Intramolecular and Intermolecular Cyclizations of Benzyl Alkynyl Sulfones:
Synthetic scope, Limitations and Mechanistic Studies

by
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Intramolecular and intermolecular cyclizations of benzyl alkynyl sulfones: synthetic scope, limitations and mechanistic studies

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This thesis encompasses the investigation of two modes of base-induced cyclizations of benzyl alkynyl sulfones. Based on works previously published by the Schwan group, the key step of the cyclization was identified to be the formation of a benzylic anion, which undergoes cyclization by temporarily breaking aromaticity. Building on the proposed theory, substrates were developed to directly probe the key step. Unfortunately, no conclusive results were obtained. However, during the study, an unexpected compound, oxathiin-S,S-dioxide was isolated. These compounds possess a heterocyclic core and belong to a family of fungicides. This discovery inspired a novel systematic approach to substrates with multiple aryl substituents. Based on retrosynthetic analysis, substrates were treated with base, followed by a benzaldehyde to effect electrophilic capture and subsequent intramolecular conjugate addition to the triple bond. After thorough optimization, the reaction affords products with (het)aryl groups at the 5- and 6-positions in 23 – 78% yield.
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CHAPTER 1:

INTRODUCTION
1.0 Introduction

Sulfones are tetra-coordinate sulfur compounds, with one sulfur bonded to two oxygens and two hydrocarbon substituents (Figure 1). They represent a large class of organosulfur compounds of interest to synthetic organic chemists. Sulfones are typically stable and non-volatile, unlike their un-oxidized sulfide relatives.\textsuperscript{1,2-23} Sulfone polymers are prominent in plastics engineering due to their strength and resistance under oxidative, corrosive, and high temperature environments.\textsuperscript{24} In pharmacology, vinyl sulfones are being explored as cysteine proteinases and are currently being developed to combat a vast number of diseases including malaria, arthritis, osteoporosis and \textit{Tritrichomonas foetus} infections.\textsuperscript{25} While there is a number of uses for sulfones as briefly described, their importance for organic chemists lies in their versatility and functionality. Sulfones can participate in a large assortment of reactions, including a variety of cycloadditions, Michael additions, alkylation, and acylation.\textsuperscript{2-23} By capitalizing on the wide variety of possible reactions, chemists can manipulate and utilize sulfones in many strategic and complex syntheses. At the end of a synthetic pathway, the sulfone moiety can be retained as is, or once its purpose has been served, can be easily removed from the molecule by de-sulfonylation reactions or further elaborated into other functional groups.\textsuperscript{2-23} The versatility and utility of the sulfone group make it an important group in synthetic chemistry.

\[ \begin{align*}
\text{R}_1\text{S} & \quad \text{R}_2 \\
\text{O} & \quad \text{O}
\end{align*} \]

\textit{Figure 1}: General structural formula of sulfone
Synthesis of sulfones can be accomplished through oxidation of sulfides via a vast number of procedures. Such procedures include the use of oxidation agents such as peroxides, HNO₃, periodate, and so on. Generally, the oxidation process proceeds from sulfides to sulfoxide to the corresponding sulfones (Scheme 1). Simple procedures are sufficient to give good yields of sulfones without concern of over-oxidation, a problem often encountered when synthesizing sulfoxides. The presence of sensitive R groups, however, may require the careful selection of an oxidant.

\[
\begin{align*}
R^1 \_S \_R^2 & \xrightarrow{[O]} R^1 \_S^\cdot \_R^2 & \xrightarrow{[O]} R^1 \_S^\cdot \cdot \_R^2 \\
\text{sulfide} & \text{sulfoxide} & \text{sulfone}
\end{align*}
\]

Scheme 1: Oxidation of sulfides

1.1 Sulfone bond and structure

The discussion of sulfones and their importance in organic synthesis cannot be completed without mentioning the nature of S-O bonds, a topic that has been debated and studied for several decades. Physical and chemical effects of the sulfonyl group seem to indicate that the S-O bond is principally semi-polar. Physical properties, such as molecular refraction, parachor values and ultraviolet absorption provide the most significant evidence. Bond refraction is the measure of the total polarizability of electrons in the molecule. Polarizability of \(\pi\)-bonds is higher than that of \(\sigma\)-bonds and therefore, the bond refractions or exaltations are substantially higher. If the S-O bond were a fully covalent double bond, a large exaltation value would be expected. However, the measured exaltation values hovering about 0 and the differences in values between
sulfides, sulfoxides and sulfones were negligible. Therefore, S-O bonds and classic carbon-carbon or carbon-oxygen double bonds do not have similar characteristics.

Parachor was a concept developed by Sunden, and is a function of molecular weight, liquid density, vapour density and surface tension. It can be interpreted as the molar volumes of liquids at a temperature where their surface tensions are equal to 1. The concept has been used to solve various structural problems, since it is approximately a sum of separate atoms and their linkages. For instance, double bonds on average have 21.3 parachor units each and triple bonds have 46.4 units. Atom carbon has 4.8 and S has 48.2 units. The observed parachor values for sulfones are roughly equal or slightly less than the calculated parachor values if the S-O bonds were single bonds. This is a typical characteristic of semi-polar bonds. If the S-O bonds were double bonds, the observed parachor values would be higher than the calculated values.

Another semi-polar bond characteristic was seen when sulfone’s S-O bonds were studied using ultraviolet absorptions. Longer wavelength ultraviolet absorptions are generally observed with functional groups possessing double bonds, such as olefins and carbonyl, carboxyl, and nitro groups. Long wavelengths correlate to the ease with which the electrons can be excited. Compared to electrons in σ-bonds, electrons in π-bonds are easier to excite. If the S-O bond were a double bond, one would expect to see some ultraviolet absorption. However, sulfonyl groups are transparent throughout the ultraviolet region. Semi-polar bonds, unlike double bonds, would be more difficult to excite. Due to their electric field, electrons are likely constrained, subsequently increasing the excitation energy. The nature of the S-O bond is still highly controversial, though
many support the view that the S-O bond is a hybrid of a double bond and a semi-polar bond, with more semi-polar bond characteristics.\textsuperscript{27,26}

1.2 Sulfonyl anions

In terms of the sulfone functionality, one of the most important properties is that it is an electron-withdrawing group. Due to this property, the $\alpha$-hydrogens of a sulfone are relatively acidic and can be removed with $n$-butyl lithium, LDA or similar bases to create relatively stable anions. The acidifying effect of sulfones on $\alpha$-hydrogens is well established. Quantitatively, the Bordwell pKa table can be called upon for comparison, which summarizes the measurements of acidity that are performed in DMSO.\textsuperscript{28} $\alpha$-Hydrogens of simple hydrocarbons have pKa values of roughly 55; the pKa value for methyl is $\sim$56.\textsuperscript{28} Simple sulfones, such as those with $\alpha$-alkyl substituents (e.g., $R_{1,2}^1$ = Me) possess a much lower pKa value, 31.1. The presence of electron withdrawing groups at the $\beta$-position will, of course, also lower pKa values further, the most noteworthy of which is the effect of having two phenylsulfonyl groups ($R_{1}^1$ = Ph, $R_{2}^2$=CH$_2$SO$_2$Ph), where the pKa value drops to 12.2 (Figure 2).\textsuperscript{28}

![Figure 2: Diphenylsulfone’s pKa value\textsuperscript{28}](image)

Modes of carbanion stabilization by sulfones can also be discussed in reference to pKa values. The pKa value of bicyclic trisulfone 1 is comparable to its acyclic analogue 2.
whereas bicyclic $\beta$-diketone 4 has a higher pKa value than its unrestricted counterpart cyclohexane-1,3-dione (3).\textsuperscript{28-29} With respect to the ketones, the structure of bicyclic $\beta$-diketone 4 structure does not allow for delocalization and hence stabilization via resonance cannot occur without breaking bonds. Delocalization brings stabilization to carbanions, decreasing pKa values substantially and therefore, increases acidity. In the case of sulfones, comparable pKa values between bicyclic trisulfone 1 and its acyclic analogue 2 demonstrate that the primary mode of stabilization does not occur via ‘classical’ delocalization.\textsuperscript{30} As presented earlier, the S-O bonds in sulfones generally do not possess double bond characteristics as one would expect from the C=O bonds in carbonyl groups. Here, the term ‘classical’ in this thesis is used to denote the familiar $\pi-\pi$ delocalization invoked by most organic chemists when p-orbitals are involved. Some researchers suggest conjugation does occur for $\alpha$-sulfonyl anion using 3d orbitals and that co-planarity is not of importance for this type of conjugation. Thus, one would not see a large discrepancy between bridged and cyclic sulfones.\textsuperscript{27,26} An important note must also be made about configuration of carbanion chemistry. Reactions achieved through enolate intermediates are stereoconvergent, where carbanions often exist in planar achiral form. Without stabilization from substituents, they often undergo rapid racemization by inversion. This difference between sulfonyl anions and enolates has led to useful stereospecific processes, which will be discussed in section 1.3.

![Figure 3: pKa value comparisons between bridged and acyclic ketones and sulfones](image-url)
The structure of α-sulfonyl anions has also been intensively examined by several groups.\textsuperscript{30-31} Studies were initiated by early observations of fast deuterium exchange by optically active acyclic sulfones with α-carbon centers. These optically active α-carbon centers undergo deuterium exchange with rates up to 40 times faster than racemization.\textsuperscript{32} Likewise, when decarboxylation reactions of α-sulfonyl carboxylic acids were performed, retention of stereochemistry at the α-carbon centers was also observed. H-D exchange α to the sulfonyl group is now known to have a well-defined stereochemistry. Even more remarkable, α-sulfonyl carbanions also retain their stereo-configuration when reacting with various electrophiles despite the use of racemization-promoting solvents such as DMSO.\textsuperscript{30} Hypotheses explaining reasons for retention of configuration have been proposed. The general consensus is that there are two extreme representations of α-sulfonyl carbanions: pyramidal $sp^3$ and planar $sp^2$ structure (Figure 4).\textsuperscript{29,30} For both proposed structures, retention of configuration is energetically favored. In the case of the pyramidal form, there is a high-energy barrier for rotation and inversion. In the planar form, the rotation of α-C-S bond also requires high-energy. The debate over the configurations of α-sulfonyl carbanions will not be fully reported here, although it should be noted that there are compelling arguments supporting both configurations, as well as evidence suggesting that configuration may depend on various R\textsubscript{1,2} groups. The existence of α-sulfonyl carbanions in chiral form and their ability to retain configuration, however, represent an important feature that synthetic organic chemists have exploited for syntheses.\textsuperscript{3,4} The orientation of the lone pair on the carbon is gauche to both of the sulfonyl oxygens, or antiperiplanar to the R-C\textsubscript{α}-S-C\textsubscript{α} bond (Figure 4).
1.3 Sulfone chemistry

Sulfonyl anions are often exploited in a wide range of organic syntheses, as these anions readily react with a broad range of electrophiles, both inter- and intramolecularly. In addition to its reactivity, as discussed previously, racemization of α-sulfonyl anion occurs at a slow rate due to its structure, leading to highly enantiospecific reactions. This approach has been widely employed in several syntheses of alkaloids and other species. These reactions include but are not limited to alkylation, acylation, alyllation and Michael additions. Acylation of simple α-sulfonyl carbanions is an excellent way to access products with additional functionality. When acyl groups are attached at the β-position, the α-hydrogens become even more labile. In 1955, Truce and Knospe, conducted one of the first studies in this area, where both inter- and intramolecular acylation were performed to produce β-ketosulfone products, sought after intermediates due to their reactivity. Tricyclic compounds were also found to be accessible when combined with alkylation. Ghera, Maurya and Ben-David, performed malonate alkylation followed by α-acylation of sulfone to generate stereoselective, highly functionalized cyclized products (Scheme 2).
Alkylation reactions of $\alpha$-sulfonyl carbanions are typically regarded as very general and high yielding. Alkylation occurs when $\alpha$-sulfonyl carbanions are treated with common electrophiles. Early alkylations done by Shriner and Greenlee in 1939, used simple alkyl halides. However, structural variations of both nucleophilic and electrophilic components have since grown. Sulfones can contain other electron withdrawing groups at the $\beta$-position to expedite the generation of $\alpha$-carbanion. Electrophiles include a variety of allylic and vinylic halides, and other electrophilic centers. Epoxides can also act as electrophiles toward $\alpha$-sulfonyl carbanions undergoing ring opening reactions to obtain alcohols. Alkylation can also be performed intramolecularly to form cyclic compounds. Stirling and co-workers carried out a series of cyclization reactions to form three-, four-, and five-membered rings at excellent yields and rates. Larger rings have also been accessed through this method (Scheme 3).
Scheme 3: Formation of 14-membered ring through alkylation of α-sulfonyl carbanion

More recently, stereospecific decarboxylative allylation was reported by Weaver and coworkers. Allyl sulfonyl acetic ester (10) undergo highly specific decarboxylative allylation using a palladium catalyst (Scheme 4). The reaction yields a stereospecific formation of tertiary homoallylic sulfones (11) at 93% ee. Once again, the slower rate of racemization played a pivotal role in the enantiospecific process.

Scheme 4: Pd-catalyzed stereospecific decarboxylative allylation

Sulfone functionality can also be employed to form double bonds (Scheme 5). Julia olefination utilizes sulfonyl carbanions prepared in situ to react with aldehydes or ketones, producing alkoxide 13. Treatment of an electrophile produces a stable intermediate 14. Desulfonylation using Na/Hg forms a trans olefin 15. The trans-selectivity stems from the increasing branching of R groups (Figure 5).
Throughout the years, a number of variations of the Julia Olefination have been developed. Heteroaryl sulfones have been used in place of phenyl sulfones in one variation.\textsuperscript{40} The added benefit to this variation is the intermediate can undergo Smiles rearrangement and the stereochemistry of the double bond is a result the counter ion and the resulting stereochemistry of the transition states (Scheme 6).\textsuperscript{40} Small counterions, such as lithium in polar solvents lead to closed transition states and large counterions lead to open transition states. The result is the ability to control stereochemistry of the alkene.

The Julia olefination reaction is often applied in numerous syntheses, such as the total synthesis of bryostatin 2 (Scheme 7). Bryostatin 2 belongs to a family of macrolide lactones isolated in the 1960s by Pettit and co-workers that are currently under investigation as anti-cancer agents.\textsuperscript{41}
Another method to generate alkenes that utilizes a sulfone group is the Ramberg-Bäcklund rearrangement (RBR), a base-mediated conversion of an α-halosulfone into E or Z alkenes through the extrusion of SO$_2$ (Scheme 8). The stereochemistry of the double bond depends on the base used; strong bases give predominantly E alkenes, and weak bases give predominantly Z alkenes. The original procedure involved halogenation of a sulfone, followed by a base-induced rearrangement in two pots. Through the Meyers’ modification, generation of α-halosulfone in situ is easily accessible, allowing sulfones to be used directly for olefin generation without problematic halogenation steps. However, Meyers’ modification called for carbon tetrachloride, an ozone depleting substance.
Several modifications following Meyers’ modification including Chan’s modification and Frank’s modification face the same problem.\(^4^3\) Recently, fellow group members, Soderman and Schwan have reported a new ozone-friendly halogenating reagent, \(\text{C}_2\text{Br}_2\text{Cl}_4\) for this rearrangement.\(^4^4\) Due to the nature of elimination, the RBR can be applied to synthesize both small and large rings (Scheme 9 and 10).\(^4^5\-^4^6\) Like the Julia Olefination, the RBR has been employed in numerous syntheses of natural products and pharmaceutical agents, such as the total synthesis of cylindrocyclophanes A & F (Scheme 11).\(^4^7\)

Scheme 8: Typical Ramberg-Bäcklund rearrangement (RBR)

Scheme 9: RBR application on smaller rings

Scheme 10: RBR application on smaller rings
As previously discussed, α-sulfonyl anions can be used as nucleophiles in alkylation, acylation reactions, as well as Michael-type additions. Michael additions are a class of reactions in which a nucleophile attacks a double-bond β to an electron deficient group. Sulfonyl functionality has been exploited to achieve conjugate additions of α-sulfonyl anions onto α, β-unsaturated compounds. Enantioselectivity can be achieved through various modifications of reaction conditions. For instance, through the use of primary amine catalysts, enantioselective Michael reactions of sulfonyl anions to α-β-unsaturated aldehydes, have been reported by several groups.

