Alkylations, Rearrangements, and Cyclizations of Oxidized Organosulfur Compounds

by

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ABSTRACT

ALKYLATIONS, REARRANGEMENTS, AND CYCLIZATIONS OF OXIDIZED ORGANOSULFUR COMPOUNDS

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Organosulfur compounds have been used by humans for centuries and played a pivotal role in shaping our history. The chemistry presented herein deals primarily with three distinct organic transformations involving organosulfur species. The three transformations are used in tandem to complete the synthesis of natural products.

The first chapter examines a new diastereoselective alkylation reaction of sulfenate anions with stereoisoduction provided by chiral amino iodides. A series of β-amino sulfoxides are accessed in good yields and selectivities from alkylations with the corresponding lithium arene- and E-1-alkenesulfenate anions. The relative reactivity of different electrophiles towards a selection of lithium sulfenate anions was also evaluated by performing competition experiments.

In the second chapter 1,2-dibromotetrachloroethane (C₂Br₂Cl₄) was evaluated as a more economical halogenating agent for the in-situ Ramberg-Bäcklund rearrangement (RBR). A series of trans-stilbenoids were successfully synthesized using this protocol in excellent yields. The new RBR system also worked well for
dialkyl and cyclic substrates, but the reaction was plagued by polyhalogenation for hexyl benzyl sulfone. The methodology was extended to the formal total synthesis of natural polyphenol E-resveratrol.

Chapter three investigates asymmetric aza-Michael reactions of chiral β-amino sulfoxides/sulfones to synthesize thiomorpholine S-oxides and S,S-dioxides, respectively. Remarkably, cyclizations of the β-amino sulfoxides provide the trans-3,5-substituted heterocycles, while the β-amino sulfones provide the complementary cis-3,5-substituted heterocycles. The aza-Michael chemistry was exploited along with the sulenate and RBR protocols to access two ant venom alkaloids.
Acknowledgements

After nearly five years in the Schwan lab it is time for me to express my gratitude for those that have helped me complete my PhD. I would like to thank NSERC, the Ontario government, and the Petroleum Research Fund for subsidizing the chemistry research I have achieved. The staff in the chemistry department was crucial in helping me achieve my goals. I thank Steve Wilson of the machine shop and Steve Seifried of the electronics shop. Many thanks go to Uwe Oehler for helping with all my computer issues. The staff at the NMR centre has been excellent and I express my sincere thanks to Valerie Robertson, Andy Lo, Pete Scheffer and Joe Meissner. Rob Reed was a great help in many of the practical aspects of the practical challenges I faced in setting up experiments.

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Lastly, my sincere gratitude goes out to Adrian for giving a psychology major a chance to do chemistry. Your support, encouragement and knowledge about chemistry/sports made my time here very enjoyable. You are a true friend and I look forward to keeping in touch with you in years to come.
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List of Abbreviations

12-c-4 = 12-crown-4

Ac = acetyl

AIBN = azobisisobutyronitrile

An = 1-anthraquinoyl

Ar = aryl

Bn = benzyl

Boc = tert-butyloxy carbonyl

Bu = butyl

c = cyclo-

Cbz = benzyl oxycarbonyl

Cl = chemical ionization

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE = 1,2-dichloroethane

DCM = dichloromethane

DMF = N, N-dimethylformamide

DMSO = dimethyl sulfoxide

DNA = deoxyribonucleic acid

dppe = 1,2-bis(diphenylphosphino)ethane

dr = diastereomeric ratio

ee = enantiomeric excess

ent = enantiomer

er = enantiomeric ratio
ESI = electrospray ionization
Et = ethyl
GCMS = gas chromatography-mass spectrometry
HPLC = high-performance liquid chromatography
HRMS = high-resolution mass spectrometry
i = iso-
Imid-H = imidazole
IR = infrared
KHMDS = potassium hexamethyldisilazide
LA = Lewis acid
LDA = lithium diisopropylamide
LG = leaving group
LiHMDS = lithium hexamethyldisilazide
mCPBA = meta-chloroperoxybenzoic acid
Me = methyl
Ms = mesyl
n = normal
NaHMDS = sodium hexamethyldisilazide
Napht = naphthyl
NMR = nuclear magnetic resonance
NOE = nuclear Overhauser effect
NOESY = nuclear Overhauser effect spectroscopy
Nuc = nucleophile
ODS = ozone-depleting substance

\( p = \textit{para} \)

PDC = pyridinium dichromate

PG = protecting group

Ph = phenyl

Pr = propyl

rt = room temperature

\( s = \textit{sec} \)

\( t = \textit{tert} \)

TBAF = tetrabutylammonium fluoride

TBDPS = \textit{tert}-butyldiphenylsilyl

TEA = triethylamine

TFA = trifluoroacetic acid

TFAA = trifluoroacetic anhydride

THF = tetrahydrofuran

TLC = thin layer chromatography

TMEDA = \textit{N},\textit{N},\textit{N}',\textit{N}'-tetramethylethylenediamine

TMSCl = trimethylsilyl chloride

TOF = time of flight

\( \text{Tol} = \textit{para}-\text{tolyl} \)

Ts = tosyl

TSA = toluenesulfonic acid

UV = ultraviolet
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Chapter 1: Diastereoselective Alkylations of Lithium Sulfenate Anions
1.0 Diastereoselective Alkylations of Lithium Sulfenate Anions

1.1 Introduction

1.1.1 Forward on Organosulfur Chemistry

Organosulfur species are organic molecules that contain sulfur atoms. From the time scientists isolated the first known organosulfur compounds centuries ago, these molecules have helped shape the history of humanity.\textsuperscript{1-5} Many organosulfur species are pivotal components of living systems, allowing cellular machinery to function unperturbed.\textsuperscript{1,6} In 1796, Lampadius accidentally isolated carbon disulfide (CS\textsubscript{2}) by heating pyrite (FeS\textsubscript{2}) with moist charcoal.\textsuperscript{2,7} Carbon disulfide has become an important chemical industrially, for instance in the synthesis of the cotton alternative semi-synthetic fiber rayon.\textsuperscript{8} Saccharin (1) has become an extremely prominent molecule in our diet as an artificial sweetener (Figure 1.1).\textsuperscript{9} However not all organosulfur molecules have been used to benefit humanity. Sulfur mustards (2) were used as a chemical weapon in both the first and second world wars to inflict severe burns and blistering and even death to the victim.\textsuperscript{10,11} Returning to beneficial compounds, allicin (3) is a molecule found in garlic, and is believed to be a naturally occurring antioxidant.\textsuperscript{12,13} Lipoic acid (4) is another naturally occurring organosulfur molecule involved in biochemical redox chemistry, wherein it oxidizes alcohols to the corresponding carbonyl compounds.\textsuperscript{1} S-Adenosylmethionine (5) is Nature’s methylating reagent, partaking in countless methyl transfer reactions.\textsuperscript{14} With such an essential role in industrial and biochemical processes, both new and old organosulfur species must continue to be studied. The organosulfur molecules
studied in this chapter are rare and unexplored reactive intermediates in synthetic organic chemistry, making their scientific probing well justified.

![Chemical structures](image)

**Figure 1.1. Some Important Organosulfur Species**

### 1.1.2 Sulfenate Anion Background Information

Sulfenate anions (RSO⁻) are an intriguing class of organosulfur compounds that have been historically scarce in synthetic chemistry.¹⁵ Interest in these reactive species has increased due to the newly realized existence and importance of sulfenate anions as intermediates in biological systems.¹⁶-²² Recently, several synthetic research groups have made developments in the study of these reactive intermediates.¹⁵ Sulfenic acids (RSOH) are the conjugate acids of sulfenates and, in theory, deprotonation delivers the corresponding sulfenate anion (Scheme 1.1).¹⁵ Sulfenates are relatively unstable to molecular oxygen and are converted to the corresponding sulfinates upon standing in air.²³
Scheme 1.1. Sulfenate Anions and Sulfenic Acids

Due to the instability of sulfenate anions, only a few have been isolated for characterization. Furukawa et al. isolated the sodium salt of 2-pyridinesulfenate in an oxygen free environment and used IR spectroscopy to observe a characteristic S-O stretch of 870 cm$^{-1}$. For comparison, the S-O stretch of an azetidinone sulfenic acid was observed as 770 cm$^{-1}$. A decrease in stretching frequency going from a sulfenate anion to its conjugate acid is consistent with having more double bond character in the S-O bond of the sulfenate. Downard et al. studied methanesulfenate anion $\text{6}$ in-silico using ab initio (MP2/6-31+G(d)//HF/6-31+G(d)) calculations (Figure 1.2). Sulfenate $\text{6}$ was predicted to possess an S-O bond length of 1.580 Å, which is between that of a sulfenic acid single S-O bond (1.679 Å) and the sulfoxide S-O bond of DMSO (1.485 Å).

Figure 1.2. Methanesulfenate Anion

Sulfenate anions are ambident nucleophiles and as such alkylation can occur at either the sulfur or oxygen atom depending on the identity of the electrophile.
(Scheme 1.2). Soft electrophiles like reactive alkyl halides (eg. BnBr or MeI) will alkylate at the softer sulfur atom,\textsuperscript{15,28} while hard electrophiles such as dimethyl sulfate alkylate the oxygen atom of the sulfenate.\textsuperscript{15,28}

\[
\text{R-S-O-CH}_3 \xrightarrow{(\text{CH}_3)_2\text{SO}_4} \xrightarrow{\text{BnBr}} \text{Bn-S-O-Bn}
\]

\textbf{Scheme 1.2. Alkylation Sites of Sulfenate Anions}

\textbf{1.1.3 Recent Progress in Sulfenate Anion Chemistry}

Sulfenate chemistry was reviewed nearly 10 years ago by O’Donnell & Schwan,\textsuperscript{15} so this introduction will focus primarily on literature contributions post-2004. Metzner et al. developed a convenient method to release sulfenates from 2-(trimethylsilyl)ethyl sulfoxides using a fluoride ion source (Table 1.1).\textsuperscript{29} Optimal conditions included using tetrabutylammonium fluoride (TBAF) (2 equiv.) in THF in the presence of 1.1 equiv. of benzyl bromide. Several aromatic sulfenates with different substituents were tolerated and the reaction sequence provided benzyl sulfoxides in good yields (Table 1.1, entries 1-4). A 2-pyridinesulfenate was alkylated cleanly with BnBr without any detection of pyridinium salt from competing nitrogen alkylation (Table 1.1, entry 5). Both alkenyl and alkynyl sulfenates were alkylated and the alkenyl sulfenate gave the corresponding sulfoxide with clean retention of the olefin geometry (Table 1.1, entries 6 and 7). Sulfenate release was attempted on a \textit{t}-butyl derivative, unfortunately the starting material remained unaffected by TBAF (Table 1.1, entry 8). The robustness of this substrate was attributed to the lack of resonance stabilization from the aliphatic \textit{t}-
butyl group necessary to delocalize negative charge build-up during fragmentation.\textsuperscript{29}

\textbf{Table 1.1. Synthesis of Benzyl Sulfoxides via Sulfenates}

\begin{center}
\begin{tabular}{|c|c|c|c|}
\hline
Entry & R & Time (min) & Yield (%) \\
\hline
1 & 4-BrC\textsubscript{6}H\textsubscript{4} & 20 & 84 \\
2 & 4-F\textsubscript{3}C\textsubscript{6}H\textsubscript{4} & 20 & 75 \\
3 & 2,6-Me\textsubscript{2}C\textsubscript{6}H\textsubscript{3} & 60 & 69 \\
4 & 2-naphthyl & 30 & 86 \\
5 & 2-pyridyl & 20 & 77 \\
6 & C=\text{Ct-Bu} & 30 & 66 \\
7 & C=CHMe & 30 & 49 \\
8 & \text{t-Bu} & 270 & 0 \\
\hline
\end{tabular}
\end{center}

Fluoride ion mediated sulfenate release has now been applied in the investigation of a proposed sulfenate intermediate in the leinamycin rearrangement (Scheme 1.3).\textsuperscript{16-19,30-33} Treatment of leinamycin analog 7 with TBAF causes the liberation of sulfenate intermediate 8. Sulfenate 8 attacks the proximal thioester moiety via the sulfenate oxygen to produce intermediate 9. Compound 9 then undergoes a cyclization involving the pendant olefin moiety to generate episulfonium ion 10, which is believed to be analogous to the leinamycin intermediate that alkylates DNA.
Attack by excess fluoride anion and methylation by diazomethane gave heterocycle 12 in good yield.\textsuperscript{19}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {7};
\node (b) at (1,0) {8};
\node (c) at (2,0) {9};
\node (d) at (0,-1) {10};
\node (e) at (1,-1) {11};
\node (f) at (2,-1) {12};
\node (g) at (1,-2) {CO\textsubscript{2}Me};
\node (h) at (0,-3) {$\text{MeLi, THF}$};
\node (i) at (1,-3) {$13$};
\node (j) at (2,-3) {$R-X$};
\node (k) at (2,-2) {$14$};
\node (l) at (2,-1) {$15$};
\node (m) at (1,0) {$\text{TBAF, THF}$};
\node (n) at (1,-1) {$\text{CH\textsubscript{2}N\textsubscript{2}}$};
\node (o) at (2,-2) {$\text{CO}_{2}\text{Me}$};
\node (p) at (1,0) {$\text{CO}_{2}\text{Me}$};
\node (q) at (2,0) {$\text{CO}_{2}\text{Me}$};
\node (r) at (2,-1) {$\text{CO}_{2}\text{Me}$};
\node (s) at (1,-3) {$\text{MeLi, THF}$};
\node (t) at (2,-3) {$\text{R-X}$};
\node (u) at (2,-2) {$14$};
\node (v) at (2,-1) {$15$};
\node (w) at (2,-0) {$16$};
\node (x) at (2,-2) {$\text{TMS}$};
\node (y) at (2,-1) {$\text{TMS}$};
\node (z) at (2,-0) {$\text{TMS}$};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.3. Leinamycin Rearrangement Model}

Perrio has developed an approach to aromatic sulenates through oxidation of the corresponding thiolates using a racemic \textit{N}-sulfonyloxaziridine 13 (Scheme 1.4).\textsuperscript{34-36} The procedure is operationally simple and provides sulfoxides via a novel paradigm.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {$\text{Ar-SH}$};
\node (b) at (1,0) {$\text{MeLi, THF}$};
\node (c) at (2,0) {$\text{Ar-SO}_{2}\text{Li}$};
\node (d) at (3,0) {$\text{R-X}$};
\node (e) at (0,-1) {$\text{Ar-SO}_{2}\text{Ph}$};
\node (f) at (1,-1) {$\text{Bu}$};
\node (g) at (2,-1) {$\text{Me}$};
\node (h) at (3,-1) {$13$};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.4. Oxidation of Aromatic Thiolates}

In 2004 Perrio et al. expanded this work using 13 to effect a highly chemoselective oxidation of dithioester enethiolates to sulenates (Table 1.2).\textsuperscript{36} The treatment of 14 with methyl lithium (MeLi) and subsequent oxidation with oxaziridine 13 led to the formation of sulenate 15 at -78 °C. Alkylation of 15 with methyl iodide at -78 °C led to the formation of ketene dithioacetal \textit{S}-oxide 16 as a 76:24 \((Z):(E)\) isomers.
mixture, which matched the selectivity of the initial deprotonation of 14 (Table 1.2, entry 1). The reaction was repeated but with rapid warming from -78 °C to rt in the presence of methyl iodide, which provided 16 in a decreased ratio of 54:46. The selectivity of the reaction was completely reversed to give the E isomer as the major product by performing the deprotonation/oxidation at -78 °C then warming to -15 °C before adding the electrophile (Table 1.2, entry 3). The reversal of selectivity was attributed to the initial formation of the kinetic (Z)-sulfenate following deprotonation/oxidation at low temperature. The (Z)-sulfenate is maintained at low temperature, so alkylation at -78 °C provides predominantly (Z)-16. An increase in temperature causes a isomerization of 15 to the thermodynamically more stable trans-sulfenate, which upon alkylation yields primarily (E)-16.

Table 1.2. Alkylation of Sulfenate 15

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>Mel (eq.)</th>
<th>(Z):(E)</th>
<th>deprotonation (Z):(E)a</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78 °C/5h in presence of Mel</td>
<td>5.0</td>
<td>76:24</td>
<td>75:25</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>rapid warming from -78 °C in presence of Mel</td>
<td>1.0</td>
<td>54:46</td>
<td>75:25</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>slow warming from -78 to -15 °C followed by Mel addition</td>
<td>1.2</td>
<td>13:87</td>
<td>75:25</td>
<td>80</td>
</tr>
</tbody>
</table>

a Determined by reaction of enethiolate with ethyl iodide
The thiolate oxidation method for sulenate generation was used in an interesting heterocyclic fragmentation to access 1-alkynyl sulenate anions.37 A selection of 1,2,3-thiadiazoles 17 were transformed to the corresponding 1-alkynyl sulfenates 18 upon treatment with methyllithium followed by oxidation with 13 (Scheme 1.5).37 Alkylation with a selection of alkyl halides (R’-X) provided the corresponding 1-alkynyl sulfoxides 19 in moderate to good yield (Scheme 1.5).37

Scheme 1.5. 1-Alkynesulfenate Anions via a Heterocyclic Fragmentation

The expansion of this work to oxidize the more nucleophilic alkanethiolates (RSLi, where R = alkyl) with N-sulfonyloxaziridine 13 failed to give the desired aliphatic sulfenate (RSOLi). Instead, the undesired product arising from transfer of two oxygens, the sulfinate salt (RSO₂Li), was isolated.38,39 The problem was remedied by the use of trans-(±)-2-tert-butyl-3-phenyl oxaziridine 20 which proved to be a more chemoselective reagent (Scheme 1.6). Oxaziridine 20 is a much weaker oxidizing agent than oxaziridine 13 so the problem of over oxidation of the aliphatic sulfenates 22 to their corresponding sulfinate salts was avoided (Scheme 1.6).39 The chemistry worked well to access the aromatic sulfoxide 23f as well as aliphatic sulfoxides 23a-e.
Scheme 1.6. Alkanesulfenates via Thiolate Oxidation

In 2005, a more general method was developed to release sulfenate anions from β-sulfinyl esters 24 (Table 1.3)\(^{40}\). Initial deprotonation of 24 by potassium t-butoxide generates an anion, which undergoes a retro-Michael reaction cleaving the S-C bond liberating a sulfenate anion. Subsequent sulfenate alkylation with reactive alkyl halides provided several sulfoxides 25 in excellent yield (Table 1.3)\(^{40}\). Tolyl and o-methoxyphenyl sulfenates were alkylated to the corresponding sulfoxides (Table 1.3, entries 1 & 2). Primary alkyl derivatives were also tolerated, as potassium methyl sulfenate and potassium n-butyl sulfenate alkylated smoothly (Table 1.3, entries 4 & 5)\(^{40}\). Potassium benzyl sulfenate provided the corresponding sulfoxide 25 in moderate yield possibly due to competing deprotonation of the acidic benzylic protons. Secondary alkyl and tertiary alkyl sulfenates were also alkylated in excellent yields (Table 1.3, entries 7 & 8)\(^{40}\).
Table 1.3. Sulfenate Anions via a Retro-Michael Addition Protocol

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tol</td>
<td>Et</td>
<td>BnBr</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>2-MeOC₆H₄</td>
<td>Et</td>
<td>MeI</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>2,6-Me₂C₆H₃</td>
<td>Et</td>
<td>BnBr</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Me</td>
<td>BnBr</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>nBu</td>
<td>Et</td>
<td>BnBr</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>Et</td>
<td>BnBr</td>
<td>57</td>
</tr>
<tr>
<td>7</td>
<td>cC₆H₁₁</td>
<td>Et</td>
<td>BnBr</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>tBu</td>
<td>Et</td>
<td>BnBr</td>
<td>79</td>
</tr>
</tbody>
</table>

Perrio was able to achieve a modest asymmetric sulfenate alkylation using a β-sulfinyl ester substrate 26 for sulfenate release (Scheme 1.7). Treatment of 26 with nBuLi/(−)-sparteine in toluene followed by the addition of methyl iodide at 45 °C gave sulfoxide 27 in 29% enantiomeric excess (ee). The alkaloid (−)-sparteine was the only chiral bidentate ligand that was evaluated. The temperature of -45 °C was optimal for achieving the highest ee. Lower temperatures (-78 °C) actually eroded the ee of the product. This effort was the first external ligand-controlled enantioselective alkylation of a sulfenate.
Perrio performed diastereoselective alkylations of (±)-[2.2]paracyclophane-4-sulfenate anion, which was liberated by the aforementioned retro-Michael addition chemistry (Scheme 1.8). In one example, potassium sulfenate 28 was liberated from sulfoxide 29, and alkylated with methyl iodide to give the corresponding sulfoxide 30 as a single diastereomer. The stereoaduction was proposed to result from the preferred conformer of sulfenate 28 having its S-O bond lying in the plane of the upper deck ring oriented toward the ortho hydrogen. Presuming a similar conformation in the transition state, alkylation occurs at the less hindered sulfur lone pair, the one protruding away from the lower deck ring (Scheme 1.8).

Conveniently, alkylation by sulfenate chemistry gives the complementary isomer 30 to an oxidation of sulfide 31 with oxaziridine 13, which gives sulfoxide 32 as the major diastereomer (Scheme 1.8).
Using the retro-Michael protocol, Perrio reported an unprecedented and conceptually novel route to enantioenriched sulfoxides by alkylating arenesulfenates in the presence of a Cinchona-derived phase-transfer catalyst 35 (Scheme 1.9). Presumably the released sodium sulfenate salt undergoes cationic exchange with the chiral ammonium salt 35 to afford a tight ion pair where enantiotopic discrimination of the sulfenate lone pairs can occur. The best ee that was achieved (ee = 59%, Scheme 1.9) came from the treatment of sulfinyl sulfone 33 with aqueous sodium hydroxide in a mixture of toluene and dichloromethane in the presence of methyl iodide and catalyst 35 (Scheme 1.9). The sulfanyl-activating group in 33 (pKa ~ 31) was crucial to the organocatalytic process as a more acidifying nitro analog (pKa ~ 17) furnished a faster reaction but gave a nearly racemic product. Switching electrophiles to more reactive benzyl bromides also
caused erosion of ee. Although the enantioselectivities are modest, this case marks the first organocatalytic alkylation of sulenate anions.

Scheme 1.9. Asymmetric Sulenate Alkylation Using a Phase-Transfer Catalyst

Madec & Poli developed a palladium-catalyzed allylic alkylation of sulenate anions to generate several allylic sulfoxides (Scheme 1.10).\textsuperscript{43,44} Using a Pd(0) catalyst in a biphasic system with potassium hydroxide as base, sulenates derived from sulfoxides 36 could be allylated to sulfoxides 37 in good yields (Scheme 1.10). Both secondary alkyl and aryl sulenates could be successfully allylated.\textsuperscript{43}

Scheme 1.10. Palladium-Catalyzed Allylic Alkylation of Sulenate Anions

Sulenate could also be allylated effectively using cyclopent-2-enyl acetate to give the corresponding sulfoxides 38, as depicted in Scheme 1.11.\textsuperscript{43} Tolyl and isopropyl sulfoxides 38a and 38c, respectively, were produced as \textasciitilde1:1 mixtures in both cases.
Interestingly, the bulkier naphthalene derivative 38b was obtained with an improved albeit modest dr of 70:30.\textsuperscript{43,44}

\[
\begin{align*}
\text{OAc} & + R'S\text{SO}_2\text{CO}_2\text{Bu} & \xrightarrow{[\text{Pd}(\text{C}_3\text{H}_5\text{Cl})_2\text{]}_2\text{ (2 mol %)}} & R'S\text{SO}_2\text{CO}_2\text{Bu} \\
\text{36a} & (R = \text{Tol}) & \xrightarrow{\text{dppe} (5 \text{ mol %})} & \text{38a (R = Tol, 65\%, dr = 50:50)} \\
\text{b} & (R = \text{Napht}) & \xrightarrow{\text{50\% aq. KOH, CH}_2\text{Cl}_2/\text{H}_2\text{O} (1:1)} & \text{b (R = Napht, 54\%, dr = 70:30)} \\
\text{c} & (R = \text{Pr}) & & \text{c (R = Pr, 43\%, dr = 55:45)}
\end{align*}
\]

**Scheme 1.11. Sulfenate Allylations with Cyclopent-2-enyl Acetate**

Similarily, Madec \& Poli achieved a palladium-catalyzed arylation of sulfenate anions with a selection of aryl iodides (Table 1.4).\textsuperscript{44,45} The reaction was achieved using a biphasic solvent system in combination with a Pd(0) catalyst and xantphos ligand. Several aromatic iodides were coupled to tolyl sulfenate including both \textit{p}- and \textit{o}-iodoanisole (Table 1.4, entries 2 \& 3). Several functional groups were tolerated on the aryl iodide including acetyl, nitro, and trifluoromethyl substituents (Table 1.4, entries 4-6). 2-Iodothiophene also provided its corresponding coupling product in excellent yield (Table 1.4, entry 7). An aspect of chemoselectivity was discovered when the reaction of 4-bromo-iodobenzene coupled solely at the iodine position without any concomitant formation of a bis-sulfoxide (Table 1.4, entry 8).\textsuperscript{44,45} The R’ group attached to the sulfenate was varied and 2-naphthalenesulfenate was coupled to \textit{p}-iodotoluene in good yield (Table 1.4, entry 9). Considering alkyl derivatives, benzyl and isopropyl sulfenates, could also be effectively coupled to \textit{p}-iodotoluene albeit in reduced yields (Table 1.4, entries 10 \& 11). Lastly, a non-aromatic iodide, (\textit{Z})-1-iodohex-1-ene, was coupled with tolyl sulfenate in moderate yield (Table 1.4, entry 12).\textsuperscript{45}
### Table 1.4. Palladium-Catalyzed Arylations of Sulfenate Anions

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R’</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeC₆H₄</td>
<td>4-MeC₆H₄</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC₆H₄</td>
<td>4-MeC₆H₄</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>2-MeOC₆H₄</td>
<td>4-MeC₆H₄</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>4-MeC(O)C₆H₄</td>
<td>4-MeC₆H₄</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>4-NO₂C₆H₄</td>
<td>4-MeC₆H₄</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>4-F₃CC₆H₄</td>
<td>4-MeC₆H₄</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>2-thienyl</td>
<td>4-MeC₆H₄</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>4-BrC₆H₄</td>
<td>4-MeC₆H₄</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>4-MeC₆H₄</td>
<td>2-naphthyl</td>
<td>79</td>
</tr>
<tr>
<td>10</td>
<td>4-MeC₆H₄</td>
<td>Bn</td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td>4-MeC₆H₄</td>
<td>iPr</td>
<td>42</td>
</tr>
<tr>
<td>12</td>
<td>1(\equiv)nBu</td>
<td>4-MeC₆H₄</td>
<td>33</td>
</tr>
</tbody>
</table>

Using the chemoselectivity of the reaction towards aryl iodides and concomitant generation of t-butyl acrylate during sulfenate liberation, a pseudo-domino type I sulfinylation/Mirozaki-Heck sequence was achieved.⁴⁴,⁴⁵ Cinnamate containing sulfoxide 39 was formed in moderate yield (Scheme 1.12).
Scheme 1.12. Pseudo-Domino Type I Sulfinylation/Mirozaki-Heck Sequence

Colobert et al. extended the work of Madec & Poli to include the Pd(0)-catalyzed coupling of tolyl sulfenate with several heteroaromatic iodides (two representative examples are shown in Scheme 1.13). In one case, heteroaryl iodide 40 was coupled cleanly to tolyl sulfenate to give sulfoxide 41 in excellent yield. Bis-sulfoxides such as 42 can be synthesized in good yield from the corresponding heteroaryl dihalide compounds 43 using this protocol.

Scheme 1.13. Palladium-Catalyzed Coupling of Tolyl Sulfenate with Heteroaromatic Halides

An enantioselective palladium-catalyzed arylation of sulfenate anions was recently described (Table 1.5). Release of a sulfenate anion with base in the presence of an
aryl iodide, a Pd(0) catalyst and a chiral Josiphos-type ligand (44) provided chiral sulfoxides 45. Tolyl sulfenate could be coupled to \( p \)-iodoanisole to give the corresponding sulfoxide in good yield and ee (Table 1.5, entry 1). In contrast, tolyl sulfenate coupling to \( o \)-iodoanisole provided the resulting sulfoxide in good yield but with no enantioselectivity (Table 1.5, entry 2).\(^{47}\) Coupling of tolyl sulfenate with \( p \)-trifluoromethyliodobenzene provided a sulfoxide in quantitative yield with good enantioselectivity (Table 1.5, entry 3). A 2-naphthalenesulfenate was also reacted with \( p \)-iodoanisole to give the resulting sulfoxide in good yield and enantioselectivity (Table 1.5, entry 4). Lastly, coupling with benzyl sulfenate was attempted, which provided the corresponding benzyl sulfoxide in good yield but with reduced selectivity (Table 1.5, entry 5).\(^{47}\)

**Table 1.5. Asymmetric Palladium-Catalyzed Arylations of Sulenate Anions**

<table>
<thead>
<tr>
<th>entry</th>
<th>( R )</th>
<th>( \text{Ar} )</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tol</td>
<td>4-MeOC(_6)H(_4)</td>
<td>83</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>Tol</td>
<td>2-MeOC(_6)H(_4)</td>
<td>78</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Tol</td>
<td>4-F(_3)CC(_6)H(_4)</td>
<td>98</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>2-Naphthyl</td>
<td>4-MeOC(_6)H(_4)</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>Tol</td>
<td>71</td>
<td>47</td>
</tr>
</tbody>
</table>
Madec & Poli exploited the existence of the allyl sulfoxide to allyl sulfenate ester equilibrium (Scheme 1.14) to generate sulfenate anions.\textsuperscript{44,48,49} As such, sulfenates were formed from allyl sulfoxides 46 by treatment with catalytic amounts of a Pd(0) complex and an appropriate nucleophilic species, capable of trapping the π-allyl palladium species thereby regenerating Pd(0). With Pd(0) and aryl sulfenate available in one-pot, another set of Ar-I coupling reactions successfully created diaryl sulfoxides 47.

\[
\begin{align*}
\text{Ar} & \quad \text{S} & \quad \text{O} & \quad \text{Ar} \\
\text{46} & \quad \text{Ar} & \quad \text{S} & \quad \text{O} & \quad \text{Ar} \\
\text{47} & \quad \text{Ar} & \quad \text{S} & \quad \text{O} & \quad \text{Ar} & \quad \text{Ar}' & \text{I} \\
\text{Pd(0)} & \quad \text{Pd} & \quad \text{Nu} & \quad \text{Nu} \\
\end{align*}
\]

**Scheme 1.14. Mechanism of Sulfenate Generation and Arylation from Allyl Sulfoxides**

By adding an aryl iodide to the reaction mixture, Madec & Poli were able to achieve the conversion of allyl sulfoxides 46 to aryl sulfoxides 47 via a pseudodomino palladium-catalyzed sulfenate generation/coupling process (Table 1.6).\textsuperscript{44,49} Using benzenesulfenate with \(p\)-iodoanisole or \(p\)-iodotoluene gave sulfoxides in acceptable yields (Table 1.6, entries 1 & 2). In contrast, the reaction of benzenesulfenate with the electron-withdrawing \(p\)-iodonitrobenzene gave the corresponding sulfoxide in poor yield (Table 1.6, entry 3). Using \(p\)-toluenesulfenate with iodoanisoles revealed an interesting trend: reaction yields decreased as the position of the methoxy group approached the iodine substituent (Table 1.6, entries 4-6). \(p\)-Toluenesulfenate was
also reacted with 4-trifluoromethyliodobenzene providing sulfoxide in satisfactory yield (Table 1.6, entry 7). A 2-naphthalenesulfenate also displayed reactivity with p-iodotoluene (Table 1.6, entry 8). Unfortunately, the reaction does not transcend to alkyl sulfenate systems as benzyl sulfenate underwent complete decomposition without any of the desired sulfoxide formed (Table 1.6, entry 9).

Table 1.6. Coupling of Aromatic Sulfenates Generated from Allyl Sulfoxides with Aryl Halides

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>Ar</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>4-MeOC₆H₄</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Tol</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>4-NO₂C₆H₄</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>Tol</td>
<td>4-MeOC₆H₄</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>Tol</td>
<td>3-MeOC₆H₄</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>Tol</td>
<td>2-MeOC₆H₄</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>Tol</td>
<td>4-F₃CC₆H₄</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>2-Naphthyl</td>
<td>Tol</td>
<td>49</td>
</tr>
<tr>
<td>9</td>
<td>Bn</td>
<td>4-MeOC₆H₄</td>
<td>0</td>
</tr>
</tbody>
</table>

In 2003 O'Donnell & Schwan developed a new addition/elimination protocol for the release of sulfenate anions from 2-sulfinyl acrylates 48 (Scheme 1.15). Adduct 49 is generated by nucleophilic attack at the sulfinyl α-carbon of 48. Adduct 49
undergoes a retro-Michael process cleaving the S-C bond and liberating the sulenate anion which is subsequently alkylated at sulfur.

![Diagram of the reaction mechanism](image)

**Scheme 1.15. Addition/Elimination Protocol for the Release of Sulenate Anions**

To fully explore the vastness of this newly discovered chemistry a series of 2-sulfinyl acrylates 48 were prepared via the conjugate addition of a thiol to methyl propiolate under basic conditions to yield the corresponding sulfide. Sulfides were immediately oxidized to give the corresponding 2-sulfinyl acrylates 48 in combined yields ranging from 47-87%. The β-sulfinyl acrylates (48) were typically isolated as a mixture of E and Z isomers; the isomeric ratio was a non-issue as experiments demonstrated that it did not affect subsequent sulenate anion generation. Sulfenates were generated by treating a THF solution of 2-sulfinyl acrylate with an alkoxide or thiolate nucleophile at -78 °C (Scheme 1.16). Following 5 to 20 minutes of stirring, sulenate anions were quenched by addition of a reactive alkyl halide (benzyl bromide or methyl iodide) at which time the reaction mixtures were allowed to slowly warm to room temperature overnight and worked up in the morning. The yields of the corresponding sulfoxides were construed as a measure of sulenate generation.
Scheme 1.16. General Protocol for Release and Capture of Sulfenate Anions from β-Sulfinyl Acrylates

Three different nucleophiles were initially evaluated: sodium methoxide, lithium cyclohexanolate, and lithium cyclohexanethiolate (Table 1.7). All three nucleophiles generated aromatic, medium and long chain alkyl, and sterically hindered alkyl sulfenates efficiently based on good yields of the corresponding sulfoxides, obtained after quench with benzyl bromide or methyl iodide (Table 1.7). Problems were encountered in generating/alkylating both methyl and benzyl sulfenates while using sodium methoxide as a nucleophile as yields were typically low and/or unreliable. Lithium cyclohexanolate gave an improved and reliable yield (75%) for the alkylation of methyl sulfenate with benzyl bromide but yields for the alkylation of benzyl sulfenate still remained low and irreproducible. Believing that deprotonation α to the sulfenate could be a competitive reaction, especially when using strongly basic alkoxide nucleophiles, using the more nucleophilic lithium cyclohexanethiolate as a nucleophile gave improved results: alkylation of benzyl sulfenate with benzyl bromide gave the corresponding sulfoxide in 75% yield. Another significant entry is the generation and alkylation of a disulfenate, which has an intriguing bifunctional structure with potential to be explored further as a metal chelating agent in the realm of organometallic complexation chemistry.
This work was pivotal because at the time there was no general means for the generation of alkyl sulfenates. The addition/elimination protocol was later extended to other substrates and surprisingly $n$-butyllithium proved to be quite useful as a nucleophile for the generation of a selection of arene- and alkanesulfenates (Table 1.8). Despite its inherent basicity, $n$-butyllithium even worked well for the sensitive benzyl sulfenate garnering a respectable 74% yield of the corresponding sulfoxide following benzyl bromide quench. Benzothiazole-2-sulfenate was also generated/alkylated by both $n$-butyllithium and lithium cyclohexanethiolate; the
latter being the more chemoselective reagent with little if any competing addition to the electrophilic benzothiazole. Further, lithium cyclohexanethiolate shows its chemoselectivity again in the generation of an ester-containing sulfenate; nucleophilic attack occurs at the desired carbon α to the sulfinyl moiety in starting sulfoxide and not at the carbonyl of the ethyl ester (Table 1.8).\textsuperscript{51}

**Table 1.8. Expansion of Scope using our Addition/Elimination Protocol**

<table>
<thead>
<tr>
<th>Nuc·M⁺</th>
<th>Sulfenate</th>
<th>R’X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Bu·Li⁺</td>
<td>p-TolSO·Li⁺</td>
<td>BnBr</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MeI</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>BnSO·Li⁺</td>
<td>BnBr</td>
<td>74</td>
</tr>
<tr>
<td>c-C₆H₁₁SO·Li⁺</td>
<td>BnBr</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>AcHN—SO·Li⁺</td>
<td>BnBr</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>N₃—SO·Li⁺</td>
<td>BnBr</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>S⁻·Li⁺</td>
<td>OEtOC(CH₂)₂—SO·Li⁺</td>
<td>2-BrC₆H₄CH₂Br</td>
<td>57</td>
</tr>
</tbody>
</table>

Recently, Verdu et al. achieved the diastereoselective synthesis of a chiral cysteine derived sulfenate (Table 1.9).\textsuperscript{52} Possessing a stereocenter that could be potentially used as a stereoinducer, the cysteinesulfenate was alkylated with a selection of alkyl halides to examine if good diastereoselectivities could be achieved. Optimization
revealed thiolates to be successful nucleophiles for the release of the
cysteinesulfenate with lithium cyclohexanethiolate as the nucleophile of choice
(Table 1.9). Product yields were fair to good with dr's ranging from good to
excellent for alkyations with benzyl bromides (Table 1.9, entries 1-9).52
Diastereoselectivities were only moderate for the alkylation of the cysteinesulfenate
with methyl iodide and allyl bromide (Table 1.9, entries 10 and 11). This is perhaps
due to the reduced steric bulk of the electrophile allowing alkylation to occur in a
less constrained or ordered transition state. In all cases the major β-amino sulfoxide
product was the \((R_C, R_S)\) diastereomer.52

**Table 1.9. Diastereoselective alkylations of a Cysteinesulfenate**

<table>
<thead>
<tr>
<th>Entry</th>
<th>RX</th>
<th>yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH₂Br</td>
<td>65</td>
<td>92:8</td>
</tr>
<tr>
<td>2</td>
<td>(p)-MeC₆H₄CH₂Br</td>
<td>75</td>
<td>92:8</td>
</tr>
<tr>
<td>3</td>
<td>(p)-BrC₆H₄CH₂Br</td>
<td>72</td>
<td>92:8</td>
</tr>
<tr>
<td>4</td>
<td>(m)-MeO₂C₆H₄CH₂Br</td>
<td>52</td>
<td>91:9</td>
</tr>
<tr>
<td>5</td>
<td>(m)-O₂NC₆H₄CH₂Br</td>
<td>66</td>
<td>89:11</td>
</tr>
<tr>
<td>6</td>
<td>(p)-NCC₆H₄CH₂Br</td>
<td>74</td>
<td>89:11</td>
</tr>
<tr>
<td>7</td>
<td>(o)-NCC₆H₄CH₂Br</td>
<td>53</td>
<td>89:11</td>
</tr>
<tr>
<td>8</td>
<td>(o)-BrC₆H₄CH₂Br</td>
<td>73</td>
<td>95:5</td>
</tr>
</tbody>
</table>
It is believed that lithium sulfenates can form internal complexes between the lithium of the sulfenate moiety and nitrogen atoms present in the molecule.\textsuperscript{34} To explore the possible role of lithium for observed stereoselectivity, alkylations of the cysteinesulfenate were performed in the presence of 12-crown-4 (12-c-4) to sequester the lithium counterion.\textsuperscript{53} The alkylation of the sulfenate with benzyl bromide following the addition of 2.5 equivalents of 12-c-4 gave a deteriorated dr value of 85:15, down from 92:8 when no 12-c-4 was present.\textsuperscript{52} With evidence for involvement of the lithium counterion in stereoselectivity, initial sulfenate anion internal complexation with the lithium counterion forming complex 50/51 was proposed (Scheme 1.17). Complex 50 is believed to be insignificant due to an unfavorable interaction between the equatorial ester and Boc group of the sulfenate. Complex 51 undergoes alkylation at the less sterically encumbered equatorial lone pair of the sulfenate complex leading to the major diastereomer with \((R_c, S_s)\) stereochemistry (Scheme 1.17).\textsuperscript{52}

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>o-HC(O)C(_6)H(_4)CH(_2)Br</td>
<td>58</td>
<td>93:7</td>
</tr>
<tr>
<td>10</td>
<td>Mel</td>
<td>51</td>
<td>83:17</td>
</tr>
<tr>
<td>11</td>
<td>Allyl bromide</td>
<td>60</td>
<td>83:17</td>
</tr>
</tbody>
</table>

\textbf{Scheme 1.17. Proposed Precoordination Complex Accounting for Diastereoselective Alkylations of a Cysteinesulfenate Anion}
Using a chiral amino alkyl group as a chiral auxiliary Perrio et al. achieved an extremely high diastereoselective alkylation of a sulfenate with benzyl bromide (Scheme 1.18). The role of the lithium counterion was underscored as addition of 12-c-4 to sequester lithium resulted in attenuated diastereoselectivity. Therefore an intramolecular precoordination complex 52 was proposed, which was similar to the one proposed for the alkylation reactions of cysteinesulfenate anions (Schemes 1.17 & 1.18). In complex 52, benzylaion presumably occurs at the less hindered sulfur lone pair directed away from the methyl group of the chiral auxiliary (Scheme 1.18).

Scheme 1.18. Asymmetric Sulfenate Alkylation Using an Amino Alkyl Chiral Auxilliary

Lithium (E)-1-alkenesulfenates can be accessed via a base induced rearrangement of thiirane S-oxides (Scheme 1.19). Following the stereoselective generation of lithium E-alkenyl sulfenates several subsequent transformations can be achieved. Primarily lithium diisopropylamide (LDA), lithium hexamethyldisilazide (LiHMDS) or methyllithium lithium bromide complex are used to stereoselectively generate a variety of trans-sulfenates (R = alkyl, cycloalkyl, benzyl, phenyl) which can be alkylated with BnBr or MeI to the corresponding (E)-1-alkenyl sulfoxides.
selection of $(E)$-1-alkenylthiosilanes could be accessed via the reduction of the corresponding trans-sulfenates in-situ with lithium aluminum hydride (LiAlH$_4$) to the corresponding $(E)$-1-alkenethiolate anions followed by subsequent capture with electrophilic chlorosilanes.$^{57}$ The $(E)$-1-alkenylthiosilanes can be used in carbon-carbon bond forming reactions and complement the more readily accessible $(Z)$-1-alkenylthiosilanes.$^{58,59}$ Other key intermediates accessed from 1-alkenesulfenates are $N,N$-bis(trimethylsilyl)alkenesulfenamides which are generated by treatment of the corresponding sulfenate with TMSCl and LiHMDS.$^{56}$ Intermediate $N,N$-bis(trimethylsilyl)alkenesulfenamides were converted to the corresponding $(E)$-1-alkenylthiophthalimides which underwent transamination then oxidation to generate a series of $(E)$-1-alkenesulfonamides.$^{60,61}$ Finally, a series $(E)$-1-alkenesulfenimines could be accessed via the treatment of $(E)-N,N$-bis(trimethylsilyl)-1-alkenesulfenamides with catalytic tetrabutylammonium fluoride (TBAF) and the corresponding carbonyl compound.$^{62}$ In summary 1-alkenesulfenates can be generated stereoselectively and can undergo a series of subsequent transformations to yield a variety of different types of compounds.
1.1.4 Proposed Diastereoselective Sulfenate Alkylations with Chiral Iodides

Several research programs have synthesized chiral sulfoxides using stereoselective sulfenate anion alkylations.\textsuperscript{34,40-42,47,52} However, there is only one literature report of the use of a chiral electrophile to effect a stereoselective alkylation of a sulfenate.\textsuperscript{63} 1-Anthraquinonyl sulfenates were alkylated by chiral (R)- and (S)-configured sulfonium salts to yield the consequent sulfoxides (Scheme 1.20). However, modest yields and poor enantioselectivities were obtained.\textsuperscript{63}
Scheme 1.20. Enantioselective Sulenate Alkylations Using Chiral Sulfonium Salts

In line with the paradigm of Kobayashi, the goal of the current investigation is to achieve stereoselective alkylations of sulenates using stereoinduction from enantiopure amino iodides to produce chiral β-amino sulfoxides (Scheme 1.21). Chiral β-amino sulfoxides in general, have proven value as organocatalysts, ligands in organometallic chemistry, synthetic building blocks, and medicinally relevant molecules. Chiral amino iodides can be accessed from cheap and readily available amino acids via a reduction/protection/iodination sequence. The Boc blocking group was chosen to protect iodides due to its past success in the diastereoselective alkylations of cysteinesulenates (Table 1.9).

Scheme 1.21. Retrosynthesis of Chiral β-Amino Sulfoxides
The ability of certain lithium sulfenate anions to form intramolecular precoordination complexes between the sulfenate oxygen, the lithium counterion and a nitrogen atom within the molecule has been proposed to give rise to the diastereoselectivity observed in alkylation reactions of these molecules (Schemes 1.17 & 1.18). Through the use of a chiral iodide [e.g., (S)-53] a similar precoordination complex may be possible in an intermolecular sense as depicted in Scheme 1.22. The formation of transition state II may be achieved by initial lithium-mediated precomplexation between the lithium sulfenate anion and chiral amino iodide (S)-53. Other low energy transition states could also be accessible through changing conformation or configuration of the precluding precoordination complex. Presumably differences in relative stabilities of the possible transition states would account for observed diastereoselectivity in the β-amino sulfoxide products. For instance, transition state II possesses the R’ group in a sterically unencumbered equatorial position making it more stable than a configurational isomer containing the R’ group in a sterically hindered axial position. As outlined in the remainder of this chapter, several types of sulfenates were alkylated with good diastereoselectivities including arene-, alkane- and trans-1-alkenesulfenates. The mechanism of stereoinduction was investigated by varying the identity of solvent, sulfenate counterion identity, and the structure of the chiral electrophiles 53. Competition experiments were also completed with sulfenates and electrophiles to explore the interplay of reactivity between a sulfenate and electrophile.
In Chapter 3, the chiral \((E)-1\)-alkenyl \(\beta\)-amino sulfoxides derived from sulfenate alkylation chemistry are manipulated further by a cyclization reaction to give chiral thiazine \(S\)-oxide products, which contain three different stereocenters in one molecule (Scheme 1.23). The six-membered heterocycles were obtained successfully in excellent yields and selectivity, so a synthetic plan was developed to access two chiral pyrrolidine alkaloids involving a Ramberg-Bäcklund reaction (RBR) with extrusion of sulfur dioxide as a key synthetic step (see Chapter 3). Many of the existing halogenating reagents used to achieve the RBR were unobtainable; therefore a new and more economical halogenating reagent was developed for the RBR (see Chapter 2).

**Scheme 1.23. Further Elaboration of \((E)-1\)-Alkenyl \(\beta\)-Amino Sulfoxides**

**Scheme 1.22. Hypothetical Mode of Stereoinduction via Transition State II**
1.2 Results and Discussion

1.2.1 Diastereoselective Alkylations of Arenesulfenate Anions

The project began with the attempt at alkylating arenesulfenates with chiral amino iodides 53 using the addition/elimination protocol from β-sulfinyl acrylate esters 48.\textsuperscript{50,51} Synthesis of arenesulfenate precursor β-sulfinyl acrylate esters 48 has been reported previously and as such only novel compounds are included in the experimental.\textsuperscript{51} Synthesis of the chiral amino iodides 53 used in the present study was accomplished by well-established literature procedures from the corresponding amino acid precursors 56 and their optical purity was affirmed by optical rotation (Chart 1.1).\textsuperscript{3,94-96} The synthesis of Boc-protected amino alcohols 54 was achieved using a one-pot reduction/protection procedure (Chart 1.1). Iodination of 54 with triphenylphosphine, imidazole and iodine gave the chiral amino iodides 53.\textsuperscript{97}

Chart 1.1 Synthesis of Chiral Amino Iodides 53
Optimization experiments focused on the alkylation of lithium p-toluenesulfenate with chiral iodide (S)-53a (Scheme 1.24). Treatment of the corresponding β-sulfinyl acrylate ester 48a with a nucleophile at low temperature released p-toluenesulfenate anion. Addition of a solution of electrophile (S)-53a provided the alkylated sulfenate anion as β-amino sulfoxide 57a (Scheme 1.24).

\[
\begin{array}{c}
\text{Tol} \quad \text{S} \quad \text{CO}_2\text{Me} \quad \text{M}^+ \text{Nuc}^- \quad \text{THF, } -78^\circ \text{C, 15 min} \\
\text{Tol} \quad \text{S} \quad \text{OM} \\
\text{Bn} \quad \text{NHboc} \\
\end{array}
\]

\[
\begin{array}{c}
\text{Tol} \quad \text{S} \quad \text{O} \quad \text{Bn} \quad \text{NHboc} \\
\end{array}
\]

**Scheme 1.24. Reaction of p-Toluenesulfenate with iodide (S)-53a**

Initially, sulfenate anions were released using methoxide and cyclohexanethiolate nucleophiles at low temperature. After ~10-15 min of stirring at -78 °C, a solution of (S)-53a in THF was added to the sulfenate mixture (Table 1.10). The reaction mixture was stirred for 2-3 h at -78 °C then allowed to slowly warm to room temperature, often stirring overnight. The effect of metal counterion identity on selectivity is evident: lithium sulfenates are more selective with dr values approaching ~9:1 whereas potassium and sodium sulfenates gave lower dr values (Table 1.10, entries 1-5). Further evidence for the importance of the lithium counterion in stereoselectivity comes from an experiment where 12-crown-4 (12-c-4) was added to the sulfenate prior to alkylation. The expectation was that the 12-c-4 would sequester lithium. The result was a deterioration of dr from 90:10 to 78:22 (Table 1.10, entries 1 & 6), which underscores the importance of the lithium counterion in achieving satisfactory selectivity.
Lithium sulfenates appear to be less reactive than sodium sulfenates with yields being lower for lithium sulfenates (Table 1.10, comparing entries 1 versus 2 or 4 versus 5). Surprisingly, generation of lithium sulfenates with \(n\)-butyllithium provided excellent selectivity of 91:9 and a good yield of 87% (Table 1.10, entry 7). The feeling is that \(n\)-butyllithium is not necessarily a superior reagent but that it ensures the lack of hydroxylic species which may decrease both yield and selectivity. It should be noted that \(n\)-butyllithium is added as a solution in hexanes whereas lithium methoxide is administered as a solution in methanol. To provide evidence for this theory, methanol was introduced following sulfenate generation with \(n\)-butyllithium but prior to the addition of the electrophilic \((S)-53a\). The resulting formation of \(57a\) occurred with decreased yield and selectivity (Table 1.10, entry 8). Also, worth mentioning is the fact that in all trials, \(\beta\)-amino sulfoxide \(57a\) was obtained as the major product, possessing \(\text{syn}\) stereochemistry at the S-O and \(\beta\) C-Bn bonds. Diastereomeric ratios were determined by chiral HPLC or analysis of the \(^1\text{H}\) NMR spectra of the diastereomeric mixture.

