Practical Site-Selective Oxidation of Glycosides with Palladium(II) Acetate/Neocuproine

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Published as part of the Cluster
Japan/Netherlands Gratama Workshop

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Received: 12.09.2023
Accepted after revision: 04.10.2023
Published online: 04.10.2023 (Accepted Manuscript), 09.11.2023 (Version of Record)
DOI: 10.1055/a-2186-1485; Art ID: ST-2023-09-0399-L

The palladium-catalyzed oxidation of the secondary C(3) hydroxy group of glycopyranoses has set a mark in the selective modification of unprotected carbohydrates. The preformed catalyst [(neocuproine)PdOAc]2(OTf)2 oxidizes di- and oligosaccharides, as well as monosaccharides. 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 was applied to a series of mono- and disaccharides, and has been applied on a 10 gram scale. The protocol is also valuable as a screening method to determine whether more-extensive studies using the preformed catalyst are worthwhile.

Keywords glycosides, oxidation, palladium catalysis, neocuproine, site-selectivity, regioselectivity

Site-selective oxidation of the secondary hydroxy groups in unprotected carbohydrates is considerably more challenging, but significant progress has been made over the past ten years. Waymouth and co-workers were able to selectively oxidize glycerol with the catalyst [(neocuproine)PdOAc]2(OTf)2 and 1,4-benzoquinone (BQ) or oxygen as a terminal oxidant (Scheme 1A).13,14 In 2013, our group used this catalyst to exploit the higher reactivity of the C(3) hydroxy group to permit its selective oxidation in glucosides and, later, in oligosaccharides and even glucopeptides (Scheme 1B).15–18 Waymouth’s group has also shown that oxygen can be used as the oxidant (Scheme 1C).19 whereas we were able to simplify the product-purification process by carrying out the oxidation of methyl α-β-glucopyranoside (1) to the 3-ketoglucose 2 in methanol on a five-gram scale (Scheme 1D).20

The carbonyl group plays the central role in synthetic organic chemistry.1–4 To modify carbohydrates, it is therefore of preeminent importance that hydroxy groups in carbohydrates can be oxidized in a site-selective manner to the corresponding carbonyl group. This can be effected by means of protecting-group strategies in which a hydroxy group is singled out and subsequently oxidized. An alternative is the site-selective oxidation of nonprotected carbohydrates. Well-established is the oxidation of the primary hydroxy group in glycopyranoses by using a bulky nitrosonium species generated from TEMPO or a related compound with hypochlorite, or by using [bis(acetoxy)iodo]benzene or anodic oxidation.5–10 The regioselectivity of this oxidation reaction is clearly based on steric hindrance.
Other approaches for the selective oxidation of 1,2-diols make use of chelating agents such as boronic acids\textsuperscript{21,22} or organotin reagents\textsuperscript{23–25} in combination with an oxidant. Recently, Kaspar and Kudova investigated the use of more-classical oxidation reagents to achieve selective oxidation of 1,2-diols in steroids.\textsuperscript{26} 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\textsuperscript{27} and, in further modifications, to allow their use in chemical biology, for example, through the introduction of an allyl or an alkyne handle, exocyclic and endocyclic epoxides, an amine or a chloride, and recently, a thiol moiety.\textsuperscript{28–31}

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 has been slow. The 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 of success. It would be highly desirable to have at hand a straightforward protocol to test the palladium-catalyzed oxidation reaction to decide on its suitability for chemical-biology or glycochemistry applications. A second reason is the laborious purification of the highly polar carbohydrates, so a protocol avoiding column chromatography would also be welcomed.

We reasoned that by using commercially available \(\text{Pd(OAc)}_2\) and neocuproine (2,9-dimethyl-1,10-phenanthroline), a catalyst might 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 \((\text{neocuproine})\text{PdOAc}}_2(\text{OTf})_2\), it had already been shown that secondary alcohols could be oxidized with \((\text{neocuproine})\text{Pd(OAc)}_2\) at high temperatures.\textsuperscript{32} This bisacetate catalyst has been applied with various solvents and with several oxidants such as \(\text{O}_2/\text{air}\)\textsuperscript{33,34} or a combination of benzoquinone and electrochemistry.\textsuperscript{35} It had also been shown that ligandless \(\text{Pd(OAc)}_2\) was also effective in some cases.\textsuperscript{36,37} Lemaire’s group combined these methods by preparing \((\text{neocuproine})\text{Pd(OAc)}_2\) in situ to selectively oxidize fatty-acid-derived 1,2-diols.\textsuperscript{38} These approaches, however, required a high temperature, which is problematic for sensitive substrates and, in addition, carbohydrates are deactivated substrates for oxidation.

We therefore decided to prepare \((\text{neocuproine})\text{Pd(OAc)}_2\) catalyst in situ and to study whether, in combination with a suitable solvent and temperature, it could act as a suitable screening catalyst for a variety of carbohydrate substrates.

