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Copper Catalyzed Alcohol Oxidation and Cleavage of β -O-4 Lignin Model Systems: From Development to Mechanistic Examination

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Abstract: Lignin, an abundant natural polymer with high aromaticity, is a potential source of renewable chemicals and fuels among other biomaterials. Herein, a study on copper catalyzed alcohol oxidation and cleavage of lignin β -O-4 model substrates is reported. The potential of CuX/BiPy/TEMPO/(additive) systems (X = halide or triflate, BiPy = 2,2'-bipyridine; TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl) was explored and the optimized protocol was studied with several type of model compounds. Mechanistic studies elucidated two types of cascade reactions: Both involve a cleavage of C α -C β bond, which is most likely activated by 1) primary alcohol oxidation in β -O-4 glycerolaryl ethers resulting in retro-aldol cleavage and 2) C β -H oxidation after secondary alcohol oxidation in β -O-4 ethanolaryl ethers leading to oxidative radical cleavage. The first process affords aromatic aldehydes while the latter delivers aryl acids.

deconstruction of lignin polymers to simple aromatics. Successful depolymerization relies on a judicious bond activation within the polymer. Since oxidation is the main pathway for lignin degradation in nature, it appears an attractive strategy to activate the natural polymer for chemical, and preferably catalytic, depolymerization.

Various studies on oxidative cleavage of lignin model compounds and/or extracted lignins have been carried out using stoichiometric oxidants,^[5] peroxidases,^[5b,6] and transition metal catalysis.^[7] DFT calculations suggest that oxidation of alcohols to carbonyls in β -O-4 lignin-mimicking systems alters the C β -O aryl ether and C α -C β bond dissociation energies,^[7f,8] allowing the cleavage of these bonds to be induced directly or by further activation.

Introduction

Biomass is the only renewable carbon resource in nature. The utilization of inedible biomass for the production of value-added chemicals, fuels and materials has gained much focus due to decreasing petroleum reserves, increasing global energy demand and concerns on environmental issues.^[1] The main constituent of biomass is lignocellulose, which is produced around 170 billion metric tons a year.^[1a] Lignocellulosics mainly consist of cellulose (30–50%), hemicellulose (20–35%) and lignin (15–30%).^[2] Lignin (Figure 1) is the second most abundant polymer after cellulose and the major aromatic resource of the bio-based economy covering almost 30% of the renewable carbon on our planet.^[3] While cellulose and hemicellulose have been successfully used in the production of various chemicals and fuels, processes of similar efficiency using lignin as a feedstock hardly exist.^[4] For an economically viable biorefinery concept effective utilization of the lignocellulose as a whole is an essential target.

Although the detailed chemical structure of lignin is species dependent, the most common linkage found in all native lignins is the β -O-4 glycerolaryl ether bond (Figure 1).^[1] The abundance of this linkage (45–60%)^[1c] makes it an ideal target for the

Figure 1. Representative structure of a hardwood lignin fragment. The β -O-4 linkage is outlined: C β -O ether bonds are bolded in blue and the adjacent C α -C β bonds in red.

Benzylic secondary alcohol oxidation of β -O-4 model compounds has been the key to produce simple monoaromatic compounds such as aryl acids,^[7f,9] aryl ketones,^[10] and aryl diketones.^[11] Targeted primary alcohol oxidation, in turn, provides a route to aldehydes.^[12] Most of the developed depolymerization strategies involve a two-step process which requires purification of the intermediates, reaction medium changes and/or subsequent reagent additions after the first step. Consequently, reported approaches for a cascade process are less common. In fact, as the promising protocol of a two-step lignin depolymerization *via* secondary alcohol oxidation delivers phenolic monoaromatics,^[11] it would still be worth designing a catalytic system for primary alcohol oxidation affording unstable aldehydes that could serve as key intermediates in a tandem process for lignin conversion.

Inspired by our previous work^[13] and others' achievements^[14] on aerobic copper-TEMPO catalyzed alcohol oxidations we felt motivated to study the protocol further for (primary) alcohol oxidation of β -O-4 lignin model compounds.^[15] Herein we present our results on the cascade oxidation-cleavage reaction to produce aromatic aldehydes or the corresponding acids.