### Table 1.10. Preliminary Diastereoselective Alkylation Reactions of Sulfenates with Chiral Electrophiles

<table>
<thead>
<tr>
<th>entry</th>
<th>(M^+\cdot\text{Nuc})</th>
<th>solvent</th>
<th>(\text{dr})</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li(^+)\cdot\text{OMe}</td>
<td>THF</td>
<td>90:10</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>Na(^+)\cdot\text{OMe}</td>
<td>THF</td>
<td>78:22</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----</td>
<td>-----</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>K(^{+})·OMe</td>
<td>THF</td>
<td>58:42</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>Li(^{+})·SC(<em>{6})H(</em>{11})</td>
<td>THF</td>
<td>91:9</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>Na(^{+})·SC(<em>{6})H(</em>{11})</td>
<td>THF</td>
<td>70:30</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>Li(^{+})·OMe</td>
<td>THF/12-c-4(^{a})</td>
<td>78:22</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>Li(^{+})·Bu</td>
<td>THF</td>
<td>91:9</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>Li(^{+})·Bu</td>
<td>THF/MeOH(^{b})</td>
<td>68:32</td>
<td>61</td>
</tr>
</tbody>
</table>

\(^{a}\)4 equiv of 12-crown-4 were added to the alkylation mixture, \(^{b}\)0.2 equiv of MeOH was introduced following sulfenate generation.

Using the optimized conditions, alkylations of lithium \(p\)-toluenesulfitenate were expanded by varying the substituent of the chiral amino iodide (Table 1.11). For the most part yields remained good and dr's remained close to the value of ~9:1. When \(R\) = Ph dr's were much lower at 73:27 while the yield remained good at 79\% (Table 1.11, entry 6). The phenyl group is well recognized for its larger steric demands compared to benzyl, isopropyl, etc.\(^{98}\) Presumably, the size of the phenyl group prevents the rigorous alignment required by the transition state (i.e. transition state II in Scheme 1.22) to achieve a high degree of stereoselectivity. Also, of note is that the reaction is stereospecific from the perspective of the chiral electrophiles \(53\): \((R)\)-53 delivers an opposite configuration to the sulfinyl unit of the \(\beta\)-amino sulfoxide \textit{ent-57a} than does its enantiomer \((S)\)-53.
### Table 1.11. Diastereoselective Sulfenate Alkylations Varying R- of the Electrophile

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>53</th>
<th>R</th>
<th>product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>57</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-53a</td>
<td>Bn</td>
<td><img src="TolS---CO2Me" alt="O:R:O" /></td>
<td>57a</td>
<td>91:9</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>(S)-53b</td>
<td>Me</td>
<td><img src="TolS---NHBOc" alt="O:R:O" /></td>
<td>57b</td>
<td>87:13</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>(S)-53c</td>
<td>iPr</td>
<td><img src="TolS---NHBOc" alt="O:R:O" /></td>
<td>57c</td>
<td>90:10</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>(S)-53d</td>
<td>iBu</td>
<td><img src="TolS---NHBOc" alt="O:R:O" /></td>
<td>57d</td>
<td>91:9</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>(S)-53e</td>
<td>CH₂OTBDPS</td>
<td><img src="TolS---NHBOc" alt="O:R:O" /></td>
<td>57e</td>
<td>87:13</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>(R)-53g</td>
<td>Ph</td>
<td><img src="TolS---NHBOc" alt="O:R:O" /></td>
<td>57g</td>
<td>73:27</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>(R)-53h</td>
<td>Et</td>
<td><img src="TolS---NHBOc" alt="O:R:O" /></td>
<td>57h</td>
<td>92:8</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>(R)-53a</td>
<td>Bn</td>
<td><img src="TolS---NHBOc" alt="O:R:O" /></td>
<td>ent-57a</td>
<td>94:6</td>
<td>81</td>
</tr>
</tbody>
</table>

<sup>a</sup>Product drawn and numbered is major isomer obtained, <sup>b</sup>Major isomer listed first.

Next, the reaction scope was expanded by alkylating a selection of lithium arenesulfenates with (S)-53a or (R)-53a as the electrophile (Table 1.12). Results were similar with generally good yields and selectivity approaching 9:1. Benzenesulfenate could be alkylated with (S)-53a or (R)-53a to the corresponding β-amino sulfoxides 57i and ent-57i, respectively in good diastereoselectivity (Table 1.12, entries 1 & 8). The o-bromobenzenesulfenate gave a reduced yield (64%) when n-butyllithium was employed as a nucleophile due to competing lithium-halogen exchange (Table 1.12, entry 4). A change to lithium methoxide allowed for
sulfoxide 57l to be synthesized cleanly although with lower dr (Table 1.12, entry 5). Lithium 2-pyridyl sulenate was alkylated to give 57m in good yield but with reduced diastereoselectivity (Table 1.12, entry 6). Lithium 2-pyridyl sulenate likely adopts an internal nitrogen to lithium complexation, mirroring the behavior of alkoxides derived from 2-pyridyl carbinols. Such an arrangement would be expected to hinder the precomplexation with (S)-53, obstructing the formation of intermolecular coordination possibly required for asymmetric induction. Alkylation of n-hexyl sulenate with (S)-53a was attempted but no reaction occurred at low temperature (Table 1.12, entry 7).

Table 1.12. Diastereoselective Sulenate Alkylations Varying R- of the Sulenate Anion

<table>
<thead>
<tr>
<th>Entry</th>
<th>53</th>
<th>R</th>
<th>Producta</th>
<th>57</th>
<th>drb</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-53a</td>
<td>Ph</td>
<td>O S: Bn</td>
<td>57i</td>
<td>91:9</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>(S)-53a</td>
<td>o-CH₃C₆H₄</td>
<td>57j</td>
<td>87:13</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(S)-53a</td>
<td>2-Napht</td>
<td>57k</td>
<td>88:12</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(S)-53a</td>
<td>o-BrC₆H₄</td>
<td>57l</td>
<td>90:10</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(S)-53a</td>
<td>o-BrC₆H₄</td>
<td>57lₜ</td>
<td>83:17</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(S)-53a</td>
<td>2-Pyridyl</td>
<td>57m</td>
<td>63:37</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(S)-53a</td>
<td>n-hexyl</td>
<td>59b</td>
<td>-</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
The major diastereomer of β-amino sulfoxides 57 could be isolated in their pure form usually after a single recrystallization from a mixture of ethyl acetate and hexanes. The assignment of the absolute configurations of 57i (RS, SC) and ent-57i (SS, RC) was based on an identical match of optical rotations to known literature values of 57i and ent-57i. Rotations for other β-amino sulfoxides 57 were consistent with the general trends of (RS, SC)- and (SS, RC)-amino sulfoxides.

In order to gauge whether or not asymmetric alkylation was occurring via a hydrogen bonding interaction between the iodide 53 and sulfenate, an alkylation reaction was carried out with lithium toluenesulfenate and pyrrolidine iodide (S)-53f. (Scheme 1.25). The resulting β-amino sulfoxide 57f was isolated in moderate yield and excellent diastereoselectivity. A single crystal X-ray structure analysis confirmed the configuration of the major isomer to be (RS, SC), consistent with the stereochemistry of other alkylations with (S)-amino iodides 53. The high diastereoselectivity indicates that H-bonding is not a significant requirement for diastereoselection, thereby leaving for consideration the interaction of the sulfenate lithium with active Lewis bases of the electrophile in this and the other examples.
1.2.2 Diastereoselective Alkylations of Alkanesulfenate Anions

Recalling entry 7 of Table 1.12, which indicates that $n$-hexyl sulfenate proved unreactive with (S)-53a, it was thought that increasing reaction temperature might provide the desired diastereoselective alkylations of aliphatic sulfenates with iodides 53. However, it has previously been established that aliphatic sulfenates generated by the addition/elimination protocol decompose if not alkylated near or below 0 °C.\(^\text{102}\) In contrast, Perrio’s retro-Michael protocol has been employed to generate sulfenates at temperatures $> 70$ °C.\(^\text{45,47}\) Switching to Perrio’s protocol for sulfenate generation a series of β-sulfinyl ester substrates 58 were synthesized using standard methodology.\(^\text{40}\) Lithium hexamethyldisilazide (LiHMDS) was chosen to release lithium benzyl sulfenate from the corresponding β-sulfinyl ester 58 because the lithium counterion had already been linked to high diastereoselectivities for the aromatic congeners (Table 1.13). Examining entries 1-3 of Table 1.13 demonstrates the onset of some alkylation as reaction temperatures approach 50 °C. Gratifyingly, refluxing for 2-3 h provided β-amino sulfoxide 59a in moderate yield with a dr = 85:15 (Table 1.13, entry 4). Entries 5-7 of Table 1.13 display the alkylation outcome of three other alkyl sulfenates with iodide (S)-53 exposed to the same reaction conditions. Compared to the values achieved by the

Scheme 1.25. Sulfenate Alkylation with Proline Derived Iodide (S)-53f

\[
\text{Scheme 1.25. Sulfenate Alkylation with Proline Derived Iodide (S)-53f}
\]
arenesulfenates from Tables 1.11 and 1.12, there is erosion of both yield and selectivity. However, lithium cyclohexanesulfenate did give suitable results, comparable with many aryl systems, providing sulfoxide 59d in 78% yield as a 91:9 diastereomeric mixture (Table 1.13, entry 7). In conclusion, although heating the reaction mixture did achieve the desired alkylations, this came at a cost of good diastereoselection. The low reactivity of 1-alkanesulfenates was surprising as they were expected to be more reactive than their corresponding unsaturated analogs. Given that the alkanesulfenates collectively failed to provide satisfactory results, this aspect of the investigation was no longer pursued.

**Table 1.13. Diastereoselective Alkylations of Aliphatic Sulfenate Anions**

<table>
<thead>
<tr>
<th>entry</th>
<th>temp</th>
<th>R</th>
<th>59</th>
<th>yield (%)</th>
<th>dr&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78 °C</td>
<td>Bn</td>
<td>59a</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>-78 °C to 0 °C</td>
<td>Bn</td>
<td>59a</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>-78 °C to 50 °C</td>
<td>Bn</td>
<td>59a</td>
<td>tr</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>-78 °C to reflux</td>
<td>Bn</td>
<td>59a</td>
<td>54</td>
<td>85:15</td>
</tr>
<tr>
<td>5</td>
<td>-78 °C to reflux</td>
<td>n-hexyl</td>
<td>59b</td>
<td>42</td>
<td>82:18</td>
</tr>
<tr>
<td>6</td>
<td>-78 °C to reflux</td>
<td>t-butyl</td>
<td>59c</td>
<td>63</td>
<td>78:22</td>
</tr>
<tr>
<td>7</td>
<td>-78 °C to reflux</td>
<td>c-hexyl</td>
<td>59d</td>
<td>78</td>
<td>91:9</td>
</tr>
</tbody>
</table>

<sup>a</sup>dr's were determined by chiral HPLC for 59a-59c and by <sup>1</sup>H NMR for 59d  
<sup>b</sup>The configuration of the major diastereomer is shown in the equation above and was assigned to be (R<sub>s</sub>, S<sub>c</sub>) for 59a, 59c, and 59d and (S<sub>s</sub>, S<sub>c</sub>) for 59b (due to a change in
atomic priority) through comparison of optical rotation trends set by the aromatic congeners.

1.2.3 Diastereoselective Alkylations of 1-Alkenesulfenate Anions

Given the success with the aromatic sulfenates demonstrated above, it was decided to investigate the alkylation chemistry of trans-1-propenesulfenate 61, an entity which like the aryl sulfenates, also contains a conjugated sulenate moiety (Scheme 1.26). Further, lithium trans-1-propenesulfenate (61) can be generated with complete stereoselectively over the cis isomer from treatment of anti-methyl thiirane S-oxide (60a) with LiHMDS or MeLi•LiBr.55,56 Therefore, the alkylation with a chiral iodide such as (S)-53 has the potential to be doubly diastereoselective regarding the olefin geometry and the sulfur configuration of the resulting β-amino sulfoxides 62.

Scheme 1.26. General Release and Alkylation of Sulfenate 8

Table 1.14 displays the optimization attempts for the alkylation reaction of trans-1-propenesulfenate with chiral iodide (S)-53a. As above with arenesulfenates, the lithium counterion provided superior dr’s compared to sodium or potassium and also the best yields (Table 1.14, entries 1-3). The diastereoselectivity of the reaction remained relatively unchanged while reaction temperature was varied or if MeLi•LiBr was employed as the base. (Table 1.14, entries 4 & 5). The practical aspects of generating alkenesulfenates from thiirane S-oxides allows for the
variation of solvent identity. Due to solubility issues the electrophile was always presented in THF solution, but *trans*-1-propenesulfenate could be generated in a selection of different solvents. The use of 1,4-dioxane lowered alkylation yields while increasing the dr to ~9:1 (Table 1.14, entry 6). In contrast, DMSO failed to provide any significant amount of sulfoxide 62a (Table 1.14, entry 7). Shifting to a less polar solvent, pentane maintained the good dr of ~9:1 while improving the reaction yield (Table 1.14, entry 8). Finally, the use of diethyl ether as the solvent provided the desired sulfoxide 62a in 81% with good dr (Table 1.14, entry 9). As was the case for the alkane- and arenesulfenates, the major isomer 62a formed contains the S-O and β C-C bond in a *syn* relationship to one another. When alkylation were performed in a solvent system containing less polar solvents possessing a cation coordination propensity weaker than that of THF, the dr’s of the resulting sulfoxide 62a were improved compared to dr’s when solely THF was used. Presumably, the weaker solvent coordination facilitates asymmetric induction through the formation of a transition state involving coordination between the sulfenate and electrophile. Moreover, minimized solvent coordination may shorten the length of the lithium-oxygen ionic bond in the sulfenate, resulting in a tighter more compact transition state and ultimately improved selectivity.
Table 1.14. Optimization of Diastereoselective Alkylations of 1-Propenesulfenate

<table>
<thead>
<tr>
<th>entry</th>
<th>base&lt;sup&gt;a&lt;/sup&gt;</th>
<th>solvent</th>
<th>temp</th>
<th>yield (%)</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiHMDS</td>
<td>THF</td>
<td>-78 °C to rt</td>
<td>68</td>
<td>84:16</td>
</tr>
<tr>
<td>2</td>
<td>NaHMDS</td>
<td>THF</td>
<td>-78 °C to rt</td>
<td>62</td>
<td>76:24</td>
</tr>
<tr>
<td>3</td>
<td>KHMDS</td>
<td>THF</td>
<td>-78 °C to rt</td>
<td>31</td>
<td>73:27</td>
</tr>
<tr>
<td>4</td>
<td>MeLi•LiBr&lt;sup&gt;c&lt;/sup&gt;</td>
<td>THF</td>
<td>-78 °C to rt</td>
<td>70</td>
<td>87:13</td>
</tr>
<tr>
<td>5</td>
<td>LiHMDS</td>
<td>THF</td>
<td>-40 °C to rt</td>
<td>77</td>
<td>86:14</td>
</tr>
<tr>
<td>6</td>
<td>LiHMDS</td>
<td>1,4-dioxane/THF (25:1)</td>
<td>rt</td>
<td>54</td>
<td>90:10</td>
</tr>
<tr>
<td>7</td>
<td>LiHMDS</td>
<td>DMSO/THF(12:1)</td>
<td>rt</td>
<td>tr</td>
<td>--</td>
</tr>
<tr>
<td>8</td>
<td>LiHMDS</td>
<td>pentane/THF(6:1)</td>
<td>-78 °C to rt</td>
<td>70</td>
<td>89:11</td>
</tr>
<tr>
<td>9</td>
<td>LiHMDS</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O/THF (4.5:1)</td>
<td>-78 °C to rt</td>
<td>81</td>
<td>90:10</td>
</tr>
</tbody>
</table>

<sup>a</sup> in THF unless otherwise indicated  
<sup>b</sup> dr established by chiral HPLC  
<sup>c</sup> In ether  
<sup>d</sup> configuration of major diastereomer shown was obtained from comparison of optical rotation values of arenesulfenates products

Using the optimized protocol with ether as the solvent, alkylations were attempted with a selection of substituted thirane S-oxides 60 and amino iodides 53. In most cases, satisfactory yields could be obtained even when the molar equivalents of 53 were reduced from 2.0 to ~1.1-1.2. Many entries exhibit dr's near or exceeding 9:1 and all dr's are ≥ 8:2. Bulkier substituents on the sulfenate β-carbon (c-hexenyl, t-
butyl, phenethyl) generally gave products with the higher dr’s of ~9:1. The only exception was when phenyl iodide \((R)-53g\) was employed, which as was the case for arenesulfenates above, provided sulfoxide \(62g\) with a modest dr of 84:16. Smaller substituents on the iodide also seemed to cause reduced dr’s, as seen in the synthesis of sulfoxide \(62b\).

**Chart 1.2. Reaction Scope of Diastereoselective 1-Alkenesulfenate Alkylations**

\[
\begin{align*}
62a & 81\%, \text{ dr} = 90:10 \\
\text{ent-62a} & 78\%, \text{ dr} = 90:10 \\
62b & 67\%, \text{ dr} = 82:18 \\
62c & 86\%, \text{ dr} = 80:20 \\
62d & 65\%, \text{ dr} = 87:13 \\
62e & 84\%, \text{ dr} = 89:11 \\
62f & 71\%, \text{ dr} = 93:7 \\
62g & 65\%, \text{ dr} = 84:16 \\
62h & 71\%, \text{ dr} = 95:5 \\
62i & 60\%, \text{ dr} = 92:8 \\
62j & 84\%, \text{ dr} = 92:8
\end{align*}
\]

\(a\) dr’s were determined by \(^1\text{H}\) NMR analysis except for \(62a\) and \(\text{ent-62a}\) (chiral HPLC)

The stereochemical outcome of this reaction was firmly established by x-ray diffraction analysis of the major diastereomeric product sulfoxide \(\text{ent-62a}\).
Configurations of all other β-amino sulfoxides 62 were assigned by analogy to ent-62a or by matching optical rotation values to trends established for the arenesulfenate alkylation products 57.

1.2.4 Sulfenate Anion Alkylation Competition Experiments

The nature of the electrophile has usually not been assessed in simple sulfenate alkylation reactions. Prior chemistry has for the most part focused on the generation of sulfenates, which in some cases possessed a chiral substituent. Alkylations are then often completed with a molar excess of highly reactive electrophiles like primary halides or benzyl bromide.36,37,106-108 The fact that sulfenate anions are significantly reactive with iodides 53 even when < 2 equiv. are used is surprising given the steric hindrance of the electrophiles. Therefore, a group of sulfenate competition reactions were performed to establish the sulfenate reactivity of (S)-53a in relation to other commonly employed electrophiles (Table 1.15).4,51 Both lithium toluenesulfenate and sulfenate 61 reacted at a faster rate with amino iodide (S)-53a than with nBuI (Table 1.15, entries 1 & 2). Ultimately, benzyl bromide proved to be a more reactive reagent than (S)-53a in a competition experiment for the alkylation of lithium toluenesulfenate as no amino sulfoxide was detected in the crude reaction mixture (Table 1.15, entry 3). The outcomes of these competition experiments (entries 1 & 2) clearly support some sort of rate-accelerating feature of iodides like (S)-53a, and nitrogen coordination between lithium and the sulfenate oxygen may account for (S)-53a being more reactive than a simple primary halide with lithium sulfinates. In contrast, the pyrrolidine iodide (S)-53f was slower to
react with lithium toluenesulfenate than nBuI (Table 1.15, entry 4). The reduced reactivity of (S)-53f compared to (S)-53a may be a consequence of increased steric encumbrance for the pyrrolidine electrophile. However, the possibility of the hydrogen atom of the carbamate moiety of (S)-53a having a rate-increasing role cannot be ruled out. Finally, in competition reactions between TolSOLi and 2-pyrSOLi, TolSOLi proved to be the more reactive sulfenate for alkylations with both BnBr and (S)-53a (Table 1.15, entries 5 & 6). Along with providing amino sulfoxide 57m with poor diastereoselectivity (Table 1.12, entry 6), lithium 2-pyridinesulfenate was slow to alkylate compared to lithium toluenesulfenate when using both chiral amino iodide (S)-53a and a reactive alkyl halide, benzyl bromide. As mentioned previously, it is entirely possible that lithium 2-pyridinesulfenate adopts an intramolecular nitrogen-to-lithium coordination that hinders the formation of an intermolecular precoordination complex with (S)-53a, which is responsible for the increase in rate and improved diastereoselection. Further, the nitrogen ring system of lithium 2-pyridinesulfenate is inductively electron-withdrawing which may be the reason for decreased reactivity of this sulfenate with benzyl bromide compared to lithium toluenesulfenate.

### Table 1.15. Competitive Sulfenate Alkylation Reactions

<table>
<thead>
<tr>
<th>entry</th>
<th>sulfenate (eq.)</th>
<th>E-I (eq.)</th>
<th>alk-X (eq.)</th>
<th>ratio</th>
<th>$k_{rel}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TolSOLi (1)</td>
<td>(S)-53a (2)</td>
<td>nBuI (10)</td>
<td>1:1.2</td>
<td>~4</td>
</tr>
<tr>
<td>2</td>
<td>61 (1)</td>
<td>(S)-53a (2)</td>
<td>nBuI (10)</td>
<td>1.4:1</td>
<td>~7</td>
</tr>
<tr>
<td>3</td>
<td>TolSOLi (1)</td>
<td>(S)-53a (5)</td>
<td>BnBr (5)</td>
<td>TolS(O)Bn</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TolSOLi (1)</td>
<td>(S)-53f (2)</td>
<td>nBuI (10)</td>
<td>TolS(0)Bn</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>------------</td>
<td>-------------</td>
<td>-----------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>TolSOLi (1) &amp; 2-pyrSOLi (5)</td>
<td>--</td>
<td>BnBr (2.5)</td>
<td>TolS(0)Bn</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>TolSOLi (5) &amp; 2-pyrSOLi (5)</td>
<td>(S)-53a (1)</td>
<td>--</td>
<td>57a</td>
<td></td>
</tr>
</tbody>
</table>

^a see Experimental Section for a description of these experiments ^b ratio of products with E-containing sulfoxide initially listed. The entry of a single compound means only that product was detected. ^c obtained by adjusting the ratio for relative equivalents of competitive reactant. No entry suggests a reactivity difference of ≥50 times.

### 1.2.5 Proposed Model for Observed Stereoiduction

Given that the major products of the β-amino sulfoxides synthesized by sulfenate alkylation consistently possess the S-O bond and β C-R bond in a syn relationship to one another, a model can be described addressing the observed selectivity (Tables 1.5-1.7, Chart 1.2). Past models explaining diastereoselective sulfenate alkylations with internal stereoiduction have invoked an intramolecular precooordination between the lithium of the sulfenate and the lone pair on a nitrogen atom. Given that the lithium counterion appears to play a key role in achieving high dr’s (up to 95:5) (Tables 1.11-1.13, Chart 1.2), and that electrophiles 53 possess some sort of rate-accelerating feature (Table 1.15, entries 1 & 2), an intermolecular precooordination between the sulfenate lithium and the nitrogen of 53 could account for observed results (Figure 1.3). Assuming the role of Li-N complexation a lithium sulfenate (R'SOLi) and (S)-53 could form a 6-membered precooordination complex leading to any of the transition states I, II, III, or IV (Figure 1.3). Transition states I and II deliver the major syn-β-amino sulfoxide, while transition states III and IV provide the minor anti-diastereomer. Transition state I features a major
destabilizing eclipsing interaction between the leaving iodide atom and the large R group of the amino iodide. The Boc group is also eclipsing the R group of (S)-53. The other major destabilizing feature of I is the R' group of the sulfenate occupying an axial position, which imparts 1,3-diaxial destabilization with the hydrogen atom of (S)-53. For the above reasons the population of I is believed to be relatively minimal compared with transition state II, a ring flip of the former. Transition state II possesses the R' group of the sulfenate in an equatorial position, so the 1,3-diaxial interaction present in I has been removed. Although, the R substituent of (S)-53 now occupies an axial position, there are no substituents or hydrogen's in place to develop a destabilizing 1,3-diaxial interaction. Further, the leaving iodide in II now eclipses the hydrogen of (S)-53 rather than the larger R as in I, so this source of destabilization is reduced. A transition state such as II is the lowest energy structure, so alkylation to deliver the observed major β-amino sulfoxide isomer likely occurs via this relative energy minimum (Figure 1.3).

By simply switching the positions of the R’ group on the sulfenate, one can evaluate transition states III and IV which deliver the minor β-amino sulfoxide diastereomer. Transition state IV possesses the R’ group of the sulfenate and the R substituent of (S)-53 contributing a major destabilizing 1,3-diaxial interaction, therefore transition state IV is believed to the least significant. A ring flip manipulation of IV provides III which possesses both the R substituent of the sulfenate and the R’ group of the (S)-53 in equatorial positions, so no major 1,3-diaxial interactions are present. However, as in transition state I, structure III has the leaving iodide atom eclipsing
the R group of (S)-53, a destabilizing interaction believed to be the source of asymmetric induction. Structure II should be more stable than III because although both structures are deficient of significant 1,3-diaxial interactions, II lacks the R group and iodide eclipsing interaction. In conclusion, the lowest energy alkylation pathway should be through transition state II, which provides the experimentally observed syn-β-amino sulfoxide diastereomer (Figure 1.3).

**Figure 1.3. Possible Transition States for the Alkylations of Sulfenates with Chiral Amino Iodides 53**
1.2.6 Sulfenate Alkylation as a Method for accessing β-Amino Sulfoxides

The sulfenate protocol is for the synthesis of \((R_S,S_C)\) and \((S_S,R_C)\) \(\beta\)-substituted \(\beta\)-amino sulfoxides. When the sulfenate substituent is aryl or 1-alkenyl, the dr’s are generally near 9:1. The yields and dr’s of the alkyl sulfoxides are less compelling and that family of compounds has less applicability going forward and as such, will not be part of the remaining discussion. There are several existing methods in the literature with which to synthesize chiral \(\beta\)-amino sulfoxides and a number of the major protocols are summarized in Scheme 1.27 below.

![Scheme 1.27. Previous Routes to Chiral β-amino Sulfoxides](image)

The most efficient methods for the preparation of enriched \(\beta\)-amino alkyl or aryl sulfoxides appear to be two from the Garcia Ruano group.\(^{101,109}\) One key contribution involves the Lewis acid mediated DIBAL reduction of \(N\)-benzyl protected \((R)\)-\(p\)-tolyl 2-iminoalkyl sulfoxides (path B, Scheme 1.27).\(^{109}\) That reduction delivers exclusively the \((R_S, R_C)\)-amino sulfoxides, generally in good yields. Although the sulfenate alkylation protocol is not as effective with regards to
asymmetric induction the sulfenate products provide the complementary $(R_s, S_C)$-β-amino sulfoxides to Garcia Ruano’s reduction method.

Using the sulfenate method provides sulfoxide $57g$ with limited stereoselectivity (Table 1.11, entry 6). For amino sulfoxide substrates with aryl groups on the sulfoxide ($R’ = Ar$) and also $\alpha$ to the amino group ($R = Ph$), an alternative protocol by Garcia Ruano is far superior to sulfenate alkylation.$^{101}$ The reaction of $\text{(S)}$-benzylidine-$p$-toluenesulfinamide with $(R)$- or $(S)$-methyl $p$-tolyl sulfoxide (path $A$, Scheme 1.27) delivers the corresponding $(R_s, R_C)$ or $(R_s, S_C)$ versions of $57g$, respectively, albeit bearing $p$-toluenesulfinyl rather than Boc nitrogen protection. Although the $\alpha$-sulfinyl anion addition protocol employs two chiral influences (a chiral sulfoxide and chiral sulfinamide), it gives the best yields and selectivities, particularly for the “matched” pair of reactants, which provide the $(R_s, R_C)$ isomer in 99% yield with $>99:1$ dr.$^{101}$

The Garcia Ruano methods begin with a chiral sulfoxide and deliver good yields and dr’s for selected β-amino sulfoxides of certain configurations.$^{101}$ Further, two chiral influences are sometimes required to achieve optimal dr’s in the β-amino sulfoxide products. The sulfenate method fulfills a function for synthetic access to selected target β-amino sulfoxides often with complementary configurations to Garcia Ruano’s methods. Further, the sulfenate method only uses the influence of one chiral center to achieve selectivity.$^{109}$

Conjugate additions of amines to chiral $\alpha,\beta$-unsaturated sulfoxides is the method depicted in path $C$ (Scheme 1.27).$^{89,110-114}$ This methodology is quite ineffective at
delivering β-amino sulfoxides because α,β-unsaturated sulfoxides show limited reactivity to amines. Often conjugate additions require prolonged reaction times (~20 days!) or prolonged heating to achieve only modest diastereoselectivities.\textsuperscript{110,112}

A more representative evaluation of asymmetric sulfenate alkylation reactions is accomplished by comparing the alkylations using iodides 53 with existing sulfoxidation methods (path D, Scheme 1.27). Chemists targeting β-amino sulfoxides have used sulfoxidation of β-aminosulfides extensively and, in essence, instinctively. In many cases, dr’s fail to exceed 60:40.\textsuperscript{66,68,76-78,82,90-93,114-126} Although high dr’s are rarely achieved by sulfoxidation, there are two general papers that perform simple oxidation creating sulfoxides similar to 57 generated by sulfenate alkylation chemistry.\textsuperscript{100,124} In a communication, the Skarzewski group outlines the diastereoselective oxidation of simple chiral amino sulfides using NaOCl/KBr/cat. TEMPO.\textsuperscript{124} In a follow-up full paper, the authors outline additional noteworthy oxidations, offer thorough characterization of the sulfoxides, and mention the low diastereoselectivity of NaIO\textsubscript{4} and MCPBA oxidations.\textsuperscript{100}

In the Skarzewski papers, the authors prepare β-amino sulfoxides in good yields, with high dr’s such as 85:15, 94:6,\textsuperscript{124} 98:2, and 92:8.\textsuperscript{100} Some of the lower dr ratios were found at 53:47 or 64:36, which are lower dr’s than even the most inefficient sulfenate alkylation examples.\textsuperscript{100} Most importantly, the major isomers were the complement to sulfenate derived β-amino sulfoxides being (R\textsubscript{s}, R\textsubscript{c}) or (S\textsubscript{s}, S\textsubscript{c}) diastereomers in every sulfoxidation example. Among the other rare examples of
oxidation reactions delivering high diastereoselectivity, the MCPBA oxidation of protected S-alkylated cysteine gave high yields of the corresponding \((R_s, R_C)\) amino sulfoxides.\(^{127}\) Similarly an enzyme-catalyzed oxidation protocol also brings about the \((R_s, R_C)\) isomer.\(^{128}\) Again, the complementarity of the sulfenate protocol delivering the complementary \(\text{syn-}\beta\)-amino sulfoxide is underscored upon comparison. It should be mentioned many of the high dr's reported in the literature are isolated examples. The arenesulfenate substitution reactions exhibit significantly more uniformity of results across all the examples studied compared with sulfoxidation protocols. As a methodology, the arenesulfenate substitution appears to hold more generality than oxidation protocols, at least based on the amino acid derived electrophiles studied.

Olefinic \(\beta\)-amino sulfoxides 62 are all new compounds, and the synthesis of close analogues of 62 by way of sulfide oxidation has not been explored; no comparison of methodologies is possible. There is one example of 1-propenethiolate reaction with serinyl chloride hydrochloride,\(^{92}\) but the ratio of sulfinyl isomers obtained by way of subsequent oxidation was not even reported. Other examples of oxidations of \((S)\)-1-alkenyl cysteine derivatives are also known, but either the existence of two sulfinyl isomers was not recognized,\(^{129,130}\) or low dr's were obtained.\(^{52,131}\) Indeed, in one case, the authors suggest the use of an alternative to the asymmetric oxidation protocol to achieve superior diastereoselectivity.\(^ {131}\)

In the current work, the overall transformation of thiirane S-oxide to \((E)\)-1-alkenyl \(\beta\)-aminoalkyl sulfoxides 62 is an example of one-pot double diastereoselection. The
thiirane S-oxide ring-opening gives exclusively the (E)-1-alkenesulfenate, while the ensuing sulenate substitution delivers products 62, with at least 4:1 dr and many products exhibiting a dr close to 9:1. Given the insignificant dr’s of the oxidation reactions the S-1-alkenyl cysteine derivatives, it is unlikely that oxidation of sulfide precursors of β-amino sulfoxides 62 will demonstrate significant asymmetric induction. Furthermore, 1-alkenesulfenates are actually easier to prepare than 1-alkenethiolates, as they do not require reducing metal conditions.\textsuperscript{92,132-135} The sulenate methodology provides compounds 62 with good dr’s and should be viewed as a preferred methodology on its own merits and because of the few alternatives available.

1.3 Conclusion

In conclusion, the alkylation of sulfenates with chiral amino iodides 53 to generate β-amino sulfoxides proved to be an effective method as yields and dr’s were both synthetically useful. In many cases, the stereochemistry of the product β-amino sulfoxides was complementary to the configurations of β-amino sulfoxides synthesized by way of existing protocols. Further, the diastereoselective alkylations of sulenate anions provides a conceptually novel paradigm to access target β-amino sulfoxides. Sulfenates remain relatively unexplored molecules in synthetic organic chemistry, yet are now being realized as important intermediates in biological systems.\textsuperscript{16-19} Therefore, the knowledge gained in the present study about the reactivity of sulenate anions may one day be applied to further our understanding of such biological environments.
With the trans-olefinic β-amino sulfoxides 62 in hand, subsequent chemistry was envisioned to use these unique molecules as chiral building blocks to access other intriguing organic molecules (Scheme 1.28). An asymmetric intramolecular aza-Michael reaction of 62 followed by oxidation of the resulting sulfoxide could provide the corresponding 3,5-substituted thiomorpholine S,S-dioxide. A subsequent Ramberg-Backlund reaction (RBR) with loss of sulfur dioxide lends access to 5-membered pyrroline compounds which are useful synthetic building blocks themselves and open the door to access chiral pyrrolidines. Certain halogenating reagents required for the RBR are listed as ozone-depleting substances (ODS) and as such are environmentally destructive and nearly impossible to obtain. The negative characteristics of these RBR reagents presented a significant hurdle to overcome in undertaking the chemistry in Scheme 28. However, the aforementioned problems also offered a significant opportunity to develop a new reagent to achieve Ramberg-Bäcklund chemistry. Therefore before attempting the cyclization chemistry within Scheme 1.28, a new more economical and environmentally benign method for the RBR was developed and is the subject of Chapter 2.

Scheme 1.28. Further Elaboration of 62
1.4 Experimental

1.4.1 General Experimental

Melting points are uncorrected. Infrared (IR) spectra were obtained on a FT-IR spectrometer as a neat film. NMR spectra for $^1$H NMR and $^{13}$C NMR were recorded at 600 and 150.9 MHz or 400 and 100.6 MHz, or 300 and 75 MHz respectively, in CDCl$_3$ unless otherwise noted. $^1$H NMR and $^{13}$C NMR chemical shifts are referenced to CHCl$_3$ or tetramethylsilane and are recorded in parts per million (ppm). Tetrahydrofuran (THF) was freshly distilled from benzophenone and sodium. All chemicals were obtained from commercial sources unless otherwise noted. MCPBA was obtained commercially and was dried and calibrated with benzyl sulfide before use. The LiHMDS used was a 1M THF solution unless noted otherwise. All air and water sensitive reagents were transferred via oven-dried nitrogen-purged syringes into flame-dried flasks under an inert nitrogen atmosphere. Flash chromatography was performed on 230–400 mesh Type 60 Å silica gel. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm, extra hard layer, 60 Å F254 glass-backed silica gel plates. Microwave reactions were carried out in a CEM Discover S-class reactor. Microwave reactions were carried out in vessels equipped with a Teflon cap. The temperature of the reaction mixture was monitored using a surface sensor. The dynamic method with maximum power 300W, 250 psi setting for maximum pressure and without powermax option was used. (Caution! Cardiac pacemakers require magnets to control their operation during checkout. Some danger exists if a pacemaker is positioned in close proximity to the instrument
cavity.) GC−MS experiments were performed using a Factor Four column (30 m length × 0.25 mm × 0.25 μm thickness). HPLC experiments were performed using a Chiralcel OJ-H or OD-H (0.46 cm × 25 cm) column with i-PrOH/hexane as the eluant.

1.4.2 Synthesis of Sulfenate Anion Precursors and Amino Iodide Electrophiles

The synthesis of known β-arylsulfinyl acrylate esters 48 has been reported previously.3,50,136 Homochiral amino iodides 53 were prepared as previously described.94,96 Thiirane S-oxides 60 used in this thesis were prepared and purified as previously described.137,138

1.4.3 Synthesis of Aryl β-Amino Sulfoxides

**General Procedure for Preparation of Aryl β-Amino Sulfoxides 57.**

2-Carbomethoxyethenyl aryl sulfoxide (1.0 equiv) was dissolved in THF (1 mL/0.1 mmol) under nitrogen and stirred at −78 °C. To the sulfoxide was added nBuLi (1.6 M/hexanes, 1.0 equiv) via syringe. Following 5–10 min of stirring, a solution of the chiral iodide (2.0 equiv) in THF (4 mL/mmol) at −78 °C was added via syringe to the sulfenate. The mixture was stirred at −78 °C for 3–4 h and then allowed to slowly warm to rt overnight. Solvent was removed under reduced pressure, and diastereomers were isolated by flash chromatography using EtOAc/hexanes as the eluent. Diastereomeric ratios were determined by HPLC using iPrOH/hexanes as the eluent. The major diastereomer was purified by recrystallization from EtOAc/hexanes. β-Amino sulfoxide yields were derived from 2-
carbomethoxyethenyl sulfoxides. The absolute stereochemistry of the major product is listed as part of the compound names.

**(Rs, 2S)-N-Boc-1-Phenyl-3-(p-tolylsulfinyl)propan-2-amine (57a)**

\[
\begin{align*}
\text{A mixture of 2-carbomethoxyethenyl } p\text{-tolyl sulfoxide (0.100 g, } 0.446 \text{ mmol) in THF (3 mL), } n\text{BuLi (0.279 mL), (S)-53a (0.322 g, 0.992 mmol) in THF (3 mL) afforded a diastereomeric mixture of } \beta\text{-amino sulfoxides 57a (87%, 0.145 g, } dr = 91:9) \text{ following flash chromatography (30\% EtOAc/hexanes); HPLC (5\% } i\text{-PrOH/hexanes, 0.4 mL/min flow rate): 17.67 min (major), 21.62 min (minor); The major diastereomer was isolated via recrystallization from EtOAc/hexanes. Major isomer: mp 141-142 °C; } ^1\text{H NMR (300 MHz, CDCl}_3) \delta 7.45 (d, } J = 8.2 \text{ Hz, 2H), 7.33-7.20 (m, 7H), 5.62 (br d, } J = 5.7 \text{ Hz, 1H), 4.21 (br m, 1H), 3.23 (m, 1H), 3.06-2.85 (m, 3H), 2.40 (s, 3H), 1.44 (s, 9H); } ^13\text{C NMR (100.6 MHz, CDCl}_3) \delta 155.5, 141.7, 140.5, 137.6, 130.1, 129.4, 128.7, 126.8, 123.8, 79.5, 60.2, 49.9, 39.8, 28.4, 21.4; IR (neat) cm}^{-1}: 3276, 3029, 2976, 2926, 2926, 1709, 1525, 1495, 1365, 1270, 1252, 1170, 1044, 1014; [\alpha]^{25}_D +120.6 (c = 0.9, CHCl}_3); \text{ Anal. calcd for } C_{21}H_{27}NO_S: \text{ C, 67.53; H, 7.29; Found: C, 65.53; H, 7.41. Minor isomer, partial characterization: } ^1\text{H NMR (400 MHz, CDCl}_3) \delta 4.86 (br s, 1H), 2.41 (s, 3H), 1.42 (s, 9H); } ^13\text{C NMR (100.6 MHz, CDCl}_3) \delta 155.2, 141.7, 140.4, 137.6, 130.1, 129.5, 128.6, 124.2, 123.8, 79.6, 61.4, 49.9, 39.8, 28.3, 21.5.}
\end{align*}
\]

**(Ss, 2R)-N-Boc-1-Phenyl-3-(p-tolylsulfinyl)propan-2-amine (ent-57a)**

\[
\begin{align*}
\text{A mixture of 2-carbomethoxyethenyl } p\text{-tolyl sulfoxide (0.100 g, }
\end{align*}
\]
0.446 mmol) in THF (3 mL), nBuLi (0.279 mL), (R)-53a (0.322 g, 0.992 mmol) in THF (3 mL) afforded a diastereomeric mixture of β-amino sulfoxides ent-57a (84%, 0.139 g, dr = 92:8) following flash chromatography (30% EtOAc/hexanes); HPLC (10% i-PrOH/hexanes, 0.4 mL/min flow rate): 12.61 min (major), 15.84 min (minor); The major diastereomer was isolated via recrystallization from EtOAc/hexanes. Major isomer: mp 141-143 °C. Spectral data as above for 57a; $[\alpha]_{D}^{25} -120.8$ (c = 0.2, CHCl$_3$); Anal. calcd for C$_{20}$H$_{25}$NO$_3$S: C, 67.53; H, 7.29; Found: C, 67.48; H, 7.40.

(Rs, 2S)-N-Boc-1-([p-Tolylsulfanyl]propan-2-amine (57b)

A mixture of 2-carbethoxyethenyl p-tolyl sulfoxide (0.100 g, 0.446 mmol) in THF (3 mL), nBuLi (0.279 mL), (S)-53b (0.254 g, 0.892 mmol) in THF (3 mL) afforded a diastereomeric mixture of β-amino sulfoxides 57b (81%, 0.070 g, dr = 88:12) following flash chromatography (30% EtOAc/hexanes); HPLC (2% i-PrOH/hexanes, 0.5 mL/min flow rate): 23.73 min (major), 28.50 min (minor); The major diastereomer was isolated via recrystallization from EtOAc/hexanes. Major isomer: mp 141-142 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.52 (d, $J$ = 8.2 Hz, 2H), 7.33 (d, $J$ = 8.2 Hz, 2H), 5.49 (br s, 1H), 4.21 (sept, $J$ = 6.7 Hz, 1H), 2.92-2.89 (m, 2H), 2.41 (s, 3H), 1.44 (s, 9H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 155.1, 141.7, 140.7, 130.1, 123.9, 79.4, 63.4, 44.19, 28.4, 21.4, 20.4; IR (neat) cm$^{-1}$: 3251, 3047, 2975, 2929, 2872, 1708, 1528, 1496, 1365, 1271, 1252, 1172, 1087, 1070, 1028; $[\alpha]_{D}^{25} +224.3$ (c = 0.4, CHCl$_3$); Anal. calcd for C$_{15}$H$_{23}$NO$_3$S: C, 60.58; H, 7.79; Found: C, 60.70; H, 8.00. Minor isomer, partial characterization: $^1$H
NMR (400 MHz, CDCl₃) δ 5.15 (br s, 1H) ¹³C NMR (100.6 MHz, CDCl₃) δ 155.1, 141.7, 140.7, 130.1, 123.9, 79.4, 63.4, 44.19, 28.4, 21.4, 20.4

(Rs, 2S)-N-Boc-3-Methyl-4-(p-tolylsulfinyl)butan-2-amine (57c)

A mixture of 2-carbomethoxyethenyl p-tolyl sulfoxide (0.100 g, 0.446 mmol) in THF (3 mL), nBuLi (0.279 mL), (S)-53c (0.266 g, 0.892 mmol) in THF (3 mL) afforded a diastereomeric mixture of β-amino sulfoxides 57c (71%, 0.101 g, dr = 90:10) following flash chromatography (30% EtOAc/hexanes); HPLC (5% i-PrOH/hexanes, 0.4 mL/min flow rate): 20.07 min (major), 25.46 min (minor); The major diastereomer was isolated via recrystallization from EtOAc/hexanes. Major isomer: mp 141-142 ⁰C; ¹H NMR (300 MHz, CDCl₃) δ 7.53 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 5.20 (br d, J = 7.5 Hz, 1H), 3.79 (m, 1H), 3.01-2.92 (m, 2H), 2.42 (s, 3H), 2.14 (m, 1H), 1.45 (s, 9H); 0.97 (d, J = 6.6 Hz, 6H); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.4, 141.5, 140.9, 130.0, 123.9, 79.3, 60.8, 53.0, 31.9, 28.4, 21.4, 19.4, 18.8; IR (neat) cm⁻¹: 3240, 3028, 3004, 2967, 2928, 2874, 1704, 1530, 1365, 1259, 1170, 1118, 1043, 1013, 764, 750; [α]D²⁵ +232.8 (c = 0.3, CHCl₃); Anal. calcd for C₁₀H₁₆NO₃S: C, 66.82; H, 7.01; Found: C, 66.90; H, 6.96.

Minor isomer, partial characterization: ¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, J = 7.7 Hz, 2H), 4.89 (br d, J = 9.0 Hz, 1H), 1.44 (s, 9H); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.4, 141.8, 141.0, 130.0, 124.4, 79.5, 61.9, 51.7, 32.2, 28.4, 21.4, 19.4, 17.8.

(Rs, 2S)-N-Boc-4-Methyl-1-(p-tolylsulfinyl)pentan-2-amine (57d)

A mixture of 2-carbomethoxyethenyl p-tolyl sulfoxide (0.100 g,
0.446 mmol) in THF (3 mL), nBuLi (0.279 mL), (S)-53d (0.291 g, 0.892 mmol) in THF (3 mL) afforded a diastereomeric mixture of β-amino sulfoxides 57d (92%, 0.138 g, \(dr = 91:9\)) following flash chromatography (30% EtOAc/hexanes); HPLC (2% i-PrOH/hexanes, 0.3 mL/min flow rate): 15.62 min (major), 20.20 min (minor); The major diastereomer was isolated via recrystallization from EtOAc/hexanes.

Major isomer:
mp 98-100 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.52 (d, \(J = 7.9\) Hz, 2H), 7.32 (d, \(J = 7.9\) Hz, 2H), 5.31 (br s, 1H), 4.07 (br m, 1H), 3.01-2.87 (m, 2H), 2.41 (s, 3H), 1.74 (m, 1H), 1.68 (m, 2H), 1.45 (s, 9H), 0.952 (d, \(J = 6.4\) Hz, 3H) 0.947 (d, \(J = 6.3\) Hz, 3H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 155.3, 141.6, 140.9, 130.0, 123.9, 79.3, 62.6, 46.3, 43.0, 28.4, 25.0, 22.7, 22.2, 21.4; IR (neat) cm\(^{-1}\): 3265, 3038, 2957, 2927, 2869, 1709, 1527, 1365, 1270, 1171, 1105, 1042, 1014, 809; \([\alpha]_D^{25}\) +235.6 (c = 0.8, CHCl\(_3\));

Anal. calcd for C\(_{18}\)H\(_{29}\)NO\(_3\)S: C, 63.68; H, 8.61; Found: C, 63.80; H, 8.67. Minor isomer, partial characterization: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.91 (br s, 1H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 155.2, 141.6, 141.0, 130.0, 124.2, 79.6, 64.0, 45.6, 43.9, 28.4, 24.7, 22.6, 21.9, 21.4.

**\((R_s, 2S)\)-N-Boc-O-TBDPS-1-Hydroxy-3-(p-tolylsulfinyl)propan-2-amine (57e)**

A mixture of 2-carbomethoxyethenyl p-tolyl sulfoxide (0.100 g, 0.446 mmol) in THF (3 mL), nBuLi (0.281 mL), (S)-53e (0.481 g, 0.892 mmol) in THF (3 mL) afforded a diastereomeric mixture of β-amino sulfoxides 57e (84%, 0.206 g, \(dr = 87:13\) by NMR integration) following flash chromatography (30% EtOAc/hexanes). The major diastereomer was isolated via recrystallization from EtOAc/hexanes. Major isomer: mp 109–110 °C; \(^1\)H NMR (400...


MHz, CDCl\textsubscript{3}) \delta 7.67-7.65 (m, 4H), 7.51 (d, J = 8.2 Hz, 2H), 7.45-7.36 (m, 6H), 7.31 (d, 
J = 8.2 Hz, 2H), 5.63 (br d, J = 6.8 Hz, 1H), 4.24 (br m, 1H), 3.90 (m, 2H); 3.13-3.11 (m, 1H), 3.00-2.97 (m, 1H), 2.41 (s, 3H), 1.44 (s, 9H), 1.08 (s, 9H); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}) \delta 155.2, 141.7, 140.9, 135.6, 132.9, 130.1, 129.9, 128.0, 123.9, 79.6, 64.7, 59.1, 49.4, 28.4, 21.5, 19.3; IR (neat) cm\textsuperscript{-1} 3276, 3071, 3049, 2999, 2961, 2930, 2982, 2858, 1709, 1494, 1427, 1391, 1364, 1276, 1248, 1171, 1111, 1087, 1027, 910, 809; [\alpha]\textsubscript{D}\textsuperscript{25} +96.8 (c = 5.4, CHCl\textsubscript{3}). Anal. calcd for C\textsubscript{31}H\textsubscript{41}NO\textsubscript{4}SSi: C, 67.47; H, 7.49. Found: C, 67.30; H, 7.60. Minor isomer, partial characterization: \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 4.96 (br s, 1H), 2.39 (s, 3H), 1.40 (s, 9H), 1.04 (s, 9H); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}) \delta 155.1, 140.9, 139.9, 135.5, 132.7, 130.0, 129.9, 128.0, 125.0, 79.6, 64.7, 59.0, 49.3, 28.4, 26.7, 21.4, 19.3.

tert-Butyl 2-(p-tolylsulfinylmethyl)pyrrolidine-1-carboxylate (57f).

