Studies of New Tandem Oxidative Methods in Organic Synthesis

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Abstract

In terms of organic chemistry, oxidation reactions are defined as a reaction that results in a product with more π bonds, heteroatoms, and/or rings than the starting compound. These reactions are just one of the conventional types of organic transformations. Although many conditions for the oxidation of organic systems have been developed, it is still a class of reactions that are being investigated in current research. Work described in this document includes the development of two new tandem oxidation reactions and the synthetic design of a catalyst with potential to perform C-H oxidation reactions with enantioselectivity.

The first section of this dissertation explores an oxidative cyclization of tryptamine derivatives towards C3a oxygenated pyrroloindolines; compounds that are found in many complex natural products. This investigation utilized 4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate (Bobbitt’s Salt) as a reagent to perform this spontaneous oxidative cyclization. Conditions were optimized and a variety of tryptamine substrates were investigated. N1-protected tryptamines were cyclized in moderate yields. Substitution on the indole ring of the tryptamines was also examined and resulted in the corresponding alkoxyamine-substituted pyrroloindolines. Protection of the indole nitrogen gave substrates that were inert, leading to the conclusion that the indole N-H plays a role in the reaction mechanism. Unfortunately, these conditions were problematic with tryptophan derivatives and resulted in complex diastereomeric mixtures.

These oxidative cyclization reactions were utilized in the attempted total synthesis of 3-hydroxy-15H-trytophenalin. The purpose of this synthesis was to determine the stereochemistry of the alcohol group at the C3a position in the isolated natural product. A diastereomeric mixture of alkoxyamine-substituted 3-hydroxy-15H-trytophenalin was obtained with one diastereomer being isolated. Conditions are being investigated to remove the 4-acetamido-2,2,6,6-tetramethyl-
1-oxopiperidinium group to access the C3a hydroxyl group. Once the hydroxy group is unveiled, the NMR spectra of the synthesized product will be compared to the reported spectra to determine the stereochemistry of the isolated natural product.

A tandem oxidation-bromination reaction was explored to access brominated unsaturated ketones from aryl allylic alcohols. This led to the development of reaction conditions utilizing TEMPO, Oxone and tetraethylammonium bromide. It is believed this process first proceeds through the oxidation of the allylic alcohol to the vinyl ketone, followed by the dibromination of the alkene. Addition of triethylamine initiates an elimination reaction resulting in the α-bromo-α, β-unsaturated ketone. These conditions were well tolerated by substrates with electron-donating groups on the aromatic ring, but not with electron-withdrawing groups. This may be due to the stronger inductive effect from the substituents. These conditions are limited to aryl allylic alcohols, as alkyl substituted allylic alcohols did not result in product. This method provides rapid access to α-bromo-α, β-unsaturated ketones in a single reaction step, using reagents that are easily handled and shelf stable.

In addition to the work described above, the design and synthesis of two new chiral quinone catalysts (CQCs) has been initiated. These catalysts are calculated to be capable of performing enantioselective C-H activation-substitution reactions. We envision one catalyst decorated with two BINOL monoethers, and another functionalized with a single 3,3-diaryl-BINOL molecule. The design of these catalysts is based on a dicyanoquinone core to mimic the reactivity of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), a common organic oxidizing agent. BINOL and BINOL monoether derivatives were envisioned to create a chiral environment around the dicyanoquinone core, with these groups being installed via S_NAr chemistry.
The synthesis of the chiral dicyanoquinones decorated with two BINOL monoethers was attempted first. The addition of two BINOL methyl ethers proved difficult, as only one molecule was added, even though a variety of conditions were attempted. The synthesis of the CQC with BINOL proved more fruitful, as a double S_NAr reaction between BINOL and 2,3,5,6-tetrafluoroterephthalonitrile was accomplished without issue. Conversion of this substrate to the desired CQC proved difficult. Multiple synthetic routes were investigated to convert the aryl fluorides to the sought after hydroxy groups. While some progress was made, the desired dihydroquinone product was difficult to purify and could not be oxidized to the desired quinone. This has led to the reevaluation of our synthetic route for these catalysts.
Studies of New Tandem Oxidative Methods in Organic Synthesis

by

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B.Sc., The Pennsylvania State University, 2016
M.Phil., Syracuse University, 2018

Dissertation
Submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in Chemistry

Syracuse University
May 2023
Acknowledgments

Pursuing my PhD in chemistry was without a doubt one of the most challenging and rewarding experiences I have undergone. The knowledge and practice as a scientist I have acquired is unparalleled and I am eternally grateful for this opportunity. As I look back over my time at Syracuse University, I feel a sense of accomplishment, gratitude, and exhilaration. I would not have reached this milestone without the help of so many people and I would like to extend my deepest gratitude to them.

First, this endeavor would not have been possible without my advisor Dr. John Chisholm. I am incredibly thankful for the privilege to collaborate with you these last 6 years. Thank you for being patient and understanding during my less than adequate moments. Thank you for always taking the time to help me understand topics I did not comprehend. You are the best advisor I could have asked for and you are one of the reasons I decided to come to Syracuse for graduate school. I could not have undertaken this journey without you. I will miss our individual meetings and our conversations about everything from chemistry to food to life experiences. Thank you for all of your support during my years here!

I also wish to thank my committee members, Dr. James Hougland, Dr. James Kallmerten, and Dr. Rachel Steinhart for serving on my committee. Thank you for supporting me in my journey and challenging me to reach my potential. Special thank you to Dr. Nancy Totah, Dr. Xiaoran Hu, and Dr. John Tillotson for taking the time to serve on my PhD defense committee. Thank you should also be extended to the staff of the Chemistry department: Jodi Randall, Amy DuPont, Kelsey Dalzell, Allison Piccioni and Cheryl Lowery. Thank you for always being so friendly and helpful with any questions/issues I had. I always enjoyed our conversations when I visited the main office.
To previous members of the group, Dr. Arijit Adhikari, Dr. Alexandre Dixon, Dr. Otto Dungan, Dr. Shea Meyer, and Dr. Nilamber Mate, thank you for being remarkable mentors and friends. Thank you for training and guiding me in the lab as well as taking time to discuss chemistry with me and answer my never-ending questions. You were excellent colleagues and you really made graduate school more enjoyable. To my fellow graduate students, Shawn Dormann, Angela Pacherille, Rob Anderson, Christos Nixaridis, and Jared Chrissley, thank you for being terrific lab mates. I have enjoyed working with you and I will miss our group outings. Thank you for sharing in all of the laughs, frustrations, and victories. I wish you all the best of luck in your continued journey and future endeavors! To the undergraduate students I had the pleasure of working with, Cassie Grossman, Eve Velmahos, and Alexandra Millimaci, thank you for giving me the opportunity to enhance my mentoring skills and share my knowledge and experiences with you. I enjoyed working with you and I hope you enjoyed it too!

Words cannot express how thankful I am for my amazing family! To my mom (Kelly Smith), Jimmy Yancik (Dum-Dum), Pop-Pop, Uncle Kevin, and Aunt Megan, thank you for always being there and supporting me. Thank you for listening to me vent when I was frustrated. Thank you for all of your advice and guidance through this journey and as I venture on to the next chapter of my life. Thank you for showing me the value of hard work, perseverance, and that anything is possible as long as I ‘keep my nose in the books’ and ‘work within my whiskers’. Thank you for everything you have done for me, including moving me into my apartment while I was in Austria. I am incredible lucky and grateful to have such a loving and supportive family. I love you all!

To my cousins (more like my siblings) Addison, Riley, and Tyler, thank you for all of the wonderful times we’ve had either when you came up to visit or when I got a chance to come visit.
I always have so much fun hanging out with you, and I hope that now that I am done with school, I can visit more often and spend more time with you. Thank you for teaching me how important it is that I have ice cream (and toppings) when you visit 😊. I hope that me earning this degree shows you that with hard work and perseverance you can achieve anything! I cannot wait to see what you will do as you move through your educational journeys and start your own careers. I love you all and I will always be there for you and will support you in any way I can.

To my fiancé, Steve Pietruniak, I cannot express enough how incredibly grateful I am to have you in my life. Thank you for standing by my side these last four years, especially the last couple of months as I was stressed to finally finish graduate school! Thank you for being so understanding and allowing me to always ‘put school first’. Thank you for taking on extra responsibilities when I was overwhelmed or had to stay late in the lab. Thank you for being supportive and thinking logically when I was frustrated. I wish to extend my gratitude to your family, especially your parents (Ed and Lori), for being so accepting of me and supportive. I love the little family we have created (Dean Doo, Zelda Puss, and Ava Baby) and I cannot wait to be your wife and spend the rest of our lives quoting Family Guy and executing ‘Sunday Deep Cleans’ of the house.

“Progress is made by trial and failure; the failures are generally a hundred times more numerous than the successes, yet they are usually left unchronicled.” – William Ramsay
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<thead>
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<tr>
<td>[α]</td>
<td>specific rotation</td>
</tr>
<tr>
<td>Å</td>
<td>angstrom</td>
</tr>
<tr>
<td>°C</td>
<td>degree Celsius</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift (ppm)</td>
</tr>
<tr>
<td>μg</td>
<td>microgram</td>
</tr>
<tr>
<td>ACAT</td>
<td>acyl-CoA:cholesterol acyltransferase</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>ACT</td>
<td>4-Acetamido-2,2,6,6-tetramethylpiperidine</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>Anal. calcd.</td>
<td>combustion elemental analysis</td>
</tr>
<tr>
<td>anhy.</td>
<td>anhydrous</td>
</tr>
<tr>
<td>approx.</td>
<td>approximately</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1′-bi-2-naphthol</td>
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<tr>
<td>Boc</td>
<td>tert-butyloxy carbonyl</td>
</tr>
<tr>
<td>br s</td>
<td>broad singlet</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>CAN</td>
<td>ceric ammonium nitrate</td>
</tr>
<tr>
<td>Cbz</td>
<td>carboxybenzyl</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>wavenumber(s)</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
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<td>1,4-diazabicyclo[2.2.2]octane</td>
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<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublet</td>
</tr>
<tr>
<td>DEAD</td>
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<tr>
<td>DMF</td>
<td>dimethylformamide</td>
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<tr>
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<td>dimethyl sulfoxide- d₆</td>
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<td>DNBSA</td>
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</tr>
<tr>
<td>DPM</td>
<td>diphenylmethyl</td>
</tr>
<tr>
<td>dt</td>
<td>doublet of triplet</td>
</tr>
<tr>
<td>DTBP</td>
<td>di-tert-butyl peroxide</td>
</tr>
<tr>
<td>EDCI</td>
<td>1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>eq.</td>
<td>equation</td>
</tr>
<tr>
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<td>equivalents</td>
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Fmoc 9-fluorenlymethoxycarbonyl
G gram(s)
GABA γ-aminobutyric acid
h hour(s)
HAT hydrogen atom transfer
HATU 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxidhexafluorophosphate
HCl hydrochloric acid
hfacac hexafluoroacetylelacetonate
HPI hexahydropyrrolo[2,3-b]indole
HPLC high performance liquid chromatography
HRMS High-resolution mass spectrometry
HWE Horner-Wadsworth-Emmons
IR infrared spectroscopy
KBr potassium bromide
kDa equilibrium dissociation constant
m multiple
M molar
mCPBA meta-chloroperoxybenzoic acid
MeCN acetonitrile
MHz megahertz
MImc methyl imidazole carbamate
min minute(s)
 mL milliliter
mmol millimole
mol mole
mp melting point
MS molecular sieves
MW Molecular weight
N-alloc N-allyloxycarbonyl
NBS N-bromosuccinimide
NCS N-chlorosuccinimide
NIS N-iodosuccinimide
nm nanometers
NMM N-Methylmorpholine
NMP N-Methylpyrrolidine
NMR nuclear magnetic resonance
N-PSP N-(phenylseleno)phthalimide
Ns 2-nitrophenylsulfonamide
Nu nucleophile
P pentet
PCC pyridinium chlorochromate
PCET proton-coupled electron transfer
pH potential of hydrogen
pKa acid dissociation constant
PMB para-methoxybenzyl
ppm parts per million
PPTS pyridinium p-toluenesulfonate
PTEN phosphatase and Tensin Homolog Protein
pTSA para–toluene sulfonic acid
q quartet
R_f retention factor
R_t retention time
s singlet
sep septet
S_N1 unimolecular nucleophilic substitution
S_N2 bimolecular nucleophilic substitution
t triplet
TCCA trichloroisocyanuric acid
td triplet of doublet
TEMPO 2,2,6,6-tetramethylpiperidine 1-oxyl
TEA triethylamine
TFA trifluoroacetic acid
THF tetrahydrofuran
TLC thin layer chromatography
TMG 1,1,3,3-tetramethylguanidine
TMSCN trimethylsilyl cyanide
TMSCl 4-toluenesulfonyl chloride
TRIP 3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-bi-2-naphthol cyclic monophosphate
Ts tosylate
UV ultraviolet
w/v weight per unit volume
Chapter 1:
Oxidative Cyclization of Tryptamines with 4-Acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium Tetrafluoroborate to Obtain C3a-Oxygenated Pyrroloindolines

Abstract

Pyrroloindolines are fused heterocyclic scaffolds derived from both tryptamine and tryptophan derivatives that are often found in natural products. Their rigid tricyclic molecular structure and fully substituted carbon center at the C3a-position pose a significant synthetic challenge to organic chemists. Pyrroloindoline-containing alkaloids display a wide array of intriguing biological activities, making them appealing targets with implications for drug development. Several different substituents at the C3a position have been observed and contribute to the assortment of biological activity. With the most common substituent being a hydroxy group, the need for ready access to C3a-oxygenated pyrroloindolines has become apparent.

Given the nucleophilic nature of the indole in tryptamine, an electrophilic oxygen source may be able to oxidize the indole C2-C3 alkene to produce a C3a-oxygenated pyrroloindoline after intramolecular cyclization of the pendant nitrogen. This work shows that the stable and simple to synthesize reagent 4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate (Bobbitt’s Salt) can be used to perform an oxidative cyclization on multiple tryptamine substrates to access a functionalized C3a-oxygenated pyrroloindoline. These optimized conditions were utilized in the synthesis of 3-Hydroxy-15H-Tryptophenalin. Conditions are being investigated to remove the 4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium group to access the required hydroxyl group at the C3a position. Upon completion of the synthesis of 3-Hydroxy-15H-Tryptophenalin, the obtained NMR spectra will be compared to the reported spectra to determine the stereochemistry at the C3a position of the natural product.
1.1 Introduction

1.1.1 Pyrroloindolines (hexahydropyrrolo[2,3-b]indoles)

Pyrroloindolines, or hexahydropyrrolo[2,3-b]indoles (HPIs), are heterocyclic scaffolds that have been found in natural products of both terrestrial and marine origin (Figure 1.1).\(^1\)-\(^3\) These alkaloids are often categorized based on the number of HPI scaffolds present in the structure.\(^4\) Monomeric HPIs contain one pyrroloindoline core and can be seen in (-)-physostigmine 1.1 and (-)-phenserine 1.2. Dimeric HPI alkaloids contain two pyrroloindoline cores that are either linked through a C3a-C3a bond such as in (+)-chimonanthine 1.3 or fused together as seen in (+)-nocardioazine B 1.5. HPIs with more than two of these cores are referred to as oligomers. An example of this can be seen in (-)-hodgkinsine B 1.6.

![Figure 1.1: Pyrroloindoline Containing Natural Products](image-url)
Aside from the number of pyrroloindoline cores present, these complex molecules can also be characterized by the substitution pattern on the fully substituted carbon at the C3a position. Present on a number of complex pyrroloindoline natural products, the most common functional group at this position is the hydroxyl group (Figure 1.2). An example of this is cruciferane 1.16. Isolated from the dried root of *Isatis indigotica*, cruciferane 1.16 is the first racemic natural product isolated containing a pyrrolo[2,3-b]indolo[5,5-a,6-b,a]quinazoline skeleton. Also known as Chinese woad, *Isatis indigotica* has been used as an ethnomedicine to treat a variety of illnesses including influenza, epidermic hepatitis, and erysipelas.\(^5\) Okaramine C and S (1.17 and 1.18), which were isolated from the fermentation extracts of *Penicillium simplicissimum* and *Aspergillus aculeatus* cultured on okara, are also examples of C3a-oxygenated pyrroloindolines.\(^6\) Similar ring systems have been isolated from *Peganum harmala* L. (Zygophyllaceae), a herb rich in B-carboline alkaloids that has been used to treat alimentary tract cancer and malaria in northwestern China.\(^7\) Both peganine A and B (1.19 and 1.20) have been isolated from the seeds of this herb.\(^8\) Protubonine A 1.21 was isolated from the marine derived fungus *Aspergillus* sp. SF-5044,\(^9\) whereas the kapakahines are a family of cyclic peptides isolated from the marine sponge *Cribrochalina olemda*.\(^10, 11\) Another hydroxypyrroloindoline is gypsetin 1.23, which was isolated from the cultured broth of *Nannizzia gypsea* var. *incurvate* IFO 9228.
1.1.2 Biological Relevance

Biologically, pyrroloindoline containing natural products show a wide range of different activities. This is believed to be due to the HPIs having a rigid structure that mimics peptide ligands that bind to a number of receptors, usually enhanced by hydrophobic interactions from the aromatic core. For example, both (-)-physostigmine 1.1 and (-)-phenserine 1.2 are inhibitors of acetyl and butyryl cholinesterase. As a result, they can be used as treatment for myasthenia and glaucoma. These compounds, as well as analogues, are also being investigated as potential treatments for Alzheimer’s Disease. The natural product (-)-flustramine B 1.7 has shown toxicity against cancer cell lines while (-)-debromoflustramine 1.8 has shown antibacterial activity. The drimentines 1.9-1.11 are a family of pyrroloindoline-ketopiperazine alkaloids that have shown anticancer, antifungal, antibacterial, and anthelmintic properties. The physostigmine derivative (-)-eseroline 1.15 acts as an opioid agonist and is used in the management of opioid dependence.
C3a-oxygenated pyrroloindolines also show a wide variety of biological properties. For example, okaramine C 1.17 shows insecticidal activity, specifically towards silkworm larvae,\textsuperscript{6} while okaramine S 1.18 has shown moderate cytotoxic activity against the HL-60 cancer cell line.\textsuperscript{21} Preliminary biological analyses of the kapakahine family indicated a modest cytotoxic activity for kapakahines A, B, C (1.22) and E with IC\textsubscript{50} values of \(\sim 5.0 \mu g/mL\) in P388 murine leukemia cells.\textsuperscript{22} The fused dimeric HPI alkaloid gypsetin 1.23 has been shown to be an acyl-CoA:cholesterol acyltransferase (ACAT) inhibitor, as well as inhibit cholesteryl ester formation in macrophages.\textsuperscript{23, 24} This has made gypsetin a compound of interest for the development of cholesterol-lowering drugs. Given the potent and diverse biological activity of these structures, synthetic organic chemists have been active in method development for the formation and decoration of the pyrroloindoline core.

1.1.3 Known Synthetic Routes to C3a Substituted Pyrroloindolines

Due to the biological activity and structural complexity of these scaffolds, pyrroloindolines have been a target for synthetic chemists for decades. Many strategies have been developed to access these structures, decorate the C3a position with a variety of functional groups, and control stereochemistry. Given that these scaffolds often differ by the substituent at the C3a position, many different approaches have been utilized to functionalize this position. One common strategy used is bromination, which is accomplished on unsubstituted pyrroloindolines using radical conditions to form 3a-bromohexahydropyrrolo[2,3-b]indoles. The bromine can then be displaced with a variety of nucleophiles.\textsuperscript{25-31} This strategy was employed by Crich et al. in the total synthesis of (+)-debromoflustramine B (Scheme 1.1).\textsuperscript{32} Pyrroloindoline 1.24 was subjected to NBS to access 3a-bromohexahydropyrrolo[2,3-b]indole 1.25. Displacement of the bromine with an allyl group provided 1.26, which was utilized in the synthesis of (+)-debromoflustramine 1.8.
Scheme 1.1: Synthesis of (+)-Debromoflustramine B by Crich

Other leaving groups have also been employed to access functionalized pyrroloindolines. Previous research in the Chisholm lab showed that trichloroacetimidates could be displaced with a variety of nucleophiles. This led to the hypothesis that trichloroacetimidates could be used in the synthesis of hexahydropyrrolo[2,3-b]indoles and used to introduce a variety of groups at the C3a position. This technique was used in the formal synthesis of psychotriasine 1.30 as well as the first synthesis of arundinine 1.33 (Scheme 1.2). \textit{N}-Alkylation of imidate 1.27 was performed to obtain intermediates 1.29 and 1.32.
Perhaps the most common strategy utilized to prepare HPIs is the biomimetic cyclization approach. This approach employs tryptamine, tryptophan, or their derivatives and includes dearomatization of the indole core at the C3 position using an electrophile (E⁺), followed by closure of the pyrroloindoline C-ring (Scheme 1.3). This approach is effective using a number of different electrophiles.

