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Aerobic Oxidation of β-1 Lignin Model Compounds with Copper and Oxovanadium Catalysts

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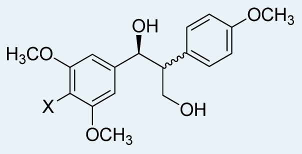
Supporting Information

ABSTRACT: The reactivity of homogeneous oxovanadium and copper catalysts toward aerobic oxidation of phenolic and nonphenolic β-1 lignin model compounds has been investigated. Aerobic oxidation of diastereomeric, nonphenolic β-1 lignin models (**1T**, **1E**) using the six-coordinate vanadium complex $(HQ)_2V^V(O)(O^iPr)$ (HQ = 8-oxyquinolinate) as a precatalyst in pyridine afforded ketone (**3**) and dehydrated ketone (**4**) derived from oxidation of the secondary alcohol. In contrast, using CuOTf/2,6-lutidine/TEMPO (OTf = trifluoromethanesulfonate, TEMPO = 2,2,6,6-tetramethyl-piperidin-1-yl-oxyl) in toluene for the same reaction afforded 3,5-dimethoxybenzaldehyde (**5**) and 4-methoxybenzaldehyde (**6**) as major products resulting from $C_\alpha-C_\beta$ bond cleavage. Reactions of the corresponding phenolic lignin model compounds (**2T**, **2E**) with 10 mol % CuOTf/2,6-lutidine/TEMPO gave ketone (**9**) as the major product, whereas 10 mol % $(HQ)_2V^V(O)(O^iPr)$ or a stoichiometric amount of CuOTf/2,6-lutidine/TEMPO yielded 2,6-dimethoxybenzoquinone (**10**) as the major product, arising from cleavage of the $C_{aryl}-C_\alpha$ bond. Different selectivity was observed in the oxidation of **2T**, **2E** using the five-coordinate complex $(dipic)V^V(O)(O^iPr)$ (dipic = dipicolinate), with α,β-unsaturated aldehyde (**14**) as the major product (formed from oxidation of the primary alcohol and dehydration). The key differences in chemoselectivity between the vanadium and copper catalysts in the oxidations of these phenolic and nonphenolic β-1 lignin models are discussed.



X = H: **1T**, **1E**
X = OH: **2T**, **2E**

KEYWORDS: *aerobic oxidation, lignin model compounds, vanadium, copper, C−C bond cleavage*

INTRODUCTION

In recent years, there has been considerable interest in developing new catalytic processes to derive chemicals and fuels from non-food-based lignocellulosic biomass, an attractive renewable carbon feedstock.[1] Lignin is a randomized polymer consisting of methoxylated phenoxypropyl units and a major biomass constituent (15−30% by weight).[2] As a result of its enzymatic synthesis through radical condensation, lignin has a diverse structure where monomeric units are connected through several different types of linkages, including β-O-4, 5−5′, β-5, 4-O-5, and β-1 (Figure 1). Because of the complex nature and insolubility of lignin, its presence has been identified as a major challenge in the production of biofuels and chemicals from lignocellulose.[3]

Over the last few decades, there has been particular interest in utilizing inexpensive earth-abundant metal catalysts and air or dioxygen for selective oxidation of lignin to value-added aromatic chemicals.[4−20] CuO oxidation has been used extensively to characterize lignin components,[21] with carboxylic acids typically obtained as products. Aldehyde and ketone products are generally more valuable and could serve as versatile intermediates for further functionalization chemistry. Although impressive strides have been reported for the catalytic wet aerobic oxidation process using heterogeneous catalysts[6] and, recently, using ionic liquids as both reaction and separation media,[19] detailed studies of complex lignin models provide the opportunity to better understand the molecular origins of oxidation selectivity. As a result, a number of catalysts have

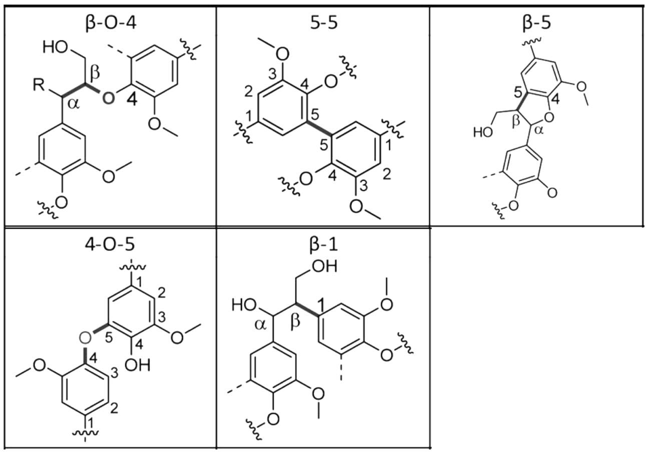


Figure 1. Most prevalent chemical linkages characterized in lignin from spruce trees. Adapted with permission from Zakzeski, J.; Bruijnincx, P. C. A.; Jongerius, A. L.; Weckhuysen, B. M. *Chem. Rev.* **2010**, *110*, 3552−3599. Copyright 2010 American Chemical Society.

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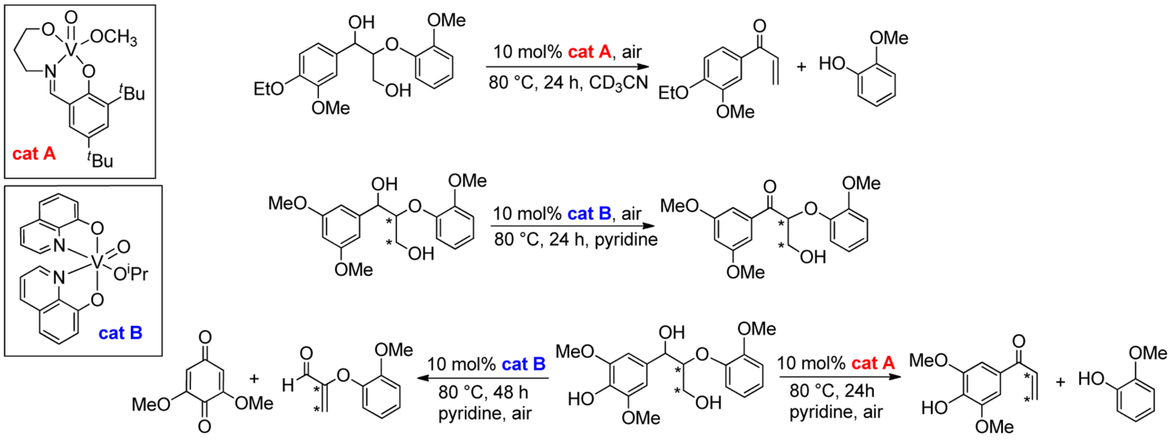
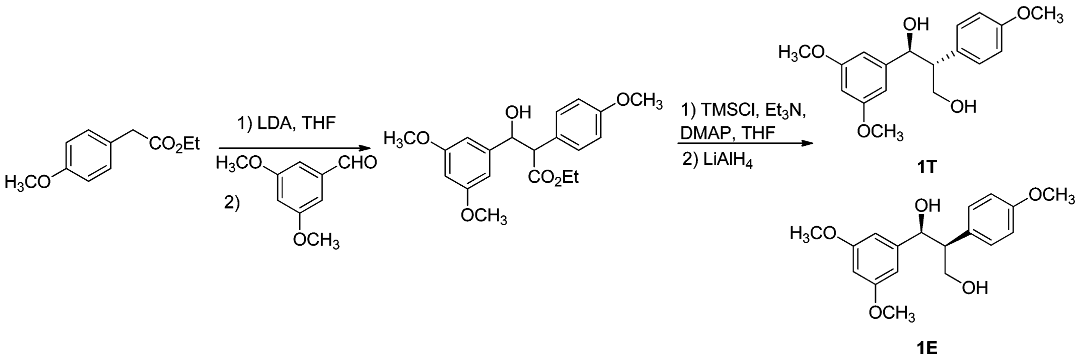


Figure 2. Ancillary ligands on oxovanadium complexes generate disparate oxidation selectivity of complex β-O-4 lignin models. The asterisk (*) symbol indicates a ^{13}C label in the lignin model compound.

Scheme 1. Synthesis of Lignin Model Compounds 1T and 1E



been applied to the oxidation of complex β-O-4 models that contain electron-rich aromatic functionalities, both primary and secondary alcohols, as well as a phenoxy linkage. Recent work from our groups[8] and that of Toste[9] has demonstrated that ancillary ligands in oxovanadium complexes can dictate the selectivity for C−O vs C−C bond cleavage in both phenolic and nonphenolic β-O-4 models. In the Toste work with salen-type ligands,[9a] C−O bond cleavage is favored, and the importance of aryloxy radicals in reoxidizing the V center was noted (Figure 2). In contrast, coaddition of base with 8-oxyquinolinate or dipicolinate−oxovanadium complexes led to secondary alcohol oxidation via a proposed 2e$^-$ base-assisted dehydrogenation mechanism.[8a,d,f] The latter catalysts also effect C−C bond cleavage of the ketone intermediates, affording phenol and carboxylic acid products. Major selectivity differences were found in reactions with phenolic lignin models with the 8-oxyquinolinate precatalysts, again favoring C−C (over C−O) bond cleavage (Figure 2).[8d,22]

We recently compared the activity and selectivity of CuCl/TEMPO and dipicolinate vanadium catalysts for the aerobic oxidation of lignin models.[8c] In particular, the CuCl/TEMPO catalytic system in pyridine was found to effect direct C−C bond cleavage in the β-O-4 lignin models, and subsequently, a more effective copper catalytic system based on CuOTf/2,6-lutidine/TEMPO was developed.[8g] Although this Cu catalyst system offers selectivity similar to that of peroxidase enzymes without the need for hydrogen peroxide, the oxidation mechanism is likely more complicated,[8g,23] and activity is hampered by competing substrate formylation and inhibition by the phenol products.[8g]

The β-1 lignin linkage (Figure 1) can be a significant component in wood lignins (i.e., ∼7−9%)[4] and differs from the β-O-4 linkage by replacement of the O-bound phenoxy unit with a C-bound aryl group. The relative abundance of the β-1 linkage in lignin is somewhat uncertain and may depend on the method of pretreatment.[24] Degradation studies (acidolysis and thioacidolysis) indicate that β-1 structures are prevalent, particularly in hardwood lignins.[25] However, NMR studies of wood have revealed only minor amounts of these structures.[26] This discrepancy may reflect an uneven distribution of the β-1 linkage or that such structures form upon treatment with acid.[27] Herein, we compare the CuOTf/2,6-lutidine/TEMPO catalyst system with oxovanadium complexes supported by dipicolinate and 8-oxyquinolinate ligands for the aerobic oxidation of nonphenolic (**1T**, *threo*; **1E**, *erythro*) and phenolic (**2T**, **2E**) β-1 lignin models. The catalysts exhibit major differences in chemoselectivity. Trends are discussed and compared with those observed previously using analogous β-O-4 lignin models.

