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Highly Efficient and Practical Aerobic Oxidation of Alcohols by Inorganic-ligand Supported Copper Catalysis

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The oxidation of alcohols to aldehydes or ketones is a highly relevant conversion for the pharmaceutical and fine-chemical industries and for biomass conversion, which is commonly performed using stoichiometric amounts of highly hazardous oxidants. The aerobic oxidation of alcohols with transition metal complexes catalysts previously required complicated organic ligands and/or nitroxyl radicals as the cocatalysts. Herein, we report an efficient and eco-friendly method to promote the aerobic oxidation of alcohols using an inorganic-ligand supported copper catalyst **1**, (NH₄)₄[CuMo₆O₁₈(OH)₆], with O₂ (1 atm) as the sole oxidant. Catalyst **1** is synthesized directly from cheap and commonly available (NH₄)₆Mo₇O₂₄·4H₂O and CuSO₄, which consists of a pure inorganic framework built from a central Cu^{II} core supported by six Mo^{VI}O₆ inorganic scaffolds. The copper catalyst **1** exhibits excellent selectivity and activity towards a wide range of substrates in the catalytic oxidation of alcohols, and can avoid the use of toxic oxidants, nitroxyl radicals, potentially air/moisture sensitive and complicated organic ligands that are not commercially available. Owing to the robust inorganic framework, catalyst **1** shows good stability and reusability, and the catalytic oxidation of alcohols with catalyst **1** could be readily scaled up to gram-scale with little loss of catalytic activity, demonstrating a great potential of the inorganic-ligand supported Cu catalysts in catalytic chemical transformations.

1 Introduction

The selective oxidation of alcohols to aldehydes or ketones is one of the most important and challenging transformations in the synthesis of fine chemicals¹. Traditionally, such transformations have been performed with stoichiometric oxidants, including MnO₂, chromium(VI) salts, “activated DMSO” methods and hypervalent iodine reagents, which need expensive, environmentally hazardous chemicals and are only suitable for use on a small scale². From both environmental and economic aspects, there is an urgent need for more efficient methods that employ clean oxidants such as O₂ and a recyclable catalyst. In light of this, over the last three decades, a number of groups have developed effective catalyst systems for aerobic alcohol oxidation based on coordination complexes of noble metals including Pd³ and Ru⁴ (Figure 1A); however, the high cost of noble metals and the use of ligands that are not commercially available limits their applications.

First-row transition metals have a tendency to undergo a

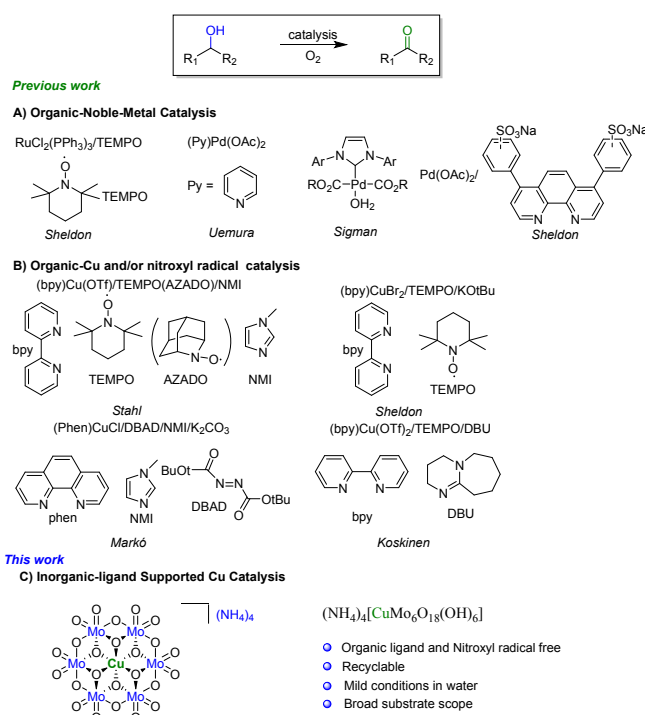


Figure 1 Representative Organic-Metal Catalyst Systems and Inorganic-ligand supported Cu-catalyst **1**

facile ligand exchange, and data from various studies suggest aerobic alcohol oxidation catalysts derived from these metals possess broader functional group tolerance (e.g., Cu⁵, Co⁷, Fe⁸, and V⁹). Recently, organo-copper catalyst systems,