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Results and Discussion

Our initial investigations began with a guaiacyl type β -O-4 model compound **1a**. First, an optimal reaction medium was screened using CuCl/BiPy/TEMPO as the catalyst system at 60 °C under O₂ atmosphere (Table 1). Acetonitrile gave the highest conversion (30%) with a moderate selectivity (ca. 50%) towards the major product aldehyde (entry 5). Highest selectivity (85%) was observed with a mixture of MeCN and *t*-BuOH, but unfortunately the conversion was low (14%) (entry 7). Good selectivity (ca. 70%) was obtained using aqueous MeCN, but also resulted in lower consumption of the starting material (23%), likely due to formation of inactive Cu(OH)₂ species turning the reaction mixture to turquoise (entry 6).

Table 1. Solvent screening for the copper catalyzed oxidation of **1a**.^[a]

Entry	Solvent	Conversion (%)	Yield of 2a (%)
1	EtOAc	14	3
2	MeOH	n.r.	3
3	Toluene	18	8
4	2-MeTHF	30	12
5	MeCN	30	14
6	MeCN/H ₂ O (1:1)	23	16
7	MeCN/ <i>t</i> -BuOH (1:1)	14	12

[a] Reactions were carried out on a 0.1 mmol scale. Conversions and yields (a percentage of the theoretical yield based on the initial amount of starting material) were determined by ¹H NMR using dimethylsulfone or 1,3,5-trimethoxybenzene as the internal standard. n.r. = not resolved.

We have earlier studied the catalytic activity dependence on catalyst components in aerobic copper/TEMPO oxidations of different alcohols.^[13] The copper counter anion plays a significant role in terms of catalyst activity and substrate specificity: Activated alcohols (benzylic and allylic) are successfully oxidized to the corresponding aldehydes using CuBr₂/BiPy/TEMPO/base systems whereas unactivated alcohols require copper species containing a loose triflate (OTf = trifluoromethanesulfonate) anion. Another important observation was that a relatively strong amine base (e.g. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene) is required to initiate the oxidation of unactivated alkyl primary alcohols when copper(II) salts were used. Later, Stahl *et al.* showed that also Cu/BiPy/TEMPO/NMI catalysts bearing noncoordinating anions generally oxidize primary alcohols rapidly,^[14] and further insights to the mechanisms of such processes have been thereafter reported.^[16]

Although various copper precatalysts bearing loose counter anions are commercially available, their typically high price

encouraged us to find a more affordable catalyst system, and we decided to test forming such species *in situ* using sodium salts of bulky and strong Brønsted acids. In our solvent trials we found that no significant secondary alcohol oxidation took place in acetonitrile (Table 1, entry 5: ca. 1% yield of ketone based on ¹H NMR analysis). We therefore decided to focus on the primary alcohol oxidation. We speculated that the primary alcohol oxidation product of **1a** is unstable under the reaction conditions and therefore chose 1-decanol as the model substrate.

All experiments led selectively to the aldehyde product (Figure 2).^[17] Rapid conversions were observed already at ambient temperature under air. *N*-methyl imidazole (NMI) as a weak base and co-ligand for copper was added to increase the oxidation rate.^[13] Copper(I)chloride with bulky sodium hexafluorophosphate or sodium tetrafluoroborate exhibited full conversions (>99%) whereas in the absence of additives the conversion remained only 51% (Figure 2a). Sodium triflate was less effective with a lower rate and conversion of 87% after 20 hours. Semmelhack *et al.*^[14a] had noted an inhibitory effect by added NaCl in their CuCl/TEMPO-catalyzed alcohol oxidations. However, this was not observed with our system. Without additives, higher reactivity was obtained upon changing the chloride to larger counter ions, bromide and iodide, in this order, and CuI was able to catalyze the reaction to complete conversion within 24 hours (Figure 2b). However, when combining the three copper precatalysts with NaBF₄, the highest activity was observed with CuCl/NaBF₄, which produced 98% conversion already in 4 hours. An explanation could be that NaCl as an anion exchange product has a very low solubility in acetonitrile and thus this can facilitate the ion exchange process resulting in greater catalyst activity.

