This chapter focuses on elucidating the origin of the observed rate difference in the oxidation of glycosides containing a vicinal cis diol or vicinal trans diols. Furthermore, the origin of the regioselectivity is investigated in more detail and unravelled. From competition experiments with methyl-α-D-glucoside, it can be concluded that the oxidation rate is retarded by chelation to a trans-axial diol, but not by preferential chelation to either a cis or a trans-equatorial diol. Furthermore, the rate is influenced by the presence of axial substituents adjacent to the C3 position. Hyperconjugation between these axial substituents and the adjacent C3-H antibonding orbital weakens the C-H bond thereby facilitating oxidation. Hyperconjugation by an axial C-H bond, such as in glucosides, is more pronounced than hyperconjugation by an axial C-O bond such as in galactose or mannose and therefore a difference in rate is observed. From the scope of the synthesized glycosides it is concluded that the anomeric substituent plays neither a role in the rate nor in the selectivity. On the other hand, oxidizing the carba analogue of 1-deoxy-glucose revealed that the endocyclic oxygen is essential for the observed C3 selectivity. The ring oxygen seems to polarize the adjacent carbons, lowering their electron density. The C3 position, being the furthest away, is the least polarized and therefore least deactivated. This indicates that it is not the catalyst but the substrate that is steering the selectivity, in other words the reaction is substrate-controlled. To verify this, different oxidation methods were studied showing that also oxidation with bromine and a photoredox reaction give selective oxidation of the C3-OH.
5.1 Introduction

The late-stage functionalization of advanced synthetic intermediates, drug (candidates) and natural products has gained considerable attention throughout the last few years.\(^1\) Methods that enable direct functionalization without the need for pre-installed synthetic handles are among the most desired methods. However, when it comes to the application of these methods on complex molecules, a complete understanding and a predictable selectivity of the applied method is crucial. As stated, one way to achieve regioselective modification is by means of directing or activating groups and this approach has shown to work quite effectively.\(^2\) However, when such a group is not present in the final target molecule, additional steps are required to remove the introduced directing group afterwards. During recent years, efforts have been made to develop novel regioselective methods that exploit the inherent subtle reactivity differences within a given substrate, rather than relying on the use of directing groups.\(^3,4\) If successful, these methods are highly effective, but predicting the regioselectivity is not straightforward. To be able to successfully apply these novel methods to complex molecules, a model for the regioselectivity is required. This can be done via careful investigation of the relation between reactivity and selectivity of a series of differently configured small molecules. These studies will ultimately lead to a working model which can be applied to reliably predict the selectivity in more complex substrates. This strategy has been used for the late stage functionalization of complex molecules by un-directed C-H activation. The group of Christina White developed a working model for their regioselective C-H activation/oxidation reaction.\(^5-7\) Based on the observation that iron catalyst 1 preferentially oxidizes electron rich C-H bonds that are not sterically congested, they predicted that C2 in terpenoid 2, which is (1) the furthest away from the carbonyl moiety and (2) sterically less hindered, would be activated preferentially. Indeed, oxidation of C2 position is the major product, with oxidation of C3 as a side product (Scheme 1).

![Scheme 1](image)

Scheme 1. Predictable regioselective C-H activation/oxidation.
In a similar fashion as C-H activation, regioselective alcohol oxidation enables late-stage functionalization of polyols. It has been shown by the group of Waymouth that cationic palladium catalyst 4 selectively oxidizes secondary alcohols over primary alcohols, as in glycerol. Furthermore, Waymouth showed that secondary alcohols that are part of a vicinal diol oxidize with an increased rate. We applied palladium catalyst 4 to the regioselective oxidation of glucosides, in which the C3-OH is selectively oxidized (see Chapter 2). Waymouth recently expanded the scope of the regioselective oxidation of glycosides, showing that also substrates bearing axial functionalities, such as rhamnopyranoside 5, undergo selective oxidation of the equatorial hydroxyl group at C3 (Scheme 2). This is in contrast to their previously reported oxidation of trans-cyclohexanediols, such as 7, in which the axial alcohol is preferentially oxidized (Scheme 2).

Factors that govern the selectivity of this reaction have been studied in some detail in this thesis. In chapters 2 and 4, it was shown that Pd-catalysed oxidation selectively occurs at the terminal C3-position of oligosaccharides due to steric hindrance at the other C3-positions. We also investigated the effect of the substitution pattern in glycosides and showed that the C2-OH, C4-OH, C6-OH or the exocyclic CH₂OH can be removed or substituted without losing any selectivity. Introducing different functionalities such as an azide or esters does also not affect the C3-selectivity. The only side reactions observed are those resulting from overoxidation as described in Chapter 4. The substitution pattern does, however, influence the reactivity. Glycosides that bear an axial substituent, such as galactosides and mannoses, show a decreased rate in the oxidation compared to glucosides. Unfortunately, the working model for the palladium catalysed regioselective oxidation is by no means complete and therefore has not yet reached the desired level of predictability. To successfully apply this oxidation method on complex (natural) oligosaccharides, a full understanding of the reactivity in monosaccharides is required.
understanding will improve the accuracy of the model and will thus enable predicting where and how efficient oxidation will occur. It is therefore essential that the following questions are addressed: How does the substitution pattern affect the oxidation rate and why does the catalyst oxidize selectively the C3-OH, independently of the glycoside substrate?

Our hypothesis was that the difference in reactivity in glycosides containing an axial hydroxyl group is due to an unfavourable chelation of the catalyst with cis diols or due to a change in electron density. In terms of the regioselectivity of this oxidation method, the role of just two functionalities had not yet been investigated, namely the anomeric position and the endocyclic oxygen.

To answer these questions and prove the hypothesis, a panel of glycopyranosides was synthesized and studied in individual oxidation reactions as well as in competition experiments. As in Chapter 4, these experiments were analysed by qNMR to both monitor the conversion to the product and characterize the product in one operation.

5.2 Results and discussion

To investigate the oxidation of glycosides bearing an axial hydroxyl group, a distinction needs to be made between chelation effects and electronic effects. To single out the effect of chelation, methyl 2-deoxy-α-D-galactoside (11) was prepared starting from tri-O-acetyl-D-galactal (9). Reaction with methanol in presence of triphenylphosphonium hydrogen bromide yielded the desired α-acetal 10. Deprotection with sodium methoxide resulted in methyl 2-deoxy-α-D-galactoside (11) (Scheme 3).

Based on the oxidation of methyl 2-deoxy-α-D-glucoside (13) we already know that when there is only a trans diol on C3 and C4 the oxidation proceeds without any rate difference compared to the benchmark compound methyl α-D-glucoside.9,13 In the same manner, methyl 2-deoxy-α-D-galactoside (11) was used to study the effect of a cis diol on the oxidation rate and to compare this rate with the reaction rate of methyl galactoside. If chelation with the cis diol is unfavourable, this effect would be more pronounced in the case of methyl 2-
deoxy-α-D-galactoside (11), which lacks the “more favourable” trans diol (see Scheme 4).


Initial attempts to oxidize methyl 2-deoxy-α-D-galactoside (11) under the standard conditions (3 equiv benzoquinone, 2.5 mol% Pd-cat, 0.3 M DMSO-d6) resulted in selective oxidation at the C3 position. Next to the expected 3-keto product 14, 3-4-diketone 18 was also observed (Scheme 5). When overoxidation was observed in other substrates, this resulted in the formation of a rearranged product (see Chapter 4). In this case, due to the lack of a C2-OH, overoxidation can only occur at the C4 position and therefore diketone 18 is observed, rather than the rearranged product (for the mechanism see Scheme 5). The observation of overoxidation is not too surprising since oxidation of methyl β-D-galactoside also results in overoxidation.

Scheme 5. Mechanism of the overoxidation of methyl 2-deoxy-α-D-galactoside.