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particularly those employing nitroxyl radicals such as TEMPO or a dialkylazodicarboxylate as redox-active co-catalysts (Figure 1B), have emerged as some of the most effective catalysts for the aerobic oxidation of alcohols to aldehydes or ketones. Such reagents are compatible with activated allylic, benzylic, propargylic and unactivated (aliphatic) alcohols, and their chemoselectivity and functional-group compatibility challenges traditional alcohol oxidation methods¹⁰. However, a serious deficiency of both systems is that they require relatively large amounts of organic ligands which are expensive, toxic, air/moisture sensitive and not commercially available. In addition, they also rely upon significant quantities of nitroxyl radicals (5-10 mol%) as co-catalysts, commonly the most expensive component of the catalyst system; this becomes a serious concern for industrial-scale applications. Furthermore, the established protocols that employ Cu-base catalysts rely on the use of environmentally detrimental halogenated solvents.

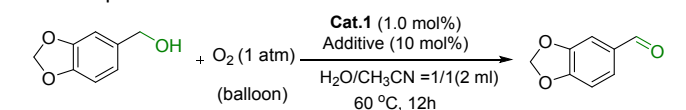
The use of water as a solvent and/or co-solvent leads to both decreased reaction rates and catalyst deactivation¹¹. It would be of considerable benefit, i.e., safer, cheaper, and more environmentally benign if alcohol oxidation processes could be performed in water or a mixture of water and organic solvents due to its natural abundance and inherently greener characteristics¹². Therefore, there is significant demand for the development of more sustainable and environmentally friendly alcohol oxidation catalyst strategies which employ molecular oxygen as the terminal oxidant in water or a mixture system.

Polyoxometalates (POMs)^{13, 14}, as a class of metal-oxide clusters with unmatched molecular structural diversity and functionality, exhibit high redox and acidic properties at the atomic and molecular levels as well as resistance toward hydrolysis and oxidative degradation. They thus offer great potentials as stable inorganic ligands for coordination with metal ions, differing from classical transition-metal complexes of organic ligands¹⁵. Very recently, our group reported firstly that the Anderson-type POMs¹⁶ can be used as the inorganic-ligand supported metal catalysts for highly efficient aerobic oxidation of aldehydes to carboxylic acids in water, or the oxidation of amines to imines under mild conditions¹⁷. This type of metal catalysts possess unique structures bearing six Mo^{VI}O₆ inorganic scaffolds that is supported by a central metal atom; this kind of structure greatly enhances the Lewis acidity of the catalytically active sites and as well as enabling the edge-sharing MoO₆ unit to act as ligands analogous to those employed in traditional organometallic complexes. These properties make POMs ideal candidates for solving those problems associated with the instability and activity of catalysts commonly used in organic-metal catalysis, and thus provides a potential alternative for the aerobic oxidation of alcohols. Herein, we report an inorganic-ligand supported copper catalyst **1**, (NH₄)₄[CuMo₆O₁₈(OH)₆]¹⁸ (Figure 1C.), which possesses a copper(II) ion core supported by six Mo^{VI}O₆ inorganic scaffolds. The catalyst **1** can be readily synthesized in one simple step in aqueous solution at 100°C (see supporting information, Figures S1 to S3), and can efficiently catalyze the oxidation of various aromatic and aliphatic alcohols to

corresponding aldehydes or ketones using O₂ as the sole oxidant in a solvent mixture of acetonitrile and water (Figure 1C). This catalyst exhibits high catalytic efficiency and possesses excellent stability throughout the catalytic cycle. Compared with organic-copper/nitroxyl radical catalyst systems, the inorganic-ligand supported copper catalysts provide significant advantages over traditional oxidation procedures in that they are robust to auto-oxidation, can be recovered easily, and avoid the use of complicated/sensitive organic ligands and expensive nitroxyl radicals.

