Development of Remote Hydroxylation via Redox Catalysis and Mild Activation of Thioglycosides for O-Glycosylation

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DEVELOPMENT OF REMOTE HYDROXYLATION VIA REDOX CATALYSIS AND MILD ACTIVATION OF THIOGLYCOSIDES FOR O-GLYCOSYLATION

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Doctor of Philosophy in

The Department of Chemistry

by

Kristina Deveaux
B.S., Georgia Southern University, 2012 December 2017
“She is clothed with strength and dignity, and she laughs without fear of the future.”
Proverbs 31:25
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ABSTRACT

The focus of this dissertation is the development of a C-H functionalization method using predox catalysis and the synthesis of saccharides using thioglycosides. Chapter 1 is a review of C-H functionalization and visible-light photoredox catalysis. Over the years there have been many significant contributions to the field of C-H functionalization. Select examples have been discussed and a foundation for the method developed in chapter 2 has been outlined. Chapter 2 discusses the development and optimization of a C-H functionalization method. This approach uses the Tz^0 directing group and Ir(ppy)_3 to activate a remote C-H bond via 1,6- and 1,7-radical translocation. It was confirmed that this method required acid and Ir(ppy)_3 to afford decent yields of the hydroxylated products. An array of sulfonamides and sulfonate esters were screened in efforts to expand the substrate scope.

Chapter 3 provides an overview of chemical O-glycosylation. Stereoselective synthesis of oligosaccharides has been a challenge that many researchers have made attempts to address over the years. Select examples of glycosylation methods have been discussed along with the benefits and shortcomings. In chapter 4, a mild, metal-free method for glycosylation with thioglycosides is established and optimized. Thioglycosides are frequently employed in glycosylations due to their chemical stability, however, the harsh/toxic conditions necessary to activate them is a major downfall. To address this concern, 4-aryl-3-butenylthioglycosides were activated using visible-light in the presence of Umemoto’s reagent. A putative EDA complex forms and initiates departure of the leaving group. Changing the light source from blue LEDs to violet LEDs, improved the reaction time (24 hours to 2 hours) without compromising yield.
Observations made during these experiments paved the way for the method developed in Chapter 5.

Chapter 5 outlines an acid-promoted glycosylation of 4-aryl-3-butenylthioglycosides. In an effort to combine the stability of thioglycosides with the reactivity of trichloroacetimidates, activation of 4-aryl-3-butenylthioglycosides was demonstrated with 10 mol% of triflic acid (or TMSOTf). Glycosidic linkages were formed within in good to excellent yields and stereoselectivity can be achieved by neighboring group participation. 4-Aryl-3-butenylthioglycosides exhibit low reactivity at -20°C and this latency will ultimately be exploited in the synthesis of a trisaccharide.
CHAPTER 1: REVIEW OF C-H FUNCTIONALIZATION AND VISIBLE-LIGHT PHOTOREDOX CATALYSIS

1.1 Introduction

Nature has served as an inspiration to scientists for centuries. Numerous synthetic transformations have been inspired by nature and chemists have aimed to develop “biomimetic” transformations in an effort to improve the step- and atom-economy of multistep synthesis. A particularly useful transformation is the selective activation of C-H bonds. When this occurs in nature, it is frequently via an enzymatic pathway. For example, classes of enzymes known to oxidize molecules during biosynthesis are called oxygenases.\textsuperscript{1a}

Hamberger and coworkers recently reported the discovery of two such enzymes of the cytochrome P450 monooxygenase class, CYP71D445 and CYP726A27\textsuperscript{1b} (Scheme 1.1). This finding came as they were researching the biosynthesis of medically relevant macrocyclic diterpenoids in plants of the genus \textit{Euphorbia}. Hamberger concluded that these monooxygenases regioselectively oxidize casbene, a simple bicyclic diterpenoid that is considered as the first intermediate toward the biosynthesis of several complex diterpenoids. CYP71D445 selectively adds a hydroxyl group to C9 of casbene while CYP726A27 hydroxylates C5. A series of subsequent oxidations and a cyclization result in a compound known as jolkinol C, a diterpine that is a potential

![Scheme 1.1 Oxidation of casbene by cytochrome P450 monooxygenases](image-url)
intermediate in the biosynthesis of ingenol mebutate, a natural product known for its anticancer activity\(^1\).

This example serves as one of many ways that nature reveals elegant and useful processes through scientific exploration. Aliphatic C-H bonds are widely regarded as unreactive or inert, however, they are ubiquitous in organic compounds. Functionalizing C-H bonds is beneficial to the synthetic chemist, as it obviates the incorporation of multiple synthetic steps in a sequence in order to form one bond. Once a bond is functionalized, you now have a reactive group that can participate in additional reactions to increase the complexity of a molecule. In addition to this benefit, recent advances in C-H functionalization\(^26\) have provided mild conditions that tolerate other functional groups present. The early years of investigation into activation of inert C-H bonds was plagued with conditions that were either harsh or low yielding. In addition to this, the processes were relatively unselective. When these otherwise inert C-H bonds are treated as synthetically useful functional groups, synthetic methods are more efficient and step-economical. This improvement has far reaching implications and could lead to the affordable synthesis of expensive and synthetically challenging natural products and drugs.

1.2 Guided vs. Innate Functionalization

Methods to functionalize C-H bonds has increased exponentially over the past century\(^22-23,26\). Since this area of investigation was discovered, a general trend has developed, and methods of functionalizing C-H bonds can be grouped into two main categories\(^27\). The first category is innate C-H functionalization. As implied, such activation is based on the innate reactivity of the molecule. Whether it is promoted by
Steric or electronic factors, functionalization depends on the natural reactivity of a C-H bond. The second category is guided C-H functionalization. This method of activation involves directing groups that are either covalently bonded or coordinated to the compounds C-H-bearing. These groups can be activated chemically, photochemically or thermally\(^\text{30}\) and guide activation to a specific C-H bond allowing for highly selective functionalization, a characteristic that is invaluable to synthetic chemists.

### 1.3 Guided and Innate Functionalization Examples

While coupling reactions such as the Suzuki and Heck reaction are popular methods for functionalizing aromatic rings, they require the use of aryl halides to determine the regioselectivity. By contrast, C-H arylation based on intrinsic reactivity obviates aryl halides. An example of direct arylation of heterocycles has been reported\(^\text{2}\) and, in this example, the regioselectivity depends on the innate reactivity of the nitrogen containing aromatic rings. Under catalysis by silver nitrate (AgNO\(_3\)) with persulfate as a co-oxidant, aryl boronic acids were coupled to heterocycles with the regioselectivity being dependent on the heterocycle used (Scheme 1.2). For example, pyridine favored functionalization at C2 twofold over functionalization at C4. Regioselectivity varied when pyrimidines, pyridazines or pyrazines were employed and also when additional functional groups such as ketones, halides, and nitriles were added to the pyridine.

![Scheme 1.2 Example of innate functionalization using pyridine derivatives](image-url)
rings. In each case, functionalization occurred at the most electron deficient site on the molecule. It is important to note that aryl halides are unreactive under the reaction conditions. More electron rich rings such as indole, imidazole and 1,3,5-triazine were low yielding or did not produce the desired product. On the other hand, this method employed a variety of aryl boronic acids. Electron rich boronic acids decreased reaction times while electron poor boronic acids required twice the amount of catalyst and persulfate.

Mechanistically speaking, the silver salt reduces the persulfate ion to two species, the sulfate dianion and a sulfate radical anion (Scheme 1.3). This radical anion then reacts with the aryl boronic acid and induces homolytic cleavage of the carbon-boron bond to furnish the corresponding aryl radical. The aryl radical then adds to the TFA salt of the heterocycle to produce an intermediary nitrogen centered radical cation. Subsequent oxidation by the silver II salt then regenerates the catalyst and furnishes the product$^2$. 

![Scheme 1.3 Direct arylation of quinine with aryl boronic acid](image-url)
Alternatively, a reported example of a guided approach to functionalizing pyridines\(^3\) resulted in products that favored the C3 and C4 position of the heterocycle (Scheme 1.4). The substrates used nicotinic and isonicotinic amide derivatives, compounds that are commonly used in the pharmaceutical industry for their biological activity. In this method, an amide group at the *para* or *meta* position relative to the nitrogen directs aryl groups to the C3 position when the amide is *para* and the C4 position when the amide is *meta*. During method development of this method, it was discovered that 3,5-dimethylphenyl was the optimal amide *N*-substituent for directing as it showed high selectivity for monoarylation with excellent yields. The more electron withdrawing amides (perfluorophenyl, 2,6-difluoro or 4-trifluoromethylphenyl) showed low selectivity and low yields. This observation shows that these groups make the pyridine rings more electron poor and less reactive. The method tolerates functional groups such as ethers, halides, and esters and yields for the monoarylated products ranged from 27% to 94%. The amide can then be converted to the acid via hydrolysis with 4M HCl.

While innate characteristics such as electronic properties can enable site predictability with regard to functionalization, steric can play a part as well. Non-heme catalysts have proven to be excellent oxidation catalysts that function under relatively
mild conditions. Such an iron catalyst designed by Costas et al., effectively functionalized various cyclohexane derivatives in a regioselective manner in the presence of hydrogen peroxide as an oxidant (Scheme 1.5). A menthol derivative, acetoxy menthane, has two sites groups, both of which are susceptible to hydroxylation under the reaction conditions. However, the system exhibits a 17:1 preference for the C1 position over C8 in 62% yield. The reasoning for this can be attributed to the bulky isopropyl group undergoing steric interactions with the methyl groups of pinene-bearing ligands found on the iron catalyst (Figure 1.1). This steric hindrance makes the hydrogen at C1 more accessible to hydrogen abstraction.

An oxygen bound to the metal center is thought the be the source of the hydroxyl group. If this is the case, then it is reasonable to predict that the functionalization will
occur at the least sterically hindered site. Also, the hydrogen at C1 that is a part of the cyclohexyl ring is in a fixed orientation as opposed to the freely rotating isopropyl group and this may contribute to the selectivity of the transformation.

Menthol has also been used to showcase a site-specific functionalization via a N-trifluoroethyl carbamate directing group. In this example, selectivity is the opposite to that of the iron-catalyzed oxidation. Several 1,3-diols were successfully synthesized by this procedure that was inspired by the Hoffmann-Löffler-Freytag reaction (Scheme 1.6). Treatment of the carbamate with acetyl hypobromite (AcOBr) oxidizes it to the N-bromocarbamate, which is then irradiated and subsequently forms a nitrogen-centered radical as a result of homolytic bond cleavage. A 1-6 hydrogen transfer occurs followed by halogen transfer resulting in an alkyl bromide at that site. Cyclization occurs to form a carbonate in the presence of silver carbonate (AgCO₃) that is then hydrolyzed to afford the diol. In this case, only one isomer is produced and functionalization occurs only on the tertiary carbon of the isopropyl group. This method was employed in the total
synthesis of eudesmane terpenes starting from commercially available reagents (butyraldehyde and methyl vinyl ketone). Remote desaturation is a useful C-H functionalization transformation as well, and several intriguing methods have been reported. Cholesterol has a myriad of C-H bonds that are relatively inert, making it an excellent model system for C-H functionalization. Breslow and co-workers found that irradiation of cholesterols in halogenated solvents such as carbon tetrachloride (CCl₄) and bromotrichloromethane (BrCCl₃) resulted in desaturation of the C ring with high selectivity for C9 with cholestanyl acetate (Scheme 1.7). In bromotrichloromethane, the reaction proceeds via radical formation at C9 and subsequent bromination. Over the course of the workup, dehydrohalogenation occurs to afford the alkene product. This transformation was, however, plagued with difficult workup and purification as a result of tar-like by products.

To combat this issue, irradiation in phenyliodine dichloride (C₆H₅ICl₂), a source of chlorine, produced a much cleaner reaction upon workup with silver perchlorate (AgClO₄) in aqueous acetone. Selectivity, however, suffered as mixtures of products were produced; 1:1 desaturation at C9 in ring C and C14 in ring D occurred. Several years later in 1976, Breslow tethered phenyliodine dichloride to a molecule of
cholesterol via an ester bond to the A ring\textsuperscript{12}. This appendage acted as a directing group and allowed for selective desaturation of cholesterol.

A more regioselective approach to desaturation of cholestanols from Breslow involved a covalently bonded benzophenone ester that directs olefin formation\textsuperscript{13} (Scheme 1.8). In this example, the rigid and bulky benzophenone group folded onto the bottom face of the molecule as the methyl groups on the top face induced negative steric interactions. The carbonyl is aptly aligned with the axial hydrogen at C14, and excitation of the benzophenone ester by irradiation in benzene results in an oxygen radical that abstracts the hydrogen at that carbon. The benzhydryl radical then removes the hydrogen at C15 to form the olefin product. This desaturation of the D ring is the only alkene product observed in 55% yield.

Alternatively, reversal of selectivity is achieved by using a silyl ether directing group (Scheme 1.9). In this example of guided desaturation, desaturation occurs at C9 of the C ring\textsuperscript{14}. This appendage impressively regenerates the active intermediate and,
as shown, enables selective olefin formation at C9 of three molecules of cholesterol that are all bonded to the silicon. Irradiation of the silyl ether with 1.2 equivalents of sulfuryl chloride per molecules of cholesterol (3.6 equivalents total) and 5-10 mol % of azobisisobutyronitrile (AIBN) results in the tri (9-chloro) intermediate. Subsequent base-promoted dehydrohalogenation results in desaturation of the C ring, the only identifiable indication of desaturation, in over 66% yield. The silyl-oxygen bond is easily formed compared to esters and therefore can be used in cases where esterification is an arduous task.

Recently, Baran and coworker reported a method for remote desaturation, which incorporated a directing group specifically designed to guide a 1-7 intramolecular hydrogen abstraction (Scheme 1.10). The o-tosyl triazene sulfonyl chloride (Tz°Cl)
covalently bonds to functional groups already present on substrate molecules such as alcohols or amines, and the corresponding compound reacts under the conditions to yield desaturation products[16]. A masked aryl diazonium ion is generated from a triazene after treatment with 2 equivalents of triflic acid at room temperature (or 3 equivalents of trifluoroacetic acid at 60°C) and subsequently accepts an electron from TEMPO (1 equivalent) to produce a high-energy aryl radical and TEMPO⁺. This radical then undergoes a 1,7 hydrogen atom transfer to furnish an alkyl radical. The radical translocation process has now remotely activated an otherwise inert C-H bond. The alkyl radical is then oxidized by TEMPO⁺ to form a carbocation and, finally, elimination produces the olefin product. Pertinent to the design of this directing group is the fact that, over the course of the reaction, the Tz⁰ group is converted to a synthetically useful tosylate, which can enable further functionalization.

This method afforded a wide range of desaturated compounds in moderate to good yields and facilitated predictable hydrogen abstraction with good functional group tolerance and a mild oxidation reagent under metal-free conditions. However, substituting TEMPO for a metal salt capable of oxidizing and reducing the respective intermediates would allow for development of a catalytic method for functionalization. Baran and coworkers initially attempted to this with copper(II) bromide (5 mol%) that underperformed and only produced up to 40% yield of the desaturation product. In addition to this low yield, they also saw evidence of trivial reduction (resulting from hydrogen abstraction from the solvent) and incorporation of bromide from the catalyst at the alkyl radical carbon. The trivial reduction product was suppressed by switching the
solvent to nitromethane, a solvent less susceptible to hydrogen abstraction, and the brominated product was no longer produced when they used TEMPO as an alternative.

Although developing a catalytic method with copper salts proved to be unsuccessful, we envisioned activation of the Tz\textsuperscript{0} group via photoredox catalysis (Scheme 1.11). Such a method would allow use of catalytic amounts of transition metal salts to reduce the diazonium salt and oxidize the alkyl radical to the carbocation. In addition to this, catalyst activation could be performed mildly by simply irradiating with visible light, and the low catalyst loading would be an improvement over the use of stoichiometric reagents demonstrated in many of the above examples. We also sought to capitalize on the radical-polar crossover and, instead, add nucleophiles to the reaction to generate new C-X bonds instead of elimination. A wide variety of nucleophiles could be employed such as water, alcohols, amines, and even nucleophilic arenes such as furan or pyrrole. We sought to approach this project by employing visible-light photoredox catalysis (VLPRC), a method that would obviate stoichiometric oxidants/reductants and allow for milder activation.

1.4 Visible-Light Photoredox Catalysis
Several of the transformations mentioned previously in this chapter depend upon the formation of a carbon-centered radical. In the past decade, there has been a significant increase in the use of transition metal polypyridyl complexes to catalyze various synthetic organic transformations using visible-light promotion\textsuperscript{17,24,25}. Exposure of these polypyridyl complexes to visible light results in an excited state species that engage in single electron transfer (SET) and they have been demonstrated to be effective species for activating C-H bonds. Common photocatalysts (Figure 1.2) include metal-based complexes of iridium and ruthenium, however, eosin Y and 9,10-dicyanoanthracene, both organic dyes, are also capable of behaving as SET catalysts following visible light irradiation.\textsuperscript{17} To give further detail on the photocatalytic processes involving SET, the properties of fac-Ir(ppy)\textsubscript{3} will be used to discuss photoredox catalytic cycles (scheme 1.12/1.13).

1.4.1 Visible-Light Photoredox Catalysis Cycle

Upon irradiation with a visible light source such as blue LEDs or a simple household light bulb, fac-Ir(ppy)\textsubscript{3} absorbs visible light and subsequently undergoes a
metal to ligand charge transfer (MLCT) resulting in an excited state species. In the presence of an electron acceptor (EA) such as an aryldiazonium salt, the catalyst enters the oxidative quenching cycle (Scheme 1.12) and reduces the salt by donating an electron. The oxidized photocatalyst is then capable of accepting an electron from a donor in solution to regenerate fac-Ir(ppy)$_3$.

In the event that an electron donor is present upon irradiation of fac-Ir(ppy)$_3$, the photocatalyst goes through the reductive quenching cycle (Scheme 1.13). Analogous to the oxidative quenching cycle, the excited state species forms upon irradiation, however, fac-Ir(ppy)$_3$ accepts an electron from an appropriate donor such as BNAH (1-benzyl-1,4-dihydrionicotinamide) and is reduced. The catalyst can then donate an electron to an acceptor in situ and consequently return to the resting state. This characteristic allows for milder transformations utilizing catalytic amounts of reagents to
initiate the reaction. In addition to this, reactions can be performed at room temperature, in some cases, with an inexpensive visible light source such as a fluorescent light bulb.

When developing a reaction, it is important to know the reduction potential of the photocatalysts. With respect to iridium, in the oxidative quenching cycle the excited species *Ir(ppy)_3 is a very effective reductant based on it’s reduction potential, $E_{1/2}^{\text{III/II}} = -1.73 \text{ V vs SCE}$ (saturated calomel electrode), when compared to ground state Ir(ppy)_3 ($E_{1/2}^{\text{IV/III}} = +0.78 \text{ V vs SCE}$). The reduction potential of the ground state, however, shows that it is a good oxidant of alkyl radicals. The catalyst can therefore play the roles of both an oxidizing and reducing agent. A similar trend is seen in the reductive quenching cycle as the excited state species is a better oxidant ($E_{1/2}^{\text{III/II}} = +0.31 \text{ V vs SCE}$) than the ground state ($E_{1/2}^{\text{III/II}} = -2.20 \text{ V vs SCE}$), however, fac-Ir(ppy)_3 is a strong reductant and can easily donate an electron to return to the resting state.

1.5 Literature Examples Supporting Proposed Transformation
We envisioned employing fac-Ir(ppy)$_3$ and visible light to promote the desired transformation. Baran’s Tz$^0$ group was identified as a viable directing group. As demonstrated by Baran and coworkers and many other researchers, arene diazonium groups are capable of accepting an electron and subsequently releasing N$_2$ to furnish an aryl radical$^{16}$. Baran further demonstrated that radical translocation followed by a radical-polar crossover could be achieved using appropriate reagents; all of these are mechanistically required for this proposed transformation.

Common aryl radical precursors include aryl halides, diaryliodonium salts, aryl sulfonyl chlorides, and triaryl sulfonium salts$^{25}$. Arene diazonium salts also fall into this category and are the easiest to reduce while being relatively simple to synthesize. A report demonstrating electrochemical reduction of arene diazonium salts by mercury electrodes was published in 1958 by Elofson and coworkers$^{33}$. This functional group has been used frequently for various synthetic transformations and reduced by several different means such as electron transfer from metal cations$^{28}$. Additionally, photocatalysts have been shown to reduce aryl diazonium salts in the presence of visible light$^{25}$.

A photo-Meerwein reaction that involved photochemical reduction of substituted arene diazonium salts ($E_{\text{red}} = -0.1$ to $+0.5$ V vs. SCE)$^{28}$ using only 0.5 mol% of a Ru(bpy)$_3^{2+}$ ($E_{1/2}^{III/II} = -0.81$ V vs SCE)$^{17}$ catalyst was reported by König and coworkers$^{31}$ (Scheme 1.14). Following the oxidative quenching cycle, the formed aryl radical adds to an olefin and produces a secondary benzylic radical. The alkyl radical is now primed to donate an electron (ED in Scheme 1.12) to the oxidized catalyst furnishing a carbocation, which is then trapped by a nitrile and then H$_2$O in situ to
ultimately form the amide product. The radical-polar crossover exhibited in this case is an advantageous process that would make functionalization using different nucleophiles a controlled and feasible transformation.

There have been many examples of radical-polar crossover processes in the literature\textsuperscript{18-21}. Notably, Murphy and coworkers showcased the use of tetrathiafulvalene as an efficient electron donor that reduced an arene diazonium salt in situ\textsuperscript{18} (Scheme 1.15). The aryl radical then cyclizes intramolecularly onto an alkene and subsequently forms a secondary alkyl radical. The radical-cation of TTF then combines with the alkyl radical and the intermediate sulfonium salt undergoes an S\textsubscript{N}2 reaction to furnish a carbocation that is then attacked by a nucleophile to produce the functionalized product.

Another example published by Weinreb tethers isatoic anhydride (Figure 1.3) to pyrrolidine and the aniline is converted to a diazonium group upon treatment with nitrous acid (Scheme 1.16)\textsuperscript{21}. Once formed, the diazonium cation accepts an electron
from copper(I) and generates an aryl radical that then undergoes a 1,5-hydrogen atom transfer. Copper (II) subsequently oxidizes the intermediary secondary radical forming an N-acyl iminium ion, which is then hydrolyzed by an alcohol in situ.

Each reaction discussed in this section involved hydrogen atom transfer. The concept of this process, however, is not a recent development. Though the mechanism was not understood until the 1950s\textsuperscript{34}, the Hoffmann-Löffler-Freytag reaction was discovered by the trio between the 1800s and 1900s\textsuperscript{32}. In their example and the reports subsequently published by researchers confirming the mechanism, a 1,5 or 1,6 hydrogen abstraction is involved in the hydrogen atom transfer step and results in an alkyl radical\textsuperscript{35}. This same reaction was the inspiration for Baran’s diol synthesis\textsuperscript{9} that was previously mentioned in this chapter.
1.6 Conclusion

In summary, there have been many advances in the realm of C-H functionalization in the past several decades. Mild methods for activating these ubiquitous bonds would enable researchers to perform late stage functionalizations of complex molecules without affecting existing functional groups. Developing a catalytic method would also make overall synthesis cheaper and easier to scale up. In this chapter, selected methods were discussed to demonstrate guided and innate functionalization of aromatic rings as well as aliphatic carbons, showcased using menthol and cholesterol derivatives. In addition, a brief discussion of visible-light photoredox catalysis, arene diazonium salts as electron acceptors, and radical-polar crossover laid the foundation for the following chapter and the initial direction of this project.

