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# Catalytic Activity Dependency on Catalyst Components in Aerobic Copper–TEMPO Oxidation

Esa T. T. Kumpulainen and Ari M. P. Koskinen\*<sup>[a]</sup>

**Abstract:** The influence of catalyst components in the copper–TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxide) catalysed aerobic oxidation of alcohols was investigated. The type and amount of base greatly influences reactivity. The bipyridyl ligand concentration had no major influence on catalysis, but ex-

cessive amounts led to a decrease in activity for longer reaction times. The kinetic dependency for TEMPO was

**Keywords:** alcohols • copper • homogeneous catalysis • oxidation • TEMPO

found to be 1.15, and for copper 2.25, which is an indication of a binuclear catalytic system. Optimised conditions with various allylic and aliphatic alcohols give good to excellent rapid oxidations.

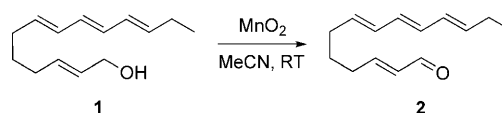
## Introduction

The oxidation of alcohols to carbonyl compounds is one of the fundamental reactions both in nature and in organic synthesis. Synthetic chemistry relies heavily on stoichiometric oxidants,<sup>[1]</sup> whereas nature uses metal catalysis and oxygen as the terminal oxidant.<sup>[2]</sup> The quest to replace stoichiometric oxidants with methodology similar to nature has recently gained increasing interest.<sup>[3–6]</sup>

Galactose oxidase (GO) is a type II mononuclear copper enzyme that converts a variety of primary alcohols to aldehydes.<sup>[7]</sup> The active site incorporates a tyrosine residue as a radical mediator, which, in combination with copper(II), can perform a two-electron oxidation process. Due to the efficiency of GO,<sup>[8]</sup> extensive research has been conducted to mimic its active site in order to produce a simple catalytic system for synthetic use.<sup>[9]</sup> One of the systems currently considered to be a GO mimic is the copper/nitroxyl-radical-catalysed oxidation, first introduced by Brackman and Gaasbeek in 1966.<sup>[10]</sup> Somewhat later Semmelhack et al. showed copper–TEMPO (TEMPO = 2,2,6,6-tetramethylpiperidine *N*-oxide) to be an efficient catalytic system in alcohol oxidation.<sup>[11]</sup> Further developments by Sheldon and co-workers<sup>[12]</sup> have led to increasing interest in such catalytic systems.<sup>[13]</sup>

## Results and Discussion

In our quest for a total synthesis of Amaminol A, we needed an effective oxidation for allylic primary alcohol **1** (Scheme 1).<sup>[14]</sup> Generally, such a delicate transformation is



Scheme 1. Challenging allylic oxidation.

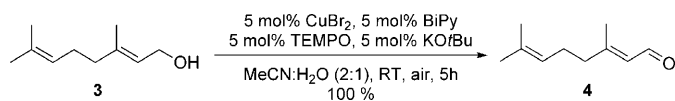
usually achieved by using stoichiometric oxidants such as pyridinium dichromate (PDC),<sup>[1]</sup> pyridinium chlorochromate (PCC),<sup>[1]</sup> activated manganese oxide,<sup>[15]</sup> Dess–Martin periodinane,<sup>[16]</sup> and *o*-iodoxybenzoic acid (IBX).<sup>[17]</sup> Allylic oxidation can be performed catalytically using the TEMPO–BAIB<sup>[18]</sup> (BAIB = bisacetoxyiodobenzene) system, in which BAIB acts as the stoichiometric oxidant. Some of these oxidation methods are not particularly sensitive or produce acidic by-products, which in our case would cause problems. We therefore chose to use the manganese oxide method. Although the reaction performs well on a small scale, scaling up is problematic due to the high excess of MnO<sub>2</sub> (10–20 equiv) needed.

Oxidation of **1** provides a particularly challenging test case, since the product **2** is highly sensitive to excessive heat, light and both strong Brønsted acids and Lewis acids. In our case, we wanted to subject **2** to an organocatalytic asymmetric intramolecular Diels–Alder reaction. Any background

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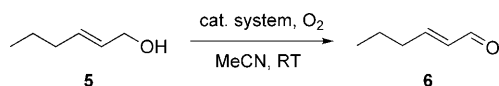
reaction would give a racemic product, thus diminishing the efficiency of the asymmetric synthesis. Any Brønsted acid produced during the oxidation would be deleterious, and similarly prolonged stirring of the product would also subject the enal to a non-asymmetric process. Therefore, speed is of vital importance for the successful outcome of the oxidation.

We turned our attention to aerobic oxidations as alternative methods for the allylic oxidation, because these use oxygen as the stoichiometric oxidant and produce water<sup>[19]</sup> or hydrogen peroxide<sup>[20]</sup> as by-products. Most of the known aerobic oxidations use forcing conditions with elevated temperatures or high pressures. The copper–TEMPO method described by Sheldon and co-workers seemed most promising to us (Scheme 2).<sup>[12]</sup>



Scheme 2. Sheldon's aerobic oxidation method.

To avoid solubility problems of highly hydrophobic substrates, we initially chose to reduce the amount of water in acetonitrile to 1–2 vol % and performed the oxidation of allylic alcohol **1** as described by Sheldon and co-workers. We occasionally obtained very active catalyst and intermittently almost inactive systems. This poor reproducibility was linked to measurement errors of solid materials in small-scale experiments (0.1 mmol of alcohol **1**). We therefore turned to model experiments using *trans*-2-hexen-1-ol **5** as a simple substrate in order to find the true cause of catalyst inhibition and activation (Scheme 3).



Scheme 3. Model system for allylic oxidation.

The effect of different bases on oxidation was examined (Figure 1). To minimise measurement errors we used standard solutions of all the different reaction components. All amine bases were fully soluble in acetonitrile (1M solution) and therefore no water was introduced into the reaction.<sup>[21]</sup> Potassium *tert*-butoxide was not soluble enough so it was added as a solid. Potassium hydroxide was dissolved in water (1M solution) and therefore a small amount of water (1–2 vol %) was also introduced.

Reactions containing potassium hydroxide showed good reactivity compared to most of the amine bases. The optimal amount of base was investigated using 5–20 mol % of KOH. A slight improvement in the reaction rate was observed when 10 mol % of KOH was used instead of 5 mol %. Addition of more KOH (marked with arrows in Figure 1) seemed to be detrimental. It was also found that a few minutes after the addition of KOH some brown solids precipitated (pre-

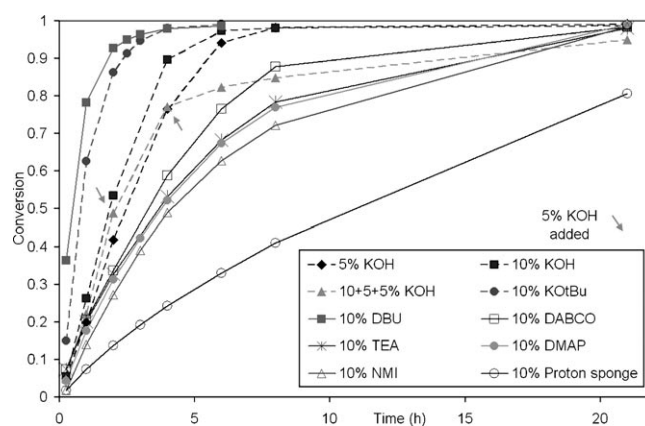


Figure 1. Effect of different bases (in mol %) on the oxidation of alcohol **5**. Solid lines are for amine bases and dashed lines are for potassium-containing bases. Conditions: Alcohol **5** (0.5 mmol), CuBr<sub>2</sub> (5 mol %), bipy (5 mol %), TEMPO (5 mol %), MeCN (5 mL), O<sub>2</sub> (balloon).

sumably copper hydroxides or oxides). This would decrease the amount of copper in solution and copper-to-ligand ratios would also be radically influenced. For the rest of the reactions we chose to use 10 mol % of base. Potassium *tert*-butoxide gave high activity but it was poorly soluble in the reaction mixture.

