Letter

N-Functionalized Amino Acids Promoted Aerobic Copper-Catalyzed Oxidation of Benzylic Alcohols in Water

779

Guofu Zhang Jie Lei Xingwang Han Yuxin Luan Chengrong Ding* Shang Shan* $\begin{array}{c} \text{copper salt, N-functionalized amino acid} \\ \hline \text{OH} \\ R^{1} \\ R^{2} \\ \hline \text{R}^{1} \\ R^{2} \\ \hline \text{H}_{2}\text{O, air, reflux} \\ \hline \text{H}_{2}\text{O, air, reflux} \\ \hline \text{H}_{2}\text{O, air, reflux} \\ \hline \text{R}^{1} \\ R^{1} = \text{aryl, thienyl, pyridyl, furyl, allylic} \\ R^{1} = \text{aryl, thienyl, furyl} \\ R^{2} \\ R^{2}$

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Abstract Instead of traditional N,N-bidentate ligands, N-functionlized amino acids were used as powerful N,O-bidentate ligands in aerobic copper/TEMPO-catalyzed system for promoting oxidation of benzylic alcohols. Under the optimized reaction conditions, a wide range of primary and secondary benzylic alcohols have been efficiently converted into aldehydes and ketones with good to excellent yields in water.

Key words N,O-bidentate ligand, N-functionalized amino acid, copper, alcohol oxidation, benzylic alcohol, water

Transition-metal-catalyzed selective aerobic alcohol oxidation is an important chemical transformation in organic synthesis.¹ Traditionally, the alcohol oxidations were performed with stoichiometric oxidants such as CrO_3 , SeO_2 , and KMnO₄,² which were usually hazardous or toxic and generated large quantities of noxious byproducts. In contrast, the oxidation systems, utilizing transition metal as catalyst and O_2 (or air) as terminal oxidant, have significant benefits from both economic and environmental viewpoints. Accordingly, various catalysts derived from precious metals have been developed, including platinum,³ ruthenium,⁴ palladium,⁵ gold,⁶ and iridium.⁷ However, considering the rarity and high cost of noble metals, it would be more desirable to develop non-noble-metal catalysts to promote alcohol oxidation, such as copper, which is an earth-abundant and commercially available metal. Moreover, compared with precious transition metals, copper catalysts not only show similar excellent activity for the oxidation of a broad range of alcohols, but also overcome the deactivation problems arose from the coordination between metal catalysts and heteroatoms in tested substrates.

During the past decades, copper-catalyzed aerobic alcohol oxidation have been widely reported.⁸ Particularly, N,Nbidentate ligands such as 1,10-phenanthroline (phen), 2,2'bipyridine (bipy) and their derivatives were widely used in these oxidation systems. For instance, Markó et al. first reported an efficient CuCl/phen catalytic system for the oxidation of primary and secondary alcohols in toluene.⁹ Sheldon and co-workers developed a CuBr₂/TEMPO/bipy (TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl) system, which provided aldehydes from primary benzylic alcohols in mixed solution.¹⁰ Later on, Stahl and co-workers investigated Cu(I)/bipy catalytic system, and various alcohols were oxidized into desired carbonyl compounds in acetonitrile or acetone.¹¹

Compared with traditional N,N-bidentate ligands, N,Obidentate ligands have been seldom developed to promote the aerobic alcohols oxidation.¹² During the past decades, amino acid as an efficient N,O-bidentate ligand has been widely applied in many fields because of its facile structure modification and commercial availability.^{13–15} Recently, we reported the discovery that L-proline could be used as an excellent N,O-bidentate ligands to accelerate selective alcohol oxidation under air.¹⁶ But these catalytic systems show low activity for benzylic alcohols in water. From an economic and environmental viewpoint, aqueous reaction media has continued to gain much interest in recent years.¹⁷ Because water-medium reaction could be regarded as one important complement of organic synthesis in volatile solvents. Therefore, in this communication, we wish to develop the application of N-functionalized amino acids as powerful ligands in aerobic copper/TEMPO-catalyzed aqueous oxidation systems to promote benzylic alcohols, particularly for secondary alcohols. To the best of our knowledge, aqueous oxidation systems for secondary alcohols are still a challenge.18

