ABSTRACT

PARKER, PATRICK DANIEL. Novel Methods for Nitrogen-Containing Heterocycles and Applications to Total Synthesis. (Under the direction of Dr. Joshua G. Pierce).

Nature provides an abundance of unique compounds containing an extensive variety of both structural diversity and function. Oftentimes, this biological function inspires their total synthesis for the purpose of discovering new therapeutic lead molecules. Among the numerous functional groups that help define a compound’s structure and activity are nitrogen-containing heterocycles. Nitrogen heterocycles are rings with one or more nitrogen atom, and they are one of the most frequently occurring functional groups found in natural products as well as FDA-approved drugs; however, installation of these privileged scaffolds into the overall synthesis of a complex molecule can prove to be challenging particularly if stereocenters are present within the ring. Therefore, it is of great interest to develop novel methods for the synthesis of nitrogen-containing heterocycles with the goal of improving the synthesis of complex natural products and allowing access to analogs not available through existing approaches.

This document describes novel methods for accessing nitrogen-containing heterocycles as well as applications to total synthesis. One of these heterocycles is the 1,2,4-oxadiazole. Complementary to previous work for accessing 1,4,2-oxathiazoles, oxidative cyclization of amidoximes provide a variety of aryl and allylic oxadiazoles. Further developments on the stereoselective synthesis of quaternary-substituted thiazolines are also described. Complementary to a previous syn-diastereoselective process, a novel anti-diastereoselective procedure has been developed via halocyclization of S-allyl thioimidate hydrobromide salts. This work provides a route to access analogs of existing thiazoline-containing natural products that are inaccessible with existing methods. With slight changes to the substrate as well as the addition of a chiral organocatalyst, the first example of enantioselective synthesis of quaternary-substituted
thiazolines via halocyclization is demonstrated. Further developments are outlined for the synthesis of thiazolines bearing exocyclic methylene esters via an $S_N2$/conjugate addition cascade between thioamides and ethyl 4-bromocrotonate. Finally, ongoing efforts for the diastereoselective synthesis of the *Amaryllidaceae* alkaloid haemanthamine using a previously developed method for hydroxy-dihydro-pyrrolones is described. When finished, this short (approximately 8 steps) synthesis should provide access to other members of the crinane-type subclass of alkaloids as well as allow for further investigations into the biological capabilities of these promising anticancer therapeutic leads.
Novel Methods for Nitrogen-Containing Heterocycles and Applications to Total Synthesis

by
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A dissertation submitted to the Graduate Faculty of
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DEDICATION

This work is dedicated to my parents Pamela Wagner and David Parker. Without their lifelong support, I would never have reached this goal.
BIOGRAPHY

Patrick Daniel Parker was born on January 3, 1992 in Nashville Tennessee to Pamela and David Parker. For his early years, he was raised in Hermitage (east Nashville) with his older sister. During this time, Patrick developed an interest in the natural and mathematical sciences. Around 2000, his parents divorced, and his family was split between Mount Juliet (east Nashville) and Spring Hill (south Nashville). Nonetheless, Patrick never lost his knack for learning, and developed his love for chemistry in 2008 during his junior year of high school. His passion for chemistry grew under the mentorship of Dr. Danielle Garrett who ultimately inspired him to pursue a Ph.D. After graduating high school in 2010 with honors, Patrick attended Lipscomb University in Nashville where he earned his B.S. degree in chemistry and applied mathematics as well as a minor in physics. In 2014, he moved to Raleigh North Carolina to begin his Ph.D. studies at NC State University under the direction of Dr. Joshua Pierce. During this time, he focused on the development of novel methods for accessing medicinally relevant nitrogen-containing heterocycles and their applications to total synthesis. This experience gave Patrick a passion for using synthetic chemistry as a tool for drug discovery. Also during his Ph.D., Patrick was a part of two collaborative medicinal chemistry projects: one with the NC State College of Veterinary Medicine and the other with Collaborations Pharmaceuticals, Inc. In 2018, he completed a three month internship in Small Molecule Process Chemistry at Genentech, Inc. in South San Francisco where he further realized his passion for drug discovery and development. Patrick hopes to continue pursuing his dream of an industrial career developing novel therapeutics as he moves into the future with his Ph.D.
ACKNOWLEDGMENTS

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LIST OF ABBREVIATIONS

AA: *Amaryllidaceae* alkaloid

Ac: Acetyl

AChE: Acetylcholinesterase

AT\(_1\): Angiotensin II receptor type 1

BINAP: 2,2’-Bis(diphenylphosphino)-1,1’-binaphthalene

Bn: Benzyl

BOx: 2,2’-Methylenebis[(4S)-4-phenyl-2-oxazoline]

BPhen: 4,7-Diphenyl-1,10-phenanthroline

Bz: Benzoyl

Bz\(_F\): Pentafluorobenzoyl

CHD: Cyclohexadiene

CSA: Camphorsulfonic acid

Cy: Cyclohexyl

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCDPH: 1,3-Dichloro-5,5-diphenylhydantoin

DCB: 1,4-Dicyanobenzene

DCN: 1,4-Dicyanonaphthalene

DDQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

1,3-DHBA: 1,3-Dihydroxybenzaldehyde

DIPEA: Diisopropylethylamine

DMF: Dimethylformamide

dppBz: 1,2-Bis(diphenylphosphino)benzene
dppf: 1,1'-Ferrocenediyl-bis(diphenylphosphine)
dppp: 1,3-Bis(diphenylphosphino)propane
Et: Ethyl
EPR: Electron paramagnetic resonance
FDA: Food and Drug Administration
Gly: Glycine
GPx: Glutathione peroxidase
HAT: Hydrogen atom transfer
HDAC: Histone deacetylase
HFIP: Hexafluoroisopropanol
HPLC: High-performance liquid chromatography
HWE: Horner-Wadsworth-Emmons
(Li, Na, K)HMDS: (Lithium, sodium, potassium) hexamethyldisilazane
iPr: Isopropyl
KIE: Kinetic isotope effect
LC-MS: Liquid chromatography-mass spectrometry
LDA: Lithium diisopropylamide
mCPBA: meta-Chloroperoxybenzoic acid
Me: Methyl
Ms: Mesyl
NBS: N-Bromosuccinimide
NCS: N-Chlorosuccinimide
NHC: N-Heterocyclic carbene
NIS: N-Iodosuccinimide
NMP: N-Methyl pyrrolidone
NMR: Nuclear magnetic resonance
$S_{\text{NAr}}$: Nucleophilic aromatic substitution
$p\text{Tol}$: para-Toluoyl
$p\text{TsOH}$: para-toluenesulfonic acid
Ts: Tosyl
Ph$_F$: Pentafluorophenyl
PTC: Phase transfer catalysis
Pr: Propyl
SET: Single electron transfer
SPhos: 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBAI: Tetrabutylammonium iodide
TBS: Tert-butyl-dimethyl silyl
TFA: Trifluoroacetic acid
TES: Triethyl silyl
TFE: Trifluoroethanol
THF: Tetrahydrofuran
TLC: Thin layer chromatography
XantPhos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
CHAPTER 1

General Introduction
1.1: Introduction to Natural Products

Nature offers an abundance of molecules that provide an extensive array of both structural diversity and function. In many cases, this function leads to new and interesting lead molecules that become targets for total synthesis to discover novel therapeutics.\(^1\) Even today, nature is being used for its ability to provide biologically relevant compounds, and many significant modern pharmaceuticals are either isolated natural products or natural product-inspired synthetic frameworks (Figure 1.1).\(^2\)

![Figure 1.1: Biologically active natural products and natural product-inspired pharmaceuticals.](image)

For thousands of years, civilizations have benefited from the use of natural products as environmental remedies for various maladies. The ancient Greeks, for example, enjoyed the tranquil effects of morphine when they consumed extracts from the opium poppy.\(^1\) Morphine has been marketed for nearly two centuries as a potent analgesic. It was determined in 2015 by the
International Narcotics Control Board (an extension of the United Nations) that between 1994 and 2013 global manufacturing of morphine more than doubled from 247.1 tons to 522.6 tons.³

In his writings on the Gallic Wars, Julius Caesar mentions the suicide of a chieftain of the Eburones named Catuvolcus who consumed an extract of a yew tree. The yew tree quickly became known as the tree of death, but its curative powers were not to be recognized until the late 20th century.¹ Paclitaxel (Taxol®) was first isolated in the 1960’s from the Pacific yew tree *Taxus brevifolia*. Its structure was determined in 1971 by Drs. Wall and Wani, and it has since been used as a potent chemotherapeutic agent against ovarian, breast, and lung cancers. Its mode of action involves the stabilization of microtubules necessary for cell division which arrests the cell at the G1/S phase checkpoint and leads to apoptosis of cancer cells. Since its discovery, paclitaxel has become one of the top-selling anticancer drugs on the market, and this has led to the development of many second-generation synthetic analogues such as taxane and docetaxel.⁴

In addition to morphine and paclitaxel, there are numerous other examples of the use of natural products and natural product-inspired frameworks as pharmaceuticals. The compound bryostatin 1 was first isolated in 1968 from the marine organism *Bugula neritina*, and its structure was determined in 1982 by Edward Arnold and coworkers (Figure 1.1).⁵ Bryostatin 1 acts as a potent protein kinase C agonist and is being studied for its ability to prevent tumor growth.⁶ Bryostatin 1 is also being studied for its memory enhancing qualities. It was discovered in 2006 by Dr. Kuzirian and coworkers that bryostatin 1 was able to drastically augment the long-term memory of the sea slug *Hermisenda crassicornis*.⁷ Other examples of therapeutically relevant natural products include the β-lactam penicillin derivative ampicillin and Norvir® which is a short peptide-derived pharmaceutical used to fight HIV/AIDS as well as hepatitis C.
1.2: Introduction to Nitrogen-Containing Heterocycles

As discussed above (Section 1.1), the finding of novel lead molecules as inspiration for new therapeutics is an important ongoing part of the drug discovery procedure. While the realm of natural products grows and a greater diversity of structures arise, novel innovative methods for the synthesis of complex molecular frameworks must also evolve with the times.

The multitude of functional groups in natural products and pharmaceutical drugs give each molecule its unique structure and properties. For example, marthiapeptide A, isolated from the deep sea sediment *Marinactinospora thermotolerans*, and monanchomycalin A, isolated from the sponge *Monanchora pulchra*, are both marine natural products with cytotoxic bioactivity (Figure 1.2).\(^2,8\) Vinblastine is a terrestrial natural product isolated from the leaves of *Catharanthus roseus*, and acts similarly to paclitaxel as an inhibitor of microtubule elongation.\(^9\) Phidianidine A is a marine natural product isolated from the sea slug *Phidiana militaris* and is a dopamine transporter protein (DAT) inhibitor.\(^10\) Emtricitabine and Tenofovir (Truvada\(^\text{®}\)) make up a combination drug used as pre-exposure prophylaxis (PrEP) for the prevention of HIV infection. Finally, brevianamide B was isolated from the fungus *Penicillium brevicompactum*, and has been studied for its insecticidal properties.\(^11\)

One feature that is common to each of these molecules is the presence of many diverse heterocycles (highlighted in red, Figure 1.2). Heterocycles are rings with one or more heteroatoms; they are both naturally and frequently occurring functional groups. As with any multifaceted scaffold, installing a heterocycle into the overall synthesis of a complex molecule can be problematic. The challenge is made worse with the presence of stereocenters in the ring. Therefore, novel methods for the synthesis of these rings, ideally in a stereoselective fashion, is desirable for the future benefit of complex molecule synthesis.
Among the most commonly found heterocycles in both nature and pharmaceuticals are those that contain nitrogen. A 2014 study shows that 84% of a database of 1086 small molecule drugs approved by the FDA contain at least one nitrogen atom. Among that same set of 1086 drugs, 59% contain a nitrogen heterocycle.12 The quantity and diversity of nitrogen-containing heterocycles in pharmaceutical drugs demonstrate the need for efficient methods of installing these rings into the synthesis of complex molecules. Therefore, the Pierce group has set out to develop methods for the synthesis of naturally occurring and medicinally relevant nitrogen-containing heterocycles.13-18

**Figure 1.2:** Various complex heterocycle-containing natural products and pharmaceutical drugs.
1.3: References


CHAPTER 2

Synthesis of Tri-Heteroatom Azoles

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Raleigh, NC 27695-8204
2.1: General Introduction: Synthesis of 1,4,2-Oxathiazoles

A nitrogen heterocycle that has attracted significant attention is the 2-thiazoline.\(^1\)\(^2\) Thiazolines will be discussed in more detail in CHAPTER 3 of this document. Dr. Bérénice Lemercier, a former graduate student, developed an efficient method for the synthesis of thiazolines relying on the copper-catalyzed cyclization of Bz\(_F\)-activated S-allyl hydroximic acids.\(^1\) During the optimization of this reaction, she observed formation of a different product when the hydroxyl group was not Bz\(_F\)-activated (highlighted in orange, Scheme 2.1).

![Scheme 2.1: Observations during copper-catalyzed thiazoline optimization.](image)

The unexpected side product was determined to be a 1,4,2-oxathiazole (Figure 2.1). Oxathiazoles are five-membered heterocycles containing an oxygen, sulfur, and nitrogen atom. Because of the limited synthetic methods available for accessing these heterocycles and due to their potential use in SAR studies alongside structurally similar yet more medicinally-privileged rings, this oxidative cyclization reaction was explored. Under the optimal conditions, one equivalent of DDQ and sub-stoichiometric amounts of oTsOH at reflux in DMF provided a variety of oxathiazoles in good yields (Table 2.1).\(^3\) The reaction works well for substrates where \(R^2\)
(highlighted in green) is aryl-(2-1 and 2-3)-, heteroaryl-(2-2)-, and cyclopropyl-(2-4)-derived. \( R^1 \) (highlighted in blue) can be aryl- as well as heteroaryl-(2-5)-derived. Furthermore, the formation of the ester-containing compound 2-6 provides a handle for further functionalization to build molecular complexity.

**Figure 2.1:** Structure of 1,4,2-oxathiazole heterocycles.

**Table 2.1:** Substrate scope highlights for 1,4,2-oxathiazole formation.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reaction Conditions</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1</td>
<td>DDQ (1 equiv) ( \overset{\bullet}{\text{TsOH}} ) (50 mol%)</td>
<td>2-2</td>
<td>81%</td>
</tr>
<tr>
<td>2-2</td>
<td>DMF, 150 °C</td>
<td>2-3</td>
<td>81%</td>
</tr>
<tr>
<td>2-3</td>
<td></td>
<td>2-4</td>
<td>38%</td>
</tr>
<tr>
<td>2-4</td>
<td></td>
<td>2-5</td>
<td>38%</td>
</tr>
<tr>
<td>2-5</td>
<td></td>
<td>2-6</td>
<td>68%</td>
</tr>
</tbody>
</table>
PART 1: Synthesis of 1,2,4-Oxadiazoles

2.2.1: Abstract

A DDQ-mediated oxidative cyclization of amidoximes is described. This method provides a rapid approach to 1,2,4-oxadiazoles some of which cannot be accessed via milder oxidative cyclizations. Moderate yields of oxadiazoles were obtained with N-benzyl- and N-allyl-derived amidoximes although cyclopropyl- and heteroaryl-containing substrates also work moderately well. Mechanistic insights are also provided. There is evidence for and against each provided pathway, and more experimentation is necessary for a mechanism to be confidently proposed.

2.2.2: Introduction and Background

As a result of our success with the DDQ-mediated cyclization of S-allyl thiohydroximic acids, we planned to apply that method to the synthesis of other similar heterocycles. One heterocycle we considered was the diazole variant formed by replacing the sulfur atom of an oxathiazole with a second nitrogen atom. 1,2,4-Oxadiazoles are five membered aromatic heterocycles that contain an oxygen atom and two nitrogen atoms (Figure 2.2). For the remainder of this document, the term oxadiazole will refer only to 1,2,4-oxadiazoles.

Figure 2.2: Structure of 1,2,4-oxadiazole heterocycles.
2.2.2.1: Oxadiazole-Containing Compounds

Oxadiazoles can be found in a variety of biologically relevant compounds with a diversity of both structure and activity (Figure 2.3). As mentioned earlier (Section 1.2), phidianidine A is a natural product with antidepressant activity.\(^4\) Pleconaril (Picovic\(^\text{®}\)) is a drug used to treat rhinovirus infections which results in the common cold.\(^5\) Other synthetic oxadiazoles include Fasiplon\(^\text{®}\) and ataluren (Translarna\(^\text{®}\)) which are used to treat anxiety and cystic fibrosis, respectively.\(^6,7\) Also shown below are other oxadiazole-containing compounds with a variety of activities from anticancer to antibacterial.\(^8-10\)

![Figure 2.3: Oxadiazole-containing natural products and biologically active compounds.](image)

Oxadiazoles are not only found in natural products and biologically relevant compounds, but they have also been employed as ligands (Figure 2.4). The tri-pyridine-containing compound on the left is known to selectively bind to G-quadruplexes. This useful technology allows scientists...
to probe the super structure of DNA.\textsuperscript{11} Other oxadiazole-containing compounds have been shown to bind to transition metals.\textsuperscript{12} Ligands such as this coordinate to metal ions such as Pt(II), and they show potent cytotoxicity to various ovarian, colon, and testicular cancer cell lines.\textsuperscript{13}

Figure 2.4: Oxadiazole-containing ligands.

2.2.2.2: Reactivity and Applications of Oxadiazoles

As a result of their poor aromaticity ($\lambda = 48$), oxadiazoles can be fairly reactive heterocycles allowing them to undergo many subsequent transformations and rearrangements.\textsuperscript{14} The photo-cleavable nitrogen-oxygen bond, the electrophilic carbon atoms, the nucleophilic N4, and the ambiphilic N2 all give rise to an assortment of applications and reactivity (Figure 2.5).\textsuperscript{15}

Figure 2.5: Overview of the reactivity of oxadiazoles.
For example, oxadiazoles bearing exocyclic amides can take advantage of the labile nitrogen-oxygen bond. Upon deprotonation, the amide oxygen atom is free to reversibly attack the electrophilic N2 and shift the oxadiazole to a new position (Scheme 2.2). Due to the inductively withdrawing oxygen atom, N2 is less likely to function as a nucleophile unless favorable stereoelectronic conditions exist; however, there are examples where the ambiphilic N2 does act as a nucleophile, but this is always in competition with the more nucleophilic N4. Treatment of compound 2-7 with a series of fluorinated β-diketones gives compound 2-8 with a C3-linked side chain. In the presence of HClO4, this reaction provides both 2-amino-pyrimidines 2-9 and 2-10 via nucleophilic attack by N2 and N4, respectively (Scheme 2.3). Conversely, N4 is predominantly only available to act as a nucleophile and is typically the atom involved in metal complexation. C3 and C5 are both electrophilic sites. C3 is less electrophilic and only undergoes aromatic substitution with good leaving groups; however, C5 is far more electrophilic than C3, and it can undergo a variety of substitutions with a wider range of nucleophiles. The mode of attack typically involves S_NAr, but there are examples of addition of a nucleophile ring-opening-ring-closing reactions (ANRORC). For instance, attack of a 1,2-di-nucleophile (highlighted in green) to C5 of oxadiazole 2-11 leads to the ring-opened intermediate 2-12 (Scheme 2.4). Depending on the nature of the C3 substituent, subsequent ring closure can occur at either C3 or the C3 side chain to form compounds 2-13 and 2-14, respectively. The C5 position can also activate adjacent functional groups, such as alkenes, for attack by nucleophiles.
Scheme 2.2: Oxadiazole-to-oxadiazole interconversion.

Scheme 2.3: Competitive nucleophilic reactivity of N2 and N4 atoms of oxadiazoles.

Scheme 2.4: Electrophilic reactivity of C5 atom of oxadiazoles to 1,2-di-nucleophiles.
The ambiphilic nature of the oxadiazole allows it to undergo a number of rearrangements. A common example involves a photo-induced rearrangement (Scheme 2.5). Light promotes the nucleophilic attack of the N2 atom of oxadiazole 2-14 onto the C5 atom to form intermediate 2-15. The oxygen atom can then shift from C5 to C3 (bond highlighted in green). This is followed by re-aromatization to oxadiazole 2-16 where the substituents R1 and R2 are now located on opposite sides of the ring. This atom-shuffling event occurs without opening of the ring. However, light can also promote cleavage of the labile nitrogen-oxygen bond to form a zwitterion 2-17. The electron-deficient nitrogen atom (formerly N2 of compound 2-14) can be attacked by the adjacent nitrogen atom (formerly N4 of compound 2-14) to form diazirine 2-18. This intermediate undergoes rearrangement to the 1,3,4-oxadiazole 2-19. The nitrene resonance form of intermediate 2-17 can also undergo a series of subsequent transformations. In the presence of a trapping agent, such as an alkene, aziridine derivatives like compound 2-20 can be formed. The nitrene can also undergo intramolecular rearrangement to a carbodiimide. This intermediate can be attacked by a nucleophile and cyclized to form triazoles and oxadiazoles that resemble compound 2-21.15,18

Scheme 2.5: Photo-induced oxadiazole rearrangements.
If C5 is particularly electron deficient, the rearrangement of oxadiazole 2-14 to compound 2-16 can also occur without light. Nucleophilic attack by hydroxylamine (highlighted in green, Scheme 2.6) onto C5 of oxadiazole 2-22 causes ring opening to intermediate 2-23. The oxygen formerly belonging to hydroxyl amine can then attack the C3 position, and this is followed by expulsion of hydroxylamine to form rearranged oxadiazole 2-24.¹⁹

**Scheme 2.6:** Nucleophile-induced oxadiazole rearrangement.

Other applications of oxadiazoles involve fluorination chemistry. Compounds such as 2-25 have been used for their ability to functionalize nucleophilic sites of polymers and large macromolecules (Figure 2.6).²⁰,²¹ Another example involves compounds such as 2-26 which have been used for functionalizing olefins with difluoromethylenes.²²

**Figure 2.6:** Oxadiazole utility in fluorination chemistry.
2.2.2.3: Synthesis of Oxadiazoles

Originally named furo[ab]1diazoles, the first recorded synthesis of an oxadiazole was in 1884 by Tiemann and Krüger. Consistent literature reports on oxadiazole synthesis did not appear until the early 1960’s. There are two very common methods for approaching the synthesis of these heterocycles. The first was disclosed by Huisgen and coworkers in 1961, and it involved a [3 + 2] cycloaddition between a nitrile and a nitrile oxide (Scheme 2.7). The nitrile oxide is typically formed in situ from a hydroxyimidoyl chloride with the use of either a base or a Lewis acid. The other common method uses the coupling of an amidoxime with a carboxylic acid which is followed by a cyclodehydration step. This second method has been demonstrated on solid support for the creation of combinatorial libraries of oxadiazole-containing compounds.

Scheme 2.7: Common methods for the synthesis of oxadiazoles.

The first route described above can also be used for the synthesis of 3-acyl-oxadiazoles. Methyl ketone derivatives can generate nitrile oxides in situ in the presence of iron(III) nitrate (Scheme 2.8). This proceeds via α-nitration of the ketone followed by loss of water to give the nitrile oxide. Addition of a nitrile to the reaction provides the C3-acylated oxadiazole. 3-Acyl-oxadiazoles such as 2-27 are human mast cell tryptase inhibitors and have been studied for the treatment of asthma.
Since 1961, several reactions have been developed for the formation of oxadiazoles. In 1967, the Boulton-Katritzky rearrangement was developed (Scheme 2.9). This transformation has been shown to work for substrates with C3-bearing side chains X-Y-Z as N-C-O, C-N-O, C-C-O, N-C-S, N-C-C, C-C-N, C-N-N, N-C-N, and N-N-N.\textsuperscript{15,29} In 1998, Young and coworkers published a palladium-catalyzed coupling of an aryl iodide with carbon monoxide (Scheme 2.10). The resulting acyl-palladium species was reacted with an amidoxime followed by cyclodehydration to form the oxadiazole. This chemistry was demonstrated on five substrates in up to 60% yield.\textsuperscript{30} In 2016, Kuram and coworkers reported a copper-catalyzed coupling and oxidative cyclization of amides with nitriles for the synthesis of biaryl oxadiazoles (Scheme 2.11). Mechanistically, this reaction is believed to proceed through an oxygen-mediated Cu(I)/Cu(II)-catalyzed oxidation of a substrate-bound Cu(II) complex to a Cu(III) species that rapidly undergoes reductive elimination to C(I) while also forming the nitrogen-oxygen bond of the oxadiazole (copper catalyst oxidation states are highlighted in green). This method worked well for 33 substrates in up to 94% yield.\textsuperscript{31}
Scheme 2.9: Boulton-Katritzky rearrangement.

Scheme 2.10: Palladium-catalyzed oxadiazole synthesis.

Scheme 2.11: Copper-catalyzed oxadiazole synthesis.

Another development by Chiba and coworkers in 2013 involves the aerobic oxidative cyclization of benzylic amidoximes to oxadiazoles. In this report, Chiba describes the use of oxygen as a single electron oxidant which reacts with the amidoxime substrate to form an oxygen-centered radical (highlighted in green, Scheme 2.12). The radical is then transferred to the benzylic position via a 1,5-hydrogen shift. A second oxidation forms a nitrogen-stabilized benzylic
carbocation, which is followed by 5-endo cyclization to the oxadiazole. This chemistry was shown to work for 16 substrates in up to 94% yield.\textsuperscript{32}

Scheme 2.12: Aerobic synthesis of oxadiazoles.

\textbf{2.2.3: Results and Discussion}

\textbf{2.2.3.1: Synthesis of Amidoximes and Reaction Optimization}

As mentioned, our strategy was to apply the success of oxathiazole synthesis to the formation of oxadiazoles. Analogous to the S-allyl thiohydroximic acids used for the synthesis of oxathiazoles, amidoximes were our target substrates for oxadiazole formation. Our synthetic route began with the corresponding aldehyde (Scheme 2.13). Treatment of aldehyde with hydroxyl amine provided the aldehyde oxime which can be subsequently reacted with NCS to form the hydroxyimidoyl chloride. Addition of base to the hydroxyimidoyl chloride was used for \textit{in situ} generation of the nitrile oxide, which upon addition of an amine, provided the amidoxime.

Scheme 2.13: Synthetic route to amidoximes.
With this route, an assortment of amidoximes were synthesized from the corresponding hydroxylimidoyl chlorides (Scheme 2.14). Compounds 2-28 through 2-41 each are derived from benzaldehyde, but they vary on the substituent at R² (highlighted in green). We were able to synthesize a variety of benzyl-derived amidoximes containing both electron-rich (2-29) and electron poor (2-30) aromatic rings as well as heteroaromatic ring (2-31 and 2-32) in good yields. Homobenzylic substituents such as 2-33 and 2-34 were synthesized as well as substrates that used amines with tertiary-substituted α-carbons (2-35 and 2-36). Aliphatic amines also work well (2-37) and so do allylic, propargylic, and cyclopropyl amines (2-38 through 2-41) in good yields. After altering the right side of the amidoximes, we investigated the R¹ (highlighted in blue) substitution (2-42 through 2-46). Aromatic and conjugated R¹ substituents were synthesized in good yields (2-42 through 2-45) as well as the ester-containing compound 2-46.
Scheme 2.14: Amidoximes synthesized from the corresponding hydroxylimidoyl chloride.
With the starting material route established, optimization of the reaction conditions could proceed. Our initial screenings were focused on the number of equivalents of DDQ necessary to promote the reaction (Table 2.2). With one equivalent of DDQ, the reaction gave oxadiazole 2-20 in 34% yield (entry 1). These were the same conditions as for the synthesis of oxathiazoles which only required one oxidation. However, given that there are two oxidations that must occur to bring an amidoxime to an oxadiazole, we tried two and three equivalents of DDQ. Increasing the equivalents of DDQ to two in refluxing DMF increased the yield to 48% (entry 2); however more than two equivalents of DDQ gave a lower yield comparable to that obtained with one equivalent (entry 3). Next, we examined the importance of the p-TsOH additive that had proven to be beneficial in the synthesis of oxathiazoles. Removing this additive did not have an effect on either the reaction’s rate or yield (entry 4). We then moved on to a solvent screen. Each of the solvents explored gave a decrease in the yield (entries 5–8). The yield was affected slightly with a change in concentration increasing to 53% at 0.1 M (entries 9 and 10). We observed that the reaction proceeds (albeit slower) at lower temperatures, so we varied the reaction temperature in another attempt to improve the yield. Lowering the temperature to 85 °C and then to room temperature lead to prolonged reaction times and lower yields (entries 11 and 12). The stability of the starting material was investigated by stirring 2-28 in DMF at 150 °C, and this resulted in no observed decomposition or conversion to 2-47 even with prolonged reaction times. The final test we conducted was to change the oxidant. Cu(OAc)_2 and Cu(O_2CCF_3)_2 (entries 13 and 14) provided oxadiazole 2-47 in significantly lower yields: 19% and 7% respectively. [Imino(phenyl)methyl]benzamide was isolated as a byproduct in the reaction with Cu(OAc)_2 in 7% yield. Although the optimized yield is modest, this reaction provides easily purified oxadiazoles in short reaction times, and we therefore moved on to explore the substrate scope.
2.2.3.2: Substrate Scope of Oxadiazole Synthesis.

We began investigating the substrate scope with amidoximes bearing variations in the R\(^2\) substituent (highlighted in green, Scheme 2.15). The benzylic-derived amidoximes worked well for oxadiazole formation. The electronically-rich compound 2-48 was synthesized from 2-29 in 38% yield whereas the electronically poor compound 2-49 was formed from 2-30 in 55% yield. Heteroaryl substrates also worked moderately well. Pyridine-containing compound 2-50 was synthesized from 2-31 in 46% yield, and the thiophene-containing compound 2-51 was accessed from amidoxime 2-32 in 52% yield. Allylic substrates 2-38 and 2-39 were converted to oxadiazoles 2-52 and 2-53 in 27% and 20% yields, respectively. Although lower in yield than other substrates, these allylic oxadiazoles cannot be accessed by other milder conditions.\(^{32}\) To our surprise, the cyclopropyl amidoxime 2-41 provided oxadiazole 2-54 in 18% yield without any observed

---

**Table 2.2: Optimization of oxadiazole formation.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>2-47 yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DDQ (1 equiv), pTsOH (50 mol%), DMF, 150 °C, 1 h</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>DDQ (2 equiv), pTsOH (50 mol%), DMF, 150 °C, 30 min</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>DDQ (3 equiv), pTsOH (50 mol%), DMF, 150 °C, 20 min</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>DDQ (2 equiv), DMF, 150 °C, 30 min</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>DDQ (2 equiv), DCE, 83 °C, 30 min</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>DDQ (2 equiv), toluene, 110 °C, 45 min</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>DDQ (2 equiv), 1,4-dioxane, 100 °C, 4 h</td>
<td>37</td>
</tr>
<tr>
<td>8</td>
<td>DDQ (2 equiv), MeCN, 82 °C, 4.5 h</td>
<td>38</td>
</tr>
<tr>
<td>9</td>
<td>DDQ (2 equiv), DMF (0.01 M), 150 °C, 30 min</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>DDQ (2 equiv), DMF (0.1 M), 150 °C, 30 min</td>
<td>53</td>
</tr>
<tr>
<td>11</td>
<td>DDQ (2 equiv), DMF (0.1 M), 85 °C, 30 min</td>
<td>51</td>
</tr>
<tr>
<td>12</td>
<td>DDQ (2 equiv), DMF (0.1 M), rt, 24 h</td>
<td>40</td>
</tr>
<tr>
<td>13</td>
<td>Cu(OAc)(_2) (1 equiv), DMF (0.1 M), rt, 10 min</td>
<td>19</td>
</tr>
<tr>
<td>14</td>
<td>Cu(O_2CFCF_3)_2 (1 equiv), DMF (0.1 M), rt, 30 min</td>
<td>7</td>
</tr>
</tbody>
</table>

\(^{a}\)All reactions were performed on 50 mg scale and at 0.05 M unless otherwise noted. \(^{b}\)Isolated product yield.
opening of the ring. This result mirrors that obtained in our synthesis of oxathiazoles (2-4, Table 2.1).

![Scheme 2.15: Substrate scope of oxadiazole formation.](image)

We also examined the substrates bearing variations at the R<sup>1</sup> substituent (highlighted in blue, Scheme 2.15). The synthesis of naphthyl- and 4-methoxyphenyl- oxadiazoles 2-55 and 2-56 was carried out in 51% to 40% yield, respectively. The styrenyl-oxadiazole 2-57 was formed from 2-44 in 45% yield, and the thiophene-containing oxadiazole 2-58 was synthesized from 2-45 in 66% yield. The most surprising result came with the 73% yield obtained for the ester-containing oxadiazole 2-59. This ester group provides a handle for further functionalization which in turn could lead to the synthesis of more complex oxadiazole-containing molecules.
2.2.2.3: Mechanistic Insights

The first step of our original proposed mechanism involves DDQ oxidation of the substrate’s hydroxy group to form an oxygen radical cation followed by proton transfer (Scheme 2.16). The resultant oxygen radical species undergoes a 1,5-hydrogen shift to transfer the radical to the benzylic position. This is followed by a second oxidation by DDQ to a benzylic carbocation that is stabilized by the adjacent nitrogen atom.\(^{33}\) This in turn undergoes a 5-endo cyclization to the dihydro-oxadiazole. Lastly, a subsequent HAT by the second equivalent of DDQ provides the oxadiazole.

\[
\begin{align*}
\text{N-O}^+ & \quad \text{DDQ} \quad \text{DDQ}^- \\
\text{N-O}^- & \quad \text{DDQH} \quad \text{DDQH}^- \\
\text{N-O} & \quad \text{DDQH}_2 \quad \text{DDQ} \\
\text{N-O} & \quad \text{DDQH} \quad \text{DDQH} \\
\text{N-O} & \quad \text{DDQH}_2 \quad \text{DDQ} \\
\text{N-O} & \quad \text{DDQH} \quad \text{DDQH} \\
\text{N-O} & \quad \text{DDQH}_2 \quad \text{DDQ}
\end{align*}
\]

Scheme 2.16: Original proposed mechanism of oxadiazole formation.

We initially believed that the reaction proceeded through a DDQ-generated radical species, but we were unsure about what part of the substrate was oxidized. In her brief mechanistic investigations, Dr. Lemercier subjected \(O\)-methyl-thiohydroximate \(2\-60\) to the reaction conditions hoping to find formation of the corresponding \(O\)-methyl-thiohydroxamate \((2\-61)\) as a result of decomposition of an unreacted thiocarbenium ion intermediate (Scheme 2.17). When no desired
product was formed and 75% of starting material was recovered, she concluded that the radical was formed initially on the oxygen atom. This kind of oxygen-centered radical and subsequent 1,5-hydrogen atom shift mechanism is supported by Chiba and coworkers.\textsuperscript{32,34–35} Furthermore, EPR studies indicate the existence of a radical in the cycloisomerization of 1,5-diynols to substituted benzofluorenes developed by Chen and coworkers.\textsuperscript{36} They attribute the radical to oxidation of an allenol intermediate by DDQ. It is possible, however, that the oxidation by DDQ, whether via HAT or hydride transfer, is a reversible process.

![Scheme 2.17: Mechanistic study of oxathiazole formation.](image)

One aspect of our substrate scope that does not seem to support the idea of a radical mechanism is the cyclopropyl-containing oxadiazole 2-54. As a radical clock, the cyclopropyl group should theoretically have opened. It is possible that the adjacent nitrogen atom (or sulfur in the oxathiazole case) is responsible for stabilizing the radical causing the rate of cyclization to outcompete the rate of ring opening. This kind of cyclopropyl preservation by radical stabilization via an adjacent heteroatom has been reported by Floreancig and coworkers.\textsuperscript{37}
More recently in 2017, the Floreancig group has reported a study on computational examinations of the mechanism of alkenic, allylic, and benzylic C–H functionalization via DDQ-mediated oxidation with intra- and intermolecular carbon and heteroatom nucleophiles. They discuss four possible mechanisms (Scheme 2.18). The first two involve SET events via a radical pathway much like our original proposed mechanism. The first pathway goes through a SET event to a charge transfer complex between a radical cationic species and a DDQ radical anion. This is followed by a HAT event to the benzylic-stabilized carbocation and a 4-hydroxyphenolate derivative (DDQH\(^{-}\)). Although consistent with the importance of substrate oxidation on reaction rate, the Floreancig group rules out this pathway on the basis of discrepancy between the oxidation potential of the typical benzylic or allylic ether (1.4–2.2 V vs SCE)\(^{39}\) and the reductive potential of DDQ (0.50 V vs SCE).\(^{40}\) The second pathway is reversed from the first in that it involves a HAT event to a neutral substrate/DDQ radical species complex followed by SET to the same carbocation complex as before. This pathway is ruled out based on the known lack of substituent effects on benzylic C–H bond strengths\(^{41}\) and its contrast to the observed cation-stabilizing influence of adjacent substituents on the reaction rate. Furthermore, KIE studies show a primary effect indicating that breaking of the C–H bond is involved in the rate determining step. This indicates that formation of a reactive intermediate prior to bond cleavage is not rate determining.\(^{42}\) The third and fourth pathways Floreancig proposes involve hydride shifts from the substrate to either an oxygen or a carbon bonded to the nitrile of DDQ. The Floreancig group found it likely that DDQ-mediated benzylic and allylic oxidations proceed through a hydride transfer rather than through SET/HAT events which contradicts our previously proposed mechanism. Either way, there has not been enough experimentation to date for a mechanism to be confidently proposed.
2.2.4: Conclusions

Our group developed a DDQ-mediated oxidative cyclization of S-benzyl- and S-allyl-thiohydroximic acids for the synthesis of 1,4,2-oxathiazoles. As a continuation, this project was expanded to the synthesis of 1,2,4-oxadiazoles from the corresponding amidoximes. The reaction translated well between these two heterocycles. Conversion of amidoximes to oxadiazoles was achieved with 2 equivalents of DDQ, and we demonstrated this on 13 substrates with up to 73\% yield. Although not fully elucidated, minimal experimentation and literature precedence has given us insights into plausible mechanisms each with their own respective support and drawbacks. We cannot confidently endorse a mechanism at this time, but further investigations could help to shed light on an unambiguous pathway to propose.
2.2.5: Experimental Section

General considerations: All reactions were performed under a nitrogen atmosphere, and all glassware was flame-dried and flushed with nitrogen prior to use. DMF (99.8%, extra dry over molecular sieves) and DDQ were purchased from Acros Organics and used as received. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F$_{254}$ plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a KMnO$_4$ solution (1.5 g of KMnO$_4$, 10 g of K$_2$CO$_3$, and 1.25 mL of a 10% NaOH solution in 200 mL of water). Reactions were also monitored by LC-MS analysis (Shimadzu LC-MS 2020 with Kinetex 2.6 mm C18 50 × 2.10 mm). Flash chromatography on SiO$_2$ was used to purify the crude reaction mixtures and performed on a Biotage Isolera using Biotage cartridges and linear gradients.

$^1$H and $^{13}$C NMR spectra were obtained on a Varian Mercury-VX 300, a Varian Mercury-VX 400, or a Varian Mercury-Plus 300 instrument in CDCl$_3$ unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard (CDCl$_3$ = 7.26 ppm for $^1$H, CDCl$_3$ = 77.16 ppm for $^{13}$C). $^1$H NMR spectra were run at 300 or 400 MHz and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, bs = broad singlet), number of protons, and coupling constant(s). $^{13}$C NMR spectra were run at 100 MHz using a proton-decoupled pulse sequence with a d$_1$ of 1 second unless otherwise noted and are tabulated by observed peak. Infrared spectra were determined on a Jasco FT/IR-4100 spectrometer. High-resolution mass spectra were obtained on a Thermo Fisher Scientific, Exactive Plus mass spectrometer (ion trap) using Heated Electrospray Ionization (HESI). Melting points were determined by using a Thomas Hoover capillary melting point apparatus.
Compounds 2-28 through 2-46 were prepared in two or three steps from the corresponding commercially available aldehydes or aldehyde oximes and amines as described below:

\[
\begin{align*}
\text{H}_2\text{NOH} \cdot \text{HCl} & \quad \xrightarrow{\text{Pyridine, EtOH}} \quad \text{NOH} \\
\text{EtOH} & \quad \xrightarrow{\text{NCS, DMF}} \quad \text{N} = \text{Cl} \\
\text{Et}_3\text{N} & \quad \xrightarrow{\text{DMF, 0 °C}} \quad \text{N} = \text{R}^2
\end{align*}
\]

\[\text{N}-\text{Benzylhydroxybenzimidamide (2-28); General protocol A.}\] To a round-bottom flask at 0 °C was added hydroxybenzimidoyl chloride (0.90 g, 5.8 mmol), DMF (19 mL), and benzylamine (0.74 g, 6.9 mmol), followed by the addition of Et$_3$N (0.58 g, 5.8 mmol), and the mixture was stirred for 2 h. The reaction was diluted with H$_2$O and extracted with EtOAc (3×). The organic layer was washed with brine, dried (MgSO$_4$), and concentrated in vacuo. The crude residue was purified by flash chromatography on SiO$_2$ (hexanes–EtOAc, 10–35%) to yield 1.1 g (86%) of 2-28 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.51$–7.48 (m, 2 H), 7.43–7.35 (m, 3 H), 7.34–7.30 (m, 2 H), 7.27–7.20 (m, 3 H), 7.16 (s, 1 H, NH), 4.25 (s, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 156.5, 139.7, 131.3, 129.7, 128.7, 128.7, 128.5, 127.3, 126.9, 47.5.$

\[\text{N-}2,4\text{-Dimethoxybenzyl)hydroxybenzimidamide (2-29); According to general protocol A,}\]

hydroxybenzimidoyl chloride (0.075 g, 0.48 mmol), (2,4-dimethoxyphenyl)methanamine (0.10 g,
0.58 mmol), and Et$_3$N (0.049 g, 0.48 mmol) were stirred in anhydrous DMF (1.6 mL) for 2 h to yield 0.084 g (61%) of 2-29 as a yellow solid after purification by flash chromatography on SiO$_2$ (hexanes–EtOAc, 5–35%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.48–7.46 (m, 2 H), 7.41 7.37 (m, 3 H), 6.90 (d, $J$ = 8.2 Hz, 1 H), 6.40 (d, $J$ = 2.4 Hz, 1 H), 6.37 (dd, $J$ = 8.2, 2.4 Hz, 1 H), 5.75 (t, $J$ = 6.2 Hz, 1 H, NH), 4.12 (d, $J$ = 6.2 Hz, 2 H), 3.78 (s, 3 H), 3.75 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 160.3, 158.4, 156.8, 131.8, 129.5, 129.0, 128.8, 128.4, 120.5, 103.8, 98.6, 55.5, 55.4, 43.1; IR (neat) 3389, 3199, 2935, 1614, 1587, 1508, 1465, 1208, 1157 cm$^{-1}$; ESIMS $m/z$ 287 [M + H]$^+$; HRMS $m/z$ [M + H]$^+$ calculated for C$_{16}$H$_{19}$N$_2$O$_3$ [M + H]$^+$ 287.1390, found 287.1390; mp = 134–137 °C.

**Hydroxy-N-[4-(trifluoromethyl)benzyl]benzimidamide (2-30);** According to general protocol A, hydroxybenzimidoyl chloride (0.20 g, 1.3 mmol), [4 (trifluoromethyl)phenyl]methanamine (0.27 g, 1.5 mmol), and Et$_3$N (0.13 g, 1.3 mmol) were stirred in anhydrous DMF (4.3 mL) for 2 h to yield 0.27 g (73%) of 2-30 as a white solid after purification by flash chromatography on SiO$_2$ (hexanes–EtOAc, 10–40%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.56–7.53 (m, 2 H), 7.45–7.34 (m, 5 H), 7.33–7.26 (m, 2 H), 5.83 (s, 1 H), 4.29 (s, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 156.4, 143.9, 130.9, 130.0, 129.8, 129.4, 128.7, 128.6, 127.0, 125.7, 125.6, 125.6, 122.9, 94.6, 47.0; IR (neat) 3384, 3192, 3061, 2939, 1627, 1575, 1496, 1327, 700 cm$^{-1}$; ESIMS $m/z$ 295 [M + H]$^+$; HRMS: $m/z$ [M + H]$^+$ calculated for C$_{15}$H$_{14}$F$_3$N$_2$O [M + H]$^+$ 295.1053, found: 295.1050; mp = 122–123 °C.
Hydroxy-\(N\)-(3-pyridylmethyl)benzimidamide (2-31); According to general protocol A, hydroxybenzimidoyl chloride (0.30 g, 1.9 mmol), 3-pyridylmethanamine (0.25 g, 2.3 mmol), and Et\(_3\)N (0.20 g, 1.9 mmol) were stirred in anhydrous DMF (6.4 mL) for 4 h. Impure product precipitated out of the reaction mixture, was filtered, washed, and sonicated with EtOAc to yield 0.24 g (54%) of 2-31 as a white solid: \(^1\)H NMR (400 MHz, DMSO) \(\delta = 9.93\) (s, 1 H), 8.38 (s, 1 H), 8.23 (s, 1 H), 7.52–7.28 (m, 7 H), 6.48 (s, 1 H), 4.18 (d, \(J = 6.3\) Hz, 2 H); \(^{13}\)C NMR (100 MHz, DMSO) \(\delta = 154.5, 148.2, 147.9, 136.3, 134.5, 132.4, 129.1, 128.3, 128.1, 123.4, 44.2\); IR (neat) 3381, 3125, 3069, 2920, 1618, 1480, 1429, 1149, 704 cm\(^{-1}\); ESIMS \(m/z\) 228 [M + H]\(^+\); HRMS \(m/z\) [M + H]\(^+\) calculated for C\(_{13}\)H\(_{14}\)N\(_3\)O [M + H]\(^+\) 228.1131, found 228.1131; mp = 174–177 °C.

