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Chemoselective Metal-Free Aerobic Alcohol Oxidation in Lignin

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Supporting Information

ABSTRACT: An efficient organocatalytic method for chemoselective aerobic oxidation of secondary benzylic alcohols within lignin model compounds has been identified. Extension to selective oxidation in natural lignins has also been demonstrated. The optimal catalyst system consists of 4-acetamido-TEMPO (5 mol %; TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl) in combination with HNO_3 and HCl (10 mol % each). Preliminary studies highlight the prospect of combining this method with a subsequent oxidation step to achieve C−C bond cleavage.

Lignin is a biopolymer that represents a major component of nonedible biomass (15−30% by weight, 40% by energy).[1] It is one of the few naturally occurring sources of high-volume aromatics and therefore represents a potentially valuable feedstock for the production of organic chemicals.[2] Harnessing this resource, however, will require the identification of new chemical transformations that proceed with high efficiency and selectivity on a complex starting material. Whereas lignin has a heterogeneous structure, one of the most common structural units is the alkyl aryl ether unit containing a β−O−4 linkage between monomeric units (up to 90%; Figure 1),[2b,3] which

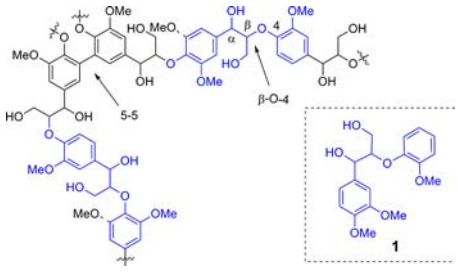

Figure 1. Representative structures of a fragment of lignin and the corresponding β−O−4-linked model compound **1**.

features a 2° benzylic alcohol and a 1° aliphatic alcohol. The present study was motivated by the recognition that chemoselective oxidation of either alcohol in this diol fragment could provide the basis for the production of low-molecular-weight aromatics from lignin (Figure 2). Here we describe a highly selective metal-free catalyst system for aerobic oxidation of the 2° benzylic alcohol in **1**, highlight its generality with a series of related lignin model compounds, and demonstrate its applicability to real lignin. Prospects for the use of this chemistry in lignin conversion are discussed.

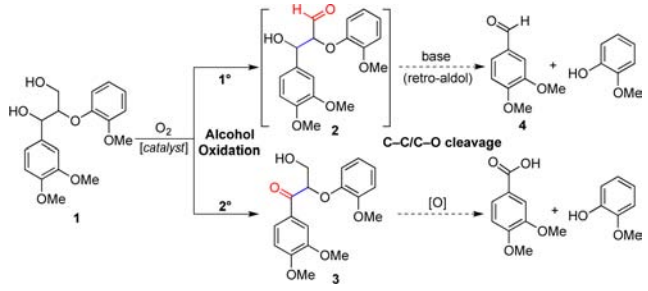

Figure 2. Chemoselective alcohol oxidation strategies for lignin and lignin model compounds.

Methods for oxidation of lignin and associated model compounds have been the focus of extensive investigation.[4] The vast majority of these methods employ harsh conditions, afford products with low selectivity and yield, and/or use simple model compounds (e.g., veratryl alcohol) that lack key lignin structural features.[2b,5] With the recognition that O_2 is the most desirable oxidant for large-scale applications, recent studies have begun to make progress in catalytic aerobic oxidation of more realistic lignin models, such as **1**. For example, the groups of Toste and Hanson have identified several vanadium complexes that show promising aerobic reactivity, in several cases promoting multistep reactions that directly afford C−C/C−O cleavage products.[6] The mechanistic complexity and number of steps in these and related transformations can make them difficult to optimize. The present study seeks to simplify the challenge by focusing on aerobic oxidation of an alcohol unit within lignin-type structures (cf. Figure 2). We anticipate that oxidation processes of this type could play an important role in the development of improved lignin-conversion technologies.

