

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

Niels R. M. Reintjens

Imke M. A. Bartels

Nittert Marinus

Sarina C. Massmann

Daan V. Bunt

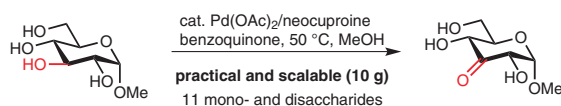
Marthe T. C. Walvoort

Martin D. Witte*

Adriaan J. Minnaard*

Stratingh Institute for Chemistry, University of Groningen, Groningen 9747 AG, Nijenborgh 7, The Netherlands
m.d.witte@rug.nl
a.j.minnaard@rug.nl

Published as part of the Cluster
Japan/Netherlands Gratama Workshop



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

License terms:

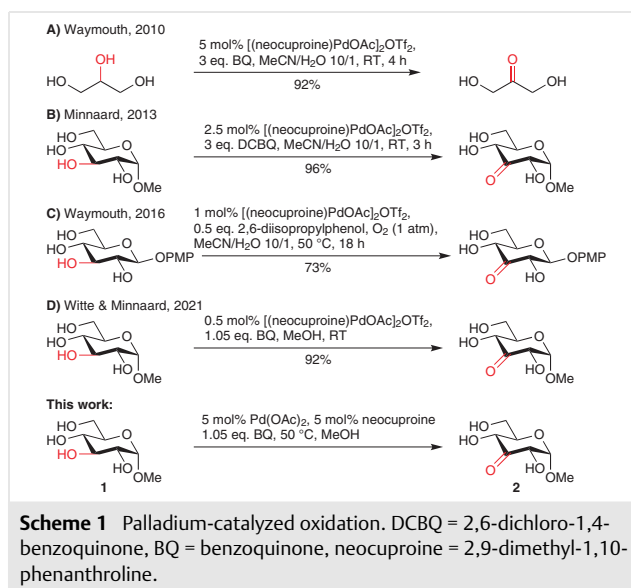
© 2023. The Author(s). This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution and reproduction, so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)

Abstract The palladium-catalyzed oxidation of the secondary C(3) hydroxy group of glycopyranosides has set a mark in the selective modification of unprotected carbohydrates. The preformed catalyst [(neocuproine)Pd(OAc)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

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.

Site-selective oxidation of the secondary hydroxy groups in unprotected carbohydrates is considerably more challenging,^{11,12} 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)Pd(OAc)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 -?-glucopyranoside (**1**) to the 3-ketoglucose **2** in methanol on a five-gram scale (Scheme 1D).²⁰



Other approaches for the selective oxidation of 1,2-diols make use of chelating agents such as boronic acids^{21,22} or organotin reagents^{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.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 sugars²⁷ 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.^{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 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 [(neocuproine)PdOAc]₂(OTf)₂, it had already been shown that secondary alcohols could be oxidized with (neocuproine)Pd(OAc)₂ at high temperatures.³² This bisacetate catalyst has been applied with various solvents and with several oxidants such as O₂/air^{33,34} or a combination of benzoquinone and electrochemistry.³⁵ It had also been shown that ligandless Pd(OAc)₂ was also effective in some cases.^{36,37} Lemaire's group combined these methods by preparing (neocuproine)Pd(OAc)₂ in situ to selectively oxidize fatty-acid-derived 1,2-diols.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 (neocuproine)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 (neocuproine)Pd(OAc)₂ was able to oxidize glucosides. The catalytic activities of [(neocuproine)PdOAc]₂(OTf)₂ and (neocuproine)Pd(OAc)₂ are dependent on the solvent.^{32,33} Dimeric [(neocuproine)PdOAc]₂(OTf)₂ dissociates in solution to the active monomeric species. Diol substrates readily coordinate to the active form of [(neocuproine)PdOAc]₂(OTf)₂, which results in a 325-fold higher turnover frequency (TOF) in acetonitrile compared with the bisacetate catalyst (neocuproine)Pd(OAc)₂.³³ Notably, however, a high catalytic activity has been reported for (neocuproine)Pd(OAc)₂ in protic solvents.^{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 [(neocuproine)PdOAc]₂(OTf)₂ (**3**; Table 1) and [(neocuproine)PdOAc]₂(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**

Pd catalyst	Yield (%)		TON ^a		TOF ^b	
	MeCN ^c	MeOH	MeCN ^c	MeOH	MeCN ^c	MeOH
3	92	93	46	47	29	77
4	41	54	21	27	5	12

^a The turnover number (TON) was calculated by dividing the conversion after 24 h by the mol% of [Pd].

