under inert conditions, triphenylphosphine (2.58 mmol, 1 equiv.) and imidazole (2.83 mmol, 1.1 equiv.) were added to a 1-L round bottom flask, followed by the inert addition of dry DCM (100 mL). The flask was cooled to 0 °C in an ice bath. In a second flask containing solid iodine (1.5 equiv.), under inert conditions, dry dichloromethane (90 mL) was
added. While stirring, the iodine solution was added dropwise to the initial flask at 0 °C through a cannula. Under inert conditions, anhydrous DCM (20 mL) was added to a third flask containing tert-butyl 2-hydroxy-1-benzylethylcarbamate (2.58 mmol, 1 equiv.). This solution of compound was then added to the initial flask, still at 0 °C, through a cannula. The reaction mixture was allowed to warm to room temperature and left to stir for 25 hours. The resulting triphenylphosphine oxide precipitate was filtered out of solution via vacuum filtration. The red/orange filtrate was washed with a few millilitres of a sodium thiosulfate solution. The organic layer was washed with water and brine, dried over magnesium sulfate, and filtered. Solvent was removed in vacuo to obtain crude product. Purification of the crude was completed through flash column chromatography (6% EtOAc / Hex) to obtain the yellow, crystal product (70%). Mp = 120-122 °C, Lit.118: 121 °C. 

1H NMR (CDCl3, 400 MHz): δ 7.29 – 7.24 (m, 5H), 4.69 (d, J = 7.6 Hz, 1H), 3.59 (m, 1H), 3.40 (dd, J = 10.1 & 4.2 Hz, 1H), 3.16 (dd, J = 10.2 & 3.8 Hz, 1H), 2.89 (dd, J = 13.3 & 7.6 Hz, 1H), 2.79 (dd, J = 13.6 & 8.2 Hz, 1H), 1.43 (s, 9H) ppm. 13C NMR (CDCl3, 400 MHz, ppm): δ = 156.2, 137.8, 129.3, 128.6, 126.5, 125.4, 79.7, 53.7, 39.4, 14.6. [α]22°D : -18 (c = 1.00). FTIR (cm⁻¹): 3470, 3436, 3150, 2980-2928, 1707, 510.

Synthesis of mesylates of Boc-protected β-amino alcohols 80

To a solution of Boc-L-aminoalcohol (1.68 mmol, 1 equiv.) in an oven dried flask is added anhydrous DCM (120 ml) at 0 °C under a dry argon atm was added Et3N (2 equiv.), followed by dropwise addition of neat methanesulfonyl chloride (1.2 equiv.). The mixture was stirred at 0 °C for 2 hours then allowed to warm to room temperature until the reaction was shown to be completed via TLC. The solution was washed with sodium thiosulfate and brine, dried over MgSO4, filtered and concentrated under reduced pressure,
resulting in a white solid with very pure NMR in high yield which could be immediately reacted to form the thioester.\textsuperscript{92}

**(S)-2-tert-Butoxycarbonylamino-3-methanesulfonyloxy-1-phenylpropane 80a (Scheme 38)**

If the NMR showed impurity peaks, the mixture would be allowed to crystallize overnight at room temperature in a solution of 5% DCM/Hexanes (98%). Mp = 118-119 °C, Lit\textsuperscript{130}: 116 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz, ppm): δ = 7.36 – 7.18 (m, 5H), 4.71 (br s, 1H), 4.22 (m, 1H), 4.10 (d, J = 8.1 Hz, 2H), 2.99 (dd, J=11.1 & 7.9 Hz, 1H), 2.81 (dd, J = 11.1 & 8.0 Hz, 2H), 1.40 (s, 9H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 300 MHz, ppm): δ = 156.2, 137.8, 130.0, 129.3, 128.6, 80.5, 71.2, 53.7, 42.2, 39.4, 28.3. FTIR (cm\textsuperscript{-1}): 3470, 3436, 3150, 2980-2928, 1716, 1355, 1175.

**(S)-2-tert-Butoxycarbonylamino-3-methanesulfonyloxy-1-isopropane 80b (Scheme 38)**

White solid appeared on the under reduced pressure and was confirmed to be the product with NMR (46% white solid obtained with pure NMR spectrum). Mp: 80-82 °C, Lit\textsuperscript{131}: 77 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz, ppm): δ = 4.74 (br s, 1H), 4.36 (m, 1H), 4.02 (d, J = 7.1 Hz, 2H), 2.95 (s, 3H), 2.42 (m, 1H), 1.35 (s, 9H), 0.95 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 300 MHz, ppm): δ = 160.3, 79.5, 66.6, 56.1, 37.4, 32.6, 29.7, 28.3, 28.1. FTIR (cm\textsuperscript{-1}): 3395, 2966, 2876, 1687, 1356, 1174.

**(S)-2-tert-Butoxycarbonylamino-3-methanesulfonyloxy-1-methane 80c (Scheme 38)**

White solid appeared when solvent is removed under reduced pressure and was confirmed to be the product by NMR (55% yield) and was used for reaction in the next step immediately to circumvent decomposition). Mp: 75-77 °C, Lit\textsuperscript{132}: 76 °C.
\[ \text{H NMR (CDCl}_3, 400 \text{ MHz, ppm): } \delta = 4.57 \text{ (br s, 1H), 3.89 (d, } J = 6.7 \text{ Hz, 2H), 3.05 (s, 3H), 2.36 (m, 1H), 1.34 (s, 9H), 1.17 (d, } J = 6.7 \text{ Hz, 3H).} \]

\[ \text{^13C NMR (CDCl}_3, 400 \text{ MHz, ppm): } \delta = 157.8, 79.6, 68.3, 53.9, 38.6, 28.4, 15.9. \]

**Synthesis of Boc-L-amino thioesters 81**

Employing either the iodinated or mesylated compounds of R=Bn (1.05 mmol, 1 equiv.), a mixture is made with KSAc (1.5 equiv) in a flame dried flask under inert conditions with dry DMF (90 mL). The clear, pale, yellow mixture was covered in aluminum foil to block light and allowed to stir for ca. 3.5 hours (until reaction was completed, monitored by TLC). The reaction was extracted with EtOAc (40 mL) followed by a wash of the organic layer with NaHCO\textsubscript{3}/water. The precipitate was removed via vacuum filtration, and the organic filtrate was washed thrice with water and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated.\textsuperscript{103}

\[ \text{^1Bu 2-Thioacetyl-1-benzylethyl carbamate 81a (Scheme 39)} \]

The resultant reddish solid was purified via flash chromatography (10% EtOAc/Hex) to obtain white crystals in an 80% yield. Mp: 89-91 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz, ppm): \( \delta = 7.29\text{-}7.19 \text{ (m, 5H), 4.61 (d, } J = 7.8 \text{ Hz, 1H), 3.98 (m, 1H), 3.06 (dd, } J = 13.8 \text{ & 4.1 Hz, 1H), 2.89 (m, 2H), 2.78 (dd, } J = 13.6 \text{ & 7.1 Hz, 1H), 2.35 (s, 3H), 1.40 (s, 9H).} \]

\[ \text{^13C NMR (CDCl}_3, 400 \text{ MHz, ppm): } \delta = 195.9, 155.3, 137.3, 129.4, 128.6, 126.7, 79.4, 51.8, 40.4, 32.7, 30.7, 28.4. [\alpha]_D^{22} : -25 (c = 1.00). \]

**FTIR (cm\textsuperscript{-1}):** 3470, 3436, 3150, 2980-2928, 1707, 1690.
Direct conversion of Boc-L-aminoalcohols to thioester derivatives

To a solution of TPP (1.1 equiv.) and protected amino alcohol in anhydrous THF was added 1.1 equiv. of DIAD at -20 °C. The solution was let to stir for 30 minutes, and was treated with thiolacetic acid (1.1 equiv.). The mixture was allowed to stir at room temperature overnight. Solution was quenched with NaHCO₃ and treated with ethyl acetate and brine to obtain the organic filtrate. Solution was dried over MgSO₄, filtered and concentrated under reduced pressure.¹⁰³

¹Bu 2-Thioacetyl-1-isopropyl carbamate 81b (Scheme 40)

The crude mixture was purified through flash chromatography (20% EtOAc/Hex) forming a white solid (80%). Mp: 57-58 °C.

