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ARTICLE

Bioinspired Aerobic Oxidation of Alcohols with a Bifunctional Ligand Based on Bipyridine and TEMPO

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A novel bioinspired bifunctional ligand incorporating metal-binding site and stable free radical has been synthesized. The catalytic system obtained from the bifunctional ligand with copper(I) iodide in the presence of *N*-methylimidazole is highly efficient for the oxidation of a broad range of primary benzylic, allylic, alkynyl, aliphatic alcohols and secondary benzylic alcohols to the corresponding aldehydes and ketones in good to excellent yields. The catalyst system exhibits broad functional-group compatibility. The reaction is carried out in acetonitrile as solvent under air balloon at room temperature. The catalyst system features excellent activity for primary aliphatic alcohol oxidation and a high chemoselective oxidation of primary alcohols over the secondary alcohols. This oxidation process is readily amenable to larger-scale application. The interaction of the different components in the reaction mixtures was studied by UV–visible spectroscopy. The data indicated that Cu(I) existed throughout the reaction. A plausible mechanism of the catalytic cycle is proposed.

Introduction

The oxidation of alcohols to carbonyl compounds is one of the most fundamental and important processes in the fine chemical industry.[1] The classical methodology is based on the stoichiometric use of the oxidants, such as MnO_2, chromium salts, and the Dess-Martin reagent.[2] Although these methods are useful, large amounts of inorganic and organic toxic waste is produced. Considerable advances in the oxidation of alcohols have been dominated by the development of catalytic green processes that utilize dioxygen or air as the sole oxidant.[3] In this case water is the only by-product. Of particular interest in this field are Cu-based methods since these reactions usually associated with mild condition. Copper is a cheap, non-toxic metal which is predominant in many enzymes which are involved in the oxidation of alcohols. For example, galactose oxidase (GAO) is a radical copper oxidase for the oxidation of primary alcohols to the corresponding aldehydes. The active site that incorporates a Cu(II) metal centre and a stable protein free radical can perform a two-electron oxidation process.[4] Inspired by the coupling of Cu redox process and an organic cofactor in alcohol oxidation by the radical copper oxidases, a variety of synthetic systems incorporation organic radical and copper complexes have been studied for this reaction.[5] Although effective catalysts for alcohol oxidation using copper-cofactor pairs have been developed, finding systems that are both highly active and broadly applicable require further effort. More generally, extending the range of substrates that can be oxidized under environmentally friendly conditions is an important goal.

Currently, conceptually related catalytic systems which incorporate copper salts and TEMPO radical is considered to be a GAO mimic for the aerobic alcohol oxidation.[6] A variety of copper salts and TEMPO based catalytic systems for the aerobic alcohol oxidation have been developed (Table 1S).[7] To the best of our knowledge, few reports attempt to put the two together as a bifunctional molecule for the aerobic oxidation of alcohols. Jan Reedijk and coworkers reported bifunctional molecules containing ligands and TEMPO moiety using 2,4,6-trichloro-1,3,5-triazine as a building block for the aerobic oxidation of primary alcohols to the corresponding aldehydes.[8] But only benzyl alcohol reported was fully converted to the aldehyde at room temperature. Allylic alcohols, such as crotyl alcohol and geraniol were needed to increase reaction temperature for full conversion. In the case of non-activated 1-octanol, the increase of the reaction temperature only results in moderate conversion. Wanzhi Chen and coworkers reported a copper-NHC complex bearing TEMPO catalyst that shows high activity in the oxidation of primary aliphatic alcohols but requires high catalyst loading (10 mol%) and high temperature.[9] Very recently, Galia Maayan and coworkers reported metallopeptoid catalysts that use of a peptoid backbone for tethering together 1,10-phenanthroline and

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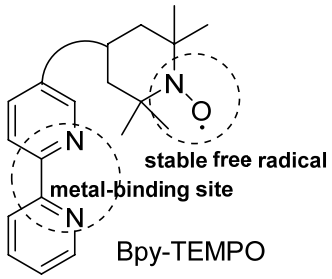

Scheme 1 Novel Bpy-TEMPO-based bifunctional ligand.

