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Copper Catalysts for Selective C–C Bond Cleavage of β-O-4 Lignin Model Compounds

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Abstract: The reactivity of homogeneous copper catalysts towards the selective C–C bond cleavage of both phenolic and non-phenolic arylglycerol β-aryl ether lignin model compounds has been explored. Several copper precursors, nitrogen ligands, and solvents were evaluated in order to optimize the catalyst system. Using the optimized catalyst system, copper(I) trifluoromethanesulfonate [Cu(OTf)]/L/TEMPO (L = 2,6-lutidine, TEMPO = 2,2,6,6-tetramethyl-piperidin-1-yl-oxyl), aerobic oxidation of the non-phenolic β-O-4 lignin model compound proceeded with good selectivity for C_α–C_β bond cleavage, affording 3,5-dimethoxybenzaldehyde as the major product. Aerobic oxidation of the corresponding phenolic β-O-4 lignin model proceeded with different selectivity, affording 2,6-dimethoxybenzoquinone and α,β-unsaturated aldehyde products resulting from cleavage of the C_α–C_{aryl} bond. At low catalyst concentrations, however, a change in selectivity was observed as oxidation of the benzylic secondary alcohol predominated with both substrates.

Keywords: aerobic oxidation; C–C bond cleavage; copper catalysts; lignin models; TEMPO; 2,2,6,6-tetramethyl-piperidin-1-yl-oxyl

Introduction

The efficient conversion of heterogeneous biomass resources to chemicals and fuels is presenting new challenges for catalysis science and engineering.[1] As a main constituent of lignocellulosic biomass, lignin – a random mixture of macromolecules containing methoxylated phenoxypropanoid units[2] – is readily separated in the wood pulping process.[3] However, isolated lignins differ widely in their molecular composition depending on the tree species and details of the pulping method. As a result, value-added products derived from lignin will likely need to be *families of chemicals* such as alkylphenols, aromatic aldehydes and acids, rather than single compounds.[4] While reductive approaches have focused on selective production of alkylphenols[5] or aromatic fuel components,[6] oxidative processes have also met with some success[7] with a simple mixed Cu-Fe homogeneous catalyst system affording 14 wt% aldehydes in one report[8] and $CuSO_4$ in an ionic liquid yielding up to 30% aldehydes in another.[9] Biocatalysis continues to play an important role in oxidative lignin conversion; first in investigations of lignin peroxidase enzymes found in white rot fungi,[10] and most recently with Mn-dependent bacterial enzymes.[11]

The investigation of metal complex-catalyzed aerobic oxidation of a variety of lignin model compounds has demonstrated some intriguing selectivity differences *vs.* traditional base-catalyzed methods.[7a] While the use of simple lignin models has allowed for evaluations of catalyst reactivity, recent work has demonstrated that the selectivity observed with simple β-O-4 lignin models, for example, may not pertain with more complex arylglycerol β-aryl ethers[12] such as **1a** and **1b** (Figure 1), which are commonly employed as models for the most prevalent lignin linkage.[31] For instance, Son and Toste showed that a five-coordinate salen-type oxo-vanadium complex catalyzed C–O bond cleavage of a non-phenolic model compound, to

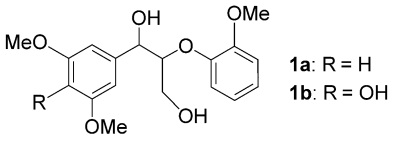


Figure 1. Syringyl β-O-4 lignin model compounds.

give 2-methoxyphenol and the functionalized enone[13] In contrast, we found that a five-coordinate dipicolinate oxovanadium complex afforded C–C bond cleavage products through the intermediacy of the ketone.[14] Hanson et al. subsequently reported disparate reactivity with similar catalysts using phenolic lignin models.[15] Using a simple CuCl/pyridine/TEMPO catalyst with **1a** led instead to *direct* C_α–C_β bond cleavage to afford the substituted benzaldehyde [TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl].[16]

Direct C_α–C_β bond cleavage has also been observed in the oxidation of **1a** using lignin peroxidase enzymes.[10] These catalysts have been shown to operate through a single-electron transfer mechanism and subsequent decomposition of the aryl cation radical.[10,17] In contrast, manganese peroxidase generates an Mn(III) carboxylate that effects hydrogen atom abstraction to afford the phenoxy radical.[18] In their studies using Co(salen) catalysts, Canevali et al. noted that the electron-rich aromatic rings in these substrates promoted electron transfer from Co(II) to O_2 followed by H atom abstraction to afford the *coordinated* phenoxy radical in the case of the phenolic lignin models.[19]

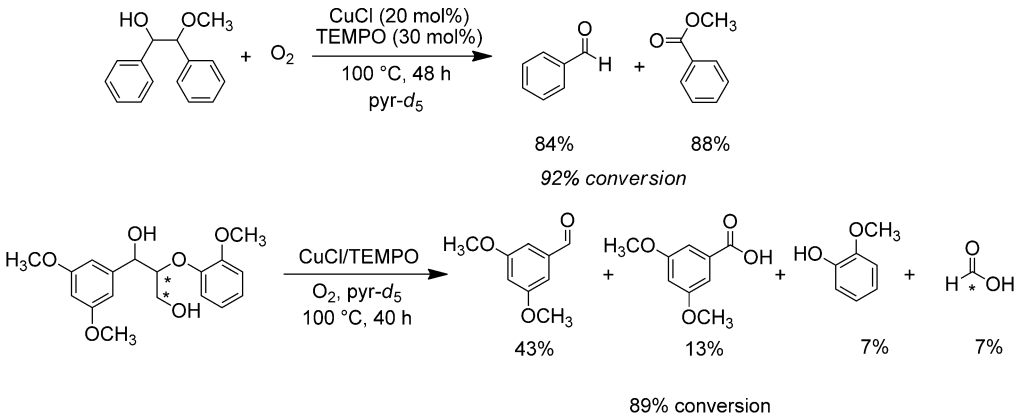
The diversity of oxidative reaction pathways observed for substrates **1a** and **1b** suggested that further catalyst development might allow for increased control over the distribution of aldehyde and acid products from real lignin extracts. In their ability to catalyze C–C bond cleavage and utilize dioxygen, copper aerobic oxidation catalysts have the potential to mimic the selectivity of peroxidase enzymes without the need for hydrogen peroxide. As previous optimizations of copper oxidation catalysts involved alcohol oxidation,[20] we sought to identify the best conditions for aerobic oxidative C–C bond cleavage in phenolic and non-phenolic β-O-4 models (**1a** and **1b**) and to see if detailed characterization of the products and soluble copper species could shed additional light on the operative reaction pathways.

Results and Discussion

Copper Catalyst Optimization for Oxidation of Non-Phenolic β-O-4 Lignin Model (1a)

In previous work, we built on diol oxidation studies by Kinoshita[21a] and by Prati and Rossi[21b] to show that aerobic oxidation of lignin model compounds using CuCl/TEMPO catalyst in pyridine proceeded by direct C–C bond cleavage, affording aldehydes as major products (Scheme 1).[16] Note that the pyridine serves as ligand, base, and solvent in these reactions.[22] Use of the doubly ^{13}C-labeled substrate (**1a***) allowed us to determine that additional, partially characterized side-products were formed.[16] With the aim of maximizing the aldehyde yield, we thus conducted a series of experiments to optimize the copper catalyst system.