¹H NMR (CDCl₃, 400 MHz, ppm): δ = 4.72 (d, J = 7.8 Hz, 1H), 4.05 (br s, 1H), 3.62 (d, J = 4.3 Hz, 1H), 3.16 (dd, J = 7.2 & 3.8 Hz, 1H), 3.10 (m, 1H), 2.67 (s, 3H), 1.74 (sept, J = 6.3 Hz, 1H), 1.37 (s, 9H), 0.82 (d, J = 6.6 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H). ¹³C NMR (CDCl₃, 400MHz, ppm): δ = 198.1, 156.5, 79.4, 64.3, 53.7, 31.3, 30.2, 25.6, 24.9, 19.8. [α]⁺¹²: -21 (c = 0.20).

FTIR (cm⁻¹): 3250, 2980-2910, 1710, 1670. Analysis calculated for C₁₂H₂₃NO₃S; C, 55.22; H, 8.90; found C, 55.50; H, 8.83.

¹Bu 2-Thioacetyl-1-methyl carbamate 81c (Scheme 40)

The reaction produced a yellow, smelly oil which was purified through flash chromatography (20% EtOAc/Hex) in order to obtain a light yellow solid (72%). Mp = 49-50 °C. ¹H NMR (CDCl₃, 300 MHz, ppm): δ = 4.76 (br s, 1H), 3.71-3.84 (m, 1H), 3.66-3.65 (m, 1H), 3.50 (m, 1H), 2.85 (s, 3H), 2.66 (dd, J = 0.8 Hz, 2H), 1.45 (s, 9H), 1.15 (d, J = 6.5, 3H). ¹³C NMR (CDCl₃, 300 MHz, ppm): δ = 185.9, 155.7, 80.3, 63.2, 50.8, 31.5, 29.6,
18.3. [α]_D^{22} = -26 (c = 0.20). FTIR (cm\(^{-1}\)): 3250, 2980-2910, 1710, 1690. HRMS (ESI) calculated for 
C\(_{10}\)H\(_{18}\)NO\(_3\)S [M+H] \(^+\) 234.1158; found: 234.1147.

**General procedure for the conversion of thioesters into allyl sulfides 82**

In an inert flask containing N-protected amino thioester (1.26 mmol, 1 equiv.), anhydrous K\(_2\)CO\(_3\) (1.5 equiv.) was added. Immediately after this, dry methanol (80 mL) was added to the flask via syringe and the reaction was left to stir for 30 minutes. Allyl bromide (1.5 equiv.) in THF (10 mL) was then added to the opaque, white/grey solution via a cannula. The mixture was stirred for 20 hours, or until TLC (10% EtOAc / 90% Hexanes) confirmed the consumption of the limiting reagent, and turned into a yellow, transparent colour. The reaction was quenched with saturated ammonium chloride solution, turning the mixture opaque white and producing a precipitate which was isolated via vacuum filtration. The precipitate was dissolved in EtOAc and washed with water/brine (3 times), and then dried over magnesium sulfate. After filtration, the solvent was removed *in vacuo.*

**\(^{1}\)Bu-1-Benzylethyl-2-allylsulfanyl carbamate 82a (Scheme 41)**

Purification of the crude \(t\)-butyl 2-allyl-1-benzylethyl carbamate was completed through flash column chromatography (15% EtOAc / 85% Hex) to obtain a white solid (92%). Mp: 55-57 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \(\delta = 7.29-7.20\) (m, 5H), 5.73 (ddt, \(J = 14.1, 10.1 \& 7.2\) Hz, 1H), 5.05-5.04 (d, \(J = 9.2\) Hz, 1H), 5.04-5.03 (d, \(J = 13.6\) Hz, 1H), 4.65 (d, \(J = 6.0\) Hz, 1H), 3.99 (m, 1H), 3.12 (d, \(J = 7.2\) Hz, 2H), 2.85 (m, 2H), 2.50 (m, 2H), 1.41 (s, 9H). \(^{13}\)C NMR (CDCl\(_3\), 400 MHz, ppm): \(\delta = 155.1, 137.5, 133.8, 129.3, \ldots\)
128.3, 126.3, 117.3, 79.2, 50.7, 39.6, 35.1, 34.3, 28.2. \( [\alpha]_D^{22} \): -34 (c = 1.00). FTIR (cm\(^{-1}\)): 3436, 3150, 2980-2928, 1707.

**1'Bu-1-Isopropyl-2-allylsulfanyl carbamate 82b (Scheme 41)**

\[
\begin{array}{c}
\text{NHBoc} \\
\text{S} \\
\text{CH} = \\
\text{CH}_2
\end{array}
\]

Purification occurred through flash chromatography (5% EtOAc/Hex) in order to obtain a white solid (76%). Mp: 120-121 °C. \( ^1H \text{NMR (CDCl}_3, 400 \text{ MHz, ppm): } \delta = 5.72-5.69 \text{ (ddt, J = 15.6, 9.2 & 7.5 Hz, 1H), 5.06-5.05 (d, J = 9.1 Hz, 1H), 5.03-5.02 (d, J = 15.0 Hz, 1H), 4.71 (m, 1H), 3.78 (m, 1H), 3.06 (d, J = 7.5 Hz, 2H), 2.50 (m, 2H), 1.77 (sept, J = 6.9 Hz, 1H), 1.38 (s, 9H), 0.87-0.86 (d, J = 6.6 Hz, 3H), 0.84-0.83 (d, J = 6.9 Hz, 3H).} \]

\( ^{13}C \text{NMR (CDCl}_3, 400 \text{ MHz, ppm): } \delta = 156.5, 133.9, 119.6, 79.4, 64.3, 53.7, 31.3, 30.2, 28.3, 28.0, 19.9. \ [\alpha]_D^{22} : -19 (c = 0.20). \) FTIR (cm\(^{-1}\)): 3250, 3122, 2980-2910, 1710.

**1'Bu-1-Methyl-2-allylsulfanyl carbamate 82c (Scheme 41)**

\[
\begin{array}{c}
\text{NHBoc} \\
\text{S} \\
\text{CH} = \\
\text{CH}_2
\end{array}
\]

Purification occurred through flash chromatography (5% EtOAc/Hex) in order to obtain a white solid (75%). Mp: 95-97 °C. \( ^1H \text{NMR (CDCl}_3, 400 \text{ MHz, ppm): } \delta = 5.70-5.68 \text{ (ddt, J= 13.9, 9.3 & 6.9 Hz, 1H), 5.04 (d, J = 14.1 Hz, 1H), 5.00 (d, J = 9.1 Hz, 1H), 4.78 (m, 1H), 3.74 (m, 1H), 3.07 (d, J = 6.9 Hz, 2H), 2.51 (m, 2H), 1.36 (s, 9H), 1.15 (d, J = 6.1, 3H).} \]

\( ^{13}C \text{NMR (CDCl}_3, 400 \text{ MHz, ppm): } \delta = 155.9, 135.7, 125.9, 80.3, 63.2, 50.8, 31.5, 29.6, 18.3. \ [\alpha]_D^{22} : -12 (c = 0.20). \) FTIR (cm\(^{-1}\)): 3250, 2980-2910, 1710, 1690. HRMS (ESI) calculated for C\(_{11}\)H\(_{21}\)NO\(_2\)S [M+H]\(^+\) 232.1365; found: 232.1365.
Conversion of allyl sulfides to cis-1-propenyl sulfides 83

