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Aerobic Oxidation of Primary Alcohols Catalyzed by Copper Salts and Catalytically Active μ-Hydroxyl-Bridged Trinuclear Copper Intermediate

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Abstract: We have developed a new protocol involving the "copper(II) chloride-cesium carbonate" system for the aerobic oxidation of primary alcohols. Cesium carbonates and the solvents such as toluene and 1,2-dichloroethane play important roles to form a catalytically active intermediate containing a μ-hydroxyl-bridged trinuclear copper moiety (complex **1**). From the X-ray crystal structure of complex **1**, an electrostatic interaction between chloride anions and cesium cations was observed, which stimulated us to understand the roles of cesium carbonate in this reaction as a base, stabilizing and "solvating" intermediates in toluene and 1,2-dichloroethane.

Keywords: aerobic oxidation; copper catalysis; intermediates; primary alcohols

Creating functional models containing similar active metal sites to metalloenzymes not only allows the biological reactivity to be deciphered but also fosters the construction of complexes with distinguished catalytic properties.[1] Copper oxidases provide elegant examples of using environmentally benign oxidants such as O_2 to perform organic transformations.[2] Inspired by the excellent performance of galactose oxidases (GOs),[3] copper catalysts supported by organic ligands have exhibited good reactivity in the aerobic oxidation of alcohols.[4] Following Markó's pioneer work[5] with the CuCl(Phen-DEADH$_2$) (Phen = 1,10-phenanthroline; DEADH$_2$ = diethylhydrazinodicarboxylate) catalytic system, Stack,[6] Wieghardt[7] and the others[8] had developed efficient copper catalysts for use in the aerobic oxidation of alcohols. In contrast to the tremendous progress on biomimetic copper catalysts supported by organic ligands, much less has been reported regarding the "ligand-free" copper-catalyzed aerobic oxidation of alcohols, which is equally important to be developed from a simple bench-top procedure and to further apply it for industrial-scale applications.[9] A good example is the "CuCl-TEMPO" system for the aerobic oxidation of alcohols developed by Semmelhack[10] and, importantly, the efficiency of this system has been demonstrated in natural product synthesis.[11] However, other than to enhance the efficiency for "ligand-free" copper catalysis, how to clarify the possible intermediates and even for their catalytic properties is another challenge for "ligand-free" catalysis.

To meet this challenge, from the view of bioinorganic chemistry, the questions such as whether active metal sites in natural metalloenzymes could be reproduced in a"ligand-free" metal catalytic system arise to understand the reaction mechanisms and further apply insights gained from metalloenzymes to organic catalysis. Indeed, although there is no ligand coordinated to the metal ion, solvents, substrates and other additives might form the primary and/or secondary coordination spheres to the metal ion. For example, Sun and co-workers isolated a oxotetracuprate $[Cu_4(\mu_4\text{-}O)Cl_{10}]^{4-}$ cluster as an active intermediate in the aerobic oxidation of 2,3,6-trimethylphenol in ionic liquid and four disordered 1-*n*-butyl-3-methyl-imidazolium cations as counterions of the tetrahedron.[12] Encouraged by this, we herein report a "$CuCl_2$ + Cs_2CO_3" protocol for the aerobic oxidation of alcohols under mild condition and found that Cs_2CO_3 and the solvents play important roles for efficient catalysis. More importantly, the structure and reactivity of a

Table 1. Optimization of reaction conditions for the aerobic oxidation of benzyl alcohol.[a]

Entry	Cat	Base	Conv. [%][b]	Yield [%][c]
1	$CuCl_2$	Cs_2CO_3	94	99
2	–	Cs_2CO_3	0	0
3	$CuCl_2$	–	0	0
4	$CuCl_2$	Cs_2CO_3	74	99
5	$CuCl_2$	Cs_2CO_3	83	99
6	CuCl	Cs_2CO_3	77	94
7	CuI	Cs_2CO_3	71	96
8	$CuSO_4$	Cs_2CO_3	23	92
9	Cu_2O	Cs_2CO_3	21	95
10	$Cu(OTf)_2$	Cs_2CO_3	49	97
11	$Cu(OAc)_2$	Cs_2CO_3	90	94
12	$Cu_2(OH)_2CO_3$	Cs_2CO_3	12	95
13	$Mn(OAc)_2$	Cs_2CO_3	79	96
14	$FeCl_3$	Cs_2CO_3	4	82
15	$CoCl_2$	Cs_2CO_3	6	95
16	$NiCl_2$	Cs_2CO_3	9	97

[a] *Reaction conditions:* benzyl alcohol (1 mmol), copper salts (0.01 mmol), base (1.2 mmol) in toluene (5 mL), the mixture was stirred in oxygen at 40 °C for 12 h.

