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ARTICLE

The roles of the phenol groups and auxiliary ligand of copper(II) complexes with tetradentate ligands in aerobic oxidation of benzyl alcohol

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Six copper (II) complexes with multidentate ligands, [Cu(**HL$_1$**)(OAc)(HOAc)] (**1**), [Cu(**HL$_2$**)(OAc)] (**2**), [Cu(**HL$_3$**)(OAc)] (**3**), [Cu**L$_4$**(OAc)] (**4**), [Cu(**HL$_2$**)Cl] (**5**), [Cu(**HL$_3$**)Cl] (**6**), {**H$_2$L$_1$** = [bis(3-*tert*-butyl-2-hydroxybenzyl)](2-pyridylmethyl)amine, **H$_2$L$_2$** = [(3-*tert*-butyl-2-hydoxybenzyl)(3-trifluoromethyl-2-hydroxybenzyl) (2-pyridylmethyl)]amine, **H$_2$L$_3$**= [bis(3-trifluoromethyl-2-hydroxybenzyl)] (2-pyridylmethyl)amine,**HL$_4$** = [bis(2-pyridylmethyl)] (3-*tert*-butyl-2-hydroxybenzyl)amine} are reported. The complexes were characterized by UV–vis spectroscopy, high resolution mass spectrum, X-ray single crystal diffraction analysis and electrochemistry.These copper(II) complexes have been investigated as catalysts for the aerobic oxidation of benzyl alcohol to benzaldehyde mediated by TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxyl) radical in water under ambient temperature. Mechanistic investigations revealed that the phenolate / phenol involved intramolecular proton transfer with bound substrate in catalysis and hence the presence of trifluomethyl group on the phenol ring affects significantly the catalysis since the substituent affects the acidity of the phenol and then the intramolecular proton transfer from the bound substrate. In the catalysis, the dissociation of the auxiliary ligand (Cl^- or OAc^-) occurred in S_N1 pathway and it is necessary for the substrate to bind. To complete the catalytic cycle, the cleaved auxiliary ligand rebinds to the metal center to regenerate the catalyst.

1. Introduction

The structural and mechanistic revelations of galactose oxidase (GOase) (Fig. 1 and Scheme S1), a copper enzyme catalyzing oxidation of an alcohol to corresponding aldehyde by molecular oxygen, have attracted a great deal of attention in both synthetic and biological community and initiated great enthusiasm in mimicking synthetically the mononuclear copper center of the enzyme in the past decades.[1, 2] This is not only because its unique function of catalyzing aerobic oxidation of primary alcohols to aldehydes with concomitant reduction of dioxygen to hydrogen peroxide under physiological conditions, but also due to the enormous industrial demand for aldehydes, which are ubiquitous "building blocks" in the synthesis of pharmaceuticals, agrochemicals and fine chemicals. During the past two decades, enormous structural and spectroscopic models of GOase have been developed.[3-25] In particular, model complexes derived from mono(pyridyl)alkylamines,[3, 19, 25] bis(pyridyl)alkylamine ligands,[9, 20, 21] triazacyclononanes[10, 22-24] and salen ligands[5, 8, 12, 15] have been extensively investigated and some of them showed from moderate to good catalytic efficiency on oxidation of alcohols to aldehydes.

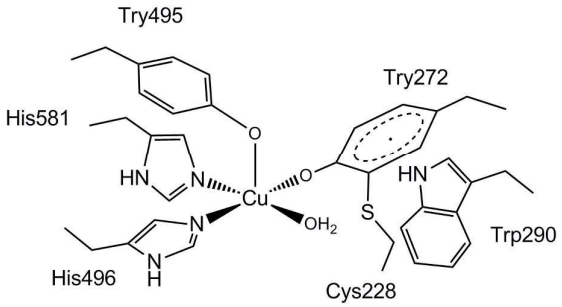

Fig. 1 The copper center of the active form of galactose oxidase (GOase).

Amongst the reported catalytic systems, a catalyst without requiring TEMPO as a co-catalyst is rare.[8, 9, 13, 25] In most cases, the presence of TEMPO for a catalyst based on either Cu(II) or Cu(I) to function is a must. Such a system was first reported by Semmelhack and coworkers in 1984.[26] Further development turned out that either Cu(I) or Cu(II) complexes with ligands of "N,N"/"N,O" donor set could be efficient catalysts for the aerobic oxidation of various alcohols.[27-30] For example, catalytic systems of the type of copper/2,2'-bipyridine/TEMPO system developed mainly by

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Electronic Supplementary Information (ESI) available:UV–vis spectra of ligands, internal standard method with calibration curve, characterization and crystallographic data of the copper complexes and mechanistic investigation. See: 10.1039/x0xx00000x.

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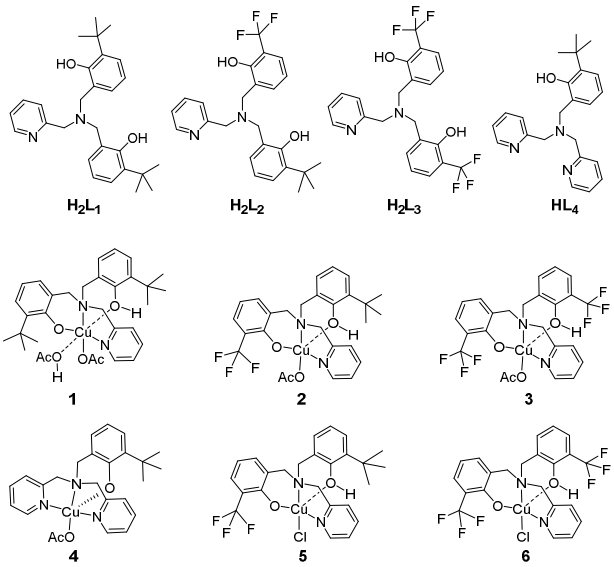
Sheldon,[31-33] Koskinen[34] and Stahl[35-38] groups showed efficient activity, particularly on the aerobic oxidation of aliphatic alcohols. However, despite considerable efforts have been devoted to this chemistry, many mechanistic issues remain to be answered. For example, how the electronic density of the metal center affects the catalytic efficiency and what is the difference in catalytic mechanism with / without phenolates as part of the coordinating sphere? Elucidating these mechanistic issues would have significance in understanding the catalyzing chemistry and developing novel catalysts for aerobic oxidation of alcohols. Furthermore, the reaction performs, in general, in organic solvents, such as acetonitrile. This is not practically favored due to obvious reason. By considering its environmental benignity and availability, water ought to be more favored solvent compared to organic ones. However, exploring catalytic system operational in water is not well developed.[39, 40]

