Copper(I)- and Mesoionic-Hydroxyamide-Catalyzed Chemoselective Aerobic Oxidation of Primary Benzylic Alcohols

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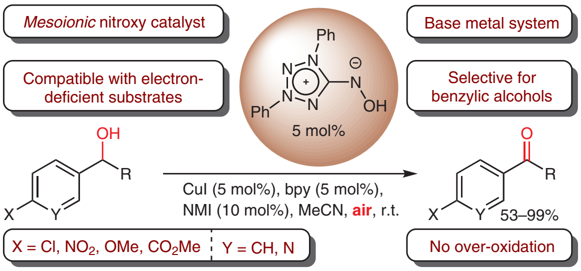


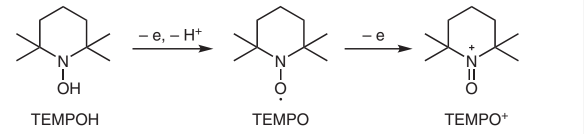
Received: 19.10.2018
Accepted after revision: 06.11.2018

DOI: 10.1055/s-0037-1611698; Art ID: st-2018-u0682-l

Abstract A new aerobic oxidation system consisting of Cu(I)I, 2,2'-bipyridine, *N*-methyl imidazole, and a mesoionic hydroxyamide was developed, with which selective oxidation of a broad range of benzylic alcohols was achieved.

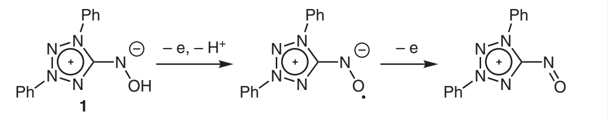
Key words mesoionic compounds, aerobic oxidation, copper, benzylic alcohols, aldehydes

The aerobic oxidation of alcohols has recently attracted attention and has been widely explored because it is a highly environment-friendly approach, with water as the only stoichiometric by-product.[1] Copper is an easily available base metal and its salts are relatively inexpensive and of low toxicity, which makes it beneficial for use as a catalyst for practical synthetic applications instead of precious metals. Homogenous Cu-catalyzed reactions thus continue to be one of the pivotal processes in synthetic chemistry, such as Cu-TEMPO-mediated aerobic oxidation of alcohols [TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl].[2–5] The Cu–TEMPO system principally consists of a copper salt, TEMPO, a ligand, and a base. Koskinen and co-workers have reported that use of *N*-methylimidazole (NMI) as a base in the (bpy)CuI–TEMPO system (bpy = 2,2'-bipyridine) promotes the rapid oxidation of alcohols.[6] Recently, Stahl et al. reported that a (bpy)Cu^I–TEMPO system consisting of Cu^I, bpy, and NMI allows aerobic oxidation to be performed under milder conditions and with an expanded substrate scope.[7] The redox reaction of TEMPO is presented in Equation 1, and the electrocatalytic activity of TEMPO derivatives is strongly correlated with their electrochemical potentials.[8]



Equation 1

We have recently focused on mesoionic 1,3-diphenyltetrazolium-5-hydroxyamide **1**,[9] and have developed an efficient and chemoselective aerobic oxidation method using 5-nitroso-1,3-diphenyltetrazolium tetrafluoroborate[10a] involving a reversible redox couple with **1** as a catalyst similar to TEMPO (Equation 2).[10b]

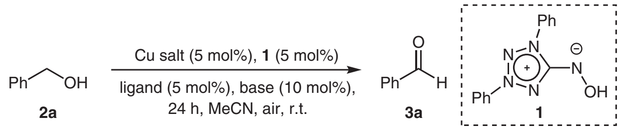


Equation 2

The redox potential of **1** is 0.10 V vs. Ag/Ag^+ in acetonitrile,[10a] which is lower than that of TEMPO.[11] This electrochemical property of **1** prompted us to apply it in a (bpy)Cu system instead of nitroxyl catalysts, with the expectation that the reoxidation of the catalyst would proceed more easily. In our previous study on the aerobic oxidation of alcohols in the presence of nitric acid, the catalytic cycle operates between **1** and its nitroso form through a two-electron-transfer process. The Cu–TEMPO redox reaction is, however, considered to function as a one-electron process between TEMPO and TEMPOH. Provided the mesoionic hydroxyamide **1** behaves like TEMPO in the oxidation of alcohols in the presence of a copper salt, a unique mesoionic radical would be expected to participate in the redox cycle.

