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Deuteration enhances catalyst lifetime in palladium-catalysed alcohol oxidation†

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The catalyst palladium/2,9-CD_3-phenanthroline has a 1.8 times higher turnover number than its non-deuterated counterpart in the aerobic alcohol oxidation of methyl glucoside and allows the regioselective oxidation with dioxygen as the terminal oxidant.

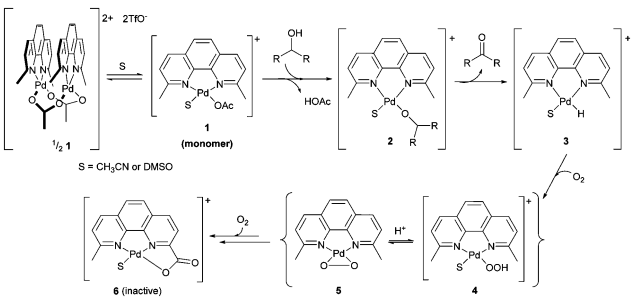
Palladium-catalyzed alcohol oxidation is an important method for the preparation of aldehydes and ketones, in particular in complex substrates.[1] Waymouth *et al.*[2] recently reported that cationic palladium/neocuproine complexes[3] catalyze the chemoselective oxidation of vicinal diols to α-hydroxy ketones at room temperature. In particular, the secondary hydroxyl group is oxidized by $[(\text{neocuproine})\text{Pd}(\text{OAc})]_2[\text{OTf}]_2$ (**1**) with excellent selectivity and yield.[4]

Extending this work, we showed that **1** is also able to discriminate between different secondary hydroxyl groups in the first catalytic, regioselective oxidation of unprotected pyranosyl glucosides to the corresponding ketosaccharides.[5]

Although designed, and effective, for aerobic oxidation, the reactions using air or dioxygen require high Pd loadings up to 10 mol%.[2,4] This is caused in part by concomitant autoxidation of the ligand (Scheme 1). Oxidation of a methyl substituent *via* C–H insertion of Pd(II) hydroperoxide (**4**), followed by subsequent further oxidation, forms an inactive palladium complex (**6**).

With other terminal oxidants, such as benzoquinone, oxidation of the ligand is much slower and the turnover number of **1** is therefore considerably enhanced. However, the use of oxygen or air is highly desirable, in particular for carbohydrate oxidation, as it strongly simplifies the isolation of the products.

The presence of substituents at the 2 and 9 position of the phenanthroline ligand is critical. In this way, the dimeric pre-catalyst is in equilibrium with the active monomeric catalyst in solution. Palladium complexes ligated by unsubstituted phenanthrolines are inactive at room temperature. Therefore, efforts were made to develop oxidation resistant 2,9-disubstituted phenanthroline ligands, but with limited success. Also, Waymouth *et al.* reported a mono-trifluoromethyl substituted phenanthroline ligand and studied it in the palladium-catalyzed oxidation of 2-heptanol.[2c] The turnover number of this catalyst doubled, and no ligand oxidation was observed, however at the cost of a 3.7 times lower initial rate compared to **1**. Furthermore, the ligand is difficult to access.



Scheme 1 Ligand oxidation in palladium-catalyzed aerobic alcohol oxidation.

Oscillating between the requirement of substituents and their desired resistance against C–H activation we realized that deuteration of the methyl groups in neocuproine could enhance the stability of the palladium catalyst against autoxidation to such an extent that the aerobic alcohol oxidation, in particular of carbohydrates, would become feasible. The lower zero-point energy of the deuterium–carbon bond compared to the hydrogen–carbon bond (around 5 kJ mol^{-1}) results in a higher activation energy for C–D bond cleavage manifested as a kinetic isotope effect.[6,7] Consequently, the deuterated catalyst should be more stable without changing its properties in catalysis.

The approach is reminiscent to deuteration strategies in drug development, that are used to enhance the stability of a drug in oxidative metabolism.[8] In synthesis, deuteration has been applied in specific cases to alter reaction selectivity.[9] To the best of our knowledge, a deuteration strategy to increase ligand stability in catalysis, however, has not been reported.

