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Comparison of Copper and Vanadium Homogeneous Catalysts for Aerobic Oxidation of Lignin Models

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Supporting Information

ABSTRACT: The reactivity of copper and vanadium catalysts toward the aerobic oxidation of lignin models has been explored. Both (dipic)V^{V}(O)(O^{i}Pr) (**3**) (dipic = dipicolinate) and CuCl/TEMPO (TEMPO = tetramethylpiperidine *N*-oxide) catalyzed the aerobic oxidation of the lignin model compound 1,2-diphenyl-2-methoxyethanol (**2**). The vanadium catalyst **3** produced benzoic acid (85%) and methyl benzoate (84%) as the major products via the intermediate ketone benzoin methyl ether (**4**). The copper catalyzed reaction afforded benzaldehyde (84%) and methylbenzoate (88%) directly, with no intermediate formation of **4**. The more complex lignin model system 1-(3,5-dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol-[2,3-$^{13}C_2$] (**5**-$^{13}C_2$) was oxidized under air by vanadium catalyst **3**, affording ketone **7**-$^{13}C_2$ (65%), dehydrated ketone **8**-$^{13}C_2$ (5%), alkene product **9**-$^{13}C_2$ (14%), 3,5-dimethoxybenzoic acid (11%), 3,5-dimethoxybenzaldehyde (2%), 2-methoxyphenol, and formic acid-$^{13}C_1$ (4%). Aerobic oxidation of ketone **7**-$^{13}C_2$ using catalyst **3** produced dehydrated ketone **8**-$^{13}C_2$, 3,5-dimethoxybenzoic acid, and formic acid-$^{13}C_1$, suggesting that **7** is further oxidized under the catalytic conditions. In contrast, oxidation of β-O-4 model **5**-$^{13}C_2$ using CuCl/TEMPO affords 3,5-dimethoxybenzaldehyde (43%), 3,5-dimethoxybenzoic acid (13%), 2-methoxyphenol (7%), formic acid-$^{13}C_1$ (7%), ketone-**7**$^{13}C_2$ (1%), dehydrated ketone **8**-$^{13}C_2$ (2%), and a number of higher molecular weight products, as determined by ^{1}H and ^{13}C NMR, GC-MS, and LC-MS. Attempted oxidation of ketone **7** using CuCl/TEMPO yielded primarily dehydrated ketone **8**, indicating that the ketone is not an intermediate in the formation of the aldehyde product. The reactivities of the copper and vanadium catalysts in the oxidation of lignin model compounds **2** and **5** are discussed. Remarkably different selectivities were observed for the vanadium and copper catalyzed reactions, suggesting the potential of homogeneous catalysts for controlling selectivity in the aerobic oxidation of lignin.

KEYWORDS: lignin models, vanadium, copper, aerobic oxidation, lignocellulose

INTRODUCTION

Non-food based biomass (lignocellulose) is an attractive renewable carbon feedstock for the production of chemicals or fuels. Lignin, a key constituent (15−30%) of lignocellulose, is an irregular polymer composed of methoxy-substituted phenyl and phenolic subunits.[1,2] Because of its structural complexity and inherent resistance to chemical reactivity, lignin has been considered a major obstacle in the production of biofuels from lignocellulose.

Recently, increasing attention has been focused on the development of methods to convert lignin into more valuable and useful products.[3,4] Reductive approaches using hydrogen or formic acid have been developed to transform lignin into mixtures of monomeric phenols and alkanes suitable for use as fuel additives.[5−9] Catalytic oxidation of lignin using environmentally friendly oxidants (O_2, H_2O_2) has also been explored as a means to break lignin down into monomeric products.[10−15] Crestini, Chen, Dolphin, and others have investigated the oxidation of lignin and lignin model compounds using H_2O_2 and transition metal catalysts, including Mn and Fe complexes of porphyrin and TACN ligands (TACN = triazacyclononane).[16−21] While the reduction of lignin is well suited for the production of fuels, aerobic oxidation is advantageous in that it requires no added reagents and could preserve a high degree of the functionality present in the original lignin polymer.

Oxidation is also the primary pathway by which lignin is broken down in nature. Both the enzymes lignin peroxidase and manganese-dependent peroxidase are thought to mediate the oxidative disassembly of lignin by wood-rotting fungi.[22−24] To establish the mechanisms of these enzymes, detailed studies have been carried out of the oxidation of arylglycerol β-aryl ether compounds,[25−28] which are models for the lignin β-O-4 linkage, a predominant structural feature representing approximately 50% of the linkages occurring in the natural polymer.[29] For example, oxidation of lignin model compound 1-(3,4-dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol (**1**) (Scheme 1) by lignin peroxidase affords products resulting from cleavage of the

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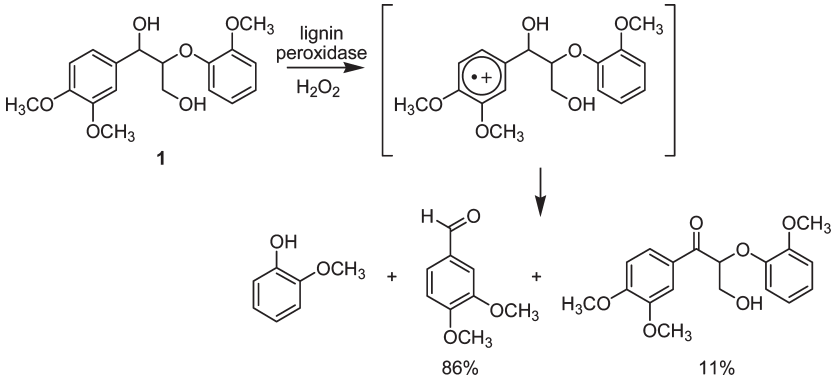
Scheme 1. Reported Oxidation of Lignin Model 1 with H_2O_2 Catalyzed by Lignin Peroxidase[34]



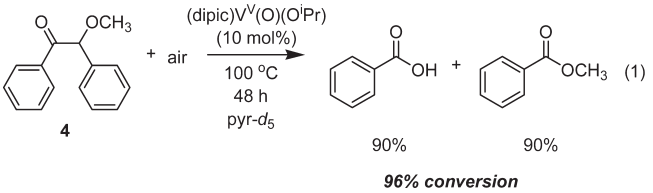
C_α-C_β bond, including veratryl aldehyde and 2-methoxyphenol.[23] The reaction of lignin peroxidase most likely occurs by a single electron transfer pathway,[30] as oxidations of **1** using the known one-electron oxidant cerium ammonium nitrate (CAN),[31] electrochemical,[32,33] or single electron transfer sensitized photochemical techniques[34] give rise to product distributions similar to those obtained with the enzyme. In contrast, Gold and co-workers proposed a hydrogen atom abstraction pathway for the reaction of manganese peroxidase, based on the observation that the product distribution was altered by selective deuterium labeling of the substrate.[35]

An alternative to the enzymatic oxidation of lignin would be an aerobic oxidation catalyzed by transition metal complexes. The use of an inexpensive, earth-abundant metal catalyst and air as the oxidant could provide advantages in terms of process cost and simplicity. Early studies of the aerobic oxidation of lignin models using stoichiometric Co and Mn acetate and oxygen in acetic acid at 170 °C gave C−C bond cleavage products in arylglycerol β-aryl ether lignin models for the β-O-4 linkage,[36] and more recent work by Partenheimer suggests that catalytic autoxidation of lignin under similar conditions can generate valuable aromatic aldehyde and acid products.[37]

In addition to cobalt and manganese, homogeneous complexes of copper and vanadium could be effective catalysts for the oxidation of lignin under mild conditions. Both copper and vanadium complexes are known to catalyze the aerobic oxidation of benzylic alcohols, diols, and phenols.[38−59] Rossi and coworkers studied the oxidation of diols using cuprous chloride or copper metal precatalysts in pyridine with oxygen, demonstrating C−C bond cleavage in both stoichiometric and catalytic reactions.[60,61] We recently showed that similar reactivity exhibited by dipicolinate vanadium complexes could be extended to C−C bond cleavage in several simple 1,2-hydroxy ether lignin models.[62,63] Furthermore, Son and Toste reported that vanadium complexes of tridentate Schiff base ligands catalyze a non-oxidative C−O bond cleavage reaction in a β-O-4 lignin model.[64] Given the precedence for both vanadium and copper-catalyzed aerobic oxidations, we were interested in comparing the activity and selectivity of these catalysts for the aerobic oxidation of lignin models. As described below, both the identity of the catalyst and the reaction conditions have a dramatic effect on the overall reaction selectivity. The different products observed with the vanadium and copper complexes suggest homogeneous catalysts could give rise to enhanced product selectivity in the aerobic oxidation of lignin.