We started by screening a number of copper salts using benzyl alcohol (**2a**) as a model substrate under ambient air conditions, and found Cu(I)I to be suitable for this reaction (Table 1, entries 1–8). Among a variety of combinations of ligands and bases, bpy and NMI provided the best results (entries 8, 11–15). With the optimal combination of salt, ligand, and base, MeCN as the solvent gave the best results (entries 8, 16, and 17). The oxidation did not proceed at all in the absence of **1** (entry 9). The absence of a base led to a large drop in the yield of benzaldehyde **3a** (entry 10).

Table 1 Optimization of the Cu–**1**-Catalyzed Aerobic Oxidation of Benzyl Alcohol[a]

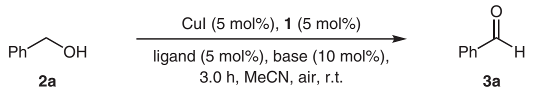


Entry	Cu salt	Ligand	Base	Yield of **3a** [%][b]	Recovery of **2a** [%][b]
1	$Cu(ClO_4)_2{\cdot}6H_2O$	bpy	NMI	4	84
2	$CuCl_2$	bpy	NMI	1	87
3	$CuBr_2$	bpy	NMI	0	91
4	$(CuOTf)_2{\cdot}C_6H_6$	bpy	NMI	38	51
5	$CuBF_4{\cdot}(MeCN)_4$	bpy	NMI	47	41
6	CuCl	bpy	NMI	22	63
7	CuBr	bpy	NMI	62	30
8	CuI	bpy	NMI	94	6
9[c]	CuI	bpy	NMI	0	83
10	CuI	bpy	none	53	42
11	CuI	bpy	K_2CO_3	72	26
12	CuI	bpy	Py	66	26
13	CuI	bpy	DBU	24	68
14	CuI	phen	NMI	32	50
15	CuI	TMEDA	NMI	36	55
16[d]	CuI	bpy	NMI	0	81
17[e]	CuI	bpy	NMI	20	63

[a] Reaction conditions: **2a** (0.40 mmol), Cu salt (5 mol%), ligand (5 mol%), base (10 mol%), and **1** (5 mol%) in MeCN unless otherwise noted (4.0 mL) at room temperature.
[b] Determined by GC.
[c] Without **1**.
[d] In THF.
[e] In CH_2Cl_2.

The yields of benzaldehyde obtained at an early stage of the reaction (after 3 h) under a series of conditions showed the same tendency as that observed above (Table 2, entries 1–4), and the combination of bpy and NMI proved again to be superior to the others examined. Use of pure oxygen improved the yield (entry 5), whereas heating resulted in a drop in yield (entry 6).

Table 2 Comparison of the Yields after 3.0 Hours in the Cu–**1** Aerobic Oxidation System[a]

