

Sequential Oxidation-Depolymerization Strategies for Lignin Conversion to Low Molecular Weight Aromatic Chemicals

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Abstract: Lignin is the largest source of bio-derived aromatic chemicals, and oxidative conversion of this polymeric material can generate valuable oxygenated aromatic compounds. Oxidative depolymerization of lignosulfonate feedstocks under alkaline conditions is used commercially for vanillin production. Recent studies have led to other oxidation methods that access different aromatic products from lignin in good yields. A particularly effective strategy that accesses some of the highest yields of aromatic monomers to date features a two-step process in which the oxidation of specific alcohol groups in lignin is followed by an oxidative, reductive, or redox-neutral step that cleaves the polymer into aromatic monomers and oligomers. Studies of model compounds have provided crucial mechanistic insights and contributed to the development of effective lignin depolymerization methods. This review provides a general overview of lignin depolymerization methods, followed by a survey of oxidation-depolymerization methods that access oxygenated aromatic monomers in good yields.

Keywords: Lignin Valorization, Oxidation, Depolymerization, Hydrolysis, Aromatics

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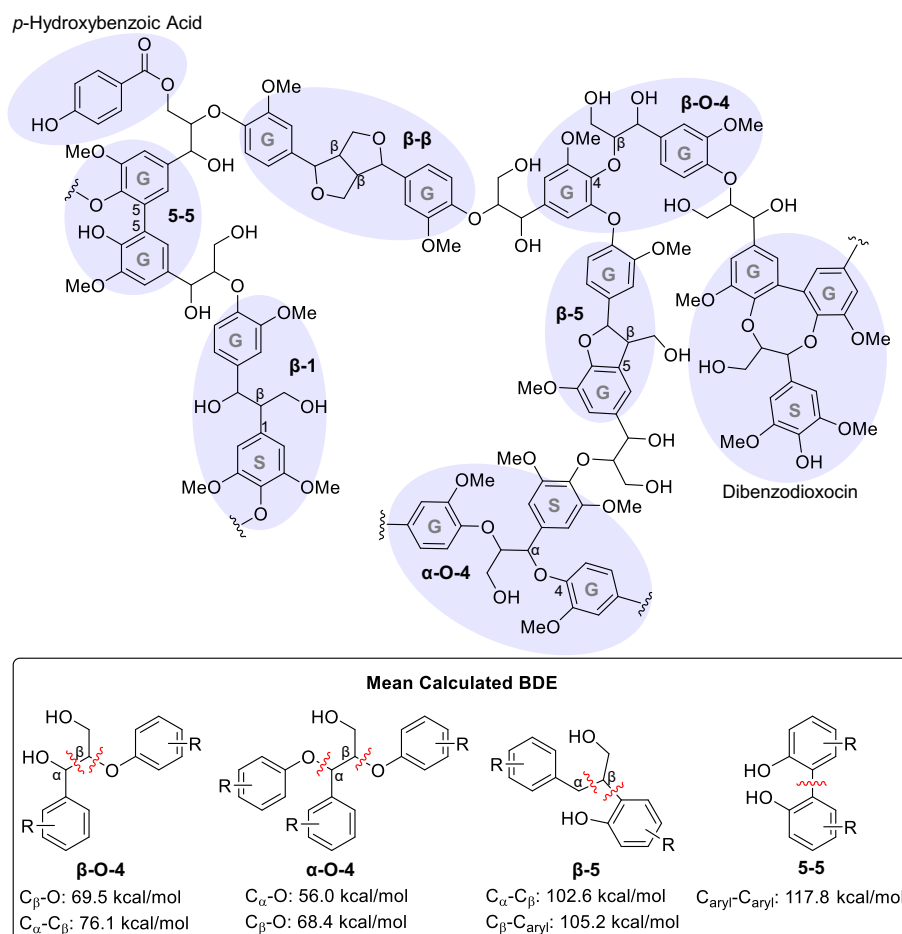
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1. Introduction

Increasing global demand for sustainable alternatives to organic chemicals derived from coal and petroleum is driving efforts to leverage biomass-derived feedstocks. Lignin is a significant component of lignocellulosic biomass and represents an abundant source of functionalized, renewable aromatics that could be used directly as valuable products or transformed into fuels or chemicals. Many tons of lignin are produced as a byproduct of the pulp and paper and biofuel industries that prioritize acquisition of cellulose;¹ however, the majority of this material is burned as low value fuel to provide energy.² Strategies to convert lignin into value-added chemicals could play an important role in supporting the economic viability of future biorefineries.

Lignin is a non-repeating, mostly linear biopolymer created by radical coupling of monolignols, consisting of *p*-hydroxy3-phenylpropanol-derived building blocks.³ Lignin is composed of different quantities of *para*-hydroxyphenyl (H), guaiacyl (G) and syringyl (S) aromatic subunits linked via C-C and C-O bonds comprising β -O-4, α -O-4, β -1, β -5, β - β , and 5-5 units (**Figure 1**). Many plant sources contain other aromatic units, such as *p*-hydroxybenzoate, appended to the alcohols in these linker units. The relative abundance of each type of subunit and linkage varies between plant species, and that amount of lignin can vary from 15-35% of the overall biomass weight.⁴ Multiple methods have been developed to extract lignin from biomass, including Kraft, enzymatic, organosolv, and mild acidolysis methods,⁵ and each can lead to modifications of the lignin structure that influence subsequent depolymerization. Some methods of lignin depolymerization, such as pyrolysis, use harsh conditions to break many inter-unit linkages and generate a wide array of small molecule products.⁶ Other depolymerization methods are tailored to cleave specific linkages and lead to a smaller distribution of products. The β -O-4 ether unit is the most common linkage in lignin (40-70 wt%) and is among the most readily

cleaved. It contains comparatively weak C-C/C-O bonds with bond dissociation energies (BDE) as low as 67.0 kcal/mol.⁷ The prevalence and reactivity of β -O-4 lignin units have made them a target for many depolymerization strategies and provide a basis for generation of S- and G-derived aromatic products in up to 45–55% (hardwoods) or 20–30% (softwood) monomer yields,^{8,9} often supplemented by *p*-hydroxybenzoate and other aromatic groups appended to the naturally occurring polymer.



[Insert Figure 1 here]
Figure 1. Lignin structure (top) and bond strengths with typical lignin linkages.

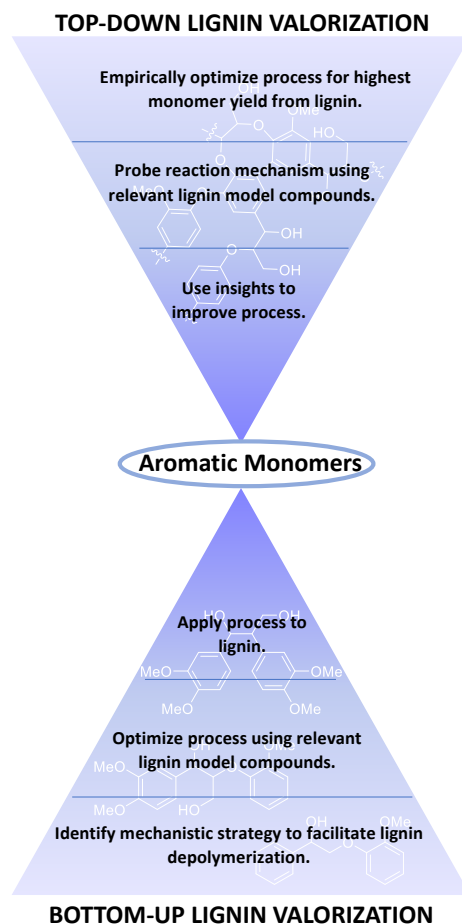
Reduction methods have been the focus of extensive attention for lignin depolymerization. These have been reviewed elsewhere,^{8,10,11} but reductive catalytic fractionation (RCF) methods are particularly noteworthy because they are capable of producing near theoretical yields of aromatics

in one step.¹²⁻¹⁸ These methods combine heterogeneous supported metal catalysts with solubilized lignin or raw biomass under elevated temperature (180-250 °C) and H₂ pressure (5-15 MPa). RCF conditions lead to hydrogenation and hydrogenolysis pathways that stabilize reactive lignin intermediates and prevent lignin degradation and condensation in the process of generating propylphenol-derived aromatics.

Oxidative lignin depolymerization strategies are appealing because they provide access to a different set of value-added aromatics relative to those obtained from reduction methods. A prominent example is vanillin, an aromatic aldehyde derived from the G subunit that is widely used in the flavor, fragrance, and cosmetic industries.¹⁹ It has been produced commercially through oxidative lignin depolymerization using copper-based catalysts under strong alkaline conditions.²⁰⁻²² Recent research has focused on identifying new oxidative depolymerization strategies to generate other lignin-derived aromatics.^{23,24} Oxidized aromatics derived from lignin have strategic benefits for microbial funneling of product mixtures into a single value-added chemical, owing to the higher solubility of these precursors in the aqueous growth media.^{25,26}

Research into the development of oxidative lignin depolymerization processes has featured two general strategies: top-down and bottom-up (**Figure 2**). *Top-down* strategies directly use raw lignocellulosic biomass or extracted lignin as the feedstock in efforts to develop new depolymerization methods. In contrast, *bottom-up* strategies start with well-defined model compounds in an effort to identify new catalytic methods and characterize mechanisms of reactions capable of cleaving strategic linkages in lignin, such as β -O-4 units. Successful examples are then tested on authentic lignin samples to assess their efficacy with complex feedstocks. This review provides a brief overview of methods that have been developed for oxidative conversion of lignin and related models into aromatic monomers, followed by an extensive presentation of two-step

alcohol oxidation/bond cleavage methods that have proven to be particularly effective for lignin conversion into oxygenated aromatic monomers. These processes correspond to bottom-up strategies originating from systematic studies of reactions with model compounds that were successfully translated to depolymerization of lignin in high yield.^{27–29}



[Insert Figure 2 here]

Figure 2. Top-down and bottom-up strategies for lignin depolymerization.

2. Top-down vs. bottom-up strategies for lignin depolymerization

2.1 Top-down strategies for efficient aromatic monomer production

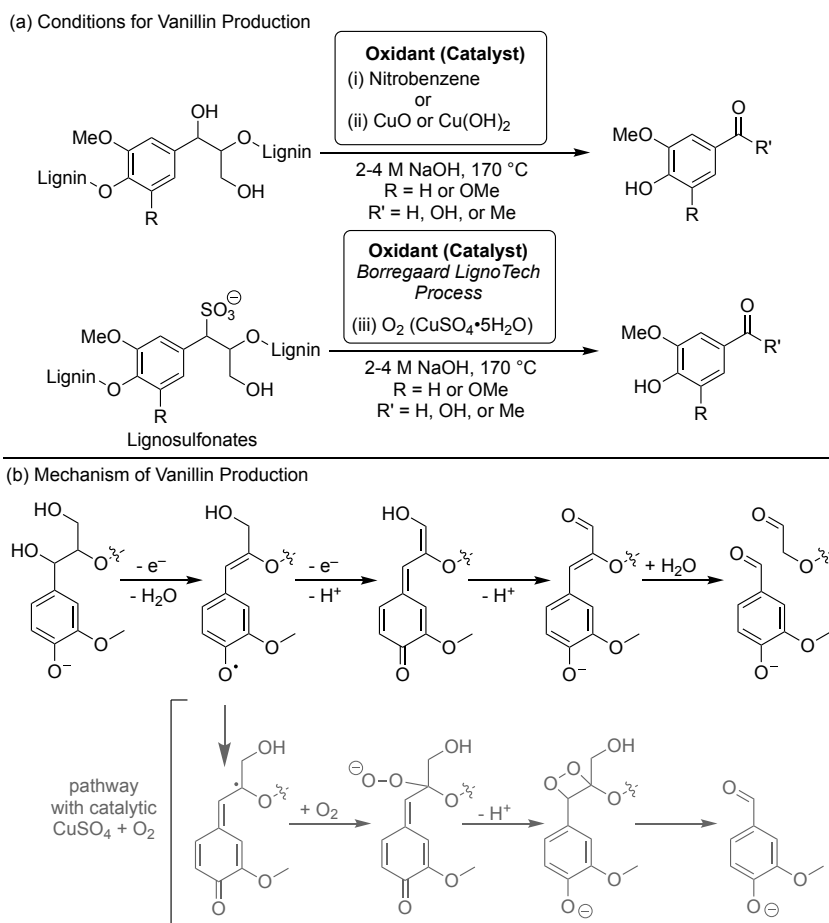
Top-down strategies for lignin depolymerization (**Figure 2**) empirically optimize methods to obtain monomers from biomass or extracted lignin, frontloading challenges associated with using

a complex polymer substrate, such as solubility, source variation, and product analysis. Reaction intermediates generated during reactions with the complex feedstock are difficult to detect or characterize, and thus limit mechanistic insights that could be used to guide process optimization. Nonetheless, top-down approaches provide the most direct test of the utility of different methods for lignin conversion into aromatic monomers.