Initially, we evaluated the stoichiometric oxidation of **1a** at 100 °C with several different copper precursors, solvents and N-donor ligands (Table 1). The reaction products were identified and quantified by ^{1}H NMR, GC/MS, and LC/MS; yields are expressed as a percentage of the theoretical maximum based on the initial amount of substrate. Moving first from pyridine to the bulkier 2,6-lutidine afforded higher yields of aldehyde (**2**) (entry 2). However, additional products (**5**, **6**) that derived from the decarboxylative coupling of the solvent were also observed (Figure 2; see also the Supporting Information, Figures S3–S6). A control experiment performed without substrate **1a** using CuCl/TEMPO under oxygen in 2,6-lutidine at 100 °C afforded the same coupling products **5** and **6**. Using *ca.* 10 equiv. of 2,6-lutidine as ligand and base in toluene solvent maintained the aldehyde yield with only a trace of **5** and **6** (entry 3), but a significant amount of **1a** was formylated to product **7** (Figure 3). Compound **7** is the result of catalyzed formylation of the secondary alcohol in **1a** with formic acid that is produced along with 2-methoxyphenol following C–C

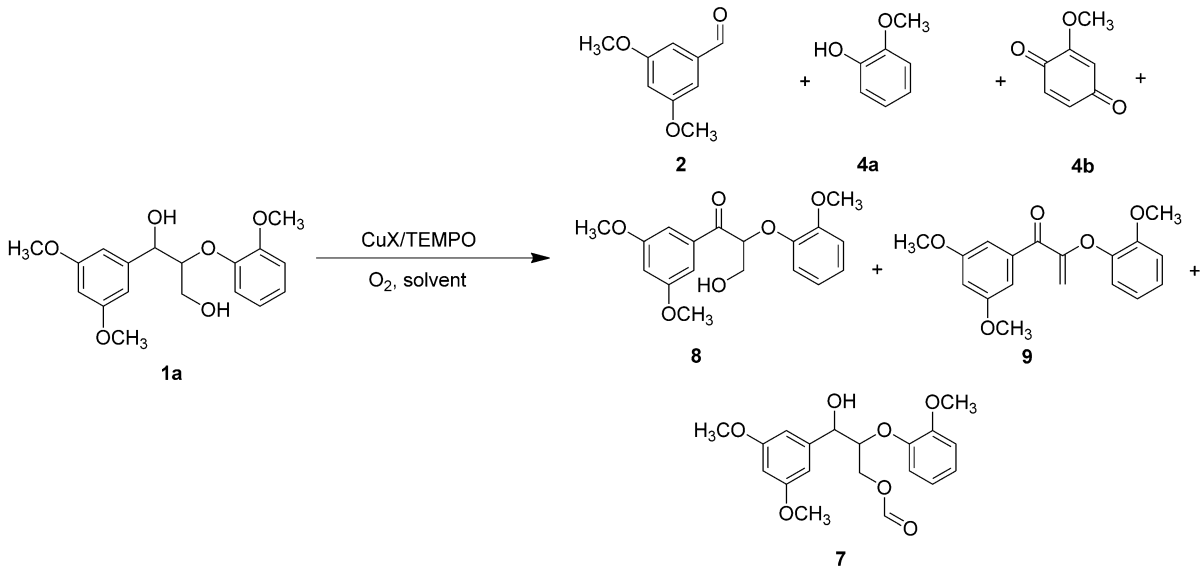


Scheme 1. Selective C–C bond cleavage using CuCl/TEMPO in pyridine.

bond cleavage of **1a**. A control reaction performed by heating **1a** with two equivalents of formic acid in the presence of 10 equivalents of 2,6-lutidine under oxygen in toluene at 100 °C for 18 h without catalyst afforded only 5% of formylation product **7**.

The nature of the copper precursor and solvent also played a significant role in these homogeneous reactions with the best results obtained using Cu(I) triflate in toluene (entry 5); the divalent triflate and sulfate derivatives gave low conversions of **1a** even after

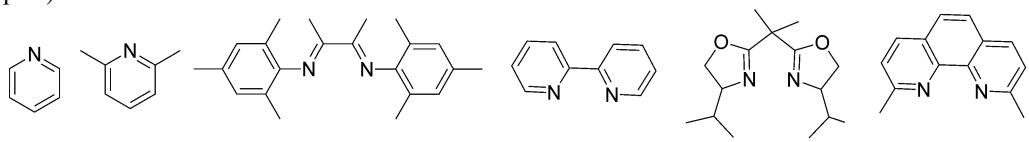
Table 1. Screening of N-donor ligands, copper precursors, and solvents for the aerobic oxidation of **1a**.[a]



Entry	N-Donor Ligand	Catalyst (+1 equiv. TEMPO)	Time [h]	Solvent	Conversion [%]	**2** [%][b]	**8** [%][b]	**9** [%][b]	**7** [%][b]	**10** [%][b]	**4a** [%][b]	**4b** [%][b]
1	pyridine[16]	CuCl	40	pyr	89	43	1	2	2	–	7	–
2	2,6-lutidine	CuCl	40	2,6-lut	79	52	–	–	4	–	8	–
3	2,6-lutidine (10 equiv.)	CuCl	40	toluene	84	51	1	10	14	1	7	5
4	2,6-lutidine (10 equiv.)	CuCl (20 mol%)	40	toluene	68	24	8	6	19	1	8	3
5	**2,6-lutidine (10 equiv.)**	**CuOTf**	**18**	**toluene**	**99**	**62**	**3**	**5**	**16**	**3**	**6**	**10**
6	2,6-lutidine	$Cu(OTf)_2$	40	2,6-lutidine	15	7	–	–	–	–	–	–
7	2,6-lutidine	$CuSO_4$	40	2,6-lutidine	6	1	–	–	–	–	–	–
8	2,6-lutidine (10 equiv.)	CuOTf	18	DMF	80	44	14	0.2	13	–	8	–
9	2,6-lutidine (10 equiv.)	CuOTf	18	DMF/ water (1:1)	5	–	–	–	–	–	–	–
10	2,6-lutidine (10 equiv.)	CuOTf	40	CH_3CN	56	20	9	0	4	–	2	–
11	diazabutadiene (5 equiv.)	CuOTf	18	toluene	76	53	5	1	8	–	5	2
12	bipy (5 equiv.)	CuOTf	18	toluene	67	36	5	0	12	–	2	3
13	bis(oxazoline) (5 equiv.)	CuOTf	18	toluene	50	24	1	0	10	3	nd	2
14	neocuproine (5 equiv.)	CuOTf	18	toluene	21	4	12	0	0	–	nd	–
15	**2,6-lutidne (10 equiv.)**	**CuOTf (20 mol%)**	**40**	**toluene**	**95**	**54**	**7**	**5**	**18**	**2**	**10**	**5**

Table 1. (Continued)

Entry	N-Donor Ligand	Catalyst (+1 equiv. TEMPO)	Time [h]	Solvent	Conversion [%]	**2** [%][b]	**8** [%][b]	**9** [%][b]	**7** [%][b]	**10** [%][b]	**4a** [%][b]	**4b** [%][b]
16[c]	2,6-lut (10 equiv.)	CuOTf	18	toluene	60	30	3	3	12	–	5	4
17[d]	2,6-lutidine (10 equiv.)	CuOTf	18	toluene	62	29	19	1	4	–	8	10



pyridine 2,6-lutidine *N,N'*-dimesityl-1,4-diazabutadiene 2,2'-bipyridine bis(oxazoline) neocuproine

[a] Temperature = 100 °C except for entries 8 (110 °C) and 10 (82 °C).
[b] NMR yields.
[c] No TEMPO added.
[d] 1 equiv. 2-methoxyphenol added; traces of 3,5-dimethoxybenzoic acid also formed.

