

N3S-ligated Copper(II) Complex Catalyzed Selective Oxidation of Benzylic Alcohols to Aldehydes under Mild Reaction Conditions[†]

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A Cu(II) complex with an three nitrogens and one sulfur coordination environment was synthesized and characterized. Its redox potential was observed at 0.483 V vs. NHE, very similar to that of a Cu-containing fungal enzyme, galactose oxidase, which catalyzes the oxidation of alcohols to corresponding aldehydes with the concomitant reduction of molecular oxygen to water. The Cu(II) complex selectively oxidizes the benzylic alcohols using TEMPO/O₂ under mild reaction conditions to corresponding aldehydes without forming any over-oxidation product. Moreover, the catalyst can be recovered and reused multiple times for further oxidation reactions, thus minimizing the waste generation.

Key Words : Copper(II) catalyst, Selective oxidation, Reusability and easy separation

Introduction

The oxidation of alcohols to aldehydes or ketones is an important reaction in synthetic organic chemistry and fine chemical synthesis.^{1,2} In general, the traditional methods to achieve such fundamental transformations use stoichiometric oxidants such as KMnO₄, MnO₂, CrO₃, SeO₂, oxone, iodine, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ); however, they suffer from inherent drawbacks from both economic and environmental viewpoints.^{3,4} Owing to the growing demand for atom-efficient and environment-friendly methods, catalytic methods employing both transition metals and clean oxidants such as O₂ in air have been reported.⁵ Among these transition metals, Cu-based catalyst systems, particularly those employing TEMPO as the co-catalyst, have been extensively studied because of environment-friendly by-product “water”.⁶⁻⁹ Ever since the first catalyst system, CuCl/TEMPO, was reported to be effective for benzylic and allylic oxidations, several related catalyst systems consisting of a Cu(II) salt, ligand, and base have been developed to perform selective alcohol oxidation using ambient air as the oxidant.¹⁰ However, most of these methods using Cu-based catalysts require a very long reaction time and high temperatures for efficient oxidation. Moreover, catalyst recovery after the oxidation is very difficult, which limits the use of these methods in practical industrial applications.

Although the reaction conditions for these Cu catalyzed alcohol oxidations, such as the ratio of Cu salt to ligand, solvent, and temperature, are well documented,⁷ the structures of Cu catalysts involved in these reactions are not well defined. Structural information of the catalyst is needed to

understand the relationship between structure and function, predict the solubility to design recyclable systems and design the new catalysts to solve existing limitations. Over the past few years, our group has been interested in the synthesis and study of Cu catalysts with tailored structures, for the purpose of establishing structure and function relationship of catalyst systems in a controlled manner. Herein, we report that a Cu(II) complex with a well-defined N3S coordination environment can catalyze the selective oxidation of benzylic and allylic alcohols to the corresponding aldehydes and ketones under aerobic conditions at room temperature. Moreover, the catalyst can be recovered and reused for further oxidation reactions for at least five times thus minimizing waste generation.

Experimental

General Procedure. All the chemicals purchased were of analytical grade and used as received without further purification. The air-sensitive procedures were carried out using a glove box or by using standard Schlenk line techniques under nitrogen atmosphere. All the solvents were distilled prior to their use: CH₃CN was distilled over CaH₂ and THF was distilled over a mixture of sodium and benzophenone under nitrogen atmosphere. The catalyst (0.10 mol) and TEMPO (0.10 mol) were dissolved in a mixture of toluene and CH₃CN, the alcohol (1.0 mol) and base (0.20 mol) were added at 27 °C under O₂ atmosphere (O₂ balloon). The reaction progress was monitored by TLC. After completion of the reaction, the catalyst was recovered by reducing the volume of the reaction mixture followed by decanting the solution. The decanted reaction mixture containing the aldehyde product was purified by silica gel column chromatography (eluent: ethyl acetate/hexane(1:1)).