As part of our efforts devoting to the chemistry of C–H bond activation catalyzed by those base metal complexes, such as iron and copper, under the inspiration of the catalytic functions of metalloenzymes, we have been interested in developing novel ligands and their iron / copper complexes as catalysts for direct hydroxylation of benzene into phenol using H_2O_2 as the oxidant. Our recent work reported a number of Fe(III) / Cu(II) complexes for the oxidation.[41-43] It has been revealed that the electron density of the metal centers correlates well to their catalytic activity. This electronic effect could be tuned accordingly by modifying the main ligands and varying auxiliary ones. With this preliminary work and being inspired by the aerobic oxidation of alcohols catalyzed by GOase, we are interested in employing multidentate ligands bearing N and phenolate O coordinating atoms to form Cu(II) complexes and further exploring their catalytic chemistry of the alcohols oxidation. Herein, we report the synthesis, characterization of copper complexes derived from multidentate ligands, $\mathbf{H_2L_1}$, $\mathbf{H_2L_2}$, $\mathbf{H_2L_3}$, and $\mathbf{HL_4}$ (Scheme 1). All the copper complexes [Cu($\mathbf{HL_1}$)(OAc)(HOAc)] (**1**), [Cu($\mathbf{HL_2}$)(OAc)] (**2**), [Cu($\mathbf{HL_3}$)(OAc)] (**3**),[Cu$\mathbf{L_4}$(OAc)] (**4**), [Cu($\mathbf{HL_2}$)Cl] (**5**), [Cu($\mathbf{HL_3}$)Cl] (**6**) were characterized by UV-vis spectra, high resolution mass spectrum, elemental analysis, cyclic voltammetry and single-crystal X-ray diffraction. These copper(II) complexes have been investigated as catalysts for the aerobic oxidation of benzyl alcohols to benzaldehydes mediated by TEMPO radical in water at ambient temperature. Our results indicated that the catalytic activity varies greatly. Among these complexes, complex **1** could quantitatively catalyze the oxidation whereas complex **3** showed extremely low activity. These variations in catalytic efficiency offer us a good opportunity to probe how the catalysis is affected by the variation in the coordination sphere of the catalysts. It turns out that the catalysis can be tuned by both the phenol / phenolate group(s) and the auxiliary ligands. Mechanistic investigations suggest that the penta-coordinated copper(II) complex underwent dissociating / rebinding of the auxiliary ligand. Based on our experimental evidences and those reported in literatures, a general catalytic mechanism was proposed.



Scheme 1 Ligands ($\mathbf{H_2L_1}$, $\mathbf{H_2L_2}$,$\mathbf{H_2L_3}$ and $\mathbf{HL_4}$) and their copper(II) complexes **1–6**.

2. Experimental

2.1 General procedures

Chemicals were purchased from Alfa Aesar and Sigma-Aldrich and used without further purification unless otherwise stated. Most of the organic solvents in this work were purified using drying agents. UV-vis absorption spectra were measured in the range from 200 nm to 800 nm on a Thermo Scientific Evolution 201 in acetonitrile. Elemental analyses were performed on an Elementar Vario MICRO. ^{1}H and ^{13}C NMRspectra were recorded on Varian 400 MR in $CDCl_3$ or d_6-DMSO.The aerobic oxidation of benzyl alcohol to benzaldehydeat room temperature in water with ambient air as the oxidant was monitored and quantitatively analyzed by gas chromatography (Agilent 7890) with a packed column of Restek capillary SE-54. The temperature of the GC column was set at 60 ^{o}C for 1 min and then was programmed to 150 ^{o}C at the rate of 15 ^{o}C min^{-1}. EPR spectra were recorded at 90 K on a Bruker EMX-10/12 spectrometer operating at 9.7 GHz and a cavity equipped with a Bruker Aquax liquid sample cell. Electrochemistry was performed in a gas-tighten three-electrode system in which avitreous carbondisk (ϕ = 1 mm) was used as a working electrode, a carbon strip as counter electrode, and Ag/AgCl (inner reference solution: 0.45 mol L^{-1}[N^nBu$_4$]BF$_4$+ 0.05 mol L^{-1}[N^nBu$_4$]Cl in dichloromethane) against which the potential of ferrocenium / ferrocenecouple is 0.55 V in 0.5 molL^{-1}[N^nBu$_4$]BF$_4$indichloromethane as described elsewhere.[44, 45] Ferrocene was added as an internal standard after electrochemical data collection was completed and all potentials are quoted against ferrocenium / ferrocene couple (Fc^+/Fc). Crystallographic data of the complexes were collected on a Gemini diffractometer with graphite-monochromated Mo–Kα radiation (λ = 0.71073 Å) or Cu–Kα radiation (λ =

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1.54178 Å or 1.54184 Å). The crystal structures were solved using direct methods in SHELXS program and refined by full-matrix least-squares routines, based on F^2, using the SHELXL package.[46] Details of crystal data and structure refinement for these complexes are provided in Table S1. Supplementary crystallographic data can further be found in CCDC *via* their CCDC numbers (1529087–1529090, 1529093 and 1529094 for complexes **1**–**6**, respectively).

2.2 Synthesis

2.2.1 Preparation of 3-*tert*-butyl-2-hydroxybenzaldehyde (A)

To a mixture of 2-*tert*-butylphenol (7.50 g, 50 mmol) in THF (100 mL) were added paraformaldehyde (10.20 g, 337 mmol), anhydrous magnesium dichloride (7.15 g, 75 mmol) and trimethylamine (26.1 mL , 187 mmol). The mixture was then heated to reflux for 12 h under stirring. After being cooled to room temperature, the mixture was acidified to pH = 3 with dilute HCl and extracted with ethyl acetate (3×30 mL). The organic layers were combined, dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give a yellow oily liquid which was purified by flash chromatography (eluent: petroleum ether). Yield: 7.22 g (81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.79 (d, J = 1.7 Hz, 1 H), 9.87 (s, 1 H), 7.54 (t, J = 12.4 Hz, 1 H), 7.38 (dt, J = 17.9, 9.0 Hz, 1 H), 6.99–6.88 (m, 1 H), 1.42 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.1, 161.2, 138.2, 134.1, 132.0, 120.6, 119.2, 34.8, 29.2.

2.2.2 Preparation of 3-trifluoromethyl-2-hydroxybenzyl (B)

B as a pale yellow solid (4.75 g, 50%) was analogously synthesized by using the same procedure employed for the preparation of **A** by replacing the 2-*tert*-butylphenolwith 2-trifluoromethylphenol (8.11 g, 50 mmol) as the reactant.^{1}H NMR (400 MHz, $CDCl_3$): δ 11.71 (s, 1H), 9.94 (s, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.75 (dd, J = 7.7, 1.3 Hz, 1H), 7.10 (t, J = 7.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.2, 159.7, 137.3, 134.0, 124.2, 121.5, 121.2, 119.2.

2.2.3 Preparation of (3-*tert*-butyl-2-hydroxybenzylaminomethyl)pyridine (C)

3-*tert*-butyl-2-hydroxybenzaldehyde (1.78 g, 10 mmol) was added to a stirred solution of 2-aminomethylpyridine (1.08 g, 10 mmol) in MeOH (30mL). The reaction turned to yellow immediately and the stirring was continued for 5–6 h at room temperature. Sodium tetrahydroborate (1.15 g, 30 mmol) was then slowly added under an ice bath, and the mixture was further stirred at ambient temperature for 12 h. Any volatiles were removed in vacuum to give a residue which was dissolved in water (50 mL). The mixture was then extracted with CH_2Cl_2 (3× 30 mL). The organic layers were combined, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The product (a white solid) was purified by flash chromatography (eluent: petroleum ether : ethyl acetate = 3 : 1). Yield: 2.25 g (83%). ^{1}H NMR (400 MHz, $CDCl_3$):δ 8.58 (d, J = 3.4 Hz, 1 H), 7.66 (td, J = 7.6, 1.4 Hz, 1 H), 7.21 (d, J = 7.7 Hz, 3 H), 6.84 (d, J = 6.6 Hz, 1 H), 6.72 (t, J = 7.5 Hz, 1 H), 3.99 (s, 2 H), 3.91 (s, 2 H), 1.43 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.9, 157.3, 149.5, 136.7,136.6, 126.8, 126.0, 122.7, 122.6, 122.4, 118.3, 53.1, 52.4, 34.7, 29.6.

2.2.4 Preparation of 2-(3-trifluoromethyl-2-hydroxybenzylaminomethyl)pyridine (D)

D as a pale yellow oily liquid (1.98 g, 70%) was analogously synthesized by using the procedure employed for the preparation of **C** by replacing the 3-*tert*-butyl-2-hydroxybenzaldehydewith3-trifluoromethyl-2-hydroxybenzaldehyde (8.11 g, 50 mmol) as the reactant. The product was purified by flash chromatography (eluent: petroleum ether : ethyl acetate = 3 : 2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, J = 4.0 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.19 (t, J = 8.7 Hz, 2H), 7.10 (d, J = 7.3 Hz, 1H), 6.79 (t, J = 7.6 Hz, 1H), 4.03 (s, 2H), 3.91 (s, 2H). ^{13}C NMR (101MHz,d_6-DMSO): δ 158.2, 157.9, 149.4, 137.5, 137.2, 132.9, 126.1, 125.4, 125.0, 123.3, 122.8, 122.8, 117.9, 53.0, 51.1.

