Tetrahedron 66 (2010) 7927–7932

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Binuclear complexes for aerobic oxidation of primary alcohols and carbohydrates

Susanne Striegler *, Natasha A. Dunaway, Moses G. Gichinga, Lisa K. Milton

Department of Chemistry and Biochemistry, 179 Chemistry Building, Auburn University, Auburn AL 36849, USA

ARTICLE INFO

Article history:
Received 17 June 2010
Received in revised form 26 July 2010
Accepted 27 July 2010
Available online 3 August 2010

ABSTRACT

The influence of electron-donating and electron-accepting properties of three pentadentate ligands was determined in connection with the aerobic oxidation ability of the corresponding binuclear copper(II) complexes for benzyl and allyl alcohols; additionally, the catalytic performance of their palladium and platinum analogs was characterized under comparable conditions. Quantitative aerobic oxidation of benzyl alcohol at 40 °C was achieved with a binuclear copper(II) complex—TEMPO catalyst in 2.5 h, while the regioselective aerobic oxidation of underivatized methyl-β-D-glucopyranoside was accomplished in about 35% yield at 60 °C after 24 h.

1. Introduction

A major obstacle to advances in glycobiology is the lack of pure and structurally well-defined oligosaccharides and glycoconjugates.[1] This shortage is particularly cumbersome for the potential use of unnatural sugars as food components with a low calorie value to fight obesity. Of particular interest in this regard are 5-*C*-hydroxymethylglycosides derived from sugar-6-carbaldehydes that cannot be digested by mammalian enzymes or intestinal bacteria.[2] Enzymatic approaches towards synthesizing the prerequisite sugar-6-carbaldehydes are compromised by the specificity of galactose oxidase for the transformation of substrates with galacto-configuration, its moderate thermal stability, narrow pH profile and comparably low reaction yields.[3] Galactose oxidase is the only enzyme known today to oxidize the primary alcohol group of carbohydrates. Conventional multi-step syntheses on the other hand typically involve numerous protection, deprotection and activation steps prior to the regioselective oxidation of the primary alcohol group of a carbohydrate, which somewhat diminishes the value of established synthetic methods.[4]

The development of a protocol for the catalytic and regioselective oxidation of primary alcohols in underivatized carbohydrates is thus a long-term goal for the work in this laboratory. The oxidation of the primary alcohol group in carbohydrates is conventionally achieved using stoichiometric amounts of two-electron oxidants, such as iodosylbenzene,[5] amine *N*-oxides,[6–8] peroxides,[9] or transition metal complexes.[10] These entities can be used in catalytic amounts when re-oxidation by molecular oxygen, sodium hypochlorite or other oxidants are provided.[7] However, unselective oxidation of both primary and secondary hydroxyl groups, over-oxidation of the primary alcohols to carboxylic acids[7,10] or limited catalyst stability during the reaction[11] currently reduce the applicability of these methods for the synthesis of hexose-6-aldehydes.

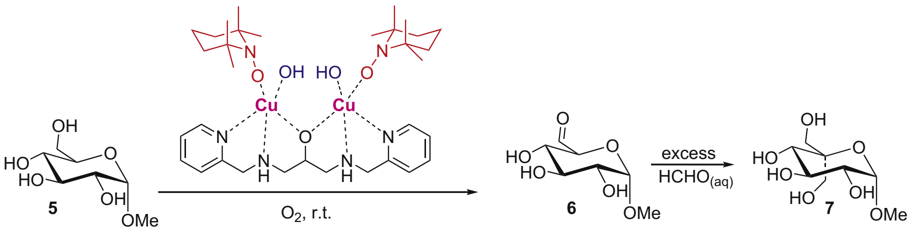
To overcome this shortcoming, we previously proposed a catalytic system for the regioselective aerobic oxidation of primary alcohols consisting of the binuclear copper(II) complex *N*, *N*′-{bis (2-pyridylmethyl)-1,3-diaminopropan-2-ol}ato dicopper(II) (μ-acetato) diperchlorate, Cu_2(bpdpo) (**1**),[12–14] and 2,2,6,6-tetramethylpiperidine-1-oxyl, TEMPO (**2**), in alkaline aqueous acetonitrile solution.[12] This earlier study disclosed a sugar-discriminating binuclear complex **1**[13] promoting the aerobic oxidation of benzyl alcohol (**3**) into benzaldehyde (**4**) in the presence of **2** and a base, while preventing over-oxidation to carboxylic acids.[12] Mononuclear complexes derived from the same or similar backbone ligands were inactive under comparable conditions.[12] The constitution of the catalytically active species was deduced from isothermal titration calorimetry and kinetic experiments.[12] A mechanism for the catalytic cycle for the oxidation of benzyl alcohols was proposed.[12] The **1**–**2** catalyst regioselectively oxidizes primary over secondary alcohols. Similar findings are reported for related catalysts for aerobic oxidations of primary alcohols with copper(II) complexes and TEMPO.[15–24]

