Room temperature aerobic oxidation of alcohols using CuBr$_2$ with TEMPO and a tetradentate polymer based pyridyl-imine ligand

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A series of tetradentate pyridyl-imine terminated Schiff-base ligands has been investigated for their ability in the catalytic oxidation of alcohols when combined with copper bromide (CuBr$_2$) and 2,2,6,6-tetramethylpiperidyl-1-oxy (TEMPO). Analogous bidentate ligands showed poorer catalytic activity and the ratio of Cu:ligand was of crucial importance in maintaining high yields. The polydimethylsiloxane (PDMS) derived pyridyl-imine terminated ligand combined with copper(II) ions affords an effective and selective catalyst for aerobic oxidations of primary and secondary alcohols under aqueous conditions. Preliminary mechanistic studies suggest that bimetallic complexes may be playing a role in the catalytic transformation.

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1. Introduction

The selective oxidation of primary and secondary alcohols to their corresponding aldehydes and ketones is an important functional group transformation in organic synthesis [1–3]. Traditionally, this is accomplished by addition of stoichiometric amounts of inorganic oxidants (e.g. KMnO$_4$, CrO$_3$, SeO$_2$, and Br$_2$), which often generate environmentally hazardous or toxic by-products [4]. There is a growing trend to develop safer and more environmentally friendly chemistry. From this perspective, it is not surprising that aerobic oxidation of alcohols using inexpensive and non-toxic air or O$_2$ as the sole terminal oxidant has continued to gain much interest in recent years [5–7]. The high atom efficiency of the reaction and non-toxic by-products make aerobic alcohol oxidations a promising and attractive synthetic method.

Many highly efficient catalysts for the aerobic oxidation of alcohols have been developed recently using palladium [8–11], platinum [12], ruthenium [13] and rhodium complexes [14–17]. In the interest of sustainability, there has been significant development in the use of more abundant and cheaper transition metals such as iron [18,19] and copper as active catalysts. Following the first reported aerobic oxidation of activated primary alcohols by Semmelhack et al. [20] in 1984, inexpensive and abundant copper has attracted much attention in the field of

alcohol oxidations. Markó et al. have done pioneering work in this field and developed three generations of CuCl–phenanthroline catalytic systems, associated with di-*tert*-butyl hydrazine-1,2-dicarboxylate (DBADH$_2$) and strong base, for aerobic oxidation of alcohols [21–25]. Also, there has been significant interest in using the free radical TEMPO (2,2,6,6-tetramethyl-piperidinyl-1-oxy) or analogues as efficient co-catalysts in the aerobic oxidation of alcohols [26–33]. Sheldon and Reedijk et al. have reported the efficient use of copper–bipyridine and copper–pyrazole/TEMPO systems in oxidation reactions under air [34–37]. Subbaryant et al. have reported a TEMPO/Copper–salen system that could efficiently oxidize a wide range of benzylic and heterocyclic alcohols (e.g. 2-furylmethanol) under an oxygen atmosphere [38]. Repo et al. recently reported a highly efficient catalytic system based on TEMPO/Copper diimine (10 bar oxygen) and 2-*N*-arylpyrrolecarbaldimino (1 atm oxygen) systems for alcohol oxidation [39,40]. In recent studies, Koskinen et al. and Stahl et al. have described improved bipyridine–Cu–TEMPO catalytic systems for the effective oxidation of alcohols [41,42]. In both of these studies, trifluoromethanesulfonate copper salts were found to afford greater activity compared with copper halides, and use of N-methyl-imidazole as the base was advantageous. Furthermore, detailed kinetic studies performed by Koskinen and Kumpulainen indicate that bimetallic copper species play a crucial role in these transformations [41].

We have previously prepared siloxane-derived ligands containing phosphorus donor atoms and used these ligands in C–C coupling reactions [43,44]. More recently, others have prepared pyridine

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terminated siloxane-derived ligands for use in a variety of applications including oxidation catalysis [45–50]. We have extended this approach to prepare a bis(pyridyl-imine) terminated siloxane ligand and herein, we report the first use of a series of tetradentate N-donor ligands in the aerobic oxidation of alcohols.