2.2.5 Preparation of ligand H_2L_1

To a solution of 2-(3-*tert*-butyl-2-hydroxybenzylaminomethyl) pyridine (1.35 g, 5 mmol) in MeOH (30 mL) was added 3-*tert*-butyl-2-hydroxybenzaldehyde (0.89 g, 5 mmol) and acetic acid (1eq.). Under ice temperature, sodium cyanotrihydroborate (0.95 g, 15 mmol) was further slowly added before the reaction was continuously stirred at ambient temperature for 24 h. The solvents were removed in vacuum to produce a residue which was dissolved in water (50 mL). The mixture was then extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent: petroleum ether). Yield: 1.30 g (60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.74 (s, 2H), 8.70 (d, J = 4.3 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.32–7.26 (m, 1H), 7.21 (d, J = 7.6 Hz, 2H), 7.09 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 7.3 Hz, 2H), 6.74 (t, J = 7.5 Hz, 2H), 3.83 (d, J = 5.2 Hz, 6H), 1.42–1.39 (m, 18H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.9, 157.3, 149.5, 136.7, 136.6, 126.8, 126.0, 122.7, 122.6, 122.4, 118.3, 53.1, 52.4, 34.7, 29.6.

2.2.6 Preparation of ligand H_2L_2

Ligand **H_2L_2** as a white solid (1.56g, 70%) was analogously synthesized by using the procedure employed for the preparation of **H_2L_1** by replacing the 3-*tert*-butyl-2-hydroxybenzaldehydewith3-trifluoromethyl-2-hydroxybenzaldehyde. The product was purified by flash chromatography (eluent : petroleum ether : ethyl acetate = 10 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 4.3 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.32 (dd, J = 16.7, 7.0 Hz, 2H), 7.22 (d, J = 7.7 Hz, 1H), 7.15 (d, J = 7.7 Hz, 1H), 6.88 (t, J = 6.7 Hz, 2H), 6.74 (t, J = 7.6 Hz, 1H), 3.86 (s, 2H), 3.81 (d, J = 8.9 Hz, 4H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.4, 156.1, 154.8, 148.0, 138.0, 137.3, 135.2, 127.9, 126.9, 126.6, 125.5, 124.3, 123.6, 123.0, 122.8, 121.5, 118.6, 118.5, 57.2, 54.5, 53.9, 34.8, 29.5.

2.2.7 Preparation of ligand H_2L_3

To a solution of 2-(3-trifluoromethyl-2-hydroxybenzylaminomethyl)pyridine (1.41 g, 5 mmol) in MeOH (30mL) was added 3-trifluoromethyl-2-hydroxybenzyl (0.95 g, 5 mmol) and acetic acid (1eq). Under ice temperature, sodium cyanotrihydroborate (0.95 g, 15 mmol) was further added slowly before the reaction was continuously stirred at ambient temperature for 12 h. The solvents were removed in vacuum to produce a residue which was dissolved in water (50 mL). The mixture was then extracted with CH_2Cl_2 (3 × 30 mL). The

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organic layers were combined, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. A white solid was collected by filtration, washed successively with small amounts of methanol (3 × 10 mL) and dried in vacuum. Yield: 1.71 g (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.84 (s, 2 H), 8.69 (d, J = 4.3 Hz, 1 H), 7.79 (td, J = 7.7, 1.6 Hz, 1 H), 7.49 (d, J = 7.3 Hz, 2 H), 7.37 (dd, J = 6.8, 5.3 Hz, 1 H), 7.23 (d, J = 8.6 Hz, 2 H), 7.16 (d, J = 7.8 Hz, 1 H), 6.87 (t, J = 7.6 Hz, 2 H), 3.86 (s, 4 H), 3.81 (s, 2 H). ^{13}C NMR (101 MHz,d_6-DMSO): δ 155.9, 155.7 148.2, 138.7, 135.0, 126.4, 125.8, 124.8, 124.4, 123.6, 123.1, 119.1, 56.2, 54.9.

2.2.8 Preparation of ligand HL_4

Ligand **HL_4** as a white solid (0.99 g, 55%) was analogously synthesized by using the procedure employed for the preparation of **H_2L_1** by replacing the 3-*tert*-butyl-2-hydroxybenzaldehydewith2-pyridinecarboxaldehyde. The product was purified by flash chromatography (eluent: petroleum ether : ethyl acetate = 1 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 2 H), 7.58 (d, J = 7.4 Hz, 2 H), 7.33 (d, J = 7.2 Hz, 2 H), 7.15 (dd, J = 21.0, 5.5 Hz, 3 H), 6.90 (d, J = 5.7 Hz, 1 H), 6.69 (t, J = 7.3 Hz, 1 H), 3.82 (d, J = 20.2 Hz, 6 H), 1.45 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0, 156.4, 149.0, 136.7, 136.6, 128.0, 126.2, 123.5, 122.7, 122.2, 118.2, 59.3, 57.7, 34.8, 29.5.

2.2.9 Preparation of complexes 1–4

A solution of $Cu(CH_3COO)_2{\cdot}H_2O$ (0.11 g, 0.55 mmol) in acetonitrile (5 mL) was mixed with a dichloromethane solution (3 mL) of ligand **H_2L_1** (0.22 g, 0.5 mmol) and the reaction turned dark blue. After being stirred at room temperature for 8 h, the solution was centrifuged and the green solid was washed with H_2O followed with hexanes and finally dried in vacuum. Dark blue crystals of complex **1** (263.6 mg, 86%) were obtained by recrystallization from dichloromethane/hexanes. HRMS (ESI, positive), *m/z* 494.1960 (calcd. for [**1**-OAc-HOAc]$^+$ = 494.1995), 535.2287 (calcd. for [**1**-OAc-HOAc+CH_3CN]$^+$ = 535.2260). Elemental analysis for complex **1** ($C_{32}H_{42}CuN_2O_6$, FW = 614.2420), calc. (%): C, 62.57; H, 6.89; N, 4.56. Found (%): C, 62.84; H, 6.89; N, 4.22.

Complexes **2–4** were synthesized by using the same procedure employed for the preparation of complex **1** by replacing the ligand **H_2L_1** with ligand **H_2L_2**, **H_2L_3** and **HL_4**, respectively. Complex **2** (254.7 mg, 90%): HRMS (ESI, positive), *m/z* 588.1378 (calcd. for [**2**+Na]$^+$ = 588.1273), 547.1547 (calcd. for [**2**-OAc+CH_3CN]$^+$ = 547.1508). Elemental analysis for complex **2** ($C_{27}H_{29}CuN_2O_4$, FW = 566.0802), calc. (%): C, 57.29; H, 5.16;N, 4.95. Found (%): C, 57.78; H, 4.95; N, 5.09. Complex **3** (231.2 mg, 80%): HRMS (ESI, positive), *m/z* 559.0736 (calcd. for [**3**-OAc+CH_3CN]$^+$ = 559.0756). Elemental analysis for complex **3** ($C_{24}H_{20}CuF_6N_2O_4$, FW = 577.9704), calc. (%): C, 49.88; H, 3.49; N, 4.85. Found (%): C, 49.83; H, 3.43; N, 4.72. Complex **4** (200.5 mg, 83%): HRMS (ESI, +), *m/z* 423.1409 (calcd. for [**4**-OAc]$^+$ = 423.1372), 464.1681 (calcd. for [**4**-OAc+CH_3CN]$^+$ = 464.1637), 905.2899 (calcd. for [2***4**-OAc]$^+$ = 905.2877). Elemental analysis for complex **4** ($C_{25}H_{29}CuN_3O_3{\cdot}1.5H_2O$, FW = 510.0935), calc. (%): C, 58.87; H, 6.32; N, 8.24. Found (%): C, 58.90; H, 6.22; N, 8.20.