To determine whether there is a rate difference between a glycoside bearing exclusively a cis diol and a glycoside that has both a cis and trans diol, a one-to-one mixture of methyl 2-deoxy-α-D-galactoside 11 and methyl β-D-galactoside
was oxidized using half an equivalent of benzoquinone with respect to the total amount of glycoside. Both galactosides have the tendency to give overoxidation and therefore consumption of the starting material was chosen as the indicator of the oxidation rate. After 40 min only a small rate difference was observed in preference of methyl β-D-galactoside (starting material ratio methyl β-D-galactoside : methyl 2-deoxy-α-D-galactoside (11) = 2 : 1, for comparison of the 13C-NMR spectra see Figure 1). Although a two-fold difference in rate was observed, a larger rate difference was to be expected if chelation played an important role. It is therefore unlikely that the difference in oxidation rates is solely caused by unfavorable chelation to the cis diol.

![Figure 1](image)

**Figure 1.** Zoom of the competition experiment of methyl β-D-galactoside/methyl 2-deoxy-α-D-galactoside. ∆ = methyl α-D-2-deoxy-galactoside • = methyl-β-D-galactoside □ = 3-keto-2-deoxy-galactoside ◊ = 3-keto-galactoside.

To unambiguously demonstrate that chelation to a cis-diol is not affecting the rate, methyl α-D-alloside (20) was also studied in the oxidation reaction. If chelation to a cis diol indeed does affect the rate of the reaction, methyl α-D-alloside (20), bearing only cis diols, should not oxidize as fast as methyl α-D-glucoside (19). For these studies, methyl α-D-alloside (20) was prepared as reported previously by our group.° Oxidizing methyl α-D-glucoside (19) with the palladium catalysed oxidation reaction followed by direct reduction with sodium borohydride yielded the epimerized product 20 (Scheme 6).
Oxidizing methyl α-D-alloside (20) under the standard conditions resulted in the expected oxidation at the C3 position in 90% yield based on NMR. To study the differences in efficiency of chelation with either cis or trans diols a competition experiment between methyl α-D-glucoside (19) and methyl α-D-alloside (20) was performed. Because both glycosides yield the same oxidation product, the consumption of starting material was used to monitor the rate of the reaction. Again, only a small rate difference was observed (starting material ratio methyl α-D-glucoside (19) : methyl α-D-alloside (20) = 1.8 : 1). These results once again indicate that chelation only plays a small role in the observed rate difference. It is likely that this rate difference is caused to a large extent due to a change in electronic nature when switching from an equatorial hydroxyl to an axial one.

Finally, to determine whether chelation plays a role at all, the anhydroglycosides 21 and 22 were oxidized (Scheme 7 + 8). 1,6-anhydro-β-D-glucose (21) contains only trans di-axial diols, a feature not studied so far. Oxidizing 1,6-anhydro-β-D-glucose (21) under the standard conditions resulted in the expected oxidation at the C3 position. Next to the C3-keto, diketones 27 and 28 were observed. Due to the absence of the primary alcohol, these are most likely formed via nucleophilic attack of hydroquinone on the formed ketone, similar as in the case of xylose in Chapter 4. Further oxidation of the resulting diol yields a ketone on either the C2 or the C4 position (Scheme 7). Due to the bicyclic nature of the molecule, the rearrangement is not observed and upon analysis the diketone is observed rather than the hemiacetal. To study the rate difference between trans di-equatorial and trans di-axial diols, a competition reaction was performed between 1,6-anhydro-β-D-glucose (21) and methyl α-D-glucoside (19). In this case, a more pronounced effect was observed favouring the oxidation of methyl α-D-glucoside (product ratio methyl 3-keto-α-D-glucoside (29) : 1,6-anhydro-3-keto-β-D-glucose (23) = 4 : 1). These results indicate that chelation with trans di-axial diol does indeed affect the oxidation rate. To verify that this rate difference results from the trans di-axial diol and not from the bridging ring in the anhydro sugar, 1,6-anhydro-α-D-galactose (22) was also oxidized. Bearing both a trans di-axial diol (C2-C3) and a cis diol (C3-C4) we
expected to observe a rate difference comparable to that of methyl α-D-alloside (20). This was indeed the case, the competition reaction between methyl α-D-glucoside (19) and 1,6-anhydro-β-D-galactose (22) showed only a small rate difference (product ratio methyl 3-keto-α-D-glucoside (29) : 1,6-anhydro-3-keto-β-D-galactose (30) = 1.5 : 1 (Scheme 8). These results indicate that most likely cis or trans-equatorial diols do not affect the rate significantly based on chelation, but a trans di-axial diol does.

Since the difference between the reactivity of cis or trans-equatorial diols is only minimal, the attention was focused next on the stereo-electronic effects of an axial alcohol compared to an equatorial alcohol on the oxidation reaction. To single out this effect, we prepared both 4-fluoro-galactoside 31 and 4-fluoro-glucoside 32. With these fluoride derivatives, the importance of the orientation of this electron withdrawing group can be probed, while excluding the chelation effect (both substrates bear a trans-equatorial diol and the fluoride does not take part in chelation). To obtain axial fluoride 31, methyl 2,3,6-tri-O-benzyl-D-glucopyranoside (33, for preparation see Chapter 4) was converted into its triflate followed by nucleophilic substitution with fluoride to yield protected 35. Removal of the benzyl groups by hydrogenolysis yielded 4-fluoro-galactoside 31 (Scheme 9).
For the synthesis of the equatorial fluoride 32, a similar route was employed. Commercially available methyl 2,3,6-tri-O-benzoyl-α-D-galactopyranoside (36) was reacted with trifluoromethansulfonic anhydride to yield triflate 37. Nucleophilic substitution with fluoride yields protected 38. Removal of the benzoyl groups with sodium methoxide yielded the equatorial fluoride 32 (Scheme 10). The yield for the 4-fluoro-glucoside 32 was significant lower (37% over two steps) than the yield for 31, most likely due to the instability of the axial triflate, which is prone to elimination.

With the 4-fluoro-glycosides in hand, their behaviour in the palladium catalysed oxidation reaction was studied. Oxidation of 4-fluoro-glucoside 32 (1 equiv. benzoquinone, 2.5 mol% Pd-cat, 0.3 M DMSO-\textit{d}_6) resulted in a noticeable difference compared to other glucosides substrates. While the majority of glucosides is fully converted within 30 minutes, 4-fluoro-glucoside 32 showed only \~10% of oxidized product in the same reaction time. Clearly, the electronegative fluoride substituent deactivates the substrate significantly. Leaving the reaction overnight resulted in nearly full consumption of
benzoquinone but in incomplete conversion of starting material. Besides the expected 3-keto product, the rearranged product was also observed, which explains the large consumption of benzoquinone. This rearrangement is unique in that it has not yet been observed for glycosides with the glucose configuration. Formation of this side product can be explained by looking at the dipole moments of cyclic α-fluoro ketones. The equatorial fluoride directly next to the formed ketone has its dipole aligned with that ketone (Scheme 11, structure \(\text{39-C}_1\)). This destabilizes this conformation, forcing it to ring flip. Upon ring flip, the equatorial fluoride adopts an axial orientation (with just a minimal energy penalty due to the small size of F) thereby minimizing the dipole moment (Scheme 11, structure \(\text{39-C}_4\)). As consequence of the ring flip, the substrate becomes predisposed to intramolecular lactol formation and concomitant overoxidation and rearrangement.

The oxidation of 4-fluoro-galactoside 31 under the same conditions was studied next, to evaluate the difference between an equatorial or axial electron withdrawing substituent. Whereas 32 with an equatorial fluoride was amenable to oxidation, 31 with an axial fluoride didn’t show any conversion after 5 h. To assure that the lack of oxidation was not caused by impurities in 31 that inhibited the catalyst, a competition experiment between 4-fluoro-galactoside 31 and methyl α-D-glucoside (19) was performed. Impurities should not only inhibit the oxidation of 31, but also hamper the oxidation of 19. Methyl α-D-glucoside (19) was cleanly and efficiently oxidized within 30 min in the presence of 4-fluoro-galactoside 31 and therefore it can be concluded that 4-fluoro-galactoside 31 is less reactive than 4-fluoro-glucoside 32. This corroborates the results with galactosides and glucosides and underlines the effect of the orientation of the electron withdrawing group on the oxidation rate. We argue that the axial substituent on C2 or C4 can give hyperconjugation onto the antibonding orbital of the C3-H bond. This results in the elongation and weakening of the C-H bond which in turn facilitates β-hydride elimination in the oxidation reaction. The higher the efficiency of the hyperconjugation by the axial substituent next to the C3-H, the faster the oxidation proceeds, and a vicinal C-H bond is more involved in hyperconjugation than a C-OH, which in turn is more effective than a C-F bond. This trend is also clearly reflected in the oxidation experiments in which
the rate of oxidation is as: glucoside > galactoside > 4-fluoro-galactosides (Figure 2).

