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neat water by using a water-soluble ligand[†]

Copper-catalyzed aerobic alcohol oxidation under air in

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A copper-catalyzed primary benzylic and allylic alcohols oxidation system has been developed under air in neat water by use of a water-soluble ligand (pytl- β -CD). The ligand was designed and synthesized *via* a click conjunction between functionalized β -cyclodextrin (β -CD) and 2-ethinylpyridine.

Copper is an inexpensive, abundant metal and its widespread applications in organic synthesis have been impressively demonstrated in recent publications.1 Of particular interest is the development of copper-catalyzed oxidation systems with economically and environmentally benign oxidants such as oxygen, whose reduction product is water.² In fact, copper has been discovered in various metalloproteins,³ that mediate the transfer of oxygen-atom to organic substrates, which indicated its enticing potential for oxygen activation.⁴ Since the report by Semmelhack and coworkers in 1984,5 copper-catalyzed aerobic alcohol oxidations have gained enormous attention and many efforts have been made to develop efficient oxidation systems.⁶ Compared with noble metals such as Pd,⁷ Au,⁸ Ru,⁹ etc., copper catalysts not only show similar excellent activity for the oxidation of a broad range of alcohols, but can also overcome the deactivation problems caused by the coordination between metal catalysts and heteroatoms in tested substrates.^{7a} However, since copper has a lower oxidizing ability (Cu/Cu²⁺ E_{ox} = +0.34 V), ligands are usually needed to promote the efficient transformation of copper-catalyzed alcohol oxidation. Traditionally, these ligands are confined to 1,10-phenanthroline (phen), 2,2'-bipyridine (bpy) and their derivatives.¹⁰ For instance, Markó and co-workers6a employed phen as a ligand in the CuClcatalyzed system, and the alcohols were oxidized into desired carbonyl compounds in toluene. Later on, Sheldon and coworkers¹¹ developed a CuBr/TEMPO/O₂ system with bpy as the

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ligand, which provided aldehydes from primary benzylic alcohols in CH₃CN/H₂O. Another Cu/ligand/TEMPO catalytic system was rendered by Knochel and co-workers,12 which contained a fluoroalkyl-substituted bpy ligand with CuBr·Me2S as catalyst in a fluorous biphasic condition (C8F17Br/PhCl), and expressed good catalytic activity. However, these ligand-assisted oxidation methods were unavoidably performed in organic solvents or mixed solutions partially due to the hydrophobicity of these ligands. Water, a readily available and non-toxic solvent, has attracted much attention due to its features as improving reactivity and selectivity, simplifying workup procedures and so on.13 Consequently there has been a growing demand for the design of efficient ligands that could promote copper-catalyzed reactions in water. However, relevant systems are rare, for example only Timo Repo reported copper(II) diimine-based and copper(II) 2-N-arylpyrrolecarbaldimine-based catalysts for the aerobic oxidation of benzylic alcohols mediated by the 2,2,6,6-tetrame-thylpiperidine-1-oxyl (TEMPO) radical in alkaline water solution.¹⁴ Therefore, the design of novel ligands that can be used in aqueous alcohol oxidation, to facilitate the synthesis of aldehydes and ketones environmentally, remains an important pursuit from the viewpoint of sustainable chemistry.

Cyclodextrins (CDs) are cyclic oligomers of D(+)-glucopyranosyl units linked by α -1,4-glycosidic bonds. Due to their hollow truncated conical structures with a hydrophobic cavity and two hydrophilic external faces, cyclodextrins (CDs) and their derivatives have been widely applied in fields such as supramolecular, bioinorganic, pharmaceutical, material chemistry, separation sciences *etc.*¹⁵ In recent years, modified CDs have been introduced into organometallic chemistry and showed perfect activities as ligands in catalytic reactions. For example, β -cyclodextrin dimers with a linked bipyridyl, 1,10-phenanthroline-2,9-dimethyl and 2,6-dimethylpyridine groups were all reported as efficient ligands to form Cu(II)/Zn(II) complexes, which could accelerate the hydrolysis rate of several esters.¹⁶

In this context, we wish to demonstrate an efficient coppercatalyzed aerobic alcohol oxidation system in neat water assisted by a water-soluble ligand pytl- β -CD (Scheme 1). The novel ligand containing a "2,2'-bipyridine analogue" fragment (pytl- β -CD) was

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Scheme 1 Synthesis of the water-soluble ligand pytl- β -CD. Reaction conditions: (a) TsCl, NaOH, H₂O, O-5 °C, 4 h, 24.3%; (b) NaN₃, DMF, 75 °C, 4 h, 93.6%; (c) 2-ethynylpyridine, CuSO₄/NaAsc, DMSO/H₂O, r.t., 1 d, 92.1%.

designed and synthesized *via* a click reaction¹⁷ between 2-ethynylpyridine and monoazido β -CD (II). Notably, the designed ligand showed excellent water-solubility as expected.

