NEW METHODS IN CARBOHYDRATE CHEMISTRY: DEHYDRATIVE GLYCOSYLATION WITH CYCLIC PHOSPHONIUM ANHYDRIDES AND α-SELECTIVE GLYCOSYLATION OF GLYCOSYL PHOSPHINITES

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Date

This thesis has been examined by the above signatories and approved to meet the Requirements for the Masters of Science in chemistry degree.
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New Methods in Carbohydrate Chemistry: Dehydrative Glycosylation with Cyclic Phosphonium Anhydrides and α-Selective Glycosylation of Glycosyl Phosphinites

Thesis directed by Assistant Professor Maciej Walczak

Achieving a high level of efficiency in carbohydrate synthesis is dependent upon reactions that can provide high yields and stereoselectivity at the anomeric position. The nature of the glycosidic bond as either α or β configuration poses the greatest obstacle. The development of methods to control this inherent feature while also giving high yields is a primary goal for the field of carbohydrate chemistry. This thesis examines the potential for two new methods to overcome these challenges: dehydrative glycosylation with cyclic phosphonium anhydrides and glycosylation of glycosyl phosphinites. A collection of cyclic phosphonium anhydrides were prepared and tested with a range of glycosylation substrates. These glycosylations demonstrated good yield and selectivities for a number of examples and represent a new and practical type of dehydrative glycosylation. A number of 1D and 2D NMR experiments were carried out to better understand the mechanistic nature of this reaction. A collection of glycosyl phosphinites were also prepared and evaluated in their potential to give highly α-selective glycosylations through in situ anomerationization. This method was used with a number of substrates giving good yield and high selectivities. The high α-selectivity of this method was explored through a number of $^{31}$P NMR experiments.
Acknowledgements

I thank all members of the Walczak lab who I have worked closely with over the years. Without their support this work would not have been possible. I would like to especially thank Dr. Rajendar Dyapa and Dr. Jie Guang who I worked closely with on the research discussed here. I am grateful for their assistance in teaching me how to become a better chemist in many ways. I thank Prof. Maciej Walczak for his guidance and assistance over the course of this work. I would like to extend a special thanks to Prof. Richard Shoemaker for his wonderful assistance in obtaining the mechanistic NMR data in this work. Lastly I would like to thank the University of Colorado Boulder for providing the financial means to pursue this degree.
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Chapter 1: Introduction

1.1: General Chemical Glycosylation

The role of carbohydrates as essential molecules for all biological organisms with key roles in structural support, energy storage, and molecular signaling demonstrates the importance of research into their chemical preparation. Synthesis of carbohydrates has been a challenge to the scientific community for decades. Studies into the biosynthetic processes of carbohydrate natural products have revealed a number of powerful enzymes capable of carrying out these transformations. The biosynthesis of carbohydrates \textit{in vivo} proceeds with ease,\textsuperscript{1,2} so much so that part of the field of biochemistry exists to explore the potential to apply these reactions \textit{in vitro} towards carbohydrate synthesis. Achieving the same high level of efficiency in carbohydrate synthesis from chemical methods in terms of high yields and stereoselectivity remains a challenge. The glycosidic bond exists as either $\alpha$ or $\beta$ configuration highlights one of the main challenges posed to carbohydrate chemists. Numerous methods have been developed over the years with the goal of excellent $\alpha/\beta$ glycosidic bond formation in mind.\textsuperscript{3}

Some of the earliest research in chemical glycosylation by Michael,\textsuperscript{4} Fischer,\textsuperscript{5-7} Helfrich,\textsuperscript{8} and Koenigs-Knorr\textsuperscript{9} provided methods for the preparation of simple carbohydrates using various activated glycosyl donor intermediates (Figure 1.1). In the case of the Fischer method, activation of the anomeric alcohol by an acid catalyst enables glycosylation by the incoming glycosyl acceptor, usually a solvent. The troublesome nature of this method as an equilibrium-driven process was improved upon by Koenigs
and Knorr who used anomeric halides (e.g. bromide) activated by a suitable Lewis acid. Direct $O$-alkylation$^{10,11}$ also represents another approach to glycosylation; however, it in addition to the earlier methods all have significant limitations in terms of yield and compatibility with a wide range of substrates.

a) Fischer

\[
\begin{align*}
\text{(HO)}_n \overset{\text{Brønsted/Lewis Acid}}{\rightarrow} \text{ROH} \rightarrow \text{(HO)}_n \overset{\text{RO}}{\rightarrow}
\end{align*}
\]

b) Koenigs-Knorr

\[
\begin{align*}
\text{(RO)}_n \overset{\text{ROH, Ag$_2$CO$_3$}}{\rightarrow} \text{Br} \rightarrow \text{(RO)}_n \overset{\text{OR}}{\rightarrow}
\end{align*}
\]

c) Schmidt

\[
\begin{align*}
\text{(RO)}_n \overset{\text{NaH or K$_2$CO$_3$, Cl$_2$CCN}}{\rightarrow} \text{Cl$_2$CCN} \rightarrow \text{(RO)}_n \overset{\text{ROH, BF$_3$•OEt$_2$ or TMSOTf}}{\rightarrow} \text{BF$_3$•OEt$_2$ or TMSOTf} \rightarrow \text{(RO)}_n \overset{\text{OR}}{\rightarrow}
\end{align*}
\]

d) $O$-alkylation

\[
\begin{align*}
\text{(RO)}_n \overset{\text{NaH, DMF}}{\rightarrow} \text{OH} \rightarrow \text{(RO)}_n \overset{\text{ROH, R-OTf}}{\rightarrow} \rightarrow \text{(RO)}_n \overset{\text{OR}}{\rightarrow}
\end{align*}
\]

**Figure 1.1** Selected glycosylation methods.

Schmidt$^{12}$ reported the use of trichloroacetimide as a leaving group (Figure 1.1) in chemical glycosylations. The trichloroacetimide glycosyl donor (the Schmidt donor) can be activated by a wide range of Lewis acids (e.g., BF$_3$•OEt$_2$ or TMSOTf) give the product in high yields.$^{13,14}$ Other similar Schmidt-type donors include $N$-phenyltrifluoroacetimidate$^{15}$ and $N$-Aryl-trifluoroacetimidate$^{16}$ donors. It is clear that among the goals for new glycosylation methods the design must incorporate easily available glycosyl donors and have high yielding reaction conditions but the primary
challenge moving forward in carbohydrate chemistry lies in the search for conditions which can give greater control over $\alpha/\beta$ selectivities.

The classical approach to control of $\alpha/\beta$ glycosylation relies upon careful design of protecting groups$^{17-20}$ wherein those groups direct the glycosylation to favor a particular anomer. Use of so-called participating groups (acetyl, benzoyl) at the C-2 position in the glycosyl ring can enhance this process. Formation of almost exclusively the $\beta$ product is observed through via neighboring group participation through formation of an ortho-ester intermediate.$^{21}$ Formation of the $\beta$-glycosylation product via neighboring group participation is widely useful for a number of standard glycosylation methods, however it necessitates additional steps in the preparation of more complex carbohydrates whereby numerous protecting group manipulations over the course of the reaction lower overall yields and erode efficiency. Methods to obtain the desired selectivities with fewer protecting group manipulations and good overall yield are of primary interest. Dehydrative glycosylation and glycosylations of glycosyl phosphinites were the focus of two particular techniques to be discussed in this thesis intended to overcome these challenges facing carbohydrate chemistry today and provide better routes to high yielding and stereoselective glycosylations.

1.2: Dehydrative Glycosylation

Direct activation of the anomeric alcohol via dehydrative glycosylations originate with the early work by Fischer but overcoming the inherent limitations of this equilibrium-driven reaction would be the focus of work by many groups over the next
few years. Historically, dehydrative glycosylation methods have focused on glycosyl halide intermediates,\textsuperscript{22,23} glycosyl sulfonate intermediates,\textsuperscript{24} Lewis acid catalysts,\textsuperscript{25,26} and oxophosphonium intermediates\textsuperscript{27-30} as the most prominent developments and applications. More recently the seminal work with glycosyl oxosulfonium intermediates\textsuperscript{31} in the activation of glycosyl donors by Gin has set the standard for a widely applicable dehydrative glycosylation method (Figure 1.3).

This method uses diphenyl sulfoxide and triflic anhydride to prepare diphenyl sulfide bis(triflate) which, when reacting with the glycosyl donor \textbf{1}, forms the corresponding oxosulfonium species \textbf{2} (Figure 1.3). This method was then applied to a number of glycosyl donor and acceptor substrates giving good yields and variable selectivities. A series of mechanistic experiments using anomeric \textsuperscript{18}O labeled glycosyl donors and low temperature \textsuperscript{1}H NMR were also explored by Gin to identify the mechanistic basis of this dehydrative glycosylation experiment. The results show that glycosyl donor \textbf{1} is activated to form oxosulfonium species \textbf{2} and anomeric pyridinium \textbf{3} which subsequently gave rise to the glycosylation product \textbf{4}. Mechanistic NMR experiments indicated anomeric pyridinium \textbf{3} to be the predominant species in this glycosylation but based on the anomeric ratios of the products, glycosylation must proceed at least in part through other reactive intermediates such as oxosulfonium species \textbf{2}.
Figure 1.2 The Gin method for dehydrative glycosylation with oxosulfonium triflate.

Early work by Mukaiyama\textsuperscript{29} demonstrated the feasibility of dehydrative glycosylations using Hendrickson’s reagent\textsuperscript{30,31} (POP) and similar oxophosphonium reagents on simple ribofuranose substrates (Figure 1.3). Among the oxophosphonium reagents examined were examples with \( R = \) phenyl, naphthyl, cyclohexyl, and \( n \)-Butyl.\textsuperscript{29} The substrate scope for this reaction was limited to 2,3,5-tri-O-benzyl-D-ribofuranose and the yields were reported for cyclohexanol, cholesterol, propanol, and azide glycosyl acceptors. Hendrickson’s reagent was further expanded to dehydrative glycosylation reactions on a wider range of substrates by Panza.\textsuperscript{32} The use of Hendrickson’s reagent in this case, however, led to significant amounts of homocoupling product 5, resulting in significantly lower yields when added directly to the glycosyl donor. Careful addition of the POP-activated glycosyl acceptor was required, significantly limiting the scope of this methodology.
With these limitations in mind, a new method was developed by Lance Dockery and Dr. Rajendar Dyapa to incorporate the enhanced electrophilic character of cyclic phosphonium salts (based on preliminary $^{31}$P chemical shifts) as dehydrative glycosylation reagents (Figure 1.3). Dehydrative glycosylations stand out as a promising method in carbohydrate chemistry because it allows glycosylations to proceed directly in one step from the anomeric alcohol, whereas the most prevalent method today (Schmidt glycosylation) represents a two-step process to the product via the Schmidt donor intermediate.

Knowing the limited substrate scope and applications of the more common oxophosphonium dehydrative glycosylations derived from Hendrickson’s reagent, cyclic
phosphonium reagents for dehydrative glycosylation represent a potential new direction for oxophosphonium species in dehydration reactions. If the cyclic phosphonium reagents are more stable than traditional POP reagents, they can be utilized in glycosylations that should proceed easily without the limited yields and selectivities of the aforementioned methods or necessarily purification of the intermediates in a traditional 2-step glycosylation.

The work in this thesis demonstrates how cyclic phosphoniums derived from corresponding bis-phosphine oxides are able to activate glycosyl donors for one-pot glycosylations with high yields and selectivities for a variety of substrates. The mechanistic nature of the cyclic phosphonium anhydrides as dehydrative reagents was further examined. Of particular interest were conditions using 1,4-bis(diphenylphosphino)butane, triflic anhydride, and 2,4,6-tri-tert-butylpyridine.

![Figure 1.4 Cyclic phosphonium anhydrides as reagents for dehydrative glycosylations.](image)

1.3: α-selective Glycosylation with Glycosyl Phosphinites

While there exist numerous methods (e.g., Schmidt donor, thioether, sulfoxide, phosphonium) which lead can to β-selective glycosylations in the presence of C-2 participating groups, in general these reactions tend to exhibit poor α-selectivity. Common C-2 sterically nondemanding/participating groups such as alkyl ethers can often give rise to α-glycosylation but not the extent desired for practical applications. Current
methods for $\alpha$-selective glycosylations rely primarily upon either careful design of $S_N^1$ reactions on an oxocarbenium intermediate,$^{33}$ *in situ* anomerization of an activated glycosylation intermediate,$^{34}$ or the use of heterogeneous catalysts.$^{35,36}$

Of these methods, *in situ* anomerization represents the easiest route to highly $\alpha$-selective glycosylation reactions. The earliest application of *in situ* anomerization was reported by Lemieux using anomic bromides in the presence of tetraethylammonium bromide (Et$_4$NBr) and a suitable glycosyl acceptor$^{37}$ (Figure 1.5). Mukaiyama later reported the use of glycosyl phosphinites activated by iodomethane followed by addition of the glycosyl acceptor$^{38-40}$ (Figure 1.5). In both cases it was assumed that the reactive intermediate (either anomic bromide or oxo-phosphonium species) exists in equilibrium between the $\alpha$ or $\beta$ anomer where the less stable stable $\beta$-intermediate undergoes displacement to give the predominant $\alpha$-glycosylation product.

**a) Lemieux**

![Chemical reaction](image)

**b) Mukaiyama**

![Chemical reaction](image)

*Figure 1.5* Common methods for $\alpha$-selective glycosylations via *in situ* anomerization
A method to improve upon current α-selective glycosylation techniques was developed by Lance Dockery to stand Jie Guang to establish mild conditions for the preparation of glycosyl phosphinites. These glycosyl phosphinites were then reacted in a variety of glycosylation substrates displaying high selectivities and yields. Mechanistic studies of this reaction were then conducted with a series of NMR techniques to better explain the origin of high selectivities in these reactions.

Chapter 2: Dehydrative Glycosylation

2.1: Cyclic phosphonium anhydrides

The preparation and characterization of a small series of cyclic phosphonium anhydrides was previously reported by Elson.\textsuperscript{40} These reagents were reported to have unique \textsuperscript{31}P NMR chemical shifts indicating the potential for enhanced electrophilicity as compared to the better-known Hendrickson’s (POP) reagent.\textsuperscript{30-31} Specifically, the reported chemical shift of cyclic phosphonium anhydrides (\textsuperscript{31}P NMR δ 92 ppm) as compared to the POP reagent (\textsuperscript{31}P NMR δ 72 ppm) supported this hypothesis.