TEMPO.[10] Although the catalysts show high performance as intramolecular cooperative catalysts in the aerobic oxidation of alcohols, the preparation of the peptoid oligomers needs several steps. To improve upon the state of the art, we are aiming to design a simple and new functional ligand incorporating both TEMPO moieties and Cu-binding sites (Scheme 1).

Herein, we demonstrated the application of the new bifunctional ligand bearing bipyridine and TEMPO in combination with Cu for the oxidation of a broad range of primary benzylic, allylic, alkynyl and aliphatic alcohols to the corresponding aldehydes under mild conditions. The reactions proceed in high yield, exhibit broad functional-group compatibility, and achieve chemoselective oxidation of primary alcohols over the secondary alcohols. This catalyst system can also achieve the oxidation of secondary alcohols. More importantly, bipyridine and TEMPO can be "one pot" combined without constructing backbones.

Experimental

General Information

All chemicals used in this study were analytical grade, commercially available and used without further purification unless otherwise noted. All products were confirmed by GC-MS with Agilent 6890N GC/5973 MS detector. The HRMS analysis was obtained on a Waters GC-TOF CA156 mass spectrometer. GC calculations of yields were performed on an Agilent 7890A with a flame ionization detector. ^{1}H NMR and ^{13}C NMR spectrum were recorded on a 400 MHz NMR spectrometer using $CDCl_3$ as the solvent with TMS as an internal reference. ^{1}H and ^{13}C positive chemical shifts (d) in ppm are downfield from tetramethylsilane ($CDCl_3$: δC = 77.1 ppm; residual $CHCl_3$ in $CDCl_3$: δH = 7.26 ppm).The UV–visible spectra were recorded on a Shimadzu-2550 spectrometer with 10mmpath length of quartz sample cells at 298 K. Wavelength range, 240–900 nm. **1-(2-Pyridylacetyl)pyridinium iodide (1), 5-Methyl-2,2-bipyridine (2) and 2,2-Bipyridinyl-5-carboxylic acid (3)** were prepared according to the known procedure.[11]

The Oxidation Reactions

A typical procedure for the oxidation of 1-octanol. A mixture of CuI (2.4 mg, 0.0125 mmol) in CH_3CN (2 ml) was stirred for 1 min at room temperature in a 25 ml flask. Bpy-TEMPO (4.4 mg, 0.0125 mmol) was added to the mixture. After stirring for 2 min, NMI (2 mg, 0.025 mmol) was added and stirred for 2 min. Then, 1-octanol (32.5 mg, 0.25mmol) was added. The solution was stirred under air atmosphere (balloon) for 6 h. GC analysis of the reaction mixtures using biphenyl as an internal standard gave a 95% yield of octanal.

Determination of yield by ^{1}H NMR. Without commercial available product, the yield of the corresponding product was determined by ^{1}H NMR using benzyl benzoate as an internal standard.

After the reaction complete, benzyl benzoate (26.5 mg, 0.125 mmol, 0.5 eq) was added to the mixture. 0.2 mL of the reaction mixture was added to a NMR tube via syringe. The yields of products were determined by ^{1}H NMR analysis with respect to the benzyl benzoate standard

General procedure for product isolation. After the reaction complete, if the alcohol completely converted by GC, the solvent was evaporated in *vacuo* and the residue was loaded directly on a small pad of silica and washed with hexane until no product could be detected from the eluent by TLC. Hexane was then removed by a rotary evaporator and the product was dried under vacuum. The purity of the product was determined by NMR. Notes: the selectivities in most reactions are more than 99%. And the catalysts cannot be washed down by hexane.

After the reaction complete, if the alcohol did not completely convert by GC, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/ hexane) to afford the aldehyde products.