Hydroxy-\(N\)-(2-thienylmethyl)benzimidamide (2-32); According to general protocol A, hydroxybenzimidoyl chloride (0.20 g, 1.3 mmol), 2-thienylmethanamine (0.17 g, 1.5 mmol), and Et\(_3\)N (0.13 g, 1.3 mmol) were stirred in anhydrous DMF (4.3 mL) for 2 h to yield 0.24 g (80%) of 2-32 as a white solid after purification by flash chromatography on SiO\(_2\) (hexanes–EtOAc, 5–35%): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.54–7.51\) (m, 2 H), 7.43–7.39 (m, 3 H), 7.19 (dd, \(J = 5.1, 1.2\) Hz, 1 H), 6.92 (dd, \(J = 5.1, 3.5\) Hz, 1 H), 6.84 (dd, \(J = 3.3, 0.97\) Hz, 1 H), 5.80 (s, 1 H, NH), 4.38 (s, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 156.4, 143.0, 131.0, 129.8, 128.6, 128.6, 126.9, 124.7, 124.7, 42.8\); IR (neat) 3401, 3188, 3105, 2935, 1631, 1575, 1484, 1445, 700 cm\(^{-1}\); ESIMS
\( m/z \ 233 [M + H]^+; \) HRMS \( m/z \ [M + H]^+ \) calculated for \( \text{C}_{12}\text{H}_{13}\text{N}_{2}\text{OS} \ [M + H]^+ \ 233.0743, \) found 233.0741; mp = 126–128 °C.

**Hydroxy-N-phenethylbenzimidamide (2-33);** According to general protocol A, hydroxybenzimidoyl chloride (0.090 g, 0.58 mmol), 2-phenylethan-1-amine (0.08 g, 0.06 mmol), and Et\(_3\)N (0.060 g, 0.58 mmol) were stirred in anhydrous DMF (1.9 mL) for 2 h to yield 0.12 g (85%) of 2-33 as a clear oil after purification by flash chromatography on Si\(_2\)O (hexanes–EtOAc, 10–50%): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.45–7.37 \) (m, 5 H), 7.30–7.20 (m, 3 H), 7.10–7.08 (m, 2 H), 5.50 (s, 1 H, NH), 3.28 (s, 2 H), 2.71 (t, \( J = 7.1 \) Hz, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 156.3, 138.7, 131.5, 129.5, 128.9, 128.6, 128.6, 128.4, 126.5, 45.2, 38.0; \) ESIMS \( m/z \ 241 [M + H]^+ \).

**N-(2-(1H-indol-3-yl)ethyl)hydroxybenzimidamide (2-34);** According to general protocol A, hydroxybenzimidoyl chloride (0.10 g, 0.64 mmol), tryptamine (0.13 g, 0.77 mmol), and Et\(_3\)N (0.065 g, 0.64 mmol) were stirred in anhydrous DMF (2.1 mL) for 2 h to yield 0.14 g (80%) of 2-34 as a white solid after purification by flash chromatography on Si\(_2\)O (hexanes–EtOAc, 15–75%): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 8.05 \) (s, 1 H), 7.41-7.26 (m, 8 H), 7.18-7.14 (m, 1 H), 7.06-7.02 (m, 1 H), 6.92 (s, 1 H), 5.54 (s, 1 H, NH), 3.32-3.31 (m, 2 H), 2.82 (t, \( J = 6.8 \) Hz, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 136.4, 131.6, 129.5, 128.6, 128.4, 127.2, 122.6, 122.0, 119.3, 118.5, 112.4,
111.3, 43.9, 31.1, 27.5; IR (neat) 3409, 3192, 3054, 2920, 1623, 1571, 1457, 1011, 912, 743, 700 cm\(^{-1}\); ESIMS \(m/z\) 280 [M + H]\(^+\); HRMS \(m/z\) [M + H]\(^+\) calculated for C\(_{17}\)H\(_{18}\)N\(_3\)O [M + H]\(^+\) 280.1444, found 280.1443; mp = 50–52 °C.

Hydroxy-\(N\)-(1-phenylethyl)benzimidamide (2-35); According to general protocol A, hydroxybenzimidoyl chloride (0.090 g, 0.58 mmol), 1-phenylethan-1-amine (0.084 g, 0.69 mmol), and Et\(_3\)N (0.059 g, 0.58 mmol) were stirred in anhydrous DMF (1.9 mL) for 2 h to yield 0.11 g (81%) of 2-35 as a clear oil after purification by flash chromatography on SiO\(_2\) (hexanes–EtOAc, 5–35%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.41–7.28\) (m, 8 H), \(7.13\) (d, \(J = 7.2\) Hz, 2 H), 5.69 (s, 1 H, NH), 4.47 (s, 1 H), 1.45 (d, \(J = 6.8\) Hz, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 156.0, 144.9, 131.8, 129.5, 128.6, 128.5, 128.3, 127.0, 125.6, 52.8, 24.6\); IR (neat) 3203, 3061, 2967, 1631, 1571, 1493, 1378, 1142, 700 cm\(^{-1}\); ESIMS \(m/z = 241\) [M + H]\(^+\); HRMS \(m/z\) [M + H]\(^+\) calculated for C\(_{15}\)H\(_{17}\)N\(_2\)O [M + H]\(^+\) 241.1335, found 241.1334.

Hydroxy-\(N\)-(1,2,3,4-tetrahydronaphthalen-1-yl)benzimidamide (2-36); According to general protocol A, hydroxybenzimidoyl chloride (0.080 g, 0.51 mmol), 1,2,3,4 tetrahydronaphthalen-1-amine (0.093 g, 0.62 mmol), and Et\(_3\)N (0.052 g, 0.51 mmol) were stirred in anhydrous DMF (1.7 mL) for 2 h to yield 0.10 g (73%) of 2-36 as a white solid after purification by flash
chromatography on SiO$_2$ (hexanes–EtOAc, 5–35%) : $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.62–7.59 (m, 2H), 7.49–7.45 (m, 1 H), 7.44–7.39 (m, 3 H), 7.22–7.14 (m, 2 H), 7.07–7.06 (m, 1 H), 5.56 (d, $J$ = 10.7 Hz, 1 H, NH), 4.44–4.42 (m, 1 H), 2.79–2.76 (m, 1 H), 2.71–2.65 (m, 1 H), 1.93–1.87 (m, 2H), 1.71–1.64 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 156.4, 138.1, 137.4, 131.8, 129.8, 129.1, 128.7, 128.5, 128.1, 127.2, 126.3, 51.8, 29.3, 20.4; IR (neat) 3377, 3354, 3216, 2935, 1638, 1575, 1488, 1445, 1382 cm$^{-1}$; ESIMS $m/z$ 267 [M + H]$^+$; HRMS $m/z$ [M + H]$^+$ calculated for C$_{17}$H$_{19}$N$_2$O [M + H]$^+$ 267.1492, found 267.1490; mp = 120–123 °C.

Hydroxy-N-isobutylbenzimidamide (2-37); According to general protocol A, hydroxybenzimidoyl chloride (0.10 g, 0.64 mmol), 2-methylpropan-1-amine (0.056 g, 0.77 mmol), and Et$_3$N (0.065 g, 0.64 mmol) were stirred in anhydrous DMF (2.1 mL) for 2 h to yield 0.099 g (80%) of 2-37 as a clear solid after purification by flash chromatography on SiO$_2$ (hexanes–EtOAc, 10–40%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.49–7.44 (m, 2 H), 7.43–7.36 (m, 3 H), 5.39 (s, 1 H, NH), 2.84–2.82 (m, 2 H), 1.66–1.59 (m, 1 H), 0.84 (d, $J$ = 6.7 Hz, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 156.9, 131.8, 129.5, 128.7, 128.4, 51.3, 30.1, 20.0; IR (neat) 3397, 3203, 2916, 1646, 1480, 1441, 897 cm$^{-1}$; ESIMS $m/z$ 193 [M + H]$^+$; HRMS $m/z$ [M + H]$^+$ calculated for C$_{11}$H$_{17}$N$_2$O [M + H]$^+$ 193.1335, found 193.1335; mp = 74–75 °C.
**N-Allyl hydroxybenzimidamide (2-38);** According to general protocol A, hydroxybenzimidoyl chloride (0.20 g, 1.3 mmol), allylamine (0.088 g, 1.5 mmol), and Et₃N (0.13 g, 1.3 mmol) were stirred in anhydrous DMF (4.3 mL) for 2 h to yield 0.18 g (80%) of 2-38 as a white solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 5–35%): **¹H NMR (400 MHz, CDCl₃)** δ = 7.50–7.56 (m, 2 H), 7.43–7.36 (m, 3 H), 5.76 (ddt, J = 17, 9.9, 4.9 Hz, 1 H), 5.47 (s, 1 H, NH), 5.20 (dq, J = 17, 1.8 Hz, 1 H), 5.08 (dq, J = 10, 1.6 Hz, 1 H), 3.64 (s, 2 H); **¹³C NMR (100 MHz, CDCl₃)** δ = 156.5, 136.0, 131.3, 129.7, 128.6, 128.4, 115.5, 45.9; ESIMS m/z 177 [M + H]⁺.

**Hydroxy-N-(2-methylallyl)benzimidamide (2-39);** According to general protocol A, hydroxybenzimidoyl chloride (0.15 g, 0.96 mmol), 2-methylprop-2-en-1-amine (0.082 g, 1.16 mmol), and Et₃N (0.098 g, 0.96 mmol) were stirred in anhydrous DMF (3.2 mL) for 2 h to yield 0.14 g (78%) of 2-39 as a white solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 0–30%): **¹H NMR (400 MHz, CDCl₃)** δ = 7.49–7.46 (m, 2 H), 7.45–7.35 (m, 3 H), 5.53 (s, 1 H, NH), 4.92 (s, 1 H), 4.81 (s, 1 H), 3.53 (s, 2 H), 1.62 (s, 3 H); **¹³C NMR (100 MHz, CDCl₃)** δ = 156.7, 143.6, 131.4, 129.6, 128.6, 128.4, 110.6, 49.3, 20.3; IR (neat) 3397, 3203, 2916, 1650, 1579, 1480, 1445, 901, 770, 704 cm⁻¹; ESIMS m/z 191 [M + H]⁺; HRMS m/z [M + H]⁺ calculated for C₁₁H₁₅N₂O [M + H]⁺ 191.1179, found 191.1179; mp = 93–94 °C.
Hydroxy-N-(prop-2-yn-1-yl)benzimidamide (2-40); According to general protocol A, hydroxybenzimidoyl chloride (0.20 g, 1.3 mmol), propargylamine (0.085 g, 1.5 mmol), and Et₃N (0.13 g, 1.3 mmol) were stirred in anhydrous DMF (4.3 mL) for 2 h to yield 0.14 g (64%) of 2-40 as a yellow solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 0–30%): ^1H NMR (400 MHz, CDCl₃) δ = 7.54–7.46 (m, 2 H), 7.44–7.39 (m, 3 H), 5.59 (s, 1 H, NH), 3.77 (s, 2 H), 2.22 (s, 1 H); ^13C NMR (100 MHz, CDCl₃) δ = 155.7, 130.6, 130.0, 128.6, 128.6, 80.9, 71.9, 33.5; IR (neat) 3393, 3286, 3061, 2935, 2119, 1631, 1575, 1496, 1441 cm⁻¹; ESIMS m/z 175 [M + H]⁺; HRMS m/z [M + H]⁺ calculated for C₁₀H₁₁N₂O [M + H]⁺ 175.0866, found 175.0868; mp = 58–61 °C.

N-(Cyclopropylmethyl)hydroxybenzimidamide (2-41); According to general protocol A, hydroxybenzimidoyl chloride (0.20 g, 1.3 mmol), cyclopropylmethanamine (0.11 g, 1.5 mmol), and Et₃N (0.13 g, 1.3 mmol) were stirred in anhydrous DMF (4.3 mL) for 2 h to yield 0.19 g (79%) of 2-41 as a clear colorless solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 10–50%): ^1H NMR (400 MHz, CDCl₃) δ = 7.49–7.45 (m, 2 H), 7.44–7.36 (m, 3 H), 5.46 (s, 1 H, NH), 2.87 (t, J = 6.3 Hz, 2 H), 0.93–0.83 (m, 1 H), 0.46–0.41 (m, 1 H), 0.10–0.03 (m, 2 H); ^13C NMR (100 MHz, CDCl₃) δ = 156.4, 131.8, 129.5, 128.7, 128.5, 48.8, 12.2, 3.3; IR (neat) 3393, 3199, 3077, 2948, 1631, 1575, 1480, 1402, 700 cm⁻¹; ESIMS m/z 191 [M + H]⁺;
HRMS $m/z$ [M + H]$^+$ calculated for C$_{11}$H$_{15}$N$_2$O [M + H]$^+$ 191.1179, found 191.1178; mp = 49–52 °C.

**N-Benzylhydroxy-2-naphthimidamide (2-42); General protocol B.** To a three-neck round-bottom flask was added 2-naphthaldehyde oxime (0.30 g, 1.8 mmol) in DMF (5.8 mL). NCS (0.24 g, 1.8 mmol) was added in 5 portions over 15 min. During each addition, the reaction mixture turned yellow and then faded to colorless. The solution was stirred for 23 h and then cooled to 0 °C. Benzylamine (0.23 g, 2.1 mmol) was added, followed by Et$_3$N (0.35 g, 3.5 mmol), and the mixture was stirred for 1 h. The reaction was diluted with H$_2$O and extracted with EtOAc (3×). The organic layer was washed with brine, dried (MgSO$_4$), concentrated in vacuo, and purified by flash chromatography on SiO$_2$ (hexanes–EtOAc, 10–40%) to yield 0.36 g (75%) of 2-42 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.01 (s, 1 H), 7.87–7.83 (m, 3 H), 7.59–7.50 (m, 3 H), 7.32–7.22 (m, 5 H), 5.82 (s, 1 H, NH), 4.28 (d, $J$ = 4.6 Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 156.7, 139.7, 133.9, 133.0, 128.7, 128.6, 128.3, 127.8, 127.3, 127.0, 126.9, 126.5, 125.7, 47.7; ESIMS $m/z$ 277 [M + H]$^+$; mp = 101–103 °C.

**N-Benzylhydroxy-4-methoxybenzimidamide (2-43);** According to general protocol B, 4 methoxybenzaldehyde oxime (0.30 g, 2.0 mmol) and NCS (0.27 g, 2.0 mmol) were added to DMF
(6.6 mL). The reaction mixture was stirred for 17 h. Benzylation (0.26 g, 2.4 mmol) and Et₃N (0.40 g, 4.0 mmol) were added and the mixture was stirred for an additional 3 h to yield 0.28 g (56%) of 2-43 as a white solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 10–50%): ¹H NMR (400 MHz, CDCl₃) δ = 9.10 (s, 1 H), 7.37 (d, J = 8.0 Hz, 2 H), 7.30–7.18 (m, 5 H), 6.92 (d, J = 8.0 Hz, 2 H), 5.94 (s, 1 H, NH), 4.26 (d, J = 6.4 Hz, 2 H), 3.80 (d, J = 1.0 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 161.3, 156.3, 141.9, 130.5, 129.2, 127.6, 127.5, 125.6, 114.3, 55.6, 47.9; ESIMS m/z 257 [M + H]⁺; mp = 135–137 °C.

_N-Benzylhydroxycinnamimidamide (2-44);_ According to general protocol B, (2E) cinnamaldehyde oxime (0.30 g, 2.0 mmol) and NCS (0.28 g, 2.0 mmol) were added to DMF (6.8 mL). The reaction mixture was stirred for 15 h. Benzylation (0.26 g, 2.5 mmol) and Et₃N (0.41 g, 4.1 mmol) were added and the mixture was stirred for an additional 1 h to yield 0.32 g (62%) of 2-44 as a yellow solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 10–50%): ¹H NMR (400 MHz, CDCl₃) δ = 7.41–7.27 (m, 10 H), 7.22 (d, J = 16 Hz, 1 H), 6.52 (d, J = 16 Hz, 1 H), 5.71 (s, 1 H, NH), 4.44 (s, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ = 154.0, 139.5, 136.0, 135.9, 128.8, 128.8, 127.5, 127.2, 126.9, 116.9, 46.9; ESIMS m/z 253 [M + H]⁺; mp = 98–101 °C.

_N-Benzylhydroxythiophene-2-carboximidamide (2-45);_ According to general protocol B, thiophene-2-carbaldehyde oxime (0.30 g, 2.4 mmol) and NCS (0.32 g, 2.4 mmol) were added to DMF (7.9 mL). The reaction mixture was stirred for 17 h. Benzylation (0.31 g, 2.8 mmol) and
Et₃N (0.48 g, 4.7 mmol) were added and the mixture was stirred for an additional 1 h to yield 0.32 g (35%) of 2-45 as a peachy solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 0–20%): ¹H NMR (400 MHz, CDCl₃) δ = 9.26 (s, 1 H), 7.39–7.24 (m, 6 H), 7.22 (dt, J = 3.6, 0.9 Hz, 1 H), 7.02 (ddd, J = 5.1, 3.7, 0.72 Hz, 1 H), 5.76 (s, 1 H, NH), 4.45 (d, J = 3.9 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ = 151.1, 139.5, 132.2, 128.8, 128.3, 127.4, 127.3, 126.9, 47.8; IR (neat) 3412, 3195, 3101, 2939, 1627, 1544, 1496, 1453, 700 cm⁻¹; ESIMS m/z 233 [M + H]⁺; HRMS m/z [M + H]⁺ calculated for C₁₂H₁₅N₂O₃ [M + H]⁺ 233.0743, found 233.0741; mp = 105–107 °C.

![Ethyl 2-(Benzylamino)-2-(hydroxyimino)acetate (2-46)](image)

**Ethyl 2-(Benzylamino)-2-(hydroxyimino)acetate (2-46);** According to general protocol A, ethyl 2-chloro-2-(hydroxyimino)acetate (0.30 g, 1.9 mmol), benzylamine (0.25 g, 2.3 mmol), and Et₃N (0.19 g, 1.9 mmol) were stirred in anhydrous DMF (6.4 mL) for 2 h to yield 0.40 g (94%) of 2-46 as a white solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 0–25%): ¹H NMR (400 MHz, CDCl₃) δ = 9.78 (s, 1 H), 7.35–7.27 (m, 4 H), 7.26–7.20 (m, 1 H), 6.00 (s, 1 H, NH), 4.57 (d, J = 6.9 Hz, 2 H), 4.16 (q, J = 7.1 Hz, 2 H), 1.18 (t, J = 7.1 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 162.2, 147.1, 141.6, 129.2, 128.0, 127.7, 61.9, 47.4, 14.2; IR (neat) 3393, 3212, 3089, 2982, 1729, 1634, 1496, 1453, 1216 cm⁻¹; ESIMS m/z 223 [M + H]⁺; HRMS m/z [M + H]⁺ calculated for C₁₁H₁₅N₂O₃ [M + H]⁺ 223.1077, found 223.1076; mp = 54–55 °C.
3,5-Diphenyl-1,2,4-oxadiazole (2-47); General protocol C To a round-bottom flask at rt was added amidoxime 2-28 (0.050 g, 0.22 mmol), DMF (2.2 mL), and DDQ (0.10 g, 0.44 mmol), and the solution was degassed with nitrogen for 5 min. The mixture was then plunged into a 150 °C oil bath and stirred for 30 min. The reaction mixture was cooled to rt, quenched with H2O, and extracted with EtOAc (3×). The organic layer was washed with aq NaHCO3, H2O, and brine, dried (MgSO4), concentrated in vacuo, and purified by flash chromatography on SiO2 (hexanes–EtOAc, 10–50%) to yield 0.026 g (53%) of 2-47 as a white solid: 1H NMR (400 MHz, CDCl3) δ = 8.24–8.18 (m, 4 H), 7.63–7.49 (m, 6 H); 13C NMR (100 MHz, CDCl3) δ = 175.8, 169.1, 132.9, 131.1, 129.2, 129.0, 128.3, 127.6, 127.1, 124.4.

5-(2,4-Dimethoxyphenyl)-3-phenyl-1,2,4-oxadiazole (2-48); According to general protocol C, amidoxime 2-29 (0.063 g, 0.22 mmol) and DDQ (0.10 g, 0.44 mmol) were stirred in DMF (4.4 mL) for 30 min to afford 2-48 after purification by flash chromatography on SiO2 (hexanes–EtOAc, 0–10%) to yield 0.024 g (38%) of # as a white solid: 1H NMR (400 MHz, CDCl3) δ = 8.19–8.12 (m, 3 H), 7.51–7.48 (m, 3 H), 6.63 (dd, J = 8.7, 2.3 Hz, 1 H), 6.57 (d, J = 2.3 Hz, 1 H), 3.98 (s, 3 H), 3.89 (s, 3 H); 13C NMR (100 MHz, CDCl3) δ = 175.1, 168.3, 164.7, 160.3, 133.2, 131.0, 128.9, 127.6, 127.5, 106.7, 105.7, 99.0, 56.2, 55.8; IR (neat) 3065, 2963, 1610, 1527, 1496, 1445, 1362, 1295, 1212 cm⁻¹; HRMS m/z [M + H]+ calculated for C16H15N2O3 [M + H]+ 283.1077, found 283.1077; mp = 108–109 °C.
3-Phenyl-5-[4-(trifluoromethyl)phenyl]-1,2,4-oxadiazole (2-49); According to general protocol C, amidoxime 2-30 (0.15 g, 0.51 mmol) and DDQ (0.23 g, 1.0 mmol) were stirred in DMF (5.1 mL) for 30 min to yield 0.081 g (55%) of 2-49 as a white solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 0–2%): ¹H NMR (400 MHz, CDCl₃) δ = 8.35 (d, J = 8.5 Hz, 2 H), 8.20–8.17 (m, 2 H), 7.83 (d, J = 8.6 Hz, 2 H), 7.57–7.50 (m, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 174.5, 169.3, 134.9, 134.5, 131.6, 129.1, 128.7, 127.7, 127.6, 126.7, 126.3, 126.3; IR (neat) 1527, 1469, 1414, 1331, 1118, 755, 719 cm⁻¹; HRMS m/z [M + H]⁺ calculated for C₁₅H₁₀F₃N₂O [M + H]⁺ 291.0740, found 291.0740; mp = 97–98 °C.

3-Phenyl-5-(3-pyridyl)-1,2,4-oxadiazole (2-50); According to general protocol C, amidoxime 2-31 (0.15 g, 0.66 mmol) and DDQ (0.30 g, 1.3 mmol) were stirred in DMF (6.6 mL) for 30 min to yield 0.068 g (46%) of 2-50 as a white solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 0–11%): ¹H NMR (400 MHz, CDCl₃) δ = 9.45 (d, J = 2.2 Hz, 1 H), 8.84 (dd, J = 4.9, 1.65 Hz, 1 H), 8.48 (dt, J = 8.0, 1.9 Hz, 1 H), 8.19–8.16 (m, 2 H), 7.54–7.49 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃) δ = 173.8, 169.2, 153.4, 149.3, 149.3, 135.4, 131.6, 129.1, 127.7, 126.6, 123.9, 120.9; IR (neat) 3065, 1606, 1579, 1555, 1476, 1461, 1445, 1415, 1362 cm⁻¹; HRMS m/z [M + H]⁺ calculated for C₁₃H₁₀N₃O [M + H]⁺ 224.0818, found 224.0815; mp = 116–118 °C.
3-Phenyl-5-(2-thienyl)-1,2,4-oxadiazole (2-51); According to general protocol C, amidoxime 2-32 (0.16 g, 0.69 mmol) and DDQ (0.31 g, 1.4 mmol) were stirred in DMF (7.1 mL) for 30 min to yield 0.082 g (52%) of 2-51 as a white solid after purification by flash chromatography on SiO2 (hexanes–EtOAc, 0–2%): 1H NMR (400 MHz, CDCl3) δ = 8.24–8.13 (m, 2 H), 7.96 (dd, J = 3.8, 1.2 Hz, 1 H), 7.66 (dd, J = 5.0, 1.2 Hz, 1 H), 7.62–7.47 (m, 3 H), 7.22 (dd, J = 5.0, 3.8 Hz, 1 H); 13C NMR (100 MHz, CDCl3) δ = 171.5, 169.0, 132.1, 132.0, 131.4, 129.0, 128.6, 127.7, 126.8, 126.0; IR (neat) 3097, 1599, 1496, 1467, 1445, 1414, 1366, 740, 691 cm⁻¹; HRMS m/z [M + H]+ calculated for C12H9F3N2OS [M + H]+ 229.0430, found 229.0429; mp = 108–109 °C.

3-Phenyl-5-vinyl-1,2,4-oxadiazole (2-52); According to a modification of general protocol C, amidoxime 2-38 (0.051 g, 0.29 mmol) and DDQ (0.066 g, 0.29 mmol) were stirred in DMF (5.8 mL) for 30 min to afford 2-52 after purification by flash chromatography on SiO2 (hexanes–EtOAc, 0–3%); further purification was performed via pTLC (hexanes–EtOAc, 2%) to yield 0.013 g (27%) of 2-25 as a white solid: 1H NMR (400 MHz, CDCl3) δ = 8.12–8.09 (m, 2 H), 7.54–7.46 (m, 3 H), 6.78 (dd, J = 18, 11 Hz, 1 H), 6.60 (dd, J = 18, 0.92 Hz, 1 H), 6.01 (dd, J = 11, 0.92 Hz, 1 H); 13C NMR (100 MHz, CDCl3) δ = 174.6, 168.4, 131.4, 129.0, 128.9, 127.6, 127.5, 126.9, 120.7.
3-Phenyl-5-(prop-1-en-2-yl)-1,2,4-oxadiazole (2-53); According to general protocol C, amidoxime 2-39 (0.18 g, 0.92 mmol) and DDQ (0.42 g, 1.8 mmol) were stirred in DMF (9.2 mL) for 30 min to yield 0.033 g (20%) of 2-53 as a white solid after purification by flash chromatography on SiO$_2$ (hexanes–EtOAc, 0–2%); further purification was attempted with pTLC (hexanes–EtOAc, 2%). 2-53 contains small amounts of impurities that could not be removed via chromatography: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.15–8.10 (m, 2 H), 7.54–7.46 (m, 3 H), 6.32 (s, 1 H), 5.69 (s, 1 H), 2.27 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 176.4, 168.9, 131.2, 129.2, 129.0, 127.7, 127.6, 127.1, 124.3, 19.2.

5-Cyclopropyl-3-phenyl-1,2,4-oxadiazole (2-54); According to general protocol C, amidoxime 2-41 (0.16 g, 0.81 mmol) and DDQ (0.37 g, 1.6 mmol) were stirred in DMF (8.2 mL) for 30 min to yield 0.027 g (18%) of 2-54 as a colorless oil after purification by flash chromatography on SiO$_2$ (hexanes–EtOAc, 0–3%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.06–8.01 (m, 2 H), 7.56–7.43 (m, 3 H), 2.26 (tt, $J$ = 8.2, 5.0 Hz, 1 H), 1.32–1.23 (m, 4 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 181.7, 168.3, 131.1, 128.9, 127.5, 127.1, 10.2, 7.9; IR (neat) 3069, 2963, 1595, 1575, 1480, 1445, 1370, 1350, 696 cm$^{-1}$; HRMS $m/z$ [M + H]$^+$ calculated for C$_{11}$H$_{11}$N$_2$O [M + H]$^+$ 187.0866, found 187.0868.
3-(2-Naphthyl)-5-phenyl-1,2,4-oxadiazole (2-55): According to general protocol C, amidoxime 2-42 (0.18 g, 0.63 mmol) and DDQ (0.29 g, 1.3 mmol) were stirred in DMF (6.3 mL) for 30 min to yield 0.088 g (51%) of 2-55 as a white solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 0–3%): ¹H NMR (400 MHz, CDCl₃) δ = 8.73 (s, 1 H), 8.28–8.22 (m, 3 H), 8.02–7.95 (m, 2 H), 7.91–7.87 (m, 1 H), 7.66–7.54 (m, 5 H); ¹³C NMR (100 MHz, CDCl₃) δ = 175.9, 169.2, 134.8, 133.2, 132.9, 129.2, 129.0, 128.8, 128.3, 128.2, 128.0, 127.6, 126.8, 124.4, 124.4, 124.0; mp = 108–110 °C.

3-(4-Methoxyphenyl)-5-phenyl-1,2,4-oxadiazole (2-56): According to general protocol C, amidoxime 2-43 (0.11 g, 0.43 mmol) and DDQ (0.19 g, 0.86 mmol) were stirred in DMF (4.3 mL) for 30 min to yield 0.043 g (40%) of 2-56 as a white solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 0–5%): ¹H NMR (400 MHz, CDCl₃) δ = 8.21 (d, J = 6.9 Hz, 2 H), 8.14–8.10 (m, 2 H), 7.62–7.52 (m, 3 H), 7.02 (d, J = 8.9 Hz, 2 H), 3.88 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 175.5, 168.8, 162.0, 132.8, 129.2, 129.2, 128.3, 124.5, 119.5, 114.4, 55.5; mp = 99-100 °C.
(E)-5-Phenyl-3-styryl-1,2,4-oxadiazole (2-57); According to general protocol C, amidoxime 2-44 (0.15 g, 0.60 mmol) and DDQ (0.27 g, 1.2 mmol) were stirred in DMF (6.7 mL) for 30 min to yield 0.066 g (45%) of 2-57 as a white solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 0–5%): ¹H NMR (400 MHz, CDCl₃) δ = 8.24–8.19 (m, 2 H), 7.82 (d, J = 16 Hz, 1 H), 7.63–7.53 (m, 5 H), 7.44–7.36 (m, 3 H), 7.13 (d, J = 16 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ = 175.1, 168.6, 139.3, 135.5, 132.9, 129.6, 129.2, 129.0, 128.3, 127.6, 124.3, 113.1; mp = 100–102 °C.

5-Phenyl-3-(2-thienyl)-1,2,4-oxadiazole (2-58); According to general protocol C, amidoxime 2-45 (0.070 g, 0.30 mmol) and DDQ (0.14 g, 0.60 mmol) were stirred in DMF (3.0 mL) for 30 min to yield 0.045 g (66%) of 2-58 as a white solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 0–2%): ¹H NMR (400 MHz, CDCl₃) δ = 8.23–8.19 (m, 2 H), 7.88 (dd, J = 3.7, 1.2 Hz, 1 H), 7.64–7.59 (m, 1 H), 7.57–7.52 (m, 3 H), 7.19 (dd, J = 5.0, 3.7 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ = 175.7, 165.2, 133.0, 129.7, 129.4, 129.2, 128.7, 128.4, 128.1, 124.1; IR (neat) 3105, 2920, 1606, 1548, 1493, 1449, 1417, 1359, 712 cm⁻¹; HRMS m/z [M + H]⁺ calculated for C₁₂H₉N₂OS [M + H]⁺ 229.0430, found 229.0428; mp = 131–133 °C.
**Ethyl 5-Phenyl-1,2,4-oxadiazole-3-carboxylate (2-59):** According to general protocol C, amidoxime 2-46 (0.15 g, 0.67 mmol) and DDQ (0.35 g, 1.4 mmol) were stirred in DMF (6.7 mL) for 30 min to yield 0.11 g (73%) of 2-59 as a yellow solid after purification by flash chromatography on SiO₂ (hexanes–EtOAc, 0–7%): ¹H NMR (400 MHz, CDCl₃) δ = 8.21–8.17 (m, 2 H), 7.64–7.50 (m, 3 H), 4.53 (q, J = 7.1 Hz, 2 H), 1.45 (t, J = 7.1 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 177.4, 162.5, 157.9, 133.6, 129.3, 128.5, 123.3, 63.2, 14.2; IR (neat) 3061, 2991, 2942, 1752, 1606, 1559, 1446, 1272, 1228 cm⁻¹; HRMS m/z [M + H]⁺ calculated for C₁₁H₁₁N₂O₃ [M + H]⁺ 219.0764, found 219.0763; mp = 47–50 °C.
2.2.6: References


PART 2: Synthesis of 1,4,2-Dioxazoles

2.3.1: Abstract

The success of DDQ-mediated oxidative cyclizations of thiohydroximic acids and amidoximes to oxathiazoles and oxadiazoles led to efforts to use this chemistry for accessing other tri-heteroatom azoles. Described here are attempts for accessing 1,4,2-dioxazoles via oxidative cyclization. Optimization of substrate formation is described as well as the oxidative cyclization attempts.

2.3.2: Introduction and Background

During our development of oxadiazole synthesis, we also pursued the oxygen variant of an oxathiazole called a 1,4,2-dioxazole (Figure 2.7). 1,4,2-Dioxazoles are five membered heterocycles that contain two oxygen atoms and a nitrogen atom. For the remainder of this document, the term dioxazole will refer only to 1,4,2-dioxazoles.

![Figure 2.7: Structure of 1,4,2-dioxazole heterocycles.](image)

2.3.2.1: Applications of Dioxazoles

Dioxazoles can be found in several biologically active compounds (Figure 2.8). Each of the compounds below are active against the intestinal parasitic protozoan Entamoeba histolytica (amoebiasis). 1–3 Amoebiasis is an infectious disease that is responsible for approximately 100,000
deaths annually and is one of the leading causes of death among parasitic diseases. Amoebiasis causes severe diarrhea as well as liver and brain abscesses. Compounds like the ones shown below are known to be as active or more active than current therapeutics, such as metronidazole, for the treatment of amoebiasis infections.

![Dioxazole-containing biologically active compounds](image)

**Figure 2.8:** Dioxazole-containing biologically active compounds.

One useful application of dioxazoles outside of the realm of drug discovery is their use as masked hydroxamic acids (Scheme 2.19). Treatment of a hydroxamic acid with 2,2-diethoxypropane and CSA provides the dioxazole. The dioxazole can be converted back to the hydroxamic acid by reaction with Nafion H. This protecting group is stable to a variety of conditions such as reduction/oxidation, acid/base, and Grignard nucleophiles.\(^4\)

![Dioxazoles as masked hydroxamic acids](image)

**Scheme 2.19:** Dioxazoles as masked hydroxamic acids.
2.3.2.2: Synthesis of Dioxazoles

There are a variety of existing methods to synthesize dioxazoles. One of the most common routes to dioxazoles involves the [3 + 2] cycloaddition of a nitrile oxide and the carbonyl of a ketone (Scheme 2.20). As in the oxadiazole case, the nitrile oxide is formed in situ by treatment of a hydroxyimidoyl chloride with a base or Lewis acid. Another method for the synthesis of dioxazoles is through the photo-induced coupling and subsequent cyclization of an acyl azide and carbonyl (Scheme 2.21). Light promotes the release of nitrogen forming an acyl nitrene. The electrophilic nitrene is attacked by the oxygen of a carbonyl forming a zwitterionic species that freely cyclizes to form the dioxazole.

Scheme 2.20: Synthesis of dioxazoles via [3 + 2] cycloaddition.

Scheme 2.21: Photo-induced dioxazole synthesis.
2.3.3: Results and Discussion

First, we required a method for the synthesis of the \( O \)-benzyl hydroxyimidate starting material. This was not as straight forward as for the synthesis of amidoximes, and we needed to optimize a method for hydroxyimidate preparation. We began our optimization with the synthesis of benzyl hydroxyimidate \( 2-62 \) (Table 2.3). Reacting the hydroxyimidoyl chloride of benzaldehyde with five equivalents of KHMDS at room temperature in THF gave 62% yield of hydroxyimidate \( 2-62 \) (entry 1). The yield changed slightly with NaHMDS to 66% (entry 2). NaH significantly lowered the yield to 20% (entry 3). Formation of NaHMDS \textit{in situ} from addition of NaH to HMDS gave a lower yield of 48% (entry 4). The next parameter to change was the equivalents of nucleophile. There was a stepwise jump in yield as the nucleophile equivalency rose. As the equivalents of benzyl alkoxide increased from 3 to 5 to 7, the yield rose from 58% to 66% to 71%, respectively (entries 2, 5, and 6).

\textbf{Table 2.3}: Optimization of \( O \)-benzyl hydroxyimidate.

<table>
<thead>
<tr>
<th>Entry(^a)</th>
<th>Base</th>
<th>( X )</th>
<th>( 2-62 ) yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KHMDS</td>
<td>5</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>NaHMDS</td>
<td>5</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>NaH/HMDS</td>
<td>5</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>NaHMDS</td>
<td>3</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>NaHMDS</td>
<td>7</td>
<td>71</td>
</tr>
</tbody>
</table>

\(^{a}\) All reactions were performed on 50 mg scale and at 0.1 M. \(^{b}\) Isolated product yield.
The optimization continued with the allyl hydroxyimidate substrate 2-63 (Table 2.4). Treatment of the hydroxyimidoyl chloride of benzaldehyde with seven equivalents of nucleophile (for comparison to previous substrate, entry 6, Table 2.3) gave 2-63 in 61% yield (entry 1). Lowering the equivalents of nucleophile to five gave 2-63 in 57% yield. Raising the concentration to 0.3 M and 0.5 M while also lowering the equivalents of nucleophile to 3 equivalents provided compound 2-63 in 51% and 52%, respectively (entries 3 and 4). Lower temperatures did not impact the yield (entry 5), nor did keeping the concentration at 0.5 M while raising the equivalents of nucleophile (entry 5). Finally, using one equivalent of alcohol (nucleophile) and three equivalents of base to generate the alkoxide and nitrile oxide gave a much lower yield of 26% (entry 7).

### Table 2.4: Optimization of O-allyl hydroxyimidate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration (M)</th>
<th>X</th>
<th>Y</th>
<th>2-63 Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>7</td>
<td>7</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>5</td>
<td>5</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>3</td>
<td>3</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>3</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.5</td>
<td>3</td>
<td>3</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>5</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>0.5</td>
<td>1</td>
<td>3</td>
<td>26</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were performed on 50 mg scale. <sup>b</sup> Isolated product yield. <sup>c</sup> Performed at 0 °C.

While the optimization of starting material formation continued, we were able to perform preliminary investigations of dioxazole formation (Scheme 2.22). Substrate 2-62 gave dioxazole 2-64 in 26% yield with one equivalent of DDQ in DMF at 150 °C (equation 1). Substrate 2-63 gave dioxazole 2-65 in a much lower yield of 2% under the same conditions (equation 2). Due to
the much lower yields of dioxazole formation, the requirement of large excess reagents for acceptable yields in starting material formation (seven equivalents of nucleophile), and the more successful synthesis as well as the better applications of oxadiazoles (these projects were developed together) optimization efforts for dioxazole formation were indefinitely postponed.

Scheme 2.22: DDQ-mediated oxidative cyclization of hydroxyimidates.

2.3.4: Conclusions

The success of our previous DDQ-mediated oxidative cyclizations led to efforts for using this chemistry to accessing other tri-heteroatom azoles. Attempts for accessing 1,4,2-dioxazoles via oxidative cyclization of O-benzyl and O-allyl hydroxyimidates were conducted. The optimal conditions for starting material formation thus far are to use excess (7 equivalents) of nucleophile at 0.1 M. With the substrate in hand, dioxazole synthesis proceeded with much lower yields as compared to both the oxathiazole and oxadiazole formations. This could be due to the greater stabilization provided by an adjacent sulfur or nitrogen as opposed to oxygen. These studies were halted when we observed greater success with oxadiazole synthesis.
2.3.5: Experimental Section

General considerations: All reactions were performed under a nitrogen atmosphere, and all glassware was flame-dried and flushed with nitrogen prior to use. DMF (99.8%, extra dry over molecular sieves) and DDQ were purchased from Acros Organics and used as received. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a KMnO₄ solution (1.5 g of KMnO₄, 10 g of K₂CO₃, and 1.25 mL of a 10% NaOH solution in 200 mL of water). Reactions were also monitored by LC-MS analysis (Shimadzu LC-MS 2020 with Kinetex 2.6 mm C18 50 × 2.10 mm). Flash chromatography on SiO₂ was used to purify the crude reaction mixtures and performed on a Biotage Isolera using Biotage cartridges and linear gradients. 

¹H and ¹³C NMR spectra were obtained on a Varian Mercury-VX 300, a Varian Mercury-VX 400, or a Varian Mercury-Plus 300 instrument in CDCl₃ unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard (CDCl₃ = 7.26 ppm for ¹H, CDCl₃ = 77.16 ppm for ¹³C). ¹H NMR spectra were run at 300 or 400 MHz and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, bs = broad singlet), number of protons, and coupling constant(s). ¹³C NMR spectra were run at 100 MHz using a proton-decoupled pulse sequence with a d₁ of 1 second unless otherwise noted, and are tabulated by observed peak. Infrared spectra were determined on a Jasco FT/IR-4100 spectrometer. High-resolution mass spectra were obtained on a Thermo Fisher Scientific, Exactive Plus mass spectrometer (ion trap) using Heated Electrospray Ionization (HESI). Melting points were determined by using a Thomas Hoover capillary melting point apparatus.
Benzyl N-hydroxybenzimidate (2-62); General protocol A. To a flame-dried and flushed with \( \text{N}_2 \) round-bottom flask was added anhydrous benzyl alcohol (0.49 g, 4.5 mmol), NaHMDS (0.67 g, 4.5 mmol), and THF (3.2 mL). Hydroxybenzimidoyl chloride (0.10 g, 0.64 mmol) was added to THF (3.2 mL) in a dry vial. The substrate was then transferred to the reaction flask dropwise via syringe, and the mixture was stirred for 10 min. The reaction was diluted with \( \text{H}_2\text{O} \) and extracted with EtOAc (3×). The organic layer was washed with brine, dried (MgSO\(_4\)), and concentrated \textit{in vacuo}. The crude residue was purified by flash chromatography on SiO\(_2\) (hexanes–EtOAc, 0–7%) to yield 0.10 g (71%) of 2-62 as a white solid: \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta = 8.17 \) (s, 1 H), 7.67-7.64 (m, 2 H), 7.46-7.32 (m, 8 H), 5.31 (s, 2 H); \( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta = 156.0, 136.6, 130.6, 130.4, 128.7, 128.6, 128.6, 128.2, 127.4, 73.5 \); IR (neat) 3318, 3061, 2884, 1634, 1453, 1295, 1098 cm\(^{-1}\); ESIMS \( m/z \) 228 \([\text{M + H}]^+\); HRMS \( m/z \) \([\text{M + H}]^+\) calculated for C\(_{14}\)H\(_{14}\)NO\(_2\) [M + H\(^+\)] 228.1019, found 228.1017; mp = 41–42 °C.

Allyl hydroxybenzimidate (2-63); According to general protocol A, allyl alcohol (0.26 g, 4.5 mmol) NaHMDS (0.67 g, 4.5 mmol) were stirred in THF (3.2 mL). Hydroxybenzimidoyl chloride (0.10 g, 0.64 mmol) in THF (3.2 mL) was added to the mixture, and the reaction stirred for 10 min to yield 0.069 g (61%) of 2-63 as a clear oil after purification by flash chromatography on SiO\(_2\) (hexanes–EtOAc, 0–10%): \( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta = 8.82 \) (s, 1 H), 7.69-7.66 (m, 2 H), 7.45-7.36 (m, 3 H), 6.07-5.98 (m, 1 H), 5.38 (ddt, \( J = 17, 1.5, 0.7 \) Hz, 1 H), 5.29-5.26 (m, 1 H),
4.77 (dt, \( J = 5.8, 1.0 \) Hz, 2 H); \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta = 155.9, 133.0, 130.6, 130.3, 128.6, 127.3, 118.8, 72.3 \); IR (neat) 3322, 3061, 2876, 1634, 1299, 1098, 940, 770, 696 cm\(^{-1}\); ESIMS \( m/z \) 177 \([\text{M} + \text{H}]^+\); HRMS \( m/z \) [M + H]\(^+\) calculated for C\(_{10}\)H\(_{12}\)NO\(_2\) \([\text{M} + \text{H}]^+\) 178.0863, found 178.0863.

![3,5-Diphenyl-1,4,2-dioxazole (2-64)]

**3,5-Diphenyl-1,4,2-dioxazole (2-64); General protocol B.** To a round-bottom flask at rt was added 2-62 (0.12 g, 0.54 mmol), DMF (11 mL), and DDQ (0.12 g, 0.54 mmol), and the solution was degassed with nitrogen for 5 min. The mixture was then plunged into a 150 °C oil bath and stirred for 20 min. The reaction mixture was cooled to rt, quenched with H\(_2\)O, and extracted with EtOAc (3×). The organic layer was washed with aq NaHCO\(_3\), H\(_2\)O, and brine, dried (MgSO\(_4\)), concentrated in vacuo, and purified by flash chromatography on SiO\(_2\) (hexanes–EtOAc, 0–2%) to yield 0.031 g (26%) of 2-64 as a clear oil: \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta = 8.87\text{-}8.85 \) (m, 2 H), 7.62-7.58 (m, 2 H), 7.55-7.43 (m, 8 H), 6.90 (s, 1 H); \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta = 159.3, 135.1, 131.8, 130.7, 128.9, 128.8, 127.1, 126.9, 122.9, 108.7 \); IR (neat) 3065, 2919, 1623, 1449, 1359, 1090, 763, 687 cm\(^{-1}\); HRMS \( m/z \) [M + H]\(^+\) calculated for C\(_{15}\)H\(_{11}\)NO\(_2\) \([\text{M} + \text{H}]^+\) 226.0863, found 226.0857.