2.2.10 Preparation of complexes 5 and 6

A solution of $CuCl_2{\cdot}2H_2O$ (0.09 g, 0.5 mmol) in methanol (3 mL) was mixed with a methanol solution (3 mL) of ligand **H_2L_2** (0.22 g, 0.5 mmol). The reaction turned blue and then a blue precipitate formed gradually. After being stirred at room temperature for 8 h, the precipitate was collected by filtration, washed successively with small amounts of H_2O and hexanes, respectively, and then dried in vacuum. Blue crystals of complex **5** (236.0 mg, 87%) were obtained by recrystallization from methanol/diethyl ether. HRMS (ESI, positive), *m/z* 547.1501 (calcd. for [**5**-Cl+CH_3CN]$^+$ = 547.1507). Elemental analysis for complex **5** ($C_{25}H_{26}ClCuF_3N_2O_2{\cdot}1.5H_2O$, FW = 542.4862), calc. (%): C, 52.73; H, 5.13; N, 4.92. Found (%): C, 52.53; H, 4.64; N, 4.75.

Complex **6** was synthesized by using the same procedure employed for the preparation of complex **5** by replacing the ligand **H_2L_2** with ligand **H_2L_3**. Complex **6** (221.7 mg, 80%): HRMS (ESI, positive), *m/z* 559.0771 (calcd. for [**6**-Cl+CH_3CN]$^+$ = 559.0756). Elemental analysis for complex **6** ($C_{22}H_{17}ClCuF_6N_2O_2$, FW = 554.3764), calc. (%): C, 47.66; H, 3.09; N, 5.05. Found (%): C, 47.12; H, 3.08; N, 4.78.

2.3 Catalytic assessment

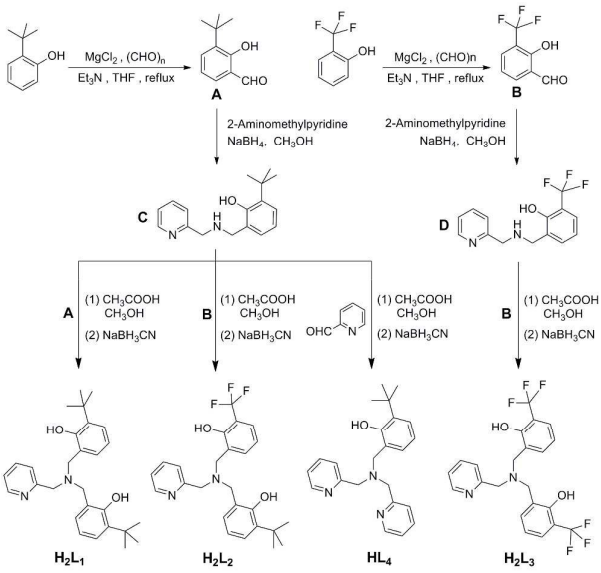
A typical procedure is as follows: In a reaction vessel fitted with a water condenser was added benzyl alcohol (0.55 g, 5 mmol), copper complex (0.015 mmol, 0.3 mol%), K_2CO_3(1.25 mmol, 2.5 mol%), TEMPO (0.25 mmol, 5 mol%) and finally water (5 mL). The reaction was carried out at 25 °C for 24 h under rigorously stirring before it was extracted with ethyl acetate (3 × 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and 0.5mL of 1,2-dichlorobenzene (138.98 mg / mL) in CH_3CN was added to the organic phase as an internal standard. The products were diluted to 20 mL with ethyl acetate and analyzed by gas chromatography using the internal standard method. Quantitative analysis of benzaldehyde was achieved by establishing their calibration curve with a linear equations under optimized conditions, A_R = 0.01716w − 0.1751 (R^2 = 0.9988) for benzaldehyde (Fig. S1), where A_R is the ratio of the peak areas of the analyte (benzaldehyde) and the internal standard 1,2-dichlorobenzene, w (mg) is the mass of the analytes. The yield of benzaldehyde was calculated as follows: benzaldehyde (mmol) / benzyl alcohol initially used (mmol) × 100%.

3. Results and discussion

3.1 Synthesis of ligands and their copper complexes

The multidentate ligands, **H_2L_1**, **H_2L_2**, **H_2L_3** and **HL_4**, were synthesized by using modified literature procedures with some modifications (Scheme 2).[47, 48] Treatment of *ortho*-substituted phenols with paraformaldehyde and $MgCl_2$with the presence of Et_3N under reflux gave substituted salicylaldehydes **A** and **B** in good yields.[49] Aldehydes **A** and **B** reacted furtherwith2-aminomethylpyridine to form the secondary amines **C** and **D**, respectively. Ligands **H_2L_1**, **H_2L_2**, **H_2L_3** and **HL_4** were subsequently obtained by the reaction of **C** and **D** with corresponding aldehydes, respectively, employing sodium cyanoborohydride as reducing reagent in the presence of a

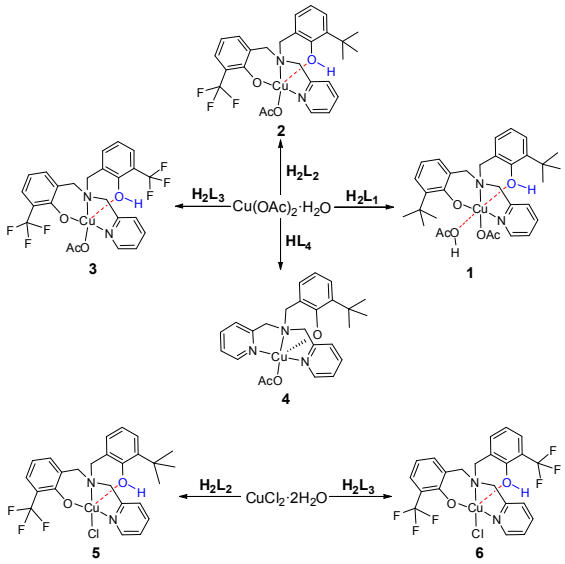
small amount of acetic acid.[48] By using the mild reducing agent $NaBH_3CN$ under acidic condition, the further reduction of the aldehydes were inhibited and the reaction yields of the ligands improved from less than 40% to around 70%. Ligands $\mathbf{H_2L_1}$ and $\mathbf{HL_4}$ were prepared in good yield (about 80%).[19, 50, 51] However, the procedure employed in this work avoided N-alkylation of an amine with substituted bromides simplified the reaction.



Scheme 2 Synthesis of ligands $\mathbf{H_2L_1}$, $\mathbf{H_2L_2}$, $\mathbf{H_2L_3}$ and $\mathbf{HL_4}$.

The synthetic routes of copper complexes are shown in Scheme 3. Treatment of $Cu(OAc)_2{\cdot}H_2O$ with the four ligands in the absence of base led to the formation of mononuclear complexes **1–4**, respectively. In complexes **1–3**, one of the phenol groups is not being deprotonated. To examine the influence of an auxiliary ligand coordinated to the metal center on the catalytic activity, ligands $\mathbf{H_2L_2}$ and $\mathbf{H_2L_3}$ were reacted respectively with $CuCl_2{\cdot}2H_2O$ and mononuclear complexes **5** and **6** formed. Similar to those in complexes **1–3**, one of the phenol groups in these complexes is also not being deprotonated. For comparison, chloride-bound analogue were attempted to be prepared by the reaction of ligand $\mathbf{H_2L_1}$ with $CuCl_2{\cdot}2H_2O$. But to our biggest surprise, although a complex analogous to complexes **2** and **3** was obtained, preliminary result showed that one of the phenol rings was chemically modified (Fig. S2). This exception makes it an unsuitable complex for the supposed comparison and we will not discuss it further in this work.

