Regioselective oxidation of carbohydrates
Eisink, Niek Nicodemus Henricus Maria

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 13-10-2019
Oxidation of secondary hydroxyl groups in vicinal diols enables the straightforward functionalization of biomolecules and biomaterials. The resulting hydroxy ketone can, for example, be used to form derivatives, such as the epimeric alcohols and imines, and it may be employed for chemical probe synthesis. Regioselectivity becomes an essential factor when this strategy is applied to compounds containing multiple hydroxyl groups, such as carbohydrates. Large advances have been made in this field in the past decade, which has led to the development of novel methodologies that enable selective oxidation of secondary hydroxyl groups of 1,2-diols in complex molecules. We here discuss these recent advances as well as some of the limitations. Future research should focus on addressing these issues, which will eventually lead to methods for the chemo- and regioselective oxidation of complex oligosaccharides.

This chapter is adapted from the original publication:
1.1 Introduction

Oxidation of alcohols is one the most well studied reactions in organic chemistry and even up to this day, new and improved methods are being reported, highlighting the need and desire for faster, more efficient, and especially more selective methods. The chemo- and/or regioselective oxidation of complex molecules that have multiple oxidation sensitive groups is still not an easy feat and, in particular, 1,2-diols prove to be challenging substrates. Side reactions, like C–C bond fission, tautomerization of the resulting α-hydroxy ketone (or carbonyl transposition), and overoxidation, are commonly observed for these substrates.

Vicinal diols are commonly found in natural products, with carbohydrates being the prime example, and oxidation of these diols into α-hydroxy ketones forms an attractive means to functionalize and modify these natural products. To achieve this, the field has largely relied on protecting group strategies. All hydroxyl groups in the substrate, except for the hydroxyl group of interest are protected, and the unprotected hydroxyl group is subsequently oxidized using conventional methods. As an example, the synthesis of methyl β-D-virenoside 4 is shown in Scheme 1.1 Starting from galactose 1 it takes 3 steps to selectively protect the alcohol groups and leave the C3-OH deprotected (2). Swern-type of oxidation results in ketone (3). Another 6 steps, both functional group transformations and deprotections, results eventually in the desired product 4. Regioselective approaches overcome the need for laborious protecting group manipulations. These may, therefore, be applied in the late stage functionalization of vicinal diol containing natural products, in a similar fashion to C–H activation, which has been used to block metabolism, to generate metabolites, to synthesize probe molecules, and for structure-activity relationship studies.2

![Scheme 1. Total synthesis of methyl β-D-virenoside 4.](image)

Key to the successful application of oxidation chemistry in complex biomolecules is the ability to use the inherent differences in reactivity of the various hydroxyl groups. Selective oxidation of the more accessible primary alcohol of a (vicinal) diol is readily achieved with a number of sterically hindered
oxidizing agents, such as TEMPO, and these methods have shown to be highly selective.\textsuperscript{3,4} Furthermore, Ru(PPh\textsubscript{3})(OH)salen complexes have been described for the aerobic oxidation of primary alcohols under ambient conditions.\textsuperscript{5} Obtaining selectivity for secondary alcohols in vicinal diols is less straightforward, even though secondary alcohols have a lower oxidation potential. As highlighted by Arterburn, the Corey–Kim oxidation,\textsuperscript{6} Swern-type oxidations,\textsuperscript{7} dimethyldioxirane,\textsuperscript{8} and several transition-metal catalysts in combination with an oxidant are effective methods for the chemoselective oxidation of the secondary alcohol, although the selectivity varies.\textsuperscript{9} For more complex substrates that contain multiple secondary alcohol groups, the selectivity is often significantly lower. Chelation control has been used to improve the chemo- and regioselectivity for 1,2-diols over the remaining hydroxyl groups.\textsuperscript{10}

Pushed by the need for more sustainable oxidation methods, the focus of the field shifted to the development of catalytic oxidation reactions that preferably employ dioxygen or hydrogen peroxide as the (co)oxidant and water as a solvent.