![3-Phenyl-5-vinyl-1,4,2-dioxazole (2-65)]

**3-Phenyl-5-vinyl-1,4,2-dioxazole (2-65)** According to general protocol B, hydroxyimide 2-63 (32 mg, 0.18 mmol) and DDQ (41 mg, 0.18 mmol) were stirred in DMF (3.6 mL) for 1 h to yield 0.0006 g (2%) of 2-65 as a clear oil after purification by flash chromatography on SiO\(_2\) (hexanes–
EtOAc, 0–2%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.83-7.82 (m, 1 H), 7.79-7.78 (m, 1 H), 7.50-7.40 (m, 3 H), 6.38 (d, $J$ = 6.3 Hz, 1 H), 6.10-5.99 (m, 1 H), 5.71 (m, $J$ = 17.1 Hz, 1 H), 5.57 (d, $J$ = 10.3 Hz, 1 H).
2.3.6: References


PART 3: Synthesis of 1,4,2-Oxaselenazoles

2.4.1: Abstract

The success of DDQ-mediated oxidative cyclizations of thiohydroximic acids and amidoximes to oxathiazoles and oxadiazoles led to efforts to use this chemistry for accessing other tri-heteroatom azoles. Described here are attempts for accessing 1,4,2-oxaselenazoles via oxidative cyclization. Optimization of substrate formation is described as well as the oxidative cyclization attempts.

2.4.2: Introduction and Background

The final tri-heteroatom azole we considered was the 1,4,2-oxaselenazole (Figure 2.9). 1,4,2-Oxaselenazoles are five membered heterocycles that contain an oxygen, selenium, and nitrogen atom. For the remainder of this document, the term oxaselenazole will refer only to 1,4,2-oxaselenazoles.

![1,4,2-oxaselenazole](image)

**Figure 2.9:** Structure of 1,4,2-oxaselenazole heterocycles.

2.4.2.1: Applications of Oxaselenazoles

Foods containing one milligram of selenium per kilogram ingested are considered toxic. Due to this high toxicity and the general instability of selenium-containing molecules, the development of selenium-containing compounds has not been studied as much as the
corresponding organosulfur analogs; however, interest in these molecules has grown over the past few decades due to the development of potent biologically active selenium-containing molecules. One of these compounds is the antioxidant ebselen (Figure 2.10).¹ Ebselen was discovered in 1984 by Muller and coworkers as a compound able to mimic GPx’s ability to relieve oxidative stress by reducing and breaking down hydroperoxides.² This activity is not present in the sulfur-containing analogue of ebselen showing the necessity of the selenium atom for its biological function. Another selenium-containing biologically relevant compound is selenazofurin. This compound was first synthesized in 1983 by Srivastava and Robins as an analog of the antitumor candidate tiazofurin.¹,³ It showed 5–10 fold more potent activity than the sulfur-containing tiazofurin in many in vitro and in vivo antitumor screenings.⁴ One last example are the selenosartans. These analogs of milfasartan are AT₁ receptor antagonists and have been studied for the treatment of hypertension. Many of the sartan derivatives have reached clinical trials and some are marketed in countries around the world.⁵

![Chemical structures of ebselen, selenazofurin, and selenomilfasartan isomer](image)

**Figure 2.10:** Selenium-containing biologically active compounds.
2.4.2.2: Synthesis of Oxaselenazoles

Analogous to oxadiazoles and dioxazoles, oxaselenazoles can be synthesized by the [3 + 2] cycloaddition of a nitrile oxide and a selenoketone or selenoaldehyde (Scheme 2.23). Selenocarbonyls, however, are very reactive and are typically generated *in situ* before addition of nitrile oxide. Due to the few existing methods for the synthesis of oxaselenazoles, along with the interest in selenium heterocycles for new interesting lead molecules, we decided to apply our method of oxathiazole formation to these rings as well.

Scheme 2.23: Synthesis of oxaselenazoles.

2.4.3: Results and Discussion

As with the aforementioned heterocycles, we required a method for the synthesis of the hydroxyselenoimidate starting material. The closest literature reports of the synthesis of selenoimidates was that by Kumar and coworkers. It involves the reduction of a diselenide to form a selenium nucleophile *in situ* which then attacks the nitrile oxide of dichloroglyoxime. Reduction of elemental selenium with sodium borohydride followed by the addition of another equivalent of selenium and two equivalents of benzyl bromide gave dibenzyl diselenide 2-66 in 55% yield (Scheme 2.24). Subsequent sodium borohydride reduction of 2-66 followed by addition of nitrile oxide gave the resulting benzyl hydroxyselenoimidate 2-67 in 70% yield.
Scheme 2.24: Synthesis of hydroxyselenoimidate.

With the desired selenoimidate in hand, investigations into the oxaselenazole formation began. The first conditions tried were those reported by us for the synthesis of oxathiazoles minus the acid additive (Table 2.5). One equivalent of DDQ in DMF at 150 °C consumed the starting material and gave a complex mixture of decomposition by LC-MS without any observable oxaselenazole 2-68 formation (entry 1). The reaction was also done at room temperature which returned the same result (entry 2). Since DDQ did not appear to be an adequate oxidant for oxaselenazole formation, the reaction was also tried with Cu(OAc)$_2$ as the oxidant (entry 3). This reaction also gave a complex mixture over time, but dibenzyl diselenide 2-66 was isolated after purification in 71% yield. The bond between the carbon of the oxime and the selenium atom was cleaved, and the resulting benzyl selenol was oxidized (possibly by copper) back to the diselenide.

Table 2.5: Attempts at oxaselenazole formation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>2-68 Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DDQ (1 equiv), DMF, 150 °C, 20 min</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>DDQ (1 equiv), DMF, rt, 1 h</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)$_2$ (1 equiv), DMF, rt, 4 d</td>
<td>--</td>
</tr>
</tbody>
</table>

*All reactions were performed on 50 mg scale and at 0.05 M. *Isolated product yield.
Due to DDQ and Cu(OAc)$_2$’s inability to furnish the desired oxaselenazole, along with the success of our research on oxadiazole formation, we decided to indefinitely postpone our investigations of oxaselenazole synthesis.

2.4.4: Conclusions

The success of our previous DDQ-mediated oxidative cyclizations led to efforts for using this chemistry to accessing other tri-heteroatom azoles. Attempts for accessing 1,4,2-oxaselenazoles via oxidative cyclization of $O$-benzyl hydroxyselenoimidates were conducted. The substrates can be synthesized by *in situ* reduction of a diselenide and subsequent addition of that nucleophile onto a nitrile oxide. With the substrate in hand, oxaselenazole synthesis proceeded. There was no observed formation of desired oxaselenazole with various oxidants. Instead, cleavage of the C–Se bond of the substrate and oxidation re-formed the diselenide starting material precursor. Selenium’s ability to be easily oxidized compared to the sulfur and nitrogen cases might have played a role in this poorly performing reaction. These studies were halted when we observed greater success with oxadiazole synthesis.
2.4.5: Experimental Section

General considerations: All reactions were performed under a nitrogen atmosphere, and all glassware was flame-dried and flushed with nitrogen prior to use. DMF (99.8%, extra dry over molecular sieves) and DDQ were purchased from Acros Organics and used as received. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F254 plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a KMnO4 solution (1.5 g of KMnO4, 10 g of K2CO3, and 1.25 mL of a 10% NaOH solution in 200 mL of water). Reactions were also monitored by LC-MS analysis (Shimadzu LC-MS 2020 with Kinetex 2.6 mm C18 50 × 2.10 mm). Flash chromatography on SiO2 was used to purify the crude reaction mixtures and performed on a Biotage Isolera using Biotage cartridges and linear gradients. 1H and 13C NMR spectra were obtained on a Varian Mercury-VX 300, a Varian Mercury-VX 400, or a Varian Mercury-Plus 300 instrument in CDCl3 unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard (CDCl3 = 7.26 ppm for 1H, CDCl3 = 77.16 ppm for 13C). 1H NMR spectra were run at 300 or 400 MHz and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, bs = broad singlet), number of protons, and coupling constant(s). 13C NMR spectra were run at 100 MHz using a proton-decoupled pulse sequence with a d1 of 1 second unless otherwise noted, and are tabulated by observed peak. Infrared spectra were determined on a Jasco FT/IR-4100 spectrometer. High-resolution mass spectra were obtained on a Thermo Fisher Scientific, Exactive Plus mass spectrometer (ion trap) using Heated Electrospray Ionization (HESI). Melting points were determined by using a Thomas Hoover capillary melting point apparatus.
**1,2-Dibenzylidiselenelane (2-66);** To a round-bottom flask at 0 °C was added NaBH₄ (0.48 g, 13 mmol), EtOH (2.2 mL, 38 mmol), and DMF (21 mL). Molecular Se (0.50 g, 6.3 mmol) was added, and the solution was allowed to stir until the hydrogen evolution ceased. EtOH (1.5 mL, 25 mmol) was added, and the reaction was allowed to stir for another 10 minutes before the second addition of a molecular Se (0.50 g, 6.3 mmol). To the resulting mixture was added benzyl bromide (1.5 mL, 13 mmol) dropwise, and the solution turned yellow. The reaction mixture was diluted with H₂O and extracted with Et₂O. The organic layer was washed with H₂O and allowed to stir overnight open to the air. The yellow solution was dried (MgSO₄), concentrated *in vacuo*, and recrystallized from hexanes to give a yellow crystalline solid (1.2 g, 55%) which was stored under argon, in the dark at rt. ¹H NMR (400 MHz, CDCl₃) δ = 7.33–7.20 (m 10 H), 3.84 (s, 4 H); ¹³C NMR (100 MHz, CDCl₃) δ = 139.1, 129.1, 128.6, 127.2, 32.7; IR (neat) 3022, 2982, 1493, 1453, 1173, 1063, 755, 696 cm⁻¹; mp = 78–79 °C.

**Benzyl-hydroxybenzimidoseleenoate (2-67);** A degassed solution of NaBH₄ (24 mg, 0.64 mmol) in H₂O (0.32 mL) was added dropwise to a solution of 2-66 (75 mg, 0.19 mmol) in dry EtOH (6.5 mL) under N₂. A degassed saturated solution of Na₂CO₃ was added dropwise until the reaction mixture became colorless. A solution of hydroxybenzimidoyl chloride (0.050 g, 0.32 mmol) in EtOH (3.2 mL) was added, and the reaction stirred at rt for 20 min. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with H₂O and brine, dried
(MgSO$_4$), concentrated in vacuo, and purified by flash chromatography on SiO$_2$ (hexanes–EtOAc, 0–15%) to yield 0.065 g (70%) of 2-67 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) δ = 9.35 (s, 1 H), 7.49-7.41 (m, 5 H), 7.25-7.14 (m, 3 H), 7.06-7.01 (m, 2 H), 3.79 (s, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 154.3, 137.6, 134.2, 129.8, 129.0, 128.9, 128.7, 128.6, 127.2, 29.9; IR (neat) 3255, 3082, 2943, 1618, 1445, 976, 908, 763, 696 cm$^{-1}$; ESIMS $m/z$ 290 [M + H]$^+$; HRMS $m/z$ [M + H]$^+$ calculated for C$_{14}$H$_{13}$NOSe [M + H]$^+$ 292.0235, found 292.0230; mp = 129–132 °C.
2.4.6: References


(8) Reactions were monitored using LC-MS by observing low resolution MS and UV absorbance.
CHAPTER 3

Synthesis of Quaternary-Substituted 2-Thiazolines

Portions of PARTs 1 and 2 of this chapter were published in the Journal of Organic Chemistry
Department of Chemistry, North Carolina State University;
Raleigh, NC 27695-8204

Portions of PART 3 of this chapter were published in Tetrahedron Letters
Department of Chemistry, North Carolina State University;
Raleigh, NC 27695-8204
3.1: General Introduction

2-Thiazolines are five membered heterocycles with a nitrogen atom, a sulfur atom, and an unsaturation between the nitrogen and C2 (Figure 3.1). For the remainder of this document, the term thiazoline will refer only to 2-thiazolines.

![2-thiazoline](image)

Figure 3.1: Structure of 2-thiazoline heterocycles.

3.1.1: Thiazoline-Containing Natural Products and Bio-Active Compounds

Thiazolines can be found in several different classes of natural products such as polyazoles, polyketides, as well as linear and cyclic peptides (Figure 3.2). This in turn provides a diversity of bioactivities such as antibacterial, anticancer, and antiviral. The cyclic peptide largazole is an HDAC 1 inhibitor\(^1\) whereas the polyketide-derived curacin A acts as an inhibitor of tubulin polymerization.\(^2\) Both compounds have been studied for their anticancer properties. Thiazolines can also be found in polyazoles such as thiangazole, an HIV-1 inhibitor,\(^3\) as well as the antibacterial compounds piscibactin,\(^4\) and althiomycin.\(^5\) Another compound with antibacterial properties is the large macrocyclic peptide thiostrepton.\(^6\) Many thiazoline-containing natural products have also found use as aromas, flavors, and pigments. D-Luciferin, for example, is responsible for the bioluminescence of fireflies, and it, along with analogs, has been studied for \textit{in vivo} imaging.\(^7\)
Figure 3.2: Thiazoline-containing natural products and biologically active compounds.
3.1.2: Reactivity and Applications of Thiazolines

Along with their prevalence in nature, the reactivity and applications of thiazolines make them interesting targets for synthesis. Thiazolines have two nucleophilic sites at both the nitrogen and sulfur atoms and one electrophilic site at C2 (Figure 3.3). They are also prone to oxidation at the C4–C5 bond as well as reduction at the C2–N bond. Each of these reactive centers give rise to an assortment of applications and reactivities.\(^8\)

\[\text{Figure 3.3: Overview of the reactivity of thiazolines.}\]

The reactivity of thiazolines allow them to undergo a number of subsequent transformations. Reactions that preserve the thiazoline ring typically coincide with reactivity at the electrophilic C2 atom and the nature of the exocyclic substituent. These transformations tend to use the thiazoline ring as an activating group for subsequent reactions. For example, thiazoline phosphonates can be synthetic intermediates for subsequent HWE reactions. In 1994, Ehrler and coworkers employed a late state HWE reaction for completion of the total synthesis of thiangazole (Scheme 3.1).\(^9\) The acidity of the exocyclic proton can be used for the synthesis of a range of more complex heterocyclic systems. In 2001, Fustero and coworkers demonstrated the use of 2-methylthiazoline in various cascade cyclizations (Scheme 3.2). Treatment of 2-methylthiazoline with LDA and 1-cyano-2-(bromomethyl)benzene gave the 3-aminooindene compound 3-1.
Replacement of 1-cyano-2-(bromomethyl)benzene with 1,2-dicyanobenzene resulted in formation of compound 3-2. Finally, pyrrolidine 3-3 was formed with addition of 3-bromo-1,1-diphenyl-1-cyanopropane as the cyclization partner.\textsuperscript{10} 2-Vinylthiazoline derivatives can act as conjugate addition acceptors for a variety of nucleophiles such as thiols as demonstrated for the synthesis of compounds like 3-4 in high yields (Scheme 3.3).\textsuperscript{8} Finally in 2005, Dominguez and coworkers reported a HWE/conjugate addition cascade for the synthesis of mannofuranosyl derivative 3-5 as an analog of the anticancer compound tiazofurin (Scheme 3.4).\textsuperscript{11}

\begin{center}
\includegraphics[width=\textwidth]{scheme_3.1.png}
\end{center}

\textbf{Scheme 3.1:} Total synthesis of thiangazole via late stage HWE reaction.

Another reactive site on a thiazoline ring is the nucleophilic nitrogen atom. Alkylation of the nitrogen atom can form thiazolinium salts 3-6 (Scheme 3.5).\textsuperscript{12} These salts have found utility as fluorescent DNA markers for malaria diagnosis,\textsuperscript{13} as dyes and photochromatic compounds,\textsuperscript{14,15} and as chiral ionic liquids.\textsuperscript{16} Another example of N2 nucleophilicity is the use of 2-vinylthiazolines as hetero-dienes in $[4 + 2]$ cycloadditions with ketenes and isocyanates (Scheme 3.6).\textsuperscript{8,17} One equivalent of ketene or isocyanate can be used to make substituted thiazolopyridinones or thiazolopyrimidinones, respectively. A second equivalent can further substitute the rings to form compounds like 3-7.
Scheme 3.2: Applications of C2-exocyclic proton acidity.

Scheme 3.3: Conjugate addition to C2-vinyl thiazolines.
Scheme 3.4: HWE/conjugate addition cascade reaction.

Scheme 3.5: Synthesis of thiazolinium salts.

Scheme 3.6: Thiazolines as hetero-dienes in [4 + 2] cycloadditions with ketenes and isocyanates.

Thiazolines can be converted to other oxidation states. For example, the C2–N bond of a thiazoline can be reduced with mercury aluminum amalgam to form the corresponding thiazolidine 3-8 (Scheme 3.7). This reduction can also be achieved with nucleophiles to form new C–C or C–
heteroatom bonds. Furthermore, the C4–C5 bond can be oxidized to the corresponding thiazole 3-9 with a variety of reagents. Thiazoles are the sixth most commonly found nitrogen heterocycle in FDA approved drugs.

Scheme 3.7: Thiazoline reduction to thiazolidines and oxidation to thiazoles.

Thiazolines can also act as masked aldehydes and ketones (Scheme 3.8). The C2 position of a thiazoline can be substituted to provide primary, secondary, and tertiary exocyclic substituents. Reduction of the C2-substituted thiazoline to the corresponding thiazolidine with mercury aluminum amalgam and subsequent cleavage of the ring with HgCl₂ provides the desired aldehydes. Also, reduction of the C2 atom with a nucleophile (such as a Grignard reagent) followed by cleavage of the ring with HgCl₂ provides the desired ketone. Furthermore, cleavage of the thiazoline itself can be achieved with aqueous acid to furnish the corresponding β-amino thiol (Scheme 3.9).
Scheme 3.8: Thiazolines as masked aldehydes and ketones via cleavage of thiazolidines.

Scheme 3.9: Thiazoline hydrolysis to β-amino thiols.

The nucleophilic and easily oxidized sulfur atom can also be used to convert thiazolines to other functional groups. Oxone has been shown to oxidatively cleave the C2–S bond of thiazoline 3-10 to a sulfinic acid derivative. This is then further converted to the corresponding disulfide 3-11 (Scheme 3.10). Treatment of 3-10 with KMnO₄ and catalytic BnEt₃NCl in a PTC system of CH₂Cl₂/H₂O provides the corresponding sulfone 3-12 without opening of the ring. Also, reacting 3-10 with mCPBA gives the corresponding sulfonic acid 3-13 via the sulfinic acid intermediate.²⁵
Scheme 3.10: Oxidation of the sulfur atom of thiazolines.

Finally, thiazolines have found use as chiral ligands for asymmetric catalysis (Figure 3.4). Ligands such as \( \text{L1} \) were used by Helmchen and coworkers in 1991 for the rhodium-catalyzed asymmetric hydrosilylation of acetophenone.\(^{26}\) Ligands of the form \( \text{L2} \) have been developed for palladium-catalyzed allylic substitution, whereas \( \text{L3} \) has been used for the asymmetric Henry reaction.\(^{8,27}\) \( \text{L4} \) has shown use in asymmetric cyclopropanations.\(^{28}\) With sterically hindered bis(thiazoline) ligands, a tendency for competition between (N,N) and (N,S) chelation to metals is something not seen with bis(oxazoline) ligands. This gives a different enantiocontrol over the reaction for bis(thiazoline) over the classic bis(oxazoline) ligands.\(^{29}\) Ligands such as \( \text{L5} \) have been used in the asymmetric Diels-Alder reaction between cyclopentadiene and 2-acryloyloxazolidinone, whereas \( \text{L6} \) has been studied for C–P bond forming reactions.\(^{8,30}\)
3.1.3: Synthesis of Thiazolines

As shown above, thiazolines have numerous applications to many fields of scientific research. Consequently, there currently exists many methods for the preparation of these heterocycles. Two of the most common methods employ β-amino thiols (3-14) and β-amino alcohols (3-15, Scheme 3.11).

**Scheme 3.11:** Thiazoline synthetic approaches.

Thiazolines can be synthesized from the corresponding β-amino thiol. β-Amino thiols like compound 3-14 can be condensed with a variety of coupling partners such as activated carboxylic
acids, nitriles, imine esters, and iminium triflates to form thiazolines (Scheme 3.12) through an intermediate resembling compound 3-16. This intermediate undergoes cyclodehydration to thiazoline 3-10.31

**Scheme 3.12:** Synthesis of thiazolines via β-amino thiols.

The other major synthetic route to thiazolines begins with β-amino alcohols. The nitrogen atom of β-amino alcohol 3-15 can be thioacylated to form compound 3-19 (Scheme 3.13). Compound 3-19 can also be accessed via thionation of compound 3-17 which is a product of the acylation of 3-15. Thionation of acylated β-amino alcohols is typically accomplished with phosphorous pentasulfide or Lawesson’s reagent.31 β-Amino alcohols can be converted to the corresponding oxazoline-containing compound 3-18 followed by thiolysis to form compound 3-19. Wipf and coworkers discovered that oxazoline rings can be selectively opened by hydrogen sulfide in the presence of amides. It is also selective for oxazoline rings lacking a C5 substitution over rings that contain a C5 substitution.31,32 Compound 3-19 can be cyclodehydrated to form the corresponding thiazoline ring. The cyclodehydration step can be accomplished with a variety of reagents that activate the alcohol such as DAST, Burgess’ reagent, tosyl chloride, or Mitsunobu conditions.

Although straightforward, the synthesis of thiazolines via β-amino thiols and β-amino alcohols comes with many disadvantages. One disadvantage of these methods is that thiazoline synthesis requires first the synthesis of the corresponding β-amino thiol or β-amino alcohol; however, there does not exist a straightforward method for the synthesis of a diverse range of β-amino thiols and β-amino alcohols when precursors do not originate from natural amino acids. The commercial availability of these substrates is limited, and most synthetic methods are lengthy, making some substrates difficult to access. Furthermore, asymmetric thiazoline synthesis via these methods requires the previous asymmetric synthesis of the corresponding β-amino thiol or β-amino alcohol. Additionally, a drawback of thioacylation of β-amino alcohols is the synthetic difficulty and instability of thioacylating reagents. The synthesis of thiazolines via thiolysis and cyclodehydration of oxazolines require extra condensation and dehydration steps to form the oxazoline, and thionation reagents such as phosphorus pentasulfide and Lawesson’s reagent typically require harsh conditions that many substrates cannot tolerate. Another drawback is the
epimerization of the exocyclic methylene groups under acidic or basic conditions (Scheme 3.14). Under basic conditions, the C4 atom of compound 3-20 can be deprotonated, and re-acidification can epimerize 3-20 to its epimer 3-20-e1. Similarly, under acidic or basic conditions, the exocyclic carbon atom bonded to C2 of compound 3-20 can be epimerized to the epimer 3-20-e2.\textsuperscript{31} However, Wipf and coworkers have demonstrated that epimerization can be minimized with the use of Burgess’ reagent in the cyclodehydration step.\textsuperscript{33}

\textbf{Scheme 3.14:} Epimerization of thiazolines under acidic or basic conditions.

There are a few methods that do not employ $\beta$-amino thiols and $\beta$-amino alcohols. One report from 1993 by Fukuyama and coworkers demonstrated the opening of a C2 quaternary-substituted $\beta$-lactone with an isopropyl thioester (Scheme 3.15). Opening occurs at the C3 position to furnish the carboxylic acid 3-21. Deprotection is followed by refluxing in benzene to give the thiazoline 3-22.\textsuperscript{34} Another example uses a one-pot Staudinger reduction/aza-Wittig cascade with the $\beta$-azido thioester 3-23 (Scheme 3.16). Treatment of this compound with PPh$_3$ promotes the
formation of a P–N bond via the release of nitrogen to form intermediate 3-24. This undergoes a [2 + 2] cycloaddition with the carbonyl of the thioester to give a strained oxazaphosphetidine 3-25. This intermediate undergoes a retro-[2 + 2] cycloaddition to furnish thiazoline 3-22 and OPPh₃.³⁵

Scheme 3.15: Synthesis of a thiazoline via opening of β-lactone.

Scheme 3.16: Synthesis of a thiazoline from a β-azido thioester.

There are also several methods for the synthesis of thiazolines that employ thioamides as substrates (Scheme 3.17). Pathak et al. treated thioamides with β-halo amines to give a variety of thiazolines such as 3-27 with substitutions at only the C2 atom.³⁶ Nötzel and coworkers reported a synthesis of thiazolines resembling 3-28 that bear substituted spyro-cyclopropanes at the C4 position with the use of thioamides and 2-chloro-2-cyclopropylideneacetate.³⁷ More recently in
2017, Li and coworkers demonstrated a one-pot di-halogenation of alkenes followed by addition of a thioamide to furnish thiazolines resembling compound 3-29.\textsuperscript{38}

Scheme 3.17: Synthesis of thiazolines from thioamides.
3.1.4: References


PART 1: *Anti*-Diastereoselective Synthesis of 2-Thiazolines

3.2.1: Abstract

An efficient synthesis of S-allyl thioimidate hydrobromide salts via coupling of thioamides with allyl bromides is described. An assortment of mono-, di-, and tri-substituted olefins as well as alkyl- and aryl-thioamides with variable electronic properties are tolerated. An anti-diastereoselective synthesis of quaternary-substituted thiazolines via halocyclization of these S-allyl thioimidate hydrobromide salts is also described. This method can be done on gram scale and provides a rapid approach to 2-thiazolines some of which cannot be accessed by other less mild conditions. Moderate to excellent yields of thiazolines were obtained with a variety of substitution patterns at both C2 and C4.

3.2.2: Introduction and Background

3.2.2.1: Syn-Diastereoselective Synthesis of 2-Thiazolines

As previously mentioned, there are several methods for the synthesis of thiazolines; however, with each method comes disadvantages. There still exists a need to develop efficient methods of thiazoline synthesis with broader substrate scopes and milder reaction conditions. We are also particularly interested in thiazolines that are quaternary-substituted at the C4 position as those structures are found in numerous thiazoline-containing natural products and biological relevant compounds (Figure 3.5).
Figure 3.5: Prevalence of quaternary-substituted thiazolines in biologically active compounds.

One reaction developed by our group involves the copper-catalyzed cyclization of OBzF-activated S-allyl thiohydroximates (Scheme 3.18). As proposed, oxidative addition of CuBr onto the activated N–O bond of compound 3-30 gives the intermediate Cu(III) species 3-31. This is followed by a cis-iminocupration to form the thiazoline ring in a syn-diastereoselective fashion. Finally, reductive elimination provides the cis-diastereomer of thiazoline 3-33 and CuOBzF. LiBr was a necessary additive to regenerate the CuBr catalyst.\(^1\)

Scheme 3.18: Synthesis of thiazolines via pentafluorobenzoyl-activated allyl thioimidates.
The Cu(I)-catalyzed system for the synthesis of thiazolines developed by our group is a syn-diastereoselective process. The reaction worked well for several alkyl- and aryl-thiohydroximates (Table 3.1). Compound 3-34 was synthesized in 50% yield, and compound 3-35 was isolated in 61% yield as a single cis-diastereomer. The reaction also worked well for conjugated aromatic substrates such as thiazoline 3-36. Variations in the R¹ substituents showed tolerability for cyclopropyl groups as in the case with thiazoline 3-37 which was formed in 52% yield. Heteroaryl groups were also tolerated as indicated by the thiophene- and thiazole-containing thiazolines 3-38 and 3-39 which were formed in 61% and 98% yield, respectively. With these results, we thought it fruitful to pursue a complementary method that could provide similar quaternary-substituted thiazolines in an anti-diastereoselective fashion.

**Table 3.1:** Substrate scope highlights for syn-diastereoselective thiazoline formation.
3.2.2.2: Original Idea and Scope

As stated, we sought to develop a complementary method for the synthesis of quaternary-substituted thiazolines like those accessed under our copper-catalyzed conditions. A good starting point, therefore, would be to use similar substrates. We decided to use a halocyclization approach by reacting S-allyl thioimidates (substrates lacking the OBzF bond to the nitrogen atom) such as 3-40 with a halogen electrophile (Scheme 3-19). This reaction would form a halonium ion intermediate that is free to undergo a 5-exo cyclization to the corresponding thiazoline 3-41.

Scheme 3.19: Synthesis of thiazolines via halocyclization of thioimidates.

Halocyclization reactions are common transformations in organic synthesis. They were first discovered in 1883 by Fittig with the bromolactonization reaction. As a result, halolactonizations have historically been the most commonly reported transformation, but in more recent decades they have been used for the synthesis of a variety of other heterocycles. For example, Dodd and coworkers reported on the halocyclization of guanidines bearing substrates 3-42 for the synthesis of 2-imidazolidinimine derivatives 3-43 using an in situ generated halogen electrophile (Scheme 3.20). Rybakova et al. demonstrated the synthesis of a series of complex yet biologically relevant fused tetracycles that resemble compound 3-46 from a halocyclization of S-
allyl triazinoindole thiol derivatives resembling compound 3-44. This reaction goes through intermediate 3-45 which re-aromatizes to compound 3-46. Finally, in 2017 Xu et al. reported a cyclization of tryptamine and tryptophol derivatives 3-47 to complex fused heterocycles 3-48 (Scheme 3.22).

Scheme 3.20: Halocyclization of protected guanidines to 2-imidazolidinimines.

Scheme 3.21: Halocyclization of S-allyl triazinoindole thiol to a complex fused tetracycle.

Scheme 3.22: Halocyclization of tryptamine/tryptophol derivatives to fused heterocyclic systems.
There have been a few demonstrations of thiazoline synthesis via intramolecular electrophile-induced nucleophilic cyclizations of $N$-allyl thioamides. In 1991, Engman and coworkers reported a proton-induced cyclization of thioamide 3-49 to furnish thiazoline 3-50 (Scheme 3.23). The same report by Engman provided conditions for the selenium-induced cyclization of 3-49 to thiazoline 3-52. In 2006, Komatsu and coworkers reported the iodo-cyclization of thioamide 3-49 to thiazoline 3-51. More recently in 2015, Zhou et al. developed a bromocyclization of allyl thioamide 3-53 to bromo thiazoline 3-54. This reaction was demonstrated on five substrates with moderate to excellent yields (Scheme 3.24). Also reported in 2015 by Foroumadi and coworkers is a bromocyclization of allyl thioureas resembling compound 3-55 to furnish 2-amidothiazolines 3-56. This chemistry was demonstrated on seven examples with moderate yields.

**Scheme 3.23**: Synthesis of thiazolines via various electrophile-induced cyclizations of thioamides.
Scheme 3.24: Synthesis of thiazolines via bromocyclization of allyl thioamides.

Scheme 3.25: Synthesis of 2-amido thiazolines via bromocyclization of allyl thioureas.

Each of these methods provide the “unnatural” thiazoline with substitution at the C5 position adjacent to the sulfur atom. These reports also provide limited substrate scope data and have not been further developed. We hoped to use this chemistry for the synthesis of quaternary-substituted thiazolines with more “natural” substitution patterns at the C4 position. In lieu of the thioamide substrates mentioned above, we would employ S-allyl thioimidates (3-40, Scheme 3.19).

The regio-selectivity of the products requires additional consideration. The halonium ion formed during the reaction is a non-classical carbocation and depending on the nature of the substitution pattern per substrate (3-40), both carbons of the three-membered ring could have differing degrees of sp³ and sp² character leading to a mixture of regio-isomers (Scheme 3.26). These regio-isomers would either be the thiazoline 3-41 resulting from 5-exo cyclization or the
thiazine 3-41-r1 resulting from 6-endo cyclization. 5-Exo cyclization should be kinetically favored over 6-endo due to the less strained transition state.\textsuperscript{10} Furthermore, Baldwin’s rules state that 5-exo-trig, 6-endo-trig, and 5-exo-tet are favored processes and 6-endo-tet is disfavored.\textsuperscript{11} Therefore, 5-exo cyclization should be favored with the regio-selectivity of halocyclization (and more generally electrophile-induced nucleophilic cyclizations) depending on the substrate and the electrophile. For example, since a “carbocation” is formed, the substitution pattern of the olefin plays a role in the regio-selectivity due to Markovnikov’s rules.\textsuperscript{12} This would render certain substrates to prefer 5-exo while others would be biased towards 6-endo cyclization.

\textbf{Scheme 3.26:} Regio-selectivity in the halocyclization of S-allyl thioimidates to thiazolines.

\textbf{3.2.3: Results and Discussion}

\textbf{3.2.3.1: Synthetic Route to S-Allyl Thioimdate Hydrobromide Salts}

Before thiazoline synthesis could be investigated, a straightforward method for preparing S-allyl thioimidates was required. Optimization of these substrates was done previously by Bérénice but highlights of that process are discussed here.\textsuperscript{13} Previous reported methods for
accessing thioimidates were scarce with only a few of them providing any detailed experimental procedures, so however, we began by employing a method for the synthesis of \( S \)-alkyl thioimidates.\textsuperscript{14–16} Treatment of thiobenzamide with 3-chloro-2-methylpropene at reflux in THF and in the presence of a base and catalytic TBAI gave no reaction (Table 3.2, entries 1 and 2). Changing the electrophile to the allylic bromide derivative also gave no reaction at room temperature (entry 3) but gave 16\% yield of the desired thioimidate \textbf{3-57} at reflux in THF (entry 4). Using \( \text{Et}_3\text{N} \) as the base increased the yield to 39\% (entry 5); however, the yield decreased significantly when a mildly acidic workup was done to remove remaining base (entry 6). Also, the yields were not reproducible and, in many cases, provided little to no product (entry 7).

\textbf{Table 3.2:} Optimization of \( S \)-allyl thioimidate \textbf{3-57}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Conditions</th>
<th>3-57 Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>LiHMDS, TBAI (10 mol%), 67 °C, 47 h</td>
<td>NR$^b$</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>NaH, TBAI (10 mol%), 67 °C, 17 h</td>
<td>NR$^{b,c}$</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>NaH (1.2 equiv), rt, 69 h</td>
<td>NR$^b$</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>KHMDS, 67 °C, 44 h</td>
<td>16%, 18% bram</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>( \text{Et}_3\text{N} ), TBAI (10 mol%), rt, 47 h</td>
<td>39%, 55% bram</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>( \text{Et}_3\text{N} ), TBAI (10 mol%), 67 °C, 6 h</td>
<td>2%$^d$</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>( \text{Et}_3\text{N} ), TBAI (10 mol%), 67 °C, 4 h</td>
<td>0-55%</td>
</tr>
</tbody>
</table>

$^a$isolated yield. $^b$observed by LC-MS. $^c$decomposition of starting material. $^d$acidic workup to remove \( \text{Et}_3\text{N} \). $^e$variations in yield over multiple trials.

It was determined by stability testing that compound \textbf{3-57} decomposes quickly at room temperature; as a result, we re-evaluated our approach. Upon treatment of thiobenzamide with one equivalent of electrophile at room temperature in THF (removing the additives), thioimidate \textbf{3-58} was observed by LC-MS (Table 3.3, entry 1). The reaction rate increased significantly when
performed at reflux in THF (entry 2). Increasing the concentration of thioamide and using two equivalents of electrophile gave the optimal yield of 92% (entry 3); however, further increasing the equivalents of allyl bromide to three reduced the yield (entry 4). The reaction provides high yields of thioimidate hydrobromide salt 3-58 as a white precipitated solid, and the purification requires only filtration and trituration. Following these results, a second stability screen was done on compound 3-58 and no decomposition was observed.\textsuperscript{17}

Table 3.3: Optimization of S-allyl thioimidate hydrobromide salt 3-58.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>THF (0.2 M), rt, 142 h</td>
<td>3-58 observed\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>THF (0.2 M), 67 °C, 24 h</td>
<td>3-58 observed\textsuperscript{a}</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>THF (0.5 M), 67 °C, 5 h</td>
<td>92%</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>THF (0.5 M), 67 °C, 3 h</td>
<td>78%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}observed by LC-MS, reactions did not go to completion.

With the optimal conditions in hand, the substrate scope was explored. We began with the substitution pattern of the allyl bromides (R\textsuperscript{2}−R\textsuperscript{4}, highlighted in green, Scheme 3.27). The reaction worked well for mono-, di-, and tri-alkyl-substituted olefins (3-58–3-61). Electronically poor allyl bromides at the R\textsuperscript{2} position also perform well, albeit at slightly lower yields (3-62 and 3-63). Vinyl bromide 3-64 was formed in 75% yield, and para-bromobenzylic substrate 3-65 was formed in 60% yield. The reaction also works well for aromatic substitution patterns (3-66–3-68). We also examined the R\textsuperscript{1} substitution pattern on the thioamide (highlighted in blue). Alkyl thioamides (3-69) provide thioimidates in good yields. Electron-rich thioamides also provide thioimidates in
good yield (3-70); however, electron-poor thioamides give lower yields (3-71). The reaction also performs well for both chloro- and bromo- as well as heteroaryl-substituted thiobenzamides (3-72–3-74). Heteroaromatic thioamides provides moderate yields of thioimidates such as the benzothiophenyl compound 3-75. Finally, we examined the performance of homo-allyl-, and alkyl- bromides over allyl bromides to give thioimidates with remote alkenes in moderate yields (3-76 and 3-77).

Scheme 3.27: Substrate scope of $S$-allyl thioimdate hydrobromide salt formation.
3.2.3.2: Optimization of Thiazoline Synthesis

After completing the optimization of substrate synthesis, we began investigations for the synthesis of thiazolines. Gratifyingly, compound 3-58 converted to compound 3-78 in 90% yield upon treatment with two equivalents of NBS in CH₂Cl₂ (Table 3.4, entry 1). The reaction became dark yellow and was finished upon addition of NBS. Lowering the equivalents of NBS provided thiazoline 3-78 in 90% and 87% yields, respectively (entries 2 and 3). Additionally, the reaction works well for the formation of iodo-thiazolines. Treatment of thioimidate 3-58 with NIS provided thiazoline 3-79 in 91% yield (entry 4); however, it should be noted that treatment of compound 3-58 with NCS provided bromo-thiazoline 3-78. The observation of bromo-thiazoline over the expected chloro-thiazoline was surprising, and it will be discussed further in PART 2 of this chapter.

Table 3.4: Optimization of thiazoline formation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Y</th>
<th>3-78 yield (%)</th>
<th>3-79 yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NBS</td>
<td>2</td>
<td>90</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>NBS</td>
<td>1.1</td>
<td>90</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>NBS</td>
<td>1</td>
<td>87</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>NIS</td>
<td>1.1</td>
<td>--</td>
<td>91</td>
</tr>
</tbody>
</table>

*aAll reactions were performed on 50 mg scale at 0.05 M. †Isolated product yield.

3.2.3.3: Substrate Scope and Applications

Next, we examined the substrate scope of thiazoline synthesis. With our panel of substrates (Scheme 3.27), we started with those containing alterations at the substitution patterns on the olefin
(R²−R⁴, highlighted in green, Scheme 3.28). Thioimidate 3-59 provided thiazoline 3-80 in 60% yield. We began to notice the 5-exo/6-exo competition when examining substrates 3-60 and 3-61. Thiazoline 3-81 was formed in 33% yield whereas its regio-isomer, thiazine 3-81-r1, was formed in 34% yield. This 1:1 ratio of isomers is not surprising when there are no distinguishing differences in partial-positive charge on either carbon atom of the halonium ion. It does, however, begin to show the effect R³ and R⁴ substituents have on the rate of 6-endo cyclization. This effect is more pronounced with substrate 3-61 where thiazoline 3-82 was formed in 12% yield and thiazine 3-82-r1 was formed in 45% yield. In this case, 6-exo cyclization outcompetes 5-exo cyclization by nearly 4:1 and favoring the formation of thiazine. The reaction shuts down completely in the presence of electron poor olefin substituents at the R² position. Neither compound 3-83 nor 3-84 were observed under the reaction conditions which gave a complex mixture containing starting material as the major component after one day. Additional attempts to synthesize compound 3-83 with elevated temperatures were met with similar results. The reaction also performed poorly with vinyl bromide-containing substrate 3-64. As with the previous two substrates, the reaction gave mostly starting material without any formation of thiazoline nor the corresponding thiazole as a result of aromatization via elimination of HBr. However, benzylic thiazoline 3-86 was formed in 75% yield. This was gratifying as it provides access to some quaternary-substituted analogs of thiazoline-containing natural products that were inaccessible via current methods. The reaction also works well for various aromatic substitutions on the olein. Thiazolines 3-87 and 3-88 were formed in moderate yields; however, thiazoline 3-89 was formed in 77% yield without any observed formation of thiazine 3-89-r1.

We also investigated this substitution patterns on the R¹ position of the thioimidates (highlighted in blue, Scheme 3.28). The reaction works well for alkyl thiazolines such as 3-90.
Electronically rich and poor substrates both provide thiazolines in high yields with thiazolines 3-91 and 3-92 being formed in 97% and 81% yield, respectively. Both chloro- and bromo-aromatic substitutions were tolerated as well providing thiazolines 3-93 and 3-94 in good yields. Thiazolines containing other heterocyclic substituents were also formed in excellent yield (3-95 and 3-96).

Finally, we examined the feasibility of this reaction with extended olefins. Homoallylic thioimidate 3-76 was converted to thiazine 3-97 in a moderate yield of 42%. There was no formation of the corresponding thiazepine (3-97-r1) resulting from 7-endo cyclization. Furthermore, there was no observed formation 7-exo thiazepine 3-98 or the 8-endo thiazocine 3-98-r1 by subjecting thioimidate 3-77 to the reaction conditions.
Scheme 3.28: Substrate scope of *anti*-diastereoselective thiazolines synthesis.
In her previous report, Bérénice demonstrated the use of these brominated thiazolines to be displaced with various nucleophiles; however, she was unable to form a hydroxylated thiazoline through this route.\textsuperscript{20} This was somewhat unfortunate because many thiazoline-containing natural products have exocyclic oxygen functionality in this position (Figure 3.2). We hoped that our iodo-thiazoline $3\text{-79}$ could help remedy this problem. In 2004, Rinaldi and coworkers reported the displacement of an iodo-oxazoline similar to thiazoline $3\text{-79}$ with CsOAc.\textsuperscript{21} Sure enough, this reaction worked to convert compound $3\text{-79}$ to thiazoline $3\text{-99}$ in 91% yield (Scheme 3.29). Further attempts to obtain thiazolines containing exocyclic oxygen functionality via thioimidates will be discussed in PART 4 of this chapter.

\begin{center}
\textbf{Scheme 3.29:} Synthesis of thiazolines bearing exocyclic oxygen functionality.
\end{center}

\subsection*{3.2.4: Conclusions}

We have optimized a method for accessing high yields of $S$-allyl thioimidate hydrobromide salts via the coupling of thioamides with allyl bromides. The reaction has a broad scope tolerating a variety of mono-, di-, and tri-substituted olefins as well as alkyl-, aryl-, and heteroaryl-thioamides. We demonstrated the utility of these salts for the rapid anti-diastereoselective synthesis of quaternary-substituted thiazolines. This reaction tolerated an array of substituted thioimidates barring electron poor substrates. Finally, we demonstrated an application of these products for the synthesis of exocyclic oxygenated thiazolines.
3.2.5: Experimental Section

General Considerations. All reactions were performed under a nitrogen atmosphere. All reagents were purchased through Acros Organics or Sigma-Aldrich and used as received. However, further purification of some thioamides was required prior to thioimidate formation. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F254 plates, 250 µm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a KMnO₄ solution (1.5 g of KMnO₄, 10 g of K₂CO₃, and 1.25 mL of a 10% NaOH solution in 200 mL of water). Reactions were also monitored by LC-MS analysis (Shimadzu LC-MS 2020 with Kinetex 2.6 mm C18 50 × 2.10 mm). Flash chromatography on SiO₂ was used to purify the crude reaction mixtures and performed on a Biotage Isolera using Biotage cartridges and linear gradients.

¹H and ¹³C NMR spectra were obtained on a Varian Mercury-VX 300, a Varian Mercury-VX 400, or a Varian Mercury-Plus 300 instrument in CDCl₃ unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard (CDCl₃ = 7.26 ppm for ¹H, CDCl₃ = 77.16 ppm for ¹³C). ¹H NMR spectra were run at 300 or 400 MHz and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, bs = broad singlet), number of protons, and coupling constant(s). ¹³C NMR spectra were run at 100 MHz using a proton-decoupled pulse sequence with a d₁ of 1 second unless otherwise noted and are tabulated by observed peak. Infrared spectra were determined on a Jasco FT/IR-4100 spectrometer. High-resolution mass spectra were obtained on a Thermo Fisher Scientific, Exactive Plus mass spectrometer (ion trap) using Heated Electrospray Ionization (HESI). Melting points were determined by using a Thomas Hoover capillary melting point apparatus.
General Protocol A: Synthesis of S-Allyl Thioimidate Hydrobromide Salts. To a solution of thioamide derivative in THF (0.5 M) was added allyl bromide derivative (2 equiv), and the solution was stirred at reflux until thioamide was consumed. The resulting solid was filtered and washed with hexanes and EtOAc. If no precipitation was observed, the solution was concentrated in vacuo. EtOAc was added to the subsequent oil, and the slurry was sonicated for 5 min. The resulting white solid was filtered and washed with hexanes and EtOAc. The solid was dissolved in CHCl₃, filtered to remove impurities, and washed with CHCl₃ to obtain pure product.