■ RESULTS AND DISCUSSION

Synthesis of Phenolic and Nonphenolic β-1 Lignin Model Compounds. The phenolic β-1 lignin model compounds *threo*-1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)-propane-1,3-diol (**2T**), and *erythro*-1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)-propane-1,3-diol (**2E**) were prepared according to a literature procedure.[28] Nonphenolic lignin model compounds **1T** and **1E** were synthesized using an analogous procedure, as shown in Scheme 1 (See the Experimental Section for details). The threo and erythro isomers were purified by silica gel chromatography, and

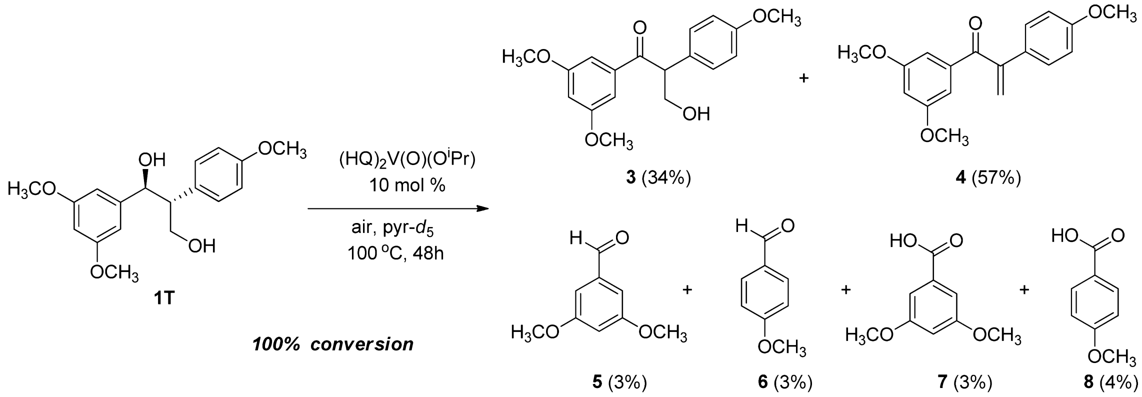


Figure 3. Aerobic oxidation of nonphenolic lignin model compound **1T** using the vanadium precatalyst (HQ)$_2$V^V(O)(O^{i}Pr) in pyr-d_5 affords predominantly products of C−H bond cleavage.

Table 1. Comparison of the Vanadium and Copper-Catalyzed Oxidation of the Non-Phenolic β-1 Lignin Model Compound 1[a]

catalyst (10 mol %)	substrate	solvent	% conv.	product, % yield					
				3	4	5	6	7	8
(HQ)$_2$V(O)(O^{i}Pr)	1T	pyr-d_5	100	34	57	3	3	3	4
(HQ)$_2$V(O)(O^{i}Pr)[b]	1T	DMSO-d_6	91	66	6	3	3	4	11
(HQ)$_2$V(O)(O^{i}Pr)	1E	toluene	100	72	<1	7	2	<1	<1
CuOTf/TEMPO	1T	toluene	100	0	0	81	69	1	1
CuOTf/TEMPO	1E	pyridine	60	3	0	48	15	<1	<1

[a] Ketone (C−H bond cleavage) products are highlighted in blue, and C−C bond cleavage products are highlighted in green. [b] Methanol (2 %) was also formed.

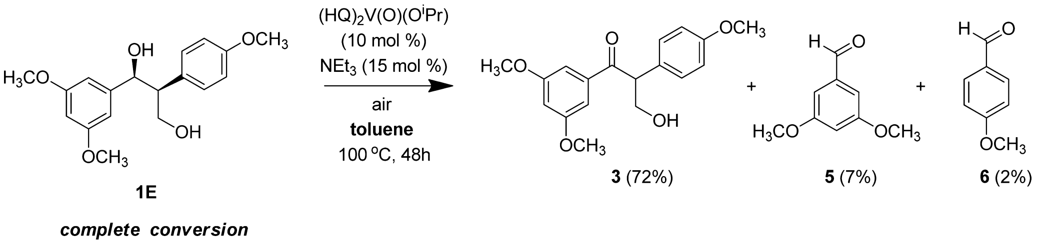


Figure 4. Aerobic oxidation of nonphenolic lignin model compound **1E** using the vanadium precatalyst (HQ)$_2$V^V(O)(O^{i}Pr) (10 mol %) in toluene with added NEt$_3$ (15 mol %) affords predominantly ketone **3**.

compounds **1T**, **1E**, **2T**, and **2E** were characterized by ^{1}H and ^{13}C NMR spectroscopy.

Oxidation Catalysis of Nonphenolic and Phenolic β-1 Lignin Model Compounds. *Nonphenolic β-1 Lignin Models.* To identify potential selectivity differences that could arise between β-O-4 and β-1 lignin model compounds, we tested the six-coordinate vanadium complex (HQ)$_2$V^V(O)(O^{i}Pr) as a precatalyst for aerobic oxidation of the nonphenolic β-1 lignin models **1T** and **1E** in pyridine solvent (HQ = 8-oxyquinolinate). When **1T** was heated with 10 mol % of the precatalyst under air at 100 °C (pyr-d_5, 48 h), complete conversion of the starting material was observed, as judged by integration of the ^{1}H NMR resonances against an internal standard (Figure 3). The major products of this reaction were the ketone **3** (34%) and dehydrated ketone **4** (57%).[29] Additional minor products included 3,5-dimethoxybenzaldehyde, 4-methoxybenzaldehyde, 3,5-dimethoxybenzoic acid, and 4-methoxybenzoic acid (**5**−**8**).

The erythro isomer (**1E**) was oxidized more slowly by the vanadium catalyst with only 76% conversion observed after 48 h, affording a similar product distribution with somewhat lower yields of the ketone **3** (29%) and dehydrated ketone **4** (38%) products (100 °C, pyr-d_5, Supporting Information Figure S1). The identity of the products was confirmed by carrying out the reaction of **1T** on a larger scale; ketone **3** and dehydrated ketone **4** were isolated and characterized by ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry.

In the oxidation of **1T** and **1E**, the dominant pathway of the vanadium-catalyzed reaction is the oxidation of the secondary benzylic alcohol, affording ketone products (~90%). Products arising from C−C bond cleavage were formed in lower yields (<10%). This selectivity for oxidation of the secondary benzylic alcohol parallels that observed in the oxidation of the analogous nonphenolic β-O-4 lignin model compound by the vanadium complex (HQ)$_2$V^V(O)(O^{i}Pr), which afforded primarily ketone products (Figure 2). Previous kinetic and computational studies of the oxyquinolinate vanadium system suggest that oxidation proceeds through a two-electron, base-assisted pathway.[8f] The observed selectivity for oxidation at the secondary benzylic alcohol of **1T** is consistent with such a mechanism.

To assess the potential influence of the solvent on the reaction selectivity,[30] we also carried out the aerobic oxidation of the nonphenolic β-1 lignin model compounds **1T** and **1E** using DMSO as the solvent and the vanadium complex (HQ)$_2$V^V(O)(O^{i}Pr). When the nonphenolic lignin model **1T** was heated with 10 mol % of precatalyst under air at 100 °C

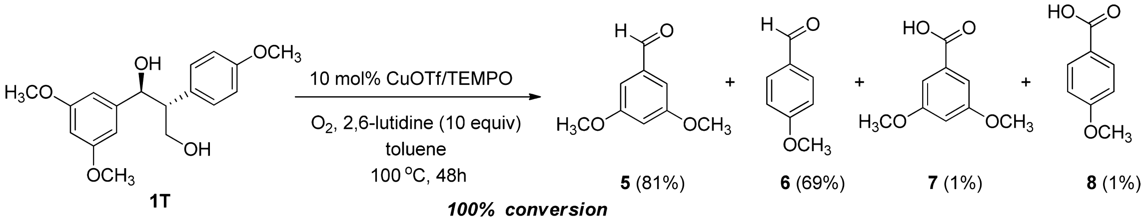


Figure 5. Aerobic oxidation of nonphenolic lignin model compound **1T** using the copper catalyst system CuOTf/TEMPO/2,6-lutidine in toluene solvent affords predominantly products of C−C bond cleavage.

