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Mild, green copper/4-dimethylaminopyridine catalysed aerobic oxidation of alcohols mediated by nitroxyl radicals in water†

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A novel copper/4-dimethylaminopyridine catalyst system has been found to catalyse the aerobic oxidation of a variety of primary and secondary alcohols in water at room temperature, in the presence of a TEMPO or ABNO nitroxyl radical. A tetranuclear Cu^{II} cluster was revealed to be a plausible reactive intermediate.

The selective oxidation of alcohols to aldehydes or ketones is a key reaction that has been widely utilized in modern synthetic chemistry and industry.[1–3] Recent years have witnessed major progress in the development of atom-economic oxidation methods including the catalytic aerobic oxidation,[4] of which the methodologies featuring both low-cost and environmentally friendly procedures are most attractive.[5] Although precious metal catalyst systems involving Pd, Ru or Ir were the popular choices for this transformation,[5a,6] recent efforts have disclosed the replacement of these precious metal catalysts with earth-abundant metals, mainly vanadium- and copper-containing catalysts, without reducing the catalytic efficiency and selectivity.[7] As a result, non-precious metal catalysed alcohol oxidation is becoming a focusing research topic for chemists.[8] On the other hand, from a viewpoint of 'green' chemistry and technologies, there will be obvious advantages if the reaction is performed in water instead of organic solvents. For instance, the oxidations in water would be much cheaper and safer than those in organic solvents, and products can be isolated by simple extractions or decantations, and thus catalysts could be recovered and reused.[7f,9] However, the majority of existing catalytic aerobic oxidation processes require the use of environmentally undesirable solvents, such as toluene and chlorinated hydrocarbons. The catalytic aerobic oxidation in water is rarely reported to date. For example, a water-soluble palladium(II) complex was found to catalyse the oxidation of primary and secondary alcohols in water by the Sheldon group in 2000.[5a] However, high temperature (100 °C) and air pressure (30 bar) were needed to carry out the conversion, except for the use of a precious metal palladium source.

Copper-catalysed, (2,2,6,6-tetramethylpiperidinyl-1-oxyl) TEMPO-mediated aerobic oxidation has been a current focus for alcohol oxidations since the introduction of the first CuCl/TEMPO/DMF system (DMF = *N*,*N*-dimethylformamide) by Semmelhack and coworkers in 1984.[10] Recent advancement highlights the use of Cu^{I} or Cu^{II} complexes with bidentate *N*,*N*′-ligands, typically, 2,2′-bipyridine (bpy) in combination with TEMPO for efficient aerobic oxidation of various primary alcohols, mainly involving the contributions from the Sheldon,[11] Koskinen[12] and Stahl groups.[8a–c,13] All the reported catalyst systems feature the combined use of bpy as a ligand and an additional base such as KO^tBu, DBU (1,8-diazabicycloundec-7-ene) or NMI (*N*-methylimidazole), and the solvent CH_3CN was used in all cases. More recently, a Cu^{I}/L-proline system was reported to convert both primary and secondary alcohols under mild conditions in the presence of additional bases in a DMF solution.[14] Although copper-based catalyst systems displayed great potential as an alternate to precious metal catalysts in aerobic alcohol oxidation,[15] they were rarely utilized for this reaction in pure water.

In this communication, we report that in combination with a nitroxyl radical a simple, inexpensive copper/4-dimethylaminopyridine (DMAP) system catalyses efficiently aerobic oxidations of a range of primary and secondary alcohols in water under mild conditions without the addition of an extra base. This protocol differs from the reported methodologies and extends our capability of advancing green synthetic chemistry.