Under inert conditions, to a flask containing the allyl sulfide (1.14 mmol, 1 equiv.), anhydrous DMSO (55 mL) was added via syringe. The reaction flask was cooled in a cold water bath where the temperature ranged between 18-22 °C. Some crystals were formed from DMSO solidifying in the vessel. iBuOK (0.75-1.25 eq.) was quickly added, and the flask was flushed with argon. The cold water was removed from underneath the flask and once the solid mixture became homogeneous, the transparent, amber solution was left to stir at room temperature (Refer to Table 3). The reaction was cooled briefly in an ice bath, and quenched with ice water. The aqueous solution was extracted with EtOAc (4 times), followed by washing the organic layer with water and brine. The organic extract was dried over magnesium sulfate. After filtration, the solvent was removed in vacuo.

cis-1-Propenyl β-N-Boc-aminobenzylethyl sulfide 83a (Scheme 42)

Reaction provided the cis isomer when starting allyl sulfide was treated 0.75 equiv. of base in 45 minutes at 19 °C. A white solid pure was obtained through flash chromatography 20% EtOAc/Hex in an 87% yield. Mp: 76-77 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \(\delta = 7.31-7.19 \text{ (m, 5H)}, 5.93 \text{ (d, J = 11.2 Hz, 1H)}, 5.66 \text{ (dq, J = 11.4 & 7.5 Hz, 1H)}, 4.80-4.78 \text{ (d, J = 4.4 Hz, 1H)}, 4.04 \text{ (m, 1H)}, 2.92-2.91 \text{ (d, J = 6.4 Hz, 2H)}, 2.79 \text{ (d, J = 5.2 Hz, 2H)}, 1.77-1.76 \text{ (d, J = 6.8 Hz, 3H)}, 1.43 \text{ (s, 9H)}. \(^1\)C NMR (CDCl\(_3\), 400 MHz, ppm): \(\delta = 155.1, 137.5, 133.8, 129.3, 128.3, 126.3, 117.3, 79.2, 50.7, 39.6, 34.3, 28.2, 25.4.[\alpha]_D^{22} = -14 \text{ (c = 1.00)}. \text{FTIR (cm}^{-1}\text{): 3436, 3150, 2980-2928, 1707. Analysis calculated for C}_{17}H_{25}O_2SN; \text{ C}, 66.35; \text{ H}, 8.13; \text{ found C}, 66.16; \text{ H}, 8.04.
cis-1-Propenyl β-N-Boc-aminoisopropyl sulfide 83b (Scheme 42)

The equivalents of base were increased to 1.25 and the reaction was completed in 80 minutes. Pure compound was obtained as a white solid in 5% EtOAc/Hex (76%). Mp: 64-65 °C. \( ^1H \) NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta \) = 5.91 (d, \( J = 9.3 \) Hz, 1H), 5.63 (dq, \( J = 9.5 \) & 7.0 Hz, 1H), 4.68 (dt, \( J = 7.1 \) & 6.8 Hz, 1H), 4.06 (br s, 1H), 3.65 (dd, \( J = 10.2 \) & 7.3 Hz, 1H), 3.60 (J = 10.0 & 7.3 Hz, 1H), 2.49 (m, 1H), 1.75 (d, \( J = 6.8 \) Hz, 3H), 1.37 (s, 9H), 0.82 (d, \( J = 7.4 \) Hz, 3H), 0.78 (d, \( J = 7.5 \) Hz, 3H). \( ^{13}C \) NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta \) = 155.1, 126.3, 117.3, 79.4, 64.3, 53.7, 31.3, 30.2, 29.3, 19.8. [\( \alpha \)]\(_D\)\(^{22}\) = -5.6 (c = 0.20). FTIR (cm\(^{-1}\)): 3436, 2980-2928, 1717. HRMS (ESI) calculated for C\(_{13}\)H\(_{25}\)NO\(_2\)S [M+H]\(^+\) 260.1679; found: 260.1679.

cis-1-Propenyl β-N-Boc-aminomethyl sulfide 83c (Scheme 42)

The mixture was stirred for 6 hours to achieve 50% conversion to a sample containing 15% trans compound (based on the NMR). Mp = 125-127 °C. \( ^1H \) NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta \) = 5.91 (d, \( J = 11.3 \) Hz, 1H), 5.63 (dq, \( J = 11.0 \) & 8.0 Hz, 1H), 4.38 (qt, \( J = 7.9 \) & 6.7 Hz, 1H), 4.06 (br s, 1H), 3.55 (dd, \( J = 7.7 \) & 6.9 Hz, 1H), 3.45 (dd, \( J = 7.5 \) & 7.0 Hz, 1H), 1.75 (d, \( J = 6.8 \) Hz, 3H), 1.45 (s, 9H), 1.15 (d, \( J = 6.5 \) Hz, 3H). \( ^{13}C \) NMR (CDCl\(_3\), 400 MHz, ppm): \( \delta \) = 155.9, 123.4, 118.6, 80.3, 63.2, 50.4, 31.5, 24.5, 18.3. [\( \alpha \)]\(_D\)\(^{22}\) = -10 (c = 0.150). FTIR (cm\(^{-1}\)): 3250, 2980-2910, 1695. HRMS (ESI) calculated for C\(_{11}\)H\(_{21}\)NO\(_2\)S [M+H]\(^+\) 264.1264; found: 264.1264.
Allyl trityl sulfide 85 (Scheme 44)

Product was not purified (77%). $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta =$ 7.59-7.12 (m, 15 H), 5.56-5.51 (ddt, J = 15.8, 10.5 & 7.1 Hz), 4.96 (dd, J = 15.9 & 12.6 Hz, 1H), 4.90 (dd, J = 12.5 & 10.1 Hz, 1H), 2.69-2.68 (d, J = 7.5 Hz, 2H). $^{13}$C NMR (400 MHz, CDCl$_3$, ppm): $\delta =$ 140.1, 132.6, 129.9, 125.2, 124.7, 118.3, 72.3, 36.6. FTIR (cm$^{-1}$): 3128-3020, 2925, 1257.

trans-1-Propenyl trityl sulfide 86 (Scheme 44)

Material was reacted as per the developed cis-isomerization protocol with a 4 hr reaction time, as this was the point where the NMR displayed the formation of a small intensity methyl peak corresponding to the formation of the trans isomer. Most of the spectra revealed the majority of starting material still present (reaction only 35% completed). $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta =$ 7.59-7.12 (m, 15 H), 5.97 (d, J = 16.6 Hz, 1H), 5.85 (dq, J = 16.2 & 6.9 Hz, 1H), 1.67 (d, J = 6.5 Hz, 3H). $^{13}$C NMR (400 MHz, CDCl$_3$, ppm): $\delta =$ 145.1, 135.6, 133.1, 130.5, 128.7, 120.3, 71.4, 24.8. FTIR (cm$^{-1}$): 3128-3020, 2925, 1257.

Allyl 2-pyridinyl sulfide 87 (Scheme 45)

Amber oil was obtained in a 90% crude yield and data corresponded with that of literature. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta =$ 8.32 (d, J = 5.5 Hz, 1H), 7.46 (t, J = 8.3 Hz, 1H), 7.17 (d, J = 5.1 Hz, 1H), 6.83-6.82 (t, J = 8.1 Hz, 1H), 5.88 (m, 1H), 5.20-5.17 (dd, J = 15.4 & 1.0 Hz, 1H), 5.00-4.99 (dd, J = 10.3 & 0.9 Hz, 1H), 2.95 (d, J = 7.6 Hz, 2H). $^{13}$C NMR (400 MHz, CDCl$_3$, ppm): $\delta =$ 158.4, 149.3, 135.9, 133.7, 122.1, 119.4, 117.5, 32.9. FTIR (cm$^{-1}$): 3070-3013, 2923, 1636, 1579, 1454.
(Z)-1-(2-Pyridyl)thio-1-propene 88 (Scheme 45)

Amber liquid was obtained in a 2 hr time frame where the product has a 3:4 of trans:cis contents. The mixture can purified via flash chromatography 5% EtOAc/Hex to obtain a colorless oil but this was not pursued. The cis NMR values are extrapolated. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta = 8.42$ (dt, $J = 5.4$ & 1.6 Hz, 1H), 7.52 (dt, $J = 5.1$ & 1.1 Hz, 1H), 7.16 (dt, $J = 5.5$ & 1.9 Hz, 1H), 6.99 (ddt, $J = 8.5$, 8.0 & 1.6 Hz, 1H), 6.75 (d, $J = 10.5$ Hz, 1H), 6.04 (dq, $J = 10.2$ & 7.2, 1H), 1.82 (d, $J = 7.8$ Hz, 3H). $^{13}$C NMR (400 MHz, CDCl$_3$, ppm): $\delta = 157.8$, 149.4, 136.1, 127.5, 121.9, 119.7, 119.6, 14.9. FTIR (cm$^{-1}$): 3070-3013, 2923, 1636, 1579, 1454.