Preliminary data furthermore suggested the catalytic oxidation of α-D-methylglucopyranoside (**5**) into the corresponding sugar 6-carbaldehyde **6** employing the **1**–**2** catalyst (Scheme 1).[25] A qualitative proof for the presence of **6** was obtained after treatment of the reaction product with excess formaldehyde solution yielding 5-*C*-hydroxymethyl-α-D-methylglucopyranoside **7**,[2] and the observation of its sodium adduct by ESI mass spectrometry ($M_{7\text{-}Na+}$=247.1). The mass peak of the sodium adduct of **7** gives evidence for the oxidation of **5** into **6** as a prerequisite for the formation of **7**.[25] In our previous attempts, **6** and **7** were isolated in less than 10% from the solution. Full characterization data for **6** and **7** are provided by Mazur and Hiler previously.[2]

---

* Corresponding author. Tel.: +1 334 844 6954; fax: +1 334 844 6959; e-mail address: Susanne.Striegler@auburn.edu (S. Striegler).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.07.077



Scheme 1. Aerobic oxidation of underivatized α-D-methylglucopyranoside (**5**) into α-D-methylglucopyranosyl-6-carbaldehyde (**6**) with a binuclear copper(II) catalyst derived from Cu_2(bpdpo) (**1**) and TEMPO (**2**), and successive reaction of **6** with excess formaldehyde yielding 5-*C*-hydroxymethyl-α-D-methylglucopyranoside (**7**).

Efforts by other researchers to apply the good selectivity of TEMPO-mediated oxidations without any copper(II) salt towards carbohydrates resulted in over-oxidation to the corresponding uronate carboxylic acids.[26–30] Optimization of the system by stopping the reaction at the aldehyde level allowed the preparation of the carbohydrate 6-aldehydes in 63% yield.[31] However, a reaction time of 110 h, a minor amount of over-oxidation to undesirable uronate carboxylic acids, the use of DMF as solvent, and a tedious experimental work-up had to be accepted in return.[31] Similar to our previous results though, a maximum aldehyde concentration of about 10% was observed in aqueous carbonate-buffered solution.[31,28]

With the goal to improve the yield for the oxidation of glycosides at the primary hydroxyl group, we hypothesized that the electron-donating and the electron-accepting properties of the ligand backbone determine the oxidation ability of the corresponding complexes. Along these lines, the catalytic performance of **1** was characterized in more detail with selected benzyl and allyl alcohols, and subsequently compared with the performance of an unsymmetric analog *N*,*N*′-{bis(2-pyridylmethyl)-1,4-diaminobutan-2-ol}ato dicopper(II) (μ-acetato) diperchlorate, Cu_2(bpdbo) (**8**), and a symmetric salicylaldehyde-based complex *N*,*N*′-{1,3-bis[{2-hydroxy-4-[2-(2-methoxyethoxy)-ethoxy]-ethoxy}benzylidene-amino]-propan-2-ol}ato dicopper(II) (μ-acetato), Cu_2(TEGbsdpo) (**9**), (Fig. 1).[14,32] We furthermore optimized the conditions for the carbohydrate oxidation and quantified the reaction yields in dependence of the reaction temperature and the catalyst amount. The recent results and insights are summarized below.

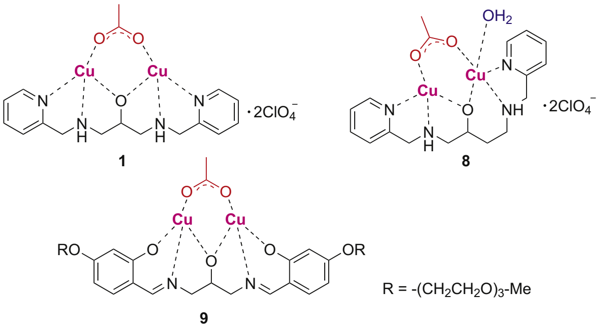


Figure 1. Structures of binuclear copper(II) complexes **1**, **8**, and **9**.

2. Oxidation of benzylic and allylic alcohols by a Cu₂bpdpo–TEMPO catalyst

Prior to modifying the structure of the binuclear catalyst **1**, its substrate scope suitable for aerobic oxidation in alkaline solution at ambient temperature was characterized in some more detail. Towards this end, the oxidation of selected *o*-, *m*-, and *p*-substituted benzyl alcohols with electron-withdrawing fluoro (**10**) and electron-donating methoxy substituents (**11**) were explored. Subsequently, the oxidation ability of the **1**–TEMPO catalyst towards allylic alcohols including *cis*-2-hexenol (**12a**), *trans*-2-hexenol (**12b**), geraniol (**12c**), cinnamyl alcohol (**12d**), and *trans*-3-hexenol (**13**) was characterized (Fig. 2).