Figure 2. Hyperconjugation of axial substituents in the adjacent C-H antibonding orbital.

With this hypothesis, it also becomes apparent why the substrates methyl α-D-alloside (20) and 1,6-anhydro-β-D-galactose (22) show an oxidation rate comparable to methyl α-D-glucoside (19). For alloside 20, there is no overlap of the antibonding orbital of the (now equatorial positioned) C-H bond with one of the adjacent hydroxyl’s. However, the equatorial C-H antibonding orbital does have an overlap with the C1-C2 and the C4-C5 bond. This hyperconjugation results in weakening of the C-H bond, thereby activating it as in the case of methyl α-D-glucoside. For 1,6-anhydro-β-D-galactoside (22), the equatorial C3-H is also overlapping with the C1-C2 and the C4-C5 bond. This shows that cis or trans-di-equatorial diols do not affect the rate due to chelation, but rather that the rate is controlled by these electronic effects (Scheme 12).


Having established the importance of electronic effects on the rate of oxidation, the attention was focused on unravelling the factors that contribute to the C3-selectivity. Of the functional groups present in pyranosides, the effect of two groups, the substitution of the anomer and the ring oxygen had not yet been probed.

Next, we decided to study the effect of the substituent at the anomeric position using 1,2-dideoxy-D-glucopyranose (42), since previous studies already had demonstrated that the C2-OH is not required for selective oxidation. To this end, D-glucal (41) was hydrogenated over Pd/C to yield compound 42 (Scheme 13).
When subjecting 1,2-dideoxy-\(\alpha\)-glucopyranose (42) to the oxidation reaction, both the 3-keto product and the 3,4-diketo product were observed. This once again validates the hypothesis that the removal of substituents results in a smaller energy difference between the different ring conformations. This in turn facilitates intramolecular lactol formation and subsequent overoxidation. As is the case for other substrates that are prone to overoxidation (see Chapter 4), lowering the benzoquinone loading to 1 equiv. effectively prevented further reactions yielding the 3-keto product in 74% selectivity. These results demonstrate that the anomeric substituent does not play a role in the selectivity at all. Furthermore, as shown before, the orientation of that substituent (when not involved in chelation) is not relevant for the regioselectivity as well.\(^9\)

Only one functionality remained which could influence the selectivity, namely the ring oxygen. By substituting the (electron withdrawing) endocyclic oxygen for a methylene unit, its effect on the selectivity and rate of the oxidation reaction could be studied. The carba analogue of 1-deoxy-glucose was kindly provided by Dr. J.D.C. Codee from the University of Leiden. Oxidizing carbasugar 43 with 1 equiv. of benzoquinone resulted in full conversion of the starting material with the formation of three products. Careful NMR analysis showed that these products were the result of an unselective oxidation of the 3 secondary hydroxy groups. The three products were formed in a 1 : 2 : 1 ratio (C2 : C3 : C4 oxidation) (Figure 3). Clearly, the regioselectivity of the oxidation reaction in pyranosides depends on the ring oxygen. We argue that the endocyclic oxygen has a polarizing effect on the ring carbons, either through bond, through space or both. As a consequence, the adjacent positions are less electron rich and therefore deactivated towards the \(\beta\)-hydride elimination. C3, being the furthest away from the ring oxygen, is least affected and thus also least deactivated (Figure 4). According to this hypothesis, in principal each hydroxyl group in a given glycoside is deactivated towards \(\beta\)-hydride elimination and all pyranosides should therefore be less reactive than their corresponding carbasugars. To test this, methyl \(\alpha\)-D-glucoside (19) and carbasugar 43 were oxidized in a competition reaction. Carbacyle 38 was oxidized preferentially over methyl \(\alpha\)-D-glucoside (remaining starting material ratio methyl \(\alpha\)-D-glucoside (19) : carbasugar (43) = 4 : 1). Indicating that the ring oxygen is indeed
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deactivating the system towards the oxidation reaction and also steering the selectivity.

Understanding now the origin of the selectivity and the connected rate difference, we were also interested to see whether there would be a rate difference between cyclic and linear polyols. Here one could expect that the conformational freedom in a linear polyol could affect the rate of oxidation. By performing a competition reaction between the linear substrate glycerol and the “deactivated” methyl α-D-glucoside the effect on the oxidation rate can be studied. If the conformational freedom in glycerol would affect the rate of oxidation.

![Figure 3](image)

**Figure 3.** Detail of the of ¹H-NMR spectrum of the oxidation of 43.

![Figure 4](image)

**Figure 4.** Effect of the ring oxygen on polarization.

Most deactivated

Most polarized

Least polarized

Least deactivated
oxidation, a comparable rate to the “deactivated” methyl α-D-glucoside could be expected. Oxidizing a mixture of methyl α-D-glucoside (19) and glycerol indeed resulted in a mixture of both oxidized compounds (product ratio methyl 3-keto-α-D-glucoside: dihydroxyacetone = 1.3 : 1). Knowing that the cyclic counterpart of glycerol, carboxylic 43, shows an increased rate of oxidation compared to methyl α-D-glucoside, the conclusion can be drawn that linear substrates oxidizes with a lower rate compared to their cyclic counterparts as they show a comparable rate to the (deactivated) glucoside.

Summarizing the results obtained throughout this thesis and the work previously published by the Waymouth group and us, the following rules can be formulated as a working model for the regioselectivity and reactivity.

1) In terms of oxidation rate:
   a. secondary alcohols of a vicinal diol > secondary alcohols > primary alcohols.
   b. Cyclic vicinal diol > linear vicinal diol

2) The ring oxygen in glycosides dictates the regioselectivity, the position furthest away is most electron rich and therefore preferentially oxidized.

3) Hyperconjugation into the antibonding orbital of the C-H results in weakening of that C-H bond which facilitates oxidation.

4) Changes in the magnitude of hyperconjugation results in observed rate differences between glycosides. Hyperconjugation of a C-H > C-OH > C-F bond in weakening the adjacent C-H bond towards oxidation.

5) Trans di-axial diols retard the rate of oxidation based on unfavourable chelation with the catalytic system.

6) Steric hindrance around the alcohol slows down the rate of oxidation.

For this model, it is important to note that these rules are applicable for oxidations in DMSO at room temperature. However, based on the results reported by Waymouth, it seems that this model also translates to other solvents and temperatures. One should just always take into account that elevated temperatures can give rise to more side product formation, such as the small amounts of C4-keto product observed in the NMR study done by Waymouth (performed in CD3CN : D2O 10:1 at 50 °C).12

First of all, these rules can now be used to understand in retrospect the results previously obtained. In Chapter 3, we described for the first time the overoxidation/rearrangement reaction. The oxidation at C1 in β-glucose may seem counter-intuitive considering the deactivation via the electron withdrawing effect of the ring oxygen (Figure 4). The C1 position should be the most deactivated, which is the case for α-glucose in which no oxidation was observed at the C1 position. However, in the case of β-glucose an equal rate of oxidation for the C3 or C1 position was observed. Here, hyperconjugation of the ring-
oxygen should also be taken into account. For β-glucose, in which the anomeric hydrogen is in the axial position, it is possible for the ring oxygen to give hyperconjugation into the antibonding C-H orbital, just like in the case of the anomeric effect (Figure 5, structure 45). This results in an elongated and weaker C-H bond and therefore the required β-hydride abstraction proceeds with more ease. Apparently, this hyperconjugation overrules the inductive electron withdrawing effect of the ring oxygen. Hyperconjugation with the C-H bond is not possible in α-glucose and therefore the selectivity is dictated by the electron withdrawing effect of the ring oxygen.

![Figure 5. Hyperconjugation on the anomeric position.](image)

As discussed in the introduction, the oxidation of cyclohexane diols reported by Waymouth et al. shows selectivity for the axial hydroxyl group, a phenomenon we didn’t understand until now. Considering the hyperconjugation in the different substituents, it becomes apparent that for the equatorial OH, the axial hydrogen only receives minimal activation from the adjacent axial hydroxyl function (Figure 6, structure 46). In the case of the axial OH, the equatorial hydrogen benefits significantly more from hyperconjugation by the overlapping C-C bonds (Figure 6, structure 47). This results once again in a weaker C-H bond and therefore in selective oxidation of the axial alcohol.