One example is a catalytic asymmetric Michael reaction done by Sun and co-workers, used toward the chiral synthesis of (R)-muscone and (S)-celery ketone. The reaction proceeds through the addition of sulfonyl anion to the unsaturated carbonyl, producing the expected product. Reduction using NaBH₄ result in the corresponding alcohol followed by desulfonylation results in the optically active alcohol (Scheme 12).
Scheme 12: Catalytic asymmetric Michael addition reaction

Alternatively, unsaturated sulfones can also act as Michael acceptors. α,β-Unsaturated sulfones can also participate in Michael type additions because of their strong electron withdrawing influence. Steert and co-workers used a Michael Addition reaction in their synthesis to make a series of cysteine proteases. In this step, thiol 31 undergoes a conjugate attack on vinyl phenyl sulfone 32 (Scheme 13).49

Scheme 13: Michael addition of thiol 31 on unsaturated sulfone.49

1.4 Sulfone as an activation group

Sulfonyl groups have also been used for the activation of cyclization onto aromatic rings. The electron-withdrawing group conjugated to the ring stabilizes intermediates and can retard the re-aromatization process, allowing for the isolation of dearomatized products. Dearomatizing cyclizations promoted by a sulfonyl group have been performed by a number of synthetic groups. Randall and Aymer utilized allenyl sulfone to aid in an intramolecular cyclization, leading to a dearomatized product (scheme 14). Beginning with sulfone 33, iodine-lithium exchange gave the corresponding...
alkyllithium 34. A 1,3-sulfonyl shift generates allenyllithium 35, primed to undergo an intramolecular cyclization to form sulfonyl anion 36. Protonation using MeOH generated bicyclic sulfone 37 at 50% yield.50

Scheme 14: Dearomatization reaction promoted by sulfonyl group

Using this reaction, Clayden and co-workers were able to make podophyllotoxin, a non-alkaloid toxin lignan currently under evaluation as an anticancer agent. Here, they successfully achieved the cyclization of an organolithium tethered to a naphthalene bearing a strategically positioned sulfone, breaking partial aromaticity of the ring in the process (Scheme 15).51-57b The synthesis begins with a transmetallation converting the tributyltin group to lithium. Attack on the aromatic ring ortho to the sulfonyl group brings about cyclization, resulting in a α-sulfonyl anion. Quenching of the α-sulfonyl anion, as discussed previously, can be done using a variety of electrophiles. A series of steps are then employed to eventually produce podophyllotoxin, during which the sulfone group plays a role in directing some stereochemistry prior to desulfonylation.51-57
Given the reactivity characteristics of α-sulfonyl anions and unsaturated sulfones, two papers from the Mukai group nicely utilize the features described herein, and provide a good lead-in to the chemistry of benzyl alkynyl sulfone cyclizations. Using allenyl sulfones with various sized alkyl chains bearing terminal aldehyde groups, the Mukai group was able to induce cyclization under basic conditions to form carbocycles and heterocycles. Under base treatment in DMF, cyclization to carbocycles was observed for five and six membered rings, n = 3 (43) and 4 (44) (Scheme 16). The proton at the γ-position of an allenyl sulfone is acidic enough to be abstracted with a mild base. The anion formed can delocalize to become a stabilized α-sulfonyl anion (45). This anion attacks the tethered carbonyl group, forming compounds 43 and 44. 58-59

**Scheme 15:** Synthesis of podophyllotoxin
When cyclization was attempted for smaller alkyl chains, where \( n = 1 \) or \( 0 \), heterocyclic pyran 46 or furan 47 products were obtained, respectively. Conjugate base 45 was also in equilibrium with its enolate resonance form, the oxygen of which can undergo Michael addition on the unsaturated sulfone (Scheme 17).\(^{58-59}\)
The preference cyclization mode depends on steric and geometric allowances. Formation of products 43, 44 and 46, 47 occurs through different attack points on the starting material. Also of interest is that the unsaturated sulfone alternates from being a nucleophilic α-sulfonyl anion to being a Michael acceptor. Under the same conditions, allenyl sulfones with various sized chains tethered to terminal aldehyde groups were able to produce carbocyclic as well as heterocyclic compounds. Therefore, Mukai and co-workers have demonstrated the importance and flexibility of conjugated sulfones as synthetic precursors.

1.5 Intramolecular cyclization of benzyl alkynyl sulfone

Recently, a previous member of our group, Hossain sought to explore a base induced cyclization of alkynyl benzyl sulfones. Prompted by the group’s previous success with benzyl alkynyl sulfides where 5-endo cyclization occurs under basic treatment to form 2-(2-iodophenyl)-2,3-dihydrothiophenes, Hossain expected to see similar results from sulfone derivatives. As a trial run, 2-iodobenzyl 1-propynyl sulfone (48a) was treated with KOTBu. Unlike analogous sulfide derivatives, sulfone 48a cyclized unexpectedly into a six-membered ring moiety 49a with a poor but promising 27% yield (Scheme 18). The product was identified using TLC, 1H and 13C NMR spectroscopies, as well as FTIR spectroscopy. The characteristic peak at 6.5 ppm in 1H NMR indicates the presence of a vinylic proton and aromatic peaks integrating to 3 protons instead of 4 as in the starting material indicating that cyclization occurred onto the aromatic ring. IR and 13C NMR spectroscopies can also be used to confirm the loss of triple bond in the starting material.
Hossain began his investigation by first optimizing the reaction conditions. Solvent, time, temperature, substrate concentration and base equivalents were thoroughly examined. The preferred choice of base was found to be LDA in Dr. Wang’s preliminary work. Hossain followed up by investigating the optimal equivalents of LDA and temperature of reaction with little success. At 1.0 equivalents of LDA at -78 °C, the yield was only 20%. Other equivalents of LDA and temperature combinations gave an even lower yield percentage; only some trace amounts of desired product. The bulk of the reaction mixture found was an undefined polymeric material, suspected to occur through bimolecular reactions. Therefore, it stands to reason that changing the concentration of the starting material would work in suppressing polymerization. Given the nature of intramolecular reactions, the resulting yield largely depends on the concentration of substrate; a balance between not diluting the solution enough and excessive dilution must be found to achieve optimal results. Table 1 summarized Hossain’s findings. In addition to varying concentrations of substrate, Hossain also varied the solvents used. Solubility of sulfone 48a was a major issue at low temperature and various solvents were quickly eliminated. In the end, THF provided the best yield (Table 1).

**Scheme 18**: Cyclization of 2-iodobenzyl 1-propynyl sulfone
Table 1: Cyclization of alkynyl sulfone 48a at various concentrations

<table>
<thead>
<tr>
<th>Concentration of substrate in THF (M)</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>20%(^b)</td>
</tr>
<tr>
<td>0.5</td>
<td>66%(^a)</td>
</tr>
<tr>
<td>0.10</td>
<td>16%(^b)</td>
</tr>
<tr>
<td>0.05</td>
<td>10%(^b)</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield by flash column chromatography and recrystallization
\(^b\)Yields were calculated by 1H-NMR of crude reaction mixture

The optimized procedure was eventually found to be 0.5 M of substrate in THF in which 1.0 equivalent of LDA was added at -78 °C. Following the addition, the mixture was allowed to warm to room temperature and stirred for 45 minutes. Under these conditions, the yield of cyclic moiety 49a was brought up to 75% at 1-2 g scale.\(^60\) Using the optimized condition, cyclization of a non-iodo substrate 48b was attempted. However, the reaction yielded an intractable mixture with no indication of the cyclized product. Several different conditions were utilized varying base equivalents as well as time of reaction. Unfortunately, all attempts using sulfone 48b resulted with polymerization dominating over cyclization. At this point, it seemed that ortho-substituents play a pivotal role in the product formation. Hossain hypothesized that steric crowding about the benzylic position is pivotal for the cyclization.

Based on reports by Eisch, benzylic protons are slightly more acidic than that of the propargylic protons (Figure 6).\(^61\) Therefore, in the case of the non-iodo substrate, deprotonation would be kinetically favored at the benzylic position. An experiment was designed to block the benzylic position on 48b and direct deprotonation to occur...
preferentially at the propargylic position, in one pot. Sulfone 48b was treated with LDA followed by methyl iodide, a small reactive electrophile. Following alkylation, another equivalent of LDA is expected to deprotonate the propargylic proton and bring about cyclization (Scheme 19). Unfortunately, after several unsuccessful trials using various conditions, no conclusive results were found.

\[
\begin{align*}
&\text{CH}_3 \quad \text{pKa} = 23 \\
&\text{benzene-SO}_2 \quad \text{pKa} = 22
\end{align*}
\]

**Figure 6:** pKa of sulfone 50

\[
\begin{align*}
\text{Scheme 19: Experiment designed to block benzylic proton prior to cyclization}
\end{align*}
\]

Going forward in exploring the mechanism and scope of the reaction, a collection of benzyl 1-alkynyl sulfones were synthesized and subjected to the optimized cyclization conditions. When there was no substituent (\(R^1=H\)) on the aryl ring and \(R^2\) was also H, an intractable mixture formed, as previously discussed. *Para* and *meta*-substituents also did not provide the desired product. *Ortho*-substituents gave moderate to good yields and allowed the following observations: yield of cyclization generally increases with increasing size of substituent. With a small methyl group, a low yield of 13% was found via \(^1\text{H}-\text{NMR}\) analysis of the reaction mixture (entry 7). With phenyl as a substituent, the
yield increased to 80% (entry 8). Similar findings were found with halogen substituents. A brominated derivative gave a 55% yield whereas a larger iodine substituent gave 66-75% yield (entry 1 and 2, respectively). It seems that steric may play a factor, but subsequent data seem to contradict this initial hypothesis. It is possible that ortho-substituents facilitated access to the geometric/rotational configuration needed for the reaction to occur. The steric demands of a substituent may force the alkyne containing side chain into a rotational geometry optimal for Michael addition onto the triple bond from the benzene ring.

**Table 2: Based induced cyclization of compounds 48a-d**

<table>
<thead>
<tr>
<th>Entry #</th>
<th>Compound 48</th>
<th>R¹, R², R³</th>
<th>Compound 49, % yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>o-I, H, CH₃</td>
<td>66-75</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>H, H, CH₃</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>o-Br, H, CH₃</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>p-F, H, CH₃</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>m-CN, H, CH₃</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>o-CF₃, H, CH₃</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>o-Me, H, CH₃</td>
<td>13</td>
</tr>
</tbody>
</table>
To gain further insight into the reaction, ReactIR™ was utilized to monitor reaction progress. ReactIR™ is a technology that allows for a real-time dynamic picture of chemistry under actual conditions by producing a 3D image of IR spectra. Figure 7 is an IR spectrum, showing the cumulene and alkyne region during the cyclization of sulfone 48, with labels of absorptions corresponding to proposed intermediates. Here, the first peak is large and appears at 2222 cm⁻¹, corresponding to the triple bond on the starting material. Once LDA is introduced, this large peak disappears very rapidly and another peak emerges at 1908 cm⁻¹, which is assigned to 50a, a value that is comparable to calculated and measured values for allenyl anions. 62 Finally, with warming of the reaction mixture, a peak at 2199 cm⁻¹ begins to appear while the 1908 cm⁻¹ peak lessens in intensity. This peak is assigned to anion 51a, which is expected to undergoes cyclization. 60

![Figure 7: Cumulene/Alkyne region of ReactIR spectrum during the cyclization reaction](image)
From this, a mechanism was proposed in which initial deprotonation occurs on the alkyne and eventually brings about cyclization, temporarily breaking aromaticity (Scheme 20). That first deprotonation occurs at the terminal methyl group, which produces a delocalized allenyl anion $50a$. A proton transfer occurs to form a benzylic anion $51a$, presumably driven by the high concentration of $50a$ and/or diisopropylamine. Benzylic anion $51a$ undergoes cyclization through a conjugate addition, thereby temporarily breaking aromaticity. Another proton transfer is required to occur to restore aromaticity to the fused phenyl ring, forming anion $52a$, which holds the anion in its most stabilized form. Evidence for anion $52a$ later came from substituting the normal acid quench for methyl iodide, where the final product $53$ isolated had a methyl group at the benzylic position.$^{60}$

![Scheme 20: Proposed mechanism for cyclization of benyl alkynyl sulfone 48.](image)

With an improved understanding of the cyclization mechanism through the use of ReactIR™, a series of benzyhydryl alkynyl sulfones were synthesized to further
investigate the substituent and multiple ring effects for the cyclization. For the most part, the cyclization occurred readily with moderate to good yields (Table 3). Various sizes of terminal alkyl groups on the alkyne were also tested; changing the terminal group from methyl to n-butyl (R³, Scheme 21) did not perturb cyclization and the reaction occurred at good yield. This opens the door for possible extension of alkyl groups if needed in future syntheses.⁶⁰

Table 3: Base-cyclized for a series of benzyhydryl alkynyl sulfones

<table>
<thead>
<tr>
<th>Entry #</th>
<th>Compound 48</th>
<th>R¹, R², R³</th>
<th>Product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>2-thienyl, H, Me</td>
<td>![image]</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>![image]</td>
<td>H, Ph, n-Bu</td>
<td>![image]</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>![image]</td>
<td>I, H, Me</td>
<td>![image]</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>![image]</td>
<td>--, Ph, n-Bu</td>
<td>![image]</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>![image]</td>
<td>--, H, Me</td>
<td>![image]</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>![image]</td>
<td>--, Ph, Me</td>
<td>![image]</td>
<td>51</td>
</tr>
</tbody>
</table>

According to the proposed mechanism (Scheme 20), aromaticity is being broken during the cyclization. Experimental data from entry 4 of table 3 supported this theory. When benzene and thiophene were both available for cyclization, the product is a cyclic
moiety fused with thiophene, not benzene. The observation is consistent with the Dewar resonance energy value of thiophene (17 kcal/mol) compared to benzene (36 kcal/mol).63

In the proposed mechanism, after the initial hydrogen abstraction by LDA, there was a proton transfer from the benzylic position before the cyclization could take place. To eliminate the extra step, another substrate was designed. The reasoning is that if direct deprotonation at the benzylic position can take place, cyclization should occur readily and any side reactions associated with anion 51 could be eliminated. With that in mind, a blocking group was introduced on the alkyne, so that the only available protons for LDA were at the benzylic position.60 The two blocking groups (R3) used were t-butyl and phenyl (compounds 48i-l). When R3 = t-butyl, intramolecular cyclization did not occur. Success came with R3 = phenyl. Previously, when an unsubstituted benzyl sulfonyl alkyne was used, no cyclization occurred (Table 1, entry 3). With phenyl as a blocking group, cyclization occurred and in good yield (80%, Table 2, entry 8). Cyclization occurred at good yields for thiophene-derivatives as well. Therefore, eliminating the proton transfer by introduction of the blocking group facilitates the cyclization.60

ReactIR™ analysis was used again to follow 48i (Table 2, entry 1). Unlike what was observed for substrates without a blocking group, with the addition of LDA, the IR absorptions of the triple bonds remained similar and were much slower to disappear. Furthermore, in these analyses, allenyl anion 51 was not observed. In fact, React IR data provided an amount of certainty that deprotonation does indeed occur at the benzylic position and it is not a hindrance to the cyclization as the initial data suggested. On yield comparison, by eliminating competitive deprotonation sites, cyclization is anticipated to occur more readily and effectively. It stands to reason that the starting material initially
chosen prevented a full evaluation of this reaction, thus prompted a component of the current MSc studies, an investigation of benzyl alkynyl sulfones, in which the alkyne substituent is an aromatic ring.\textsuperscript{60} As such, the first section of this MSc thesis is to perform further mechanistic studies, probing electronic effects of cyclization, utilizing that knowledge to optimize the reaction and expanding the scope of the cyclization to other heteroaromatic groups and other functional groups such as the carbonyl unit.

\[ \text{Scheme 21: Base induced cyclization of compounds with } \beta\text{-blocking groups} \]

\[ \begin{array}{c|c|c|c}
\text{Entry #} & \text{Substrates (48)} & \text{R}_1^1, \text{R}_2^2, \text{R}_3^3 & \% \text{ yield} \\
1 & i & \text{H, H, Ph} & 59 \\
2 & j & \text{H, Ph, Ph} & 71 \\
3 & k & \text{I, H, Ph} & 59 \\
4 & l & \text{H, H, 'Bu} & 0 \\
\end{array} \]

\textbf{Table 4: Results of base induced cyclization of compounds with } \beta\text{-blocking groups}

\textbf{1.6 Unexpected results}

As briefly mentioned earlier, when substrate 48l was subjected to the cyclization conditions, intramolecular cyclization did not occur, yet a major product was obtained. Standard characterization data failed to assist in the elucidation of the structure of the
unknown. X-Ray analysis was eventually required to secure the structure of the product, which is shown in scheme 22. The product proved to be a heterocycle possessing the 1,4-oxathiin-S,S-dioxide backbone.

Scheme 22: Cyclization of sulfone 48l

Through examination of the product 54 of the cyclization attempt of sulfone 48l, a retro-synthesis can be envisioned where disconnections can be made at the indicated positions (Scheme 23). The reactants could be sulfone 48l and 2-iodobenzaldehyde (55). Beginning with the deprotonation at the benzylic position, the sulfonyl anion attacks the carbonyl position of 2-iodobenzaldehyde (55). Cyclization can be induced through a Michael addition by alkoxide 56. Since the reaction only has one substrate, which is the sulfone, the formation of benzaldehyde must be in-situ and Hossain hypothesized, also via carbene chemistry (vide infra). The theory is sulfonyl anion was generated by LDA treatment of the starting material. Since the substrate is slow to cyclize due to its tert-butyl group, time is granted for elimination of sulfinate anion generating carbene. Recombination, as shown in the preceding scheme followed by the release of sulfenate anion generates 2-iodobenzaldehyde (55), which undergoes the reaction outline above. To confirm that carbonyl was generated in-situ for the formation of oxathiin-S,S-dioxide, benzaldehyde was added to a mixture of sulfone 48k and LDA by Lilly Ho and co-workers (Scheme 24). As expected, 1,4-oxathiin-S,S-dioxide (58) was generated. The
The discovery of this product served as an inspiration for the synthetic access of 5,6-dihydro-1,4-oxathiin S,S-dioxides, the details of the journey is therein described in the third chapter of this thesis.

Scheme 23: Retrosynthetic analysis of the unexpected product 54

Scheme 24: Generation of 1,4-oxathiin-S,S-dioxide

1.7 Oxathiin S,S-dioxides

The oxathiin S,S-dioxide heterocyclic core is central to a well-recognized family of fungicides. These compounds display potent fungicidal activities against a number of
pathogens, with potential expansions of applications in pharmaceutical and agrochemicals. Whereas a variety of synthetic approaches to the ring system are documented, generally applicable methodologies are rare, as are accesses to substrates with multiple aryl substituents.