To benchmark the intrinsic reactivity of lignin model **1** and characterize possible oxidation products, we investigated reactions with various traditional reagents for alcohol oxidation [Chart 1A; for additional screening data and full reaction conditions, see the Supporting Information (SI)]. Good-to-excellent yields and selectivities for oxidation of the 2° benzylic alcohol were observed with chromium(VI) oxide, Dess−Martin periodinane, and TEMPO-derived oxoammonium reagents (entries 1, 2, 4, and 5; TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl). Veratraldehyde (**4**), observed as a minor product

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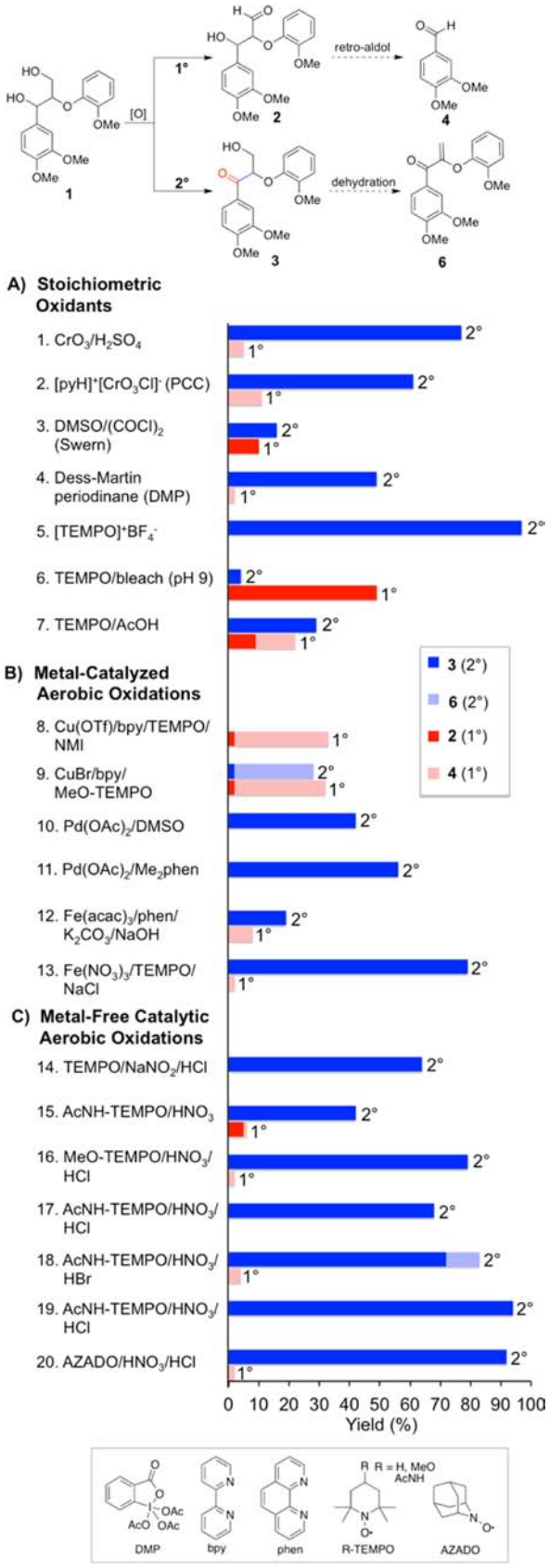
Chart 1. Oxidation Products of 1 and Yields Obtained with Different Reagents and Catalysts[a]



[a]Reactions were performed on a 0.05 mmol scale; for the conditions associated with each reaction, see the SI.

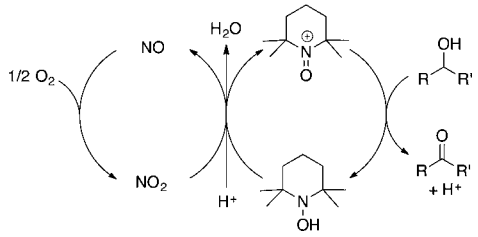
in several of these reactions, is believed to arise from oxidation of the 1° alcohol followed by retro-aldol bond cleavage.[7] Activated dimethyl sulfoxide (DMSO) methods (e.g., Swern; entry 3) and stoichiometric TEMPO in AcOH (entry 7) exhibited poor selectivities, affording products derived from both 1° and 2° alcohol oxidation. Bleach, in combination with catalytic TEMPO (2 mol %) at pH 9, was the only reagent that exhibited good selectivity for 1° alcohol oxidation (entry 6).