![Figure 6. Hyperconjugation in cyclohexanediols 46 & 47.](image)

With this predictive model in hand, it is concluded that to a large extend the selectivity of the oxidation reaction is determined by the electronic effects in the glycoside itself and not due to the nature of the catalyst. Selective oxidation of the C3-OH of pyranosyl monosaccharides should therefore also be feasible with other methods that selectively oxidize secondary alcohols. For more
complex substrates, straightforward oxidation methods will be less feasible compared to the palladium catalysed reaction because this catalyst steers the selectivity also by steric and chelation. Testing a variety of different oxidation methods on methyl α-D-glucoside (19) however proved unfruitful (Table 1, entry 1-11). No or little conversion was observed for most of the used oxidation systems, presumably due to an inherent insufficient reactivity of the applied reagents. Being, in most cases, developed to give selective oxidation of secondary alcohols in the presence of primary alcohols, these reagents have been selected to be not too active, and deactivated substrates such as methyl α-D-glucoside are consequently not oxidized. The results are congruent with a sole report, back in 1957, that describes the chromium trioxide oxidation of methyl α-D-glucoside. Although mainly starting material was recovered, the main product that could be identified was C3-keto 29 (in 4.5% yield) next to even considerably smaller amounts of the 2-keto and 4-keto products. The paper was never referred to.

We also tried to oxidize methyl α-D-glucoside (19) with the method developed for the selective oxidation of the anomeric position in glucose, namely

Table 1. Overview of tested secondary selective oxidation methods on methyl α-D-glucoside.

<table>
<thead>
<tr>
<th>#</th>
<th>Ref.</th>
<th>Reagents</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Dess-Martin periodinane</td>
<td>oxidation primary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OH</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>NaBrO3, NaHSO3</td>
<td>No Conversion</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>KBrO3, KHSO4</td>
<td>Very low conversion</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>4-OMe-PhB(OH)2, DBI, K2CO3</td>
<td>Very low conversion</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>Pyr-SO3, Et3N</td>
<td>No conversion</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>PCC</td>
<td>No conversion</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>FeOTf2, di-(2-picolyl)amine, H2O2</td>
<td>Very low conversion</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>CuCl2/neocuproine, H2O2</td>
<td>Very low conversion</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>CuCl2, t-BuOOH</td>
<td>No conversion</td>
</tr>
<tr>
<td>10</td>
<td>26</td>
<td>Oxone, trifluoroacetone, NaHCO3</td>
<td>No conversion</td>
</tr>
<tr>
<td>11</td>
<td>27</td>
<td>Mn(ClO4)2, pyridine-2-carboxylic acid, butanedione, NaOAc, H2O2</td>
<td>No conversion</td>
</tr>
<tr>
<td>12</td>
<td>16</td>
<td>Bromine, NaHCO3</td>
<td>~15% conversion, 12% isolated yield</td>
</tr>
</tbody>
</table>

a DBI: Dibromoisoncyanuric acid
bromine in combination with NaHCO$_3$.$^{16}$ Although the conversion was low (~15%), isolation of the major product proved to be C3-keto $^{29}$ in 12% yield (Table 1, entry 12). This underlines that it is indeed possible to oxidize the C3 position selectively with other oxidation methods. Unfortunately, attempts to further optimize this reaction were unsuccessful. This is most likely due to the complex nature of the oxidation species when bromine in water is used.$^{18}$

Inspired by the excellent regioselectivities in this oxidation, our group recently demonstrated the feasibility of regioselective alkylation of carbohydrates building on the work of MacMillan regarding the selective C-H functionalization of alcohols (see Scheme 13 for an overall reaction and Scheme 15 for the mechanism belonging to this reaction).$^{28}$ During the optimization of the reaction conditions, it was observed that when the somophile (in Scheme 14, 49) was omitted, C3-oxidation of methyl α-D-glucoside ($^{19}$) was the major product (~10% conversion). From this point, we started to investigate if we could increase the conversion by varying the reaction conditions. When the DMSO-$_d$$^6$ was not degassed the reaction still proceeded (Table 3, entry 1). Based on this observation we attempted the reaction under an atmosphere of oxygen. Although an increase in conversion was observed, these results proved to be irreproducible and yields varied between 10 – 30% (Table 3, entry 2). When performing the reaction under oxygen, the formation of a new deuterated compound appeared, that turned out to be dimethylsulfone, the oxidation product of DMSO. To study whether the DMSO was playing a role in the oxidation, the effect of the solvent was investigated. Because methyl α-D-glucoside is not soluble in most organic solvents, 1,2-propanediol 51 was chosen as a model substrate. Oxidizing 51 in either DMSO or in acetonitrile gave in both cases oxidation of the secondary position with ~12% conversion (Scheme 15), excluding a specific solvent effect in this oxidation reaction.

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**Scheme 14.** General scheme of C-H alkylation of alcohols via selective C-H activation.
Next, we investigated the effect of the hydrogen bonding agent, dihydrogen phosphate. Excluding this from the reaction mixture did not change the conversion (Table 2, entry 3), which corroborates the observation made by MacMillan et al. for the alkylation reaction. In the reactions reported by MacMillan, a lower rate and only a small decrease in yield was observed (84% with and 67% without H$_2$PO$_4$) when the hydrogen bonding agent was excluded during the alkylation of alcohols. According to the mechanism (Scheme 16), after excitation of the iridium catalyst a Single Electron Transfer (SET) from the quinuclidine to the iridium catalyst takes places. The resulting quinuclidine radical cation can now abstract a hydrogen (Hydrogen Atom Transfer) of the substrate, which results in a carbon radical next to the hydroxyl group. To verify whether the currently observed oxidation reaction follows a similar mechanism, the quinuclidine was excluded (Table 3, entry 4). In this case, no conversion was observed, clearly showing the importance of this reagent in the catalytic cycle. To test whether the conversion was limited by the loading of the catalytic system (Ir-cat, quinuclidine and NBu$_4$H$_2$PO$_4$), its loading was doubled. This resulted in a doubling of the conversion (Table 2, entry 5). The same was the case when

**Scheme 15.** DMSO plays no specific role in the photo oxidation
the loading of the catalytic system was quadrupled; the conversion quadrupled as well (from 15% to 60%). To see whether we could obtain full conversion, the catalytic system was taken in 10-fold, and indeed the 3-keto product was observed as the major product with full conversion of the starting material (Table 2, entry 8). It seems that throughout the reaction the catalyst is degrading, or the ligands act as an electron sink, to result eventually in the oxidation of the alcohol. Although there isn’t yet an unambiguous answer to how this oxidation reaction works, it seems that the C3 radical is an intermediate. However, how this radical is then further oxidized to the observed ketone is up to now unknown. However, the results of this photoredox oxidation in combination with the bromine oxidation clearly show that the selective oxidation of pyranosides is not dependent on the catalytic system.

![Scheme 16. Mechanism of the C-alkylation of alcohols.](image)

### 5.3 Conclusion

Palladium/neocuproine catalysed oxidation has proven to be a highly effective method for the selective oxidation of polyols. This study demonstrates that the observed rate differences between glycosides result from hyperconjugation with the antibonding orbital of the C3-H and not from selective chelation to either cis or trans-equatorial diols. The weakening of the C-H bond results in a faster β-hydride elimination. Next to this, it was observed that trans
di-axial diols do show a decreased rate of oxidation resulting from unfavourable chelation with the catalyst. The study of different substrates with regard to regioselective oxidation showed that the substituent at the anomeric position has no effect on the selectivity. However, the ring oxygen proved to be a crucial element to obtain selectivity. Oxidizing the carbacycle analogue of 1-deoxy-glucose showed no selectivity for one of the three secondary alcohols. Based on this it is concluded that, as the ring oxygen has an electron withdrawing effect through the ring, the C3 position being the furthest away is the most electron rich. Therefore, selective oxidation is observed at that position. Based on the results obtained throughout this thesis and the work previously done by us and Waymouth a working model for the regioselectivity was developed. Based on this model, the regioselectivity is to a large extend controlled by the electronic effects present in the glycoside itself and not by the catalyst. This was shown to be correct by employing different oxidation methods. Bromine in combination with aqueous NaHCO₃ proved to give selective oxidation, albeit with low conversion. Furthermore, photocatalytic oxidation showed also to be able to oxidize glucosides selectively on the C3 position.