The Synthetic Procedure and Characterization of bpy-TEMPO

1-(2-Pyridylacetyl)pyridinium iodide (1).[11] A solution of iodine (7.1 g, 28.0 mmol) and 2-acetylpyridine (2.8 mL, 25.0 mmol) in pyridine (30 mL) was prepared in a reaction flask equipped with a condenser and drying tube and the reaction mixture was stirred for 6 h at 90 °C. At this time, the resulting suspension was filtered, and the residue was refluxed in EtOH (300 mL) with activated charcoal (3.0 g) for 4 h. The suspension was then filtered while hot, and the filtrate was concentrated under reduced pressure to give crude 1. Recrystallization of the crude product from a saturated EtOH solution was performed to purify **1** (5.8 g, 60%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 9.02 (d, J = 5.5 Hz, 1H), 8.88 (d, J = 4.7 Hz, 1H), 8.74 (t, J = 7.8 Hz, 1H), 8.29 (t, J = 6.7 Hz, 1H), 8.07-8.14 (m, 1H), 7.83-7.86 (m, 1H), 6.52 (s, 2H); ^{13}C NMR (101 MHz, DMSO) δ 191.9, 150.9, 150.1, 146.8, 146.8, 138.6, 129.6, 128.2, 122.5, 67.1.

5-Methyl-2,2-bipyridine (2).[11] Methacrolein (1.8 mL, 22.0 mmol) and H_4NOAc (9.3 g, 120.0 mmol) were sequentially added to the solution of 1 (6.5 g, 20 mmol) in formamide (200 mL). The mixture was stirred at 80 °C for 16 h. At this time, the crude mixture was cooled and extracted with diethyl ether (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (5% MeOH in CH_2Cl_2) to yield **2** (3.7 g, 98%) as

a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.37 (s, 1H), 8.24 (d, J = 8.9 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.63 (ddd, J = 7.9, 4.9, 1.8 Hz, 1H), 7.50 – 7.41 (m, 1H), 7.19 – 7.04 (m, 1H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 153.4, 149.4, 148.8, 137.2, 136.6, 133.2, 123.2, 120.6, 120.4, 18.1.

2,2-Bipyridinyl-5-carboxylic acid (3).[11] Potassium permanganate (12.3 g, 78 mmol) was added in 7 portions at 1 h intervals to a solution of 2 (3.4 g, 20 mmol) in water (200 mL). The mixture was heated at 70 °C for 3 h and then at 90 °C for 4 h more. The brown mixture was then filtered while hot through celite and washed with hot water (2 x 25 mL). The filtrate was concentrated to approximately 10 mL under reduced pressure, and then 1 M HCl was added slowly until a pH of 4 was obtained. The residue was then filtered and dried to obtain pure 3 (1.2 g, 30%) as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 9.19 (s, 1H), 8.76 (d, J = 4.3 Hz, 1H), 8.42-8.54 (m, 3H), 8.01 (t, J = 7.1 Hz, 1H), 7.52-7.55 (m, 1H); ^{13}C NMR (101 MHz, DMSO) δ 166.6, 158.8, 154.7, 150.6, 150.0, 138.7, 137.9, 127.0, 125.4, 121.7, 120.7.

Bpy-TEMPO (4).[12] To a solution of 2,2-Bipyridinyl-5-carboxylic acid (232 mg, 1.16 mmol), EDCI (268 mg, 1.4 mmol, 1.2 equiv) and HOBt (214 mg, 1.4 mmol, 1.2 equiv) in DMF (8 mL) was added 4-aminoTEMPO (240 mg, 1.4 mmol, 1.2 equiv.). The mixture was stirred at room temperature for 30 h, poured into water and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Filtration, concentration in vacuo, and purification by silica gel flash column chromatography (AcOEt / Petroleum ether /EtN_3= 2/1/1) gave 287 mg (70%) of a light brown solid. HRMS (ESI) for $C_{20}H_{26}N_4O_2$ $[M+H]^+$, calcd: 354.2011, found: 354.2064.

Tetradecanal[13] white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, J = 1.8 Hz, 1H), 2.41 (td, J = 7.4, 1.8 Hz, 2H), 1.66 – 1.56 (m, 2H), 1.27 (d, J = 16.5 Hz, 20H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.9, 43.9, 31.9, 29.7, 29.7, 29.6, 29.6, 29.4, 29.4, 29.2, 22.7, 22.1, 14.1.

Cinnamaldehyde[14] light yellow liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, J = 7.7 Hz, 1H), 7.46– 7.48 (m, 2H), 7.40 – 7.29 (m, 4H), 6.66 – 6.53 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 152.8, 133.9, 131.3, 129.1, 128.6, 128.5.