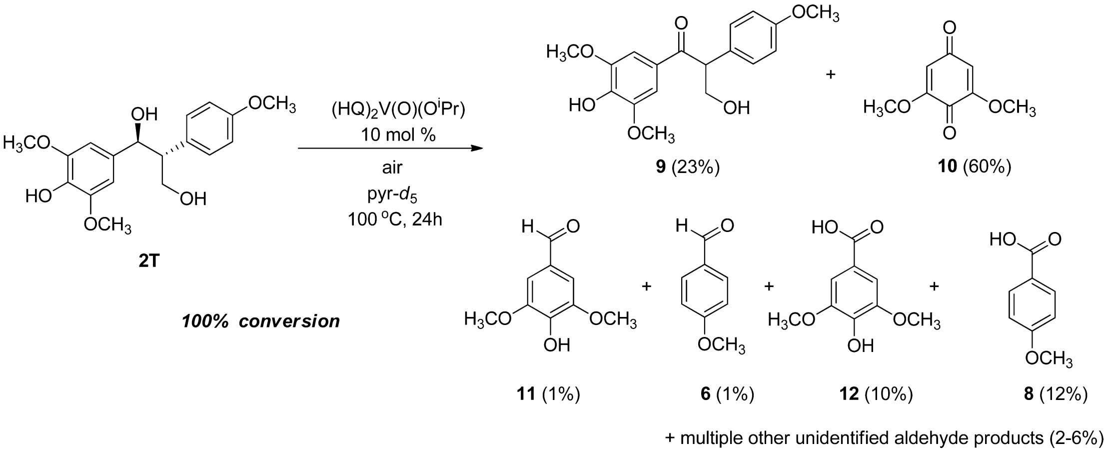


Figure 6. Aerobic oxidation of the phenolic lignin model compound **2T** using the vanadium catalyst $(HQ)_2V^V(O)(O^iPr)$ in pyr-d_5 affords a mixture of C−H and C−C bond cleavage products.

(DMSO-d_6, 48 h), 91% conversion of the starting material was observed after 48 h. The major product of this reaction was the ketone **3** (66%). Additional minor products included the dehydrated ketone **4** (6%), 3,5-dimethoxybenzaldehyde (**5**), 4-methoxybenzaldehyde (**6**), 3,5-dimethoxybenzoic acid (**7**), 4-methoxybenzoic acid (**8**), and methanol (Table 1).

Toluene was also an effective solvent for the oxidation of the β-1 lignin model compounds. Using $(HQ)_2V^V(O)(O^iPr)$ (10 mol %) as a precatalyst in combination with the base promoter NEt_3 (15 mol %), complete conversion of **1E** was observed after heating in toluene for 48 h (100 °C). The major product of this reaction was the ketone **3** (~72%), with minor amounts of 3,5-dimethoxybenzaldehyde (~7%) and 4-methoxybenzaldehyde (~2%) also formed (Figure 4). Overall, changing the solvent from pyridine to toluene did not have a dramatic impact on the reaction selectivity in the vanadium-catalyzed oxidation of **1T** and **1E**; preferential oxidation at the secondary benzylic alcohol position was observed in both cases.

A previous comparison of copper and vanadium catalysts for the aerobic oxidation of β-O-4 lignin model compounds revealed that vanadium and copper catalysts exhibited dramatically different selectivities.[8c] To further evaluate selectivity differences between the vanadium and copper catalysts, the aerobic oxidation of the β-1 lignin models was also carried out using a copper-based catalytic system. When compound **1T** was heated with a combination of CuOTf (10 mol %) and TEMPO (10 mol %) in toluene with added 2,6-lutidine (10 equiv with respect to substrate) under O_2 (1 atm) at 100 °C, complete conversion of the starting material was observed within 48 h (Figure 5). Examination of the ^1H NMR spectrum of the reaction mixture revealed the formation of 3,5-dimethoxybenzaldehyde (**5**, 81%) and 4-methoxybenzaldehyde (**6**, 69%) as the major products (Figure 5). The carboxylic acids 3,5-dimethoxybenzoic acid (**7**) and 4-methoxybenzoic acid (**8**) were also formed in very low yields (~1%). There was no significant difference in reactivity of the two diastereomers **1T** and **1E** with the copper catalyst; comparable yields were observed in both cases. The last entry in Table 1 indicates that better catalyst performance is obtained using bulkier 2,6-lutidine (vs pyridine), as noted previously for the β-O-4 lignin models.[8g] Control experiments were also conducted for **1T** and **1E** under identical conditions but without added copper (with TEMPO and excess 2,6-lutidine under O_2 in toluene at 100 °C). Examination of the ^1H NMR spectrum revealed that no reaction had occurred.

The copper-catalyzed aerobic oxidation of **1T** differs markedly in selectivity from the vanadium-catalyzed reaction (Table 1). For the copper catalyst, aldehyde products arising from C_α−C_β bond cleavage in **1T** dominate, and no ketone products were observed. Here, the selectivity of the copper-catalyzed oxidation of the β-1 lignin model **1T** resembles that observed for β-O-4 lignin model compounds in previously reported copper-catalyzed reactions. Prior work in our laboratories found that aerobic oxidation of a β-O-4 lignin model compound using CuCl/TEMPO afforded primarily products of C−C bond cleavage.[8c,g] A similar observation was noted by Stahl and co-workers, who tested a combination of CuOTf/bpy/TEMPO/*N*-methylimidazole for the aerobic oxidation of a β-O-4 lignin model compound.[20] Veratryl aldehyde was observed as a major product, which was attributed to initial oxidation of the primary alcohol, followed by a retro-aldol reaction to break the C_α−C_β bond.[31] Alternatively, the C−C bond cleavage reaction could proceed by an initial one-electron oxidation, forming a radical cation that undergoes subsequent C−C bond fission. In support of this idea, Langan and co-workers have studied the oxidation of both β-O-4 and

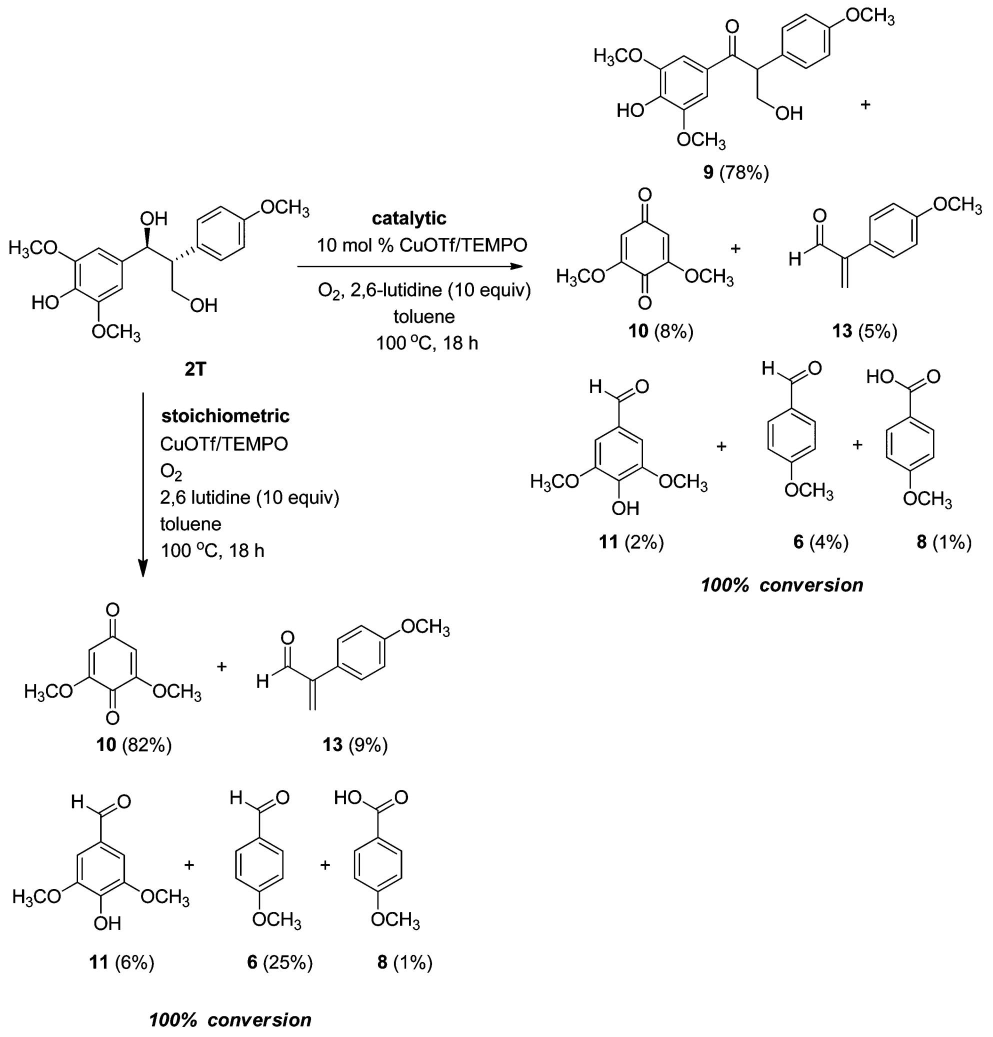


Figure 7. Comparison of the oxidation of phenolic lignin model compound **2T** using catalytic (10 mol %) vs stoichiometric CuOTf/TEMPO.

