Deuteration enhances catalyst lifetime in palladium-catalysed alcohol oxidation†

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The catalyst palladium/2,9-CD₃-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. Waymouth et al.² recently reported that cationic palladium/neocuproine complexes³ catalyze the chemoselective oxidation of vicinal diols to α-hydroxy ketones at room temperature. In particular, the secondary hydroxyl group is oxidized by [(neocuproine)Pd(OAc)]₂[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.

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 for carbohydrates, would become feasible. The lower zero-point energy of the deuterium–carbon bond compared to the hydrogen–carbon bond 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.
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/D2O at high temperature. More recently, Neranon and Ramström used a similar method to exclusively deuterate the methyl moieties, employing microwave heating. 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. Treatment of 9 with aqueous sodium deuteroxide at 190 °C for 180 min in a microwave provided 9-d6 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, Waymouth et al. found that comproportionation of (neocuproine)Pd(OAc)2 and the ditriflate analogue (neocuproine)Pd(MeCN)2(OTf)2 in acetonitrile afforded the dimeric acetate-bridged complex [(neocuproine)Pd(μ-OAc)2](OTf)2, 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. The new deuterated-neocuproine palladium precursor complexes 10-d6 and 11-d6 were prepared similar to their non-deuterated analogues. Complexation of ligand 9-d6 with palladium acetate gave 10-d6 in 87% yield (pure according to NMR and elemental analysis), and subsequent treatment of 10-d6 with triflic acid furnished 11-d6 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-d12 (3 mol% of the Pd dimer) prepared in situ from the deuterated complexes 10-d6 and 11-d6 (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 dial 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.

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-d12 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-d12 (1.5 mol%) resulted in 68% conversion of 2-heptanol after 24 h (TON = 23).

Compared to the activity of 1-d12, 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-d12 in the oxidation of mono-alcohols, against non-deuterated 1 (Fig. 2) and the increase in maximum turnover number for 1-d12 over 1 underlines this further.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Pd cat.</th>
<th>Conv. (%)</th>
<th>TON</th>
<th>TOF (h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMSO</td>
<td>1-d12</td>
<td>81</td>
<td>13.5</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>DMSO/H2O</td>
<td>1-d12</td>
<td>100°</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>DMSO/H2O</td>
<td>1-d12</td>
<td>68°</td>
<td>Max (23)</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>DMSO/H2O</td>
<td>1</td>
<td>84</td>
<td>Max (14)</td>
<td>20</td>
</tr>
</tbody>
</table>

*Reaction conditions: 12 (1 mmol, 0.5 M), O2 (1 atm), Pd cat. (3 mol%), solvent, rt, 24 h. Conversion determined by GC-MS (ratemetric method, see ESI). After 14 h. Reaction conditions: 12 (2 mmol, 1 M), O2 (1 atm), Pd cat. (1.5 mol%), DMSO/H2O (1 mol% with respect to DMSO), rt, 24 h. After 30 h the conversion had not changed. TOF determined by interpolation of reaction progress curves, see ESI.*
of 1-d_{14} in the oxidation of glucopyranosides as well. The TON for 1-d_{14} 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 \( \alpha \)-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_{14} 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_{4} (9-d_{4}) 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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Notes and references

6 After submission of this manuscript a study was reported on the mechanism of the palladium-catalyzed alcohol oxidation in which also d_{5}-neocuproine was involved, however not in catalysis, see: A. J. Ingram, K. L. Walker, R. N. Zare and R. M. Waymouth, J. Am. Chem. Soc., 2015, 137, 13632.