OXIDATION OF β-O-4 LIGNIN MODEL COMPOUNDS AND APPLICATION TO LIGNIN LINKAGE DEGRADATION FACILITATED BY MECHANOCHEMICAL TREATMENT AND TWO-STEP OXIDATIVE DEPOLYMERIZATION

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OXIDATION OF β-O-4 LIGNIN MODEL COMPOUNDS AND APPLICATION TO LIGNIN LINKAGE DEGRADATION FACILITATED BY MECHANOCHEMICAL TREATMENT AND TWO-STEP OXIDATIVE DEPOLYMERIZATION

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Arts and Sciences at the University of Kentucky

By
Soledad G. Yao
Lexington, Kentucky

Director: Dr. Mark S. Meier, Professor of Chemistry
Lexington, Kentucky
2018

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ABSTRACT OF DISSERTATION

OXIDATION OF $\beta$-O-4 LIGNIN MODEL COMPOUNDS AND APPLICATION TO LIGNIN LINKAGE DEGRADATION FACILITATED BY MECHANOCHEMICAL TREATMENT AND TWO-STEP OXIDATIVE DEPOLYMERIZATION

The oxidation of lignin model compounds was studied in conventional solvents in parallel with oxidations in ionic liquid solvents. Catalyst systems were investigated in ionic liquid solvents to determine how reaction rates and the selectivity for benzylic carbon oxidation were affected. Oxidation rates were often lower in ionic liquids than in conventional solvents – as indicated by lower conversion in a standard reaction time – likely due, at least in part, to the higher viscosity of ionic liquids. Mechanochemical treatment of Indulin AT kraft lignin by ball milling with KOH and toluene produced significant carbonyl functionality, among other changes. The chemical reactivity of the lignin was increased, resulting in greater lignin degradation from porphyrin oxidation followed by Baeyer-Villiger oxidation. The mechanochemical treatment produced a level of lignin oxidation that was similar to that produced by porphyrin-catalyzed oxidation. Combining mechanochemical treatment with porphyrin oxidation produced a synergistic positive effect on the depolymerization of lignin, as demonstrated by a significantly higher yield of monomers. The methyl ester of vanillic acid was obtained as the main monomeric product (after methylation), along with a small amount of methyl 5-carbomethoxyvanillate.

Keywords: $\beta$-O-4 lignin model compounds, Indulin AT kraft lignin, ionic liquids, mechanochemical treatment, porphyrin oxidation, oxidative depolymerization.

Soledad G. Yao

01/05/18
OXIDATION OF β-O-4 LIGNIN MODEL COMPOUNDS
AND APPLICATION TO LIGNIN LINKAGE DEGRADATION
FACILITATED BY MECHANOCHEMICAL TREATMENT AND
TWO-STEP OXIDATIVE DEPOLYMERIZATION

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01/05/18
To my beloved family:

Sio Len, Jr.
Shervin and Marie Angelet
Shermaigne and Mark Andrew
Sherlock, Dina May, and Agatha Joy
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<tr>
<td>%</td>
<td>per cent</td>
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<tr>
<td>°C</td>
<td>degree centigrade</td>
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<td>$^{13}$C NMR</td>
<td>carbon-13 nuclear magnetic resonance</td>
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<tr>
<td>$^1$H NMR</td>
<td>proton nuclear magnetic resonance</td>
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<tr>
<td>aq</td>
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<td>atm</td>
<td>atmosphere</td>
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<tr>
<td>BF$_3$•OEt$_2$</td>
<td>boron trifluoride diethyl etherate</td>
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<td>BMWL</td>
<td>ball milled wood lignin</td>
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<td>BV</td>
<td>Baeyer-Villiger</td>
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<tr>
<td>CAER</td>
<td>Center for Applied Energy Research</td>
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<td>CEL</td>
<td>cellulolytic enzyme lignin</td>
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<tr>
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<td>centipoise</td>
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<td>dimethyl formamide</td>
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<td>$E_a$</td>
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<tr>
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<td>methyltrioxorhenium</td>
</tr>
<tr>
<td>MWL</td>
<td>milled wood lignin</td>
</tr>
<tr>
<td>pH</td>
<td>potential of hydrogen</td>
</tr>
<tr>
<td>POMs</td>
<td>polyoxometalates</td>
</tr>
<tr>
<td>Porp</td>
<td>porphyrin</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>RTILs</td>
<td>room temperature ionic liquids</td>
</tr>
<tr>
<td>S</td>
<td>syringyl</td>
</tr>
<tr>
<td>Salen</td>
<td>salicylaldehyde ethylenediamine</td>
</tr>
<tr>
<td>SM</td>
<td>starting material</td>
</tr>
<tr>
<td>t-BuOOH</td>
<td>tert-butylhydroperoxide</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-tetramethylpiperidine 1-oxyl</td>
</tr>
<tr>
<td>TEMPOH</td>
<td>2,2,6,6-tetramethylpiperidine 1-oxyl (reduced form)</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TPPFeCl</td>
<td>tetraphenylporphyrin iron chloride</td>
</tr>
<tr>
<td>TSILs</td>
<td>task-specific ionic liquids</td>
</tr>
<tr>
<td>USDA</td>
<td>United States Department of Agriculture</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>ε</td>
<td>dielectric constant</td>
</tr>
<tr>
<td>η</td>
<td>viscosity</td>
</tr>
<tr>
<td>μL</td>
<td>microliter</td>
</tr>
</tbody>
</table>
Chapter 1. GENERAL INTRODUCTION

1.1 Renewables

1.1.1 Introduction

Tapping renewable energy sources is the ultimate key to a sustainable economy. Fossil-based fuels triggered the industrial revolution and moved the world economy to where it currently is, but due to their finite nature, the ability to keep this economy going cannot be relied upon. Fossil fuel supplies are being depleted and will eventually vanish for good, bringing world economy down with them, just as they moved the economy up at the time when these fuels were abundant. The clock has been ticking for fossil fuels and the time to go renewables is actually long overdue.

1.1.2 Fuels and feedstocks

Renewable energy sources are those that are naturally replenished on a human timescale, as opposed to non-renewable sources, like fossil fuels, which are formed from organic material in the geological past, over the course of millions of years.¹

Among the renewables (wind, solar, geothermal, hydropower, tides, and waves), bioenergy may be considered as one of the most promising. Biofuels are particularly attractive, being currently the only renewable source of liquid transportation fuels. As such, they are strongly supported by the US Department of Energy (DOE) and the US Department of Agriculture (USDA) as a way of moving away from fossil fuels and are expected to replace 30% of US petroleum consumption by the year 2030.² Additionally, these fuels are carbon-neutral, as the carbon dioxide they emit is cancelled by that which is taken in by plants as they grow.
Biofuels include various transportation fuels such as bio-ethanol, butanol, bio-oil, and biodiesel, most of which are derived from plant material. Their feedstock refers to any biomass that is used as raw material for their production. The first-generation biofuels, which use the fruits and seeds of food crop materials like corn, sugarcane, and palm oil as feedstocks, have not gained popular support due to the direct food-versus-fuel competition that goes with it. As an alternative, the second-generation biofuels, which use the rest of the plant (collectively known as lignocellulosic biomass, LCB) as feedstocks, have been developed. Presently, feedstocks for biofuels have been expanded to include agricultural, industrial, urban and suburban wastes, as well as dedicated plants such as switchgrass, miscanthus, sorghum, and eucalyptus, some of which are adapted to poor soils and marginal agricultural lands and therefore minimally compete for food production. Figure 1.1 outlines some of the most common biomass feedstocks.
1.1.3 Why lignin

Lignocellulosic biomass (LCB) is organic matter derived from biological origin, made up principally of the biopolymers lignin, cellulose, and hemicellulose. In LCB, the cellulose component has always been the primary focus of interest, being the main feedstock in ethanol production and in the pulp and paper industry. After being relegated for a long time to the role of low-grade solid fuel for heat, the lignin component has of late been being given a good share of attention, partly because it’s too abundant to ignore, and partly because initial studies have revealed that just like cellulose, it could also be a potential source of renewable energy, as well as of other chemical commodities, like aromatic compounds.
1.1.4 Lignin structure and biosynthesis

The term “lignin” was used for the first time by the Swiss botanist A. P. Candolle from the Latin word “lignum,” meaning wood. It was previously referred to as the “encrusting material” for embedding cellulose in the wood, and is present in the cell wall, strongly bound to the two other major components of wood – cellulose and hemicellulose (Fig. 1.2a). Cellulose is the main building block that lends wood its firm structure, while lignin acts as a “glue” that keeps cellulose fibrillar structures together, imparting rigidity and strength to lignocellulose (Fig. 1.2b). Together with hemicellulose to which it is covalently bonded, lignin also serves to regulate the water content within the cell wall, thus maintaining its integrity.

Lignin is the most abundant substance in nature that has aromatic moieties. It is a group of complex, amorphous, three-dimensional polymers that have the phenylpropanoid group as a common structural feature.

Elucidation of lignin’s structure presents a real challenge due to the complexity and irregularity of such structure, which is altered depending on how it is isolated from the lignocellulosic material (LCM). Notwithstanding its variability, lignin biosynthesis is generally considered to be a result of polymerization of the three monolignol precursors p-coumaryl, coniferyl, and sinapyl alcohols, which are incorporated into the polymer as p-hydroxyphenyl (H), guaiacyl (G), and syringyl (S) units, respectively (Fig. 1.3).
Figure 1.2. a) The biopolymers that make up wood\textsuperscript{11}; b) Arrangement of the biopolymers lignin, cellulose, and hemicellulose in the plant cell wall (Reproduced with permission from W. Boerjan, Bio-Energy and Bio-Aromatics, https://www.psb.ugent.be/bio-energy/313-lignin)\textsuperscript{12}
Figure 1.3. Lignin composition: a) the monolignol precursors; b) the monolignol aromatic moieties when incorporated in the lignin polymer.\textsuperscript{13}

Although there is no single structure for lignin, some recurring structural features have been elucidated, including the linkages between monolignol precursors (Table 1.1) and some of the functional groups that are commonly present (Table 1.2). A structural representation of lignin has also been proposed (Fig. 1.4).

Table 1.1. Linkages between monomer units in softwood lignin.\textsuperscript{14-18}

<table>
<thead>
<tr>
<th>Linkage Type</th>
<th>Dimer Structure</th>
<th>% Total Linkages</th>
</tr>
</thead>
<tbody>
<tr>
<td>β – O - 4</td>
<td>Phenylpropane β-aryl ether</td>
<td>45-50</td>
</tr>
<tr>
<td>5 - 5</td>
<td>Biphenyl and Dibenzodioxocin</td>
<td>18-25</td>
</tr>
<tr>
<td>β - 5</td>
<td>Phenylcoumaran</td>
<td>9-12</td>
</tr>
<tr>
<td>β - 1</td>
<td>1,2-Diaryl propane</td>
<td>7-10</td>
</tr>
<tr>
<td>α - O - 4</td>
<td>Phenylpropane α-aryl ether</td>
<td>6-8</td>
</tr>
<tr>
<td>4 – O - 5</td>
<td>Diaryl ether</td>
<td>4-8</td>
</tr>
<tr>
<td>β - β</td>
<td>β – β-linked structures</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 1.2. Functional groups per 100 phenyl propane units present in softwood lignin.7

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Abundance per 100 C9 units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonyl</td>
<td>10-15</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>15-20</td>
</tr>
<tr>
<td>Phenolic hydroxyl (free)</td>
<td>15-30</td>
</tr>
<tr>
<td>Methoxy</td>
<td>92-96</td>
</tr>
</tbody>
</table>

Figure 1.4. A lignin fragment, highlighting component monolignols and linkages.19
The polymerization of monolignols to form lignin is believed to proceed through enzymatic dehydrogenation, initiated by electron transfer yielding resonance-stabilized phenoxy radicals (Fig. 1.5).

Phenoxy radicals can couple to form quinone methides, which react further by addition of water or alcohol group to form dilignols [Fig. 1.6a; Fig. 1.6b (1-4)]. A dilignol undergoes dehydrogenation to form a stabilized radical [(Fig. 1.6b (4)], as in monolignols, and couples with a monolignol radical forming a trilignol [Fig. 1.6b (5-8)]. The process is repeated, where a monolignol radical adds to an end of a growing oligomer radical, instead of coupling with another monolignol radical, in what is known as end-wise polymerization. As polymerization proceeds, dimerization of monomer radical becomes less likely compared to crosslinking with a dilignol, or with an oligomer.\(^9\) In enzyme-mediated reactions, radical-radical dimerization is often unimportant - even though it’s very fast, because radical concentrations are so low.
Figure 1.6a. Dilignols formed by phenoxy radical coupling.

Figure 1.6b. Resonance-stabilized dilignol phenoxy radicals.
1.1.5 Lignin isolation

Isolation of lignin from native biomass or from wood pulp is very critical in the lignin structure elucidation process. Due to its close association with the polysaccharide component of biomass, it’s extremely difficult to isolate lignin without modifying its structure and care must be taken that the structural change be as minimal as possible.