2. Experimental

2.1. Materials and methods

All functionalized silicon-containing chemicals were purchased from Gelest. Alcohols and other chemicals were purchased from Aldrich and Alfa Aesar and were used without further purification. The ^{1}H NMR spectra of the pyridyl-imine ligands were acquired on a Bruker AVANCE 500 MHz spectrometer. The ^{13}C NMR spectra were obtained on a Bruker AVANCE III 300 MHz spectrometer equipped with a BBFO probe. Chemical shifts are reported in ppm using the residual protons of the deuterated solvent as an internal reference. All solution-state spectra of **L1** and **L2** were obtained in tetramethylsilane free CDCl$_3$ due to any overlap with –OSiMe$_2$– resonances that might occur. Yield and selectivity were determined by GC–MS (gas chromatography–mass spectrometry) analyses using an Agilent Technologies 7890A GC system coupled to an Agilent Technologies 5975C mass selective detector (MSD). Dodecane was used as an internal standard. The GC system was equipped with electronic pressure control, split/splitless and on-column injectors, and a capillary column DB-5 (column length: 30.0 m and column diameter: 0.25 mm). MALDI-TOF MS spectra were recorded on an Applied Biosystems Voyager DE-PRO. Observations of cloud point data and reaction homogeneity in supercritical carbon dioxide (scCO$_2$) were performed using a Supercritical Fluid Technologies Phase Monitor II (40 mg of **L1** was placed in the variable volume view cell and the mixture was allowed to equilibrate for approximately 15 min under each temperature/pressure condition prior to observations being made).

2.2. Ligand synthesis

For **L1**: 2-Pyridinecarboxaldehyde (1.04 g, 9.71 mmol) was added to a mixture of diamino terminated PDMS (5.00 g, approx. 3 mmol) and anhydrous sodium sulfate (5.02 g, 35.3 mmol) in 50 mL dry THF. The mixture was stirred at room temperature. The reaction was judged to be complete after 12 h by monitoring the disappearance of the C=O absorption band and the formation of the newly formed C=N bond using infrared spectroscopy. The mixture was filtered via cannula. Solvent and unreacted starting materials were evaporated under vacuum. The product **L1** was isolated as an orange oil, 91% yield. The other ligands were synthesized following the same method. Characterization data are available as Supplementary Data.

2.3. Oxidation of alcohols

The oxidation reactions were carried out under air in a 25 mL three-necked round-bottom flask equipped with a magnetic stirrer. Typically, 5.0 mmol alcohol and 1.67 mmol dodecane (GC internal standard) were dissolved in 10 mL acetonitrile. 0.25 mmol (56 mg) of CuBr$_2$ (from a stock solution of 22.4 mg/mL in water) and 0.25 mmol (28 mg) of potassium *tert*-butoxide (from a stock solution of 11.2 mg/mL in water) were then added leading to the formation of a green suspension. 0.125 mmol (232 mg) **L1** was then added and the reaction mixture turned dark-blue. Finally, 0.25 mmol (39 mg) TEMPO was introduced and the reaction mixture immediately turned brown and ultimately a red solution formed. The progress of the oxidation reaction was monitored by
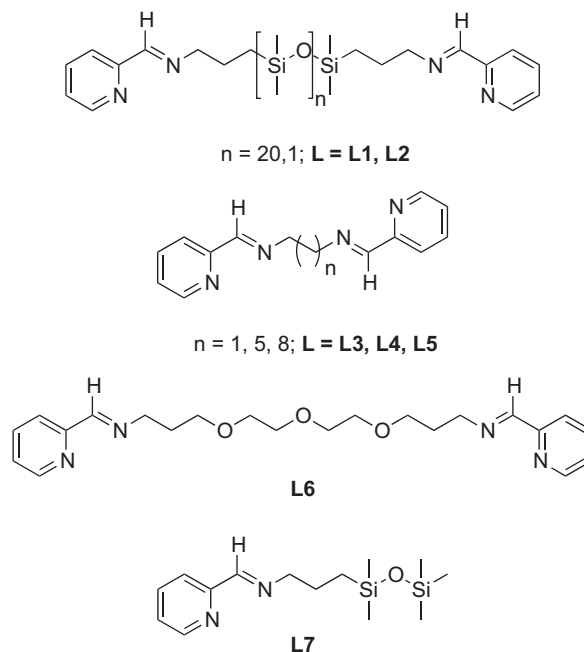

n = 20,1; **L = L1, L2**

n = 1, 5, 8; **L = L3, L4, L5**

L6

L7

Fig. 1. Schematic structures of the ligands used in this catalytic study.