The activity of the amine bases correlates with their basicities. Proton sponge showed the poorest performance. Moderate activities were found with *N*-methyl imidazole (NMI), *N,N*-dimethyl aminopyridine (DMAP) and triethylamine (TEA). 1,4-Diazabicyclo[2.2.2]octane (DABCO) was found to be slightly more active. The highest activity was obtained with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). All reactions with amine bases were homogenous until approximately > 95 % conversion, when green solids with unknown composition appeared. After this point the catalyst showed only moderate activity when another equivalent of alcohol **5** was added. Similar deactivation was also reported in the literature.<sup>[22]</sup>

We now had a reproducible oxidation method in which all reaction components could be added as solutions. We then turned our focus towards different catalyst components. First, we decreased the amount of catalyst from 5 to 2 mol % in order to slow the reaction enough to be able to see the differences between the component amounts. We wanted to see whether excess base also has a detrimental effect when amine bases are used. When the amount of DBU is increased from 4 mol %, a decrease in catalytic activity is indeed observed (Figure 2). This appears even more dramatic when alcohol **5** consumption is plotted on a second-order reaction plot (Figure 3). This plot also shows that the oxidation proceeds with a second-order correlation with alcohol concentration. Similar findings have been presented in the literature.<sup>[23]</sup>

Copper catalysts for aerobic oxidations have been shown to have various numbers of nitrogen ligands.<sup>[24]</sup> We therefore also investigated the effects of the quantity of the 2,2'-bipyridine (bipy) ligand. When the amount of bipy was increased

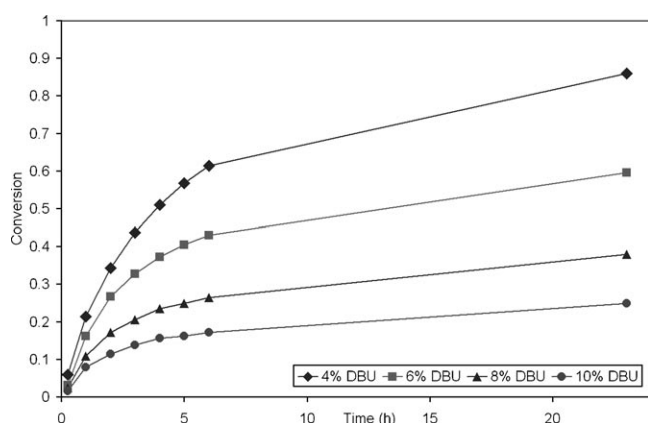


Figure 2. Effect of DBU (in mol%). Conditions: Alcohol **5** (1 mmol), CuBr<sub>2</sub> (2 mol %), bipy (2 mol %), TEMPO (2 mol %), MeCN (5 mL), O<sub>2</sub> (balloon).

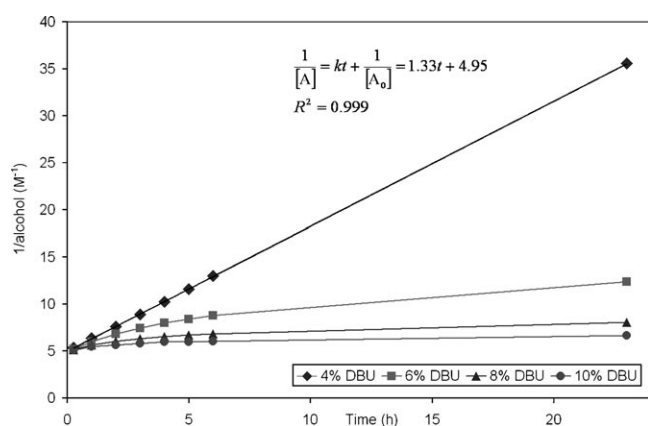


Figure 3. Second-order plot (1/[5] vs. time) of Figure 2.

from 2 to 4 mol% the reaction rate increased slightly (Figure 4). Initially it seemed that the ligand amount does not have a major influence on the reaction. After a few hours the reaction started to slow down when 8 or 6 mol% was used in comparison with 2 and 4 mol%. Although

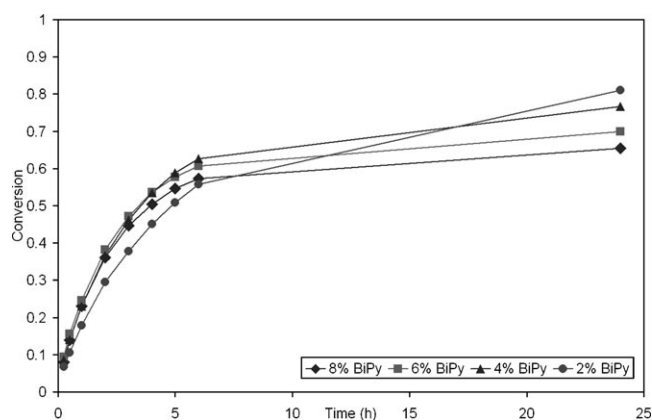


Figure 4. Effect of bipy (in mol%). Conditions: Alcohol **5** (1 mmol), CuBr<sub>2</sub> (2 mol %), TEMPO (2 mol %), DBU (4 mol %), MeCN (5 mL), O<sub>2</sub> (balloon).

4 mol% was initially faster than 2 mol%, we found that in a prolonged reaction (24 h) the reactivity was reversed. The effect becomes clearer when a second-order plot is used, although the linear fit is not perfect for the whole reaction time (Figure 5). We envisioned that this behaviour is caused

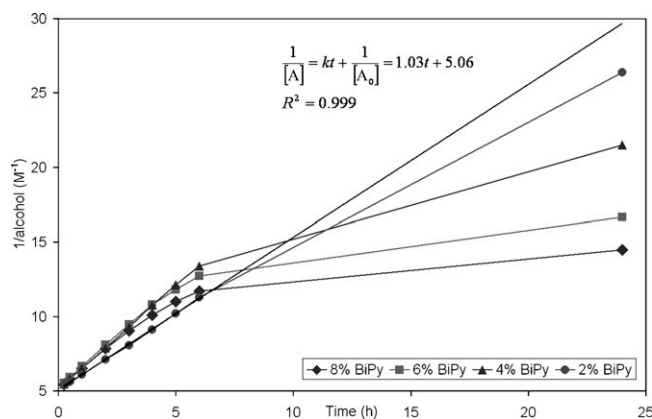
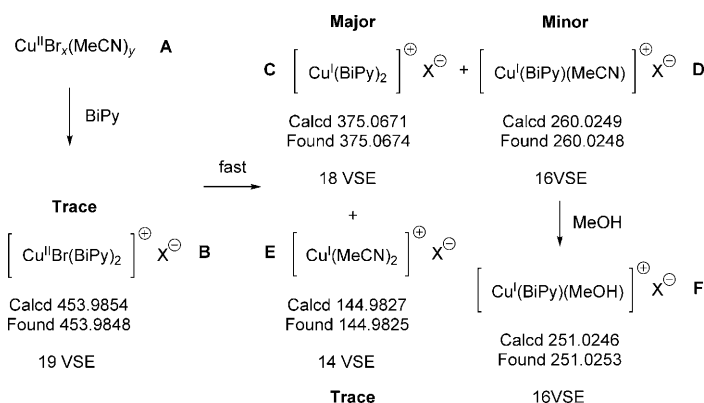


Figure 5. Second-order plot (1/[5] vs. time) of Figure 4.

by equilibrations. At high dilution, copper coordinates more easily to one bipy when more than one equivalent is present in the solution. Eventually more bipy ligands coordinate to copper and fill its coordination sphere, thereby rendering the catalyst inactive.