RESULTS

Simple Lignin Models. Previous work investigating the catalytic oxidation of 1,2-diphenyl-2-methoxyethanol (**2**) with air and (dipic)V^V(O)(O^iPr) (**3**) (10 mol %) in pyridine found that initial alcohol oxidation to the ketone benzoin methyl ether (**4**) (45% overall yield at 56% conversion) was followed by C−C bond cleavage and further oxidation to benzoic acid (85%) and methyl benzoate (84%).[63] Benzaldehyde (9%), methanol (6%), benzil (<5%), and benzoin (<5%) were formed as minor products in the reaction.[63] The viability of **4** as an intermediate in the formation of benzoic acid and methyl benzoate was confirmed by a subsequent experiment involving oxidation of **4** with air using **3** (10 mol %) in pyridine-d_5. After 48 h at 100 °C, 96% conversion of **4** was observed, affording benzoic acid (90%) and methyl benzoate (90%) as the major products (eq 1).[65] Benzil was also detected as a minor product in this reaction (ca. 6%), but benzaldehyde or methanol were not detected (^{1}H NMR spectroscopy). Compound **4** is also subject to aerobic oxidation under air with no added catalyst, albeit at a slower rate. In a control experiment, compound **4** was heated under air in pyr-d_5 with no catalyst. After 48 h at 100 °C, 43% conversion was observed, with the major products consisting of benzoic acid (39%), methyl benzoate (34%), benzil (8%), and methanol.



In contrast, oxidation of **2** with O_2 using catalytic CuCl (20 mol %) and TEMPO (30 mol %) in pyridine at 100 °C afforded benzaldehyde (84%) and methyl benzoate (88%) directly without apparent intermediacy of the ketone (eq 2).[65] The active copper catalytic species was not stable under the reaction conditions; two additions of CuCl (10 mol % each) and three additions of TEMPO (10 mol % each) were required to achieve 92% conversion in 48 h. Only trace (4%) benzoin methyl ether was observed in NMR spectra of the reaction mixture obtained at intermediate reaction times. Consistent with the proposal that benzoin methyl ether (**4**) is not an intermediate in the formation of benzaldehyde, catalytic oxidation of **4** with O_2 using 10 mol % CuCl/TEMPO at 100 °C in pyridine for 18 h afforded predominantly

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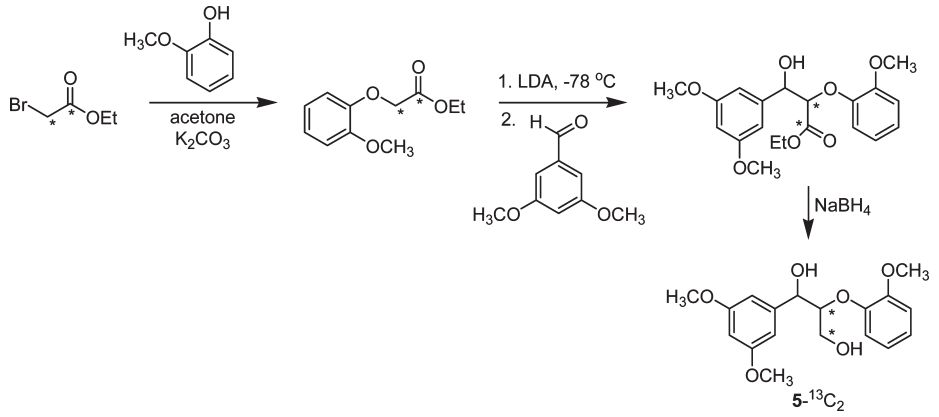
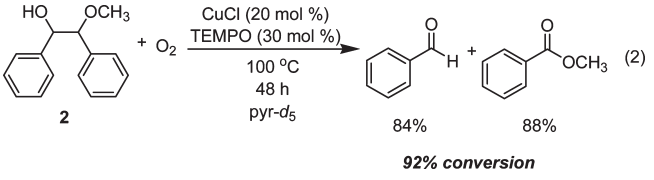
Scheme 2. Synthesis of Labeled Lignin Model Compound 5-$^{13}C_2$[a]



[a] * = ^{13}C label.

methyl benzoate (85%), benzoic acid (76%), and methanol (5%), with only 5% benzaldehyde at 87% conversion. To gain further insight into the reactivity differences between the vanadium and the copper catalysts, the stoichiometric oxidation of **2** was tested with cerium ammonium nitrate (CAN), a well-known one-electron oxidant. Carrying out the reaction of **2** with CAN under oxygen for 18 h at 100 °C afforded a mixture of benzaldehyde, methyl benzoate, and methanol in a 4:1:1.8 ratio at 80% conversion. Prompted by the differences in selectivity observed in the oxidation of the simple lignin model **2**, we proceeded to compare the copper and vanadium catalysts using more complex arylglycerol β-aryl ether lignin models.



Synthesis of Arylglycerol β-Aryl Ether Lignin Models. A variety of compounds have been studied as models for the β-O-4 linkage.[10−28] The lignin model compound 1-(3,5-dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol-[2,3-$^{13}C_2$] (**5**-$^{13}C_2$) was selected as a synthetic target as it was anticipated that incorporation of ^{13}C labels into the positions β- and γ- to the benzylic alcohol group could help identify reaction products derived from the β- and γ-carbons. Previous studies of lignin model compound oxidations suggest that it is often difficult to determine the oxidation products that result from this portion of the molecule.[23,25] Hammel and co-workers have demonstrated that selective labeling (^{14}C and ^{13}C) of the substrate facilitated product analysis in the enzymatic oxidation.[22,24]

Compound **5**-$^{13}C_2$ is similar to previously reported lignin model compounds,[31,34,64] and was prepared as an 4:1 mixture of diastereomers (erythro: threo) in three steps (Scheme 2) from ethyl bromo-[1,2-$^{13}C_2$]-acetate, by a modified version of a published procedure.[64] The major diastereomer is assigned as the erythro isomer, based on comparison of the ^{1}H and ^{13}C NMR data with the closely related reported compounds *erythro*- and *threo*-1-(3,4-dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol[34] and (1*R**,2*S**)-1-(4-ethoxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol.[64] An identical procedure was used for the preparation of a diastereomeric mixture of the unlabeled analogue **5**. The structural assignment for **5** and **5**-$^{13}C_2$ was confirmed by ^{1}H and ^{13}C NMR spectroscopy and high resolution mass spectroscopy (HR-MS).

Vanadium Catalyzed Oxidation. Vanadium complexes (dipic)V^V(O)(O^iPr) (**3**) and V^V(O)(O^iPr)$_3$ (**6**) were tested as catalysts for the aerobic oxidation of **5**-$^{13}C_2$. When lignin model **5**-$^{13}C_2$ was heated under air with (dipic)V^V(O)(O^iPr) (10 mol %) in DMSO-d_6 solvent at 100 °C for 48 h, complete conversion of the starting material was observed. Examination of the ^{1}H and ^{13}C NMR spectra of the reaction mixture (Supporting Information, Figure S24) revealed the formation of a mixture of products, including ketone **7**-$^{13}C_2$ (65%), dehydrated ketone **8**-$^{13}C_2$ (5%), alkene **9**-$^{13}C_2$ (14%), 3,5-dimethoxybenzaldehyde (**11**) (2%), formic acid-$^{13}C_1$ (**12**-$^{13}C_1$) (4%), and 3,5-dimethoxybenzoic acid (**13**) (11%) (Scheme 3).[65] Consideration of the yields (Table 1) of the products derived from the 3,5-dimethoxyarene ring (**7**, **8**, **9**, **11**, and **13**) shows that the carbon balance is about 95% for this portion of the original lignin model compound.[66] The mass balance for the remainder of the molecule is not as good; formic acid-$^{13}C_1$ is formed as a coproduct, most likely arising from a deeper oxidation of the labeled β- and γ-carbons. 2-Methoxyphenol (**10**) was also detected as a product by GC-MS, but it was not possible to quantify by ^{1}H NMR because of overlap with resonances from the other products. Carbon dioxide-$^{13}C_1$ could also potentially be formed as a product; this would be difficult to detect under the reaction conditions (air).

