Regioselective Carbohydrate Oxidations: A Nuclear Magnetic Resonance (NMR) Study on Selectivity, Rate, and Side-Product Formation

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S *Supporting Information*

ABSTRACT: Palladium/neocuproine catalyzed oxidation of glucosides shows an excellent selectivity for the C3-OH, but in mannosides and galactosides, unselective oxidation was initially observed. For further application in more-complex (oligo)saccharides, a better understanding of the reaction, in terms of selectivity and reactivity, is required. Therefore, a panel of different glycosides was synthesized, subjected to palladium/neocuproine catalyzed oxidation and subsequently analyzed by qNMR. Surprisingly, all studied glucosides, mannosides, galactosides, and xylosides show selective oxidation of the C3-OH. However, subsequent reaction of the resulting ketone moiety is the main culprit for side product formation. Measures are reported to suppress these side reactions. The observed differences in reaction rate, glucosides being the most rapidly oxidized, may be exploited for the selective oxidation of complex oligosaccharides.

KEYWORDS: oxidation, regioselective, glycosides, palladium, qNMR
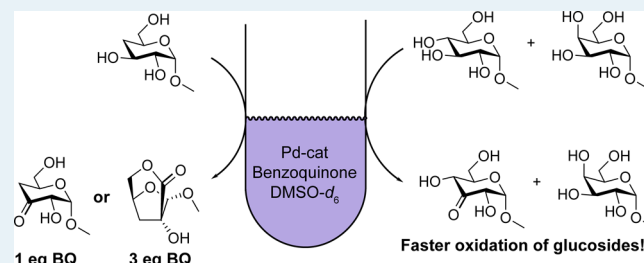
INTRODUCTION

Monosaccharides, oligosaccharides, and polysaccharides are involved in a large variety of biological processes, such as cellular transport, cell−cell interactions, and immunology. They are also important structural components (for example, the cell wall of bacteria and plants and the exoskeleton of insects consist for a large part of polysaccharides).[1] In glycochemistry, molecularly well-defined carbohydrates are synthesized from a relatively limited set of readily available monosaccharides (Figure 1) to
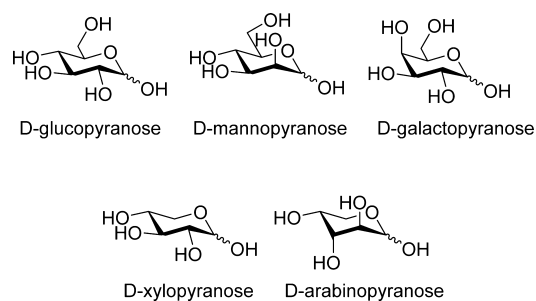

Figure 1. Overview of various common glycopyranoses.

study these biomolecules and the processes in which they are involved.[2,3] Monosaccharides and oligosaccharides also serve as starting points for the synthesis of other natural products and biomaterials.[4]

The field of glycochemistry traditionally relies heavily on protecting group manipulations to single out one of the hydroxyl functionalities, but the attention has recently broadened to the development of protection group-free synthesis routes.[5] These studies have led to methods that enable the selective functionalization of the primary OH or the anomeric hydroxyl group of reducing saccharides. Activating agents, such as 2-chloro-1,3-dimethylimidazolinium chloride (DMC) and 2-chloro-4,6-dimethoxy-1,3,5-triazine, react selectively with the anomeric hydroxyl group of monosaccharides and oligosaccharides. Sequential nucleophilic substitution with azide, alcohols, and thiols readily converts the resulting reactive intermediates to glycosyl azides, glycosides, and thioglycosides.[6−8] Modification of the primary hydroxyl group is relatively straightforward by reacting the glycoside with bulky reagents.[9,10]

