# Selectivity of Hydrosilylative Ether Cleavage by Cationic Bis(phosphine) Iridium Complexes

By

Caleb Andrew Hampton Jones

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Approved:

Nathan D. Schley, Ph.D.

Janet E. Macdonald, Ph.D.

Timothy P. Hanusa, Ph.D.

Paul E. Laibinis, Ph.D.

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## List of Abbreviations

| | |
|---|---|
| $(Et_3Si)_2O$ | hexamethyldisiloxane |
| $[(Et_3Si)_2H]B(C_6F_5)_4$ | (triethylsilylium)triethylsilane tetrakis(pentaflourophenyl)borate |
| $[Ph_3C]BAr^F{}_4$ | triphenylcarbenium tetrakis[3,5-bis(trifuoromethyl)phenyl]borate |
| °C | degrees celcius |
| 2° | secondary |
| 10-CSA | (1S)-(+)-10-camphorsulfonic acid |
| $Ac_2O$ | acetic anhydride |
| AcCl | acetyl chloride |
| APCI | atmospheric pressure chemical ionization |
| $BAr^F{}_3$ | tris[3,5-bis(trifluoromethyl)phenyl]borate |
| $BAr^F{}_4$ | tetrakis[3,5-bis(trifluoromethyl)phenyl]borate |
| BCF | tris(pentafluorophenyl)borane |
| Bn | benzyl |
| Bpin | pinacol borane |
| COD / cod | cyclooctadiene |
| CPME | cyclopentyl methyl ether |
| CyH | cyclohexane |
| DCM | dichloromethane |
| DI | deionized |
| DIB | (diacetoxyiodo)benzene |
| DMAP | dimethylamino pyridine |
| DMF | dimethyl formamide |
| DMSO | dimethyl sulfoxide |
| equiv. | equivalents |
| EtOAc | ethyl acetate |
| FG | functional group |
| FLPs | Frustrated Lewis Pairs |
| g | gram(s) |
| h | hour |
| $H_2SiEt_2$ | diethylsilane |
| HRMS | high resolution mass spectrometry |
| $HSiEt_2Me$ | diethyl(methyl)silane |
| $HSiEt_3$ | triethylsilane |
| $HSi^tBuMe_2$ | tert-butyl-dimethylsilane |
| $^iPr_2NEt$ | diisopropyl(ethyl)amine |
| M | molar |
| MeI | methyl iodide |
| MeMgBr | methyl magnesium bromide |

| | |
|---|---|
| MeOH | methanol |
| MHz | megahertz |
| min | minutes |
| mL | milliliters |
| mmol | millimol |
| MTBE | methyl tert-butyl ether |
| NMR | nuclear magnetic resonance |
| OAc | acetate |
| OMe | methoxy |
| OTf | trifluoromethanesulfonate |
| Ph | Phenyl |
| PhMe | toluene |
| $PPh_3$ | triphenyl phosphine |
| ppm | parts per million |
| Q-TOF | quadrupole Time-of-Flight |
| $SOCl_2$ | thionyl chloride |
| TBAF | tetrabutylammonium flouride |
| TBDPS | *tert*-butyl-diphenylsilane |
| TBDPSCl | *tert*-butylchlorodiphenylsilane |
| $^t$Bu | *tert*-butyl |
| TES-OCy | triethylsilyl cyclohexyl ether |
| THF | tetrahydrofuran |
| TIPS | tri-isopropylsilane |
| TLC | thin layer chromatography |
| TMDS | 1,1,3,3-tetramethyldisiloxane |
| Tol | toluene |
| Ts | p-toluenesulfonyl |

# Chapter 1: Introduction to Hydrosilylative Reductions via Electrophilic Silane

## I. Scope of this Work

This dissertation outlines research on cationic bis(phosphine) iridium catalysis for the hydrosilylative reduction of ethereal C-O bonds. Chapter 1 provides a brief introduction on the subject of heterolytic silane Si–H bond cleavage mediated by both borane and iridium catalysts. Chapter 2 focuses on the reactivity of two cationic bis(phosphine) iridium complexes for C-O bond cleavage of unsymmetric ethereal substrates. The chapter addresses four main topics: regioselectivity of unsymmetric ether reduction, functional group compatibility of benzyl ether cleavage, the determinants of selectivity in 6-membered carbocyclic methyl ether cleavage, and mechanistic investigations through comparative NMR studies. Chapter 3 then expands the cyclohexyl methyl ether cleavage research for carbohydrates. The chapter begins with a brief review of the field of carbohydrate synthesis including methods of methyl ether cleavage in carbohydrates. The remainder of the chapter discusses our efforts to improve this methodology with the use of phenyl glycosides. Chapter 4 provides an outlook on future work on the demethylation of O-methyl phenyl glycosides, specifically an investigation aimed at improving the functional group compatibility of the process. This dissertation ends with a summary chapter outlining the significant discoveries in each chapter.

## II. Hydrosilylative Cleavage of Ethereal complexes

Alkyl ethers are a robust class of organic functional groups that typically require rigorous conditions for C-O bond cleavage. Traditional means of ethereal cleavage require the use of strong acids[68] or the use of hydrogenolysis over heterogenous catalysts.[69] Though for more complex systems these methods may not be suitable for complex compounds such as carbohydrate derivatives.[70]

Recently, the use of silanes for reductive ether cleavage has been developed. Typically, a catalyst will promote Si–H heterolysis to generate a silyloxonium ion and a reducing hydride. Past examples of this transformation have been promoted by perfluoroaryl borane catalysts as well a single example of an iridium catalyst.[46,71-77] Within the following chapters we expand on the use of bisphosphine irdium catalysts for C–O bond cleavage in ethers. This system offers a simpler synthesis than past examples as well avenues for greater tunability than their borane analogs.[78]

**III. Heterolytic Bond Cleavage:**

During the course of a reaction covalent bonds can be cleaved homolytically or heterolytically. In homolytic cleavage each atom receives an electron (Figure 1.1).[1] This type of bond cleavage is observed in radical transformations such as the photolytic cleavage of halogen bonds,[2-4] or the thermolysis of a peroxide,[5-7] and is often the initiating step in radical chain reactions. When both electrons in a bond are distributed to a single atom on cleavage, the process is described as a heterolytic cleavage (Figure 1.1).[1,8] Heterolytic cleavage is common in substitution,[9] and elimination[10] reactions, and is the basis for proton transfer chemistry. The focus of this dissertation will be on the heterolytic cleavage of silanes that have been activated with a cationic iridium catalyst to generate a metal hydride and silylium ion pair.

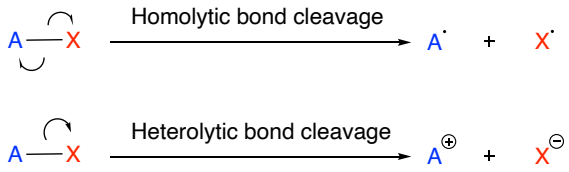



Figure 1.1: Homolytic and heterolytic bond cleavage

**IV. Sigma complexes**

Sigma complexes in organometallic chemistry are compounds that are formed by the donation of electrons from a σ-bond to a $d_\sigma$ orbital (Figure 1.2). Of these complexes, molecules

with a H–X bond (X = H, C, Si, Sn, B, or Ge) are the most common.[11-18] This orientation of the bound molecule and the metal center creates a 2-electron-3-center bond where two electrons are shared between the atoms contributing to the sigma bond.[19] For example the donation of electrons from a dihydrogen ($H_2$) σ-bond gives a sigma complex where the $H_2$ molecule serves as a dative ligand. In this geometry the metal donates electrons from its $d_\pi$ orbital into the hydrogen σ* orbital (Figure 1.2) which produces a stabilizing effect for the sigma complex.[11, 19]

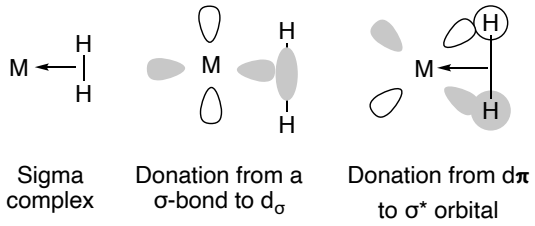
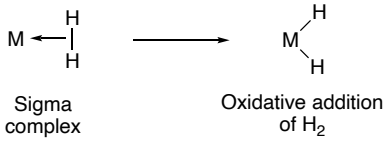



Figure 1.2: Binding motif of sigma complexes

However, if the metal complex is sufficiently electron rich, backdonation of $d_\pi$ electron density into σ* of $H_2$ results in the cleavage of the corresponding σ-bond, forming a metal dihydride via oxidative addition (Scheme 1.1).[19] Sigma complexes of electron poor metal complexes, such as cationic complexes, can polarize the $H_2$ bond. This polarization of dihydrogen increases its acidity allowing it to be deprotonated. Deprotonation of a bound $H_2$ ligand results in $H_2$ heterolysis to give the conjugate acid of the base and a metal hydride (Figure 1.3).[20-22]




Scheme 1.1: Oxidative addition of $H_2$ due to strong backbonding

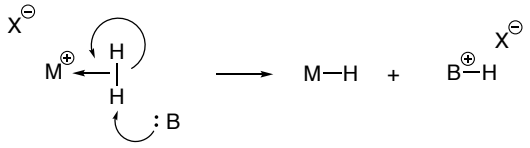
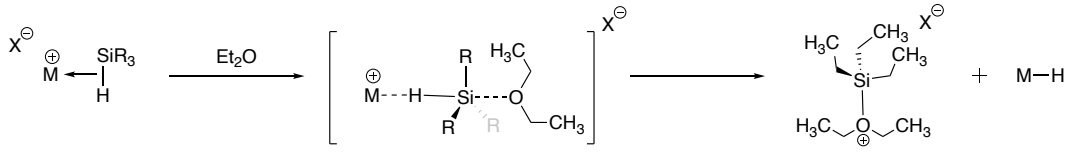



Figure 1.3: Deprotonation of molecular hydrogen bound to a cationic metal complex

## V. Silane Si-H Heterolysis

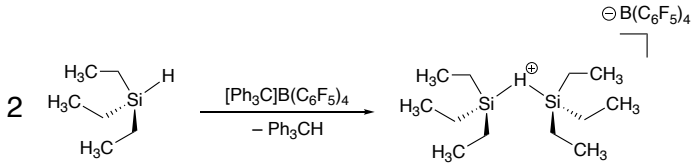
There are three common methods employed for Si-H heterolysis for its use in reduction chemistry: hydride abstraction, activation via a borane catalyst, and activation via a transition metal catalyst. The use of borane catalysts for hydrosilylative reductions have been in the literature since the late 1990s.[23] However, these catalysts have limited tunability as their reactivity is dependent on the substituents bound to the boron atom. The electron richness of the borane determines both the electrophilicity of the silane and the hydricity of the borohydride formed on Si-H heterolysis.[24,25]

This work will focus on iridium catalysis for generating reactive electrophilic silane species. Sigma complexes formed with a tertiary silane ($R_3SiH$) can be also heterolytically cleaved by an attack of a nucleophile.[13, 26] One example is the nucleophilic attack of diethyl ether on a cationic metal complex shown below (Scheme 1.2). Diethyl ether attacks the silane via backside attack which donates the oxygen atom lone pair electrons to the Si-H σ* orbital to give a silyloxonium ion and a metal hydride.[27]




Scheme 1.2: Nucleophilic attack of diethyl ether to a metal silane complex

*V.I. Generation of Silylinium ions via Hydride Abstraction*




Scheme 1.3: Hydride abstraction of triethylsilane by trityl $B(C_6F_5)_4$

The simplest example of silane heterolysis can be observed by treatment of a hydrosilane with a triphenylcarbenium salt of a non-coordinating ion such as $[B(C_6F_5)_4]^-$. Hydride abstraction of the silane in solution gives a silylium ion which forms an adduct with another silane molecule to form a silane-stabilized silylium ion (Scheme 1.3).[28, 29] The resulting silylium ion can then react with a Lewis base. Free hydrosilane in the solution can then reduce the resulting salt regenerating the silylium ion.[30, 31] A proposed mechanism for the reduction of tosyl-imines is provided below as a representative general reduction by a silylnium ion (Figure 1.4).

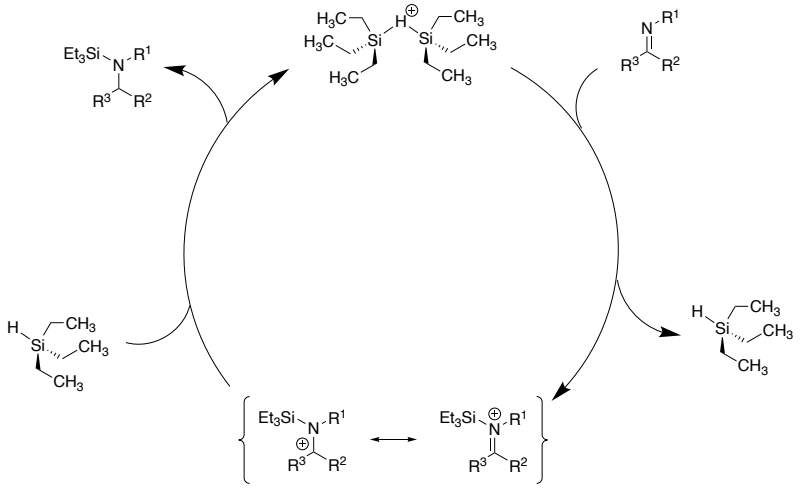
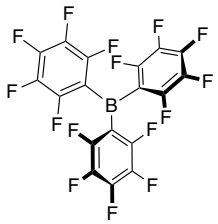


Figure 1.4: Mechanism of imine reduction using silylium ions[31]

*V.II. Hydrosilylative Reduction with Perfluoroarylboranes*



tris(pentafluorophenyl)borane
(BCF)

Figure 1.5: Structure of BCF

Perfluoroarylboranes are a unique class of Lewis acids that have found utility for the reduction of various compounds.[32, 33] Most widely used, tris(pentafluorophenyl)borane (BCF), was

originally synthesized in 1964, however its use as a catalyst was not common for many years after.[34] The hydrosilylation of various oxygen-containing molecules with BCF was first reported in the late 1990s.[23] Carbonyl functionality including aldehydes and ketones are reduced with BCF as catalyst with loadings as low as 1 mol %.[35, 36] Additionally, carboxylic acid derivatives are also reduced with BCF to give the silyl ether or exhaustive reduction to give the alkane.[36] Brookhart and coworkers found it was possible to reduce carboxylic acids to the disilyl acetal which is then converted to an aldehyde after acidic workup.[37] In contrast, amides undergo complete deoxygenation in preference to other reducible functionality to yield a substituted amine.[38, 39]

BCF in the presence of silanes catalytically reduces X–O bonds (X = S, P, N, and C) such as sulfoxides, phosphonic esters, and N-oxides. [40-42] Similarly to aldehydes and ketones, sulfoxides and sulfones are completely reduced to the thioether.[40, 41] Alkyl-N-oxides are reduced to tertiary amines and pyridine-N-oxides are reduced to pyridines with siloxane as the byproduct of the reaction.[41] When trialkylsilanes are used, phosphonic esters are reduced to a phosphonic silyl ether. However, when more reducing alkyl or dialkyl silanes are used, the phosphorus containing ester is completely reduced to the phosphine.[42]

The catalytic conversion of an alcohol to a silyl ether with BCF and silanes has been known since 1999 and due to relatively fast reaction rates the dehydrosilative system is compatible with a wide array of functionality.[23] Shortly after, Yamamoto and coworkers revisited the dehydrosilylation of alcohols and by varying the equivalents of silane, were able to fully reduce alcohols to the corresponding alkane.[43] More interesting was the utilization of this system for the reduction of ethers for the synthesis of silyl ethers and alkanes.[43] A proposed mechanism for this reduction is shown in Figure 1.6 with diethyl ether as substrate. Silane first coordinates with the borane, polarizing the Si–H bond and making the silane susceptible to nucleophilic attack. A lone

pair of diethyl ether's oxygen attacks the silane via an $S_N2$ type attack cleaving the Si–H bond to give a borohydride and a silyloxonium intermediate. Hydride delivery to one of the ethyl groups cleaves the C–O bond of the silyloxonium producing ethane gas, an ethyl silyl ether, and regenerating the borane catalyst. Variations of this ether cleavage were also observed for vinyl[44], thio[45] and silyl ethers.[46]

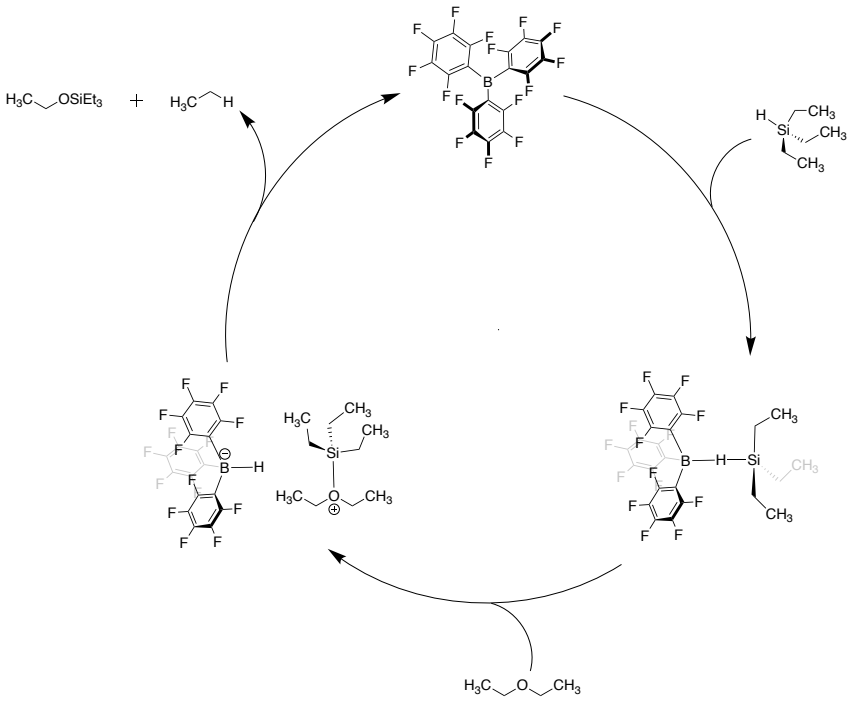
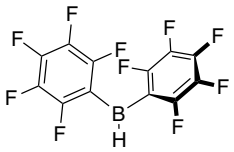


Figure 1.6: Mechanism for the cleavage of diethyl ether using BCF for silane heterolysis

The reactivity of BCF is highly dependent on the aryl rings bound to boron.[47, 48] This necessarily requires the synthesis of a new borane in order to tune the reactivity of reactivity of the system. Recent efforts by Michel Gagné and coworkers showed that the addition of phosphine additives might provide *in situ* modification of the system without direct alteration of the borane catalyst. While computational work has shown the addition of trisubstituted phosphines alter the electrophilicity of the silane, experimental success has been limited to the demethylation of anisole thus far.[49, 50]

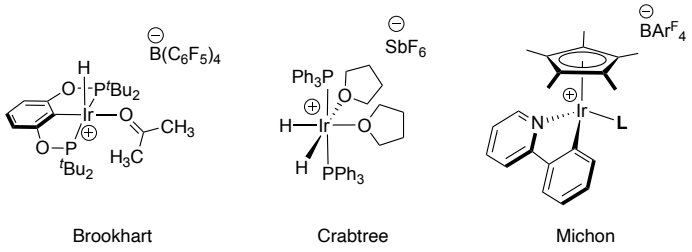


bis(pentafluorophenyl)borane
Piers' borane

Figure 1.7: Structure of Piers' borane

Bis(pentafluorophenyl)borane, (Piers' borane, named for Warren Piers), was synthesized for its use in hydroboration chemistry.[51] The original synthesis of Piers' borane involved the transmetallation of a bis(pentafluorophenyl)tin with trichloroborane, followed by a hydride transfer with dimethyl(chloro)silane. This route was later replaced by one involving the thermal decomposition of BCF with triethylsilane in benzene.[52] Piers' borane has also found utility in the reduction of cyclic ethers and epoxides to give the corresponding silyl ether.[53] It has also been applied to persilylated glycosides with both pyranose ring and $C_1$ deoxygenation being observed.[54]

*V.III. Hydrosilylative Reduction with Iridium Catalysts*



Brookhart Crabtree Michon

Figure 1.8: Cationic Iridium Catalysts for Silane activation

Iridium catalysts operate similarly to their borane analogs in silane heterolysis, and follow a similar mechanism as seen in Figure 1.9. Silane binds to the metal center as a sigma complex which polarizes the Si–H bond. Attack by a nucleophile leads to heterolytic cleavage of the silane Si–H bond producing a metal hydride and a silylium ion pair. The metal center then delivers a hydride to the silylium ion producing a reduced silyl species and regenerating the catalyst. A key

difference between the borane and iridium catalyst is the formation of a neutral hydride species and the silyloxonium ion pair. Further mechanistic insight is provided in the following chapter.

An early example of this reactivity was the dehydrosilylation of alcohols first reported in the 1980s, with the Crabtree system (Figure 1.8) being the only cationic example.[55-57] Reactivity of iridium complexes for hydrosilylative C–X bond cleavage (X = halogen, O, N) was not further investigated until 2007 when Brookhart and coworkers demonstrated the use of an iridium pincer complex for the reduction of alkyl halides.[58] From this study it was found that the reactivity of the catalyst was dependent on the nucleophilic properties of the substrate.

A year later the same iridium complex was found to be capable of cleaving acyclic ethers to give an alkane and a silyl ether. The product silyl ethers were subject to further reduction to the corresponding alkane over an extended period of time.[27] Cyclic ethers such as epoxides and tetrahydrofuran (THF) are reduced to the silyl ether as well.[59] Similar to ethereal reduction carbonyl containing molecules are reduced to the corresponding silyl ether. Additionally, reduction of amides was shown to produce the respective amine.[60, 61] This system has also shown an ability to reduce carbon dioxide to methane with very low catalyst loadings.[62]

Christophe Michon and coworkers also used cationic iridium catalysts for the reduction of polarized bonds with a focus on nitrogen-containing compounds. The first of these studies was the reduction of imines to the corresponding amines.[63] Similarly to the POCOP complex reported by Brookhart, Michon showed that esters were reduced to the silyl acetal to give an aldehyde upon aqueous workup with a wide range of functional group compatibility.[64] Other carbonyl containing functionalities were investigated including the reduction of secondary and tertiary amides.[65] The scope of this system was then expanded to include α,β-unsaturated amides which were reduced to

either the saturated amide or amines.[66] Additionally, other carbonyl derivatives were reduced to give either a secondary or primary alcohol.[67]

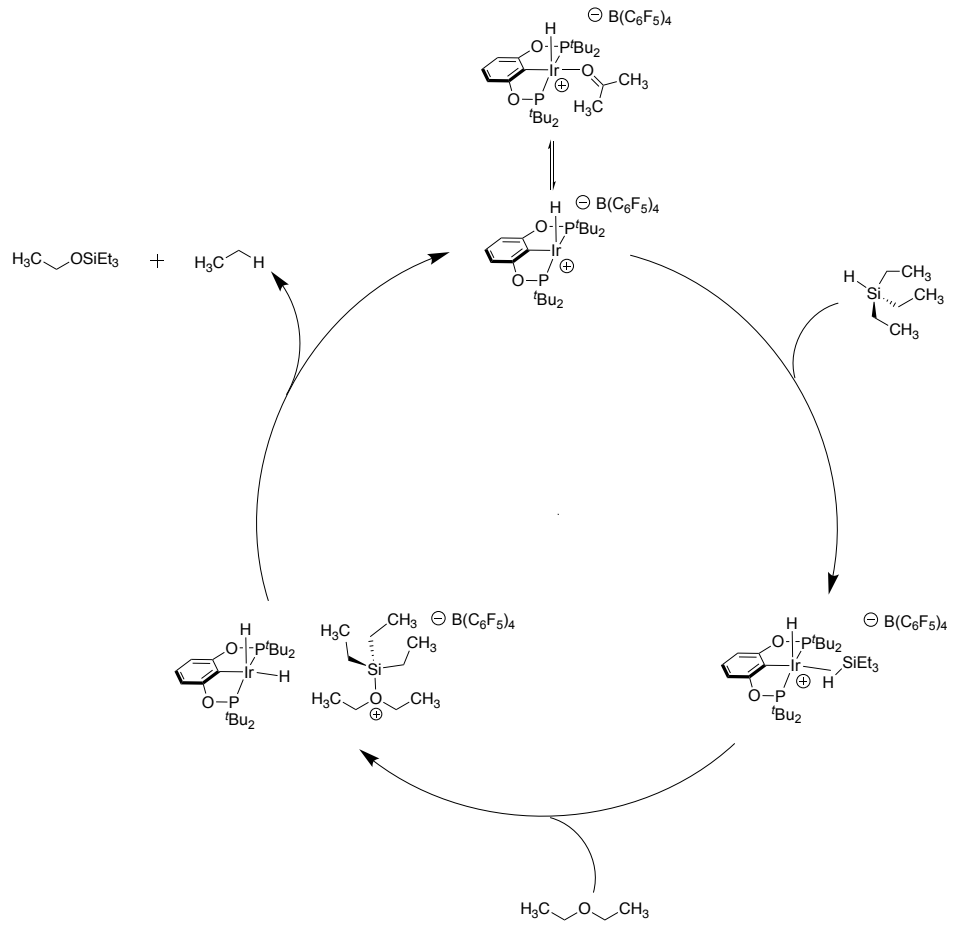


Figure 1.9: Proposed Mechanism of Ether Cleavage by an Iridium Pincer Complex[27]

**VI. Conclusion**

Both borane and iridium catalysts are competent for a wide range of hydrosilylative reductions via heterolytic cleavage of silanes. Additionally, both systems proceed through a similar mechanism where the silane is polarized and the generated silylium ion drives reactivity. Iridium systems, however, offer greater tunability due to the electron density of the metal center being dependent on the bound ligands. The remainder of this work will focus on the utilization of cationic

bis(phosphine) iridium complexes for C–O bond cleavage in ethereal substrates via silane heterolysis.

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## Chapter 2: Selective alkyl ether cleavage by a cationic bis(phopsphine) iridium complex*

### I. Introduction

Primary and secondary alkyl ethers are robust organic functional groups for which forcing conditions are typically required to effect C-O cleavage. Traditional methods for ether cleavage rely on their conversion to alkyl halides under the influence of strong mineral acids[1] or exhaustive hydrogenolysis to alkanes over heterogeneous catalysts.[2] Although well-developed and inexpensive, these methods lack the intrinsic selectivity that would be required for their application to complex polyether-containing molecules including carbohydrate derivatives.[3]

In recent years a strategy for reductive ether cleavage through catalytic silylation has emerged. These approaches make use of catalyst-promoted silane Si-H heterolysis to generate electrophilic silyloxonium ions which are subject to subsequent attack by hydride. The use of a catalyst opens up avenues for the development of systems with catalyst-controlled selectivity that would be applicable to complex molecules. Promising classes of catalysts for this transformation include electrophilic triaryl- and diarylboranes[4-9] as well as a single example of a cationic iridium complex of a weakly-coordinating anion.[10-11] In both cases the initial Si-O bond-forming step is thought to proceed via Lewis acid-promoted silane activation to give a silyloxonium ion and an equivalent of the catalyst hydride.[12]

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*Jones, C. A. H.; Schley, N. D. Selective alkyl ether cleavage by cationic bis(phosphine) iridium complexes, *Organic & Biomolecular Chemistry* **2019**, 17(7), 1744-1748 - Reproduced with permission of The Royal Society of Chemistry

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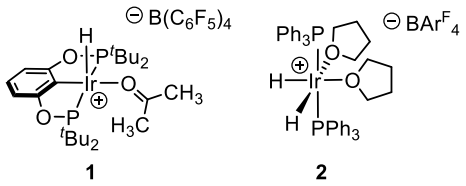
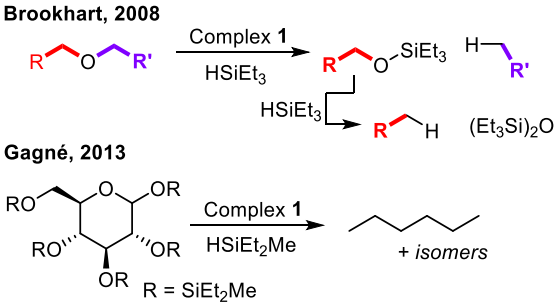



Figure 2.1: Cationic iridium complexes of weakly coordinating anions.

To our knowledge the only iridium catalyst reported to cleave ethers via C-O single bond reduction with silanes is Brookhart's cationic bis(phosphine)pincer iridium complex **1** (Figure 2.1, left).[13] Related non-pincer complexes have been previously reported by Crabtree to effect dehydrosilylation of alcohols.[14] Although the two transformations are distinct, both implicate nucleophilic attack on an iridium σ-silane complex in their respective Si-O bond-forming steps.

Our research group's interest in reactions of alkyl ethers at cationic bis(phosphine)iridium complexes has now led us to explore catalytic ether cleavage via C-O silylation. In recent work we demonstrated the stoichiometric C-O cleavage of methyl tert-butyl ether by $[(PPh_3)_2IrH_2(THF)_2]PF_6$.[15] We now show that the corresponding $BAr^F_4$ ($Ar^F$ = 3,5-bis(trifluoromethyl)phenyl) salt (**2**) is an active catalyst for the cleavage of alkyl ethers with trialkyl silanes. In a key advance, we demonstrate substantially improved selectivity over previous iridium catalysts for this transformation and have applied this system to a promising protecting group-interconversion process that allows for debenzylation in the presence of reductively-labile alkyl and aryl halides.



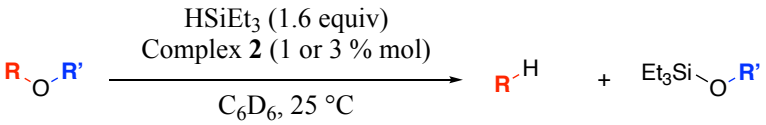

Scheme 2.1. Exhaustive ether cleavage by **1**.

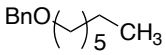
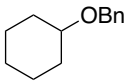
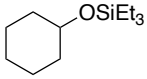
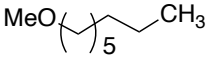
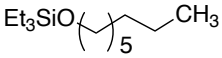
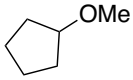
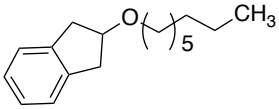
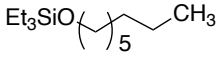
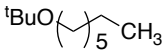
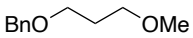
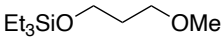
### II. Cleavage of Unsymmetrical Ethers

At the outset of this study we identified a need for iridium catalysts with improved selectivity profiles. Primary, secondary and tertiary ethers are rapidly cleaved by Brookhart's POCOP iridium catalyst (**1**) to give silyl ethers; however, the resulting silyl ether products are subject to subsequent reduction to the alkanes (Scheme 2.1, top). This reactivity was employed to great effect by Gagné in a recent report detailing the exhaustive deoxygenation of glucose to hexanes,[11] but is also a sign of a lack of intrinsic selectivity that limits applications in the synthesis of functionalized molecules.

The mechanistic similarity between ether and alcohol silylation encouraged us to explore non-pincer bis(phosphine)iridium complexes for reductive ether cleavage catalysis. Our hypothesis was that these complexes would also serve as catalysts for ether cleavage, and would provide a tunable platform for 2$^{nd}$ generation catalyst development through the preparation of variants of commercially available monophosphines. Although the hexafluorophosphate complex[15] $[(PPh_3)_2IrH_2(THF)_2]PF_6$ is inactive under the conditions tested, the $BAr^F{}_4$ salt[16] (**2**) rapidly cleaves a variety of alkyl ethers with triethylsilane.

Table 2.1: Cleavage of unsymmetrical ethers by complex **2**.




| Entry | Substrate | Conditions | Silyl ether | NMR yield |
|---|---|---|---|---|
| 1 |  | 1 mol %<br>1 h |  | >98% |
| 2 |  | 3 mol %<br>2 h |  | 70% |
| 3 |  | 1 mol %<br>8 h |  | 75% |
| 4 |  | 1 mol %<br>2 h | $SiEt_3OMe$ | 61% |
| 5 |  | 3 mol %<br>48 h |  | 26% |
| 6 | $^tBuO-Bn$ | 1 mol %<br>48 h | NR | - |
| 7 |  | 1 mol %<br>48 h | NR | - |
| 8 |  | 3 mol %<br>40 min |  | >98% |

Initial studies on a collection of unsymmetric ethers suggest that the reactivity of complex **2** depends strongly on the ether (Table 2.1). Benzyl ethers are highly reactive, with benzyl heptyl ether undergoing cleavage at the benzylic position. Benzyl cyclohexyl ether is also cleaved at the benzylic position, but requires an elevated catalyst loading of 3 mol % (Table 2.1, entry 2). Primary methyl ethers undergo demethylation while the secondary methyl ethers tested here are cleaved at the 2° position (Entries 4 and 5). Primary secondary ethers show poor reactivity, even with long reaction times and high catalyst loading. In nearly all cases the resulting silyl ethers appear to be stable with respect to further reduction, the exception being the formation of silylmethyl ethers that could undergo further reduction to produce hexamethyldisiloxane and methane. Although

complex **2** is able to cleave methyl-tert-butyl ether (MTBE), other tertiary ethers including *t*-butyl benzyl ether were not reduced (Table 2.1, entries 6-7). Surprisingly, benzylic ether cleavage could be accomplished selectively even in the presence of a methyl ether (Table 2.1, entry 8). These preliminary observations on the reactivity of complex **2** show significantly attenuated reactivity versus Brookhart's complex **1**, validating our hypothesis that more-selective iridium catalysts could be obtained through the use of cationic non-pincer bis(phosphine)iridium complexes.

### III. Functional Group Tolerance of Catalyst

The rapid and selective cleavage of benzyl ethers suggested that complex **2** could potentially serve as a catalyst for the conversion of benzylic ethers to silyl ethers. Benzylic ethers are typically cleaved by hydrogenolysis under mild conditions with heterogeneous metal catalysts. The ease of benzylic ether formation and subsequent deprotection has led to applications of benzyl ethers as versatile protecting groups for alcohols.[17] Benzyl ether hydrogenolysis over heterogeneous Pd catalysts is compatible with an array of functional groups, but alkenes, alkynes and azides undergo reduction, while alkyl and aryl halides and psuedohalides are also subject to competitive hydrodehalogenation or catalyst poisoning under certain conditions.[18-21]

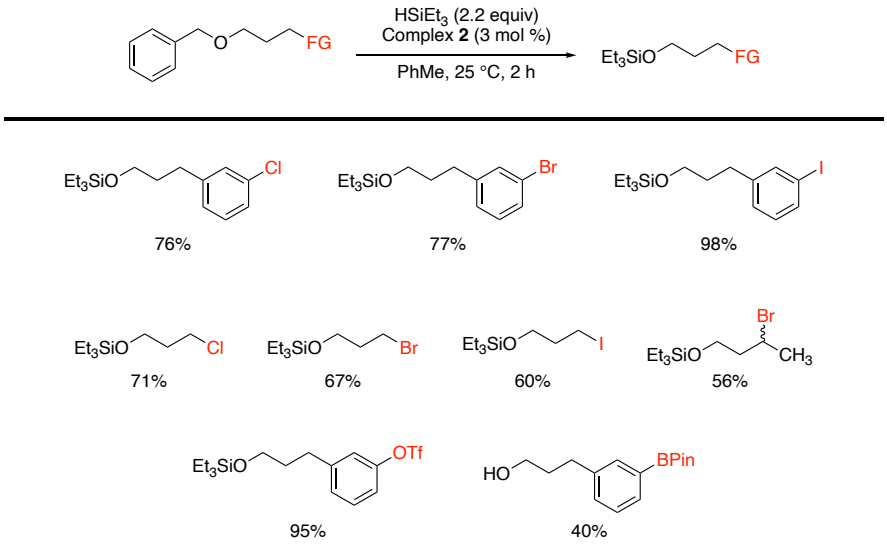
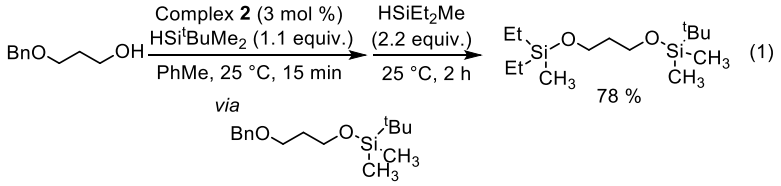



Figure 2.2: Isolated yields obtained in the conversion of benzyl ethers to silyl ethers by **2**.

Under our optimized conditions, a variety of alkyl and aryl halides are tolerated. (Figure 2.2). Benzyl ether cleavage is observed without reduction of an aryl chloride, bromide or iodide. An aryl triflate is similarly untouched under our conditions. Although primary alkyl chlorides, bromides, and iodides all survive benzyl ether silylation in moderate to good yield, somewhat lower yields are obtained for a substrate containing a secondary alkyl bromide. In contrast to our results with **2**, complex **1** is a reported hydrodehalogenation catalyst under closely-related conditions.[22]

In line with the reported dehydrosilylation activity of related complexes, substrates containing free alcohols undergo dehydrosilylation more rapidly than ether cleavage. We have been able to exploit this property in the selective disilylation of 3-(benzyloxy)propanol (eqn. 1). Sequential treatment with tert-butyl(dimethyl)silane (1.1 equiv.) and diethyl(methyl)silane (2.2 equiv.) gives the unsymmetrically silylated 1,3-propanediol.




