

available at [www.sciencedirect.com](http://www.sciencedirect.com)journal homepage: [www.elsevier.com/locate/chnjc](http://www.elsevier.com/locate/chnjc)

## Article

# CuI/N4 ligand/TEMPO derivatives: A mild and highly efficient system for aerobic oxidation of primary alcohols

Shufang Zhang<sup>a,b</sup>, Chengxia Miao<sup>a,#</sup>, Daqian Xu<sup>a</sup>, Wei Sun<sup>a,\*</sup>, Chungu Xia<sup>a</sup><sup>a</sup> State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, Gansu, China<sup>b</sup> University of Chinese Academy of Sciences, Beijing 100049, China

## ARTICLE INFO

## Article history:

Received 1 May 2014

Accepted 3 June 2014

Published 20 November 2014

## Keywords:

Alcohol

Aerobic oxidation

Tetradentate nitrogen ligand

Copper

2,2,6,6-tetramethylpiperidine-1-oxyl

## ABSTRACT

A new system consisting of a copper(I) complex generated in situ from a tetradentate nitrogen ligand and CuI in combination with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) derivatives was successfully developed. The system was suitable for efficient and selective aerobic oxidation of primary benzyl and allyl alcohols with a wide range of functional groups to the corresponding aldehydes at room temperature. The best result was obtained with *N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)ethane-1,2-diamine as the ligand and 4-OH-TEMPO as a cocatalyst in CH<sub>3</sub>CN. In addition, high-resolution mass spectrometry, ultraviolet-visible spectroscopy, and electrochemical experiments were used to provide evidence of intermediates.

© 2014, Dalian Institute of Chemical Physics, Chinese Academy of Sciences.

Published by Elsevier B.V. All rights reserved.

## 1. Introduction

Metal complexes with nitrogen ligands have been extensively studied as models of monooxygenase active sites and as oxidation catalysts in organic synthesis [1–3]. Metal porphyrins such as cytochrome P-450 [1], which play a central role in many biological processes, have been mimicked using various synthetic ligands. Recently, biologically inspired and more flexible tetradentate nitrogen (N4) ligands and their corresponding metal complexes have been attracting increasing attention [4–7]. Our group has also developed a series of N4 ligands and corresponding metal complexes for asymmetric epoxidation of olefins [8–10]. Until now, there have been few reports on the oxidation of alcohols catalyzed by metal complexes with N4 ligands.

The selective oxidation of alcohols to the corresponding al-

dehydes or ketones is a common transformation in organic synthesis because aldehydes and ketones are important as intermediates in pharmaceuticals, plastic additives, perfumes, flavoring compounds, and certain dyes in the textile industry. Recently, the use of the stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in combination with various oxidants in the oxidation of alcohols has attracted interest [11–13]. However, many TEMPO-based systems use stoichiometric amounts of terminal oxidants such as sodium chlorite and hypervalent iodine(III) compounds, so large amounts of waste are produced [14,15], and longer reaction time or high temperature is also often needed [16].

Air, oxygen, and hydrogen peroxide are clean oxidants, and only water is formed as the by-product, so they have been attracting much interest for use in green chemistry. However, TEMPO, which is expensive, cannot be regenerated directly by

\* Corresponding author. Fax: +86-931-8277088; E-mail: [wsun@licp.cas.cn](mailto:wsun@licp.cas.cn)# Corresponding author. E-mail: [chxmiao@licp.cas.cn](mailto:chxmiao@licp.cas.cn)

This work was supported by the National Natural Science Foundation of China (21103207, 21133011).

DOI: 10.1016/S1872-2067(14)60161-3 | <http://www.sciencedirect.com/science/journal/18722067> | Chin. J. Catal., Vol. 35, No. 11, November 2014

molecular oxygen alone, so a cocatalyst is required for activation of molecular oxygen [17].

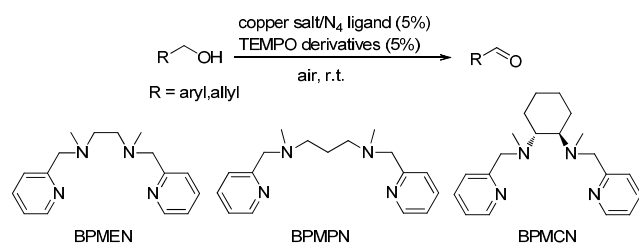
Copper complexes are more attractive as they are biomimetic functional models of the mononuclear copper enzyme galactose [18]. In 1984, Semmelhack et al. [19] reported the aerobic oxidation of allyl and benzyl alcohols to the corresponding aldehydes and ketones catalyzed by 10 mol% CuI/TEMPO in *N,N*-dimethylformamide (DMF) at room temperature. Subsequent research mainly focused on the choice and design of nitrogen-containing ligands such as 1,10-phenanthroline [20], 2,2'-bipyridine (bpy) [21–25], 1,4-diazabicyclo[2.2.2]octane [26], 4-pyrrolidinopyridine [27], pyrazole-pyridine [28], salen-H<sub>4</sub> [29], and 1,4,7-triazacyclononane [30] to improve the catalytic activity and extend the substrate scope. Recently, a breakthrough was achieved by Stahl and coworkers [21–25]. They used *N*-methylimidazole as an additive in a CuI-bpy/TEMPO catalyst system for the highly selective and efficient transformation of a broad range of alcohols, including allylic, benzyl, and aliphatic derivatives, with heterocycles and other heteroatom-containing groups. It should be noted that this catalyst system used non-commercial CuI(OTf) as the copper source.