A mixture of 2-carbomethoxyethenyl p-tolyl sulfoxide (0.100 g, 0.446 mmol) in THF (3 mL), nBuLi (0.279 mL), (S)-\textsuperscript{53f} (0.277 g, 0.892 mmol) in THF (3 mL) afforded a diastereomeric mixture of \beta-amino sulfoxide \textit{57f} (61%, 0.087 g, \textit{dr} = 95:5) following flash chromatography (45% EtOAc/hexanes); HPLC (1% i-PrOH/hexanes, 0.3 mL/min flow rate): 63.36 min (minor), 68.49 min (major); mp 82-84 °C; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 7.53 (br m, 4H), 7.33 (br m, 4H), 4.31 (m, 1H), 4.13 (m, 1H), 3.42-3.23 (m, 5H), 3.03 (m, 1H), 2.82-2.71 (m, J = 11 Hz, 2H), 2.41 (s, 6H), 2.19-2.01(m, 4H), 1.88 (m, 4H), 1.44 (s, 18H); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}) \delta 154.0, 141.7, 141.1, 130.0, 123.9, 80.2, 79.6, 63.1, 61.5, 54.6, 53.4, 46.4, 45.87, 31.5, 30.4, 28.47, 23.7, 22.9, 21.4; IR (Neat) cm\textsuperscript{-1}
2973, 2929, 2878, 1692, 1393, 1252, 1169, 1114, 1090, 1041; \[\alpha\]_D^{25} +46.7 (c = 1.1, CHCl_3)(95:5 mixture); Anal. calcd for C_{17}H_{25}NO_3S: C, 63.13; H, 7.79; Found: C, 62.95; H, 7.63. The major diastereomer was present as a mixture of rotational isomers whose \(^1\)H NMR and \(^{13}\)C NMR peaks could be coalesced (in the NMR) upon heating.

\((S\text{, }2R)\)-N-Boc-1-phenyl-2-(p-tolylsulfinyl)ethan-1-amine (57g)

\[
\begin{align*}
\text{Tol} & \quad \text{O} \\
\text{S} & \quad \text{Ph} \\
\text{NHBoc} & \quad \text{H}
\end{align*}
\]

A mixture of 2-carbomethoxyethenyl p-tolyl sulfoxide (0.100 g, 0.446 mmol) in THF (3 mL), nBuLi (0.279 mL), (R)-53g (0.309 g, 0.892 mmol) in THF (3 mL) afforded a diastereomeric mixture of \(\beta\)-amino sulfoxides 57g (79%, 0.126 g, \(d_r = 73:27\)) following flash chromatography (30% EtOAc/hexanes); HPLC: (3% \(i\)-PrOH/hexanes, 0.5 mL/min flow rate): 25.77 min (major), 34.79 min (minor); The major diastereomer was isolated via recrystallization from EtOAc/hexanes. Major isomer: mp 140-142 °C; \(^1\)H NMR (400 MHz, CDCl_3) \(\delta\) 7.49 (d, \(J = 8.0\) Hz, 2H), 7.35-7.28 (m, 7H), 6.39 (br s, 1H), 5.17 (br m, 1H), 3.17 (br m, 2H), 2.40 (s, 3H), 1.42 (s, 9H); \(^{13}\)C NMR (100.6 MHz, CDCl_3) \(\delta\) 155.1, 141.8, 140.6, 140.1, 130.1, 128.9, 127.8, 126.3, 124.1, 79.8, 63.1, 52.1, 29.4, 21.4; IR (neat) cm\(^{-1}\): 3267, 3031, 2976, 2927, 1713, 1522, 1495, 1250, 1168, 1043, 1014, 810; \([\alpha]_D^{25}\) -144.3 (c = 0.2, CHCl_3); Anal. calcd for C_{13}H_{18}NO_3S: C, 66.82; H, 7.01; Found: C, 66.90; H, 6.96. Minor isomer, partial characterization: \(^1\)H NMR (400 MHz, CDCl_3) \(\delta\) 6.49 (br s, 1H), 5.0 m, 1H); \(^{13}\)C NMR (100.6 MHz, CDCl_3) \(\delta\) 155.2, 141.7, 140.8, 140.2, 130.0, 128.9, 127.9, 127.7, 124.3, 79.7, 64.4, 52.0, 28.3, 21.4.
(S₅, 2R)-N-Boc-4-(p-tolylsulfinyl)butan-3-amine (57h)

A mixture of 2-carbomethoxyethenyl p-tolyl sulfoxide (0.100 g, 0.446 mmol) in THF (3 mL), nBuLi (0.279 mL), (R)-53h (0.266 g, 0.892 mmol) in THF (3 mL) afforded a diastereomeric mixture of β-amino sulfoxides 57h (81%, 0.101 g, dr = 94:6) following flash chromatography (30% EtOAc/hexanes); HPLC (2% i-PrOH/hexanes, 0.4 mL/min flow rate): 18.59 min (major), 23.32 min (minor); The major diastereomer was isolated via recrystallization from EtOAc/hexanes. Major isomer: mp 145-147 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.52 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 5.39 (br s, 1H), 3.92 (br s, 1H), 2.99-2.90 (m, 2H), 2.41 (s, 3H), 1.79 (br m, 2H), 1.45 (s, 9H), 0.99 (t, J = 7.4 Hz, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.4, 141.6, 140.8, 130.1, 123.9, 79.4, 61.8, 49.6, 28.4, 21.4, 10.7; IR (neat) cm⁻¹: 3261, 3047, 2969, 2931, 2875, 1709, 1528, 1364, 1248, 1170, 1134, 1086, 1050, 1014; [α]D²⁵⁺ -179.1 (c = 0.9, CHCl₃);

Anal. calcd for C₉H₁₈NO₅S: C, 61.70; H, 8.09; Found: C, 61.53; H, 7.99. Minor isomer, partial characterization: ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 7.4 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 4.77 (br d, J = 6.5 Hz, 1H), 3.77 (m, J = 7.2 Hz, 1H), 0.91 (t, J = 7.4 Hz, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.3, 141.7, 140.8, 130.8, 124.2, 79.7, 63.2, 48.8, 28.4, 27.9, 21.4, 10.2.

(Rₛ, 2S)-N-Boc-1-phenyl-3-(phenylsulfinyl)propan-2-amine (57i)

A mixture of 2-carbomethoxyethenyl phenyl sulfoxide (0.100 g, 0.478 mmol) in THF (3 mL), nBuLi (0.299 mL), (S)-53a (0.345 g, 0.956 mmol) in THF (3 mL) afforded a diastereomeric mixture of β-amino sulfoxides
\textbf{57i} (71\%, 0.121 g, \( dr = 91:9 \)) following flash chromatography (30\% EtOAc/hexanes); HPLC (3\% \( i\)-PrOH/hexanes, 0.5 mL/min flow rate): 21.79 min (major), 26.87 min (minor). The major diastereomer was isolated via recrystallization from EtOAc/hexanes. Major isomer: mp: 140-142 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.60-7.46 (m, 5H), 7.34-7.21 (m, 5H), 5.57 (br s, 1H), 4.21 (br m, 1 H), 3.22 (br m, 1H), 3.03-2.96 (m, 2H). 2.89 (dd, \( J = 13.2 \& 3.8 \) Hz, 1H), 1.45 (s, 9H); \(^{13}\)C NMR (100.6 MHz) \( \delta \) 155.2, 143.9, 137.6, 131.2, 129.4, 128.7, 126.8, 123.8, 79.6, 60.5, 49.9, 39.8, 28.4; IR (Neat) cm\(^{-1}\): 3266, 3059, 3028, 2976, 2928, 1709, 1528, 1365, 1271, 1252, 1169, 1086, 1043, 1019, 750; [\( \alpha \)\(^{25}\)\(_D\)] +115.0 (c = 0.8, CHCl\(_3\)) [lit.\(^{100}\) +115.0 (c = 0.9, CHCl\(_3\)). Anal. calcd for C\(_{20}\)H\(_{25}\)NO\(_3\)S: C, 66.82; H, 6.01; Found: C, 66.92; H, 7.20. Minor isomer, partial characterization: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.90 (br s, 1H), 1.42 (s, 9H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) 155.2, 143.9, 136.8, 131.1, 129.5, 128.6, 127.0, 124.1, 78.6, 61.4, 48.5, 40.4, 28.3.

\textbf{(S\(_5\), 2\(R\))-N-Boc-1-phenyl-3-(phenylsulfinyl)propan-2-amine (ent-57i)}

\begin{center}
\includegraphics[scale=0.5]{structure}
\end{center}

A mixture of 2-carbomethoxyethenyl phenyl sulfoxide (0.100 g, 0.478 mmol) in THF (3 mL), nBuLi (0.299 mL), (\( R \))-53a (0.345 g, 0.956 mmol) in THF (3 mL) afforded a diastereomeric mixture of \( \beta \)-amino sulfoxides \textit{ent-57i} (73\%, 0.124 g, \( dr = 93:7 \)) following flash chromatography (30\% EtOAc/hexanes); HPLC (10\% \( i\)-PrOH/hexanes, 0.5 mL/min flow rate): 10.95 min (major), 14.28 min (minor); The major diastereomer was isolated via recrystallization from EtOAc/hexanes. Major isomer: mp 144-145 °C; Spectral data
as above for 57i. \([\alpha]_{D}^{25} -115.7 \ (c = 0.2, \text{CHCl}_3) \ [\text{lit.}^{100} -114.6 \ (c = 1.3, \text{CHCl}_3)] \) Anal. calcd for C_{20}H_{25}NO_{3}S: C, 66.82; H, 7.01; Found: C, 67.00; H, 7.16.

**(Rs, 2S)-N-Boc-1-phenyl-3-(o-tolylsulfinyl)propan-2-amine (57j)**

\[
\begin{array}{c}
\text{O} \\
\text{o-Tol} \\
\text{\text{\text{\H-boc}}} \\
\text{NHBoc}
\end{array}
\]

A mixture of 2-carbomethoxyethenyl o-tolyl sulfoxide (0.100 g, 0.446 mmol) in THF (3 mL), nBuLi (0.279 mL, 0.446 mmol), (S)-53a (0.322 g, 0.892 mmol) in THF (3 mL) afforded a diastereomeric mixture of \(\beta\)-amino sulfoxides 57j (81%, 0.134 g, \(dr = 87:13\)) following flash chromatography (30% EtOAc/hexanes); HPLC (5% \(i\)-PrOH/hexanes, 0.5 mL/min flow rate): 15.05 min (major), 20.10 min (minor); The major diastereomer was isolated via recrystallization from EtOAc/hexanes. Major isomer: mp 150-152 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.92 (dd, \(J = 7.7, 1.3\) Hz, 1H), 7.43 (t, \(J = 7.3\) Hz, 1H), 7.37 (dt, \(J = 7.4, 1.3\) Hz, 1H) 7.32-7.21(m, 5H), 7.15 (d, \(J = 7.4\) Hz, 1H); \(^{13}\)C NMR (100.6 MHz) \(\delta\) 155.5, 142.0, 137.7, 134.2, 130.9, 129.3, 128.6, 127.4, 126.7, 123.8, 123.6, 79.5, 60.2, 49.9, 39.8, 28.4, 21.4; IR (neat) cm\(^{-1}\): 3361, 3277, 3057, 3027, 2976, 2928, 2868, 1706, 1688, 1520, 1495, 1251, 1170, 1039, 1014; \([\alpha]_{D}^{25} +118.7 \ (c = 0.4, \text{CHCl}_3)\); Anal. calcd for C_{21}H_{27}NO_{3}S: C, 67.53; H, 7.29; Found: C, 67.77; H, 7.38. Minor isomer, partial characterization: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.86 (br s, 1H); 1.42 (s, 9H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 155.5, 141.9, 136.8, 134.2, 130.1, 129.5, 128.6, 127.4, 126.8, 124.2, 123.6, 79.5, 61.4, 48.5, 40.5, 28.3, 21.4.
(Rs, 2S)-N-Boc-1-phenyl-3-(2-naphthylsulfinyl)propan-2-amine (57k)

A mixture of 2-carbomethoxyethenyl 2-naphthyl sulfoxide (0.100 g, 0.384 mmol) in THF (3 mL), nBuLi (0.240 mL), (S)-53a (0.277 g, 0.768 mmol) in THF (3 mL) afforded a diastereomeric mixture of β-amino sulfoxides 57k (91%, 0.142 g, dr = 88:12) following flash chromatography (30% EtOAc/hexanes); HPLC (3% i-PrOH/hexanes, 0.5 mL/min flow rate): 35.97 min (major), 44.68 min (minor); The major diastereomer was isolated via recrystallization from EtOAc/hexanes. Major isomer: mp 130-132 °C; 1H NMR (400 MHz, CDCl3) δ 8.16 (s, 1H), 7.96-7.88 (m, 3H), 7.59 (m, 2H), 7.47 (d, J = 8.3 Hz, 1H), 7.34-7.23 (m, 5H), 5.58 (br d, J = 7.4 Hz, 1H), 4.26 (br s, 1H), 3.25 (m, 1H), 3.09-3.03 (m, 2H), 2.95 (dd, J = 13.4, 3.4 Hz, 1H), 1.43 (s, 1H); 13C NMR (100.6 MHz, CDCl3) δ 155.2, 140.9, 137.4, 134.5, 132.9, 129.4, 128.7, 128.5, 128.1, 127.8, 127.4, 126.8, 124.4, 119.6, 79.7, 60.2, 49.9, 39.9, 28.5; IR (Neat) cm⁻¹ 3279, 3057, 2976, 2927, 2855, 1708, 1525, 1250, 1167, 1133 1068, 1048; [α]D²⁵ +217.2 (c = 0.8, CHCl₃); HRMS (TOF, ESI) calcd for C₂₅H₂₇O₃NS [M⁺]: 409.1712; found: 409.1716. Minor isomer (partial characterization): 1H NMR (300 MHz, CDCl3) δ 8.19 (s, 1H), 4.9 (br s, 1H), 1.38 (s, 9H); 13C NMR (100.6 MHz, CDCl3) δ 155.2, 140.8, 136.9, 134.6, 132.9, 129.6, 129.5, 128.6, 128.5, 128.1, 127.9, 127.3, 126.8, 124.9, 119.9, 79.6, 61.0, 48.4, 40.6, 28.3.

(Rs, 2S)-N-Boc-1-phenyl-3-(o-bromophenylsulfinyl)propan-2-amine (57l)

A mixture of 2-carbomethoxyethenyl 2-bromophenyl sulfoxide (0.100 g, 0.345 mmol) in THF (3 mL), nBuLi (0.216
mL, 0.347 mmol), (S)-53a (0.250 g, 0.694 mmol) in THF (3 mL) afforded a mixture of β-amino sulfoxides 57I (71%, 0.146 g, \( dr = 83:17 \)) following flash chromatography (30% EtOAc/hexanes); HPLC (2% \( i\)-PrOH/hexanes, 0.4 mL/min flow rate): 35.78 min (major), 44.03 min (minor); The major diastereomer was isolated via recrystallization from EtOAc/hexanes. Major isomer: mp 165-167 °C; \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.91 (dd, \( J = 7.8 \& 1.6 \) Hz, 1H), 7.56 (t, \( J = 7.5 \) Hz, 1H), 7.52 (d, \( J = 7.9 \) Hz, 1H), 7.36 (t, \( J = 7.1 \) Hz, 1H), 7.31-7.20 (m, 5H), 5.60 (br d, \( J = 6.9 \) Hz, 1H), 4.28 (br m, 1H), 3.44-3.39 (m, 1H), 3.27 (dd, \( J = 13.2, 6.6 \) Hz, 1H), 3.02 (dd, \( J = 13.2, 8.2 \) Hz, 1H), 2.76 (dd, \( J = 13.3, 3.1 \) Hz, 1H) 1.45 (s, 9H); \(^1^3^C\) NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) 155.1, 143.5, 137.4, 132.9, 132.4, 129.5, 128.7, 128.6, 126.7, 126.3, 118.4, 79.6, 57.6, 49.9, 39.8, 28.4; IR (neat) cm\(^{-1}\) 3369, 3061, 3027, 2977, 2926, 1688, 1522, 1269, 1170, 1050,1013; \( [\alpha]_D^25 \) +231.3 (c = 0.6, CHCl\(_3\)); Anal. calcd for C\(_{20}\)H\(_{24}\)BrNO\(_3\)S: C, 54.80; H, 5.62; Found: C, 54.72; H, 5.62. Minor isomer (partial characterization): \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.86 (br s, 1H), 1.40 (s, 9H); \(^1^3^C\) NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) 155.1, 143.6, 137.2, 132.9, 132.2, 129.6, 128.7, 128.6, 126.7, 126.5, 118.6, 79.5, 58.5, 49.1, 39.8, 28.3.

(RS, 2S)-N-Boc-1-Phenyl-3-(2-pyridylsulfanyl)propan-2-amine (57m).

A mixture of 2-carbomethoxyethyl 2-pyridyl sulfoxide (0.100 g, 0.473 mmol) in THF (3 mL), nBuLi (0.295 mL), and electrophile (S)-53a (0.341 g, 0.947 mmol) in THF (3 mL) afforded a diastereomeric mixture of β-amino sulfoxides 57m (82%, 0.140 g, \( dr = 63:37 \) by NMR integration) following flash chromatography (30% EtOAc/hexanes). mp 100-104 °C; \(^1^H\) NMR
(400 MHz, CDCl$_3$) δ 8.60–8.57 (m, 2H), 8.01–7.89 (m, 4H), 7.38–7.18 (m, 12 H), 5.51 (br s, 1H, minor isomer), 4.85 (br s, 1H, major isomer), 4.40–4.31 (m, 2H), 3.43–2.93 (m, 8H), 1.43 (s, 9H, minor isomer), 1.38 (s, 9H, major isomer); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ major isomer 164.6, 154.8, 149.7, 138.0, 137.1, 129.46, 128.54, 126.7, 124.5, 120.1, 79.5, 58.0, 48.2, 40.4, 28.3; minor isomer 164.6, 155.1, 149.7, 138.1, 137.2, 129.5, 128.6, 127.3, 124.6, 119.9, 79.5, 58.2, 49.2, 41.6, 28.4; IR (neat) cm$^{-1}$ 3288, 3084, 3052, 2976, 2929, 1707, 1562, 1522, 1452, 1422, 1391, 1365, 1251, 1169, 1084, 1036, 771; $[^{25}]$D $^{[\alpha]} -14.8$ (c = 1.2, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_{19}$H$_{24}$N$_2$O$_3$S [M + H]$^+$ 361.1586, found 361.1573.

**1.4.4 Synthesis of 2-(Carboethoxy)ethyl Alkyl Sulfoxides**

Methyl 2-(benzylsulfinyl) acrylate and methyl 2-(n-hexylsulfinyl) acrylate have been prepared previously. These compounds were evaluated for their release of alkanesulfenates according to the procedure above (Preparation of Aryl β-Amino Sulfoxides 57). Capture with (S)-57a as outlined above did not result in an alkyl β-amino sulfoxide.

**General Preparation of 2-(Carboethoxy)ethyl Alkyl Sulfoxides (58).**

Ethyl acrylate (1 equiv) was added dropwise to a suspension of potassium carbonate (0.05 equiv) and thiol (1 equiv) in DCM (1 mL/mm mol of thiol). The resulting mixture was stirred at room temperature for 12 h. Next, the reaction mixture was washed successively with aqueous 1 M NaOH solution, water, and then brine and dried over MgSO$_4$. Filtration and solvent evaporation under reduced
pressure provided 2-(carboethoxy)ethyl alkyl sulfide, which was used in the next step without further purification. A solution of the 2-(carboethoxy)ethyl alkyl sulfide (1 equiv) in MeOH (2 mL/mmol sulfide) was cooled to 0 °C, and a solution of NaIO₄ (1.05 equiv) in water (1 mL/mmol sulfide) was added dropwise. The reaction mixture was stirred for 18 h at room temperature. Sodium iodate was filtered, methanol was removed under vacuum, and the residue extracted with EtOAc. The combined organic layers were washed with brine solution, dried over MgSO₄, filtered, and evaporated under reduced pressure. The crude product was then purified by column chromatography on silica gel to afford pure 2-(carboethoxy)ethyl alkyl sulfoxide 58. The data for 2-(carboethoxy)ethyl benzyl sulfoxide and 2-(carboethoxy)ethyl tert-butyl sulfoxide matched that from the literature.⁴⁰

2-(Carboethoxy)ethyl n-Hexyl Sulfoxide.

Application of the general procedure above to n-hexyl mercaptan (5.97 mL, 42.3 mmol) provided crude 2-(carboethoxy)ethyl n-hexyl sulfide. Yield 81% (7.45 g). ¹H NMR (400 MHz, CDCl₃) δ 4.15 (q, J = 7.2 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H), 2.59 (t, J = 7.6 Hz, 2H), 2.53 (t, J = 7.2 Hz, 2H), 1.62-1.54 (m, 2H), 1.41-1.25 (m, 9H), 0.89 (t, J = 6.0 Hz, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ 172.0, 60.6, 35.0, 32.1, 31.4, 29.5, 28.5, 27.0, 22.5, 14.2, 14.0. Application of the general oxidation procedure above to the crude sulfide (1.00 g, 4.58 mmol) afforded 2-(carboethoxy)ethyl n-hexyl sulfoxide as a white solid. (87%, 994 mg). Mp 28–29 °C; ¹H NMR (600 MHz, CDCl₃) δ 4.18 (q, J = 4.8 Hz, 2H), 3.05–3.01 (m, 1H), 2.90–2.74
(m, 4H), 2.70–2.68 (m, 1H), 1.78 (m, 2H), 1.46 (m, 2H), 1.34–1.31 (m, 4H), 1.28 (t, 4.8 Hz, 3H), 0.90 (t, J = 4.4 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 171.4, 61.2, 52.8, 46.8, 31.4, 28.5, 27.2, 22.6, 22.4, 14.2, 14.0; IR (neat) cm$^{-1}$ 2978, 2953, 2924, 2857, 1740, 1467, 1421, 1374, 1242, 1179, 1019, 980. Anal. calcd for C$_{11}$H$_{22}$O$_3$S: C, 56.37; H, 9.46. Found: C, 56.51; H, 9.44.

2-(Carboethoxy)ethyl c-Hexyl Sulfoxide.

Application of the general procedure above to c-hexyl mercaptan (4.22 mL, 34.4 mmol). Yield 81% (6.01 g). Colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 4.16 (q, J = 7.2 Hz, 2H), 2.82 (m, 2H), 2.58 (t, J = 7.4 Hz, 3H), 2.00–1.95 (m, 2H), 1.79–1.76 (m, 2H), 1.63–1.51 (m, 1H), 1.38–1.24 (m, 8H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 172.0, 60.5, 43.2, 35.3, 33.6, 26.0, 25.8, 25.0, 14.3. Application of the general oxidation procedure above to the crude sulfide (6.01 g, 20.2 mmol) afforded sulfoxide 2-(carboethoxy)ethyl c-hexyl sulfoxide as a yellow oil (84%, 3.50 g). $^1$H NMR (600 MHz, CDCl$_3$) δ 4.18 (q, J = 7.2 Hz, 2H), 3.06–2.99 (m, 1H), 2.89– 2.81 (m, 3H), 2.59 (m, 1H), 2.15–2.12 (m, 1H), 1.96–1.88 (m, 3H), 1.72 (m, 1H), 1.51–1.27 (m, 5H), 1.28 (t, J = 7.4 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 171.6, 61.2, 59.4, 43.7, 27.4, 26.2, 25.5, 25.4, 25.1, 25.0, 14.2; IR (neat) cm$^{-1}$ 2981, 2932, 2856, 1735, 1450, 1393, 1373, 1348, 1235, 1184, 1039, 851. Anal. calcd for C$_{11}$H$_{20}$O$_3$S: C, 56.86; H, 8.68. Found: C, 56.69; H, 8.52.
1.4.5 Synthesis of Alkyl β-Amino Sulfoxides

**General Procedure: Synthesis of Alkyl β-Amino Sulfoxides (59).**

Sulfoxide 58 (1.0 equiv) was dissolved in THF (1 mL/0.1 mmol) under nitrogen and stirred at −78 °C. To the sulfoxide was added LiHMDS (1.0 M/hexanes, 1.00–1.2 equiv) via syringe. Following 15–20 min of stirring, a solution of the chiral iodide (~2.0 equiv) in THF (4 mL/ mmol) at −78 °C was added via syringe to the sulenate. Immediately after addition of electrophile the reaction mixture was refluxed for 2–3 h. Solvent was removed under reduced pressure, and diastereomers of 59 were isolated by flash chromatography using EtOAc/hexanes as the eluent. Diastereomeric ratios were determined by HPLC using iPrOH/hexanes as the eluent or by ¹H NMR peak integration. β-Amino sulfoxide yields were derived from starting sulfoxides. The absolute stereochemistry of the major product is listed as part of the compounds name.

(R$_s$2S)-N-Boc-1-Phenyl-3-(benzylsulfinyl)propan-2-amine (59a).

2-(Carboethoxy)ethyl benzyl sulfoxide (0.100 g, 0.416 mmol) in THF (3 mL) was treated dropwise with LiHMDS (0.437 mL). Next, electrophile (S)-53a (0.360 g, 0.832 mmol) in THF (3 mL) was added to the sulfenate via syringe. A diastereomeric mixture of β-amino sulfoxides 59a (54%, 0.084 g, dr = 85:15 HPLC integration) was isolated following flash chromatography (30% EtOAc/hexanes). HPLC (5% i-PrOH/hexanes, 0.4 mL/min flow rate, OD-H column): 39.47 min (minor), 60.03 min (major). The diastereomeric mixture was recrystallized from EtOAc/hexanes to give an improved dr of 97:3: mp 203–204 °C;
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.50 (m, 3H), 7.26–7.21 (m, 5H), 7.10 (d, \(J = 6.8\) Hz, 2H), 5.47 (br d, \(J = 6.4\) Hz, 1H), 4.20 (m, 1H), 4.00 (ABq, \(\Delta \delta_{AB} = 0.09\), \(J_{AB} = 4.4\) Hz, 2H), 3.18–3.15 (m, 1H), 2.91 (dd, \(J = 12.8, 8\) Hz, 1H), 2.83–2.78 (m, 1H), 2.72–2.69 (m, 1H), 1.40 (s, 9H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 155.2, 137.4, 130.1, 129.4, 129.3, 129.0, 128.6, 128.5, 126.7, 79.6, 58.9, 53.3, 49.5, 39.9, 28.4; IR (neat) cm\(^{-1}\) 3354, 3028, 2962, 2932, 1688, 1523, 1266, 1251, 1170, 1045, 1013; \([\alpha]_{D}^{25}\) +70.0 (c = 0.1, CHCl\(_3\)). Anal. calcd for C\(_{21}\)H\(_{27}\)NO\(_3\)S: C, 67.53; H, 7.29. Found: C, 67.42; H, 7.50. Minor isomer, partial characterization: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.13 (br s, \(J = 7.2\) Hz, 1H), 1.35 (s, 9H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 155.3, 136.8, 130.3, 129.3, 128.8, 128.6, 128.3, 126.9, 79.8, 57.5, 53.4, 49.4, 39.9, 28.4.

(R\(_S\),2S)-N-Boc-1-Phenyl-3-(n-hexylsulfinyl)propan-2-amine (59b).

\(\text{2-(Carboethoxy)ethyl \(n\)-hexyl sulfoxide (2a) (0.100 g, 0.426 mmol) in THF (3 mL) was treated dropwise with LiHMDS (0.447 mL). Next, electrophile (S)-53a (0.307 g, 0.892 mmol) in THF (3 mL) was added to the sulenate via syringe. A diastereomeric mixture of \(\beta\)-amino sulfoxides 59b (42%, 0.065 g, dr = 82:18 HPLC integration) was isolated following flash chromatography (30% EtOAc/hexanes). HPLC (8% \(i\)-PrOH/hexanes, 0.4 mL/min flow rate, OD-H column): 18.89 min (minor), 20.15 min (major). The diastereomeric mixture was recrystallized from EtOAc/hexanes to give an improved diastereomeric purity of 93:7: mp 142–144 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.32–7.22 (m, 5H), 5.56 (br d, \(J = 8.0\) Hz, 1H), 4.24 (m, 1H), 3.22 (dd, \(J = 13.6, 6.8\) Hz, 1H), 3.00 (dd, \(J = 13.6, 8.4\) Hz, 1H), 2.89–2.70 (m, 3H), 2.66–2.58 (m, 1H), 1.82–1.68 (m, 2H), 1.49–1.38 (m, 2H),
1.42 (s, 9H), 1.32–1.28 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H); 13C NMR (100.6 MHz, CDCl3) δ 155.2, 137.6, 129.3, 128.6, 126.7, 79.5, 54.6, 53.1, 49.6, 39.9, 31.3, 28.4, 28.4, 22.5, 22.4, 14.0.; IR (neat) cm⁻¹ 3362, 3244, 3062, 3028, 3005, 2957, 2926, 2857, 1689, 1523, 1454, 1366, 1268, 1251, 1171, 1043, 1016; [α]D²⁵ +28.7 (c = 0.2, CHCl₃); HRMS (TOF, ESI) calcd for C₂₀H₃₃NO₃S [M + Na]⁺ 390.2079, found 390.2079. Minor isomer, partial characterization: 1H NMR (400 MHz, CDCl₃) δ 4.95 (br s, 1H); 13C NMR (100.6 MHz, CDCl₃) δ 155.2, 137.0, 129.5, 128.6, 126.9, 56.5, 53.0, 48.8, 40.8, 31.3, 28.5, 28.3, 22.4, 14.

(RS,25)-N-Boc-1-Phenyl-3-(tert-butylsulfinyl)propan-2-amine(59c).

2-(Carboethoxy)ethyl tert-butyl sulfoxide (0.100 g, 0.485 mmol) in THF (3 mL) was treated dropwise with LiHMDS (0.509 mL). Next, electrophile (S)-53a (0.350 g, 0.970 mmol) in THF (3 mL) was added to the sulfinate via syringe. A diastereomeric mixture of β-amino sulfoxides 59c (63%, 0.104 g, dr = 78:22 HPLC integration) was isolated following flash chromatography (30% EtOAc/hexanes). HPLC (5% i-PrOH/hexanes, 1.0 mL/min flow rate, OD-H column): 9.59 min (minor), 10.51 min (major). The diastereomeric mixture was recrystallized from EtOAc/hexanes to give improved diastereomeric purity of 84:16: mp 130–133 °C; 1H NMR (400 MHz, CDCl₃) δ 7.32–7.20 (m, 5H), 5.78 (br d, J = 8.0 Hz, 1H), 4.24 (m, 1H), 3.28 (dd, J = 13.6, 6.8 Hz, 1H), 3.02 (dd, J = 13.6, 8.8 Hz, 1H), 2.74 (dd, J = 12.8, 6.4 Hz, 1H), 6.60 (dd, J = 13.2, 4.0 Hz, 1H), 1.42 (s, 9H), 1.21 (s, 9H); 13C NMR (100.6 MHz, CDCl₃) δ 155.2, 137.9, 129.4, 128.6, 126.7, 79.4, 53.2, 50.1, 46.8, 39.7, 28.4, 22.7; IR (neat) cm⁻¹ 3266, 3028, 2976, 2930, 2869,
1708, 1525, 1455, 1391, 1365, 1271, 1252, 1172, 1043, 1011, 733, 699; $[\alpha]_D^{25} +32.7$
(c = 0.7, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_{38}$H$_{29}$NO$_3$S [M + Na]$^+$ 362.1766, found 362.1748. Minor isomer, partial characterization: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.05 (br s, 1H); 2.48 (dd, $J = 13.2, 5.6$ Hz, 1H) $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 155.2, 137.4, 129.6, 128.5, 79.6, 53.4, 49.8, 47.0, 41.3, 28.3, 22.7.

(R$_S$,2S)-N-Boc-1-Phenyl-3-(c-hexylsulfinyl)propan-2-amine (59d).

2-(Carboethoxy)ethyl c-hexyl sulfoxide (0.100 g, 0.431 mmol) in THF (3 mL) was treated dropwise with LiHMDS (0.431 mL). Next, electrophile (S)-53a (0.374 g, 1.034 mmol) in THF (3 mL) was added to the sulfenate via syringe. A diastereomeric mixture of $\beta$-amino sulfoxides 59d (78%, 0.122 g, dr = 91:9 by NMR integration) was isolated following flash chromatography (30% EtOAc/hexanes). The product was isolated as a 91:9 diastereomeric mixture: mp 152−154 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.312−7.23 (m, 5H), 5.72 (br d, $J = 6.8$ Hz, 1H), 4.26 (m, 1H), 3.24 (dd, $J = 13.2, 6.4$ Hz, 1H), 3.01 (dd, $J = 12.8, 8.4$ Hz, 1H), 2.88−2.83 (m, 1H), 2.76 (dd, $J = 12.8, 3.2$ Hz, 1H), 2.57 (m, 1H), 2.12−2.09 (m, 1H), 1.93-1.71 (m, 4H), 1.69-1.27 (m, 5 H), 1.42 (s, 9H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 155.3, 137.8, 129.4, 128.6, 126.7, 79.4, 59.9, 50.9, 50.0, 39.8, 28.4, 26.2, 25.5, 25.3, 25.1, 25.0; IR (neat) cm$^{-1}$ 3365, 3260, 3062, 3028, 2976, 2929, 2853, 1690, 1519, 1450, 1391, 1365, 1298, 1268, 1250, 1169, 1042, 1016, 742, 699; $[\alpha]_D^{25} +24.42$ (c = 0.95, CHCl$_3$ ); HRMS (TOF, ESI) calcd for C$_{20}$H$_{31}$NO$_3$S [M + Na]$^+$ 388.1922, found 388.1927. Minor isomer, partial characterization: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.97
(br s, 1H); \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}) \(\delta\) 155.3, 137.8, 129.6, 128.9, 126.8, 79.4, 58.9, 52.7, 49.2, 40.4, 28.3, 26.5, 25.5, 25.3, 25.1, 25.0.

1.4.6 Synthesis of 1-Alkenyl \(\beta\)-Amino Sulfoxides

**General Procedure: Synthesis of 1-Alkenyl \(\beta\)-Amino Sulfoxides (62).**

All sulfenate reactions were performed under anhydrous conditions under an inert N\textsubscript{2} (g) atmosphere. To a solution of LiHMDS (1.0 M in THF, 1.1 equiv) in Et\textsubscript{2}O (10 mL/mmol LiHMDS) at \(-78^\circ\)C was added dropwise a solution of the thiirane S-oxide (1.0 equiv) in Et\textsubscript{2}O (~5.4 mL/mmol thiirane S-oxide) at \(-78^\circ\)C. The mixture was allowed to stir for ca. 15 min, at which time a precooled (~78 \(^\circ\)C) solution of the amino iodide (53, 1.1 equiv) in THF (~2.5 mL/mmol iodide) was added dropwise via syringe. After 2–3 h of stirring at \(-78^\circ\)C the reaction vessel was removed from the cold bath and allowed to warm to rt. Reactions were stirred until completion as monitored by TLC (usually 1 h at rt). Following completion the solvent was removed under reduced pressure, and the residue was dissolved in DCM. The organic layer was washed with satd ammonium chloride solution, water, and brine and then dried over MgSO\textsubscript{4}. The organic layer was then filtered, and solvent was removed under reduced pressure. The crude reaction mixture was subjected to flash chromatography, using mixtures of ethyl acetate/hexanes as the eluent, which yielded the \(\beta\)-amino sulfoxides 62 as a mixture of diastereomers. The diastereomeric ratios were determined by comparison of relative \(^1\text{H}\) NMR peak integrations and/or relative integrations of peaks from an HPLC separation on a chiral column (Daicel chiralpak OJ-H or OD-H column). In most cases the
diastereomeric mixture could be recrystallized from mixtures of ethyl acetate and hexanes to provide the major diastereomer. The absolute stereochemistry of the major product is listed as part of the compound names.

(Rs,2S)-N-Boc-1-Phenyl-3-(E)-propenylsulfinyl)propan-2-amine (62a).

A solution of LiHMDS (1.22 mL), propylene thiirane S-oxide (0.100 g, 1.11 mmol), and (S)-53a (0.441 g, 1.22 mmol) (3 mL) afforded a diastereomeric mixture of β-amino sulfoxide 62a (82%, 0.292 g, dr = 90:10) following flash chromatography (60% EtOAc/ hexanes); HPLC (1% i-PrOH/hexanes, 1.0 mL/min flow rate): 21.23 min (major), 28.52 min (minor). The major diastereomer was isolated via recrystallization from EtOAc/hexanes (66%, 0.234 g). Major isomer: mp 145–147 °C; 1H NMR (400 MHz, CDCl₃) δ 7.32–7.21 (m, 5H), 6.47 (dq, J = 15.1, 6.7 Hz, 1H), 6.23 (d, J = 15.1 Hz, 1H), 5.50 (br d, J = 6.3 Hz, 1H), 4.21 (m, 1H), 3.18 (dd, J = 13.0, 6.5 Hz, 1H), 2.99 (dd, J = 12.8, 7.7 Hz, 1H), 2.91–2.87 (m, 1H), 2.82 (dd, J = 13.2, 3.9 Hz, 1H), 1.91 (d, J = 6.7 Hz, 3H), 1.42 (s, 9H); 13C NMR (100.6 MHz, CDCl₃) δ 155.2, 137.5, 137.0, 133.3, 129.4, 128.6, 126.7, 79.5, 56.6, 49.4, 39.9, 28.4, 17.8; IR (neat) cm⁻¹ 3358, 3267, 3086, 3062, 2978, 2915, 1691, 1522, 1366, 1268, 1251, 1171, 1047, 1022, 959; [α]D²⁵ +16.6 (c = 1.2, CHCl₃); HRMS (HRMS (TOF, ESI) calcd for C₁₇H₂₅NO₃S [M]⁺ 323.1555; found: 323.1547. Minor isomer, partial characterization: 1H NMR (400 MHz, CDCl₃) δ 4.85 (br s, 1H), 1.42 (s, 9H); 13C NMR (100.6 MHz, CDCl₃) δ 155.1, 137.02, 136.99, 133.3, 129.5, 128.6, 126.8, 79.4, 58.3, 48.2, 40.8, 28.4, 17.8.

A solution of LiHMDS (1.22 mL), propylene thiirane S-oxide (0.100 g, 1.11 mmol), and (R)-53a (0.441 g, 1.22 mmol) afforded a diastereomeric mixture of β-amino sulfoxide ent-62a (78%, 0.279 g, dr = 90:10) following flash chromatography (60% EtOAc/hexanes); HPLC (1% i-ProOH/hexanes, 1.0 mL/min flow rate): 25.37 min (major), 37.31 min (minor). The major diastereomer was isolated via recrystallization from EtOAc/hexanes (59%, 0.211 g). Major isomer: mp 145–147 °C. See enantiomer above for spectral data \[ [\alpha]_D^{25} = -16.7 \ (c = 1.6, \ CHCl_3) \]. Anal. calcd for C_{17}H_{25}NO_3S: C, 63.13; H, 7.79. Found: C, 62.90; H, 7.50.

(RS,2S)-N-Boc-(E)-1-Propenylsulfanyl)propan-2-amine (62b).

A solution of LiHMDS (1.11 mL), propylene thiirane S-oxide (0.100 g, 1.11 mmol), and (S)-53b (0.443 g, 1.55 mmol) afforded a diastereomeric mixture of β-amino sulfoxide 62b (67%, 0.187 g, dr = 82:18 by \(^1\)H NMR integration of mixture) following flash chromatography (60% EtOAc/hexanes). The major diastereomer was isolated via recrystallization from EtOAc/hexanes (46%, 0.126 g). Major isomer: mp 107–108 °C; \(^1\)H NMR (400 MHz, CDCl_3) δ 6.51 (dq, J = 15.2, 6.8 Hz, 1H), 6.29 (dd, J = 15.2, 1.6 Hz, 1H), 5.31 (br s, 1H), 4.14 (m, 1H), 2.90–2.89 (m, 1H), 2.83 (dd, J = 12.8, 4.8 Hz, 1H), 1.94 (dd, J = 6.8, 1.6 Hz, 3H), 1.438 (s, 9H) 1.41 (d, J = 6.8 Hz, 3H); \(^{13}\)C NMR (100.6 MHz, CDCl_3) δ 155.0, 137.1, 133.4, 79.5, 59.7, 43.8, 28.4, 20.4, 17.9; IR (neat) cm\(^{-1}\) 3232, 3040, 2973, 2930, 2872, 1698, 1539, 1449, 1364, 1272, 1252, 1174, 1093, 1028; \[ [\alpha]_D^{25} = +19.3 \ (c =}
Minor isomer, partial characterization: $^1$H NMR (400 MHz, CDCl$_3$) δ 6.40 (d, $J = 15.4$ Hz, 1H), 5.63 (br d, $J = 7.9$ Hz, 1H), 4.01 (m, 1H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 155.0, 136.3, 133.2, 79.0, 60.9, 42.8, 28.3, 20.9, 17.7.

**(R$_S$,2S)-N-Boc-3-Methyl-1-(E)-1-propenylsulfinyl)butan-2-amine (62c).**

A solution of LiHMDS (1.22 mL), propylene thiirane S-oxide (0.100 g, 1.11 mmol), and (S)-53c (0.381 g, 1.22 mmol) afforded a diastereomeric mixture of β-amino sulfoxide 62c (86%, 0.262 g, dr = 80:20 by $^1$H NMR integration of mixture) following flash chromatography (60% EtOAc/hexanes). The major diastereomer was isolated via recrystallization from EtOAc/hexanes (52%, 0.159 g). Major isomer: mp 149–150 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 6.89 (br d, $J = 8.9$ Hz, 1H), 6.51 (dd, $J = 15.0$, 1.4 Hz, 1H), 6.30 (dq, $J = 15.0$, 6.7 Hz, 1H), 3.68 (m, 1H), 2.78–2.68 (m, 1H), 2.59 (dd, $J = 13$, 2.5 Hz, 1H), 1.85 (dd, $J = 6.8$, 1.3 Hz, 3H), 1.74 (m, 1H), 1.37 (s, 9H), 0.80 (dd, $J = 6.8$, 2.0 Hz, 6H); $^{13}$C NMR (100.6 MHz, DMSO-$d_6$) δ 155.2, 134.8, 134.1, 77.6, 56.6, 50.1, 32.2, 28.2, 18.4, 18.0, 17.3; IR (neat) cm$^{-1}$ 3230, 3034, 2969, 2915, 2872, 1700, 1542, 1449, 1367, 1297, 1252, 1174, 1038, 1018, 957; $\left[\alpha\right]_D^{25} +23.9$ ($c = 0.9$, CHCl$_3$). Anal. calcd for C$_{13}$H$_{25}$NO$_3$S: C, 56.69; H, 9.15. Found: C, 56.52; H, 9.30. Minor isomer, partial characterization: $^1$H NMR (400 MHz, CDCl$_3$) δ 6.95 (br d, $J = 9.2$ Hz, 1H), 1.35 (s, 9H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 155.1, 135.4, 134.3, 77.7, 56.2, 49.9, 32.0, 28.0, 18.7, 17.8, 17.4.
(Rs,2S)-N-Boc-O-TBDPS-1-Hydroxy-3-(E)-1-propenylsulfinyl)propan-2-amine (62d).

A solution of LiHMDS (0.59 mL), propylene thiirane S-oxide (0.050 g, 0.554 mmol), and (S)-53e (0.538 g, 0.997 mmol) afforded a diastereomeric mixture of β-amino sulfoxide 62d (65%, 0.181 g, dr = 87:13 by $^1$H NMR integration of mixture) following flash chromatography (60% EtOAc/hexanes). The major diastereomer was isolated via recrystallization from EtOAc/hexanes (43%, 0.120). Major isomer: mp 167–169 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.65–7.63 (m, 4H), 7.46–7.37 (m, 6H), 6.47 (dq, $J$ = 15.2, 6.8 Hz, 1H), 6.26 (dd, $J$ = 15.2, 1.6 Hz, 1H), 5.40 (br d, $J$ = 8.0 Hz, 1H), 4.19 (m, 1H), 3.87–3.83 (m, 2H), 3.03 (dd, $J$ = 12.8, 6.8 Hz, 1H), 2.92 (m, 1H), 1.92 (dd, $J$ = 6.8, 1.6 Hz, 3H), 1.43 (s, 9H), 1.07 (s, 9H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 155.1, 137.1, 135.6, 133.7, 132.9, 129.9, 127.9, 79.6, 64.8, 55.5, 48.9, 28.4, 26.9, 19.3, 17.9; IR (neat) cm$^{-1}$ 3234, 3071, 3050, 3027, 2971, 2957, 2933, 2908, 2859, 1705, 1543, 1443, 1427, 1315, 1280, 1249, 1175, 1106, 1012, 961, 828 706; $\left[\alpha\right]_D^{25} +297.3$ (c = 0.8, CHCl$_3$). Anal. calcd for C$_{27}$H$_{41}$NO$_4$SSi: C, 64.37; H, 8.20. Found: C, 64.63; H, 7.87. Minor isomer, partial characterization: $^1$H NMR (400 MHz, CDCl$_3$) δ 6.43 (dd, $J$ = 13.2, 6.8 Hz, 1H), 4.99 (br d, $J$ = 8.4 Hz, 1H), 4.01 (m, 1H), 1.44 (s, 9H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 155.1, 137.2, 135.5, 133.3, 133.0, 129.9, 127.9, 79.6, 65.4, 57.3, 48.2, 28.4, 26.9, 19.3, 17.9.
**(R<sub>S</sub>,2S)-N-Boc-1-Phenyl-3-(vinylsulfinyl)propan-2-amine (62e).**

A solution of LiHMDS (1.45 mL), ethylene thiirane S-oxide (0.100 g, 1.314 mmol), and iodide (S)-53a (0.569 g, 1.58 mmol) afforded a diastereomeric mixture of β-amino sulfoxide 62e (84%, 0.341 g, dr = 89:11 by ¹H NMR integration of mixture) following flash chromatography (60% EtOAc/hexanes). The major diastereomer was isolated via recrystallization from EtOAc/hexanes (68%, 0.277). Major isomer: mp 137–139 °C; ¹H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.32–7.21 (m, 5H), 6.60 (dd, J = 16.4, 9.8 Hz, 1H), 6.12 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 9.8 Hz, 1H), 5.41 (br d, J = 6.2 Hz, 1H), 4.23 (m, 1H), 3.20 (dd, J = 12.3, 7.0 Hz, 1H), 3.00 (dd, J = 13.5, 7.6 Hz, 2H), 2.78 (dd, J = 13.2, 3.9 Hz, 1H), 1.43 (s, 9H); ¹³C NMR (100.6 MHz, CDCl<sub>3</sub>) δ 155.2, 140.5, 137.3, 129.4, 128.7, 126.8, 122.0, 79.7, 56.5, 49.4, 39.9, 28.4; IR (neat) cm⁻¹ 3455, 3359, 3033, 2980, 2920, 1690, 1522, 1267, 1250, 1170, 1052, 1022; [α]<sub>D</sub><sup>25</sup> +41.9 (c = 0.8, CHCl<sub>3</sub>). Anal. calcd for C<sub>16</sub>H<sub>23</sub>NO<sub>3</sub>S: C, 62.11; H, 7.49; Found: C, 61.96; 7.48. Minor isomer, partial characterization: ¹H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.73 (dd, J = 16.8, 9.8 Hz, 1H), 5.97 (d, J = 9.8 Hz, 1H), 4.84 (br s, 1H); ¹³C NMR (100.6 MHz, CDCl<sub>3</sub>) δ 155.2, 140.5, 136.8, 128.6, 128.4, 126.9, 122.1, 79.7, 57.9, 49.0, 40.7, 28.3.

**(R<sub>S</sub>,2S)-N-Boc-1-(Cyclohexenylsulfinyl)-3-phenylpropan-2-amine (62f).**

A solution of LiHMDS (0.92 mL) in THF (6 mL), cyclohexene thiirane S-oxide (0.100 g, 0.767 mmol) in THF (3 mL), and (S)-53a (0.332 g, 0.920 mmol) in THF (3 mL) afforded a diastereomeric mixture of β-amino sulfoxide (62f) (71%, 0.197 g, dr = 93:7 by ¹H NMR integration of mixture)
following flash chromatography (40% EtOAc/hexanes). The major diastereomer was isolated via recrystallization from EtOAc/Hexanes (53%, 0.147) Major isomer: mp 131–133 °C; \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.32–7.21 (m, 5H), 6.44 (s, 1H), 5.60 (br d, \(J = 5.7\) Hz, 1H), 4.16 (m, 1H), 3.22 (dd, \(J = 13.4, 6.0\) Hz, 1H), 3.00 (dd, \(J = 13.5, 8.1\) Hz, 1H), 2.87–2.77 (m, 2H), 2.22–2.15 (m, 3H), 2.04–2.01 (m, 1H), 1.67 (m, 4H), 1.43 (s, 9H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 155.2, 140.8, 137.7, 132.3, 129.4, 128.6, 126.7, 79.4, 53.6, 49.8, 39.9, 28.4, 25.5, 22.2, 21.9, 20.7; IR (neat) cm\(^{-1}\) 3263, 3027, 2975, 2932, 2860, 1709, 1525, 1364, 1269, 1252, 1171, 1043, 1007, 699; \(\left[\alpha\right]_D^{25}\) +81.1 (\(c = 0.5, \text{CHCl}_3\)). Anal. calcd for C\(_{20}\)H\(_{29}\)NO\(_3\)S: C, 66.08; H, 8.04. Found: C, 66.04; H, 7.87. Minor isomer, partial characterization: \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.00 (br d, \(J = 8.0\) Hz, 1H), 4.01 (br m, 1H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 155.2, 140.5, 137.2, 134.1, 129.5, 129.0, 126.8, 79.4, 54.4, 49.7, 40.9, 28.4, 25.6, 22.1, 21.9, 19.6.

\((S_S,1R)-N\text{-Boc-2-}(E)-3,3\text{-Dimethyl-1-butenylsulfinyl)-1-phenylethanamine (62g)}\).