[b] Conversions were determined by GC with chlorobenzene as internal standard.

[c] Yields were calculated based on conversions, mass balances >90%.

Table 2. Base effect of the copper(II)-catalyzed aerobic oxidation of benzyl alcohol.[a]

Entry	Cat.	Base	Conv. [%][b]	Yield [%][c]
1	$CuCl_2$	Cs_2CO_3	94	99
2	$CuCl_2$	K_2CO_3	16	92
3	$CuCl_2$	Na_2CO_3	15	92
4	$CuCl_2$	Rb_2CO_3	3	95
5	$CuCl_2$	NaOH	14	86
6	$CuCl_2$	KOH	17	94
7	$CuCl_2$	CsOH	15	99
8	$CuCl_2$	*t*-BuOK	15	93
9	$CuCl_2$	K_3PO_4	7	82
10	$CuCl_2$	DMAP	1	97
11	$CuCl_2$	$CsHCO_3$	80	88[d]
12	$CuCl_2$[e]	Cs_2CO_3	20	95

[a] *Reaction conditions:* benzyl alcohol (1 mmol), copper salts (0.01 mmol), base (1.2 mmol) in toluene (5 mL), the mixture was stirred in oxygen at 40 °C for 12 h.

[b] Conversions were determined by GC with chlorobenzene as internal standard.

[c] Yields were calculated based on conversions, mass balances >90%.

[d] The other product was benzyl benzoate.

[e] 10% TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl free radical) was used.

catalytically active intermediate containing the $[Cu_3(\mu_3\text{-}OH)(\mu_3\text{-}Cl)]^{4+}$ moiety with cesium cations as counterions have been determined.

Through optimization of reaction conditions as shown in Table 1, when 1.2 equivalents of Cs_2CO_3 were employed as base, benzyl alcohol could be oxidized to benzaldehyde (conversion: 94%, selectivity > 99%) by molecular oxygen catalyzed by $CuCl_2$ (1 mol%) at 40 °C for 12 h (Table 1, entry 1). The control experiments in the absence of copper catalyst or cesium carbonate showed no oxidized product formation (Table 1, entries 2 and 3). Using air to replace molecular O_2 resulted in lower yield (74%, Table 1, entry 4). The effect of 4 Å molecular sieves (4 Å MS) was not significant; the yield of alcohol (83%, Table 1, entry 5) without 4 Å MS was slightly lower. Different Cu(I) or Cu(II) sources were employed as catalysts and the product yields varied from 11–85% (Table 1, entries 6–12). In addition, other metal salts such as $Mn(OAc)_2$, $FeCl_3$, $CoCl_2$ and $NiCl_2$ (Table 1, entries 13–16) were examined and, except for $Mn(OAc)_2$ which gave 76% yield, others showed product yields less than 10%.

Interestingly, this reaction was highly dependent on the type of bases. When Cs_2CO_3 was replaced by other metal carbonates such as Na_2CO_3, K_2CO_3 and Rb_2CO_3, the conversions of benzyl alcohol were lower than 20% (Table 2, entries 2–4). Similar poor reactivity was observed using metal hydroxides such as NaOH, KOH and CsOH (Table 2, entries 5–7). Employment of other bases such as *t*-BuOK, K_3PO_4, and DMAP also afforded low conversions (Table 2, entries 8–10). However, 80% conversion was achieved when 2 equivalents of $CsHCO_3$ were used instead of Cs_2CO_3 (Table 2, entry 11), although the over-oxidized product benzyl benzoate was detected. In this work, an attempt to increase the efficiency by adding a catalytic amount of TEMPO (10%) was unsuccessful and, surprisingly, the conversion dropped drastically (20%, Table 2, entry 12), different from the previously reported "CuCl-TEMPO" system.[13] These results suggested that Cs_2CO_3 plays an important role to increase the reactivity of copper salts in the aerobic oxidation of alcohols.