2 Results and discussion

Initially, our studies began with the oxidation of piperonyl alcohol as a model substrate using the copper catalysts **1** and one atmospheric pressure O₂ as the sole oxidant at 60 °C (Table S1). No product was detected in the absence of catalysts **1** over 24 h. Gratifyingly, water was found to be a suitable solvent for the oxidation of piperonyl alcohol with the desired product being obtained in 72% yield and >99% selectivity within 24 h, which commonly inhibits reactivity in organic-copper/ nitroxyl radicals system when is employed as a co-solvent. Acetonitrile - being the best solvent for organic-copper/ nitroxyl radicals systems - also provided the desired product in 66% yield with >99% selectivity over 10h. With regards to others solvents, dioxane, DMF and DMSO all proved to be ineffective except the DCM (60% yield with 99% selectivity). When the reaction was carried out using acetonitrile as the solvent, the oxidation of piperonyl alcohol proceeded much slower because of poor solubility of the catalyst **1** in this reaction medium. Not surprisingly, when acetonitrile was employed as a co-solvent (a solvent mixture of acetonitrile and water, v/v=1:1), the oxidized product was obtained in 90% yield within 12 h. The ratio of water/acetonitrile in the mixed solvent system was investigated and an increase in the proportion of water had no effect on the reaction efficiency (Table S2). The addition of additives can influence the reaction apparently (Table 1, entries 1-21). Among those tested, salts bearing the chloride ion gave the highest conversion to the corresponding aldehyde (>99%) with excellent yield (99%) after 12 h at 60 °C; this is most likely due to the Cl⁻ acting as an electron-transfer mediator to improve the electron transfer efficiency. Subsequently, the counterion effect of inorganic chloride on the oxidation was investigated. In addition to NH₄⁺, other cations including K⁺, Rb⁺, Cs⁺, Mg²⁺, Ca²⁺, Zn²⁺ and Li⁺ proved to be ineffective (Table 1, entries 10-15). When 18-crown-6 was used in combination with NaCl, the reaction became much slower, showing the obvious effect of the cation (Table S3). Furthermore, in consideration of the aldehyde being easily oxidized further to the corresponding acid, the reactions under the standard conditions was monitored, and none of the over-oxidized product was formed (Table S4). Furthermore, the impact of the catalyst loading and reaction temperature were investigated. Lowering the loading of **1** from 1 mol% to 0.5 or 0.1 mol% resulted in the aldehyde product being obtained in 92% and 90% reduced yield, respectively (Table 1, entries 16 and 17).

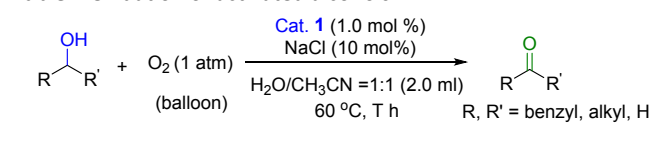
Table 1 Optimization of reaction conditions^a

Entry	Cat. (mmol%)	Additive (10mmol%)	Con.(%)/Sel.(%) ^b	Yield (%) ^c
1	1	Na ₂ CO ₃	97/86	70
2	1	Na ₂ SO ₄	95/83	46
3	1	NaHSO ₃	69/39	<10
4	1	NaClO ₄	99/98	92
5	1	NaHSO ₄	48/19	16
6	1	NaF	70/65	18
7	1	NaCl	>99/99	99
8	1	NaBr	87/93	69
9	1	NaI	83/90	65
10	1	KCl	92/97	72
11	1	RbCl	85/93	62
12	1	CsCl	85/90	68
11	1	NH ₄ Cl	99/99	95
12	1	CaCl ₂	27/52	<10
13	1	MgCl ₂	22/82	<5
14	1	ZnCl ₂	19/95	<5
15	1	LiCl	26/97	<10
16	0.5	NaCl	99/99	92
17	0.1	NaCl	98/99	90
18 ^d	1	NaCl	90/99	83
19 ^e	1	NaCl	95/97	87
20 ^f	1	NaCl	94/96	80
21 ^g	1	NaCl	<5/<5	<5

^aReaction conditions: Cat. **1** (1.0 mol%), alcohols (1.0 mmol), O₂ (1 atm), additives (10 mol%) and MeCN/H₂O=1/1 (2 mL) at 60°C. Unless otherwise noted. ^bSelectivity were determined by GC and confirmed by GC-MS. ^cYields and conversion were calculated from ¹H NMR spectra. ^dat 25 °C. ^eat 70 °C. ^fReactions were carried out under atmospheric air. ^gReactions were carried out under nitrogen atmosphere.