Methods to selectively functionalize one of the secondary hydroxyl groups are still limited.[11−13] Current research mainly focuses on regioselective acylation and silylation, which is an approach that has been applied in an elegant way in the total synthesis of the ellagitannins, glucoside esters of gallic acid, and hexahydroxy phenoic acid, by the Kawabata group,[14,15] and these regioselective acylation/silylation methods have been thoroughly reviewed recently.[5,16] We reported on the regioselective oxidation of glucosides using Waymouth's palladium catalyst,[17,18] [(neocuproine)PdOAc]₂OTf₂, in the presence of 3 equiv of benzoquinone and showed that glucopyranosides give selective oxidation of the C3-OH.[19] For differently configured substrates such as methyl β-D-galactopyranoside, methyl
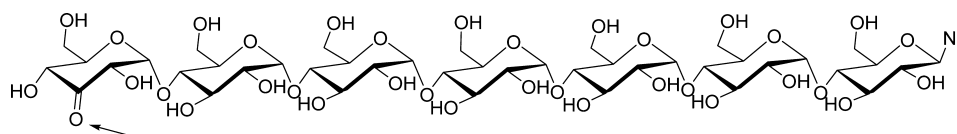
Figure 2. Regio and chemoselective oxidation of the terminal glucoside residue in azido-β-D-ketomaltoheptaoside.

α-D-mannopyranoside, and methyl α-D-xylopyranoside (for the structures of the parent pyranoses, see Figure 1), unselective oxidation was observed. We recently expanded on this work and showed that the reducing carbohydrates α-D-glucopyranose and N-acetyl α-D-glucosamine also are selectively oxidized with the catalytic system.[20] The C3-OH is oxidized, while the more readily accessible hydroxyl at C6 and the more reactive anomeric hydroxyl do not react primarily under these conditions. Waymouth and co-workers recently showed that 6-deoxy-glycopyranosides, xylopyranosides, and arabinopyranosides (for the structures of the parent pyranoses, see Figure 1) also can be oxidized selectively with $[(\text{neocuproine})\text{PdOAc}]_2\text{OTf}_2$ by reducing the amount of benzoquinone to 1.5 equiv or using oxygen as a co-oxidant.[21] Even substrates that contain an axial alcohol give the 3-ketoglycoside as the major product, with methyl α-L-fucopyranoside being the exception. In that case, the C4 ketone was also observed in a 1:1 ratio, together with the C3-keto product. Moreover, 1,6-anhydromannose and 1,6-anhydrogalactose can be oxidized selectively using these conditions.

Palladium-catalyzed regioselective oxidation is also feasible on disaccharides and oligosaccharides. We revealed that the methyl glucosylglucose disaccharides cellobiose and maltose,[19] and 1,4-oligoglucoses up to the heptamer can be oxidized using our methodology.[22] Reacting these substrates with the catalyst results in selective oxidation of the C3-OH of the terminal glucose residue at the nonreducing end of the 1,4-linked glucan (Figure 2).

The scope of oligosaccharides used in these oxidation reactions has been largely limited to oligoglucosides and before the method can be extended to other (more) complex oligosaccharides, three important questions need to be addressed, namely,

(1) why does oxidation occur exclusively at the terminal glucose residue of 1,4-linked glucans,

(2) why is the oxidation of galactopyranosides and mannopyranosides (that are not conformationally locked like their anhydro derivatives) unselective, and

(3) is there a difference in oxidation rate for differently configured substrates,

since this is a potential tool for selective oxidation in complex oligosaccharides.

One hypothesis for the exquisite terminal selectivity in the oxidation of 1,4-linked glucans is that the 3-OH of the terminal glucose residue is sterically less congested than the 3-OH of the internal glucose residues. An alternative hypothesis is that a free C4-OH is essential for chelation with the catalyst. By monitoring the oxidation of protected 4-OH and 4-deoxygluco-sides, it should be possible to assess which of these hypotheses is valid. Bulky protecting groups will block chelation and introduce steric hindrance, while deoxygenation of the C4 of methyl glucose will only affect chelation. Previously, we also employed this deoxygenation strategy to demonstrate that the C2-OH is not essential to direct the oxidation to the 3-position.[19]

For the second question—why mannosyl and galactosyl derivatives are nonselectively oxidized—we originally hypothesized