Phenylpropiolaldehyde[14] yellow liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.53 (dd, J = 5.2, 3.3 Hz, 2H), 7.42 (ddd, J = 6.7, 4.5, 1.3 Hz, 1H), 7.34 (t, J = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 133.4, 131.4, 128.8, 119.5, 95.2, 88.5.

Benzaldehyde[15] colourless oil liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.75 (d, J = 8.1 Hz, 2H), 7.49 (dd, J = 11.9, 4.1 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6, 135.3, 133.4, 128.6, 127.9.

4-Methylbenzaldehyde[15] colourless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 145.6, 134.2, 129.9, 129.8, 21.9.

4-Nitrobenzaldehyde[16] light yellow acicular crystal, ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.40 (d, J = 8.6 Hz, 2H), 8.08 (d, J = 8.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 151.2, 140.1, 130.6, 124.4.

4-Fluorobenzaldehyde[16] colourless liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.89 – 7.78 (m, 2H), 7.13 (t, J = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6, 166.6 (d, J = 255 Hz), 133.0 (d, J = 3.0 Hz), 132.3 (d, J = 10 Hz), 116.4 (d, J = 23 Hz).

3,4-Dimethoxybenzaldehyde[14] white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.45 (d, J = 9.6 Hz, 1H), 7.40 (s, 1H), 6.97 (d, J = 8.2 Hz, 1H), 3.96 (s, 3H), 3,93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9, 154.5, 149.7, 130.2, 126.9, 110.4, 108.9, 56.2, 56.1

1-Naphthaldehyde[9] light yellow liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 9.16 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.88 (d, J = 7.0 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.65 – 7.55 (m, 1H), 7.51 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 136.7, 135.3, 133.8, 131.4, 130.6, 129.1, 128.5, 127.0, 124.9.

Results and discussion

The first step toward the preparation of bifunctional ligand holding a bipyridine unit and TEMPO is to synthesize bipyridine derivatives bearing a side arm containing a functional group, which will be used to connect TEMPO (Scheme 1S). 2,2'-Bipyridinyl-5-carboxylic acid was prepared according to the literature procedure.[11] The bifunctional ligand was prepared following the procedure by using 2,2'-bipyridinyl-5-carboxylic acid and 4-amino-TEMPO. The obtained solid labeled as Bpy-TEMPO was characterized by HRMS and by EPR (see Supporting Information). An EPR spectrum of Bpy-TEMPO was recorded at room temperature. The characteristic triplet (g = 2.008) arising from the hyperfine structure coupling of the single electron shows the existence of the nitroxyl radical.

Then, we evaluate the activity of the catalyst in the oxidation of alcohols. 1-Octanol was used as a test substrate to optimize the reaction conditions. The results are summarized in Table 1. Several frequently used Cu salts were examined (Table 1, entries 1-10). Among the screened Cu salts, cuprous salts show much better catalytic activity than cupric salts (Table 1, entries 1-7). The use of CuI afforded the desired aldehyde in high yield in the presence of NMI as the additive and CH_3CN as the solvent for 12 h (Table 1, entry 3). To our great surprise, excellent yield could also be obtained in reducing reaction time (Table 1, entry 8). Cu(OTf) used as Cu salt only 40% of yield was achieved, whereas $[Cu(CH_3CN)_4]OTf$ was used giving in 88% of yield (Table 1, entries 9 and 10). A series of frequently used additives were examined (Table 1, entries 11-13). When DBU was used as the additive, trace product was obtained (Table 1, entry 11). The use of DMAP and DABCO afforded 89% and 14% yields, respectively (Table 1, entries 12 and 13). When the additive was not used, the product was obtained in only 8% of yield (Table 1, entry 14). The reaction can also be conducted under open air, albeit with slightly low yield (Table 1, entry 15). Finally, we demonstrated the practical applicability of the present catalytic system. The oxidation of 1-octanol was performed on a 5 mmol scale (20 times scale) and afforded products in 95% yield, albeit with a somewhat longer reaction time.