Von Schmeling and Kulka first reported the systemic fungicidal nature of this family of compounds in 1966. By 1971, they were registered as an active ingredient for control of rust on carnations, under the name Plantvax. In von Schmeling and Kulka’s preliminary study, compounds 2,3-dihydro-5-carboxanilide-6-methyl-1,4-oxathiin-4,4-dioxide and its sulfide analogue were tested for fungicidal activity against bean rust and loose smut. The key in its activity was the six-membered ring dioxo-oxathiin core and the attached phenyl group; elimination of the benzene ring from the molecule destroyed all fungicidal activity. The sulfone derivative gave 100% disease control when used against the development of rust symptoms on primary bean leaves and was also shown to be more stable within the plant than its sulfide derivative. The mode of action of these compounds is to inhibit succinate oxidation of succinate dehydrogenase in the fungal class Basiomycetes. Following this preliminary study, numerous reports have appeared concerning the potential value of oxathiins for controlling various plant diseases. It was discovered that both compounds were highly effective without adversely affecting the host and showed high specificity against other fungicides as well such as Puccinia Rubigo-Vera Triticci, Uromyces Phaseoli Typical, Ustilago Nuda, etc..

A great deal of synthetic effort was put forth for the preparation of oxathiins and oxycarboxins, as well as their derivatives. A convenient industrially relevant synthesis was developed by Kulka and co-workers and patented by UniRoyal (Scheme 25). The
synthesis produces carboxin in 6 steps in 80% yield. The synthesis begins by obtaining ethyl α-chloroacetoacetate (59) by chlorination of ethyl acetoacetate (60) using sulfuryl chloride in benzene. 2-Mercaptoethanol (61) is deprotonated by a mild base and attacks α-chloroacetoacetoacetate, displacing chloride, producing an intermediate 62 which cyclizes into compound 63. Dehydration of this cyclic moiety produces the oxathiin backbone. The final product is obtained through a conversion of the carboxylic acid to acyl chloride and finally to amide. Finally, oxidation using MCPBA results in the production of oxycarboxin (64).\textsuperscript{76}

![Scheme 25: Synthesis of oxycarboxin 64, patented by Uniroyal\textsuperscript{76}](image)

Another group from the University of Napoli Federico II published a novel method towards the synthesis of 5,6-dihydro-1,4-oxathiin and its sulfone derivative (Scheme 26).\textsuperscript{77} The synthesis requires the use of acetoacetanilide 1,3-oxathiolane (65) and one equivalent of N-bromosuccinimide (NBS).\textsuperscript{72} NBS acts as a source of positive bromine which induces an oxidative rearrangement to produce the 5,6-dihydro-1,4-oxathiin moiety in one pot. Oxidation is still required to produce oxycarboxin.\textsuperscript{78}
Scheme 26: Synthesis of 5,6-dihydro-1,4-oxathiin and its sulfone derivative

Capozzi and coworkers described another access to these compounds in 1995. Utilizing Diels-Alder chemistry to produce the 1,4-oxathin rings, α-α’-dioxothiones (66), an efficient electron-poor dienophile found to show complete regioselectivity was generated using α-α’-dioxothiophthalimides (67). The dienophile was treated with a series of electron-rich dienes, which also retain their geometry in the cycloadduct. Oxidation of oxathiin S-oxide with MCPBA affords the corresponding sulfones. The advantage of this synthesis is the ability to utilize various dienes, making it possible to create a library of compounds for study. However, the limitation is that the dienes must be electron-rich.67

A series of similar compounds that also possess the oxathiin-S,S-dioxide ring were designed to simulate the D ring of lanosterol (Scheme 28). These compounds were reported to have potent activity against murine systemic candidosis and aspergillosis and work by inhibiting the cytochrome P450 lanosterol-14-α-demethylase, thereby eliminating the biosynthesis of ergosterol in the bacteria. Candidosis, commonly known as thrush or yeast infection is a fungal infection of any of the Candida species. While Candida bacteria are normally present in healthy humans, overgrowth can cause
symptoms such as itching and discomfort if localized. In cases where systemic infection occurs and left untreated, serious conditions resulting in fatality can develop.

Scheme 27: Synthesis of 1,4-oxathiin-S,S-oxide using Diels-Alder chemistry

The synthesis of these compounds begins with a Friedel-Crafts acylation with α-bromopropionyl bromide and aluminum chloride to form compound 67. Treatment with sodium hydride and 2-mercaptoethanol followed by a protection of the alcohol group makes sulfide 68. Epoxide ring opening on the sulfide is achieved using triazole and sodium hydroxide to form compound 69. Deprotection of the alcohol group using p-TsOH and methanol generates diol 70, which undergoes an intramolecular Mitsunobu to generate oxathiane 71. Oxidation with hydrogen peroxide and catalytic sodium tungstate produces 4,4-dioxo-oxathianes (72). Methylation using methyl iodide and sodium hydride affords the final product as a single isomer.
From our literature search, it seems that compounds possessing the oxathiin-S,S-dioxide core have value in both the agriculture and pharmaceutical industries. The side reaction observed from the attempt at cyclization of sulfone 481 sparked our interest in a conceptually new approach to production of such (het)aryl substituted oxathiins. The preparation of such heterocycles has been demonstrated but lack generalities. The second part of this thesis will describe the optimization of this reaction and expansion of the scope of the reaction, in particular, the kinds of aldehydes that are suitable for the chemistry. Finally, it may also be possible to gather some mechanistic information about the overall transformation.
CHAPTER 2:
INTRAMOLECULAR CYCLIZATION OF BENZYL ALKYNYL SULFONES
2.0 Results and Discussion

The initial goal of this project entailed further examination and expansion of the intramolecular cyclization of benzyl alkynyl sulfones. This was previously worked on by Selim Hossain who began his study on 2-iodobenzyl 1-propynyl sulfone (48a). After thorough optimization, a 66% yield of sulfone 49a was achieved under the conditions of 0.5 M substrate in dry THF and the introduction of 1 eq. of LDA at -78 °C with subsequent slow warming to ambient temperature (Scheme 29). Synthetic scope of the reaction was explored and it was found that the reaction tolerated various substrates on the aromatic ring, other aryl systems such as heteroaromatic substrates, and non-propynyl systems. Mechanistic studies indicate that non-propynyl systems may be better candidates for the cyclization study. The mechanism, determined from ReactIR™ studies and various experiments, begins with deprotonation at the propargylic position and is followed by a proton transfer to form a benzylic anion 50a. Cyclization occurs through delocalization of the anion into the aromatic ring and a conjugate addition onto the triple bond. Restoration of aromaticity drives the final proton transfer, forming anion 61a. Acid quench produces cyclized product 49a (Scheme 30). According to this proposed mechanism, anion 51a is the key intermediate in the cyclization reaction. If prior steps were circumvented, the cyclization could be better and more directly evaluated. Therefore, non-propynyl systems were synthesized with this in mind, where the terminal methyl groups were replaced by blocking groups such as t-butyl and phenyl ring. Unfortunately, t-butyl substrates did not yield the expected cyclized sulfone presumably due to steric hindrance. For terminal phenyl substrates, Hossain reported 57% yield of
cyclized material from 2-iodobenzyl alkynyl sulfone and 59% yield from benzyl 1-alkynyl sulfone (Scheme 31).

**Scheme 29:** Intramolecular cyclization of 2-iodobenzyl 1-propynyl sulfone \(48a\)

**Scheme 30:** Proposed mechanism for cyclization of benzyl sulfone \(48a\).

**Scheme 31:** Intramolecular cyclization of sulfones with terminal blocking groups
Due to the promising nature of this reaction, the initial goal of this M.Sc. project is to further explore the synthetic scope and mechanistic details of this base induced cyclization reaction using benzyl alkynyl sulfone. Specifically, the objective of this master’s thesis includes: (1) thorough optimization of the cyclization, (2) establish and study reaction rates and mechanism parameters, which include (3) probe for electronic substituent effects, (4) determine and establish regioselectivity of cyclization, and (5) expansion of the synthetic scope of the reaction by varying aromatic rings and ring substituents. This chapter will begin by describing the synthesis of starting materials, adapted from methods developed by previous group members, attempts to repeat and optimized previous works by Hossain and synthetic attempts for various substrates.

Benzyl alkynyl sulfone was chosen as the substrate for optimization since it possesses only one type of acidic proton located at the benzylic position (pKa ~ 23). The lack of substituents on either phenyl rings would ideally circumvent complications such as unnecessary proton transfers. The synthesis utilized was adapted from Hossain’s procedures and begins with the commercially available benzyl bromide (73). After a nucleophilic substitution reaction with potassium thiocyanate in acetonitrile, benzyl thiocyanate (74) was generated at 98% yield. To make sulfide 75, phenylacetylene was treated with 1.2 eq of nBuLi in THF at -78 °C and stirred for one hour. To that reaction mixture, benzyl thiocyanate in THF is added dropwise to the solution. The reaction was then warmed to room temperature and stirred overnight. Finally, oxidation with mCPBA (2.5 eq, 75-86% Aldrich) yields the final sulfone (76, scheme 32). Progress of each reaction was monitored by thin layer chromatography (TLC) and proton nuclear magnetic resonance (¹H NMR). Prior to quenching these reactions, analytical methods were
employed to confirm complete consumption of starting materials. Benzylic protons were utilized as diagnostic peaks to identify and confirm each transformation from benzyl bromide, to thiocyanate 74 to sulfide 75 and finally sulfone 76. On the $^{13}$C NMR spectrum, the benzyl and the triple bonded carbons of sulfone 76 can be seen at 64, 81 and 94 ppm respectively.

![Scheme 32: General synthetic pathway to starting materials](image)

In Hossain’s protocol to synthesize sulfone 76 from sulfide 75, a solution of $m$CPBA in dichloromethane was slowly added to benzyl 1-alkynyl sulfide in dichloromethane at 0 °C. Almost immediately, a heavy white precipitate formed and the reaction mixture had a slurry consistency requiring the mixture to be stirred efficiently with a magnetic stir bar. The reaction mixture was then slowly warmed to room temperature and stirred overnight. Once the reaction was completed, the solid was filtered off and the filtrate was concentrated in vacuo. The resulting residue was diluted with ethyl acetate and washed with sodium carbonate solution. Back-extraction was performed
to ensure all sulfone was recovered. Initially, while following Hossain’s protocol, no purification method was used until the final step of scheme 32 and 48% yield is the overall yield from the starting material, benzyl bromide. The sulfone was purified using flash column chromatography in hexanes and EtOAc. However, the yield recovered was relatively low and the column was unsuccessful at completely removing mCPBA or m-chlorobenzoic acid from the crude mixture. Trace amounts of mCPBA often co-eluted with the product, despite the drastically different rf values. With m-chlorobenzoic acid related contaminants in the mixture, further purification through recrystallization was difficult, low yielding and generally unsuccessful. Additional columns were required, which is time consuming and environmentally unfriendly due to excessive use of solvent. Due to these reasons, modification of the post synthetic protocol was needed for better yields and efficiency.

The preliminary literature search reveals that saturated solution of Na$_2$S$_2$O$_3$ is often used to quench peracetic acids. Using a general procedure as a guide, the reaction mixture was treated with sat. Na$_2$S$_2$O$_3$ and stirred for 30 minutes. However, with the treatment of sat. Na$_2$S$_2$O$_3$, yield decreased substantially to 25% over all yield. At this point, it is evident that excess mCPBA is the source of separation problem; we decided to lower the equivalence of mCPBA to 2.0 equiv. However, in doing so, we must also obtain pure sulfide substrate to ensure correct stoichiometric calculation. mCPBA is commercially available at $\leq 77\%$ from Aldrich and contains m-chlorobenzoic acid and water as stabilizers. Pure mCPBA cannot be sold as it can be detonated by shock or sparks can cause fire upon contact with flammable materials. To ensure we have exactly 2.0 equiv for the reaction, purification and calibration techniques were required to be
performed on the commercial material. Purified mCPBA is reasonably stable against
decomposition when stored in polyethylene containers at low temperature. However,
precautions have to be taken during purification process. For instance the removal of
dichloromethane needs to proceed as rapidly as possible because contact with glass and
heat cause rapid decomposition of the peracid or explosion. This requires the use of a
good vacuum as concentration must be done at very low temperature as well. In the end,
this modification of the procedure yielded better results (62% over all yield), but
concurrently introduced two extra purifications and one calibration step. It was decided
that the new protocol was not still feasible to carry out in large scale for multiple
substrates. While the yield had improved, further optimization was desired.

Hydrogen peroxide (30%), also a peracid, was tested as an oxidation candidate.
A major advantage in utilizing H$_2$O$_2$, unlike mCPBA, is it can be washed away with
water, allowing for a quick and effortless purification process. In spite of this, using this
protocol, the yield of sulfone was ~50%, approximately 12% lower than when mCPBA
was utilized. While the low yield obtained can be attributed to separation issues with by-
products, it is also possible that oxidation of the triple bond was also occurring and
contributed to the low yield. While the triple bond is less reactive to oxidation than the
benzylic sulfide, it is possible that there were side products forming during this reaction,
detracting from the overall yield. In the early 1970s, Ciabattoni and coworkers observed
several side products when performing a reaction with di-tert-butyl acetylene (77) and
mCPBA (Scheme 33). Product formation was believed to proceed through an oxirene
intermediate 78, likely to be in equilibrium with the corresponding oxocarbene (79,
scheme 34). 83-84
As previously described, commercially available mCPBA is a mixture of the peracid, the corresponding acid and water. Each component possesses differing solubilities and miscibility in dichloromethane. Exploiting this property, there was potential for separation to be obtained quickly. The peracid is very soluble in dichloromethane whereas the acid is quite insoluble at room temperature. Therefore, using dichloromethane as the solvent, the acid can be quickly filtered off through gravitational filtration and the filtrate can be immediately used for the reaction. In this method, one drawback is that the exact amount of mCPBA used is unknown. Therefore, the amount of mCPBA measured out initially is still 2.5 eq to ensure the stoichiometric requirement is met. Following the completion of the reaction, the acid was filtered off using vacuum filtration. To remove by-products from the mixture, primarily m-chlorobenzoic acid, the filtrate was cooled to -10 - 0 °C. Solids precipitate at low temperatures and were subsequently filtered off through a bed of Celite™. To eliminate any remaining m-chlorobenzoic acid from the solution, the organic layer was washed
with sat. Na₂CO₃ until white precipitate (m-chlorobenzoic anion) stopped forming in the aq. layer (usually requires 2 washes). The organic layer was combined and washed with water, brine and dried over MgSO₄. These modifications of the initial protocol brought the yield up to 67%.

Once the synthesis of starting material 48i was completed, the cyclization reaction was performed. Following the protocol outlined by Hossain, starting material was dissolved in THF at 0.05 M and treated with freshly made LDA (1.2 eq) at -78 °C. The resultant mixture was slowly warmed to rt, stirred for 45 minutes and worked up with NH₄Cl. However, the reaction did not yield the expected cyclized materials. Instead, the starting material was recovered at ~30% yield using column chromatography and the ¹H NMR spectrum of the crude mixture showed a large integration over the aromatic region suggesting polymerization of the starting materials occurred. To ensure proper laboratory techniques were utilized during the experiment, cyclization of another substrate, 2-iodobenzyl 1-propynyl sulfone was attempted. The experiment yielded 8-iodo-4-methyl-1H-isothiochromene S, S-dioxide (49a) in 62% yield, comparable to a 66 % yield obtained by Hossain. Hossain suggested the cyclization of the iodo-substrate may occur more readily. In his thesis, Hossain described a metal-halogen exchange reaction at the iodine bearing aryl carbon, which cyclizes intramolecularly by way of conjugate addition to form the cyclized product 49a. Therefore 2-iodobenzyl 2-phenylethynyl sulfone (48k) was synthesized. The synthesis followed that of benzyl 2-phenylethynyl sulfone with the initial requirement that 2-iodobenzyl bromide was synthesized through a bromination reaction with NBS and AIBN from the commercially available 2-iodotoluene.
Unfortunately, cyclization attempts with 2-iodobenzyl 2-phenylethynyl sulfone were also unsuccessful (Scheme 35). Thorough examination of laboratory techniques was performed, checking for potential water or contamination sources that could hinder cyclization. Needles, syringes and all glassware were oven dried, cooled in desiccators and purged extra carefully with inert gas prior to being used. Separate experiments were carried out using two different inert gases: argon and nitrogen. Due to its higher density compared to N₂, some believe Ar increases experimental yields by being slower to leak out of the apparatus and by forming a bed of gas directly over the compounds, protecting the reaction. The method of transfer of starting material into reaction flask was also changed. Instead of putting the starting material (a solid) directly into the flask, followed by the addition of THF, the solid was dissolved in THF prior to adding it into the reaction flask to minimize exposure to atmospheric air and therefore moisture.

Scheme 35: Intramolecular cyclization attempt for substrate 48k

The source of anhydrous solvents is a communal solvent purification system. Other users made several complaints about the integrity of the dispensing system and this prompted an investigation of whether there was a water source in the reaction. Using Karl Fisher titration to determine the amounts of water in a sample of THF, we were able to invalidate previous complaints. Next on the list of investigative parameters was the base
itself. Diisopropylamine was distilled following protocols outline by purification of laboratory chemicals. Several LDA preparation protocols were employed at various temperatures and reaction times to ensure LDA has been formed, and different calibration methods to ensure the effective concentration of LDA agreed with the calculated values were employed. One of the titrations methods used was a procedure developed by Chong and coworkers. LDA was stochiometrically titrated against N-benzylbenzamide (80) to a blue color end-point. While N-benzylbenzamide (80) is commercially available, for economical reasons, it was synthesized from benzoyl chloride (81), triethylamine (82) and benzylamine (83, Scheme 36). When one equivalent of base is added to the solution of N-benzylbenzamide, the solution remains colorless, though lithium exchange has taken place. Upon beginning the addition of the second equivalent of base, a deep blue color is developed and persists and at -20 °C, indicative of the second end point (Scheme 37). The experiments were repeated three times, to eliminate any outliers. After performing the necessary calculations, it is evident that the source of error is not from LDA.