Complexes **1–6** are soluble in polar solvents such as MeOH, DMF and MeCN, and slightly soluble in water. All complexes were synthesized in decent yields (over 80%) and fully characterized by UV-vis spectra, high resolution mass spectrum, elemental analysis, cyclic voltammetry (CV, *vide infra*) and X-ray single-crystal diffraction. The UV-vis spectra of complexes **1–6** and the ligands are shown in Fig. 2. With the exception of two intense absorption bands at around 250 and 300 nm deriving from intraligand $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions (Fig. S3), the spectra of these Cu(II) complexes exhibit similar spectral profiles, displaying a dominating band at *ca*. 480 nm (ε = 800-1300 L mol^{-1} cm^{-1}) and a less intense shoulder at *ca*. 700 nm (ε = 100-270 L mol^{-1} cm^{-1}) (Table S3). Comparison with the literature data[9, 52] shows that the former band arises from a phenolate-to-copper(II) charge transfer (CT) while the latter is assigned to d–d transitions.



Scheme 3 Synthesis of copper complexes **1–6**.

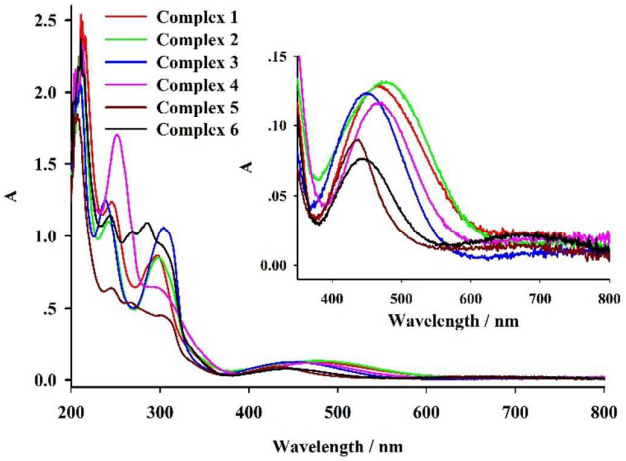


Fig. 2 UV–Vis absorption spectra of complexes **1–6** (10^{-4} mol L^{-1}) in MeCN

3.2 X-ray crystal structures

Crystals suitable for X-ray diffraction analysis were obtained upon slow evaporation in methanol / dichloromethane or methanol / diethyl ether solution. The ellipsoid plots of complexes **1–6** are depicted in Fig. 3. All the crystallographic data are given in Table S1 and selected bonding parameters are tabulated in Table S2. The geometries around the copper center in complexes **2–6** can be considered as a distorted

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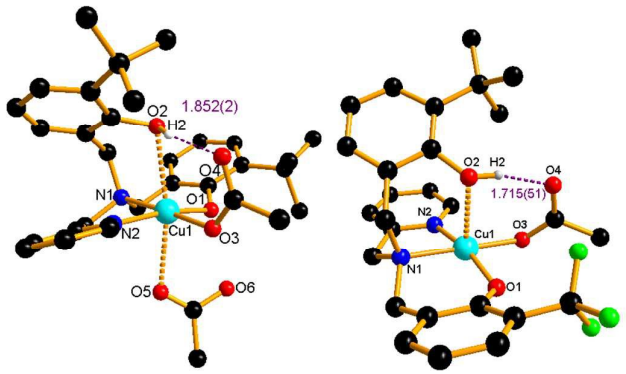
square pyramid with "$N_1N_2O_1O_3$", "$N_1N_2O_1Cl_1$" or "$N_1N_2O_1O_2$" as the basal plane. The equatorial square plane around the Cu(II) center in these complexes were formed by one tertiary amine N1, one pyridine N2 and one phenolato oxygen O1 donors from the ligand, as well as one oxygen O3 from an acetate anion (complexes **1**–**3**) or chloride Cl1 (complexes **5** and **6**) or pyridine N3 (complex **4**). The axial positions are occupied by a non-deprotonated phenol while the other axial binding site is unoccupied. But complex **1** adopts a distorted octahedral geometry in which the sixth coordinating site is loosely bound by an acetic acid.

The disparity of the Cu–N bond distances, the one assigned to Cu–$N_{pyridine}$ (Cu1–N2 and Cu1–N3) being slight shorter than the bond (Cu1–N1) concerning the tertiary amine N-atoms (Table S2), is usual and comparable with those reported in the literatures.[25, 43, 53] The distances of Cu1–O2 bond assigned to Cu–O_{phenol} in complexes **1**–**3**, **5** and **6** are over 0.4 Å longer than the Cu1–O1 bonds, reflecting the weak donor capability of the phenol in these complexes (Table S2). However, complex **1** adopts a octahedral coordination geometry because the bound acetic acid, as mentioned above, proximity to the copper center (Cu1···O5 bond distance of 2.645 Å) led to a six-coordinated mode. In this case, the Cu environment will be defined as "$N_1N_2O_1O_3$" in the equatorial plane and two O-atoms from the chelating ligand and the acetic acid, respectively, in the two axial sites. It is noticeable that the Cu1–O2 bond distance (2.637(2) Å) in complex **1** is much longer than those observed in complexes **2**, **3**, **5** and **6**, indicative of very weak coordination between the phenol and metal center. The distances of Cu–N and other Cu–O bonds are similar to those observed in complexes **2**–**6**. It is noteworthy that in complexes **1**–**3**, the auxiliary ligand acetate anion forms a strong intramolecular hydrogen bond, O2–H2···O4, with the hydrogen atom of the axial phenol to form a six-member ring, Fig. 3. In complex **3**, further intramolecular hydrogen bond of the same O atom with one F atom on the axial phenol ring is observed to form again a six-member ring, Fig. 3. This may explain why the acetate anion dissociates more difficultly than Cl^- as indicated by its conductivity in acetonitrile (*vide infra*). The involvement of F atom in forming intramolecular hydrogen bond is also observed in complex **6** as shown in Fig. 3.



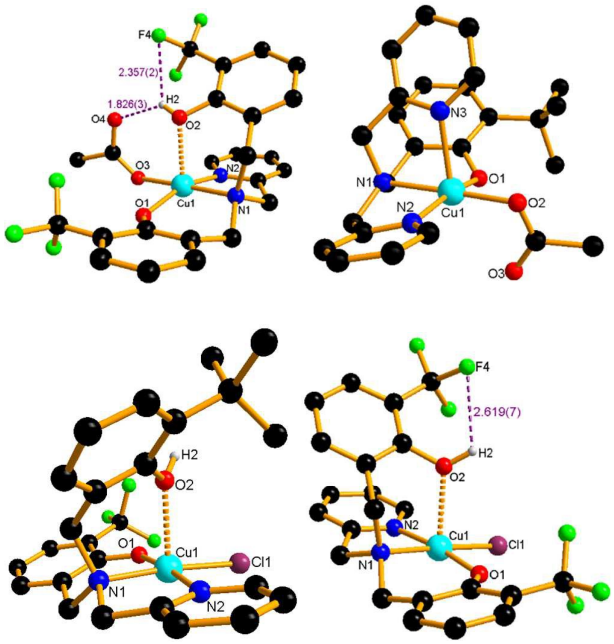


Fig. 3 Crystal structures of complexes **1**–**6** (most of the hydrogen atoms and solvent are omitted for clarity) and their numbering begins from the top-left to the bottom right with complex **6** as the last one.