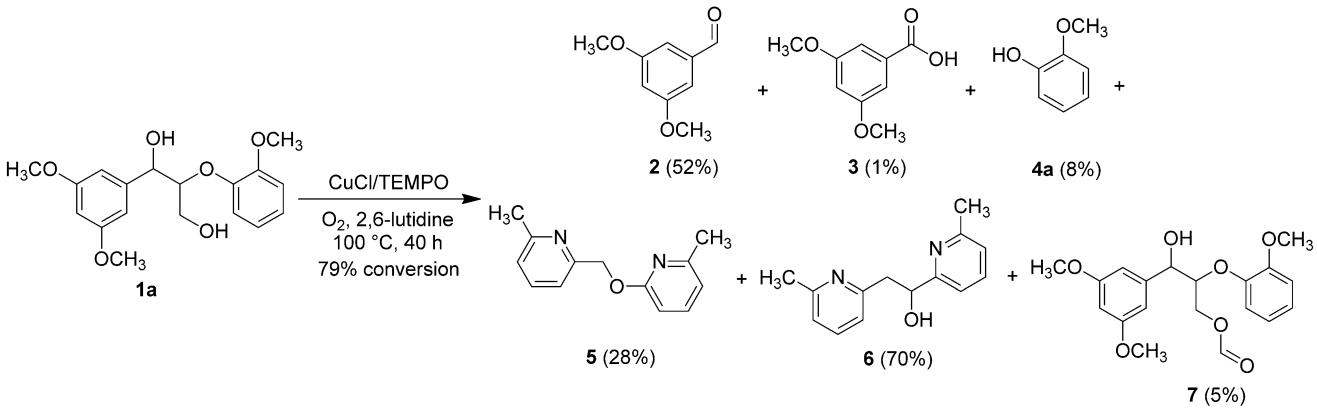


Figure 2. Aerobic oxidation of **1a** in 2,6-lutidine mediated by stoichiometric CuCl/TEMPO (yields of **5** and **6** are based on the initial amount of **1a**).

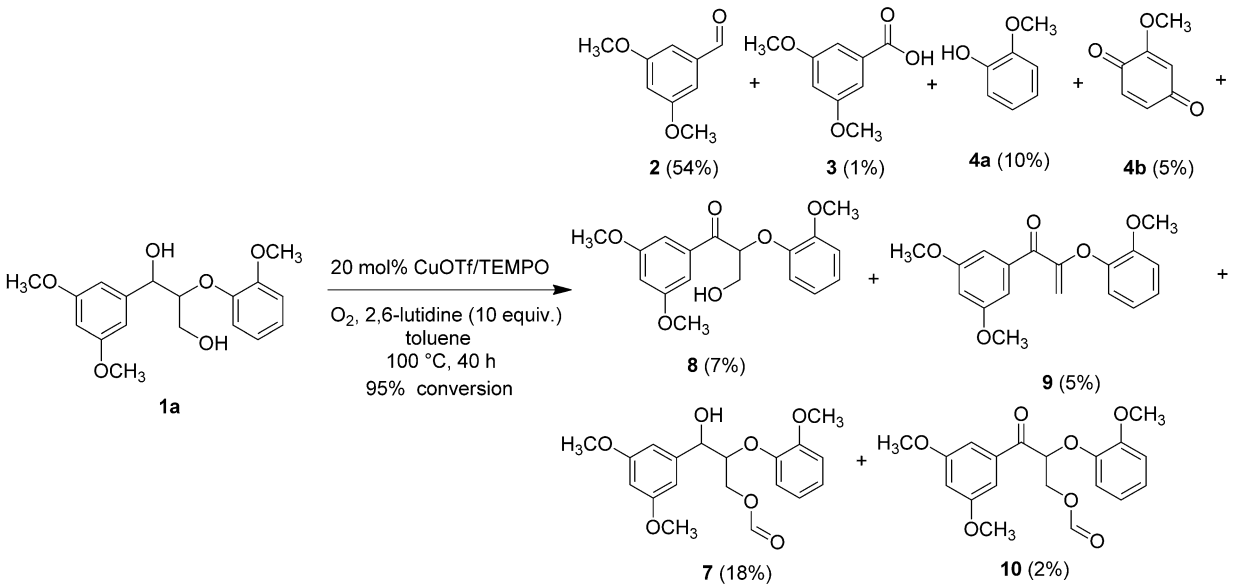


Figure 3. Copper complex-catalyzed aerobic oxidation of **1a**.

48 h in 2,6-lutidine solvent (entries 6 and 7). The selectivity to **2** dropped significantly in DMF solvent (entry 8) and both activity and selectivity decreased in acetontrile (entry 10). No additional benefits accrued from the use of bidentate ligands such as diimine, bipyridine, bis(oxazoline), or neocuproine,[23] with lower conversions and selectivities observed (entries 11–14).

Next, we tested the oxidation of **1a** using the optimized copper precursor and ligand combination, but under catalytic conditions. Using 20 mol% Cu(OTf)/TEMPO in the presence of 10 equivalents of 2,6-lutidine, 95% conversion of **1a** and 54% yield of 3,5-dimethoxybenzaldehyde (**2**) were observed after 40 h (entry 15, Figure 3). In another experiment, **1a** was heated using Cu(OTf)/2,6-lutidine without TEMPO under oxygen in toluene. After 18 h, only 60% of the starting material had been consumed, thus illustrating the role of TEMPO as co-catalyst (entry 16). In contrast, heating **1a** with 10 equivalent of 2,6-lutidine under oxygen in toluene with no catalyst afforded only ~2% conversion. The reaction rate drops significantly at lower catalyst concentrations and given the extensive phenol oxidation to quinone (**4b**),[24a–d] we surmised that the latter could be one source of the rate decrease. Indeed, heating **1a** with stoichiometric Cu(OTf)/2,6-lutidine/TEMPO and 2-methoxyphenol under oxygen in toluene for 18 h at 100 °C gave only 60 % conversion (entry 17). Note also that for the reaction in Figure 3, the carbon balance of products containing the dimethoxylated aryl ring is 87%, whereas that for the monomethoxylated ring is only 47%, suggesting that the benzoquinone product (**4b**) undergoes further conversion under our reaction conditions. Finally, the identity of the oxidation products was confirmed by carrying out the reaction on a larger scale and isolating the products using column chromatography.