Further insight was provided by HRMS monitoring of the oxidation experiment with KOH as the base. The solvated form of CuBr<sub>2</sub> was rapidly converted to complexes **B–E** after bipy addition (Scheme 4). We were able to identify



Scheme 4. Reaction monitoring (35 min after KOH) with HRMS spectrometer.

only a trace of Cu<sup>II</sup> species **B**. The majority of copper complexes were rapidly reduced to Cu<sup>I</sup>. Similar findings have previously been reported using UV/Vis analysis.<sup>[25]</sup> The ratio between the major and minor complexes **C:D** was approximately 2:1. After two hours the ratio of major components remained the same, but complexes **B** and **E** could not be observed anymore. The major complex **C** has two bipy ligands,

which fill the coordination sphere of  $\text{Cu}^{\text{I}}$ , giving 18 valence shell electrons (VSE). This complex should therefore be inactive for re-oxidation. The minor complex **D** has only one bipy and one acetonitrile, filling its sphere only partially with 16 VSE. Such a complex should be able to coordinate to oxygen, which would be followed by the re-oxidation of copper. After monitoring the reaction for several hours, our HRMS instrument became contaminated with reaction components. After extensive washing with methanol, complex **D** was not found any more in the following samples. Complex **D** had lost acetonitrile, which was replaced by methanol to give complex **F**. This ligand exchange can also occur in the reaction medium, and at the same time influence the electronic nature of copper, possibly facilitating re-oxidation. We also found that when the conversion approaches 100% the catalyst starts to be deactivated. We were not able to identify the form of anions in these complexes.

We expect that oxidation follows a pseudo-second-order rate law [Eq. (1)] in which the oxygen concentration can be considered constant, and  $k$  is a function of the catalyst [Eq. (2)].

$$\text{rate} = k[\text{A}]^2[\text{O}_2] \quad (1)$$

$$k = k_{\text{cat}}[\text{TEMPO}]^a[\text{Cu}]^b \quad (2)$$

Information from base and ligand quantities indicated that the  $\text{CuBr}_2$ :bipy:DBU ratio should be 1:1:2. We chose this ratio for further studies, starting with the influence of TEMPO on the reaction rate. By increasing the amount of TEMPO from 2 to 5 mol% we noticed a clear increase in the reaction rate (Figure 6). A second-order plot excluding

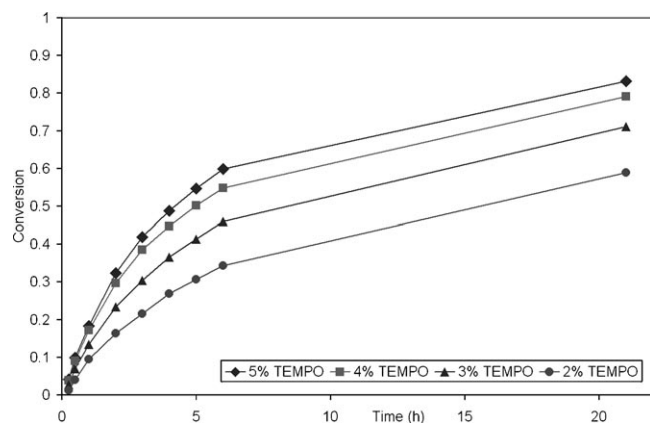


Figure 6. Effect of TEMPO (in mol %). Conditions: Alcohol **5** (1 mmol),  $\text{CuBr}_2$  (2 mol %), bipy (2 mol %), DBU (4 mol %), MeCN (5 mL),  $\text{O}_2$  (balloon).

the data points at 21 h is shown in Figure 7. The linear fit gave the slopes for different TEMPO amounts. These slopes were then plotted against TEMPO concentrations in a bi-logarithmic graph, revealing an approximately first-order (1.15) correlation with reaction rate (Figure 8). Similar results have been reported for a binuclear copper catalyst.<sup>[26]</sup>

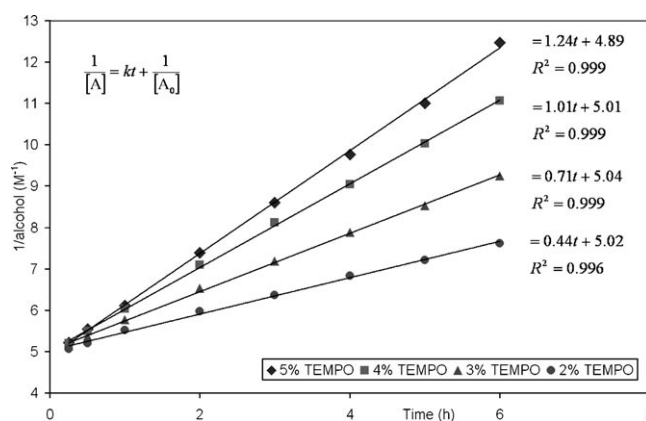


Figure 7. Second-order plot ( $1/[\text{5}]$  vs. time) of Figure 6 excluding data points at 21 h.

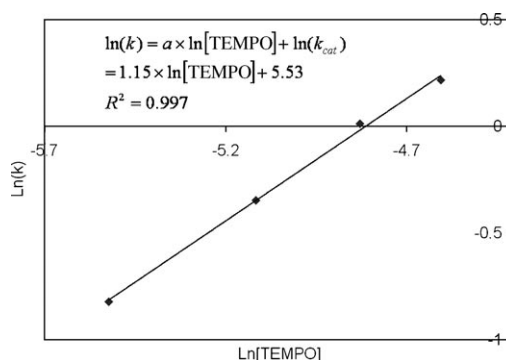


Figure 8. Logarithmic plot ( $\ln(k)$  vs.  $\ln[\text{TEMPO}]$ ) from slopes in Figure 7.

Once we had obtained correlations of DBU, bipy and TEMPO with the reaction rate, we turned to the most important catalyst species, copper. We chose to use a constant amount of TEMPO (5 mol%) in all experiments and change the quantity of copper, keeping the previously determined  $\text{CuBr}_2$ /bipy/DBU ratio at 1:1:2. The previously used initial alcohol **5** concentration of 0.2 M was found to be inappropriate due to high conversions even at 15 min reaction time when larger quantities of copper were used. We therefore lowered the initial alcohol **5** concentration to 0.1 M in order to slow down the reaction.

As expected, increasing the amount of copper dramatically enhanced the reaction rates (Figure 9). We also found that 1 mol% of copper was completely inactive. The reaction medium seemed to have small amounts of impurities, which inhibited the reaction. It was assumed that inhibition is also present at higher copper concentrations, but is not as apparent. These reactions did not follow second-order correlation in all cases, so the influence of copper was determined using the initial rate method, excluding data of the inactive reaction. When initial rates (5–15 min) were plotted on a logarithmic chart against copper concentration, an approximate second-order (2.25) correlation for copper was obtained (Figure 10).