(S,Z)-tert-Butyl(1-phenyl-3-((3-phenylprop-1-en-1-yl)thio)propan-2-yl)carbamate 89 (Scheme 46)

To a solution of $^1$Bu 2-thioacetyl-1-benzylethyl carbamate (1 equiv., 5.44 mmol) in anhydrous MeOH under Ar was added K$_2$CO$_3$ (1.5 equiv., 8.16 mmol). Mixture was left to stir for 5 minutes, where a solution of 3,3-dimethylallylbromide (1.7 equiv., 9.25 mmol) in DMF was added via syringe over the course of 10 minutes. Solution was let to stir for 48 hours and turned black when quenched with NH$_4$Cl$_{(aq)}$. TLC showed the consumption of all the starting materials pure compound was obtained though flash chromatography 10% EtOAc/Hex in a 38% yield though starting thioester was recoverable. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta = 7.36$-7.30 (m, 5H), 5.28 (m, 1H), 4.79 (br s, 1H), 4.08-4.07 (m, 1H), 3.46 (d, $J = 7.9$ Hz, 1H), 3.23 (d, $J = 5.7$ Hz, 1H), 3.18 (d, $J = 7.8$ Hz, 1H), 2.98 (d, $J = 6.9$ Hz, 1H), 2.93 (d, $J = 6.1$ Hz, 1H), 2.90-2.89 (d, $J = 7.2$ Hz, 1H), 2.63 (d, $J = 6.0$ Hz, 1H), 2.58 (d, $J = 5.8$ Hz, 1H), 1.79 (br s, 3H), 1.69 (br s, 3H), 1.51 (s, 9H). $^{13}$C NMR (400 MHz, CDCl$_3$,}
ppm): $\delta = 155.3, 137.8, 135.9, 129.6, 128.5, 126.5, 119.0, 79.4, 51.1, 39.9, 37.3, 35.1, 30.3, 28.5, 25.8$.

**(S,E)-tert-Butyl (1-(cinnamylthio)-3-phenylprop-2-yl)carbamate 91 (Scheme 47)**

Product was isolated as a white solid (77%) from a flash column with 5%EtOAc/Hex. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta = 7.18$ (m, 10H), 6.27 (d, $J = 15.4$ Hz, 1H), 6.05-6.02 (dq, $J = 15.1$ & 8.7 Hz, 1H), 4.57 (br s, 1H), 4.02-3.99 (m, 1H), 3.20-3.19 (d, $J = 8.4$ Hz, 2H), 2.77 (br d, $J = 6.6$ Hz, 2H), 2.46 (d with AB coupling, $J = 7.9$ & 6.8 Hz, 2H), 1.32 (s, 9H). $^{13}$C NMR (400 MHz, CDCl$_3$, ppm): $\delta = 156.1, 138.9, 138.1, 132.3, 130.0, 129.8, 128.3, 126.5, 120.9, 80.4, 60.1, 53.2, 40.3, 36.6, 29.7, 16.7$. FTIR (cm$^{-1}$): 3448, 3160-3095, 2970-2932, 1658.

**General procedure for the formation of the sulfone 93**

Formation of cis-sulfones was performed with mCPBA (cal. 90%, 3 equiv.) at 0 °C in anhydrous DCM under an argon atm. The reaction was allowed to warm to room temperature and left to stir until the reaction was shown to be completed via TLC. The solution was quenched with saturated aq. Na$_2$S$_2$O$_3$, and extracted 5 times with NaHCO$_3$ in order to remove any remaining mCPBA/chlorobenzoic acid. The organic extract was dried over magnesium sulfate. After filtration, the solvent was removed *in vacuo*. 

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**Sulfone was purified using flash chromatography (20% ethyl ether/Hex) in order to provide a white solid (82%).** Mp: 182-184 °C. $^1$H NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 7.32$-$7.24$ (m, 5H), $6.50$-$6.49$ (dq, $J = 11.2$ & 7.6 Hz, 1H), $6.24$ (d, $J = 11.2$ Hz, 1H), $4.98$ (br s, 1H), $4.20$-$4.19$ (m, 1H), $3.39$ (d, $J = 8.0$ Hz, 2H), $3.17$ (dd, $J = 12.1$ & 6.8 Hz, 1H), $3.00$ (dd, $J = 12.0$ & 7.4 Hz, 1H), $2.13$ (d, $J = 7.8$ Hz, 3H), $1.43$ (s, 9H). $^{13}$C NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 155.1$, $144.2$, $136.9$, $129.6$, $129.5$, $128.8$, $127.0$, $79.9$, $57.3$, $48.7$, $39.8$, $28.3$, $14.2$. $[\alpha]_D^{22}$: -16 (c = 1.00). FTIR (cm$^{-1}$): 3370, 3060-2928, 1691, 1603, 1281, 1079. HRMS (ESI) calculated for C$_{17}$H$_{25}$NO$_4$S [M+H]$^+$ 340.1576; found: 340.1577.

**Sulfone was purified using flash chromatography (10% EtOAc/Hex) in order to provide a white solid (74%).** Mp: 108-110 °C. $^1$H NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 6.45$-$6.43$ (dq, $J = 11.1$ & 7.6 Hz, 1H), $6.24$ (d, $J = 11.7$ Hz, 1H), $5.50$ (br s, 1H), $4.61$ (m, 1H), $3.48$ (m, 1H), $3.26$ (dd, $J = 12.3$ & 7.9 Hz, 1H), $3.01$ (dd, $J = 12.5$ & 7.2 Hz, 1H), $1.75$ (d, $J = 7.8$ Hz, 3H), $1.37$ (s, 9H), $0.82$ (d, $J = 6.6$ Hz, 3H), $0.78$ (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 155.9$, $140.8$, $135.5$, $80.3$, $63.2$, $50.4$, $38.6$, $31.5$, $27.3$, $18.3$. $[\alpha]_D^{22}$: -19 (c = 1.00). FTIR (cm$^{-1}$): 3250, 2980-2910, 1695, 1603, 1275, 1081.
(S)-cis-1-Propenyl β-N-Boc-aminomethyl sulfone 93c (Scheme 48)

Sulfone was purified using flash chromatography (10% EtOAc/Hex) in order to provide a white solid (52%). Mp: 71-73 °C. $^1$H NMR (CDCl$_3$, 400 MHz, ppm): δ= 6.39 (dq, J = 10.2 & 7.4 Hz, 1H), 6.24 (d, J = 9.9 Hz, 1H), 5.63 (br s, 1H), 4.46 (m, 1H), 3.51 (dd, J = 14.2 & 7.4 Hz, 1H), 3.25 (dd, J = 14.0 & 7.7 Hz, 1H), 1.75 (d, J = 7.8 Hz, 3H), 1.45 (s, 9H), 1.15 (d, J = 7.5, 3H). $^{13}$C NMR (CDCl$_3$, 400 MHz, ppm): δ = 155.9, 144.2, 136.9, 80.3, 63.2, 31.5, 30.0, 26.7, 18.3. $[\alpha]_D^{22}$: -13 (c = 0.20). FTIR (cm$^{-1}$): 3315, 2995-2950, 1689, 1277, 1050.