Oxidation of Phenolic Lignin Model 1b

Phenolic β-O-4 lignin model (**1b**) was heated at 100 °C using a stoichiometric amount of Cu(OTf)/2,6-lutidine/TEMPO with oxygen in toluene (Figure 4). After 18 h, complete consumption of **1b** was observed, with 2,6-dimethoxybenzoquinone (**11**) and ene-al (**12**) formed as the major products. In a control reaction omitting the copper triflate, no reaction was observed after 18 h. When the catalyst loading was decreased to 10 mol%, approximately 98% conversion of (**1b**) was observed after 6 h, with formation primarily of ketone (**13**) (55%) along with 2,6-dimethoxybenzoquinone (**11**) (20%), ene-al (**12**) (6%), and 4-hydroxy-3,5-dimethoxybenzaldehyde (3%) from C–C bond cleavage of the ketone. After 18 h, the product distribution was largely unchanged but no 4-hydroxy-3,5-dimethoxybenzaldehyde or 2-methoxyphenol were detected (Figure 5). The poor carbon balance for the 2-methoxyphenoxy aromatic ring may be

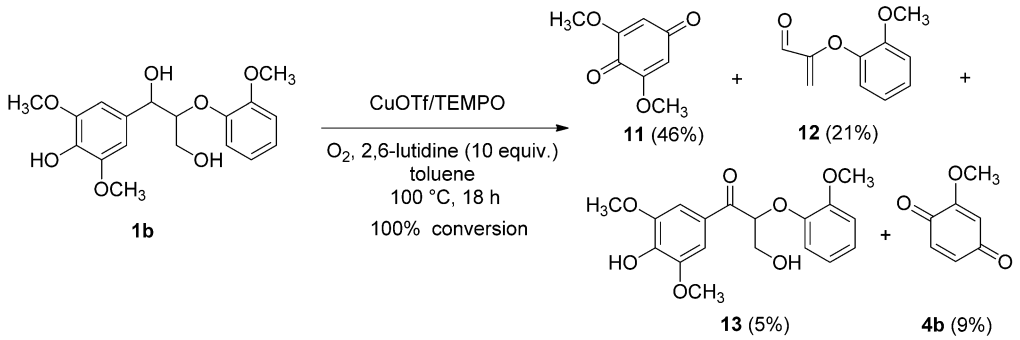


Figure 4. Aerobic oxidation of **1b** mediated by stoichiometric Cu(OTf)/2,6-lutidine/TEMPO.

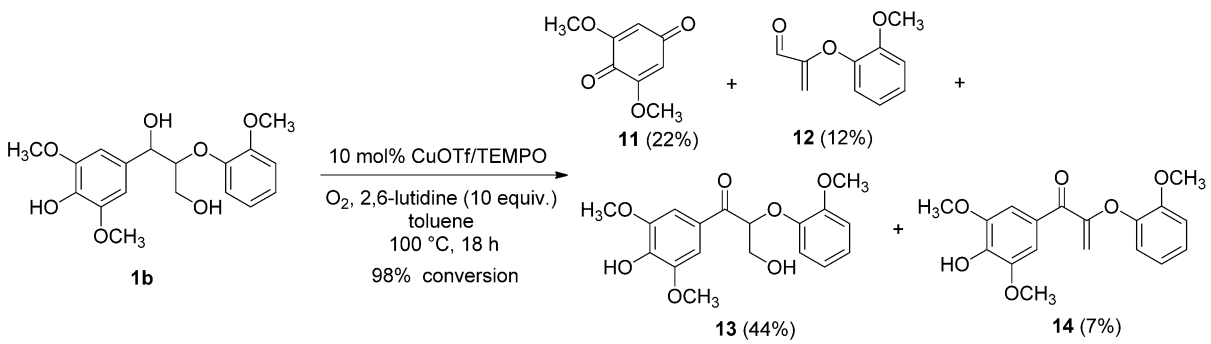


Figure 5. Copper complex-catalyzed aerobic oxidation of **1b**.

due to instability of ene-al (**12**) under the reaction conditions.[15] An LC/MS trace of the reaction mixture showed several peaks corresponding to higher molecular masses.

Activity of Copper Catalysts

As described above, the copper complex cleaved the C_α–C_β bond in non-phenolic β-O-4 lignin model (**1a**) to afford 3,5-dimethoxybenzaldehyde as the major product. The other half of the molecule underwent further conversion to generate 2-methoxyphenol and formic acid. Subsequent experiments indicated that the 2-methoxyphenol or its oxidation products such as 2-methoxy-1,4-benzoquinone (**4b**) may deactivate the Cu catalyst. In order to gain insight into copper speciation in the presence of 2,6-lutidine (L) we recorded the ESI-mass spectra using both Cu(I) and Cu(II) precursors (see Supporting Information, Figures S36–S41). The results for CuCl, Cu(OTf) and $Cu(OTf)_2$ revealed a mixture of mono- and divalent species with one or two coordinated ligands; isotope patterns were consistent with $[CuL_2]^+$ (**A**), $[(CuL)_2(\mu\text{-}Cl)]^+$ (**B**) and $[CuL_2S_4]^{2+}$(**C**) where S = MeCN, H_2O (Figure 6, Supporting Information, Figures S37, S38, and S40). Attempts to grow crystals from the reaction mixture afforded resting state complex bis(2,6-lutidine)-$Cu(II)Cl_2$, confirmed by X-ray diffraction.[25] After heating CuCl in the presence of TEMPO at 100 °C under O_2 for 18 h both mono- and dinuclear cations are still observed (Supporting Information, Figure S42). Finally, mass spectra recorded after oxidation of 2-methoxyphenol (HOAr) at 100 °C under O_2 for 40 h using CuCl/L/TEMPO/showed formation of several additional ions such as [Cu(II)(OAr)-(HOAr)]$^+$, in addition to cations **A–C** (Supporting Information, Figure S43). It appears, then, that the phenol and/or its oxidation products serve as a catalyst *inhibitor* rather than a catalyst poison.

Mechanistic Considerations

A variety of copper/TEMPO catalyst systems has been utilized for the aerobic oxidation of alcohols, diols, and lignin model compounds, and several common mechanisms have been proposed.[17,20,26] The most relevant to this work are the recent reports by Stahl et al. that account for the higher activity of Cu(I) precursors in the absence of very strong bases such as KO-*t*-Bu.[26] While their proposed mechanism pertains to alcohol oxidation under mild conditions, several steps are likely to play key roles in the more demanding C–C bond cleavage reactions described here. These include use of nitrogen donor ligands to modulate the Cu(I)/Cu(II) redox couple, activation of dioxygen by two different Cu(I) centers, and improved catalyst performance using the weakly coordinating triflate ligand (*vs.* Cl^-). Under our harsh reaction conditions (100 °C), the lability of both Cu(I) and Cu(II) complexes with N-donor ligands reduce their impact as a potential source of improved catalyst activity and selectivity.[27]

Recently, Stahl and co-workers reported the aerobic oxidation of a complex β-O-4 lignin model compound similar to **1a** using their Cu(OTf)/bpy/TEMPO/*N*-methylimidazole catalyst system to afford veratryl aldehyde as the major product.[28] They proposed that oxidation of the primary alcohol followed by a retro-aldol reaction led to cleavage of the Cα–C_β bond.[29] This then provides an alternate mechanism (Scheme 2) to the well-studied single electron transfer mechanism in which reagents like ceric ammonium nitrate generate aryl cations that undergo subsequent cleavage of the Cα–C_β bond.[10,17]

Although the complexity of copper speciation makes it difficult to test electrochemically if the divalent Cu 2,6-lutidine cations are sufficiently oxidizing to generate aryl cations from substrates **1a** and **1b**, another observation tends to disfavor the primary alcohol oxidation route. We recently showed that oxidation of β–1 models (which bear an aryl group in the place of the aryloxy of **1a** and **1b**) using an oxovanadium complex gave rise to primary alcohol oxidation, as these products are not susceptible to the retro-aldol reaction. As in this study, use of 10 mol% Cu(OTf)/L/TEMPO catalyst favored benzylic alcohol oxidation while the stoichiometric reaction led to cleavage of the C_α–C_{aryl} bond. Moreover, use of the Cu catalyst with simple lignin models that lack the electron-rich aromatic ring, such as 1-phenyl-2-phenoxyethanol, afforded primarily oxidation products with the Cα–C_β bond still intact.[16c] Thus, while Cu/TEMPO catalyst systems are well recognized for their primary alcohol selectivity under mild conditions,[20n] at the elevated