A solution of LiHMDS (0.83 mL), tert-butyl propylene thiirane S-oxide (0.100 g, 0.757 mmol), and (R)-\(53g\) (0.315 g, 0.908 mmol) afforded a diastereomeric mixture of \(\beta\)-amino sulfoxide \(62g\) (65%, 0.172 g, \(\text{dr} = 84:16\) by NMR integration of diastereomeric mixture) was isolated following flash column chromatography (60% EtOAc/hexanes). The major diastereomer was isolated via recrystallization from EtOAc/hexanes (40%, 0.105 g). Major isomer: mp 180–182 °C; \(^{1}\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.38–7.33 (m, 4H), 7.32–7.28 (m, 1H), 6.44
(d, J = 15.4 Hz, 1H), 6.24 (br s, 1H), 6.11 (d, J = 15.4 Hz, 1H), 5.24 (br s, 1H), 3.12–3.10 (m, 2H), 1.41 (s, 9H), 1.08 (s, 9H); \(^{13}\)C NMR (150.6 MHz, CDCl\(_3\)) \(\delta\) 155.1, 151.7, 140.3, 128.8, 127.8, 127.8, 126.3, 79.8, 59.8, 51.9, 34.3, 28.8, 28.4; IR (neat) cm\(^{-1}\) 3264, 3033, 2963, 2868, 1707, 1528, 1365, 1251, 1170, 1045, 1019; \(\left[\alpha\right]_{D}^{25}\) −32.0 (c = 0.7, CHCl\(_3\)). Anal. calcd for C\(_{19}\)H\(_{29}\)NO\(_3\)S: C, 64.92; H, 8.32. Found: C, 64.70; H, 8.12. Minor isomer, partial characterization: \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.47 (d, J = 15.2 Hz, 1H), 6.13 (d, J = 15.2 Hz, 1H), 5.07 (br m, 1H); \(^{13}\)C NMR (150.6 MHz, CDCl\(_3\)) \(\delta\) 154.9, 151.6, 140.4, 128.8, 128.1, 127.8, 126.3, 79.7, 61.0, 51.7, 34.2, 28.7, 28.3.

\(\text{(S,2R)}\)-N-Boc-1-(E)-3,3-Dimethyl-1-butenylsulfinyl)butan-2-amine (62h).

A solution of LiHMDS (0.83 mL), tert-butyl propylene thiirane S-oxide (0.100 g, 0.757 mmol), and (R)-53h (0.248 g, 0.832 mmol) afforded a diastereomeric mixture of \(\beta\)-amino sulfoxide 62h (71\%, 0.163 g, dr = 95:5 by \(^{1}\)H NMR integration of mixture) following flash chromatography (60\% EtOAc/hexanes). The major diastereomer was isolated via recrystallization from EtOAc/hexanes (52\%, 0.119 g). Major isomer: mp 146–147 °C; \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.47 (d, J = 15.4 Hz, 1H), 6.16 (d, J = 15.4 Hz, 1H), 5.31 (br d, J = 7.5 Hz, 1H), 3.92 (app sextet, J = 7.7 Hz, 1H), 2.95 (dd, J = 13.0, 7.2 Hz, 1H), 2.85 (dd, J = 13.1, 3.4 Hz, 1H), 1.78 (m, 2H), 1.44 (s, 9H), 1.10 (s, 9H), 0.99 (t, J = 7.4 Hz, 3H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 155.3, 151.1, 128.3, 79.4, 58.3, 49.3, 34.2, 28.8, 28.4, 27.3, 10.7; IR (neat) cm\(^{-1}\) 3220, 3039, 2966, 1698, 1545, 1363, 1289, 1249, 1174, 1053, 1028, 979; \(\left[\alpha\right]_{D}^{25}\) −5.7 (c = 0.2, CHCl\(_3\)). Anal. calcd for C\(_{15}\)H\(_{29}\)NO\(_3\)S: C, 59.37; H, 9.63. Found:
C, 59.26; H, 9.42. Minor isomer, partial characterization: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.86 (br s, 1H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 155.3, 151.1, 128.3, 79.4, 58.3, 49.3, 34.2, 28.8, 28.4, 28.0, 10.7.

**(R$_{s}$,2S)-N-Boc-1-(E)-3,3-Dimethyl-1-butenylsulfinyl)-3-phenylpropan-2-amine (62i).**

A solution of LiHMDS (0.83 mL), tert-butyl propylene thiirane S-oxide (0.100 g, 0.757 mmol), and iodide (S)-53a (0.300 g, 0.832 mmol) afforded a diastereomeric mixture of $\beta$-amino sulfoxide 62i (60%, 0.166 g, dr = 92:8 by NMR integration of diastereomeric mixture) following flash chromatography (60% EtOAc/hexanes). The major diastereomer was isolated via recrystallization from EtOAc/hexanes (47%, 0.129 g). Major isomer: mp 147−149 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32−7.22 (m, 5H), 6.46 (d, $J$ = 15.4 Hz, 1H), 6.09 (d, $J$ = 15.4 Hz, 1H), 5.50 (br d, $J$ = 6.9 Hz, 1H), 4.21 (m, 1H), 3.21 (dd, $J$ = 13.3, 6.8 Hz, 1H), 3.00 (dd, $J$ = 13.5, 8.0 Hz, 1H), 2.89 (m, 1H), 2.81 (dd, $J$ = 13.2, 3.9 Hz, 1H), 1.43 (s, 9H), 1.09 (s, 9H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 155.2, 151.1, 137.6, 129.4, 128.7, 128.0, 126.7, 79.5, 56.7, 49.6, 39.9, 34.2, 28.8, 28.4; IR (neat) cm$^{-1}$ 3361, 3251, 3039, 2963, 2906, 2867, 1706, 1525, 1365, 1270, 1253, 1173, 1046, 1020; $[\alpha]_D^{25}$ +14.2 (c = 1.0, CHCl$_3$). Anal. calcd for C$_{20}$H$_{31}$NO$_3$S: C, 65.72; H, 8.55. Found: C, 65.44; H, 8.68. Minor isomer, partial characterization: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.00 (br d, $J$ = 8 Hz, 1H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 155.2, 151.3, 137.0, 129.5, 129.0, 128.0, 126.8, 79.5, 58.3, 48.4, 40.7, 34.2, 28.8, 28.4.
(Rs,2S)-N-Boc-1-Phenyl-3-(E)-4-phenyl-1-butenylsulfinyl)-propan-2-amine (62j).

A solution of LiHMDS (0.61 mL), 4-phenylbut-1-ene thirane S-oxide (0.100 g, 0.555 mmol), and (S)-53a (0.221 g, 0.610 mmol) afforded a diastereomeric mixture of β-amino sulfoxide 62j (84%, 0.192 g, dr = 92:8 by 1H NMR integration of mixture) following flash chromatography (60% EtOAc/hexanes). The major diastereomer was isolated via recrystallization from EtOAc/hexanes (62%, 0.142). Major isomer: mp 154–155 °C; 1H NMR (400 MHz, CDCl₃) δ 7.31–7.12 (m, 10H), 6.49 (dt, J = 15.1, 6.8 Hz, 1H), 6.16 (d, J = 15.1 Hz, 1H), 5.42 (br d, J = 7.2 Hz, 1H), 4.20 (m, 1H), 3.17 (dd, J = 13.5, 6.4 Hz, 1H), 2.97 (dd, J = 13.4, 7.9 Hz, 1H), 2.84–2.72 (m, 4H), 2.55 (q, J = 7.6 Hz, 2H), 1.42 (s, 9H); 13C NMR (100.6 MHz, CDCl₃) δ 155.2, 140.4, 139.9, 137.5, 132.8, 129.4, 128.7, 128.5, 128.4, 126.8, 126.3, 79.6, 56.7, 49.4, 39.9, 34.4, 33.7, 28.4; IR (neat) cm⁻¹ 3362, 3269, 3061, 3025, 2977, 2924, 2857, 1690, 1522, 1267, 1252, 1170, 1102, 1046, 1020, 894; [α]D²⁵ +16.6 (c = 1.2, CHCl₃). Anal. calcd for C₂₄H₃₁NO₃S: C, 69.70; H, 7.56. Found: C, 70.05; H, 7.12. Minor isomer, partial characterization: 1H NMR (400 MHz, CDCl₃) δ 6.23 (d, J = 15.2 Hz, 1H), 4.95 (br d, J = 7.9 Hz, 1H), 4.09 (m, 1H); 13C NMR (100.6 MHz, CDCl₃) δ 155.2, 140.6, 140.0, 137.0, 132.7, 129.5, 129.0, 129.0, 128.66, 126.9, 126.3, 79.6, 58.4, 48.3, 40.8, 34.4, 33.7, 28.4.
1.4.7 Sulfenate Alkylation Competition Experiments (Table 15).

*Entry 1.* 2-(carbomethoxy)ethenyl tolyl sulfoxide (0.100 g, 0.446 mmol) was dissolved in THF (3 mL) under nitrogen and stirred at −78 °C. To the sulfoxide was added nBuLi (0.279 mL, 1.6 M in hexanes) via syringe. Following 5–10 min of stirring, a solution of the chiral iodide (S)-53a (0.322 g, 0.892 mmol) and butyl iodide (0.508 mL, 4.46 mmol) in THF (3 mL) at −78 °C was added via syringe to the sulfenate. The mixture was stirred at −78 °C for 3–4 h and then allowed to slowly warm to rt overnight. Solvent was removed under reduced pressure. Column chromatography using an EtOAc/hexanes (30:70) mixture as the eluent provided p-tolyl butyl sulfoxide139 (33%, 0.029 g) as an orange oil and a 91:9 diastereomeric mixture of 57a as a solid (27%, 0.043 g).

*Entry 2.* A solution of LiHMDS (1.22 mL) in diethyl ether (12 mL) at −78 °C was treated dropwise with precooled (−78 °C) propylene thirane S-oxide (0.100 g, 1.11 mmol) in diethyl ether (6 mL). Next a −78 °C solution of (S)-53a (0.801 g, 2.22 mmol) and butyl iodide (1.26 mL, 11.1 mmol) in THF (3 mL) was added to the sulfenate via syringe. The reaction was stirred for 3 h at −78 °C then allowed to warm to rt overnight. Solvent was removed under reduced pressure. The product ratio of 1-propenyl butyl sulfoxide:62a was found to be 1:1.4 as determined by analysis of 1H NMR peak integration. Data for 1-propenyl butyl sulfoxide: 1H NMR (400 MHz, CDCl3) δ 6.47 (dq, J = 15.2, 6.8 Hz, 1H), 6.24 (dq, J = 15.2, 1.6 Hz, 1H), 2.71 (t, J = 8.0 Hz, 2H), 1.93 (dd, J = 6.4, 1.6 Hz, 3H), 1.76–1.64 (m, 2H), 1.50 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); 13C NMR (100.6 MHz, CDCl3) δ 136.70, 133.56, 53.63, 24.10, 21.95,
Entry 3. 2-(carbomethoxy)ethenyl tolyl sulfoxide (0.100 g, 0.446 mmol) was dissolved in THF (3 mL) under nitrogen and stirred at −78 °C. To the sulfoxide was added nBuLi (0.279 mL, 1.6 M in hexanes) via syringe. Following 5–10 min of stirring, a solution of the chiral iodide (S)-53a (0.805 g, 2.23 mmol) and benzyl bromide (0.237 mL, 2.23 mmol) in THF (3 mL) at −78 °C was added via syringe to the sulfenate. The mixture was stirred at −78 °C for 3–4 h and then allowed to slowly warm to rt overnight. Solvent was removed under reduced pressure. Column chromatography using an EtOAc/hexanes (30:70) mixture as the eluent provided p-tolyl benzyl sulfoxide as a white solid and the sole product (96%, 0.101 g). Mp: 138–140 °C [lit.40 139–140 °C].

Entry 4. 2-(carbomethoxy)ethenyl tolyl sulfoxide (0.100 g, 0.446 mmol) was dissolved in THF (3 mL) under nitrogen and stirred at −78 °C. To the sulfoxide was added nBuLi (0.279 mL, 1.6 M in hexanes) via syringe. Following 5–10 min of stirring, a solution of the chiral iodide (S)-53f (0.277 g, 0.892 mmol) and butyl iodide (0.508 mL, 4.46 mmol) in THF (3 mL) at −78 °C was added via syringe to the sulfenate. The mixture was stirred at −78 °C for 3–4 h and then allowed to slowly warm to rt overnight. Solvent was removed under reduced pressure. Column chromatography using an EtOAc/hexanes (30:70) mixture as the eluent provided p-tolyl butyl sulfoxide139 as the sole product as an orange oil (92%, 0.081 g).

Entry 5. A 1:1 molar solution of 2-(carbomethoxy)ethenyl 2-pyridyl sulfoxide (0.094
g, 0.446 mmol) and 2-(carbomethoxy)ethenyl tolyl sulfoxide (0.100 g, 0.446 mmol) in THF (3 mL) at −78 °C was treated dropwise with 1.6 M nBuLi (0.558 mL, 0.892 mmol). The solution was stirred for ~10 min at −78 °C to ensure sulenate generation. Next a −78 °C solution of benzyl bromide (0.026 mL, 0.223 mmol) in THF (3 mL) was added to sulenate pot via syringe. The reaction was stirred for 3 h at −78 °C and then allowed to warm to rt overnight. Following standard workup the crude 1H NMR revealed the sole formation of the p-tolyl benzyl sulfoxide, which was isolated via column chromatography using EtOAc/hexanes (40:60) as the eluent.

*Entry 6.* A 1:1 molar solution of 2-(carbomethoxy)ethenyl 2-pyridyl sulfoxide (0.094 g, 0.446 mmol) and 2-(carbomethoxy)ethenyl tolyl sulfoxide (0.100 g, 0.446 mmol) in THF (3 mL) at −78 °C was treated dropwise with 1.6 M nBuLi (0.558 mL, 0.892 mmol). The solution was stirred for ~10 min at −78 °C to ensure sulenate generation. Next a −78 °C solution of (S)-53a (0.032 g, 0.089 mmol) in THF (3 mL) was added to sulenate pot via syringe. The reaction was stirred for 3 h at −78 °C and then allowed to warm to rt overnight. Following standard workup the crude NMR revealed the sole formation of the 57a (78%, 0.025 g), which was isolated via column chromatography using EtOAc/hexanes (40:60) as the eluent.
1.5 References


Chapter 2: A New Halogenating Reagent for the Ramberg-Bäcklund Rearrangement
2.0 A New Halogenating Reagent for the Ramberg-Bäcklund Rearrangement

2.1 Introduction

2.1.1 Background Information

Since its inception by Swedish chemists in 1940 the Ramberg-Bäcklund rearrangement (RBR) has endured as a classic carbon-carbon bond forming reaction used many times through the modern history of organic synthesis.\(^1,2\) The rearrangement has been applied in the synthesis of important organic building blocks, natural products and several stilbenoid anti-cancer agents.\(^3\) The RBR is the base promoted conversion of an α-halosulfone into an episulfone followed by the loss of SO\(_2\) to give an alkene through connection of the sulfone’s two α-carbons (Scheme 2.1). In the beginning the transformation was a two-pot process; the halogenation of the sulfone was followed by the base induced rearrangement.\(^3\)

![Scheme 2.1. The General Ramberg-Bäcklund Rearrangement](image)

The RBR is believed to progress through an anionic reaction mechanism (Scheme 2.2). The mechanism commences with fast and reversible α-deprotonation followed by a rate-determining 1,3-cyclization with the loss of halide to form an episulfone.\(^3\)

Relative rates of 1,3-cyclization mirror leaving-group (LG) ability with \(k_I > k_{Br} > k_{Cl}\)

![Scheme 2.2. RBR Mechanism](image)
Intermolecular displacement reactions of α-halosulfones with carbanionic nucleophiles are typically ineffective due to electronic repulsion from the sulfonyl moiety's polar oxygen atoms. Fortunately, in the case of the RBR an intramolecular displacement keeps the nucleophilic centre remote from the sulfonyl oxygen atoms, therefore avoiding the electronic factors that hinder the desired reactivity for the intermolecular case. There is also an important stereochemical preference for a “W-type” or co-planar arrangement of the α-proton and the LG (Scheme 2.3). This preference is nicely illustrated by the evaluation of RBR conditions on sulfones 1 and 3 respectively (Scheme 2.3). Upon treatment with base, sulfone 1, which possesses “W-type” geometry, undergoes a RBR to give the corresponding alkene 2 in good yield. In contrast, sulfone 3 gives primarily a 1,2-elimination product 4 when subjected to identical conditions.

\[
\begin{align*}
\text{1, "W geometry"} &\xrightarrow{\text{KOtBu, THF, -15 °C}} \text{2, 71\%} \\
\text{3} &\xrightarrow{\text{KOtBu, THF, -15 °C}} \text{2, 0.4\%} + \text{4, 73\%}
\end{align*}
\]

**Scheme 2.3. Preference for “W-geometry” in RBR**

Heating of the episulfone between room temperature and 110 °C causes the loss of sulfur dioxide to garner the corresponding alkene stereospecifically. There are several plausible mechanisms for the stereospecific loss of sulfur dioxide. As the rate of episulfone decomposition increases with the concentration of base, it is now
generally accepted that nucleophilic attack of the sulfone group occurs in the first step forming intermediate 5 (Scheme 2.4). Following the formation of the hypervalent intermediate 5 there are two postulated pathways proposed to account for the stereospecific decomposition. Bordwell et al.\textsuperscript{5} advocated formation of a 1,3-diradical species 6 with significant rotational barriers so that SO\textsubscript{2} extrusion is significantly faster than rotation around the carbon-carbon bond. In contrast, Woodward and Hoffman developed a theory in which decomposition occurs via a non-linear chelotropic extrusion from the hypervalent adduct.\textsuperscript{6} Hence, although the initial addition step is generally accepted the precise decomposition pathway remains elusive.\textsuperscript{7}

Scheme 2.4. RBR Sulfur Dioxide Extrusion Pathways

Various studies have explored the stereochemical outcome of the RBR (Scheme 2.5). In an early study, Neureiter\textsuperscript{8} observed changes in selectivity of an RBR reaction of α-chloroethyl ethyl sulfone dependent upon base identity. When potassium hydroxide (KOH) was used the Z-alkene predominated and when potassium tert-butoxide (tBuOK) was used the E-alkene predominated. In another study, α-chlorobenzyl benzyl sulfone was found to give the E-stilbene byproduct exclusively even when treated with KOH.\textsuperscript{3}
Scheme 2.5. Base and Substrate Controlled Stereoselectivity in the RBR

To investigate these observations further experiments were completed on diastereomERICally pure cis-1,2-dimethylthiirane dioxide.\textsuperscript{3,8} Interestingly, treatment with hydroxide or thermolysis gives only the Z-olefin, while treatment with KO\textsubscript{t}Bu gives the E-alkene as the major product (Scheme 2.6).

Scheme 2.6. Stereochemical Studies of the RBR

The results have been interpreted as shown below (Scheme 2.7).\textsuperscript{3} The population of cis- and trans- episulfones is established from the intramolecular cyclization step of the corresponding α-halosulfone. Since the base-mediated loss of SO\textsubscript{2} is stereospecific, the relative populations of cis and trans-episulfones should be equivalent to the ratio of Z and E olefin products. However, if there are acidifying substituents (e.g. R = Ph) attached to the episulfone or a stronger base than KOH (e.g. tBuOK) is used epimerization can occur to the more thermally stable trans-episulfone, thus giving the E-alkene.
An important breakthrough came when Meyers discovered a one-pot RBR with *in-situ* halogenation of the sulfone followed by rearrangement and alkene formation.\(^9\) This was achieved for benzyl sulfone using carbon tetrachloride (CCl\(_4\)), potassium hydroxide (KOH) and \(t\)-butyl alcohol reaction system (Scheme 2.8).\(^9\) For benzyl sulfone the chemistry worked very well giving quantitative yield of exclusively \(E\)-stilbene. However, Meyers’ method is plagued by polyhalogenation and carbene-alkene insertion for dialkyl sulfone systems often giving complex mixtures of products.\(^9\) Many of these problems were remedied by Chan’s modification which employed alumina-supported KOH, dibromodifluoromethane (CF\(_2\)Br\(_2\)), and \(t\)-butyl alcohol.\(^{10,11}\) Chan’s protocol gave excellent yields and moderate selectivities for dialkyl systems without any significant carbene insertion or polyhalogenation. Although Chan’s modification was a considerable breakthrough for the *in-situ* RBR, there existed examples of sulfones which required higher temperatures to undergo the RBR and provided poor yields using Chan’s conditions.\(^{12}\) Low yields were attributed to loss of the low boiling CF\(_2\)Br\(_2\) when reactions required increased temperatures. Franck solved this problem by trading relatively low boiling CF\(_2\)Br\(_2\) (23 °C) for its higher boiling homolog dibromotetrafluoroethane (C\(_2\)Br\(_2\)F\(_4\), 47 °C).\(^{12}\) Using Chan’s system with C\(_2\)Br\(_2\)F\(_4\), in place of CF\(_2\)Br\(_2\), Franck was able to achieve the
in-situ RBR on some otherwise stubborn glycolipid precursors to give the corresponding alkenes in good yields.\textsuperscript{12}

\begin{center}
\begin{tikzpicture}

\node (RBR) at (0,0) {\textbf{RBR}};
\node (in situ) at (0,-1) {\textbf{in situ}};
\node (KOH-Al\textsubscript{2}O\textsubscript{3}, CF\textsubscript{2}Br\textsubscript{2}) at (1.5,-2) {\textbf{KOH-Al\textsubscript{2}O\textsubscript{3}, CF\textsubscript{2}Br\textsubscript{2}}};
\node (R, R) at (2.5,-3) {R \rightleftharpoons R};
\node (KOH, CCl\textsubscript{4}, tBuOH, \Delta) at (5,-2) {\textbf{KOH, CCl\textsubscript{4}, tBuOH, \Delta}};
\node (Meyers method) at (5,-3) {\textbf{Meyers method}};
\node (Chan modification) at (1.5,-3.5) {\textbf{Chan modification}};
\node (Franck variant) at (5,-4) {\textbf{Franck variant}};
\node (100 \% \text{; } E \text{ only}) at (6,-3) {100 \% \text{; } E \text{ only}};
\node (100 \% \text{; } E \text{ only}) at (6,-4) {100 \% \text{; } E \text{ only}};
\node (100 \% \text{; } E \text{ only}) at (6,-5) {100 \% \text{; } E \text{ only}};
\node (100 \% \text{; } E \text{ only}) at (6,-6) {100 \% \text{; } E \text{ only}};
\node (R = alkyl) at (2.5,-3.5) {R = alkyl};
\node (excellent yield) at (1.5,-3.6) {excellent yield};
\node (good selectivity) at (1.5,-3.7) {good selectivity};
\node (difficult substrates) at (5.2,-4.2) {difficult substrates};
\node (R \rightleftharpoons R) at (0,-4) {R \rightleftharpoons R};
\node (KOH-Al\textsubscript{2}O\textsubscript{3}, C\textsubscript{2}Br\textsubscript{2}F\textsubscript{4}, tBuOH, \Delta) at (5,-4) {\textbf{KOH-Al\textsubscript{2}O\textsubscript{3}, C\textsubscript{2}Br\textsubscript{2}F\textsubscript{4}, tBuOH, \Delta}};
\node (R \rightleftharpoons R) at (0,-5) {R \rightleftharpoons R};
\node (KOH-Al\textsubscript{2}O\textsubscript{3}, C\textsubscript{2}Br\textsubscript{2}F\textsubscript{4}, tBuOH, \Delta) at (5,-5) {\textbf{KOH-Al\textsubscript{2}O\textsubscript{3}, C\textsubscript{2}Br\textsubscript{2}F\textsubscript{4}, tBuOH, \Delta}};
\node (difficult substrates) at (5.2,-5.2) {difficult substrates};
\end{tikzpicture}
\end{center}

**Scheme 2.8. Key Improvements to the RBR**

The RBR has been used countless times throughout the history of organic synthesis and examples in the literature have been reviewed in 1977\textsuperscript{13} and 2004.\textsuperscript{3} Therefore this review will focus primarily on contributions made to the literature from 2004 to present.

Recent efforts using the RBR reaction to access cyclic olefins has proved fruitful. Yao developed a creative way to produce cyclic dienes by way of a ring-closing metathesis (RCM)/ RBR strategy (Scheme 2.9).\textsuperscript{14}

\begin{center}
\begin{tikzpicture}

\node (R\textsuperscript{1}OH) at (0,0) {\textbf{R\textsuperscript{1}OH}};
\node (X) at (1.5,0) {\textbf{X}};
\node (R\textsuperscript{3}R\textsuperscript{4}) at (2.5,0) {\textbf{R\textsuperscript{3}R\textsuperscript{4}}};
\node (sulfone formation) at (1.5,0.5) {sulfone formation};
\node (R\textsuperscript{1}OH, X, R\textsuperscript{3}R\textsuperscript{4}) at (0,0) {R\textsuperscript{1}OH + X \rightleftharpoons R\textsuperscript{3}R\textsuperscript{4}};
\node (R\textsuperscript{1}S\textsuperscript{O}R\textsuperscript{3}R\textsuperscript{4}) at (4,0) {R\textsuperscript{1}S\textsuperscript{O}R\textsuperscript{3}R\textsuperscript{4}};
\node (RCM) at (5,0) {RCM};
\node (sulfone diene) at (4,0.5) {sulfone diene};
\node (cyclic sulfone) at (5,0.5) {cyclic sulfone};
\node (cyclic diene) at (6,0.5) {cyclic diene};
\node (sulfone diene) at (4,1) {sulfone diene};
\node (cyclic sulfone) at (5,1) {cyclic sulfone};
\node (cyclic diene) at (6,1) {cyclic diene};
\end{tikzpicture}
\end{center}

**Scheme 2.9. Cyclic Dienes via a RCM/RBR Strategy**

Synthesis of the sulfone diene precursors using well established chemistry (Scheme 2.9). First, a Mitsunobu reaction of an alkenyl alcohol 7 with thioacetic acid gave the corresponding thioester. In situ hydrolysis and alkylation of the resulting thiolate
with an alkenyl halide 8 garnered the corresponding sulfide. Oxidation of the sulfide to the corresponding sulfone diene proceeded in excellent yields using mCPBA.

**Scheme 2.10. Synthesis of Cyclic Olefins via RCM/RBR Strategy**

With dienes 9 and 12 in hand, Yao used Grubbs’ ruthenium-based catalyst to effect a RCM garnering the corresponding cyclic sulfones 10 and 13, respectively. Subsequent in-situ RBR of 10 and 13 using CF₂Br₂ gives the corresponding cyclic dienes 11 and 14, respectively. Block has recently developed a “prepackaged” Ramberg-Bäcklund reagent which he used in a tandem Diels-Alder/RBR process. Chloromethanesulfonyl ethene was used as a synthetic equivalent of allene in a [4+2] cycloaddition followed by a base-mediated RBR to garner the corresponding allene cycloadduct (Scheme 2.11). Allene synthons are valuable because using allene itself is often impractical because of its low reactivity, cost and experimental complexity.

**Scheme 2.11. “Prepackaged” RBR Reagent**
Chloromethanesulfonylethene was heated in toluene with a selection of dienes to give the corresponding Diels-Alder adducts in excellent yield (Table 1). Subsequent treatment with tBuOK in THF gives the RBR products in moderate to excellent yields (Table 2.1).15

Table 2.1. Diels-Alder/RBR Sequence

<table>
<thead>
<tr>
<th>Diene</th>
<th>Cycloadduct</th>
<th>yield (%)</th>
<th>Product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image1" alt="Cycloadduct" /></td>
<td>96</td>
<td><img src="image2" alt="Product" /></td>
<td>59</td>
</tr>
<tr>
<td></td>
<td><img src="image3" alt="Cycloadduct" /></td>
<td>95&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image4" alt="Product" /></td>
<td>51</td>
</tr>
<tr>
<td></td>
<td><img src="image5" alt="Cycloadduct" /></td>
<td>97</td>
<td><img src="image6" alt="Product" /></td>
<td>79</td>
</tr>
</tbody>
</table>

<sup>a</sup>exo:endo = 6.3:1

Intrigued by these results Block evaluated alkene 15 as a potential partner for an ene reaction/RBR tandem sequence (Scheme 2.12). When β-pinene was heated with alkene 15 in toluene at 135 °C for 1.5 h the ene adduct 16 was formed as a crystalline solid in good yield.15 Treating adduct 16 with base and heat in THF afforded triene 18 in low yield. When 16 was treated with tBuOK at 0 °C intermediate 17 could be isolated in low yield. Thus, triene 18 is believed to be formed by the ene/1,2-elimination/vinylogous RBR tandem sequence outlined in
Scheme 2.12. Although, not synthetically useful due to low yields the result was particularly exciting because it is the first example of an ene/RBR tandem sequence.

Scheme 2.12. Ene/1,2-elimination/RBR Tandem Sequence

In recent years the RBR has been used as a key step in the synthesis of stilbenoid natural products, drugs, and biologically active targets. Many of the targets contain E stereochemistry about the double bond but some contain Z stereochemistry making them difficult targets to obtain using the RBR (Figure 2.1). This is due to the fact that exclusively the E isomer is typically generated from dibenzylic sulfones because of fast epimerization of the intermediate episulfone.

Figure 2.1. Bioactive Z-Stilbenoids

In a recent paper, Taylor was able to effect Ramberg-Bäcklund transformations on a selection of dibenzylic sulfones to yield predominantly the Z olefin. This result was truly remarkable as high Z selectivity in the RBR of dibenzylic systems is unprecedented. The best Z selectivities were achieved when a free hydroxyethyl group was attached to one of the aromatic rings (Scheme 2.13).
Taylor proposed a mechanism to account for such a high degree of Z selectivity in the systems containing free hydroxyethyl groups. First, a predominance of the cis-episulfone is formed likely due to a favorable intramolecular π-stacking interaction that minimizes the contact of the sulfone molecules with the solvent molecules, thereby directing the cis-orientation initially (Scheme 2.14). Next, an intramolecular base promoted loss of sulfur dioxide was invoked before any epimerization of the intermediate thiirane S,S-dioxide can occur. Thus, retention of the cis-configuration of the episulfone is evident as the Z alkene. Specifically, alkoxide attack from the hydroxyethyl group of the episulfone 19 occurs, opening the episulfone to form a five-membered intermediate 20 (Scheme 2.14). With the –SO₂ group anti-periplanar to the leaving group 20 undergoes a 5-exo-tet ring breaking process via a pseudo E1cB elimination mechanism to give stilbenoid 21.

**Scheme 2.13. High Z Selectivity in RBR of Stilbenoid Systems**

**Scheme 2.14. Mechanism for cis-Olefin Formation**
In the same paper, Taylor applied his methodology to synthesize the integrastatin nucleus, the important core structure of the integrastatin family of natural products (Scheme 2.15). Sulfone 22 underwent a Z-selective RBR followed by alcohol oxidation to form the corresponding Z-alkene 23 in excellent dr. The importance of accessing primarily the cis-isomer 23 is made apparent by the fact that only the cis-isomer of 23 underwent the key Lewis acid-promoted cyclization reaction to give the corresponding tetracycle 24. Subsequent benzylic oxidation of 24 with PDC-tBuOOH provides the integrastatin nucleus 25 in good yield.\(^{19}\)

![Scheme 2.15. Synthesis of Integrastatin Nucleus via a Z-selective RBR](image)

Taylor has also used the RBR to synthesize biologically active trans-stilbenes.\(^{20}\) In one example, the resveratrol derived anti-cancer agent DMU-212 was synthesized via a Ramberg-Bäcklund protocol (Scheme 2.16). The synthesis began with sulfide formation from the coupling of thiol 26 to benzyl bromide 27. The product was oxidized to the corresponding sulfone 28 using \(m\)CPBA. Sulfone 28 was subjected to Ramberg-Bäcklund conditions to give DMU 212 in excellent yield and E selectivity.\(^{20}\)
Scheme 2.16. Synthesis of DMU-212 from a Ramberg-Bäcklund Protocol

A Ramberg-Bäcklund approach has also been used to synthesize a variety of other naturally occurring polyphenols belonging to the resveratrol family of natural products. A racemic synthesis of polyphenol quadrangularin A was achieved using an E-selective RBR as a key step in the synthesis. Subsequent demethylation with boron tribromide provided the free polyphenol in moderate yield (Scheme 2.17).

Scheme 2.17. Synthesis of Quadrangularin A

The RBR has also been applied as a strategy to synthesis a variety of conjugated polyenes. Recently, Brückner has synthesized some very intriguing linear distannylated polyenes stereoselectively using a RBR. Judicious choice of synthetic
strategy can provide complementary isomers: the all $E$-polyene or mono-$Z$-polyene (Scheme 2.18). In one example a distannylated mono-$Z$-pentaene was accessed in high $Z$ selectivity from a Julia olefination using aldehyde 31 and sulfone 32. Using a RBR approach, the complementary all $E$-pentaene could be accessed with high selectivity from sulfone 33. This example highlights the potential of the RBR as a highly stereoselective reaction.

![Scheme 2.18. RBR versus Julia Olefination in Synthesis of a Distannylated Pentaene](image)

The RBR has also been used in the synthesis of some polyene natural products. Apoptolidin, a polyene natural product produced by the actinomycete, *Nocardiopsis sp.*, has considerable activity toward inducing selective apoptotic cell death of rat glia cells transformed with adenovirus E1A and E1A/E1B19 K oncogenes. Vogel recently synthesized the key C(1)-C(11) polyene fragment 34 of apoptolidin using a RBR as the key step (Scheme 2.19). Sulfone 35 was protected using tert-butyl dimethylsilyl chloride in DMF followed immediately by exposure to Ramberg-
Bäcklund conditions. This provided polyene 35 in good yield and excellent selectivity without epimerization.²⁴

\[
\text{O} \quad \text{O} \quad \text{S} \\
\text{O} \quad \text{OH} \\
\text{TES}
\]

³⁴ OTBS

\[ \text{OTBS}, \text{72\%}, \text{99\% ee, (E,E,E)/(E,E,Z) = 12:1} \]

**Scheme 2.19. Synthesis of the C(1)-C(11) Polyene Fragment of Apoptolidin**

Recently, canthaxanthin 36, a naturally occurring keto-carotenoid, was prepared using a RBR (Scheme 2.20).²⁵,²⁶ Sulfone 37 underwent the RBR using a CCl₄ and sodium methoxide protocol to provide stable compound 38. Subsequent dehydrosulfonation gave canthaxanthin 36 in excellent yield.²⁶ Canthaxanthin has been synthesized directly from β-carotene via oxidation, but these protocols remain impractical due to the poor stability of carotenoids under oxidative conditions.²⁶ The main advantage of the Ramberg-Bäcklund/sulfone chemistry is that the intermediates are stable easily handle solids which can be purified by recrystallization with ease.
Ramberg-Bäcklund chemistry has also been used to synthesize several natural products. Nicolaou used an ingenious cyclodimerization/RBR strategy as the key step in the syntheses of cyclophane natural products cylindrocyclophane A and F (Scheme 2.21). First, cleavage and subsequent cyclodimerization of thioacetate 39 occurred, followed by immediate oxidation to provide sulfone 40 in good yield. Next Nicolaou invoked a RBR to transform sulfone 40 into alkene 41. The Ramberg-Bäcklund reagents provided the corresponding alkene 41 in an isomeric ratio of $E,E/E,Z = 12:1$, however complete isomerization to $E,E-41$ was achieved by treatment with $[\text{Pd(CH_3CN)}_2\text{Cl}_2]$. The use of the RBR ensured the proper trans geometry was established in the olefins so that future transformations provided cylindrocyclophanes A and F.  

Scheme 2.20. Canthaxanin Synthesis

\[
\text{canthaxanin 36 86%}
\]
Scheme 2.21. Synthesis of Cylindrocyclophanes A and F

A ring-closing metathesis (RCM)-RBR sequence for the synthesis of macrocyclic natural product aigialomycin D (Scheme 2.22). One of the alkene functionalities was masked by a sulfone group because attempting RCM on a triene precursor with an alkene already in place becomes problematic. This is due to the competing and kinetically favored metathesis reaction producing a six-membered ring. Following macrocyclization by RCM the sulfonyl compound underwent the RBR with ease and good $E$ selectivity to reveal the masked alkene.

Scheme 2.22. Synthesis of Aigialomycin D via RCM-RBR Sequence
Sesquiterpene artemisinin is a natural product with antimalarial activity and some of its derivatives are now widely used to treat malarial infection.\textsuperscript{29} A Ramberg-Bäcklund protocol was employed to synthesize a selection of exo-olefinated deoxoartemisinin derivatives (Table 2.2).\textsuperscript{30}

Table 2.2. Synthesis of exo-Olefinated Deoxoartemisinin Derivatives via the RBR

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>E/Z ratio</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R\textsuperscript{1} = H, R\textsuperscript{2} = Br</td>
<td>50:50</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>R\textsuperscript{1} = CH\textsubscript{3}, R\textsuperscript{2} = Br</td>
<td>84:16</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>R\textsuperscript{1} = n-propyl, R\textsuperscript{2} = Br</td>
<td>92:8</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>R\textsuperscript{1} = R\textsuperscript{2} = CH\textsubscript{3}</td>
<td>-</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>R\textsuperscript{1} = H, R\textsuperscript{2} = Ph</td>
<td>70:30</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>R\textsuperscript{1} = vinyl, R\textsuperscript{2} = Br</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

Under RBR conditions, 10-α-methanesulfonyl dihydroartemisinin gave a racemic mixture of 10-bromomethylene deoxoartemisinin (Table 2.2, entry 1). Increasing the chain length (R\textsuperscript{1} or R\textsuperscript{2}) in the starting sulfone improved the diastereoselectivity with
the E-olefin as the major product (Table 2.2, entries 1-3). The steric bulk of an isopropyl substituted sulfone led to an attenuated yield of 26% (Table 2.2, entry 4). Interestingly, unlike alkyl substituted systems, the benzyl substituted sulfone led to a mixture of E- and Z-isomers of 10-benzylidenedeoxyartemisinin containing no bromine atom (Table 2.2, entry 5). Surprisingly, no product was obtained from the allyl substituted sulfone (Table 2.2, entry 6). Of note is the fact that this is a rare literature example when a bromo-olefinated product has been synthesized from a RBR. Such mono-brominated olefinic species have the potential to be subject to further transformations (e.g. organometallic coupling reactions).

The RBR has a recent history of application in carbohydrate and related syntheses. Zhu has reported the synthesis of methylene exo-glycals 42, important synthetic building blocks for the synthesis of glycoconjugate mimetics and other C-glycosidic molecules of biological interest (Scheme 2.23). Compound 44 was obtained from the corresponding glycosyl thiol 43 via its reaction with dichloromethane to the corresponding sulfide, which underwent subsequent oxidation with mCPBA. Previous synthesis of methylene exo-glycals 42 are typically low yielding and involve the use of harsh conditions or starting materials that are challenging to obtain. Therefore, this simple and mild Ramberg-Bäcklund strategy is a solution to provide these elusive and valuable methylene exo-glycals.

Scheme 2.23. Synthesis of Methylene exo-Glycals 42
Conduritols are molecules possessing interesting biological properties as antibiotics, growth regulators, and antileukemics.\textsuperscript{32,33} Recently, sugar derived thiepanes were used to synthesize conduritols in a solid-supported synthesis (Scheme 2.24).\textsuperscript{34} In one instance, thiepane 45 was attached to a polystyrene-CHO resin to give solid-supported thiepane 46. Sulfoxidation of 46 followed by sequential treatment under Meyer’s Ramberg-Bäcklund conditions provided the resin-supported cyclohexene derivative 47. Finally, mobilization of the conduritol 48 from the solid phase with trifluoroacetic acid (TFA) occurred with no memory of immobilization.\textsuperscript{34} Excitingly, this is the first example of Ramberg-Bäcklund chemistry occurring on a solid-phase supported substrate. Moreover, this solid-phase supported synthesis provided highly pure conduritol derivatives in higher yields than the comparable solution phase synthesis.

Scheme 2.24. RBR on a Solid-phase Support

Pathak et al. recently synthesized sugar substituted pyrroline 49 from a Ramberg-Bäcklund transformation using CBr\textsubscript{2}F\textsubscript{2}/KOH-Al\textsubscript{2}O\textsubscript{3} on a sugar derived thiomorpholine-S,S-dioxide 50 (Scheme 2.25).\textsuperscript{35} Although the reaction occurs in low yield (33\%) it lends access to molecule 49 which is a valuable synthetic building
block that can be further derivatized to biologically active compounds uniflorine A analogue 51 and sugar substitute dihydroxylated pyrroline 52.\textsuperscript{36,37}

![Scheme 2.25. Synthesis of 51 and 52 via a RBR](image)

Polyoxygenated cycloalkenes are currently being investigated as carbohydrate mimetics and have been recently synthesized using a RBR.\textsuperscript{38} Sugar-derived chlorosulfones were treated with tBuOK to effect the rearrangement providing the corresponding cycloalkenes (Scheme 2.26). Tri-substituted chlorosulfone 53 underwent the base-mediated rearrangement in tetrahydrofuran to cyclopentene 54 in good yield. Even the \( \alpha \)-substituted sterically hindered chlorosulfone 55 could be transformed to tetra-substituted cyclopentene 56 in moderate yield via the RBR.\textsuperscript{38} Finally, the Ramberg-Bäcklund transformation was attempted on a 7-membered chlorosulfone 57, and worked successfully providing cyclohexene 58 in moderate yield.
2.1.2 Proposed Reagent for RBR

Although there is no disputing the efficacy of the halogenating agents in the aforementioned *in-situ* RBR protocols, significant economic and environmental drawbacks do exist. As previously mentioned CCl$_4$ only works well for diaryl systems so CF$_2$Br$_2$ and C$_2$Br$_2$F$_4$ are the reagents of choice for most substrates.$^{10,12}$ One problem with using these reagents is that they are relatively expensive each costing 10 USD/g.$^{39}$ The other major problem is that CCl$_4$, CF$_2$Br$_2$ and C$_2$Br$_2$F$_4$ are all listed as Ozone Depleting Substances (ODS) in North America and are being actively phased out.$^{40}$ In fact, to the author’s knowledge, only one supplier in the US provides CF$_2$Br$_2$ and C$_2$Br$_2$F$_4$. Our group was not even allowed to purchase these chemicals from the US and ship them to Canada due to federal regulations.$^{41}$ Hence, these practical limitations to the common *in-situ* halogenating reagents for the RBR create
a demand for a new halogenating agent devoid of such restrictions. After a literature search it was discovered that the non-ODS hexachloroethane (C$_2$Cl$_6$) had been attempted before for the \textit{in-situ} RBR.\textsuperscript{42} However, the reaction proved to be highly substrate specific, working only on activated cyclic systems containing an ethyl ester $\alpha$ to the sulfonyl group as in the example of Scheme 2.27.\textsuperscript{42}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme227.png}
\end{center}

\textbf{Scheme 2.27. An RBR using Hexachloroethane}

1,2-Dibromotetrachloroethane (C$_2$Br$_2$Cl$_4$) is a common brominating reagent in organic synthesis and has been used numerous times to this end.\textsuperscript{43-47} The compound has several attractive properties compared with the aforementioned RBR reagents. As a solid, it is practical to use as quantitative molar equivalents can be measured and introduced with ease. CBr$_2$F$_2$, on the other hand, has a boiling point of 23 $^\circ$C and challenges may arise for its quantitation. Indeed, some papers report the use of 75\textsuperscript{48} and even >1000\textsuperscript{49} molar equivalents of CBr$_2$F$_2$ under the Chan conditions. As noted, 1,2-dibromotetrachloroethane is relatively inexpensive and it is not listed as an ODS. To the author’s knowledge C$_2$Br$_2$Cl$_4$ has never been used as a reagent for the $\alpha$-bromination of sulfones or in an \textit{in-situ} RBR, although there is a literature report of the reagent being used to halogenate a cyclic sulitone.\textsuperscript{50} Given this lack of literature precedent the goal was to evaluate C$_2$Br$_2$Cl$_4$ as a general reagent for the \textit{in-situ} RBR on unactivated substrates.
2.2 Results and Discussion

2.2.1 Sulfone RBR Precursor Synthesis and RBR Optimization Experiments

Most sulfone starting materials were synthesized by established protocols usually involving a thiolate alkylation/oxidation protocol shown in Scheme 2.28 below (see Experimental section for detailed procedures and yields).

Scheme 28. Preparation of Sulfone Precursors for the RBR

Benzyl sulfone was chosen as the substrate to begin initial investigations using C$_2$Br$_2$Cl$_4$ as the halogenating agent because this substrate is known to undergo the \textit{in-situ} RBR with excellent yields and selectivity using Meyers' conditions.$^{39}$ For the first attempt, benzyl sulfone was dissolved in a mixture of tBuOH : H$_2$O (5:1) and stirred at room temperature (rt). Potassium hydroxide (KOH) was added followed by C$_2$Br$_2$Cl$_4$. The reaction was sluggish and after 3 days of stirring at rt, NMR analysis revealed only 10% conversion of starting material to exclusively the \textit{E}-stilbene product (Table 2.3, entry 1). In hopes of improving the reaction rate, the base component of Chan’s reagent (KOH-Al$_2$O$_3$) was evaluated and gave an improved conversion of starting material:product ratio after 24 h of stirring at rt and increasing the equivalents of C$_2$Br$_2$Cl$_4$ to 1.5 advanced the conversion still further (Table 2.3, entries 2 & 3). In a parallel result increasing the temperature to reflux for 12 hr gave an improved conversion to 90% \textit{E}-stilbene (Table 2.3, entry 4). Next, in entry 5, the amounts of both KOH-Al$_2$O$_3$ and C$_2$Br$_2$Cl$_4$ were increased and the
mixture was refluxed for 12 h. Gratifyingly, increasing the amounts of both reagents brought about full substrate conversion to E-stilbene as analyzed by $^1$H NMR and an eventual 95% isolated yield.

To achieve the RBR on more sensitive substrates, it was felt that a lower reaction temperature should be sought. By visual inspection, the solubility of benzyl sulfone in $t$BuOH was rather low, which may have been a cause for the long reaction times at rt. To combat solubility issues, THF was added initially to a flask charged with benzyl sulfone to ensure full solubility. Upon complete dissolution of benzyl sulfone in THF at rt, $t$BuOH was added. Next, KOH-Al$_2$O$_3$ was added followed immediately by the dropwise addition of a solution of C$_2$Br$_2$Cl$_4$ in THF. Evaluation of a $^1$H NMR spectrum of the crude reaction mixture after showed complete conversion to E-stilbene at rt without any detection of the Z isomer. Purification by filtration through a silica plug and subsequent flash chromatography gave exclusively E-stilbene in excellent yield (Table 2.3, entry 6).

Table 2.3. Optimization of in-situ RBR with C$_2$Br$_2$Cl$_4$ (E+) as the Halogenating Agent

<table>
<thead>
<tr>
<th>entry</th>
<th>base (eq.)</th>
<th>E+ (eq.)</th>
<th>solvent</th>
<th>T</th>
<th>time</th>
<th>Conv. (%)$^a$</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH (1.0)</td>
<td>1.1</td>
<td>$t$BuOH/H$_2$O(5/1)</td>
<td>rt</td>
<td>3 d</td>
<td>10</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>KOH-Al$_2$O$_3$ (15.1)</td>
<td>1.1</td>
<td>$t$BuOH</td>
<td>rt</td>
<td>24 h</td>
<td>72</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td>KOH-Al₂O₃</td>
<td>tBuOH</td>
<td>rt</td>
<td>24 h</td>
<td>77</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
<td>-------</td>
<td>-----</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(15.1)</td>
<td></td>
<td>rt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(15.1)</td>
<td></td>
<td>reflux</td>
<td>12 h</td>
<td>90</td>
<td>nd</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(18.9)</td>
<td></td>
<td>reflux</td>
<td>12 h</td>
<td>100</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(18.9)</td>
<td></td>
<td>rt</td>
<td>4 h</td>
<td>100</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) % reaction conversion estimated by NMR. \( ^b \) The E/Z ratio was 100:0 in all cases (NMR).

### 2.2.2 Expansion of RBR Substrate Scope

Using the optimized reaction procedure, an exploration of the scope of the reaction on other substrates was undertaken (Table 2.4). Initially a series of sulfones containing \( \alpha \)-aromatic substituents were evaluated, as these have been shown to react favorably under other in-situ RBR systems (Table 2.4, entries 2-9). Substituted 3-nitro- and 3-bromobenzyl sulfones also gave excellent yields and complete stereoselectivities (Table 2.4, entries 2 & 3). As expected, a 2-naphthyl substituted sulfone gave excellent yield and complete E stereoselectivity (Table 2.4, entry 9).

Indeed all stilbenoid substrates attempted gave yields of \( \geq 82\% \) with complete E selectivity, including a 2-pyridyl based system which was generated from the corresponding sulfone in 92\% yield (Table 2.4, entry 5). A 2,6-disubstituted pyridine containing disulfone substrate was also attempted and yielded the
corresponding \( E,E\)-bis(2-styryl)pyridine with complete E selectivity in moderate yield (Table 2.4, entry 10).

**Table 2.4. Scope of the \( \text{C}_2\text{Br}_2\text{Cl}_4 \) Mediated Ramberg-Bäcklund Rearrangement**

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>equiv. of ( \text{C}_2\text{Br}_2\text{Cl}_4 )</th>
<th>time (h)</th>
<th>yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H, H, CH</td>
<td>1.8</td>
<td>8</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>3-Br, H, CH</td>
<td>1.8</td>
<td>8</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>3-NO(_2), H, CH</td>
<td>1.8</td>
<td>8</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>4-CF(_3), H, CH</td>
<td>1.8</td>
<td>8</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>H, H, N</td>
<td>1.8</td>
<td>2</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>4-MeO, 3,5-bis(MeO), CH</td>
<td>1.8</td>
<td>8</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>4-MeO, H, CH</td>
<td>1.8</td>
<td>8</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>3,5-bis(MeO), H, CH</td>
<td>1.8</td>
<td>8</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td><img src="image1" alt="Diagram" /></td>
<td>1.8</td>
<td>8</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td><img src="image2" alt="Diagram" /></td>
<td>2.8</td>
<td>8</td>
<td>49</td>
</tr>
</tbody>
</table>
Isolated yield of pure material unless otherwise indicated. Obtained as an E:Z isomeric ratio of 72:28. Products were obtained 91% pure. Contaminants were monobrominated congeners. Mixture was heated at 79 °C. Reaction performed under microwave conditions (300 W instrument) at 78 °C.