Syn<mark>lett</mark>

G. Zhang et al.

Initially, p-tolylmethanol was selected as the model substrate to obtain the best reaction conditions of benzylic alcohol oxidation in neat water. From the results summerized in Table 1. only 46% conversion of the substrate was obtained when the oxidation was catalyzed by CuCl/TEMPO with L-proline as the ligand under air (Table 1, entry 1). And some commercially available mono N-Ac-protected amino acid ligands showed poorer activity within half an hour (Table 1, entries 2-5). But N-phenylglycine exhibited great prospects by providing the desired aldehyde in 97% conversion (Table 1, entry 6). Whilst employing some other Nphenylated amino acids as the ligand in the oxidation system did not yet provide comparable results with N-phenylglycine (Table 1, entries 7–11). Hence, N-phenylglycine was selected as the best ligand. And the effect of copper salt on the transformation was then examined (Table 1, entries 6 and 12–19). It was found that copper(I) salts such as CuBr and CuI displayed moderate catalytic activity with 82% and 87% conversion of substrate (Table 1, entries 12 and 13). Gratifyingly, an approximately quantitative conversion was obtained when the reaction was catalyzed by CuBr₂ (Table 1, entry 14),¹⁹ but other copper(II) salts could only offer lower conversions (Table 1, entries 15-19). Subsequently, the screen of different bases showed that Na₂CO₃ was the best base, the others were found to dramatically decrease the conversion (Table 1, entries 14 and 20-28). Finally, the control experiments showed that CuBr₂, N-phenylglycine, and TEMPO are essential for the alcohol oxidation system. When CuBr₂, *N*-phenylglycine, or TEMPO was omitted, only 7%. 10%. and trace *p*-tolymethanol were transformed into *p*tolualdehyde (Table 1, entries 29-31). Hence, the optimized reaction conditions were obtained (Table 1, entry 14): alcohol (1.0 mmol), CuBr₂ (5 mol%), N-phenylglycine (5 mol%), TEMPO (5 mol%), Na₂CO₃ (1.0 mmol), H₂O (3.0 mL), in air under reflux.



780

Entry	Copper salt	Ligand	Base	Conv. (%) ^b
1	CuCl	Α	Na ₂ CO ₃	46
2	CuCl	В	Na ₂ CO ₃	19
3	CuCl	c	Na ₂ CO ₃	15
4	CuCl	D	Na ₂ CO ₃	17
5	CuCl	E	Na ₂ CO ₃	18
6	CuCl	F	Na ₂ CO ₃	97
7	CuCl	G	Na ₂ CO ₃	89
8	CuCl	н	Na ₂ CO ₃	60
9	CuCl	I	Na ₂ CO ₃	55
10	CuCl	J	Na ₂ CO ₃	48
11	CuCl	К	Na ₂ CO ₃	74
12	CuBr	F	Na ₂ CO ₃	82

Syn lett

G. Zhang et al.

Letter

Table 1	(continued)
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Entry	Copper salt	Ligand	Base	Conv. (%) ^b	
13	Cul	F	Na ₂ CO ₃	87	
14	CuBr ₂	F	Na ₂ CO ₃	>99 (90) ^f	
15	Cu(OAc) ₂	F	Na ₂ CO ₃	40	
16	CuSO ₄	F	Na ₂ CO ₃	53	
17	Cu(OTf) ₂	F	Na ₂ CO ₃	58	
18	CuCl ₂	F	Na ₂ CO ₃	60	
19	Cu(NO ₃) ₂	F	Na ₂ CO ₃	57	
20	CuBr ₂	F	K ₃ PO ₄	23	
21	CuBr ₂	F	NaOH	15	
22	CuBr ₂	F	NaHCO ₃	36	
23	CuBr ₂	F	KOt-Bu	15	
24	CuBr ₂	F	КОАс	78	
25	CuBr ₂	F	K ₂ CO ₃	49	
26	CuBr ₂	F	CsOAc	69	
27	CuBr ₂	F	CF ₃ COONa	55	
28	CuBr ₂	F	NaOAc	66	
29 ^c	-	F	Na ₂ CO ₃	7	
30 ^d	CuBr ₂	-	Na ₂ CO ₃	10	
31 ^e	CuBr ₂	F	Na ₂ CO ₃	trace	