1.1.5.1 Lignin isolation methods

There are two general approaches to lignin isolation: 1) dissolving the non-lignin components to yield lignin as residue; and 2) dissolving lignin, either without reacting with the extracting solvent, or by forming soluble derivatives. In the process, it has become customary to categorize lignin based on the method of its isolation or on the person that developed the method. These methods are summarized in Table 1.3.

1.1.5.2 Common lignin preparations

Some lignin preparations that have become commercially available have different properties and are isolated/extracted from source in different ways. These include technical lignins, like Kraft and lignin sulfonates, which are lignins that have been recovered during pre-treatment and pulping processes. There are also those that are extracted using different solvents (organosolv).

1.1.5.2.1 Kraft lignin

The main objective of the pulping process is to remove lignin from the lignocellulosic material in order to liberate cellulose fibers and make them accessible to enzymatic hydrolysis. Kraft process accounts for most of the world’s paper pulp. During
Table 1.3. Lignin isolation methods.\textsuperscript{16,23}

<table>
<thead>
<tr>
<th>METHOD/REMARKS</th>
<th>TREATMENT</th>
<th>LIGNIN PREPARATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lignin as residue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acid hydrolysis of polysaccharides</td>
<td>$\text{H}_2\text{SO}_4$</td>
<td>Sulfuric acid lignin (Klason lignin)</td>
</tr>
<tr>
<td></td>
<td>$\text{H}_2\text{SO}_4/\text{HBr}$</td>
<td>Sulfuric acid lignin (Runkel lignin)</td>
</tr>
<tr>
<td></td>
<td>$\text{HCl}$</td>
<td>Hydrochloric acid lignin (Willstatten lignin)</td>
</tr>
<tr>
<td></td>
<td>$\text{HCl}/\text{H}_2\text{SO}_4$</td>
<td>Hydrochloric acid lignin (Halse lignin)</td>
</tr>
<tr>
<td></td>
<td>$\text{HF}$</td>
<td>Hydrofluoric acid lignin</td>
</tr>
<tr>
<td></td>
<td>$\text{CF}_3\text{COOH}$</td>
<td>Trifluoroacetic acid lignin</td>
</tr>
<tr>
<td>Oxidation of polysaccharides</td>
<td>$\text{Na}_3\text{H}_2\text{IO}_6$</td>
<td>Periodate lignin (Purves lignin)</td>
</tr>
<tr>
<td>Hydrolysis/Dissolution of polysaccharides</td>
<td>$\text{NaOH}/\text{H}_2\text{SO}_4$</td>
<td>Cuoxam lignin/cuproaxam/cuprammonium lignin (Freudenberg lignin)</td>
</tr>
<tr>
<td></td>
<td>$\text{Cu(NH}_3)_4(\text{OH})_2$</td>
<td></td>
</tr>
<tr>
<td><strong>Lignin by dissolution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No appreciable reaction between lignin and solvent</td>
<td>Alcohol extraction</td>
<td>Native lignin (Brauns lignin)</td>
</tr>
<tr>
<td></td>
<td>Vibratory milling/dioxane-water extraction</td>
<td>Milled wood lignin (MWL) Björkman lignin</td>
</tr>
<tr>
<td></td>
<td>Ball milling/$\text{H}_2\text{O}-\text{NaSCN-C}_6\text{H}_5\text{CH}_2\text{OH-DMF}$ dissolution/extraction</td>
<td>Ball-milled wood lignin (BMW) Linin</td>
</tr>
<tr>
<td></td>
<td>Brown-rot fungi treatment</td>
<td>Enzymically liberated lignin (ELL)</td>
</tr>
<tr>
<td></td>
<td>Milling/enzymic treatment/solvent extraction</td>
<td>Cellulolytic enzyme lignin (CEL)</td>
</tr>
<tr>
<td><strong>Organosolv lignins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactions between lignin and solvent</td>
<td>Alcohol/HCl</td>
<td>Alcohol lignin</td>
</tr>
<tr>
<td></td>
<td>Dioxane/HCl</td>
<td>Dioxane acidolysis lignin</td>
</tr>
<tr>
<td></td>
<td>$\text{CH}_3\text{COOH}/\text{MgCl}_2$</td>
<td>Acetic acid lignin</td>
</tr>
<tr>
<td></td>
<td>$\text{HSCH}_2\text{COOH}/\text{HCl}$</td>
<td>Thioglycolic acid lignin (TGA-L)</td>
</tr>
<tr>
<td></td>
<td>Phenol/HCl</td>
<td>Phenol lignin</td>
</tr>
<tr>
<td></td>
<td>Mild hydrogenation</td>
<td>Hydrogenolysis lignin</td>
</tr>
<tr>
<td></td>
<td>Hydrotropic solvents</td>
<td>Hydrotropic lignin</td>
</tr>
<tr>
<td><strong>Derivatives by inorganic reagents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General technical pulping processes</td>
<td>Sulfite/bisulfite</td>
<td>Lignin sulfonates (Lignosulfonates)</td>
</tr>
<tr>
<td></td>
<td>$\text{NaOH}$</td>
<td>Alkali lignin (Soda lignin)</td>
</tr>
<tr>
<td></td>
<td>$\text{Na}_2\text{S/NaHS}$</td>
<td>Thiolignin</td>
</tr>
<tr>
<td></td>
<td>$\text{NaOH/Na}_2\text{S}$</td>
<td>Kraft lignin (Sulfate lignin)</td>
</tr>
</tbody>
</table>
kraft cooking, wood chips are reacted with a mixture of sodium hydroxide and sodiumsulfide (white liquor), at a temperature of 155-175 °C for several hours. This step separates the mixture into a solid (cellulose) and a fluid referred to as black liquor from which Kraft lignin can be precipitated by neutralizing the alkali mixture with an acid solution (pH 1-2), and drying to a solid form. The resulting Kraft lignin is hydrophobic and water-insoluble but soluble in aqueous alkali.8

Kraft pulping partially depolymerizes lignin, reducing its molecular weight.22 Treatment with white liquor causes alkali cleavage of β-aryl ether bonds in the nonphenolic aryl propane units of the polymer (see Section 1.2.2, Scheme 1.4), and sulfidolytic cleavage (of the same type of bonds) in the phenolic aryl propane portions forming enol ether units (see Section 1.2.2, Scheme 3). However, the presence of alkali can also induce condensation reactions during the Kraft “cook” phase, forming alkali-stable C-C linkages24 which reduces lignin solubility and makes it harder to separate from the cellulose.

1.1.5.2.2 Lignin sulfonates

Sulfite pulping using salts of sulfurous acids (sulfites or bisulfites) produce lignin sulfonates. This pulping procedure can be performed under different conditions, serving different purposes (Table 1.4). Using acidic conditions solubilizes lignin through introduction of hydrophillic sulfonate groups (sulfonation), while neutral conditions are used to “soften” the lignin. As in Kraft pulping, alkaline sulfite is used for fragmentation, in addition to sulfonation. Most other sulfite pulping conditions (acidic and neutral) do not fragment lignin, hence lignin sulfonates have molecular weights that are higher than that of Kraft lignin and more closely resemble the original native lignin. In terms of
structure, lignin sulfonates incorporate both hydrophobic and hydrophilic properties and are water soluble (Fig. 1.7).

![Structure representation of lignin sulfonates.](image)

**Figure 1.7. Structure representation of lignin sulfonates.**

<table>
<thead>
<tr>
<th>Process</th>
<th>Reactive Agents</th>
<th>pH</th>
<th>T (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid sulfite</td>
<td>SO₂/HSO₃⁻</td>
<td>1-2</td>
<td>125-145</td>
</tr>
<tr>
<td>Bisulfite</td>
<td>HSO₃⁻</td>
<td>3-5</td>
<td>150-175</td>
</tr>
<tr>
<td>Neutral sulfite</td>
<td>HSO₃⁻/SO₃²⁻</td>
<td>6-7</td>
<td>150-175</td>
</tr>
<tr>
<td>Alkaline sulfite/Anthraquinone</td>
<td>Na₂SO₃</td>
<td>9-13</td>
<td>150-175</td>
</tr>
</tbody>
</table>

### 1.1.5.2.3 Organosolv lignin

Organosolv lignins are prepared by extraction from biomass using organic solvent/water mixtures at high temperature/pressure. Eight procedures for organosolv lignin preparation have been described (Table 1.5). The most commonly used extracting solvents are alcohols, mixed with other solvents and reagents, and as in the Kraft process, lignin is isolated by acid precipitation. Of the different organosolv preparations, only Alcell and Organocell lignin preparations are commercially available.
Table 1.5. Organosolv lignins.\textsuperscript{8}

<table>
<thead>
<tr>
<th>Lignin type</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcell</td>
<td>Ethanol/water</td>
</tr>
<tr>
<td>Alcetocell</td>
<td>Acetic acid/water</td>
</tr>
<tr>
<td>Acetosolv\textsuperscript{25}</td>
<td>Acetic acid/HCl pulping</td>
</tr>
<tr>
<td>ASAM</td>
<td>Alkaline sulfite/anthraquinone/methanol</td>
</tr>
<tr>
<td>Batelle/Geneva phenol\textsuperscript{26}</td>
<td>Phenol/acid/water</td>
</tr>
<tr>
<td>Formacell</td>
<td>Acetic acid/formic acid/water</td>
</tr>
<tr>
<td>Milox\textsuperscript{27}</td>
<td>Formic acid/hydrogen peroxide</td>
</tr>
<tr>
<td>Organocell\textsuperscript{28}</td>
<td>Methanol pulping, followed by methanol, NaOH, and anthraquinone pulping</td>
</tr>
</tbody>
</table>

1.1.6 Potential products from lignin

The various applications of isolated lignin depend on whether it is used as it is, without chemical modification, or fragmented in different ways to give an assortment of potential products. As unmodified polymers, technical lignins have been used in different forms as macromolecules and applied as fillers, extenders, binders, preservatives, pharmaceuticals (anti-oxidants\textsuperscript{29} and free-radical scavengers\textsuperscript{30}), additives to other polymers to modify polymer properties (for example imparting biodegradable property to polyolefins),\textsuperscript{31} and material in manufacture of adhesives.\textsuperscript{32-34} However, higher value products can be obtained if lignin is deconstructed/fragmented, making it a potential source of fuel and bulk and fine chemicals.\textsuperscript{19} Oxidation is one of the various deconstruction techniques commonly employed, making lignin a possible source of carbon and aromatic monomers. Fig. 1.8 shows some of the utilization of and possible products that can be obtained from fragmented/deconstructed and oxidized lignin.
Figure 1.8. The biomass tree showing utilization and potential products from biomass.19,35,36

1.2 Lignin Deconstruction/Depolymerization

1.2.1 Introduction

Compared to its native form, deconstructed/fragmented lignin offers much more value-added products, not only biofuels, but bio-based platform molecules as well. These small molecules that are derivable from biomass can be utilized as building blocks for higher-value chemicals and materials.37-46 Hence cost-effective lignin depolymerization is a goal that has been shared by numerous research groups for decades,37-39,41,42,45,47-62 and will likely remain to be so in the foreseeable future. Due to the random assortment of linkages within the polymer, lignin depolymerization presents a real
challenge, and the several strategies that have been applied were able to depolymerize lignin with only limited success. Fig. 1.9 summarizes some of these strategies.

![Figure 1.9. Summary of lignin transformation/depolymerization showing typical temperature range of lignin conversion in the abscissa.](image)

1.2.2 Acid-catalyzed depolymerization

Acid-catalyzed treatment is one of the earliest and most widely used methods of fractionating lignocellulose into its components.\(^{45,63}\) In an early study, it was applied in the fractionation of lignin, through ethanolysis, into water-soluble and water-insoluble components as part of initial efforts to help elucidate the structure of the polymer.\(^{64}\) However, the temperature applied (78 °C – 200 °C) was not high enough to fragment the polymer to monomers.

Recently acid-catalyzed lignin depolymerization was investigated at a higher-than-usual temperature range in order to break up the polymer. Using wheat straw lignin
at 360 °C – 380 °C, the major monomer products obtained after depolymerization were methoxyphenol, catechol, and phenol. With 10 wt% formic acid and 77 wt% of ethanol at 360 °C, a combined yield of 2.1 wt% was obtained,\textsuperscript{65} while the same concentration of the acid and the alcohol at 380 °C gave a total yield of 5.2 wt%.\textsuperscript{66} With 10 wt% formic acid and 81 wt% of ethanol at 380 °C, an improved total yield of 6.4 wt% was observed.\textsuperscript{66}

It has been shown that acids facilitate breaking of the \( \alpha \)- and \( \beta \)-aryl ether linkages in lignin which are more easily cleaved compared to the much more stable aryl-aryl ether and C-C bonds. The acid catalysts that have been used to cleave aryl ether bonds in lignin and lignin model compounds include various mineral acids (HCl, H\(_2\)SO\(_4\)),\textsuperscript{67-70} Lewis acids (FeCl\(_3\), ZnCl\(_2\), BF\(_3\), and AlCl\(_3\)),\textsuperscript{71-74} acidic ionic liquids,\textsuperscript{75-77} and organic acids.\textsuperscript{78,79} It has been found that an \( \alpha \)-aryl ether hydrolyzes faster (102 times) compared to \( \beta \)-aryl ether,\textsuperscript{37,80} with the activation energy for hydrolysis being much lower (80 - 118 kJ/mol) than that for \( \beta \)-aryl ether (148 - 151 kJ/mol).\textsuperscript{78,81} This indicates that when lignin undergoes acid-catalyzed depolymerization, the \( \alpha \)-aryl ether linkages are cleaved first before the \( \beta \)-aryl ether bonds.