GC analysis. Upon completion, the reaction mixture was extracted with diethyl ether. The organic layer was washed with water and brine. Prior to GC–MS analysis, the organic phase was dried with anhydrous magnesium sulfate and filtered through a short silica column. As an example, after concentrating under vacuum the product of the reaction from benzyl alcohol oxidation, benzaldehyde was obtained without further purification as a pale yellow liquid, 96% yield, ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): δ = 10.02 (s, 1H), 8.35 (s, 2H), 7.89–7.87 (m, 2H), 7.64–7.61 (m, 1H), 7.54–7.51 (m, 2H). The NMR spectroscopic data were in good agreement with those reported in the literature [51]. It should be noted that the isolated products were not contaminated with the PDMS-derived ligand, as evidenced by the absence of –SiMe$_2$O– resonances. Also, all ^{1}H resonances of the product were sharp and well-defined indicating that the product was likely not contaminated with any paramagnetic Cu(II) residues.

GC-traces and mass spectra for all products are available as Supplementary Data.

3. Results and discussion

3.1. Ligand effect

In order to further improve catalytic activity and strive towards a heterogeneous Cu/TEMPO based system, our research was focused on employing new chelating N-donor ligands to substitute the classical bipyridine and salen-type ligands used in these homogeneous oxidation reactions. In our studies, a series of α-ω pyridyl-imine terminated ligands were prepared (Fig. 1). These ligands can be easily synthesized by the condensation reactions between pyridine-2-carboxylaldehyde and different diamines. This simple synthetic approach means that the ligand synthesis is amenable to forming heterogeneous solid-supported catalytic systems [52]. In our study, the resulting ligands contain backbones of differing chemical type and length attached to the donor groups. **L1**–**L6** are potentially tetradentate ligands whereas **L7** is bidentate.

The oxidation of benzyl alcohol was chosen as a model reaction to investigate the utility of these ligands and any ligand effects (Fig. 2). As previously reported by Sheldon et al., TEMPO is
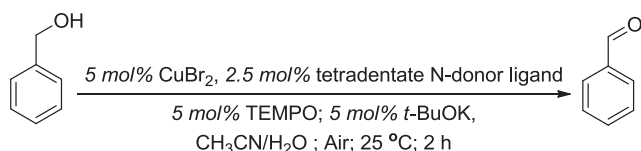
Fig. 2. CuBr$_2$ catalyzed aerobic alcohol oxidation model reaction.

crucial for the CuBr$_2$ catalyzed aerobic oxidation [35]. Furthermore, bases are used as co-catalysts to deprotonate the alcohol and increase the reaction rate. Catalysis using CuBr$_2$ with **L1–L7** also required TEMPO and base. Therefore, 5 mol% TEMPO and 5 mol% potassium *tert*-butoxide (*t*-BuOK) were chosen for screening ligand effects within our catalytic system (Table 1). The same results were obtained if potassium hydroxide was used as the base co-catalyst, however, *t*-BuOK was used as it can be more accurately weighed on a laboratory scale. Furthermore, it should be noted that in the absence of added base, the reaction still progressed albeit at a slower reaction rate. For example, under similar conditions to entry 2, Table 1, a yield of 40% is obtained after 2 h reaction time in the absence of base and we presume that the organic basic groups within the ligand act as deprotonating co-catalysts. A quantitative yield of benzaldehyde was obtained after 8 h in the absence of added base. It should be noted that organic bases, e.g. N-methyl-imidazole, have been used in recent studies by other groups [41,42].

Encouraged by previous reports that some aerobic oxidation copper catalysts can be easily prepared *in situ* by mixing the copper salt and ligand in the reaction medium [40,53], we chose an *in situ* approach to yield copper(II) complexes to be used with TEMPO and *t*-BuOK in our catalytic system. As revealed in Table 1, the yield of benzyl alcohol to benzaldehyde was very low in the absence of ligand (Table 1, entry 1). N-donor ligands are essential for the catalytic oxidation process. The PDMS derived tetradentate N-donor ligands (**L1** and **L2**) afforded very good yields when they were employed with CuBr$_2$ at 2:1 metal:L mole ratio (entries 2 and 3). **L6** and the other tetradentate ligands employed also showed excellent activity (entries 4–7). By comparing yields using these similar α-ω pyridyl-imine terminated ligands, we found that the chain length of the ligand appears to have some influence on the activity of the catalytic system. The ligands where donor groups were separated by a long chain led to greater catalytic activity than those containing short chains. These differences are possibly associated with freedom of movement and steric effects within the [Cu$_2$L] catalytic system. When provided with a long chain ligand, the copper coordination sphere has more space (less steric congestion). Therefore,