1.7 References


CHAPTER 2: REMOTE C-H FUNCTIONALIZATION VIA REDOX CATALYSIS

2.1 Introduction

We envisioned using a guided method of C-H functionalization catalyzed by a visible-light photoredox catalyst. The ability of the catalyst to play a dual role in the transformation by reducing and oxidizing intermediates would eliminate the need for external oxidants or reducing agents. By reacting Baran’s o-triazenesulfonyl chloride (2.1, Figure 2.1) with an alcohol or amine, generation of several sulfonate esters and sulfonamides would be possible, enabling development of a site selective method as this directing group demonstrated a preference for 1-7 hydrogen abstraction.

The initial mechanistic proposal (Scheme 2.1) involved release of aryl diazonium ion 2.2 by treatment of the TzO substrate with two equivalents of a strong acid such as tetrafluoroboric acid. Irradiation of the photocatalyst fac-Ir(ppy)3 with visible light (λ=455 nm, 4W blue LEDs) will enable the excited-state transitional metal complex (E1/2IV/III = -1.73 V vs. SCE)2 to reduce the formed diazonium ion (Ered = 0.1 to +0.5 V vs. SCE)3 which spontaneously releases nitrogen via homolytic cleavage to furnish aryl radical 2.3. This high energy, electron-poor radical then translocates as the substrate

Figure 2.1 o-triazenesulfonyl chloride (TzOCl)

*Portions of this chapter previously appeared in [Kyle A. Hollister, Elizabeth S. Conner, Mark, L. Spell, Kristina Deveaux, Léa Maneval, Micheal W. Beal, Justin R. Ragains, Remote Hydroxylation through Radical Translocation and Polar Crossover, 5/26/2015]. They are reprinted by permission of [John Wiley and Sons.]
undergoes a 1,7-hydrogen atom abstraction. The more energetically favorable, stable alkyl radical 2.4 \( (E_{ox} = 0 \text{ to } +0.75 \text{ V vs. SCE}) \) can then be oxidized to carbocation 2.5 by \( \text{Ir(ppy)}_3^+ \) \( (E_{1/2}^{IV/III} = +0.77 \text{ V vs. SCE}) \). Subsequent nucleophilic attack would furnish the desired functionalized product 2.6. It is important to note that, in the course of this transformation, the \( \text{Tz}^\circ \) group is converted to a tosylate, which is a common leaving group in organic synthesis. This provides the opportunity for further functionalization of the substrate.

**2.2 Synthesis of Sulfonamides and Sulfonate Esters**

To explore our proposed method for remote functionalization, a series of substrates was synthesized using \( \text{Tz}^\circ \text{Cl} \) (Figure 2.1, Scheme 2.2) and commercially available

\[
\begin{align*}
\text{Tz}^\circ \text{Cl} + \text{HO} & \xrightarrow{\text{DMAP, DCM}} \text{Tz}^\circ \text{O} \\
2.1 & \quad 2.7 & \quad 2.8 \quad (92%)
\end{align*}
\]

Scheme 2.2 Synthesis of sulfonate ester for optimization
alcohols and amines. Two general methods were employed. For generation of sulfonate esters, the corresponding alcohol reacted with TzOCl (2.1) in the presence of 4-dimethylaminopyridine in DCM (Scheme 2.2) in this manner, isoamyl alcohol was coupled to the sulfonyl chloride. The corresponding sulfonate ester 2.8 was isolated in 92% yield and used for optimization of this remote functionalization method.

Sulfonamides were synthesized (Figure 2.2) similarly by treatment of several commercially available amines with TzOCl (2.1) and sodium bicarbonate (instead of DMAP) in dichloromethane in good yields. The results are summarized in Figure 2.2 and range between 64 and 84% yield. Three of the sulfonamides were further subjected to methylation (Figure 2.3). After reacting each substrate with sodium hydride followed
by iodomethane, the corresponding methylated sulfonamides 2.14 to 2.16 were generated in good to excellent yields (91-93%).

\[
\begin{align*}
\text{Tz}^o\text{-NR}_1 \xrightarrow{\text{NaH}, \text{MeI}, \text{THF}} & \quad \text{Tz}^o\text{-NR}_1 \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{align*}
\text{Tz}^o\text{-N} \quad \text{CH}_3
\end{align*}
\] | 93% |
| 2     | \[
\begin{align*}
\text{Tz}^o\text{-N} \quad \text{Ph}
\end{align*}
\] | 93% |
| 3     | \[
\begin{align*}
\text{Tz}^o\text{-N} \quad \text{Ph}
\end{align*}
\] | 91% |

Figure 2.3 Methylation of sulfonamides

Four additional sulfonate esters were synthesized for a study on the substrate scope. With the goal of showing examples of hydroxilation adjacent to a heteroatom, pyrrolidine and tetrahydrofuran derivatives were synthesized. However, since the corresponding alcohol in each case was not commercially available, multi-step synthesis was employed. Sulfonyl ester 2.22 was generated in five steps beginning with silyl protection of pentene-1-ol using TBDMSCl\textsuperscript{7} (Scheme 2.3).

The alcohol was initially protected as Mol and Dinger reported that primary alcohols assist in the degradation of 1\textsuperscript{st} and 2\textsuperscript{nd} generation Grubbs catalysts (Scheme 2.3)\textsuperscript{8}. TBDMS protected compound 2.18 was then converted to alpha-beta unsaturated ester 2.19 via cross metathesis with methyl acrylate in the presence of Grubbs 2\textsuperscript{nd} generation catalyst while refluxing in dichloromethane\textsuperscript{9}. Formation of intermediate 2.20 was initially
a separate deprotection and cyclization procedure however, a paper by Rouche and co-workers demonstrated an intramolecular Michael addition using TBAF. Their proposed mechanism suggests that TBAF (Bu\textsubscript{4}N\textsuperscript{+} F\textsuperscript{-}) acts as a mild base to deprotonate the alcohol substrate, which then attacks the alkene to furnish the cyclized product. Since TBAF is a common reagent used to liberate alcohols from the corresponding silyl ether, I proposed a one-pot deprotection/Michael addition reaction. By adding an extra equivalent of TBAF, the alcohol was deprotected in situ and the excess TBAF initiated the cyclization. The resulting methyl ester 2.20 was isolated in 77% yield then reduced to the primary alcohol using lithium aluminum hydride. To complete the synthesis, 2.21 was converted to the Tz\textsuperscript{o} ester in 84% yield.

Synthesis of the pyrrolidine derivative (2.26) followed a similar synthetic pathway (Scheme 2.4). In this case, the amine was protected as the corresponding carbamate. As previously mentioned, amines reductively quench photocatalysts and, for this reason, the final substrate needed to have a protecting group to prevent this undesired process. This sequence of steps, however, came with much trial and error. The initial attempt involved converting the 4-penten-1-amine (2.23) to the corresponding methyl N-(5-pentenyl)carbamate 2.24 using methyl chloroformate. This product was isolated in
52% yield and was then subjected to cross metathesis with methyl acrylate. The alpha-beta unsaturated ester 2.25 was then cyclized to give heterocycle 2.26 in 77% yield. Initial attempts to reduce the ester to the primary alcohol with LAH were futile as reduction of the methyl carbamate protecting group also occurred. This was evident as the crude $^1$H NMR spectrum showed loss of both methyl ester and methyl carbamate.

![Chemical reaction diagram]

Scheme 2.4 Attempted synthesis of carbamate-protected pyrrolidine derivative

The alternate protecting group proposed was tosylate as it was expected to be less susceptible to reduction but also stable to the acidic conditions of the hydroxylation method. Proceeding with synthesis of the sulfonate ester, 4-penten-1-amine was protected as sulfonamide 2.27 using p-toluenesulfonyl chloride (TsCl) and pyridine (Scheme 2.5). The resulting compound was then converted to the alpha-beta unsaturated ester via cross metathesis with methyl acrylate in the presence of Grubbs' second-generation catalyst. Intermediate 2.28 was then treated with potassium tert-butoxide in an attempt to furnish the tetrahydropyrrole 2.29, a procedure specifically optimized for aza-Michael additions using tosyl-protected amines. This reaction, however, was unsuccessful as trace amounts of the anticipated product were
recovered. Alternatively, in the presence of TBAF, compound 2.28 was converted to the tosylated pyrrolidine in 85% yield\textsuperscript{10}. The methyl ester was successfully reduced to primary alcohol\textsuperscript{12} 2.30 and subsequent coupling with Tz\textsuperscript{o}Cl furnished the sulfonate ester 2.31 in 52% yield.

The third heterocyclic analog synthesized was compound 2.35 (Scheme 2.6). Proline was tosylated using TsCl under basic conditions\textsuperscript{17}. Subsequent reduction of carboxylic acid 2.33 to the primary alcohol is completed by sodium borohydride in the presence of boron trifluoride diethyletherate\textsuperscript{17}. The desired substrate was isolated in 89% yield after treatment of prolinol derivative 2.35 with Tz\textsuperscript{o}Cl, DMAP and DCM. These compounds were ultimately subjected to the optimized reaction conditions.
2.3 Sulfonamide Substrate Screen

Irradiation of sulfonamide 2.11 under the optimized reaction conditions for 18 hours yielded 28% of the desired hydroxylated product 2.38. The isoamyl sulfonamide analog 2.9 yielded 29% of the corresponding hydroxyl substituted product, however, the diazenylation product 2.37 shown in Figure 2.4 was also isolated in 11% yield. It is noteworthy that this side reaction was not observed in the reaction with the diphenyl derivative 2.11. This by-product would arise from another molecule of the diazonium species coupling with the tertiary radical or the carbocation that forms upon radical translocation (Scheme 2.1).

As the experimental results of sulfonamide derivatives show in entries 1 and 2 of Figure 2.4, these substrates produce significantly less of the hydroxylated product than...
the corresponding sulfonate ester derivatives. The methylated sulfonamides 2.14 and 2.16 were subjected to the standard conditions (entries 3 and 4, Figure 2.4). Slightly better yields were afforded, 34% and 41% respectively. It is important to note that the diazenylation product was not observed with the methylated analog of 2.9 (Figure 2.4).

2.4 Control Experiments

Treatment of isoamyl sulfonate ester 2.8 with 10 mol% fac-Ir(ppy)$_3$ and 48% aqueous HBF$_4$ in a 5:1 mixture of MeNO$_2$/H$_2$O with vigorous stirring and irradiation for 18 hours with 4W blue LEDs (455 nm) yielded 57% of the hydroxylated product 2.41 (Scheme 2.7)$_2^1$. This result was used as the standard when analyzing the results of the control experiments that are summarized in figure 2.5.

Scheme 2.7 Standard conditions for remote hydroxylation

To gauge the necessity of acid in this method, 48% HBF$_4$ was omitted. Upon treatment with 2 equivalents of acid, the triazene is expected to generate the diazonium ion, which is then reduced by excited state fac-Ir(ppy)$_3$. For this reason, we predicted that the reaction would not proceed without acid and entry 1 of Figure 2.4 confirmed

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from Std. Cond.</th>
<th>Irradiation time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no acid</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>fac-Ir(ppy)$_3$ excluded</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>light excluded</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>light excluded</td>
<td>18</td>
<td>50</td>
</tr>
</tbody>
</table>

Figure 2.5 Deviations from standard conditions in Scheme 2.10
this. No desired product was isolated since the reactive species, the diazonium ion, remained masked as the triazene and this confirms that its release is necessary to initiate the reaction.

The second control experiment was performed without addition of the iridium catalyst. After 18 hours of irradiation, the hydroxylated product 2.41 was isolated in 11% yield (entry 2, Figure 2.5). This result suggests that the aryl radical is still being generated albeit in lower concentrations than in the presence of fac-Ir(ppy)$_3$. Diazonium salts are known to spontaneously release nitrogen gas while in solution$^3$ and this could account for the small amount of product being generated. Although product was isolated, this reaction shows that the catalyst is necessary as it greatly increases the efficiency of the method with regards to yield and reaction time.

The most enlightening control experiment was performed in the absence of light (entries 3 and 4, Figure 2.5). This reaction was conducted twice for different lengths of time (4 hours and 18 hours). Since we confirmed that the reaction is not initiated until acid has been added, all of the reagents except 48% HBF$_4$ were added to the reaction before the flask was double wrapped in aluminum foil to omit all light sources. After this was done, HBF$_4$ was added to the reaction, which was monitored in the dark for the specified amount of time. Surprisingly, the hydroxylated product 2.41 was isolated in 40% after 4 hours while a longer reaction time led to a slightly higher yield of 50%. Formation of the product without irradiation in a percent yield range close to that of the optimized conditions suggests that this reaction is not a true photochemical process. This also implies that ground state fac-Ir(ppy)$_3^2$ could possibly undergo SET to generate the aryl radical (Scheme 2.8) and ultimately form 2.41.
Finally, to determine whether or not this transformation was an intramolecular process, one equivalent of 3-phenylpropyl 4-methylbenzenesulfonate (2.42) was added to a typical reaction employing the standard conditions (Scheme 2.9). After 18 hours of irradiation, $^1$H NMR revealed no hydroxylation of the benzene sulfonate as resonances corresponding to the benzyl alcohol 2.43 were absent. However, evidence of the hydroxylated isoamyl product 2.41 was detected. This result suggests that the radical translocation is an intramolecular event.

2.5 Attempted Hydroxylation of Tetrahydropyrrole and Tetrahydrofuran Derivatives

Experiments using the pyrrolidine and tetrahydrofuran derivatives (2.22, 2.31, and 2.35) were performed using the standard reaction conditions (2 equiv. 48% HBF₄,
10 mol % *fac*-Ir(ppy)$_3$, 5:1 CH$_3$NO$_2$·H$_2$O). 1,7 radical translocation from the aryl ring to the tertiary carbon adjacent to the heteroatom in both substrates was expected (Figure 2.6). The neighboring electronegative oxygen or nitrogen would decrease the oxidation potential$^{22}$ of the alkyl radical allowing it to be converted easily to the carbocation. This tertiary carbocation would also be resonance stabilized by the presence of the heteroatom.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Structure 2.22" /></td>
<td><img src="image" alt="Structure 2.44" /></td>
</tr>
<tr>
<td></td>
<td>not observed</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Structure 2.31" /></td>
<td><img src="image" alt="Structure 2.45" /></td>
</tr>
<tr>
<td></td>
<td>not observed</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Structure 2.35" /></td>
<td><img src="image" alt="Structure 2.46" /> (73%)</td>
</tr>
</tbody>
</table>

Figure 2.6 Results from attempted hydroxylation of heterocycle derivatives

Initial screening of sulfonyl ester **2.22** under the hydroxylation conditions did not yield the expected product (**2.44**, Figure 2.6). In an effort to troubleshoot the reaction, alternative acids were substituted in place of 48% HBF$_4$ as there was a concern about degradation of the heterocycle under the strongly acidic conditions. Considering that the pKa of HBF$_4$ is -0.44$^{23a}$, acids that were slightly less acidic but strong enough to liberate the diazonium salt were proposed as alternatives. Attempts to hydroxylate with two equivalents of acetic acid (pKa: 4.76)$^{23b}$ were unsuccessful. After stirring under
irradiation overnight, there was still no consumption of the sulfonyl ester via TLC. This observation led to the use of the more acidic trifluoroacetic acid (pKa: 0.23)\(^{23c}\). In this case, the diazonium salt was liberated, however, the reaction did not show a clean conversion to hydroxylation product as seen with previous substrates. The \(^1\)H NMR spectrum was complex and suggested degradation of the substrate or product. Similar results were seen with sulfonate ester 2.31 as no product (2.45) was observed upon screening with the standard conditions.

Subjecting the tetrahydropyrrole derivative 2.35 to the hydroxylation conditions did not produce the desired product although when monitoring the reaction by TLC, new spots were observed. The \(^1\)H NMR spectrum looked promising as evidence of a hydroxyl-bearing carbon was present. The crude mixture was purified via flash chromatography in an attempt to identify any products that may have formed. Purification led to compound in 2.46, and its structure was confirmed based on NMR analysis and comparison to literature reports\(^{24}\).

A paper published by Haufe and coworkers\(^{25}\) provided insight as to how compounds 2.46 formed under the reaction conditions (Scheme 2.10). The authors

![Scheme 2.10 Proposed mechanism for Flourolead-mediated ring expansion](image)

Scheme 2.10 Proposed mechanism for Flourolead-mediated ring expansion
demonstrated that N-tosyl prolinol 2.34 could displace a leaving group generated by Fluolead in situ in the presence of Olah’s reagent (Py*9HF) (Scheme 2.10). This substitution forms an intermediate aziridinium ion (2.48). Subsequent attack by fluorine results in ring expansion and alkyl fluoride 2.49. Likewise, I proposed that sulfonamide 2.35 could follow a similar pathway in the acidic environment of the standard conditions (Scheme 2.11). Sulfonamide 2.35 would have released the diazonium ion to form the tosylated prolinol 2.50. Nucleophilic attack by water on 2.48 would explain the hydroxylated product observed (2.46).

\[
\begin{align*}
\text{Ts} & \quad \text{N} \\
\begin{array}{c}
\text{2.35} \\
\text{OTz}^\circ
\end{array} & \quad \text{fac-Ir(ppy)}_3 \\
\text{HBF}_4 & \quad \text{MeNO}_2\cdot\text{H}_2\text{O}
\end{align*}
\]

\[
\begin{align*}
\text{Ts} & \quad \text{N} \\
\begin{array}{c}
\text{2.48} \\
\text{2.46}
\end{array} & \quad \text{2.50}
\end{align*}
\]

Scheme 2.11 Proposed mechanism for ring expansion

2.6 Screening of Sulfonamides with Light Excluded

After screening the initial sulfonamides and sulfonate esters with the optimized reaction conditions, efforts were turned to screening several of the substrates in the dark. Such experiments were necessary after the results from the light excluded controls. A comparison of isolated yields of the functionalized products is summarized in
In addition to the sulfonamides screened in section 2.5, the 3-phenyl propyl amine (2.15), tyramine (2.12), and methyl leucine (2.13) sulfonamides were subjected to the standard conditions with light excluded.

Similar to the control experiment, when the reactions were performed without irradiation, the hydroxylated products were isolated in nearly the same yields. Of the examples shown, each result was slightly lower than with irradiation with the exception of the tyramine and methyl leucine derivatives (entries 4 and 5, Figure 2.7). The

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>% yield with irradiation</th>
<th>% yield w/o irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tz²NCH₃</td>
<td>TsNCH₃</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>Tz²NPh</td>
<td>TsNPh</td>
<td>56</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>Tz²NPh</td>
<td>TsNPh</td>
<td>41</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>Tz²NHPhOH</td>
<td>TsNHPhOH</td>
<td>56</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>Tz²NHCO₂Me</td>
<td>TsNHCO₂Me</td>
<td>47</td>
<td>48</td>
</tr>
</tbody>
</table>

Figure 2.7 Results from light excluded experiments using sulfonamides

difference, however, is still negligible. These two sulfonamides both produced interesting results. Isolation of 2.52 demonstrated that, when 1,7 hydrogen abstraction is not an option, 1,6 abstraction occurs just as efficiently provided the abstracted hydrogen is
benzylic. From the methyl leucine sulfonamide, compound 2.53 is generated when the carbonyl of the methyl ester attacks the carbocation. Loss of the methoxy group to affords the lactone compound.

Due to the results of the light exclusion experiments we proposed a mechanistic hypothesis (Scheme 2.12) similar to the initial mechanism proposed in Scheme 2.1. Instead of SET from the excited species, electron transfer would occur from ground state $\text{fac-Ir(ppy)}_3$ ($E_{1/2}^{IV/III} = +0.77 \text{ V vs. SCE}$)\(^2\) to the diazonium ion 2.2 ion ($E_{\text{red}} = 0.1$ to $+0.5 \text{ V vs. SCE}$). This process seems quite unfavorable however, when paired with the subsequent irreversible release of $\text{N}_2$, SET could happen. Radical translocation affords the tertiary radical 2.4 that can return the catalyst to ground state by SET to furnish the

![Scheme 2.12 Mechanistic hypothesis for light excluded experiments](image-url)
carbocation 2.5. The functionalized product 2.6 is then generated after nucleophilic attack of the carbocation.

2.7 Attempted Arylation Using Nucleophilic Arenes as Cosolvents

After observing the hydroxylation of the isoamyl sulfonate ester (2.8 Scheme 2.7), the next goal was to exploit the intermediate carbocation by employing other nucleophiles. Nucleophilic arenes such as furan, thiophene and 1-methyl indole were used as cosolvents X in place of water (Scheme 2.13). Since the acid in the standard conditions was an aqueous tetrafluoroboric acid solution, it was substituted with trifluoroacetic acid to completely eliminate water from the experiment. The use of 10 mol % fac-Ir(ppy)₃ and nitromethane remained the same and the reactions were observed for 18 hours.

Initial experiments performed with the nucleophilic arenes were unsuccessful. After analysis of the crude ¹H NMR showed none of the desired product, several additives were used to attempt to promote intermediate formation. The first additive used was hexafluoroisopropanol (HFIP) in a 5:1:1 ratio of CH₃NO₂:X:HFIP. We hypothesized that the polar environment resulting from water in the standard reaction conditions was necessary for carbocation formation. Therefore, a polar additive was

Scheme 2.13 Conditions for the attempted arylation of isoamyl sulfonate ester

2.8

Tz

\[ \text{CF}_3\text{COOH (2 equiv)} \]
\[ \text{fac-Ir(ppy)}_3 \text{ (10 mol %)} \]
\[ 5:1 \text{ CH}_3\text{NO}_2: X \]
(with or without TFE, HFIP or CAN)

\[ 18 \text{ hrs} \]

No product observed

X = furan, thiophene, 1-methyl indole
employed. Unfortunately, HFIP and subsequent attempts using trifluoroethanol (5:1:1 ratio of CH₃NO₂:X:TFE) were ineffective.

Next, to further encourage formation of the carbocation, an external oxidant was added in an effort to generate a higher concentration of Ir(ppy)₃⁺. To accomplish this, tris(4-bromophenyl)ammoniumyl hexachloroantimonate (TBAH) and ceric ammonium nitrate (CAN) were used as additives (5 mol %). In each of these six experiments (each oxidizing agent and the three nucleophilic arenes) none of the arylated product was observed.

The final attempt to arylate the tertiary carbon involved the use of an alternative reagent for single electron transfer and radical-polar crossover. Murphy and coworkers demonstrated that tetrathiofulvalene (TTF) was capable of SET and the intermediate radical cation facilitates radical-polar crossover. For this reason, we hypothesized that release of diazonium ion 2.54 in the presence of TTF would generate aryl radical 2.55 (Scheme 2.14). Subsequent translocation and radical-polar crossover would afford carbocation 2.58 followed by nucleophilic attack by furan.

Scheme 2.14 Mechanistic hypothesis for TTF-promoted hydroxylation
We substituted \textit{fac}-Ir(ppy)$_3$ with 10 mol % TTF and used 48\% HBF$_4$ to release the diazonium ion (Scheme 2.15). The isoamyl substrate 2.8 was stirred with these reagents in a 5:1 mixture of CH$_3$NO$_2$ and furan. After 18 hours, there was no desired product present in the crude $^1$H NMR spectrum, however, column chromatography resulted in the isolation of compound 2.58. This result suggests that reaction of the aryl radical with furan competes with radical translocation and efforts to discourage this process will be considered in the future.

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme_215.png}
\end{center}

Scheme 2.15 Conditions for attempted TTF-promoted arylation

\textbf{2.8 Conclusion}

In summary, we have demonstrated that catalyst and acid are vital to good isolated yields of the functionalized product of a variety of sp$^3$ C-H bonds. However, we have also shown that this is not a photoredox process since the transformation proceeds in an efficient manner in the absence of light. Attempts to hydroxylate the pyrrolidine and tetrahydrofuran derivates were ineffective though the ring expansion results were intriguing and warrant further research. Finally, efforts made to employ nucleophilic arenes were unsuccessful and resulted in addition of the nucleophile to the aryl radical.