Initially, the aerobic oxidation of benzylic alcohol was tested using cuprous chloride (5 mol%) and DMAP (10 mol%) in the

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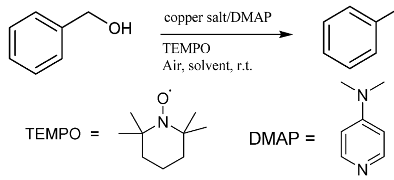
presence of TEMPO (5 mol%) in CH_3CN at room temperature, we were pleased to find that 77% of benzaldehyde was detected after 20 hours by GC-MS analysis (entry 1, Table 1). Increasing the catalyst loading (10 mol% CuCl and 15 mol% DMAP) led to a higher conversion of the substrate (94% conv., entry 2, Table 1). It is worth noting that no extra bases were used in the present reaction, remarkably distinct with previously reported copper catalyst systems,[8,13,14] where a strong base was often required. CuBr and CuI (10 mol% for each) were found to convert the substrate in CH_3CN in almost quantitative yields (entries 3 and 4, Table 1). Solvent effects were then screened by using 10 mol% CuCl and 15 mol% DMAP (entries 5–9, Table 1). MeOH was found to be a better solvent than CH_3CN, while reactions in EtOH and iPrOH were more sluggish. Reactions in other solvents did not proceed smoothly. Surprisingly, when the reaction was tested in pure water, a quantitative conversion of the substrate to benzaldehyde was observed in 20 h and even in the presence of a lower catalyst loading (5 mol% CuCl and 10 mol% DMAP) (entries 10 and 11, Table 1). The 1 : 2 metal–ligand ratio appears necessary as the yield drops drastically when 5 mol% CuCl and 5 mol% DMAP were added (entry 12, Table 1). Pyridine also acted as a ligand for CuCl catalysed oxidation in water, but a lower conversion (79%) was detected (entry 13, Table 1). Next, several Cu^{II} salts were examined under the same conditions. It was found that high conversion was exclusively found in the presence of $CuCl_2$, $Cu(OAc)_2$, $Cu(NO_3)_2$ or $CuSO_4$ (5 mol% Cu^{II} and 10 mol% DMAP) (entries 14–17, Table 1). However, reactivity difference between the copper salts used was disclosed when the reaction time was shortened (Table S1†). Both CuCl and CuI efficiently catalysed the reactions in a period of 5 h with >99% conversion of the substrate, indicating that Cu^{I} salts were slightly more active than the Cu^{II} ones. To this end, controlled experiments revealed that no conversion was found in the absence of either copper salt or TEMPO, and only 9% conversion was detected while using CuCl/TEMPO without the addition of DMAP.

We next applied the optimized reaction conditions to other benzylic alcohols and evaluated the substrate scope of this methodology. As shown in Table 2, a variety of benzylic alcohols were oxidized successfully to the corresponding aldehydes. Primary alcohols bearing either electron-donating or electron-withdrawing groups such as methyl or methoxy at the benzene ring (entries 2–11, Table 2) proved to be good substrates for the aerobic oxidations, while elevated temperature was required for a complete conversion of

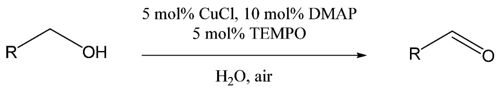
Table 1 The condition optimization for copper-catalysed, TEMPO-mediated aerobic oxidation of benzylic alcohol[a]



Entry	Copper	Ligand	Solvent	Conv.[b] (%)
1[c]	CuCl	DMAP	CH_3CN	77
2	CuCl	DMAP	CH_3CN	94
3	CuBr	DMAP	CH_3CN	>99
4	CuI	DMAP	CH_3CN	>99
5	CuCl	DMAP	CH_3OH	>99
6	CuCl	DMAP	EtOH	87
7	CuCl	DMAP	iPrOH	35
8	CuCl	DMAP	THF	59
9	CuCl	DMAP	$CHCl_3$	74
10	CuCl	DMAP	H_2O	>99
11[c]	CuCl	DMAP	H_2O	>99
12[d]	CuCl	DMAP	H_2O	57
13	CuCl	Pyridine	H_2O	79
14[c]	$CuCl_2$	DMAP	H_2O	>99
15[c]	$Cu(OAc)_2$	DMAP	H_2O	>99
16[c]	$Cu(NO_3)_2$	DMAP	H_2O	>99
17[c]	$CuSO_4$	DMAP	H_2O	98
18	No	DMAP	H_2O	0
19	CuCl	No	H_2O	9
20[e]	CuCl	DMAP	H_2O	0
21[f]	**1**	DMAP	H_2O	97
22[f]	**1**	No	H_2O	19

