Oxidation with Air

Efficient, Copper-Catalyzed, Aerobic Oxidation of Primary Alcohols**

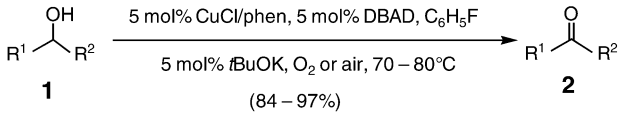
István E. Markó, Arnaud Gautier, Raphaël Dumeunier, Kanae Doda, Freddi Philippart, Stephen M. Brown, and Christopher J. Urch*

The oxidation of alcohols into aldehydes and ketones is of paramount importance in organic chemistry and numerous reagents have been reported to accomplish this transformation efficiently and selectively.[1] However, most of these oxidants are either toxic, hazardous, or required in large excess. From an economical and environmental viewpoint, catalytic oxidations are particularly interesting,[2] and major efforts have been devoted over the last few years to the discovery and development of efficient procedures employing O_2 (or air) or hydrogen peroxide as the ultimate stoichiometric oxidant.[3] These attractive catalytic systems utilize cheap and readily available reactants, display high atom economy[4] and release only innocuous by-products such as H_2O.[5] Whilst a large variety of ruthenium complexes have been shown to catalyze this reaction, either on their own[6] or with the assistance of various co-catalysts,[7] only a limited number of other metals, such as cobalt[8] and palladium,[9] have been successfully employed so far. In most cases, however, the range of substrates tolerated in these aerobic oxidations is limited to certain classes of alcohols.[10]

Sometime ago, we reported that the inexpensive and readily available CuCl/phen/DBAD complex (DBAD = di-*tert*-butyl azodicarboxylate, phen = 1,10-phenanthroline) was a competent catalyst for the aerobic oxidation of a wide range of alcohols **1** to give carbonyl compounds **2** (Scheme 1).[11] Subsequent optimization of our initial catalytic system led to an improved and highly efficient protocol for the oxidation of primary allylic and benzylic as well as secondary aliphatic, allylic, and benzylic alcohols under neutral conditions.[12] Unfortunately, and despite extensive efforts, primary aliphatic alcohols remained elusive recalcitrant substrates.

In this communication we report that the addition of a simple and inexpensive additive provides a modified catalyst that quantitatively oxidizes a large variety of primary alcohols to the corresponding aldehydes. To the best of our knowledge, the Yamaguchi–Mizuno heterogeneous ruthenium system[9h] and our CuCl/phen/DBAD complex are thus far the only systems for the aerobic oxidation of all classes of alcohols.

Closer examination of the oxidation of several primary aliphatic alcohols revealed intriguing features (Table 1). Whilst poor conversion of 1-decanol (**3**) to decanal (**4**) was achieved (Table 1, entry 1), dibenzyl leucinol (**5**) and *N*-Boc-prolinol (**7**) were quantitatively transformed into the corresponding aldehydes (entries 2 and 3). No racemization is observed with these enantiomerically pure substrates. The enhanced reactivity of **5** and **7** could be due either to an increased steric effect at the α-carbon center, to an electronic influence of the α-nitrogen substituent, or to a combination of both. To test the importance of steric hindrance, the aerobic oxidation of cyclohexanylmethanol (**9**) and adamantylmethanol (**11**) was carried out. Much to our surprise, oxidation of **9** afforded **10** in 70% conversion (entry 4) and transformation of **11** to **12** proceeded with 80% conversion (entry 5). Clearly, increased substitution at the α-position favors the oxidation of primary aliphatic alcohols, though the conversions are still not optimum.

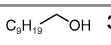
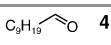
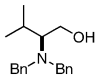
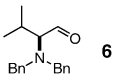
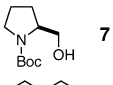
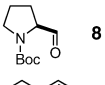
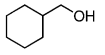
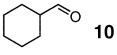
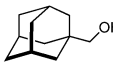
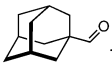


R^1, R^2 = aryl, alkyl, vinyl, H; DBAD = $tBuO_2C$-N=N-CO_2tBu

Scheme 1. Copper-catalyzed aerobic oxidation of alcohols.