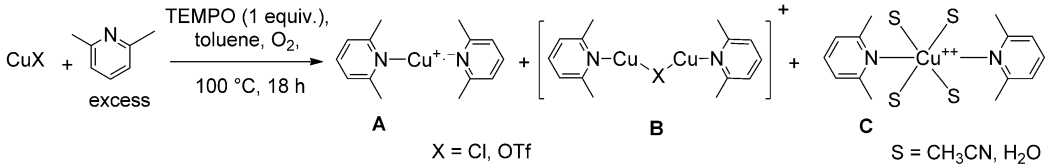
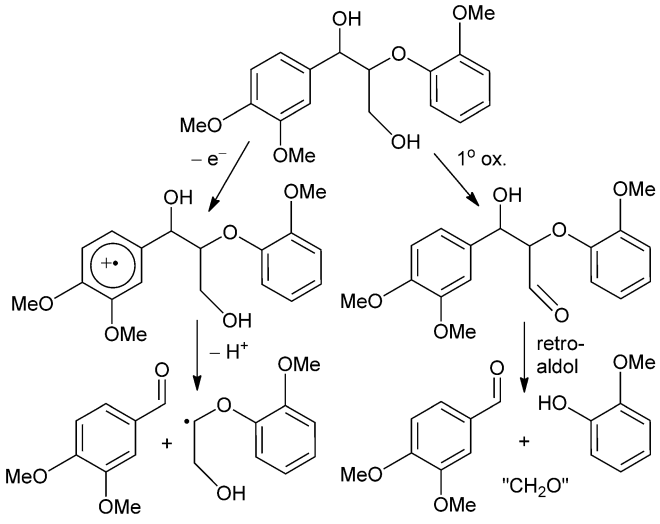


Figure 6. Mono- and divalent cations derived from CuX and 2,6-lutidine.



Scheme 2. Two routes to oxidative C–C bond cleavage.

temperatures employed in this study, we suggest that an alternate pathway predominates. Also unclear is the origin of the selectivity dependence on the substrate to catalyst ratio observed in this study and with the β–1 substrates. Previous work has demonstrated that basic nitrogen ligands are capable of reducing divalent copper to its monovalent state[20k,26b] and our goal in catalyst optimization was to employ excess ligand to favor mononuclear copper centers. Multinuclear copper catalysts have been reported to promote C–C bond formation[30] which would be deleterious to lignin depolymerization. The MS studies, however, indicate significant amounts of dinuclear Cu cations even with excess L and the weakly coordinating triflate anion.

Conclusions

In this study we demonstrate that the promising selectivity for oxidative C–C bond cleavage exhibited by soluble copper catalysts with simple lignin models[16a] is hampered by several additional factors with more complex β-O-4 models such as **1a** and **1b**. Although catalyst optimization improved the yields of the target aromatic aldehyde, the catalyst was inhibited by the phenol by-product and reduction of the catalyst loading led primarily to the ketone derived from oxidation of the secondary benzylic alcohol. Moreover, while Co salen-type catalysts oxidize lignin-derived phenols to benzoquinones in good yields under mild conditions,[24c,d] the elevated temperatures required for C–C bond cleavage of **1a** and **1b** leads to futher reactivity of the phenol oxidation products.

Experimental Section

General Considerations

Unless specified otherwise, all reactions were carried out in the presence of air. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker AV400 MHz spectrometer, with chemical shifts (δ) referenced to the residual solvent signal. GC-MS analysis was obtained using a Hewlett Packard 6890 GC system equipped with a Hewlett Packard 5973 mass selective detector. 2-Methoxyphenol was quantified with response factors using GC/MS. HPLC-MS analyses were performed on a Dionex Ultimate 3000 Liquid Chromatograph and an Applied Biosystem API2000 triple quadrupole mass spectrometer (LC-MS delay 0.27 min), using a reversed-phase gradient column (RSLC PA2 2.2 μm 120 Å, 2.1×150 mm) and 0.5% acetic acid in H_2O, acetonitrile/methanol as mobile phases. The analysis employed a DAD UV-Vis detector or mass spectrometry (Q1MS) with electrospray ionization (ESI-MS) in positive mode (ion spray voltage: 5000 V, TEM: 400 °C, declustering potential: 11.00 V and focusing potential: 300.0 V). ESI-MS analyses were performed using in an Applied Biosystem API2000 with triple quadrupole mass spectrometer in positive mode using CH_3CN solvent. CuCl, Cu(OTf), $Cu(OTf)_2$, $CuSO_4$, TEMPO, 2,2′-bipyridine, and neocuproine were used as received from Aldrich. Deuterated solvents were purchased from Cambridge Isotope Laboratories and dried with molecular sieves. The β-O-4 lignin models compounds 1-(3,5-dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol **1a** and 1-(4-hydroxy-3,5-dimethoxy-phenyl)-2-(2-methoxyphenoxy)propane-1,3-diol **1b** were synthesized according to the literature procedures.[13,15] Oxygen was purchased from Linde Canada.

Oxidation of Non-Phenolic β-O-4 Lignin Model 1a using CuCl/TEMPO in 2,6-Lutidine

In an NMR tube, non-phenolic lignin model **1a** (40 mg, 0.12 mmol) was dissolved in $CDCl_3$ (1 mL) containing dimethylsulfone (3 mg, 0.03 mmol) as an internal standard. An initial spectrum was recorded and solvent was removed. The reaction mixture was transferred to a thick-walled 50 mL Schlenk tube equipped with Teflon stopcock containing CuCl (11 mg, 0.11 mmol) and TEMPO (9 mg, 0.06 mmol) in 2,6-lutidine (4 mL) under air. Oxygen was bubbled into the reddish orange reaction mixture for 2 min and the reactor sealed. The reaction mixture was heated at 100 °C with constant stirring. After 40 h, the reaction was cooled to room temperature and solvent was removed under vacuo. To an aliquot of the reaction mixture, $CDCl_3$ (1 mL) was added and filtered thorough glass wool and examined by ^{1}H NMR spectroscopy (Supporting Information, Figure S1). A second aliquot was dissolved in acetonitrile and passed through a silica plug to remove copper salts. The solvent was removed under vacuum and the residue dissolved in $CDCl_3$ for NMR analysis (Supporting Information, Figure S2). Conversion and product yields (expressed as a percentage of the theoretical maximum based on the initial amount of substrate) are shown in Figure 2. ^{1}H NMR resonances not assigned to products **2**–**7**: $\delta = 6.55$ (d, $J = 2$ Hz), 6.30 (br), 4.69 (br), 4.66 (s), 4.63 (s), 4.62 (br), 4.59 (br), 4.43 (d, $J =$

3.2 Hz), 4.41 (d, $J=2.4$ Hz), 4.35 (br), 4.16 (br), 3.95 (s), 2.66 (s), 2.50 (s), 1.72 (br), 1.54 (br).

New 2,6-lutidine decarboxylative coupling products **5** and **6** were isolated from a large-scale reaction (500 mg **1a** in 10 mL of 2,6-lutidine) by column chromatography with silica gel using 85:15 mixture of hexanes: ethyl acetate.