We first investigated whether \((\text{neocuproine})\text{Pd(OAc)}_2\) was able to oxidize glucosides. The catalytic activities of \((\text{neocuproine})\text{PdOAc}}_2(\text{OTf})_2\) and \((\text{neocuproine})\text{Pd(OAc)}_2\) are dependent on the solvent.\textsuperscript{32,33} Dimeric \((\text{neocuproine})\text{PdOAc}}_2(\text{OTf})_2\) dissociates in solution to the active monomeric species. Diol substrates readily coordinate to the active form of \((\text{neocuproine})\text{PdOAc}}_2(\text{OTf})_2\), which results in a 325-fold higher turnover frequency (TOF) in acetonitrile compared with the bisacetate catalyst \((\text{neocuproine})\text{Pd(OAc)}_2\).\textsuperscript{32,33} Notably, however, a high catalytic activity has been reported for \((\text{neocuproine})\text{Pd(OAc)}_2\) in protic solvents.\textsuperscript{32,34,39} This observation is highly relevant because unprotected carbohydrates do not dissolve well in acetonitrile, but are reasonably soluble in protic solvents such as methanol.

To assess the effect of the solvent on the activity of \((\text{neocuproine})\text{PdOAc}}_2(\text{OTf})_2\) (3; Table 1) and \((\text{neocuproine})\text{PdOAc}}_2(\text{OTf})_2\) (4), we performed the oxidation of meth-

![Table 1 Oxidation of Glucoside 1 in 9:1 Acetonitrile–H2O or Methanol with Catalysts 3 and 4](image-url)
yl α-ᴅ-glucopyranoside (1) in 9:1 v/v acetonitrile–water and in methanol (Table 1).30,41 In line with previous studies on the oxidation of 2-heptanol and glycerol,33,39 3 showed higher turnover frequencies, and it turned out to be the more active in methanol. Although the oxidation reaction with the bisacetate catalyst 4 was considerably slower than that with 3, the TOF almost doubled when methanol was used instead of acetonitrile–water, indicating that oxidation of glucosides with the bisacetate catalyst 4 is facilitated by a protic polar solvent (Table 1). 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 much more readily in methanol than in acetone–water, the hydroquinone and neocuproine were removed by filtration. The moderate yield of 39 was due to its greater solubility in diethyl ether. For the synthesis of 10–12, 1.5 equivalents of benzoquinone were used, because 1.05 equivalents led to incomplete conversion. Compound 13 was purified by column chromatography because of its low solubility in water.

Our 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 the previously reported yield.15 The tert-butylbenzyl β-maltoside 15, on the other hand, proved to be a more challenging substrate: NMR analysis showed that several byproducts were formed, and purification by column chromatography gave 15 in only 27% yield. Oxidation of the Type 2 diabetes drug dapagliflozin50,51 completed our study on gluco-configured substrates, and the 3-ketosaccharide 1652 was obtained in 62% yield.

The scope was expanded with substrates possessing a non-glucose configuration. As shown previously, substrates such as mannose and galactose are prone to overoxidation and rearrangements, and provide moderate yields with 3.49 Indeed, attempts to oxidize methyl L-rhamnopyranoside, methyl D-mannopyranoside, and methyl D-galactopyranoside, as well as TIPS-protected methyl D-mannopyranoside (17; Scheme 2) led to complex mixtures of compounds, precluding the isolation of the desired ketosaccharides (see SI). We conclude, therefore, that for these and related compounds, the in-situ-formulated catalyst in methanol is suitable to determine whether oxidation occurs, whereas catalyst 3 should subsequently be employed to prepare the desired products.19,48

It was noticed that next to the products of non-gluco-configured monosaccharides, as well as several oxidized C-glycosides, can be quite sensitive to overoxidation and rearrangement (Scheme 2). The oxidation of puerarin (19) with Pd-catalyst 3 has been reported by Nakamura et al. to give 3-ketopuerarin in 70% yield.33 With the current in-situ-prepared catalyst, a mixture of 2054 and 21 was obtained in-

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**Figure 1 Oxidation of gluco-configured substrates. Reaction conditions: substrate (1 mmol), Pd(OAc)$_2$ (0.05 equiv), neocuproine (0.05 equiv), BQ (1.05 equiv), 0.2 M in MeOH, 50 °C, 18 h. a BQ (1.5 equiv). b After 4 h, an additional 0.5 equivalents of BQ were added.**

Yield reported in the literature: 15,29,46,50
instead of the desired C(3)-keto saccharide. These products are probably formed by migration of the keto functionality from C(3) to C(2), followed by a rearrangement reaction, because a migration of 3-ketopuerarin was observed by Nakamura et al., and the formation of such rearranged products from β-glycosides has been observed before by us. 49 Oxidation of glycoside 22 provided the desired product 23 56 in 32% yield together with the 2-keto saccharide 24 58 in 9% yield. The latter is probably formed through an intramolecular deprotonation of the C(2) position by adventitiously formed phenolate.

In conclusion, the catalyst prepared in situ from Pd(OAc)2 and neocuproine in methanol proved to be a suitable catalyst system for rapid screening of the C(3)-selective oxidation of carbohydrates. A straightforward purification protocol that avoids column chromatography permits rapid isolation of the products. For gluco-configured substrates, high yields are obtained and the reaction can be readily scaled up. The sensitivity of some substrates to overoxidation gives lower yields or mixtures of products. Nevertheless, even for these substrates, the protocol functions as a suitable and rapid screening method to determine whether it is worth preparing the Waymouth catalyst for the oxidation of a particular substrate. This protocol should lead to more-widespread application of the site-selective modification of unprotected carbohydrates and, in addition, is not limited to this substrate class, as shown by the oxidation of C-glycosides.