Top-down strategies have led to several effective oxidative methods to obtain vanillin from lignin. In the 1940s, stoichiometric oxidants under basic conditions were found to convert lignin materials into vanillin (**Figure 3a-i/ii**).^{30,31} Mechanistic studies implicate a single-electron-transfer (SET) pathway that generates radicals in alkaline solution, which result in homolytic cleavage of the C_α-C_β bond of β-O-4 linkages to form the aldehyde product (**Figure 3b**, top sequence).³² As a representative protocol, nitrobenzene (2-4 M NaOH, 160-180 °C, 2-3 h) yields up to 16 wt% vanillin from softwood sulfite lignin as the major product.^{20,33} The cost and toxic by-products of nitrobenzene relegate its use to laboratory scale applications, for example, to quantify the β-O-4 linkages and/or the relative amounts of uncondensed H, G, and S units of various lignin sources.³⁴ CuO was also identified as an effective oxidant, although it was used at rather high loading (up to 600 wt%) and the vanillin is slowly converted to vanillic acid under the oxidizing alkaline conditions.^{22,35}

Molecular oxygen (O₂) is an ideal oxidant, and high yields of vanillin are possible by controlling the O₂ partial pressure, reaction temperature, and reaction pH in the presence of CuSO₄ as a catalyst (**Figure 3a-iii**).^{36,37} The reaction pathway is proposed to be initiated by SET, similar to the stoichiometric CuO conditions; however, the organic radicals react with O₂ to form reactive intermediates that lead to formation of the benzaldehyde product (**Figure 3b**, bottom).³⁸ A variation of this method was developed by Borregaard for conversion of lignosulfonates, which

provides the basis for commercial production of bio-based vanillin.^{20,22,39} Other variations of this method have been used for direct treatment of raw biomass, enabling direct conversion to low molecular weight chemicals.⁴⁰⁻⁴²



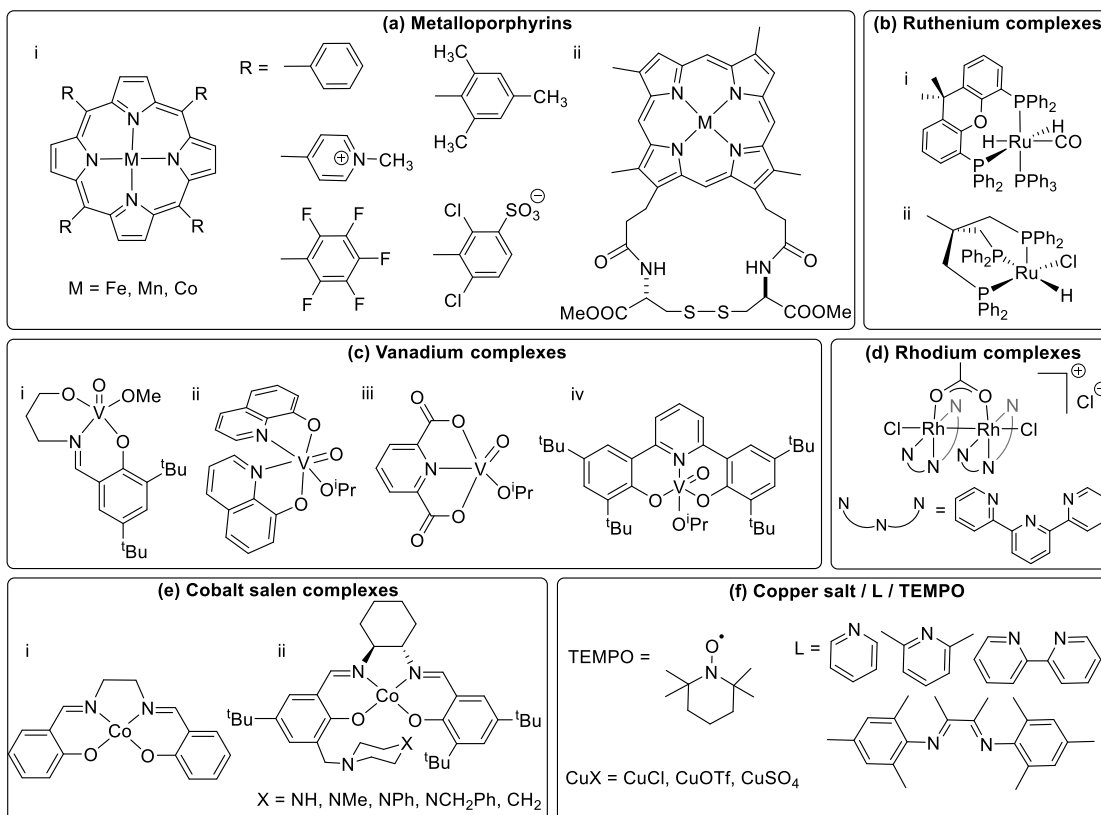
[Insert Figure 3 here]

Figure 3. (a) Typical reacting conditions to depolymerize lignosulphonates through (i) nitrobenzene, (ii) copper-based catalyst, or (iii) commercial vanillin production used by Borregaard; (b) proposed mechanism of vanillin formation under alkaline oxidative conditions.

2.2 Bottom-up strategy for mechanistic insight of lignin depolymerization process

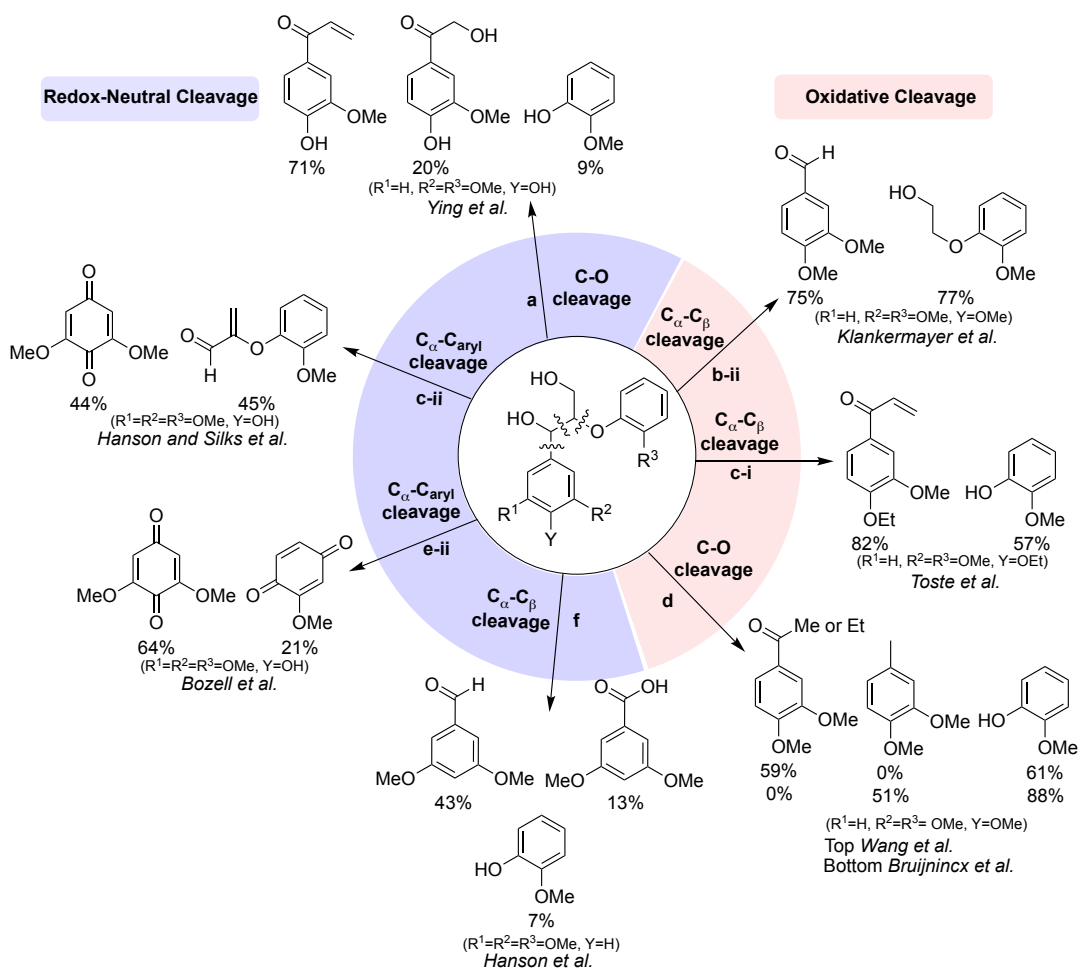
Bottom-up lignin depolymerization (**Figure 2**) refers to studies that start with low molecular weight model substrates containing representative fragments of native lignin (e.g., β -O-4 units). These lignin-like models allow for straightforward testing and analysis of chemical reactivity and facilitate mechanistic studies. Numerous homogeneous transition-metal catalysts have been used

for selective cleavage of C-C and C-O bonds in β -O-4 model compounds via oxidative and redox neutral pathways (**Figure 4**). As summarized in **Figure 5** and elaborated below, a number of these methods generate aromatic monomers in good yield.



[Insert Figure 4 here]

Figure 4. Metal complex catalysts used for selective bond cleavage of lignin model compounds.



[Insert Figure 5 here]

Figure 5. Yields of aromatic monomer products through selective bond cleavage of β -O-4 model compounds via different metal complex catalysts listed in Figure 4.

Naturally occurring enzymes, such as Fe and Mn-based peroxidases, contribute to fungal degradation of lignin,^{43,44} and biomimetic Fe, Mn, and Co porphyrins have been widely tested as synthetic catalysts for lignin and lignin-model degradation (**Figure 4a-i**). Various oxidants such as H₂O₂, tBuOOH, and oxone have been used to generate high-valent metal-oxo reactive species.^{45,46} The metal-oxo species are proposed to promote SET from electron-rich phenol and non-phenolic compounds to generate a radical cation that initiates further reaction and degradation of the lignin material. Early studies showed that sterically-hindered porphyrins mimic enzyme activity and limit oxidative degradation of the porphyrin scaffold.^{47,48} More recently, Ying and coworkers demonstrated that cobalt-containing deuteroporphyrin derivatives with tethered

disulfide groups (**Figure 4a-ii**) depolymerize phenolic lignin models, accessing >90% yield of monomers from C_β-O cleavage monomers with oxone as the oxidant (**Figure 5a**).⁴⁹ A lower yield of guaiacol monomer reflects overoxidation of the phenol, resulting in ring cleavage. Subsequent application of this catalyst to various lignin samples generated significant quantities (30+ wt% in several cases) of a lignin oil containing H/G/S-derived aromatics and aliphatic material.