For \( \beta \)-aryl ether linkages, acid hydrolysis proceeds through dehydration as the primary and rate-determining step, forming an enol aryl ether intermediate. The enol ether intermediate then hydrolyzes in a fast step to guaiacol and \( \alpha \)-ketocarbinol, with the latter being converted through rearrangement to a mixture of compounds known as Hibbert’s ketones (Scheme 1.1).\textsuperscript{73,82,83}
Scheme 1.1a. Acid-catalyzed hydrolysis of the β-aryl ether linkage in lignin.84

Scheme 1.1b. Hibbert’s ketones.83
One of the major hindrances in designing lignin depolymerization based on acid catalysis is the condensation/repolymerization reaction that accompanies depolymerization. Up to this time, this issue remains to be successfully resolved, although some of the reasons for its occurrence have been identified, like the formation of reactive intermediate that leads to condensation. In this case, one way to suppress condensation is to capture the reactive intermediate by transforming it into a stable form. An example of such reactive species is an aldehyde (see Scheme 1.1a) that is formed in trace amount during acid-catalyzed lignin depolymerization. Some ways that this aldehyde can be stabilized are through i) acetal formation with diols, ii) hydrogenation, and iii) decarbonylation. When the aldehyde intermediate formed was stabilized by hydrogenation, a moderate increase in the monomer yield from about 1 wt% to 7 wt% has been observed. In addition to the unwanted condensation side-reaction, another drawback of lignin depolymerization design based on acid catalysis is the harsh reaction condition under acidic environment which can increase the cost of maintaining reaction facility if and when acid-catalyzed depolymerization is applied in a biorefinery.

1.2.3 Base-catalyzed depolymerization

Base-catalyzed depolymerization provides another possible route to the production of aromatic chemicals. The reagents (LiOH, NaOH, and KOH) are cheap and commercially available, although the reaction temperatures are higher than what are typically used in acid-catalyzed depolymerization (up to 300 °C or higher). As in acid catalysis, monomer product yields are not that high. For example, when 2 wt% - 5 wt% NaOH (wt/wt) were used at temperatures of 270 °C – 330 °C, major monomer product yields obtained ranged from 3 wt% - 7 wt%.
As in acid-catalyzed depolymerization, cleavage of α- and β-aryl ether linkages are the dominant reactions in alkaline-mediated lignin depolymerization processes. Using lignin model compounds, it has been shown that the hydrolysis route depends on the presence or absence of free phenols at a position para to the propanoid side chain.\(^{15,91}\) α-aryl ether linkages in phenolic compounds cleave easily when the phenolate ion converts into the corresponding quinone methide intermediate (Scheme 1.2). In the case of the β-aryl ether linkage, cleavage in phenolic compounds is facilitated if suitable leaving groups are present at the α-position. Under these conditions, the phenolate ion is converted into a quinone methide intermediate, which adds a hydrosulfide ion to produce a benzyl mercaptide anion. By attacking the adjacent β-carbon, the mercaptide anion facilitates elimination of the β-aryloxy group as a phenol (Scheme 1.3). For non-phenolic compounds, cleavage of the β-aryl ether bond proceeds by the attack at the β-carbon by an alkoxide group either at the α- or γ-position (Scheme 1.4).

![Scheme 1.2. Alkaline cleavage of α-aryl ether bond in phenolic propane units.](image)

\(^{15,91-94}\)
Scheme 1.3. Sulfidolytic cleavage of the β-aryl ether linkage in phenolic arylpropane units and conversion into enol ether compound.15,91-95

Scheme 1.4. Base-catalyzed cleavage of the β-aryl ether linkage in non-phenolic lignin model compounds.15,91,93,94

While the base-catalyzed process may be a simple way to depolymerize lignin, the high temperature under which it is typically conducted renders selectivity difficult to control. Several side-products, including significant amount of gases, prevent the formation of the desired monomer products.63 In addition, accompanying repolymerization/condensation reactions limit the total amount of products obtained, as is the case in acid catalysis.87
1.2.4 Thermal depolymerization: Pyrolysis

Pyrolysis involves heating an organic substance in the absence of air, breaking said substance into smaller units. The limited amount of oxygen available prevents further oxidation of products to \( \text{CO}_2 \). The composition of the pyrolysis product mixture depends on the pyrolysis condition, specifically the temperature and heating rate. At a temperature lower than 450 °C and slow heating rate, pyrolysis products are mainly biochar, while at temperatures higher than 800 °C and rapid heating rates, the products are mainly gases. At intermediate temperatures and relatively high heating rates, the major product is bio-oil.\(^9\)

Initial stages of pyrolysis at low temperature (120 °C – 300 °C) gives volatile products including \( \text{CO} \), \( \text{CO}_2 \), \( \text{H}_2\text{O} \), formic acid and formaldehyde. Thermal degradation proceeds progressively from weaker bonds at lower temperatures, to the more resistant linkages at higher temperatures. Low temperature breaks ether bonds and hydroxyl groups attached to \( \beta \) or \( \gamma \) carbon giving condensable volatile products and water.\(^9\) Water is formed from cleavage of OH group from \( \beta \) or \( \gamma \) carbon, while formaldehyde is formed from breaking \( \beta-\gamma \) carbon bond. The C-C bond such as the 5-5 linkage is the most resistant and is broken only at very high temperature, while the \( \beta-\text{O}-4 \) and \( \alpha-\text{O}-4 \)\(^9\) are easier to cleave.

Pyrolysis of lignin provides renewable source of various types of phenolic compounds, examples of which are shown in Fig. 1.10. Total yields of phenolic pyrolysis products vary with temperature, without necessarily being favored by higher temperature. To illustrate, the maximum yields of phenolic compounds observed in the pyrolysis of Alcell lignin at 400 °C, 600 °C, and 800 °C, were about 13 wt%, 17 wt%, and 12 wt%, respectively.
respectively.\textsuperscript{99} In another experiment, a similar yield of about 13\% phenolic fraction was obtained from Alcell lignin at 400 °C.\textsuperscript{100}

![Diagram of lignin pyrolysis products](image)

**Figure 1.10.** Major products of lignin pyrolysis: a) Volatile compounds including H\textsubscript{2}O resulting from cleavage of OH group from β or γ carbon, and HCHO from breaking of β-γ carbon bond; b) Various phenols including guaiacol (A), methyl guaiacol (B), syringol (C), methyl syringol (D), vanillin (E), syringaldehyde (F), vinyl guaiacol (G), vinyl syringol (H), and phenol (I).\textsuperscript{101}

### 1.2.5 Reductive depolymerization: Hydroprocessing

Hydroprocessing, which involves thermal reduction by hydrogen, is a commonly used strategy of depolymerizing lignin into oligomers, phenols, and other valuable chemicals, as well as in upgrading of the small molecule products into hydrocarbon fuels. It includes reactions such as hydrogenolysis, deoxygenation, and hydrogenation.\textsuperscript{37}
1.2.5.1 Hydrogenolysis

Hydrogenolysis is a process where carbon-carbon or carbon-heteroatom bonds are cleaved by hydrogen. Because it is done with heating, it may also be viewed as pyrolysis performed in the presence of hydrogen, cleaving C-C or C-X bond (Scheme 1.5). It has the advantage over neat pyrolysis in that it results to higher conversion to bio-oil and less char formation. For example, pyrolysis of Alcell lignin at 400 °C produced 37 wt% bio-oil and 35 wt% char\textsuperscript{100} while hydrogenolysis of organocell lignin at 380 °C and 10-18 MPa H\textsubscript{2} using Pd/C catalyst gave an oil yield of up to 80 wt% and only 1 wt% char.\textsuperscript{102}

\[ \text{R - X} \xrightarrow[H_2, \text{cat}]{} \text{R - H} + \text{H - X} \quad \text{X} = \text{alkyl chain, OH, SH, NH}_2, \text{OR, NR, etc.} \]

Scheme 1.5. Breaking C-C bond by hydrogenolysis.

Hydrogenolysis may be affected by such factors as the catalyst used, the type of lignin starting material, and reaction conditions including temperature, hydrogen partial pressure, and time of reaction.\textsuperscript{102}

In the hydrogenolysis of different types of lignin at various reaction conditions,\textsuperscript{102} it was observed that using Pd/C as catalyst, up to 80 wt% oil product could be obtained (as mentioned in the preceding paragraph), while with nickel-molybdenum, the oil product was about 65 wt%. Without any catalyst, the oil yield was about 18 wt%. Kraft and organocell lignin were both found to give better oil to char product % yield ratios of about 62:1 and 55:2, respectively, compared to acetosolv lignin which had a ratio of about 38:27. Increasing the temperature promotes lignin fragmentation, as shown by an increase in the amount of monophenol products quantified by GC as the temperature was
increased: 7 wt% at 350 °C, 11 wt% at 400 °C, and 23 wt% at 450 °C. Char formation was likewise enhanced at high temperatures (higher than 400 °C). The highest amount of oil was obtained at 400 °C, showing that high oil yield does not automatically translate to high monomer products. Increasing the hydrogen partial pressure also promotes oil production. Oil yields were observed to increase from about 18 wt% at initial partial pressure of 3 MPa to about 63 wt% at 12 MPa. At the same time, char formation decreased from 41 wt% to 3 wt%. Surprisingly, reaction time had only a slight influence on oil product yield, probably because of the high temperature (420 °C) at which the influence of time was studied. In a reaction mixture which is heated to a high temperature, it is possible for the reaction to already attain completion by the time the desired temperature is reached so that prolonged heating may not increase the yield any further. The effect of reaction time may have been noticeable had the experiment been conducted at lower temperature, say 350 °C.

Hydrogenolysis is a useful reaction for upgrading lignin for fuel production. In particular, cleaving the C-O bond is desired as it decreases the oxygen content of lignin and thus increases the fuel value of the products. The process is usually performed under basic conditions, employing metal catalysts such as Pt, Ru, Ni, Pd, or Cu.103,104

1.2.5.2 Hydrodeoxygenation (HDO)

As the name indicates, hydrodeoxygenation is the removal of oxygen by reaction with H₂, forming water and deoxygenated compounds, typically hydrocarbons. Just like hydrogenolysis, it may be considered as pyrolysis carried out in the presence of hydrogen. Oxygen is removed usually in the form of water under high H₂ partial pressure (100-200 bar) and at high temperature (570-670 K). This process is commonly used in upgrading
bio-oils that were derived from fast hydrolysis of biomass, including lignin. These bio-oils have low fuel quality. They have high oxygen content (10-50 wt%), low heating value, high viscosity, high water content, and are acidic in nature (causing undesired corrosion of vessels and pipes). The high oxygen content also contributes to the bio-oil’s chemical and thermal instability and makes it prone to re-polymerization/condensation which can induce char formation.\textsuperscript{105-110} Hence, removal of oxygen is necessary in order to improve bio-oil’s fuel grade and stability. Final deoxygenated compound products are hydrocarbons, while the removed oxygen is primarily in the form of water. Oxygen may also be removed as CO\textsubscript{2}, CO, and methanol. Several catalysts have been employed to promote HDO including metals, metal sulfides, metal phosphides, metal carbides, and metal nitrides. Noble metals such as Pt, Ni, Rh, and Pd have been used as well, but they can be so expensive that their use may not be practical and advisable. In addition, these metals are active for hydrogenation of the aromatic ring which is undesirable as it increases H\textsubscript{2} consumption.\textsuperscript{111-116}

1.2.5.3 Hydrogenation

Hydrogenation utilizes a pair of hydrogen atoms to reduce or saturate organic compounds. Typical reactive centers include C=C double and triple bonds, and the C=O bond which become saturated by the addition of hydrogen atoms across the multiple bonds. Selectivity of hydrogenation towards aromatic C=C, linear C=C, and C=C, varies according to the catalyst used,\textsuperscript{117,118} while for hydrogenation of C=O, zero-valent metals including Al, Fe, Mg, and Zn have been found to be active.\textsuperscript{119} Hydrogenation commonly occurs simultaneously with hydrogenolysis, or is included in
hydrodeoxygenation. A reaction network illustrating these three reductive processes is shown in Fig. 1.11.