Scheme 1.3: Mechanism of Biomimetic Cyclization Approach to Obtain Pyrroloindolines

Movassaghi et al. employed this strategy in the total synthesis of (+)-11,11'-dideoxyverticillin A, a fungal metabolite. In this case N-bromosuccinimide (NBS) was used as the source bromine, which served as the electrophile. It was found that the addition of the weakly acidic catalyst pyridinium p-toluenesulfonate (PPTS) increased the yield of the C3a-bromohexahydro pyrrolo[2,3-b]indole product. Similar conditions were also employed by Rainer
and Espejo in the synthesis of C(3)-N(1′) Heterodimeric Indoline 1.40 and 1.41 (Scheme 1.4).²⁵

**Scheme 1.4: Synthesis of C(3)-N(1′) Heterodimeric Indoline by Rainier and Espejo**

Another strategy employed by synthetic chemists is to perform the cyclization using a phenylselenium electrophile, with the selenide then being able to be replaced with a number of other groups. This route is often referred to as a selenocyclization strategy. This method was employed by Danishefsky and co-workers in the total synthesis of amauromine 1.48 and 5-N-acetylardeemin (Scheme 1.5).⁴²

**Scheme 1.5: Total Synthesis of Amauromine by Danishefsky**

A similar selenocyclization route was employed by Ley and co-workers to access the required 3a-hydroxy-pyrroloindole for the synthesis of the 10b-hydroxypyrrazino[1′,2′:1,5]
pyrrolo[2,3-b]indole-1,4-dione core, a structure found in many biologically active natural compounds. Meta-chloroperoxybenzoic acid (mCPBA) and potassium carbonate were used to convert the C3a selenide to a hydroxy group. Later, this method was utilized in the total synthesis of okaramine C by the same group (Scheme 1.6).44

Scheme 1.6: Synthesis of Okaramine C by Ley

![Scheme 1.6: Synthesis of Okaramine C by Ley](image)

Oxygen electrophiles have been used to access C3a-oxygenated pyrroloindolines via an oxidative cyclization. Danishefsky showed that C3a-oxygenated pyrroloindolines could be accessed directly from the protected tryptophans 1.55 and 1.57 using dimethyldioxirane (DMDO) (Scheme 1.7).45-47 It was found that the steric bulk of the protecting group on the amino acid amine correlated with the diastereoselectivity, with the large trityl group resulting in a single diastereomer 1.56. The other diastereomer could be accessed using a different synthetic route. Bromocyclization followed by elimination gave tricyclic indole 1.58, which was then oxidized to pyrroloindoline 1.59. The stereochemistry was controlled by the stereocenter adjacent to the ester, with the DMDO approaching the indole from the opposite side of the ring system.
Other groups have developed methods to access C3a-oxygenated pyrroloindolines more directly. Crich and co-workers showed benzylic oxidation of pyrroloindoline 1.60 with ceric ammonium nitrate (CAN) provided C3a-oxygenated pyrroloindoline 1.61 along with nitrate ester 1.62 in a 65% combined yield. Fortunately, the nitrate ester could be reduced back to the desired alcohol with tributyltin hydride and AIBN. Takayama reported the most rapid access to C3a-oxygenated pyrroloindolines, in exceptionally high yields, through subjecting protected tryptamine 1.63 to m-CPBA and TFA (Scheme 1.8).

**Scheme 1.8: Crich and Takayama Conditions to C3a-Oxygenated Pyrroloindolines**

Crich et al.

Takayama et al.
The previously discussed strategies are just a few of the many methods available to access C3a substituted pyrroloindolines. Other strategies include but are not limited to alkylation cyclization of oxoindoles,\textsuperscript{49-54} reductive cyclization,\textsuperscript{55} Fischer indole synthesis,\textsuperscript{56, 57} and rearrangements including [3,3]-sigmatropic\textsuperscript{58-61} as well as [1,2] rearrangements.\textsuperscript{62} A great deal of work employing transition metal catalysts have also been investigated.\textsuperscript{63-70} These synthetic routes have been reviewed previously.\textsuperscript{1, 2, 4, 39}

1.1.4 Use of Trichloroacetimidates to Access C3a Functionalized Pyrroloindolines Derived from Tryptophan Substrates in the Synthesis of Kapakahine C

Imidate chemistry performed in the Chisholm research group (Scheme 1.2) was hypothesized to be utilized in the total synthesis of natural product kapakahine C \textsuperscript{1.22}. We were specifically interested in this compound due to its more complex structure as compared to other members of the kapakahine family. This compound contains a pentapeptide on the right half of the molecule and two pyrroloindoline units on the left which is unique to kapakahines C and D. Both of these pyrroloindoline units are tryptophan derivatives which are connected by N1-C3 bond. There also has been no reported synthesis of kapakahine C. Retrosynthetically, kapakahine C can be disconnected into 3 portions: the pentapeptide \textsuperscript{1.67}, the pyrroloindoline alcohol \textsuperscript{1.65} and the pyrroloindoline imidate \textsuperscript{1.66} (Scheme 1.9). Both of these sections of the molecule required a flexible method for the synthesis of highly functionalized C3a-hydroxy pyrroloindolines.
Scheme 1.9: Retrosynthetic Analysis of Kapakahine C

Synthesis of the required pyrroloindoline fragment 1.65 proved difficult when cyclization with the established *m*-CPBA/TFA conditions on the suitably protected tryptophan derivative resulted in endo/exo mixture (Scheme 1.10). Additional attempts with other reported reagents including DMDO\(^{45-47, 72, 73}\) and CuCl/TEMPO\(^{74}\) were also found to be problematic and gave sporadic yields and/or complex mixtures. Danishefsky’s conditions utilizing DMDO (Scheme 1.7) were shown to be very dependent on the protecting groups on the amino acid and any variation gave mixtures. While surveying other potential oxidizing agents to perform this task, oxoammonium salts were identified as promising reagents that can facilitate cyclization and lead to C3a-oxygenated pyrroloindoline structures.

Scheme 1.10: Established *m*-CPBA/TFA Oxidative Cyclization Conditions Effects on Tryptophan 1.168
1.1.5 Oxoammonium Salts for Oxidative Cyclization Reactions

Oxoammonium salts have primarily been used to oxidize alcohols to their corresponding aldehydes or ketones. These electrophilic oxidizing agents are environmentally friendly, simple to handle, can be easily regenerated, and are readily synthesized from inexpensive reagents. More recently oxoammonium salts have been recognized as useful allylic oxidation reagents, and have found applications in C-H activation. An underutilized property of these reagents is their ability to activate alkenes for nucleophilic attack (Scheme 1.1). This was first described by Endo and co-workers, who noted that oxoammonium salt 1.71 gave chloro-oxidation products like 1.73 when exposed to alkenes such as 4-methoxystyrene 1.72. Later, Brower and co-workers explored the electrophilic addition of the nitrate salt 1.74 and silylated heterocycles (like 1.76) to enol ethers. These transformations were used to synthesize nucleoside analogs. Reactions with promoter 1.75 were limited to enamides and enol ethers, with the authors noting that 4-methoxystyrene gave no addition products with nitrogen nucleophiles. More recently Liu and co-workers used the perchlorate salt 1.78 and trimethylsilyl cyanide (TMSCN) in a carbotherification of enol ethers, such as 1.79, and vinyl azides. Reports by Colomer describes the in situ formation of the N-oxoammonium salt, which then activates alkenes such as 1.82 and provides difunctionalized products such as 1.81 and 1.83 in a similar fashion. The Chisholm group has also been active in this area, and recently published an amino-oxidation of alkenes using N-o xoammonium salts.
Possibly the most utilized oxoammonium salt in organic synthesis is (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO). Xia and coworkers were able to access C3a oxygenated pyrroloindoline 1.86 with a CuCl2/TEMPO reactant system. Through mechanistic studies, they were able to confirm a radical annulation process that originates at the N1 position of the indole (Scheme 1.12). They proposed that copper chloride oxidizes the indole N1 to generate the radical 1.88, which then reacts at the C3 position to form imine 1.89. The imine may then undergo cyclization through two different pathways. In pathway A, the imine undergoes a 5-exo-trig
cyclization process followed by quenching of the C3 radical by TEMPO. In pathway B, the radical is quenched by TEMPO, followed by cyclization. They also proposed that pathway A is favored by sulfonamide protected tryptamines, while pathway B is favored by acetyl protected tryptamines. This is speculated due to sulfonamides being more nucleophilic than acetyl groups. The resulting alkoxyamine group was shown to be easily removed with zinc and acetic acid.

**Scheme 1.12: Copper Catalyzed Cyclization by Xia**

An oxidative proton-coupled electron transfer (PCET) strategy was employed under photo redox conditions by Knowles to obtain pyrroloindolines. Using photocatalyst tris(2-phenylpyridine)iridium(III), a variety of alkoxyamine-substituted pyrroloindolines were obtained with excellent enantioselectivity (Scheme 1.13). This group proposed a prospective catalytic cycle mechanism. First the iridium catalyst is transformed to its excited state by visible light irradiation. This photoexcited iridium is believed to catalyze the oxidation of the tryptamine substrate through a PCET. The chiral phosphate base forms a hydrogen bond with the indole N-H of the tryptamine substrate. Indole radical cation-phosphate ion 1.99 reacts with TEMPO to form a new C-O bond.
at the C3 position of the tryptamine substrate. The desired alkoxyamine-substituted pyrroloindoline 1.92 is obtained when the iminium ion is captured by the amine nucleophile. The reduced state of the iridium photocatalyst and the conjugate acid of the phosphate base reduces the second equivalent of TEMPO in a PCET process to make TEMPO-H. The resulting alkoxyamine group at the C3a position was shown to be displaced with a number of nucleophiles.90

**Scheme 1.13: Enantioselective PCET to Access C3a-Substituted Pyrroloindolines by Knowles**
Xia has also reported subjecting tryptamine substrates to TEMPO in the presence of UV light and a chiral phosphoric acid to obtain pyrroloindolines in high yields and excellent enantioselectivity (Scheme 1.14). Their reported mechanism was similar to Knowles in that a radical mechanism occurs, however, they report that TEMPO is directly excited by visible light and coverts tryptamine into the radical, without the assistance of an iridium catalyst. They report that this reaction occurs through a hydrogen atom transfer (HAT) pathway that begins with the excitation of TEMPO by blue LED lights. The now excited state TEMPO engages in a HAT with tryptamine 1.87 to generate the imine radical. This radical intermediate then undergoes a phosphoric acid-catalyzed asymmetric cyclization. The observed enantioselectivity is based on the TEMPO trapping the imine radical intermediate from the less steric Re face of the imine and catalyst complex. These conditions were then utilized in the synthesis of (-)-verrupyroloindoline.

**Scheme 1.14: Enantioselective Radical Cyclization of Tryptamines by Xia**

Recently Kanai and co-workers developed transition metal-free conditions to perform bioconjugation of tryptophan containing peptides (Scheme 1.15). This captured our attention as we needed to cyclize tryptophan derivative 1.68 to access kapakahine C fragment 1.65. Subjecting
a variety of tryptophan containing peptides such as 1.108 to radical 1.109 resulted in alcohol 1.110 as well as adducts 1.111 and 1.112. Mechanistic studies suggested that the oxoammonium salt of keto-ABNO that is formed in situ is actually the reactive species, indicating that these reactions may proceed through a different mechanism than the radical pathways previously reported by Xia and Knowles. These systems were then explored on tryptophan derivatives as a new method for bioconjugation of proteins to dyes, anticancer drugs and biotin.92

**Scheme 1.15: Tryptophan-Selective Bioconjugation of Peptides by Kanai**

![Scheme 1.15](image)

In the presence of a suitable anion, such as HBF₄, TEMPO can be oxidized into the corresponding oxoammonium salt 1.114, with the removal of one electron.93 As mentioned above it is believe that the oxoammonium salt is the reactive species. In contrast, the addition of one electron in the presence of a suitable acid results in its hydroxyamine salt 1.113. The TEMPO radical 1.94 can also undergo disproportionation under acidic conditions, leading to the formation of the oxoammonium salt 1.114 and the cation 1.113 from the radical, this is called the Golubev disproportionation.94 This disproportionation can make studying the mechanisms of these transformations more difficult.
Since the mCPBA conditions for pyrroloindoline formation gave us complex mixtures and/or sporadic yields on tryptophan substrates and attempts to perform the reactions under Xia’s conditions with TEMPO and CuCl$_2$ were difficult to reproduce, we turned our attention to using Bobbitt’s Salt (4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate) to access the C3a oxygenated pyrroloindolines. As in many of the above cases the oxoammonium salt may be the active reagent, we focused on using these reagents to access pyrroloindolines. The oxoammonium salts derived from TEMPO are often unstable and explosive but work by Bobbitt has shown that the addition of an acetamide to the system results in a bench stable oxoammonium that can be employed in these reactions. Synthesized from 4-acetamido-2,2,6,6-tetramethylpiperidine, Bobbitt’s salt 1.120 contains the tetrafluoroborate counterion and is a safer, more stable, and less expensive analogue of the N-oxoammonium salt derived from TEMPO. This oxoammonium salt is also shown to be more stable than the TEMPO derived salts. Bobbitt’s Salt was synthesized in our lab using the literature conditions (Scheme 1.17). The evaluation of Bobbitt’s salt in the formation of C3a-oxygenated pyrroloindolines was then undertaken and the reaction conditions utilized in the synthesis of natural product 3-hydroxy-15H-tryptophenalin.
1.2 Results and Discussion

1.2.1 Optimization of Bobbitt’s Salt Cyclization

We began our investigation to find optimal conditions by subjecting protected tryptamine 1.121 to Bobbitt’s Salt in MeCN (Table 1, entry 1). A trace amount of product could be seen by $^1$H NMR, however the majority was the starting protected tryptamine. Since the base, potassium t-butoxide, was utilized in Xia’s CuCl$_2$/TEMPO reaction system, we hypothesized that base would be required for this reaction to occur. Employing DBU (1,8-diazabicyclo(5.4.0)undec-7-ene) as the base at room temperature gave 28% yield of the desired pyrroloindoline (entry 2). The addition of base was found to be necessary for access of the oxidation/cyclization product. This may be due to the base deprotonating the sulfonamide, providing the sulfonamide anion and the protonated amine which does not bind to the N-oxoammonium competitively (Scheme 1.22). No product was isolated when the reaction was heated to reflux (entry 3). This could be due to the sensitivity of the $N,N$-acetal, which may be hydrolyzed at higher temperatures by the ammonium salt of HBF$_4$ formed during the reaction. A higher yield of 45% was isolated when the reaction was run at lower temperatures (entry 4). Though addition of DBU resulted in formation of desired product, a small amount of oxidized DBU was observed in the reaction mixture. Employing DBU as base became problematic as the oxidized DBU and reaction product were difficult to separate.
issues with compound purity and characterization of substrates. TMG (1,1,3,3-tetramethylguanidine) was investigated as an alternate base which resulted in a higher yield of 65% (entry 5) and avoided difficult purification. DCM was investigated as an alternative solvent, but this resulted in no change in yield (entry 6). Other bases were also investigated and resulted in lower yields or no product (entries 7-9). The equivalents of TMG and Bobbitt’s salt used were increased to 2.0 equivalents, but this change also did not increase the yield (entry 10). When the reaction was run longer, a decrease in yield was observed (entry 11). When THF was used as the solvent, a drastic decrease in yield was observed when the reaction was run at -50°C (entry 12). However, raising the reaction temperature to 0 °C resulted in an acceptable yield of 78%. Optimal conditions were found to be 1.2 equivalents of TMG and 1.2 equivalents of Bobbitt’s salt in THF at 0 °C for 15 minutes (entry 13).
**Table 1.1: Optimization of Oxidative Cyclization Conditions**

1.2.2 Synthesis of Tryptamine-Based Substrates for Oxidative Cyclization Studies

With optimized conditions in hand, we wanted to investigate the scope of these reaction conditions on a variety of tryptamine-based substrates. \(N\)-protected tryptamine substrates were prepared through protection of the primary amine with the corresponding sulfonyl chloride in the presence of triethylamine (Scheme 1.18). This resulted in moderate yields of sulfonamides \textbf{1.121}, \textbf{1.124}, and \textbf{1.125}. Aromatic substituted tryptamines \textbf{1.126-1.128} were protected using 4-toluenesulfonyl chloride and triethylamine. Protected tryptamines \textbf{1.132-1.134} were obtained by subjecting tryptamine to the appropriate anhydride and triethylamine. Indole-3-acetic acid and 2-(3-indole)-ethanol were purchased and subjected to optimized cyclization conditions.
The synthesis of protected tryptamines with substitution at the 4 and 7 positions of the benzene ring were more complex (Scheme 1.19). Chloro-substituted indole 1.135 was subjected to phosphoryl chloride to obtain carboxaldehyde 1.137 in an excellent yield of 99%. A Henry reaction with nitromethane followed by an elimination with ammonium acetate were used to obtain nitroalkene 1.139 in a yield of 64%. This substrate was then reduced to the primary amine using lithium aluminum hydride. The crude amine was then protected using 4-toluenesulfonyl chloride with triethylamine to give sulfonamide 1.141 in a yield of 85% after silica gel chromatography. This reaction sequence was repeated with 7-methoxyindole to obtain sulfonamide 1.142 in a 69% yield.
Scheme 1.19: Synthesis of 4- and 7- Substituted N-Protected Tryptamines

Indole N-substituted tryptamines were also prepared (Scheme 1.20). Synthesis of N-methylated tryptamine proved difficult due to dimethylation at the indole nitrogen and the primary α-amine. To overcome this problem, the tryptamine α-amine was phthalimide protected to prevent methylation at the primary amine. The indole was N-methylated with sodium hydride and methyl iodine resulting in a 45% yield of 1.144. The phthalimide group was removed with hydrazine and the crude mixture subjected to 4-toluenesulfonyl chloride to obtain protected tryptamine 1.145. Sulfonamide 1.146 was obtained by first subjecting tryptamine to 4-toluenesulfonyl chloride to obtain protected tryptamine 1.121. The indole nitrogen was also sulfonamide protected using 4-toluenesulfonyl chloride with DMAP and DIPEA. This provided the desired compound 1.146 in a 14% yield.
Scheme 1.20: Synthesis of Indole N-Substituted Tryptamines

Conditions reported by Shu-Lu You and co-workers were then used to obtain the required 2-methy-6-bromotryptamine (Scheme 1.21).\(^7\) 3-bromophenyl hydrazine hydrochloride 1.147 was combined with phthalimide 1.148 in a Fischer indole synthesis to obtain a mixture of protected tryptamines 1.149 and 1.150. The required isomer 1.149 was separated by column chromatography in a 17\% yield. Hydrazine hydrate was used to remove the phthalimide group and replaced with a tosyl group to obtain desired protected tryptamine 1.153.

Scheme 1.21: Synthesis of 2-Methyl-5-Bromotryptamine
1.2.3 Scope of Oxidative Cyclization Reaction Conditions

With the required tryptamine substrates in hand, the scope of the Bobbitt’s salt mediated oxidative cyclization was investigated (Scheme 1.22). We first looked at sulfonamide protected tryptamines. Reaction of substrates 1.121, 1.124, and 1.125 resulted in moderate yields (48-78%). Acetyl protected tryptamine did not give any product, which may be due to TMG not being a strong enough base to deprotonate the amide nitrogen. In contrast, the more acidic trifluoroacetyl amide resulted in a high yield of 86%. Due to the presence of the tertiary amide, slow rotation around the amide bond resulted in complicated NMRs, making it difficult to characterize the compound. Carbamate protecting groups, such as Boc and Cbz, were also investigated but did not result in any product. A substrate with electron withdrawing groups at the 2-position were also investigated and resulted in a respectable yield of 78% of compound 1.160 with an aldehyde protection of the α-amine. A substrate with a C2-methyl was also investigated and resulted in a yield of 48% of 1.161. These conditions were also utilized to synthesis 1H-furo[2,3-b]indole 1.162 in 60% yield. Cyclization of indole-3-acetic acid led to decomposition instead of the cyclized product. Cyclization of 1H-pyrrolo[2,3-b]indol-2-one was also attempted but did not result in product. Believing that the unprotected nitrogen was not acidic enough, we protected it with methyl benzoate before attempting the cyclization. We chose this protecting group as successful cyclization of this substrate could be implemented in the synthesis of natural product cruciferane 1.16. Unfortunately, reaction of this substrate also did not result in product.
Scheme 1.22: Scope of the Oxoammonium Salt Mediated Cyclization: N-Protected Tryptamines

The effects of substitution of the aromatic ring were examined next (Scheme 1.22). The presence of a weak electron donating groups at the 7-position resulted in exceptional yield of 78% of 1.166. However, the presence of a stronger electron donating group, such as methoxy groups, was not well tolerated. Bromo and chloro substituents were well tolerated giving moderate yields of 47%-73%. Indole N-substituted substrates were also investigated but gave no reaction. This suggests that the indole nitrogen must be unprotected for the reaction to occur.
1.2.4 Proposed Mechanism of Oxoammonium Salt Mediated Oxidative Cyclization Reaction

Because Cbz protected tryptamine did not react with our conditions, but did for Xia and Knowles, we believe our conditions proceed through a different, non-radical mechanism. A proposed mechanism of the oxidative cyclization reaction is shown in Scheme 1.24. Since N-methyl tryptamines also did not react under our conditions, like Xia and Knowles, we believe the reaction begins with the deprotonation of the indole N-H and the formation of the imine. The electron rich indole is able to perform an attack on the oxygen of Bobbitt’s Salt resulting in the formation of iminium intermediate 1.177, and a newly formed C-O bond at the C3 position of the indole. The base also deprotonates the amine nitrogen forming anion intermediate 1.178.
The pyrroloindoline ring is formed when an intramolecular attack of the protected amine occurs at the C2 position. The indole nitrogen is protonated from the conjugate acid.

**Scheme 1.24: Proposed Mechanism of Oxidative Cyclization Reaction**

1.2.5 Synthesis of 3-Hydroxy-15H-Tryptophenalin

3-Hydroxy-15H-tryptophenalin 1.180 is a natural product isolated from the endophytic fungus *Aspergillus versicolor* (Figure 1.3). Associated with the *Piper aduncum* plant, this cyclic dipeptide has been shown to inhibit signals from potassium ion membrane channels. Although the structure of the compound was confirmed by $^1$H and $^{13}$C NMR spectroscopy as well as HRMS analysis, the configuration pyrroloindoline ring junction was not determined.

![Figure 1.3: Structure of 3-Hydroxy-15H-Tryptophenalin](image)

Recent work in the Chisholm group has shown that diketopiperazines, such as 1.181, can also be cyclized using the previously developed oxoammonium salt conditions resulting in pyrroloindoline 1.182 and 1.183 as a 1:1 mixture of diastereomers (Scheme 1.25). As diketopiperazine 1.181 is similar to the structure of 1.180, we reasoned that our oxidative cyclization conditions could be utilized to synthesize 3-hydroxy-15H-tryptophenalin.
Scheme 1.25: Oxoammonium Salt Mediated Cyclization of Ketopiperazine 1.170

Retrosynthetically, we envisioned obtaining 3-hydroxy-15H-tryptophenalin by cyclizing diketopiperazine 1.185, utilizing our optimized cyclization conditions, followed by the removal of the ACT group. The required diketopiperazine 1.185 can be obtained from dipeptide 1.186 which can be synthesized from a peptide coupling reaction between protected L-tryptophan and protected L-phenylalanine. We expect the cyclization of 1.185 to result in a diastereomer mixture of alkoxyamine substituted pyrroloindoline 1.184. Ideally, these diastereomers will be separated by HPLC and compared to the reported NMR data of 3-hydroxy-15H-tryptophenalin to identify the naturally occurring diastereomer.