Scheme 2.2: Reduction of 3-benzyloxypropanol with **2**.

A survey of the scope of compatible functionality with our silyl ether cleavage conditions also revealed some limitations. As many iridium complexes including **1** are excellent hydrosilylation catalysts for olefins and carbonyl derivatives,[23-24] substrates containing such functionality were not suitable for ether cleavage by **2**. Similarly, substrates containing Lewis basic functionality including nitriles, amines, thioethers, azides and nitroarenes are totally unreactive under our optimized conditions (Figure 2.3). Thus, substrates which are either more Lewis-basic than ethers or are known to undergo rapid hydrosilylation appear to pose a challenge for this

system. We suspect further catalyst development may provide solutions for certain substrate classes, but given the kinetic stability of ethers relative to other functionality, these limitations are unsurprising.

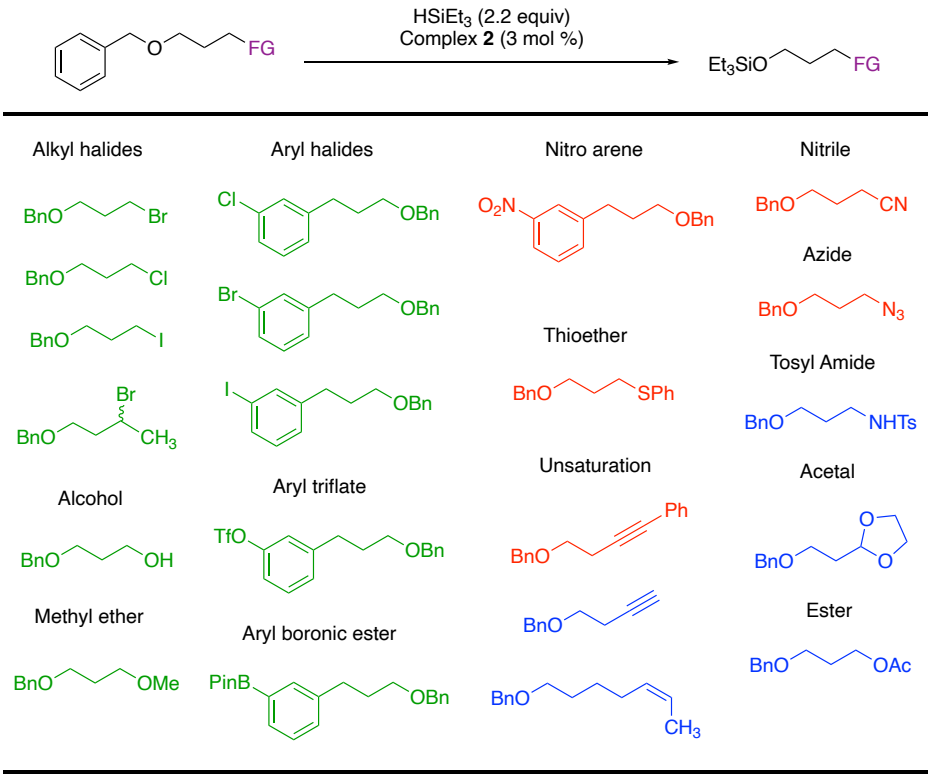
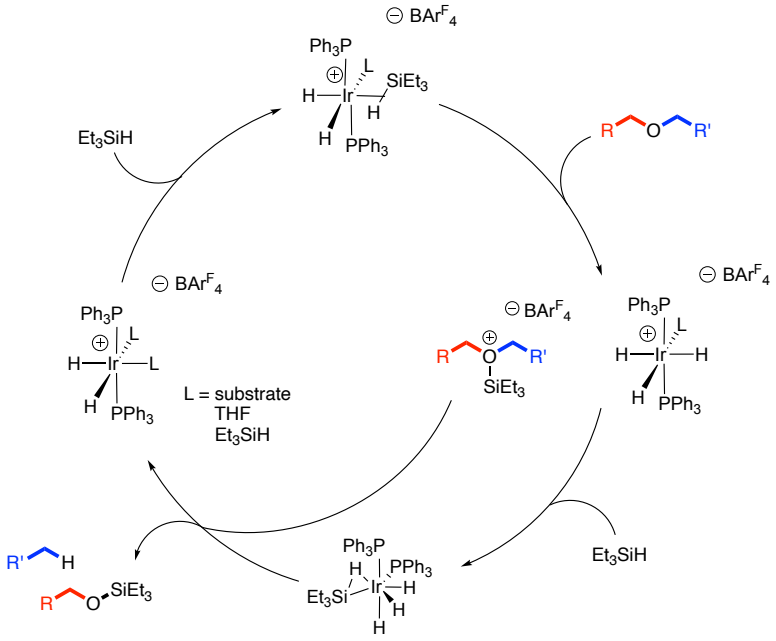



Figure 2.3: Substrates examined for functional group compatibility and tolerance of complex **2**: green = debenzylation observed, red = no reaction, blue = reactivity at functional group

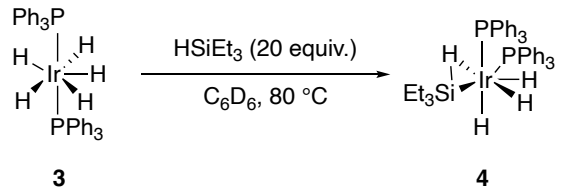
### IV. Mechanistic Investigation

A proposed mechanism for ether cleavage catalyzed by **2** is given in Scheme 2.3.[13] An interesting feature of iridium-catalyzed ether silylation is its resemblance to the borane-catalyzed reaction.[25] The key mechanistic similarity between both iridium and borane-catalyzed ether silylation is the heterolytic cleavage of the silane to give a silyloxonium ion and a metal or borohydride respectively. When the reduction of benzyl heptyl ether by **2** is monitored by $^{31}P\{^{1}H\}$ NMR, a single major resonance appears at 13.7 ppm. We have found that the same species can be

generated by treatment of the neutral iridium pentahydride $(PPh_3)_2IrH_5$ (**3**) with $Et_3SiH$, indicating that the major iridium-containing species during the reaction is a neutral complex lacking the $BAr^F_4$ anion. This complex has been previously characterized as the neutral iridium tetrahydrido silyl complex **4** (Scheme 2.4).[26] Formation of **4** during catalysis likely occurs via attack of an ether on a σ-Si-H complex[13] to give $(PPh_3)_2IrH_3$ (**5**) followed by oxidative addition of a second equivalent of $Et_3SiH$. The presence of **4** as the major iridium-containing species during catalysis is compatible with the general framework for the overall mechanism proposed by Brookhart[13] and well as studies on a related catalytic reaction by Oestrich.[12]



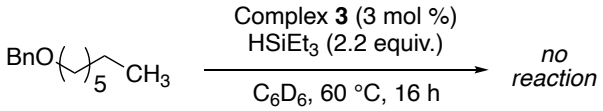

Scheme 2.3: Proposed mechanism for ether cleavage by **2**.



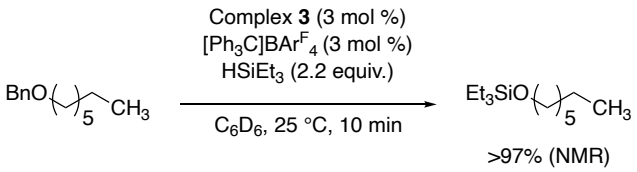

**3** **4**

Scheme 2.4: Synthesis of iridium(V)silyltetrahydride.

In both iridium and borane-catalyzed variants of this transformation, hydride attack on the dialkysilyloxonium ion is proposed to be responsible for the C-O bond cleavage step. Brookhart has proposed that the neutral iridium(III)dihydride resulting from silyl transfer to the ether may be responsible for this step.[13] Studies on a closely related system by Oestreich have also implicated a neutral iridium(V)silyltrihydride or iridium(III)dihydrido σ-silane, though recent calculations appear to support the hypothesis that the iridium(III)dihydride is the responsible hydride source in that system.[27] Our observation of complex **4** during catalysis is wholly consistent with Oestreich's mechanistic proposal and allows us to tentatively suggest that complex **4** may be responsible for hydride transfer to the silyloxonium ion. Importantly, complex **4** itself does not serve as a catalyst for ether reduction when generated in situ from **3** (Scheme 2.5). This observation suggests that a cationic precursor is required for silyloxonium ion formation. On the other hand, complex **4** is extremely active when applied in the presence of equimolar $[CPh_3]BAr^F{}_4$ (Scheme 2.6). For this experiment, $[CPh_3]BAr^F{}_4$ was added to a benzene solution of triethylsilane to generate a triethylsilylium ion equivalent[28] which was then treated with substrate ether to give the silyloxonium ion. Subsequent addition of a solution of **4** leads to rapid catalysis (Scheme 2.6). Alternatively, $[CPh_3]BAr^F{}_4$ or a triethylsilylium ion generated in situ may serve to abstract a hydride from **4** to give a cationic iridium species related to **2**. Indeed treatment of a THF solution of **4** with $[CPh_3]BAr^F{}_4$ appears to give **2** by $^{31}P$ NMR. In either case, complex **4** alone is clearly insufficiently electrophilic to transfer an equivalent of triethylsilylium to substrate ether.



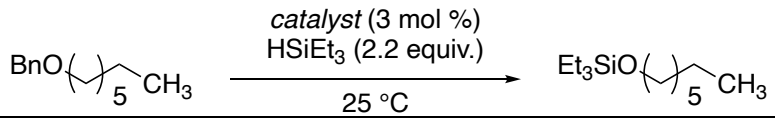

Scheme 2.5: Attempted reduction of benzyl heptyl ether with Complex **3**



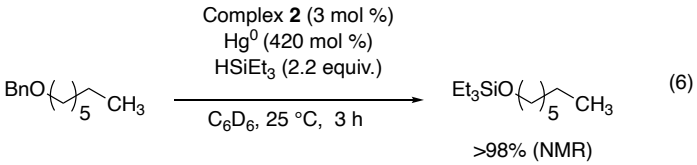

Scheme 2.6: Reduction of benzyl heptyl ether with Complex **3** and $[Ph_3C]BAr^F_4$ as an additive

The efficacy of borane catalysts with structurally similar motifs to the weakly coordinating anions used in this study warrants discussion. B-C cleavage might be expected to generate the triaryl borane $BAr^F_3$ [tris(3,5-bis(trifluoromethyl)phenyl)borane]. The similarity of $BAr^F_3$ to tris(pentafluorophenyl)borane (BCF), a known catalyst for ether hydrosilylation led us to investigate the possibility that anion degradation to an active catalyst could be responsible for our observed reactivity. Under our catalytic conditions, the $BAr^F_4$ anion remains unchanged by $^{19}$F-NMR spectroscopy, which precludes the formation of $BAr^F_3$ at detectable concentrations. Furthermore, $NaBAr^F_4$ is inactive for ether cleavage both on its own and in the presence of the neutral tetrahydridosilyliridium complex **4**. Finally, we independently prepared the $BAr^F_3$ borane and compared its reactivity to reactions catalyzed by **2**. $BAr^F_3$ is a poor catalyst for ether reduction under our optimized conditions (Table 2, entry 1), and while it improves in $CD_2Cl_2$ solvent, catalysis by $BAr^F_3$ is significantly slower than catalysis by **2**. For instance, after 15 minutes we see complete conversion using **2** (> 30 turnovers) and only 3 turnovers when $BAr^F_3$ is used as the catalyst. Therefore, these results allow us to rule out the possibility that the observed catalytic behavior of **2** results from trace borane generated by anion degradation. In a related experiment we found that catalysis by **2** is not inhibited by the presence of excess Hg metal, providing evidence against degradation of **2** to active iridium nanoparticles in situ (Scheme 2.7).[29-30]

Table 2.2: Comparison of catalysis by **2** versus the borane $BAr^F_3$.



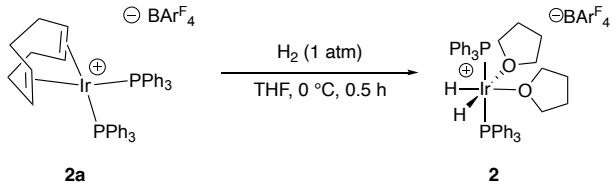

| Entry | Catalyst | Solvent | Time | NMR Yield |
|---|---|---|---|---|
| 1 | $BAr^F_3$ | $C_6D_6$ | 2 h | < 1% |
| 2 | Complex **2** | $CD_2Cl_2$ | 15 min | > 98% |
| 3 | $BAr^F_3$ | $CD_2Cl_2$ | 15 min | 9% |
| 4 | $BAr^F_3$ | $CD_2Cl_2$ | 1 h | 39% |
| 5 | $BAr^F_3$ | $CD_2Cl_2$ | 4 h | 85% |




Scheme 2.7: Catalytic ether silylation conducted in the presence of excess mercury.

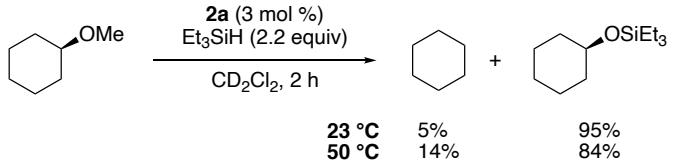
**V. Selectivity between equatorial and axial ethers**

In our study of unsymmeteric ether cleavage with complex **2** we discovered that cyclopentyl methyl ether (CPME) underwent selective demethoxylation at the secondary position to give cyclopentane (Table 2.1). This observation contrasts with the selectivity observed from BCF which gives preferential cleavage at the methyl position.[31, 32] As secondary alcohols and ethers are common functional groups in biologically-relevant compounds including carbohydrates, we were encouraged to develop a catalytic system capable of the direct demethoxylation of secondary methyl ethers.




Scheme 2.8: Hydrogenation of **2a** to **2**

Seen in Table 2.1 the use of complex **2** effects the selectivity of the CPME cleavage at the secondary position in preference to the methyl ether. Complex **2** is synthesized by hydrogenation of the air-stable 1,5-cyclooctadiene complex **2a** in THF solvent, but this step has been found to be unnecessary, as complex **2a** serves as a comparably competent precatalyst to **2**. Conversely to the CPME cleavage, the homologated substrate cyclohexyl methyl ether does not show the same preference, giving triethylsiloxycyclohexane as the major product (95:5 TES-OCy:CyH) (Scheme 2.9).




Scheme 2.9: Reduction of cyclohexylmethyl ether with complex **2a**

The difference in selectivity for cleavage of cyclohexyl and cyclopentyl methyl ethers provided an impetus to examine the factors that influence the selectivity of iridium-catalyzed 2° methyl ether cleavage in detail. The conformationally-biased pair of substrates *cis*- and *trans*-(tert-butyl)-4-methoxycyclohexane were prepared (*cis*-**6** and *trans*-**6** respectively). By virtue of the 1,3-diaxial interactions with the tertiary butyl group, these substrates adopt conformations that place the methoxy substituent axial and equatorial in the *cis* and *trans*, isomers respectively.[33,]

Under catalytic conditions, we observe that *cis*-**6** is cleaved to **7** and that *trans*-**6** is selectively demethylated to give silyl ether **8** (Figure 2.4). These observations appear to argue for the importance of substrate conformation in hydrosilylative ether cleavage by **2a**. Similarly, cholestanol derivatives **9** (equatorial) and **11** (axial), are conformationally locked due to the fused ring structure provided by the *trans*-decalin within the structures. When reacted under our

conditions, both **9** and **11** mirrored the reactivity of *cis*-**6** and *trans*-**6** where the equatorial methyl ether was demethylated (**10**) and the axial ether underwent demethoxylation (**12**). This indicates the reactivity observed in Scheme 2.9 is due to the fluxional nature of cyclohexyl-methyl ether. At room temperature the major conformer in solution will persist with the equatorial methyl ether and thus favoring demethylation. However, upon heating the energy required for a ring flip is met and more axial conformer will populate in solution. As a result, a decreased ratio between the cyclohexyl-silyl ether and cyclohexane is observed.

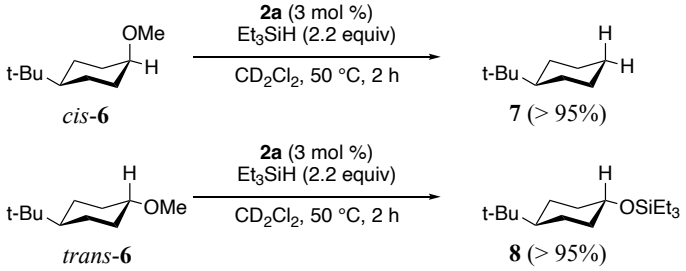



Figure 2.4: Effect of conformation on the reduction with **2a**

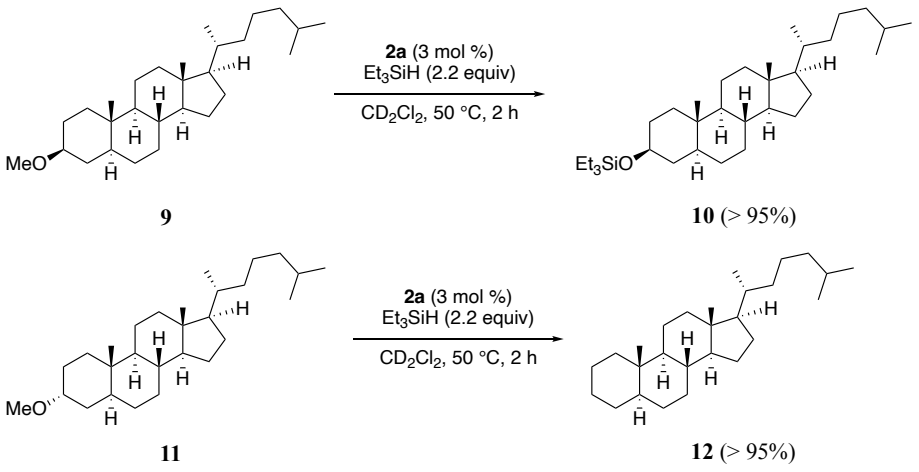
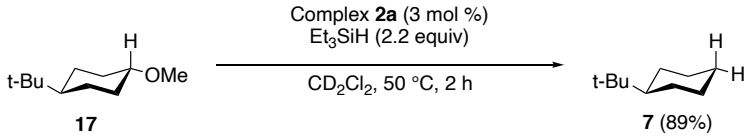



Figure 2.5: Reduction of Cholestanol derivatives

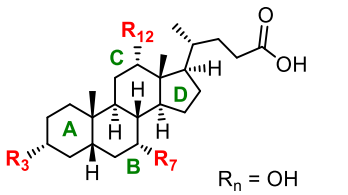
The selectivity for methyl versus 2° C-O cleavage is likely dictated by the relative rates of $S_N1$ cleavage of the silyloxonium versus $S_N2$ cleavage of the methyl group. The apparent preference for $S_N1$ reactivity at substrates with significant axial silyloxonium populations can be

rationalized on the basis of the known increased rate of solvolysis of axial cyclohexane substituents relative to their equatorial isomers.[33,35] Experimentation by my colleague Caleb Fast determined this through deuterium studies and reducing *trans*-(tert-butyl)-4-ethoxycyclohexane (**17**) with our current system. When *cis*-**6** is subjected to reaction conditions with $Et_3SiD$, a near-1:1 mixture of cis and trans **4**-$d_1$ is obtained. Production of both diastereomers suggest the formation of a carbocation, consistent with demethoxylation occurring via $S_N1$ reactivity. Evidence for an $S_N2$ mechanism for demethylation was collected by subjecting **17** to our reaction conditions (Scheme 2.10). Selective deethoxylation was observed which is the expected outcome due to the much lower rate of $S_N2$ reactions of ethyl groups versus methyl groups.




Scheme 2.10: Demethylation versus demethoxylation of ethers.

## IV. Reduction of Sterols




| | |
|---|---|
| cholic acid | n = 3, 7, 12 |
| chenodeoxycholic acid | n = 3, 7 |
| deoxycholic acid | n = 3, 12 |
| lithocholic acid | n = 3 |

Figure 2.6: Hydroxylation pattern of cholic acids.

The selectivity observed in cyclohexyl methyl ether C-O cleavage encouraged the examination of more-complex substrates derived from cholic acid (Figure 2.6).[36] Cholic acid and

its derivatives are synthesized in the liver from cholesterol[37] and play an important role in cholesterol homeostasis[38] and lipid metabolism.[39] In particular, they function as signaling molecules for nuclear receptors[40] with unnatural variants occasionally possessing desirable target selectivity.[41,42] The sites of hydroxylation, their stereochemistry, and the degree of polyhydroxylation are species-dependent, with the parent cholic acid being hydroxylated on the α face at the 3, 7, and 12 positions on the A, B and C rings respectively (Figure 2.6). Their biological relevance has inspired studies of the relative reactivity of each site of hydroxylation. Deoxycholic acid has been previously prepared by B-ring deoxygenation via selective oxidation of the 7α-hydroxyl to the mono ketone[43,44] followed by Wolff-Kishner reduction.[45] A similar strategy has been used to deoxygenate the C ring of 6,12-dihydroxy-cholanoic acid.[46] For the unprotected triols, the A-ring hydroxyl is considered to be the least reactive site with respect to oxidation by chromic oxide.[47-49]

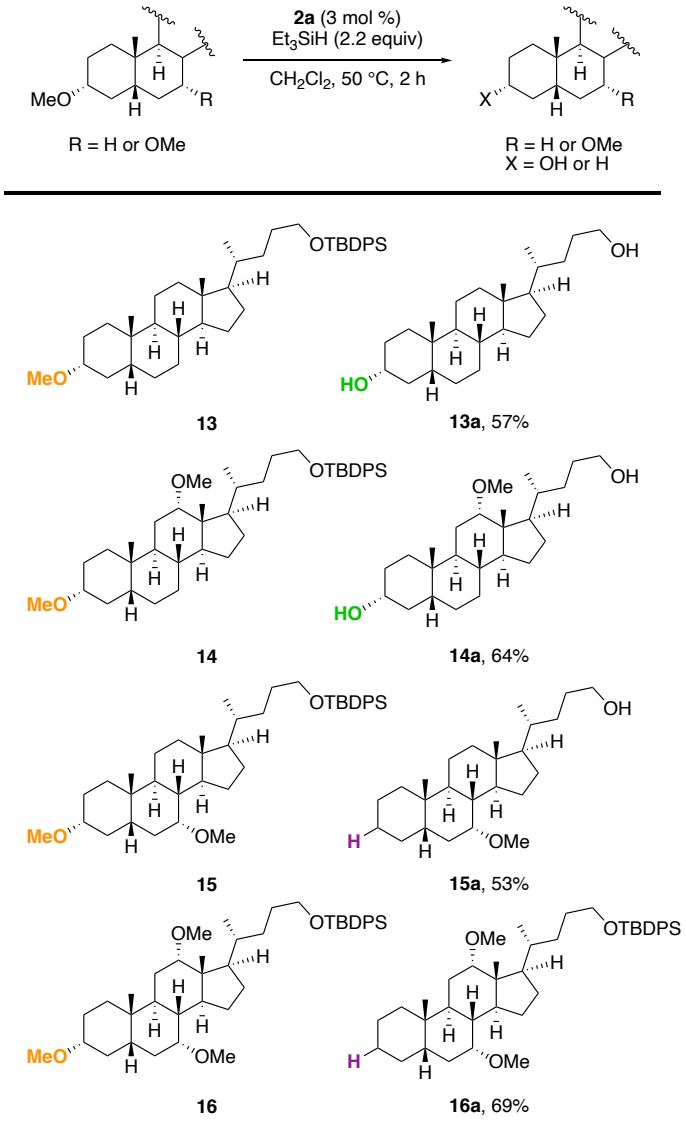



Figure 2.7: Reduction of cholic acid derivatives

When methyl ether substrates **13-16** were subjected to optimized catalytic conditions using complex **2a** as a catalyst we observed in all cases selective reaction at the 3α-methoxy substituent of the A ring. (Figure 2.7) This observation is particularly noteworthy given the number of potential positions for reduction in cholanol derivative **16**. While all four cholanol derivatives **13-16** undergo selective reaction at the 3α-substituent on the A ring, the fate of this methyl ether appears to be dictated by substitution on the neighboring B ring. For both the protected lithocholanol and

deoxycholanol derivatives **13** and **14**, the 3α-methoxy group undergoes demethylation – an outcome consistent with the selectivity expected for an equatorial methyl ether with **2a** as the catalyst. With the same catalyst however, chenodeoxycholanol **15** and cholanol **16** undergo 2° cleavage of the 3α-methoxy substituent. When examining the four cholanol substrates together it appears that the presence or absence of the 7α-methoxy substituent on the B ring controls the fate of the 3α-methoxy group under our silylation conditions with **2a**.

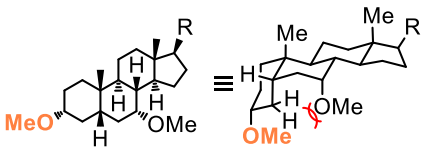



Figure 2.8: Depiction of the interaction of the 7α substituent with the cis-fused A ring.

A depiction of the cis-fusion of the A and B rings of cholic acids is shown in Figure 2.8. The 7α group is spatially located to participate in a pseudo syn-pentane interaction with the $C_4$ methylene of the A ring. This steric interaction likely destabilizes the chair conformation of the A-ring relative to the twist-boat. Since the ionization of cyclohexane substituents is believed to proceed through the twist-boat and not directly from the chair in many cases,[35,50,51] our hypothesis is that differential destabilization of the chair by the 7α-OMe group in **15** and **16** increases the rate of $S_N1$ substitution of the 3α-silyloxonium intermediate and thus promotes demethoxylation.

### IV. Experimental

Syntheses and manipulations were conducted in air unless otherwise specified. Tetrahydrofuran, toluene, dichloromethane, pentane, and diethyl ether were degassed with argon and dried over activated alumina using a solvent purification system. All reagents and building blocks including 3-benzyloxy-propanol were procured from commercial vendors. Complex **2**[16], $BAr^F_3$,[52] and $[CPh_3]BAr^F_4$[53,54] were prepared using reported procedures. $^1H$, $^{13}C$ and $^{31}P$ NMR

spectra were recorded on Bruker NMR spectrometers at ambient temperature unless otherwise noted. $^{1}H$ and $^{13}C$ chemical shifts are referenced to residual solvent signals; $^{31}P$ chemical shifts are referenced to an external $H_3PO_4$ standard.

**Benzyl heptyl ether:** This compound was prepared using a reported method[55]

**Benzyl cyclohexyl ether:** This compound was prepared using a reported method[55]

**Benzyl tert-butyl ether:** This compound was prepared using a reported method[56]

**Methyl octyl ether:** This compound was prepared using a reported method[57]

**Tert-butyl heptyl ether:** A 50 mL round bottom flask was charged with a stir bar and fitted with a reflux condenser, $Mg(ClO_4)_2$ (0.310 g, 1.09 mmol, 0.1 equiv.) and heptanol (1.6 mL, 10.9 mmol, 1.0 equiv.) were combined in 16 mL dichloromethane. This solution was treated with di-tert-butyl dicarbonate (5.47 g, 25.1 mmol, 2.3 equiv.) and was refluxed while the reaction progress was monitored by TLC. Upon completion, the sample was diluted with 40 mL of water and extracted with three 30 mL portions of dichloromethane. The combined organic layers were then dried with $Na_2SO_4$, filtered and concentrated on a rotary evaporator. The crude oil was then purified by silica gel chromatography (5 % EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.6725 g (36%). Spectroscopic data for this product has been previously reported.[58]

$^{1}H$ NMR (300 MHz, $C_6D_6$) $\delta$: 3.37 (t, J = 6.5 Hz, 2H), 1.70 (p, J = 6.1Hz, 2H), 1.46-1.50 (m, 2H), 1.36 (bs, 6H), 1.24 (s, 9H), 0.96-0.98 (m, 3H)

**2-(octyloxy)-2,3-dihydro-1*H*-indene:** A flame-dried Schlenk flask was charged with NaH (90%, 0.546 g, 22.8 mmol, 2.2 equiv.) and THF (43.5 mL) in the glove box and fitted with a rubber stopper. The vessel was then brought outside of the box and attached to an oil bubbler. 1-indanol (2.78 g, 20.17 mmol, 2.0 equiv.) was added slowly using a syringe. The resulting mixture was allowed to stir at room temperature for 30 minutes after which 1-bromooctane (1.8 mL, 10.4 mmol,

1.0 equiv.) was added dropwise. The reaction mixture was then refluxed for 6 hours at which point the reaction was quenched with saturated $NH_4Cl$ and the layers separated. The aqueous layer was extracted with three 50 mL portions of ethyl acetate. The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The resulting oil was then purified by silica gel chromatography (10% EtOAc/hexanes) to give the product as a colorless oil. Yield: 1.15 g (45%).

$^1H$ NMR (400 MHz, $CDCl_3$) *δ:* 7.12-7.22 (m, 4H), 4.33 (p, J = 6.5 Hz, 1H), 3.48 (t, J = 6.8 Hz, 2H), 2.94-3.20 (ddd, J = 16.5, 8.2, 6.8 Hz, 4H), 1.59 (p, J = 7.0 Hz, 2H), 1.28-1.36 (m, 10H), 0.89 (t, J = 7.3 Hz, 3H)

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ:* 141.15, 126.59, 124.83, 80.43, 69.49, 39.51, 31.98, 30.11, 29.61, 29.42, 26.40, 22.81, 14.25

HRMS (APCI/Q-TOF) m/z $[M+H]^+$ calcd for $C_{17}H_{26}OH^+$: 247.2062, found: 247.2054

**((3-methoxypropoxy)methyl)benzene:** A flame-dried Schlenk flask was charged with NaH (90%, 0.330 g, 13.8 mmol, 1.2 equiv.) and THF (11.5 mL) in the glove box and fitted with a rubber stopper. The vessel was then brought outside of the box and attached to an oil bubbler. 3-benzyloxy-propanol (1.9 mL, 11.46 mmol, 1.0 equiv.) was added slowly using a syringe. The resulting mixture was allowed to stir at room temperature for 30 minutes after which iodomethane (2.1 mL, 34.4 mmol, 3.0 equiv.) was added dropwise. The reaction progress was monitored by TLC. Upon completion, the reaction was quenched with saturated $NH_4Cl$ and the layers separated. The aqueous layer was extracted with three 50 mL portions of ethyl acetate. The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated on a rotary evaporator to give the product as a yellow oil. Yield: 1.65 g (80%). The compound has been previously reported.[59]

**(3-(benzyloxy)propyl)(phenyl)sufane**: Triethylamine (6.4 mL, 45.9 mmol, 4.0 equiv.) was added to a solution of 3-benzyloxy-1-propanol (1.9 mL, 11.5 mmol, 1.0 equiv.) in 88 mL THF.

Methanesulfonyl chloride (2.6 mL, 22.9 mmol, 2.0 equiv.) was then added and the solution was allowed to stir overnight at room temperature. The reaction was then quenched with 25 mL saturated $NH_4Cl$. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were then dried over $Na_2SO_4$, filtered and concentrated to give an orange oil. This oil was taken up in 1.8 mL DMF and was treated with thiophenol (1.8 mL, 17.2 mmol, 1.5 equiv.) and $K_2CO_3$ (2.38 g, 17.2 mmol, 1.5 equiv.). The resulting suspension was stirred at room temperature for 2 hours, after which the reaction was quenched with a 5% aqueous KOH solution and then extracted with three 20 mL portions of dichloromethane. The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under vacuum. The resulting residue was purified by silica gel chromatography (2%-10% EtOAc/hexanes) to give the product as an oil. Yield: 0.3375 g (11%). Spectroscopic data for this product has been previously reported.[60]

**((3-azidopropoxy)methyl)benzene**: Triethylamine (3.4 mL, 24.1 mmol, 4.0 equiv.) was added to a solution of 3-benzyloxy-1-propanol (0.95 mL, 6.0 mmol, 1.0 equiv.) in 46 mL THF. Methanesulfonyl chloride (0.95 mL, 12.0 mmol, 2.0 equiv.) was then added and the solution was allowed to stir overnight at room temperature. The reaction was then quenched with 25 mL saturated $NH_4Cl$. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were then dried over $Na_2SO_4$, filtered and concentrated to give an orange oil. This oil was taken up in 40 mL DMF and was treated with $NaN_3$ (2.0 g, 30.1 mmol, 5.0 equiv.) and then heated to 60 °C for five hours. The crude reaction mixture was then treated with brine and extracted with diethyl ether. The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under vacuum. This crude residue was purified by silica gel chromatography (10% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.424 g (37%). Spectroscopic data for this product has been previously reported.[61]

$^1$H NMR (500 MHz, $C_6D_6$) *δ:* 7.18-7.32 (m, 5H), 4.30 (s, 2H), 3.23 (t, J = 6.1 Hz, 2H), 2.99 (t, J = 6.5 Hz, 2H), 1.54 (p, J = 6.2 Hz, 2H)

**4-(benzyloxy)butanenitrile:** This compound was prepared using a reported method.[62]

**(Z)-((hex-4-en-1-yloxy)methyl)benzene**: This compound was prepared using a reported method.[63]

**((but-3-yn-1-yloxy)methyl)benzene:** This compound was prepared using a reported method.[64]

**(4-(benzyloxy)but-1-yn-1-yl)benzene:** This compound was prepared using a reported method.[65]

**N-(3-benzyloxy)propyl)-4-methylbenzenesulfonamide:** This compound was prepared using a reported method.[66]

**2-(2-(benzyloxy)ethyl)-1,3-dioxolane:** This compound was prepared using a reported method.[67]

**3-(benzyloxy)propanal:** DMSO (8.5 mL, 120.3 mmol, 10 equiv.), triethylamine (6.7 mL, 48.1 mmol, 4 equiv.), and $SO_3$·pyridine (5.7g, 36.1 mmol, 3.0 equiv.) were added sequentially to a solution of 3-benzyloxy-1-propanol (1.9 mL, 12.0 mmol, 1.0 equiv.) in 60 mL dichloromethane at 0 °C and the resulting mixture was stirred for 1.5 hours. The crude reaction mixture was then quenched with $NaHCO_3$ and the layers separated. The organic layer was washed three times with saturated aqueous $NH_4Cl$, two times with water, and three times with brine followed by drying over $Na_2SO_4$. The resulting solution was filtered concentrated under vacuum to give a yellow oil. This crude residue was purified by silica gel chromatography (25% EtOAc/hexanes) to give the product as an oil. Yield: 1.34 g (68%). The crude aldehyde used without further purification. Spectroscopic data for this product has been previously reported.[68]

$^1$H NMR (500 MHz, $CDCl_3$) *δ:* 9.78 (d, J = 1.6 Hz, 1H), 7.24-7.35 (m, 5H), 4.51 (s, 2H), 3.80 (t, J = 6.4 Hz, 2H), 2.68 (t, J = 6.0 Hz, 2H)

**4-(benzyloxy)butan-2-ol:** A solution of 3-(benzyloxy)propanal (0.960 g, 5.85 mmol, 1.0 equiv.) in 12 mL THF was cooled to 0 °C and treated with a 3M solution of MeMgBr in THF (2.1 mL, 6.43 mmol, 1.1 equiv.) dropwise. The cold bath was removed after stirring for 10 minutes and the reaction was allowed to come to room temperature. After 2 hours the reaction mixture was quenched with saturated aqueous $NH_4Cl$, diluted with 50 mL of water, and extracted with diethyl ether. The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under vacuum to give the product as an oil. Yield: 1.03g (98%). Spectroscopic data for this product has been previously reported.[69]

$^1$H NMR (400 MHz, $CDCl_3$) *δ:* 7.26-7.34 (m, 5H), 4.52 (s, 2H), 3.98-4.03 (m, 1H), 3.61-3.74 (m, 2H), 2.87 (s, 1H), 1.68-1.80 (m, 2H), 1.19 (d, J= 6.3 Hz, 3H)

**3-(benzyloxy)propyl acetate.** A 25 mL flame-dried Schlenk flask was charged with 3-benzyloxy-1-propanol (0.48 mL, 3.00 mmol, 1.0 equiv.), pyridine (0.32 mL, 3.90 mmol, 1.3 equiv.), and 6 mL of dichloromethane. The flask was then cooled to 0 °C and acetic anhydride (0.37 mL, 3.90, 1.3 equiv.) was added dropwise. The cooling bath was removed and the reaction was allowed to come to room temperature. The reaction progress was monitored by TLC. Upon completion the solution was poured into 20 mL of 1M aqueous HCl and extracted with three 20 mL portions of $Et_2O$. The combined organic extracts were then washed with saturated $NaHCO_3$ and dried over $Na_2SO_4$. Removal of the solvent on a rotary evaporator gave the product as a yellow oil. Yield: 0.4941 g (79%).

