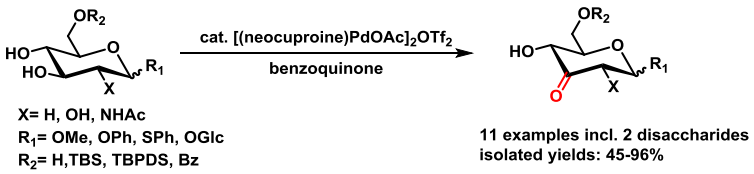
# Summary

Carbohydrates are the most abundant class of natural products and are therefore a vivid field of research. Due to the similar reactivity of the hydroxyl groups present in carbohydrates, carbohydrate chemistry often relies on long and inefficient protection and deprotection strategies.

The main goal of this research was the development of a catalytic oxidation method, which would be able to discriminate between several secondary hydroxyl groups, which are present in carbohydrates in particular in glycosides.

**Chapter 2** describes the development of a method for the regioselective oxidation of glucosides. It was shown that the catalyst, which was used before by Waymouth for the selective oxidation of diols, such as propandiol,[1,2] was also able to distinguish between several secondary hydroxyl groups. Several mono- and diglucosides were selectively oxidized on C3 and were isolated, as single oxidation products, in moderate to excellent yields.

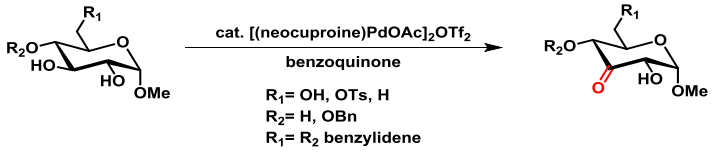



**Scheme 1 Selective oxidation of glycosides at the C3-position**

As explanation for the excellent selectivity, the kinetic coordination of the most nucleophilic hydroxyl group of the glucoside as product-determining step, was suggested. As an illustration of the usability of the keto-glucosides, they were used in the synthesis of methyl $\alpha$-D-

allopyranoside and methyl 3-amino-3-deoxy-$\alpha$-D-allose, which could be isolated in 91% and 56%, respectively, in only 2-3 synthetic steps.

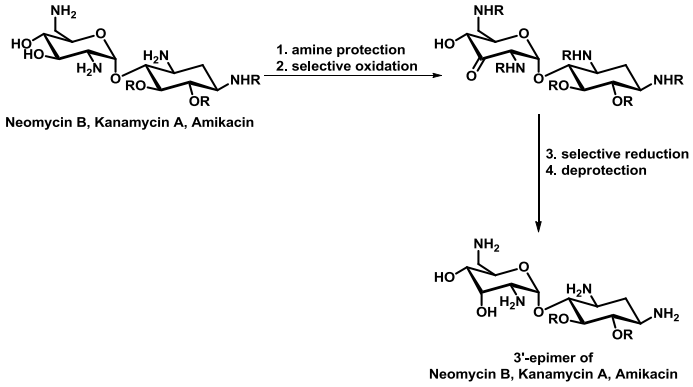
The extension of the substrate scope to partial protected glucosides in order to get further insight in the origin of the selectivity is described in **Chapter 3**. Earlier, it was shown that the oxidation of diols, such as propandiol, using [(neocuproine)PdOAc]$_2$OTf$_2$ was not only faster but also more selective than primary and secondary alcohols.[3] Two diol motifs can be assigned in a unprotected glucoside, which both would lead to oxidation on C3, the 2,3-diol and the 3,4-diol. Substrates described in **Chapter 2** suggested that the 3,4 diol motif should be important for the selectivity, since substrates like 2-desoxy methyl glucopyranoside or 2-acetamido methyl glucopyranoside were still oxidized on C3. Moreover, it was important to know whether substitution on C6 has an influence on the selectivity. Therefore, several substrates have been synthesized, where the C4, C6 or both positions have been protected or modified.