Scheme 1.26: Retrosynthetic Analysis of 3-Hydroxy-15H-Tryptophenalin

Diketopiperazine 1.185 was synthesized using a known procedure (Scheme 1.27).99 L-Tryptophan was subjected to a Fischer esterification with thionyl chloride. L-phenylalanine was
protected with a tert-butyloxycarbonyl (Boc) group. The two resulting protected amino acids were coupled with the help of EDCI and NMM to obtain dipeptide 1.186 in a yield of 86%. Diketopiperazine 1.185 was obtained after the removal of the Boc group and subjecting the resulting amine to ammonium hydroxide. With diketopiperazine 1.185 in hand, it was subjected to our oxidation cyclization conditions. Proton NMR of the reaction mixture suggested a 2:3 mixture of both diastereomers, based on seeing duplicate peaks corresponding to the ACT group as well as the C2 and C3 protons. We were able to isolate one diastereomer in a yield of 48%, however, we were unable to identify which one by either $^1$H or $^{13}$C NMR. We were unable to completely isolate the other diastereomer from other impurities. The isolated diastereomer was taken on to remove the alkoxyamine group.

**Scheme 1.27: Proposed Synthesis of 3-Hydroxy-15H-Tryptophenalin**

1.2.6: Attempted Removal of the Alkoxyamine Group

Reported conditions by Xia using zinc in a water, tetrahydrofuran, and acetic acid solvent mixture were employed to try and remove the alkoxyamine protecting group, which resulted in no
reaction occurring and the starting diketopiperazine 1.185 being recovered (Table 1.2, entry 1). The amount of acetic acid was increased, but again no reaction occurred (entry 2). To increase the rate of the reaction, the temperature of the reaction was increased to 50°C (entry 3). This resulted in the recovery of diketopiperazine 1.185. Since no reaction occurred with acetic acid, a stronger acid, HCl, was used, which again resulted in no reaction (entry 4). Increasing the temperature of the reaction resulted in a complex mixture (entry 5). This made us believe our compound may be acid sensitive, so we tried using ammonium chloride (entry 6), which resulted in an unknown compound being formed. Indium was investigated as an alternative to zinc in both acidic and basic conditions (entries 7-8), but no reactions occurred. A reduction reaction with sodium borohydride (entry 9) and a hydrogenation reaction with palladium on carbon (entry 10) were tried to reduce the nitrogen-oxygen bond, but to no avail. Another member of the Chisholm lab was able to remove the alkoxy-amine group from using LiAlH₄ and NiCl₂ from a substrate resulting from an Oxoammonium Salt Mediated Amino-Oxidation. These conditions were attempted and resulted in the formation of a complex mixture (entry 11). These conditions were attempted with the less harsh reducing agent NaBH₄, but unfortunately resulted in no reaction occurring (entry 12). Reaction conditions to remove the ACT group are still under investigation.
### Table 1: Conditions Investigated for the Removal of the ACT Group

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal (equiv)</th>
<th>Acid/Base (equiv)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zn (10.0)</td>
<td>-</td>
<td>AcOH:H₂O:THF</td>
<td>rt</td>
<td>24</td>
<td>n/r&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Zn (10.0)</td>
<td>-</td>
<td>AcOH</td>
<td>rt</td>
<td>24</td>
<td>n/r&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Zn (8.0)</td>
<td>AcOH (8.0)</td>
<td>THF</td>
<td>50°C</td>
<td>2</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Zn (10.0)</td>
<td>Conc. HCl</td>
<td>MeOH</td>
<td>rt</td>
<td>24</td>
<td>n/r&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Zn (10.0)</td>
<td>Conc. HCl</td>
<td>MeOH</td>
<td>60°C</td>
<td>0.5</td>
<td>0&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>Zn (3.0)</td>
<td>NH₄Cl</td>
<td>MeOH</td>
<td>70°C</td>
<td>1</td>
<td>0&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>In (10.0)</td>
<td>AcOH</td>
<td>THF</td>
<td>reflux</td>
<td>24</td>
<td>n/r&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>In (10.0)</td>
<td>Sat. NH₄Cl</td>
<td>EtOH</td>
<td>reflux</td>
<td>24</td>
<td>n/r&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>NaBH₄</td>
<td>-</td>
<td>EtOH</td>
<td>rt</td>
<td>24</td>
<td>n/r&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>10% Pd/C</td>
<td>-</td>
<td>MeOH</td>
<td>60°C</td>
<td>24</td>
<td>n/r&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>NiCl₂ (3.0)</td>
<td>LiAlH₄ (3.0)</td>
<td>THF</td>
<td>-78°C to rt</td>
<td>24</td>
<td>0&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>NiCl₂ •6H₂O (5.0)</td>
<td>NaBH₄ (15.0)</td>
<td>MeOH:THF</td>
<td>rt</td>
<td>24</td>
<td>n/r</td>
</tr>
</tbody>
</table>

**Reaction Conditions:** Alkoxynamine-substituted pyrroloindoline 1.179 was dissolved in solvent (.1M). Metal complex was added followed by acid/base if applicable. *No reaction occurred and only starting material was isolated. 
<sup>b</sup>Diketopiperazine 1.179 formed. 
<sup>c</sup>A complex mixture resulted. 
<sup>d</sup>Unknown compound isolated.

### 1.3 Conclusions and Future Work

A new method for accessing C3α-hydroxy pyrroloindolines has been developed. Protected tryptamines are cyclized in the presence of Bobbitt’s salt using TMG as a base. A variety of N-protected tryptamines were investigated and resulted in moderate yields of 47-78%. Carbamate protected tryptamines and indole-N substituted tryptamines did not react. These conditions were utilized toward the total synthesis of 3-hydroxy-15H-tryptophenalin and resulted in the isolation of one of the diastereomers of the required diketopiperazine in a 48% yield. Reported conditions of zinc and acetic acid were utilized to remove the alkoxynamine and access the C3α hydroxy group, but to no avail. Multiple reaction conditions were investigated to cleave the nitrogen-oxygen bond and resulted in either no reaction occurring or a complex mixture. Conditions to remove the ACT...
group are still under investigation. Once the isolated diastereomer of the natural product is obtained, the NMR spectra will be compared to the reported to determine which isomer of 3-hydroxy-15H-tryptophenalin was isolated from nature.
1.4 Experimental

General Information

All anhydrous reactions were run under a positive pressure of argon. All syringes, needles, and reaction flasks required for anhydrous reactions were dried in an oven and cooled under an argon atmosphere. All reagents and solvents were purchased from commercial sources and used without further purification. Analysis and Purification. Analytical thin layer chromatography (TLC) was performed on precoated glass backed plates (silica gel 60 F254; 0.25 mm thickness). The TLC plates were visualized by UV illumination and by staining. Solvents for chromatography are listed as volume:volume ratios. Flash column chromatography was conducted on silica gel (40-63 μm). Melting points were recorded using an electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed on an elemental analyzer with a thermal conductivity detector and 2-meter GC column maintained at 50 °C. Identity. Proton (^1H NMR) and carbon (^13C[^1H] NMR) nuclear magnetic resonance spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Coupling constants are reported in hertz (Hz). The spectra were recorded in solutions of deuterated chloroform (CDCl₃), with residual chloroform (δ 7.26 ppm for ^1H NMR, δ 77.06 ppm for ^13C[^1H] NMR) as the internal reference. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; td = triplet of doublets; tt = triplet of triplets; qd = quartet of doublets; ddd = doublet of doublet of doublets; br s = broad singlet). Where applicable, the number of protons attached to the corresponding carbon atom was determined by DEPT 135 NMR. Infrared (IR) spectra were obtained neatly by placing the sample directly on the instrument.
1.4.1 General Procedure for Oxidative Cyclization Using Bobbitt’s Salt:

To an oven dried round bottom flask, protected tryptamine (1.0 equiv.), was dissolved in anhydrous tetrahydrofuran (.15 M). The reaction mixture was cooled to 0°C, then 1,1,3,3-tetramethylguanidine (1.2 equiv.) was slowly added followed by Bobbitt’s Salt (1.2 equiv.). The mixture was stirred at 0°C until the reaction showed to reach completion by TLC. The reaction was warmed to room temperature and saturated aqueous sodium bicarbonate was added. The organic layer was extracted out with CH$_2$Cl$_2$. The organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The compound was purified by silica gel column chromatography to give the cyclized product.

![Chemical Structure](image)

(1.122). The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 15 minutes. Purification of the resulting crude residue by silica gel column chromatography (80% ethyl acetate/20% hexanes) resulted in the isolation of 200 mg (78%) of product 1.122 as a purple solid.

1.122. Purple solid (200 mg, 78%); TLC $R_f$ = 0.39 (80% ethyl acetate/20% hexanes); m.p. = 106°C (decomposes); IR (neat) 3378, 3287, 2974, 2938 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J = 8.4$ Hz, 2H), 7.31 (d, $J = 8.1$ Hz, 2H), 7.24 (d, $J = 8.2$ Hz, 1H), 7.10 (t, $J = 7.6$ Hz, 1H), 6.75 (t, $J = 7.3$ Hz, 1H), 6.50 (d, $J = 7.9$ Hz, 1H), 5.96 (s, 1H), 5.08 (d, $J = 7.5$ Hz, 1H), 4.67 (bs, 1H), 4.10-4.01 (m, 1H), 3.55 (t, $J = 8.7$ Hz, 1H), 3.03 (sext, $J = 5.8$ Hz, 1H), 2.42 (s, 3H), 2.31 (dd, $J = 11.9$, 5.6 Hz, 1H), 1.92 (s, 3H), 1.76-1.70 (m, 2H), 1.25-1.18 (m, 3H), 1.15 (s, 3H), 1.08 (s, 3H), 0.76
(s, 3H), 0.70 (s, 3H); $^{13}$C [$^1$H] NMR (100 MHz, CDCl$_3$) δ 169.3, 150.5, 143.5, 136.6, 130.0, 129.6, 129.3, 127.4, 125.9, 118.9, 109.5, 98.2, 80.6, 60.3, 59.6, 46.8, 46.6, 46.1, 40.9, 40.8, 32.7, 32.6, 23.5, 21.5, 21.1, 20.9. Anal. Calcd for C$_{28}$H$_{38}$N$_4$O$_4$S: C, 63.85; H, 7.27; N, 10.64; Found: C, 63.65; H, 7.15; N, 10.45.

(1.154). The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 1 hr. Purification of the resulting crude residue by silica gel column chromatography (65% ethyl acetate/35% hexanes) resulted in the isolation of 140 mg (50%) of product 1.154 as a tan solid.

1.154. Tan solid (140 mg, 50%); TLC $R_f$ = 0.29 (100% ethyl acetate); m.p. = 139°C (decomposes); IR (neat) 3360, 3269, 2975, 2932 cm$^{-1}$, $^1$H NMR (400 MHz, CDCl$_3$) δ 7.33 (d, $J$ = 7.4 Hz, 1H), 7.17 (t, $J$ = 7.7 Hz, 1H), 6.87 (t, $J$ = 7.4 Hz, 1H), 6.63 (d, $J$ = 7.9 Hz, 1H), 6.15 (s, 1H), 5.12 (brs, 1H), 4.59 (brs, 1H), 4.10 (brs, 1H), 3.67 (t, $J$ = 8.6 Hz, 1H), 3.07-3.01 (m, 1H), 2.99 (s, 3H), 2.84-2.74 (m, 1H), 2.44 (dd, $J$ = 12.0, 5.3 Hz, 1H), 1.93 (s, 3H), 1.80-1.74 (m, 2H), 1.36-1.24 (m, 2H), 1.23 (s, 3H), 1.13 (s, 3H), 1.04 (s, 3H), 0.59 (s, 3H). $^{13}$C [$^1$H] NMR (100 MHz, CDCl$_3$) δ 169.2, 150.2, 131.0, 130.1, 125.5, 120.2, 110.5, 98.1, 79.6, 60.4, 59.6, 46.6, 46.2, 46.1, 40.8 40.7, 39.2, 33.2, 32.4, 23.5, 21.2, 20.8. Anal. Calcd for C$_{22}$H$_{34}$N$_4$O$_4$S: C, 58.64; H, 7.61; N, 12.43; Found: C, 58.88; H, 7.27; N, 12.12.
(1.155). The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 1 hour. Purification of the resulting crude residue by silica gel column chromatography (65% ethyl acetate/35% hexanes) resulted in the isolation of 120 mg (48%) of product 1.155 as a light brown solid.

1.155. light brown solid (0.12g, 48%); TLC $R_f = 0.28$ (100% ethyl acetate); m.p. = 117°C (decomposes); IR (neat) 3386, 3273, 3090, 2973, 2929 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J = 7.2$ Hz, 1H), 7.75-7.60 (m, 3H), 7.29 (d, $J = 7.7$ Hz, 1H), 7.11 (t, $J = 7.5$ Hz, 1H), 6.79 (t, $J = 7.4$, 1H), 6.49 (d, $J = 8.0$ Hz, 1H), 6.19 (s, 1H), 5.10 (brs, 1H), 4.92, (brs, 1H), 4.16-4.00 (m, 1H), 3.86 (t, $J = 8.4$, 1H), 3.21-3.10 (m, 1H), 2.80-2.67 (m, 1H), 2.42 (dd, $J = 12.1$, 5.3, 1H), 1.93 (s, 3H), 1.80-1.68 (m, 2H), 1.37-1.22 (m, 2H), 1.19 (s, 3H), 1.12 (s, 3H), 0.84 (s, 3H), 0.68 (s, 3H); $^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) $\delta$ 169.4, 150.2, 148.2, 133.6, 133.2, 131.7, 130.5, 130.1, 129.7, 125.6, 124.1, 119.3, 109.4, 98.6, 79.8, 60.4, 59.7, 47.6, 46.5, 46.1, 41.1, 40.9, 32.7, 32.5, 23.6, 21.2, 20.9. HRMS (QTOF) calculated for C$_{27}$H$_{35}$N$_5$O$_6$S Na [M+H]+ m/z 557.2308, found, 557.2305
The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 1 hour. Purification of the resulting crude residue by silica gel column chromatography (65% ethyl acetate/35% hexanes) resulted in the isolation of 230 mg (86%) of product 1.156 as a tan solid.

1.156. Tan solid (230 mg, 86%); TLC \( R_f = 0.47 \) (100% ethyl acetate); m.p. = 107°C (decomposes); IR (neat) 3361, 3289, 2918 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.32 (d, \( J = 7.4 \) Hz, 1H), 7.14 (t, \( J = 7.5 \) Hz, 1H), 6.89-6.76 (m, 1H), 6.55 (d, \( J = 7.9 \) Hz, 1H), 6.26 (s, 1H), 5.29 (bs, 1H), 4.96 (bs, 1H), 4.15-3.95 (m, 2H), 3.34 (sext, \( J = 6.4 \) Hz, 1H), 2.84-2.69 (m, 1H), 2.54 (dd, \( J = 12.6, 6.2 \) Hz, 1H), 1.92 (s, 3H), 1.83-1.70 (m, 3H), 1.19 (s, 3H), 1.14 (s, 3H) 0.82 (s, 3H), 0.72 (s, 3H). \(^{13}\)C\({\{^1\}H}\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 169.4, 150.1, 130.4, 129.0, 125.8, 119.4, 109.5, 95.6, 78.7, 60.6, 60.0, 46.6, 46.1, 40.9, 40.6, 32.7, 32.1, 23.6, 21.2, 21.1. Anal. Calcd for C\(_{23}\)H\(_{31}\)F\(_3\)N\(_4\)O\(_3\): C, 58.96; H, 6.67; N, 11.96; Found: C, 58.54; H, 7.02; N, 11.58.

The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 1 hour. Purification of the resulting crude residue by silica
gel column chromatography (80% ethyl acetate/20% hexanes) resulted in the isolation of 100 mg (78%) of product 1.160 as a white solid.

1.160. white solid (100 mg, 78%); TLC $R_f = 0.37$ (80% ethyl acetate/20% hexanes); m.p. = 113°C (decomposes); IR (neat) 3303, 2975, 2933, 1696 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.16 (s, 1H), 7.25 (d, $J = 7.3$ Hz, 1H), 7.08 (t, $J = 7.6$ Hz, 1H), 6.67 (t, $J = 7.4$ Hz, 1H), 6.50 (d, $J = 7.9$ Hz, 1H), 5.97 (s, 1H), 5.09 (brs, 1H), 4.26 (q, $J = 7.2$ Hz, 2H), 4.13-4.00 (m, 1H), 3.76-3.62 (m, 2H), 3.55 (d, $J = 12.6$ Hz, 1H), 2.85 (d, $J = 12.6$ Hz, 1H), 1.92-1.82 (m, 7H), 1.55 (d, $J = 12.6$ Hz, 1H), 1.39 (s, 3H), 1.37-1.25 (m, 8H), 1.13 (s, 3H), 1.04-0.96 (m, 3H), 0.25 (s, 3H). $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$) $\delta$ 169.3, 168.2, 167.7, 163.8, 151.7, 130.6, 130.0, 124.9, 117.8, 110.1, 90.9, 89.5, 71.2, 63.3, 62.7, 60.6, 59.9, 46.9, 46.9, 46.9, 46.4, 45.9, 41.0, 35.0, 30.3, 23.6, 22.0, 21.5, 18.8, 13.9, 13.7. Anal. Calcd for C$_{29}$H$_{42}$N$_4$O$_7$: C, 62.35; H, 7.58; N, 10.03; Found: C, 62.62; H, 7.83; N, 9.82.

(1.161). The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 1 hour. Purification of the resulting crude residue by silica gel column chromatography (70% ethyl acetate/30% hexanes) resulted in the isolation of 80 mg (48%) of product 1.161 as a reddish brown solid.

1.161. Reddish Brown Solid (80 mg, 48%); TLC $R_f = 0.37$ (70% ethyl acetate/30% hexanes); m.p. = 97°C (decomposes); IR (neat) 3391, 3304, 2977, 2929, 1629 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.64 (d, $J = 8.2$ Hz, 2H), 7.25-7.19 (m, 3 H), 7.05 (t, $J = 7.7$, 1H), 6.67 (t, $J = 7.4$ Hz, 1H), 6.42
(d, J = 7.8 Hz, 1H), 5.39 (s, 1H), 5.12 (brs, 1H), 4.09-3.98 (m, 1H), 3.34 (t, J = 8.4 Hz, 1H), 2.84-2.74 (m, 1H), 2.59 (dd, J = 11.7, 5.6 Hz, 1H), 2.38 (s, 3H), 2.31-2.20 (m, 1H), 1.89 (s, 3H), 1.87-1.79 (m, 4H), 1.54-1.49 (m, 1H), 1.34 (s, 3H), 1.32-1.25 (m, 1H), 1.24 (s, 3H), 1.12 (s, 3H), 0.97 (t, J = 12.3, 1H), 0.19 (s, 3H). $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$) $\delta$ 169.2, 150.8, 143.1, 137.3, 130.0, 129.5, 128.4, 127.1, 126.2, 117.9, 109.5, 94.2, 90.5, 60.5, 59.8, 46.9, 46.5, 46.4, 40.9, 38.0, 34.9, 30.3, 23.6, 22.4, 22.0, 21.5, 21.4. Anal. Calcd for C$_{29}$H$_{40}$N$_4$O$_4$: C, 64.42; H, 7.46; N, 10.36. Found: C, 64.04; H, 7.57; N, 10.26.

(1.162). The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 15 minutes. Purification of the resulting crude residue by silica gel column chromatography (90% ethyl acetate/10% toluene) resulted in the isolation of 164 mg (47%) of product 1.162 as a light brown solid.

1.162. Light brown solid (164 mg, 47%); TLC $R_f = 0.41$ (100% ethyl acetate) m.p. = 134°C (decomposes); IR (thin film) 3293, 3058, 2999, 2971, 2935, 1669 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 (d, J = 7.3 Hz, 1H), 7.11 (t, J = 7.1 Hz, 1H), 6.77 (t, J = 7.3 Hz, 1H), 6.54 (d, J = 7.9 Hz, 1H), 6.10 (brs, 1H), 5.11 (brs, 1H), 4.09 (t, J = 8.2 Hz, 2H), 3.66-3.58 (m, 1H), 2.73-2.62 (m, 1H), 2.33 (dd, J = 11.7, 4.8 Hz, 1H), 1.92 (s, 3H), 1.83-1.73 (m, 2H), 1.37-1.24 (m, 3H), 1.22 (s, 3H), 1.19 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H). $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$) $\delta$ 169.0, 150.3, 130.1, 129.3, 126.1, 118.4, 108.5, 98.6, 95.8, 67.2, 59.9, 59.3, 46.5, 46.0, 43.3, 40.8, 32.6, 32.5,
23.4, 21.0, 20.8. Anal. Calcd for C_{21}H_{31}N_{3}O_{3}: C, 67.53; H, 8.37; N, 11.25; Found: C, 67.30; H, 8.00; N, 11.62.

(1.166). The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 1 hour. Purification of the resulting crude residue by silica gel column chromatography (70% ethyl acetate/30% hexanes) resulted in the isolation of 65 mg (61%) of product 1.166 as a brown solid.

1.166. Brown solid (65 mg, 61%); TLC R_{f} = 0.23 (70% ethyl acetate/30% hexanes); m.p. = 132°C (decomposes); IR (neat) 3385, 3252, 3086, 2939, 1623 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.79 (d, \(J = 8.3\) Hz, 2H), 7.29 (d, \(J = 8.0\) Hz, 2 H), 7.10 (d, \(J = 7.6\) Hz, 1 H), 6.91 (d, \(J = 7.4\) Hz, 1H), 6.69 (t, \(J = 7.4\) Hz, 1H), 6.05 (d, \(J = 2.9\) Hz, 1H), 5.13 (brs, 1H), 4.37 (d, \(J = 2.3\) Hz, 1H), 4.11-3.99 (m, 1H), 3.59 (t, \(J = 8.6\) Hz, 1H), 3.01-2.92 (m, 1H), 2.58-2.47 (m, 1H), 2.42 (s, 3H), 2.31 (dd, \(J = 12.1, 5.3\) Hz, 1H), 1.99 (s, 3H), 1.92 (s, 3H), 1.73 (dd, \(J = 12.4, 2.9\) Hz, 2 H), 1.26-1.17 (m, 2 H), 1.16 (s, 3H), 1.07 (s, 3H), 0.82 (s, 3H), 0.61 (s, 3H). \(^{13}\)C\({^{1}\text{H}}\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 169.4, 149.2, 143.5, 136.8, 130.6, 129.6, 129.2, 127.6, 123.3, 119.3, 119.1, 98.7, 80.4, 60.5, 59.7, 46.9, 46.7, 46.2, 41.0, 40.8, 32.9, 32.7, 23.6, 21.6, 21.3, 21.0, 16.5. Anal. Calcd for C_{29}H_{40}N_{4}O_{4}S: C, 64.42; H, 7.46; N, 10.36 Found: C, 64.54; H, 7.53; N, 10.19.
The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 1 hour. Purification of the resulting crude residue by silica gel column chromatography (65% ethyl acetate/35% hexanes) resulted in the isolation of 175 mg (73%) of product 1.169 as a white solid.