$^1$H NMR (500 MHz, $CDCl_3$) *δ:* 7.29-7.37 (m, 5H), 4.51 (s, 2H), 4.20 (t, J = 6.9 Hz, 2H), 3.56 (t, J = 6.3 Hz, 2H), 2.03 (s, 3H), 1.95 (p, J = 6.7 Hz, 2H)

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) *δ:* 171.19, 138.42, 128.48, 127.72, 127.71, 73.10, 66.74, 61.81, 29.13, 21.05

HRMS (APCI/Q-TOF) m/z [M+H]+ calcd for $C_{12}H_{16}O_3H^+$: 209.1178, found: 209.1177

(**(3-chloropropoxy)methyl)benzene**: A solution of 3-benzyloxy-1-propanol (0.95 mL, 6.0 mmol, 1.0 equiv.) in 20 mL diisopropyl ether was treated with triethylamine (0.13 mL, 0.90 mmol, 0.15 equiv.) and was then cooled to -10 °C with a salt-ice bath. Separately, a solution of 0.5 mL of $SOCl_2$ (7.06 mmol, 1.18 equiv.) in 20 mL of diisopropyl ether was prepared. A 10 mL portion of the $SOCl_2$ solution was added dropwise to the reaction mixture at -10 °C. The resulting solution was allowed to stir for 10 minutes, after which point the cooling bath was removed and the second portion of the $SOCl_2$ solution was added. The reaction mixture was then heated to 75 °C and stirred overnight. After cooling, the crude reaction mixture was treated with saturated aqueous $NaHCO_3$ and layers separated. The aqueous layer was extracted with three 50 mL portions of dichloromethane. The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated on a rotary evaporator to give the product as a yellow oil. Yield: 0.6792 g (61%). The compound has been previously reported.[70]

$^{1}H$ NMR (500 MHz, $CDCl_3$) *δ:* 7.22-7.28 (m, 5H), 4.44 (s, 2H), 3.60 (t, J = 6.6 Hz, 2H), 3.54 (t, J = 6.0 Hz, 2H), 1.98 (p, J = 6.1 Hz, 2H)

**((3-bromopropoxy)methyl)benzene**: A solution of $PPh_3$ (3.15 g, 12.0 mmol, 1.0 equiv.) in 34 mL of dichloromethane in the dark was treated with $Br_2$ (0.6 mL, 12.0 mmol, 1.0 equiv.) dropwise over 20 minutes. After an additional 15 minutes, a solution of 3-benzyloxy-1-propanol (1.9 mL, 12.03 mmol, 1.0 equiv.) and imidazole (0.982 g, 14.4 mmol, 1.2 equiv.) in 24 mL of DCM was added dropwise over 15 minutes. The reaction mixture was then stirred at room temperature for 2.5 hours. Upon completion, the mixture was treated with excess solid $Na_2SO_3$

and the resulting suspension concentrated under vacuum. The resulting residue was extracted with pentane, filtered, and concentrated to give a crude oil which was purified by silica gel chromatography (25% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.8104 g (58%). The compound has been previously reported.[71]

$^1$H NMR (500 MHz, $CDCl_3$) *δ:* 7.24-7.35 (m, 5H), 4.51 (s, 2H), 3.59 (t, J = 5.5 Hz, 2H), 3.52 (t, J =7.1 Hz, 2H), 2.13 (p, J = 6.1 Hz, 2H)

**((3-bromobutoxy)methyl)benzene**: A solution of $PPh_3$ (1.50 g, 5.70 mmol, 1.0 equiv.) in 16 mL of DCM in the dark was treated with $Br_2$ (0.3 mL, 5.70 mmol, 1.0 equiv.) dropwise over 20 minutes. After an additional 15 minutes, a solution of 4-(benzyloxy)butan-2-ol (1.03 g, 5.70 mmol, 1.0 equiv.) and imidazole (0.466 g, 6.84 mmol, 1.2 equiv.) in 11 mL of DCM was added dropwise over 15 minutes. The reaction mixture was then stirred at room temperature for 2.5 hours. Upon completion, the mixture was treated with excess solid $Na_2SO_3$ and the resulting suspension concentrated under vacuum. The resulting residue was extracted with pentane, filtered, and concentrated to give a crude oil which was purified by silica gel chromatography (25% EtOAc/hexanes) to give the product as a yellow oil. Yield: 0.883 g (64%).

$^1$H NMR (400 MHz, $CDCl_3$) *δ:* 7.27-7.39 (m, 5H), 4.54 (d, J = 2.2 Hz, 2H), 4.37 (sextet, J = 6.6 Hz, 1H), 3.65 (t, J = 5.6 Hz, 2H), 2.04-2.13 (m, 2H), 1.76 (d, J = 6.7 Hz, 3H)

$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) *δ:* 138.40, 128.53, 127.80, 127.78, 73.32, 68.28, 48.43, 41.22, 26.75

**((3-iodopropoxy)methyl)benzene**: A solution of $PPh_3$ (3.15 g, 12.03 mmol, 1.0 equiv.) in 34 mL of dichloromethane in the dark was treated with $I_2$ (3.05 g, 12.03 mmol, 1.0 equiv.) and stirred for 15 minutes. A solution of 3-benzyloxy-1-propanol (1.9 mL, 12.03 mmol, 1.0 equiv.) and imidazole (0.982 g, 14.4 mmol, 1.2 equiv.) in 24 mL of DCM was added over dropwise over 15

minutes. The resulting mixture was stirred at room temperature for 2.5 hours. Upon completion, the mixture was treated with excess solid $Na_2SO_3$ and the resulting suspension concentrated under vacuum. The resulting residue was extracted with pentane, filtered, and concentrated to give a crude oil which was purified by silica gel chromatography (25% EtOAc/hexanes) to give the product as a clear oil. Yield: 2.78 g (84%). The compound has been previously reported.[72]

$^1$H NMR (500 MHz, $CDCl_3$) *δ:* 7.24-7.36, (m, 5H), 4.51 (s, 2H), 3.53 (t, J = 5.8 Hz, 2H), 3.30 (t, J =6.6 Hz, 2H), 2.08 (p, J = 6.1 Hz, 2H)

**3-(3-chlorophenyl)propan-1-ol:** This compound was prepared using a reported method.[73]

**1-(3-(benzyloxy)propyl)3-chlorobenzene**: A flame-dried Schlenk flask was charged with NaH (90%, 0.066 g, 2.76 mmol, 1.3 equiv.) and 2.1 mL THF in an inert atmosphere glove box. The vessel was then brought outside of the box and attached to an oil bubbler. 3-(3-chlorophenyl)propan-1-ol (0.362 g, 2.12 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was allowed to stir at room temperature for 30 minutes before the addition of benzyl bromide (0.33 mL, 2.76 mmol, 1.3 equiv.). Upon completion, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ and the layers separated. The aqueous layer was extracted with three 50 mL portions of ethyl acetate. The combined organic layers were washed with 20 mL of 1M NaOH and 20 mL water, then dried over $Na_2SO_4$, filtered and concentrated under vacuum to give the product as a colorless oil. Yield: 0.4985 g (90%).

$^1$H NMR (500 MHz, $CDCl_3$) *δ:* 7.06-7.38 (m, 9H), 4.52 (s, 2H), 3.49 (t, J = 6.3 Hz, 2H), 2.72 (t, J = 8.0 Hz, 2H), 1.94 (p, J = 7.4 Hz, 2H)

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ:* 144.18, 138.63, 134.20, 129.68, 128.77, 128.53, 127.82, 127.73, 126.83, 126.10, 73.10, 69.30, 32.21, 31.25

HRMS (APCI/Q-TOF) m/z [M+H]+ calcd for $C_{16}H_{17}ClOH^+$: 261.1046, found: 261.1036

**3-(3-bromophenyl)propan-1-ol:** This compound was prepared using a reported method.[74]

**1-(3-(benzyloxy)propyl)3-bromobenzene:** A flame-dried Schlenk flask was charged with NaH (90%, 0.060 g, 1.93 mmol, 1.3 equiv.) and 3 mL THF in an inert atmosphere glove box. The vessel was then brought outside of the box and attached to an oil bubbler. 3-(3-bromophenyl)propan-1-ol (0.363 g, 1.48 mmol, 1.0 equiv.) was added drowise. The resulting mixture was stirred for 30 minutes at room temperature before the addition of benzyl bromide (0.23 mL, 1.92 mmol, 1.3 equiv.). Upon completion, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ and the layers separated. The aqueous layer was extracted with three 50 mL portions of ethyl acetate. The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under vacuum. The resulting oil was then purified by silica gel chromatography (5% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.4084 g (91%). This compound has been previously reported.[75]

$^1$H NMR (500 MHz, $CDCl_3$) *δ:* 7.32-7.38 (m, 7H), 7.11-7.17 (m, 2H), 4.52 (s, 2H), 3.49 (t, J = 6.2 Hz), 2.71 (t, J = 8.1 Hz, 2H), 1.94 (p, J = 6.1 Hz, 2H)

**3-(3-iodophenyl)propanoic acid:** A flame-dried Schlenk flask was charged with formic acid (0.25 mL, 6.46 mmol, 3.0 equiv.) and triethylamine (0.36 mL, 2.59 mmol, 1.2 equiv.) under nitrogen. After 15 min, 2 mL DMF was added followed by 3-iodobenzaldehyde (0.500 g, 2.15 mmol, 1.0 equiv.) and Meldrum's acid (0.311 g, 2.16 mmol, 1.0 equiv.). The resulting mixture was heated to 100 °C and stirred overnight. Upon completion, the solution was poured into 15 mL ice water and extracted two 15 mL portions of dichloromethane. The combined organic layers were shaken with a 10% aqueous NaOH solution and the layers were separated. The aqueous layer was acidified with concentrated aqueous HCl and extracted with EtOAc. The organic extract was washed with water, brine, dried over $Na_2SO_4$ and concentrated under vacuum to give the product

as an off-white solid. Yield: 0.5664 g (95%). Spectroscopic data for this product has been previously reported.[76]

$^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.55-7.58 (m, 2H), 7.17-7.19 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 2.90 (t, J = 7.8 Hz, 2H), 2.67 (t, J = 7.7 Hz, 2H)

**3-(3-iodophenyl)propan-1-ol:** This compound was prepared using a reported method.[77]

**1-(3-(benzyloxy)propyl)3-iodobenzene:** A flame-dried Schlenk flask was charged with NaH (90%, 0.053 g, 2.22 mmol, 1.3 equiv.) and 1.7 mL THF in an inert atmosphere glove box. The vessel was then brought outside of the box and attached to an oil bubbler. 3-(3-iodophenyl)propan-1-ol (0.448 g, 1.71 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was allowed to stir at room temperature for 30 minutes before the addition of benzyl bromide (0.26 mL, 2.22 mmol, 1.3 equiv.). Upon completion, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ and the layers separated. The aqueous layer was extracted with three 50 mL portions of ethyl acetate. The combined organic layers were washed with 20 mL of 1M NaOH and 20 mL water, then dried over $Na_2SO_4$, filtered and concentrated under vacuum to give the product as a colorless oil. Yield: 0.1027 g (90%)

$^1$H NMR (500 MHz, $CDCl_3$) *δ:* 7.51-7.57 (m, 2H), 7.31-7.41 (m, 5H), 7.13-7.18 (m, 1H), 7.01 (t, J = 7.7 Hz, 1H), 4.51 (s, 2H), 3.48 (t, J = 6.2 Hz, 2H), 2.67 (t, J = 7.9 Hz, 2H), 1.90 (p, J = 6.7 Hz, 2H)

$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) *δ:* 144.62, 138.63, 137.68, 135.01, 130.20, 128.55, 127.94, 127.82, 127.74, 94.62, 73.11, 69.31, 32.10, 31.30

HRMS (APCI$^-$/Q-TOF) m/z [M+H]- calcd for $C_{16}H_{17}IO^-$: 351.0246, found: 351.0232

**Methyl 3-(3-hydroxyphenyl)propanoate**: This compound was prepared using a reported method.[78]

**Methyl 3-(3-((triisopropylsilyl)oxy)phenyl)propanoate**: A flame-dried Schlenk flask was charged with 6 mL DMF, methyl 3-(3-hydroxyphenyl)propanoate (2.12 g, 11.8 mmol, 1.0 equiv.), and imidazole (2.41 g, 35.4 mmol, 3.0 equiv.) under nitrogen. The mixture was stirred for 10 min at room temperature followed by the dropwise addition of triisopropylchlorosilane (3.8 mL, 17.7 mmol, 1.5 equiv.). After stirring overnight the reaction mixture was quenched with $H_2O$ and extracted with diethyl ether. The combined organic layers were washed with water and brine and dried over $Na_2SO_4$ then concentrated under vacuum. The resulting crude residue was purified using silica gel chromatography to give the product as a pale yellow oil. Yield: 2.98 g (75%)

$^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.12 (t, J = 8.4 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 6.72 (s, 2H), 3.67 (s, 3H), 2.89 (t, J = 8.2 Hz, 2H), 2.61 (t, J = 8.2 Hz, 2H), 1.24 (sextet, J = 7.7 Hz, 3H), 1.10 (d, J = 7.7 Hz, 18H)

$^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ 173.46, 156.28, 142.10, 129.46, 121.08, 119.98, 117.90, 51.72, 35.79, 30.98, 18.05, 12.81

HRMS (APCI/Q-TOF) m/z [M+H]+ calcd for $C_{19}H_{32}O_3SiH^+$: 337.2199, found: 337.2194

**3-(3-((triisopropylsilyl)oxy)phenyl)propan-1-ol**: A solution of $LiAlH_4$ (0.402 g, 10.6 mmol, 1.2 equiv.) in 9 mL dry THF was prepared and cooled to 0 °C. A solution of methyl 3-(3-((triisopropylsilyl)oxy)phenyl)propanoate (2.98 g, 8.85 mmol, 1.0 equiv.) in 9 mL THF was then added dropwise. The bath was removed and the mixture was allowed to come to room temperature where it was stirred for 3 hours. At this point the vessel was cooled back to 0 °C and treated with 10 mL of ether followed by the dropwise addition of 0.6 mL of water, 0.6 mL of a 15% aqueous NaOH solution and 1.8 mL of water. The reaction mixture was then warmed to room temperature and stirred for 15 minutes. Anhydrous $Na_2SO_4$ was then added with vigorous stirring for an additional 15 minutes. The material was filtered and the filtrate layers were separated. The organic

layer was dried over $Na_2SO_4$ and concentrated under vacuum to give the product as a yellow oil. Yield: 2.27 g (56%).

$^1H$ NMR (500 MHz, $CDCl_3$) *δ:* 7.12 (t, J = 7.9 Hz, 1H), 6.71-6.78 (m, J = 7.5 Hz, 3H), 3.66 (s, 2H), 2.65 (t, J = 7.9 Hz, 2H), 1.87 (p, J = 7.4 Hz, 2H), 1.25 (sextet, J = 8.0 Hz, 3H), 1.10 (d, J = 7.2 Hz, 18H)

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ:* 156.23, 143.41, 129.31, 121.28, 120.16, 117.49, 62.43, 34.26, 32.12, 18.06, 12.82

HRMS (APCI/Q-TOF) m/z [M+H]+ calcd for $C_{18}H_{32}O_2SiH^+$: 309.2250, found: 309.2262

**(3-(3-(benzyloxy)propyl)phenoxy)triisopropylsilane:** A flame-dried Schlenk flask was charged with NaH (90%, 0.229 g, 9.55 mmol, 1.3 equiv.) and 7.3 mL THF in an inert atmosphere glove box. The vessel was then brought outside of the box and attached to an oil bubbler. A solution of 3-(3-((triisopropylsilyl)oxy)phenyl)propan-1-ol (2.27 g, 7.35 mmol, 1.0 equiv.) in 7 mL THF was added dropwise. The reaction mixture was allowed to stir at room temperature for 30 minutes before the addition of benzyl bromide (1.1 mL, 9.6 mmol, 1.1 equiv.). Upon completion, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ and the layers separated. The aqueous layer was extracted with three 50 mL portions of ethyl acetate. The combined organic layers were washed with 20 mL of 1M NaOH and 20 mL water, then dried over $Na_2SO_4$, filtered and concentrated under vacuum. The resulting oil was then purified by silica gel chromatography (1% to 2% EtOAc/hexanes) to give the product as a colorless oil. Yield: 2.01 (69%).

$^1H$ NMR (500 MHz, $CDCl_3$) *δ:* 7.24-7.35 (m, 5H), 7.08-7.12 (m, 1H), 6.69-6.75 (m, 3H), 4.49 (s, 2H), 3.48 (t, J = 6.4 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 1.91 (p, J =7.1 Hz, 2H), 1.24 (sextet, J = 7.6 Hz, 3H), 1.09 (d, J = 7.1 Hz, 18H)

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) *δ:* 156.17, 143.60, 138.74, 129.22, 128.51, 127.78, 127.66, 121.38, 120.23, 117.41, 73.09, 69.71, 32.41, 31.41, 18.08, 12.83

HRMS (APCI/Q-TOF) m/z $[M+H]^+$ calcd for $C_{25}H_{38}O_2SiH^+$: 399.2719, found: 399.2730

**3-(3-(benzyloxy)propyl)phenol:** (3-(3-(benzyloxy)propyl)phenoxy)triisopropylsilane (1.66 g, 4.16 mmol, 1.0 equiv.) was taken up in 21 mL THF and treated with tetra-n-butylammonium fluoride (1.71 g, 5.41 mmol, 1.3 equiv.) at 0 °C. After stirring overnight at room temperature 20 mL ethyl acetate was added. The solution was extracted with three 20 mL portions of water and three 15 mL portions of brine. The organic phase was then dried over $Na_2SO_4$, filtered, and concentrated under vacuum. The residue was then purified by silica gel chromatography to give the product as an oil. Yield: 0.7405 g (74%).

$^{1}H$ NMR (400 MHz, $CDCl_3$) *δ:* 7.37 (d, J = 4.4 Hz, 4H), 7.28-7.34 (m, 1H), 7.14 (t, J = 7.8 Hz, 1H), 6.75 (d, 7.5 Hz, 1H), 6.61-6.66 (m, 2H), 5.08 (bs, 1H), 4.53 (s, 2H), 3.51 (t, J = 6.3 Hz, 2H), 2.67 (t, J = 7.8 Hz, 2H), 1.90-1.97 (m, 2H)

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) *δ:* 155.72, 143.97, 138.55, 129.61, 128.54, 127.95, 127.74, 121.02, 115.54, 112.85, 73.05, 69.52, 32.30, 31.23

HRMS ($APCI^-$/Q-TOF) m/z $[M-H]^-$ calcd for $C_{16}H_{17}O_2^-$: 241.1229, found: 241.1219

**3-(3-(benzyloxy)propyl)phenyl trifluoromethanesulfonate:** A flame dried Schlenk flask was charged with 3-(3-(benzyloxy)propyl)phenol (0.200 g, 0.83 mmol, 1.0 equiv.), 4.1 mL dichloromethane, 2,6-lutidine (0.15 mL, 1.24 mmol, 1.5 equiv.) and DMAP (0.020 g, 0.17 mmol, 0.2 equiv.). The resulting solution was cooled to 0 °C and triflic anhydride (0.21 mL, 1.24 mmol, 1.5 equiv.) was added dropwise. The mixture was then allowed to come to room temperature and the reaction was stirred for 3.5 hours. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ and then extracted with two 30 mL portions of dichloromethane. The combined organic

layers were then washed sequentially with 30 mL water, 30 mL saturated aqueous $NaHCO_3$, and 30 mL water. The organic layer was then dried over $Na_2SO_4$, filtered, and concentrated under vacuum. The resulting residue was then purified by silica gel chromatography (10% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.2061 g (67%).

$^1H$ NMR (400 MHz, $CDCl_3$) *δ:* 7.10-7.39 (m, 9H), 4.52 (s, 2H), 3.49 (t, J = 5.9 Hz, 2H), 2.79 (t, J = 8.0 Hz, 2H), 1.91-1.98 (m, 2H)

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ:* 149.80, 145.24, 138.54, 130.15, 128.71, 128.56, 127.85, 127.79, 121.43, 118.91 (q, $^1J_{C-F}$ = 320.9 Hz), 118.74, 73.17, 69.05, 32.23, 31.18

HRMS (APCI$^-$/Q-TOF) m/z $[M-H]^-$ calcd for $C_{17}H_{16}F_3O_4S^-$: 373.0721, found: 373.0705

**2-(3-((3-(benzyloxy)propoxy)methyl)phenyl)-4,4,5,5,-tetramethyl-1,3,2-dioxaborolane:**

A flame-dried Schlenk flask under $N_2$ was charged with 1-(3-(benzyloxy)propyl)3-bromobenzene (0.200 g, 0.65 mmol, 1.0 equiv.) and 2.2 mL THF and the resulting solution was cooled to -78 °C. A solution of 2.5M $^n$BuLi in hexanes (0.3 mL, 0.72 mmol, 1.1 equiv.) was then added and the solution was allowed to stir for one hour. A solution of $B_2Pin_2$ (0.219 g, 0.87 mmol, 1.2 equiv.) in 2.2 mL THF was then added, at which point the solution was allowed to warm to room temperature overnight. Upon completion the reaction mixture was quenched with 1M aqueous HCl and the phases separated. The aqueous layer was extracted with three 25 mL portions of diethyl ether and the combined organic extracts were then dried over $Na_2SO_4$, filtered, and concentrated under vacuum. The resulting residue was purified by silica gel chromatography (5% to 10% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.1518 g (66%)

$^1H$ NMR (400 MHz, $CDCl_3$) *δ:* 7.64-7.67 (m, 2H), 7.35 (d, J = 4.5 Hz, 4H), 7.29 (d, J = 5 Hz, 3H), 4.51 (s, 2H), 3.49 (t, J = 6.3 Hz, 2H), 2.73 (t, J = 8.0 Hz, 2H), 1.96 (p, J = 7.5 Hz, 2H), 1.35 (s, 12H)

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) *δ:* 141.38, 138.76, 134.98, 132.38, 131.63, 128.49, 127.89, 127.81, 127.64, 83.86, 73.04, 69.75, 32.44, 31.56, 25.01 (*Note:* A $^{13}C$ resonance for the aromatic boron-attached carbon is not observed.)

HRMS (APCI/Q-TOF) m/z $[M+H]^+$ calcd for $C_{22}H_{29}BO_3H^+$: 353.2288, found: 353.2274

**3-(3-nitrophenyl)propanol:** This compound was prepared using a reported method.[79]

**1-(3-(benzyloxy)propyl)phenyl-3-nitrobenze:** A flame-dried Schlenk flask was charged with NaH (90%, 0.1630 g, 6.67 mmol, 1.3 equiv.) and 5.1 mL THF in an inert atmosphere glove box. The vessel was then brought outside of the box and attached to an oil bubbler. A solution of 3-(3-nitrophenyl)propanol: (0.929 g, 5.13 mmol, 1.0 equiv.) in 5 mL THF was added dropwise. The reaction mixture was allowed to stir at room temperature for 30 minutes before the addition of benzyl bromide (0.8 mL, 6.67 mmol, 1.3 equiv.). Upon completion, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ and the layers separated. The aqueous layer was extracted with three 50 mL portions of ethyl acetate. The combined organic layers were washed with 20 mL of 1M NaOH and 20 mL water, then dried over $Na_2SO_4$, filtered and concentrated under vacuum. The resulting oil was then purified by silica gel chromatography (10% to 25% EtOAc/hexanes) to give the product as a yellow oil. Yield: 0.972 g (70%).

$^{1}H$ NMR (300 MHz, $CDCl_3$) *δ:* 8.03-8.06 (m, 2H), 7.25-7.51 (m, 7H), 4.51 (s, 2H), 3.49 (t, J = 6.2 Hz, 2H), 2.84 (t, J = 8.0 Hz, 2H), 1.96 (pent, J = 6.7 Hz, 2H)

**General procedure for ether silylation:**

In an inert-atmosphere glove box a 20 mL scintillation vial was charged with a stir bar, the solid precatalyst $[H_2Ir(PPh_3)_2(THF)_2]BAr^F{}_4$ (0.03 equiv.), and dry, degassed toluene (1 mL per 0.30 mmol of ether substrate). The $HSiEt_3$ (2.2 equiv.) was then added followed by the substrate ether (1.0 equiv.). The vial was fitted with a cap and removed from the glove box. The reaction mixture

was stirred at room temperature for 2 hours and the resulting products purified by silica gel chromatography.

**(3-chloropropoxy)triethylsilane:** This compound was prepared according to the general procedure. $[H_2Ir(PPh_3)_2(THF)_2]BAr^F_4$ (0.028 g, 0.016 mmol, 0.03 equiv.), and 1.8 mL toluene were combined in a vial which was treated with $HSiEt_3$ (0.19 mL, 1.19 mmol, 2.2 equiv.) followed by ((3-chloropropoxy)methyl)benzene (0.100 g, 0.54 mmol, 1.0 equiv.). The crude reaction mixture was purified by silica gel chromatography (1% EtOAc/hexanes to 2% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.0799 g (71%).

$^1H$ NMR (500 MHz, $CDCl_3$) *δ:* 3.75 (t, J = 6.0, 2H), 3.65 (t, J = 6.4 Hz, 2H), 1.96 (p, J = 5.9 Hz, 2H), 0.96 (t, J = 8.0 Hz, 9H), 0.60 (q, J = 7.9 Hz, 6H)

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ:* 59.25, 41.89, 35.62, 6.84, 4.47

HRMS (APCI/Q-TOF) m/z $[M+H]^+$ calcd for $C_9H_{21}ClOSiH^+$: 209.1128, found: 209.1131

**(3-bromopropoxy)triethylsilane:** This compound was prepared according to the general procedure. $[H_2Ir(PPh_3)_2(THF)_2]BAr^F_4$ (0.0226 g, 0.013 mmol, 0.03 equiv.), and 1.5 mL toluene were combined in a vial which was treated with $HSiEt_3$ (0.16 mL, 0.96 mmol, 2.2 equiv.) followed by ((3-bromopropoxy)methyl)benzene (0.100 g, 0.44 mmol, 1.0 equiv.). The crude reaction mixture was purified by silica gel chromatography (1% EtOAc/hexanes to 2% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.074 g (67%).

$^1H$ NMR (300 MHz, $CDCl_3$) *δ:* 3.74 (t, J = 5.5, 2H), 3.52 (t, J = 6.4 Hz, 2H), 2.04 (p, J = 5.8 Hz, 2H), 0.96 (t, J = 8.1 Hz, 9H), 0.61 (q, J = 8.1 Hz, 6H)

$^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) *δ:* 60.26, 35.73, 30.77, 6.87, 4.46

**(3-iodopropoxy)triethylsilane:** This compound was prepared according to the general procedure. $[H_2Ir(PPh_3)_2(THF)_2]BAr^F_4$ (0.0190 g, 0.011 mmol, 0.03 equiv.), and 1.2 mL toluene

were combined in a vial which was treated with $HSiEt_3$ (0.13 mL, 0.80 mmol, 2.2 equiv.) followed by ((3-iodopropoxy)methyl)benzene (0.100 g, 0.36 mmol, 1.0 equiv.). The crude reaction mixture was purified by silica gel chromatography (1% EtOAc/hexanes to 2% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.0656 g (60%).

$^1H$ NMR (500 MHz, $CDCl_3$) *δ:* 3.67 (t, J = 5.6, 2H), 3.28 (t, J = 6.6 Hz, 2H), 2.00 (p, J = 6.0 Hz, 2H), 0.96 (t, J = 8.4 Hz, 9H), 0.61 (q, J = 7.8 Hz, 6H)

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ:* 62.25, 36.40, 6.92, 4.52, 3.73

HRMS (APCI/Q-TOF) m/z $[M+H]^+$ calcd for $C_9H_{21}IOSiH^+$: 301.0485, found: 301.0475

**(3-bromobutoxy)triethylsilane:** This compound was prepared according to the general procedure. $[H_2Ir(PPh_3)_2(THF)_2]BAr^F_4$ (0.0213 g, 0.012 mmol, 0.03 equiv.), and 1.4 mL toluene were combined in a vial which was treated with $HSiEt_3$ (0.15 mL, 0.90 mmol, 2.2 equiv.) followed by ((3-bromobutoxy)methyl)benzene (0.100 g, 0.41 mmol, 1.0 equiv.). The crude reaction mixture was purified by silica gel chromatography (1% EtOAc/hexanes to 2% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.051 g (46%).

$^1H$ NMR (500 MHz, $CDCl_3$) *δ:* 4.32 (sext, J = 6.8 Hz, 1H), 3.75 (t, J = 5.6, 2H), 1.98 (q, J = 6.1 Hz, 2H), 1.74 (d, J = 6.6 Hz, 3H), 0.96 (t, J = 7.71 Hz, 9H), 0.61 (q, J = 7.8 Hz, 6H)

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ:* 60.80, 48.46, 43.03, 26.83, 6.91, 4.51

HRMS (ESI/Q-TOF) m/z $[M+H]^-$ calcd for $C_{10}H_{22}BrOSi^-$: 265.0623, found: 265.0630

**(3-(3-bromophenyl)propoxy)triethylsilane:** This compound was prepared according to the general procedure. $[H_2Ir(PPh_3)_2(THF)_2]BAr^F_4$ (0.020 g, 0.012 mmol, 0.03 equiv.), and 1.3 mL toluene were combined in a vial which was treated with $HSiEt_3$ (0.14 mL, 0.84 mmol, 2.2 equiv.) followed by 1-(3-(benzyloxy)propyl)-3-chlorobenzene (0.100 g, 0.38 mmol, 1.0 equiv.). The crude

reaction mixture was purified by silica gel chromatography (1% EtOAc/hexanes to 2% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.0836 g (76%).

$^{1}$H NMR (500 MHz, $CDCl_3$) *δ:* 7.14-7.20 (m, 3H), 7.06 (d, J = 7.7 Hz, 1H), 3.62 (t, J = 6.3, 2H), 2.66 (t, J = 7.6 Hz, 2H), 1.82 (p, J = 7.5 Hz, 2H), 0.96 (t, J = 7.9 Hz, 9H), 0.60 (q, J = 7.9 Hz, 6H)

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) *δ:* 144.43, 134.16, 129.63, 128.74, 126.78, 126.00, 61.94, 34.28, 31.96, 6.93, 4.57

HRMS (APCI$^-$/Q-TOF) m/z $[M-H]^-$ calcd for $C_{15}H_{24}ClOSi^-$: 283.1285, found: 283.1298

**(3-(3-bromophenyl)propoxy)triethylsilane:** This compound was prepared according to the general procedure. $[H_2Ir(PPh_3)_2(THF)_2]BAr^F_4$ (0.017 g, 0.010 mmol, 0.04 equiv.), and 1.1 mL toluene were combined in a vial which was treated with $HSiEt_3$ (0.12 mL, 0.72 mmol, 2.7 equiv.) followed by 1-(3-(benzyloxy)propyl)-3-bromobenzene (0.081 g, 0.27 mmol, 1.0 equiv.). The crude reaction mixture was purified by silica gel chromatography (1% EtOAc/hexanes to 2% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.0672 g (77%).

$^{1}$H NMR (500 MHz, $CDCl_3$) *δ:* 7.34 (s, 1H), 7.31 (d, J = 6.24 Hz, 1H), 7.10-7.14 (m, 2H), 3.62 (t, J = 5.8, 2H), 2.65 (t, J = 8.0 Hz, 2H), 1.82 (p, J = 6.9 Hz, 2H), 0.96 (t, J = 7.7 Hz, 9H), 0.60 (q, J = 7.7 Hz, 6H)

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) *δ:* 144.75, 131.68, 129.95, 128.93, 127.25, 122.49, 61.91, 34.29, 31.94, 6.93, 4.58

HRMS (APCI/Q-TOF) m/z $[M+H]^+$ calcd for $C_{15}H_{24}BrOSiH^+$: 329.0936, found: 329.0948

**(3-(3-iodophenyl)propoxy)triethylsilane:** This compound was prepared according to the general procedure. $[H_2Ir(PPh_3)_2(THF)_2]BAr^F_4$ (0.0142 g, 0.0082 mmol, 0.03 equiv.), and 0.95 mL toluene were combined in a vial which was treated with $HSiEt_3$ (0.10 mL, 0.62 mmol, 2.2 equiv.) followed by 1-(3-(benzyloxy)propyl)-3-iodobenzene (0.100 g, 0.28 mmol, 1.0 equiv.). The crude

reaction mixture was purified by silica gel chromatography (1% EtOAc/hexanes to 2% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.1051 g (98%).

$^{1}$H NMR (500 MHz, $CDCl_3$) *δ:* 7.56 (s, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.14 (d, J = 7.7 Hz, 2H), 6.99 (t, J = 8.1 Hz, 1H), 3.61 (t, J = 6.3, 2H), 2.62 (t, J = 7.8 Hz, 2H), 1.81 (p, J = 6.6 Hz, 2H), 0.96 (t, J = 8.1 Hz, 9H), 0.60 (q, J = 7.9 Hz, 6H)

$^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) *δ:* 144.85, 137.65, 134.91, 130.14, 127.88, 94.55, 61.89, 34.28, 31.82, 6.94, 4.58

HRMS (APCI/Q-TOF) m/z $[M+H]^+$ calcd for $C_{15}H_{24}IOSiH^+$: 377.0798, found: 377.0785

**(3-(3-(triethylsilyl)oxy)propyl)phenyl) triflate:** This compound was prepared according to the general procedure. $[H_2Ir(PPh_3)_2(THF)_2]BAr^F_4$ (0.0138 g, 0.0080 mmol, 0.03 equiv.), and 0.90 mL toluene were combined in a vial which was treated with $HSiEt_3$ (0.95 mL, 0.59 mmol, 2.2 equiv.) followed by 3-(3-(benzyloxy)propyl)phenyl triflate (0.100 g, 0.27 mmol, 1.0 equiv.). The crude reaction mixture was purified by silica gel chromatography (1% EtOAc/hexanes to 2% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.101 g (95%).

$^{1}$H NMR (500 MHz, $CDCl_3$) *δ:* 7.33 (t, J = 7.7, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.08-7.10 (m, 2H), 3.63 (t, J = 6.2, 2H), 2.74 (t, J = 7.7 Hz, 2H), 1.84 (p, J = 6.9 Hz, 2H), 0.97 (t, J = 7.6 Hz, 9H), 0.60 (q, J = 8.1 Hz, 6H)

$^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) *δ:* 149.81, 145.52, 130.08, 128.67, 121.37, 118.91 (q, $^{1}J_{C-F}$ = 320.9 Hz), 118.64, 61.71, 34.14, 31.97, 6.88, 4.54

HRMS (APCI/Q-TOF) m/z $[M+H]^+$ calcd for $C_{16}H_{25}F_3O_4SSiH^+$: 399.1273, found: 399.1268

**3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-1-ol:** This compound was prepared according to the general procedure. $[H_2Ir(PPh_3)_2(THF)_2]BAr^F_4$ (0.0147 g, 0.0085 mmol, 0.03 equiv.), and 1.0 mL toluene were combined in a vial which was treated with

$HSiEt_3$ (1.0 mL, 0.62 mmol, 2.2 equiv.) followed by 2-(3-(3-(benzyloxy)propyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.100 g, 0.28 mmol, 1.0 equiv.). After 2 hours, the solution was concentrated on a rotatory evaporator and the resulting residue was dissolved in 1.4 mL of THF. The mixture was cooled to 0 °C and tetra-n-butylammonium fluoride (0.200 g, 0.63 mmol, 2.2 equiv.) was added. This solution was allowed to come to room temperature and was stirred for 30 minutes before being diluted with 2 mL of EtOAc and extracted with water and brine. The organic layer was separated, dried over $Na_2SO_4$, and concentrated on a rotary evaporator. This residue was purified by silica gel chromatography (25% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.0299 g (40%).

*Note:* NMR Analysis suggests benzyl cleavage proceeds in high yield (>90%); however, we have not been able to purify the resulting triethylsilyl ether. We suspect the low yields of the free alcohol obtained results from challenges in the selective desilylation of the product of benzylic ether cleavage.

$^1$H NMR (500 MHz, $CDCl_3$) *δ:* 7.65 (s, 2H), 7.29 (d, J = 4.0 Hz, 2H), 3.66 (t, J = 6.3, 2H), 2.71 (t, J = 7.3 Hz, 2H), 1.90 (p, J = 7.4 Hz, 2H), 1.34 (s, 12H)

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ:* 141.20, 134.88, 132.50, 131.57, 127.97, 83.90, 62.47, 34.45, 32.10, 25.00. (*Note:* A $^{13}$C resonance for the aromatic boron-attached carbon is not observed.)