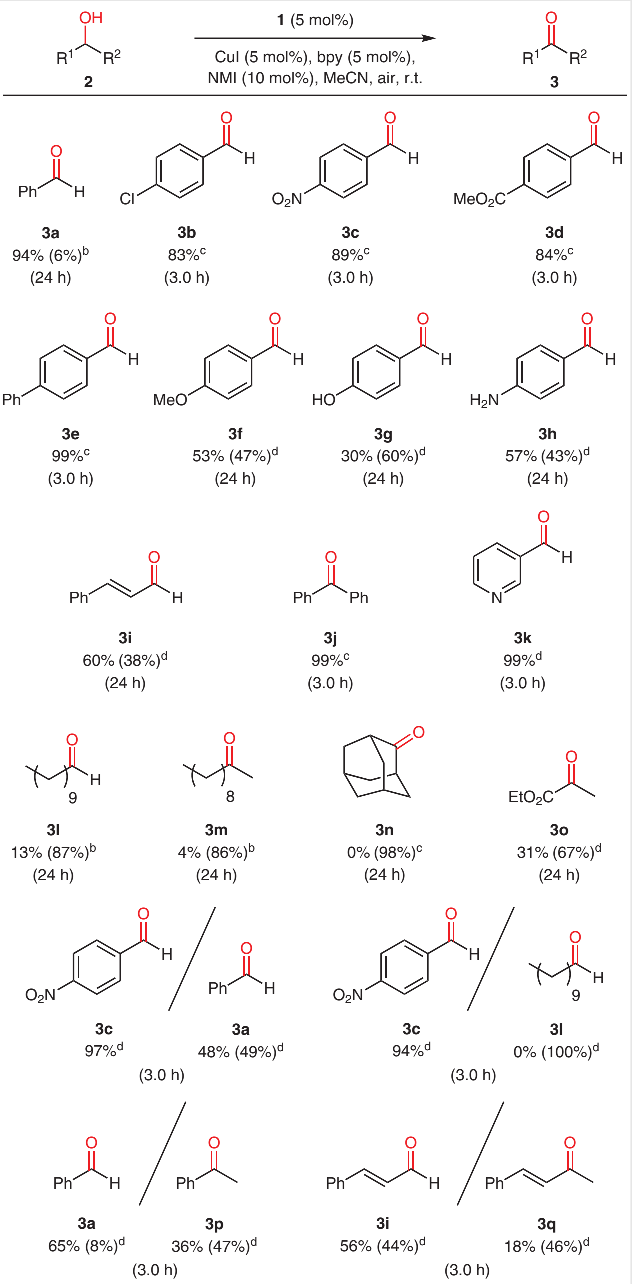


Entry	Ligand	Base	Yield of **3a** [%][b]	Recovery of **2a** [%][b]
1[c]	bpy	NMI	68	21
2	bpy	DBU	33	52
3	phen	NMI	14	70
4	TMEDA	NMI	18	67
5[d]	bpy	NMI	78	16
6[e]	bpy	NMI	49	39

[a] Reaction conditions: **2a** (0.40 mmol), CuI (5 mol%), ligand (5 mol%), base (10 mol%), and **1** (5 mol%) in MeCN (4.0 mL) at room temperature.
[b] Determined by GC.
[c] For a profile at an earlier stage, see Figure S1.
[d] Under O_2 (balloon).
[e] At 40 °C.

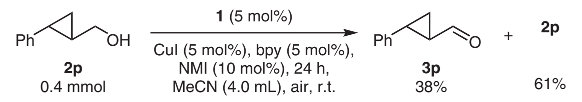
Having the optimal conditions in hand, we investigated the scope of the alcohols (Scheme 1). Benzylic alcohols with an electron-withdrawing group such as an ester or halogen were efficiently oxidized to afford the corresponding aldehydes (**3b**–**e**), whereas *p*-anisalcohol led to a moderate yield (**3f**). A competitive oxidation between *p*-nitrobenzyl and benzyl alcohol showed that oxidation of the former was strongly favored; *p*-nitrobenzyl alcohol was oxidized two times faster than benzyl alcohol. Intriguingly, *p*-hydroxy- and *p*-aminobenzyl alcohols were also oxidized to the corresponding aldehydes in moderate yields (**3g** and **3h**), in sharp contrast to the TEMPO–Cu-catalyzed oxidation, in which such functionalities completely suppress the conversion. This is presumably due to a strong coordination to the copper atom.[12] Cinnamyl alcohol was converted into cinnamyl aldehyde **3i** in a moderate yield. Benzhydrol and 3-pyridinemethanol were successfully oxidized to aldehydes **3j** and **3k**. In contrast to HNO_3-catalyzed aerobic oxidation,[10b] oxidation of aliphatic alcohols occurred with low yields or not at all (**3l**–**n**).

When *p*-nitrobenzyl alcohol was allowed to react competitively with 1-undecanol, **3c** was selectively obtained and 1-undecanol was completely recovered. Ethyl lactate (**2o**) was converted into the corresponding ketone **3o** in 31% yield, while styrene glycol and (2,2-dimethyl-1,3-dioxolan-4-yl)methanol (solketal) were recovered intact. Since a high selectivity of benzylic alcohols was revealed in this study, a preference for primary/secondary alcohols was next examined by competitive oxidations of benzylic alcohols **2a**/1-phenylethanol (**2p**) and allylic substrates **2i**/**2q**. In both oxidations, primary **2a** and **2i** were preferably converted into the corresponding aldehydes than into secondary alcohols **2p** and **2q**. The Cu–**1** system proved to be capable of oxidizing **2o** as well as **2g** and **2h**, albeit in modest yield, which