Conflict of Interest
The authors declare no conflict of interest.

Funding Information
I.M.A.B. and S.C.M. thank ARC-CBBC for funding. N.M. thanks NWO (project number 718.016.001) for funding.

Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/a-2186-1485.

References and Notes

Synlett 2023, 34, A–E
Characterization data for 12: amorphous solid; yield: 0.15 g 0.85 mmol (85%) [+] 20 mg (0.11 mmol) starting material. 1H NMR (400 MHz, CD3OD): δ = 4.99 (d, J = 4.4 Hz, 1 H), 4.42 (dd, J = 4.4, 1.5 Hz, 1 H), 3.89 (dd, J = 9.4, 1.4 Hz, 1 H), 3.76-3.68 (m, 1 H), 3.38 (s, 4 H), 1.39 (d, J = 6.2 Hz, 3 H). 13C NMR (101 MHz, CD3OD): δ = 206.5, 103.6, 78.6, 76.1, 72.0, 55.7, 18.9. HRMS (ESI): m/z [M–H]– calculated for C9H14O5: 175.0612; found: 175.0612.

Characterization data for 13: amorphous solid; yield: 0.22 g, 0.73 mmol (73%). 1H NMR (400 MHz, CD3OD): δ = 5.08 (d, J = 4.3 Hz, 1 H), 4.41 (dd, J = 4.2, 1.2 Hz, 1 H), 4.27 (dd, J = 9.7, 1.2 Hz, 1 H), 4.06–3.92 (m, 2 H), 3.68 (dd, J = 9.7, 4.4, 2.0 Hz, 1 H), 3.43 (t, J = 20 Hz, 1 H), 3.09 (s, 3 H), 0.98 (s, 9 H), 0.16 (s, 6 H). 13C NMR (101 MHz, CD3OD): 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 [M + Na]+ calculated for C15H22NaO5Si: 329.1391; found: 329.1391.

Characterization data for 16: colorless oil; yield: 0.25 g, 0.62 mmol (62%). 1H NMR (400 MHz, CD3OD): δ = 7.42–7.25 (m, 3 H), 7.09 (d, J = 8.6 Hz, 2 H), 6.79 (d, J = 8.6 Hz, 2 H), 4.39 (d, J = 10.0 Hz, 1 H), 4.23 (s, 2 H), 4.11–3.90 (m, 5 H), 3.82 (dd, J = 12.1, 4.7 Hz, 1 H), 3.49 (dd, J = 10.0, 4.8, 1.9 Hz, 1 H), 1.35 (t, J = 7.0 Hz, 4 H). 13C NMR (101 MHz, CD3OD): δ = 208.4, 158.9, 140.1, 139.3, 135.0, 132.1, 130.7, 130.3, 123.8, 115.4, 85.2, 84.7, 78.6, 74.0, 64.2, 39.2, 152. HRMS (ESI): m/z [M–H]– calculated for C13H18O4: 305.1110 and 407.1081; found: 405.1105 and 407.1076.

Characterization data for 20: isolated as an oil together with 21; yield: 0.12 g, 0.06 mmol (48%). 1H NMR (400 MHz, CD3OD): δ = 8.13 (s, 1 H), 8.03–7.96 (m, 1 H), 7.41–7.31 (m, 2 H), 6.91–6.82 (m, 3 H), 5.80 (s, 1 H), 4.79 (d, J = 9.3 Hz, 1 H), 4.09–3.92 (m, 2 H), 3.91–3.85 (m, 1 H), 3.20 (s, 3 H). 13C NMR (101 MHz, CD3OD): 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 [M–H]– calculated for C7H10O4 [M–H]–: 145.1129; found: 145.1124.

Characterization data for 23: isolated as an oil together with 24; yield: 0.96 g, 0.32 mmol (32%). 1H NMR (400 MHz, CD3OD): δ = 8.44 (d, J = 2.7 Hz, 1 H), 8.10 (dd, J = 9.0, 2.8 Hz, 1 H), 6.94 (d, J = 9.0 Hz, 1 H), 4.82 (d, J = 10.0 Hz, 1 H), 4.54 (dd, J = 10.0, 1.6 Hz, 1 H), 4.44 (dd, J = 10.0, 1.5 Hz, 1 H), 3.95 (dd, J = 12.3, 1.9 Hz, 1 H), 3.84 (dd, J = 12.3, 4.8 Hz, 1 H), 3.55 (dd, J = 10.0, 4.8, 2.0 Hz, 1 H). 13C NMR (101 MHz, CD3OD): δ = 208.4, 163.0, 141.9, 127.3, 126.4, 116.6, 84.8, 78.8, 78.1, 74.0. HRMS (ESI): m/z [M–H]– calculated for C7H10O4 [M–H]–: 145.1129; found: 145.1124.