Figure 1.11. Reaction network in hydroprocessing of lignin depolymerization products (in rectangles) with H₂ catalyzed by Pt/γ-Al₂O₃ at 573K and 1.40 bar: Hydrogenolysis (Green); Hydrodeoxygenation (Red); Hydrogenation (Blue).¹⁰⁵,¹²⁰

1.2.6 Oxidative depolymerization

Depolymerization of lignin via oxidation is a promising route considering the abundance of hydroxyl groups in the polymer. It involves cleavage of aryl ether and C-C bonds, aromatic rings, and other linkages within the polymer. The method is particularly useful in depolymerizing lignin for production of polyfunctional aromatic chemicals. Unlike the reductive approach which removes functionalities, the oxidative method preserves the functional groups and allows for their conversion into other groups and may even pave the way to further functionalization. Oxidation products range from aromatic aldehydes to carboxylic acids, based on how rigorous the reaction conditions are.¹²¹
Vanillin and vanillic acid are obtained from alkaline oxidation of softwood while syringaldehyde and syringic acid are produced from hardwood lignin. By far, vanillin is one of the most important low-MW chemicals produced from technical lignin in industrial quantities by alkaline oxidation in air.\textsuperscript{49,122,123} The most popular oxidants that have been used for lignin oxidation include nitrobenzene, metal oxides, hydrogen peroxide, and molecular oxygen, while the catalysts that have been employed may be heterogeneous, homogeneous, or enzymatic.

Heterogeneous catalysis has played an important role in the pulp and paper industry as a way of improving the quality of paper product by the removal of lignin and other compounds from wood. Some common examples of this type of catalysis involve TiO\textsubscript{2}\textsuperscript{124} supported expensive metals such as Pt/TiO\textsubscript{2},\textsuperscript{125} and methylrhenium trioxide (MTO) catalysts immobilized in poly(4-vinylpyridine) or polystyrene.\textsuperscript{126} Immobilized MTO catalysts have been demonstrated to oxidize vanillyl and veratryl alcohols to acids, aldehydes, and quinones. Other examples of catalysts include Ni/MgO, catalysts which are used in the conversion of lignin to H\textsubscript{2}, CH\textsubscript{4}, and CO\textsubscript{2}.\textsuperscript{45,127}

Homogeneous catalysis is one of the most promising routes to lignin oxidative depolymerization for the production of fine chemicals. Homogeneous catalysts exhibit some very attractive properties, particularly the ability to employ an infinite variety of ligands with different electronic and steric characteristics that can dramatically affect catalyst stability, solubility, and reactivity. This makes it possible to design catalysts with reactivity and selectivity that target a specific lignin linkage or a particular functionality while leaving other linkages and functional groups unaffected.
Based on the ligand employed, some categories of homogeneous catalysts include biomimetic catalysts which consists of metalloporphyrins, Schiff-base catalysts like Co(salen), iron catalysts with tetra-amidomacrocyclic ligands (TAML), polyoxometalates (POMs), and simple metal salts. The development of biomimetic catalysts is actually an attempt to replicate the process of lignin degradation carried out by the enzymes lignin peroxidase and manganese-dependent peroxidase which are present in white rot fungi.

Functionalization of porphyrins with aryl substituents in the meso-position of the heme moiety provides an opportunity for fine-tuning the catalyst to produce desired reactivity and solubility (Fig 1.12).

![Figure 1.12. Neutral (left) and ionic (right) metalloporphyrins.](image)

### 1.2.7 Outstanding problems in lignin depolymerization

Several methods of lignin depolymerization have been reported including i. depolymerization using acids and bases, ii. thermal depolymerization (pyrolysis), iii. reductive depolymerization, and iv. oxidative depolymerization. Depolymerization with acids and bases has historically been used in pulping process to remove lignin from lignocellulose for paper production, rather than to make use of the lignin. In the process,
the products formed from lignin is a complex mixture of aromatic compounds, the separation of which is a tedious task. Nevertheless, lignin depolymerization using acid and base catalyses has been explored. One major problem that is encountered with this method is the occurrence of condensation/repolymerization, alongside depolymerization, which limits the amount of desired monomer products. In addition, the use of acids and bases can accelerate corrosion of the reactor which can add to production cost if the process were to be applied in a biorefinery. Pyrolysis is another way to depolymerize lignin, forming various types of phenols as major products. Due to the high temperatures that are required of the process, breaking up of lignin by pyrolysis follows a random and complicated pattern producing products that are extremely varied. Numerous products are possible, many of which are present in very small amounts, and thus isolating the major products from the mixture can be extremely challenging. Moreover, the process is often accompanied by undesired char formation. Depolymerization by reduction is another method of deriving products from lignin. However, since reductive reactions tend to remove functionalities from the aromatic compound products, it is not the best approach to apply if the desired products are functionalized fine aromatic chemicals. For this type of target compound products, the oxidative depolymerization approach works better.

For practical reasons, many investigations on methods to transform lignin are done with lignin model compounds first before the investigation is extended to real lignin. Working with small, simple molecules that have similar reactivity and chemistry as lignin simplifies collection and interpretation of results and gives a clearer picture of the changes that occur in the starting material because its exact structure is known. It saves time and energy and spares one the trouble of having to deal numerous times with a very
stable and insoluble starting material just to experiment on what reaction conditions work. However, one problem with this practice is that the model compounds used may not fully represent the exact nature of the polymer. The models used may contain the same linkages and functional groups as are found in real lignin, but there’s one quality of the polymer that model compounds can’t perfectly mimic – its molecular size, structural complexity and stability. Hence, it’s not surprising if depolymerization strategies that have been demonstrated to work well on lignin model compounds turn out not to work as well (>95% yield from model compounds but only <10% from real lignin)\textsuperscript{63,130} or not to work at all (there’s a lot of this for sure, but not reported), when applied to real lignin.\textsuperscript{63} Solubilization of the reactants, particularly of the lignin starting material, could be the missing element in trying to transform lignin. Because of its size and stability, it is highly possible that the organic solvent that was used to study the model compounds is unable to dissolve the lignin, which can result in the process not working well on the latter. Very few solvents are capable of dissolving raw lignin. It is in this light that ionic liquids (ILs) are being employed in this study.

1.3 Ionic Liquids

1.3.1 What are ionic liquids?

Ionic liquids are salts that are liquid at or near room temperature. While they may be relatively new in the bio-refinery concept, they have long found their niche in the science research arena. One of the earliest, truly room-temperature ionic liquids (RTILs) is ethylammonium nitrate (m.p. 12 °C) which was synthesized by Paul Walden in 1914.\textsuperscript{131} However, it was not until the discovery in the 1990’s of air- and water-stable RTILs that a resurgence of interest in ILs was noted.\textsuperscript{132} Since then, ILs have been used in
a wide array of practical applications such as in chemical synthesis,\textsuperscript{133,134} catalysis,\textsuperscript{135-138} biocatalysis,\textsuperscript{138,139} electrochemical devices,\textsuperscript{140} and as engineering fluids.\textsuperscript{141} They have also been used in industry.\textsuperscript{142}

To date, three generations of ILs can be distinguished (Fig. 1.13).

Figure 1.13. Commonly used 1st and 2nd generation ILs.\textsuperscript{143}

The first generation is based on pyridinium, pyrrolidinium, and ammonium cations while the second generation, which is described as room temperature ionic liquids (RTILs), are derived from phosphonium, imidazolium, and guanidinium cations, together with either strongly or weakly coordinating anions.\textsuperscript{143} The latter group of ILs combines together an inorganic anion and organic cation that are so different in molecular structure so that the bonding between ions is weak enough for the salt to exist as liquid at room temperature.\textsuperscript{144} The third generation, which is referred to as task-specific ionic liquids (TSILs) or designer ILs, can have certain functional groups incorporated into their structure in order to impart desired properties or reactivity.\textsuperscript{145} Typically, the cations in
ILs involve organic groups, while the anions are either organic or inorganic, and are polyatomic (except the halides), with the negative charge distributed over several atoms.

1.3.2 Ionic liquids: structure and properties

1.3.2.1 Structure of ILs

X-ray analyses reveal that ILs assume supramolecular structure which is defined by extensive H-bonding interactions ranging in strength from weak to moderate. For imidazolium-based ILs like 1-butyl-3-methylimidazolium chloride ([C₄C₃im]Cl), the strongest H-bond is exhibited by H(2) of the ring.

A typical supramolecular structural model of imidazolium-based ILs is shown in Fig. 1.14. In addition to H-bonding, other interactions that lead to formation of supramolecular structure include electrostatic, π-π stacking (between the aromatic rings), and C-H--→ π interaction.

Figure 1.14. Supramolecular structures in imidazolium-based ILs: (Top) showing typical Hydrogen bonding interactions (Bottom) A) two- and B) three-dimensional supramolecular structures of imidazolium ILs.¹⁴⁶
H-bonding interactions are evident in phosphonium-based ILs as well, as in tributyl-propylphosphonium chloride (\([\text{P}_{4443}]\text{Cl}\)), leading to layered structure (Fig. 1.15).

1.3.2.2 Solvent Properties of ILs

1.3.2.2.1 Polarity

Solvent polarity is one of the most significant determinants of solvation properties. For the conventional organic solvents, polarity is commonly expressed in terms of the dielectric constant, \(\varepsilon\), which measures a solvent’s ability to reduce the field strength surrounding a charged particle, and where a higher value means higher solvent polarity.

Several studies have been devoted to determining the polarity of ionic liquids. One such study, based on solvatochromic technique, placed imidazolium-based ILs into a similar polarity scale as that of low-molecular weight alcohols, such as ethanol and butanol.\(^{148,149}\) Solvatochromism is the ability of a chemical substance to change color due
to change in solvent polarity. A more recent investigation placed the $\varepsilon$ values for the same group of ILs in the range of 8.8 and 15.2, which were observed to decrease with increasing chain length of the alkyl group of the cation.

In another study based on the solvatochromism of betaine dye, an empirical scale called the $E_{NT}^{N}(30)$ scale, was employed to compare polarity of commonly used conventional organic solvents on one hand, and of some ILs on the other hand (Fig. 1.16; Table 1.6A, Table 1.6B).

![Normalized solvent polarity scale $E_{NT}^{N}(30)$ with $E_{NT}^{N}(30) = 0$ for tetramethyl silane (TMS) and $E_{NT}^{N}(30) = 1.0$ for water as arbitrary fixed points](Reproduced by permission of The Royal Society of Chemistry).

Figure 1.16. Normalized solvent polarity scale $E_{NT}^{N}(30)$ with $E_{NT}^{N}(30) = 0$ for tetramethyl silane (TMS) and $E_{NT}^{N}(30) = 1.0$ for water as arbitrary fixed points (Reproduced by permission of The Royal Society of Chemistry).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric constant ($\varepsilon$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichloromethane (DCM)</td>
<td>9.1</td>
</tr>
<tr>
<td>Dichloroethane (DCE)</td>
<td>10.42</td>
</tr>
<tr>
<td>[C4C1im] PF$_6$</td>
<td>11.4</td>
</tr>
<tr>
<td>[C4C1im] BF$_4$</td>
<td>11.7</td>
</tr>
<tr>
<td>Acetonitrile (MeCN)</td>
<td>37.5</td>
</tr>
</tbody>
</table>

Table 1.6A. Dielectric constants of the solvents used in this study.
Table 1.6B. Polarity of ILs based on $E_N^\text{T}(30)$ values.$^{151}$

<table>
<thead>
<tr>
<th>ILs</th>
<th>$E_N^\text{T}(30)$</th>
<th>Molecular solvents with corresponding $E_N^\text{T}(30)$ values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\text{P}_{4444}]\text{Cl}$</td>
<td>43</td>
<td>Acetone (42)</td>
</tr>
<tr>
<td>$[\text{C}_4\text{C}_1\text{im}]\text{Cl}$</td>
<td>50.6</td>
<td>Ethanol (52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acetonitrile (46)</td>
</tr>
</tbody>
</table>

*Shows molecular solvents with similar polarity as the ILs

As it turns out, single-parameter polarity scales are not capable of describing the various interactions that give rise to an IL solvent’s polarity. While solvatochromic technique puts the imidazolium-based ILs into a similar polarity scale as low-MW alcohols such as ethanol and methanol ($\varepsilon = 24.6$ and 32.6, respectively), the measured dielectric constant value of $[\text{C}_4\text{C}_1\text{im}]\text{BF}_4$, for example, is much lower (11.7). Hence, multi-parameter polarity scales have been introduced. One such scale is based on the Abraham solvation parameter model, which describes the solvation process in terms of various solute-solvent interactions:$^{153}$

$$\log k = c + rR + s\pi + a\alpha + b\beta + l\log L$$

In this model, $R$ represents molar refraction calculated from the solute’s refractive index, $\pi$ refers to the solute’s dipolarity/polarizability, $\alpha$ and $\beta$ express the solute’s HB acidity (HBA) and basicity (HBB), respectively, and $L$ is the gas-hexadecane partition coefficient. On the other hand, the coefficients $r$, $s$, $a$, $b$, and $l$ are the solvent interaction parameters, which measure a solvent’s ability to interact with the solute through $\pi$/nonbonding electrons, dipole–dipole interactions, HBB, HBA, or dispersion forces, respectively. Values of the various solvent interaction parameters for some ionic liquids are shown in Table 1.7.$^{154}$ These values indicate that the principal solvating properties of $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$ arise from its HBB, $a$, (H-bond acceptance through its chloride anion), as
as from its interactions with the solute through π/nonbonding electrons and through
dipole - dipole interactions. For phosphonium-based ILs, the predominant interactions are
from their HBB, dipolarity, and dispersive force properties.