![Scheme 36: Synthesis of N-benzylbenzamide (80)](image)
After exhausting numerous possible sources of error in calculations and practical work, with all efforts yielding only the starting material and polymeric material, it was decided that work should go forward with the optimization, hoping to recreate the conditions in which the reaction proceeded as desired. There were a number of criteria we aimed to evaluate. Given the nature of intramolecular reactions, the resulting yield largely depends on the concentration of substrate; a balance between not diluting the solution enough and excessive dilution must be found to achieve optimal results. Concentration is likely the biggest contributor toward the polymeric material recovered from failed intramolecular cyclization attempts. The polymeric materials can be seen on $^1$H NMR spectrum of the crude reaction mixture, where there is an abundance of aromatic peaks, but no other diagnostic protons. Formation of polymeric materials can be attributed through first a deprotonation at the benzylic position. Instead of delocalization into the aromatic ring, as needed for intramolecular cyclization, anion 50 attacks the adjacent molecule in a Michael-addition manner, creating intermediate 81. A proton transfer from the benzylic to the vinylic position creates another benzylic anion leading to the propagation of the chain polymerization (Scheme 38). By lowering the concentration and therefore the frequency of collisions between starting materials, this should allow for higher rates of intramolecular reaction. Hossain found that the best concentration for

**Scheme 37: Titration of LDA to a blue end point**

![Scheme 37: Titration of LDA to a blue end point](image-url)
cyclization by way of indirect deprotonation was 0.05 M. Despite sound theoretical justifications, decreasing concentrations did not prove to be beneficial. It did, however, work in decreasing the rate of polymerization and slowing down the consumption of starting material.

According to the proposed mechanism to form polymers from the starting material, effective concentration plays a pivotal role. Another experiment was designed to minimize the effective concentration. Instead of having the starting material in the reaction flask, followed by the addition of base, the reaction begins with the base in the reaction flask, followed by the slow introduction of starting sulfone \textit{48i}. The sulfone should deprotonate immediately by the excess amount of base and then cycle intramolecularly. Two reactions were performed at different temperatures: one was at -78°C and slowly warmed to room temperature following the slow addition, and another

\textbf{Scheme 38: Chain Polymerization of benzyl alkynyl sulfone \textit{48i}}
occurred at 0 °C and slowly warmed to room temperature. Unfortunately, neither produced the intramolecular cyclized product. The last two studies were performed where both the base and starting sulfone were slowly introduced to a solution at THF at 0 °C and a refluxing temperature. Again, only polymers and some starting sulfones were recovered.

Moving forward with other parameters, base identity was the next criteria. The estimated pKa of benzylic proton in substrate 48i is ~22-25. pKa’s of benzyl sulfones when R = alkyl group are ~23-25 (Figure 8). In our substrate R = phenyl; it is possible that its pKa value will be on the lower end of 22-25 due to the electron withdrawing effect of the triple bond. LDA was the optimized base for 2-iodobenzyl 1-propynyl sulfone systems (48a, R³ = methyl), where there were two available deprotonation sites. However, when comparing pKa values, the conjugate acid of LDA has pKa of 36 much higher than that of our substrate. Since non-propynyl systems (R³ = phenyl) direct deprotonation at the benzylic site, other bases can be used and do not need to possess steric characteristics. For instance, ‘BuOK may be a better candidate than LDA as it proved effective in the cyclization of sulfide substrates (pka = 30.8 in DMSO), suggesting it should be basic enough for the sulfones at hand. Other strong bases we sought to explore were: ‘BuLi and NaH. Unfortunately, several trials with varying equivalents of these bases did not yield the desired product (Table 5). Again, polymeric materials and starting materials were recovered.
Figure 8: pKa range of benzyl sulfones

Table 5: Various base/solvent combinations utilized in the optimization attempts

<table>
<thead>
<tr>
<th>Base (equiv)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaH (1.0)</td>
<td>CH₃CN</td>
</tr>
<tr>
<td>NaH (1.5)</td>
<td>CH₃CN</td>
</tr>
<tr>
<td>tBuOK (0.5)</td>
<td>CH₃CN and THF</td>
</tr>
<tr>
<td>tBuOK (1.0)</td>
<td>CH₃CN and THF</td>
</tr>
<tr>
<td>tBuOK (1.5)</td>
<td>CH₃CN and THF</td>
</tr>
<tr>
<td>LDA (0.5)</td>
<td>THF</td>
</tr>
<tr>
<td>LDA (1.0)</td>
<td>THF</td>
</tr>
<tr>
<td>LDA (1.5)</td>
<td>THF</td>
</tr>
<tr>
<td>nBuLi (0.5)</td>
<td>THF</td>
</tr>
<tr>
<td>nBuLi (0.75)</td>
<td>THF</td>
</tr>
<tr>
<td>nBuLi (1.0)</td>
<td>THF</td>
</tr>
<tr>
<td>nBuLi (1.5)</td>
<td>THF</td>
</tr>
<tr>
<td>nBuLi (2.0)</td>
<td>THF</td>
</tr>
</tbody>
</table>
In terms of temperature, it is currently unclear whether the rise in temperature from -78 °C to room temperature is necessary for cyclization. It is also unclear which step of the reaction is promoted by the temperature increase. By doing temperature studies, we were hoping to obtain the required temperature for cyclization and understand which step of the reaction benefits the most from the temperature change. If optimal cyclization temperature is lower than room temperature, it could be possible to prevent or minimize side reactions. To obtain optimal cyclization temperature, we monitored the reaction while slowly raising the temperature from -78 °C to reflux. At each 10 °C increments, a sample was taken out, worked up and concentrated. Each sample was analyzed by NMR and examined for the appearance of vinylic proton in the cyclized material. This method should indicate if and at what temperature there are substrate losses to polymerization or by-product formation.

Once more, experimental results were examined and probed for possible sources of error. The syringes and needles used to extract samples from the reaction mixture were oven-dried, cooled in a desiccator and purged with inert gas. However, nine samples were taken out of the apparatus, puncturing the septum, which could lead to experimental errors and chance of contaminations. Furthermore, the experimental design does not allow the reaction time to proceed at quenching temperatures. Therefore, nine experiments were carried out at different temperatures, also in 10 °C increments and monitored for consumption of starting materials. Unfortunately, the temperature studies results mirrored that of the concentration study. Lower temperature led to less polymerization, but none of the cyclized product. High temperature, which should promote delocalization of anion 50 into the aromatic ring, instead yield only polymeric
Regardless, no positive results were obtained and at this point, this project was temporarily halted.

During the cyclization attempts, syntheses of other starting materials were performed co-currently. Using the protocol described, several other sulfones with various substituents on the phenyl ring were synthesized from benzyl bromides (Table 6).

**Table 6: Synthesis of sulfones benzyl bromide and the respective yields**

<table>
<thead>
<tr>
<th>Substituent</th>
<th>SCN (%)</th>
<th>S (%)</th>
<th>SO₂ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-H</td>
<td>98ᵃ</td>
<td>87ᵃ</td>
<td>78ᵇ</td>
</tr>
<tr>
<td>4-Bromo</td>
<td>100ᵃ</td>
<td>62ᵃ</td>
<td>44ᵇ</td>
</tr>
<tr>
<td>4-CH₃</td>
<td>100ᵃ</td>
<td>90ᵃ</td>
<td>90ᵇ</td>
</tr>
<tr>
<td>3-Bromo</td>
<td>89ᵃ</td>
<td>62ᵃ</td>
<td>46ᵇ</td>
</tr>
<tr>
<td>2-Iodo</td>
<td>82%</td>
<td>67%</td>
<td>87ᵇ</td>
</tr>
<tr>
<td>4-OCH₃</td>
<td>91ᵃ</td>
<td>91ᵃ</td>
<td>65ᵇ</td>
</tr>
<tr>
<td>3-Cl</td>
<td>92%</td>
<td>83ᵃ</td>
<td>78ᵇ</td>
</tr>
<tr>
<td>4-NO₂</td>
<td>100ᵃ</td>
<td>90ᵃ</td>
<td>64ᵇ</td>
</tr>
<tr>
<td>4-CN</td>
<td>85ᵃ</td>
<td>88ᵃ</td>
<td>85ᵇ</td>
</tr>
</tbody>
</table>

ᵃ Yields of thiocyanates and sulfides were calculated from crude reaction mixtures (little impurities)

ᵇ Yields of sulfones were calculated from pure, isolated compounds
Initially, the plan for this thesis was to extend the reaction to other substrates once a better understanding of the intermolecular cyclization has been obtained. In particular, the reaction would be extended to heteroaromatic substrates, such as the pyridine derivative 82. If the substrate undergoes the expected cyclization, where the nitrogen of the pyridine ring undergoes the Michael addition, compound 83 formed would be the first member of a new family of heterocycles. It follows that other nitrogen heterocycles such as thiazoles, oxazoles and isoxazoles could also be employed to create novel products.

**Scheme 39:** Cyclization of pyridine derivative 82 to form a novel heterocycle

In attempts to synthesize this substrate, the general synthetic pathway described for previous substrates was employed (Scheme 32). The synthesis begins at 2-pyridinyl methyl bromide (84) reacting with thiocyanate to form 2-pyridinylmethyl thiocyanate (85). A nucleophilic attack by phenylacetylide anion produces the resulting sulfide. Oxidation of sulfide to sulfone, however, proved to be more difficult than the phenyl derivatives. Several procedures were utilized. All reactions yielded an intractable mixture. It was strongly suspected that the nitrogen in pyridine was also being oxidized in preference to, or in addition to the sulfur. Several sources report the oxidation of the nitrogen on the pyridine ring could be obtained using mCPBA and H$_2$O$_2$. Therefore, the reaction was attempted under acidic conditions to protect the nitrogen, using acetic acid
as solvent. Other oxidants explored were: H$_2$O$_2$ with tungstate as catalyst, NaIO$_4$, mCPBA under a different solvent such as MeOH,\textsuperscript{87} and mCPBA used concurrently with Na$_2$CO$_3$. In total, the following reagents were used: mCPBA, mCPBA with acetic acid, mCPBA with HCl, oxone, H$_2$O$_2$ with acetic acid, H$_2$O$_2$ with Na$_2$WO$_4$/H$_2$O. Unfortunately, none yielded the desirable sulfone.

Scheme 40: Synthetic pathway towards

A quick literature search revealed that not only m-CPBA oxidation on substrates possessing an amine group is not an efficient route, there has been several reports where amine plays a pivotal role in providing an alternative product at fair to high yields.\textsuperscript{88-89} Recently, Cui, Zhang, Peng and Zhang exploited the oxidation of amine to nitrones and utilized it in the oxidation of alkynes to generate tetrahydrobenz[b]azepin-4-ones (87, Scheme 41).\textsuperscript{88} Initially, their research focused on the gold catalysis reaction. However, to their surprise, alkynyl substrates with a terminal electron-withdrawing group underwent cyclization without any gold catalyst. Despite alkynes are generally inert to mCPBA oxidation at mild conditions, an electron-withdrawing group or gold activation was enough to facilitate the relaying of oxygen from mCPBA to the tethered triple bond (R” = EWG). In one particular example in their paper, most comparable to our substrate, R” = 4-nitrobenzene (44%).
Scheme 41: MCPBA oxidation utilized in the generation of tetrahydrobenz[b]azepin-4-ones (87)

In our case, it is possible that oxidation of mCPBA (used at 2.5 equiv) of our sulfide substrate was oxidize to its corresponding sulfoxide or sulfone (EWG groups). Concurrently, the nitrogen in pyridine was being converted to N-oxide. The proximity of these groups allow for a 7-membered transition state, mirroring the mechanism as proposed by the Zhang group (Scheme 42), the result is a reactive carbene which could undergoes a multitude of reactions upon warming to rt, providing an intractable mixture.

Scheme 42: Proposed mechanism of the oxidation of 2-pyridinylmethyl 1-propynyl sulfide using MCPBA
Another intended path for this reaction is to extend this reaction to a similar system, a conjugate ketone. Conjugate ketones are electron withdrawing groups known to undergo Michael addition readily and can be envisioned to undergo the proposed mechanism to bring about cyclization (Scheme 43). The synthesis of 1,4-diphenyl-3-butyn-2-one (89) begins with the coupling of phenylacetylene (90) with phenylacetaldehyde (91) and ends with an oxidation of resulting alcohol 92 (Scheme 44).

![Scheme 43: Cyclization envisioned for conjugated ketone substrate](image)

![Scheme 44: Synthesis of 1,4-diphenyl-3-butyn-2-one (89)](image)

The initial conditions tested were 0.05 M in THF using 1.0 equiv of LDA. Unfortunately, the reaction yielded only the starting materials and some unidentified materials presumably polymers. The crude reaction mixture was screened by $^1$H NMR for diagnostic peaks of the expected products, such a vinylic peak expected in the 5.5-6.5 ppm range. When the product wasn’t found, no further investigation was performed on
the crude mixture as TLC showed numerous peaks. One hypothesis is that lithium enolates were formed when LDA was added to the reaction mixture. Unlike the sulfone derivatives, the benzylic anion can delocalize to two directions, one into the ring and the other to form lithium enolate. This enolate is able to undergo an aldol formation with itself via a cyclic mechanism in the coordination sphere of the lithium atom. The product is initially the lithium alkoxide of the aldol, which goes on to give the aldol product after aqueous work-up (Scheme 45). This would explain the large peaks over the aromatic regions in $^1$H NMR, which was initially attributed to polymerization. On a second look at the crude NMR, one can see a small peak at ~2.2 ppm, which could indicate an aldol proton.

Scheme 45: Aldol reaction of substrate 89

To eliminate the formation of lithiated enolate, crown ethers were introduced to the reaction mixture alongside with LDA. Crown ethers are simply large polyether rings with electron-rich cavities full of oxygen lone pairs allowing for ionic interaction with cations. While the concept is simple, it is quite brilliant as different crown ethers can be used selectively for different cations. The most effective crown ethers would have cavity
diameters that are comparable to that of the ionic radius of the desired cation. This highly selective structure specific interactions was works done by Charles Pedersen (Du Pont), Donald Cram (UCLA), and Jean-Marie Lehn (France), collectively earned them a Nobel Prize in 1987. Lithium cation has a radius of 1.39 Å and therefore would bind strongest to 12-crown-4 (1.2-1.4 Å diameter). Unfortunately, the addition of 12-crown-4 did not lead to success even at refluxing temperatures. It is likely that due to the rigid angle of the triple bond, orbital overlap was just not feasible. To counter this problem, a trans-double bond can replace the triple bond. This would bring the tethering side closer to the reaction site and form a 6-membered ring transition state, which is highly energetically favourable.

![Transition state of triple-bond substrate vs. double-bond substrate](image)

**Figure 9:** Transition state of triple-bond substrate vs. double-bond substrate

### 2.1 Future Work

Isothiochromene 2,2-dioxide skeleton has been incorporated in the synthesis of coumarin isoteres and are currently being investigated as the inhibitors of gyrase B. Products of intramolecular cyclization of benzyl alkynyl sulfones can be a source of carbocycles after the extrusion of SO₂. The chemistry of sulfones has been extensively studied and widely exploited in organic synthesis for the past several decades. As
described in this proposal, their roles as organic synthetic precursors are evidently extensive due to their versatility. This cyclization is another reaction that utilizes the sulfonyl group to facilitate carbon-carbon formation. Therefore, it is hoped that this study will provide a general understanding of this base induced cyclization and more importantly reveal useful mechanistic information that can be applied more broadly in synthesis.

Despite failing to find the conditions optimal for the intramolecular cyclization of benzyl alkynyl sulfones, there are other venues that can still be explored and studied. For instance, some solvents facilitate in \( \pi \)-stacking interactions, bringing the two aromatic rings closer in proximity in solution. This would also increase the proximity of reaction sites on the same compound.\(^{93-94}\) This, in theory, should allow for higher chance of intramolecular cyclization, while decreasing intermolecular reactions, such as polymerization.

For the pyridine-based substrate, by utilizing different oxidizing agents that selectively reacts with sulfides instead of the nitro-group, it is possible to obtain the corresponding sulfone. For instance, in the pursuit of understanding the structure-activity relationship of the sulfone moiety in a series of morpholinopyridines, the Finlay group sought to find a one-pot sulfide to sulfone oxidation method that selectively oxidize sulfide groups and minimize over-oxidation problems of N-oxidation of the pyrimidine ring. Using sodium permanganate, a known mild and selective oxidant for sulfoxides to sulfones in combination with mCPBA, they were able to achieve a selectively oxidized product at fair to good yields (Scheme 46).\(^{95}\) The condition tolerated various R groups on the sulfone moiety, including amides, aromatic rings with electron-donating and withdrawing substituents, ethers, cyano groups, as well as amines. This is a very
promising method that our pyridinyl substrate can utilize to form the corresponding sulfone. Following the sulfone synthesis, it can undergo the proposed intramolecular cyclization. The intramolecular reaction once established, would extend to the pyridine derivative, as well as other heterocycles, such as thiazoles, oxazoles and isoxazoles to create novel products.