These RBR conditions also worked reasonably well for a primary dialkyl system (Table 2.4, entry 11), which can be plagued with polyhalogenation and carbene insertion byproducts (for CCl₄). The dioctyl sulfone gave the corresponding alkene in moderate yield and selectivities comparable to that garnered by Chan’s protocol without any detection of polyhalogenated byproducts. Unfortunately, dicyclopentylsulfone did not undergo the in-situ RBR with our C₂Br₂Cl₄ system. Even with prolonged heating, increased equivalents of reagent or microwave irradiation, starting material remained without any observed evidence of alkene formation (Table 2.4, entries 14 & 15). This result contrasts Chan’s conditions, which can bring about the conversion of dicyclopentyl sulfone to the corresponding alkene. The difference in reactivity could be attributed to steric factors of the brominating agent; C₂Br₂Cl₄ is a bulkier reagent than Chan’s CBr₂F₂ and may be unable to brominate an
already sterically hindered sulfonyl α-anion of dicyclopentylsulfone. It is anticipated that CBr₂F₂ also has reduced entropic requirements in the transition state for the release of a Br to a nucleophile.

Cyclic sulfones have proved to be quite acquiescent to in-situ RBR. As such, an N-Boc protected thiazine S,S-dioxide was exposed to the RBR conditions, which delivered the corresponding Boc protected 3-pyrroline in 52% isolated yield (Table 2.4, entry 12), a yield similar to other 5-membered cyclic alkenes prepared under RBR conditions.³⁴⁸,⁵¹ Finally, the RBR protocol was evaluated for the olefination of benzyl hexyl sulfone, a reaction which gave the corresponding alkene with complete E stereoselectivity and 65% yield by NMR analysis (Table 2.4, entry 13). However, there was the significant formation of brominated alkene byproducts assigned to be E- and Z-PhBrC=CHC₅H₁₁ (ca. 10%, inseparable by flash chromatography, detected by GC-MS) as a consequence of dihalogenation of the sulfone substrate. This result can be explained by differences in the relative basicities of the α-protons on the benzylic and hexyl sides of the sulfone. The benzylic protons are more acidic (lower pKa ~ 23.4)⁵² than the alkyl α-protons (pKa ~ 31.0).⁵² Therefore, assuming kinetic deprotonations mirror thermodynamic pKa values, the benzylic carbon is more readily deprotonated and subsequently brominated than the hexyl α-carbon. Consequently, dibromination could occur at the benzylic site in competition with anion formation at the α-carbon on the hexyl side of the molecule. If two bromines are incorporated at the benzyl site, eventual formation of the α-sulfonyl anion on the hexyl side of the molecule leads to the formation of a brominated episulfone. Fast extrusion of SO₂ would yield a brominated alkene byproduct. Indeed, an analysis of
the $^1$H NMR spectrum of the reaction mixture indicated that the minor products of this 2-pentylstyrene-forming mixture possessed triplets for their lone vinylic resonance. This is fully consistent with bromine incorporation at the benzylic site and not at the 2-position of the pentylstyrene byproducts (vide supra). Substantial effort was expended to adapt the reaction conditions to reduce the amount of monobromoalkene, but improvements were minimal.

The RBR chemistry of benzyl hexyl sulfone and particularly the presence of a monobrominated alkene allow some conclusions about the reaction chemistry of C$_2$Br$_2$Cl$_4$ with $\alpha$-sulfonyl anions. Although there is an instance of C$_2$Br$_2$Cl$_4$ acting as a source of electrophilic chlorine in the literature,$^{50}$ GC-MS analysis of the benzyl hexyl sulfone RBR mixture did not reveal any evidence in support of chlorine incorporation. Based on this example, C$_2$Br$_2$Cl$_4$ delivers only bromine atoms to the sulfones.

In addition to the preference for bromination and the steric arguments noted above, the observed chemistry permits additional remarks about the bromination chemistry of C$_2$Br$_2$Cl$_4$, particularly in relation to that of CF$_2$Br$_2$. Since the RBR with both reagent systems occurs with the same solid phase base, the dehydrohalogenation step of the RBR under each set of conditions might be expected to be comparable, particularly since the two conditions share similar solvent systems. Assuming this is true then differences in observed chemistry of the two electrophiles should be based on bromination tendencies. One difference has already been noted for steric effects (C$_2$Br$_2$Cl$_4$ being bulkier than CF$_2$Br$_2$). The chemistry of benzyl hexyl sulfone suggests that the bromination chemistry using
C₂Br₂Cl₄ may be faster than with CF₂Br₂ for non-sterically demanding sulfones, presumably since the reagent at hand brominates with concurrent E2 chemistry as opposed to carbanion or carbene formation. Chan evaluated CF₂Br₂ with benzyl hexyl sulfone in his original paper, and there is no mention of additional bromination,¹⁰ whereas the C₂Br₂Cl₄ system delivered some minor brominated impurities as outlined above. For comparison, there are several examples of CCl₄ delivering unwanted chlorines.³ It would appear that the balance between bromination and dehydrobromination is optimal for the CF₂Br₂ RBR system.

2.2.3 Formal Total Synthesis of Resveratrol

Given the success of this RBR method for the synthesis of stilbenoids it was decided to attempt the total synthesis of E-resveratrol, a naturally occurring phenolic stilbenoid found in the skins of red grapes. Currently E-resveratrol is the subject of numerous biological studies for several properties including anticancer,⁵³ cardiovascular,⁵⁴ anti-inflammatory,⁵⁵ anti-aging⁵⁶ and anti-diabetic.⁵⁴ The synthesis of E-resveratrol has been achieved before using an in-situ RBR protocol employing the ODS, CCl₄, as the halogenating reagent.⁵⁷ Our synthesis began with a thioetherification reaction between thiol ⁵⁹ and 3,5-dimethoxybenzyl bromide, which gave the resulting crude sulfide ⁶⁰ in 96% yield (Scheme 2.29). Next, sulfide ⁶⁰ was oxidized to sulfone ⁶¹ with mCPBA in good yield. Sulfone ⁶¹ was then exposed to the in situ RBR protocol to give methoxy E-resveratrol ⁶² in complete stereoselectivity and excellent yield concluding the formal synthesis of E-resveratrol. Subsequent demethylation with boron tribromide to give the phenolic
*E*-resveratrol is well established chemistry and in one example has been reported in 84% yield.\(^{57}\)

![Scheme 2.29. A Formal Synthesis of Resveratrol](image)

### 2.3 Conclusion

In conclusion, \(\text{C}_2\text{Br}_2\text{Cl}_4\) has proven to be an effective reagent for the *in-situ* RBR of dibenzylic, primary dialkyl and cyclic alkyl sulfones. The principal drawbacks occur for highly hindered alkyl sulfones and when pKa differences of \(\alpha\)-hydrogens on opposite sides of the sulfone substrate are the largest. The reagent system is clearly a greener, more practical and economically favorable substitute to the ozone-depleting reagents that have been successfully used in the recent past for *in-situ* RBRs. It is anticipated that synthetic chemists will recognize the value, availability and practical convenience of 1,2-dibromotetrachloroethane and that they will give it due consideration for future synthetic targets.
2.4 Experimental

2.4.1 Synthesis of Sulfones

**Benzyl sulfone.** Benzyl sulfide (2.00 g, 9.33 mmol) was dissolved in DCM (100 mL) and stirred at 0 °C. Next, MCPBA (ca ~ 77%) was added (4.03 g, 23.3 mmol) and the reaction was stirred for 8 h at rt. The crude reaction mixture was washed with sat Na$_2$S$_2$O$_4$ (aq.), NaHCO$_3$ (aq), H$_2$O, then brine. The organic layer was dried over MgSO$_4$, filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent to yield a white solid (81%, 1.85 g). Mp 151-152 °C [lit.$^{58}$ 151 °C]; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.42-7.38 (m, 10H), 4.13 (s, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 130.9, 129.1, 129.0, 127.6, 58.0

**3-Bromobenzyl benzyl sulfone.** Benzyl thiol (0.378 mL, 3.22 mmol) was put under a nitrogen atmosphere and dissolved in dry THF (5 mL). The solution was chilled to 0 °C then solid NaH (neat) (0.081 g, 3.38 mmol) was added and the mixture was stirred for ~10 minutes. Next a THF (2 mL) solution of 3-bromobenzyl bromide (0.967 g, 3.86 mmol) was added dropwise and the mixture was stirred overnight. The next day the reaction was quenched by the addition of water and the mixture was extracted with EtOAc (3×10 mL). The organic layer was washed successively with a 10% NaOH (aq) solution (2×15 mL), then H$_2$O (15 mL), then brine (15 mL). The organic layer was dried over MgSO$_4$, filtered and concentrated under reduced pressure to yield the crude sulfide as a yellow oil (98%, 0.927 g). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.53 (s, 1H), 7.41-7.30 (m, 6H), 7.27-7.13 (m, 2H), 3.59 (s, 2H), 3.53 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 140.6, 137.8, 132.0,
130.1, 130.0, 129.0, 128.6, 127.7, 127.2, 122.5, 35.7, 35.0. Next, 3-bromobenzyl benzyl sulfide (0.927 g, 3.16 mmol) was dissolved in DCM (60 mL) and stirred at 0 °C. Next, MCPBA (ca ~77%) was added (2.13 g, 9.48 mmol) and the reaction was stirred for 8 h at rt. The crude reaction mixture was washed with sat Na₂S₂O₃(aq), NaHCO₃(aq), H₂O and brine. The organic layer was dried over MgSO₄, filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent to yield a white solid (63%, 0.640 g). Mp 134-135 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.53 (td, J = 1.6, 7.8 Hz, 1H), 7.48 (t, J = 1.6 Hz, 1H), 7.45 - 7.35 (m, 5H), 7.35 - 7.31 (m, 1H), 7.28 (t, J = 7.7 Hz, 1H), 4.17 (s, 2H), 4.06 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 133.8, 132.2, 130.8, 130.5, 129.6, 129.5, 129.2, 129.1, 127.3, 122.8, 58.6, 57.1; IR (neat) cm⁻¹ 3064, 3033, 2987, 2941, 1643, 1633, 1412, 1302, 1277, 1116, 1072, 793; Anal. calcd for C₁₄H₁₃BrO₂S: C, 51.70; H, 4.03; Found: C, 51.79; H, 4.19.

3-Nitrobenzyl benzyl sulfone. Benzyl thiol (0.378 mL, 3.22 mmol) was put under a nitrogen atmosphere and dissolved in dry THF (5 mL). The solution was chilled to 0 °C then solid NaH (neat) (0.081 g, 3.38 mmol) was added and the mixture was stirred for ~10 minutes. Next a THF (2 mL) solution of 3-nitrobenzyl bromide (0.835 g, 3.86 mmol) was added dropwise and the mixture was stirred overnight. The next day the reaction was quenched by the addition of water then the mixture was extracted with EtOAc (3×10 mL). The organic layer was washed successively with a 10% NaOH (aq) (2×15 mL), H₂O (15 mL) and brine (15 mL). The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to yield the crude sulfide as a yellow oil (88%,
0.734 g). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.11-8.08 (m, 2H), 7.61-7.59 (m, 1H), 7.47-7.45 (m, 1H), 7.34-7.23 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 148.3, 140.6, 137.4, 135.1, 129.4, 128.9, 127.3, 123.9, 122.1, 35.9, 34.9. Next, 3-nitrobenzyl benzyl sulfide (0.734 g, 2.83 mmol) was dissolved in DCM (60 mL) and stirred at 0 °C. MCPBA (ca ~77%) was added (1.903 g, 8.49 mmol) and the reaction was stirred for 8 h at rt. The crude reaction mixture was washed with sat Na$_2$S$_2$O$_3$ (aq), NaHCO$_3$ (aq), H$_2$O, then brine. The organic layer was dried over MgSO$_4$, filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent to yield a white solid (62%, 0.513 g). Mp 152-153 °C [lit.$^{59}$ 151 °C]; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.25 (ddd, $J$ = 8.2, 2.2, 1.2 Hz, 1H), 8.16 (t, $J$ = 1.9 Hz, 1H), 7.73 (d, $J$ = 7.7 Hz, 1H), 7.59 (t, $J$ = 6.7 Hz, 1H), 7.44 (s, 5H), 4.26 (s, 2H), 4.18 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 148.4, 137.0, 130.7, 129.9, 129.4, 129.3, 129.2, 127.3, 125.9, 124.0, 59.4, 56.7.

**4-Trifluoromethylbenzyl benzyl sulfone.** Benzyl thiol (0.945 mL, 8.05 mmol) was put under a nitrogen atmosphere and dissolved in dry THF (5 mL). The solution was chilled to 0 °C then solid NaH (neat) (0.213 g, 8.86 mmol) was added and the mixture was stirred for ~10 minutes. A THF (2 mL) solution of 4-trifluoromethylbenzyl bromide (1.245 g, 4.18 mmol) was added dropwise and the mixture was stirred overnight. The next day the reaction was quenched by the addition of water then the mixture was extracted with EtOAc (3×10 mL). The organic layer was washed successively with a 10% NaOH (aq) solution (2×15 mL), then H$_2$O (15 mL), then brine (15 mL). The organic layer was dried over MgSO$_4$, filtered and concentrated under reduced
pressure to yield the crude sulfide as a clear yellow oil (89%, 1.050 g): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.55 (d, $J = 8.0$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.33-7.29 (m, 5H), 3.61 (s, 2H), 3.59 (s, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 142.4, 137.7, 129.3 (q, $J = 32.3$ Hz), 129.3, 129.0, 128.6, 127.2, 125.4 (q, $J = 3.7$ Hz), 122.2 (q, 272.3 Hz), 35.7, 35.1. 4-trifluoromethylbenzyl benzyl sulfide (1.050 g, 3.72 mmol) was dissolved in DCM (60 mL) and stirred at 0 °C. MCPBA (ca ~77%) was added (2.086 g, 9.30 mmol) and the reaction was stirred for 8 h at rt. The crude reaction mixture was washed with sat Na$_2$S$_2$O$_3$ (aq), NaHCO$_3$ (aq), H$_2$O and brine. The organic layer was dried over MgSO$_4$, filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent to yield a white solid (82%, 0.978). Mp 146-147 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.65 (d, $J = 8.0$ Hz, 2H), 7.49 (d, $J = 8.0$ Hz, 2H), 7.45 - 7.36 (m, 5H), 4.20 (s, 2H), 4.15 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 131.6, 131.3, 131.2 (q, $J = 31.4$ Hz), 130.8, 129.3, 129.2, 127.4, 125.9 (q, $J = 3.8$ Hz), 123.9 (q, $J = 271.6$ Hz), 58.9, 57.2; IR (neat) cm$^{-1}$ 3048, 2982, 2938, 1636, 1417, 1332, 1298, 1155, 1120, 858; Anal. calcd for C$_{15}$H$_{13}$F$_3$O$_2$S: C, 57.32 ; H, 4.17; Found: C, 57.31 ; H, 4.30.

**2-Pyridinylmethyl benzyl sulfone.** Benzyl thiol (0.378 mL, 3.22 mmol) was put under a nitrogen atmosphere and dissolved in dry THF (5 mL). The solution was chilled to 0 °C and solid NaH (neat) (0.158 g, 6.60 mmol) was added and the mixture was stirred for ~10 minutes. Next, 2-pyridylmethyl bromide•HBr (0.977 g, 3.86 mmol) was added and the mixture was stirred overnight. The next day the reaction was quenched by the addition of water then the mixture was extracted with EtOAc (3×10 mL). The organic layer was
washed successively with a 10% NaOH\textsubscript{(aq)} solution (2×15 mL), then H\textsubscript{2}O (15 mL) and brine (15 mL). The organic layer was dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure to yield the crude sulfide as a brown oil (99%, 0.690 g). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 8.54-8.53 (m, 1H), 7.63-7.58 (m, 1H), 7.30-7.12 (m, 7H), 3.74 (s, 2H), 3.68 (s, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 158.6, 149.3, 138.1, 136.6, 129.1, 128.5, 127.0, 123.1, 121.9, 37.5, 35.9. Next, 2-pyridylmethyl benzyl sulfide (0.927 g, 3.16 mmol) was dissolved in DCM (60 mL) and stirred at -78 °C. A solution of MCPBA (ca ~83%) (2.125 g, 9.48 mmol) in DCM (25 mL) was added dropwise via a dropping funnel. The reaction was warmed slowly and allowed to stir at rt overnight. The crude reaction mixture was washed with sat Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} (aq), NaHCO\textsubscript{3} (aq), H\textsubscript{2}O and brine. The organic layer was dried over MgSO\textsubscript{4}, filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent to yield a white solid (56%, 0.455 g). Mp 115-116 °C; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 8.66 (dd, \( J = \) 4.9, 0.8 Hz, 1H), 7.73 (dt, \( J = \) 7.7, 1.8 Hz, 1H), 7.56 (dd, \( J = \) 7.3, 2.1 Hz, 2H), 7.45 (d, \( J = \) 7.9 Hz, 1H), 7.43 - 7.35 (m, 3H), 7.31 (ddd, \( J = \) 7.6, 4.9, 0.9 Hz, 1H), 4.33 (s, 2H), 4.31 (s, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 149.9, 149.7, 137.3, 131.3, 129.0, 128.9, 128.0, 126.3, 123.6, 59.2, 58.2. The \textsuperscript{1}H NMR and \textsuperscript{13}C NMR were in good agreement with literature data.\textsuperscript{60}

4-Methoxyphenyl-3′,5′-dimethoxyphenyl sulfone. 4-Methoxybenzyl thiol (1.87 mL, 12.9 mmol) was put under a nitrogen atmosphere and dissolved in dry THF (5 mL). The solution was chilled to 0 °C then solid NaH (neat) (0.326 g, 13.6 mmol) was added and the mixture was stirred for ~10 minutes. Next a THF (2 mL)
solution of 3,5-dimethoxybenzyl bromide (3.15 g, 13.6 mmol) was added dropwise and the mixture was stirred overnight. The next day the reaction was quenched by the addition of water and the mixture was extracted with EtOAc (3x10 mL). The organic layer was washed successively with a 10% NaOH \textsubscript{(aq)} solution (2x15 mL), then H\textsubscript{2}O (15 mL), then brine (15 mL). The organic layer was dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure to yield the crude sulfide as a clear yellow oil (96%, 3.42 g). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.21 (d, \(J = 8.8\) Hz, 2H), 6.84 (d, \(J = 8.8\) Hz, 2H), 6.45-6.44 (m, 2H), 6.35-6.34 (m, 1H), 3.80 (s, 3H), 3.78 (s, 6H), 3.58 (s, 2H), 3.53 (s, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 160.8, 158.6, 140.6, 130.1, 130.1, 113.9, 106.9, 99.1, 55.3, 55.3, 35.8, 35.1. The sulfide (3.30 g, 10.8 mmol) was dissolved in DCM (70 mL) and stirred at 0 °C. MCPBA (ca \~77\%) was added (5.61 g, 25.0 mmol) and the reaction was stirred for 8 hr at rt. The crude reaction mixture was washed with sat Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} \textsubscript{(aq)}, NaHCO\textsubscript{3} \textsubscript{(aq)}, H\textsubscript{2}O, then brine. The organic layer was dried over MgSO\textsubscript{4}, filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent to yield a white solid (78%, 2.85 g). Mp 95-96 °C; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.29 (d, \(J = 8.7\) Hz, 2H), 6.91 (d, \(J = 8.7\) Hz, 2H), 6.52 (d, \(J = 2.2\) Hz, 2H), 6.47 (t, \(J = 2.2\) Hz, 1H), 4.11 - 4.07 (m, 2H), 4.06 - 4.01 (m, 2H), 3.80 (s, 3H), 3.78 (s, 6H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 161.0, 160.2, 132.2, 129.7, 119.2, 114.4, 108.8, 100.9, 58.1, 57.3, 55.4, 55.3. The \textsuperscript{1}H NMR and \textsuperscript{13}C NMR were in good agreement with literature data.\textsuperscript{57}
Benzyl 4-methoxybenzyl sulfone. 4-Methoxybenzyl thiol (1.356 mL, 9.72 mmol) was put under a nitrogen atmosphere and dissolved in dry THF (5 mL). The solution was chilled to 0 °C then solid NaH (neat) (0.303 g, 12.6 mmol) was added and the mixture was stirred for ~10 minutes. Next a THF (2 mL) solution of benzyl bromide (1.21 g, 10.2 mmol) was added dropwise and the mixture was stirred overnight. The next day the reaction was quenched by the addition of water then the mixture was extracted with EtOAc (3×10 mL). The organic layer was washed successively with a 10% NaOH (aq) solution (2×15 mL), H$_2$O (15 mL) and brine (15 mL). The organic layer was dried over MgSO$_4$, filtered and concentrated under reduced pressure to yield the crude sulfide as a clear yellow oil (97%, 2.30 g). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36-7.15 (m, 7H), 6.84 (d, $J = 8.4$ Hz, 2H), 3.79 (s, 3H), 3.58 (s, 2H), 3.55 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.6, 138.3, 130.1, 129.1, 129.0, 128.5, 127.0, 113.9, 55.3, 35.5, 35.0.

The sulfide (2.30 g, 9.41 mmol) was dissolved in DCM (60 mL) and stirred at 0 °C. MCPBA (ca ~77%) was added (5.69 g, 32.9 mmol) and the reaction was stirred for 8 hr at rt. The crude reaction mixture was washed with sat Na$_2$S$_2$O$_3$ (aq), NaHCO$_3$ (aq), H$_2$O, then brine. The organic layer was dried over MgSO$_4$, filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent to yield a white solid (75%, 1.951 g). Mp 126-127 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41-7.37 (m, 5H), 7.29 (d, $J = 8.8$ Hz, 2H), 6.92 (d, $J = 8.8$ Hz, 2H), 4.11 (s, 2H), 4.07 (s, 2H), 3.82 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 160.2, 132.1, 130.9, 129.0, 127.7, 119.3, 114.5, 57.8, 57.4, 55.4; IR (neat) cm$^{-1}$
Benzyl 3,5-dimethoxybenzyl sulfone. Benzyl thiol (9.45 mL, 8.05 mmol) was put under a nitrogen atmosphere and dissolved in dry THF (5 mL). The solution was chilled to 0 °C and solid NaH (neat) (0.232 g, 9.66 mmol) was added and the mixture was stirred for ~10 minutes. Next a THF (2 mL) solution of 3,5-dimethoxybenzyl bromide (1.86 g, 8.05 mmol) was added dropwise and the mixture was stirred overnight. The next day the reaction was quenched by the addition of water and the mixture was extracted with EtOAc (3×10 mL). The organic layer was washed successively with a 10% NaOH(aq) solution (2×15 mL), H₂O (15 mL) and brine (15 mL). The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to yield the crude sulfide as a clear yellow oil (96%, 2.11 g). ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.23 (m, 5H), 6.46-6.44 (m, 2H), 6.35-6.34 (m, 1H), 3.78 (s, 6H), 3.62 (s, 2H), 3.54 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 160.8, 140.5, 138.1, 129.1, 128.5, 127.0, 106.9, 99.2, 55.3, 35.8, 35.6.

The sulfide (2.11 g, 7.69 mmol) was dissolved in DCM (60 mL) and stirred at 0 °C. MCPBA (ca ~77%) was added (4.00 g, 23.1 mmol) and the reaction was stirred for 8 h at rt. The crude reaction mixture was washed with sat Na₂S₂O₅ (aq), NaHCO₃ (aq), H₂O and brine. The organic layer was dried over MgSO₄, filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent to yield a white solid (71%, 1.674 g). Mp 94-95 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.39 (m, 5H), 6.56-6.52 (m, 2H), 6.47 (m, 1H), 4.14 (s, 2H), 4.06 (s, 2H), 3.79 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 161.0, 130.9, 129.6, 129.0,
129.0, 127.5, 108.8, 101.0, 58.3, 57.9, 55.5; IR (neat) cm⁻¹ 3063, 3004, 2967, 2937, 2839, 1597, 1457, 1431, 1312, 1206, 1154, 1116, 1064, 932; Anal. calcd for C₁₆H₁₈O₄S: C, 62.72; H, 5.92; Found: C, 62.72; H, 5.81.

2-Naphthylmethyl benzyl sulfone. Benzyl thiol (0.945 mL, 8.05 mmol) was put under a nitrogen atmosphere and dissolved in dry THF (5 mL). The solution was chilled to 0 °C and solid NaH (neat) (0.203 g, 8.45 mmol) was added and the mixture was stirred for ~10 minutes. A THF (2 mL) solution of 2-naphthylmethyl bromide (2.14 g, 9.66 mmol) was added dropwise and the mixture was stirred overnight. The next day the reaction was quenched by the addition of water and the mixture was extracted with EtOAc (3×10 mL). The organic layer was washed successively with a 10% NaOH (aq) (2×15 mL), H₂O (15 mL) and brine (15mL). The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to yield the crude sulfide as a white solid (100%, 2.13 g). ¹H NMR (400 MHz, CDCl₃) δ 7.84-7.81 (m, 3H), 7.68 (s, 1H), 7.53-7.46 (m, 3H), 7.35-7.26 (m, 5H), 3.77 (s, 2H), 3.63 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 139.1, 135.5, 133.2, 132.7, 129.1, 128.5, 128.4, 128.0, 127.7, 127.6, 127.3, 127.1, 126.2, 125.8, 35.9, 35.5. Crude sulfide (2.13 g, 8.05 mmol) was dissolved in DCM (60 mL) and stirred at 0 °C. MCPBA (ca ~77%) was added (4.48 g, 20.0 mmol) and the reaction was stirred for 8 hr at rt. The crude reaction mixture was washed with sat Na₂S₂O₃ (aq), NaHCO₃ (aq), H₂O and brine. The organic layer was dried over MgSO₄, filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent to yield a white solid (65%, 1.556 g). Mp 181-182 °C [lit.⁶¹ 184.5-185.5 °C]; ¹H NMR (400 MHz, CDCl₃) δ
7.92 - 7.78 (m, 4H), 7.59 - 7.46 (m, 3H), 7.44 - 7.35 (m, 5H), 4.29 (s, 2H), 4.15 (s, 2H);

\[ \text{13C NMR (100 MHz, CDCl}_3\) \delta 133.3, 133.2, 130.9, 130.6, 129.1, 129.0, 128.8, 128.0, 127.8, 127.5, 126.9, 126.7, 125.0, 58.3, 58.1} \]

**2,6-Bis[benzylsulfonylmethyl]pyridine.** Benzyl thiol (0.798 mL, 6.79 mmol) was put under a nitrogen atmosphere and dissolved in dry THF (5 mL). The solution was chilled to 0 °C then solid NaH (neat) (0.199 g, 8.30 mmol) was added and the mixture was stirred for ~10 minutes. Next a THF (2 mL) solution of 2,6-bis(bromomethyl)pyridine (0.900 g, 3.40 mmol) was added dropwise and the mixture was stirred overnight. The next day the reaction was quenched by the addition of water and the mixture was extracted with EtOAc (3×10 mL). The organic layer was washed successively with a 10% NaOH (aq) (2×15 mL), H$_2$O (15 mL) and brine (15 mL). The organic layer was dried over MgSO$_4$, filtered and concentrated under reduced pressure to yield the crude sulfide as a clear yellow oil (77%, 0.921 g) \(^1\)H NMR (400 MHz, CDCl$_3$) \( \delta 7.58 \) (t, \( J = 7.6 \) Hz, 1H), 7.35-7.20 (m, 10 H), 7.17 (d, \( J = 7.6 \) Hz, 2H), 3.74 (s, 4H), 3.71 (4H);

\[ \text{13C NMR (100 MHz, CDCl}_3\) \delta 158.3, 138.1, 137.3, 129.1, 128.5, 127.0, 121.2, 37.4, 35.9} \]

The sulfide (0.278 g, 0.79 mmol) was dissolved in DCM (60 mL) and stirred at -78 °C. MCPBA (ca ~83%) was added (0.660 g, 3.16 mmol) as a DCM (50 mL) solution dropwise. After stirring at -78 °C for 2 h the reaction was allowed to warm to rt and stirred for 12 h. The crude reaction mixture was washed with sat Na$_2$S$_2$O$_3$ (aq), NaHCO$_3$ (aq), H$_2$O and brine. The organic layer was dried over MgSO$_4$, filtered and the solvent was removed in vacuo to yield crude product as a white solid. The solid was triturated with DCM several times to remove residual impurities and excess
solvent was removed \textit{in vacuo} to yield pure product as a white solid (82\%, 0.269 g); Mp 228-229 °C; \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6) \( \delta \) 7.93 (t, \( J = 7.6 \) Hz, 1H), 7.53 (d, \( J = 7.6 \) Hz, 2H), 7.46-7.42 (m, 4H), 7.40-7.36 (m, 6H), 4.66 (s, 4H), 4.63 (s, 4H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 149.6, 138.1, 131.3, 128.4, 128.4, 127.5, 58.9, 57.8; IR (nujol mull) cm\textsuperscript{-1} 3084, 3063, 3004, 2853, 1589, 1299, 1284, 1126, 774, 694; Anal. calcd for \( \text{C}_{21}\text{H}_{21}\text{NO}_{4}\text{S}_{2} \): C, 60.70; H, 5.09; Found: C, 60.59; H, 5.16.

Octyl sulfone. Octanethiol (1.78 mL, 10.2 mmol) was put under a nitrogen atmosphere and dissolved in dry THF (10 mL). The solution was chilled to 0 °C then solid NaH (neat) (0.258 g, 10.7 mmol) was added and the mixture was stirred for \( \sim \)10 minutes. A THF (4 mL) octyl bromide (2.14 mL, 12.3 mmol) was added dropwise and the mixture was stirred overnight. The next day the reaction was quenched by the addition of water then the mixture was extracted with EtOAc (3×10 mL). The organic layer was washed successively with a 10\% NaOH\textsubscript{(aq)} solution (2×15 mL), H\textsubscript{2}O (15 mL) and brine (15 mL). The organic layer was dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure to yield the crude sulfide as a colorless oil (100\%, 2.65 g). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 2.50 (t, \( J = 7.2 \) Hz, 4H), 1.61-1.54 (m, 4H), 1.39-1.27 (m, 20H), 0.88 (t, \( J = 6.8 \) Hz, 6H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 32.2, 31.8, 29.7, 29.2, 29.2, 29.0, 22.7, 14.1. \( n \)-Octyl sulfide (2.648 g, 10.3 mmol) was dissolved in DCM (60 mL) and stirred at 0 °C. MCPBA (ca \( \sim \)77\%) was added (5.71 g, 25.6 mmol) and the reaction was stirred for 8 h at rt. The crude reaction mixture was washed with sat Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} \textsubscript{(aq)}, NaHCO\textsubscript{3} \textsubscript{(aq)}, H\textsubscript{2}O, then brine. The organic layer was dried over MgSO\textsubscript{4}, filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography
using EtOAc/hexanes as the eluent to yield a white solid (68%, 2.04 g). Mp : 53-54 °C [lit.62 53-54 °C]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.01 - 2.87 (m, 4H), 1.80-178 (m, 4H), 1.44 (quin, \(J = 7.0\) Hz, 4H), 1.38 - 1.17 (m, 16H), 0.88 (t, \(J = 6.8\) Hz, 6H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 52.7, 31.7, 29.0, 28.9, 28.5, 22.6, 21.9, 14.1.

**N-Boc thiomorpholine sulfone.** Thiomorpholine (3.89 mL, 38.8 mmol) was dissolved in dry THF (25 mL) and stirred at 0 °C under an inert N\(_2\) (g) atmosphere. Next, triethylamine (6.48 mL, 46.5 mmol) was added dropwise via syringe. A solution of Boc\(_2\)O (8.73 g, 40.0 mmol) in dry THF (20 mL) was added slowly via a dropping funnel. The reaction was stirred for 18 h then EtOAc was added (35 mL) and the organic layer was washed with 0.6 M HCl (20 mL), then brine (20 mL). The organic layer was dried over MgSO\(_4\), filtered and concentrated under reduced pressure to give the crude sulfide. Purification by flash chromatography eluting with chloroform provided the pure N-Boc thiomorpholine as a white solid\(^63\) (83%, 6.54 g). Mp: 72-74 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.70-3.67 (m, 4H), 2.57 (t, \(J = 4.8\) Hz, 4H), 1.46 (s, 9); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 154.3, 80.0, 28.4, 27.2. N-Boc thiomorpholine sulfide (3.00 g, 14.8 mmol) was dissolved in DCM (60 mL) and stirred at 0 °C. MCPBA (ca ~77%) was added (7.65 g, 44.3 mmol) and the reaction was stirred for 8 hr at rt. The crude reaction mixture was washed with sat Na\(_2\)S\(_2\)O\(_3\) (aq), NaHCO\(_3\) (aq), H\(_2\)O, then brine. The organic layer was dried over MgSO\(_4\), filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent to yield a white solid\(^63\) (89%, 3.09 g). Mp 134-138 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.93 (t, \(J = 7.2\) Hz, 4H), 3.01 (t, \(J = 7.2\) Hz, 4H), 1.48 (s, 9H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 153.6, 81.6, 51.9, 28.3.
**Benzyl hexyl sulfone.** 

*n*-Hexanethiol (1.79 mL, 12.7 mmol) was dissolved in dry THF (25 mL) and put under a nitrogen atmosphere. The solution was chilled to 0 °C and solid NaH (NEAT) (0.334 g, 13.9 mmol) was added and the mixture was stirred for ~10 minutes. A THF (2 mL) solution of benzyl bromide (0.158 mL, 13.3 mmol) was added dropwise and the mixture was stirred overnight. The next day the reaction was quenched by the addition of water and the mixture was extracted with EtOAc (3×10 mL). The organic layer was washed successively with a 10% NaOH(aq) solution (2×15 mL), then H2O (15 mL), then brine (15mL). The organic layer was dried over MgSO4, filtered and concentrated under reduced pressure to yield the crude sulfide as a clear colorless oil (100%, 2.64 g). ¹H NMR (600 MHz, CDCl3) δ 7.32-7.29 (m, 4H), 7.25-7.22 (m 1H), 3.70 (s, 2H), 2.40 (t, J = 7.2 Hz, 2H), 1.57-1.52 (m, 2H), 1.36-1.21 (m, 6H), 0.87 (t, J = 7.2 Hz, 3H); ¹³C NMR (150.9 MHz, CDCl3) δ 138.7, 128.9, 128.5, 126.9, 35.6, 31.5, 31.4, 29.2, 28.6, 22.6, 14.1. Benzyl *n*-hexyl sulfide (2.64 g, 12.7 mmol) was dissolved in DCM (75 mL) and stirred at 0 °C. MCPBA (ca ~77%) was added (6.13 g, 35.5 mmol) and the reaction was stirred for 8 h at rt. The crude reaction mixture was washed with sat Na₂S₂O₃ (aq), NaHCO₃ (aq), H₂O, then brine. The organic layer was dried over MgSO₄, filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent to yield a white solid (37%, 1.14 g). Mp 55-56 °C [lit. ⁶⁴ 56-57 °C; ¹H NMR (400 MHz, CDCl3) δ 7.40 (m, 5H), 4.21 (s, 2H), 2.81 (m, 2H), 1.78 (m, 2H), 1.40-1.24 (m, 6H), 0.87 (t, J = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl3) δ 130.54, 129.07, 129.01, 128.20, 59.41, 51.09, 31.17, 28.09, 22.27, 21.73, 13.93
Cyclopentyl sulfone. Cyclopentanethiol (1.05 mL, 9.79 mmol) was added to a stirred solution of bromocyclopentane (1.10 mL, 10.3 mmol) and Cs$_2$CO$_3$ (6.376 g, 19.6 mmol) in dry DMF (25 mL) under inert N$_2$ (g) atmosphere. The reaction was stirred for 3 h at room temperature and quenched by the addition of saturated NaHCO$_3$ (aq) (20 mL) solution. The mixture was extracted with diethyl ether (3×30 mL) and the organic layers were combined then dried over MgSO$_4$. The organic solution was filtered and concentrated under reduced pressure to give the crude sulhide as a clear colorless oil (76%, 1.262 g). $^1$H NMR (400 MHz, CDCl$_3$) δ 3.15-3.06 (m, 2H), 2.05-1.96 (m, 4H), 1.78-1.48 (m, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 43.8, 34.2, 24.9. The sulfide (1.26 g, 7.42 mmol) was dissolved in DCM (60 mL) and stirred at 0 °C. MCPBA (ca ~77%) was added (3.20 g, 18.5 mmol) and the reaction was stirred for 8 h at rt. The crude reaction mixture was washed with sat Na$_2$S$_2$O$_3$ (aq), NaHCO$_3$ (aq), H$_2$O, then brine. The organic layer was dried over MgSO$_4$, filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography using EtOAc/hexanes as the eluent to yield a white solid (80%, 1.202 g). Mp 68-69 °C [lit.65 68-70 °C]; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.42-3.37 (m, 2H), 2.12-1.97 (m, 8H), 1.85-1.78 (m, 4H), 1.69-1.67 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 59.6, 26.7, 25.9.

2.4.2 RBR Experiments

General One-pot RBR Procedure for Preparation of Alkenes

The sulfone (100-120 mg, 0.307-0.510 mmol) was dissolved in THF/°BuOH (2.5 mL/7.5 mL) and stirred at rt. Next, KOH-Al$_2$O$_3$ (19 equiv.) was added to the reaction
mixture. Immediately following base addition, a solution of 1,2-
dibromotetrachloroethane (equiv. indicated in Table 4) in THF (2 mL) was added
slowly dropwise via a syringe. The reaction mixture was stirred for 2-48 hr (see
Table 4 for precise times) at rt. Upon sulfone consumption (TLC monitoring), the
reaction mixture was flushed through a silica plug with EtOAc to remove inorganic
components. Fractions were combined and concentrated. Purification by flash
chromatography or recrystallization gave pure material.

**E-Stilbene.** The sulfone (0.100 g, 0.405 mmol) in THF/tBuOH
(2.5 mL/ 7.5 mL), KOH-Al₂O₃ (0.974 g, 7.65 mmol) and 1,2-
dibromotetrachloroethane (0.237 g, 0.729 mmol) gave a white residue after
workup. No Z-isomer was detected in the ¹H NMR of the crude reaction mixture.
Purification by flash chromatography eluting with hexanes gave E-stilbene as a
white solid (90%, 66 mg). Mp: 122-123 °C [lit.66 124-125 °C]; ¹H NMR (400 MHz,
CDCl₃) δ 7.52-7.49 (m, 4H), 7.51-7.33 (m, 4H), 7.28-7.24 (m, 2H), 7.11 (s, 2H); ¹³C
NMR (100 MHz, CDCl₃) δ 137.4, 128.7 (overlapping), 127.7, 126.6.

**E-2-(3-Bromophenyl) styrene.** The sulfone (0.100 g, 0.307
mmol) in THF/tBuOH (2.5 mL/ 7.5 mL), KOH-Al₂O₃ (0.736 g, 5.80
mmol) and 1,2-dibromotetrachloroethane (0.179 g, 0.553 mmol)
gave a white residue after workup. No Z-isomer was detected in the ¹H NMR of the
crude reaction mixture. Recrystallization of the residue from EtOAc/hexanes gave E-
2-(3-bromophenyl) styrene as a white solid (90%, 72 mg). Mp: 88-89 °C [lit.67 89-90
°C]; ¹H NMR (400 MHz, CDCl₃) δ 7.66 (t,  J = 1.8 Hz, 1H), 7.53 - 7.47 (m, 1H), 7.44 -
7.32 (m, 4H), 7.28 (m, 1H), 7.25 - 7.18 (m, 1H), 7.10 (d, \( J = 16.4 \) Hz, 1H), 7.01 (d, \( J = 16.4 \) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 139.5, 136.8, 130.4, 130.2, 129.3, 128.8, 128.1, 127.1, 126.7, 125.2, 122.9.

**E-2-(3-Nitrophenyl)styrene.** The sulfone (0.100 g, 0.343 mmol) in THF/\(^t\)BuOH (2.5 mL/ 7.5 mL), KOH-Al\(_2\)O\(_3\) (0.857 g, 6.48 mmol) and 1,2-dibromotetrachloroethane (0.202 g, 0.618 mmol) gave a white residue after workup. No \( Z \)-isomer was detected in the \(^1\)H NMR of the crude reaction mixture. Recrystallization of the residue from EtOAc/hexanes gave E-2-(3-nitrophenyl)styrene as a white solid (88%, 68 mg). Mp 96-97 °C [lit.\(^68\) 92-95 °C]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.34 (s, 1H), 8.07 (dd, \( J = 8.0, 1.2 \) Hz, 1H), 7.77 (d, \( J = 8.0 \) Hz, 1H), 7.54-7.48 (m, 3H), 7.39 (t, \( J = 7.2 \) Hz, 2H), 7.33-7.29 (m, 1H), 7.21 (d, \( J = 16.4 \) Hz, 1H), 7.11 (d, \( J = 16.4 \) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 148.7, 139.2, 136.3, 132.3, 131.8, 129.6, 128.9, 128.6, 126.9, 126.1, 122.0, 120.9.

**E-2-(4-Trifluoromethylphenyl) styrene.** The sulfone (0.100 g, 0.318 mmol) in THF/\(^t\)BuOH (2.5 mL/ 7.5 mL), KOH-Al\(_2\)O\(_3\) (0.763 g, 6.01 mmol) and 1,2-dibromotetrachloroethane (0.186 g, 0.572 mmol) gave a white residue after workup. No \( Z \)-isomer was detected in the \(^1\)H NMR of the crude reaction mixture. Recrystallization of the residue from hexanes gave E-2-(4-trifluoromethylphenyl) styrene as a clear colorless needles (82%, 64 mg). Mp 131-132 °C [lit.\(^69\) 132.1-133.4 °C]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.61-7.56 (m, 4H), 7.53 (d, \( J = 7.2 \) Hz, 2H), 7.38 (t, \( J = 5.5 \) Hz, 2H), 7.32-7.28 (m, 1H), 7.19 (d, \( J = 16.4 \) Hz, 1H), 7.11 (d, \( J = 16.4 \) Hz, 1H); \(^{13}\)C NMR (150.9 MHz, CDCl\(_3\)) \( \delta \) 140.8, 136.7, 132.2,
129.3 (q, $J = 32.4$ Hz), 128.8, 128.3, 127.1, 126.8, 126.6, 125.7 (q, $J = 3.7$ Hz), 124.3 (q, $J = 272.6$ Hz).

**E-2-Pyridyl styrene.** The sulfone (0.100 g, 0.404 mmol) in THF/tBuOH (2.5 mL/ 7.5 mL), KOH-Al$_2$O$_3$ (0.970 g, 7.64 mmol) and 1,2-dibromotetrachloroethane (0.236 g, 0.727 mmol) gave a white residue after workup. No Z-isomer was detected in the $^1$H NMR of the crude reaction mixture. Purification by flash chromatography eluting with EtOAc/hexanes (2:98) gave E-2-pyridyl styrene as a white solid (92%, 66 mg). Mp 61-62 °C [lit. 70 63-64 °C]; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.60 (dd, $J = 4.8$, 0.9 Hz, 1H), 7.67 - 7.60 (m, 2H), 7.60 - 7.55 (m, 2H), 7.42 - 7.33 (m, 3H), 7.32 - 7.23 (m, 1H), 7.17 (d, $J = 16.1$ Hz, 1H), 7.12 (ddd, $J = 7.5$, 4.8, 1.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 155.6, 149.7, 136.7, 136.6, 132.7, 128.8, 128.4, 128.0, 127.1, 122.1, 122.1.

**E-4-Methoxyphenyl-3',5'-dimethoxyphenylethene.**

The sulfone (0.100 g, 0.297 mmol) in THF/tBuOH (2.5 mL/ 7.5 mL), KOH-Al$_2$O$_3$ (0.713 g, 5.61 mmol) and 1,2-dibromotetrachloroethane (0.174 g, 0.535 mmol) gave a white residue after workup. No Z-isomer was detected in the $^1$H NMR of the crude reaction mixture. Recrystallization of the residue from hexanes gave E-4-methoxyphenyl-3',5'-dimethoxyphenylethene as a clear colorless needles (81%, 65 mg). Mp: 52-54 °C [lit. 71 52-54 °C]; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.45 (d, $J = 8.8$ Hz, 2H), 7.04 (d, $J = 16.4$ Hz, 1H), 6.92-6.89 (m, 3H), 6.65 (d, $J = 2.4$ Hz, 2H), 6.38 (t, $J = 2$ Hz, 1H), 3.83 (s, 9H);
\[^{13}\text{C}\ \text{NMR}\ (100\ \text{MHz, CDCl}\text{$_3$})\ \delta\ 161.0, 159.4, 139.7, 129.9, 128.8, 127.8, 126.6, 114.2, 104.3, 99.6, 55.4.\]

**E-4-Methoxystilbene.** The sulfone (0.120 g, 0.434 mmol) in THF/BuOH (2.5 mL/ 7.5 mL), KOH-Al$_2$O$_3$ (1.04 g, 6.59 mmol) and 1,2-dibromotetrachloroethane (0.254 g, 0.781 mmol) gave a white residue after workup. No Z-isomer was detected in the $^1$H NMR of the crude reaction mixture. Purification by flash chromatography eluting with hexanes gave E-4-methoxystilbene as a white solid (95%, 86 mg). Mp 134-137 °C [lit.\textsuperscript{72} 134-136 °C]; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50-7.44 (m, 4H), 7.34 (t, $J = 7.6$ Hz, 2H), 7.25-7.21 (m, 1H), 7.07 (d, $J = 16.4$ Hz, 1H), 6.97 (d, $J = 16.4$ Hz, 1H), 6.92-6.88 (m, 2H), 3.83 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.3, 137.7, 130.2, 128.7, 128.2, 127.7, 127.2, 126.6, 126.3, 114.1, 55.3.

**E-3,5-Dimethoxystilbene.** The sulfone (0.110 g, 0.359 mmol) in THF/BuOH (2.5 mL/ 7.5 mL), KOH-Al$_2$O$_3$ (0.862 g, 5.45 mmol) and 1,2-dibromotetrachloroethane (0.210 g, 0.646 mmol) gave a white residue after workup. No Z-isomer was detected in the $^1$H NMR of the crude reaction mixture. Recrystallization of the residue from hexanes gave E-3,5-dimethoxystilbene as a clear colorless needles (87%, 86 mg). Mp = 53-54 °C [lit.\textsuperscript{71} 53-55 °C]; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52-7.49 (m, 2H), 7.37-7.33 (m, 2H), 7.28-7.24 (m, 1H), 7.09 (d, $J = 16.4$ Hz, 1H), 7.03 (d, $J = 16.4$ Hz, 1H), 6.68 (s, 2H), 6.40 (s, 1H), 3.825 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) d = 161.0, 139.4, 137.2, 129.2, 128.7, 128.7, 127.8, 126.6, 104.6, 100.0, 55.4.
**E-2-Naphthyl styrene.** The sulfone (0.100 g, 0.337 mmol) in THF/tBuOH (2.5 mL/ 7.5 mL), KOH-Al$_2$O$_3$ (0.809 g, 6.36 mmol) and 1,2-dibromotetrachloroethane (0.197 g, 0.607 mmol) gave a white residue after workup. No Z-isomer was detected in the $^1$H NMR of the crude reaction mixture. Recrystallization of the residue from hexanes gave E-2-naphthyl styrene as clear colorless crystals (87%, 67 mg). Mp 145-147 °C [lit. 144-146 °C]; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.88 - 7.76 (m, 4H), 7.73 (dd, $J$ = 8.5, 1.7 Hz, 1H), 7.59 - 7.52 (m, 2H), 7.49 - 7.40 (m, 2H), 7.40 - 7.33 (m, 1H), 7.31 - 7.18 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 137.4, 134.9, 133.7, 133.1, 129.1, 128.8, 128.4, 128.0, 127.8, 126.7, 126.6, 126.4, 126.0, 123.5

**2,6-Bis(E-2-styryl) pyridine.** The sulfone (0.100 g, 0.241 mmol) in THF/tBuOH (2.5 mL/ 7.5 mL), KOH-Al$_2$O$_3$ (0.578 g, 4.55 mmol) and 1,2-dibromotetrachloroethane (0.219 g, 0.675 mmol) gave a white residue after workup. No Z-isomer was detected in the $^1$H NMR of the crude reaction mixture. Recrystallization of the residue from EtOAc/hexanes gave 2,6-bis(E-2-styryl) pyridine as clear colorless crystals (49%, 33 mg). Mp: 151-152 °C [lit.$^{73}$ 165-166 °C]; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71 (d, $J$ = 16.0 Hz, 2H), 7.66-7.61 (m, 5H), 7.41-7.37 (m, 4H), 7.32-7.25 (m, 4H), 7.21 (d $J$ = 16.0 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 155.4, 137.0, 136.8, 132.9, 128.7, 128.3, 127.2, 120.5.

**E,Z-8-Hexadecene.** The sulfone (0.100 g, 0.344 mmol) in THF/tBuOH (2.5 mL/ 7.5 mL), KOH-Al$_2$O$_3$ (0.826 g, 6.40 mmol) and 1,2-
dibromotetrachloroethane (0.403 g, 1.24 mmol) gave a white residue after workup. No Z-isomer was detected in the $^1$H NMR of the crude reaction mixture. Purification by flash chromatography eluting with hexanes gave $E$:$Z$-diheptylethenes as a clear colorless oil$^{10}$ (51%, 39 mg, $E$:$Z$ = 72:38 by NMR integration). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.38 (m, 1H), 5.35 (t, $J$ = 4.6 Hz, 1H), 1.96 (d, $J$ = 5.0 Hz, 4H), 1.40 - 1.18 (m, 20H), 0.94 - 0.81 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 130.4, 129.9, 32.6, 31.9, 29.8, 29.7, 29.3, 29.2, 29.2, 29.1, 27.2, 22.7, 14.1.