[a] Condition: 1.0 mmol of the substrate, 0.10 mmol (10 mol%) of copper salts and 0.15 mmol (15 mol%) of DMAP, and 0.050 mmol (5 mol%) of TEMPO in 5 mL of solvents, 1 atm. air, room temperature, 20 h. [b] Conversions based on GC-MS analysis, selectivity > 99% in all cases. [c] 5 mol% of copper salts and 10 mol% of DMAP were used. [d] 5 mol% of copper salts and 5 mol% of DMAP were used. [e] Reaction run without TEMPO. [f] 1 mol% of **1**, 5 mol% of DMAP and 5 mol% TEMPO, air, 20 h.

Table 2 CuCl/DMAP/TEMPO catalysed aerobic alcohol oxidations in water[a]



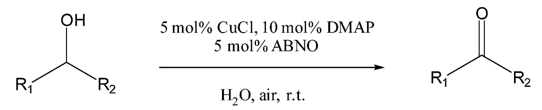
Entry	R	T (h)	Conv.[b] (%)	Yield[c] (%)
1	C_6H_5	5	>99	95
2	4-$CH_3C_6H_5$	5	97	92
3	4-$CH_3OC_6H_5$	10	>99	93
4	2-$CH_3C_6H_5$	10	82	78
5	2-$CH_3OC_6H_5$	5	>99	94
6[d]	3,4-$(CH_3O)_2C_6H_5$	10	>99	95
7	4-$NO_2C_6H_5$	10	95	90
8	4-ClC_6H_5	10	97	94
9	4-BrC_6H_5	5	>99	95
10	4-IC_6H_5	10	>99	93
11	2-ClC_6H_5	10	95	90
12[d]	4-(2-Furyl)C_6H_5	18	98	95
13[d]	2-Furyl	10	93	86
14[d]	2-Thienyl	10	98	92
15[d]	3-Pyridyl	18	80	72
16[d]	Cyclohexyl	18	0	—
17[d]	1-Phenylethanol	18	20	—

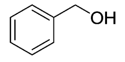
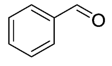
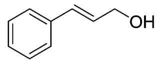
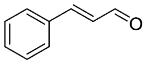
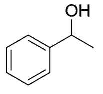
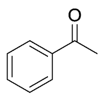
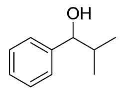
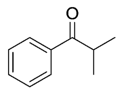
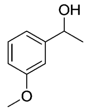
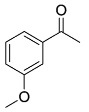
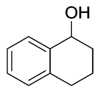
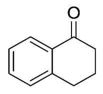
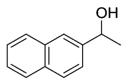
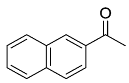
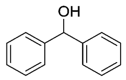
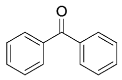
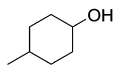
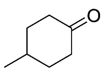
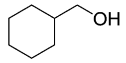
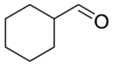
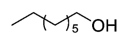
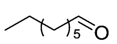
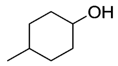
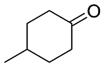
[a] Condition: substrate (1 mmol), CuCl (5 mol%), DMAP (10 mol%), TEMPO (5 mol%), in H_2O (5 mL) and in the air, room temperature. [b] Conversions based on GC-MS analysis. [c] Isolated yields. [d] Reaction run at 55 °C.

