

Copper(II)-catalysed aerobic oxidation of primary alcohols to aldehydes

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[CuBr₂(2,2'-bipyridine)] catalyses the selective and very mild aerobic oxidation of primary alcohols to aldehydes in acetonitrile : water (2 : 1) in the presence of 2,2,6,6-tetramethylpiperidiny-1-oxy (TEMPO) and a base as cocatalysts.

The controlled oxidation of alcohols is one of the most important reactions in organic chemistry.¹ In particular, the conversion of primary alcohols to aldehydes is crucial for the synthesis of fine chemicals such as fragrances or food additives.² Generally, it either requires stoichiometric amounts of toxic heavy metal salts³ or expensive catalysts containing transition metals such as palladium, rhodium or ruthenium.⁴

Copper is an abundant metal on the earth's crust and is found in various metalloproteins, especially in enzymes implicated in the binding of molecular oxygen or in mild and highly selective aerobic oxidation transformations.⁵ Thus, it is surprising that only a few examples using cheap and "green" copper catalysts and molecular oxygen⁶ or hydrogen peroxide are known so far.^{7–11} Markó *et al.*⁷ first reported the efficient use of the CuCl(Phen-DEADH₂) (Phen = 1,10-phenanthroline; DEADH₂ = diethylhydrazinodicarboxylate) catalytic system for the oxidation of primary and secondary alcohols under dioxygen at 90 °C. Stack *et al.*⁸ described a Cu(II) species, namely [Cu(II)BSP] where BSP symbolises a salen-type ligand with a binaphthyl backbone and thioether functions, able to catalyse the oxidation of benzylic and allylic alcohols under dioxygen at room temperature. Wieghardt *et al.*⁹ similarly reported the catalytic oxidation of primary and secondary alcohols by a dinuclear Cu(II)-phenoxyl complex at 20 °C under air with moderate conversions. More recently, Knochel *et al.*¹⁰ followed by Gree *et al.*¹¹ developed CuCl-TEMPO catalytic systems for the oxidation of alcohols under dioxygen, at 90 °C under fluoruous biphasic conditions and at 65 °C in an ionic liquid, respectively.

The novel, mild oxidation procedure reported here is based on an uncomplicated CuBr₂(Bipy)-TEMPO (Bipy = 2,2'-bipyridine) catalyst which can be easily handled. Typically, 10 mmol of the alcohol were reacted with air in an acetonitrile/water (2 : 1) solvent mixture at room temp. The aerobic oxidation is catalysed by the presence of 5 mol% CuBr₂(Bipy) and 5 mol% TEMPO and base as co-catalysts (Fig. 1).[†] As shown in Table 1, only 6% of benzaldehyde was produced in 1.5 h when no Bipy was added (entry 1). This may be due to the poor solubility of the copper catalyst without ligand and the absence of beneficial electronic effects caused by the pyridine rings. No conversion of benzyl alcohol was observed without TEMPO present (entry 2). The role of TEMPO is unclear. It

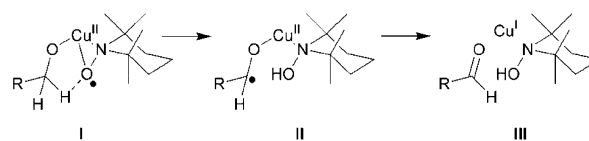
might act as a hydrogen acceptor during the catalytic cycle (Fig. 2).¹² TEMPO most likely coordinates to the Cu(II) ion in an η² manner (I).¹³ The β-hydrogen is then transferred to TEMPO resulting in a radical-TEMPOH copper species (II). Intramolecular one-electron transfer leads to the aldehyde, TEMPOH and Cu(I) species (III). The CuBr₂(Bipy)-TEMPO catalytic system is active without base but 24 h are necessary for the total conversion of benzyl alcohol when only 2.5 h are needed with 5 mol% *t*-BuOK (entries 3 and 4). At this point, it should be noted that NaOH or KOH could equally be employed as basic co-catalyst. The role of the base is probably to deprotonate the alcohol and, thus, favor the coordination of the resulting alcoholate to the copper species, increasing the activity.