Electrochemistry. Cyclic voltammetry studies were carried out using a ZAHNER elektrik IM6 potentiostat. The cell

[†]This paper is to commemorate Professor Myung Soo Kim's honourable retirement.

consisted of a standard three-electrode system with a Pt wire counter electrode, a Pt working electrode, and (0.01 M) Ag/AgNO₃ reference electrode. The measurements were performed at room temperature in CH₃CN containing 100 mM tetrabutylammonium hexafluorophosphate{(Bu₄N)PF₆} and the Cu complex. The E_{1/2} of ferrocene was +0.091 V vs. Ag/AgNO₃ with a peak-to-peak separation of 77 mV. The half-wave potential of the ferrocene/ferrocenium couple in CH₃CN has been reported to be located at +0.63 V vs. NHE. Therefore, in the voltammogram, +0.548 V should be added to convert the potentials with respect to NHE.¹¹

Single Crystal X-ray Crystallography. A crystal was mounted on the tips of quartz fibers coated with Partone-N oil at room temperature, and cooled under a stream of cold nitrogen. The intensity data were collected using a Bruker CCD area diffractometer running the SMART software package with Mo K α radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods and refined on F^2 using SHELXTL software package.¹² An empirical absorption correction was applied with SADABS,¹³ a part of the SHELXTL program package, and the structure was checked for higher symmetry with PLATON.¹⁴ All non-hydrogen atoms were refined anisotropically. In general, the hydrogen atoms were assigned idealized position and thermal parameters equivalent to 1.2 times of the thermal parameter of the carbon atom to which they are attached. The data and experimental details for the complex are summarized in Table 1 and the relevant interatomic distances and angles are listed in Table 2.

Synthesis of 1-(Bis(pyridin-2-ylmethyl)amino)propane-2-thiol. Propylene sulfide (0.400 mL, 3.70 mmol) was added

Table 2. Selected Inter atomic bond distance (Å) and bond angle (°) for **1**

Interatomic distances		Interatomic angles	
Cu(1)-N(2)	1.979(5)	N(2)-Cu(1)-O(1)	92.03(19)
Cu(1)-O(1)	1.980(4)	O(1)-Cu(1)-N(1)	99.50(19)
Cu(1)-N(1)	1.990(5)	N(1)-Cu(1)-N(3)	83.20(19)
Cu(1)-N(3)	2.045(4)	N(2)-Cu(1)-N(3)	83.73(19)
Cu(1)-S(1)	2.6212(19)	N(2)-Cu(1)-S(1)	95.54(15)
Cu(1)-O(3)	2.654(4)	N(3)-Cu(1)-O(3)	86.73(16)

to a 20 mL CH₃CN solution of dipicolylamine (0.500 g, 2.50 mmol) and the resulting reaction mixture was refluxed for 12 h under nitrogen atmosphere. The solution was then cooled to room temperature and CH₃CN and excess propylene sulfide were removed to afford yellow oil. Yield (0.630 g, 92%). ¹H NMR (CDCl₃) 500 MHz δ 8.53 (m, 2H), 7.67 (m, 2H), 7.55 (m, 2H), 7.16 (m, 2H), 3.88 (dd, ²J = 14.50 Hz, 2H), 3.76 (dd, ²J = 14.50 Hz, 2H), 3.20 (m, 1H), 2.65 (dd, ²J = 13.30 Hz, ³J = 5.50 Hz, 1H), 2.55 (dd, ²J = 13.78, ³J = 5.00 Hz, 1H), 2.00 (s, 1H), 1.23 (d, ³J = 6.50 Hz, 3H). ES-MS: calculated (m/z): 273.13, found [M+H]⁺: 274.10.