We recently reported a Cu^I/TEMPO catalyst system that showed good selectivity for 1° alcohol oxidation with a number of unprotected diols.[8] This catalyst system exhibited good selectivity, affording **4** as the major product (Chart 1, entry 8), but the formation of unidentified byproducts limits its utility. Other Cu/TEMPO-based systems were investigated (Chart 1, entry 9, and Table S1 in the SI), but no improvements in the reaction selectivity were identified.

Other catalyst systems for aerobic alcohol oxidation have been reported in the literature, and a number of these were tested (Chart 1, entries 10−13, and Table S1). Most of these methods afforded low conversion and/or selectivity in the oxidation of the dimeric model compound **1** (Chart 1). Pd(II) catalysts, including $Pd(OAc)_2$ in DMSO[9] and a $Pd(OAc)_2$/2,9-dimethyl-1,10-phenanthroline (Me_2phen) complex,[10] exhibited good selectivity for oxidation of the 2° benzylic alcohol, but the reactions were complicated by suboptimal mass balance (discrepancies between the conversion of **1** and the yield of **3**). Among transition-metal catalysts for aerobic oxidation of **1**, an $Fe(NO_3)_3$/TEMPO catalyst system[11] gave the highest yield of **3** (78%).

The effectiveness of TEMPO-based reagents and cocatalysts in the aerobic oxidation of **1** prompted us to consider other nitroxyl-catalyzed oxidation methods. Recently, several groups have described metal-free aerobic alcohol oxidation reactions that employ a catalytic nitroxyl species in combination with an inorganic nitrogen oxide cocatalyst. The latter species is proposed to mediate regeneration of an oxoammonium species by O_2 (e.g., Scheme 1).[12] We tested a variety of TEMPO and

Scheme 1. Simplified Proposed Catalytic Cycle for the Metal-Free Aerobic Oxidation of Alcohols



related nitroxyl derivatives as catalysts, with nitric acid and/or sodium nitrite as the cocatalyst. These conditions proved to be quite effective; highly selective oxidation of **1** to **3** was observed, with isolated yields of up to 94% (Chart 1, entry 19). The selected data in entries 14−20 of Chart 1 (see Table S2 for additional results) show that good results were obtained with a number of nitroxyl-based catalysts, but the best results were obtained with 4-acetamido-TEMPO (AcNH-TEMPO). The full reaction conditions associated with entry 19 featured 5 mol % AcNH-TEMPO in combination with 10 mol % HNO_3 and 10 mol % HCl as cocatalysts in 19:1 CH_3CN/H_2O as the solvent (1 atm O_2, 45 °C, 24 h). Other solvents such as acetic acid, ethyl acetate, and dioxane, which have been used in related alcohol oxidation methods, were less effective (see the SI for details).

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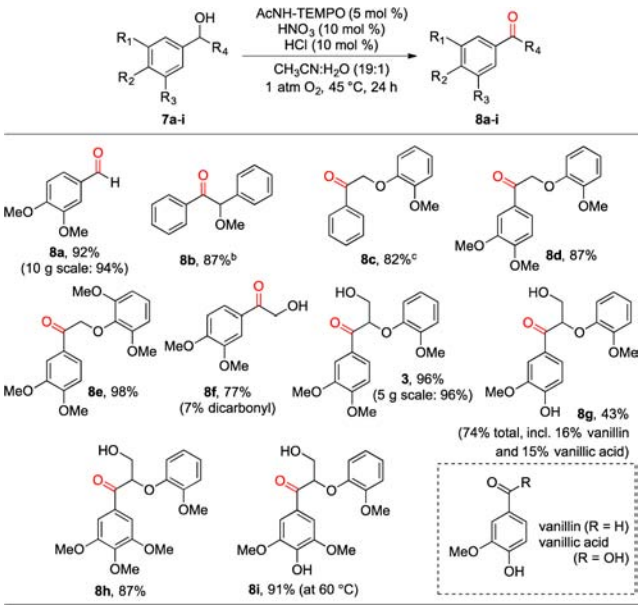
Chart 2. Metal-Free Aerobic Oxidation of Lignin Models[a]



[a]Conditions: 1 mmol of alcohol **7a–j** (0.2 M in 19:1 CH_3CN/H_2O). [b]10 mol % AA-TEMPO after 36 h. [c]Yield after 36 h.

