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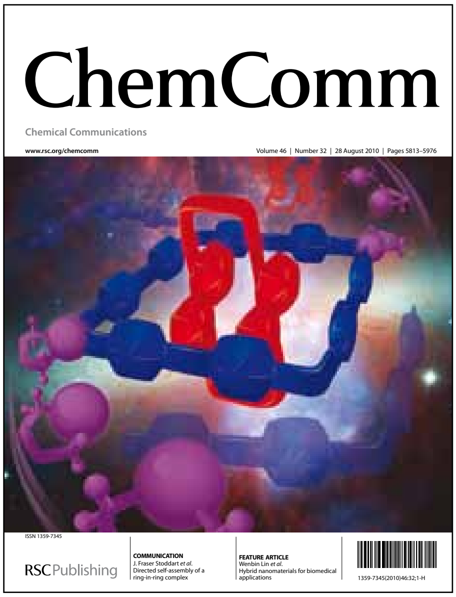

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ARTICLE TYPE

L-Proline: an efficient N,O-bidentate ligand for copper-catalyzed aerobic oxidation of primary and secondary benzylic alcohols at room temperature

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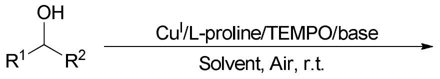
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A novel and highly practical copper-catalyzed aerobic alcohol oxidation system with L-proline as the ligand at room temperature has been developed. A wide range of primary and secondary benzylic alcohols tested have been smoothly transferred into corresponding aldehydes and ketones with high yields and selectivities.

The selective alcohol oxidation to aldehyde or ketone with oxygen as the terminal oxidant is a pivotal reaction in organic synthesis.[1] However, the direct utilization of oxygen for oxidative reactions is always unpromising and should be assisted by transition metal catalysts.[2] During the past decades, such noble metals as Pd,[3] Au,[4] etc., or their corresponding metal complexes have been well applied in aerobic alcohol oxidation subsequently. While, considering their rarity and price, those noble catalysts turn out to be impractical in large-scale industrial applications. Compared with these transition metals, copper is an inexpensive, earth-abundant metal and its widespread applications in organic synthesis have been impressively demonstrated in recent publications.[5] In many catalytic systems, copper catalysts not only show similar excellent activity for the oxidation of a wide range of alcohols, but can also overcome the deactivation problems caused by the coordination between metal catalysts and heteroatoms in tested substrates.[6]

During the past years, many copper-catalyzed systems have been reported and shown efficient catalytic activity for primary alcohols.[7] Yet their ability for secondary alcohol oxidation was usually unsatisfying to our knowledge. And only a few examples have been reported to facilitate the aerobic oxidation of secondary alcohols.[8] For instance, Markó and co-workers[9a] employed 1,10-phenanthroline as ligand in CuCl/DBADH$_2$/O$_2$-catalyzed system, in which second alcohols were smoothly oxidized into desired ketones in toluene. Another copper-catalyzed secondary alcohol oxidation was rendered by Knochel and co-workers,[8b] which contained a fluoroalkyl-substituted bipyridyl ligand with CuBr·Me$_2$S as catalyst in a fluorous biphasic condition (C$_8$F$_{17}$Br/PhCl) at 90 °C. It was found that the rendered ligands in copper-catalyzed alcohol oxidations by far are confined to N,N-bidentate ligands such as bipyridyl, 1,10-phenanthroline, 1,4-diazabicyclo[2.2.2]octane, etc.[9] While the progress in the design of N,O-dentate ligands for copper-catalyzed alcohol oxidation under air or oxygen condition is sluggish, although Punniyamurthy's group reported a salen analogue N,O-ligand to achieve the efficient primary alcohol oxidation to corresponding aldehydes under oxygen condition.[10] Therefore, the application of N,O-dentate ligand for secondary alcohols oxidation with air or oxygen as oxidant under mild conditions is still a challenge. In this paper, we wish to render a commercially available and inexpensive N,O-didentate ligand L-proline[11] and its high efficient performance in copper-catalyzed aerobic oxidation of alcohols under mild conditions, particularly for secondary alcohols (eq. 1).