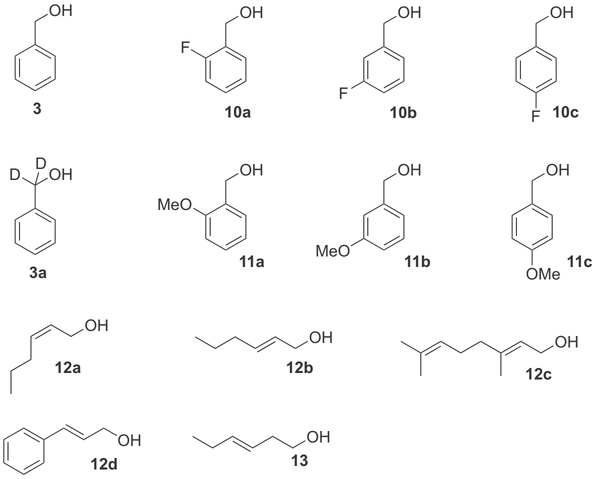


Figure 2. Selected benzyl and allyl alcohol substrates.

The oxidation of all substrates **3**, **10**–**12** follows classical saturation kinetics; the product formation was followed and quantified by gas chromatography. The product identity was established by comparison of the retention times with commercial samples. The data obtained were fitted using non-linear regression to determine the turnover rate (k_{cat}) and the substrate affinity (K_M) with the Michaelis–Menten model (Table 1). The initial rate of the oxidation of all substrates depends linearly on the catalyst concentration. The use of water-soluble 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl, 4-OH-TEMPO (**2a**), instead of **2** was intended to provide a water-soluble catalytic system that might improve the oxidation of biomolecules in aqueous solution; however, the observed catalytic oxidation of **3** by a **1**–**2a** catalyst (Table 1, entry 2) was 3-fold slower than with the **1**–**2** catalyst (Table 1, entry 1). Other catalytic

Table 1
Catalytic oxidation of benzylic and allylic alcohols

Entry	Catalyst	Substrate	k_{cat} [min^{-1}][a]	K_M [M][a]
1[b]	**1–2**	**3**	0.64±0.06	0.340±0.054
2	**1–2a**	**3**	0.18±0.04	0.594±0.182
3	**1–2**	**3a**	0.02±0.01	0.385±0.103
4	**1–2**	**10a**	0.04±0.01	0.031±0.001
5	**1–2**	**10b**	0.48±0.17	0.895±0.404
6	**1–2**	**10c**	0.21±0.04	0.581±0.190
7	**1–2**	**11a**	0.42±0.06	0.442±0.108
8	**1–2**	**11b**	0.48±0.18	0.953±0.469
9	**1–2**	**11c**	0.41±0.10	0.780±0.284
10	**1–2**	**12a**	0.02±0.01	0.158±0.016
11	**1–2**	**12b**	0.05±0.01	0.364±0.128
12	**1–2**	**12c**	0.25±0.09	0.569±0.279
13	**1–2**	**12d**	0.02±0.01	0.357±0.051
14	**1–2**	**13**	n.d.[c]	n.d.[c]

[a] Each experiment was conducted in triplicate or more under aerobic oxidation conditions at ambient temperature.

[b] Values were taken from Ref. 12.

[c] n.d.=not determined; oxidation not observed.

systems derived from **2a** were therefore not explored. A mononuclear complex derived from *N*,*N*′-1,3-bis[(pyridin-2-ylmethyl) amino]propan-2-ol, bpdpo (**14**), and equimolar amounts of Cu(II) ions is not catalytically active.[12] The use of deuterated benzyl alcohol **3a** instead of **3** showed a very large primary isotope effect (k_H/k_D) of 33 (Table 1, entry 3), suggesting the abstraction of one benzylic hydrogen atom as the rate-determining step as previously proposed.[12]

All substrates with fluoro substituents **10a**–**c** are oxidized slower than **3**, which is in agreement with the general pattern expected for oxidation of benzylic alcohols derivatized with electron-withdrawing substituents.[30] The oxidation of fluorinated benzyl alcohols is slowest for the fluoro substituent in *o*-position. The effect is not as pronounced, when the electron-withdrawing group is in *p*-position and smallest when in *m*-position (Table 1, entries 4–6). A similar trend is observed for benzyl alcohols **11a**–**c** substituted with an electron-donating methoxy-group (Table 1, entries 7–9). While the turnover rate remains on average higher for **11a**–**c** than for **10a**–**c**, it is overall slower than for the oxidation of **3**. This finding suggests contributions of steric effects in addition to electronic effects of the substituents to the overall rate of the oxidation. Over-oxidation of the substituted benzylic alcohols to the corresponding acids was not observed in contrast to reports about other catalysts based on copper(II) complexes and TEMPO.[30]

The oxidation of the allylic alcohols **12a**–**d** is more than one order of magnitude, i.e., about 30-fold, slower than the oxidation of **3** (Table 1, entries 10–13) The **1**–**2** catalyst oxidizes an allylic alcohol with a trans-substituted double bond twice as fast as corresponding analogs with a cis-double bond. However, the turnover rate for the allylic alcohols **12a**–**d** is not faster than 3 h^{-1}. The substitution of the E-double bond with an electron-donating methyl group, as given in geraniol (**12c**) (Table 1, entry 12), accelerates the oxidation about one order of magnitude compared to the rate determined for all other allylic alcohol substrates studied. The oxidation of geraniol (**12c**) is only about 3-fold slower than the oxidation of **3** and comparable in its turnover rate to the oxidation of **10c**. The oxidation of *trans*-3-hexenol (**13**) was unsuccessful; corresponding oxidation products were not detected. While the aerobic oxidation of selected benzylic and allylic alcohols is feasible with the **1**–**2** catalyst in alkaline, aqueous acetonitrile solution, alterations of the ligand backbone structure might allow the transformation of less activated primary alcohols in sufficient quantities and turnover rates. Subsequent experiments and results along these lines are summarized below.