In this chapter, an overview will be given of the recent advances made in the field, with a particular emphasis on the chemoselective oxidation of non-activated secondary hydroxyl groups in vicinal diols. Benzylic vicinal diols readily oxidize with high selectivity and will therefore not be discussed. Both modified procedures of well-known oxidation methods and novel oxidation methods will be discussed. Special attention will be given to oxidation methods that are based on chelation control. These methods often show increased selectivity and enhanced rates for the oxidation of vicinal diols and are, therefore, often more selective in the oxidation of substrates bearing multiple hydroxyl groups. These methods are inherently suitable for the application in more complex molecules, such as in carbohydrate chemistry, and the synthesis of renewables from feedstocks.

1.2 General methods to oxidize simple vicinal diols

The methods that have an inherent preference for secondary alcohols have been successfully applied on simple vicinal diols, as shown in the review of Arterburn.\textsuperscript{9} However, these methods have their limitations, such as harsh conditions, the use of toxic reagents, and small substrate scope. In the past decade, several modified procedures that address these issues have been developed. A limitation of most DMSO-based oxidation methods is that these require strictly anhydrous conditions and consequently, the use of these methods is limited to compounds that are soluble in aprotic solvents. To oxidize 1,2-diols in aqueous solutions with DMSO, the Konwar group developed a modified procedure that employs in situ generated HI, formed from hydrazine and iodine,
to activate DMSO. Hydroxyacetone and dihydroxyacetone can be synthesized from propane-1,2-diol and glycerol, respectively, in moderate yields using this procedure.

Also, chromium-based reagents have shown to be suitable oxidants for the oxidation of the secondary alcohol in simple 1,2-diols. Grinding (±)-3-chloropropane-1,2-diol with one equivalent of pyridinium fluorochromate at room temperature in the absence of solvent results in the selective oxidation of the secondary alcohol and 1-chloro-3-hydroxypropanone can be isolated in 87% yield. However, stoichiometric amounts of the highly toxic chromium-based oxidant are needed to achieve full oxidation. To lower the amount of chromium reagent required, a method that employs catalytic amounts of 3,5-dimethylpyrazolium fluorochromate (DmpzHFC) in combination with hydrogen peroxide as the co-oxidant has been developed by Chaudhuri and coworkers (Figure 1).

![Figure 1. Structure of catalyst 5.](image)

Oxidation of (±)-3-chloropropane-1,2-diol using this modified procedure gave the resulting α-hydroxy ketone in a comparable yield to the stoichiometric procedure and again, exclusive oxidation of the secondary position was observed. In order to completely abandon chromium oxidants, Garonne and Martín studied the use of iron(III) reagents. Hydrogen peroxide in the presence of a catalytic amount of FeBr₃ oxidized octane-1,2-diol, both in acetonitrile and under solvent-free conditions, to the keto product with complete selectivity. Since this method only was tested on octane-1,2-diol, Bauer and Lenze aimed to develop a broadly applicable approach for the iron-catalysed chemoselective oxidation. They screened several iron(II) complexes that can oxidize alcohols using H₂O₂ as an oxidant for their activity and their selectivity for secondary alcohols over primary alcohols. Bis(picolyl)amine–iron(II) catalyst showed excellent activity at room temperature (Figure 2). Using hydrogen peroxide (2.6 equiv) as the internal oxidant, a range of diols including several vicinal diols could be oxidized in good yields (75–84%) within 15 minutes. However, longer reaction times led to oxidation of the primary hydroxyl group as well.

Farnetti and Crotti applied iron catalyst in the oxidation of glycerol. Initial experiments led to 46% overall conversion and approximately a one-to-one mixture of dihydroxyacetone and formic acid was obtained. Lowering the
reaction temperature and using an excess of a 10% solution of hydrogen peroxide resulted in full selectivity for dihydroxyacetone, albeit at the expense of the conversion (~20%).

Besides iron and chromium reagents, also polyoxometalates have been used as catalysts for the chemoselective oxidation of vicinal diols with hydrogen peroxide. Wang and co-workers demonstrated that Na₄H₃[Si₉W₆Al₃(H₂O)₆O₃7]-12H₂O is an excellent, recyclable catalyst. Full conversion is reached within 10 hours by performing the reaction neat with hydrogen peroxide as the co-oxidant. Upon complete conversion, the reaction mixture is extracted with an organic solvent and the aqueous layer can be reused for a successive oxidation reaction.