Work by Panza\textsuperscript{32} (Figure 1.3) indicated the potential to use the POP reagent in a limited fashion for dehydrative glycosylation. The scope of this method was limited by the tendency to form homocoupling product. As a result the Panza method required the glycosyl acceptor to be mixed with the POP reagent and then added to the donor, still with significant byproduct formed. It was envisioned the stability of the cyclic phosphonium species and corresponding oxophosphonium glycosylation intermediate
would prevent formation of the homocoupling product and provide a simpler and more efficient dehydrative glycosylation method.

The work described herein shows how a library of cyclic phosphonium anhydrides were prepared and characterized from the corresponding bis-phosphine oxides by $^1$H, $^{31}$P, and $^{13}$C NMR and in one case X-ray crystallography. It was envisioned that the corresponding cyclic phosphonium analogues could be screened as dehydrating agents and subsequently used in dehydrative glycosylations which would exhibit enhanced yield and selectivities compared to more common methods. The optimized reaction conditions were then successfully used by Dr. Rajendar Dyapa in a series of glycosylation reactions with various glycosyl donor and acceptors exhibiting high yields and strong selectivities.

2.1.1: Preparation of cyclic phosphonium anhydrides

A series of bis-phosphine oxides exhibiting a variety of electronic, stereochemical, and steric properties in addition to previously reported cyclic POP anhydrides were selected to generate a library of potential dehydrating agents (Figure 2.1). Characterization of the cyclic phosphonium anhydrides was done by $^1$H, $^{31}$P, and $^{13}$C NMR. Under inert atmosphere the corresponding bis-phosphine oxides (1 equiv) were dissolved in deuterated methylene chloride and mixed with trifluoromethanesulfonic anhydride (1.25 equiv).
The cyclic phosphonium anhydride reagents exhibited a range of $^{31}\text{P}$ NMR chemical shifts indicating varied electrophilic potential (Table 2.1) as compared to Hendrickson’s reagent ($^{31}\text{P}$ NMR δ 77 ppm). To further characterize the cyclic phosphonium anhydrides a series of recrystallization and X-ray crystallography experiments were performed. A crystal structure of cyclic phosphonium 8 was successfully obtained (Figure 2.2), supporting the proposed structure and of this particular compound. A key difference is that the bond lengths observed for cyclic
phosphonium 8 are longer than that reported for Hendrickson’s reagent (1.612 Å vs 1.597 Å), providing further support to the electrophilic potential of this particular cyclic phosphonium. This library of cyclic phosphonium anhydrides was prepared in situ and evaluated as dehydrative glycosylation reagents for a variety of reaction conditions (see below).

<table>
<thead>
<tr>
<th>Anhydride</th>
<th>$^{31}$P $\delta$</th>
<th>Anhydride</th>
<th>$^{31}$P NMR $\delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>60.2</td>
<td>12</td>
<td>95.8</td>
</tr>
<tr>
<td>7</td>
<td>85.4</td>
<td>13</td>
<td>79.2</td>
</tr>
<tr>
<td>8</td>
<td>90.6</td>
<td>(R)-14</td>
<td>40.9</td>
</tr>
<tr>
<td>9</td>
<td>62.0</td>
<td>(S)-14</td>
<td>40.9</td>
</tr>
<tr>
<td>10</td>
<td>51.8</td>
<td>(R)-15</td>
<td>58.4</td>
</tr>
<tr>
<td>11</td>
<td>68.7</td>
<td>(S)-15</td>
<td>58.4</td>
</tr>
</tbody>
</table>

Table 2.1 $^{31}$P NMR chemical shifts for the library of prepared cyclic phosphonium triflate salts.

Figure 2.2 X-ray crystal structure of cyclic phosphonium anhydride 3.
2.2: Optimization and glycosylations

With a library of cyclic phosphoniums prepared, optimization experiments were undertaken to evaluate the potential of these reagents in dehydrative glycosylation reactions. Each cyclic phosphonium anhydride was prepared in situ from trifluoromethanesulfonic anhydride and reacted with 2,3,4,6-tetra-O-benzyl glucopyranoside in the presence of 2,4,6-tri-tert-butylpyridine. A suitable glycosyl acceptor (either cyclohexanol or benzyl alcohol) was then added to the reaction mixture (See Table 2.2).

2.2.1: Evaluation of cyclic phosphonium anhydrides in glycosylations

Evaluation of the optimization reactions proceeded as follows: cyclic phosphoniums 1-10 were prepared from their corresponding bis-phosphine oxides and trifluoromethanesulfonic anhydride (15 min) before adding the glycosyl donor (30 min) followed by cyclohexanol. Cyclic phosphonium anhydrides 6, 8, 10, and (S)-15 were the most promising (Table 2.2) in terms of both yields and selectivities. Cyclic phosphonium 8 with an observed yield of 91% had the highest yield and selectivity with cyclohexanol, despite lackluster selectivity with benzyl alcohol. The ease of these reactions to form the presumed cyclic intermediate 24 could further explain their reactivity in glycosylation reactions. A particular outlier in the screened examples was cyclic phosphonium 7, which gave only trace amounts of product. A number of mechanistic studies with cyclic phosphonium 7 later revealed that it interacts poorly with the glycosyl donor and does not
activate it for dehydration. The exact explanation for this phenomenon remains to be
determined is likely due to its either unique molecular geometry or electrophilic
character.

While cyclic phosphonium 10 showed moderate yield and good selectivity with
cyclohexanol, larger similar phosphoniums 11-13 gave poor yield. It is likely that the
bulky size of these anhydrides led to poor interaction with the glycosyl donor. It is
notable that while the $^{31}$P $\delta$ values for phosphoniums such as 8 reflected high yielding
glycosylation reactions, other larger phosphoniums (7, 12, 13) having similarly high $^{31}$P $\delta$
values acted poorly in glycosylation reactions. This is likely due to the combination of
electrophilic and steric factors affecting the stability of the cyclic phosphonium-glycosyl
donor intermediate. The various chiral cyclic phosphonium anhydrides prepared had
both greatly reduced yields and limited control over selectivity with the exception of
chiral cyclic phosphonium (S)-15; however, the difference between corresponding $R$ and
$S$ enantiomers likely indicates little effect on phosphonium configurations. The high yield
and dr. of glycosylation with 8 combined with the easy commercial availability of the
precursor [1,4-bis(diphenylphosphino)butane] ultimately led to the selection of this
reagent as the dehydrating agent for the future reactions.

<table>
<thead>
<tr>
<th>Anhydride</th>
<th>ROH</th>
<th>Yield</th>
<th>$\alpha : \beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>CyOH</td>
<td>56%</td>
<td>36:64</td>
</tr>
</tbody>
</table>
Table 2.2 Optimization of cyclic phosphonium anhydrides in dehydrative glycosylations.

2.2.2: Evaluation of dehydrative glycosylation reaction conditions

With cyclic phosphonium 8 selected as the optimal dehydrating agent, additional optimizations were undertaken to determine the effect of various solvents, reaction times, and reaction temperatures on the glycosylation reactions.

Despite evaluation of different solvents (PhMe, THF, Et₂O, MeCN) and solvent mixtures in glycosylation reactions, methylene chloride was found to give both the
highest yields and selectivities. Other solvents and mixtures severely decreased the solubility of 8 and hindered the formation of the presumed cyclic phosphonium intermediate. For these reactions no glycosylation was observed and the primary product was elimination (2,3,4,6-tetra-O-benzyl-D-glucal) or no reaction at all. The overall yield for the reaction was highest when allowing the prepared cyclic phosphonium anhydride to react with the glycosyl donor for 20 min followed by addition of the glycosyl acceptor. Less reaction time resulted in leftover unreacted glycosyl donor while longer reaction times gave poor yield due to elimination. Reactions carried out at 0°C were found to be optimal as increased (room temperature) or decreased (-20 °C and -78 °C) temperatures gave significant amounts of elimination products or unreacted starting material, respectively and only trace amounts of the desired glycosylation product.

2.2.3: Improved glycosylation selectivities through anomeric iodides

Based on work by Mukaiyama and other work disclosed in this thesis (Chapter 3) it was known that glycosylation of anomeric iodides via in situ anomerization proceeds well with high α–selectivity.37,39 While the work by Dr. Rajendar Dyapa demonstrated the applicability of this method for a wide range of glycosyl donors and acceptors with good selectivity and yield, there were still examples from these studies where the observed selectivities were not satisfactory. It was thus envisioned that once the glycosyl donor was activated by cyclic phosphonium 8, addition of tetrabutylammonium iodide (TBAI) could furnish the corresponding anomeric iodide (Scheme 2.1). Addition of the glycosyl
acceptor would then give the product in high $\alpha$–selectivity due to in situ anomerization to the reactive $\beta$-iodide and subsequent glycosylation.

Scheme 2.1 Dehydrative glycosylation in the presence of TBAI.

The first step to evaluate the potential for TBAI in highly $\alpha$–selective glycosylations was to identify conditions which would lead to formation of the anomeric iodide but minimize the formation of elimination product. Direct addition of TBAI to activated glycoside 17 gave almost exclusively elimination product and trace amounts of the glycosylation product. It was hypothesized that in these reactions conversion to the anomeric iodide in the presence of TBAI proceeded rapidly and in high concentrations the unstable anomeric iodide (reacting with glycosyl acceptor) would undergo elimination before it had sufficient time to react with the glycosyl acceptor. As a way to overcome this problem a protocol was devised whereby a solution of TBAI (0.03 M in DCM) and the glycosyl acceptor were added slowly via syringe pump (3.7 mL/hr) to activated glycoside 17 at 0 °C. In this new procedure activated glycoside 17 would
rapidly convert to the iodide and undergo glycosylation nearly simultaneously with limited time for the formation of elimination byproducts.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Donor</th>
<th>Acceptor</th>
<th>Product</th>
<th>Yield</th>
<th>$\alpha : \beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Donor Structure" /></td>
<td>CyOH</td>
<td><img src="image2" alt="Product Structure" /></td>
<td>64%</td>
<td>71:29</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Donor Structure" /></td>
<td><img src="image4" alt="Acceptor Structure" /></td>
<td>N.D.</td>
<td>N.R.</td>
<td>N.D</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Donor Structure" /></td>
<td>CyOH</td>
<td><img src="image6" alt="Product Structure" /></td>
<td>76%</td>
<td>only $\alpha$</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Donor Structure" /></td>
<td>CyOH</td>
<td><img src="image8" alt="Product Structure" /></td>
<td>72%</td>
<td>63:37</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Donor Structure" /></td>
<td>PhOH</td>
<td><img src="image10" alt="Product Structure" /></td>
<td>&gt;5%</td>
<td>71:29</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Donor Structure" /></td>
<td><img src="image12" alt="Acceptor Structure" /></td>
<td><img src="image13" alt="Product Structure" /></td>
<td>89%*</td>
<td>85:15</td>
</tr>
</tbody>
</table>
With the ideal conditions screened a series of reactions were performed (Table 2.3) with a variety of substrates and glycosyl acceptors in order to evaluate the potential for this method to afford improved α-selectivities in dehydrative glycosylation reactions. The experiments with 2,3,4-tri-O-benzyl-D-fucose/cyclohexanol gave moderate yields with promising selectivities, prompting further exploration of this method. Attempting this method with a highly hindered secondary alcohol donor (Entry 2) was unsuccessful as was also the result under standard conditions. Further experiments with 2,3,5-tri-O-benzyl-D-ribose and cyclohexanol (Entry 3) were more promising, with exclusively the α-product observed in 76% yield. Reaction of 2,3-di-O-benzyl-4,6-O-[(R)-phenylmethylene]-D-mannose and 2,3,4,6-tetra-O-benzyl-D-glucose/phenol (Entries 4-5) both gave moderate to poor yields with poor selectivities. Benzyl glucose reacted with methyl 2,3,4-tri-O-benzyl-D-glucopyranoside gave to corresponding product in high yield and moderate selectivity with a modified method using a 1:1 ratio of methylene chloride:1,2,-dichloroethane (DCE) as the solvent mixture (Entry 6).

The most promising result of this method came when reacting benzyl glucose with cholesterol as the glycosyl acceptor (Entry 7). The corresponding glycosylation
product was observed in 88% yield although with diminished selectivities. Regardless, this result was promising due to it being the first application of this glycosylation method with a large and complex glycosyl, indicating promise for expanding the method further to glycosylations which could be essential for synthesizing natural products.

2.3: Mechanistic studies

With the knowledge that cyclic phosphonium 8 functions as an efficient dehydrating agent however, we were unable to observe any trehalose products, a series of mechanistic NMR studies were undertaken to better understand the nature of this reaction. Of particular interest was an explanation for the lack of observed homocoupling product and a clearer understanding of the reactive intermediates responsible for the glycosylation, potentially due to a stable oxophosphonium intermediate between the intact cyclic phosphonium and the glycosyl donor.

2.3.1: Cyclic phosphonium-glycosyl donor interaction studies

Initial work into the investigation of the dehydrative glycosylation mechanism focused on identifying and characterizing the intermediate formed upon addition of the cyclic phosphonium anhydride to the glycosyl donor in the proposed mechanism (Scheme 2.2). Supported by the lack of observed homocoupling product in these dehydrative glycosylation reactions it was expected that the cyclic phosphonium remains intact once activating the glycosyl donor yielding intermediate 24, the reactive species in
the glycosylation. A series of \(^1\text{H}, \ ^{13}\text{C}, \ ^{31}\text{P}\), and 2D NMR experiments were performed to identify this intermediate.