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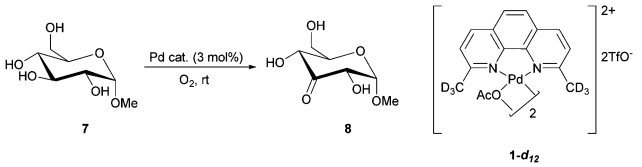


Scheme 2 Regioselective aerobic oxidation of methyl α-D-glucopyranoside at room temperature.

In order to go beyond proof of principle, deuteration of the ligand should be straightforward. Browne *et al.* have described a practical perdeuteration of bipyridine and phenanthroline ligands with NaOD/D_2O at high temperature.[10] More recently, Neranon and Ramström used a similar method to exclusively deuterate the methyl moieties, employing microwave heating.[11]

Herein we report that deuteration of neocuproine leads to a significant increase in turnover number in the aerobic palladium-catalyzed oxidation of methyl glucoside (7) and allows this reaction to be carried out using oxygen as the sole terminal oxidant (Scheme 2).

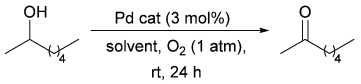
Deuteration of the methyl groups of neocuproine was carried out according to the procedure reported for a similar substrate, 6,6′-dimethyl-2,2′-bipyridine.[11] Treatment of **9** with aqueous sodium deuteroxide at 190 °C for 180 min in a microwave provided **9-d_6** in 99% isotopic purity and 92% isolated yield. The degree of deuteration was determined by NMR using the residual solvent peak as internal standard.

In their early work,[2a] Waymouth *et al.* found that comproportionation of (neocuproine)Pd(OAc)$_2$[3a] and the ditriflate analogue (neocuproine)Pd(MeCN)$_2$(OTf)$_2$[12] in acetonitrile afforded the dimeric acetate-bridged complex [(neocuproine)Pd(μ-OAc)]$_2$[OTf]$_2$ **1**, which could be isolated and used in aerobic alcohol oxidations. Later, it was shown that dimer formation can be carried out *in situ* preceding the catalysis, and we followed the latter method for the preparation of the deuterated catalyst.[2c] The new deuterated-neocuproine palladium precursor complexes **10-d_6** and **11-d_6** were prepared similar to their non-deuterated analogues. Complexation of ligand **9-d_6** with palladium acetate gave **10-d_6** in 87% yield (pure according to NMR and elemental analysis), and subsequent treatment of **10-d_6** with triflic acid furnished **11-d_6** in 93% yield (pure according to NMR, see ESI†).

In order to accurately determine the difference in activity between the deuterated and the non-deuterated catalyst, first, the oxidation of 2-heptanol under an oxygen atmosphere at room temperature was studied as a model reaction. This reaction is readily monitored by GC-MS, contrary to the oxidation of methyl α-D-glucopyranoside.

As the goal was aerobic oxidation of carbohydrates, which is carried out in DMSO, we chose this solvent also for the oxidation of 2-heptanol (**12**, 1 mmol, 0.5 M). Deuterated catalyst **1-d_{12}** (3 mol% of the Pd dimer) prepared *in situ* from the deuterated complexes **10-d_6** and **11-d_6** (3 mol% each) exhibited a turnover frequency (TOF) of 13 h^{-1}. The conversion was 81% after 24 h (TON = 13.5, entry 1, Table 1). Waymouth and coworkers reported that the addition of water has an accelerating effect on the rate of diol oxidation, but not on the rate of mono-alcohol oxidation and that water, produced by oxygen reduction, does not inhibit the catalyst. In fact, the addition of molecular sieves even leads to a lower initial rate and conversion.[2a]

Table 1 Deuterated *versus* non-deuterated neocuproine in the palladium-catalyzed aerobic oxidation of 2-heptanol (**12**)[a]