Bergman and Ellman showed that a Ru-based complex, Ru(H)₂(CO)(PPh₃)(xantphos) (**Figure 4b-i**) effects C-O bond cleavage in simplified β-O-4 model compounds that lack the -C_γH₂OH functional group.⁵⁰ The catalyst mediates tandem catalytic dehydrogenation/C-O bond cleavage in a redox-neutral process. Incorporation of the C_γH₂OH fragment that is present in lignin, however, blocks dehydrogenation and prevents subsequent C-O bond cleavage.^{51,52} Modified methods from other groups, using KOH addition or acetylation of the γ-hydroxyl group, were able to overcome this problem.^{53,54} A Ru-triphos catalyst system (**Figure 4b-ii**) was developed by Klankermayer and coworkers to cleave the C_α-C_β bond in β-O-4 model compounds containing a -C_γH₂OH moiety. The process involves primary alcohol dehydrogenation followed by retro-aldol reaction to achieve C-C bond cleavage (**Figure 5b-ii**).⁵⁵

Oxovanadium catalysts have been used for cleavage of lignin model compounds in both redox-neutral and oxidative methods.⁵⁶ Toste and coworkers used Schiff-base vanadium catalysts (**Figure 4c-i**) to generate monomeric enone and guaiacol products from dimeric and trimeric β-O-4 models (**Figure 5c-i**). The authors proposed that the reaction is initiated by hydrogen atom abstraction (HAT) from the β-O-4 secondary alcohol, followed by subsequent homolysis of the C_β-O bond.⁵⁷ When the catalytic oxovanadium system was applied to organosolv grass lignin, a decrease in the lignin polymer molecular weight was observed and selective β-O-4 degradation was demonstrated by 2D NMR spectroscopy, but less than 3 wt% yield of identified monomers

was recovered.⁵⁸ Under similar reaction conditions using V-quinolate catalysts (**Figure 4c-ii**), Hanson, Silks, and coworkers propose an oxidative mechanism in which the catalyst promotes SET oxidation of phenolic model compounds to generate a phenoxy radical, followed by subsequent C_{aryl}-C_α bond cleavage (**Figure 5c-ii**).⁵⁹ Baker et al. showed that V-quinolate complexes catalyze oxidation of mixed-hardwood organosolv lignin, decreasing the average molecular weight by 77%, although monomer yields were not reported.⁶⁰ Other types of vanadium-based catalysts, (dipic)V^V(O)OiPr (**Figure 4c-iii**) and V-bisphenolate (**Figure 4c-iv**) are less selective and generated a mixture of C_α-C_β and redox-neutral C_β-O bond cleavage products depending on substrate structure and reaction condition.^{61,62}

A binuclear Rh complex, reported by Li and Wang (**Figure 4d**), was used to cleave a series of lignin model compounds and authentic lignin via hydrogen-transfer methods. Rh-catalyzed dehydrogenation of the benzylic alcohol produces a ketone intermediate that undergoes subsequent C_β-O bond cleavage (110 °C, Ar, NaOH) to afford 61-64% guaiacol and 58-61% methyl- and ethylarene products (**Figure 5d**).⁶³ Almost complete deconstruction of raw basswood powder sample resulted in 26.6 wt % aromatic oil, although monomer yields of only 2.3 wt% (based on the starting raw basswood powder) were generated. Bruijninx and coworkers used Sc(OTf)₃ as a Lewis acid catalyst to promote cleavage of ether bonds. When paired with Rh-catalyzed decarbonylation of aliphatic aldehydes, a Rh/Sc(OTf)₃ catalyst system provided stable aromatic product mixtures. This chemistry led to good yields of methylarenes (51%) and guaiacols (88%) from model compounds, and also accessed aromatic monomers from pine (6.8 wt%) and poplar (9.8 %) sawdust.⁶⁴

Cobalt-Schiff base complexes have been studied extensively for phenol oxidation with O₂.^{65,66} Bozell and coworkers have investigated Co(salen) complexes (**Figure 4e**) that react with O₂ to

form a superoxide adduct that can abstract a hydrogen atom from phenols, generating a phenoxyl radical that can induce cleavage of C_α-C_{aryl} bonds in the lignin models.^{67,68} Catalysts from a family of unsymmetrical Co-Schiff base complexes, each bearing a bulky heterocyclic nitrogen base on the ligand (**Figure 4e-ii**), convert phenolic lignin models to benzoquinones in yields up to 64% (**Figure 5e-ii**).⁶⁸ When applied to organosolv poplar lignin, however, only small quantities of monomers were obtained due to the low phenolic content of organosolv lignin.

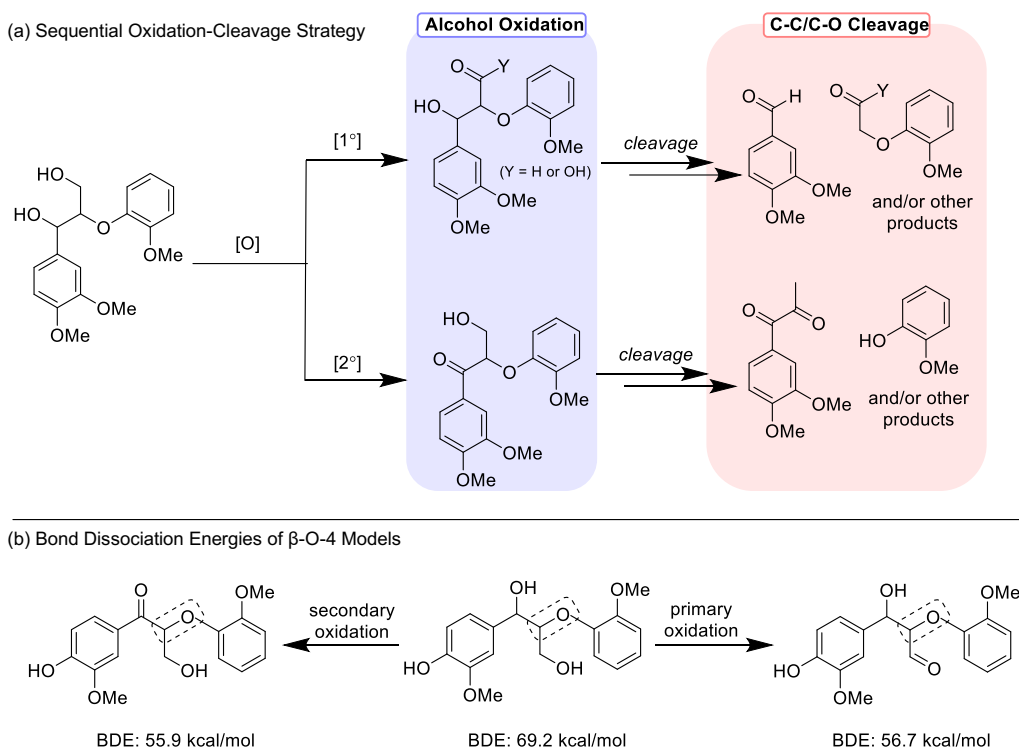
Copper/nitroxyl catalyst systems for aerobic alcohol oxidation⁶⁹ have been investigated with lignin model compounds. Initial studies by Baker, Wu, Hanson and coworkers used 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as the nitroxyl catalyst in combination with CuCl, pyridine, and O₂ at 100 °C. Limited activity for aerobic oxidative cleavage of simplified lignin models was attributed to instability of the active copper catalyst (**Figure 4f**).^{56,61} Use of stoichiometric CuCl/TEMPO with an S/G lignin β-O-4 dimer led to 89% conversion to cleavage products, albeit with only 7-43% yield of monomeric aromatic products (**Figure 5f**). A modified Cu/bpy/TEMPO catalyst system (bpy = 2,2'-bipyridine),⁷⁰ investigated by Stahl and coworkers,²⁷ is somewhat more effective and will be revisited below.

This brief survey of catalytic methods is not comprehensive, but it illustrates the types of "bottom-up" strategies that have been pursued using well-defined model compounds. The attempts to achieve direct conversion of dimeric models into aromatic monomers in a single step has led to mixed success, and oxidative methods derived from these studies have not (yet) led to lignin depolymerization strategies that are competitive with reductive methods or previously known oxidative methods (cf. section 2.1 and Figure 3).

3. Sequential oxidation/cleavage methods for lignin depolymerization

3.1. Concepts and initial discovery of the alcohol oxidation/cleavage strategy

Bottom-up approaches to lignin depolymerization necessarily incorporate uncertainty because the model compounds lack the complexity intrinsic to natural biomass or extracted lignin samples. But, studies of relevant model compounds provide a means to access valuable insights that could be applied to biomass conversion. This principle is illustrated by a different bottom-up strategy initiated within the Stahl laboratory in 2011. The central hypothesis in this approach was that selective oxidation of either alcohol within the β -O-4 unit of lignin could facilitate a subsequent cleavage step to generate monomeric aromatic products (**Figure 6a**). For example, oxidation of the primary (1°) alcohol would form an aldehyde susceptible to retro-aldol cleavage, while the oxidation of the secondary (2°) benzylic alcohol could be cleaved by various redox and non-redox reaction pathways. Computational studies of lignin suggest that alcohol oxidation weakens the β -O-4 C-O bond by 12-13 kcal/mol, thereby facilitating homolytic cleavage pathways for lignin depolymerization (**Figure 6b**).^{7,71-73}



[Insert Figure 6 here]

Figure 6. Sequential oxidation-cleavage strategies selectively oxidize β -O-4 alcohol groups to (a) weaken the C-O ether bond towards (b) subsequent bond cleavage in a separate step.

Stahl and coworkers tested the reaction of numerous common stoichiometric oxidants and catalytic alcohol oxidation methods with a β -O-4 dimeric model compound, and methods employing nitroxyl catalysts proved to be the most effective (**Figure 7a**).²⁷ Nitroxyl catalysts, such as TEMPO and 4-acetamido-TEMPO (ACT), undergo reversible $1 e^-$ oxidation to the corresponding oxoammonium and a quasireversible $1 e^-/1 H^+$ reduction to hydroxylamines.⁷⁴ The TEMPO radical is generally unreactive with organic species, but various chemical and electrochemical oxidation methods may be used to generate the reactive oxoammonium species from the nitroxyl or hydroxylamine form of the catalyst.⁷⁵ The oxoammonium, generated in situ or isolated as a salt, mediates hydride-transfer oxidation of alcohols. This reactivity is evident in the reaction with stoichiometric Bobbitt's salt, which oxidizes the 2° benzylic alcohol to the corresponding ketone in 97% yield. In contrast, use of TEMPO/bleach (NaOCl) under mildly basic conditions leads to preferential oxidation of the more sterically accessible 1° alcohol, affording the aldehyde product in 49% yield, with only 4% yield of the benzylic ketone. An aerobic Cu^I /TEMPO catalyst system also shows selectivity for 1° alcohol oxidation, and, while proceeding in only moderate yield, induces retro-aldol reactivity to generate aromatic monomers as the major products. Two other aerobic oxidation methods, employing $(FeNO_3)_3$ /TEMPO and ACT/ HNO_3 /HCl, led to good yields and selectivity for formation of the ketone, with the latter method generating a 94% yield of ketone. The ACT/ HNO_3 /HCl oxidation condition was then tested on poplar lignin extracted using cellulolytic enzymes (CEL), which retains much of the native lignin structure. Analysis of the oxidized lignin by 2D HSQC NMR spectroscopy suggests that nearly all of the benzylic alcohols adjacent to G and S aromatic units are oxidized in the final lignin material.