![Chemical Structure](image)

**Scheme 2.2** Proposed dehydrative glycosylation mechanism

Studies into the intermediate generated from addition of the cyclic phosphonium 8 to the glycosyl donor were carried out under inert atmosphere in an NMR tube at room temperature on a 400 MHz NMR spectrometer. 2,3,4,6-Tetra-O-benzyl-D-glucopyranoside was added to cyclic phosphonium 8 (\(^{31}\text{P}\) NMR \(\delta\) 91.8 ppm) and thoroughly mixed. Upon addition of the glycosyl donor to cyclic phosphonium 8 (Figure 2.3), new \(^{31}\text{P}\) chemical shifts were observed at 73.7, 73.2, 43.1, 42.8, and 32.5 ppm. \(^1\text{H}\) NMR, \(^{13}\text{C}\) NMR, COSY, HSQC, and HMBC NMR were also recorded for this sample. Based on the 2D NMR experiments the protons located at \(^1\text{H}\) NMR \(\delta\)=6.0 ppm, \(\delta\)=5.8 ppm (\(J_H\) 3.3, 6.8 Hz) represent \(\alpha\)-anomeric protons observed as a doublet of doublets.
The pattern of the $^{31}$P signals observed as symmetric doublets is predicted to be the result of two separate anomeric insertions at the chiral phosphorus atom with the relative ratios of the peaks corresponding to the relative ratios of the $^1$H anomeric protons observed at $\delta=6.0$ ppm, $\delta=5.8$ ppm. Examination of the anomeric peaks in COSY spectroscopy indicated coupling to only one other proton, supporting that those anomeric peaks were coupled to an additional spin $\frac{1}{2}$ nuclei, presumed to be $^{31}$P. A series of selective $^{31}$P-$^1$H decoupled experiments were performed to confirm the interaction between the anomeric peak and the nearby $^{31}$P nuclei proposed in the initial mechanism (Figure 2.4).
Figure 2.4 Proposed glycosylation intermediate 24 with observed coupling interactions to C-2 and nearby $^{31}\text{P}$ nuclei.

Selective $^{31}\text{P}$ NMR decoupling at 73.7, 43.1, and 32.1 ppm revealed $^1\text{H}-^{31}\text{P}$ coupling between the anomeric proton and the phosphorus nuclei represented by $\delta$ 73 ppm with the decoupling reducing the doublet of doublets to a doublet (Figure 2.5). The alternate anomeric peak was also reduced to a triplet due to decoupled overlap of the neighboring nuclei in the $^{31}\text{P}$ spectrum. Decoupling experiments between the anomeric protons at $^{31}\text{P} \delta$ 43.1 ppm and $\delta$ 32.1 ppm showed no change in the $^1\text{H}$ spectra. Broadband $^{31}\text{P}$ decoupling reduced both anomeric peaks to doublets and no other changes were observed. A $^1\text{H}-^{31}\text{P}$ HMBC spectrum was obtained for the proposed intermediate 24 to further support the results of the selective $^1\text{H}-^{31}\text{P}$ decoupling experiments (Appendix 7).
From these experiments it is evident that the cyclic phosphonium 8 reacts with the glycosyl donor smoothly to provide a number of intermediates with $^{31}$P 73.7 ppm, 43.1 ppm, and 32.1 ppm. Long range $^1$H-$^{31}$P coupling experiments confirm the interaction between the anomeric proton and the nearby phosphonium species at 73.7 ppm, similar to that described in proposed intermediate 24. The $^{31}$P signal observed at 32.1 ppm is predicted to be that of the decomposed intermediate 24 to the corresponding elimination product and DPPBO$_2$ based on observations that this $^{31}$P signal grows in intensity as the NMR experiment proceeds and the C-1 elimination $^1$H signal becomes more prominent. It
is possible that this peak could be assigned to a brief open chain P=O intermediate. That no homocoupling product is observed supports the relative stability of cyclic intermediate 24, and further suggesting it is the predominant intermediate responsible for the glycosylation. Direct evidence for the prevalence of this intermediate in glycosylation reactions could most easily be supported through X-ray crystal structure of proposed intermediate 24. Due to the long term instability of intermediate 24 observed in the mechanistic studies, another model system would need to be developed which would be more stable.

2.3.2: Cyclic phosphonium-glycosyl acceptor interaction studies

In order to determine the nature of the incoming glycosyl acceptor in this glycosylation a series of experiments were performed to determine the extent to which an incoming glycosyl acceptor may interact with both the cyclic phosphonium and the proposed glycosylation intermediate 24 (Scheme 2.2). Two model acceptors were examined: cyclohexanol and 2,2,2-trifluoroethanol (TFE).

The reaction of cyclohexanol with 24 was found to occur too rapidly on the NMR time scale to observe via $^1$H and $^{31}$P NMR. The glycosylation product was observed in addition to elimination byproduct (2,3,4,6-tetra-O-benzyl-D-glucal). Addition of cyclohexanol to the POP-butane 24 caused decomposition of 24 into the corresponding bis-phosphine oxide. As a result of these experiments a less nucleophilic glycosyl acceptor without β-protons (TFE) was used which may be more stable and likely to directly interact with the POP-butane and intermediate 24.
Addition of TFE to POP-butane in 0.5 equivalent increments up to 2.0 equiv resulted in the attachment of TFE to the phosphonium as observed in $^{31}$P and NOESY NMR spectra (Figure 2.7) with the peaks at $^{31}$P NMR 80.0 ppm representing the mono-TFE-bound phosphonium and the peak at 60.3 ppm and 59.0 ppm representing the TFE saturated phosphorus (Figure 2.6). Despite an excess of TFE there was always an equilibrium observed between bound and non-bound TFE. These experiments suggest the possibility for intermediate 24 to interact with the incoming glycosyl acceptor in a manner in which the free phosphonium may become bound and in turn allow for intramolecular delivery of the glycosyl acceptor, a unique concept with dehydrative glycosylation reactions.
Figure 2.6 $^{31}$P NMR of cyclic phosphonium 8 (a) following addition of 0.5 (b), 1.0 (c), and 2.0 (d) equiv of TFE.
Figure 2.7 NOESY spectra of cyclic phosphonium 8 after addition of 2.0 equiv. of TFE showing long-range interaction between CH₂ protons of TFE and the aryl protons in 8.

2.4: Methods

General: All chemicals used were reagent grade without further purification, unless otherwise noted. DCM, THF, Et₂O, PhME, and DMF were filtered through a column of activated alumina prior to use. All reactions were carried out under dry N₂ atmosphere. Glassware used was dried in an oven. Trifluoromethanesulfonic anhydride was distilled
from phosphorus pentoxide. TLC analyses were performed on Merck TLC plates and visualizations were performed with Hanessian stain. Column chromatography was performed on silica gel (230-400 mesh). $^1$H and $^{13}$C NMR spectra were recorded on Bruker/Varian/Varian 300/400/500 MHz instruments are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. NMR experiments carried out under inert atmosphere were performed within a glovebox. The residual solvent reference peaks were used from published literature.$^{43}$ 2D NMR experiments were performed using standard parameters (200 and More NMR Experiments, S. Berger, S. Braun, Wiley-VCH, 2004). IR measurements were performed on Agilent Cary 630 FT/IR instrument and optical rotations were measured on JASCO P-1030 and are reported as an average of ten data points.

2.4.1: Preparation of cyclic phosphonium anhydrides

1,2-Bis(diphenylphosphino)ethane. A solution of 1,2-Bis(diphenylphosphino)ethane (0.298 g, 0.748 mmol) in anhydrous THF (8 mL) was treated with 33% H$_2$O$_2$ (2.5 mL) added slowly via syringe. The reaction was stirred at rt for 2 h, excess THF was removed by rotary evaporator and the precipitated solid was filtered, washed with cold H$_2$O and dried overnight under high vacuum with spectra matching reported data$^{44}$: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.75 – 7.61 (m, 8H), 7.57 – 7.50 (m, 4H), 7.50 – 7.38 (m, 8H), 2.03 (s, 4H); $^{31}$P NMR (122 MHz, CDCl$_3$) δ 32.6.
1,3-Bis(diphenylphosphine oxide)propane. A solution of 1,3-bis(diphenylphosphine)propane (0.526 g, 1.28 mmol) in anhydrous THF (10 mL) was treated with 33% H₂O₂ (4 mL) added slowly via syringe. The reaction was stirred at rt for 2 h, excess THF was removed by rotary evaporator and the remaining water removed by high vacuum over night in a 50 °C oil bath. After overnight drying the product was formed a white powder with spectra matching reported data: ¹H NMR (300 MHz, CDCl₃) δ 7.95 – 7.61 (m, 8H), 7.59 – 7.36 (m, 12H), 2.51 (d, J = 2.6 Hz, 4H), 1.69 (s, 2H); ³¹P NMR (122 MHz, CDCl₃) δ 29.2.

1,4-Bis(diphenylphosphine oxide)butane. A solution of 1,4-bis(diphenylphosphine)butane (3.05 g, 7.15 mmol) in anhydrous THF (20 mL) was treated with 33% H₂O₂ (10 mL) added via syringe. The reaction was stirred at rt for 2 h as the reaction mixture turned from opaque to a clear solution upon completion. THF was removed by rotary evaporator, and the precipitate was filtered, washed with cold H₂O, and dried overnight under high vacuum with spectra matching reported data: ¹H NMR (300 MHz, CDCl₃) δ 7.77 – 7.62 (m, 8H), 7.60 – 7.36 (m, 12H), 2.23 (ddd, J = 11.3, 8.5, 5.1 Hz, 4H), 1.75 – 1.64 (m, 4H); ³¹P NMR (122 MHz, CDCl₃) δ 31.8.

1,5-Bis(diphenylphosphine oxide)pentane. A solution of 1,5-bis(diphenylphosphino)pentane (0.510 g, 1.16 mmol) in anhydrous THF (9 mL) was treated with 33% H₂O₂ (3 mL) added via syringe. The reaction was stirred at rt for 2 h, THF was removed by rotary evaporator and the product partially precipitated in the
remaining aqueous layer. The water was removed under high vacuum overnight at 50 °C to afford a flaky white solid with spectra matching reported data\textsuperscript{46}: $^1$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.84 – 7.62 (m, 8H), 7.57 – 7.36 (m, 12H), 2.32 – 2.11 (m, 4H), 1.69 – 1.44 (m, 6H); $^{31}$P NMR (122 MHz, CDCl\textsubscript{3}) $\delta$ 32.9.

1,1'-\((1,2\text{-phenylene})\text{bis}(1,1\text{-diphenyl-phosphine oxide})\). A solution of 1,1'-\((1,2\text{-phenylene})\text{bis}(1,1\text{-diphenyl-phosphine})\) (0.3 g, 0.6 mmol) in anhydrous THF (8 mL) was treated with 33\% H\textsubscript{2}O\textsubscript{2} (2.5 mL) added via syringe. The reaction was stirred at rt for 2 h, THF was removed by rotary evaporator, and the remaining water was removed under high vacuum overnight to give a white powder with spectra matching reported data\textsuperscript{47}: $^1$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.82 – 7.65 (m, 2H), 7.59 (ddq, $J$ = 5.5, 3.7, 2.1 Hz, 2H), 7.54 – 7.38 (m, 9H), 7.36 – 7.20 (m, 7H); $^{31}$P NMR (122 MHz, CDCl\textsubscript{3}) $\delta$ 32.3.

1,8-Bis(diphenylphosphine oxide)naphthalene. A solution of 1,4-bis(diphenylphosphino)naphthalene (0.15 g, 0.30 mmol) in anhydrous THF (4 mL) was treated with 33\% H\textsubscript{2}O\textsubscript{2} (1.1 mL) added via syringe. The reaction mixture was stirred at rt for 2 h as the mixture turned from opaque to a clear upon completion. THF was removed by rotary evaporator and the precipitated solid was filtered, washed with cold H\textsubscript{2}O and dried overnight under high vacuum with spectra matching reported data\textsuperscript{48}: $^1$H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 8.10 – 7.93 (m, 2H), 7.79 – 7.64 (m, 2H), 7.59 – 7.28 (m, 20H); $^{13}$C NMR (101 MHz, CDCl\textsubscript{3}) $\delta$ 138.2, 137.8, 137.7, 137.1, 134.3, 132.9, 131.5, 131.4, 130.5, 127.8, 127.7, 124.1, 124.0; $^{31}$P NMR (162 MHz, CDCl\textsubscript{3}) $\delta$ 31.3.
1,2-Bis(diphenylphosphine oxide)xylene. A solution of 1,4-bis(diphenylphosphino)xylene (0.15 g, 0.38 mmol) in anhydrous THF (4 mL) was treated with 33% H₂O₂ (1.1 mL) added via syringe. The reaction was stirred at rt for 2 h as the reaction mixture turned from opaque to a clear solution upon completion. THF was removed by rotary evaporator and the precipitated solid was filtered, washed with cold H₂O, and dried overnight under high vacuum: ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.31 (m, 2H), 7.11 (dd, J = 5.6, 3.4 Hz, 2H), 3.82 (d, J = 11.4 Hz, 4H), 1.20 (d, J = 13.2 Hz, 33H); ¹³C NMR (101 MHz, CDCl₃) δ 134.6, 134.6, 134.5, 132.5, 126.5, 36.8, 36.2, 29.6, 29.1, 27.1, 26.1. IR (ATR) 3056, 2960, 2926, 2855, 1439, 1194, 1115 cm⁻¹; ³¹P NMR (162 MHz, CDCl₃) δ 63.5. HRMS (ESI) m/z calc for C₂₄H₄₄O₂P₂ (M+H⁺) 427.2895; found, 427.2895.

1,1’Bis(diphenylphosphine oxide)ferrocene. A solution of 1,1’-bis(diphenylphosphino)ferrocene (0.408 g, 0.736 mmol) in anhydrous THF (10 mL) was treated with 33% H₂O₂ (4 mL) added via syringe. The reaction was stirred at rt for 2 h, THF was removed by rotary evaporator and DPPFO₂ partially precipitated in the remaining aqueous layer. The remaining water was removed under high vacuum overnight at 50 °C. After overnight drying, DPPFO₂ formed an orange powder: ¹H NMR (400 MHz, CDCl₃) δ 7.69 – 7.21 (m, 20H), 4.68 (s, 4H), 4.27 (s, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 131.6, 131.3, 131.2, 128.3, 128.2, 128.1, 74.1, 74.0, 73.5, 73.4; ³¹P NMR (162 MHz, CDCl₃) δ 28.6; IR (ATR) 3484, 3098, 3052, 1439, 1168, 1123 cm⁻¹; HRMS (ESI) m/z calc for C₃₄H₄₆FeO₂P₂ (M+Li⁺), 593.1075, found 593.1073.
**2,2'-Bis(diphenylphosphine oxide)-1,1'-binaphthyl.** A solution of 1, (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) (0.255 g, 0.410 mmol) in anhydrous THF (20 mL) was treated with 33% H$_2$O$_2$ (3 mL) added slowly via syringe. The reaction was inc. at rt. for 2 hr. Excess THF was removed by rotary evaporator. The remaining water was removed from BINAPO$_2$ under high vacuum overnight. After overnight drying, BINAPO$_2$ formed a white powder spectra matching reported data$^{44}$: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.89 – 7.79 (m, 1H), 7.71 (ddd, $J$ = 12.2, 8.3, 1.4 Hz, 1H), 7.49 – 7.32 (m, 5H), 7.30 – 7.19 (m, 4H), 6.83 – 6.78 (m, 1H). $^{31}$P NMR (122 MHz, CDCl$_3$) δ 28.4.