that the presence of an axial hydroxyl group at the C2 or the C4 position results in oxidation of these positions as well. However, the recent observation by Waymouth and co-workers that conformationally locked 1,6-anhydromannopyranose and 1,6-anhydrogalactopyranose are selectively oxidized at the C3 position revealed that probably not the substitution pattern but other factors, such as the stability of the product, influence the outcome of the reaction.
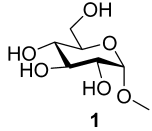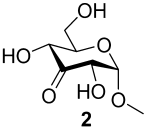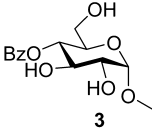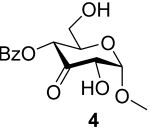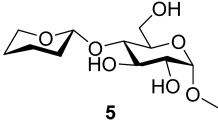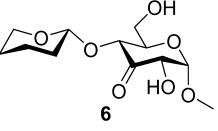
To study these hypotheses and to determine the difference in reactivity of the various glycosides, we synthesized a panel of glycopyranosides and st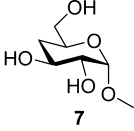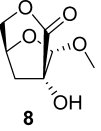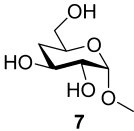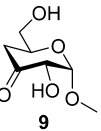udied their behavior in individual oxidation reactions, as well as competition experiments with the benchmark substrate methyl α-D-glucopyranoside (**1**). Here, we report the results of these studies.

■ RESULTS AND DISCUSSION

Previous experience revealed that, because of the water solubility of the products and the difficulties encountered in their purification, there is no reliable relationship between the selectivity in the oxidation and the isolated yield of the product. To circumvent this issue and define a reasonably accurate method to determine the selectivity in the oxidation, we decided to monitor the reactions by qNMR.[23,24] Using the residual solvent signal as the internal standard, we could both monitor the conversion to the product and characterize the product in one operation. Methyl α-D-glucopyranoside (**1**) (Table 1, entry 1) was used as a test substrate for this method. Under the reaction conditions for the NMR experiment; 2.5 mol % of palladium catalyst and 3 equiv of benzoquinone in DMSO-d_6 (0.3 M), **1** was fully converted within 1 h with 86% selectivity toward the desired product, that is, **2** was formed in 86% NMR yield.[25] This NMR yield was confirmed by repeating the NMR experiment using tetrachloronitrobenzene (TCNB) or mesitylene as an internal standard; in both cases, an NMR yield of 86% was obtained. No other products were observed by ¹H NMR. Although this yield is somewhat lower than obtained on a preparative scale with the reported optimized conditions,[19] we decided to continue performing the reactions under the given NMR conditions. Having established this qNMR analysis method, we applied it to several C4-OH modified glucosides (please note that, in all cases, unless otherwise stated, the given product is the only identifiable product, with an estimated detection limited of 3%).

Oxidation of 4-benzoyl glucopyranoside **3** (Table 1, entry 2) gave the expected 3-keto product **4** with 78% selectivity, indicating that the presence of a free C4-OH is not a prerequisite for selective oxidation of the C3-OH. To mimic oxidation of internal glucose residues of 1,4-glucans more closely, we synthesized C4-OH THP-protected derivative **5**. The THP protecting group at C4, in this case, closely resembles the terminal glucosyl residue at the nonreducing end, but without its hydroxyl groups. As expected, two diastereomers were formed upon THP protection, but the diastereomers could be separated and the stereochemistry of the major diastereomer was identified by X-ray analysis (see the Figures S1 and S2 in the Supporting Information for the X-ray spectrum of the benzyl-protected

Table 1. Selective Oxidation of C4-Modified Glucopyranosides[a]

#	SM	Product	Selectivity
1	**1**	**2**	87%
2	**3**	**4**	78%[b]
3	**5**	**6**	70%
4	**7**	**8**	57%
5	**7**	**9**	94%[c, d]

[a]Reaction conditions: 2.5 mol % of [(neocuproine)PdOAc]$_2$OTf$_2$, 3 equiv of benzoquinone, 0.3 M in DMSO-d_6. Selectivity determined by qNMR using the residual DMSO-d_6 as an internal standard. Unless otherwise stated, no other products could be assigned by ^{1}H NMR, with an estimated detection limit of 3%. [b]Incomplete conversion, 72% conversion of starting material. Selectivity calculated according to this conversion. [c]Performed with 1 equiv of benzoquinone. [d]Incomplete conversion, 68% conversion of starting material. Selectivity calculated according to this conversion.

