Practical Site-selective Oxidation of Glycosides with Pd(OAc)2/Neocuproine

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DOI: 10.1055/a-2186-1485

Please cite this article as: Reintjens N, Bartels I, Marinus N et al. Practical Site-selective Oxidation of Glycosides with Pd(OAc)2/Neocuproine. Synlett 2023. doi: 10.1055/a-2186-1485

Conflict of Interest: The authors declare that they have no conflict of interest.

This study was supported by NWO, 718.016.001, ARC CBBC

Abstract:
Palladium-catalyzed oxidation of the secondary C3 hydroxy group in glycopyranosides has set its mark in the selective modification of unprotected carbohydrates. The pre-formed catalyst [(neocuproine)PdOAc]2(OTf)2 oxidizes besides monosaccharides also di-, and oligosaccharides. Here, we provide a more convenient protocol for this reaction in which the Pd-catalyst is formed in situ from Pd(OAc)2 and neocuproine in methanol at 50 °C. Together with a simplified product isolation, this protocol is applied to a series of mono- and disaccharides and has been applied on 10-gram scale. The protocol is also valuable as a screening method to determine whether more extensive studies using the pre-formed catalyst are worthwhile.

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Abstract Palladium-catalyzed oxidation of the secondary C3 hydroxy group in glycopyranosides has set its mark in the selective modification of unprotected carbohydrates. The pre-formed catalyst [(neocuproine)Pd(OAc)$_2$](OTf)$_2$ oxidizes besides monosaccharides also disaccharides and oligosaccharides. Here, we provide a more convenient protocol for this reaction in which the Pd-catalyst is formed in situ from Pd(OAc)$_2$ and neocuproine in methanol at 50 °C. Together with a simplified product isolation, this protocol is applied to a series of mono- and disaccharides and has been applied on 10-gram scale. The protocol is also valuable as a screening method to determine whether more extensive studies using the pre-formed catalyst are worthwhile.

Keywords Glycosides, Oxidation, Palladium, Site-selectivity, Regioselectivity

Introduction

The carbonyl group plays the central role in synthetic organic chemistry. In order to modify carbohydrates, it is therefore of eminent importance that hydroxy groups in carbohydrates can be oxidized in a site-selective manner to the corresponding carbonyl group. This can be effected by protecting group strategies in which a hydroxy group is singled out and subsequently oxidized. An alternative is the site-selective oxidation of unprotected carbohydrates. Well-established is the oxidation of the primary hydroxy group in glyco-pyranoses using a bulky nitrosomethane species generated from TEMPO or related compounds with hypochlorite, bis(acetoxy)iodo]benzene, or anodic oxidation. Despite all these illustrations of the versatility and applicability of Waymouth’s catalyst in carbohydrate oxidation, its incorporation in the toolbox of the carbohydrate chemist is slow. A main reason is probably that the catalyst is not commercially available and has to be prepared. This forms a barrier to applying the method to novel substrates, without a guarantee for success. It would be highly desirable to have a straightforward protocol to “test” the palladium-catalyzed oxidation reaction for a chemical biology or glycochemistry application at hand, in order to decide about its suitability. A second reason is the laborious purification of the highly polar carbohydrates, so a protocol avoiding column chromatography would be welcomed as well.

We reasoned that by using commercially available Pd(OAc)$_2$ and neocuproine (2,9-dimethyl-1,10-phenanthroline), a catalyst could be prepared in situ and that this system, although potentially less active and selective, would form a versatile screening system to determine whether substrates are suitable and could provide access to ketosaccharides. Before the advent of [(neocuproine)Pd(OAc)$_2$](OTf)$_2$, it had already been shown that secondary alcohols could be oxidized with [(neocuproine)Pd(OAc)$_2$] at higher temperatures. These bisacetate catalyst was applied with various solvents and several oxidants, such as O$_2$/air or a combination of benzoquinone and electrochemistry. It was shown that also “ligandless” Pd(OAc)$_2$ was effective in some cases. The group of Lemaire combined these methods by preparing in situ oxidise fatty-acid derived 1,2-diols. These approaches, however, require a high temperature which is problematic for sensitive substrates, and in addition, carbohydrates are deactivated substrates for oxidation.

reagents in combination with an oxidant. Recently, Kaspar and Kudova investigated the use of more classical oxidation reagents to obtain selective oxidation of 1,2-diols in steroids. Although it was possible to achieve the selective oxidation of hydroxy groups at different positions in the steroid, no selectivity was observed for 1,2-diols.

Our group has exploited the keto-functionality of unprotected ketosaccharides in the synthesis of rare sugars and in further modifications to allow their use in chemical biology, such as the introduction of an allyl – and an alkyn handle, exocyclic and endocyclic epoxides, an amine or a chloride, and recently, a thiol moiety.

Despite all these illustrations of the versatility and applicability of our group has exploited the keto-functionality of unprotected ketosaccharides in the synthesis of rare sugars and in further modifications to allow their use in chemical biology, such as the introduction of an allyl – and an alkyn handle, exocyclic and endocyclic epoxides, an amine or a chloride, and recently, a thiol moiety.

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We decided therefore to prepare catalyst 4 in situ and study whether, in combination with a suitable solvent and temperature, this could act as a suitable screening catalyst for a variety of carbohydrate substrates.