2-Methyl-6-[(6-methylpyridin-2-yl)methoxy]pyridine (5): colorless solid; isolated yield: 20%; ^{1}H NMR: $\delta=7.95$, 7.33, 7.24, 7.07 (d, 1H, $J=7.5$ Hz, pyridyl), 7.71, 7.56 (tr, 1H, $J=7.5$ Hz, pyridyl), 5.5 (s, 2H, CH_2), 2.65, 2.54 (s, 3H, CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): $\delta=165.13$ (s), 159.28 (s), 158.22 (s), 155.05 (s), 147.34 (s), 137.02 (s), 126.87 (s), 122.65 (s), 122.48 (s), 118.67 (s), 67.97 (s), 24.68 (s), 24.43 (s); IR: $\nu=3445$ (w), 2726 (w), 2927 (s), 2981 (m), 1727 (s), 1591 (s), 1456 (s), 1299 (s), 1232 (s), 1173 (s), 921 (m), 784 (s), 761 (s); GC/MS (CH_3CN): $m/z=214.0$, 197, 122, 106, 93 65, 53; ESI/MS: $m/z=215.20$, calcd. for $C_{13}H_{14}N_2O$ $[M+H]^+$: 215.68 *(consistent with ^{1}H,H COSY).*

6,6′-Oxybis(2-methylpyridine) (6): pale yellow oil; isolated yield: 12%; ^{1}H NMR: $\delta=7.54$, 7.47 (t, 1H, $J=7.8$ Hz, pyridyl), 7.29, 6.95 (d, 1H, $J=7.8$ Hz, pyridyl), 7.02 (ov d, 2H, $J=7.8$ Hz, pyridyl), 5.14 (dd, 1H, $J=9.3$, 3.0 Hz, C*H*OH), 3.27 (dd, 1H, $J=14$, 3 Hz, CH_2), 3.01 (dd, 1H, $J=14$, 9.3 Hz, CH_2), 2.53 (s, 6H); ^{13}C{^{1}H} NMR: $\delta=162.13$ (s), 159.09 (s), 157.21 (s), 157.20 (s), 136.90 (s), 136.86 (s), 121.30 (s), 121.28 (s), 120.89 (s), 117.15 (s), 73.7 (s), 44.5 (s), 24.41 (s), 24.39 (s); IR: $\nu=3310$ (br), 1594 (s), 1576 (s), 1458 (s), 1264 (m), 1154 (m), 1072 (m), 791 (s), 761 (s); ESI/MS: $m/z=229.20$, calcd, for $C_{14}H_{16}N_2O$ $[M+H]^+$: 229.29 *(consistent with ^{1}H,H COSY).*

Oxidation of Non-Phenolic β-O-4 Lignin Model 1a using Cu(OTf)$_2$/TEMPO in 2,6-Lutidine

This experiment was performed in the similar fashion as above except using 39 mg of Cu(OTf)$_2$ (0.109 mmol) instead of CuCl. After 18 h, oxygen was bubbled into the reaction mixture for 2 min the reactor was sealed again and heated at 100 °C. Conversion and product yields after 40 h are shown in Table 1. ^{1}H NMR resonances not assigned to products **2**–**7**: $\delta=9.83$ (s), 4.60 (s), 1.70 (s), 1.43 (s), 1.40 (br), 1.19 (br).

Oxidation of Non-Phenolic β-O-4 Lignin Model 1a using CuSO$_4$/TEMPO in 2,6-Lutidine

This experiment was performed in the similar fashion as above except using 29 mg of $CuSO_4$ (0.116 mmol) instead of CuCl. After 18 h, oxygen was bubbled into the reaction mixture for 2 min the reactor was sealed again and heated at 100 °C. Conversion and product yields after 40 h are shown in Table 1. ^{1}H NMR resonances not assigned to products **2**–**7**: $\delta=2.50$ (s), 1.34 (s), 1.23 (s).

Oxidation of 1a using CuCl/TEMPO with 2,6-Lutidine (10 equiv.) in Toluene

This reaction was performed as above except replacing 4 mL of 2,6-lutidine with 0.14 mL of 2,6-lutidine (1.19 mmol) in 6 mL of toluene. After 18 h, oxygen was bubbled into the reaction mixture for 2 min the reactor was sealed again and heated at 100 °C. Conversion and product yields after 40 h are shown in Table 1. ^{1}H NMR resonances not assigned to products **2**–**4**, **7**–**10** or **1a**: $\delta=6.62$ (br), 6.60 (br), 6.56 (br), 5.93 (s), 5.82 (d, $J=2$ Hz), 5.63 (br), 5.50 (d, $J=2$ Hz), 4.44 (br), 4.51 (br), 3.71 (s), 1.58 (br), 1.32 (br), 1.23 (s), 1.19 (br).

Catalytic Oxidation of 1a using CuCl/TEMPO with 2,6-Lutidine (10 equiv.) in Toluene

This reaction was performed as above except replacing 11 mg of CuCl with 2 mg (0.02 mmol) and 9 mg of TEMPO with 3.75 mg (0.024 mmol). The red reaction mixture was heated at 100 °C. After 18 h, oxygen was bubbled into the reaction mixture for 2 min the reactor was sealed again and heated at 100 °C. After 40 h, the reaction was cooled to room temperature, the solvent was removed under vacuum and the products analyzed as above. Conversion and product yields are shown in Table 1. ^{1}H NMR resonances not assigned to products **2**–**4**, **7**–**10**: $\delta=6.62$ (br), 6.60 (br), 6.58 (br), 5.82 (d, $J=2$ Hz), 5.51 (d, $J=2$ Hz), 4.47 (br), 4.04 (br), 1.69 (br), 1.58 (br), 1.32 (br), 1.23 (s), 1.19 (br).

Formyl esters **7** and **10** were isolated from a large-scale reaction (400 mg **1a** in 1.4 mL of 2,6-lutidine) by column chromatography with silica gel using 80:20 mixture of hexanes: ethyl acetate.

3-(3,5-Dimethoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propyl formate (7): colorless oil; isolated yield: 11%; ^{1}H NMR: $\delta=8.05$ (s, 1H, C*H*O), 7.23 (d, 2H, $=2.64$ Hz, aryl), 7.06 (d, 1H, $J=7.5$ Hz, aryl), 6.93 (d, 1H, $J=7.5$ Hz, aryl), 6.67 (t, 1H, $J=2.6$ Hz, aryl), 6.56 (d, 1H, $J=2.6$ Hz, aryl), 6.34 (t, 1H, $J=2.6$ Hz, aryl), 4.89 (d, 1H, $J=3.5$ Hz, C*H*OH), 4.52 (dd, 1H, $J=12$, 8 Hz, CH_2CH), 4.42 (ddd, 1H, $J=8$, 3.5, 3 Hz, CH$_2$C*H*), 4.14 (dd, 1H, $J=12$, 3 Hz, CH_2CH), 3.82 (s, 6H, OCH_3), 3.76 (s, 3H, OCH_3); ^{13}C{^{1}H} NMR: $\delta=161.08$ (s), 151.84 (s), 146.40 (s), 140.94 (s), 131.06 (s), 124.50 (s), 121.57 (s), 121.16 (s), 112.37 (s), 107.64 (s), 106.73 (s), 103.88 (s), 99.72 (s), 84.51 (s), 71.91 (s), 62.23 (s), 55.90 (s), 55.62 (s), 55.22 (s); HR-MS (EI): $m/z=362.1370$, calcd. for $C_{19}H_{22}O_7$ $[M]^+$: 362.1366.