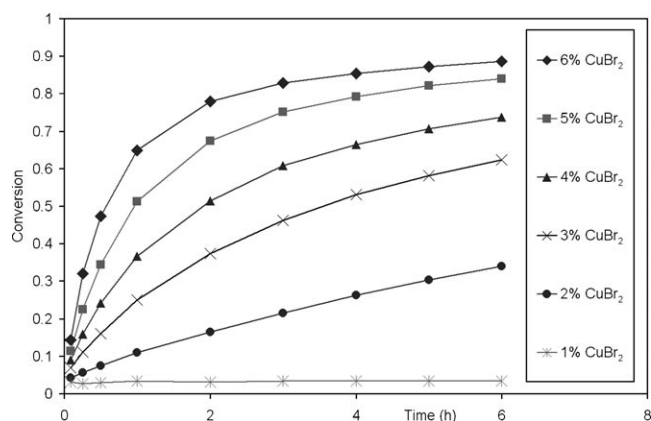


Figure 9. Effect of copper (in mol %). Conditions: Alcohol **5** (1 mmol), CuBr<sub>2</sub>:bipy:DBU (1:1:2), TEMPO (5 mol %), MeCN (10 mL), O<sub>2</sub> (balloon).

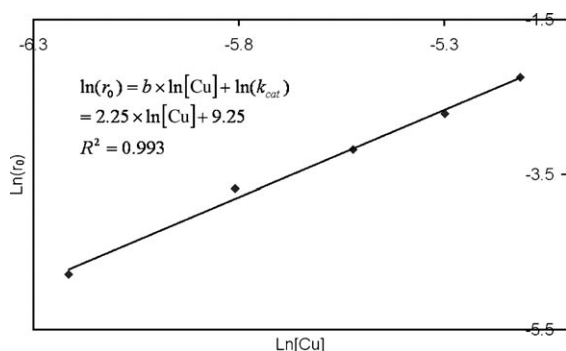


Figure 10. Logarithmic plot ( $\ln(r_0)$  vs.  $\ln[\text{Cu}]$ ) from initial rates (5–15 min) of Figure 9.

Inhibition of the 1 mol % copper-catalysed reaction led us to search for the cause of such behaviour. We found that our unpurified starting material **5** contained some 6 % of aldehyde **6** and 3 % of (*E*)-hex-2-enoic acid **7**, as revealed by <sup>1</sup>H NMR analysis. Copper(II) acetate has been found to be a poor catalyst in aerobic oxidations.<sup>[27]</sup> It is possible that the acid **7** replaces bromine atoms from the initial copper catalyst, forming a very stable copper complex. The stability of such a complex prevents the TEMPO-initiated reduction to copper(I) species and therefore inhibits the catalytic cycle.

We then performed the catalytic aerobic oxidation using 3 mol % of copper and introducing 3 or 6 mol % of crotonic acid **8** into the reaction (Figure 11). To find out if the inhibition is only caused by increased acidity we compensated the added acid with an equal amount of DBU in control experiments. As expected, the reactions with added crotonic acid **8** lost some of their catalytic activity. The reaction with 6 mol % of crotonic acid was found to be almost completely inactive.<sup>[28]</sup> The reaction with addition of extra base to compensate the acidic impurities did regain some catalytic activity, although less than in the control experiment. Addition of more DBU would not resolve the carboxylic-acid-derived

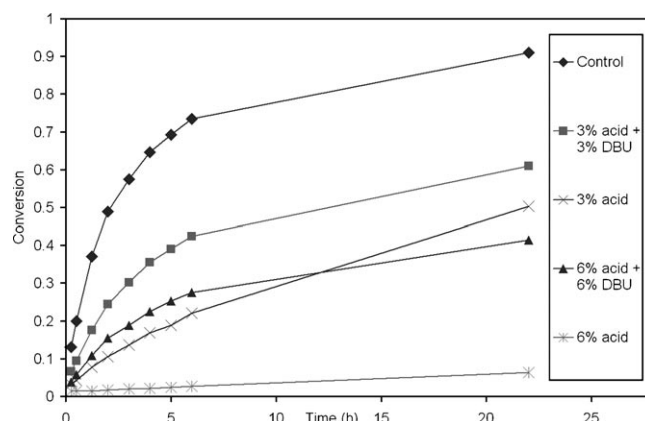


Figure 11. Effect of crotonic acid **8** impurities (in mol %). All reactions: Alcohol **5** (1 mmol), CuBr<sub>2</sub> (3 mol %), bipy (3 mol %), TEMPO (3 mol %), DBU (6 mol %), MeCN (5 mL), O<sub>2</sub> (balloon).

deactivation because it also acts as an inhibitor in excessive quantities (Figure 2).

We finally investigated the effect of concentration on the reaction rate (Figure 12). The rates of reactions with initial

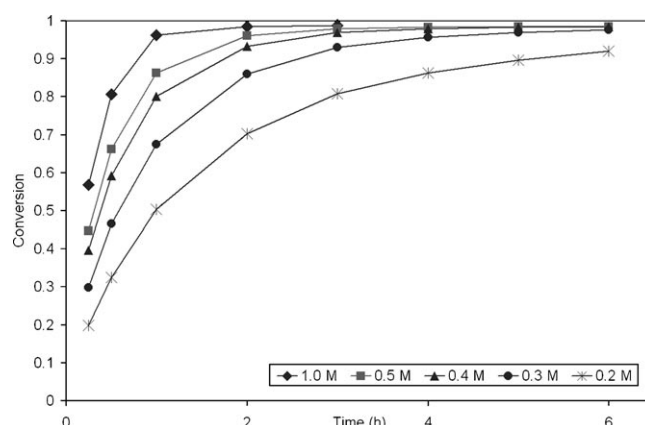


Figure 12. Effect of initial alcohol **5** concentration in acetonitrile. Conditions: Alcohol **5** (1 mmol), CuBr<sub>2</sub> (3 mol %), bipy (3 mol %), TEMPO (3 mol %), DBU (6 mol %), O<sub>2</sub> (balloon).

alcohol concentrations of 0.2–0.5 M were measured using standard solutions of different reaction components. For the most concentrated case, with 1.0 M alcohol **5** in acetonitrile, the rate was measured adding catalyst species as solids. We noticed that when solids are used there is a need for 10–15 min premixing after the addition of copper and bipyridyl. This ensures that most of the copper ions have only one co-ordinated bipy ligand. Otherwise initial reaction rates differed largely, although total reaction times were similar when reactions at this concentration were repeated. As expected, reactions became faster when performed at higher concentrations. A recent publication on copper–TEMPO oxidation shows that these reactions can also be performed without a solvent.<sup>[29]</sup>

The use of pure oxygen is not practical when reactions are scaled up, due to the high risk of explosion. We therefore examined the use of air instead of oxygen in order to see if oxygen dissolution is rate limiting at higher reaction concentrations. To minimise measurement errors we used an initial alcohol **5** concentration of 0.5 M, because this was the highest practical concentration for loading reactions using standard solutions. As expected, the reaction with air is slower than with pure oxygen (Figure 13). It was interesting