Entry	Solvent	Pd cat.	Conv.[b] (%)	TON	TOF[e] (h^{-1})
1	DMSO	**1-d_{12}**	81	13.5	13
2	DMSO/H_2O	**1-d_{12}**	100[c]	17	19
3	DMSO/H_2O	**1-d_{12}**	68[d]	Max (23)	—
4	DMSO/H_2O	**1**	84	Max (14)	20

[a] Reaction conditions: **12** (1 mmol, 0.5 M), O_2 (1 atm), Pd cat. (3 mol%), solvent, rt, 24 h. [b] Conversion determined by GC-MS (ratiometric method, see ESI). [c] After 14 h. [d] Reaction conditions: **12** (2 mmol, 1 M), O_2 (1 atm), Pd cat. (1.5 mol%), DMSO/H_2O (1 mol% with respect to DMSO), rt, 24 h. After 30 h the conversion had not changed. [e] TOF determined by interpolation of reaction progress curves, see ESI.

Therefore, the oxidation of **12** (0.5 M) in DMSO in the presence of 1 mol% of water (with respect to DMSO) was evaluated. Under these conditions, **1-d_{12}** showed a higher TOF (19 h^{-1}) compared to the reaction in pure DMSO, and full conversion of **12** was reached in 14 h (entry 2, Table 1). Although an explanation for this improvement is currently lacking, we attribute it to this solvent system (Fig. 1).

Subsequently, the maximum turnover number for the deuterated catalyst was determined by doubling the amount of substrate to prevent complete conversion. The oxidation of **12** (1 M) catalyzed by **1-d_{12}** (1.5 mol%) resulted in 68% conversion of 2-heptanol after 24 h (TON = 23).

Compared to the activity of **1-d_{12}**, complex **1** shows a similar TOF (20 h^{-1}) but during the course of the reaction the rate decreases to afford 84% conversion after 24 h (entry 4, Table 1). Since the oxidation of **12** with catalyst **1** did not result in full conversion, the maximum turnover number of **1** could be directly determined (TON = 14). The comparison of the reaction curves highlights the improved stability of the new deuterated neocuproine palladium complex **1-d_{12}** in the oxidation of mono-alcohols, against non-deuterated **1** (Fig. 2) and the increase in maximum turnover number for **1-d_{12}** over **1** underlines this further.

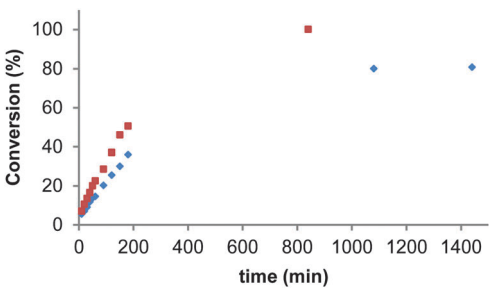


Fig. 1 Reaction progress curves for the aerobic oxidation of 2-heptanol (**12**) with catalyst **1-d_{12}** in DMSO (♦) and in DMSO/H_2O (■) at room temperature. The reaction was carried out in *quadruplo* and the mean values were plotted.

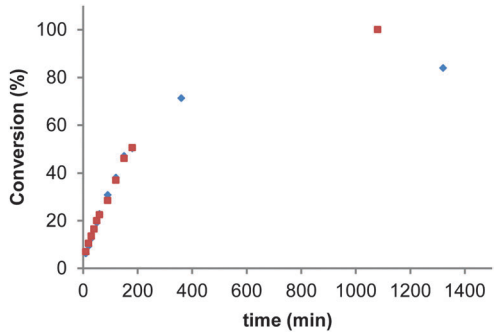
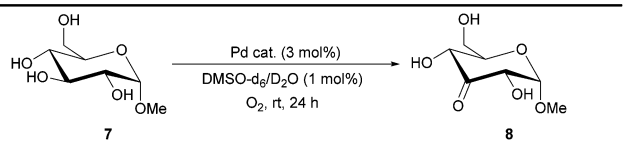


Fig. 2 Reaction progress curves for the aerobic oxidation of 2-heptanol (**12**) with catalysts **1-d_{12}** (■) and **1** (♦) in DMSO/H_2O at room temperature. Reactions were carried out in *duplo* with the mean conversion being plotted.