General deprotection of Boc-protected β-Amino sulfone/sulfoxide to TFA salts

To a 1:1 solution of TFA:DCM (10 mL/mmol) at 0 °C was added a solution of protected β-amino sulfone or sulfoxide in DCM (1.5 mL/mmol). The reaction mixture was then allowed to warm to 20 °C and stirred for 1 hr at rt to reach completion. Solvent was removed under reduced pressure, and then 20 mL of hexanes was added to the residue and removed under reduced pressure. This process was repeated three times in order to ensure removal of TFA. Excess solvent was removed $in vacuo$ to yield the TFA ammonium salt.

cis-1-Propenyl β-amino-benzylethyl sulfone TFA salt 94a (Scheme 48)

Benzyl sulfone TFA salt was obtained after 4 washes with distilled hexanes to afford an amber oily solid. $^1$H NMR (CDCl$_3$, 400 MHz, ppm): δ = 8.40 (br s, 3H), 7.24-7.32 (m, 5H), 6.52-6.51 (dq, J = 10.5 & 7.6 Hz, 1H), 6.19 (d, J = 10.8 Hz, 1H), 3.62 (m, 1H), 3.36 (dd, J= 12.3 & 7.5 Hz, 1H), 3.20
(dd, J = 12.0 & 7.8 Hz, 1H), 2.97 (d, J = 7.4 Hz, 2H), 1.91 (d, J = 7.5 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 400 MHz, ppm): δ = 147.2, 133.9, 129.6, 129.5, 128.8, 127.0, 57.3, 48.7, 38.8, 14.2. \([\alpha]_D^{22} -5.3 (c = 1.00)\). FTIR (cm$^{-1}$): 3435, 3183-3033, 2929, 1778, 1675, 1628, 1500, 1456, 1433, 1305, 1148.

cis-1-Propenyl β-amino-isopropyl sulfone TFA salt 94b (Scheme 48)

A brown oil was obtained after distilled 3 hexane washes. $^1$H NMR (CDCl$_3$, 400 MHz, ppm): δ = 8.23 (br s, 3H), 6.50-6.49 (dq, J = 9.0 & 3.1 Hz, 1H), 6.24 (d, J = 9.5 Hz, 1H), 4.61 (br s, 1H), 3.50 (m, 2H), 3.01 (dd, J = 10.2 Hz, 2H), 1.75 (dd, J = 6.8 & 1.5 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 400 MHz, ppm): δ = 144.2, 136.9, 63.2, 31.5, 18.3. FTIR (cm$^{-1}$): 3435, 2929, 1778, 1675, 1628, 1500, 1456, 1433, 1290, 1158.

cis-1-Propenyl β-amino-methyl sulfone TFA salt 94c (Scheme 48)

Amber oil compound was obtained. $^1$H NMR (CDCl$_3$, 400 MHz, ppm): δ = 8.25 (br s, 3H), 6.65-6.64 (dq, J = 10.0 & 7.6 Hz, 1H), 6.35 (d, J = 10.9 Hz, 1H), 3.66 (m, 1H), 3.25-3.24 (d, J = 6.2 Hz, 2H), 2.16 (d, J = 7.1 Hz, 3H), 1.53 (d, J = 7.5 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 400 MHz, ppm): δ = 144.2, 136.9, 63.2, 31.5, 26.4, 18.3. FTIR (cm$^{-1}$): 3435, 2929, 1778, 1675, 1628, 1501, 1456, 1433, 1298, 1134.

General Procedure for Cyclizations of TFA Salts

The TFA salt (1.0 equiv.) was dissolved in MeOH (30 mL/mmoll) and stirred at rt. Triethylamine (2.0-4.0 equiv.) was added to the reaction mixture via syringe and the mixture was stirred at the indicated temperature until completion (monitored by TLC). The solvent was
removed in vacuo to give a crude residue, which was dissolved into DCM (30 mL/mmol) and transferred to a separatory funnel. The organic layer was successively with 1 M aqueous NaOH, H₂O, and brine then dried over MgSO₄, filtered and concentrated in vacuo to give the cyclized product. The product was purified by flash chromatography.

**Heterocycles of the cis-1-Propenyl β-amino-benzylethyl sulfone 95a/b (Scheme 55)**

A mixture of the TFA salt (1 equiv.) and triethylamine (2 equiv.) in methanol (15 mL) was stirred for 6 h at rt under Ar(g) to provide heterocycles as a diastereomeric mix. The diastereomers were separated by flash chromatography (5% MeOH/CHCl₃) to provide white solids (71%, dr = 62:38).

**Major isomer (95a):** ¹H NMR (600 MHz, CDCl₃, ppm): δ = 7.35-7.29 (m, 5H), 3.62 (m, 2H), 3.02 (m, 4H), 1.19 (d, J = 6.6 Hz, 3H).¹³C NMR (600 MHz, CDCl₃, ppm): δ = 137.0, 129.3, 128.9, 126.9, 57.8, 54.2, 52.8, 45.6, 38.6, 20.4. [α]D²²: -4.1 (c = 1.00). FTIR (cm⁻¹): 3330-3030, 2980-2915, 1508, 1445, 1312, 1267, 1150. Analysis calculated for C₁₂H₁₆N₂O₂S; C, 60.17; H, 6.69; found C, 60.24; H, 7.00.

**Minor Isomer (95b):** ¹H NMR (600 MHz, CDCl₃, ppm): δ = 7.28-7.20 (m, 5H), 3.40 (m, 1H), 3.17 (m, 1H), 2.86 (m, 2H), 2.76 (m, 2H), 2.62 (dd, J = 13.4 & 11.6 Hz, 1H), 2.59 (dd, J = 12.0 & 11.0 Hz, 1H), 1.74 (br s, 1H), 1.11 (d, J = 6.6 Hz, 3H).¹³C NMR (600 MHz, CDCl₃, ppm): δ = 136.2, 129.2, 129.0, 127.3, 58.3, 56.4, 55.4, 49.9, 42.1, 21.6. FTIR (cm⁻¹): 3330-3030, 2980-2915, 1508, 1445, 1312, 1267, 1150. Data corresponding with the major isomer as observed by Söderman.³⁸
**Heterocycles of the cis-1-Propenyl β-amino-isopropyl sulfone 95c/d (Scheme 56)**

A mixture of the TFA salt (1 equiv.) and triethylamine (2.5 equiv.) in methanol (15 mL) was stirred for 6 h at 21 °C under argon to provide heterocycles as a diastereomeric mix. The diastereomers appeared as an amber oil (70%, dr = 55:45).

![Structure of 95c](image)

**Major isomer (95c):** $^1$H NMR (600 MHz, CDCl$_3$, ppm): $\delta = 3.77$ (m, 1H), 3.07-3.05 (m, 2H), 2.93 (m, 1H), 2.78 (dd, $J = 12.3$ & 3.6 Hz, 1H), 2.63-2.59 (dd, $J = 12.3$ & 9.6 Hz, 1H), 2.08 (sep, $J = 6.8$ Hz, 1H), 1.94 (d, $J = 7.5$ Hz, 1H), 1.28 (d, $J = 6.9$ Hz, 3H), 0.89 (d, $J = 6.9$ Hz, 6H). $^{13}$C NMR (600 MHz, CDCl$_3$, ppm): $\delta = 58.4$, 57.2, 56.3, 45.8, 29.2, 19.8, 19.1, 18.1.

![Structure of 95d](image)

**Minor isomer (95d):** $^1$H NMR (600 MHz, CDCl$_3$, ppm): $\delta = 3.20$ (m, 1H), 3.16 (m, 2H), 2.97 (m, 1H), 2.73 (dd, $J = 12.3$ & 3.6 Hz, 1H), 2.69-2.66 (dd, $J = 12.3$ & 9.6 Hz, 1H), 1.70 (sep, $J = 6.8$ Hz, 1H), 1.68 (d, $J = 7.5$ Hz, 1H), 1.17 (d, $J = 6.9$ Hz, 3H), 0.90 (d, $J = 6.9$ Hz, 6H). $^{13}$C NMR (600 MHz, CDCl$_3$, ppm): $\delta = 59.6$, 53.8, 49.9, 46.1, 32.5, 21.3, 19.9, 18.6.