2-Methylallyl benzimidothioate hydrobromide (3-58); General Protocol A. Prepared from thiobenzamide (7.5 g, 52 mmol) and 3-bromo-2-methylpropene (14 g, 104 mmol) according to general procedure A to yield 13 g (91%) of 3-58 as a white solid: ¹H NMR (400 MHz, CDCl₃) δ = 12.42 (s, 1 H), 11.62 (s, 1 H), 8.09 (d, J = 8.1 Hz, 2 H), 7.67 (t, J = 7.4 Hz, 1 H), 7.55 (t, J = 7.7 Hz, 2 H), 5.26 (s, 1 H), 5.07 (s, 1 H), 4.40 (s, 2 H), 1.90 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 187.7, 135.9, 135.9, 130.1, 129.5, 129.1, 118.1, 41.5, 21.9; IR (neat) 3172, 2916, 1595, 1449, 1267, 936, 861 cm⁻¹; HRMS m/z [M − Br]⁺ calculated for C₁₁H₁₄NS [M − Br]⁺ 192.0841, found 192.0842; mp = 143–144 °C.

Allyl benzimidothioate hydrobromide (3-59); Prepared from thiobenzamide (1.0 g, 6.9 mmol) and allyl bromide (1.7 g, 14 mmol) according to general procedure A to yield 1.5 g (86%) of 3-59
as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 12.41 (s, 1 H), 11.63 (s, 1 H), 8.07 (d, $J$ = 8.5 Hz, 2 H), 7.65 (t, $J$ = 7.5 Hz, 1 H), 7.49 (t, $J$ = 7.6 Hz, 2 H), 5.91 (ddt, $J$ = 17, 10, and 6.8 Hz, 1 H), 5.61 (dd, $J$ = 17 and 0.9 Hz, 1 H), 5.34 (dq, $J$ = 10 and 0.9 Hz, 2 H), 4.41 (dt, $J$ = 6.8 and 1.1 Hz, 1 H), 5.61 (dd, $J$ = 17 and 0.9 Hz, 1 H), 5.34 (dq, $J$ = 10 and 0.9 Hz, 2 H), 4.41 (dt, $J$ = 6.8 and 1.1 Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 187.1, 135.8, 130.0, 129.4, 129.1, 127.9, 122.4, 36.9; IR (neat) 3035, 2907, 1594, 1249, 1120, 947, 865, 698 cm$^{-1}$; HRMS m/z [M − Br]$^+$ calculated for C$_{10}$H$_{12}$NS [M − Br]$^+$ 178.0685, found 178.0683; mp = 140–142 °C.

(E)-But-2-en-1-yl benzimidothioate hydrobromide (3-60): Prepared from thiobenzamide (1.0 g, 6.9 mmol) and crotyl bromide (2.2 g, 14 mmol) according to general procedure A to yield 1.6 g (87%) of 3-60 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 12.64 (s, 1 H), 11.91 (s, 1 H), 8.05 (d, $J$ = 8.4 Hz, 2 H), 7.63 (t, $J$ = 7.5 Hz, 1 H), 7.46 (t, $J$ = 7.5 Hz, 2 H), 6.03 (dqt, $J$ = 15, 8.5, and 1.3 Hz, 1 H), 5.51 (dtq, $J$ = 15, 7.2, and 1.7 Hz, 1 H), 4.35 (dd, $J$ = 7.2 and 1.1 Hz, 2 H), 1.67 (dd, $J$ = 6.6 and 1.7 Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 187.3, 135.7, 134.6, 130.0, 129.3, 129.0, 120.3, 36.9, 18.0; IR (neat) 3035, 2899, 1598, 1245, 1120, 974, 865, 698 cm$^{-1}$; HRMS m/z [M − Br]$^+$ calculated for C$_{11}$H$_{14}$NS [M − Br]$^+$ 192.0842, found 192.0834; mp = 150–152 °C.

3-Methylbut-2-en-1-yl benzimidothioate hydrobromide (3-61); Prepared from thiobenzamide (1.0 g, 6.9 mmol) and 1-bromo-3- methyl-2-butene (2.1 g, 14 mmol) according to general procedure A to yield 1.7 g (86%) of 3-61 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 12.35 (s, 1 H), 11.65 (s, 1 H), 8.08 (d, $J$ = 7.4 Hz, 2 H), 7.66 (t, $J$ = 7.5 Hz, 1 H), 7.51 (t, $J$ = 7.9 Hz, 2
$^1$H NMR (400 MHz, CDCl$_3$) δ = 12.51 (s, 1 H), 11.92 (s, 1 H), 8.07 (d, $J = 7.3$ Hz, 2 H), 7.70 (t, $J = 7.5$ Hz, 1 H), 7.53 (t, $J = 7.5$ Hz, 2 H), 6.28 (s, 1 H), 6.04 (s, 1 H), 4.70 (s, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 186.9, 136.4, 130.3, 130.0, 129.7, 129.6, 129.4, 127.2, 127.1, 127.1, 127.0, 33.4; IR (neat) 3062, 2907, 1605, 1168, 1113, 857, 842, 698 cm$^{-1}$; HRMS m/z [M − Br]$^+$ calculated for C$_{11}$H$_{11}$F$_3$NS [M − Br]$^+$ 246.0559, found 246.0551; mp = 141–142 °C.

2-(Methylcarboxylate)allyl benzimidothioate hydrobromide (3-63); Prepared from thiobenzamide (0.069 g, 0.48 mmol) and methyl-2- (bromomethyl)acrylate (0.18 g, 0.96 mmol) according to general procedure A to yield 0.096 g (64%) of 3-63 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) δ = 12.38 (s, 1 H), 11.83 (s, 1 H), 8.09 (d, $J = 7.3$ Hz, 2 H), 7.70 (t, $J = 7.5$ Hz, 1 H), 7.54 (t, $J = 8.2$ Hz, 2 H), 6.57 (s, 1 H), 6.49 (s, 1 H), 4.73 (s, 2 H), 3.82 (s, 3 H); $^{13}$C NMR
(100 MHz, CDCl₃) δ = 187.4, 165.7, 136.1, 132.5, 132.3, 130.1, 129.6, 129.3, 52.7, 35.2; IR (neat) 2950, 1721, 1605, 1442, 1337, 1206, 1144, 761, 702 cm⁻¹; HRMS m/z [M − Br⁺] calculated for C₁₂H₁₄NO₂S [M − Br⁺] 236.0740, found 236.0732; mp = 126–127 °C.

2-Bromoallyl benzimidothioate hydrobromide (3-64); Prepared from thiobenzamide (1.0 g, 6.9 mmol) and 2,3-dibromopropene (3.5 g, 14 mmol) according to general procedure A to yield 1.7 g (75%) of 3-64 as a white solid: ¹H NMR (400 MHz, CDCl₃) δ = 12.49 (s, 1 H), 11.79 (s, 1 H), 8.13 (d, J = 7.4 Hz, 2 H), 7.72 (t, J = 7.5 Hz, 1 H), 7.57 (d, J = 7.6 Hz, 2 H), 6.51 (t, J = 2.3 Hz, 1 H), 5.76 (d, J = 2.3 Hz, 1 H), 4.89 (s, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ = 186.7, 136.4, 130.0, 129.7, 129.6, 125.2, 122.6, 44.4; IR (neat) 2915, 1598, 1276, 1195, 1124, 865, 698 cm⁻¹; HRMS m/z [M − Br⁺] calculated for C₁₀H₁₁BrNS [M − Br⁺] 255.9790, found 255.9783; mp = 142–143 °C.

2-(4-Bromobenzyl)allyl benzimidothioate hydrobromide (3-65); Prepared from thiobenzamide (0.027 g, 0.19 mmol) and 3-bromo-2-(4-bromobenzyl)propene (0.12 g, 0.19 mmol) according to general procedure A to yield 0.048 g (60%) of 3-65 as a white solid: ¹H NMR (400 MHz, CDCl₃) δ = 12.45 (s, 1 H), 11.62 (s, 1 H), 8.03 (d, J = 8.5 Hz, 2 H), 7.70 (t, J = 7.7 Hz, 1 H), 7.53 (t, J = 7.3 Hz, 2 H), 7.41 (d, J = 8.3 2 H), 7.12 (d, J = 8.5 2 H), 5.46 (s, 1H), 5.08 (s, 1H), 4.41 (s, 2 H),
3.53 (s, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 187.5, 139.3, 136.7, 136.0, 131.9, 131.1, 130.1, 129.6, 129.2, 120.8, 119.0, 41.6, 39.2; IR (neat) 3387, 2915, 1598, 1487, 1276, 1070, 1011, 700 cm$^{-1}$; HRMS $m/z$ [M − Br]$^+$ calculated for C$_{17}$H$_{17}$BrNS [M − Br]$^+$ 346.0260, found 346.0268; mp = 105–106 °C.

2-Phenylallyl benzimidothioate hydrobromide (3-66); Prepared from thiobenzamide (0.58 g, 4.0 mmol) and 2,3-dibromopropene (1.6 g, 8.1 mmol) according to general procedure A to yield 1.2 g (91%) of 3-66 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 12.50 (s, 1 H), 11.86 (s, 1 H), 8.05 (d, $J$ = 7.7 Hz, 2 H), 7.67 (t, $J$ = 7.5 Hz, 1 H), 7.52–7.49 (m, 4 H), 7.38–7.33 (m, 3 H), 5.72 (s, 1 H), 5.68 (s, 1 H), 4.97 (s, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 187.8, 139.1, 137.6, 136.0, 130.1, 129.5, 129.3, 128.9, 128.8, 126.4, 120.0, 40.2; IR (neat) 2915, 1598, 1446, 1241, 1128, 869, 780, 698 cm$^{-1}$; HRMS $m/z$ [M − Br]$^+$ calculated for C$_{16}$H$_{16}$NS [M − Br]$^+$ 254.0998, found 254.0990; mp = 154–155 °C.

2-(Naphthalen-2-yl)allyl benzimidothioate hydrobromide (3-67); Prepared from thiobenzamide (0.19 g, 1.3 mmol) and 3-bromo-2-(naphthalen-2-yl)propene (0.34 g, 1.3 mmol) according to general procedure A to yield 0.36 g (70%) of 3-67 as a white solid: $^1$H NMR (400 MHz, DMSO) $\delta$ = 12.01 (s, 1 H), 8.20 (s, 1 H), 7.96–7.94 (m, 3 H), 7.85–7.79 (m, 4 H), 7.76–7.53
(m, 4 H), 5.96 (s, 1 H), 5.77 (s, 1 H), 4.88 (s, 2 H); \(^{13}\)C NMR (100 MHz, DMSO) \(\delta = 186.9, 138.9, 135.3, 134.4, 132.9, 132.7, 131.0, 129.5, 128.4, 128.3, 128.3, 127.5, 126.7, 126.6, 125.2, 124.0, 119.1, 37.0; IR (neat) 3047, 2861, 1613, 1591, 1445, 1276, 1231, 1126, 920, 870, 826 cm\(^{-1}\); HRMS \(m/z [M-Br]^+\) calculated for C\(_{20}\)H\(_{18}\)NS [M – Br]\(^+\) 304.1155, found 304.1156; mp = 168–169 °C.

3-Phenylallyl benzimidothioate hydrobromide (3-68); Prepared from thiobenzamide (0.50 g, 3.5 mmol) and cinnamyl bromide (1.4 g, 6.9 mmol) according to general procedure A to yield 1.1 g (98%) of 3-68 as a white solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 12.37 (s, 1 H), 11.84 (s, 1 H), 8.12 (d, \(J = 7.9\) Hz, 2 H), 7.67 (t, \(J = 7.5\) Hz, 1 H), 7.52 (t, \(J = 8.0\) Hz, 2 H), 7.37 (d, \(J = 8.3\) Hz, 2 H), 7.30–7.24 (m, 3 H), 6.94 (d, \(J = 16\) Hz, 1 H), 6.26 (dt, \(J = 16\) and 7.4 Hz, 1 H) 4.64 (d, \(J = 7.4\) Hz, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 187.3, 137.5, 135.9, 135.6, 130.0, 129.5, 129.2, 128.7, 128.5, 126.7, 118.5, 37.5; IR (neat) 3055, 3028, 2915, 1598, 1446, 1272, 1233, 1124, 698 cm\(^{-1}\); HRMS \(m/z [M-Br]^+\) calculated for C\(_{16}\)H\(_{16}\)NS [M – Br]\(^+\) 254.0998, found 254.0992; mp = 178–179 °C.

2-Methylallyl ethanimidothioate hydrobromide (3-69); Prepared from thioacetamide (0.50 g, 6.5 mmol) and 3-bromo-2-methylpropene (1.8 g, 13 mmol) according to general procedure A to yield 1.0 g (75%) of 3-69 as a white solid; mp 114–116 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 12.28 (s, 1 H), 11.23 (s, 1 H), 5.11 (s, 1 H), 4.94 (s, 1 H), 4.05 (s, 2 H), 2.64 (s, 3 H), 1.75 (s, 1 H); \(^{13}\)C
NMR (100 MHz, CDCl₃) δ = 191.4, 135.5, 117.5, 40.2, 24.0, 21.5; IR (neat) 2923, 2652, 2574, 1656, 1602, 1423, 1377, 1287, 857 cm⁻¹; HRMS m/z [M − Br]⁺ calculated for C₆H₁₂NS [M − Br]⁺ 130.0685, found 130.0683; mp = 114–116 °C.

2-Methylallyl 4-methoxybenzimidothioate hydrobromide (3-70); Prepared from 4-methoxythiobenzamide (0.75 g, 4.4 mmol) and 3-bromo-2-methylpropene (1.2 g, 8.7 mmol) according to general procedure A to yield 1.1 g (86%) of 3-70 as a white solid: ¹H NMR (400 MHz, CDCl₃) δ = 7.97 (d, J = 9.0 Hz, 2 H), 7.19 (d, J = 9.0 Hz, 2 H), 5.25 (s, 1 H), 5.15 (s, 1 H), 4.87 (s, 2 H), 4.15 (s, 2 H), 3.94 (s, 3 H), 1.96 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 189.4, 167.7, 138.2, 132.1, 123.9, 117.7, 116.3, 56.7, 40.6, 21.7; IR (neat) 3182, 2965, 1671, 1604, 1501, 1278, 1185, 1013, 836 cm⁻¹; HRMS m/z [M − Br]⁺ calculated for C₁₂H₁₆NOS [M − Br]⁺ 222.0947, found 222.0946; mp = 170–173 °C.

2-Methylallyl 4-nitrobenzimidothioate hydrobromide (3-71); Prepared from 4-nitrothiobenzamide (0.60 g, 3.2 mmol) and 3-bromo-2-methylpropene (0.89 g, 6.4 mmol) according to general procedure A to yield 0.59 g (58%) of 3-71 as a white solid: ¹H NMR (400 MHz, CDCl₃) δ = 8.36 (d, J = 8.7 Hz, 2 H), 8.24 (d, J = 8.7 Hz, 2 H), 5.30 (s, 1 H), 5.14 (s, 1 H), 4.44 (s, 2 H), 1.92 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 186.7, 151.6, 135.3, 135.1, 130.5,
124.4, 118.8, 42.2, 21.9; IR (neat) 3055, 2815, 1619, 1526, 1347, 848, 726, 691 cm\(^{-1}\); HRMS m/z [M – Br]\(^+\) calculated for C\(_{11}\)H\(_{13}\)N\(_2\)O\(_2\)S [M – Br]\(^+\) 237.0692, found 237.0690; mp = 152–155 °C.

![Image of 2-Methylallyl 4-chlorobenzimidothioate hydrobromide (3-72)]

**2-Methylallyl 4-chlorobenzimidothioate hydrobromide (3-72);** Prepared from 4 chlorothiobenzamide (0.50 g, 2.8 mmol) and 3- bromo-2-methylpropene (0.79 g, 5.7 mmol) according to general procedure A to yield 0.75 g (86%) of 3-72 as a white solid: mp 165–166 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 12.47 (s, 1\ H), 11.67 (s, 1\ H), 8.06 (d, J = 8.9\ Hz, 2\ H), 7.50 (d, J = 8.9\ Hz, 2\ H), 5.27 (s, 1\ H), 5.09 (s, 1\ H), 4.40 (s, 2\ H), 1.90 (s, 3\ H); ^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 186.7, 142.8, 135.8, 130.5, 129.9, 128.4, 118.4, 41.7, 21.9; IR (neat) 3082, 2973, 1590, 1485, 1404, 1233, 1128, 1093, 876, 838 cm\(^{-1}\); HRMS m/z [M – Br]\(^+\) calculated for C\(_{11}\)H\(_{13}\)ClINS [M – Br]\(^+\) 226.0452, found 226.0446; mp = 165–166 °C.

![Image of 2-Methylallyl 4-bromobenzimidothioate hydrobromide (3-73)]

**2-Methylallyl 4-bromobenzimidothioate hydrobromide (3-73);** Prepared from 4 bromothiobenzamide (0.50 g, 2.2 mmol) and 3- bromo-2-methylpropene (0.62 g, 4.5 mmol) according to general procedure A to yield 0.63 g (80%) of 3-73 as a white solid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 12.46 (s, 1\ H), 11.68 (s, 1\ H), 7.97 (d, J = 8.4\ Hz, 2\ H), 7.66 (d, J = 8.3\ Hz, 2\ H), 5.26 (s, 1\ H), 5.09 (s, 1\ H), 4.39 (s, 2\ H), 1.90 (s, 3\ H); ^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 186.9, 135.7, 132.9, 131.6, 130.5, 128.8, 118.4, 41.7, 21.9; IR (neat) 3031, 2973, 1602, 1586, 1481, 1396,
1117, 1070, 1009, 729 cm$^{-1}$; HRMS $m/z$ [M − Br]$^+$ calculated for C$_{11}$H$_{13}$BrNS [M − Br]$^+$ 269.9947, found 269.9941; mp = 162−164 °C.

**2-Methylallyl 4-(2-methylthiazol-4-yl)benzimidothioate hydrobromide (3-74);** Prepared from 4-(2 methyl-4-thiazolyl)thiobenzamide (0.50 g, 2.1 mmol) and 3-bromo-2-methylpropene (0.59 g, 4.3 mmol) according to general procedure A to yield 0.69 g (88%) of 3-74 as a white solid: $^1$H NMR (400 MHz, DMSO) δ = 11.85 (s, 1 H), 8.35 (s, 1 H), 8.34 (d, $J$ = 8.3 Hz, 2 H), 8.01 (d, $J$ = 8.4 Hz, 2 H), 5.23 (s, 1 H), 5.07 (s, 1 H), 4.24 (s, 2 H), 2.73 (s, 3 H), 1.87 (s, 3 H); $^{13}$C NMR (100 MHz, DMSO) δ = 186.7, 166.9, 152.1, 140.8, 137.6, 130.0, 129.8, 126.9, 118.7, 117.0, 39.4, 21.8, 19.4; IR (neat) 3066, 2915, 1412, 1268, 1172, 846, 714 cm$^{-1}$; HRMS $m/z$ [M − Br]$^+$ calculated for C$_{15}$H$_{17}$N$_2$S$_2$ [M − Br]$^+$ 289.0828, found 289.0823; mp = 165−166 °C.

![Structure 3-74](image.jpg)

**2-Methylallyl benzothiophene-3-carbimidothioate hydrobromide (3-75);** Prepared from 1 benzothiophene-3-carbothioamide (0.51 g, 2.6 mmol) and 3-bromo-2-methylpropene (0.74 g, 5.3 mmol) according to general procedure A to yield 0.60 g (69%) of 3-75 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) δ = 12.34 (s, 1 H), 11.59 (s, 1 H), 8.92 (s, 1 H), 8.31 (d, $J$ = 8.2 Hz, 1 H), 7.89 (d, $J$ = 8.2 Hz, 1 H), 7.52 (t, $J$ = 7.7 Hz, 1 H), 7.45 (t, $J$ = 7.9 Hz, 1 H), 5.32 (s, 1 H), 5.13 (s, 1 H), 4.46 (s, 2 H), 1.96 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 180.9, 140.8, 139.5, 136.0, 134.6,
But-3-en-1-yl benzimidothioate hydrobromide (3-76); Prepared from thiobenzamide (0.75 g, 5.2 mmol) and 4-bromo-1-butene (1.4 g, 10 mmol) according to general procedure A to yield 0.69 g (49%) of 3-76 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 12.35$ (s, 1 H), 11.67 (s, 1 H), 8.04 (d, $J = 7.4$ Hz, 2 H), 7.64 (t, $J = 7.5$ Hz, 1 H), 7.48 (t, $J = 8.0$ Hz, 2 H), 5.83 (ddt, $J = 17$, 10, and 6.7 Hz, 1 H), 5.17 (dd, $J = 17$ and 1.4 Hz, 1 H), 5.11 (dd, $J = 10$ and 1.2 Hz, 1 H), 3.78 (t, $J = 6.8$ Hz, 2 H), 2.58 (dt, $J = 6.7$ and 6.7 Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 187.9$, 135.7, 133.9, 130.2, 129.3, 128.9, 118.5, 33.8, 31.3; IR (neat) 3051, 2899, 1594, 1446, 1405, 1273, 1231, 1123, 866, 703 cm$^{-1}$; HRMS $m/z$ [M − Br]$^+$ calculated for C$_{13}$H$_{14}$NS [M − Br]$^+$ 248.0562, found 248.0561; mp = 143–144 °C.

Pent-4-en-1-yl benzimidothioate hydrobromide (3-77); Prepared from thiobenzamide (0.75 g, 5.2 mmol) and 5-bromo-1-pentene (1.6 g, 10 mmol) according to general procedure A to yield 0.73 g (49%) of 3-77 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 12.37$ (s, 1 H), 11.64 (s, 1 H), 8.05 (d, $J = 8.4$ Hz, 2 H), 7.64 (t, $J = 7.5$ Hz, 1 H), 7.49 (t, $J = 8.0$ Hz, 2 H), 5.75 (ddt, $J = 17$, 10, and 6.7 Hz, 1 H), 5.05 (dd, $J = 17$ and 1.5 Hz, 1 H), 4.99 (dt, $J = 10$ and 1.2 Hz, 2 H), 3.69 (t, $J = 7.2$ Hz, 2 H), 2.27 (dt, $J = 7.3$ and 7.3 Hz, 2 H), 1.91 (p, $J = 7.3$ Hz, 3 H); $^{13}$C NMR (100 MHz,
CDCl$_3$ $\delta = 187.9, 136.3, 135.6, 130.2, 129.3, 128.9, 116.5, 33.6, 32.1, 26.6$; IR (neat) 3442, 3055, 2919, 1594, 1265, 845, 699 cm$^{-1}$; HRMS $m/z$ [M − Br]$^+$ calculated for C$_{12}$H$_{16}$NS [M − Br]$^+$ 206.0998, found 206.0994; mp = 131−132 °C.

**General Procedure B: anti-Diastereoselective Synthesis of 2-Thiazolines.** S-Allyl thioimidate hydrobromide salt was dissolved in CH$_2$Cl$_2$ (0.05 M). NBS (or NIS) (1.1 equiv) was added, and the solution turned orange. The reaction was complete upon addition of NBS, quenched with Na$_2$S$_2$O$_3$, and extracted with CH$_2$Cl$_2$ ($\times$3). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel.

![Structure](image)

4-(Bromomethyl)-4-methyl-2-phenyl-4,5-dihydrothiazole (3-78): Prepared from 3-58 (0.05 g, 0.18 mmol) and NBS (0.036 g, 0.20 mmol) according to general procedure B and purified (hexanes–EtOAc: 0–2%) to yield 0.045 g (90%) of 3-78 as a clear oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.82$ (d, $J = 6.8$ Hz, 2 H), 7.50–7.37 (m, 3 H), 3.66 (d, $J = 10$ Hz, 1 H), 3.62 (d, $J = 11$ Hz, 1 H), 3.60 (d, $J = 10$ Hz, 1 H), 3.18 (d, $J = 11$ Hz, 1 H), 1.59 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 167.6, 133.2, 131.6, 128.6, 128.5, 81.9, 41.7, 40.5, 24.9$. 

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4-(Iodomethyl)-4-methyl-2-phenyl-4,5-dihydrothiazole (3-79); Prepared from 3-58 (0.05 g, 0.18 mmol) and NIS (0.036 g, 0.20 mmol) according to general procedure B and purified (hexanes–EtOAc: 0–2%) to yield 0.045 g (90%) of 3-79 as a clear oil: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ = 7.82 (d, $J$ = 6.7 Hz, 2 H), 7.50–7.37 (m, 3 H), 3.55 (d, $J$ = 10 Hz, 1 H), 3.54 (d, $J$ = 11 Hz, 1 H), 3.48 (d, $J$ = 10 Hz, 1 H), 3.20 (d, $J$ = 11 Hz, 1 H), 1.61 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 167.0, 133.2, 131.5, 128.6, 128.5, 81.1, 43.1, 26.0, 16.9; IR (neat) 3060, 2926, 1593, 1576, 1446, 689 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{11}$H$_{13}$INS [M + H]$^+$ 317.9808, found 317.9805.

4-(Bromomethyl)-2-phenyl-4,5-dihydrothiazole (3-80); Prepared from 3-59 (0.10 g, 0.39 mmol) and NBS (0.077 g, 0.43 mmol) according to general procedure B and purified (hexanes–EtOAc: 0–5%) to yield 0.059 g (60%) of 3-80 as a clear oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.83 (d, $J$ = 7.0 Hz, 2 H), 7.48 (t, $J$ = 7.6 Hz, 1 H), 7.42 (t, $J$ = 7.7 Hz, 2 H), 5.00 (tdd, $J$ = 8.4, 7.1, and 3.9 Hz, 1 H), 3.76 (dd, $J$ = 10 and 3.9 Hz, 1 H), 3.58 (dd, $J$ = 11 and 8.5 Hz, 1 H), 3.57 (dd, $J$ = 10 and 8.3 Hz, 1 H), 3.44 (dd, $J$ = 11 and 7.1 Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 132.9, 131.8, 128.7, 128.6, 77.9, 36.8, 34.3; IR (neat) 3060, 2958, 1604, 1576, 1490, 1446, 1244, 1014, 942, 767, 690, 607 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{10}$H$_{11}$BrNS [M + H]$^+$ 255.9790, found 255.9788.
4-(1-Bromoethyl)-2-phenyl-4,5-dihydrothiazole (3-81); Prepared from 3-60 (0.10 g, 0.37 mmol) and NBS (0.073 g, 0.40 mmol) according to general procedure B and purified (hexanes–EtOAc: 0–3%) to yield 0.068 g (69%) of a mixture of 3-81 and 3-81-r1. Further purification was accomplished by reverse-phase chromatography (H₂O–CH₃CN: 10–90%) to yield 0.033 g (33%) of 3-81 as a clear oil and 0.034 g (34%) of 3-81-r1 as a clear oil. In this reaction, the starting material contains a small amount of the cis-alkene, which leads to a small amount of the corresponding minor diastereomer and these compounds are not readily separable: ¹H NMR (400 MHz, CDCl₃) δ = 7.85 (d, J = 8.4 Hz, 2 H), 7.50 (t, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 4.83 (td, J = 8.6 and 6.5 Hz, 1 H), 4.51 (p, J = 6.8 Hz, 1 H), 3.60 (dd, J = 11 and 8.9 Hz, 1 H), 3.50 (dd, J = 11 and 8.3 Hz, 1 H), 1.90 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 132.1, 131.9, 128.8, 128.7, 82.6, 52.7, 36.1, 24.0; IR (neat) 3028, 2926, 1670, 1604, 1577, 1491, 1445, 1491, 1190, 1000, 768, 690 cm⁻¹; HRMS m/z [M + H]⁺ calculated for C₁₁H₁₃BrNS [M + H]⁺ 269.9947, found 269.9942.

5-Bromo-4-methyl-2-phenyl-5,6-dihydro-4H-1,3-thiazine (3-81-r1); ¹H NMR (400 MHz, CDCl₃) δ = 7.80 (d, J = 8.4 Hz, 2 H), 7.60 (t, J = 7.5 Hz, 1 H), 7.48 (t, J = 8.4 Hz, 2 H), 4.47–4.37 (m, 2 H), 3.70 (dd, J = 13 and 3.3 Hz, 1 H), 3.54 (ddd, J = 13, 7.1, and 1.3 Hz, 1 H), 1.60 (d, J = 6.6 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 133.7, 129.3, 128.9, 127.6, 57.3, 43.1, 32.7, 20.9;
IR (neat) 3060, 2927, 1673, 1605, 1425, 1130, 765, 687 cm\(^{-1}\); HRMS \textit{m}/\textit{z} [M + H]\(^+\) calculated for C\(_{11}\)H\(_{13}\)BrNS [M + H]\(^+\) 269.9947, found 269.9942.

4-(2-Bromopropan-2-yl)-2-phenyl-4,5-dihydrothiazole (3-82): Prepared from 3-61 (0.10 g, 0.35 mmol) and NBS (0.069 g, 0.38 mmol) according to general procedure B and purified (hexanes–EtOAc: 0–2%) to yield 0.068 g (68%) of a mixture of 3-82 and 3-82-r1. Further purification was accomplished by reverse-phase chromatography (H\(_2\)O–CH\(_3\)CN: 10–65%) to yield 0.012 g (12%) of 3-82 as a clear oil and 0.045 g (45%) of 3-82-r1 as a white solid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.88\) (d, \(J = 7.3\) Hz, 2 H), 7.49 (t, \(J = 6.9\) Hz, 1 H), 7.42 (t, \(J = 7.8\) Hz, 2 H), 4.79 (t, \(J = 9.1\) Hz, 1 H), 3.63 (dd, \(J = 9.7\) and 7.4 Hz, 1 H), 3.58 (dd, \(J = 8.1\) and 5.9 Hz, 1 H), 1.98 (s, 3 H), 1.90 (s, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 132.0, 129.1, 128.7, 126.7, 68.9, 35.9, 33.1, 30.4, 25.8\); IR (neat) 3028, 2925, 1606, 1578, 1490, 1447, 1106, 992, 942, 766, 689 cm\(^{-1}\); HRMS \textit{m}/\textit{z} [M + H]\(^+\) calculated for C\(_{12}\)H\(_{15}\)BrNS [M + H]\(^+\) 284.0103, found 284.0097.

5-Bromo-4,4-dimethyl-2-phenyl-5,6-dihydro-4H-1,3-thiazine (3-82-r1): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.75\) (d, \(J = 8.2\) Hz, 2 H), 7.44–7.35 (m, 3 H), 4.35 (dd, \(J = 10\) and 4.2 Hz, 1 H), 3.61 (dd, \(J = 13\) and 10 Hz, 1 H), 3.50 (dd, \(J = 13\) and 4.2 Hz, 1 H), 1.53 (s, 3 H), 1.44 (s, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 154.5, 138.8, 130.6, 128.5, 126.5, 56.4, 54.2, 31.5, 30.2, 24.4\); IR
4-(4-Bromobenzyl)-4-(bromomethyl)-2-phenyl-4,5-dihydrothiazole (3-86); Prepared from 3-65 (0.043 g, 0.099 mmol) and NBS (0.020 g, 0.11 mmol) according to general procedure B and purified (hexanes−EtOAc: 0−4%) to yield 0.032 g (75%) of 3-86 as a clear oil: $^1$H NMR (400 MHz, CDCl₃) $\delta = 7.80$ (d, $J = 7.2$ Hz, 2 H), 7.49 (t, $J = 7.3$ Hz, 1 H), 7.44−7.41 (m, 4 H), 7.23 (d, $J = 8.3$ Hz, 2 H), 3.59 (d, $J = 11$ Hz, 1 H), 3.54 (s, 2 H), 3.26 (d, $J = 11$ Hz, 1 H), 3.20 (d, $J = 14$ Hz, 1 H), 3.12 (d, $J = 14$ Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl₃) $\delta = 135.4$, 133.8, 132.6, 131.8, 131.3, 128.7, 128.5, 121.0, 84.7, 42.7, 40.2, 38.4; IR (neat) 3062, 2923, 1594, 1488, 1445, 1258, 1072, 1012, 942, 766, 689 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{12}$H$_{15}$BrNS [M + H]$^+$ 284.0103, found 284.0099; mp = 44−47 °C.

4-(Bromomethyl)-2,4-diphenyl-4,5-dihydrothiazole (3-87); Prepared from 3-66 (0.10 g, 0.30 mmol) and NBS (0.059 g, 0.33 mmol) according to general procedure B and purified (hexanes−EtOAc: 0−4%) to yield 0.065 g (66%) of 3-87 as a clear oil: $^1$H NMR (400 MHz, CDCl₃) $\delta = 7.96$ (d, $J = 7.1$ Hz, 2 H), 7.57 (d, $J = 7.2$ Hz, 1 H), 7.51−7.45 (m, 3 H), 7.39 (t, $J = 7.4$ Hz, 2 H), 7.32 (t, $J = 7.3$ Hz, 2 H), 4.03 (d, $J = 11$ Hz, 1 H), 3.95 (d, $J = 10$ Hz, 1 H), 3.83 (d, $J = 10$ Hz,
1 H), 3.71 (d, J = 11 Hz, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 143.4, 133.1, 131.7, 128.7, 128.7, 128.6, 128.1, 126.3, 86.6, 41.9, 41.9\); IR (neat) 3060, 2956, 1606, 1575, 1492, 1447, 1031, 942, 767, 690 cm\(^{-1}\); HRMS \(m/z\) [M + H]\(^+\) calculated for C\(_{16}\)H\(_{15}\)BrNS [M + H]\(^+\) 332.0103, found 332.0099.

4-(Bromomethyl)-4-(naphthalen-2-yl)-2-phenyl-4,5-dihydrothiazole (3-88); Prepared from 3-67 (0.10 g, 0.26 mmol) and NBS (0.051 g, 0.29 mmol) according to general procedure B and purified (hexanes–EtOAc: 0–4%) to yield 0.057 g (57%) of 3-88 as a clear oil: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.03–7.99\) (m, 3 H), 7.89–7.83 (m, 3 H), 7.67 (dd, J = 8.6 and 1.8 Hz, 1 H), 7.55–7.45 (m, 5 H), 4.10 (d, J = 11 Hz, 1 H), 4.03 (d, J = 10 Hz, 1 H), 3.94 (d, J = 10 Hz, 1 H), 3.83 (d, J = 11 Hz, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 140.6, 133.2, 133.1, 133.0, 131.8, 128.8, 128.7, 128.5, 128.5, 127.7, 126.5, 126.4, 125.4, 124.3, 86.8, 41.9, 41.7\); IR (neat) 3057, 1601, 1490, 1446, 1257, 1243, 1036, 942, 768, 750, 690 cm\(^{-1}\); HRMS \(m/z\) [M + H]\(^+\) calculated for C\(_{20}\)H\(_{17}\)BrNS [M + H]\(^+\) 382.0260, found 382.0258.

4-(Bromo(phenyl)methyl)-2-phenyl-4,5-dihydrothiazole (3-89); Prepared from 3-68 (0.10 g, 0.30 mmol) and NBS (0.059 g, 0.33 mmol) according to general procedure B; the reaction was
filtered and washed with hexanes and EtOAc to yield 0.077 g (77%) of 3-89 as a white solid: $^1$H NMR (400 MHz, DMSO) $\delta$ = 7.84 (d, $J = 7.0$ Hz, 2 H), 7.69 (t, $J = 6.8$ Hz, 1 H), 7.59 (t, $J = 7.5$ Hz, 2 H), 7.47−7.40 (m, 5 H), 5.50 (d, $J = 5.6$ Hz, 1 H), 5.08−5.03 (m, 1 H), 3.75 (dd, $J = 14$ and 6.9 Hz, 1 H), 3.56 (dd, $J = 14$ and 3.1 Hz, 1 H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 138.7, 133.3, 129.2, 128.9, 128.6, 127.5, 127.0, 126.2, 64.1, 44.3, 32.0; IR (neat) 1591, 1568, 1409, 1225, 1017, 795, 761, 743, 701 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{16}$H$_{15}$BrNS [M + H]$^+$ 332.0103, found 332.0110; mp = 203−205 °C.

4-(Bromomethyl)-2,4-dimethyl-4,5-dihydrothiazole (3-90); Prepared from 3-69 (0.10 g, 0.48 mmol) and NBS (0.094 g, 0.52 mmol) according to general procedure B and purified (hexanes−EtOAc: 0−12%) to yield 0.068 g (69%) of 3-90 as a clear oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 3.55 (d, $J = 10$ Hz, 1 H), 3.51 (d, $J = 12$ Hz, 1 H), 3.48 (d, $J = 10$ Hz, 1 H), 3.06 (d, $J = 11$ Hz, 1 H), 2.19 (s, 3 H), 1.46 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 166.9, 81.5, 42.8, 40.6, 24.9, 20.5; IR (neat) 3229, 2929, 1623, 1434, 1371, 1150, 785, 671 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_6$H$_{11}$BrNS [M + H]$^+$ 207.9790, found 207.9790.

4-(Bromomethyl)-2-(4-methoxyphenyl)-4-methyl-4,5-dihydrothiazole (3-91); Prepared from 3-70 (0.10 g, 0.33 mmol) and NBS (0.065 g, 0.36 mmol) according to general procedure B and
purified (hexanes–EtOAc: 0–8%) to yield 0.057 g (97%) of 3-91 as a clear oil: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.76 \text{ (d, } J = 9.0 \text{ Hz, } 2 \text{ H}), 6.90 \text{ (d, } J = 9.0 \text{ Hz, } 2 \text{ H}), 3.84 \text{ (s, } 3 \text{ H}), 3.63 \text{ (d, } J = 10 \text{ Hz, } 1 \text{ H}), 3.59 \text{ (d, } J = 11 \text{ Hz, } 1 \text{ H}), 3.58 \text{ (d, } J = 10 \text{ Hz, } 1 \text{ H}), 3.15 \text{ (d, } J = 11 \text{ Hz, } 1 \text{ H}), 1.58 \text{ (s, } 3 \text{ H}); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 162.3, 130.2, 125.9, 113.9, 81.7, 55.6, 41.7, 40.4, 24.9\); IR (neat) 2969, 2838, 1606, 1509, 1308, 1254, 1172, 1033, 962, 836 cm\(^{-1}\); HRMS \(m/z\) [M + H]\(^+\) calculated for C\(_{12}\)H\(_{15}\)BrNOS [M + H]\(^+\) 300.0052, found 300.0059.

4-(Bromomethyl)-4-methyl-2-(4-nitrophenyl)-4,5-dihydrothiazole (3-92); Prepared from 3-71 (0.10 g, 0.32 mmol) and NBS (0.062 g, 0.35 mmol) according to general procedure B and purified (hexanes–EtOAc: 0–8%) to yield 0.080 g (81%) of 3-92 as a white solid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.24 \text{ (d, } J = 9.0 \text{ Hz, } 2 \text{ H}), 7.96 \text{ (d, } J = 9.0 \text{ Hz, } 2 \text{ H}), 3.68 \text{ (d, } J = 11 \text{ Hz, } 3 \text{ H}), 3.68 \text{ (d, } J = 10 \text{ Hz, } 1 \text{ H}), 3.60 \text{ (d, } J = 10 \text{ Hz, } 1 \text{ H}), 3.25 \text{ (d, } J = 11 \text{ Hz, } 1 \text{ H}), 1.58 \text{ (s, } 3 \text{ H}); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 165.4, 149.5, 138.6, 129.4, 123.7, 82.4, 42.2, 40.3, 24.8\); IR (neat) 3066, 2929, 1585, 1521, 1346, 966, 855, 688 cm\(^{-1}\); HRMS \(m/z\) [M + H]\(^+\) calculated for C\(_{11}\)H\(_{12}\)BrN\(_2\)O\(_2\)S [M + H]\(^+\) 314.9797, found 314.9795; mp = 65–66 °C.

4-(Bromomethyl)-2-(4-chlorophenyl)-4-methyl-4,5-dihydrothiazole (3-93); Prepared from 3-72 (0.10 g, 0.33 mmol) and NBS (0.065 g, 0.36 mmol) according to general procedure B and
purified (hexanes–EtOAc: 0–5%) to yield 0.081 g (81%) of 3-93 as a clear oil: $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.75 (d, $J = 8.7$ Hz, 2 H), 7.37 (d, $J = 8.8$ Hz, 2 H), 3.64 (d, $J = 10$ Hz, 1 H), 3.63 (d, $J = 11$ Hz, 1 H), 3.59 (d, $J = 10$ Hz, 1 H), 3.19 (d, $J = 11$ Hz, 1 H), 1.58 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 137.7, 131.6, 129.8, 128.9, 82.0, 41.9, 40.4, 24.8; IR (neat) 3055, 2973, 1598, 1488, 1399, 1271, 1090, 961, 833, 608 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{11}$H$_{12}$BrClNS [M + H]$^+$ 303.9557, found 303.9557.

4-(Bromomethyl)-2-(4-bromophenyl)-4-methyl-4,5-dihydrothiazole (3-94); Prepared from 3-73 (0.10 g, 0.28 mmol) and NBS (0.056 g, 0.31 mmol) according to general procedure B and purified (hexanes–EtOAc: 0–10%) to yield 0.076 g (77%) of 3-94 as a clear oil: $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.68 (d, $J = 8.5$ Hz, 2 H), 7.53 (d, $J = 8.4$ Hz, 2 H), 3.64 (d, $J = 10$ Hz, 1 H), 3.62 (d, $J = 11$ Hz, 1 H), 3.59 (d, $J = 10$ Hz, 1 H), 3.19 (d, $J = 11$ Hz, 1 H), 1.57 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 132.0, 131.8, 130.0, 126.2, 82.0, 41.9, 40.3, 24.8; IR (neat) 3052, 2974, 1595, 1486, 1396, 1269, 1068, 1011, 961, 831, 608 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{11}$H$_{12}$Br$_2$NS [M + H]$^+$ 347.9052, found 347.9053.
4-(4-(Bromomethyl)-4-methyl-4,5-dihydrothiazol-2-yl)phenyl)- 2-methylthiazole (3-95); Prepared from 3-74 (0.10 g, 0.27 mmol) and NBS (0.054 g, 0.30 mmol) according to general procedure B and purified (hexanes–EtOAc: 0–11%) to yield 0.089 g (90%) of 3-95 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.90 (d, $J$ = 8.3 Hz, 2 H), 7.84 (d, $J$ = 8.3 Hz, 2 H), 7.38 (s, 1 H), 3.66–3.59 (m, 3 H), 3.17 (d, $J$ = 11 Hz, 1 H), 2.76 (s, 3 H), 1.59 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 167.2, 166.2, 154.1, 137.4, 132.4, 129.0, 126.3, 113.9, 81.9, 41.7, 40.4, 24.8, 19.5; IR (neat) 3112, 2972, 2927, 1593, 1410, 1273, 1171, 961, 851, 757 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{15}$H$_{16}$BrN$_2$S$_2$ [M + H]$^+$ 366.9933, found 366.9932; mp = 104–107 °C.

2-(Benzo[b]thiophen-3-yl)-4-(bromomethyl)-4-methyl-4,5-dihydrothiazole (3-96); Prepared from 3-75 (0.10 g, 0.30 mmol) and NBS (0.060 g, 0.34 mmol) according to general procedure B and purified (hexanes–EtOAc: 0–4%) to yield 0.087 g (88%) of 3-96 as a clear oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.72 (ddd, $J$ = 8.1, 1.3, and 0.64 Hz, 1 H), 7.94 (s, 1 H), 7.85 (ddt, $J$ = 7.8, 1.2, and 0.62 Hz, 1 H), 7.47 (td, $J$ = 8.0 and 1.2 Hz, 1 H), 7.41 (td, $J$ = 7.8 and 1.4 Hz, 1 H), 3.72 (d, $J$ = 10 Hz, 1 H), 3.68 (d, $J$ = 10 Hz, 1 H), 3.59 (d, $J$ = 11 Hz, 1 H), 3.16 (d, $J$ = 11 Hz, 1 H), 1.65 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 140.3, 136.5, 133.1, 125.5, 125.4, 122.5, 41.0, 40.5, 25.0;
IR (neat) 3064, 2928, 1594, 1497, 1424, 1117, 880, 759 cm⁻¹; HRMS m/z [M + H]⁺ calculated for C₁₃H₁₃BrNS₂ [M + H]⁺ 325.9667, found 325.9665.

![Chemical structure of 4-(Bromomethyl)-2-phenyl-5,6-dihydro-4H-1,3-thiazine (3-97)](image)

4-(Bromomethyl)-2-phenyl-5,6-dihydro-4H-1,3-thiazine (3-97); Prepared from 3-76 (0.10 g, 0.37 mmol) and NBS (0.073 g, 0.40 mmol) according to general procedure B and purified (hexanes–EtOAc: 0–4%) to yield 0.042 g (42%) of 3-97 as a clear oil: ¹H NMR (400 MHz, CDCl₃) δ = 7.81 (dd, J = 8.2 and 1.4 Hz, 2 H), 7.45–7.36 (m, 3 H), 3.84–3.79 (m, 2 H), 3.57 (dd, J = 11 and 8.6 Hz, 1 H), 3.25 (td, J = 12 and 4.3 Hz, 1 H), 3.12 (dt, J = 12 and 4.5 Hz, 1 H), 2.32 (ddd, J = 14, 7.6, and 4.5 Hz, 1 H), 1.68 (dddd, J = 14, 12, 9.3, and 4.3 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ = 159.9, 139.1, 130.7, 128.4, 126.6, 57.8, 38.0, 25.6, 23.0; IR (neat) 3449, 3059, 2956, 2848, 1603, 1576, 1444, 1309, 1287, 1229, 936 cm⁻¹; HRMS m/z [M + H]⁺ calcd for C₁₁H₁₃BrNS [M + H]⁺ 269.9947, found 269.9951.

