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THE EXPLORATION OF NOVEL SYNTHETIC METHODS OF BIOLOGICALLY RELEVANT NITROGEN AND HALOGEN CONTAINING MOLECULES

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THE EXPLORATION OF NOVEL SYNTHETIC METHODS OF BIOLOGICALLY RELEVANT NITROGEN AND HALOGEN CONTAINING MOLECULES

by
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A Thesis

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Dedications

To the woman who embodies the perfect balance of grace and strength. You have shown me time and again how truly hardworking and kind you are. The respect I have for where I have come from only grows the more I learn about you and your past. I would not be half the person I am today without you. To the beaming sunflower in the room, to my mommom Barbara Driscoll, you truly are an angel on earth.

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Abstract

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Visible light has become a highly useful, and regarded, tool to the organic chemist. The additions and transformations of an abundance of molecules can be achieved with the use of visible light and photocatalysts, when appropriate. More specifically compounds that contain nitrogen, halogens, or both are highly useful structures in nearly every chemical industry. They are elements found in naturally occurring molecules and have the capacity to mimic biologically active and relevant structures. This makes them useful targets for pharmaceutical compounds. Bromine and chlorine can acts as leaving groups; this property makes molecules with these elements reactive and thus able produce desirable effects in vivo. Nitrogen can be found within and outside of cyclic structures and is one of the most commonly functionalized elements in pharmaceuticals. The element can be found in nearly every class of pharmaceuticals ranging from chemotherapeutic to antifungal agents.

Herein is reported the methodological development of synthetic nitrogen and halogen placement through a wide variety of chemical moieties. This work shows that visible light and photocatalysts can be used to furnish small heteroatomic compounds and halogenated products. These works highlight the value of substituted hydroxylamines for their nitrogen transfer capability; metal-halogen compounds in visible light transformations will also be highlighted.

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Chapter 1

Vinyl Oxaziridines

1.1 Oxaziridine Discovery

The first oxaziridine was synthesized in 1956 by William Emmons. He accomplished this by reacting azomethines with carboxylic acids. Emmons produced oxazidirines, at the time referred to as oxaziranes, with varying substitution patterns on the carbon and nitrogen atoms. He observed the surprising stability of the strained ring structures and noted their ability to be useful in oxidation reactions when compared to organic peroxides (Emmons, 1956). Since this groundbreaking discovery dozens of methods to produce oxaziridines have been published.

1.2 Current Methods

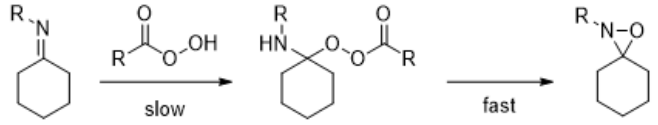
The synthesis of oxaziridines is a well explored region of organic chemistry. The different substitution patterns make the products useful in for different reactions discussed in the next section. As stated above, the first oxaziridine was synthesized and characterized by William Emmons in 1956 (Emmons, 1956). This was done through oxidation of an imine with peracids and m-chloroperbenzoic acid (mCPBA) and these remain some of the most common methods.

Since this time, dozens of methods have been published detailing the unique synthesis of oxaziridines. These methods highlight the ability to create oxaziridines synthetically with nearly any substitution pattern imaginable. In 1973 Ogata and Sawaki detailed their methods for the synthesis of N-alkyloxaziridines. They were able to perform a single step synthesis using peracids to oxidize N-alkyl imines to their corresponding oxaziridines. . It is noted besides other oxidizing conditions, such as cobalt

and O_2, various peroxide systems yield successful results. These products have been reached through photochemically induced rearrangements of nitrones (Ogata, & Sawaki, 1973).

Figure 1

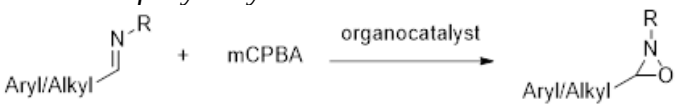
Ogata and Sawaki Synthesis of C-substituted Oxaziridines



The Jørgensen group used both aryl and allyl imines and oxidized them with mCPBA and a chiral Brønsted base organocatalyst to yield aryl and allyl oxaziridines, respectively. The group reported success only with tosyl-substituted imines, owing the observed reactivity to the electron-deficient nature of the substrate. These chiral and electron-deficient oxaziridines are known to be useful in asymmetric synthesis including enolates and asymmetric epoxidation of olefins. (Lykke, Carles, Jørgenson, 2011).

Figure 2

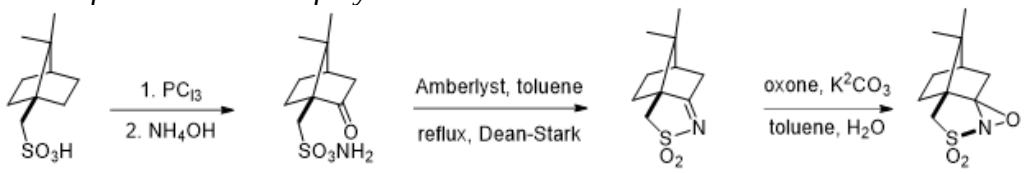
Enantioselective Oxidation of aryl/allyl Imines to Oxaziridines



Oxaziridines are highly sought after due to their ability to act as organic oxidants. N-sulfonyl oxaziridines are commonly used organic oxidants. They are also extremely useful in further reactions due to their stability, ease of synthesis, and excellent oxidizing ability. Their methods are often revisited to be improved. The N-sulfonyloxaziridines became nicknamed the Davis oxaziridine, which Davis et al. synthesized through oxidation of the related N-sulfonyl imines with mCPBA. Further research led the Davis group to the synthesis of additional N-sulfonyloxaziridines using chiral camphor based peracids; however, these were low yielding reactions. The researchers changed their approach to synthesizing camphor sulfonic acid derived imines and oxidizing them with oxone to yield chiral N-sulfonyloxaziridines (Davis et. al., 1986).

Figure 3

Chiral Camphor-based N-sulfonyloxaziridines

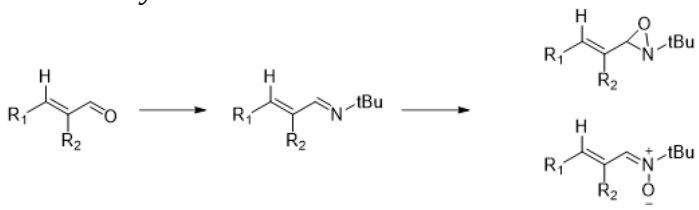


An underexplored region of oxaziridine synthesis is the synthesis of vinyl oxaziridines. Vinyl oxaziridines have the added benefit of an additional reactive points within the molecule that can help yield more complex heterocycles in further reactions. The Mlochowski group reported a synthesis of these three-membered heterocycles using starting materials with a heterocycle conjugated with an unsaturated compound. These

substrates were reacted with tert-butylamine in the presence of molecular sieves to produce the aldimine intermediate product. This structure was reacted with mCPBA to oxidize into the vinyl oxaziridine. The Mlochowski group reported the presence of a nitrone byproduct as well (Said et. al., 1990).

Figure 4

Vinyl Oxaziridine and Nitrone Synthesis



1.3 Applications of Oxaziridines

1.3.1 Oxaziridine-Mediated Oxidation Reactions

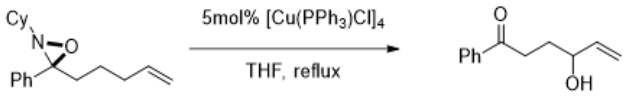
Oxaziridines have become an important class of organic molecules. They have proven to be a useful organic oxidant. They are highly useful molecules in heteroatom transfer; oxidation and epoxidation can be performed using them. N-(benzylsulfonyl)oxaziridines can be used to oxidize alkenes into epoxides.

Oxaziridines have been knowns to oxidize sulfur as well. N-sulfonyloxazidirines are useful in the oxidation of sulfides to sulfoxides with the use of optically active oxaziridines. Several groups have published methods utilizing N-sulfonyloxaziridines as a reagent to oxidize secondary sulfides into sulfoxides; chirality within the reagent helps transfer chirality to the final product.

The oxidation of amines, enamines, and enolates are possible as well. Along with oxidation of various heteroatoms oxaziridines are also able to functionalize carbon-hydrogen bonds. This process requires high oxidizing power to be successfully achieved. Early reports of this chemical transformation were completed using electron-deficient oxaziridines. Fluorine-containing oxaziridines have been utilized by several groups to be useful in this reaction. More recent reactions have moved away from the use of perfluorinated oxaziridines; the Aube group used copper (I) catalyst to oxidize N-cyclohexyloxaziridines into phenyl ketones (Motiwala, Gülgeze, & Aube, 2012).

Figure 5

The Aube Group C-H Bond Functionalization



The Shi group was also able to perform a similar oxidation using t-butyloxaziridines as the organic oxidant reagent (Williamson, Michealis, & Yoon, 2014).

Oxidation of sulfur within a compound is also possible. N-sulfonyloxazidirines are also useful in the oxidation of sulfides to sulfoxides with the use of optically active oxaziridines. Several groups have published methods utilizing N-sulfonyloxaziridines as a reagent to oxidize secondary sulfides into sulfoxides; the presence of chirality in the oxaziridine has the potential to transfer chirality to the product. Not only is the sulfoxide

of interest, but these molecules are also produced with chirality in mind. These reactions have been found to be not only successful and scalable but stereoselective, which is of particular interest within pharmaceutical production. Some methods have shown oxidation to occur within minutes. N-sulfonyl oxaziridines have been used in the production of the proton-pump inhibitor rabeprazole (Williamson, Michealis, & Yoon, 2014).

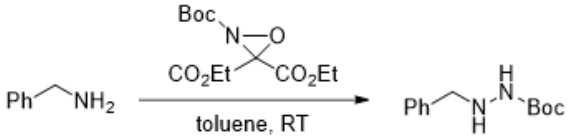
1.3.2 Nitrogen Atom Transfer Reactions

The use of oxaziridines is not limited to the oxidation of heteroatoms; they can also be used for heteroatom transfer. The use of N-substituted oxaziridines with small groups substituted are useful in the transfers of nitrogen atoms. Being one of the most commonly occurring elements in pharmaceutical drugs, nitrogen is a useful element to add. More importantly, it is valuable to add nitrogen either already within a cyclic structure, or with the potential to easily form a heterocycle in the final product. While oxaziridines are unlikely to be found in drug structures themselves, larger heteroatom ring sizes are found quite commonly. These are especially common in antibiotics, antifungal agents, and anticancer agents. According to Williamson, groups have been able to use various techniques to aminate amines, sulfides, alkoxides, and sp^3 carbons using oxaziridines. The Collet group used oxaziridines to aminate nitrogen nucleophiles. A N-carbamoyloxaziridine, designed by the Collet group, was used to aminate primary and secondary amines. This approach, while showing good yields, resulted in the formation of a competitive byproduct, 4-cyanobenzaldehyde, which occasionally decreased overall product yields. However, numerous research groups have used N-Boc-hydrazine to aminate nitrogen (Williamson, Michealis, & Yoon, 2014).

The Armstrong group addressed this reaction utilizing N-Boc-oxaziridine; using this oxidant they were able to aminate several primary amines. This reaction yielded N-Boc-hydrazides (Armstrong et. al., 2005).

Figure 6

N-Boc-oxaziridine Mediated Amination of Primary Amines



Oxaziridines can also be used to the aminate carbon (Armstrong et. al., 2005). N-sulfonyloxaziridines have been used as starting material by the Yoon group to aminate sp^3-hybridized carbons to exclusive formation of a nitrogen containing six-membered ring. This product can then be used as a starting material in two subsequent reactions to add a ketone or an alkene, producing piperidine-containing molecules. The group reported no evidence of insertion of the nitrogen into other alkane positions in the product (Williamson, Michealis, & Yoon, 2014).

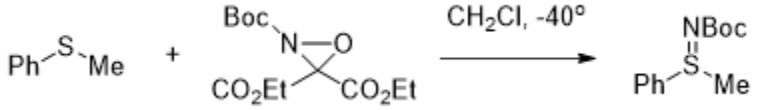
Nitrogen nucleophiles are not the only nucleophiles oxaziridines can aminate. Under certain conditions they can aminate nucleophilic carbon. Past works have shown that the use of N-Boc-oxaziridines with enolates to aminate carbon is mildly successful, but byproducts of 4-cyanobenzaldehyde limit the reaction efficiency. The use of amide and ester enolates showed similar results. Further research showed that N-Boc-oxaziridines can transfer nitrogen to organometallic species through a metathesis

reaction. It was proposed that nitrogen transfer was favored over oxygen transfer in this reaction due to the oxaziridine acting as a Lewis base and the formation of a zincate complex. The nitrogen acts as an electrophile and attacks the organozinc complex (Williamson, Michealis, & Yoon, 2014).