**(-)-2,2-Dimethyl-4,5-(Bis(diphenylphosphine oxide)dimethyl)dioxolane.** A solution of (R,R)-DIO (0.166 g, 0.333 mmol) in anhydrous THF (4 mL) was treated with 33% H$_2$O$_2$ (1 mL) added via syringe. The reaction was stirred at rt for 2 h, and THF was removed by rotary evaporator. The partially precipitated (R,R)-DIOPO$_2$ in the remaining aqueous was dried under high vacuum overnight at 50 °C giving a white powder spectra matching reported data$^{50}$: $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ 7.86 – 7.69 (m, 8H), 7.57 – 7.42 (m, 12H), 4.17 (q, $J$ = 5.5, 4.9 Hz, 2H), 2.93 (td, $J$ = 15.0, 4.6 Hz, 2H), 2.61 (ddd, $J$ = 15.2, 8.8, 6.2 Hz, 2H); $^{31}$P NMR (122 MHz, CD$_2$Cl$_2$) δ 29.3.

Phosphonium salt 6. In an NMR tube a solution of 1,2-Bis(diphenylphosphine oxide)ethane (7.5 mg, 0.017 mmol, 1 equiv.) in anhydrous CD$_2$Cl$_2$ (0.5 mL) was treated with distilled triflic anhydride (10 µL, 0.060 mmol, 3.5 equiv.) under inert nitrogen atmosphere of a glovebox. The solution was vortexed, stirred at 0 °C for 30 min, and characterized by NMR: $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 8.10 – 7.54 (m, 20H), 4.46 (d, $J$ =
7.2 Hz, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 140.0, 135.6, 135.5, 135.4, 132.7, 132.6, 132.5, 123.5, 122.2, 119.3, 118.3, 117.9, 117.0, 24.9, 24.8, 24.1, 24.0; $^{31}$P NMR (122 MHz, CD$_2$Cl$_2$) δ 60.2.

Phosphonium salt 7. In an NMR tube a solution of 1,3-Bis(diphenylphosphine oxide)propane (23.8 mg, 0.054 mmol, 1 equiv.) in anhydrous CD$_2$Cl$_2$ (0.5 mL) was treated with distilled triflic anhydride (10.8 µL, 0.064 mmol, 1.2 equiv.) under inert nitrogen atmosphere of a glovebox. The solution was vortexed, stirred at 0 °C for 30 min, and was characterized by NMR: $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ 7.89 – 7.61 (m, 20H), 3.12 (dt, $J = 11.2$, 7.9 Hz, 4H), 2.04 (dt, $J = 16.0$, 7.9 Hz, 2H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ 135.4, 135.4, 135.4, 131.5, 131.4, 131.4, 131.3, 130.1, 130.1, 130.0, 129.9, 129.9, 125.8, 122.2, 121.6, 120.8, 117.3, 113.1, 27.0, 26.8, 26.1, 25.9, 14.1, 14.0, 14.0; $^{31}$P NMR (122 MHz, CD$_2$Cl$_2$) δ 85.4.

Phosphonium salt 8. In an NMR tube a solution of 1,4-Bis(diphenylphosphine oxide)butane (11.3 mg, 0.025 mmol, 1 equiv.) in anhydrous CD$_2$Cl$_2$ (0.5 mL) was treated with distilled triflic anhydride (4.5 µL, 0.024 mmol, 1.1 equiv.) under inert nitrogen atmosphere of a glovebox. The solution was vortexed, stirred at 0 °C for 30 min, and analyzed by NMR: $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ 8.03 – 7.61 (m, 20H), 3.84 (q, $J = 5.7$ Hz, 4H), 2.61 – 2.38 (m, 4H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ 139.9, 135.0, 134.9, 134.8, 132.9, 132.8, 132.8, 130.0, 128.4, 124.1, 122.2, 120.0, 119.4, 119.3, 118.6, 117.9, 117.8, 23.4, 23.1, 22.7, 19.2; $^{31}$P NMR (122 MHz, CD$_2$Cl$_2$) δ 90.6.
Phosphonium salt 9. In an NMR tube a solution of 1,5-Bis(diphenylphosphine oxide)pentane (12.6 mg, 0.027 mmol, 1 equiv.) in anhydrous CD$_2$Cl$_2$ (0.5 mL) was treated with distilled triflic anhydride (5 µL, 0.029 mmol, 1.1 equiv.) under inert nitrogen atmosphere of a glovebox. The solution was vortexed, stirred at 0 °C for 30 min, and analyzed by NMR: $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 7.91 – 7.52 (m, 20H), 2.90 – 2.64 (m, 4H), 1.69 (d, $J = 4.5$ Hz, 6H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ 135.1, 135.1, 131.4, 131.3, 129.9, 129.7, 125.8, 123.0, 121.6, 117.4, 113.2, 30.4, 26.0, 25.2, 19.9, 19.9; $^{31}$P NMR (122 MHz, CD$_2$Cl$_2$) δ 62.0.

Phosphonium salt 10. In an NMR tube a solution of 1,1’-(1,2-phenylene)bis(1,1-diphenylphosphine oxide) (17.0 mg, 0.036 mmol, 1.5 equiv.) in anhydrous CD$_2$Cl$_2$ (0.4 mL) was treated with distilled triflic anhydride (8.0 µL, 0.045 mmol, 1.25 equiv.) under inert nitrogen atmosphere of a glovebox. The solution was vortexed, and inc. at 0 °C for 30 min. After 30 min. the reaction was characterized by $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ 7.91 – 7.80 (m, 2H), 7.72 – 7.63 (m, 4H), 7.60 – 7.38 (m, 18H). $^{31}$P NMR (122 MHz, CD$_2$Cl$_2$) δ 51.81. $^{13}$C NMR (101 MHz, CD$_2$Cl$_2$) δ 139.3, 134.8, 134.3, 134.3, 134.2, 131.3, 125.7, 125.6, 124.7, 124.6, 121.3, 119.7, 118.1, 116.5, 115.4, 114.3.

Phosphonium salt 11. In an NMR tube a solution of 1,8-Bis(diphenylphosphine oxide)naphthalene (25.3 mg, 0.048 mmol, 1 equiv.) in anhydrous CD$_2$Cl$_2$ (0.5 mL) was treated with distilled triflic anhydride (9.6 µL, 0.057 mmol, 1.2 equiv.) under inert nitrogen atmosphere of a glovebox. The solution was vortexed, stirred at 0 °C for 30 min,
and analyzed by NMR: $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 8.92 – 8.73 (m, 2H), 8.15 (dq, $J$ = 26.6, 8.8, 8.3 Hz, 4H), 8.01 – 7.42 (m, 20H); $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 68.7.

Phosphonium salt 12. In an NMR tube a solution of 1,2-Bis(diphenylphosphine oxide)xylene (26.7 mg, 0.063 mmol, 1 equiv.) in anhydrous CD$_2$Cl$_2$ (0.5 mL) was treated with distilled triflic anhydride (12.6 μL, 0.075 mmol, 1.2 equiv) under inert nitrogen atmosphere of a glovebox. The solution was vortexed, stirred at 0 °C for 30 min, and analyzed by NMR: $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ 7.49 – 7.35 (m, 4H), 3.97 (d, $J$ = 10.8 Hz, 2H), 1.35 (d, $J$ = 15.6 Hz, 32H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ 135.8, 131.3, 127.9, 123.6, 119.4, 115.2, 39.2, 38.6, 28.0; $^{31}$P NMR (122 MHz, CD$_2$Cl$_2$) δ 95.8.

Phosphonium salt 13. In an NMR tube a solution of 1,1’Bis(diphenylphosphine oxide)ferrocene (43.9 mg, 0.075 mmol, 1 equiv) in anhydrous CD$_2$Cl$_2$ (0.5 mL) was treated with distilled triflic anhydride (15.1 μL, 0.09 mmol, 1.2 equiv) under inert nitrogen atmosphere of a glovebox. The solution was vortexed, stirred at 0 °C for 30 min, and analyzed by NMR: $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 10.12 – 9.59 (m, 4H), 7.27 (s, 2H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ 140.2, 134.9, 134.8, 134.7, 133.3, 133.2, 133.1, 119.2, 119.0, 118.2, 117.9, 117.4, 117.2, 82.6, 82.5, 82.4, 80.1, 80.0, 80.0; $^{31}$P NMR (122 MHz, CD$_2$Cl$_2$) δ 79.2.

Phosphonium salt (R)-14. In an NMR tube a solution of (R)-2,2’-Bis(diphenylphosphine oxide)-1,1’-binaphthyl (29 mg, 0.044 mmol, 1.5 equiv) in anhydrous CD$_2$Cl$_2$ (0.5 mL) was treated with distilled triflic anhydride (7.0 μL, 0.037 mmol, 1.25 equiv) under inert
nitrogen atmosphere of a glovebox. The solution was vortexed and immediately characterized by $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$ 8.00 – 7.90 (m), 7.86 – 7.68 (m), 7.65 (d, $J$ = 1.7 Hz), 7.51 – 7.41 (m), 7.38 – 7.04 (m), 7.02 – 6.87 (m). $^{31}$P NMR (122 MHz, CD$_2$Cl$_2$) $\delta$ 40.85. $^{13}$C NMR (101 MHz, CD$_2$Cl$_2$) $\delta$ 134.9, 134.4, 133.1, 132.3, 132.2, 130.6, 130.5, 130.3, 130.1, 129.8, 129.7, 129.5, 128.6, 128.5, 128.2, 128.1, 127.8, 127.6, 126.8, 121.0, 120.7, 117.8, 117.6.

Phosphonium salt ($R$)-15. In an NMR tube a solution of (-)-2,2-Dimethyl-4,5-(Bis(diphenylphosphine oxide)dimethyl)dioxolane (11.5 mg, 0.022 mmol, 1 equiv) in anhydrous CD$_2$Cl$_2$ (0.4 mL) was treated with distilled triflic anhydride (4.4 µL, 0.026 mmol, 1.2 equiv.) under inert nitrogen atmosphere of a glovebox. The solution was vortexed, stirred at 0 °C for 30 min, and analyzed by NMR: $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$ 8.07 – 7.73 (m, 13H), 7.73 – 7.50 (m, 7H), 4.36 – 4.21 (m, 2H), 3.96 (d, $J$ = 12.3 Hz, 1H), 3.48 (td, $J$ = 16.6, 16.2, 1.8 Hz, 2H), 2.98 (ddd, $J$ = 15.5, 9.0, 6.2 Hz, 1H), 1.07 (s, 6H); $^{13}$C NMR (101 MHz, CD$_2$Cl$_2$) $\delta$ 137.6, 137.4, 136.2, 135.3, 135.0, 132.8, 132.6, 131.8, 131.6, 131.5, 129.8, 129.7, 129.4, 129.3, 74.6, 74.5, 74.4, 74.3, 25.9; $^{31}$P NMR (122 MHz, CD$_2$Cl$_2$) $\delta$ 58.4.

2.4.2: Mechanistic studies of glycosyl donor and cyclic phosphonium interaction

In an NMR tube a solution of DPPBO$_2$ (60.0 mg, 0.131 mmol, 1 equiv) and 2,4,6-tri-tert-butylpyridine (97.1 mg, 0.393 mmol, 3 equiv) in anhydrous CD$_2$Cl$_2$ (0.3 mL) was treated with distilled Tf$_2$O (33.0 µL, 0.197 mmol, 1.5 equiv) under inert
nitrogen atmosphere of a glove box. The solution was vortexed and reacted at rt for 5 min. After 10 minutes the mixture was characterized by $^1$H and $^{31}$P NMR. A solution of 2,3,4,6-tetra-O-benzyl-D-glucopyranoside (70.8 mg, 0.131 mmol, 1 equiv) in anhydrous DCM (0.3 mL) was added to the prepared cyclic phosphonium 10 and vortexed to mix before immediate characterization by $^1$H and $^{31}$P NMR. For full characterization see Appendix 2.

2.4.3 General dehydrative glycosylation procedure

A typical dehydrative glycosylation procedure: A mixture of diphenyl[4-(diphenylphosphinyl)butyl]phosphine oxide (0.105 g, 0.230 mmol) and 2,4,6-tri-tert-butylpyridine (0.170 g, 0.690 mmol) was azeotropically dried with PhMe (2 x 3 mL) and under high vacuum for 1 h. Freshly activated 4 Å MS (0.10 g) were added to the above mixture and further dried under high vacuum for 1 h. Anhydrous dichloromethane (3.0 mL) was added, the mixture was cooled to 0 °C, Tf$_2$O (64.9 µL, 0.230 mmol) was added and stirred at 0 °C for 30 min. 2,3,4,6-Tetra-O-benzyl-D-glucopyranoside (0.083 g, 0.153 mmol) in anhydrous dichloromethane (0.8 mL) was added, stirred for 15 min at 0 °C, followed by cyclohexanol (32.1 µL, 0.307 mmol). This mixture was stirred at 0 °C for 2 h, quenched with Et$_3$N. The crude product was extracted into additional DCM and worked up with sat. NaHCO$_3$, brine, dried (Mg$_2$SO$_4$), filtered, and concentrated. The crude compound was purified by chromatography on SiO$_2$ (Hexanes:EtOAc, 10:1) to afforded cyclohexyl 2,3,4,6-tetra-O-benzyl-β-D-glucopyranoside 10 (0.950 g, 83%, α/β = 35/65) as a white solid matching reported data$^{38}$. 