Although significant progress has been made in developing TEMPO/Cu catalyst systems, readily available systems for the efficient oxidation of alcohols under mild conditions are still needed. In our continuing efforts to develop new systems for oxidation of alcohols catalyzed by TEMPO derivatives [31–34] and new applications of N<sub>4</sub> ligands in different reactions [8–10], we considered that a tetradentate nitrogen ligand (Scheme 1) combined with copper(I) ions and TEMPO derivatives might be active in oxidation of alcohols. We found that an easily obtainable catalyst system comprising CuI, *N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)ethane-1,2-diamine (BPMEN), and 4-OH-TEMPO exhibited high efficiency and wide substrate scope, including allylic, benzyl, and aliphatic primary alcohols, at room temperature using air as the oxidant without any additives such as a base.

## 2. Experimental

### 2.1. General information

Gas chromatography-mass spectrometry (GC-MS) was performed using an Agilent Technologies 7890A/5975C system. <sup>1</sup>H



**Scheme 1.** Oxidation of alcohols catalyzed by copper salt/TEMPO derivative/*N*<sub>4</sub> ligand. BPMEN = *N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)ethane-1,2-diamine, BPMPN = *N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)propane-1,3-diamine, BPMCN = *trans-N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)cyclohexane-1,2-diamine.

and <sup>13</sup>C nuclear magnetic resonance (NMR) spectra were recorded using a Bruker Avance III 400 MHz spectrometer. The chemical shifts ( $\delta$ ) are reported in parts per million (ppm) and coupling constants (*J*) in Hz. GC analysis was performed using an Agilent Technologies 6820 instrument with a flame-ionization detector. High-resolution (HR) MS was performed using a Bruker Daltonics microTOF-QII mass spectrometer. Ultraviolet (UV)-visible spectra were recorded using an Agilent Cary 60 spectrometer. Electrochemical measurements were conducted with a CHI 660E potentiostat using a platinum-button working electrode, non-aqueous Ag/Ag<sup>+</sup> reference, and a platinum wire counter electrode at a scan rate of 100 mV/s. Elemental analysis was performed using a Vario EL cube elemental analyzer.

### 2.2. Preparation and characterization of ligands and Cu(BPMEN)I complex

The ligands, i.e., BPMEN, BPMPN, and BPMCN, were synthesized as previously reported [35,36].

BPMEN: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 8.54 (ddd, *J* = 4.9, 1.7, 0.8 Hz, 2H), 7.63 (td, *J* = 7.7, 1.8 Hz, 2H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.14 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 2H), 3.69 (s, 4H), 2.65 (s, 4H), 2.28 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 159.4, 149.1, 136.3, 123.0, 121.9, 64.2, 55.5, 42.9.

BPMPN: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 8.53 (d, *J* = 4.5 Hz, 2H), 7.63 (t, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.14 (dd, *J* = 6.8, 5.5 Hz, 2H), 3.65 (s, 4H), 2.54–2.44 (m, 4H), 2.25 (s, 6H), 1.83–1.73 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 159.5, 149.0, 136.3, 123.0, 121.9, 63.9, 55.8, 42.5, 25.2.

BPMCN: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 8.42 (dt, *J* = 4.9, 1.3 Hz, 2H), 7.53–7.49 (m, 4H), 7.08–7.01 (m, 2H), 3.79 (dd, *J* = 48.3, 14.6 Hz, 4H), 2.65–2.55 (m, 2H), 2.22 (s, 6H), 1.92 (dd, *J* = 10.4, 2.4 Hz, 2H), 1.74–1.65 (m, 2H), 1.22 (td, *J* = 12.3, 6.4 Hz, 2H), 1.13–1.05 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 161.2, 148.6, 136.3, 123.0, 121.6, 64.5, 60.4, 36.7, 25.8, 25.8.

CuI (0.25 mmol) and BPMEN (0.25 mmol) were added to CH<sub>3</sub>CN (1 mL) in an Ar atmosphere, and the mixture was stirred at room temperature for 2 h. After the reaction, the solvent was removed under vacuum to yield a Cu(BPMEN)I complex, which was then washed with CH<sub>3</sub>CN and diethyl ether and dried under vacuum. HRMS (ESI-MS) calcd for C<sub>16</sub>H<sub>22</sub>CuN<sub>4</sub> [*M* – I]<sup>+</sup>: 333.1121; found: 333.1135. Anal. calcd for C<sub>16</sub>H<sub>22</sub>CuN<sub>4</sub>·0.7MeCN: C 42.84%, H 5.12%, N 13.38%; found C 42.69%, H 4.96%, N 13.45%.