1.169. White solid (175 mg, 73%); TLC $R_f = 0.41$ (100% ethyl acetate); m.p. = 144°C (decomposes); IR (neat) 3406, 3287, 2976, 2942, 2924, 2874 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.77 (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.1$ Hz, 2H), 7.01 (t, $J = 7.9$, 1H), 6.70 (d, $J = 7.9$ Hz, 1H), 6.40-6.36 (m, 2H), 5.11 (d, $J = 7.2$ Hz, 1H), 4.85 (brs, 1H), 4.15-4.02 (m, 1H), 3.52-3.44 (m, 1H), 3.15-3.06 (m, 1H), 2.78-2.71 (m, 1H), 2.67-2.57 (m, 1H), 2.43 (s, 3H), 1.94 (s, 3H), 1.83 (dt, $J = 12.6$, 3.4, 1H), 1.70 (dt, $J = 12.6$, 3.4, 1H), 1.35-1.18 (m, 2H), 1.23 (s, 3H), 1.15 (s, 3H), 1.00 (s, 3H), 0.41 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$) $\delta$ 169.3, 151.1, 143.7, 136.2, 131.1, 130.9, 129.6, 127.8, 127.6, 120.1, 107.7, 98.2, 77.6, 60.7, 59.9, 46.4, 46.2, 46.1, 40.9, 39.0, 33.7, 32.0, 23.6, 21.5, 21.4, 21.2. Anal. Calcd for C$_{28}$H$_{37}$ClN$_4$O$_4$S: C, 59.93; H, 6.65; N, 9.98 Found: C, 59.70; H, 6.67; N, 9.58.
The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 15 minutes. Purification of the resulting crude residue by silica gel column chromatography (70% ethyl acetate/30% hexanes) resulted in the isolation of 60 mg (47%) of product 1.170 as a white solid.

1.170. White solid (60 mg, 47%); TLC Rf = 0.24 (70% ethyl acetate/30% hexanes); m.p. = 194°C (decomposes); IR (neat) 3406, 3262, 2979, 1649 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ, 7.77 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 2.0 Hz, 1H), 7.06 (dd, J = 8.4, 2.0 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 5.94 (s, 1H), 5.12 (d, J = 7.0 Hz, 1H), 4.14-4.01 (m, 1H), 3.54 (t, J = 8.8 Hz, 1H), 3.05 (sextet, J = 5.8 Hz, 1H), 3.43 (s, 3H), 2.43 (s, 3H), 2.29 (dd, J = 12.2, 5.0 Hz, 1H), 1.93 (s, 3H), 1.80-1.70 (m, 2H), 1.36-1.18 (m, 4H), 1.15 (s, 3H), 1.10 (s, 3H), 0.78 (s, 3H), 0.76 (s, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 169.3, 149.0, 143.7, 136.4, 130.8, 130.0, 129.7, 127.3, 126.1, 123.4, 110.3, 97.7, 81.2, 60.4, 59.7, 46.9, 46.5, 46.1, 40.81, 40.79, 32.9, 32.6, 23.6, 21.5, 21.2, 20.9. Anal. Calcd for C₂₈H₃₇ClN₄O₄S: C, 59.93; H, 6.65; N, 9.98 Found: C, 60.32; H, 6.80; N, 9.93.
The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 15 minutes. Purification of the resulting crude residue by silica gel column chromatography (70% ethyl acetate/30% hexanes) resulted in the isolation of 70 mg (57%) of product \textbf{1.171} as a tan solid.

\textbf{1.171}. Tan solid (70 mg, 57%); TLC \( R_f = 0.21 \) (70% ethyl acetate/30% hexanes); m.p. = 187°C (decomposes); IR (neat) 3405, 3256, 3003, 2884, 1648 cm\(^{-1}\); \( ^{1} \text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 7.77 (d, \( J = 8.2 \) Hz, 2H), 7.35 (d, \( J = 2.0 \) Hz, 1H), 7.31 (d, \( J = 8.1 \) Hz, 2H), 7.20 (dd, \( J = 8.4, 2.0 \) Hz, 1H), 6.41 (d, \( J = 8.4 \) Hz, 1H), 5.94 (s, 1H), 5.12 (d, \( J = 6.6 \) Hz, 1H), 4.14-4.01 (m, 1H), 3.59-3.51 (m, 1H), 3.05 (sextet, \( J = 5.9 \) Hz, 1H), 2.49-2.38 (m, 4 H), 2.29 (dd, \( J = 12.4, 4.7 \) Hz, 1H), 1.93 (s, 3H), 1.80-1.70 (m, 2 H), 1.35-1.18 (m, 3 H), 1.15 (s, 3H), 1.10 (s, 3H), 0.78 (s, 3H), 0.76 (s, 3H). \( ^{13} \text{C\{\text{\textsuperscript{1}H}\}} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 169.3, 149.5, 143.7, 136.4, 132.8, 131.1, 129.7, 129.0, 127.3, 110.9, 97.9, 81.1, 60.5, 59.8, 46.9, 46.5, 46.1, 40.8, 32.9, 32.5, 23.6, 21.5, 21.2, 21.0. Anal. Calcd for C\(_{28}\)H\(_{37}\)BrN\(_{4}\)O\(_{4}\): C, 55.53; H, 6.16; N, 9.25 Found: C, 55.83; H, 6.45; N, 9.01.
The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 15 minutes. Purification of the resulting crude residue by silica gel column chromatography (50% ethyl acetate/50% Toluene) resulted in the isolation of 118 mg (61%) of product \textbf{1.172} as an orange solid.

\textbf{1.172}. Orange Solid (118 mg, 61%); TLC \( R_f = 0.24 \) (50% ethyl acetate/50% toluene); m.p. = 105°C (decomposes); IR (neat) 3376, 3286, 2975, 2936, 1653 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.65 (d, \( J = 8.1 \) Hz, 2H), 7.37-7.33 (m, 1H), 7.25 (d, \( J = 6.1 \) Hz, 2H), 7.20-7.15 (m, 1H), 6.34 (d, \( J = 8.4 \) Hz, 1H), 5.44 (s, 1H), 5.13 (brs, 1H), 4.14-4.02 (m, 1H), 3.34 (t, \( J = 8.5 \) Hz, 1H), 2.88-2.79 (m, 1H), 2.56 (dd, \( J = 11.7, 5.4 \) Hz, 1H), 2.46-2.34 (m, 6H), 2.31-2.21 (m, 1H), 1.92 (s, 3H), 1.84 (s, 3H), 1.39-1.30 (m, 4H), 1.28-1.21 (m, 4H), 1.03 (t, \( J = 12.2 \) Hz, 1H), 0.24 (s, 3H). \(^{13}\)C\{\(^1\)H\} NMR (100 MHz, CDCl\(_3\)) \( \delta \) 169.1, 149.6, 143.1, 136.9, 132.6, 131.2, 129.4, 128.3, 127.0, 110.7, 109.2, 93.8, 90.5, 60.5, 59.8, 46.7, 46.3, 46.3, 46.2, 40.7, 37.8, 34.8, 30.3, 23.4, 22.1, 21.8, 21.34, 21.27. HRMS (QTOF) calculated for C\(_{29}\)H\(_{39}\)BrN\(_4\)O\(_4\)S Na \([M+H]^+\) m/z 618.1875, found, 618.1872.
The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 1 hour. Purification of the resulting crude residue by silica gel column chromatography (100% ethyl acetate) resulted in the isolation of 214 mg (67%) of product 1.173 as a tan solid.

1.173. Tan solid (214 mg, 67%); TLC $R_f = 0.56$ (100% ethyl acetate); m.p. = 112°C (decomposes); IR (neat) 3406, 3287, 2976, 2942, 2874 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (d, $J = 8.1$ Hz, 2H), 7.25 (d, $J = 5.8$ Hz, 2H), 7.07 (d, $J = 7.9$, 1H), 6.79 (d, $J = 7.9$ Hz, 1H), 6.49 (s, 1H), 5.38 (s, 1H), 5.03 (brs, 1H), 4.06 (brs, 1H), 3.38 (t, $J = 8.4$ Hz, 1H), 2.87-2.80 (m, 1H), 2.55 (dd, $J = 11.7$, 5.4 Hz, 1H), 2.42 (s, 3H), 2.31-2.20 (m, 1H) 1.90 (s, 3H), 1.88-1.80 (m, 4H), 1.60-1.57 (m, 1H), 1.31 (s, 3H), 1.30-1.25 (m, 1H), 1.24 (s, 3H), 1.12 (s, 3H), 1.00 (t, $J = 12.5$ Hz, 1H) 0.25 (s, 3H); $^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) $\delta$ 169.1, 151.5, 143.2, 136.9, 129.4, 129.2, 126.8, 125.1, 123.7, 120.6, 112.3, 93.4, 90.3, 60.4, 59.7, 46.7, 46.4, 46.2, 40.7, 37.4, 34.8, 30.3, 23.4, 22.1, 21.8 21.3, 21.2. HRMS (QTOF) calculated for C$_{29}$H$_{30}$BrN$_4$O$_4$S Na [M+H]$^+$ m/z 619.1948, found, 619.1945.
The general procedure for oxidative cyclization using Bobbitt’s Salt was used. The reaction mixture was stirred at 0°C for 3 hours. Purification of the resulting crude residue by silica gel column chromatography (4% methanol/96% dichloromethane) resulted in the isolation of 600 mg (48%) of one diastereomer of 1.184.

1.184. Orange solid (600 mg, 48%); TLC $R_f = 0.11$ (4% methanol/dichloromethane); m.p. = 172°C (decomposes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$7.38-7.28 (m, 4H), 7.25-7.19 (m, 2H), 7.15 (t, $J = 7.6$ Hz, 1H), 6.89 (t, $J = 7.6$ Hz, 1H), 6.57 (d, $J = 7.9$ Hz, 1H), 6.33 (bs, 1H), 5.70-5.61 (m, 1H), 5.16-5.09 (m, 1H), 4.28-4.21 (m, 1H), 4.14-4.03 (m, 2H), 3.64-3.56 (m, 1H), 2.90 (dd, $J = 12.4$, 6.4 Hz, 1H), 2.85-2.70 (m, 2H), 1.92 (s, 3H), 1.81-1.72 (m, 2H), 1.71 (s, 1H), 1.33-1.21 (m, 2H), 1.19 (s, 3H), 1.16 (s, 3H), 0.80 (s, 3H), 0.78 (s, 3H); $^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) $\delta$ 169.4, 168.1, 165.2, 150.4, 135.5, 130.5, 129.3, 129.2, 128.5, 127.7, 126.3, 119.4, 109.7, 94.9, 77.6, 60.5, 59.9, 58.2, 56.3, 46.5, 46.1, 43.9, 40.9, 37.5, 32.8, 32.2, 29.8, 23.6, 21.2, 21.1. HRMS (QTOF) calculated for C$_{31}$H$_{39}$N$_{5}$O$_{4}$ Na [M+H]$^+$ m/z 546.3075, found, 546.3072.
1.5 $^1$H and $^{13}$C Supplement to Chapter 1
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1.6 References


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Chapter 2:  
**Tandem Oxidation-Bromination of Allylic Alcohols with a TEMPO-Oxone-Et₄NBr System**

**Abstract**

Allylic alcohols can be converted directly to $\alpha$-bromo-$\alpha$, $\beta$-unsaturated ketones in a single reaction with a mixture of TEMPO, Oxone and tetraethylammonium bromide. This process proceeds first through the oxidation of the alcohol to the ketone, followed by dibromination of the alkene with bromine that is generated from Oxone and tetraethylammonium bromide. Quenching the reaction with triethylamine facilitates elimination and forms the vinyl bromide. The presence of electron-donating groups on the aromatic ring led to faster reactions and higher yields. Alternatively, substrates decorated with electron withdrawing groups on the aromatic ring are slower to oxidize resulting in lower yields. This method provides a rapid means to access these bromoalkenes using conditions that are operationally simple with reagents that are stable and easy to handle.
2.1 Introduction

2.1.1 Tandem Reactions

Traditionally, organic synthesis is performed in a stepwise manner with each intermediate being isolated and purified. While effective, modern pressures to access complex molecules in a more rapid manner have led to the exploration of reaction conditions that can perform multiple transformations in a single reaction mixture. These types of reactions are often referred to as tandem, cascade, or domino processes.\textsuperscript{1-3} Domino reactions occur quite often in nature. A common example of this reaction is the biosynthesis of fatty acids from acetate (Scheme 2.1).\textsuperscript{4} This reaction occurs when acetate 2.1 is reacted with eight equivalents of malonyl-SCoA 2.2, resulting in either palmitic acid or stearic acid 2.3.

Scheme 2.1: Biosynthesis of Fatty Acids

\[
\text{H}_3\text{C} - \text{S} - \text{CoA} \quad + \quad \text{OOC} - \text{S} - \text{CoA (8.0 equiv.)} \quad \rightarrow \quad \text{H}_3\text{C} - (\text{CH}_2)_{16} - \text{COOH}
\]

Another example can be found in the biosynthesis of steroids from squalene epoxide which is selectively transformed into lanosterol.\textsuperscript{5,6} This occurs with the formation of four C-C bonds and six stereocenters. This biological process was replicated by Johnson and co-workers to synthesize progesterone (Scheme 2.2).\textsuperscript{7} An acid-catalyzed domino cyclization of monocyclic trieneyne 2.4 resulted in tetracyclic 2.6 which was further transformed into progesterone 2.8.
Synthetic chemists have spent decades developing ways to mimic these biological domino reactions. A well-known example of this is the biomimetic synthesis of tropinone (Scheme 2.3).\(^8\) Schöpf and Robinson performed the first domino reaction of a natural product by reacting a mixture of succindialdehyde \(2.9\), methylamine \(2.10\), and acetonedicarboxylic acid \(2.11\) in a double Mannich reaction to obtain tropinone \(2.12\). This bicyclic compound is a structural component of several alkaloids such as cocaine and atropine.\(^9\)

**Scheme 2.3: Biomimetic Domino Synthesis of Tropinone**

Performing multiple transformations in a single reaction results in a process with significantly improved time economy.\(^10\) With a shorter time to synthesize a product, the utility and energy cost from heating and cooling the reaction mixture are reduced. Given that only a single purification is needed, labor and solvent costs are also significantly lowered. These types of
reactions are particularly useful when the intermediates are reactive, volatile, lachrymatory, or otherwise difficult to manage.

### 2.1.2 Previous Syntheses of α-Bromo-α,β-unsaturated Ketones

The α-bromo-α,β-unsaturated ketone products that are the subject of this investigation have significant utility in complex molecule synthesis, as they can be rapidly transformed into a variety of more complex substrates (Scheme 2.4). Palladium catalyzed couplings can be performed to displace the bromide in structure 2.14 with an aromatic ring.\textsuperscript{11, 12} The bromide can also be exchanged for other heteroatoms, like in the trifluoromethylthiolation that leads to 2.16.\textsuperscript{13} Additionally, the alkene is an excellent Michael acceptor which is amenable to tandem 1,4-addition-intramolecular S\textsubscript{N}2 processes, like in the formation of cyclopropane 2.17\textsuperscript{14} and aziridine 2.18.\textsuperscript{15} This concept has been extended to other heterocycles,\textsuperscript{16, 17} including aminoimidazoles like 2.19.\textsuperscript{18}

**Scheme 2.4: Synthesis and Utility α-Bromo-α,β-unsaturated Ketones**

![Scheme 2.4](image-url)
Most synthetic routes to \(\alpha\)-bromo-\(\alpha,\beta\)-unsaturated ketones proceed in a stepwise fashion by formation of the unsaturated ketone from the alcohol, bromination to the dibromide, and elimination (Scheme 2.5).\textsuperscript{12, 19-21} In a typical example, Corey and co-workers oxidized vinyl alcohol 2.20 with manganese dioxide. The resulting ketone 2.21 was dibrominated followed by elimination with triethylamine.\textsuperscript{22} Fang and coworkers also performed a similar synthesis using pyridinium perbromide as a brominating agent.\textsuperscript{12} To accelerate access to these materials, the Chisholm laboratory previously developed a tandem oxidation-halogenation reaction of allylic alcohols using modified Moffatt-Swern conditions.\textsuperscript{23} These conditions avoided the isolation of the intermediate vinyl ketone, which often proved to be volatile and could be easily lost during the solvent evaporation. Aryl allylic alcohols, such as 2.28, were converted to \(\alpha\)-bromo-\(\alpha,\beta\)-unsaturated ketone 2.30 using oxalyl bromide and dimethyl sulfoxide. These conditions also worked well with chlorination. While electron poor aromatic rings were well tolerated under these modified Moffatt-Swern conditions,\textsuperscript{23} electron rich aromatics resulted in the formation of an allylic halide such as 2.31 and 2.32. Therefore, we have undertaken a study of alternative conditions that would perform a similar tandem reaction for a wider range of substrates.

**Scheme 2.5: Previous Synthesis of \(\alpha\)-Bromo-\(\alpha,\beta\)-Unsaturated Ketones**

Corey et al.

\[
\begin{align*}
\text{OH} & \xrightarrow{\text{MnO}_2, \text{CH}_2\text{Cl}_2, \text{0°C}, \text{30 min}} \text{75\%} & \xrightarrow{\text{Br}_2, \text{CH}_2\text{Cl}_2, \text{-78°C}, \text{30 min}} \xrightarrow{\text{Et}_3\text{N}, \text{Et}_2\text{O}, \text{-78°C, 2 h}} \text{70\% over 2 steps}
\end{align*}
\]

Fang et al.

\[
\begin{align*}
\text{OH} & \xrightarrow{\text{MnO}_2, \text{CH}_2\text{Cl}_2, \text{rt}} \text{2.24} & \xrightarrow{\text{CpH}_3\text{Br}_3\text{N, K}_2\text{CO}_3, \text{CMe}_2\text{Cl}_2, \text{rt}} \text{2.25} & \xrightarrow{\text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2, \text{rt}} \text{2.27}
\end{align*}
\]

Chisholm et al.

\[
\begin{align*}
\text{OH} & \xrightarrow{\text{XCOCOX (3 equiv), DMSO (4 equiv)}} \text{2.28} & \xrightarrow{\text{then Et}_3\text{N, \text{CMe}_2\text{Cl}_2, -78°C, rt}} \text{2.29 R = EWG, X = Cl} & \text{2.30 R = EWG, X = Br} & \text{2.31 R = EDG, X = Cl} & \text{2.32 R = EDG, X = Br}
\end{align*}
\]
2.1.3 Sodium Halides and Oxone in Oxidation and Halogenation Reactions

A literature survey of methods that could be adapted to a tandem oxidation-bromination showed that Oxone \([2(\text{KHSO}_5)\cdot\text{KHSO}_4\cdot\text{K}_2\text{SO}_4]\) may be useful as the stoichiometric oxidant in these processes. Oxone is often referred to as a green oxidant since the environmentally benign \(\text{K}_2\text{SO}_4\) is the by-product of the oxidations. Oxone has been a popular oxidizing agent in organic synthesis due to its low cost, stability, and ease of handling. While Oxone does not directly oxidize alcohols, it can promote this transformation when halide salts are added. Giannis and co-workers showed that when subjected to sodium chloride, Oxone can oxidize benzylic alcohols, such as \(2.33\), to the corresponding ketone (Scheme 2.6). Lee showed that a similar process can be performed in the presence of Oxone and sodium bromide in a biphasic solvent system to obtain aldehydes such as \(2.39\). The combination of Oxone with a sodium halide has also been used to halogenate enones, such as \(2.35\) by Dieter, as well as aromatic rings. Tong showed that with Oxone and sodium chloride, allylic alcohols such as \(2.40\) undergo dichlorination of the double bond. A base such as triethylamine can be added to induce an elimination and result in the \(\alpha\)-chloro alkene. Since sodium halides and Oxone have been shown to perform both alcohol oxidations and alkene halogenations of similar systems, we speculated that both reactions could occur in a tandem process, maximizing efficiency.
2.2 Results and Discussion

2.2.1 Optimization of Tandem Oxidation-Bromination Reaction

In order to ensure that the reaction would perform adequately on electron rich allylic alcohols, 1-(4-methoxyphenyl)-2-propen-1-ol 2.43 was utilized to determine the optimal reaction conditions. Subjecting benzylic alcohol 2.43 to 2 equivalents of Oxone and 2 equivalents of a bromide salt (LiBr, NaBr, KBr) in acetonitrile (Table 1, entries 1–3) resulted in no reaction occurring, with starting material being recovered in all cases. Concerned that the bromide salt was not reacting due to the poor solubility in the organic solvent, we next employed a biphasic solvent system of acetonitrile and water (entry 4), however this resulted in a complex mixture that did not appear to contain the desired bromoalkene 2.44 or intermediates 2.45 or 2.46. The alkene peaks did disappear in $^1$H NMR, however, implicating that an unwanted decomposition of the alkene by the Oxone and/or the bromine took place. The solubility of the bromide ion was then addressed by using tetraethylammonium bromide (TEAB) as a soluble bromide source in MeCN. In addition, believing that the oxidation of the allylic alcohol needed to be the first reaction to occur, otherwise bromination of the alkene may be competitive,\(^\text{32}\) we changed the sequence of addition of the
reactants so that the TEAB was added last after stirring the other reactants together for 15 min. These changes resulted in the formation of trace amounts of the ketone 2.45 in the crude $^1$H NMR (entry 5), leading to the conclusion that the rate of the initial oxidation of the alcohol was indeed sluggish. To increase the rate of alcohol oxidation, a catalytic amount of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) (entry 6) was added. This resulted in only the $\alpha,\beta$-unsaturated ketone 2.45 being observed, although in a significant yield of 45%. Increasing the equivalents of both Oxone and TEAB resulted in the formation of the desired bromoketone 2.44 (entries 7–9). Optimized conditions were found to be 4.0 equivalents of Oxone, 3.0 equivalents of TEAB, 10 mol% of TEMPO, in acetonitrile (0.1 M) for 24 h followed by quenching with 10 equivalents of TEA (entry 9). An oxidation-chlorination was also attempted with tetraethylammonium chloride, however only a complex mixture was obtained (entry 10).
Table 2.1: Optimization of Oxidation-Bromination Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. Oxone</th>
<th>Halide (equiv.)</th>
<th>TEMPO (mol%)</th>
<th>Isolated Yield (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2.0</td>
<td>LiBr (2.0)</td>
<td>-</td>
<td>0 d</td>
</tr>
<tr>
<td>2a</td>
<td>2.0</td>
<td>NaBr (2.0)</td>
<td>-</td>
<td>0 d</td>
</tr>
<tr>
<td>3a</td>
<td>2.0</td>
<td>KBr (2.0)</td>
<td>-</td>
<td>0 d</td>
</tr>
<tr>
<td>4ab</td>
<td>2.0</td>
<td>NaBr (2.0)</td>
<td>-</td>
<td>0 e</td>
</tr>
<tr>
<td>5a</td>
<td>2.0</td>
<td>Et4NBr (2.0)</td>
<td>-</td>
<td>Trace (2.45)</td>
</tr>
<tr>
<td>6c</td>
<td>2.0</td>
<td>Et4NBr (2.0)</td>
<td>10</td>
<td>45 (2.45)</td>
</tr>
<tr>
<td>7c</td>
<td>2.0</td>
<td>Et4NBr (2.0)</td>
<td>10</td>
<td>43 (2.44) + 33 (2.45)</td>
</tr>
<tr>
<td>8e</td>
<td>3.0</td>
<td>Et4NBr (3.0)</td>
<td>10</td>
<td>55 (2.44) + 25 (2.45)</td>
</tr>
<tr>
<td>9c</td>
<td>4.0</td>
<td>Et4NBr (3.0)</td>
<td>10</td>
<td>71 (2.44)</td>
</tr>
<tr>
<td>10c</td>
<td>4.0</td>
<td>Et4NCl (3.0)</td>
<td>10</td>
<td>0 e</td>
</tr>
</tbody>
</table>

a1-(4-Methoxyphenyl)-2-propen-1-ol 9 was dissolved in dry MeCN. Oxidizing agent, bromine source, and TEMPO (if applicable) was added sequentially. After 24 h, 10 equivalents of Et4N were added to the reaction mixture and stirred for 30 min. bA 1:1 mixture of MeCN:H2O was used as solvent. c1-(4-Methoxyphenyl)-2-propen-1-ol 9 was dissolved in dry MeCN. Oxone was added, followed by TEMPO. The reaction mixture was stirred for 15 min before adding bromide source. After 24 h, 10 equivalents of Et4N were added to the reaction mixture and stirred for 30 min. dStarting alcohol was recovered. eA complex mixture resulted.