Finally, ruthenium-based methods have been developed to oxidize vicinal diols. Plietker utilized in situ generated RuO₄ for the synthesis of enantiopure α-hydroxy ketones starting from alkenes. Asymmetric Sharpless dihydroxylation of alkenes (see Scheme 2, structure 7 or 8) followed by regioselective catalytic monooxidation of the isolated vicinal diol (9 or 10) using 1 mol% RuCl₃ in combination with an internal oxidant gives the desired α-hydroxy ketones (11 or 12) in high isolated yields (~90%) and high e.e. within 1 hour (Scheme 2). The nature of the oxidant has a large effect on the outcome of the reaction. NaIO₄ and NaBrO₃ gave a large amount of C–C bond fission, while Oxone gave the desired α-hydroxy ketone as the major product.

Scheme 2. Asymmetric dihydroxylation followed by regioselective oxidation.
More recently, the catalytic dehydrogenation of 1,2- and 1,3-diols with Casey/Shvo catalyst 13 was studied, with the aim to convert lignocellulose into useful fine chemicals (Figure 3).\textsuperscript{20} When Ford and Weber performed the reaction in a closed vessel, low conversions were obtained (~0.25%). However, refluxing the reaction mixture in diglyme under air resulted in a significant increase (~40% conversion) and they therefore hypothesized that the elevated temperatures facilitate the elimination of H\textsubscript{2} from the catalyst. By employing cyclohexanone, as a hydrogen acceptor, the conversion towards the α-hydroxy ketone increased further to 64% within 10 minutes. Again, simple vicinal diols (propane-1,2-diol and butane-1,2-diol) were tested and these showed isolated yields of ~70%.

![Figure 3. Structure of Cases/Shvo catalyst 13.](image)

Other reagent combinations and catalysts have been reported to selectively oxidize secondary alcohols in the presence of primary alcohols. Examples include the polymeric phosphotungstate catalyst reported by Uozumi and co-workers,\textsuperscript{21} 2-iodoxybenzoic acid (IBX) oxidations in the presence of a catalytic amount cyclodextrin,\textsuperscript{22} IBX oxidations under phase-transfer conditions,\textsuperscript{23} oxidations using a combination of TEMPO/TBAB/H\textsubscript{5}IO\textsubscript{6} on wet alumina,\textsuperscript{24} and finally oxidations with bromide salts in the presence of peroxides,\textsuperscript{25–27} but most of these methods have not been employed for the oxidation of aliphatic vicinal diols.

While most of the methods that have a preference for secondary diols can be applied on simple substrates that contain 1,2-diols, the oxidation of substrates that contain more hydroxyl groups either has not been studied or the methods are not suitable for these substrates.

## 1.3 Chelation-controlled oxidation

### 1.3.1 Tin, boronic acid and bromonium catalysed oxidations

Reagents that chelate to or coordinate with vicinal diols have been used to enhance the selectivity for the secondary hydroxyl unit of a vicinal diol over other hydroxyl groups in the molecule of interest. Already in the 1970s, David and Thieffry showed that stannyl ethers and stannylene acetals 14 (see Table 1...
for the chelation mode), formed by refluxing di- and triorganotin compounds with 1,2-diols can be oxidized to α-hydroxy ketones with halonium oxidants.\(^\text{10}\)

**Table 1. Overview tin catalysed oxidation methods.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me₂SnCl₂ (0.1 equiv), 3.0 Fmol⁻¹, Et₄NBr (1.0 equiv), MeOH 0 °C, 30 min.</td>
<td>76%</td>
</tr>
<tr>
<td>2</td>
<td>Me₂SnCl₂ (0.1 equiv), Br₂ (2.0 equiv), K₂CO₃ (3.0 equiv), MeOH, 0 °C, 30 min.</td>
<td>86%</td>
</tr>
<tr>
<td>3</td>
<td>Me₂SnCl₂ (0.1 equiv), K₂CO₃ (1.2 equiv), DBI(^a) (1.0 equiv), H₂O 0 °C, 1 h</td>
<td>82%</td>
</tr>
<tr>
<td>4</td>
<td>Me₂SnCl₂ (0.1 equiv), NIS(^b) (2.0 equiv), CH₂Cl₂, 0 °C, 3 h</td>
<td>26%(^c)</td>
</tr>
</tbody>
</table>