3. Alternation of the ligand backbone and of the metal ion in the catalytic system

The backbone ligands of **1**, *N*,*N*′-1,3-bis[(pyridin-2-ylmethyl) amino]propan-2-ol, bpdpo (**14**) and of **8**, *N*,*N*′-bis(2-pyridylmethyl)-1,4-diaminobutan-2-ol, bpdbo (**15**), differ only in one methylene group causing a slight distortion of **8** in comparison to **1** (Fig. 1); in turn, this distortion causes a small decrease of the intermetallic Cu⋯Cu distance from **1** to **8** by about 0.1 Å.[33] A detailed discussion on the structural comparison of both complexes was recently disclosed.[33] However, the H-bond donating functionality at both N-atoms in **14** and **15**, and their overall electron-donating ability in the corresponding binuclear copper (II) complexes **1** and **8** remains similar. The performance of a complex **9** derived from backbone ligand *N*,*N*′-1,3-bis[{2-hydroxy-4-[2-(2-methoxyethoxy)-ethoxy]-ethoxy}benzylideneamino]-propan-2-ol, TEG(bsdpo) (**16**), is therefore contrasted to the oxidation ability of **1** and **8**. Ligand **16** has a H-bond accepting function at the N-atoms, causing electron-withdrawing properties of the backbone ligand on the metal ions in **9**. The intermetallic distances between **1** and **9** are comparable.[33]

The catalytic oxidation of **3** was initially studied using catalytic systems derived from the binuclear copper(II) complexes **1**, **8**, and **9** and TEMPO (**2**) under the conditions described above. Subsequently, the study was extended to derive catalytic systems from the ligands **14** and **15**, and Pd(II) and Pt(II) ions. Over-oxidation of **3** to benzoic acid (**17**) was not detected at any time; corresponding carbonyl carbon atoms in the ^{13}C NMR spectra at ∼170 ppm, as typically observed in carboxylic acids, are absent; instead, a signal for the aldehyde carbonyl carbon at 194 ppm is observed for the formation of benzaldehyde (**4**).

The kinetic parameters for the oxidation of **3** with the **8**–**2** and the **1**–**2** catalyst are similar (Table 1, entry 1 for the oxidation of **3** with **1**–**2**; $k_{cat(\mathbf{8}-\mathbf{2})}=0.59\pm0.02\ \text{min}^{-1}$; $K_{M(\mathbf{8}-\mathbf{2})}=0.427\pm0.042$ M). Thus, the distortion of complex **8** and the accompanying shortening of the intramolecular Cu⋯Cu distance in comparison to **2** has only a minor effect on the ability of **8** to oxidize **3** in the presence of TEMPO.

At ambient temperature, the yield of **4** is less than 30%, when oxidizing **3** with the **1**–**2** catalyst (Table 2). The use of binuclear copper(II) complex **1** is nevertheless favorable over the use of complexes derived from the same backbone ligand and Pd(II) or Pt (II) ions. In-situ formed binuclear Pd(II) and Pt(II) catalysts did not promote any significant oxidation of **3** under comparable conditions. Surprisingly, the use of the symmetric ligand **14** as backbone ligand for the binuclear metal complexes provides slightly higher reaction yields than the use of unsymmetric **15**. All oxidation reactions of **3** with catalysts derived from backbone ligand **16** and Cu (II), Pd(II) or Pt(II) ions yielded **4** in less than 1%. Ligand **16** was therefore not considered any further.

Table 2
Aerobic oxidation of **3** into **4** with catalytic systems derived from backbone ligand **14** and **15**, the metal ions Cu(II), Pd(II) and Pt(II), and TEMPO (**2**) at ambient temperature[a]

Entry	L	M_A	M_B	Molar ratio $L:M_A:M_B$	Yield [%][b]
1[c]	**14**	Cu	—	1:2	29.0
2	**14**	Cu	—	1:1	—[d]
2	**14**	Pd	—	1:2	1.5
3	**14**	Pt	—	1:2	—[d]
4	**14**	Cu	Pd	1:1:1	23.1
5	**14**	Cu	Pt	1:1:1	10.3
6	**14**	Pd	Pt	1:1:1	—[d]
7	**15**	Cu	—	1:2	17.5
8	**15**	Pd	—	1:2	—[d]
9	**15**	Pt	—	1:2	—[d]
10	**15**	Cu	Pd	1:1:1	17.0
11	**15**	Cu	Pt	1:1:1	8.8
12	**15**	Pd	Pt	1:1:1	—[d]

[a] Each experiment was conducted in triplicate or more.
[b] Determined by gas chromatography after a reaction time of 24 h.
[c] Values taken from Ref. 12.
[d] Not detectable or less than 1%.