3.3 Catalytic oxidation of benzyl alcohol to benzyl aldehyde

To optimize the reaction conditions, complex **1** was used as the catalyst. It was found that no catalytic activity could be observed without TEMPO (Entries 1 and 2, Table 1). In analogues copper complexes catalytic systems, aerobic oxidation of benzylic alcohol to benzaldehyde by using air as an oxidant in the absence of TEMPO has been achieved.[13, 25] It was argued that the strong electron-donating effect of the *tert*-butyl group can significantly diminishes the ability of the phenolate ring to delocalize the phenoxy radical during the catalysis, particularly on the ortho-position of the equatorial phenolate ring.[13, 25, 54] Furthermore, absence of TEMPO means that the metal center ought to be sufficiently nucleophilic to activate oxygen. Indeed, there was a report when the copper center is strongly nucleophilic, good catalytic efficiency could be also achieved without the addition of TEMPO.[55]

In addition to the radical, both the base and solvent affect severely the catalytic reaction as well (Entries 4-12, Table 1). As shown in Table 1, in aqueous medium, either Cs_2CO_3 or K_2CO_3 gave nearly quantitative yield (Entries 4 and 5, Table 1). Throughout the investigation, K_2CO_3 was employed as the external base by using water as the solvent. To examine whether the application of an external base depends on the acidity of the phenol groups, complex **3** which bears a trifluomethyl group was used as the catalyst under various basic conditions (Entries 18-22, Table 1). The results show that both complexes prefer K_2CO_3 as the external base.

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Without any ligand, simple copper salts, either $(Cu(OAc)_2$ or $CuCl_2)$, gave quite low yields whereas the addition of bipyridine can improve significantly the catalysis (Entries 13 and 14; 23 and 24, Table 1). This is attributed to that coordinating the ligand to the metal center increases its electron density and hence improves the catalysis. Using $(NH_4)_2S_2O_8$ or $(C_6H_5CO)_2O_2$ to replace TEMPO led to nearly no activity (Entries 15 and 16, Table 1).

Table 1 Optimizing the reaction conditions for the oxidation of benzyl alcohol to benzylaldehyde.[a]

Entry	Catalyst	Base / solvent	Yield (%)[b]
1	**1**	K_2CO_3/H_2O	trace
2	**1**	K_2CO_3/CH_3CN	trace
3	**1**/TEMPO	K_2CO_3/CH_3CN	20 ± 3
4	**1**/TEMPO	K_2CO_3/H_2O	96 ± 3
5	**1**/TEMPO	Cs_2CO_3/H_2O	97 ± 1
6	**1**/TEMPO	H_2O	21 ± 3
7	**1**/TEMPO	K_2CO_3/H_2O/CH_3CN [c]	26 ± 3
8	**1**/TEMPO	KOC_4H_9/H_2O	71 ± 1
9	**1**/TEMPO	Et_3N/H_2O	61 ± 1
10	TEMPO	K_2CO_3/H_2O	trace
11	**1**/TEMPO	Et_3N /CH_3CN	59 ± 1
12	**1**/TEMPO	Et_3N /CH_2Cl_2	15 ± 3
13	$Cu(OAc)_2$/TEMPO	K_2CO_3/H_2O	18 ± 1
14	$CuCl_2$/TEMPO	K_2CO_3/H_2O	28 ± 3
15	**1** / $(NH_4)_2S_2O_8$	K_2CO_3/H_2O	7 ± 3
16	**1** / $(C_6H_5CO)_2O_2$	K_2CO_3/H_2O	6 ± 1
17[d]	**1**/TEMPO	K_2CO_3/H_2O	81 ± 2
18	**3**/TEMPO	K_2CO_3/H_2O	14 ± 2
19	**3**/TEMPO	Et_3N/H_2O	11 ± 1
20	**3**/TEMPO	KOC_4H_9/H_2O	20 ± 5
21	**3**/TEMPO	KOH/H_2O	13 ± 3
22	**3**/TEMPO	Cs_2CO_3/H_2O	33 ± 3
23	**bpy**/TEMPO/$CuCl_2$	K_2CO_3/H_2O	67 ± 4
24	**bpy**/TEMPO/$Cu(OAc)_2$	K_2CO_3/H_2O	63 ± 1

[a]Reaction conditions: solvent(s) (5 mL), benzyl alcohol (5 mmol), catalyst (0.015 mmol), air, K_2CO_3 (1.25 mmol), TEMPO (0.25 mmol), 25 ^oC, 24 h.
[b]Yields calculated by GC analysis.
[c]H_2O : CH_3CN = 1 : 1
[d]Reaction conditions: solvent (5 mL), benzyl alcohol (5 mmol), catalyst (0.015 mmol), air, K_2CO_3 (1.25 mmol), TEMPO (0.125 mmol), 25 ^oC, 24 h. When TEMPO was changed to 1%, 0.5% and 0.3%, the yield dropped further to 61%, 39% and 28%, respectively.

Under the optimized conditions, the rest of the complexes were examined for their catalysis on the oxidation of benzyl alcohol, Table 2. As shown in Table 2, it was found that complex **1** exhibited the best catalytic performance among the copper complexes. By further analyzing the yields shown in Table 2, it turns out that there are three factors affecting significantly the catalytic performance of these complexes, the substituents on the phenol groups, the auxiliary ligands, and the number of phenol group. As suggested by the reduction potentials (Table 2 and Fig. S4), either varying the substituents on the phenol groups or the number of the phenol group, the reduction potentials does not change substantially, which suggests that the two factors do not have much direct electronic effect on the copper center.

However, replacing the acetate with a chloride shifts the reduction potential positively by about 300 mV. For complex **1**, no comparison can be made due to lacking of its chloride analogue as mentioned earlier. However, for the other two pairs, complexes **2** and **5**; **3** and **6**, this replacement enhanced greatly the catalytic activity, Table 2. The observations suggest that relatively low electron density on the metal center is beneficial to the catalysis, which is opposite to what we reported previously in the oxidation of benzene to phenol by hydrogen peroxide catalyzed by iron or copper complexes, that is, complexes with more negative potentials showed better catalytic activity.[42, 43] This may be due to that in the hydroxylation of benzene, the oxidant binding to the metal center to generate hydroxyl radical is essential in the catalysis. In the oxidation of alcohols, substrate binding may be important since strong Lewis acidity, i. e. low electron density on the metal center or more positive reduction potential, is an advantage for this process. The observations indicate also that although the presence of trifluoromethyl group on the phenol ring(s) does not affect significantly the electron density on the metal center, it does drastically decrease the catalytic activity. Therefore, questions arisen are: How does the trifluoromethyl group on the phenol ring(s) affect the catalytic activity? What is the role of the phenol group in the catalysis? How does the auxiliary ligand correlate to the catalytic activity? There is no doubt that having answers to these questions might shed some light on the catalytic mechanism.

Table 2 Comparison in catalytic activity on the aerobic oxidation of benzyl alcohol to benzyl aldehyde.[a]

Complex	Auxiliary	Number	Number	[c]Ep(Cu^{2+}	Yield(%)[b]

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	ligand	of phenol group	of $-CF_3$ group	$\rightarrow Cu^+$)	
1	Acetate	2	0	–1.08	96 ± 3
2	Acetate	2	1	–1.05	45 ± 1
3	Acetate	2	2	–0.97	14 ± 2
4	Acetate	1	0	–1.00	70 ± 1
5	Cl^-	2	1	–0.67	82 ± 2
6	Cl^-	2	2	–0.67	50 ± 2

[a]Reaction conditions: solvent(s) (5 mL), benzyl alcohol (5 mmol), catalyst (0.015 mmol), air, K_2CO_3 (1.25 mmol), TEMPO (0.25 mmol), 25 °C, 24 h.
[b]Yields calculated by GC analysis.