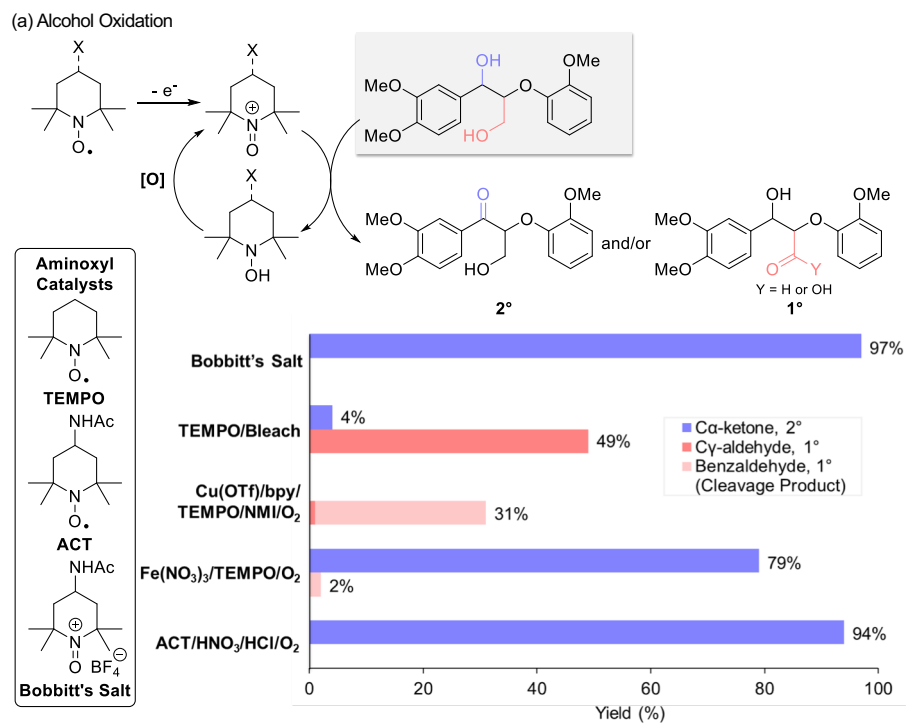
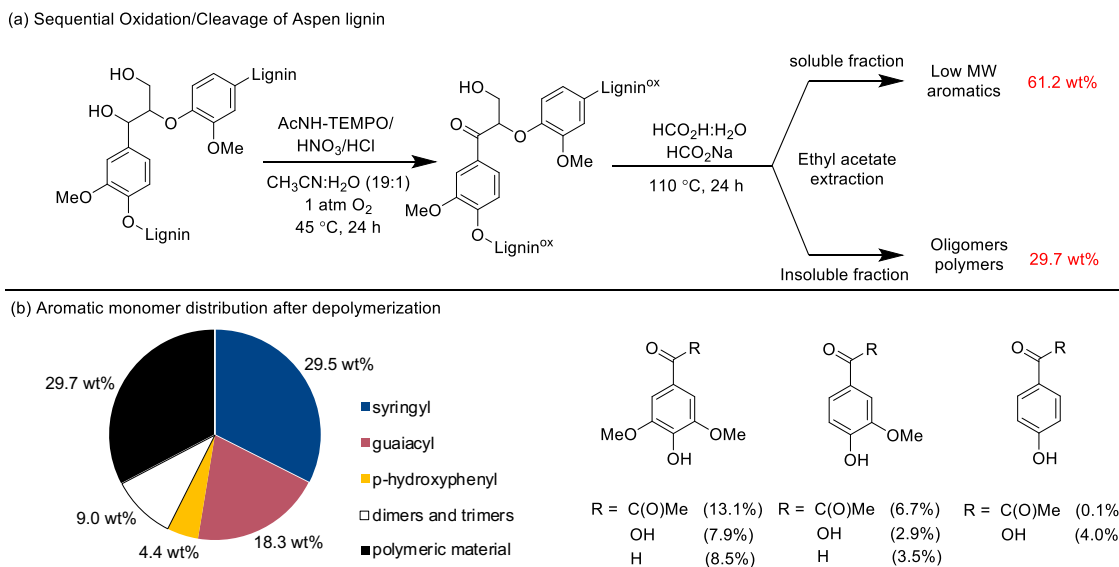


Figure 7. (a) Selective alcohol primary or secondary alcohol oxidation through various reaction systems; (b) different bond cleavage methods on secondary alcohol oxidized lignin models.

An oxidized β -O-4 model compound bearing a benzylic ketone was shown to undergo cleavage into aromatic monomers under oxidizing, reducing, and redox-neutral conditions (**Figure 7b**).^{27,28} Alkaline hydrogen peroxide led to partial degradation of the phenol monomer,²⁷ while a redox neutral transformation in the presence of aqueous formic acid/formate led to the best results (**Figure 7b**).²⁸ Excellent yields of both products were obtained from S-, G-, and H-derived β -O-4 dimer models (89-92% isolated yield of diketone monomer).

ACT/HNO₃/HCl oxidation of CEL poplar lignin, followed by treatment with formic acid/formate, induced lignin depolymerization to afford >60 wt% yield of low molecular weight aromatic compounds, including a 52 wt% yield of characterized aldehyde, carboxylic, and diketone aromatics (**Figure 8**).²⁸ These results were later extended to lignin samples obtained from other biomass sources (poplar, maize, and maple) and extracted by different methods, including mild acidolysis,⁷⁶ γ -valerolactone/dilute sulfuric acid (GVL),⁷⁷ extractive ammonia (EA),^{78,79} and copper-alkaline hydrogen peroxide (Cu-AHP).⁸⁰ Aromatic yields of 3–42% were obtained when this two-step oxidation-depolymerization sequence was applied to these different lignin samples, with the best yield of aromatics obtained from poplar sample extract via mild acidolysis (42%) or Cu-AHP conditions (31%).²⁹

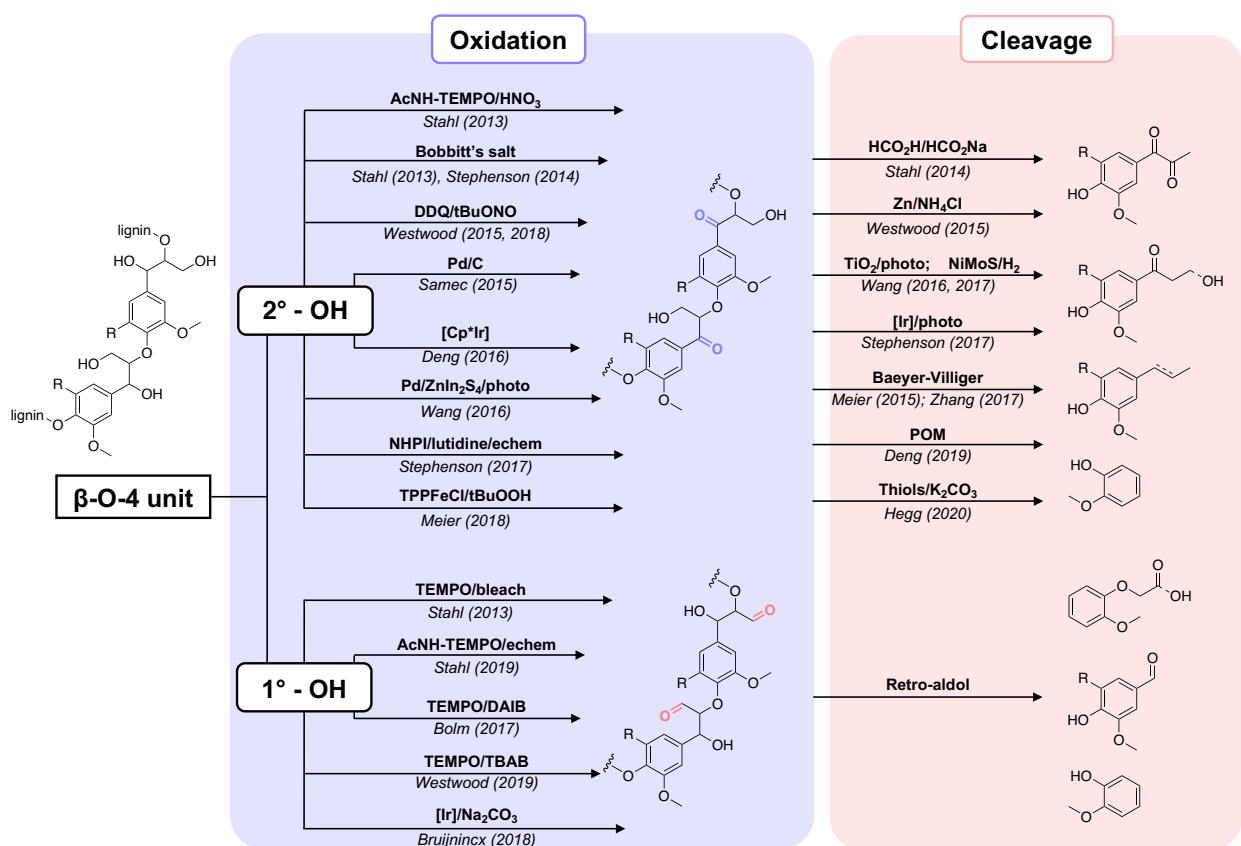


[Insert Figure 8 here]

Figure 8. (a) Depolymerization of aspen lignin with formic acid following oxidation (b) Monomer distribution from depolymerization of oxidized aspen lignin.

This sequential oxidation/cleavage method demonstrated the best yields of aromatics to date for a lignin depolymerization method originating from a bottom-up strategy. These results provided a foundation for numerous other studies employing a two-step sequence to access

aromatic monomers from lignin. These studies include the development of different alcohol oxidation methods, including those with selectivity for the 2° and 1° positions in β-O-4 units (sections 3.2 and 3.3), and different methods for bond cleavage/depolymerization from the oxidized lignin and lignin model compounds (section 3.4). A summary of these various methods is provided in **Figure 9**.



[Insert Figure 9 here]

Figure 9. Overview of the sequential oxidation/cleavage approaches applied in real lignin.

3.2. Secondary alcohol oxidation/cleavage methods

Oxidation methods that exhibit selective oxidation of 2° alcohols in lignin include those employing TEMPO, N-hydroxyphthalimide (NHPI), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and transition-metal catalyst systems. Some of these oxidants are used in stoichiometric quantities, while others are components of catalyst systems.

3.2.1 TEMPO and TEMPO derivatives

TEMPO derivatives are among the most effective reagents and catalyst systems available for 2° alcohol oxidation in lignin.²⁷ As noted above, Stahl and coworkers showed that stoichiometric Bobbitt's salt and ACT/HNO₃/HCl (O₂, MeCN/H₂O, 45 °C, 20 h) produced up to 97% yields of oxidized lignin model compounds (**Figure 10a** and **10b**).²⁷ Meier et al. obtained similar results, albeit with somewhat lower yields, for similar model compounds using modified catalytic conditions (TEMPO/NaNO₂/HCl/NaCl, O₂, DCM, 19 h).⁸¹

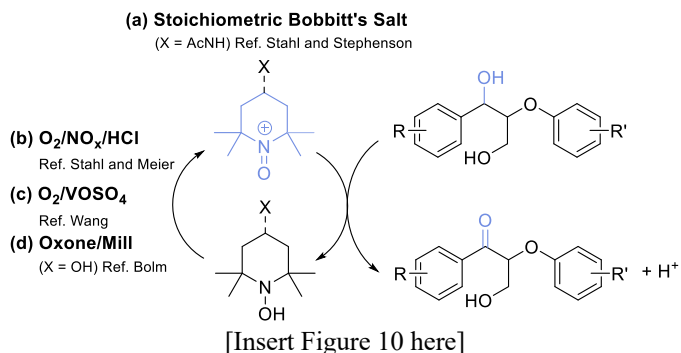


Figure 10. TEMPO and its derivatives mediated benzylic alcohol oxidation in lignin and its models.

Wang and coworkers developed an aerobic system using VOSO₄ as a co-catalyst to generate the oxoammonium species (**Figure 10c**), followed by aerobic C-C bond cleavage over a Cu/phen catalyst for production of aromatic acids and phenols. Oxidation of non-phenolic β-O-4 lignin models (20% VOSO₄/TEMPO, 0.4 MPa O₂, MeCN, 90 °C, 6 h) generated the corresponding β-O-4 ketone product in 53% yield, together with a 20% yield of the retro-aldol cleavage product 2-phenoxyacetophenone. When the VOSO₄/TEMPO system was tested on organosolv Alcell lignin, 2D heteronuclear single quantum coherence (HSQC) NMR analysis revealed partial oxidation of the β-O-4 linkages in lignin. Details on the cleavage step are elaborated below (see section 3.4.2).⁸²

Bolm et al. achieved benzylic oxidation (>94% yield) of non-phenolic β-O-4 lignin model compounds through mechanochemical methods using catalytic amounts of HO-TEMPO/KBr in

the presence of oxone as terminal oxidant (20% HO-TEMPO/KBr, 25 Hz, 90 min) (**Figure 10d**).⁸³ Dimeric models containing phenols oxidatively cleaved under these conditions, likely reflecting oxone-promoted generation of phenoxy radicals that led to formation of benzoquinone (82-91%) and guaiacol (76-82%) products. Optimized reaction conditions were applied to organosolv beechwood lignin. GPC analysis and HSQC NMR and IR spectroscopic data supported a high degree of oxidation and some cleavage of β -O-4 linkages of lignin.