Mixture: $\alpha$$_D^{22}$: 0.2 (c = 0.20) . FTIR (cm$^{-1}$): 3448, 2990-2900, 1506, 1450, 1335, 1268, 1117. HRMS (ESI) calculated for C$_8$H$_{17}$NO$_2$S [M+H]$^+$ 192.1053; found: 192.1052.

**General procedure for the formation of the sulfoxide isomers**

**mCPBA oxidation method**

The sulfide was placed in a reaction flask containing a stir bar and was dissolved in dichloromethane (9 mL). This flask was purged with argon and the contents were stirred at -78 °C. mCPBA (calib. 90% max, 1 eq.) was dissolved in dichloromethane (40 mL) in a separate reaction flask. A pressure equalizing dropping funnel was purged with argon and then placed on the neck
of the reaction flask stirring at -78 °C. The mCPBA solution was added to the dropping funnel via syringe and then was added dropwise to the reaction flask. After addition was complete, the reaction was left to stir at -78 °C for 5 hours. The opaque, white/grey reaction mixture transformed to a clear, yellow tinted solution upon warming to room temperature. The organic mixture was washed with sat’d aq. Na$_2$S$_2$O$_3$ (3 times), saturated sodium bicarbonate, water, and brine, and dried over MgSO$_4$. After filtration, the solvent was removed in vacuo. $^1$H NMR and TLC analysis showed the presence of two compounds. Purification of the crude was completed through flash column chromatography using silica with either 50% EtOAc/ 50% Hexanes or 2% MeOH/DCM. The two compounds were inseparable, suggesting the production of a diastereomeric mixture (76%).

**H$_2$O$_2$ oxidation method with TFE**

A solution of sulfide was prepared with TFE at 0°C. Aq. H$_2$O$_2$ (30%) was added and the solution was left to warm to room temperature. Mixture slowly turns yellow and the reaction was completed after 12 hrs. The solution was quenched with sat’d aq. Na$_2$S$_2$O$_3$ (2 equiv.) and heated slightly following lit. protocol.$^{135}$ The solution is filtered through Celite™ where crude NMR shows formation of cis sulfoxides as well as an additional doublet of methyl with a trans coupling.

**H$_2$O$_2$ oxidation method with HFIP**

To a solution of cis-sulfide in RBF with 2 mL HFIP at 0 °C was added aq. H$_2$O$_2$ (30%). Solution was warmed to room temperature, became yellow and TLC showed reaction completion after 5 minutes. Quench occurred with a slow addition of Na$_2$S$_2$O$_3$(aq) under an ice bath. The organic mixture was washed with sat’d aq. Na$_2$S$_2$O$_3$ (3 times), saturated sodium bicarbonate, water,
and brine, and dried over magnesium sulfate. After filtration, the solvent was removed in vacuo. 

$^1$H NMR and TLC analysis showed the presence of two compounds. Purification of the crude was completed through flash column chromatography using silica and a 1% MeOH/CHCl$_3$ solvent as the eluent. The two compounds were inseparable, suggesting the production of a diastereomeric mixture (95%) though one spot would appear yellow and the other purple once charring on the TLC plate.

**(S)-cis-1-Propenyl 2-N-Boc-aminobenzylethyl sulfoxide 96/97a (Scheme 49)**

A mixture of syn and anti isomers were obtained with respect to the S-O bond as a white solid (dr=50:50, 80%) using H$_2$O$_2$/HFIP at room temperature for 5 minutes.

**Isomer (96):** $^1$H NMR (CDCl$_3$, 400 MHz, ppm): $\delta =$ 7.30 – 7.25 (m, 5 H), 6.32 (dq, J= 11.5 & 6.9 Hz, 1H), 6.18 (d, J = 11.2 Hz, 1H), 5.56-5.55 (br s, 1H), 4.22 (m, 1H), 3.23 (dd, J = 12.1 & 6.7 Hz, 1H), 3.23 (d, J = 7.5 Hz, 2H), 2.96 (dd, J = 12.0 & 6.9 Hz, 1H), 1.97 (d, J= 7.1 Hz, 3H), 1.41 (s, 9 H). $^{13}$C NMR (CDCl$_3$, 400 MHz, ppm): $\delta =$ 155.2, 137.4, 136.8, 135.2, 129.5, 129.4, 128.7, 79.7, 57.5, 49.4, 41.0, 28.3, 15.3.

**Isomer (97):** $^1$H NMR (CDCl$_3$, 400 MHz, ppm): $\delta =$ 7.30-7.25 (m, 5 H), 6.31 (m, 2H), 5.01-5.00 (br s, 1H), 4.08 (m, 1H), 3.23 (dd, J = 13.7 & 7.7 Hz, 1H), 3.21 (d, J = 7.6 Hz, 2H), 2.82 (dd, J = 13.0 & 7.2 Hz, 1H), 1.97 (d, J= 7.1 Hz, 3H), 1.40 (s, 9 H). $^{13}$C NMR (CDCl$_3$, 400 MHz, ppm): $\delta =$ 154.9, 137.9, 137.4, 136.8, 135.2, 126.9, 126.8, 79.5, 55.8, 48.3, 39.9, 28.4, 15.3.

Mixture: Mp: 99-101 °C. $[\alpha]_{D}^{22}$: -14 (c = 1.00). FTIR (cm$^{-1}$): 3264, 3028-3005, 2976-2867, 1708, 1626, 1019, 1005. Analysis calculated for C$_{17}$H$_{25}$NO$_3$S; C, 63.21; H, 7.50; found C, 63.17; H, 7.69.
(S)-\textit{cis-1-Propenyl 2-N-Boc-aminoisopropyl sulfoxide 96/97b (Scheme 49)}

Sulfoxide isomers were purified using flash chromatography (20% EtOAc/Hex) in order to provide a white solid mixture of both sulfoxides (dr=50:50 – syn:anti) that cannot be distinguished at this time (63%).

Mp: 75-78 °C. $^1$H NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 6.30$ (dq, $J = 10.8$ & 7.0 Hz, 1H), 6.26 (m, 2H), 6.09 (d, $J = 11.0$ Hz, 1H), 4.21 (m, 1H), 4.06 (m, 1H), 3.43 (m, 1H), 3.20 (m, 1H), 3.05 (dd, $J = 12.5$ & 7.8 Hz, 1H), 2.92 (dd, $J = 13.0$ & 7.5 Hz, 1H), 2.79 (dd, $J = 13.5$ & 7.0 Hz, 1H), 2.56 (dd, $J = 13.2$ & 7.2 Hz, 1H), 1.88 (d, $J = 6.9$ Hz, 3H), 1.76 (d, $J = 7.2$ Hz, 3H), 0.82 (d, $J = 6.6$ Hz, 6H), 0.78 (d, $J = 6.9$ Hz, 6H). $^{13}$C NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 155.2$, 154.9, 129.4, 128.7, 126.9, 126.8, 57.5, 55.8, 49.4, 48.3, 41.0, 39.9, 30.2, 29.9, 25.4, 25.1, 15.3, 15.3. $\left[\alpha\right]_D^{22}: -23$ (c = 0.20). FTIR (cm$^{-1}$): 3264, 2976 - 2867, 1626, 1050. HRMS (ESI) calculated for C$_{13}$H$_{25}$NO$_3$S [M+H]$^+$ 276.1628; found: 276.1629.

\textit{cis-1-Propenyl β-amino-benzylethyl sulfoxide TFA salt 98a (Scheme 50)}

The solvent was removed \textit{in vacuo} to obtain an oily, grey/yellow residue. This residue was washed with hexanes (5 x 15 mL), which were removed \textit{in vacuo}. Product was a diastereomeric mixture (50:50) of sulfoxide salts (83%) that received no further purification. It is possible to distinguish between the syn and anti conformation in $^1$H NMR.