![Figure 1. Palladium-catalyzed oxidation, DCBQ: 2,6-dichloro-1,4-benzoquinone, BQ: benzoquinone. Neocuproine: 2,9-dimethyl-1,10-phenanthroline.](image)

**Results and discussion**

We first investigated whether catalyst 4 was able to oxidize glucosides. The catalytic activity of 3 and 4 is dependent on the solvent. Dimeric [([neocuproine])Pd(OAc)₂]OTf₃ dissociates in solution to the active monomeric species. Dial substrates readily coordinate to the active form of catalyst 3, which in acetonitrile results in a 325-fold higher turnover frequency (TOF) compared to bisacate catalyst 4. Notably, however, high catalytic activity has been reported for 4 in protic solvents. In this work, we performed the oxidation of methyl α-D-glucose 1 in acetonitrile/water and in methanol (Table 1). In line with previous studies on the oxidation of 2-heptanol and glycerol, [(neocuproine)Pd(OAc)₂]OTf₃ showed the highest turnover frequencies. Catalyst 3 turned out to be the most active in methanol.

Although the oxidation reaction with the bisaceta catalyst 4 is considerably slower than with 3, the TOF almost doubled when methanol was used instead of acetonitrile/water, indicating that oxidation of glucosides with the bisaceta catalyst 4 is facilitated by a protic solvent. The origin of the higher activity of catalyst 4 in methanol was not studied in detail, but we hypothesize that it is caused by differences in the dissociation constant of the acetate ligand. The pKa of acetic acid is considerably higher in acetonitrile (pKa = 23.5) than in methanol (pKa = 9.63). We reason that the acetate anion will dissociate much more readily in methanol than in acetonitrile. After the dissociation of acetate, the substrate or the solvent can coordinate to the vacant site. Methanol thus facilitates a fast equilibrium between the inactive palladium acetate complex and the active substrate-bound catalyst.

**Table 1. Oxidation of glucoside 1 in methanol with catalysts 3 and 4**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield</th>
<th>TON%</th>
<th>TOF (mol%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[([neocupr.)Pd(OAc)]OTf)₃</td>
<td>92%</td>
<td>46</td>
<td>77</td>
</tr>
<tr>
<td>([neocupr.)Pd(OAc)]_2</td>
<td>41%</td>
<td>21</td>
<td>5</td>
</tr>
</tbody>
</table>

The TON was calculated by dividing the conversion after 24 h by mol% [Pd].

With methanol and pre-prepared (neocuproine)Pd(OAc)₂ (4) as a suitable catalyst system for the oxidation of 1, we subsequently focused our attention on in situ prepared catalyst 4. We were pleased to note that overnight reaction at room temperature, provided partial conversion of glucoside 1.

In order to obtain full conversion, we screened various solvents (MeOH, MeCN, MeCN, HFIP, TFE, MeOH/water) and temperatures (room temperature and 50 °C). With Pd(OAc)₂ (0.05 eq), neocuproine (0.05 eq), and benzoquinone (1.05 eq) in MeOH (0.2 M) at 50 °C overnight, near full conversion was obtained and these conditions were selected.

A simplified product purification method was designed to ensure general applicability of the procedure. Upon concentrating the reaction mixture in vacuo, and addition of water, hydroquinone, and neocuproine were removed by washing with diethyl ether. Filtration of the water layer through syringe filters of 0.45 μm (twice) and 0.1 μm (once) removed palladium black and polymerized benzoquinone/hydroquinone. Subsequent lyophilization provided the product with >90% purity. With these optimized oxidation and purification methods in hand, 1 was oxidized on a 10-g gram scale and produced 3-keto-glucoside 2 in quantitative yield.

To explore the scope of this procedure, various glucoside substrates were oxidized, including a thio-glucopyranoside, protected glucopyranosides, a xylopyranose, and gluconopyranoside. The corresponding ketosaccharides were isolated in high yield, with the exception of 7 (Figure 2). Some products contained trace.
amounts of starting material, which was not removed by filtration. The moderate yield of 7 is due to the increased solubility of 7 in diethyl ether. For the synthesis of 10-12, 1.5 eq of benzoquinone was used, since 1.05 eq led to incomplete conversion. Compound 13 was purified by column chromatography because of its low water solubility. The study continued with the disaccharides cellobiose and maltose. Regioselective oxidation of methyl β-cellobioside proceeded smoothly and 14 was isolated in 62% yield, which was slightly higher than previously reported. 15,15-Bu-benzyl β-maltoside, on the other hand, proved to be a more challenging substrate. NMR analysis showed that several side products had formed, and purification by column chromatography gave 15 in just 27%. Oxidation of the Type 2 diabetes drug dapagliflozin 56,51 completed the study on gluco-configured substrates, and 3-ketosaccharide 16 was obtained in 62% yield.