### 2.3. Typical procedure for oxidation of alcohols

The copper salt and the ligand (each 0.025 mmol) were added to CH<sub>3</sub>CN (1 mL) in an Ar atmosphere and stirred for 30 min. Then 4-OH-TEMPO (0.025 mmol) and substrate (0.5 mmol) were added successively, and the mixture was stirred at room temperature. The reaction progress was checked using thin-layer chromatography. The reaction conversion and yield were obtained from GC measurements using nitrobenzene or nonane as an internal standard, or by column chromatography.

### 2.4. NMR data of some products

Phenylpropargyl aldehyde:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 9.34 (s, 1H), 7.51 (dd,  $J$  = 5.2, 3.2 Hz, 2H), 7.43–7.37 (m, 1H), 7.32 (t,  $J$  = 7.5 Hz, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 175.7, 132.3, 130.3, 127.7, 118.4, 94.1, 87.4.

$\alpha$ -Methylcinnamaldehyde:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 9.47 (s, 1H), 7.45–7.39 (m, 2H), 7.38–7.25 (m, 3H), 7.16 (d,  $J$  = 6.7 Hz, 1H), 1.97 (d,  $J$  = 1.3 Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 195.5, 149.8, 138.3, 135.2, 130.1, 129.6, 128.7, 10.9.

Neral:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 9.82 (d,  $J$  = 8.2 Hz, 1H), 5.80 (d,  $J$  = 8.2 Hz, 1H), 5.07–4.99 (m, 1H), 2.51 (t,  $J$  = 7.5 Hz, 2H), 2.16 (q,  $J$  = 7.4 Hz, 2H), 1.91 (d,  $J$  = 1.2 Hz, 3H), 1.61 (s, 3H), 1.52 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 190.7, 163.7, 133.6, 128.6, 122.3, 32.5, 27.0, 25.6, 25.0, 17.7.

### 3. Results and discussion

#### 3.1. Optimization of reaction conditions

Exploratory experiments were performed to test this protocol and screen the reaction conditions using benzyl alcohol as the model substrate (Table 1). The copper complex was generated from a copper salt and N4 ligand, which were stirred for 30 min before every reaction. The copper salt, TEMPO, and N4 ligand were essential in the aerobic oxidation of benzyl alcohol (Table 1, entries 1–3 vs 15–17). Initially, three different ligands, BPMEN, BPMPN, and BPMCN (Scheme 1), in combination with CuBr were used in the oxidation of benzyl alcohol under the

**Table 1**

Oxidation of benzyl alcohol catalyzed by TEMPO/copper salt/N4 ligand, using air as oxidant.

Entry	Cu salt	Solvent	Conversion <sup>a</sup> (%)	Yield <sup>a</sup> (%)
1	CuBr	$\text{CH}_3\text{CN}$	69 (88)	66 (86) <sup>b</sup>
2	CuBr	$\text{CH}_3\text{CN}$	37 (77)	33 (75) <sup>c</sup>
3	CuBr	$\text{CH}_3\text{CN}$	71 (>99)	69 (99)
4	CuBr	$\text{CH}_2\text{Cl}_2$	35	32
5	CuBr	THF	52	48
6	CuBr	DMF	46	40
7	CuBr	hexane	—	—
8	CuBr	1,4-dioxane	18	17
9	CuBr	toluene	29	28
10	CuBr	DMSO	55	46
11	CuBr	acetone	60	50
12	CuI	$\text{CH}_3\text{CN}$	94	92
13	CuCl	$\text{CH}_3\text{CN}$	49	46
14	$\text{Cu}(\text{MeCN})_4\text{BF}_4$	$\text{CH}_3\text{CN}$	51	46
15	CuI	$\text{CH}_3\text{CN}$	9	8 <sup>d</sup>
16	—	$\text{CH}_3\text{CN}$	—	0 <sup>e</sup>
17	CuI	$\text{CH}_3\text{CN}$	10	7 <sup>f</sup>
18	$\text{CuCl}_2$	$\text{CH}_3\text{CN}$	trace	trace
19	$\text{CuBr}_2$	$\text{CH}_3\text{CN}$	trace	trace

Reaction conditions: CuX (10%) and BPMEN (10%) in 1 mL of solvent were stirred for 30 min at room temperature under Ar; benzyl alcohol (0.5 mmol) and TEMPO (10%) were added, and the mixture was stirred for another 30 min in air.

<sup>a</sup> Conversion and yield were determined by GC using nitrobenzene as the internal standard. The number in parentheses indicates a reaction time of 50 min.

<sup>b</sup> BPMPN was used instead of BPMEN.

<sup>c</sup> BPMCN was used instead of BPMEN.

<sup>d</sup> Stirring at rt for 24 h without TEMPO.