Scheme 1 Scope of the Cu–**1**-catalyzed aerobic oxidation of alcohols. [a] Reaction conditions: **2** (0.40 mmol), CuI (5 mol%), bpy (5 mol%), NMI (10 mol%), and **1** (5 mol%) in MeCN (4.0 mL) at room temperature. Values in parentheses are the recoveries of **2**. [b] Determined by GC. [c] Isolated yield. [d] Determined by ^{1}H NMR spectroscopy.

are difficult to oxidize with the (bpy)Cu^I–TEMPO system.[7] 2-Phenylcyclopropylmethanol (**2r**), a radical clock substrate, was subjected to this aerobic oxidation in order to gain insight into the mechanism. Although we anticipated that aliphatic alcohols would be resistant to the oxidation, as seen in Scheme 1, the corresponding aldehyde **3r** was obtained in moderate yield and no ring-opened product was observed (Equation 3). This result suggests that radical intermediates may not be involved in the Cu–**1**-catalyzed aerobic oxidation, similar to the Cu–TEMPO system.[12]



Equation 3

In summary, mesoionic hydroxyamide **1** and a copper salt can function as a catalytic system for the aerobic oxidation of benzylic alcohols to the corresponding carbonyl compounds.[13–15] In the presence of **1** (5 mol%), CuI (5 mol%), bpy (5 mol%), and NMI (10 mol%), benzyl alcohol and benzylic alcohols bearing electron-withdrawing groups were oxidized to aldehydes in 83–99% yield, whereas benzylic alcohols with amino or oxygenated functionalities, some of which are incapable of being oxidized by the Cu–TEMPO catalyst, were transformed into the corresponding aldehydes in 30–57% yield. Aliphatic alcohols, in contrast, were oxidized with low yields or not at all, and thus benzylic alcohols can be selectively oxidized in the presence of aliphatic alcohols.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611698.

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(13) **Improved Synthetic Procedure for 1,3-Diphenyltetrazolium-5-hydroxyamide (1):** To a suspension of $NH_2OH•HCl$ (3.48 g, 50.0 mmol) in MeCN (200 mL) was added Et_3N (6.93 mL, 50.0 mmol), and the mixture was stirred for 2 h at room temperature, followed by addition of 5-chloro-1,3-diphenyltetrazolium tetrafluoroborate (3.44 g, 10.0 mmol). The mixture was stirred for a further 3 h and then the solvent was evaporated in vacuo. To the residue was added saturated $NaHCO_3$ (12.0 g, 143 mmol) solution. The resulting mixture was extracted with CH_2Cl_2 and shaken with 1M HCl (100 mL). The aqueous phase was washed with CH_2Cl_2 and basified with saturated $NaHCO_3$. The resulting precipitate was extracted with CH_2Cl_2 and dried with anhydrous Na_2SO_4, and the resulting solution was evaporated in vacuo to give brown crystals of **1** (1.65 g, 65%).

(14) **General Procedure for the Optimization of the Cu–1-Catalyzed Aerobic Oxidation of Benzyl Alcohol (Table 1):** A mixture of benzyl alcohol **2a** (0.4 mmol), Cu salt (0.02 mmol), ligand (0.02 mmol), base (0.04 mmol), and **1** (0.02 mmol) was vigorously stirred in MeCN (4.0 mL) at room temperature for 24 h in the presence of PhCN (0.2 mmol) as an internal standard. At intervals, aliquots were analyzed by GC after being passed through a SiO_2 column eluted with CH_2Cl_2. The yield of benzaldehyde **3a** (t_R = 4.3 min) and the recovery of **2a** (t_R = 9.4 min) were calculated on the basis of calibration curves by using authentic samples.

(15) **Representative Procedure for the Cu–1-Catalyzed Aerobic Oxidation of Benzylic Alcohols (Scheme** 1, **Benzhydrol 2j):** A mixture of benzhydrol **2j** (74 mg, 0.40 mmol), CuI (3.7 mg, 0.019 mmol), 2,2'-bipyridine (3.1 mg, 0.020 mmol), *N*-methyl imidazole (3.5 mg, 0.043 mmol), and **1** (5.1 mg, 0.020 mmol) was vigorously stirred in MeCN (4.0 mL) at room temperature for 3 h. The solvent was evaporated under reduced pressure and the residue was passed through a SiO_2 column eluted with CH_2Cl_2 to give **3j** (73 mg, 99%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.49 (t, *J* = 7.5 Hz, 4 H), 7.60 (t, *J* = 7.2 Hz, 2 H), 7.81 (d, *J* = 6.9 Hz, 4 H).