β-1 lignin model compounds by several one-electron oxidants; products of $C_\alpha-C_\beta$ bond fission were observed.[7] The manganese peroxidase enzyme, which catalyzes the natural degradation of lignin, is also proposed to react by a one-electron oxidation pathway.[32]

Phenolic β-1 Lignin Models. Prior studies of the aerobic oxidation of β-O-4 lignin model compounds suggested that important selectivity differences could occur between phenolic and nonphenolic lignin model compounds.[8d] Consequently, we tested $(HQ)_2V^V(O)(O^iPr)$ as a precatalyst for the aerobic oxidation of the phenolic β-1 lignin model compounds **2T** and **2E**. When compound **2T** was heated with 10 mol % of the precatalyst under air in pyridine at 100 °C, complete consumption of the starting material was observed (Figure 6). The major products of this reaction were the ketone **9** (23%) and 2,6-dimethoxybenzoquinone (**10**, 60%). In addition, multiple minor products formed, including 4-hydroxy-3,5-dimethoxybenzoic acid (**13**), 4-hydroxy-3,5-dimethoxybenzaldehyde (**12**), 4-methoxybenzoic acid (**8**), 4-methoxybenzaldehyde (**6**), and several unidentified aldehyde species (1−12% yields, see Figure 6). In the catalytic aerobic oxidation of the erythro isomer **2E** using $(HQ)_2V^V(O)(O^iPr)$, complete conversion of the starting material was also observed, affording the ketone **9** (7%), 2,6-dimethoxybenzoquinone (**10**, 43%), and minor amounts of the corresponding carboxylic acid and aldehyde products. The identity of ketone **9** was confirmed by isolation from a larger scale reaction mixture; compound **9** was characterized by ^1H and ^{13}C NMR spectroscopy and HRMS analysis. In control experiments conducted under identical conditions with no added catalyst, no reaction of **2T** was observed.

In the reactions of the phenolic lignin model compounds **2E** and **2T**, an incomplete mass balance was obtained; however, no additional major products were evident in the ^1H NMR spectrum of the reaction mixture which could account for all of the missing material, and the reaction mixture was a dark brown color with some solid material formed. An incomplete mass balance in the oxidation of lignin model compounds has been noted in previous reports and has been attributed to polymerization or other reactions of radical intermediates.[33] To evaluate this idea, the aerobic oxidation of 2,6-dimethoxyphenol was carried out using the vanadium complex $(HQ)_2V^V(O)(O^iPr)$ (5 mol %) as a precatalyst with added base (NEt_3, 10 mol %). After 24 h of heating at 80 °C, more than 98% of the 2,6-dimethoxyphenol had reacted, affording a dark brown solid. No soluble organic products were detected in the ^1H NMR spectrum of an aliquot of the reaction mixture ($CDCl_3$), consistent with polymerization or other reactions to afford intractable solid products.[33]

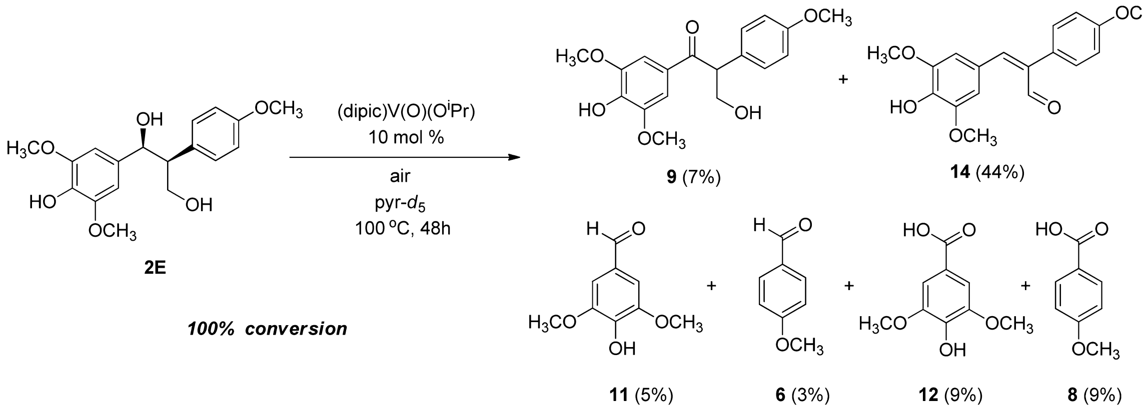


Figure 8. Oxidation of phenolic lignin model compound **2E** using catalytic (10 mol %) (dipic)$V^V(O)(O^iPr)$ yields an aldehyde derived from oxidation of the primary alcohol.

Table 2. Comparison of the Vanadium and Copper-Catalyzed Oxidation of the Phenolic β-1 Lignin Model Compound 2[a]

catalyst (10 mol %)	substrate	solvent	product, % yield							
			9	10	11	6	12	8	13	14
$(HQ)_2V^V(O)(O^iPr)$	2T	pyr-d_5	23	60	1	1	10	12	0	0
$(dipic)V^V(O)(O^iPr)$	2E	pyr-d_5	7	<2	5	3	9	9	0	44
CuOTf/TEMPO	2T	toluene	78	8	2	4	0	1	5	0
stoichiometric CuOTf/TEMPO	2T	toluene	0	82	6	25	0	1	9	0

[a]The ketone product is highlighted in blue, C−C bond cleavage products are highlighted in green, and the primary alcohol oxidation product **14** is highlighted in pink.

For the vanadium-catalyzed oxidations, the incorporation of a phenolic group into the substrate had a significant impact on the reaction selectivity. Although the nonphenolic lignin model compound **1T** was oxidized at the secondary alcohol position to give ketone products, the phenolic model compound **2T** underwent $C_{aryl}-C_\alpha$ bond cleavage to generate the 2,6-dimethoxybenzoquinone product. A similar trend was previously noted in the oxidation of phenolic and nonphenolic β-O-4 lignin model compounds using the vanadium catalyst $(HQ)_2V^V(O)(O^iPr)$.[8d] The formation of quinone products upon oxidation of phenolic β-O-4, β-1, and β-5 model compounds has also been observed by Crestini and co-workers,[11] and Bozell et al.,[18] who reported several cobalt-catalyzed reactions. In the cobalt systems, the $C_{aryl}-C_\alpha$ bond cleavage was proposed to proceed through a radical pathway involving a cobalt−superoxo intermediate.[34,35]

We were interested in evaluating the selectivity of the copper-catalyzed oxidation of the phenolic β-1 lignin model compound, but previous work in our lab suggested that the copper catalyst is inhibited by phenolic functionalities.[8c,g] Consequently, the oxidation of the phenolic β-1 lignin model compound **2T** was tested with both catalytic copper (10 mol %) and stoichiometric copper (Figure 7). With the catalytic copper load, **2T** was heated with CuOTf/TEMPO (10 mol %) in toluene with added 2,6-lutidine (10 equiv with respect to substrate) under oxygen in toluene at 100 °C. Complete consumption of the starting material **2T** was observed within 18 h, affording ketone **9** (78%), 2,6-dimethoxybenzoquinone (**10**, 8%), 4-methoxybenzaldehyde (**6**), acrylaldehyde (**13**), syringaldehyde (**11**), and 4-methoxybenzoic acid (**8**) as products (1−5% yields, Figure 7). Formation of ketone **9** is suggestive of a mechanism change as observed previously with β-O-4 models at low Cu loadings.[8g]

The reaction selectivity changed when a stoichiometric amount of CuOTf/TEMPO was used for the oxidation. Complete consumption of **2T** occurred, affording 2,6-dimethoxybenzoquinone (**10**, 82%) and 4-methoxybenzaldehyde (**6**, 25%) as the major products. The acrylaldehyde (**13**, 9%), syringaldehyde (**11**, 6%), and 4-methoxybenzoic acid (**8**) were formed as minor products (Figure 7). The products were identified and quantified by GC/MS and ^1H NMR spectroscopy. The observed selectivity for C−C bond cleavage in **2T** with stoichiometric copper is consistent with the general tendency of the copper systems to catalyze C−C bond cleavage.

Given the range of selectivities observed in the aerobic oxidation of the β-1 lignin model compounds, we tested the 5-coordinate vanadium complex $(dipic)V^V(O)(O^iPr)$ as a precatalyst for the aerobic oxidation of the phenolic β-1 lignin model **2E**. On heating **2E** with 10 mol % of the precatalyst under air (100 °C, 48 h, pyr-d_5), complete conversion of the starting material was observed (^1H NMR spectroscopy). The formation of a new aldehyde product **14** (44%) was detected (Figure 8). Compound **14** was identified by carrying out a reaction on a larger scale, isolating the product, and characterizing it by ^1H and ^{13}C NMR spectroscopy and HRMS. Other minor products of the reaction included the ketone **9**, 4-hydroxy-3,5-dimethoxybenzoic acid (**12**), 4-hydroxy-3,5-dimethoxybenzaldehyde (**11**), 4-methoxybenzoic acid (**8**), and 4-methoxybenzaldehyde (**6**). The formation of aldehyde **14** was unanticipated; compound **14** was not observed as a product with the vanadium precatalyst $(HQ)_2V^V(O)(O^iPr)$, and its mechanism of formation is unclear at this time. Complex **14** apparently results from oxidation of the primary alcohol and dehydration of the secondary alcohol in **2E**. The product distributions from each of the vanadium and copper catalyzed oxidations of the phenolic β-1 model compound are shown in Table 2.