Table 1
Influence of the ligand structure on the oxidation of benzyl alcohol to benzaldehyde.[a]
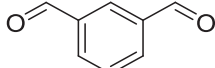
Entry	Catalytic system	Yield[b] (%)	TON (mol product/mol of Cu)
1	CuBr$_2$	4	1
2	CuBr$_2$ + **L1** (2:1)	91[c]	19
3	CuBr$_2$ + **L2** (2:1)	89	18
4	CuBr$_2$ + **L3** (2:1)	78	16
5	CuBr$_2$ + **L4** (2:1)	83	17
6	CuBr$_2$ + **L5** (2:1)	86	17
7	CuBr$_2$ + **L6** (2:1)	90	18
8	CuBr$_2$ + **L1** (1:1)	12	2
9	CuBr$_2$ + **L7** (1:1)	37	7
10	CuBr$_2$ + phen (1:1)	72	14
11	CuBr$_2$ + bipyridine (1:1)	85	17

[a] *Reaction conditions*: 5 mmol benzyl alcohol in the solvent mixture of 10 mL CH$_3$CN and 5 mL H$_2$O. 5 mol% catalyst (Cu) loading, 5 mol% TEMPO, 5 mol% *t*-BuOK, air, 2 h.
[b] GC yields (mol of benzaldehyde/100 mol of benzyl alcohol) using dodecane as an internal standard; in all cases selectivity was >99%. Yields were averaged for five runs under identical conditions, all values ± 2%.
[c] As per reaction conditions (a) but in the absence of *t*-BuOK, 40% yield obtained.

Table 2
Optimization of the reaction medium for aerobic oxidation of benzyl alcohol.[a]

Entry	Solvent mixture (v/v)	Time (h)	Yield[b] (%)	TON (mol product/mol of Cu)
1	Acetonitrile	3	76	15
2	Water	12	28	6
3	Acetonitrile/water (2/1)	2	91	18
4	Acetonitrile/water (1/2)	2	93	19
5	Acetonitrile/water (1/3)	2	82	16
6	Acetonitrile/water (1/15)	12	90	18
7	Acetone/water (1/2)	2	52	10
8	Dioxane/water (1/2)	2	84	17

[a] *Reaction conditions*: 5 mmol benzyl alcohol. 5 mol% CuBr$_2$, 2.5 mol% **L1**, 5 mol% TEMPO, 5 mol% *t*-BuOK, air, 2 h.
[b] GC yields (mol of benzaldehyde/100 mol of benzyl alcohol) using dodecane as an internal standard; in all cases selectivity was >99%.

it is easier for the substrate to enter the coordination sphere of the copper and become activated. These findings may be significant when designing heterogeneous tethered-Cu catalyst systems for aerobic oxidation processes, as two linked copper centres appear to be superior to copper centres that behave independently. It should be noted that replacement of tetradentate ligands (**L1–L6**) with a closely related pyridyl-imine bidentate ligand (**L7**) resulted in a much lower yield (entry 9). Also, under our reaction conditions, the employment of 1,10-phenanthroline (phen) and 2,2′-bipyridine ligands (entries 10 and 11) gave lower yields than tetradentate ligands **L1–L6**. However, when TON are taken into account, commercially available ligands such as phen and 2,2′-bipyridine give very good results and would be more useful than tetradentate ligands **L1–L6** at the present time for practical chemistry applications.

The ratio of tetradentate ligand to copper was also important. When the amount of tetradentate ligand was increased to an equimolar amount with respect to CuBr$_2$, the yield dramatically dropped down to 12% (entry 8). This can be explained by strong coordination of 4 N-donors to the copper centre and a difficulty in dissociating these to yield a vacant site. Cyclic coordination oligomers might be forming as previously reported for bis(pyridyl)siloxane ligands with palladium acetate [49]. Formation of such cyclic species would mean that coordination of the alcoholate group with the metal centre would be challenging.

3.2. Solvent effect

Acetonitrile has been broadly used as a solvent in oxidation reactions. Gamez et al. has reported the great effect of acetonitrile on the Cu(II)-catalyzed oxidative coupling of 2,6-dimethylphenol [53]. The aerobic Cu(II)-catalyzed oxidation of primary alcohols has also been reported using a similar catalytic system [35]. In comparison with these results, our catalytic system can tolerate a greater proportion of water in the solvent mixture and also achieves moderate yield levels in pure acetonitrile when we use poly(dimethylsiloxane) derived **L1**, Table 2. Probably due to the insolubility of *t*-BuOK base in pure acetonitrile, water is essential to obtain catalytic activity when using 2,2′-bipyridine as the ligand. As shown in Table 2, using **L1** a moderate yield can be achieved in neat acetonitrile (Table 2, entry 1). Recently, Repo and co-workers reported the aerobic oxidation of alcohols using copper(II) 2-N-arylpyrrolecarbaldimino complexes under aqueous conditions (no added organic co-solvent), they achieved 100% yield in 2 h under an O$_2$ atmosphere and 17% using air [54]. They also found that upon addition of co-solvents yields decreased. For our catalytic system, 28% yield was obtained in water after 12 h using air (entry 2). However, in our study, improved yields could be achieved when the amount of water was increased in acetonitrile/water solvent mixtures. 90% yield was obtained in 12 h with a 1:15 (v/v) acetonitrile/water solvent mixture (entry 6). This reversal in activity trends