As indicated in Table 2, various primary benzylic, allylic and aliphatic alcohols have been successfully oxidised. Benzyl alcohol is totally and selectively converted to benzaldehyde in 2.5 h (entry 1). This corresponds to a TOF of 14 h⁻¹ which is an excellent result for a room temperature oxidation reaction involving a copper catalyst. Surprisingly, no reaction is

Table 1 CuBr₂-catalysed oxidation of benzyl alcohol to benzaldehyde^a

| Entry | Bipy | TEMPO | <i>t</i> -BuOK | Conversion (%) | |
|-------|------|-------|----------------|----------------|-----------------|
| | | | | 0.5 h | 1.5 h |
| 1 | no | yes | yes | < 1 | 6 |
| 2 | yes | no | yes | No reaction | |
| 3 | yes | yes | no | 10 | 27 ^b |
| 4 | yes | yes | yes | 38 | 83 ^c |

^a Selectivity > 99% based on GC. ^b 100% Conversion after 24 h. ^c 100% Conversion after 2.5 h.

Fig. 2 Proposed role of TEMPO.¹²Table 2 CuBr₂(Bipy)-TEMPO-catalysed oxidation of alcohols to aldehydes under air

| Entry | Alcohol | Time/h | Conversion (%) ^a |
|-------|-----------------------------|--------|-----------------------------|
| 1 | Benzyl alcohol | 2.5 | 100 |
| 2 | 1-Phenylethanol | 5 | No reaction |
| 3 | Crotyl alcohol | 5 | 91 |
| 4 | Geraniol | 5 | 100 |
| 5 | Octan-1-ol | 24 | 61 |
| 6 | Octan-1-ol | 24 | 95 ^b |
| 7 | Octan-2-ol | 5 | No reaction |
| 8 | Benzyl alcohol + octan-2-ol | 1.5 | 67/0 ^c |

^a Selectivity always > 99% based on GC. ^b Reaction performed at 40 °C with 7.5 mol% TEMPO. ^c 67% Benzaldehyde and no octan-2-one detected.

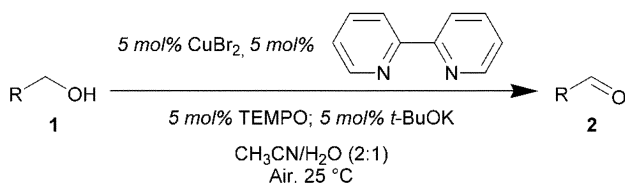


Fig. 1 Copper-catalysed aerobic oxidation of primary alcohols.

observed with 1-phenylethanol, an activated benzylic alcohol (entry 2). This may be explained by steric effects of the methyl group which hinder the formation of species **IV** (Fig. 3), crucial for the C–H abstraction from the alcohol by the coordinated TEMPO molecule. In addition, in the case of primary alcohols, the second β -hydrogen atom can be bonded to the oxygen atom of TEMPOH, stabilising the radical intermediate **VI** (Fig. 3). This is obviously not possible with secondary alcohols. These results are indeed confirmed when octan-1-ol and octan-2-ol are used (entries 5 and 7). Octan-1-ol was oxidised in 61% conversion and >99% selectivity after one day at room temp. (95% at 40 °C, entry 6) while no octan-2-one formation is observed with octan-2-ol. Allylic alcohols, crotyl alcohol and geraniol (entries 3 and 4) were converted to the corresponding aldehydes in excellent yields (91 and 100%, respectively) and selectivities as no by-products were detected by gas chromatography. These data (entries 1, 3, 4 and 5) clearly demonstrate that the oxidation of activated alcohols is faster than aliphatic ones, indicating that the hydrogen abstraction from the α -carbon atom by TEMPO (**I** to **II**, Fig. 2) is the rate-determining step of the reaction. Finally, a mixture of benzyl alcohol and octan-2-ol was reacted with air in the presence of the copper(II)–TEMPO–base catalyst (entry 8). The result shows the specificity of the catalytic system towards primary alcohols. Thus, 67% of the benzyl alcohol was converted whereas octan-2-ol remained unreacted. This may be of great interest in synthetic organic chemistry when several alcoholic functions (primary and secondary) are present in the same molecule.