Table 1.7. Solvent interaction parameters for some ILs.\textsuperscript{154}

<table>
<thead>
<tr>
<th></th>
<th>$R$</th>
<th>$s$</th>
<th>$a$</th>
<th>$b$</th>
<th>$l$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\text{C}<em>4\text{C}</em>{1}\text{im}]\text{Cl}$</td>
<td>0.291</td>
<td>2.01</td>
<td>5.23</td>
<td>-0.32</td>
<td>0.45</td>
</tr>
<tr>
<td>$[\text{P}_{66614}]\text{Cl}^a$</td>
<td>-0.15</td>
<td>1.51</td>
<td>6.60</td>
<td>-0.58</td>
<td>0.83</td>
</tr>
<tr>
<td>$[\text{P}_{66614}]\text{NTf}_2^b$</td>
<td>-0.28</td>
<td>1.55</td>
<td>1.55</td>
<td>-0.15</td>
<td>0.75</td>
</tr>
<tr>
<td>$[\text{P}_{8888}]\text{NTf}_2^b$</td>
<td>-0.33</td>
<td>1.58</td>
<td>1.67</td>
<td>-0.25</td>
<td>0.75</td>
</tr>
</tbody>
</table>

\textsuperscript{a}taken to estimate values for $[\text{P}_{4444}]\text{Cl}$
\textsuperscript{b}cited to show that cation does not significantly change values for $s$, $a$, and $l$, (the predominant
interactions in phosphonium-based ILs), thus justifying taking values for $\text{P}_{66614}\text{Cl}$ to estimate values for
$[\text{P}_{4444}]\text{Cl}$

1.3.2.2 Viscosity

Viscosity is another property of ILs that greatly impacts their solvent behavior. In
fact, this inherent property is one of the principal hindrances to ILs’ utilization as
industrial solvent. Highly viscous solvents slow down diffusion of dissolved particles and
decrease the frequency of collision per unit time, causing a rapid decrease in reaction
rates with increasing solvent viscosity.

The effect of solvent viscosity on the rate of a reaction can be expressed through
the diffusion coefficient, $D$, which in most case $s$ is governed by the Stokes-Einstein
equation:
D = kT/6πηr    where D = diffusion coefficient

k = Boltzmann constant

T = temperature

η = viscosity

r = radius of the diffusing particle

With the diffusion coefficient known, the rate constant can be computed using the Smoluchowski equation:

\[ k = 4aN'RD \]

where k = rate constant (M\(^{-1}\)s\(^{-1}\))

N' = Avogadro’s number per mmole

R = encounter distance (sum of molecular radii)

D = relative diffusion coefficient (= DA + DB)

The Stokes-Einstein equation shows that the diffusion coefficient of reactant particles in a solvent varies inversely with the solvent’s viscosity. However, viscous solvents have been shown not to obey the Stokes-Einstein equation. For these solvents, the diffusion rate varies inversely with the square root of the viscosity, instead of varying inversely with viscosity.\(^\text{155}\) Using this information, the relative diffusion coefficients for the solvents used in this study were computed and are given in Table 1.8.

In general, ILs are much more viscous than the conventional organic solvents, with viscosity values that are two to three orders of magnitude higher for most ILs than those of conventional organic solvents.\(^\text{156}\) Values are significantly influenced by the strength of both Van der Waals forces and H-bonding. For example, the high viscosity of
[C₄C₅im]Cl, and of 1,3-dialkylimidazolium halides, in general, has been ascribed to extensive 3-dimensional H-bonding networks in these liquids.¹⁵⁷

Table 1.8. Viscosity values¹⁴⁷,¹⁵⁸ and computed relative diffusion coefficient for the solvents used in this study.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Viscosity (cP)</th>
<th>Relative Diffusion coefficient, ( D^a \times (kT/6\pi) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeCN</td>
<td>0.38 (15 °C)</td>
<td>1.61 (2.63)</td>
</tr>
<tr>
<td>DCM</td>
<td>0.44 (20 °C)</td>
<td>1.52 (2.27)</td>
</tr>
<tr>
<td>DCE</td>
<td>0.84 (20 °C)</td>
<td>1.09 (1.19)</td>
</tr>
<tr>
<td>[P₄₄₄₄]Cl</td>
<td>115-120 (80 °C)*</td>
<td>0.09</td>
</tr>
<tr>
<td>[C₄C₅im]Cl</td>
<td>142 (80 °C)</td>
<td>0.084</td>
</tr>
</tbody>
</table>

*interpolated from available data on other phosphonium salts of formula P₄₄₄₄ where \( n = 1, 6, 8, 10, 12 \)

\( a \) values of \( D \) based on a study¹⁵⁵; values in parentheses are computed based on the Stokes-Einstein equation.

Viscosity is highly dependent on temperature, as described by the Arrhenius equation:¹⁵⁷,¹⁵⁹

\[
\ln \eta = \ln \eta_\infty + \frac{E_\eta}{RT}
\]

where

\( \eta \) = viscosity

\( \eta_\infty \) = viscosity at infinite temperature

\( E_\eta \) = activation energy for viscous flow (the energy barrier which must be overcome for ions to move past each other)

\( T \) = temperature in K

\( R \) = gas constant
1.3.3 Ionic liquids in biomass processing

1.3.3.1 Ionic liquids as solvents for lignin and lignocellulosic biomass

Graenacher was the first to observe that the organic salt N-ethylpyridinium chloride, mixed with pyridine, could dissolve cellulose.\textsuperscript{160} Inspired by this observation, Rogers et al. in 2002, investigated several ILs and found that [C\textsubscript{4}C\textsubscript{1}im]Cl was the most effective solvent for cellulose,\textsuperscript{161} dissolving up to 25 wt-%.\textsuperscript{162} Further studies indicated that it could also dissolve wood partially.\textsuperscript{163} In a later work, they found that 1-ethyl-3-methylimidazolium acetate ([C\textsubscript{2}C\textsubscript{1}im]OAc) was an even better solvent than [C\textsubscript{4}C\textsubscript{1}im]Cl, being able to dissolve both softwood (southern yellow pine) and hardwood (red oak) after mild grinding.\textsuperscript{164} At about the same time, other groups reported similar findings on [C\textsubscript{2}C\textsubscript{1}im]OAc, including its ability to decrease lignin content of biomass,\textsuperscript{165,166} to facilitate lignin extraction,\textsuperscript{165,166} and to diminish cellulose crystallinity, with the latter resulting in the advantageous effect of improving cellulase-catalyzed hydrolysis of cellulose.\textsuperscript{165} An IL containing the [C\textsubscript{2}C\textsubscript{1}im] cation, combined with a mixture of alkylbenzenesulfonate with xylenesulfonate as the main anions, was also able to extract over 93 % of the lignin present from sugarcane bagasse at atmospheric pressure and elevated temperature (170–190 °C).\textsuperscript{167}

The solubility of LCB in ILs depends on factors such as the IL (the cation and the anion), the lignocellulosic biomass used (type, moisture, size and loading), temperature, length of time of pre-treatment, and the precipitating solvent used.\textsuperscript{168} Several studies have demonstrated that the counter-ion plays a crucial role in determining solubility of LCB in ILs. One of the earliest reports was one by Pu et. al. which indicated that ILs with anions that are strongly H-bonding, like [MeSO\textsubscript{4}]\textsuperscript{-}, were efficient solvents for lignin,
whereas those with anions that are large and non-coordinating, like [BF\textsubscript{4}]\textsuperscript{-} and [PF\textsubscript{6}]\textsuperscript{-}, had limited ability to solubilize lignin. Using ILs containing [C\textsubscript{4}C\textsubscript{1}im]\textsuperscript{+} to solubilize softwood Kraft lignin, the order of solubility using various anions was found to be: 

\[ \text{[CF}_3\text{SO}_3]^- \approx \text{[MeSO}_4]^- \gg \text{[OAc]}^- \gg \text{[HCOO]}^- \gg \text{Cl}^- \approx \text{Br}^- \gg \text{[BF}_4]^- \gg \text{[PF}_6]^- \].

On the other hand, the effect of the cation was generally quite small.

In a more recent study on the pretreatment of pine wood chips, a strong correlation was observed between HBB (exhibited by the anion) and lignocellulose solubility. It was thought that the anion disrupts the extensive hydrogen bonding interactions in LCB, loosening the binding between lignin and cellulose.

While a number of studies have clearly demonstrated the important role of the IL anion on lignin dissolution, the participation of the cation is known to be much less significant, but remains to be fully established. For aromatic cations like those that are imidazolium-based, \(\pi-\pi\) interactions have been identified as making an important contribution to lignin solubilization. Among the cations tested, [AC\textsubscript{1}im]Cl (A = allyl group) was shown to completely dissolve many kinds of wood chips. In a recent review, Hossain and Aldous provided a comprehensive description of the various roles of ILs in lignin processing which include dissolution and isolation.

1.3.3.2 Ionic liquids in biomass pretreatment

Pretreatment is a crucial step in the biomass conversion and transformation. Its primary purpose is to disrupt the lignin-hemicellulose-cellulose (LHC) complex that characterizes the biomass composition (Fig. 1.17).
At the same time, pretreatment brings about other benefits including the separation of lignin, hemicellulose and inhibitors (such as aliphatic acids, furan derivatives and some phenols which can inhibit the fermentation process), reduction of cellulose crystallinity, and an increase in porosity or surface area, all of which contribute to making cellulose more accessible to enzymatic hydrolysis.

Recently, the use of ILs for pretreatment has been gaining significant following and recognition as a promising “green” solvent. A list of the ILs that have been used so far for pretreatment of biomass was compiled in a very recent review by Kumar. In another review, Brandt and co-workers described two different approaches to LCB pretreatment using ILs: The Ionosolv Process (name derived from the similar Organosolv Process) uses ILs that dissolve lignin while leaving the cellulose basically intact, and the Dissolution Process which employs ILs that can dissolve cellulose, leaving lignin as a residue.

Pretreatment is a major step towards overcoming LCB recalcitrance through disruption of non-covalent interactions between component biopolymers (Fig. 1.16).
When employing ILs for pretreatment, the effect can be more far-reaching. For example, it was observed that pretreatment with [C$_2$C$_1$im]OAc resulted in some structural changes in isolated poplar alkaline lignin, as summarized in Fig. 1.18. It was observed that increasing the temperature and time of pretreatment resulted in a decrease in the number of aliphatic hydroxyl groups, a result that can be interpreted as being due to dehydration reactions. This change was coupled with an increase in the number of phenolic groups and reduction of molecular weight, both of which are indications of depolymerization, most likely through cleavage of the β-O-4 linkage, as well as degradation of β-β and β-5 linkages. There were also evidences of demethoxylation reactions, selective degradation of guaiacyl lignin fractions, and condensation reactions which were observed to occur more easily in syringyl than in the guaiacyl units.
An earlier study has also demonstrated size reduction of lignin on IL pretreatment, particularly by using certain anion components. Specifically, it has been reported that lignin fragmentation is a function of the IL anion which follows the order: sulfates > lactate > acetate > chlorides > phosphates, in terms of the relative impact on reducing lignin molecular weight. As the determinant moiety in reducing lignin MW, it is hypothesized that the anion either catalyzes nucleophilic attack, or undertakes a nucleophilic attack itself, on the β-O-4 linkage.
1.3.3.3 Ionic liquids in lignin oxidation and degradation/depolymerization

Lately, reports on the useful application of ILs in biomass processing continue to appear frequently in the literature. Of particular interest are those involving the use of ILs for lignin oxidation and depolymerization, as these provide routes to lignin conversion/transformation to biofuels and other bio-products.

Recently, Chatel and Rogers\textsuperscript{182} published a review of studies that have been done on oxidation of lignin and lignin model compounds in ILs. In most of the studies included in the review, ILs were employed to either dissolve or enhance the solubility of the reactants/products,\textsuperscript{183-188} except for one which used a task-specific IL involving salen-Co hexafluorophosphate, which served as the catalyst.\textsuperscript{189} For the oxidant, either air or molecular oxygen was used by the investigators, but there was one study that employed H$_2$O$_2$ used together with an iron porphyrin catalyst.\textsuperscript{184} Chatel and Rogers also reviewed works that applied ILs in the oxidation of real lignin using ILs based on phosphate and sulfate which are known to efficiently dissolve lignin.\textsuperscript{186-188,190,191}

More recently, Dai\textsuperscript{192} presented an update on the recent developments in the chemical degradation of lignin, including the oxidative approach. The review also includes some of the recent studies on the separation and dissolution of lignin using ILs that are based on imidazolium,\textsuperscript{193-195} ammonium,\textsuperscript{196} and pyridinium.\textsuperscript{197} These studies highlight the structural changes that lignin undergo when dissolved in ILs, notably degradation to lower molecular weight oligomers.

In a recent work, Prado\textsuperscript{198} showed that lignin could be partially depolymerized directly in black liquor using butylimidazolium hydrogen sulfate and triethylammonium hydrogen sulfate as extracting solvents and H$_2$O$_2$ as oxidant. It was demonstrated that
lignins derived from butylimidazolium hydrogen sulfate were more easily depolymerized, producing vanillic acid, benzoic acid, and 1,2-dicarboxylic acid as the principal degradation products. However, it was observed that at high H$_2$O$_2$ (10%), the IL was also partly oxidized, causing the main acid products to be contaminated with 1-butyl-2,4,5-trioxoimidazolidine.