\textbf{Syn Isomer 98a}: $^1$H NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 8.62$ (br s, 3H), 7.30 – 7.21 (m, 5 H), 6.32 (dq, $J = 10.5$ & 7.9 Hz, 1H), 6.15 (d, $J = 10.2$ Hz, 1H), 4.11 (m, 1H), 3.43 (d, $J = 7.0$ Hz, 2H), 3.05 (dd, $J = 14.1$ & 7.2 Hz, 1H), 2.79 (dd, $J = 14.5$ & 7.3 Hz, 1H), 1.88 (d, $J = 7.9$ Hz, 3H).
Anti Isomer 98a: $^1$H NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 8.62$ (br s, 3H), 7.30 – 7.21 (m, 5 H), 6.31 (m, 2H), 4.06 (m, 1H), 3.20 (d, J = 6.8 Hz, 2H), 2.92 (dd, J = 13.2 & 7.3 Hz, 1H), 2.56 (dd, J = 13.7 & 7.1 Hz, 1H), 1.76 (d, J = 7.2 Hz, 3H).

Mixture: $^{13}$C NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 139.1, 137.9, 137.4, 136.8, 135.2, 134.8, 129.5, 129.4, 128.7, 126.9, 126.8, 57.5, 55.8, 49.4, 48.3, 41.0, 39.9, 15.3, 15.3. FTIR (cm$^{-1}$): 3264, 3028–3005, 2976–2867, 1626, 1050.

cis-1-Propenyl $\beta$-amino-isopropyl sulfoxide TFA salt 98b (Scheme 50)

The solvent was then removed in vacuo to obtain a brown oil. This residue was washed with hexanes (5 x 15 mL), which were removed under reduced pressure. Compound did not receive further purification and proceeded to cyclization (dr=50:50).

$^1$H NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 8.62$ (br s, 3H), 6.30 (dq, J= 11.2 & 7.0 Hz, 1H), 6.26 (m, 2H), 6.09 (d, J = 11.0 Hz, 1H), 4.21 (dt, J = 7.7 & 6.8 Hz, 1H), 4.06 (dt, J = 7.7 & 6.9 Hz, 1H), 3.20 (d, J = 7.0 Hz, 2H), 3.18 (d, J = 7.1 Hz, 2H), 3.05 (m, 1H), 2.92 (m, 1H), 2.79 (d, J = 11.5 Hz, 3H), 2.56 (d, J = 11.2 Hz, 3H), 1.88 (d, J = 6.9 Hz, 6H), 1.76 (d, J = 7.2 Hz, 6H). $^{13}$C NMR (CDCl$_3$, 400 MHz, ppm): $\delta = 129.4, 128.7, 126.9, 126.8, 57.5, 55.8, 49.4, 48.3, 41.0, 39.9, 15.3, 15.3.

(S,E)-tert-Butyl (1-(cinnamylsulfonyl)-3-phenylpropan-2-yl)carbamate 99 (Scheme 51)

Compound underwent oxidation via mCPBA (90%) to produce the corresponding sulfone (68%) in 5 hours. $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta = 7.28-7.12$ (m, 10H), 6.61-6.60 (d, J = 15.8 Hz, 1H), 6.13 (dt, J = 15.8 & 6.3 Hz, 1H), 4.93-4.92 (br s, 1H), 4.22 (m, 1H), 3.83 (m, 2H), 3.21-3.20 (m, 1H), 3.06-3.05 (dd, J = 7.2 &
1.6 Hz, 1H), 2.95 (d, J = 1.2 Hz, 1H), 2.94 (dd, J = 7.2 & 1.8 Hz, 1H), 1.53 (s, 9H). \(^{13}\)C NMR (400 MHz, CDCl\(_3\), ppm): \(\delta = 154.2, 138.3, 135.7, 134.5, 128.3, 127.7, 127.6, 125.7, 114.0, 79.1, 57.4, 52.4, 47.2, 39.1, 28.7, 27.3\). FTIR (cm\(^{-1}\)): 3448, 3160-3095, 2970-2932, 1658, 1120, 1030.

\((S,E)\)- (1-(Cinnamylsulfonyl)-3-phenylpropan-2-yl 3-amine TFA salt 100 (Scheme 51)

There was 20% starting material still present in the NMR after over 2 hrs of TFA treatment, though carbon NMR displayed that the majority of the Boc had been removed. Product appears as white solid. \(^1\)H NMR (600 MHz, CDCl\(_3\), ppm): \(\delta = 8.40\) (br s, 3H), 7.28-7.18 (m, 10H), 6.45 (d, J = 15.8 Hz, 1H), 5.94 (dt, J = 15.8 & 7.2 Hz, 1H), 4.12 (br s, 1H), 3.94 (dd, J = 13.8 & 7.2, 1H), 3.87-3.86 (dd, J = 13.8 & 7.1 Hz, 1H), 3.60 (t, J = 10.3 Hz, 1H), 3.39 (d, J = 14.7 Hz, 1H), 2.94 (t, J = 10.9 Hz, 1H). \(^{13}\)C NMR (600 MHz, CDCl\(_3\), ppm): \(\delta = 135.1, 129.4, 128.9, 128.7, 128.6, 127.9, 127.0, 126.9, 126.8, 113.4, 57.7, 50.3, 48.5, 38.5, 29.7, 28.3\). FTIR (cm\(^{-1}\)): 3448, 3160-3095, 2970-2932, 1275, 1120, 1030.

\((4S)-4\)-Benzy1-2-ethylthiazolidine 102 (Scheme 52)

To a solution of 83a in DCM at 0 °C was added a 1:1 mixture of TFA:DCM under argon. Solution was left to warm to room temperature until the reaction was completed. Sample was treated with distilled hexanes (3 x 3 mL) under reduced pressure to obtain a white solid of two isomers in a 3:4 ratio.

Major Isomer (102a) : \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 7.24\)\-7.17 (m, 5H), 4.60-4.59 (dd, J = 7.3 & 7.0 Hz, 1H), 3.95-3.94 (ddt, J = 13.1, 6.2 & 5.6 Hz, 1H), 3.21-3.20 (dd, J = 13.0 & 5.5 Hz, 1H), 3.00-2.99 (dd, J = 12.8 & 5.5 Hz, 1H), 2.56 (d,
J = 6.2 Hz, 2H), 2.04-2.03 (dq, J = 7.5 & 7.0 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H). 13C NMR (600 MHz, CDCl$_3$): δ = 135.3, 129.1, 128.9, 128.9, 66.5, 65.7, 37.1, 33.8, 27.8, 11.3.

Minor Isomer (102b): 1H NMR (600 MHz, CDCl$_3$): δ = 7.26-7.12 (m, 5H), 4.69-4.68 (dd, J = 7.8 & 7.1 Hz, 1H), 4.13-4.12 (ddt, J = 12.1 & 7.8 Hz, 1H), 2.96 (dd, J = 12.1 & 5.6 Hz, 1H), 2.49 (d, J = 6.8 Hz, 2H), 1.76-1.75 (dq, J = 7.8 & 7.5 Hz, 2H), 0.93 (t, J = 7.8 Hz, 3H). 13C NMR (600 MHz, CDCl$_3$): δ = 134.8, 129.2, 128.7, 127.9, 65.9, 64.1, 36.5, 33.3, 27.1, 10.9.

Mixture: FTIR (cm$^{-1}$): 3413, 3135-3028, 2954-2892, 1051. HRMS (ESI) calculated for C$_{12}$H$_{18}$NS [M+H]$^+$ 208.1154; found: 208.1144.