2.2.2 Synthesis of Vinyl Alcohol Based Substrates

To evaluate the scope of the newly found conditions, a variety of benzyl allylic alcohols were synthesized using a Grignard reaction employing the appropriate aldehyde and vinyl magnesium chloride. Most of the desired alcohols were obtained in moderate to excellent yields (Scheme 2.7). Allylic alcohol substrates were also synthesized in respectable yields of 66-92% by using sodium borohydride to reduce the appropriate aromatic aldehydes and ketones.
2.2.3 Scope of Tandem Oxidation-Bromination Reaction

The scope of this oxidation-bromination reaction was first investigated with a variety of aromatic 2-propen-1-ols (Scheme 2.8). Electron rich aromatic rings with alkoxy groups gave moderate yields between 47–71%, with the exception of vinyl ketone 2.77. An alkoxy group in the meta position of the aromatic ring resulted in an undesirable yield of 23%. While these yields may seem moderate, it is important to note that they are the culmination of a tandem three step sequence, so a 50% yield is the equivalent of preforming three transformations in approximately
80% yield for each individual step, with the major advantage being the time and effort saved from having to isolate and purify the intermediates. Additionally, these conditions are complementary to our previously discovered modified Swern conditions,\textsuperscript{23} as electron rich aromatic systems did not provide the α-bromo ketone product, but instead an allylic bromide was formed. A slightly lower yield was obtained with the methoxy group present in the ortho position (2.76, 2.78, and 2.81), which may be due to the steric effects. Surprisingly, 2.80 was not produced when 1-(2,4-trimethoxyphenyl)prop-2-en-1-ol was subjected to these conditions. Although steric effects may be playing a role in the decrease in yield for substrates containing the substituent in the ortho position, product was still obtained. As a result, we would still expect to obtain 2.80, even if in a lower yield. A similar trend to methoxy substituted benzyl alcohols was observed for alkyl substituted benzyl alcohols 2.83-2.87, with the lowest yield being observed for vinyl ketone 2.87 due to the presence of the two ortho substituents on the aromatic ring.
Scheme 2.8: Formation of α-Bromo Unsaturated Ketones from Electron Rich Aryl Allylic Alcohols

The effects of electron withdrawing groups on the aromatic ring were also evaluated in this oxidation-bromination reaction (Scheme 2.9). Halogen substituents in the meta and para position were well tolerated (2.89-2.93), providing yields of 46–60%. Similar to the previously mentioned electron rich aromatic systems, a halogen substituent in the ortho position resulted in poor yields, such as in 2.88. The presence of stronger electron withdrawing groups resulted in significantly lower yields than most other substrates as seen in 2.94-2.96. This could be attributed to the stronger inductive effect from the substituents, as electron poor benzylic alcohols have been observed to react more slowly in TEMPO oxidations\textsuperscript{33} and in Oxone mediated alcohol oxidations.\textsuperscript{26, 34} This trend was continued to be observed with 2.97, as the addition of a second electron withdrawing group did not produce product.
Other aromatic allylic alcohols were evaluated as well as aliphatic alcohols (Scheme 2.10). Benzothiophene 2.98 was also successfully oxidized under these conditions with no oxidation of the thiophene sulfur. While Oxone is known to oxidize sulfides to their sulfones, oxidation of the aromatic thiophene usually requires more vigorous conditions like heating or ball-milling. Benzodioxole 2.23 was obtained in a moderate yield of 48%. 1-(furan-2-yl)-2-propen-1-ol and vinyl-2-naphthylcarbinol did not give any product. Aryl substituted benzyl derivatives were also obtained in moderate yield, as seen in 2.101. Unfortunately, these conditions appear to be limited to aromatic vinyl alcohols as aliphatic allylic alcohols did not result in product as seen in 2.102-2.104.
Scheme 2.10: Formation of α-Bromo Unsaturated Ketones from Other Allylic Alcohols

The oxidation-bromination protocol was then evaluated on a number of other allylic alcohols (Scheme 2.11). Cinnamyl alcohol participated well in the transformation, providing a 40% yield of α-bromoaldehyde 2.105. Only a single alkene stereoisomer was observed in the product. This is commonly observed with these types of transformations, as the (Z) isomer is more stable, and this isomerization often can occur due to light, heat, or the presence of acid. Substitution on the aromatic ring of similar cinnamyl substrates (2.106 and 2.107) was also tolerated, with electron donating and weak electron withdrawing groups all providing product. The chloride electron withdrawing group did slow the bromination reaction, so some 4-chlorocinnamaldehyde was also isolated. Strong electron withdrawing groups deactivated the alkene for bromination, so in the presence of nitro substituents, only oxidation to the aldehyde 2.108 was observed. Secondary allylic alcohols also participated in the transformation as long as an aromatic substituent was present on the alkene such as in 2.109a, 2.109b, and 2.110. Alkyl substituted allylic alcohols were significantly less reactive, and did not provide product, instead a complex mixture of products was observed. This may be due to the slower oxidation of the alcohol, which then allows for some unwanted halogenation reactions with the alkene.
2.2.4 Proposed Mechanism of Tandem Oxidation-Bromination Reaction

On the basis of the results of the substrate scope and literature reports, we have proposed a mechanism for this transformation (Scheme 2.12). Initially, TEMPO 2.111 is oxidized to nitrosonium cation 2.112 by Oxone. The nitrosonium cation reacts with alcohol anion 2.113 and proceeds through transition state 2.114, resulting in hydroxyl amine 2.115 and the corresponding alcohol. The catalytic cycle is completed when hydroxyl amine 2.115 is reoxidized to nitrosonium cation 2.112 by a suitable oxidant.

Similar to the reported reaction between Oxone and sodium bromide, the Oxone and tetraethylammonium bromide may react and form bromine in situ. The vinyl ketone, resulting from the Oxone/TEMPO oxidation reaction, reacts with the generated bromine ion to give dibrominated ketone 2.118. Triethylamine is utilized to perform an elimination reaction to acquire the sought after α-bromo-α,β-unsaturated carbonyl compound 2.119.
2.3 Conclusions

A new protocol for the direct conversion of allylic alcohols to α-bromo-α,β-unsaturated ketones and aldehydes has been developed. This method uses the green oxidant Oxone along with TEMPO and tetraethylammonium bromide to accomplish the transformation. While the yields of the transformation are moderate, the conditions are operationally simple, and the reagents are all shelf stable and easy to handle. The presence of electron-donating groups on the aromatic ring leads to faster reactions and higher yields, which is complementary to our previously developed Swern-based system where these substrates gave allylic bromides as products. Substrates with electron withdrawing groups on the aromatic ring tend to be slower to oxidize and provide significantly lower yields. Some steric effects were observed with substitution at the C2 position of the aromatic ring, which slows the initial oxidation of the alcohol. These conditions are limited to aromatic substrates, as alkyl substituted allylic alcohols do not participate. This tandem method is highlighted by operational simplicity and the use of an environmentally friendly stoichiometric oxidant.
2.4 Experimental

General Experimental Information

All anhydrous reactions were run under a positive pressure of argon. Dichloromethane (DCM) was dried by passage through an alumina column. 1,2-Dichloroethane (1,2-DCE) was freshly distilled from calcium hydride before use. Tetrahydrofuran (THF) was freshly distilled from Na/benzophenone before use. Ethyl acetate (EA), hexanes and other solvents were used as received from the manufacturer.

Identity. Proton (\(^1\)H NMR) and carbon (\(^{13}\)C NMR) nuclear magnetic resonance spectra were recorded at 400 MHz and 100 MHz respectively. The chemical shifts are given in parts per million (ppm) on the delta (\(\delta\)) scale. Coupling constants are reported in hertz (Hz). For spectra recorded in solutions of deuterated chloroform (CDCl\(_3\)), residual chloroform or TMS was used as the internal reference. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; td = triplet of doublets; tt = triplet of triplets; qd = quartet of doublets; ddd = doublet of doublet of doublets; br s = broad singlet). Where applicable, the number of protons attached to the corresponding carbon atom was determined by DEPT135 NMR. Infrared (IR) spectra were obtained neat using an attenuated total reflectance (ATR) attachment.

Analysis and Purity. Analytical thin layer chromatography (TLC) was performed on precoated glass backed plates (silica gel 60 F254; 0.25 mm thickness). The TLC plates were visualized by UV illumination and by staining. Solvents for chromatography are listed as volume:volume ratios. Flash column chromatography was conducted on silica gel (40-63 μm). Melting points were recorded using an electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed on an elemental analyzer with a thermal conductivity detector and 2-meter GC column maintained at 50 °C.
Most of the allylic alcohols used in this study were synthesized from the corresponding aldehydes as reported previously (2.43, 2.47, 2.48, 2.49, 2.50, 2.52, 2.56, 2.57, 2.59, 2.60, 2.64, 2.65, 2.66, 2.67, 2.70, 2.71, 2.72 and 2.73) or purchased from commercial sources. Others were synthesized following the general procedure below.

**General Procedure for Grignard Reduction of Aromatic Aldehydes:**

To an oven dried round bottom flask equipped with stir bar, the appropriate aldehyde (300 mg) was added, evacuated, and back filled with argon. The aldehyde was dissolved in dry THF (0.5 M), then cooled to 0 °C. Vinyl magnesium chloride (1.2 equivalents) was added dropwise, and the reaction stirred at 0 °C for 30 minutes. The reaction was warmed to room temperature and stirred until no starting material was present by TLC. The mixture was quenched with saturated NH₄Cl solution, and the organic layer extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The resulting crude residue was purified by silica gel flash column chromatography.

![Chemical Structure](image)

**1-(2,3,4-Trimethoxyphenyl)prop-2-en-1-ol (2.63):** The general procedure for synthesis of vinyl alcohols was followed to provide compound 2.63 as a cloudy oil (162 mg, 47%). TLC Rₓ = 0.24 (20% EA/hexanes); IR (neat) 3437, 3081, 2939, 2836, 1090 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.98 (d, J = 8.6 Hz, 1H), 6.66 (d, J = 8.6 Hz, 1H), 6.14-6.06 (m, 1H), 5.34-5.29 (m, 2H), 5.19 (d, J = 10.4 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 2.59 (d, J = 5.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 153.6, 151.6, 142.3, 140.5, 128.7, 122.0, 114.5, 107.4, 71.4, 61.3, 60.9, 56.2. Anal. Calcd for C₁₂H₁₆O₄: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.00.
1-(3,4-Dimethylphenyl)prop-2-en-1-ol (2.67): The general procedure for synthesis of vinyl alcohols was followed to provide compound 2.67 as a white solid (438 mg, 72%). TLC Rf = 0.24 (10% EA/hexanes); IR (neat) 3347, 3074, 2970, 2921, 1892, 1856, 1449, 924 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.15-7.09 (m, 3H), 6.09-6.01 (m, 1H), 5.36 (d, J = 17.3 Hz, 1H), 5.20-5.15 (m, 2H), 2.27 (s, 3H), 2.26 (s, 3H), 1.86 (bs, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 140.5, 140.3, 137.0, 136.3, 130.0, 127.7, 123.9, 114.9, 75.4, 19.9, 19.6. Anal. Calcd for C₁₁H₁₄O: C, 81.44; H, 8.70. Found: C, 81.43; H, 8.52.

**General Procedure for Reduction of Methyl Vinyl Ketones:**

To an oven dried round bottom flask equipped with stir bar, the appropriate vinyl ketone (300 mg) was added, evacuated, and back filled with argon. The ketone was dissolved in dry MeOH (0.67 M), then cooled to 0 °C. NaBH₄ (0.6 equivalents) was added. The reaction was warmed to room temperature and stirred until no starting material was present by TLC. The solvent was removed in vacuo and the reaction mixture redissolved in ethyl acetate. Saturated NaHCO₃ was added, and the organic layer extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The resulting crude residue was purified by silica gel flash column chromatography.

**General Procedure for Tandem Oxidation-Bromination Reaction:**

To a round bottom flask equipped with a stir bar, vinyl alcohol (70 mg) was dissolved in 0.1 M dry acetonitrile. Oxone (4.0 equivalents) was added, followed by 10 mol% of TEMPO. The reaction mixture was stirred for 15 minutes. Tetraethylammonium bromide (3.0 equivalents) was added, and the reaction stirred at room temperature for 24 hours. Triethylamine (10.0 equivalents)
was added to the mixture and stirred for 30 minutes. The reaction mixture was poured over ice cold 1M HCl (5 mL) and the organic layer extracted with DCM (2 x 10 mL). The organic layers were combined, washed with brine (1 x 10 mL), dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The resulting crude residue was purified by silica gel flash column chromatography.

![Chemical Structure](image)

**2-Bromo-1-(4-methoxyphenyl)prop-2-en-1-one (2.44):** General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.44 as a yellow oil (73 mg, 71%). TLC $R_f = 0.27$ (5% EA/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.87 (d, $J = 8.8$ Hz, 2H), 6.95 (d, $J = 8.9$ Hz, 2H), 6.41 (d, $J = 2.3$ Hz, 1H), 6.37 (d, $J = 2.3$ Hz, 1H), 3.89 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 189.1, 164.1, 132.5, 129.0, 128.0, 127.6, 114.0, 55.7. This compound has been previously reported.$^{48}$

![Chemical Structure](image)

**2-Bromo-1-(2-methoxyphenyl)prop-2-en-1-one (2.76):** General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.76 as a yellow oil (48 mg, 47%); TLC $R_f = 0.36$ (50% DCM/hexanes); IR (neat) 3007, 2838, 1676, 1251 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45 (td, $J = 8.0$, 1.6 Hz, 1H), 7.32 (dd, $J = 7.5$, 1.4 Hz, 1H), 7.02-6.95, (m, 2H), 6.51 (d, $J = 2.2$ Hz, 1H), 6.47 (d, $J = 2.2$ Hz, 1H), 2.82 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 190.2, 157.5, 132.7, 132.5, 131.7, 129.5, 126.7, 120.6, 111.7, 55.9. Anal. Calcd for C$_{10}$H$_9$BrO$_2$: C, 49.82; H, 3.76. Found: C, 49.76; H, 3.53.
**2-Bromo-1-(3-methoxyphenyl)prop-2-en-1-one (2.77):** General procedure for tandem oxidation-bromination reaction was followed to provide compound **2.77** as a yellow oil (24 mg, 23%). TLC $R_f = 0.29$ (50% dichloromethane/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.36 (m, 2H), 7.34-7.31 (m, 1H), 7.16-7.11 (m, 1H), 6.53 (d, $J = 2.4$ Hz, 1H), 6.48 (d, $J = 2.4$ Hz, 1H) 3.86 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 190.1, 159.8, 136.5, 130.2, 129.63, 129.59, 122.5, 119.8, 114.2, 55.7. This compound has been previously reported.\(^{23}\)

**2-Bromo-1-(2,5-dimethoxyphenyl)prop-2-en-1-one (2.78):** General procedure for tandem oxidation-bromination reaction was followed to provide compound **2.78** as a yellow oil (47 mg, 48%). TLC $R_f = 0.42$ (70% DCM/hexanes); IR (neat) 3001, 2942, 2835, 1678, 1493, 1215 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.99 (dd, $J = 9.0$, 3.1 Hz, 1H), 6.90 – 6.86 (m, 2H), 6.52 (d, $J = 2.1$ Hz, 1H), 6.49 (d, $J = 2.1$ Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 190.0, 153.5, 151.6, 132.3, 131.8, 127.3, 118.2, 114.4, 113.2, 56.6, 56.0. Anal. Calcd for C$_{11}$H$_{11}$BrO$_3$: C, 48.73; H, 4.09. Found: C, 48.92; H, 3.94.

**2-Bromo-1-(3,4-dimethoxyphenyl)prop-2-en-1-one (2.79):** General procedure for tandem oxidation-bromination reaction was followed to provide compound **2.79** as a pale-yellow solid (59 mg, 60%). mp = 117-120 °C; TLC $R_f = 0.28$ (15% EA/hexanes); IR (neat) 3099, 3075, 2999, 2932,
2847, 1638 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.49 (dd, J = 8.4, 1.4 Hz, 1H), 7.42 (s, 1H), 6.88 (d, \(J = 8.4\) Hz, 1H), 6.37 (dd, \(J = 9.1, 1.9\) Hz, 2H), 3.94 (s, 3H), 3.92 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 189.1, 153.9, 149.3, 128.5, 127.7, 127.5, 125.3, 111.9, 110.1, 56.3, 56.2\). Anal. Calcd for C\(_{11}\)H\(_{11}\)BrO\(_3\): C, 48.73; H, 4.09. Found: C, 48.75; H, 4.02.

\[\text{H}_3\text{CO} \quad \text{O} \quad \text{Br} \quad \text{H}_3\text{CO}\]

**2-Bromo-1-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (2.81):** General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.81 as a yellow oil (49 mg, 52%). TLC \(R_f = 0.20\) (100% DCM); IR (neat) 2940, 2841, 1671, 1589, 1282, 1093 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.13 (d, J = 8.7\) Hz, 1H), 6.69 (d, \(J = 8.7\) Hz, 1H), 6.48 (d, \(J = 2.1\) Hz, 1H), 6.42 (d, \(J = 2.1\) Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 189.2, 157.0, 152.9, 142.3, 132.3, 130.3, 125.1, 124.1, 124.1, 106.9, 62.0, 61.1, 56.3\). Anal. Calcd for C\(_{12}\)H\(_{13}\)BrO\(_4\): C, 47.86; H, 4.35. Found: C, 47.55; H, 4.20.

\[\text{H}_3\text{CO} \quad \text{O} \quad \text{Br} \quad \text{H}_3\text{CO}\]

**2-Bromo-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (2.82):** General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.82 as a yellow solid (47 mg, 50%). mp = 43-47 °C; TLC \(R_f = 0.17\) (100% DCM); IR (neat) 3007, 2939, 2833, 1655, 1581, 1118 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.10 (s, 2H), 6.46 (d, J = 2.2\) Hz, 1H), 6.44 (d, \(J = 2.2\) Hz, 1H), 3.93 (s, 3H), 3.91 (s, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 189.2, 157.0, 152.9, 142.3, 132.3, 130.3, 125.1, 124.1, 106.9, 62.0, 61.1, 56.3\). Anal. Calcd for C\(_{12}\)H\(_{13}\)BrO\(_4\): C, 47.86; H, 4.35; Found: C, 47.80; H, 4.46.
2-Bromo-1-(o-tolyl)prop-2-en-1-one (2.83): General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.83 as a clear oil (42 mg, 40%). TLC $R_f$ = 0.33 (30% DCM/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.32 (m, 2H), 7.27 – 7.21 (m, 2H), 6.63, (d, $J = 2.2$ Hz, 1H), 6.44 (d, $J = 2.2$ Hz, 1H), 2.34 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 191.9, 137.0, 136.2, 133.2, 132.8, 131.2, 130.9, 128.3, 125.3, 19.8. This compound has been previously reported.$^{49}$

2-Bromo-1-(m-tolyl)prop-2-en-1-one (2.84): General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.84 as a clear oil (17 mg, 28%); TLC $R_f$ = 0.27 (30% dichloromethane/hexanes); IR (neat) 3346, 3074, 2970, 2921, 1892, 1856, 1449, 924 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62-7.59 (m, 2H), 7.41-7.33 (m, 2H), 6.53 (d, $J = 2.3$ Hz, 1H), 6.46 (d, $J = 2.3$ Hz, 1H), 2.42 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 190.5, 138.7, 135.3, 134.1, 130.3, 129.8, 128.5, 127.2, 21.5. Anal. Calcd for C$_{10}$H$_9$BrO: C, 53.36; H, 4.03. Found: C, 53.54; H, 4.18.