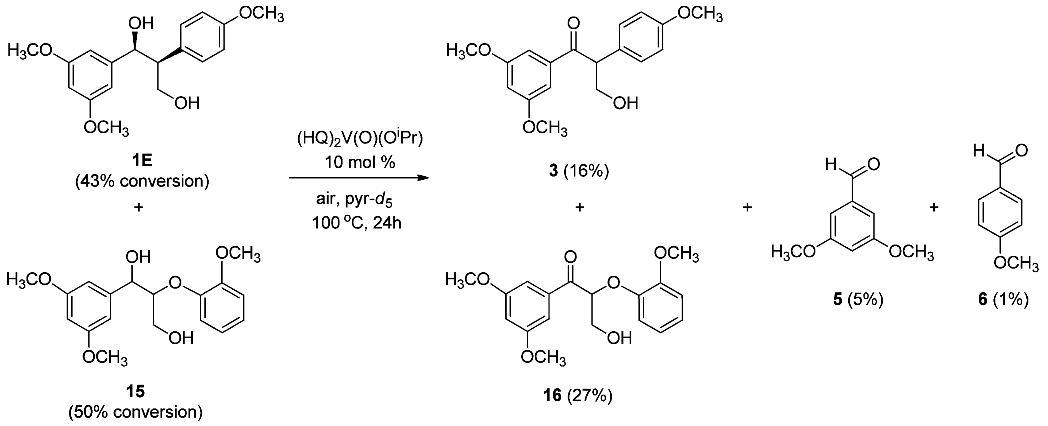


Figure 9. Aerobic oxidation of a 1:1 mixture of *β*-1 (**1E**) and *β*-O-4 (**15**) lignin model compounds using the vanadium precatalyst $(HQ)_2V^V(O)(O^iPr)$.

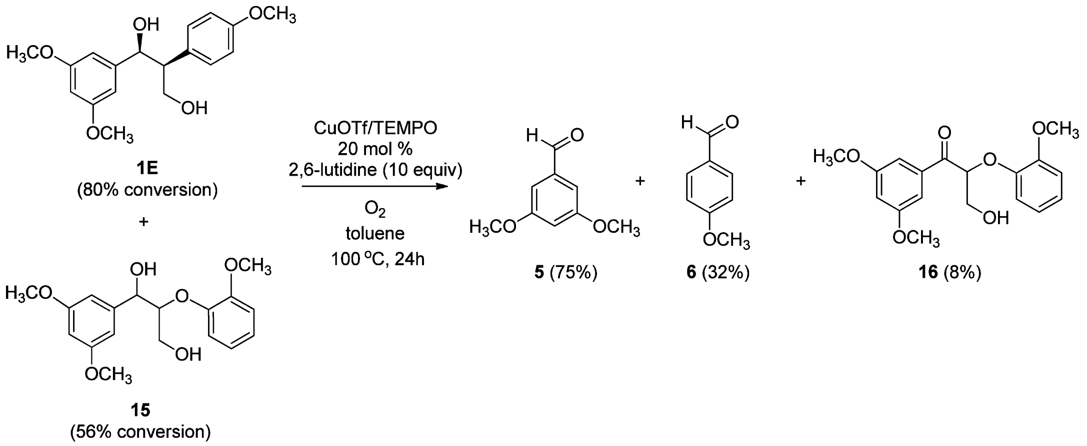


Figure 10. Aerobic oxidation of a 1:1 mixture of *β*-1 (**1E**) and *β*-O-4 (**15**) lignin model compounds using CuOTf/TEMPO (20 mol %) with added 2,6-lutidine (10 equiv).

Competitive Oxidation of *β*-O-4 and *β*-1 Lignin Model Compounds. Internal competition experiments were carried out to assess the relative reactivities of the vanadium and copper catalysts with *β*-O-4 and *β*-1 lignin model compounds. A 1:1 mixture of **1E** and the *β*-O-4 lignin model compound **15** (Figure 9) was heated under air with the vanadium precatalyst $(HQ)_2V^V(O)(O^iPr)$ (10 mol %) in pyr-d_5 solvent. After 24 h, ~50% conversion of **15** and ~43% conversion of **1E** were observed. The products of this reaction were a mixture of ketone **16** (~27%, derived from **15**) and ketone **3** (~16%, derived from **1E**). 3,5-Dimethoxybenzaldehyde (**5**, 5%) and 4-methoxybenzaldehyde (**6**, 1%) were also observed as minor products. The predominant selectivity of the vanadium catalyst for oxidation of the secondary benzylic alcohol was maintained, and the *β*-O-4 lignin model compound reacted only slightly faster than the *β*-1.

The oxidation of a 1:1 mixture of *β*-O-4 and *β*-1 lignin model compounds was also carried out using the copper catalyst system (Figure 10). Model compounds **15** and **1E** were heated in toluene under O_2 with a combination of CuOTf (20 mol %), TEMPO (20 mol %), and 2,6-lutidine (10 equivalents). After 24 h, ~80% of the *β*-1 lignin model **1E** had reacted, and only ~56% of the *β*-O-4 lignin model compound **15** had reacted. The major products of this reaction consisted of 3,5-dimethoxybenzaldehyde (**5**, 75%), 4-methoxybenzaldehyde (**6**, 32%), and ketone **16** (8%). These results suggest that the *β*-1 lignin model reacts somewhat faster than the *β*-O-4 lignin model with the copper catalyst and confirm that the copper-catalyzed oxidation reactions proceed with selectivity for C−C bond cleavage for both substrates.

■ SUMMARY AND CONCLUSIONS

Major selectivity differences are observed in the copper- and vanadium-catalyzed aerobic oxidation reactions. Although both metals are effective catalysts for the aerobic oxidation of the nonphenolic *β*-1 lignin model compound **1**, the vanadium precatalyst $(HQ)_2V^V(O)(O^iPr)$ affords primarily ketone products, whereas the copper catalytic system (CuOTf/TEMPO) generates products of C−C bond cleavage. These selectivity trends parallel the reactivity previously reported for the *β*-O-4 lignin model compounds, likely reflecting different mechanisms of oxidation between vanadium and copper catalysts. For the copper catalysts, the C−C bond cleavage reaction may proceed through a pathway involving either a one-electron oxidation or a selective oxidation of the primary alcohol position, followed by a retro-aldol reaction. The products observed in the vanadium catalyzed reaction are more consistent with a two-electron oxidation pathway, in line with previous studies of the reactivity of $(HQ)_2V^V(O)(O^iPr)$.

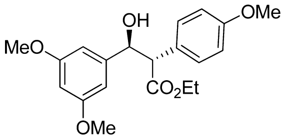
The reactivity of both catalysts changed dramatically upon incorporation of a phenolic group into the *β*-1 lignin model compound, and a different type of C−C (C_{aryl}−C_α) bond cleavage was observed upon oxidation of the phenolic β-1 model compound **2**. Although the copper catalyst was inhibited by the phenolic functionality, oxidation of **2** with stoichiometric CuOTf/TEMPO afforded 2,6-dimethoxybenzoquinone and 4-methoxybenzaldehyde, coproducts arising from breaking the $C_{aryl}-C_{\alpha}$ bond of **2**. The vanadium complex $(HQ)_2V^V(O)(O^iPr)$ also yielded products of $C_{aryl}-C_{\alpha}$ bond cleavage, 2,6-dimethoxybenzoquinone and 4-methoxybenzoic acid. The incorporation of the phenolic group had a detrimental impact on the selectivity for the formation of monomeric products, with lower product yields and some formation of solids detected with both copper and vanadium catalysts.[35]

The diversity of pathways available to copper and vanadium catalysts highlights the challenges associated with controlling reaction selectivity in the aerobic oxidation of lignin, where multiple different linkages and functional groups are present. These results suggest that for the development of catalytic reactions, testing catalyst reactivity with more than one type of linkage model may be useful in trying to fully evaluate the selectivity. Given the complexity of structures present within lignin as well as the multiple reaction modes available to earth-abundant metal catalysts, reaction selectivity could be otherwise difficult to predict. Despite these challenges, the different selectivities exhibited by the copper and vanadium catalysts provide a promising indication that it may be possible to influence or control selectivity in the aerobic oxidation of lignin.

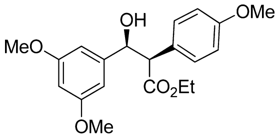
■ EXPERIMENTAL SECTION

General Considerations. Unless specified otherwise, all reactions were carried out in the presence of air. ^{1}H and ^{13}C{^{1}H} NMR spectra were obtained at room temperature on a Bruker AV400 MHz spectrometer, with chemical shifts (δ) referenced to the residual solvent signal. GC/MS analysis was performed using a Hewlett-Packard 6890 GC system equipped with a Hewlett-Packard 5973 mass selective detector. Deuterated solvents were purchased from Cambridge Isotope Laboratories and dried with molecular sieves. $(CuOTf)_2\cdot$toluene, 2,6-lutidine, and TEMPO were purchased from Sigma Aldrich. The phenolic β-1 lignin model compounds *threo*-1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)-propane-1,3-diol (**2T**), and *erythro*-1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)-propane-1,3-diol (**2E**) were synthesized according to a literature procedure.[28] Oxygen was purchased from Linde Canada.

Synthesis of Nonphenolic β-1 Lignin Model Compounds (1T and 1E). To a solution of diisopropylamine (1.85 mL, 13.2 mmol) in THF (18.0 mL) was added *n*-butyllithium (8.25 mL, 13.2 mmol, 1.6 M in hexanes) dropwise via syringe pump at 0 °C. The mixture was stirred at this temperature for 20 min and then cooled to −78 °C. A solution of ethyl 2-(4-methoxyphenyl)acetate (2.33 g, 12.0 mmol) in THF (12.0 mL) was added dropwise via a cannula, followed by addition of a solution of 3,5-dimethoxybenzaldehyde (1.99 g, 12.0 mmol) in THF (6.0 mL) via a cannula. The mixture was stirred at this temperature for 1 h, and then saturated ammonium chloride solution was added to quench the reaction. The mixture was warmed to room temperature and extracted with diethyl ether; the combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. Diethyl ether was then added, and the mixture was stirred at room temperature overnight. The solids were filtered and washed with diethyl ether to provide 0.191 g (4.4%) of the threo isomer (2*S*,3*S*)-ethyl 3-(3,5-dimethoxyphenyl)-3-hydroxy-2-(4-methoxyphenyl)propanoate. The filtrate was concentrated and purified on silica gel with 25% ethyl acetate in hexanes to provide 1.034 g (23.9%) of the erythro isomer (2*R*,3*S*)-ethyl 3-(3,5-dimethoxyphenyl)-3-hydroxy-2-(4-methoxyphenyl)propanoate and 2.38 g (55.0%) of a mixture of both isomers.