Overall, however, this method represents a mild and efficient procedure for site-selective installation of hydroxyl groups at remote C-H sites. The tosylate generated in
the product is also useful as the leaving group can be further functionalized by other nucleophiles. Future work on this project will address the issues encountered with employment of alternative nucleophiles and hydroxylation of heterocycles.

2.9 Experimental

2.9.1 General Methods

$^1$H NMR and $^{13}$C NMR spectroscopy was conducted using a Bruker AV-400 or AV-500 spectrometer. Mass spectra were attained using an Agilent 6210 electrospray time-of-flight mass spectrometer. Optical rotation was measured using a JASCO P-2000 polarimeter. All materials were received from commercial suppliers and used without further purification. Flash column chromatography was accomplished using high purity grade 60 Å silica gel (Fluka® Analytical). Qualitative TLC was performed on aluminum sheets (Merck, silica gel, F254) and observed via UV absorption (254 nm) and staining with anisaldehyde or KMnO$_4$. Deuterated solvents were acquired from Cambridge Isotope Labs. Tz$^\circ$Cl and all Tz$^\circ$-containing compounds were synthesized according to literature procedure.$^1$ All reactions were carried out under an atmosphere of dry nitrogen. Remote hydroxylation reactions were conducted in round bottom flasks and irradiated with 4W blue LEDs (Creative Lighting Solutions, $\lambda_{\text{max}} = 455$ nm), which were wrapped around a crystallizing dish or kept in the dark by wrapping the flask in aluminum foil.

2.9.2 Procedures and Characterization

Synthesis of 2.8:

\[
\text{Tz}^\circ\text{O}\quad\text{isoamyl alcohol, 0.675}
\]

Started with 1.0 g (3.5 mmol) Tz$^\circ$Cl, 0.243 g (2.76 mmol) isoamyl alcohol, 0.675
g (5.53 mmol) DMAP and 5.6 mL CH₂Cl₂. Silica gel chromatography (gradient run from 10% EtOAc in hexanes to 20% EtOAc in hexanes) afforded 0.895 g (95%) of a yellow oil. Spectral data matched that previously reported in literature.²¹

Synthesis of 2.9:

\[
\text{Tz}^\circ \text{NH} \quad \quad \quad \text{Ph}
\]

Started with 0.300 g (1.04 mmol) Tz₇Cl, 0.17 mL (1.5 mmol) isoamyl amine, 4.5 mL sat. NaHCO₃, and 4.5 mL CH₂Cl₂. Silica gel chromatography (20% EtOAc in hexanes) afforded 0.261 g (74%) of a yellow oil. Spectral data matched that previously reported in literature.²¹

Synthesis of 2.10:

\[
\text{Tz}^\circ \text{NH} \quad \quad \quad \text{Ph}
\]

Started with 0.300 g (1.04 mmol) Tz₇Cl, 0.21 mL (1.5 mmol) 3-phenylpropylamine, 4.5 mL sat. NaHCO₃, and 4.5 mL CH₂Cl₂. Silica gel chromatography (gradient run from 5% EtOAc in hexanes to 20% EtOAc in hexanes) afforded 0.330 g (82%) of an orange oil. ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 1.3 Hz, 1H), 7.27 – 7.20 (m, 2H), 7.19 – 7.14 (m, 1H), 7.10 – 7.05 (m, 2H), 7.02 (ddd, J = 8.1, 1.7, 0.8 Hz, 1H), 5.56 (t, J = 6.4 Hz, 1H), 3.85 (app. d, J = 6.9 Hz, 2H), 3.75 (app. d, J = 6.7 Hz, 2H), 2.92 (q, J = 6.8 Hz, 2H), 2.65 – 2.55 (m, 2H), 2.39 (s, 3H), 1.82 – 1.72 (m, 2H), 1.43 – 1.22 (m, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 147.5, 144.0, 141.3, 129.3, 129.2, 128.6, 128.5, 126.1, 125.7, 118.3, 50.0, 43.4, 42.5, 33.1, 31.6, 21.8, 14.6, 11.4; HRMS m/z calcd for C₂₀H₂₉N₄O₂S [M+H]⁺ 389.2006, found 389.2000.

Synthesis of 2.11:
Started with 0.150 g (0.520 mmol) Tz\textsuperscript{o}Cl, 0.153 g (0.720 mmol) 3,3-diphenylpropylamine, 2 ml sat. NaHCO\textsubscript{3} and 2 mL CH\textsubscript{2}Cl\textsubscript{2}. Silica gel chromatography (15% EtOAc in hexanes) afforded 0.202 g (84%) of an off-white residue. Spectral data matched that previously reported in literature.\textsuperscript{21}

Synthesis of 2.12:

\[
\text{Tz}\textsuperscript{o}NH \quad \text{Ph}
\]

Started with 0.200 g (0.690 mmol) Tz\textsuperscript{o}Cl, 0.133 g (0.970 mmol) tyramine, 3 ml sat. NaHCO\textsubscript{3} and 3 mL CH\textsubscript{2}Cl\textsubscript{2}. Silica gel chromatography (gradient run from 20% EtOAc in hexanes to 40% EtOAc in hexanes) afforded 0.207 g (77%) of a yellow oil. Spectral data matched that previously reported in literature.\textsuperscript{21}

Synthesis of 2.13:

\[
\text{Tz}\textsuperscript{o}NH \quad \text{OH}
\]

To a round bottom flask containing 0.263 mg (1.45 mmol) L-leucine methyl ester HCl salt\textsuperscript{2}, 9.0 mL sat. NaHCO\textsubscript{3} and 4.5 mL CH\textsubscript{2}Cl\textsubscript{2} was added a solution of 0.300 g (1.04 mmol) Tz\textsuperscript{o}Cl in 1 mL CH\textsubscript{2}Cl\textsubscript{2} dropwise. The resulting mixture was allowed to stir under N\textsubscript{2} at room temperature for 15 h until complete consumption of starting material was observed via TLC. The aqueous layer was then separated from the organic layer.
and extracted with 3 x 10 mL CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. Silica gel chromatography (gradient run from 10% EtOAc in hexanes to 20% EtOAc in hexanes) afforded 0.266 g (64%) of a pale yellow solid. Spectral data matched that previously reported in literature¹.

Synthesis of 2.14:

![Structure of 2.14](image)

To a stirred 0°C solution of 0.261 g (0.770 mmol) 2.11 in 12 mL dry THF was added 0.037 g (0.92 mmol) 60% oil-dispersed sodium hydride. After 1 hour, the reaction mixture was removed from the ice bath and placed in an 80°C oil bath. 0.11 mL (2.4 mmol) iodomethane was then added. After 2 hours, the reaction mixture was removed from the oil bath and allowed to cool. 15 mL H₂O was then added at once followed by 15 mL CH₂Cl₂ and the layers were separated. The aqueous layer was extracted with an additional 2 x 15 mL CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. Silica gel chromatography (12 g silica gel, gradient run from 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded 0.255 g (93%) of a pale yellow oil. Spectral data matched that previously reported in literature.²¹

Synthesis of 2.15:

![Structure of 2.15](image)

For procedure, see synthesis of 2.14. Started with 0.330 g (0.850 mmol) 2.10, 0.041 g (1.02 mmol) 60% oil-dispersed sodium hydride, 0.13 mL (2.0 mmol) iodomethane and 13.5 mL dry THF. Obtained 0.320 g (93%) of an orange oil. ¹H NMR
(500 MHz, CDCl₃) δ 7.79 (d, J = 8.1 Hz, 1H), 7.36 – 7.22 (m, 3H), 7.20 – 7.11 (m, 3H), 6.99 (d, J = 8.1 Hz, 1H), 3.80 (s, 4H), 3.24 (t, J = 7.2 Hz, 2H), 2.85 (s, 3H), 2.63 (t, J = 8.0 Hz, 2H), 2.38 (s, 3H), 1.86 (t, J = 7.7 Hz, 2H), 1.34 (s, 3H), 1.23 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 149.3, 143.8, 141.7, 130.8, 128.5, 128.4, 125.9, 125.3, 119.6, 49.8, 49.1, 41.8, 34.7, 32.9, 29.7, 21.6, 14.6, 11.5; HRMS (m/z) calcd for C₂₁H₃₁N₄O₂S [M+H]+' 403.2162, found 403.2162.

Synthesis of 2.16:

For procedure, see synthesis of 2.14. Started with 0.282 g (0.610 mmol) 2.11, 0.029 g (0.73 mmol) 60 % oil-dispersed sodium hydride, 0.09 mL (2 mmol) iodomethane and 9.5 mL dry THF. Obtained 0.265 g (91%) of a viscous yellow oil. Spectral data matched that previously reported in literature.²¹

Synthesis of 2.18:

1.50 g (17.4 mmol) 4-pentene-1-ol was dissolved in 58.0 mL DMF under N₂ and cooled to 0°C. 3.41 g (22.6 mmol) tert-butyldimethylsilyl chloride and 3.56 g (52.3 mmol) imidazole was then added to the solution and the reaction slowly warmed to room temperature and stirred overnight. The solution was diluted with 110 mL 1M HCl (aq) and extracted with Et₂O (2 x 120 mL). The organic layers were concentrated and the resulting residue was partitioned between 110 mL 10% LiBr (aq) and Et₂O (2 x 120 mL) then dried over MgSO₄. Purification of the crude material via flash chromatography on
silica gel (10% DCM in hexanes) afforded 2.36 g (68%) of a colorless oil, known compound 2.18. Spectral data matched that previously reported in literature.  

Synthesis of 2.19:

![TBDMSO-CH=CH-OCH3](image)

7.14 g (74.9 mmol) methyl acrylate was added to a solution of 1.50 g (7.49 mmol) 2.19 and 0.064 g (0.075 mmol) Grubbs 2nd generation catalyst in CH2Cl2 under N2. The solution was refluxed overnight in an oil bath. Upon cooling to room temperature, the solvent was evaporated and the crude mixture was purified via flash chromatography on silica gel (3% EtOAc in hexanes) to afford 1.72 g (89%) of colorless oil, known compound 2.19. Spectral data matched that reported in literature.

Synthesis of 2.20:

![O-CH3](image)

0.300 g (1.16 mmol) 2.19 was dissolved in 5.4 mL THF under N2 followed by the addition of 5.1 mL (5.1 mmol) 1M TBAF in THF and the reaction stirred overnight at room temperature. To the reaction mixture was added 10 mL H2O and 10 mL sat. NaHCO3 (aq). The aqueous layer was extracted with CH2Cl2 (2 x 10 mL) and washed with 10 mL sat. NaCl (aq) then dried over MgSO4. Purification of the crude material via flash chromatography on silica gel (15% EtOAc in hexanes) afforded 0.128 g (77%) of a pale yellow oil, known compound 2.20. Spectral data matched that previously reported in literature.

Synthesis of 2.21:
0.100 g (0.694 mmol) **2.20** was dissolved in 10 mL Et₂O under N₂ and cooled to 0°C followed by the slow addition of a solution of 0.053 g (1.4 mmol) LAH in 14 mL Et₂O. The mixture stirred at 0°C for 30 mins then continued stirring at room temperature for 3 hrs. The solution was once again cooled to 0°C then treated with 2.2 mL 5M NaOH, filtered, washed with THF (3 x 5 mL) and concentrated to yield 0.076 g (94%) of a colorless oil which required no further purification. Spectral data matched that previously reported in literature.³³

Synthesis of **2.22**:

\[ \text{O} \bigg\|--\text{OH} \]

Started with 0.237 g (0.817 mmol) Tz⁰Cl, 0.076 g (0.65 mmol) **2.21**, 0.160 g (1.31 mmol) DMAP and 1.3 mL CH₂Cl₂. Silica gel chromatography (gradient run from 10% EtOAc in hexanes to 25% EtOAc in hexanes) afforded 0.201 g (84%) of an orange oil.

\(^1\)H NMR (400 MHz, CDCl₃) δ 7.83 (d, J = 8.1 Hz, 1H), 7.36 (s, 1H), 6.98 (d, J = 8.1 Hz, 1H), 4.13 (t, J = 6.6 Hz, 2H), 3.87 – 3.74 (m, 6H), 3.63 (q, J = 7.4 Hz, 1H), 2.38 (s, 3H), 1.95 – 1.86 (m, 1H), 1.85 – 1.77 (m, 4H), 1.45 – 1.38 (m, 1H), 1.34 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 6.9 Hz, 3H).

\(^{13}\)C NMR (100 MHz, CDCl₃) δ 149.3, 145.2, 130.6, 126.0, 125.2, 118.4, 75.6, 68.0, 67.7, 49.4, 42.4, 35.0, 31.3, 25.6, 21.8, 14.6, 11.4; HRMS m/z calcd for C₁₇H₂₇N₃O₄S (M+Na)⁺ 370.1780, found 370.1805.

Synthesis of **2.24**:

\[ \text{H₃C} \bigg\|--\text{N} \bigg\|--\text{CH}=\text{CH} \]
To a solution of 1.0 g (12 mmol) 4-penten-1-amine in 11 mL Et₂O was added a solution of 5.2 g (37 mmol) K₂CO₃ in 15 mL H₂O. 1.4 mL (17 mmol) methyl chloroformate was added dropwise over 30 minutes and the reaction was stirred at room temperature for 1 hour. The aqueous layer was separated and organic layer was washed with 20 mL 1N HCl, 20 mL sat. NaCl (aq), and dried over MgSO₄. Upon filtration, solvent was evaporated to give x g crude material. Silica gel chromatography (gradient run from 5% EtOAc in hexanes to 15% EtOAc in hexanes) afforded 0.898 g (52%) of a colorless liquid. Spectral data matched that previously reported in literature.²⁹

Synthesis of 2.25:

\[
\text{OCH}_3
\]

5.0 mL (55 mmol) methyl acrylate was added to a solution of 0.790 g (5.52 mmol) 2.24 and 0.047 g (0.055 mmol) Grubbs 2nd generation catalyst in 20 mL CH₂Cl₂ under N₂. The solution was refluxed overnight in an oil bath. Upon cooling to room temperature, the solvent was evaporated and the crude mixture was purified via flash chromatography on silica gel (35% EtOAc in hexanes) to afford 0.917 g (83%) of colorless oil, known compound 2.25. Spectral data matched that previously reported in literature.²⁷

Synthesis of 2.26:

\[
\text{OCH}_3
\]

\[
\text{OCH}_3
\]
0.100 g (0.500 mmol) **2.25** was dissolved in 5.0 mL THF under N\textsubscript{2} and cooled to 0°C followed by the addition of 0.55 mL (0.55 mmol) 1M TBAF in THF. The reaction was allowed to warm slowly to room temperature and stirred overnight. The mixture was quenched with 7 mL sat. NH\textsubscript{4}Cl (aq) and extracted with EtOAc (2 x 7 mL) then dried over MgSO\textsubscript{4}. Purification of the crude material via flash chromatography on silica gel (25% EtOAc in hexanes) afforded 0.076 g (76%) of a colorless oil. Spectral data matched that previously reported in literature.\textsuperscript{28}

**Synthesis of 2.27:**

\[
\text{TsHN} \quad \text{OCH}_3
\]

To a solution of 1.1 g (12 mmol) 4-penten-1-amine in 24 mL CH\textsubscript{2}Cl\textsubscript{2} was added in succession 2.6 g (13 mmol) TsCl and 3.0 mL (36 mmol) pyridine under N\textsubscript{2}. The reaction stirred overnight at room temperature, then 24 mL H\textsubscript{2}O and 24 mL Et\textsubscript{2}O was added. The aqueous layer was extracted with Et\textsubscript{2}O (2 x 24 mL) then washed with 24 mL sat. NaCl (aq) and dried over MgSO\textsubscript{4}. Purification of the crude material via flash chromatography on silica gel (40% EtOAc in hexanes) afforded 1.4 g (48%) of a pale yellow oil. Spectral data matched that reported in literature.\textsuperscript{29}

**Synthesis of 2.28:**

\[
\text{TsHN} \quad \text{OCH}_3
\]

4.5 mL (58 mmol) methyl acrylate was added to a solution of 1.2 g (5.0 mmol) **2.27** and 0.43 g (0.059 mmol) Grubbs 2\textsuperscript{nd} generation catalyst in 20 mL CH\textsubscript{2}Cl\textsubscript{2} under N\textsubscript{2}. The solution was refluxed overnight in an oil bath. Upon cooling to room temperature, the solvent was evaporated and the crude mixture was purified via flash.
chromatography on silica gel (35% EtOAc in hexanes) to afford 1.13 g (76%) of a colorless oil. Spectral data matched that reported in literature.\textsuperscript{30}

Synthesis of \textbf{2.29}:

\[
\begin{array}{c}
\text{Ts} \\
\text{OCH}_3 \\
\text{O}
\end{array}
\]

0.500 g (1.680 mmol) ester \textbf{2.28} was dissolved in 17.0 mL THF under \textsubscript{N}\textsubscript{2} and cooled to 0°C followed by the addition of 1.85 mL (1.85 mmol) 1M TBAF in THF. The reaction was allowed to warm slowly to room temperature and stirred overnight. The mixture was quenched with 25 mL sat. NH\textsubscript{4}Cl (aq) and extracted with EtOAc (2 x 25 mL) and then dried over MgSO\textsubscript{4}. Purification of the crude material via flash chromatography on silica gel (25% EtOAc in hexanes) afforded 0.425 g (85%) of a white solid. Spectral data matched that reported in literature.\textsuperscript{31}

Synthesis \textbf{2.30}:

\[
\begin{array}{c}
\text{Ts} \\
\text{OH}
\end{array}
\]

0.311 g (1.05 mmol) \textbf{2.29} was dissolved in 3.4 mL Et\textsubscript{2}O under \textsubscript{N}\textsubscript{2} followed by the slow addition of 0.34 mL (0.340 mmol) 1M LAH in Et\textsubscript{2}O at room temperature. The mixture stirred for 3 hours, then the solution was cooled to 0°C and then treated sequentially with 2.5 mL Et\textsubscript{2}O, 0.06 mL H\textsubscript{2}O, 0.06 mL 1N NaOH, and 0.19 mL H\textsubscript{2}O. The precipitate was filtered and the filtrate was dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated to yield 0.261 g (92%) of a pale yellow oil which required no further purification. Spectral data matched that reported in literature.\textsuperscript{32}

Synthesis of \textbf{2.31}:
 Started with 0.067 g (0.23 mmol) Tz°Cl, 0.050 g (0.19 mmol) 2.30, 0.046 g (0.37 mmol) DMAP, and 0.40 mL CH2Cl2. Silica gel chromatography (gradient run from 10% EtOAc in hexanes to 40% EtOAc in hexanes) afforded 0.051 g (52%) of a yellow oil. 1H NMR (400 MHz, CDCl3) δ 7.84 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.39 (s, 1 H), 7.29 (d, J = 7.9 Hz, 2H), 7.00 (d, J = 8.0 Hz, 1H) 4.17 (t, J = 6.2 Hz, 2H), 3.83 (q, J = 7.12 Hz, 4H), 3.66 (quin, J = 6.4 Hz, 1H), 3.34 (quin, J = 5.7 Hz, 1H), 3.17 – 3.11 (m, 1H) 2.42 (s, 3H), 2.40 (s, 3H), 2.31 - 2.23 (m, 1H), 1.88 – 1.79 (m, 1H), 1.62 – 15.7 (m 3H), 1.46 – 1.40 (m, 1 H), 1.36 (t, J = 7.0 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 149.2, 145.2, 143.4, 134.2, 130.4, 129.7, 127.5, 125.8, 125.0, 118.3, 67.7, 57.7, 49.3, 49.0, 42.4, 35.6, 31.1, 24.0, 21.7, 21.5, 14.5, 11.3; HRMS m/z calcd for C24H34N4O5S2 (M+Na)+ 523.2080, found 523.2051.

Synthesis of 2.33:

To a solution of 5.0 g (43 mmol) proline in 43.4 mL H2O at 0°C was added 12.6 g (91.2 mmol) K2CO3 added followed by 9.9 g (52 mmol) TsCl in three portions over 1 hour. The reaction mixture warmed slowly to room temperature over night and was subsequently acidified to pH 2 using conc. HCl and then extracted with 250 mL CH2Cl2. The organic layer was dried over Na2SO4, filtered, and solvent was removed in vacuo. Crude material was redissolved in CH2Cl2 and the product was precipitated with
pentane to give 11.6 g (quantitative yield) of a white solid. Spectral data matched that previously reported in literature.\textsuperscript{17}

Synthesis of 2.34:

![Chemical structure](image)

To a mixture of 3.3 g (86 mmol) NaBH\textsubscript{4} in 75 mL dry THF at 0\textdegree C was added 13.9 mL (113 mmol) BF\textsubscript{3}\textsuperscript{+}OEt\textsubscript{2} dropwise over 1 hour. A solution of 11.6 g (43.1 mmol) 2.33 in 55 mL dry THF was added dropwise to the reaction, which was then allowed to warm slowly to room temperature overnight. Slow addition of 75 mL MeOH quenched the reaction followed by addition of 50 mL 10% HCl (aq). The resulting solution was stirred at 60\textdegree C in an oil bath. After two hours, the reaction was cooled to room temperature and neutralized to pH 7 with 29 mL 3N NaOH. Volatiles were removed \textit{in vacuo} and product was extracted into 30 mL CH\textsubscript{2}Cl\textsubscript{2}. Concentration afforded 9.4 g (86%) of a white solid that required no further purification. Spectral data matched that previously reported in literature.\textsuperscript{17}

Synthesis of 2.35:

![Chemical structure](image)

Started with 0.500 g (1.73 mmol) Tz\textsuperscript{O}Cl, 0.353 g (1.38 mmol) 2.34, 0.337 g (2.76 mmol) DMAP and 2.8 mL CH\textsubscript{2}Cl\textsubscript{2}. Silica gel chromatography (gradient run from 10% EtOAc in hexanes to 30% EtOAc in hexanes) afforded 0.627 g (89%) of a white solid. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.86 (d, \(J = 8.1\) Hz, 1H), 7.64 (d, \(J = 8.3\) Hz, 2H), 7.39 (s, 1H), 7.29 (d, \(J = 8.1\) Hz, 2H), 7.02 (d, \(J = 8.1\) Hz, 1H), 4.31 (dd, \(J = 9.9, 3.7\) Hz, 1H), 3.90 (q, 3H), 3.72 (t, 2H), 3.16 (s, 3H), 2.65 (d, \(J = 10.1\) Hz, 1H), 2.49 (d, \(J = 7.2\) Hz, 1H), 1.65 (s, 3H), 1.30 (s, 3H).
3.97 (t, J = 10.0, 8.9 Hz, 1H), 3.84 (q, J = 6.6 Hz, 4H), 3.78 – 3.71 (m, 1H), 3.42 – 3.34 (m, 1H), 3.05 (ddd, J = 10.0, 8.5, 6.5 Hz, 1H), 2.42 (s, 3H), 2.41 (s, 3H), 1.97 – 1.89 (m, 1H), 1.86 – 1.74 (m, 1H), 1.64 – 1.49 (m, 2H), 1.36 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 149.5, 145.6, 143.9, 134.0, 130.8, 129.9, 127.7, 125.9, 125.4, 118.6, 71.3, 58.0, 49.5, 42.5, 28.7, 23.9, 21.9, 21.7, 14.6, 11.5; HRMS m/z calcd for C$_{23}$H$_{32}$N$_4$NaO$_5$S$_2$ [M+Na]$^+$ 531.1706, found 531.1701. $\alpha$-TsO = -68.5 (c = 1, DCM).