Altering the reaction temperature led to a significant decrease in the yields of the aldehyde product (Table 1, entries 18 and 19). While optimized conditions employed one atmosphere of O₂, the reaction can also be conducted in air, albeit requiring a prolonged reaction time (Table 1, entry 20). When the reaction was performed under nitrogen atmosphere, the desired product was obtained in <5% yield (Table 1, entry 21), showing that O₂ is an essential oxidant for the reaction. It should be noted that CuSO₄, Na₂MoO₄ or (NH₄)₆Mo₇O₂₄·4H₂O = (NH₄)₆[MoMo₆O₁₈(O)₆]·4H₂O (which is also considered to be an isomerized Anderson-structured POM with an Mo core instead of Cu as the central atom) when used as the catalyst alone, provided only trace amounts of product even with a prolonged reaction time up to 24 h. Yet, when a mixture of 1.0 mol% of CuSO₄ and 1.0 mol% of the (NH₄)₆Mo₇O₂₄ was used as the catalyst, the desired product can be obtained in a low yield of 37%.

The superior aerobic oxidation efficiency of the combined catalyst platform indicates that every constituent plays a vital role in the inorganic-ligand supported copper catalysis.

Table 2 Oxidation of activated alcohols^{a, b}

R = H, 15h, 95% (91%) R = CH ₃ , 13h, 99% (96%) R = OCH ₃ , 12h, 99% (95%) R = CH(CH ₃) ₂ , 18h, 97% (92%)	2 3 4 5	X = F, 20h, 87% (95%) X = Cl, 20h, 90% (87%) X = Br, 24h, 91% (88%) X = NO ₂ , 20h, 82% (80%)	6 7 8 9
X = F, 16h, 93% (90%) X = Br, 16h, 90% (87%) X = OH, 15h, 96% (92%)	10 11 12		
13h, 96% (92%)	15h, 98% (92%)	20h, 87% (81%)	16h, 96% (90%)
16h, 95% (82%)	18h, 99% (92%)	X = H, 16h, 95% (89%) X = CH ₃ , 14h, 99% (93%) X = F, 18h, 95% (86%) X = Cl, 18h, 92% (83%) X = NO ₂ , 18h, 90% (85%)	19 20 21 22 23
24h, 92% (90%)	20h, 96% (88%)	18h, 93% (90%)	12h, 97% (92%)
24h, 97% (88%)	X = H, 12h, 94% (90%) X = CH ₃ , 16h, 98% (89%) X = OCH ₃ , 18h, 99% (87%) X = Cl, 18h, 92% (80%)	18h, 96% (83%)	20h, 95% (80%)
22h, 98% (89%)	24h, 93% (83%)	24h, 97% (91%)	18h, 96% (85%)

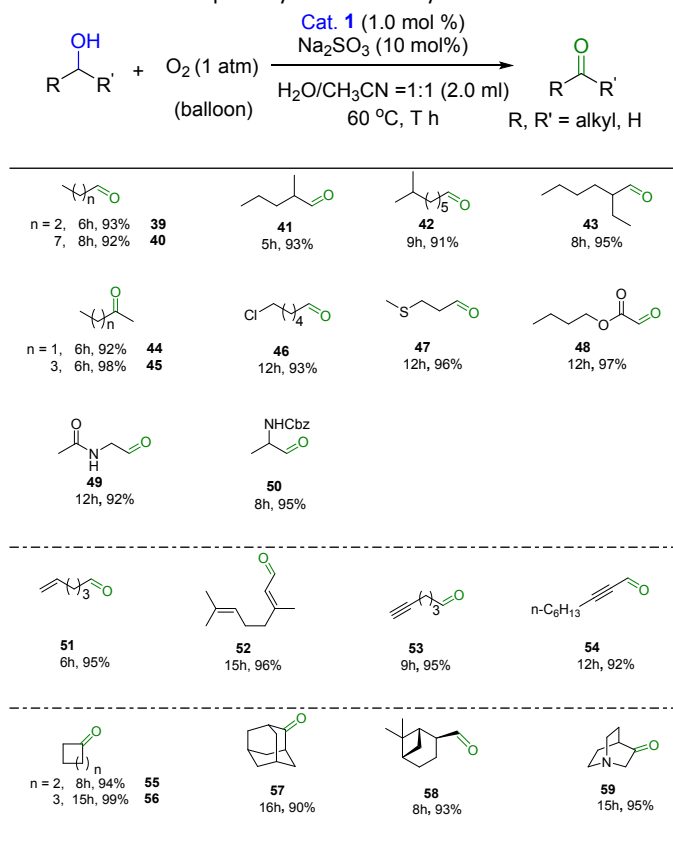
^aReaction conditions: Cat. **1** (1.0 mol%), alcohols (1.0 mmol), O₂ (1 atm), NaCl (10 mol%) and MeCN/H₂O=1/1 (2 mL) at 60°C. ^bYields were determined by GC-MS analysis of the crude reaction mixtures, values in parentheses are the isolated yields.