In order to improve this transformation, selected additives were tested in the aerobic oxidation of 1-decanol (**3**). The high affinity of heterocyclic amines for copper salts, coupled with their ubiquitous presence as ligands in biologically active copper-containing proteins,[13] prompted us to investigate them initially. Some selected results are collected in Table 2. As can be seen, the conversion of 1-decanol (**3**) to the desired aldehyde **4** proceeded poorly in the absence of additive (Table 2, entry 1). In the presence of 5 mol% DMAP (4-*N*,*N*-dimethylaminopyridine), a significant increase in the transformation of **3** to **4** was observed (entry 2) and complete conversion was eventually reached using 10 mol% DMAP (entry 3). Interestingly, only 7 mol% NMI (*N*-methylimidazole) was required to transform **3** completely into **4** (entry 4).

Table 1: Copper-catalyzed aerobic oxidation of selected primary alcohols.

Entry	Substrate	Product	Conv. [%]	Yield [%][a]
1	 **3**	 **4**	60	51
2	 **5**	 **6**	100	84
3	 **7**	 **8**	100	97
4	 **9**	 **10**	70	64
5	 **11**	 **12**	80	77

[a] Yield of isolated, pure product.

These conditions were next applied to the aerobic oxidation of a variety of primary alcohols. A selection of pertinent examples is displayed in Table 3. All the primary alcohols employed were quantitatively converted into the corresponding aldehydes with 100% selectivity. It is noteworthy that no trace of carboxylic acid was observed under these aerobic conditions.[14] The reaction tolerates both simple aliphatic primary alcohols (Table 3, entry 1) and more hindered derivatives (entries 2 and 3) as well as various protecting groups (entries 4 and 8). Simple alkenes are

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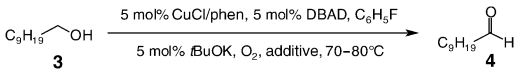
unaffected (entry 5), and base-sensitive substrates are smoothly oxidized (entry 6). It is interesting to note that under these neutral conditions, highly acid-sensitive substrates are also quantitatively converted into the correspond-

Table 2: Influence of additives on the aerobic oxidation of 1-decanol (**3**).



Entry	Additive	Amount [mol%]	Conv. [%][a]
1	–	–	60
2	DMAP 	5	80
3	DMAP 	10	100
4	NMI 	7	100

[a] The conversions were measured by capillary gas chromatography with an internal standard.

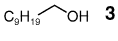
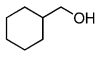
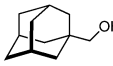
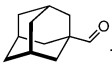
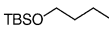
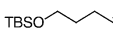
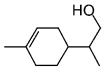
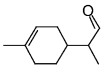
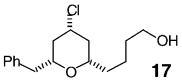
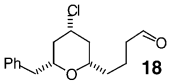
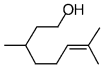
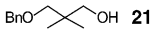
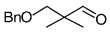
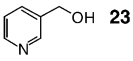
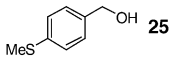
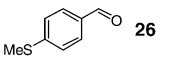
ing aldehydes (entry 7). Finally, a serious impediment in all the other reported aerobic oxidation protocols is their inability to oxidize alcohols possessing a chelating function, a nitrogen atom or a sulfur substituent. Such is not the case for the copper catalyst which transforms the strongly coordinating substrate **21** quantitatively into the aldehyde **22** (entry 8) and tolerates both heteroatoms (entries 9 and 10).

The remarkable effect of DMAP and NMI on the ability of the copper catalyst to oxidize efficiently a wide range of primary alcohols is surprising, and the origin of this effect was investigated, initially with the mechanistically simpler anaerobic system. In the absence of oxygen and NMI, 1-decanol was smoothly and quantitatively oxidized to decanal. Addition of 7 mol% NMI did not improve the conversion, nor the rate of the reaction; rather, NMI had a slightly retarding effect.[15]

In order to reconcile these observations with the previously established catalytic cycle for the aerobic oxidation of alcohols using the CuCl/phen/DBAD system, a new catalytic manifold has to be operative in the presence of NMI. The productive catalytic cycle begins with the ternary loaded complex **A** (Scheme 2). Intramolecular hydrogen transfer from the alkoxo ligand to the azo ligand generates copper(I) hydrazide **B**. Subsequent release of the aldehyde produces complex **C**, which is rapidly captured by oxygen, affording Cu^{II} hydrazide derivative **D**. Reorganization of **D** under the thermal conditions of the reaction leads to the hydroxocopper(I) species **E**. Finally, ligand exchange and elimination of water regenerates the active, loaded complex **A**, and a new catalytic cycle ensues.