^b The turnover frequency (TOF) was calculated by dividing the conversion after 0.5 h by the mol% of [Pd] and the reaction time. See the Supporting Information (SI) Tables S1 and S2 for the results at all time points.

^c MeCN–H₂O (9:1 v/v) was used to completely dissolve **1**.

yl α - β -glucopyranoside (**1**) in 9:1 v/v acetonitrile–water and in methanol (Table 1).^{40,41} 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 pK_a of acetic acid is considerably higher in acetonitrile ($pK_a = 23.5$)⁴² than in methanol ($pK_a = 9.63$).⁴³ We reason that the acetate anion dissociates much more readily in methanol than in acetonitrile and, after dissociation of acetate, the substrate or the solvent can coordinate to the vacant site.³² Methanol thus facilitates a rapid equilibrium between the inactive palladium acetate complex and the active substrate-bound catalyst.

Having identified methanol as a solvent and preprepared (neocuproine)Pd(OAc)₂ (**4**) as a suitable catalyst system for the oxidation of **1**, we subsequently focused our attention on the in-situ-prepared catalyst **4**. We were pleased to note that overnight reaction at room temperature, provided partial conversion of glucoside **1** (SI, Table S3).

In attempts to achieve full conversion, we screened various solvents (MeOH, MeOH–MeCN, HFIP, TFE, MeOH/water) and temperatures (room temperature and 50 °C). With Pd(OAc)₂ (0.05 equiv), neocuproine (0.05 equiv), and benzoquinone (1.05 equiv) in MeOH (0.2 M) at 50 °C overnight, a near full conversion was achieved, and these conditions were selected for further study.

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

To explore the scope of this procedure, various *gluco*-configured glycosides were oxidized, including a thioglucopyranoside, various protected glucopyranosides, a xylopyranoside, and glucuronopyranoside (Figure 1).⁴⁴ The corresponding ketosaccharides **6–13**^{45–48} were isolated in high yields, with the exception of **7**. Some products contained trace amounts of starting material, which was not removed by filtration. The moderate yield of **7** 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.

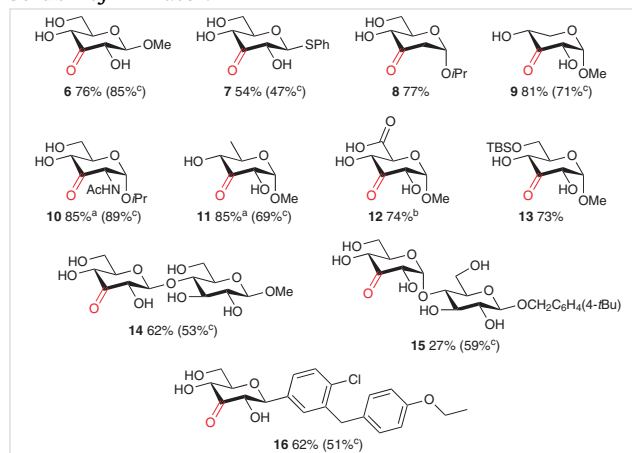
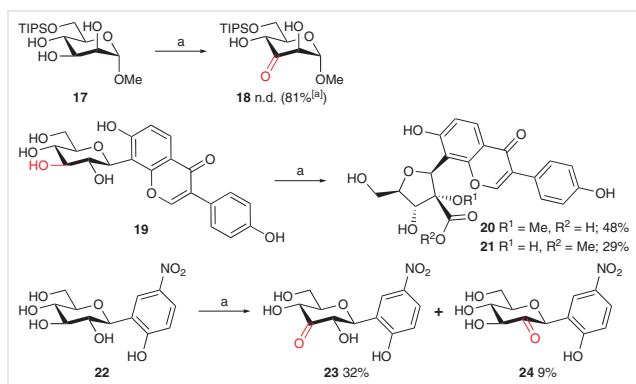


Figure 1 Oxidation of *gluco*-configured substrates. *Reaction conditions:* substrate (1 mmol), Pd(OAc)₂ (0.05 equiv), neocuproine (0.05 equiv), BQ (1.05 equiv), 0.2 M in MeOH, 50 °C, 18 h. ^a BQ (1.5 equiv). ^b After 4 h, an additional 0.5 equivalents of BQ were added. ^c Yield reported in the literature.^{15,29,49,50}

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 dapagliflozin^{50,51} completed our study on *gluco*-configured substrates, and the 3-ketosaccharide **16**⁵² was obtained in 62% yield.