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2.4.4 General dehydrative glycosylation procedure with TBAI modification

A typical dehydrative glycosylation procedure with TBAI: A mixture of diphenyl[4-(diphenylphosphinyl)butyl]phosphine oxide (0.105 g, 0.230 mmol) and 2,4,6-tri-tert-butylpyridine (0.170 g, 0.690 mmol) was azeotropically dried with PhMe (2 x 3 mL) and under high vacuum for 1 h. Freshly activated 4 Å MS (0.10 g) were added to the above mixture and further dried under high vacuum for 1 h. Anhydrous dichloromethane (3.0 mL) was added, the mixture was cooled to 0 °C, Tf₂O (64.9 µL, 0.230 mmol) was added and stirred at 0 °C for 30 min. 2,3,4,6-Tetra-O-benzyl-D-glucopyranoside (0.083 g, 0.153 mmol) in anhydrous dichloromethane (0.8 mL) was added, stirred for 15 min at 0 °C. A solution of TBAI (0.113 g, 0.306 mmol) and benzyl alcohol (15.9 µL, 0.153 mmol) in DCM (3 mL) was then added to the reaction at a race of 3.7mL/hr for approximately 45 minutes. After TLF had indicated the reaction was complete (1hr) the crude product was extracted into additional DCM and worked up with 1x sat. NaHCO₃, 1x brine, dried over Mg₂SO₄, filtered, and concentrated. The crude compound was purified by chromatography on SiO₂ (Hexanes:EtOAc, 10:1) afforded benzyl 2,3,4,6-tetra-O-benzyl-β-D-glucopyranoside (0.048 g, 50%, only α) as a colorless oil matching reported data⁴¹.

Cyclohexyl 2,3,4-tri-O-benzyl-6-deoxy-β-L-fucopyranose. A mixture of diphenyl[4-(diphenylphosphinyl)butyl]phosphine oxide (0.105 g, 0.230 mmol) and 2,4,6-tri-tert-butylpyridine (0.170 g, 0.690 mmol) was azeotropically dried with PhMe (2 x 3 mL) and under high vacuum for 1 h. Freshly activated 4 Å MS (0.10 g) were added to the above
mixture and further dried under high vacuum for 1 h. Anhydrous dichloromethane (3.0 mL) was added, the mixture was cooled to 0 °C, Tf₂O (23.2 μL, 0.138 mmol) was added and stirred at 0 °C for 30 min. 2,3,4-tri-O-benzyl-6-deoxy-β-L-fucopyranose (0.040 g, 0.092 mmol) in anhydrous dichloromethane (0.8 mL) was added, stirred for 15 min at 0 °C. A solution of TBAI (0.070 g, 0.184 mmol) and cyclohexanol (4.6 µL, 0.046 mmol) in DCM (3 mL) was then added to the reaction at a race of 3.7mL/hr for approximately 45 minutes. After TLC had indicated the reaction was complete (1hr) the crude product was extracted into additional DCM and worked up with 1x sat. NaHCO₃, 1x brine, dried over Mg₂SO₄, filtered, and concentrated. The crude compound was purified by chromatography on SiO₂ (Hexanes:EtOAc, 10:1) afforded cyclohexyl 2,3,4-tri-O-benzyl-6-deoxy-β-L-fucopyranose (0.030 g, 64%, only 71:29 α:β) as a colorless oil. [α]D²³ -0.3 (c 0.6, CHCl₃); IR (ATR) 2944, 2859, 1455, 1366, 1071, 1030 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.27 (m, 15 H), 4.98 (dd, J = 11.3, 5.0 Hz, 1H), 4.80 – 4.69 (m, 4H), 4.42 (d, J = 7.7 Hz, 1H), 3.78 (dd, J = 9.7, 7.7 Hz, 1H), 3.70 – 3.63 (m, 1H), 3.54 (dd, J = 3.0, 1.0 Hz, 1H), 3.49 (dd, J = 9.7, 3.0 Hz, 1H), 3.44-3.40 (m, 1H), 1.97 – 1.90 (m, 2H), 1.76 – 1.72 (m, 2H), 1.52 – 1.20 (m, 7H), 1.15 (d, J = 6.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 139.0, 138.8, 138.7, 128.6, 128.3, 128.2(2), 128.1, 127.5(2), 127.4, 101.8, 82.8, 79.5, 76.3, 75.1, 74.4, 73.2, 70.2, 33.6, 31.8, 25.7, 24.1, 24.0, 17.0; HRMS (ESI) m/z calc for C₃₅H₄₀O₅Li (M+Li⁺) 523.3036, found 523.3037.

**Cyclohexyl 2,3,5-tri-O-benzyl-α-D-ribofuranoside.** A mixture of diphenyl[4-(diphenylphosphinyl)butyl]phosphine oxide (0.40.8 g, 0.089 mmol) and 2,4,6-tri-tert-butylpyridine (0.52.9 g, 0.089 mmol) was azeotropically dried with PhMe (2 x 3 mL)

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and under high vacuum for 1 h. Freshly activated 4 Å MS (0.10 g) were added to the above mixture and further dried under high vacuum for 1 h. Anhydrous dichloromethane (3.0 mL) was added, the mixture was cooled to 0 °C, Tf₂O (18.0 µL, 0.107 mmol) was added and stirred at 0 °C for 30 min. 2,3,5-tri-O-benzyl-α-D-ribofuranoside (0.030 g, 0.071 mmol) in anhydrous dichloromethane (0.8 mL) was added, stirred for 15 min at 0 °C. A solution of TBAI (0.053 g, 0.143 mmol) and cyclo58hexanol (2.2 µL, 0.021 mmol) in DCM (3 mL) was then added to the reaction at a rate of 3.7 mL/hr for approximately 45 minutes. After TLC had indicated the reaction was complete (1 hr) the crude product was extracted into additional DCM and worked up with 1x sat. NaHCO₃, 1x brine, dried over Mg₂SO₄, filtered, and concentrated. The crude compound was purified by chromatography on SiO₂ (Hexanes:EtOAc, 10:1) afforded Cyclohexyl 2,3,5-tri-O-benzyl-α-D-ribofuranoside (0.011 g, 76%, only α) as a white foam. [α]ᵩ⁺²³ +103.6 (c 0.5, CHCl₃); IR (ATR) 2937, 1455, 1221, 1030 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.21 (m, 15H), 5.18 (d, J = 4.2 Hz, 1H), 4.72 (d, J = 13.2 Hz, 2H), 4.62 (d, J = 12.3 Hz, 1H), 4.54 – 4.41 (m, 3H), 4.24 (q, J = 3.9 Hz, 1H), 3.84 – 3.82 (m, 1H), 3.77 – 3.75 (m, 1H), 3.62 – 3.58 (m, 1H), 3.46 (dd, J = 10.6, 3.7 Hz, 1H), 3.37 (dd, J = 10.5, 4.2 Hz, 1H), 1.98 – 1.92 (m, 2H), 1.77 – 1.75 (m, 2H), 1.56 -1.17 (m, 7H); ¹³C NMR (75 MHz, CDCl₃) δ 138.6, 138.2, 138.0, 128.3 (2), 128.2, 128.0 (2), 127.7, 127.6 (2), 127.5, 99.6, 80.9, 76.2, 75.5, 73.4, 72.3, 72.1, 69.9, 33.8, 31.9, 25.7, 24.6, 24.5; HRMS (ESI) m/z calc for C₃₂H₃₈O₅Li (M+Li⁺) 509.2880, found 509.2880.

**Cyclohexyl 2,3-bis-O-(phenylmethyl)-4,6-O-[(R)-phenylmethylene]-β-D-mannopyranoside.** A mixture of diphenyl[4-(diphenylphosphinyI)butyl]phosphine oxide
(0.077 g, 0.167 mmol) and 2,4,6-tri-tert-butylpyridine (0.099 g, 0.400 mmol) was azeotropically dried with PhMe (2 x 3 mL) and under high vacuum for 1 h. Freshly activated 4 Å MS (0.10 g) were added to the above mixture and further dried under high vacuum for 1 h. Anhydrous dichloromethane (1.5 mL) and 1,2-dichloroethane (1.5 mL) was added, the mixture was cooled to 0 °C, Tf₂O (34.0 µL, 0.200 mmol) was added and stirred at 0 °C for 30 min. 2,3-bis-O-(phenylmethyl)-4,6-O-[(R)-phenylmethylene]-β-D-mannopyranoside (0.050 g, 0.111 mmol) in anhydrous dichloromethane (1.5 mL) and 1,2-dichloroethane (1.5 mL) with TBAI (0.098 g, 0.266) was added via syringe pump at a rate of 3.7 mL/hr. at 0 °C. After TLC had indicated the reaction was complete (1 hr) the crude product was extracted into additional DCM and worked up with 1x sat. NaHCO₃, 1x brine, dried over MgSO₄, filtered, and concentrated. The crude compound was purified by chromatography on SiO₂ (Hexanes:EtOAc, 10:1) afforded cyclohexyl 2,3-bis-O-(phenylmethyl)-4,6-O-[(R)-phenylmethylene]-β-D-mannopyranoside (0.010 g, 56%, 67:33 α:β) as a colorless oil. [α]D²³ -73 (c 0.45, CHCl₃); IR (ATR) 2937, 2863, 1459, 1221, 1093 cm⁻¹; 1H NMR (500 MHz, CDCl₃) δ 7.51 – 7.28 (m, 15 H), 5.62 (s, 1H), 5.02 (d, J = 12.5 Hz, 1H), 4.91 (d, J = 12.5 Hz, 1H), 4.66 (d, J = 12.5 Hz, 1H), 4.59 – 4.57 (m, 2H), 4.30 (dd, J = 10.4, 4.8 Hz, 1H), 4.22 (t, J = 9.6 Hz, 1H), 3.95 (t, J = 10.3 Hz, 1H), 3.88 (d, J = 3.2 Hz, 1H), 3.73-3.68 (m, 1H), 3.58 (dd, J = 9.9, 3.2 Hz, 1H), 3.32 (td, J = 9.7, 4.8 Hz, 1H), 1.92 – 1.70 (m, 4H), 1.56 – 1.26 (m, 7H); 13C NMR (75 MHz, CDCl₃) δ 138.5, 138.4, 137.6, 128.8, 128.7, 128.3, 128.2, 128.1, 127.5, 126.0, 101.4, 100.0, 78.6, 78.1, 76.2, 74.6, 72.3, 68.7, 67.5, 33.4, 31.4, 25.6, 23.7, 23.6; HRMS (ESI) m/z calc for C₃₃H₃₈O₆Li (M+Li⁺) 537.2829, found 537.2842.
Methyl 6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)- 2,3,4-tri-O-benzyl-α-D-glucopyranoside. A mixture of diphenyl[4-(diphenylphosphinyl)butyl]phosphine oxide (0.105 g, 0.230 mmol) and 2,4,6-tri-tert-butylpyridine (0.170 g, 0.690 mmol) was azeotropically dried with PhMe (2 x 3 mL) and under high vacuum for 1 h. Freshly activated 4 Å MS (0.10 g) were added to the above mixture and further dried under high vacuum for 1 h. Anhydrous dichloromethane (1.5 mL) and 1,2-dichloroethane (1.5 mL) was added, the mixture was cooled to 0 °C, Tf₂O (25.5 µL, 0.152 mmol) was added and stirred at 0 °C for 30 min. 2,3,4-tri-O-benzyl-α-D-glucopyranoside (0.055 g, 0.101 mmol) in anhydrous dichloromethane (0.8 mL) and 1,2-dichloroethane (0.8 mL) was added, stirred for 15 min at 0 °C. A solution of Methyl 6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (0.016, 0.034 mmol) in DCM (1 mL) was then added to the reaction. After TLC had indicated the reaction was complete (1hr) the crude product was extracted into additional DCM and worked up with 1x sat. NaHCO₃, 1x brine, dried over MgSO₄, filtered, and concentrated. The crude compound was purified by chromatography on SiO₂ (Hexanes:EtOAc, 10:1) afforded Methyl 6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)- 2,3,4-tri-O-benzyl-α-D-glucopyranoside (0.030 g, 89%, 85:15 α:β) as a colorless oil as a clear oil: [α]D²³ +7.7 (c 2, CHCl₃); IR (ATR) 2930, 1731, 1264, 1072, 1031 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.09 (dd, J = 8.3, 1.4 Hz, 2H), 8.05 (dd, J = 8.3, 1.4 Hz, 2H), 7.90 – 7.92 (m, 2H), 7.84 (dd, J = 8.4, 1.4 Hz, 2H), 7.61 – 7.26 (m, 27H), 6.08 (t, J = 10.1 Hz, 1H), 5.89 (dd, J = 10.1, 3.3 Hz, 1H), 5.74 (dd, J = 3.4, 1.8 Hz, 1H), 5.17 (d, J = 1.8 Hz, 1H), 5.03 (dd, J = 11.1, 2.7 Hz, 2H), 4.85 – 4.80 (m, 2H), 4.70 (dd, J = 11.7, 3.1 Hz, 2H), 4.66 – 4.63 (m, 2H), 4.43 – 4.40 (m, 1H), 4.35 (dd, J = 12.1, 4.4 Hz, 1H), 4.05 (t, J = 9.2 Hz, 1H), 3.95 (dd, J = 11.0, 5.1 Hz, 1H), 3.89 – 3.86 (m,
1H), 3.82 (dd, J = 11.0, 1.8 Hz, 1H), 3.60 – 3.52 (m, 2H), 3.46 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 166.1, 165.4(2), 165.3, 138.7, 138.2(2), 133.4, 133.2, 133.1, 129.9(2), 129.7(2), 129.4, 129.1, 129.0, 128.6, 128.5(2), 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6(2), 97.9, 97.8, 82.1, 80.2, 77.7, 75.7, 75.0, 73.5, 70.3, 70.0, 69.9, 68.9, 66.9, 66.7, 62.7, 55.2; HRMS (ESI) m/z calc for C$_{62}$H$_{58}$O$_{15}$Li (M+Li$^+$) 1049.3937, found 1049.3922.