Earlier, Wang reviewed the recent developments in chemical depolymerization including acid-, base-, and metal-catalyzed and ILs-and supercritical fluids-assisted depolymerization.$^{51}$ By way of comparison, it was shown that ILs- and supercritical fluids-assisted depolymerization had high selectivity and conversion, but high cost makes them not practical for wide applications.

Earlier studies have employed ILs in lignin depolymerization in various roles such as solvent,$^{199-202}$ as facilitator of oxidative depolymerization,$^{187,203}$ as participant in catalytic depolymerization,$^{58,87,204}$ and even as a promoter of depolymerization in the absence of a catalyst.$^{48}$

1.4 Mechanochemical Treatment

1.4.1 Introduction

Written records show that mechanochemistry has been around as early as the 4$^{th}$ century B.C., as exemplified by the isolation of elemental mercury by grinding natural cinnabar with vinegar using a mortar and pestle made of copper.$^{205}$ Several centuries later (1820), Michael Faraday applied mechanochemistry in his experiment on the reduction of AgCl to Ag with Zn, Cu, Sn, and Fe in a pestle and mortar.$^{206}$ In the 1890s, Carey Lea performed a mechanochemical reaction on mercury and silver halides and found that the reaction favored decomposition, rather than the usual melting/sublimation that happen in
thermal reactions. This work showed that mechanochemical reactions are distinct and separate from thermal ones.\textsuperscript{207} Later, Wilhelm Ostwald classified mechanochemistry as another sub-discipline of chemistry, in addition to thermochemistry, electrochemistry, and photochemistry - a classification that is based on the type of energy input.\textsuperscript{208}

In this modern era, mechanochemistry has found very useful applications in the biorefinery where it has played crucial roles in lignocellulosic biomass processing, specifically during pretreatment.

1.4.2 Pretreatment in lignocellulosic biomass processing

Pretreatment methods can be classified as physical/mechanical, chemical, biological, and a combination thereof. The physical/mechanical pretreatment involves chipping, grinding, milling, and extrusion,\textsuperscript{174} depending on desired particle size. Chipping, for example reduces particle size to about 10-30 mm, while grinding or milling yields 0.2-2 mm particle size.\textsuperscript{209} Chemical method uses acids, bases, and other chemicals that induce hydrolysis and remove lignin, while biological pretreatment is based upon the use of enzymes such as the white- and brown-rot fungi that degrade lignin and disrupt biomass structure.\textsuperscript{174}

Size reduction is an essential step in increasing biomass conversion efficiency: the smaller the particle size, the greater the surface area which leads to improved reaction kinetics. Hence the physical/mechanical pretreatment has become an integral part of most biomass processing procedures. Size reduction is achieved through various mechanical stresses such as impact, compression, friction, and shear that are generated by various mechanical tools. For example, an extruder reduces size by generating shear stress, while ball mill powderizes by impact (Fig. 1.19).
Figure 1.19. Mechanical stresses that effect size reduction (a), and Impact stress generated in a ball mill.\textsuperscript{210}

Mechanical pretreatment, as a subgroup of physical method requires energy input to generate forces that can reduce particle size such as by grinding and milling.\textsuperscript{174} However, due to the relatively high power requirement involved, the mechanical method, when taken alone, is unlikely to be an economically feasible pretreatment option.\textsuperscript{211} A more practical alternative is one that combines mechanical with other methods. Mechanochemistry is one such combination.
1.4.3 Mechanochemistry in lignocellulosic biomass pretreatment

Mechanochemistry refers to reactions, typically in the solid state, that are induced by the input of mechanical energy, such as by grinding in ballmills where reactants can be efficiently mixed with no or minimal solvent.\textsuperscript{208,212} By adding a chemical component to mechanical treatment, the resulting mechanochemical method becomes more economically viable compared to plain mechanical approach, and actually makes for a more effective pretreatment technique. It has been demonstrated that combining mechanical and chemical methods produced a synergistic effect resulting from the combined effects of the heat generated during mechanical treatment and from the chemical which served like a catalyst that modified the biomass and made it more susceptible to enzymatic hydrolysis.\textsuperscript{213}

There have been several studies that incorporate chemicals into a mechanical process employ screw extruder in the presence of alkali (NaOH). The screw extruder exhibits a relatively reduced energy consumption and increased pretreatment efficiency due to its high mixing rate and shear stress.\textsuperscript{174} In 1989, an extrusion machine with an injection port for introduction of appropriate chemicals was developed for the processing of biomass like wood chips, sawdust, food fibers, and agricultural residue.\textsuperscript{214} Some of the reported benefits of the screw extruder-alkali combination include removal of lignin (up to 65\%\textsuperscript{215}/77\%\textsuperscript{216}), an increase in the sugar yield of up to 3.5 times compared to the untreated material,\textsuperscript{217} a good glucan yield of 86.9 \% from barley straw,\textsuperscript{218} and increased bioethanol production also from barley straw.\textsuperscript{219}
1.4.4 Mechanochemistry in lignin degradation/depolymerization

The ball mill is another commonly used mechanical tool, where size reduction of biomass is attained through impact generated during collisions between balls and walls of the mill. Like the extruder, it has also been used in combination with alkali and other chemicals for biomass pretreatment purposes. In more recent studies, however, other beneficial outcomes of ball milling with alkali have emerged. For example, it has been demonstrated that ball milling in the presence of alkali (like NaOH) degrades lignin into low-molecular weight oligomers via cleavage of the β-O-4 linkage, most likely following free-radical routes.

1.5 The Study

Our approach to the deconstruction of lignin focuses on a two-step oxidation process that takes advantage of the numerous benzylic hydroxyl groups in lignin. We believe that oxidation of these hydroxyls to form carbonyl groups, followed by Baeyer-Villiger oxidation to form esters, presents a viable route for reducing the molecular weight of lignin, producing either small molecules or oligomers that are small enough that traditional refining and thermal treatments can produce useful materials from previously intractable lignin. This approach is shown schematically below.
Starting with raw lignin (Fig. 1.20):

![Figure 1.20. Structure of raw lignin.](image)

Benzylic oxidations produce ketones (Fig. 1.21):

![Figure 1.21. Lignin after benzylic hydroxyl oxidation.](image)
Baeyer-Villiger oxidations produce esters, which can be hydrolyzed to liberate small molecule fragments of the original lignin (Fig. 1.22).

Figure 1.22. Lignin after Baeyer-Villiger oxidation.
Chapter 2. β-O-4 LIGNIN MODEL COMPOUNDS: SYNTHESIS AND NON-CATALYTIC OXIDATION

Note: This chapter was taken from the following papers:
1) Yao, S. G.; Meier, M. S.; Pace, R. III B.; Crocker, M. A comparison of the oxidation of lignin model compounds in conventional and ionic liquid solvents and application to the oxidation of lignin. *RSC Adv.*, 2016, 6, 104742.

2.1 Introduction

Considering the complex and recalcitrant nature of lignin, any endeavor towards its investigation is typically initiated using model compounds. Compounds exhibiting the β-O-4 linkage are almost always the models of choice for this purpose, basically due to the prevalence of this linkage in lignin. This chapter describes the different model compounds used in our investigation, including their synthesis and testing using a reliable, conventional, non-catalytic oxidation reaction – the Swern.

2.2 Synthesis of β-O-4 Lignin Model Compounds

We prepared and studied eleven β-O-4 model compounds in this work (Fig. 2.1). These compounds include a β-phenethyl phenyl ether unit, the structure that defines the β-O-4 linkage, and a benzylic hydroxyl group (except 1) where oxidation is expected to take place. The compounds vary in complexity and are functionalized at various positions in the aryl and alkyl groups, affording them different reactivity toward oxidants. For example, compounds 3 - 5, and 7 - 11 include a γ carbon, with a hydroxyl group in 5 and 9 - 11 but none in 3, 4, 7 and 8. Additionally, compounds 4, 8, 10, and 11 have unprotected phenols
at position 4, while 3, 5, 7, and 9 have methoxy groups. Moreover, 2 - 5 and 11 each has an n-propyl handle at the B ring to provide an additional test of selectivity of the benzylic position towards oxidation (benzylic alcohol vs benzylic methylene group).

Figure 2.1. The β-O-4 models used in this study.

The preparation of the model compounds was done in two phases. In the first phase, the model compounds with n-propyl chain handle (2 - 5 and 11) were synthesized, along with the simplest one which has no functionality at all in the A and B rings (1). The rest of the models (6 - 10) were prepared in the second phase. These models are basically analogs
of 2 - 5 and 11, with the propyl chain excluded and the methoxy group in the B ring moved from position 6’ to 1’.

Model compounds 1 - 8 and 11 were prepared using known procedures\textsuperscript{223-226} while 9 - 10 were synthesized based on a modified procedure\textsuperscript{223} using a different phenol (Scheme 2.1).

![Scheme 2.1. Preparation of 9 and 10.]

\textbf{2.3 Non-Catalytic Oxidation of $\beta$-O-4 Lignin Model Compounds: The Swern}

With the model compounds in hand, we then got set to test their reactivity and selectivity toward oxidation reaction. At the outset of our project, we wanted to see the outcome of a simple, reliable, stoichiometric oxidation before we started working on more exotic, catalytic oxidation systems. Hence, for our first test reaction, we chose the Swern oxidation, a non-catalytic, but highly reliable method of converting alcohols to ketone, which is the transformation that we need for our first oxidation step. For the starting materials we used our models with n-propyl handle at the benzylic position of the B ring, in addition to having benzylic -OH at the A ring (2 – 5 and 11). Through these models, we
wanted to test the selectivity of a given oxidation reaction, \textit{i.e.} benzylic -OH vs benzylic – CH₂ group.

2.4 Results and Discussions

Compound 2, which is our simplest alcohol model for the Swern oxidation study, gave an excellent (97%) isolated yield of the expected benzylic ketone, as evidenced by NMR analysis of the Swern oxidized product 2' (Scheme 2.2). The $^{13}$C NMR spectrum included a carbonyl group chemical shift at 195 ppm and the $^1$H NMR spectrum included a singlet at 5.25 ppm, corresponding to the two $\beta$C-H protons that are adjacent to the $\alpha$-ketone group (See $^1$H NMR and $^{13}$C NMR spectra of Swern product 2').

Scheme 2.2. Swern oxidation of 2.

The more functionalized model compound 3 (with -OCH₃ group at positions 3, 4, and 6', a $\gamma$-CH₃, and n-propyl at 2' position) also gave the expected $\alpha$-ketone product at a good isolated yield of 87% (Scheme 2.3). As in Swern product 2', $\alpha$-ketone formation was shown by NMR results, \textit{i.e.} disappearance of the signals at 4.61 and 4.96 ppm for the $\beta$C-H protons in the alcohol starting material (two diastereomers) and appearance of a quartet at 5.4 ppm and a carbonyl group signal at \textit{ca} 198 ppm in the $^1$H and $^{13}$C NMR spectra, respectively. In addition, a distinct change was also observed in the resonances of the A Ring \textit{ortho} protons: from a multiplet at 6.95 ppm to a doublet at 7.61 ppm and a doublet of doublets at 7.79 ppm for the C₂ and C₆ protons, respectively.
Scheme 2.3. Swern oxidation of 3.

Model compounds 4, 5, and 11 are as heavily functionalized as 3, but with some variations as to the functionalities present at different positions. Specifically, this group of models is characterized by the presence of -OH groups at certain positions. For example, in compound 4, there is an -OH at position 4 instead of a -OCH₃ group. Then in model 5, there is γ-CH₂OH instead of γ-CH₃ group, while in 11, there is -OH at position 4 and γ-CH₂OH instead of a γ-CH₃ group. These models are noteworthy of attention because they are better representations of lignin which contains an abundance of -OH groups. (see Chapter 1.1, Table 1.2).

It will be noted that the introduction of –OH groups at certain specific positions in the model compounds resulted in significant changes on the structure of the Swern oxidation products (Scheme 2.4). For example, the presence of γ-CH₂OH group provides an additional site for oxidation, hence a doubly oxidized compound was obtained as the major Swern oxidation product of 5 in 88% isolated yield. The diketone structure (as the enol tautomer) is indicated by the disappearance of ¹H NMR multiplet peaks at 4.97 ppm, 4.37 - 4.15 ppm, and 3.94 - 3.92 ppm corresponding to the α, β, and γ protons, respectively. The existence of the enol tautomer form of the diketone is evidenced by the presence of ¹³C NMR peaks at 180.7 ppm, 97.5 ppm, and 190.7 ppm for the α, β, and γ carbons respectively.
A totally unexpected product was observed, however, when Swern conditions were applied on compound 4 which has an unprotected phenol group. Instead of getting oxidized, this model underwent elimination, forming an enol ether product in 52% isolated yield. The enol ether structure is demonstrated by the absence of the $^1$H NMR $\beta_{C-H}$ proton peak and of the $^{13}$C NMR ketone resonance. Furthermore, high-resolution mass spectroscopy employing electron spray ionization (ESI) confirmed a molecular formula C$_{20}$H$_{25}$O$_4$ which is consistent with the (M+H)$^+$ ion of compound 4.