The scope was expanded with substrates possessing a non-*gluco* 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-formed catalyst in methanol is suitable to determine whether oxidation occurs, whereas catalyst **3** should subsequently be employed to prepare the desired products.^{19,49}

It was noticed that next that 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.⁵³ With the current in-situ-prepared catalyst, a mixture of **20**⁵⁴ and **21** was obtained in-



Scheme 2 Reaction conditions a: Pd(OAc)₂ (0.05 equiv), neocuproine (0.05 equiv), BQ (1.05 equiv), 0.2 M in MeOH, 50 °C. Isolated yields are reported. ^a Yield reported in the literature.⁴⁹

stead 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**⁵⁵ in 32% yield together with the 2-keto saccharide **24**⁵⁶ 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

- (1) Seebach, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 96.
- (2) Tojo, G.; Fernández, M. I. *Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice*; Springer: New York, **2006**, 255.
- (3) Xu, C.; Zhang, C.; Li, H.; Zhao, X.; Song, L.; Li, X. *Catal. Surv. Asia* **2016**, *20*, 13.
- (4) *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, **2004**.
- (5) Furukawa, K.; Shibuya, M.; Yamamoto, Y. *Org. Lett.* **2015**, *17*, 2282.
- (6) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564.
- (7) Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293.
- (8) Shibuya, M.; Sato, T.; Tomizawa, M.; Iwabuchi, Y. *Chem. Commun.* **2009**, 1739.
- (9) Lee, W.; Youn, J.-H.; Kang, S. H. *Chem. Commun.* **2013**, *49*, 5231.
- (10) Schämamm, M.; Schäfer, H. J. *Eur. J. Org. Chem.* **2003**, 351.
- (11) Eisink, N.; Minnaard, A.; Witte, M. *Synthesis* **2017**, *49*, 822.
- (12) Marinus, N.; Eisink, N. N. H. M.; Reintjens, N. R. M.; Dijkstra, R. S.; Havenith, R. W. A.; Minnaard, A. J.; Witte, M. D. *Chem. Eur. J.* **2023**, e202300318.
- (13) Painter, R. M.; Pearson, D. M.; Waymouth, R. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9456.
- (14) Chung, K.; Banik, S. M.; De Crisci, A. G.; Pearson, D. M.; Blake, T. R.; Olsson, J. V.; Ingram, A. J.; Zare, R. N.; Waymouth, R. M. *J. Am. Chem. Soc.* **2013**, *135*, 7593.
- (15) Jäger, M.; Hartmann, M.; de Vries, J. G.; Minnaard, A. J. *Angew. Chem. Int. Ed.* **2013**, *52*, 7809.
- (16) Eisink, N. N. H. M.; Lohse, J.; Witte, M. D.; Minnaard, A. J. *Org. Biomol. Chem.* **2016**, *14*, 4859.
- (17) Reintjens, N. R. M.; Yakovlieva, L.; Marinus, N.; Hekelaar, J.; Nuti, F.; Papini, A. M.; Witte, M. D.; Minnaard, A. J.; Walvoort, M. T. C. *Eur. J. Org. Chem.* **2022**, 2022, e202200677.
- (18) Wan, I. C.; Hamlin, T. A.; Eisink, N. N. H. M.; Marinus, N.; Boer, C.; Vis, C. A.; Codée, J. D. C.; Witte, M. D.; Minnaard, A. J.; Bickelhaupt, F. M. *Eur. J. Org. Chem.* **2021**, 2021, 632.
- (19) Chung, K.; Waymouth, R. M. *ACS Catal.* **2016**, *6*, 4653.
- (20) Marinus, N.; Walvoort, M. T. C.; Witte, M. D.; Minnaard, A. J.; van Dijk, H. M. In *Carbohydrate Chemistry: Proven Synthetic Methods, Vol. 5, Chap. 16* Wrodnigg T. M., Stütz A., CRC Press, Boca Raton, 2021.
- (21) William, J. M.; Kuriyama, M.; Onomura, O. *Adv. Synth. Catal.* **2014**, *356*, 934.
- (22) Feng, L.; Zhang, S.; Sun, X.; Dong, A.; Chen, Q. *J. Mater. Sci.* **2018**, *53*, 15025.
- (23) Maki, T.; Iikawa, S.; Mogami, G.; Harasawa, H.; Matsumura, Y.; Onomura, O. *Chem. Eur. J.* **2009**, *15*, 5364.
- (24) William, J. M.; Kuriyama, M.; Onomura, O. *RSC Adv.* **2013**, *3*, 19247.
- (25) Muramatsu, W. *Org. Lett.* **2014**, *16*, 4846.
- (26) Kaspar, M.; Kudova, E. *J. Org. Chem.* **2022**, *87*, 9157.
- (27) Zhang, J.; Eisink, N. N. H. M.; Witte, M. D.; Minnaard, A. J. *J. Org. Chem.* **2019**, *84*, 516.