**N-Boc-3-pyrroline.** The sulfone (0.120 g, 0.510 mmol) in THF/tBuOH (2.5 mL/7.5 mL), KOH-Al$_2$O$_3$ (1.22 g, 7.74 mmol) and 1,2-dibromotetrachloroethane (0.299 g, 0.918 mmol) gave a white residue after workup. No Z-isomer was detected in the $^1$H NMR of the crude reaction mixture. Purification by flash chromatography eluting with EtOAc/hexanes (2:98) gave N-boc-3-pyrroline as a clear, colorless oil (52%, 45 mg).$^{74}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.81-5.73 (m, 2H), 4.14-4.08 (m, 4H), 1.48 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.3, 125.9, 125.8, 79.3, 53.1, 52.8, 28.5 (rotamers)

**E-1-Phenyl-1-heptene.** The sulfone (0.100 g, 0.416 mmol) in THF/BuOH (2.5 mL/7.5 mL), KOH-Al$_2$O$_3$ (0.998 g, 7.86 mmol) and 1,2-dibromotetrachloroethane (0.135 g, 0.416 mmol) gave a clear, colorless oil after work up. Flash chromatography eluting with EtOAc/hexanes (2:98) gave an inseparable mixture of E-1-phenyl-1-heptene and two isomeric 1-bromo-1-phenyl-1-heptenes were obtained as a clear liquid (53 mg; brominated:desired (91:9) by $^1$H NMR; ca. 64% of desired alkene).$^{75}$ No Z-isomer of
E-1-phenyl-1-heptene was detected in the $^1$H NMR or GC-MS of the reaction mixture. E-1-Phenyl-1-heptene: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34–7.25 (m, 4H), 7.21–7.15 (m, 1H), 6.37 (d, $J = 15.6$ Hz, 1H), 6.22 (dt, $J = 15.6$, 6.8 Hz, 1H), 2.19 (q, $J = 6.9$ Hz, 2H), 1.50–1.43 (m, 2H), 1.38–1.29 (m, 4H), 0.91 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 138.00, 131.3, 129.7, 128.5, 126.9, 125.9, 32.6, 31.6, 29.1, 22.6, 14.1; GC-MS m/z 174 [M+] (100), 175 (63), 173 (43), 161 (10), 143 (9), 117 (21), 105 (14). Minor, E and Z monobrominated inseparable components. 1-Bromo-1-phenyl-1-heptene 1: GC-MS m/z 252 [M+] (63), 254 (62), 197 (14), 195 (15), 171 (18), 143 (9), 131 (10), 117 (36), 105 (100). 1-Bromo-1-phenyl-1-heptene 2: GC-MS m/z 252 [M+] (100), 254 (98), 197 (14), 195 (15), 173 (78), 171 (33), 157 (11), 143 (17), 129 (10), 117 (42), 105 (89).
2.5 References


(39) prices from a Synquest chemicals quotation


(44) Lin, W.; Baron, O.; Knochel, P. Org. Lett. 2006, 8, 5673.


Chapter 3: Cyclization Chemistry of β-Aminoalkyl Alkenyl Sulfoxides/Sulfones
3.0 Cyclization Chemistry of β-Aminoalkyl Alkenyl Sulfoxides/Sulfones

3.1 Introduction

3.1.1 Background Information

Optically pure α,β-unsaturated sulfoxides have been used abundantly in asymmetric synthesis as chiral auxiliaries because the sulfinyl moiety is a strong chiral influence.\(^1\)\(^2\) This introduction will focus on recent developments in the asymmetric Michael addition reactions of nucleophiles to α,β-unsaturated sulfoxides, a strategy that has been used extensively toward the organic synthesis of optically pure natural products and biologically active compounds. Select examples are shown in Figure 3.1, with the bond generated by asymmetric addition to a chiral α,β-unsaturated sulfoxide highlighted.\(^3\)\(^5\)

![Figure 3.1. Natural Products and Biologically Relevant Molecules from Conjugate Additions to Chiral α,β-Unsaturated Sulfoxides]

Posner et al. were one of the first to realize the great potential of α,β-unsaturated sulfoxides as chiral auxiliaries in the formation of carbon-carbon (C-C) bonds.\(^6\) In 1981, that group achieved the asymmetric addition of a methyl Grignard reagent to chiral cyclopentenone 1 to give cyclopentanone 2 (Scheme 3.1). The sulfinyl moiety
of product 2 was reductively cleaved into \((R)/(+)-3\)methylcyclopentanone 3 in good yield and enantiomeric excess. The observed stereoselectivity was rationalized via a model involving nucleophilic attack of the Grignard reagent to the less hindered face of magnesium complex 4.\(^6\)

![Scheme 3.1. Synthesis of \((R)/(+)-3\)-methylcyclopentanone 3](image)

Garcia Ruano et al. developed a hydrocyanation reaction of chiral alkenyl sulfoxides that occurred with complete stereoselectivity.\(^7\) In one example, \(\text{Et}_2\text{AlCN}\) reacted with alkenyl sulfoxide 5 to give the corresponding nitrile 6 in excellent yield and complete stereoselectivity (Scheme 3.2). Hydrolysis of the nitrile with the assistance of \(\text{BF}_3\cdot\text{OEt}_2\), followed by desulfurization with Raney nickel gave the corresponding amide 8 possessing a quaternary chiral centre.\(^7\)

![Scheme 3.2. Synthesis of Amide 8](image)

This methodology was later applied to the synthesis of the unnatural fungicide \((R)\)-systhane, which is used for controlling powdery mildews (Scheme 3.3).\(^3\) \((R)\)-Systhane contains a quaternary carbon center adjacent to a cyano group, making this challenging target accessible to this hydrocyanation methodology. Indeed, the
initial hydrocyanation reaction of alkenyl sulfoxide 9 led to the corresponding β-cyano sulfoxide 10 in excellent diastereoselectivity. Compound 10 underwent a one-pot two-step sequence involving Pummerer chemistry followed by reduction of the corresponding hemithioacetal to give alcohol 11 in good yield. Subsequent functional group interconversion delivered (R)-systhane in good overall yield.\(^3\)

**Scheme 3.3. Synthesis of Fungicide (R)-Systhane**

Satoh *et al.* achieved the synthesis of 4,4-disubstituted 2-cyclopentenones 14 from chiral 1-chlorovinyl \(p\)-tolyl sulfoxides.\(^8\) Reaction of sulfoxides 12 with excess cyanomethyllithium gave quaternary centre containing enaminonitriles 13 in excellent yields and enantioselectivities (Scheme 3.4). Enaminonitriles 13 were heated with phosphoric acid to furnish the corresponding chiral 4,4-disubstituted 2-cyclopentenones 14 in good yield.

**Scheme 3.4. Synthesis of chiral cyclopentanones 14**
This methodology was later applied to the synthesis of (+)-α-cuparenone, a natural product containing a chiral quaternary carbon isolated from *Mayur panki* (Scheme 3.5).\(^9\) Chiral sulfoxide 15 was treated with excess cyanomethyllithium to give the corresponding enaminonitrile, which underwent hydrolytic decyanation to give the corresponding chiral ketone 16. Alkylation of the enolate of 16 with methyl iodide followed by hydrogenation provided (+)-α-cuparenone in good yield.\(^9\)

![Scheme 3.5. Synthesis of (+)-α-cuparenone](image)

The observed stereochemical preference is explained by initial attack of cyanomethyllithium on the organometallic complex 17 (Scheme 3.6).\(^9\) Attack of the cyanomethyl anion occurs at the *Re* face and avoids the bulky tolyl group of 17 to give adduct 18 preferentially. Treatment of 18 with another equivalent of cyanomethyllithium leads to cyclized product 19.\(^9\)

![Scheme 3.6. Stereochemical Mechanism for Cyanomethyllithium Addition to Chiral 1-Chlorovinyl p-Tolyl Sulfoxides](image)
Satoh and Sugiyama used similar chiral substrates for the synthesis of chiral esters and γ-lactones to form tertiary or quaternary carbon stereogenic centres at the β-position (Scheme 3.7).\textsuperscript{10} Chiral sulfoxide 20 was treated with a lithium ester enolate to give the 1,4-adduct 21 as a single diastereomer in excellent yield. The chlorine atom was reduced with tributyltin hydride to give sulfoxide 22 in excellent yield. Reductive cleavage of sulfur with nickel followed by acidic ester hydrolysis provided carboxylic acid 23, containing a β-stereocenter.

\begin{center}
\begin{tikzpicture}
\node[draw, text width=2cm, align=center, font=\footnotesize] (a) at (0,0) {20};
\node[draw, text width=2cm, align=center, font=\footnotesize] (b) at (2,0) {21 \ 91\% \ single \ isomer};
\node[draw, text width=2cm, align=center, font=\footnotesize] (c) at (4,0) {22 \ 94\%};
\node[draw, text width=2cm, align=center, font=\footnotesize] (d) at (6,0) {23 \ 91\%, \ ee = 99\%};
\node[draw, text width=2cm, align=center, font=\footnotesize] (e) at (0,-2) {1. Raney-Ni \ EtOH};
\node[draw, text width=2cm, align=center, font=\footnotesize] (f) at (0,-3) {2. TFA, DCM};
\node[draw, text width=2cm, align=center, font=\footnotesize] (g) at (2,-2) {Me};
\node[draw, text width=2cm, align=center, font=\footnotesize] (h) at (4,-3) {CO_2H};
\node[draw, text width=2cm, align=center, font=\footnotesize] (i) at (0,-1) {Bu_3SnH \ AIBN};
\node[draw, text width=2cm, align=center, font=\footnotesize] (j) at (2,-1) {C_6H_6};
\node[draw, text width=2cm, align=center, font=\footnotesize] (k) at (4,-2) {Cl \ Tol \ C(O)O \ tBu};
\node[draw, text width=2cm, align=center, font=\footnotesize] (l) at (0,-1.5) {Cl \ Tol \ C(O)O \ tBu};
\node[draw, text width=2cm, align=center, font=\footnotesize] (m) at (2,-1.5) {Ph \ H \ H \ Tol \ Cl \ S};
\node[draw, text width=2cm, align=center, font=\footnotesize] (n) at (4,-1.5) {Ph \ H \ H \ Tol \ Cl \ S};
\node[draw, text width=2cm, align=center, font=\footnotesize] (o) at (0,-0.5) {Ph \ H \ H \ Tol \ Cl \ S};
\node[draw, text width=2cm, align=center, font=\footnotesize] (p) at (2,-0.5) {Ph \ H \ H \ Tol \ Cl \ S};
\node[draw, text width=2cm, align=center, font=\footnotesize] (q) at (4,-0.5) {Ph \ H \ H \ Tol \ Cl \ S};
\node[draw, text width=2cm, align=center, font=\footnotesize] (r) at (0,-2.5) {Ph \ H \ H \ Tol \ Cl \ S};
\node[draw, text width=2cm, align=center, font=\footnotesize] (s) at (2,-3) {Bu_3SnH \ AIBN};
\node[draw, text width=2cm, align=center, font=\footnotesize] (t) at (4,-3) {C_6H_6};
\node[draw, text width=2cm, align=center, font=\footnotesize] (u) at (0,-3.5) {Cl \ Tol \ C(O)O \ tBu};
\node[draw, text width=2cm, align=center, font=\footnotesize] (v) at (2,-3.5) {Ph \ H \ H \ Tol \ Cl \ S};
\node[draw, text width=2cm, align=center, font=\footnotesize] (w) at (4,-3.5) {Ph \ H \ H \ Tol \ Cl \ S};
\node[draw, text width=2cm, align=center, font=\footnotesize] (x) at (0,-4.5) {Cl \ Tol \ C(O)O \ tBu};
\node[draw, text width=2cm, align=center, font=\footnotesize] (y) at (2,-4.5) {Ph \ H \ H \ Tol \ Cl \ S};
\node[draw, text width=2cm, align=center, font=\footnotesize] (z) at (4,-4.5) {Ph \ H \ H \ Tol \ Cl \ S};
\end{tikzpicture}
\end{center}

**Scheme 3.7. Synthesis of Chiral Carboxylic Acid 23**

Similarly, chiral sulfoxide 24 was treated with a lithium ester enolate to garner sulfoxide 25 as a single isomer in excellent yield (Scheme 3.8).\textsuperscript{10} Treatment with trifluoroacetic anhydride (TFAA) and sodium iodide (NaI) promoted a cyclization reaction, which provided lactone 26. Reductive cleavage of sulfur produced the quaternary carbon-containing γ-lactone 27 as a single enantiomer. These examples clearly exhibit the utility of chiral sulfoxides as Michael acceptors in asymmetric organic synthesis.
Much work has been accomplished recently in regard to diastereoselective conjugate additions of chiral alkylidene bis(sulfoxides) 28 (Scheme 3.9). The bis-sulfinyl moiety is quite valuable and flexible and has been shown to be a powerful chiral inducer which can also serve as a masked carbonyl group, being liberated by subsequent Pummerer chemistry. Based on x-ray crystallography and molecular modeling studies, alkylidene bis(sulfoxides) such as 28 will adopt conformation A in the solid-state due to a highly favorable π-π stacking interaction (Scheme 3.9). Nucleophilic attack occurs from the Si face to give isomer 29 as the major product. Alkylidene bis(sulfoxides) also offer the opportunity for highly tunable control of stereochemistry through chelation control. Indeed, with addition of a Lewis acid, reactive conformation A predominates wherein the Lewis acid is complexed between the two sulfinyl oxygen atoms. Nucleophilic attack occurs from the re-face of complex B to give complementary isomer 30 as the major product (Scheme 3.9). The ability for control of stereochemistry via chelation/non-chelation control
coupled with the easy cleavage of the auxiliary make alkylidene bis(sulfoxide) chemistry a valuable tool for asymmetric synthesis.\textsuperscript{11}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme3.9.png}
\caption{Scheme 3.9. Mechanism of Nucleophilic Addition to Chiral Alkylidene Bis(sulfoxides)}
\end{figure}

Malacria \textit{et al.} first looked at the addition of amine nucleophiles to chiral alkylidene bis(sulfoxides) (Scheme 3.10).\textsuperscript{11} Addition of morpholine to 28 provided the amino adduct 31 (via conformation mode A) in quantitative yield with complete stereoselectivity. Adduct 31 could was transformed into chiral amino alcohol 32 or chiral methyl ester 33 by way of subsequent Pummerer chemistry (Scheme 3.10).\textsuperscript{11} Similarly, sodium alkoxide nucleophiles provided adducts with high yields and complete stereoselectivity through attack of non-chelation mode A.
Scheme 3.10. Nucleophilic Addition/Pummerer Reaction Sequence

The stereoselectivity was shifted to give the complementary isomer by the use of copper-based reagents. Copper salts have the ability to coordinate to the sulfinyl oxygens of the alkylidene bis(sulfoxide) 34, giving adducts 35 via mode B in Scheme 3.9 (Scheme 3.11).

Scheme 3.11. Addition of Copper Salts to Alkylidene Bis(sulfoxides)

Malacria et al. applied this methodology to the first total synthesis of (+)-erythro-roccellic acid, a natural product with antituberculosis activity (Scheme 3.12). Alkylidene bis(sulfoxide) 36 was treated with the lithium enolate of Heathcock’s ester, which provided adduct 37 in good yield (79% with 10% minor diastereomers). Exposing 37 to Pummerer conditions followed by a dual
saponification reaction gave (+)-erythro-roccellic acid in good yield.\textsuperscript{11} The asymmetric synthesis of two isomers of sphaeric acid was also later achieved via a similar approach using the addition of lithium enolates to an alkylidene bis(sulfoxide) precursor.\textsuperscript{15}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme312.png}
\caption{Scheme 3.12. Total Synthesis of (+)-Roccellic Acid}
\end{figure}
\end{center}

An extension of this methodology has been used on dienyl bis(sulfoxide) 38.\textsuperscript{16} Attack of a carbon nucleophile at the $\beta$-position gave the cyclopropanated addition product 39 as a single diastereomer (Scheme 3.13).\textsuperscript{16} Low temperature is a necessity to avoid competitive attack at the $\delta$-carbon. Also, the addition of a methylcopper reagent gave the product of chelation control (model B) 40 in quantitative yield and complete stereoselectivity (Scheme 3.13).\textsuperscript{16}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme313.png}
\caption{Scheme 3.13. Nucleophilic Additions to Dienyl Bis(sulfoxide) 38}
\end{figure}
\end{center}

An intermolecular conjugate addition reaction of a piperidine nucleophile to a chiral $\alpha,\beta$-unsaturated sulfoxide has been previously described.\textsuperscript{17} Despite this example, the intermolecular approach has not yet been widely used in total synthesis, likely due
to the low relative reactivity of these Michael-acceptors. A few select examples do exist in the literature however. Pyne et al. investigated the intermolecular addition of benzyl amine to enantiopure isomeric (E)- and (Z)-vinyl sulfoxides (Scheme 3.14). Interestingly, the addition of isomeric Z and E isomers (41 and 42 in Scheme 3.14) is a diastereoconvergent process with each olefinic substrate yielding the major isomeric product 43. Studies have confirmed that isomer 42 is most stable in a s-cis conformation where the S=O and C=C bonds are in a syn relationship. In contrast, isomer 41 prefers to be in an s-trans conformation where the S=O and C=C are anti to one another (Scheme 3.14). In both cases nucleophilic attack occurs on the less hindered face of the π-bond leading to diastereomer 43 as the major product.

![Scheme 3.14. Conjugate Additions of Benzyl Amine to Chiral α,β- Unsaturated Sulfoxides](image)

Recently, Podlech and Ulshöfer conducted a study investigating the stereoelectronic effects of conformationally fixed vinylic sulfoxides 44 and 45 (Scheme 3.15). For the carbonyl group, the stabilizing effect of conjugation between C=C and C=O is best when p-orbitals are collinear. This is not applicable between C=C and S=O bonds, since a π bond is virtually nonexistent between S and O atoms. However,
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 collinear arrangement, as in compound 44. In fact, a bathochromic shift of 14 nm was observed between 45 and 44 when comparing UV-vis spectra, indicating an increase in the stereoelectronic stabilization of 44.\textsuperscript{23} Further, \textit{ab initio} calculations quantifying hyperconjugative stabilizing interactions showed a similar conclusion. Calculation of selected delocalization energies of 44 exhibited a significant contribution of 12.8 KJ/mol from a $\pi_{\text{c=c}} \rightarrow \sigma^*_{\text{s-o}}$ stereoelectronic interaction which was effectively non-existent in sulfoxide 45.\textsuperscript{23} Evidence for a related stabilizing interaction in 44 involving an antiperiplanar lone pair and S=O bond ($n_c \rightarrow \sigma^*_{\text{s-o}}$) was obtained from differing diastereomeric ratios of conjugate additions of 44 or 45 with piperidine. Sulfoxide 44 gave amine 46 as the major diastereomer, which occurred via intermediate betaine 48 possessing the $n_c \rightarrow \sigma^*_{\text{s-o}}$ stabilizing interaction made possible by the antiperiplanar arrangement of the anionic lone pair and S=O bond. In contrast, compound 45 gave amine 47 as the major isomer presumably through betaine 49. Intermediate 49 employs participation of the $\sigma^*_{\text{s-c}}$ as acceptor orbitals since the $\sigma^*_{\text{s-o}}$ orbital is not antiperiplanar to the anionic lone pair. Competition experiments between 44 and 45 provided evidence that acceptor stabilization from the $\sigma^*_{\text{s-o}}$ orbital is greater than from the $\sigma^*_{\text{s-c}}$ orbital.\textsuperscript{23}
Podlech expanded upon this investigation to include natural bond order (NBO) analyses for the evaluation of the stereoelectronic effects in α-carbanions of thiane derived sulfones and sulfoxides (Scheme 3.16). Sulfones 50 and 51 were found to have almost identical energies, which means the n_c → σ^*_{s-o} interaction of 51 contributes significantly less to anion stabilization than in the case of a corresponding sulfoxide analog (Scheme 3.16). This is because 50 possesses three major stabilizing effects including an n_c → σ^*_{s-c} hyperconjugation, a σ_{c-H} → σ^*_{s-o} interaction, and a synclinal n_c → σ^*_{s-o} interaction into the axial S=O bond following rehybridization of the lone pair to anion 52 (Scheme 3.16).
Scheme 3.16. Evaluation of the Stereoelectronic Effects in α-Carbanions of Thiane Derived Sulfones

Matsuyama et al. developed an asymmetric conjugate addition of another six-membered nitrogen heterocycle, piperidazine, to a chiral vinylic sulfoxide (Scheme 3.17). The base-mediated asymmetric addition-cyclization on sulfoxide \((R)-53\) gave a heterocyclic sulfoxide intermediate, which was desulfurized with SmI\(_2\) to give compound \((S)-54\) in good yield and excellent selectivity.\(^4\) Heterocycle \((S)-54\) was used as an initial chiral building block in the total synthesis of the macrocyclic alkaloid \((S)-(-)-celacinnine\).\(^4\) The diastereoselectivity was explained by transition state 55, which involves nucleophilic attack occurring on the less hindered face of the \(\pi\)-system. A hydrogen bonding interaction was also thought to play a role in determining the diastereoselectivity.\(^4\)
Scheme 3.17. Synthesis of (-)-Celacinnine

Recently, Fernandez de la Pradilla et al. were able to synthesize enantiopure 1,4-diols and 1,4-amino alcohols via a stereoselective acyclic sulfoxide-sulfenate rearrangement sequence that commenced with the conjugate addition of an amine nucleophile to a chiral dienyl sulfoxide (Scheme 3.18). Conjugate addition of amine nucleophiles provided vinyl sulfoxides, which underwent a base-induced diastereoselective formation of allylic sulfoxides. Subsequent asymmetric [2,3]-sigmatropic rearrangement and sulfenate cleavage provided chiral diols and amino alcohols in excellent yields and diastereoselectivities.

Scheme 3.18. Asymmetric Nucleophilic Addition/[2,3]-Sigmatropic Rearrangement Sequence
The intramolecular asymmetric aza-Michael reaction of nitrogen nucleophiles with α,β-unsaturated sulfoxides has been used more successfully in synthesis. In 1986, Pyne and Chapman accomplished the first intramolecular reaction of this type (Scheme 3.19). Basic hydrolysis of (Z)-vinylic sulfoxide 60 gave cycloadduct 61 as the major isomer in excellent yield and diastereoselectivity. The observed selectivity is likely due to a facial preference of the nitrogen to attack via the less hindered face of the π-bond.

![Scheme 3.19. Synthesis of (+)-Carnegine](image)

The work of Pyne was later extended to the synthesis of (R)-(+)‐canadine, a member of the tetrahydroprotoberberine family of alkaloids (Scheme 3.20). Vinylic sulfoxide 62 was transformed into cycloadduct 63 upon exposure to benzyltrimethyl ammonium hydroxide with acceptable diastereoselectivity. Subsequent Pummerer chemistry and cyclization provided the fused pentacyclic molecule 64. Reductive desulfurization with Raney-nickel catalyst provided (R)-(+)‐canadine in excellent yield. A similar aza-Michael-Pummerer strategy was later used in the synthesis of (R)-(+)‐tetrahydropalmatine. In line with this, Lee et al.
achieved the synthesis of (R)-(+)-(+)-carnegine and (R)-(+)-(+)-tetrahydroharman using synthetic routes involving aza-Michael reactions to chiral acetylenic sulfoxides.\textsuperscript{28,29}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_3.20}
\end{center}

**Scheme 3.20. Synthesis of (+)-Canandine**

Montoro et al. developed an intricate strategy to cyclize chiral vinylic sulfoxides containing a free homoallylic hydroxyl group (Scheme 3.21).\textsuperscript{30} Two N-Boc-protected (2-sulfinylallyl)amino alcohols, 65 and 66 were exposed to a “one-pot” procedure involving initial acidic nitrogen deblocking, followed by subsequent cyclization with excess triethylamine. This procedure garnered good yields of sulfinylpiperidine 69 and sulfinylindolizidine 70 in excellent diastereoselectivities with the hydroxyl and sulfinyl groups existing in a cis-relationship in the major isomer. This cis-relationship can be explained in terms of near-complete π-facial stereoselectivity in the conjugate addition step followed by fast protonation of the developing carbanion by the protic solvent.\textsuperscript{30} This is set up by stabilization of intermediate 71 involving an intramolecular hydrogen bonding interaction between the sulfinyl
oxygen and hydroxyl group. The existence of intermediate 52 was corroborated by the fact that the corresponding methoxy derivatives of 46 and 47 afforded a nearly 1:1 diastereomeric mixture of cycloadducts.\textsuperscript{30}

\begin{center}
\[
\text{Scheme 3.21. Synthesis of 69 and 70}
\]
\end{center}

With all the modern developments in conjugate additions to chiral vinylic sulfoxides it is perhaps the earliest example reported in the literature that spawned the idea for the chemistry of this thesis. Over 40 years ago Nobel laureate and “grandfather” of \textit{Allium} chemistry, Artturi Virtanen, isolated the hydrochloride hydrate of a sulfur containing amino acid from an ethanol extract of onion (Scheme 3.22).\textsuperscript{31,32} This amino acid is the chiral cyclic sulfoxide that is known today as cycloalliin.\textsuperscript{33} Currently, cycloalliin is believed to be a molecule partially responsible for many of the health benefits of an \textit{Allium} rich diet.\textsuperscript{34-39} At the time Virtanen proposed a possible biosynthesis of cycloalliin from alliin, another amino acid found in onion plants (Scheme 3.22).\textsuperscript{33} Of note is the fact that the final step in the biosynthesis
involves a stereoselective intramolecular attack of an amino nucleophile at the β-carbon of a chiral sulfoxide intermediate.\textsuperscript{33}

\[
\text{Scheme 3.22. Proposed Biosynthesis of Cycloalliin}
\]

The initial isolation of cycloalliin by Virtanen piqued the interest of other scientists who began study of this rare amino acid. Isoalliin, a chiral vinylic sulfoxide possessing a trans double bond, was isolated from onions a few years later (Scheme 3.23).\textsuperscript{40} Wonderfully, the treatment of isoalliin with aqueous ammonium hydroxide followed by acidic work up provided cycloalliin hydrochloride hydrate 72 via a completely stereoselective intramolecular conjugate addition reaction (Scheme 3.23).\textsuperscript{41} Palmer and Lee later showed by x-ray analyses that crystalline cycloalliin 72 has the chair conformation with the S=O bond axial and in a trans relationship to the carboxyl and methyl groups.\textsuperscript{42}

\[
\text{Scheme 3.23. Cyclization of Isoalliin}
\]

Carson \textit{et al.} later attempted the cyclization of a homolog of isoalliin, sulfoxide 73 (Scheme 3.24).\textsuperscript{43} Unfortunately, 73 could only be prepared as a diastereomeric
mixture that could not be resolved into optically pure isomers. Nevertheless, 73 was treated with base and cyclization occurred to give a mixture of stereoisomers 74 and 75. Since the cyclization occurred on a diastereomeric mixture 73 the precise degree of stereoselectivity is unclear.

Scheme 3.24. Cyclization Reaction of Sulfoxide 73

Carson and Boggs also evaluated the reactivity of cis-isoalliin 76 (Scheme 3.25). Again, diastereomerically pure starting material was unattainable; therefore an unknown diastereomeric ratio was cyclized. A complex mixture with unspecified yields was obtained that included cycloalliin, sulfoxide 77 (with unknown sulfinyl configuration) and two other ninhydrin active products. Although the chemistry was tested on a mixture of diastereomers the cyclization of cis-isoalliin 76 gives a complicated mixture of products compared to the corresponding reaction of cycloalliin.

Scheme 3.25. Cyclization Reaction of Sulfoxide 76
3.1.2 Proposed Cyclization Chemistry

Although progress was made on the cyclization of isoalliin and its derivatives in the 1950s and 1960s, several questions and problems regarding this chemistry remain unanswered. For one, the mode of cyclization or mechanism of the complete stereoselectivity in the case of isoalliin to cycloalliin was not examined or explained. Also, this reaction is sluggish occurring over a timescale of one week. Further, the extension of this chemistry to the homolog or Z-analog proved largely unfruitful. The present goal of our chemistry is to better evaluate this type of cyclization chemistry; including expanding reaction scope and evaluating the variables governing asymmetric induction (Scheme 3.26).

![Diagram of proposed synthesis of 1,4-thiazane-S-oxides](image)

**Scheme 3.26. Proposed Synthesis of 1,4-Thiazane-S-Oxides**

The aforementioned asymmetric sulfenate alkylation chemistry (Chapter 1) provides access to chiral E-vinylc β-amino sulfoxides as rational starting materials to explore subsequent cyclization reactivity (Scheme 3.27). Sulfenate chemistry allows variation at the R and R’ positions to explore trends in cyclization selectivity and reactivity.
Scheme 3.27. Synthesis of β-Amino Sulfoxides from Thiirane S-Oxides

Presumably, a small array of chiral 3,5-substituted-1,4-thiazane-S-oxides will be synthesized. Examples of these heterocycles have been found to display significant biological activity. Cycloalliin is partially responsible for the beneficial health effects such as decreased risk of cardiovascular disease linked to an Allium rich diet (Figure 3.2). Heterocycle 78 inhibits an enzyme called dihydrodipicolinate synthase in E. coli, which gives this molecule antibiotic properties. Given the medicinal importance of chiral 3,5-substituted-1,4-thiazane-S-oxides, the molecules and synthetic methodology generated from this study may have value in broader scientific fields such as biology.

Figure 3.2. Medicinally Relevant 3,5-Substituted-1,4-Thiazane-S-Oxides

Finally, if acceptable yields and selectivities are achieved, functional group transformations leading to pyrrolidine building blocks will be attempted (Scheme 3.28). Chiral pyrrolidines have proved to be highly useful organic molecules in catalysis and comprise a family of naturally occurring alkaloids.
3.2 Results and Discussion

3.2.1 Optimization and Scope of Cyclization Reaction

Sulfoxide 79a was chosen for the initial cyclization trials because it is obtained with ease through sulenate alkylation in high yield and excellent diastereoselectivity. Cyclization efforts began with employing cesium carbonate (Cs$_2$CO$_3$) as a base in DCM (Table 3.1, entry 1). Stirring under these conditions for several days left the starting material unaffected, therefore the molar equivalents of base were increased three fold and the mixture was refluxed for several hours. However, excess base and heating failed to affect the substrate (Table 3.1, entries 2 & 3). In light of initial failures in DCM, cyclizations were tried in higher boiling solvents toluene and dichloroethane (DCE) in attempts to see if higher temperatures could overcome energy barriers hampering cyclization. Unfortunately, even with microwave irradiation at high temperature Cs$_2$CO$_3$ failed to provide any cyclized compound (Table 3.1, entries 4 & 5). Next, the base was changed to sodium hydride (NaH). Similarly to Cs$_2$CO$_3$, NaH failed to provide the desired product even while using an excess of base with prolonged heating (Table 3.1, entries 7-9). When triethylamine was employed as the base in methanol with heating, a mixture of products believed
to result from incorporation of methanol at the β-position of 79a resulted (Table 3.1, entry 10). Shifting to the higher boiling solvent toluene also failed to deliver cyclization after sustained heating (Table 3.1, entry 11). Using DBU and K₂CO₃ also failed to give any detectable amount of heterocycle after prolonged heating (Table 3.1, entries 12 & 13). Lastly, initial deprotonation of the carbamate proton with n-butyllithium followed by stirring at rt to reflux gave a complex mixture of decomposition products (Table 3.1, entry 14). At this stage it was felt that the Boc group was preventing cyclization of 79a by a combination of two factors. One, the bulky t-butyl group of Boc may impart too much steric encumbrance for attack of nitrogen to occur at the β-carbon of 79a. Two, being a carbamate, the nucleophilic lone pair on nitrogen is involved in resonance with the carbonyl and will not be as nucleophilic. Therefore, the cyclization of the free amine was pursued, as the nucleophilic lone pairs would be free to partake in nucleophilic attack without being sterically hindered or engaged in resonance as in 79a.

**Table 3.1. Cyclization attempts on Boc-protected β-amino sulfoxide 79a**

<table>
<thead>
<tr>
<th>entry</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>T</th>
<th>Time</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cs₂CO₃(1.0)</td>
<td>DCM</td>
<td>RT</td>
<td>36 h</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>Cs₂CO₃(3.3)</td>
<td>DCM</td>
<td>RT</td>
<td>6 h</td>
<td>SM</td>
</tr>
<tr>
<td></td>
<td>Reagent</td>
<td>Solvent</td>
<td>Conditions</td>
<td>Time</td>
<td>SM</td>
</tr>
<tr>
<td>---</td>
<td>------------------</td>
<td>-------------</td>
<td>------------</td>
<td>------</td>
<td>----</td>
</tr>
<tr>
<td>3</td>
<td>Cs₂CO₃(3.3)</td>
<td>DCM</td>
<td>reflux</td>
<td>6 h</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>Cs₂CO₃(1.0)</td>
<td>DCE</td>
<td>MW 300W</td>
<td>30 min</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>Cs₂CO₃(1.0)</td>
<td>Toluene</td>
<td>MW 300W</td>
<td>30 min</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>Cs₂CO₃(1.0) + LiBr</td>
<td>DCE/DMSO</td>
<td>MW 300W</td>
<td>30 min</td>
<td>SM</td>
</tr>
<tr>
<td>7</td>
<td>NaH (1.0)</td>
<td>DCM</td>
<td>RT</td>
<td>36 h</td>
<td>SM</td>
</tr>
<tr>
<td>8</td>
<td>NaH (9.0)</td>
<td>DCM</td>
<td>RT</td>
<td>6 h</td>
<td>SM</td>
</tr>
<tr>
<td>9</td>
<td>NaH (9.0)</td>
<td>DCM</td>
<td>reflux</td>
<td>6 h</td>
<td>SM</td>
</tr>
<tr>
<td>10</td>
<td>NEt₃ (1.0)</td>
<td>MeOH</td>
<td>reflux</td>
<td>18 h</td>
<td>·OMe addition</td>
</tr>
<tr>
<td>11</td>
<td>NEt₃ (1.0)</td>
<td>Toluene</td>
<td>reflux</td>
<td>18 h</td>
<td>SM</td>
</tr>
<tr>
<td>12</td>
<td>K₂CO₃ (1.0)</td>
<td>Toluene</td>
<td>reflux</td>
<td>18 h</td>
<td>SM</td>
</tr>
<tr>
<td>13</td>
<td>DBU(1.5)</td>
<td>DCE</td>
<td>reflux</td>
<td>24 h</td>
<td>SM</td>
</tr>
<tr>
<td>14</td>
<td>BuLi (1.0)</td>
<td>Toluene</td>
<td>-78 °C-rt- reflux</td>
<td>24 h-3 hr</td>
<td>--</td>
</tr>
</tbody>
</table>
Protected 79a can be deblocked with an easy procedure employing TFA in DCM to give the free amine 80a or TFA salt 81a (Scheme 3.29).

![Scheme 3.29. Deprotection of Boc-Protected Sulfoxide 79a](image)

With 80a in hand optimization attempts were attempted as depicted in Table 3.2. DCM was chosen as the solvent for the initial trials. Bases Cs₂CO₃, K₂CO₃, and NEt₃ all failed to provide heterocycle 82a even with prolonged heating (Table 3.2, entries 1-6). The solvent was switched to methanol at this stage to permit increased reaction temperatures. Unfortunately, both K₂CO₃ and Triton B in methanol led to mixtures of products with methoxide incorporated at the β-carbon, likely originating from a significant concentration of methoxide in the reaction solution (Table 3.2, entries 7 and 8). Therefore, a base possessing a conjugate acid with a lower pKa was chosen (HNR₃⁺ pKa ~ 8-9). Gratifyingly, refluxing 80a with one equivalent of NEt₃ in methanol gave the corresponding 3,5-trans heterocycle 82a in excellent yield with complete stereoselectivity (as detected by ¹H NMR analysis). The 3,5-trans stereochemistry of the product was confirmed by a selective gradient NOE experiment in which one of the methine protons was irradiated. No NOE effect was observed between the irradiated methine proton and the other methine proton, which was taken as evidence for the trans compound. A NOESY NMR experiment corroborated the result of the selective gradient NOE experiment. The reaction was
then attempted catalytically using 20 mol % of NEt₃, however the reaction time was almost 20 h versus only 5 h for a full equivalent of base. It is clear that the role of methanol is crucial to reaction success. A polar protic solvent may aid in stabilizing a transition state that is more polar than a neutral starting material and it is likely that methanol delivers a proton to the α-sulfinyl carbon as part of the cyclization transition state.

**Table 3.2. Cyclization Optimization of β-Amino Sulfoxide 80a to 82a**

<table>
<thead>
<tr>
<th>entry</th>
<th>base (eq.)</th>
<th>solvent</th>
<th>T</th>
<th>time</th>
<th>yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CsCO₃ (1.0)</td>
<td>DCM</td>
<td>RT</td>
<td>96 h</td>
<td>SM</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CsCO₃ (1.0)</td>
<td>DCM</td>
<td>reflux</td>
<td>16 h</td>
<td>SM</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>NEt₃ (1.0)</td>
<td>DCM</td>
<td>RT</td>
<td>48 h</td>
<td>SM</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>NEt₃ (1.0)</td>
<td>DCM</td>
<td>reflux</td>
<td>5 h</td>
<td>SM</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>K₂CO₃ (1.0)</td>
<td>DCM</td>
<td>RT</td>
<td>96 h</td>
<td>SM</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>K₂CO₃ (1.0)</td>
<td>DCM</td>
<td>reflux</td>
<td>15 h</td>
<td>SM</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>K₂CO₃ (0.96)</td>
<td>MeOH</td>
<td>reflux</td>
<td>10 h</td>
<td>OMe incorp.</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Triton B (1.0)</td>
<td>MeOH</td>
<td>reflux</td>
<td>2 h</td>
<td>OMe incorp.</td>
<td>-</td>
</tr>
</tbody>
</table>
With the conditions for cyclization of the sulfoxide optimized, the goal was to expand the scope of the reaction beginning with alteration of the alkyl group of the amino acid component. Several Boc-protected trans-alkenyl β-amino sulfoxides 79a-c could be obtained in enantiopure form from the aforementioned sulfenate alkylation chemistry (see Chapter 1). Amino deprotection to the corresponding TFA salts 81a-c was achieved in good to excellent yields using TFA (Scheme 3.30). Isolation of the β-amino sulfoxides as free amines using basic work-up gave generally lower and less reproducible yields, therefore isolation of the TFA salts was preferred.

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>NEt₃ (1.0)</td>
<td>MeOH</td>
<td>reflux</td>
<td>5 h</td>
<td>95</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>10</td>
<td>NEt₃ (0.2)</td>
<td>MeOH</td>
<td>reflux</td>
<td>19.5 h</td>
<td>85</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>11</td>
<td>NEt₃ (1.0)</td>
<td>IPA</td>
<td>reflux</td>
<td>12 h</td>
<td>OfPr incorp.</td>
<td>-</td>
</tr>
</tbody>
</table>

Scheme 3.30. Deprotection Reactions of 1-Propenyl β-Amino Sulfoxides
Treatment of the β-amino sulfoxides $81a$-$c$ with an extra molar equivalent of base to free the TFA salt under optimized cyclization conditions gave the corresponding heterocycles $82a$-$c$ as a single diastereomers ($^1$H NMR) in excellent yields (Scheme 3.31). Similarly a sulfoxide possessing the complementary stereochemistry $ent-81a$ was cyclized to give $ent-82a$ as a single stereoisomer. In all cases the $trans$-$3,5$-substituted stereoisomer was the only one detected in the $^1$H NMR spectrum.

![Scheme 3.31. Cyclizations of 1-Propenyl β-Amino Sulfoxides](image)

Next, the olefin methyl substituent was varied to see if similar trends levels of stereoselectivity and reaction proficiency could be obtained. Initially, a phenethyl substituted amine $80d$ was accessed from deprotection of the corresponding sulfenate alkylation product $79d$ (Scheme 3.32). Unfortunately, the optimized procedure failed to effect the cyclization of $80d$ and none of heterocycle $82d$ was detected even after heating for over 20 h.
New conditions were pursued to effect cyclization of 80d as depicted in Table 3.3. The equivalents of base used were increased; however after refluxing for > 20 h mainly starting material was recovered with no evidence of 82d. Varying the solvent from methanol to other polar solvents like CH3CN or DMF failed to provide heterocycle 82d even at high temperatures (~140 °C). Changing the base to K2CO3 in DCE also failed to provide any of the cyclized product. It is likely that the inherent steric hindrance of the phenethyl group is likely too great to overcome. Rotation about the sp²-sp³ σ bond likely causes the phenethyl group to block the Bürgi-Dunitz angle of attack for the nitrogen nucleophile.

**Table 3.3. Further Cyclization Attempts of β-Amino Sulfoxide 80d**

<table>
<thead>
<tr>
<th>entry</th>
<th>base (eq.)</th>
<th>solvent</th>
<th>T (°C)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NEt₃ (6)</td>
<td>MeOH</td>
<td>reflux</td>
<td>&gt; 20</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>NEt₃ (6)</td>
<td>CH₃CN</td>
<td>reflux</td>
<td>&gt; 20</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>NEt₃ (6)</td>
<td>DMF</td>
<td>~140</td>
<td>&gt; 20</td>
<td>0</td>
</tr>
</tbody>
</table>
With the phenethyl derivative 80d failing to give any desired product 82d a cyclization with t-butyl derivative 80e was attempted. However, like the phenethyl case the t-butyl derivative also failed to give any of the desired heterocycle 82e after prolonged heating (Scheme 3.33). The lack of reactivity can be attributed to the large steric encumbrance of the t-butyl group.

**Scheme 3.33. Cyclization Attempt of 80e**

Based on literature evidence it is well established that α,β-unsaturated sulfones are more effective Michael acceptors than the corresponding sulfoxide analogues and respective pKa values offer one piece of evidence of this trend (Figure 3.3). The α-hydrogen of dimethyl sulfoxide has a pKa value of ~35 which is significantly higher than the α-hydrogen of dimethyl sulfone (pKa ~ 31). The aforementioned computations of Podlech are also supportive of the relative reactivities.

**Figure 3.3. Relative pKa Values of Dimethyl Sulfoxide and Dimethyl Sulfones**

<table>
<thead>
<tr>
<th></th>
<th>K₂CO₃(6)</th>
<th>DCE</th>
<th>reflux</th>
<th>&gt; 20</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
With respect to Michael addition a lower pKa value means that sulfones are more effective at stabilizing negative charge build up on their α-carbon in the transition state of cyclization than sulfoxides. Ultimately, this equates to a lowered relative transition state for the conjugate addition of an α,β-unsaturated sulfone compared with the parallel reaction for an α,β-unsaturated sulfoxide. For this reason it was decided that the cyclization chemistry of the phenethyl and t-butyl sulfoxides (80d and 80e, respectively) should be abandoned in favour of pursuing cyclization reactions of the corresponding sulfones (Scheme 3.34). Sulfoxide 79d was oxidized using MCPBA to give the corresponding sulfone 83d in excellent yield. Following oxidation, sulfone 83d was deprotected to the free amine using TFA to give amine 84d in good yield. The Boc group was removed because this was necessary for an analogous reaction in the literature. \(^{51}\) Exposure of sulfone 84d to our original optimized conditions provided heterocycle 86d in excellent yield and diastereoselectivity. Surprisingly, in contrast to the sulfoxide examples which furnished major isomers with trans-3,5 stereochemistry, the major diastereomer of sulfone 86d possessed cis-3,5 stereochemistry. This led to the hypothesis that the chirality at the sulfur atom was dictating the stereochemistry of the products.
Scheme 3.34. Cyclization of Sulfone 84d

To corroborate this unexpected result β-amino sulfoxide 79a was oxidized to the corresponding sulfone 83a in good yield. Deprotection with acid and basic work-up led to a ~1:2 mixture of acyclic 84a and cyclic 86a. This mixture was treated with base to complete the conversion of 84a to 86a and gratifyingly provided cis-86a as the major isomer in good diastereoselectivity. This result was extremely exciting because it meant that complementary diastereomers could be accessed from identical precursors simply by tuning the oxidation state of the β-amino sulfur compound as shown in Scheme 3.35!

Scheme 3.35. Control of Relative Stereoselectivity by Sulfur Oxidation State

With the knowledge that the steric hindrance of cyclization could be overcome by oxidation to the sulfone, t-butyl derivatives 79e and 79f were evaluated (Scheme 3.36). Oxidation of sulfoxides 79e and 79f with MCPBA gave sulfones 83e and 83f,
respectively. Subsequent deblocking with TFA provided sulfones 84e and 85f, each in excellent yield. Pleasantly, treatment of amine 84e with NEt3 at reflux for ~9 h provided the corresponding cis-3,5-heterocycle 86e with complete stereoselectivity. Similarly, sulfone 85f provided cis-3,5-heterocycle 86f as the major isomer in good yield upon heating with NEt3 (2.0 equiv.) (Scheme 3.36).

![Scheme 3.36. Cyclization Reactions of Sulfones 84e and 85f](image)

Another sulfone cyclization was attempted to further verify this pattern of stereochemical outcome (Scheme 3.37). The oxidation of sulfoxide 79g with MCPBA garnered sulfone 83g in excellent yield. Sulfone 83g was subjected to the standard deprotection conditions yielding free amine 84g which was refluxed with triethylamine (4 equiv.) in methanol to give heterocycle 86g in excellent yield and good diastereoselectivity. The preferential formation of the 3,5-cis isomers of heterocycles 86e-g from the corresponding acyclic sulfones lends further support for stereochemical control originating at the sulfur atom.
The next consideration was to expand the reaction scope by investigating cyclization attempts of a chiral cyclohexene sulfoxide molecule 80h (Scheme 3.38). Successful cyclization of sulfoxide 80h would provide a bicyclic molecule with four stereocenters. Unfortunately, refluxing sulfoxide 80h for two days with triethylamine failed to provide any conversion to product 82h.

Therefore, the corresponding sulfone 84h was pursued to achieve a cyclization. A diastereomeric mixture of 79h was oxidized with MCPBA to the corresponding sulfone 83h in good yield. Subsequent deprotection with TFA provided free amine 84h in excellent yield. Gratifyingly, the treatment of unprotected amine 84h with triethylamine provided bicyclic heterocycle 86h in good yield as a single diastereomer (Scheme 3.39). Similarly to other sulfone cyclizations compound 86h
also possessed cis geometry of substituents at the 3,5-position of the heterocyclic ring.

Scheme 3.39. Cyclization of Sulfone 84h

The stereochemistry at the 3- and 5-positions for all heterocycles synthesized was confirmed by a combination of NMR techniques. Initial inspection of coupling constants within doublet of doublet type multiplets belonging to the methylene and methine ring protons in the $^1$H NMR spectrum for a given compound provided initial insight into relative stereochemistry. One example is depicted in Figure 4 below. The signals for H_b and H_b' in the cis heterocycle 87, would be a pair of doublet of doublets, with each possessing two large coupling constants ($J_{ax} - J_{ax} \sim 10$ Hz and $J_{vic} - J_{vic} \sim 12$ Hz). In the trans heterocycle 88, the doublet of doublets for H_b' would still possess two large coupling constants as in 87, however H_b will now display a doublet of doublets with one large coupling constant ($J_{vic} - J_{vic} \sim 12$ Hz) and one smaller coupling constant ($J_{ax} - J_{eq} \sim 3$ Hz) because H_a no longer lies in an axial position. Analysis of coupling constants and simple 2D NMR experiments like those
mentioned for heterocycle 82a proved sufficient to decipher stereochemistry in all cases.

![Figure 3.4. 3D Diagram of Prototypical Sulfones 87 and 88](image)

### 3.2.2 Ant Venom Alkaloid Syntheses

The discovery and synthesis of new natural products continues to play an incredibly significant role in the discovery and development of novel drugs and therapeutics.\(^{52,53}\) Natural products are often challenging to synthesize, containing a highly intricate arrangement of bonds and atoms that must be accessed from much simpler precursor molecules. Therefore, one of the ultimate goals of the synthetic chemist is to access natural product target molecules using new chemical methodology developed in their lab. As such, it was thought that the aforementioned synthetic methods could be applied to the synthesis of a selection of 2,5-pyrrolidine alkaloids.

Jones \textit{et al.} isolated 14 alkaloids from venom extracts of the ant \textit{Myrmicaria melanogaster},\(^{54}\) two of which include chiral 2,5-substituted pyrrolidines 89 and 90 (Figure 3.5). The authors indicated the presence of both trans and cis isomers, 89 and 90, respectively, but did not elucidate the absolute configuration at either
stereocenter. Alkaloids of the same structural family have been isolated from frog skin extracts and extracts of the venoms from other ant species. In nature, alkaloids 89 and 90 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. Also, the biological study of insect venoms has led to the discovery of new therapeutic agents. Further, several other 2,5-disubstituted pyrrolidine natural products and derivatives have already been identified as highly biologically active compounds.

![Pyrrolidine Alkaloids Isolated From *Myrmicaria melanogaster*](image)

Coldham and Leonori have recently pursued the synthesis of venom alkaloids 89 and 90 using a combination of two stereoselective copper(I)-promoted allylation reactions as key steps (Scheme 3.40). Zinc-copper promoted allylation of 91 gave pyrrolidine 92 in excellent yield and enantioselectivity. Hydrogenation of 92 provided pyrrolidine 93 in good yield. A second metallation was attempted with (-)-sparteine for asymmetric deprotonation; however this only returned starting material. Deprotonation of 93 was achieved using sec-butyllithium/TMEDA and subsequent crotylation gave a mixture of the corresponding di-substituted pyrrolidines 94 in low yield and poor diastereoselectivity (Scheme 3.40). Although, the diastereoselectivity of the formation of 4 was poor there was no evidence of
degradation of enantiomeric excess. Reduction and TFA-mediated Boc-deprotection of 94 yielded the TFA salts of 89 and 90.

**Scheme 3.40. Previous Synthesis of 89 and 90**

Although Coldham and Leonori were able to synthesize 89 and 90 there are several problems with the above synthetic route. For one, the yield is well below 50% for the crotylation reaction. Secondly, the diastereoselectivity (dr = 1.8:1) of that crotylation is not synthetically practical and flash column chromatography is required to separate diastereomers. Lastly, (-)-sparteine is no longer commercially available from all major suppliers and the synthesis of this molecule is not trivial.

The present synthetic route involves all three key reactions that were developed over the course of this thesis (Scheme 3.41). Also, it allows selective access to either diastereomer (89 or 90) or enantiomer (via the choice of D- or L-amino acid starting material). The retrosynthesis of 90 commences with the RBR of 95 forming
the five-membered heterocycle. Next, an asymmetric *aza*-Michael addition of sulfone 96 gives heterocycle 95 with preferential *cis* stereochemistry at the 3- and 5-positions. The last key step forms a S-C bond via a sulenate alkylation reaction between the *trans*-sulenate released from thiirane-**S**-oxide 97 and a chiral amino iodide 98 derived from D-norvaline. As in the case for 90, the retrosynthetic analysis of 89 begins with a RBR of a sulfone derived from chiral sulfoxide 99. Next, an asymmetric *aza*-Michael reaction of chiral sulfoxide 100 was employed to form heterocycle 99 possessing the complementary *trans*-stereochemistry. Lastly, the exact same asymmetric sulenate alkylation reaction used in the synthesis of intermediate 96 is employed to access 100 with the desired *syn* relationship between the sulfinyl and propyl groups. The beauty of this design is that each diastereomer 89 or 90 can be accessed from the same starting materials simply by controlling the oxidation state of the sulfur atom prior to the asymmetric *aza*-Michael addition step, which is really only an issue of the timing of the conversion of sulfoxide to sulfone! Further, simply selecting the appropriate isomer of norvaline (D or L are both commercially available) permits entry to the desired enantiomer of the venom alkaloid.
Scheme 3.41. Retrosynthesis of Alkaloids 89 and 90

The synthesis of 89 was attempted initially and commenced with sulenate alkylation chemistry using iodide 98, which was synthesized from D-norvaline in two steps (Scheme 3.42).