The identity of the products was confirmed by carrying out the reaction on a larger scale; ketone **7**-$^{13}C_2$, dehydrated ketone **8**-$^{13}C_2$, and alkene **9**-$^{13}C_2$ were isolated and characterized by ^{1}H and ^{13}C NMR spectroscopy and HR-MS.[67] Ketone **7**-$^{13}C_2$ displays resonances in the $^{13}C\{^1H\}$ NMR spectrum ($CDCl_3$) at 84.7 and 63.7 ppm ($^1J_{C-C}$ = 38 Hz), as well as a characteristic resonance in the ^{1}H NMR spectrum for the proton on the labeled carbon adjacent to the ketone, which appears as a multiplet at 5.42 ppm with $^1J_{C-H}$ = 148 Hz. The $^{13}C\{^1H\}$ NMR spectrum of dehydrated ketone **8**-$^{13}C_2$ shows signals at 157.7 and 101.5 ppm ($^1J_{C-C}$ = 82 Hz), while the ^{1}H NMR spectrum shows signals for the olefinic protons at 5.25 ($^1J_{C-H}$ = 165 Hz) and 4.79 ($^1J_{C-H}$ = 160 Hz) ppm. Alkene **9**-$^{13}C_2$ shows ^{13}C NMR resonances at 132.6 and 130.4 ppm ($^1J_{C-C}$ = 69 Hz). The vinylic protons on **9**-$^{13}C_2$ appear as complex multiplets centered at 7.11, 6.45, and 5.93 ppm. Alkene **9** is the product of a C−O bond

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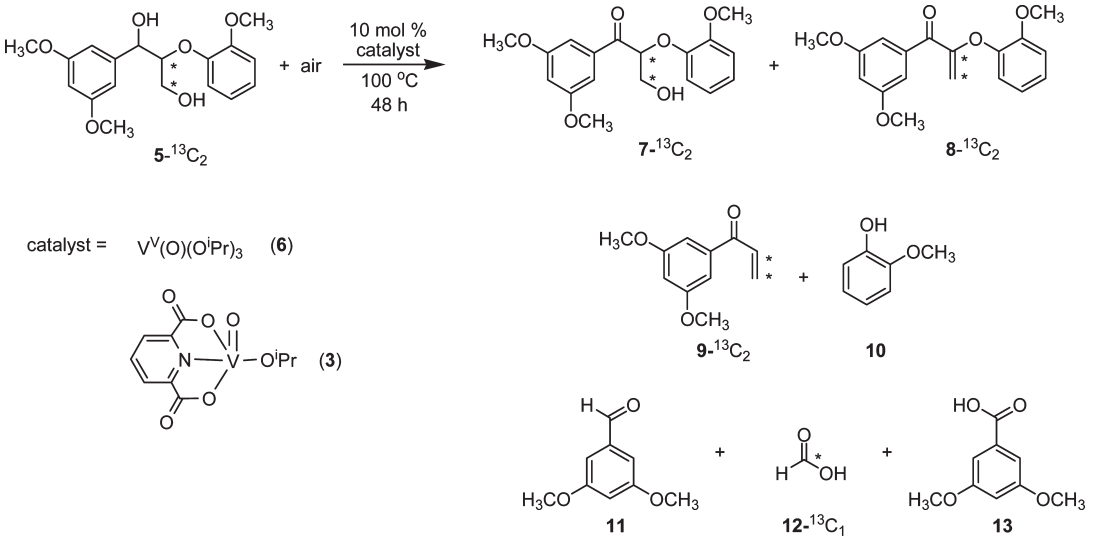
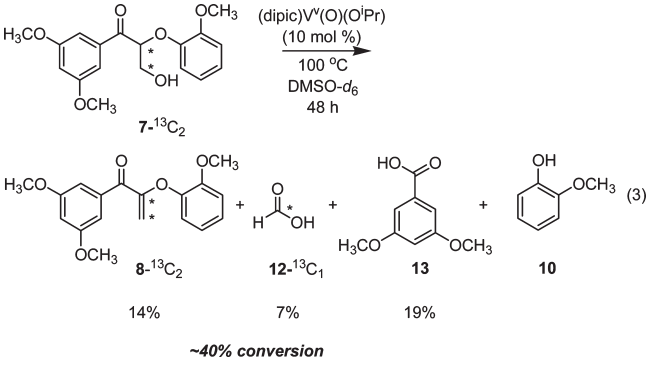
Scheme 3. Vanadium-Catalyzed Oxidation of 5-$^{13}C_2$ Using Air[a]



[a] * = ^{13}C label.

cleavage reaction analogous to that previously reported by Son and Toste.[64]

To determine whether ketone 7-$^{13}C_2$ was an intermediate in the formation of any of the other products, the oxidation of an isolated sample of 7-$^{13}C_2$ with air was tested using **3** (10 mol %) in DMSO-d_6 solvent at 100 °C. After 48 h, examination of the ^{1}H and ^{13}C NMR spectra of the reaction mixture (Supporting Information, Figure S25) showed that approximately 40% of the ketone had been consumed, affording dehydrated ketone 8-$^{13}C_2$ (14%), 3,5-dimethoxybenzoic acid (19%) and formic acid-$^{13}C_1$ (7%) (eq 3). 2-Methoxyphenol was also detected as a product by GC-MS. In a control experiment in the absence of the vanadium catalyst, where the ketone 7-$^{13}C_2$ was heated under air in DMSO-d_6 at 100 °C for 48 h, no reaction occurred.



Compared to the dipicolinate vanadium complex **3**, V^V(O)(OiPr)$_3$ (**6**) was a somewhat slower catalyst for the aerobic oxidation of 5-$^{13}C_2$. When a solution of 5-$^{13}C_2$ and **6** (10 mol %) was heated under air in DMSO-d_6 solvent at 100 °C for 48 h, approximately 75% of the starting material was consumed, as judged by integration of the ^{1}H NMR resonances against an internal standard. The primary products of the oxidation were the ketone 7-$^{13}C_2$ (39%), the alkene product 9-$^{13}C_2$ (16%), 3,5-dimethoxybenzoic acid (12%), 3,5-dimethoxybenzaldehyde (7%), and formic acid-$^{13}C_1$ (7%).

Carrying out the oxidation of 5-$^{13}C_2$ with the dipicolinate vanadium complex **3** in a different solvent (pyridine-d_5) had a significant impact on the product distribution, increasing the yields of the alkene product 9-$^{13}C_2$ and dehydrated ketone 8-$^{13}C_2$ relative to ketone 7-$^{13}C_2$. Heating 5-$^{13}C_2$ with **3** (10 mol %) in pyr-d_5 solvent under air resulted in approximately 85% conversion of the starting material, affording 7-$^{13}C_2$ (27%), 8-$^{13}C_2$ (14%), 9-$^{13}C_2$ (29%), **11** (4%), and **13** (6%) (Figure 1). 2-Methoxyphenol (**10**) was also detected in the GC-MS trace of the reaction.

Table 1. Products from the Vanadium-Catalyzed Oxidation of 5-$^{13}C_2$ Using Air[66]

entry	catalyst	solvent	% conv.	7	8	9	11	12	13
1	**6**	DMSO-d_6	~75%	39		16	7	7	12
2	**3**	DMSO-d_6	>95%	65	5	14	2	4	11
3	**3**	pyr-d_5	~85%	27	14	29	4	<1	6

Using catalyst **3**, a signal corresponding to the *cis*-dioxo vanadium(V) complex [(dipic)V^V(O)$_2$]$^-$ (**12**)[63] was detected at −518 ppm by ^{51}V NMR at the end of the reactions in both DMSO-d_6 and pyr-d_5 solvent. No signals were observed in the ^{51}V NMR spectrum of the oxidation reaction carried out using V^V(O)(OiPr)$_3$ in DMSO-d_6 solvent.

Oxidation Using CuCl/TEMPO. In light of the limited catalyst activity and lifetime of the CuCl/TEMPO system, we investigated the stoichiometric reaction of CuCl/TEMPO with 5-$^{13}C_2$ at 100 °C under oxygen. After 18 h and 70% conversion, the products consisted of 3,5-dimethoxybenzaldehyde (**11**, 36%), 3,5-dimethoxybenzoic acid (**13**, 9%), 2-methoxyphenol (**10**, 5%), ketone (7-$^{13}C_2$, 2%), dehydrated ketone (8-$^{13}C_2$, ca. 1%), and formic acid **12**-$^{13}C_1$ (5%), as determined by ^{1}H and ^{13}C NMR, GC/MS and LC/MS (Supporting Information, Figures S33–S34). After 40 h, 89% conversion was observed, affording 3,5-dimethoxybenzaldehyde (43%), 3,5-dimethoxybenzoic acid (**13**, 13%), 2-methoxyphenol (7%), ketone 7-$^{13}C_2$ (ca. 1%), dehydrated ketone (8-$^{13}C_2$, ca. 2%), and formic acid **12**-$^{13}C_1$ (7%) (eq 4). In addition to resonances for the known products, the ^{13}C{^{1}H} NMR spectra (Figure 2) included several doublet resonances clustered around 65 and 82 ppm presumably arising from condensation products; LC-MS analysis confirmed the