5.4 Experimental Section

5.4.1 General information

Solvents and Reagents
All solvents used for reactions were of commercial grade, and used without further purification. Reagents were purchased from Sigma-Aldrich, Acros and were used without further purification. [(Neocuproine)PdOAc]₂OTf₂ and methyl 2,3,6-tri-O-benzyl-4-deoxy-α-D-xylo-hexo-pyranoside were prepared according to the literature procedure.²⁹,³⁰

5.4.2 General procedure

Standard oxidation experiment
Substrate (0.18 mmol, 1 equiv.) and benzoquinone (0.54 mmol, 3 equiv.) were dissolved in DMSO-d₆ (600 µl, 0.3 M) and transferred to an NMR tube. T1 was determined, followed by an NMR spectrum at t=0 to determine the ratio of DMSO : starting material. [(Neocuproine)PdOAc]₂OTf₂ (4.5 µmol, 2.5 mol%) was added to the NMR tube and mixed. Upon full conversion, the selectivity was determined and product characterized by ¹H- and ¹³C-NMR.
5.4.3. Synthesis procedure

Synthesis of the starting materials

Methyl 3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranoside (10)

To a mixture of tri-O-acetyl-D-galactal (1 g, 3.7 mmol, 1 eq) and dry methanol (450 μl, 11 mmol, 3 eq) in dry dichloromethane (18 ml, 0.2 M) was added triphenylphosphine hydrobromide (63 mg, 0.18 mmol, 5 mol%). The resulting solution was stirred for 4 h at rt. Upon complete conversion (monitored by TLC, eluent 30% EtOAc/pentane), the reaction mixture was quenched by the addition of saturated aq. NaHCO\textsubscript{3} (25 ml). Layers were separated and the organic layer was washed with brine (1 x 25 ml), dried over magnesium sulfate, filtered and concentrated in \textit{vacuo}. The crude material was purified by silica column chromatography (elucent: 20% EtOAc/pentane) to yield the α-anomer as a white solid (670 mg, 2.2 mmol, 60%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 5.15 (d, \(J = 3.0\) Hz, 1H), 5.09 (ddd, \(J = 12.4, 5.1, 3.0\) Hz, 1H), 4.74 (d, \(J = 2.4\) Hz, 1H), 4.00 – 3.89 (m, 3H), 3.19 (s, 3H), 1.97 (s, 3H), 1.95 – 1.84 (m, 4H), 1.81 (s, 3H), 1.70 (ddt, \(J = 12.7, 5.1, 1.2\) Hz, 1H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 170.1, 170.0, 169.6, 98.2, 66.4, 66.3, 65.9, 62.2, 54.6, 29.9, 20.5, 20.4, 20.4. Characterization matches the literature.\textsuperscript{31}

Methyl 2-deoxy-α-D-galactoside (11)

To a solution of methyl 3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranoside (670 mg, 2.20 mmol, 1 eq) in dry methanol (7.3 ml, 0.3 M) was added a small sliver of sodium. The resulting solution was stirred for 3.5 h at rt. Upon complete conversion (monitored by TLC, eluent 30% EtOAc/pentane), the reaction mixture was quenched by the addition of Amberlite H\textsuperscript{+}. After stirring for 15 min, the solution was filtered over a piece of cotton wool and the resin washed thoroughly with methanol. The resulting solution was concentrated in \textit{vacuo} to yield the product as a white powder (377 mg, 2.12 mmol, 96%). \textsuperscript{1}H NMR (400 MHz, CD\textsubscript{3}OD) \(\delta\) 4.76 (d, \(J = 3.6\) Hz, 1H, H1), 3.87 (ddd, \(J = 12.0, 5.1, 3.0\) Hz, 1H, H3), 3.73 (d, \(J = 3.1\) Hz, 1H, H4), 3.71 – 3.60 (m, 3H, H5 + H6\textsubscript{ab}), 3.29 (s, 3H, OMe), 1.89 (td, \(J = 12.4, 3.8\) Hz, 1H, H2\textsubscript{a}), 1.72 (ddt, \(J = 12.8, 5.1, 1.2\) Hz, 1H, H2\textsubscript{b}). \textsuperscript{13}C NMR (101 MHz, CD\textsubscript{3}OD) \(\delta\) 99.9 (C1), 72.2 (C5), 69.4 (C4), 66.5 (C3), 63.1 (C6), 55.0 (OMe), 33.5 (C2). HRMS (ESI) calculated for C\textsubscript{7}H\textsubscript{14}O\textsubscript{5}Na ([M+Na\textsuperscript{+}]): 201.073, found: 201.073
**Methyl 2,3,6-tri-O-benzyl-4-deoxy-4-triflate-D-glucopyranoside (34)**

To an oven-dried flask equipped with a stirring bar was added methyl-2,3,6-tri-O-benzyl-D-glucopyranoside (1.3 g, 3.0 mmol, 1 eq), dry pyridine (1.9 ml, 25 mmol, 8.2 eq) and dry dichloromethane (15 ml, 0.2 M). The resulting solution was cooled down to -20 °C followed by the dropwise addition of triflic anhydride (1.0 ml, 6.0 mmol, 2 eq). The reaction was allowed to reach room temperature at which it was stirred for an additional 30 min. Upon complete conversion (monitored by TLC, eluent 40% EtOAc/pentane), the reaction mixture was diluted with dichloromethane (60 ml) and washed with 1 M aq. HCl (60 ml), sat. NaHCO₃ (60 ml), water (60 ml) and finally with brine (60 ml). The dichloromethane was dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting product was used crude in the next step. 

**Methyl 2,3,6-tri-O-benzyl-4-deoxy-4-fluoro-α-D-galactopyranoside (35)**

To an oven-dried flask equipped with a stirring bar was added crude methyl 2,3,6-tri-O-benzyl-4-deoxy-4-triflate-D-glucopyranoside (3.0 mmol, 1 eq) and dry THF (12 ml, 0.25 M). TBAF (3.3 ml, 3.3 mmol, 1 M in THF) was added dropwise to the solution. Upon addition of the TBAF, a color change from yellow to red/orange was observed. The reaction was stirred at room temperature for 16 h. Upon complete conversion (monitored by TLC, eluent 20% EtOAc/pentane), the reaction mixture was concentrated in vacuo. The residue was dissolved in dichloromethane (30 ml) and washed with brine (2 x 6 ml), dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was further purified by silica column chromatography (eluent: 20% EtOAc/pentane) to yield the product as a white solid (1.08 g, 2.3 mmol, 77% over two steps).
127.6, 127.5 (C-arom.), 98.6 (C1), 87.4 (d, J_C,F = 182.6 Hz, C4), 75.9 (d, J_C,F = 17.6 Hz, C3), 75.7 (d, J_C,F = 1.8 Hz, C2), 73.7, 73.4, 72.5 (3 x OCH2Ph), 68.0 (d, J_C,F = 4.6 Hz, C6), 67.85 (d, J_C,F = 17.4 Hz, C5) 55.4 (OMe).