HRMS (APCI/Q-TOF) m/z $[M+H]^+$ calcd for $C_{15}H_{23}BrO_3H^+$: 263.1818, found: 263.1831

**(3-(benzyloxy)propoxy)(tert-butyl)dimethylsilane:**

In an inert atmosphere glovebox, a 20 mL scintillation vial was charged with $[H_2Ir(PPh_3)_2(THF)_2]BAr^F_4$ (0.0312 g, 0.018 mmol, 0.03 equiv.) and 2 mL toluene followed by tert-butyl(dimethyl)silane (0.11 mL, 0.662 mmol, 1.1 equiv.) and 3-benzyloxy-1-propanol (95 μL, 0.602 mmol, 1.0 equiv.). The resulting solution was stirred for 15 minutes before being filtered

through a short filter pad of silica using diethyl ether. The filtrate was then concentrated by rotatory evaporation and the resulting residue was purified by silica gel chromatography (5% EtOAc/hexanes) to give the product as a yellow oil. Yield: 0.1533 g (91%). Spectroscopic data for this product have been previously reported.[80]

$^1$H NMR (500 MHz, $CDCl_3$) δ: 7.26-7.34 (m, 5H), 4.50 (s, 2H), 3.72 (t, J = 6.3 Hz, 2H), 3.57 (t, J = 6.3 Hz, 2H), 1.83 (t, J = 6.3, 2H), 0.89 (s, 9H), 0.05 (s, 6H)

**9,9-diethyl-2,2,3,3-tetramethyl-4,8-dioxa-3,9-disilaundecane:**

This compound was prepared according to a variation to the general procedure. In an inert atmosphere glovebox, a 20 mL scintillation vial was charged with $[H_2Ir(PPh_3)_2(THF)_2]BAr^F{}_4$ (0.0312 mg, 0.018 mmol, 0.03 equiv.) and 2 mL toluene followed by tert-butyl(dimethyl)silane (0.11 mL, 0.662 mmol, 1.1 equiv.) and 3-benzyloxy-1-propanol (95 µL, 0.602 mmol, 1.0 equiv.). The resulting solution was stirred for 15 minutes, at which point ethyl(dimethyl)silane (0.20 mL, 1.05 mmol, 2.2 equiv.) was added. The reaction mixture stirred for two hours and was purified by silica gel chromatography (1% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.1365 g (78%).

$^1$H NMR (500 MHz, $CDCl_3$) *δ:* 3.67-3.71 (m, 4H), 1.73 (t, J = 6.4 Hz, 2H), 0.95 (t, J = 7.9 Hz, 6H), 0.90 (s, 9H), 0.56-0.61 (m, 4H), 0.05 (2s, 9H)

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ:* 59.83, 59.50, 36.05, 26.07, 18.45, 6.89, 6.37, -4.88, -5.22

HRMS (APCI/Q-TOF) m/z $[M+H]^+$ calcd for $C_{14}H_{34}O_2Si_2H^+$: 291.2175, found: 291.2174

**Catalytic ether silylation conducted with $(PPh_3)_2IrH_5$ (3) as the precatalyst (eqn. 3):**

In an inert-atmosphere glove box, a septum-capped NMR tube was charged with $(PPh_3)_2IrH_5$ (**3**) (0.0032 g, 0.0045 mmol, 0.03 equiv.) followed by 0.5 mL of $C_6D_6$. Triethylsilane (53 µL, 0.33 mmol, 2.2 equiv.) was then added and the NMR tube was inverted to ensure appropriate mixing.

Benzyl heptyl ether (37 μL, 0.15 mmol, 1.0 equiv.) was then added and the NMR tube was inverted once more. The reaction was monitored by $^{1}H$ NMR. As no change was observed at 25 °C, the sample was heated to 40 °C for 2 hours and then to 60 °C for 16 hours. No substrate reduction was observed. Analysis by $^{31}P\{^{1}H\}$ NMR at various points show complete consumption of **3** and formation of complex **4**.

**Catalytic ether silylation conducted with complex 4 and $[CPh_3]BAr^F_4$ (eqn. 4):**

In an inert-atmosphere glove box, a septum-capped NMR tube was charged with $(PPh_3)_2IrH_5$ (**3**) (0.0032 g, 0.0045 mmol, 0.03 equiv.) followed by 0.25 mL of $C_6D_6$. Triethylsilane (26.2 μL, 0.17 mmol, 1.1 equiv.) was then added and the NMR tube was heated to 80 °C for three minutes with periodic agitation of the reaction vessel. Analysis of this sample by $^{31}P\{^{1}H\}$ and $^{1}H$ NMR show complete consumption of **3** and formation of complex **4**. The NMR tube was then brought back into the glovebox and the solution was frozen solid using a cold well. In a separate vial a solution of $[CPh_3]BAr^F_4$ (0.0053 g, 0.0048 mmol, 0.032 equiv.) in 0.25 mL of $C_6D_6$ was prepared. Triethylsilane (26.2 μL, 0.17 mmol, 1.1 equiv.) was then added followed by benzyl heptyl ether (37 μL, 0.15 mmol, 1.0 equiv.). The resulting solution was transferred into the NMR tube and layered onto the frozen iridium solution in the cold well. The sample was allowed to freeze solid. The sealed NMR tube was then brought out of the box and thawed immediately before analysis by NMR. Quantitative conversion of benzyl heptyl ether to triethyl(heptyloxy)silane was observed within 10 minutes.

**Catalytic ether silylation conducted in the presence of excess mercury (eqn. 6).**

To a 4 mL vial containing a stir bar was added $Hg^0$ (0.033 g, 0.17 mmol, 4.20 equiv.) followed by $[H_2Ir(PPh_3)_2(THF)_2]BAr^F_4$ (0.0020 g, 0.0012 mmol, 0.03 equiv.) as a solution in $C_6D_6$. The solution was then diluted to 0.5 mL of $C_6D_6$. Triethylsilane (13.7 μL, 0.085 mmol, 2.2 equiv.) was

then added and the solution was stirred briefly to ensure appropriate mixing. Benzyl heptyl ether (8.9 μL, 0.039 mmol 1.0 equiv.) was then added and the solution was allowed to stir vigorously for two hours, ensuring maximal contact between the liquid mercury and the reaction solvent. The solution was then transferred to an NMR tube and 10 μL of pyridine was added as an internal standard. The NMR yield was determined to be >98%.

**Catalytic ether silylation conducted with complex 4 and $NaBAr^F_4$:**

In an inert-atmosphere glove box, a septum-capped NMR tube was charged with $(PPh_3)_2IrH_5$ (3) (0.0032 g, 0.0045 mmol, 0.03 equiv.) followed by 0.25 mL of $C_6D_6$. Triethylsiane (26.2 μL, 0.17 mmol, 1.1 equiv.) was then added and the NMR tube was heated to 80 °C for three minutes with periodic agitation of the reaction vessel. Analysis of this sample by $^{31}P\{^1H\}$ and $^1H$ NMR show complete consumption of **3** and formation of complex **4**. The NMR tube was then brought back into the glovebox and the solution was frozen solid using a cold well. In a separate vial a solution of $NaBAr^F_4$ (0.0043 g, 0.0048 mmol, 0.032 equiv.) in 0.25 mL of $C_6D_6$ was prepared. Triethylsilane (26.2 μL, 0.17 mmol, 1.1 equiv.) was then added followed by benzyl heptyl ether (37 μL, 0.15 mmol, 1.0 equiv.). The resulting solution was transferred into the NMR tube and layered onto the frozen iridium solution in the cold well. The sample was allowed to freeze solid. The sealed NMR tube was then brought out of the box and thawed immediately before analysis by NMR. No reaction was observed over 30 minutes at room temperature.

**Observation of complex 2 resulting from hydride abstraction from 4:**

In an inert-atmosphere glove box, a septum-capped NMR tube was charged with $(PPh_3)_2IrH_5$ (**3**) (0.0100 g, 0.0139 mmol, 1.0 equiv.) followed by 0.5 mL of $C_6D_6$ and triethylsilane (22.5 μL, 0.139 mmol, 10 equiv.). The suspension was then heated to 80 °C until a clear solution formed (~ 3 minutes). The mixture was brought back into the glove box and the solution was concentrated

under vacuum. The resulting solid was dissolved in 0.5 mL of THF and was treated with $[Ph_3C]BAr^F{}_4$ (0.0153 g, 0.0139 mmol, 1.0 equiv). Analysis by $^{31}P\{^1H\}$ NMR gave a single signal at 30.4 ppm which was assigned as complex **2** by comparison to the authentic material in THF.

**Methoxycyclohexane:** This compound was prepared by a reported method.[81]

***Trans*-4-(tert-butyl)cyclohexan-1-ol:** This compound was prepared by a reported method.[82]

***Trans*-4-(tert-butyl)cyclohexan-1-ol:** This compound was prepared by a reported method.[82]

***Trans*-1-(tert-butyl)-4-methoxycyclohexane:** This compound was prepared by a reported method.[83]

***Cis*-1-(tert-butyl)-4-methoxycyclohexane:** This compound was prepared by a reported method.[83]

**5α-cholestan-3α-ol:** This compound was prepared by a reported method.[84]

**3α,7α,12α,24-tetrahydroxycholane:** This compound was prepared by a reported method at 23 °C.[85]

**3α,7α,12α-trihydroxy-24-*t*-butyldiphenylsiloxycholane:** This compound was prepared by a reported method.[86]

**3α,7α,24-trihydroxycholane:** This compound was prepared by a reported method.[87]

**3α,12α,24-trihydroxycholane:** This compound was prepared by a reported method at 23 °C.[85]

**3α,24-dihydroxycholane:** This compound was prepared by a reported method.[88]

**Representative procedure for the TBDPS protection of cholic acid derivatives**

**24-tert-butyldiphenylsilyloxy-3α,7α-dihydroxycholane:** A flame-dried Schlenk flask under $N_2$ was charged with 3α,7α,24-trihydroxycholane (7.52 g, 19.9 mmol) in 15.0 mL of dry DMF and cooled to 0 °C. The flask was then charged with imidazole (2.70 g, 39.7 mmol) and was allowed

to stir until the mixture was homogeneous. To the Schlenk flask was added tert-butylchlorodiphenylsilane (TBDPSCl) dropwise (21.35 mmol, 5.7 mL). The reaction was allowed to stir for 16 hours at 0 °C and allowed to warm to room temperature. The residue was purified on silica gel (5% EtOAc/Hexanes – 100 % EtOAc) to yield a white solid. Yield: 7.90 g (64%)

$^{1}$H NMR (500 MHz, 23 °C, $CDCl_3$): δ 0.65 (s, 3H), 0.90 – 0.91 (m, 6H), 0.94 – 1.01 (m, 1H), 1.05 (s, 9H), 1.12 – 1.73 (m, 21H), 1.80 – 1.85 (m, 3H), 1.96 – 2.00 (m, 2H), 2.22 (q, J = 11.4 Hz, 1H), 3.46 (m, 1H), 3.63 (t, J = 6.0 Hz, 2H), 3.85 (q, J = 2.7 Hz, 1H), 7.36 – 7.43 (m, 6H), 7.67 – 7.68 (m, 4H)

$^{13}$C{$^{1}$H} NMR (151 MHz, 23 °C, $CDCl_3$): δ 11.7, 18.6, 19.1, 20.5, 22.7, 23.7, 26.8, 28.1, 29.0, 30.6, 31.8, 32.8, 34.5, 35.0, 35.3, 35.4, 39.4, 39.6, 39.8, 41.4, 42.6, 50.4, 55.9, 64.4, 68.5, 71.9, 127.5, 129.4, 134.1, 135.5

**24-tert-butyldiphenylsilyloxy-3α,12α-dihydroxycholane:** This compound was prepared using the general procedure for the TBDPS protection of cholic acid derivatives described above using 3α,12α,24-trihydroxycholane (6.59 g, 17.3 mmol). The residue was purified on silica gel using 5% EtOAc/Hexanes then 80% EtOAc/Hexanes as the eluent to yield a white solid. Yield: 5.03 g (48%)

$^{1}$H NMR (500 MHz $CDCl_3$) δ 0.67 (s, 3H), 0.91 (s, 3H), 0.94 (d, J = 6.7 Hz, 3H), 0.98 – 1.01 (m, 1H), 1.05 (s, 9H), 1.10 – 1.30 (m, 4H), 1.32– 1.48 (m, 8 H), 1.48 – 1.55 (m, 5H), 1.57 – 1.70 (m, 5H), 1.73 – 1.86 (m, 5H), 3.56-3.65 (t overlapping m, J = 6.2 Hz, 3H), 3.99 (br, 1H), 7.36 – 7.43 (m, 6H), 7.68 (d, J = 6.6 Hz, 4H)

$^{13}$C{$^{1}$H} NMR (126 MHz $CDCl_3$) δ 12.7, 17.7, 19.1, 23.1, 23.6, 26.1, 26.8, 27.1, 27.4, 28.5, 29.1, 30.5, 31.8, 33.6, 34.0, 35.1, 35.2, 36.0, 36.4, 42.0, 46.4, 47.6, 48.2, 64.4, 71.8, 73.2, 127.5, 129.4, 134.1, 135.5

**24-tert-butyldiphenylsilyloxy-3α-hydroxycholane:** This compound was prepared using the general procedure for the TBDPS protection of cholic acid derivatives described above using 3α,24-dihydroxycholane (9.38 g, 25.9 mmol). The sample was moved forward without further purification. For characterization purposes, the residue was recrystallized in EtOAc/Pentanes at -40 °C. Yield: 14.79 g (95%)

$^{1}$H NMR (400 MHz, 23 °C, $CDCl_3$): δ 0.63 (s, 3H), 0.88 (d, J = 6.5 Hz, 3H), 0.92 (s, 3H), 1.04 (s, 12H), 1.07–1.49 (m, 18H), 1.54–1.85 (m, 7H), 1.96 (d, J = 12 Hz, 1H), 3.63 (t, J = 6.4 Hz, 3H), 7.35–7.42 (m, 6H), 7.66–7.68 (m, 4H)

$^{13}$C{$^{1}$H} NMR (101 MHz, 23 °C, $CDCl_3$): δ 12.0, 18.6, 19.2, 20.8, 23.4, 24.2, 26.4, 26.8, 27.2, 28.2, 29.1, 30.5, 31.9, 34.5, 35.3, 35.4, 35.8, 36.4, 40.2, 40.4, 42.1, 42.6, 56.2, 56.5, 64.5, 71.8, 127.5, 129.4, 134.1 134.2, 135.5.

**Representative procedure (A) for the synthesis of methyl ether substrates:**

**3β-methoxy-5α-cholestane:** A flame-dried 250 mL two-necked Schlenk flask was charged with NaH (0.3300g, 12.90 mmol, 2 equiv.) in an inert atmosphere glove box. The vessel was then brought outside of the box and attached to a Schlenk line and an oil bubbler and a flow of $N_2$ applied. Dry THF (60 mL) was loaded into the flask to make an NaH suspension which was cooled to 0 °C. 5α-cholestan-3β-ol (2.51g, 6.43 mmol) was dissolved in dry THF (20 mL) and added dropwise over the course of 1 hour and allowed to stir at 0 °C for 1 hour. Maintaining a 0 °C reaction temperature, MeI (1.8308 g, 12.90 mmol, 2 equivalents, 0.80 mL) was added dropwise over the course of 1 hour. The reaction was slowly quenched with saturated aqueous $NH_4Cl$ and was diluted with water until all solid is dissolved (~ 50 mL). The aqueous solution was extracted with EtOAc (3 x 150 mL) and washed with DI $H_2O$ (2 x 100 mL) and brine (3 x 100 mL). The resulting organic layer was dried over $Na_2SO_4$ and filtered. The solution was concentrated under

vacuum and the residue was purified on silica gel using 15% EtOAc/Hexanes as eluent to give a white solid as the product. Yield: 1.9440 g (79%). The $^{1}$H NMR shifts match previously reported values.[89]

**3α-methoxy-5α-cholestane:** This compound was prepared according to general procedure (**A**) for the preparation of methyl ether substrates using 0.8501 g of **11a**. The extracted organic layer was concentrated under vacuum and the residue was sonicated in acetonitrile (10 mL) to yield a white solid, which was filtered and washed with acetonitrile (2 x 5 mL) and dried under vacuum. Yield: 0.6137 g (70%). This is a previously reported molecule.[90]

**Representative procedure (B) for the synthesis of methyl ether substrates:**

**3α,7α,12α,-trimethoxy-24-tert-butyldiphenylsilyloxycholane:** A flame-dried 250 mL two-necked Schlenk flask was charged with NaH (3.7218 g, 155.1 mmol, 10 equiv.) in an inert atmosphere glove box. The vessel was then brought outside of the box and attached to a Schlenk line and an oil bubbler and a flow of $N_2$ applied. Dry DMF (30.0 mL) was loaded into the flask to make an NaH suspension which was cooled to 0 °C. 3α,7α,12α-trihydroxy-24-*t*-butyldiphenylsiloxycholane (6.3200 g, 9.98 mmol) was dissolved in 15 mL of dry DMF and added dropwise to the NaH suspension at 0 °C over the course of 30 minutes and allowed to stir for 2 hours. The temperature was held at 0 °C and MeI (22.0 g, 155 mmol, 9.7 mL) was added slowly over the course of 2 hours and allowed to stir for 18 hours and warm to room temperature. The reaction was slowly quenched with saturated aqueous $NH_4Cl$ and was diluted with water until all solid was dissolved (~ 50 mL). The aqueous solution was extracted with EtOAc (3 x 150 mL) and washed with deionized water (2 x 100 mL) and brine (3 x 100 mL). The resulting organic layer was dried over $Na_2SO_4$ and filtered. The crude oil was purified on silica gel (15% EtOAc/Hexanes) to give a white solid. Yield: 4.12 g (61%)

$^{1}$H NMR (400 MHz, 23 °C, $CDCl_3$): δ 0.66 (s, 3H), 0.90 – 0.92 (overlapping s,d, 6H), 0.94 – 1.01 (m, 1H), 1.06 (s, 9H), 1.16 – 1.87 (m, 19H), 1.93 (q, J = 9.7 Hz, 1H), 2.04 – 2.16 (m, 2H), 2.22 (q, J = 12.6 Hz, 1H), 3.01 (m, 1H), 3.16 (bq, J = 2.7 Hz, 1H), 3.23 (s, 3H), 3.28 (s, 3H), 3.35 (s, 3H), 3.38 (bt, J = 2.3 Hz, 1H), 3.64 (t, J = 6.3 Hz, 2H), 7.35 – 7.45 (m, 6H), 7.69 (dd, J = 6.2 Hz, J = 1.6 Hz, 4H)

$^{13}$C{$^{1}$H} NMR (101 MHz, 23 °C, $CDCl_3$): δ 12.4, 17.7, 19.1, 21.9, 22.8, 23.1, 26.7, 26.8, 27.4, 27.7, 27.9, 29.1, 31.8, 34.4, 34.9, 35.2*, 39.6, 41.9, 42.6, 46.0, 46.5, 55.3, 55.6, 55.8, 64.5, 76.9, 80.7, 82.0, 127.5, 129.4, 134.1, 134.2, 135.5

**3α,7α-dimethoxy-24-tert-butyldiphenylsilyloxycholane:** This compound was prepared according the general procedure **(B)** for the preparation of methyl ether substrates using 24-tert-butyldiphenylsilyloxy-3α,7α-dihydroxycholane (7.90 g, 12.8 mmol). The solution was concentrated under vacuum and the residue was purified on silica gel using hexanes and then 5% EtOAc/Hexanes as the eluent to yield a white solid. Yield 2.10 g (25%).

$^{1}$H NMR (400 MHz, 23 °C, $CDCl_3$): δ 0.63 (s, 3H), 0.88 – 0.91 (s overlapping d, 6H), 0.95 – 1.01 (m, 1H), 1.06 (s, 9H), 1.15 – 1.31 (m, 6H), 1.31 – 1.58 (m, 10H), 1.63 – 1.67 (m, 1H), 1.68 – 1.87 (m, 6H), 1.93 (dt, J = 11.8 Hz, J = 3.1 Hz, 1H), 2.17 (q, J = 12.5 Hz, 1H), 2.97 – 3.05 (m, 1H), 3.18 (bq, J = 2.3 Hz, 1H), 3.24 (s, 3H), 3.34 (s, 3H), 3.63 (t, J = 6.5 Hz, 2H), 7.36 – 7.44 (m, 6H), 7.67 – 7.69 (m, 4H)

$^{13}$C{$^{1}$H} NMR (126 MHz, 23 °C, $CDCl_3$): δ 11.6, 18.6, 19.1, 20.8, 22.9, 23.6, 26.6, 26.8, 27.9, 28.1, 29.0, 31.8, 33.6, 34.6, 35.2, 35.3, 35.4, 39.4, 39.5, 41.9, 42.3, 50.1, 55.3, 55.8, 55.8, 64.5, 77.3, 80.6, 127.5, 129.4, 134.1, 135.5

**3α,12α-dimethoxy-24-tert-butyldiphenylsilyloxycholane:** This compound was prepared according the general procedure **(B)** for the preparation of methyl ether substrates using 24-tert-

butyldiphenylsilyloxy-3α,12α-dihydroxycholane (15.00 g, 24.3 mmol). The solution was concentrated under vacuum and the residue was purified on silica gel using 100% hexanes to 10% EtOAc/Hexanes as eluent to yield an off-white oil. Yield: 1.22 g (8%). Crystals suitable for X-ray crystallography were obtained from a concentrated solution in dichloromethane at 23 °C

$^{1}$H NMR (600 MHz $CDCl_3$) δ 0.65 (s, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.92 (s, 3 H), 0.94 – 1.01 (m, 2 H), 1.05 (s, 9H), 1.11 – 1.52 (m, 13H), 1.56 – 1.69 (m, 3H), 1.71 – 1.89 (m, 8H), 3.15 (septet, J = 4.4 Hz, 1H), 3.26 (s, 3H), 3.34 (s, 3H), 3.39 (bs, 1H), 3.63 (t, J = 6.3 Hz, 2H), 7.36 – 7.43 (m, 6H), 7.68 (d, J = 6.6 Hz, 4H)

$^{13}$C{$^{1}$H} NMR (126 MHz $CDCl_3$) δ 12.7, 17.7, 19.1, 21.9, 23.2, 23.6, 26.1, 26.7, 26.8, 27.3, 27.4, 29.1, 31.8, 32.5, 33.5, 34.4, 35.2, 35.3, 36.0, 42.0, 46.2, 46.7, 48.8, 55.4, 55.6, 64.5, 80.4, 82.3, 127.5, 129.4, 134.1, 135.5

**3α-methoxy-24-tert-butyldiphenylsilyloxycholane:** This compound was prepared according the general procedure **(B)** for the preparation of methyl ether substrates using 24-tert-butyldiphenylsilyloxy-3α-hydroxycholane (14.79 g, 24.61 mmol). The solution was concentrated under vacuum and the residue was purified on silica using 1% EtOAc/Hexanes then 10% EtOAc/Hexanes as eluent to yield a viscous oil. Yield: 3.61 g (24%)

$^{1}$H NMR (400 MHz, 23 °C, $CDCl_3$): δ 0.63 (s, 3H), 0.86–0.90 (m, 4H), 0.92–0.93 (m, 3H), 0.95–0.98 (m, 1H), 1.01–1.08 (m, 13H), 1.10–1.46 (m, 14H), 1.60–1.85 (m, 7H), 1.95 (dt, 1H) 3.16 (m, 1H), 3.35 (s, 3H), 3.63 (t, J = 6.2 Hz, 2H), 7.35–7.42 (m, 6H), 7.66–7.69 (m, 4H)

$^{13}$C{$^{1}$H} NMR (126 MHz, 23 °C, $CDCl_3$): δ 12.0, 18.6, 19.1, 20.7, 23.4, 24.2, 26.4, 26.7, 26.8, 27.3, 28.2, 29.1, 31.8, 32.7, 34.8, 35.2, 35.4, 35.8, 40.1, 40.3, 42.0, 42.6, 55.5, 56.1, 56.4, 64.4, 80.4, 127.5, 129.4, 134.1, 135.5

**General Procedure (A) for Catalytic Ether Deoxygenation/Silylation of Bile acids:**

In air, a 20 mL scintillation vial was charged with a stir bar, the solid precatalyst [(cod)Ir($PPh_3$)$_2$]$BAr^F{}_4$ (**2a**) (0.0201 g, 0.03 equiv., 0.0120 mmol), dichloromethane (2.0 mL). The $Et_3SiH$ (0.1023g, 0.880 mmol, 2.2 equiv., 0.14 mL) was allowed to stir vigorously until the reaction mixture changes from a red color to a pale yellow, indicating the catalyst is activated (10 – 30 seconds). Substrate ether (0.400 mmol, 1.0 equiv.) was then added to the reaction mixture and was allowed to stir at 50 °C for 2 hours. The reaction mixture was removed from heat and the solvent was removed under vacuum. The residue was dissolved in dichloromethane and purified on silica gel. The resulting residue was redissolved in THF (2.0 mL) and $NBu_4F{\cdot}3H_2O$ (0.6300 g, 2.00 mmol, 5 equiv.) was added and the mixture was allowed to stir at 40 °C overnight. The resulting reaction mixture was quenched with saturated aqueous $NH_4Cl$. The organic layer was extracted twice with EtOAc and dried with anhydrous $Na_2SO_4$, filtered, and concentrated under vacuum. The respective residue was purified on silica gel.

**General Procedure (B) for Catalytic Ether Deoxygenation/Silylation of Bile acids:**

In air, a 20 mL scintillation vial was charged with a stir bar, the solid precatalyst [(cod)Ir($PPh_3$)$_2$]$BAr^F{}_4$ (**2a**) (0.0201g, 0.03 equiv., 0.0120 mmol), dichloromethane (2.0 mL). The $Et_3SiH$ (0.2046 g, 1.76 mmol, 4.4 equiv., 0.28 mL) was allowed to stir vigorously until the reaction mixture changes from a red color to a pale yellow, indicating the catalyst is activated (10 – 30 seconds). Substrate ether (0.4000 mmol, 1.0 equiv.) was then added to the reaction mixture and was allowed to stir at 50 °C for 2 hours. The reaction mixture was removed from heat and the solvent was removed under vacuum. The residue was dissolved in dichloromethane and purified on silica gel. The resulting residue was redissolved in THF (2.0 mL) and $NBu_4F{\cdot}3H_2O$ (0.6300 g, 2.00 mmol, 5 equiv.) was added and the mixture was allowed to stir at 40 °C overnight. The resulting reaction mixture was quenched with saturated aqueous $NH_4Cl$. The organic layer was

extracted twice with EtOAc and dried with anhydrous $Na_2SO_4$, filtered, and concentrated under vacuum. The respective residue was purified on silica gel.

**7α,12α,-dimethoxy-24-tert-butyldiphenylsilyloxycholane:** This compound was synthesized according to general catalytic procedure **(A)** for catalytic ether silylations from **18** (0.2700 g, 0.40 mmol) with no deprotection step. The residue was purified on silica gel using 0.5% to 2% EtOAc in hexanes to yield the product as an off-white residue. Yield: 0.1732 g (69%).

$^1$H NMR (400 MHz, 23 °C, $CDCl_3$): δ 0.66 (s, 3H), 0.91 (s and d overlapped, 6H), 0.35 – 1.01 (m, 2H), 1.06 (s, 9H), 1.15 – 1.22 (m, 2H), 1.23 – 1.40 (m, 8H), 1.42 – 1.57 (m, 5H), 1.69 – 1.88 (m, 5H), 1.94 (q, J = 9.8 Hz, 1H), 2.03 – 2.25 (m, 3H), 3.15 (bq, J = 2.8 Hz, 1H), 3.23 (s, 3H), 3.29 (s, 3H), 3.38 (t, J = 2.5 Hz, 1H), 3.64 (t, J = 6.4 Hz, 2H), 7.35 – 7.45 (m, 6H), 7.67 – 7.71 (m, 4H)

**24-hydroxy-7α-methoxycholane:** This compound was synthesized according to general catalytic procedure **(A)** for catalytic ether silylations from 3α,7α-dimethoxy-24-tert-butyldiphenylsilyloxycholane (0.2580 g, 0.40 mmol). The residue obtained prior to deprotection was purified on silica gel using 10% to 25% EtOAc in hexanes. After the deprotection, the residue was purified on silica gel using 5% to 10% to 25% EtOAc in hexanes to give the product as a white solid. Yield: 0.0805 g (53%). Crystals suitable for X-ray diffraction were obtained from a concentrated solution in dichloromethane at 0 °C.

$^1$H NMR (600 MHz, 23 °C, $CDCl_3$) δ 0.64 (s, 3H), 0.90 (s, 3H), 0.92 (d, J = 6.5 Hz. 3H), 1.02 – 1.09 (m, 3H), 1.14 – 1.35 (m, 9H), 1.37 – 1.54 (m, 8H), 1.61 – 1.66 (m, 3H), 1.73 – 1.87 (m, 4H), 1.89 – 1.94 (m, 1H), 2.09 (qd, J = 13.4 Hz, J = 3.8 Hz, 1H), 3.17 (bq, J = 2.1 Hz, 1H), 3.24 (s, 3H), 3.61 (m, 2H)

$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) δ 11.6, 18.6, 20.8, 21.4, 23.6, 23.7, 27.6, 28.1, 28.2, 29.0, 29.3, 31.8, 33.9, 35.8, 35.7, 37.5, 39.3, 39.6, 42.4, 43.6, 50.3, 55.7, 55.9, 63.5, 77.8

$^{13}C\{^{1}H\}$ NMR (151 MHz, 23 °C, $CDCl_3$): δ 11.5, 16.8, 18.2, 20.4, 21.0, 22.2, 22.6, 25.9, 26.4, 26.7, 26.9, 27.1, 27.9, 28.1, 30.9, 34.27, 34.3, 36.6, 38.6, 41.9, 42.7, 45.1, 45.6, 54.7, 54.8, 63.5, 76.4, 81.2, 126.5, 128.4, 132.2, 134.6

**3α,24-dihydroxy-12α-methoxycholane:** This compound was synthesized according to general catalytic procedure **(B)** for catalytic ether silylations from 3α,12α-dimethoxy-24-tert-butyldiphenylsilyloxycholane (0.2581 g, 0.40 mmol). The initial residue was purified on silica gel using 0.1% to 10% EtOAc in hexanes. After the deprotection, the residue was purified on silica gel using 5% MeOH/$CH_2Cl_2$ as the eluent to yield a colorless oil. Yield: 0.1009 g (64%). Crystals suitable for X-ray diffraction were obtained from a concentrated solution in acetonitrile at 0 °C.

$^{1}H$ NMR (600 MHz, 23 °C, $CDCl_3$): δ 0.60 (s, 3H), 0.84 (s, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.91 – 1.07 (m, 4H), 1.11 – 1.19 (m, 3H), 1.26 – 1.44 (m, 8H), 1.48 (bt, J = 8.6 Hz, 2H), 1.55 – 1.64 (m, 2H), 1.65 – 1.76 (m, 6H), 1.80 (q, J = 9.6 Hz, 3H), 3.21 (s, 3H), 3.34 (t, J = 2.8 Hz, 1H), 3.53 (apparent td overlapping m, J = 6.4 Hz, J = 2.4 Hz, 3H)

$^{13}C\{^{1}H\}$ NMR (151 MHz, 23 °C, $CDCl_3$): δ 11.7, 16.7, 21.0, 22.2, 22.7, 25.1, 26.1, 26.6, 28.4, 29.4, 30.8, 32.6, 33.1, 34.3, 34.4, 35.0, 35.4, 41.1, 45.3, 45.8, 48.0, 54.7, 62.5, 70.8, 81.5

**3α,24-dihydroxycholane (15a):** This compound was synthesized from **15** (0.2516 g, 0.40 mmol) according to general catalytic procedure **(A)** for catalytic ether silylations. The initial residue was purified on silica gel using 10% to 50% EtOAc in hexanes. After the deprotection, the residue was purified on silica gel using 5% to 10% to 25% EtOAc/Hexanes to yield a white solid. Yield: 0.0856 g (58%). Crystals suitable for X-ray crystallography were grown from a saturated solution in acetonitrile at 23 °C. NMR shifts match that of the previously reported values.[9]

**General Procedure for Small Scale Catalytic Reactions for cyclohexyl methyl ether Deoxygenation/Silylation:**

In air, a 4 mL vial was charged with 0.15 mL of an 8.0 mM stock solution of $[(cod)Ir(PPh_3)_2]BAr^F{}_4$ (0.0012 mmol) in $CD_2Cl_2$ followed by the addition of triethylsilane (0.0102 g, 0.0875 mmol, 14.0 μL, 2.2 equiv.) the resulting mixture was mixed for approximately 30 seconds. The substrate ether (0.03927 mmol) was then added, and the vessel heated at 50 °C for 2 hours. After cooling, the solution was diluted with 0.50 mL $CD_2Cl_2$ and transferred to an NMR tube; yields were calculated using an internal standard of mesitylene (0.0065 g, 0.036 mmol, 5.0 μL).

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## Chapter 3. Regioselective Methyl Ether Cleavage of Phenyl glycosides

### I. Introduction:

Selective functionalization for carbohydrates is challenging due to each site on the pyran ring having similar reactivity.[57] As a result a typical synthesis of complex carbohydrates are dependent on the deliberate installation of protecting groups to direct reactivity away from sites of interest.[58] Methyl ethers, though simple, are avoided due to forcing conditions necessary for their removal.[58,59] Herein we provide research on the first hydrosilylative catalyst for the reduction of methyl ethers with minimal reduction to the $C_1$-deoxy-glycoside or to the sugar alcohol.

In the following sections a brief review on carbohydrates is given to provide nomenclature for monosaccharides as well their stereochemical centers. This is then followed by previous examples of hydrosilylative reductions of carbohydrates and their selectivity. Lastly, before our research on substituted aryl-glycosides, a discussion on previous methods used for methyl ether reduction on carbohydrates is given.

### II. A Review on Carbohydrates

Carbohydrates are abundant in nature with a large portion being present in biologically relevant molecules.[1,2] Carbohydrates are comprised of monomer units known as monosaccharides, which link to form dimers termed disaccharides, or higher-order saccharides such as oligo- and polysaccharides. Additionally, glycosidic bonds can be made with other molecules such as sterols[3] and peptides[4] affecting their physical and chemical properties. The glycosidic portion of these molecules are termed the glycone (with sugar) and the other portion is termed the aglycone (without sugar).

The classic definition of a carbohydrate is the collection of organic molecules having the formula $C_n(H_2O)_n$, that is, being described as hydrates of carbon. This definition has been

expanded to describe saccharides of varying composition, including carbohydrate varients with heteroatoms such as aminoglycosides which are common in protein glycosylation.[5-7] Carbohydrates describe a large class of molecules possessing enormous structural diversity including compounds with varying chain lengths and distinct stereoisomers (Figure 3.1). Carbohydrates with an aldehyde group, called an *aldose*, are shown together based on their chain length. Glyceraldehyde is the shortest of the aldoses and is composed of three functional groups: an aldehyde, a secondary alcohol (HCOH), and a primary alcohol ($H_2COH$). *Aldotetraoses* can be derived from an insertion of (HCOH) between the carbonyl and the prior stereocenter, this homologation in turn gives two diastereomers: erythrose and therose.[8] This homologation process can be repeated to give *aldopentoses* and once more for *aldohexoses*, examples of which can be seen in Figure 3.1.

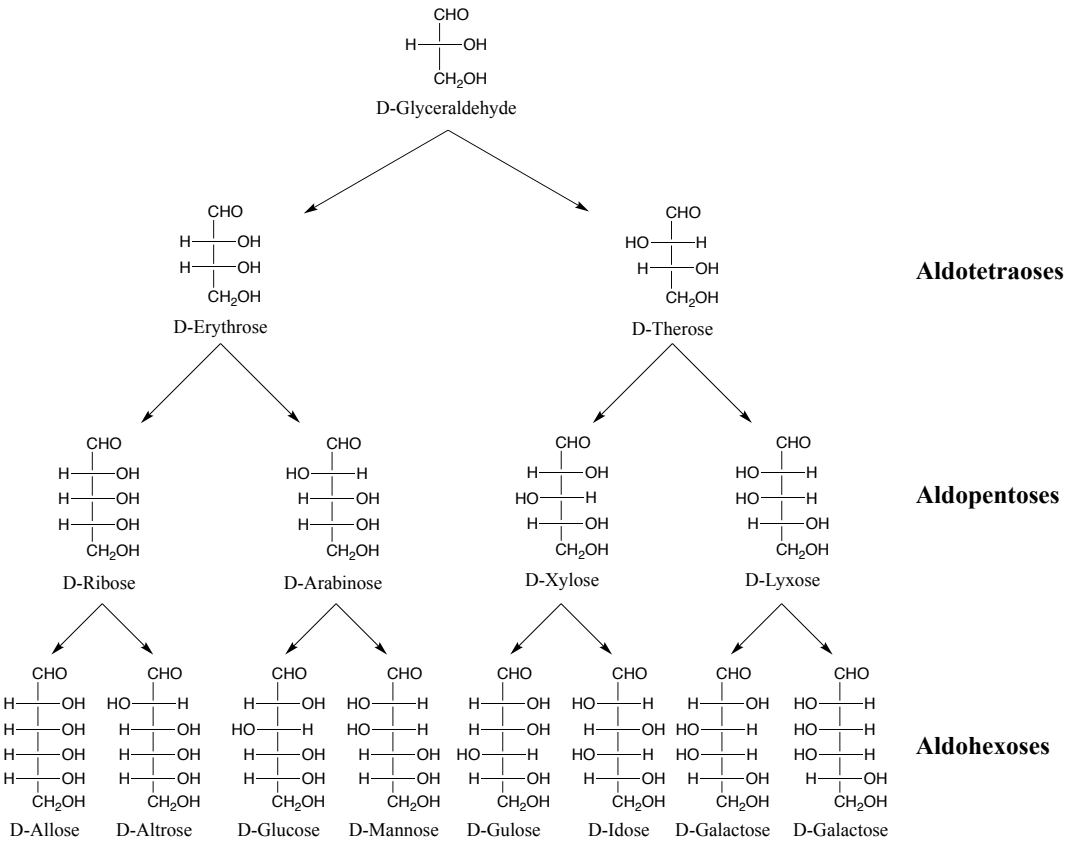



Figure 3.1: Nomenclature of Monosaccharides

The D/L-conformation of carbohydrates are determined by the $C_5$ position from the Fischer projection. When the alcohol functionality is to the right, the carbohydrate is in the D-conformation the converse is the L-conformation.[8] Aldoses can cyclize from either the $C_4$ or the $C_5$ position to the aldehyde to give a hemiacetal as the furanose or pyranose ring, respectively.[9]

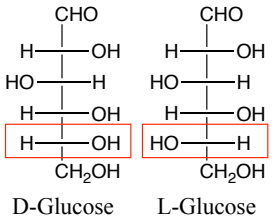



Figure 3.2: Highlighting the difference between D- and L-Glucose

Carbohydrates can be represented by four different depictions: A Fischer projection, the Mills depiction, the Haworth representation, or a chair conformation. Most commonly, the chair conformation is used for pyranose rings since it provides the most accurate depiction of the geometry of the molecule. D/L-conformations are portrayed in the chair conformation in either the $^4C_1$ form for D-conformations, or $^1C_4$ form for the L-conformation.