Initially, p-tolylmethanol was selected as the model substrate to optimize the oxidation conditions, and the results are presented in Table 1. An 88% yield of the product was obtained when the oxidation was carried out with CuCl/pytl-β-CD/TEMPO/^tBuOK in water under reflux (Table 1, entry 1). Notably, neither carboxylic acid nor ester as byproduct was detected. Since the copper source has always shown a significant influence on organic transformations, different copper sources were screened. From Table 1, it was found that the oxidations proceeded smoothly as well by using other copper salts, such as CuCl₂, CuBr, CuBr₂, CuSO₄ and CuI, yet with similar or slightly lower conversions (87-96%, entries 2-6). To our delight, a nearly quantitative conversion was achieved when the reaction was catalyzed by $Cu(OAc)_2 \cdot H_2O$ (entry 7). So considering its easier accessibility and lower cost, Cu(OAc)2·H2O was chosen as the ideal catalyst. Next, we turned our attention to investigate the effect of base. Na₂CO₃ led to further improvement of the green transformation and furnished full consumption of

Table 1 The optimization of copper-catalyzed alcohol oxidation^a

OH Cat, Ligand, TEMPO, Base							
	H_2O , Air, Reflux						
Entry	Cat.	Base	$\operatorname{Conv.}(\%)^b$	Yield(%) ^c			
1	CuCl	^t BuOK	93	88			
2	CuCl ₂	^t BuOK	92	86			
3	CuBr	^t BuOK	93	87			
4	CuBr ₂	^t BuOK	92	88			
5	CuSO ₄	^t BuOK	87	81			
6	CuI	^t BuOK	96	90			
7	$Cu(OAc)_2 \cdot H_2O$	^t BuOK	98	93			
8	$Cu(OAc)_2 \cdot H_2O$	K_2CO_3	94	91			
9	$Cu(OAc)_2 \cdot H_2O$	NaHCO ₃	85	80			
10	$Cu(OAc)_2 \cdot H_2O$	K_3PO_4	86	82			
11	$Cu(OAc)_2 \cdot H_2O$	Na ₂ CO ₃	100	95			
12	$Cu(OAc)_2 \cdot H_2O$	NaOH	87	82			
13^d		Na_2CO_3	5	_			
14^e	$Cu(OAc)_2 \cdot H_2O$	Na_2CO_3	8	_			
15 ^f	$Cu(OAc)_2 \cdot H_2O$	Na_2CO_3	23	_			

^{*a*} Reaction conditions: *p*-tolylmethanol (1.0 mmol), copper salt (5 mol%), TEMPO (5 mol%), base (1.0 mmol), pytl-β-CD (5 mol%), H₂O (4.0 mL), reflux for 10 h. ^{*b*} Determined by GC. ^{*c*} Isolated yield. ^{*d*} Copper salt was omitted. ^{*e*} The reaction was carried out in the absence of TEMPO. ^{*f*} No pytl-β-CD was employed.

Table 2 Aerobic alcohol oxidation of primary alcohols to aldehydes^a

$R \xrightarrow{5 \text{ mol}\% \text{ Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}, 5 \text{ mol}\% \text{ pytl-}\beta \cdot \text{CD}}{5 \text{ mol}\% \text{ TEMPO}, 1 \text{ equiv. Na}_2\text{CO}_3} R \xrightarrow{6} 0$					
		Т	Yield	Selec.	
Entry	R	(h)	$(\%)^{D}$	(%) ^c	
1	C ₆ H ₅	10	94	>99	
2	$4-CH_3C_6H_4$	10	95	> 99	
3	$4-CH_3OC_6H_4$	10	93	> 99	
4	1-naphthyl	12	95	> 99	
5	3,4-CH ₃ C ₆ H ₃	12	95	> 99	
6	$3,4-CH_3OC_6H_3$	10	93	> 99	
7	$2-CH_3OC_6H_4$	12	91	> 99	
8	$2\text{-ClC}_6\text{H}_4$	16	92	> 99	
9	$3-ClC_6H_4$	12	93	> 99	
10	$4\text{-ClC}_6\text{H}_4$	10	93	> 99	
11	2-BrC ₆ H ₃	14	93	> 99	
12	$3-NO_2C_6H_4$	14	95	> 99	
13	$4-FC_6H_4$	12	93	> 99	
14	2,4-ClC ₆ H ₃	16	93	> 99	
15	3-pyridyl	12	95	> 99	
16	2-thienyl	12	80	> 99	
17	2-furyl	12	81	> 99	
18	C ₆ H ₅ CH=CH	10	58	63	
19	1-phenethyl alcohol	24	13	> 99	
20	<i>n</i> -octyl alcohol	24	NR		
21^d	benzyl alcohol + 1-phenethyl alcohol	24	A-B 92:0	—	
22^e	$4-CH_3C_6H_4$	15	93	> 99	