Typical procedure for remote hydroxylation and control experiments:

Synthesis of 2.41:

![Tso-OH](image)

To a vigorously stirred 20°C solution of 0.100 g (0.293 mmol) triazene 2.8 and 0.0192 g (0.0293 mmol) fac-Ir(ppy)$_3$ in 10 mL CH$_3$NO$_2$ and 2 mL deionized H$_2$O was added 76.5 µL (0.586 mmol) 48% HBF$_4$ via gas-tight syringe. After 4 minutes, irradiation of the solution with blue LEDs ($\lambda_{\text{max}}$=455 nm) commenced and the reaction mixture was stirred vigorously for 18.5 h. 10 mL of 5% NaHCO$_3$(aq.) was then added at once followed by 10 mL CH$_2$Cl$_2$ and the resulting layers were separated. The aqueous layer was extracted with an additional 2 x 10 mL CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated to yield 117.3 mg crude material. Silica gel chromatography (gradient run from 20% EtOAc in hexanes to 30% EtOAc in hexanes) afforded 43.4 mg (57%) of a yellow oil. Spectral data matched that previously reported in literature.$^{21}$
Entry 2, Figure 2.4: No catalyst

Started with 0.100 g (0.293 mmol) triazene 2.8, 76.5 µL (0.586 mmol) 48% HBF₄, 2 mL deionized H₂O (2 mL) and 10 mL MeNO₂. Purification via flash chromatography on silica gel (30% EtOAc in hexanes) afforded 0.009 g (10%) of 2.41 after concentration.

Entry 4, Figure 2.4: No light (18.5 h)

Started with 0.100 g (0.293 mmol) triazene 2.8, 0.0192 g (0.0293 mmol) fac-Ir(ppy)₃, 76.5 µL (0.586 mmol) 48% HBF₄, 2 mL deionized H₂O (2 mL) and 10 mL MeNO₂. The reaction flask was wrapped in foil before addition of the acid. Purification via flash chromatography on silica gel (30% EtOAc in hexanes) afforded 0.038 g (51%) of 2.41 after concentration.

Entry 3, Figure 2.4: No light (4 h)

Started with 0.100 g (0.293 mmol) triazene 2.8, 0.0192 g (0.0293 mmol) fac-Ir(ppy)₃, 76.5 µL (0.586 mmol) 48% HBF₄, 2 mL deionized H₂O (2 mL) and 10 mL MeNO₂. The reaction flask was wrapped in foil before addition of the acid. Purification via flash chromatography on silica gel (30% EtOAc in hexanes) afforded 0.030 g (41%) of 2.41 after concentration.

Synthesis of 2.36 and 2.37:

![Structures of 2.36 and 2.37](image)

Started with 0.100 g (0.293 mmol) 2.9, 0.0192 g (0.0293 mmol) fac-Ir(ppy)₃, 76.5 µL (0.586 mmol) 48% HBF₄, 2 mL deionized H₂O and 10 mL CH₃NO₂. Irradiated for 18 h. Silica gel chromatography (gradient run from 20% EtOAc in hexanes to 30% EtOAc...
in hexanes) afforded 0.022 g (29%) of 2.36 (yellow-brown solid) and 0.017 g (11%) of 2.47 (yellow oil). 2.36: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.76 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 5.65 (t, J = 5.7 Hz, 1H), 3.09 (q, J = 6.2 Hz, 2H), 2.42 (s, 3H), 1.91 (s, 1H), 1.63 (t, J = 6.4 Hz, 2H), 1.16 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 143.4, 136.8, 129.8, 127.2, 71.5, 40.8, 39.8, 29.6, 21.6; HRMS m/z calcd for C$_{12}$H$_{19}$NO$_3$S (M+Na)$^+$ 280.0984, found 280.0984.

2.37: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.95 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 7.8 Hz, 2H), 7.16 (s, 1H), 5.06 (t, J = 6.0 Hz, 1H), 4.96 (t, J = 5.8 Hz, 1H), 3.02 (quin, J = 6.9 Hz, 4H), 2.48 (s, 3H), 2.41 (s, 3H), 2.11 (t, J = 7.06 Hz, 2H), 1.62 – 1.55 (m, 1H), 1.39 – 1.35 (m, 2H), 1.33 (s, 6H), 0.84 (s, 3H), 0.82 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 148.0, 144.9, 143.3, 136.9, 133.0, 130.8, 129.7, 129.4, 127.0, 117.5, 71.3, 41.9, 40.4, 39.2, 38.3, 25.4, 25.0, 22.2, 21.5, 21.5; HRMS m/z calcd for C$_{24}$H$_{36}$N$_4$O$_4$S$_2$ (M+Na)$^+$ 509.2280, found 509.2254.

Synthesis of 2.38:

\[
\begin{array}{c}
\text{TsHN} \\
\text{HO} \\
\text{Ph} \\
\text{Ph}
\end{array}
\]

Started with 0.136 g (0.293 mmol) 2.11, 0.0192 g (0.0293 mmol) fac-Ir(ppy)$_3$, 76.5 µL (0.586 mmol) 48% HBF$_4$, 2 mL deionized H$_2$O and 10 mL CH$_3$NO$_2$. Irradiated for 18 h. Silica gel chromatography (gradient run from 20% EtOAc in hexanes to 30% EtOAc in hexanes) afforded 0.031 g (28%) of a pale yellow solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (d, J = 8.2 Hz, 2H), 7.33-7.15 (m, 12H), 5.26 (t, J = 5.9 Hz, 1H), 2.92 (q, J = 6.1 Hz, 2H), 2.48 (t, J = 6.2 Hz, 2H), 2.41 (d, J = 3.6 Hz, 3H); $^{13}$C NMR (100 MHz,
CDCl$_3$ δ 145.9, 143.3, 136.8, 129.7, 128.5, 127.4, 127.2, 126.0, 79.1, 40.2, 39.8, 21.6;
HRMS m/z calcd for C$_{22}$H$_{23}$NO$_3$S (M+Na)$^+$ 404.1297, found 404.1288.

Synthesis of 2.39:

\[
\text{TsN} \quad \text{OH} \\
\text{CH}_3
\]

Started with 0.103 g (0.289 mmol) 2.14, 0.0192 g (0.0293 mmol) fac-Ir(ppy)$_3$, 76.5 µL (0.586 mmol) 48% HBF$_4$, 2 mL deionized H$_2$O and 10 mL CH$_3$NO$_2$. Irradiated for 18 h. Silica gel chromatography (gradient run from 30% EtOAc in hexanes to 40% EtOAc in hexanes) afforded 0.026 g (33%) of a yellow oil. Spectral data matched that previously reported in literature.$^{21}$

Synthesis of 2.40:

\[
\text{TsN} \quad \text{Ph} \quad \text{OH} \\
\text{CH}_3 \quad \text{Ph}
\]

Started with 0.140 g (0.293 mmol) 2.16, 0.0192 mg (0.0293 mmol) fac-Ir(ppy)$_3$, 76.5 µL (0.586 mmol) 48% HBF$_4$, 2 mL deionized H$_2$O and 10 mL CH$_3$NO$_2$. Irradiated for 18 h. Silica gel chromatography (gradient run from 10% EtOAc in hexanes to 30% EtOAc in hexanes) afforded 0.048 g (41%) of a yellow solid. Spectral data matched that previously reported in literature.$^{21}$

Synthesis of 2.46:
Started with 0.075 g (0.15 mmol) **2.35**, 0.010 mg (0.015 mmol) *fac-*Ir(ppy)$_3$, 38.3 µL (0.293 mmol) 48% HBF$_4$, 1 mL deionized H$_2$O and 5 mL CH$_3$NO$_2$. Irradiated for 18 h. Silica gel chromatography (gradient run from 10% EtOAc in hexanes to 30% EtOAc in hexanes) afforded 0.028 g (73%) of a yellow oil. Spectral data matched that reported in literature.$^{30}$

Representative procedure for dark reactions:

**Synthesis of 2.51:**

\[
\text{Tsn} - \text{Ph} \\
\text{CH}_3
\]

Started with 0.118 g (0.293 mmol) triazene **2.15**, 0.0192 g (0.0293 mmol) *fac-*Ir(ppy)$_3$, 76.5 µL (0.586 mmol) 48% HBF$_4$, 2 mL deionized H$_2$O and 10 mL MeNO$_2$. The reaction flask was wrapped in foil before addition of the acid. Quenched with 5 mL 5% NaHCO$_3$ then extracted three times with 10 mL CH$_2$Cl$_2$. The organic layers were dried over Na$_2$SO$_4$ then filtered and concentrated. Purification via flash chromatography on silica gel (30% EtOAc in hexanes) afforded 0.048 g (51%) of a yellow oil. Spectral data matched that previously reported in literature.$^{21}$

**Synthesis of 2.52:**

\[
\text{Tsn} - \text{Ph} \\
\text{OH}
\]

Started with 0.114 g (0.293 mmol) triazene **2.12**, 0.0192 g (0.0293 mmol) *fac-*Ir(ppy)$_3$, 76.5 µL (0.5858 mmol) 48% HBF$_4$, 2 mL deionized H$_2$O and 10 mL MeNO$_2$. The reaction flask was wrapped in foil before addition of the acid. Quenched with 5 mL 5%
NaHCO$_3$ then extracted three times with 10 mL CH$_2$Cl$_2$. The organic layers were dried over Na$_2$SO$_4$ then filtered and concentrated. Purification via flash chromatography on silica gel (30% EtOAc in hexanes) afforded 0.055 g (61%) of a yellow oil. Spectral data matched that previously reported in literature.$^{21}$

Synthesis of 2.53:

\[ \text{TsHN} \]

Started with 0.117 g (0.293 mmol) triazene 2.13, 0.0192 g (0.0293 mmol) fac-Ir(ppy)$_3$, 76.5 µL (0.586 mmol) 48% HBF$_4$, 2 mL deionized H$_2$O and 10 mL MeNO$_2$. The reaction flask was wrapped in foil before addition of the acid. Quenched with 5 mL 5% NaHCO$_3$ then extracted three times with 10 mL CH$_2$Cl$_2$. The organic layers were dried over Na$_2$SO$_4$ then filtered and concentrated. Purification via flash chromatography on silica gel (gradient run from 10% EtOAc in hexanes to 30% EtOAc in hexanes) afforded 0.040 g (48%) of a pale yellow oil. Spectral data matched that previously reported in literature.$^{21}$

Synthesis of 2.58:

\[ \text{O}_2\text{S}^{-}\text{O} \]

Started with 0.100 g (0.293 mmol) triazene 2.8, 0.006 g (0.03 mmol) TTF, 76.5 µL (0.586 mmol) 48% HBF$_4$, 2 mL deionized H$_2$O and 10 mL MeNO$_2$. Reaction stirred without irradiation under ambient light for 18 hours. Quenched with 5 mL 5% NaHCO$_3$
then extracted three times with 10 mL CH₂Cl₂. The organic layers were dried over Na₂SO₄ then filtered and concentrated. Silica gel chromatography (gradient run from 100% hexanes to 5% EtOAc in hexanes) afforded 0.023 g (26%) of an orange oil. ¹H NMR (500 MHz, CDCl₃) δ 8.04 (d, J = 8.2 Hz, 1H), 7.67 (s, 1H), 7.56 (d, J = 1.7 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 3.5 Hz, 1H), 6.54 (dd, J = 3.5, 1.8 Hz, 1H), 4.01 (t, J = 6.6 Hz, 2H), 2.48 (s, 3H), 1.56 (dt, J = 13.5, 6.7 Hz, 1H), 1.44 (q, J = 6.7 Hz, 2H), 0.81 (s, 3H), 0.80 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 149.3, 144.5, 143.2, 131.2, 128.5, 112.8, 112.1, 69.6, 38.8 37.5, 24.5, 23.1, 22.3, 21.7; HRMS m/z calcd for C₁₆H₂₁O₄S [M+H]^+ 309.1155, found 309.1152.

2.10 References


CHAPTER 3: REVIEW OF CHEMICAL O-GLYCOSYLATION

3.1 Introduction

Over the past few decades, research efforts to understand the role of carbohydrates in the body and its implications in medical and biological research has increased.\(^1\) When oligosaccharides are covalently linked to molecules such as proteins or lipids they are called glycoconjugates (glycoproteins and glycolipids, respectively).\(^2\) Glycoconjugates were found to have specialized roles in biological processes such as cell-cell recognition.\(^3\) One can envision exploiting this function of membrane-bound oligosaccharides to improve drug-targeting accuracy or develop carbohydrate-based therapeutic agents.

While great progress has been made towards elucidating the function of glycosylation and oligosaccharides in the body, scientists would greatly benefit from the amount of material that can be provided through improved methods of chemical glycosylation. Methods to isolate oligosaccharides from biological sources often produce small amounts of a complex mixture of carbohydrates.\(^4\) In an effort to generate serviceable quantities of homogeneous oligosaccharides, methods for developing stereoselective glycosidic linkages via chemical glycosylations have been heavily investigated. These methods have to be robust and versatile to overcome the many challenges of generating oligosaccharides synthetically. The reactivity of both the glycosyl donor and acceptor, choice of solvent, and conformation induced by the protecting groups are important considerations.

3.2 Possible Mechanistic Pathways and Contributors to Stereochemical Outcomes
Formation of glycosidic linkages involves substitution at the anomeric carbon of a sugar. The electrophile, or glycosyl donor, “donates” the anomeric carbon while the glycosyl acceptor serves as the nucleophile. A leaving group bonded to the anomeric carbon is displaced after being activated by a promoter and subsequent attack on that carbon results in the formation of a glycosidic linkage. O-glycosylation is the term used to describe the transformation when the nucleophile is a hydroxyl (-OH) group. Chemical glycosylations generally undergo $S_N1$ and $S_N2$-like mechanistic pathways similar to those depicted in Scheme 3.1$^5,6$.

3.2.1 $S_N1$ & $S_N2$-like Mechanistic Pathways

Following an $S_N1$ pathway, departure of the leaving group is facilitated by activation of the glycosyl donor by promoter “A” (Scheme 3.1). Attack from the top or bottom face of oxocarbenium ion 3.3 by the glycosyl acceptor (ROH) forms the desired glycosylation product (3.4). This pathway generally leads to a mixture of anomers as the stereochemistry of the newly formed anomeric bond is not controlled.

Alternatively, via the $S_N2$ pathway (Scheme 3.1), activation of the leaving group by promoter “A” results in a contact ion pair (3.7) that has a positive charge at the anomeric carbon. The anomeric carbon is then attacked on the opposite face resulting
in inversion at the anomeric carbon. While Scheme 3.1 illustrates this pathway with C-X in the axial position, one can envision the same process with the leaving group in the equatorial position as well\textsuperscript{5,6}.

*Alpha* and *beta* are the terms used to describe the configuration of glycosides at the anomeric carbon. A *trans* relationship between the C\textsubscript{5}-C\textsubscript{6} bond and the C-X bond of the anomeric carbon, for the purposes of this dissertation, is referred to as the *alpha* anomer (Figure 3.1). On the other hand, a *cis* relationship depicts the *beta* anomer. The ability to selectively form *alpha* or *beta* anomers is key in the synthesis of oligosaccharides, especially for glycobiology applications where enzyme catalyzed glycosyllations are stereoselective.

![Figure 3.1 General representations of alpha and beta anomers (PG = protecting group)](image)

3.2.2 Anomeric Effect

Also known as the Edward-Lemieux effect\textsuperscript{7}, the anomeric effect refers to the propensity of electronegative atoms at the anomeric carbon to lie in the axial position as opposed to the equatorial position. This axial preference, according to molecular orbital theory (MOB), suggests that the lone pair on the ring oxygen stabilizes the aptly aligned \(\sigma^*\) of the C-X bond through hyperconjugation\textsuperscript{8} (3.9) (Figure 3.2). To further support this predilection, the dipole moment theory (DMT) suggests that the dipoles of the heteroatoms repel when the C-X bond is in the equatorial position\textsuperscript{7b} (3.12). However,
when in the axial position (3.11), the dipoles are situated opposite of each other, thus making it the more favorable orientation. Based on these proposed theories, the anomeric effect is worth keeping in consideration when interpreting the stereochemical outcome of an equilibrated reaction. The anomeric effect, however, plays a minor role as far as kinetic control is concerned and poor selectivity is often observed with glycosylations.

![Figure 3.2 Molecular orbital theory (MOB) and dipole moment theory (DMT) of the anomeric effect](image)

3.2.3 Neighboring Group Participation

Additional factors contribute to the selectivity of chemical glycosylations. One of the most powerful techniques employed to encourage complete selectivity is the installment of a carbonyl containing protecting group at the C₂ position. Acetyl-, benzoyl-, and pivaloyl-protecting groups are common examples. Following the formation of oxocarbenium ion 3.13, attack of the carbonyl on the anomeric carbon results inonium ion 3.14 (Scheme 3.2) where one face of the intermediate is blocked. Nucleophilic
attack on the top face results in generation of a single isomer. While this is generally the observation, in some cases the minor isomer also forms. This anomer is a result of the reversible nature of the orthoester intermediate$^{9,10}$. Onion ion 3.14 reverts back to 3.13 and attack on the bottom face results in the alpha anomer (3.17).

![Scheme 3.2 Neighboring group participation]

3.2.4 Effect of Solvents on Stereochemical Outcome

It has been observed that the solvent used for glycosylation affects the stereochemical outcome of the transformation. Common solvents employed for glycosylations range from dichloromethane, diethyl ether, and dioxane to less nonpolar solvents such as acetonitrile and nitromethane. It was postulated that nucleophilic solvents such as nitriles and ethers have a more direct impact on stereochemical outcome as they coordinate to the oxocarbenium ion$^{7a,11}$. The selective formation of either the alpha or beta anomer, however, depended on more than the solvent. It was determined that, in some cases, the reactivity of the glycosyl donor and the reaction temperature$^{11d}$ were the biggest determinants of how selective the reaction was.
Ethers favored formation of the \textit{alpha} anomer regardless of the type of donor and glycosylations at low temperatures (below 0°C) showed excellent stereoselectivity\textsuperscript{12}. It is suggested that solvolysis (Scheme 3.3 A) of the oxacarbenium ion (3.18) by ethers such as tetrahydrofuran (THF) or diethyl ether (Et\textsubscript{2}O) results in oxonium ion with a preference for the \textit{beta} anomer (3.19). \textit{S}_{\text{N}}2-like nucleophilic attack of the glycosyl acceptor leads to formation of the \textit{alpha} anomer (3.20) as the major product\textsuperscript{13}.

Solvents such as nitriles depend on both temperature and reactivity of the glycosyl donor to guide selectivity. Acetonitrile and propionitrile have been used in a series of investigations into the effect of nitriles on stereochemistry. In one example, Schmidt\textsuperscript{11d} demonstrated that treatment of trichloroacetimidates (a highly reactive class of glycosyl donors) with trifluoromethyl trifluoromethanesulfonate (TMSOTf) at -80°C in propionitrile afforded \textit{beta}-glycosides as the major products. Schmidt attributes this result to the formation of the \textit{α}-nitrilium ion (similar to 3.21 in Scheme 3.3 B) that is quickly generated due to the facile release of the leaving group under the reaction.
conditions. Since the observed α:β ratio is not reliant on the anomeric configuration of the glycosyl donor, the nitrilium ion is presumed to be the common intermediate and formation of the products follow an S_N2-like pathway.

Alternatively, another report by Schmidt and coworkers demonstrated that step-wise addition of the substrates was necessary to observe the desired selectivity. Stereoselective glycosylation relied on pre-activation of the halogen leaving group of glycosyl bromides and chlorides in acetonitrile at -15°C before addition of the acceptor. Subsequent generation of the alpha anomer as the major product led to the assumption that attack of the acceptor on the anomeric carbon occurred via an S_N2-like pathway with the β-nitrilium ion as the leaving group.

In recent years another theory about solvent effects has been proposed. Hünmenberger and coworkers postulate that the solvents are not actively participating in the reaction mechanism. Instead, the polarity of the solvent determines the preferred conformation of the oxocarbenium ion. In addition, the proximity and location of the counterion relative to the oxocarbenium cation ultimately dictates which face the acceptor attacks to afford the corresponding anomer. This concept is termed by the authors as the “conformer and counterion distribution” hypothesis.

Based on quantum-mechanical (QM) calculations, when in acetonitrile the oxocarbenium-triflate ion complex prefers to adopt mainly the B_{2,5} ring conformation (3.23) (Scheme 3.4). In this configuration, the alpha side of the ring is inaccessible by nucleophiles due to the steric interactions of the exocyclic substituents in addition to the propensity for the counterion to coordinate on the alpha face. Thus, attack occurs from the more accessible face of the intermediate resulting in predominantly the β anomer.
(3.24), the selectivity seen experimentally with glycosylations in nitrile solvents\textsuperscript{11}. In dioxane, the \textsuperscript{4}H\textsubscript{3} conformer (3.25) is preferred (Scheme 3.4). Though steric seems to have less control on nucleophilic attack, the counterion (when in dioxane) tightly coordinates to the oxocarbenium ion on the \textit{beta} side of the intermediate\textsuperscript{14}. Attack therefore occurs on the \textit{alpha} side and results in the corresponding \textit{alpha} anomer, the selectivity experimentally observed with glycosylations in ethereal solvents\textsuperscript{12}. It was observed that the polarity of the solvent determines how strongly coordinated the counterion is with the oxocarbenium ion. In solvents with lower polarity such as dioxane, the counterion lies very close to the carbocation (on the \textit{beta} side) while in more polar solvents like acetonitrile, the counterion exhibits a weaker coordination (on the \textit{alpha} side)\textsuperscript{14}.

3.3 Glycosyl Acceptors
As previously mentioned, glycosyl acceptors are the nucleophiles involved in the formation of glycosidic linkages. O-Glycosylation is a result of unprotected hydroxyl groups of, e.g., carbohydrate alcohols attacking the anomeric carbon of the glycosyl donor (Figure 3.3). Nucleophilicity of the acceptor plays a major role in reactivity and mechanistic pathways of glycosylation with less reactive acceptors favor $S_N1$ pathways and more reactive acceptors favor the $S_N2$ pathway. Primary alcohols like the unprotected hydroxyl group at C$_6$ (3.26) are generally more reactive than secondary alcohols (C$_{1-4}$). Of the secondary alcohols, C$_4$ (3.27, 3.29) hydroxyl groups are among the least nucleophilic and thus the least reactive. Another observation is that equatorial hydroxyl groups are generally more nucleophilic than axial hydroxyl groups (3.28).

Protecting groups also have an influence on the nucleophilicity of the acceptor. While the structure of the protecting groups can affect the conformation, the bulkiness of

![Figure 3.3 Generic representations of glycosyl acceptors](image-url)
the group can affect the reactivity of the alcohol. For example, a bulky group such as a tert-butyldimethylsilyl at C₆ would greatly reduce the nucleophilicity of C₄ hydroxyl groups (3.29) and thus makes formation of a glycosidc linkage exceedingly difficult. Also, as can be expected, the presence of electron donating groups (i.e. PG = Bn, Me) on the glycosyl acceptor contributes to an increase in reactivity of the nucleophile while the opposite affect is observed with electron withdrawing groups (i.e. PG = Bz, Ac).

3.4 Glycosyl Donors

3.4.1 Protecting Groups

Similar to glycosyl acceptors, glycosyl donors are generally protected with groups that mask the hydroxyl substituents on the sugar. While the protecting groups, in some cases, affect the nucleophilicty of the heteroatom at the anomeric carbon, glycosyl donors are categorized according to the propensity of the protecting groups to stabilize the intermediate oxocarbenium ion. Superarmed donors are those that are protected with bulky groups (i.e. tert-butyldimethylsilyl ethers) that prompt formation of a twist boat conformation of the donor with the C-O bonds adopting a pseudoaxial orientation (Figure 3.4). Electrostatic interactions between the C-O bonds and the forming oxocarbenium ion result in a highly stable intermediate. Armed donors are less reactive than the superarmed donors but are still capable of stabilizing the oxocarbenium ion.