- (28) Marinus, N.; Tahiri, N.; Duca, M.; Mouthaan, L. M. C. M.; Bianca, S.; van den Noort, M.; Poolman, B.; Witte, M. D.; Minnaard, A. J. *Org. Lett.* **2020**, *22*, 5622.
- (29) Zhang, J.; Reintjens, N. R. M.; Dhineshkumar, J.; Witte, M. D.; Minnaard, A. J. *Org. Lett.* **2022**, *24*, 5339.
- (30) Reintjens, N. R. M.; Witte, M. D.; Minnaard, A. J. *Org. Biomol. Chem.* **2023**, *21*, 5098.
- (31) Ahmadian-Moghaddam, M.; Reintjens, N. R. M.; Witte, M. D.; Minnaard, A. J. *Eur. J. Org. Chem.* **2023**, *26*, e202300281.
- (32) ten Brink, G.-J.; Arends, I. W. C. E.; Hoogenraad, M.; Verspui, G.; Sheldon, R. A. *Adv. Synth. Catal.* **2003**, *345*, 1341.
- (33) Conley, N. R.; Labios, L. A.; Pearson, D. M.; McCrory, C. C. L.; Waymouth, R. M. *Organometallics* **2007**, *26*, 5447.
- (34) Bailie, D. S.; Clendenning, G. M. A.; McNamee, L.; Muldoon, M. J. *Chem. Commun.* **2010**, *46*, 7238.
- (35) Lybaert, J.; Tehrani, K. A.; De Wael, K. *Electrochim. Acta* **2017**, *247*, 685.
- (36) Amatore, C.; Cammoun, C.; Jutand, A. *Synlett* **2007**, 2173.
- (37) Dornan, L. M.; Muldoon, M. J. *Catal. Sci. Technol.* **2015**, *5*, 1428.
- (38) Vu, N. D.; Guicheret, B.; Duguet, N.; Métay, E.; Lemaire, M. *Green Chem.* **2017**, *19*, 3390.
- (39) Wang, H.; Vu, N. D.; Chen, G.-R.; Métay, E.; Duguet, N.; Lemaire, M. *Green Chem.* **2021**, *23*, 1154.
- (40) Because of the low solubility of **1** in acetonitrile, we used a 9:1 (v/v) mixture of acetonitrile and water.
- (41) To a stock solution of methyl α -D-glucopyranoside (**1**; 45 mg, 0.23 mmol, 1 equiv) and BQ (26 mg, 0.24 mmol, 1.05 equiv) in MeOH (0.1 M) or 9:1 MeCN–H₂O (0.1 M) was added catalyst **3** (5 mg, 5 μ mol, 2 mol%) or **4** (2 mg, 5 μ mol, 2 mol%), and the mixture was stirred for 24 h at rt under air. A portion of the mixture was diluted with CD₃OD and analyzed by ¹H NMR. The conversion was calculated by dividing the product integral by the sum of the product and starting material integrals. The TON was calculated by dividing the conversion by the mol% [Pd]. The TOF was calculated by using the conversion after 0.5 h by dividing the TON by the reaction time.
- (42) Kütt, A.; Tshepelevitsh, S.; Saame, J.; Lõkov, M.; Kaljurand, I.; Selberg, S.; Leito, I. *Eur. J. Org. Chem.* **2021**, *2021*, 1407.
- (43) Miguel, E. L. M.; Silva, P. L.; Pliego, J. R. J. *Phys. Chem. B* **2014**, *118*, 5730.
- (44) **Compounds 6–16; General Procedure**
BQ (114 mg, 1.05 mmol, 1.05 equiv), neocuproine (10.5 mg, 50 μ mol, 5 mol%), and Pd(OAc)₂ (11.2 mg, 50 μ mol, 5 mol%) were added to a solution of the appropriate substrate (1.0 mmol, 1 equiv) in MeOH (0.2 M). The reactions were monitored by ¹H NMR analysis of a 50 μ L portion of the reaction mixture diluted with CD₃OD. After stirring overnight, the mixture was concentrated in vacuo and the residue was dissolved in H₂O (15 mL; Milli-Q), and the solution was washed with Et₂O (2 \times 30 mL). The aqueous layer was filtered twice through a 1.0 μ m pore-size syringe filter and once through a 0.45 μ m pore-size syringe filter, then concentrated in vacuo.