Figure 2. Conditions: 3 mmol of 1-decanol in MeCN (3 mL) in open flask with 3 mol% of Cu source, TEMPO, BiPy, 4 mol% of possible salt additive and 6 mol% of NMI. Conversions were determined with GC.

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Although 1-decanol oxidized rapidly already at room temperature, elevated temperatures for the oxidation of the sterically hindered primary alcohol on **1a** were presumably needed to ensure high conversions. We thus increased the temperature to 80°C and explored the influence of different copper counter ions and initial oxidation states in the reaction first using initially anhydrous conditions (Table 2, entries 1–6). CuI and CuBr gave slightly weaker activity while CuBr₂ exhibited hardly any, and addition of NMI had no positive effect. Interestingly, Cu(OTf)₂ was very active with 73% conversion; however, the product distribution could not be resolved. Surprisingly, NMI was not beneficial with CuCl either (entry 7). Control reactions compared to entry 1 either without TEMPO, bipyridine or CuCl addressed (almost) complete loss of catalyst performance

Table 2. Screening copper catalyst systems for the conversion of **1a** providing **2a** as the major product.^[a]

Entry	Cu source	Base additive	Salt additive	Conversion (%)	Yield of 2a (%)
1 ^[b]	CuCl	-	-	42	23
2 ^[b]	CuI	-	-	35	19
3 ^[b]	CuBr	-	-	33	20
4 ^[b]	CuBr ₂	-	-	8	3
5 ^[b]	CuBr ₂	NMI	-	7	3
6 ^[b]	Cu(OTf) ₂	NMI	-	73	4
7 ^[b]	CuCl	NMI	-	38	21
8 ^[b]	CuCl	NMI	NaBF ₄	43	23
9 ^[b]	CuCl	-	NaBF ₄	46	30
10	CuCl	-	NaBF ₄	41	26
11	CuCl	NMI	NaBF₄	50	30
12	CuCl	NMI	NaPF ₆	34	28
13	CuCl	NMI	NaBPh ₄	47	13
14	Cu(OTf) ₂	NMI & DBU	-	71	25
15 ^[c]	Cu(OTf) ₂	<i>t</i> -BuOK	-	96	2
16 ^[d]	CuCl	NMI	NaBF ₄	18	13
17 ^[e]	CuCl	NMI	NaBF ₄	47	25
18 ^[f]	CuCl	NMI & DBU	NaBF ₄	48	19
19 ^[g]	CuCl	NMI	NaBF ₄	45	19
20 ^[h]	CuCl	NMI	NaBF ₄	55	24
21 ^[i]	CuCl	NMI	NaBF ₄	47	23

[a] Reactions were carried out on a 0.1 mmol scale (0.1 M of **1a**). Conversions and yields (a percentage of the theoretical yield based on the initial amount of starting material) were determined by ¹H NMR using 1,3,5-trimethoxybenzene (or dimethylsulfone) as the internal standard [b] Dry acetonitrile as a solvent. [c] Solvent = MeCN:H₂O (2:1). [d] Solvent = MeCN:H₂O (4:1) [e] 20 mol% NMI [f] 5 mol% NMI and DBU. [g] Under air (balloon). [h] Ligand = 4,4'-Dimethoxy-2,2'-bipyridine. [i] Ligand = 1,10-phenanthroline.

(Supporting Information, Section 6.2), thus highlighting their importance on the oxidation of **1a**.

We next examined the effect of the salt additives. Gratifyingly, sodium tetrafluoroborate and sodium hexafluorophosphate indeed gave better results whereas even more bulky sodium tetraphenylborate led to a weaker performance in terms of aldehyde selectivity (Table 2, entries 11–13). Copper(II)triflate with DBU and NMI showed higher activity but slightly lower selectivity towards the aldehyde product (entry 14). Addition of DBU as a stronger base with a Cu^{II} source gave much higher yield for aldehyde **2a** (entries 14 and 6). Switching to a strong alkoxy base, the selectivity was completely lost, and the product distribution could not be determined (entry 15).