Next, we applied the optimum reaction conditions to examine the substrate scope. The results are summarized in Table 2. As we know, the oxidation of unactivated primary aliphatic alcohols to the aldehydes is a challenging issue in the

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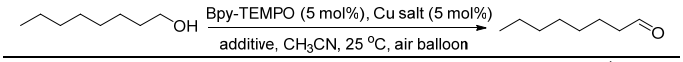
Table 1 Optimization of Bpy-TEMPO/Cu catalyst system for the oxidation of 1-octanol[a]



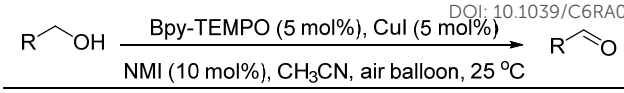
Entry	Cu salt	Additive	Time [h]	Yield[b][%]
1	CuBr	NMI	12	85
2	CuCl	NMI	12	61
3[c]	CuI	NMI	12	(100) 96
4	$[Cu(CH_3CN)_4]PF_6$	NMI	12	73
5	$CuBr_2$	NMI	12	ND
6	$CuCl_2$	NMI	12	ND
7	$Cu(OTf)_2$	NMI	12	4
8	CuI	NMI	6	95
9	Cu(OTf)	NMI	6	40
10	$[Cu(CH_3CN)_4]OTf$	NMI	6	88
11	CuI	DBU	6	0.6
12	CuI	DMAP	6	89
13	CuI	DABCO	6	14
14	CuI	No	6	8
15[d]	CuI	NMI	6	81
16[e]	CuI	NMI	10	(100) 95

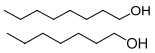
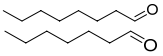
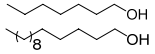
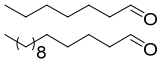
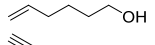
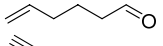
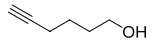
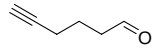
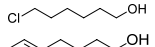
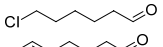
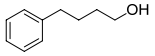
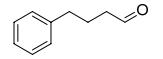
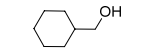
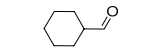
[a] 1-octanol (0.25 mmol), additive (10 mol%), CH_3CN (2 mL). [b] Determined by GC using internal standard. [c] Value in parenthese is conversion of 1-octanol. [d] Open air. ND = Not Detected. [e] 1-octanol (5 mmol).

alcohol oxidation reactions. The products of the aliphatic aldehydes are more reactive than aliphatic alcohols and more susceptible to over-oxidation to the carboxylic acids. In a preliminary effort to assess the potential utility of this catalyst system for the oxidation of aliphatic alcohols, the oxidation of a series of aliphatic alcohols was examined firstly. Excellent yields can be obtained for the oxidation of non-functional group straight-chain primary alcohols (Table 2, entries 1-3). No over-oxidation of aldehyde products to the corresponding carboxylic acids was observed. Excellent product yields were obtained with substrates bearing common functional groups, including alkene (Table 2, entry 4), alkynes (Table 2, entry 5), halogen (Table 2, entry 6), and aryl (Table 2, entry 7). A decreased reactivity for sterically encumbered substrate such as cyclohexylmethanol was observed (Table 2, entry 8). Next, the catalytic system was used for the oxidation of allylic and propargylic alcohols (Table 2, entries 9-13). No oxidation of the alkene or alkyne is observed and the corresponding α,β-unsaturated carbonyl compounds were obtained in excellent yields. Finally, various types of primary benzylic alcohols with electron donating and electron withdrawing groups gave excellent yields of their corresponding aromatic aldehydes under optimal reaction conditions (Table 2, entries 14-22). Notably, the catalytic system was efficient for the oxidation of alcohols that are considered to be highly challenging substrates in most transition metal catalyst systems. Alcohols containing oxygen and sulfur heteroatom undergo efficient oxidation in excellent yields (Table 2, entries 23 and 24).