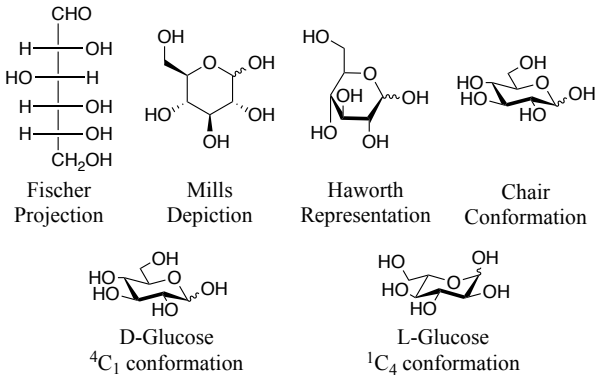
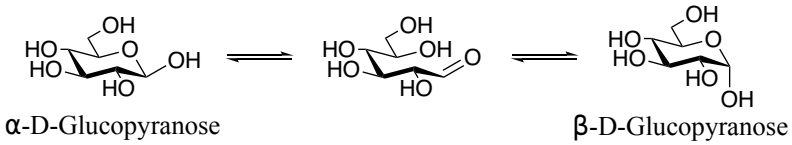



Figure 3.3: Different representations of carbohydrates

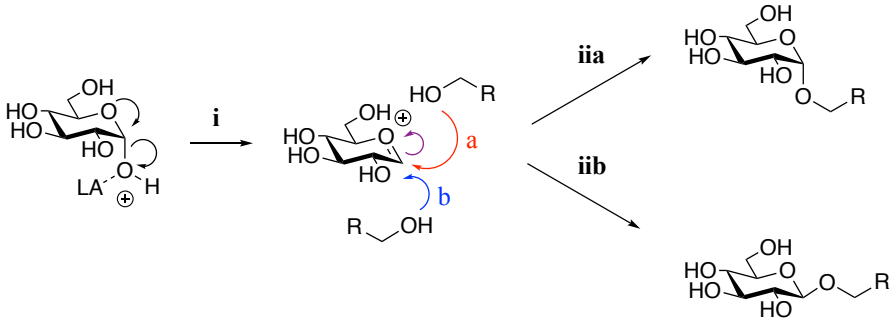
In the hemiacetal form an additional stereocenter exists at $C_1$ and is termed the anomeric position. The two epimeric isomers of the resulting hydroxyl group are described by notation indicating their arrangement relative to $C_5$, with the *trans* epimer notated as being α, and the *cis*

epimer being β.[9] In solution, the α and β hemiacetals interconvert through an equilibrium process called mutarotation.[10,11] This occurs via lone pair donation from the anomeric hydroxyl group to the pyranose ring which then reverts the pyranose ring back to the open chain structure. The $C_5$ hydroxyl group can then attack from the opposite face of the aldehyde to form the other epimer.[11]




Scheme 3.1: Mutarotation of Glucopyranose

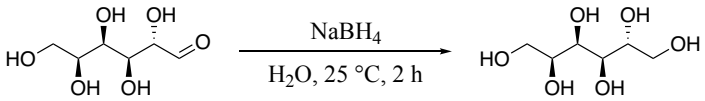
An important reaction for the addition of glycones to a carbohydrate is the Fischer-glycosylation.[12] This reaction is typically mediated by either a Brønsted or Lewis acid through the formation of an oxocarbenium ion via elimination of the $C_1$ substituent (Scheme 3.2, i).[13] Once the oxocarbenium is formed, a nucleophile can attack from the bottom face to give the α product (Scheme 3.2, iia) or the top face to give the β product (Scheme, 3.2, iib). Proximal protecting groups can assist in the glycosylation selectivity via neighboring group participation, which can favor one anomer over another. Acetyl groups are a common neighboring participant due to their easy installation and removal under mild reaction conditions.[14-17]




Scheme 3.2: Fischer Glycosylation of Glucopyranose

### III. Hydrosilylative reduction of carbohydrates

An early example of reductions within carbohydrate chemistry was the reduction of the aldehyde in the open chain form to give the polyol known as a sugar alcohol.[18] These compounds have found their use as sweeteners with approximately half the caloric load of dietary carbohydrates.[19] In contrast to the reduction of the aldehyde, reduction of other sites on a carbohydrate involves C–O bond cleavage. This requires a two-step process that first converts the hydroxyl group to reductively liable group such as: halides[20,21], triflates[22], epoxides[23,24], followed by a reduction. Additionally, Barton-McCombie deoxygenation strategies are also viable for C–O bond reduction on the pyran ring.[25,26] Hydrosilanes are capable of serving as reducing agents for carbohydrates as well, but require a catalyst. In the presence of catalytic amounts of trimethylsilyl triflate, pyranoses are reduced by hydrosilanes at the anomeric position to give the 1-deoxy-saccharide.[27]




Scheme 3.3: Reduction of glucose to sorbitol

Borane catalysts have emerged as selective Lewis Acid catalysts for the reduction of carbohydrates with hydrosilanes, exemplified in the use of BCF for the reduction of persilylated saccharides. The typical site of reduction is $C_1$, either via the loss of the glycone or via ring opening of the pyranose to give protected sugar alcohols.[28-30] Alteration of the aryl rings on BCF from pentafluorophenyl to 3,5-bis(trifluoromethyl)phenyl gives comparable selectivity for anomeric reduction, but can also isomerize the pyranose ring to the corresponding furanose.[31] Additionally, Piers borane has been found to reduce carbohydrates similarly to BCF, however the site of reduction is dependent on the pendent aglycone.[32]

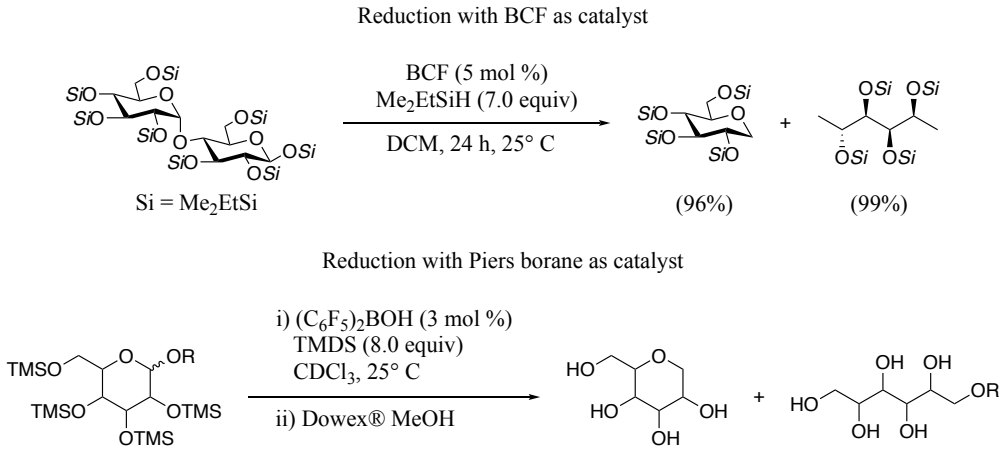
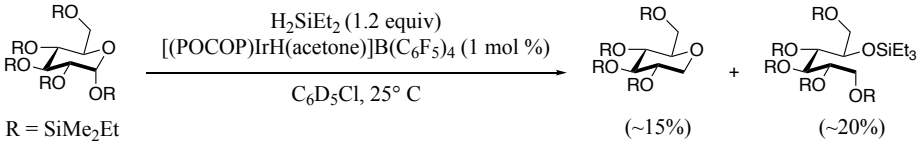



Figure 3.4: Reduction of Carbohydrates with borane catalysts

Cationic iridium complexes are less explored for the hydrosilylative reduction of carbohydrates. To our knowledge, prior to our work the only iridium-catalyzed carbohydrate hydrosilylative reduction that has been reported was the exhaustive reduction of a pentasilyl glycopyranose to generate a mixture of hexanes.[33] This reactivity is similar to that observed for BCF under forcing conditions, and while it can be considered as a model transformation for the conversion of glucose to biofuels, it lacks synthetic utility. Applying what we learned from our previous studies outlined in chapter 2, we decided to apply $[(COD)Ir(PPh_3)_2]BAr^F_4$ as a catalyst for selective methyl ether cleavage in carbohydrate derivatives.




Scheme 3.4: Reduction of persilylated methyl-glucose with an iridium catalyst

**IV. Previous accounts of methyl ether cleavage in carbohydrates**

To date there has not been a catalytic, hydrosilylative method which preserves the pyranose ring or anomeric position in favor of reduction at an alternate site. However, the carbohydrate derivatives of past examples are silylated at multiple sites which primes nucleophilic delivery at

$C_1$.[28-32, 60] Methyl ethers are less common due to their stability, but are less arming than silyl groups and could aid in prevent $C_1$ reduction.[58-60] Additionally, given the selectivity observed by the bisphosphine system in Chapter 2 a method can be developed for catalytic demethylation in pyranose ring systems. Current demethylation methods are stoichiometric and are dependent on neighboring protecting groups.[34-36] A brief description of this past work is outlined below.

A report published in 2004 by Suárez et. al., found that it was possible to remove methyl ether groups on $C_4$ through a radical oxidative method with a free $C_6$ hydroxyl group (Figure 3.5).[34] This method took advantage of the ability to form an acetal with the neighboring methyl group that then can be removed with a basic work-up. Two years later, this approach was revisited by Suárez et. al, who found that it was possible to perform this chemistry at different sites of the pyranose ring, though with diminished yields.[35] Ten years later, a method developed by Zhao et. al. utilized cobalt octacarbonyl as a reagent capable of reducing methyl ethers while being compatible with other ethereal protecting groups. These conditions require the use of excess silane, cobalt, and an atmosphere of carbon monoxide with gentle heating, which presents an opportunity to improve hydrosilyative demethylation of monosaccharides.[36]

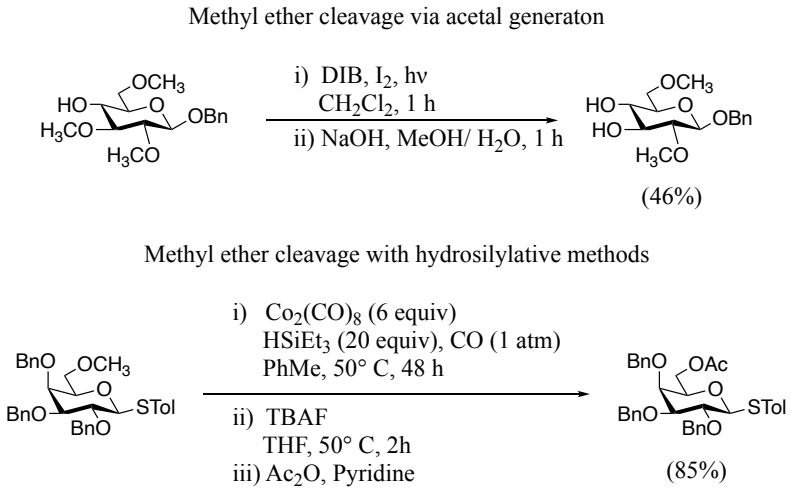
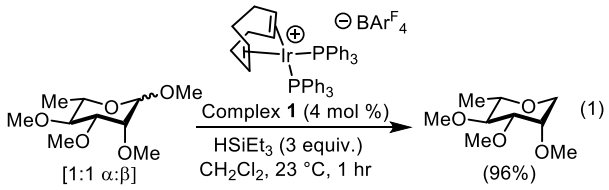



Figure 3.5: Demethylation of methyl ethers in carbohydrates

The remainder of this chapter will focus on our efforts to develop a hydrosilylative catalyst capable of methyl ether cleavage while avoiding anomeric reduction. We investigate the use of 2'-substituted phenyl rings as a way of protecting the anomeric position with L-rhamnose derivatives followed by an investigation with other glycosides. Additionally, we compare our system with previously reported systems such as BCF, and $[Ph_3C]BAr^F{}_4$, to determine the overall effectiveness of our system.

**V. Reactivity of Phenyl-L-Rhamnopyranose derivatives**

When tetra-*O*-methylrhamnose is subjected to hydrosilylation with the iridium precatalyst **1**, $C_1$ demethoxylation occurs in preference to reduction at other positions (eqn. 1). This preference for $C_1$ reduction mirrors results obtained with the previously reported catalysts described in the previous section (**Chapter 3, section II**).[29, 31-33, 37-40] Preferential reduction at $C_1$ likely arises from the increased nucleophilicity of the acetal functionality relative to the methyl ethers at the 2, 3, and 4 positions, which promotes silyloxonium ion formation at this site. C-O cleavage likely occurs through elimination of the silyloxonium ion to give an oxocarbenium ion that is reduced *in situ*. In our case overreduction is not observed, which contrasts with many previously examined catalysts.[33, 37, 38-40]

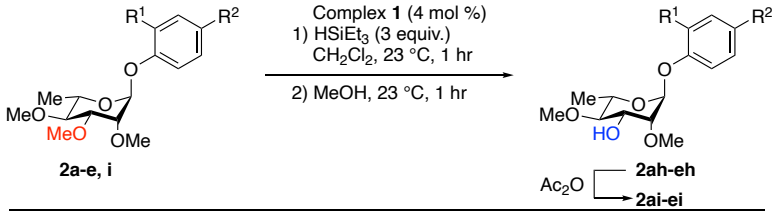



Scheme 3.5: Reduction of tetra-O-methyl Rhamnose with complex **1**

We hypothesized that *O*-aryl glycosides would show increased resistance to $C_1$ reduction owing to the decreased nucleophilicity of the aryloxy group as well as the potential for steric protection of the acetal oxygen atoms. Reduction of a series of 1-aryloxy-2,3,4-tri-*O*-methyl-L-

rhamnose derivatives show that *ortho*-substituted aryloxy groups protect $C_1$ under iridium-catalyzed hydrosilylation conditions. Comparison of the *o*-methyl, isopropyl, and t-butyl derivatives **2a**, **2b** and **2c** show progressively increasing yields of the 3-demethylation products with retention of the $C_1$ aryloxy group. The *o*-methoxy derivative **2e** is found to be unsuitable for this purpose, as **2e** undergoes exclusive $C_1$ reduction to give 1-deoxy-2,3,4-tri-*O*-methyl-rhamnose. As part of this study, compounds **2a**-**2d** were characterized by X-ray crystallography, and the site of reduction was confirmed to be $C_3$ by crystallization of **2ai**, the product of **2a** reduction and acylation. Although bulky ortho-substituted aryloxy groups serve as the best protecting groups of $C_1$ in the rhamnose derivatives in Table 3.1, their synthesis was nontrivial compared to less-bulky variants like **2a**.

Table 3.1: Selective demethylation of *O*-aryl rhamnosides



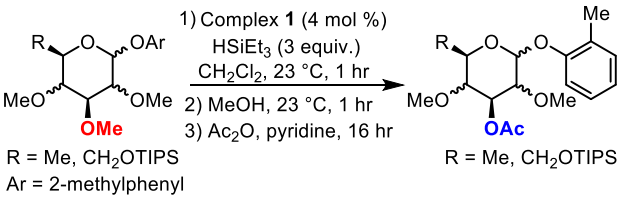

| Entry | $R^1$ | $R^2$ | NMR Yield **2ah-2eh (%)** | Isolated Yield **2ai-2ei** (%) |
|---|---|---|---|---|
| **2a** | Me | H | 74 | 70 |
| **2b** | iPr | H | 78 | 73 |
| **2c** | tBu | H | 97 | 83 |
| **2d** | Cl | Cl | 86 | 65 |
| **2e** | OMe | H | 0 ($C_1$ red. obsv.) | - |
| **2i** | H | H | Unselective reduction | |

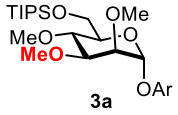
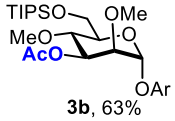
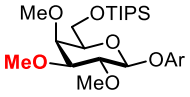
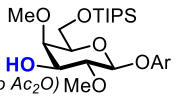
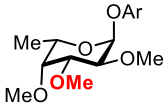
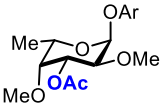
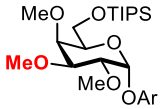
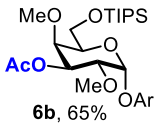
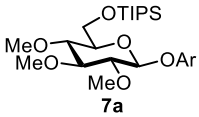
**VI. Reactivity of other Phenyl-glycosides**

Yields of 2,3,4-tri-*O*-methyl-*O*-aryl rhamnoside starting materials **2a**-**2d** decreased with increasing steric bulk of the aryloxy group, and this difficulty was exacerbated for carbohydrate derivatives bearing functionality at $C_6$. Therefore, we chose to explore the scope of selective $C_3$-demethylation of *O*-aryl glycosides using the 2-methylphenyl-protected hexopyranoses shown in

Table 3.2. *O*-aryl-α-mannose and β-galactose derivatives **3a** and **4a** both undergo selective $C_3$-demethylation under our optimized conditions. The α-L-fucose derivative **5a** is also reduced via $C_3$ demethylation. The catalytic reaction appears to be somewhat insensitive to the stereochemistry at $C_1$, with α-galactose derivative **6a** undergoing $C_3$ demethylation in comparable yield to the β anomer, though in this single case small amounts of $C_2$ demethylation (**6c**) are also observed (see the supporting information). By comparison, the glucose derivative **7a** only undergoes slow $C_1$ reduction. Except in 6-deoxy examples, we found it necessary to protect $C_6$ as the corresponding triisopropylsilyl ether to prevent the formation of multiple products during catalysis.

Table 3.2: Selective demethylation of *O*-aryl glycosides




| Derivative | Substrate | Product |
|---|---|---|
| α-D-mannose |  **3a** |  **3b**, 63% |
| β-D-galactose |  **4a** |  **4b**, 75% |
| L-fucose |  **5a** [10:1 α:β] |  **5b**, 67% |
| α-D-galactose |  **6a** |  **6b**, 65% **6c**, 13% ($C_2$) |
| β-D-glucose |  **7a** | recovered **7a** (**63%** **NMR*) |

The poor reactivity of glucose contrasts with the relative success of rhamnose, mannose, galactose, and fucose derivatives to suggest a potential role for the relative stereochemistry of the 2 and 4 positions in controlling the reactivity of the 3-methoxy group.[41] In the successful examples in Tables 1 and 2, the 3-methoxy group is *cis* to one neighboring methoxy group and *trans* to the other, whereas the neighboring substituents are mutually *trans* in glucose derivative **7a**. Consistent with this hypothesis, the minor $C_2$ demethylation product **6c** is only observed for the α anomer of galactose, in which $C_2$ also posses a *cis* and *trans* pair of neighboring groups. When we examined allose derivative **8a** in which the 2, 3, and 4 methoxy groups are mutually *cis*, we found that C-O bond cleavage proceeds unselectively to give a complex mixture of products. More generally, the successful substrates possess a triad of mutually gauche alkoxy groups with the same directionality [g(+)/g(+) or g(-)/g(-)] (Figure 3.6). Attempts to reduce pentose derivatives **9a** and **10a** also gave complex mixtures, with their failure likely stemming from reduced protection of the pyranose oxygen relative to the hexoses. These observations are summarized in Figure 3.7.

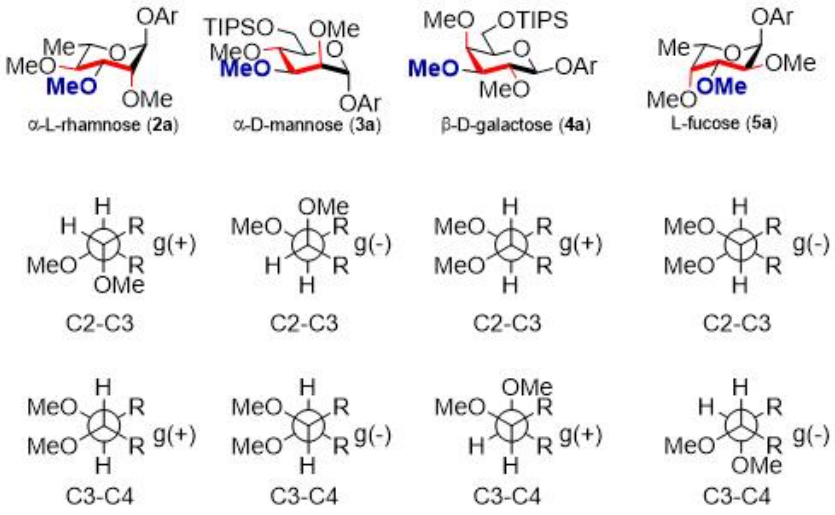



Figure 3.6: Gauche interactions of successful substrates

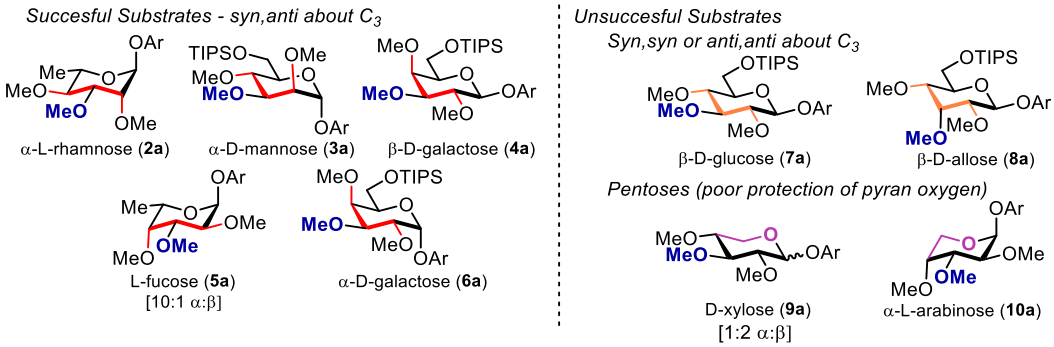



Figure 3.7: Summary of successful and unsuccessful substrates with the relative stereochemistry of the 2 and 4 positions highlighted. Ar = 2-methylphenyl.

Thus, under optimized conditions, the use of iridium precatalyst **1** and a suitable aryloxy group at C1 position allows for the selective 3-demethylation of 2,3,4-tri-*O*-methyl rhamnose, mannose, fucose, and galactose derivatives

**VII. Mechanism**

A proposed mechanism for this transformation is shown in Figure 3.8 and is based on previous work presented in Chapter 2. Ir-mediated silane heterolysis presumably gives silyloxonium ion $\mathbf{A_3}$ which undergoes nucleophilic attack by the neutral iridium hydride **1a**, a species that we independently synthesized and characterized in the report on which Chapter 2 is based.[42] In that study we showed that **1a** is the catalyst resting state and provided evidence that hydride transfer to the silyloxonium ion is rate-limiting. When the reduction of **2b** is monitored by $^{31}$P NMR spectroscopy, **1a** is observed as a major phosphorus-containing species alongside a species assigned as its cationic bis(σ-triethylsilane) precursor[43] **1b** (see the experimental section, **Chapter 3, Section VIII**). This observation is consistent with a case where the rates of silyloxonium ion formation and hydride delivery to the silyloxonium ion are comparable. A similar case was identified by Brookhart.[44] As silyloxonium ions are known to undergo reversible exchange[44] it is likely that the selectivity for cleavage at the 3-position is controlled by Curtin-

Hammett-like kinetics. In the case of 6-deoxycarbohydrates like rhamnose derivative **2a**, silyloxonium ion formation could equilibrate between each of the 5 oxygen atoms, with selectivity for C-O cleavage being determined by the relative populations of the silyloxonium ions and their rate of reaction with the nucleophilic iridium hydride **1a**.

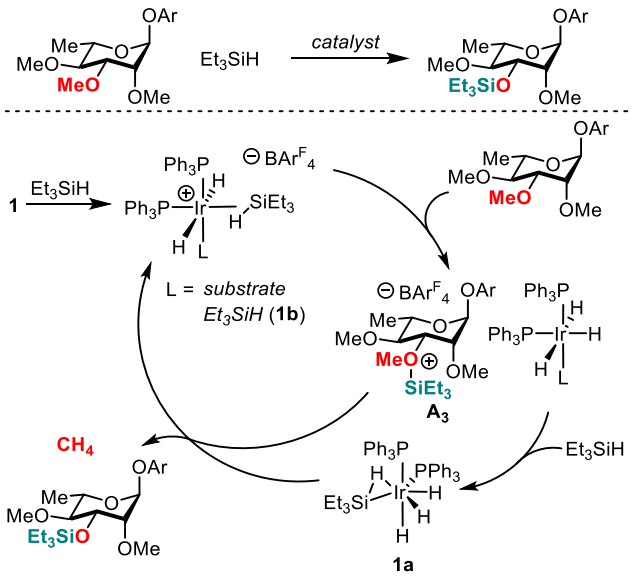


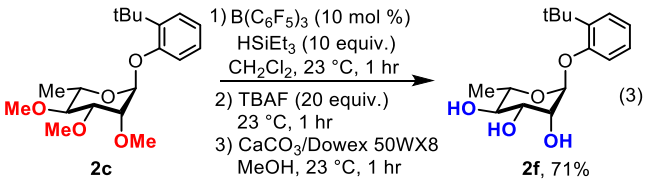

Figure 3.8: Proposed mechanism for selective demethylation of *O*-aryl glycosides by **1**.

Reduction of the anomeric position represents a special case, as elimination of an incipient silyloxonium ion would give the corresponding oxocarbenium ion as illustrated in eqn. 2. Slow reduction of $C_1$ in aryloxy derivatives like **2a** could therefore stem from either a reduced population of the $C_1$ silyloxonium ion or a reduced rate of oxocarbenium ion formation, the latter of which would allow for migration of the triethylsilylium ion to other positions including $C_3$.


Figure 3.9: Generation and elimination of the silyloxnium ion

In order to better understand the factors that lead to selective $C_3$ demethylation we undertook a computational investigation of the **2a**-derived silyloxonium ions. Optimized geometries were computed for triethylsilyloxonium derivatives of **2a** at all 5 oxygen atoms in both chair conformations, and their free energies were compared. The energies of the $O_3$ and $O_4$ silyloxonium ions were found to be equal, and *ca.* 3-6 kcal/mol more stable than silyloxonium ions at other positions. Thus, the experimental selectivity for $C_3$ demethylation stems at least in part from kinetic control, since essentially no $C_4$ reduction is observed.

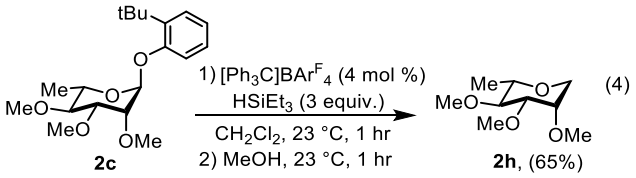
**VIII. Reactivity of other hydrosilylative reducing catalysts**



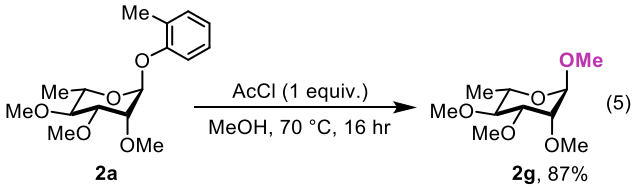

Scheme 3.6: Reduction of **2c** with BCF as catalyst

In previous studies the Gagné group showed that the electron deficient borane BCF is capable of extensive reduction of carbohydrate derivatives with the initial site of C-O cleavage being $C_1$.[30, 37-39] We have found that 1-aryloxy groups are also capable of protecting $C_1$ against BCF-catalyzed hydrosilylation. The rhamnose derivative **2c** undergoes BCF-catalyzed reduction to give the tri-*O*-demethylated product **2f**. Lower molar equivalents of silane did not lead to selective reduction at $C_2$, $C_3$, or $C_4$, but 10 equivalents is sufficient for complete demethylation without reduction of $C_1$. Thus, 1-aryloxy groups appear to be applicable anomeric protecting groups beyond iridium-catalyzed hydrosilylative ether cleavage. The nature of the hydride equivalent is still an important factor however. When $[Ph_3C][BArF_4]$ is employed as the catalyst alone in the reduction of **2c**, $C_1$ reduction is observed in preference to other sites of potential C-O

cleavage (eqn. 4). In this case triethylsilane itself is presumed to act as the hydride source for reduction of the $C_1$ silyloxonium or resulting oxocarbenium ion.




Scheme 3.7: Reduction of **2c** with $[Ph_3C]BAr^F{}_4$ as catalyst




Scheme 3.8: Reduction of **2c** with $[Ph_3C]BAr^F{}_4$ as catalyst

While the apparent stability of the 1-aryloxy group under hydrosilylative conditions is sufficient to protect the anomeric position, it can still be exchanged under suitable reaction conditions. Treatment of **2a** with a methanolic solution of hydrogen chloride, generated by the addition of acetyl chloride in methanol, gives the corresponding methyl glycoside **2g** with liberation of free *o*-cresol (eqn. 5). The hydrolytic lability of *O*-aryl glycosides has been previously identified in studies of wine grapes fouled by exposure to wood smoke. In that case slow hydrolysis of the wood-derived phenols guaiacol or *o*-cresol gives undesired odors and flavors associated with the phenol aglycones.[46] The lability of 1-aryloxy groups in this context should allow for the use of this methodology in the construction of polysaccharides via glycosylation. In particular, one can envision applying this methodology to selectively obtain a 3-hydroxy-*O*-aryl glycoside (**2b-6b**), conducting a glycosylation to obtain an *O*-aryl-3'-disacchride, then hydrolyzing the 1-aryloxy group for further elaboration. The 3-position is a common site of glycosylation in carbohydrates, which further increases the value of this transformation.[47-49]

## IX. Experimental

**General Considerations.** Syntheses and manipulations were conducted in air unless otherwise specified. Tetrahydrofuran, toluene, dichloromethane, pentane, and diethyl ether were degassed with argon and dried over activated alumina using a solvent purification system. All reagents and building blocks were procured from commercial vendors. $[(COD)Ir(PPh_3)_2]BAr^F{}_4$[50], and $[CPh_3]BAr^F{}_4$[51, 52] were prepared using reported procedures.

**tetraacetyl-L-rhamnopyranoside (11):** This compound was prepared according to a reported procedure.[53]

**(2-methylphenyl)-2,3,4-O-triacetyl-α-L-rhamnopyranoside (12):** A round bottom flask was charged with tetraacetyl-L-rhamnose, (2.0 g, 5.71 mmol, 1.0 equiv.) dichloromethane (19 mL) and $BF_3$•$OEt_2$ (1.1 mL, 8.57 mmol, 1.5 equiv.) followed by dropwise addition of 2-methylphenol (0.679 g, 6.28 mmol, 1.1 equiv.). The reaction was then stirred at room temperature overnight at which point the mixture was neutralized with saturated $NaHCO_3$ and extracted twice with dichloromethane. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting residue was recrystallized from ethyl acetate/hexane to give the product as an off-white solid. Yield: 1.46 g (56%)

$^1$H NMR (600 MHz $CDCl_3$) δ 7.12-7.17 (m, 2H), 7.06-7.07 (m, 1H), 6.95 (td, 7.4, 0.8 Hz, 1H), 5.51-5.54 (m, 1H), 5.45 (m, 2H), 5.17 (t, J = 10.0 Hz, 1H), 3.98-4.02 (m, 1H), 2.29 (s, 3H), 2.19 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.22 (d, J =6.3 Hz, 3H)

$^{13}$C{$^1$H} NMR (151 MHz $CDCl_3$) δ 170.1, 170.1, 170.0, 154.2, 131.0, 127.4, 126.9, 122.5, 114.0, 95.7, 70.9, 69.9, 69.1, 67.2, 20.9, 20.8, 20.7, 17.5, 16.2

**(2-methylphenyl)-α-L-rhamnopyranoside (13):** Compound **12** (1.46 g, 3.2 mmol, 1.0 equiv.) was suspended in MeOH (3.2 mL) followed by the addition of NaOMe (0.052 g, 0.97

mmol, 30 mol %) and was stirred overnight. The reaction mixture was then neutralized with Dowex® 50WX8-100 and filtered through a pad of Celite. The filtrate was concentrated under vacuum to give the product as a colorless solid. Yield: 0.909 g (87%)

$^{1}$H NMR (600 MHz DMSO) δ 7.11-7.15 (m, 2H), 7.03-7.04 (m, 1H), 6.87 (td, J = 7.4 Hz, J = 0.5 Hz, 1H), 5.36 (d, 1.4 Hz, 1H), 5.04 (bs, 1H), 4.87 (bs, 2H), 3.85 (q, J = 1.2 Hz, 1H), 3.67 (dd, J = 9.3 Hz, J = 3.4 Hz, 1H), 3.41-3.46 (m, 1H), 3.28 (t, J = 9.4 Hz, 1H), 2.15 (s, 3H), 1.09 (d, J = 6.2 Hz, 3H)

$^{13}$C{$^{1}$H} NMR (151 MHz DMSO) δ 154.5, 131.1, 127.3, 126.9, 121.9, 114.5, 98.5, 72.3, 71.1, 70.9, 70.0, 18.4, 16.3

**(2-methylphenyl)-2,3,4-O-trimethyl-α-L-rhamnopyranoside (2a):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (90%, 0.301 g, 12.5 mmol, 4.5 equiv.) and fitted with a rubber septum. The vessel was then brought out of the box and attached to a nitrogen manifold. DMF (3 mL) was added followed by a solution of **13** (0.909 g, 2.8 mmol, 1.0 equiv.) in DMF (3 mL). The resulting mixture was stirred at room temperature for 30 minutes then cooled to -20 °C. At this point iodomethane (0.8 mL, 12.5 mmol, 4.5 equiv.) was added dropwise. The reaction mixture was then warmed to room temperature, diluted with a 4 mL aliquot of DMF, and stirred overnight at which point the reaction was quenched with water and extracted three times with ethyl acetate. The combined organics were then washed twice with water and brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum to give the product as a colorless solid. Yield: 0.715 g (70%)

$^{1}$H NMR (500 MHz $CDCl_3$) δ 7.12-7.17 (m, 3H), 6.91-6.94 (td, 6.9, 2.1 Hz, 1H), 5.56 (d, 1.9 Hz, 1H), 3.77-3.79 (dd, 3.3, 2.0 Hz, 1H), 3.68-3.71 (dd, 9.5, 3.2 Hz, 1H), 3.63-3.67 (m, 1H), 3.58 (s, 3H), 3.57 (s, 3H), 3.56 (s, 3H), 3.20-3.24 (t, 9.5 Hz, 1H), 2.22 (s, 3H), 1.26-1.28 (d, 6.3 Hz, 3H)

$^{13}C\{^{1}H\}$ NMR (126 MHz $CDCl_3$) δ 154.5, 130.7, 126.9, 126.9, 121.8, 113.7, 94.8, 82.0, 81.2, 77.4, 68.6, 60.9, 59.1, 57.8, 17.8, 16.1

**(2-isopropylphenyl)-2,3,4-O-triacetyl-α-L-rhamnopyranoside (14):** A round bottom flask was charged with tetraacetyl-L-rhamnose, (5.0 g, 14.3 mmol, 1.0 equiv.) dichloromethane (48 mL) and $BF_3$•$OEt_2$ (2.6 mL, 21.4 mmol, 1.5 equiv.) followed by the slow addition of 2-isopropylphenol (2.6 mL, 15.7 mmol, 1.1 equiv.). The reaction was then stirred at room temperature overnight at which point the mixture was neutralized with saturated $NaHCO_3$ and extracted twice with dichloromethane. The combined organic extracts were then washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was purified using silica gel chromatography (10% to 25% EtOAc/hexanes) to give the product as a colorless solid. Yield: 2.57 g (44%)

$^{1}H$ NMR (600 MHz $CDCl_3$) δ 7.22-7.25 (m, 1H), 7.09-7.15 (m, 2H), 7.02 (td, J = 7.5 Hz, J = 1.1 Hz, 1H), 5.52 (dd, J = 10.2 Hz, J = 3.0 Hz, 1H), 5.44-5.45 (m, 2H), 5.19 (t, J = 10.0 Hz, 1H), 3.98-4.03 (m, 1H), 3.32 (septet, J = 6.7 Hz, 1H), 2.19 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 1.27 (t, J = 6.7 Hz, 6H), 1.23 (d, J = 6.2 Hz, 3H)