The Collet group also studied aminating sulfides using oxaziridines. Their work was met with competitive oxygen transfer which led to lowered yields. However, Armstrong and Cooke showed higher levels of amidation could be achieved with the use of N-Boc oxaziridine.

Figure 7

Amination of Sulfides Through N-Boc-oxaziridines



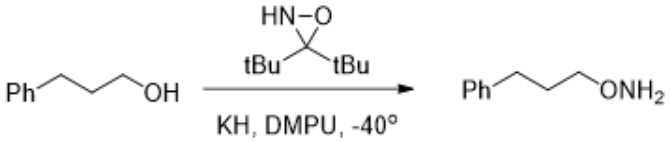
Armstrong and Cooke demonstrated that when the amination of the sulfur occurs, an intermediate sulfimide complex forms, which then undergoes [2,3]-sigmatropic rearrangement yielding the final amines. The researchers were also able to develop an application of this reaction. When amination is applied to chiral allylic sulfides, the reaction proceeds with complete chirality transfer. Moreover, Armstrong and Cooke were also able to demonstrate the viability of a one-pot strategy to this reaction in good yields (Armstrong & Cooke, 2002).

When nitrogen transfer is the goal N-H and N-Boc-oxaziridines are both able to aminate alkoxides yielding alkoxyamines. The Choong group discovered that 3,3-di-tert-

butyloxaziridine can be used to aminate primary and secondary alcohols. The steric hindrance that accompanies this oxaziridine led to its success in this reaction in good yields. However, the steric hindrance of the nitrogen source can also lead to encumbrance. This limits its scope, as tertiary alcohol products were isolated in low yields (Choong & Ellman, 1999).

Figure 8

Oxy-amination of Primary Alcohols by Choong



Other research groups were able to produce novel synthetic pathways to achieve this oxaziridine-mediated amination. Electrophilic amination of alkoxides was achieved by Foot and Knight, utilizing chlorine-based oxaziridines. Their method was shown to achieve amination of primary, secondary, tertiary, allylic, propargylic, and phenolic alkoxides in good to excellent yields (Williamson, Michealis, & Yoon, 2014).

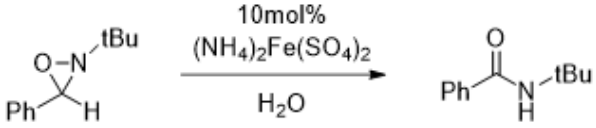
1.3.3 Transition-Metal-Promoted Reactions

While there are an extensive number of methods and oxaziridines that can be synthesized, there are even more extensive applications for these oxaziridines. The oxaziridine is capable of undergoing rearrangement, specifically initiated by a single-electron transfer. This property is what leads to the photochemical isomerization of vinyl nitrones that will be discussed later in this chapter. Transition metals can also be used to

perform these rearrangements and transformations. After his first publication of synthesizing the first oxaziridines, Emmons reported the treatment of t-butyl-oxaziridines with catalytic concentrations of ammonium iron (II) sulfate in water to yield N-tert-butylbenzamides in good yields.

Figure 9

N-tert-butyloxaziridine Transition-Metal-Mediated Ring Opening



β-scission cleavage of the oxaziridine could be achieved when using a triethyloxaziridine as the starting material. The cleavage yields a mixture of diethyl ketone, N-ethylpropionamide, and ammonia. The cleavage is believed to follow a nitrogen-centered radical intermediate pathway as opposed to the oxygen-centered radical. An oxygen-centered radical is not as likely given the higher energetic cost of creating this radical in situ. The increased stability of the nitrogen radical leads to the single-electron reduction of the alkyl chain (Emmons, 1957).

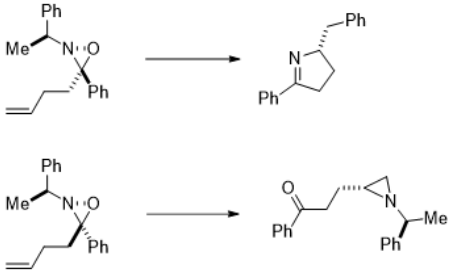
The oxidation of imines can lead to amides through an oxaziridine intermediate. As reported in Williamson et al., the Black group was able to demonstrate that a similar pathway could successfully yield the rearrangement of oxaziridines. The group used stoichiometric iron (II) sulfate, and through a nitrogen-radical rearrangement pathway,

they were able to synthesize similar amides to those Emmons produced (Williamson, Michealis, & Yoon, 2014).

These catalyzed reactions hold potential outside of the synthesis of amides. The formation of nitrogen-containing radicals has also been found to be useful in intramolecular cyclization and fragmentations. The Aube group was able to find, while studying intramolecular radical cyclization with oxaziridines, that product distribution is highly dependent on the substitution of the oxaziridine. They proposed treatment of the starting material with 5mol% of copper (I) catalyst would generate the nitrogen-centered radical indicative of this rearrangement. This leads to the formation of an aziridine with the (S,R) enantiomer, and a pyridine with the (S,S) enantiomer (Aube, et. al., 1992).

Figure 10

(S,S) Intramolecular Cyclization and (S,R) C-H Functionalized Alkylation



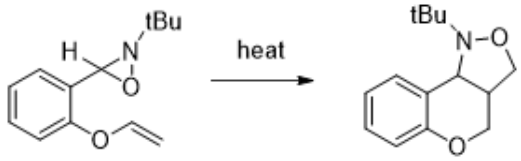
The Aube group also studied nitrogen-radical reactions leading to the formation of amides. They found that substitution beta to the nitrogen produces a stable nitrogen-radical leading to the formation of a stable amide. Moreover, they found the carbon-radical that forms can be utilized in subsequent reactions (Aube et al., 1992).

1.3.4 Oxaziridines in Cycloadditions

The highly strained nature of oxaziridines is what leads to the observed reactivity. Cleavage of the ring can occur at the carbon-nitrogen, carbon-oxygen, or nitrogen-oxygen bond. The production of cyclic structures within pharmaceutical moieties is highly coveted; the rigidity of ring structures allows for the synthesis of products that will interact with the desired targets while reducing reactivity in vivo. The addition of heterocycles can introduce favorable electronic effects to the structure as well. Several cycloaddition reactions can be performed using oxaziridines. The Padwa group utilized a thermal rearrangement of an oxaziridine to a nitrone bound to an alkene; they used this product to synthesize an isoxazolidine product in good yields. The same product can be achieved through the independently synthesized nitrone in similar yields (Padwa & Koehler, 1986).

Figure 11

Intramolecular Cyclization on Aromatic N-tert-butyloxaziridines

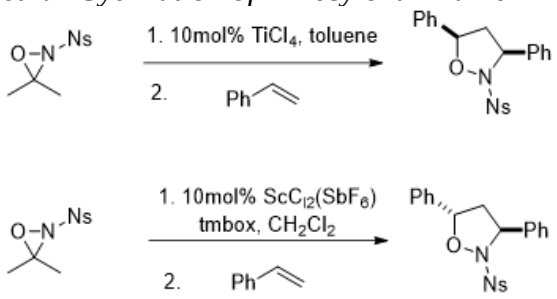


It was also discovered the catalytic rearrangement of N-nosyloxaziridines was possible. In the presence of catalytic $TiCl_4$ N-nosyloxaziridine isomerizes into the nitrone, and when reacted with a terminal alkene a cis 1,2-isoxazolidine was formed. When the same N-nosyloxaziridine is reacted with catalytic $ScCl_2(SbF_6)$ the oxaziridine

isomerizes into a N-nosyl methylamide and when reacted with the same terminal alkene the trans 1,2-isoxazolidine is formed (Williamson, Michealis, & Yoon, 2014).

Figure 12

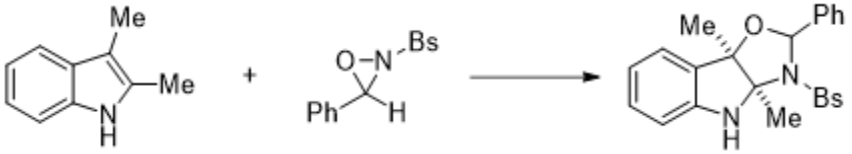
Enantioselective Intramolecular Cyclization of N-nosyloxaziridine



Cleavage of the nitrogen-oxygen bond in cycloaddition reactions can lead to the production of different isoxazolidines. The use of oxaziridines and alkenes in these catalyzed reactions yields 1,3-isoxazolidines; however, uncatalyzed reactions between these two substrates are rare. Despite this, the Desmarteau groups reported this same reaction uncatalyzed using 1,1-difluoroalkenes producing 1,3-oxazolidine in good yield. The Dmitrienko group also observed the oxyamination of 2,3-dimethylindole using N-sulfonyloxaziridine to form aminal products towards the synthesis of an antitumor alkaloid below (Lam & DesMarteau, 1982).

Figure 13

Intermolecular Cyclization Between Dimethylindole and N-sulfonyloxaziridine



The production of oxaziridines has also been proven to be successful using irradiation of nitrones. It has been known for over a century that nitrones are particularly sensitive to light. Alessandri was the first to note the transformation of nitrones via visible light conditions (Splitter & Calvin, 1965). The use of light to irradiate nitrones opened the doors to new possible structures that could not be oxidized via acid-promoted conditions. The dipolar nature of these molecules is what makes them likely to react under heat and light conditions, despite being surprisingly stable under standard conditions. The zwitterionic nature of nitrones, with the nitrogen carrying a positive charge and the oxygen carrying a negative charge, is what promotes the intermolecular cyclization into an oxaziridine product.

1.4 Bioactivity of Oxaziridine-Derived Products

Oxaziridines are known to exist as reactive species. The highly strained, three-membered heterocycle has become known as one of the most useful organic oxidizing agents. The different lengths of the bonds between each of the three atoms comprising the ring contributes to the reactivity of the molecule. Due to the weakest of the three bonds being between oxygen and nitrogen, oxaziridines have a high ability to add nitrogen and oxygen to molecules in subsequent reactions. The high electronegativity of these atoms contributes to the bond being weak. Oxygen having the greater electronegativity leads to

its bond with carbon being the weakest (Vishnu et. al., 2019). Rearrangements, both thermochemical and photochemical, yield nitrones and amides.

The main use of an oxaziridine is in the production of more complex organic structures. The predominance of one process over another regarding oxaziridine use as a reagent is reflected by the substitution of the nitrogen. Bulky, electron-withdrawing N-substitutions tend to act as oxygen transfer agents, while small substituents tend to act as nitrogen transfer agents (Vishnu et. al., 2019). These molecules are highly non-polar structures regardless of the substitution pattern. Electron withdrawing groups substituted at the nitrogen electron density is pulled away from the oxygen in the ring, allowing for bond breakage. Small substituents do not have this electronic effect, and bond breakage no longer favors the carbon-oxygen bond. This is due to the more electron donating ability of nitrogen into the oxygen orbitals. While the bioactivity specifically of oxaziridines has not been studied, non-polar moieties have increased lipophilicity. The increase in lipophilicity can lead to an increase of intracellular concentrations in vivo. When oxaziridines are found in natural products they have been known to possess antifungal, antibacterial, and chemotherapeutic properties (Said, Młochowski, & Skawźewski, 1990).

1.5 Pharmaceutical Relevance

Oxaziridines are not common in drug products but can be used to help produce final products that may become pharmaceutical agents. Nature can produce these structures integrated into complex molecules in a manner that is highly challenging synthetically. Natural products that contain oxaziridines possess the potential to be useful antifungal and antibacterial agents, as well as anticancer agents (Vishnu et. al., 2019).

Natural products are the target molecule of pharmacophores and pharmaceutically relevant compounds, with researchers attempting to synthesize these natural products and other biologically relevant molecules. For centuries, humans have relied on the ecosystem around them as a source of relief from ailment and illness. The bulk of these products came from flora and fauna. Although humans no longer rely on their backyard as a source of medical relief, medicinal chemistry still takes advantage of the abundance of natural products. These natural products offer biological activity found in nature to current classes of pharmaceutical compounds. Oxaziridines with electron-withdrawing groups are particularly attractive due to the resultant oxyfunctionalization of previously unactivated carbon-hydrogen bonds. (Motiwala, Gülgeze, & Aube, 2012)

While nature has a limited supply of structures it can produce, the synthetic chemist can alter a molecule into thousands of deviations. Utilizing natural product modeling of molecules known to induce desired effects in vivo allows for a starting ground to improve the efficacy of the compound. These natural product-like compounds have become popular targets for the improved treatment of many diseases, including AIDS, cancer, and infectious diseases (Newman, Cragg, & Kingston, 2015). The ability of a man-made molecule to mimic nature's ability to oxidize carbon-hydrogen bonds has been of ever-growing interest.