Table 3
CuBr$_2$/**L1**/TEMPO-catalyzed aerobic oxidation of benzylic alcohols.[a]

Entry	Substrate	Product	Yield[b] (%)	Selectivity[b] (%)
1			100 (96[c])	>99
2			100	>99
3			100	>99
4			100	>99
5			100	>99
6			99	>99
7			98	>99
8			100	>99
9			100	>99
10			100[d]	>99
11			97[d]	>99
12			92[d]	>99

[a] *Reaction conditions*: 5 mmol benzyl alcohol in 5 mL CH$_3$CN and 10 mL H$_2$O. 5 mol% CuBr$_2$, 2.5 mol% **L1**, 5 mol% TEMPO, 5 mol% *t*-BuOK, air, 4 h.
[b] GC yields (mol of aldehyde/100 mol of alcohol) using dodecane as an internal standard; selectivities were also measured by GC–MS. TONs between 18 (entry 12, *p*-nitro benzyl alcohol) and 20 (entries 1–10).
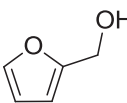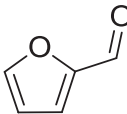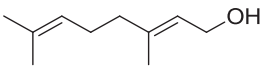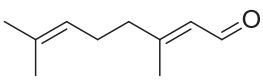[c] Isolated yield.
[d] 6 h.
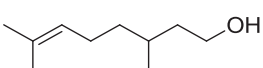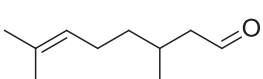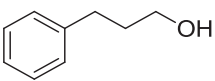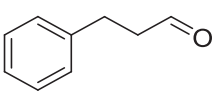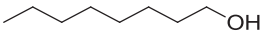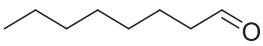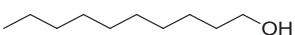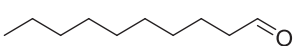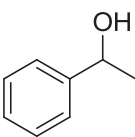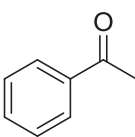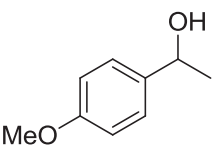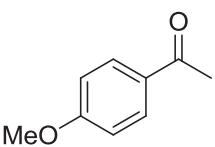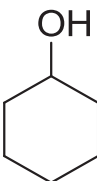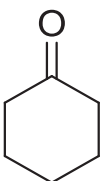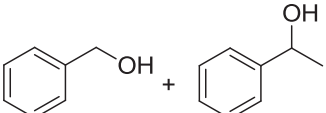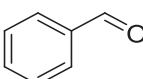
compared with the results of other researchers may imply that our catalytic system operates via a different mechanism to theirs. Also, at this stage, we assume that the presence of water assists in solubilising *t*-BuOK and the presence of an organic solvent assists in solubilising the substrates. Two other water-miscible co-solvents were also tested in place of acetonitrile for the oxidation of benzyl alcohol (entries 7 and 8). A lower yield was obtained using acetone (entry 7), but a good yield was achieved with a dioxane/water solvent mixture (entry 8). An attempt at biphasic catalysis using a water/toluene system afforded a yield of 8% (TON 1.6) using

conditions similar to those in Table 2 (entries 7 and 8). The low TON in this case was likely due to the an inefficient mixing of the reactants [35], and the catalyst and co-catalyst residing in separate phases (TEMPO in the toluene phase and the copper-species in the aqueous phase). Furthermore, when two equiv. CuBr$_2$ were mixed with **L1** in toluene, **L1** formed a homogeneous solution but the CuBr$_2$ remained insoluble (black precipitate) and the organic phase remained colourless.