Compound 11 combines the unique features of 4 and 5, i.e. unprotected phenol and $\gamma$-CH$_2$OH group, respectively. Thus, it’s not surprising that its Swern oxidation product which was isolated in 81% yield reflects both elimination at the benzylic position and
The formation of a quinone methide intermediate has been proposed to be involved in the elimination of benzylic alcohol group in compounds with unprotected phenols at position 4 of the ring.\textsuperscript{227}

2.5 Conclusions

We have synthesized eleven β-O-4 lignin model compounds for use in the preliminary investigation of lignin. These models include a β-phenethyl phenyl ether unit, and a benzylic hydroxyl group (except 1) where oxidation is expected to take place. They were chosen based on the known abundance of the β-O-4 linkage in the polymer structure. The compounds were prepared in two batches. The first batch (2 - 5 and 11) includes the models with n-propyl chain handle, among other functionalities, and a simple model that is devoid of any functionality other than the phenyl ether (1). The latter served as a standard for comparing relative reactivity of the models toward various treatments. These compounds were used in model studies for the catalytic oxidation of organosolv lignin\textsuperscript{223} and for Swern oxidation of Kraft lignin.\textsuperscript{227} The second batch (6 – 10) are analogs of 2 - 5 and 11 and were used, together with the first batch, in another set of model studies in conventional and ionic liquid solvents.\textsuperscript{228}

Swern oxidation of 2 - 5 and 11 gave moderate to excellent isolated yields of the products. The reaction converted the alcohol group of the non-phenolic compounds at the α-/benzylic and γ- positions to carbonyl without affecting the benzylic methylene group. The phenolic models underwent elimination at the benzylic position giving an enol ether, rather than undergoing the usual oxidation to ketone.
2.6 Experimental Section

All reagents, chemicals, solvents and materials were purchased from commercial suppliers and were used without further purification. Gas chromatography-mass spectra (GC-MS) were measured using Agilent Technologies 6890N with 5973N electron impact (EI) ionization mass detector while $^1$H and $^{13}$C NMR spectra were recorded on a Varian Inova 400 MHz spectrometer.

Preparation of 1

Model compound 1 was prepared by the method of Patil et al.$^{223}$

Preparation of 2

Model compound 2 was prepared by the method of Patil et al.$^{223}$

Preparation of 3

Model compound 3 was prepared by the method of Patil et al.$^{223}$

Preparation of 4

Model compound 4 was prepared by the method of Patil et al.$^{223}$

Preparation of 5

Model compound 5 was prepared by the method of Patil et al.$^{223}$

Preparation of 6

Model compound 6 was prepared by the method of Nichols et al.$^{226}$

Preparation of 7

Model compound 7 was prepared by the method of Kawamoto et al.$^{224}$

Preparation of 8

Model compound 8 was prepared by the method of Kawamoto et al.$^{224}$

Preparation of 9
β-keto ester 14 (44.2 mg, 0.120 mmol) was stirred in THF (1.6 mL) and H₂O (0.16 mL) at room temperature. Sodium borohydride (44.9 mg, 1.13 mmol) was added over 3 h and the solution was further stirred for 24 h at room temperature. The mixture was quenched with saturated aqueous NH₄Cl (5 mL) and concentrated under vacuum. The residue was diluted with water (15 mL) and extracted with EtOAc (3 x 10 mL). The solvent was evaporated under vacuum and the residue was subjected to column chromatography on silica gel (EtOAc:hexane 1:1) to yield 9 (16.1 mg, 0.0497 mmol, 41%). ¹H NMR (400 MHz, CDCl₃, mixture of diastereomers): δ 7.0-6.72 (m, 7H), δ 4.98-4.93 (m, 1H, Cα), δ 4.25-4.16 (m, 1H, Cβ), δ 3.96-3.5 (m, 2H, Cγ), δ 3.85, 3.84, 3.83, 3.74, 3.73 (s, 9H). ¹³C NMR (100 MHz, CDCl₃, mixture of diastereomers): δ 154.7, 154.7, 152.1, 151.7, 149.0, 148.9, 148.8, 148.5, 133.2, 132.4, 119.3, 118.7, 118.3, 118.1, 114.7, 114.6, 111.0, 109.9, 109.5, 84.4, 83.4, 73.8, 73.6, 61.4, 61.0, 55.9, 55.7, 55.6. GC-MS m/z (relative intensity): Major diastereomer: 376(M⁺-18, 3), 298(4), 286(100), 271(24), 257(16), 238 (2), 226(8), 207(10), 193(8), 183(3), 165(5), 151(15), 135(5), 123(15), 107(10), 92(8), 77(15), 63(5), 51(4). HRMS (ESI) m/z [M+Na]⁺ calculated for C₁₈H₂₂O₆Na 357.1309, found 357.1308.

**Preparation of 14**

In three separate one-neck round bottom flasks were placed NaH (60 % dispersion in mineral oil; 0.662 g, 16.5 mmol), 12 (4.37 g, 13.2 mmol) and 4-methoxyphenol (2.05 g, 16.5 mmol). The flasks were purged with N₂ for 15 min, after which 4.6 mL THF and 17.2 mL DMF were added to each. The solution of NaH in THF/DMF was cooled to 0 °C and the solution of 4-methoxyphenol was
added. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C again. The solution of 12 was added and the resulting mixture was stirred at room temperature for 8 h, then poured onto ice water (200 mL). The resulting aqueous layer was extracted with EtOAc (3 x 100 mL). The extract was washed with water, dried over MgSO$_4$, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel (EtOAc:hexane 3:7) to yield 14 (3.64 g, 9.89 mmol, 74%). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.83 (dd, $J_1$=8.5, $J_2$=2.2 Hz, 1H), δ 7.62 (d, $J$=2.1 Hz, 1H), δ 6.94-6.87 (m, 3H), δ 6.83-6.77 (m, 2H), δ 5.63 (s, 1H, C$_\beta$), δ 4.28 (q, $J$=6.9 Hz, 2H), δ 3.94 (s, 3H), δ 3.91 (s, 3H), δ 3.74 (s, 3H), δ 1.24 (t, $J$=7.3 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 190.0 (C$_\alpha$), 167.1 (C$_\gamma$), 155.0, 154.2, 151.0, 149.0, 126.9, 124.8, 116.8, 114.7, 111.3, 110.1, 82.3 (C$_\beta$), 62.2, 56.0, 55.9, 55.6 14.0. GC-MS m/z (relative intensity): 374 (M$^+$, 8), 301(1) 273 (2), 165 (100), 151(2), 137(4), 123(5), 107(2), 92(4), 77(5), 64(1), 51(1).

**Preparation of 12**

Compound 12 was prepared by the method of Patil *et al.*

**Preparation of 10**

A solution of 15 (1.0 g, 2.8 mmol) in THF (25 mL) and H$_2$O (2.5 mL) was stirred at room temperature. Sodium borohydride (1.06 g, 27.8 mmol) was added portion-wise over 3 h and the solution was further stirred for 24 h at room temperature. The reaction mixture was quenched with a saturated solution of ammonium chloride, (15 mL) and was then concentrated under vacuum. The residue was diluted with water (100 mL) and extracted with dichloromethane (3 x 50 mL). The solvent was evaporated under vacuum, and the residue was subjected to column...
chromatography on silica gel (EtOAc:hexane 1:1) to produce 10 (0.68 g, 2.1 mmol, 77%). $^1$H NMR (400 MHz, CDCl$_3$, mixture of diastereomers): δ 7.0-6.76 (m, 7H), δ 4.99-4.92 (m, 1H, $C_\alpha$), δ 4.25-4.19 (m, 1H, $C_\beta$), δ 3.95-3.51 (m, 2H, $C_\gamma$), δ 3.87, 3.86, 3.77, 3.75 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$, mixture of diastereomers): δ 154.7, 152.1, 151.7, 151.6, 146.7, 146.6, 145.5, 145.2, 132.5, 131.8, 119.9, 119.3, 118.3, 118.1, 114.8, 114.7, 114.4, 114.3, 109.5, 109.0, 84.4, 83.5, 73.8, 73.7, 61.4, 61.0, 55.9, 55.7. GC-MS m/z (relative intensity): Major diastereomer: 302(M$^+$-18, 0.4), 284(2), 272(100), 255(0.8), 243(2.8), 211(1.3), 183(1.7), 149(1.3), 133(1.5), 124(1.6), 109(1.5), 89(1.0), 77(1.4), 63(0.6), 51(0.6). Minor diastereomer: 302(M$^+$-18, 0.4), 284(84), 272(87), 253(18), 243(51), 225(14), 207(45), 197(11), 183(13), 169(3), 161(29), 149(33), 137(34), 124(100), 109(79), 89(24), 77(39), 63(19), 53(16). HRMS (ESI) m/z [M+Na]$^+$ calculated for C$_{17}$H$_{20}$O$_6$Na 343.1152, found 343.1152.

**Preparation of 15**

In three separate one-neck round bottom flasks were placed NaH (60 % dispersion in mineral oil; 1.12 g, 28.1 mmol), 13 (4.95 g, 15.6 mmol) and 4-methoxyphenol (3.96 g, 31.2 mmol). The flasks were purged with N$_2$ for 15 min after which 5.5 mL THF and 20.5 mL DMF were added to each. The solution of NaH in THF/DMF was cooled to 0o C and the solution of 4-methoxyphenol was added. The mixture was stirred at room temperature for 1 h and then cooled to 0o C again. The solution of 13 was added, and the resulting mixture was stirred at room temperature for 8 h, then poured onto ice water (120 mL). The resulting aqueous layer was extracted with EtOAc (3 x 60 mL). The extract was washed with water,
dried over MgSO₄, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel (EtOAc:hexane 3:7) to yield 15 (1.0 g, 2.8 mmol, 18%). ¹H NMR (400 MHz, CDCl₃): δ 7.76 (dd, J₁=8.4, J₂=2.0 Hz, 1H), δ 7.63 (d, J=2.0 Hz, 1H), δ 6.94 (d, J=8.5 Hz, 1H), δ 6.93-6.88 (m, 2H), δ 6.83-6.76 (m, 2H), 5.62 (s, 1H, Cβ), δ 4.28 (q, J=7.2 Hz, 2H), δ 3.92 (s, 3H), δ 3.74 (s, 3H), δ 1.23 (t, J=7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 190.00(Cα), 167.10(Cγ), 155.03, 151.43, 151.03, 146.64, 126.67, 125.43, 116.77, 114.76, 114.13, 111.21, 82.17, 62.27, 56.10, 55.60, 14.00. GC-MS m/z (relative intensity): 360(M⁺, 0.9), 281(0.2), 259(0.1), 207(0.7), 151(100), 135(0.2), 123(0.9), 109 (0.6), 92(0.2), 77(0.3), 65(0.2), 52(0.1).

**Preparation of 13**

Compound 13 was prepared by the method of Patil *et al.*²²³

**Preparation of 11**

Compound 11 was prepared by the method of Patil *et al.*²²³

**Swern oxidation of lignin model compounds**

**Oxidation of model 2:** A solution of DMSO (781.3 mg, 10.00 mmol) in CH₂Cl₂ (0.25 mL) was added dropwise, under N₂, to a cold (-78 °C) solution of (COCl)₂ (647.6 mg, 5.000 mmol) in CH₂Cl₂ (0.25 mL) and the resulting solution stirred at -78 °C for 15 min. A solution of 2 (256 mg, 1.00 mmol) in CH₂Cl₂ (0.75 mL) was added dropwise and the resulting mixture stirred at -40 °C for 30 min. Et₃N (1.53 g, 15.0 mmol) was added dropwise, the resulting mixture stirred at -78 °C for 30 min., then cooled to room temperature. After adding CH₂Cl₂ (15 mL), the resulting organic phase was washed with dilute HCl, then with water, and concentrated under vacuum. The product was isolated by
silica gel column chromatography (EtOAc/hexanes 1:5) to produce 2’ (246 mg, 1.00 mmol, 97%). \( ^1 \text{H NMR (400 MHz, CDCl}_3 \) \( \delta 8.13-8.09 \) (m, 1H), \( \delta 8.02-7.98 \) (m, 1H), \( \delta 7.63-7.57 \) (m, 1H), \( \delta 7.51-7.45 \) (m, 2H), \( \delta 7.20-7.14 \) (m, 1H), \( \delta 6.82-6.62 \) (m, 3H), \( \delta 5.25 \) (s, 2H), \( \delta 2.54 \) (t, \( \text{J}=7.53 \) Hz, 2H), \( \delta 1.66-1.56 \) (m, 2H), \( \delta 0.92 \) (t, \( \text{J}=7.3 \) Hz, 3H). \( ^{13} \text{C NMR (100 MHz, CDCl}_3 \) \( \delta 194.94, 157.99, 144.59, 134.62, 130.20, 129.26, 128.83, 128.19, 121.98, 115.29, 111.68, 70.80, 38.02, 24.37, 13.82. GC-MS \text{ m/z (relative intensity): 254(M}^+,40), 236(2.5), 207(7), 178(2), 165(1), 149(1), 119(3), 105(100), 91(14), 77(23), 65(4),51(4)