Characterization matches the literature.\textsuperscript{33}

**Methyl 4-deoxy-4-fluoro-\alpha-D-galactopyranoside (31)**

To a solution of methyl 2,3,6-tri-O-benzyl-4-deoxy-4-fluoro-\alpha-D-galactopyranoside (1.07 g, 2.3 mmol, 1 eq) in a mixture of acetone/methanol (1:8, 9 ml, 0.3 M) was added Pd/C 10 w/w % (245 mg, 0.23 mmol, 10 mol%). The reaction flask was put under a hydrogen atmosphere and stirred at room temperature for 18 h. Upon complete conversion (monitored by TLC, eluent 30% Et2O/pentane), the reaction mixture was filtered over celite and the celite was washed with methanol. The resulting solution was concentrated in vacuo and further purified by silica column chromatography (eluent: 10% MeOH/CH2Cl2) to yield the product as a white solid (330 mg, 1.68 mmol, 73%). \textsuperscript{1}H NMR (400 MHz, CDCl3) δ 4.83–4.65 (m, 1H, H4), 4.73 (d, J = 3.2 Hz, 1H, H1), 3.87–3.81 (m, 1H), 3.80–3.72 (m, 2H), 3.72–3.64 (m, 2H), 3.42 (s, 3H). \textsuperscript{13}C NMR (101 MHz, CD3OD) δ 101.3 (C1), 91.1 (d, J_C,F = 179.7 Hz, C4), 70.15 (C2), 70.04 (d, J = 6.5 Hz, C3), 70.0, 61.3 (d, J = 6.1 Hz, C6), 55.8 (OMe). \textsuperscript{19}F NMR (376 MHz, CD3OD) δ -79.98. HRMS (ESI) calculated for C7H13FO5Na ([M+Na]+): 219.064, found: 219.064.

**Methyl 2,3,6-tri-O-benzoyl-4-deoxy-4-triflate-\alpha-D-galactopyranoside (37)**

To an oven-dried flask equipped with a stirring bar was added methyl-2,3,6-tri-O-benzoyl-D-galactopyranoside (1 g, 2 mmol, 1 eq), dry pyridine (640 µl, 7.9 mmol, 4 eq) and dry dichloromethane (10 ml, 0.2 M). The resulting solution was cooled down to -20 °C followed by the dropwise addition of triflic anhydride (670 µl, 3.95 mmol, 2 eq). The reaction was allowed to reach room temperature at which it was stirred for an additional 30 min. Upon complete conversion (monitored by TLC, eluent 30% EtOAc/pentane), the reaction mixture was diluted with dichloromethane (40 ml) and washed with 1 M HCl (40 ml), sat. NaHCO3 (40 ml), water (40 ml) and finally with brine (40 ml). The dichloromethane was dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting product was used crude in the next step. \textsuperscript{1}H NMR (400 MHz, CDCl3) δ 8.08–7.92 (m, 6H), 7.63–7.29 (m, 9H), 5.95 (dd, J = 10.8, 2.9 Hz, 1H), 5.65–5.54 (m, 2H), 5.29 (d, J = 3.8 Hz, 1H, H1), 4.70 (dd, J = 11.2, 6.6 Hz, 1H, H6a), 4.59 (t, J = 6.8 Hz, 1H), 4.35 (dd, J = 11.2, 7.0 Hz, 1H, H6b), 3.47 (s, 3H, OMe). \textsuperscript{13}C NMR (101 MHz, CDCl3) δ 166.0, 165.8, 165.8, 133.9, 133.7, 133.7, 130.2, 130.0, 129.9, 129.2, 129.0, 128.7, 128.6, 128.5, 97.6, 83.0, 68.4, 67.6, 65.9, 61.5, 56.2. Characterization matches the literature.\textsuperscript{34}
Methyl 2,3,6-tri-\(O\)-benzoyl-4-deoxy-4-fluoro-\(\alpha\)-\(D\)-glucopyranoside (38)

To an oven-dried flask equipped with a stirring bar was added crude methyl 2,3,6-tri-\(O\)-benzoyl-4-deoxy-4-triflate-\(D\)-galactopyranoside (1.97 mmol, 1 eq) and dry THF (7.2 ml, 0.25 M). TBAF (2 ml, 2 mmol, 1 M in THF) was added dropwise to the solution. Upon addition of the TBAF, a color change from yellow to red/orange was observed. The reaction was stirred at room temperature for 16 h. Upon complete conversion (monitored by TLC, eluent 20% EtOAc/pentane), the reaction mixture was concentrated in vacuo. The residue was dissolved in dichloromethane (18 ml) and washed with brine (2 x 9 ml), dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was further purified by silica column chromatography (eluent: 20% EtOAc/pentane) to yield the product as a white solid (367 mg, 0.72 mmol, 37% over two steps).

\[ \begin{align*} \text{1H NMR (400 MHz, CDCl}_3 & \delta 8.12 (d, J = 7.5 \text{ Hz}, 1H), 8.02 (ddd, J = 9.9, 8.1, 1.5 \text{ Hz}, 2H), 6.19 (dt, J = 14.2, 9.7 \text{ Hz}, 0H), 5.27 (dd, J = 10.3, 3.6 \text{ Hz}, 1H), 5.21 (t, J = 3.4 \text{ Hz}, 0H), 4.94 - 4.69 (m, 1H), 4.64 (dd, J = 12.2, 5.1 \text{ Hz}, 0H), 4.41 - 4.31 (m, 1H), 3.45 (s, 1H).} \\
\text{13C NMR (101 MHz, CDCl}_3 & \delta 166.0, 165.7, 165.5, 133.4, 133.2, 133.2, 129.9, 129.7, 129.6, 128.4, 128.4, 128.3, 96.8, 87.4 (d, J = 188.0 \text{ Hz}), 71.4 (d, J = 7.7 \text{ Hz}), 70.5 (d, J = 19.8 \text{ Hz}), 67.1 (d, J = 23.1 \text{ Hz}), 62.6, 55.5.} \\
\text{Characterization matches the literature.} \end{align*} \]

Methyl 4-deoxy-4-fluoro-\(\alpha\)-\(D\)-glucopyranoside (32)

Methyl 2,3,6-tri-\(O\)-benzoyl-4-deoxy-4-fluoro-\(\alpha\)-\(D\)-glucopyranoside (575 mg, 1.13 mmol, 1 eq) was dissolved in dry methanol (4 ml, 0.3 M). To the resulting solution was added a small sliver of sodium. The reaction mixture was stirred at room temperature for 16 h. Upon complete conversion (monitored by TLC, eluent 10% EtOAc/pentane), the reaction mixture was quenched by the addition of Amberlite H\(^+\), filtered and the resin was thoroughly washed with methanol and concentrated in vacuo. The crude material was further purified by silica column chromatography (eluuent: 10% MeOH/CH\(_2\)Cl\(_2\)) to yield the product as a white solid (105 mg, 0.54 mmol, 47%). \(\text{1H NMR (400 MHz, CD}_3\text{OD) } \delta 4.68 (t, J = 3.5 \text{ Hz), 1H, H1}), 4.22 (dt, J = 51.3, 8.9 \text{ Hz), 1H, H4}), 3.85 (dt, J = 16.0, 9.2 \text{ Hz), 1H, H3}), 3.78 (dd, J = 10.1, 2.4 \text{ Hz), 1H, H6a}), 3.71 - 3.65 (m, 2H, H5, H6b)), 3.44 (m, 1H, H2)), 3.41 (s, 3H, OMe).\(\text{13C NMR (101 MHz, CD}_3\text{OD) } \delta 101.0 (d, J_{CF} = 1.6 \text{ Hz), C1}), 90.7 (d, J_{CF} = 180.6 \text{ Hz), C4}), 73.1 (d, J_{CF} = 14.0 \text{ Hz), C3}), 72.9 (d, J_{CF} = 4.3 \text{ Hz), C2}), 70.9 (d, J_{CF} = 24.2 \text{ Hz), C5}), 61.6 (C6), 55.7 (OMe).\(\text{19F NMR (376 MHz, CD}_3\text{OD) } \delta -199.2 (dd, J = 52.0, 16.0 \text{ Hz}).\(\text{HRMS (ESI) calculated for C}_7\text{H}_{13}\text{FO}_5\text{Na ([M+Na]+): 219.064, found: 219.064.} \)
1,2-dideoxy-D-glucose (42)