Scheme 46: Selective oxidation of sulfide over amine-groups

In addition, while the pursuit of extending the reaction from benzyl alkynyl sulfones to the corresponding carbonyl substrate was abandoned, it is worth noting that the lack of success is likely attributed to the difference in the structure of carbanions of enolates and sulfonyl anions. As discussed in the preceding chapter, sulfonyl anions are thought to possess a pyridinyl structure, whereas carbanions of enolates have trigonal planar configurations. The significant angle difference is likely to be the culprit for an unreacted substrate, with some polymerization. Instead of having a triple bond, a trans-double bond should be in placed instead. This will bring the group closer to the aromatic ring, primed for a highly favorable 6-membered transition state (Scheme 47). Once the intramolecular cyclization can be established, expansions to other groups and an analogy for carbonyl substrate could bring about interesting studies and provoke fascinating questions, including a novel cyclic compound.
Scheme 47: Cyclization of carbonyl substrate with a trans-double bond in place of the triple bond
CHAPTER 3:
THE SYNTHESIS OF OXATHIIN S,S-DIOXIDES
3.0 Project introduction

As a part of the investigation of the anionic chemistry of benzyl alkynyl sulfones, a novel preparation of 5,6-dihydro-1,4-oxathiin S,S-dioxides was uncovered. As previously discussed in sections 1 and 2.2, during the pursuit of the scope of the aforementioned intramolecular cyclization chemistry of benzyl alkyl sulfones, it was discovered that intramolecular cyclization was severely hindered by placement of a t-butyl group on the alkyne opposite the sulfone. Whereas 48a was found to form in 59% yield by intramolecular cyclization, compound 48i was not observed at all. Instead, an unexpected compound was isolated as the major product (recall Scheme 22). After extensive characterization, the compound isolated was identified to possess an oxathiin-S,S-dioxide core. Coincidentally, 1,4-oxathiin based compounds display potent fungicidal activities against a number of pathogens, with potential expansion of applications in pharmaceutical and agrochemicals. The chemical pathway piqued our interest, given that the product’s mode of formation may be adapted toward developing a conceptually novel synthetic approach to het(aryl)substituted oxathiins. This chapter of the thesis will describe our efforts to develop and optimize the reaction, and includes an assessment of the breadth of the reaction and a description of efforts to minimize an unwanted by-product.

The synthetic strategy toward oxathiin-S,S-dioxide compounds, illustrated below in scheme 48, was developed utilizing retrosynthetic analysis previously described in chapter 1. Two disconnections can be made to form 2-iodobenzyl alkynyl sulfone (48a) and o-iodobenzaldehyde (55). The in-situ formation of benzaldehyde is the working
hypothesis. To assess this theory, benzaldehyde was added to a mixture of sulfone 48i and LDA and as expected, 1,4-oxathiin-S,S-dioxide was generated (Scheme 49).

\[
\begin{align*}
\text{Scheme 48: Retrosynthetic analysis of the unexpected product 54}
\end{align*}
\]

The first attempt gave a modest 24% yield; while it served as a proof-of-principle basis for the mechanism, the reaction evidently required optimization. The trial reaction conditions were as follows: \(n\text{BuLi (1.0 equiv)}\) was added to a solution of substrate in THF (1.0 equiv, 0.05 M) at -78 °C. The reaction mixture was allowed to warm to r.t. and stirred for 0.5 hours. Freshly distilled benzaldehyde in THF (2.0 equiv, 0.40 M) was then added to the reaction mixture which was left to warm up to room temperature overnight.
After no change was observed on TLC, the reaction was quenched. The mechanism of the reaction is thought to begin with a deprotonation of a benzyl alkynyl sulfone (48i), creating an anion that is subsequently captured by benzaldehyde. Cyclization by way of an intramolecular conjugate addition to the triple bond completes formation of the heterocycle (Scheme 50). Therefore, the key to establishing the chemistry is to intercept the benzyl anion prior to intramolecular cyclization or competitive polymerization. The goal is to determine the conditions that satisfy these demands.

**Scheme 50: Mechanism of the formation of oxathiin 58**

Various criteria were under examination: temperature, concentration, timing and base choices. Base identity was the first to undergo inspection (Table 7). Judging by the outcome of the reactions, nBuLi was preferred as well as the most convenient and was therefore used in future experiments. The initial trial reaction proceeded at 1.0 eq. of BuLi, but a significant amount of starting material remained in the reaction mixture following the work-up. We hypothesized that in order to fully deprotonate the benzylic
proton, additional time of exposure to base was required. Another experiment was performed where the mixture was allowed to stir for 2 hours instead of only 30 minutes following the addition of $n$BuLi. More consumption of starting material was found, though a significant amount of starting sulfone still persisted in the crude mixture. To push for more consumption of sulfone 48i, higher equivalents of base were used. Experiments addressing the variation of base equivalents were performed and tabulated (Table 7). With increasing equivalents of base, more starting material was consumed but unfortunately, the yield of polymeric materials also increased. It seemed that the higher equivalents of base encouraged the competitive polymerization, not the desired cyclization. However, the benefit seemed to outweigh the disadvantage at 1.2 equivalents of $n$BuLi, where more starting materials were consumed and higher yields of the desired product were recovered.

At this point, the experimental procedure was still proceeding at -78 °C and following the addition all reagents, the reaction was slowly warmed to room temperature and stirred overnight. Based on Hossain’s research, intramolecular cyclization is driven by the rise of temperature to room temperature. We believe the key to establishing the chemistry is to intercept the benzyl anion prior to its intramolecular cyclization. In order to circumvent the intramolecular cyclization, several experiments were carried out at temperatures below room temperature. They were performed at various temperatures in increments of 10 °C in order to probe the incorporation of aldehyde (Table 8). Lower temperatures appeared to hinder cyclization as crude mixtures still contained significant starting material (Entry 1 - 3). However, higher temperature facilitated formation of polymeric materials and what was later identified as a by-product (Entry 7 - 10). The
optimal temperature for intermolecular cyclization was found to be -35 °C, providing product in 54% yield and a balance between hindering polymerization and yet providing enough energy for deprotonation and aldehyde attack.

Table 7: The study of base identity and equivalents effect on yields

<table>
<thead>
<tr>
<th>Base</th>
<th>Equivalents</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaH</td>
<td>1.2</td>
<td>5% (NMR)</td>
</tr>
<tr>
<td>LDA</td>
<td>1.2</td>
<td>48%</td>
</tr>
<tr>
<td>tBuOK</td>
<td>1.2</td>
<td>39%</td>
</tr>
<tr>
<td>BuLi</td>
<td>1.0</td>
<td>50%</td>
</tr>
<tr>
<td>BuLi</td>
<td>1.2</td>
<td>54%</td>
</tr>
<tr>
<td>BuLi</td>
<td>1.5</td>
<td>42%</td>
</tr>
<tr>
<td>BuLi</td>
<td>2.0</td>
<td>36%</td>
</tr>
</tbody>
</table>

Examination of $^1$H NMR spectra of the crude reaction mixtures of higher temperature experiments showed a large integration over the aromatic region, indicating the presence of polymeric materials. NMR data also contains a large peak at ~ 4.48 ppm, corresponding to the benzylic protons of sulfone 48i. Thin column chromatography revealed 3 major components in the crude mixtures, with very close $R_f$ values. Several
trials were performed to establish the optimal separation conditions. The best separation that could be obtained was 70% hexanes and 30% ether, where the 3 spots had very close $R_f$ values: 0.08, 0.13 and 0.20. Nevertheless, we were able to isolate and identify the first band as the product by $^1$H and $^{13}$C NMR analysis. Specifically, the lone vinylic proton was evident as a sharp singlet in the 5.85-6.46 ppm range. Two doublets present in the 5.81-6.38 and 4.81-5.57 ppm regions denote two lone methine protons. The coupling constant was found at 11.7 Hz, in keeping with trans coupling (10-14 Hz, 180°).^96

The two latter bands on the TLC plate were more difficult to separate and assess. The third band on the TLC plate was isolated and through co-spotting and NMR analysis, and was confirmed to be starting material. Isolation of the middle peak was much more difficult; during separation via flash column chromatography, this band co-eluted with the starting material in earlier fractions and co-eluted with the product in the latter fractions. This compound contained NMR data that was similar to that of the starting material; possessing the only diagnostic peak at 4.43 ppm. At first glance, it was dismissed to be the starting sulfone. However, with the analysis of TLC showing two distinct bands, it was clear a second compound was present.

For the time being, optimal temperature for intermolecular cyclization was decided to be -35 °C, which provided 54% yield of product from sulfone 48i. At this point, the experiment proceeds with the addition of base at -78 °C, followed by a wait period of 2 hours to ensure all starting material has been sufficiently deprotonated before the rise in temperature to -35 °C. Despite being left to stir overnight, starting material was still recovered. To this point, there was no condition that consumed all of the starting material. As such, experiments were performed to push the limit of the reaction: one
where the reaction was raised up to 50 °C and another where the reaction was kept at -35 °C for over 4 days. Unfortunately, neither mixture produced any desired results since both conceded very poor yields of ~5%, as estimated from NMR analysis of the crude reaction mixture.

Table 8: The study of temperature effect on yields

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-65 °C</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>-55 °C</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td>-45 °C</td>
<td>38%</td>
</tr>
<tr>
<td>4</td>
<td>-35 °C</td>
<td>54%</td>
</tr>
<tr>
<td>5</td>
<td>-25 °C</td>
<td>40%</td>
</tr>
<tr>
<td>6</td>
<td>-15 °C</td>
<td>32%</td>
</tr>
<tr>
<td>7</td>
<td>0 °C</td>
<td>37%</td>
</tr>
<tr>
<td>8</td>
<td>10 °C</td>
<td>22%</td>
</tr>
<tr>
<td>9</td>
<td>20 °C</td>
<td>15%</td>
</tr>
<tr>
<td>10</td>
<td>Reflux</td>
<td>5% (NMR)</td>
</tr>
</tbody>
</table>
At this point, it was felt that optimization was relatively adequate and it was time to examine the reaction with other substrates. A number of sulfones were conveniently available in the laboratory, so they were the next substrates to undergo study. Whilst the reaction proceeded for several substrates, it occurred in poor to fair yields (Table 9). Similar separation problems were encountered and played a pivotal role in our inability to obtain high yields. In some cases, flash chromatography columns had to be performed twice to separate all of the products from the crude mixture. 2-Iodobenzyl-3,3-dimethyl-1-butynyl sulfone (48l) when reacted with benzaldehyde (57) yielded oxathiin 93 in 39% (Scheme 51). The presence of a large bulky group at the end of the triple bond is likely culpable for the lower yield. Crowding about the triple bond carbon poses a large steric hindrance for the oxo-anion, likely limiting its ability to attack.

<table>
<thead>
<tr>
<th>Compound #</th>
<th>Structure</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>58</td>
<td><img src="image58.png" alt="Structure" /></td>
<td>54</td>
</tr>
<tr>
<td>93</td>
<td><img src="image93.png" alt="Structure" /></td>
<td>39</td>
</tr>
</tbody>
</table>
Scheme 51: Formation of oxathiin 93
A number of aldehydes were utilized, with benzaldehyde remaining as the best aldehyde for the reaction while the butyraldehyde proved unsuitable for the reaction. The \( \alpha \)-proton of butyraldehyde has a pKa of 17 (DMSO, Bordwell),\(^{28}\) which can act as a kinetic electron sink and proton exchange is likely to occur before the benzylic anion can attack the carbonyl. Regardless, several other substrates also failed to obtain reasonable yields, so we decided to re-address reaction optimization.

Each experiment, up to this point, has been qualitatively monitored by TLC. Following the work-up, the crude mixture was examined by \(^1\)H NMR spectroscopy for the presence of the cyclized product. Integration values were exploited to calculate the approximate ratios between starting material, desired cyclized product and polymeric materials. From previous experiments that were designed to push the limits of the reaction, it was known that after 4 days of reaction time, lower product yield was recovered. This indicates that the product was decomposing following its synthesis under the reaction conditions. While following the reaction by TLC, the focus had always been the disappearance of starting materials. However, the starting materials remained regardless of time and after no change to the reaction was observed, the reaction was quenched. However, since TLC only offered qualitative not quantitative knowledge, an opportunity to further examine the reaction may have been overlooked. Hence it was decided to revisit the optimization experiments, with a plan to observe the reaction via \(^1\)H NMR instead of following the reaction by TLC. Table 10 summarizes the findings and compares the reaction time to ratio of starting sulfone, desired product, and by-products with relations to mass recovery. Mass recovery is calculated based on the elimination of polymeric materials by flash column chromatography. The ratio between starting sulfone,
oxathiin-S,S-dioxide, and by-product is calculated based on proton integration values of the NMR spectra obtained from crude mixtures.

Based on these findings, the cyclized product was undergoing decomposition over time and 6 hours was the optimal reaction time. What is more interesting is that with the decrease of cyclized material, an increase in by-product formation was observed. This insinuates that the by-product originated from the cyclized material. Inferring from similar compounds, allylic sulfone, which has pKa of 22.5 and benzyl sulfones (pKa = 22.3, Bordwell), one can anticipate these compounds would be under acid-base equilibrium. A proton transfer is likely to occur from intermediate 99 to form compound 100. An elimination reaction could undergo to form enolate 101 (Scheme 52). Hydrogens that are α to a carbonyl and a sulfone group are documented to have pKa values as low as 10.1 (DMSO). This enolate would effectively act as an electron sink, leading to the breakdown of the cyclized product.

![Scheme 52: Proposed mechanism for by-product](image)
Table 10: The effect of time on the production of product, by-product, starting material recovery and over all mass recovery

<table>
<thead>
<tr>
<th>Time of reaction</th>
<th>Equivalency of Mass recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Starting materials</td>
</tr>
<tr>
<td>45 min</td>
<td>2.0</td>
</tr>
<tr>
<td>4 hours</td>
<td>0.8</td>
</tr>
<tr>
<td>6 hours</td>
<td>0.3</td>
</tr>
<tr>
<td>18 hours</td>
<td>0.1</td>
</tr>
<tr>
<td>4 days</td>
<td>0</td>
</tr>
</tbody>
</table>

This hypothesis relieved us of a number of unassigned peaks in the NMR of the crude mixture. Aside from the starting sulfone and desired product peaks found, unexplained peaks at 6.68 and 4.37 ppm from the crude mixtures were very curious. Initial glances hinted at the intramolecular cyclization product with a peak at 6.68 ppm, and starting material at 4.37 ppm. Isolation of the side product was difficult, as previously described and this side product often co-eluted with the starting sulfone, or with the desired product. Regardless, the co-elution made it possible to dismiss that 4.37 ppm belonged to the starting material. In the proton NMR of the side product and starting material mixture, 4.37 ppm and 4.51 ppm were both observed. In addition, integration at 4.51 ppm is usually twice that of the peak at 6.68 ppm, further supporting our hypothesis.

Besides optimization, we were concurrently working toward the identification of the by-product of the reaction. Based on $^1$H NMR of the crude material, taking account of
the product and starting material peaks, the remaining constituents are presumed to be the by-product. There are 2 H’s at the 4.43 ppm, 1 H at 6.63 ppm and 15 H’s in the aromatic region. This data is in agreement with the proposed decomposition mechanism. Unfortunately, several attempts to try and isolate the by-product have been unsuccessful. The by-product, with its keto-sulfonyl group can be an important synthetic target and has been synthesized and isolated through numerous methodologies. Despite that, alkenyl keto-sulfones are less known and subsequently, their stabilities are also not known. It’s possible that the double bond changes the chemistry, causing decomposition to occur rapidly, especially under flash chromatography conditions. Silica gel was the adsorbent utilized for the separation and are known to be a weak Lewis acid. It is likely that under this condition, the carbonyl group was weakly coordinated with silica gel resulting in a keto-enol equilibrium. Since conjugation can occur through a sulfonyl group, the system is highly conjugated and primed for various chemistry to take place.

In a paper by Schwan and co-workers, a similar equilibrium was described for the preparation of alkenylsulfinylmethyl ketones (Scheme 53).97 Ironically, in their pursuit for these substrates, isolation proved highly difficult due to chromatography-induced rearrangement to 1,4-oxathiin S-oxide (104). A reaction between sulfinyl chloride 105 and TMS enol ether 106 was expected to yield 1-alkenylsulfinylmethyl ketone 107. However, despite observing the characteristic peaks of compound 107 in the NMR spectrum of the crude mixture, cyclic isomer 104 was obtained instead. The cause for the rearrangement was attributed the acidity of the hydrogens between two strong electron withdrawing groups as well as the β-keto sulfoxide groups’ tendency to enolize.97 In our
substrate, sulfones are in place of sulfoxides, but a similar equilibrium can be envisioned for the sulfone derivative.

![Chemical Structure]

**Scheme 53:** 1-alkenylsulfinylmethone synthesis and rearrangement

With the theory of by-product formation, the $^1$H NMR data of the crude mixtures of previous base optimization experiments was revisited and a trend was recognized. There was a steady increase of by-product concurrently with the increase in base equivalents; by-product formation is encouraged by the increase in base. Recalling the pKa discussion in the previous paragraphs, where cyclized anion 101 has pKa values similar to that of benzyl sulfone 48i, there is potential for cyclization with catalytic base or sub-stoichiometric amounts. Anion 101 could theoretically deprotonate the starting material until the reaction goes to completion. Based on this theory, we decided to reevaluate the effects of base equivalents on the reaction (Table 11). The optimal equivalents of base were found to be 0.5 of $n$BuLi by $^1$H NMR analysis. The amount of by-product in the crude mixture was substantially diminished due to the reduced base equivalents. Other bases were studied for comparison; tBuOK and NaH gave small 5% yields at 0.5 equiv, but LDA continues to provide comparable results to that of $n$BuLi. This will be useful for substrates that are incompatible with BuLi due to the risk of undergoing a metal-halide exchange.