3.4 Mechanistic investigation

It is well known that a phenol radical in the galactose oxidase plays an important role in the catalytic oxidation of alcohol by oxygen.[2, 6-9, 48, 56] As the schematic structural view of the metal center indicated (Fig. 1), the copper center is surrounded by two imidazole and two phenol groups. Being inspired by this chemistry, we synthesized three tetradentate ligands, $\mathbf{H_2L_{1-3}}$, which bear two phenol groups and $\mathbf{HL_4}$ in which there is only one phenol group (Scheme 2). The reaction of these ligands with $Cu(OAc)_2$ and / or $CuCl_2$ led to complexes **1**–**6**. Since there have been many reports showing that it is not a must for a copper complex to possess phenol groups to function as catalysts for the alcohol oxidation,[27, 28, 57, 58] it comes to a question, whether the phenol groups in complexes **1**–**6** play such a role of forming a radical at all.

To clarify this, we tuned the ligand by changing the substituents on the phenol ring from $C(CH_3)_3$ to CF_3 and varied the number of phenol group in the ligand ($\mathbf{HL_4}$). As suggested by the reduction potentials of the complexes (Table 2), the change in substituent exerted weak electronic effect on the metal center. However, the catalytic activity changed dramatically with the alterations. When the auxiliary ligand is the same (acetate), the substituent *ortho* to the phenol group switching from $C(CH_3)_3$ to CF_3 group decreases the activity significantly. One CF_3 group led to decreases in activity by half. When both $C(CH_3)_3$ groups were replaced by a CF_3 group, the activity decreased by 80%. Reducing the number of phenol group in the multidentate ligand ($\mathbf{HL_4}$, complex **4**), the activity dropped by about 30%. It is clear that the phenolate / phenol groups in the catalysis are not a spectator. Furthermore, the effect is not exerted through altering the electronic density of the metal center as indicated by their hardly changed reduction potentials.

As we observed before,[43] an alcohol can bind to the sixth binding site. Electronic spectrally-monitoring and electrochemistry indicate substantial change when the substrate is added, Fig. S5. This is also in agreement with the EPR evidence (Fig. S6). There is a slight exception for complex **1** which bears a loosely bound acetic acid at its axial position. This acetic acid ought to dissociate easily in water. Thus for the substrate binding, there are two possible pathways. The substrate can approach the metal center at the second axial position and then the auxiliary ligand dissociates to restore the preferred five-coordinated mode, that is, S_N2 pathway. If S_N1 pathway is adopted, the auxiliary ligand, OAc^- or Cl^-, must dissociate first for the substrate to bind. As shown in Table 1, complex **1** exhibited enhanced activity in polar solvent. This solvent-dependent catalytic activity suggests strongly that a S_N1 mechanism may be adopted in the catalysis. To confirm this, we measured simply their conductivity (Table S4). Indeed, complexes **5** and **6** show much large conductivity compared to their acetate-bound analogues. The relative difficulty in dissociation of the acetate from the metal center is in good agreement with the intramolecular hydrogen bonding discussed earlier, which may strengthen its coordination to the copper center to deter its dissociation. For the bound chloride, no such an intramolecular hydrogen bonding exists. This may explain their variation in catalytic activity with the auxiliary ligands.

If the dissociation is a necessary step in the catalysis, to regenerate the catalyst, the initially cleaved auxiliary ligand must undergo rebinding. To confirm this hypothesis, we examined how the catalysis is affected by additionally added either acetate or chloride by using complex **6** as the catalyst. The results are tabulated in Table 3. It is clear that acetate affects severely the catalysis while chloride is much less influential on the catalysis despite the over doubled concentration of sodium chloride compared to that of sodium acetate. The addition of chloride would deter the dissociation, on one hand, to suppress the activity and on the other hand, facilitate the re-binding of the chloride to restore the catalyst. But the latter effect is off-set by the former one. Therefore, it is not surprising that the presence of extra chloride did not significantly change the activity. However, the presence of extra acetate exhibited an entirely different scenario in affecting the catalysis. While the added acetate would not substantially exert influence on the dissociation of the chloride from complex **6**, it competes definitely with the dissociated chloride in the re-binding step to produce presumably species analogous to complex **3** rather than its parent complex **6**. As shown in Table 2, complex **3** is much less efficient than complex **6**. Therefore, this is in agreement with the observed catalytic behaviours. Thus, in the catalysis, dissociation and re-binding of the auxiliary ligand are two of the necessary steps.

Table 3 Comparison in catalytic activity on the aerobic oxidation of benzyl alcohol to benzyl aldehyde by complex **6** in the presence of various amount of chloride / acetate salt.[a]

Entry	Added anion (mmol)	Yield (%)[b]
1	/	50 ± 2
2	CH_3COONa (0.075 mmol)	48 ± 1
3	CH_3COONa (0.225 mmol)	31 ± 3
4	CH_3COONa (0.3mmol)	26 ± 1
5	NaCl (0.15 mmol)	47 ± 1
6	NaCl (0.45 mmol)	42 ± 2
7	NaCl (0.75 mmol)	41 ± 1

[a]Reaction conditions and yield calculations are the same as those described in Table 1 and TEMPO was employed in each entry.
[b]Yields calculated by GC analysis.

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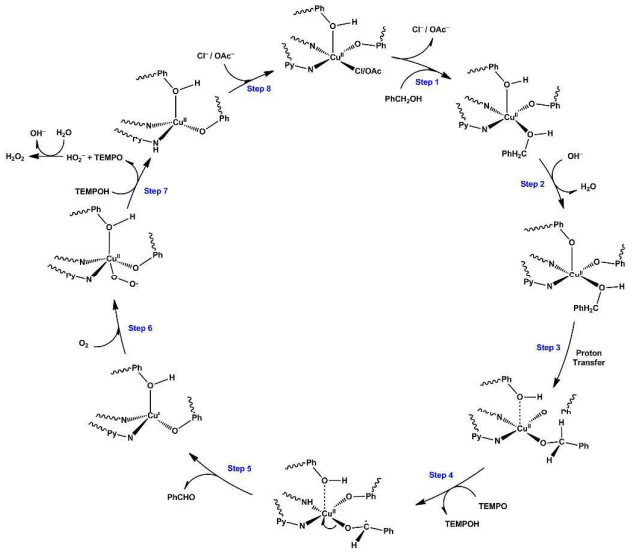
As shown in Table 1, the employment of an appropriate base can significantly improve the catalysis and K_2CO_3 / Cs_2CO_3 are the most suitable ones for the catalysis. In aqueous medium, these weak bases can maintain a certain concentration of OH^- in solution. During the catalysis, deprotonating the substrate is a necessary step and this explains the essentialness of the base in the catalysis. However, for complexes **1**–**3**, **5** and **6**, they possess a weakly bound and unprotonated phenol group and hence, it is also deprotonable in addition to the substrate. Since phenol is relatively a strong acid whose pK_a is about 10 whereas the pK_a value of benzyl alcohol (the substrate) is over 15, the bound phenol would be first deprotonated to generate its phenolate form. Subsequently, this phenolate can deprotonate the bound substrate *via* intramolecular proton transfer. In other word, the phenol group may just be an internal base to facilitate the deprotonation of the bound substrate. Without such a phenol, an external base will take this role. This explains why a copper complex without a phenol group works as well. The presence of the $–CF_3$ group(s) shows no much electronic effect on the metal center as suggested by the reduction potentials but decreases very much the catalytic activity of the copper complexes as shown in Table 2. This may further strengthen the argument that the phenol maybe act as an internal base since the basicity of the corresponding phenolate becomes much weaker due to the strong electron-withdrawing nature of $–CF_3$ group. By examining the effect of an external base on the catalysis of complex **3** (entries 18-22, Table 1), it is suggested that the decrease in catalytic activity is probably due to the decrease in the basicity of the phenolate bearing two $–CF_3$ groups.