![Chemical structure of (4-Methyl-2-phenyl-4,5-dihydrothiazol-4-yl)methyl Acetate (3-99)](image)

(4-Methyl-2-phenyl-4,5-dihydrothiazol-4-yl)methyl Acetate (3-99); Thiazoline 3-79 (0.027 g, 0.085 mmol) was dissolved in DMF (0.23 mL). Cesium acetate (0.082 g, 0.43 mmol) was added, and the solution was stirred at room temperature for 24 h. The reaction was brought to room temperature, quenched with H₂O, and extracted with EtOAc (×3). The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The crude residue was
purified by flash chromatography over silica gel (hexanes–EtOAc: 0–10%) to yield 0.019 g (91%) of 3-99 as a clear oil: ¹H NMR (400 MHz, CDCl₃) δ = 7.81 (d, J = 7.0 Hz, 2 H), 7.46 (t, J = 6.4 Hz, 1 H), 7.39 (t, J = 7.0 Hz, 1 H), 4.27 (d, J = 11 Hz, 1 H), 4.23 (d, J = 11 Hz, 1 H), 3.44 (d, J = 11 Hz, 1 H), 3.14 (d, J = 11 Hz, 1 H), 2.08 (s, 3 H), 1.46 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ = 171.1, 167.2, 133.2, 131.5, 128.6, 128.5, 81.2, 68.9, 40.6, 23.3, 21.1; IR (neat) 3062, 2973, 1742, 1604, 1447, 1370, 1236, 1043, 948, 768, 690 cm⁻¹; HRMS m/z [M + H]⁺ calculated for C₁₃H₁₆NO₂S [M + H]⁺ 250.0896, found 250.0895.
3.2.6: References


(2) Fittig, R. *Ann Physik* **1883**, *26*.


(17) Compound 3-58 was freebased with NaHCO$_3$ to give quantitative yield of 3-57. Decomposition of 3-57 was observed by $^1$H NMR after one day at room temperature, whereas 3-58 is stable indefinitely at room temperature.

(18) Reactions were monitored using LC-MS by observing low resolution MS and UV absorbance.


PART 2: Asymmetric Synthesis of Quaternary-Substituted 2-Thiazolines

3.3.1: Abstract

Initial developments and optimization of an enantioselective synthesis of quaternary-substituted thiazolines via organocatalyzed asymmetric halocyclization of S-allyl thioimidate sulfonate salts is described. The reaction works in moderate yields and high enantioselectivity for the optimized model substrate; however, applications to a broader substrate scope are currently limited. Nonetheless, this is an attractive starting point for further developments in the asymmetric synthesis of thiazolines.

3.3.2: Introduction and Background

3.3.2.1: Organocatalyzed Asymmetric Halocyclization Reactions

Halocyclization reactions were introduced in PART 1 of this chapter. As mentioned, halocyclizations were first discovered by Fittig in 1883 with the bromolactonization reaction.¹ Among the different forms of this reaction, halolactonizations have been studied the most; however, it was not until the second half of the twentieth century that asymmetric versions were reported. In 1981, Takano reported the first substrate-controlled asymmetric halolactonization of compound 3-100 using a chiral amine auxiliary to achieve 24% ee of compound 3-101 (Scheme 3.30).² The first example of reagent-controlled asymmetric halocyclization was reported in 1992 by Taguchi and coworkers. They demonstrated the iodolactonization of α-hydroxy carboxylic acid 3-102 with stoichiometric amounts of a chiral titanium complex to obtain 3-103 in 65% ee.³ The first organocatalyzed asymmetric halocyclization was disclosed by Wang and coworkers in 2004. This iodolactonization of carboxylic acid 3-104 to lactone 3-105 was achieved in 42% ee via a PTC system and a chiral quinine-derived catalyst.⁴ Since 2004, there has been an increase in
reports of organocatalyzed asymmetric halocyclization reactions, and the potential for this area of synthetic chemistry is still being revealed.\(^5\)\(^–\)\(^9\)

**Scheme 3.30:** Evolution of organocatalyzed asymmetric halocyclizations.
As surmised, it took a century for asymmetric versions of halocyclizations to appear in the literature. The reason for this is due to olefin-to-olefin halogen exchange (Scheme 3.31). The halonium ion is first formed asymmetrically through a process governed by a chiral catalyst. A free olefin can engage with the halonium ion to form a $\pi$ complex and draw the halogen away from the originally enantio-biased substrate. This forms a new halonium ion in a non-stereocontrolled process ultimately eroding the enantiomeric excess and racemizing the product. If the halogen exchange is faster than nucleophile trapping, the reaction will be racemic even if the initial halogenation of the olefin was asymmetric.\textsuperscript{10} These side reactions tend to be suppressed with lower temperatures and more dilute concentrations to produce enantioenriched products.

**Scheme 3.31:** Olefin-to-olefin halonium ion exchange.

Due to the side reaction, difficulties in developing new asymmetric halocyclization reactions often do not arise from catalysis but rather from controlling the rate of cyclization. Currently, there are four main strategies employed to suppress halogen exchange side reactions by maintaining a close association between the substrate and the catalyst (Figure 3.6).\textsuperscript{11} Firstly, a chiral Lewis basic catalyst can directly associate with the substrate during the halogenation and cyclization steps. Secondly, either a charged chiral catalyst counterion or a chiral catalyst coordinated to a charged counterion can associate with the substrate. Thirdly, a catalyst can act as
a hydrogen bond donor/acceptor complex. This strategy has been employed more often than the others due to the availability of chiral catalysts that contain hydrogen bond donor/acceptor functionalities. Lastly, a chiral Lewis acid catalyst can be used to coordinate with an appended Lewis basic groups on the substrate.

Figure 3.6: Strategies for achieving enantiomeric excess in halocyclization reactions.

3.3.2.2: Original Idea and Scope

As mentioned, halocyclization reactions have been developed for the synthesis of a number of different types of heterocycles and ring sizes. One ring closely related to thiazolines are oxazolines; conveniently, there currently exists a number of efficient organocatalytic asymmetric halocyclization reactions for the formation of oxazolines. Borhan and coworkers employed the quinine-derived organo-catalyst (DHQD)$_2$PHAL and DCDPH as the halogen source to cyclize amides 3-106 to oxazolines 3-107 in excellent yield and enantiomeric excess (Scheme 3.32). In 2014, Borhan also reported the use of chloramine T as the halogenating agent to give oxazolines 3-107 in excellent yield and enantiomeric excess. Hamashima and coworkers developed a method for oxazolines that employed the binaphthyl phosphorous catalyst (S)-DTBM-BINAP and NBS to provide bromo-oxazolines 3-108 in excellent yield and enantiomeric excess. Finally, an
asymmetric PTC method was developed by Toste in 2012. This process was catalyzed by TIPS-TRIP for the cyclization of amides 3-109 to oxazines 3-110.\(^8\)

Scheme 3.32: Examples of catalytic asymmetric halocyclization of amides.
Each of these examples describe the synthesis of oxazolines and oxazines which are closely related to thiazolines. Although numerous other examples of organocatalyzed asymmetric halocyclizations exist for the synthesis of other types of heterocycles, we decided to begin our investigations with these examples for the catalytic enantioselective synthesis of thiazolines.

3.3.3: Results and Discussion

3.3.3.1: Initial Investigations

Initially, we needed to obtain racemic mixtures of halogenated thiazolines for our chiral HPLC separations. Treatment of thioimidate 3-58 with NBS in CH₂Cl₂ gave the desired brominated thiazoline 3-78 in 90% yield; treatment with NCS also gave the brominated thiazoline as the only observed product. Although intriguing, this result will be discussed momentarily (vide infra). Finally, treatment with NIS gave the desired iodinated thiazoline 3-79 in 91% yield.

Scheme 3.33: Racemic halogenated thiazolines as standards for chiral HPLC separations.
With chiral HPLC separations of racemic thiazolines in hand, initial screening of different catalytic asymmetric halocyclization conditions could commence. The first conditions chosen were by Borhan and coworkers for the asymmetric synthesis of oxazoline rings (Scheme 3.32). Performing their conditions directly on compound 3-58 gave racemic bromo-thiazoline 3-78; however, with the addition of base, the reaction gave thiazoline 3-78 in 53% yield and 26% ee (Table 3.5, entry 1). Increasing the equivalents of catalyst incrementally to 50 mol% gave gradual increases in selectivity up to 58% ee. (entries 2–4). Due to the drop in yield for 50 mol% of catalyst, we decided to stick with 20 mol% moving forward.

**Table 3.5:** Catalyst equivalency optimization on hydrobromic acid thioimidate salt.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y</th>
<th>3-111 yield (%)</th>
<th>3-111 % ee</th>
<th>3-78 yield (%)</th>
<th>3-78 % ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>--</td>
<td>--</td>
<td>53</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>--</td>
<td>--</td>
<td>53</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>--</td>
<td>--</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>--</td>
<td>--</td>
<td>44</td>
<td>58</td>
</tr>
</tbody>
</table>

*aAll reactions were performed on 100 mg scale and at 0.05 M. †Isolated product yield.

To minimize the undesired background reaction, a temperature and concentration screening was performed (Table 3.6). Lowering the temperature to -45 °C did not have an effect on the selectivity (entry 2), while only starting material remained after 46 hours at -78 °C in CH₂Cl₂ (entry 3). Finally, lower concentrations did not change the selectivity (entry 4).
Table 3.6: Temperature and concentration optimization on hydrobromic acid thioimidate salt.

While observing the reaction’s progress by LC-MS, it appears that the majority of starting material is converted to product within the first 30 minutes while the rest slowly disappears over the remaining hours.\textsuperscript{76} Stopping the reaction at ten minutes shows that the majority of the conversion is occurring quickly while selectivity remains relatively steady (Table 3.7, entry 1). Stopping the reaction at 1 hour showed a slight increase in yield (entry 2).

Table 3.7: Investigation into the effect of time on reaction yield and selectivity.
At this stage, we began to rethink how the reaction was functioning mechanistically. The racemic reactions described above (Scheme 3.32) turned yellow and were finished upon addition of the halogenating agents. With no chlorinated thiazoline 3-111 observed by LC-MS, it could not be reasonably argued that 3-111 is formed initially followed by a Finkelstein displacement with bromide in solution at -30 °C and on a neopentyl carbon atom to form the brominated thiazoline 3-78. We hypothesized that the bromide in solution was disrupting the enantioselectivity by reacting with the halogenating agent to form bromine chloride. Bromine chloride is a yellow gas and is known to be electrophilic on the bromine atom. To examine this hypothesis we stirred DCDPH with TBAB, and the solution turned yellow upon addition of bromide. Either way, the nature of this species was operating as the active electrophile and was responsible for brominating the olefin. Washing bromide salt 3-58 with NaHCO₃ and extracting with CH₂Cl₂ provided thioimidate 3-57. This free-based thioimidate was subjected to the best reaction conditions thus far, and 83% ee of chloro-thiazoline 3-111 was obtained albeit in much lower yield (Scheme 3.34). These two experiments help to show that the presence of the nucleophilic bromide had a significant effect on enantioselectivity.

**Scheme 3.34:** Halocyclization performed on free-based thioimidate.
There are a few other organocatalytic asymmetric halocyclization conditions that were tried on substrate 3-58, the first being a set of conditions published by Borhan for the asymmetric synthesis of oxazoline rings (Scheme 3.35).\textsuperscript{6} Treatment of compound 3-58 with chloramine T in the presence of (DHQD)\textsubscript{2}PHAL and HFIP at room temperature in TFE gave a complex mixture of unidentified products by LC-MS without any sign of 3-78.

![Scheme 3.35: Halocyclization reaction on thioimide with chloramine T.](image)

Another set of conditions were published by Hamashima for the synthesis of oxazoline rings.\textsuperscript{7} Treatment of substrate 3-58 with NBS in the presence of (S)-DTBM-BINAP gave 99% of compound 3-78 with only 4% ee (Table 3.8, entry 1). Since (DHQD)\textsubscript{2}PHAL gave a racemic mixture without the presence of base, the reaction was also done with one equivalent of Hünig’s base which resulted in only starting material after 48 hours. It is possible that the data in entry 1 is a result of successful catalysis without stereo control. Furthermore, there was only starting material after 24 hours at lower temperatures.
Table 3.8: Halocyclization reaction on thioimidate with chiral BINAP catalyst.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Time (h)</th>
<th>3-78 Yield (%)</th>
<th>3-78 % ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>22</td>
<td>99</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>(Pr)₂EtN</td>
<td>48</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*All reactions were performed on 50 mg scale and at 0.05 M. Isolated product yield.

Finally, a PTC reaction reported by Toste for the formation of oxazine rings was tried on compound 3-58. The solvent system used by Toste was not adequate for our substrate, as a solvent system that would keep the substrate and catalyst in one phase and the bromine source in another phase was needed. Both the substrate and catalyst were soluble in CH₂Cl₂ whereas the bromine source was not. Performing this reaction with 5 mol% of catalyst provided thiazoline 3-78 in 73% yield and 0% ee (Table 3.9, entry 1). Doing the reaction without catalyst provided thiazoline 3-78 in a similar yield of 75% (entry 2). This means that the bromine source is able to form thiazoline with or without catalyst assistance. The reaction temperature was lowered without catalyst to determine when thiazoline is no longer formed. Significant amounts of thiazoline were observed at 0 °C (entry 3), only traces were seen at -30 °C after 2 hours (entry 4), and none at -78 °C (entry 5). The reaction was done again at -30 °C with 5 mol% of catalyst, and only trace amounts of thiazoline were formed after 24 hours. It was concluded that the phosphoric acid catalyst is most likely not assisting in the formation of thiazoline 3-78, so no further investigations with this method were pursued.
### Table 3.9: Halocyclization reaction on thioimidate with chiral phosphoric acid catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y</th>
<th>Temp. (°C)</th>
<th>time (h)</th>
<th>3-78 yield (%)</th>
<th>3-78 % ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>rt</td>
<td>2</td>
<td>73</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>rt</td>
<td>2</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>-30</td>
<td>2</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>-78</td>
<td>2</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>-30</td>
<td>24</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*All reactions were performed on 50 mg scale and at 0.05 M. Isolated product yield.

---

### 3.3.3.2: Optimization of Reaction Conditions

Since the free-based thioimidate 3-57 showed a 30% rise in enantiomeric excess over the HBr salt for the reaction with (DHQD)$_2$PHAL and DCDPH, the next step was to exchange the bromide of the salt for a less nucleophilic counterion. After some trial and error, ion exchange was successfully achieved when the free-based thioimidate 3-57 was mixed with one equivalent of $p$TsOH in THF at room temperature (Scheme 3.36). After a short time, the $p$TsOH salt 3-112 precipitated as a white solid in 99+% yield.

---

**Scheme 3.36:** Synthesis of $p$TsOH thioimidate salt.
With the salt of a less nucleophilic counterion in hand, it was time to revisit the halocyclization reaction conditions to see the effect on selectivity. Using the best conditions obtained for the HBr salt on substrate 3-112 provided the desired chloro-thiazoline 3-111 in 41% yield and 87% ee (Table 3.10, entry 1). Lowering the equivalents of catalyst to 10 and 5 mol% did not have a significant effect on yield or selectivity (entries 2 and 3); however, at two mol% of catalyst, the selectivity dropped to 83% (entry 4).

**Table 3.10:** Catalyst equivalency optimization on $\rho$TsOH thioimidate salt.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y</th>
<th>3-111 yield (%)</th>
<th>3-111 % ee</th>
<th>3-78 yield (%)</th>
<th>3-78 % ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>41</td>
<td>87</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>45</td>
<td>87</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>37</td>
<td>87</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>38</td>
<td>83</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*All reactions were performed on 100 mg scale and at 0.05 M. *Isolated product yield.

Given that the chloro-thiazoline 3-111 is formed when employing the $\rho$TsOH salt, it was necessary to obtain a racemic mixture for chiral HPLC separation. As in the case with the HBr salt, treatment of compound 3-112 with NCS did not provide the desired thiazoline. The halocyclization reaction was performed on 3-112 with (DHQ)2PHAL (the pseudo-enantiomer of (DHQD)2PHAL) which provided thiazoline 3-112 in 36% yield and 89% ee of the opposite enantiomer (Scheme 3.37). Mixing one equivalent of this product with the product of the reactions with (DHQD)2PHAL provided a racemic mixture of thiazoline 3-112 for chiral HPLC separation.
Scheme 3.37: Halocyclization of $\beta$TsOH salt with (DHQ)$_2$PHAL.

With a racemic standard for chiral HPLC obtained, further optimization of reaction conditions could proceed. Due to the difference in selectivity between the free-based thioimidate 3-57 and that obtained with the $\beta$TsOH salt, investigations into the effect of the counterion were carried out. The MsOH salt 3-113 was prepared in 99+\% yield and was converted to thiazoline 3-111 in 32% yield and 86\% ee (Scheme 3.38). To examine whether a chiral counterion would show an effect on selectivity, both (+)-CSA and (-)-CSA salts were prepared in 59\% and 81\%, respectively. Thiazoline 3-111 was formed from 3-114 in 36\% yield and 89\% ee and from 3-115 in 22\% yield and 86\% ee. It appears from these results that there may not be any further effect of these non-nucleophilic counterions on the enantioselectivity of the reaction.
Following the investigations of the counterion effect, a probe into variations of the catalyst and their effect on the reaction were examined. Thiazoline 3-111 was synthesized with 5 mol% of (DHQD)$_2$AQN in 13% yield and 12% ee (Scheme 3.39). Using 5 mol% of (DHQD)$_2$PYR, thiazoline 3-111 was synthesized in 28% yield and 19% ee. From these results and the fact that racemic thiazoline was not obtained from 3-112 and NCS, it can be assumed that the catalyst has an influence on the reaction rate as well as the selectivity. An NMR was taken of a mixture of one equivalent of both (DHQD)$_2$PHAL and thiazoline 3-78, and the doublets corresponding to the thiazoline protons became doublet of doublets indicating catalyst complexation and diastereomer formation. An NMR was also taken of a mixture of one equivalent of 3-58 and the catalyst. The alkenic protons were shifted upfield indicating that they are being shielded by the catalyst.
Scheme 3.39: Investigation into alternate of catalyst systems.

A solvent screen was performed to find an optimal reaction solvent. Of the solvents tried, only THF, chlorobenzene, and ethanol gave any trace of thiazoline 3-111 (Table 3.11). In each case, the starting material disappeared. It appears from these results that TFE remains as the optimal solvent for this reaction.
Table 3.11: Solvent screen on $^\beta$TsOH thioimidate salt.

<table>
<thead>
<tr>
<th>Entry</th>
<th>solvent</th>
<th>time (h)</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>1</td>
<td>SM gone, no DP</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>1</td>
<td>SM gone, no DP</td>
</tr>
<tr>
<td>3</td>
<td>CH$_3$CN</td>
<td>1</td>
<td>SM gone, no DP</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>2</td>
<td>SM gone, DP observed</td>
</tr>
<tr>
<td>5</td>
<td>PhMe</td>
<td>2</td>
<td>SM gone, no DP</td>
</tr>
<tr>
<td>6</td>
<td>PhCl</td>
<td>3</td>
<td>SM gone, DP observed</td>
</tr>
<tr>
<td>7</td>
<td>EtOH</td>
<td>2</td>
<td>SM gone, DP observed</td>
</tr>
<tr>
<td>8</td>
<td>iPrOH</td>
<td>2</td>
<td>SM gone, no DP</td>
</tr>
</tbody>
</table>

*All reactions were performed on 100 mg scale and at 0.05 M. $^\text{isolated product yield.}$

The problem of enantioselectivity was solved with removal of the nucleophilic HBr salt, but the problem of low yield remained. To examine the causes of the low yields bromo-thiazoline product 3-78 was subjected to the reaction conditions (Scheme 3.40). After 23 hours at -30 °C, only 24% of thiazoline was recovered.

Scheme 3.40: Decomposition of product under reaction conditions.

As a result of this apparent product decomposition, a stability screen was performed. Stirring 3-78 in TFE at -30 °C for 3 hours showed no decomposition by NMR (Table 3.12, entry
1). Stirring 3-78 with one equivalent of the \( p \)TsOH salt of Et\(_3\)N as well as stirring with 5 mol% of catalyst also provided no decomposition (entries 3 and 4); however, decomposition was detected by NMR when thiazoline 3-78 was stirred with DCDPH (entry 2). This decomposition explains why no product is formed when the reaction was performed with slow addition of 3-58. In this case, only starting material is observed. Since 3-58 is added slowly, any product formed is quickly decomposed by the excess halogenating agent. Once all of the halogenating agent had been consumed, there was only starting material observed.

**Table 3.12:** Stability screen of thiazoline product under reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>No decomposition by NMR</td>
</tr>
<tr>
<td>2</td>
<td>DCDPH (1.1 equiv)</td>
<td>Decomposition by NMR</td>
</tr>
<tr>
<td>3</td>
<td>Et(_2)N, ( p )TsOH (1 equiv)</td>
<td>No decomposition by NMR</td>
</tr>
<tr>
<td>4</td>
<td>(DHQD)(_2)PHAL (5 mol%)</td>
<td>No decomposition by NMR</td>
</tr>
</tbody>
</table>

*All reactions were performed on 25 mg scale and at 0.05 M.*

Since the halogenating agent is responsible for product decomposition, the reaction was performed with one equivalent of DCDPH and no change in the method of DCDPH addition, providing thiazoline 3-111 in 43% yield and 83% ee (Table 3.13, entry 1). When DCDPH was added in 5 aliquots over 20-minute intervals, thiazoline 3-111 was formed in 52% yield and 76% ee (entry 2). As expected, there was a slight increase in reaction yield when there is no longer an extra 0.1 equivalent of DCDPH present to decompose the product. These are presently the best
conditions for this reaction. Other common halogenating agents were also screened with no effect on the reactions yield or enantioselectivity.

**Table 3.13:** Thiazoline synthesis performed with one equivalent of DCDPH.

![Chemical structure](image1)

<table>
<thead>
<tr>
<th>Entry</th>
<th>DCDPH addition method</th>
<th>3-111 yield (%)</th>
<th>3-111 % ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no change</td>
<td>43</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>5 aliquots at 20 min intervals</td>
<td>52</td>
<td>85</td>
</tr>
</tbody>
</table>

*aAll reactions were performed on 100 mg scale and at 0.05 M. bIsolated product yield.*

At this point, we still needed to determine the absolute stereochemistry for thiazoline 3-111. Compound 3-111 is an oil, so we formed the salt 3-116 by treatment with HBr in THF (Scheme 3.41). Crystals were carefully grown, and an X-ray structure was obtained for compound 3-116 providing us with the *R* enantiomer.

![Chemical structure](image2)

**Scheme 3.41:** Determination of absolute stereochemistry via X-ray crystallography.
To date, we have successfully resolved the issue with the reaction’s selectivity. There are three issues, however, with this reaction that have been identified as having an effect on yield. Firstly, the product inhibition of the catalyst as determined by NMR. Due to the product decomposition, any inhibition of the catalyst by the product would slow the reaction rate and allow for a negative effect on the yield. Secondly, the decomposition of the product by the halogenating agent. And thirdly, the isolation of a side product. Typically, this compound is formed quickly, before significant amounts of thiazoline have been formed, and it slowly disappears as the reaction progresses. Its $^1$H NMR spectrum is similar to that of the thioimdate starting material. Three of the possible structures for this compound are either halogenation on the nitrogen or sulfur or a thiranium ion that would be formed by 3-exo cyclization of the sulfur onto the halonium ion (Figure 3.7). The isolated side product remained stable at -30 °C for weeks as determined by NMR but disappears in the reaction as it progresses. This disappearance could be due to either conversion to product or decomposition. If the compound is chlorinated on nitrogen or sulfur, it may be able to self-halogenate and convert to thiazoline; however, there was no sign of thiazoline by NMR after the compound had remained at -30 °C for weeks. Furthermore, the compound was stirred with 5 mol% of (DHQD)$_2$PHAL at -30 °C to determine if the catalyst could assist in self-halogenation, but there was no sign of thiazoline formation after three hours. If the compound is a thiranium ion, the corresponding thiirane could leave upon attack by a nucleophile or decompose to the corresponding thiirane and benzonitrile. Either way, the formation of this side product has an effect on the overall yield of thiazoline and is a problem to be addressed.
Moving forward with our best conditions, we decided to examine how our reaction would translate to a substrate scope. We chose to subject substrates with varying electronic properties to the reaction. The electronically rich thioimidate 3-117 was converted to 3-118 in 89% yield (Scheme 3.42). Compound 3-118 was subjected to the halocyclization, and an isolated mixture of both chloro-thiazoline 3-119 and 4-cyanoanisole (verified by IR spectroscopy) in an approximately 1:2 mole ratio was obtained. From this information, the yield for compound 3-119 was calculated to be 31%. Treatment of compound 3-118 with Et$_3$N showed the formation of 4-cyanoanisole indicating that substrate 3-118 is prone to elimination and is base-sensitive; however, subjecting compound 3-118 to the asymmetric conditions without Et$_3$N gave some 4-cyanoanisole without the formation of thiazoline 3-119. Further investigations were done on the electronically poor thioimidate 3-120. This free-based substrate could not be protonated because the resulting salt, 3-121, is more acidic than $p$TsOH. It is apparent that further optimization is needed before an extensive substrate scope can be carried out.

**Figure 3.7:** Possible structures of the isolated side product.
Scheme 3.42: Early substrate scope investigations.

Even with all of its limitations, there are no other ways to access enantio-enriched quaternary-substituted thiazolines from simple non-chiral substrates. Furthermore, these results provide the first example of an organocatalyzed asymmetric synthesis of a quaternary-substituted thiazoline. We communicated these findings along with our anti-diastereoselective process discussed in PART 1 of this chapter. Further optimization of this reaction to overcome the modest yields by evaluation of these shortcomings will require future investigations.

3.3.4: Conclusions

The initial developments for an efficient enantioselective synthesis of quaternary-substituted thiazolines via the organo-catalyzed halocyclization of sulfonate thioimidate salts has been demonstrated. The reaction provides chlorinated thiazolines in high enantioselectivities but at a sacrifice of yield. Although problems exist, this is the first example of accessing enantio-enriched thiazolines through asymmetric organocatalysis and efforts to improve the yield of this reaction are an endeavor for future investigations.
3.3.5: Experimental Section

General Considerations. All reactions were performed under a nitrogen atmosphere. All reagents were purchased through Acros Organics or Sigma-Aldrich and used as received. However, further purification of some thioamides was required prior to thioimidate formation. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F254 plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a KMnO4 solution (1.5 g of KMnO4, 10 g of K2CO3, and 1.25 mL of a 10% NaOH solution in 200 mL of water). Reactions were also monitored by LC-MS analysis (Shimadzu LC-MS 2020 with Kinetex 2.6 mm C18 50 × 2.10 mm). Enantiomeric excess was monitored by chiral HPLC analysis (Shimadzu HPLC with Lux 5 μm Amylose-2 LC Column 250 × 4.6 mm). Solvent system for chiral HPLC was as follows: isocratic flow at 40% of a 20 mM solution of NH4HCO3 in H2O, 60% CH3CN, and 0.1% diethylamine. Flash chromatography on SiO2 was used to purify the crude reaction mixtures and performed on a Biotage Isolera using Biotage cartridges and linear gradients.

1H and 13C NMR spectra were obtained on a Varian Mercury-VX 300, a Varian Mercury-VX 400, or a Varian Mercury-Plus 300 instrument in CDCl3 unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard (CDCl3 = 7.26 ppm for 1H, CDCl3 = 77.16 ppm for 13C). 1H NMR spectra were run at 300 or 400 MHz and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, bs = broad singlet), number of protons, and coupling constant(s). 13C NMR spectra were run at 100 MHz using a proton-decoupled pulse sequence with a d1 of 1 second unless otherwise noted and are tabulated by observed peak. Infrared spectra were determined on a Jasco FT/IR-4100 spectrometer. High-resolution mass spectra were obtained on a Thermo Fisher Scientific, Exactive Plus mass spectrometer (ion trap) using Heated Electrospray
Ionization (HESI). Melting points were determined by using a Thomas Hoover capillary melting point apparatus.

**General Protocol A:** Synthesis of S-allyl thioimidate sulfonate salts. First, each thioimidate was washed with saturated aq. NaHCO$_3$ and dried. Free-based thioimidate was dissolved in THF (0.5 M). Sulfonic acid derivative (1 equiv) was added, and the solution was stirred at room temperature for 30 min. The solvent was removed, and the crude residue was triturated in EtOAc. The resulting white precipitate was filtered, washed with EtOAc, dissolved in CHCl$_3$, and filtered to remove insoluble impurities.

![Image of 2-Methylallyl benzimidothioate p-toluenesulfonic acid (3-112)](image)

**2-Methylallyl benzimidothioate p-toluenesulfonic acid (3-112):** According to general protocol A, free-based thioimidate 3-57 (0.048 g, 0.18 mmol) and p-TsOH (0.034 g, 0.18 mmol) were stirred in THF (0.37 mL) for 30 min to yield 0.068 g (99+% of 3-112 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.87 (d, $J$ = 7.8 Hz, 2 H), 7.70 (d, $J$ = 6.6 Hz, 2 H), 7.60 (t, $J$ = 7.4 Hz, 1 H), 7.44-7.39 (m, 2 H), 7.09 (d, $J$ = 7.7 Hz, 2 H), 5.13 (s, 1 H), 5.02 (s, 2 H), 4.13 (s, 2 H), 2.31 (s, 3 H), 1.81 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 188.4, 142.1, 140.0, 136.2, 135.2, 131.0, 129.4, 128.8, 128.8, 126.1, 117.9, 40.1, 21.7, 21.4; IR (neat) 3460, 3125, 2939, 1638, 1236, 1181, 1169, 680 cm$^{-1}$; ESIMS $m/z$ 192 [M + H]$^+$; HRMS $m/z$ [M + Na]$^+$ calculated for C$_{18}$H$_{21}$NO$_3$S$_2$Na [M + Na]$^+$ 386.0855, found 386.0846; mp = 135–136 °C.
2-Methylallyl benzimidothioate methanesulfonic acid (3-113); According to general protocol A, free-based thioimidate 3-57 (0.14 g, 0.73 mmol) and MsOH (0.071 g, 0.73 mmol) were stirred in THF (1.5 mL) for 30 min to yield 0.25 g (99+%) of 3-113 as a clear oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 7.94-7.91 (m, 2 H), 7.69-7.65 (m, 1 H), 7.54-7.50 (m, 2 H), 5.21 (s, 1 H), 5.07 (s, 1 H), 4.14 (s, 2 H), 2.74 (s, 3 H), 1.89 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta =$ 188.6, 136.1, 135.5, 130.9, 129.5, 128.6, 118.0, 39.9, 39.4, 21.8; IR (neat) 3437, 2975, 1650, 1449, 1280, 1204, 1046, 917 cm$^{-1}$; ESIMS m/z 192 [M + H]$^+$.  

2-Methylallyl benzimidothioate (+)-camphorsulfonic acid (3-114); According to general protocol A, free-based thioimidate 3-57 (0.3 g, 1.1 mmol) and (+)-CSA (0.26 g, 1.1 mmol) were stirred in THF (2.2 mL) for 30 min to yield 0.27 g (59%) of 3-114 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 7.96-7.94 (m, 2 H), 7.66-7.62 (m, 1 H), 7.55-7.49 (m, 2 H), 5.20 (s, 1 H), 5.05 (s, 1 H), 4.23 (s, 2 H), 3.24 (d, $J =$ 15 Hz, 1 H), 2.68 (d, $J =$ 15, 1 H), 2.55 (ddd, $J =$ 15, 12, 4.0 Hz, 1 H), 2.27-2.21 (m, 1 H), 1.96-1.78 (m, 8 H), 1.58 (ddd, $J =$ 14, 9.3, 4.7 Hz, 1 H), 1.27 (ddd, $J =$ 13, 9.4, 4.0 Hz, 1 H), 0.97 (s, 3 H), 0.74 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta =$ 216.8, 188.0, 136.5, 135.1, 131.2, 129.4, 128.8, 117.9, 58.4, 47.9, 47.3, 42.9, 42.6, 40.1, 27.1, 24.4, 21.8, 20.0, 19.8; IR (neat) 3448, 2959, 1740, 1642, 1189, 1042, 704, 617 cm$^{-1}$; ESIMS m/z 192 [M + H]$^+$; HRMS m/z [M + Na]$^+$ calculated for C$_{21}$H$_{29}$NO$_4$S$_2$Na [M + Na]$^+$ 446.1430, found 446.1419; mp = 138–139 °C.
2-Methylallyl benzimidothioate (-)-camphorsulfonic acid (3-115); According to general protocol A, free-based thioimidate 3-57 (0.3 g, 1.1 mmol) and (-)-CSA (0.26 g, 1.1 mmol) were stirred in THF (2.2 mL) for 30 min to yield 0.38 g (81%) of 3-115 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.98$ - 7.96 (m, 2 H), 7.69 - 7.65 (m, 1 H), 7.55 - 7.51 (m, 2 H), 5.23 (s, 1 H), 5.08 (s, 1 H), 4.24 (s, 2 H), 3.28 (d, $J = 15$ Hz, 1 H), 2.74 (d, $J = 15$, 1 H), 2.60 - 2.53 (m, 1 H), 2.27 (dt, $J = 18$, 4.0 Hz, 1 H), 2.00 - 1.80 (m, 7 H), 1.65 - 1.58 (m, 1 H), 1.34 - 1.27 (m, 1 H), 1.00 (s, 3 H), 0.77 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 216.9$, 188.1, 136.5, 135.2, 131.3, 129.5, 128.8, 118.1, 58.5, 48.0, 47.4, 43.0, 42.7, 40.2, 27.1, 24.6, 21.9, 20.0, 19.9; IR (neat) 3491, 3168, 2919, 1737, 1610, 1189, 1042, 621 cm$^{-1}$; ESIMS m/z 192 [M + H]$^+$; HRMS m/z [M + Na]$^+$ calculated for C$_{21}$H$_{29}$NO$_4$S$_2$Na [M + Na]$^+$ 446.1430, found 446.1421; mp = 139 - 140 °C.

2-methylallyl 4-methoxybenzimidothioate $^p$toluenesulfonic acid (3-118); According to general protocol A, free-based thioimidate 3-117 (0.42 g, 1.9 mmol) and $^p$TsOH (0.37 g, 1.9 mmol) were stirred in THF (3.8 mL) for 30 min to yield 0.63 g (89%) of 3-118 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 11.99$ (s, 1 H), 11.16 (s, 1 H), 7.91 (d, $J = 9.0$ Hz, 2 H), 7.74 (d, $J = 8.2$ Hz, 2 H), 7.08 (d, $J = 8.4$ Hz, 2 H), 6.84 (d, $J = 9.0$ Hz, 2 H), 5.10 (t, $J = 1.1$ Hz, 1 H), 4.98 (t, $J = 1.4$ Hz, 1 H), 4.09 (d, $J = 1.1$ Hz, 2 H), 3.79 (s, 3 H), 2.28 (s, 3 H), 1.79 (t, $J = 1.1$ Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 186.2$, 165.6, 142.5, 139.7, 136.5, 131.3, 128.7, 126.1, 122.9, 117.7, 114.7,
(R)-4-(Chloromethyl)-4-methyl-2-phenyl-4,5-dihydrothiazole (3-111); Thioimidate (R)-4-(Chloromethyl)-4-methyl-2-phenyl-4,5-dihydrothiazole (3-111): Thioimidate 3-112 (0.10 g, 0.28 mmol), (DHQD)$_2$PHAL (0.011 g, 0.014 mmol), and Et$_3$N (0.028 g, 0.28 mmol) were dissolved in TFE (5.5 mL) in a screw cap vial. The vial was capped and placed in a chiller set to −30 °C for 10 min. DCDPH (0.022 g, 0.069 mmol) was added as one aliquot. An aliquot of DCDPH was added every 30 min until a total of 0.28 mmol was reached (4 aliquots total). The reaction stirred at −30 °C for 4 h. The reaction was quenched with Na$_2$S$_2$O$_3$ and extracted with CH$_2$Cl$_2$ (×3). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The crude residue was purified by flash chromatography SiO$_2$ (hexanes–EtOAc, 0–2%) to yield 0.040 g (52%) of 3-111 as a clear oil: 85% ee (S enantiomer Rt = 7.6 min; R enantiomer Rt = 9.0 min); $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.82 (dd, $J = 8.0$, 1.6 Hz, 2 H), 7.49-7.38 (m, 3 H), 3.76-3.68 (m, 2 H), 3.61 (d, $J = 11$ Hz, 1 H), 3.16 (d, $J = 11$ Hz, 1 H), 1.56 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 167.8, 133.1, 131.6, 128.6, 128.5, 82.5, 50.6, 40.8, 24.1; IR (neat) 3061, 2975, 1599, 1449, 1267, 964, 940, 687 cm$^{-1}$; ESIMS $m/z$ 226 [M + H]$^+$; HRMS $m/z$ [M + H]$^+$ calculated for C$_{11}$H$_{13}$CINS [M + H]$^+$ 226.0451, found 226.0451.
(R)-4-(Chloromethyl)-4-methyl-2-phenyl-4,5-dihydrothiazole Hydrobromide (3-116); To a round bottom flask were added thiazoline 6a (0.18 g, 0.80 mmol) and THF (1.6 mL). Hydrobromic acid (0.13 g, 0.80 mmol) was added, and the reaction stirred for 30 min. The solvent was removed, and the crude residue was triturated in EtOAc. The resulting white precipitate was filtered, washed with EtOAc, dissolved in CHCl₃, and filtered to remove insoluble impurities to yield 0.21 g (85%) of 11a as a white solid: $^1$H NMR (400 MHz, CDCl₃) δ = 8.29 (d, $J$ = 7.5 Hz, 2 H), 7.71 (t, $J$ = 7.5 Hz, 1 H), 7.54 (t, $J$ = 7.8 Hz, 2 H), 4.46 (d, $J$ = 12 Hz, 1 H), 4.02 (d, $J$ = 12 Hz, 1 H), 3.95 (d, $J$ = 12 Hz, 1 H), 3.60 (d, $J$ = 12 Hz, 1 H), 1.91 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl₃) δ = 186.3, 137.1, 130.7, 129.8, 124.8, 76.1, 49.2, 39.7, 24.3; IR (neat) 3050, 2984, 1589, 1572, 1449, 1387, 1376, 996, 954, 771, 711 cm⁻¹; HRMS m/z [M − Br]$^+$ calculated for C₁₁H₁₃ClNS [M − Br]$^+$ 226.0451, found 226.0450; mp = 188–189 °C.
3.3.6: References


(12) Reactions were monitored using LC-MS by observing low resolution MS and UV absorbance.

PART 3: Synthesis of 2-Thiazolines via S\textsubscript{N}2/Conjugate Addition Cascade

3.4.1: Abstract

A rapid and efficient one-pot synthesis of functionalized thiazolines via an S\textsubscript{N}2/conjugate addition cascade process is described. A range of alkyl- and aryl-thioamides with varied substitution patterns are well tolerated. Furthermore, the presence of the exocyclic ester provides a convenient handle for the synthesis of more complex thiazoline-containing natural products and biologically-relevant compounds.

3.4.2: Original Discovery and Scope

PART 1 of this chapter featured our substrate scope for the synthesis of thioimidate hydrobromide salts through the coupling of a thioamide and an allyl bromide (Scheme 3.27). When ethyl 4-bromocrotonate was used as the electrophile, the HBr salt of thiazoline \textit{3-123} was obtained (Scheme 3.43). Thioimidate \textit{3-122} was formed followed by rapid intramolecular conjugate addition cyclization to compound \textit{3-123}. An X-ray crystal structure of this compound not only verified that it was thiazoline \textit{3-123} but also confirmed the regio-chemistry of the product.

\textbf{Scheme 3.43}: Initial reaction discovery and X-ray crystal structure of \textit{3-123}. 
Two reports of rapid, one-pot syntheses of thiazolines through the condensation of simplified precursors were reported during the course of the efforts described herein.\textsuperscript{1,2} However, due to the reaction’s simplicity along with the ability to rapidly construct functionalized thiazolines in a one-pot cascade-like process, we decided to optimize this reaction for the preparation of ester- and acid-substituted thiazolines that can be useful building blocks for the synthesis of more complex molecules.

3.4.3: Results and Discussion

3.4.3.1: Optimization of Reaction Conditions

Firstly, during our studies on the development of this reaction, a similar method was published by Alsharif and co-workers which outlined the use of HFIP as the solvent and NaOAc as an exogenous base;\textsuperscript{2} however, our reaction led to the use of a much cheaper and less exotic solvent as well as the removal of unnecessary additives (vide infra).

Following its discovery, we pursued this process as an efficient one-pot route to functionalized thiazolines bearing exocyclic methylene esters. To ensure reliable yields from batch to batch, each reaction underwent a basic workup and was purified by flash chromatography to obtain thiazolines in their free-based forms (Table 3.14). The equivalents of ethyl 4-bromocrotonate did not have a significant effect on the reaction yield. Increasing the equivalents from 1 to 1.5 provided compound 3-124 in 59% and 65%, respectively (entries 1–2); however, the yield of compound 3-124 remained constant when the equivalency was increased further to two and three (entries 3–4). The reaction concentration, on the other hand, seemed to be a key variable affecting the yield of this reaction. Raising the concentration incrementally from 0.1 M to 4 M increased the yield of thiazoline from 45% (entry 5) to as high as 81% (entry 7). Unfortunately,
neat conditions showed a drop in the yield of compound 3-124 to 73% (entry 8). Furthermore, lowering the temperature to 40 °C showed a drop in yield to 63% (entry 9). Finally, a solvent screen was performed. CH$_2$Cl$_2$ provided 74%, EtOAc 83%, and hexanes 83% yield of desired thiazoline 3-124 (entries 10–12).

**Table 3.14: Optimization of thiazoline synthesis.**

<table>
<thead>
<tr>
<th>Entry*</th>
<th>X</th>
<th>solvent</th>
<th>conc. (M)</th>
<th>Temp. (°C)</th>
<th>3-124 yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>THF</td>
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<td>65</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>THF</td>
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<td>65</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>THF</td>
<td>0.5</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>THF</td>
<td>0.5</td>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>THF</td>
<td>0.1</td>
<td>65</td>
<td>45</td>
</tr>
<tr>
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<td>1.5</td>
<td>THF</td>
<td>2</td>
<td>65</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>THF</td>
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<td>65</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>-</td>
<td>neat</td>
<td>65</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>1.5</td>
<td>THF</td>
<td>4</td>
<td>40</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
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<td>4</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
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<td>1.5</td>
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<td>4</td>
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</tr>
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<td>1.5</td>
<td>hexanes</td>
<td>4</td>
<td>65</td>
<td>81</td>
</tr>
</tbody>
</table>

*All reactions were performed on 100 mg scale. $^b$isolated product yield.

**3.4.3.2: Substrate Scope**

With optimized conditions in hand, the reaction’s substrate scope was evaluated (Scheme 3.44). Along with the model substrate (3-124, 81%), various alkyl- and aryl-substituted thiazolines were synthesized in good yields. Initially, the substituents at R$^1$ (highlighted in blue) were varied while R$^2$ (highlighted in green) remained an ethyl ester. The reaction tolerated electron-rich substituents providing thiazolines 3-125 and 3-126 in 59% and 62% yields, respectively. The opposite effect was observed for the electron poor thiazoline 3-127 which was formed in 15%
yield. The reaction worked well for halogenated substrates, providing thiazoles 3-128 and 3-129 in 76% and 71% yield, respectively. Heteroaryl substituents were also well tolerated. Thiazole-containing compound 3-130 was formed in 77% yield while benzothiophene-containing compound 3-131 was formed in 67% yield. Additionally, the alkyl thiazole 3-132 was synthesized in 53% yield.

Next, the substituent at R^2 was varied while the R^1 remained a phenyl group. Employing 4-bromocrotonate as the electrophile provided thiazole 3-133 in 17% yield. Further, using a nitro substituent as the electron withdrawing group provided thiazole 3-134 in 26% yield, highlighting that changes to this region of the molecule are less tolerated.

Scheme 3.44: Substrate scope of thiazole synthesis.
3.4.4: Conclusions

We have developed a rapid one-pot synthesis of thiazolines bearing exocyclic methylene esters via an $S_N$2/conjugate addition cascade process. We have investigated the substrate scope and the reaction tolerates a variety of alkyl-, aryl-, and heteroaryl-thioamides to provide thiazolines in good yields. Additionally, the presence of the exocyclic ester provides a convenient handle for further functionalization for the synthesis of more complex thiazoline-containing molecules. This reaction, along with our aforementioned methods, can be added to the toolbox of efficient methods to construct these oftentimes difficult-to-access heterocycles.
3.4.5: Experimental Section

General Considerations. All reactions were performed under a nitrogen atmosphere. All reagents were purchased through Acros Organics or Sigma-Aldrich and used as received. However, further purification of some thioamides was required prior to thioimidate formation. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F254 plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a KMnO4 solution (1.5 g of KMnO4, 10 g of K2CO3, and 1.25 mL of a 10% NaOH solution in 200 mL of water). Reactions were also monitored by LC-MS analysis (Shimadzu LC-MS 2020 with Kinetex 2.6 mm C18 50 × 2.10 mm). Flash chromatography on SiO2 was used to purify the crude reaction mixtures and performed on a Biotage Isolera using Biotage cartridges and linear gradients.