Table 11: Further optimization: base identity, base eq. and aldehyde eq.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Equivalents</th>
<th>Aldehyde equivalents</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BuLi</td>
<td>1.0</td>
<td>2.0</td>
<td>58%</td>
</tr>
<tr>
<td>2</td>
<td>BuLi</td>
<td>0.7</td>
<td>2.0</td>
<td>23%</td>
</tr>
<tr>
<td>3</td>
<td>BuLi</td>
<td>0.6</td>
<td>2.0</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td>BuLi</td>
<td>0.45</td>
<td>2.0</td>
<td>57%</td>
</tr>
<tr>
<td>5</td>
<td>BuLi</td>
<td>0.4</td>
<td>2.0</td>
<td>12%</td>
</tr>
<tr>
<td>6</td>
<td>BuLi</td>
<td>0.25</td>
<td>2.0</td>
<td>19%</td>
</tr>
<tr>
<td>7</td>
<td>BuLi</td>
<td>0.5</td>
<td>2.0</td>
<td>70%</td>
</tr>
<tr>
<td>8</td>
<td>LDA</td>
<td>0.5</td>
<td>2.0</td>
<td>68%</td>
</tr>
<tr>
<td>9</td>
<td>tBuOK</td>
<td>1.2</td>
<td>2.0</td>
<td>38%, 39%</td>
</tr>
<tr>
<td>10</td>
<td>tBuOK</td>
<td>1.2</td>
<td>Xs</td>
<td>5% (NMR)</td>
</tr>
<tr>
<td>12</td>
<td>NaH</td>
<td>1.2</td>
<td>2.0</td>
<td>5% (NMR)</td>
</tr>
</tbody>
</table>
Table 12: Final optimization with benzaldehyde equivalents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base identity</th>
<th>Base eq.</th>
<th>Aldehyde eq.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BuLi</td>
<td>0.5</td>
<td>1.5</td>
<td>72-76</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>0.5</td>
<td>1.5</td>
<td>58</td>
</tr>
</tbody>
</table>

These yields are calculated based on the isolated product and entries 1, 3, 4 and 8 seem to provide similar yields. However, when the crude mixture was analyzed by $^1$H NMR spectroscopy, it was apparent that more products were formed and that by integration ratio, there was more product than polymer and starting material. The yields were inaccurate due to the difficult separation as previously described. At this point, it is clear flash column chromatography was not going to provide satisfactory results. Due to the close $R_f$ values, the separations were performed with long columns and utilized a substantial amount of silica gel and solvent. Moreover, multiple columns had to be performed in order to extract all the products of the crude mixture, leading to losses due to excessive manipulation and large waste output. Furthermore, the sulfone components of the crude mixtures often crystallized in the column, forming a solid barrier that blocks solvent flow. To retrieve the compound, columns had to be flushed with a more polar solvent, usually methylene chloride. Fractions collected possessed all three components and therefore, had to be concentrated and then reloaded onto the column.
Recrystallization is one of the methods used most often for the purification of solids. The process of recrystallization involves dissolution of the solid in an appropriate solvent at an elevated temperature and subsequent reformation of the crystals upon cooling, so that any impurities remain in solution. The choice of solvent is obviously the most critical step in the process of recrystallization. Optimal solvent must be selective and provide good yields of pure compounds. Common solvents used for recrystallization were tried and tested: hexanes/EtOAc, toluene/EtOAc, acetone/hexanes, methanol/hexanes. However, none provided satisfactory results. Most recrystallization efforts resulted in a mixture of starting sulfone, cyclized product and benzaldehyde in similar compositions in both the crystals and mother liquors. In one of the final efforts to recrystallize the compound, diethyl ether was used. Diethyl ether was added first to a sample of crude mixture. Upon heating, the solid was dispersed to a fine precipitate and the yellow color was dissipated into the solution. The solid was slow to dissolve in ether, and failed to fully dissolve even with a large volume, presumably due to the compound’s high polarity. Using a Pasteur pipette, the mother liquor was removed from the vial containing the white solid and analyzed by TLC and $^1$H NMR. The mother liquor disappointingly possessed all 3 components as well as a large portion of benzaldehyde. Much to our delight, when the mother liquor was left to stand on a bench, more white precipitate formed. TLC of both of the solids excitingly revealed only one band on the TLC, corresponding to that of the cyclized product, which was later confirmed by $^1$H NMR analysis.

A significant amount of product still remained in the mother liquor. Recrystallization was not the perfect method to recover all of the products. The presence
of excess benzaldehyde seemed to be a hindrance to product recovery. Evident by the unreacted benzaldehyde and the proposed reaction mechanism, 2.0 equivalents were not needed for the reaction to proceed. An additional experiment was performed with 1.5 equiv of benzaldehyde. This time, the crude mixture was a white solid, not pale yellow – a good sign. \textsuperscript{1}H NMR analysis of the crude mixture shows that the product is the predominant component. Washings of the crude mixture with warm diethyl ether removed all the impurities, leaving a beautiful white, fine solid at 72\% yield. However, one drawback is this purification method is not suited for microscale synthesis. An experiment performed at 2.0 mmol scale, instead of 1.0 mmol brought the yield up to 76\% from 72\%. Regardless, the experiment was repeated for LDA, to confirm that results would be similar for halide-substituents (Table 12). At last, we felt confident to move forward with our research and expand the scope of the reaction. To investigate the influence of various aromatic substituents on the scope of the cyclization reaction, a variety of benzyl 1-alkynyl sulfones were synthesized. Their synthesis was previously described in Chapter 2.

The reactions of different substrates follow the same procedure and purification techniques as described above. However, in some instances, where washing with diethyl ether does not adequately recover the entire product, column chromatography was performed on the concentrated mother-liquor. Since the majority of the product was recovered through washings, purification through flash column chromatography was less problematic with regard to crystallization and separation issues.
Table 13: Cyclization yield of a series of substrates

<table>
<thead>
<tr>
<th>Compound #</th>
<th>Structure</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>58</td>
<td><img src="image" alt="Structure 58" /></td>
<td>74</td>
</tr>
<tr>
<td>97</td>
<td><img src="image" alt="Structure 97" /></td>
<td>78</td>
</tr>
<tr>
<td>108</td>
<td><img src="image" alt="Structure 108" /></td>
<td>72</td>
</tr>
<tr>
<td>109</td>
<td><img src="image" alt="Structure 109" /></td>
<td>34</td>
</tr>
<tr>
<td>110</td>
<td><img src="image" alt="Structure 110" /></td>
<td>35</td>
</tr>
<tr>
<td>111</td>
<td><img src="image" alt="Structure 111" /></td>
<td>78</td>
</tr>
</tbody>
</table>
This collection of results permits some useful observations. The data seem to indicate that electron-donating substituents facilitate the reaction and higher yields were observed for 4-MeO, 4-Br, 2-I substrates. On the other hand, substrates with strong electron-withdrawing substituents such as 3-CN and 4-NO$_2$ provided lower yields. This is in keeping with the proposed mechanism, where the benzylic anion is created through the

| **112** | ![Structure](image1) | 44 |
| **113** | ![Structure](image2) | 39 |
| **114** | ![Structure](image3) | 64 |
| **115** | ![Structure](image4) | 38 |
| **116** | ![Structure](image5) | 12$^a$ |

$^a$: yield was calculated based on NMR. Product was not successfully isolated.
addition of $n$BuLi. Electron-donating substituents increase the nucleophilicity of the anion particularly in the case of 4-methoxy. Electron-withdrawing substrates would have the reverse effect by stabilizing the anion. In doing so, those groups decrease the nucleophilicity of the benzylic anion and a well-stabilized anion may be slow to attack benzaldehyde. In cases where $R^1 = \text{methyl}$ instead of phenyl, yields were much lower (compound 115 and 116). This is expected, as previously discussed, the propargylic proton has a pKa of ~23 making it prone to deprotonation under the reaction condition. More importantly, in case of 2-iodobenzyl 1-propynyl sulfone (48a), competition by intramolecular cyclization was expected and interfered with the intermolecular cyclization.

To further investigate the influence of various aromatic substituents on the scope of the cyclization reaction, various benzaldehydes were subjected to reaction conditions (Table 14). A few trends could be extracted. Whereas in sulfones, electron-donating substituents correlated with higher yields, with benzaldehydes, electron-withdrawing groups often yielded higher products. This is likely due to the increase in electrophilicity of the carbonyl group as well as stabilizing the negative charge in the intermediate, through inductive means. Fair to good yields were achieved with electron-withdrawing and electron-donating substituents. Higher yields were observed for strongly electron-withdrawing groups, such as 3-CN, 2-CF$_3$, which are strong electron withdrawing groups through inductive. The reaction yielded 69 % and 78 %, respectively.
### Table 14: Cyclization yield of a series of substrates

<table>
<thead>
<tr>
<th>Compound #</th>
<th>Structure</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td><img src="image95" alt="Structure 95" /></td>
<td>35</td>
</tr>
<tr>
<td>117</td>
<td><img src="image117" alt="Structure 117" /></td>
<td>69</td>
</tr>
<tr>
<td>118</td>
<td><img src="image118" alt="Structure 118" /></td>
<td>74</td>
</tr>
<tr>
<td>119</td>
<td><img src="image119" alt="Structure 119" /></td>
<td>34</td>
</tr>
<tr>
<td>120</td>
<td><img src="image120" alt="Structure 120" /></td>
<td>78</td>
</tr>
<tr>
<td>121</td>
<td><img src="image121" alt="Structure 121" /></td>
<td>55</td>
</tr>
</tbody>
</table>
Nitrobenzaldehyde was an anomaly and only provided a modest yield of 35%, when reacted with sulfone 48i, despite nitro being a strong electron-withdrawing group. Previously, non-substituted sulfone 48i and para-methyl benzyl sulfone 82c reacted with benzaldehyde at 74 % and 78 % yield. We hypothesized that the inductive effect of the methyl group increased the nucleophilicity of the anion, leading to a more efficient reaction and higher yields. To see if the effect could be observed for 4-nitrobenzaldehyde, sulfone 82c used and as expected, the yield was brought up to 55% from 35%. Various aldehyde systems, however, were unable to undergo the intermolecular cyclization. When cinnamaldehyde was introduced, the reaction failed and as well when 2-pyridinecarboxaldehyde was used. Both reactions, after six hours, did not produce any desired product. Instead, only starting materials were recovered. 1,4-Addition of sulfonyl anion onto cinnamaldehyde may occur slower than expected. The pathway requires that following the addition, the electrons are to delocalize towards the oxygen of the carbonyl group. Once the enolate is formed, Michael addition onto the triple bond can take place. However, since the electrons are delocalized through more
atoms, nucleophilicity may decrease and the cyclization is retarded compared to other systems.

3.1 Future work and conclusion

While the chemistry has been established, there are still a number of factors that require further investigation. For instance, the by-product needs to be isolated and fully characterized. To do so, a reaction must be performed with the purpose of maximizing the formation of the by-product. Reactions performed for this thesis was usually performed at 1.0 mmol scale, making isolation of a minor product difficult. Since less equivalents of base reduce by-product formation, higher base equivalents should be utilized to push the proposed ring-opening forward and increase the by-product yield. Increasing the scale of the reaction and the base equivalents should bring about a higher yield of the by-product and allow for characterization. In addition, due to the high value of β-keto sulfonyl groups, optimization for the by-product could bring about yet another method towards these sought after synthetic intermediates.

Besides pharmaceutical and agricultural purposes, oxathiins are also great synthetic intermediates. For instance, 3,5-diphenyl-6-(2-iodophenyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (97), can further chemistry can be performed on the group. Pd-catalyzed metallation reactions can lead to a fully conjugated ring system (Scheme 54).
Scheme 54: Pd-catalyzed reaction of a oxathiin-S, S-dioxide

The chemistry of this thesis successfully demonstrates the reaction of benzyl anion derived from benzyl alkynyl sulfones can be captured with aromatic aldehydes for the formation of 5,6-di(het)aryl-5,6-dihydro-1,4-oxathiin S,S-dioxides. The breath of reaction was investigated and a large range of substituents was tolerated; electron-withdrawing and donating groups yield product at fair to good yields. The chemistry covered in this thesis provides a novel pathway for synthesis of oxathiin-S,S-dioxide with aromatic substituents at the 2, 5 and 6 position, so while synthesis of oxathiin -S,S-dioxide has been reported, the chemistry presented provides an alternative synthetic pathway and substrates.
CHAPTER 4

EXPERIMENTAL PROCEDURES
4.0 General Synthetic Procedures

All reactions were carried out in flame-dried glassware under nitrogen unless otherwise noted. TLC analysis was performed on glass plates pre-coated with Silica Gel 60 (250 µm) containing a fluorescent indicator. The plates were visualized under UV and/or charred with a p-anisaldehyde solution. Flash column chromatography was performed with silica gel particle size 30–63 (mesh 230–400) supplied by Silicycle®. Solvents were distilled and dried according to standard procedures, and organic solutions were dried over MgSO₄ and concentrated under reduced pressure at 50 - 60 °C. THF were freshly distilled over sodium/benzophenone under inert atmosphere prior to use or obtained from an air-free solvent dispensing system. Diisopropylamine was dried over calcium hydride, distilled off and stored over Linde type 4A molecular sieves in a bottle and used under inert atmosphere. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 300 (300 MHz ¹H), a Bruker Avance 400 (400 MHz ¹H, 100.6 MHz ¹³C) or a Bruker Avance 600 (600 MHz ¹H, 150.9 MHz ¹³C). Chemical shifts (ppm) and coupling constants (J, Hz) were obtained from a first-order analysis of one-dimensional spectra and assignments of carbon were based on APT experiments. The proton spectra are reported as follows δ (multiplicity, coupling constant J, number of protons). ¹H NMR data are reported using standard abbreviations: singlet (s), doublet (d), triplet (t), doublet of doublet (dd), quartet (q), and multiplet (m). High-resolution mass spectrometry was carried out using a Q-TOF micro (Waters, Cambridge, MA, USA). Samples were infused at a concentration of approximately 10 µM in 9:1 acetonitrile:water with 0.1 mM ammonium acetate at a flow rate of 5 µL/min through an ESI source in positive ionization mode with a spray voltage of 3700 V. Gentle source conditions including a cone voltage
of 20 V and a collision cell voltage of 8 V were used with N₂ nebulizer (300 l/h) and cone (30 l/h) gas. External mass calibration was carried out using [Glu¹]-Fibrinopeptide. Elemental analyses were performed by MHW Laboratories of Phoenix, AZ.

4.1 General Method for Synthesis of Benzyl Thiocyanates⁸⁵

Under dry, inert atmosphere (N₂), benzyl bromide (1.0 eq) was dissolved in acetonitrile (20 mL/1 g). KSCN (3.0 eq) was added to the reaction and the mixture was stirred at rt for 45 min to 4 hours. The solid was removed by vacuum filtration. The acetonitrile was evaporated and the residue was diluted with EtOAc. The organic mixture was washed with water, which was back-extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over MgSO₄, and evaporated under reduced pressure. The crude product was used for the next step without further purification.

2-Thiocyanatobenzyl-pyridine (85)⁸⁵ Yield: 73%. ¹H NMR (400 MHz, CDCl₃): δ 8.61, (d, J = 4.6 Hz, 1H, Ar H), 7.75, (dd, J = 7.7 & 1.6 Hz, 1H, Ar H), 7.37 (d, J = 7.8 Hz, 1H, Ar H); 7.30-7.28 (dd, J = 2.0 and 7.5 Hz, 1H, Ar H); 4.31 (s, 2H, CH₂). ¹³C NMR (100.6 MHz, CDCl₃): δ 153.85, 150.04, 137.20, 123.40, 123.06, 112.15, 39.65.

Benzyl thiocyanate (74a)⁸⁵ Yield: 98%. ¹H NMR (400 MHz, CDCl₃): 7.36 (m, 5H, Ar H), 4.15 (s, 2H, CH₂).
4-Bromobenzyl thiocyanate (74b)\textsuperscript{85} Yield: %. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 7.53 (dd, \( J = 8.4, 1.9 \text{ Hz}, 2 \text{H, Ar H} \)), 7.25 (d, \( J = 8.4 \text{ Hz}, 2 \text{H, Ar H} \)), 4.10 (s, 2H, CH\textsubscript{2}).

4-Methylbenzyl thiocyanate (74c)\textsuperscript{85} Yield: 100%. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 7.28 (d, \( J = 8.0 \text{ Hz}, 2 \text{H, Ar H} \)), 7.22 (d, \( J = 8.0 \text{ Hz}, 2 \text{H, Ar H} \)), 4.16 (s, 2H, CH\textsubscript{2}), 2.39 (s, 3H, CH\textsubscript{3}).

3-Bromobenzyl thiocyanate (74d)\textsuperscript{85} Yield: 89%. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 7.48 (m, 2H, Ar H), 7.28 (m, 2H, Ar H), 4.10 (s, 2H, CH\textsubscript{2}).

2-Iodobenzyl thiocyanate (74e)\textsuperscript{85} Yield: 82%. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 7.85 (d, \( J = 7.9 \text{ Hz}, 1 \text{H, Ar H} \)), 7.40 (d, \( J = 7.5 \text{ Hz}, 1 \text{H, Ar H} \)), 7.35 (t, \( J = 7.4 \text{ Hz}, 1 \text{H, Ar H} \)), 7.02 (t, \( J = 7.5 \text{ Hz}, 1 \text{H, Ar H} \)), 4.20 (s, 2H, CH\textsubscript{2}).\textsuperscript{13}C NMR (150.9 MHz, CDCl\textsubscript{3}): \( \delta \) 141.03, 136.92, 130.48, 130.45, 128.95, 111.56, 100.17, 44.13.