The negative effect observed by the addition of NMI in initially anhydrous conditions was surprising. One explanation could be that due to coordination of NMI catalytic H₂O (instead of the hindered primary alcohol **1a**) forms the putative relevant [(BiPy)Cu^{II}(NMI)(OH)]⁺BF₄⁻ species^[16] prior to the alcohol oxidation step and thus may accelerate the oxidation reaction. Indeed, addition of NMI was beneficial when the reaction was not carried out in initially anhydrous reaction medium (Table 2, entries 8–11). However, oxidation in 4:1 MeCN:H₂O (entry 16) decreased the reactivity notably suggesting that only a small amount of water could increase the oxidation rate, but (too) high amounts would result in premature deactivation of the catalytic species forming Cu(OH)₂.

The amount of NMI had little effect on either the conversion of **1a** or yield of **2a** (entry 11, 10 mol% NMI (one equivalent with copper) vs entry 17, 20 mol% NMI). Combining DBU and NMI with CuCl led to significant decrease in selectivity towards **2a** (entry 18). Reaction under air gave lower yield for **2a** suggesting rate dependence on oxygen concentration (Table 2, entries 19 and 11). Finally, switching the ligand to more electron rich bipyridine analogue or to larger phenanthroline also resulted in slightly lower reactivity towards **2a** (entries 20, 21 vs 11).

Using the optimal conditions in non-dried medium (Table 2, entry 11; for a corresponding time-course reaction see Figure S1 in the Supporting Information, Section 6.1) we then explored the reactivity with other β-O-4 lignin model compounds (Table 3). When using 10 mol% of catalyst, the reactions could be run at 0.1 M concentration to reach completion in 20 hours, whereas with 20 mol% catalyst, a lower substrate concentration (0.05 M) and higher reaction time (40 h) gave slightly better catalyst performance (Supporting Information, Table S1, Section 6.1).

Interestingly, the alkoxy substituent pattern on the left aromatic ring did not significantly affect the generation of the aldehyde (**2a–c**). No ketones (less than 2% by NMR) as secondary alcohol oxidation products (of **1a–c**) were observed. We could also not detect aromatic acids by NMR or HPLC as potential overoxidation products. Formylated products **3a–c** are plausibly formed through catalyzed formyl transfer from **4**, since a control reaction of **1a** with added **4** (1 equiv) increased the formation of **3a** from 7% to 34% (Supporting Information, Section 6.2). The poor mass balance of the phenoxy moiety is due to further conversion of 2-methoxyphenol to form insoluble products which were mostly absorbed on silica together with copper salts before NMR analysis.

Table 3. Copper catalyzed one-pot oxidation-cleavage of structurally different β -O-4 diol substrates.^[a]

R-C6H4-CH(OH)-CH(OH)-CH2-O-C6H4-OMe
 $\xrightarrow{\text{Cu cat. (10-20 mol\%)}}$
R-C6H4-CHO + minor products

1a-c
2a-c

Entry	Conversion	Products and yields			
 1a		 2a	 3a	 4	
1 ^[b]	52%	30%	7%	6%	
2 ^[c]	80%	52%	12%	4%	
 1b		 2b	 3b	 4	
3 ^[b]	53%	28%	7%	3%	
4 ^[c]	84%	51%	8%	7%	
 1c		 2c	 3c	 4	
5 ^[b]	52%	27%	7%	2%	
6 ^[c]	84%	51%	8%	5%	

[a] Reactions were performed on a 0.2 mmol scale (Cu cat. = CuCl/NaBF₄/BiPy/TEMPO/NMI) in acetonitrile at 80 °C under O₂ (balloon). Conversions and yields (a percentage of the theoretical yield based on the initial amount of starting material) were determined by ¹H NMR using 1,3,5-trimethoxybenzene as the internal standard. [b] 10 mol% of catalyst, 0.1 M of 1, 20 h. [c] 20 mol% of catalyst, 0.05 M of 1, 40 h.

Copper/TEMPO based oxidations have previously been suggested to follow a concerted retro-aldol route^[15a] or a single-electron-transfer (SET) mechanism^[7c] (Scheme 1). However,

Scheme 1. Previously suggested mechanisms in association with other copper catalyzed oxidations of β -O-4 lignin model compounds.^[7c,15a,18] (We added mechanism arrows to illustrate the pathways.)

due to limited mechanistic investigations available and differences between the reaction systems, we decided to explore the copper catalyzed (oxidative) cleavage process in more detail.