The previously mentioned methods for the synthesis of oxaziridines is not even the tip of the iceberg in the number of available synthetic pathways. Their reactivity is not the only attractive property about them. Oxaziridines tend to be surprisingly stable molecules despite their reactivity. Many products have been reported to withstand molecular modifications through addition reactions without losing the main functional

group; these products also resist decomposition at reduced temperatures. The ease of purification through standard chromatographic conditions is an additional attractive feature as well (Williamson, Michealis, & Yoon, 2014)

These molecules can act as oxidants to an asymmetric design which permits asymmetric oxidation as well as enantiomerically pure products. Their design affects the stereoselectivity influencing which active site is oxidized (Davis et. al This quality to yield enantiomerically pure products is highly attractive to pharmaceutical design; biological systems are enantiomerically driven systems. The molecules in vivo will only yield the desired effects when they are the proper confirmation, otherwise non-desirable effects may be experienced if anything at all. The Davis oxaziridine, obtained through the imine oxidation of camphor derived carbonyls, can be useful in the asymmetric hydroxylation, epoxidation, and oxidation of sulfides (Page et. al., 1997). The synthesis of enantiomerically pure oxaziridines is even more useful than the molecule itself. When enantiomerically pure oxaziridines are used as oxidants they produce specific molecules due to their target attack to certain groups on the substrate molecule (Gioia et. al., 2005).

The most useful aspect of an oxaziridine lies not in its structural significance in biologically active molecules, but the ability to aid in the production of more complex molecules. . It owes its reactivity to the highly strained ring structure along with the presence of two highly electronegative elements within the heterocycle. They have proven to be most useful in oxidative transformations. Despite oxaziridines' usefulness in this area of synthesis, their usefulness in a number of other reactions has also been proven. The driving force of these reactions is the heteroatom transfer and the release of

ring strain through the formation of carbonyl, imine, or oxometal pi-bonds (Gioia et. al., 2005).

These larger nitrogen-containing heterocycles, specifically oxazolidines, isoxazolidines, and oxazepines, are commonly found within drugs available on the market. Isoxazolidines are non-aromatic heterocycles containing a nitrogen-oxygen bond. These structures can produce multi-functional β-amino acid derivatives, including alcohols, aldehydes, esters, amides, and imides. They can act as natural building blocks for biomolecules (Ayed et. al., 2017). Their concerted ability to act as building blocks and produce the derivatives mentioned previously makes them good targets for medicinal products. They have demonstrated biological activity including antibiotic capabilities, gene expression regulation, and cancer cell toxicity. These last two biological qualities make them excellent chemotherapeutic targets (Floresta et. al., 2017). These structures can be found as a fused cyclic structure with other cyclic and heterocyclic structures, or unfused in pharmaceutical target molecules.

Oxazolidines are similar to isoxazolidines in that they are oxygen-nitrogen-containing five-membered heterocycles. However, they differ in the cyclic arrangement. In oxazolidines the nitrogen and oxygens atoms are separated by a carbon atom. This re-arrangement of bond location can have drastic effects on the biological properties of the structure. Chiral oxazolidine rings are crucial structures of many natural products. Given their chirality and utility they are important to the production of many chiral pharmaceuticals (Wu et. al., 2017). Oxazolidines have been known to be useful antibiotics, antidepressants, and HIV-1 protease inhibitors (Wang, Yuan, & Yao, 2017). Structures responsible for cancer treatment with drug-resistant tumors have occasionally

contained oxazolidines. These drugs work through the fragmentation of DNA within the cancerous cells (Andrade et. al., 2017). Despite being the most common classes of pharmaceuticals oxazolidines can be found in, the structure is observed in nearly every class of drug on the market, like many nitrogen-containing heterocylces.

While the previously two discussed ring structures were both nonaromatic five-membered rings, the oxazepine is a seven-membered heterocycle. This structure can exist as the non-aromatic equivalent, which contains either one or two double bonds within the ring, or the aromatic equivalent also referred to as benzoxazepines. Benzodiazepines, one of the benzoxapines, are more commonly found in pharmaceutically active agents. They display a range of biologically relevant properties and mimicry of natural products. Pharmacological properties of these structures worth mentioning include anti-inflammatory, antifungal, antithrombotic, anti-epileptic, antipsychotic, and anticonvulsant properties, as well as analgesic and progesterone antagonistic properties. The array of potential physical properties, depending on the substitution patterns of the target molecules, are thought to be in part due to the general structure of the ring. A nitrogen-carbon-oxygen bond structure is observed in the most common oxazepine pharmacophores available today, and this structure is similar to a peptide amide bond. The peptide bond is one of the most important and prevalent structural units in biological systems, and as such the importance of these rings structures in medicinal chemistry is high (Armstrong et. al., 2005).

Oxaziridines are both valuable intermediates and highly useful reagents in the synthesis of larger target molecules. Specifically, they are useful for cycloaddition and ring expansion reactions that can be used to produce much more than the heterocyclic

structures discussed briefly here. Herein, is described the methods for photochemically induced isomerization of vinyl nitrones to vinyl oxaziridines.

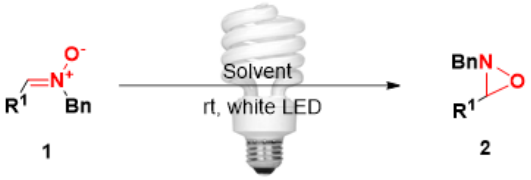
1.6 Results and Discussion

Due to the utility of oxaziridines and the limited methods of synthesizing vinyl oxaziridines, it was hypothesized that these structures could be achieved through a photocatalyzed isomerization of vinyl nitrones. The nitrones were synthesized using a previously discovered method. With a library of nitrones available photoisomerization of these substrates to form their respective vinyl oxaziridines was pursued. T-cinnamaldehyde derived nitrones were used for optimization studies; the respective oxaziridine was produced in good to excellent yields under visible light conditions (Quinn, 2017). Optimization of the isomerization was explored using the nitrones formed from 4-phenyl-but-2-enal and cinnamaldehyde. Different sources of visible light were explored to find the most useful source for oxaziridine formation. Visible light through sunlight by leaving the reaction on a windowsill for 18 hours showed the lowest conversion and this method was not pursued further after a single test. Sunlight is not as direct as white LED light bulbs and the reaction material is not being excited to a state where isomerization occurs. Following conditions included either the use of a white LED light in a lightbox with and without catalyst. Benzene and toluene were tested as solvents, but without the use of a photocatalyst due to the conjugated nature of the compounds. This property allows the molecules to absorb and emit wavelengths of light allowing them to play a part in the excitation state of the intermediate. With the exclusion of using sunlight as the light source, the previously tested reaction conditions were repeated using cinnamyl nitrone. Using both substrates the test for ideal conditions it was found that the

use of the benzene as the solvent with no photocatalyst present at 0.1M concentrations was ideal.

Table 1

Vinyl Oxaziridine Synthesis Optimization Studies



1 2

Entry	R^1	additive	solvent	concentration (M)	yield (%)[d]
1	Ph[c]	visible light[a]	benzene	0.05	12
2	Ph	visible light[b]	benzene	0.05	48
3	Ph	$Ru(bpy)_3Cl_2$ 5 mol %	CH_3CN	0.05	38
4	Ph	visible light[b]	CH_3CN	0.05	40
5	Ph	visible light[b]	toluene	0.05	44
6	Ph	visible light[b]	CH_2Cl_2	0.05	20
7	Ph	$Ru(bpy)_3Cl_2$ 5 mol %	CH_3CN	0.05	40
8	Ph	visible light[b]	benzene	0.01	28
9	Ph	visible light[b]	benzene	0.025	20
10	cinnamyl	visible light[b]	benzene	0.05	96
11	cinnamyl[c]	visible light[b]	benzene	0.05	28
12	cinnamyl	visible light[b]	CH_3CN	0.05	75
13	cinnamyl	visible light[b]	CH_2Cl_2	0.05	35
14	cinnamyl	$Ru(bpy)_3Cl_2$ 5 mol %	CH_3CN	0.05	82
15	cinnamyl	visible light[b]	benzene	0.01	80
16	cinnamyl	visible light[b]	benzene	0.025	64

a. By the windowsill over 18 h. *b*. White LED. *c*. Nitrone intermediate was isolated prior to photocyclization. *d*. Isolated yields.

Completion of a scope containing vinyl oxaziridines formed from aldehyde derived nitrones was pursued. The range of substitution patterns explored on both the conjugated aldehyde and hydroxylamine used to produce the nitrone highlights the versatility of the reaction scope. One trend that can be noticed is there is a slight difference in the trend of isomerization between the aromatic oxaziridines formed and the allylic oxaziridines formed. While yields were still great in both substrate categories overall, the aromatic oxaziridines showed higher yield in comparison to the allylic oxaziridines. The conjugated nature of aromatic compounds, and the lower overall energy state they exist in, contributes to the higher conversion observed with these substates. All oxaziridines were isolated using manual column chromatography. Being highly polar compounds, they proved relatively simple to isolate.

Table 2

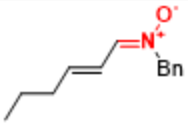
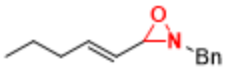
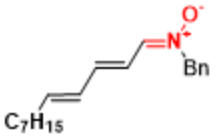
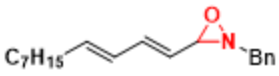
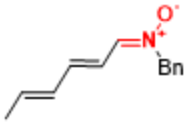
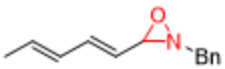
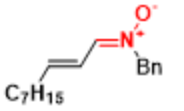
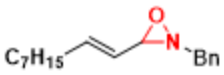
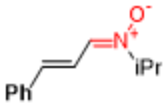
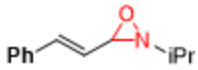
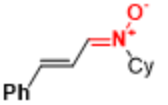
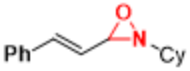
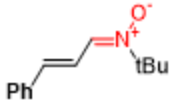
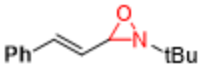
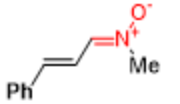
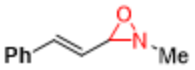
Aromatic Vinyl Oxaziridine Synthesis Scope

Entry	nitrone	product[c]	Yield (%)[a,b]
1	1a	2a	98
2	1b	2b	93
3	1c	2c	84
4	1d	2d	92
5	1e	2e	91
6	1f	2f	97
7	1g	2g	96
8	1h	2h	95
9	1i	2i	93

a. Conditions: Nitrone (1 mmol) in benzene (0.05M) for 22h. b. Isolated yields.
c. Reaction crude was purified by standard silica gel chromatography.

Table 3

Nonaromatic Vinyl Oxaziridine Scope

Entry	nitrone		product[c]		Yield (%)[a,b]
1	1j		2j		79
2	1k		2k		82
3	1l		2l		84
4	1m		2m		75
8	1n		2n		91
7	1o		2o		92
8	1p		2p		91
9	1q		2q		95

a. Conditions: Nitrone (1 mmol) in benzene (0.05M) for 22h. b. Isolated yields.
c. Reaction crude was purified by standard silica gel chromatography.

1.7 Conclusion

The results obtained show a simplistic method for the conversion of nitrones to oxaziridines through a visible light irradiation photocatalytic processes. The GML lab was able to demonstrate a wide range of chemical diversity by utilizing t-cinnamaldehyde derived nitrones with various hydroxylamines. The wide range of substitutions patterns explored on both the conjugated aldehyde and hydroxylamine used to produce the nitrone highlights the versatility of the reaction scope. One trend that can be noticed is there is a slight difference noticed in the isomerization between the aromatic oxaziridines formed and the allylic oxaziridines formed. All oxaziridines were isolated using manual column chromatography. As highly polar compounds, they were relatively simple to isolate. This method boasts the utility of not only substituted hydroxylamines in the synthesis of heteroatomic moieties, but also visible light in the pursuit of more complex molecular scaffolds.

1.8 Experimental

Reagents were obtained from Aldrich Chemical, Acros Organics and Alfa Aesar and used without further purification. Reactions were performed in 4- mL glass vials. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate (KMnO4). Silica flash chromatography was performed on E. Merck 101 230–400 mesh silica gel 60. Automated chromatography was performed on an ISOLERA Prime instrument with 10 g. SNAP silica gel normal phase cartridges using a flow rate of 12.0 mL/min and a gradient of 0–30% EtOAc in Heptanes over 12 column volumes with UV detection at 254 nm. NMR spectra were recorded on Varian Mercury II 400 MHz Spectrometer at 24 °C in CDCl3

unless otherwise indicated. Chemical shifts are expressed in ppm relative to solvent signals: CDCl3 (1 H, 7.23 ppm; 13C, 77.0 ppm); coupling constants are expressed in Hz.