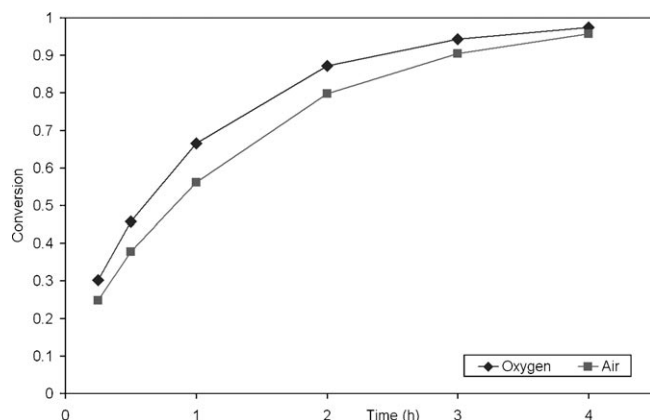


Figure 13. Effect of oxygen source. Conditions: Alcohol **5** (1 mmol), CuBr<sub>2</sub> (3 mol %), bipy (3 mol %), TEMPO (3 mol %), DBU (6 mol %), MeCN (2 mL), O<sub>2</sub>/air flow.

to see that usage of air decreased the reaction rate only slightly. Such behaviour is possibly linked to the relatively small scale (1 mmol) used. Another interesting observation was that reactions with air followed first-order kinetics for the whole reaction time (4 h), and the reaction with pure oxygen only for the first 2 h (Figure 14). This indicates that

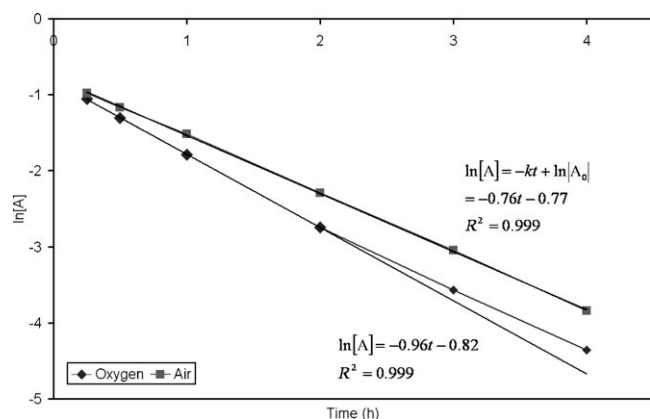


Figure 14. First-order plot (ln[**5**] vs. time) of Figure 13.

oxygen becomes a limiting factor for the reaction rate. A similar observation has been made by Kozłowski and co-workers for aerobic copper-catalysed phenolic biaryl coupling, which showed first-order dependency on oxygen.<sup>[30]</sup>

Interestingly, a fresh bottle of alcohol **5**, devoid of any acidic impurities, also affected the reactivity. The reaction with DBU failed to reach full conversion. We envisioned that such behaviour is due to the excessively basic conditions, which were previously partially neutralised by acid impurities. Once the base was changed to *N*-methyl imidazole, reactivity was regained.

We also examined the use of different solvents (Table 1). Fluorobenzene and pure dichloromethane were found to be

Table 1. Solvent effect and oxygen source effect on conversion [%] with time.

	Solvent <sup>[a]</sup>	1/2 h	1 h	2 h	3 h
1	MeCN	82	99	99	99
2	MeCN:CH <sub>2</sub> Cl <sub>2</sub> (1:1)	64	86	97	98
3	MeCN:H <sub>2</sub> O (9:1)	66	95	99	99
4	MeCN: <i>t</i> BuOH (9:1)	82	99	99	99

[a] Conditions: Alcohol **5** (2 mmol), CuBr<sub>2</sub> (3 mol %), bipy (3 mol %), TEMPO (3 mol %), NMI (6 mol %), solvent (2 mL), O<sub>2</sub> (balloon).

almost inactive due to the insoluble catalyst system. Acetonitrile was found to be most suitable due to good catalyst solubility and reaction rate. The solvent can be partially replaced with dichloromethane although reaction slows down slightly (Table 1, entry 2). Addition of water reduces the reaction rate slightly (Table 1, entry 3). This behaviour is most likely to be caused by competing coordination to the copper catalyst. Addition of *tert*-butanol had no effect on reactivity (Table 1, entry 4). Coordination of *tert*-butanol to copper is evidently much less preferred than that of allylic alcohol **5**.

In summary, we found a first-order kinetic correlation for TEMPO and second-order correlation for copper. Also, bipyridyl ligand stoichiometry and careful basicity control are important factors in determining catalytic activity. The substrate alcohol has second-order and oxygen first-order kinetic dependency.

Commonly, copper–TEMPO oxidations are represented using a reactive catalytic species postulated by Sheldon and co-workers (Figure 15).<sup>[12]</sup> In this complex, TEMPO is coordinated to copper in an η<sup>2</sup> manner. This postulation is not supported by our findings because in such a case copper and TEMPO should have identical kinetic factors. Copper–

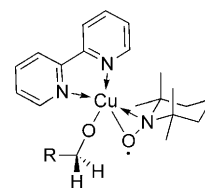
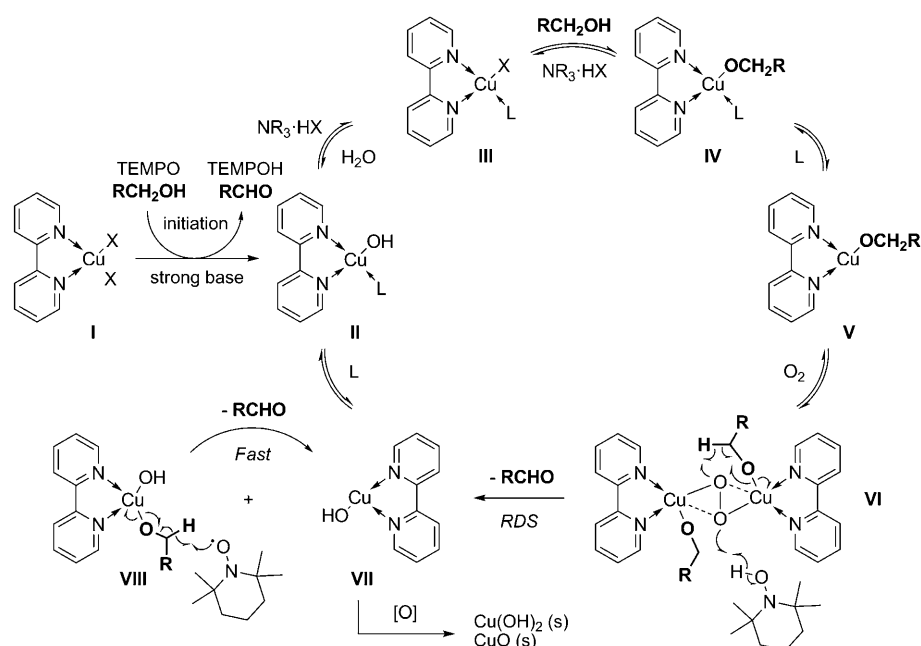


Figure 15. Reactive species reported by Sheldon and co-workers.

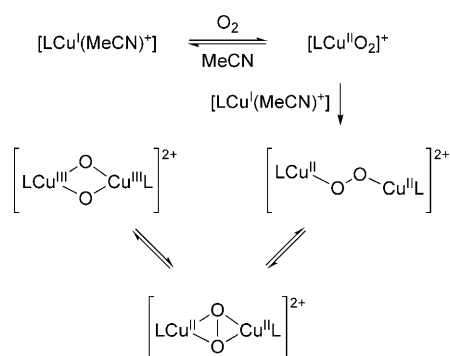
TEMPO systems are also considered to be monocopper enzyme galactose oxidase (GO) mimetic. Our findings would support a binuclear copper system, which is not in agreement with the assumption of GO mimicry.