1H and 13C NMR spectra were obtained on a Varian Mercury-VX 300, a Varian Mercury-VX 400, or a Varian Mercury-Plus 300 instrument in CDCl3 unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard (CDCl3 = 7.26 ppm for 1H, CDCl3 = 77.16 ppm for 13C). 1H NMR spectra were run at 300 or 400 MHz and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, bs = broad singlet), number of protons, and coupling constant(s). 13C NMR spectra were run at 100 MHz using a proton-decoupled pulse sequence with a d1 of 1 second unless otherwise noted and are tabulated by observed peak. Infrared spectra were determined on a Jasco FT/IR-4100 spectrometer. High-resolution mass spectra were obtained on a Thermo Fisher Scientific, Exactive Plus mass spectrometer (ion trap) using Heated Electrospray Ionization (HESI). Melting points were determined by using a Thomas Hoover capillary melting point apparatus.
Ethyl 2-(2-phenyl-4,5-dihydrothiazol-4-yl)acetate hydrobromide (3-123); Compound 3-123 was prepared under non-optimal conditions. Ethyl 4-bromocrotonate (1.8 g, 6.9 mmol) was added to a solution of thiobenzamide (0.50 g, 3.5 mmol) in THF (14 mL). The reaction stirred for 3 h. The reaction was filtered, washed with EtOAc and hexanes, and dried to yield 0.56 g (49%) of 3-123 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.29 (d, $J$ = 8.3 Hz, 2 H), 7.72 (t, $J$ = 7.5 Hz, 1 H), 7.55 (t, $J$ = 8.0 Hz, 2 H), 5.28 (tdd, $J$ = 9.5, 7.6 and 3.2 Hz, 1 H), 4.18—4.06 (m, 3 H), 3.66 (dd, $J$ = 17 and 3.2 Hz, 1 H), 3.60 (dd, $J$ = 12 and 7.6 Hz, 1 H), 3.07 (dd, $J$ = 17 and 9.6 Hz, 1 H), 1.21 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 186.7, 169.1, 137.0, 130.6, 129.7, 124.8, 63.8, 61.4, 36.8, 35.8, 14.0; IR (neat) 2980, 1729, 1598, 1493, 1376, 1256, 1195, 768 cm$^{-1}$; HRMS m/z [M – Br]$^+$ calculated for C$_{13}$H$_{16}$NO$_2$S [M – Br]$^+$ 250.0896, found 250.0893; mp = 111–113 °C.

**General Protocol A:** To a solution of thioamide derivative in THF (4 M) was added ethyl 4-bromocrotonate (1.5 equiv), and the solution was stirred at reflux until thioamide was consumed. Upon completion, the reaction was diluted with a saturated solution of NaHCO$_2$ and extracted with CH$_2$Cl$_2$ ($\times$3). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel.
Ethyl 2-(2-phenyl-4,5-dihydrothiazol-4-yl)acetate (3-124); Prepared from thiobenzamide (0.28 g, 2.0 mmol) and ethyl 4-bromocrotonate (0.77 g, 3.0 mmol) according to general protocol A and purified (hexanes–EtOAc: 0–10%) to yield 0.40 g (81%) of 3-124 as a yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.82 (d, $J = 7.0$ Hz, 2 H), 7.46 (t, $J = 7.0$ Hz, 1 H), 7.40 (t, $J = 7.2$ Hz, 2 H), 5.05 (tdd, $J = 8.6$, 7.3 and 5.2 Hz, 1 H), 4.19 (q, $J = 7.1$ Hz, 2 H), 3.63 (dd, $J = 11$ and 8.4 Hz, 1 H), 3.19 (dd, $J = 11$ and 7.2 Hz, 1 H), 2.95 (dd, $J = 16$ and 5.1 Hz, 1 H), 2.64 (dd, $J = 16$ and 9.1 Hz, 1 H), 1.28 (t, $J = 7.1$ Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 171.3, 133.1, 131.5, 128.6, 128.6, 73.7, 60.9, 39.1, 38.2, 14.4; IR (neat) 3062, 2980, 1733, 1602, 1489, 1372, 1249, 1181, 943, 768, 691 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{13}$H$_{16}$NO$_2$S [M + H]$^+$ 250.0896, found 250.0895.

Ethyl 2-(2-(4-methoxyphenyl)-4,5-dihydrothiazol-4-yl)acetate (3-125); Prepared from 4-methoxythiobenzamide (0.17 g, 1.0 mmol) and ethyl 4-bromocrotonate (0.39 g, 1.5 mmol) according to general protocol A and purified (hexanes–EtOAc: 0–10%) to yield 0.17 g (59%) of 3-125 as a yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.77 (d, $J = 8.8$ Hz, 2 H), 6.90 (d, $J = 8.8$ Hz, 2 H), 5.07–4.95 (m, 1 H), 4.19 (q, $J = 7.1$ Hz, 2 H), 3.84 (s, 3 H), 3.60 (dd, $J = 11$ and 8.2 Hz, 1 H), 3.17 (dd, $J = 11$ and 7.1 Hz, 1 H), 2.93 (dd, $J = 16$ and 5.1 Hz, 1 H), 2.62 (dd, $J = 16$ and 9.1 Hz, 1 H), 1.28 (t, $J = 7.1$ Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 171.2, 167.3, 162.1, 130.1,
Ethyl 2-(2-(4-hydroxyphenyl)-4,5-dihydrothiazol-4-yl)acetate (3-126); Prepared from 4-hydroxythiobenzamide (0.16 g, 1.0 mmol) and ethyl 4-bromocrotonate (0.39 g, 1.5 mmol) according to general protocol A and purified (hexanes–EtOAc: 0–20%) to yield 0.17 g (62%) of 3-126 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.59 (d, $J$ = 8.6 Hz, 2 H), 6.65 (d, $J$ = 8.6 Hz, 2 H), 5.08–4.96 (m, 1 H), 4.15 (q, $J$ = 7.2 Hz, 2 H), 3.62 (dd, $J$ = 11 and 8.3 Hz, 1 H), 3.19 (dd, $J$ = 11 and 7.0 Hz, 1 H), 2.93 (dd, $J$ = 16 and 5.1 Hz, 1 H), 2.65 (dd, $J$ = 16 9.0 Hz, 1 H), 1.24 (t, $J$ = 7.1 Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 171.1, 160.3, 130.4, 123.8, 115.6, 72.3, 60.9, 38.7, 37.7, 14.4; IR (neat) 3378, 3122, 2982, 2738, 1729, 1607, 1322, 1285, 1243, 1172, 948, 839, 612 cm$^{-1}$; HRMS $m/z$ [M + H]$^+$ calculated for C$_{14}$H$_{18}$NO$_3$S [M + H]$^+$ 280.1002, found 280.1000; mp = 105–106 °C.

Ethyl 2-(2-(4-nitrophenyl)-4,5-dihydrothiazol-4-yl)acetate (3-127); Prepared from 4-nitrothiobenzamide (0.19 g, 1.0 mmol) and ethyl 4-bromocrotonate (0.39 g, 1.5 mmol) according
to general protocol A and purified (hexanes–EtOAc: 0–20%) to yield 0.045 g (15%) of 3-127 as a yellow solid: \(^1^H \text{NMR} (400 \text{ MHz, CDCl}_3) \delta = 8.22 (d, J = 8.8 \text{ Hz, 2 H}), 7.95 (d, J = 8.8 \text{ Hz, 2 H}), 5.15–4.98 (m, 1 H), 4.18 (q, J = 7.2 \text{ Hz, 2 H}), 3.68 (dd, J = 11 and 8.5 \text{ Hz, 1 H}), 3.24 (dd, J = 11 and 7.8 \text{ Hz, 1 H}), 2.93 (dd, J = 16 and 5.5 \text{ Hz, 1 H}), 2.65 (dd, J = 16 and 8.7 \text{ Hz, 1 H}), 1.26 (t, J = 7.1 \text{ Hz, 3 H}); \(^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3) \delta = 170.1, 166.5, 149.4, 138.3, 129.4, 123.6, 73.8, 60.9, 38.6, 14.2; \text{IR (neat)} 3411, 3103, 3048, 2853, 1713, 1378, 1318, 1193, 1039, 948, 757, 688 \text{ cm}^{-1}; \text{HRMS m/z [M + H]}^+ \text{ calculated for C}_{13}\text{H}_{15}\text{N}_{2}\text{O}_4\text{S} [M + H]^+ 295.0747, \text{found 295.0746}; \text{mp} = 91–92 ^\circ\text{C}.

Ethyl 2-(2-(4-chlorophenyl)-4,5-dihydrothiazol-4-yl)acetate (3-128); Prepared from 4-chlorothiobenzamide (0.18 g, 1.0 mmol) and ethyl 4-bromocrotonate (0.39 g, 1.5 mmol) according to general protocol A and purified (hexanes–EtOAc: 0–10%) to yield 0.22 g (76%) of 3-128 as a yellow oil: \(^1^H \text{NMR} (400 \text{ MHz, CDCl}_3) \delta = 7.76 (d, J = 8.5 \text{ Hz, 2 H}), 7.37 (d, J = 8.6 \text{ Hz, 2 H}), 5.10–4.97 (m, 1 H), 4.18 (q, J = 7.0 \text{ Hz, 2 H}), 3.64 (dd, J = 11 and 8.4 \text{ Hz, 1 H}), 3.20 (dd, J = 11 and 7.4 \text{ Hz, 1 H}), 2.94 (dd, J = 16 and 5.2 \text{ Hz, 1 H}), 2.64 (dd, J = 16 and 9.2 \text{ Hz, 1 H}), 1.28 (t, J = 7.2 \text{ Hz, 3 H}); \(^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3) \delta = 170.7, 166.3, 137.0, 131.2, 129.4, 128.3, 73.4, 60.4, 38.7, 38.0, 13.9; \text{IR (neat)} 3620, 3440, 2981, 2936, 1732, 1604, 1399, 985, 912, 607 \text{ cm}^{-1}; \text{HRMS m/z [M + H]}^+ \text{ calculated for C}_{13}\text{H}_{15}\text{ClNO}_2\text{S} [M + H]^+ 284.0507, \text{found 284.0504}. 
Ethyl 2-(2-(4-bromophenyl)-4,5-dihydrothiazol-4-yl)acetate (3-129); Prepared from 4-bromothiobenzamide (0.23 g, 1.0 mmol) and ethyl 4-bromocrotonate (0.39 g, 1.5 mmol) according to general protocol A and purified (hexanes–EtOAc: 0–10%) to yield 0.20 g (62%) of 3-129 as a yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.66$ (d, $J = 8.5$ Hz, 2 H), 7.50 (d, $J = 8.5$ Hz, 2 H), 5.01 (dddd, $J = 8.8$, 7.7, 6.3 and 4.5 Hz, 1 H), 4.17 (q, $J = 7.1$ Hz, 2 H), 3.62 (dd, $J = 11$ and 8.4 Hz, 1 H), 3.18 (dd, $J = 11$ and 7.4 Hz, 1 H), 2.91 (dd, $J = 16$ and 5.3 Hz, 1 H), 2.61 (dd, $J = 16$ and 8.9 Hz, 1 H), 1.26 (t, $J = 7.1$ Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 171.0$, 166.9, 131.9, 131.6, 129.9, 125.8, 73.7, 60.7, 38.9, 38.3, 14.2; IR (neat) 3444, 2981, 2931, 1734, 1601, 1588, 1485, 1319, 1068, 733, 607 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{13}$H$_{15}$BrNO$_2$S [M + H]$^+$ 328.0001, found 328.0002.

Ethyl 2-(2-(4-(2-methylthiazol-4-yl)phenyl)-4,5-dihydrothiazol-4-yl)acetate (3-130); Prepared from 4-(2-methylthiazol-4-yl)thiobenzamide (0.12 g, 0.50 mmol) and ethyl 4-bromocrotonate (0.19 g, 0.75 mmol) according to general protocol A and purified (hexanes–EtOAc: 0–20%) to yield 0.13 g (77%) of 3-130 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.91$ (d, $J = 8.3$ Hz, 2 H), 7.89 (d, $J = 8.4$ Hz, 2 H), 7.40 (s, 1 H), 5.10–5.01 (m, 1 H), 4.19 (q, $J = 7.3$ Hz, 2 H), 3.65
(dd, J = 11 and 8.3 Hz, 1 H), 3.21 (dd, J = 11 and 7.2 Hz, 1 H), 2.99 (dd, J = 16 and 5.1 Hz, 1 H), 2.77 (s, 3 H), 2.66 (dd, J = 16 and 9.1 Hz, 1 H), 1.28 (t, J = 7.1 Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 171.1, 166.2, 155.3, 154.1, 137.4, 132.0, 126.3, 113.9, 73.2, 60.7, 38.9, 38.0, 19.3, 14.2; IR (neat) 3436, 3108, 2981, 2924, 2848, 1730, 1599, 1373, 1177, 1027, 943, 850, 731, 677 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{17}$H$_{19}$N$_2$O$_2$S$_2$ [M + H]$^+$ 347.0883, found 347.0881; mp = 74–75 °C.

![Ethyl 2-(2-(benzo[b]thiophen-3-yl)-4,5-dihydrothiazol-4-yl)acetate (3-131)](image)

**Ethyl 2-(2-(benzo[b]thiophen-3-yl)-4,5-dihydrothiazol-4-yl)acetate (3-131);** Prepared from 1-benzothiophene-3-carbothioamide (0.20 g, 1.0 mmol) and ethyl 4-bromocrotonate (0.39 g, 1.5 mmol) according to general procedure above and purified (hexanes–EtOAc: 0–10%) to yield 0.67 g (67%) of 3-131 as a yellow solid: $^1$H NMR (400 MHz, CDCl$_3$) δ = 8.70 (d, J = 8.6 Hz, 4 H), 8.00 (s, 1 H), 7.85 (d, J = 7.8 Hz, 1 H), 7.50–7.35 (m, 2 H), 5.22–5.10 (m, 1 H), 4.22 (q, J = 7.1 Hz, 2 H), 3.62 (dd, J = 11 and 8.3 Hz, 1 H), 3.19 (dd, J = 11 and 7.1 Hz, 1 H), 3.01 (dd, J = 16 and 5.6 Hz, 1 H), 2.71 (dd, J = 16 and 8.7 Hz, 1 H), 1.31 (t, J = 7.2 Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 171.3, 162.0, 148.4, 140.3, 136.5, 133.4, 129.9, 125.5, 125.4, 122.5, 74.2, 60.9, 39.4, 37.4, 14.4; IR (neat) 3442, 2980, 2932, 1730, 1601, 1459, 1370, 1025, 881, 824, 760 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{15}$H$_{16}$NO$_2$S$_2$ [M + H]$^+$ 306.0617, found 306.0617; mp = 35–37 °C.
Ethyl 2-(2-methyl-4,5-dihydrothiazol-4-yl)acetate (3-132); Prepared from thioacetamide (0.15 g, 2.0 mmol) and ethyl 4-bromocrotonate (0.77 g, 3.0 mmol) according to general protocol A and purified (hexanes–EtOAc: 0–10%) to yield 0.20 g (53%) of 3-132 as a yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 4.66–4.53$ (m, 1 H), 3.96 (q, $J = 7.2$ Hz, 2 H), 3.33 (dd, $J = 11$ and 8.5 Hz, 1 H), 2.88 (dd, $J = 11$ and 7.5 Hz, 1 H), 2.61 (dd, $J = 16$ and 5.6 Hz, 1 H), 2.34 (dd, $J = 16$ and 8.6 Hz, 1 H), 2.01 (s, 3 H), 1.07 (t, $J = 7.2$ Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 170.6$, 166.8, 72.7, 60.2, 38.7, 19.8, 13.8; IR (neat) 3374, 3273, 3065, 2983, 2932, 2242, 1729, 1632, 1435, 1279, 1029, 921, 853 cm$^{-1}$; HRMS $m/z$ [M + H]$^+$ calculated for C$_8$H$_{14}$NO$_2$S [M + H]$^+$ 188.0740, found 188.0739.

2-(2-phenyl-4,5-dihydrothiazol-4-yl)acetic acid hydrobromide (3-133); Prepared from thiobenzamide (0.29 g, 2.0 mmol) and 4-bromocrotonate (0.60 g, 3.0 mmol) according to general protocol A and purified by trituration in EtOAc to yield 0.29 g (48%) of 3-133 as a white solid: $^1$H NMR (400 MHz, DMSO) $\delta = 7.85$ (d, $J = 7.1$ Hz, 2 H), 7.66 (t, $J = 7.4$ Hz, 1 H), 7.61 7.51 (m, 2 H), 5.08–4.92 (m, 1 H), 3.81 (dd, $J = 11$ and 8.9 Hz, 1 H), 3.39 (dd, $J = 11$ and 8.1 Hz, 1 H), 2.85 (dd, $J = 16$ and 5.7 Hz, 1 H), 2.76 (dd, $J = 16$ and 7.6 Hz, 1 H); $^{13}$C NMR (100 MHz, DMSO) $\delta = 171.7$, 133.3, 130.0, 129.1, 128.6, 70.0, 38.0, 37.1; IR (neat) 3457, 2450, 1798, 1727, 1593, 1567,
1491, 1442, 1400, 1338, 1316, 1240, 1040, 812, 690 cm\(^{-1}\); HRMS \(m/z\) [M + H]\(^+\) calculated for C\(_{11}\)H\(_{12}\)NO\(_2\)S [M + H]\(^+\) 222.0583, found 222.0580; mp = 177–178 °C.

![structure](image)

4-(Nitromethyl)-2-phenyl-4,5-dihydrothiazole (3-134); Prepared from thiobenzamide (0.053 g, 0.37 mmol) and (\(E\))-3-bromo-1-nitroprop-1-ene (0.092 g, 0.55 mmol) according to general procedure above and purified (hexanes–EtOAc: 5–30%) to yield 0.022 g (26%) of 3-134 as an orange oil: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.84\) (d, \(J = 7.6\) Hz, 2 H), 7.64—7.00 (m, 3 H), 5.75 5.17 (m, 1 H), 4.82 (dd, \(J = 13\) and 5.4 Hz, 1 H), 4.58 (dd, \(J = 13\) and 8.3 Hz, 1 H), 3.67 (dd, \(J = 12\) and 8.6 Hz, 1 H), 3.34 (dd, \(J = 12\) and 6.8 Hz, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 132.4, 132.2, 128.9, 128.9, 76.6, 73.6, 36.0\); IR (neat) 3424, 2920, 2848, 1550, 1378, 1248, 943, 767, 690, 611 cm\(^{-1}\); HRMS \(m/z\) [M + H]\(^+\) calculated for C\(_{10}\)H\(_{11}\)N\(_2\)O\(_2\)S [M + H]\(^+\) 223.0536, found 223.0533.
3.4.6: References


PART 4: Synthesis of 2-Thiazolines \textit{via} Epoxidation of \textit{S}-Allyl Thioimidate Salts

3.5.1: Abstract

Efforts to directly obtain thiazolines bearing exocyclic oxygen functionality at the C4 position via Lewis acid-assisted epoxide opening and cyclization are described. This method could further streamline the synthesis of thiazoline-containing complex molecules by eliminating oxidation steps required by previously reported methods.

3.5.2: Introduction and Background

Along with our previous developments, we envisioned a synthesis of thiazolines \textit{via} the Lewis acid-assisted opening of an epoxidated \textit{S}-allyl thioimidate and subsequent cyclization. Previous work on this project is described by Dr. Lemercier.\textsuperscript{1} Her attempts to access an epoxidized substrate through the coupling of a thioamide with a neopentyl epoxide precursor were unsuccessful. A newer strategy was to directly epoxidize thioimidate 3-\textsuperscript{40} to obtain compound 3-\textsuperscript{135} (Scheme 3.45). The opening of epoxide 3-\textsuperscript{135} could be assisted by both a Lewis acid and the appended nitrogen nucleophile to give oxygenated thiazoline 3-\textsuperscript{136}.

\begin{center}
\begin{tikzpicture}
    \node (a) at (0,0) {\(3-40\)};
    \node (b) at (2,0) {\(3-135\)};
    \node (c) at (4,0) {\(3-136\)};
    \node (d) at (1,0) {\text{epoxidation}};
    \node (e) at (3,0) {\text{Lewis acid (LA)}};
    \node (f) at (2,-1) {\text{LA-assisted epoxide opening}};
    \draw [->] (a) -- (d);
    \draw [->] (d) -- (b);
    \draw [->] (b) -- (e);
    \draw [->] (e) -- (c);
\end{tikzpicture}
\end{center}

\textbf{Scheme 3.45:} Asymmetric epoxidation of thioimidates and subsequent thiazoline formation.

Directly accessing thiazolines bearing oxygen functionality would streamline previously reported methods and allow for the synthesis of thiazoline containing natural products and
biologically active compounds many of which are both quaternary-substituted and contain oxygen at that position (Figure 3.2). Additionally, this method of epoxide-opening and cyclization would provide both the oxygen functionality and the quaternary center in the same step.

3.5.3: Results and Discussion

We began our investigation with the HBr thioimidate 3-58. Reacting this substrate with mCPBA in CH₂Cl₂ at room temperature gave, surprisingly, 81% yield of the bromine thiazoline 3-78 with no observed formation of epoxide 3-137 (Table 3.15, entry 1). Thiazoline 3-78 was also formed in 67% yield with DMDO at room temperature (entry 2). In each case, the reaction was finished upon addition of epoxidizing agent. As in the case with the halocyclization of 3-58, it is not reasonable to assume that the epoxide is formed, opened by the imine to the hydroxy thiazoline, and hydroxide is displaced by bromide instantaneously. Similar to the halocyclization reactions, we suspected that electrophilic epoxidizing reagents were reacting with the bromide in solution to form BrOH which was acting to halogenate the olefin of 3-58 resulting in thiazoline 3-78. BrOH is a deep yellow liquid. When mCPBA and DMDO were independently stirred in the presence of TBAB, the solutions turned yellow instantaneously, supporting our hypothesis.

Table 3.15: Epoxidation of HBr thioimidate salt.

<table>
<thead>
<tr>
<th>Entry</th>
<th>conditions</th>
<th>3-137 yield (%)</th>
<th>3-78 yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>mCPBA, DCM, rt</td>
<td>--</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>DMDO, Acetone, rt</td>
<td>--</td>
<td>67</td>
</tr>
</tbody>
</table>

aAll reactions were performed on 100 mg scale. bIsolated product yield.
With this result, we subjected the $\text{p}^\text{TsoH}$ thioimidate 3-112 to epoxidation conditions. Treatment of substrate 3-112 with DMDO consumed the starting material, but there was no observed mass of epoxidized thioimidate 3-138 (Table 3.16, entry 1). This was also the case with the addition of a base to the reaction (entry 2). It is likely that the sulfur of the thioimidate is oxidized followed by decomposition.

**Table 3.16:** Epoxidation of $\text{p}^\text{TsoH}$ thioimidate salt.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>3-138 yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMDO, Acetone, rt, 24 h</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>DMDO, Acetone, Et$_3$N, rt, 24 h</td>
<td>--</td>
</tr>
</tbody>
</table>

*All reactions were performed on 100 mg scale. $^a$Isolated product yield.*

These studies were done simultaneously with our investigations on halocyclization. Due to the success of that chemistry, we suspended our investigations with asymmetric epoxidation of $S$-allyl thioimidates.

**3.5.4: Conclusions**

Herein were described efforts to access quaternary-substituted thiazolines bearing exocyclic oxygen functionality. Although attractive targets for synthesis, the investigations of substrate synthesis were unsuccessful; however, further investigations, if successful, could streamline the synthesis of thiazoline-containing complex molecules by eliminating oxidation steps required in previously reported methods.
3.5.5: References


(2) Reactions were monitored using LC-MS by observing low resolution MS and UV absorbance.
CHAPTER 4

Efforts Towards the Stereoselective Synthesis of Haemanthamine and Related Alkaloids
4.1: Abstract

Efforts towards the total synthesis of haemanthamine and related crinine-derived alkaloids is described. The synthetic strategy rapidly builds molecular complexity using an efficient one-pot MCR for the synthesis of hydroxy-dihydro-pyrrolones. A subsequent reductive cyclization diastereoselectively provides three contiguous stereocenters in one step. A ring-closing metathesis provides the natural product scaffold in four steps from the MCR. The current route is three steps away from haemanthamine and eight steps overall. The efficient stereoselective synthesis should allow for further investigations into the biological capabilities of these natural products as lead therapeutics for the treatment of life-threatening cancers.

4.2: Introduction and Background

4.2.1: The Amaryllidaceae Alkaloids and Their Biological Relevance

Amaryllidaceae is a family of terrestrial bulbous flowering plants found mostly in tropical and subtropical regions of the world including Andean South America, the Mediterranean, and southern Africa.\textsuperscript{1} The Amaryllidaceae’s centuries-long use in medicine amongst indigenous natives of these territories has prompted investigations into the causes of their drug-like properties. As a result, hundreds of alkaloids have been isolated and studied for their biological properties for more than sixty years;\textsuperscript{2} although extensively explored, however, the scope and capabilities of these compounds as lead small molecule therapeutics is, in many cases, still in a stage of very early development.

The many polycyclic alkaloids isolated from the Amaryllidaceae are believed to originate biosynthetically via a similar pathway. The biogenetic route was first hypothesized by Barton in 1957 who used the Amaryllidaceae alkaloids to illustrate his pioneering theory that a critical
diversifying step in alkaloid biosynthesis involved intramolecular phenol-phenol oxidative coupling from a common intermediate.\(^3\) In the case of the *Amaryllidaceae* alkaloids, this common intermediate is 4’-O-methylnorbelladine (Scheme 4.1). The construction of norbelladine from the reduction of the Schiff base formed between 1,3-DHBA and tyramine followed by methylation gives 4’-O-methylnorbelladine. From there, the biosynthesis of the *Amaryllidaceae* alkaloids diverge into eight major skeletally-distinct subclasses.

4’-O-Methylnorbelladine can undergo a number of intramolecular transformations assisted by an oxidative phenol-phenol coupling enzyme based on the positioning of the aromatic rings relative to the phenol groups. *Ortho-para* coupling provides access to norpluviine (Scheme 4.1). This intermediate can be converted into a number of scaffolds such as the lycorine-type subclass.\(^4\) Lycorine was first isolated in 1956 and its structure was determined by Nakagawa and coworkers.\(^5\) It has been studied for its antiviral and antibacterial properties as well as its cytotoxic affects against a number of cancer cell lines.\(^6,7\) In fact, knowledge of the cytotoxic effects of the *Amaryllidaceae* has been reported since the fourth century BCE when Hippocrates described use of daffodil oil for the treatment of uterine tumors.\(^7\) Norpluviine can also undergo an enzyme-catalyzed benzylic hydroxylation to the hemiaminal 4-1. This intermediate, in equilibrium with its ring-opened form (4-2), can undergo C–C bond rotation to the rotational isomer 4-3. Acetal 4-3 is O- and N-methylated via two methyltransferase enzymes to provide the lycorenine-type subclass.\(^4\) Lycorenine was first isolated in 1955 by Kitagawa et al. and has been studied for its antimalarial properties.\(^8,9\)
In *The Odyssey*, Homer describes Odysseus’s men being poisoned by a witch named Circe. Odysseus was able to save his men by giving them an herbal antidote provided to him by the god Hermes. It is believed that Circe’s poison came from jimson weed and its anticholinergic components such as scopolamine which can cause hallucinations and amnesia. The antidote provided by Hermes is possibly *Galanthus nivalis* or the common snowdrop. Contained within the common snowdrop is the compound galanthamine which is a potent inhibitor of AChE and is an FDA approved drug for the treatment of Alzheimer’s disease.

The galanthamine-type subclass of *Amaryllidaceae* alkaloids are biosynthesized from 4’-*O*-methylnorbelladine through *para-ortho* oxidative coupling (Scheme 4.2). This coupling
pathway leads to a spirocyclic 1,4-cyclohexadieneone intermediate 4-4 which can undergo an intramolecular conjugate addition to benzofuran 4-5. Methylation of 4-5 by N-methyltransferase gives the galanthamine-type subclass.\(^4\)

Scheme 4.2: Biosynthesis of AAs via intramolecular para-ortho oxidative coupling.

The remaining five subclasses of the Amaryllidaceae alkaloids derive via para-para coupling of 4'-O-methylnorbelladine (Scheme 4.3). The crinine-type subclass is accessed through this route with the formation of vittatine (the enantiomer of crinine). Enzyme-catalyzed hydroxylation and O-methylation of vittatine gives rise to haemanthamine. Second in abundance amongst the Amaryllidaceae alkaloids (behind lycorine), haemanthamine was first isolated in 1954 by Biot, and its structure was determined by Wildman in 1960.\(^{11,12}\) It has been studied for its highly potent antitumoral properties particularly against apoptosis-resistant cell lines.\(^6,7,13–15\) Biosynthetically, haemanthamine is an intermediate in the formation of other alkaloids. Isomerization of the quaternary carbon leads to the montanine-type subclass, whereas removal of the two-carbon bridge connecting the nitrogen atom to the quaternary center leads to the
narciclasine-type subclass. Montanine has been studied for its antiarthritic and neurological properties.\textsuperscript{16,17} Also, SAR studies of montanine and narciclasine show anticancer activity against a number of apoptosis-resistant cell lines.\textsuperscript{18} Furthermore, benzylic oxidation of haemanthamine leads to haemanthidine. Haemanthidine can undergo reversible C–C bond rotation followed by methylation to give pretazettine which is a member of the tazettine-type subclass. Finally, the plicamine-type subclass can be accessed via amination of the tazettine alkaloids.\textsuperscript{1,4}

\textbf{Scheme 4.3}: Biosynthesis of AAs via intramolecular \textit{para-para} oxidative coupling.
4.2.2: Introduction to Haemanthamine and the Crinine-Type Subclass

4.2.2.1: Members of the Crinine-Type Subclass

Of the eight major subclasses of *Amaryllidaceae* alkaloids, we were interested in members of the crinine-type. Despite sixty-plus years of study with high potential as novel lead molecules for the treatment of cancer, their use in drug discovery efforts has been scarcely reported. As one of the largest subclasses, these alkaloids have the generalized scaffold of a non-natural product known as crinane (highlighted in red, Figure 4.1). The main structural differences that distinguish the roughly sixty members of the subclass involve variations in oxidation states and stereochemistry at different sites of the crinane scaffold.\textsuperscript{15,19,20}

![Figure 4.1: Diversity of the crinine-subclass of Amaryllidaceae alkaloids.](image)

\textsuperscript{15,19,20}
4.2.2.2: Haemanthamine as a Target for Drug Discovery

With regards to biological capabilities, the crinine-like alkaloid that stands out in particular is haemanthamine. As mentioned, haemanthamine was isolated in 1954 and is the second most abundant alkaloid in the *Amaryllidaceae* family.\(^\text{11}\) Not only is it an attractive target for total synthesis due to its intermediacy in a divergent pathway to other subclasses, but of the crinine-type alkaloids, haemanthamine has the most potent cytostatic activity. Since a majority of chemotherapeutics exhibit cytotoxic activity by activation of cell death pathways, it is very difficult to treat apoptosis-resistant tumors. Cytostatic therapeutics act by inhibiting cell proliferation as opposed to triggering cell death. Additionally, since detached cells survive via apoptosis resistance, cytostatic therapies could be ideal for the treatment of metastatic cancers.\(^\text{21}\)

Despite sixty years of research, the extent of current SAR studies on haemanthamine involve direct synthetic modifications of the extracted natural product. Haemanthamine itself exhibits single digit μM and sometimes nM range *in vitro* GI\(_{50}\) values against numerous cancer cell lines including some that are apoptosis resistant (Figure 4.1).\(^\text{6,7,13–15}\) Modifications to haemanthamine followed by examination against four cancer cell lines was reported in 2015 by Estévez-Braun and coworkers.\(^\text{13}\) The four cell lines are as follows: A2780 an apoptosis-resistant ovarian carcinoma line, SW1573 an alveolar (lung) epithelial carcinoma line, T-47D a ductal (breast) epithelial carcinoma line, and WiDr a colorectal epithelial adenocarcinoma line. Haemanthamine is active against these four cell lines with GI\(_{50}\) values as follows: 0.68, 2.1, 0.87 and 1.2 μM, respectively. Acylation of the ethano-bridge hydroxyl group gave either a slightly worse GI\(_{50}\) value (compounds 4-7 and 4-9) or showed a complete loss of activity (compounds 4-6 and 4-8). This observation demonstrated the level of activity intolerance for acyl groups in this position. Further examination of the ethano-bridged C11 hydroxyl group was carried out by
oxidation, oxime formation, and epoxidation to further study the activity tolerance at that site of
the molecule (4-11 through 4-13). Estévez-Braun also investigated the importance of the
cyclohexene olefin (4-10 and 4-16), the nitrogen (4-14), and the benzodioxole heterocycle (4-15).
Despite these insightful observations, the scope of accessible analogs of haemanthamine is limited,
which in turn, prohibits further SAR investigations and stalls the exploration of haemanthamine
as a novel antiproliferative lead therapeutic.

Following the SAR studies of Estévez-Braun and coworkers, haemanthamine’s mechanism
of action was elucidated by Pellegrino et al. in 2018. It was found that haemanthamine binds to
the large ribosomal subunit A-site cleft of the peptidyl transferase center on the eukaryotic 80S
ribosome. The binding creates interactions with the 25S rRNA causing a steric clash with long-
chain amino acid backbones thereby inhibiting elongation during protein synthesis through
rejection of the aa-tRNA. This discovery helped explain previous SAR studies. Pellegrino found
that C11 and C3 stereochemistry has little impact on the activity. Although derivatization of the
C11 hydroxyl group is not achievable due to steric clashes in the binding site, the C3 hydroxyl
group has plenty of space within the pocket for further functionalization to generate a more potent
compound. Furthermore, the extra C6 hydroxyl group found in haemanthidine is tolerated due to
the extra hydrogen bonding within the 25S rRNA. Finally, the stereochemistry of the ethano-bridge
is critical for activity, and the enantiomeric natural products, such as buphanisine (Figure 4.1), are
virtually inactive.
Figure 4.2: Extent of current SAR studies of haemanthamine.
Since protein synthesis is vital for cancer cell proliferation, inhibitors of this process could be promising cytostatic agents for cancer therapy. Although this is a practical strategy on its own, haemanthamine shows a number of advantages over other translation inhibitors. In the same report describing the mechanism of action, Pellegrino found that haemanthamine not only inhibits peptide elongation, but it also has a highly specific inhibitory effect on ribosomal biogenesis. This additional property also affects cancer cells due to activation of signaling cascades such as the antitumor nucleolar surveillance pathway. This leads to the stabilization of the tumor-suppressor protein p53. Hdm2-mediated ubiquitylation causes the degradation of p53. During ribotoxic stress, unassembled ribosomal components capture Hdm2 stabilizing p53 and activating programmed cell death. An attractive feature of this strategy is that it is often highly selective for cancer cells as normal cells do not tend to activate programmed cell death in the presence of ribosome biogenesis inhibitors. In addition to its activity, haemanthamine has the advantage of being water soluble at higher concentrations (greater than 1 mg/mL). Also, the basic nitrogen allows it to be administered in the salt form as opposed to the similarly active narciclasine-type subclass (Scheme 4.3). Furthermore, pharmacokinetic studies in rats demonstrated a rapid distribution phase of 30 minutes, a 70.4 minute half-life, and renal elimination as the major form of clearance. Haemanthamine also shows a high intracellular penetration with plasmatic concentrations greater than 1 μM for the first hour. All of these advantages help to support haemanthamine as a candidate for future preclinical studies.

4.2.2.3: Previous Synthetic Efforts Towards the Crinine-Type Subclass

Crinine was first isolated in 1955 by Wildman and coworkers. One year later, Wildman reported the synthesis of crinane as a simplified analog of crinine which involved a Pictet-Spengler
cyclization in the final step to install the benzylic methylene group and furnish the scaffold.\textsuperscript{19} Since then, the most common route to the crinine-type alkaloids is a formal synthesis by way of either a Pictet-Spengler or Bischler-Napieralski cyclization of derivatives resembling octahydro-indole 4-17 (Scheme 4.4); however, these routes do not typically lend themselves to efficiency in the area of step economy nor are they amenable for the synthesis of analogs to further probe the SAR and biological capabilities of these alkaloids.\textsuperscript{25–32}

\textbf{Scheme 4.4:} Common retrosynthesis of crinine-type alkaloids.

Haemanthamine has also been scarred by this synthetic strategy, and there are a limited number of reports on its synthesis. The first total synthesis of haemanthamine was reported by Tsuda et al. in 1971.\textsuperscript{33} Starting with 3,4-(Methylenedioxy)phenylacetonitrile, treatment with diethyl oxalate in sodium ethoxide gave enol 4-18, which was reductively cyclized to the hydroxy-dihydro-pyrrolone 4-19 with Raney nickel (Scheme 4.5). A Diels-Alder cycloaddition provided the core quaternary-substituted indole (4-20) needed for the Pictet-Spengler cyclization. Epoxidation to compound 4-21 was followed by lewis acid-assisted ring opening to give the desired regio-isomer 4-22-\textsuperscript{r1} in 50% yield. Reduction to compound 4-23 gave the octahydro-indole substrate for the Pictet-Spengler reaction which provided compound 4-24 in 50% yield.
Finally, selective tosylation of the 1,2-diol followed by elimination gave the natural product. Altogether, Tsuda’s synthesis is ten linear steps and less than 3% overall yield.

Scheme 4.5: Total synthesis of haemanthamine by Tsuda in 1971.
In the years following, the only other reported synthesis of haemanthamine is from Chida in 2007. This route begins with compound 4-25, a commercially available protected analog of D-glucose (Scheme 4.6). Chida cites eight steps from compound 4-25 to the cyclic enone 4-26 in 38% overall yield. A Grignard addition followed by oxidative manipulations gives the allylic alcohol 4-27. Compound 4-27 is then converted to α-hydroxy epimers 4-28-e1 and 4-28-e2. Chida demonstrated the ability to convert both epimers of 4-28 to epoxide 4-29 individually in similarly moderate yields. Methylation and epoxide opening were followed by hydrogenation and dissolved metal reduction to give compound 4-30. Intramolecular aminomercurial and subsequent demercuration was followed by protection and reaction with carbon disulfide to provided carbonodithioate 4-31. Elimination of 4-31 yielded the quaternary-substituted indole substrate for the Pictet-Spengler cyclization (4-32), which gave haemanthamine in quantitative yield. Altogether, Chida’s synthesis was 26 steps and 0.64% overall yield in its shortest linear route.
Scheme 4.6: Total synthesis of haemanthamine by Chida in 2007.
4.2.3: Original Idea and Scope

As discussed, haemanthamine is a promising candidate for the development of a novel anticancer therapeutic; however, previous efforts for the synthesis of this molecule are scarce and none of the existing routes are amenable for further biological investigations. We were highly interested in haemanthamine’s potential as a drug candidate and desired to develop a more efficient and stereoselective synthesis of this molecule to further probe its biological capabilities. A structural feature of haemanthamine that could pose difficulty for synthetic efforts is the presence of three contiguous stereocenters with one these being an all-carbon quaternary center (Figure 4.3). We sought to access these three contiguous stereocenters in one step stereoselectively while also avoiding a formal synthesis as mentioned earlier (Scheme 4.4).

Figure 4.3: Three contiguous stereocenters in the structure of haemanthamine.

Dr. Nataliia Shymanska, a graduate of our group, previously reported the total synthesis of syn-oxazolidinones A and B. The developed procedure used an efficient MCR between an in situ-formed imine and a pyruvic acid chloride to rapidly build the 4-oxazolidinone scaffold 4-33, and this research has become an ongoing drug discovery project in our group (Scheme 4.7).\textsuperscript{35-37} Dr. Shymanska found that use of the pyruvic acid methyl ester instead of the chloride provided access to hydroxy-dihydro-pyrrolones 4-34, and she was able to demonstrate this method on a panel of
substrates in moderate to excellent yields as well as their ability to be transformed into quaternary-substituted $\beta^{2,3,3}$-amino acids.\textsuperscript{38} We wondered if the proper hydroxy-dihydro-pyrrolone could be a suitable intermediate for the efficient stereoselective synthesis of haemanthamine.

**Scheme 4.7:** MCR for the synthesis of 4-oxazolidinones and hydroxy-dihydro-pyrrolones.

Our designed retrosynthesis begins with a late-stage allylic oxidation on compound 4-35 (Scheme 4.8). The natural product scaffold is formed by an RCM to furnish the olefin and a reductive cyclization on compound 4-36. The reductive cyclization should provide the three contiguous stereocenters with selectivity towards the desired diastereomer. Finally, compound 4-36 is formed by the MCR for the synthesis of hydroxy-dihydro-pyrrolones.

**Scheme 4.8:** Retrosynthesis of haemanthamine.
4.3: Results and Discussion

To begin our investigations, we required access to the substrates for the MCR. Starting with \((E)\)-cinnamaldehyde, we employed the Dakin protocol for the synthesis of pyruvic acids (Scheme 4.9). Formation of an aza-lactone with \(N\)-Ac-Gly is the first step followed by hydrolysis to cinnamylpyruvic acid 4-36. Methylation of 4-36 provides cinnamylpyruvic ester 4-37 in 80% yield. Finally, bromo-piperonylamine 4-38 was synthesized by the treatment of bromo-piperonyl bromide with ammonium hydroxide.

![Scheme 4.9: Synthesis of substrates for the MCR.](image)

With these substrates in hand, optimization of the MCR began. Stirring two equivalents of 4-pentenal with 4-37 and 4-38 in \(\text{CH}_3\text{CN}\) at 0.4 M (the original conditions) gave 40% yield of compound 4-39 after 22 h (entry 1, Table 4.1). A yield dependence on concentration was observed when the reaction was performed at 0.05 M which gave 17% of 4-39 at a much slower rate (entry 2). Switching solvents to \(\text{CH}_2\text{Cl}_2\) not only had a significant effect on the yield but also increased the rate of formation of 4-39 by nine fold (entry 3). Increasing the concentration to 0.1 M gave a
slightly increased yield as well as reaction rate, and this translated similarly with a decrease in aldehyde equivalents from 2 to 1.1 (entries 4 and 5). Finally, incremental increases in reaction concentration demonstrated that 0.5 M is optimal to provide compound **4-39** in 91% yield after 1 h (entries 6–8). This MCR is an efficient process providing high yields of desired product in a short time without the need for column chromatography for purification. Furthermore, it is a scalable reaction with little effect on the yield on gram scale (entry 7).

**Table 4.1**: Optimization of the MCR.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>X</th>
<th>solvent</th>
<th>conc. (M)</th>
<th>time (h)</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>0.4</td>
<td>22</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>0.05</td>
<td>72</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.05</td>
<td>8</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.1</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.1</td>
<td>4</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.25</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>1.1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.5</td>
<td>1</td>
<td>91, 85&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1.0</td>
<td>1</td>
<td>46</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions were performed on 100 mg scale unless otherwise noted. <sup>b</sup>Isolated product yield. <sup>c</sup>Reaction performed on 3 g scale.

Following MCR optimization, we expanded the scope of hydroxy-dihydro-pyrrolone synthesis (Scheme 4.10). To briefly demonstrate the feasibility of this method for an anticipated future analog development, we synthesized a panel of compounds bearing variations with the amine substitution. This reaction works well for electronically rich and poor substituted benzylic
substrates (4-39 through 4-44). It can also be extended to the incorporation of heterocycles such as thiophene-containing compound 4-45.

Scheme 4.10: Expanded scope of the MCR.

4.3.1: A Tale of Two Routes

With the desired hydroxy-dihydro-pyrrolone in hand, we began our investigations into the subsequent transformations. From a theoretical standpoint, the RCM and reductive cyclization can be preferred interchangeably (Scheme 4.11). Following route A, the RCM of compound 4-39 would lead to the hydroxy-tetrahydro-indolone 4-46. Subsequent reductive cyclization would provide the natural product scaffold 4-48. Conversely, route B starts with a reductive cyclization
of compound 4-39 to give the bridged bicyclic compound 4-47. Subsequent RCM of 4-47 also provides compound 4-48. Through these investigations, we hope to discover which route provides a more appealing outcome for the total synthesis of haemanthamine.

Scheme 4.11: The two routes from hydroxy-dihydro-pyrrolone to the natural product scaffold.

As mentioned, there are two routes to follow for our synthesis of haemanthamine, and our initial investigations demonstrate pros and cons for both. Performing an RCM on compound 4-39 with Grubbs II as a catalyst gave only starting material at room temperature; however, at elevated temperatures, we were able to observe full conversion to compound 4-46 (Scheme 4.12). The pros of this route are that we reproducibly observe full conversion to the desired product. The con, however, is that, much like the hydroxy-dihydro-pyrrolone substrates, compound 4-46 is unstable to column chromatography, and we were ultimately unable to separate the compound from the ruthenium catalyst using a variety of approaches. Following route B, successful formation of
compound 4-47 from 4-39 was observed with the use of reductive Heck conditions. The pros of this route were that purification of 4-47 from residual catalyst was simpler than for compound 4-46, but separation of product from remaining starting material was difficult. Furthermore, due to the instability of 4-39 to column chromatography, we could not provide accurate brsm yields or recycle the unreacted material. Additionally, the reaction suffered from problems with conversion as well as reproducibility and scalability as we obtained a wide variability in isolated yield.

Scheme 4.12: Routes A and B on non-protected substrate 4-39.

Another problem observed with route B was the formation of other side products. The unfortunate part of these observations was that quantitative determination of the relative amounts of these products was difficult as they each elute with the same retention on both TLC and LC-MS; however, with LC-MS we noticed a difference in UV absorption for the desired product 4-47 and the side products formed.\textsuperscript{41} We believe that one of the side products is possibly caused by $\beta$-hydride elimination with the hydroxyl group to form a 1,2-dicarboxyl of compound 4-47, and as a result, we observe the mass of compound 4-47 minus hydrogen. The other side product was believed to be de-brominated starting material. Since these hydroxy-dihydro-pyrrolones decompose on silica, we were unable to purify this observed side product; however, we were able
to synthesize the de-brominated substrate. Using piperonyl amine in the MCR, we obtained compound 4-49 in 78% yield and confirmed that its elution and UV trace by LC-MS matched the observed side product (Scheme 4.13).