Scheme 3.42. Synthesis of Amino Iodide 98

Sulenate precursor 97 was synthesized from the corresponding epoxide in two steps using established procedures in our lab (Scheme 3.43).
Scheme 3.43. Synthesis of Thiirane S-Oxide 97

Thiirane-S-oxide 97 was treated with LiHMDS at -78 °C to generate the corresponding trans-sulfenate which was alkylated with iodide 98 after stirring for several hours at rt (Scheme 3.44). Like analogous sulfenate alkylations, the use of a solvent mixture dominated by diethyl ether rather than THF provided 101 with high diastereoselectivity. The major isomer of 101 could be isolated from the minor by way of flash chromatography or a single recrystallization. At this stage it was decided that the protecting group should be removed before cyclization attempts based on the lack of reactivity with other Boc-protected β-amino sulfoxides. The major isomer of 101 was deprotected as the free amine 100 upon treatment with TFA/DCM. Refluxing of amine 100 in methanol with excess NEt₃ gave adduct 99 in excellent yield. Gratifyingly, heterocycle 99 was isolated as a single diastereomer based on inspection of the ¹H NMR of the crude reaction mixture. A selective gradient NOE experiment identified 99 as the predicted 3,5-trans diastereomer. To avoid problems during the subsequent sulfur oxidation or RBR steps the free amine was blocked. The benzyloxy carbamate (Cbz) was chosen because removal could occur with concomitant olefin hydrogenation of 104 upon treatment with H₂/Pd/C. Exposure of 99 to CbzCl under standard conditions provided 102 in good overall yield. The generation of sulfone 103 was achieved by way of oxidation with MCPBA.
Next, in-situ RBR conditions were used with to give pyrroline 104 with a typical yield for the formation of pyrrolines via RBR chemistry.\textsuperscript{66}

![Scheme 3.44. Synthesis of Pyrroline 104](image)

To form 89 from 104 a Pd/C/H\₂ catalyst system was chosen so that hydrogenation of the double bond with simultaneous protecting group cleavage could occur in one pot (Scheme 3.45). However, upon treatment of 104 with Pd/C/H\₂ an erosion of the diastereomeric ratio was observed in the \(^1\text{H}\) NMR spectrum of the crude reaction mixture. Two distinct sets of methine peaks could be observed, the major of which being at higher ppm than the minor. Typically, trans 2,5-substituted pyrrolidines
have methine peaks shifted further downfield than their cis analogs. The erosion of dr was presumably due to a Pd-mediated isomerization of the double bond from the 3,5-position to the 2,3-position or 1,2-position followed by subsequent hydrogenation.

**Scheme 3.45. Hydrogenolysis/Hydrogenation Attempt of Pyrroline 104**

The Pd/C/H₂ catalyst system was abandoned in favor of a Pt/C/H₂ catalyst system that would reduce the double bond without Cbz hydrogenolysis. Treatment of 104 with the platinum based catalyst system gave pyrrolidine 105 in excellent yield with much less erosion of the diastereomeric ratio (Scheme 3.46). Unfortunately, separation of the two diastereomers of 105 could not be achieved by chromatography so they were carried on to the next step as a 93:7 mixture. Treatment of 105 with Pd/C/H₂ provided the free amine, which was treated with TFA to form the TFA salt 106 in 84% yield over two steps. The dr is conserved at 93:7 following the hydrogenolysis of the Cbz group, therefore hydrogenation of the olefin bond is where the erosion of the dr occurs. Treatment of 106 with NaOH provided the free amine 89 with an improved dr of 95:5. The optical rotation value obtained of the 95:5 dr of 89 closely matched the negative value of a diastereomerically pure and relatively optically pure sample of the enantiomer of 89 (ee = 94%). Overall, the synthesis of 89 proceeded relatively well, albeit with some erosion of stereochemical information.
The path to venom alkaloid 90 begins with the oxidation of 101 to sulfone 107 which proceeded in excellent yield (Scheme 3.47). Removal of the Boc group with TFA to give the free amine 96 proceeded smoothly. A delay in lab activity prevented immediate base induced cyclization attempts on 96; therefore it was left to sit neat at rt. Following one month at rt, $^1$H NMR analysis revealed that 96 had transformed to heterocycle 95 to the anticipated cis diastereomer with complete stereoselectivity. To achieve faster reaction times base-induced cyclization attempts of 96 were pursued. Using NEt$_3$ in methanol at 40 °C, 95 could be yielded from 96 in quantitative yield as a ~11:1 diastereomeric mixture. An attempt at 0 °C to rt failed to improve diastereoselectivity, so 40 °C was used as the optimal temperature. The major diastereomer 95 (cis-3,5-substituted) could be isolated via flash chromatography and used in the next step. An attempt at cyclizing the Boc-protected sulfone 107 to the corresponding heterocycle 108 by heating with excess NEt$_3$ for two days failed. A RBR was attempted on sulfone 95 but heating under
standard RBR conditions did not convert any starting material to the desired pyrroline. Therefore, carbamate protection of 95 was pursued.

![Scheme 3.47. Synthesis of Sulfone 95](image)

Initial protection of cis-95 with the conditions used for the protection of trans sulfoxide 99 provided sulfone 109 in an acceptable yield of 53% (Table 3.4, entry 1). Since this yield was ~20% lower than that for the protection of sulfoxide 99, other trials were attempted for the protection of 95. Reducing the equivalents of base and CbzCl while heating failed to provide any desired product as indicated by TLC (Table 3.4, entry 2). Changing the co-solvent from DCM to THF gave a similar yield to that of entry 1 (Table 3.4, entry 3). Using NEt₃ as the base in a mono-phasic
solvent system with heating failed to provide any of 109 after two days of stirring (Table 3.4, entry 4). With no improvement in yield for other attempts the entry 1 conditions were used and sulfone 109 was carried on to the next step.

Table 3.4. Cbz Protection Attempts of 95

<table>
<thead>
<tr>
<th>entry</th>
<th>base (eq.)</th>
<th>CbzCl (eq.)</th>
<th>solvent</th>
<th>time (h)</th>
<th>T</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na₂CO₃ (15.0)</td>
<td>5.0</td>
<td>DCM/H₂O</td>
<td>48</td>
<td>rt</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>Na₂CO₃ (2.8)</td>
<td>1.55</td>
<td>DCM/H₂O</td>
<td>15</td>
<td>reflux</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Na₂CO₃ (3.3)</td>
<td>14.0</td>
<td>THF/H₂O</td>
<td>48</td>
<td>rt</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>NEt₃ (5.0)</td>
<td>1.2</td>
<td>DCM</td>
<td>48</td>
<td>reflux</td>
<td>0</td>
</tr>
</tbody>
</table>

Sulfone 109 was treated with typical in-situ RBR conditions, which resulted in the smooth conversion to pyrroline 110 without heating (Scheme 3.48). The RBR of 109 proceeded under milder conditions than the trans analogue 103, presumably due to the reduced steric hindrance in forming the cis pyrroline.
The cis pyrroline 110 was treated with the Pd/C/H₂ catalyst system in hopes that one-pot hydrogenation/hydrogenolysis could be achieved (Scheme 3.49). The pyrrolidines were isolated as their TFA salts to avoid mass loss due to high volatility of the free amines. As in the trans pyrrolidine example (Scheme 3.45) a mixture of cis and trans pyrrolidines was obtained likely due to a competitive isomerization reaction to the more thermodynamically stable olefin followed by hydrogenation of the double bond (Scheme 3.49).

At this stage the Pd/C/H₂ catalyst system was abandoned in favour of a system involving Pt metal (Scheme 3.50). Gratifyingly, treatment of 110 with Pt/C/H₂ gave the corresponding Cbz-protected cis-pyrrolidine 111 in excellent yield without any erosion of dr. The hydrogenation of olefins is much faster with Pt than with Pd; therefore for 110 Pt allows hydrogenation to occur fast before any isomerization.
can occur \(k_{\text{hydrogenation}} \gg k_{\text{isomerization}}\).\textsuperscript{68} Subsequent hydrogenolysis of \textbf{110} with Pd/C/H\textsubscript{2} followed by treatment with TFA provided the cis alkaloid as its TFA salt \textbf{112} with full conservation of dr. The trans pyrroline \textbf{104} was more prone to erosion of dr likely due to the instability of the system possessing an alkyl substituent an axial position.

![Scheme 3.50. Revised Hydrogenation/Hydrogenolysis Sequence for the Synthesis of 112](image)

**Scheme 3.50. Revised Hydrogenation/Hydrogenolysis Sequence for the Synthesis of 112**

### 3.2.3 Discussion of Cyclization Stereochemistry

Another experiment was done using the minor diastereomer \textbf{113}, which could be isolated via flash chromatography from \textbf{101} (Scheme 3.51). Sulfoxide \textbf{113} was deprotected to free amine \textbf{114} using TFA/DCM. The cyclization of \textbf{114} proved to be slow relative to the cyclization of the diastereomer \textbf{100}. Using a 10-fold excess of base while refluxing for over 40 h provided 80% consumption of \textbf{114} with clean conversion to heterocycle \textbf{115}. Inspection of the $^1$H NMR spectrum of the crude reaction mixture revealed the sole presence of the cis substituted stereoisomer, the complementary product to the cyclization of \textbf{100} (Scheme 3.44 and Scheme 3.51).
Thus, varying the stereochemical configuration at the sulfoxide or the oxidation state at the sulfur atom can control the stereochemical outcome of the reaction.

Scheme 3.51. Cyclization of Minor β-Amino Sulfoxide Diastereomer 114

To summarize, cyclization of β-amino sulfoxides with the S-O bond and C-R’ bond in an anti arrangement provide cis 3,5-substituted heterocycles. In contrast, cyclization of β-amino sulfoxides possessing the S-O and C-R’ bond in a syn relationship give the trans 3,5-substituted heterocycles (as drawn in Scheme 3.52).

Scheme 3.52. Cyclization Chemistry Summary

This remarkable ability for stereocontrol of the aza-Michael reaction can be explained by differences in H-bonding propensities between sulfoxides and sulfones. It is well established that the S-O bond in sulfoxides has more semi-polar
character than the S-O bonds in sulfones. As a result, sulfoxides are one of the strongest H-bond accepting functional groups while sulfones are relatively weak H-bond acceptors. Quantitatively, sulfoxides have a $\beta_{2}^{\mathrm{H}}$ value of 8.9 while sulfones have a $\beta_{2}^{\mathrm{H}}$ value of 6.3, indicating that sulfoxides have are significantly stronger H-bond acceptors than sulfones.\(^{69,70}\) There are examples of intramolecular hydrogen bonding between sulfoxides and hydroxyl functional groups causing changes in molecular conformations. Through $^1$H NMR experiments Chasar showed that a hydroxyl containing thioxanthene 6-oxide exists in CDCl\(_3\) as conformation 116 caused by an intramolecular hydrogen bond which is stable upon heating up to 170 °C (Scheme 3.53).\(^{71}\) With DMSO as the solvent this intramolecular hydrogen bond is broken in favor of an intermolecular hydrogen bond with DMSO and the molecule exists as conformer 117.

\[ \text{Scheme 3.53. Inter- and Intramolecular H-Bonding in a Thioxanthene 6-Oxide} \]

Kinsbury et al. studied the favored conformations of $\gamma$-hydroxy sulfone 118 and the corresponding $\gamma$-hydroxy sulfoxide 119 using intricate analysis of $^1$H NMR and IR spectra (Scheme 3.54).\(^{72,73}\) Sulfoxide 119 existed solely as cyclic conformer 119b containing an intramolecular hydrogen bond. In contrast, the sulfone analog 118 exists exclusively as the acyclic conformer 118a, which does not possess an
intramolecular hydrogen bond.\textsuperscript{73} This example demonstrates the stark contrasts in hydrogen bond strength between sulfoxides and sulfones.

![Scheme 3.54. Conformations of a γ-Hydroxy Sulfoxide and Sulfone](image)

It is suggested here that the intramolecular cyclization reactions of these β-amino sulfones proceed by way of a six-membered transition state in which there exists no significant hydrogen bonding between the sulfone and amine moieties (Scheme 3.55). Transition state \textbf{120} possesses the R group in an axial position, where it participates in a developing 1,3-diaxial interaction with the vinylic hydrogen. In contrast, transition state \textbf{121} contains both R and R' in pseudo equatorial positions where these alkyl substituents are not involved in developing 1,3-diaxial interactions.
Scheme 3.55. Proposed Cyclization Mode for β-Amino Sulfones

If chair transition states are employed for the cyclizations of β-amino sulfoxides with syn stereochemistry between the S-O and C-R such as 122, then the cis 3,5-substituted heterocycle would be formed and not the trans-3,5-substituted heterocycles that are observed (Scheme 3.56). However, if a hydrogen bonded pseudo twist-boat intermediate 124 is formed prior to cyclization, the trans-3,5-substituted heterocycle would be obtained. Twist-boat 124 features a stabilizing hydrogen bond interaction between the sulfinyl oxygen and amine functionalities analogous to the hydrogen bond interaction noted in Kingsbury’s γ-hydroxy sulfoxide 119b.73 The stabilizing hydrogen bonding interaction in 124 replaces the unfavorable 1,4-flagpole interaction present in the twist-boat conformation of cyclohexane. Also, R’ and R substituents are quite remote from one another, avoiding any steric encumbrance. A similar hydrogen bonded intermediate 125 can also be envisioned for the cyclization of β-amino sulfoxides possessing anti stereochemistry between the S-O and C-R such as 123, which leads to the experimentally observed cis-3,5-substituted heterocycle. In 125, the R and R’ substituents are cis to one another and a steric interaction may develop as transformation to the product occurs, which may account for the slower relative
reaction rate seen in the cyclization of amine 114 (Scheme 3.44 & Scheme 3.51). The possibility of anti-β-amino sulfoxides 123 cyclizing by way of a chair conformation similar to the sulfone analogs in Scheme 55 cannot be eliminated. Through this pathway one would anticipate anti-β-amino sulfoxides 123 to react slower than the corresponding β-amino sulfones as observed. Further, the attenuated reaction rate displayed by anti-β-amino sulfoxide 114 compared to syn-β-amino sulfoxides 80 and 100 may underscore the importance of the intramolecular H-bonding in 124 as a rate-accelerating feature.

Scheme 3.56. Proposed Cyclization Modes for β-Amino Sulfoxides

3.3 Conclusion

In conclusion, a new aza-Michael cyclization reaction has been explored and developed. Stereocontrol can be achieved simply by changing the configuration or oxidation state at sulfur. In combination with the RBR the cyclization chemistry has proven useful for the diastereoselective synthesis of two ant venom alkaloids.
The syn arrangement of the S-O bond and β-substituent in the major isomer of the β-amino sulfoxide products 79 obtained by the sulenate alkylation chemistry was crucial to the development of the chemistry achieved thereafter. The subsequent cyclization of the syn-β-amino sulfoxides 122 led to trans substituted heterocycles, while the cyclization of the minor anti-diastereomer 123 gave the complementary cis-heterocycle. Further, by oxidation of the sulfur atom of the syn-β-amino sulfoxides prior to cyclization, the cis-heterocycles can be accessed. Had the anti-β-amino sulfoxides been obtained from sulenate alkylation chemistry, then such a relative stereochemical differentiation of the heterocycles based on sulfoxidation would not have been possible. Further, this led to the development of new and more economical conditions for the RBR, which gave way to the synthesis of alkaloids 89 and 90. Again, at the core of all of this work is the relative stereochemistry of the β-amino sulfoxides obtained from the sulenate alkylation chemistry.

3.4 Experimental

3.4.1 Synthesis of Sulfones 83

**General Procedure for the Oxidation of Sulfoxides to Sulfones 83**

The β-amino sulfoxide 79 (1.0 equiv.) was dissolved in DCM (20 mL/mmol) and stirred at -78 °C. MCPBA (calibrated to 77 or 83%, 1.2–1.5 equiv) was added, and the reaction was slowly warmed to rt stirring for 4-8 h. The crude reaction mixture was washed with saturated Na₂S₂O₃ (aq.), NaHCO₃ (aq.), H₂O and brine. The organic layer was dried over MgSO₄ and filtered, and the solvent was removed in vacuo. The
crude product 83 was purified by flash chromatography using EtOAc/hexanes as the eluent.

**Synthesis of Sulfone 83a**

A mixture of β-amino sulfoxide 79a (0.487 g, 1.51 mmol) in DCM (30 mL) and MCPBA (ca. 77%, 0.507 g, ca. 2.26 mmol) in DCM (25 mL) afforded β-amino sulfone 83a as a white solid (76%, 0.388 g) following flash chromatography (50% EtOAc/hexanes). Mp 190-191 °C; 1H NMR (600 MHz, CDCl3) δ 7.33-7.30 (m, 2H), 7.26-7.19 (m, 3H), 6.92 (dq, J = 14.9, 7.0 Hz, 1H), 6.32 (d, J = 14.9 Hz, 1H), 4.92 (br s, 1H), 4.18 (m, 1H), 3.27 (m, 1H), 3.12 (dd, J = 14.5, 4.6 Hz, 1H), 3.06 (m, 1H), 3.00 (dd, J = 13.6, 7.0 Hz, 1H), 1.96 (dd, J = 6.9, 1.1 Hz, 3H), 1.42 (s, 9H); 13C NMR δ 155.0, 145.3, 136.8, 130.0, 129.5, 128.8, 126.7, 79.9, 56.8, 48.5, 40.0, 28.4, 17.5; IR (neat) cm⁻¹ 3358, 3045, 3031, 2979, 2922, 2852, 1689, 1530, 1443, 1277, 1171, 1127, 1117, 1048, 954; [α]D25 +0.2 (c = 0.4, CHCl3); HRMS (TOF, ESI) calcd for C17H26NO4S [M+H]+ 340.1577; found: 340.1569.

**Synthesis of Sulfone 83d**

A mixture of β-amino sulfoxide 79d (1.02 g, 2.46 mmol) in DCM (40 mL) and MCPBA (ca. 77%, 0.720 g, ca. 3.22 mmol) in DCM (25 mL) afforded β-amino sulfone 83d as a white solid (61%, 0.645 g) following flash chromatography (50% EtOAc/hexanes). Mp: 123-124 °C; 1H NMR (600 MHz, CDCl3) δ 7.33-7.24 (m, 5H), 7.21-7.19 (m, 3H), 7.15 (d, J = 7.2 Hz, 2H), 6.93 (dt, J = 15.1, 6.8 Hz, 1H), 6.27 (d, J = 15.1 Hz, 1H), 4.84 (br s, 1H), 4.14 (m, 1H), 3.21 (m, 1H), 3.07 (dd, J = 14.6, 4.7 Hz, 1H), 3.04 (m, 1H), 2.97 (dd, J = 13.4,
6.9 Hz, 1H), 2.80 (t, J = 7.6 Hz, 2H), 2.59 (m, 2H), 1.42 (s, 9H); $^{13}$C NMR (150.6 MHz, CDCl$_3$) δ 155.0, 148.5, 140.0, 136.8, 129.5, 129.3, 128.7, 128.6, 128.4, 127.0, 126.5, 79.9, 56.9, 48.4, 40.0, 33.8, 33.3, 28.4; IR (neat) cm$^{-1}$ 3086, 3059, 3028, 3010, 2979, 2967, 2928, 2859, 1691, 1527, 1497, 1443, 1367, 1319, 1282, 1250, 1218, 1171, 1126, 1046, 1027; $\left[\alpha\right]^{25}_D$ -4.8 (c = 1.3, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_{24}$H$_{31}$NO$_4$S [M+H]$^+$ 430.2047; found: 430.2030.

### Synthesis of Sulfone 83e

A mixture of β-amino sulfoxide 79e (0.603 g, 1.72 mmol) in DCM (30 mL) and MCPBA (ca ~77%, 0.503 g, ca ~ 2.92 mmol) in DCM (25 mL) afforded β-amino sulfone 83e as a white solid (77%, 0.485 g) following flash chromatography (50% EtOAc/hexanes). Mp: 83-84 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39-7.29 (m, 5H), 6.76 (d, J = 15.3 Hz, 1H), 5.69 (br s, 1H), 5.66 (d, J = 15.3 Hz, 1H), 5.21 (br m, 1H), 3.56 (dd, J = 14.2, 6.6 Hz, 1H), 3.44 (dd, J = 14.5, 4.0 Hz, 1H), 1.42 (s, 9H), 0.96 (s, 9H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 158.9, 154.8, 139.6, 129.0, 128.2, 126.4, 124.7, 80.2, 60.5, 50.5, 34.1, 28.3, 28.2; IR (neat) cm$^{-1}$ 3361, 3063, 3031, 2965, 2933, 2907, 2870, 1702, 1626, 1512, 1366, 1293, 1249, 1169, 1121, 1045, 1019, 757, 732, 699; $\left[\alpha\right]^{25}_D$ 4.8 (c = 1.1, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_{19}$H$_{29}$NO$_4$S [M+H]$^+$ 368.189; found: 368.1880.

### Synthesis of Sulfone 83f

A mixture of β-amino sulfoxide 79f (0.460 g, 1.52 mmol) in DCM (25 mL) and MCPBA (ca ~77%, 0.387 g, ca ~ 1.72 mmol) in DCM...
(20 mL) afforded β-amino sulfone 83f as a white solid (82%, 0.393 g) following flash chromatography (30% EtOAc/hexanes). Mp: 75-76 °C; ¹H NMR (600 MHz, CDCl₃) δ 6.90 (d, J = 15.3 Hz, 1H), 6.25 (d, J = 15.3 Hz, 1H), 4.90 (br s, 1H), 3.91 (m, 1H), 3.20 (ABX, J_AB = 14.4 Hz, J_AX = 6.8 Hz, J_BX = 4.8 Hz, 2H), 1.84-1.60 (m, 2H), 1.45 (s, 9H), 1.12 (s, 9H), 0.96 (t, J = 7.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 158.5, 155.1, 125.1, 79.5, 58.2, 48.5, 34.1, 28.3 (tBu's overlapping), 27.6, 10.3; IR (neat) cm⁻¹ 3361, 3053, 2966, 2934, 2874, 1709, 1518, 1460, 1391, 1365, 1292, 1246, 1171, 1127, 979, 772; [α]D²⁵ + 22.7 (c = 0.7, CHCl₃); Anal. calcd for C₁₅H₂₉NO₄S: C, 56.40; H, 9.15; Found: C, 56.40; H, 8.97.

Synthesis of Sulfone 83g

A mixture of β-amino sulfoxide 79g (0.740 g, 2.02 mmol) in DCM (30 mL) and MCPBA (ca ~77%, 0.524 g, ca ~ 2.34 mmol) in DCM (20 mL) afforded β-amino sulfone 83g as a white solid (90%, 0.697 g) following flash chromatography (50% EtOAc/hexanes). Mp: 137-138 °C; ¹H NMR (600 MHz, CDCl₃) δ 7.32-7.30 (m, 2H), 7.26-7.24 (m, 1H), 7.21 (d, J = 7.2 Hz, 2H), 6.89 (d, J = 15.3 Hz, 1H), 6.18 (d, J = 15.3 Hz, 1H), 4.94 (br s, 1H), 4.19 (app sex, J = 7.2 Hz, 1H), 3.29-3.25 (m, 1H), 3.13 (dd, J = 14.4, 4.2 Hz, 1H), 3.08 (m, 1H), 3.00 (dd, J = 13.5, 7.2 Hz, 1H), 1.42 (s, 9H), 1.11 (s, 9H); ¹³C NMR (150.6 MHz, CDCl₃) δ 159.0, 154.9, 136.9, 129.4, 128.7, 126.9, 124.8, 79.9, 56.9, 48.7, 40.0, 34.3, 28.4(tBu CH₃s overlapping); IR (neat) cm⁻¹: 3385, 3057, 3029, 2974, 2933, 2872, 1698, 1514, 1440, 1391, 1365, 1321, 1284, 1250, 1172, 1127, 1026, 873, 825, 774; [α]D²⁵ : -4.53 (c = 1.7, CHCl₃); Anal. calcd for C₂₀H₃₁NO₄S: C, 62.96 ; H, 8.19 ; Found: C, 62.77 ; H, 8.02.

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Synthesis of Sulfone 83h

A mixture of β-amino sulfoxide 79h (0.329 g, 0.906 mmol) in DCM (30 mL) and MCPBA (ca ~83%, 0.207 g, ca ~ 1.00 mmol) in DCM (25 mL) afforded β-amino sulfone 83h as a white solid (70%, 0.240 g) following flash chromatography (30% EtOAc/hexanes). Mp 115-116 °C; 1H NMR (400MHz, CDCl3) δ 7.36-7.21 (m, 5H), 6.93 (m, 1H), 4.97 (br s, 1H), 4.10 (m, 1H), 3.19 (dd, J = 14.4, 7.2 Hz, 1H), 3.09-3.05 (m, 2H), 2.98 (dd, J = 13.6, 7.2 Hz, 1H), 2.30-2.14 (m, 4H), 1.76-1.61 (m, 4H), 1.42 (s, 9H); 13C NMR (100 MHz, CDCl3) δ 155.0, 140.9, 138.2, 137.0, 129.5, 128.7, 126.9, 79.8, 53.6, 48.7, 40.1, 28.4, 25.6, 23.2, 21.8, 20.7; IR (neat) cm⁻¹ 3367, 3084, 3061, 3028, 2975, 2934, 2863, 1699, 1646, 1517, 1453, 1306, 1289, 1250, 1167, 1131, 1079, 1047, 1022; [α]D 25° -9.8 (c = 0.9, CHCl3); HRMS (TOF, ESI) calcd for C20H29NO4S [M+H]+ 380.1890; found: 380.1876.

3.4.2 Deprotection Protocols of β-Amino Sulfones/Sulfoxides

General Deprotection of Boc-Protected β-Amino Sulfone/Sulfoxide (79/83) to Amine (80/84)

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 stirred for 1 hr at rt to reach completion. Following completion solvent was removed in vacuo to give an oily residue. The residue was dissolved in DCM (10 mL/mmol) and washed with a 2 M NaOH solution until a basic pH (pH ~ 8) was achieved. The aqueous layer was extracted with DCM. The organic layers were
combined, washed sequentially with water, brine, then dried over MgSO4, filtered and concentrated under reduced pressure to yield the free amine.

**Synthesis of Amine 80a**

A mixture of a 1:1 solution of TFA:DCM (22 mL) and protected β-amino sulfoxide 79a (0.725 g, 2.24 mmol) in DCM (3 mL) provided the deprotected β-amino sulfoxide 80a as a clear colorless solid (80%, 0.399 g); Mp 41-42 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.33-7.31 (m, 2H), 7.26-7.24 (m, 1H), 7.21-7.19 (m, 2H), 6.49 (dq, \(J = 15.0, 6.8\) Hz, 1H), 6.19 (dq, \(J = 15.0, 1.5\) Hz, 1H), 3.70 (m, 1H), 2.89 (dd, \(J = 13.5, 5.9\) Hz, 1H), 2.81-2.76 (m, 2H), 2.67 (dd, \(J = 13.2, 10.0\) Hz, 1H), 2.03 (br s, 2H), 1.93 (dd, \(J = 6.8, 1.6\) Hz, 3H); \(^13\)C NMR (150.6 MHz, CDCl\(_3\)) \(\delta\) 137.5, 136.8, 133.2, 129.4, 128.8, 126.9, 60.4, 47.9, 44.0, 17.9; IR (neat) cm\(^{-1}\) 3364, 3286, 3038, 3060, 3004, 2914, 2852, 1633, 1601, 1494, 1453, 1440, 1396, 1353, 1091, 1030, 951, 880, 825, 800, 746, 701; \([\alpha]^{25}_{D}\) +24.0 (c = 0.8, CHCl\(_3\)); HRMS (TOF, ESI) calcd for C\(_{12}\)H\(_{17}\)NOS [M+H]\(^+\) 224.1104; found: 224.1109.

**Synthesis of Amine 80d**

A mixture of a 1:1 solution of TFA:DCM (30 mL) and protected β-amino sulfoxide 79d (0.895 g, 2.17 mmol) in DCM (3 mL) provided the deprotected β-amino sulfoxide 80d as a cloudy oil (84%, 0.572 g); Mp 65-67 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.34-7.16 (m, 10H), 6.50 (dt, \(J = 15.2, 6.9\) Hz, 1H), 6.14 (dt, \(J = 15.2, 1.4\) Hz, 1H), 3.62 (m, 1H), 2.85-2.76 (m, 3H), 2.73-2.65 (m, 2H), 2.60-2.52 (m, 3H), 1.60 (br s, 2H); \(^13\)C NMR (100 MHz, CDCl\(_3\))
δ 140.5, 139.5, 137.6, 129.3, 128.7, 128.5, 128.4, 126.8, 126.3, 61.3, 47.7, 44.4, 34.5, 33.7; IR (neat) cm⁻¹ 3407, 3373, 3283, 3083, 3061, 3024, 2936, 2917, 2886, 2852, 1602, 1495, 1452, 1387, 1036, 949, 888, 747, 697; [α]D²⁵ +10.2 (c = 5.1, CHCl₃); HRMS (TOF, ESI) calcd for C₁₉H₂₃NOS [M+H]⁺ 314.1573; found: 314.1561.

**Synthesis of Amine 80e**

A mixture of a 1:1 solution of TFA:DCM (20 mL) and protected β-amino sulfoxide 79e (0.544 g, 1.55 mmol) in DCM (3 mL) provided the deprotected β-amino sulfoxide 80e as a white solid (83%, 0.322 g); Mp 159-160 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.26 (m, 5H), 6.51 (d, J = 15.6 Hz, 1H), 6.11 (d, J = 15.6 Hz, 1H), 4.58 (dd, J = 9.6, 3.2 Hz, 1H), 2.94 (ABX, J₁₂ = 13.2 Hz, Jₓₐ = 9.6 Hz, Jₓₜ = 3.2 Hz, 2H), 2.15 (br s, 2H), 1.09 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 151.1, 143.7, 128.9, 128.0, 127.8, 126.3, 63.2, 50.5, 34.3, 28.9; IR (neat) cm⁻¹ 3353, 3252, 3164, 3028, 2963, 2934, 2898, 2868, 1493, 1464, 1369, 1269, 1135, 1042, 1032, 975, 940, 916, 794, 772, 710; [α]D²⁵ +21.3 (c = 0.6, CHCl₃); HRMS (TOF, ESI) calcd for C₁₄H₂₁NOS [M+H]⁺ 252.1417; found: 252.1409.

**Synthesis of Amine 80h**

A mixture of a 1:1 solution of TFA:DCM (20 mL) and protected β-amino sulfoxide 79h (0.456 g, 1.26 mmol) in DCM (3 mL) provided the deprotected β-amino sulfoxide 80h as a white solid (91%, 0.300 g); Mp 93-94 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.18 (m, 5H), 6.46 (m, 1H), 3.63 (m, 1H), 2.84 (dd, J
= 13.4, 5.7 Hz, 1H), 2.79 (dd, J = 13.2, 2.7 Hz, 1H), 2.68 (dd, J = 13.4, 8.1 Hz, 1H), 2.59 (dd, J = 13.0, 9.9 Hz, 1H), 2.23 (m, 2H), 2.21 (m, 2H) 1.75-1.62 (m, 4H), 1.55 (br s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 140.6, 137.9, 131.8, 129.3, 128.7, 126.8, 58.2, 47.8, 44.4, 25.5, 22.2, 21.9, 21.0; IR (neat) cm$^{-1}$ 3359, 3287, 3082, 3063, 3026, 2935, 2888, 2857, 2830, 1507, 1447, 1138, 1096, 1049, 1035, 1008, 834, 801; $^{[\alpha]}_{D}^25$ +87.7 (c = 0.8, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_{15}$H$_{21}$NOS [M+H]$^+$ 264.1417; found: 264.1423.

**Synthesis of Amine 84a**

A mixture of a 1:1 solution of TFA:DCM (14 mL) and protected β-amino sulfone 83a (0.333 g, 0.982 mmol) in DCM (3 mL) provided the deprotected β-amino sulfone 84a and its corresponding heterocycle 86a (~5:1) as a clear colorless oil (77%, 0.181 g); $^1$H NMR (600 MHz, CDCl$_3$) δ 7.35-7.24 (m, 3H), 7.19-7.18 (m, 2H), 6.90 (dq, J = 15.0, 6.9 Hz, 1H), 6.32 (dq, J = 15.0, 1.4 Hz, 1H), 3.68 (m, 1H), 3.08 (dd, J = 14.2, 2.5 Hz, 1H), 2.96 (dd, J = 14.2, 9.5 Hz, 1H), 2.76 (m, 2H), 1.95 (dd, J = 6.9, 1.7 Hz, 3H), 1.74 (br s, 2H); $^{13}$C NMR (150.6 MHz, CDCl$_3$) δ 144.7, 137.2, 130.24, 129.4, 128.8, 127.0, 60.9, 48.0, 42.1, 16.9. See below for full characterization data of cyclized heterocycle.

**Synthesis of Amine 84d**

A mixture of a 1:1 solution of TFA:DCM (20 mL) and protected β-amino sulfone 83d (0.636 g, 2.48 mmol) in DCM (3 mL) provided the deprotected β-amino sulfone 84d as a cloudy oil (74%, 0.359 g); $^1$H NMR (600 MHz, CDCl$_3$) δ 7.34-7.25 (m, 5H), 7.22-7.19 (m, 1H), 7.17-7.15 (m,
4H), 6.91 (dt, J = 15.2, 7.2 Hz, 1H), 6.26 (d, J = 15.2 Hz, 1H), 3.59 (m, 1H), 3.01 (dd, J = 14.2, 2.5 Hz, 1H), 2.88 (dd, J = 14.2, 9.5 Hz, 1H), 2.80 (m, 1H), 2.72 (m, 4H), 2.59 (m, 2H), 1.71 (br s, 2H); $^{13}$C NMR (150.6 MHz, CDCl$_3$) δ 147.9, 139.9, 137.2, 129.6, 129.4, 128.8, 128.7, 128.4, 127.0, 126.5, 61.0, 43.9, 33.8, 33.2; IR (neat) cm$^{-1}$ 3308, 3083, 3060, 3026, 3003, 2923, 2854, 1754, 1494, 1453, 1382, 1296, 1129, 879, 750, 700; $\left[\alpha\right]_{D}^{25}$ +6.7 (c = 0.9, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_{19}$H$_{23}$NO$_2$S [M+H]$^+$ 330.1522; found: 330.1507.

**Synthesis of Amine 84e**

A mixture of a 1:1 solution of TFA:DCM (15 mL) and protected β-amino sulfone 83e (0.404 g, 1.10 mmol) in DCM (3 mL) provided the deprotected β-amino sulfone 84e as a white solid (86%, 0.252 g); Mp: 75-76 °C; $^1$H NMR (600 MHz, CDCl$_3$) δ 7.39-7.27 (m, 5H), 6.90 (d, J = 15.4 Hz, 1H), 6.12 (d, J = 15.4 Hz, 1H), 4.64 (dd, J = 9.3, 3.2 Hz, 1H), 3.27 (AB of ABX, $J_{AB} = 14.1$ Hz, $J_{AX} = 9.3$ Hz, $J_{BX} = 3.2$ Hz, 2H), 1.92 (br s, 2H), 1.08 (s, 9H); $^{13}$C NMR (150.6 MHz, CDCl$_3$) δ 158.7, 143.1, 130.0, 128.1, 126.4, 125.0, 63.3, 51.2, 34.3, 28.4; IR (neat) cm$^{-1}$ 3361, 3274, 3194, 3045, 3026, 2961, 2933, 2907, 2869, 1475, 1314, 1306, 1270, 1130, 1098, 982, 899, 830; $\left[\alpha\right]_{D}^{25}$ -14.1 (c = 1.3, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_{14}$H$_{21}$NO$_2$S [M+H]$^+$ 268.1366; found: 268.1360.

**Synthesis of Amine 84g**

A mixture of a 1:1 solution of TFA:DCM (25 mL) and protected β-amino sulfone 83g (0.548 g, 1.44 mmol) in DCM (3 mL) provided
the deprotected β-amino sulfone 84g as a cloudy oil (77%, 0.312 g); 1H NMR (600 MHz, CDCl3) δ 7.34-7.31 (m, 2H), 7.27-7.24 (m, 1H), 7.19-7.17 (m, 2H), 6.88 (d, J = 15.6 Hz, 1H), 6.15 (d, J = 15.6 Hz, 1H), 3.66 (m, 1H), 3.09 (dd, J = 9.0, 2.4 Hz, 1H), 2.95 (dd, J = 13.8, 9 Hz, 1H), 2.75 (m, 2H), 1.64 (br s, 2H), 1.09 (s, 9H); 13C NMR (150.6 MHz, CDCl3) δ 158.7, 137.3, 129.3, 128.8, 127.0, 124.9, 61.0, 48.2, 43.9, 34.3, 28.4; IR (neat) cm⁻¹ 3377, 3312, 3060, 3027, 2962, 2932, 2869, 1624, 1603, 1495, 1476, 1366, 1293, 1240, 1127, 1030, 877, 830, 764, 702; [α]D25 +7.2 (c = 0.8, CHCl3); HRMS (TOF, ESI) calcd for C15H23NO2S [M+H]+ 282.1522; found: 282.1511.

Synthesis of Amine 84h

A mixture of a 1:1 solution of TFA:DCM (15 mL) and protected β-amino sulfone 83h (0.203 g, 0.535 mmol) in DCM (3 mL) provided the deprotected β-amino sulfone 84h as a clear colorless oil (90%, 0.134 g); 1H NMR (400MHz, CDCl3) δ 7.34-7.18 (m, 5H), 6.91 (m, 1H), 3.57 (m, 1H), 3.05 (dd, J = 14.1, 2.2 Hz, 1H), 2.86 (dd, J = 14.1, 9.3 Hz, 1H), 2.74 (AB of ABX, JAB = 13.4 Hz, JAX = 7.2 Hz, JBX = 6.9 Hz, 2H), 2.30-2.25 (m, 3H), 1.96-1.89 (m, 1H), 1.75 (br s, 2H), 1.72-1.54 (m, 4H); 13C NMR (100 MHz, CDCl3) δ 140.4, 138.2, 137.4, 129.3, 128.8, 126.9, 57.5, 48.3, 43.7, 25.5, 23.2, 21.8, 20.8; IR (neat) cm⁻¹ 3376, 3310, 3060, 3026, 2933, 2860, 1643, 1495, 1452, 1304, 1289, 1129, 1049, 1026, 941, 856, 749, 702; [α]D25 +7.2 (c = 0.8, CHCl3); HRMS (TOF, ESI) calcd for C15H21NO2S [M+H]+ 280.1366; found: 280.1357.
General Deprotection of Boc-Protected β-Amino Sulfone/Sulfoxide (79/83) to TFA Salt (81/85)

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 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 trifluoroacetic acid. Excess solvent was removed in vacuo to yield the TFA ammonium salt. The product was purified by flash chromatography if necessary.

Synthesis of TFA Salt 81a

A mixture of a 1:1 solution of TFA:DCM (15 mL) and protected β-amino sulfoxide 79a (0.673 g, 2.08 mmol) in DCM (3 mL) provided the deprotected β-amino sulfoxide 81a as a clear colorless oil (95%, 0.668 g) following flash chromatography (10% MeOH/DCM); ^1^H NMR (400 MHz, CDCl₃) δ 8.78 (br s, 3H), 7.34-7.16 (m, 5H), 6.51 (dq, J = 14.8, 6.8 Hz, 1H), 5.87 (dd, J = 14.8, 1.6 Hz, 1H), 4.06 (m, 1H), 3.41 (dd, J = 14.8, 9.6 Hz, 1H), 3.34 (dd, J = 13.6, 4.8 Hz, 1H), 2.98 (dd, J = 13.6, 10.8 Hz, 1H), 2.53 (dd, J = 14.8, 1.6 Hz, 1H), 1.94 (dd, J = 6.8, 1.6 Hz, 3H); 13C NMR (100.6 MHz, CDCl₃) δ 140.5, 134.2, 129.2, 129.1, 128.6, 127.9, 49.4, 48.3, 38.6, 17.8; IR (neat) cm⁻¹ 3420, 3032, 2977, 2923, 1680, 1497, 1436, 1203, 1135, 1009, 952, 837, 801, 747; [α]_D^{25} -
56.8 (c = 2.0, CHCl$_3$). Anal. calcd for C$_{14}$H$_{18}$F$_3$NO$_3$S: C, 49.84; H, 5.38. Found: C, 49.83; H, 5.31.

**Synthesis of TFA Salt *ent*-81a**

A mixture of a 1:1 solution of TFA:DCM (15 mL) and protected β-amino sulfoxide *ent*-79a (0.502 g, 1.55 mmol) in DCM (3 mL) provided the deprotected β-amino sulfoxide *ent*-81a as a clear colorless oil (94%, 0.493 g) following flash chromatography (10% MeOH/DCM); Spectral data identical as above for 81a; $[\alpha]_D^{25} +55.8$ (c = 2.0, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_{12}$H$_{17}$NOS [M+H]$^+$ 224.1109; found: 224.1104.

**Synthesis of TFA Salt 81b**

A mixture of a 1:1 solution of TFA:DCM (15 mL) and protected β-amino sulfoxide 79b (0.237 g, 0.959 mmol) in DCM (3 mL) provided the deprotected β-amino sulfoxide 81b as a clear colorless oil (52%, 0.137 g) following flash chromatography (10% MeOH/DCM); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.51 (br s, 3H), 6.58 (dq, $J$ = 15.0, 6.8 Hz, 1H), 6.24 (app dd, $J$ = 15.0, 1.6 Hz, 1H), 3.95 (m, 1H), 3.43 (dd, $J$ = 14.6, 9.2 Hz, 1H), 2.69 (dd, $J$ = 14.6, 2.5 Hz, 1H), 1.99 (dd, $J$ = 6.8, 1.5 Hz, 3H), 1.48 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.5, 130.0, 51.6, 44.3, 18.9, 17.9; IR (neat) cm$^{-1}$ 3428, 2980, 2923, 2853, 2739, 1677, 1429, 1202, 1132, 1026, 1016, 955; $[\alpha]_D^{25} +3.3$ (c = 0.3, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_6$H$_{13}$NOS [M+H]$^+$ 148.0791; found: 148.0797.
Synthesis of TFA Salt 81c

A mixture of a 1:1 solution of TFA:DCM (15 mL) and protected β-amino sulfoxide 79c (0.431 g, 1.33 mmol) in DCM (3 mL) provided the deprotected β-amino sulfoxide 81c as a clear colorless oil (98%, 0.337 g) following flash chromatography (10% MeOH/DCM); 1H NMR (400 MHz, CDCl3) δ 8.40 (br s, 3H), 6.57 (dq, J = 14.9, 6.6 Hz, 1H), 6.23 (d, J = 14.9 Hz, 1H), 3.60-3.59 (m, 1H), 3.46 (m, 1H), 2.67 (m, 1H), 2.15 (m, 1H), 1.98 (d, J = 6.0 Hz, 3H), 1.01 (m, 6H); 13C NMR (100 MHz, CDCl3) δ 139.5, 129.7, 52.6, 48.3, 30.9, 18.4, 17.8, 17.4; IR (neat) cm⁻¹: 3436, 2973, 1677, 1634, 1524, 1428, 1400, 1202, 1180, 1026, 956; [α]D25 +2.8 (c = 0.3, CHCl3); HRMS (TOF, ESI) calcd for C8H17NOS [M+H]+ 176.1104; found: 176.1110.

Synthesis of TFA Salt 85f

A mixture of a 1:1 solution of TFA:DCM (15 mL) and protected β-amino sulfone 83f (0.220 g, 0.689 mmol) in DCM (3 mL) provided the deprotected β-amino sulfone 85f as a white solid (98%, 0.224 g) following flash chromatography (10 % MeOH/DCM); Mp: 100-101 °C; 1H NMR (600 MHz, CDCl3) δ 7.97 (br s, 3H), 7.04 (d, J = 15.0 Hz, 1H), 6.31 (d, J = 15.0 Hz, 1H), 3.80 (m, 1H), 3.58 (m, 1H), 3.35 (m, 1H), 1.94 (m, 1H), 1.83 (m, 1H), 1.13 (s, 9H), 1.05 (t, J = 5.9 Hz, 3H); 13C NMR (150.6 MHz, CDCl3) δ 162.4, 123.2, 54.3, 49.1, 34.7, 28.0, 25.9, 9.3; IR (neat) cm⁻¹: 3188, 3052, 2968, 2910, 2874, 1674, 1622, 1530, 1464, 1295,
1202, 1181, 1133, 836, 799, 772, 721; \( [\alpha]_{D}^{25} \) -7.5 (c = 0.9, CHCl\textsubscript{3}); Anal. calcd for C\textsubscript{12}H\textsubscript{22}F\textsubscript{3}NO\textsubscript{4}S: C, 43.24; H, 6.65; Found: C, 43.34; H, 6.55.

3.4.3 Cyclization Reaction Experiments

**General Procedure for Cyclizations of TFA Salts (Cyclization Method A)**

The TFA salt (1.0 equiv.) was dissolved in MeOH (30 mL/mmol) and stirred at rt. Triethylamine (2.0-2.5 equiv.) was added to the reaction mixture via syringe which 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, H\textsubscript{2}O, and brine then dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo to give the cyclized product.

**General Procedure for Cyclizations of Free Amines (Cyclization Method B)**

The free amine (1.0 equiv.) was dissolved in MeOH (30 mL/mmol) and stirred at rt. Triethylamine (1.0-10.0 equiv.) was added to the reaction mixture via syringe which was stirred at the indicated temperature until completion (monitored by TLC). The solvent and excess triethylamine was removed in vacuo to give the cyclized product.

**Synthesis of Heterocycle 82a**

Using *Cyclization Method A*, a mixture of the TFA salt 81a (0.333 g, 0.99 mmol) and triethylamine (0.34 mL, 2.5 mmol) in methanol (15 mL) refluxed for 8 h provided heterocycle 82a as a single diastereomer (93%, 0.124...
g). Greyish solid. Mp: 59-60 ºC; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.35-7.32 (m, 2H), 7.27-7.25 (m, 1H), 7.21 (d, $J = 7.2$ Hz, 2H), 3.87 (m, 1H), 3.45 (m, 1H), 3.21 (dd, $J = 13.2$, 8.4 Hz, 1H), 3.06 (dd, $J = 13.8$, 6.6 Hz, 1H), 2.98 (dd, $J = 13.2$, 2.4 Hz, 1H), 2.89-2.85 (m, 1H), 2.82 (dd, $J = 12.8$ Hz, 2.6 Hz, 1H), 2.72 (dd, $J = 13.2$, 6.6 Hz, 1H), 1.78 (br s, 1H), 1.20 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.2, 129.2, 128.8, 126.7, 54.4, 51.6, 51.0, 41.3, 41.2, 21.0; IR (neat) cm$^{-1}$ 3447, 3284, 3060, 3025, 2965, 2915, 1601, 1494, 1453, 1376, 1249, 1200, 1050, 1028, 913, 743, 701; $\left[\alpha\right]_{D}^{25}$ +18.7 ($c = 0.95$, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_{12}$H$_{17}$NOS [M+H]$^+$ 224.1104; found: 224.1099.

**Synthesis of Heterocycle ent-82a**

Using Cyclization Method A, a mixture of the TFA salt ent-81a (0.201 g, 0.596 mmol) and triethylamine (0.17 mL, 1.2 mmol) in methanol (15 mL) refluxed for 8 h provided heterocycle ent-82a as a single diastereomer (93%, 0.124 g). Greyish solid. Mp 59-60 ºC; Spectral data as above for 82a; $\left[\alpha\right]_{D}^{25}$ +18.3 ($c = 0.2$, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_{12}$H$_{17}$NOS [M+H]$^+$ 224.1104; found: 224.1107.

**Synthesis of Heterocycle 82b**

Using Cyclization Method A, a mixture of the TFA salt 81b (0.103 g, 0.394 mmol) and triethylamine (0.110 mL, 0.788 mmol) in methanol (15 mL) refluxed for 8 h provided heterocycle 82b as a single diastereomer (91%, 0.053 g). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.79 (m, 1H), 3.35 (m, 1H), 3.17 (dt, $J = 12.3$, 7.7 Hz, 1H), 2.89-2.85 (m, 1H), 2.82 (dd, $J = 12.8$ Hz, 2.6 Hz, 1H), 2.72 (dd, $J = 13.2$, 6.6 Hz, 1H), 1.78 (br s, 1H), 1.20 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.2, 129.2, 128.8, 126.7, 54.4, 51.6, 51.0, 41.3, 41.2, 21.0; IR (neat) cm$^{-1}$ 3447, 3284, 3060, 3025, 2965, 2915, 1601, 1494, 1453, 1376, 1249, 1200, 1050, 1028, 913, 743, 701; $\left[\alpha\right]_{D}^{25}$ +18.7 ($c = 0.95$, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_{12}$H$_{17}$NOS [M+H]$^+$ 224.1104; found: 224.1107.
2.4 Hz, 1H), 3.07 (dq, J = 12.3, 2.1 Hz, 1H), 2.69 (dd, J = 12.3, 3.6 Hz, 1H), 2.46 (dd, J = 12.3, 9.1 Hz, 1H), 1.65 (br s, 1H), 1.34 (d, J = 6.6 Hz, 3H), 1.28 (d, J = 7.0 Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 56.3, 55.2, 44.6, 43.9, 22.3, 20.6; IR (neat) cm\(^{-1}\) 3398, 3279, 2972, 1650, 1134, 1005, 772; \(\left[\alpha\right]_D^{25}\) +0.3 (c = 0.6, CHCl\(_3\)); HRMS (TOF, ESI) calcd for C\(_6\)H\(_{13}\)NOS [M+H]\(^+\) 148.0791; found: 148.0797.