A wide range of lignin model compounds have been used in previous oxidation studies.[4,6,13] Many of these are relatively simple benzylic alcohols (**7a–e**) that lack the additional hydroxymethyl fragment featured in lignin. The AcNH-TEMPO/HNO_3/HCl catalyst system is quite effective in the oxidation of these compounds, affording the corresponding benzylic carbonyl compounds (**8a–e**) in 82–98% isolated yield (Chart 2). The reactions of the similar compounds **7c–e** revealed that more electron-rich substrates reacted more rapidly and afforded higher yields of ketones **8c–e**. Oxidation of the vicinal diol **7f** was also selective, affording α-hydroxy benzylic ketone **8f** in 77% yield together with a 7% yield of the vicinal dicarbonyl product arising from oxidation of both the 1° and 2° alcohols. Of greater significance is the effectiveness of this oxidation method with a series of β–O–4-linked diols, including **1**, those with trioxygenated aromatic rings similar to the syringyl (**S**) unit in lignin (**7h** and **7i**), and those with guaiacyl (**G**)- and **S**-type phenols (**7g** and **7i**, respectively). Compounds containing free phenols present unique reactivity challenges, as they have been shown to decompose into complex product mixtures with other oxidation catalysts[14] and the acidic O–H group can lead to catalyst inhibition.[8] Each of these compounds exhibited good reactivity; excellent yields of ketones **8h** (87%) and **8i** (91%) were obtained with the corresponding **S**-type substrates. Oxidation of the **G**-type phenol **7g** gave **8g** in 43% yield, together with vanillin (16%) and vanillic acid (15%). The mechanistic origin of this product mixture remains to be elucidated; however, these products represent potentially valuable C–C cleavage products. Larger-scale reactions of **7a** (10 g) and **1** (5 g) showed excellent reproducibility.

Preliminary studies showed that this oxidation method also exhibits good reactivity and similar chemoselectivity with real lignin. Figure 3 shows 2D HSQC NMR spectra from an isolated sample of Aspen lignin (a typical hardwood lignin with an **S**:**G** ratio of ~2:1) before and after oxidation under the optimized conditions (cf. Chart 2[15]). The aromatic regions (Figure 3C,D) reveal that most of the **S** units and all of the **G** units were oxidized to their benzylic ketone analogues **S′** and **G′**. The aliphatic region (Figure 3A,B) further supports these chemical changes. Most of the correlations corresponding to the β-ether units (**A**) were replaced by ones corresponding to the analogues **A′** and the special case **A″**. The assignments of β-ethers **A′** and **A″** are based on comparison with known lignin spectra and available model-compound data.[16] The data suggest that a small fraction (~9%) of unoxidized β-**S** ether units were still present. It remains to be determined how other structures in lignin, such as the β–5-linked (phenylcoumaran) units (**B**) and the β–β-linked (resinol) units (**C**) reacted. We also note that cinnamaldehyde end groups (**X2**) in the original lignin disappeared (Figure 3B inset) but that vanillate units (**VA**) appeared in the oxidized materials (Figure 3D). In summary, these preliminary studies show that oxidation