1.8.1 General Method for the Synthesis of Vinyl Oxaziridines

1mMol of nitrone is dissolved in 30mL of Benzene to a 0.1M solution. Solution delivered to a 50mL round bottom flask (borosilicate) UV cutoff approximately 300nM. Nitrone solution is irradiated under a 105-Watt Compact Fluorescent Lamp (Limo Studio Full Spectrum Light) for 6 hours. After irradiation, the solvent is reduced by rotary evaporation to afford the respective oxaziridine. Filtration by silica gel with 20% EtOAc in Heptanes over 12 column volumes provided the desired oxaziridine in good to excellent yields.

1.8.2 Synthesis of Vinyl Oxaziridines

Due to the COVID-19 pandemic of spring 2020 incorporation of data analysis, chromatograms, and spectral data was not able to be completed.

Chapter 2

Haloamines and Aromatic Bromides

2.1 Haloamine Discovery

Haloamines are molecules containing both a halogen and an amine group. This includes N-haloamines, molecules where the halogen is bound directly to the nitrogen, vicinal haloamines, where the amine and halogen are on adjacent carbons, and molecules containing both functional groups in remaining substitution patterns. The use of these compounds can be dated back to 1883, first cited in the Hofmann-Löffler reaction. Hofmann utilized N-bromoamides and N-bromoamines to perform an intramolecular cyclization to produce tertiary amines; this method became a quick and simple process for the synthesis of pyrrolidines. Later, Löffler expanded on this process, and found that alkyl bromoamines failed to yield the same results Hofmann produced. However, he found that alkyl chloramines could be utilized to form the same pyrrolidines Hofmann synthesized (Corey & Walter, 1960).

Even more useful than the Hofmann-Löffler reaction is the dozens of alkene difunctionalization reactions discovered within the last century. More specifically is the 1,2-functionalization of alkenes with amines and halogens. The derivatives of these reactions are useful in subsequent reactions towards the synthesis of more highly complex molecules in medicinal and organic chemistry (Thakur, Talluri, & Sudalia, 2003).

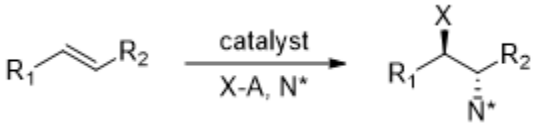
2.2 Current Methods

Many groups have studied methods to produce haloamines. The Chemler group studied several catalytic processes for making these molecules starting with alkenes,

allenes, and alkynes to yield vicinal haloamines using fluorine, bromine, and chlorine. Their method was shown to not only be successful, but regioselective, diastereoselective, and enantioselective as well. The catalyst varied depending on halogen added in the reaction they were studying, but all catalysts used were transition metal based. Methods to add iodine across the alkene were unsuccessful (Chemler & Bovini, 2013).

Figure 14

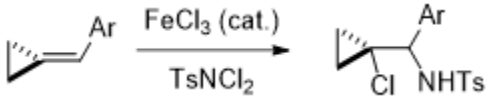
Chemler Method for the Synthesis of Vicinal Haloamines



Production of haloamines is not limited to starting with an alkene. Li discovered the use of α-β-unsaturated carboxylic esters and ketones under various catalytic conditions. This reaction is believed to follow an aziridinium-based intermediate mechanism. The cyclopropane starting material was reacted with 20 mol% iron (II) chloride in acetonitrile at room temperature; this method gave good to excellent yield depending on the substitution pattern of the starting substrate. The reaction scope showed the presence of electron-donating groups on the cyclopropane gave higher conversion rates, aiding in cleavage of the ring. Products with highly electron donating groups containing a halogen could continue to be reactive species in future reactions, as the halogen may act as a leaving group in several future steps. (Li et. al., 2006).

Figure 15

Li Method for the Synthesis of Vicinal Haloamines Adjacent to a Heterocyclic Species



Aminohalogenation can be performed using various nitrogen and halogen sources from amines, amides, sulfonamides, carbamates, and imides. Addition of the two functional groups across the alkene can occur through heterolytic or homolytic cleavage. Homolytic cleavage can be initiated by peroxides, light, or heat.

2.3 Applications of Haloamines

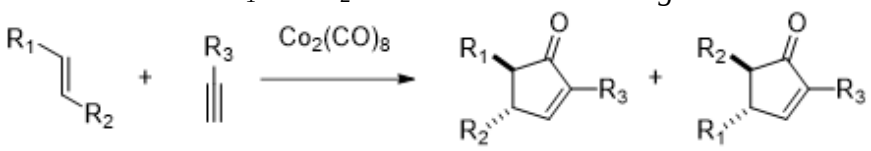
Compounds containing both a halogen and an amine functional group are attractive molecules due to their similarity to molecules with bioactivity that occur in nature. Haloamines can be found as secondary metabolites; secondary metabolites are molecules that are produced by bacteria, fungi, and plants that while not necessary to sustain life, increase the survivability of the organism. The importance of these molecules lies in their activity. The propensity of the halogen to act as a leaving group contributes to the usefulness of haloamines in cross-coupling and substitution reactions (Chemler & Bovini, 2013).

Most notably, haloamines are highly useful in the steps to synthesize a piperidine heterocycle fused with a five-membered carbocyclic ring. This fused cyclic structure is an alkaloid system that presents biological activity; the product is formed through the Pauson-Khand reaction which is a [2+2+1] cycloaddition where a triple bond, double

bond, and carbon monoxide react to form a cyclopentenone. The Pauson-Khand reaction is most useful in its construction of greater molecular complexity in a single step (Blanco-Urgoiti et. al., 2004). Recent works have focused on the intramolecular bicyclization of molecules containing both an alkene and alkyne functional group to create this fused ring structure, and eventually natural products (Llobat et. al., 2020). The reaction has been shown to be useful in the synthesis with fluorinated substrates as well.

Figure 16

Pauson-Khand Reaction Where R_1 and R_2 are Fluorine Containing Substituents



2.4 Antimicrobial Properties of Halogenated Molecules

Halogenated species are also useful as antimicrobial agents due to their ability to act as strong oxidizers. An aqueous solution of bromine readily reacts with nitrogen sources to form bromoamines, which possess antimicrobial properties (Ji et. al., 2013). Bromine containing compounds have been found to be useful in the treatment of medical devices and equipment. Due to their antimicrobial properties, molecules such as Bronopol have been designed as antibacterial agents that do not react within the body with undesired side effects (Bryce et. al., 1978).

While vicinal haloamines are the products being formed in the reaction studied, they are not the only haloamines that can be formed. N-haloamines can be formed

through the electrophilic addition of N-X compounds to alkyl groups. These compounds are capable of reacting with carbon-based nucleophiles. N-haloamines can also be used in the synthesis of primary, secondary, and tertiary amines (Erdik & Ay, 1989) These amines can potentially be used later in the pursuit of nitrogen-containing heterocycles with further applications and potential amino acid derivatives.

Despite this, chlorine is still the most abundant water antiseptic agent used. Chlorine containing molecules are commonly used to sterilize water for public and private pools, and municipal and industrial water supplies. Chlorine containing compounds are also used to reduce the growth of microorganisms on medical devices and equipment. These tend to be liquid chlorine and hypochlorite, but recent research has found that organic chloramines are just as effective at inactivating microorganisms. Iodine has been used for its antiseptic properties but is only used in its elemental form; fluorine is not seen as an antimicrobial agent (Odlaug, 2009). The other major drawback to elemental iodine used as an antimicrobial agent is the compound can only be used for external use and does not have the same in vivo characteristics.

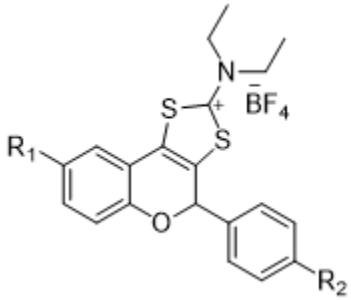
One of the most important characteristics of haloamines is the synthesis of more efficient antibiotics to treat drug-resistant infections. Developing drugs useful against harmful bacteria has become of increasing importance due to the rise in cases of drug resistance bacterial infections. Infections such as MRSA, multidrug-resistant staphylococcus aureus, and MDR-TB, multidrug-resistant tuberculosis, have become problems in developing and developed countries alike. Designing drugs intended to mediate these issues has been met with many challenges. These challenges can be attributed to not only the bacterium's resistance to traditional bactericides, but also the

structure of their cells (Exner et. al., 2017). Most drug resistant bacteria are gram negative, which have outer membranes that allow for selective permeability. This makes penetration of antibacterial agents more difficult and specificity is necessary. Incorporating new pharmacophore groups as well as introducing novel mechanisms of actions have been the two most explored methods to alleviate this epidemic (Exner et. al., 2017 &, Benson et. al., 2020). Multidrug resistance is defined as "the resistance to at least one agent in three or more antimicrobial categories". The reservoir of introduction of drug-resistant microorganisms comes in varying forms, however the impacts it has on healthcare, medicine, and economic resources is huge (Exner et. al., 2017).

The influence halogen-containing compounds have on the antibacterial properties of flavonoids has been documented. Flavonoids are secondary metabolites found in plants with antioxidative properties. These compounds have extended bioactivity outside of this that make them attractive structures to synthesize for pharmaceutical purposes. Various flavonoids have been found to have any of the following properties: anticancer, anti-inflammatory, antiviral, antifungal, and antibacterial. It's known that flavonoids can exhibit antibacterial properties, but the structures that Stefan and Birsa studied were not known to show antimicrobial properties. Tricyclic flavonoids used in their research were known to be selective estrogen receptor-β agonists with no related tricyclic structures known for antibacterial capabilities in the literature. Stefan and Birsa showed the antibacterial potential of these structures when halogens were inserted into the structure (Bahrain et al., 2016).

Figure 17

Flavonoid Studied by Stefan and Birsa for Antibacterial Properties



They found that the introduction of halogen groups or hydrogen to the two R positions indicated in the structure above showed the greatest antibacterial properties of all the modifications made to the ring. It was also observed that the size of the halogen directed the efficacy of the structures. Halogen substitutions of fluorine were least effective against S. aureus and E. coli, while iodine substitutions were the most effective. Regardless of this, bactericidal properties noticeably increased when the atom bound went from a hydrogen to a halogen. A second series of biological tests were done where substitutions were made at both R group positions. These tests showed the same trend, the presence of a smaller group at these positions led to decreased antibacterial activity. These compounds, which showed antibacterial efficacy, were compared to Kanamycin and Ampicillin and showed similar if not better results. Stefan and Kirsa believe antibacterial properties of the halogenated flavonoids is influenced most by the size of the halogen substituted (Bahrain et. al., 2016). Due to the high level of specificity required to enter a gram-negative cell, size would be one of the first factors to be excluded from cell uptake.

2.5 Bioactivity of Haloamines

The synthesis of highly complex organic molecules has led increasingly towards hybrid structures consisting of two or more pharmacophore groups in one molecule. Doing so allows for the formation of a new compound with potentially high biological activity, varied selectivity, and possibly reduced side effects. Pharmaceutical chemistry is constantly in the pursuit of designing new biologically active compounds using structures and substructures found in known drugs and nature alike. Structures containing nitrogen, specifically amines, are the most common heterocyclic atoms found in pharmaceutical products on the market. One of the most attractive qualities of halogens being incorporated into biologically active molecules is their ability to halogen bond and how this changes their in vivo interactions.

2.6 Halogen Bonding in Vivo

An attractive property of halogen containing molecules is how they interact with cell membrane receptors and biomolecules when introduced in the body. Halogens bound to a carbon can interact with other molecules through halogen bonding, an intermolecular force similar to hydrogen bonding that occurs between specific heteroatoms and halogens. The halogen usually undergoes this interaction between nitrogen, oxygen, and sulfur containing functional groups on adjacent molecules. Due to the halogen groups innate ability to participate in a pseudo-bonding event it has become more attractive to add halogens to pharmaceutical compounds in an effort to increase efficacy in vivo (Xu et. al., 2014). The carbon-halogen bond serves as an electron-deficient structure in a molecule that can interact with a nucleophilic region of another molecule. The directional

ability of bonding, it is specific in its three-dimensional orientation, making it an ideal binding interaction to occur between a drug and its binding target in the body (Yang & Wong, 2020).