A significant solvent effect was also observed and the results are summarized in Table 3. In non-polar solvents such as CH_2Cl_2, *n*-hexane, toluene and 1,2-dichloroethane, the conversions of benzyl alcohol (> 50%, Table 3, entries 1–4) were much higher than that in polar solvents such as acetonitrile, THF, DMF, methanol, acetone and H_2O (<40%, Table 3, entries 5–10), opposite to the solvent effect of the "CuCl-TEMPO" system[13] which exhibited much higher reactivity in polar solvents such as DMF, acetonitrile and H_2O. More importantly, we fould that the polarity of the solvents is not the only factor for the solvent effect in the "$CuCl_2$-Cs_2CO_3" system. As shown in Table 3, higher conversions were obtained (93% and 94%, entries 1 and 2, respectively) in 1,2-dichloroethane and toluene than in the other solvents.

Table 3. Solvent effect of the copper(II)-catalyzed aerobic oxidation of benzyl alcohol.[a]

Entry	Solvent	Conv. [%][b]	Yield [%][c]
1	1,2-dichloroethane	93	99
2	toluene	94	99
3	CH_2Cl_2	70	79
4	*n*-hexane	53	84
5	CH_3CN	6	99
6	THF	38	98
7	DMF	15	99
8	CH_3OH	31	89
9	acetone	6	89
10	H_2O	8	96

[a] Benzyl alcohol (1 mmol), $CuCl_2 \cdot 2H_2O$ (0.01 mmol), Cs_2CO_3 (1.2 mmol) in solvent (5 mL), the mixture was stirred in oxygen at 40 °C for 12 h.
[b] Conversions were determined by GC with chlorobenzene as internal standard.
[c] Yields were calculated based on conversions, mass balances >90%.

According to the previous studies,[5,14] the higher reactivity in toluene was hypothesized for the interaction between copper ions and aromatic solvent. Similarly, interactions between 1,2-dichloroethane and cesium cations had also been demonstrated by theoretical and crystallographic studies.[15] Thus, we assumed that the possible interactions between the solvents and copper and/or cesium cations might be another factor for the solvent effect. Since $CuCl_2$ and Cs_2CO_3 are not soluble in solvents such as 1,2-dichloroethane, toluene and *n*-hexane, according to Markó's catalytic system[5] and the recently reported "$NaAuCl_4$/Cs_2CO_3" system,[16] another role of Cs_2CO_3 may be as a heterogeneous support.

Hammett plots were constructed by measuring the rate of oxidation of various *para*-substituted benzyl alcohols in toluene and 1,2-dichloroethane (Figure 1).