(2*S*,3*S*)-Ethyl 3-(3,5-dimethoxyphenyl)-3-hydroxy-2-(4-methoxyphenyl)propanoate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, 2H, *J* = 8.7 Hz, aryl), 6.86 (d, 2H, *J* = 8.7 Hz, aryl), 6.45 (d, 2H, *J* = 2.2 Hz, aryl), 6.36 (t, 1H, *J* = 2.2 Hz, aryl), 5.19 (d, 1H, *J* = 7.2 Hz, ArC*H*OH), 4.04 (m, 2H, OCH_2CH_3), 3.80 (s, 3H, $-OCH_3$), 3.74 (s, 6H, $-OCH_3$), 1.10 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.0, 160.7, 159.5, 143.4, 130.5, 126.8, 114.2, 104.7, 100.4, 75.2, 61.2, 58.8, 55.5, 55.4, 14.2.



(2*R*,3*S*)-Ethyl 3-(3,5-dimethoxyphenyl)-3-hydroxy-2-(4-methoxyphenyl)propanoate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, 2H, *J* = 8.7 Hz, aryl), 6.74 (d, 2H, *J* = 8.7 Hz, aryl), 6.26 (m, 3H, aryl), 5.07 (dd, 1H, *J* = 9.2, 4.2 Hz, ArC*H*OH), 4.19 (m, 2H, OCH_2CH_3), 3.78 (d, 1H, *J* = 9.1 Hz), 3.75 (s, 3H, $-OCH_3$), 3.67 (s, 6H, $-OCH_3$), 1.23 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.9, 160.6, 159.1, 143.5, 129.8, 127.6, 114.0, 104.6, 100.2, 61.4, 59.0, 55.5, 55.4, 19.6, 14.3.

***Threo*-1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)-propane-1,3-diol (1T).** To a solution of (2*S*,3*S*)-ethyl 3-(3,5-dimethoxyphenyl)-3-hydroxy-2-(4-methoxyphenyl)-propanoate (2.14 g, 5.95 mmol) and triethylamine (1.20 g, 1.66 mL, 11.9 mmol) in tetrahydrofuran (27.0 mL) was added chlorotrimethylsilane (0.97 g, 1.1 mL, 8.9 mmol) dropwise via a syringe at 0 °C, followed by addition of 4-(*N*,*N*-dimethylamino)pyridine (10 mg). The mixture was allowed to warm to room temperature and stirred for 15 min and then cooled using an ice bath. Lithium aluminum hydride (0.452 g, 11.9 mmol) was added portionwise to the reaction mixture, and then it was allowed to warm to room temperature and stirred for 30 min, at which time TLC analysis revealed that the reaction was complete. The mixture was cooled using an ice bath and then quenched by sequential addition of 450 μL of H_2O, 450 μL of 15% aqueous KOH, and 3 × 450 μL of H_2O. The precipitate was filtered and washed thoroughly with diethyl ether. The solvent was removed under reduced pressure, and the residue was purified on silica gel with 45% ethyl acetate in hexanes to provide 1.202 g (63%) of the title product as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, 2H, *J* = 8.4 Hz, aryl), 6.85 (d, 2H, *J* = 8.4 Hz, aryl), 6.38 (d, 2H, *J* = 2.4 Hz, aryl), 6.36 (t, 1H, *J* = 2.4 Hz, aryl), 4.88 (d, 1H, *J* = 6.8 Hz, ArC*H*OH), 3.79 (s, 3H, $-OCH_3$), 3.77−3.70 (m, 2H, C*H*$_2$OH), 3.73 (s, 6H, $-OCH_3$), 3.07 (q, 1H, *J* = 7.2 Hz, C*H*Ar). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 160.8, 159.0, 144.8, 130.4, 130.3, 114.2, 104.6, 100.0, 75.9, 64.3, 55.5, 55.4, 54.8. ESI/MS: Calculated m/*z* [**1T** + Na] = 341.1, found 341.4.

***Erythro*-1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)-propane-1,3-diol (1E).** To a solution of (2*R*,3*S*)-ethyl 3-(3,5-dimethoxyphenyl)-3-hydroxy-2-(4-methoxyphenyl)-propanoate (3.024 g, 8.39 mmol) and triethylamine (1.70 g, 2.34 mL, 16.8 mmol) in tetrahydrofuran (48 mL) was added chlorotrimethylsilane (1.37 g, 1.60 mL, 12.6 mmol) dropwise via a syringe at 0 °C, followed by addition of 4-(*N*,*N*-dimethylamino)pyridine (10 mg). The mixture was allowed to warm to room temperature, stirred for 15 min, and then cooled using an ice bath. Lithium aluminum hydride (0.637 g, 16.8 mmol) was added portionwise to the reaction mixture, and it was allowed to warm to room temperature and stirred for 30 min, at which time TLC analysis revealed that the reaction was complete. The mixture was cooled using an ice bath and then quenched by sequential addition of 640 μL of H_2O, 640 μL of 15% aqueous KOH, and 3 × 640 μL of H_2O. The precipitate was filtered and washed thoroughly with diethyl ether. The solvent was removed from the filtrate under reduced pressure, and the residue was purified on silica gel with 45% ethyl acetate in hexanes to provide 2.091 g (78%) of the title product as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, 2H, J = 8.4 Hz, aryl), 6.76 (d, 2H, J = 8.4 Hz, aryl), 6.32 (d, 2H, J = 2.0 Hz, aryl), 6.29 (t, 1H, J = 2.0 Hz, aryl), 4.95 (d, 1H, J = 8.4 Hz, ArC*H*OH), 4.17 (dd, 1H, J = 10.8 Hz, J = 7.2 Hz, C*H*$_2$OH), 3.96 (dd, 1H, J = 10.8 Hz, J = 4.8 Hz, C*H*$_2$OH), 3.75 (s, 3H, $-OCH_3$), 3.70 (s, 6H, $-OCH_3$), 3.11 (m, 1H, C*H*Ar). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 160.8, 158.7, 145.6, 131.4, 129.7, 114.1, 104.7, 99.9, 66.5, 63.2, 55.5, 55.4, 54.0. Calculated m/*z* [**1E** + Na] = 341.1, found 341.4.

General Procedure for the Vanadium Catalyzed Oxidation of β-1 Lignin Model Compounds. In an NMR tube, the lignin model compound (~20 mg, ~0.06 mmol) was dissolved in pyr-*d*$_5$ (1 mL) containing dimethylsulfone added as an internal standard. An initial ^{1}H NMR spectrum was recorded, and then the solution was added to a 50 mL round-bottom flask containing $(HQ)_2V(O)(O^iPr)$ (~2.5 mg, ~0.006 mmol). The flask was equipped with a stir bar and an air condenser and then heated with stirring under air at 100 °C for 48 h. The reaction mixture was cooled to room temperature and then transferred into an NMR tube. The extent of conversion and yields of the products were determined by integration of the ^{1}H NMR spectrum against the internal standard.

Catalytic Oxidation of Nonphenolic β-1 Lignin Model 1T Using 10 mol % $(HQ)_2V(O)(O^iPr)$ in Pyr-*d*$_5$. Compound **1T** (20 mg, 0.063 mmol) was oxidized following the general procedure described above for the vanadium-catalyzed reactions. After 48 h, integration of the ^{1}H NMR spectrum against the internal standard revealed that all of **1T** had reacted, affording the ketone (**3**, 34%), the dehydrated ketone (**4**, 57%), 4-methoxybenzoic acid (**8**, 4%), 3,5-dimethoxybenzoic acid (**7**, 3%), 4-methoxybenzaldehyde (**6**, 3%), and 3,5-dimethoxybenzaldehyde (**5**, 3%).

Catalytic Oxidation of Nonphenolic β-1 Lignin Model 1E Using 10 mol % $(HQ)_2V(O)(O^iPr)$ in Pyr-*d*$_5$. This reaction was carried out using the general procedure for the vanadium-catalyzed oxidations. After 48 h, examination of the ^{1}H NMR spectrum revealed that 76% conversion had occurred, affording the ketone (**3**, 29%), dehydrated ketone (**4**, 38%), 4-methoxybenzoic acid (**8**, 6%), 3,5-dimethoxybenzoic acid (**7**, 8%), 4-methoxybenzaldehyde (**6**, 4%), and 3,5-dimethoxybenzaldehyde (**5**, 4%).

The ketone (**3**) and dehydrated ketone (**4**) were isolated by prep-scale TLC, eluting with 7:3 hexanes:ethylacetate.

*Ketone (**3**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, 2H, J = 8.8 Hz, aryl), 7.08 (d, 2H, J = 2.0 Hz, aryl), 6.85 (d, 2H, J = 8.8 Hz, aryl), 6.58 (t, 1H, J = 2.0 Hz, aryl), 4.70−4.66 (m, 1H, ArC*H*), 4.25−4.21 (m, 1H, C*H*$_2$OH), 3.86−3.79 (m, 1H, C*H*$_2$OH), 3.77 (s, 6H, $-OCH_3$), 3.76 (s, 3H, $-OCH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 200.8, 160.9, 159.3, 138.4, 129.6, 114.9, 107.1, 105.8, 65.3, 55.9, 55.7, 55.4, 42.9. HRMS (EI): *m*/*z* calcd for $C_{18}H_{20}O_5$ $[M + H]^+$: 317.1389; found: 317.1387.