(eq.1)

Initially, 1-phenethyl alcohol was selected as the model substrate to gain the optimal conditions. First, solvent effect on this oxidative transformation was examined (Table 1, entries 1-6). Trace conversion of acetophenone was obtained, when the reaction was performed in CH$_3$OH or C$_2$H$_5$OH with 5 mol% CuCl, 5 mol% L-proline in the presence of 1.0 equiv. ^{t}BuOK under air at room temperature (entries 1-2). While the employment of CH$_3$CN, CH$_2$Cl$_2$ or toluene led to moderate conversions of the substrate (entries 3-5). Intriguingly, when switching the solvent to DMF, the conversion reached to 94% (entry 6). Subsequently, different copper salts were further screened (entries 7-12). It was found that Cu^{I} salts exhibited higher catalytic reactivity than Cu^{II} salts in this catalytic system. As showed in Table 1, CuCl$_2$, CuBr$_2$, CuSO$_4$ and Cu(OAc)$_2$ led to the oxidative reaction with only 68%, 78%, 73% and 79% substrate conversions respectively after 5 h (Table 1, entries 7-8, 10-11). And CuI turned out to be the most effective catalyst precursor compared with other Cu^{I} salts tested, offering almost quantitative conversion of 1-phenethyl alcohol to acetophenone was observed in 5 h (entries 6, 9, 12). Furthermore, some other N,O-bidentate ligands were also tested (entries 13-16). Compared with other ligands, L-proline is the ideal one. Finally, controlled experiments showed that the starting material gave low conversion in the absence of CuI or TEMPO, and a drastic decrease in conversion was observed when L-proline or base was omitted (entries 17-20). Thus, we obtained the optimized reaction conditions (entry 12): alcohol (1.0 mmol), TEMPO (5 mol%), ^{t}BuOK (1.0 equiv) under air at room temperature with CuI (5 mol%) as catalyst and L-proline as ligand (5 mol%).

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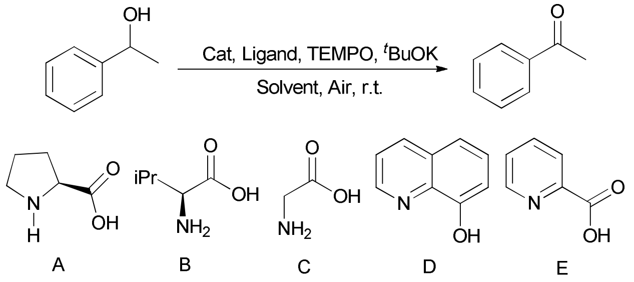
Table 1 The optimization of copper-catalyzed alcohol oxidation[a]



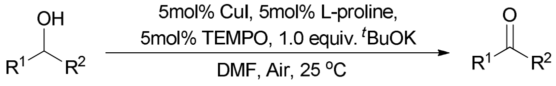
Entry	Solvent	Cat.	Ligand	Conv.(%)[b]
1	CH_3OH	CuCl	A	trace
2	C_2H_5OH	CuCl	A	trace
3	CH_3CN	CuCl	A	56
4	CH_2Cl_2	CuCl	A	69
5	toluene	CuCl	A	63
6	DMF	CuCl	A	94
7	DMF	$CuCl_2$	A	68
8	DMF	$CuBr_2$	A	78
9	DMF	CuBr	A	98
10	DMF	$CuSO_4$	A	73
11	DMF	$Cu(OAc)_2$	A	79
12	**DMF**	**CuI**	**A**	**>99**
13	DMF	CuI	B	30
14	DMF	CuI	C	36
15	DMF	CuI	D	56
16	DMF	CuI	E	95
17[c]	DMF	-	A	12
18[d]	DMF	CuI	A	10
19[e]	DMF	CuI	-	8
20[f]	DMF	CuI	A	5

[a] Reaction condition: 1-phenethyl alcohol (1.0 mmol), copper salt (5 mol%), TEMPO (5 mol%), tBuOK (1.0 mmol), L-proline (5 mol%), Solvent (4.0 mL), 5 h, 900r/min. [b] Determined by GC-MS. [c] Copper salt was omitted. [d] The reaction was carried out in the absence of TEMPO. [e] No L-proline was employed. [f] Base was omitted.