The scope was expanded with substrates possessing a non-glucose configuration. As has been shown previously, substrates such as mannose and galactose are prone to overoxidation and rearrangements and provide moderate yields with 3. 15 Indeed, attempts to oxidize methyl L-rhamnioside, methyl D-mannoside, and methyl D-galactoside as well as TIPS-protected methyl D-mannoside 17 (Scheme 1) led to a complex mixture of compounds, precluding isolation of the desired keto-saccharide (see SI). We conclude, therefore, that for these and related compounds the in situ formed catalyst in methanol is suitable to determine whether oxidation occurs, but that catalyst 3 should subsequently be employed to prepare the products. 15,49

It was noticed that next to the products of non-gluco-configured monosaccharides, also several oxidized C-glycosides can be quite sensitive to overoxidation and rearrangement. These examples are shown in Scheme 1. The oxidation of puerarin 19 with Pd-catalyst 3 has been reported by Nakamura et al. to give 3-keto-puerarin in 70% yield. 52 With the current in situ prepared catalyst, a mixture of 20 and 21 was obtained instead of the desired C3-keto saccharide. These products are probably formed by migration of the keto-functionality on the C3 to the C2 followed by a rearrangement reaction since the migration of 3-keto-puerarin was observed by Nakamura et al. and the formation of such rearranged products of β-glycosides have been observed before by us. 49 Oxidation of 22 provided the desired 23 in 32% yield together with 2-keto saccharide 24 in 9% yield. The latter is probably formed via intramolecular deprotonation of the C2 position by adventitiously formed phenolate.

**Conclusion**

An in situ formed catalyst of Pd(OAc)2 and neocuproine in methanol provides a suitable catalyst system for rapid screening of the C3-selective oxidation of carbohydrates. A straightforward purification protocol that avoids column chromatography allows quick isolation of the products. For gluco-configured substrates, high yields are obtained and the reaction is readily scaled up. Substrates’ sensitivity for over-oxidation gives lower yields or a mixture of products. Nevertheless, also for these substrates, the protocol functions as a suitable and fast screening method to determine whether it is worth preparing the Waymouth catalyst for the oxidation of a particular catalyst. This protocol should lead to a more widespread application of the site-selective modification of unprotected carbohydrates, and in addition not be limited to this substrate class as the oxidation of C-glycosides shows.

**Funding Information**

I. M. A. B. and S.C.M. acknowledge ARC-CBC for funding. N.M. acknowledges NWO, project number 718.016.001, for funding.

**Supporting Information**

YES (this text will be updated with links prior to publication)
Scheme 1. Reactions carried out with 0.05 eq Pd(OAc)₂, 0.05 eq neocuproine, 1.05 eq benzoquinone, 0.2 M in MeOH at 50 °C. Isolated yields. (i)The reported yield in literature.

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

References and Notes


(31) Ahmadian-Moghaddam, M.; Reintjens, N. R. M.; Witte, M. D.;
Synlett


Due to the low solubility of 1 in acetonitrile, we used a 9:1 mixture of acetonitrile/water.

To a stock solution of methyl α-D-glucopyranoside 1 (45 mg, 0.23 mmol, 1 eq) and 1,4-benzenoquinone (26 mg, 0.24 mmol, 1.05 eq) in methanol (0.1 M) or acetonitrile/water (9/1 v/v, 0.1 M) was added catalyst 3 (5 mg, 5 μmol, 2 mol%) or 4 (2 mg, 5 μmol, 2 mol%). The mixtures were stirred for 24 h at rt under air.

The reactions were analysed by 1H NMR by dilution of a portion of the reaction mixture with CD3OD. Conversion was calculated by dividing the product integral with the sum of product and starting material integrals. The turnover numbers were calculated by dividing the conversion with mol[Pd]. TOF was calculated using the conversion after 0.5 h by dividing TON with the reaction time.


General procedure: To a solution of substrate [1.0 mmol, 1 eq] in methanol (0.2 M) was added 1,4-benzenoquinone (114 mg, 1.05 mmol, 1.05 eq), neocuprine (10.5 mg, 50 μmol, 5 mol%), and Pd(II)Ac2 (11.2 mg, 50 μmol, 0.5 mol%). The reactions were followed by 1H NMR by dilution of 50 μL of the reaction mixture with CD3OD. After stirring overnight, the reaction mixture was concentrated in vacuo, dissolved in Milli-Q water (15 mL), and washed with Et2O (2× 30 mL) the aqueous layer was filtered twice over a 1.0 μm pore size syringe filter and once over a 0.45 μm pore size syringe filter. The aqueous layer was concentrated in vacuo to give the keto-saccharide.

Analysis of compound B: 1H NMR (400 MHz, Methanol-d4) δ 5.39 (d, J = 4.2 Hz, 1H), 4.40 – 4.14 (m, 1H), 3.95 (d, J = 2.4, 6.2 Hz, 1H), 3.89 – 3.77 (m, 3H), 2.88 (d, d, J = 13.9, 4.6, 1.1 Hz, 1H), 2.43 (dd, J = 13.9, 0.9 Hz, 1H), 1.15 (dd, J = 12.2, 6.2 Hz, 6H). 13C NMR (101 MHz, Methanol-d4) δ 207.6, 97.9, 76.6, 74.2, 70.0, 62.6, 47.1, 23.5, 21.4. HRMS (ESI neg) m/z calcd for C5H16O2[M-Me]: 203.0925, found: 203.0925.