Yang et. al. theorized how this electrostatic interaction is occurring. It is believed that this occurs in a planar, linear fashion and due to the high electron density of the nucleophilic species involved and electron-deficiency of the halogen causing a sigma hole to form. The magnitude of this sigma hole depends on how polarizable the halogen is, with iodine being the most polarizable and fluorine being the least polarizable, and how electron-withdrawing the atom bound to the halogen is (Yang & Wong, 2020). The polarizability of the element and the electron-withdrawing capability of the other atom creates an electrostatic potential throughout the attractive force, with greater electrostatic potential being created when halogens with higher polarizability are involved with bonding; the larger the electrostatic potential the stronger the bond interaction. However, this is with the caveat that fluorine's polarizability is so low that halogen bonding can only occur between groups that are strongly electronegative (Xu et. al., 2014).

Another theory, still under further investigation, explaining halogen bonding involves electron orbital structure. P orbitals have 3 electron nodes, each with a capacity of 2 electrons with opposite spin. Halogens have 1 lone electron in their valency, which is housed in the z node of their P orbital. This configuration depletes the distribution of electron charge in the planar direction, compared to the free halogen, promoting the formation of the sigma hole characterized in halogen bonds. The sigma hole promotes a positive electrostatic interaction between the electron donor and acceptor. (Franchini et. al., 2020).

The driving force behind this interaction could also be explained by molecular orbital theory. The lowest unoccupied molecular orbital (LUMO) of the halogen-electron donor complex interacts with an electron pair in the highest occupied molecular orbital (HOMO) on the nucleophile. The HOMO-LUMO interaction leads to a lower energy stabilization of the bonding interaction between the two atoms. Therefore the interaction is stronger the larger the halogen, as the valence electrons of larger radii are stabilized through the HOMO-LUMO interaction (Yang & Wong, 2020). Despite the working theories that explain this coveted interaction, halogen bonding is a phenomenon that has been observed, and plays a key role in how halogen-containing-molecules interact within chemical space, being particularly important to the pharmaceutical significance halogenated molecules. The ability to incorporate halogen bonding to interactions with target receptors and enzymes within the body may aid in the increased efficacy and distribution of pharmaceutically relevant compounds.

2.7 Pharmaceutical Relevance

Haloamines are important building blocks in organic synthesis; difunctionalization of alkenes and alkynes can be achieved through catalytic addition of these two functional groups. This allows for a greater order of desired reactivity and more control to the desired product. The chemical properties of target molecules can be controlled to a degree through this approach. By controlling the chemical properties of lead molecules, the pharmaceutical activity of the molecule can be controlled more easily. This practice is used when using the receptor's and enzyme's endogenous ligands target is the structure the lead molecules are based upon. Many drugs have been discovered through this route, especially estrogen and progesterone-based contraceptives.

This type of approach can also be seen in the ingenious design of prodrugs and drugs with secondary biologically activity after metabolism. Even haloamines of non-natural origin have been found to have significant biological activity, and shown to be successful DNA alkylating agents (Chemler & Bovini, 2013)

Molecules that contain halogens also can create halogen bonds with other molecules. Halogen bonding has been found to be like hydrogen bonding, an electrostatic reaction between a halogen bound to a carbon, and a nucleophile on a neighboring molecule. The dipole moment created between the carbon and the halogen creates an extension of the electrostatic region allowing for interactions with the appropriate functional groups. The ability to create molecules with the capability of this, despite not being well understood, allows for increased potential of the versatility of the halogens in medicinal chemistry. This can only increase the drug-target binding affinity; the higher the affinity the more competitive towards the endogenous receptor. Interactions that occur between these molecules are increased, leading to higher stability of the ligand-target complex which prompts for a favorable interaction.

Recent studies have highlighted the importance of halogen bonding in medicinal compounds. Within the body organohalogens are believed to take part in halogen bonding with endogenous proteins being involved in all the biological processes a drug is exposed to in vivo. They are capable of interacting with all proteins, as they most commonly undergo this interaction with oxygen, nitrogen, and sulfur groups (Xu et. al., 2014). It has been characterized that iodine, within the thyroid, exploits the use of its ability to halogen bond with oxygen-species. These interactions play a huge role in the recognition of hormones within the thyroid. This characteristic can be exploited in drug

design. Aldose reductase-inhibitors are already known to use this mechanism by interactions between a bromine on the inhibitor and an oxygen on the aldose ligand, preventing the binding of the reductase protein (Auffinger et al., 2004).

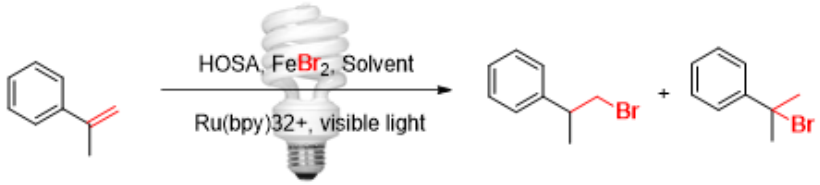
Halogen bonding is no stranger to biomolecular interactions. It's estimated that at least 25% of the drug market is made up of organohalogens, and it is hypothesized that halogen bonding plays a role in at least one of their ADME properties (Xu et. al., 2014). Here is described the methods currently being studied in the GML lab to brominate styrenes and stilbenes in a visible-light promoted radical-mediated mechanism.

2.8 Results and Discussion

Given previous reactions studied in the GML group the haloamination of alkenes alpha to aromatic species was pursued. The reaction was optimized based on the methods in which the reaction was desired to take place. Styrene was used in initial optimization studies with iron (II) bromide. Previous reactions relied on a heat driven reaction, and despite the efforts to aminate the product, amination has not been observed through spectral or analytical data. However, with the desire to utilize visible light the review of viable photocatalysts was performed. Organocatalyst studies showed the use of ruthenium-tris(2,2'-bipyridyl) dichloride was most successful in achieving high conversion of styrene and bromination simultaneously.

Table 4

Aromatic Bromine Synthesis Optimization Studies



Entry	$FeBr_2$ (equiv)	catalyst	solvent	concentration (M)	conversion(%)
1	1.0 eq	5.0 mol%	toluene	0.1	80a
2	1.0 eq	5.0 mol%	toluene	0.5	75
3	1.0 eq	5.0 mol%	toluene	0.75	50
4	1.0 eq	5.0 mol%	ACN	0.5	15
5	1.0 eq	5.0 mol%	ACN	0.75	0
6	1.5 eq	5.0 mol%	toluene	0.1	60
7	2.0 eq	5.0 mol%	toluene	0.1	40
8	1.0 eq	5.0 mol%	toluene	0.1	50
9	1.0 eq	5.0 mol%	toluene	0.1	0
10	1.0 eq	2.5 mol%	toluene	0.1	90
11	1.0 eq	1.25 mol%	toluene	0.1	40

a. Reacted prior to addition of fan on light box. % conversion was determined using crude NMR.

With favorable catalyst conditions a scope was explored for this reaction. Styrenes and stilbenes were reacted with hydroxylamine-o-sulfonic acid and iron (II) bromide under photocatalytic conditions afforded diastereomeric brominated products in good yields. However, crude NMRs showed the formation of several uncharacterized side products. Due to the long reaction period (48 hours) of this reaction the temperature of the light box was explored, and reactions were being heated to 47°C. It was theorized that the temperature was a major contributor to the formation of undesired products.

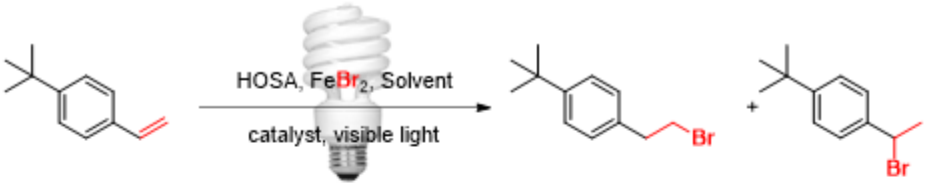
A ventilation fan was installed on the light box which cooled the internal temperature to 27°C removing heat from being a factor in product formation. Reactions

ran after the installation of the fan showed crude NMRs with less side products and higher product formation. It is hypothesized that the ventilation and cooling of the light box allowed for the prominent mechanism to control product formation.

The previously studied reactions utilized toluene as the solvent at 0.1M concentration, and due to the success of the visible light reaction under the same solvent system this condition was used. Now the scope was fully explored. The reaction proved successful in good to excellent yields to transform styrenes and stilbenes into their corresponding brominated product. The reaction led to the formation of regioisomeric products, with ratios of regioisomers being affected by the group bound to the aromatic ring.

Table 5

Aromatic Bromine Catalyst Optimization Studies



Entry	catalyst	concentration (mol%)	solvent	concentration (M)	conversion(%)
1	Eosin B	5.0 mol%	toluene	0.1	0
2	hematoxyline	5.0 mol%	toluene	0.1	50
3	tetrabromofluoroscein	5.0 mol%	toluene	0.1	0
4	TPP	5.0 mol%	toluene	0.1	0
5	$Ru(bpy)_3^{2+}$	5.0 mol%	toluene	0.1	80
6	methyl viologen	5.0 mol%	toluene	0.1	20
7	benzyl viologen	5.0 mol%	toluene	0.1	0
8	1,1-mesityl-10 methyl acridinium	5.0 mol%	toluene	0.1	15

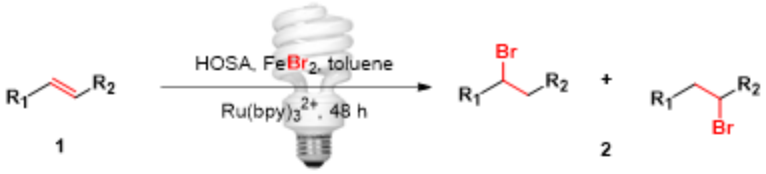
Catalyst screenings were performed prior to addition of fan to the light box.

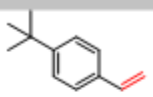
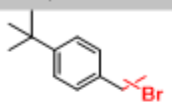
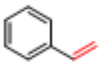
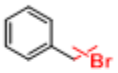
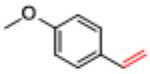
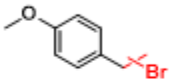
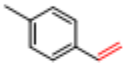
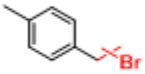
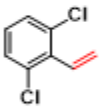
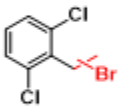
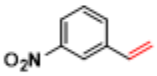
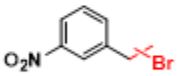
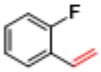
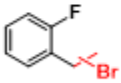
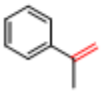
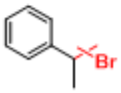
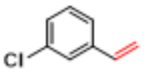
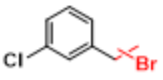
Isolation of the product mixture was unsuccessful at the start. The mixture did not appear by NMR to elute through a silica gel column, both in manual and automatic columns. Considering the unfruitful efforts of standard purification methods, and the theory that the product was binding with silica gel in the column, preparatory TLC was attempted. Much to our excitement this method was successful in isolating the regioisomeric product mixture. Efforts to utilize this technique to separate the mixtures proved unsuccessful.

With an interest in separating the regioisomers for spectral analysis and confirmation, HPLC conditions were tested to determine if the products could be separated with this technique. A 1mg/mL sample of pure mixture in acetonitrile was prepared. Separation conditions were tested on a reverse-phase HPLC. Separation was first tested with 40% H2O to 60% H2O with acetonitrile as the organic phase over 20 minutes. The first injection showed two distinct peaks, albeit overlapping with each other. With analytical data showing two peaks conditions were adjusted to isolate each peak. After several trials the chromatograms showed separation of each isomer with conditions where a 20% to 80% acetonitrile mobile phase over 25 minutes was used. A small peak was observed with a retention time of 10 minutes, the smaller regioisomer equivalent, and the remaining product showed a retention time of 20 minutes under this mobile phase. Due to lack of access to a preparatory HPLC to isolate the components of the mixture the completion of this method has been postponed until access to the proper equipment is met.