Different copper(II) salts were tested as catalyst precursors for the oxidation of benzyl alcohol and the results are reported in Table 3. CuCl_2 and $\text{Cu}(\text{NO}_3)_2$ led to less active catalysts with only 60 and 66% conversion, respectively, after 1.5 h (entries 1 and 2). CuBr_2 afforded 83% conversion of benzyl alcohol in the same reaction time. $\text{Cu}(\text{ClO}_4)_2$ was the best catalyst precursor with 90% conversion reached after 1.5 h. These differences are likely related to the propensity for dissociation of the anion from

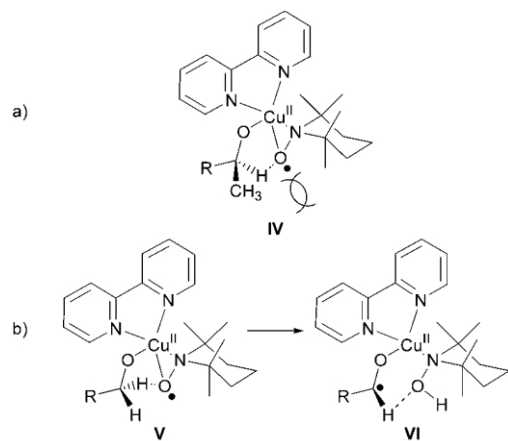


Fig. 3 Possible explanations for the lack of reactivity of secondary alcohols. a) Steric hindrance due to the methyl group of the secondary alcohol preventing the formation of species **IV**; b) stabilisation of the radical species **VI** by the second β -hydrogen of the primary alcohol.

Table 3 Influence of the copper salt on the oxidation of benzyl alcohol to benzaldehyde

| Entry | Copper salt | Conversion (%) | |
|-------|-----------------------------|----------------|-------|
| | | 0.5 h | 1.5 h |
| 1 | CuCl_2 | 30 | 60 |
| 2 | $\text{Cu}(\text{NO}_3)_2$ | 30 | 66 |
| 3 | CuBr_2 | 38 | 83 |
| 4 | $\text{Cu}(\text{ClO}_4)_2$ | 42 | 90 |

the catalytic copper complex. Chloride and nitrate ions are more strongly coordinated to copper than bromide or perchlorate anions, the last even being non-coordinating. Consequently, it is easier, for the alcoholate, to enter the copper coordination sphere when perchlorate is the counter-ion rather than chloride. This is a plausible explanation for the activities observed.

In conclusion, a new and very mild oxidation of primary alcohols to aldehydes with excellent conversions has been developed. The reaction is carried out under air at room temp. and is catalysed by a $[\text{CuBr}_2(\text{Bipy})]$ catalyst which is very easy to handle. In the reaction mechanism, TEMPO seems to be involved as a hydrogen acceptor. The mechanism of the oxidation is under investigation and further investigations are aimed at improving the rate of oxidation of aliphatic alcohols. For this purpose, studies using other N ligands are currently in progress.

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Notes and references

† *Experimental.* All alcohols and solvents were used as received without any further purification. The oxidation of alcohols was carried out under air in a 50 mL three-necked round-bottom flask equipped with a magnetic stirrer. Typically, the alcohol (10.0 mmol) and decane (2.0 mmol; GC internal standard) were dissolved in 15 mL of a $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (2 : 1) solvent mixture. 56 mg (0.5 mmol) of *t*-BuOK were added followed by 112 mg (0.5 mmol) of $\text{Cu}(\text{II})\text{Br}_2$, resulting in a blue-green suspension. 78 mg (0.5 mmol) of 2,2'-Bipy were then introduced leading to a dark-blue mixture. Finally, TEMPO (78 mg; 0.5 mmol) was added and the reaction suspension immediately turned brown-orange and clear dark-red after 2–3 min. Samples of the reaction mixture were taken out regularly to monitor the reaction by GC. The products of the reaction were determined by comparison with the commercially available carbonyl compounds.

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