![Scheme 4.13: Synthesis of non-brominated substrate.](image)

Due to the seemingly fewer complications, we chose to proceed initially with route A. As mentioned, the purification of compound 4-46 proved unsuccessful, so we decided to protect substrate 4-39 (Table 4.2). Throughout these trials on both routes A and B, we investigated various protected hydroxy-dihydro-pyrrolones, and for ease of flow of this document these protected substrates are highlighted together; however, the protected substrates investigated for route A were compounds 4-50, 4-51, and 4-55 (entries 1, 2 and 6). As a result, these protected hydroxy-tetrahydro-indolones proved to be easily isolable from residual ruthenium catalyst. Subjecting TBS-protected substrate 4-50 to the RCM gave compound 4-56 in 96% yield (entry 1, Table 4.3). This was a scalable process and we obtained compound 4-56 in 88% yield on 400 mg scale. The Ac-protected substrate 4-51 provided compound 4-57 in 79% yield (entry 2), whereas the 4′Tol-protected substrate 4-55 gave compound 4-58 in nearly quantitative yield (entry 3). A positive note about compound 4-58 is that it can be purified by trituration in ethyl acetate without the need for
column chromatography. An additional attractive feature of this route is that the protection of hydroxy-dihydro-pyrrolones and subsequent RCM can be done together in one-pot.

**Table 4.2**: Synthesis of various protected substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>conditions</th>
<th>R</th>
<th>product #</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBSCI, imidazole</td>
<td>TBS</td>
<td>4-50</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>Ac₂O, K₂CO₃</td>
<td>Ac</td>
<td>4-51</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>PivCl, imidazole</td>
<td>Piv</td>
<td>4-52</td>
<td>99⁺</td>
</tr>
<tr>
<td>4</td>
<td>BzCl, imidazole</td>
<td>Bz</td>
<td>4-53</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>Bz₂Cl, imidazole</td>
<td>Bz₂</td>
<td>4-54</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>³⁵TolCl, imidazole</td>
<td>³⁵Tol</td>
<td>4-55</td>
<td>99⁺</td>
</tr>
</tbody>
</table>

*All reactions were performed on gram scale unless otherwise noted. †Isolated product yield.

**Table 4.3**: RCM of selected protected hydroxy-dihydro-pyrrolones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>SM #</th>
<th>product #</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBS</td>
<td>4-50</td>
<td>4-56</td>
<td>96, 88²</td>
</tr>
<tr>
<td>2</td>
<td>Ac</td>
<td>4-51</td>
<td>4-57</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>³⁵Tol</td>
<td>4-55</td>
<td>4-58</td>
<td>99³</td>
</tr>
</tbody>
</table>

*All reactions were performed on 50 mg scale unless otherwise noted. †Isolated product yield. ²reaction performed on 400 mg scale. ³reaction performed on 500 mg scale.
With the substrates in hand, we began investigations into reductive cyclization. Under reductive Heck conditions with non-ligated palladium and sodium formate as the hydride donor, compound 4-56 gave full conversion to the undesired de-brominated and deprotected substrate (entry 1, Table 4.4). At lower temperatures, however, full decomposition was observed before the reaction could reach full conversion (entry 2). Compound 4-57 also gave full de-bromination as well as a mixture of protected and deprotected substrate (entry 3). Finally, the pTol-protected compound 4-58 gave nearly full conversion as well to the undesired de-brominated substrate. With these results, we decided to pursue to route B as the alternate pathway.

**Table 4.4:** Exploration of reductive Heck reaction on differentially protected 4-46 substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>R</th>
<th>SM #</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>TBS</td>
<td>4-56</td>
<td>de-brominated and deprotected 4-56</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>TBS</td>
<td>4-56</td>
<td>decomp. of 4-56 before full conversion(^a)</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>Ac</td>
<td>4-57</td>
<td>de-brominated 4-57, mix of protected and not</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>pTol</td>
<td>4-58</td>
<td>de-brominated 4-58</td>
</tr>
</tbody>
</table>

\(^a\)All reactions were performed on 75 mg scale unless otherwise noted. \(^b\)Reaction gave 50% conversion at 2 h, but decomposed.
4.3.2: One Heck of a Reaction

It was not ideal to protect compound 4-39 for purification of the RCM product only to have the protecting group cleaved under the reductive cyclization conditions. Furthermore, the non-requirement of protecting groups for route B was more attractive, and therefore, we turned our attention to the optimization of this route. Furthermore, we observed higher yields for the reductive cyclization of hydroxy-dihydro-pyrrolone 4-39 than we were observing with the hydroxy-tetrahydro-indolone substrates, and regardless of the problems faced, we believed the reaction could be optimized further.

Although true that the reductive Heck reaction gave the first sign of desired product formation, it was not the only cyclization attempt that was tried. To highlight a few examples, reduction under radical chain conditions with AIBN and Bu₃SnH gave only the de-brominated starting material (entry 1, Table 4.5). Reductive cyclization via photoredox catalysis with both ruthenium-based and organic catalysts was also attempted with little success (entries 2 and 3).

Table 4.5: Selected reductive cyclization conditions for the synthesis of compound 4-61.

<table>
<thead>
<tr>
<th>Entry</th>
<th>conditions</th>
<th>result</th>
<th>conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AIBN, Bu₃SnH, benzene, 80 °C, 1 h</td>
<td>only de-brominated SM</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Pt(OAc)₂ (1 mol%), Ru(bpy)₃Cl₂ (1 mol%), Et₃N, DMF, blue LEDs, rt</td>
<td>only SM at 4 h, decomp. overnight</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Eosin Y (3 mol%), CH₃CN, blue LEDs, rt</td>
<td>only SM at 12 h, no DP</td>
<td></td>
</tr>
</tbody>
</table>

*All reactions were performed on 50–100 mg scale.*
Oxidative cyclization via photoredox catalysis was also tried. Several reports by Pandey et al. demonstrated the aerobic oxidative annulation of silyl enol ethers with appended electronically rich aromatic rings using DCN as an organic photocatalyst.\textsuperscript{42,43} This reaction was performed on both substrates 4-49 and 4-62 with both providing only starting material by LC-MS and no sign of the 1,2-dicarbonyl 4-63 (entries 1 and 2, Table 4.6). This reaction was also tried with DCB as the photocatalyst which also gave only starting material by crude \textsuperscript{1}H NMR.

\textbf{Table 4.6:} Selected oxidative cyclization conditions for the synthesis of compound 4-62.

\begin{center}
\begin{tabular}{cccc}
\hline
Entry\textsuperscript{a} & R & catalyst & result \\
\hline
1 & TBS & DCN & only SM by LC-MS \\
2 & H & DCN & only SM by LC-MS \\
3 & TBS & DCB & mostly SM by crude NMR, complex mixture \\
4 & H & DCB & only SM by crude NMR \\
\hline
\end{tabular}
\end{center}

\textsuperscript{a}All reactions were performed on 50 mg scale at 0.003 M.

Since the reductive Heck conditions provided the desired product, albeit with limitations, we decided to continue with the optimization of that process. Some of the first parameters we screened were solvents and temperature (Table 4.7). The reaction with TBS-protected substrate 4-50 in DMF gave 71\% yield of an impure mixture of mostly 4-47 (entry 3), and NMP gave a similar result at 64\% yield (entry 2); however, toluene did not prove to be a competent solvent for this
transformation (entry 3). The reaction did not progress at lower temperatures giving decomposition at 80 °C and only deprotected starting material (4-49) at 60 °C (entries 4 and 5).

**Table 4.7**: Solvent and temperature screen for the reductive cyclization of compound 4-50.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>100</td>
<td>71% yield of 4-47 and impure product&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>NMP</td>
<td>100</td>
<td>64% yield of 4-47 and impure product&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>100</td>
<td>only 4-39 after 7 h</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>80</td>
<td>decomp. to complex mixture overnight</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>60</td>
<td>only 4-39 after 5 h</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions were performed on 50 mg scale at 0.05 M. <sup>b</sup>Observations by LC-MS. <sup>c</sup>Impurities often include: SM, de-brominated SM (4-49), and possibly compound 4-62.

Additionally, a catalyst screen was performed (Table 4.8). For a reference, the result with Pd(OAc)<sub>2</sub> is provided (entry 1). PdCl<sub>2</sub> gave only mostly de-brominated starting material (4-49, entry 2), whereas PdBr<sub>2</sub> gave 54% of an impure mixture of deprotected product 4-47 (entry 3). Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> and Pd(CO<sub>2</sub>CF<sub>3</sub>)<sub>2</sub> gave 66% and 69% yield of mostly compound 4-47, respectively (entries 4 and 5). Finally, using the pre-ligated catalyst Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> gave 52% yield of an impure mixture of 4-47 (entry 6).
As inferred, there seemed to be recurring themes with each of these trials: the difficulty of purifying the resulting undesired deprotected product (4-47) from impurities, the variability in conversion, and the problem of reproducibility. We sought to discover which element of the reaction was causing this de-protection and to know if the yield variability was solely proportional to the low conversion or if there existed an element causing in situ decomposition of the starting material and/or the product. Therefore, we performed a stability screen by subjecting the starting material to each individual reaction condition (Table 4.9). At 100 °C, the control experiment in DMF provided only trace decomposition after 24 hours with no sign of deprotected substrate (entry 1); however, in the presence of sodium formate and DIPEA, hydrolysis of compound 4-51 to compound 4-39 was observed as well as full decomposition by 3 h (entry 2). Individual screening of these components showed that sodium formate was responsible for both the hydrolysis and decomposition of the substrate (entries 3 and 4). Sodium formate was also found to give decomposition of both the unprotected substrate 4-39 as well as each of the other protected
substrates 4-52 through 4-55 (entries 5–9). With these results, we became confident that further optimization would assist in alleviating these problems.

Table 4.9: Stability screen of hydroxy-dihydro-pyrrolones to reductive Heck conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Catalyst</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac</td>
<td>None</td>
<td>-trace decomp. after 24 h</td>
</tr>
<tr>
<td>2</td>
<td>Ac</td>
<td>NaHCO₃, DIPEA</td>
<td>-hydrolyzed SM, full decomp by 3 h</td>
</tr>
<tr>
<td>3</td>
<td>Ac</td>
<td>NaHCO₃</td>
<td>-hydrolyzed SM, full decomp by 3 h</td>
</tr>
<tr>
<td>4</td>
<td>Ac</td>
<td>DIPEA</td>
<td>-only SM by 3 h</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>NaHCO₃</td>
<td>-major decomp by 3 h</td>
</tr>
<tr>
<td>6</td>
<td>Piv</td>
<td>NaHCO₃</td>
<td>-hydrolyzed SM, trace SM by 18 h</td>
</tr>
<tr>
<td>7</td>
<td>Bn</td>
<td>NaHCO₃</td>
<td>-hydrolyzed SM, full decomp by 3 h</td>
</tr>
<tr>
<td>8</td>
<td>BnF</td>
<td>NaHCO₃</td>
<td>-hydrolyzed SM, trace SM by 3 h</td>
</tr>
<tr>
<td>9</td>
<td>Tol</td>
<td>NaHCO₃</td>
<td>-hydrolyzed SM, still a lot of SM by 18 h</td>
</tr>
</tbody>
</table>

*All reactions were performed on 10 mg scale at 0.05 M. °Observations by LC-MS.

Therefore, we sought to determine whether the presence of the extra conjugated olefin (cinnamyl alkene) or the terminal olefin (or both) were responsible for the conversion problems we were observing. Hydroxy-dihydro-pyrrolones 4-64 (containing no extraneous alkenes) and 4-66 (containing only the terminal olefin) were prepared in 68% and 59% yields, respectively (Scheme 4.14). Subjecting compound 4-64 to the reductive Heck conditions provided full conversion to compound 4-65 in 68% yield, and subjecting compound 4-66 to the reaction conditions also gave full conversion to compound 4-67 in 65% yield. These results show the impact that the extraneous olefins have on the turnover ability of the palladium catalyst. This is
particularly true for the cinnamyl-olefin as it provides further conjugation with the reaction site alkene.

Scheme 4.14: Investigations on how terminal and styrenyl olefins affect conversion.

Since sodium formate is responsible for protecting group hydrolysis as well as decomposition, we needed to find a hydride source that alleviated these problems. Firstly, we desired to test the ability of DIPEA as a hydride donor by simply removing sodium formate (entry 1, Table 4.10). This resulted in mostly starting material after 21 hours. Exchanging DIPEA for Et$_3$N gave the same result (entry 2). Using DBU quickly hydrolyzed the starting material to 4-47 (entry 3). Successful reduction was observed with the use of 1,4-CHD which gave over 67% conversion to the desired protected product 4-68 (entry 4). This reaction also worked on the non-protected hydroxy-dihydro-pyrrolone 4-39 with the same result (entry 5). With a brief screen of concentration, we found that higher concentrations give poorer results (entry 6), whereas lower
concentrations lead to increases in the conversion (entry 7). Finally, we screened a number of CHD derivatives and found 1,4-CHD to be the most competent (entries 8–11).

Table 4.10: Hydride source screen for the reductive cyclization of compounds 4-51 and 4-39.

| Entry | R   | hydride source | conc. (M) | result
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac</td>
<td>None</td>
<td>0.05</td>
<td>mostly SM after 21 h</td>
</tr>
<tr>
<td>2</td>
<td>Ac</td>
<td>Et$_3$N</td>
<td>0.05</td>
<td>mostly SM after 21 h</td>
</tr>
<tr>
<td>3</td>
<td>Ac</td>
<td>DBU</td>
<td>0.05</td>
<td>only hydrolyzed SM after 5 min</td>
</tr>
<tr>
<td>4</td>
<td>Ac</td>
<td>1,4-CHD</td>
<td>0.05</td>
<td>over 67% conversion by 2 h</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>1,4-CHD</td>
<td>0.05</td>
<td>over 67% conversion by 2 h</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>1,4-CHD</td>
<td>0.1</td>
<td>less than 33% conversion by 7 h</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>1,4-CHD</td>
<td>0.01</td>
<td>around 75% conversion by 1 h</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>1-Me-1,4-CHD</td>
<td>0.01</td>
<td>over 67% conversion by 1 h</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>1-OMe-1,4-CHD</td>
<td>0.01</td>
<td>around 67% conversion by 4 h</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>1,5-diOMe-1,4-CHD</td>
<td>0.01</td>
<td>mostly SM by 4 h</td>
</tr>
<tr>
<td>11</td>
<td>H</td>
<td>1,3-CHD</td>
<td>0.01</td>
<td>mostly SM by 4 h</td>
</tr>
</tbody>
</table>

*All reactions were performed on 75 mg scale. *Observations by LC-MS.

The use of 1,4-CHD alleviated the problem of starting material hydrolysis and *in situ* decomposition, but we were still experiencing problems with reaction conversion and reproducibility. Due to the electronically rich nature of our substrate, we hypothesized that the rate of oxidative addition may be too slow for the palladium to give a high turnover number before catalyst decomposition and the formation of palladium black. Acylation of piperonylamine followed by ortho-iodination and subsequent deprotection gave iodo-piperonylamine 4-69 in 35% yield over three steps (Scheme 4.15). Using compound 4-69 in the MCR gave iodinated substrate 4-70, which increase the rate of oxidative addition. Subjecting compound 4-70 to the newly
optimized reductive Heck conditions gave trace amounts of 4-47 indicating that the limiting step responsible for hindering catalyst turnover might not be oxidative addition (entry 1, Table 4.1). Furthermore, we investigated various additives with the iodinated substrate 4-70. Addition of five equivalents of LiCl gave only starting material (entry 2). We also wanted to determine if addition of silver could assist in the catalyst turnover by precipitation of silver iodide; however, incorporation of silver triflate gave rapid decomposition (entry 3).

Scheme 4.15: Synthesis of aryl-iodide substrate 4-70.

Table 4.11: Investigations of reductive Heck cyclization on aryl-iodide substrate 4-70.

<table>
<thead>
<tr>
<th>Entry</th>
<th>additive</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>-trace amounts of 4-47 observed</td>
</tr>
<tr>
<td>2</td>
<td>LiCl</td>
<td>-no observed formation of 4-47</td>
</tr>
<tr>
<td>3</td>
<td>AgOTf</td>
<td>-full decomp. by 5 min</td>
</tr>
</tbody>
</table>

*All reactions were performed on 50 mg scale at 0.01 M. *Observations by LC-MS.
If oxidative addition is not the cause of the inability of catalyst turnover, we hypothesized that the organo-palladium species formed as the product of oxidative addition might not be able to rapidly undergo migratory insertion with our desired alkene. The presence of a free hydroxyl group might make the alkene too electron rich, and this effect might be amplified by the additional conjugation with the cinnamyl olefin. The latter claim being supported by the full conversion of compounds 4-64 and 4-66 to compounds 4-65 and 4-67 in the absence of the cinnamyl olefin (Scheme 4.14). Furthermore, there were no existing studies on the ability of the hydroxy-dihydro-pyrrrole to tautomerize under basic conditions at elevated temperatures to the dihydroxy pyrrole (Scheme 4.16). Therefore, we hoped that we might be able to alleviate this by screening our various protected substrates (Table 4.12). Subjecting Piv-protected substrate 4-52 to the reaction gave compound 4-71 in 49% yield and 70% brsm (entry 1). The Bz-protected substrate 4-53 gave compound 4-72 in 46% yield and 70% brsm (entry 2), whereas the BzF-protected substrate 4-54 gave compound 4-73 in 31% yield and 45% brsm (entry 3). Finally, pTol-protected substrate 4-55 gave compound 4-61 in 64% yield and 85% brsm (entry 4). Although none of these helped to improve the reaction conversion, in each case we were able to separate the unreacted starting materials from the products to obtain brsm yields. With that ability, we chose to move forward with substrate 4-55 as it gave the easiest separation as well as the highest yield.

\[ \text{4-39} \xrightarrow{\text{tautomerization}} \text{dihydroxy pyrrole} \]

**Scheme 4.16:** Base-promoted tautomerization of compound 4-39 to a dihydroxy pyrrole.
Table 4.12: Protecting group screen for the reductive Heck cyclization.

If neither oxidative addition nor migratory insertion were responsible for issues with catalyst turnover, we wondered if the use of a non-ligated catalyst was too unpredictable and rapidly prone to decompose to palladium black. We decided to screen various ligands to stabilize the Pd(0) complex and determine if the conversion problem arises from an unstable catalytic species that rapidly decomposes (Table 4.13). Using 12 mol% of PPh\(_3\) gave surprisingly full conversion of compound 4-55 to desired product 4-61 after 2 hours (entry 1). A second trial of this reaction gave full conversion after 24 h and 51% yield. Both PCy\(_3\) and PBu\(_3\) gave trace amounts of 4-61 after 21 hours (entries 2 and 3); however, PPh\(_3\)(CF\(_3\))\(_6\) gave full conversion to compound 4-61 in 55% yield (entry 4). A second trial with the same ligand also gave full conversion to 4-61 in 64% yield. We did not have as much luck, however, with the screening of bidentate ligands. Using rac-BINAP, dppp, dppf, and dppBz each gave trace amounts of desired product 4-61 (entries 5–8); however, XantPhos gave about 50% conversion after 4 hours (entry 9). Both the phenanthroline ligand BPhen and the BOx ligand gave only starting material (entries 10 and 11). Although most of the ligands were unsuccessful, we were happy to finally observe reproducibility.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>SM #</th>
<th>product #</th>
<th>yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Piv</td>
<td>4-52</td>
<td>4-71</td>
<td>49%, 70% brsm</td>
</tr>
<tr>
<td>2</td>
<td>Bz</td>
<td>4-53</td>
<td>4-72</td>
<td>46%, 70% brsm</td>
</tr>
<tr>
<td>3</td>
<td>Bz(_F)</td>
<td>4-54</td>
<td>4-73</td>
<td>31%, 45% brsm</td>
</tr>
<tr>
<td>4</td>
<td>PTol</td>
<td>4-55</td>
<td>4-61</td>
<td>64%, 85% brsm</td>
</tr>
</tbody>
</table>

\(^a\)All reactions were performed on 75 mg scale at 0.01 M. \(^b\)Isolated product yield.
and full conversion of hydroxy-dihydro-pyrrolones to the desired products under reductive Heck conditions, and we were now ready to move forward with our synthesis of haemanthamine.

Table 4.13: Ligand screen for the reductive cyclization of compound 4-55.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>X</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh$_3$</td>
<td>12</td>
<td>-Trial 1: 59% at 2 h, Trial 2: 51% at 24 h</td>
</tr>
<tr>
<td>2</td>
<td>PCy$_3$</td>
<td>12</td>
<td>-mostly 4-55 with trace 4-61 by 21 h</td>
</tr>
<tr>
<td>3</td>
<td>PnBu$_3$</td>
<td>12</td>
<td>-mostly 4-55 with trace 4-61 by 21 h</td>
</tr>
<tr>
<td>4</td>
<td>PPh$_3$(CF$_3$)$_6$</td>
<td>12</td>
<td>-Trial 1: 55% at 3 h, Trial 2: 64% at 2 h</td>
</tr>
<tr>
<td>5</td>
<td>rac-BINAP</td>
<td>6</td>
<td>-mostly 4-55 with trace 4-61 by 21 h</td>
</tr>
<tr>
<td>6</td>
<td>dppp</td>
<td>6</td>
<td>-mostly 4-55 with trace 4-61 by 7 h, messy</td>
</tr>
<tr>
<td>7</td>
<td>dppf</td>
<td>6</td>
<td>-mostly 4-55 with trace 4-61 by 7 h</td>
</tr>
<tr>
<td>8</td>
<td>dppBz</td>
<td>6</td>
<td>-mostly 4-55 with trace 4-61 by 21 h</td>
</tr>
<tr>
<td>9</td>
<td>XantPhos</td>
<td>6</td>
<td>-50% conversion by 4 h, same result by 19 h</td>
</tr>
<tr>
<td>10</td>
<td>BPhen</td>
<td>6</td>
<td>-only 4-55 by 7 h, full decomp. by 22 h</td>
</tr>
<tr>
<td>11</td>
<td>BOx</td>
<td>6</td>
<td>--mostly 4-55 with trace 4-61 by 22 h</td>
</tr>
</tbody>
</table>

*All reactions were performed on 75 mg scale at 0.01 M. *bObservations by LC-MS. *cIsolated product yield.

Although not quite as much of a ‘eureka’ moment as Archimedes had whilst discovering a precise method for determining the purity of gold, we were indeed elated; however, now is the time of interjection to convey the age old idiom of overconfidence: famous last words. Upon the second attempt to reproduce the success of the PPh$_3$(CF$_3$)$_6$ ligand, we were met with only 50% conversion (entry 1, Table 4.14). The conversion eroded even further to 33% with the third attempt (entry 2). Further attempts were made paying close attention to methodically reproduce the reaction set up and were met with similar results. It was reported by Amatore et al. that using two equivalents of PPh$_3$ relative to palladium acetate causes the formation of an unstable catalyst due
to a singly-ligated Pd(0) complex after PPh₃-mediated reduction of Pd(II). They claim that the use of excess ligand in up to ten equivalents relative to the catalyst alleviates this by forming a properly-ligated Pd(0) complex. Therefore, we increased the equivalency of the ligand to 50 mol% (ten equivalents relative to palladium acetate) and that resulted in the formation of trace amounts of product 4-61 (entry 3). Next, the reaction was performed as dry as possible by using a high purity bottle of PPh₃ in the dry box. This was done for 12, 25, and 50 mol% of the ligand. We found that 12 mol% of PPh₃ gave nearly full conversion at 90% (entry 4), whereas the other two trials gave only traces of desired product (entries 5 and 6). Therefore, we decided to reproduce the trial with 12 mol% in triplicate; however, this resulted in only traces of desired product 4-61 for each trial (entries 7–9).

Table 4.14: Reproducibility screen for the reductive cyclization of compound 5-55.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>X</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh₃(CF₃)₅</td>
<td>12</td>
<td>-50% conversion at 24 h</td>
</tr>
<tr>
<td>2</td>
<td>PPh₃(CF₃)₅</td>
<td>12</td>
<td>-33% conversion at 24 h</td>
</tr>
<tr>
<td>3</td>
<td>PPh₃</td>
<td>50</td>
<td>-mostly 4-55 with trace 4-61 by 3 h</td>
</tr>
<tr>
<td>4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>PPh₃</td>
<td>12</td>
<td>-over 90% conversion by 2 h</td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>PPh₃</td>
<td>25</td>
<td>-mostly 4-55 with trace 4-61 by 5 h</td>
</tr>
<tr>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>PPh₃</td>
<td>50</td>
<td>-mostly 4-55 with trace 4-61 by 5 h</td>
</tr>
<tr>
<td>7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>PPh₃</td>
<td>12</td>
<td>-mostly 4-55 with trace 4-61 by 5 h</td>
</tr>
<tr>
<td>8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>PPh₃</td>
<td>12</td>
<td>-mostly 4-55 with trace 4-61 by 5 h</td>
</tr>
<tr>
<td>9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>PPh₃</td>
<td>12</td>
<td>-mostly 4-55 with trace 4-61 by 5 h</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were performed on 75 mg scale at 0.01 M. <sup>b</sup> Observations by LC-MS. <sup>c</sup> Reactions were performed with new high purity PPh₃ and weighed out in a glove box.
Although disappointing, we were now back at square one and trying to understand what was causing the inability of the catalyst to turnover. Based on these observations, we hypothesized that the nature of the catalytic species upon the start of the reaction is critical and either in an active state or is inactive similar to the observations mentioned by the Buchwald group. They note the inefficiency of *in situ* reduction of Pd(II) complexes for a range of coupling reactions. With the development of precatalyst systems, the Buchwald group has been highly successful at expanding the scope of palladium cross couplings.45,46 Currently in their 4th generation, these precatalysts are N-methyl-2-aminobiphenyl palladacycles (Scheme 4.17). Base promotes the reductive elimination of L Pd G4 to form an equivalent of properly ligated active catalyst and N-methyl carbazole as a byproduct. We are currently in the process of screening these precatalysts; however, initial investigations have been met with disappointing results (Table 4.15). Using both PCy3 Pd G4 and SPhos Pd G4 as precatalysts gave trace amounts of 4-61 (entries 1 and 2). Although discouraging, there are still a number of these precatalysts to screen, and we hope to proceed with this moving forward as part of our ongoing optimization and understanding of this reaction.

Scheme 4.17: Generation of active catalyst from 4th generation Buchwald pre-catalysts.
Table 4.15: Precatalyst screen for the reductive cyclization of compound 4-55.

Regardless of the precatalyst screening results, supplementary investigations were done to further examine the oxidative addition. Protection of fluorinated compound 4-42 gave compound 4-74 in quantitative yield (Table 4.16). Subjecting 4-74 to the reaction conditions without PPh₃ ligand gave only starting material after 6 hours (entry 1). Using 12 mol% of PPh₃ gave trace amounts of 4-74 (entry 2). This further supports the earlier conclusion that the variable conversion may not be due to the inability of the catalyst to efficiently undergo oxidative addition (Table 4.10).
This is the current extent of our investigations into the reductive cyclization process. From the MCR and $^{p}$Tol-protection, we obtain compound 4-55 in 91% yield (Scheme 4.18). Under the current optimized conditions for the reductive Heck, we obtained compound 4-61 in 59% yield. With the limited amount of compound 4-61 in hand, subsequent RCM gave compound 4-60 in 61% yield. Finally, treatment of 4-60 with SeO$_2$ gave one diastereomer as the major product. We believe that to be the $\alpha$-epimer (shown), as the C11 protected alcohol likely blocks the $\beta$-face of the alkene making the $\alpha$-face more accessible. We are currently investigating this to elucidate the relative stereochemistry of compound 4-76. Either way, the stereocenter at C11 should be invertible and give access to the opposite epimer. From compound 4-76, we are three steps away from haemanthamine. We require a methylation of the C3 hydroxyl group, a reduction of the carbonyl, and a hydrolysis of the C11 protecting group. This gives an eight step synthesis over all from the MCR.
Scheme 4.18: Current synthetic route from MCR.

4.4: Project Direction and Outlook

As a streamlined process for accessing complex biologically relevant alkaloids, there are a number of directions and applications for this project. An elegant aspect of this synthesis is that each step provides a particular service to the construction of haemanthamine as opposed to previously reported routes that require multiple steps to accomplish the same goal. For instance, the MCR rapidly builds molecular complexity from simple building blocks to provide all of the atoms needed for the natural product scaffold to take shape. The reductive cyclization, regardless of its current limitations, provides the three contiguous stereocenters in one step with the proper relative stereochemistry found in numerous members of the crinine-type subclass, including haemanthamine (highlighted in red, Figure 4.4). The RCM not only completes the scaffold in 4 steps from the MCR, but it also provides the olefin found in numerous members of this subclass (highlighted in green). Finally, the allylic hydroxylation diastereoselectively gives the desired α-
epimer found in haemanthamine that can be inverted to provide access to other members of the crinine-type subclass (highlighted in blue). This demonstrates not only the efficiency of the synthesis, but it can also allow access to many natural product members of this scaffold some of whose total synthesis may not have been previously reported.

**Figure 4.4:** Applications of our synthetic route for the synthesis of other crinine-type alkaloids.

Along with these efforts to access other members of the crinine-type subclass, we hope to further investigate the biological capabilities of these molecules. As opposed to the complexity and length of previously reported syntheses of haemanthamine that do not amend themselves to the development of analogs for a drug discovery program, our route has the advantage of having each step provide a necessary bond connection without interfering with the rest of the molecule. Therefore, the synthesis allows for the diversification of haemanthamine at numerous sites on the molecule for the development of analogs to further probe the SAR (Scheme 4.19). Furthermore, benzylic oxidation should allow access to analogs of haemanthidine which is known to be
converted to pretazettine upon treatment with MeI. Haemanthidine shows similar biological activity to haemanthamine, and pretazettine has been studied for its antiviral and cytotoxic affects against numerous cancer cell lines, including fibroblastic tumors and leukemia. It is also known that treatment of haemanthamine with SOCl\textsubscript{2} leads to intermediate 4-77 (some substitutions are removed for clarity). The alkene of compound 4-77 is then attacked by chloride causing a rearrangement to the montanine-type subclass. Activation of the alcohol followed by addition of various nucleophiles could be an attractive route for further diversification of montanine. As mentioned, montanine has been studied for its antiarthritic and neurological properties. It has also undergone preliminary SAR studies for its anticancer activity against a number of apoptosis-resistant cell lines. As a result, we hope to investigate the synthesis of haemanthamine and its biological studies as an intermediate in an ensuing ‘divergent drug discovery’ program.

![Scheme 4.19: Divergent drug discovery approach to analogs of other Amaryllidaceae alkaloids.](image-url)
4.5: Conclusions

Efforts towards the total synthesis of haemanthamine and related crinine-type alkaloids have been described. The approached route rapidly builds molecular complexity using an efficient one-pot MCR for the synthesis of hydroxy-dihydro-pyrrolones. A subsequent reductive cyclization diastereoselectively provides three contiguous stereocenters in one step. A ring-closing metathesis gives the natural product scaffold in four steps from the MCR. Although limitations exist, the current route is three steps away from haemanthamine and eight steps overall. The efficient stereoselective synthesis should allow for further investigations into the biological capabilities of these natural products as novel lead therapeutics for the treatment of life-threatening cancers.
4.6: Experimental Section

General Considerations. All reactions were performed under a nitrogen atmosphere. All reagents were purchased through Acros Organics or Sigma-Aldrich and used as received. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F254 plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a KMnO₄ solution (1.5 g of KMnO₄, 10 g of K₂CO₃, and 1.25 mL of a 10% NaOH solution in 200 mL of water). Reactions were also monitored by LC-MS analysis (Shimadzu LC-MS 2020 with Kinetex 2.6 mm C18 50 × 2.10 mm). Flash chromatography on SiO₂ was used to purify the crude reaction mixtures and performed on a Biotage Isolera using Biotage cartridges and linear gradients. 

¹H and ¹³C NMR spectra were obtained on a Varian Mercury-VX 300, a Varian Mercury-VX 400, Varian Mercury-Plus 300, or a Bruker NEO Ascend 500 instrument in CDCl₃ unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard (CDCl₃ = 7.26 ppm for ¹H, CDCl₃ = 77.16 ppm for ¹³C). ¹H NMR spectra were run at 300, 400 or 500 MHz and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, bs = broad singlet), number of protons, and coupling constant(s). ¹³C NMR spectra were run at 100 or 125 MHz using a proton-decoupled pulse sequence with a d₁ of 1 second unless otherwise noted and are tabulated by observed peak. Infrared spectra were determined on a Jasco FT/IR-4100 spectrometer. High-resolution mass spectra were obtained on a Thermo Fisher Scientific, Exactive Plus mass spectrometer (ion trap) using Heated Electrospray Ionization (HESI). Melting points were determined by using a Thomas Hoover capillary melting point apparatus.
General Protocol A: Synthesis of hydroxy-dihydro-pyrrolones. To a solution of pyruvic acid ester derivative in CH$_3$CN (0.5 M) at 0 °C was added aldehyde derivative (1.1 equiv) followed by amine derivative (1.1 equiv). The solution was stirred until pyruvic ester was consumed. The reaction was concentrated in vacuo, and the crude mixture was triturated in CH$_3$CN (unless otherwise noted), filtered, and dried to obtain the pure product.

(E)-1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-5-(but-3-en-1-yl)-3-hydroxy-4-styryl-1,5-dihydro-2H-pyrrol-2-one (4-39); Prepared from methyl (E)-2-oxo-5-phenylpent-4-enoate (2.2 g, 11 mmol), 4-pentenal (1.0 g, 12 mmol), and 6-bromo-1,3-benzodioxole-5-methylamine (2.8 g, 12 mmol) according to general procedure A to yield 4.3 g (85%) of 4-39 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 9.07 (s, 1 H), 7.46 (d, $J = 7.3$ Hz, 2 H), 7.33 (t, $J = 7.5$ Hz, 2 H), 7.25 (t, $J = 7.3$ Hz, 1 H), 7.02 (d, $J = 17$ Hz, 1 H), 7.01 (s, 1 H), 6.84 (s, 1 H), 6.81 (d, $J = 17$ Hz, 1 H), 5.96 (d, $J = 1.3$ Hz, 2 H), 5.70 (ddt, $J = 17$, 10, and 6.6 Hz, 1 H), 5.09 (d, $J = 16$ Hz, 1 H), 4.98–4.91 (m, 2 H), 4.41 (d, $J = 16$ Hz, 1 H), 4.25 (t, $J = 3.4$ Hz, 1 H), 2.14–1.95 (m, 2 H), 1.80–1.69 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 167.8, 148.2, 148.1, 143.4, 137.5, 137.2, 131.3, 129.2, 128.8, 128.1, 126.6, 122.2, 117.6, 115.3, 113.8, 112.7, 110.0, 102.1, 56.7, 44.0, 28.6, 25.8; IR (neat) 3424, 2930, 1658, 1503, 1479, 1451, 1396, 1235, 1038, 964 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{24}$H$_{23}$BrNO$_4$ [M + H]$^+$ 468.0805, found 468.0809; mp = 162–165 °C.
(E)-5-(But-3-en-1-yl)-3-hydroxy-1-((6-iodobenzod[1,3]dioxol-5-yl)methyl)-4-styryl-1,5-dihydro-2H-pyrrol-2-one (4-70); Prepared from methyl (E)-2-oxo-5-phenylpent-4-enoate (0.19 g, 0.93 mmol), 4-pentenal (0.088 g, 1.0 mmol), and 6-iodo-1,3-benzodioxole-5-methylamine (0.34 g, 1.0 mmol) according to general procedure A to yield 0.41 g (86%) of 4-70 as a white solid: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 10.35\) (s, 1 H), 7.50 (d, \(J = 7.1\) Hz, 2 H), 7.40 (s, 1 H), 7.33 (t, \(J = 7.5\) Hz, 2 H), 7.23 (t, \(J = 7.3\) Hz, 2 H), 7.08 (d, \(J = 17\) Hz, 1 H), 6.80 (s, 1 H), 6.80 (d, \(J = 17\) Hz, 1 H), 6.05 (d, \(J = 4.6\) Hz, 2 H), 5.67 (ddt, \(J = 17, 10,\) and 6.5 Hz, 1 H), 4.92–4.85 (m, 2 H), 4.25 (d, \(J = 16\) Hz, 2 H), 1.94–1.92 (m, 2 H), 1.61–1.56 (m, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 166.3, 148.4, 147.8, 144.5, 137.8, 137.2, 132.6, 129.3, 128.7, 127.7, 126.3, 120.8, 118.2, 117.9, 115.0, 108.9, 102.0, 86.9, 55.4, 48.3, 28.0, 25.5; IR (neat) 3165, 3036, 2917, 1656, 1477, 1445, 1393, 1270, 1231, 1035, 917, 691 cm\(^{-1}\); HRMS m/z [M + H]\(^+\) calculated for C\(_{24}\)H\(_{23}\)INO\(_4\) [M + H]\(^+\) 516.0666, found 516.0667; mp = 189–191 °C.

(E)-1-(Benzod[1,3]dioxol-5-ylmethyl)-5-(but-3-en-1-yl)-3-hydroxy-4-styryl-1,5-dihydro-2H-pyrrol-2-one (4-49); Prepared from methyl (E)-2-oxo-5-phenylpent-4-enoate (1.0 g, 4.9 mmol), 4-pentenal (0.47 g, 5.4 mmol), and piperonylamine (0.84 g, 5.4 mmol) according to general
procedure A to yield 1.51 g (79%) of 4-49 as a white solid: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 9.19 (s, 1 H), 7.48 (d, $J$ = 7.6 Hz, 2 H), 7.36 (t, $J$ = 7.6 Hz, 2 H), 7.28 (d, $J$ = 7.9 Hz, 1 H), 7.05 (d, $J$ = 17 Hz, 1 H), 6.83–6.81 (m, 4 H), 5.98 (s, 2 H), 5.73 (ddt, $J$ = 13, 10, and 6.6 Hz, 1 H), 5.19 (d, $J$ = 15 Hz, 1 H), 4.98 (d, $J$ = 17 Hz, 1 H), 4.96 (d, $J$ = 9.5 Hz, 1 H), 4.25 (s, 1 H), 4.07 (d, $J$ = 15 Hz, 1 H), 2.03 (dt, $J$ = 9.6 and 5.7 Hz, 2 H), 1.87–1.81 (m, 1 H), 1.79–1.69 (m, 1 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 167.5, 148.2, 147.4, 143.6, 137.5, 137.3, 131.0, 130.6, 128.8, 128.0, 126.6, 121.9, 121.6, 117.6, 115.3, 108.8, 108.5, 101.3, 56.2, 44.2, 28.6, 25.7; IR (neat) 3083, 2933, 2896, 1681, 1651, 1483, 1439, 1396, 1237, 1032, 917 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{24}$H$_{24}$NO$_4$ [M + H]$^+$ 390.1700, found 390.1702; mp = 167–169 °C.

(E)-1-(2-Bromobenzyl)-5-(but-3-en-1-yl)-3-hydroxy-4-styryl-1,5-dihydro-2H-pyrrol-2-one (4-40): Prepared from methyl (E)-2-oxo-5-phenylpent-4-enoate (1.0 g, 4.9 mmol), 4-pentenal (0.47 g, 5.4 mmol), and 2-bromobenzylamine (1.0 g, 5.4 mmol) according to general procedure A to yield 1.9 g (93%) of 4-40 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.59 (d, $J$ = 7.7 Hz, 1 H), 7.46 (d, $J$ = 7.4 Hz, 2 H), 7.35–7.29 (m, 4 H), 7.29–7.23 (m, 1 H), 7.18 (td, $J$ = 7.1 and 6.2 Hz, 1 H), 7.04 (d, $J$ = 17 Hz, 1 H), 6.81 (d, $J$ = 17 Hz, 1 H), 5.70 (ddt, $J$ = 17, 10, and 6.6 Hz, 1 H), 5.21 (d, $J$ = 16 Hz, 1 H), 4.97–4.92 (m, 2 H), 4.49 (d, $J$ = 16 Hz, 1 H), 4.27 (t, $J$ = 3.3 Hz, 1 H), 2.14–2.06 (m, 1 H), 2.04–1.95 (m, 1 H), 1.86–1.70 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 167.9, 143.5, 137.4, 137.2, 135.9, 133.1, 131.2, 130.1, 129.5, 128.8, 128.1, 128.1, 128.1, 126.6, 123.3, 122.3, 117.6, 115.4, 56.8, 44.1, 28.6, 25.9; IR (neat) 3154, 2921, 1657, 1450, 1397, 1274, 966,
749, 693 cm\(^{-1}\); HRMS \textit{m/z} [M + H]\(^+\) calculated for C\(_{23}\)H\(_{23}\)BrNO\(_2\) [M + H]\(^+\) 424.0907, found 424.0905; mp = 170–172 °C.

(E)-1-(2-Bromo-6-fluorobenzyl)-5-(but-3-en-1-yl)-3-hydroxy-4-styryl-1,5-dihydro-2H-pyrrol-2-one (4-41); Prepared from methyl (E)-2-oxo-5-phenylpent-4-enoate (0.69 g, 3.4 mmol), 4-pentenal (0.32 g, 3.7 mmol), and 2-bromo-6-fluorobenzylamine (0.79 g, 3.7 mmol) according to general procedure A to yield 1.2 g (80%) of 4-41 as a white solid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.45–7.42\) (m, 3 H), 7.32 (t, \(J = 7.5\) Hz, 2 H), 7.26–7.19 (m, 2 H), 7.09 (t, \(J = 8.9\) Hz, 1 H), 6.98 (d, \(J = 17\) Hz, 1 H), 6.76 (d, \(J = 17\) Hz, 1 H), 5.70 (ddt, \(J = 17, 10,\) and \(6.6\) Hz, 1 H), 5.25 (dd, \(J = 15\) and 2.2 Hz, 1 H), 4.98–4.91 (m, 2 H), 4.58 (d, \(J = 15\) Hz, 1 H), 4.05 (t, \(J = 3.2\) Hz, 1 H), 2.13–2.05 (m, 1 H), 1.98–1.90 (m, 1 H), 1.81–1.68 (m, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 167.0,\) 163.2, 160.7, 143.1, 137.5, 137.2, 131.2, 130.8, 130.7, 129.4, 128.8, 128.1, 126.6, 123.5, 123.4, 121.4, 117.5, 115.3, 56.6, 38.6, 28.5, 25.6; IR (neat) 3168, 2916, 2848, 1673, 1657, 1448, 1438, 1394, 966, 778, 693 cm\(^{-1}\); HRMS \textit{m/z} [M + H]\(^+\) calculated for C\(_{23}\)H\(_{22}\)BrFNO\(_2\) [M + H]\(^+\) 442.0813, found 442.0813; mp = 192–194 °C.
(E)-1-(2-Bromo-4-fluorobenzyl)-5-(but-3-en-1-yl)-3-hydroxy-4-styryl-1,5-dihydro-2H-pyrrol-2-one (4-42); Prepared from methyl (E)-2-oxo-5-phenylpent-4-enoate (0.69 g, 3.4 mmol), 4-pentenal (0.32 g, 3.7 mmol), and 2-bromo-4-fluorobenzylamine (0.79 g, 3.7 mmol) according to general procedure A to yield 1.3 g (89%) of 4-42 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 9.18 (s, 1 H), 7.46 (d, $J$ = 7.3 Hz, 2 H), 7.36–7.24 (m, 5 H), 7.05 (td, $J$ = 7.7 and 2.6 Hz, 1 H), 7.02 (d, $J$ = 16 Hz, 1 H), 6.81 (d, $J$ = 17 Hz, 1 H), 5.69 (ddt, $J$ = 17, 10, and 6.6 Hz, 1 H), 5.15 (d, $J$ = 16 Hz, 1 H), 4.97–4.92 (m, 2 H), 4.45 (d, $J$ = 16 Hz, 1 H), 4.26 (t, $J$ = 3.2 Hz, 1 H), 2.14–1.96 (m, 2 H), 1.85–1.78 (m, 1 H), 1.76–1.66 (m, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 167.9, 163.1, 160.6, 143.4, 137.3, 137.1, 132.0, 131.4, 131.4, 131.3, 128.9, 128.2, 126.6, 122.3, 120.4, 120.2, 117.5, 115.4, 56.8, 43.5, 28.6, 25.8; IR (neat) 3169, 2918, 2848, 1657, 1488, 1450, 1394, 1226, 749, 693 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{23}$H$_{23}$BrFNO$_2$ [M + H]$^+$ 422.0813, found 442.0813; mp = 189–190 °C.

(E)-1-(2-Bromo-4-methylbenzyl)-5-(but-3-en-1-yl)-3-hydroxy-4-styryl-1,5-dihydro-2H-pyrrol-2-one (4-43); Prepared from methyl (E)-2-oxo-5-phenylpent-4-enoate (0.51 g, 2.5 mmol), 4-pentenal (0.24 g, 2.8 mmol), and 2-bromo-4-methylbenzylamine (0.55 g, 2.8 mmol) according
to general procedure A to yield 0.89 g (81%) of 4-43 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) \( \delta = 10.34 \) (s, 1 H), 7.50 (d, \( J = 8.2 \) Hz, 3 H), 7.33 (t, \( J = 7.6 \) Hz, 2 H), 7.24 (d, \( J = 7.4 \) Hz, 1 H), 7.20 (d, \( J = 7.4 \) Hz, 1 H), 7.14 (d, \( J = 7.8 \) Hz, 1 H), 7.07 (d, \( J = 17 \) Hz, 1 H), 6.79 (d, \( J = 17 \) Hz, 1 H), 5.67 (ddt, \( J = 17, 10, \) and 6.5 Hz, 1 H), 4.88 (d, \( J = 15 \) Hz, 1 H), 4.86–4.85 (m, 2 H), 4.32 (d, \( J = 16 \) Hz, 1 H), 4.20 (s, 1 H), 2.28 (s, 3 H), 1.95–1.90 (m, 2 H), 1.62–1.56 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) \( \delta = 166.1, 144.4, 139.3, 137.7, 137.1, 133.0, 133.0, 129.7, 129.3, 128.8, 128.7, 127.6, 126.2, 122.2, 120.8, 117.9, 114.9, 55.4, 43.3, 27.8, 25.5, 20.1; IR (neat) 3150, 2926, 1670, 1651, 1445, 1390, 1271, 969, 690 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{24}$H$_{25}$BrNO$_2$ [M + H]$^+$ 438.1063, found 438.1074; mp = 187–189 °C.