![Figure 3.4 Examples of protected glycosyl donors](image)

Figure 3.4 Examples of protected glycosyl donors
due to the electron donating nature of the protecting groups. Groups in this category are generally ethers such as benzyl or methyl ethers. Lastly, disarmed donors typically bear electron-withdrawing groups like benzoyl, pivaloyl or acetyl esters and are the least reactive donors. Due to the electron-withdrawing characteristics of the esters, the oxocarbenium ion is destabilized.

3.4.2 Types of Glycosyl Donors

A. Glycosyl Halides

Glycosyl halides have been exploited as glycosyl donors for more than a century. Reported independently by Koenigs and Knorr and also Fischer and Armstrong, glycosyl bromides and chlorides successfully formed glycosidic linkages with alcohols in the presence of halophiles. Examples of halophiles used are salts of silver or mercury (introduced as an activator decades after reports with silver salts) such as AgOTf, AgClO₄, HgBr₂, or Hg(CN)₂.

Synthesis of disaccharide 3.38 was achieved by activating disarmed donor 3.35 in the presence of silver perchlorate (Scheme 3.6). Coordination of chloride 3.35 to the silver salt results in a more electrophilic anomeric carbon. Attack of C₄ acceptor 3.37 resulted in formation of 3.38. This selective transformation affords only the α anomer, even in the presence of the benozyl ester at C₂.

Scheme 3.6 AgClO₄ promoted glycosylation with glycosyl chloride
Later, glycosyl iodides were presented as more reactive donors that may obviate toxic heavy metals. Similar to bromides, iodides were quite unstable, however, it was demonstrated that glycosyl iodides were highly tunable and varying the temperature along with the protecting groups on the donors could afford highly stereoselective reactions\(^\text{22b}\). Non-heavy metal salts were also found to be efficient for activation of the reactive halides.

In one example reported by Stachulski and coworkers\(^\text{23}\), disarmed glycosyl iodides were activated in the presence of \(N\)-iodosuccinimide (NIS) and iodine (I\(_2\)) along with trifluoromethyl trifluoromethanesulfonate (TMSOTf) (0\(^\circ\)C to -15\(^\circ\)C) (Scheme 3.7). It was observed that this system would produce beta anomers as the major glycosides even when metal salts such as FeCl\(_3\) and CuCl were used (with I\(_2\) at 20\(^\circ\)C). Activation of glycosyl iodide 3.39 with iodine results in intermediate 3.40. Loss of the triiodide leaving group and neighboring group participation by the acetate group is followed by attack of the alcohol acceptor onto the oxonium species. The observed orthoester 3.43 reported

Scheme 3.7 NIS-I\(_2\)-TMSOTf promoted glycosylation of disarmed glycosyl iodide
by the authors is then converted to glycoside 3.44 upon addition of TMSOTf, added after complete consumption of 3.39. This selective reaction afforded 81% of beta glycoside 3.44.23

The instability of glycosyl halides was addressed when Mukaiyama demonstrated activation of glycosyl fluorides with SnCl₂-AgClO₄. More stable than other glycosyl halides, chemically and thermally, glycosyl fluorides were viable alternatives. In recent years, methods using TMSOTf and triflic acid (TfOH) have also materialized adding to the portfolio of mild activation of glycosyl fluorides. Since the introduction of glycosyl halides as glycosyl donors, many advancements have been made that continue to tackle the downfalls of these reactive but unstable glycosides.27

B. Chalcogenoglycosides (Alkyl/Aryl)

Chalcogenoglycosides generally bear alkyl or aryl selenides or sulfides at the anomeric carbon (selenglycosides and thioglycosides). The stability of chalcogenoglycosides is useful for the orthogonal synthesis of oligosaccharides as activation of other glycosyl donors in their presence can be carried out without disturbing the C-S or C-Se bond (Scheme 3.8). At the inception of their use as glycosyl donors, these highly stable glycosides often required mercury and silver salts.

\[
\begin{align*}
\text{AcO} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{F} & \quad + \\
\text{BnO} & \quad \text{BnO} & \quad \text{BnO} & \quad \text{BnO} & \quad \text{NPhth} & \quad \text{CpHfCl₂} & \quad \text{AgClO₄} \\
\text{AcO} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{SPh} & \quad \text{DCM} & \quad -78°C \text{ to r.t.} \quad \text{72%} \\
\text{BnO} & \quad \text{BnO} & \quad \text{BnO} & \quad \text{BnO} & \quad \text{NPhth} & \quad \text{BnO} & \quad \text{PPh} & \quad \text{NPhth}
\end{align*}
\]

Scheme 3.8 Glycosylation of thioglycoside acceptor with glycosyl fluoride donor
(similar to glycosyl halides) for their activation (e.g., PhHgOTf\textsuperscript{29} and AgOTf\textsuperscript{30}).

However, in later years, methods for activation without the use of silver or mercury were realized and reports of activation with systems such as NIS/TfOH\textsuperscript{30} and iodonium dicollidine perchlorate\textsuperscript{31} (IDCP). The common denominator here is the use of electrophilic species that have an affinity for sulfur and selenium. Generation of sulfonium and selenonium ions converts the sulfides and selenides into more efficient leaving groups resulting in formation of the oxocarbenium intermediate. Lönn demonstrated this process when ethyl thioglycoside \textbf{3.45} was activated by methyl triflate (MeOTf) to form an intermediate sulfonium ion\textsuperscript{32} (Scheme 3.9). Ethyl methyl sulfide was

\begin{equation}
\text{Scheme 3.9 Synthesis of trisaccharide via thioglycoside donor}
\end{equation}

the resulting by-product and attack of \textbf{3.48} afforded the corresponding trisaccharide \textbf{3.49}.

A mild procedure for activation was established when Sinay and coworkers exposed seleno and thioglycosides to an electric current\textsuperscript{33}. This process resulted in selenium and sulfur radical cations via single electron transfer (SET) following anodic oxidation. The
oxocarbenium ion is generated after the radical cations fragment rapidly and irreversibly. The desired saccharides are isolated accompanied by disulfides and diselenides as by-products. This SET process was also observed when chalcogenoglycosides were activated under visible-light promotion\textsuperscript{34}. Photochemical oxidation provided access to the mild activation of chalcogenoglycosides without the use of the specialized equipment employed with electrochemical oxidation.

Spell and coworkers demonstrated glycosylation of phenylselenoglycosides utilizing visible-light (blue LEDs) and diphenyldiselenide to promote activation (Scheme 3.10)\textsuperscript{35}. Visible-light induced homolysis of the Se-Se bond results in a phenylselenyl radical that reacts with carbon tetrabromide (CBr\textsubscript{4}) to generate PhSeBr \textit{in situ}. PhSeBr then reacts with selenium at the anomeric carbon of the glycosyl donor \textbf{3.50} resulting in intermediate \textbf{3.53}. The promoter, diphenyldiselenide (PhSeSePh), is then regenerated as the alcohol acceptor reacts to form the corresponding disaccharide \textbf{3.54}.

Scheme 3.10 Activation of phenylselenoglycosides with catalytic diphenyldiselenide (DTBMP = 2,6-di-\textit{tert}-butyl-4-methylpyridine)
Overall, chalcogenoglycosides represent a very versatile group of glycosyl donors. The stability of seleno and thioglycosides enables selective activation of other donors in their presence. Exploiting their stability and continued development of mild reaction conditions would make chalcogenoglycosides a viable tool for the synthesis of oligosaccharides.

C. Glycosyl Imidates

Glycosyl imidates are a highly reactive class of glycosyl donors with O-glycosyl trichloroacetimidates, first reported by Schmidt and coworkers, being among the most widely used glycosides. It has been demonstrated on numerous occasions that a variety of promoters efficiently activate trichloroacetimidates. Popular conditions include TMSOTf and BF₃·OEt₂, however, methods using lanthanide salts such as Yb(OTf)₃ and HClO₄-SiO₂ have also been developed. Coordination (or protonation) of the nitrogen of the leaving group to (or by) the promoter activates the glycosyl donor (see 3.55 and 3.56, Scheme 3.11). This interaction triggers departure of the imidoyl leaving group resulting in generation of trichloroacetamide as the by-product accompanied by the glycoside product.

Scheme 3.11 Activation of trichloroacetimidate donor with mild acid
Schmidt and coworkers demonstrated that weak acids such as $p$-toluenesulfonic acid (TsOH) protonated trichloroacetimidate donors 3.55 to generate 3.56 (Scheme 3.11)\(^\text{38}\).

Expulsion of the leaving group affords trichloroacetamide and subsequent attack of cholesterol affords glycoside 3.60. In this manner, the glycosylation of cholesterol was formed in 70% yield (2:1 $\alpha$:\(\beta\)). Schmidt also demonstrated that the activation was more selective with boron trifluoride diethyl etherate ($\text{BF}_3\cdot\text{OEt}_2$) at lower temperatures. At -18°C with $\text{BF}_3\cdot\text{OEt}_2$, 3.60 was isolated in 78% and 1:13 $\alpha$:\(\beta\) ratio.\(^\text{38}\)

$S$-imidates (thioimidates) are also used in chemical glycosylations, activated by a range of conditions from mercury salts ($\text{Hg(NO}_3\text{)}_2$)\(^\text{39}\) to alkylating agents such as methyl triflate ($\text{MeOTf}$) and benzyl bromide ($\text{BnBr}$)\(^\text{40}\). $S$-Thiazolinyl (STaz) glycosides, reported by Demchenko and coworkers, were activated by $\text{BnBr}$, which resulted in alkylation of the nitrogen to afford 3.62 (Scheme 3.12). This positively charged species facilitates

\[
\begin{align*}
\text{BnBr (3 equiv.)} & \quad \text{DCE, 3Å MS} & \quad 56^\circ\text{C} \\
3.61 & \quad \text{Bn} \quad \text{BzO} \quad \text{BzO} \quad \text{BzO} \\
& \quad \text{S} \quad \text{N} \\
& \quad \text{BzO} \quad \text{BzO} \quad \text{BzO} \quad \text{BzO} \\
3.62 & \quad \text{S} \quad \text{N}^+ \\
& \quad \text{Bn} \\
& \quad \text{BzO} \quad \text{BzO} \quad \text{BzO} \quad \text{BzO} \\
3.63 & \quad \text{S} \quad \text{N} \\
& \quad \text{Bn} \\
& \quad \text{BzO} \quad \text{BzO} \quad \text{BzO} \quad \text{BzO} \\
3.64 & \quad \text{OMe} \\
& \quad \text{OMe} \\
& \quad \text{OMe} \\
& \quad \text{OMe} \\
\text{3.65} & \quad \text{OMe} \\
& \quad \text{OMe} \\
& \quad \text{OMe} \\
& \quad \text{OMe} \\
\text{3.66} & \quad 79\% \\
& \quad \beta\text{ only}
\end{align*}
\]

Scheme 3.12 Remote activation of STaz leaving group via alkylation

departure of the leaving group and generation of the alkylated thiazolinyl by-product observed (3.64)\(^\text{40}\)

D. Alkenyl Glycosides
A well-known glycosyl donor in this category is the \( n \)-pentenyl glycoside. First introduced by Frasier-Reid\(^{41} \), this class of glycosides bears a pendant alkene that is activated by reaction of the alkene to form a bromonium (3.68) or iodonium ion generated from NBS or NIS, respectively (Scheme 3.13). The resulting halonium ion is then attacked by the anomeric oxygen, which affords a cationic tetrahydrofuran intermediate (3.69). The oxocarbenium ion is then generated as the active leaving group departs and glycosidic linkages are formed following attack of a glycosyl acceptor.\(^{41} \)

The rate of reaction of \( n \)-pentenyl glycosides was drastically increased with the introduction of *geminal* methyl groups. For example, *gem*-2,2-dimethyl 4-pentenyl glycosides exhibited an eleven fold increase (16-24h to 1h) in the reaction rate\(^{42} \) (Scheme 3.14). This observation is a result of the conformation induced by the methyl groups (Thorpe-Ingold effect). By bringing the alkene in closer proximity with the exocyclic oxygen, cyclization and ultimately the formation of the glycosidic linkage
occurs more efficiently. This analog of the \( n \)-pentenyl glycoside is also activated with NBS and follows the same mechanistic pathway in scheme 3.13. These glycosyl donors exhibit great stability, similar to thioglycosides, and the mechanism of activation of them makes them attractive options for glycosylation.

Scheme 3.14 \textit{gem}-2,2-dimethyl 4-pentenyl glycoside

3.5 Conclusion

Since oligosaccharides were identified as vital to bodily functions, research efforts have been continuously made to develop mild and selective chemical glycosylation methods to provide serviceable quantities of pure oligosaccharides for study. A reliable procedure to generate oligosaccharides depends greatly upon the ability to tune the leaving groups’ reactivity to encourage orthogonality under the reaction conditions. The above discussion of select leaving groups, however, is not all-inclusive. Many other leaving groups for glycosylations have been developed over the years including, but not limited to, sulfoxides, diazirines, silyl ethers, carbonates, and phosphates (Figure 3.5). We would eventually seek to design a glycosyl donor that combines the incredible stability of thioglycosides with the easy activation using catalytic acid of the trichloroacetimidates. Inspired by the mechanistic pathway of \( n \)-pentenyl
glycosides, efforts toward the development of such an O-glycosylation is discussed in the following chapters.

3.6 References


CHAPTER 4: TOWARDS THE DEVELOPMENT OF METAL-FREE O-GLYCOSYATION METHODS USING THIOGLYCOSIDES

4.1 Introduction

Activation of thioglycosides has proven to be challenging over the years due to their stability. Methods for their activation generally fall into four categories: halonium reagents (NIS/AgOTf, Selectfluor/BF$_3$-OEt$_2$)$^{2,3}$, organosulfur/selenium promoters (PhSeOTf, MPBT/Tf$_2$O)$^{4,5}$, thiophilic metal salts (AgBF$_4$, Hg(OAc)$_2$)$^{6,7}$, and chemical/electrochemical/photochemical induced single electron transfer (-e$^-$/Bu$_4$NBF$_4$, DDQ/hv)$^{8,9}$ (Figure 4.1). Visible-light photochemical methods for thioglycoside activation are especially appealing as the use of visible light to promote the transformation would be a gateway into development of a mild method for glycosylation.

---

Figure 4.1 Selected reagents used to activate thioglycosides

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*Portions of this chapter previously appeared in [Mark L. Spell, Kristina Deveaux, Caitlin G. Bresnahan, Bradley L. Bernard, William Sheffield, Revati Kumar, Justin R. Ragains, A Visible-Light-Promoted O-Glycosylation with a Thioglycoside Donor*, 4/18/2016]. They are reprinted by permission of [John Wiley and Sons.]*
Similar to the mechanistic pathway of \(n\)-pentenyl glycosides where the anomeric oxygen attacks the tethered bromonium species to form a cyclized intermediate\(^{10}\), we envisioned a system that promoted nucleophilic attack by sulfur. Along with literature precedent demonstrating interception of trifluoromethyl radicals by styrene in the presence of visible-light photocatalysts\(^{11}\), we anticipated using a visible-light photocatalyst with a thioglycoside that incorporated a styrenic moiety to avoid direct generation of a sulfur centered radical cation. However, we would soon discover that photocatalysts were not necessary for our method.

Thioglycoside 4.1 containing the electron rich styrenic moiety was found to form an electron donor-acceptor (EDA) complex with Umemoto’s reagent 4.2 (Scheme 4.1). This complex may facilitate the generation and transfer of trifluoromethyl radical to styrene as 4.3 absorbs a photon of visible-light \textit{in the absence of a metal catalyst}. Once this intermediate forms, sulfur is primed to attack the electrophilic benzyl carbon eventually generating the tetrahydrothiophenium intermediate 4.4 via an \(S_N1\) (B, Scheme 4.1) or \(S_N2\)-like (A, Scheme 4.1) pathway. Loss of the tetrahydrothiophene and attack of an alcohol would result in generation of the glycosylated product 4.7. Efforts
toward supporting the proposed mechanism and attendant experimental observations that changed the course of this project are described herein.

4.2 Synthesis of Thioglycoside Donors

Styrene bearing alkyl iodides 4.12 and 4.13 used for the synthesis of the thioglycosides were synthesized starting with 3-bromopropanol (Scheme 4.2). Phosphonium 4.9 was generated in 89% yield after heating 3-bromopropanol with triphenylphosphine at 120°C. Wittig reaction between 4.9 and the benzaldehyde derivatives in the presence of LHMDS at -20°C gave alcohols 4.10 and 4.11 in moderate yields. Then, 4.10 and 4.11 were converted to the alkyl iodides 4.12 and 4.13 following treatment with triphenylphosphine, I₂ and imidazole in DCM. Two additional alcohols were generated from tosylate 4.15 that was a result of reacting 3-buten-1-ol with tosyl chloride in pyridine (Scheme 4.3). Cross-metathesis of 4.15 with styrene or p-chlorostyrene in the presence of Grubbs second generation catalyst gave...
4.16 (80%) and 4.17 (50%)\textsuperscript{16a}. Substitution with sodium iodide in acetone produced alkyl iodides 4.18 and 4.19 in good yields\textsuperscript{14b}.

\textbf{Scheme 4.3 Synthesis of alkyl iodides from 3-buten-1-ol}

The synthesis of the thioglycoside donors followed a general procedure with substitution of the various styrenes to generate the corresponding product (Scheme 4.4). Beginning with glucose pentaacetate, conversion to glycosyl bromide 4.21 was achieved by treatment with 33\% HBr/\text{AcOH} and \text{Ac}_2\text{O}\textsuperscript{17}. 4.21 then reacted with CS\textsubscript{2} and Na\textsubscript{2}S•9H\textsubscript{2}O in DMF to form mercapto glucose 4.22\textsuperscript{18}.

Alkylation of 4.22 with alkyl iodides 4.12, 4.13, 4.18, and 4.19 results in a series of tetra-acetyl donors bearing the corresponding side chain\textsuperscript{14b}. Thioglycosides 4.23 - 4.26 were then deacetylated using 0.5M NaOMe in MeOH and subsequently converted to the benzylated donors 4.27 – 4.30 after reacting with benzyl bromide, NaH, and TBAI in DMF\textsuperscript{14b}. These substrates were used for initial experiments exploring the proposed transformation in Scheme 4.1.

\textbf{4.3 Importance of the $\rho$-Methoxy Side Chain for Glycosylation}
Scheme 4.4 Synthesis of tetrabenzyl thioglycoside donors

The pilot experiment (Figure 4.2) using 0.15 mmol of \( p \)-methoxy donor 4.27 resulted in 75% of the glycosylated product (4.32) when irradiated (blue LEDs, 455 nm)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Thioglycoside</th>
<th>Yield (%)</th>
<th>( \alpha:\beta ) Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.27</td>
<td>75</td>
<td>1.6:1</td>
</tr>
<tr>
<td>2</td>
<td>4.28</td>
<td>61</td>
<td>1.4:1</td>
</tr>
<tr>
<td>3</td>
<td>4.29</td>
<td>0</td>
<td>n.a.</td>
</tr>
<tr>
<td>4</td>
<td>4.30</td>
<td>0</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

Figure 4.2 Glycosylation experiments with metal-free glycosylation conditions
in the presence of C6-OH acceptor \textit{4.31} (0.5 equiv), Umemoto’s reagent \textit{4.2} (1.07 equiv.) and 4Å MS (150 mg) for 24 hours (entry 1, Figure 4.2)\textsuperscript{14b}. Upon addition of Umemoto’s reagent, a color change from colorless to yellow was observed signaling the formation of the putative EDA complex (Figure 4.3).\textsuperscript{24} Glycosyl donor \textit{4.28}, irradiated under the same conditions afforded 61% of the desired product. The yellow color of \textit{4.28} however, made it questionable to assume that an EDA complex with Umemoto’s reagent was formed. Thioglycosides with the more electron poor styrenic moieties (\textit{4.29} and \textit{4.30}) showed no consumption of the donors resulting in no disaccharide formation. There was also no color change observed in the presence of \textit{4.2}, leading to the assumption that generation of the EDA complex requires electron rich styrenes.

![Figure 4.3 Putative EDA complex](image)

Alkyl and most aryl thioglycosides do not absorb visible light, and the thioglycoside donor does not react without irradiation and Umemoto’s reagent. If an EDA complex forms with the styrene of the glycosyl donor and Umemoto’s reagent, we predicted that the mixture of both would show absorbance in the visible light region. UV-vis spectra of donor \textit{4.27} in MeCN (Figure 4.4) showed no absorbance in the visible-light region while a solution of Umemoto’s reagent alone showed weak absorbance between 385 and 410 nm. However, upon mixing the two compounds, absorbance increased and trailed well into the visible light region\textsuperscript{14b}. The absorbance of
thioglycoside 4.29 was also measured (Figure 4.5). After no product was formed using this donor, it was expected that the UV-vis spectrum of a solution of 4.29 would show no
new absorbance in the visible-light region and this was subsequently confirmed. Similarly, as predicted, a mixture of glycosyl donor 4.29 with Umemoto’s reagent did not show any change in absorbance.

Along with the results from the irradiation of 4.29 and 4.30 under the glycosylation conditions, the lack of color change, and the UV-vis analysis of 4.29, the necessity of the electron rich styrene was confirmed. The lack of reactivity of the electron-poor thioglycosides can be attributed to the lack of EDA complex formation with electron-poor styrenes indicated by a lack of new absorption at 455 nm in the visible light region in the presence of Umemoto’s reagent.

4.4 Exploring Thioglycoside Activation Under Ultraviolet Irradiation

While Umemoto’s reagent alone did not show much absorbance in the visible light window, analysis of the compound’s UV-vis spectra indicated that it was capable of absorbing ultraviolet light. As such, we predicted that UV irradiation would lead to higher reactivity. Not only this, but the putative EDA complex appeared to have a higher extinction coefficient at lower wavelengths. A trial experiment was performed with donor 4.27, acceptor 4.31, Umemoto’s reagent, and 4Å MS, however the reaction was irradiated with violet LEDs (405 nm) (Scheme 4.5). After 24 hours, the reaction was complete with a 62% isolated yield (1.7:1 α:β) of disaccharide 4.32. While this result was slightly lower in yield compared to the blue LEDs-irradiated experiment (75%), it

![Scheme 4.5 O-Glycosylation experiment with UV light](image-url)
was promising and warranted further optimization.

For a direct comparison of the reaction efficiency between blue and violet LEDs, an NMR experiment was performed. Two solutions of thioglycoside \( 4.27 \), acceptor \( 4.31 \), Umemoto’s reagent and 2,6-di-tert-butyl-4-methylpyridine (DTBMP) in CD\(_3\)CN were irradiated. DTMBP was used in place of molecular sieves to ensure a homogenous solution and neutralize any triflic acid that may be generated. One of the prepared solutions was irradiated with blue LEDs while the other was exposed to violet LEDs. After 3 hours, 52% of \( 4.27 \) had been converted at 455nm while 86% of \( 4.27 \) was converted with violet LEDs. As a follow-up experiment, I dissolved Umemoto’s reagent in CD\(_3\)CN and subjected the solution to irradiation for 1 hour with blue LEDs and violet LEDs separately. While the reagent remained in tact after exposure to blue LEDs, 32% of the reagent was consumed under ultraviolet light irradiation and peaks corresponding to dibenzothiophene were present in the aromatic region.