C4-THP methyl α-D-glucopyranoside).[26] It turned out to have the configuration as depicted in Table 1, entry 3. Derivative **5** was oxidized at the C3 position with 70% selectivity. The observation that the bulky THP group at the C4-OH did not block oxidation demonstrates that palladium-catalyzed oxidation of internal glucose residues of 1,4-glucans is, as such, feasible. Therefore, this suggests that the selectivity for oxidation of the terminal residue in diglucoses and oligoglucoses is caused by a difference in reaction rate, rather than a complete shielding of the internal C3-OH positions. To validate this, a one-to-one mixture of methyl α-D-glucopyranoside (**1**) and THP-protected glucopyranoside **5** was subjected to the oxidation reaction, using half an equivalent of benzoquinone, with respect to the total amount of glycoside. qNMR analysis confirmed that methyl α-D-glucopyranoside **1** is indeed preferentially oxidized over THP derivative **5** (product ratio 3-ketoglucopyranoside **2**:4-THP-3-ketoglucopyranoside **6** = 4:1; see Figure S6 in the Supporting Information). Apparently, bulky groups on the C4-OH do not influence the selective oxidation at C3, but have a considerable effect on the reaction rate. To dissect if the reduced reaction rate is caused by the inability to chelate to the C4-OH or by the steric effects of the THP group, methyl 4-deoxyglucopyranoside **7** was synthesized.[27]

Upon oxidation of **7** with the palladium catalyst in the presence of 3 equiv of benzoquinone, the ^{1}H NMR spectrum after 1 h revealed that (i) all C4-deoxy **7** had been consumed and (ii) at least two new products (Figure 3, 1 h) had been formed. Oxidation of the C3-OH of glucosides typically results

in a downfield shift of H2 and H4 in the ^{1}H NMR,[28] but this downfield shift was not observed for any of the products. Allowing the reaction to proceed for 24 h led to an increase in one of the products at the expense of the other one (Figure 3, 24 h). The ^{13}C NMR and ^{1}H NMR spectra of this major product showed similarities to the lactone product obtained in the oxidation of β-glucopyranose in our previous study.[20] We observed very distinct diastereotopic protons for the exocyclic CH$_2$ group and small coupling constants, indicating that rearranged product **8** is formed over the course of the reaction. The signals at 172 and 77 ppm in the ^{13}C NMR spectrum, which are indicative for the ester carbonyl and the tertiary alcohol, further confirmed that compound **8** had been obtained. Based on the results obtained in the oxidation of glucose, we propose that the formation of lactone **8** follows a similar mechanism (Scheme 1). Oxidation at C3 (**9**) is followed by intramolecular lactol formation (**10**). Sequential oxidation at C2 (**11**) and subsequent α-ketol rearrangement results in lactone **8**. This is apparently facilitated by the absence of an equatorial hydroxyl group at the C4 position, since the rearrangement had not been observed for any of the methyl α-D-glucopyranosides used in the oxidation reaction thus far. Based on this mechanism, the second species that is observed after 1 h and slowly converted to **8** should belong to one of the intermediates (Scheme 1). The absence of a signal for H2, in combination with the long-range J-coupling and the diastereotopic protons, suggest that these signals correspond to lactol **11** (Figure 3 and Scheme 1).
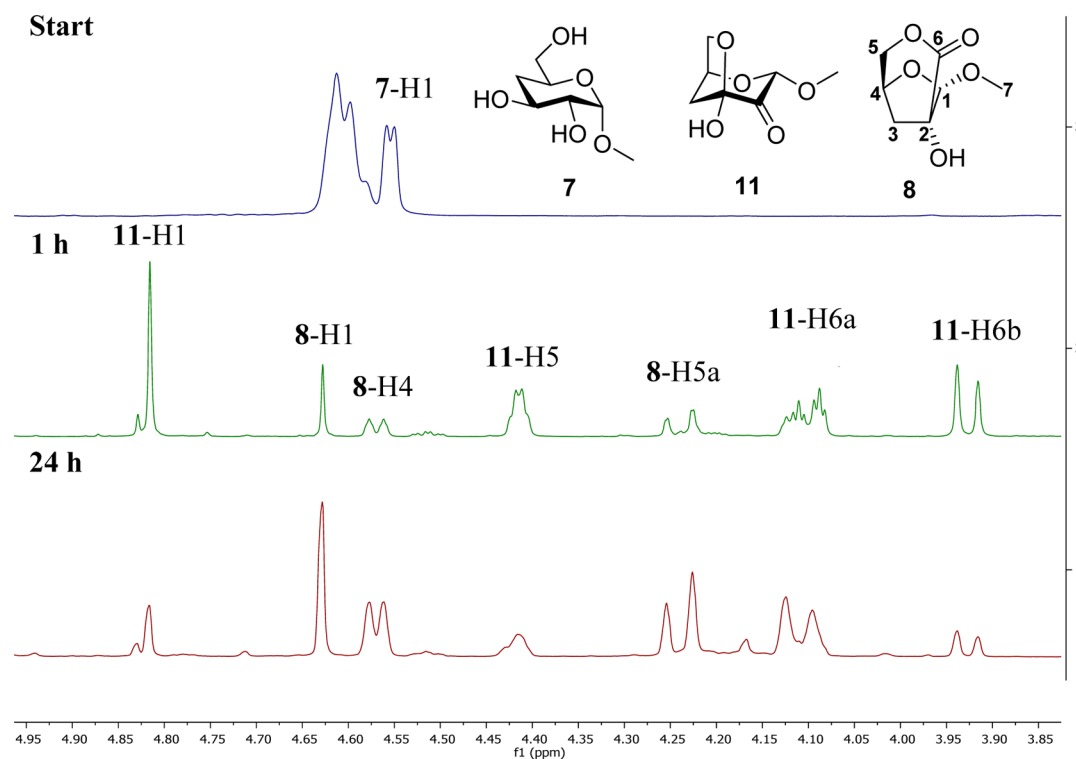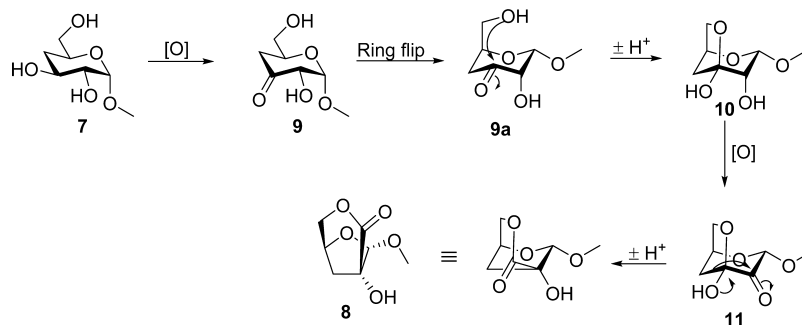
Figure 3. Batchwise oxidation of C4-deoxy (**7**): 1 h = 1 equiv of benzoquinone, 24 h = 3 equiv of benzoquinone.