Synthesis of [2-(Benzylthio)-N,N-bis((pyridin-2-yl)methyl)propan-1-amine] (BTPMPA). Cs₂CO₃ (0.773 g, 2.37 mmol) and tetrabutylammonium iodide (TBAI) (0.879 g, 2.37 mmol) were added to a 50 mL solution of 1-(bis(pyridin-2-ylmethyl)amino)propane-2-thiol (0.650 g, 2.37 mmol). After stirring for 1 h, benzyl bromide (0.338 mL, 2.85 mmol) was added and the resulting reaction mixture was heated for 2 h at 50 °C. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with ethyl acetate and DM water. The layers were separated, and the organic layer was dried over Na₂SO₄, and evaporated to dryness to afford a sticky yellow solid. Yield (0.62 g, 74%). ¹H NMR (CDCl₃) 500 MHz (Fig S1) δ 8.51 (m, 2H), 7.66 (m, 2H), 7.55 (m, 2H), 7.30 (m, 4H), 7.14 (m, 3H), 3.81 (s, 2H), 3.75 (dd, ²J = 13.50 Hz, 2H), 3.69 (dd, ²J = 12.00 Hz, 2H), 2.86 (m, 1H), 2.71 (m, 1H), 2.52 (m, 1H), 1.22 (d, ³J = 6.10 Hz, 3H); ¹³C NMR (CDCl₃) 125 MHz δ 159.71, 149.12, 136.63, 129.05, 127.30, 123.31, 122.20, 60.88, 60.40, 37.76, 35.05, 19.73; ES-MS: calculated (m/z); 363.18, found [M+H]⁺; 364.20.

Synthesis of {[Cu(BTPMPA)(OH₂)(OTf)]OTf}, **1.** [Cu(CF₃SO₃)-benzene] complex (0.224 g, 0.446 mmol) was dissolved in 4 mL of CH₃CN and BTPMPA (0.108 g, 0.298 mmol) was added under anaerobic conditions. After 3 h, the yellow solution was exposed to air, and the resulting green solution was diffused with THF to afford block-shaped blue crystals after 2 days. Yield (0.134 g, 60%). Elemental Analysis (%): calculated; C, 38.78; H, 3.66; N, 5.65; S, 12.94 found; C, 38.74; H, 3.62; N, 5.62; S, 12.99. UV-visible in CH₃CN: λ_{\max} (ϵ) 620 nm (49 cm⁻¹M⁻¹) and 828 nm (56 cm⁻¹M⁻¹). FT-IR (KBr, cm⁻¹); 3436 (s), 3086 (w), 2965 (w), 2931 (w), 2857 (w), 1645 (m), 1610 (s), 1482 (w), 1445 (s), 1386 (w), 1283 (s), 1255 (s), 1158 (s), 1029 (s), 865 (m), 766 (m), 704 (m), 640 (s), 572 (m), 517(m).

Table 1. X-ray Crystallographic Data for the **1**

formula	C24 H27 Cu F6 N3 O7 S3
formula weight, g mol ⁻¹	743.21
T, K	200(2)
radiation, Å	0.71073
crystal system	Triclinic
space group	P $\bar{1}$
a, Å	8.7256(16)
b, Å.	9.1729(18)
c, Å	20.222(4)
α , (deg)	87.314(4)
β , (deg)	89.047(4)
γ , (deg)	71.513(5)
V, Å ³	1533.3(5)
Z	2
ρ_{calc} , g/cm ⁻³	1.610
Crystal size, mm ³	0.16 × 0.14 × 0.13
μ , mm ⁻¹	1.000
R1 ^a	0.0513
wR2 ^b	0.0935
R1 ^a	0.1755
wR2 ^b	0.1653
Goodness-of-fit on F ²	0.729
Reflections collected	11486
Independent reflections	7487

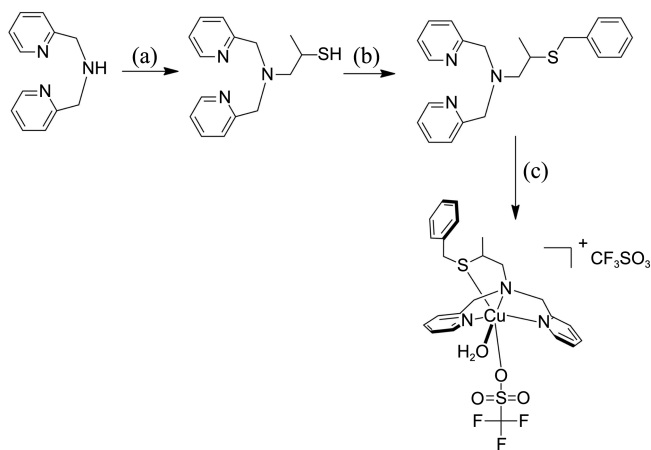
^aR1 = $\Sigma||F_o| - |F_c||/\Sigma|F_o|$. ^bwR2 = $\{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$