Subsequently, the reaction temperature was raised in an attempt to improve the reaction yields for aerobic oxidations with the **1**–**2** catalyst in alkaline, aqueous acetonitrile. The transformation of **3** into **4** was consequently conducted at 30, 40, 50, 60, and 70 °C, and the product formation quantified by using GC analysis. At 70 °C, the catalytic system changes its color from dark green to brown even before substrate addition indicating catalyst decomposition. Consequently, reactions at 70 °C were not considered further. Increasing the catalyst amount from 1.5 mol % (4.57 mmol) to 5 mol % (15.2 mmol) allows quantitative formation of **4** from **3** within 2.5 h at 40–60 °C (see Supplementary data). This result is comparable to the performance of other copper(II) catalysts for aerobic oxidations of primary alcohols.[20,19]

4. Oxidation of methyl-β-D-glucopyranoside

Subsequently, the oxidation of methyl-β-D-glucopyranoside (**18**) into methyl-β-D-glucopyranoside-6-carbaldehyde (**19**) was explored at 30, 40, 50, and 60 °C with the **1**–**2** catalyst in alkaline acetonitrile over a 24 h time period. The catalyst was then decomposed by precipitating the copper(II) ions as sulfides. The supernatant remaining after centrifugation was treated with excess of aqueous formaldehyde to capture the primary oxidation product **19** as 5-*C*-hydroxymethyl derivative **20** as described for the oxidation of **6** (see above, Scheme 1). The oxidation of **18** was performed under comparable conditions with catalyst concentrations of 1.5 and 5 mol %.

Evidence for the oxidation of **18** into **19** was obtained by observing the sodium adduct of 5-*C*-hydroxymethyl-methyl-β-D-glucopyranoside (**20**) using ESI mass spectrometry (Fig. 3). Side products, including over-oxidation of **19** to glucuronic acid, were not detected at any time. The reaction yield of **20** was determined by quantitative HPLC and remains constant at about 28% for the use of 1.5 mol % catalyst for the aerobic oxidations between 30 and 60 °C (Fig. 4a and b). A slight increase in the formation of **20** from 29 to 35% is observed, when 5 mol % of catalyst are used under otherwise identical reaction conditions. While the yield of the oxidation reaction follows general trends observed for increased reaction temperatures and catalyst amounts, the effect is not as pronounced in the current system.

In summary, we have explored and compared three structurally related binuclear Cu(II) complexes for their ability to oxidize primary allylic and benzylic alcohols. The catalytic system derived from the symmetric complex Cu_2(bpdpo) (**1**) and TEMPO (**2**) is superior during the oxidation of such substrates. The reaction is quantitative at 40 °C within 2.5 h for the oxidation of benzyl alcohol. Remarkably, the regioselective oxidation of an underivatized, non-activated carbohydrate **18** at its primary alcohol function is also accomplished. Most interesting in that regard is the fact that **18** is not a substrate to galactose oxidase, which is the only enzyme known today to promote the same reaction on underivatized sugars. Thus, a new promising biomimetic system with galactose-oxidase like ability has been developed that will be explored further in future studies. The current results nevertheless also provide a first promising step towards the synthesis of sugar-6-carbaldehydes as prerequisites for the syntheses of unnatural sugars in the fight against obesity. Optimization of the catalytic system to avoid the necessity of a fairly alkaline solution should allow to improve the reaction yields while avoiding side reactions of the primary oxidation product. This might be accomplished by re-designing the binuclear catalyst employing manganese ions and a pentadentate ligand with oxygen donor atoms. Corresponding work is topic of current investigations and will be reported in due course.

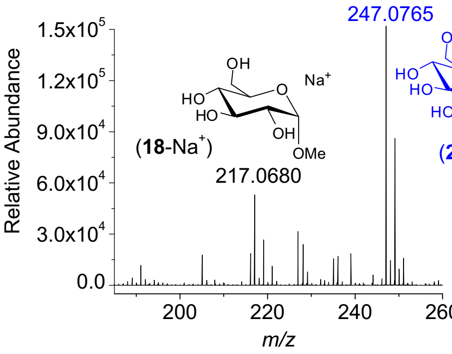


Figure 3. Evidence for the formation of **19** from **18** captured as sodium adduct of 5-*C*-hydroxymethyl-methyl-β-D-glucopyranoside (**20**) by ESI mass spectrometry; reaction at 30 °C, 1.5 mol % catalyst in aqueous alkaline acetonitrile.