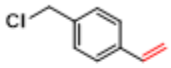
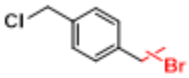
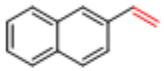
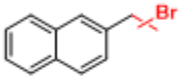
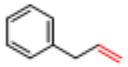
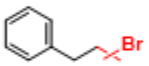
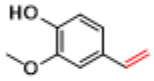
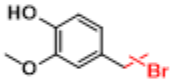
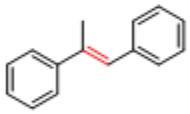
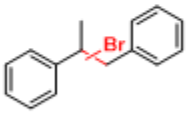
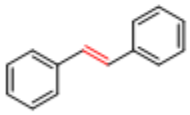
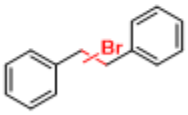
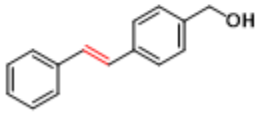
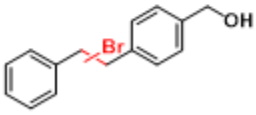
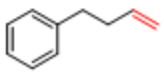
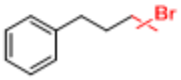
Table 6

Aromatic Bromine Synthesis Scope



Entry		alkene		product	conversion[b](%)	Product ratio[b](alpha:beta)
1	1a		2a		98	1:0
2	1b		2b		93	1:1
3	1c		2c		84	4:1
4	1d		2d		92	2:1
5	1e		2e		91	1:1
6	1f		2f		97	1:1
7	1g		2g		96	4:1
8	1h		2h		95	1:1
9	1i		2i		93	1:1

a. Conditions: alkene (1 equiv.), HOSA (2 equiv.), and $FeBr_2$(1 equiv.) in .1M toluene for 48 h. b. Based on crude NMR. c. Reaction crude was purified by standard preparative TLC.

Entry		alkene		product	conversion(%)	product ratio[b](alpha:beta)
10	1j		2j		79	2:1
11	1k		2k		82	1:0
12	1l		2l		84	3:2
13	1m		2m		75	4:3
14	1n		2n		91	1:0
15	1o		2o		92	1[c]
16	1p		2p		91	2:1
17	1q		2q		95	1:1

a. Conditions: alkene (1 equiv.), HOSA (2 equiv.), and $FeBr_2$(1 equiv.) in .1M toluene for 48 h. b. Based on crude NMR. c. Reaction crude was purified by standard preparative TLC.

2.9 Conclusion

Styrenes and stilbenes were converted to their respective aromatic α-bromides while showing good to excellent product formation. Complete consumption of the starting material was consistently observed; where this was not observed, the product was still formed in good to great yields. This method provides a wide scope showing transformation of a double bond to a saturated substrate. The use of visible light led to the increased integrity of the functional groups and subsequent products that may not be guaranteed with other methods. Further research may include incorporation of acyclic systems to further understand the contribution of the electronic system of aromatic substrates in the reaction.

The lack of a preparatory HPLC for use in separating the regioisomers formed with this method has impeded the full completion of this project. Due to this most product mixtures formed have not yet been isolated through use of preparatory TLC, but the crude reaction medium was isolated through rotary evaporation and frozen in benzene to be completed at a date following access to a preparatory HPLC. As such, products discussed further will not include pure data. Upon acquiring pure yields (mixtures and isolated diastereomers) the electronic and steric effects of the benzylic starting materials may be studied further to better understand their impact on the method outcome. This may lead to a better understanding of the mechanism that leads to the product ratios, and why ratios differing for each substrate has been observed.

2.10 Experimental

Reagents were obtained from Aldrich Chemical, Acros Organics or Alfa Aesar and used without further purification. Reactions were performed in 20- mL glass vials

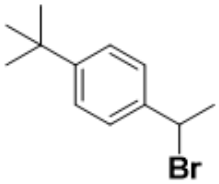
with magnetic stirring. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$). Purification was performed by preparatory TLC on silica gel 60 F254 preparatory TLC plates (1mm silica gel thickness, 10 - 40 μm) in 25% EtOAc in heptanes mobile phase and run 3 times and visualized under UV light (254 nm). Product mixture was isolated through collection of UV active spots on the preparatory TLC plate, sonicated while suspended in DMC, and gravity filtered. The dissolved pure mixture was isolated through rotary evaporation to afford the respective mixture. NMR spectra were recorded on Varian Mercury II 400 MHz Spectrometer at 24 °C in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm relative to solvent signals: $CDCl_3$ (1 H, 7.23 ppm; 13C, 77.0 ppm; coupling constants are expressed in Hz).

2.10.1 General Methods for the Synthesis of Aromatic Bromides

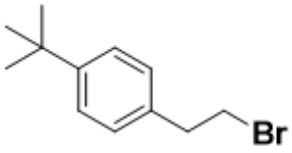
In a 20mL glass vial, 100mg styrene or stilbene, 2 mmol eq. of hydroxylamine-o-sulfonic acid, and 1 mmol eq. of iron (II) bromide were dissolved in 0.1M toluene with 1mL 2.5mol% ruthenium tris(2,2'-bipyridyl) chloride dissolved in acetonitrile. The mixture was stirred on high at room temperature in an enclosed visible light box with a ventilation fan for 48 hours. Iron and ruthenium reaction complexes were removed from the mixture by vacuum filtration through 1:1 silica:celite and washed with excess ethyl acetate. The mixture was concentrated by rotary evaporation to afford the crude product. The crude product mixture was isolated through preparatory TLC in 20% ethyl acetate in heptanes; the preparatory TLC was run three times to ensure separation of the pure regioisomer mixtures. The product mixture are to be separated through preparatory HPLC to afford pure regioisomers.

2.10.2 Synthesis of Aromatic Bromides from Table 6

Due to the COVID-19 pandemic of 2020 data available for the bromination of alkenes alpha to aromatic rings. All NMR data was based on crude NMR; the GML lab does not currently have access to a preparatory HPLC which hinders the completion of this method.

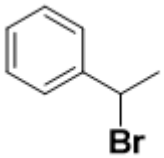


a



b

1-(1-bromoethyl)-4-(tert-butyl)benzene[a]; 1-(2-bromoethyl)-4-(tert-butyl)benzene[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).



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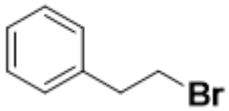
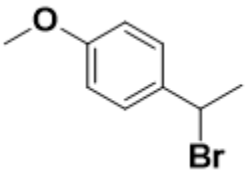
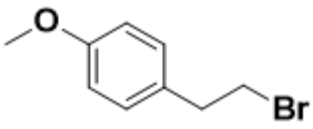


b

(1-bromoethyl)benzene[a]; (2-bromoethyl)benzene[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).



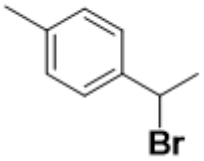
a



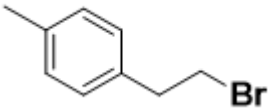
b

1-(1-bromoethyl)-4-methoxybenzene[a]; 1-(2-bromoethyl)-4-methoxybenzene[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J

= 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).

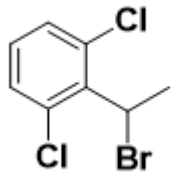


a



b

1-(1-bromoethyl)-4-methylbenzene[a]; 1-(2-bromoethyl)-4-methylbenzene[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).



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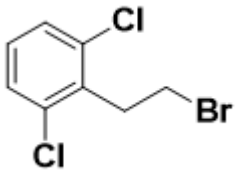
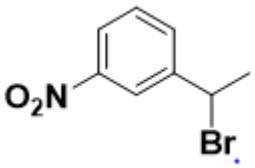
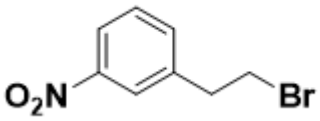


b

2-(1-bromoethyl)-1,3-dichlorobenzene[a]; 2-(2-bromoethyl)-1,3-dichlorobenzene[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).

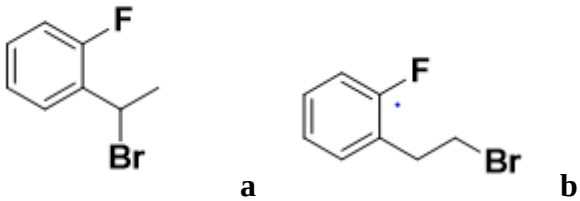


a



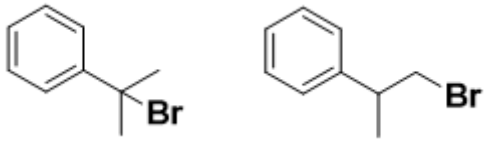
b

1-(1-bromoethyl)-3-nitrobenzene[a]; 1-(2-bromoethyl)-3-nitrobenzene[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).



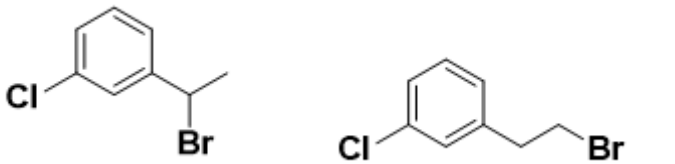
a b

1-(1-bromoethyl)-2-fluorobenzene[a]; 1-(2-bromoethyl)-2-fluorobenzene[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).



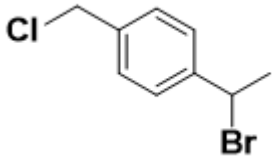
a b

(2-bromopropan-2-yl)benzene[a]; (1-bromopropan-2-yl)benzene[b]: Purification by silicon gel 60 F254 preparatory TLC (1mm silica gel thickness, 10 - 40 microm, 25% EtOAc in heptanes mobile phase, run 3 times) yielded the brominated benzylic product 1b (115 mg, 90%) as a yellow oil. 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).

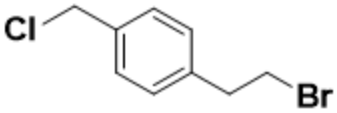


a b

1-(1-bromoethyl)-3-chlorobenzene[a]; 1-(2-bromoethyl)-3-chlorobenzene[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).

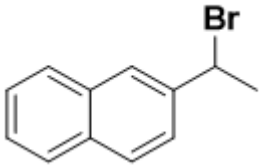


a

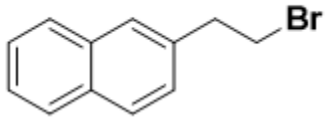


b

1-(1-bromoethyl)-4-(chloromethyl)benzene[a]; 1-(2-bromoethyl)-(chloromethyl)benzene[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).

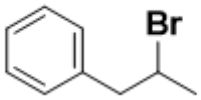


a

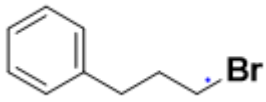


b

2-(1-bromoethyl)naphthalene[a]; 2-(2-bromoethyl)naphthalene[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).

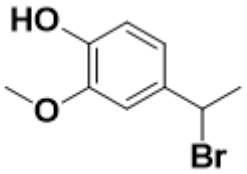


a

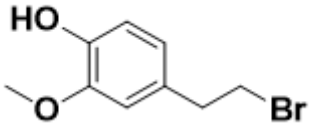


b

(2-bromopropyl)benzene[a]; (3-bromopropyl)benzene[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).

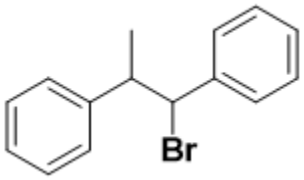


a

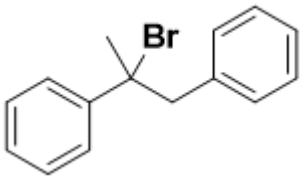


b

4-(1-bromoethyl)-2-methoxyphenol[a]; 4-(2-bromoethyl)-2-methoxyphenol[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).

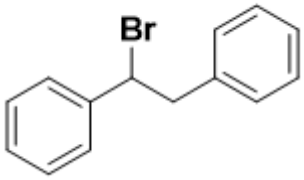


a

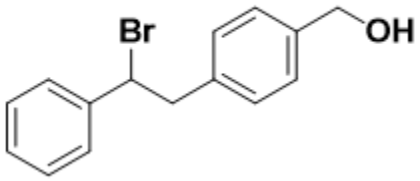


b

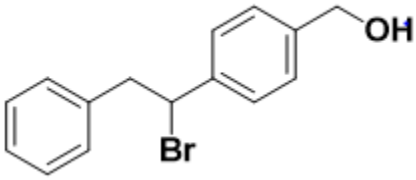
(1-bromopropane-1,2-diyl)dibenzene[a]; (2-brompropane-1,2-diyl)dibenzene[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).



(1-bromoethane-1,2-diyl)dibenzene: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).

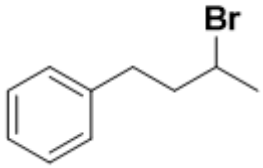


a

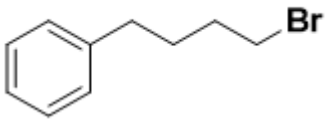


b

(4-(2-bromo-2-phenylethyl)phenyl)methanol[a]; (4(1-bromo-2-phenylethyl)phenyl)methanol[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).



a



b

(3-bromobutyl)benzene[a]; (4-bromobutyl)benzene[b]: 1 H NMR (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, N Bn O O (T7A) EM-141 MeOPh 75 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H).