Results and Discussion

General Consideration and Synthesis of Catalyst. Cu-catalyzed oxidations of alcohols to aldehydes have been extensively studied because galactose oxidase (GO), a Cu-containing fungal enzyme oxidizes alcohols to corresponding aldehydes with the concomitant reduction of molecular oxygen to water.¹⁵ In GO's active site, the Cu(II) cation is coordinated by two equatorial histidines, an axial tyrosine, and a water molecule, along with the cross linked tyrosine. Very recently, Rokhsana *et al.* have reported that the Tyr-Cys cross linked sulfur environment is essential for fine-tuning the electronic structure of the GO's active site,¹⁶ and the sulfur environment may be responsible for the selective oxidation of benzylic alcohols over the aliphatic alcohols. We hypothesize that a Cu complex with an N3S coordination environment may mimic the activity of the active site of GO, leading to similar catalytic activity.

In order to prepare the N3S ligated Cu(II) catalyst **1**, first, the tetradentate ligand, BTPMPA was synthesized from dipicolylamine and an excess amount of propylene sulfide under reflux conditions; followed by benzylation¹⁷ (Scheme 1). Catalyst **1** was synthesized by treating a slight excess of the Cu(I)triflatebenzene complex with BTPMPA in acetonitrile at room temperature under-inert atmosphere, and the resulting yellow solution was exposed to air after 3 h. The resulting green solution was then diffused with THF to afford the block-shaped blue crystals after 2 days. The mass spectra of **1** show the molecular ion peak at 426.10 after the dissociation of H₂O and triflates with expected isotopic distribution ratio for Cu(BTPMPA), as shown in Fig. S1.

Crystal Structure of 1. Catalyst **1** crystallizes in a monoclinic system with the $P\bar{1}$ space group. Figure 1 shows the structure of catalyst, and Table 1 lists the selected inter atomic distances and angles. The crystal structure shows that the Cu(II) ion is coordinated to BTPMPA and a water molecule along with the labile triflate in the axial position. The bond distances between the Cu-N_(pyridyl) and Cu-N_(amine) are 1.990(5) Å and 2.045(4) Å, respectively.¹⁸ The distance between the S atom of benzyl thioether and Cu is 2.6212(19)



Scheme 1. (a) Propylene sulfide, CH₃CN, 120 °C; (b) benzyl bromide, Cs₂CO₃, TBAI, CH₃CN, 50 °C; (c) [Cu(CF₃SO₃)]-benzene, CH₃CN.

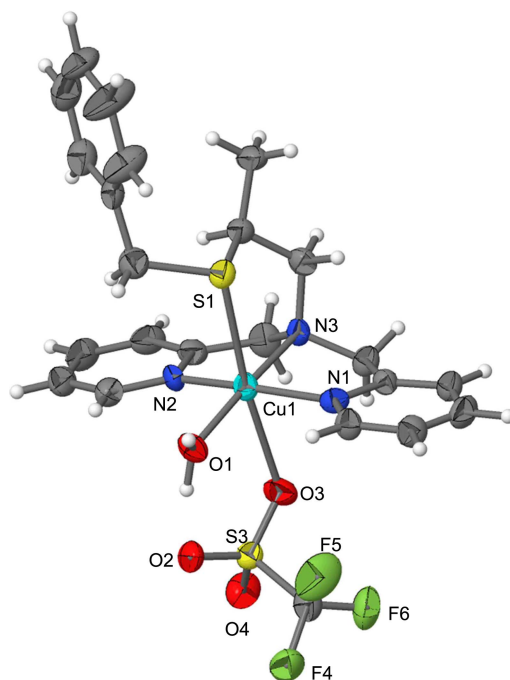


Figure 1. ORTEP drawing of **1** partial labeling without a counter ion (CF₃SO₃⁻), showing 50% probability of thermal ellipsoids.