2-Bromo-1-(p-tolyl)prop-2-en-1-one (2.85): General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.85 as a clear oil (54 mg, 51%). TLC $R_f$ = 0.33 (5% EA/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.73 (d, $J = 8.1$ Hz, 2H), 7.27 (d, $J = 8.1$ Hz, 2H), 6.48, (d, $J = 2.3$ Hz, 1H), 6.43 (d, $J = 2.3$ Hz, 1H) 2.43 (s, 3H); $^{13}$C NMR (100 MHz,
This compound has been previously reported.\textsuperscript{49}

**2-Bromo-1-(3,4-dimethylphenyl)prop-2-en-1-one (2.86):** General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.86 as a yellow oil (52 mg, 50%). TLC $R_f = 0.39$ (50% DCM/hexanes); IR (neat) 3024, 2920, 1663, 1603 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61 (s, 1H), 7.56 (d, $J = 7.5$ Hz, 1H), 7.22 (d, $J = 7.9$ Hz, 1H), 6.47 (d, $J = 2.3$ Hz, 1H), 6.42 (d, $J = 2.2$ Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 190.2, 143.2, 137.3, 132.9, 131.0, 129.8, 129.6, 129.3, 127.8, 20.2, 19.9. Anal. Calcd for C$_{11}$H$_{11}$BrO: C, 55.25; H, 4.64. Found: C, 55.27; H, 4.80.

**2-Bromo-1-(2,4,6-trimethylphenyl)prop-2-en-1-one (2.87):** General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.87 as a yellow oil (15 mg, 15%). TLC $R_f = 0.45$ (50% DCM/hexanes); IR (neat) 3021, 2856, 1680, 1378 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.85 (s, 2H), 6.61 (d, $J = 1.8$ Hz, 1H), 6.44 (d, $J = 1.8$ Hz, 1H), 2.30 (s, 3H), 2.13 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 194.3, 139.4, 134.8, 134.6, 133.7, 133.3, 128.5, 21.3, 19.3. Anal. Calcd for C$_{12}$H$_{13}$BrO: C, 56.94; H, 5.18. Found: C, 56.77; H, 5.17.

**2-Bromo-1-(2-chlorophenyl)prop-2-en-1-one (2.88):** General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.88 as a yellow oil (20 mg, 20%); TLC
R_f = 0.31 (30% dichloromethane/hexanes); ^1^H NMR (400 MHz, CDCl_3) δ 7.44-7.43 (m, 2H), 7.35-7.34 (m, 2H), 6.68 (d, J = 2.5 Hz, 1H), 6.47 (d, J = 2.5 Hz, 1H); ^1^C NMR (100 MHz, CDCl_3) δ 189.1, 136.7, 134.2, 131.8, 131.5, 130.4, 129.0, 126.9. This compound has been previously reported. ^23^  

![2-Bromo-1-(3-chlorophenyl)prop-2-en-1-one](image)  

**2-Bromo-1-(3-chlorophenyl)prop-2-en-1-one (2.89):** General procedure for tandem oxidation-bromination reaction was followed to provide 2.89 as a yellow oil (53 mg, 52%). TLC R_f = 0.41 (5% EA/hexanes); ^1^H NMR (400 MHz, CDCl_3) δ 7.78 (t, J = 1.5 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.59-7.55 (m, 1H), 7.42 (t, J = 15.7 ,7.8 Hz, 1H), 6.75, (d, J = 2.5 Hz, 1H), 6.49 (d, J = 2.5 Hz, 1H); ^1^C NMR (100 MHz, CDCl_3) δ 188.8, 136.7, 134.8, 133.1, 130.7, 129.9, 129.6, 129.0, 127.8. This compound has been previously reported. ^23^  

![2-Bromo-1-(4-chlorophenyl)prop-2-en-1-one](image)  

**2-Bromo-1-(4-chlorophenyl)prop-2-en-1-one (2.90):** General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.90 as a yellow oil (61 mg, 60%). TLC R_f = 0.28 (30% DCM/hexanes); ^1^H NMR (400 MHz, CDCl_3) δ 7.77 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 6.52, (d, J = 2.5 Hz, 1H), 6.45 (d, J = 2.5 Hz, 1H); ^1^C NMR (100 MHz, CDCl_3) δ 189.2, 140.0, 133.5, 131.3, 130.0, 129.1. (Only 6 resonances are seen in the ^1^C NMR due to overlapping signals) This compound has been previously reported. ^23^
**2-Bromo-1-(4-bromophenyl)prop-2-en-1-one (2.91)**: General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.91 as a yellow solid (38 mg, 40%); TLC R_f = 0.27 (30% dichloromethane/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 6.53 (d, J = 2.5 Hz, 1H), 6.45 (d, J = 2.5 Hz, 1H); ^13C NMR (100 MHz, CDCl_3) δ 189.3, 133.9, 132.1, 131.4, 130.2, 129.1, 128.6. This compound has been previously reported.\(^{23}\)

![2-Bromo-1-(4-bromophenyl)prop-2-en-1-one](image)

**2-Bromo-1-(3-fluorophenyl)prop-2-en-1-one (2.92)**: General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.92 as a yellow oil (56 mg, 54%). TLC R_f = 0.39 (40% DCM/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.60 (d, J = 7.6 Hz, 1H), 7.52-7.44 (m, 2H), 7.33-7.27 (m, 1H), 6.56 (d, J = 2.5 Hz, 1H), 6.49 (d, J = 2.5 Hz, 1H); ^13C NMR (100 MHz, CDCl_3) δ 189.0 (d, J = 2.2 Hz), 162.6 (d, J = 247.2 Hz), 137.2 (d, J = 6.6 Hz), 130.7, 130.4 (d, J = 7.7 Hz), 129.1, 125.6 (d, J = 2.9 Hz), 120.4 (d, J = 21.1 Hz), 116.7 (d, J = 22.9 Hz). This compound has been previously reported.\(^{23}\)

![2-Bromo-1-(3-fluorophenyl)prop-2-en-1-one](image)

**2-Bromo-1-(4-fluorophenyl)prop-2-en-1-one (2.93)**: General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.93 as a yellow oil (48 mg, 46%). TLC R_f = 0.34 (30% DCM/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.89-7.86 (m, 2H), 7.16 (t, J = 8.6 Hz, 2H), 6.50 (d, J = 2.5 Hz, 1H), 6.43 (d, J = 2.5 Hz, 1H); ^13C NMR (100 MHz, CDCl_3) δ 188.7,
165.9 (d, $J = 256.0$ Hz), 132.5 (d, $J = 9.5$ Hz), 131.2 (d, $J = 2.9$ Hz), 129.4, 128.9, 115.8 (d, $J = 22.0$ Hz). This compound has been previously reported.49

![2-Bromo-1-(2-nitrophenyl)prop-2-en-1-one (2.94)](image)

2-Bromo-1-(2-nitrophenyl)prop-2-en-1-one (2.94): General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.94 as a yellow oil (12 mg, 12%); TLC $R_f = .31$ (30% dichloromethane/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.24 (d, $J = 8.2$ Hz, 1H), 7.79 (t, $J = 7.4$ Hz, 1H), 7.69 (t, $J = 7.8$ Hz, 1H), 7.47 (d, $J = 7.5$ Hz, 1H), 6.51 (d, $J = 2.4$ Hz, 1H), 6.38 (d, $J = 2.4$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 187.4, 146.5, 134.5, 134.3, 131.6, 131.3, 131.1, 128.9, 124.8. This compound has been previously reported.23

![2-Bromo-1-(4-nitrophenyl)prop-2-en-1-one (2.95)](image)

2-Bromo-1-(4-nitrophenyl)prop-2-en-1-one (2.95): General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.95 as a yellow oil (17 mg, 17%); TLC $R_f = .38$ (10% ethyl acetate/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.33 (d, $J = 8.8$ Hz, 2H), 7.95 (d, $J = 8.8$ Hz, 2H), 6.65 (d, $J = 2.6$ Hz, 1H), 6.52 (d, $J = 2.6$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 188.6, 150.4, 140.5, 132.0, 130.6, 129.1, 123.9. This compound has been previously reported.23

![2-Bromo-1-(4-cyanophenyl)prop-2-en-1-one (2.96)](image)

2-Bromo-1-(4-cyanophenyl)prop-2-en-1-one (2.96): General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.96 as a pale-yellow solid (26 mg, 25%). mp = 93-97 °C; TLC $R_f = 0.37$ (70% DCM/hexanes); IR (neat) 3107, 3023, 2922, 2233, 1662, 1271, 966 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.87 (d, $J = 8.2$ Hz, 2H), 7.78 (d, $J = 8.2$ Hz, 2H), 6.51 (d, $J = 2.4$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 188.6, 150.4, 140.5, 132.0, 130.6, 129.1, 123.9. This compound has been previously reported.23
6.62 (d, $J = 2.4$ Hz, 1H), 6.49 (d, $J = 2.5$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 188.8, 138.9, 132.5, 131.7, 130.1, 129.0, 117.8, 116.6. Anal. Calcd for C$_{10}$H$_6$BrNO: C, 50.88; H, 2.56; N, 5.93. Found: C, 50.93; H, 2.61; N, 5.64.

![Structure of 1-(Benzo[b]thiophene)-2-bromoprop-2-en-1-one](image)

**1-(Benzo[b]thiophene)-2-bromoprop-2-en-1-one (2.98):** General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.98 as a yellow solid (45 mg, 46%). mp = 81-84 °C; TLC $R_f = 0.27$ (30% DCM/hexanes); IR (neat) 3088, 3030, 2921, 2850, 1640 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.51 (d, $J = 8.0$ Hz, 1H), 8.24 (s, 1H), 7.90 (d, $J = 8.1$ Hz, 1H), 7.52 (t, $J = 7.1$ Hz, 1H), 7.46 (t, $J = 7.1$ Hz, 1H), 6.56 (d, $J = 2.2$ Hz, 1H), 6.49 (d, $J = 2.4$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 184.2, 140.1, 139.1, 137.0, 132.2, 130.3, 128.6, 126.14, 126.08, 125.3, 122.6. Anal. Calcd for C$_{11}$H$_7$BrOS: C, 49.46; H, 2.64. Found: C, 49.59; H, 2.71.

![Structure of 2-bromo-(3,4-methylenedioxyphenyl)-2-propenone](image)

**2-bromo-(3,4-methylenedioxyphenyl)-2-propenone (2.23):** General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.23 as a yellow oil (48 mg, 48%); TLC $R_f = .28$ (50% dichloromethane/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.47 (dd, $J = 8.1, 1.6$ Hz, 1H), 7.35 (d, $J = 1.4$ Hz, 1H), 6.86 (d, $J = 8.2$ Hz, 1H), 6.40 (d, $J = 2.3$ Hz, 1H), 6.37 (d, $J = 2.3$ Hz, 1H), 6.07 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 188.7, 152.5, 148.3, 129.3, 128.6, 128.0, 126.9, 109.7, 108.1, 102.2. This compound has been previously reported.$^{22}$

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1-(Biphenyl)-2-bromoprop-2-en-1-one (2.101): General procedure for tandem oxidation-bromination reaction was followed to provide compound 2.101 as a yellow solid (48 mg, 51%). mp = 73-75 °C; TLC R_f = 0.38 (50% DCM/hexanes); IR (neat) 3121, 3037, 2923, 1898, 1652, 1596 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 7.3 Hz, 2H), 7.49 (t, J = 14.7, 7.0 Hz, 2H), 7.42 (t, J = 14.7, 7.3 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 189.9, 146.3, 139.8, 133.9, 130.6, 129.8, 129.5, 129.2, 128.6, 127.45, 127.35. Anal. Calcd for C₁₅H₁₁BrO: C, 62.74; H, 3.86. Found: C, 62.69; H, 3.97.

(Z)-2-Bromo-3-phenylacrylaldehyde (2.105): The general procedure for tandem oxidation-bromination was followed to provide compound 2.105 as a pale-yellow solid (44 mg, 40%). TLC R_f = 0.26 (40% DCM/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 9.36 (s, 1H), 8.02-8.00 (m, 2H), 7.90 (s, 1H), 7.53-7.46 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 187.3, 149.2, 133.1, 131.1, 131.0, 128.9, 124.4. This compound has been previously reported.

(Z)-2-Bromo-3-(2-methoxyphenyl)acrylaldehyde (2.106): The general procedure for tandem oxidation-bromination was followed to provide compound 2.106 as a pale-brown solid (39 mg, 38%). TLC R_f = 0.24 (10% ethyl acetate/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 9.37 (s, 1H), 8.36 (dd, J = 7.8, 1.4 Hz, 1H), 8.32 (s, 1H), 7.47 (td, J = 7.8, 1.6 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H),
6.96 (d, J = 8.4 Hz, 1H), 3.92 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 187.4, 158.3, 144.5, 133.2, 130.2, 124.8, 122.2, 120.5, 111.0, 55.94. This compound has been previously reported.$^{50}$

![Chemical structure](image)

(Z)-2-Bromo-3-(4-chlorophenyl)acrylaldehyde (2.107): The general procedure for tandem oxidation-bromination was followed to provide compound 2.107 as a pale-yellow solid (36 mg, 35%). TLC R$_f$ = 0.27 (100% toluene); $^1$H NMR (400 MHz, CDCl$_3$) δ 9.35 (s, 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.85 (s, 1H), 7.47 (d, J = 8.5 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 187.0, 147.5, 137.8, 132.2 131.5, 129.3, 124.9. This compound has been previously reported.$^{51}$

![Chemical structure](image)

(E)-3-Bromo-4-phenyl-3-buten-2-one (2.109a): The general procedure for tandem oxidation-bromination was followed to provide compound 2.109a as a yellow oil (20 mg, 19%). TLC R$_f$ = 0.44 (40% DCM/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36-7.35 (m, 4H), 7.27-7.24 (m, 2H), 2.26 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 197.8, 137.3, 134.9, 128.9, 128.5, 121.0, 29.1. This compound has been previously reported.$^{51}$

![Chemical structure](image)

(Z)-3-Bromo-4-phenyl-3-buten-2-one (2.109b): The general procedure for tandem oxidation-bromination was followed to provide compound 2.109b as an orange oil (16 mg, 15%). TLC R$_f$ = 0.12 (40% DCM/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.03 (s, 1H), 7.89-7.85 (m, 2H), 7.45-
7.43 (m, 3H), 2.61 (s, 3H); \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) δ 193.3, 140.1, 133.8, 130.60, 130.55, 128.6, 123.4, 27.2. This compound has been previously reported.\(^{51}\)

![Chemical Structure](image)

**{(E)-2-Bromo-3-diphenylprop-2-en-1-one (2.100)}**: The general procedure for tandem oxidation-bromination was followed to provide compound 2.100 as a yellow oil (25 mg, 26%). TLC R\(_f\) = 0.33 (35% DCM/hexanes); \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) δ 7.99-7.97 (m, 2H), 7.55 (t, \(J = 7.4\) Hz, 1H), 7.42 (t, \(J = 7.7\) Hz, 2H), 7.38 (s, 1H), 7.19-7.15 (m, 5H); \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) δ 192.0, 136.1, 134.5, 134.4, 133.6, 130.1, 129.0, 128.9, 128.8, 128.4, 116.8. This compound has been previously reported.\(^{52}\)
2.5 $^1$H and $^{13}$C Spectra Supplement to Chapter 2

EL-05-124 High Vac

$^1$H Spectra

$^{13}$C Spectra
KL-05-134 pure

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{O} \quad \text{Br} \\
\text{CH}_3\text{O} & \quad 2.78
\end{align*}
\]

KL-05-134 13C

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{O} \quad \text{Br} \\
\text{CH}_3\text{O} & \quad 2.78
\end{align*}
\]
KL-05-102 pure

2.94

KL-05-102 13C

2.94
KL-05-129 pure

2.98

KL-05-129 13C

2.98
EL-95-119 pure

2.23

EL-95-119 13C

2.23
2.6 References


Chapter 3:
Investigations of New Chiral Quinone Catalysts for Asymmetric C-H Activation

Abstract

The design and synthesis of new chiral quinone catalysts (CQCs) has been initiated. These catalysts are designed to mimic the reactivity of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), a common organic oxidizing agent. A route to chiral quinone catalysts that maintains a dicyanoquinone core is now being developed starting from tetrachloroterephthalonitrile. BINOL derivatives are installed via S_NAr chemistry and used to engender a chiral environment around the dicyanoquinone core. Once these CQCs are obtained, a variety of BINOL derivatives will be utilized to access a series of the CQCs that will be evaluated for their ability to provide enantioselectivity in C-H activation-substitution reactions.
3.1 Introduction

3.1.1 Significance

Various new pharmaceutical candidates continue to be small molecules. Organic chemistry plays a key role in the development of these systems, and despite the advances in this field, the synthesis of these small molecules continues to produce significant challenges, specifically in the efficiency of the reactions as well as with regard to the environmental impacts of the synthesis. Pharmaceutical candidates that contain chirality centers provide additional challenges to development. Most pharmaceuticals are sold as a single enantiomer to avoid potentially dangerous off target effects, resulting in a requirement for optically pure chiral compounds in the synthesis of pharmaceuticals. While the separation of racemic mixtures is one source of these chiral compounds, these separations are time consuming and may complicate synthetic routes. Alternatively, a number of catalytic methods have been developed to access enantiomerically enriched chiral molecules. Many of these catalysts are based on transition metals, which have become more costly as the price of these metals have increased. This has led to the use of chiral small organic molecules that are able to catalyze reactions that provide enantioenriched products. The use of small molecule organic compounds in enantioselective catalysis, or asymmetric organocatalysis, has become a mainstream approach to access useful new chiral intermediates. The popularity of this approach can be attributed to the lower cost of the catalysts compared to metal-based catalysts, usually mild reaction conditions, and broad functional group tolerance.

One research area which is still dominated by transition metal catalysis is asymmetric C-H activation. This type of reactivity is appealing as the C-H bond is the most common bond in organic molecules, with new C-H activations facilitating the use of inexpensive hydrocarbons as starting
materials. Due to the potential of this strategy, a transition metal catalyzed C-H bond activation processes have been developed.\textsuperscript{12-16} The excessive cost of transition metals has now led researchers to investigate more sustainable and environmentally friendly approaches to C-H activation, including electrochemical\textsuperscript{17,18} and photochemical\textsuperscript{19,20} methods. While some advances have been made in the use of asymmetric organocatalysis for C-H activation,\textsuperscript{21-24} these methods fall behind more traditional metal-based approaches.

### 3.1.2 C-H Activation Reactions with DDQ

One of the most versatile oxidizing agents in organic chemistry, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)\textsuperscript{25} promotes a variety of organic transformations based on the activation of allylic and benzylic C-H bonds (Figure 3.1).\textsuperscript{26,27} DDQ is often used as a reagent for dehydrogenation of organic molecules to form aromatic systems\textsuperscript{28,29} and \(\alpha,\beta\)-unsaturated carbonyls.\textsuperscript{26,30,31} More recently DDQ has been used to oxidize activated methylenes and form new carbon-heteroatom\textsuperscript{32-35} and C-C bonds.\textsuperscript{33,36-42}

![Figure 3.1: Examples of DDQ Promoted Transformations](image)

In many of the above cases, DDQ is used as a catalyst with a reoxidant resulting in a catalytic method for C-H activation. These reoxidants are usually stoichiometric salts based on
manganese, due to their low cost.\textsuperscript{43,44} More recently, the reoxidation has been coupled to a second catalyst that regenerates the quinone without affecting the C-H activation. Usually, oxygen gas is the terminal oxidant however air is sometimes also used.\textsuperscript{34,36,45-48} Since many of these reactions can be performed under ambient conditions in green solvents, the use of chiral quinone catalysts (CQCs) could provide an environmentally friendly method for enantioselective activation of C-H bonds.

Organic chemists have already begun using DDQ in enantioselective C-H activation. Several groups have utilized DDQ in asymmetric reactions to generate an ion pair in the presence of a chiral additive.\textsuperscript{49-59} An example of this has been shown by Floreancig (Scheme 3.1). An enantioselective addition reaction was performed between allylsilane and pyran 3.18 using phosphoramidate catalyst 3.19.\textsuperscript{50} It was suggested that ion pairing of the phosphoramidate anion with the oxonium cation generated from DDQ reacted with the pyran leading to the enantioselective addition of allylsilane. DDQ has also been used in transformations with catalysts that use H-bonding to control the addition of nucleophiles to reactive electrophiles.\textsuperscript{53} An example of this is shown in the addition of indole to the quinone methide generated from phenol 3.21. Phosphoric acid 3.22 acts as an H-bonding catalyst and controls the stereochemistry of alkyne 3.23.

**Scheme 3.1: Examples of Chiral Transformations with DDQ and Chiral Additives**

![Scheme 3.1 Diagram]
In the previously described examples, DDQ is used to generate a reactive intermediate that interacts with a chiral additive through either H-bonding or ion pairing. The resulting chiral complex reacts with a nucleophile giving an enantioenriched product. Although these approaches have led to useful transformations, most of these examples employ a stoichiometric amount of DDQ. Only one enantioselective example has been reported that uses a catalytic amount of DDQ, using MnO₂ as the terminal oxidant (Scheme 3.1). Stoichiometric DDQ is thought to be necessary due to the chiral organocatalyst and the reoxidant being in the same reaction mixture. Nonpolar solvents are usually required for enantioinduction with these additives since both ion pairing and H-bonding are sensitive to solvent effects. The necessity of nonpolar solvents may also limit the choice of reoxidant.

3.1.3 Chiral Quinone Catalysts

Because of DDQ’s versatile oxidizing abilities, we propose to synthesize original chiral variants based on the DDQ quinone scaffold. One design for a chiral quinone catalyst (CQC) will be a dicyanoquinone decorated with two BINOL ethers (Scheme 3.2). A new chiral disubstituted dicyanoquinone like 3.26 could be synthesized from C2-alkoxy-BINOL derivatives such as 3.24 and the benzenedicarbonitrile 3.25. We hypothesize the chiral BINOLS will form a macromolecular structure around the quinone. Formation of a donor-acceptor (DA) complex with an electron rich substrate will provide an identical complex should the substrate stack on either face of the quinone, minimizing diastereomeric transition states. The catalyst will be optimized by incorporation of electron withdrawing groups on the BINOL and changing the nature of the ether group (the OR group in BINOL 3.24). These changes will be explored to find a chiral quinone catalyst (CQC) that is capable of catalyzing C-H activations.
Scheme 3.2: Chiral Dicyanoquinones Decorated with Two BINOL Ethers

A second design for a chiral dicyanoquinone can also be envisioned using a single BINOL (Scheme 3.3). The synthesis of this catalyst can be envisioned by the addition of a 3,3’-disubstituted BINOL like 3.30 to the benzenedicarbonitrile 3.25 leading to quinones like 3.31. Modification of the R<sup>1</sup> groups on the 3,3’ positions of the BINOL will be explored to define the chiral area around the quinone and create enantioselectivity. Additionally, electron withdrawing groups will be added to the BINOL to ensure that the quinone maintains a high redox potential.