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Table S1. Oxidation of methyl α-D-glucopyranoside 1 with [(neocuproine)PdOAc]$_2$(OTf)$_2$ (3).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>MeOH*</th>
<th>acetonitrile/water (9/1 v/v)</th>
<th>Yield</th>
<th>TON</th>
<th>TOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 h</td>
<td>Yield</td>
<td>77%</td>
<td>38</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>TON</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>Yield</td>
<td>87%</td>
<td>43</td>
<td>42</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>TON</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 h</td>
<td>Yield</td>
<td>90%</td>
<td>45</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>TON</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 h</td>
<td>Yield</td>
<td>96%</td>
<td>48</td>
<td>65</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>TON</td>
<td>48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>Yield</td>
<td>93%</td>
<td>46</td>
<td>92</td>
<td>46</td>
</tr>
</tbody>
</table>

[a] Too much signal overlap to use SM integration, thus the SM integration of t0 (compared to IS) was used to calculate conversion.
[b] After 24 h a black solid formed that stuck to the wall of the flask

Table S2. Oxidation of methyl α-D-glucopyranoside 1 with (neocuproine)Pd(OAc)$_2$ (4).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>MeOH*</th>
<th>acetonitrile/water (9/1 v/v)</th>
<th>Yield</th>
<th>TON</th>
<th>TOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 h</td>
<td>Yield</td>
<td>12%</td>
<td>6</td>
<td>5%</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>TON</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TOF</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>Yield</td>
<td>16%</td>
<td>8</td>
<td>8%</td>
<td>4</td>
</tr>
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<td></td>
<td>TON</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 h</td>
<td>Yield</td>
<td>25%</td>
<td>12</td>
<td>12%</td>
<td>6</td>
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<tr>
<td></td>
<td>TON</td>
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<tr>
<td>4 h</td>
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<td>19%</td>
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<td></td>
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<td>16</td>
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<td></td>
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<tr>
<td>24 h</td>
<td>Yield</td>
<td>54%</td>
<td>27</td>
<td>41%</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>TON</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Slightly overlapping signal of the SM with methanol, but still used those integrals.
Table S3. Screening 1: Oxidation conditions of methyl α-D-glucopyranoside 1 followed by TLC analysis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(OAc)$_2$ (eq)</th>
<th>Neocuproine (eq)</th>
<th>Benzoquinone (eq)</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Concentration (M)</th>
<th>Additive (eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>0.05</td>
<td>1.05</td>
<td>MeOH</td>
<td>RT</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>0.1</td>
<td>1.05</td>
<td>MeOH</td>
<td>RT</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.05</td>
<td>0.05</td>
<td>3.0</td>
<td>MeOH</td>
<td>RT</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>0.05</td>
<td>1.05</td>
<td>CF$_3$CH$_2$OH</td>
<td>RT</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.05</td>
<td>0.05</td>
<td>1.05</td>
<td>HFIP</td>
<td>RT</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
<td>0.05</td>
<td>1.05</td>
<td>MeOH/MeCN 4/1 v/v</td>
<td>RT</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.05</td>
<td>0.05</td>
<td>1.05</td>
<td>MeOH</td>
<td>50</td>
<td>0.2</td>
<td></td>
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<tr>
<td>8</td>
<td>0.05</td>
<td>0.05</td>
<td>1.05</td>
<td>MeOH</td>
<td>RT</td>
<td>0.4</td>
<td></td>
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<tr>
<td>9</td>
<td>0.05</td>
<td>0.05</td>
<td>1.05</td>
<td>MeOH</td>
<td>RT</td>
<td>0.6</td>
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</tr>
<tr>
<td>10</td>
<td>0.05</td>
<td>0.05</td>
<td>1.05</td>
<td>MeOH</td>
<td>RT</td>
<td>0.2</td>
<td>AcOH (0.01)</td>
</tr>
<tr>
<td>11</td>
<td>0.05</td>
<td>0.05</td>
<td>1.05</td>
<td>MeOH/H$_2$O 1/1 v/v</td>
<td>RT</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>12*</td>
<td>0.05</td>
<td>0.05</td>
<td>1.05</td>
<td>MeOH</td>
<td>RT</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>13*</td>
<td>0.05</td>
<td>0.05</td>
<td>1.05</td>
<td>MeOH/MeCN 4/1 v/v</td>
<td>RT</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

*The catalyst was prepared in situ without the presence of the substrate and benzoquinone. Therefore, neocuproine and Pd(OAc)$_2$ were added first to the solvent and stirred for 15 min before the addition of the substrate and BQ.
Table S4. Screening 2: Oxidation conditions of methyl α-D-glucopyranoside 1 followed by NMR analysis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>( \text{Pd(OAc)}_2 ) (eq.)</th>
<th>Neocuproine (eq.)</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>NMR conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4-5 h</td>
</tr>
<tr>
<td>1</td>
<td>0.05</td>
<td>0.05</td>
<td>MeOH</td>
<td>RT</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>0.05</td>
<td>MeOH</td>
<td>50</td>
<td>72</td>
</tr>
<tr>
<td>3[a]</td>
<td>0.05</td>
<td>0.05</td>
<td>MeOH</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>0.05</td>
<td>MeOH/MeCN (4/1, v/v)</td>
<td>RT</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>0.05</td>
<td>0.05</td>
<td>MeOH/MeCN (4/1, v/v)</td>
<td>50</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
<td>0.05</td>
<td>MeOH/DCM (4/1, v/v)</td>
<td>RT</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>0.05</td>
<td>0.05</td>
<td>MeOH/DCM (4/1, v/v)</td>
<td>50</td>
<td>57</td>
</tr>
</tbody>
</table>

[a] 2-tert-butyl-1,4-benzoquinone was used instead of 1,4-benzoquinone.
Table S5. Practical observations during work-up.