Stephenson and coworkers developed a sequential alcohol oxidation/photochemical reductive cleavage method using stoichiometric Bobbitt's salt for the alcohol oxidation step (**Figure 10a**).⁸⁴ Initial efforts to use catalytic ACT/HNO₃/HCl oxidation method²⁷ were not compatible with the subsequent photochemical cleavage step, elaborated below in section 3.4.3. Non-phenolic β -O-4 dimers were oxidized, the reaction was filtered, solvent was removed, and the mixture was subjected to depolymerization conditions with further purification. Hegg and coworkers explored a sequential oxidation/depolymerization method with poplar lignin extracted using the Cu-AHP method.⁸⁵ Although some alcohols are oxidized during the oxidative Cu-AHP extraction process (CuSO₄/bpy, H₂O₂, NaOH, 30 °C), treatment of the extracted lignin with Bobbitt's salt led to an approximately five-fold increase in oxidation at the benzylic position, as revealed by HSQC-NMR spectroscopic analysis. The latter material proved much more susceptible to cleavage by a biomimetic thiol-mediated process than the lignin obtained directly from the Cu-AHP process (see section 3.4.3 for discussion of the cleavage process).

3.2.2 NHPI

N-hydroxyphthalimide (NHPI) is the stable precursor to another type of nitroxyl mediator used in organic oxidation reactions (**Figure 11**). Unlike TEMPO, the imidoxyl radical phthalimide-N-

oxyl (PINO) is generated from NHPI in situ. Although it has limited stability in solution, PINO mediates efficient HAT from weak C-H bonds, such as those in benzylic alcohols.^{74,86} A number of different NHPI oxidation methods have been employed to achieve NHPI/PINO-catalyzed oxidation of lignin and lignin model compounds (**Figure 11**).

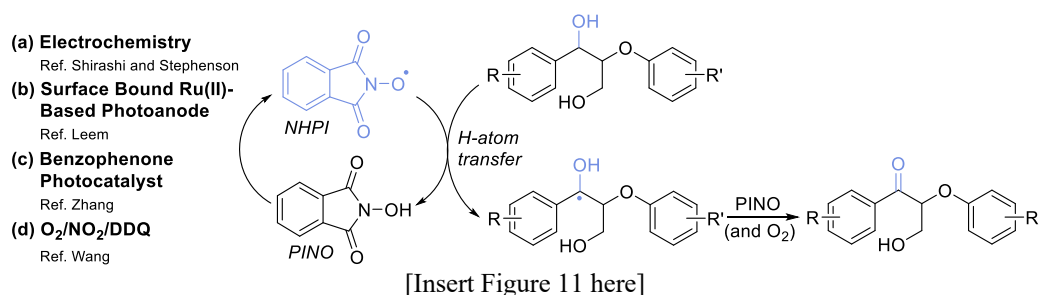


Figure 11. NHPI mediated benzylic alcohol oxidation in lignin and its models. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Shiraishi and coworkers reported an NHPI-mediated electrochemical oxidation of non-phenolic β -O-4 dimer into the C_{α} -ketone derivative in excellent yield (93%; conditions: LiClO₄, 2,6-lutidine, MeCN, 0.7 V vs. Ag/Ag⁺) (**Figure 11a**).⁸⁷ The lutidine base facilitates electrochemical reoxidation of NHPI to PINO. Stephenson et al. used a similar NHPI/2,6-lutidine electrocatalytic oxidation method,⁸⁸ and showed that inclusion of O₂ in the reaction mixture led to increased yield of the ketone for a series of model compounds. O₂ reacts rapidly with benzylic radicals generated by PINO-mediated HAT, contributing to oxidation at this site.⁸⁹⁻⁹¹ Analysis of simplified model compounds suggested excellent reactivity and selectivity for benzylic alcohol oxidation; no primary alcohol oxidation was detected. Pine dioxosolv-lignin was subjected to electrochemical NHPI oxidation using a modified acetone:DMSO (98:2) solvent system to solubilize the lignin, and characteristic signals for oxidation of β -O-4 to the C_{α} -ketone were observed by HSQC NMR spectroscopy. This reactivity was paired with a photochemical reduction process to achieve partial depolymerization of the lignin (see section 3.4.3 for the cleavage step). A photoelectrochemical variant of NHPI-catalyzed alcohol oxidation in lignin and lignin model

compounds was recently developed by Leem et al. using electrode-immobilized Ru^{II}-polypyridyl complexes (**Figure 11b**).⁹²

Aromatic ketones, such as benzophenone and its derivatives, have been widely used for photochemically initiated HAT, including reactions with weak O-H bonds.^{93, 94} Zhang and coworkers utilized donor-substituted aromatic ketones 4,4'-bis(diphenylamino)benzophenone (DPA-BP) to generate PINO through chemical photocatalysis (**Figure 11c**).⁹⁵ The DPA-BP/NHPI/O₂ photocatalytic system exhibits good reactivity and selectivity for the aerobic oxidation of phenolic and non-phenolic β -O-4 lignin models. The benzylic ketone products were obtained in excellent isolated yields (81–99%). Finally, the combination of NHPI, DDQ, and O₂ is a known catalyst system for oxidation of benzylic C-H bonds.⁹⁶ Wang and coworkers supplemented this co-catalyst mixture with a NO_x source to achieve oxidation of benzylic ketones from β -O-4 model compounds in 35-45% yields (**Figure 11d**).⁹⁷

3.2.3 DDQ

DDQ is a common reagent for dehydrogenation of benzylic alcohols.⁹⁸ Lignin oxidation with stoichiometric or catalytic DDQ has been proposed to be initiated by SET, HAT, or hydride transfer,^{99, 100} although the reaction mechanisms have seldom been the focus of specific investigation. Aerobic oxidation of the benzylic alcohol in lignin β -O-4 model compounds was developed by employing NO_x-based co-catalysts (e.g., NaNO₂, tert-butyl nitrite, HNO₃) to promote reoxidation of the reduced quinone (DDQH₂).^{101–103} Moody et al. reported oxidation of lignin model compounds at ambient temperature using catalytic amounts of DDQ and NaNO₂ or tert-butyl nitrite (*t*BuONO) under visible light irradiation, affording excellent yield (>92%) of the benzylic ketone in β -O-4 model compounds (**Figure 12a,b**).¹⁰⁴ Photoexcitation of DDQ to a long-lived triplet state was proposed to initiate electron transfer from the substrate.¹⁰⁵

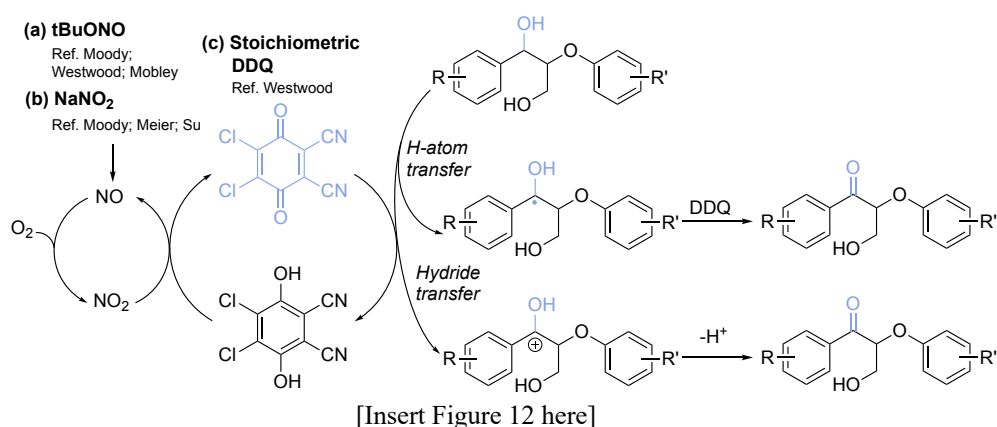


Figure 12. DDQ-mediated benzylic alcohol oxidation in lignin and its models.

Westwood et al. applied the DDQ/*t*BuONO catalytic system for the oxidation of simple β -O-4 model compounds and polymeric models at elevated temperature (80 °C) rather than promoting the reaction with light. The reactions produce ketones with high yield and complete selectivity.¹⁰⁶ The optimized catalytic conditions were applied to the oxidation of organosolv birch lignin, and the desired β -O-4 ketone was identified by 2D HSQC NMR spectroscopy. This study was the first to use DDQ in the sequential oxidation/depolymerization of authentic lignin. Aromatic monomers were isolated in 6 wt% following a Zn-mediated reductive cleavage method, elaborated in section 3.4.3 below (**Figure 12a**). The same group oxidized organosolv beech lignin with varying amounts of stoichiometric DDQ (i.e., no reoxidation method was employed), and used 2D HSQC NMR analysis to track linkage reactivity with increasing amounts of oxidant (**Figure 12c**).¹⁰⁷ This stoichiometric DDQ-based method generated oxidized lignin with six hardwood dioxasolv lignins, including those from beech, oak, maple, hickory, cherry, and birch, and the protocol was validated at 20 g scale.

DDQ is also capable of oxidizing benzylic ethers.^{100,108} Luterbacher and coworkers have developed an aldehyde-protecting group strategy that enables much higher yields of lignin to be

extracted via acidolysis from various biomass sources.¹⁰⁹ They subsequently showed that the acetal-protected lignin is amenable to stoichiometric or catalytic DDQ-promoted oxidation of the benzylic position to afford the corresponding oxidized lignin.¹¹⁰ The oxidation method was demonstrated on a series of β -O-4 model compounds and then applied to the oxidation of acetal-protected birch and genetically-modified, poplar lignin enriched in syringyl units.

A number of subsequent studies have employed stoichiometric DDQ and catalytic DDQ/*t*BuONO or NaNO₂/O₂ catalyst systems to carry out lignin oxidation.^{81,111} Bugg et al. generated oxidized lignin from multiple plant sources using stoichiometric DDQ oxidation and evaluated the monomer yield from a Zn-based depolymerization method.¹¹² The best results were obtained with poplar organosolv lignin, which had the highest β -O-4 content of the investigated lignins. Other examples will be discussed in section 3.4.2 in connection with depolymerization studies of these materials.

3.2.4 Additional oxidation methods

Several other metal-catalyzed methods have been evaluated for lignin (model) oxidation. Meier et al. investigated the use of iron tetraphenylporphyrin chloride (TPPFeCl) and *tert*-butylhydroperoxide (*t*BuOOH) for catalytic oxidation of benzylic alcohols in lignin model compounds.^{81,113} Ball-milling treatment in KOH and toluene resulted in an increase in the carbonyl content in Kraft lignin, and the mechanochemical processing with TPPFeCl-catalyzed oxidation has a synergistic, positive effect on the depolymerization of lignin. When the TPPFeCl/*t*BuOOH oxidation method was applied to Kraft lignin, 2D HSQC NMR spectra suggested that the β -O-4 benzylic alcohol groups were oxidized, and a Baeyer-Villiger oxidation method was used in a subsequent depolymerization method to generate aromatic monomers (cf. section 3.4.2).

Deng, Fu, and coworkers employed Cp*Ir catalysts bearing a cooperative bipyridone ligand to promote dehydrogenation of β -O-4 lignin model compounds (**Figure 13**).¹¹⁴ These reactions promote thermal dehydrogenation of the benzylic alcohols, generating H₂. Good conversions and yields were observed with a series of model compounds.