Amongst the various active species in this system, complex **C**, bearing an empty coordination site, appears to be the most likely candidate to suffer a competitive deactivation by the primary alcohols.[16] Indeed, whilst **C** usually reacts rapidly with oxygen, it can occasionally undergo competitive coordination to an alcohol, producing the copper derivative **F** that might undergo hydrogen transfer and loss of the hydrazine substituent, resulting in the inactive complex **G**.[17,18]

Table 3: The copper-catalyzed aerobic oxidation of primary alcohols with NMI as an additive.[a]

Entry	Substrate	Product	Yield [%][a]
1	 **3**	 **4**	95
2	 **9**	 **10**	93
3	 **11**	 **12**	95
4	 **13**	 **14**	94
5	 **15**	 **16**	94
6	 **17**	 **18**	83
7	 **19**	 **20**	82
8	 **21**	 **22**	97
9	 **23**	 **24**	93
10	 **25**	 **26**	95

[a] Reaction conditions: entry 4, Table 2. [b] All yields are for pure, isolated products.

In the case of secondary alcohols, competitive coordination to **C** of the OH function or of dioxygen, largely favors the latter and the bis(copper) peroxide **D** is formed. However, when primary aliphatic alcohols are employed, coordination of the less hindered OH group now becomes competitive. The formation of inactive complex **G** gradually depletes the catalytic cycle in the active oxidizing species, and the reaction grinds to a halt. This mechanistic proposal also explains the observed increased conversions when more hindered aliphatic primary alcohols are employed.

The role of NMI and DMAP would thus be to bind rapidly and reversibly to copper complex **C**, generating intermediate **H**. Such coordination would preclude the competitive addition of the alcohol and suppress the undesired formation of the inert derivative **G**.[19,20]

In summary, we have shown that the use of the simple and inexpensive additive NMI strongly modified the course of the copper-catalyzed aerobic oxidation of primary aliphatic alcohols. Under these novel conditions, a wide range of primary substrates could be transformed efficiently into the corresponding aldehydes with no trace of overoxidized carboxylic acids. Moreover, the neutral conditions employed are compatible with base- and acid-sensitive substrates. Furthermore, these results have shed some light on an unsuspected decomposition pathway, the inhibition of which held the key to a highly successful aerobic oxidation

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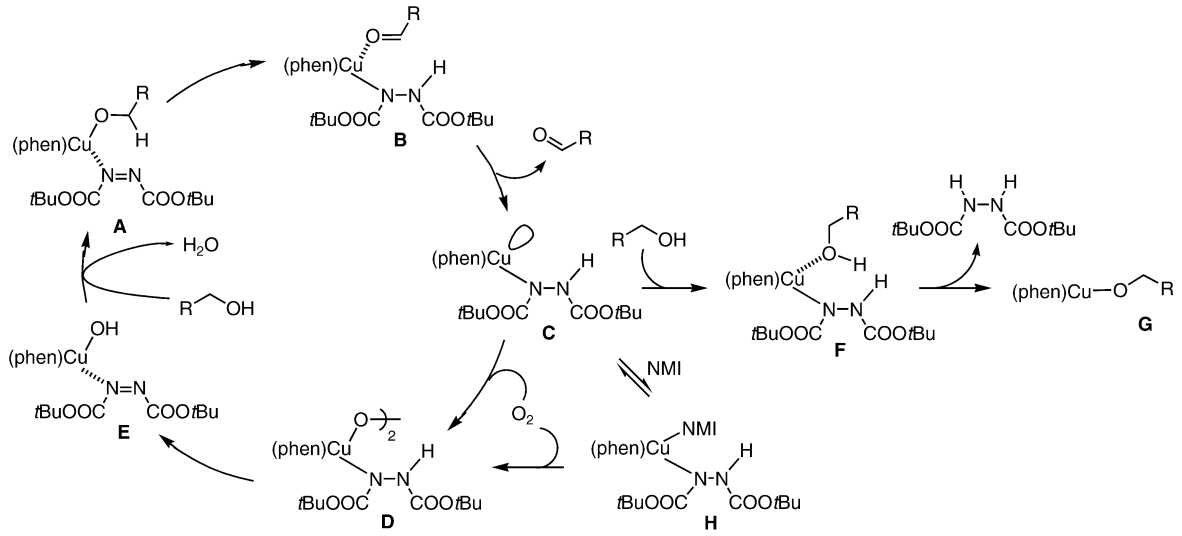