These results suggested that further optimization could be beneficial and that higher reactivity may be achieved with violet LED irradiation. Ye and coworkers reported that simply irradiating a solution of S-trifluoromethyldibenzothiophenium \( 4.2 \) with UV light caused homolytic fragmentation resulting in the formation of dibenzothiophene radical cation and CF\(_3\) radical (Scheme 4.6)\(^{19a}\). Generation of a high concentration of CF\(_3\) radical with UV light irradiation could possibly reduce the reaction time (24 hours

\[
\begin{align*}
\text{CF}_3^+ & \quad \text{OTf} \\
\text{UV light} & \\
\text{4.2} & \quad \text{h} \quad \text{4.33} + \quad \text{4.34}
\end{align*}
\]

Scheme 4.6 Fragmentation of Umemoto’s reagent by UV light
with blue LEDs) potentially resulting in an increase in yield. Bearing in mind that the EDA complex appears to have a higher extinction coefficient at 405nm than Umemoto’s reagent, it is possible that both the EDA complex and UV light induced fragmentation of Umemoto’s reagent are contributing to the yield.

While molecular sieves are generally used to maintain anhydrous conditions, they also act as a base to prevent generation of triflic acid and proved to be necessary for the efficient glycosylation with blue LEDs\textsuperscript{14b}. Concerns that the shorter wavelength of the violet LEDs were unable to efficiently irradiate the reaction (thus resulting in lower yields) led to the use of a bulky, nonnucleophilic base in place of molecular sieves because of the light scattering that they cause\textsuperscript{19b}.

Substituting DTMBP for molecular sieves resulted in 61% of disaccharide 4.32 (1.6:1 α:β) (entry 1, Figure 4.6). This result was similar to the glycosylation with molecular sieves (62%; α:β). Decreasing the amount of base to 0.6 equivalents, however, resulted in a clean transformation that was complete \textit{in only 2 hours} and yielded 83% of the disaccharide (1.2:1 α:β) (entry 2). To probe whether or not a more electron rich donor would result in higher yields, dimethoxy glycosyl donor 4.28 was reacted under the glycosylation conditions from entry 2 and resulted in a slightly lower yield (72%, 1.1:1 α:β) after 2 hours of irradiation (entry 3).

Interestingly, when irradiated with blue LEDs in the presence of DTBMP (0.6 equiv.) \textit{p}-methoxy donor 4.27 afforded only 51% yield (1.1:1 α:β) of the disaccharide while 2,4-dimethoxy donor 4.28 yielded 86% (1.2:1 α:β) (entries 4 and 5). These reactions, however, still took 24 hours to complete. Since violet light resulted in high
yields coupled with shorter reactions times using \( p \)-methoxy thioglycoside 4.27, violet LEDs were used in the experiments that followed.

\[
\text{Figure 4.6 Glycosylation experiments with DTBMP}
\]

Initial attempts to expand the substrate scope began with structurally simple alcohol, 5-hexen-1-ol (Figure 4.7) After 1 hour of stirring, TLC showed evidence of consumption of the alcohol leading to the assumption that the reaction was complete. Analysis of the crude \( ^1 \text{H} \) NMR revealed peaks corresponding to the tetrahydrothiophene

\[
\text{Figure 4.7 Glycosylation experiments with selected acceptors}
\]
by-product 4.6, however, none of the desired glycosylated product was detected. It appeared that the alkene of the acceptor was being degraded under the reaction conditions. To suppress this unwanted reaction, sacrificial alkenes were used as additives (hexane and styrene). In both cases, there was still consumption of the acceptor without any significant amount of the desired product. Though these initial results were exciting, incompatibility with electroneutral alkenes was discouraging. We opted to develop an alternative alkene-compatible method.

4.5 Conclusion

In summary, synthesis of four thioglycosides bearing a 4-aryl-3-butenyl side chain and subsequent screening with the initial visible light irradiation conditions led to the conclusion that electron rich rings assist with the generation of the putative EDA complex. Observation of the absorption spectra of Umemoto’s reagent resulted in glycosylation experiments that utilized UV-light as an alternative irradiation source. This change, along with the use of DTBMP as an alternative base, produced very exciting results as the reaction time of the previous method exhibited a twelvefold decrease while maintaining good yields. Although initial attempts to synthesize other glycosidic linkages were unsuccessful, efforts were continued to expand the scope of this reaction. Further details on scope and additional optimization of this method are described in Chapter V.

4.6 Experimental

4.6.1 General Methods

Reagents were purchased from Sigma Aldrich and used as received. Flash column chromatography was performed using 60Å silica gel purchased from Sigma
Aldrich. $^1$H NMR and $^{13}$C NMR spectroscopy were performed on a Bruker AV-400 and AV-500 spectrometer. Mass spectra were obtained using an Agilent 6210 electrospray time-of-flight mass spectrometer. UV-vis spectrophotometry was performed on a Varian Cary50 UV/vis spectrophotometer. Analytical and preparative TLC were conducted on aluminum sheets (Merck, silica gel 60, F254). Compounds were visualized by UV absorption (254 nm) and staining with anisaldehyde. 5 mL Pyrex micro reaction vessels (Supelco) were used in the glycosylation reactions. The triflate salt of Umemoto's reagent was used in all glycosylations. All glassware was flame-dried under vacuum and backfilled with dry nitrogen prior to use. Deuterated solvents were obtained from Cambridge Isotope Labs. All solvents were purified according to the method of Grubbs.  

4.6.2 Procedures and Characterization

Synthesis of 4.10

To a mixture of 4.0 g (9.97 mmol) 3-hydroxypropyltriphenylphosphonium bromide\textsuperscript{12} in 23 mL dry THF at -20\textdegree C was added 22.9 mL (22.9 mmol) LHMDS (1M in THF) dropwise. The mixture stirred for one hour at -20\textdegree C then 1.0 mL (8.2 mmol) of anisaldehyde was added dropwise. This resulting mixture stirred for another hour at -20\textdegree C before slowly warming to room temperature and was then stirred overnight. The reaction was quenched using 50 mL sat. NH$_4$Cl (aq), extracted with 50 mL EtOAc, then dried over Na$_2$SO$_4$. Silica gel chromatography (20% EtOAc in hexanes) afforded 0.890 g (61\%) of a white solid Spectral data matched that reported in literature.\textsuperscript{13b}
Synthesis of 4.11

See synthesis of 4.10 for procedure. Started with 4.0 g (9.97 mmol) 4.9, 20 mL dry THF, 22.9 mL (22.9 mmol) LHMDS, and 1.4 g (8.4 mmol) 2,4-dimethoxy benzaldehyde in 2.9 mL dry THF. Silica gel chromatography (gradient run from 20% EtOAc in hexanes to 30% EtOAc in hexanes) afforded 0.700 g (40%) of a colorless oil. Spectral data matched that reported in literature.\textsuperscript{13b}

Synthesis of 4.12

1.8 g (6.9 mmol) triphenylphosphine and 1.7 g (6.7 mmol) I\textsubscript{2} was dissolved in 26 mL CH\textsubscript{2}Cl\textsubscript{2} and stirred for 10 minutes at room temperature. 0.77 g (11 mmol) imidazole was added in one portion and reaction stirred for another 10 minutes at room temperature. A solution of 0.80 g (4.5 mmol) 4.10 in 5 mL CH\textsubscript{2}Cl\textsubscript{2} was added to the reaction. 30 mL sat. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{5} was added and the layers were separated. The aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 x 30 mL) and the organic layers were dried over MgSO\textsubscript{4}. Silica gel chromatography (5% EtOAc in hexanes) afforded 1.1 g (84%) of a yellow solid. Spectral data matched that reported in literature.\textsuperscript{14b}

Synthesis of 4.13
See synthesis of 4.12 for procedure. Started with 1.2 g (4.6 mmol) triphenylphosphine, 1.2 g (4.7 mmol) I₂, 0.52 g (7.6 mmol) imidazole, 0.64 g (3.1 mmol) 4.11 in 21 mL CH₂Cl₂. Silica gel chromatography (5 % EtOAc in hexanes) afforded 0.82 g (84%) of a colorless oil. \(^1\)H NMR (500 MHz, CDCl₃) δ 7.33 (d, \(J = 8.4\) Hz, 1H), 6.69 (d, \(J = 15.9\) Hz, 1H), 6.46 (d, \(J = 8.4\) Hz, 1H), 6.42 (s, 1H), 6.02 (dt, \(J = 15.9, 7.0\) Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.22 (t, \(J = 7.4\) Hz, 2H), 2.76 (q, \(J = 7.3\), 2H). \(^{13}\)C NMR (126 MHz, CDCl₃) δ 160.3, 157.6, 127.4, 127.1, 126.7, 119.2, 104.9, 98.5, 55.5, 55.4, 37.66, 5.7. HRMS m/z Calcd for C₁₂H₁₆I₂O₂ [M+H]\(^+\) 319.0189, found 319.0196.

Synthesis of 4.15

TsO

3.6 mL (42 mmol) of 3-buten-1-ol was added to 6.0 mL pyridine and cooled to 0°C. 7.9 g (42 mmol) TsCl was added in one portion to the solution and the reaction was stirred at that temperature until completed via TLC. The mixture was diluted with 100 mL Et₂O then poured into 50 mL of a cold 25% aqueous HCl solution. The resulting layers were separated and extracted with 50 mL Et₂O then dried over MgSO₄. Concentration of the filtrate afforded 7.3 g (77%) of a colorless liquid. Spectral data matched that reported in literature. \(^{15b}\)

Synthesis of 4.16

7.6 mL (66 mmol) styrene was added to a solution of 1.50 g (6.63 mmol) 4.15 and 0.056 g (0.066 mmol) Grubbs 2\(^{nd}\) generation catalyst in 20 mL CH₂Cl₂ under N₂. The solution was refluxed overnight in an oil bath. Upon cooling to room temperature, the
solvent was evaporated to give the crude mixture. Silica gel chromatography (gradient run from 100% hexanes to 20% EtOAc in hexanes) afforded 1.6 g (80%) of a white solid. Spectral data matched that reported in literature.\textsuperscript{14b}

Synthesis of \textit{4.17}

\[
\text{TsO} - \text{C}_6\text{H}_4 - \text{Cl}
\]

See synthesis of \textit{4.16} for procedure. Started with 4.0 mL (33.15 mmol) \(p\)-chlorostyrene, 0.056 g (0.066 mmol) Grubbs 2\textsuperscript{nd} generation catalyst, and 1.5 g (6.6 mmol) \textit{4.15} in 20 mL CH\(_2\)Cl\(_2\). Silica gel chromatography (gradient run from 100% hexanes to 20% EtOAc in hexanes) afforded 1.1 g (50%) of a white solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.78 (d, \(J = 8.3\) Hz, 2H), 7.30 (d, \(J = 8.2\) Hz, 2H), 7.25 (d, \(J = 8.6\) Hz, 2H), 7.18 (d, \(J = 8.5\) Hz, 2H), 6.34 (d, \(J = 15.9\) Hz, 1H), 5.98 (dt, \(J = 15.8, 7.0\) Hz, 1H), 4.13 (t, \(J = 6.5\) Hz, 2H), 2.54 (q, \(J = 7.8, 7.2\) Hz, 2H), 2.42 (s, 3H). \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 144.8, 135.4, 133.1, 132.1, 129.9, 128.7, 127.9, 127.4, 124.7, 69.5, 32.5, 21.6.

Synthesis of \textit{4.18}

\[
\text{I} - \text{C}_6\text{H}_4 - \text{H}
\]

2.2 g (15 mmol) NaI was added to 1.5 g (5.0 mmol) \textit{4.16} in 14 mL acetone at room temperature. The reaction was stirred until completed via TLC followed by filtration through a pad of celite. The filter cake was washed with pentane (2 x 15 mL). The filtrate was then washed with 20 mL H\(_2\)O then 20 mL sat. NaCl (aq), dried over Na\(_2\)SO\(_4\) and concentrated to afford 1.0 g (78%) of a colorless oil that required no further purification. Spectral data matched that reported in literature.\textsuperscript{14b}
Synthesis of 4.19

See synthesis of 4.18 for procedure. Started with 1.5 g (10.2 mmol) NaI and 1.1 g (3.3 mmol) 4.17 in 10 mL acetone. Following workup, 0.76 g (79%) of a yellow oil was isolated. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.28 (s, 4H), 6.41 (d, \(J = 15.8 \text{ Hz}, 1\)H), 6.11 (dt, \(J = 15.8, 6.9 \text{ Hz}, 1\)H), 3.23 (t, \(J = 7.2 \text{ Hz}, 2\)H), 2.77 (q, \(J = 7.1, 6.5 \text{ Hz}, 2\)H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 135.7, 133.2, 131.3, 129.4, 128.9, 127.6, 37.3, 4.9.

Synthesis of 4.23

0.70 mL (4.7 mmol) of DBU was added to 1.7 g (4.7 mmol) of 2,3,4,6-tetra-O-acetyl-1-mercapto-\(\beta\)-D-glucopyranoside\(^1\) in 10 mL toluene at -10\(^\circ\)C. After 10 minutes, 1.3 g (4.7 mmol) of alkyl iodide 4.12 in 3.7 mL toluene was added dropwise. The reaction was stirred at -10\(^\circ\)C for 2 hours until completed via TLC. 20 mL of H\(_2\)O was added to quench the reaction. The resulting solution was then extracted with CH\(_2\)Cl\(_2\) (2 x 58 mL). The organic layer was further diluted with 58 mL CH\(_2\)Cl\(_2\), washed with 43 mL 1M H\(_2\)SO\(_4\), 43 mL sat. NaHCO\(_3\) (aq), and 43 mL sat. NaCl (aq) then dried over Na\(_2\)SO\(_4\). Silica gel chromatography (gradient run from 15% EtOAC in hexanes to 25% EtOAc in hexanes) afforded 1.9 g (77%) of a white solid. Spectral data matched that previously reported in literature.\(^{14b}\)

Synthesis of 4.24

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See synthesis of 4.23 for procedure. Started with 0.36 mL (2.4 mmol) DBU, 0.87 g (2.4 mmol) 4.22 in 5 mL toluene, 0.76 g (2.4 mmol) alkyl iodide 4.13 in 2 mL toluene. Silica gel chromatography (gradient run from 20% EtOAc in hexanes to 50% EtOAc in hexanes) afforded 1.1 g (83%) of a pale yellow solid. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.29 (d, $J = 8.4$ Hz, 1H), 6.64 (d, $J = 15.9$ Hz, 1H), 6.50 – 6.36 (m, 2H), 6.05 (dt, $J = 15.9$, 6.9 Hz, 1H), 5.20 (t, $J = 9.4$ Hz, 1H), 5.06, (t, $J = 9.8$ Hz, 1H), 5.02 (t, $J = 9.8$ Hz, 1H), 4.52 (d, $J = 10.2$ Hz, 1H), 4.22 (dd, $J = 12.3$, 5.0 Hz, 1H), 4.11 (dd, $J = 12.3$, 2.3 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.69 (ddd, $J = 10.1$, 5.0, 2.4 Hz, 1H), 2.88 – 2.67 (m, 2H), 2.49 (dddd, $J = 10.6$, 8.8, 4.5, 2.6 Hz, 2H), 2.05 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.6, 170.1, 169.4, 169.4, 160.2, 157.4, 127.2, 126.3, 125.9, 119.3, 104.8, 98.4, 83.7, 75.8, 73.9, 69.9, 68.3, 62.2, 55.4, 55.3, 33.9, 30.1, 20.7, 20.7, 20.6, 20.6. HRMS m/z Calcd for C$_{26}$H$_{35}$O$_{11}$S [M+H]$^+$ 555.1895, found 555.1896. $[\alpha]_D^5$ = -28.7 (c = 1, DCM).

Synthesis of 4.25

See synthesis of 4.23 for procedure. Started with 0.58 mL (3.9 mmol) DBU, 1.4 g (3.8 mmol) 4.22 in 11.4 mL toluene, and 1.0 g (3.9 mmol) alkyl iodide 4.14 in 2.6 mL toluene. Silica gel chromatography (gradient run from 20% EtOAc in hexanes to 30%
EtOAc in hexanes) afforded 0.820 g (44%) of a white solid. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.34 (d, $J = 7.2$ Hz, 2H), 7.29 (t, $J = 7.6$ Hz, 2H), 7.21 (t, $J = 7.2$ Hz, 1H), 6.44 (d, $J = 15.8$ Hz, 1H), 6.20 (dt, $J = 15.8$, 6.9 Hz, 1H), 5.26 - 5.18 (m, 1H), 5.14 - 5.00 (m, 2H), 4.52 (d, $J = 10.1$ Hz, 1H), 4.25 (dd, $J = 12.4$, 5.0 Hz, 1H), 4.15 (dd, $J = 12.4$, 2.3 Hz, 1H), 3.72 (ddd, $J = 10.1$, 5.0, 2.4 Hz, 1H), 2.91 - 2.74 (m, 2H), 2.59 - 2.45 (m, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.8, 170.3, 169.5, 137.4, 131.8, 128.7, 128.0, 127.4, 126.2, 83.8, 76.1, 74.1, 70.0, 68.5, 62.3, 33.4, 29.4, 20.9, 20.9, 20.8, 20.2. HRMS m/z Calcd for C$_{24}$H$_{30}$NaO$_5$S [M+Na]$^+$ 517.1503, found 517.1499. $[\alpha]_D^2 = -40.3$ (c = 1, DCM).$^{14b}$

Synthesis of 4.26

See synthesis of 4.23 for procedure. Started with 0.33 mL (2.2 mmol) DBU, 0.80 g (2.2 mmol) 4.22 in 4 mL toluene, and 0.64 g (2.2 mmol) alkyl iodide 4.15 in 2.5 mL toluene. Silica gel chromatography (gradient run from 20% EtOAc in hexanes to 30% EtOAc in hexanes) afforded 0.61 g (55%) of a white solid. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.28 (app. s, 4H), 6.41 (d, $J = 15.8$ Hz, 1H), 6.19 (dt, $J = 15.8$, 6.9 Hz, 1H), 5.24 (d, $J = 9.4$ Hz, 1H), 5.16 – 5.04 (m, 2H), 4.53 (d, $J = 10.0$ Hz, 1H), 4.27 (dd, $J = 12.4$, 4.9 Hz, 1H), 4.17 (d, $J = 14.6$ Hz, 1H), 3.74 (ddd, $J = 10.0$, 4.9, 2.3 Hz, 1H), 2.93 – 2.77 (m, 2H), 2.53 (m, 2H), 2.09 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.8, 170.4, 169.6, 135.9, 133.0, 130.7, 128.9, 128.8, 127.58, 83.7, 76.9, 76.2, 74.0, 69.9, 68.5, 62.3, 33.4, 29.7, 20.9, 20.9, 20.8, 20.8.
HRMS m/z Calcd for C_{24}H_{30}ClO_{9}S [M+H]^+ 529.1294, found 529.1286. [\alpha]_D^0 = -10.2 (c = 0.94, DCM).

Synthesis of 4.27

To a solution of 1.9 g (3.6 mmol) 4.23 in 44.4 mL MeOH was added 1.9 mL (1.9 mmol) of 1M NaOMe. The reaction was stirred overnight at room temperature. Solvent was removed in vacuo and the resulting solid was redissolved in 36.0 mL DMF. To this solution was added 0.261 g (0.706 mmol) of TBAI followed by 1.1 g (26 mmol) of 60% oil dispersed NaH at 0°C. After 30 minutes at this temperature, 2.8 mL (24 mmol) of benzyl bromide was added dropwise. The reaction warmed slowly to room temperature and stirred overnight until complete via TLC. At 0°C the reaction was quenched with 45 mL sat. NH_4Cl (aq.) then extracted with Et_2O (2 x 45 mL), washed with 45 mL sat. NaCl (aq.), and dried over Na_2SO_4. Silica gel chromatography (gradient run from 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded 0.960 g (37%) of a white solid. Spectral data matched that previously reported in literature.\textsuperscript{14b}

Synthesis of 4.28

See synthesis of 4.27 for procedure. Started with 0.801 g (1.44 mmol) 4.24, 18.1 mL MeOH, and 0.79 mL (0.79 mmol) of 1M NaOMe. Resulting solid was dissolved in
14.7 mL DMF followed by 0.106 g (0.290 mmol) TBAI, 0.432 g (10.8 mmol) of 60% oil dispersed NaH, and 1.2 mL (9.9 mmol) of benzyl bromide. Silica gel chromatography (gradient run from 20% EtOAc in hexanes to 30% EtOAc in hexanes) afforded 0.495 g (46%) of a pale yellow solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.43 – 7.20 (m, 20H), 7.16 (d, \(J = 5.0\) Hz, 3H), 6.67 (d, \(J = 15.9\) Hz, 1H), 6.43 (d, \(J = 9.9\) Hz, 2H), 6.12 (dd, \(J = 16.1, 8.0, 5.9\) Hz, 1H), 4.92 (dd, \(J = 10.6, 5.9\) Hz, 2H), 4.82 (dd, \(J = 14.6, 11.0\) Hz, 2H), 4.73 (d, \(J = 10.1\) Hz, 1H), 4.66 – 4.51 (m, 2H), 4.48 (dd, \(J = 9.9, 2.4\) Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.72 – 3.64 (m, 2H), 3.61 (t, \(J = 9.3\) Hz, 1H), 3.51 – 3.39 (m, 2H), 2.86 (qt, \(J = 12.7, 7.5\) Hz, 2H), 2.57 (q, \(J = 7.4\) Hz, 2H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 160.3, 157.7, 138.7, 138.4, 138.3, 138.2, 128.6, 128.6, 128.6, 128.6, 128.2, 128.0, 127.9, 127.9, 127.9, 127.8, 127.5, 127.2, 125.8, 119.8, 104.9, 98.6, 86.9, 85.5, 82.0, 79.3, 78.2, 75.9, 75.7, 75.3, 73.7, 69.3, 55.6, 55.6, 34.3, 31.2. HRMS m/z Calcld for C\(_{46}\)H\(_{51}\)O\(_7\)S [M+H]\(^+\) 747.3350, found 747.3333. \([\alpha]_D^{25} = +2.8\) (c = 0.17, DCM).