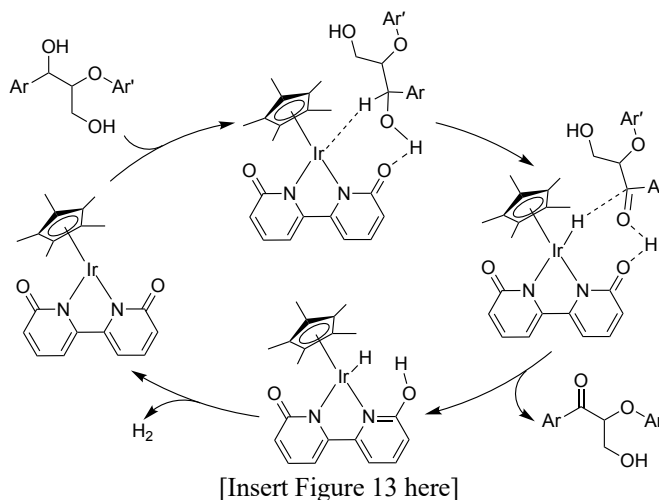
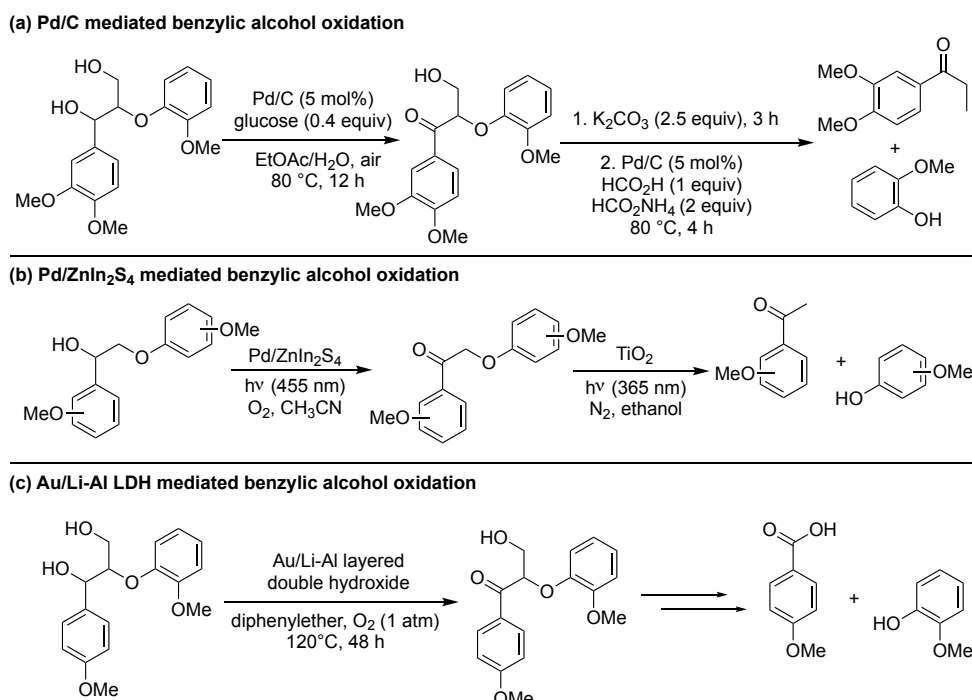


Figure 13. Transition metal mediated secondary alcohol oxidation in lignin models using (a) TPPFeCl and (b) [Ir(Cp*)L], where L = 1,10 phenanthroline or bipyridine.

Samec and coworkers demonstrated the selective oxidation of benzylic alcohols in lignin model compounds using carbon supported Pd nanoparticles under mild conditions (**Figure 14a**).^{115,116} Use of oxidizing conditions led to benzylic ketone formation without cleavage of C-O or C-C bonds or dehydrogenation of the γ 1° alcohol. The highest yields of ketone were obtained in the presence of glucose, which was proposed to stabilize the Pd catalyst to prevent aggregation. Zhang, Wang and coworkers studied cerium oxide-supported Pd catalyst (Pd/CeO₂) for the aerobic oxidation of various model compounds, in addition to a source of organosolv lignin. Low yields of monomers were obtained from the latter process: vanillin (5.2%), guaiacol (0.87%) and 4-hydroxybenzaldehyde (2.4%).¹¹⁷



[Insert Figure 14 here]

Figure 14. Heterogeneous catalyst-mediated secondary alcohol oxidation in lignin model compounds using (a) Pd/C, (b) Pd/ZnIn₂S₄, and (c) Au/Li-Al LDH.

ZnIn₂S₄ is a ternary chalcogenide semiconducting material with a band gap that supports photochemistry with visible light irradiation. Wang et al. found that Pd/ZnIn₂S₄ promoted oxidation of benzylic alcohols with lignin models upon illumination with 455 nm light under ambient conditions (**Figure 14b**). This step was paired with TiO₂-mediated photochemical cleavage (365 nm illumination) of the models into aromatic monomers.^{82,118}

Crocker et al. employed heterogeneous catalyst Au/Li-Al layered double hydroxide (LDH) to catalyze aerobic oxidation of dimeric lignin models with 1 atm O₂ and observed excellent activity for benzylic alcohol oxidation in β-O-4 models (**Figure 14c**).¹¹⁹ The high surface area and strong basicity of the Li-Al LDH support facilitated substrate adsorption and reaction on the Au surface. Lignin, one sample sourced from the γ-valerolactone extraction method¹⁷⁷ and another from Kraft lignin, were subjected to aerobic oxidation conditions with this catalyst. Alkaline hydrolysis of the

resulting oxidized lignin materials led to lignin depolymerization, with monomer yields as high as 40% for γ -valerolactone extracted lignin and 10% for Kraft lignin.

3.3 Primary alcohol oxidation

Under basic conditions, oxoammonium generated from TEMPO or ACT mediates alcohol oxidation by an inner sphere mechanism that favors reaction with sterically unhindered primary alcohols.⁷⁵ This selectivity was demonstrated by using bleach/TEMPO conditions at pH 9 (cf. **Figure 7a**).²⁷ The Cu/TEMPO-catalyzed aerobic oxidation method, which features a different mechanism,¹²⁰ also shows selectivity for primary alcohol oxidation.²⁷

Bolm et al. reported that the hypervalent iodine reagent (diacetoxy)iodobenzene (DAIB), in combination with TEMPO, leads to selective oxidation of non-phenolic β -O-4 primary hydroxyl groups to aldehydes in 43% yield (**Figure 15a**).¹²¹ Stoichiometric DIAB and a TEMPO catalyst were used to oxidize organosolv beech lignin. A reduction of C_γ - H_γ signals was revealed by 2D HSQC NMR analysis, corresponding to an increase in carbonyl content typical for aldehydes. Depolymerization of this material is presented in section 3.4.1 below.

The groups of Takano and Stahl have used electrochemical methods to support TEMPO-catalyzed oxidation of lignin and/or lignin model compounds. Stahl et al. used ACT as the mediator for the oxidation of β -O-4 model substrates lacking free phenols under basic conditions (5% ACT, pH 10, 70:30 H₂O:MeCN, 0.8 V vs. Ag/AgCl). Higher turnover frequencies (TOF) were observed for models containing primary alcohols with β -ether fragments, similar to those in the β -O-4 unit in lignin.¹²² A systematic comparison of various 1° and 2° alcohol substrates shows that 1° alcohols are much more reactive under these conditions, and β -O-4 models with both types of alcohols undergo selective oxidation of the primary alcohol to the carboxylic acid in >90% yield (**Figure 15b**). Takano and coworkers observed comparable yields and selectivity with similar β -O-4 model

compounds under modified conditions 90:10 dioxane:phosphate buffer (pH 7, 20 mol% ACT) conditions.¹²³ Stahl and coworkers also tested the reactivity of a mild-acidolysis poplar lignin material under their optimized reaction conditions. 2D HSQC NMR spectroscopy showed a decrease in characteristic β -O-4 primary alcohol β - and γ - signals, with no change to the secondary alcohol signals. An acid-base titration of oxidized lignin revealed an approximately 12-fold increase in acidic functionality, attributed to the introduction of carboxylic acid functional groups in the polymer. Some lignin cleavage is observed by GPC during the oxidation step, but the oxidized polymer was also amenable to depolymerization under acidic conditions, as described below (see section 3.4.1).

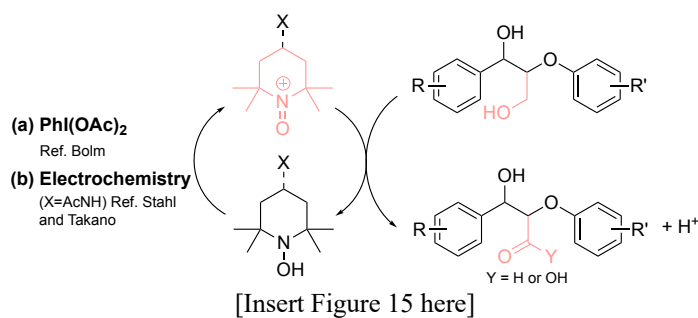
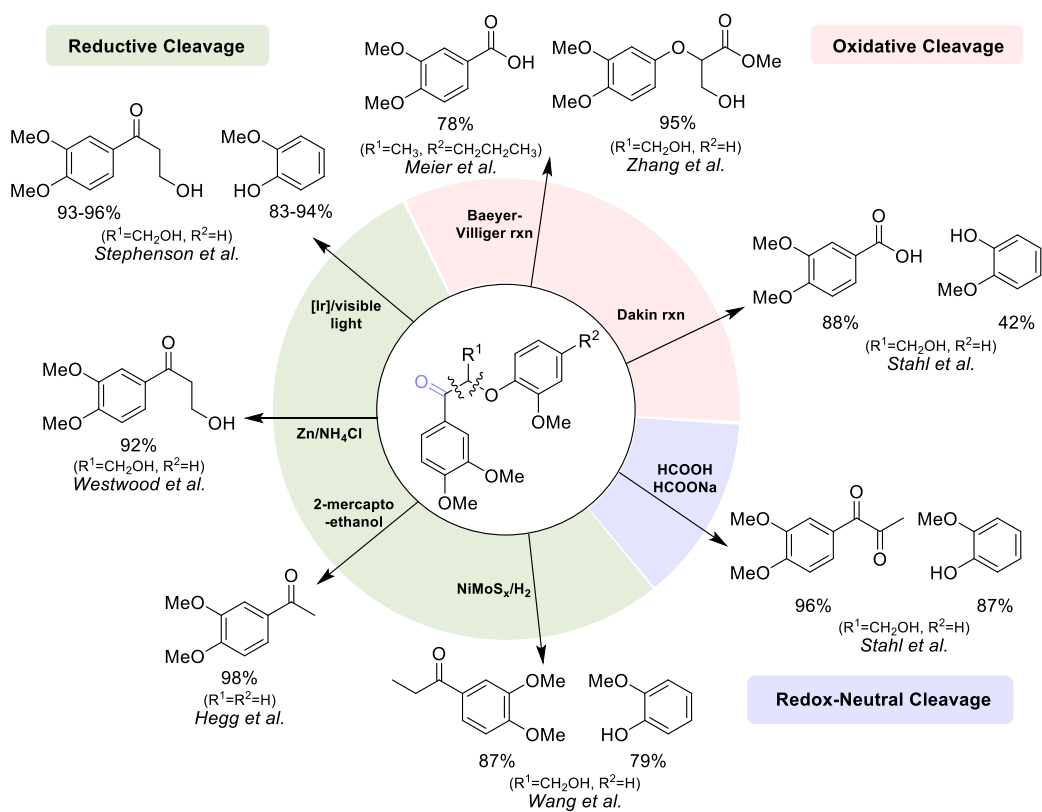


Figure 15. Mechanism of TEMPO mediated primary alcohol oxidation of a lignin model compound.

Lancefield, Bruijninx and coworkers reported an efficient catalytic dehydrogenation system using a Cp^*Ir -bipyridonate complex (same as that in **Figure 13**) in a 1,4-dioxane/water solution at pH ~ 11 . This approach exhibited selectivity for primary over secondary alcohol dehydrogenation and led to cleavage of the $\text{C}_\alpha\text{-C}_\beta$ bond. This catalytic system was applied to enzyme-extracted lignin and dioxasolv softwood lignins and led significant reduction in the lignin molecular weight and low yields of monoaromatic compounds.¹²⁴

3.4 Bond cleavage methods

The two-step oxidation/depolymerization strategy allows for systematic optimization of the two steps, whereby elective oxidation of the primary or secondary alcohols in the backbone may be subjected to different conditions that enable efficient cleavage of the C_β-O aryl, C_α-C_β, or other bonds in the linkers between aromatic units. A variety of methods, including oxidative, reductive, and redox-neutral reactions, have been developed for this second-step in the process (**Figure 16**). Secondary alcohol oxidation has been paired with both redox and non-redox depolymerization methods, while primary alcohol oxidation has been typically paired with redox-neutral processes.



[Insert Figure 16 here]

Figure 16. Different bond cleavage patterns in lignin model with C_α ketone structure.