3,4-dimethoxybenzyl alcohol. The primary alcohols containing a heterocyclic ring such as 4-(2-thienyl)benzyl, 2-thienyl, 2-furyl and 3-pyridyl methanols were also converted to aldehydes in good to high yields with prolonged reaction time and at 55 °C (entries 12–15, Table 2). Unfortunately, primary aliphatic alcohols showed no reactivity under the optimized conditions, and only 20% conversion was detected for the reaction using a secondary aromatic alcohol (entries 16 and 17, Table 2).

In order to improve the results of this methodology and apply the green protocol to a broader range of substrates we sought to replace the TEMPO radical with other nitroxyl radicals having different electronic or steric properties. It was recently revealed by the Stahl group that ABNO (ABNO = 9-azabicylco[3.3.3]nonane *N*-oxyl), a less sterically encumbered radical than TEMPO promoted significantly the oxidations of secondary alcohols in combination with a Cu^I/bpy system.[16] Thus, when ABNO (5 mol%) combined with CuCl/DMAP was first applied to the oxidation of benzylic alcohol in water, complete conversion was obtained (entry 1, Table 3). This is identically effective for the oxidation of an allylic alcohol, cinnamyl alcohol (entry 2, Table 3). To our delight, when the secondary alcohol, 1-phenylethanol was tested for the oxidation under the same conditions, acetophenone was isolated in 96% yield, highlighting that CuCl/DMAP/ABNO is a more active catalytic system. Several other aromatic secondary alcohols including cyclic alcohols were also tested for the aerobic oxidation in water, and high yields of ketone were exclusively achieved (entries 4–8, Table 3). Aliphatic secondary alcohol such as 4-methylcyclohexanol was oxidized to the corresponding ketone but the conversion was low as 33%, and even lower at elevated temperature. Again, primary aliphatic alcohols are still less reactive substrates for this reaction (entries 9–12, Table 3). Nevertheless, the capability of the CuCl/DMAP/ABNO system in oxidizing secondary alcohols in water is remarkable, as only a few catalysts reported thus far were active for secondary alcohols and none of them was performed in water.[14,16] It is noteworthy that since the aerobic oxidations were performed in water, the resulting work-up procedure for purification of products was quite straightforward. Generally pure aldehydes and ketones have been obtained in high yields and good purity by a simple extraction procedure using organic solvents such as ethyl acetate or ether, followed by filtration over silica gel, avoiding the use of cumbersome column chromatography (see ESI†).

Table 3 CuCl/DMAP/ABNO catalysed aerobic oxidations of alcohols in water[a]



Entry	Substrate	Product	*T* (h)	Conv.[b] (%)	Yield[c] (%)
1			5	>99	96
2			5	>99	95
3			5	>99	96
4			5	98	94
5			5	>99	94
6			8	97	92
7			18	99	95
8			18	>99	96
9			24	33	—
10			24	10	—
11			24	13	—
12[d]			24	11	—

[a] Condition: substrate (1 mmol), CuCl (5 mol%), DMAP (10 mol%), ABNO (5 mol%), in H_2O (5 mL) and in the air, room temperature. [b] Conversions based on GC-MS analysis. [c] Isolated yields. [d] Reaction run at 55 °C.