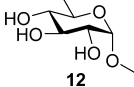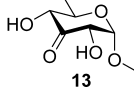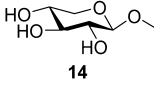**Scheme 1. Mechanism of the Rearrangement Taking Place in the Oxidation of Methyl 4-Deoxyglucopyranoside (7)**
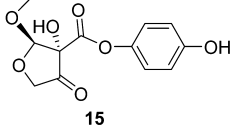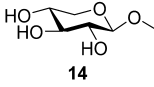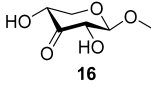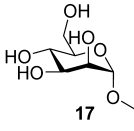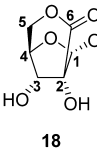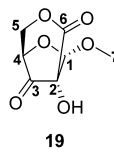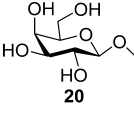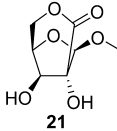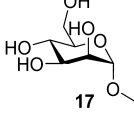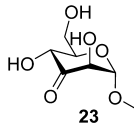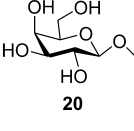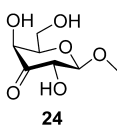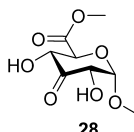

The key steps in this sequence are the formation and subsequent oxidation of the hemiacetal intermediate, and, therefore, we reasoned that its formation might be suppressed by decreasing the benzoquinone loading. Indeed, the initially expected C3-keto **9** was the major product observed when **7** was oxidized with 1 equiv of benzoquinone (>60% conversion of SM, >90% selectivity toward the product). Batchwise addition of benzoquinone up to 2.5 equiv resulted in the formation of lactol **11**, which rearranged to form **8** when left for a prolonged time (>16 h, see Figure S3 in the Supporting Information).