**Scheme 3.3: Chiral Dicyanoquinones Functionalized with a single 3,3-Diaryl-BINOL**

3.1.4 Mechanism of DDQ Catalyzed C-H activation

Unlike metal complexes, which function by insertion of the metal into a C-H bond, quinones activate C-H bonds in an oxidative manner. Several different pathways for the oxidation of C-H bonds with DDQ have been proposed and have been followed by a number of mechanistic investigations.<sup>60-67</sup> Studies performed by Linstead, Jackman, and co-workers<sup>68-71</sup> concluded that DDQ oxidations of benzylic C-H bonds occur through a rate-determining hydride transfer that leads to a delocalized carbocation. The resulting carbocation either loses a proton to form an alkene or is trapped by a nucleophile. Ab initio calculations on the oxidation of 1,4-cyclohexadiene with DDQ support this mechanism and predict an ionic mechanism in which an initial hydride transfer
occurs.\textsuperscript{72} Similar computational studies by Crabtree and Batista\textsuperscript{73} as well as Mayr\textsuperscript{74,75} also support the formation of carbocations when DDQ reacts with other substrates.

A diagram of the mechanism of a DDQ C-H substitution is shown in Figure 2. DDQ and the arene substrate \textbf{3.33} form a donor-acceptor (DA) complex \textbf{3.34}. This complex transfers a hydrogen from the benzylic position of the substrate to the quinone through a transition state resembling TS1 \textbf{3.35}, forming ion pair \textbf{3.36}.\textsuperscript{73,75} Liu and Floreancig found that in some cases a transition state occurs in which the hydride transfer occurs to the vinyl nitrile of DDQ (H transfer to C, as shown in TS2, \textbf{3.39}) instead of the carbonyl. This alternative transition state is actually preferred over H transfer to O (as in \textbf{3.35}) in some instances, specifically with some benzylic ether and allylic ether substrates.\textsuperscript{76} TS1 \textbf{3.35} is still close in energy compared to transition state TS2 \textbf{3.39}. Mayr has investigated the activation of a variety of other benzylic and allylic systems with DDQ and reports that H transfer to the carbonyl oxygen is preferred for most substrates.\textsuperscript{75} This suggests that as long as we focus on benzylic and allylic systems without an adjacent ether, we can assume that H transfer to O is preferred. There have been several reports of the formation of the DDHQ ether intermediate (like \textbf{3.37}) in the pathway.\textsuperscript{30,77-80} This ether forms when the addition of the nucleophile to the cation is slow, and the dihydroquinone intercepts the cation instead resulting in ether \textbf{3.37}. However, the phenyl ether \textbf{3.37} can act as a leaving group and can be displaced by a nucleophile. As the environment around the cation controls the stereochemistry of the aryl ether, a chiral quinone may provide the enantioenriched ether product \textbf{3.37}, which can be displaced under \textit{S\textsubscript{N}2} conditions to provide an enantiopure product like \textbf{3.38}. Given that the aryl ether will form from the same face that is blocked by the dihydroquinone in ion pair \textbf{3.36}, nucleophilic attack on cation \textbf{3.36} or ether \textbf{3.37} will lead to the same enantiomer of product \textbf{3.38}. This suggests that either pathway (free carbocation or aryl ether) can provide an enantioenriched substitution product.
Figure 3.2: Mechanism for C-H Activation of 4-Ethylanisole by DDQ

An obstacle in the design of these CQCs is that the quinones are planar. Since C-H activation proceeds through DA complexes that use pi-stacking interactions to stabilize the transition states, the quinone must be placed in a chiral environment where a substrate can be activated and undergo nucleophilic attack. The face of the nucleophilic attack should be controlled as the reduced quinone blocks one face of the cation. The orientation of the carbocation substituent must be controlled to achieve enantioselectivity. For example, even if nucleophilic attack is favored on one face of the cation, if the conformation of the methyl group attached to the cation in 3.36 is not controlled the transformation will not be enantioselective. Consequently, the catalyst design must account for both the face selectivity in the nucleophilic attack and control the conformation of the substituent on the cation. Both proposed CQCs like 3.26 and 3.31 should be able to control these two aspects and function as innovative asymmetric C-H activation catalysts. A model for the enantioinduction with catalysts like 3.26 is presented below (Figure 3.3).

The quinone will interact with the substrate through pi-stacking interactions, leading to two possible DA complexes (Figure 3.3A and Figure 3.3B). In both cases the R substituent on the substrate (in blue) orients away from the large BINOL groups. MM2 calculations predict that conformation B is favored by ~0.9 kcal/mol when the R groups are methyl groups. This is attributed to interactions between the BINOL OR group and the R group on the substrate (steric clash in purple). As the size of the OR group on the BINOL ether increases, the conformation in
Figure 3.3B is more favored due to steric interactions. Next, hydride abstraction occurs which leads to a cation with one face blocked by the reduced quinone (Figure 3.3C). As the cation remains stacked above the quinone and in the chiral pocket good selectivity is anticipated. Alternatively, the CQC may react with the carbocation, forming a covalent bond (Figure 3.3D). The alkylated dihydroquinone will then serve as a leaving group. We predict that the trapping of cation C by the dihydroquinone will be stereoselective, and therefore displacement of the aryl ether will provide the same enantiomer as direct substitution on the carbocation in figure 3.3C.

\[ \text{Figure 3.3: Model of Benzylic Activation and Substitution Using CQCs Like 3.26} \]

A similar model for enantioselectivity has been developed for our second design of CQC’s like 3.31 (Figure 3.4). The electron rich aromatic substrate (in blue) will first form a DA complex with the quinone, in which the substrate can align in two different ways (Figure 3.4A and Figure 3.4B). In both cases the R group on the substrate points away from the BINOL due to sterics. The conformation in figure 3.4B will be favored as the smaller methoxy group on the substrate is in proximity to one of the aromatic rings on the 3,3’-positions of the BINOL. MM2 calculations predict that conformation B is favored by ~1.1 kcal/mol when R is a methyl group, which again can be rationalized due to the shorter C-O bond and smaller nature of the oxygen atom compared to a methylene. C-H activation then leads to the carbocation in figure 3.4C. Attack of the nucleophile occurs from the opposite side of the dihydroquinone, leading to an enantioenriched product. Alternatively, the quinone may form a chiral covalent adduct as shown in figure 3.4D,
where the quinone acts a leaving group. Both predicted transition states from figure 3.4C and figure 3.4D lead to the same enantiomer of the product, so either can occur to achieve an enantioselective transformation.

![Figure 3.4: Model of Benzylic Activation and Substitution Using CQCs like 3.31](image)

These catalyst designs have several advantages in the development of CQCs. BINOL groups are utilized as the source of chirality to create the necessary chiral environment around the quinone. BINOL is an inexpensive source of the needed chirality that can be easily modified utilizing common procedures. In addition, the BINOL groups allow for the synthesis of catalysts with C2 symmetry, which minimizes the number of diastereotopic transition states that are accessible to the reactants. This accelerates catalyst design and facilitates modeling the possible transition states, allowing for a more rational development process.

Because these CQCs utilize pi-stacking as their primary mode of interacting with the substrate, these new CQCs may complement other chiral transformations as pi-stacking is affected by solvent effects differently.\(^{81}\) Pi-stacking is often enhanced in polar solvents due to solvation/desolvation effects.\(^{82}\) In addition, the use of more polar solvents may be more amenable to using the CQCs under catalytic conditions that make use of inexpensive stoichiometric oxidants like oxygen or air. These conditions will also reduce the formation of stoichiometric byproducts and generate less waste than other C-H activation strategies.
3.1.5 Synthetic Studies on and Evaluation of Chiral Quinone Catalysts

The original synthesis of the chiral dicyanoquinones began with the reduction of DDQ (Scheme 3.5). The resulting dihydroquinone 3.41 would then be protected as the corresponding PMB ether 3.25. The most direct method would be to add BINOL derivatives to DDQ itself, but reports show this approach is complicated by side reactions and results in low yields.\textsuperscript{83} Better results are obtained by reducing the DDQ, protecting the phenols and then performing the S\textsubscript{N}Ar reactions. This route was employed effectively by Tsivadze and coworkers in their synthesis of tetra-15-crown-5-dibutoxyoxanthrenocyanines.\textsuperscript{84} Addition of two BINOL methyl ethers would occur under S\textsubscript{N}Ar conditions like those used by Tsivadze.\textsuperscript{84} Removal of the PMB protecting groups was proposed to be accomplished with ceric ammonium nitrate (CAN). This reagent has been shown to oxidize dihydroquinones to quinones,\textsuperscript{85, 86} so using excess CAN should result in the formation of the desired quinone in a single step. This modular route is appealing as the S\textsubscript{N}Ar substrate can be prepared, and then decorated with the desired ethers and oxidized to the corresponding quinone in just four overall steps.
A second type of quinone catalyst was envisioned where both BINOL oxygens are attached to the quinone. An S_NAr reaction between BINOL and the protected dichlorobenzene 3.25 will result in 3.46 (Scheme 3.6). The PMB groups will be removed and the dihydroquinone oxidized to the CQC 3.47 using CAN.

Scheme 3.5: Proposed Synthesis of Chiral Dicyanoquinones Functionalized with a 3,3-Diaryl-BINOL

As they become available, the new CQCs will be evaluated in C-H activation processes catalyzed by DDQ, as well as in some other transformations (Figure 3.5). These reactions will
include benzylic and allylic C-H substitution reactions with a variety of nucleophiles including anilines, sulphonamides, amides, thiols, carboxylic acids, ketones, indoles, nitroalkanes, and silyl enol ethers. In addition to these nucleophiles, the use of fluoride sources will be explored to facilitate the enantioselective introduction of fluorine. Few methods are known for enantioselective C-H activation/fluorination, and these methods usually rely upon directing groups and palladium catalysts. Fluorine incorporation into small molecules is a pressing need in the development of new medicines, as many of these entities are fluorinated to improve lipophilicity and stability. Sodium fluoride has been reported to displace DDQ ethers from phosphates to provide organophosphorus fluorides, so there is some precedence for this addition. Alternatively, C-H amination reactions may be useful in the synthesis of amino acids like 3.53 and 3.56. Recently DDQ was shown to induce Nazarov type rearrangements of ethers like 3.57, so these chiral catalysts will be evaluated in these rearrangements to determine if they can control enantioselectivity. This type of cyclization has significant utility in complex molecule synthesis. Additionally, the allylic rearrangement of amine 3.59 may be initiated by C-H activation, providing access to allylic amines. This reactivity will be investigated to access allylic amines like 3.61.

![Figure 3.5: Evaluating the Reactivity of CQCs in New Asymmetric Transformations](image)

### 3.2 Results and Discussion

#### 3.2.1 Original Synthetic Route for Chiral Dicyanoquinone Catalysts

We began the synthesis of our quinone catalysts with the reduction of DDQ followed by the PMB protection of the resulting diol. Unfortunately, when the addition of BINOL or BINOL
methyl ether to PMB ether 3.25 was attempted, removal of the PMB group was observed instead (Scheme 3.7). We hypothesize the BINOL anion nucleophile was instead attacking the benzylic carbon of the PMB group and displacing this group instead of the chlorines. A variety of other protecting groups were investigated including benzyl and methyl groups, however, these groups were also removed. This led us to reevaluate our synthetic route.

Scheme 3.6: First Generation Synthetic Route of Chiral Dicyanoquinone Catalysts

3.2.2 New Synthetic Route for Chiral Dicyanoquinone Catalysts

We revised our synthetic approach, using tetrafluoroterephthalonitrile as the source of our dicyanoquinone core (Scheme 3.8). Tetrafluoroterephthalonitrile 3.65 was synthesized from the less expensive tetrachloroterephthalicnitrile 3.64 in a nucleophilic aromatic substitution (SNAr) reaction with potassium fluoride. We first focused on the synthesis of chiral dicyanoquinones decorated with two BINOL methyl ethers. We began the synthesis of this catalyst with the etherification of BINOL with methyl iodide and potassium carbonate to access 3.43. An SNAr reaction was performed to combine tetrafluoroterephthalonitrile and BINOL methyl ether 3.43 and obtain compound 3.66 and potentially compound 3.67. Unfortunately, mass spectrometry showed that only one BINOL methyl ether was added to the dicyanonoquinone. Reaction conditions were investigated to add both BINOL methyl ether molecules.
Reported conditions for a similar SNAr reaction which utilized potassium carbonate as the base in THF at reflux (Table 3.1, entry 1) were initially employed. Again, mass spectrometry determined that only one of the BINOL methyl ethers was added. Since the reaction was only allowed to run for 2 hours, the reaction time was increased to 24 hours (entry 2). Elemental analysis suggested that again only one BINOL methyl ether was added. We speculated that a more reactive reaction medium was required for the second addition to occur. Sodium hydride in DMA was investigated, and at room temperature, no reaction occurred (entry 3). When heated, only one BINOL methyl ether added, even after 24 hours (entry 4). Doubling the equivalents of base also resulted in the addition of only one BINOL methyl ether (entry 5). Conditions are currently being investigated to obtain the desired compound 3.66.
Table 3.1: S_NAR Conditions Attempted to Access Chiral Dicyanoquinones with Two BINOL Ethers

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Solvent (M)</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K_2CO_3 (3.0)</td>
<td>THF (.08 M)</td>
<td>reflux</td>
<td>2</td>
<td>0^a</td>
</tr>
<tr>
<td>2</td>
<td>K_2CO_3 (3.0)</td>
<td>THF (.08 M)</td>
<td>reflux</td>
<td>24</td>
<td>0^b</td>
</tr>
<tr>
<td>3</td>
<td>NaH (3.0)</td>
<td>DMA (.1 M)</td>
<td>rt</td>
<td>24</td>
<td>n/a</td>
</tr>
<tr>
<td>4</td>
<td>NaH (3.0)</td>
<td>DMA (.2 M)</td>
<td>80°C</td>
<td>24</td>
<td>0^c</td>
</tr>
<tr>
<td>5</td>
<td>NaH (6.0)</td>
<td>DMA (.2 M)</td>
<td>80°C</td>
<td>24</td>
<td>0^c</td>
</tr>
</tbody>
</table>

Reaction Conditions: Base was suspended in dry solvent under argon. BINOL methyl ether (2.0 equiv.) was added. Tetrafluoroterephthalonitrile (1.0 equiv.) was added. The reaction mixture was stirred at the designated temperature for the specified amount of time. ^aAmount of BINOL methyl ether molecules added was determined by mass spectrometry. ^bAmount of BINOL methyl ether molecules added was determined by elemental analysis. ^cAmount of BINOL methyl ether molecules added was determined by NMR spectroscopy.

As described above, we also wished to explore the reactivity of chiral dicyanoquinones decorated with 3,3-diaryl-BINOL such as 3.47. We envisioned performing a double S_NAr reaction with tetrafluoroterephthalonitrile and BINOL to obtain dicyano compound 3.70. The remaining fluorine atoms would be displaced with alcohols using sodium hydroxide, and the resulting diol oxidized, using TBN, to obtain the sought after quinone 3.72.
Although this synthetic route would result in an ortho quinone, instead of our original para quinone design, we still chose to explore this route as the starting materials were readily available.

In order to obtain a para quinone product, we would have to use 3,4,5,6-tetrafluorophthalonitrile as our dicyanoquinone core (Scheme 3.10). When subjected to 3,4,5,6-tetrafluorophthalonitrile, a double $S_N$Ar reaction with BINOL can either occur at the 3,4 or 4,5 positions. Banerjee et al. reported that a 3,4- addition is preferred in a double nucleophilic aromatic substitution reaction between catecholate and 3,4,5,6-tetrafluorophthalonitrile. This was rationalized by the electron withdrawing effects of the cyano groups being more pronounced on the ortho carbons. Using 3,4,5,6-tetrafluorophthalonitrile would still result in an ortho quinone, but also possibly a para quinone, which would result in a complex mixture. Maly also showed that a double $S_N$Ar reaction between catecholate and 2,3,5,6-tetrafluoroterephthalonitrile resulted in one product. Based on these findings, we decided to continue with 2,3,5,6-tetrafluoroterephthalonitrile to avoid any potential complex reaction mixtures.
Although we would be synthesizing an ortho quinone, we believe a CQC of this type will still have C-H activation potential, as literature reports support this. For example, Kobayashi showed that 1,3-benzodioxoles can be formed by the benzylic oxidation of alkyl-substituted benzenes using $\sigma$-chloranil. An ortho quinone catalyst developed by Cheng was also shown to catalyze an aerobic oxidative dehydrogenation reaction of primary amines to imines. These examples suggest that ortho quinones have similar reactivity to DDQ type systems. To further demonstrate that this CQC design could still control the face selectivity and conformation of the cation substituent, a model for the enantioinduction with a catalyst like 3.72 is presented below in Figure 3.6. Again, the BINOL can control the orientation of the substituent on the aromatic ring and the position of the electron rich benzene ring in a DA complex, which can lead to an enantioenriched product.
We began to explore the synthesis of these catalysts by adding BINOL to tetrafluoroterephthalonitrile, which occurred using potassium carbonate with DMF as the solvent in a 63% yield (Scheme 3.11). An $S_{N}$Ar reaction with sodium hydroxide was performed to displace the fluorine atoms with alcohols, which would then be oxidized to the desired quinone. Unfortunately, mass spectrometry showed only one displacement took place, providing compound 3.73. A variety of conditions were investigated to obtain both alcohols, but to no avail. We hypothesize this is due to difficulty in forming the required Meisenheimer complex A, as after the addition of the first molecule of water the phenol is likely deprotonated. This results in having an intermediate where the two negative charges are in proximity, which may disfavor the addition of the second equivalent of hydroxide.
We then attempted to displace the fluorines with 4-methoxybenzyl (PMB) alcohol to introduce the oxygens, as formation of the ether should not have the problem shown in Meisenheimer complex A. The PMB group could be oxidized to the alcohol with CAN, which can be further oxidized and give us the sought after quinone. Unfortunately, the addition of the PMB group proved difficult. Subjected difluoro compound 3.70 to 4-methoxybenzyl alcohol and sodium hydride in DMA resulted in only one of the PMB groups being added (Table 3.2, entry 1). Increasing the temperature of the reaction also did not displace both fluorine atoms, even after 48 hours (entry 2). Entries 1 and 2 both showed starting materials on TLC. Concerned that the PMB alcohol was not being fully deprotonated, we increased the equivalents of sodium hydride as well as allowed the base and PMB alcohol to stir together for some time before adding difluoro compound 3.70 (entry 3). Again, only one PMB group was inserted. We investigated potassium carbonate as base (entry 4), which resulted in an unidentified compound as the product. PMB introduction was also attempted on the dichloro compound (entry 5) which resulted in the isolation of an unknown product.
Table 3.2: Conditions for the Addition of PMB Protecting Group

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Solvent (M)</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH (2.0)</td>
<td>DMA (0.1 M)</td>
<td>rt</td>
<td>24</td>
<td>0ᵃ</td>
</tr>
<tr>
<td>2</td>
<td>NaH (2.0)</td>
<td>DMA (0.1 M)</td>
<td>80°C</td>
<td>48</td>
<td>0ᵇ</td>
</tr>
<tr>
<td>3</td>
<td>NaH (2.2)</td>
<td>DMA (0.1 M)</td>
<td>rt</td>
<td>24</td>
<td>0ᶜ</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃ (6.0)</td>
<td>DMA (0.1 M)</td>
<td>80°C</td>
<td>24</td>
<td>0ᵈ</td>
</tr>
<tr>
<td>5</td>
<td>NaH (2.0)</td>
<td>DMA (0.1 M)</td>
<td>80°C</td>
<td>24</td>
<td>0ᵈ</td>
</tr>
</tbody>
</table>

Reaction Conditions: Base was suspended in dry solvent under argon. 4-methoxybenzyl alcohol (2.0 equiv.) was added. Compound 70 (1.0 equiv.) was added. The reaction mixture was stirred at the designated temperature for the specified amount of time. ᵃAmount of PMB groups added was determined by ¹H NMR Spectroscopy. ᵇ4-methoxybenzyl alcohol and base were allowed to stir for 15 minutes before compound 70 was added. ᶜAn unidentified product was isolated. ᵈDichloro compound was used.

Alternatively, use of 4-methoxyphenol as a nucleophile was able to displace both fluorines with potassium carbonate in DMA providing a 68% yield of 3.76 (Scheme 3.10). Ceric ammonium nitrite (CAN) was implemented to oxidize compound 3.75, however, nitration was observed at the 3-position of the anisole group instead of oxidation and cleavage of the ether. DDQ was also investigated, however no reaction occurred, even at elevated temperatures. We speculated that adding an additional electron donating group would make the anisole group easier to remove. Therefore 3,5-dimethoxy phenol was added to the difluoro compound without issue in a yield of 85%. Unfortunately, when subjected to DDQ and CAN no reactions had occurred. Oxone was investigated to oxidize this system, however, the methoxy groups were removed instead, resulting in the formation of 3.78 instead.
Scheme 3.11: Introduction of Electron Donating Aromatic Groups to Compound 3.70

To avoid the ether cleavage we observed on 3.77, we turned to 2-nitrophenol as an alternative phenyl ether, since aromatic nitro ethers have been reported to be cleaved with piperidine.\textsuperscript{110} We were able to displace the fluorine atoms with 2-nitrophenol without issue in a remarkable yield of 90%. However, when stirred in neat piperidine, only aromatic nitro group was removed.
We attempted to introduce the alcohols by adding benzyl alcohol, followed by cleaving the benzyl ethers with hydrogenation. Benzyl alcohol displaced both fluorine atoms of 3.70 successfully in a yield of 43% (Scheme 3.14). The benzyl group was successfully removed by Pd/C hydrogenation. Unfortunately, the resulting diol proved difficult to purify. We speculate the sought-after diol was affixing to the silica gel of the column resulting in a low yield as well as overlapping fractions with impurities. This continued to be a problem even after adding acetic acid to the chromatography solvent system. Instead, the hydrogenation reaction was taken on crude.