To begin our mechanistic studies we first explored the role of the β -methyl alcohol substituent by removing it. Such substrates have been commonly used for modeling the β -O-4 lignin linkage from various lignin sources and have been found to serve as key model compounds for several types of catalytic

strategies.^[7f,10a,19] When substrate **1d** was subjected to the copper oxidation, instead of *p*-anisaldehyde *p*-anisic acid (**2d**) was formed (Table 4).^[20] Aryl formate **4** was also formed in larger amounts. Optimal conditions were found to be 10 mol% of the copper catalyst at 80 °C (Table 4, entry 2).

Table 4. Optimizing conditions for the one-pot oxidation-cleavage of **1d**.^[a]

Entry	Conditions	Conv. (%)	5a (%)	2d (%) ^[b]	4 (%) ^[b]
1	5 mol%, 80 °C	81	2	40	45
2	10 mol%, 80 °C	>99	6	62	55
3	10 mol%, 60 °C	>99	45	25	33

[a] All reactions on 0.2 mmol scale in acetonitrile (0.1 M) under O₂ (balloon) for 20 h (Cu cat. = CuCl/NaBF₄/BiPy/TEMPO/NMI). Conversions and yields were determined by ¹H NMR as described in Table 3. [b] Rough quantity due to bad peak resolution.

On scale-up to isolate carboxylic acid **2d** aryl formate **4** was hydrolyzed to 2-methoxyphenol (Scheme 2). Additional methoxy-group at the *meta*-position to the benzylic alcohol resulted also in full conversion of **1e** and almost same yields were obtained for veratric acid (**2e**) and 2-methoxyphenol as in the reaction sequence of *p*-anisic analogue **1d**. The oxidative cleavage of the suspected intermediate ketone **5a** occurs without TEMPO and almost full conversion with high selectivity was obtained with 5 mol% of catalyst.

Scheme 2. Above: 5 mmol scale in acetonitrile (0.1 M) under O₂ (balloon) at 80 °C for 20 h (Cu cat. = CuCl/NaBF₄/BiPy/TEMPO/NMI). Below: 1 mmol scale, same conditions (5 mol% catalyst, no TEMPO) All oxidations were followed by basic work-up; formate **4** hydrolyzed to 2-methoxyphenol.

The mechanism of the oxidative process is assumed to include C _{β} -H bond oxidation by oxo-copper species followed by a homolytic cleavage of the activated C _{α} -C _{β} bond.^[21] The formation of a radical at C _{β} is supported also in our experiments

since we were able to isolate the β -TEMPO-substituted ketone derivatives **5b** and **6** (Scheme 3) in 6% yields after the oxidations shown in Scheme 2 (upper part).^[22] Based on these and recent literature findings^[7f,21] on similar processes we propose an overall reaction pathway from β -aryl ether ketones **I**. The path begins with a) formation of an enolate **II**, which is b) oxidized by Cu^{II} to the corresponding radical and further by oxygen or oxo-copper species to a peroxide intermediate **III** (Scheme 3). This species then undergoes c) a homolytic O–O scission followed by C α –C β bond cleavage providing **IV** and carbonyl radical **V** that d) oxidizes to carboxylic acid **VI**.

Scheme 3. Proposed reaction pathway from β -aryl ether ketones **I** to formate **IV** and carboxylic acid **VI**. **In frame:** Isolated TEMPO-trapped species **5b** and **6** from the oxidations of **1d** and **1e**.

We next tested whether a ketone derivative of **1a** bearing the methyl alcohol at C β would react under the reaction conditions. Compound **1f** gave only slight conversion to aryl acid **2f** with minor amounts of the dehydration product **7** (recognized by the enone ¹H signals^[23]) (Scheme 4). These results indicate that 1) ketone **1f** is not an intermediate towards aldehyde **2a** in the oxidation of **1a**, and suggest that 2) the expected oxidation of the C β –H bond is reduced likely due to the increased steric hindrance caused by the β -methyl alcohol substituent.