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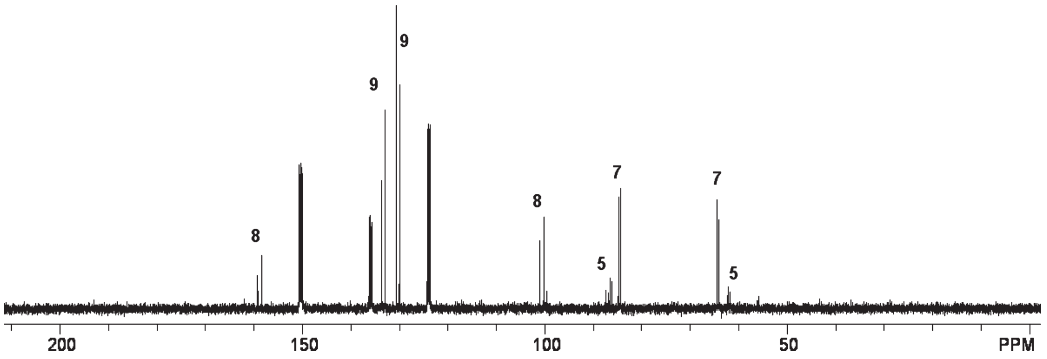
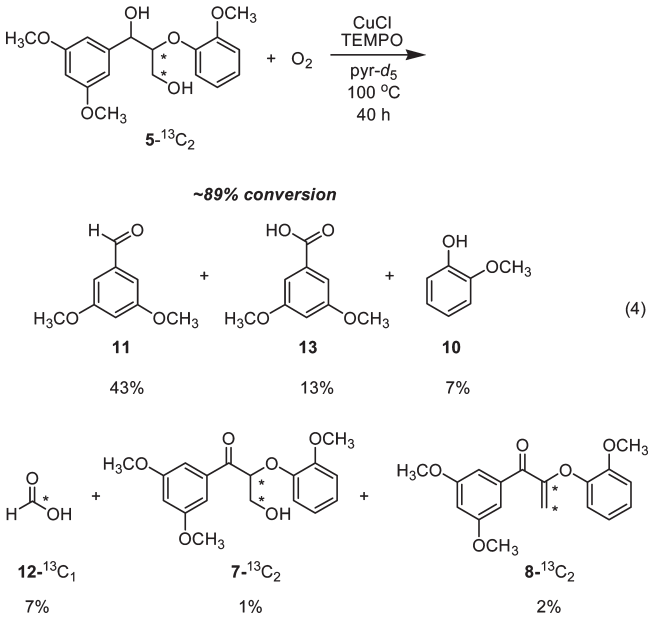


Figure 1. $^{13}C\{^{1}H\}$ NMR spectrum of the reaction mixture (pyr-d_5 solution) from the oxidation of **5**-$^{13}C_2$ with air using **3** (10 mol %) after 48 h at 100 °C.

presence of higher molecular weight compounds in the reaction mixture.



(4)

To explore whether ketone **7** could be an intermediate in the formation of any of the other products, we also treated the ketone **7** with 10 mol % CuCl/TEMPO at 100 °C under oxygen. After 18 h, 48% conversion was observed, affording the dehydrated ketone (18%) and several unidentified products; no aldehyde products were detected.

DISCUSSION

Copper and vanadium complexes catalyze the aerobic oxidation of alcohols, diols, and phenols, and several common mechanisms have been proposed for these reactions.[38−59] Sheldon and co-workers reported a CuCl/bipy/TEMPO/KO^{t}Bu system that catalyzes the aerobic oxidation of primary alcohols at room temperature.[40,41] Computational studies of this system suggest that alcohol oxidation proceeds through a pathway involving coordination of the TEMPO to copper, followed by a hydrogen atom abstraction.[42] In contrast, Rogić and co-workers postulated an initial single electron transfer mechanism for the aerobic oxidation of catechols using catalytic CuCl.[53] Itoh and co-workers carried out detailed studies of phenol oxidation by dicopper dioxygen complexes, suggesting a proton-coupled electron transfer mechanism.[54] For vanadium, a one electron pathway involving a vanadium(IV) intermediate is proposed for the oxidative dimerization of phenols to binaphthols.[56,57] Ohde and Limberg favored a hydrogen atom transfer pathway for a metavanadate-cinnamic acid catalyst for alcohol oxidation,[52] and work by Toste and Chen proposed a hydride transfer pathway for several vanadium-catalyzed alcohol oxidation reactions.[48−51] Given the variety of potential pathways, we were interested in comparing the selectivity obtained in the copper and vanadium catalyzed aerobic oxidations of lignin model compounds.

Both CuCl/TEMPO and (dipic)V^V(O)(O^{i}Pr) (**3**) were found to catalyze the aerobic oxidation of lignin model compounds **2** and **5**. While the vanadium-catalyzed oxidation proceeded smoothly under air, oxidation with CuCl/TEMPO in pyridine solvent required a pure oxygen atmosphere to achieve reasonable rates. A high catalyst loading or multiple additions of CuCl/TEMPO were typically necessary to increase the conversion rate. The requirement for a high CuCl/TEMPO catalyst loading is most likely due to the instability of the active catalytic species, as catalytic reactions monitored periodically showed a sharp decrease in activity at longer reaction times. Although more active copper catalysts for aerobic alcohol oxidation have been reported by Sheldon and Marko, the multicomponent systems typically require strong base (KO^{t}Bu).[38−41] Initial efforts to oxidize lignin model **2** using the CuCl/bipy/TEMPO/KO^{t}Bu catalytic system reported by Sheldon[40] resulted in multiple products most likely due to side reactions arising from the strong base.

Comparison of the copper and vanadium catalyzed oxidations of the simple lignin model compound 1,2-diphenyl-2-methoxyethanol (**2**) revealed key differences in selectivity. Using vanadium catalyst **3**, the aerobic oxidation of **2** in pyr-d_5 solvent afforded methyl benzoate (84%) and benzoic acid (85%) as the major products.[63] Minor reaction products included benzaldehyde, methanol, benzil, and benzoin. The ketone benzoin methyl ether (**4**) is a likely intermediate in this reaction, as it was detected in the reaction mixture in high yield (45% overall yield at 56% conversion) at intermediate reaction times.[63] Lending further support to the intermediacy of **4**, the oxidation of **4** using catalytic **3** in pyr-d_5 solvent produced a mixture of benzoic acid (90%) and methyl benzoate (90%). No benzaldehyde or methanol was detected in the oxidation of **4**, suggesting that these products are formed by a different reaction pathway that does not involve **4** as an intermediate.

In contrast to the vanadium catalyst, the oxidation of **2** using CuCl/TEMPO afforded a mixture of benzaldehyde (84%) and methyl benzoate (88%) directly. When the reaction was monitored

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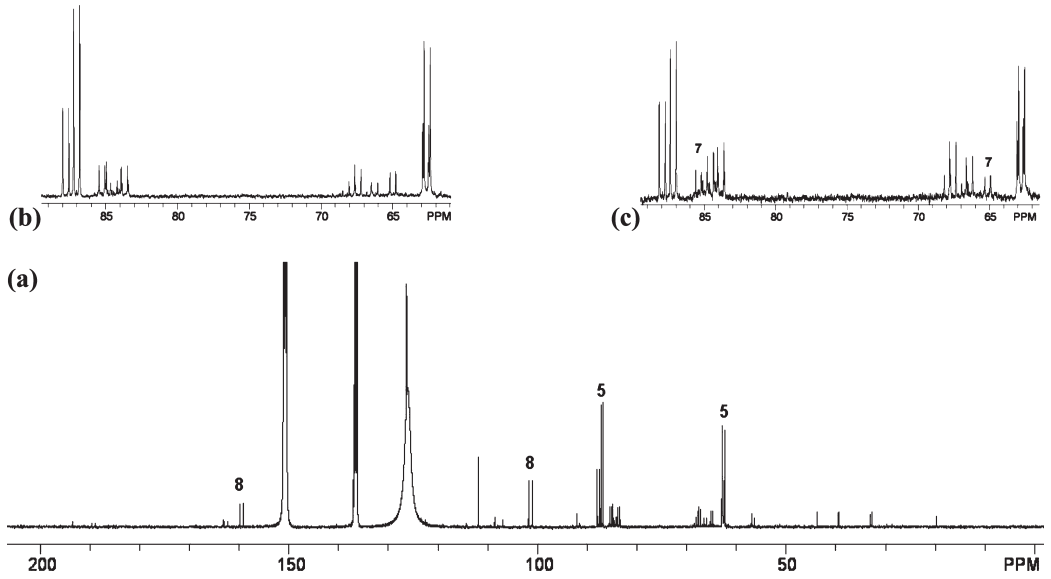

Figure 2. (a) $^{13}C\{^{1}H\}$ NMR spectra of reaction mixture (pyr-d_5 solution) from the oxidation of **5**-$^{13}C_2$ with O_2 using stoichiometric CuCl/TEMPO after 18 h at 100 °C; (b) expanded view of the spectrum after 18 h; (c) expanded view of the spectrum after 40 h.

by ^{1}H NMR at intermediate reaction times, only trace benzoin methyl ether (4%) was observed. Benzoin methyl ether (**4**) is not likely an intermediate in the formation of the benzaldehyde product, as oxidation of **4** with O_2 and catalytic CuCl/TEMPO in pyr-d_5 solvent afforded benzoic acid, methyl benzoate, and only 5% benzaldehyde. The different product distributions observed in the copper and vanadium catalyzed oxidations of **2** suggest that different reaction pathways are operative. Whereas the copper catalyst appears to directly cleave the C−C bond, the vanadium catalyst performs C−H bond cleavage to generate the ketone intermediate which then undergoes oxidative C−C bond cleavage. Notably, similar product distributions were obtained from the aerobic oxidation of **2** with catalytic CuCl/TEMPO and the stoichiometric oxidation of **2** with cerium ammonium nitrate, suggesting that a single electron transfer pathway could be operating in the copper system.