^a Reaction conditions: *p*-tolymethanol (1.0 mmol), copper salt (5 mol%), ligand (5 mol%), TEMPO (5 mol%), base (1.0 equiv), H₂O (3.0 mL), in air under reflux, 0.5 h.

^b Determined by GC–MS.

^c Copper salt was omitted.

^d The reaction was carried out in the absence of ligand.

^e No TEMPO was used.

^f Isolated yields.

Having gained the optimized reaction conditions, we next evaluated the substrate scope of the catalytic system and representative results are summarized in Scheme 1. Generally, various primary alcohols were efficiently oxidized into the corresponding aldehydes. Notably, the formation of overoxidized products was not detected in all cases. A variety of aromatic primary alcohols bearing electron-donating groups, such as methyl and methoxy, all participated in catalytic oxidations smoothly and yielded the corresponding aldehydes in good yields under standard reaction conditions (1-8). Notably, the efficient transformations of *p*-methylthiobenzyl alcohol into the desired aldehyde were observed without transformation to sulfoxide or sulfone (9). Moreover, electron-deficient substrates, including halogen, nitro, and cyano substrates, exhibited good activity with almost quantitative conversions in two or three hours (10-17). Notably, sterically hindered alcohols bearing an electron-withdrawing group were also converted into the desired aldehydes with high yields and selectivities, demonstrating the broad substrate scope of the oxidation approach (18–22).

Notably, heteroatoms also seem to be well tolerated, 2thienyl, 2-furyl, 5-Me-2-furyl, and 3-pyridyl methanol were conveniently transformed into the desired carbonyl compounds under the standardized conditions and 91%, 89%, 82%, and 80% yields were obtained, respectively (**23–26**). Gratifyingly, when the catalytic oxidation was examined using aliphatic alcohols as substrates such as cinnamyl alcohol, the allylic alcohols were excellent substrates giving the corresponding aldehydes in 90% isolate yields (**27**). Unfortunately, phenethyl alcohol was essentially unreactive under these conditions (**28**).

Subsequently, 1-phenylethyl alcohol, a secondary benzylic alcohol, was applied to the aforementioned oxidation conditions used for primary alcohols; only 53% conversion was observed. To our delight, by rescreening different ligands, copper salts and bases, the optimal reaction conditions for the secondary alcohol oxidation was obtained: secondary benzylic alcohol (1.0 mmol), CuBr₂ (10 mol%), Nphenylphenylalanine (10 mol%), TEMPO (10 mol%), NaOAc (2.0 mmol), H₂O (3.0 mL), in air, reflux (Table S1 in Supporting Information).²⁰ After the optimized reaction conditions



Scheme 1 Aerobic alcohol oxidation of primary alcohols to aldehydes. *Reagents and conditions*: substrate (1.0 mmol), CuBr₂ (5 mol%), N-phenylglycine (5 mol%), TEMPO (5 mol%), Na₂CO₃ (1.0 mmol), H₂O (3.0 mL), in air, under reflux, determined by GC–MS and isolated yields in parentheses. ^a With 2.0 mmol Na₂CO₃. ^b With 10 mol% each of CuBr₂, *N*-phenylglycine, and TEMPO.