To a solution of D-glucal (1 g, 6.8 mmol, 1 eq) in a mixture of THF/MeOH (34 ml, 1 : 3.5, 0.2 M) was added Pd/C (73 mg, 0.68 mmol, 10 mol%). The resulting suspension was put under a hydrogen atmosphere and stirred for 6 h at rt. Upon complete conversion (monitored by TLC, eluent 20% MeOH/CH₂Cl₂), the reaction mixture was directly filtered over a patch of celite. The filtrate was concentrated in vacuo and further purified by silica column chromatography (eluent: 10% MeOH/CH₂Cl₂) to yield the product as a white powder (776 mg, 5.24 mmol, 77%) ¹H NMR (400 MHz, CD₃OD) δ 3.82 (ddd, J = 11.7, 5.0, 1.6 Hz, 1H), 3.74 (dd, J = 11.8, 2.2 Hz, 1H), 3.54 (dd, J = 11.8, 5.5 Hz, 1H), 3.43 (ddd, J = 11.2, 8.1, 5.0 Hz, 1H), 3.34 (td, J = 12.2, 2.1 Hz, 1H), 3.11 – 2.99 (m, 2H), 1.81 (dt, J = 13.1, 3.4 Hz, 1H), 1.57 – 1.42 (m, 1H). ¹³C NMR (101 MHz, CD₃OD) δ 82.4, 74.1, 73.6, 66.6, 63.2, 35.1. Characterization matches the literature.³⁶

Methyl α-D-alloside (15)

To a mixture of methyl α-D-glucose (1 g, 5.2 mmol, 1 equiv.) and benzoquinone (835 mg, 7.73 mmol, 1.5 equiv.) in DMSO (5 ml, 1.0 M) was added [(2,9-dimethyl-1,10-phenanthroline)-Pd(μ-OAc)]²(OTf)² (54 mg, 51.5 μmol, 1 mol%). The reaction mixture was stirred at rt for 1.5 h. Upon complete conversion (monitored by TLC, eluent 15% MeOH/CH₂Cl₂), the reaction mixture was directly used for the successive reduction step. The reaction mixture was diluted with water (2:1 DMSO/water solvent). A cold solution of NaBH₄ (195 mg, 5.15 mmol, 1 equiv.) in water (2.5 ml) was added dropwise to the reaction mixture at 0 °C and the solution stirred for 1.5 h. When the reaction showed complete conversion as indicated by TLC, Amberlite H⁺ was added to quench the reaction. The reaction was filtered, the resin washed with water and the resulting solution was lyophilized. The crude material was further purified by silica column chromatography (eluent: 20% MeOH/CH₂Cl₂) to yield the product as a brown oil (430 mg, 2.2 mmol, 43%). ¹H NMR (400 MHz, CD₃OD) δ 4.66 (d, J = 3.8 Hz, 1H), 3.96 (appt, J = 3.3 Hz, 1H), 3.85 – 3.76 (m, 1H), 3.72 – 3.62 (m, 2H), 3.57 (appt, J = 3.7 Hz, 1H), 3.44 (dd, J = 9.6, 3.2 Hz, 1H), 3.39 (s, 3H). ¹³C NMR (101 MHz, CD₃OD) δ 101.3, 73.2, 69.3, 68.8, 68.1, 62.6, 56.1.
Oxidation experiments

Methyl 2-deoxy-3-keto-α-D-galactoside (12)

Oxidized according to the general procedure. Methyl 2-deoxy-α-D-galactoside 6 (21 mg, 0.12 mmol, 1 equiv.), benzoquinone (13 mg, 0.12 mmol, 1 equiv.) and [(neocuproine)PdOAc]2OTf (3 mg, 3 µmol, 2.5 mol%) were dissolved in DMSO-d6 (400 µl, 0.3 M) and reacted for 45 min.

Conversion of starting material: 49%
Selectivity towards the 3-ketone 10: 24% (49% based on conversion)
Selectivity towards the diketone 14: 15% (31% based on conversion)
Due to overlapping signals, the selectivity was determined based on the H1 and H2 signals which were isolated.

Oxidation of 1,6-anhydro-β-D-glucose (21)

Oxidized according to the general procedure. 1,6-anhydro-β-D-glucose 21 (19.5 mg, 0.12 mmol, 1 equiv.), benzoquinone (13 mg, 0.12 mmol, 1 equiv.) and [(neocuproine)PdOAc]2OTf (3 mg, 3 µmol, 2.5 mol%) were dissolved in DMSO-d6 (400 µl, 0.3 M) and reacted for 30 min.

Conversion: 66%
Selectivity towards the 3-ketone 23: 35% (53% based on conversion)
Selectivity towards the diketone 27/28: 16% (24% based on conversion)

NMR data 3-keto 23:

1H NMR (400 MHz, DMSO-d6) δ 5.40 (s, 1H, H1), 4.58 (d, J = 5.6 Hz, 1H, H5), 3.93 (s, 1H, H2), 3.90 (d, J = 8.1 Hz, 1H, H6a), 3.72 (s, 1H, H4), 3.67 (t, J = 6.8 Hz, 1H, H6b).

13C NMR (101 MHz, DMSO-d6) 206.2 (C3), 104.1 (C1), 78.6 (C5), 75.6 (C2), 75.3 (C4), 66.7 (C6)

NMR data diketo 27/28:

1H NMR (400 MHz, DMSO-d6) δ 5.64 (s, 1H, H1), 5.08 (d, J = 6.0 Hz, 1H, H5), 4.05 (s, 1H) (H6 overlapping with 3-keto) 13C NMR (101 MHz, DMSO-d6) 194.2 (ketone), 190.5 (ketone), 104.7 (C1), 79.5 (C5), 75.3, 66.5

Oxidation of 1,6-anhydro-β-D-galactose (22)

Oxidized according to the general procedure. 1,6-anhydro-β-D-galactose 22 (19.5 mg, 0.12 mmol, 1 equiv.), benzoquinone (13 mg, 0.12 mmol, 1 equiv.) and [(neocuproine)PdOAc]2OTf (3 mg, 3 µmol, 2.5 mol%) were dissolved in DMSO-d6 (400 µl, 0.3 M) and reacted for 40 min.

Conversion: 83%
Selectivity towards the 3-ketone 30: 68% (82% based on conversion)

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 5.44 (d, \(J = 2.0\) Hz, 1H, H1), 4.69 (t, \(J = 5.0\) Hz, 1H, H5), 4.44 (d, \(J = 5.3\) Hz, 1H, H4), 3.70 (d, \(J = 7.8\) Hz, 1H, H6b), 3.63 (d, \(J = 2.1\) Hz, 1H, H2), 3.52 (dd, \(J = 7.7, 4.9\) Hz, 1H, H6a).

\(^1\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 206.5 (C3), 102.4 (C1), 75.9 (C5), 75.4 (C2), 72.8 (C4), 63.9 (C6).

Oxidation of 4-eq-fluoride (32)

Methyl 4-deoxy-4-fluoro-\(\alpha\)-D-glucopyranoside 22 (23.5 mg, 0.12 mmol, 1 equiv.) and [(neocuproine)PdOAc]2OTf (3 mg, 3 \(\mu\)mol, 2.5 mol%) were dissolved in DMSO-\(d_6\) (400 \(\mu\)l, 0.3 M) and reacted for 16 h.

Difficult Integration of \(^1\)H NMR. Estimation of selectivity

Conversion: ~60%
Selectivity towards the 3-ketone 39: ~30%
Selectivity towards the rearrangement 53: ~30%
Products partially characterized by \(^1\)H-NMR due to severe overlap, full characterization given in \(^1\)C-NMR.

NMR data 3-keto-4-fluoro 39:

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 5.14 (ddd, \(J_{H4-F} = 48.0\), \(J_{H4-H5} = 9.7\), \(J_{H4-H2} = 1.4\) Hz, 1H, H4), 4.98 (dd, \(J_{H1-H2} = 4.2\), \(J_{H1-F} = 1.7\) Hz, 1H, H1), 4.33 (dappt, \(J_{H2-H1} = 4.3\), \(J_{H2-F, H2-H4} = 1.0\) Hz, 1H, H2). 1\(^3\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 201.15 (d, \(J_{C,F} = 12.5\) Hz, C3), 102.0 (C1), 87.55 (d, \(J_{CF} = 165.7\) Hz, H4), 74.8 (C2), 72.3 (d, \(J_{CF} = 23.6\) Hz, C5), 59.8 (C6), 54.9 (OMe)

NMR data rearrangement product 53:

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 5.19 (d, \(J_{H3-F} = 53.9\) Hz, 1H, H3), 4.84 (ddd, \(J_{H5-F} = 12.0\), \(J_{H5-H6a} = 2.3\), \(J_{H5-H6b} = 1.3\) Hz, 1H, H5), 4.77 (s, 1H, H1), 4.26 (dappt, \(J_{H6b-F, H6b-H6a} = 11.5\), \(J_{H6a-H5} = 1.3\) Hz, 1H, H6a), 4.11 (ddd, \(J_{H6a-H6b} = 11.5\), \(J_{H6b-F} = 6.6\), \(J_{H6b-H5} = 1.3\) Hz, 1H, H6b). 1\(^3\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 170.9 (d, \(J = 10.4\) Hz, C6), 102.7 (C1), 89.5 (d, \(J_{CF} = 174.7\) Hz, C3), 80.7 (d, \(J_{CF} = 16.5\) Hz, C2), 76.0 (d, \(J_{CF} = 18.3\) Hz, C4), 71.2 (d, \(J_{CF} = 9.6\) Hz, C4), 56.3 (OMe).