$^{13}C\{^{1}H\}$ NMR (151 MHz $CDCl_3$) δ 170.1, 170.1, 170.0, 153.4, 137.5, 126.8, 126.5, 122.8, 114.0, 95.9, 70.8, 70.0, 69.2, 67.4, 27.4, 22.8, 22.7, 20.9, 20.8, 20.8, 17.5

**(2-isopropylphenyl)-α-L-rhamnopyranoside (15):** Compound **14** (2.57 g, 5.35 mmol, 1.0 equiv.) was suspended in MeOH (5.4 mL) followed by the addition of NaOMe (0.087 g, 3.2 mmol, 30 mol %) and was stirred overnight. The reaction mixture was neutralized with Dowex® 50WX8-100 and filtered through a pad of Celite. The filtrate was then concentrated under vacuum to give the product as a colorless solid. Yield: 1.513 g (99%)

$^{1}$H NMR (600 MHz DMSO) δ 7.20 (dd, J = 7.7 Hz, J = 1.5 Hz, 1H), 7.11-7.14 (m, 1H), 7.06-7.07 (m, 1H), 6.94 (td, J = 7.4 Hz, J = 0.9 Hz, 1H), 5.35 (d, J = 1.5 Hz, 1H), 5.01 (bs, 3H), 3.85-3.86 (m, 1H), 3.67 (dd, J = 9.6 Hz, J = 3.3 Hz, 1H), 3.44-3.48 (m, 1H), 3.31 (t, J = 9.2 Hz, 1H), 3.20 (septet, J = 6.9 Hz, 1H), 1.17 (d, J = 7.4 Hz, 6H), 1.12 (d, J = 6.2 Hz, 3H)

$^{13}$C{$^{1}$H} NMR (151 MHz DMSO) δ 153.79, 137.0, 127.2, 126.6, 122.1, 114.4, 98.7, 72.3, 71.1, 70.9, 70.1, 27.3, 23.2, 23.0, 18.4

**(2-isopropylphenyl)-2,3,4-O-trimethyl-α-L-rhamnopyranoside (2b):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (60% in mineral oil, 1.29 g, 32.15 mmol, 6.0 equiv.) and fitted with a rubber septum. The vessel was then brought outside of the box and attached to a nitrogen manifold. DMF (3.6 mL) was added followed by a solution of **15** (1.513 g, 5.4 mmol, 1.0 equiv.) in DMF (54 mL). The resulting mixture was stirred at room temperature for 30 minutes after which the solution was cooled to 0 °C and iodomethane (2.0 mL, 32.2 mmol, 6.0 equiv.) was added over the course of an hour in four portions. The reaction mixture was then allowed to warm to room temperature with stirring overnight at which point the reaction was quenched with 50 mL water and extracted with three 50 mL portions of ethyl acetate. The combined organic extracts were washed sequentially with three 50 mL portions of water and then brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum giving a pale-yellow oil. The residue was then purified using silica gel chromatography (10% to 25% EtOAc/hexanes) to give the product as a colorless solid. Yield: 1.31 g (75%)

$^{1}$H NMR (600 MHz $CDCl_3$) δ 7.22-7.23 (m, 1H) 7.14-7.19 (m, 2H), 7.00 (td, J = 7.4 Hz, J = 0.9 Hz, 1H), 5.56 (d, J = 1.8 Hz, 1H), 3.77-3.78 (m, 1H), 3.66-3.71 (m, 2H) 3.58 (s, 3H), 3.58 (s, 3H), 3.56 (s, 3H), 3.22-3.26 (m, 2H), 1.29 (d, J = 6.3 Hz, 3H), 1.24 (dd, J = 7.2 Hz, J = 3.2 Hz, 6H)

$^{13}C\{^{1}H\}$ NMR (151 MHz $CDCl_3$) δ 153.9, 137.1, 126.8, 126.3, 122.2, 114.0, 95.2, 82.1, 81.4, 77.5, 68.8, 61.0, 59.2, 57.9, 27.4, 22.8, 22.6, 17.9

**(2-*t*-butylphenyl)-2,3,4-O-triacetyl-α-L-rhamnopyranoside (16):** A round bottom flask was charged with tetraacetyl-L-rhamnose, (5.0 g, 14.3 mmol, 1.0 equiv.) dichloromethane, (48 mL) and $BF_3$•$OEt_2$ (2.6 mL, 21.4 mmol, 1.5 equiv.) followed by dropwise addition of 2-tertbutylphenol (2.4 mL, 15.7 mmol, 1.1 equiv.). The reaction was stirred at room temperature overnight at which point the reaction was neutralized with saturated $NaHCO_3$ and extracted twice with dichloromethane. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (25% EtOAc/hexanes) and then recrystallized from ethanol to give the product as a colorless solid. Yield: 2.216 g (35%)

$^{1}H$ NMR (600 MHz $CDCl_3$) δ 7.33 (dd, J = 7.9, 1.2 Hz, 1H), 7.15-7.19 (m, 2H), 6.97-7.00 (m, 1H), 5.54 (dd, J = 10.2, 3.1 Hz, 1H), 5.49-5.50 (m, 2H), 5.21 (t, J = 10.2 Hz, 1H), 3.96-4.01 (m, 1H), 2.19 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.45 (s, 9H), 1.24 (d, J = 6.2 Hz, 3H)

$^{13}C\{^{1}H\}$ NMR (151 MHz $CDCl_3$) δ 170.2, 170.2, 170.2, 155.3, 138.5, 127.4, 127.1, 122.4, 114.4, 95.9, 70.8, 69.8, 69.4, 67.7, 34.9, 30.3, 21.0, 21.0, 20.8, 17.7

**(2-t-butylphenyl)-α-L-rhamnopyranoside (17):** A suspension of compound **16** (3.06 g, 6.92 mmol, 1.0 equiv.) in 7 mL MeOH was treated with NaOMe (0.110 g, 2.04 mmol, 30 mol %) and was stirred for one hour. The reaction mixture was then neutralized with Dowex® 50WX8-100 and filtered through a pad of Celite. The filtrate was concentrated under vacuum to give the product as a colorless solid. Yield: 2.39 g (99%)

$^{1}$H NMR (600 MHz DMSO) δ 7.22-7.24 (m, 1H), 7.13-7.15 (m, 2H), 6.88-6.91 (m, 1H), 5.37 (s, 1H), 5.11 (bs, 3H), 3.90 (m, 1H), 3,72 (dd, J = 9.5 Hz, J = 3.3 Hz, 1H), 3.47-3.49 (m, 1H), 3.34 (t, J = 9.3 Hz, 1H), 1.33 (s, 9H), 1.15 (d, J = 6.3 Hz, 3H)

$^{13}$C{$^{1}$H} NMR (151 MHz DMSO) δ 155.7, 137.5, 127.7, 126.9, 121.5, 114.3, 99.0, 72.3, 71.2, 70.9, 70.2, 34.8, 30.3, 18.5

**(2-t-butylphenyl)-2,3,4-O-trimethyl-α-L-rhamnopyranoside (2c):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (90%, 0.982 g, 40.9 mmol, 6.0 equiv.) and fitted with a rubber septum. The vessel was then brought outside of the box and attached to a nitrogen manifold. DMF (27 mL) was added followed by a solution of **17** (2.0 g, 6.8 mmol, 1.0 equiv.) in DMF (68 mL). The resulting mixture was stirred at room temperature for 30 minutes after which the solution was cooled to 0 °C and iodomethane (2.5 mL, 40.9 mmol, 6.0 equiv.) was added dropwise. The reaction mixture was then allowed to warm to room temperature with stirring overnight at which point the reaction was quenched with 100 mL water and extracted with three 50 mL portions of ethyl acetate. The combined organic extracts were washed with 100 mL of water and 100 mL of brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The resulting residue was then purified using silica gel chromatography (6% to 60% EtOAc/hexanes) to give the product as a white solid. Yield: 1.25 g (54%)

$^{1}$H NMR (600 MHz $CDCl_3$) δ 7.30-7.31 (dd, J = 7.8, 1.6 Hz, 1H), 7.28 (d, 0.90 Hz, 1H), 7.17-7.19 (td, 7.4, 1.6 Hz, 1H), 6.96-6.98 (td, 7.6, 1.1 Hz, 1H), 5.58 (d, 1.7 Hz, 1H), 3.80-3.81 (dd, 3.3, 2.0 Hz, 1H), 3.73-3.75 (dd, 9.5, 3.2 Hz, 1H), 3.66-3.71 (m, 1H), 3.58 (s, 3H), 3.57 (s, 3H), 3.56 (s, 3H), 3.23-3.26 (t, 9.5 Hz, 1H), 1.40 (s, 9H), 1.30-1.31 (d, 6.22 Hz, 3H)

$^{13}$C{$^{1}$H} NMR (151 MHz $CDCl_3$) δ 155.8, 137.9, 127.4, 126.8, 121.8, 114.4, 95.5, 82.0, 81.4, 77.4, 68.9, 61.0, 59.3, 57.9, 34.7, 30.1, 17.9

**(2,4-dichlorophenyl)-2,3,4-O-triacetyl-α-L-rhamnopyranoside (18):** A round bottom flask was charged with tetraacetyl-L-rhamnose, (10.6 g, 31.9 mmol, 1.0) 102 mL dichloromethane, and $BF_3$•$OEt_2$ (5.5 mL, 44.6 mmol, 1.4 equiv.) followed by the slow addition of 2,4-dichlorophenol (5.38 g, 33.0 mmol, 1.1 equiv.). The reaction was then stirred at room temperature overnight at which point the reaction was neutralized with saturated $NaHCO_3$ and extracted twice with dichloromethane. The combined organic extracts were then washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was recrystallized with ethyl acetate and hexane to give an off-white solid. Yield: 4.18 g (30%)

$^1$H NMR (600 MHz $CDCl_3$) δ 7.39 (d, J = 2.0 Hz, 1H), 7.17 (dd, J = 9.0, 1.9 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 5.53 (dd, J = 9.8, 3.5 Hz, 1H), 5.49 (s, 1H), 5.44 (s, 1H), 5.16 (t, J = 10.2 Hz, 1H), 3.98-4.03 (m, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.20 (d, J = 6.3 Hz, 3H)

$^{13}$C{$^1$H} NMR (151 MHz $CDCl_3$) δ 170.1, 170.1, 170.0, 150.3, 130.4, 128.4, 127.9, 125.2, 117.6, 96.7, 70.8, 69.6, 68.8, 68.0, 21.0, 20.9, 20.8, 17.5

**(2,4-dichlorophenyl)-α-L-rhamnopyranoside (19):** A suspension of **18** (4.18 g, 9.6 mmol, 1.0 equiv.) in 8 mL MeOH was treated with NaOMe (0.175 g, 3.2 mmol, 30 mol %) and was stirred overnight. The reaction mixture was then neutralized with Dowex® 50WX8-100 and filtered through a pad of Celite. The filtrate was concentrated under vacuum to give the product as a colorless solid. Yield: 2.94 (99%)

$^1$H NMR (600 MHz DMSO) δ 7.59 (d, J = 2.6 Hz, 1H), 7.35-7.37 (m, 1H), 7.29-7.30 (m, 1H), 5.49 (d, 1.3 Hz, 1H), 5.15 (bs, 1H), 4.96 (bs, 1H), 3.87-3.88 (dd, 3.5, 1.8 Hz, 1H), 3.67-3.69 (dd, 9.4, 3.3 Hz, 1H), 3.40-3.45 (m, 1H), 3.34 (bs, 1H), 3.29-3.32 (t, 9.4 Hz, 1H), 1.08-1.09 (d, 6.1 Hz, 3H)

$^{13}$C{$^1$H} NMR (151 MHz DMSO) δ 150.8, 129.9, 128.6, 126.3, 124.0, 118.6, 99.4, 72.0, 70.8, 70.6, 70.4, 18.3

**(2,4-dichlorophenyl)-2,3,4-O-trimethyl-α-L-rhamnopyranoside (2d):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (90%, 0.466 g, 19.4 mmol, 6.0 equiv.) and fitted with a rubber septum. The vessel was then brought outside of the box and attached to a nitrogen manifold. 13 mL DMF was added followed by a solution of **19** (1.0 g, 3.2 mmol, 1.0 equiv.) in 31 mL DMF. The resulting mixture was stirred at room temperature for 30 minutes after which the solution was cooled to 0 °C and iodomethane (1.2 mL, 19.4 mmol, 6.0 equiv.) was added over the course of an hour in four portions. The reaction mixture was then allowed to warm to room temperature with stirring overnight at which point the reaction was quenched with 50 mL water and extracted with three 50 mL portions of ethyl acetate. The combined organic extracts were washed sequentially with three 50 mL portions of water and then brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum giving the product as pale-yellow oil. Yield: 0.930 g (82%)

$^1$H NMR (600 MHz $CDCl_3$) δ 7.37 (d, J = 2.6 Hz, 1H), 7.17-7.19 (m, 1H), 7.13-7.14 (m, 1H), 5.50 (d, J =1.9 Hz, 1H), 3.84-3.85 (dd, J = 3.4, 2.1 Hz, 1H), 3.70-3.72 (dd, 9.5, 3.3 Hz, 1H), 3.62-3.67 (m, 1H), 3.57 (s, 6H), 3.56 (s, 3H), 3.19-3.23 (t, 9.5 Hz, 1H), 1.25-1.27 (d, 6.3 Hz, 3H)

$^{13}$C{$^1$H} NMR (151 MHz $CDCl_3$) δ 150.7, 130.0, 127.8, 127.6, 124.7, 117.6, 96.4, 81.8, 80.9, 77.1, 69.2, 60.9, 59.4, 58.0, 17.8

**(2-methoxyphenyl)-2,3,4-O-triacetyl-α-L-rhamnopyranoside (20):** A round bottom flask was charged with tetraacetyl-L-rhamnose, (5.44 g, 15.5 mmol, 1.0 equiv.) 31 mL dichloromethane, and $BF_3$•$OEt_2$ (3.8 mL, 31.1 mmol, 2.0 equiv.) followed by the slow addition of 2-methoxyphenol (3.5 mL, 31.1 mmol, 2.0 equiv.). The reaction was then stirred at room temperature overnight after which the reaction was neutralized with saturated $NaHCO_3$ and extracted twice with dichloromethane. The combined organic extracts were washed with brine,

dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was then purified using silica gel chromatography (25% to 50% EtOAc/hexanes) to give the product as a white solid. Yield: 2.99 g (46%)

$^1$H NMR (600 MHz $CDCl_3$) δ 7.02-7.098 (m, 2H), 6.86-6.91 (m, 2H), 5.57 (dd, J = 10.1 Hz, J = 3.4 Hz, 1H), 5.53 (dd, J = 3.7 Hz, J = 1.8 Hz, 1H) 5.37 (d, J = 1.5 Hz, 1H), 5.14 (t, J = 10.1 Hz, 1H), 4.18-4.23 (m, 1H), 3.84 (s, 3H), 2.17 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.21 (d, J = 6.5 Hz, 3H)

$^{13}$C{$^1$H} NMR (151 MHz $CDCl_3$) δ 170.1, 170.0, 169.9, 150.8, 145.1, 124.2, 120.9, 119.2, 112.7, 97.6, 71.1, 69.8, 69.0, 67.3, 55.9, 20.9, 20.8, 20.8, 17.4

**(2-methoxyphenyl)-α-L-rhamnopyranoside (21):** A suspension of **20** (2.94 g, 7.10 mmol, 1.0 equiv.) in 7.1 mL MeOH was treated with NaOMe (0.115 g, 2.13 mmol, 30 mol %) and was stirred overnight. The reaction mixture was then neutralized with Dowex® 50WX8-100 and filtered through a pad of Celite. The filtrate was then concentrated under vacuum to give the product as a colorless solid. Yield: 1.99 g (97%)

$^1$H NMR (600 MHz DMSO) δ 7.06 (dd, J = 7.9, 1.1 Hz, 1H), 6.97-7.01 (m, 2H), 6.85-6.88 (m, 1H), 5.24 (d, J = 1.5 Hz, 1H), 3.85 (dd, J = 3.5, 1.8 Hz, 1H), 3.76 (s, 3H), 3.65 (dd, J = 9.5, 3.3 Hz, 1H), 3.58-3.61 (m, 1H), 3.41 (bs, 3H), 3.27 (t, J = 9.4 Hz, 1H), 1.09 (d, J = 6.2 Hz, 3H)

$^{13}$C{$^1$H} NMR (151 MHz DMSO) δ 150.7, 145.7, 123.4, 121.2, 118.5, 113.3, 100.1, 72.2, 70.9, 70.8, 70.0, 56.1, 18.3

**(2-methoxyphenyl)-2,3,4-O-trimethyl-α-L-rhamnopyranoside (2e):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (60% in mineral oil, 1.63 g, 40.8 mmol, 6.0 equiv.) and fitted with a rubber septum. The vessel was then brought outside of the box and attached to a nitrogen manifold. 27 mL DMF was added followed by a solution of

**21** (1.96 g, 6.80 mmol, 1.0 equiv.) in 68 mL DMF. The resulting mixture was stirred at room temperature for 30 minutes after which the solution was cooled to 0 °C and iodomethane (2.5 mL, 40.8 mmol, 6.0 equiv.) was added over the course of an hour in four portions. The reaction mixture was then allowed to warm to room temperature with stirring overnight at which point the reaction was quenched with 50 mL water and extracted with three 50 mL portions of ethyl acetate. The combined organic extracts were washed with 50 mL of water and 50 mL of brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum to give the product as a waxy colorless solid. Yield: 1.82 g (81%)

$^1$H NMR (600 MHz $CDCl_3$) δ 7.11 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H), 7.02 (td, J = 7.7 Hz, 1.4 Hz, 1H), 6.88-6.92 (m, 2H), 5.50 (d, J = 1.7 Hz, 1H), 3.88 (dd, J = 3.3 Hz, J = 2.0 Hz, 1H), 3.82-3.85 (m, 4H), 3.74 (dd, J = 9.5 Hz, J = 3.4 Hz, 1H), 3.58 (s, 3H), 3.57 (s, 3H), 3.55 (s, 3H), 3.20 (t, J = 9.4 Hz, 1H), 1.27 (d, J = 6.3 Hz, 3H)

$^{13}$C{$^1$H} NMR (151 MHz $CDCl_3$) δ 150.5, 145.5, 123.5, 121.0, 118.9, 112.4, 96.7, 82.1, 80.8, 77.4, 68.7, 60.9, 59.1, 57.9, 55.8, 17.7

**(2-methylphenyl)-2,3,4,6-O-tetraacetyl-β-D-glucopyranoside (22):** A round bottom flask was charged with pentaacetyl-β-D-glucopyranoside, (5.0 g, 12.81 mmol, 1.0 equiv.) 26 mL dichloromethane, and 2-methylphenol. (2.77 g, 25.62 mmol, 2.0 equiv.) The mixture was then cooled to 0 °C and $BF_3$•$OEt_2$ (2.4 mL, 19.21 mmol, 1.5 equiv.) was added dropwise after which the mixture was allowed to warm to room temperature with stirring overnight. The reaction was neutralized with saturated $NaHCO_3$ and extracted twice with dichloromethane. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was then recrystallized from ethyl acetate/hexanes to give the product as a colorless solid. Yield: 4.353 g (78%)

$^{1}$H NMR (600 MHz $CDCl_3$) δ 7.12-7.15 (m, 2H), 6.97-6.99 (m, 2H), 5.28-5.35 (m, 2H), 5.17 (t, J = 9.7 Hz 1H), 5.03 (d, J = 7.8 Hz, 1H), 4.28-4.31 (m, 1H), 4.17-4.19 (m, 1H), 3.84-3.87 (m, 1H), 2.17 (s, 3H), 2.04-2.08 (m, 12H)

$^{13}$C{$^{1}$H} NMR (151 MHz $CDCl_3$) δ 170.6, 170.3, 169.4, 169.2, 155.2, 131.0, 128.1, 126.9, 123.2, 115.1, 99.4, 72.7, 71.9, 71.1, 68.4, 62.0, 20.7, 20.7, 20.6, 20.6, 16.0

**(2-methylphenyl)-β- D-glucopyranoside (23):** A suspension of **22** (4.35 g, 9.93 mmol, 1.0 equiv.) in 10 mL MeOH was treated with NaOMe (0.161 g, 2.98 mmol, 30 mol %) and was stirred overnight. The reaction mixture was then neutralized with Dowex® 50WX8-100 and filtered through a pad of Celite. The filtrate was then concentrated under vacuum to give the product as a colorless solid. Yield: 2.753 (*quant.*)

$^{1}$H NMR (600 MHz DMSO) δ 7.11-7.14 (m, 2H), 7.05-7.06 (m, 1H), 6.89 (td, J = 7.4, 0.8 Hz, 1H), 5.27 (bs, 3H), 4.78-4.79 (m, 1H), 4.60 (bs, 1H), 3.69 (dd, J = 11.8, 1,9 Hz, 1H), 3.47 (dd, J = 11.9, 5.7 Hz, 1H), 3.25-3.31 (m, 3H), 3.16-3.19 (m, 1H), 2.20 (s, 3H)

$^{13}$C{$^{1}$H} NMR (151 MHz DMSO) δ 156.1, 130.8, 127.3, 127.2, 122.0, 115.1, 101.4, 77.5, 77.1, 73.8, 70.2, 61.2, 16.5

**(2-methylphenyl)-6-O-triisopropylsilyl-β-D-glucopyranoside (24):** A solution of **23** (2.753 g, 10.19 mmol, 1.0 equiv.) in 51 mL DMF was treated with imidazole (2.08 g, 30.56 mmol, 3.0 equiv.) and 4-(dimethylamino)pyridine (0.062 g, 0.51 mmol, 5 mol %) and was stirred at room temperature for 10 minutes. The flask was then cooled to 0 °C and triisopropylchlorosilane (2.6 mL, 12.22 mmol, 1.2 equiv.) was added dropwise. The crude mixture was then warmed to room temperature and stirred overnight. Upon completion the reaction was quenched with water and extracted three times with ethyl acetate. The combined organic extracts were washed with 1M HCl, water, then brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting

residue was purified by silica gel column chromatography (50% to 100% EtOAc/hexanes) to give the product as a colorless solid. Yield: 3.65 g (84%)

$^{1}$H NMR (600 MHz $CDCl_3$) δ 7.09 -713 (m, 2H), 7.03-7.04 (m, 1H), 6.94 (t, J = 7.3 Hz, 1H), 4.85 (d, J = 7.3 Hz, 1H), 3.96 (d, J = 5.4 Hz, 2H), 3.90 (bs, 1H), 3.67-3.72 (m, 2H), 3.62-3.65 (m, 1H), 2.24 (s, 3H), 1.08-1.14 (m, 3H), 1.05-1.06 (m, 18H)

$^{13}$C{$^{1}$H} NMR (151 MHz $CDCl_3$) δ 155.5, 130.9, 128.1, 127.0, 122.9, 115.7, 101.4, 76.5, 74.7, 73.5, 73.0, 65.2, 18.0, 16.5, 11.9

**(2-methylphenyl)-6-O-triisopropylsilyl-2,3,4-O-trimethyl-β-D-glucopyranoside (7a):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (60% in mineral oil, 2.063 g, 51.57 mmol, 6.0 equiv.) and fitted with a rubber septum. The vessel was then brought outside of the box, attached to a nitrogen manifold, and cooled to 0 °C. 34 mL DMF was added followed by a solution of **24** (3.65 g, 8.60 mmol, 1.0 equiv.) in 86 mL DMF. The resulting mixture was stirred for one hour after which iodomethane (3.2 mL, 51.57 mmol, 6.0 equiv.) was added in four portions over two hours. The reaction mixture was then warmed to room temperature and stirred overnight at which point the reaction was quenched with water and extracted three times with ethyl acetate. The combined organics were then washed twice with water, once with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The resulting residue was then purified by silica gel column chromatography (5% to 25% EtOAc/hexanes) to give the product as a colorless oil. Yield: 3.285 g (82%)

$^{1}$H NMR (600 MHz $CDCl_3$) δ 7.13 (d, J = 7.6 Hz, 1H), 7.07-7.10 (m, 2H), 6.91-6.94 (m, 1H), 4.80 (d, J = 7.2 Hz, 1H), 3.97 (dd, J = 11.0 Hz, J = 1.8 Hz, 1H), 3.86 (dd, J = 11.0, J = 5.1, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 3.58 (s, 3H), 3.23-3.33 (m, 4H), 2.28 (s, 3H), 1.03-1.12 (m, 21H)

$^{13}C\{^{1}H\}$ NMR (151 MHz $CDCl_3$) δ 155.8, 130.6, 127.7, 126.8, 122.3, 115.7, 101.5, 86.8, 83.9, 79.2, 76.4, 62.6, 61.0, 60.8, 60.4, 18.0,, 17.9, 16.5, 11.9

**Pentaacetyl-α-D-mannopyranoside (25):** This compound was prepared according to a reported procedure.[54]

**(2-methylphenyl)-2,3,4,6-O-tetraacetyl-α-D-mannopyranoside (26):** A round bottom flask was charged with pentaacetyl-D-mannopyranoside, (5.0 g, 12.81 mmol, 1.0 equiv.) 26 mL dichloromethane, and 2-methylphenol (2.77 g, 25.62 mmol, 2.0 equiv.). The mixture was then cooled to 0 °C and $BF_3$•$OEt_2$ (2.4 mL, 19.21 mmol, 1.5 equiv.) was added dropwise. After addition the flask was allowed to warm to room temperature with stirring overnight. The reaction was neutralized with saturated $NaHCO_3$ and extracted twice with dichloromethane. The combined organic extracts were then washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was purified by column chromatography (25% to 50% EtOAc/hexanes) followed by recrystallization from ethyl acetate/hexanes to give the product as a colorless solid. Yield: 3.122 g (56%)

$^{1}H$ NMR (600 MHz $CDCl_3$) δ 7.17 (d, J = 7.4 Hz, 1H), 7.11-7.14 (m, 1H), 7.07-7.09 (m, 1H), 6.96 (td, J = 7.4, 1.1 Hz, 1H), 5.57 (dd, J = 10.0, 3.5 Hz, 1H), 5.51 (d, J = 1.6 Hz, 1H), 5.46 (dd, J = 3.6, 1.9 Hz, 1H), 5.38 (t, J = 10.2 Hz, 1H), 4.27-4.30 (m, 1H), 4.07-4.12 (m, 2H), 2.29 (s, 3H), 2.19 (s, 3H), 2.06 (s, 3H), 2.03 (s, 6H)

$^{13}C\{^{1}H\}$ NMR (151 MHz $CDCl_3$) δ 170.5, 170.0, 169.9, 169.7, 153.9, 131.1, 127.5, 126.9, 122.8, 114.2, 95.9, 69.6, 69.2, 69.0, 65.9, 62.2, 20.9, 20.7, 20.7, 16.2

**(2-methylphenyl)-α-D-mannopyranoside (27):** A suspension of **26** (3.092 g, 7.05 mmol, 1.0 equiv.) in 7.1 mL MeOH was treated with NaOMe (0.114 g, 2.11 mmol, 30 mol %) and was allowed to stir for three hours. The reaction mixture was then neutralized with Dowex® and filtered

through a pad of Celite. The filtrate was then concentrated under vacuum to give the product as a colorless solid. Yield: 1.914 g (quant.)

$^{1}$H NMR (600 MHz DMSO) δ 7.10-7.15 (m, 3H), 6.89 (td, J = 7.1, 1.6 Hz, 1H), 5.36 (d, J = 1.6 Hz, 1H), 5.01 (bs, 1H), 4.88 (bs, 1H), 4.45 (bs, 1H), 3.86 (dd, J = 3.4, 1.9 Hz, 1H), 3.71 (dd, J = 9.5, 3.3 Hz 1H), 3.59 (dd, J = 11.7, 2.0 Hz, 1H), 3.51 (t, J = 9.4 Hz, 1H), 3.45-3.48 (m, 1H), 3.38-3.41 (m, 1H), 3,35 (bs, 1H), 2.16 (s, 3H)

$^{13}$C{$^{1}$H} NMR (151 MHz DMSO) δ 154.9, 131.0, 127.4, 127.1, 122.0, 115.2, 99.0, 75.4, 71.3, 70.7, 67.2, 61.5, 16.4

**(2-methylphenyl)-6-O-triisopropylsilyl-α-D-mannopyranoside (28):** A solution of **27** (1.884 g, 6.97 mmol, 1.0 equiv.) in 35 mL DMF was treated with imidazole (1.423 g, 20.91 mmol, 3.0 equiv.) and 4-(dimethylamino)pyridine (0.043 g, 0.35 mmol, 5 mol %), and was stirred at room temperature for 10 minutes. The mixture was then cooled to 0 °C and triisopropylchlorosilane (1.8 mL, 8.36 mmol, 1.2 equiv.) was added dropwise. The mixture was then warmed to room temperature and stirred overnight. Upon completion the reaction was quenched with water and extracted three times with ethyl acetate. The combined organic extracts were washed with 1M HCl, water, then brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (50% to 100% EtOAc/hexanes) to give the product as a colorless solid. Yield: 0.826 g (28%)

$^{1}$H NMR (600 MHz $CDCl_3$) δ 7.09-7.14 (m, 3H), 6.92 (td, J = 7.0 Hz, J = 1.3 Hz, 1H), 5.55 (d, J = 1.5 Hz, 1H), 4.17 (bs, 1H), 4.10-4.13 (m, 1H), 3.90-3.99 (m, 3H), 3.87 (s, 1H). 3.73-3.76 (m, 1H), 3.55 (d, J = 3.8 Hz, 1H), 3.18 (d, J = 3.1 Hz, 1H), 2.22 (s, 3H), 0.99-1.11 (m, 21H)

$^{13}$C{$^{1}$H} NMR (151 MHz $CDCl_3$) δ 154.3, 130.9, 127.2, 126.9, 122.1, 114.1, 97.5, 71.6, 71.5, 70.5, 70.3, 65.8, 17.8, 17.8, 16.2, 11.7

**(2-methylphenyl)-6-O-triisopropylsilyl-2,3,4-O-trimethyl-α-D-mannopyranoside**

**(3a):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (60% in mineral oil, 0.452 g, 11.30 mmol, 6.0 equiv.) and fitted with a rubber septum. The vessel was then brought outside of the box and attached to a nitrogen manifold and cooled to 0 °C. 19 mL DMF was added followed by a solution of **28** (0.800 g, 1.88 mmol, 1.0 equiv.) in 7.5 mL DMF. The resulting mixture was stirred for one hour after which iodomethane (0.7 mL, 11.30 mmol, 6.0 equiv.) was added in four portions over two hours. The reaction mixture was then warmed to room temperature and stirred overnight at which point the reaction was quenched with water and extracted three times with ethyl acetate. The combined organics were then washed twice with water, once with brine, dried over $Na_2SO_4$, filtered, and concentrated under vacuum. The resulting residue was then purified by silica gel column chromatography (5% to 15% EtOAc/hexanes) to give the product as a colorless solid. Yield: 0.725 g (82%)

$^1$H NMR (600 MHz $CDCl_3$) δ 7.11-7.19 (m, 3H), 6.92 (t, J = 7.2 Hz, 1H), 5.60 (d, J = 1.5 Hz, 1H), 3.86-3.89 (m, 2H), 3.78-3.79 (m, 1H), 3.76 (dd, J = 9.3 Hz, J = 3.1 Hz, 1H), 3.67 (t, J = 9.3 Hz, 1H), 3.58 (s, 6H), 3.51 (s, 3H), 2.23 (s, 3H), 0.99-1.12 (m, 21H)

$^{13}$C{$^1$H} NMR (151 MHz $CDCl_3$) δ 154.7, 130.6, 127.0, 126.9, 121.8, 114.3, 94.8, 81.2, 77.0, 75.9, 73.7, 62.6, 60.6, 58.3, 57.8, 17.9, 17.8, 16.2, 12.0

**(2-methylphenyl)-2,3,4,6-O-tetraacetyl-β-D-allopyranoside (29):** To a 40 mL scintillation vial was added D-allose (1.000 g, 5.55 mmol, 1.0 equiv.), acetic anhydride (5.2 mL, 55.51 mmol, 10.0 equiv.), and pyridine (4.5 mL, 55.51 mmol, 10.0 equiv.). The mixture was then stirred overnight at room temperature. The following day the mixture was concentrated under vacuum and the resulting viscous oil was dissolved in 11 mL dichloromethane and treated with 2-methylphenol (1.200 g, 11.10 mmol, 2.0 equiv.). The mixture was then cooled to 0 °C and

$BF_3$•$OEt_2$ (1.0 mL, 8.33 mmol, 1.5 equiv.) was added dropwise, at which point the reaction was allowed to warm to room temperature with stirring overnight. The reaction was neutralized with saturated $NaHCO_3$ and extracted twice with dichloromethane. The combined organic extracts were then washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was purified by column chromatography (25% to 50% EtOAc/hexanes) followed by recrystallization from diethyl ether/n-pentane to give the product as a colorless solid. Yield: 0.776 g (32%)

$^1$H NMR (600 MHz $CDCl_3$) δ 7.14-7.17 (m, 2H), 7.07 (d, J = 8.1 Hz, 1H), 6.98 (t, J = 7.4 Hz, 1H), 6.98 (t, J = 7.4 Hz, 1H) 5.74 (t, J = 3.0 Hz, 1H), 5.32 (d, J = 8.1 Hz, 1H), 5.23 (dd, J = 8.3, 3.0 Hz, 1H), 5.06 (dd, J = 9.2, 2.7 Hz, 1H), 4.23-4.29 (m, 2H), 2.17 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H)

$^{13}$C{$^1$H} NMR (151 MHz $CDCl_3$) δ 170.7, 169.8, 169.1, 169.0, 155.5, 131.0, 128.1, 126.9, 123.1, 115.2, 97.9, 70.4, 68.8, 68.6, 66.3, 62.4, 20.7, 20.7, 20.6, 20.6, 16.0

**(2-methylphenyl)-β-D-allopyranoside (30):** A suspension of **29** (0.746 g, 1.70 mmol, 1.0 equiv.) in 1.7 mL MeOH was treated with NaOMe (0.028 g, 0.51 mmol, 30 mol %) and was allowed to stir for three hours. The reaction mixture was then neutralized with Dowex® 50WX8-100 and filtered through a pad of Celite. The filtrate was concentrated under vacuum to give the product as a colorless solid. Yield: 0.433 g (94%)

$^1$H NMR (600 MHz DMSO) δ 7.11-7.14 (m, 2H), 7.04 (d, J = 8.1 Hz, 1H), 6.88 (t, J = 7.2 Hz, 1H), 5.06 (d, J = 7.9 Hz, 1H), 5.00 (d, J = 6.9 Hz, 1H), 4.92 (d, J = 3.6 Hz, 1H), 4.64 (d, J = 7.4 Hz, 1H), 4.49 (t, J = 5.5 Hz, 1H), 3.39 (m, 1H), 3.65-3.69 (m, 2H), 3.39-3.47 (m, 3H) 2.19 (s, 3H)

$^{13}$C{$^1$H} NMR (151 MHz DMSO) δ 156.4, 130.8, 127.3, 127.2, 121.9, 115.0, 99.5, 75.1, 72.0, 70.8, 67.8, 61.5, 16.5

**(2-methylphenyl)-6-O-triisopropylsilyl-β-D-allopyranoside (31):** A solution of **30** (0.403 g, 1.49 mmol, 1.0 equiv.) in 7.5 mL DMF was treated with imidazole (0.304 g, 4.47 mmol, 3.0 equiv.) and 4-(dimethylamino)pyridine (0.009 g, 0.075 mmol, 5 mol %), and was stirred at room temperature for 10 minutes. The mixture was then cooled to 0 °C and triisopropylchlorosilane (0.38 mL, 1.79 mmol, 1.2 equiv.) was added dropwise. The soluion was then warmed to room temperature and stirred overnight. Upon completion the reaction was quenched with water and extracted three times with ethyl acetate. The combined organic extracts were washed with 1M HCl, water, then brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (50% to 100% EtOAc/hexanes) to give the product as a clear, viscous oil. Yield: 0.490 g (77%)

$^1$H NMR (600 MHz $CDCl_3$) δ 7.11-7.14 (m, 2H), 7.05 (d, J = 8.1 Hz, 1H), 6.94 (td, J = 7.5 Hz, J = 0.7 Hz, 1H), 5.26 (d, J = 7.8 Hz, 1H), 4.33 (s, 1H), 3.99-4.02 (m, 1H), 3.90-3.94 (m, 2H), 3.76-3.78 (m, 3H), 2.98 (s, 1H), 2.72 (d, J = 6.8 Hz, 1H), 2.27 (s, 3H), 1.04-1.15 (m, 21H)

$^{13}$C{$^1$H} NMR (151 MHz $CDCl_3$) δ 154.5, 129.8, 126.8, 125.8, 121.5, 114.1, 98.1, 71.1, 70.2, 69.8, 69.3, 64.7, 16.8, 15.3, 10.7