Chapter 3

Fluorination of Activated Styrenes and Stilbenes

3.1 Fluorine - Discovery and First Uses

In 1835 the first reaction resulting in the formation of a synthetic organofluorine compound was carried out. Dumas et. al. reported the synthesis of methylfluoride compounds prepared from dimethyl sulfate and potassium fluoride. In 1862 Alexander Borodin reported the first nucleophilic halogen exchange reaction using benzoyl chloride and potassium fluoride. The halogen exchange reaction has become one of the most broadly used reactions in fluorine chemistry (Okazae, 2009).

Figure 18

Nucleophilic Halogen Exchange Reaction

Despite these initial synthetic discoveries, mineral fluoride was discovered and used as early as the 1500's. It took another 200 years for the characterization of the new element, fluorine, to occur. It took over 300 years from its original recognition for elemental fluorine to be isolated. The element was successfully isolated by Moissan who used electrolysis on a melt mixture of potassium hydrogen difluoride and hydrogen fluoride. Due to the highly reactive nature and safety hazards of the element

organofluorides were not utilized in industry until the 1920's (Okazae, 2009, & Filler & Saha, 2009).

Prior to industrial uses fluorine compounds were used in the 16th and 17th centuries for glass etching. From here the usefulness of fluorine-containing compounds became known in the 1920's. Aliphatic fluorides were introduced as inert refrigerants in 1928, the late 1920's and early 1930's brought about Freon. Soon after fluoroplastics began to develop and find their way into the general population (Okazoe, 2009).

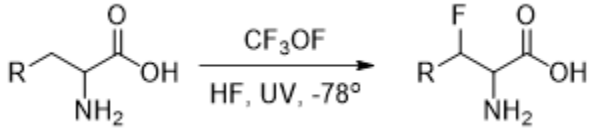
3.2 Current Fluorination Methods

With few exceptions, fluorine is not naturally occurring in a chemical compound. However, fluorine has many chemical and physical properties that make it an attractive atom to add to a compound, coupled with the increased bioactivity this element brings to compounds it is bound to make methods for the fluorination a highly sought after endeavor. Fluorine gas has a recognized radical reactivity due to the weak bond between the two atoms. The high electronegative nature of the element contributes to the weak bond when in diatomic form, allowing for homolytic cleavage (Okazae, 2009, & Chatalova-Sazepin et. al., 2015).

The Kollonitsch group showed that benzene, when reacted with trifluoromethyl hypofluorite, could be fluorinated under UV irradiation in good yields. They showed this was also successful with cyclohexane. The group was able to prove that the reaction was successful with various amino acid derivatives.

Figure 19

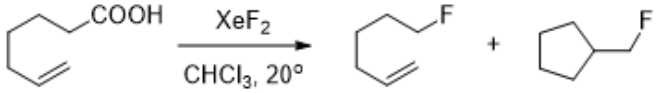
UV Irradiation Fluorination of Amino Acid Derivatives



Fluorination of compounds is not limited to addition reactions. Patrick et. al. reported the use of xenon difluoride as a reagent in a substitution reaction. The group reacted to aliphatic carboxylic acids in chloroform to produce a mixture of open-chain terminal fluorinated molecules and cyclic α-fluorinated molecules (Chatalova-Sazepin et. al., 2015).

Figure 20

Fluorine Substitution and Intermolecular Cyclization Through Xenon Difluoride

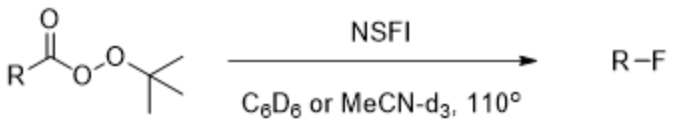


Fluorinated nitrogen sources could also be used as viable sources of atomic fluorine. Commercially available N-fluorobenzenesulfonimide (NSFI) is frequently used due to the stability of the molecule and the ease of handling the fluorine source. The reagent readily radicalizes in reaction. Sammis, Paquin, and Kennepohl theorized this could be used as an atomic source of fluorine to fluorinate tertiary peresters. Using NSFI they were able to perform a radical-mediated fluorination of diacyl and tertiary peresters

under both thermal and photochemical conditions. The reaction was performed on starting materials where R was equivalent to primary, secondary, tertiary, alkyl, and benzyl substrates. Through this method they were able to produce complex steroid derivatives through the formation of a radical alpha to the heteroatom as well (Chatalova-Sazepin et. al., 2015).

Figure 21

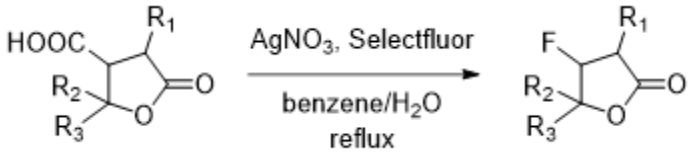
Radical Fluorination of Peresters Using N-fluorobenzenesulfonimide



Selectfluor, an electrophilic positively charged bridged piperazine fluorine source, can also be used in the presence of silver catalyst to perform a decarboxylation and subsequent fluorination at the same site. In fact, it is one of the most utilized sources of radical atomic fluorine in synthetic chemistry. The quenching of the positive charge on the nitrogen when the fluorine leaves drives the formation of the highly electrophilic fluorine. Being the most electronegative element, electrophilic fluorine will react with the most accessible nucleophilic source in situ. This method was used by the Su group in the pursuit of improving the synthesis of fluticasone propionate. The Pohmakotr group also reported using the same silver catalyst in a similar manner to β-fluorinated butyrolactones (Chatalova-Sazepin et. al., 2015).

Figure 22

Silver Catalysis Promoted Decarboxylation and Selective Fluorination



Sammis and Paquin also reported the use of UV light to decarboxylate and fluorinate 2-aryloxy and 2-aryl carboxylic acids. The substrate is pushed into an excited electron state and Selectfluor oxidizes, decarboxylates and finally fluorinates the alkyl radicals successfully in good yields. They also reported the same product formed when the aryloxy compounds were treated with 2,6-di-tert-butyl-4-methylpyridine and NFSI were used as a mild oxidizing agent under 300-350nm wavelengths light (Chatalova-Sazepin et. al., 2015).

Figure 23

Method 1 of the Sammis and Paquin's Photofluorodecarboxylation of Aryloxy Acids

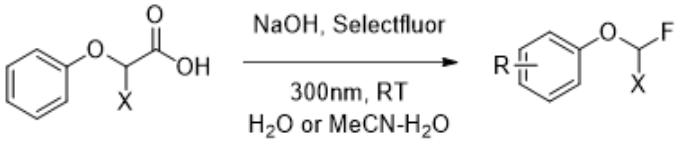
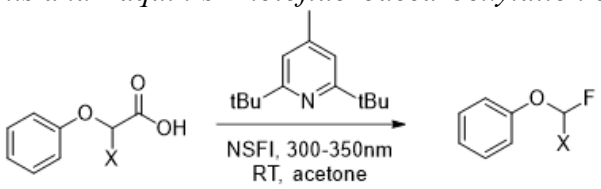


Figure 24

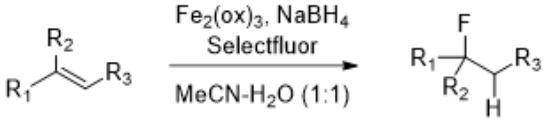
Method 2 of the Sammis and Paquin's Photofluorodecarboxylation of Aryloxy Acids



While adding fluorine to a compound has proven challenging, once completed a carbon-fluorine bond is the strongest bond available. Fluorination is not limited to the functional groups that are most reactive. Fluorination of alkenes and alkynes can also be performed. The Boger group was the first to report a radical fluorination of alkenes with the use of Selectfluor. The group was able to successfully convert inactivated alkenes into fluorinated compounds using Selectfluor as the fluorine source and iron (III) oxalate catalyst and sodium borohydride as a hydride source. They demonstrated this method was successful when R_1 was alkyl, R_2 was hydrogen or alkyl and R_3 was alkyl, amine, amide, or aryl. The method shows exclusive Markovnikov regioselectivity (Chatalova-Sazepin et. al., 2015).

Figure 25

Iron Metal Catalyzed Alkyl Fluorination

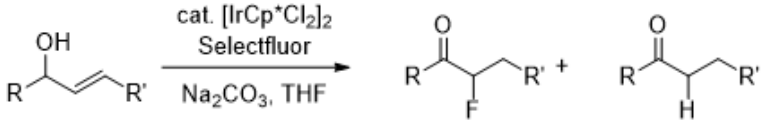


Early works towards the fluorination of alkynes relied on the use of gold catalysts. The Sadighi group reported the use of gold catalyst and vinyl fluorides to perform a hydrofluorination of alkynes. However, fluorination of carbon-carbon multiple bonds does not always result in an open-chain fluorinated product. The Gouveneur group performed a gold catalyzed alkoxyfluorination of alkynes. The reaction caused an intramolecular cyclization of the open-chain molecule to a difluorinated pyranone alpha position to the carbonyl and a bond formed between gold and the other alpha position. It was reported that protonation of the second alpha position could not be controlled and two final products were observed, alkoxyfluorinated pyranone and alkoxyhydrogenated pyranone. Gouveneur noted that without formation of the difluorine intermediate only hydroalkoxylation was observed (Ahlsted & Martín-Manute, 2011).

More recently the Martín-Manute group reported the use of iridium catalytic conversion of allylic alcohols to α-fluoroketones. Compounds that fluorination was observed in had R groups of hydrogen, alkyl, or aryl groups. They propose the final product is reached through an iridium-catalyzed isomerization of the alcohol and subsequent oxidative fluorination of the iridium-allyl complex formed. They reported all fluoroketones were observed as one isomer, but they were only able to produce eight successful examples of this method (Ahlsted & Martín-Matute, 2011).

Figure 26

Iridium-catalyzed Fluorination of Allylic Alcohols



3.3 Bioactivity of Fluorine Containing Molecules

Fluorine is a highly coveted element that is sought after for its set of unique chemical and physical properties. It forms unique bonds and can drastically change the characteristics of a compound. The presence of even one fluorine atom can improve the solubility, bioavailability, and metabolic stability of the compound, making them particularly useful in pharmaceuticals (Liu, 2012). Despite recent years to push drug molecules towards the new less known region of biological medicine and away from small molecule medications, fluorine-containing small molecules still remain useful and desirable.

Being the most electronegative element alters how atoms bound to it behave electronically. This will also affect its chemical and physical behavior. Due to its small size fluorine has been observed to mimic hydrogen in terms of steric requirements in enzyme-receptor sites. The bond fluorine forms with carbon is also met with increased thermal and oxidative stability. This helps increase its stability in the body, allowing it to reduce side effects by more selectively metabolizing at the desired locations in vivo to reduce side effects. The element also significantly increases lipophilicity which enhances its rates of absorption; the drug becomes present in higher ratios inside of the cell. Moving past the cell's lipid-bilayer increases the efficiency of the drug with lower doses. The more fluorine is present in the molecule, such as trifluoromethyl groups, the higher the pharmacological activity.

Despite its high dipole the element creates, it has not been observed to make halogen bonds as bromine, chlorine, and iodine containing compounds have exhibited. The electronegative qualities of the carbon-fluorine bond affect the chemical reactivity

and properties of the molecule. (Purser et. al., 2008). While halogen bonding is rarely plausible for fluorine, the element's size and electronegative nature allow it to mimic hydrogen bonding. Its inability to participate in halogen bonding merely limits the functional groups it can interact with electrostatically. The increased stability of the carbon-fluorine bond leads to increased stability during absorption and metabolism. The more stable the molecule is, the longer it can stay active in the body to deliver therapeutic effects. Conversely, this can also aid in drug delivery of prodrugs. The more stable the prodrug is, the longer it can remain inactive in the body. This allows for more specific activity of therapeutics. Alterations to the time a drug remains active in the body allow for fewer doses required for the patient, lowering the number of doses the patient is required to take (Hagmann, 2008).

3.4 Pharmaceutical Relevance

Fluorine started to enter the stage of pharmaceuticals in the 1940's. The original goal was to fluorinate medicinally relevant molecules. As just discussed, the presence of fluorine enhances the bioavailability and bioactivity of the molecule. The element is also capable of interacting with enzymes in vivo at the receptor site in a manner that mimics that of hydrogen (Filler & Saha, 2009, & Purser et. al., 2008). The use of it in specific categories of medications became more popular; the pursuit to incorporate it into anesthesia, steroids, nonsteroidal anti-inflammatories, and CNS medications began (Filler & Saha, 2009, & Purser et. al., 2008).