(E)-1-(2-Bromo-5-methoxybenzyl)-5-(but-3-en-1-yl)-3-hydroxy-4-styril-1,5-dihydro-2H-pyrrol-2-one (4-44): Prepared from methyl (E)-2-oxo-5-phenylpent-4-enoate (0.26 g, 1.3 mmol), 4-pentenal (0.12 g, 1.4 mmol), and 2-bromo-5-methoxybenzylamine (0.30 g, 1.4 mmol) according to general procedure A to yield 0.38 g (66%) of 4-44 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) \( \delta = 9.11 \) (s, 1 H), 7.55 (d, \( J = 7.3 \) Hz, 2 H), 7.52 (d, \( J = 8.8 \) Hz, 1 H), 7.34 (t, \( J = 7.5 \) Hz, 2 H), 7.25 (t, \( J = 7.3 \) Hz, 1 H), 7.11 (d, \( J = 17 \) Hz, 1 H), 6.97 (d, \( J = 17 \) Hz, 1 H), 6.92 (d, \( J = 3.0 \) Hz, 1 H), 6.86 (dd, \( J = 8.8 \) and 3.1 Hz, 1 H), 5.72 (ddt, \( J = 17, 10, \) and 6.6 Hz, 1 H), 4.99 (d, \( J = 16 \) Hz, 1 H), 4.91 (dd, \( J = 17 \) and 1.9 Hz, 1 H), 4.86 (dd, \( J = 10 \) and 0.95 Hz, 1 H), 4.46 (d, \( J = 16 \) Hz, 1 H), 4.38 (t, \( J = 3.4 \) Hz, 1 H), 3.76 (s, 3 H), 2.12–2.07 (m, 2 H), 1.79–1.70 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) \( \delta = 167.6, 160.5, 144.9, 138.7, 138.5, 138.4, 134.5, 131.6, 129.6, 128.6, 127.3,
122.2, 118.5, 116.7, 115.7, 115.2, 113.7, 57.4, 55.9, 44.9, 29.3, 26.7; IR (neat) 3146, 3079, 3004, 2933, 1651, 1442, 1390, 1271, 1234, 745, 690 cm⁻¹; HRMS m/z [M + H]⁺ calculated for C₂₄H₂₅BrNO₃ [M + H]⁺ 454.1012, found 454.1020; mp = 138–140 °C.

(E)-1-[(2-Bromothiophen-3-yl)methyl]-5-(but-3-en-1-yl)-3-hydroxy-4-styril-1,5-dihydro-2H-pyrrol-2-one (4-45): Prepared from methyl (E)-2-oxo-5-phenylpent-4-enoate (0.92 g, 4.5 mmol), 4-pentenal (0.43 g, 4.9 mmol), and 2-bromo-3-aminomethylthiophene (1.0 g, 4.9 mmol) according to general procedure A to yield 0.27 g (14%) of 4-45 as a white solid: ¹H NMR (400 MHz, CDCl₃) δ = 9.07 (s, 1 H), 7.47 (d, J = 8.0 Hz, 2 H), 7.34 (t, J = 7.6 Hz, 2 H), 7.26 (d, J = 5.5 Hz, 2 H), 7.01 (d, J = 17 Hz, 1 H), 6.96 (d, J = 5.7 Hz, 1 H), 6.81 (d, J = 17 Hz, 1 H), 5.68 (ddt, J = 13, 10, and 6.7 Hz, 1 H), 4.99 (d, J = 15 Hz, 1 H), 4.95–4.91 (m, 2 H), 4.32 (d, J = 15 Hz, 1 H), 4.21 (t, J = 3.0 Hz, 1 H), 2.17–2.08 (m, 1 H), 2.05–1.96 (m, 1 H), 1.82–1.60 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ = 167.5, 143.4, 137.5, 137.2, 136.6, 131.3, 128.8, 128.5, 128.1, 126.9, 126.6, 122.1, 117.5, 115.3, 111.2, 56.9, 38.7, 28.5, 25.7; IR (neat) 3165, 2918, 2848, 1657, 1450, 1394, 1274, 749, 690 cm⁻¹; HRMS m/z [M + H]⁺ calculated for C₂₁H₂₁BrNO₅S [M + H]⁺ 430.0471, found 430.0474; mp = 62–65 °C.
1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-3-hydroxy-5-pentyl-4-phenyl-1,5-dihydro-2H-pyrrol-2-one (4-64); Prepared from methyl 2-oxo-3-phenylpropanoate (0.30 g, 1.7 mmol), hexanal (0.19 g, 1.9 mmol), and 6-bromo-1,3-benzodioxole-5-methylamine (0.43 g, 1.9 mmol) according to general procedure A to yield 0.53 g (68%) of 4-64 as a white solid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.27 (s, 1 \text{ H}), 7.62 (d, J = 8.4 \text{ Hz}, 2 \text{ H}), 7.38 (t, J = 7.7 \text{ Hz}, 2 \text{ H}), 7.27 (t, J = 7.4 \text{ Hz}, 1 \text{ H}), 7.01 (s, 1 \text{ H}), 6.84 (s, 1 \text{ H}), 5.97 (s, 2 \text{ H}), 5.09 (d, J = 16 \text{ Hz}, 1 \text{ H}), 4.45 (s, 1 \text{ H}), 4.43 (d, J = 15 \text{ Hz}, 1 \text{ H}), 2.01–1.91 (m, 1 \text{ H}), 1.84–1.76 (m, 1 \text{ H}), 1.15–1.00 (m, 4 \text{ H}), 0.91–0.85 (m, 2 \text{ H}), 0.75 (t, J = 7.1 \text{ Hz}, 3 \text{ H}); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 167.9, 148.1, 142.0, 131.6, 129.3, 128.7, 127.7, 127.5, 122.1, 113.7, 112.7, 109.9, 102.1, 57.1, 44.1, 31.7, 28.9, 22.5, 20.8, 14.1; IR (neat) 3184, 2930, 2860, 1664, 1503, 1480, 1453, 1389, 1236, 1038, 932, 763, 695 cm\(^{-1}\); HRMS \(m/z\) [M + H]\(^+\) calculated for C\(_{23}\)H\(_{25}\)BrNO\(_4\) [M + H]\(^+\) 458.0962, found 458.0963; mp = 179–181 °C.

1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-5-(but-3-en-1-yl)-3-hydroxy-4-phenyl-1,5-dihydro-2H-pyrrol-2-one (4-66); Prepared from methyl 2-oxo-3-phenylpropanoate (0.50 g, 2.8 mmol), 4-pentenal (0.27 g, 3.1 mmol), and 6-bromo-1,3-benzodioxole-5-methylamine (0.71 g, 3.1 mmol) according to general procedure A to yield 0.73 g (59%) of 4-66 as a white solid: \(^1\)H NMR


(400 MHz, CDCl$_3$) $\delta =$ 8.67 (s, 1H), 7.63 (d, $J =$ 7.3 Hz, 2 H), 7.39 (t, $J =$ 7.7 Hz, 2 H), 7.27 (t, $J =$ 7.4 Hz, 1 H), 7.01 (s, 1 H), 6.86 (s, 1 H), 5.96 (s, 2 H), 5.59 (ddt, $J =$ 19, 9.7, and 6.5 Hz, 1 H), 5.11 (d, $J =$ 16 Hz, 1 H), 4.88–4.83 (m, 2 H), 4.49 (t, $J =$ 3.5 Hz, 1 H), 4.44 (d, $J =$ 16 Hz, 1 H), 4.33 (d, $J =$ 16 Hz, 1 H), 4.21 (t, $J =$ 3.2 Hz, 1 H), 2.15–2.05 (m, 1 H), 2.01–1.92 (m, 1 H), 1.76–1.69 (m, 2 H), 1.07 (s, 9 H), 0.36 (s, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta =$ 168.0, 148.2, 148.1, 142.3, 137.4, 131.6, 129.2, 128.7, 127.7, 127.5 121.9, 115.1, 113.8, 112.8, 110.0, 102.1, 56.8, 44.2, 28.3, 25.8; IR (neat) 3184, 2979, 2932, 1664, 1503, 1480, 1453, 1389, 1236, 1038, 931, 763, 696 cm$^{-1}$; HRMS $m/z$ [M + H]$^+$ calculated for C$_{22}$H$_{21}$BrNO$_4$ [M + H]$^+$ 442.0649, found 442.0648; mp = 168–170 °C.

(E)-1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-5-(but-3-en-1-yl)-3-((tert-butyldimethylsilyl)oxy)-4-styryl-1,5-dihydro-2H-pyrrol-2-one (4-50); To a solution of 4-39 (0.88 g, 1.9 mmol) in CH$_2$Cl$_2$ (3.8 mL) was added imidazole (0.15 g, 2.3 mmol) followed by TBSCl (0.35 g, 2.3 mmol), and the solution was stirred for 30 min. The reaction was concentrated in vacuo, and the crude residue was purified by flash chromatography on silica gel (hexanes–EtOAc: 0–4%) to yield 0.99 g (91%) of 4-50 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 7.42 (d, $J =$ 7.2 Hz, 2 H), 7.35 (t, $J =$ 7.5 Hz, 2 H), 7.27 (t, $J =$ 7.3 Hz, 1 H), 7.01 (d, $J =$ 16 Hz, 1 H), 6.99 (s, 1 H), 6.79 (s, 1 H), 6.72 (d, $J =$ 17 Hz, 1 H), 5.96 (s, 2 H), 5.70 (dtd, $J =$ 17, 6.5, and 4.2 Hz, 1 H), 5.03 (d, $J =$ 16 Hz, 1 H), 4.97–4.91 (m, 2 H), 4.33 (d, $J =$ 16 Hz, 1 H), 4.21 (t, $J =$ 3.2 Hz, 1 H), 2.15–2.05 (m, 1 H), 2.01–1.92 (m, 1 H), 1.76–1.69 (m, 2 H), 1.07 (s, 9 H), 0.36 (s, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta =$ 167.2, 148.0, 143.9, 137.6, 137.0, 130.8, 129.7, 128.9, 128.6, 128.2, 126.5,
117.6, 115.2, 113.7, 112.7, 109.7, 102.0, 55.5, 43.7, 28.8, 25.9, 25.8, 18.7; IR (neat) 3028, 2930, 2858, 1695, 1638, 1479, 1236, 1038, 835, 787 cm$^{-1}$; HRMS $m/z$ [M + H]$^+$ calculated for C$_{30}$H$_{37}$BrNO$_4$Si [M + H]$^+$ 582.1670, found 582.1668; mp = 134–136 °C.

(\textit{E})-1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-5-(but-3-en-1-yl)-2-oxo-4-styryl-2,5-dihydro-1H-pyrrol-3-yl acetate (4-51); To a solution of 4-39 (0.5 g, 1.1 mmol) in CH$_2$Cl$_2$ (2.1 mL) was added K$_2$CO$_3$ (0.15 g, 1.1 mmol) followed by Ac$_2$O (0.11 g, 1.1 mmol), and the solution was stirred for 1 h. The reaction was concentrated \textit{in vacuo}, and the crude residue was purified by flash chromatography on silica gel (hexanes–EtOAc: 10–30%) to yield 0.52 g (95%) of 4-51 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.45$ (d, $J = 7.1$ Hz, 2 H), 7.37–7.29 (m, 3 H), 6.98 (s, 1 H), 6.87 (s, 1 H), 6.82 (d, $J = 17$ Hz, 1 H), 6.77 (d, $J = 17$ Hz, 1 H), 5.94 (s, 2 H), 5.68 (ddt, $J = 17$, 9.9, and 6.5 Hz, 1 H), 5.02 (d, $J = 16$ Hz, 1 H), 4.96–4.90 (m, 2 H), 4.38 (t, $J = 3.8$ Hz, 1 H), 4.37 (d, $J = 15$ Hz, 1 H), 2.38 (s, 3 H), 2.23–2.14 (m, 1 H), 2.01–1.92 (m, 1 H), 1.81–1.75 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 167.6$, 165.0, 148.1, 148.0, 139.2, 138.0, 137.1, 135.8, 135.0, 129.3, 129.2, 128.9, 127.0, 115.9, 115.4, 113.7, 112.5, 110.0, 101.9, 56.5, 43.8, 28.8, 25.5, 20.5; IR (neat) 3060, 3036, 2917, 1777, 1698, 1503, 1479, 1366, 1234, 1188, 1038, 930, 742, 692 cm$^{-1}$; HRMS $m/z$ [M + H]$^+$ calculated for C$_{28}$H$_{25}$BrNO$_5$ [M + H]$^+$ 510.0911, found 510.0908; mp = 62–64 °C.
(E)-1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-5-(but-3-en-1-yl)-2-oxo-4-styryl-2,5-dihydro-1H-pyrrol-3-yl pivalate (4-52); To a solution of 4-39 (0.5 g, 1.1 mmol) in CH$_2$Cl$_2$ (2.1 mL) was added imidazole (0.073 g, 1.1 mmol) followed by PivCl (0.13 g, 1.1 mmol), and the solution was stirred for 30 min. The reaction was concentrated in vacuo, and the crude residue was purified by flash chromatography on silica gel (hexanes−EtOAc: 0−15%) to yield 0.59 g (99+% of 4-52 as a yellow solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.44–7.31 (m, 5 H), 6.99 (s, 1 H), 6.87 (s, 1 H), 6.83 (d, $J$ = 17 Hz, 1 H), 6.73 (d, $J$ = 17 Hz, 1 H), 5.95 (s, 2 H), 5.69 (ddt, $J$ = 17, 10, and 6.4 Hz, 1 H), 5.02 (d, $J$ = 16 Hz, 1 H), 4.95 (dd, $J$ = 17 and 1.8 Hz, 1 H), 4.92 (dd, $J$ = 10 and 1.7 Hz, 1 H), 4.37 (d, $J$ = 16 Hz, 1 H), 4.36 (t, $J$ = 3.2 Hz, 1 H), 2.24–2.12 (m, 1 H), 2.02–1.91 (m, 1 H), 1.84–1.79 (m, 2 H), 1.43 (s, 6 H), 1.23 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 184.4, 175.6, 165.1, 148.0, 139.7, 137.7, 137.2, 135.9, 135.0, 129.3, 129.2, 128.9, 127.0, 115.8, 115.3, 113.7, 112.5, 110.0, 102.0, 56.7, 43.7, 39.3, 38.5, 28.7, 27.2, 27.1, 25.5; IR (neat) 3069, 3032, 2975, 1764, 1700, 1479, 1366, 1236, 1095, 1036, 930, 747, 692 cm$^{-1}$; HRMS $m/z$ [M + H]$^+$ calculated for C$_{29}$H$_{31}$BrNO$_5$ [M + H]$^+$ 552.1380, found 552.1380; mp = 38–40 °C.
(E)-1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-5-(but-3-en-1-yl)-2-oxo-4-styryl-2,5-dihydro-1H-pyrrol-3-yl benzoate (4-53); To a solution of 4-39 (0.5 g, 1.1 mmol) in CH$_2$Cl$_2$ (2.1 mL) was added imidazole (0.073 g, 1.1 mmol) followed by BzCl (0.15 g, 1.1 mmol), and the solution was stirred for 19 h. The reaction was concentrated in vacuo, and the crude residue was purified by flash chromatography on silica gel (hexanes–EtOAc: 5–25%) to yield 0.57 g (93%) of 4-53 as a yellow solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 8.24$ (d, $J = 7.7$ Hz, 2 H), 7.66 (t, $J = 7.5$ Hz, 1 H), 7.52 (t, $J = 7.7$ Hz, 2 H), 7.43 (d, $J = 7.8$ Hz, 2 H), 7.33–7.29 (m, 3 H), 7.01 (s, 1 H), 6.94 (s, 1 H), 6.86 (d, $J = 6.3$ Hz, 2 H), 5.97 (s, 2 H), 5.73 (ddt, $J = 17$, 12, and 5.4 Hz, 1 H), 5.08 (d, $J = 15$ Hz, 1 H), 5.01–4.94 (m, 2 H), 4.46 (s, 1 H), 4.43 (d, $J = 16$ Hz, 1 H), 2.29–2.20 (m, 1 H), 2.07–1.99 (m, 1 H), 1.91–1.88 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 165.2$, 163.7, 148.2, 148.1, 139.5, 138.5, 137.3, 135.8, 135.2, 134.1, 130.7, 130.2, 129.3, 128.9, 128.7, 128.3, 127.2, 116.0, 115.5, 113.8, 112.6, 110.2, 102.0, 56.8, 43.9, 29.0, 25.7; IR (neat) 3468, 3062, 2917, 1748, 1700, 1503, 1479, 1450, 1239, 1054, 1038, 1020, 930, 710 cm$^{-1}$; HRMS $m/z$ [M + H]$^+$ calculated for C$_{31}$H$_{26}$BrNO$_5$ [M + H]$^+$ 572.1067, found 572.1062; mp = 61–63 °C.
(E)-1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-5-(but-3-en-1-yl)-2-oxo-4-styryl-2,5-dihydro-1H-pyrrol-3-yl pentafluorobenzoate (4-54); To a solution of 4-39 (0.5 g, 1.1 mmol) in CH₂Cl₂ (2.1 mL) was added imidazole (0.073 g, 1.1 mmol) followed by BzFCl (0.25 g, 1.1 mmol), and the solution was stirred for 19 h. The reaction was concentrated in vacuo, and the crude residue was purified by flash chromatography on reverse phase silica gel (water−CH₃CN: 10−70%) to yield 0.19 g (26%) of 4-54 as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ = 7.46 (d, J = 7.2 Hz, 2 H), 7.37 (d, J = 7.7 Hz, 3 H), 7.01 (s, 1 H), 6.89−6.87 (m, 3 H), 5.97 (s, 2 H), 5.71 (ddt, J = 13, 10, and 6.5 Hz, 1 H), 5.08 (d, J = 15 Hz, 1 H), 4.98 (d, J = 16 Hz, 1 H), 4.94 (d, J = 9.9 Hz, 1 H), 4.46 (s, 1 H), 4.42 (d, J = 16 Hz, 1 H), 2.30−2.21 (m, 1 H), 2.06−1.98 (m, 1 H), 1.87−1.82 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ = 164.6, 148.4, 148.2, 139.4, 138.0, 137.0, 136.6, 135.5, 129.7, 129.1, 127.3, 115.7, 115.2, 113.9, 112.7, 110.2, 102.1, 57.1, 44.1, 28.9, 25.6; IR (neat) 3422, 2917, 2848, 1764, 1702, 1649, 1525, 1503, 1479, 1236, 1194, 1038, 1004, 931, 694 cm⁻¹; HRMS m/z [M + H]⁺ calculated for C₃₁H₂₂BrF₅NO₅ [M + H]⁺ 662.0596, found 662.0584; mp = 63−65 °C.

(E)-1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-5-(but-3-en-1-yl)-2-oxo-4-styryl-2,5-dihydro-1H-pyrrol-3-yl 4-methylbenzoate (4-55); To a solution of 4-39 (2.0 g, 4.3 mmol) in
CH₂Cl₂ (8.5 mL) was added imidazole (1.5 g, 21 mmol) followed by p-TolCl (3.3 g, 21 mmol), and the solution was stirred for 30 min. The reaction was concentrated in vacuo, and the crude residue was purified by flash chromatography on silica gel (hexanes−EtOAc: 0−15%) to yield 2.5 g (99+%) of 4-55 as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ = 8.12 (d, J = 7.8 Hz, 2 H), 7.42 (d, J = 7.6 Hz, 2 H), 7.34−7.28 (m, 5 H), 7.00 (s, 1 H), 6.93 (s, 1 H), 6.88 (d, J = 17 Hz, 1 H), 6.82 (d, J = 17 Hz, 1 H), 5.97 (s, 2 H), 5.73 (ddt, J = 17, 10, and 6.5 Hz, 1 H), 5.07 (d, J = 15 Hz, 1 H), 4.98 (d, J = 17 Hz, 1 H), 4.94 (d, J = 11 Hz, 1 H), 4.45 (t, J = 3.2 Hz, 1 H), 4.42 (d, J = 16 Hz, 1 H), 2.46 (s, 3 H), 2.27−2.19 (m, 1 H), 2.06−1.97 (m, 1 H), 1.90−1.84 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ = 165.3, 163.7, 148.2, 148.1, 145.0, 139.6, 138.3, 137.3, 135.9, 135.0, 130.7, 129.4, 129.2, 128.9, 127.1, 125.5, 116.1, 115.4, 113.8, 112.6, 110.2, 102.0, 56.7, 43.9, 28.9, 25.6, 21.9; IR (neat) 3060, 3034, 2920, 1746, 1700, 1611, 1503, 1479, 1256, 1236, 1177, 1087, 1054, 1038, 1016, 744, 689 cm⁻¹; HRMS m/z [M + H]⁺ calculated for C₃₂H₂₉BrNO₅ [M + H]⁺ 586.1224, found 586.1224; mp = 65−67 °C.

(E)-1-(Benzo[d][1,3]dioxol-5-ylmethyl)-5-(but-3-en-1-yl)-3-((tert-butyldimethylsilyl)oxy)-4-styryl-1,5-dihydro-2H-pyrrol-2-one (4-62): To a solution of 4-49 (1.0 g, 2.6 mmol) in CH₂Cl₂ (5.1 mL) was added imidazole (0.21 g, 3.1 mmol) followed by TBSCl (0.48 g, 3.1 mmol), and the solution was stirred for 30 min. The reaction was concentrated in vacuo, and the crude residue was purified by flash chromatography on silica gel (hexanes−EtOAc: 0−7%) to yield 0.61 g (47%) of 4-62 as a white solid: ¹H NMR (500 MHz, CDCl₃) δ = 7.41 (d, J = 7.5 Hz, 2 H), 7.34 (t, J = 7.6
Hz, 2 H), 7.26 (t, $J = 7.2$ Hz, 1 H), 7.00 (d, $J = 17$ Hz, 1 H), 6.78–6.72 (m, 3 H), 6.68 (d, $J = 17$ Hz, 1 H), 5.94 (s, 2 H), 5.69 (ddt, $J = 17$, 10, and 6.6 Hz, 1 H), 5.10 (d, $J = 15$ Hz, 1 H), 4.96–4.91 (m, 2 H), 4.18 (t, $J = 3.2$ Hz, 1 H), 3.96 (d, $J = 15$ Hz, 1 H), 2.22–2.15 (m, 1 H), 2.06–1.99 (m, 1 H), 1.93–1.81 (m, 2 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 171.8, 165.4, 163.6, 162.8, 160.8, 145.0, 144.5, 139.5, 138.4, 137.1, 135.8, 135.2, 132.3, 130.7, 130.2, 129.4, 129.2, 128.9, 127.8, 1185, 1036, 824, 779 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{30}$H$_{39}$NO$_4$Si [M + H]$^+$ 504.2565, found 504.2576; mp = 111–114 °C.

(E)-1-(2-Bromo-4-fluorobenzyl)-5-((but-3-en-1-yl)-2-oxo-4-styryl-2,5-dihydro-1H-pyrrol-3-yl 4-methylbenzoate (4-74); To a solution of 4-42 (0.50 g, 1.1 mmol) in CH$_2$Cl$_2$ (2.3 mL) was added imidazole (0.39 g, 5.7 mmol) followed by $^{p}$TolCl (0.88 g, 5.7 mmol), and the solution was stirred for 30 min. The reaction was concentrated in vacuo, and the crude residue was purified by flash chromatography on silica gel (hexanes–EtOAc: 5–30%) to yield 0.66 g (99+%%) of 4-74 as a yellow solid: $^1$H NMR (500 MHz, CDCl$_3$) $\delta = 8.11$ (d, $J = 8.1$ Hz, 2 H), 7.98 (d, $J = 8.1$ Hz, 2 H), 7.44–7.40 (m, 3 H), 7.33–7.24 (m, 4 H), 7.04 (t, $J = 9.5$ Hz, 1 H), 6.87 (d, $J = 17$ Hz, 1 H), 6.82 (d, $J = 17$ Hz, 1 H), 5.71 (ddt, $J = 17$, 10, and 6.5 Hz, 1 H), 5.12 (d, $J = 16$ Hz, 1 H), 4.99–4.93 (m, 2 H), 4.47 (d, $J = 16$ Hz, 1 H), 4.45 (s, 1 H), 2.44 (s, 3 H), 2.42 (s, 3 H), 2.22–2.15 (m, 1 H), 2.06–1.99 (m, 1 H), 1.93–1.81 (m, 2 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 171.8, 165.4, 163.6, 162.8, 160.8, 145.0, 144.5, 139.5, 138.4, 137.1, 135.8, 135.2, 132.3, 130.7, 130.2, 129.4, 129.2, 128.9,
127.1, 126.7, 125.5, 123.3, 123.2, 120.1, 119.9, 116.0, 115.5, 115.3, 56.9, 43.3, 28.9, 25.6, 21.8, 21.8; IR (neat) 3049, 2922, 1741, 1692, 1606, 1483, 1413, 1223, 1174, 1051, 1032, 835 cm⁻¹; HRMS m/z [M + H]⁺ calculated for C₃₁H₂₈BrFNO₃ [M + H]⁺ 560.1231, found 560.1234; mp = 60–62 °C.

**General Protocol B: Ring closing metathesis procedure.** To a solution of the substrate in toluene (0.01 M) was added Grubbs II (0.05 mol%), and the solution was submerged in an oil bath at 50 °C until the starting material was consumed. The solvent was concentrated *in vacuo* and the crude residue was purified by flash chromatography unless otherwise noted to obtain the pure product.

![Image of molecule](image)

**1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-3-((tert-butyldimethylsilyl)oxy)-1,6,7,7a-tetrahydro-2H-indol-2-one (4-56);** Prepared from 4-50 (1.0 g, 2.1 mmol) and Grubbs II (0.092 g, 0.11 mmol) according to general procedure B and purified (hexanes–EtOAc: 0–6%) to yield 0.91 g (89%) of 4-56 as a white solid: ¹H NMR (400 MHz, CDCl₃) δ = 6.96 (s, 1 H), 6.77 (s, 1 H), 6.45 (d, J = 9.7 Hz, 1 H), 5.94 (s, 2 H), 5.87 (dt, J = 9.3 and 3.9 Hz, 1 H), 4.78 (d, J = 16 Hz, 1 H), 4.50 (d, J = 16 Hz, 1 H), 3.74 (dd, J = 13 and 4.1 Hz, 1 H), 2.38–2.17 (m, 3 H), 1.37–1.27 (m, 1 H), 0.98 (s, 9 H), 0.27 (s, 6 H); IR (neat) 3492, 3038, 2952, 2928, 2855, 1693, 1662, 1594, 1503, 1480, 1254, 1237, 1061, 1038, 838, 788 cm⁻¹; HRMS m/z [M + H]⁺ calculated for C₂₂H₂₉BrNO₄Si [M + H]⁺ 478.1044, found 478.1047; mp = 115–117 °C.
1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-2-oxo-2,6,7,7a-tetrahydro-1H-indol-3-yl acetate (4-57); Prepared from 4-51 (1.0 g, 2.1 mmol) and Grubbs II (0.092 g, 0.11 mmol) according to general procedure B and purified (hexanes–EtOAc: 10–40%) to yield 0.58 g (67%) of 4-57 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 6.94$ (s, 1 H), 6.83 (s, 1 H), 6.33 (dd, $J = 9.8$ and 2.4 Hz, 1 H), 6.07 (dd, $J = 9.4$ and 5.7 Hz, 1 H), 5.93 (d, $J = 3.8$ Hz, 2 H), 4.80 (d, $J = 16$ Hz, 1 H), 4.52 (d, $J = 16$ Hz, 1 H), 3.90 (dd, $J = 13$ and 4.2 Hz, 1 H), 2.43–2.22 (m, 3 H), 2.30 (s, 3 H), 1.49–1.40 (m, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 167.7$, 166.1, 148.0, 148.0, 137.5, 135.6, 133.1, 129.9, 118.2, 113.4, 112.4, 109.9, 102.0, 56.0, 44.4, 28.7, 25.3, 20.6; IR (neat) 3043, 2920, 1777, 1698, 1503, 1479, 1366, 1239, 1193, 1054, 1036, 929, 730 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{18}$H$_{17}$BrNO$_5$ [M + H]$^+$ 406.0285, found 406.0281; mp = 149–151 °C.

1-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-2-oxo-2,6,7,7a-tetrahydro-1H-indol-3-yl 4-methylbenzoate (4-58); Prepared from 4-55 (0.50 g, 0.85 mmol) and Grubbs II (0.037 g, 0.043 mmol) according to general procedure B and purified (hexanes–EtOAc: 0–20%) to yield 0.84 g (99%) of 4-58 as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 8.07$ (d, $J = 8.1$ Hz, 2 H), 7.28 (d, $J = 8.0$ Hz, 2 H), 6.98 (s, 1 H), 6.91 (s, 1 H), 6.42 (d, $J = 12$ Hz, 1 H), 6.08 (d, $J = 5.5$ Hz, 1 H),
5.95 (d, \(J = 4.3\) Hz, 2 H), 4.85 (d, \(J = 16\) Hz, 1 H), 4.58 (d, \(J = 16\) Hz, 1 H), 3.98 (dd, \(J = 13\) and 4.3 Hz, 1 H), 2.47–2.41 (m, 1 H), 2.44 (s, 3 H), 2.34–2.28 (m, 1 H), 1.56–1.48 (m, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 166.2, 163.7, 148.1, 144.9, 137.7, 135.5, 133.6, 130.7, 130.1, 129.4, 125.8, 118.6, 113.5, 112.5, 110.1, 102.0, 56.2, 44.5, 28.9, 25.4, 21.9; IR (neat) 2946, 2933, 2885, 2859, 1696, 1490, 1234, 1174, 1092, 1036, 928 cm\(^{-1}\); HRMS m/z [M + H]\(^+\) calculated for C\(_{24}\)H\(_{21}\)BrNO\(_5\) [M + H]\(^+\) 482.0598, found 482.0595; mp = 177–179 °C.

**11-(But-3-en-1-yl)-8-hydroxy-9-((E)-styryl)-8,9-dihydro-6,9-methano[1,3]dioxolo[4',5':4,5]benzo[1,2-c]azepin-7(5H)-one (4-47)**: To a flame dried flask flushed with N\(_2\) was added 4-39 (0.10 g, 0.22 mmol), sodium formate (0.024 g, 0.36 mmol), and anhydrous DMF (3.6 mL). DIPEA (0.047 g, 0.36 mmol) was added followed by Pd(OAc)\(_2\) (2.0 mg, 8.7 μmol). The reaction was degassed for 10 min and then submerged in an oil bath at 100 °C until the starting material was consumed. The reaction was cooled and extracted with CH\(_2\)Cl\(_2\) (×3). The organic layer was dried (Na\(_2\)SO\(_4\)), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (hexanes–EtOAc: 5–23%) to yield 0.053 g (61%) of 4-47 as a white solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.75\) (s, 1 H), 7.44 (d, \(J = 8.2\) Hz, 2 H), 7.33 (t, \(J = 7.4\) Hz, 2 H), 7.25 (d, \(J = 7.82\) Hz, 1 H), 6.99 (d, \(J = 17\) Hz, 1 H), 6.79–6.75 (m, 4 H), 5.94 (d, \(J = 1.6\) Hz, 2 H), 5.73–5.63 (m, 1 H), 5.16 (d, \(J = 15\) Hz, 1 H), 4.95–4.90 (m, 2 H), 4.20 (s, 1 H), 4.02 (d, \(J = 15\) Hz, 1 H), 1.99–1.95 (m, 2 H), 1.82–1.59 (m, 2 H).
General Protocol C: Reductive Heck procedure. To a flame dried flask flushed with N\textsubscript{2} was added substrate and anhydrous DMF (0.01 M). Pd(OAc)\textsubscript{2} (5 mol\%) was added followed by DIPEA (2 equiv) and 1,4-CHD (2 equiv). The reaction was degassed for 10 min and then submerged in an oil bath at 100 °C until the starting material was consumed. The reaction was cooled and extracted with CH\textsubscript{2}Cl\textsubscript{2} (×3). The organic layer was dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography to obtain the pure product.

11-(But-3-en-1-yl)-7-oxo-9-((E)-styryl)-5,7,8,9-tetrahydro-6,9-methano[1,3]dioxolo-[4',5':4,5]benzo[1,2-c]azepin-8-yl pivalate (4-71): Prepared from 4-52 (0.10 g, 0.18 mmol), Pd(OAc)\textsubscript{2} (2.0 mg, 9.1 μmol), DIPEA (0.048 g, 0.36 mmol), and 1,4-CHD (0.030 g, 0.36 mmol) according to general procedure C and purified (hexanes–EtOAc: 0–15%) to yield 0.042 g (49%, 70% brsm) of 4-71 as a yellow solid: \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ = 7.41 (t, \textit{J} = 7.4 Hz, 2 H), 7.34 (dt, \textit{J} = 7.4 and 6.6 Hz, 3 H), 6.81 (d, \textit{J} = 16 Hz, 1 H), 6.83–6.70 (m, 3 H), 6.73 (d, \textit{J} = 17 Hz, 1 H), 5.94 (s, 2 H), 5.69 (ddt, \textit{J} = 17, 10, and 6.7 Hz, 1 H), 5.09 (d, \textit{J} = 15 Hz, 1 H), 4.96–4.91 (m, 2 H), 4.31 (t, \textit{J} = 3.2 Hz, 1 H), 4.00 (d, \textit{J} = 15 Hz, 1 H), 2.09–2.01 (m, 1 H), 1.99–1.90 (m, 1 H), 1.83–1.73 (m, 2 H), 1.43 (d, \textit{J} = 0.81 Hz, 9 H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ = 165.3, 163.7, 148.2, 148.1, 145.0, 139.6, 138.4, 137.3, 135.8, 135.1, 130.7, 129.4, 128.9, 127.1, 125.5, 116.1, 115.4, 113.7, 112.6, 110.2, 102.0, 56.7, 43.9, 28.9, 25.6, 21.9; IR (neat) 3065, 3028, 2975, 2918, 1764, 1700, 1501, 1491, 1445, 1245, 1097, 1038, 926 cm\textsuperscript{-1}; HRMS \textit{m}/\textit{z} [M + H]\textsuperscript{+} calculated for C\textsubscript{29}H\textsubscript{32}NO\textsubscript{5} [M + H]\textsuperscript{+} 474.2275, found 474.2272; mp = 124–127 °C.
11-(But-3-en-1-yl)-7-oxo-9-((E)-styryl)-5,7,8,9-tetrahydro-6,9-methano[1,3]dioxolo-[4',5':4,5]benzo[1,2-c]azepin-8-yl benzoate (4-72); Prepared from 4-53 (0.10 g, 0.17 mmol), Pd(OAc)$_2$ (2.0 mg, 8.7 μmol), DIPEA (0.046 g, 0.35 mmol), and 1,4-CHD (0.029 g, 0.35 mmol) according to general procedure C and purified (hexanes–EtOAc: 0–20%) to yield 0.040 g (46%, 70% brsm) of 4-72 as a yellow solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.24 (dd, $J$ = 7.9 and 1.3 Hz, 2 H), 7.67 (t, $J$ = 7.5 Hz, 1 H), 7.53 (t, $J$ = 7.8 Hz, 2 H), 7.41 (d, $J$ = 6.4 Hz, 2 H), 7.35–7.28 (m, 3 H), 6.87 (d, $J$ = 17 Hz, 1 H), 6.83 (s, 1 H), 6.82 (d, $J$ = 17 Hz, 1 H), 6.79 (s, 1 H), 5.96 (s, 2 H), 5.72 (ddt, $J$ = 17, 10, and 6.4 Hz, 1 H), 5.15 (d, $J$ = 15 Hz, 1 H), 5.00–4.93 (m, 2 H), 4.41 (t, $J$ = 3.5 Hz, 1 H), 4.04 (d, $J$ = 15 Hz, 1 H), 2.12–2.06 (m, 1 H), 2.03–1.97 (m, 1 H), 1.87–1.77 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 164.9, 163.7, 148.2, 147.3, 139.7, 138.1, 137.3, 135.9, 135.0, 134.1, 130.8, 130.7, 129.2, 128.9, 128.8, 128.4, 127.2, 121.6, 116.1, 115.5, 108.8, 108.5, 101.3, 56.2, 44.1, 28.8, 25.6; IR (neat) 3060, 3030, 2920, 1746, 1698, 1501, 1488, 1446, 1243, 1054, 1040, 710, 696 cm$^{-1}$; HRMS $m/z$ [M + H]$^+$ calculated for C$_{31}$H$_{28}$NO$_5$ [M + H]$^+$ 494.1962, found 494.1960; mp = 58–60 °C.
11-(But-3-en-1-yl)-7-oxo-9-((E)-styryl)-5,7,8,9-tetrahydro-6,9-methano[1,3]dioxolo-[4',5':4,5]benzo[1,2-c]azepin-8-yl pentfluorobenzoate (4-73); Prepared from 4-54 (0.10 g, 0.15 mmol), Pd(OAc)$_2$ (1.7 mg, 7.5 μmol), DIPEA (0.040 g, 0.30 mmol), and 1,4-CHD (0.025 g, 0.30 mmol) according to general procedure C and purified (hexanes–EtOAc: 0–15%) to yield 0.027 g (31%, 45% brsm) of 4-73 as a yellow solid: $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.45 (d, $J = 6.6$ Hz, 2 H), 7.39–7.32 (m, 3 H), 6.86–6.78 (m, 4 H), 5.96 (s, 2 H), 5.70 (ddt, $J = 17$, 10, and 6.4 Hz, 1 H), 5.13 (d, $J = 15$ Hz, 1 H), 4.99–4.93 (m, 2 H), 4.40 (t, $J = 3.6$ Hz, 1 H), 4.03 (d, $J = 15$ Hz, 1 H), 2.15–2.06 (m, 1 H), 2.03–1.94 (m, 1 H), 1.86–1.80 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 163.9, 148.3, 138.7, 137.1, 137.1, 136.2, 135.6, 129.6, 129.1, 127.2, 121.7, 115.7, 115.3, 108.8, 108.5, 101.3, 56.4, 44.1, 28.7, 25.6; IR (neat) 2916, 2848, 1762, 1700, 1501, 1328, 1245, 1194, 1038, 1004 cm$^{-1}$; HRMS m/z [M + H]$^+$ calculated for C$_{31}$H$_{23}$F$_5$N$_5$ [M + H]$^+$ 584.1491, found 584.1482; mp = 55–57 °C.

![Diagram](image.png)

11-(But-3-en-1-yl)-7-oxo-9-((E)-styryl)-5,7,8,9-tetrahydro-6,9-methano[1,3]dioxolo-[4',5':4,5]benzo[1,2-c]azepin-8-yl 4-methylbenzoate (4-61); To a flame dried flask flushed with N$_2$ was added 4-55 (0.075 g, 0.13 mmol), Pd(OAc)$_2$ (1.4 mg, 6.4 μmol), PPh$_3$ (4.0 mg, 0.015 mmol), and anhydrous DMF (13 mL). The solution was degassed for 15-20 min. During the degassing, DIPEA (0.034 g, 0.26 mmol) was added followed by 1,4-CHD (0.021 g, 0.26 mmol). The reaction was then submerged in an oil bath at 100 °C until the starting material was consumed. The reaction was cooled and extracted with CH$_2$Cl$_2$ (×3). The organic layer was dried (Na$_2$SO$_4$),
filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (hexanes−EtOAc: 0−16%) to yield 0.038 g (59%) of 4-61 as a white solid. 1H NMR (400 MHz, CDCl3) δ = 8.12 (d, J = 8.1 Hz, 2 H), 7.40 (d, J = 6.9 Hz, 2 H), 7.33–7.28 (m, 5 H), 6.86 (d, J = 17 Hz, 1 H), 6.82 (s, 1 H), 6.79 (d, J = 16 Hz, 1 H), 6.79 (s, 1 H), 5.96 (s, 2 H), 5.71 (ddt, J = 17, 10, and 6.8 Hz, 1 H), 5.14 (d, J = 15 Hz, 1 H), 4.97 (d, J = 17 Hz, 1 H), 4.93 (d, J = 9.0 Hz, 1 H), 4.40 (t, J = 3.4 Hz, 1 H), 4.04 (d, J = 15 Hz, 1 H), 2.46 (s, 3 H), 2.11–2.05 (m, 1 H), 2.01–1.98 (m, 1 H), 1.87–1.76 (m, 2 H); 13C NMR (100 MHz, CDCl3) δ = 165.0, 163.7, 148.2, 147.3, 145.0, 139.8, 138.0, 137.4, 135.9, 134.9, 130.9, 130.8, 129.5, 129.2, 128.9, 127.1, 125.6, 121.6, 116.2, 115.4, 108.8, 108.5, 101.3, 56.1, 44.0, 25.6, 22.0; IR (neat) 3067, 3032, 2920, 1744, 1695, 1609, 1501, 1488, 1443, 1415, 1243, 1177, 1038, 742, 689 cm−1; HRMS m/z [M + H]+ calculated for C32H30NO5 [M + H]+ 508.2119, found 508.2115; mp = 57–59 °C.

11-But-3-en-1-yl)-7-oxo-9-((E)-styryl)-5,7,8,9-tetrahydro-6,9-methano[1,3]dioxolo-[4',5':4,5]benzo[1,2-c]azepin-8-yl pentafluorobenzoate (4-60); Prepared from 4-61 (0.16 g, 0.31 mmol) and Grubbs II (0.013 g, 0.015 mmol) according to general procedure B and purified (hexanes−EtOAc: 5–20%) to yield 0.077 g (61%) of 4-60 as a white solid: 1H NMR (700 MHz, CDCl3) δ = 8.09 (d, J = 7.6 Hz, 2 H), 7.29 (d, J = 7.6 Hz, 2 H), 6.82 (s, 1 H), 6.76 (s, 2 H), 6.42 (d, J = 9.5 Hz, 1 H), 6.08 (s, 1 H), 5.94 (s, 2 H), 4.84 (d, J = 15 Hz, 1 H), 4.34 (d, J = 15 Hz, 1 H), 3.95 (dd, J = 13 and 3.9 Hz, 1 H), 2.44 (s, 4 H), 2.31–2.26 (m, 2 H), 1.53–1.47 (m, 1 H); 13C NMR (175 MHz, CDCl3) δ = 165.9, 163.6, 148.1, 147.1, 144.8, 137.3, 135.2, 133.6, 131.4, 130.6, 129.3,
125.8, 121.3, 118.5, 108.6, 108.3, 101.2, 55.7, 44.6, 28.5, 25.2, 21.9; IR (neat) 3036, 2922, 1744, 1695, 1609, 1503, 1491, 1443, 1261, 1236, 1177, 1066, 1038, 926, 744 cm\(^{-1}\); HRMS \(m/z\) [M + H]\(^+\) calculated for C\(_{24}\)H\(_{22}\)NO\(_5\) [M + H]\(^+\) 404.1493, found 404.1486; mp = 56–58 °C.

3-Hydroxy-13-oxo-4,4a-dihydro-3H,6H-11b,5-ethano[1,3]dioxolo[4,5-j]phenanthridin-12-yl 4-methylbenzoate (4-76); To a screw cap vial was added 4-60 (0.011 g, 0.027 mmol), SeO\(_2\) (9.1 mg, 0.082 mmol) and 1,4-dioxane (0.34 mL). The vial was capped and submerged in an oil bath at 100 °C for 10 h. The reaction was quenched with saturated NaHCO\(_3\) and extracted with EtO\(_2\) (×2). The combined organic layer was dried (Na\(_2\)SO\(_4\)), filtered, and concentrated \textit{in vacuo}. The crude residue was purified by flash chromatography (hexanes–EtOAc: 5–50%) to yield 4.8 mg (42%, 48% brsm) of 4-76 as a clear oil: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta = 8.05\) (d, \(J = 7.9\) Hz, 2 H), 7.28 (d, \(J = 8.0\) Hz, 2 H), 6.80–6.72 (m, 3 H), 6.54 (d, \(J = 9.7\) Hz, 1 H), 6.08 (dd, \(J = 9.8\) and 5.1 Hz, 1 H), 5.94 (s, 2 H), 4.73 (d, \(J = 15\) Hz, 1 H), 4.57–4.55 (m, 1 H), 4.40–4.37 (m, 1 H), 4.39 (d, \(J = 15\) Hz, 1 H), 2.44 (s, 3 H), 2.44–2.40 (m, 1 H), 1.64–1.56 (m, 2 H).
4.7: References


(32) Lan, P.; Banwell, M. G.; Willis, A. C. J. Org. Chem. 2019, DOI: 10.1021/acs.joc.9b00018


(40) Normal and reverse phase flash chromatography, trituration in numerous solvents, and various techniques known to separate Grubbs II from compounds such as the use of charcoal adsorption were all unsuccessful.

(41) The desired product absorbed 280 nm greater than 254 nm, but the side products absorbed 254 nm greater than 280 nm. We noticed the growing amounts of side products based on the relative ratio of UV absorbance for 280 and 254 nm.