\(\text{a) DBI: dibromoisocyanuric acid b) NIS: \(N\)-iodosuccinimide c) Low yields are obtained when oxidizing dodecanediol (5) with NIS, but yields for the oxidation of heane-1,2,6-triol with NIS or bromine are comparable.}\n
In cyclic substrates, stannylenes also have shown to improve the regio- and stereoselectivity. The axial hydroxyl group of *cis*-diols in cyclic substrates is more accessible for the oxidant and is therefore preferentially oxidized over the equatorial hydroxyl group (Figure 4). This stereoselectivity has been exploited for the regioselective oxidation of monosaccharides.\(^{28,29}\) Arabinosides, galactosides, and mannosides have been successfully converted into the corresponding C2 and C4 ketoglycosides using stoichiometric amounts of bis(tributyltin) oxide and bromine.\(^{28}\) To lower the amount of toxic organostannanes being used, Onomura and co-workers developed an electrochemical oxidation method.\(^{30}\) A catalytic amount of dibutyltin oxide (10 mol\%) gave good conversion, but the stannylene acetal still had to be generated in situ prior to oxidation, due to the poor solubility of dibutyltin oxide. In the past decade, a variety of trialkyl- and dialkyltin compounds have been screened for their ability to mediate the oxidation of vicinal diols without preheating the reaction mixture.\(^{31}\) All of the organotin derivatives studied by Onomura and

**Figure 4.** Selective oxidation of vicinal diols in cyclic substrates. Arrow indicates the alcohol which is preferentially oxidized.
co-workers oxidized cyclic diols in reasonable to good yields in methanol, but only a subset was suitable for the oxidation of acyclic diols. Of these, dimethyltin dichloride proved to have the best catalytic activity, most likely due to its increased solubility in methanol compared to dibutyltin oxide and its higher reactivity for tin acetal formation. With this catalyst, dodecane-1,2-diyl (15) is efficiently converted into the corresponding hydroxymethyl ketone 16 using electrochemically generated ‘Br+’ (Table 1, entry 1) or reagents like bromine and dibromoisoocyanuric acid (DBI), as oxidants (Table 1, entries 2 and 3). Oxidation of diol 15 with NIS gave ketone 16 in low yields (Table 1, entry 4), but this oxidant has successfully been applied to hexane-1,2,6-triol.

Muramatsu recently demonstrated that catalytic tin-mediated oxidation is also applicable to a range of glycosides. Dioctyltin dichloride rather than dimethyltin dichloride gives the best yields for glycosides. Trimethyl(phenyl)ammonium tribromide ([TMPhA]+ Br–) in THF/MeOH in the presence of 2 mol% of organotin and K2CO3 converts glycosides containing an axial hydroxyl at C4, such as galactoside 19, into the corresponding 4-keto products with excellent selectivity (Figure 5). Protecting C3–OH in galactosides with a benzyl group completely blocked oxidation, which underlines the importance of the presence of a 1,2-diol system and thus chelation. Oxidation of glucosides 20 and mannoses 21 using the same conditions gave the expected keto products (Figure 5), albeit in lower yields than the stoichiometric procedure described by Tsuda and co-workers. However, a mixture of oxidation products is obtained when the glycoside bears two axial hydroxyl groups, as in arabinose.

In the search for more environmentally benign alternatives to organotin compounds, Onomura and co-workers explored the feasibility of using boronic acids to activate 1,2-diols in water. They hypothesized that boronate esters (see Scheme 3, structure 22 for the chelation mode) that can be formed in situ by reacting 1,2-diols with boronic acids, would react in a similar fashion with halonium reagents as the corresponding stannylene acetals. Both cyclic and acyclic 1,2-diols could indeed be oxidized with either DBI or electrochemically generated ‘Br+’ using 4-methoxyphenylboronic acid (only tested on

![Figure 5](image-url)
Chemo- and Regioselective Oxidation of Secondary Alcohols in Vicinal Diols

Scheme 3. Boronic acid catalysed oxidation of vicinal diols.