<table>
<thead>
<tr>
<th>Et₂O layer (left), water layer (right) after washing the reaction mixture with ether.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left: the water layer after 2x filtration. Right: the water layer after 3x filtration</td>
</tr>
<tr>
<td>Filters after 1x, 2x, 3x filtration.</td>
</tr>
</tbody>
</table>
Experimental procedures

General procedures

General Information
Palladium(II) acetate, 99+% (99.95+%-Pd) was bought from STREM. All solvents used for reaction, extraction, filtration, and chromatography were of commercial grade and used without further purification. Automated flash chromatography was performed on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 grams). $^1$H-, $^{13}$C-, HSQC-, and COSY-NMR were recorded on a Varian AMX400 spectrometer (400, 101 MHz, respectively) using methanol-$d_4$ as solvent. Chemical shifts are given in ppm ($\delta$) relative to the solvent residual peak. Data are reported as follows: chemical shifts ($\delta$), multiplicity (s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, dt = double triplet, t = triplet, m = multiplet), coupling constants $J$ (Hz), and integration.

High Resolution Mass measurements were performed using a ThermoScientific LTQ OrbitrapXL spectrometer. As a 1.0 µm pore size syringe filter was used the Chromafil Xtra GF-100/13 glass fiber 13 mm membrane and as a 0.45 µm pore size syringe filter was used the Chromafil Xtra RC-45/13 regenerated cellulose 13 mm membrane. The synthesis of 22 will be published separately.

General procedure for the oxidation of methyl α-D-glucopyranoside (1) with catalyst 3 & 4
To a stock solution of methyl α-D-glucopyranoside (1) (45 mg, 0.23 mmol, 1 eq.) and 1,4-benzoquinone (26 mg, 0.24 mmol, 1.05 eq.) in methanol (0.1 M) or acetonitrile/water (9/1 v/v, 0.1 M) was added catalyst 3 (5 mg, 5 µmol, 2 mol%) or 4 (2 mg, 5 µmol, 2 mol%). The mixtures were stirred for 24 h at rt under air. The reactions were analysed by $^1$H NMR by dilution of a part of the reaction mixture with CD$_3$OD. Conversion was calculated by dividing the product integral with the sum of product and starting material integrals. The turnover numbers were calculated by dividing the conversion with mol% [Pd]. TOF was calculated using the conversion after 0.5 h by dividing TON with the reaction time.

Oxidation and purification method A
To a solution of substrate (1.0 mmol, 1 eq.) in methanol (0.2 M) was added 1,4-benzoquinone (114 mg, 1.05 mmol, 1.05 eq.), neocuproine (10.5 mg, 50 µmol, 5 mol%), and Pd(OAc)$_2$ (11.2 mg, 50 µmol, 5 mol%). The reaction mixture was heated to 50 °C. The reactions were followed by $^1$H NMR by dilution of 50 µL of the reaction mixture with CD$_3$OD. After stirring overnight, the reaction mixture was concentrated in vacuo, dissolved in Milli-Q water (15 mL) and washed with Et$_2$O (2x 30 mL). The aqueous layer was filtered twice over a 1.0 µm pore size syringe filter and once over a 0.45 µm pore size syringe filter. The aqueous layer was concentrated in vacuo to give the keto-saccharide.

Oxidation and purification method B
To a solution of substrate (1.0 mmol, 1 eq.) in methanol (0.2 M) was added 1,4-benzoquinone (0.17 g, 1.5 mmol, 1.5 eq.), neocuproine (10.5 mg, 50 µmol, 5 mol%), and Pd(OAc)$_2$ (11.2 mg, 50 µmol, 5 mol%). The reaction mixture was heated to 50 °C. The reactions were followed by $^1$H NMR by dilution of 50 µL of the reaction mixture with CD$_3$OD. After stirring overnight, the reaction mixture was concentrated in vacuo, dissolved in Milli-Q water (15 mL) and washed with Et$_2$O (2x 30 mL). The aqueous layer was filtered twice over a 1.0 µm pore size syringe filter and once over a 0.45 µm pore size syringe filter. The aqueous layer was concentrated in vacuo to give the keto-saccharide.

Oxidation and purification method C
To a solution of substrate (1.0 mmol, 1 eq.) in methanol (0.2 M) was added 1,4-benzoquinone (114 mg, 1.05 mmol, 1.05 eq.), neocuproine (10.5 mg, 50 µmol, 5 mol%), and Pd(OAc)$_2$ (11.2 mg, 50 µmol, 5 mol%). The reaction mixture was heated to 50 °C. After stirring for 4 h, additional 1,4-benzoquinone (57 mg, 0.5 mmol, 0.5 eq.) was added. The
reactions were followed by $^1$H NMR by dilution of 50 µL of the reaction mixture with CD$_3$OD. After stirring overnight, the reaction mixture was concentrated in vacuo, dissolved in Milli-Q water (15 mL) and washed with Et$_2$O (2x 30 mL). The aqueous layer was filtered twice over a 1.0 µm pore size syringe filter and once over a 0.45 µm pore size syringe filter. The aqueous layer was concentrated in vacuo to give the keto-saccharide.