Inspired by the vast amount of literature<sup>[31]</sup> on oxygen activation using copper complexes combined with our experimental data, we envisioned an alternative mechanism for copper–TEMPO systems (Scheme 5). The copper(II) salt **I**



Scheme 5. Proposed oxidation mechanism. L = ROH, MeCN, or  $\text{NR}_3$  type neutral  $\sigma$ -donor ligand.

enters the cycle with the help of a strong base and TEMPO, and reduces to the copper(I) complex **II** or **III** by oxidation of the substrate alcohol. An equilibrium replaces the leaving group X or hydroxide with alcohol, giving an 18-electron complex **IV**. This needs to lose a ligand to give the 16-electron copper(I) complex **V**, which is oxidised with oxygen to a binuclear copper(II) complex **VI**. Such a complex can be formulated as a copper(II)–1,2- $\mu$ -peroxo, copper(II)– $\mu$ - $\eta^2$ : $\eta^2$ -peroxo (as presented in Scheme 5) or copper(III)<sup>[32]</sup>–bis( $\mu$ -oxo)<sup>[33]</sup> complex, because these are represented as being in equilibrium and the true nature of the system is unclear (Scheme 6). Once the biscopper complex **VI** meets TEMPO,



Scheme 6. Equilibria between different copper oxygen complexes.

the rate-determining step (RDS), that is, oxidation of the coordinated alcohol, occurs through a radical mechanism and generation of TEMPO, complexes **VII** and **VIII**. The

generated TEMPO rapidly oxidises another alcohol with copper(II) complex **VIII**, because only copper(I) species are observed during the course of the reaction. A possible deactivation of the catalytic species can occur when copper hydroxides, such as complex **VII**, become insoluble by forming copper oxides or non-ligated hydroxides.

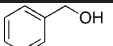
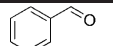
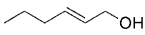
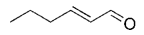


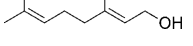
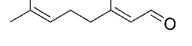
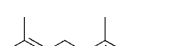
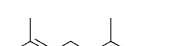
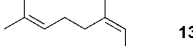
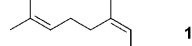
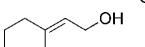
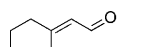
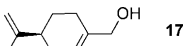
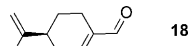
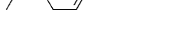
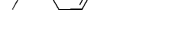

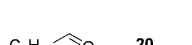
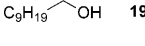
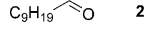
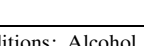
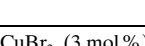
After optimising the reaction conditions, we wanted to test the scope and limitations of the method on the oxidation of various alcohols (Table 2). Both benzylic and allylic alcohols were converted to the corresponding aldehydes at room temperature in good isolated yields (Table 2, entries 1–8). When DBU was used with geraniol **11**, full conversion could not be obtained due to catalyst

deactivation (Table 2, entry 3). DMAP was able to produce 99% conversion, but a small portion of citral **12** was also isomerised to neral **14** (Table 2, entry 4). By using NMI, a rapid reaction and good isolated yield could be obtained without isomerisation of the *E* double bond (Table 2, entry 5). Such conditions were also tested for the oxidation of nerol **13**, which produced neral **14** without isomerisation to citral **12** (Table 2, entry 6). Similarly, isomerisation of an exocyclic double bond to an endocyclic one was not observed (Table 2, entry 7). The slightly more sterically demanding substrate perillyl alcohol **17** was also easily converted to perillaldehyde **18** (Table 2, entry 8).

The catalyst system was also tested for 1-decanol **19** (Table 2, entries 9–12). When DBU was used as the base, only a small amount of decanal **20** was obtained (Table 2, entry 9). As previously noted, excessively basic conditions result in premature catalyst deactivation. When the base was changed to NMI we could not obtain any reactivity (Table 2, entry 10). It seems that a strong base is needed to initiate the reduction to copper(I) species. When combining the beneficial effect of DBU as a strong base and the selectivity of NMI as a weak base, we obtained rapid conversion to 35%, after which the reaction rate diminished due to catalyst precipitation out of the reaction medium (Table 2, entry 11). After 20 h only 49% conversion was obtained. In order to prove our hypothesis on the strong base effect in initiation, we chose to use copper(I) bromide<sup>[34]</sup> in an experiment with only NMI as base (Table 2, entry 12). Rapid conversion to 51% was obtained in 30 min, after which major catalytic activity loss was observed due to the catalyst solidifying. After 20 h we obtained 87% conversion. Although higher conversion could be obtained using copper(I) bro-



Table 2. CuBr<sub>2</sub>-catalysed oxidation of alcohols to carbonyl compounds.<sup>[a]</sup>

$\text{R-OH} \xrightarrow[\text{MeCN, RT, O}_2 \text{ (balloon)}]{\text{3 mol\% CuBr}_2, \text{3 mol\% BiPy, 3 mol\% TEMPO, 6 mol\% base}} \text{R=O}$						
Substrate	Product	Base	<i>t</i> [h]	Conv. [%] <sup>[b]</sup>	Yield [%] <sup>[c]</sup>	
1 		DBU	0.7	100	78	
2 		NMI	2	99	84	
3 		DBU	2	73 <sup>[d]</sup>	–	
4 		DMAPI	2	99	–	
5 		NMI	1	99	94	
6 		NMI	2	99	93	
7 <sup>[e]</sup> 		NMI	0.5	99	86	
8 		NMI	1.5	99	94	
9 		DBU	0.5	17 <sup>[d]</sup>	–	
10 		NMI	3	NR <sup>[f]</sup>	–	
11 		NMI/DBU <sup>[g]</sup>	20	49	–	
12 		NMI <sup>[h]</sup>	20	87	–	

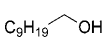
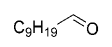
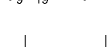
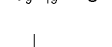
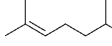
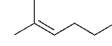
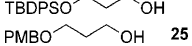
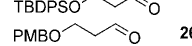
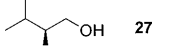
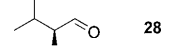
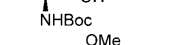
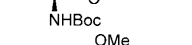
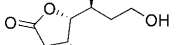
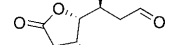
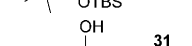
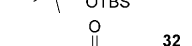
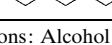
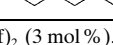
[a] Conditions: Alcohol (10 mmol), CuBr<sub>2</sub> (3 mol %), bipy (3 mol %), TEMPO (3 mol %), base (6 mol %), MeCN (10 mL), O<sub>2</sub> (balloon), room temperature. [b] Determined with GC. [c] Isolated yield of analytically pure material. [d] No significant activity was observed after specified time. [e] Performed with 5 mmol of alcohol. [f] No reaction. [g] Both bases 3 mol %. [h] CuBr (3 mol %), bipy (3 mol %), TEMPO (3 mol %), NMI (3 mol %) were used.

vide, the poor catalyst solubility after some reaction cycles could not be resolved.

We turned our attention to the copper counter ions. We envisioned that ammonium salts (NR<sub>3</sub>·HX), which are formed in the initiation, could influence copper hydroxide intermediates by trapping them and forming the corresponding copper salts (Scheme 5). By changing the copper source to Cu(OTf)<sub>2</sub> we were able to oxidise 1-decanol **19** to almost full conversion (98%) without copper precipitating out of the solution (Table 3, entry 1). We postulated that the water generated in the reaction might have two detrimental effects: water competes with the substrate alcohol in coordination to the catalyst, and it can also form hydrates from the product aldehyde, which would eventually lead to over-oxidation once the alcohol concentration dropped. In the presence of molecular sieves 1-decanol (**19**) was oxidised with complete conversion in three hours with excellent isolated

yield (Table 3, entry 2). A small-scale (0.2 mmol) experiment using 5 mol % of catalyst reduced the reaction time to only one hour (Table 3, entry 3). Citronellol (**21**) was also rapidly converted to citronellal (**22**; Table 3, entry 4). Partially protected 1,3-diols can be oxidised to aldehydes without elimination, but complete conversion could not be obtained (Table 3, entries 5 and 6). Protected valinol **27** was also converted to aldehyde **28** in good conversion (Table 3, entry 7). Unfortunately, enantiopurity of the fragile α-stereocenter dropped from 97 to 40% *ee*. The complex substrate **29**, with exceptionally easily eliminating methoxy functionality, can be converted to the corresponding aldehyde **30** without elimination (Table 3, entry 8).