*Dehydrated Ketone (**4**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, 2H, J = 8.8 Hz, aryl), 7.06 (d, 2H, J = 2.4 Hz, aryl), 6.88 (d, 2H, J = 8.8 Hz, aryl), 6.65 (t, 1H, J = 2.4 Hz, aryl), 5.96 (s, 1H, C=C*H*H), 5.36 (s, 1H, C=CH*H*), 3.82 (s, 3H, $-OCH_3$), 3.81 (s, 6H, $-OCH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 197.7, 160.9, 160.0, 147.8, 139.3, 128.5, 119.1, 114.3, 108.0, 105.9, 105.2, 55.8, 55.5. HRMS (EI): *m*/*z* calcd for $C_{18}H_{18}O_4$ $[M + H]^+$: 299.1283; found: 299.1277.

Catalytic Oxidation of Nonphenolic β-1 Lignin Model 1T Using 10 mol % $(HQ)_2V(O)(O^iPr)$ in DMSO-*d*$_6$. Compound **1T** (20 mg, 0.063 mmol) was oxidized following the general procedure for the vanadium-catalyzed reactions using DMSO-*d*$_6$ (1 mL) as the solvent. After 48 h, integration of the ^{1}H NMR spectrum against the internal standard revealed 91% conversion of the starting material, affording the ketone (**3**, 66%), the dehydrated ketone (**4**, 6%), 4-methoxybenzoic acid (**8**, 11%), 3,5-dimethoxybenzoic acid (**7**, 4%), 4-methoxybenzaldehyde (**6**, 3%), 3,5-dimethoxybenzaldehyde (**5**, 3%), and methanol (2%).

Catalytic Oxidation of Nonphenolic β-1 Lignin Model 1E Using 10 mol % $(HQ)_2V(O)(O^iPr)$ in DMSO-*d*$_6$. This reaction was carried out following the general procedure for the vanadium-catalyzed aerobic oxidations. After 48 h, examination of the ^{1}H NMR spectrum against the internal standard revealed 42% of **1E** reacted, affording the ketone (**3**, 27%), the dehydrated ketone (**4**, <1%), 4-methoxybenzoic acid (**8**, 10%), 3,5-dimethoxybenzoic acid (**7**, 3%), 4-methoxybenzaldehyde (**6**, 4%), 3,5-dimethoxybenzaldehyde (**5**, 8%), and methanol (2%).

Catalytic Oxidation of Nonphenolic β-1 Lignin Model 1E Using 10 mol % $(HQ)_2V(O)(O^iPr)$ in Toluene with Added NEt_3 (15 mol %). This reaction was carried out using the general procedure for the vanadium-catalyzed oxidations, except using toluene as the solvent and triethylamine (15 mol %) as a base promoter. In addition, the reaction was heated under air at 100 °C using a water condenser. After 48 h, examination of the ^{1}H NMR spectrum revealed that all of **1E** had been consumed, affording the ketone **3** (72%), 3,5-dimethoxybenzaldehyde (**5**, 7%), and 4-methoxybenzaldehyde (**6**, 2%).

General Procedure for the Aerobic Oxidation of β-1 Lignin Model Compounds Using CuOTf/TEMPO (10 mol %) with 2,6-Lutidine (10 equiv). In an NMR tube, the β-1 lignin model compound (~12 mg, ~0.038 mmol) was dissolved in $CDCl_3$ (1 mL) containing dimethylsulfone (~1 mg, ~0.01 mmol) as an internal standard. An initial spectrum was recorded, and then the solvent was removed under vacuum. The solid material was redissolved in toluene (5 mL) and then transferred to a thick-walled 50 mL Schlenk tube equipped with Teflon stopcock containing $[(CuOTf)_2\cdot toluene]$ (~2 mg, ~0.004 mmol), TEMPO (0.6 mg, 0.004 mmol), and 2,6-lutidine (~0.044 mL, ~0.38 mmol) under air. Oxygen was bubbled into the reaction mixture for 3 min, and the reactor was sealed. The reaction mixture was heated at 100 °C with constant stirring. After 18 h, the reaction was cooled to room temperature, oxygen was bubbled again through the solution for 2 min, the reactor was sealed, and the reaction mixture was heated at 100 °C. After 48 h, the reaction was cooled to room temperature. An aliquot was taken from the reaction mixture, the solvent was removed under weak vacuum (~100 Torr), and $CDCl_3$ was added to the residue. The mixture was then filtered through glass wool, and the extent of conversion and yields of the products were determined by ^1H NMR spectroscopy (integration of the spectrum against the internal standard). Where indicated, the identity of the products was also verified by GC/MS analysis.

Catalytic Oxidation of Nonphenolic *β*-1 Lignin Model 1T Using 10 mol % CuOTf/TEMPO with 2,6-Lutidine (10 equiv) in Toluene. Compound **1T** was oxidized following the general procedure for the copper-catalyzed aerobic oxidation reactions. After 48 h, integration of the ^1H NMR spectrum against the internal standard revealed that all of **1T** had reacted, with the products consisting of 3,5-dimethoxybenzaldehyde (**5**, 81%), 4-methoxybenzaldehyde (**6**, 69%), 3,5-dimethoxybenzoic acid (**7**, 1%), and 4-methoxybenzoic acid (**8**, 1%). The products were identified and quantified by ^1H NMR spectroscopy and GC/MS. Yields are expressed as a percentage of the theoretical maximum based on the initial amount of substrate.

Catalytic Oxidation of Nonphenolic *β*-1 Lignin Model 1E Using 10 mol % CuOTf/TEMPO with 2,6-Lutidine (10 equiv) in Toluene. This reaction was carried out according to the general procedure for the copper-catalyzed aerobic oxidations. After 48 h, integration of the ^1H NMR spectrum against the internal standard revealed that all of **1E** had been consumed, with the products consisting of 3,5-dimethoxybenzaldehyde (**5**, 78%), 4-methoxybenzaldehyde (**6**, 60%), 3,5-dimethoxybenzoic acid (**7**, 1%), and 4-methoxybenzoic acid (**8**, 1%). The products were identified and quantified by ^1H NMR and GC/MS.

Attempted Oxidation of Nonphenolic *β*-1 Lignin Model 1T Using 10 mol % TEMPO with 2,6-Lutidine (10 equiv) in Toluene (control experiment with no copper catalyst). This reaction was carried out using the general procedure for the copper complex-catalyzed aerobic oxidations, except that no copper catalyst was added. After 48 h, the reaction mixture was examined by ^1H NMR spectroscopy. No reaction had occurred.

Attempted Oxidation of Nonphenolic *β*-1 Lignin Model 1E Using 10 mol % TEMPO with 2,6-Lutidine (10 equiv) in Toluene (control experiment with no copper catalyst). This control experiment was carried out using the same general procedure for the copper complex-catalyzed aerobic oxidations, except that no copper catalyst was added. After 48 h, an aliquot of the reaction mixture was examined by ^1H NMR spectroscopy. No reaction had occurred.

Catalytic Oxidation of Nonphenolic *β*-1 Lignin Model 1E Using 10 mol % CuOTf/TEMPO in Pyridine. This reaction was carried out using the general procedure for the copper-catalyzed aerobic oxidations, except pyridine was used instead of toluene and 2,6-lutidine. After 48 h of reaction time, integration of the ^1H NMR spectrum against the internal standard revealed that 60% of **1E** had reacted, with the products consisting of 3,5-dimethoxybenzaldehyde (**5**, 48%), 4-methoxybenzaldehyde (**6**, 15%), and ketone **3** (3%).

Catalytic Oxidation of Phenolic *β*-1 Lignin Model 2T Using 10 mol % $(HQ)_2V(O)(O^iPr)$ in Pyr-d_5. This reaction was carried out using the general procedure for the vanadium-catalyzed oxidations. After 24 h of heating at 100 °C, the starting material **2T** was completely consumed, and a mixture of products was detected, including ketone (**9**, 23%), 2,6-dimethoxybenzoquinone (**10**, 60%), 4-methoxybenzoic acid (**8**, 12%), 4-hydroxy-3,5-dimethoxybenzoic acid (**12**, 10%), 4-methoxybenzaldehyde (**6**, 1%), 4-hydroxy-3,5-dimethoxybenzaldehyde (**11**, 1%), and several minor unidentified aldehyde products (~2−6%).

Catalytic Oxidation of Phenolic *β*-1 Lignin Model 2E Using 10 mol % $(HQ)_2V(O)(O^iPr)$ in Pyr-d_5. This reaction was carried out using the general procedure for the vanadium-catalyzed aerobic oxidations. After 24 h, a mixture of reaction products was formed, including ketone (**9**, 7%), 2,6-dimethoxybenzoquinone (**10**, 43%), 4-methoxybenzoic acid (**8**, 14%), 4-hydroxy-3,5-dimethoxybenzoic acid (**12**, 7%), 4-methoxybenzaldehyde (**6**, 6%), 4-hydroxy-3,5-dimethoxybenzaldehyde (**11**, 3%), and several minor unidentified aldehyde products (1−6%).

The ketone (**9**) was isolated by chromatography on silica gel, eluting first with 7:3 hexanes/ethylacetate, then 4:6 hexanes/ethyl acetate.