That TEMPO binds to a metal center is not unprecedented. However, in our case, both EPR data and electrochemical behaviour indicate that the interaction of TEMPO with the copper (II) center is not significant (Figs. S5 and S6). Quite likely, TEMPO abstracts one of the H atoms of the methylene group of the phenylmethanolate (the deprotonated and bound substrate) to form a ketyl radical. That the reaction yield decreased when the usage of TEMPO was reduced may further support the role of TEMPO in the catalysis. Consequently, one electron transfer from the ketyl radical to Cu(II) occurs to yield the product aldehyde and a four coordinated Cu(I) species.[1, 2, 59, 60] Then O_2 reacts readily with this reduced Cu(I) species to form supposedly a superoxide which binds to the metal center. During the process, the metal center is brought back to Cu(II). Then the bound superoxide is further reduced to peroxide (HO_2^-) by TEMPOH to regenerate the radical TEMPO.[17, 30, 61] Finally, to complete the catalytic cycle, the dissociated auxiliary ligand re-bind to the metal center to restore the catalyst. Based on the above discussion alongside with those mechanisms reported in the literatures,[2, 30, 38, 62-67] a catalytic mechanism for the oxidation of benzyl alcohol catalyzed by the complexes (**1**–**6**) is depicted in Scheme 4. In this mechanism, involving the dissociation of the auxiliary ligand (acetate or chloride) for the substrate to bind resembles highly the enzymatic catalysis.



Scheme 4 The proposed catalytic mechanism with the Cu(II) complexes as the catalyst. For simplicity, its schematic structure is highly simplified by emphasizing the coordinating atoms and replacing the rest with wavy lines.

3.5 Oxidation of various alcohols catalyzed by complex 1

To find out whether the complexes catalyze the oxidation of other alcohols, complex **1** was employed as a catalyst under the optimized reaction conditions. As shown in Table 4, complex **1** exhibited effective catalytic performance for the oxidation of the benzyl alcohol or its analogues. Apparently, the electronic nature of substituent groups on benzyl alcohols exerts impact on the catalytic oxidation. In general, aromatic compounds with electron-donating substituents (Me, OMe, Cl, Br) (Table 4, entries 1–4) showed high reaction activity compared to the substrates with electron-withdrawing substituents (NO_2, CF_3) (Table 4, entries 6 and 8). The inactivity may be attributed to their poorer electron donating capability and binding affinity compared to benzyl alcohol. Bond dissociation energy (BDE) of the α-C–H bond could vary with the substituents. But for the C–H bonds of these substrates, such a change is not significant[68] and in this case, it may not contribute too much to the lowering of the reaction yield. Moderate product yields could be also obtained for substrates containing heterocycle or allylic alcohols which are not quite surprising since somewhat these substrates are analogous to benzyl alcohol (Table 4, entries 5 and 9). For aliphatic or secondary alcohols, the complex is almost inactive under the same conditions (Table 4, entries 10–13). For these alcohols, the BDE of the C–H bond may play a significant role. In addition to this BDE contribution, steric factor may also lead to the inactivity for secondary alcohols.

Table 4 Selected alcohols for their aerobic oxidation to aldehydes or ketones catalyzed by complex **1**.[a]

Entry	Substrate	Yield(%)[b]

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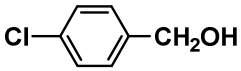
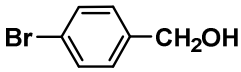
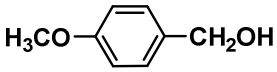
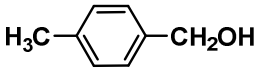
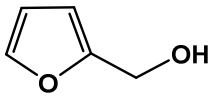
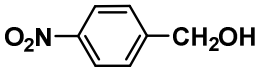
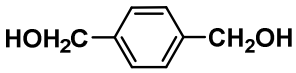
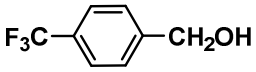
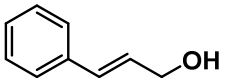
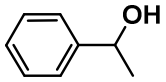
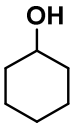
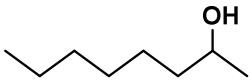
1		99±0.2
2		99±0.47
3		92±2
4		85±3.5
5		55±4
6		51±1.1
7		37±3.2[c]/16±4[d]
8		46±2.1
9		45±0.6
10		trace
11		trace
12		Trace/10[e]
13		trace

[a]Reaction conditions and yield calculations were the same as those described in Table 1.
[b]Yields calculated by GC-MS analysis.
[c]*p*-phthalaldehyde.
[d]*p*-(Hydroxymethyl)benzaldehyde.
[e]80 °C.

4. Conclusions

In summary, we have described the synthesis and characterization of six bioinspired copper(II) complexes **1–6** derived from four multidentate ligands. All these copper complexes were fully characterized by a number of analytical techniques including X-ray single crystal diffraction analysis. These complexes possess a coordinating atmosphere resembling that of the GOase except for complex **1**. Complex **1** showed the highest catalytic activity with high selectivity towards the oxidation of benzyl alcohol under the optimized reaction conditions. Mechanistic investigation allowed us to propose a catalytic mechanism, which involves the dissociation / re-binding of the auxiliary ligand (OAc^- or Cl^-) in S_N1 pathway. The dissociation and the substrate binding occur likely concomitantly. In the catalysis, the intramolecular proton transfer, Step 3 in Scheme 4, may be one of the important steps. This is indirectly supported by that the presence of the $-CF_3$ group weakens the basicity of the phenolate and hence the intramolecular proton transfer. The phenol group of the catalysts could act as an internal base to facilitate the deprotonation of the bound substrate although further investigation is needed to support such a role for the phenol group in the catalysis. Acetate affects the catalysis *via* forming intramolecular hydrogen bonding with the axial phenol and decreases the Lewis acidity of the metal center.

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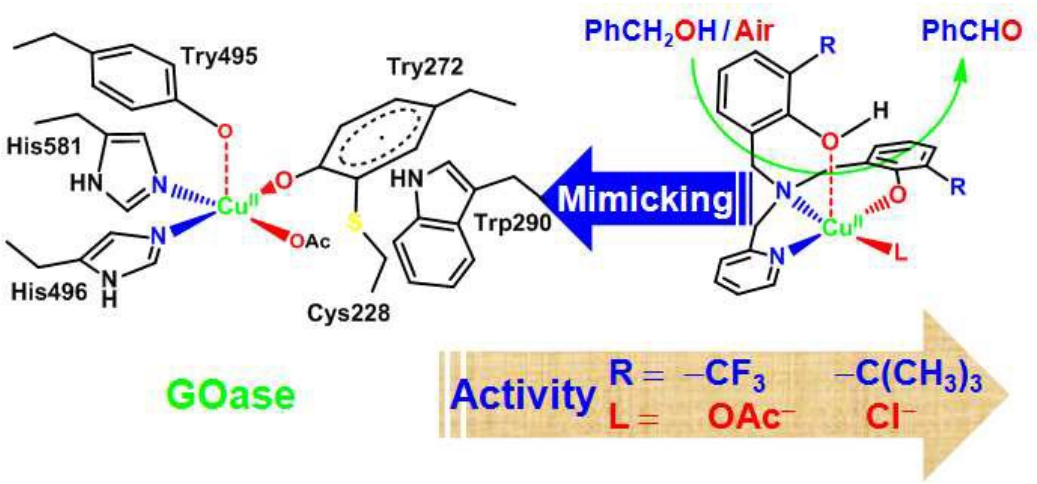
Graphic Abstract



The mimics assemble structurally the metal center of GOase. The phenol group(s) and the substituent (**R**), and the auxiliary ligand (**L**) of the mimics affect significantly their catalysis on the aerobic oxidation of benzyl alcohol.