Å, which is comparable to that of the reported complexes.¹⁹ Moreover, the equatorially coordinated H₂O molecule show intramolecular hydrogen bonding with the axially coordinated triflate anion. The distance between Cu-O_(triflate) and Cu-O_(H₂O) are 2.654(4) Å and 1.980(4) Å, respectively.²⁰ The relatively long distance from the Cu(II) ion to the triflate anion and H₂O molecule clearly shows that the latter two species can easily dissociate from the Cu(II) center to afford the {Cu(BTPMPA)}²⁺ species.

Electrochemical Studies of 1. The electrochemical property of the metal centre was tuned with the appropriate ligand environment. Lee *et al.* reported that the redox potential of a Cu cation with an N4 coordination environment was more negative than that with an N3S coordination environment.²¹ This result shows that the introduction of a soft ligand in the metal environment leads to a more positive redox potential than that in the Cu(N4) environment. In order to determine the redox potential of **1**, the cyclic voltammogram was recorded in CH₃CN using (Bu₄N)PF₆ as the electrolyte. Complex **1** showed a quasi-reversible voltammogram at a scan rate of 100 mV/s. A cathodic peak appeared at -0.247 mV and an anodic peak at -0.059 mV, and the redox couple was observed at 0.483 V vs. NHE, which is attributed to the Cu(II)/Cu(I) couple ($\Delta E = 188$ mV), as shown in Figure 2. Surprisingly, the redox potential of **1** was similar to the GO (400-500 mV vs. NHE).²²

Catalytic Activity of Complex 1. The similar structural feature and redox potential of complex **1** and the GO's active site inspired us to test the oxidation of alcohols using **1**. A Cu(II)-TEMPO/base system was chosen to evaluate the catalytic activity of **1** because the Cu(I) or Cu(II)/TEMPO/base systems have been extensively studied under aerobic

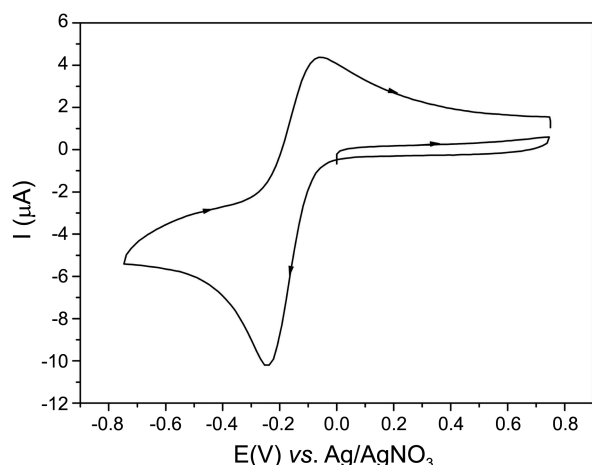


Figure 2. Cyclic voltammogram of **1** in CH₃CN at the scan rate of 100 mV/s.

and O₂ conditions and produce an environment-friendly by-product water.⁸ First, 4-methoxybenzyl alcohol was treated with 0.10 mol of the catalyst, 0.10 mol of TEMPO and 0.20 mol of a base, as the co-catalyst, under O₂ atmosphere in CH₃CN at 27 °C. The alcohol was completely converted to the corresponding aldehyde in 92% yield within 2 h at room temperature without any over-oxidized product. The reaction solvent was optimized, when DMF or toluene/CH₃CN was used, complete conversion was achieved, as opposed to the case when THF or CH₂Cl₂ was used. Thus, complete conversion of benzyl alcohol was achieved when either polar aprotic or mixed solvents (polar aprotic and non-polar) were used (Table S1). This result may be attributed to the improved solubility of the catalyst in polar solvents.