4-Methoxybenzyl thiocyanate (74f)\textsuperscript{85} Yield: 91%. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 7.23 (d, \( J = 7.8 \text{ Hz}, 2 \text{H, Ar H} \)), 6.88 (d, \( J = 7.8 \text{ Hz}, 2 \text{H, Ar H} \)), 4.17 (s, 2H, CH\textsubscript{2}), 3.84 (s, 3H, CH\textsubscript{3}).

3-Chlorobenzyl thiocyanate (74g)\textsuperscript{85} Yield: 92%. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 7.35 (m, 3H, Ar H), 7.27 (m, 2H, Ar H), 4.12 (s, 2H, CH\textsubscript{2}).\textsuperscript{13}C NMR
(150.9 MHz, CDCl$_3$): $\delta$ 133.59, 132.35, 130.92, 130.68, 123.11, 101.73, 60.44, 37.59.

4-Cyanobenzyl thiocyanate (74h)$^{85}$ Yield: 100%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.15 (dd, $J = 6.8$ & 1.9 Hz, 2H, Ar H), 7.48 (dd, $J = 6.8$ & 1.9 Hz, 2H, Ar H), 4.12 (s, 2H, CH$_2$).

3-Cyanobenzyl thiocyanate (74i)$^{85}$ Yield: 85%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.66 (d, $J = 7.6$ Hz, 1H, Ar H), 7.61 (d, $J = 8.0$ Hz, 1H, Ar H), 7.52 (t, $J = 8.0$ Hz, 1H, Ar H), 7.49 (s, 1H, Ar H), 4.13 (s, 2H, CH$_2$).

4.2 General Method for Synthesis of Sulfides$^{85}$

Under a dry, inert atmosphere (N$_2$), a solution of phenyl acetylene (1.05 eq) in dry THF (1g/10 mL) was cooled to -78 °C. nBuLi (1.1 eq; 2.5M/1.6M in hexanes, Aldrich) was added dropwise to the solution. The resulting mixture was stirred at -78 °C for 2 hours. A solution of corresponding thiocyanate (1.0 eq) in dry THF (1 g/20 mL) was added dropwise and the resulting solution was allowed to warm to rt and stirred overnight. Water was added to quench the reaction and aqueous layers were extracted (3 x 10 mL) with EtOAc. The combined organic layers were washed with brine, dried over MgSO$_4$ and the solvent was evaporated under reduced pressure. The crude product was obtained as brown oil and used for the next step without further purification.
2-Pyridinylmethyl 2-phenylethynyl sulfide (86)<sup>85</sup> Yield: 72 %. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.55 (dd, J = 0.7 & 4.8 Hz, 1H, py H), 7.65 (m, 1H, py H), 7.23 (m, 7H, Ar & py H), 3.98 (s, 2H, CH<sub>3</sub>). <sup>13</sup>C NMR δ (100.6 MHz, CDCl<sub>3</sub>): δ 156.79, 149.47, 136.34, 123.35, 122.32, 91.31, 67.84, 41.49, 4.92.

Benzyl 2-phenylethynyl sulfide (75a) Yield: 87%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.28 (m, 10 H, Ar H), 3.94 (s, 2H, CH<sub>2</sub>). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): δ 136.75, 131.44, 129.27, 128.68, 128.41, 128.21, 127.87, 123.51, 94.83, 79.50, 40.59.

4-Bromobenzyl 2-phenylethynyl sulfide (75b) Yield 62%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.51 (dd, J = 6.5 & 1.9 Hz, 2H, Ar H), 7.32 (m, 7H, Ar H), 3.97 (s, 2H, CH<sub>2</sub>).

4-Methylbenzyl 2-phenylethynyl sulfide (75c) Yield: 90%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.28 (d, J = 8.0 Hz, 2H, Ar H), 7.22 (d, J = 8.0 Hz, 2H, Ar H), 7.21 (m, 5H, Ar H), 3.97 (s, 2H, CH<sub>2</sub>), 2.39 (s, 3H, CH<sub>3</sub>).
3-Bromobenzyl 2-phenylethynyl sulfide (75d) Yield 62%. ¹H NMR (400 MHz, CDCl₃): δ 7.53 (s, 1H, Ar H), 7.30 (m, 8H, Ar H), 3.90 (s, 2H, CH₂). ¹³C NMR (100.6 MHz, CDCl₃): δ 138.89, 132.13, 131.52, 131.52, 130.81, 130.09, 128.26, 127.68, 123.05 122.39, 95.32, 78.37, 39.52.

2-Iodobenzyl 2-phenylethynyl sulfide (75e) Yield: 67%. ¹H NMR (400 MHz, CDCl₃) δ:

<table>
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<th>Chemical Structure</th>
<th>¹H NMR (400 MHz, CDCl₃)</th>
<th>¹³C NMR (100.6 MHz, CDCl₃)</th>
</tr>
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<tr>
<td>Br</td>
<td>δ 7.82 (d, J = 8.0 Hz, 1H, Ar H), 7.37 (d, J = 7.6 Hz, 1H, Ar H), 7.36 (m, 6H, Ar H), 6.93 (m, 1H, Ar H), 4.06 (s, 2H, CH₂).</td>
<td>δ 139.70, 138.97, 132.01, 131.24, 130.54, 129.37, 128.19, 128.12, 123.19, 100.53, 94.99, 78.60, 45.33.</td>
</tr>
<tr>
<td>I</td>
<td>δ 7.82 (d, J = 8.0 Hz, 1H, Ar H), 7.37 (d, J = 7.6 Hz, 1H, Ar H), 7.36 (m, 6H, Ar H), 6.93 (m, 1H, Ar H), 4.06 (s, 2H, CH₂).</td>
<td>δ 139.70, 138.97, 132.01, 131.24, 130.54, 129.37, 128.19, 128.12, 123.19, 100.53, 94.99, 78.60, 45.33.</td>
</tr>
<tr>
<td>MeO</td>
<td>δ 7.27 (m, 2H, Ar H), 7.18 (m, 4H, Ar H), 6.87 (d, J = 7.6 Hz, 1H, Ar H), 6.857 (t, J = 2.2 Hz, 1H, Ar H), 6.76 (m, 1H, Ar H), 3.96 (s, 2H, CH₂), 3.76 (s, 2H, CH₃).</td>
<td>δ 159.73, 138.08, 131.43, 130.17, 127.76, 123.38, 121.47, 113.55, 94.72, 79.26, 55.24, 40.53.</td>
</tr>
<tr>
<td>Cl</td>
<td>δ 7.42 (s, 1H, Ar H), 7.37 (m, 2H, Ar H), 7.30 (m, 6H, Ar H), 3.97 (s, 2H, CH₂).</td>
<td>δ 138.71, 134.30, 131.42, 129.89, 129.31, 128.36, 128.27, 127.99, 127.32, 123.15, 95.36, 76.90, 39.64.</td>
</tr>
</tbody>
</table>

4-Methoxybenzyl 2-phenylethynyl sulfide (75f) Yield: 91%. ¹H NMR (300 MHz, CDCl₃): δ 7.27 (m, 2H, Ar H), 7.18 (m, 4H, Ar H), 6.87 (d, J = 7.6 Hz, 1H, Ar H), 6.857 (t, J = 2.2 Hz, 1H, Ar H), 6.76 (m, 1H, Ar H), 3.96 (s, 2H, CH₂), 3.76 (s, 2H, CH₃). ¹³C NMR (150.9 MHz, CDCl₃): δ 159.73, 138.08, 131.43, 130.17, 127.76, 123.38, 121.47, 113.55, 94.72, 79.26, 55.24, 40.53.

3-Chlorobenzyl 2-phenylethynyl sulfide (75g) Yield%. ¹H NMR (400 MHz, CDCl₃): δ 7.42 (s, 1H, Ar H), 7.37 (m, 2H, Ar H), 7.30 (m, 6H, Ar H), 3.97 (s, 2H, CH₂). ¹³C NMR (100.6 MHz, CDCl₃): δ 138.71, 134.30, 131.42, 129.89, 129.31, 128.36, 128.27, 127.99, 127.32, 123.15, 95.36, 76.90, 39.64.
4-Nitrobenzyl 2-phenylethynyl sulfide (75h) Yield 90%. $^1$H NMR (300 MHz, CDCl$_3$):
$\delta$ 8.15 (dd, $J$ = 6.8 & 1.9 Hz, 2H, Ar H), 7.48 (dd, $J$ = 6.8 & 1.9 Hz, 2H, Ar H), 7.24 (m, 5H, Ar H), 3.96 (s, 2H, CH$_2$).

3-Cyanobenzyl 2-phenylethynyl sulfide (75i) Yield 88%. $^1$H NMR (400 MHz, CDCl$_3$):
$\delta$ 7.67 (m, 1H, Ar H), 7.60 (m, 1H, Ar H), 7.46 (m, 2H, Ar H), 7.30 (m, 5H, Ar H), 3.95 (s, 2H, CH$_2$).

4.3 General method for synthesis of sulfones.$^{85}$

In an Erlenmeyer flask, MCPBA (72%, 2.5 eq) was dissolved in CH$_2$Cl$_2$ (25 mL). Solids were filtered off and the filtrate was added to a mixture of alkynyl sulfide (1.0 eq) also in CH$_2$Cl$_2$ (25 mL) stirring at -78 °C. The resulting mixture was slowly warmed to 0 °C and stirred overnight. Following the disappearance of the starting material (TLC), the solid was removed by vacuum filtration. The filtrate was left to cool at 0 °C for 2 hours then filtered with suction through filter agent Celite® 545. The filtrate was collected and washed with sodium carbonate (20 mL), water (20 mL), brine (20 mL), dried over MgSO$_4$, filtered, and concentrated. The product was purified by flash column chromatography on silica gel with hexanes/EtOAc and recrystallized from hexanes/EtOAc to yield pure sulfone.
**Benzyl 2-phenylethynyl sulfone (48i)** was obtained as a white solid. Yield: 78%. Mp: 81 – 82 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.52-7.36 (m, 10H, Ar H), 4.51 (s, 2H, CH$_2$). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ 132.77, 131.72, 131.25, 129.43, 128.90, 128.77, 127.24, 117.50, 94.14, 82.57, 64.61. IR (cm$^{-1}$, neat): 3063, 3034, 2978, 2919, 2182, 1489, 1329, 1199, 1148, 1124.

**4-Bromobenzyl 2-phenylethynyl sulfone (82b)** was obtained as a white solid. Yield: 44%. Mp: 157 – 158 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.55 (m, 5H, Ar H), 7.50 (m, 2H, Ar H), 7.38 (m, 2H, Ar H), 4.48 (s, 2H, CH$_2$). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ 132.87, 132.80, 132.18, 131.95, 128.88, 126.23, 124.06, 117.28, 94.49, 82.37, 63.89. IR (cm$^{-1}$, neat): 2988, 2181, 1487, 1328, 1149, 1126, 887, 750. Analysis calculated for C$_{15}$H$_{11}$BrO$_2$S; C, 53.74; H, 3.31; found C, 53.60; H, 3.50.

**4-Methylbenzyl 2-phenylethynyl sulfone (82c)** was obtained as a white solid. Yield: 90%. Mp: 75-76 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.50 (m, 3H, Ar H), 7.41 (m, 4H, Ar H), 7.25 (m, 2H, Ar H), 4.49 (s, 2H, CH$_2$), 2.41 (s, 3H, CH$_3$). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ 132.78, 131.73, 131.21, 129.42, 128.87, 128.62, 127.42, 117.46, 94.16, 82.54, 64.62, 21.21; IR (cm$^{-1}$, neat): 3061, 2979, 2921, 2183, 1512, 1488, 1443, 1199, 1149, 1126, 759. Analysis calculated for C$_{16}$H$_{14}$O$_2$S; C, 71.08; H, 5.22; found C, 71.23; H, 5.40.
2-Iodobenzyl 2-phenylethynyl sulfone (48k)\textsuperscript{85} was obtained as a white solid. Yield: 87%. Mp: 104.5 – 105 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.95 (m, 1H, Ar H), 7.52 (m, 1H, Ar H), 7.46 (m, 3H, Ar H), 7.44 (m, 3H, Ar H), 7.12 (m, 1H, Ar H), 4.83 (s, 2H, CH\textsubscript{2}). \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}): δ 140.25, 132.92, 132.46, 131.78, 131.00, 130.91, 128.78, 128.00, 117.59, 102.36, 94.19, 82.97, 67.67. IR (cm\textsuperscript{-1}, neat): 3061, 2979, 2921, 2182, 1488, 1471, 1442, 1331, 1154, 1132, 1015.

4-Methoxybenzyl 2-phenylethynyl sulfone (82f) was obtained as a white solid. Yield: 65%. Mp: 74 – 75 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.51 (m, 3H, Ar H), 7.43 (m, 4H, Ar H), 6.97 (m, 2H, Ar H), 4.48 (s, 2H, CH\textsubscript{2}), 3.85 (s, 3H, CH\textsubscript{3}). \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}): δ 160.54, 132.82, 132.53, 131.72, 128.79, 118.96, 117.60, 114.37, 94.04, 82.67, 64.00, 55.38. IR (cm\textsuperscript{-1}, neat): 3001, 2967, 2838, 2182, 1610, 1328, 1305, 1253, 1127. Analysis calculated for C\textsubscript{16}H\textsubscript{14}O\textsubscript{3}S; C, 67.11; H, 4.93; found C, 66.89; H, 5.24.

3-Chlorobenzyl 2-phenylethynyl sulfone (82g) was obtained as a white solid. Yield: 78%. Mp: 84 – 85 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.51 (m, 4H, Ar H), 7.46 (m, 5H, Ar H), 4.49 (s, 2H, CH\textsubscript{2}). \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}): δ 134.73, 132.88, 131.94, 131.28, 130.20, 129.71, 129.47, 129.18, 128.86, 117.24, 94.72, 82.27, 63.95. IR (cm\textsuperscript{-1}, neat): 3064, 2983, 2924, 2182, 1330, 1256, 1151, 1127. ESI HRMS, calculated for [C\textsubscript{15}H\textsubscript{11}ClO\textsubscript{2}S+NH\textsubscript{4}]\textsuperscript{+}: 308.0507; found: 308.0496.
4-Nitrobenzyl 2-phenylethynyl sulfone (82h) was obtained as a white solid. Yield: 64%. Mp: 169 – 170 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.53 (m, 9H, ArH), 4.49 (s, 2H, CH$_2$). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ 134.15, 132.91, 131.94, 130.49, 129.93, 128.86, 122.75, 117.22, 94.78, 82.24, 63.89. IR (cm$^{-1}$, neat): 3077, 3061, 2932, 2181, 1522, 1490, 1348, 1332, 1150, 1127. Analysis calculated for C$_{15}$H$_{11}$NO$_4$S; C, 59.79; H, 3.68; found C, 59.55; H, 3.71.

3-Cyanobenzyl 2-phenylethynyl sulfone (82i) was obtained as a white solid. Yield: 75%. Mp: 95.4 – 96.0 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.75 (m, 3H, Ar H), 7.10 (m, 6H, Ar H), 4.56 (s, 2H, CH$_2$). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ 135.64, 134.62, 133.06, 133.06, 132.88, 132.21, 129.90, 129.00, 117.96, 116.93, 113.28, 95.11, 82.12, 63.60. IR (cm$^{-1}$, neat): 3064, 2981, 2922, 2233, 2182, 1332, 1294, 1267, 1229, 1178, 1154, 1126, 1070.

4.4 General Method for Oxathiin-S,S-Dioxides

Under dry, inert atmosphere, starting sulfone (1.0 eq) was dissolved in THF (0.05 M) and cooled to -78 °C. nBuLi (1.6 M, 0.5 eq in hexanes) or LDA (0.88 M, 0.5 eq in THF) was added dropwise and stirred at -78 °C for 15 minutes. Aldehyde (1.5 eq) was then added to the solution and the reaction mixture was warmed slowly to -35 °C. After 6 hours of stirring, the reaction was quenched with NH$_4$Cl and warmed to rt. The aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed
with brine, dried over MgSO₄ and the solvent was evaporated under reduced pressure. Wash/trituration in anhydrous ethyl ether affords pure product, unless otherwise noted.

**3,5,6-Triphenyl-5,5-dihydro-1,4-oxathiin S,S-dioxide (58)** was obtained as a white solid from sulfone 48i and benzaldehyde, 74% yield; mp = 187-189 °C (dec.). ¹H NMR (600 MHz, CDCl₃), δ: 7.47–7.25 (m, 15H), 6.46 (s, 1H), 6.18 (d, J = 11.7 Hz, 1H), 4.81 (d, J = 11.7 Hz, 1H); ¹³C NMR (150.9 MHz, CDCl₃), δ: 159.49, 134.92, 132.03, 131.52, 131.13, 129.47, 129.29, 128.79, 128.71, 128.64, 128.12, 126.38, 125.42, 101.37, 83.08, 67.96; IR (cm⁻¹, neat): 3067, 1609, 1575, 1364, 1283, 1127, 1078, 910, 695; ESI HRMS, calculated for [C₂₂H₁₈SΟ₃+H]⁺: 363.1050; found: 363.1066.