Synthesis of 4.29

![Diagram](image_url)

See synthesis of 4.27 for procedure. Started with 0.210 g (0.425 mmol) 4.25, 5.4 mL MeOH, and 0.23 mL (0.23 mmol) of 1M NaOMe. Resulting solid was dissolved in 4.3 mL DMF followed by 0.03 g (0.09 mmol) TBAI, 0.13 g (3.2 mmol) of 60% oil dispersed NaH, and 0.35 mL (2.9 mmol) of benzyl bromide. Silica gel chromatography (gradient run from 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded 0.153 g (52%) of a white solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.39 - 7.14 (m, 25H), 6.43 (d, \(J =\)
15.8 Hz, 1H), 6.24 (dt, J = 15.8, 6.9 Hz, 1H), 4.92 (d, J = 10.7 Hz, 2H), 4.86 - 4.79 (m, 2H), 4.74 (d, J = 10.2 Hz, 1H), 4.62 - 4.53 (m, 3H), 4.49 (d, J = 9.7 Hz, 1H), 3.75 (dd, J = 10.9, 1.9 Hz, 1H), 3.71 - 3.65 (m, 2H), 3.61 (m, J = 9.4 Hz, 1H), 3.50 - 3.43 (m, 2H), 2.94 - 2.80 (m, 2H), 2.59 (q, J = 6.7 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.7, 138.4, 138.2, 138.1, 137.6, 131.5, 128.6, 128.6, 128.6, 128.5, 128.5, 128.5, 128.12 127.9, 127.9, 127.9, 127.8, 127.7, 127.3, 126.3, 86.8, 85.5, 82.0, 79.3, 78.1, 75.9, 75.7, 75.2, 73.6, 69.3, 33.8, 30.9. HRMS m/z Calcd for C$_{44}$H$_{46}$NaO$_5$S [M+Na]$^+$ 709.2958, found 709.2977. $\alpha^3 = -7.5$ (c = 1, DCM).$^{14b}$

**Synthesis of 4.30**

![Chemical structure image]

See synthesis of 4.27 for procedure. Started with 0.57 g (1.1 mmol) 4.26, 13.6 mL MeOH, and 0.59 mL (0.59 mmol) of 1M NaOMe. Resulting solid was dissolved in 11 mL DMF followed by 0.08 g (0.2 mmol) TBAI, 0.32 g (8.1 mmol) of 60% oil dispersed NaH, and 0.88 mL (7.420 mmol) of benzyl bromide. Silica gel chromatography (gradient run from 10% EtOAc in hexanes to 15% EtOAc in hexanes) afforded 0.395 g (50%) of a white solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.39 – 7.12 (m, 24H), 6.37 (d, J = 15.9 Hz, 1H), 6.21 (dt, J = 15.8, 6.8 Hz, 1H), 4.91 (dd, J = 10.6, 5.3 Hz, 2H), 4.87 – 4.79 (m, 2H), 4.75 (d, J = 10.2 Hz, 1H), 4.57 (q, J = 12.3 Hz, 3H), 4.48 (d, J = 9.7 Hz, 1H), 3.75 (dd, J = 10.9, 1.9 Hz, 1H), 3.71 – 3.65 (m, 2H), 3.61 (t, J = 9.3 Hz, 1H), 3.51 – 3.43 (m, 2H), 2.94 – 2.79 (m, 2H), 2.58 (qd, J = 7.3, 1.4 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.7, 138.4, 138.2, 138.1, 136.1, 132.9, 130.4, 129.4, 128.9, 128.8, 128.7, 128.6, 128.6, 128.6,
128.5, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.5, 86.8, 85.5, 82.0, 79.3, 78.2, 76.0, 75.7, 75.3, 73.7, 69.4, 33.8, 30.8. HRMS m/z Calcd for C_{44}H_{46}ClO_{5}S [M+H]^+ 721.2749, found 721.2784. \left[\alpha\right]_D^{25} = -6.1 (c = 0.47, DCM).

General procedure for glycosylation with blue LED irradiation:

A flame-dried 5 mL Pyrex reactor vial was charged with the glycosyl donor (1 equiv., 0.150 mmol), Umemoto’s reagent (1.07 equiv., 0.160 mmol), the glycosyl acceptor (0.5 equiv., 0.0752 mmol), 150 mg of freshly activated 4 Å molecular sieves and 1 mL of dry dichloromethane under nitrogen atmosphere. The reactor vial was placed 1-2 cm away from the light source (4W blue LEDs, 2 strips, Sapphire Blue LED Flex Strips from Creative Lighting Solutions were wrapped around a 150 × 75 Pyrex crystallizing dish) and irradiated from the side for 24 hours. The reaction mixture was then filtered to remove molecular sieves and washed with 5 mL DCM. The crude products were concentrated and then purified by gradient silica gel chromatography to afford a mixture of anomeric products.

General procedure for glycosylation with violet LEDs:

A flame-dried 5 mL Pyrex reactor vial was charged with the glycosyl donor (1 equiv., 0.150 mmol), Umemoto’s reagent (1.07 equiv., 0.160 mmol), the glycosyl acceptor (0.5 equiv., 0.0752 mmol), DTBMP (0.6 equiv., 0.090mmol), and 1 mL of dry dichloromethane under nitrogen atmosphere. The reactor vial was placed 1-2 cm away from the light source (4W violet LEDs, 2 strips, Purple/UV LED Flex Strips from Creative Lighting Solutions were wrapped around a 150 × 75 Pyrex crystallizing dish) and irradiated from the side for 2 hours. The crude products were concentrated and then purified by gradient silica gel chromatography to afford a mixture of anomeric products.
Determination of anomeric ratios:

The anomeric ratio ($\alpha:\beta$) was determined based on the integration of key resonances identified with the assistance of published $^1$H NMR data. In the cases where spectral data was unavailable, the anomeric products were separated with silica gel chromatography or preparative TLC.

Synthesis of disaccharide 4.32

![Disaccharide Structural Formula]

Started with 0.108 g (0.15 mmol) of thioglycoside 4.27, 0.064 g (0.16 mmol) Umemoto’s reagent, 0.035 g (0.075 mmol) methyl 2,3,4-tri-O-benzyl-$\alpha$-D-glucopyranoside 4.31, 0.018 g (0.090 mmol) DTBMP), and 1 mL of dry dichloromethane. Silica gel chromatography (gradient run from 5% Et$_2$O in hexanes to 30% Et$_2$O in hexanes) afforded 0.061 g (83%; 1.2:1 $\alpha:\beta$) of a white solid, disaccharide 4.32. Spectral data matched that previously reported in literature.$^{22}$

4.7 References


CHAPTER 5: DEVELOPMENT OF ACID-PROMOTED GLYCOSYLATION OF ALCOHOLS WITH THIOGLYCOSIDES

5.1 Introduction

Halonium-based reagents such as N-bromosuccinimide (NBS) or N-iodosuccinimide (NIS) often accompany acid promotion when thioglycosides are used as O-glycosylation donors. For example, a popular combination, first reported by van Boom and co-workers, is trifluoromethanesulfonic acid (TfOH) and NIS\textsuperscript{1}. Alternatively, hypervalent iodine(III) reagents have provided mild access to electrophilic iodonium species for the activation of thioglycosides\textsuperscript{2-4}. Recently, Kita and colleagues demonstrated that phenyliodine(III) bis(trifluoroacetate) (PIFA) in the presence of TfOH or trimethylsilyl trifluoromethanesulfonate (TMSOTf) was an effective promoter for thioglycoside activation (Scheme 5.1)\textsuperscript{4}.

Another class of sulfur-containing glycosyl donors known as sulfinyl glycosides are commonly activated using triflic anhydride (Tf\textsubscript{2}O) (Scheme 5.2)\textsuperscript{5a}. Activation of these sulfoxides is accompanied by bulky, non-nucleophilic bases, such as di-\textit{tert}-butyl-4-methylpyridine (DTBMP), as acid scavengers. The reactivity of sulfinyl glycosides

![Scheme 5.1 Hypervalent iodine(III) reagent (PIFA)-promoted glycosylation](image)
obviates halonium-based reagents, however, they are less stable than thioglycosides and decomposition is often a limitation. A similar trend is seen with the frequently used trichloroacetimidate glycosyl donors\textsuperscript{5b,c} (Figure 5.1).

\begin{equation}
\text{Scheme 5.2 Glycosylation with a Pivaloate-protected sulfinyl glycoside. (Piv = pivaloate)}
\end{equation}

In an effort to combine the best of both worlds (stability of thioglycosides and reactivity of trichloroacetimidate donors), we have developed an acid-catalyzed glycosylation with thioglycoside donors. Disaccharides were successfully obtained when 4-aryl-3-butenylthioglycosides reacted with selected glycosyl acceptors in the presence of acid. Optimization and development of this method is discussed herein.

\begin{equation}
\text{Figure 5.1 Trichloroacetimidate glycosyl donor}
\end{equation}

\section*{5.2 Mechanistic Proposal for Acid-Promoted Remote Glycosylation}

We hypothesized that acid in the presence of the electron rich 4-aryl-3-butenylthioglycoside side chain could result in activation of the thioglycoside donor. We proposed a plausible mechanism for the transformation. The mechanistic proposal for
an acid-promoted glycosylation is shown in Scheme 5.3 and is similar to the visible-light glycosylation with Umemoto's reagent and 5.1. Protonation of the styrenic moiety of 4-

![Scheme 5.3 Mechanistic proposal for acid-promoted glycosylation. PMP = p-methoxyphenyl](image)

aryl-3-butenylthioglycoside 5.1 by triflic acid results in intermediate 5.5. The stable benzylic carbocation can then be attacked by sulfur to generate sulfonium intermediate 5.6. This activated donor is now suited to react with an acceptor (ROH) to form glycosidic linkages via an S_N1 or S_N2-like pathway (B and A, respectively).

5.3 Pilot Experiment and Optimization of Glycosylation Method

Following the color change observation, I ran an experiment using 1 equivalent of triflic acid and omitted UV-light, DTBMP, and Umemoto’s reagent in an effort to support the mechanistic proposal. To my surprise, the disaccharide was isolated in 68% yield (1.5:1 α:β) after one hour (Scheme 5.4). Tetrahydrothiophene 5.9 (Scheme 5.3) was isolated as a reaction by-product.

To begin optimization, we looked at the affect of the amount of acid on the thioglycoside donor (Figure 5.2). Lowering the equivalents of triflic acid to 10 mol % constituted an improvement (entry 2). After one hour, the desired disaccharide was
isolated in 87% yield (1.4:1 \(\alpha:\beta\)). This result was very promising and thus represented an irradiation and metal-free/thiophile-free catalytic activation of a bench stable thioglycoside. Prior to attempting entry 5, glycosylation experiments were simply concentrated in vacuo upon complete consumption of the glycosyl acceptor. Quenching the reaction with sat. NaHCO\(_3\) (aq), however, did not appear to have a beneficial effect on the reaction as the yield decreased to 61% with a negligible difference in the anomeric ratio (1.6:1 \(\alpha:\beta\)). This result suggests that the presence of triflic acid in the workup doesn’t cause epimerization at the anomeric carbon.

Interestingly, when trimethylsilyl trifluoromethylsulfonate (TMSOTf) was employed (instead of TfOH), 85% (1.4:1 \(\alpha:\beta\)) of the disaccharide was isolated (entry 3) presumably as a result of triflic acid generated \textit{in situ} via silylation of the alcohol by TMSOTf. Efforts to employ even milder acid sources were unsuccessful as attempts with 2-naphthol as a photoacid\(^8\) (irradiated with violet LEDs) showed no consumption of donor (entry 4). To probe the reactivity of the thioglycoside under these conditions at low temperatures, glycosylation was carried out at -20°C. After 5 hours of stirring at that temperature, there was no evidence of the desired product by TLC analysis (entry 7).
The same reaction was warmed to 0°C and yielded 70% of the disaccharide after 3 hours and slightly favored the beta anomer (1:1.1 α:β).

While entry 7 confirms that thioglycoside 5.1 performs better at warmer temperatures (0°C to r.t.) than at -20°C, this experiment also demonstrates the orthogonality of this thioglycoside donor to donors that react under acid catalysis at -20°C and lower. One can imagine activation of a trichloroacetimidate at a low temperature with a 4-aryl-3-butenylthioglycoside-bearing acceptor (Scheme 5.5). Upon warming to room temperature, activation of the side chain with the acid-catalyzed

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>X</th>
<th>Additive</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>α:β</th>
</tr>
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<tr>
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<td>TfOH</td>
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<td>n.a.</td>
<td>0.5</td>
<td>68</td>
<td>1.5:1</td>
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<tr>
<td>2</td>
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<td>10</td>
<td>n.a.</td>
<td>1</td>
<td>87</td>
<td>1.4:1</td>
</tr>
<tr>
<td>3</td>
<td>TMSOTf</td>
<td>10</td>
<td>n.a.</td>
<td>1</td>
<td>85</td>
<td>1.4:1</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2-naphthol</td>
<td>30</td>
<td>n.a.</td>
<td>1</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>TfOH</td>
<td>10</td>
<td>n.a.</td>
<td>1</td>
<td>61</td>
<td>1.6:1</td>
</tr>
<tr>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>TfOH</td>
<td>10</td>
<td>4Å MS</td>
<td>1</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>TfOH</td>
<td>10</td>
<td>n.a.</td>
<td>8</td>
<td>70</td>
<td>1:1.1</td>
</tr>
<tr>
<td>8&lt;sup&gt;e&lt;/sup&gt;</td>
<td>n.a.</td>
<td>n.a.</td>
<td>AW-MS</td>
<td>1</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>9&lt;sup&gt;e&lt;/sup&gt;</td>
<td>TfOH</td>
<td>10</td>
<td>AW-MS</td>
<td>2</td>
<td>75</td>
<td>1.5:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Irradiated with violet LEDs for 5hrs.  
<sup>b</sup> Reaction quenched with 5 ml aq. NaHCO<sub>3</sub>.  
<sup>c</sup> 150 mg 4Å molecular sieve.  
<sup>d</sup> Reaction stirred at -20 °C for 5 hrs. then warmed to 0 °C and stirred for 3 hrs.  
<sup>e</sup> Acid washed molecular sieves (AW-MS 150mg, crushed and heated to activate).

Figure 5.2 Glycosylation optimization
conditions would result in a trisaccharide. Orthogonality is an important aspect of oligosaccharide synthesis and therefore the observation as a result of entry 7 is noteworthy.

The effect of molecular sieves on the acid-promoted glycosylation was also tested. 150 mg of 4Å molecular sieves were added to the reaction, and after stirring for 1 hour, there was only a trace amount of the disaccharide (entry 6). This suggested that the molecular sieves effectively neutralized any triflic acid in previous visible-light glycosylation experiments. Further examination of crude $^1$H NMR spectra from Ch. 4 photochemical glycosylations indicated that 5.9 was not present in these examples. Alternatively, to capitalize on the beneficial water absorbing quality of molecular sieves without neutralization of triflic acid, acid-washed molecular sieves (AW-MS) were used. While the reaction took longer to complete (2 hours), the disaccharide was obtained in 75% yield ($\alpha:\beta$) in the presence of 4Å AW-500 MS (entry 9). A report demonstrating glycosylation with alkyl- and arylthioglycosides in the presence of NIS and AW-MS$^7$ prompted the experiment outlined in entry 8 in which only AW-MS were used as a potential acid catalyst. I discovered, however, that using only AW-MS was not an effective way to activate donor 5.1.

5.4 Establishment Of Substrate Scope
Several additional donors and acceptors were screened using the optimal conditions for glycosylation (4-aryl-3-butenylthioglycoside 5.1 (0.150 mmol) and a glycosyl acceptor (0.075 mmol), TfOH or TMSOTf (0.0150 mmol), and 1 mL dichloromethane) (Figure 5.2). These conditions were applied to several additional acceptors and donors. Donor 5.1 provided good to excellent yields of glycosides and disaccharides with relatively low stereoselectivity (entries 1-4, Figure 5.3).

Phtalimide-protected methyl-D-serine afforded 62% of the glycosidic product (entry 5) and favored the alpha anomer (3:1) while more challenging linkages using secondary acceptors were successful as disaccharide 5.13 (entry 2) was isolated in 85% yield with a 2:1 α:β ratio. Product 5.14 was formed in 88% yield when 5-hexen-1-ol was employed. It is important to note that this acceptor was not tolerated in the presence of the Umemoto’s reagent, DTBMP, and UV-light (Chapter IV). Another alkene-containing acceptor, cholesterol (entry 4), resulted in a 72% of 5.15 (1:1 α:β).

Given the reactivity that alkenes frequently exhibit to conditions that are also used to activate thioglycosides, this is a significant observation.\(^{7b}\)

With glycosyl donor 5.12 (acetate at the 2-position), neighboring group participation affords the beta anomer exclusively. C-2 acceptor (entry 7) showed a slight decrease in yield (79%) compared to donor 5.1 (85%, entry 2), however, only the beta anomer was isolated. Furthermore, entry 6 showed that acid sensitive protecting groups are also tolerated. Acetylated donor 5.11 (completely unreactive in the presence of Umemoto’s reagent, 4Å molecular sieves, and blue LEDs) unexpectedly afforded 25% of disaccharide 5.23 (entry 12). Consumption of the acceptor, however, was sluggish as
Unless otherwise stated, 0.15 mmol donor, 0.075 mmol acceptor, and 10 mol% TfOH in 1 mL DCM were stirred until acceptor was consumed via TLC. [a] 0.15 mmol donor, 0.15 mmol acceptor, 10 mol% TfOH in 1 mL DCM. [b] By-product isolated along with 5.11 from glycosylation with donor 5.11.

Figure 5.3 Glycosylation substrate scope
the reaction took 4 hours to complete. Under the reaction conditions, the nucleophilic C-6 acceptor was acetylated and glycoside 5.24 was isolated in 37% yield (entry 12a).

Benzoylated thioglycoside donor 5.10 was synthesized and employed in an effort to suppress the acylation of the acceptor while still demonstrating activation of a disarmed donor (glycosyl donor with electron withdrawing protecting groups). Efforts with 5.10 were successful and afforded the beta anomers of C-6 and C-2 disacccharides (entries 8 and 9). Entry 10 further showed the orthogonality of alkyl thioglycosides to these conditions as the disaccharide using a 1-octylthioglycoside acceptor was isolated in 76% yield. Activation of donor 5.10 in the presence of 1-octylthioglycoside is especially noteworthy and could lead to the development of a one-pot method for oligosaccharide synthesis as many methods exist for glycosylation with alkylthioglycoside donors (Scheme 5.1, for example). Though entry 11 was low yielding, this result was very encouraging. C-4 acceptors are among the least reactive and most challenging linkages to form. Attempts to generate the corresponding disaccharide with donors 5.1 and 5.12 were successful in that crude 1H NMR showed product formation. Purification, however, was extremely difficult. Disaccharide 5.22 was finally obtained in 21% yield from tetrabenzoyl donor 5.10 after silica gel chromatography and preparative TLC. Unsurprisingly, glycosylations with this disarmed donor and exceptionally unreactive acceptor took twice as long to go to completion but still performed much better than that tetraacetate thioglycoside 5.11.

A slight drawback to using donor 5.10 was the hydrolysis by-products formed over the course of the reaction (Scheme 5.6). These impurities had retention factors on TLC that were very similar to the desired products and made purification very
challenging. Isolation of the impurities and structural analysis of the NMR spectra confirmed that a mixture of the C-1 (5.25) and C-2 (5.26) hydroxyl products of hydrolysis were being formed. The desired disaccharides were obtained chromatographically through varying mixtures of DCM:EtOAC:Hexanes which still makes donor 5.10 an overall excellent choice for good yields and selectivity in spite of the by-products observed and difficult purification.

Scheme 5.6 By-products from glycosylation with tetrabenzoyl donor 5.10

5.5 Future Work

Efforts are ongoing to demonstrate scalability of the developed glycosylation method through a 1 mmol scale reaction (optimized procedure: 0.1504 mmol). In addition to this, optimization of a one-pot synthesis of a trisaccharide is currently underway. As previously discussed, we intend to exploit the low reactivity of the 4-aryl-3-butenylthioglycoside at -20°C and capitalize on the reactivity of trichloroacetimidates at that temperature. Therefore, we envision synthesis of a trisaccharide (5.30, Scheme 5.7) using compound 5.28 with the styrenic moiety as the glycosyl acceptor at low
temperature to form disaccharide 5.29. Subsequent warming to room temperature will enable the 4-aryl-3-butynylthioglycoside to form another glycosydic linkage with acceptor 5.2 using our method.

5.6 Conclusion

A method for remote activation of thioglycosides for O-glycosylation was developed using only a catalytic amount of triflic acid. The reaction conditions tolerated electroneutral alkene-containing acceptors as well as acid sensitive functional groups (acetonides) and very challenging linkages such as C-4 (5.22, Figure 5.3) were obtained albeit in low yields. In addition, benzoylated glycosyl donor 5.10 performed extremely well while also affording complete selectivity for the beta anomer along with donors 5.11 and 5.12. Orthogonality was demonstrated when the 1-octylthioglycoside acceptor (Entry 10, Figure 5.3) was employed and, furthermore, the low reactivity of the styrenic side chain at low temperature provides an opportunity for a one-pot synthesis of trisaccharides. Overall, this user-friendly method will potentially be useful for the synthesis of oligosaccharides.

5.7 Experimental

5.7.1 General Methods

Reagents were purchased from Sigma Aldrich and used as received. Flash column chromatography was performed using 60Å silica gel purchased from Sigma Aldrich. $^1$H NMR and $^{13}$C NMR spectroscopy were performed on a Bruker AV-400 and AV- 500 spectrometer. Mass spectra were obtained using an Agilent 6210 electrospray time-of-flight mass spectrometer. Analytical and preparative TLC were conducted on aluminum sheets (Merck, silica gel 60, F254). Compounds were visualized by UV
absorption (254 nm) and staining with anisaldehyde. 5 mL Pyrex micro reaction vessels (Supelco) were used in the glycosylation reactions. Deuterated solvents were obtained from Cambridge Isotope Labs. All solvents were purified according to the method of Grubbs.  

5.7.2 Procedures and Characterization

Synthesis of (E)-1-iodo-4-(4-methoxyphenyl)-3-buten

1.8 g (6.9 mmol) triphenylphosphine and 1.7 g (6.7 mmol) I$_2$ was dissolved in 26 mL CH$_2$Cl$_2$ and stirred for 10 minutes. 0.77 g (11 mmol) imidazole was added in one portion and the reaction stirred for another 10 minutes. A solution of 0.80 g (4.5 mmol) (E)-4-(4-methoxyphenyl)but-3-en-1-yl-p-toluenesulfonate in 5 mL CH$_2$Cl$_2$ was added to the reaction. 30 mL sat. Na$_2$S$_2$O$_5$ was added and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 30 mL) and the organic layers were dried over MgSO$_4$. Silica gel chromatography (5% EtOAc in hexanes) afforded 1.1 g (84%) of a yellow solid. Spectral data match that previously reported in literature. 