<sup>e</sup> Stirring at rt for 24 h without CuI and BPMEN.

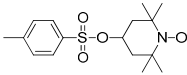
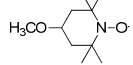
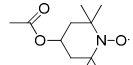
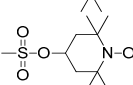
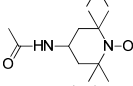
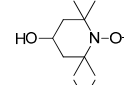
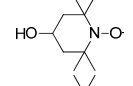
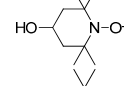
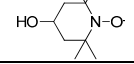
<sup>f</sup> Stirring at rt for 24 h without BPMEN.

same conditions; BPMEN proved to be the best ligand choice (Table 1, entries 1–3), giving 99% yield after prolonging the reaction time to 50 min (Table 1, entry 3). A series of organic solvents were then systematically investigated (Table 1, entries 3–11). The results indicated that the solvent had a significant effect on the oxidation reaction, and 69% yield was obtained in  $\text{CH}_3\text{CN}$  within 30 min. The oxidation did not proceed in hexane; this may be attributable to the insolubility of the in situ-generated copper complex or failure to form the corresponding copper complex. A series of copper salts, i.e., CuCl, CuI, and  $\text{Cu}(\text{MeCN})_4\text{BF}_4$ , were also screened; the best catalytic performance was obtained using CuI as the copper source (Table 1, entries 3 and 12–14).  $\text{CuCl}_2$  and  $\text{CuBr}_2$  were inert in the reaction, unlike the case for the bpy-Cu system reported by Stahl et al. [21].

The effects of TEMPO derivatives on the reaction were also examined. Most tested TEMPO derivatives gave above 90% conversions and yields, except 4- $\text{CH}_3\text{SO}_2\text{O}$ -TEMPO (Table 2, entries 1–7). 4-OH-TEMPO gave nearly quantitative conversion and yield and proved to be the most efficient TEMPO derivative when the oxidation was carried out in the presence of 10% CuI and BPMEN in air for 30 min. The 4-OH-TEMPO, CuI, and BPMEN loadings were then screened (Table 2, entries 8–10). A

**Table 2**

Oxidation of benzyl alcohol catalyzed by different TEMPO derivatives.

Entry	R-TEMPO	t/h	Conversion <sup>a</sup> (%)	Yield <sup>a</sup> (%)
1	TEMPO	0.5	94	92
2		0.5	95	91
3		0.5	90	89
4		0.5	96	94
5		0.5	76	70
6		0.5	96	93
7		0.5	>99	99
8		0.5	99	91 <sup>b</sup>
9		1.5	99	88 <sup>c</sup>
10		1	99	99 <sup>d</sup>

Reaction conditions: CuI (10%) and BPMEN (10%) in 1 mL of solvent were stirred for 30 min at room temperature in Ar; benzyl alcohol (0.5 mmol) and R-TEMPO (10%) were added, and the mixture was stirred for another 30 min in air.

<sup>a</sup> Conversion and yield were determined by GC using nitrobenzene as the internal standard.

<sup>b</sup> CuI (5%), BPMEN (5%), and HO-TEMPO (10%) were used.

<sup>c</sup> CuI (2%), BPMEN (2%), and HO-TEMPO (10%) were used.

<sup>d</sup> CuI (5%), BPMEN (5%), and HO-TEMPO (5%) were used.

91% yield was still achieved with 5% CuI, 5% BPMEN, and 10% 4-OH-TEMPO under the same conditions (Table 2, entry 8). When the loadings of CuI and BPMEN were further reduced to 2%, a comparable yield was obtained by prolonging the reaction time to 1.5 h (Table 2, entry 9). Overall, the reaction proceeded smoothly with 5% each of 4-OH-TEMPO, CuI, and BPMEN, giving 99% yield of aldehyde in 1 h (Table 2, entry 10).

### 3.2. Substrate scope and limitations



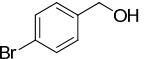
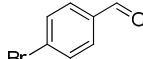








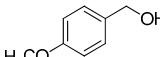
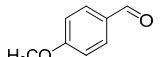


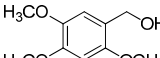
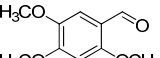
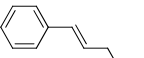
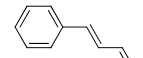
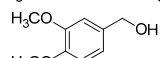
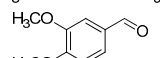
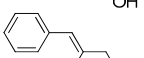
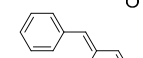
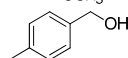
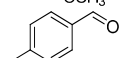
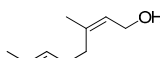
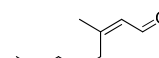
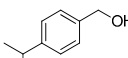
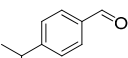
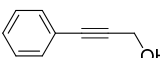
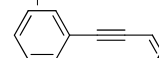
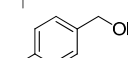
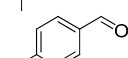
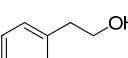
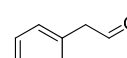