Scale up of this procedure is hampered by the low solubility of DBI in water and its high cost. Inspired by the work of Ishii et al. who showed that hypobromous acid can be generated in situ using sodium bromate and sodium bisulfite, Onomura and co-workers applied a similar reagent combination in the boronic acid mediated oxidation of 1,2-diols. Potassium bromate and potassium hydrogensulfate were used rather than the reagents reported by Ishii to minimize the effect of the addition order and the pH on hypobromous acid formation. Remarkably, the secondary alcohol of vicinal diols was not only oxidized in the presence of the methylboronic acid catalyst, but also in its absence (Scheme 4). It was therefore postulated that the formed bromonium species transiently interacts with the diol (see Scheme 4, structure 23 for the chelation mode), thereby activating the diol and facilitating oxidation of the secondary alcohol.

Scheme 4. Bromonium catalysed oxidation of vicinal diols.

1.3.2 Transition metal catalysed

Many transition-metal-catalyst systems have been reported to oxidize primary and secondary mono-alcohols, pronounced examples being the Pd(OAc)$_2$/pyridine system of Uemura, the Pd(OAc)$_2$/neocuproine system of Sheldon, and the Pd–NHC system of Sigman. The ligands used in these systems play an essential role in the oxidation reaction. They stabilize the catalyst to prevent palladium black formation, lower the energy barrier for $\beta$-hydride elimination, and facilitate alkoxide formation by proton-coupled ligand
exchange. Based on this, novel systems have been developed that have improved catalytic activity and that enable chelation-controlled regioselective oxidation of 1,2-diols. The Lee group explored the use of NHC ligands to both stabilize and activate the palladium for oxidation chemistry. The neutral Pd–NHC (η^3-allyl) complexes showed excellent selectivity for the secondary hydroxyl of 1,2-diols, with complex 26 being the most efficient catalyst (Scheme 5). Although the reaction is performed at 80 °C with 20 bar of air, only minimal amounts of palladium black are formed and 74% conversion of propane-1,2-diol (24) into hydroxyacetone (25) was achieved in 5 hours using only 1 mol% of catalyst (Scheme 5).

\[
\text{Scheme 5. Vicinal secondary alcohol oxidation with palladium catalyst.}
\]

1,3-Diols are also oxidized by 26, albeit far less efficiently, and it has therefore been recently proposed that the catalyst may form the corresponding chelate 27 (Figure 6). For similar catalysts, chelation is initiated by proton-coupled ligand exchange of the η^3-allyl ligand by one of the hydroxyl functionalities, thereby forming a palladium alkoxide. The remaining hydroxyl of the vicinal diol coordinates to palladium and expels propene, which is favourable for 1,2-diols and may thus explain the regioselectivity.

The Waymouth group pioneered the use of cationic palladium complexes that have an open coordination site and a basic acetate ligand for the oxidation of alcohols. They showed that the catalyst reacts with alcohols to form
aldehydes and ketones under mild conditions using air as the co-oxidant (Scheme 6). When the same catalyst was applied to vicinal diols, a dramatic increase in reaction rate and selectivity was observed. Glycerol (29) was converted into dihydroxyacetone (30) in 92% yield and >95% selectivity within 15 minutes using 2.5 mol% of catalyst and benzoquinone as the internal oxidant (Scheme 6). Primary and secondary alcohols and 1,3-diols react only slowly under these conditions.


Other cationic palladium complexes, such as PyOX ligand 31 (Figure 7), which was designed for enantioselective oxidation, give similar regioselectivities and yields for propane-1,2-diol (24) and glycerol (29). In the enantioselective oxidation reactions, however, only moderate ee’s were obtained. Even though harsher conditions are required, also bis-cationic palladium–pyridyl complex 32 (Figure 7) selectively oxidizes the secondary alcohol of propane-1,2-diol (24).

Figure 7. Structure of palladium catalyst 31 and 32 respectively.