The reactivities of the vanadium and copper catalysts were also tested for the aerobic oxidation of the lignin model **5**. Extensive previous work has involved using arylglycerol β-aryl ether compounds similar to **5** to model the β-O-4 linkage in lignin.[10−28] A variety of techniques have been explored for the oxidation of arylglycerol β-aryl ether compounds, including enzymatic oxidation (lignin peroxidase or manganese-dependent peroxidase and H_2O_2),[23−25,28] stoichiometric one-electron oxidation (using reagents like cerium ammonium nitrate or potassium-12-tungstocobalt(III)ate),[25,30,31,34] single electron transfer sensitized photochemical oxidation,[34] electrochemical oxidation,[32,33] and transition metal catalyzed oxidations.[36,37,62,64] In general, stoichiometric one-electron oxidants react with the lignin model compound **1** to form a radical cation which undergoes oxidative cleavage of the C_α-C_β bond, generating veratryl aldehyde as the major product.[25,30,31,34]

In contrast to the reactivity documented for single electron transfer oxidants, aerobic oxidation of lignin model **5** using dipicolinate vanadium catalyst **3** in DMSO-d_6 or pyr-d_5 afforded ketone **7**, dehydrated ketone **8**, and alkene **9** as the major products. Alkene product **9** is the result of a non-oxidative C−O bond cleavage reaction analogous to that recently described by Son and Toste for a closely related arylglycerol β-aryl ether lignin model.[64] Unlike the reported Schiff base vanadium(V) catalyst for which the non-oxidative C−O bond cleavage pathway is predominant,[64] dipicolinate vanadium complex **3** affords mostly ketone **7** and dehydrated ketone **8**. The two vanadium catalysts are also distinct in that **3** catalyzes oxidative C_α-C_β bond cleavage in ketone **7** (affording 3,5-dimethoxybenzoic acid and formic acid), whereas the Schiff base catalyst reported by Toste did not react with the analogous ketone under the catalytic conditions.[64]

The oxidation of lignin model **5** with stoichiometric CuCl/TEMPO afforded 3,5-dimethoxybenzaldehyde (43%) as the major product. Minor products of this reaction include 3,5-dimethoxybenzoic acid, 2-methoxyphenol, ketone **7**, dehydrated ketone (**8**-$^{13}C_2$), and formic acid. Several higher molecular weight condensate products were also detected by ^{13}C NMR and LC-MS spectroscopy. The product distribution obtained in the oxidation of **5** using CuCl/TEMPO resembles those previously reported for oxidations of arylglycerol β-aryl ether lignin models using well-known one-electron oxidants,[25,30,31,34] suggesting that CuCl/TEMPO might oxidize **5** by a single electron transfer pathway. This differs dramatically from the selectivity for the ketone **7** observed for the dipicolinate vanadium catalyst **3**, revealing that a different mechanism is likely operative for the vanadium system.

Overall, major differences in selectivity are observed in the aerobic oxidations of lignin models **2** and **5** using CuCl/TEMPO and dipicolinate vanadium complex **3**. For both models **2** and **5**, oxidation with CuCl/TEMPO appears to break the C_α-C_β bond directly, generating an aldehyde as the major product. This reactivity closely resembles that reported for known one-electron oxidants and the enzyme lignin peroxidase.[31] In contrast, oxidation of **2** and **5** with dipicolinate vanadium catalyst **3** proceeds primarily by cleavage of the C−H bond, affording a ketone intermediate. Both ketones **4** and **7** are subject to deeper oxidation under the catalytic conditions, affording carboxylic acids as final products. Ultimately, the observation that different reactivity patterns can be obtained in the oxidation of lignin model compounds upon modifying the catalyst is a promising indication

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of the potential of homogeneous catalysts for the selective oxidation of lignin.

CONCLUSIONS

The reactivities of the dipicolinate vanadium complex **3** and CuCl/TEMPO have been compared for the aerobic oxidation of lignin model compounds. Both the copper and the vanadium complexes catalyzed the aerobic oxidation of lignin model compounds under mild conditions. Using CuCl/TEMPO, oxidation of **2** and **5** proceeded by direct C−C bond cleavage, affording benzaldehyde and 3,5-dimethoxybenzaldehyde (respectively) as major products. A different pattern was observed for dipicolinate vanadium catalyst **3**, which reacted with **2** and **5** to break the C−H bond, generating **4** and **7** (respectively) as initial products. Both **4** and **7** were subject to further oxidation under the reaction conditions, affording benzoic acid and 3,5-dimethoxybenzoic acid as final products.

A major challenge in the production of more valuable chemicals and fuels from lignin is the complex, irregular nature of the polymer. New ways to control the selectivity of chemical transformations within lignin could significantly improve our ability to harness this renewable resource. Homogeneous catalysts are attractive candidates for the aerobic oxidation of lignin, offering the potential for tuning the metal and ligand framework to direct the reaction toward specific linkages or toward a desired product. As described above, the observation that copper and vanadium catalysts display different reactivity patterns for the aerobic oxidation of lignin model compounds highlights the viability of using homogeneous catalysts to control selectivity in the reactions of lignin.

EXPERIMENTAL SECTION

General Considerations. Unless specified otherwise, all reactions were carried out in the presence of air. ^{1}H, ^{13}C, and ^{51}V NMR spectra were obtained at room temperature on a Bruker AV400 MHz spectrometer, with chemical shifts (δ) referenced to the residual solvent signal or referenced externally to $V^{V}(O)(Cl)_3$ (0 ppm). GC-MS analysis was obtained using a Hewlett-Packard 6890 GC system equipped with a Hewlett-Packard 5973 mass selective detector. 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 the mass spectrometry (Q1MS) with electrospray ionization (ESI-MS) in positive mode (ion spray voltage: 5000.0 V, TEM: 400.0 °C, declustering potential: 11.00 V and focusing potential: 300.0 V). Deuterated solvents were purchased from Cambridge Isotope Laboratories and pyridine-d_5 was dried over CaH_2. Oxygen was purchased from Linde Canada. The complex $(dipic)V^{V}(O)(O^{i}Pr)$ (**3**) was prepared using a published procedure.[68] High resolution mass spectra (HRMS) were obtained by the Laboratory for Biology Mass Spectrometry at Texas A&M University, College Station, TX.

Oxidation of Benzoin Methyl Ether (4) Using Dipicolinate Vanadium Catalyst 3 in Air. In an NMR tube, benzoin methyl ether (32 mg, 0.14 mmol) and $(dipic)V^{V}(O)(O^{i}Pr)$ (5.0 mg, 0.014 mmol) were dissolved in pyr-d_5 (1 mL) containing dimethylsulfone (8 mM) as an internal standard. An initial spectrum was recorded, and then the reaction mixture transferred to a 50 mL round-bottom flask. The flask was equipped with a stir bar and an air condenser and heated at 100 °C for 48 h. The mixture was cooled to room temperature and transferred to an NMR tube. Integration of the ^{1}H NMR spectrum against the internal standard revealed that ∼96% of the starting material had been consumed. The products of the reaction consisted of benzoic acid (90%), methyl benzoate (90%), and benzil (<10%). The identity of the products was confirmed by comparison with commercial samples of the authentic compounds.

Oxidation of 4 in Air with No Catalyst. In an NMR tube, benzoin methyl ether (43 mg, 0.19 mmol) was dissolved in pyr-d_5 (0.9 mL) containing dimethylsulfone (7 mM) as an internal standard. An initial ^{1}H NMR spectrum was recorded, and then the solution transferred to a 50 mL round-bottom flask equipped with a stirbar and an air condenser. The reaction was heated at 100 °C for 48 h, cooled to room temperature, and the reaction mixture transferred to an NMR tube. Integration against the internal standard revealed that 43% of the starting material had been consumed, affording benzoic acid (39%), methyl benzoate (34%), benzil (8%), and methanol. Trace benzaldehyde (1% or less) was also present in the spectrum.