To examine the utility and generality of the catalyst system in the oxidation of alcohols, we used it for the oxidation of various alcohols; the results are summarized in Table 3. All the primary aromatic alcohols with either electron-donating or electron-withdrawing groups on the benzene ring were smoothly converted to aldehydes, giving more than 85% yields of the desired products; no over-oxidation products were detected. It was found that the electronic properties and steric hindrance of the substituents on the benzene ring influence the reactivity of primary benzyl alcohols; for example, the reactivity of *p*-OMe-benzyl alcohol was better than those of *o*- and *m*-OMe-benzyl alcohol (Table 3, entries 2–4). Benzyl alcohols bearing more electron-donating groups on the benzene ring exhibited higher reactivity (Table 3, entries 2–4 vs 5 and 6).

Moreover, stronger electron-donating groups promoted oxidation (Table 3, entries 2–4 vs 7 and 8).

Primary aromatic alcohols with electron-withdrawing groups on the benzene ring had poorer activity than the opposite ones, but comparable yields were obtained by prolonging the reaction time to 24 h in an oxygen atmosphere (Table 3, entries 9–12). A series of heterocyclic benzyl alcohols were also tested. Furfuryl alcohol and 2-thiophenemethanol gave yields of more than 90% (Table 3, entries 13 and 14), but only 8% yield of the desired product was obtained using pyridine-2-methanol as the substrate (Table 3, entry 15). The present protocol was also applicable to the oxidation of allylic alcohols such as cinnamyl alcohol, nerol, and 2-methyl-3-phenyl-2-propen-1-ol and gave good conversions (Table 3, entries 16–18). Propargyl alcohols such as 3-phenylprop-2-yn-1-ol also tolerated the optimized reaction conditions, affording the corresponding aldehyde in 51% yield (Table 3, entry 19). Unfortunately, the catalyst system was unsuitable for the oxidation of aliphatic alcohols and secondary alcohols, giving only 15% phenylacetaldehyde and 7% acetophenone, respectively (Table 3, entries 20 and 21).

The different reactivity of benzyl, allylic, and secondary alcohols suggest that the designed oxidation system should be chemoselective. We chose an equimolar mixture of benzyl al-

**Table 3**  
Catalytic aerobic oxidation of various alcohols.

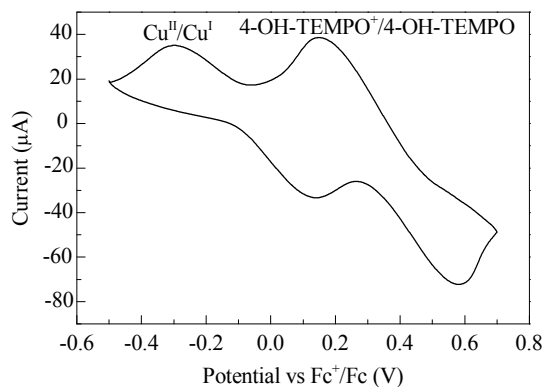
Entry	Substrate	Product	t/h	Yield <sup>a</sup> (%)	Entry	Substrate	Product	t/h	Yield <sup>a</sup> (%)
1			1	99	12			24	90 <sup>b</sup>
2			3	85	13			4	97 <sup>c</sup>
3			3	87	14			3	92
4			3	93	15			24	8
5			2	97	16			3	90
6			2	90	17			3	71
7			4	89	18			2	80
8			4	86	19			24	51 <sup>b</sup>
9			24	89 <sup>b</sup>	20			24	15 <sup>d</sup>
10			24	87 <sup>b</sup>	21			24	7 <sup>d</sup>
11			24	85 <sup>b</sup>					

Reaction conditions: CuI (5%) and BPMEN (5%) in 1 mL of solvent were stirred for 30 min at room temperature in Ar; benzyl alcohol (0.5 mmol) and 4-OH-TEMPO (5%) were added, and the mixture was stirred for a certain time in air at room temperature.

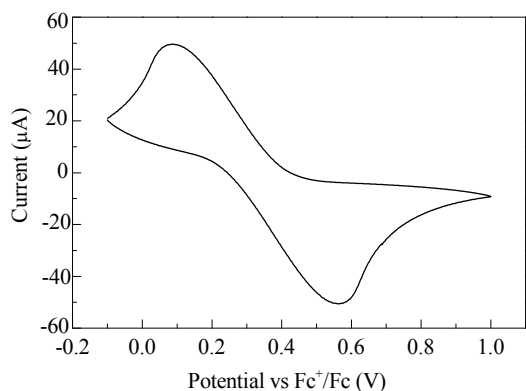
<sup>a</sup> Isolated yield. <sup>b</sup> Reaction conditions: 25 °C with oxygen balloon. <sup>c</sup> Determined by GC. <sup>d</sup> Reaction conditions: 50 °C with oxygen balloon.

cohol and 1-phenylethanol (0.5 mmol each) as intermolecular oxidation substrates for the reaction under the optimized reaction conditions. The benzyl alcohol was completely transformed to benzaldehyde and 1-phenylethanol was recovered completely after 0.5 h. These results clearly demonstrate the excellent chemoselectivity of the Cu(BPMEN)I/TEMPO system in the aerobic oxidation of alcohols, providing considerable potential advantages in synthetic organic chemistry.