**(2-methylphenyl)-6-O-triisopropylsilyl-2,3,4-O-trimethyl-β-D-allopyranoside (8a):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (60% in mineral oil, 0.266 g, 6.64 mmol, 6.0 equiv.) and fitted with a rubber septum. The vessel was then brought outside of the box, attached to a nitrogen manifold, and cooled to 0 °C. 4.4 mL DMF was added followed by a solution of **31** (0.470 g, 1.11 mmol, 1.0 equiv.) in 11 mL DMF. The resulting mixture was stirred for one hour after which iodomethane (0.4 mL, 6.64 mmol, 6.0 equiv.) was added in four portions over two hours. The reaction mixture was then warmed to room temperature and stirred overnight at which point the reaction was quenched with water and extracted three times

with ethyl acetate. The combined organic extracts were then washed twice with water, once with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (10% to 25% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.346 g (67%)

$^1$H NMR (600 MHz $CDCl_3$) δ 7.07-7.14 (m, 3H), 6.89-6.91 (m, 1H), 5.28 (d, J = 7.8 Hz, 1H), 4.08 (t, J = 2.5, 1H), 3.96-3.96 (m, 1H), 3.84-3.88 (m, 2H), 3.64 (s, 3H), 3.63 (s, 3H), 3.46 (s, 3H), 3.34 (dd, J = 9.6 Hz, J = 2.6 Hz, 1H), 3.28 (dd, J = 7.8 Hz, J = 2.6 Hz, 1H), 2.27 (s, 3H), 1.01-1.11 (m, 21H)

$^{13}$C{$^1$H} NMR (151 MHz $CDCl_3$) δ 156.0, 130.4, 127.7, 126.7, 122.0, 115.8, 99.3, 81.2, 77.3, 76.0, 73.8, 62.8, 61.3, 59.4, 57.4, 18.0, 18.0, 16.5, 12.0

**(2-methylphenyl)-2,3,4,6-O-tetraacetyl-β-D-galactopyranoside (32):** This compound was prepared according to a reported procedure.[55]

**(2-methylphenyl)-β-D-galactopyranoside (33):** This compound was prepared according to a reported procedure.[55]

**(2-methylphenyl)-6-O-triisopropylsilyl-β-D-galactopyranoside (34):** A solution of **33** (1.698 g, 7.34 mmol, 1.0 equiv.) in 37 mL DMF was treated with imidazole (1.500 g, 22.03 mmol, 3.0 equiv.) and 4-(dimethylamino)pyridine (0.045 g, 0.36 mmol, 5 mol %), and was stirred at room temperature for 10 minutes. The reaction mixture was then cooled to 0 °C and triisopropylchlorosilane (1.9 mL, 8.81 mmol, 1.2 equiv.) was added dropwise. The mixture was then warmed to room temperature and stirred overnight. Upon completion the reaction was quenched with water and extracted three times with ethyl acetate. The combined organic extracts were washed with 1M HCl, water, then brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (25% to 100%

EtOAc/hexanes) followed by recrystallization from EtOAc/hexanes at -20 °C to give the product as a colorless solid. Yield: 0.651 g (21%)

$^{1}$H NMR (600 MHz $CDCl_3$) δ 7.10-7.15 (m, 2H), 7.07-7.08 (m, 1H), 6.95 (td, J = 7.3 Hz, J = 1.1 Hz, 1H), 4.82 (d, J = 7.8 Hz, 1H), 4.13 (d, J = 3.0 Hz, 1H), 3.96-4.03 (m, 3H), 3.69 (dd, J = 9.7 Hz, J = 3.5 Hz, 1H), 3.61 (td, J = 5.4 Hz, J = 0.6 Hz, 1H), 3.14 (bs, 2H), 2.85 (bs, 1H) 2.26 (s, 3H), 1.04-1.12 (m, 21H)

$^{13}$C{$^{1}$H} NMR (151 MHz $CDCl_3$) δ 155.4, 130.8, 128.0, 126.8, 122.7, 115.7, 101.8, 74.8, 73.7, 72.0, 69.0, 63.1, 17.9, 17.9, 16.4, 11.8

**(2-methylphenyl)-6-O-triisopropylsilyl-2,3,4-O-trimethyl-β-D-galactopyranoside**

**(4a):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (60% in mineral oil, 0.368 g, 9.20 mmol, 6.0 equiv.) and fitted with a rubber septum. The vessel was then brought outside of the box, attached to a nitrogen manifold, and cooled to 0 °C. DMF (6.0 mL) was added followed by a solution of **34** (0.651 g, 1.53 mmol, 1.0 equiv.) in 15 mL DMF. The resulting mixture was stirred for one hour after which iodomethane (0.6 mL, 9.20 mmol, 6.0 equiv.) was added in four portions over two hours. The reaction mixture was then warmed to room temperature and stirred overnight at which point the reaction was quenched with water and extracted three times with ethyl acetate. The combined organics were then washed twice with water, once with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The resulting residue was then purified by silica gel column chromatography (10% to 25% EtOAc/hexanes) to give the product as a colorless oil. Yield: 0.623 g (89%)

$^{1}$H NMR (600 MHz $CDCl_3$) δ 7.09-7.13 (m, 2H), 7.00 (d, J = 7.9 Hz, 1H), 6.90-6.92 (m, 1H), 4.84 (d, J = 8.0 Hz, 1H), 3.91-3.94 (m, 1H), 3.82-3.85 (m, 2H), 3.68 (s, 3H), 3.65-3.67 (m, 1H), 3.64

(s, 3H), 3.59 (s, 3H), 3.52-3.54 (m, 1H), 3.27 (dd, J = 9.8 Hz, J = 2.9 Hz, 1H), 2.28 (s, 3H), 0.97-1.15 (m, 21H)

$^{13}C\{^{1}H\}$ NMR (151 MHz $CDCl_3$) δ 155.7, 130.7, 127.6, 126.7, 122.0, 114.6, 101.4, 84.2, 80.8, 75.1, 74.3, 61.5, 61.3, 61.1, 58.5, 18.0, 18.0, 16.5, 11.9

**(2-methylphenyl)-2,3,4,6-O-tetraacetyl-α-D-galactopyranoside (35):** This compound was prepared according to a reported procedure.[55]

**(2-methylphenyl)-α-D-galactopyranoside (36):** This compound was prepared according to a reported procedure.[55]

**(2-methylphenyl)-6-O-triisopropylsilyl-α-D-galactopyranoside (37):** A solution of **36** (1.081 g, 4.00 mmol, 1.0 equiv.) in 20 mL DMF was treated with imidazole (0.817 g, 12.00 mmol, 3.0 equiv.) and 4-(dimethylamino)pyridine (0.024 g, 0.20 mmol, 5 mol %), and was stirred at room temperature for 10 minutes. The reaction mixture was then cooled to 0 °C and triisopropylchlorosilane (1.0 mL, 4.80 mmol, 1.2 equiv.) was added dropwise. The mixture was then warmed to room temperature and stirred overnight. Upon completion the reaction was quenched with water and extracted three times with ethyl acetate. The combined organic extracts were washed with 1M HCl, water, then brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (50% to 100% EtOAc/hexanes) to give the product as a colorless solid. Yield: 1.33 g (78%)

$^{1}H$ NMR (600 MHz $CDCl_3$) δ 7.12-7.16 (m, 3H), 6.94 (td, J = 7.1 Hz, J = 1.6 Hz, 1H), 5.60 (d, J = 3.9 Hz, 1H), 4.24 (s, 1H), 4.10 (td, J = 9.8 Hz, J= 3.8 Hz, 1H), 3.97-4.02 (m, 2H), 3.90-3.93 (m, 2H), 3.68 (s, 1H), 3.30 (d, J = 6.3 Hz, 1H), 2.55 (d, J = 9.7 Hz, 1H), 2.25 (s, 3H), 1.03-1.11 (m, 21H)

$^{13}C\{^{1}H\}$ NMR (151 MHz $CDCl_3$) δ 154.8, 130.8, 127.3, 127.1, 122.3, 114.8, 97.6, 71.5, 70.5, 70.1, 69.7, 64.0, 17.9, 17.8, 16.4, 11.8

**(2-methylphenyl)-6-O-triisopropylsilyl-2,3,4-O-trimethyl-α-D-galactopyranoside (6a):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (60% in mineral oil, 0.751 mg, 18.80 mmol, 6.0 equiv.) and fitted with a rubber septum. The vessel was then brought outside of the box, attached to a nitrogen manifold, and cooled to 0 °C. 12.5 mL DMF was then added followed by a solution of **37** (1.330 g, 3.13 mmol, 1.0 equiv.) in 31 mL DMF. The resulting mixture was stirred for one hour after which iodomethane (1.2 mL, 18.80 mmol, 6.0 equiv.) was added in four portions over two hours. The reaction mixture was then warmed to room temperature and stirred overnight at which point the reaction was quenched with water and extracted three times with ethyl acetate. The combined organics were then washed twice with water, once with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (10% to 25% EtOAc/hexanes) to give the product as a colorless oil. Yield: 1.256 g (86%)

$^{1}H$ NMR (600 MHz $CDCl_3$) δ 7.11-7.14 (m, 3H), 6.901-6.94 (m, 1H), 5.60 (d, J = 3.0 Hz, 1H), 3.93-3.95 (m, 2H), 3.86-3.89 (t, J = 8.6 Hz, 1H), 3.78-3.83 (m, 2H), 3.70-3.72 (m, 1H), 3.65 (s, 3H), 3.61 (s, 3H), 3.50 (s, 3H), 2.29 (s, 3H), 1.02-1.10 (m, 21H)

$^{13}C\{^{1}H\}$ NMR (151 MHz $CDCl_3$) δ 155.6, 130.7, 128.2, 126.9, 122.2, 115.5, 96.4, 80.4, 77.9, 74.9, 71.6, 61.3, 61.3, 58.5, 58.0, 18.0, 18.0 16.2, 11.8

**(2-methylphenyl)-2,3,4-O-triacetyl-α-L-arabinopyranoside (38):** A round bottom flask was charged with tetraacetyl-L-arabinopyranoside, (5.50 g, 17.28 mmol, 1.0 equiv.) 70 mL dichloromethane, and 2-methylphenol (3.74 g, 34.56 mmol, 2.0 equiv.). The mixture was then cooled to 0 °C and $BF_3$•$OEt_2$ (3.2 mL, 25.92 mmol, 1.5 equiv.) was added dropwise, after which

the flask was allowed to come to room temperature with stirring overnight. The reaction was neutralized with saturated $NaHCO_3$ and extracted twice with dichloromethane. The combined organic extracts were then washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was purified by column chromatography (50% EtOAc/hexanes) to give the product as a colorless solid. Yield: 2.49 g (40%)

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.09-7.05 (m, 2H), 7.00 (d, J = 8.2 Hz, 1H), 6.88 (t, J = 7.4 Hz, 1H), 5.64 (d, J = 3.5 Hz, 1H), 5.50 (dd, J = 10.8 Hz, J = 3.5 Hz, 1H), 5.37 (m, 1H), 5.28 (dd, J = 10.7 Hz, J = 3.4 Hz, 1H), 4.02 (d, J = 13.2 Hz, 1H), 3.71 (dd, J = 13.4 Hz, J = 2.0 Hz, 1H), 2.21 (s, 3H), 2.10 (s, 3H), 1.98 (s, 3H), 1.98 (s, 3H).

$^{13}$C NMR (151 MHz, $CDCl_3$) δ 170.3, 170.3, 170.1, 154.9, 130.9, 127.7, 127.0, 122.6, 114.5, 95.6, 68.9, 68.1, 67.3, 61.1, 30.0, 20.8, 20.7, 16.2

**(2-methylphenyl)-α-L-Arabinopyranoside (39):** A suspension of **38** (1.72 g, 4.69 mmol, 1.0 equiv.) in 5 mL MeOH (5 mL) was treated with NaOMe (0.076 g, 1.41 mmol, 30 mol %) and was stirred overnight. The reaction mixture was then neutralized with Dowex® 50WX8-100 and filtered through a pad of Celite. The filtrate was then concentrated under vacuum to give the product as a colorless solid. Yield: 1.11 g (98%)

$^1$H NMR (600 MHz, DMSO) δ 7.16-7.09 (m, 2H), 7.05 (d, J = 8.4 Hz, 1H) 6.88 (t, J = 7.4 Hz, 1H), 5.46 (d, J = 2.5 Hz, 1H), 4.99 (bs, 3H), 3.88-3.77 (m, 3H), 3.69 (d, J = 12.0 Hz, 1H), 3.51 (d, 12.0 Hz, 1H), 2.21 (s, 3H).

$^{13}$C NMR (151 MHz, $CDCl_3$) δ 155.4, 131.0, 127.5, 127.2, 121.7, 114.7, 98.3, 69.3, 68.9, 68.7, 64.5, 16.4

**(2-methylphenyl)-2,3,4-O-trimethyl-α-L-arabinopyranoside (10a):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (60% in mineral oil,

0.830 g, 9.40 mmol, 4.5 equiv.) and fitted with a rubber septum. The vessel was then brought outside of the box, attached to a nitrogen manifold, and cooled to 0 °C. 13 mL DMF was added followed by a solution of **39** (1.11 g, 4.62 mmol, 1.0 equiv.) in 46 mL DMF. The resulting mixture was stirred for one hour after which iodomethane (1.3 mL, 4.62 mmol, 4.5 equiv.) was added in four portions over two hours. The reaction mixture was then warmed to room temperature and stirred overnight at which point the reaction was quenched with water and extracted three times with ethyl acetate. The combined organics were then washed twice with water, once with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The crude material was purified via flash chromatography with 10-40% EtOAc/hexanes to give the product as a colorless solid. Yield 0.980g (75%)

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.09-7.01 (m, 3H), 6.86 (dt, J = 7.4 Hz, J = 1.2 Hz, 1H), 5.62 (d, J = 3.0 Hz, 1H), 3.89 (dd, J = 12.6 Hz, J = 2.2, 1H), 3.78-3.83 (m, 2H), 3.76 (dd, J = 12.6 Hz, J = 0.6 Hz, 1H), 3.72-3.73 (m, 1H), 3.56 (s, 3H), 3.51 (s, 3H), 3.50 (s, 3H), 2.29 (s, 3H)

$^{13}$C NMR (151 MHz, $CDCl_3$) δ 155.4, 130.8, 127.9, 126.9, 122.1, 114.6, 96.2, 78.4, 77.6, 75.5, 59.5, 59.0, 57.6, 57.5, 16.2

**(2-methylphenyl)-2,3,4-O-trimethyl-D-xylopyranoside (9a):**

A round bottom flask was charged with tetraacetyl xylose, (5.00g, 15.72 mmol, 1.0 equiv.) 79 mL dichloromethane, and 2-methylphenol (2.04 g, 18.86 mmol, 1.2 equiv.). The mixture was then cooled to 0 °C and $BF_3$•$OEt_2$ (3.9 mL, 31.43 mmol, 2.0 equiv.) was added dropwise, after which the flask was allowed to warm to room temperature with stirring overnight. The reaction was neutralized with saturated $NaHCO_3$ and extracted twice with dichloromethane. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. Excess 2-methylphenol was then removed via silica gel column chromatography to give

the crude tri-O-acetyl-1-aryloxyxylose as an oil. This material was then dissolved in 16 mL MeOH followed by the addition of NaOMe (0.249 g, 4.70 mmol, 30 mol %) and was allowed to stir for two hours. The reaction mixture was then neutralized with Dowex® 50WX8-100 and filtered through a pad of Celite. The filtrate was then concentrated under vacuum to give the crude 1-aryloxyxylose as a colorless solid (2.29 g). In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with the crude 1-aryloxyxylose as a solution in 100 mL DMF and NaH (60% in mineral oil, 2.28 g, 56.99 mmol, 6.0 equiv.). The flask was fitted with a rubber septum as was brought outside of the box, attached to a nitrogen manifold, and cooled to 0 °C. Iodomethane (3.5 mL, 56.99 mmol, 6.0 equiv.) was then added over the course of an hour in four portions. The reaction mixture was then warmed to room temperature and stirred overnight at which point the reaction was quenched with water and extracted three times with ethyl acetate. The combined organic extracts were then washed twice with water and twice with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum to give a pale-yellow oil. The residue was then purified using silica gel chromatography (10% to 25% EtOAc/hexanes) to give the product as a mixture of anomers (1:2 α/β) as a yellow oil. Yield 2.198 g, (49%)

$^1$H NMR (600 MHz $CDCl_3$) δ 7.12-7.16 (m, 6H), 7.06-7.08 (m, 1H), 6.99 (d, J = 8.0 Hz, 2H), 6.92-7.00 (m, 3H), 5.57 (d, J = 3.4 Hz, 1H), 4.88 (d, J = 7.2 Hz, 2H), 4.05 (dd, J = 11.7 Hz, J = 5.0 Hz, 2H) 3.76-3.78 (m, 2H), 3.69 (s, 3H), 3.65-3.67 (m, 12H), 3.56-3.58 (m, 2H), 3.47-3.52 (m, 15 H), 3.22-3.38 (m, 11H), 2.31 (s, 3H), 2.29 (s, 6H)

$^{13}$C{$^1$H} NMR (151 MHz $CDCl_3$) δ 155.3, 155.0, 130.9, 130.9, 127.7, 126.9, 126.8, 122.4, 122.1, 114.9, 114.4, 101.6, 95.1, 85.1, 83.1, 82.5, 81.5, 79.7, 79.3, 63.2, 60.9, 60.7, 60.7, 60.2, 58.9, 58.8, 58.7, 16.4.

**(2-methylphenyl)-2,3,4-O-trimethyl-L-fucopyranoside (5a):**

A round bottom flask was charged with tetraacetyl-L-fucose, (4.34g, 13.07 mmol, 1.0 equiv.) 65 mL dichloromethane, and 2-methylphenol (1.70 g, 15.78 mmol, 1.2 equiv.). The reaction was then cooled to 0 °C and $BF_3$•$OEt_2$ (4.8 mL, 39.20 mmol, 3.0 equiv.) was added dropwise and the warmed to room temperature and stirred overnight at room temperature. The reaction was neutralized with saturated $NaHCO_3$ and extracted twice with dichloromethane. The combined organic extracts were then washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. Excess 2-methylphenol was then removed via silica gel column chromatography to give the crude tri-O-acetyl-1-aryloxyfucose as an oil. This material was taken up in 10.7 mL MeOH followed by the addition of NaOMe (0.174 g, 3.21 mmol, 30 mol %) and was allowed to stir for two hours. The reaction mixture was then neutralized with Dowex® 50WX8-100 and filtered through a pad of Celite. The filtrate was then concentrated under vacuum to give the crude 1-aryloxyfucose as a colorless solid (2.79 g).

In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with the crude 1-aryloxyfucose as a solution in 100 mL DMF and NaH (60% in mineral oil, 2.77 g, 64.28 mmol, 6.0 equiv.). The flask was fitted with a rubber septum as was brought outside of the box, attached to a nitrogen manifold, and cooled to 0 °C. Iodomethane (4.1 mL, 64.28 mmol, 6.0 equiv.) was added over the course of an hour in four portions. The reaction mixture was then warmed to room temperature and stirred overnight at which point the reaction was quenched with water and extracted three times with ethyl acetate. The combined organic extracts were washed twice with water and twice with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum to give a pale-yellow oil. The residue was then purified using silica gel chromatography (10% to 25% EtOAc/hexanes) to give the product as a mixture of anomers (10:1 α/β) as a colorless oil. Yield 2.17 g, (56%)

$^{1}$H NMR (600 MHz $CDCl_3$) δ 7.12-7.14 (m, 3H), 6.91-6.93 (m, 1H), 5.60 (d, J = 3.0 Hz, 1H), 4.03 (q, J = 6.4 Hz, 1H), 3.76-3.80 (m, 2H), 3.64 (s, 3H), 3.58 (s, 3H), 3.53-3.53 (m, 1H), 3.47 (s, 3H), 2.28 (s, 3H), 1.25 (d, J = 6.6 Hz, 3H)

$^{13}$C{$^{1}$H} NMR (151 MHz $CDCl_3$) δ 155.6, 130.7, 127.9, 126.9, 121.9, 114.8, 95.9, 80.4, 79.0, 77.4, 67.1, 61.8, 58.4, 58.0, 16.5, 16.2

**phenyl-2,3,4-tri-*O*-acetyl-α-L-rhamnopyranoside (40):**

A round bottom flask was charged with tetraacetyl-L-rhamnose, (9.7 g, 27.4 mmol, 1.0 equiv.) dichloromethane (137 mL) and phenol (3.10 g, 32.9 mmol, 1.2 equiv.). The reaction vessel was cooled to 0 °C and $BF_3$•$OEt_2$ (10.2 mL, 82.3 mmol, 3.0 equiv.) was added dropwise. The reaction was then warmed to room temperature and stirred overnight at which point the mixture was neutralized with saturated $NaHCO_3$ and extracted twice with dichloromethane. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting residue was then washed with pentane to give a white solid which was then filtered and then collected to give the product. Yield: 6.69 g (67%).

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.28-7.31 (m, 2H), 7.03-7.08 (m, 3H), 5.52 (dd, J = 10.2 Hz, J = 3.5 Hz, 1H), 5.45 (d, J = 1.8, 1H), 5.43 (dd, J = 3.7 Hz, J = 1.9 Hz, 1H), 5.15 (t, J = 9.9 Hz, 1H), 2.19, (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.20 (d, J = 6.4 Hz, 3H)

$^{13}$C{$^{1}$H} NMR (151 MHz, $CDCl_3$) δ 170.2, 170.2, 170.1, 156.0, 129.7, 122.8, 116.5, 95.8, 71.1, 69.9, 69.0, 67.2, 21.0, 20.9, 20.9, 17.6

**phenyl-α-L-rhamnopyranoside (41):**

Compound **40** (5.0 g, 13.6 mmol, 1.0 equiv.) was suspended in MeOH (13.6 mL) followed by the addition of NaOMe (0.221 g, 4.1 mmol, 30 mol %) and was stirred overnight. The reaction

mixture was then neutralized with Dowex® 50WX8-100 and filtered through a pad of Celite. The filtrate was concentrated under vacuum to give the product as a colorless solid. Yield: 3.37 g (*quant.*).

$^{1}$H NMR (600 MHz, DMSO) δ 7.30 (t, J = 7.4 Hz, 2H), 7.03 (d, J = 7.7 Hz, 2H), 6.99, (t, J = 7.4 Hz, 1H), 5.37 (d, J = 1.2 Hz, 1H), 4.99 (bs, 3H), 3.84 (dd, J = 3.1 Hz, J = 1.8 Hz, 1H), 3.67 (dd, J = 9.4 Hz, J = 3.3 Hz, 1H), 3.46-3.51 (m, 1H0, 3.30 (t, J = 9.8 Hz, 1H), 1.11 (d, J = 6.5 Hz, 3H)

$^{13}$C{$^{1}$H} NMR (151 MHz, DMSO) δ 156.2, 129.5, 121.8, 116.5, 98.4, 71.9, 70.5, 70.3, 69.5, 17.9

**phenyl-2,3,4-tri-*O*-methyl-α-L-rhamnopyranoside (2i):**

In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (60%, 0.998 g, 25.0 mmol, 6.0 equiv.) and fitted with a rubber septum. The vessel was then brought out of the box and attached to a nitrogen manifold. DMF (12.5 mL) was added followed by a solution of **41** (1.0 g, 4.2 mmol, 1.0 equiv.) in DMF (21 mL). The resulting mixture was stirred at room temperature for 30 minutes then cooled to 0 °C. At this point iodomethane (1.6 mL, 25.0 mmol, 6.0 equiv.) was added in four equal portions over the course of 2 hours. The reaction mixture was then warmed to room temperature, diluted with a 4 mL aliquot of DMF, and stirred overnight at which point the reaction was quenched with water and extracted three times with ethyl acetate. The combined organic phases were then washed twice with water and brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The resulting residue was then purified using silica gel chromatography (10% to 25% EtOAc/Hex) to give the product as a colorless oil. Yield: 0.991 g (84%).

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.28-7.31 (m, 2H), 7.06-7.07 (m, 2H), 7.01-7.03 (m, 1H), 5.55 (d, J = 1.8 Hz, 1H), 3.76 (dd, J = 3.4 Hz, J = 2.0 Hz, 1H), 3.65-3.70 (m, 2H), 3.57 (s, 6H), 3.55 (s, 3H), 3.20 (t, J = 9.0, 1H), 1.26 (d, J= 6.3 Hz, 3H)

$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 156.5, 129.6, 122.3, 116.4, 95.2, 82.2, 81.0, 77.5, 68.7, 61.1, 59.4, 58.0, 17.9

**General procedure for iridium-catalyzed 3-demethylation/acetylation:**

In air, a 20 mL scintillation vial was charged with the phenol-glycoside (0.426 mmol, 1.0 equiv.) and $[(COD)Ir(PPh_3)_2]BAr^F{}_{24}$ (0.029 g, 0.0170 mmol, 4 mol %). The vial was then fitted with a screw cap septum and a vent needle. 1.4 mL dichloromethane was added through the septum followed by triethylsilane (0.2 mL, 1.278 mmol, 3 equiv.). The reaction was then stirred at room temperature for 1 hour at which point 2 mL of methanol was added and the mixture was allowed to stir for an additional hour. The crude mixture was then concentrated under vacuum and 2 mL pyridine and 2 mL acetic anhydride was added and the solution stirred overnight. Upon completion the reaction mixture was concentrated under vacuum, and the resulting residue was purified according to the procedures for each product below.

**(2-methylphenyl)-3-O-acetyl-2,4-O-dimethyl-α-L-rhamnopyranoside (2ai):** This product was prepared according to the general procedure for demethylation/acetylation above using **2a** (0.126 g, 0.426 mmol). After completion the reaction was purified by column chromatography (5%-50% EtOAc/hexanes) to give the product as a colorless oil. Yield 0.097 g (70%)

$^{1}H$ NMR (600 MHz $CDCl_3$) δ 7.11-7.16 (m, 3H), 6.93 (td, J = 7.1 Hz, J = 1.5 Hz, 1H), 5.51 (d, J = 1.9 Hz, 1H), 5.35 (dd, J = 9.7 Hz, J = 3.3 Hz 1H), 3.89 (dd, J = 3.6, J = 2.1 1H), 3.76-3.79 (m, 1H), 3.51-3.51 (m, 6H), 3.41 (t, J = 9.5 Hz, 1H), 2.25 (s, 3H), 2.18 (s, 3H), 1.30 (d, J = 6.2 Hz, 3H)

$^{13}C\{^{1}H\}$ NMR (151 MHz $CDCl_3$) δ 170.4, 154.5, 130.9, 127.4, 126.9, 122.0, 113.8, 95.2, 80.3, 78.7, 73.7, 68.6, 60.6, 59.4, 21.2, 17.9, 16.2

**(2-isopropyl)Phenyl-3-O-acetyl-2,4-O-dimethyl-α-L-rhamnopyranoside (2bi):** This product was prepared according to the general procedure for demethylation/acetylation above using **2b** (0.138 g, 0.426 mmol). After completion the reaction was purified by column chromatography (10%-50% EtOAc/hexanes) to give the product as a colorless solid. Yield 0.108 g (72%)

$^{1}H$ NMR (600 MHz $CDCl_3$) δ 7.23 (d, J = 7.2 Hz, 1H), 7.13-7.16 (m, 2H), 6.99-7.01 (m, 1H), 5.50 (d, J = 1.9 Hz, 1H), 5.34 (dd, J = 9.6 Hz, J = 3.5 Hz, 1H), 3.86 (dd, J = 3.4 Hz, J = 2.1 Hz, 1H), 3.76-3.81 (m, 1H), 3.52 (s, 3H), 3.51 (s, 3H), 3.35 (t, J = 9.6 Hz, 1H), 3.29 (pent, J = 7.0 Hz, 1H), 2.19 (s, 3H), 1.31 (d, J = 6.2 Hz, 3H), 1.24 (d, J = 6.9 Hz, 6H)

$^{13}C\{^{1}H\}$ NMR (151 MHz $CDCl_3$) δ 170.4, 153.8, 137.5, 126.7,126.4, 122.3, 113.8, 95.3, 80.3, 78.7, 73.7, 68.7, 60.6, 59.4, 27.5, 22.8, 22.6, 21.3, 17.9

**(2-tertbutyl)Phenyl-3-O-acetyl-6-2,4-O-dimethyl-α-L-rhamnopyranoside (2ci):**

This product was prepared according to a minor modification of the general procedure for demethylation/acetylation above using **2c** (0.144 g, 0.426 mmol). For this substrate, 2 hours was allowed to elapse prior to the addition of methanol. After completion the reaction was purified by column chromatography (6%-25% EtOAc/hexanes) to give the product as a colorless oil. Yield 0.124 g (83%)

$^{1}H$ NMR (600 MHz $CDCl_3$) δ 7.24 (dd, J = 7.8 Hz, J = 1.6 Hz, 1H), 7.17 (dd, J = 8.3 Hz, J = 1.1 Hz, 1H), 7.10 (td, J = 8.2 Hz, J = 1.7 Hz, 1H), 6.89 (td, J = 7.7 Hz, J = 1.2 Hz, 1H), 5.46 (d, J = 1.8 Hz, 1H), 5.30 (dd, J = 9.9 Hz, J = 3.4 Hz 1H), 3.83 (dd, J = 3.3, J = 2.1 1H), 3.68-3.73 (m, 1H),

3.45 (s, 3H), 3.43 (s, 3H), 3.31 (t, J = 9.6 Hz, 1H), 2.11 (s, 3H), 1.35 (s, 9H), 1.26 (d, J = 6.3 Hz, 3H)

$^{13}C\{^{1}H\}$ NMR (151 MHz $CDCl_3$) δ 170.5, 155.6, 138.4, 127.2, 126.9, 121.8, 114.2, 95.3, 80.1, 78.5, 73.9, 68.8, 60.7, 59.5, 34.7, 30.1, 21.2, 17.9

**(2,4-dichloro)Phenyl-3-O-acetyl-2,4-O-dimethyl-α-L-rhamnopyranoside (2di):** This product was prepared according to the general procedure for demethylation/acetylation above using **2d** (0.126 g, 0.426 mmol). After completion the reaction was purified by column chromatography (25%-50% EtOAc/hexanes) followed by a recrystallization from n-pentane at -20 °C to give the product as a colorless solid. Yield 0.105 g (65%)

$^{1}H$ NMR (600 MHz $CDCl_3$) δ 7.38 (d, J = 2.5 Hz, 1H), 7.17 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 5.45 (d, J = 2.1 Hz, 1H), 5.35 (dd, J = 9.5 Hz, J = 3.3 Hz, 1H), 3.93 (t, J = 3.1 Hz, 1H), 3.76-3.80 (m, 1H), 3.52 (s, 3H), 3.51 (s, 3H), 3.32 (t, J = 10.0 Hz, 1H), 2.18 (s, 3H), 1.29 (d, J = 6.2 Hz, 3H)

$^{13}C\{^{1}H\}$ NMR (151 MHz $CDCl_3$) δ 170.3, 150.7, 130.1, 127.8, 127.7, 125.1 117.8, 96.7, 80.3, 78.2, 73.1, 69.1, 60.5, 59.6, 21.2, 17.9

**(2-methylphenyl)-6-O-triisopropylsilyl-2,3,4-O-trimethyl-β-D-glucopyranoside (7a):** The attempted reduction of **7a** (0.194 g, 0.415 mmol) was conducted according to the general procedure for demethylation/acetylation above. After completion the unconverted starting material was separated by column chromatography (5%-25% EtOAc/hexanes). Recovery 0.074 g (38%) **7a**. No products of 3-demethylation are observed.

**(2-methylphenyl)-3-O-acetyl-6-O-triisopropylsilyl-2,4-O-dimethyl-α-D-mannopyranoside (3b):** This product was prepared according to a minor modification of the general procedure for demethylation/acetylation above using **3a** (0.194 g, 0.415 mmol). For this

substrate, 2 hours was allowed to elapse prior to the addition of methanol. After completion the reaction was purified by column chromatography (5%-40% EtOAc/hexanes) to give the product as a colorless oil. Yield 0.130 g (63%)

$^{1}$H NMR (600 MHz $CDCl_3$) δ 7.10-7.16 (m, 3H), 6.92 (td, J = 7.3 Hz, J = 1.0 Hz, 1H), 5.54 (d, J = 2.1 Hz, 1H), 5.40 (dd, J = 9.44 Hz, J = 3.3 Hz 1H), 3.85-3.91 (m, 3H), 3.80 (t, J = 9.5 Hz, 1H), 3.66 (ddd, J = 9.7 Hz, J = 4.3 Hz, J = 1.6 Hz, 1H), 3.52 (s, 3H), 3.43 (s, 3H), 3.46 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H), 1.06-1.11 (m, 21H)

$^{13}$C{$^{1}$H} NMR (151 MHz $CDCl_3$) δ 170.5, 155.6, 130.8, 127.2, 126.9, 121.8, 114.2, 95.3, 78.3, 74.2, 73.7, 73.6, 62.5, 60.3, 58.6, 21.3, 17.9, 17.9, 16.2, 12.0

**(2-methylphenyl)-6-O-triisopropylsilyl-2,4-O-dimethyl-β-D-galactopyranoside (4b):**

This product was prepared according to a minor modification of the general procedure for demethylation/acetylation above using **4a** (0.194 g, 0.415 mmol). For this substrate, 2 hours was allowed to elapse prior to the addition of methanol. The product was isolated as the 3-hydroxy derivative by omission of the acylation step. After completion the reaction was purified by column chromatography (5%-40% EtOAc/hexanes) to give the product as a colorless solid. Yield 0.140 g (75%)

$^{1}$H NMR (600 MHz $CDCl_3$) δ 7.10-7.14 (m, 2H), 6.97 (d, J = 8.1 Hz, 1H), 6.92 (td, J = 7.4 Hz, J = 0.6 Hz, 1H), 4.87 (d, J = 7.7 Hz, 1H), 3.91-3.94 (m, 1H), 3.84-3.86 (m, 1H) 3.77 (d, J = 3.1 Hz, 1H), 3.72 (s, 3H), 3.68-3.71 (m, 1H), 3.67 (s, 3H), 3.59-3.61 (m, 1H), 3.54-3.57 (m, 1H), 2.28 (s, 3H), 1.00-1.14 (m, 21H)

$^{13}$C{$^{1}$H} NMR (151 MHz $CDCl_3$) δ 155.4, 130.8, 127.4, 126.8, 122.1, 114.3, 101.0, 81.6, 77.2, 75.4, 74.2, 61.7, 61.4, 61.3, 18.0, 18.0, 17.9, 16.6, 11.9

**(2-methylphenyl)-6-O-triisopropylsilyl-2,4-O-dimethyl-β-D-galactopyranoside (6b & 6c):** This product was prepared according to the general procedure for demethylation/acetylation above using **6a** (0.194 g, 0.415 mmol). After completion the reaction was purified by column chromatography (6%-50% EtOAc/hexanes) to give a 5:1 mixture of **6b**:**6c** as a colorless oil. Yield 0.165 g (78%)

$^{1}$H NMR (400 MHz $CDCl_3$) δ 7.08-7.14 (m, 3H), 6.91-6.95 (m, 1H), 5.62 (d, J = 3.4 Hz, 1H), 5.42 (dd, J = 10.5 Hz, J = 3.0 Hz, 1H), 4.02-4.05 (m, 1H), 3.93 (m, 1H), 3.83-3.91 (m, 2H), 3.70-3.73 (m, 1H), 3.57 (s, 3H), 3.46 (s, 3H), 2.29 (s, 3H), 2.18 (s, 3H), 0.98-1.10 (m, 21H)

$^{13}$C{$^{1}$H} NMR (151 MHz $CDCl_3$) δ 170.5, 155.4, 130.7, 126.8, 122.2, 115.2, 96.1, 76.6, 76.0, 72.9, 71.1, 61.4, 61.1, 58.6, 21.2, 17.9, 16.1, 11.8, 11.8

**(2-methylphenyl)-3-O-acetyl-2,4-O-trimethyl-α-L-fucopyranoside (5b):** This product was prepared according to the general procedure for demethylation/acetylation above using **5a** (0.126 g, 0.426 mmol). After completion the reaction was purified by column chromatography (5%-40% EtOAc/hexanes) to give the product as a colorless oil. Yield 0.092 g (67%)

$^{1}$H NMR (600 MHz $CDCl_3$) 7.11-7.15 (m, 3H), 6.91-6.94 (m, 1H), 5.63 (d, J = 3.7 Hz, 1H), 5.36 (dd, J = 10.9 Hz, J = 3.1 Hz, 1H), 4.12 (q, J = 6.3 Hz, 1H), 3.88 (dd, J = 10.6, J = 3.3 Hz, 1H), 3.59 (d, J = 2.6 Hz, 1H), 3.55 (s, 3H), 3.44 (s, 3H), 2.28 (s, 3H), 2.17 (s, 3H), 1.23 (d, J = 6.6 Hz, 3H)

$^{13}$C{$^{1}$H} NMR (151 MHz $CDCl_3$) δ 170.7, 155.3, 130.7, 127.9, 126.8, 121.9, 114.3, 95.6, 80.1, 75.4, 73.2, 66.6, 61.8, 58.5, 21.1, 16.1, 16.0

**General procedure for iridium-catalyzed 3-demethylation/acetylation (NMR-Scale):** A 4 mL vial was charged with the 1-aryloxy-glycoside (0.030 mmol, 1.0 equiv.), 0.1 mL of a 0.020 g/mL stock solution of $[(COD)Ir(PPh_3)_2]BAr^{F}_{24}$ in dichloromethane (0.0012 mmol, 0.04 equiv.) followed by triethylsilane (14 μL, 0.10 mmol, 3 equiv.). The reaction was then allowed to stand at

room temperature for 1 hour at which point 0.3 mL of methanol was added and the mixture was stirred for an additional hour. Upon completion the solution was concentrated under vacuum and taken up in $CDCl_3$ for analysis by $^1H$ NMR. 5 μL of tetrachloroethane as an internal standard.