3,4-diketo-1,2-dideoxy-D-glucose (54)

Oxidized according to the general procedure. 1,2-dideoxy-D-glucose 42 (18 mg, 0.12 mmol, 1 equiv.) and [(neocuproine)PdOAc]2OTf (3 mg, 3 \(\mu\)mol, 2.5 mol%) were dissolved in DMSO-\(d_6\) (400 \(\mu\)l, 0.3 M) and reacted for 30 min.

Selectivity towards the diketone 54: 52%
Selectivity towards the 3-ketone 55: 39%
Difficult Integration of NMR, characterization took place via the $^{13}$C NMR spectrum. The selectivity was determined based on the H5 signal. $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 193.9 (ketone), 191.4 (ketone), 87.1 (C5), 62.8 (C1), 61.4 (C6), 42.0 (C2).

3-keto-1,2-dideoxy-D-glucose (55)

Oxidized according to the general procedure. 1,2-dideoxy-D-glucose 42 (18 mg, 0.12 mmol, 1 equiv.), benzoquinone (13 mg, 0.12 mmol, 1 equiv.) and [(neocuproine)PdOAc]$_2$OTf$_2$ (3 mg, 3 µmol, 2.5 mol%) were dissolved in DMSO-$d_6$ (400 µl, 0.3 M) and reacted for 30 min. Selectivity towards the desired product: 74% $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 4.12 (ddd, $J = 8.6, 7.4, 3.7$ Hz, 1H, H1b), 3.97 (dd, $J = 10.0, 1.4$ Hz, 1H, H4), 3.68 (dd, $J = 11.8, 1.8$ Hz, 1H, H6a), 3.57 – 3.48 (m, 2H, H6b, H1a), 3.23 (ddd, $J = 10.0, 5.2, 1.9$ Hz, 1H, H5), 2.70 (td, $J = 13.2, 7.4$ Hz, 1H, H2a), 2.26 (d, $J = 14.0$ Hz, 1H, H2b). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 207.7 (C3), 84.1 (C5), 73.6 (C4), 66.2 (C1), 61.4 (C6), 41.4 (C2).

Oxidation of methyl α-D-alloside (20)

Oxidized according to the general procedure. Methyl α-D-alloside 20 (28 mg, 0.14 mmol, 1 equiv.), benzoquinone (15.6 mg, 0.144 mmol, 1 equiv.) and [(neocuproine)PdOAc]$_2$OTf$_2$ (3.8 mg, 3.6 µmol, 2.5 mol%) were dissolved in DMSO-$d_6$ (480 µl, 0.3 M) and reacted for 30 min. Selectivity towards the desired product: 90% $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 4.95 (d, $J = 4.2$ Hz, 1H), 4.30 (dd, $J = 4.3, 1.5$ Hz, 1H), 4.08 (dd, $J = 9.7, 1.5$ Hz, 1H), 3.69 (dd, $J = 11.9, 2.0$ Hz, 1H), 3.60 (dd, $J = 11.9, 4.9$ Hz, 1H), 3.47 (ddd, $J = 9.9, 5.0, 1.8$ Hz, 1H), 3.27 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 206.2, 102.2, 75.4, 74.7, 72.0, 60.8, 54.5. Characterization matches literature.¹
Oxidation of carbacycle (43)

Oxidized according to the general procedure. Carbacycle 43 (19.5 mg, 0.12 mmol, 1 equiv.), benzoquinone (13 mg, 0.12 mmol, 1 equiv.) and [(neocuproine)PdOAc]$_2$OTf$_2$ (3 mg, 3 µmol, 2.5 mol%) were dissolved in DMSO-$d_6$ (400 µl, 0.3 M) and reacted for 45 min.

Selectivity towards the 2-keto 43-2: ~22%
Selectivity towards the 3-keto 43-3: ~40%
Selectivity towards the 4-keto 43-2: ~38%

Products partially characterized by $^1$H-NMR, full characterization given in $^{13}$C-NMR.

NMR data 2-keto 43-2:
$^1$H NMR (400 MHz, DMSO-$d_6$) δ 3.94 (d, $J = 8.8$ Hz, 1H, H3, overlaps with H3 of 43-4), 3.71 – 3.64 (m, 1H, H6$_a$, overlaps with H6$_a$ of 43-4), 3.39 (dd, $J = 10.4, 6.6$ Hz, 1H, H6$_b$), 3.14 (apt, $J = 9.8$ Hz, 1H, H4) $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 208.9 (C2), 80.6 (C3) 75.5 (C4), 61.93 (C6), 44.3 (C5), 38.2 (C1), 31.4 (C7, overlaps with C1 of 27-4).

NMR data 3-keto 43-3:
$^1$H NMR (400 MHz, DMSO-$d_6$) δ 4.12 (ddd, $J = 12.2, 6.6, 1.7$ Hz, 1H, H2) 3.88 (dd, $J = 9.3, 1.4$ Hz, 1H, H4), 3.57 (dd, $J = 10.4, 2.8$ Hz, 1H, H6$_a$), 3.46 (dd, $J = 10.5, 5.4$ Hz, 1H, H6$_b$) 2.15 (dtt, $J = 15.8, 6.5, 2.8$ Hz, 1H, H1) $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 211.1 (C3), 81.5 (C4) 73.5 (C2), 61.88 (C6), 49.3 (C5), 34.9 (C1), 22.9 (C7).

NMR data 4-keto 43-4:
$^1$H NMR (400 MHz, DMSO-$d_6$) δ 3.94 (d, $J = 8.8$ Hz, 1H, H3, overlaps with H3 of 43-2), 3.71 – 3.64 (m, 1H, H6$_a$, overlaps with H6$_a$ of 43-2), 3.35 – 3.26 (m, 2H, H2 + H6$_b$) $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 209.0 (C4), 75.4 (C2), 74.3 (C3), 59.6 (C6), 49.9 (C5), 31.4 (C1, overlaps with C7 of 43-2), 24.5 (C7).

General procedure of the photo-oxidation:
A 4-mL glass vial equipped with a Teflon septum and magnetic stir bar was charged with Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.8 mg, 2.5 µmol, 1 mol%), methyl α-D-glucoside (48.5 mg, 0.25 mmol, 1 equiv.), quinuclidine (2.8 mg, 0.025 mmol, 10 mol%) and tetra-n-butylammonium phosphate (21 mg, 0.063 mmol, 25 mol%).

The mixture was dissolved in DMSO-$d_6$ and the vial was sealed and placed approximately 10 cm away from a Kessil® LED illuminator (model H150 blue). The reaction mixture was stirred and irradiated for 24 h. The internal temperature was kept close to room temperature by an electric fan placed
approximately 25 cm underneath the vial. After 24 h the conversion was monitored by \(^1\)H-NMR.

Selectivity towards the desired product: 12%.

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 4.95 (d, \(J = 4.2\) Hz, 1H), 4.30 (dd, \(J = 4.3, 1.5\) Hz, 1H), 4.08 (dd, \(J = 9.7, 1.5\) Hz, 1H), 3.69 (dd, \(J = 11.9, 2.0\) Hz, 1H), 3.60 (dd, \(J = 11.9, 4.9\) Hz, 1H), 3.47 (ddd, \(J = 9.9, 5.0, 1.8\) Hz, 1H), 3.27 (s, 3H).

\(^{13}\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 206.2, 102.2, 75.4, 74.7, 72.0, 60.8, 54.5.

Characterization matches literature.\(^9\)

### 5.5 References

Regioselective Carbohydrate Oxidations; Origins of Selectivity and Reactivity.