Semmelhack et al. [19] proposed that an oxoammonium species was involved in CuCl/TEMPO-catalyzed aerobic alcohol oxidation with DMF as the solvent, and oxoammonium involvement in alcohol oxidation is well known in many catalyst systems [37–39]. Based on kinetic experiments, Stahl et al. [21–25] showed that TEMPO<sup>+</sup> is not the active oxidant in the CuI(bpy)/TEMPO catalyst system. Their electrochemical studies also indicated that copper(II) cannot oxidize TEMPO to TEMPO<sup>+</sup> under their reaction conditions. Based on the similarity to Stahl's system [21–25], electrochemical experiments were performed on a CH<sub>3</sub>CN solution of CuI, BPMEN, and 4-OH-TEMPO (each 0.06 mmol) after stirring at room temperature for 5 min in Ar atmosphere. The cyclic voltammogram of our developed system shows reversible redox potentials at 0.35 and -0.09 V (vs Fc<sup>+</sup>/Fc), corresponding to 4-OH-TEMPO<sup>+</sup>/4-OH-TEMPO and Cu<sup>II</sup>/Cu<sup>I</sup>, respectively (Fig. 1). In the case of 4-OH-TEMPO<sup>+</sup>/4-OH-TEMPO, the one-electron reduction potential is approximately equal to that observed with a solution



**Fig. 1.** Cyclic voltammogram of Cu(BPMEN)I/4-OH-TEMPO in CH<sub>3</sub>CN under Ar. Conditions: 0.6 mmol CuI, 0.6 mmol BPMEN, 0.6 mmol TEMPO, 300 mg LiClO<sub>4</sub>, scan rate 100 mV/s.

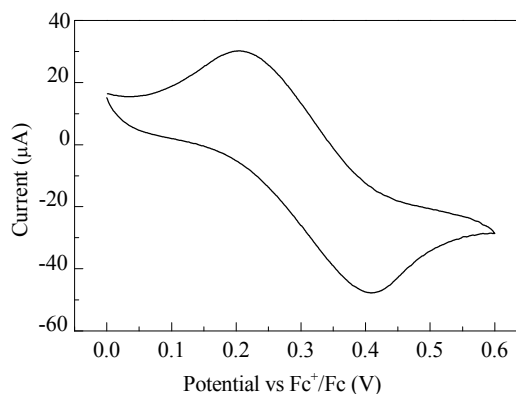


**Fig. 2.** Cyclic voltammogram of 4-OH-TEMPO under Ar.

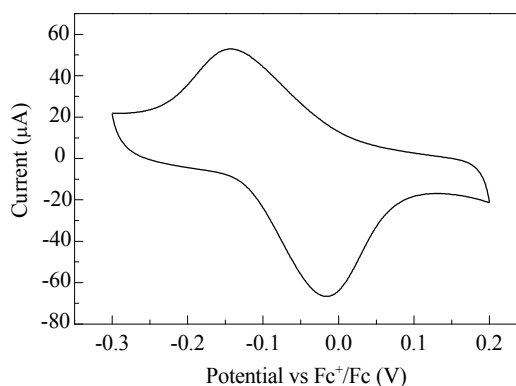
containing only 4-OH-TEMPO (Fig. 2). However, the one-electron reduction potential shifts from 0.3 to -0.09 V (vs Fc<sup>+</sup>/Fc) in the presence of BPMEN (Figs. 3 and 4). This indicates that the BPMEN ligand coordinated with CuI, leading to an increase in the overall electron density of the metal ion, resulting in a large negative shift in the reduction potential. This finding is in good accord with Stahl's system [21]. Copper(II) cannot oxidize 4-OH-TEMPO to 4-OH-TEMPO<sup>+</sup> in our catalyst system.

Electron-spray ionization (ESI)-MS is an effective method for the characterization of reaction mechanisms [40]. An equimolar mixture of CuI and BPMEN was stirred for 30 min, and a major peak appeared at  $M_r/z = 333.1121$ ; it was assigned to [Cu(BPMEN)]<sup>+</sup> (calculated:  $M_r/z = 333.1135$ ). The formation of the Cu(BPMEN)I complex was also confirmed by elemental analysis. Then 4-OH-TEMPO was added to a copper complex generated from CuI and BPMEN and exposed to air or Ar. The peak corresponding to 4-OH-TEMPO ([M + Na]<sup>+</sup>  $M_r/z = 195.1227$ ) was not detected when the system was exposed to air, but the 4-OH-TEMPO peak was clearly observed under Ar. These results indicate that the transformation of 4-OH-TEMPO must be assisted by both the Cu(BPMEN)I complex and oxygen.