*Ketone (**9**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 2H, aryl), 7.18 (d, 2H, J = 8.4 Hz, aryl), 6.85 (d, 2H, J = 8.4 Hz, aryl), 4.68 (dd, 1H, J = 8.8 Hz, J = 4.8 Hz, ArC*H*), 4.24 (1H, dd, J = 11.2 Hz, J = 8.4 Hz, CH_2OH), 3.88−3.82 (m, 1H, CH_2OH), 3.86 (s, 6H, $-OCH_3$), 3.76 (s, 3H, $-OCH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 198.7, 159.2, 146.8, 140.0, 129.5, 127.8, 114.9, 106.6, 105.2, 65.4, 56.5, 55.6, 55.4. HRMS (EI): m/z calcd for $C_{18}H_{20}O_6$ $[M + H]^+$: 333.1338; found: 333.1352

Control Reaction: Attempted Oxidation of 2E with No Catalyst. In an NMR tube, **2E** (19.5 mg, 0.058 mmol) was dissolved in pyr-d_5 (0.8 mL) containing dimethylsulfone as an internal standard. An initial ^1H NMR spectrum was recorded, and then the reaction mixture was heated under air with stirring in a 25 mL round-bottom flask at 80 °C for 4 days. The reaction mixture was then cooled to room temperature. Examination of the ^1H NMR spectrum revealed that no reaction occurred.

Catalytic Oxidation of Phenolic *β*-1 Lignin Model 2T Using 10 mol % $(HQ)_2V(O)(O^iPr)$ in DMSO-d_6. This reaction was carried out using the general procedure for the vanadium-catalyzed aerobic oxidations. After 48 h, examination of the ^1H NMR spectrum against the internal standard revealed all **2T** reacted, affording 2,6-dimethoxybenzoquinone (**10**, 44%), 4-methoxybenzoic acid (**8**, 35%), methanol (16%), 4-methoxybenzaldehyde (**6**, 2%), 4-hydroxy-3,5-dimethoxybenzoic acid (**12**, <1%), 4-hydroxy-3,5-dimethoxybenzaldehyde (**11**, <1%), and other unidentified aldehyde products (3%).

Catalytic Oxidation of Phenolic *β*-1 Lignin Model 2T Using 10 mol % CuOTf/TEMPO with 2,6-Lutidine (10 equiv) in Toluene. This reaction was carried out using the general procedure for the copper-catalyzed aerobic oxidations. After 18 h of reaction time, integration of the ^1H NMR spectrum against the internal standard revealed that all of **2T** had reacted, with the products consisting of ketone (**9**, 78%), 2-(4-methoxyphenyl)acrylaldehyde (**13**, 5%), 2,6-dimethoxybenzoquinone (**10**, 8%), 4-hydroxy-3,5-dimethoxybenzaldehyde (**11**, 2%), 4-methoxybenzaldehyde (**6**, 4%), and 4-methoxybenzoic acid (**8**, 1%). The products were identified and quantified by both ^{1}H NMR and GC/MS.

Stoichiometric Oxidation of Phenolic β-1 Lignin Model 2T Using CuOTf/TEMPO with 2,6-Lutidine (10 equiv) in Toluene. This reaction was carried out using the same general procedure for the copper-catalyzed reactions, except that a stoichiometric amount of CuOTf/TEMPO was added. After 18 h, integration of the ^{1}H NMR spectrum against the internal standard revealed that all of **2T** had reacted, with the products consisting of 2,6-dimethoxybenzoquinone (**10**, 82%), 2-(4-methoxyphenyl)acrylaldehyde (**13**, 9%), 4-hydroxy-3,5-dimethoxybenzaldehyde (**11**, 6%), 4-methoxybenzaldehyde (**6**, 25%), and 4-methoxybenzoic acid (**8**, 1%). The products were identified and quantified by ^{1}H NMR and GC/MS. Yields are expressed as a percentage of the theoretical maximum based on the initial amount of substrate.

Catalytic Oxidation of Phenolic β-1 Lignin Model 2E Using 10 mol % CuOTf/TEMPO with 2,6-Lutidine (10 equiv) in Toluene. This reaction was carried out using the same general procedure for the copper-catalyzed aerobic oxidations. After 18 h, integration of the ^{1}H NMR spectrum against the internal standard revealed that all of **2E** had reacted, with the products consisting of ketone (**9**, 82%), 2-(4-methoxyphenyl)acrylaldehyde (**13**, 3%), 2,6-dimethoxybenzoquinone (**10**, 7%), 4-hydroxy-3,5-dimethoxybenzaldehyde (**11**, 1%), 4-methoxybenzaldehyde (**6**, 5%), and 4-methoxybenzoic acid (**8**, 1%). The products were identified and quantified by ^{1}H NMR and GC/MS.

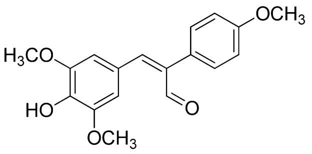
Stoichiometric Oxidation of Phenolic β-1 Lignin Model 2E using CuOTf/TEMPO with 2,6-Lutidine (10 equiv) in Toluene. This reaction was carried out using the same general procedure as for the copper-catalyzed aerobic oxidations, except that a stoichiometric amount of CuOTf/TEMPO was added. After 18 h, integration of the ^{1}H NMR spectrum against the internal standard revealed that all of the **2E** had reacted, with the products consisting of 2,6-dimethoxybenzoquinone (**10**, 68%), 2-(4-methoxyphenyl)-acrylaldehyde (**13**, 7%), 4-hydroxy-3,5-dimethoxybenzaldehyde (**11**, 3%), 4-methoxybenzaldehyde (**6**, 14%), and 4-methoxybenzoic acid (**8**, 2%). The products were identified and quantified by ^{1}H NMR and GC/MS.

Attempted Oxidation of Phenolic β-1 Lignin Model 2T Using TEMPO with 2,6-Lutidine (10 equiv) in Toluene (control experiment with no copper catalyst). This control experiment was carried out using the general procedure for the copper-catalyzed aerobic oxidations, except that no copper catalyst was added. After 18 h, the examination of the ^{1}H NMR spectrum revealed that no reaction had occurred.

Oxidation of Phenolic β-1 Lignin Model 2E Using TEMPO with 2,6-Lutidine (10 equiv) in Toluene (control experiment with no added copper catalyst). This control experiment was carried out according to the general procedure for the copper-catalyzed aerobic oxidations, except that no copper catalyst was added. After 18 h, the examination of the ^{1}H NMR spectrum revealed that no reaction had occurred.

Catalytic Oxidation of Phenolic β-1 Lignin Model 2E Using (dipic)V^V(O)(O^{i}Pr). This reaction was carried out following the general procedure for the vanadium-catalyzed aerobic oxidation reactions. After 48 h, complete conversion of the starting material was observed. The products of the reaction consisted of the aldehyde **14** (44%), the ketone **9** (7%), 4-hydroxy-3,5-dimethoxybenzoic acid (**12**, 9%), 4-hydroxy-3,5-dimethoxybenzaldehyde (**11**, 5%), 4-methoxybenzoic acid (**8**, 9%), and 4-methoxybenzaldehyde (**6**, 3%).

The aldehyde (**14**) was isolated by prep-scale TLC eluting with 4:6 hexanes/ethyl acetate.



14

14: ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.72 (s, 1H, *H*C═O), 7.26 (s, 1H, *H*C═C), 7.17 (d, 2H, *J* = 8.4 Hz, aryl), 6.99 (d, 2H, *J* = 8.4 Hz, aryl), 6.54 (s, 2H, aryl), 3.83 (s, 3H, −OCH$_3$), 3.66 (s, 6H, −OCH$_3$). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): 194.2, 159.8, 150.6, 146.9, 140.0, 137.2, 131.1, 126.2, 125.7, 114.7, 108.3, 56.2, 55.6. HRMS (EI): *m*/*z* calcd for $C_{18}H_{18}O_5$ $[M + H]^+$: 315.1232; found: 315.1223.

Control Reaction: Attempted Oxidation of 2T with No Catalyst. In an NMR tube, **2T** (19.5 mg, 0.058 mmol) was dissolved in pyridine-d_5 (0.8 mL) containing dimethylsulfone added as an internal standard. The solution was transferred to a 25 mL round-bottom flask and then heated at 80 °C under air with stirring for 4 days. The reaction mixture was cooled to room temperature and then examined by ^{1}H NMR spectroscopy. Integration against the internal standard revealed that no reaction had occurred.

Catalytic Oxidation of a 1:1 Mixture of Nonphenolic β-1 Lignin Model 1E and β-O-4 Model 15 Using 10 mol % (HQ)$_2$V(O)(O^{i}Pr) in Pyr-d_5. A mixture containing a 1:1 ratio of **1E** and **15** was oxidized following the general procedure for the vanadium-catalyzed aerobic oxidation reactions. After 24 h, integration of the ^{1}H NMR spectrum against the internal standard revealed that 43% of **1E** and 50% of **15** had reacted, with the products consisting of ketone **16** (27%, derived from the β-O-4 lignin model), ketone **3** (16%, derived from the β-1 lignin model), 3,5-dimethoxybenzaldehyde (**5**, 5%), and 4-methoxybenzaldehyde (**6**, 1%).

Catalytic Oxidation of a 1:1 Mixture of Nonphenolic β-1 Model 1E and β-O-4 Model 15 Using 20 mol % CuOTf/TEMPO with 2,6-Lutidine (10 equiv) in Toluene. A mixture containing a 1:1 ratio of **1E** and **15** was oxidized following the general procedure for the copper-catalyzed aerobic oxidation reactions. After 24 h, integration of the ^{1}H NMR spectrum against the internal standard revealed that 80% of **1E** and 56% of **15** had reacted, with the products consisting of 3,5-dimethoxybenzaldehyde (**5**, 75%), 4-methoxybenzaldehyde (**6**, 32%), and ketone **16** (8%, derived from the β-O-4 lignin model).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional experimental details and NMR spectra of reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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