**Oxidation and purification method D**

To a solution of substrate (1.0 mmol, 1 eq.) in methanol (0.2 M) was added 1,4-benzoquinone (114 mg, 1.05 mmol, 1.05 eq), neocuproine (10.5 mg, 50 µmol, 5 mol%), and Pd(OAc)$_2$ (11.2 mg, 50 µmol, 5 mol%). The reaction mixture was heated to 50 °C. The reactions were followed by $^1$H NMR by dilution of 50 µL of the reaction mixture with CD$_3$OD. After stirring overnight, the reaction mixture was concentrated in vacuo. Purification by Grace flash chromatography on a 15 g silica cartridge using DCM/MeOH (0 to 20% MeOH in DCM) gave the keto-saccharide.

**Isopropyl 2-deoxy-α-D-glucopyranoside (S1)**

To a mixture of 2-deoxy-α-D-glucose (1.0 g, 6.1 mmol, 1.0 eq.) in isopropanol (12 mL) was added acetyl chloride (43 µL, 0.6 mmol, 0.1 eq.). After stirring overnight at 50 °C, the clear solution was neutralized with basic amberlyst® A21 free base to pH = 7, filtered and concentrated in vacuo. Purification by Grace flash chromatography on a 25 g silica cartridge using DCM/MeOH (0 to 20% MeOH in DCM) gave S1 (0.76 g, 3.7 mmol, 61%). $^1$H NMR (400 MHz, Methanol-d$_4$) δ 5.02 (dd, $J = 3.7$, 1.3 Hz, 1H), 3.92 (p, $J = 6.2$ Hz, 1H), 3.87 – 3.77 (m, 2H), 3.69 (dd, $J = 11.7$, 5.5 Hz, 1H), 3.58 (ddd, $J = 9.9$, 5.5, 2.5 Hz, 1H), 3.23 (t, $J = 9.3$ Hz, 1H), 1.98 (ddd, $J = 12.8$, 5.1, 1.3 Hz, 1H), 1.60 (ddd, $J = 12.8$, 11.7, 3.7 Hz, 1H), 1.19 (d, $J = 6.3$ Hz, 3H), 1.13 (d, $J = 6.1$ Hz, 3H). $^{13}$C NMR (101 MHz, Methanol-d$_4$) δ 96.3, 74.0, 73.4, 69.9, 69.4, 62.8, 39.3, 23.7, 21.6. HRMS (ESI) m/z calcd for C$_9$H$_{18}$O$_5$Na [M+Na]$^+$: 229.1046, found: 229.1046.

**Oxidation of monosaccharides**

**Methyl 3-keto-α-D-glucopyranoside (2)**

The preparative synthesis of compound 1 was done via a slightly modified method A. To a solution of methyl α-D-glucopyranoside (10.0 g, 51 mmol, 1 eq.) in methanol (0.26 L) was added 1,4-benzoquinone (5.8 g, 54 mmol, 1.05 eq), neocuproine (0.54 g, 2.6 mol, 5 mol%), and Pd(OAc)$_2$ (0.58 g, 2.6 mol, 5 mol%). The reaction mixture was heated to 50 °C. The reaction was monitored by $^1$H NMR by dilution of 50 µL of the reaction mixture with CD$_3$OD. After stirring overnight, the reaction mixture was concentrated in vacuo, dissolved in Milli-Q water (50 mL), and filtered thrice over a 1.0 µm pore size syringe filter. The aqueous layer was then washed with Et$_2$O (2x 300 mL) and concentrated in vacuo. The residue was then redissolved in Milli-Q water (40 mL) and filtered twice over a 1.0 µm pore size syringe filter and once over a 0.45 µm pore size syringe filter. The aqueous layer was concentrated in vacuo to give the title compound (12.1 g, quant.). The analysis is in agreement with literature.$^1$

**Methyl 3-keto-β-D-glucopyranoside (6)**

The oxidation of methyl β-D-glucopyranoside (0.19 g, 1.0 mmol) was performed with method A to give a mixture of 6 (0.15 g, 0.76 mmol, 76%) and starting material (13 mg, 69 µmol. The analysis is in agreement with literature.$^2$
Phenyl 3-keto-1-thio-β-D-glucopyranoside (7)

The oxidation of phenyl 1-thio-β-D-glucopyranoside (0.27 g, 1.0 mmol) was performed with method A to give a mixture of 7 (0.15 g, 0.54 mmol, 54%) and starting material (21 mg, 77 µmol). The analysis is in agreement with literature.3

Isopropyl 2-deoxy-3-keto-α-D-glucopyranoside (8)

