

A Photochemical Strategy for Lignin Degradation at Room Temperature

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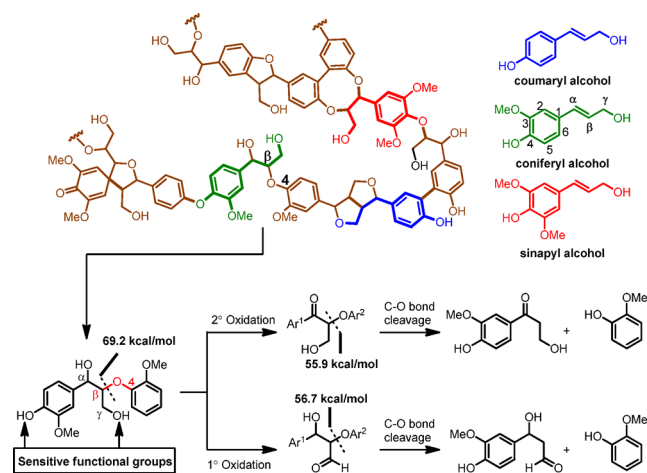
S Supporting Information

ABSTRACT: The development of a room-temperature lignin degradation strategy consisting of a chemoselective benzylic oxidation with a recyclable oxidant ([4-AcNH-TEMPO]BF₄) and a catalytic reductive C–O bond cleavage utilizing the photocatalyst [Ir(ppy)₂(dtbbpy)]PF₆ is described. This system was tested on relevant lignin model substrates containing β -O-4 linkages to generate fragmentation products in good to excellent yields.

Lignin, an important aromatic biopolymer responsible for the strength and shape of plants, constitutes 30% of non-fossil organic carbon.¹ The primary structure of lignin is composed of a diversely linked network of electron-rich phenylpropanols: coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol (Scheme 1).² Its abundance in nature, as well as its potential for providing high-value low-molecular weight aromatics,³ has made the controlled depolymerization of lignin an intense focus for both industrial and academic research. In industry, biomass is processed using the traditional kraft, sulfite, or soda pulping methods.⁴ Although these processes have yielded some marketable substances, the harsh and energy-intensive conditions do not allow for the production of useful quantities of commodity compounds from lignin. Several environmentally benign pulping processes have been investigated, such as the organosolv process,⁵ but they have yet to be widely implemented. Furthermore, although oxidative,⁶ reductive,⁷ and redox-neutral⁸ lignin degradation protocols have been demonstrated on processed lignin, native lignin, and lignin model systems, the development of a reliable procedure for the production of fine and specialty compounds from lignin remains underdeveloped.⁹

Several of the most promising catalytic lignin degradation methods to date have been recently developed by Baker, Hanson, Silks,^{6g,h,k} Hartwig,^{7f,h} Bergman, Ellman,^{8a} and Toste.^{8b,d} These methods represent diverse strategies toward lignin degradation utilizing transition-metal catalysis; however, these approaches also reveal significant challenges that have yet to be addressed. Specifically, catalytic lignin degradation typically requires elevated temperatures (>80 °C) and functional groups such as free phenols and γ -alcohols are not well tolerated. Therefore, we sought to address these issues by developing a room temperature lignin degradation method that could be performed efficiently in the presence of functional groups found in native and processed lignin. Herein we report a lignin degradation strategy that involves a two-step redox-neutral method. In the first step, Bobbitt's salt ([4-AcNH-TEMPO]BF₄)¹⁰ mediates a benzylic oxidation, which is followed by a chemoselective visible-light-

Scheme 1. Two-Step Redox-Neutral Lignin Degradation Strategy^a



^aRepresentation of the structure of lignin. Bond dissociation enthalpies, calculated with M06-2X functional and 6-311++G(d,p) basis set, indicate that alcohol oxidation can significantly weaken β -O-4 linkages.¹²

mediated reductive C–O bond cleavage promoted by the photocatalyst [Ir(ppy)₂(dtbbpy)]PF₆.¹¹