Table 3. Cu(OTf)<sub>2</sub>-catalysed oxidation of alcohols into carbonyl compounds.<sup>[a]</sup>

$\text{R-OH} \xrightarrow[\text{MeCN, RT, O}_2 \text{ (balloon), 3 \AA MS}]{\text{3 mol\% Cu(OTf)}_2, \text{3 mol\% BiPy, 3 mol\% TEMPO, 3 mol\% NMI, 3 mol\% DBU}} \text{R=O}$						
Substrate	Product	<i>t</i> [h]	Conv. [%] <sup>[b]</sup>	Yield [%] <sup>[c]</sup>		
1 		5	98 <sup>[d]</sup>	–		
2 		3	100	95		
3 <sup>[e]</sup> 		1	100	–		
4 		2	100	91		
5 		4	84 <sup>[f]</sup>	76		
6 		3	87 <sup>[f]</sup>	55		
7 		4	95	82		
8 <sup>[g]</sup> 		3	90	65		
9 <sup>[h]</sup> 		48	59	–		

[a] Conditions: Alcohol (10 mmol), Cu(OTf)<sub>2</sub> (3 mol %), bipy (3 mol %), TEMPO (3 mol %), NMI (3 mol %), DBU (3 mol %), MeCN (10 mL), 3 Å molecular sieves, O<sub>2</sub> (balloon), room temperature. [b] Determined with GC. [c] Isolated yield of analytically pure material. [d] Without 3 Å molecular sieves. [e] Performed with 5 mol % of all catalyst components and 0.2 mmol of alcohol in 0.5 mL of MeCN. [f] No significant activity was observed after specified time. [g] As entry 3 but with 0.23 mmol of alcohol, conversion estimated from crude <sup>1</sup>H NMR spectroscopy. [h] Reaction carried at 40 °C.

Even secondary alcohols oxidise to ketones, but an elevated temperature of 40 °C and long reaction time (48 h) was needed (Table 3, entry 9).

## Conclusions

In conclusion, the effect of catalyst components in aerobic copper–TEMPO oxidation of alcohols to carbonyl compounds was studied. The amount of base is critical for the outcome of the oxidation. Stoichiometric amounts of copper and bipy should be used to ensure good activity. We found a 1.15-order kinetic correlation for TEMPO, and a 2.25-order correlation for copper. We also found that these oxidations follow a second-order dependency on the substrate alcohol at low concentrations, and a first-order dependency on oxygen at high alcohol concentrations. The copper(II) bromide system was found to be a fast and mild method for allylic alcohol oxidations. A catalytic system based on copper(II) trifluoromethanesulfonate was suitable for more challenging alcohol substrates. This methodology is more active than previously described ones, and further studies are warranted to elucidate its full potential.

## Experimental Section

All commercial reagents were used without further purification. Acetonitrile (Rathburn HPLC grade, water content unknown) was used without further purification. Other solvents were used as obtained from supplier, unless otherwise noted. Merck 3 Å molecular sieves were flame-dried under high vacuum and kept in an oven (120 °C). Analytical TLC was performed using Merck silica gel F<sub>254</sub> (10–12 µm) plates, and analysed by UV light or by staining with PMA solution. For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (40–63 µm) and p.a. grade solvents unless otherwise noted. IR spectra were recorded on a Perkin–Elmer Spectrum One spectrometer. Optical rotations were obtained with a Perkin–Elmer 343 polarimeter. The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> on a Bruker Avance 400 (<sup>1</sup>H 399.98 MHz; <sup>13</sup>C 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to residual CHCl<sub>3</sub> (δ = 7.26 ppm) for <sup>1</sup>H NMR. For the <sup>13</sup>C NMR spectra, the solvent peak CDCl<sub>3</sub> (δ = 77.0 ppm) was used as the internal standard. Spectral data of the product aldehydes were compared to commercially available compounds or to the literature data. HRMS spectra were recorded on Waters LCT Premier spectrometer. Conversions were analysed with a Shimadzu GC-2010 gas chromatograph equipped with FID detector. The enantiomeric excess (*ee*) of aldehyde **28** (RT<sub>major</sub> = 26.18 min, RT<sub>minor</sub> = 26.30 min) was determined by GC using a Hewlett Packard HP 5890 instrument, Supelco β-Dex™ 120 column (30 m × 0.25 mm, 0.25 µm film), using the gradient method (70 °C, 4 min, 4 °C min<sup>-1</sup>, to 220 °C), helium as carrier gas (30.6 cm s<sup>-1</sup>), with a Hewlett Packard 5971 MS detector (270 °C).

**Typical oxidation experiment for catalyst component study (Figures 1–13):** A standard solution of *trans*-2-hexen-1-ol **5** in acetonitrile (1.0 mmol, 100 mol %, 0.5 M, 2 mL) and internal standard *o*-xylene (1.0 mmol, 100 mol %) in acetonitrile was added into a 25 mL round-bottomed flask equipped with magnetic stirrer bar. A solution of copper(II) bromide in acetonitrile (0.02 mmol, 2 mol %; 20 mM, 1 mL) was added and the ensuing mixture turned green. On addition of a solution of bipy in acetonitrile (0.02 mmol, 2 mol %, 20 mM, 1 mL) the colour of the solution changed to brown and then back to green. After 6 min, a solution of TEMPO in acetonitrile (0.02 mmol, 2 mol %, 20 mM, 1 mL) was added without any significant colour change. Finally, a solution of DBU in acetonitrile (0.04 mmol, 4 mol %, 1 M, 40 µL) was added, transforming the colour to brown and gradually back to green. The reaction was stirred (500 rpm) under an oxygen atmosphere (balloon) at room temperature. Samples (0.1 mL) were regularly taken and diluted with dichloromethane (1 mL) for GC analysis.

**Typical oxidation experiment for allylic substrates with CuBr<sub>2</sub> (Table 2):** Geraniol **11** (1.54 g, 10.0 mmol, 100 mol %) was dissolved in acetonitrile (10 mL). Copper(II) bromide (0.067 g, 0.3 mmol, 3 mol %) was added, followed by bipy (0.047 g, 0.3 mmol, 3 mol %), transforming the colour to brown and back to green. TEMPO (0.047 g, 0.3 mmol, 3 mol %) was added to the reaction mixture, followed by *N*-methyl imidazole (0.049 g, 0.048 mL, 0.6 mmol, 6 mol %), giving a brown solution. Slight exothermicity was observed after the reaction mixture was covered with oxygen balloon. The reaction mixture was stirred at room temperature for one hour (GC showed >99% conversion). The appearance of blue solids and a colour change of the solution to green were observed. The reaction mixture was partitioned between hexane (30 mL) and distilled water (30 mL). The aqueous phase was extracted with hexane (2 × 20 mL). The combined organic extracts were washed with aqueous 0.5 M H<sub>3</sub>PO<sub>4</sub> solution (30 mL) and brine (30 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to afford citral **12** as an oil (1.43 g, 94 %). No further purification was needed.