(3β)-cholest-5-en-3-ol 2,3,4,6-tetra-O-benzyl-D-galactopyranose. A mixture of diphenyl[4-(diphenylphosphinyl)butyl]phosphine oxide (0.014 g, 0.032 mmol) and 2,4,6-tri-tert-butylpyridine (0.093 g, 0.078 mmol) was azeotropically dried with PhMe (2 x 3 mL) and under high vacuum for 1 h. Freshly activated 4 Å MS (0.10 g) were added to the above mixture and further dried under high vacuum for 1 h. Anhydrous dichloromethane (3.0 mL) was added, the mixture was cooled to 0 °C, Tf$_2$O (6.5 µL, 0.039 mmol) was added and stirred at 0 °C for 30 min. 2,3,4,6-tetra-O-benzyl-D-galactopyranose (0.014 g, 0.026 mmol) in anhydrous dichloromethane (0.8 mL) was added, stirred for 15 min at 0 °C. A solution of TBAI (0.019 g, 0.052 mmol) and benzyl alcohol (0.004g, 0.010 mmol) in DCM (3 mL) was then added to the reaction at a race of 3.7mL/hr for approximately 45 minutes. After TLC had indicated the reaction was complete (1hr) the crude product was extracted into additional DCM and worked up with 1x sat. NaHCO$_3$, 1x brine, dried over Mg$_2$SO$_4$, filtered, and concentrated. The crude compound was purified by chromatography on SiO$_2$ (Hexanes:EtOAc, 10:1) afforded (3β)-cholest-5-en-3-ol 2,3,4,6-tetra-O-benzyl-D-galactopyranose (0.009 g, 88%, 64:36 α:β) as a colorless oil matching reported data$^{32}$. 

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2.4.5: Mechanistic studies of TFE and cyclic phosphonium interaction

In an NMR tube a solution of DPPBO$_2$ (60.0 mg, 0.131 mmol, 1 equiv.) and 2,4,6-tri-tert-butylpyridine (97.1 mg, 0.393 mmol, 3 equiv) in anhydrous CD$_2$Cl$_2$ (0.35 mL) was treated with distilled Tf$_2$O (33.0 µL, 0.197 mmol, 1.5 equiv.) under inert nitrogen atmosphere of a glovebox. The solution was vortexed and reacted at 0°C for 30 min. After 30 minutes this mixture was characterized by NMR: $^1$H NMR (400 MHz, CD$_2$Cl$_2$) 7.89 (dq, $J = 13.8, 7.6$ Hz, 12H), 7.70 (dt, $J = 10.8, 5.2$ Hz, 4H), 3.86 (d, $J = 7.3$ Hz, 4H), 2.47 (dt, $J = 16.0, 5.8$ Hz, 4H); $^{31}$P NMR (162 MHz, CD$_2$Cl$_2$) δ 91.7. To this solution was added freshly distilled 2,2,2-triflouroethanol (60.0 mg, 0.131 mmol, 1 equiv.) under inert atmosphere. This was repeated with 0.5, 1.0, and 2.0 equiv. The new solution was vortexed and characterized by 1D NMR: $^1$H NMR (400 MHz, CD$_2$Cl$_2$); $^{31}$P NMR; and 2D NOESY experiments.

Chapter 3: α-Selective Glycosylation of Glycosyl Phosphinites

3.1: α-selective glycosylation reactions

The use of in situ anomerization in highly α-selective glycosylations has been well reported by Lemieux$^{34}$ and Mukaiyama$^{37-39}$ with anomeric bromides but with limited substrate scope. In the case of the work by Lemieux, α-glycosyl halides were reacted with quaternary ammonium halide salts. Addition of excess of halide salt promoted in
situ anomerization between the stable α-halide and the more reactive β-halide. Once the reactive β-halide forms, it undergoes glycosylation to give the α-anomer (Scheme 3.1). The method used by Lemieux was limited by the necessity to prepare unstable anomeric bromides as glycosyl donors.

Later work by Mukaiyama\textsuperscript{37} relied primarily upon the preparation of the more stable glycosyl phosphinates but under harsh conditions and with limited ribofuranose substrates. Typical conditions for preparation of glycosyl phosphinates relied upon the use of \textit{n}-butyl lithium with a suitable glycosyl donor in the presence of chlorodiphenylphosphine. The corresponding glycosyl phosphinates were then reacted with TBAI in the presence of a glycosyl acceptor. While the yields and selectivities of this reaction were high, application of this method to more complicated glycosyl donors would be problematic while using strongly basic reagents such as \textit{n}-butyl lithium. It was envisioned that development of a new method to prepare glycosyl phosphinates under mild conditions with a wide range of functional groups would allow for an expanded reaction scope to this method and also allow for application to more complicated molecules with a high degree of α-glycosidic linkages.

The work described herein shows how a library of glycosyl phosphinates were prepared under mildly basic conditions from the corresponding chlorophosphines and characterized. The optimized reaction conditions were then used in a number of glycosylation examples demonstrating high α-selectivity and good yields. A series of mechanistic \textsuperscript{1}H and \textsuperscript{31}P NMR studies were performed to better understand the mechanism of this glycosylation reaction. Development of highly α-selective glycosylation methods is highly useful because inherently α-selective reactions with wide functional group
tolerances and substrate scope are still uncommon. While β-selective glycosylations are relatively easy with the use of protecting groups, exploration of anomeric in situ anomerization as a route to α-selective glycosylations could possibly represent an analogous method to C-2 neighboring group participation, enabling the practical synthesis of practical α-glycosides, especially carbohydrate-containing natural products with numerous α-glycosidic linkages such as Axinellioside A

3.2: Preparation of glycosyl phosphinites

It was known based on work by Mukaiyama that preparation of ribose glycosyl phosphinites from 2,3,5-tri-O-benzyl-D-ribose preceded smoothly with n-butyl lithium in the presence of a suitable chlorophosphine (CIPR₂). In an effort to expand this method to a range of substrates and with wide functional group compatibility, a series of mild bases were first evaluated with commercially available chlorodiphenylphosphine (Table 3.1). The base optimization experiments indicated that 1,8-Diazabicycloundec-7-ene (DBU) resulted in the highest yield and the shortest reaction time as well as giving minimal elimination product of all bases tested. An excess of DBU (3 equiv) was also found to be optimal. It was notable that DBU had similar efficiency for the preparation of glycosyl phosphinitite 27 than the reported Mukaiyama procedure using n-butyllithium however, under more mild conditions.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Time (min)</th>
<th>Yield</th>
<th>α:β</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>nBuLi</td>
<td>5</td>
<td>85%</td>
<td>21:79</td>
</tr>
<tr>
<td>2</td>
<td>nBuLi</td>
<td>&gt;5</td>
<td>&lt;5%</td>
<td>N.D.</td>
</tr>
<tr>
<td>3</td>
<td>Et₃N</td>
<td>5</td>
<td>32%</td>
<td>58:42</td>
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<tr>
<td>4</td>
<td>Et₃N</td>
<td>30</td>
<td>45%</td>
<td>58:42</td>
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<tr>
<td>5</td>
<td>Et₃N</td>
<td>60</td>
<td>70%</td>
<td>56:44</td>
</tr>
<tr>
<td>6</td>
<td>pyridine</td>
<td>30</td>
<td>30%</td>
<td>18:82</td>
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<td>DABCO</td>
<td>30</td>
<td>65%</td>
<td>10:90</td>
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<tr>
<td>8</td>
<td>DBU</td>
<td>30</td>
<td>89%</td>
<td>45:55</td>
</tr>
<tr>
<td>9</td>
<td>DBU</td>
<td>60</td>
<td>71%</td>
<td>45:55</td>
</tr>
<tr>
<td>10</td>
<td>DIPEA</td>
<td>12 hr</td>
<td>&lt;5%</td>
<td>49:51</td>
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</table>

**Table 3.1** Base optimizations for the preparation of glycosyl phosphinites.

With these conditions in place, a collection of various glycosyl phosphinites were prepared from a number of commercially available chlorophosphines. These chlorophosphines were then screened in glycosylation reactions with cyclohexanol in the presence of iodomethane as an electrophile in methylene chloride over the course of several days (Table 3.2). Ultimately chlorophosphines (ClPR₂) where R = phenyl, 4-methoxyphenyl (PMP), and aminodiisopropyl (N(iPr)₂) had the highest yields however, only the glycosyl phosphinite prepared from ClPPh₂ gave the desired α-selective product (Table 3.2). The glycosylation was also tested in DMF, toluene, MeCN, and THF however, in each case the yield and selectivities observed were inferior to conditions with DCM.
3.2 Optimization of glycosyl phosphinites in α-selective glycosylations.

3.3.1: Substrate scope

In order to test the scope of this method with more complex molecules, various glycosyl donors were prepared and subjected to the conditions described above for the preparation of glycosyl phosphinites followed by reaction with iodomethane and a suitable glycosyl acceptor (Table 3.3). Glycosylation of 2,3,4,6-tetra-O-benzyl glucose and galactose with 1,2:3,4-Di-O-isopropylidene-α-galactose yielded the glycosylation products in 80% and 60% yields, respectively with excellent α : β selectivities of 92:8->99:1. Glycosylation with 3,4-di-O-benzoyl-2-O-benzyl-arabinose and the same acceptor gave the corresponding product in 73% yield with only the α -anomer observed.

<table>
<thead>
<tr>
<th>Donor</th>
<th>Acceptor</th>
<th>Yield</th>
<th>α : β</th>
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<td></td>
<td></td>
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</table>
Table 3.3 Reaction scope of glycosylation with anomeric phosphinites. examples using the reported optimized conditions for preparation of glycosyl phosphinites and corresponding glycosylation.

This method was also used with a number of other glycosyl donors and acceptors by Dr. Jie Guang demonstrating similar yields and selectivities. Taken together these results show that glycosyl phosphinites can be prepared under mild basic conditions from a number of glycosyl donors and used in glycosylation reaction that give highly α-selective and high yielding products.

3.4: Mechanistic studies

A number of mechanistic NMR studies were undertaken to better understand
the observed high α-selectivity of these reactions and the significant time (3d) required for the reaction to go to completion. It was predicted that glycosylation with glycosyl phosphinites proceeds through *in situ* anomerization of the glycosyl iodide (Scheme 3.1). The glycosyl phosphinite 31 with iodomethane electrophile was observed every hour by $^{31}$P NMR for 13 hours (Figure 3.1) during conversion via pathway 32.

**Scheme 3.1** Proposed mechanism of α-selective glycosylation with glycosyl phosphinites.
Figure 3.1 glycosyl phosphinite 31 reacted with iodomethane observed via $^{31}$P NMR each hour over the course of 12 hours.

The α/β glycosyl phosphinites ($^{31}$P NMR $\delta = 155.9, 114.2$) were slowly consumed over the course of the experiment (14h). After approximately 14 hours almost none of the glycosyl phosphinite remained. At this point cyclohexanol was added and the reaction was observed every 12 hours an additional 72 hours (Figure 3.2). After 72 hours no further change was observed in the $^{31}$P NMR spectra. The reaction progress was monitored via TLC, indicating that the glycosylation to give product 20 was complete. Over the course of the glycosylation the $^{31}$P shift of the corresponding methyldiphenylphosphine oxide (prepared and observed independently) peak can be
explained by the anomeric iodide existing as an iodine-phosphine oxide complex with the shift corresponding to the consumption of anomeric iodide as the reaction progresses.

![Figure 3.2](image-url)

**Figure 3.2** $^{31}$P NMR of glycosyl intermediate 32 reacted with cyclohexanol over the course of 3 days.

Given these observations, conversion to the anomeric iodide is relatively fast (13 hours) compared to the glycosylation (72 hours). Under these conditions the more reactive β-iodide reacts readily once formed to give the α-glycosylation product whereas slow conversion of anomeric-effect-stabilized α-iodide to the reactive β-intermediate
explains the extended reaction times and the nature of observed high $\alpha$-selectivity.

3.5: Methods

**General:** All chemicals used were reagent grade without further purification, unless otherwise noted. DCM, THF, Et$_2$O, PhME, and DMF were filtered through a column of activated alumina prior to use. All reactions were carried out under dry N$_2$ atmosphere. Glassware used was dried in an oven. Trifluoromethanesulfonic anhydride was distilled from phosphorus pentoxide. MeCN, pyridine, DIPEA, and Et$_3$N were distilled from CaH$_2$. TLC analyses were performed on Merck TLC plates and visualizations were performed with Hanessian stain. Column chromatography was performed on silica gel (230-400 mesh). $^1$H and $^{13}$C NMR spectra were recorded on Bruker/Varian/Varian 300/400/500 MHz instruments are reported as follows: chemical shift ($\delta$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. NMR experiments carried out under inert N$_2$ atmosphere were performed within a glovebox. The residual solvent reference peaks were used from published literature. 2D NMR experiments were performed using standard parameters (200 and More NMR Experiments, S. Berger, S. Braun, Wiley-VCH, 2004). IR measurements were performed on Agilent Cary 630 FT/IR instrument and optical rotations were measured on JASCO P-1030 and are reported as an average of ten data points.
3.5.1: General preparation of glycosyl phosphinites

2,3,4,6-tetra-O-benzyl-D-glucose 19 was evaporated 2x azeotropically from PhMe and then dried under high vacuum for 30 min. Under N₂ atm. at rt 19 was dissolved in anhydrous CH₂Cl₂ and stirred. To this stirring solution was added DBU followed by ClP(R)² via microsyringe. For ClP(PMP)² and ClP(N(iPr))₂, chlorophosphines were dried under high vacuum in a 10 mL rbf before dissolving in 1 mL anhydrous CH₂Cl₂ and adding to the stirred solution via syringe after addition of DBU. DBU, nBuLi, Et₃N, or pyridine bases were via microsyringe. DABCO was dissolved with the initial glucopyranoside 19 and dried azeotropically from PhMe, dried under high vacuum and dissolved in anhydrous CH₂Cl₂ before stirred as described above. Chlorophosphines were directly added as described above. Glycosyl phosphinites were purified via flash chromatography over SiO₂ (Hexanes:EtOAc) over SiO₂ and characterized by ¹H, ³¹P, ¹³C, and HSQC (see Appendix 4).

2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl diphenylphosphinite (27).