Having confirmed that 4-deoxyglucopyranoside **7** is oxidized selectively at the C3 position when 1 equiv of benzoquinone is used, we employed the substrate in a competition experiment to determine the effect of the C4-OH on the oxidation rate. In similar fashion as that previously observed, a one-to-one mixture of methyl α-D-glucopyranoside (**1**) and C4-deoxy **7** was subjected to the oxidation reaction, using half an equivalent of benzoquinone, with respect to the total amount of glycoside. Surprisingly, after complete consumption of benzoquinone, an approximate 1:1 mixture of oxidation products was obtained, suggesting that chelation of the palladium catalyst with C4-OH

does not play a role at all! Therefore, the selectivity for the terminal glucose residue in oligosaccharides is fully controlled by sterics.

We subsequently focused our attention on addressing the second question: why does the oxidation of xylosides, galactosides, and mannosides in the presence of 3 equiv of benzoquinone lead to complex mixtures? Based on the observation that lactone **8** is formed when 4-deoxyglucopyranoside **7** is reacted with an excess of benzoquinone, we hypothesized that a similar reaction may cause side product formation upon oxidation of xylosides, galactosides, and mannosides. As for deoxygenation of C4, the axial hydroxyl group in methyl $\al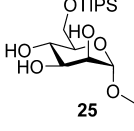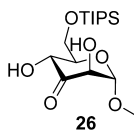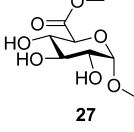pha$-D-mannopyranoside **17** and methyl β-D-galactopyranoside **20** and the absence of an equatorial CH_2OH, as in methyl β-D-xylopyranoside **14**, may reduce the difference in the free energies of the tetrahydropyranoside conformers. As such, this may facilitate lactol formation and subsequent overoxidation and α-ketol rearrangement. Rather than a lack of regioselectivity in the oxidation of **14**, **17**, and **20** as reported previously, side products may therefore have been derived from the formed 3-keto products.

Table 2. Regioselective Oxidation of (Modified) Glucopyranosides, Mannopyranosides, and Galactopyranosides[a]

#	SM	Product	Selectivity
1	**12**	**13**	69%
2	**14**	**15**	38%
3	**14**	**16**	64%[b]
4	**17**	**18** + **19**	26% + 19%
5	**20**	**21**	27%
6	**17**	**23**	30%[b]
7	**20**	**24**	21%[b]
8	**25**	**26**	81%[b,c]
9	**27**	**28**	82%[d]

[a]Reaction conditions: 2.5 mol % of [(neocuproine)PdOAc]$_2$OTf$_2$, 3 equiv of benzoquinone, 0.3 M in DMSO-d_6. Selectivity determined via qNMR using the residual DMSO-d_6 as an internal standard. Unless otherwise stated, no other products could be assigned by ^{1}H NMR, with an estimated detection limit of 3%. [b]Performed with 1 equiv of benzoquinone. [c]Incomplete conversion, 58% conversion of starting material. Selectivity calculated according to this conversion. [d]Isolated yield.

To study if this was the case, we first subjected methyl 6-deoxyglucopyranoside **12** and methyl β-D-xylopyranoside (**14**) to the oxidation reaction. While **12** gave oxidation of the C3-OH with 69% selectivity, the oxidation of **14** resulted in rearranged product **15** when 3 equiv of benzoquinone was applied as a co-oxidant (Table 2, entries 1 and 2). Since an intramolecular primary alcohol is lacking in xylopyranoside **14**, the formed 3-keto-xylopyranoside reacted with hydroquinone, resulting from the reoxidation of the catalyst by benzoquinone. The resulting hemiacetal rapidly oxidized at C2 and hydroquinone ester **15** was obtained after α-ketol rearrangement with

38% selectivity as the major product. Ester **15** is the major product and no other identifiable products were visible. Waymouth and co-workers demonstrated that, in the oxidation of xylopyranoside **14**, lowering the amount of benzoquinone or switching to oxygen as the co-oxidant reduced the formation of side product.[21] Switching to oxygen prevents the formation of hydroquinone that, as a nucleophile, gives rise to subsequent reactions such as hemiacetal formation, oxidation, and rearrangement. This was also the case for our reaction. Upon carrying out the reaction with 1.2 equiv of benzoquinone, the expected 3-keto product **16** was observed (76% conversion of

starting material, 84% selectivity toward product **16**) (Table 2, entry 3). Using our reaction conditions (room temperature in DMSO, compared to acetonitrile at 50 °C in the case of Waymouth et al.[21]), we did not observe the reported C4-keto side product. Furthermore, switching to our deuterated catalyst and employing oxygen as the co-oxidant also prevented the formation of the hemiacetal and thus provides another means to reduce the amount of side product.[29]