Next, we tried to assess the ability of the present catalytic system to catalyze oxidation of the secondary benzylic alcohols, which is known to be difficult for Cu/bpy/TEMPO system due to the steric hindrance effect. Our catalytic system is capable of catalyzing the oxidation of secondary alcohols and gives

Table 2 CuI/Bpy-TEMPO-catalyzed aerobic oxidation of primary alcohols to aldehydes[a]



Entry	Substrate	Product	Time [h]	Yield[b][%]
unactivated alcohols				
1			6	95
2			7	92
3			8	>99 (88)
4			5	91
5[c]			9	89
6[c]			11	94
7[c]			7	92
8			10	72
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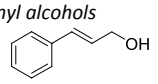
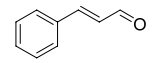
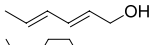
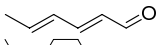
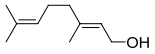
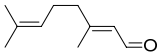
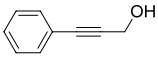
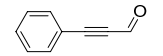
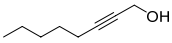
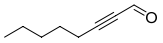
9			4	94 (87)
10			3.5	>99
11			3.5	>99
12			4	98 (83)
13			4	98
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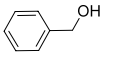
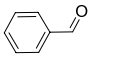
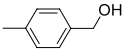
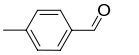
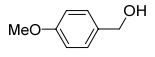
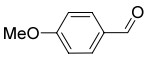
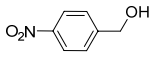
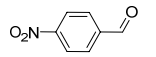
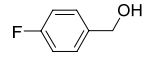
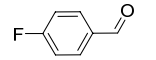
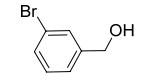
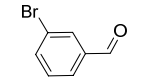
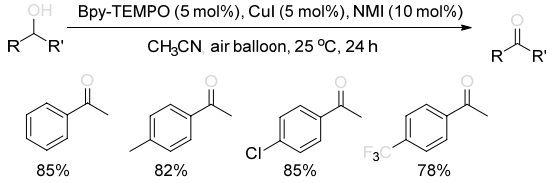
14			5	>99 (95)
15			2	>99 (94)
16			3	>99 (96)
17			3	>99 (92)
18			3	>99 (90)
19			3	>99
20			6	98
21			1.5	>99 (88)
22			2	>99 (95)
heterocycles				
23			4	>99
24			7	>99

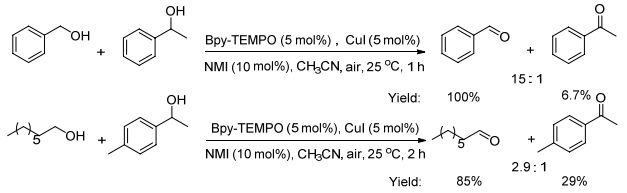
[a] Alcohols (0.25 mmol), CH_3CN (2mL).[b] Determined by GC using internal standard, values in parentheses refer to isolated yields. [c] Determined by NMR.

good yields by prolonging the reaction time (Scheme 2).

The present catalytic system can achieve the oxidation of secondary alcohols, giving us a chance to hold a study on the competition experiments between primary alcohols and



Scheme 2 The oxidation of the secondary benzylic alcohols.



Scheme 3 Selectivity competition experiments.

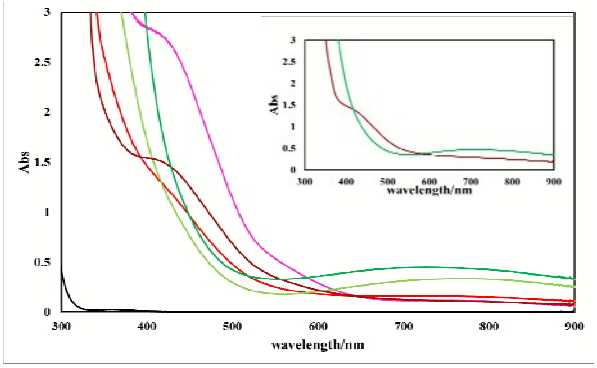


Figure 1 Conditions: CuI (3.3 mmol·L^{-1}), Bpy-TEMPO(3.3 mmol·L^{-1}), NMI (6.6 mmol·L^{-1}). Subsequent UV-visible spectra of CuI in CH_3CN solution (black), +bpy-TEMPO (pink), +NMI immediately (red), +NMI after 2min under open air (green), +benzyl alcohol (dark red), after reaction (dark green). Subsequent UV-vis spectra (inset) of benzyl alcohol added to the after reaction solution (dark red), after reaction (green)

secondary alcohols (Scheme 3). When a mixture of activated benzyl alcohol and 1-phenylethanol was used, benzyl alcohol was fully consumed, whereas only 6.7% of the 1-phenylethanol was oxidized. The competition reaction between unactivated 1-octanol and activated 1-(4-methylphenyl)ethanol resulted in a 2.9:1 ratio in favour of the oxidation of 1-octanol. These results show the specificity of the catalytic system towards primary alcohols.