- (45) Characterization data for **8**: amorphous solid; yield: 0.14 g, 0.69 mmol (77%). ¹H NMR (400 MHz, CD₃OD): δ = 5.39 (d, J = 4.2 Hz, 1 H), 4.20–4.14 (m, 1 H), 3.95 (dt, J = 12.4, 6.2 Hz, 1 H), 3.89–3.77 (m, 3 H), 2.88 (ddd, J = 13.9, 4.6, 1.1 Hz, 1 H), 2.43 (dd, J = 13.9, 0.9 Hz, 1 H), 1.15 (dd, J = 12.2, 6.2 Hz, 6 H). ¹³C NMR (101 MHz, CD₃OD): δ = 207.6, 97.9, 76.6, 74.2, 70.0, 62.6, 47.1, 23.5, 21.4. HRMS(ESI⁻): m/z [M–H]⁻ calcd for C₉H₁₅O₅: 203.0925; found: 203.0925.
- (46) Characterization data for **11**: 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, 78.8, 76.1, 72.0, 55.7, 18.9. HRMS(ESI⁻): m/z [M–H]⁻ calcd for C₇H₁₁O₅: 175.0612; found: 175.0612.
- (47) Characterization data for **12**: amorphous solid; yield: 0.15 g, 0.74 mmol (85%) [+ starting material: 15 mg (7 μ mol)]. ¹H NMR (400 MHz, CD₃OD): δ = 5.11 (d, J = 4.2 Hz, 1 H), 4.49 (dd, J = 4.1, 1.2 Hz, 1 H), 4.45 (d, J = 9.8 Hz, 1 H), 4.08 (d, J = 9.8 Hz, 1 H), 3.44 (d, J = 4.8 Hz, 3 H). ¹³C NMR (101 MHz, CD₃OD) δ = 205.4, 104.3, 76.0, 75.0, 75.0, 56.2. HRMS (ESI⁻): m/z [M–H]⁻ calcd for C₇H₉O₇: 205.0354; found: 205.0354.
- (48) 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 (ddd, J = 9.7, 4.4, 2.0 Hz, 1 H), 3.43 (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]⁺ calcd for C₁₃H₂₆NaO₆Si: 329.1391; found: 329.1391.
- (49) Eisink, N. N. H. M.; Witte, M. D.; Minnaard, A. J. *ACS Catal.* **2017**, *7*, 1438.
- (50) Zhiyuan, Z.; Shaoqiang, H.; Zhaolan, Z.; Yanning, S. U.; Yan, R. E. *N. WO 2016041470* **2016**.
- (51) Balkanski, S. *Pharmacia (Sofia, Bulg.)* **2021**, *68*, 591.
- (52) Characterization data for **16**: colorless oil; yield: 0.25 g, 0.62 mmol (62%). ¹H NMR (400 MHz, CD₃OD): δ = 7.42–7.35 (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 (ddd, 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, 132.8, 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⁻): m/z [M–H]⁻ calcd for C₂₁H₂₂ClO₆: 405.1110 and 407.1081; found: 405.1105 and 407.1076.
- (53) Nakamura, K.; Zhu, S.; Komatsu, K.; Hattori, M.; Iwashima, M. *Biol. Pharm. Bull.* **2019**, *42*, 417.
- (54) Characterization data for **20**: isolated as an oil, together with **21**; yield: 51 mg, 0.11 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]⁻ calcd for C₂₂H₂₁O₁₀ [M+H]⁺: 445.1129; found: 445.1124.
- (55) Characterization data for **23**: isolated as an oil together with **24**; yield: 96 mg, 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 (ddd, 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, 126.0, 116.6, 84.8, 78.8, 78.1, 74.0, 62.9. HRMS (ESI⁻): m/z [M–H]⁻ calcd for C₁₂H₁₂NO₈: 298.0568; found: 298.0563.
- (56) Characterization data for **24**: isolated as an oil together with **23**; yield: 26 mg, 90 μ mol (9%). ¹H NMR (400 MHz, CD₃OD): δ = 8.22 (d, J = 2.8 Hz, 1 H), 8.08 (dd, J = 8.9, 2.8 Hz, 1 H), 6.88 (d, J = 9.1 Hz, 1 H), 5.37 (s, 1 H), 4.43 (d, J = 9.3 Hz, 1 H), 4.02 (d, J = 10.3 Hz, 1 H), 3.94–3.79 (m, 2 H), 3.68 (t, J = 9.4 Hz, 1 H). ¹³C NMR (101 MHz, CD₃OD): δ = 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⁻): m/z [M–H]⁻ calcd for C₁₂H₁₂NO₈: 298.0568; found: 298.0564.