3-(3,5-Dimethoxyphenyl)-2-(2-methoxyphenoxy)-3-oxopropyl formate (10): colorless oil; isolated yield: 3%; ^{1}H NMR: $\delta=8.08$ (s, C*H*O), 7.23 (d, 2H, $J=2.5$ Hz, aryl), 6.996.78 (m, 4H, aryl), 6.66 (t, 1H, $J=2.5$ Hz, aryl), 5.63 (dd, 1H, $J=3.70$, 6.70 Hz, CH$_2$C*H*), 4.75 (dd, $J=3.7$, 11.8 Hz, CH_2), 4.56 (dd, 1H, $J=6.7$, 11.8 Hz, CH_2), 3.80 (s, 6H, OCH_3), 3.74 (s, 3H, OCH_3); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): $\delta=194.88$ (s), 160.95 (s), 160.65 (s), 150.38 (s), 146.56 (s), 140.1 (s), 136.55 (s), 123.73 (s), 121.00 (s), 118.65 (s), 112.58 (s), 106.56 (s), 106.43 (s), 105.1 (s), 80.07 (s), 63.79 (s), 55.79 (s), 55.71 (s), 55.39 (s); HR-MS (EI): $m/z=360.1239$, calcd. for $C_{19}H_{20}O_7$ $[M+H]^+$: 360.1209.

Oxidation of 1a using Cu(OTf)/TEMPO/2,6-Lutidine in Toluene

This experiment was performed as for the stoichiometric CuCl one above except using 61 mg of $[Cu(OTf)]_2$·toluene (0.12 mmol). The orange-red reaction mixture was dark red after 18 h at 100 °C. Conversion and product yields are shown in Table 1. ^{1}H NMR resonances not assigned to products **2**–**4** or **7**–**10**: $\delta=6.65$ (br), 6.62 (br), 6.40 (br), 5.82 (d, $J=2$ Hz), 5.51 (d, $J=2$ Hz), 4.43(br), 4.19 (m), 2.15 (s), 1.68 (br), 1.44 (s), 1.23 (s).

Oxidation of 1a using Cu(OTf)/TEMPO/2,6-Lutidine in DMF

This experiment was performed as for the stoichiometric Cu(OTf) one above except the toluene was replaced by 6 mL of dimethylformamide. The orange mixture was dark red after 18 h at 110 °C. Conversion and product yields are shown in Table 1. ^{1}H NMR resonances not assigned to products **2–4** or **7–10**: $\delta = 6.60$ (br), 6.65 (br), 6.45 (br), 5.82 (br), 5.50 (br), 4.44 (br), 3.89 (s), 3.88 (s), 1.67 (br), 1.44 (br), 1.23 (s).

Oxidation of 1a using Cu(OTf)/TEMPO/2,6-Lutidine in DMF/Water

This experiment was performed as for the stoichiometric Cu(OTf) one above except the DMF (3 mL) was replaced by 3 mL of water. The greenish mixture was reddish green after 18 h at 100 °C. Conversion and product yields are shown in Table 1. ^{1}H NMR resonances not assigned to products **2–4** or **7–10**: $\delta = 2.85$ (s), 2.63 (s), 1.67 (s), 1.57 (s), 1.23 (s).

Oxidation of 1a using C(uOTf)/TEMPO/2,6-Lutidine in Acetonitrile

This experiment was performed as for the stoichiometric Cu(OTf) one above except the toluene was replaced by 6 mL of acetonitrile. The orange-red reaction mixture was dark red after 18 h at 80 °C. Conversion and product yields are shown in Table 1. ^{1}H NMR resonances not assigned to products **2–4** or **7–10**: $\delta = 6.65$ (br), 4.44 (br), 3.61(br), 1.66 (br), 1.41 (s), 1.34 (s).

Oxidation of 1a using Cu(OTf)/2,6-Lutidine in Toluene (no TEMPO)

This experiment was performed as for the stoichiometric Cu(OTf) one above except without TEMPO. The orange-red reaction mixture was red after 18 h at 100 °C. Conversion and product yields are shown in Table 1. ^{1}H NMR resonances not assigned to products **2–4** or **7–10**: $\delta = 6.63$ (br), 6.60 (br), 6.56 (br), 5.82 (d, $J = 2$ Hz), 5.51 (br), 4.44 (br), 1.23 (s).

Oxidation of 1a using Cu(OTf)/TEMPO/2,6-Lutidine with 2-Methoxyphenol (1 equiv.) in Toluene

This experiment was performed as for the stoichiometric Cu(OTf) one above except with equimolar mixture of **1a** and 2-methoxyphenol (14 mg, 0.11 mmol). The orange-red reaction mixture was dark red after 18 h at 100 °C. Conversion and product yields are shown in Table 1. ^{1}H NMR resonances not assigned to products **2–4** or **7–10**: $\delta = 6.65$ (br), 6.60 (br), 5.82 (d, $J = 2$ Hz), 5.50 (d, $J = 2$ Hz), 3.89 (s), 1.66 (s), 1.44 (br), 1.23 (s).

Catalytic Oxidation of 1a using Cu(OTf)/TEMPO/2,6-Lutidine in Toluene

This experiment was performed as for the catalytic CuCl one above except using 12 mg of $[Cu(OTf)]_2$·toluene (0.02 mmol) and 4 mg of TEMPO (0.02 mmol). The orange-red reaction mixture was dark red after 18 h at 100 °C. After 18 h, oxygen was bubbled into the reaction mixture again for 2 min and the reactor was sealed again. After 40 h, the reaction was cooled to room temperature, the solvent was removed under vacuum and the products analyzed as above. Conversion and product yields are shown in Table 1. ^{1}H NMR resonances not assigned to products **2–4**, **7–10**: $\delta = 6.65$ (br), 6.60 (br), 6.40 (br), 5.82 (d, $J = 2$ Hz), 5.51 (d, $J = 2$ Hz), 4.44 (br), 1.67 (br), 1.44 (s), 1.23 (s).

Oxidation of 1a using Cu(OTf)/TEMPO/*N,N′*-Dimesityl-1,4-diazabutadiene (5 equiv.) in Toluene

This experiment was performed as for the stoichiometric Cu(OTf) one above except the 2,6-lutidine was replaced by 5 equiv. of *N,N′*-dimesityl-1,4-diazabutadiene (0.19 g, 0.59 mmol). The purple-yellow reaction mixture was dark red after 18 h at 100 °C. Conversion and product yields are shown in Table 1. ^{1}H NMR resonances not assigned to products **2–4** or **7–10**: $\delta = 10.4$ (br), 8.82 (s), 8.25 (s), 8.10 (br), 7.71 (br), 1.66 (s), 1.44 (br), 1.23 (s).

Oxidation of 1a using Cu(OTf)/TEMPO/2,2′-Bipyridine (5 equiv.) in Toluene

This experiment was performed as for the stoichiometric Cu(OTf) one above except the 2,6-lutidine was replaced by 5 equiv. of 2,2′-bipyridine (92 mg, 0.59 mmol). The purple-red reaction mixture was dirty green after 18 h at 100 °C. Conversion and product yields are shown in Table 1. ^{1}H NMR resonances not assigned to products **2–4** or **7–10**: $\delta = 8.25$ (s), 7.81 (m), 6.60 (br), 6.12 (br), 5.12 (s), 4.44 (br), 3.89 (s), 1.63 (br), 1.43 (br), 1.23 (s).

Oxidation of 1a using Cu(OTf)/TEMPO/Bis(oxazoline) (5 equiv.) in Toluene

This experiment was performed as for the stoichiometric Cu(OTf) one above except the 2,6-lutidine was replaced by 5 equiv. of bis(oxazoline) (0.16 g, 0.59 mmol). The reaction mixture was light green after 18 h at 100 °C. Conversion and product yields are shown in Table 1. ^{1}H NMR resonances not assigned to products **2–4** or **7–10**: $\delta = 7.49$ (br), 6.60 (br), 6.00 (br), 3.89 (s), 1.70 (br), 1.46 (br), 1.22 (s).