Oxidation of 2 Using Catalytic CuCl/TEMPO under Oxygen. In an NMR tube, 1,2-diphenyl-2-methoxyethanol (50 mg, 0.22 mmol, an 85:15 mixture of u:l diastereomers)[69] was dissolved in pyridine-d_5 (1 mL) containing *p*-xylene (5.7 mg, 0.054 mmol) as an internal standard. An initial spectrum was recorded, and then the reaction mixture was transferred to a thick-walled 50 mL Schlenk tube equipped with Teflon stopcock containing 10 mol % of CuCl (2.2 mg, 0.021 mmol) and 10 mol % of TEMPO (3.1 mg, 0.021 mmol) in pyridine-d_5 (2 mL) under air. Oxygen was bubbled into the red homogeneous reaction mixture for 2 min and the reactor sealed. The reaction was heated at 100 °C with constant stirring and monitored periodically by both ^{1}H NMR and GC-MS. After 8 h an additional 10 mol % of TEMPO (3.1 mg, 0.021 mmol) was added and oxygen was again bubbled into the reaction mixture and the reactor sealed and heated. After 16 h, approximately 62% of the starting material had been consumed, with formation of benzaldehyde (52%), methyl benzoate (50%), and benzoin methyl ether (4%) (yields are expressed as a percentage of the theoretical maximum based on the initial amount of substrate). After 24 h an additional 10 mol % each of TEMPO and CuCl were added to the reaction mixture which was then saturated with oxygen, sealed, and heated for an additional 24 h. After this time 92% conversion was observed with formation of benzaldehyde (84%), methyl benzoate (88%), and benzoin methyl ether (4%). No reaction was observed in a control experiment where the internal standard *p*-xylene was heated with CuCl/TEMPO under oxygen at 100 °C for 18 h.

Oxidation of 4 with CuCl/TEMPO. In an NMR tube, benzoin methyl ether (50 mg, 0.20 mmol) was dissolved in pyridine-d_5 (1 mL) containing *p*-xylene (21 mg, 0.20 mmol) as an internal standard. An initial spectrum was recorded, and then the reaction mixture was transferred to a thick-walled 50 mL Schlenk tube equipped with Teflon stopcock containing 10 mol % of CuCl (2.2 mg, 0.020 mmol) and 10 mol % of TEMPO (3.1 mg, 0.020 mmol) in pyridine-d_5 (2 mL) under air. Oxygen was bubbled into the reaction mixture for 2 min and the reactor sealed. The reaction was heated at 100 °C with constant stirring for 18 h and then the products were quantified by both ^{1}H NMR and GC-MS. After 18 h, approximately 87% of the starting material had been consumed, with formation of methyl benzoate (85%), benzoic acid (76%), and benzaldehyde (5%). Yields are expressed as a

percentage of the theoretical maximum based on the initial amount of substrate.

Oxidation of 1,2-Diphenyl-2-methoxyethanol (2) with Stoichiometric Cerium(IV) Ammonium Nitrate (CAN). 1,2-Diphenyl-2-methoxyethanol (10 mg, 0.043 mmol of an 85:15 mixture of u:l diastereomers)[69] was dissolved in pyridine-d_5 (1 mL) in a thick-walled 50 mL Schlenk tube equipped with Teflon stopcock containing CAN (24 mg, 0.043 mmol) in pyridine-d_5 (1 mL) under air. Oxygen was bubbled into the reaction mixture for 2 min, and the reactor was sealed. After heating at 100 °C for 18 h with constant stirring, ^{1}H NMR and GC-MS analysis indicated formation of benzaldehyde, methyl benzoate, and methanol in a ratio 4:1:1.8 with 80% conversion.

Synthesis of Ethyl 2-(2-methoxyphenoxy)-[1,2-$^{13}C_2$]acetate (14). In a 250 mL single necked round-bottom flask, 2-methoxyphenol (6.207 g, 50.00 mmol), K_2CO_3 (7.602 g, 55.00 mmol), and ethyl bromo-[1,2-$^{13}C_2$]acetate (8.872 g, 52.50 mmol) were suspended in dry acetone (100 mL). The reaction mixture was stirred overnight. Examination of the solution by ^{13}C NMR spectroscopy indicated partial completion. Refluxing for an additional 24 h gave rise to a complete reaction. The reaction solvent was removed and the residue was purified by flash column chromatography using 10% ether/hexanes (v/v) to give 10.575 g (100%) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00−6.80 (m, 4H, J = 2.4 Hz, aryl), 4.68 (dd, 2H, $^1J_{C-H}$ = 147, $^2J_{C-H}$ = 4.5 Hz, CH_2-OAr), 4.26 (dq, $^2J_{C-H}$ = 3 Hz, J_{H-H} = 7 Hz, -OCH_2CH$_3$), 3.89 (s, 3H, -OCH$_3$), 1.29 (t, 3H, J = 7 Hz, -OCH$_2$CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.3 ($^1J_{C-C}$ = 64 Hz), 122.7, 120.9, 114.6, 112.3, 99.4, 98.4, 66.8 ($^1J_{C-C}$ = 64 Hz), 56.0, 14.4.

Synthesis of Diastereomers of Ethyl 3-Hydroxy-3-(3,5-dimethoxyphenyl)-2-(2-methoxyphenoxy)-[1,2-$^{13}C_2$]propanoate (15). Initial attempts to prepare **15** using a previously published procedure did not give rise to appreciable yields of this compound.[34] However, using an alternate procedure reported by Son and Toste afforded the aldol product in high yield.[64] A tetrahydrofuran (THF) solution (30 mL) of diisopropyl amine (3.1 mL, 22 mmol) was cooled to 0 °C under argon, and n-butyllithium (8.8 mL of a 2.5 M solution in hexanes, 22 mmol) was added dropwise. The mixture was stirred at 0 °C for 20 min and then chilled to −78 °C. A solution of ethyl 2-(2-methoxyphenoxy)-[1,2-$^{13}C_2$]-acetate in THF (20 mL) was added dropwise via cannula, followed by dropwise cannula addition of a solution of 3,5-dimethoxybenzaldehyde (3.324 g, 20.0 mmol) in THF (10 mL). The mixture was stirred at −78 °C for 1.5 h. A saturated aqueous solution of NH_4Cl (10 mL) was then added, the solution was allowed to warm to room temperature, and then the solution was extracted with ethyl acetate (3 × 20 mL). The extracts were combined, the solvent was removed under vacuum, and the residue was purified by silica gel flash chromatography (25% EtOAc/hexanes) to give 0.557 g of a first fraction and 6.818 g (90%) of a second fraction that contained the product, a mixture of the threo and erytho isomers which was a colorless syrup. The major diastereomer is assigned as the erythro form based on comparison with the closely related compounds *erythro*- and *threo*-ethyl 3-hydroxy-3-(3,4-dimethoxyphenyl)-2-(2-methoxyphenoxy)-propanoate.[34] ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06−6.83 (m, 4H, aryl), 6.63 (d, 2H, J = 2.1 Hz, aryl of major diastereomer), 6.59 (d, 2H, J = 2.1 Hz, aryl of minor diastereomer), 6.40 (t, 1H, aryl), 5.16 (m, 1H, CHOH of major diastereomer), 5.06 (m, 1H, CHOH of minor diastereomer), 4.74 (m, 1H, $^1J_{C-H}$ = 149.7 Hz, CHOAr of major diastereomer), 4.49 (m, 1H, $^1J_{C-H}$ = 152.1 Hz, CHOAr of minor diastereomer), 4.16 (q, 2H, J = 7.2 Hz, -OCH_2CH$_3$ of minor diastereomer), 4.15 (q, 2H, J = 7.2 Hz, -OCH_2CH$_3$ of major diastereomer), 3.88 (s, 3H, -OCH$_3$ of major diastereomer), 3.87 (s, 3H, -OCH$_3$ of minor diastereomer), 3.79 (s, 6H, -OCH$_3$ of major diastereomer), 3.78 (s, 6H, -OCH$_3$ of minor diastereomer), 1.16 (t, 3H, J = 7.2 Hz, -OCH$_2$CH_3 of major diastereomer), 1.10 (t, 3H, J = 7.2 Hz, -OCH$_2$CH_3 of minor diastereomer). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$), major diastereomer: 169.3 (d, $^1J_{C-C}$ = 85 Hz), 84.1 (d, $^1J_{C-C}$ = 85 Hz); minor diastereomer δ 169.6 (d, $^1J_{C-C}$ = 85 Hz), 85.5 (d, $^1J_{C-C}$ = 85 Hz).