As anticipated, the oxidation of methyl α-D-mannopyranoside (**17**) and methyl β-D-galactopyranoside (**20**), in the presence of 3 equiv of benzoquinone, also gave rise to the corresponding rearranged products **18** and **21** (Table 2, entries 4 and 5). Prolonged reaction times (72 h) were required to obtain these products and further oxidation to ketolactone **19** was observed for the mannopyranoside. Based on the results obtained in the oxidation of 4-deoxyglucopyranoside **7** and xylopyranoside **14**, which could be converted rather selectively to **9** and **16** when the amount of benzoquinone was kept to the minimum, we reasoned that the overoxidation of **17** and **20** and subsequent rearrangement could be circumvented by decreasing the benzoquinone loading. Although this yielded the 3-keto products **23** and **24**, respectively, the selectivity was significantly lower, compared to glucopyranosides and xylopyranosides. Various side products due to overoxidation and rearrangement were detected in the NMR spectrum (see Table 2, entries 6 and 7, respectively). Clearly, successive nucleophilic attack of the C6-OH on the formed carbonyl is favored in these glycosides, resulting in fast side product formation after the initial oxidation of the C3-OH. Blocking the intramolecular nucleophilic attack of the C6-OH should circumvent lactone formation, and the reported selectivity for the oxidation of 1,6-anhydrogalactose and 1,6-anhydromannose supports the validity of this reasoning. Unfortunately, the 1,6-anhydrosugar approach cannot be extended to oligosaccharides. Therefore, we protected the C6-OH of methyl α-D-mannopyranoside with a TIPS group. Oxidizing this mannose derivative (**25**) with 1.2 equiv of benzoquinone surprisingly resulted in a decreased conversion of the starting material (58%). However, calculating the selectivity based on the converted starting material resulted in a selectivity of 81% toward the desired 3-keto product (**26**). These experiments reveal that (i) both mannopyranoside **17** and galactopyranoside **20** are selectively oxidized at C3 and (ii) subsequent side product formation could be circumvented by lowering the co-oxidant and protecting the C6-OH. These results are in agreement with the observations of Waymouth and co-workers for the oxidation of pyranosides that contain an axial substituent, such as rhamnosides, fucosides, and arabinosides, in acetonitrile/water at elevated temperature (50 °C). The C3 ketoglycoside is obtained for the majority of these substrates as well.[21] In trifluoroethanol, next to these pyranosides, even methyl α-D-galactopyranoside could be oxidized selectively. However, for all of these substrates, epimerization of the axial substituents was observed. Apparently, trifluoroethanol at elevated temperatures induces rapid epimerization. In the case of methyl α-D-galactopyranoside, epimerization results in the more-stable gluco-configured product and intramolecular lactol formation is unfavorable for this configuration. As a consequence, epimerization prevents further oxidation of the ketoproduct. Under the conditions we used (DMSO at room temperature), no epimerization has been observed. Therefore, in this case, nucleophilic attack by the primary hydroxyl group is favored, which results in side product formation via the rearrangement described above.

Finally, we aimed to determine the effect of the substitution pattern on the reactivity in the oxidation. The prolonged reaction times required for mannopyranoside and galactopyranoside oxidation suggested that there might be a difference between these and the rate of glucoside oxidation. Competition experiments of **1** with xylopyranoside **14**, galactopyranoside **20**, and mannopyranoside **17** were performed. These experiments revealed that the rate of oxidation of xylopyranoside **14** is comparable to that of benchmark **1**. This is not very surprising, because the primary hydroxyl group does not play a role in the oxidation mechanism, and the β-hydride elimination, which is most likely the rate-determining step, is not expected to be significantly influenced by this change in substitution pattern. However, the competition experiments indicated a clear decrease in reactivity of mannopyranosides and galactopyranosides, in comparison to **1**. 3-Ketoglucopyranoside **2** is formed preferentially over the corresponding product of the galactopyranoside **20** (product ratio 3-ketoglucopyranoside **2**:3-ketogalactopyranoside **24** = 5.7:1) and over that of the corresponding product of mannopyranoside **17** (product ratio 3-ketoglucopyranoside **2**:3-ketomannopyranoside **24** = 3:1) (see Figures S4 and S5, respectively, in the Supporting Information). Interestingly, in the above discussion, we showed, with competition experiments, that deoxygenation of the C4 position did not affect turnover of the substrate. These results in combination with those of the competition of glucopyranoside and galactopyranoside indicate that an axial OH considerably decreases the reactivity of the substrate in the oxidation reaction, but when the hydroxyl is omitted, the rate is not influenced. To complete the study and to verify that the same was applicable for the C2 position, we performed a similar competition experiment with methyl 2-deoxy-α-D-glucopyranoside and methyl α-D-glucopyranoside **1**. This showed that, also in this case, a product ratio of 1:1 was obtained. In other words, [(neocuproine)PdOAc]$_2$OTf$_2$ can chelate to both the C2−C3 and C3−C4 vicinal diol, as has also been reported for palladium TMEDA complexes.[30,31] Chelation to one of these vicinal diols is sufficient for oxidation. Removal of either the hydroxyl group at C2 or C4 does not have a marked effect on the rate of the oxidation reaction. However, an axial hydroxyl group at C2 or C4 largely affects the rate of oxidation, as indicated by the competition experiment with galactopyranoside and mannopyranoside, respectively. This may be explained by an unfavorable chelation with the cis diol or by an electronic effect induced by the axial hydroxyl group.