5-Methyl-3-benzylsulfinylmorpholine isomers (Scheme 53)

The 98a salt isomers were dissolved in MeOH (20 mL), purged with argon, and stirred at room temperature. Triethylamine (2 equiv.) was added to the reaction flask via syringe. A water cooling condenser was purged with argon and added to the neck of the flask. The reaction mixture was placed in an oil bath while stirring, and was refluxed at 70 °C. The reaction was monitored by removing samples for 1H NMR and TLC analysis, and the reflux was stopped after 72 hrs. The flask was allowed to cool to room temperature and the solvent was then removed in vacuo to produce a brown/orange residue. The residue was dissolved in dichloromethane and transferred to a separatory funnel to be washed with 1 M NaOH(aq), water, and brine. The organic solution was then dried over magnesium sulfate, filtered, and then concentrated in vacuo. 1H NMR and TLC (10% MeOH /DCM) showed the presence of a few products. Purification of the crude was completed through flash column chromatography using silica and a 10% MeOH /DCM with 1% TEA in order to separate the formed heterocycles. It was observed that the syn isomer was the only one to cyclize while the anti-isomer formed the cis-amine sulfoxide.
Sulfoxide Heterocycle 103 (Scheme 53): \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \(\delta = 7.36-7.33\, (m,\, 2H), 7.27-7.19\, (m,\, 3H), 3.84\, (m,\, 1H), 3.45\, (m,\, 1H), 3.31\, (dd,\, J = 13.2 & 8.4\, Hz,\, 1H), 3.05-3.04\, (m,\, 1H), 2.92-2.91\, (m,\, 1H), 2.84\, (d,\, J = 3.8\, Hz,\, 2H), 2.34\, (dd,\, J = 13.0 & 7.5\, Hz,\, 1H), 1.18\, (d,\, J = 6.8\, Hz,\, 3H). \(^1\)C NMR (CDCl\(_3\), 400 MHz, ppm): \(\delta = 138.2, 129.2, 128.8, 126.7, 54.4, 51.6, 51.0, 41.3, 41.2, 21.0\). FTIR (cm\(^{-1}\)): 3285-3025, 2965, 2915, 1601, 1494, 1453, 1376, 1240.

Deprotected cis-sulfoxide 104 (Scheme 53): \(^1\)H NMR (CDCl\(_3\), 400 MHz, ppm): \(\delta = 7.30-7.25\, (m,\, 5\, H), 6.31\, (m,\, 2H), 5.01\, (br\, s,\, 2H), 4.08\, (m,\, 1H), 3.23\, (dd,\, J = 13.7 & 6.7\, Hz,\, 1H), 3.21\, (d,\, J = 7.3\, Hz,\, 2H), 2.82\, (dd,\, J = 13.0 & 7.2\, Hz,\, 1H), 1.97\, (d,\, J = 8.1\, Hz,\, 3H). \(^1\)C NMR (CDCl\(_3\), 400 MHz, ppm): \(\delta = 139.9, 137.4, 136.8, 135.2, 126.9, 126.8, 55.8, 48.3, 39.9, 28.4\). FTIR (cm\(^{-1}\)): 3264, 3028-3005, 2976-2867, 1458, 1005.

3-(acetylthio)-Methyl ester propanoic acid 105 (Scheme 63)

Solvent-free synthesis of methyl 3-(acetylthio)-propanoate occurred by mixing methyl acrylate (1 equiv.) with thioacetic acid (2 equiv.) at room temperature overnight under Ar. Ethyl acetate was added (2 mL/mmol) with NaCO\(_3\) to quench. Mixture was extracted and dried over MgSO\(_4\), resulting in a brown oil. Flash column was conducted with 5% ethyl ether/hexanes for an 86% yield of a yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm): \(\delta = 3.69\, (s,\, 3H), 3.10\, (t,\, J = 7.0\, Hz,\, 2H), 2.63\, (t,\, J = 7.0\, Hz,\, 2H), 2.32\, (s,\, 3H). \(^1\)C NMR (400 MHz, CDCl\(_3\), ppm): \(\delta = 195.6, 174.3, 53.2, 30.1, 28.9, 26.7\). FTIR (cm\(^{-1}\)): 2950-2905, 1715, 1679, 1420.
Synthesis of sulfenyl chloride intermediate 106 (Scheme 64)

Under anhydrous conditions, compound 105 was dissolved in minimal amounts of dry DCM at -78 °C. Neat SO\textsubscript{2}Cl\textsubscript{2} was added (1 equiv.) and reaction proceeded for 5 hours. Acetyl chloride and DCM were removed under vacuum at cold conditions. NMR was collected of the crude product of an amber oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): \(\delta = 3.70\) (s, 3H), 3.35 (t, \(J = 7.2\) Hz, 2H), 2.90 (t, \(J = 7.2\) Hz, 2H). \textsuperscript{13}C NMR (400 MHz, CDCl\textsubscript{3}, ppm): \(\delta = 176.3, 53.2, 30.1, 28.9\). FTIR (cm\textsuperscript{-1}): 2954, 1734, 1576, 1417, 1168.

Phenyl allenyl sulfoxide ethyl ester synthesis 107 (Scheme 64)

To a solution of sulfenyl chloride 106 at -78 °C was added a cold mixture of alcohol and trimethylamine (1.1 equiv.) dissolved in THF. Solution was left to warm to room temperature over the course of 12 hours forming compound 107 in a 28% yield as brown oil after purification with flash chromatography (40% EtOAc/Hex). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ppm): \(\delta = 7.35\) - 7.33 (m, 5H), 5.68 - 5.64 (d, \(J = 13.1\) Hz, 1H), 5.60 - 5.55 (d, \(J = 13.4\) Hz, 1H), 3.65 (s, 3H), 3.15 - 3.14 (ddd, \(J = 12.1, 6.2\) & 6.0 Hz, 1H), 2.90 - 2.87 (ddd, \(J = 12.1, 6.5\) & 6.1 Hz, 1H), 2.79 - 2.78 (ddd, \(J = 12.3, 6.5\) & 6.1 Hz, 1H), 2.67 - 2.66 (ddd, \(J = 12.0, 6.6\) & 6.3 Hz, 1H). \textsuperscript{13}C NMR (400 MHz, CDCl\textsubscript{3}, ppm): \(\delta = 204.6, 171.7, 130.0, 129.1, 128.8, 127.0, 113.8, 85.0, 52.1, 46.8, 26.1\). FTIR (cm\textsuperscript{-1}): 3059-2851, 1980-1950, 1738, 1597, 1490, 1439, 1361, 1319, 1242, 1132, 1045. HRMS (ESI) calculated for C\textsubscript{13}H\textsubscript{15}NO\textsubscript{3}S [M+H]\textsuperscript{+} 251.0736; found: 251.0735.
(E)-Methyl 3-((1-chloro-3-hydroxy-1-phenylprop-1-en-2-yl)thio)propanoate 108 (Figure 16)

By product of the allenyl sulfonate reaction. Clear liquid (23%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.31$-$7.30$ (m, 5H), 4.52 (s, 2H), 3.60 (br s, 1H), 3.56 (s, 3H), 2.76 (t, J = 6.6, 2H), 2.42-2.41 (t, J = 6.6, 2H).

$^{13}$C NMR (400 MHz, CDCl$_3$, ppm): $\delta = 172.2, 139.4, 137.1, 129.8, 128.6, 127.9, 116.9, 63.0, 32.5, 31.8, 51.4$.

2-(Trimethylsilyl)ethanethiol 109 (Scheme 65)

Thiolacetic acid (1 equiv.) was refluxed at 60°C overnight with cat. AIBN and vinyltrimethylsilane (1.12 equiv.) to obtain a yellow solution whose NMR indicated formation of desired compound.$^{136}$ $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta = 3.02$ (t, J = 5.6 Hz, 2H), 2.56 (s, 3H), 1.05 (2H, m), 0.10 (s, 9H). $^{13}$C NMR (400 MHz, CDCl$_3$, ppm): $\delta = 196.7, 30.9, 25.4, 21.6, 0.02$.

bis(Trimethylsilyl) diethyl disulfide 110 (Scheme 65)

To a solution of 2-(Trimethylsilyl)ethanethiol was added methanol and KOH(1.4 equiv.). Reaction was left overnight at room temperature under open air to form the corresponding disulfide as a yellow liquid. Compound was distilled in order to obtain a clear liquid.$^{136}$ $^1$H NMR (400 MHz, CDCl$_3$, ppm): $\delta = 2.10$ (t, J = 4.4 Hz, 2H), 1.15 (2H, m), 0.10 (s, 9H). $^{13}$C NMR (400 MHz, CDCl$_3$, ppm): $\delta = 25.4, 22.3, 0.02$. 

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