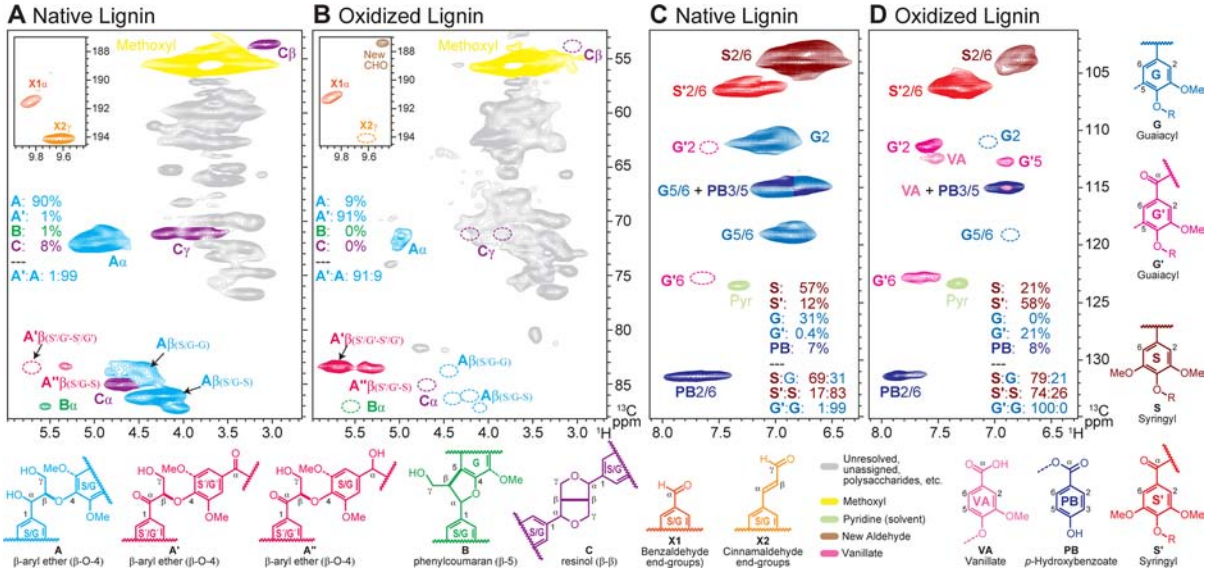


Figure 3. Partial 2D HSQC NMR spectra of an isolated Aspen lignin (in 4:1 DMSO-d_6/pyridine-d_5) before and after aerobic oxidation. Contours are color-coded to the structures responsible. Percentages are from volume integrals; **PB** is reported on an **S** + **G** basis, as it acylates aspen lignin and is not part of the core lignin structure.

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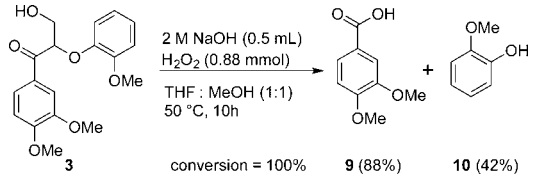
of the β−O−4-linked diols in lignin proceeds with high selectivity, similar to that seen with the simpler model compounds.

These results provide an important foundation for future efforts focused on selective C−C bond cleavage reactions. Preliminary studies toward this end are encouraging. Treatment of benzylic ketone **3** with H_2O_2 under basic conditions afforded veratric acid (**9**) in 88% yield together with a 42% yield of guaiacol (**10**) (Scheme 2; see the SI for further details). These

Scheme 2. Preliminary Study of Selective C−C Bond Cleavage



conditions were derived from previously reported methods for oxidative cleavage of diketones and α-alkoxy ketones with H_2O_2.[17] Although they are not necessarily optimized for the present application, they nevertheless provide strong support for the proposed lignin-conversion strategy illustrated in Figure 2.

In summary, we have identified a highly effective catalytic method for chemoselective aerobic oxidation of benzylic 2° alcohols in the presence of unprotected 1° alcohols, which are prevalent in lignin. The optimized catalyst system is entirely metal-free, consisting of a readily available TEMPO derivative and mineral acids, and is potentially suitable for large-scale conversion applications. Successful demonstration of this oxidation method with authentic lignin validates the utility of chemically and structurally faithful model compounds in the development of lignin-conversion technologies.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full catalyst screening data, experimental procedures, and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): A patent application has been submitted based on this work.

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