Having obtained the optimized conditions (Table 1, entry 12), we turned our attention to examine the substrate scope of this method. As shown in Table 2, various secondary alcohols were successfully oxidized into corresponding ketones. Aromatic secondary alcohols bearing electron-donating groups such as methyl or methoxy at the aromatic ring proceeded smoothly and yielded the corresponding ketones in good to excellent yields (Table 2, entries 1-7). Moreover, substrates bearing an electron-withdrawing group on the aromatic ring such as halogen, trifluoromethyl afforded the products with yields up to 89-93% yet with a prolonged time (entries 8-15). Of particular note was the effective oxidation of steric hindrance alcohols, which also provided the products in excellent yields (entries 11, 13). Gratifyingly, the novel system showed promising activity for the oxidation of heterocyclic secondary alcohols such as 1-(3-pyridyl)ethanol and 1-(2-furfuryl)ethanol (entries 16-17). While aliphatic alcohol like cyclohexyl showed lower activity even under 60 °C with 10 mol% catalyst loading (entries 18-19).

Furthermore, the extensive application of Cu/TEMPO/L-proline for primary alcohols was also tested. During the reaction conditions optimization, it was found that the Cu^I salts exhibit higher activity than Cu^{II} salts for primary alcohols as well. And the model substrate *p*-tolylmethanol could nearly completely convert to aldehyde with CuBr as copper source, Na_2CO_3 as base in methanol phase (see SI, Table S1). As shown in Table 3, a wide range of primary alcohols bearing electron-donating or electron-drawing groups were converted into their corresponding aldehydes with high yields and selectivities (Table 3, entries1-13). Notably, the efficient transformations of allylic alcohols to the desired aldehydes were observed without over-oxidation (entry 14). Even with heterocyclic alcohols, 2-thienyl, 2-furyl and 3-pyridyl methanol, the products were obtained in 90%, 87% and 92% respectively (entries 15-17). Although, the primary aliphatic alcohol displayed no acitivity under the optimized conditions (entry 18).

Table 2 Aerobic alcohol oxidation of secondary alcohols to ketones[a]

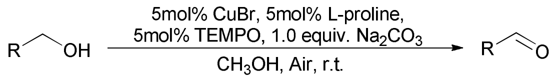


Entry	R^1	R^2	T (h)	Conv. (%)[b]	Yield (%)[c]
1	Ph	CH_3	5	>99	93
2	Ph	Ph	5	>99	94
3	Ph	COC_6H_5	5	>99	93
4	4-MeC_6H	CH_3	5	>99	94
5	4-$MeOC_6H_4$	CH_3	5	>99	94
6	3,4-$MeOC_6H_3$	CH_3	5	>99	94
7	3,4,5-$MeOC_6H_2$	CH_3	5	>99	93
8	4-FC_6H_4	CH_3	7	>99	91
9	4-ClC_6H_4	CH_3	8	>99	91
10	4-BrC_6H_4	CH_3	8	>99	93
11	2-ClC_6H_4	CH_3	6	>99	91
12	3-ClC_6H_4	CH_3	8	>99	92
13	2,4-ClC_6H_3	CH_3	8	98	90
14	3-$CF_3C_6H_4$	CH_3	10	96	89
15	4-PhC_6H_4	CH_3	6	>99	90
16	3-pyridyl	CH_3	5	98	90
17	2-furyl	CH_3	5	>99	93
18	cyclohexyl	H	12	5	-
19[d]	cyclohexyl	H	12	20	-

[a] Reaction condition: substrate (1.0 mmol), CuI (5 mol%), L-proline (5 mol%), TEMPO (5 mol%), base (1.0 mmol), DMF (4.0 mL), 900r/min. [b] Determined by GC-MS. [c] Isolated yield, [d] Under 60 °C with CuI (10 mol%), L-proline (10 mol%), TEMPO (10 mol%).