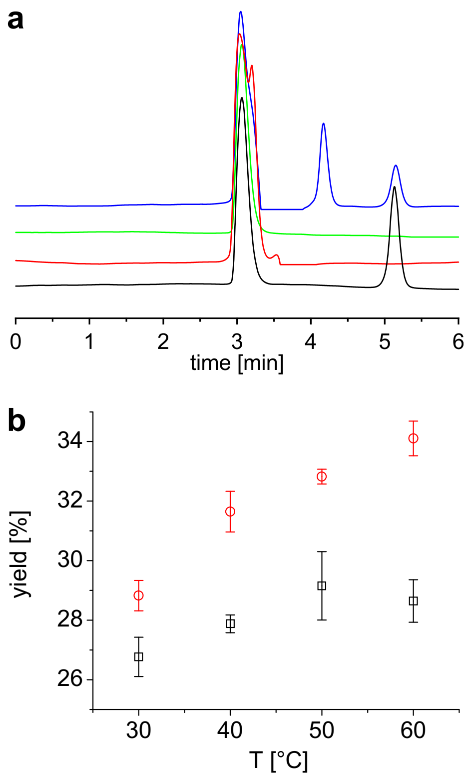


Figure 4. (a) Typical HPLC chromatogram (blue line) used for quantitative analysis of the oxidation of β-D-methylglucopyranoside (black line); the solvent (green line) and formaldehyde (red line) are given for comparison. (b) Yield of 5-*C*-hydroxymethyl-methyl-β-D-glucopyranoside (**20**) in dependence of the reaction temperature with 1.5 mol % catalyst (black square) and 5 mol % (red circle) catalyst in aqueous alkaline acetonitrile; the reactions were conducted in triplicate.

5. Experimental section

5.1. Typical procedure for oxidation of benzyl and allyl alcohols

The procedure was previously described.[12] In short: 50 mL round bottom flasks were charged with the dinuclear copper(II) complexes **1**, **8** or **9** (4.57 mmol) dissolved in 9 mL of alkaline aqueous acetonitrile each ($CH_3CN/H_2O=2/1$; NaOH 22 mM). Alternatively, the flasks were charged with the ligands **14**, **15** or **16** and appropriate amounts of Pt(II), Pd(II) and Cu(II) ions. The solutions turned from dark blue to yellow-green after vigorous stirring at ambient temperature for 45 min. Subsequently, 30 μL aliquots of a TEMPO stock solution in acetonitrile were added to adjust the total TEMPO concentration in the final reaction mixtures to 22 mM. The solutions were stirred for another 30 min to allow formation of catalytically active species. Darkening of the yellow-green solutions to dark green is observed. Varying amounts of substrate are then added to each flask, and the total volume of each solution is adjusted with the solvent mixture to a final volume of 10 mL. The final substrate concentrations typically range from 50 to 450 mM. Sample aliquots (200 μL) of the reaction mixtures were taken in 60 s intervals, diluted with 10 μL of a 1 M aqueous Na_2S solution and 100 μL acetonitrile, centrifuged to remove precipitated CuS and filtered. The supernatant was subjected to GC analysis.

5.2. General procedure for temperature- and catalyst amount-dependent oxidation reactions in microscale

The procedures followed the general description of the oxidation of benzyl and allyl alcohols given above in microscale. The reactions were allowed proceed in open vials with mechanical stirring at 30, 40, 50, 60 or 70±0.1 °C for 24 h. All reactions were performed in triplicate by varying the stock solution of complex **1**.

5.3. Typical procedure for reactions with 1.5 mol % catalyst

An alkaline, aqueous acetonitrile solution was prepared by diluting 5 mL of an aqueous sodium hydroxide solution (48.53 mg, 1.21 mmol) into a 50 mL measuring flask by addition of a solution of CH_3CN/H_2O (2:1, v/v). Complex **1** (19.88 mg, 0.03 mmol) was dissolved in 6 mL of alkaline, aqueous acetonitrile (see above) to prepare a 5.04 mM stock solution. Subsequently, 1 mL from this stock solution were transferred to 7 mL vials and stirred for 90 min. Then, 3 μL of a 8.09 M TEMPO (252.77 mg, 1.62 mmol in 200 μL of CH_3CN) solution in acetonitrile was added to each vessel, and stirring continued for another 45 min at ambient temperature.

5.4. Typical procedure for reactions with 5.0 mol % catalyst

An alkaline, aqueous acetonitrile solution was prepared by diluting 10 mL of an aqueous sodium hydroxide solution (323.53 mg, 8.09 mmol) into a 100 mL measuring flask by addition of a solution of CH_3CN/H_2O (2:1, v/v). Complex **1** (66.27 mg, 0.10 mmol) was dissolved in 6 mL of alkaline, aqueous acetonitrile (see above) to prepare a 16.80 mM stock solution. Subsequently, 1 mL from this stock solution were transferred to 7 mL vials and stirred for 90 min. Then, 3 μL of a 26.96 M TEMPO (842.57 mg, 5.39 mmol in 200 μL of CH_3CN) solution in acetonitrile was added to each vessel, and stirring continued for another 45 min at ambient temperature.