Although many types of C–O bonds are found in the lignin biopolymer, the most common type is the β -O-4 linkage (see Scheme 1), comprising >50% of all linkages found in lignocelluloses.^{9a} DFT calculations have indicated that the C–O bond of the β -O-4 linkage is significantly weakened (~ 14 kcal/mol) upon the oxidation of the α - or γ -carbon.¹² Based upon these calculations, we postulated that it would be possible to chemoselectively cleave the C–O bond of the β -O-4 linkage after selective oxidation (benzylic or primary) followed by a single electron-transfer event to allow access to complementary fragmentation partners. The cleavage of C–O bonds utilizing visible-light-active photocatalysts has been reported by Hasegawa,¹³ Ollivier,¹⁴ and our group.¹⁵ In particular, the groups of Hasegawa and Ollivier studied the reductive cleavage of strained C–O bonds of ketoepoxides with the photocatalyst Ru(bpy)₃Cl₂ to generate β -hydroxy ketones. However, a generalized visible-light-mediated reductive cleavage of C $_{\alpha}$ –O bonds (C $_{\beta}$ in lignin is the equivalent to C $_{\alpha}$ for a carbonyl) has not yet been reported. We identified this opportunity to develop such a method in the

Received: November 6, 2013

context of our goal toward a mild and chemoselective lignin degradation.

We began our investigation by exploring C α –O bond cleavage of ketones and aldehydes. Based on our previous success with cleaving C–X bonds,¹⁶ we hypothesized that we could apply photoredox catalysis^{17,18} toward the C α –O bond cleavage of lignin model substrate **1**. Evaluation of a series of common photoredox catalysts including Ru(bpy)₃Cl₂,¹⁹ *fac*-Ir(ppy)₃,²⁰ [Ir(ppy)₂(dtbbpy)]PF₆,¹¹ [Ir{dF(CF₃)ppy}₂(dtbbpy)]PF₆,²¹ Cu(dap)₂Cl,²² and eosin Y²³ revealed that *fac*-Ir(ppy)₃ and [Ir(ppy)₂(dtbbpy)]PF₆ could effectively promote the C α –O bond cleavage of **1** to give 4'-methoxyacetophenone and guaiacol in high conversions.²⁴ Upon discovering that [Ir(ppy)₂(dtbbpy)]PF₆ could be employed without degassing, we were able to develop optimized reaction conditions capable of fully fragmenting **1** in 12 h to generate 4'-methoxyacetophenone and guaiacol in 88% and 89% yield, respectively (Table 1, entry 1).

We next examined the C α –O bond cleavage in more detail by varying the ether substituents (Table 1). A substrate bearing an α -acetoxy group instead of guaiacol (**2**) reached full conversion in significantly less time, indicating that the reaction rate is

strongly influenced by the pK_a of the leaving group. The reaction is also influenced by the reactivity of the carbonyl portion of the molecule, as illustrated by the absence of fragmentation products upon substitution of the phenyl ketone with a methyl ketone (**3**), presumably due to the larger reduction potential of methyl ketones in comparison to phenyl ketones.²⁵ On the contrary, commercially available 2-(benzyloxy)acetaldehyde (**4**) underwent efficient fragmentation, cleaving the much stronger C–O bond, to give benzyl alcohol in high yield. Substrates **5–8** were selected to test the generality of the catalytic C–O bond cleavage reaction on relevant lignin model systems. Specifically, substrates **5–7** represent products of a benzylic oxidation on each of the different phenylpropanol monomers, whereas substrate **8** represents a lignin model system of coniferyl alcohol that has been oxidized at the primary alcohol (see Scheme 1). As expected, lignin model systems **5–8** all underwent efficient fragmentation. However, although the fragmentation of substrate **8** gave good yields of guaiacol, the complementary aldehyde fragment could not be isolated (Table 1, entry 8), possibly due to polymerization of the expected cinnamaldehyde product. Instead, we were able to isolate ethyl 3,4-dimethoxybenzoate in 30% isolated yield, which represents a unique oxidative cleavage of the α – β linkage.²⁴

Overall, the mild reaction conditions allow for the atom-economical reductive fragmentation of the lignin model systems to generate guaiacol and β -hydroxy phenyl ketones. No evidence of undesired oxidation²⁶ or further fragmentation of the guaiacol^{7f} was observed, and the β -hydroxy phenyl ketones did not undergo retro-aldol or elimination reactions under our conditions.^{8b} The ability to generate these fragmentation products under mild conditions and in high yields highlights the potential ability of this method to assist in the production of commodity compounds.⁹ In addition, the successful fragmentation of substrate **8** highlights the versatility of this lignin degradation strategy because γ -alcohols typically survive lignin pulping methods, whereas benzylic alcohols are known to undergo substitution to form benzylic thiols (kraft), benzylic sulfones (sulfite), and benzylic ethers (organosolv).^{9a} Furthermore, the β -hydroxy phenyl ketone fragments produced from substrates **5–7** have not been generated by any other lignin degradation method in high yields, particularly **7**, which is a difficult substrate due to the free phenol.^{6a,b,h,i,7g,8a–d}