^{*a*} Reaction condition: substrate (1.0 mmol), Cu(OAc)₂·H₂O (5 mol%), pytl-β-CD (5 mol%), TEMPO (5 mol%), Na₂CO₃ (1.0 mmol), H₂O (4.0 mL), in air under reflux. ^{*b*} Determined by GC-MS. ^{*c*} Isolated yield. ^{*d*} A represents benzaldehyde, B indicates acetophenone. ^{*e*} The reaction was carried out on a 20.0 mmol-scale.

the starting material under similar conditions (entry 11). Other bases such as K_2CO_3 , NaHCO₃, K_3PO_4 and NaOH were inferior to Na₂CO₃ (entries 8–10, 12). Finally, control experiments showed that the starting material gave rare product in the absence of Cu(OAc)₂·H₂O or TEMPO, and a drastic decrease in yield was observed when pytl- β -CD was omitted (entries 13–15).

Having obtained the optimized reaction conditions: 1.0 mmol alcohol, 5 mol% TEMPO, 5 mol% ligand, 5 mol% Cu(OAc)₂·H₂O, 1.0 mmol Na₂CO₃, 4.0 mL water, reflux under air, we turned our attention to explore the substrate scope. The results are summarized in Table 2. To our delight, most tested substrates could be selectively transformed into the corresponding aldehydes with high yields and over oxidation products such as acids and esters were not observed during the reaction. Substrates containing electron-donating substituents like methyl and methoxy groups on the phenyl ring turned into the corresponding benzaldehyde in excellent yields with high selectivity (Table 2, entries 1-7). Similar results were also observed for electrondeficient benzylic alcohols yet with a prolonged reaction time (entries 8-14). It is noteworthy to mention that the oxidation protocol also allowed the smooth transformation of heterocyclic alcohols under reflux with good to excellent yields (entries 15-17). However, the aerobic oxidative transformation of secondary alcohols like 1-phenylethanol oxidation was inhibited (entry 19), which might be ascribed to the steric effect of the methyl group in



Scheme 2 Reuse of the catalyst (Cu/pytl-β-CD) for the oxidation of *p*-tolylmethanol.

the *α*-position. A typical reaction involving a mixture of p-tolylmethanol and 1-phenylethanol reconfirmed the specificity of this copper(II)/TEMPO/ligand system (entry 21). Interestingly, when the primary allyl alcohol, cinnamyl alcohol, was subjected to the present reaction condition, 35% yield of benzaldehyde (product of C=C cleavage) was detected by GC-MS (entry 18). We are excited by this rarely observed phenomenon in copper catalyzed oxidations. The related research in Cu/TEMPO catalyzed selective transformation with a C=C cleavage is now being further investigated in our lab. In addition, more efforts should also be made to design novel ligand to promote the oxidation of aliphatic alcohols such as 1-octanol(entry 20). Since the alcohol oxidation is of great importance in industrial production, the gram-scale application of this protocol was further investigated with p-tolylmethanol as a representative substrate. To our delight, the desired product was isolated in a 93% yield (entry 22). This promising result demonstrated that this method could provide a valuable and convenient protocol for practical application.

To demonstrate the additional advantage of this aqueous aerobic oxidation system, we turned our attention to the reuse of the catalyst (Cu/pytl- β -CD) in *p*-tolylmethanol oxidation. The use of this water-soluble ligand made it easy to separate the product from the system by simple extraction. After the extraction, another fresh substrate and 5 mol% TEMPO were added to the aqueous phase and stirred under the standard conditions. To our delight, the catalyst can be reused for at least six cycles without losing its activity, which is a prerequisite for its practical application (Scheme 2).

Conclusions

In conclusion, we have developed a green and efficient coppercatalyzed system for aerobic alcohol oxidation in aqueous media by using a novel water-soluble ligand. This catalytic system encompassed a broad substrate scope, oxidizing a range of primary alcohols to the corresponding carbonyl compounds both efficiently and selectively in refluxed water using air as the ultimate oxidant. The use of green reagents, such as air as oxidant and water as the solvent, made the system attractive for environmentally sustainable processes.

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