**Global demethylation with $B(C_6F_5)$ as the catalyst (2f) (eqn. 3):**

A dry 20 mL scintillation vial equipped with a stir bar in the glove box was charged with **2c** (0.154 g, 0.43 mmol, 1.0 equiv.) and tris(pentafluorophenyl)borane (0.022 g, 0.043 mmol, 10 mol %). 1.4 mL dichloromethane was then added followed by triethylsilane (0.7 mL, 4.26 mmol, 10.0 equiv.). The reaction was fitted with a cap and stirred for one hour. Upon completion the reaction mixture was quenched with 3 mL of methanol and stirred for an additional hour. The crude mixture was then concentrated under vacuum, and the resulting residue was taken up in 3.0 mL THF and treated with solid tetrabutylammonium fluoride hydrate (2.6 g, 9.94 mmol, 20 equiv.). After one hour the reaction mixture was diluted with 6.0 mL methanol and 1.0 g of calcium carbonate and 2.0 g of Dowex® 50WX8-100 were added. The resulting suspension was stirred for an additional hour. Upon completion the mixture was filtered through a pad of Celite which was washed with methanol. The filtrate was then concentrated under vacuum to give the crude triol as a colorless solid. An unidentified tetrabutylammonium salt could not be separated from the product, however the material was assessed to be 85% **2f** by mass using $^1H$ NMR against an internal standard. Yield: 0.113 g (71% yield of **2f**).

Spectral details match independently prepared **2f** (given above for **17**).

**Acid catalyzed displacement of the 2-methylphenol protecting group (2g):**

A 20 mL scintillation vial was charged with 5.1 mL methanol followed by the addition of acetyl chloride (70 μL, 1.01 mmol, 1.0 equiv.) and **2a** (0.300 g, 1.01 mmol, 1.0 equiv.). The vial was fitted with a screw cap and the solution was then heated to 70 °C and stirred overnight. The next

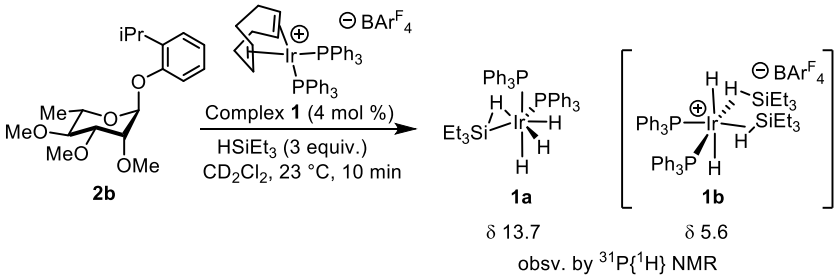
day the reaction mixture was concentrated under vacuum and the resulting residue was purified by silica gel column chromatography (10% to 25% to 80% EtOAc/hexanes) to give the product as a colorless oil. Yield 0.198 g (89%). The product matched previously reported spectra.[56]

**Anomeric reduction of 2c by [triphenylcarbenium][$BAr^F_4$]:**

A one dram vial was charged with **2c** (0.030 mmol, 1.0 equiv.), 0.1 mL of a freshly-prepared 0.013 g/mL stock solution of $[Ph_3C]BAr^F_4$ in dichloromethane (0.0012 mmol, 0.04 equiv.) followed by triethylsilane (14 µL, 0.10 mmol, 3 equiv.). The vial was fitted with a screw cap and the reaction was stirred at room temperature for 1 hour at which point 0.3 mL of methanol was added and the mixture was allowed to stir for an additional hour. Upon completion, the solution was concentrated under vacuum and taken up in $CDCl_3$ for analysis by $^1H$ NMR. 5 µL of tetrachloroethane was added as an internal standard. NMR yield of **2h**: 65±8%, average of 4 runs.

$^1H$ NMR (600 MHz $CDCl_3$) δ 4.09 (dd, J = 12.9 Hz, J = 2.2 Hz, 1H), 3.59 (t, J = 2.4 Hz, 1H), 3.55 (s, 3H), 3.48 (s, 3H), 3.45 (s, 3H), 3.25 (dd, J = 12.9 Hz, J = 0.8 Hz, 1H), 3.13-3.20 (m, 2H), 3.08-3.11 (m, 1H), 1.30 (d, J = 6.0 Hz, 3H)

$^{13}C\{^1H\}$ NMR (151 MHz $CDCl_3$) δ 84.4, 82.3, 76.4, 75.6, 65.8, 61.2, 57.5, 57.3, 18.2

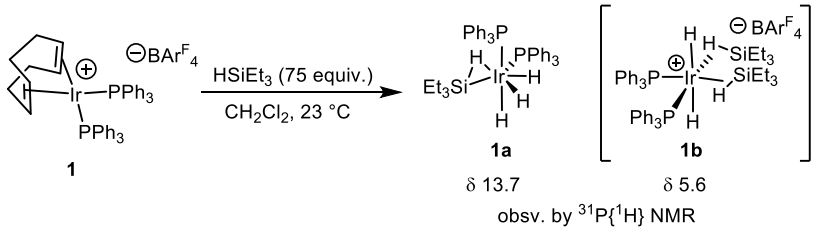



Scheme 3.9: Observation of $^{31}P$-containing species during catalysis

**Observation of $^{31}P$-containing species during catalysis (A):**

A septum-capped NMR tube was charged with **2b** (0.055 g, 0.15 mmol, 1.0 equiv.), and [(COD)Ir(PPh$_3$)$_2$]BAr$^F_{24}$ (0.010 g, 0.0060 mmol, 4 mol %) followed by 0.5 mL of $CD_2Cl_2$. Triethylsilane (70 µL, 0.45 mmol, 3 equiv.) was then added through the septum and the reaction was monitored by $^{31}P\{^1H\}$ NMR. After 10 minutes two species are observed by $^{31}P\{^1H\}$ NMR with relative intensity **1a**/**1b** 1 : 2.27.

$^{31}P\{^1H\}$ (162 MHz $CD_2Cl_2$) δ 13.7 (s, **1a**), 5.6 (s, **1b**)

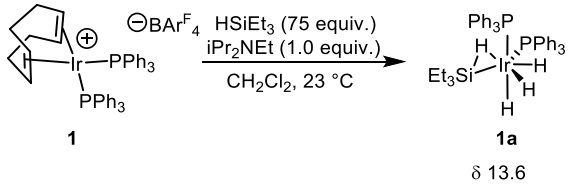



Scheme 3.10: Observation of $^{31}P$-containing species in the absence of substrate (B)*:*

**Observation of $^{31}P$-containing species in the absence of substrate (B)*:***

A septum-capped NMR tube was charged with [(COD)Ir(PPh$_3$)$_2$]BAr$^F_{24}$ (0.010 g, 0.0060 mmol, 1.0 equiv.) in 0.5 mL of $CD_2Cl_2$. Triethylsilane (70 µL, 0.45 mmol, 75 equiv.) was then added through the septum and the reaction was monitored by $^{31}P\{^1H\}$ NMR. After 10 minutes two species are observed by $^{31}P\{^1H\}$ NMR with relative intensity **1a**/**1b** 1: 15.8.

$^{31}P\{^1H\}$ (162 MHz $CD_2Cl_2$) δ 13.7 (s, 1P, **1a**), 5.6 (s, 16P, **1b**)




Scheme 3.11**:** Observation of $^{31}P$-containing species with $iPr_2NEt$ instead of substrate (C)

**Observation of $^{31}P$-containing species with $iPr_2NEt$ instead of substrate (C):**

A septum-capped NMR tube was charged with $[(COD)Ir(PPh_3)_2]BAr^F{}_{24}$ (0.010 g, 0.0060 mmol, 1.0 equiv.) in 0.5 mL of $CD_2Cl_2$. Triethylsilane (70 μL, 0.45 mmol, 75 equiv.) and diisopropyl(ethyl)amine (1.0 μL, 0.0060 mmol, 1.0 equiv.) were then added through the septum and the reaction was monitored by $^{31}P\{^1H\}$ NMR. After 10 minutes a single species is observed corresponding to **1a**.

$^{31}P\{^1H\}$ (162 MHz $CD_2Cl_2$) δ 13.6.

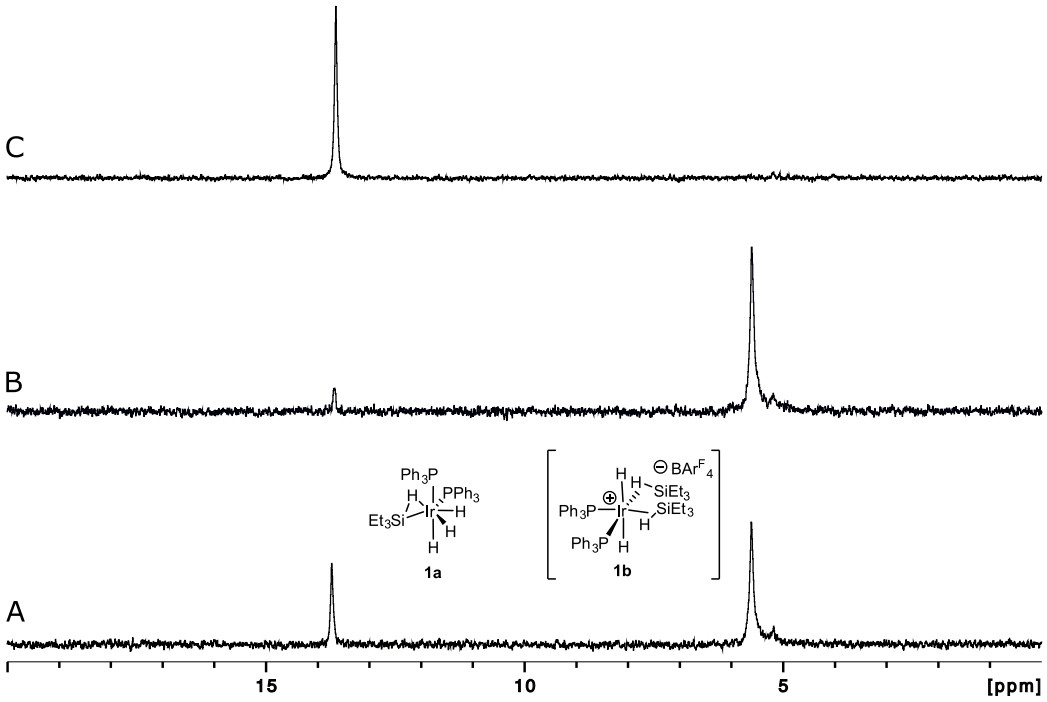



Figure 3.10: $^{31}P\{^1H\}$ spectra of **1a** and **1b** corresponding to experiments **A**-**C** above.

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## Chapter 4. Functional Group Compatibility for Ether Cleavage in Monosaccharides

### I. The use of Benzylidenes with Phenol Protected Glycosides

The previous chapter demonstrated the competence of iridium catalysts for the selective reduction of methyl ethers in substituted phenyl glycosides. Though various monosaccharides were studied, non-anomeric protecting groups were limited to methyl and silyl ethers. The complexity of carbohydrates demands a breadth of protecting groups suitable for complex transformations. However, benzylidene acetal groups are of specific interest due to their ease of installation, removal, and the availability of methods for their selective monodeprotection (for instance, at the $C_4$ or $C_6$ position).[1-5] Development of an iridium-catalyzed system with compatibility for benzylidene groups will provide a method for 2-O-methyl glycosides within more-complex synthetic schemes. Based on the preliminary substrate scope conducted in Chapter 2, it was clear at the outset that care would have to be taken with respect to selection of the acetal or ketal protecting group, given their apparent sensitivity to hydrosilylative conditions.

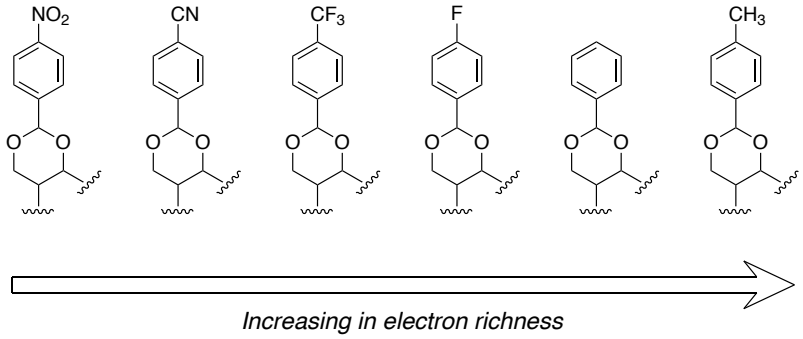



Figure 4.1: Para-substituted benzylidenes

We identified a selection of benzylidene groups that would probe the necessary electronics required for survival of the benzylidene acetal. Substitution at the para-position can alter the electronics of the functional group and in turn stabilize or destabilize the intermediate silyloxonium ion. We hypothesized that electron rich benzylidenes would likely undergo reduction, but electron

poor variants should destabilize the silyloxonium ion and prevent reduction at the benzylidene carbon. The electron richness of a selection of 4-substituted benzylidene acetals is given in ascending order: cyano, fluoro, trifluoromethyl, hydrogen, and methyl (Figure 4.1). Based on studies found in chapter 2 poisoning of the catalyst might occur when cyano or nitro groups are present, thus these group were avoided for this study.

D-galactose derivatives will present a special case due to the steric environment resulting from the synthesis of a 4,6-benzylidene. The galactose 4,6-benzylidene adopts a *cis*-decalin like structure. As previously seen in Chapter 2, this can have a significant effect on the reactivity of the developed system. Additionally, the electronic nature of $C_4$ will be affected due to the benzylidene being directly bound. The unique electronic and steric environment of the galactose benzylidenes could have significant implications for overall reactivity.

Similar to benzylidenes, isopropylidene groups are used to protect both the $C_4$ and $C_6$ position simultaneously.[6, 7] This functional group lacks the intrinsic tunability of benzylidene acetals, but presents a distinct steric environment that might disfavor silyloxonium ion formation. Due to the sensitivity of silyloxonium formation to the steric environment, the increased bulk could prevent the reduction of the ketal and $C_6$ while favoring $C_3$ demethylation (Figure 4.2).

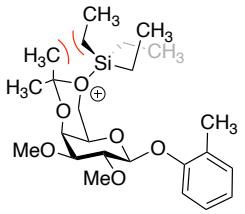



Figure 4.2: Steric congestion of silyloxonium formation on an isopropylidene

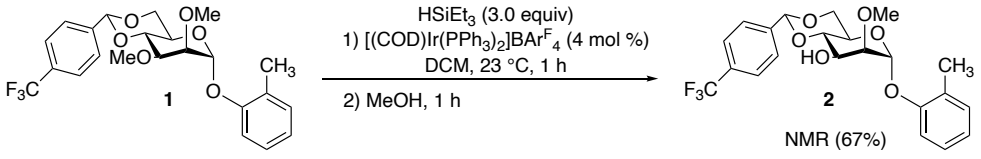
**II. Methyl ether cleavage in Substituted Thioglycosides**

The success of aryl glycosides as anomeric protecting groups in Chapter 3 inspired an exploration of their thioglycoside congener. Thioglycosides are versatile intermediates in

oligosaccharide synthesis due to their reactivity in glycosylations mediated by N-iodosuccinimide.[9-10] Additionally, thioglycosides are more resilient than a typical glycoside to hydrolysis under acidic conditions making them more tolerant than the (2-methyl)phenyl glycosides presented in chapter 3.[11, 12] Their acid stability makes them useful carbohydrate mimics for the study of enzyme active sites as well.[13] Accordingly, being able to extend our selective methyl ether cleavage chemistry to thioglycosides would provide significant synthetic utility.

Unfortunately, substrate scope exploration in chapter 2 demonstrated that a thioether-containing substrate served as a catalyst poison. We were also concerned that the increased Lewis basicity of the sulfur atom may be more prone to silylation (and thus undesired anomeric reduction) under our catalytic conditions. Drawing inspiration from the approach used with aryl glycosides in chapter 3, we anticipated that increasing the steric bulk at the 2'-position of the thiophenol would decrease the likelihood of silylium ion attack at this position. This approach should also reduce the likelihood of direct binding of the thioether to the metal center owing to the steric encumbrance of the thioglycoside.

### III. Preliminary Results



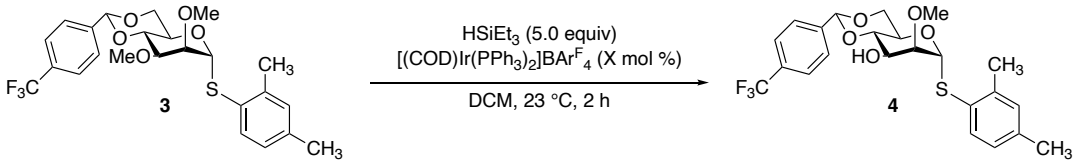

Scheme 4.1: Demethylation of mannose derivative **1**

A mannose derivative (**1**) was the first to be investigated due to the equatorial 4-hydroxyl group and the relative ease of synthesis of the (2-methyl)phenyl derivative. A 4,6-benzylidene is installed via an acidic condensation. Due to the known reactivity of benzyl ethers, (Chapter 2) we first tested a para-$CF_3$ benzylidene, hoping to prevent unwanted reduction at $C_4$ or $C_6$. This proved

to be an appropriate protecting group as demethylation was observed in comparable yields to the TIPS protected 2'-arylmannopyranose (Table 3.2, **3b**).

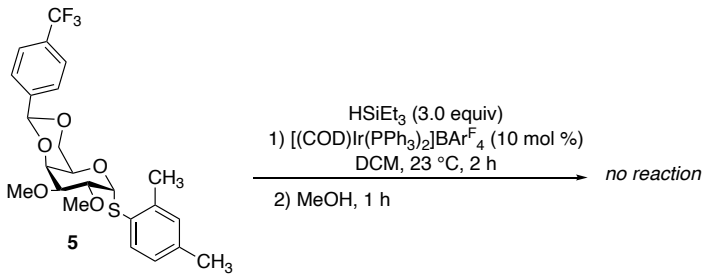
With successful demethylation observed, a mannose derivative was synthesized with a thiophenol at $C_1$. Unsurprisingly, when reacted under the previously established conditions no significant turnover was observed. However, this was remedied by an increase in catalyst loading, silane equivalents, and reaction time. Through a 2 % increase of catalyst loading a significant yield difference was observed (Table 4.1). Further doubling the catalyst loading only benefited the reaction yields.

Table 4.1: Variation of catalyst loading for the demethylation of **3**




| Catalyst loading (% mol) | Product Yield (% NMR) | Unreacted starting material (% NMR) |
|---|---|---|
| 4 % | 20 % | 60 % |
| 6 % | 77 % | 27 % |
| 8 % | 97 % | 15 % |
| 10 % | 88 % | 6 % |

In our previous study, in Chapter 3, the only reactive saccharides of selective demethylation and capable of forming a 4,6-benzylidene was mannose and galactose. With the success of complex **3** we were interested if similar reactivity would be observed for a thio-galactose derivative (**5**). Unfortunately, when subjected to the conditions developed in Table 4.1, **5** displayed no reactivity (Scheme 4.2). This could be a result from the unique steric and electronic environment induced by the benzylidene or catalyst poisoning by the thioether. Currently our lab is making efforts to improve the reactivity of thio-galactopyranose derivatives through examination of different thiophenol derivatives.




Scheme 4.2: Reaction of **5** with increased catalyst loading

**IV. Future work**

Currently, the use of thio-galactose derivatives is not viable, and requires substrate modification. Poisoning of the catalyst by the thioether is likely to be the reason for the lack of reactivity. Substitution on the thiophenol can provide a different steric and electronic environment near the sulfur atom. Increasing steric bulk at the 2 or 6 position of the phenol will decrease the likelihood of binding to the metal center due to steric congestion. Though this would be beneficial for the demethylation system, however, difficult substrate synthesis as an increase of steric bulk at this position greatly diminishes glycosylation yields. Electron deficient thiophenols can be used to reduce the Lewis basic nature of the thioether. If catalyst poisoning is occurring this would reduce binding of the sulfur atom to the metal center.

As previously mentioned, the benzylidene could also greatly affect the steric and electronic environment necessary for demethylation. This can be remedied by increasing the electron-richness of the benzylidene by the substitution of the para-trifluoromethyl with a fluoride group. Though weakly withdrawing, the fluorine atom could permit the reaction to proceed without benzylidene reduction. Additionally, the use of isopropylidenes can provide a sterically encumbered site with minimal changes in electron density compared to complex in chapter 3.

## V. Experimental

**General Considerations.** Syntheses and manipulations were conducted in air unless otherwise specified. Dichloromethane was degassed with argon and dried over activated alumina using a solvent purification system. All reagents and building blocks were procured from commercial vendors. $[(COD)Ir(PPh_3)_2]BAr^F{}_4$[14] was prepared using reported procedures.

**1-(dimethoxymethyl)-4-(trifluoromethyl)benzene (6):** This compound was prepared by a reported method.[15]

**(2-methyl)phenyl-4,6-O-(4-trifluoromethyl)benzylidene-α-D-mannopyranoside (7):** To an oven dried 40 mL scintillation vial (2-methyl)phenyl-α-D-mannopyranoside (0.618 g, 2.29 mmol, 1.0 equiv.) was dissolved in 7.6 mL of anhydrous acetonitrile followed by the addition of 10-CSA (0.531 g, 2.29 mmol, 1.0 equiv.) and (**6**) (0.8 mL, 4.57 mmol, 2.0 equiv., ρ = 1.22 g•mol$^{-1}$). The reaction was then stirred overnight and quenched with triethylamine. The resulting mixture was made concentrated under vacuum. The crude material was purified by silica gel column chromatography with 50% EtOAc/hexanes to give the product as a white solid. Yield 0.416 g (43%) – CAHJ-IV-216

**(2-methyl)phenyl-2,3-O-dimethyl-4,6-O-(4-trifluoromethyl)benzylidene-α-D-mannopyranoside (1):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (60% in mineral oil, 0.156 g, 3.91 mmol, 4.0 equiv.) and fitted with a rubber septum. The vessel was then brought outside of the box, and cooled to 0 °C. 2.0 mL DMF was added followed by a solution of **7** (0.416 g, 0.98 mmol, 1.0 equiv.) in 5.0 mL DMF. The resulting mixture was stirred for one hour after which iodomethane (0.24 mL, 3.91 mmol, 4.0 equiv.). The reaction mixture was then warmed to room temperature and stirred overnight at which point the reaction was quenched with water and extracted three times with ethyl acetate. The combined organics

were then washed twice with water, once with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The crude material was purified via silica gel flash chromatography with 10-25% EtOAc/hexanes to give the product as a colorless solid. Yield 0.382 g (86%) – CAHJ-IV-219

**(2,4-dimethylphenyl)thio-2,3,4,6-O-tetraacetyl-D-mannopyranose (8):** To a round bottom flask D-mannose (2.50 g, 13.88 mmol, 1.0 equiv.) was dissolved in pyridine (11.2 mL, 138.77 mmol, 10.0 equiv.) and acetic anhydride (13.1 mL, 138.77 mmol, 10.0 equiv.) and was stirred overnight at room temperature. The following day the reaction mixture was evaporated down to a syrup and redissolved in DCM. Organics was then washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, filtered and made concentrated. The resulting syrup was redissolved in 67 mL of anhydrous DCM followed by the addition of 2,4-dimethylbenzenethiol (2.1 mL, 15.82 mmol, 1.2 equiv.). The mixture was then cooled to 0 °C followed by the dropwise addition of $BF_3$•$OEt_2$ (2.9 mL, 39.55, 3.0 equiv.). The reaction was then warmed to room temperature and stirred overnight. The next day the reaction was quenched with saturated $NaHCO_3$ and extracted twice with DCM. Combined organics were then washed with brine, dried over $Na_2SO_4$, filtered and made concentrated under vacuum. The crude material was then purified via silica gel flash chromatography with 25-50% EtOAc/hexanes to give a mixture of α and β anomers as a solid. Yield: 4.02 g (62%) – CAHJ-IV-226

**(2,4-dimethylphenyl)thio-2,3,4,6-O-tetraacetyl-D-mannopyranose (9):** A suspension of **8** (4.02 g, 8.58 mmol, 1.0 equiv.) in 9.0 mL MeOH was treated with NaOMe (0.139 g, 2.57 mmol, 30 mol %) and was stirred for 2 hours. The reaction mixture was then neutralized with Dowex® 50WX8-100 and filtered through a pad of Celite. The filtrate was then concentrated under vacuum to give the product as a pale orange solid. Yield: 2.500 g (97%) – CAHJ-IV-227

**(2,4-dimethylphenyl)thio-4,6-O-(4-trifluoromethyl)benzylidene-α-D-mannopyranoside (10):** To an oven dried 40 mL scintillation vial **9** (1.331 g, 4.57 mmol, 1.0 equiv.) was dissolved in 15 mL of anhydrous acetonitrile followed by the addition of 10-CSA (1.030 g, 4.43 mmol, 1.0 equiv.) and (**6**) (0.8 mL, 4.43 mmol, 1.0 equiv., $\rho$ = 1.22 g•mol$^{-1}$). The reaction was then stirred overnight and quenched with triethylamine. The resulting mixture was made concentrated under vacuum. The crude material was purified by silica gel column chromatography to give the product as a white solid. Yield 0.699 g (35%) – CAHJ-IV-227

**(2,4-dimethylphenyl)thio-2,3-O-dimethyl-4,6-O-(4-trifluoromethyl)benzylidene-α-D-mannopyranoside (4):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (60% in mineral oil, 0.245 g, 6.13 mmol, 4.0 equiv.) and fitted with a rubber septum. The vessel was then brought outside of the box, and cooled to 0 °C. 3.0 mL DMF was added followed by a solution of **10** (0.699 g, 1.53 mmol, 1.0 equiv.) in 8.0 mL DMF. The resulting mixture was stirred for one hour after which iodomethane (0.4 mL, 6.13 mmol, 4.0 equiv.). The reaction mixture was then warmed to room temperature and stirred overnight at which point the reaction was quenched with water and extracted three times with ethyl acetate. The combined organics were then washed twice with water, once with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The crude material was purified via silica gel flash chromatography with 10-25% EtOAc/hexanes to give the product as a colorless solid. Yield 0.535 g (72%) – CAHJ-IV-228

**(2,4-dimethylphenyl)thio-2,3,4,6-O-tetraacetyl-D-galactopyranose (11):** To a round bottom flask peracetyl-β-D-galactose (5.0 g 12.81 mmol, 1.0 equiv.) was dissolved in 64 mL of anhydrous DCM followed by the addition of 2,4-dimethylbenzenethiol (2.3 mL, 16.65 mmol, 1.3 equiv.). The mixture was then cooled to 0 °C followed by the dropwise addition of $BF_3$•$OEt_2$ (4.7

mL, 38.43, 3.0 equiv.). The reaction was then heated to 50 °C and stirred for three days. Upon completion the reaction was quenched with saturated $NaHCO_3$ and extracted twice with DCM. Combined organics were then washed with brine, dried over $Na_2SO_4$, filtered and made concentrated under vacuum. The crude material was then purified via silica gel flash chromatography with 25% EtOAc/hexanes to give a mixture of α and β anomers as a white solid. Yield: 1.85 g (31%) – CAHJ-IV-237

**(2,4-dimethylphenyl)thio-2,3,4,6-O-tetraacetyl-D-galactopyranose (12):** A suspension of **11** (1.85 g, 3.97 mmol, 1.0 equiv.) in 4.0 mL MeOH was treated with NaOMe (0.063 g, 1.19 mmol, 30 mol %) and was stirred for 2 hours. The reaction mixture was then neutralized with Dowex® 50WX8-100 and filtered through a pad of Celite. The filtrate was then concentrated under vacuum to give the product as a pale orange solid. Yield: 0.998 g (84%) – CAHJ-IV-227

**(2,4-dimethylphenyl)thio-4,6-O-(4-trifluoromethyl)benzylidene-α-D-galactopyranoside (13):** To an oven dried 40 mL scintillation vial **12** (0.978 g, 3.32 mmol, 1.0 equiv.) was dissolved in 11 mL of anhydrous acetonitrile followed by the addition of 10-CSA (0.386 g, 1.66 mmol, 1.0 equiv.) and (**6**) (1.2 mL, 6.64 mmol, 2.0 equiv., $\rho = 1.22\ g \bullet mol^{-1}$). The reaction was then stirred overnight and quenched with triethylamine. The resulting mixture was made concentrated under vacuum. The crude material was purified by silica gel column chromatography with 40-80% EtOAc/hexanes to give the product as a white solid. Yield 0.875 g (56%) – CAHJ-IV-242

**(2,4-dimethylphenyl)thio-2,3-O-dimethyl-4,6-O-(4-trifluoromethyl)benzylidene-α-D-galactopyranoside (5):** In an inert-atmosphere glove box, a flame-dried Schlenk flask was charged with NaH (90% in mineral oil, 0.204 g, 7.66 mmol, 4.0 equiv.) and fitted with a rubber septum. The vessel was then brought outside of the box, and cooled to 0 °C. 4.0 mL DMF was

added followed by a solution of **13** (0.875 g, 1.92 mmol, 1.0 equiv.) in 9.6 mL DMF. The resulting mixture was stirred for one hour after which iodomethane (0.5 mL, 7.66 mmol, 4.0 equiv.). The reaction mixture was then warmed to room temperature and stirred overnight at which point the reaction was quenched with saturated $NH_4Cl$ and extracted three times with ethyl acetate. The combined organics were then washed with 10% $Na_2SO_3$, twice with water, twice with brine, dried over $Na_2SO_4$, filtered and concentrated under vacuum. The product was obtained as a white solid without further purification. Yield 0.806 g (87%) – CAHJ-IV-243

**Demethylation of 1:**

A 4 mL vial was charged with **1** (0.015 g, 0.030 mmol, 1.0 equiv.), and dissolved in 0.1 mL of a 0.020 g/mL stock solution of $[(COD)Ir(PPh_3)_2]BAr^F{}_{24}$ in dichloromethane (0.0012 mmol, 0.04 equiv.) followed by triethylsilane (14 µL, 0.10 mmol, 3 equiv.). The reaction was then allowed to stand at room temperature for 1 hour at which point 0.3 mL of methanol was added and the mixture was stirred for an additional hour. Upon completion the solution was concentrated under vacuum and taken up in $CDCl_3$ for analysis by $^1H$ NMR. 5 µL of tetrachloroethane as an internal standard. Yield: (67%) – CAHJ-IV-222

**Catalyst screen for the demethylation of 3:**

*6 mol % catalyst loading:*

A 4 mL vial was charged with **1** (0.015 g, 0.030 mmol, 1.0 equiv.), and dissolved in 60 µL of a 0.050 g/mL stock solution of $[(COD)Ir(PPh_3)_2]BAr^F{}_{24}$ in dichloromethane (0.0015 mmol, 0.10 equiv.) then diluted with 40 µL of dichloromethane, followed by triethylsilane (23 µL, 0.13 mmol, 5 equiv.). The reaction was then allowed to stand at room temperature for 2 hours at which point 0.3 mL of methanol was added and the mixture was stirred for an additional hour. Upon completion

the solution was concentrated under vacuum and taken up in $CDCl_3$ for analysis by $^1H$ NMR. 5 μL of tetrachloroethane as an internal standard. Yield: (77%) -- CAHJ-IV-230

*8 mol % catalyst loading:*

A 4 mL vial was charged with **1** (0.015 g, 0.030 mmol, 1.0 equiv.), and dissolved in 80 μL of a 0.050 g/mL stock solution of $[(COD)Ir(PPh_3)_2]BAr^F{}_{24}$ in dichloromethane (0.0015 mmol, 0.04 equiv.) then diluted with 20 μL of dicloromethane, followed by triethylsilane (23 μL, 0.13 mmol, 5 equiv.). The reaction was then allowed to stand at room temperature for 2 hours at which point 0.3 mL of methanol was added and the mixture was stirred for an additional hour. Upon completion the solution was concentrated under vacuum and taken up in $CDCl_3$ for analysis by $^1H$ NMR. 5 μL of tetrachloroethane as an internal standard. Yield: (97%) -- CAHJ-IV-230

*10 mol % catalyst loading:*

A 4 mL vial was charged with **1** (0.015 g, 0.030 mmol, 1.0 equiv.), and dissolved in 0.1 mL of a 0.050 g/mL stock solution of $[(COD)Ir(PPh_3)_2]BAr^F{}_{24}$ in dichloromethane (0.0015 mmol, 0.10 equiv.) followed by triethylsilane (23 μL, 0.13 mmol, 5 equiv.). The reaction was then allowed to stand at room temperature for 2 hours at which point 0.3 mL of methanol was added and the mixture was stirred for an additional hour. Upon completion the solution was concentrated under vacuum and taken up in $CDCl_3$ for analysis by $^1H$ NMR. 5 μL of tetrachloroethane as an internal standard. Yield: (88%) -- CAHJ-IV-230

**Attempted demethylation of 5:**

A 4 mL vial was charged with **5** (0.015 g, 0.030 mmol, 1.0 equiv.), and dissolved in 0.1 mL of a 0.050 g/mL stock solution of $[(COD)Ir(PPh_3)_2]BAr^F{}_{24}$ in dichloromethane (0.0015 mmol, 0.10 equiv.) followed by triethylsilane (14 μL, 0.10 mmol, 3 equiv.). The reaction was then allowed to stand at room temperature for 2 hours at which point 0.3 mL of methanol was added and the

mixture was stirred for an additional hour. Upon completion the solution was concentrated under vacuum and taken up in $CDCl_3$ for analysis by $^1H$ NMR. 5 μL of tetrachloroethane as an internal standard, no reaction was observed. -- CAHJ-IV-230

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## Chapter 5. Summary

Throughout this work cationic bis(phosphine) iridium catalysts have been used for the cleavage of ethereal C-O bonds. In chapter 2 we demonstrated a method for functional group interconversion and as a demethoxylation strategy. The study of methyl ether reduction is expanded in chapter 3 towards applications in carbohydrate chemistry for the selective demethylation of tri-O-methyl-phenyl glycosides. Though catalysts such as BCF are prevalent in this field, this work presents an air-stable, tunable system with superior selectivity in the catalytic reduction of C-O bonds.

In chapter 2, the first non-pincer bis(phosphine) iridium catalyst for hydrosilylative ether cleavage was developed. Both regioselectivity and functional group compatibility was investigated for $[H_2Ir(PPh_2)_2(THF)_2]BAr^F_4$ with further reactivity studies on benzyl and methyl ether cleavage. Unsymmetric ethers were studied in an intermolecular competition experiment to determine the selectivity of C-O bond cleavage. Benzyl ethers were found to be the most reactive of the ethereal substrates and became the focus of the study. Functional group compatibility was then investigated by surveying compounds with a benzyl ether and an additional functional group moiety. Alkyl and aryl halides proved to be stable under these conditions, providing a method for debenzylation for halides sensitive to traditional hydrogenolysis strategies for benzylic ether cleavage. The mechanism was then found to be comparable to previous hydrosilylative ether cleavage systems.

It was later found that the precatalyst to the aforementioned catalyst, $[(COD)Ir(PPh_3)_2]BAr^F_4$, was equally effective for ether C-O cleavage. Due to the air stability and relative ease of use, this catalyst was employed for cyclohexyl methyl ether cleavage. Differences in selectivity for demethylation versus 2° C-O cleavage were observed for axial or equatorial stereoisomers. This observation was confirmed in a pair of cholestanol-derived *trans*-decalins. Selectivity for

demethylation versus 2° C-O cleavage in compounds with a *cis*-decalin structure were found to be dependent on the substitution of the neighboring ring, which provided an additional dimension to the impact of substrate structure on observed reactivity.

Chapter 3 then builds on the previous chapter by applying the same system to the selective reduction of 2,3,4-tri-O-methyl carbohydrate derivatives. Substituted phenols are found to be suitable protecting groups for the anomeric position for the first catalytic hydrosilylative method for C-O bond cleavage with minimal anomeric reduction. The success of this system is attributed to the relative stereochemistry around the 3-position found in rhamnose, galactose, mannose, and fucose. Though selectivity is not observed under borane catalysis, the protection of the anomeric position is similarly effective.

Chapter 4 then looks forward to expand the functional group compatibility for the demethylation of aryl glycosides. Early success was found with both electron deficient benzylidenes and thioglycoside derivatives of mannose. However, more work is needed to find the appropriate protecting groups for galactose derivatives. As it currently stands, evidence for thiophenol as protecting group for $C_1$ in galactose derivatives is still lacking. A future survey of different benzylidenes and thiophenols will have to be done.