Because the structure of POMs is pH dependent, the oxidation selectivity was also tested at different pH values. The desired product was obtained in good yield and with good selectivity when the pH of the reaction medium was in the range of 5-9; moving out of this region significantly reduced both the conversion and selectivity (Figure S7) due to the decomposition of catalyst **1** in strongly acidic or basic solution.

Using the optimized reaction conditions, we explored the substrate scope of this catalytic oxidation system. On the basis of our initial efforts to obtain high selectivity for the alcohol oxidation, the oxidation of aromatic alcohols bearing various functional groups was examined. (Table 2). All substituted benzyl alcohols with electron-donating and electron-withdrawing groups were easily oxidized into the corresponding aldehydes or ketones with excellent selectivity (compounds **2-28**). Electron-donating substituents on

the phenyl group accelerated the reaction, while reactions of alcohols with electron-withdrawing groups required longer reaction times. It is worth noting that primary benzylic alcohols can be

Table 3 Oxidation of primary and secondary unactivated alcohols^a



^aReaction conditions: Cat. **1** (1.0 mol%), alcohols (1.0 mmol), O₂ (1 atm), Na₂SO₃ (10 mol%) and MeCN/H₂O=1/1 (2 mL) at 60°C.

^bYields were determined by GC-MS analysis of the crude reaction mixtures.

quantitatively oxidized to the corresponding aldehydes. Compared with primary benzylic alcohols, secondary benzylic alcohols are less reactive. For unsaturated aromatic alcohols, cinnamyl alcohol, bearing a carbon-carbon double bond, provided excellent yields of the corresponding products (compounds **29-32**). The reactions display functional-group compatibility similar to that observed with heteroaromatic alcohols, including tolerance of sulfur, oxygen and nitrogen atoms, such as pyridin-2-ylmethanol/1-(pyridin-2-yl)ethan-1-ol, thiophen-2-ylmethanol/1-(thiophen-2-yl)ethan-1-ol, furan-2-ylmethanol/1-(furan-2-yl)ethan-1-ol, with which organometallic catalyst systems generally cannot effect the catalytic oxidation of these alcohols because of strong coordination to the metal center, could also be transformed into the corresponding aldehydes or ketones almost in quantitative yields (compounds **33-38**).

The high reactivity of the substituted activated alcohols prompted us to employ our methodology for the selective oxidation of more challenging linear and cyclic unactivated aliphatic alcohols (Table 3). However, linear alcohols, such as octan-1-ol, gave low selectivities for the corresponding aldehydes owing to an overoxidation to form the carboxylic acid under the standard conditions. This problem was circumvented by using Na₂SO₃ in

place of NaCl as the additive, affording an increase in aldehyde yields from 27 to 95% (Table S5). The selective oxidation of linear aliphatic alcohols proceeded smoothly giving the corresponding products in excellent yields (compounds **39-45**). A series of functionalized alcohols, linear aliphatic alcohols bearing chloro, thioether and amide groups, could all be oxidized chemoselectively to afford the corresponding aldehydes or ketones with excellent yields (compounds **46-49**). Furthermore, *N*-protecting groups, such as Cbz, was tolerated, and substrates bearing these groups were oxidized in excellent yields under the standard conditions (compounds **50**).