Although the bidentate bpy ligand remains dominating in copper-catalysed aerobic oxidations, it was reported that the reactions could be suppressed by a high concentration of water.[13c] The fact that simple, monodentate DMAP can act as an effective ligand for base-free, in-water aerobic oxidation is, therefore, unusual. To gain insights into the reactive intermediates from Cu/DMAP catalysed oxidation, a $CuCl_2$/DMAP/TEMPO combination was reacted with benzylic alcohol (2.0 equiv.) in a CH_2Cl_2–MeOH solution, after filtration of a grey-green precipitate, the light-brown solution was left to evaporate upon exposure to the air for 48 h (see ESI†). Yellow-brown crystals of **1** were isolated and structurally determined by X-ray crystallography. Notably, a tetranuclear Cu^{II} cluster complex was revealed, featuring a novel $Cu_4(\mu\text{-}O)Cl_6$ core surrounded by four DMAP ligands at the apical position of each copper atom (Fig. 1). A central O^{2-} ion bonds to the four Cu^{II} centers in a tetrahedral geometry, balancing the charges of Cu^{II}. The tetracopper(II) structure unit is unexpected, as a mononuclear $Cu(DMAP)_4Cl_2$ complex would form without the presence of TEMPO during the reaction of $CuCl_2$ with DMAP as previously reported.[17] Although we were unable to obtain crystals of intermediates from a CuCl/DMAP/TEMPO reaction system, the

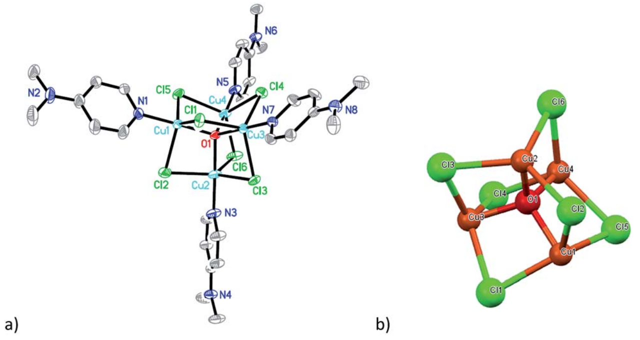


Fig. 1 The X-ray structure of tetranuclear complex **1** (a) and the $Cu_4(\mu\text{-}O)Cl_6$ core found in **1** (b).

observation of **1** has important implications in the possible active catalytic species, considering that $CuCl_2$ also served as a good metal source for the aerobic oxidation in water (entry 14, Table 1). **1** was also tested as a catalyst in the presence of added TEMPO. It was observed that when 1 mol% of **1**, 5 mol% of DMAP and 5 mol% TEMPO were employed for the oxidation of benzylic alcohol in water, 97% conversion was detected. However, if the reaction was run without additional DMAP, the conversion was only 19% (entries 21 and 22, Table 1). This indicates that **1** was likely to be an active intermediate during the catalysis, which is in good agreement with the fact that a 1 : 2 Cu/DMAP ratio was required to ensure a complete conversion (entry 12, Table 1). Therefore, we assume that during the reaction DMAP acts bifunctionally as both a monodentate ligand and a base to promote the reaction, similar to the best-performing Cu/bpy/base systems previously reported by the Sheldon, Koskinen and Stahl groups.[7,8,11–13] Although it is difficult to conclude that tetranuclear **1** was the real reactive intermediate during the catalytic process, it has been previously indicated that dimeric copper species could be active intermediates in Cu/bpy/TEMPO catalytic aerobic alcohol oxidations, on the basis of both kinetic and spectroscopic studies, in relevant work by both the Koskinen and Stahl groups.[12,13d] A recent report by Waymouth and coworkers also revealed that a trinuclear Pd_3O_2 cluster was an active intermediate for Pd^{II}-catalysed aerobic oxidation of alcohols.[18] In addition, our own work also suggested that tetranuclear copper cluster was a more active catalyst for the same reaction than a dinuclear analog.[19]

In conclusion, we have developed a Cu/DMAP/nitroxyl radical catalyst system that successfully converted in water a variety of primary and secondary alcohols into corresponding aldehydes and ketones with high yields and selectivities. A novel tetranuclear complex, $Cu_4(\mu\text{-}O)Cl_6(DMAP)_4$ was isolated from a closely related reaction and structurally determined by X-ray crystallography, and the catalytic results indicated it was likely to be the reactive intermediate during the catalytic oxidation. We are currently seeking to observe more efficient copper-based catalyst systems for aerobic alcohol oxidations with a broad substrate scope.

Acknowledgements

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