Even though **L1** is soluble in scCO$_2$ (a single continuous phase is observed at pressures exceeding 6000 psi between 50 and 90 °C),

Table 4
CuBr$_2$/**L1**/TEMPO-catalyzed aerobic oxidation of other selected alcohols.[a]

Entry	Substrate	Product	Time (h)	Yield[b] (%)
1			4	100 (20)
2			4	91 (18) 95[c] (19) 24 h
3			4	88 (18) 89[c] (18) 36 h
4			6	75 (15)
5			8 / 24	59 (12) / 61 (12)
6			8	64 (13) 60[c] (12) 36 h
7			12	88 (18) 71[c] (14) 36 h
8			12	87[d] (17) 68[c] (14) 36 h
9			24	3 (0.6)
10			4	100/0[e] (20)

[a] *Reaction conditions*: 5 mmol alcohol in 5 mL CH$_3$CN and 10 mL H$_2$O. 5 mol% CuBr$_2$, 2.5 mol% **L1**, 5 mol% TEMPO, 5 mol% *t*-BuOK, air.
[b] GC yields (mol of aldehyde/100 mol of alcohol) using dodecane as an internal standard; selectivities were also measured by GC–MS. TON values (mol product/mol of Cu) in parentheses.
[c] Reaction conditions same as other entries but 1 mL CH$_3$CN and 15 mL H$_2$O.
[d] Reaction conditions same as other entries but 4 mL CH$_3$CN and 12 mL H$_2$O.
[e] Competitive oxidation experiment, 100% selectivity for 1° benzyl alcohol oxidation shown in 4 h.

oxidation reactions were not studied in this reaction medium, as under the conditions studied (25–120 °C, 4000–7500 psi) homogeneity for a mixture of CuBr$_2$/**L1** (2:1) was not achieved. It should also be noted that due to the high pressures and moderate temperatures required to achieve a homogeneous supercritical phase, and that the reaction could be performed effectively in aqueous solution, studies using co-solvents and reagents to encourage solubilisation of the CuBr$_2$/**L1** catalyst system in scCO$_2$ were not performed. However, it should be noted that the alcohol substrates may be able to act as co-solvents and yield a homogeneous reaction system in the future.

3.3. Aerobic oxidation of benzylic alcohols

Through the studies reported above and in order to compare results with a future heterogeneous catalyst system, we chose to focus on the *in situ* CuBr$_2$/**L1** (2:1) complex in combination with TEMPO and base for an investigation of substrate scope. The oxidation reactions of a variety of benzylic alcohols were carried out in a 2:1 (v/v) water/acetonitrile solvent mixture (Table 3). As shown in Table 3, a range of benzylic primary alcohols was converted into the desired aldehydes with high yields and selectivities. The electronic property of the substituent on the benzene ring had

no significant effect on the yields and selectivities. All the benzylic primary alcohols whether containing electron-donating or -withdrawing groups were smoothly oxidized to the corresponding aldehydes. Benzyl alcohols with electron-donating groups, e.g. entry 9, achieved slightly faster reaction rates compared with substrates bearing electron-withdrawing groups (entries 10–12).

3.4. Aerobic oxidation of other primary and secondary alcohols into aldehydes and ketones

The **L1**-based catalytic system was also examined for aerobic oxidations of other alcohols (Table 4). 2-Furylmethanol, geraniol and citronellol were oxidized to their corresponding aldehydes with high yields (entries 1–3). To our delight, aryl-aliphatic and aliphatic primary alcohols could also be converted to the aldehydes with moderate to good yields (entries 4–6). However, the reaction rates were much slower in comparison with the oxidation of benzylic and allylic alcohols. This is most likely due to stronger C_α–H bond strengths in these species compared with those in benzylic and allylic alcohols [55]. Even when we increased the reaction time to 24 h, the yields did not improve significantly. This might be explained by the presence of aliphatic aldehydes and oxygen which could lead to decomposition of the oxoammonium ion in our catalytic cycle and therefore decrease the overall catalytic activity [20]. We were pleased to find that benzylic secondary alcohols could also be oxidized to ketones. However, in order to achieve high yields, longer times were essential (entries 7 and 8). Also, the reactions of non-benzylic alcohols proceeded well in the presence of increased water content but longer reaction times were required (entries 2, 3, and 6–8). Unfortunately, the **L1**-based catalytic system was unable to oxidize secondary aliphatic alcohols (entry 9).