Oxidation of 1a using Cu(OTf)/TEMPO/Neocuproine (5 equiv.) in Toluene

This experiment was performed as for the stoichiometric Cu(OTf) one above except the 2,6-lutidine was replaced by 5 equiv. of neocuproine (0.12 g, 0.60 mmol). The reaction mixture turned dark red after 18 h at 100 °C. Conversion and product yields are shown in Table 1. ^{1}H NMR resonances not assigned to products **2–4** or **7–10**: $\delta = 9.20$ (br), 6.81 (br), 3.89 (s), 3.63 (s), 1.66 (s), 1.44 (br), 1.23 (s).

Oxidation of 2-Methoxyphenol using Cu(OTf)/TEMPO/2,6-Lutidine in Toluene

This experiment was performed as for the stoichiometric Cu(OTf) one above except substrate 1a was replaced by 2-methoxyphenol (20 mg, 0.161 mmol). The orange-red reaction mixture was black after 18 h at 100 °C. Approximately

75% of 2-methoxyphenol had been consumed, with the products consisting of quinone products consistent with the literature.[20d,e] ^{1}H NMR: $\delta = 8.14$ (t, $J = 7.5$ Hz), 7.50 (d, $J = 7.5$ Hz), 7.07 (m), 7.05 (br), 6.99 (br), 6.97 (br), 6.95 (br), 6.93 (br), 6.70 (s), 5.82 (d, $J = 2$ Hz), 5.50 (d, $J = 2$ Hz), 3.83 (s), 3.87 (s), 2.86 (s), 1.98 (s), 1.68 (br), 1.44 (s), 1.23 (s).

Control Experiment: Aerobic Thermolysis of 1a with 2,6-Lutidine (10 equiv.) in Toluene

In an NMR tube, **1a** (20 mg, 0.059 mmol) was dissolved in $CDCl_3$ (1 mL) containing dimethylsulfone (1.39 mg, 0.015 mmol) as an internal standard. An initial spectrum was recorded and solvent was removed. The reaction mixture was transferred to a thick-walled 50 mL Schlenk tube equipped with Teflon stopcock containing 2,6-lutidine (0.07 mL, 0.59 mmol) in toluene (4 mL) under air. Oxygen was bubbled into the mixture for 2 min and the reactor sealed. After heating at 100 °C for 18 h with constant stirring the solvent was removed under vacuum and the residue analyzed by ^{1}H NMR spectroscopy; no conversion or products were detected.

Representative LC/MS Data for Copper Complex-Catalyzed Oxidation of 1a

2-Methoxyphenol (**4**) $[M+H]^+$ (7.86 min, $m/z = 125.06$, calcd.: 125.06); TEMPO $[M]^+$ (22.61 min, $m/z = 156.14$, calcd.: 156.14); 1-(3,5-dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol (**1a**) $[M+H]^+$ (26.60 min, $m/z =$ 335.13, calcd.: 335.16); 3,5-dimethoxybenzaldehyde (**2**) $[M+H]^+$ (30.76 min, $m/z = 167.16$, calcd.: 167.07); 1-(3,5-dimethoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propan-1-one (**8**) $[M+H]^+$ (33.78 min, $m/z = 333.05$, calcd.: 333.13); 1-(3,5-dimethoxyyphenyl)-2-(2-methoxyphenoxy)-prop-2-en-1-one (**9**) $[M+H]^+$ (36.76 min, $m/z = 315.05$, calcd.: 315.13); 3-(3,5-dimethoxyphenyl)-2-(2-methoxyphenoxy)-3-oxopropyl formate (**10**)$[M+H]^+$ (41.97 min, $m/z = 361.10$, calcd.: 361.37); 3-(3,5-dimethoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propyl formate (**7**) $[M+H]^+$ (47.14 min, $m/z =$ 363.20; calcd.: 363.38); unidentified compounds: * (17.61, 40.67, 44.06, 49.74, 44.06 min, unknown compounds)

Oxidation of Phenolic β-O-4 Lignin Model 1b using Cu(OTf)/TEMPO/2,6-Lutidine in Toluene

This experiment was performed as for the stoichiometric Cu(OTf) one above except substrate **1a** was replaced by **1b** (40 mg, 0.11 mmol). The orange-red reaction mixture was dark red after 18 h at 100 °C. Conversion and product yields are shown in Figure 4. ^{1}H NMR resonances not assigned to products **11**–**13**: $\delta = 7.96$ (t, $J = 7.5$ Hz), 7.33 (d, 7.5 Hz), 3.86 (s),, 2.79 (s), 1.68 (br), 1.45 (s).

Catalytic Oxidation of 1b using Cu(OTf)/TEMPO/ 2,6-Lutidine in Toluene

This experiment was performed as for the catalytic Cu(OTf) one above except substrate **1a** was replaced by **1b** (40 mg, 0.11 mmol). The orange-red reaction mixture was dark red after 6 h at 100 °C. Conversion and product yields after 6, 12, and 18 h are shown in Table 2. After the 6 h run *ca.* 3% of 4-hydroxy-3,5-dimethoxybenzaldehyde was identified by ^{1}H NMR. ^{1}H NMR resonances not assigned to products **11**–**14**: $\delta = 8.25$ (s), 7.94 (t, $J = 7.5$ Hz), 7.39 (br), 7.31 (d, 7.5 Hz), 3.96 (s), 2.79 (s), 1.67 (br), 1.44 (s), 1.23 (s).

Table 2.

Time [h]	Conv. [%]	**11**	**12**	**13**	**14**	**13+14**
6	98	20	6	55	0	55
12	100	23	10	48	5	53
18	100	22	12	44	7	51

Control Experiment: Aerobic Thermolysis of Phenolic β-O-4 Lignin Model 1b with 2,6-Lutidine (10 equiv.) in Toluene

In an NMR tube, phenolic lignin model **1b** (20 mg, 0.06 mmol) was dissolved in $CDCl_3$ (1 mL) containing dimethylsulfone (1.3 mg, 0.01 mmol) as an internal standard. An initial spectrum was recorded and solvent was removed. The reaction mixture was transferred to a thick-walled 50 mL Schlenk tube equipped with Teflon stopcock containing 2,6-lutidine (0.07 mL, 0.57 mmol) in toluene (4 mL) under air. Oxygen was bubbled into the reaction mixture for 2 min and the reactor sealed. The reaction mixture was heated at 100 °C with constant stirring. After 18 h, approximately 6% starting material had been consumed and the yield of 2,6-dimethoxy-1,4-benzoquinone **11** (4%) was determined by ^{1}H NMR spectroscopy.

Representative LC/MS Data for Oxidation of 1b using Cu(OTf)/TEMPO/2,6-Lutidine in Toluene

2-(2-Methoxyphenoxy)acrylaldehyde (**12**) $[M+H]^+$ (1.58 min, $m/z = 179.20$, calcd.: 179.19); 2,6-dimethoxy-1,4-benzoquinone (**11**) $[M+H]^+$ (1.83 min, $m/z = 169.20$, calcd.: 169.15), 3-hydroxy-1-(4-hydroxy-3,5-dimetho-xyphenyl)-2-(2-methoxyphenoxy)propan-1-one (**13**) $[M+H]^+$ (2.25 min, $m/z = 349.30$, calcd. 349.36), unidentified compounds: * (2.62, 2.88, 3.85 min, unknown compounds).

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