Native lignin, as well as processed lignin, is not typically obtained in an oxidized form,^{9a} and therefore an efficient method for oxidation, prior to any C–O bond reduction, is necessary. Thus, we next examined the development of an oxidation method that could be used to oxidize either the α - or γ -carbon of β -O-4 lignin model systems. Such an oxidation would give α -alkoxyketones or α -alkoxyaldehydes that could undergo reductive fragmentation, as described above. During our investigation of oxidation conditions,²⁴ the Stahl group reported an elegant catalytic aerobic benzylic alcohol oxidation of lignin model systems utilizing 4-AcNH-TEMPO (5 mol%), HNO₃ (10 mol%), and HCl (10 mol%).²⁶ This set of conditions can be applied to produce ketones such as **1** and **5–7**, which can subsequently be used as substrates in our reductive C α –O bond cleavage reaction to give the fragmentation products in high yields. Unfortunately, we have not yet been able to successfully implement Stahl's oxidation in sequence with the photocatalytic reductive fragmentation without purification, precluding a one-pot procedure. It is possible that the presence of 4-AcNH-TEMPO may be interfering with photocatalyst turnover. Consequently, we turned to [4-AcNH-TEMPO]BF₄ for three

Table 1. Substrate Scope of Visible-Light-Mediated C α –O Bond Cleavage

$\text{X}-\text{C}(=\text{O})-\text{CH}(\text{R}^1)-\text{O}-\text{R}^2 \xrightarrow[\text{visible light, MeCN, RT}]{[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6 (1.0 \text{ mol } \%), \text{DIPEA} (3.0 \text{ equiv}), \text{HCO}_2\text{H} (3.0 \text{ equiv})} \text{X}-\text{C}(=\text{O})-\text{CH}(\text{R}^1) + \text{R}^2\text{OH}$			
entry	substrate	time (h)	products ^a
1		12	
2		4	 Not isolated
3		24	No reaction
4		12	Not isolated
5		15	
6		18	
7		48	
8		24	

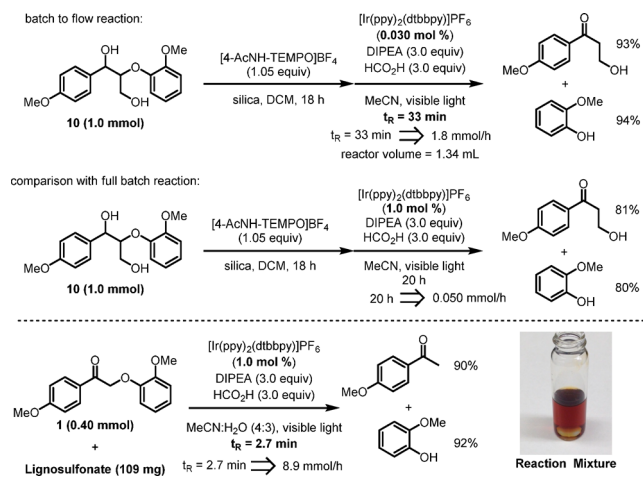
^aYields of products isolated via column chromatography and based on an average of two runs.

main reasons. First, [4-AcNH-TEMPO]BF₄ has been shown to selectively oxidize benzylic alcohols at room temperature. Second, the hydroxylamine byproduct can be removed from the reaction mixture by adsorption onto silica. Third, the spent oxidant can be recycled using hydrogen peroxide and fluoroboric acid.^{10a,c} As predicted, substrates **9–11** were efficiently oxidized to benzylic ketones with [4-AcNH-TEMPO]BF₄, and simple filtration provided the products in high purity.²⁷