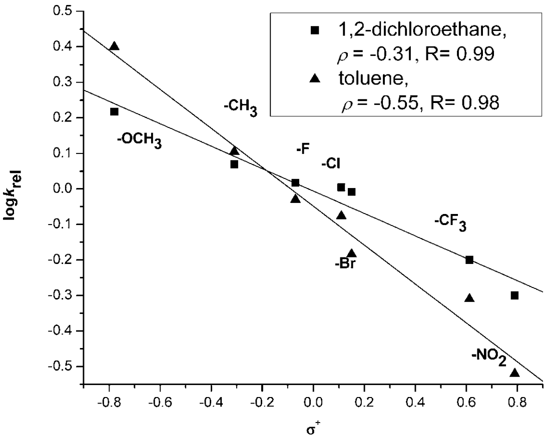


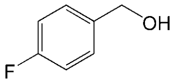
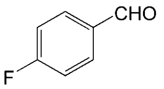
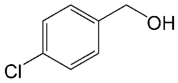
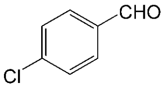
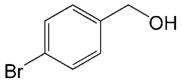
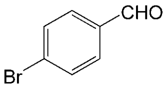
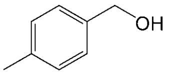
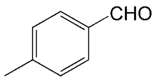
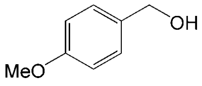
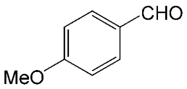
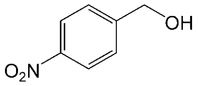
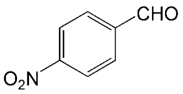
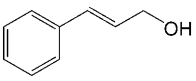
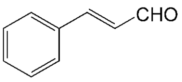
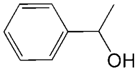
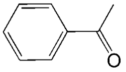
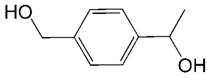
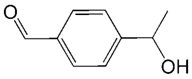
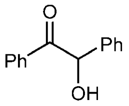
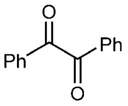
Figure 1. Hammett plots for the reaction of *para*-substituted benzyl alcohols in toluene and 1,2-dichloroethane.

The logarithm of the relative rates plotted against the σ^+ value of the *para*-substituent resulted in a linear relationship. Hammett ρ values of -0.55 in toluene and -0.31 in 1,2-dichloroethane were obtained, which are larger than the ρ value (-0.16) observed in "CuCl-TEMPO",[13] indicating a mechanism involving the formation of more charge character in the transition state. The primary kinetic isotope effect (k_H/k_D) for the $CuCl_2/Cs_2CO_3$-catalyzed aerobic oxidation of this alcohol at 25 °C was determined to be 1.45. This value indicates C–H bond cleavage on progressing to the transition state. Thus, a possible mechanism is proposed. According to previous reports, the catalytic reaction may be started from the deprotonated alcohol reacted with Cs_2CO_3. Through coordinating to the copper (II) center, alcohols' α-H could be abstracted with 1e transfer and a new C=O bond formed. An active Cu(II) species would be regenerated from O_2 oxidizing the Cu(I) intermediate(s).

To extend the scope of the substrate, a series of alcohols was oxidized to the corresponding carbonyl compounds under the optimized conditions and the results are summarized in Table 4. All the primary alcohols could be selectively oxidized to aldehydes and the formation of over-oxidized carboxylic acids was not observed. Allylic and benzyl alcohols can be oxidized to the corresponding aldehydes in good conversions (>80%, Table 4, entries 1–7). An aliphatic primary alcohol showed much a lower conversion (50%, Table 4, entry 8). However, the secondary alcohols such as 2-phenylethanol (Table 4, entry 9) could not be oxidized to acetophenone. Interestingly, when both the primary and secondary benzyl alcohols are present in one molecule such as 4-(1-hydroxyethyl)benzyl alcohol (Table 4, entry 10), only the primary alcohol was selectively oxidized and the secondary alcohol was left intact. An exception was observed for 2-hydroxy-1,2-diphenylethanone which was oxidized to the diketone in 72% yield together with 20% benzaldehyde (Table 4, entry 11). It is probably due to the more acidic α-H which could be much more easily abstracted than that of other secondary alcohols. We assumed that the lack of observed reactivity of primary alkyl alcohols and secondary alcohols may be due to their greater α–H bond strengths or/and steric effect of the alkyl group for secondary alcohols compared with benzylic or allylic alcohols.[4,5,6e,8e,10]

To further investigate the possible intermediate in the "$CuCl_2 + Cs_2CO_3$" protocol in toluene or 1,2-dichloroethane, we attempted to study the reaction between $CuCl_2$ (0.01 mmol), Cs_2CO_3 (0.01 mmol) with benzyl alcohol (0.5 mL) in toluene or 1,2-dichloroethane (2 mL). Under these conditions, we isolated *a red crystalline solid* (*ca.* 5%). Nevertheless, similar treatments afforded only blue precipitates when toluene or 1,2-dichloroethane was replaced by other solvents. The same phenomenon was also observed when

Table 4. Copper(II)-catalyzed aerobic oxidation of different alcohols.[a]

Entry	Substrate	Product	Cat.	Yield [%]
1			$CuCl_2$	87
2			$CuCl_2$	89
3			$CuCl_2$	88
4			$CuCl_2$	90
5			$CuCl_2$	87
6			$CuCl_2$	86
7			$CuCl_2$	82
8	n-$C_{10}H_{21}OH$	n-$C_9H_{19}CHO$	$CuCl_2$	28
9			$CuCl_2$	0
10			$CuCl_2$	80
11			$CuCl_2$	72

[a] Alcohol (1 mmol), catalyst (0.01 mmol), Cs_2CO_3 (1.2 mmol), toluene (5 mL), 40 °C, 12 h.