1-(3,5-Dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol-[2,3-$^{13}C_2$] (5-$^{13}C_2$). The mixture of diastereomers of ethyl 3-hydroxy-3-(3,4-dimethoxyphenyl)-2-(2-methoxyphenoxy)-[1,2-$^{13}C_2$]propanoate (3.78 g, 10 mmol), was dissolved in a THF/water mixture (33 mL/11 mL). To this was added solid $NaBH_4$ (1.892 g, 50 mmol)[64] at ambient temperature, and the reaction mixture was stirred overnight, until thin layer chromatography (TLC) analysis indicated the absence of starting material. The mixture was then extracted with ethyl acetate (3 × 20 mL) and dried over Na_2SO_4. Filtration followed by removal of the solvent under vacuum gave rise to the crude material. Purification by silica gel flash chromatography using 60% ethyl acetate/hexane afforded 2.9243 g (87%) of the diol diastereomers as a colorless syrup. The major diastereomer is assigned as the erythro isomer, based on comparison of the ^{1}H and ^{13}C NMR data with the closely related reported compounds *erythro*- and *threo*-(1-(3,4-dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol[34] and (1*R**,2*S**)-1-(4-ethoxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol.[64] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12−6.90 (m, 6H, aryl), 6.62 (d, 2H, J = 2.0 Hz, aryl of minor diastereomer), 6.56 (d, 2H, J = 2.0 Hz, aryl of major diastereomer), 6.41 (t, 1H, J = 2.0 Hz, aryl of minor diastereomer), 6.37 (t, 1H, J = 2.0 Hz, aryl of major diastereomer), 4.99−4.94 (br m, 1H, -OH), 4.19 (m, 1H, $^1J_{C-H}$ = 144 Hz, CHOH of major diastereomer), 4.06 (m, 1H, $^1J_{C-H}$ = 143 Hz, CHOH of minor diastereomer), 4.13−3.45 (m, 3H, CH_2OH and CH-OAr), 3.90 (s, 3H, -OCH$_3$ of minor diastereomer), 3.88 (s, 3H, -OCH$_3$ of major diastereomer), 3.78 (s, 6H, -OCH$_3$ of minor diastereomer), 3.77 (s, 6H, -OCH$_3$ of major diastereomer), 3.37 (br s, 1H, -OH of minor diastereomer), 2.86 (br s, 1H, -OH of major diastereomer). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), major diastereomer: δ 161.0, 151.8, 146.9, 142.5, 124.4, 121.2 (d, $^2J_{C-H}$ = 1.8 Hz), 112.4, 104.1, 99.8, 87.3 (d, $^1J_{C-C}$ = 41 Hz), 72.8, 60.8 (d, $^1J_{C-C}$ = 41 Hz), 55.5; minor diastereomer: δ 161.0, 151.4, 147.8, 142.2, 124.4, 121.8, 121.1, 112.3, 105.2, 100.5, 89.3 (d, $^1J_{C-C}$ = 40 Hz), 73.2, 61.3 (d, $^1J_{C-C}$ = 40 Hz), 56.1. ^{13}C NMR (100 MHz, $CDCl_3$), major diastereomer: δ 87.3 (ddt, $^1J_{C-H}$ = 144 Hz, $^1J_{C-C}$ = 41 Hz, $^2J_{C-H}$ = 4.4 Hz), 60.8 (tdq, $^1J_{C-H}$ = 143 Hz, $^1J_{C-C}$ = 41 Hz, $^2J_{C-H}$ = 4.7 Hz, $^3J_{C-H}$ = 2.2 Hz), minor diastereomer: δ 89.3 (ddd, $^1J_{C-H}$ = 143 Hz, $^1J_{C-C}$ = 40 Hz, $^2J_{C-H}$ = 3.6 Hz), 61.3 (tdd, $^1J_{C-H}$ = 143 Hz, $^1J_{C-C}$ = 40 Hz, $^2J_{C-H}$ = 1.4 Hz). HRMS (EI): m/z calcd for $C_{16}{}^{13}C_2H_{23}O_6$ $[M+H]^+$: 337.1562, found: 337.1553.

1-(3,5-Dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol (5). The natural abundance carbon analogue (**5**) was prepared according to the same procedure as **5**-$^{13}C_2$. A mixture of diastereomers (4:1) was isolated as a syrup. The major diastereomer is assigned as the erythro isomer, based on comparison of the ^{1}H and ^{13}C NMR data with the closely related reported compounds *erythro*- and *threo*-(1-(3,4-dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol[34] and (1*R**,2*S**)-1-(4-ethoxy-

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3-methoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol.[64] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12−6.88 (m, 6H, aryl), 6.61 (d, 2H, J = 2.0 Hz, aryl of minor diastereomer), 6.55 (d, 2H, J = 2.0 Hz, aryl of major diastereomer), 6.40 (t, 1H, J = 2.0 Hz, aryl of minor diastereomer), 6.37 (t, 1H, J = 2.0 Hz, aryl of major diastereomer), 4.98−4.95 (br m, 1H, O*H*), 4.20−4.17 (m, 1H, C*H*OH of major diastereomer), 4.08−4.04 (m, 1H, C*H*OH of minor diastereomer), 3.94−3.64 (m, 3H, CH_2OH and C*H*-OAr), 3.88 (s, 3H, -OCH_3 of minor diastereomer), 3.86 (s, 3H, -OCH_3 of major diastereomer), 3.77 (s, 6H, -OCH_3 of minor diastereomer), 3.76 (s, 6H, -OCH_3 of major diastereomer), 3.54 (br s, 1H, -O*H* of minor diastereomer), 2.96 (br s, 1H, -O*H* of major diastereomer). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), major diastereomer: δ 161.0, 151.7, 146.9, 142.6, 124.3, 121.8, 121.0, 112.3, 104.2, 99.8, 87.2, 73.0, 60.8, 55.5; minor diastereomer: δ 161.0, 151.3, 147.8, 142.3, 124.2, 121.8, 121.0, 112.3, 105.1, 100.4, 89.1, 74.3, 61.3, 56.0. HRMS (EI): m/z calcd for $C_{18}H_{23}O_6$ $[M+H]^+$: 335.1495, found: 335.1504.

Oxidation of 5-$^{13}C_2$ in DMSO-d_6. In an NMR tube, lignin model **5**-$^{13}C_2$ (0.0288 g, 0.0857 mmol) was dissolved in DMSO-d_6 (1 mL) containing dimethylsulfone (0.025 M) as an internal standard. An initial spectrum was recorded, and then the reaction mixture was transferred to a 50 mL round-bottom flask containing (dipic)V^V(O)O^{i}Pr (3.1 mg, 8.8 μmol) under air. The reaction mixture was heated under air with stirring at 100 °C for 48 h, and then cooled to room temperature. The solution was transferred to an NMR tube and additional spectra were recorded. Yields were determined by integration against the internal standard and calculated from an average of two runs of this type. GC-MS analysis of the reaction mixture revealed that 2-methoxyphenol was formed in the reaction.

Oxidation of 5-$^{13}C_2$ in Pyridine-d_5. Lignin model **5**-$^{13}C_2$ (0.0348 g, 0.104 mmol) was dissolved in pyridine-d_5 (1 mL) containing a dimethylsulfone (3 mM) internal standard. An initial spectrum was recorded, and then the solution was transferred under air to a 50 mL round-bottom flask containing (dipic)V^V(O)O^{i}Pr (3.6 mg, 0.010 mmol). The flask was equipped with a reflux condenser and stirbar, and the reaction was heated at 100 °C for 48 h. The reaction was cooled to room temperature, the solution was transferred to an NMR tube, and a final NMR spectrum was recorded. Yields were determined by integration against the internal standard and calculated from an average of two runs of this type. GC-MS analysis of the reaction mixture revealed that 2-methoxyphenol was formed in the reaction.

Isolation of Reaction Products. In a 100 mL round-bottom flask, lignin model **5**-$^{13}C_2$ (0.141 g, 0.419 mmol) and (dipic)V(O)O^{i}Pr (0.015 g, 0.042 mmol) were dissolved in dimethylsulfoxide (DMSO, 3 mL). The flask was equipped with a stir bar and a reflux condenser, and the reaction was heated at 100 °C for 48 h. After cooling to room temperature, the DMSO solvent was removed under vacuum. The brown residue was purified by column chromatography on silica gel using 70:30 hexanes/ethyl acetate followed by 90:10 ethyl acetate/methanol, affording ketone **7** (oil), dehydrated ketone **8** (oil), and C−O cleavage product **9** (oil).

Ketone: 1-(3,5-Dimethoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propan-1-one-[2,3-$^{13}C_2$] (7-$^{13}C_2$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, 2H, J = 2.4 Hz, aryl), 7.01 (dt, 1H, J = 8.0, 2.0 Hz, aryl), 6.91 (dd, 2 H, J = 8.0, 1.6 Hz, aryl), 6.83 (dt, 1H, J = 8.0, 1.2 Hz, aryl), 6.68 (t, 1H, J = 2.4 Hz, aryl), 5.42 (m, 1H, $^1J_{C-H}$ = 148 Hz, C*H*-OAr), 4.07 (m, 2H, $^1J_{C-H}$ = 145 Hz, CH_2OH), 3.85 (s, 3H, -OCH_3), 3.82 (s, 6H, -OCH_3). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 196.4 (d, $^1J_{C-C}$ = 45 Hz), 161.1, 150.7, 147.1, 137.0 (d, $^2J_{C-C}$ = 14 Hz), 124.0, 121.4, 119.0, 112.6, 106.7, 106.4, 84.7 (d, $^1J_{C-C}$ = 38 Hz), 63.7 (d, $^1J_{C-C}$ = 38 Hz), 56.0, 55.8. HRMS (EI): m/z calcd for $C_{16}{}^{13}C_2H_{21}O_6$ $[M+H]^+$: 335.1406, found: 335.1414.