248.0 mg (0.459 mmol) of 2,3,4,6-tetra-O-benzyl glucopyranoside 19 was evaporated 2x azeotropically from PhMe and then dried under high vacuum for 30 min. Under N₂ atm. at rt 19 was dissolved in anhydrous CH₂Cl₂ (12 mL) and stirred. To this stirring solution was added 1,8-Diazabicycloundec-7-ene (194.0 µL, 1.377 mmol) followed by chlorodiphenylphosphine (98.9.0 µL, 0.551 mmol) via microsyringe. This reaction was stirred for 35 minutes at rt before TLC indicated the reaction was complete. The reaction
mixture was evaporated under reduced pressure and purified via flash chromatography over SiO₂ to give 296.0 mg of the title compound as a white solid in 89% yield (45:55 α:β) matching data reported in literature. ¹H NMR (300 MHz, Methylene Chloride-d₂) 7.58 - 7.39 (m, 8H), 7.35 - 7.01 (m, 21H), 6.99 - 6.91 (m, 1H), 5.40 (dd, J = 8.3, 3.5 Hz, 1H), 4.86 (d, J = 11.0 Hz, 1H), 4.80 - 4.73 (m, 2H), 4.72 - 4.68 (m, 1H), 4.66 - 4.54 (m, 3H), 4.48 (d, J = 26.3 Hz, 1H), 4.41 - 4.36 (m, 1H), 4.32 (d, J = 15.4 Hz, 1H), 3.98 - 3.88 (m, 0H), 3.64 - 3.45 (m, 7H). ¹³C NMR (75 MHz, CD₂Cl₂) 142.0, 141.7, 141.6, 141.4, 139.1, 138.8, 138.5, 138.4, 138.3, 138.3, 131.5, 131.2, 130.5, 130.2, 130.1, 129.8, 129.8, 129.1, 129.0, 128.4, 128.3 (2), 128.2, 128.2, 128.1, 128.1 (2), 27.8, 127.7, 127.6, 127.5, 127.5, 127.4, 103.4, 103.4, 98.6, 98.3, 84.6, 81.6, 80.9, 80.8, 77.7, 77.5, 75.5, 75.4, 75.3, 74.9, 74.8, 74.8, 73.4, 73.1, 72.7, 71.4, 68.7, 68.3, 54.1, 53.8, 53.4, 53.1, 52.7. ³¹P NMR (122 MHz, CD₂Cl₂) 115.9, 114.2.

3.5.2: Optimization of glycosylation conditions with glycosyl phosphinites

2,3,4,6-tetra-O-benzyl-D-glucose 26 (71.8 mg, 0.099 mmol, 1 equiv.) was evaporated 2x azeotropically from PhMe and then dried under high vacuum for 30 min. Under N₂ atm. at rt 26 was then dissolved in anhydrous CH₂Cl₂ (5 mL) and stirred. To this stirring solution was added 1,8-Diazabicycloundec-7-ene (44.4 µL, 0.297 mmol, 3 equiv.) followed by chlorodiphenylphosphine (21.3 µL, 0.119 mmol, 1.2 equiv.) via microsyringe. This reaction was stirred for 35 minutes at rt before TLC indicated the reaction was complete. The reaction mixture was evaporated under reduced pressure and filtered through a small plug of SiO₂ to remove excess base (2:1 Hexanes:EtOAc) to give
the crude glycosyl phosphinite 27 as a white solid in quantitative yield. The filtered product was dried under high vacuum for 30 min. Under N\textsubscript{2} atm. and at rt 27 was dissolved in anhydrous CH\textsubscript{2}Cl\textsubscript{2} and stirred. To this stirring solution was added iodomethane (10.2 µL, 0.163 mmol, 1.6 equiv.) followed by a solution of distilled cyclohexanol (11.4 mg, 0.109 mmol 1.1 equiv.) in 0.5 mL anhydrous CH\textsubscript{2}Cl\textsubscript{2}. The reaction mixture was allowed to stir at rt for 3 d. before TLC indicated the reaction was complete. The reaction was then concentrated under reduced pressure, dissolved in EtOAc and worked up with 1x75mL sat. NaHCO\textsubscript{3}, 50 mL dH\textsubscript{2}O, and 50 mL sat. NaCl solution. The organic layer was then dried over MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure. The crude product was purified over SiO\textsubscript{2} (4:1 Hexanes:EtOAc) to give 45.0 mg of cyclohexyl 2,3,4,6-tetra-O-benzyl-\textbeta-D-glucopyranoside as a colorless oil in 69% yield (95:5 α:β): matching data previously reported in literature.\textsuperscript{41}

3.5.3: Glycosylations with glycosyl phosphinites

1,2,3,4-di-O-isopropylidine galactopyranoside-(2-O-benzyl-3,4-O-di-benzoyl-α-D-arabinopyranoside) A typical glycosylation using glycosyl phosphinites follows as such: 2-O-benzyl-3,4-O-di-benzoyl-α-D-arabinopyranoside (53.0 mg, 0.118 mmol, 1 equiv) was evaporated 2x azeotropically from PhMe and then dried under high vacuum for 30 min. Under N\textsubscript{2} atm. at rt 30 was dissolved in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (5 mL) and stirred. To this stirring solution was added 1,8-Diazabicycloundec-7-ene (50.0 µL, 0.355 mmol, 3 equiv) followed by chlorodiphenylphosphine (26.0 µL, 0.143 mmol, 1.2 equiv) via microsyringe. This reaction was stirred for 35 minutes at rt before TLC indicated the
reaction was complete. The reaction mixture was evaporated under reduced pressure and filtered through a small plug of SiO\textsubscript{2} to remove excess base (2:1 hexanes:EtOAc) to give the crude arabinosyl phosphinite as a white solid. The filtered product was dried under high vacuum for 30 min. Under N\textsubscript{2} atm. and at rt the white solid was dissolved in anhydrous CH\textsubscript{2}Cl\textsubscript{2} and stirred. To this stirring solution was added iodomethane (22.0 µL, 0.089 mmol) followed by a solution of 1,2,3,4-di-isopropylidene-D-galactopyranoside (23 mg, 0.075mmol) in 0.5 mL anhydrous CH\textsubscript{2}Cl\textsubscript{2}. The reaction mixture was allowed to stir at rt for 3 d. before TLC indicated the reaction was complete. The reaction was then concentrated under reduced pressure, dissolved in EtOAc and worked up with 75mL sat. NaHCO\textsubscript{3}, 50 mL dH\textsubscript{2}O, and 50 mL sat. NaCl solution. The organic layer was then dried over MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure. The crude product was purified over SiO\textsubscript{2} (2:1 Hexanes:EtOAc) to give 36.1 mg of the title compound as a colorless oil in 73% yield (only α). \textsuperscript{1}H, \textsuperscript{13}C, and HSQC NMR characterization data can be found in Appendix 10. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \textsuperscript{δ} 7.96 (d, \textit{J} = 8.1 Hz, 2H), 7.89 (d, \textit{J} = 8.1 Hz, 2H), 7.60 (t, \textit{J} = 7.0 Hz, 1H), 7.52 (t, \textit{J} = 7.0 Hz, 1H), 7.45 (t, \textit{J} = 7.5 Hz, 2H), 7.39 – 7.24 (m, 7H), 5.73 (dd, \textit{J} = 10.2, 3.2 Hz, 1H), 5.66 (s, 1H), 5.58 (d, \textit{J} = 5.0 Hz, 1H), 5.23 (d, \textit{J} = 3.1 Hz, 1H), 4.73 (q, \textit{J} = 12.4 Hz, 2H), 4.64 (d, \textit{J} = 7.9 Hz, 1H), 4.39 – 4.33 (m, 2H), 4.25 (d, \textit{J} = 13.1 Hz, 1H), 4.20 – 4.09 (m, 5H), 3.92 (dd, \textit{J} = 10.5, 6.2 Hz, 1H), 3.87 – 3.75 (m, 2H), 1.53 (s, 3H), 1.47 (s, 3H), 1.36 (d, \textit{J} = 15.9 Hz, 6H). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \textsuperscript{δ} 165.7, 165.5, 161.3, 137.9, 133.2, 133.0, 129.9, 129.8, 129.7, 129.7, 128.40, 128.3, 128.3, 127.9, 127.7, 109.3, 108.6, 97.7, 96.3, 73.5, 72.3, 71.0, 70.6, 70.5, 69.6, 67.0, 66.3, 60.9, 60.4, 30.9, 26.1, 26.0, 24.9, 24.6, 21.1, 14.2.
1,2,3,4-di-O-isopropylidine galactopyranoside-(2,3,4,6-tetra-O-benzyl mannopyranoside). 86.0 mg (0.159 mmol) of 2,3,4,6-tetra-O-benzyl mannopyranoside 29 was evaporated 2x azeotropically from PhMe and then dried under high vacuum for 30 min. Under N₂ atm. at rt 29 was dissolved in anhydrous CH₂Cl₂ (7 mL) and stirred. To this stirring solution was added 1,8-Diazabicycloundec-7-ene (28.0 µL, 0.239 mmol) followed by chlorodiphenylphosphine (34.3 µL, 0.191 mmol) via microsyringe. This reaction was stirred for 35 minutes at rt before TLC indicated the reaction was complete. The reaction mixture was evaporated under reduced pressure and filtered through a small plug of SiO₂ to remove excess base (2:1 Hexanes:EtOAc) to give the crude arabinosyl phosphinite as a white solid. The filtered product was dried under high vacuum for 30 min. Under N₂ atm. and at rt the white solid was dissolved in anhydrous CH₂Cl₂ and stirred. To this stirring solution was added iodomethane (20.0 µL, 0.318 mmol) followed by a solution of 1,2,3,4-di-isopropylidine-D-galactopyranoside (19 mg, 0.075) in 0.5 mL anhydrous CH₂Cl₂. The reaction mixture was allowed to stir at rt for 3 d. before TLC indicated the reaction was complete. The reaction was then concentrated under reduced pressure, dissolved in EtOAc and worked up with 1x75mL sat. NaHCO₃, 1x 50 mL dH₂O, and 1x50 mL sat. NaCl solution. The organic layer was then dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified over SiO₂ (2:1 Hexanes:EtOAc) to give 36.1 mg of the title compound as a colorless oil in 60% yield (>99:1 α:β). ¹H, ¹³C, and HSQC NMR characterization data can be found in Appendix 11. ¹H NMR (500 MHz, CDCl₃) δ 7.54 (d, J = 7.2 Hz, 1H), 7.33 (m, 16H), 7.21 – 7.16 (m, 4H), 5.55 (d, J = 5.0 Hz, 1H), 4.89 (d, J = 10.6 Hz, 1H), 4.76 (d, J = 5.5 Hz, 2H), 4.74 – 4.69 (m, 1H), 4.66 – 4.58 (m, 5H), 4.54 (dd, J = 15.3, 9.6 Hz, 4H), 4.38 –
4.32 (m, 2H), 4.18 (dd, J = 7.9, 1.4 Hz, 2H), 4.08 – 4.02 (m, 2H), 4.02 – 3.90 (m, 3H),
3.87 – 3.78 (m, 6H), 3.74 (qd, J = 10.4, 6.4 Hz, 3H), 1.53 (s, 3H), 1.46 (s, 3H), 1.35 (s,
6H). $^{13}$C NMR (75 MHz, CDCl$_3$) 138.6, 138.5, 138.5, 138.4, 128.7, 128.3, 128.2, 128.1,
128.0, 127.9, 127.8, 127.6, 127.56, 127.5, 127.4, 109.5, 109.4, 108.8, 108.6, 102.4,
97.3, 96.4, 96.4, 81.9, 80.1, 77.5, 77.0, 76.6, 75.1, 74.9, 74.6, 73.3, 72.3, 72.1, 70.9, 70.7,
70.6, 69.1, 68.1, 65.4, 65.3, 29.7, 26.2, 26.0, 25.1, 24.9, 24.6, 24.4.

$^{1,2,3,4}$-di-O-isopropylidine galactopyranoside-(2,3,4,6-tetra-O-benzyl galactopyranoside). 71.0 mg (0.131 mmol) of 2,3,4,6-tetra-O-benzyl galactopyranoside (26) was evaporated 2x azeotropically from PhMe and then dried under high vacuum for 30 min. Under N$_2$ atm. at rt 26 was dissolved in anhydrous CH$_2$Cl$_2$ (7 mL) and stirred. To this stirring solution was added 1,8-Diazabicycloundec-7-ene (28.0 µL, 0.197 mmol) followed by chlorodiphenylphosphine (28.3 µL, 0.158 mmol) via microsyringe. This reaction was stirred for 35 minutes at rt before TLC indicated the reaction was complete. The reaction mixture was evaporated under reduced pressure and filtered through a small plug of SiO$_2$ to remove excess base (2:1 Hexanes:EtOAc) to give the crude arabinosyl phosphte as a white solid. The filtered product was dried under high vacuum for 30 min. Under N$_2$ atm. and at rt the white solid was dissolved in anhydrous CH$_2$Cl$_2$ and stirred. To this stirring solution was added iodomethane (16.0 µL, 0.263 mmol) followed by a solution of 1,2,3,4-di-isopropylidine-D-galactopyranoside (17.0 mg, 0.066 mmol) in 0.5 mL anhydrous CH$_2$Cl$_2$. The reaction mixture was allowed to stir at rt for 3 d. before TLC indicated the reaction was complete. The reaction was then concentrated under reduced pressure, dissolved in EtOAc and worked up with 1x75mL sat. NaHCO$_3$, 1x 50 mL
dH₂O, and 1x50 mL sat. NaCl solution. The organic layer was then dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified over SiO₂ (2:1 Hexanes:EtOAc) to give 36.1 mg of the title compound as a colorless oil in 80% yield (92:8 α:β): ¹H, ¹³C, and HSQC NMR characterization data can be found in Appendix 12. ¹H NMR (300 MHz, CD₂Cl₂) δ 7.58 – 7.39 (m, 8H), 7.35 – 7.01 (m, 12H), 6.99 – 6.91 (m, 1H), 5.40 (dd, J = 8.3, 3.5 Hz, 1H), 4.86 (d, J = 11.0 Hz, 1H), 4.80 – 4.73 (m, 2H), 4.72 – 4.68 (m, 1H), 4.66 – 4.54 (m, 3H), 4.48 (d, J = 26.3 Hz, 1H), 4.41 – 4.36 (m, 1H), 4.32 (d, J = 15.4 Hz, 1H), 3.98 – 3.88 (m, 1H), 3.64 – 3.45 (m, 6H). ¹³C NMR (75 MHz, CD₂Cl₂) δ 142.0, 141.7, 141.6, 141.4, 139.1, 138.8, 138.5, 138.4, 138.3, 138.3, 131.5, 131.2, 130.5, 130.2, 130.1, 129.8, 129.8, 129.8, 129.1, 129.0, 128.4, 128.3, 128.3, 128.2, 128.1, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 127.4, 103.4, 103.2, 98.6, 98.3, 84.6, 81.6, 80.9, 80.8, 77.7, 77.5, 75.5, 75.4, 75.3, 74.9, 74.8, 74.8, 73.4, 73.1, 72.7, 71.4, 68.7, 68.4, 54.1, 53.8, 53.4, 53.1, 52.7.