5.4.1. Benzyl alcohol as the substrate. After formation of the catalytically active species via addition of TEMPO, 100 μL of 3.31 M benzyl alcohol (1.25 g, 11.58 mmol in 3.50 mL of 67% aqueous acetonitrile) solution was added, and the reaction was allowed to proceed at its corresponding reaction temperature. Sample aliquots (100 μL) were collected from each reaction mixture at 45 min intervals for a total reaction time of 3.75 h. To facilitate the subsequent analysis, 200 μL of 67% aqueous acetonitrile solvent was added to the reaction vessel prior to sample collection. The catalyst was then decomposed by addition of 200 μL (300 μL) of 0.02 M (0.06 M) aqueous sodium sulfide solution for a catalyst concentration of 1.5 mol % (5.0 mol %). The supernatant for each sample aliquot was separated by centrifugation and subjected to GC analysis.

5.4.2. Methyl-β-D-glucopyranoside as the substrate. After formation of the catalytically active species via addition of TEMPO, 100 μL of 3.31 M aqueous methyl-β-D-glucopyranoside solution was added, and the reaction was allowed to proceed at its corresponding reaction temperature for 24 h. To facilitate the subsequent analysis, 300 μL of 67% aqueous acetonitrile solvent was added to the reaction vials. The catalyst was then decomposed by addition of 200 μL (300 μL) of 0.09 M (0.26 M) aqueous sodium sulfide solution for a catalyst concentration of 1.5 mol % (5.0 mol %). The supernatant of each sample was separated by centrifugation. Lastly, an equal amount of 37% aqueous formaldehyde solution was added to the centrifuged supernatant, and the resulting solution subjected to analysis by ESI mass spectroscopy in positive ion mode, quantitative HPLC on an amino column, and ^1H and ^{13} C NMR spectroscopy.

GC analysis. The GC experiments were conducted as described previously.[12] In short, all oxidation experiments with allyl and benzyl alcohols were monitored on a A14 gas chromatograph (Shimadzu) with AOC-20 autoinjector and flame ionization detector. Helium was used as a carrier gas, a Rtx-1 capillary column (30 m×0.25 mm×0.25 μm) was employed as the stationary phase. Sample aliquots were treated prior to analysis as described above. The analysis was performed isocratic at 100, 125 or 150 °C, 0.25 μL injection (1/100 split) at 200 °C and flame ionization detection at 220 °C. The compound identity of the aldehydes was confirmed by comparison to commercially available samples.

5.4.3. ESI mass spectrometry experiments. Electrospray Ionization (ESI) Mass spectrometric experiments were performed on a Q-ToF Premier (Waters) in positive ion mode by injecting a 5 μL sample aliquot of the reaction mixtures after work-up (see above) directly into the ion source and scanning the masses between 100 and 500 *m*/*z*.

5.4.4. HPLC analysis. The HPLC analysis of the sample aliquots for the carbohydrate oxidation was conducted with a Shimadzu HPLC system employing an amino phase (Phenomenex® Luna 5 μ, NH_2, 250×4.60 mm, 100 Å) and 70% acetonitrile isocratic at 1 mL/min as eluent at ambient temperature; 5 μL injection. The analysis was followed by refractive index detection at ambient temperature. The retention of the α/β-methyl 5-*C*-hydroxymethyl-D-glycopyranosides allows baseline separation from the corresponding α/β-methyl-D-glycopyranosides under these conditions (e.g., R_f (**19**)= 4.1 min; R_f (**18**)=4.9 min).

5.4.5. NMR experiments. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV400 (400.2 MHz for ^1H, and 100.6 MHz for ^{13}C). Chemical shifts (δ) in ^1H NMR are expressed in ppm and coupling constants (*J*) in hertz. Signal multiplicities are denoted as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Deuterated DMSO was used as solvent, and chemical shift values are reported relative to the residual signals of this solvent (DMSO-d_6: δ=2.59 for ^1H and δ=39.5 for ^{13}C).

*5.4.6. 5-C-Hydroxymethyl-methyl-β-D-glucopyranoside (**20**).* The synthesis of the title compound was carried out using methyl-β-D-glucopyranoside as the substrate and the **1**–**2** catalyst as described above. After precipitation of the copper(II) ions as copper(II) sulfide, all volatile compounds were evaporated to obtain a colorless residue. The residue was dried in vacuum for 4 h and subsequently extracted with DMSO. After filtration, the title compound was obtained as colorless oil (22 mg, 34%) δ_H 4.73 (d, 1H, 6.88, H-1), 4.11 (d, 1H, 7.77, H-4), 3.37 (s, 2H, $-CH_2-$), 3.34 (s, 2H, $-CH_2-$), 3.30 (s, 3H, $-CH_3$), 3.12 (1H, t, 8.86, H-2), 3.02 (1H, t, 8.08, H-3); δ_C 103.8 (C-1), 73.3 (C-5), 72.3 (C-2), 72.2 (C-3), 70.2 (C-4), 66.6 (C-6), 61.0 (C-7), 55.9 (Me); HRMS, ESI-TOF$^+$, calcd for $C_8H_{16}NaO_7$ $(M+Na)^+$: 247.0794; found: 247.0765.