Interestingly, the Waymouth group revealed that 28 can also be used to discriminate between two secondary alcohols. Palladium catalyst 28 oxidized cyclohexanediols 17 and 18 with the same selectivity as organotin catalysts; that is, the axial alcohol of a cyclic cis-diol is preferentially oxidized over the equatorial (Figure 8).
At the same time, we demonstrated that palladium catalyst 28 enables selective oxidation of one of the three contiguous secondary alcohol groups in glycosides. Reacting methyl glucoside 33 (both the α- and the β-epimer) with 28 in CH₃CN/H₂O gave a single product, which turned out to be the 3-keto glucoside (Figure 9). Changing the solvent system to DMSO/dioxane or DMSO led to a significant rate enhancement, as was also reported for glycerol, but it did not affect the selectivity. All of the studied glucose-configured saccharides react at the C3 position, independent of the substituent at the anomeric position. Thioglucosides and C-glucosides both are reported to give the C3 keto product. The Waymouth group recently extended the scope of the reaction and demonstrated that xylosides 34, fucosides 35, rhamnosides 36, arabinosides 37, 6-deoxyglucosides, and also conformationally locked 1,6-anhydropyranose such as 1,6-anhydro-galactoside 38 give selective oxidation at the C3 position (Figure 9). In this work, the authors also proposed a mechanism for the oxidation reaction. Although it shows how the catalyst is oxidizing the carbohydrates, it does not explain why the C3 position is selectively oxidized (see Figure 10). According to the mechanism, upon dissolving catalyst 28 it dissociates to its monomeric form 39. Ligand exchange with a vicinal diol, in this case methyl α-D-glucoside 33, gives rise to hydroxy-alkoxy species 40. Coordination to the C3-H and subsequent β-hydride elimination (41), which is stated as the rate-determining step, gives the ketone complex 42. Release of the product (43) gives the palladium hydride species 44, which upon deprotonation
yields Pd(0). Pd(0) is then re-oxidized by benzoquinone (45) via formation of hydroquinone (46) to yield the active Pd(II) complex 39 back.

In contrast to cyclohexanediols 17 and 18, the equatorial C3–OH is predominantly oxidized in glycosides, even for those that bear an axial substituent at C2 or at C4. Clearly, stereoelectronic effects in the substrate dominate the regioselectivity.

A major practical hurdle in the oxidation of glycosides is the tedious purification of the keto products, which is hampered by their polarity, the solvent used in the oxidation reaction and the use of benzoquinone. The latter issue can be addressed by using dioxygen as co-oxidant. However, competing oxidation of the methyl groups in the neocuproine ligand inhibits the catalyst and conversion. The two methyl groups play an essential role in the dissociation of the dimeric complex into the catalytically active monomeric species and can therefore not be omitted. The Waymouth group demonstrated

Figure 10. Oxidation mechanism of glycoside by palladium catalyst 28.
that catalyst inactivation can be minimized using ligands that are less oxidation sensitive. Palladium complexes of 4-methyl-2-(trifluoromethyl)-1,10-phenanthroline (Figure 11, structure 47) showed an approximately 2-fold increase in turnover numbers (TON) and turnover frequencies (TOF) (after 24 h) compared to catalyst 28.\textsuperscript{50} We showed that deuteration of the methyl groups in neocuproine (Figure 11, structure 48) has a similar effect on the catalyst stability and also leads to an approximate 2-fold increase in TON and TOF.\textsuperscript{51}

![Figure 11. Structure of oxidation resistant ligands.](image)

Besides improvements in the catalyst, also the reaction conditions have been optimized. The Waymouth group recently showed that sacrificial reductants that react with peroxides, such as 2,5-diispropylphenol have a beneficial effect on the catalyst lifetime, when dioxygen is used as a co-oxidant.\textsuperscript{49} Lowering the amount of benzoquinone simplifies purification and improves the selectivity. Finally, the Waymouth group showed that depending on the substrate, trifluoroethanol or acetonitrile/water can be used as solvents in the oxidation reaction. Although this greatly simplifies the workup procedure, it comes at the cost of epimerization of some of the products.\textsuperscript{49}

### 1.4 Applications

The regioselective oxidation of vicinal diols has been applied in a wide range of research fields. It has been used for the valorization of glycerol, a major side product of the production of biodiesel. Palladium catalyst 28 and iron-based catalyst 6 convert glycerol selectively into dihydroxyacetone. This added value building block forms a starting point for the synthesis of fine chemicals and it can be applied in cosmetics.