Considering the above promising results and related published researches,[12] a mechanism for the present Cu/L-proline/TEMPO-catalyzed alcohol oxidation was proposed as shown in Scheme 1. The initial step of the reaction was involved in the formation of complex A, which reacted with O_2 to afford a Cu^{II}-superoxide

Table 3 Aerobic alcohol oxidation of primary alcohols to aldehydes[a]



Entry	R	T (h)	Conv. (%)[b]	Yield (%)[c]
1	C_6H_5	5	>99	94
2	4-$CH_3C_6H_4$	5	>99	94
3	4-$CH_3OC_6H_4$	5	>99	93
4	3,4-$CH_3C_6H_3$	5	>99	94
5	2-$CH_3OC_6H_4$	5	>99	95
6	1-naphthyl	3	>99	95
7	4-$NO_2C_6H_4$	6	96	90
8	4-FC_6H_4	6	97	91
9	4-ClC_6H_4	6	98	92
10	4-BrC_6H_4	6	>99	92
11	2-ClC_6H_3	7	>99	91
12	3-ClC_6H_4	6	>99	92
13	2,4-ClC_6H_3	6	>99	92

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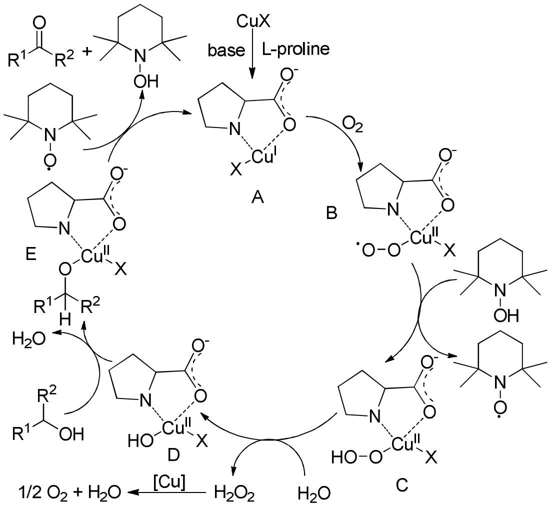
14	$C_6H_5CH{=}CH$	5	96	92
15	2-thienyl	5	96	90
16	2-furyl	5	95	87
17	3-pyridyl	5	98	92
18	n-C_7H_{15}	10	NR	-

[a]Reaction condition: substrate (1.0 mmol), CuBr (5 mol%), L-proline (5 mol%), TEMPO (5 mol%), Na_2CO_3 (1.0 mmol), CH_3OH (4.0 mL), 900r/min. [b]Determined by GC-MS. [c]Isolated yield.



Scheme 1 A plausible mechanism for the copper/L-proline/TEMPO catalyzed alcohol oxidation.

species B. Then it resembled the reactions of O_2 with biomimetic N-chelated Cu^I complexes,[13] which abstracted hydrogen radical from TEMPOH to form C. Subsequent reaction of the Cu^{II}-OOH intermediate with water released H_2O_2 and afford a Cu^{II}-OH species D. Then, the insertion of an alcohol to afford an alkoxo copper specie E (Cu^{II}-OCH_2R). β-Hydrogen elimination of the alkoxo moiety in E would occur to give a carbonyl product and TEMPOH, and regenerated A.

Conclusions

In conclusion, a novel and mild copper-catalyzed aerobic alcohol oxidation system particularly for secondary alcohols was successfully developed. Under the optimized reaction conditions, various kinds of alcohols such as primary/secondary benzyl and allylic alcohols were smoothly converted into corresponding aldehydes or ketones with high yields and selectivities. To the best of our knowledge, this is the first example of copper-catalyzed aerobic oxidations for efficient secondary alcohol oxidation using L-proline as ligand. The use of green reagents, such as air as oxidant and inexpensive L-proline as ligand, made it a convenient procedure for practical applications.

We acknowledge financial support from the National Natural Science Foundation of China (No. 20702051), the Natural Science Foundation of Zhejiang Province (LY13B020017) and the Key Innovation Team of Science and Technology in Zhejiang Province (No. 2010R50018).

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, the optimization of copper-catalyzed primary alcohol oxidation and NMR data for products. See DOI: 10.1039/b000000x/

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