[b] Isolated yield of the product after column chromatography.

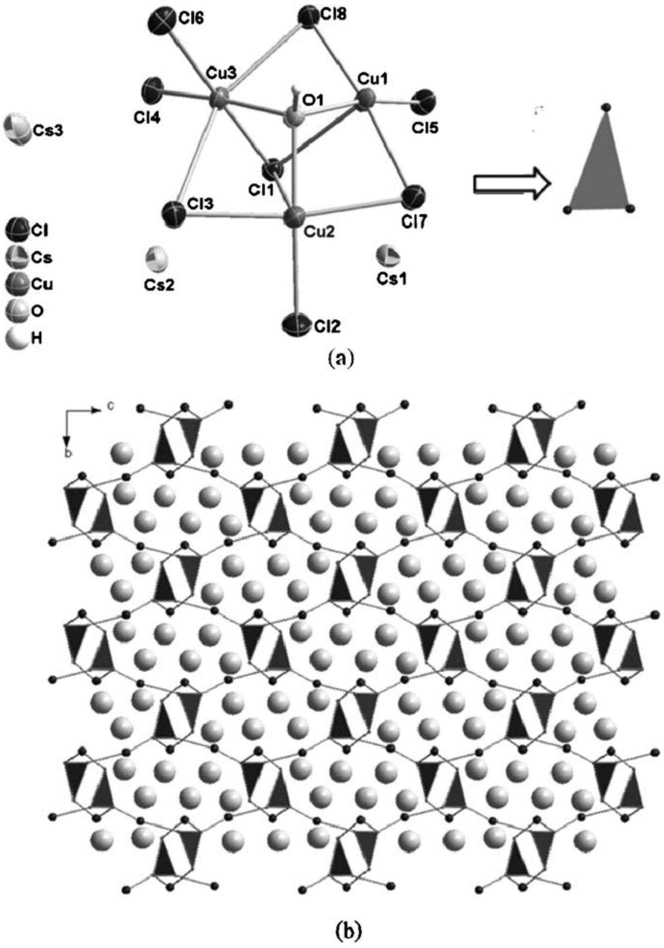


Figure 2. (**a**) ORTEP structure of complex **1**. (**b**) Crystal parking structure complex **1**. The triangles represent the tricopper clusters linked by Cl anions (black ball). Gray balls represent Cs cations

Cs_2CO_3 was replaced by other metal carbonates. X-ray diffraction quality crystals of the red species (complex **1**) were obtained by slow diffusion of diluted benzyl alcohol containing $CuCl_2$ to toluene containing Cs_2CO_3. The molecular structure of complex **1** (Figure 2, **a**) revealed that **1** consists of a trinuclear $[Cu_3(\mu_3\text{-}OH)(\mu_3\text{-}Cl)]^{4+}$ core in which the copper ions, consisting of three independent copper ions linked by μ_3-OH, μ_3-Cl and μ_2-Cl bridges to a scalene triangle with the distances of 3.086 Å (Cu1···Cu2), 3.102 Å (Cu2···Cu3), and 3.072 Å (Cu3···Cu1).[17] The lengths of Cu–Cu bonds are shorter than those supported by oxime-/oximate, *N*,*N*-pyrazole-, or *N*,*N*-triazole type peripheral ligands (3.165–3.322 Å)[18] but much longer than those in the $[Cu_3(\mu_3\text{-}O)]$ moiety (2.812–2.862 Å)[19]. All copper ions in the trimetric unit adopt an $(OH)Cl_5$ coordination environment and present the distorted octahedral geometry with two long Cu–Cl bonds (2.773 Å–2.852 Å) for each copper ion defining the Jahn–Teller distortion axis. The trimetric cluster is created by μ_2-Cl bridges and by the capping μ_3-OH and μ_3-Cl groups. The oxygen of the hydroxy group is located 0.846 Å above the [Cu3] plane and the μ_3-Cl (Cl1) is 1.993 Å below the plane. Crystal packing of **1** shows a that 2D coordination polymer is built from trinuclear $[Cu_3(\mu_3\text{-}OH)(\mu_3\text{-}Cl)]^{4+}$ core units. The Cl2 atoms acts as μ_2 bridges and join neighboring clusters by the Cu1–Cl2–Cu2A bond and form a zig-zag chain. The double bridges Cu2–Cl6–Cu3A and Cu3–Cl6A–Cu2A hold the chain together into a 2D framework. To the best of our knowledge, structurally characterized trinuclear copper oxo or hydroxide systems, like the $[Cu_3(\mu_3\text{-}OH)]$ moiety in **1**, were not unprecedented but are extremely rare with μ_2-Cl anion bridging. Moreover, complex **1** is hitherto the only example of the hydroxide complex of a $[Cu_3(\mu_3\text{-}OH)]$ unit isolated from the "ligand-free" copper-catalyzed aerobic oxidation of alcohols.