3.5. Comparison with known Cu–ligand–TEMPO catalyst systems for the oxidation of benzyl alcohol and some other alcohols

In order to more clearly present the activity of our catalyst system, Table 5 compares the Cu–**L1**/TEMPO system with some other reported Cu–ligand/TEMPO catalytic systems. As shown in entry 1, one of the early Cu–bipyridine/TEMPO systems oxidized benzyl alcohol to benzaldehyde smoothly at room temperature and under atmospheric air. However, this system was unable to oxidize secondary alcohols. For a Cu–pyrazole/TEMPO system (entry 2), only the oxidation of benzyl alcohol to benzaldehyde was reported. For the Cu–DABCO/TEMPO system, oxidation of aliphatic alcohols was much less efficient compared with the oxidation of benzyl alcohol (entry 3). Copper(II) 2-N-arylpyrrolecarbaldimino complexes combined with TEMPO have been shown to efficiently oxidize benzyl alcohol with low catalyst loadings in water (entry 4). However, aliphatic alcohols could not be converted under these conditions. Compared to the selected literature catalytic systems described above, our **L1**-Cu/TEMPO system was more general for the aerobic oxidation of alcohols at room temperature and under atmospheric air (entry 5), as moderate to good conversions for primary aliphatic and secondary benzylic alcohols could be obtained in shorter reaction times compared with those reported in the literature.

### 3.6. Preliminary mechanistic insights

In order to investigate the selectivity of the catalytic system towards primary and secondary alcohols, a competitive oxidation experiment with equal amounts of benzyl alcohol and 1-phenylethanol was performed (Table 4, entry 10). The result shows the specificity of our CuBr$_2$/**L1**/TEMPO catalytic system towards the primary alcohol because 100% of the benzyl alcohol was converted into benzaldehyde, whereas 1-phenylethanol remained unreacted
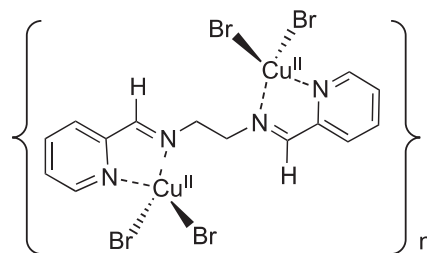
Cu$_2$(**L3**)$_2$Br$_4$, Harris and McKenzie, 1969
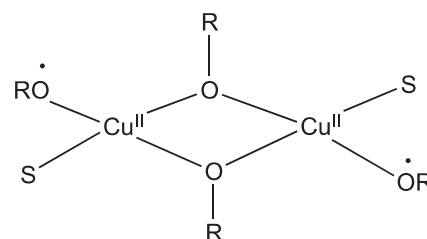
Chaudhuri, Wieghardt and co-workers, 1998
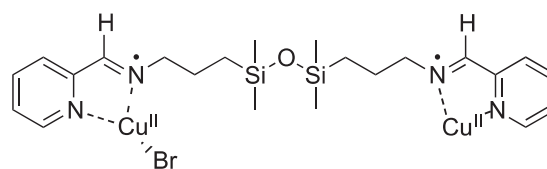
"Cu$_2$(**L2**)Br" observed by MALDI-TOF MS

Fig. 3. Bimetallic Cu-species of relevance to this study.

within 4 h. This chemoselectivity is consistent with one of the typical characteristics of the natural copper protein galactose oxidase (GOase) and can be used for the selective oxidation of different alcohols [57–61]. Also, this potentially offers some insight into the reaction mechanism in this system and the increased yields seen for **L1**–**L6** compared with **L7**. **L3** is known to form a di-copper complex [62] and we propose that the tetradentate ligands shown here are efficient in forming such species, Fig. 3. Although monometallic mechanisms dominate this field, there is some precedent for highly active bimetallic species [61]. Recently, a kinetic dependency for copper of 2.25 was identified for Cu–bipyridine/TEMPO complexes in aerobic alcohol oxidation reactions [41]. Also, it should be noted that given the differences in reactivity observed for our catalyst system compared with those in the literature (Table 5), Cu–**L1** is likely to perform such oxidation reactions via a different mechanism compared with bipyridine-derived systems. We monitored the metal-centred reaction process by MALDI-TOF mass spectrometry using **L2** as an example. MALDI-TOF mass spectrometry is developing as a useful method for probing metal-centred reactions, especially when the paramagnetic nature of a metal centre thwarts NMR based methods of interrogation [63,64]. An aliquot of the reaction mixture was mixed with matrix (dithranol) and the solution was spotted onto the MALDI plate and allowed to evaporate. The resulting mass spectrum showed two main peaks at $m/z = 493$ and 633. By inspection of their isotope distribution and on the basis of their mass, they could be assigned to species containing one Cu atom and one equivalent of **L2** ($m/z = 493$) and two copper atoms, one ligand and one Br atom ($m/z = 633$), Fig. 3 (see Supplementary Data). This data provides some evidence to support the presence of a bimetallic species in the catalytic

Table 5
Comparison of literature catalysts and our catalytic system for the aerobic oxidation of benzyl alcohol, 1-phenylethanol, 1-decanol and 1-hexanol.