Synthesis of 5.11

0.70 mL (4.7 mmol) of DBU was added to 1.7 g (4.7 mmol) of 2,3,4,6-tetra-O-acetyl-1-mercapto-β-D-glucopyranoside in 10 mL toluene at -10°C. After 10 minutes, 1.3 g (4.7 mmol) of (E)-1-iodo-4-(4-methoxyphenyl)-3-buten in 3.7 mL toluene was
added dropwise. The reaction was stirred at -10°C until completed via TLC. 20 mL of H₂O was added to quench the reaction. The resulting solution was then extracted with CH₂Cl₂ (2 x 58 mL). The organic layer was further diluted with 58 ml CH₂Cl₂, washed with 43 mL 1M H₂SO₄, 43 mL sat. NaHCO₃ (aq), and 43 mL sat. NaCl (aq) then dried over Na₂SO₄. Silica gel chromatography (gradient run from 15% EtOAC in hexanes to 25% EtOAc in hexanes) afforded 1.9 g (77%) of a white solid. Spectral data matched that previously reported in literature.¹⁴

Synthesis of 5.1

![Chemical structure]

To a solution of 1.9 g (3.6 mmol) 5.11 in 44.4 mL MeOH was 1.9 mL (1.9 mmol) of 1M NaOMe added. The reaction was stirred overnight at room temperature. Solvent was removed in vacuo and the resulting solid was redissolved in 36.0 mL DMF. To this solution was added 0.261 g (0.706 mmol) of TBAI followed by 1.1 g (26 mmol) of 60% oil dispersed NaH at 0°C. After 30 minutes at this temperature, 2.8 mL (24 mmol) of benzyl bromide was added dropwise. The reaction warmed slowly to room temperature and stirred overnight until complete via TLC. At 0°C the reaction was quenched with 45 mL sat. NH₄Cl (aq.) then extracted with Et₂O (2 x 45 mL), washed with 45 mL sat. NaCl (aq.), and dried over Na₂SO₄. Silica gel chromatography (gradient run from 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded 0.960 g (37%) of a white solid. Spectral data matched that previously reported in literature.¹⁴

Synthesis of 5.10
See synthesis of 5.11 for procedure. Started with 0.48 mL (3.2 mmol) DBU, 1.8 g (2.9 mmol) tetra-O-benzoyl-1-mercapto-β-D-glucopyranoside in 8 mL toluene, and 0.83 g (2.5 mmol) (E)-4-(4-methoxyphenyl)but-3-en-1-yl-p-toluenesulfonate in 4.8 mL toluene. Silica gel chromatography (gradient run from 35% DCM in hexanes to 80% DCM in hexanes then 20% EtOAc in hexanes) afforded 0.283 g (15%) α (off-white solid) and 1.07 g (55%) β (white solid) of 5.10. α anomer: $^1$H NMR (500 MHz, CDCl$_3$) δ 8.04 (d, $J = 6.9$ Hz, 2H), 7.96 (dd, $J = 11.8$, 7.0 Hz, 4H), 7.88 (d, $J = 6.9$ Hz, 2H), 7.54 – 7.45 (m, 3H), 7.42 (t, $J = 7.5$ Hz, 1H), 7.36 (ddd, $J = 8.4$, 6.9, 5.1 Hz, 6H), 7.28 (t, $J = 7.8$ Hz, 2H), 7.16 (d, $J = 8.8$ Hz, 2H), 6.79 (d, $J = 8.7$ Hz, 2H), 6.28 (d, $J = 16.0$ Hz, 1H), 6.09 (t, $J = 9.8$ Hz, 1H), 5.98 (d, $J = 5.8$ Hz, 1H), 5.93 (dt, $J = 15.8$, 7.0 Hz, 1H), 5.68 (t, $J = 9.8$ Hz, 1H), 5.52 (dd, $J = 10.2$, 5.7 Hz, 1H), 4.90 (ddd, $J = 10.2$, 5.7, 2.7 Hz, 1H), 4.61 (dd, $J = 12.2$, 2.8 Hz, 1H), 4.52 (dd, $J = 12.2$, 5.8 Hz, 1H), 3.77 (s, 3H), 2.77 (ddd, $J = 12.8$, 8.2, 6.5 Hz, 1H), 2.68 (dt, $J = 12.8$, 7.6 Hz, 1H), 2.51 – 2.42 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 166.31, 165.80, 165.61, 165.50, 159.08, 133.65, 133.37, 133.30, 131.26, 130.19, 130.18, 130.08, 129.89, 129.87, 129.78, 129.23, 129.02, 128.96, 128.65, 128.61, 128.58, 128.48, 127.40, 125.62, 114.04, 82.54, 71.89, 71.05, 69.74, 68.46, 63.29, 55.43, 33.12, 30.25. HRMS m/z Calcd for C$_{45}$H$_{40}$NaO$_{10}$S $[M+Na]^+$ 795.2234, found 795.2250. [α]$_D^+ = +79.2$ (c = 1, DCM). β anomer: $^1$H NMR (500 MHz, CDCl$_3$) δ 8.00 (d, $J = 7.2$ Hz, 2H), 7.93 (d, $J = 7.2$ Hz, 2H), 7.89 (d, $J = 7.2$ Hz, 2H), 7.80
(d, J = 7.2 Hz, 2H), 7.48 (q, J = 7.3 Hz, 3H), 7.40 (t, J = 7.4 Hz, 1H), 7.37 – 7.29 (m, 6H), 7.24 (d, J = 7.5 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.27 (d, J = 15.8 Hz, 1H), 6.00 – 5.88 (m, 2H), 5.66 (t, J = 9.8 Hz, 1H), 5.56 (t, J = 9.7 Hz, 1H), 4.88 (d, J = 10.0 Hz, 1H), 4.64 (dd, J = 12.2, 3.0 Hz, 1H), 4.48 (dd, J = 12.2, 5.5 Hz, 1H), 4.21 – 4.13 (m, 1H), 3.78 (s, 3H), 2.93 – 2.85 (m, 1H), 2.85 – 2.76 (m, 1H), 2.55 – 2.43 (m, 2H). 13C NMR (126 MHz, CDCl3) δ 166.30, 166.00, 165.41, 159.08, 133.68, 133.52, 133.46, 133.34, 131.09, 130.31, 130.09, 130.05, 129.94, 129.93, 129.76, 129.33, 128.99, 128.95, 128.63, 128.61, 128.59, 128.51, 127.42, 125.88, 114.07, 84.24, 76.57, 74.29, 70.81, 69.81, 63.48, 55.48, 33.59, 30.28. HRMS m/z Calcd for C45H40NaO10S [M+Na]+ 795.2234, found 795.2267. [α]D = +4.4 (c = 1, DCM).

Synthesis of 5.12

See synthesis of 5.11 for procedure. Started with 0.10 mL (0.67 mmol) DBU, 0.320 g (0.629 mmol) 2-O-acetyl-3,4,6-tri-O-benzyl-1-deoxy-1-mercaptop-β-D-glucopyranoside10 in 2 mL toluene, and 0.230 g (0.692 mmol) (E)-4-(4-methoxyphenyl)but-3-en-1-yl-p-toluenesulfonate9 in 1 mL toluene. Silica gel chromatography (gradient run from 15% DCM in hexanes to 20% DCM in hexanes, then 7.5% EtOAc in hexanes) afforded 0.299 g (71%) of a white solid. Spectral data matched that previously reported in literature.14

Representative procedure for optimized glycosylation conditions:

A 5 mL Pyrex reactor vial was charged with the glycosyl donor (1 equiv., 0.150
mmol), the glycosyl acceptor (0.5 equiv., 0.0752 mmol), and 1 mL of dry dichloromethane under nitrogen atmosphere. The reaction vessel was vacuum-purged and backfilled twice. Then, TfOH (0.1 equiv., 0.015 mmol) was added via gastight syringe. The reaction stirred at room temperature until consumption of acceptor was observed via TLC. Triethylamine (0.2 equiv., 0.030 mmol) was then added to the reaction mixture and the crude products were concentrated and then purified by gradient silica gel chromatography to afford the desired glycosides.

Determination of anomeric ratios:

The anomeric ratio (α:β) was determined based on the integration of key resonances identified with the assistance of published $^1$H NMR data. In the cases where spectral data was unavailable, the anomeric products were separated with silica gel chromatography or preparative TLC.

Synthesis of 5.4

![Diagram of 5.4](attachment:image.png)

Started with 0.108 g (0.151 mmol) of glycosyl donor 5.1, 0.035 g (0.075 mmol) of methyl-2,3,4-tri-O-benzyl-α-D-glucopyranoside, 1.3 µL (0.015 mmol) TfOH, in 1 mL of DCM. Silica gel chromatography (gradient run from 10% EtOAc in hexanes to 15% EtOAc in hexanes) afforded 0.065 g (88%, 1.4:1 α:β) of a white solid. Ratio determined via $^1$H NMR analysis of the α:β mixture. Spectral data matched that previously reported.
in literature.\textsuperscript{11}

Synthesis of \textbf{5.13}

\begin{center}
\includegraphics[width=0.5\textwidth]{5.13.png}
\end{center}

Started with 0.108 g (0.151 mmol) of glycosyl donor \textbf{5.1}, 0.035 g (0.075 mmol) of methyl-3,4,6-tri-O-benzyl-\(\alpha\)-D-glucopyranoside, 1.3 \(\mu\)L (0.015 mmol) TfOH, in 1 mL of DCM. Silica gel chromatography (gradient run from 1\% Et\(_2\)O in DCM to 15\% Et\(_2\)O in DCM) afforded 0.063 g (85\%, 2:1 \(\alpha\):\(\beta\)) of a colorless oil. Anomers were separated and weighed to determine anomeric ratio. Spectral data matched that previously reported in literature.\textsuperscript{15}

Synthesis of \textbf{5.14}

\begin{center}
\includegraphics[width=0.5\textwidth]{5.14.png}
\end{center}

Started with 0.108 g (0.151 mmol) of glycosyl donor \textbf{5.1}, 9.0 \(\mu\)L (0.07 mmol) of 5-hexen-1-ol, 1.3 \(\mu\)L (0.015 mmol) TfOH, in 1 mL of DCM. Silica gel chromatography (gradient run from 5\% EtOAc in hexanes to 25\% EtOAc in hexanes) afforded 0.041 g (88\%, 1:1.5 \(\alpha\):\(\beta\)) of a colorless oil. Ratio determined via \(^1\)H NMR analysis of the \(\alpha\):\(\beta\) mixture. Spectral data matched that previously reported in literature.\textsuperscript{16}

Synthesis of \textbf{5.15}
Started with 0.108 g (0.151 mmol) of glycosyl donor 5.1, 0.029 g (0.075 mmol) of (3β)-cholest-5-en-3-ol, 1.3 µL (0.015 mmol) TfOH, in 1 mL of DCM. Silica gel chromatography (5% EtOAc in hexanes) afforded 0.049 g (72%, 1:1 α:β) of an off-white solid. Ratio determined via 1H NMR analysis of the α:β mixture. Spectral data matched that previously reported in literature.17

Synthesis of 5.16

Started with 0.108 g (0.150 mmol) of glycosyl donor 5.1, 0.019 g (0.076 mmol) of (R)-methyl 2-(1,3-dioxoisoiindolin-2-yl)-3-hydroxypropanoate, 1.3 µL (0.015 mmol) TfOH, in 1 mL of DCM. Preparative TLC (1:4:6 DCM:EtOAc:hexanes) afforded 0.036 g (62%, 3:1 α:β) of an off-white solid. Ratio determined via 1H NMR analysis of the α:β ratio, 1H NMR (400 MHz, CDCl3) δ 7.77 (dd, J = 5.5, 3.1 Hz, 2H), 7.72 (dd, J = 5.5, 3.1 Hz, 0.6H, β anomer), 7.65 – 7.59 (m, 3H), 7.38 – 7.20 (m, 23H), 7.19 – 7.15 (m, 1H), 7.14 – 7.09 (m, 1H), 7.09 – 7.00 (m, 3H), 6.91 (d, J = 6.8 Hz, 0.6H, β anomer), 5.29 (dd, J = 10.7, 4.4 Hz, 0.3H, β anomer), 5.24 (dd, J = 9.2, 5.4 Hz, 1H), 4.93 (d, J = 3.5 Hz, 1H), 4.82 (d, J = 10.9 Hz, 1H), 4.80 – 4.62 (m, 6H), 4.62 – 4.40 (m, 3H), 4.39 – 4.21 (m, 5H), 3.81 –
3.75 (m, 1H), 3.75 (m, 2H), 3.73 (s, 3H), 3.62 – 3.52 (m, 2H), 3.52 – 3.47 (m, 3H), 3.45 – 3.32 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.98, 167.57, 138.97, 138.57, 138.50, 138.09, 134.31, 131.99, 128.56, 128.52, 128.50, 128.45, 128.41, 128.23, 128.11, 128.05, 127.95, 127.92, 127.87, 127.82, 127.69, 127.56, 123.75, 103.80, 96.61, 81.85, 79.87, 77.43, 75.74, 74.89, 73.71, 73.62, 73.03, 70.93, 68.25, 64.31, 53.04, 51.16. HRMS m/z Calcd for C$_{46}$H$_{45}$NaNO$_{10}$ [M+Na]$^+$ 794.2985, found 794.2966.

Synthesis of 5.17

![Chemical structure of 5.17]

Started with 0.101 g (0.151 mmol) of glycosyl donor 5.12, 0.020 g (0.077 mmol) of 1,2,3,4-di-O-isopropylidene-D-galactopyranose, 1.3 µL (0.015 mmol) TfOH, in 1 mL of DCM. Silica gel chromatography (gradient run from 7.5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded 0.037 g (65%, β only) of a colorless oil. Spectral data matched that previously reported in literature.$^{13}$

Synthesis of 5.18

![Chemical structure of 5.18]

Started with 0.101 g (0.151 mmol) of glycosyl donor 5.12, 0.035 g (0.075 mmol)
of methyl-3,4,6-tri-O-benzyl-α-D-glucopyranoside, 1.3 µL (0.015 mmol) TfOH, in 1 mL of DCM. Silica gel chromatography (gradient run from 18% EtOAc in hexanes to 20% EtOAc in hexanes) afforded 0.056 g (79%, β only) of 5.18. Spectral data matched that previously reported in literature.12

Synthesis of 5.19

Started with 0.116 g (0.150 mmol) of glycosyl donor 5.10, 0.070 g (0.151 mmol) of methyl-2,3,4-tri-O-benzyl-α-D-glucopyranoside, 1.3 µL (0.015 mmol) TfOH, in 1 mL of DCM. Preparative TLC (6:1:3 DCM:EtOAc:hexanes) afforded 0.073 g (46%, β only) of a white solid. Spectral data matched that previously reported in literature.19

Synthesis of 5.20

Started with 0.116 g (0.150 mmol) of glycosyl donor 5.10, 0.070 g (0.151 mmol) of methyl-3,4,6-tri-O-benzyl-α-D-glucopyranoside, 1.3 µL (0.015 mmol) TfOH, in 1 mL of DCM. Preparative TLC (5:1:4 DCM:EtOAc:hexanes) afforded 0.074 g (47%, 1.4:1 α:β) of a white solid. Spectral data matched that previously reported in literature.19
Synthesis of 5.21

Started with 0.116 g (0.150 mmol) of glycosyl donor 5.10, 0.044 g (0.076 mmol) of octyl β-D-1-thio-2,3,4-tri-O-benzylglucopyranoside, 1.3 µL (0.015 mmol) TfOH, in 1 mL of DCM. Preparative TLC (30% EtOAc in hexanes) afforded 0.067 g (76%, β only) of a white solid. 1H NMR (400 MHz, CDCl₃) δ 8.01 (d, J = 7.2 Hz, 2H), 7.91 (t, J = 8.6 Hz, 4H), 7.82 (d, J = 7.3 Hz, 2H), 7.55 – 7.38 (m, 5H), 7.38 – 7.21 (m, 20H), 7.14 (d, J = 7.6 Hz, 2H), 5.86 (t, J = 9.6 Hz, 1H), 5.68 (t, J = 9.7 Hz, 1H), 5.56 (t, J = 7.9 Hz, 1H), 4.91 (d, J = 7.8 Hz, 1H), 4.89 – 4.81 (m, 2H), 4.73 (d, J = 11.0 Hz, 1H), 4.65 (t, J = 10.9 Hz, 3H), 4.54 – 4.47 (m, 1H), 4.45 (d, J = 11.0 Hz, 1H), 4.33 (d, J = 9.7 Hz, 1H), 4.14 (d, J = 10.7 Hz, 1H), 4.07 (dt, J = 8.4, 4.4 Hz, 1H), 3.75 (dd, J = 11.2, 5.1 Hz, 1H), 3.57 (t, J = 8.6 Hz, 1H), 3.42 (m, 2H), 3.31 (t, J = 9.3 Hz, 1H), 2.64 (dt, J = 13.7, 6.9 Hz, 1H), 2.59 – 2.49 (m, 1H), 1.63 – 1.51 (m, 4H), 1.40 – 1.20 (m, 8H), 0.88 (t, J = 6.7 Hz, 3H). 13C NMR (126 MHz, CDCl₃) δ 166.32, 166.02, 165.36, 165.18, 138.70, 138.22, 138.14, 133.60, 133.42, 133.37, 133.30, 130.04, 129.99, 129.97, 129.80, 129.48, 129.07, 129.04, 128.63, 128.60, 128.58, 128.57, 128.51, 128.03, 128.01, 127.90, 127.81, 101.47, 86.69, 85.10, 81.82, 78.83, 77.90, 75.79, 75.63, 75.05, 73.20, 72.40, 72.11, 69.92, 68.76, 63.36, 32.07, 30.77, 29.80, 29.47, 28.99, 22.90, 14.33. HRMS m/z Calcd for C₆₉H₇₂NaO₄S [M+Na]⁺ 1179.4535, found 1179.4559. [α]D = +15.9 (c = 1, DCM).

Synthesis of 5.22
Started with 0.116 g (0.150 mmol) of glycosyl donor 5.10, 0.035 g (0.075 mmol) of methyl-2,3,6-tri-O-benzyl-α-D-glucopyranoside, 1.3 µL (0.015 mmol) TfOH, in 1 mL of DCM. Preparative TLC (5:1:4 DCM:EtOAc:hexanes) afforded 0.016 g (20%, β only) of a white solid. Spectral data matched that previously reported in literature.²⁰

Synthesis of 5.23 and 5.24

Started with 0.079 g (0.151 mmol) of glycosyl donor 5.11, 0.035 g (0.075 mmol) of methyl-2,3,4-tri-O-benzyl-α-D-glucopyranoside, 1.3 µL (0.015 mmol) TfOH, in 1 mL of DCM. Silica gel chromatography (gradient run from 1% EtOAc in DCM to 5% EtOAc in DCM) afforded 0.015 g (25%, β only) of 5.23 (white solid) and 0.014 g (37%) of 5.24 (white solid). Spectral data matched that previously reported in literature.²⁰,²¹

Synthesis of 2-(4-methoxyphenyl)tetrahydrothiophene

The compound was purified from early-eluting column chromatography fractions from an O-glycosylation procedure using preparative TLC with hexanes as eluent.
Spectral data matched that previously reported in literature\textsuperscript{22}.

5.8 References


APPENDIX A: COPYRIGHT RELEASES

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TERMS AND CONDITIONS

Nov 13, 2017

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APPENDIX B: NMR SPECTRA OF COMPOUNDS FOUND IN CHAPTER 2
\[
\text{Tz}^2\text{NH} \quad 2.9
\]
$\text{Tz}^9\text{NH} \overset{\text{Ph}}{\text{---}}$

2.10

$^1\text{H NMR (CDCl}_3)$
Tz²N — Ph
CH₃

2.15

¹H NMR (CDCl₃)
1H NMR (CDCl3)
O

OTz°

2.22

$^{1}H$ NMR (CDCl₃)
$^{13}$C NMR (CDCl$_3$)

13C NMR (CDCl3)
\[ ^1H \text{ NMR (CDCl}_3) \]
H NMR (CDCl3)

TsHN

2.36
TsHN

2.36

$^{13}$C NMR (CDCl$_3$)
TsHN

N

O

2

S

N

2.37

1H NMR (CDCl3)
$\text{TsHN}$

2.37

$\text{N}$

$\text{O}_2\text{SN}$

$\text{H}$

$\text{13C NMR (CDCl3)}$
$\text{TsHN} \quad \text{OH} \quad \text{Ph}$

$2.38$

$1^H$ NMR (CDCl$_3$)

Frequency (f1) in ppm.

Field strength (ppm): 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5.

Intensities (arbitrary units): 0, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000.
**$^1$H NMR (CDCl$_3$)**

The spectrum shows a chemical shift of 2.46 ppm for the hydroxyl group (OH). The structure of the compound includes a nitrogen (N) and a tosyl (Ts) group, consistent with the molecular structure labeled on the left of the figure.
$^{13}$C NMR (CDCl$_3$)

TsN$\overbrace{\text{CH}_3}^{2.51}$Ph

OH
$^{1}H$ NMR (CD$_3$OD)

TsHN

OH

2.52
$^{13}$C NMR (CD$_3$OD)

TsHN

$\text{OH}$

OH

2.52
$\text{TsHN}^\text{O}$

2.53

$^1\text{H NMR (CDCl3)}$
$^{13}$C NMR (CDCl$_3$)
$\text{H NMR (CDCl}_3\text{)}$
APPENDIX C: NMR SPECTRA OF COMPOUNDS FOUND IN CHAPTER 4

1H NMR (CDCl3)
$^{1}$H NMR (CDCl$_3$)
\[ ^1H \text{ NMR (CDCl3)} \]

- TsO
- 4.17
$^{13}$C NMR (CDCl$_3$)

TsO$\text{-CH=CH-}$Cl

4.17
4.19

\[ \text{1H NMR (CDCl3)} \]
\[ \text{I} \text{C} \text{Cl} \]

4.19

\[ ^{13}\text{C} \text{NMR (CDCl}_3) \]

\begin{align*}
\text{f1 (ppm)} & \quad 200 & 190 & 180 & 170 & 160 & 150 & 140 & 130 & 120 & 110 & 100 & 90 & 80 & 70 & 60 & 50 & 40 & 30 & 20 & 10 & 0 & -10 \\
\text{f2 (ppm)} & \quad 12000 & 11000 & 10000 & 9000 & 8000 & 7000 & 6000 & 5000 & 4000 & 3000 & 2000 & 1000 & 0 & -10 & -20 & -30 & -40 & -50 & -60 & -70 & -80 & -90 & -100 \\
\end{align*}
$^1$H NMR (CDCl$_3$)

![Chemical structure](image)

- $OAc$
- $O$
- $O$
- $O$
- $O$
- $Me$
- $4.23$

**Chemical Shifts:**
- 0.0 - 9.0 ppm

**Intensities:**
- Varied across the spectrum

**Integration:**
- Various peaks indicate different chemical shifts and integrations.
$^{13}$C NMR (CDCl3)

4.24
$^{1}H$ NMR (CDCl$_3$)
$^{13}$C NMR (CDCl$_3$)
$^1$H NMR (CDCl$_3$)

![Chemical Structure](attachment:image.png)

4.26
$^{13}$C NMR (CDCl$_3$)
\[^1\text{H} \text{NMR (CDCl}_3\text{)}\]

![Chemical Structure](image)

\[\text{4.27} \]

\[\text{OCH}_3\]
$^1$H NMR (CDCl$_3$)

4.28
\[13\text{C NMR (CDCl}_3\text{)}\]

![Chemical Structure](image)

**4.29**
$^{13}$C NMR (CDCl$_3$)
4.32

1H NMR (CDCl3)

f1 (ppm)

4500
4000
3500
3000
2500
2000
1500
1000
500
0

0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0
APPENDIX D: NMR SPECTRA OF COMPOUNDS FOUND IN CHAPTER 5

5.10-α

BzO

OBz

BzO

BzO

O

S

O

OBz

OCH₃

1H NMR (CDCl₃)
$\begin{align*}
\text{5.10-} & \alpha \\
\text{13C NMR (CDCl3)}
\end{align*}$
\[ 13^\text{C} \text{NMR (CDCl}_3) \]
$^{1}$H NMR (CDCl$_3$)
AV 400-3

$1^\text{H}$ NMR (CDCl3)

5.13-$\alpha$
1H NMR (CDCl3)

KD-III-81(1)
F1c.1.fid

KD-III-81(1)
F1c
(C-2 Acceptor)

AV 400-3

1H NMR

5.13-β
$^1$H NMR (CDCl$_3$)

![NMR spectrum image]

Chemical structure:

- Benzyl ethers (BnO)
- Oxygen (O)
- Fatty acid chain

5.14 ppm
1H NMR (CDCl3)
$\text{H NMR (CDCl}_3\text{)}$
$^1$H NMR (CDCl$_3$)

Chemical shifts (in ppm):

- 5.18
$^1$H NMR (CDCl$_3$)

5.19
13C NMR (CDCl3)
$^1$H NMR (CDCl$_3$)
The image contains a chemical structure with a labeled peak at 5.9 ppm in a 
$^1$H NMR spectrum recorded in CDCl$_3$. The compound contains a sulfur atom, a benzene ring, and a methoxy (OMe) group.
VITA

Kristina Danielle Deveaux-Lacey was born on the island of Grand Bahama in the beautiful country of The Bahamas to Wentworth C. Deveaux and Angela P. Deveaux. She is married to Brandon G. Lacey. After graduating high school, she began her studies at Georgia Southern University in Statesboro, Georgia. In 2012 she earned her Bachelor’s degree in Chemistry and completed her honors thesis under the tutelage of Dr. Karelle Aiken. She then journeyed to Baton Rouge, Louisiana and joined the Department of Chemistry’s doctoral program at Louisiana State University. Since January 2013 she has been a part of Dr. Justin R. Ragain’s research group. Currently a PhD candidate, Kristina will be awarded with a doctoral degree in Chemistry at the December 2017 commencement ceremony.