**2-Cyclohexylideneacetaldehyde (16):** Synthesised according to typical procedure with CuBr<sub>2</sub> from alcohol **15**.<sup>[35]</sup> *R*<sub>f</sub> = 0.28 (20 % EtOAc/hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 10.01 (d, *J* = 8.2 Hz, 1H), 5.82 (d, *J* = 8.2 Hz, 1H), 2.70 (dd, *J* = 5.4 Hz, 6.2 Hz, 2H), 2.29 (dd, *J* = 5.3 Hz, 6.0 Hz, 2H), 1.60–1.76 ppm (m, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 190.3, 167.8, 125.0, 37.8, 29.3, 28.1, 27.9, 25.9 ppm. These data match those reported in the literature.<sup>[36]</sup>

**Typical oxidation experiment for non-activated substrates with Cu(OTf)<sub>2</sub> (Table 3):** 1-Decanol (**19**; 1.58 g, 10.0 mmol, 100 mol %) was dissolved in acetonitrile (10 mL). Copper(II) trifluoromethanesulfonate (0.108 g, 0.3 mmol, 3 mol %) was added, followed by bipy (0.047 g, 0.3 mmol, 3 mol %) to give a blue solution. TEMPO (0.047 g, 0.3 mmol, 3 mol %) was added, transforming the colour to green. *N*-Methyl imidazole (0.025 g, 0.024 mL, 0.3 mmol, 3 mol %) and DBU (0.046 g, 0.045 mL, 0.3 mmol, 3 mol %) were added, giving a brown solution. The reaction flask was covered with an oxygen balloon. After 15 min, 3 Å molecular sieves (1.5 g) were added. The reaction mixture was stirred at room temperature for 3 h. The colour was transformed first to green and then gradually to blue. The reaction mixture was filtered through celite, and partitioned between hexane (30 mL) and distilled water (30 mL). The aqueous phase was extracted with hexane (2 × 20 mL). The combined organic extracts were washed with aqueous 0.5 M H<sub>3</sub>PO<sub>4</sub> solution (30 mL) and brine (30 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to afford decanal **20** as an oil (1.49 g, 95 %). No further purification was needed.

**3-(tert-Butyldiphenylsilyloxy)propanal (24):** Synthesised according to typical procedure with Cu(OTf)<sub>2</sub> from alcohol **23**.<sup>[37]</sup> and purified with silica gel chromatography. *R*<sub>f</sub> = 0.45 (20 % EtOAc/hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.82 (t, *J* = 2.1 Hz, 1H), 7.63–7.69 (m, 4H), 7.35–7.47 (m, 6H), 4.03 (t, *J* = 5.9 Hz, 2H), 2.61 (dt, *J* = 2.1 Hz, 6.0 Hz, 2H), 1.05 ppm (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 201.8, 135.5, 133.2, 129.7, 127.7, 58.2, 46.3, 26.7, 19.1 ppm. These data match those reported in the literature.<sup>[38]</sup>

**3-(4-Methoxybenzyloxy)propanal (26):** Synthesised according to typical procedure with Cu(OTf)<sub>2</sub> from alcohol **25**.<sup>[39]</sup> and purified with silica gel chromatography. *R*<sub>f</sub> = 0.40 (50 % EtOAc/hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.78 (t, *J* = 1.8 Hz, 1H), 7.22–7.28 (m, 2H), 6.85–6.91 (m, 2H), 4.46 (s, 2H), 3.80 (s, 3H), 3.78 (t, *J* = 6.0 Hz, 2H), 2.67 ppm (dt, *J* = 1.8 Hz, 6.0 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 201.1, 159.2, 129.9, 129.3, 113.8, 72.8, 63.4, 55.2, 43.8 ppm. These data match those reported in the literature.<sup>[40]</sup>

***N*-Boc-L-valinal (28):** Synthesised according to typical procedure with Cu(OTf)<sub>2</sub> from *N*-Boc-L-valinol **27**. *R*<sub>f</sub> = 0.55 (50 % EtOAc/hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.64 (s, 1H), 5.09 (br s, 1H), 4.17–4.32 (m, 1H), 2.15–2.38 (m, 1H), 1.45 (s, 9H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.94 ppm (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 200.1, 155.6, 79.7, 64.4, 28.8, 28.0, 18.8, 17.3 ppm. These data match those reported in the literature.<sup>[41]</sup>

**Typical oxidation small scale experiment with Cu(OTf)<sub>2</sub> (Table 3, entries 3 and 8)**

(*S*)-3-[(2*R*,3*R*)-3-(tert-Butyldimethylsilyloxy)-4,4-dimethyl-5-oxotetrahydrofuran-2-yl]-3-methoxypropanal (**30**): A round-bottomed flask was charged with alcohol **29**<sup>[42]</sup> (0.076 g, 0.23 mmol, 100 mol %) in acetonitrile (0.29 mL). A standard solution (0.05 M, 0.23 mL) containing copper(II) trifluoromethanesulfonate (11.5 μmol, 5 mol %), bipy (11.5 μmol, 5 mol %), *N*-methyl imidazole (11.5 μmol, 5 mol %), and DBU (11.5 μmol, 5 mol %) in acetonitrile was added. A standard solution of TEMPO in acetonitrile (11.5 μmol, 5 mol %, 0.4 M, 0.058 mL) was added to the ensuing green solution, followed by 3 Å molecular sieves, making the colour slightly darker. The reaction mixture was stirred for 3 h at room temperature under an oxygen atmosphere (balloon). The reaction mixture was diluted with ether (3 mL) and filtered through celite. Distilled water (3 mL) water was added and the phases were separated. The aqueous phase was extracted with ether (2 × 2 mL). The combined organic extracts were washed with aqueous 0.5 M H<sub>3</sub>PO<sub>4</sub> solution (4 mL) and brine (4 mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to afford 0.066 g of oil. The crude product was purified by silica gel chromatography using 20–40% ethyl acetate in hexanes to afford aldehyde **30** as a clear oil (0.050 g, 65 %). *R*<sub>f</sub> = 0.47 (50% EtOAc/hexanes); [α]<sub>D</sub><sup>20</sup> = –20.7° (*c* = 1.0 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 9.84 (t, *J* = 1.1 Hz, 1H), 4.41 (dd, *J* = 3.9 Hz, 6.4 Hz, 1H), 4.22 (d, *J* = 6.5 Hz, 1H), 4.04 (dt, *J* = 4.0 Hz, 6.1 Hz, 1H), 3.40 (s, 3H), 2.82 (ddd, *J* = 1.1 Hz, 6.1 Hz, 17.7 Hz, 1H), 2.76 (ddd, *J* = 1.4 Hz, 6.0 Hz, 17.7 Hz, 1H) 1.26 (s, 3H), 1.20 (s, 3H), 0.94 (s, 9H), 0.12 (s, 3H), 0.11 ppm (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 200.2, 180.6, 81.5, 76.9, 72.6, 58.0, 44.8, 43.6, 25.9, 25.8, 19.2, 18.2, –4.0, –4.0 ppm; IR (thin film):  $\tilde{\nu}$  = 2955, 2932, 2859, 1777, 1724, 1472, 1390, 1257, 1132, 1098, 836, 778 cm<sup>–1</sup>; HRMS (ESI) *m/z* calcd for [M+Na] C<sub>16</sub>H<sub>30</sub>O<sub>5</sub>SiNa: 353.1760; found: 353.1756; Δ = 1.1 ppm.

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