Entry	Catalytic system	Reaction conditions for BnOH oxidation	Yield (%)	TON
1	Sheldon et al. [35]	5 mol% CuBr$_2$, 5 mol% t-BuOK, 5 mol% 2,2′-bipyridine, 5 mol% TEMPO, air, 25 °C, CH$_3$CN/H$_2$O (2:1), 2.5 h	100 0[a]	20 0[a]
2	Reedijk et al. [36]	5 mol% CuBr$_2$, 5 mol% t-BuOK, 5 mol% 2-(1-methyl-1H-pyrazol-5-yl)pyridine, 5 mol% TEMPO, air, 25 °C, CH$_3$CN/H$_2$O (2:1), 24 h	89	19
3	Sekar et al. [56]	5 mol% CuCl, 5mol% TEMPO, 5 mol% 1,4-diazabicyclo[2.2.2]octane (DABCO), 5 mol% TEMPO, 1 atm O$_2$, 80 °C, toluene, 2 h	85 20[b] (72 h)	17 4
4	Repo et al. [54]	1 mol% of CuSO$_4$, 2 mol% N-((1H-pyrrol-2-yl)methylene)-4-fluoroaniline, 0.1 M K$_2$CO$_3$, 5 mol% TEMPO, 1 atm O$_2$, 80 °C, water, 2 h	100 6[c] (20 h)	100 6
5	This work	5 mol% CuBr$_2$, 5 mol% t-BuOK, 2.5 mol% **L1**, 5 mol% TEMPO, air, 25 °C, CH$_3$CN/H$_2$O (1:2), 4 h	100 88[a] (12 h) 64[b] (8 h) 56[c] (8 h)	20 19 13 11

[a] Oxidation of 1-phenylethanol to acetophenone.
[b] Oxidation of 1-decanol to decan-1-al.
[c] Oxidation of 1-hexanol to hexan-1-al.

cycle but further experiments are needed in the future to confirm this possibility. Another option that we cannot overlook at this stage is a mechanism that involves reaction of the imine ligand. However, similar imine ligands once coordinated to metals have been shown to be stable in water [65]. No evidence of ligand decomposition was seen in the mass spectra of reaction mixtures.

In order to understand the limitations of the catalyst system under investigation here, some catalyst deactivation studies were performed. For the model reaction studied, after benzyl alcohol oxidation was complete (same as Table 3, entry 1), the acetonitrile solvent and benzaldehyde produced were removed under vacuum. Additional amounts of benzyl alcohol (5 mmol) and acetonitrile (10 mL) were added to the aqueous residue remaining from the initial reaction. If an additional 5 mol% of TEMPO was added at this time, 86% yield of benzaldehyde was obtained in 4 h (c.f. 100% in 4 h for initial reaction). For a similar Cu–**L1** catalyst recycling study, only 7% yield was obtained when additional TEMPO was not used. Therefore, the activity of the copper complex is maintained after the reaction but the TEMPO has degraded and is the limiting reagent/factor with regards to catalyst re-use.

4. Conclusions

In conclusion, we have developed a new catalyst system for room temperature CuBr$_2$–TEMPO catalyzed aerobic oxidation of alcohols based on known and novel tetradentate pyridyl-imine ligands. The polydimethylsiloxane (PDMS) derived pyridyl-imine ligand and other tetradentate ligands studied showed catalytic activity as good as 2,2′-bipyridine based systems. However, the bidentate pyridyl-imine ligands studied showed poor catalytic activity and for tetradentate ligands a ratio of 2Cu:L was crucial in maintaining good catalyst TON. A number of primary and some secondary alcohols could be oxidized to the corresponding aldehydes and ketones with high yields and selectivities. The exact mechanistic details are still under investigation, but likely involve a di-copper species. With these initial homogeneous catalyst based results as a starting point, in the future, we aim to use pyridyl-imine ligands within heterogeneous or recyclable homogeneous catalyst systems for aerobic oxidation reactions [66]. A combination of PEG-modified Cu catalyst and PEG-modified TEMPO catalyst have previously been used to good effect [67], and therefore, there is the potential to use Cu–**L1** with a modified-TEMPO or other stable radical co-catalyst in future studies.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.apcata.2011.11.024.

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