UV-visible spectroscopy was also performed to obtain an insight into the mechanism. An equimolar mixture of CuI and BPMEN (5 mmol/L in CH<sub>3</sub>CN) was stirred in Ar atmosphere for 30 min; the maximum absorption was located at 705 nm (Cu(BPMEN)I complex); the maximum absorption of 4-OH-TEMPO (5 mmol/L in CH<sub>3</sub>CN) added to the above mixture in air was 810 nm (Fig. 5). When oxidation took place after the



**Fig. 3.** Cyclic voltammogram of CuI under Ar.



**Fig. 4.** Cyclic voltammogram of CuI + BPMEN (1:1) under Ar.

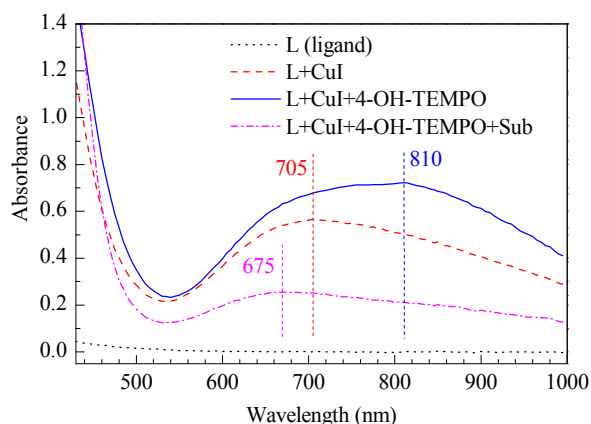


Fig. 5. UV-vis spectra in  $\text{CH}_3\text{CN}$ . Conditions: 5 mmol/L BPMEN, 5 mmol/L CuI, 5 mmol/L 4-OH-TEMPO in  $\text{CH}_3\text{CN}$ .

addition of benzyl alcohol, the intensity of the absorption peak at 810 nm gradually decreased, and a new shoulder appeared at 675 nm as the reaction proceeded. This indicates that the species causing the absorption at 810 nm may be the real intermediate responsible for the oxidation of alcohols.

#### 4. Conclusions

We developed an easily obtained and efficient catalyst system consisting of CuI, BPMEN, and 4-OH-TEMPO for aerobic oxidation of primary alcohols under mild conditions. In all cases, primary benzyl and allylic alcohols were selectively oxidized to the corresponding aldehydes, and no over-oxidized products such as carboxylic acids were observed. The catalyst system exhibited excellent chemoselectivity for the oxidation of primary alcohols. Electrochemical experiments further revealed that copper(II) was not able to oxidize 4-OH-TEMPO to 4-OH-TEMPO<sup>+</sup>. HRMS confirmed that the transformation of 4-OH-TEMPO must be assisted by both the Cu(BPMEN)I complex and air. The UV-visible spectra clearly indicated that a new species was formed in the presence of the Cu(BPMEN)I complex and 4-OH-TEMPO in air, which showed good reactivity in alcohol oxidation. More investigations of the proposed mechanism and

application of the Cu(BPMEN)I/4-OH-TEMPO catalyst system to oxidation reactions are underway in our laboratory.

#### References

- [1] de Montellano P R O. *Cytochrome P450: Structure, Mechanism, and Biochemistry*. 2nd Ed. New York: Plenum Press, 1995
- [2] Turlington C R, White P S, Brookhat M, Templeton J L. *J Am Chem Soc*, 2014, 136: 3981
- [3] Jacobsen E N. In: Abel E W, Stone F G A, Wilkinson G Eds. *Comprehensive Organometallic Chemistry II*. Oxford (UK): Pergamon, 1995
- [4] McDonald A R, Que L Jr. *Coord Chem Rev*, 2013, 257: 414
- [5] White M C, Doyle A G, Jacobsen E N. *J Am Chem Soc*, 2001, 123: 7194
- [6] Prat I, Font D, Company A, Junge K, Ribas X, Beller M, Costas M. *Adv Syn Catal*, 2013, 355: 947
- [7] Chen M S, White M C. *Science*, 2007, 318: 783
- [8] Wu M, Wang B, Wang S F, Xia C G, Sun W. *Org Lett*, 2009, 11: 3622
- [9] Wang B, Miao C X, Wang S F, Xia C G, Sun W. *Chem Eur J*, 2012, 18: 6750
- [10] Wang B, Wang S F, Xia C G, Sun W. *Chem Eur J*, 2012, 18: 7332
- [11] Sheldon R A, Arends I W C E, ten Brink G J, Dijkman A. *Acc Chem Res*, 2002, 35: 774
- [12] Zhang H, Fu L L, Zhong H M. *Chin J Catal*, 2013, 34: 1848
- [13] Wang L Y, Li J, Lv Y, Zhao G D, Gao S. *Appl Organomet Chem*, 2012, 26: 37
- [14] Fritz-Langhals E. *Org Process Res Dev*, 2005, 9: 577
- [15] Mu R Z, Liu Z Q, Yang Z J, Liu Z G, Wu L M, Liu Z L. *Adv Synth Catal*, 2005, 347: 1333
- [16] Yu Y L, Gao B J, Li Y F. *Chin J Catal*, 2013, 34: 1776
- [17] Vogler T, Studer A. *Synthesis*, 2008: 1979
- [18] Sasano Y, Nagasawa S, Yamazaki M, Shibuya M, Park J, Iwabuchi Y. *Angew Chem Int Ed*, 2014, 53: 3236
- [19] Semmelhack M F, Schmid C R, Cortes D A, Chou C S. *J Am Chem Soc*, 1984, 106: 3374
- [20] Markó I E, Giles P R, Tsukazaki M, Chellé-Regnaut I, Gautier A, Brown S M, Urch C J. *J Org Chem*, 1999, 64: 2433
- [21] Hoover J M, Stahl S S. *J Am Chem Soc*, 2011, 133: 16901
- [22] Greene J F, Hoover J M, Mannel D S, Root T W, Stahl S S. *Org Process Res Dev*, 2013, 17: 1247
- [23] Steves J E, Stahl S S. *J Am Chem Soc*, 2013, 135: 15742
- [24] Hoover J M, Ryland B L, Stahl S S. *ACS Catal*, 2013, 3: 2599