Different bases were screened for the catalyst system, however, it was found that the bases had no effect on the reaction time needed for complete conversion or the yield of the reaction (Table S2). In order to easily separate the catalyst from the reaction mixture, a mixture of CH₃CN and toluene with K₂CO₃ were used. With the optimized reaction condition, the oxidation of other substituted benzyl alcohols with the electron donating and withdrawing groups was tested using this method.

Table 3 shows that electron donating and withdrawing groups have no effect on the catalytic efficiency of **1**. The worst-case scenario for the catalyst was checked by raising the temperature to 75 °C and 100 °C in the oxidation of 4-methoxybenzyl alcohol. Even at the elevated temperature, only the corresponding aldehyde was obtained, and no over-oxidized product, *i.e.*, the corresponding carboxylic acid, was formed (Figs. S2 and S3). After the successful selective oxidation of primary benzylic alcohols, secondary benzylic alcohols and allylic alcohols were tested. The secondary benzylic alcohol, 1-phenylethanol was completely converted to acetophenone after 12 h and the allylic alcohol was selectively converted to the corresponding aldehyde after 8 h (Table 3). Furthermore, catalyst **1** was applied for the oxidation of benzylic alcohols containing heteroatoms, and the corresponding aldehydes were obtained in moderate yields.

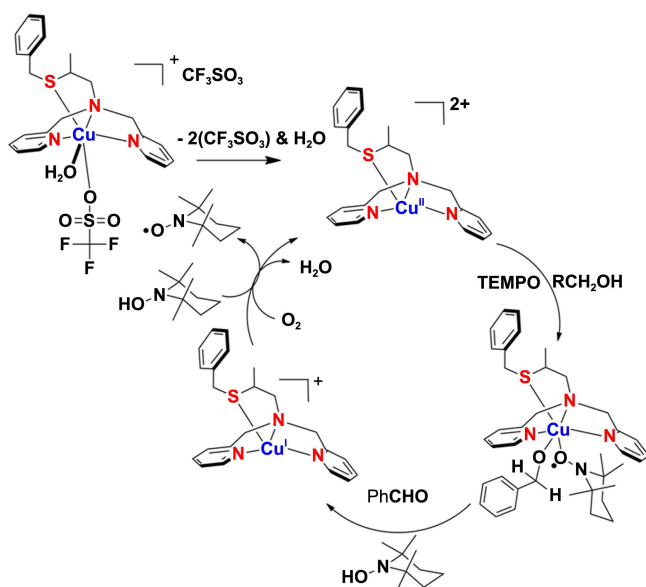
Table 3. Benzylic alcohols to corresponding aldehydes

$\text{R-CH}_2\text{-OH} \xrightarrow[\text{Toluene/CH}_3\text{CN, 27 }^\circ\text{C, O}_2 \text{ (balloon)}]{\text{0.1 mol } \mathbf{1}, \text{ 0.1 mol TEMPO, 0.2 mol K}_2\text{CO}_3} \text{R-CHO}$			
S.No	Product	Time (h)	Yield (%) ^a
1		2	92
2		3	80
3		4	72
4		6	63
5		5	88
6		12	91
7		14	92
8		8	88
9		20	60
10		20	68
11		3	90
12		5	85
13		12	none

Reaction Conditions: ^aIsolated yield, catalyst **1** (0.10 mol), TEMPO (0.10 mol), toluene/CH₃CN (1:1) mixture (10 mL), alcohol (1.00 mol), base (0.20 mol), 27 °C (O₂ balloon).

However, the oxidation of 2-phenylethanol with benzylic protons in β-carbon to the hydroxyl group, did not afford the corresponding aldehyde. Thus, catalyst **1** can selectively oxidize benzylic alcohols in preference to aliphatic alcohols.