Chapter 4: Conclusions

4.1: Cyclic phosphonium anhydrides as reagents for dehydrative glycosylations

A library of cyclic phosphonium anhydrides have been prepared from their corresponding bis-phosphine oxides and evaluated for their potential as dehydrating agents in a series of dehydrative glycosylations. Of these cyclic phosphoniums, 1,1,3,3-diphenylphenyl-2-oxa-1,3-phosphepane ditriflate (3) consistently gave the highest glycosylation yields and was the easiest to prepare from the corresponding bis-oxide.
Optimizations with cyclic phosphonium 3 and a number of conditions for dehydrative glycosylations (solvent, temperature, reactions times) eventually afforded a standard protocol for dehydrative glycosylation in good yields and selectivities.

In order to better understand the mechanism of this reaction and explain the differences in this methodology compared to similar dehydrative glycosylation reactions with Hendrickson’s POP reagent, a series of mechanistic studies were performed. Cyclic phosphonium 3 reacts readily with glycosyl donors (e.g. 2,3,4,6-tetra-O-benzyl-D-glucose) to form the presumed intermediate 10 (Scheme 2.1). The overall stability of this intermediate would explain the lack of observed homocoupling product between two molecules of the glycosyl donor in this dehydrative glycosylation methodology, a common problem with similar methods. Support for the proposed mechanism comes from a series of 1D and 2D experiments including long range $^1$H-$^{31}$P coupling observed between the anomeric proton and the nearby phosphorus in the proposed intermediate 10.

4.2: Glycosyl phosphinites yield highly $\alpha$-selective glycosylation products

Glycosyl phosphinites represent a powerful tool for highly $\alpha$-selective glycosylations via in situ anomerization of the corresponding anomeric iodide. In this thesis a library of glycosyl phosphinites was prepared in mild conditions (DBU) and evaluated in glycosylation reactions promoted by the presence of iodomethane and a suitable glycosyl acceptor. Glycosyl phosphinites prepared from chlorodiphenylphosphine were ultimately chosen as the model system to test the scope of
this method. Various glycosyl phosphinites were demonstrated with a variety of glycosyl donors and acceptors to give highly $\alpha$-selective glycosylations in good yields (Table 3.3).

To gain a better understanding of the high $\alpha$-selectivity of these reactions a number of $^1$H and $^{31}$P NMR experiments were performed to observe the reaction progress from start to completion. The presumed mechanism (Scheme 3.1) is supported by $^{31}$P experiments showing addition of the methyl electrophile to the glycosyl phosphinite, a reaction that proceeds relatively rapidly. Subsequent addition of the acceptor and the corresponding glycosylation proceed slowly, supporting that the less prevalent but highly reactive $\beta$-iodide affords the product in high $\alpha$-selectivity.

References


Appendix

Appendix 1: $^1$H, $^{13}$C, and $^{31}$P NMR spectra for 1,1,3,3-diphenylphenyl-2-oxa-1,3-phosphepane ditriflate.

Appendix 2: $^1$H, $^{13}$C, and HSQC NMR spectra for cyclohexyl 2,3,4-tri-O-benzyl-6-deoxy-D-fucopyranose.

Appendix 3: $^1$H, $^{13}$C, and HSQC NMR spectra for cyclohexyl 2,3-bis-O-(phenylmethyl)-4,6-O-[(R)-phenylmethylene]-D-mannopyranoside.

Appendix 4: $^1$H, $^{13}$C, and HSQC NMR spectra for phenyl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside.

Appendix 5: $^1$H, $^{13}$C, and HSQC NMR spectra for methyl 6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-2,3,4-tri-O-benzyl-D-glucopyranoside.

Appendix 6: $^1$H, $^{13}$C, and HSQC NMR spectra for (3β)-cholest-5-en-3-ol-2,3,4,6-tetra-O-benzyl-D-glucopyranoside.

Appendix 7: $^{31}$P, $^{31}$P selective decoupling, $^{31}$P broadband decoupling, and $^1$H-$^{31}$P HMBC NMR spectra for dehydrative glycosylation mechanistic experiments.

Appendix 8: NOESY NMR spectra for dehydrative glycosylation mechanistic experiments with acceptor 2,2,2-trifluoroethanol.

Appendix 9: $^1$H, $^{31}$P, $^{13}$C, and HSQC NMR spectra for 2,3,4,6-tetra-O-benzyl-D-glycosyl phosphinite.

Appendix 10: $^1$H, $^{13}$C, and HSQC NMR data for 1,2,3,4-di-O-isopropylidine galactopyranoside-(2-O-benzyl-3,4-O-di-benzoyl-α-D-arabinopyranoside).
Appendix 11: $^1$H, $^{13}$C, and HSQC NMR data for 1,2,3,4-di-O-isopropylidene galactopyranoside-(2,3,4,6-tetra-O-benzyl-D-mannopyranoside).

Appendix 12: $^1$H, $^{13}$C, and HSQC NMR data for 1,2,3,4-di-O-isopropylidene-D-galactopyranoside-(2,3,4,6-tetra-O-benzyl-D-galactopyranoside).
Appendix 1.1: $^1$H NMR spectra for 1,1,3,3-diphenylphenyl-2-oxa-1,3-phosphepane ditriflate (8).
Appendix 1.2: $^{13}$C NMR spectra for 1,1,3,3-diphenylphenyl-2-oxa-1,3-phosphepane ditriflate.
Appendix 1.3: $^{31}$P NMR spectra for 1,1,3,3-diphenylphenyl-2-oxa-1,3-phosphepane ditriflate.
Appendix 2: $^1$H, $^{13}$C, and HSQC NMR spectra for cyclohexyl 2,3,4-tri-O-benzyl-6-deoxy-D-fucopyranose.

Appendix 2.1: $^1$H NMR spectra for cyclohexyl 2,3,4-tri-O-benzyl-6-deoxy-D-fucopyranose.
Appendix 2.2: $^{13}$C NMR spectra for cyclohexyl 2,3,4-tri-O-benzyl-6-deoxy-D-fucopyranose.
Appendix 2.3: HSQC NMR spectra for cyclohexyl 2,3,4-tri-\(\text{O}\)-benzyl-6-deoxy-D-fucopyranose.
Appendix 3: $^1$H, $^{13}$C, and HSQC NMR spectra for cyclohexyl 2,3-bis-$O$-(phenylmethyl)-4,6-$O$-[(R)-phenylmethylene]-D-mannopyranoside.

Appendix 3.1: $^1$H NMR spectra for cyclohexyl 2,3-bis-$O$-(phenylmethyl)-4,6-$O$-[(R)-phenylmethylene]-D-mannopyranoside.
**Appendix 3.2:** $^{13}$C NMR spectra for cyclohexyl 2,3-bis-\(O\)-(phenylmethyl)-4,6-\(O\)-[(\(R\))-phenylmethylene]-D-mannopyranoside.
Appendix 3.3: HSQC NMR spectra for cyclohexyl cyclohexyl 2,3-bis-\(O\)-(phenylmethyl)-4,6-\(O\)-[(\(R\))-phenylmethylene]-D-mannopyranoside.
Appendix 4: $^1$H, and HSQC NMR spectra for phenyl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside.

Appendix 4.1: $^1$H NMR spectra for phenyl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside.
Appendix 4.3: HSQC NMR spectra for prepared phenyl 2,3,4,6-tetra-\(O\)-benzyl-D-glucopyranoside.
Appendix 5: $^1$H, $^{13}$C, and HSQC NMR spectra for methyl 6-O-(2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranosyl)-2,3,4-tri-O-benzyl-D-glucopyranoside.

Appendix 5.1: $^1$H NMR spectra for methyl 6-O-(2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranosyl)-2,3,4-tri-O-benzyl-D-glucopyranoside.
Appendix 5.2: $^{13}$C NMR spectra for methyl 6-O-(2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranosyl)-2,3,4-tri-O-benzyl-D-glucopyranoside.
**Appendix 5.3:** HSQC NMR spectra for methyl 6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-2,3,4-tri-O-benzyl-D-glucopyranoside.
Appendix 6: $^1$H, $^{13}$C, and HSQC NMR spectra for (3β)-cholest-5-en-3-ol-2,3,4,6-tetra-$O$-benzyl-D-glucopyranoside.

Appendix 6.1: $^1$H NMR spectra for (3β)-cholest-5-en-3-ol-2,3,4,6-tetra-$O$-benzyl-D-glucopyranoside.
Appendix 6.2: $^{13}$C NMR spectra for (3β)-cholest-5-en-3-ol-2,3,4,6-tetra-O-benzyl-D-glucopyranoside.
**Appendix 6.3:** HSQC NMR spectra for (3β)-cholest-5-en-3-ol-2,3,4,6-tetra-O-benzyl-D-glucopyranoside.
Appendix 7.1: $^{31}$P NMR spectra for dehydrative glycosylation mechanistic experiments.
Appendix 7.2: $^1$H NMR with $^{31}$P selective decoupling NMR spectra for dehydrative glycosylation mechanistic experiments.

Appendix 7.2.1: $^1$H NMR without $^{31}$P decoupling.
Appendix 7.2.1: $^{31}$P selective decoupling at 73.2 ppm
Appendix 7.2.2: $^{31}$P selective decoupling at 73.7 ppm
Appendix 7.3: $^{31}$P broadband decoupling NMR spectra for dehydrative glycosylation mechanistic experiments.
Appendix 7.4: $^1$H-$^{31}$P HMBC NMR spectra for dehydrative glycosylation mechanistic experiments.
Appendix 8: NOESY NMR spectra for dehydrative glycosylation mechanistic experiments with 2,2,2-trifluoroethanol.
**Appendix 9:** $^1$H, $^{31}$P, $^{13}$C, and HSQC NMR spectra for 2,3,4,6-tetra-$O$-benzyl-D-glycosyl diphenylphosphinite.

**Appendix 9.1:** $^1$H NMR spectra for 2,3,4,6-tetra-$O$-benzyl-D-glycosyl diphenylphosphinite.

benzyl glucose glycosyl

$^1$H NMR (300MHz)
Appendix 9.2: $^{31}$P NMR spectra for 2,3,4,6-tetra-$O$-benzyl-D-glycosyl diphenylphosphinite.
Appendix 9.3: $^{13}$C NMR spectra for 2,3,4,6-tetra-O-benzyl-D-glycosyl diphenylphosphinite.

$^{13}$C NMR (75MHz)
Appendix 9.4: Decoupled HSQC NMR spectra for 2,3,4,6-tetra-O-benzyl-D-glycosyl diphenylphosphinite.
Appendix 9.5: Coupled HSQC NMR spectra for 2,3,4,6-tetra-O-benzyl-D-glycosyl diphenylphosphinite.
Appendix 10: $^1$H, $^{13}$C, and HSQC NMR data for 1,2,3,4-di-O-isopropylidene-D-galactopyranoside-(2-O-benzyl-3,4-O-di-benzoyl-α-D-arabinopyranoside).

Appendix 10.1: $^1$H NMR data for 1,2,3,4-di-O-isopropylidene-D-galactopyranoside-(2-O-benzyl-3,4-O-di-benzoyl-α-D-arabinopyranoside).

$^1$H NMR (500MHz)
Appendix 10.2: $^{13}$C NMR data for 1,2,3,4-di-$O$-isopropylidene-D-galactopyranoside-(2-$O$-benzyl-3,4-$O$-di-benzoyl-$\alpha$-D-arabinopyranoside).

$^{13}$C NMR (75MHz)
Appendix 10.3: Decoupled HSQC NMR data for 1,2,3,4-di-O-isopropylidene-D-galactopyranoside-(2-O-benzyl-3,4-O-di-benzoyl-α-D-arabinopyranoside).
Appendix 10.4: Coupled HSQC NMR data for 1,2,3,4-di-O-isopropylidene-D-galactopyranoside-(2-O-benzyl-3,4-O-di-benzoyl-α-D-arabinopyranoside).
Appendix 11: $^1$H, $^{13}$C, and HSQC NMR data for 1,2,3,4-di-O-isopropylidene-D-galactopyranoside-(2,3,4,6-tetra-O-benzyl-D-mannopyranoside).

Appendix 11.1: $^1$H NMR data for 1,2,3,4-di-O-isopropylidene-D-galactopyranoside-(2,3,4,6-tetra-O-benzyl-D-mannopyranoside).

$^1$H NMR 500MHz)
Appendix 11.2: $^{13}$C NMR data for 1,2,3,4-di-$O$-isopropylidene-D-galactopyranoside-(2,3,4,6-tetra-$O$-benzyl-D-mannopyranoside).

$^{13}$C NMR 75MHz)
Appendix 11.3: Decoupled HSQC NMR data for 1,2,3,4-di-O-isopropylidene-D-galactopyranoside-(2,3,4,6-tetra-O-benzyl-D-mannopyranoside).
Appendix 12: \(^1\)H, \(^{13}\)C, and HSQC NMR data for 1,2,3,4-di-\(O\)-isopropylidene-D-galactopyranoside-(2,3,4,6-tetra-\(O\)-benzyl-D-galactopyranoside).

Appendix 12.1: \(^1\)H NMR data for 1,2,3,4-di-\(O\)-isopropylidene-D-galactopyranoside-(2,3,4,6-tetra-\(O\)-benzyl-D-galactopyranoside).

\(^1\)H NMR (500MHz)
**Appendix 12.2:** $^{13}$C NMR data for 1,2,3,4-di-$O$-isopropylidene-D-galactopyranoside-(2,3,4,6-teta-$O$-benzyl-D-galactopyranoside).
Appendix 12.3: Decoupled HSQC NMR data for 1,2,3,4-di-\textit{O}-isopropylidene-D-galactopyranoside-(2,3,4,6-tetra-\textit{O}-benzyl-D-galactopyranoside).
Appendix 12.4: Coupled HSQC NMR data for 1,2,3,4-di-O-isopropylidene-D-galactopyranoside-(2,3,4,6-tetra-O-benzyl-D-galactopyranoside).