Scheme 4. Conditions: 0.2 mmol scale in acetonitrile (0.1 M) under O₂ (balloon) at 80 °C for 20 h (Cu cat. = CuCl/NaBF₄/BiPy/TEMPO/NMI). Conversions and yields were determined by ¹H NMR as described in Table 3 (yield of **2f** was confirmed by HPLC analysis).

We then investigated the role of the two alcohol groups. While both retro-aldol^[15a] and single-electron transfer^[7c] pathways have been previously suggested in association with other Cu/TEMPO based catalyst systems, one cannot exclude the possibility of a retro-Claisen rearrangement^[24] taking place with a 3-hydroxy-1-propanal adduct (1° OH-oxidation product). However, it should react through an intermediate with loss of aromaticity on the left aryl ring, and to overcome such energy barrier, essentially high temperatures are typically required. Nevertheless, keeping

all these three mechanistic possibilities in mind, we chose model compounds **1g–i** (Table 5) for the study.

First, we masked the secondary alcohol on **1a**. Substrate **1g** underwent almost full conversion delivering mainly aldehyde **8** (48%), which apparently reacted further to give enal **9** (4%) and the phenoxycetate derivative **10** (7%) (Table 5, entry 1). Compound **10** is possibly formed through a radical cleavage between the newly formed carbonyl carbon and C β in **8** followed by a rapid oxidation of the resulting C β radical. The process would thus follow the same principles as was depicted in Scheme 3. Interestingly, aryl aldehyde **2a** and methyl ester **11** were also formed. We consider that the former could result from 1,4-addition of H₂O to enal **9** followed by rapid retro-aldol reaction. Likewise, methyl ester **11** may form through a benzylic C α –H oxidation of **10** followed by a radical cleavage of the activated C α –C β bond (again a process similar to that in Scheme 3).

Next, we studied compound **1h**, where the primary alcohol is masked. Smoothly, oxidation of the secondary alcohol gave ketone **12** as the sole product (Table 5, entry 2) (only traces, less than 1%, of benzoic acid **2f** were detected). Compared to ketone **1f**, ketone **12** has a methoxy group in the place of the primary alcohol and could thus prevent C β –H bond oxidation. No aldehyde products were detected, showing that the unmasked, oxidizable primary alcohol group seems essential for the delivery of benzaldehydes such as **2a**. This observation is still in accordance with the retro-aldol (and retro-Claisen) route, but does not support the SET-mechanism.

Table 5. Additional β -O-4 lignin model substrates for mechanistic rationalization of the cleavage pathway to give aryl aldehyde as the main product.^[a]

Entry	Conversion	Products and yields			
1	99%	48%	4%
		7%	6%	5%	
2 ^[b]	98%	94%			
3 ^[c]	46%	28%	6%	2%	

[a] Conditions: 0.2 mmol scale in acetonitrile (0.1 M) under O₂ (balloon) at 80 °C for 20 h (Cu cat. = CuCl/NaBF₄/BiPy/TEMPO/NMI). Conversions and yields were determined by ¹H NMR as described in Table 3. [b] Traces (<1%) of benzoic acid **2f** were detected by HPLC. [c] Reaction in CD₃CN (due to the volatile nature of **13**).

Third, we investigated substrate **1i** bearing a saturated cyclohexyl ring in place of the original left aryl moiety (Table 5, entry 3). The outcome of the reaction was similar to the aromatic diol analogues **1a–c** (Table 3) providing cyclohexylcarbaldehyde **13** as the main product in 28% yield, which is very close to the ones observed for **2a–c**. Due to the high volatility of **13** the reaction was carried out in CD₃CN to ensure better quantification. The saturated compound should disfavor radical cation formation at the saturated ring that could induce the cleavage of the C α –C β bond in a SET oxidation process.^[5b,7c,25] Moreover, a retro-Claisen pathway is no more possible. Hence, it is quite safe to assume that **13** forms solely through a retro-aldol pathway. Since substrates **1a–c** and **1i** differ only at the left cyclic hydrocarbon moiety and afford similar product distribution (almost equal aldehyde quantities), the same depolymerization pathway seems logical.