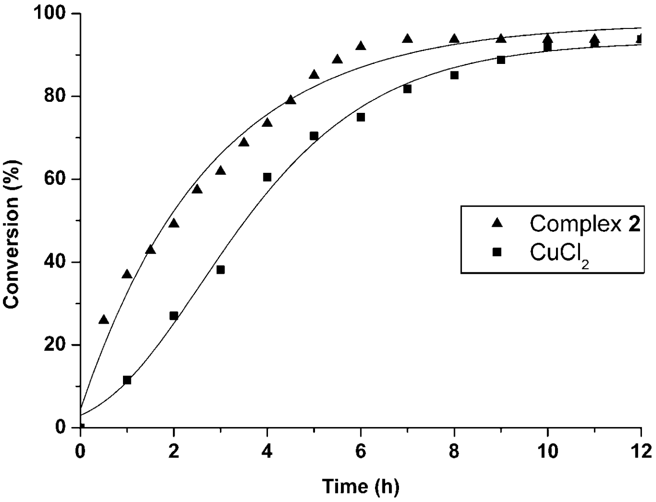
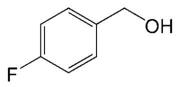
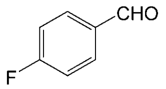
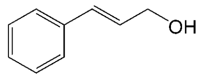
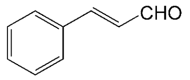
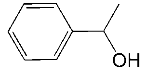
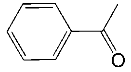
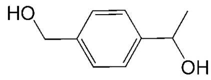
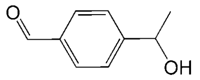


Figure 3. Time-dependent course of the copper-catalyzed aerobic oxidation of benzyl alcohol in toluene.

Table 5. Complex **1** catalyzed aerobic oxidation of different alcohols.[a]

Entry	Substrate	Product	Cat.	Yield [%]
1			**1**	94
2			**1**	75
3	$n\text{-}C_{10}H_{21}OH$	$n\text{-}C_9H_{19}CHO$	**1**	15
4			**1**	0
5			**1**	86

[a] Alcohol (1 mmol), catalyst (0.01 mmol), Cs_2CO_3 (1.2 mmol), toluene (5 mL), 40 °C, 12 h.

[b] Isolated yield of the product after column chromatography.

From Figure 2, (**b**), we observed that Cs cations act as counterions dispersed in the channels and between layers of the 2D network, which shows that the distances of the inter-ion contacts between Cs and Cl varied from 3.422 to 3.996 Å. The interaction between Cl anions and Cs cations had been shown in the crystal of Cs_2CuCl_4 and the distances between Cs and Cl varied from 3.460 to 3.630 Å. Although such an interaction was observed in the crystalline solid state of complex **1**, it suggested that the electrostatic interaction between Cs cations and the $[Cu_3(\mu_3\text{-}OH)]$ moiety or other copper intermediates might exist in solution. Thus, the Cs cation plays a role stabilizing and "solvating" intermediates such as $[Cu_3(\mu_3\text{-}OH)(\mu_3\text{-}Cl)]^{4+}$ unit through the interaction of Cl counterions and solvents like 1,2-dichloroethane and toluene.