**Synthesis of Heterocycle 82c**

Using Cyclization Method A, a mixture of the TFA salt 81c (0.095 g, 0.33 mmol) and triethylamine (0.092 mL, 0.66 mmol) in methanol (15 mL) refluxed for 7 h provided heterocycle 82c as a single diastereomer (97%, 0.056 g). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.76 (m, 1H), 3.20-3.06 (m, 2H), 2.88-2.82 (m, 1H), 2.68 (dd, J = 12.3, 3.6 Hz, 1H), 2.55 (dd, J = 12.3, 9.6 Hz, 1H), 2.04 (app sex, J = 6.8 Hz, 1H), 1.54 (br s, 1H), 1.25 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 55.7, 53.6, 52.5, 44.8, 31.8, 20.5, 18.9, 18.8; IR (neat) cm\(^{-1}\) 3445, 3293, 2962, 2930, 2872, 1465, 1375, 1025, 772; \(\left[\alpha\right]_D^{25}\) -8.3 (c = 4.1, CHCl\(_3\)); HRMS (TOF, ESI) calcd for C\(_8\)H\(_{17}\)NOS [M+H]\(^+\) 176.1104; found: 176.1107.

**Synthesis of Heterocycle 86a**

Using Cyclization Method B, a \(\sim\) 5:1 (uncyclized/cyclized) mixture of amine (84a/86a) (0.175 g, 0.73 mmol) and triethylamine (0.102 mL, 0.73 mmol) in methanol (15 mL) at 0 °C slow warming to rt over 1 h gave the cyclized product 86a as a yellow solid (97%, 90 mg, \(dr = 91:9\) by \(^1\)H NMR analysis of the crude reaction mixture). Major isomer: \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.28-7.26
(m, 2H), 7.22-7.19 (m, 1H), 7.15-7.10 (m, 2H), 3.36 (m, 1H), 3.18 (m, 1H), 2.91-2.84 (m, 2H), 2.72-2.66 (m, 2H), 2.63 (dd, \( J = 13.4, 11.6 \) Hz, 1H), 2.60 (dd, \( J = 13.1, 11.4 \) Hz, 1H); 1.74 (br s, 1H), 1.08 (d, \( J = 6.6 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 136.2, 129.2, 129.0, 127.3, 58.3, 56.4, 55.4, 49.9, 42.1, 21.6; IR (neat) cm\(^{-1}\) 3320, 3083, 3061, 3027, 2971, 2925, 2852, 1495, 1455, 1298, 1257, 1124, 755, 701; [\( \alpha \)]\(_{D}^{25}\) +2.9 (c = 2.3, CHCl\(_3\), for 91:9 mixture); HRMS (TOF, ESI) calcd for \( C_{12}H_{17}NO_2S \) [M+H]\(^+\) 240.1053; found: 240.1044. Minor isomer, partial characterization: \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 3.68-3.60 (m, 2H), 3.03-2.98 (m, 4H), 1.18 (d, \( J = 6.6 \) Hz, 3H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) 137.0, 129.3, 128.9, 126.9, 57.8, 54.2, 52.8, 45.6, 38.6, 20.4.

**Synthesis of Heterocycle 86d**

Using *Cyclization Method B*, a mixture of the amine \( 84d \) (0.096 g, 0.29 mmol) and triethylamine (0.04 mL, 0.29 mmol) in methanol (15 mL) refluxed for \(~7 \) h to give the cyclized product \( 86d \) as a pale pink solid (94%, 90 mg, \( dr = 91:9 \) by \(^1\)H NMR analysis of the crude reaction mixture. Recrystallization from EtOAc/hexanes gave the major *cis*-isomer as a white solid. Major isomer: Mp 104-105 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.40-7.17 (m, 8H), 6.93-6.90 (m, 2H), 3.33 (m, 1H), 3.06-2.92 (m, 3H), 2.80 (dd, \( J = 13.4, 5.2 \) Hz, 1H), 2.72 (app t, \( J = 15.7 \) Hz, 1H), 2.70 (app t, \( J = 11.5 \) Hz, 2H), 2.54 (m, 2H), 1.74 (q, \( J = 6.8 \) Hz, 2H), 1.61 (br s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 140.2, 136.4, 129.3, 129.0, 128.7, 128.2, 127.4, 126.4, 57.2, 57.0, 55.3, 53.3, 42.0, 37.0, 31.6; IR (neat) cm\(^{-1}\) 3542, 3306, 3061, 3026, 2922, 2853, 1602, 1494, 1454, 1297, 1129, 1071; [\( \alpha \)]\(_{D}^{25}\) +12.7 (c = 2.8, CHCl\(_3\)); HRMS (TOF, ESI) calcd for \( C_{19}H_{23}NO_2S \) [M+H]\(^+\) 330.1522; found: 330.1534. Minor isomer,
Synthesis of Heterocycle 86e

Using Cyclization Method B, a mixture of the amine 84e (0.095 g, 0.36 mmol) and triethylamine (0.05 mL, 0.36 mmol) in methanol (15 mL) refluxed for 10 h. \textsuperscript{1}H NMR Analysis of the crude reaction mixture revealed a single diastereomer of cyclized product 86e and ~ 5% unreacted starting material. Flash chromatography with EtOAc/hexanes/TEA (30:65:5) afforded heterocycle 86e as a white solid (79%, 75 mg). Mp 125-127 °C; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.40-7.33 (m, 5H), 4.24 (dd, \( J = 11.2, 1.6 \) Hz, 1H), 3.09 (app br d, \( J = 12.8 \) Hz, 2H), 3.03-2.95 (m, 2H), 2.83 (app t, \( J = 12.0 \) Hz, 1H), 1.85 (br s, 1H), 0.99 (s, 9H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 140.8, 129.1, 128.6, 126.7, 63.3, 58.8, 58.4, 53.1, 33.8, 26.3; IR (neat) cm\textsuperscript{-1} 3316, 3062, 3031, 2959, 2903, 2871, 2838, 1704, 1494, 1299, 1130, 878, 769, 751, 699; \([\alpha]_D^{25}\) -51.0 (c = 4.1, CHCl\textsubscript{3}); HRMS (TOF, ESI) calcd for C\textsubscript{14}H\textsubscript{21}NO\textsubscript{2}S [M+H]\textsuperscript{+} 268.1366; found: 268.1360.

Synthesis of Heterocycle 86f

Using Cyclization Method A, a mixture of the TFA salt 85f (0.164 g, 0.49 mmol) and triethylamine (0.14 mL, 0.98 mmol) in methanol (15 mL) refluxed for 8 h provided heterocycle 86f as a pale yellow solid (70%, 75 mg, \( dr = 91:9 \) by \textsuperscript{1}H NMR analysis). Diastereomers were separated by flash chromatography (50% EtOAc/hexanes) as the eluent (68 mg of cis-isomer; 7 mg of trans-isomer). cis-
Isomer: Mp: 76-77 °C; $^1$H NMR (400 MHz, CD$_6$D$_6$), δ: 2.84-2.77 (m, 2H), 2.73 (dd, $J = 11.6$, 1.6 Hz, 1H), 2.61 (dt, $J = 13.2$, 2.4 Hz, 1H), 2.30 (dd, $J = 12.9$, 11.9 Hz, 1H), 2.07 (dd, $J = 12.8$, 11.6 Hz, 1H), 0.97 (m, 2H), 0.59-0.53 (m, 4H), 0.58 (s, 9H); $^{13}$C NMR (100 MHz, CD$_6$D$_6$), δ: 62.8, 56.6, 55.5, 53.4, 33.2, 28.6, 25.7, 9.7; IR (neat) cm$^{-1}$ 3313, 2961, 2875, 1465, 1368, 1294, 1242, 1151, 1130, 874, 772; $[\alpha]_D^{25} +7.64$ (c = 1.4, CHCl$_3$); Anal. calcd for C$_{10}$H$_{21}$NO$_2$S: C, 54.76; H, 9.65; Found: C, 55.12; H, 9.57. Minor isomer, partial characterization: Mp 84-85 °C; $^1$H NMR (600 MHz, CDCl$_3$) δ 3.39 (br m, 1), 3.12 (m, 1H), 3.02 (m, 3H), 2.73 (m, 1H), 2.04 (m, 1H), 1.71 (m, 1H), 1.49 (br s, 1H), 0.97 (s, 9H), 0.94 (t, $J = 7.8$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 56.6, 54.2, 53.9, 33.8, 29.7, 26.2, 23.3, 11.4; IR (neat) cm$^{-1}$ 3399, 2964, 2938, 2869, 1295, 1219, 1130, 798; $[\alpha]_D^{25} +10.0$ (c = 0.1, CHCl$_3$)

Synthesis of Heterocycle 86g

Using Cyclization Method B, a mixture of the amine 84g (0.246 g, 0.878 mmol) and triethylamine (0.488 mL, 3.50 mmol) in methanol (15 mL) refluxed for 8 h to give the cyclized product 86g as a pale pink solid (99%, 0.244 g, $dr = 92:8$ by $^1$H NMR analysis of the crude reaction mixture). Recrystallization from EtOAc/hexanes provided the major cis diastereomer (76%, 0.187 g). Major cis-isomer: Mp 133-134 °C; $^1$H NMR (600 MHz, CD$_6$D$_6$) δ 7.07-7.05 (m, 2H), 7.02-7.00 (m, 1H), 6.84 (d, $J = 7.2$ Hz, 2H), 3.19 (m, 1H), 2.72 (m, 1H), 2.64-2.60 (m, 2H), 2.32 (dd, $J = 13.2$, 12.0 Hz, 1H), 2.24 (dd, $J = 13.2$, 11.4 Hz, 1H), 2.17 (AB of ABX, $J_{AB} = 13.8$ Hz, $J_{AX} = 9.1$ Hz, $J_{BX} = 4.8$ Hz, 2H), 1.11 (br s, 1H), 0.45 (s, 9H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 137.4, 129.3, 129.0, 127.2, 63.0, 57.3, 55.1, 53.7, 41.9, 33.4,
25.8; IR (neat) cm⁻¹ 3355, 3312, 3084, 3062, 3025, 2961, 2904, 2868, 2842, 1493, 1477, 1454, 1291, 1263, 1125, 893, 775, 747, 701; [α]D°C 13.6 (c = 1.2, CHCl₃);
HRMS (TOF, ESI) calcd for C₁₅H₂₃NO₂S [M+H]⁺ 282.1522; found: 282.1530. Minor isomer, partial characterization: ¹H NMR (400 MHz, CDCl₃) δ 3.78 (m, 1H), 3.22-3.17 (m, 3H), 3.01-3.05 (m, 2H), 0.87 (s, 9H); ¹³C NMR (100.6 MHz, CDCl₃) δ 138.6, 129.5, 128.7, 126.7, 56.9, 54.1, 54.0, 52.6, 36.7, 33.7, 26.3.

**Synthesis of Heterocycle 86h**

Using Cyclization Method B, a mixture of the amine 84h (0.119 g, 0.43 mmol) and triethylamine (0.06 mL, 0.43 mmol) in methanol (15 mL) refluxed for 7 h. ¹H NMR Analysis of the crude reaction mixture revealed a single diastereomer of cyclized product 86h and ~ 5% unreacted starting material. Flash chromatography (50% EtOAc/hexanes) afforded heterocycle as a white solid (79%, 94 mg). Mp 149-150 °C; ¹H NMR (600 MHz, C₆D₆) δ 7.13-7.10 (m, 2H), 7.07-7.05 (m, 1H), 6.93 (d, J = 7.2 Hz, 2H), 3.30 (m, 1H), 3.28 (m, 1H), 2.54 (m, 1H), 2.48 (dd, J = 13.8, 11.4 Hz, 1H), 2.40 (ddd, J = 13.2, 3.6, 2.4 Hz, 1H), 2.27 (AB of ABX, JAB = 13.8 Hz, JAX = 7.8 Hz, JBX = 6.0 Hz, 2H), 1.94 (m, 1H), 1.71 (m, 1H), 1.48 (m, 1H), 1.32 (m, 1H), 1.05 (m, 1H), 0.95 (m, 1H), 0.89 (m, 1H), 0.82-0.74 (m, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 137.4, 129.5, 129.0, 127.1, 61.6, 55.6, 52.7, 52.2, 42.1, 32.2, 25.4, 22.1, 19.4; IR (neat) cm⁻¹ 3330, 3082, 3063, 3029, 2987, 2969, 2936, 2892, 2854, 1446, 1290, 1255, 1221, 1114, 1104, 1067,1011, 766, 748; [α]D²⁵°C -38.4 (c = 1.0, CHCl₃); HRMS (TOF, ESI) calcd for C₁₅H₂₁NO₂S [M+H]⁺ 280.1366; found: 280.1360.
3.4.4 Synthesis of Venom Alkaloids 89 & 90

The syntheses of thiirane S-oxide 97 and chiral iodide 98 have been reported previously. Spectral data for these compounds was in good agreement with literature reports.

Synthesis of Boc-Protected Sulfoxide 101

Under anhydrous conditions under an inert N₂(g) atmosphere a solution of LiHMDS (1.0 M in THF, 3.81 mL, 3.81 mmol) in Et₂O (35 mL) at -78 °C was added dropwise a solution of the n-butyl thiirane S-oxide 97 (0.458 g, 3.47 mmol) in Et₂O/THF (5:2 mL) at -78 °C. The mixture was allowed to stir for ca. 15 min, at which time a precooled (-78 °C) solution of the amino iodide 98 (1.30 g, 4.15 mmol) in THF (4 mL) was added dropwise via syringe. After 1 h of stirring at -78 °C the reaction vessel was removed from the cold bath and allowed to warm to rt stirring for ~8 h. Following completion the solvent was removed under reduced pressure, and the residue was dissolved in EtOAc. The organic layer was washed with sat’d ammonium chloride solution, water, and brine and then dried over MgSO₄. The organic layer was then filtered, and solvent was removed under reduced pressure. The crude reaction mixture was subjected to flash chromatography (40% EtOAc/hexanes), which yielded the β-amino sulfoxide as a mixture of diastereomers (74%, 0.931 g, dr = 91:9 from ¹H NMR analysis of reaction mixture). Flash chromatography (5% to 40% EtOAc/hexanes) provided the pure major diastereomer 101 as a white solid (65%, 0.827 g). Mp: 73-74 °C; ¹H NMR (300 MHz, CDCl₃) δ 6.49 (dt, J = 15.2, 6.8 Hz, 1H), 6.25 (d, J = 15.2 Hz, 1H), 5.27 (br d, J =
7.9 Hz, 1H), 4.01 (sex, \( J = 5.9 \) Hz, 1H), 2.96-2.82 (m, 2H), 2.24 (m, 2H), 1.78-1.62 (m, 2H), 1.51-1.29 (m, 6H), 1.43 (s, 9H), 0.95 (t, \( J = 7.3 \) Hz, 3H), 0.91 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 155.3, 141.7, 132.2, 79.4, 58.4, 47.6, 36.4, 31.8, 30.2, 28.4, 22.1, 19.4, 13.8 (CH\(_3\)'s overlapping); IR (neat) cm\(^{-1}\) 3226, 3038, 3003, 2960, 2930, 2873, 1702, 1541, 1454, 1363, 1270, 1253, 1175, 1041, 1025, 971, 742, 704; \([\alpha]_D^{25}\) -29.8 (c = 1.3, CHCl\(_3\)); Anal. calcd for C\(_{16}\)H\(_{31}\)NO\(_3\)S: C, 60.53; H, 9.84; Found: C, 60.74; H, 9.90.

**Synthesis of Amine 100**

A mixture of a 1:1 solution of TFA:DCM (30 mL) and protected β-amino sulfoxide 101 (1.19 g, 3.27 mmol) in DCM (3 mL) provided the deprotected β-amino sulfoxide 100 as a clear colorless semi-solid (91%, 0.647); \(^1\)H NMR (600 MHz, CD\(_3\)OD) \( \delta \) 6.53 (dt, \( J = 15.0, 7.2 \) Hz, 1H), 6.44 (d, \( J = 15.0 \) Hz, 1H), 3.35 (br m, 1H), 2.84-2.77 (m, 2H), 2.32 (m, 2H), 1.53-1.37 (m, 8H), 0.97 (t, \( J = 7.3 \) Hz, 3H), 0.96 (t, \( J = 7.3 \) Hz, 3H); \(^{13}\)C NMR (150.6 MHz, CD\(_3\)OD) \( \delta \) 143.3, 132.6, 61.4, 47.4, 40.7, 32.8, 31.5, 23.2, 20.0, 14.2, 15.0; IR (neat) cm\(^{-1}\) 3288, 2957, 2929, 2871, 1665, 1630, 1464, 1378, 1200, 1127, 1034, 970; \([\alpha]_D^{25}\) -5.0 (c = 0.50, CHCl\(_3\)); Anal. calcd for C\(_{11}\)H\(_{23}\)NO\(_3\): C, 60.78; H, 10.66; Found: C, 60.87; H, 10.47.

**Synthesis of Heterocycle 99**

Using *Cyclization Method B*, a mixture of the amine 100 (0.304 g, 1.4 mmol) and triethylamine (0.975 mL, 7.0 mmol) in methanol (20 mL) was refluxed for 8 h affording heterocycle 99 as single diastereomer (96%, 292 mg).
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.47 (m, 1H), 3.21-3.10 (m, 2H), 3.05 (m, 1H), 2.71 (dd, \(J = 12.0, 3.2\) Hz, 1H), 2.46 (dd, \(J = 12.0, 9.2\) Hz, 1H), 1.74-1.26 (m, 11H), 0.96-0.90 (m, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 55.3, 54.5, 49.4, 47.9, 37.9, 33.1, 28.5, 22.4, 19.3, 14.0, 13.9; IR (neat) cm\(^{-1}\) 3442, 3287, 2956, 2929, 2871, 1465, 1378, 1203, 1168, 1035, 771; \([\alpha]_{D}^{25}\) +21.0 (c = 0.5, CHCl\(_3\)); HRMS (TOF, ESI) calcd for \(\text{C}_{11}\text{H}_{23}\text{NOS}\) [M+H]\(^+\) 218.1573; found: 218.568.

**Synthesis of Cbz-Protected Heterocycle 102**

To a solution of \(\text{Na}_2\text{CO}_3\) (4.00 g, 37.8 mmol) in \(\text{H}_2\text{O}/\text{DCM}\) (12 mL: 15 mL) at rt was added a solution of unprotected amine 99 (0.547 g, 2.52 mmol) in DCM (3 mL). Next, the reaction mixture was cooled to 0 °C and benzyl chloroformate (1.21 mL, 12.6 mmol) was added via syringe. Reaction completion was reached after 2 h of stirring at rt. The reaction mixture was extracted with DCM (3 × 10 mL) then the organic layers were combined and washed sequentially with a saturated solution of \(\text{NH}_4\text{Cl}, \text{H}_2\text{O},\) and brine. The organic phase was dried over MgSO\(_4\), filtered and solvent was removed in vacuo to give the crude sulfoxide. The sulfoxide was purified via column chromatography eluting first with EtOAc/hexanes (50%), followed by elution with EtOAc/MeOH (50%) to give the pure Cbz-protected sulfoxide 102 as a white solid (0.638 g, 72%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.35-7.27 (m, 5H), 5.14 (m, 2H), 4.43 (m, 1H), 4.10 (m, 1H), 3.12 (dd, \(J = 13.6, 8.0\) Hz, 1H), 2.85-2.76 (m, 3H), 2.28 (m, 1H), 1.97 (m, 1H), 1.82 (m, 1H), 1.55-1.48 (m, 1H), 1.37-1.31 (m, 6H), 0.93-0.88 (m, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)), mixture of rotamers \(\delta\) 156.1, 136.2, 128.6, 128.3, 128.2, 67.5, 52.1, 51.8, 50.6, 50.5,
49.1, 49.0, 47.6, 47.4, 35.5, 35.3, 33.1, 33.0, 29.0, 28.6, 22.3, 22.2, 20.1, 19.7, 14.0, 13.9, 13.7, 13.6; IR (neat) cm\(^{-1}\) 3063, 3032, 2957, 2930, 2871, 1700, 1455, 1406, 1316, 1285, 1233, 1218, 1087, 1039, 770; \([\alpha]_{D}^{25} +13.4 \text{ (c = 0.8, CHCl}_3\); Anal. calcd for C\(_{19}\)H\(_{29}\)NO\(_3\)S: C, 64.92; H, 8.32; Found: C, 64.64; H, 8.22.

**Synthesis of Heterocyclic Sulfone 103**

Using the general method for oxidizing β-amino sulfoxides to β-amino sulfones. A mixture of cyclic sulfoxide 102 (0.547 g, 1.55 mmol) in DCM (30 mL) and MCPBA (ca ~83%, 0.612 g, ca ~ 2.95 mmol) in DCM (25 mL) afforded cyclic sulfone 103 as clear colorless oil (90%, 0.511 g) after standard workup procedure. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.39-7.33 (m, 5H), 5.14 (m, 2H), 4.22 (br m, 2H), 3.12-3.03 (m, 4H), 2.15-2.09 (m, 2H), 1.72-1.64 (m, 2H), 1.39-1.24 (m, 6H), 0.93-0.88 (m, 6H); \(^{13}\)C NMR (150.6 MHz, CDCl\(_3\)) \(\delta\) 155.8, 135.8, 128.7, 128.5, 128.3, 67.9, 55.1, 52.0, 51.8, 33.8, 31.5, 29.7, 28.6, 22.2, 19.7, 13.9, 13.6; IR (neat) cm\(^{-1}\) 3065, 3023, 2958, 2932, 2872, 1703, 1456, 1430, 1379, 1237, 1129, 1088, 998, 770, 752, 698; \([\alpha]_{D}^{25} +13.1 \text{ (c = 0.6, CHCl}_3\); Anal. calcd for C\(_{19}\)H\(_{29}\)NO\(_4\)S: C, 62.10; H, 7.95; Found: C, 62.30; H, 7.86.

**Synthesis of Pyrroline 104**

Sulfone 103 (472 mg, 1.29 mmol) was dissolved in THF:tBuOH (5 mL/15 mL) and stirred at rt. KOH-Al\(_2\)O\(_3\) (24.5 mmol, 3.09 g) was added to the reaction mixture followed by a solution of 1,2-dibromotetrachloroethane (0.755 g, 2.32 mmol) in THF (2 mL) was added slowly via
syringe. The reaction mixture was stirred for 45 min at 70 °C to reach completion. The reaction mixture was flushed through a silica plug with EtOAc to remove inorganic components. Fractions were combined and concentrated. Purification by flash chromatography (5% EtOAc/hexanes) gave the pure pyrroline 104 as a clear colorless oil (50%, 0.195). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.26 (m, 5H), 5.67 (m, 2H), 5.23 (dd, $J =$ 12.3, 2.4 Hz, 1H), 5.07 (dd, $J =$ 12.4, 6.7 Hz, 1H), 4.55 (m, 2H), 1.95-1.60 (m, 4H), 1.32-1.03 (m, 6H), 0.92-0.85 (m, 3H), 0.81-0.77 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$), mixture of rotamers $\delta$ 154.1, 137.0, 136.9, 129.2, 129.1, 128.4, 128.1, 128.0, 127.9, 66.5, 66.4, 64.6, 35.7, 34.1, 33.1, 31.5, 26.3, 25.8, 22.8, 22.7, 17.5, 17.0, 14.2, 14.1, 14.0; IR (neat) cm$^{-1}$ 3089, 3065, 3033, 2958, 2932, 2872, 1717, 1525, 1498, 1455, 1393, 1351, 1304, 1239, 1103, 1054, 1028, 984, 773; $[\alpha]_D^{25}$ -25.7 ($c =$ 0.9, CHCl$_3$); Anal. calcd for C$_{19}$H$_{27}$NO$_2$: C, 75.71; H, 9.03; Found: C, 75.88; H, 8.79.

**Synthesis of Pyrrolidine 105**

To a suspension of Pt/C (10% by wt., 15 mg) in MeOH (10 mL) under H$_2$ (g) (1 atm) a solution of pyrroline 104 (0.111 g, 0.368 mmol) in MeOH (1 mL) was added. Reaction completion was reached after stirring for 15 min at rt. The reaction mixture was filtered through Celite® column, which was washed with EtOAc. The solvent was removed in vacuo to yield a diastereomeric mixture of pyrrolidine 105 (96%, 0.107 g, $dr =$ 93:7 by $^1$H NMR integration); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.31-7.19 (m, 5H), 5.14-4.97 (m, 2H), 3.72-3.67 (m, 2H), 1.88-1.77 (m, 3H), 1.62-1.51 (m, 3H), 1.28-1.12 (m, 8H), 0.87-0.74 (m, 6H); $^{13}$C NMR (150 MHz,
CDCl₃ (mixture of rotamers) δ 154.3, 137.2, 128.4, 127.9, 127.8, 127.7, 66.4, 66.3, 58.2, 58.0, 57.7, 57.5, 36.2, 34.9, 33.7, 32.3, 28.9, 28.8, 27.6, 26.7, 22.7, 22.6, 19.9, 19.8, 14.2, 14.1, 14.0, 13.9; IR (neat) cm⁻¹ 3023, 2957, 2931, 2872, 2862, 1695, 1405, 1206, 1135, 790; [α]D²⁵ -14.8 (c = 0.3, CHCl₃); HRMS (TOF, ESI) calcd for C₁₉H₂₉NO₂ [M+H]+ 304.2271; found: 304.2264.

**Synthesis of TFA Salt 106**

To a suspension of Pd/C (10% by wt., 20 mg) in MeOH (10 mL) under H₂ (g) (1 atm) a solution of pyrrolidine 105 (0.094 g, 0.31 mmol) in MeOH (1 mL) was added. Reaction completion was reached after stirring for 15 min at rt. The reaction mixture was filtered through Celite® column, which was washed with EtOAc. The solvent was removed in vacuo to give crude pyrrolidine as a clear oily residue. The residue was immediately dissolved in DCM (10 mL) and chilled to 0 °C. Trifluoroacetic acid (5 mL) was added via syringe and the mixture was stirred for 1 h at rt. Solvent was removed in vacuo and then 20 mL of hexanes was added and evaporated three times to ensure removal of excess TFA which provided TFA salt 106 as a diastereomeric mixture (84%, 0.074 g, dr = 93:7). Major trans diastereomer: ¹H NMR (400 MHz, CDCl₃) δ 9.33 (br s, 2H), 3.54 (m, 2H), 2.18 (m, 2H), 1.81-1.55 (m, 6H), 1.43-1.30 (m, 6H), 0.92 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 59.6, 59.4, 34.6, 32.2, 30.8 (CH₂’s overlapping), 28.5, 22.3, 19.9, 13.7, 13.6. NMR spectra are in good agreement with literature values. [α]D²⁵ 2.7 (c = 0.5, CHCl₃, for 93:7 diastereomeric mixture). To get a comparative optical rotation the TFA salt was converted to the free amine. TFA
salt 106 (0.074 g, 0.261 mmol) was dissolved in 5 mL DCM and washed with an aqueous solution of 2M NaOH (4 mL). The organic layer was washed with brine (1 mL) dried over MgSO₄, filtered, and then concentrated by blowing N₂(g) over the solution to give the corresponding free amine 89 in an improved diastereomeric ratio (70%, 31 mg, dr = 95:5 (trans/cis) by ¹H NMR analysis. Major isomer: ¹H NMR (400 MHz, CDCl₃) δ 3.51 (m, 2H), 2.14-2.11 (m, 2H), 1.87-1.82 (m, 2H), 1.63-1.50 (m, 4H), 1.48-1.25 (m, 7H), 0.96-0.84 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 59.4, 59.2, 35.1, 32.7, 30.6 (CH₂'s overlapping), 28.9, 22.4, 20.1, 14.0; GC–MS: m/z 170 [M+H]+ (100), 168 (8), 126 (9), 111 (10) [α]D²⁵ +2.0 (c = 1.6, CHCl₃); lit. value for 94% ee of enantiomer [α]D²⁵ + 2.0 (c = 0.5, CHCl₃).⁶⁰

**Synthesis of Sulfone 107**

Using general method for oxidizing β-amino sulfoxides to β-amino sulfones. A 9:1 diastereomeric mixture of β-amino sulfoxide 101 (1.92 g, 5.26 mmol) in DCM (30 mL) and MCPBA (ca ~83%, 1.92 g, ca ~ 7.86 mmol) in DCM (25 mL) afforded β-amino sulfone 107 as a white solid (95%, 1.90 g) after standard workup procedure. Mp: 82-83 °C; ¹H NMR (600 MHz, CDCl₃) δ 6.93 (dt, J = 15.6, 6.6 Hz, 1H), 6.34 (d, J = 15.6 Hz, 1H), 4.90 (br d, J = 6.6 Hz, 1H), 3.98 (m, 1H), 3.19 (AB of ABX, JAB = 14.4 Hz, JAX = 6.4 Hz, JBX = 3.9 Hz, 2H), 2.28 (m, 2H), 1.72-1.66 (m, 2H), 1.50-1.35 (m, 6H), 1.44 (s, 9H), 0.93 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H); ¹³C NMR (150.6 MHz, CDCl₃) δ 155.2, 149.7, 128.7, 79.7, 58.4, 46.9, 36.5, 31.3, 29.6, 28.3, 22.1, 19.1, 13.7, 13.6; IR (neat) cm⁻¹ 3355, 3045, 3010, 2982, 2961, 2934, 2860, 1687, 1526, 1462, 1389, 1364, 1301, 1268, 1251, 1171, 1129, 1092,
1064, 976, 902, 861; \([\alpha]_D^{25} +17.5 \ (c = 0.2, \text{CHCl}_3)\); Anal. calcd for C\(_{16}\)H\(_{31}\)NO\(_4\)S: C, 57.63; H, 9.37; Found: C, 57.41; H, 9.25.

**Synthesis of Amine 96**

A mixture of a 1:1 solution of TFA:DCM (25 mL) and protected ϒ-amino sulfone 107 (1.89 g, 24.9 mmol) in DCM (3 mL) provided the deprotected ϒ-amino sulfone 96 as a clear colorless oil (95%, 1.10 g); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.94 (dt, \(J = 15.1, 6.9\) Hz, 1H), 6.34 (dt, \(J = 15.1, 1.6\) Hz, 1H), 3.41 (m, 1H), 2.98 (AB of ABX, \(J_{AB} = 14.0\) Hz, \(J_{AX} = 9.5\) Hz, \(J_{BX} = 2.4\) Hz, 2H), 2.30 (m, 2H), 1.64 (br s, 2H), 1.52-1.32 (m, 8H), 0.94 (t, \(J = 7.2\) Hz, 3H), 0.92 (t, \(J = 7.6\) Hz, 3H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 149.4, 128.8, 61.9, 46.4, 39.9, 31.3, 29.7, 22.2, 18.9, 13.8, 13.7; IR (neat) cm\(^{-1}\) 3382, 3322, 3045, 2958, 2931, 2872, 1634, 1465, 1380, 1287, 1123, 977, 816; \([\alpha]_D^{25} -14.3 \ (c = 0.4, \text{CHCl}_3)\); HRMS (TOF, ESI) calcd for C\(_{11}\)H\(_{23}\)NO\(_2\)S [M+H]+ 234.1522; found: 234.1532.

**Synthesis of Heterocycle 95**

Using *Cyclization Method B*, a mixture of the amine 96 (0.854 g, 3.7 mmol) and triethylamine (0.51 mL, 3.7 mmol) in methanol (15 mL) was stirred for 1 h at 40 °C to give the cyclized product 95 as a white (99%, 852 mg, \(dr = 92:8\) by \(^1\)H NMR analysis of the mixture). Flash chromatography (30% EtOAc/hexanes) on 1.16 g of the diastereomeric mixture (\(dr = 92:8\)) from several combined different reactions provided the pure major diastereomer (82%, 0.966 g). Mp: 34-35 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.19-3.12 (m, 2H), 2.97 (app d, \(J = 13.4\) Hz, 1H).
Hz, 2H), 2.63 (app t, \( J = 12.3 \) Hz, 2H), 1.53-1.34 (m, 11H), 0.97-0.91 (m, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 57.1 (overlapping SO\(_2\)-CH\(_3\)'s), 54.4, 54.1, 37.9, 35.5, 27.6, 22.4, 18.7, 13.9 (overlapping terminal CH\(_3\)'s); IR (neat) cm\(^{-1}\) 3305, 2958, 2931, 2872, 1466, 1380, 1326, 1128, 1082, 992, 957, 904, 870, 770; [\( \alpha \)\(_D\)]\(^{25}\) + 1.33 (c = 0.75, CHCl\(_3\)); Anal. calcd for C\(_{11}\)H\(_{23}\)NO\(_2\)S: C, 56.61; H, 9.93; Found: C, 56.38; H, 9.87. Minor isomer, partial characterization: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.42 (m, 1H), 3.07 (m, 1H), 2.86-2.82 (m, 1H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) 56.3, 56.2, 50.5, 50.2, 35.2, 32.8, 28.4, 22.4, 19.4, 14.0, 13.8.

**Synthesis of Cbz-protected Heterocycle 109**

To a solution of Na\(_2\)CO\(_3\) (2.13 g, 20.1 mmol) in H\(_2\)O/DCM (12 mL: 15 mL) at rt was added a solution of unprotected amine 95 (0.312 g, 1.34 mmol) in DCM (3 mL). Next, the reaction mixture was cooled to 0 °C and benzyl chloroformate (0.941 mL, 6.69 mmol) was added via syringe. Reaction completion was reached after 48 h of stirring at rt. The reaction mixture was extracted with DCM (3 \( \times \) 10 mL) then the organic layers were combined and washed sequentially with a saturated solution of NH\(_4\)Cl, H\(_2\)O, and brine. The organic phase was dried over MgSO\(_4\), filtered and solvent was removed in vacuo to give the crude sulfone. The sulfone was purified via column chromatography eluting first with EtOAc/Hexanes (50%), followed by elution with EtOAc/MeOH (50%) to give the pure Cbz-protected sulfone 109 as a white solid (53%, 0.262 g); Mp: 85-86 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.39-7.32 (m, 5H), 5.15 (s, 2H), 4.85 (br m, 2H), 3.21-3.05 (m, 4H), 2.03-1.84 (m, 4H), 1.39-1.25 (m, 6H), 0.92 (t, \( J = 7.1 \) Hz, 3H), 0.88 (t, \( J = 6.8 \) Hz, 3H) \(^{13}\)C NMR (150.6
MHz, CDCl$_3$) $\delta$ 155.6, 135.8, 128.6, 128.4, 128.2, 68.3, 53.1, 52.9, 51.6 (overlapping CH$_2$'s), 35.4, 33.0, 29.2, 22.3, 20.3, 13.9, 13.6; IR (neat) cm$^{-1}$ 3065, 3033, 2958, 2932, 2871, 1693, 1456, 1413, 1386, 1319, 1218, 1114, 1088, 1002, 771; $[\alpha]_{D}^{25}$ +2.67 (c = 0.5, CHCl$_3$); Anal. calcd for C$_{19}$H$_{29}$NO$_4$S: C, 62.10; H, 7.95; Found: C, 62.14; H, 8.17.

**Synthesis of Pyrroline 110**

Sulfone 109 (461 mg, 1.26 mmol) was dissolved in THF:tBuOH (5 mL/15 mL) and stirred at rt. KOH-Al$_2$O$_3$ (23.8 mmol, 3.01 g) was added to the reaction mixture followed by a solution of 1,2-dibromotetrachloroethane (0.766 g, 2.35 mmol) in THF (2 mL) was added slowly via syringe. The reaction mixture was stirred for 3.5 h at rt. The reaction mixture was flushed through a silica plug with EtOAc to remove inorganic components. Fractions were combined and concentrated. Purification by flash chromatography (5% EtOAc/hexanes) gave the pure pyrroline 110 as a clear colorless oil (65%, 0.246 g).

$^1$H NMR (600 MHz, CDCl$_3$), mixture of rotamers $\delta$ 7.37-7.29 (m, 5H), 5.76 (m, 2H), 5.19-5.14 (m, 2H), 4.53-4.48 (m, 2H), 1.95-1.75 (m, 2H), 1.44-1.29 (m, 8H), 0.95-0.85 (m, 6H); $^{13}$C NMR (150.6 MHz, CDCl$_3$), mixture of rotamers $\delta$ 155.1, 137.1, 129.4, 129.3, 129.2, 129.1, 128.4, 127.8, 127.7, 66.5, 65.7, 64.9, 64.7, 38.1, 37.6, 35.6, 35.1, 27.8, 27.7, 22.8, 22.7, 19.0, 18.8, 14.2, 14.1, 14.0; IR (neat) cm$^{-1}$ 3067, 3033, 2957, 2931, 2871, 1703, 1455, 1406, 1357, 1312, 1212, 1184, 1094, 1029, 990, 793, 732, 697; $[\alpha]_{D}^{25}$ +5.3 (c = 0.6, CHCl$_3$); Anal. calcd for C$_{19}$H$_{27}$NO$_2$: C, 75.71 ; H, 9.03; Found: C, 75.56; H, 8.97.
Synthesis of Pyrrolidine 111

To a suspension of Pt/C (10% by wt., 25 mg) in MeOH (10 mL) under H₂ (g) (1 atm) a solution of pyrroline 110 (0.130 g, 0.431 mmol) in MeOH (1 mL) was added. Reaction completion was reached after stirring for 15 min at rt. The reaction mixture was filtered through Celite® column, which was washed with EtOAc. The solvent was removed in vacuo to yield a diastereomerically pure pyrrolidine 111 (94%, 0.122 g); ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.28 (m, 5H), 5.12 (m, 2H), 3.88 (m, 2H), 1.90-1.61 (m, 6H), 1.28-1.26 (m, 8H), 0.88 (m, 6H); ¹³C NMR (400 MHz, CDCl₃), mixture of rotamers δ 155.4, 137.2, 128.4, 127.7 (overlapping C-H carbons), 66.4, 59.0, 58.9, 58.3, 58.2, 38.2, 37.9, 35.7, 35.3, 29.7, 29.3, 28.6, 22.7, 19.6, 14.2, 14.1; IR (neat) cm⁻¹ 3065, 3033, 2957, 2931, 2872, 1698, 1464, 1456, 1405, 1354, 1317, 1251, 1207, 1131, 1099, 770, 732, 696; [α]D²⁵ +8.3 (c = 0.4, CHCl₃); HRMS (TOF, ESI) calcd for C₁₉H₂₉NO₂ [M+H]⁺ 304.2271; found: 304.2261.

Synthesis of TFA Salt 112

To a suspension of Pd/C (10% by wt., 15 mg) in MeOH (10 mL) under H₂ (g) (1 atm) a solution of pyrrolidine 111 (0.093 g, 0.31 mmol) in MeOH (1 mL) was added. Reaction completion was reached after stirring for 15 min at rt. The reaction mixture was filtered through Celite® column, which was washed with EtOAc. The solvent was removed in vacuo to give crude pyrrolidine as a clear oily residue. The residue was immediately dissolved in DCM (10 mL) and chilled to 0 °C. Trifluoroacetic acid (5 mL) was added via syringe and the mixture was stirred for 1 h at rt. Solvent was removed in vacuo and then 20 mL of hexanes was added.
and evaporated three times to ensure removal of excess TFA which provided TFA salt 112 as the pure cis diastereomer (95%, 0.083 g). Mp 33-34 °C; \( ^1 \text{H NMR} (400 \text{ MHz, CDCl}_3) \) \( \delta \) 10.13 (br s, 1H), 8.62 (br s 1H), 3.46 (m, 2H), 2.20-2.11 (m, 2H), 1.87-1.74 (m, 4H), 1.69-1.58 (m, 2H), 1.44-1.30 (m, 6H), 0.92 (t, \( J = 7.2 \text{ Hz} \), 3H), 0.89 (t, \( J = 7.2 \text{ Hz} \), 3H); \( ^{13} \text{C NMR} (400 \text{ MHz, CDCl}_3) \) \( \delta \) 60.3, 60.0, 34.3, 31.8, 28.8, 28.7, 28.6, 22.2, 21.9, 13.7, 13.6; The \( ^1 \text{H NMR} \) and \( ^{13} \text{C NMR} \) spectra were in good agreement with literature data.\(^{60}\) \( [\alpha]_{D}^{25} \) 0.0 (c = 1.6, CHCl\(_3\)). To get a comparative optical rotation the TFA salt was converted to the free amine. TFA salt 112 (0.074 g, 0.261 mmol) was dissolved in 5 mL DCM and washed with an aqueous solution of 2M NaOH (4 mL). The organic layer was washed with brine (1 mL) dried over MgSO\(_4\), filtered, and then concentrated by blowing N\(_2\)(g) over the solution to give the corresponding free amine 90 (79%, 15 mg); \( ^1 \text{H NMR} (400 \text{ MHz, CDCl}_3) \) \( \delta \) 2.95 (m, 2H), 1.87-1.78 (m, 2H), 1.55-1.22 (m, 14H), 0.93-0.85 (m, 6H); \( ^{13} \text{C NMR} (400 \text{ MHz, CDCl}_3) \) \( \delta \) 59.4, 59.1, 39.0, 36.5, 31.3 (CH\(_2\)'s overlapping), 29.7, 22.9, 20.7, 14.3, 14.1; The \( ^1 \text{H NMR} \) and \( ^{13} \text{C NMR} \) spectra were in good agreement with literature data.\(^{60}\); GC-MS: m/z 170 [M+H] (50), 126 (81), 112 (100), 95 (12), 67 (19), 56 (17); \( [\alpha]_{D}^{25} \) 0.0 (c = 0.75, CHCl\(_3\)) lit. value: \( [\alpha]_{D}^{25} \) 0.0 (c = 0.6, CHCl\(_3\)).\(^{60}\)

### 3.4.5 Cyclization Chemistry of Minor Diastereomer 113

**Synthesis of Boc-Protected Sulfoxide 113**

A sample of \( \beta \)-amino sulfoxide 101/113 mixture from the mother liquors of several recrystallization attempts (\( dr \sim 70:30 \))
(major: minor), 0.504 g) was subjected to flash chromatography (10% to 30% EtOAC/hexanes) to give pure major isomer 101 (65%, 326 mg) and pure minor diastereomer 113 (22%, 111 mg). Minor diastereomer 113: Mp 82-83 °C; 1H NMR (400 MHz, CDCl₃) δ 6.50 (dt, J = 15.2, 6.8 Hz, 1H), 6.34 (d, J = 15.2 Hz, 1H), 4.73 (br d, J = 8.0 Hz, 1H), 3.90 (m, 1H), 2.96-2.86 (m, 2H), 2.26 (m, 2H), 1.61-1.57 (m, 2H), 1.48-1.32 (m, 6H), 1.44 (s, 9H), 0.93 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); 13C NMR (150.6 MHz, CDCl₃) δ 155.2, 141.5, 132.0, 79.7, 60.5, 47.0, 37.2, 31.8, 30.3, 28.4, 22.2, 19.1, 13.8, 13.7; IR (neat) cm⁻¹ 3347, 3025, 2957, 2928, 2872, 1683, 1526, 1463, 1366, 1354, 1170, 1038, 1001, 969, 772; [α]D²⁵ -58.7 (c = 0.7, CHCl₃); HRMS (TOF, ESI) calcd for C₁₆H₃₁NO₃S [M+H]⁺ 318.2097; found: 318.2104.

**Synthesis of Amine 114**

To a 0°C solution of protected β-amino sulfoxide 113 (0.075 g, 0.21 mmol) in DCM (5 mL) was added TFA (4 mL) via syringe. The ice bath was removed and the reaction mixture was stirred for 1 hr at rt. Following completion the reaction mixture was poured into a saturated solution of NaHCO₃. The pH was tested to ensure a basic pH (pH ~ 8) was achieved. The aqueous layer was extracted with DCM (3 × 5 mL). Organic layers were combined, washed with brine (1 × 5 mL), then dried over MgSO₄, filtered and concentrated under reduced pressure. The deprotected β-amino sulfoxide 114 was obtained as a clear colorless oil (93%, 0.042 g); 1H NMR (400 MHz, CDCl₃) δ 6.49 (dt, J = 15.2, 6.8 Hz, 1H), 6.29 (d, J = 15.2 Hz, 1H), 3.30 (m, 1H), 2.79-2.68 (m, 2H), 2.25 (m, 2H), 1.60 (br s, 2H), 1.57-1.31 (m, 9H), 0.94 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H); 13C NMR (150.6 MHz,
CDCl$_3$ $\delta$ 141.4, 132.5, 61.9, 47.9, 40.2, 31.8, 30.2, 22.1, 18.9, 13.9, 13.8; IR (neat) cm$^{-1}$ 3363, 3280, 2957, 2929, 2872, 1659, 1630, 1464, 1379, 1131, 1028, 970, 772; $[^{25}\mathrm{C}]_D -4.8$ ($c = 0.5$, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_{11}$H$_{23}$NOS [M+H]$^+$ 218.1573; found: 218.1566.

**Synthesis of Heterocycle 115**

Using *Cyclization Method B*, a mixture of the amine 114 (0.040 g, 0.184 mmol) and triethylamine (0.256 mL, 1.84 mmol) in methanol (8 mL) refluxed for $\sim$ 42 h. $^1$H NMR Analysis of the crude reaction mixture revealed a single diastereomer of cyclized product and $\sim$ 20% unreacted starting material. Flash chromatography (5% MeOH/DCM) afforded the cis heterocycle 115 as a clear colorless oil (75%; 94% based on consumed starting material, 30 mg). $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 3.61-3.53 (m, 2H), 2.41 (m, 2H), 1.54 (dd, $j = 13.2$, 11.2 Hz, 2H, overlapping axial methylene ring protons), 1.18-0.98 (m, 11H), 0.82 (t, $j = 7.2$ Hz, 3H), 0.77 (t, $j = 7.2$ Hz, 3H); $^{13}$C NMR (150.6 MHz, CDCl$_3$) $\delta$ 50.4, 46.0, 45.8, 38.6, 36.2, 27.4, 22.7, 18.4, 13.9, 13.8; IR (neat) cm$^{-1}$ 3438, 3267, 2957, 2929, 2871, 1678, 1465, 1380, 1328, 1153, 1139, 1068, 1026; $[^{25}\mathrm{C}]_D -3.6$ ($c = 1.4$, CHCl$_3$); HRMS (TOF, ESI) calcd for C$_{11}$H$_{23}$NOS [M+H]$^+$ 218.1573; found: 218.1566.
3.5 References


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Chapter 4: Future Work
4.0 Future Work

4.1 Proposed Research Projects

The asymmetric methodology developed in this thesis can be elaborated and applied to new ideas and exciting synthetic pathways. One aspect of asymmetric sulenate alkylation chemistry that has yet to be explored is the combination of using a chiral electrophile with a chiral sulenate. Such a system has the potential for extremely high diastereoselectivities with a possibility for a matched sulenate/electrophile pair (Scheme 4.1). Alkylation of chiral lithium cysteinesulfenates 1 with chiral amino iodide electrophiles 2 may provide the corresponding chiral sulfoxides 3 with high stereoinduction, provided a good match is found between sulenate 1 and iodide 2. Molecules such as 3 have potential to serve as tridentate ligands for asymmetric or organometallic synthesis themselves, as they possess multiple coordination sites.\(^1\)

![Scheme 4.1. Sulenate Alkylations Using Chiral Induction in the Sulenate and Electrophile](image_url)

Chiral sulfoxides such as 3 have also been used as organocatalysts so pursuits toward that end could also be attempted.\(^2-4\) Other groups have found chiral multi-dentate chiral sulfoxides useful as organocatalysts in allylation/crotylation reactions of \(N\)-benzoyl hydrazones to give the corresponding chiral hydrazides in excellent
Chiral sulfoxides such as 3 or the aryl β-amino sulfoxides synthesized in Chapter 1 could be employed as organocatalysts similar types of allylation reactions to achieve good yields and selectivities (Scheme 4.2).

**Scheme 4.2. Chiral Amino Sulfoxide Products as Potential Organocatalysts in Asymmetric Allylation reactions**

Adaptation of the asymmetric sulfenate alkylation methodology has the potential to use an enantiopure cysteine derived amino iodide/mesylate 8 (Scheme 4.3). The synthesis of 8 will commence with the sulfur protection of 4 to generate S-protected cysteine ethyl ester 5. Following sulfur protection the amine moiety of 5 will be blocked to give doubly protected compound 6. Subsequent reduction of 6 will give a sulfur/nitrogen protected cysteinol 7. Transformation of the hydroxyl functionality to a good leaving group will be accomplished to give iodide or mesylate 8.
Scheme 4.3. Synthesis of Enantiopure Cysteine Derived Electrophile 8

With 8 in hand the diastereoselective alkylation reactions of both arene- and trans-1-alkenesulfenates will be attempted, which if successful would deliver new chiral $\beta$-amino sulfoxide derivatives 9 and 10, respectively (Scheme 4.4). The aromatic derivatives 9 could be alkylated at sulfur then oxidized further to give the corresponding bis(sulfoxide) derivative. The oxidation would be expected to display some diastereoselectivity via stereoaduction from the chiral sulfoxide already in place. The corresponding bis(sulfoxide) derivatives of 9 could be explored as tridentate ligands\(^1\) or organocatalysts.\(^3\)

Scheme 4.4. Diastereoselective Sulfenate Alkylations Using Iodide 8
The *trans*-1-alkenyl β-amino sulfoxides 10 allow for further potential elaboration to a unique class of heterocycles 12 (Scheme 4.5). A *thia*-Michael reaction could deliver 7-membered heterocycles 11 asymmetrically from the corresponding sulfones of 10. A subsequent RBR could provide the interesting chiral 6-membered thianes 12, which possess two stereocenters.\(^5,6\)

![Scheme 4.5. Synthesis of Chiral Thianes](image)

A general method for the asymmetric alkylation of achiral sulfenates using a chiral ligand has yet to be developed. The idea has been attempted but only mild levels of enantioselectivity have been achieved.\(^7\) The use of a chiral bidentate \(C_2\) symmetric ligand such as a bis-oxazoline may work to induce chirality in bidentate lithium sulfenates (eg lithium pyridyl sulfenate) through a complex like 13 as depicted in Scheme 4.6. Such a method would be a conceptually different paradigm for preparing chiral sulfoxides compared to the common asymmetric sulfoxidation protocols.\(^8\)

![Scheme 4.6. Asymmetric Sulfenate Alkylation via Bidentate Chiral Ligands](image)
4.2 References


APPENDIX

NOESY NMR (C₆D₆) spectral data for heterocycle 86h