**3,5-Diphenyl-6-(2-iodophenyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (97)** was obtained as a white solid from sulfone 48l and benzaldehyde, 78% yield. ¹H NMR (600 MHz, CDCl₃), δ: 7.71 (dd, J = 8.0, 1.0 Hz, 1H), 7.58 (d, J = 7.4 Hz, 2H), 7.46–7.02 (m, 11H), 6.85 (m, 1H), 6.39 (s, 1H), 6.07 (d, J = 11.4 Hz, 1H), 5.57 (d, J = 11.4 Hz, 1H); ¹³C NMR (150.9 MHz, CDCl₃), δ: 159.48, 140.29, 134.34, 131.91, 131.56, 131.27, 130.69, 129.67, 129.38, 128.78, 128.67, 128.27, 128.06, 126.44, 104.48, 101.69, 83.94, 70.12; IR (cm⁻¹, neat): 3068, 2931, 1609, 1575, 1495, 1451, 1307, 1283, 1120, 1078; ESI HRMS, calculated for [C₂₂H₁₇SΟ₃I+H]⁺: 489.0016; found: 488.9979.
3-(t-Butyl)-6-(2-iodophenyl)-5-phenyl-5,6-dihydro-1,4-oxathiin S,S-dioxide (93) was obtained as a white solid from sulfone 48i and benzaldehyde, 39% yield; mp = 180 - 182°C (dec.). \(^1\)H NMR (600 MHz, CDCl₃), δ: 7.66 (dd, \(J = 8.4, 1.2\) Hz, 1H), 7.42 (dd, \(J = 8.1, 1.8\) Hz, 1H), 7.20–7.17 (m, 6H), 6.82 (dt, \(J = 7.8, 1.2\) Hz, 1H), 5.85 (s, 1H), 5.81 (d, \(J = 11.5\) Hz, 1H), 5.19 (d, \(J = 11.5\) Hz, 1H), 1.12 (s, 9H); \(^{13}\)C NMR (150.9 MHz, CDCl₃), δ: 171.40, 140.25, 134.62, 131.14, 130.62, 129.52, 129.48, 128.56, 128.03, 127.98, 104.45, 100.08, 83.45, 69.75, 37.27, 27.48; IR (cm\(^{-1}\), neat): 2967, 1608, 1468, 1305, 1287, 1218, 1136, 1103; ESI HRMS, calculated for [C\(_{20}\)H\(_{21}\)SO\(_3\)I+H]\(^+\): 469.0329; found: 469.0310.

3,5-Diphenyl-6-(3-cyanophenyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (114) was obtained as a white solid from sulfone 82i and benzaldehyde, 64% yield; mp = 210.2 – 211.0 °C (dec.). \(^1\)H NMR (600 MHz, CDCl₃), δ: 7.61 – 7.39 (m, 14 H), 6.49 (s, 1H), 6.17 (d, \(J = 11.7\) Hz, 1H), 4.86 (d, \(J = 11.7\) Hz, 1H); \(^{13}\)C NMR (100.6 MHz, CDCl₃), δ: 159.61, 134.49, 134.46, 131.81, 131.65, 131.15, 129.80, 129.72, 129.57, 129.23, 128.82, 128.03, 127.42, 126.39, 101.17, 82.89, 67.41; IR (cm\(^{-1}\), neat): 3067, 3036, 1609, 1574, 1302, 1280, 1127, 1081 cm\(^{-1}\); ESI HRMS, calculated for [C\(_{23}\)H\(_{17}\)SO\(_3\)N+H]\(^+\): 388.1002; found: 388.1272.

3,5-Diphenyl-6-(4-methylphenyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (111) was obtained as a white solid from sulfone 82c and benzaldehyde, 76% yield; mp = 225.5-226.3 °C (dec.). \(^1\)H
NMR (600 MHz, CDCl$_3$), $\delta$: 7.64 (m, 2H), 7.48 (m, 1H), 7.42 (m, 2H), 7.36 (m, 2H), 7.31 (m, 3H), 7.23 (m, 2H), 7.09 (m, 2H), 6.48 (s, 1H), 6.19 (d, $J = 11.7$ Hz, 1H), 4.82 (d, $J = 11.7$ Hz, 1H), 2.28 (s, 3H); $^{13}$C NMR (100.6 MHz, CDCl$_3$), $\delta$: 159.44, 139.27, 135.06, 132.09, 131.47, 129.43, 128.77, 128.72, 128.18, 126.36, 122.08, 101.38, 83.01, 67.65, 21.23; IR (cm$^{-1}$, neat): 3067, 3034, 2922, 1609, 1574, 1301, 1283, 1126, 1079; Analysis calculated for C$_{23}$H$_{20}$O$_3$S; C, 73.38; H, 5.36; found C, 73.56; H, 4.99.

3,5-Diphenyl-6-(4-bromophenyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (108) was obtained as a white solid from sulfone 82b and benzaldehyde, 72% yield; mp = 193.5 – 194.2 °C (dec.). $^1$H NMR (400 MHz, CDCl$_3$), $\delta$: 7.51 – 7.26 (m, 15 H), 6.49 (s, 1H), 6.24 (d, $J = 11.7$ Hz, 1H), 4.88 (d, $J = 11.7$ Hz, 1H); $^{13}$C NMR (100.6 MHz, CDCl$_3$), $\delta$: 159.48, 134.36, 132.82, 132.02, 131.53, 131.32, 130.83, 129.48, 129.06, 128.91, 128.64, 127.30, 126.39, 101.45, 83.06, 57.70; IR (cm$^{-1}$, neat): 3066, 2369, 1663, 1647, 1608, 1126, 1072; ESI HRMS, calculated for [C$_{22}$H$_{17}$BrO$_3$S+NH$_4$]$^+$: 458.0420; found: 458.0407.

3,5-Diphenyl-6-(4-chlorophenyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (110) was obtained as a white solid from sulfone 82g and benzaldehyde, 35% yield; mp = 173.5 – 174.9 °C (dec.). $^1$H NMR (600 MHz, CDCl$_3$), $\delta$: 7.44 – 7.21 (m, 14H), 6.48 (s, 1H), 6.16 (d, $J = 11.7$ Hz, 1H), 4.79 (d, $J = 11.7$ Hz, 1H); $^{13}$C NMR (100.6 MHz, CDCl$_3$), $\delta$: 159.61, 134.50, 134.48, 131.81, 131.65, 131.14, 129.80, 129.72, 129.56, 129.24, 128.89, 128.82, 128.03, 127.43, 126.39, 101.16, 82.89, 67.39; IR (cm$^{-1}$, neat): 3067, 3035, 1608, 1574,
1302, 1280, 1127, 1081 cm\textsuperscript{−1}; Analysis calculated for C\textsubscript{22}H\textsubscript{17}ClO\textsubscript{3}S; C, 66.58; H, 4.32; found C, 66.54; H, 4.41.

3,5-Diphenyl-6-(4-methoxyphenyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (112) was obtained as a white solid from sulfone 82f and benzaldehyde, 44% yield; mp = 163.2 – 164.2 °C (dec.). \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}), δ: 7.44 – 7.27 (m, 12 H), 6.71 (m, 2H), 6.38 (s, 1H), 6.06 (d, J = 11.7 Hz, 1H), 4.70 (d, J = 11.7 Hz, 1H), 3.66 (s, 3H); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}), δ: 160.22, 159.45, 132.12, 131.47, 131.17, 129.54, 128.77, 128.64, 128.14, 127.46, 127.08, 126.37, 114.21, 101.27, 83.06, 67.28, 55.19; IR (cm\textsuperscript{−1}, neat): 3056, 2967, 1610, 1328, 1305, 1253, 1127, 1081 cm\textsuperscript{−1}; Analysis calculated for C\textsubscript{23}H\textsubscript{20}O\textsubscript{4}S; C, 70.39; H, 5.14; found C, 70.50; H, 5.21.

3,5-Diphenyl-6-(4-nitrophenyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (95) was obtained from sulfone 48i and benzaldehyde as a white solid, 35% yield; mp = 213–215 °C (dec.). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}), δ: 8.14 (d, J = 8.8 Hz, 2H) 7.63 (d, J = 7.2 Hz, 2H), 7.55–7.28 (m, 10H), 6.52 (s, 1H), 6.31 (d, J = 11.6 Hz, 1H), 4.79 (d, J = 11.6 Hz, 1H); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}), δ: 159.13, 148.30, 141.65, 131.80, 131.55, 130.92, 129.83, 129.02, 128.96, 128.92, 126.28, 124.73, 123.90, 102.02, 81.90, 67.82; IR (cm\textsuperscript{−1}, neat): 3072, 1609, 1523, 1349, 1281, 1127, 1086 cm\textsuperscript{−1}; ESI HRMS, calculated for [C\textsubscript{22}H\textsubscript{17}SO\textsubscript{3}N+H]\textsuperscript{+}: 408.0901; found: 408.0923.
6-(2-Iodophenyl)-5-phenyl-3-methyl-5,6-dihydro-1,4-oxathiin S,S-dioxide (115) was obtained as a white solid from sulfone 48a and benzaldehyde, 38% yield; mp = 165-166 °C (dec.). $^1$H NMR (600 MHz, CDCl$_3$), δ: 7.76 (dd, J = 8.0 & 2.2 Hz, 1 H), 7.45 (dd, J = 8.0 & 1.6 Hz, 1 H), 7.29 (m, 6H), 6.92 (m, 1H), 5.96 (d, J = 11.4 Hz, 1 H), 5.89 (s, 1H), 5.50 (d, J = 11.4 Hz, 1 H), 2.08 (s, 3H); $^{13}$C NMR (100.6 MHz, CDCl$_3$), δ: 161.54, 140.25, 134.26, 131.15, 130.65, 129.68, 129.347, 128.68, 128.18, 128.06, 104.48, 103.10, 83.63, 69.42, 21.39; IR (cm$^{-1}$, neat): 3064, 2924, 2853, 1626, 1468, 1305, 1288, 1206, 1165, 1117; Analysis calculated for C$_{17}$H$_{15}$O$_3$I; C, 47.90; H, 3.55; found C, 48.11; H, 3.70.

3,6-Diphenyl-5-(4-cyanophenyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (117) was obtained as a white solid from sulfone 48i and 4-cyanobenzaldehyde, 69% yield; mp = 215.1-215.9 °C (dec.). $^1$H NMR (600 MHz, CDCl$_3$), δ: 7.50-7.19 (m, 15 H), 6.41 (s, 1H), 6.15 (d, J = 11.6 Hz, 1H), 4.67 (d, J = 11.6 Hz, 1H); $^{13}$C NMR (100.6 MHz, CDCl$_3$), δ: 159.19, 139.85, 132.52, 131.81, 131.59, 130.94, 129.80, 129.00, 128.92, 128.69, 126.31, 124.78, 117.95, 113.47, 101.92, 82.19, 67.77; IR (cm$^{-1}$, neat): 3061, 2998, 2946, 2228, 1679, 1596, 1447, 1276, 1125, 1074; Analysis calculated for C$_{23}$H$_{17}$NO$_3$S; C, 71.30; H, 4.42; found C, 71.24; H, 4.67.
3,6-Diphenyl-5-(4-methoxyphenyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (118) was obtained from sulfone 48i and 4-methoxybenzaldehyde as a white solid, 74% yield; mp = 164.5-165.0 °C (dec.). $^1$H NMR (400 MHz, CDCl3), δ: 7.38 -7.16 (m, 11H), 6.70 (dd, $J = 6.8$ Hz, $J = 1$ Hz, 2H), 6.36 (s, 1H), 6.06 (d, $J = 11.7$ Hz, 1H), 4.73 (d, $J = 11.7$ Hz, 1H), 3.65 (s, 3H); $^{13}$C NMR (100.6 MHz, CDCl3), δ: 160.18, 159.50, 132.12, 131.47, 131.17, 129.54, 129.21, 128.77, 128.64, 128.14, 127.46, 127.08, 126.39, 125.61, 114.40, 114.08, 101.24, 82.70, 67.91, 55.23; IR (cm$^{-1}$, neat): 3067, 2838, 1610, 1575, 1516, 1283, 1251, 1178, 1126; Analysis calculated for C$_{23}$H$_{20}$O$_4$S; C, 70.39; H, 5.14; found C, 70.07; H, 5.24.

3,6-Diphenyl-5-(4-bromophenyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (119) was obtained from sulfone 48i and 4-bromobenzaldehyde as a white solid, 34% yield; mp = 164.5 - 165.3 °C (dec.). $^1$H NMR (400 MHz, CDCl3), δ: 7.54 - 7.13 (m, 14H), 6.39 (s, 1H), 6.08 (d, $J = 11.7$ Hz, 1H), 4.69 (d, $J = 11.7$ Hz, 1H); $^{13}$C NMR (100.6 MHz, CDCl3), δ: 159.32, 134.01, 131.99 131.83, 131.64, 131.05, 129.67, 129.54, 128.84, 126.33, 125.13, 123.69, 101.57, 82.38, 67.77; IR (cm$^{-1}$, neat): 3066, 2921, 1610, 1575, 1516, 1283, 1286, 1220, 1126, 1012; Analysis calculated for C$_{22}$H$_{17}$BrO$_3$S; C, 59.87; H, 3.88; found C, 60.0; H, 3.96.
3,6-Diphenyl-5-(4-flourophenyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (120) was obtained from sulfone 48i and 4-flourobenzaldehyde as a white solid, 78% yield; mp = 198.0-198.8 °C (dec.). \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\): 7.64 – 7.00 (m, 12H), 7.698 (t, J = 2.2 Hz, 2H), 6.49 (s, 1H), 6.20 (d, J = 11.7 Hz, 1H), 4.80 (d, J = 11.7 Hz, 1H); \(^1^3\)C NMR (100.6 MHz, CDCl\(_3\)), \(\delta\): 162.99 (d, \(^1\)J = 247.5 Hz, FC), 159.36, 131.92, 131.60, 131.07, 130.95 (d, \(^4\)J = 3.6 Hz, FCC), 129.96 (d, \(^3\)J = 8.5 Hz, FCC), 129.43, 128.84, 128.76, 126.35, 125.32, 115.86 (d, \(^2\)J = 21.68 Hz, FCC), 101.52, 82.34, 67.99; IR (cm\(^{-1}\), neat): 3067, 2926, 1607, 1330, 1318, 1286, 1220, 1128; Analysis calculated for C\(_{22}\)H\(_{17}\)FO\(_3\)S; C, 69.46; H, 4.50; C, 69.49; H, 4.78

3,6-Diphenyl-5-(2-furyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (94) was obtained from sulfone 48i and furfural, as a white solid, 35% yield; mp = 144 - 146 °C (dec.). \(^1\)H NMR (600 MHz, CDCl\(_3\)), \(\delta\): 7.63 (d, J = 7.8 Hz, 2H), 7.48– 7.26 (m, 9H), 6.42 (s, 1H), 6.39 (s, 1H), 6.24, (d, J = 11.7 Hz, 1H), 6.23 (s, 1H), 4.96 (d, J = 11.7 Hz, 1H); \(^1^3\)C NMR (150.9 MHz, CDCl\(_3\)), \(\delta\): 159.25, 147.37, 143.91, 131.94, 131.56, 130.72, 129.44, 128.44, 128.79, 128.63, 126.43, 125.20, 112.18, 110.49, 101.52, 65.61; IR (cm\(^{-1}\), neat): 3070, 1609, 1575, 1496, 1283, 1127, 1078; ESI HRMS, calculated for [C\(_{20}\)H\(_{16}\)SO\(_4\)\(^+\)H\(^+\)]: 353.0843; found: 353.0878.
5-(4-Nitrophenyl)-6-(4-methylphenyl)-3-phenyl-5,6-dihydro-1,4-oxathiin S,S-dioxide

(121) was obtained from sulfone 82c and 4-nitrobenzaldehyde as a white solid, 55% yield; mp = 213–215 °C (dec.). ¹H NMR (400 MHz, CDCl₃), δ: 8.15 (td, J = 6.8 & 2.0 Hz, 2H), 7.53 – 7.00 (m, 11 H), 6.41 (s, 1H), 6.19 (d, J = 11.7 Hz, 1H), 4.67 (d, J = 11.7 Hz, 1H), 2.19 (s, 3H); ¹³C NMR (100.6 MHz, CDCl₃), δ: 159.12, 148.29, 141.80, 139.90, 131.78, 131.61, 129.81, 129.04, 128.92, 126.30, 123.94, 121.37, 101.99, 81.86, 67.52, 21.24; IR (cm⁻¹, neat): 3073, 2943, 2859, 1609, 1575, 1447, 1303, 1281, 1221, 117, 1082 cm⁻¹; ESI HRMS, calculated for [C₂₃H₁₉NO₅S+NH]⁺: 439.1322; found: 439.1310.

3,6-Diphenyl-5-(2-flouro methylphenyl)-5,6-dihydro-1,4-oxathiin S,S-dioxide (122)

was obtained from sulfone 48i and 2-flouro methylbenzaldehyde as a white solid, 35% yield; mp = 188.0-188.8 °C (dec.). ¹H NMR (400 MHz, CDCl₃), δ: 7.64 – 7.00 (m, 13H), 6.55 (d, J = 11.7 Hz, 2H), 6.36 (s, 1H), 5.02 (d, J = 11.7 Hz, 1H), 4.80 (d, J = 11.7 Hz, 1H); ¹³C NMR (100.6 MHz, CDCl₃), δ: 159.49, 132.54, 132.32, 131.88, 131.61, 131.04, 129.82, 129.71, 129.42, 128.85, 128.80, 124.95, 123.90 (q, J = 271.5 Hz, CF₃), 101.94, 67.02; IR (cm⁻¹, neat): 3070, 2933, 1609, 1312, 1222, 1165; Analysis calculated for C₂₃H₁₇F₃O₃S; C, 64.18; H, 3.98; C, 64.80; H, 3.90.
CHAPTER 5

REFERENCES