In order to determine the effect of co-catalysts, oxidation reactions were carried out in the absence of a base and TEMPO. In the absence of the base, the reaction was prolonged for more than 24 h to allow for completion. In the absence of the co-catalyst, even after 6 h, only a negligible amount of the aldehyde was formed, indicating that the oxidation of alcohols using catalyst **1** also depends on the



Scheme 2. Proposed mechanism for catalytic cycle of complex **1**.

co-catalyst TEMPO and the base.

Based on previous reports and the above mentioned experiment results, including single crystal X-ray structure and product analysis, a possible mechanism for the oxidation was proposed, as shown in Scheme 2. The H₂O molecule and labile triflate ion may easily dissociate from catalyst **1**, resulting in a {CuN3S}²⁺ system having open coordination sites. Next, TEMPO and benzyl alcohol coordinate to the Cu(II) center of the catalyst, and TEMPO abstracts the benzylic proton, resulting in the {Cu(I)N3S}⁺ system and corresponding aldehyde. Finally, the {Cu(I)N3S}⁺ system may be oxidized by O₂ to {Cu(II)N3S}²⁺, thus completing the catalytic cycle.

Notably, catalyst **1** displays dramatic variation in solubility in various solvents. Therefore, it may be possible to separate **1** from the reaction mixture after the catalysis. Experiments were carried out using 4-methoxybenzyl alcohol as the substrate under the optimized reaction conditions to check the possibility. After the alcohol was converted to corresponding aldehyde, the solvent, CH₃CN, was removed from the reaction mixture to precipitate the catalyst. The precipitate was

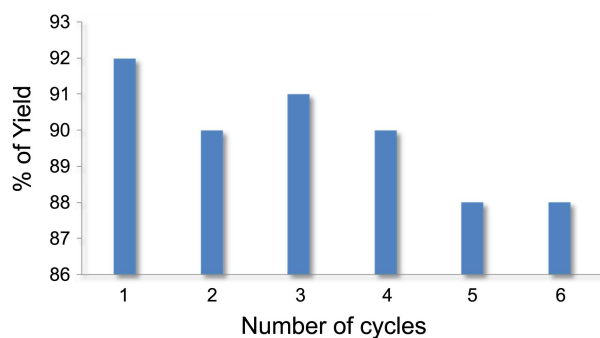


Figure 3. The yield of 4-methoxybenzaldehyde obtained at the number of re-cycles. Catalyst **1** (0.10 mol), TEMPO (0.10 mol), toluene/CH₃CN (1:1) mixture (10 mL), 4-methoxy benzyl alcohol (1.00 mol), base (0.20 mol), 27 °C (O₂ balloon).

then first washed with toluene to remove the product (aldehyde) and redissolved in CH₃CN to remove K₂CO₃. Thus, the catalyst could be recovered and reused in further oxidation reactions. Although the original color of the catalyst was changed from blue to green, 80-85% of the catalyst could be recovered from every cycle of the reaction and the catalytic activity was retained (Fig. 3). As expected, with the increase in the number of catalytic cycles of **1**, the reaction time for complete conversion of the alcohol to aldehyde also increased. In the sixth cycle, the reaction time for complete conversion was 3 h. The reusability of catalyst **1** shows that it is an environmentally benign and green catalyst that may reduce the waste generation.

Conclusions

Selective oxidation of alcohols to the corresponding aldehydes with structurally well-defined catalysts was needed to design recyclable catalyst systems by evaluating their solubility and other characteristics. Furthermore, the relationship between the structure and function of the catalyst was established to solve the existing limitations. The newly synthesized Cu(II) complex with an N3S coordination environment exhibits a redox potential of 0.483 V vs. NHE, similar to that of GO enzyme. Catalyst **1** selectively oxidized benzylic alcohols to the corresponding aldehydes without the formation of any over-oxidized product; however, aliphatic alcohols could not be oxidized. The catalyst can be recovered and reused for further oxidation reactions for at least six times, thus minimizing waste generation.

Supporting Information. CCDC 842409 contains the supplementary crystallographic data for compound **1**. This data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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