Having established the importance of the glucose configuration and the substituent at the C5 position, we realized that methyl α-D-glucuronide methyl ester (**27**) would be an excellent substrate for this palladium-catalyzed oxidation. Glucuronic acid is an important building block for proteoglycans, such as hyaluronic acid and heparan, and is also commonly found in secondary metabolites. If selective oxidation of glucuronic acid proved feasible, it would open up a method to functionalize glucuronide-containing secondary metabolites and glucuronic-acid-containing carbohydrate polymers.[32,33] Because of the purification difficulties involved in the synthesis of methyl α-D-glucuronic acid, we decided to synthesize the corresponding methyl ester. When methyl ester **27** was subjected to the conditions of the oxidation reaction, the desired ketoglucuronide **29** was isolated in 82% yield, showing that ester functionalities at C5 are tolerated by the catalyst.

CONCLUSIONS

Palladium-catalyzed oxidation provides an attractive means to functionalize glucose-configured monosaccharides and oligosaccharides. This study demonstrates that the oxidation of glycopyranosides with catalytic $[(neocuproine)PdOAc]_2OTf_2$ occurs selectively at the C3 position, independent of the substitution pattern. Deoxygenation of the C2, C4, or C6 positions has a minimal effect on the selectivity and substrates that contain bulky groups at the C4 position or an axial hydroxyl group at C2 or C4 are also readily oxidized at the C3 position.

However, the substitution pattern does have a large effect on the rate of the reaction. Oxidation of C4-protected substrates is significantly slower than the benchmark compound methyl α-D-glucopyranoside, which indicates that the selective oxidation of the terminal residue in oligoglucosides is due to steric shielding of the internal residues. Furthermore, competition experiments between galactopyranosides and glucopyranosides, and mannopyranosides and glucopyranosides reveal that axial hydroxyl groups at the C2 or C4 position reduce the rate of the oxidation. These differences in reaction rate may be exploited for the selective oxidation of complex oligosaccharides. For example, it may be feasible to selectively oxidize terminal glucoside residues in the presence of terminal galactoside residues.

Besides the reaction rate, the substitution pattern also affects the stability of the resulting 3-keto derivatives. Although the initial oxidation is C3 selective, axial hydroxyl groups, deoxygenation of the C4 position, or removal of the CH_2OH make the product prone to further reactions, such as α-ketol rearrangements. These modifications presumably facilitate conformational changes in the 3-keto products. We identified the major products by NMR, and, in addition, showed that these competing side reactions can be largely circumvented. When the amount of the co-oxidant benzoquinone is kept to the minimum, when oxygen is used as the co-oxidant to avoid formation of hydroquinone, or when the C6-OH is protected, the desired product is the major product, although at the expense of conversion. Finally, with the knowledge obtained, we realized that methyl glucuronide methyl ester would be an excellent substrate for the oxidation reaction, which provided a new route to functionalize glucuronic-acid-containing biomolecules.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b03459.

> Associated analytical data (^{1}H NMR, ^{13}C NMR for all compounds (PDF)
> Crystallographic data of **5** (CIF)

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Notes

The authors declare no competing financial interest.

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