Having obtained the good results with the present catalytic system, we try our best to learn more about the interaction of the different components in the reaction mixtures by UV–visible spectroscopy (Figure 1). The sequential experiments were conducted at room temperature. The UV–visible spectrum of CuI in CH_3CN shows no obvious absorption peak. Upon adding the bpy-TEMPO, new band is seen at 410 nm from metal-to-ligand charge-transfer (MLCT), indicating the replacement of coordinated solvent molecules at the Cu(I) site by byp-TEMPO. The characteristic absorption of Cu(II) arising from d-d transition cannot be observed obviously, which demonstrated that Cu(II) might not be obtained via one-electron oxidation of Cu(I) by TEMPO. This result is consistent with the literature.[17a] After adding the NMI, new metal-to-ligand charge-transfer appeared as a shoulder at 415 nm. Then the mixtures were stirred under open air. The colour of the solution gradually changed from red-brown to green. The corresponding UV–visible spectrum shows band at 760 nm arising from d-d transition of Cu(II), indicating the oxidation of Cu(I) to Cu(II) by dioxygen. Then, benzyl alcohol was added to the above solution. The colour of the solution changed from green to the original red-brown immediately. Simultaneously, the d-d band of Cu(II) disappeared, and the MLCT band of Cu(I) reappeared. The oxidation of benzyl alcohol to benzaldehyde was observed at the same time. This clearly shows that Cu(II) formed in situ from Cu(I) is a active species for alcohol oxidation and that alcohol oxidation step is faster than the formation of Cu(II). When the benzyl alcohol is completely consumed, the colour of the solution is changed to green and the d-d band of Cu(II) reappeared. Another portion of benzyl alcohol is added to the system resulting in a rapid change of the colour back to red-brow until the benzyl alcohol is fully converted to benzaldehyde thus excluding catalyst deactivation (Figure 1, (inset)). These observed results are consistent with Stahl's system.[17b,c]

Recently, the mechanism of Cu/bpy/TEMPO/NMI catalytic system for the alcohol oxidation has been well studied by Stahl group and Brückner group.[17]They have given sufficient experimental evidence for their proposed mechanisms. There exists some divergence on the role of TEMPO between the two mechanisms. On the basis of our observations, we are more inclined to the mechanism that Brückner proposed.[17c] Cu(I)(TEMPO-bpy)(NMI) can activate O_2 to form an active species (Cu(II)-$O_2^{\cdot-}$-TEMPO-bpy)(NMI) in the presence of TEMPO. β-H was abstracted by active $O_2^{\cdot-}$ through alcohol coordinated to the Cu(II). The carbonyl compound and Cu(I)(TEMPO-bpy)(NMI) were released.

Conclusions

In summary, we have developed a simple and new bifunctional molecule incorporating both a TEMPO unit and a bipyridine ligand. The bipyridine ligand moiety is a metal-binding site for forming metal-ligand complex. The TEMPO unit is a stable free radical as a co-catalyst in alcohol oxidation. The new bifunctional molecule was investigated as biomimetic catalyst in combination with Cu for the aerobic oxidation of alcohols in the presence of NMI as additive. The catalytic systems exhibited high catalytic activity for the oxidation of unactivated primary aliphatic alcohols as well as activated alcohols. The corresponding products were obtained in good to excellent yields. Moreover, our developed catalyst system shows a high selective oxidation of primary alcohols over secondary alcohols. Very importantly, the catalytic system is very easy to handle.

Acknowledgements

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Bioinspired Aerobic Oxidation of Alcohols with a Bifunctional Ligand Based on Bipyridine and TEMPO

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A new bifunctional ligand bearing bipyridine and TEMPO in combination with copper for the oxidation of alcohols was developed.