**Scheme 2 Selective oxidation of C4 and C6 protected glycosides**

Surprisingly, all substrates show the same selectivity, sole oxidation on C3, indicating that the 2,3-diol motif as well as the 3,4 diol motif lead to oxidation on C3. Electron withdrawing substituents, such as tosyl group, however showed reduced reaction rate than previously observed. In order to see whether the reduced reaction rate is connected to the electronic properties of the substituent on C6, a thorough NMR study was conducted. A correlation between the chemical shift on C3 and electronic properties of the substituents on C6 was not observed, indicating either the absence of long range effect or the long range effects are not measurable by the chemical shift.

The selective oxidation and modification of aminoglycoside antibiotics is described in **Chapter 4**. Aminoglycosides are an important group of broadband antibiotics, which are mainly used in the hospital setting. The development of resistances by, among others, aminoglycoside modifying enzymes creates the necessity for the development of new antibiotics. An important class of aminoglycoside modifying enzyms are the APH(3')s, which phosphorylate the 3'-position of an aminoglycoside upon which the antibiotic activity is lost. This chapter shows the selective oxidation of nitrogen protected neomycin B, kanamycin A and amikacin at the 3'-postion. The 3'-keto-aminoglycosides could be isolated in moderate to good yields and could be reduced selectively by treatment with sodium borohydride to the 3'-epi-aminoglycoside. In order to tackle two mechanisms of bacterial resistance, the selective oxidation/reduction strategy was combined with a selective azide transfer-strategy as described by Bastian *et al.*.[4] In that way, neomycin B could be modified to the 3'-epi-3-dimethyl-neomycin B in only 6 steps. The intermediates allow further modification of 3'- or the 3-position in the future. Although low to moderate isolated yields have been observed for all of the modified aminoglycosides after deprotection and purification, this approach allows efficient and rapid access to 3'-modified aminoglycosides.




**Scheme 3 Convenient synthesis of the 3'-epimer of several aminoglycosides via selective oxidation of the 3'-position**

**Chapter 5** gives an overview over the future prospects and challenges for the selective oxidation of glycosides. In order to apply this method in industry it would be advantages to use oxygen as terminal oxygen. Earlier, it was shown that oxidation of ligand is the main reason for catalyst deactivation, when oxygen is used as terminal oxidant.[2] Based on the kinetic isotope effect, it was proposed that the deuteration of the ligand could enhance the stability of the catalyst. Preliminary results show a higher total turnover number in case of the deuterated ligand compared to the non-deuterated ligand, these results have to be confirmed in the future.

Several natural sweeteners such as glycyrrhizin, mogrosides or the steviol glycosides could be novel substrates for the selective oxidation. This approach opens opportunity to either synthesize more potent sweeteners or to study their biological activity.[5–8]

Aminoglycosides could be transformed via the 3′-keto-aminoglycoside by deoxygenation, reductive amination, or fluorination to the corresponding 3′-deoxy-aminoglycoside, 3′-deoxy-3′-amino-aminoglycoside and the 3′,3′-difluoro-aminoglycoside, respectively. This would not only circumvent alteration by aminoglycoside modifying enzymes at the 3′-position, but could also improve binding affinity for RNA[9–14] or decrease the toxicity. [15]

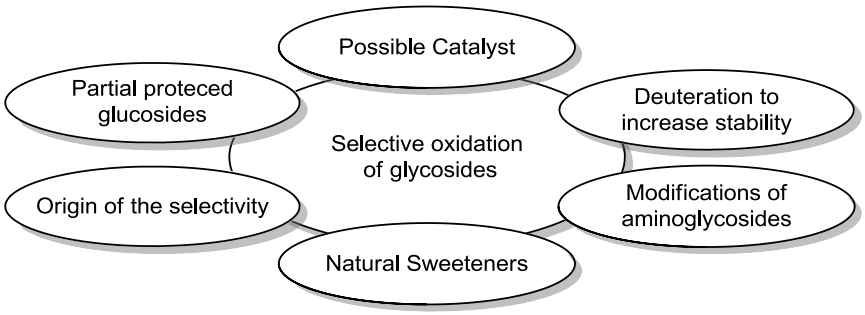



**Figure 1 Overview of the possibilities enabled by the selective oxidation of glycosides**

In conclusion, the method described in this thesis, allows the selective oxidation and therefore modification of glycosides. Using this method, long and inefficient protection and deprotection strategies can be circumvented, giving fast access to modified highly complex natural products.

# LITERATURE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