We then turned our attention to the suspected retro-aldol cleavage of lignin-like β -O-4 diol systems such as **1a**. Traces of primary alcohol oxidation adduct **16** were observed when the oxidation of **1a** was conducted at room temperature, but not at higher temperatures (Supporting Information, Section 6.1). The retro-aldol step is considered faster than the alcohol oxidation. Since trapping the intermediate aldehyde was not seen feasible, we decided to prepare **16** from **1a** under mild conditions. A well-known TEMPO/bleach protocol^[26] was found to favor the primary alcohol oxidation at pH 8–9, 0°C where basically no retro-aldol (<1%) was observed. Subsequent bisulfite treatment was used to purify the sensitive aldehyde **16** by isolating it as the bisulfite adduct **15**.^[27] Pure model substrate **16** was liberated with excess of NaHCO₃ (Scheme 5). The bisulfite addition was found to be diastereoselective so we ended up with almost pure *erythro* isomer **16** (dr 20:1).

Scheme 5. Preparation of plausible intermediate **16**.

In order to identify the species responsible for the retro-aldol cleavage we conducted experiments with selected catalyst components adding one by one the species ending up to the standard catalyst system (Table 6). First, at room temperature neither 10 mol% of CuCl or CuCl/NaBF₄ gave significant reaction on the C α –C β bond (Table 6, entries 1 and 3). Both catalyst systems gave considerable reactivity at 80°C (entries 2 and 4). With bipyridine some reactivity was observed already at room temperature (entry 5), suggesting that bipyridine could enhance copper coordination to the carbonyl group making even weak bases (such as bipyridine itself) able to deprotonate the secondary alcohol. At 80°C, the ternary catalyst system CuCl/NaBF₄/BiPy delivered **2a** quantitatively together with 66% of **4** (entry 6). Further addition of NMI gave similar results as expected, however with slightly lower quantity of **4** (entry 7). Finally, under the standard conditions with each catalyst component under oxygen atmosphere **16** was again fully

converted to aldehyde giving 92% of **2a** and formate **4** in 33% yield (entry 8).

Control reactions with bipyridine or NMI alone gave no conversions even at 80 degrees (entries 10–11) indicating that copper likely activates the carbonyl group as a Lewis-acid ensuring reasonable push-pull effect for the retro-aldol reaction to occur more easily. At elevated temperatures additional bases are not necessary, since only copper salt was enough to drive the cleavage to almost completion. A blank reaction at 80°C in the absence of any catalyst component gave only trace amount of **2a** excluding (any significant) thermally induced self-retro-aldol. The decreasing amount of **4** when adding NMI (entry 7) and TEMPO+O₂ (entry 8) suggests that hydrolysis and/or further oxidation of the formate likely play a role.

Table 6. Screening of catalyst components for the retro-aldol cleavage of **16**.^[a]

Entry	CuCl	NaBF ₄	BiPy	NMI	TEMPO	2a (%)	4 (%)
1 ^[b]	x					4	2
2	x					87	61
3 ^[b]	x	x				3	2
4	x	x				82	65
5 ^[b]	x	x	x			33	22
6	x	x	x			99	66
7	x	x	x	x		97	53
8 ^[c]	x	x	x	x	x	92	33
9						3	1
10			x			2	-
11				x		1	-

[a] Yields were determined by ¹H NMR (as described in Table 3). Entries 2 and 8: 0.03 mmol of **16**; entries 1,3–7: 0.023 mmol of **16**; entries 9–11: 0.01 mmol scale. Reactions under air (sealed vial). [b] at rt. [c] under O₂ (balloon).

Finally, since the retro-aldol reaction of **16** should first lead to aryloxyacetaldehyde **17** (or enol equivalent), we confirmed its reactivity under the standard conditions (Scheme 6). Full conversion was observed and 2-methoxyphenyl formate (**4**) was obtained as the major product (60%), suggesting that in the absence of alcohols (and other fragmentation products) the deformylation of **4** is decreased. The fragmentation likely follows the same route as proposed earlier for ketone **1** analogues as this was supported by the formation of TEMPO-adduct **18**. We also identified **18** from the oxidation products of **1a–c** and **1i** as well as after retro-aldol reaction of **16** (Table 6, entry 8) in low yields. The expected formic acid byproduct presumably oxidizes to CO₂ under the catalyst system since a corresponding control reaction with HCO₂H carried in CD₃CN (to directly analyze the reaction by ¹H NMR) following otherwise the conditions shown in Scheme 6 resulted in complete conversion within 20 hours. A similar

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observation has been made under aerobic CuCl/TEMPO/2,6-lutidine system.^[22b]

Scheme 6. Conditions: 0.2 mmol scale in acetonitrile (0.1 M) under O₂ (balloon) at 80 °C for 20 h (Cu cat. = CuCl/NaBF₄/BiPy/TEMPO/NMI). Conversion and yields were determined by ¹H NMR as described in Table 3.