Scheme 3.13: Introduction of Benzyl Alcohol to Compound 3.70

The crude diol mixture was subjected to a variety of oxidants (Table 3.3). Potassium permanganate in 1,4-dioxane resulted in the formation of BINOL with no starting material left over (entry 1). A weaker oxidizing agent (DDQ) resulted in a complex mixture with BINOL being
the major component (entry 2). Ceric Ammonium Nitrate also resulted in a complex mixture, however, BINOL was not observed (entry 3). Silver oxide resulted in the formation of BINOL as well as an unidentified side product (entry 4). Manganese dioxide and pyridinium chlorochromate (PCC) both also only provided BINOL (entries 5 and 6). When subjected to t-butyl nitrite an unidentified product was isolated (entry 7). No reaction occurred when subjected to Oxone at room temperature (entry 8), however, when refluxed (entry 9) a complex mixture resulted in which the sought after product was not found.

Table 3.3: Conditions Investigated for the Oxidation of Diphenol 3.71

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant (equiv.)</th>
<th>Solvent (M)</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KMnO₄ (8.0)</td>
<td>1,4-Dioxane (0.1 M)</td>
<td>90°C</td>
<td>24</td>
<td>0⁷</td>
</tr>
<tr>
<td>2</td>
<td>DDQ (4.0)</td>
<td>10:1 1,4-Dioxane:H₂O (0.1 M)</td>
<td>rt</td>
<td>24</td>
<td>0⁸,⁹</td>
</tr>
<tr>
<td>3</td>
<td>CAN (10.0)</td>
<td>1:1 MeCN:H₂O (0.1 M)</td>
<td>rt</td>
<td>24</td>
<td>0³</td>
</tr>
<tr>
<td>4</td>
<td>Ag₂O (2.0)</td>
<td>DCM (0.2 M)</td>
<td>rt</td>
<td>24</td>
<td>0⁸,⁹,c</td>
</tr>
<tr>
<td>5</td>
<td>MnO₂ (1.1)</td>
<td>THF (0.2 M)</td>
<td>rt</td>
<td>24</td>
<td>0³</td>
</tr>
<tr>
<td>6</td>
<td>PCC (2.5)</td>
<td>THF (0.2 M)</td>
<td>rt</td>
<td>24</td>
<td>0³</td>
</tr>
<tr>
<td>7</td>
<td>t-butyl nitrite (2.0)</td>
<td>DCE (0.2 M)</td>
<td>rt</td>
<td>24</td>
<td>0³</td>
</tr>
<tr>
<td>8</td>
<td>Oxone (5.0)</td>
<td>DCM (0.1 M)</td>
<td>rt</td>
<td>24</td>
<td>n/r</td>
</tr>
<tr>
<td>9</td>
<td>Oxone (5.0)</td>
<td>DCE (0.2 M)</td>
<td>90°C</td>
<td>24</td>
<td>0³</td>
</tr>
</tbody>
</table>

Reaction Conditions: Compound 3.71 was dissolved in the designated solvent. Oxidant was added and the reaction mixture was stirred at the designated temperature for the specified amount of time. ⁷BINOL was isolated as a product. ⁸A complex mixture resulted. ⁹An unidentified product was isolated.
3.3 Conclusions and Future Work

Progress towards the synthesis of Chiral Quinone Catalysts has been made. BINOL derivatives were positioned around tetrafluoroterephthalonitrile through $S_{\text{NAr}}$ chemistry, creating a chiral environment around the dicyanoquinone core. Oxidation to the sought after quinone has proved difficult. We have re-evaluated our synthetic route and believe the quinone will need to be accessed before the addition of the BINOL derivatives. Once these CQCs are accessed they will be evaluated in their ability to perform enantioselective C-H activation substitution reactions.

These catalysts will also be optimized using different electron poor chiral BINOLS and BINOL ethers. These electron poor systems will be investigated to align with the electron withdrawing nature of the chlorides on DDQ. As these catalysts are completed, they will be investigated in their proficiency in enantioselective C-H activation substitution reactions, as well as benzylic and allylic C-H substitution reactions with a variety of nucleophiles.
3.4 Experimental

(3.70). To a flame dried round bottom flask, evacuated and back filled with argon, tetrafluoroterephthalonitrile (172 mg, 1.0 equivalent), R-BINOL (246 mg, 1.0 equivalent), and K₂CO₃ (357 mg, 3.0 equivalent) were added. The solids were then suspended in dry THF (11 ml, 0.08 M). The resulting mixture was heated to reflux for 24 hours, then cooled to room temperature. Water was added to the reaction mixture. The organic layer was extracted with ethyl acetate (3x), washed with brine (1x), dried over Na₂SO₄ and concentrated in vacuo. The resulting crude residue was purified by silica gel flash column chromatography (5% ethyl acetate/95% hexanes) to provide compound 3.70 as a pale yellow solid (243 mg, 63%)

3.70. mp = 249-251°C; TLC Rᵣ = .29 (5% ethyl acetate/95% hexanes); IR (neat) 3121, 3037, 2923, 1898, 1652, 1596 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, J = 8.9 Hz, 2H), 8.00 (d, J = 8.2 Hz, 2H), 7.60-7.54 (m, 2H), 7.52 (d, J = 8.9 Hz, 2H), 7.50-7.40 (m, 4H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 149.0, 148.3 (d, J = 15.5 Hz), 147.2 (t, J = 2.9 Hz), 145.6 (d, J = 15.7 Hz), 132.4, 132.0, 131.8, 128.6, 127.7, 126.7 (d, J = 6.1 Hz), 124.9, 120.1, 108.9, 103.1 (q, J = 6.8 Hz). HRMS-ESI (m/z): [M+H]+ calcd for C₂₈H₁₂F₂N₂O₂ Na+, 469.075905; found, 469.075866.

(3.75). To a flame dried round bottom flask, 4-methoxyphenol (60 mg, 2.2 equiv.) was dissolved in DMA (2.2 mL). K₂CO₃ (500 mg, 16.0 equiv.) was added and stirred, under argon, at 110°C for 15 minutes. 3.70 (100 mg, 1.0 equiv.) was added to the reaction mixture and stirred at 110°C for
3 h. The reaction mixture was diluted with ethyl acetate and washed with 2% LiCl solution (3x 3 mL). The organic layers were washed with brine (1x 5 mL), dried over Na$_2$SO$_4$, and concentrated \textit{in vacuo}. The resulting crude residue was purified by silica gel flash column chromatography (5% DCM/95% toluene) to provide compound 3.75 as an off-white solid (100 mg, 68%).

3.75. mp = 241-243°C; TLC Rf = .40 (5% DCM/95% toluene); IR (neat) 3066, 2957, 2838, 2233, 1500, 1439 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.09 (d, J = 8.9 Hz, 2H), 8.00 (d, J = 8.9 Hz, 2H), 7.61 (d, J = 8.9 Hz, 2H), 7.58-7.53 (m, 2H), 7.51-7.46 (m, 2H), 7.45-7.39 (m, 2H), 6.79-6.73 (m, 4H), 6.69-6.63 (m, 4H), 3.77 (s, 6H); $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$) $\delta$ 156.1, 150.5, 149.4, 147.7, 146.4, 132.3, 132.1, 131.6, 128.5, 127.5, 126.8, 126.4, 125.1, 120.6, 117.3, 114.6, 111.1, 108.6, 55.7. Anal. Calcd for C$_{42}$H$_{26}$N$_2$O$_6$: C, 77.05; H, 4.00; N, 4.28 Found: C, 77.08; H, 3.62; N, 4.39.

![Compound 3.75](image)

(3.76). To a flame dried round bottom flask, 3.75 (50 mg, 1.0 equiv.) was dissolved in MeCN (.80 mL). CAN (417 mg, 10.0 equiv.) was added and stirred, under argon, at room temperature for 24 hours. The reaction mixture was diluted with ethyl acetate and the organic layers were extracted (3x, 5 mL) with ethyl acetate. The organic layers were washed with brine (1x 5 mL), dried over Na$_2$SO$_4$, and concentrated \textit{in vacuo}. The resulting crude residue was purified by silica gel flash column chromatography (40% ethyl acetate/60% hexanes) to provide compound 3.76 as a rust colored solid (90 mg, 35%).

3.76. mp = 146-148°C; TLC Rf = .26 (40% ethyl acetate/60% hexanes); IR (neat) 3072, 2943, 2843, 2183, 1527, 1436 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.11 (d, J = 9.0 Hz, 2H), 8.01 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.60-7.54 (m, 2H), 7.51-7.46 (m, 2H), 7.46-7.41 (m, 2H),
7.21 (d, $J = 2.2$ Hz, 2H) 7.06-6.98 (m, 3H), 3.93 (s, 6H); $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$) $\delta$
149.9, 149.2, 148.8, 148.6, 144.7, 139.2 132.4, 132.0, 131.8, 128.6, 127.6, 126.7, 126.6, 124.9,
122.2, 120.5, 114.9, 113.5, 110.5, 108.7, 57.1. HRMS-ESI (m/z): [M+H]+ calcd for C$_{42}$H$_{24}$N$_4$O$_{10}$
Na+, 767.138464; found, 767.138427.

(3.77). To a flame dried round bottom flask, 3,5-dimethoxyphenol (152 mg, 2.2 equiv.) was
dissolved in DMA (4.5 mL). K$_2$CO$_3$ (1.13 g, 16.0 equiv.) was added and stirred, under argon, at
110°C for 15 minutes. 3.70 (200 mg, 1.0 equiv.) was added to the reaction mixture and stirred at
110°C for 3 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate
The organic layers were washed with 2% LiCl solution (3x 3 mL), brine (1x 5 mL), dried over
Na$_2$SO$_4$, and concentrated in vacuo. The resulting crude residue was purified by silica gel flash
column chromatography (90% DCM/10% toluene) to provide compound 3.77 as a white solid (271
mg, 85%).

3.77. mp = 122-124°C; TLC Rf = .17 (90% DCM/10% toluene); IR (neat) 3007, 2936, 2829,
2160, 1593, 1427 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.10 (d, $J = 8.9$ Hz, 2H), 8.01 (d, $J = 8.2$
Hz, 2H), 7.62 (d, $J = 8.9$ Hz, 2H), 7.59-7.53 (m, 2H), 7.51-7.47 (m, 2H), 7.45-7.39 (m, 2H), 6.19
(t, $J = 2.1$ Hz, 2H), 5.86 (d, $J = 2.1$ Hz, 4H), 3.70 (s, 12H); $^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$) $\delta$
161.4, 158.2, 149.4, 148.0, 145.5, 132.3, 132.1, 131.7, 128.6, 127.5, 126.8, 126.4, 125.0, 120.6,
110.9, 108.8, 95.9, 95.3, 55.5. HRMS-ESI (m/z): [M+H]+ calcd for C$_{44}$H$_{30}$N$_2$O$_8$ H+, 715.207492;
found, 715.207508.
(3.79). To a flame dried round bottom flask, 2-nitrophenol (69 mg, 2.2 equiv.) was dissolved in DMA (2.2 mL). K$_2$CO$_3$ (567 mg, 16.0 equiv.) was added and stirred, under argon, at 110°C for 15 minutes. 3.70 (100 mg, 1.0 equiv.) was added to the reaction mixture and stirred at 110°C for 18 h. The reaction mixture was diluted with ethyl acetate. The organic layers were washed with 2% LiCl solution (3x 3 mL), brine (1x 5 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The resulting crude residue was purified by silica gel flash column chromatography (90% DCM/10% toluene) to provide compound 3.79 as white solid (137 mg, 90%).

3.79. mp = 180-182°C; TLC Rf = .32 (90% DCM/10% toluene); IR (neat) 3074, 2903, 2187, 1523, 1438 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.12 (d, $J = 8.9$ Hz, 2H), 8.02 (d, $J = 8.1$ Hz, 2H), 7.91 (dd, $J = 8.2$, 1.5 Hz, 2H), 7.61 (d, $J = 8.9$ Hz, 2H), 7.59-7.47 (m, 6H), 7.47-7.41 (m, 2H), 7.27 (d, $J = 1.0$ Hz, 1H), 7.24 (d, $J = 0.9$ Hz, 1H), 6.86 (dd, $J = 8.3$, 0.8 Hz, 2H); $^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) $\delta$ 149.2, 148.8, 143.4, 139.2, 134.9, 132.4, 132.0, 131.8, 128.6, 127.7, 126.8, 126.6, 126.5, 125.0, 124.9, 120.4, 117.7, 110.2, 108.1. HRMS-ESI (m/z): [M+H]$^+$ calcd for C$_{40}$H$_{20}$N$_4$O$_8$ Na+, 707.117335; found, 707.116789.

(3.81). To a flame dried round bottom flask, benzyl alcohol (1.00 mL, 2.2 equiv.) was added to a slurry of NaH (485 mg, 2.8 equiv.) in DMA (10 mL) under argon. The mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0°C and 3.70 (1.93 g, 1.0 equiv.) added. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture
was diluted with ethyl acetate and washed with 2% LiCl solution (3x 5 mL). The organic layers were washed with brine (1x 10 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The resulting crude residue was purified by silica gel flash column chromatography (75% toluene/25% hexanes) to provide compound 3.81 as a yellow solid (1.16 g, 43%)

3.81. mp = 103-105°C; TLC R$_f$ = .37 (75% toluene/25% hexanes); IR (neat) 3369, 3349, 3229, 2235, 1430 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.04 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.1 Hz, 2H), 7.56-7.51 (m, 2H), 7.50 (s, 1H), 7.49-7.43 (m, 7H), 7.43-7.35 (m, 8H), 5.24 (s, 4H); $^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) δ 149.9, 149.5, 146.7, 134.8, 132.2, 132.0, 131.5, 129.2, 128.8, 128.5, 127.4, 126.7, 126.3, 125.1, 120.6, 112.0, 108.2. Anal. Calcd for C$_{42}$H$_{26}$N$_2$O$_4$: C, 81.01; H, 4.21; N, 4.50 Found: C, 80.90; H, 4.20; N, 4.69.
3.5 $^1$H and $^{13}$C Supplement to Chapter 3
3.4 References


44. Liu, L.; Floreancig, P. E., 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone-Catalyzed Reactions Employing MnO2 as a Stoichiometric Oxidant. *Organic Letters* 2010, 12 (20), 4686-4689.


47. Hu, Y.; Chen, L.; Li, B., Fe(NO3)3/2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ): An efficient catalyst system for selective oxidation of alcohols under aerobic conditions. *Catalysis Communications* 2018, 103, 42-46.


76. Morales-Rivera, C. A.; Floreancig, P. E.; Liu, P., Predictive Model for Oxidative C–H Bond Functionalization Reactivity with 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone. *Journal of the American Chemical Society* 2017, 139 (49), 17935-17944.
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PROFILE

Searching for a Synthetic Chemist position that will enable me to leverage my expertise in the synthesis, purification, and characterization of small and complex molecule targets to contribute toward the manufacturing of new drug candidates while enhancing my knowledge and experience in up-to-date synthetic methods.

LABORATORY EXPERIENCE

Organic Chemistry Graduate Research Assistant
Syracuse University May 2017 - January 2023

- Designed and executed novel and complex synthetic routes to challenging chemical targets in large and small scale
- Developed new methodology to access desired compounds in reduced number of synthetic steps
- Purified synthesized compounds through silica gel flash column chromatography, recrystallization, and high-performance liquid chromatography
- Analyzed intermediate and final targets using techniques such as nuclear magnetic resonance spectroscopy, infrared spectrometry, and elemental combustion
- Maintained detailed notebook of reaction procedures performed and data obtained
- Troubleshooting of analytical equipment including coordinating on-site vendor repairs and maintenance
- Administered maintenance of laboratory equipment
- Composed SOPs and organized training sessions for proper use of laboratory machinery
- Authored and reviewed project reports and presented them to research group
- Designed and performed poster presentations at local and national conferences

Summer Undergraduate Research Assistant
Graz University of Technology June 2016 - August 2016

- Successfully replicated sought after expressed gene through molecular gene cloning techniques such as Polymerase Chain Reaction (PCR), agarose gel electrophoresis, and Southern Blotting
- Performed protein purification techniques such as ion-exchange/affinity chromatography
- Characterized separated proteins using SDS Page gel, gel-filtration-HPLC, and Western Blotting
- Performed suspension cell culture techniques
- Authored project reports and presented them to research group
- Maintained detailed notebook of procedures performed and data obtained

Summer Undergraduate Research Assistant
Syracuse University June 2015 - August 2015

- Performed peptide coupling reactions in the synthesis of natural products in small and large scale
- Purified synthesized compounds through silica gel flash column chromatography, recrystallization, and high-performance liquid chromatography
- Analyzed intermediates and final targets using analytical techniques such as nuclear magnetic resonance spectroscopy, infrared spectrometry, and elemental combustion
- Authored project reports and presented them to research group
- Maintained detailed notebook of reaction procedures performed

SKILLS

- Column, Gas, and Liquid Chromatography
- Nuclear Magnetic Resonance Spectroscopy (NMR)
- Infrared Spectroscopy (IR)
- Elemental Combustion System (ECS)
- Liquid-Liquid Extraction
- Thin Layer Chromatography (TLC)
- Recrystallization
- Synthesis and Application of Catalysts
- Good Laboratory Practice (GLP)
- Documentation and Organization
- ChemDraw
- TopSpin

EDUCATION

Doctor of Philosophy in Chemistry
Syracuse University 2018 - 2023

Master of Philosophy in Chemistry
Syracuse University 2016 - 2018

Bachelor of Science in Biochemistry and Molecular Biology
The Pennsylvania State University 2011 - 2016
KATELYN LEETS
SYNTHETIC ORGANIC CHEMIST

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EXPERTISE

- Synthesis Design and Method Development
- Retrosynthetic Analysis
- Experimental Set Up and Design (Wet and Air-Free Techniques)
- Compound Purification and Characterization
- Data Analysis
- Problem-Solving
- Laboratory Safety and Housekeeping
- Scientific Writing and Communication
- Literature Search and Review
- Standard Operating Procedure (SOP) Composition
- Laboratory Equipment Maintenance
- Troubleshooting
- University Teaching and Mentoring

REFERENCES

John D. Chisholm
315-443-6894
jdcbisho@syr.edu

Shea T. Meyer
814-389-6979
stmeyer@syr.edu

Undergraduate Research Assistant

The Pennsylvania State University
January 2015 - May 2016

- Constructed a standard curve using a Vernier SpectroVis Plus spectrophotometer
- Performed computation molecular modeling on Spartan software of predicted reaction products
- Analyzed isolated products using FT-IR spectrometer

TEACHING/MENTORING EXPERIENCE

Graduate Chemistry Recitation and Laboratory Instructor

Syracuse University
August 2016 - December 2022

- Instructed recitation sessions weekly to review lecture topics as well as facilitate group work
- Designed and reviewed practice problem worksheets for students
- Held office hours to assist students in comprehension of lecture material
- Led out-of-class review and private tutoring sessions
- Assisted professor with grading student exams, quizzes, and laboratory reports
- Conducted pre-laboratory discussion and demonstrated laboratory system set up
- Supervised lab sessions of ~30 students and assisted students with experimental set-up

Graduate Student Teaching Mentor

Syracuse University
August 2020 - August 2021

- Led ‘Small Group’ and ‘Microteaching’ discussion sessions for incoming graduate students
- Developed and implemented ‘Teaching Assistant Program’ activities during the university wide Teaching Assistant Orientation Program
- Functioned as a teaching consultant for incoming Teaching Assistants
- Interviewed and assisted in the selection of additional Graduate Student Teaching Mentors

Graduate Research Mentor to Undergraduate Research Student

Syracuse University
August 2018 - December 2018
August 2019 - December 2020

- Supervised undergraduate students, in the laboratory, on separate research projects
- Trained students in experimental set up, synthetic purification techniques, and instrumentation usage
- Assisted students in comprehension of research project objective and organic synthetic research concepts

Chemistry Undergraduate Teaching Assistant

The Pennsylvania State University
August 2012 - May 2016

- Supervised laboratory sessions of ~24 students
- Aided students in comprehending laboratory protocol and concept
- Assisted students in completing practice worksheets during group work
- Led out-of-class reviews and private tutoring sessions
- Assisted professor with grading student exams and laboratory reports
CONTACT
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ADDITIONAL EMPLOYMENT
Bottle Preservation Specialist
Suburban Water Testing Laboratory
April 2014 - May 2016
- Performed bottle preparation and preservation for water samples prior to testing
- Prepared required preservation reagents according to Standard Operating Procedure
- Managed testing supply inventory as well as organization of supply and bottle storage
- Assembled bottle orders requested by project managers or clients
- Conducted sample disposal according to proper procedure

Part Time Bakery Associate and Cashier
Acme Markets
May 2009 - February 2011
Giant Food Stores
October 2011 - September 2014
- Prepared product for next day sale
- Assisted customers with cake and party tray orders
- Maintained and organized department according to health department regulations
- Supervised department when manager was absent
- Assisted customers with purchasing groceries

ACTIVITIES
Member of the American Chemical Society (ACS)
Volunteer at B & R Bunkhouse Dog Shelter
Member of Burn Kickboxing
Currently Learning German as a Second Language

PUBLICATIONS
Mahajani, N. S.; Leets, K. A.; Millimaci, A. M.; Chisholm, J. D. “Oxidative Cyclization of Tryptamines with 4-Acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium Tetrafluoroborate Provides Rapid Access to C3a-Oxygenated Pyrroloindolines.” *In preparation.*

AWARDS AND SCHOLARSHIPS
William D. Johnson Award for Outstanding Graduate Teaching Assistant; 2021
Penn State Berks Science Division Service Award; 2015
Edward M. and Dorothy S. Roderick Memorial Scholarship; 2015
Robert E. Newnham Memorial Trustee Scholarship; 2013 and 2014
UFCW Local 1776 Wendell W. Young III Scholarship; 2012

PRESENTATIONS
Nivedita M. Mahajani, Katelyn A. Leets, Alexandra M. Millimaci, and John D. Chisholm. Oxidative Cyclization of Tryptamines with 4-Acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium Tetrafluoroborate Provides Rapid Access to C3a-Oxygenated Pyrroloindolines Poster Presentation: 2019 American Chemical Society Northeast Regional Meeting, Saratoga Springs, New York, June 2019