Scheme 2. Proposed mechanism for the copper-catalyzed aerobic oxidation of alcohols.

procedure for primary alcohols. To the best of our knowledge, the Yamaguchi–Mizuno heterogeneous ruthenium system and our copper-catalyzed aerobic protocol are thus far the only catalytic procedures that are able to oxidize, with equal efficiency, substrates from all classes of alcohols.

Experimental Procedure

Aerobic oxidation of **3:** First 1,10-phenanthroline (180 mg, 1 mmol, 5 mol%) and then solid CuCl (100 mg, 1 mmol, 5 mol%) were added to 200 mL anhydrous FC_6H_5. After the suspension had been stirred for 5 min at room temperature, **3** (3.16 g, 20 mmol) was added followed by solid KO*t*Bu (112 mg, 1 mmol, 5 mol%). The resulting yellowish solution was stirred at room temperature for 10 min before NMI (120 mg, 1.4 mmol, 7 mol%) and DBAD (230 mg, 1 mmol, 5 mol%) were added. The reaction mixture was heated at reflux under a gentle stream of O_2 for 100 min. After the reaction mixture was cooled to 20 °C, celigel (4 g, 80/20 w/w mixture of celite and silica gel) was added and stirring was continued for 2 min. The solid residue was removed by filtration and washed with 200 mL ether. Evaporation of the solvents in vacuo afforded pure **4** as a colorless liquid (2.95 g, 95%).

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Keywords: aerobic oxidation · alcohols · aldehydes · molecular oxygen · oxidation

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[14] The overoxidation of the aldehyde into the corresponding carboxylic acid has never been observed with this aerobic oxidation protocol. Whilst no proper explanation can be provided at this stage, it is possible that the copper catalyst protects the aldehyde towards further reaction with dioxygen. A similar observation has been reported by Sheldon et al.[7a]
[15] Whilst quantitative conversion of **3** into **4** occurred in the absence and presence of 7 mol% NMI, the oxidation of **3** proceeded more slowly in the presence of this additive (87% conversion after 30 min in the absence of NMI and 75% conversion after 30 min in the presence of NMI). The coordination of NMI to copper results in a slower exchange with the excess DBAD and hence, in a longer reaction time.
[16] Studies performed on the anaerobic version of this catalytic system revealed that aliphatic primary alcohols were oxidized with the same efficiency as all the other classes of alcohols, thus ruling out complexes **A**, **B**, and **E** as the culprit for the decomposition pathway. Whilst we could not experimentally rule out complex **D**, coordination of an alcohol to **D** should involve the participation of a pentacoordinated copper species. Whilst these are not uncommon, their formation requires a higher activation energy than the coordination to **C**.
[17] This hydrogen transfer is essentially an intramolecular acid–base reaction. The hydrogen on the coordinated alcohol function is acidified by coordination to the copper centre whilst the hydrazine ligand has basic properties. The elimination of the hydrazine substituent is irreversible under these neutral conditions. Indeed, in the absence of excess base, $DBADH_2$ is unable to displace the alkoxo ligand from the copper complex **G**.
[18] We have previously demonstrated[11a] that **G** was not a competent catalyst in the aerobic oxidation protocol when R = alkyl. Under anaerobic conditions, that is, in the presence of 1 equiv DBAD, **G** can efficiently regenerate the loaded ternary complex **A** and smooth oxidation ensues.
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[20] In full accord with this mechanistic rationale, the use of NMI and other heterocyclic nitrogen derivatives allows the preferential kinetic oxidation of primary aliphatic alcohols over secondary ones. Whilst the selectivities are not yet perfect, initial experiments have shown that the nature of the additive strongly affects the selectivity of this oxidation.

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