By combining the chemoselective benzylic oxidation utilizing [4-AcNH-TEMPO]BF₄ and our visible-light-mediated C_α–O bond cleavage, we successfully developed a lignin degradation method that can be performed at ambient temperature. Substrates **9–11** were cleanly oxidized to benzylic ketones by mixing with a slight excess of [4-AcNH-TEMPO]BF₄ and silica. Upon completion of the oxidation, the mixture was filtered, and dichloromethane was removed in vacuo. Next, DIPEA, formic acid, [Ir(ppy)₂(dtbbpy)]PF₆, and MeCN were added, and the reaction mixture was irradiated with blue LEDs to produce the fragmentation products in high yields (Table 2). This system is particularly amenable to a batch-to-flow^{28,29} reaction setup in which the oxidation is performed in batch and the reductive cleavage is performed in flow. Utilizing an easily assembled flow reactor,²⁴ the rate of substrate consumption for **10** could be increased to 1.8 mmol/h in flow from 0.050 mmol/h in batch, even when the catalyst loading is reduced from 1.0 to 0.030 mol% (Scheme 2, top). The ability to perform the reductive C_α–O bond cleavage reaction at lower catalyst loading is not exclusive to flow reactions, as is demonstrated by the gram-scale batch fragmentation of substrate **11** with only 0.030 mol% catalyst loading (not shown). Surprisingly, in both of these cases the use of 0.030 mol% catalyst loading gave slightly improved yields for both fragmentation products as compared to 1.0 mol%.

At the outset, we were aware of the potential difficulty of irradiating darkly colored solutions of lignin. Therefore, we performed the photocatalytic reduction of **1** (0.4 mmol) in the presence of an equivalent weight of liginosulfonate. The dark brown color of the resulting solution prevented efficient irradiation of the reaction medium in batch, which resulted in

Scheme 2. Improving Lignin Degradation Strategy Utilizing Continuous Flow and Lower Catalyst Loading



no conversion after 48 h. However, when the same reaction was carried out in flow, we observed full consumption of **1**, providing a high yield of both guaiacol and 4'-methoxyacetophenone, despite reduced light transmittance (Scheme 2). This clearly demonstrates the ability of our reaction to operate in the presence of sulfonate groups, solvent quantities of water, and dark colored impurities found in liginosulfonate.

We propose that the mechanism of the reductive C_α–O bond cleavage is based on the well-established reductive quenching cycle of [Ir(ppy)₂(dtbbpy)]PF₆ and is analogous to the reductive dehalogenation mechanism previously studied by our group.¹⁶ Visible light absorption by the photocatalyst initiates a metal-to-ligand charge transfer to generate the excited state [Ir]^{3+*}. This excited state accepts an electron from the amine or amine–formate complex to generate [Ir]²⁺, a strong reductant (−1.51 V vs SCE). The [Ir]²⁺ complex performs a single electron transfer to the benzylic ketone or aliphatic aldehyde to generate a radical anion, which undergoes a fragmentation to generate an alkoxy anion and the corresponding C_α–radical. Protonation of the alkoxy anion and H-atom abstraction by C_α–radical produces the fragmentation products.

In conclusion, we have described a potential mild and efficient two-stage lignin degradation strategy that proceeds through a selective [4-AcNH-TEMPO]BF₄-mediated oxidation and a photoredox-catalyzed reductive C–O bond cleavage. The separation of the oxidation and reduction steps, as well as the mild nature of the reaction conditions, allows for greater control of bond construction and cleavage to ultimately maintain the integrity of the fragmentation products. This proof-of-principle approach addresses many of the challenges in the chemoselective degradation of lignin, which include functional group tolerance and mild reaction conditions; however, aspects of scalability, stoichiometric waste, and cost remain to be addressed. Further development of a photocatalytic depolymerization that obviates the need for superstoichiometric additives is currently ongoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Table 2. Two-Step Degradation of Lignin Model Systems

substrate	oxid. time (h)	red. time (h)	products ^a
 9	15	16	85% 83%
 10	18	20	81% 80%
 11	15	14	84% 93%

^aYields of products isolated via column chromatography and based on an average of two runs.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the University of Michigan, the Alfred P. Sloan Foundation, and the Camille and Henry Dreyfus Foundation is gratefully acknowledged. J.D.N. thanks The American Chemical Society Division of Organic Chemistry and Amgen for a graduate fellowship. B.S.M. thanks Vertex for a graduate fellowship.

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