Based on the studies with all our model substrates we propose that lignin β-O-4 diol model compounds **1a–c** undergo primary alcohol oxidation followed by a rapid retro-aldol C_α–C_β cleavage under our standard reaction conditions (Scheme 7, top). The cascade reaction delivers aldehydes **2a–c** without overoxidation to the carboxylic acids. The key component for the retro-aldol step herein is copper(I)chloride likely acting as a Lewis-acid that activates the carbonyl. In the absence of β-methyl alcohol, substrates **1d,e** react through benzylic alcohol oxidation followed by plausible C_β–H oxidation, after which oxidative cleavage of the C_α–C_β bond leads to aromatic carboxylic acids **2d,e** and aryl formate **4** (Scheme 7, bottom). TEMPO as a co-oxidant with copper acts also as a radical trapping agent and showed that β-phenoxy carbonyl substrates such as **5a** or **17** plausibly undergo enolization followed by one electron oxidation with Cu^{II} giving a free radical at C_β susceptible to oxygen attack. The unstable intermediate then oxidatively degrades to carboxylic acid and 2-methoxyphenyl formate (**4**).

Scheme 7. Proposed pathways for the one-pot alcohol oxidation to cleavage of C_α–C_β bond providing aromatic aldehydes or acids as the major products.

Conclusions

To conclude, we have demonstrated a versatile and cost-effective copper catalyst system for aerobic Cu/TEMPO alcohol oxidations and activated C–C bond cleavage reactions. We found that NaBF₄ serves as a convenient salt additive for CuCl, and combining these with BiPy, TEMPO and NMI forms a catalyst system especially useful for aerobic primary alcohol oxidation. This operationally simple and catalytically highly active system consisting of inexpensive salt additive and copper source provides a viable alternative to the previously reported methods using ready-made Cu^I-complexes such as [Cu(MeCN)₄]BF₄.

When applied to lignin model compounds, mechanistic studies elucidated that the catalyst system most likely operates via selective primary alcohol oxidation of non-phenolic β-O-4 glycerolaryl ethers and catalyzes the subsequent retro-aldol reaction providing aromatic aldehydes as the major products. In the absence of β-methyl alcohol, the catalyst system also oxidatively cleaves β-O-4 ethanolaryl ethers via benzylic alcohol oxidation to afford aromatic acids. This protocol could be further tuned and applied to other alcohols or carbonyl containing substrates as well.

In particular, the study herein showed that selective primary alcohol oxidation of lignin β-O-4 diol systems offers a viable route for subsequent retro-aldol cleavage thus enabling a two-step cascade process to operate with suitable catalyst. Instead of added bases or acids, a Lewis-acid (here: CuCl) catalyst activation with a control over temperature can lead to effective retro-aldol reactions affording aromatic aldehydes and phenoxy derivatives with high selectivity. To develop a working catalyst system that provides controlled deconstruction of lignin to selectively afford monomeric aromatic compounds with high mass balance, and preferably, with high catalyst turnover remains a challenge to be studied.

Supporting Information Summary

Experimental procedures, additional optimization and control reactions, and characterization data of new compounds.

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Keywords: biomass conversion · catalysis · copper · lignin · oxidation

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Versatile catalyst system: Combination of CuCl/NaBF₄/BiPy/(NMI) offers an inexpensive and highly active copper catalyst system for aerobic copper–TEMPO alcohol oxidations and activated C–C bond cleavage reactions. Mechanistic studies suggest that a selective primary alcohol oxidation of β-O-4 lignin models is followed by Cu-catalyzed retro-aldol reaction delivering aryl aldehydes. Combined secondary alcohol and C_β-H oxidation leads to the corresponding acids.