Alcohols with an isolated C=C double bond or with a C=C double bond conjugated to the hydroxyl group, such as hex-5-enal, (E)-pent-2-enal and (Z)-3,7-dimethylocta-2,6-dienal, were all amenable to the reaction conditions with the oxidation proceeding quantitatively or nearly quantitatively (compounds **51** and **52**). Alcohols with a terminal C-C triple bond could also be oxidized to aldehydes or ketones in excellent yields (compounds **53** and **54**).

Annular unactivated alcohols can also undergo facile oxidation to the corresponding aldehydes or ketones. Single ring alcohols underwent oxidation to give the corresponding ketones in almost quantitative yields (compounds **55** and **56**). Sterically hindered polycyclic alcohols can also be oxidized in high yields to the corresponding aldehydes and ketones (compounds **57** and **58**). Heterocyclic alcohols containing a tertiary amine underwent efficient oxidation in excellent yields (compounds **59**).

To further demonstrate the practicality of this catalytic system, a 50 mmol reaction of benzyl alcohol was conducted using pure O₂ to give 4.7754g of benzaldehyde in 90% isolated yield with 99% selectivity within 24h (Scheme S1). These results suggest that in the case of reaction systems using a low catalyst loading of **1**, high activity, selectivity, and practicability can be achieved for the aerobic oxidation of alcohols. Next, the ability of the catalyst **1** to be recycled and used in successive reactions was also evaluated. The solid catalyst was isolated by filtration and reused directly for the subsequent oxidation of benzyl alcohol without further purification (precipitation of catalyst after adding ether to the reaction system). The catalyst **1** could be used at least six times without any degradation in catalyst performance (Figure S7). To confirm the high stability of the catalyst and its associated performance, the structure and morphology of the catalyst was further investigated using FTIR and XRD. The structure and morphology of the recycled catalyst remains unchanged from its original state (see supporting information, Figures S9 and S10).

In order to ascertain the mechanism of the reaction, a number of control experiments were conducted. When Cu-POM catalyst **1** was used stoichiometrically under an inert atmosphere, trace amounts of benzyl alcohol are converted into benzaldehyde, indicating that catalyst **1** is not as an oxidant (Figure S8 Aa). When 1.0 mmol Cu-catalyst **1** is used under an O₂ atmosphere at 60 °C for 2 hours, the Cu catalyst **1** activates molecular oxygen to afford an active species B, which undergoes O-O bond heterolysis to give metal-oxo species C (the ESI-MS analysis showed m/z 1246(M + 23) peaks attributed to B and m/z 1230 (M + 23) peaks attributed to C, Figure S8 Ab and Ac, Figure S11 and S12). Next, the combination of metal-oxo species C and a stoichiometric amount of benzyl alcohol react under an inert atmosphere, with benzaldehyde

obtained in 90% yield. This confirms that metal-oxo species C is the active catalyst.

Two types of deuterium kinetic isotope effects were measured for the oxidation of PhCH₂OH (Figure S8B), including independent rate measurements for the oxidation of RCH₂OH and RCD₂OH (Figure S8B b), and intramolecular competition experiments (Figure S8B a). Each of these studies provides unique insights into the reaction mechanism. The oxidations of PhCHDOH reveal a large kinetic isotope effect for the C-H cleavage step, $k_H/k_D = 7.09$. Measurement of the independent rates for the oxidations of PhCH₂OH and PhCD₂OH showed no significant isotope effect ($k_H/k_D = 1.06$). These data show that C-H cleavage is not turnover limiting in the oxidation of PhCH₂OH.

The cyclic voltammograms of catalyst **1**/NaCl (1:10) in a H₂O/CH₃CN(1:1) solvent system shows two oxidative waves at -0.25 V and +0.47 V versus Fc/Fc⁺ (Fc, ferrocene). We assign these features to the Cu^I/Cu^{II} and the Mo^V/Mo^{VI} couples, respectively. These waves are both quasireversible and at relatively low potentials, suggesting that a Cu^I/Cu^{II} cycle is possible with this ligand system.