were obtained, a wide range of secondary benzylic alcohols were subjected to the oxidation system and representative results are presented in Scheme 2. The transformation of alcohols with electron-rich groups at the aromatic rings were carried out efficiently in almost quantitative conversion in neat water (**29–37**). Secondary alcohols with electron-deficient substituents, such as halogen and nitro, were suitable substrates as well, giving the desired products in excellent conversions in 12 or 16 hours (**38–43**). Satisfactory conversions were also gained for substrates with S/O-containing heterocycle alcohols, as shown in the oxidations of 1-(2thienyl)ethanol and 1-(2-furyl)ethanol with air as the terminal oxidant (**44** and **45**). As already noted, 1-phenylpropan-1-ol derivatives are less reactive than primary benzylic substrates. In other aqueous catalytic systems, oxidation of 1-phenylpropan-1ol derivatives to their corresponding ketones is still a challenge. To our delight, after rescreening the reaction conditions, the derivatives of propiophenone were obtained with high yields in our oxidation system (**46–48**)

In summary, an efficient Cu/TEMPO/N-functionalized amino acid catalyzed aerobic alcohol oxidation system for primary and secondary benzylic alcohol in neat water has been developed. Under the optimized reaction conditions, a wide range of benzylic alcohols were successfully converted into the corresponding aldehydes or ketones in good to excellent yields.

782

Synlett G. Zhang et al.



783

Scheme 2 Aerobic alcohol oxidation of secondary benzylic alcohols to ketones. *Reagents and conditions*: substrate (1.0 mmol), CuBr₂ (10 mol%), N-phenylphenylalanine (10 mol%), TEMPO (10 mol%), NaOAc (2.0 mmol), H₂O (3.0 mL), in air, under reflux, determined by GC–MS and isolated yields in parentheses. ^a With 15 mol% each of CuBr, N-phenylphenylalanine, and TEMPO.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380126.

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G. Zhang et al.

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- (19) General Procedures for the Copper-Catalyzed Primary Benzylic Alcohol Oxidation under Air in Water (*p*-Methylbenzyl Alcohol)

A mixture of *p*-methylbenzyl alcohol (1.0 mmol), *N*-phenylglycine (0.0076 g, 0.05 mmol), CuBr₂ (0.0112 g, 0.05 mmol), Na₂CO₃ (0.1060 g, 1.0 mmol), TEMPO (0.0078 g, 0.05 mmol), H₂O (3.0 mL) were added to a 100 mL Schlenk tube, which was vigorously stirred in air under reflux for 0.5 h. After the reaction, the product was extracted with CH₂Cl₂ (3 × 2.0 mL). The combined organic phase was washed with H₂O (3.0 mL) and dried over anhydrous MgSO₄. After concentration under vacuum, the residue was purified by column chromatography to afford *p*-methylbenzaldehyde.Isolated yield: 0.1080 g (90%). ¹H NMR (500 MHz, CDCl₃): δ = 2.38(s, 3 H), 7.27 (d, *J* = 4.3 Hz, 2 H), 7.73 (d, *J* = 4.0 Hz, 2 H), 9.91 (s, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 21.5, 129.4, 129.5, 134.0, 145.2, 191.6.

(20) General Procedures for Copper-Catalyzed Secondary Alcohol Oxidation under Reflux in Neat Water (1-Phenethyl Alcohol) A mixture of 1-phenethyl alcohol (1.0 mmol), *N*-(phenyl)phenylalanine (0.0241 g, 0.1 mmol), CuBr₂ (0.0223 g, 0.1 mmol), NaOAc (0.1640 g, 2.0 mmol), TEMPO (0.0156 g, 0.1 mmol), and H₂O (3.0 mL) were placed into a 100 mL Schlenk tube, which was vigorously stirred in air under reflux for 12 h. After the reaction, the product was extracted with CH₂Cl₂ (3 × 2.0 mL). The combined organic phase was washed with H₂O (3.0 mL) and dried over anhydrous MgSO₄. After concentration under vacuum, the residue was purified by column chromatography to afford acetophenone.Isolated yield: 0.1080 g (90%). ¹H NMR (500 MHz, CDCl₃): δ = 2.52 (s, 3 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.51 (t, *J* = 7.0 Hz, 1 H), 7.91 (d, *J* = 4.3 Hz, 2 H).¹³C NMR (125 MHz, CDCl₃): δ = 26.5, 128.2, 128.5, 133.0, 137.1, 198.1. Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.