The oxidation of isopropyl 2-deoxy-α-D-glucopyranoside 5 (0.21 g, 1.0 mmol) was performed with method A to give 8 (0.14 g, 0.69 mmol, 77%). 1H NMR (400 MHz, Methanol-d4) δ 5.39 (d, J = 4.2 Hz, 1H), 4.20 – 4.14 (m, 1H), 3.95 (dt, J = 12.4, 6.2 Hz, 1H), 3.89 – 3.77 (m, 3H), 2.88 (ddd, J = 13.9, 4.6, 1.1 Hz, 1H), 2.43 (dd, J = 13.9, 0.9 Hz, 1H), 1.15 (dd, J = 12.2, 6.2 Hz, 6H). 13C NMR (101 MHz, Methanol-d4) δ 206.7, 97.9, 76.6, 74.2, 70.0, 62.6, 47.1, 23.5, 21.4. HRMS (ESI neg) m/z calcd for C13H13O5 [M-H]-: 203.0925, found: 203.0925.

Methyl 3-keto-β-D-xylopyranoside (9)

The oxidation of methyl β-D-xylopyranoside (0.16 g, 1.0 mmol) was performed with method A to give a mixture of 9 (0.13 g, 0.81 mmol, 81%) and starting material (7 mg, 41 µmol). The analysis is in agreement with literature.2

Isopropyl 2-acetamido-2-deoxy-3-keto-α-D-glucopyranoside (10)

The oxidation of isopropyl 2-acetamido-2-deoxy-α-D-glucopyranoside (0.26 g, 1.0 mmol) was performed with method B to give 10 (0.22 g, 0.85 mmol, 85%). The analysis is in agreement with literature.4

Methyl 6-deoxy-3-keto-α-D-glucopyranoside (11)

The oxidation of methyl 6-deoxy-α-D-glucopyranoside (0.18 g, 1.0 mmol) was performed with method B to give a mixture of 11 (0.15 g, 0.85 mmol, 85%) and starting material (20 mg, 0.11 mmol). 1H NMR (400 MHz, Methanol-d4) δ 4.99 (d, J = 4.8 Hz, 1H), 4.42 (dd, J = 4.4, 1.5 Hz, 1H), 3.76 – 3.68 (m, 1H), 3.38 (s, 4H), 1.39 (d, J = 6.2 Hz, 3H). 13C NMR (101 MHz, Methanol-d4) δ 206.5, 103.6, 78.8, 76.1, 72.0, 55.7, 18.9. HRMS (ESI neg) m/z calcd for C13H12Os [M-H]-: 175.0612, found: 175.0612.

Methyl 3-keto-α-D-glucopyranosiduronic acid (12)

The oxidation of methyl α-D-glucopyranosiduronic acid (0.18 g, 1.0 mmol) was performed with method C to give a mixture of 12 (0.15 g, 0.74 mmol, 73%) and starting material (15 mg, 7 µmol). 1H NMR (400 MHz, Methanol-d4) δ 5.11 (d, J = 4.2 Hz, 1H), 4.49 (dd, J = 4.1, 1.2 Hz, 1H), 4.45 (d, J = 9.8 Hz, 1H), 4.08 (d, J = 9.8 Hz, 1H), 3.44 (d, J = 4.8 Hz, 3H). HRMS (ESI neg) m/z calcd for C9H12O5 [M-H]-: 205.0354, found: 205.0354.

Methyl 3-keto-6-O-tert-butyldimethylsilyl-α-D-glucopyranoside (13)

The oxidation of methyl 6-O-tert-butyldimethylsilyl-α-D-glucopyranoside (0.31 g, 1.0 mmol) was performed with method D to give 13 (0.22 g, 0.73 mmol, 73%). 1H NMR (400 MHz, Methanol-d4) δ 5.08 (d, J = 4.3 Hz, 1H), 4.41 (dd, J = 4.2, 1.2 Hz, 1H), 4.27 (dd, J = 9.7, 1.2 Hz, 1H), 4.06 – 3.92 (m, 2H), 3.68 (ddd, J = 9.7, 4.4, 2.0 Hz, 1H), 3.43 (s, 3H), 0.98 (s, 9H), 0.16 (s, 6H). 13C NMR (101 MHz, Methanol-d4) δ 207.0, 103.7, 76.8, 76.0, 73.2, 63.9, 55.6, 26.4, -5.1, -5.2. HRMS (ESI) m/z calcd for C13H27O6SiNa [M+Na]+: 329.1391, found: 329.1391.
Oxidation of disaccharides

Methyl β-3-ketocellobioside (14)

The oxidation of methyl β-cellobioside (0.36 g, 1.0 mmol) was performed with method D to give a mixture of 14 (0.22 g, 0.62 mmol, 62%) and starting material (13 mg, 37 µmol). The analysis is in agreement with literature.3

4-tert-butylbenzyl-β-3-ketomaltoside (15)

The oxidation of 4-tert-butylbenzyl-β-maltoside (0.24 g, 0.5 mmol) was performed with method D to give 15 (64 mg, 0.13 mmol, 27%). The analysis is in agreement with literature.2

Oxidation of C-glycosides

Oxidation of Dapagliflozin (16)