Table 2 Catalyst efficiency in the selective oxidation of glucopyranoside (**7**)[a]



7 **8**

Entry	Pd cat.	Conv.[b] (%)	TON	TOF[e] (h^{-1})
1	**1-d_{12}**	100[c]	17	8
2	**1**	58	Max (10)	7
3	**1-d_{12}**	53[d]	Max (18)	—

[a] Reaction conditions: **7** (1.25 mmol, 0.5 M), O_2 (1 atm), Pd cat. (3 mol%), DMSO-d_6/D_2O, rt, 24 h. [b] Conversion determined by ^{1}H-NMR (ratiometric method, see ESI). [c] After 18 h. [d] Reaction conditions: **7** (2.5 mmol, 1 M), O_2 (1 atm), Pd cat. (1.5 mol%), DMSO-d_6/D_2O, rt, 24 h. After 30 h the conversion had not changed. [e] TOF determined by Interpolation of reaction progress curves, see ESI.

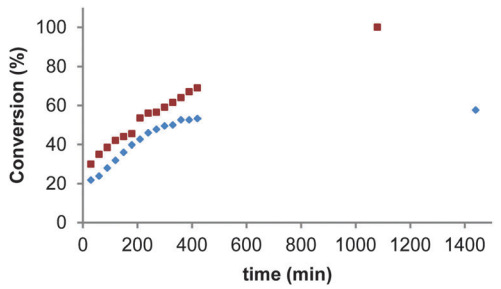


Fig. 3 Reaction progress curves for the oxidation of glucopyranoside (**7**) with catalyst **1-d_{12}** (■) and **1** (♦) in DMSO-d_6/D_2O (1 mol%) at room temperature. Reactions were carried out in *duplo* with the mean conversion being plotted.

With these results in hand, we focussed on the oxidation of methyl α-D-glucopyranoside (**7**) under the same conditions. As we reported,[5] **7** is selectively oxidized at the C3 position and this permits accurate determination of the conversion by ^{1}H-NMR.

The oxidation of **7** (0.5 M) in DMSO-d_6/D_2O with **1-d_{12}** (3 mol% Pd cat.) gave a TOF of 8 h^{-1} and full conversion to the sole product **8** within 14 h (entry 1, Table 2). Non-deuterated catalyst **1** under the same reaction conditions gave a slightly lower rate (TOF = 7 h^{-1}) and a considerably lower conversion (58% after 24 h, TON = 10, Fig. 3). These results demonstrate the increased stability of **1-d_{12}** in the oxidation of glucopyranosides as well. The TON for **1-d_{12}** was determined by doubling the amount of glucopyranoside. The oxidation of **7** (1 M) catalyzed by **1-*d*12** (1.5 mol%) resulted in 53% conversion of α-D-glucopyranoside after 24 h (TON = 18).

For both substrates **7** and **12**, turnover numbers of the deuterated catalyst are increased by a factor of at least 1.6 compared to the non-deuterated catalyst.

Concluding, the straightforward deuteration of the methyl substituents in neocuproine allowed the development of a catalyst system (**1-d_{12}**) that increased the turnover number in aerobic alcohol oxidation with at least 1.6 times and for methyl glucoside with 1.8 times. The turnover frequency of the catalyst is similar, as expected, but as inactivation of the catalyst by intramolecular C–H activation is retarded due to the kinetic isotope effect, the catalyst **1-d_{12}** has a longer lifetime. The increase in turnover number allows the aerobic oxidation of glycosides with acceptable catalyst loadings and this is a major practical advantage compared to the use of benzoquinone, as purification of the oxidation products is considerably simplified.

Deuteration of neocuproine and other pyridine and phenanthroline-type ligands is so straightforward and inexpensive that neocuproine-d_6 (**9-d_6**) should find application in related catalytic oxidation reactions as well. Although the problem of ligand oxidation is not solved in this way, it is significantly relaxed.

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