3.4.1 Redox-neutral cleavage

A retro-aldol reaction following selective primary alcohol oxidation enables cleavage of the C_α-C_β bond, resulting in lignin depolymerization.⁵⁵ In some cases, this reactivity proceeds directly

under the oxidative reaction conditions (cf. **Figure 7a**), while other cases (emphasized here) feature treatment of the oxidized lignin under modified conditions to promote cleavage. Lignin model compounds with terminal C_γ -aldehydes undergo facile retro-aldol under basic conditions to generate benzaldehyde and an aryl ether fragment (**Figure 17a**). Bolm and coworkers use DL-proline as an organocatalyst to promote this reactivity at ambient temperature, generating veratraldehyde and guaiacol in 70% and 26% yields, respectively.¹²¹ Treatment of oxidized organosolv beech lignin (cf. section 3.3) led to reduction in the molecular weight of the polymer, consistent with bond cleavage in the backbone. Stahl and coworkers explored acidic conditions to promote depolymerization of poplar lignin containing C_γ -carboxylic acids. This approach generated up to 30 wt% yields of monomeric aromatic compounds from an oxidized poplar lignin sample.¹²² Various aqueous acids proved effective (HCl, H₂SO₄, and HCO₂H) for cleavage of the oxidized model compounds, but the highest monomer yields from lignin were obtained with a 9:1 mixture of HCO₂H and H₂O. These products can arise from acid-induced elimination of the benzylic hydroxyl group to afford a vinyl ether that is susceptible to hydrolysis, resulting in generation of α -ketoacid and phenol aromatic monomers (**Figure 17b**).¹²⁵ Subsequent decarboxylation of the ketoacid generates the observed aromatic monomer containing an aliphatic aldehyde. The aldehyde is susceptible to subsequent aldol condensation, resulting in the formation of by-products. The latter condensation reactions present major challenges for lignin depolymerization methods that generate aliphatic aldehydes, although strategies to protect the aldehydes and minimize the byproduct formation have been developed.¹²⁶

Westwood and coworkers developed an N-heterocyclic carbene-mediated internal redox esterification method for depolymerizing oxidized lignin containing C_γ -aldehydes (generated from a modified method of Einhorn et al.)¹²⁷ (**Figure 17c**).¹²⁸ Incorporation of butylethers at the C_α

position of lignin during the "butanosolv" extraction method supports this process as it prevents competing retro-aldol reaction. The proposed mechanism involves initial formation of a Breslow-type intermediate from the reaction of the NHC with the C γ -aldehyde, followed by elimination of the phenolate and formation of the enol intermediate. Tautomerization leads to an acylazolium that reacts with butanol.¹²⁹ The process takes advantage of the inherent structure of the β -aryl ether units present in the butanosolv lignin and delivers novel functionalized aromatic monomers in modest yield (6 wt%).

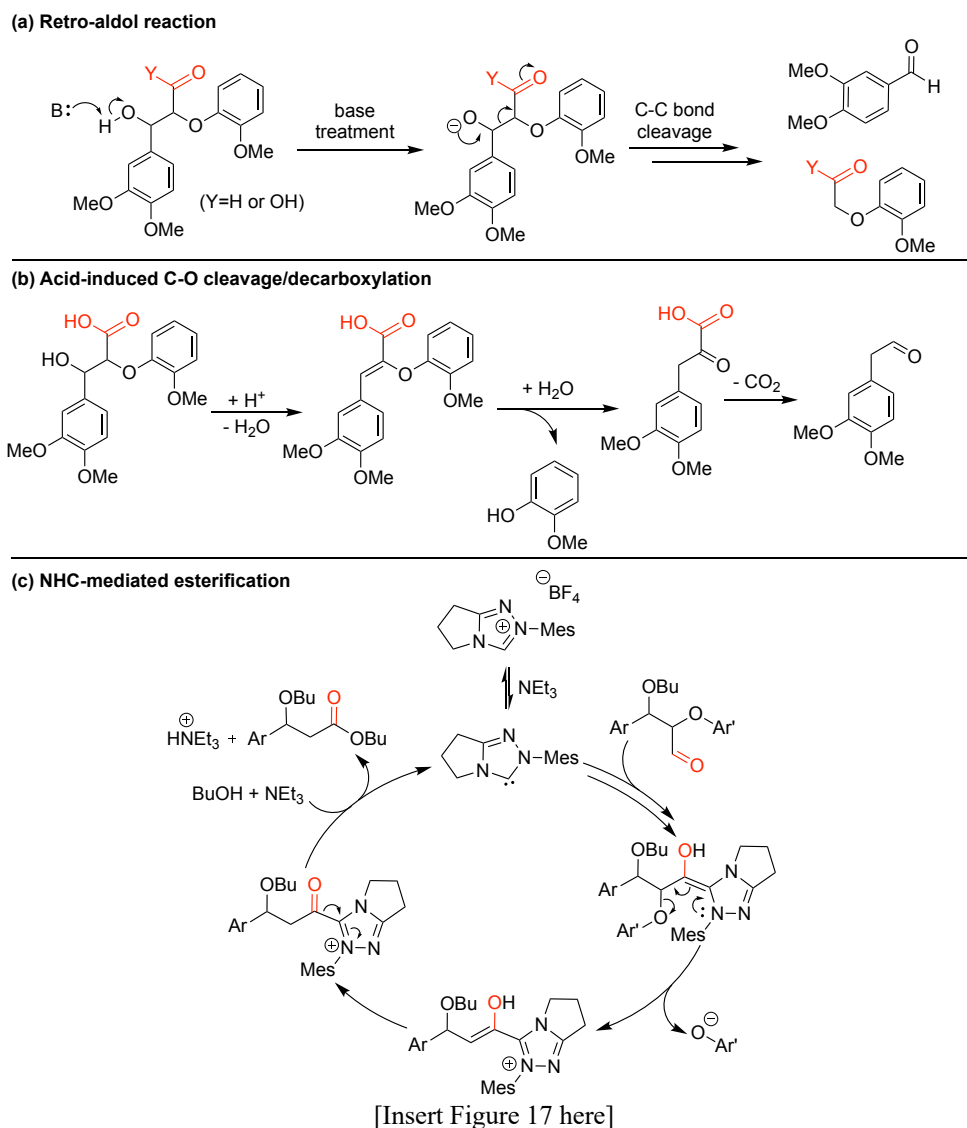
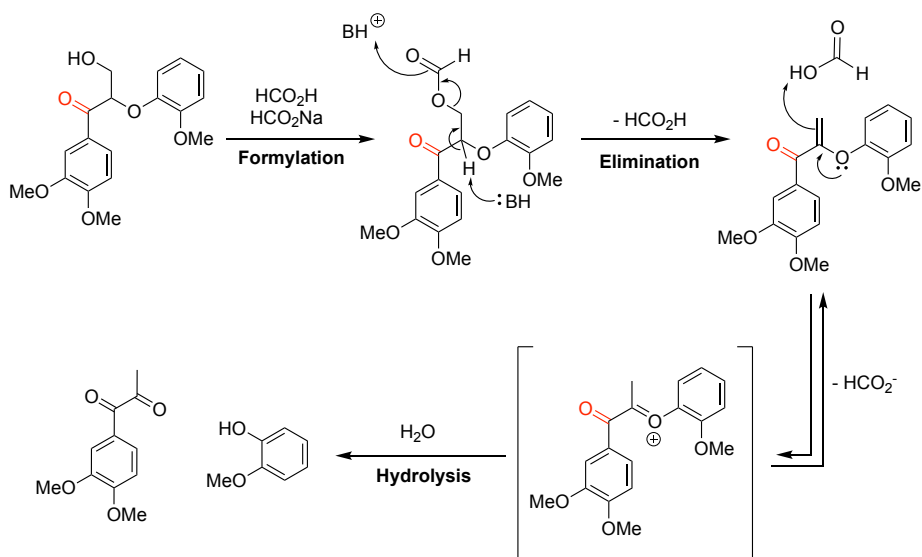


Figure 17. Mechanisms of redox-neutral bond cleavage method of primary alcohol oxidized lignin.

Redox-neutral processes also support cleavage of lignin oxidized at the 2° benzylic alcohol position (see section 3.1 for oxidation conditions). Stahl and coworkers showed that aqueous formic acid/formate supports bond cleavage of such structures. In an application with CEL poplar lignin, ACT/HNO₃/HCl oxidation of the lignin followed by HCO₂H/HCO₂Na treatment led to a 52 wt% yield of aromatic monomers. Diketones are the major product of this reaction (cf. **Figure 8**), and mechanistic studies supported the mechanism shown in **Figure 18**. Acylation of the 1° C_γ-OH group generates a formic ester intermediate that undergoes formate-induced elimination to generate the aryl vinyl ether species. Hydrolysis of the vinyl ether releases the phenol and diketone products (**Figure 18**).²⁸ This redox neutral process is noteworthy because it avoids degradation of phenols that can occur under oxidative cleavage conditions. As noted in section 3.1, this method was also used successfully in the oxidation/depolymerization of lignin samples from various biomass sources and pretreatment protocols.²⁹



[Insert Figure 18 here]

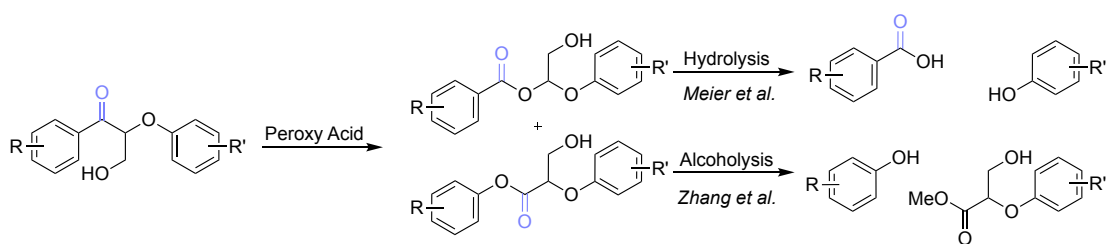
Figure 18. Mechanism of formic acid-mediated redox-neutral bond cleavage method on secondary alcohol oxidized lignin model.

The formic acid/formate depolymerization method developed by Stahl et al. has been employed in other two-step oxidation/depolymerization methods to afford aromatic monomers from oxidized lignin with benzylic ketones. Luterbacher and coworkers employed HCO₂H/HCO₂Na depolymerization step following DDQ-mediated oxidation of their extracted acetal-protected lignin (see section 3.2.3).¹¹⁰ A yield of up to 36% aromatic monomers (diketones, carboxylic acids, and aldehydes) was obtained from propylidene acetal protected birch lignin by using a two-step DDQ oxidation/HCO₂H-HCO₂Na depolymerization sequence. A 52% yield of monomers was obtained with F5H poplar lignin (a genetically modified poplar with high syringyl content). The syringyl propanedione monomer was the major product in both cases, consistent with the mechanism shown in **Figure 18**. Mobley and Crocker found that the HCO₂H/HCO₂Na depolymerization process was most effective for conversion of DDQ-oxidized Kraft pine lignin.¹¹¹

3.4.2 Oxidative cleavage

Oxidative conditions also support cleavage of oxidized lignin; however, these methods are susceptible to further oxidation and/or oxidative degradation of the monomeric products. This reactivity was noted above in the use of H₂O₂ under basic conditions to cleave benzylic ketone model compounds, resulting in an 88% yield of veratric acid but only 42% yield of guaiacol (**Figures 7b**).^{27,67} Baeyer-Villiger oxidation methods provide an alternative strategy for cleavage of the oxidized lignin (models) (**Figure 19**). Meier et al. employed in situ generated performic acid to convert benzylic ketones into esters,⁸¹ and ester hydrolysis resulted in 78% of aromatic acids from models resembling oxidized β-O-4 structures. The corresponding aldehyde and phenol cleavage products were not recovered, likely reflecting their oxidative degradation under the reaction conditions. Oxidized Kraft lignin was subjected to these cleavage conditions (8 eq. H₂O₂,

4 eq. HCOOH, DCE, 50 °C, 24 h), and the resulting aromatic carboxylic acids were esterified in a work-up step to give a 10 wt% yield of methyl ester products.¹¹³ Major products included methyl vanillate 7.8 wt% and methyl 5-carbomethoxyvanillate 2.2 wt%. Zhang et al. used modified Baeyer-Villiger conditions, and paired this method with alcoholysis (K₂CO₃, 45°C, MeOH) to achieve high yields (>90%) in the cleavage of various model compounds to phenol and methyl benzoate derivatives (**Figure 19b**).¹³⁰