The oxidation of dapagliflozin (0.41 g, 1.0 mmol) was performed with method D to give compound 16 (0.25 g, 0.62 mmol, 62%). 1H NMR (400 MHz, Methanol-d4) δ 7.42 – 7.35 (m, 3H), 7.09 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 4.39 (d, J = 10.0 Hz, 1H), 4.23 (s, 2H), 4.11 – 3.90 (m, 5H), 3.82 (dd, J = 12.1, 4.7 Hz, 1H), 3.49 (ddd, J = 10.0, 1.9 Hz, 1H), 1.35 (t, J = 7.0 Hz, 4H). 13C NMR (101 MHz, Methanol-d4) δ 208.4, 158.9, 140.1, 139.3, 135.0, 132.8, 131.7, 130.8, 130.3, 128.0, 115.4, 85.2, 84.7, 78.6, 74.0, 64.4, 62.9, 39.2, 15.2. HRMS (ESI neg) m/z calcd for C21H22O6Cl [M-H]-: 405.1110 and 407.1081, found: 405.1105 and 407.1076.

Sideproducts from the oxidation of puerarin (20 and 21)

The oxidation of puerarin 19 (0.10 g, 0.24 mmol) was performed with method D to give a mixture of 20 (51 mg, 0.11 mmol, 48%) and 21 (31 mg, 70 µmol, 29%). NMR analysis is given for the major product (20). 1H NMR (400 MHz, Methanol-d4) δ 8.13 (s, 1H), 8.03 – 7.96 (m, 1H), 7.41 – 7.31 (m, 2H), 6.91 – 6.82 (m, 3H), 5.80 (s, 1H), 4.79 (d, J = 9.3 Hz, 1H), 4.09 – 3.92 (m, 2H), 3.91 – 3.85 (m, 1H), 3.20 (s, 3H). 13C NMR (101 MHz, Methanol-d4) δ 177.8, 173.5, 162.9, 158.7, 156.2, 154.2, 131.3, 127.9, 125.8, 124.0, 117.9, 117.5, 116.2, 110.1, 87.6, 86.1, 83.3, 74.1, 59.6, 52.6. HRMS (ESI) m/z calcd for C22H22O10 [M+H]+: 445.1129, found: 445.1124.

S9
Oxidation of C-glycoside 22 (to provide 23 and 24)

The oxidation of C-glycoside 22 (0.30 g, 1.0 mmol) was performed with method D to give a mixture of 23 (96 mg, 0.32 mmol, 32%), 24 (26 mg, 90 µmol, 9%) and starting material (0.10 g, 0.35 mmol). 23: $^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 8.44 (d, $J = 2.7$ Hz, 1H), 8.10 (dd, $J = 9.0$, 2.8 Hz, 1H), 6.94 (d, $J = 9.0$ Hz, 1H), 4.82 (d, $J = 10.0$ Hz, 1H), 4.44 (dd, $J = 10.0$, 1.5 Hz, 1H), 3.95 (dd, $J = 12.3$, 1.9 Hz, 1H), 3.84 (dd, $J = 12.3$, 4.8 Hz, 1H), 3.55 (ddd, $J = 10.0$, 4.8, 2.0 Hz, 1H). $^{13}$C NMR (101 MHz, Methanol-d$_4$) $\delta$ 208.4, 163.0, 141.9, 127.3, 126.4, 126.0, 116.6, 84.8, 78.8, 78.1, 74.0, 62.9. HRMS (ESI neg) m/z calcd for C$_{12}$H$_{12}$O$_{8}$ [M-H]: 298.0568, found: 298.0563. 24: $^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 8.22 (d, $J = 2.8$ Hz, 1H), 8.08 (dd, $J = 8.9$, 2.8 Hz, 1H), 6.88 (d, $J = 9.1$ Hz, 1H), 5.37 (s, 1H), 4.43 (d, $J = 9.3$ Hz, 1H), 4.02 (d, $J = 10.3$ Hz, 1H), 3.94 – 3.79 (m, 2H), 3.68 (t, $J = 9.4$ Hz, 1H). $^{13}$C NMR (101 MHz, cd$_3$od) $\delta$ 202.1, 162.0, 141.8, 126.2, 125.2, 124.6, 115.5, 82.7, 81.3, 78.6, 76.2, 62.7. HRMS (ESI neg) m/z calcd for C$_{12}$H$_{12}$O$_{8}$ [M-H]: 298.0568, found: 298.0564.
NMR and HRMS spectra
Isopropyl 2-deoxy-α-D-glucopyranoside (S1)

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Accepted Manuscript
Methyl 3-keto-α-D-glucopyranoside (1)

$^1$H NMR of the large scale oxidation.
Isopropyl 2-deoxy-3-keto-\(\alpha\)-D-glucopyranoside (8)
Methyl 6-deoxy-3-keto-α-D-glucopyranoside (11)
Methyl 3-keto-α-D-glucopyranosiduronic acid (12)
Methyl 3-keto-6-O-tert-butyldimethylsilyl-α-D-glucopyranoside (13)
Sideproducts from the oxidation of puerarin (to provide 20 and 21)

20 \( R^1 = \text{Me}, \ R^2 = \text{H} \)
21 \( R^1 = \text{H}, \ R^2 = \text{Me} \)
Oxidation of C-glycoside 22 (to provide 23 and 24)
References