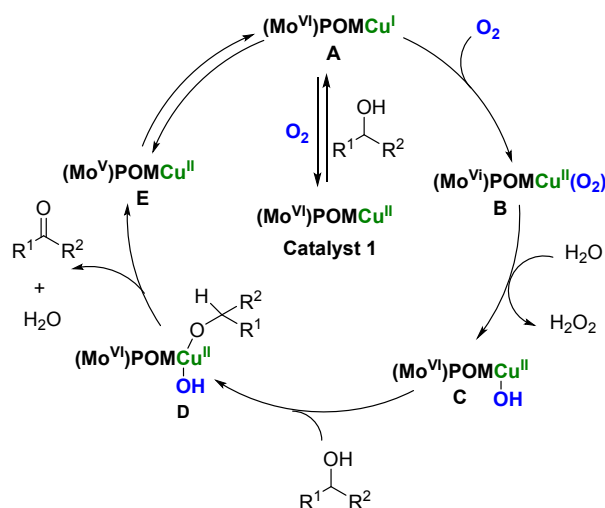


Figure 2 Proposed mechanism for the Cu-catalyzed oxidation of alcohols

Based on these experimental results, a tentative mechanism for the oxidation of alcohols has been proposed (Figure 2). For the inorganic-ligand supported copper catalyst **1**, the two oxidizing equivalents required for oxidation are not only stored at the copper center but are also delocalized on the six edge-sharing MoO₆ units. The Cu-POM catalyst **1** reaction with alcohol to generate an active species **A**, and the **A** and **E** are a pair of isomers that can be converted to each other, this may be via the transfer of electrons through an intramolecular oxygen bridge, Cu-O-Mo, to an inorganic ligand, MoO₆ where one of the Mo unit changes from a positive hexavalent species to a positive pentavalent species. The Cu-POM **A** first activates molecular oxygen to generate an active species **B**. Subsequently, the species **B** undergoes O = O bond heterolysis to give the highly reactive metal-oxo species **C** as active oxidants. During this process, water participates in the reaction to produce

hydrogen peroxide (detected by GC-MS) and the Cu-POM catalyzed reactions more closely resemble galactose oxidase, in which Cu^I and a hydroxyl radical operate jointly as the one-electron oxidant to mediate a two electron alcohol oxidation reaction; in galactose oxidase, a single Cu center reacts with O₂ to afford H₂O₂ as a byproduct. The highly reactive Cu-oxo species **C** then reacts with the alcohol to give the intermediate **D**, followed by H-atom abstraction to produce the aldehyde and regenerate **E**. Finally, the intermediate **E** (Cu^{II}) is oxidized by hydrogen peroxide back to species **A** (Cu^I).

4 Conclusions

In summary, we have developed a highly efficient inorganic-ligand coordinated copper-catalyst system for the oxidation of alcohols to aldehydes or ketones. The catalyst system exhibits a wide alcohol substrate tolerance (more than 59 substrates, including primary and secondary allylic, benzylic, and aliphatic) with excellent selectivity and recoverability. The oxidation reaction is carried out under mild reaction conditions in water. This catalytic system takes operational simplicity into account and avoids using any organic ligand and nitroxyl radical, which is beneficial for its practical use in pharmaceuticals, fragrances, and food additives. The method of improving the activity and selectivity of a catalytic reaction by picking the additives was first introduced into the polyoxometalate catalyzed oxidation of alcoholic systems, which is of great significance both academically and industrially. The generality of this methodology gives it the potential to be used on an industrial scale.

Conflicts of interest

There are no conflicts to declare.

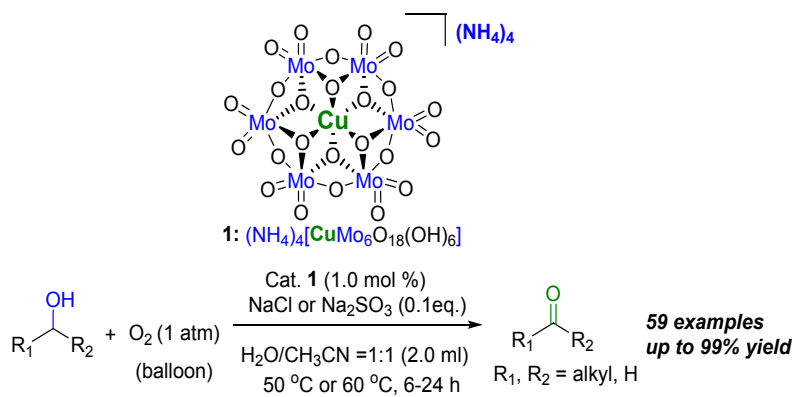
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