[Insert Figure 19 here]

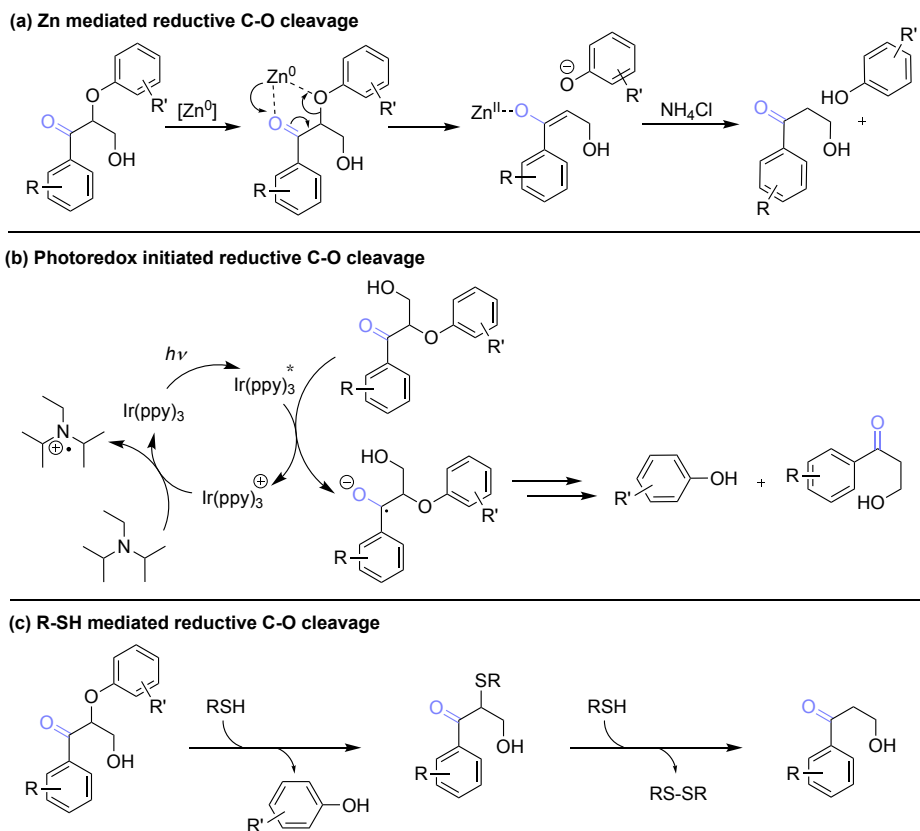
Figure 19. Baeyer-Villiger bond cleavage for β -O-4 linkages.

A variety of aerobic cleavage methods have also been explored using organometallic catalysts. Lignin models oxidized to the ketone by Wang et al. were subjected to oxidative cleavage by a variety of Cu salts bearing nitrogen donor ligands.⁸² The Cu(OAc)₂/1,10-phenanthroline complex led to selective C α -C β bond cleavage to form aromatic acids in 92% yield under mild conditions (0.4 MPa O₂, 150 °C, MeOH, 6 h). Deng et al. employed polyoxometalates (POM) as a regenerable catalyst to depolymerize pre-oxidized dioxasolv lignin. The optimized oxidative conditions (150 °C, 10 bar O₂, MeOH) used a phosphomolybdic acid (H₃PMo₁₂O₄₀) catalyst to generate monomer yields up to 33 wt%. Aromatic monomers account for 19.4 wt% of these products, with other products derived from aromatic ring-opening. Overoxidation also converts low molecular weight depolymerization products to CO, CO₂, and H₂O.¹³¹

Su and coworkers reported a mechanochemical approach for selective cleavage of C_β-O bonds and C_α-C_β bonds of lignin β-O-4 ketones via NaOH-promoted oxidation under milling conditions (5 equiv. NaOH, 25 Hz milling, 2 h).¹³² In contrast to other oxidative cleavage methods, the yield of phenol (87-92%) is always 13-22% *higher* than the yield of the corresponding aromatic acid. Dioxasolv birch lignin milled with DDQ/NaNO₂ (see section 3.2.3 for oxidation conditions) led to a 9.1 wt% yield of aromatic monomers. When the lignin was independently oxidized with the DDQ/tBuONO conditions of Westwood (see section 3.2.3 for oxidation conditions)¹⁰⁶, mechanochemical cleavage generated a 15.5 wt% yield of aromatic monomers, with syringate as the major product (7.5 wt%).

3.4.3 Reductive cleavage

Oxidized β-O-4 fragments with the benzylic ketone correspond to O-aryl acyloin derivatives that are susceptible to reductive cleavage. Zinc is an effective reductant in these reactions,¹³³⁻¹³⁵ and could initiate single-electron transfer or direct two-electron reactivity (**Figure 20a**). This reactivity was among those demonstrated by Stahl and coworkers using β-O-4 model compounds in their initial report on two-step oxidation/depolymerization of lignin.²⁸ Westwood and coworkers used Zn/NH₄Cl at 80 °C after DDQ-mediated oxidation of benzylic alcohol in both lignin and model compounds.¹⁰⁶ The approach generates β-hydroxy phenyl ketone products in >80% yield for different types of β-O-4 model compounds, and modest yields of phenolic monomers were also obtained from the oxidation/reductive depolymerization of birch lignin. Deng and Fu et al. used this method for lignin depolymerization following Cp*Ir-catalyzed dehydrogenation of benzyl alcohols in lignin (cf. **Figure 13**).¹¹⁴



[Insert Figure 20 here]

Figure 20. Mechanisms of reductive bond cleavage methods.

Reductive cleavage of oxidized lignin and lignin model compounds also may be achieved via photoredox-initiated SET. Stephenson and coworkers reported that an $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ photocatalyst under blue LED irradiation could promote $\text{C}_\alpha\text{-O}$ bond cleavage, generating phenols (yield >70%) and β -hydroxyaryl ketones (yield >81%) from oxidized lignin model compounds (**Figure 20b**).^{84,88} Bond cleavage is proposed to proceed via fragmentation of the ketone radical anion generated by SET from the photocatalyst. N,N-diisopropylethylamine (DIPEA) and formic acid provide a source of reducing equivalents for the reaction. Modest yields of aromatic monomers were also obtained from a two-step oxidation/photoreductive cleavage sequence when applied to purified dioxosolv pine lignin (2.4 wt% guaiacol and phenyl ketone monomers were recovered).⁸⁸ (**Figure 20a**). The latter process was implemented as a batch-to-flow sequence

involving electrochemical NHPI-mediated lignin oxidation in batch, followed by photochemically initiated reductive cleavage in flow.⁸⁸ Zhang and coworkers expanded on this work by developing a thiol-functionalized mesoporous cellular silica foam (MCF) with immobilized Ir(ppy)₂(bpy) photocatalyst.¹³⁶ The Ir(ppy)₂(bpy)-MCF material was effective for the reductive cleavage of oxidized lignin β-O-4 model compounds under mild reaction conditions (yield >90%). The photocatalyst could be reused at least six times without a significant drop in performance.

Wang and coworkers showed that oxidized lignin models are amenable to hydrogenolytic cleavage with a NiMoS_x catalyst. The C_β-OPh bond is cleaved without hydrogenation of the aromatic ring or the C_α ketone to afford phenols and benzylic ketones. The authors propose direct cleavage of the C_β-OPh bond on the NiMoS_x catalyst surface. This process was combined with an initial oxidation step using a NaNO₂/DDQ/NHPI oxidation system to afford a 32% yield of aromatic monomers from birch powder.⁹⁷

Wood-digesting bacteria feature enzymes that use thiol-containing tripeptide glutathione as a redox active cofactor to promote aryl ether cleavage in lignin. Examples include the Lig enzymes E, P, F (etherases) and G (lyase) *Sphingobium* sp. strain SYK 6.^{137,138} In this context, Hegg and coworkers demonstrated complementary chemical reactivity, exploiting the nucleophilic and reductive reactivity of small organic thiols to cleave aryl alkyl ether linkages in oxidized lignin model compounds (**Figure 20c**). Organic thiols, such as β-mercaptoethanol and dithiothreitol can promote cleavage in nearly quantitative yields with certain β-O-4 model compounds in acetonitrile containing K₂CO₃ as a basic additive.¹³⁹ They further employed small thiols (such as propanedithiol, 2-mercaptoethanol, and dithiothreitol) to support cleavage of model polymers and oxidized lignin materials bearing the C_α-ketone functionality. Thiol-dependent depolymerization is proposed to proceed via S_N2 attack adjacent to the ketone to release a phenol. The thiol is

regenerated by nucleophilic attack of another thiol on the S-atom of the thioether to form a disulfide and ketone. Poplar lignin derived from a Cu-AHP extraction method⁸⁰ was oxidized using Bobbitt's salt (cf. **Figure 10**) and then incubated with β -mercaptoethanol. This oxidation/reductive cleavage sequence resulted in approximately 65% reduction of the lignin molecular weight.⁸⁵

4. Conclusion and future outlook

Lignin valorization remains a persistent challenge that is complicated by the complex structure of lignin and the difficulty in obtaining high-quality native-like lignin materials from biomass fractionation methods. Nonetheless, new methods for conversion of lignin into low molecular weight aromatic chemicals continue to emerge. The content outlined herein highlights the merits of bottom-up strategies to address this long-standing challenge. Consideration of the fundamental reactivity of individual functional groups prevalent in lignin – 1° aliphatic and 2° benzylic alcohols – has enabled the development of sequential oxidation/depolymerization methods that successfully convert lignin into oxygenated aromatic chemicals. These efforts greatly benefitted from fundamental studies of well-defined model compounds that incorporate structural features directly present in lignin, especially those present in the common β -O-4 linkage. The development of selective, high-yielding methods for oxidation of the 1° or 2° alcohol in these compounds sets the stage for systematic development of various bond cleavage pathways that are enabled by the initial oxidation step. Insights gained from the well-defined model compounds were then translated into successful lignin depolymerization methods employing similar two-step methods. This approach has been used with a diverse array of lignin materials derived from different biomass plant sources, albeit favoring hardwoods, and different pretreatment/lignin-extraction methods. An appealing feature of this sequential depolymerization strategy is the ability to optimize each step

independently, allowing the overall process to be optimized more effectively for individual feedstocks to maximize the yield of aromatic monomers.

Future work will benefit from studies focused on cleaving a broader array of linkages, as the majority of studies to date have focused on the alcohol-containing β -O-4 unit. Although the β -O-4 fragment is prevalent in lignin, the development of methods capable of cleaving other linkages could greatly improve the monomer yield.

Another future priority will be the development of improved methods for direct oxidative catalytic fractionation (OCF) of biomass,^{41, 140, 141} resembling existing methods for reductive catalytic fractionation (RCF).¹²⁻¹⁸ Essentially all processes for lignin extraction damage the native lignin, generating recalcitrant subunits that limit the yields of aromatics that may be obtained from lignin. For example, under acidic conditions commonly used for lignin extraction, protonation of the benzylic alcohol in the β -O-4 unit can lead to the loss of water and formation of a benzyl cation that can cross-link the lignin polymer (i.e., via Friedel-Crafts alkylation). This reactivity converts a β -O-4 fragment, which is amenable to cleavage, into a new fragment that blocks depolymerization. OCF methods that oxidize the benzylic alcohol while lignin is still integrated within the biomass could provide a means to "protect" the lignin, while generating a material that is more amenable to depolymerization once the lignin is separated from the sugar. This concept and related approaches take inspiration from the two-step oxidation/depolymerization studies outlined herein and could provide the basis for cost-effective valorization of whole biomass.

Acknowledgments. The lignin-based research in our laboratory and preparation of this article was supported in part by the Great Lakes Bioenergy Research Center, U.S. Department of Energy, Office of Science, Office of Biological and Environmental Research under Award Numbers DE-

SC0018409 and DE-FC02-07ER64494 and in part by the U.S. Department of Energy, Office of Energy Efficiency & Renewable Energy under Contract No. DE-EE0008148.

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