Acknowledgements

A CAREER award from the National Science Foundation (CHE-0746635) and a supplemental award (CHE-0938791) to S.S. for partial support of this work are gratefully acknowledged; the help of Ms Hae-In Kim during early stages of the project is highly appreciated.

Supplementary data

Representative GC, HPLC, and mass spectrometric traces and chromatograms observed during substrate oxidation. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.07.077. This data include MOL files and InChiKeys of the most important compound described in this article.

References and notes

1. Kim, J.-H.; Yang, H.; Boons, G.-J. *Angew. Chem.* **2005**, *117*, 969–971.
2. Mazur, A. W.; Hiler, G. D. *J. Org. Chem.* **1997**, *62*, 4471–4475.
3. Kren, V.; Thiem, J. *Chem. Soc. Rev.* **1997**, *26*, 463–473.
4. Oshima, K.; Aoyama, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2315–2316.
5. Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051–1071.
6. Bragd, P. L.; van Bekkum, H.; Besemer, A. C. *Top. Catal.* **2004**, *27*, 49–66.

7. Trombotto, S.; Violet-Courtens, E.; Cottier, L.; Queneau, Y. *Top. Catal.* **2004**, *27*, 31–37.
8. Annunziatini, C.; Gerini, M. F.; Lanzalunga, O.; Lucarini, M. *J. Org. Chem.* **2004**, *69*, 3431–3438.
9. Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420.
10. Besson, M.; Gallezot, P. *Catal. Today* **2000**, *57*, 127–141.
11. Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343–3352.
12. Striegler, S. *Tetrahedron* **2006**, *62*, 9109–9114.
13. Striegler, S.; Dittel, M. *J. Am. Chem. Soc.* **2003**, *125*, 11518–11524.
14. Striegler, S.; Gichinga, M. G. *Chem. Commun.* **2008**, 5930–5932.
15. Ahmad, J. U.; Figiel, P. J.; Raeisaenen, M. T.; Leskelae, M.; Repo, T. *Appl. Catal., A* **2009**, *371*, 17–21.
16. Arends, I. W. C. E.; Li, Y.-X.; Sheldon, R. A. *Biocatal. Biotransform.* **2006**, *24*, 443–448.
17. Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Org. Biomol. Chem.* **2003**, *1*, 3232–3237.
18. Figiel, P. J.; Sibaouih, A.; Ahmad, J. U.; Nieger, M.; Raeisaenen, M. T.; Leskelae, M.; Repo, T. *Adv. Synth. Catal.* **2009**, *351*, 2625–2632.
19. Gamez, P.; Arends, I. W. C. E.; Reedijk, J.; Sheldon, R. A. *Chem. Commun.* **2003**, 2414–2415.
20. Gamez, P.; Arends, I. W. C. E.; Sheldon, R. A.; Reedijk, J. *Adv. Synth. Catal.* **2004**, *346*, 805–811.
21. Jiang, N.; Ragauskas, A. J. *Org. Lett.* **2005**, *7*, 3689–3692.
22. Jiang, N.; Ragauskas, A. J. *J. Org. Chem.* **2006**, *71*, 7087–7090.
23. Jiang, N.; Ragauskas, A. J. *ChemSusChem* **2008**, *1*, 823–825.
24. Yang, G.; Zhu, W.; Zhang, P.; Xue, H.; Wang, W.; Tian, J.; Song, M. *Adv. Synth. Catal.* **2008**, *350*, 542–546.
25. Gichinga, M. G.; Striegler, S. *Chem. Ind. (Boca Raton, FL, U.S.)* **2009**, *123*, 473–477.
26. Van den Bos, L. J.; Litjens, R. E. J. N.; Van den Berg, R. J. B. H. N.; Overkleeft, H. S.; Van der Marel, G. A. *Org. Lett.* **2005**, *7*, 2007–2010.
27. Schamann, M.; Schafer, H. J. *Eur. J. Org. Chem.* **2003**, 351–358.
28. de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Tetrahedron* **1995**, *51*, 8023–8032.
29. Kraus, T.; Budesinsky, M.; Zavada, J. *Eur. J. Org. Chem.* **2000**, 3133–3137.
30. Geisslmeir, D.; Jary, W. G.; Falk, H. *Monatsh. Chem.* **2005**, *136*, 1591–1599.
31. Breton, T.; Bashiardes, G.; Leger, J.-M.; Kokoh, K. B. *Eur. J. Org. Chem.* **2007**, 1567–1570.
32. Striegler, S.; Gichinga, M. G.; Dittel, M. *Org. Lett.* **2008**, *10*, 241–244.
33. Striegler, S.; Dunaway, N. A.; Gichinga, M. G.; Barnett, J. D.; Nelson, A.-G. D. *Inorg. Chem.* **2010**, *49*, 2639–2648.