To demonstrate the reactivity of trinuclear **1** containing $[Cu_3(\mu_3\text{-}OH)(\mu_3\text{-}Cl)]^{4+}$ moiety, we carried out a time-course study of the aerobic oxidation of benzyl alcohol catalyzed by **1** and copper chloride under the optimized condition (Figure 3). An initial induction period (0–3 h) using copper chloride was observed whereas **1** exhibited a similar rate without induction period. Thus, formation of **1** may be the intermediate to the active specie(s) during the catalysis using $CuCl_2$ as catalyst.

From Table 5, we found that **1** exhibited comparable reactivity to copper chloride. For benzyl alcohol, allylic primary alcohol (R = Ph), **1** could catalytically oxidize them to the corresponding aldehyde in similar yields (Table 5, entries 1 and 2) to that achieved with $CuCl_2$ (Table 1, entry 1 and Table 4, entry 7). Oxidation of aliphatic primary alcohol by **1** showed lower yield (15%, Table 5, entry 3) than that with $CuCl_2$ (28%, Table 4, entry 8).

Chemoselective oxidation of primary alcohols were also observed with **1** as catalyst (Table 5, entries 4 and 5). Thus, we speculated such trinuclear $[Cu_3(\mu_3\text{-}OH)(\mu_3\text{-}Cl)]^{4+}$ intermediate was generated through copper(II) chloride with molecular oxygen and, more importantly, acts as a entire catalytic center or dissociates to mononuclear copper active species to perform aerobic oxidation of alcohols.[20] Such polynuclear Cu(II) centers in multicopper oxidases like particulate methane monooxygenase (pMMO) and nitrous oxide reductase were proposed to be important to catalyze the four-electron reduction of molecular dioxygen.[1] Moreover, synthetic model complexes containing $[Cu_3(\mu_3\text{-}O/OH)]$ moieties had been demonstrated to be active for oxidative coupling phenols by molecular oxygen.[6,20] Addition of 10 mol% TEMPO to the reaction resulted in decrease of reactivity which resembled that with $CuCl_2$ as catalyst. These results indicated that complex **1** containing $[Cu_3(\mu_3\text{-}OH)(\mu_3\text{-}Cl)]$ moiety is catalytically active towards oxidation of alcohol and possesses similar reactivity in comparison to that using $CuCl_2$ as catalyst.

In summary, we have developed a new protocol of "$CuCl_2$-Cs_2CO_3" system for aerobic oxidation of primary alcohols. In such catalytic system, cesium carbonate and solvents such as toluene and 1,2-dichloroethane play important roles to form catalytically active intermediate containing $[Cu_3(\mu_3\text{-}OH)(\mu_3\text{-}Cl)]^{4+}$ moiety (complex **1**). From the X-ray crystal structure of complex **1**, the electrostatic interaction between Cl anions and Cs cations was observed, which stimulated us to understand the roles of Cs_2CO_3 in this reaction as a base, stabilizing and "solvating" intermediates in toluene and 1,2-dichloroethane. To our knowledge, although synthetic models of multicopper oxidases containing $[Cu_3(\mu_3\text{-}O/OH)]$ moieties such as ascorbate oxidase, laccase, ceruloplasmin and particulate methane monooxygenase (pMMO) have been extensively studied, few of them have been employed as catalysts in oxidations. The structural information we obtained may provide a unique avenue toward further design of polynuclear copper catalysts mimicking the active metal sites of multicopper oxidases. Detailed mechanism is under investigation and further studies are aimed at improve this system to become more applicable to different varieties of alcohols.

Experimental Section

General Procedure for the Aerobic Oxidation of Benzyl Alcohol Catalyzed by $CuCl_2$

Alcohol substrate (1 mmol), $CuCl_2 \cdot 2H_2O$ (1.70 mg, 0.01 mmol), Cs_2CO_3 (392 mg, 1.2 mmol) were added in toluene (5 mL), the mixture was stirred under oxygen in 40 °C for 12 h (***CAUTION: volatile organic solvents in combination with pure oxygen maybe explosive!***). The solution was then filtered on a thin layer silicon chromatograph and analyzed by GC (chlorobenzene was used as internal standard). Reaction mxitures were worked up by flash column chromatography (petroleum ether/EtOAc 20:1) to give the pure aldehydes.

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