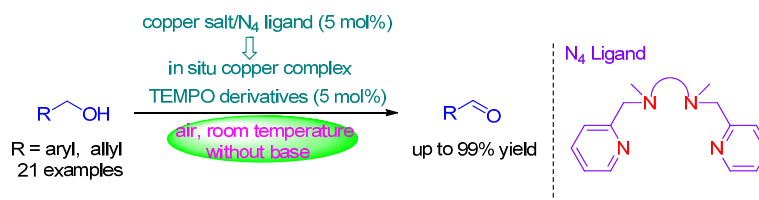
#### Graphical Abstract

*Chin. J. Catal.*, 2014, 35: 1864–1873 doi: 10.1016/S1872-2067(14)60161-3

#### CuI/*N*<sub>4</sub> ligand/TEMPO derivatives: A mild and highly efficient system for aerobic oxidation of primary alcohols

Shufang Zhang, Chengxia Miao\*, Daqian Xu, Wei Sun\*, Chungu Xia

Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences; University of Chinese Academy of Sciences



A copper(I) complex generated in situ from *N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)ethane-1,2-diamine (a tetradentate nitrogen) ligand and CuI in combination with 4-OH-TEMPO catalyzed the aerobic oxidation of primary benzyl and allyl alcohols at room temperature.

- [25] Hoover J M, Ryland B L, Stahl S S. *J Am Chem Soc*, 2013, 135: 2357
- [26] Mannam S, Alamsetti S K, Sekar G. *Adv Synth Catal*, 2007, 349: 2253
- [27] Jiang N, Ragauskas A J. *ChemSusChem*, 2008, 1: 823
- [28] Lu Z L, Costa J S, Roubeau O, Mutikainen I, Turpeinen U, Teat S J, Gamez P, Reedijk J. *Dalton Trans*, 2008: 3567
- [29] Velusamy S, Punniyamurthy T. *Eur J Org Chem*, 2003: 3913
- [30] Contel M, Izuel C, Laguna M, Villuendas P R, Alonso P J, Fish R H. *Chem Eur J*, 2003, 9: 4168
- [31] Miao C X, Wang J Q, Yu B, Cheng W G, Sun J, Chanfreau S, He L N, Zhang S J. *Chem Commun*, 2011, 47: 2697
- [32] Miao C X, He L N, Wang J L, Wu F. *J Org Chem*, 2010, 75: 257
- [33] Miao C X, He L N, Wang J Q, Gao J. *Synlett*, 2009: 3291
- [34] Miao C X, He L N, Wang J Q, Wang J L. *Adv Synth Catal*, 2009, 351: 2209
- [35] Karmakar T K, Aromi G, Ghosh B K, Usman A, Fun H K, Mallah T, Behrens U, Solans X, Chandra S K. *J Mater Chem*, 2006, 16: 278
- [36] Yu S J, Miao C X, Wang D Q, Wang S F, Xia C G, Sun W. *J Mol Catal A*, 2012, 353-354: 185
- [37] Semmelhack M F, Chou C S, Cortés D A. *J Am Chem Soc*, 1983, 105: 4492
- [38] Wang X L, Liu R H, Jin Y, Liang X M. *Chem Eur J*, 2008, 14: 2679
- [39] Liu R H, Liang X M, Dong C Y, Hu X Q. *J Am Chem Soc*, 2004, 126: 4112
- [40] Cole R B. *Electrospray Ionization Mass Spectrometry: Fundamentals, Instrumentation, and Applications*. New York: Wiley, 1997

*Page numbers refer to the contents in the print version, which include both the English and Chinese versions of the paper. The online version only has the English version. The pages with the Chinese version are only available in the print version.*