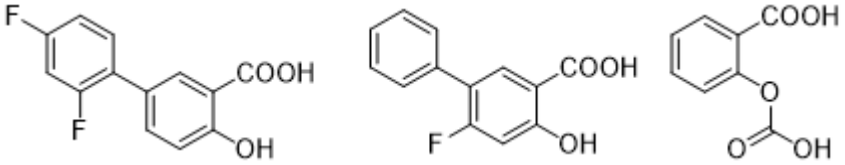
The incorporation of fluorine into steroids has had the greatest impact on a drug many people take. Anti-inflammatory agents containing fluorine were originally pioneered to be more efficacious than cortisone and cortisol, and combat electrolyte

retention as an undesirable side effect. More important is the means of administration of corticosteroids. These are usually used as topical agents requiring a high lipid-water ratio to be absorbed into the cell. Due to its chemical properties to help increase lipophilicity the presence of fluorine favorably enhances that ratio, leading to a highly effective treatment for conditions such as allergic rhinitis and asthma (Filler & Saha, 2009, & Purser et. al., 2008).

Included in anti-inflammatory agents are over-the-counter drugs, nonsteroidal anti-inflammatory agents (NSAIDS). These drugs include medications such as Ibuprofen®, Aspirin®, and Aleve®. The search for methods to synthesize these medications began in the 1960's due to the limitations of current cortical steroids, and to surpass the effectiveness of salicylates, such as Aspirin®. Research into this area of pharmaceutical chemistry has brought to market two fluorine-containing NSAIDS - diflunisal (Dolobid®) and flurbiprofen (Froben®) (Filler & Saha, 2009, & Purser et. al., 2008, & Hagmann, 2008).

Figure 27

Structural Similarities Between Dolobid®(left), Froben®(middle), and Aspirin®(right)



The addition of the bulky benzene group and fluorine contributes to increasing the lipophilicity of these compounds. Benzene may participate in pi-pi stacking interactions with aromatic groups at the receptor. Due to the integrity of the pharmacophore, the benzoic acid group, each drug can have similar effects in the body. While drugs such as Aspirin® and Ibuprofen® are frequently prescribed and used, these drugs are useful in the alleviation of pain due to osteoarthritis. They have also found in clinical trials these compounds, while more expensive to produce than their competitors, have greater in vitro activity, longer analgesic efficacy, and reduced gastrointestinal irritation (Filler & Saha, 2009, & Hagmann, 2008).

The small size of fluorine also leads to production of smaller molecules, characterized by being less than 500g/mol in size. With these smaller biologically relevant molecules, there is a greater chance they can pass the blood-brain barrier and exhibit CNS activity. Treatment of mental illness becomes exponentially improved with drugs capable of this in vivo activity. The use of fluorine in these compounds has been crucial in the synthesis of viable and effective psychotropics. At the start of the exploration of medications for mental illness trifluoromethyl and fluoro-substituted aryl compounds were used as the main sources of fluorine in the production of psychiatric medications. The lipophilicity of the compounds, coupled with their small size, enhanced their absorption allowing for ease of cross the blood-brain barrier. Fluorine-incorporated medication can be prescribed for several psychiatric diseases, with some of the most well-known being benzodiazepines (Flurazepam®) and antidepressant fluoxetine (Prozac®) (Filler & Saha, 2009, & Purser et. al., 2008).

Despite fluorine lacking the ability to participate in halogen bonding, organofluorines still make up about 63% of the available pharmaceutical drugs containing halogens available on the market today. This is due to the interesting chemical and physical properties fluorine adds to a molecule (Xu et. al., 2014, & Hagmann, 2008). The element has found its way into nearly every drug type on the market. It now represents drugs such as anticancer and antiviral drugs, biologics, antibiotics, statins, and more (Filler & Saha, 2009, Purser et. al., 2008, & Hagmann, 2008).

3.5 Results and Discussion

The success of brominating α-alkene compounds prompted the exploration of the same reaction with fluorinating agents. Due to the difficulty many chemists have met when fluorinating substrates it was decided the concentration of the photocatalyst would be increased to the original 5.0mol%. The reaction was attempted using α-methylstyrene and para-methylstyrene to determine if the reaction would proceed. While α-methylstyrene showed no conversion after 48 hours under visible light conditions, para-methylstyrene showed complete conversion of the starting material with good product yield. Substrates with alpha substituents were not included in the scope due to no conversion observed when α-methylstyrene was tested.

As with the reaction brominating styrenes and stilbenes regioisomeric ratios have been observed here as well. The reaction was attempted with the use of molecular sieves to understand if the presence of water in the reaction mixture was affecting the outcome of the reaction. The opposite was found, as the reaction did not show any conversion by crude NMR when molecular sieves were used. Given this new information the exploration of the scope began.

However, it was quickly discovered that while the reaction would proceed with compounds with electron-donating groups, the reaction did not appear to be successful when compounds with electron-withdrawing groups are used. Due to this optimization of the reaction was revisited with a wider array of conditions to be tested. However due to the coronavirus pandemic the GML lab was incapable of completing the optimization studies at this time.

Conditions to be tested include the fluorine source, solvent, solvent concentration, equivalence of additives (fluorine source and HOSA), catalyst used, and catalyst concentrations. Fluorine sources available to be tested are iron (III) fluorine, zinc (IV) fluoride, chromium (III) fluoride, and cesium fluoride. Due to the decreased conversion when acetonitrile is used as the solvent it is not planned to be tested again at this time. However, the solvents chosen at this time were determined based on the polarity of the solvent as well as whether it is aromatic or not. This is to determine the effects polarity and aromaticity have on the overall conversion of this method. The remaining concentrations and equivalences will be to attempt to find the best ratios to yield the highest conversion. Catalysts to test are identical to the catalysts tested in the brominating method.

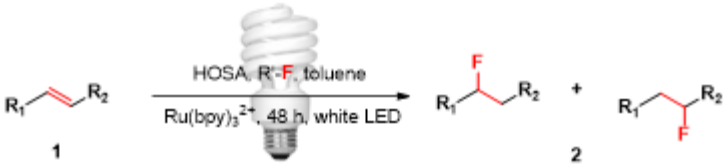
Despite the pitfalls of purification that accompanied bromination of the same substrates, the fluorinated products did not show the same issues. The product mixtures of para-methylstyrene were easily separated through automated standard silica gel chromatography. This may be attributed to the electronegative nature of fluorine; compounds fluorine is bound to tend to be more polar than their other halogen

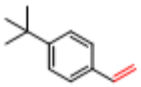
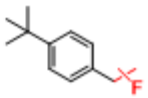
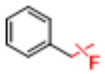
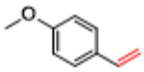
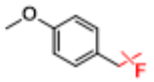
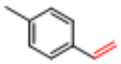
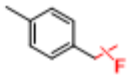
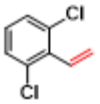
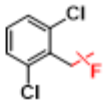
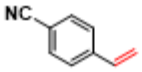
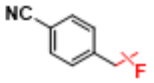
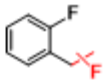
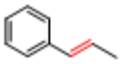
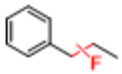
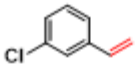
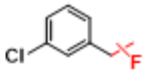
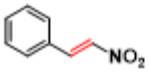
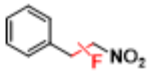
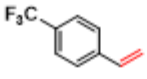
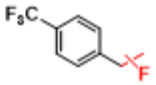
counterparts. The separation by TLC from the starting materials was much more drastic, simplifying the isolation process of the regioisomeric mixture.

Due to the similarities in reaction, reactivity, and product formation between the halogenating reactions it is hypothesized that both reactions follow a similar radical-mediated mechanism. The differences in starting material conversion and regioisomer ratios may be explained by the differences in chemical properties between fluorine and bromine. Not only is their atomic size drastically different, the electronegative properties of fluorine are vastly larger than that of bromine. As such, the electronic activity of the aromatic ring and the electron-withdrawing and electron-donating qualities of the substituents to the ring, may play an important role in the halogenation ratios that occur with each different substrate.

Table 7

Planned Aromatic Fluorine Synthesis Scope



Entry		alkene		product
1	1a		2a	
2	1b		2b	
3	1c		2c	
4	1d		2d	
5	1e		2e	
6	1f		2f	
7	1g		2g	
8	1h		2h	
9	1i		2i	
10	1j		2j	
11	1k		2k	

a. Conditions: alkene (1 equiv.), HOSA (2 equiv.), and R'-F(1equiv.) in .1M toluene for 48 h.

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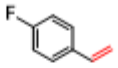
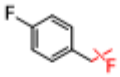
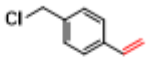
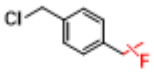
12	1l		2l	
13	1m		2m	
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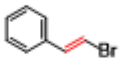
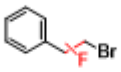
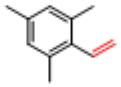
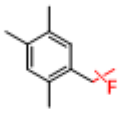
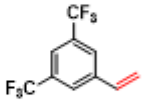
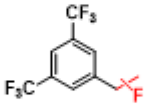
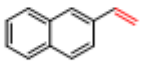
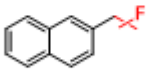
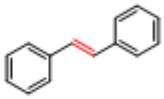
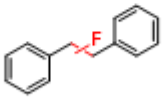
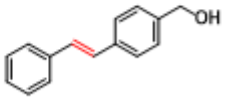
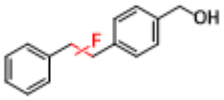
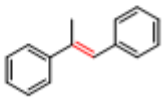
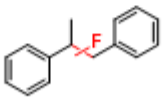
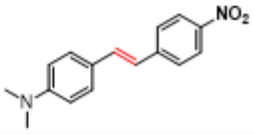
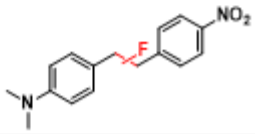
15	1o		2o	
16	1p		2p	
17	1q		2q	
18	1r		2r	
19	1s		2s	
20	1t		2t	
21	1u		2u	
22	1v		2v	

a. Conditions: alkene (1 equiv.), HOSA (2 equiv.), and R'-F(1equiv.) in .1M toluene for 48 h.

3.6 Conclusion

As previously mentioned the completion of optimization reactions and the true validity of this method have not been explored at this time due to the COVID-19 pandemic. However, preliminary reactions to test the legitimacy of the hypothesized method shows promise in the fluorination of styrenes and stilbenes. Given its similarity to the bromination method discussed in the previous chapter, it will be interesting to see if the regioisomer ratios of their respective products differ and by how much. Testing the reaction with α-methylstyrene and para-methylstyrene showed no conversion with α-methylstyrene despite para-methylstyrene showing excellent yields (based on crude NMR). What's more, the effects electron-donating and -withdrawing groups may have on the product formation and ratios has yet to be explored. Completion of the optimization and scope may help understand how important these electronic effects are to successful fluorination.

3.7 Experimental

Reagents were obtained from Aldrich Chemical, Acros Organics or Alfa Aesar and used without further purification. Reactions were performed in 20- mL glass vials with magnetic stirring. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate (KMnO4). Automated chromatography was performed on a ISOLERA Prime instrument with 10 g. SNAP silica gel normal phase cartridges using a flow rate of 12.0 mL/min and a gradient of 0–30% EtOAc in Heptanes over 20 column volumes with UV detection at 254 nm. NMR spectra were recorded on Varian Mercury II 400 MHz Spectrometer at 24 °C in $CDCl_3$ unless otherwise indicated. Chemical shifts are

expressed in ppm relative to solvent signals: $CDCl_3$ (1 H, 7.23 ppm; 13C, 77.0 ppm; coupling constants are expressed in Hz).

3.7.1 General Methods for the Synthesis of Aromatic Fluorides

In a 20mL glass vial, 100mg styrene or stilbene, 2 mmol eq. of hydroxylamine-o-sulfonic acid, and 1 mmol eq. of iron (II) fluoride were dissolved in .1M toluene with 1mL 5.0mol% ruthenium tris(2,2'-bipyridyl) chloride dissolved in acetonitrile. The mixture was stirred on high at room temperature in an enclosed visible light box with a ventilation fan for 48 hours. Iron and ruthenium reaction complexes were removed from the mixture by vacuum filtration through 1:1 silica:celite and washed with excess 1% methanol in ethyl acetate. The mixture was concentrated by rotary evaporation to afford the crude product. Filtration by silica gel with 0-30% EtOAc in Heptanes over 20 column volumes provided the desired fluorinated product mixture in good yield.

3.7.2 Synthesis of Aromatic Fluorides

Due to the COVID-19 pandemic of 2020 exploration of the optimization and full scope of this method was unable to be fulfilled. The methods detailed are variables to be tested upon full return to academic research.

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