In organic synthesis, regioselective oxidation reactions have been employed to functionalize diols in partly protected intermediates to synthesize chemical probes\textsuperscript{52} and to synthesize natural products. We exploited the excellent regioselectivity offered by catalyst 28 for the protection group-free synthesis of the Colorado potato beetle pheromone 51 (Scheme 7).\textsuperscript{53} Asymmetric epoxidation of commercial available geraniol 49 followed by regioselective hydrolysis of the epoxide yielded triol 50. Selective oxidation of the secondary alcohol using catalyst 28 yielded the desired product 51, in 80% yield over three steps. Other
natural products containing a hydroxymethyl ketone moiety may be synthesized in a similar fashion.

![Scheme 7. Synthesis of the Colorado potato beetle pheromone 51 via regioselective oxidation.](image)

When applied on (partially protected) saccharides, regio-selective oxidation enables the synthesis of rare monosaccharides, the modification of aminoglycosides, and the straightforward synthesis of derivatives of glycosylated natural products. Palladium catalyst 28 has also been employed to synthesize drug derivatives. Analogues of the C-glycoside dapagliflozin (Figure 12, structure 52), an inhibitor of the glucose transporter SGLT-2, have been prepared using palladium catalyst 28.

![Figure 12. Structure of the C-glycoside dapagliflozin.](image)

### 1.5 Outline of this thesis

In the past decade, considerable advances have been made in the regioselective oxidation of vicinal diols. This has led to the development of methods that are environmentally more benign and that can be used to oxidize relatively simple 1,2-diols with excellent selectivities. Although insightful, the real potential of regioselective oxidation lies in the ability to modify more complex molecules, like monosaccharides, oligosaccharides, and glycosylated natural products and this is exemplified by a recent patent on the selective modification of natural products using oxidation.

To fully exploit the potential of regioselective oxidation reactions, methods that enable selective modification of specific glycoside residues within a complex oligosaccharide will have to be developed. To this end, further insights have to be obtained to predict how and which hydroxyl group will be oxidized in more complex systems.
The aim of this thesis is to further investigate the regioselective palladium catalysed oxidation of glycosides. The focus lies on expanding the substrate scope, understanding the reactivity and eventually study the origin of the regioselectivity.

In Chapter 2, an investigation is reported on the oxidation of oligosaccharides. By oxidizing oligosaccharides bearing an anomeric azide, bifunctional linkers can be prepared in only two steps. The applicability of these linkers is highlighted in the conjugation of a model protein with biotin.

In Chapter 3, the oxidation method is further extended towards reducing carbohydrates. In this manner, the rare sugars allose and allitol can be prepared in a two-step one pot procedure from glucose. Furthermore, it is shown that overoxidation leads to a novel (side) product formed by skeletal rearrangement.

In Chapter 4, the scope and limitations of the oxidation method are further investigated. To be able to monitor, analyse and characterize the reaction in one simple operation, it was decided to apply quantitative NMR (qNMR). In this manner, we were able to show that glucosides, mannosides, galactosides and xylosides all show selective oxidation of the C3-OH. However, subsequent reaction of the resulting ketone moiety is the main culprit for side product formation.

In Chapter 5, an extension is made to the work described in chapter 4, focusing on the question why glucosides show an increased rate of oxidation compared to glycosides bearing an axial substituent. Furthermore, a hypothesis is formulated on the origin of the excellent regioselectivity. With the combined information obtained throughout this research and in previous studies, a working model for the regioselectivity is developed.

In Chapter 6, an outlook and future perspective for the selective oxidation of glycosides will be given. Several possible directions of further investigation of this oxidation method will be presented. Furthermore, possible routes for oxidation of the different positions in (oligo)saccharides will be described.
1.6 References