1-(3,5-Dimethoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)-propan-1-one (7). The natural abundance carbon analogue (**7**) was also isolated by chromatography on silica gel. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, 2H, J = 2.0 Hz, aryl), 7.02 (dt, 1H, J = 8.0 Hz, 2.0 Hz, aryl), 6.93 (d, 2H, J = 8.0 Hz, aryl), 6.84 (t, 2H, J = 8.0 Hz, aryl), 6.68 (t, 1H, J = 2.0 Hz, aryl), 5.42 (dd, 1H, J = 6.4, 4.0 Hz, C*H*-OAr), 4.11−4.02 (m, 2H, CH_2OH), 3.86 (s, 3H, -OCH_3), 3.83 (s, 6H, -OCH_3), 3.04 (br s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 196.2, 161.0, 150.4, 146.9, 136.8, 123.7, 121.2, 118.5, 112.4, 106.5, 106.2, 84.4, 63.5, 55.8, 55.6. HRMS (EI): m/z calcd for $C_{18}H_{21}O_6$ $[M+H]^+$: 333.1338, found: 333.1346.

C−O Product: 1-(3,5-Dimethoxyphenyl)prop-2-en-1-one-[2,3-$^{13}C_2$] (9-$^{13}C_2$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (m, 1H, $^1J_{C-H}$ = 154.8 Hz, C*H*=CH_2), 7.09 (d, 2H, J = 2.4 Hz, aryl), 6.68 (t, 1H, J = 2.4 Hz, aryl), 6.45 (m, 1H, CH=C*H*H), 5.93 (m, 1H, $^1J_{C-H}$ = 157.2 Hz, CH=CH*H*), 3.86 (s, 6H, -OCH_3). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 200.7 (d, $^1J_{C-C}$ = 41 Hz), 161.1, 139.4 (d, $^2J_{C-C}$ = 16 Hz), 132.6 (d, $^1J_{C-C}$ = 69 Hz), 130.4 (d, $^1J_{C-C}$ = 69 Hz), 106.7, 105.6, 105.2, 55.8. HRMS (EI): m/z calcd for $C_9{}^{13}C_2H_{13}O_3$ $[M+H]^+$: 195.0933, found: 195.0941.

Dehydrated Ketone: 1-(3,5-Dimethoxyphenyl)-2-(2-methoxyphenoxy)prop-2-en-1-one-[2,3-$^{13}C_2$] (8-$^{13}C_2$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.20 (d, 2H, J = 2.4 Hz, aryl), 7.16 (t, 1H, J = 7.2 Hz, aryl), 7.09 (d, 1H, J = 8.0 Hz, aryl), 6.99 (d, 1H, J = 8.0 Hz, aryl), 6.95 (t, 1H, J = 7.6 Hz, aryl), 6.66 (t, 1H, J = 2.4 Hz, aryl), 5.25 (m, 1H, $^1J_{C-H}$ = 164.8 Hz, C=C*H*H), 4.79 (m, 1H, $^1J_{C-H}$ = 160.4 Hz, *C* = CH*H*), 3.87 (s, 3H, -OCH_3), 3.85 (s, 6H, -OCH_3). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 193.8 (d, $^1J_{C-C}$ = 55 Hz), 160.7, 157.7 (d, $^1J_{C-C}$ = 82 Hz), 138.6, 129.5, 129.0, 126.0, 122.0, 121.4, 113.1, 107.9, 105.7, 101.5 (d, $^1J_{C-C}$ = 82 Hz), 56.0, 55.8. HRMS (EI): m/z calcd for $C_{16}{}^{13}C_2H_{19}O_5$ $[M+H]^+$: 317.1301, found: 317.1311.

Vanadium-Catalyzed Oxidation of 1-(3,5-Dimethoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propan-1-one-[2,3-$^{13}C_2$] (7-$^{13}C_2$). In an NMR tube, ketone **7**-$^{13}C_2$ (33.8 mg, 0.101 mmol) and (dipic)V^V(O)O^{i}Pr (3.8 mg, 0.011 mmol) were dissolved in DMSO-d_6 (1 mL) containing dimethylsulfone (5 mM) as an internal standard. An initial ^{1}H NMR spectrum was recorded, and then the reaction mixture was transferred to a 50 mL round-bottom flask. The flask was equipped with an air condenser and a stir bar, and heated at 100 °C for 48 h under air. The reaction was cooled to room temperature, at which time examination of the NMR spectrum revealed ~40% conversion of **7**-$^{13}C_2$, affording dehydrated ketone **8**-$^{13}C_2$ (14%), 3,5-dimethoxybenzoic acid (19%), and formic acid-$^{13}C_1$ (7%). The GC-MS trace of the reaction mixture revealed that 2-methoxyphenol was also formed as a product.

Reaction of 5-$^{13}C_2$ with Stoichiometric CuCl/TEMPO. In an NMR tube, lignin model **5**-$^{13}C_2$ (30 mg, 0.089 mmol) was dissolved in pyridine-d_5 (1 mL) containing dimethylsulfone (2.3 mg, 0.0244 mmol) as an internal standard. An initial spectrum was recorded, and then the reaction mixture was transferred to a thick-walled 50 mL Schlenk tube equipped with Teflon stopcock containing CuCl (8.9 mg, 0.089 mmol) and TEMPO (14.0 mg, 0.089 mmol) in pyridine-d_5 (2 mL) under air. Oxygen was bubbled into the red reaction mixture for 2 min, and the reactor sealed. The reaction mixture was heated at 100 °C with constant

stirring. The reaction was then monitored periodically by both ^{1}H NMR and GC-MS. After 18 h, approximately 70% of the starting material had been consumed, with the products consisting of 3,5-dimethoxybenzaldehyde (36%), ketone **7**-$^{13}C_2$ (2%), 3,5-dimethoxybenzoic acid (9%), 2-methoxyphenol (5%), dehydrated ketone **8**-$^{13}C_2$ (ca. 1%), and formic acid-$^{13}C_1$ (5%). Oxygen was bubbled into the reaction mixture for 2 min, the reactor was sealed, and then the reaction mixture heated at 100 °C. After 40 h, approximately 89% of the starting material had been consumed, with the products consisting of 3,5-dimethoxybenzalaldehyde (43%), 3,5-dimethoxybenzoic acid (13%), ketone **7**-$^{13}C_2$ (ca. 1%), dehydrated ketone **8**-$^{13}C_2$ (ca. 2%), 2-methoxyphenol (7%), and formic acid-$^{13}C_1$ (7%). Yields are expressed as a percentage of the theoretical maximum based on the initial amount of substrate. $^{13}C\{^1H\}$ NMR (100 MHz, pyr-d_5): δ 84.3 (s), 83.8 (d, $^1J_{C-C}$ = 44 Hz), 83.1 (d, $^1J_{C-C}$ = 44 Hz), 83.0 (d, $^1J_{C-C}$ = 45 Hz), 67.2 (d, $^1J_{C-C}$ = 44.5 Hz), 66.8 (d, $^1J_{C-C}$ = 44 Hz), 65.7 (d, $^1J_{C-C}$ = 44.5 Hz), 56.0 (d, $^1J_{C-C}$ = 43 Hz). For LC/MS data, see Supporting Information, Figure S34.

Reaction of 7 with Catalytic CuCl/TEMPO. In an NMR tube, ketone **7** (25 mg, 0.075 mmol) was dissolved in pyridine-d_5 (1 mL) containing dimethylsulfone (0.019 mmol) as an internal standard. An initial spectrum was recorded, and the reaction mixture was transferred to a thick-walled 50 mL Schlenk tube equipped with Teflon stopcock containing 10 mol % of CuCl (0.7 mg, 0.007 mmol) and 10 mol % of TEMPO (1.1 mg, 0.007 mmol) dissolved in pyridine-d_5 (1 mL) under air. Oxygen was bubbled into the red reaction mixture for 2 min, the reactor was sealed, and then the reaction was heated at 100 °C with constant stirring for 18 h. After cooling to room temperature, integration of the ^{1}H NMR spectrum revealed approximately 48% starting material was consumed and about 18% of the dehydrated ketone was formed. Several unidentified products were also formed; see Figure S32.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra and LC chromatograms for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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