**Oxidation of model 3:** A solution of DMSO (117.2 mg, 1.500 mmol) in CH\(_2\)Cl\(_2\) (0.25 mL) was added dropwise, under \( \text{N}_2 \), to a cold (-78 °C) solution of (COCl\(_2\)) (97.1 mg, 0.750 mmol) in CH\(_2\)Cl\(_2\) (0.25 mL) and the resulting solution was stirred at -78 °C for 15 min. A solution of 3 (54 mg, 0.15 mmol) in CH\(_2\)Cl\(_2\) (0.75 mL) was then added dropwise and the resulting mixture stirred at -40 °C for 30 min. Et\(_3\)N (227 mg, 2.25 mmol) was added dropwise, the resulting mixture stirred at -78 °C for 30 min., then cooled to room temperature. After adding CH\(_2\)Cl\(_2\) (15 mL), the resulting organic phase was washed with dilute HCl, then with water, and concentrated under vacuum. The product was isolated by silica gel column chromatography (EtOAc/hexanes 1:5) to produce 3’ (47 mg, 0.13 mmol, 87%). \( ^1 \text{H NMR (400 MHz, CDCl}_3 \) \( \delta 7.79 \) (dd, \( \text{J}=8.56, 2.08 \) Hz, 1H), \( \delta 7.61 \) (d, \( \text{J}=2.11 \) Hz, 1H), \( \delta 6.88 \) (d, \( \text{J}=8.64 \) Hz, 1H), \( \delta 6.33-6.25 \) Hz (m, 3H), \( \delta 5.40 \) (q, \( \text{J}=6.67 \) Hz, 1H), \( \delta 3.94 \) (s, 3H), \( \delta 3.90 \) (s, 3H), \( \delta 3.71 \) (s, 3H), \( \delta 2.46 \) (t, \( \text{J}=7.67 \) Hz, 2H), \( \delta 1.69 \) (d, \( \text{J}=7.07 \) Hz, 3H), \( \delta 1.61-1.50 \) (m, 2H), \( \delta 0.88 \) (t, \( \text{J}=7.39 \) Hz, 3H). \( ^{13} \text{C NMR (100 MHz, CDCl}_3 \) \( \delta 197.62, 160.62, 158.48, 153.69, 149.08, 145.25, 127.18, 123.5, 111.09, 110.10, 107.52, 107.25, 98.73, 76.59, 56.05, 55.92, 55.17, 38.24, 24.16, 19.06, 13.76. GC-MS \text{ m/z (relative intensity): 358(M}^+,17), 340(52), 325(3), 311(10), 295(1), 280(6), 265(4), 249(1.5), 237(1),
Oxidation of model 4: A solution of DMSO (97.1 mg, 1.24 mmol) in CH₂Cl₂ (0.25 mL) was added dropwise, under N₂, to a cold (-78 °C) solution of (COCl)₂ (80.5 mg, 0.622 mmol) in CH₂Cl₂ (0.25 mL) and the resulting solution stirred at -78 °C for 15 min. A solution of 4 (43 mg, 0.12 mmol) in CH₂Cl₂ (0.75 mL) was added dropwise and the resulting mixture stirred at -40 °C for 30 min. Et₃N (189.2 mg, 1.869 mmol) was added dropwise, the resulting mixture stirred at -78 °C for 30 min., then cooled to room temperature. After adding CH₂Cl₂ (15 mL), the resulting organic phase was washed with dilute HCl, then with water, and concentrated under vacuum. The product was isolated by silica gel column chromatography (33% EtOAc/hexanes) to produce 4’ (21 mg, 0.060 mmol, 52%). ¹H NMR (400 MHz, CDCl₃) δ 7.193 (d, J=1.94 Hz, 1H), δ 6.92 (dd, J=8.48, 2.05 Hz, 1H), δ 6.794 (d, J=8.24 Hz, 1H), δ 6.46-6.39 Hz (m, 3H), δ 5.55 (s, 1H), δ 3.76 (s, 3H), δ 3.72 (s, 3H), δ 2.514 (t, J=7.47 Hz, 2H), δ 1.65-1.55 (m, 2H), δ 0.916 (t, J=7.40 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 160.76, 156.4, 147.15, 145.41, 127.70, 125.99, 122.29, 121.72, 114.98, 114.02, 111.59, 110.43, 108.22, 98.67, 55.19, 50.69, 38.104, 24.31, 19.63, 13.76. GC-MS m/z (relative intensity): 328(M⁺, 100), 313(2), 299(2), 285(26), 270(2), 253(5), 242(5), 225(4), 211(12), 193(1), 179(2), 162(59), 147(26), 131(9), 119(7), 103(17), 91(20), 77(10), 65(8), 51(3).

Oxidation of model 5: A solution of DMSO (117.2 mg, 1.500 mmol) in CH₂Cl₂ (0.25 mL) was added dropwise, under N₂, to a cold (-78 °C) solution of (COCl)₂ (97.1 mg, 0.750 mmol) in CH₂Cl₂ (0.25 mL) and the resulting solution stirred at -78 °C for 15 min. A solution of 5 (56.4 mg, 0.150 mmol) in CH₂Cl₂ (0.75 mL) was added dropwise and the
resulting mixture stirred at -40 °C for 30 min. Et₃N (227.7 mg, 2.250 mmol) was added dropwise, the resulting mixture stirred at -78 °C for 30 min., then cooled to room temperature. After adding CH₂Cl₂ (15 mL), the resulting organic phase was washed with dilute HCl, then with water, and concentrated under vacuum. The product was isolated by silica gel column chromatography (EtOAc/hexanes 1:5) to produce 5’ (49 mg, 0.13 mmol, 88%). ¹H NMR (400 MHz, CDCl₃) δ 9.514 (s, 1H), 7.83 (dd, J=8.60, 2.15 Hz, 1H), δ 7.564 (d, J=2.14 Hz, 1H), δ 6.81 (d, J=8.72 Hz, 1H), δ 6.48-6.38 Hz (m, 3H), δ 3.87 (s, 3H), δ 3.84 (s, 3H), δ 3.66 (s, 3H), δ 2.414 (t, J=7.67 Hz, 2H), δ 1.55-1.41 (m, 2H), δ 0.806 (t, J=7.32 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 187.82, 186.5, 160.98, 155.09, 153.92, 149.45, 146.09, 126.55, 125.15, 112.85, 111.09, 110.96, 110.69, 102.43, 81.24, 56.67, 56.51, 55.85, 38.58, 24.62, 14.13. GC-MS m/z (relative intensity): 372(M⁺ 100), 342(3), 329(42), 311(9), 297(9), 281(5), 269(10), 253(3), 240(2), 224(2), 207(14), 197(3), 186(5), 165(10), 148(3), 133(2), 121(4), 77(2).

**Oxidation of model 11:** A solution of DMSO (117.2 mg, 1.500 mmol) in CH₂Cl₂ (0.25 mL) was added dropwise, under N₂, to a cold (-78 °C) solution of (COCl)₂ (97.1 mg, 0.750 mmol) in CH₂Cl₂ (0.25 mL) and the resulting solution stirred at -78 °C for 15 min. A solution of 6 (54.3 mg, 0.150 mmol) in CH₂Cl₂ (0.75 mL) was added dropwise and the resulting mixture stirred at -40 °C for 30 min. Et₃N (227.7 mg, 2.250 mmol) was added dropwise, the resulting mixture stirred at -78 °C for 30 min., then cooled to room temperature. After adding CH₂Cl₂ (15 mL), the resulting organic phase was washed with dilute HCl, then with water, and concentrated under vacuum. The product was isolated by silica gel column chromatography (EtOAc/hexanes 1:5) to produce 6’ (41 mg, 0.12 mmol, 81%). ¹H NMR (400 MHz, CDCl₃) δ 9.46 (s, 1H), 7.37 (dd, J=6.1, 2.06 Hz, 1H), δ 7.22-
7.19 Hz (m, 1H), δ 6.99 Hz (s, 1H), δ 6.42-6.35 Hz (m, 4H), δ 6.22 (s, 1H), δ 3.76 (s, 3H),
δ 3.74 (s, 3H), δ 2.485 (t, J=7.69 Hz, 2H), δ 1.64-1.52 (m, 2H), δ 0.90 (t, J=7.36 Hz, 3H).
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 187.59, 160.78, 156.74, 146.98, 146.39, 145.58, 127.01,
126.18, 124.33, 123.89, 114.69, 111.04, 108.41, 107.62, 98.84, 55.94, 55.27, 38.17, 24.22,
13.76. GC-MS m/z (relative intensity): 342(78), 314(6), 299(11), 281(10), 267(6), 253(7),
239(8), 207(44), 191(6), 177(46), 167(100), 148(12), 138(24), 125(13), 105(14), 91(18),
77(15), 65(8), 51(8).
Chapter 3.  CATALYTIC OXIDATION OF $\beta$-O-4 LIGNIN MODEL

COMPOUNDS: CONVENTIONAL VERSUS IONIC LIQUID SOLVENTS

Note: This chapter was taken from the following paper:
Yao, S. G.; Meier, M. S.; Pace, R. III B.; Crocker, M. A comparison of the oxidation of lignin model compounds in conventional and ionic liquid solvents and application to the oxidation of lignin. *RSC Adv.*, 2016, 6, 104742.

3.1 Introduction

A two-step approach involving oxidation of benzylic hydroxyl groups to ketones, followed by C-C/C-O bond cleavage, has recently started gaining attention as an effective strategy for lignin depolymerization. For example, in a previous work,\textsuperscript{223} we used a two-step oxidation approach to selectively cleave the $\text{C}_\alpha$-$\text{C}_\beta$ bond in $\beta$-O-4 lignin model compounds. In that work, we first oxidized the benzylic alcohols catalytically, then further oxidized the resulting ketones to esters by Baeyer-Villiger reaction.\textsuperscript{223} Cleavage of the $\text{C}_\alpha$-$\text{C}_\beta$ bond was achieved by hydrolysis of the ester, yielding carboxylic acids and phenols. Very recently, Wang\textsuperscript{229} described another route to selective C-C bond cleavage of the $\beta$-O-4 linkage by first oxidizing the $\beta$-O-4 alcohol to a ketone over a $\text{VOSO}_4$/TEMPO catalyst, followed by further oxidation over a Cu/1,10-phenanthroline catalyst.

In the case of cleaving the $\beta$-O-4 $\text{C}_\beta$-O bond, initial oxidation of adjacent alcohols to ketones is particularly useful. Calculations have shown that this oxidation step weakens $\beta$-O-4 linkages, specifically the $\text{C}_\beta$-O bond, by lowering its bond energy from 247.9 kJ/mol to 161.1 kJ/mol.\textsuperscript{230} Recently, Lancefield\textsuperscript{231} applied this oxidation strategy in a one-pot depolymerization of birch lignin to phenolic monomers by first oxidizing the $\beta$-O-4
benzylic alcohols to ketones using a DDQ catalyst, followed by reductive cleavage of the C-O aryl bond with Zn. This method gave a 5% yield of pure phenolic monomer. A similar oxidation-reduction strategy was applied by Nguyen\textsuperscript{232} on lignin model compounds using a TEMPO-based catalyst for oxidation and an iridium photocatalyst for reduction. The process was not applied, however, to real lignin. A notable procedure was applied by Rahimi\textsuperscript{233} who used formic acid to depolymerize TEMPO – oxidized Aspen lignin yielding about 52% total aromatic monomers, as identified and quantified by high-resolution MS and LC-MS.

Over the years, catalytic oxidation of lignin hydroxyl groups to ketones has found increasing applications in lignin depolymerization methods.\textsuperscript{45,128,234} Aside from TEMPO-based catalysts, some others that have been employed are based on transition metals such as vanadium,\textsuperscript{235-237} palladium,\textsuperscript{238} copper,\textsuperscript{239,240} and cobalt\textsuperscript{241} to achieve oxidation for the purpose of selective C-C / C-OH bond cleavage, and for lignin conversion to aromatic compounds. Studies using DDQ-based catalyst systems for cleavage and modification of certain lignin linkages\textsuperscript{43,242} and for selective benzylic/allylic oxidation,\textsuperscript{243-245} have also been reported. Of late, dehydrogenative\textsuperscript{246} and heterogeneous catalytic oxidations have been investigated as well.\textsuperscript{247}

As mentioned earlier (Section 1.2.5), one of the significant barriers to the application of oxidation and other conversion processes to lignin is its notorious poor solubility - which is why ionic liquids came into the picture of this study. What ionic liquids are and the various ways that they have been used in the processing of lignocellulosic biomass have been discussed previously (Chapter 1.3). Their use in studies on oxidation of
lignin and lignin-like compounds,\textsuperscript{24,180,198,247-250} cleavage of lignin $\beta$-O-4 linkage\textsuperscript{251} and lignin depolymerization\textsuperscript{252,253} have also been described.

This chapter describes our study of oxidation of alcohols to ketones in ionic liquid solvents in an effort to determine if such liquids are useful in lignin deconstruction. Specifically, we aimed to determine how the oxidation rate may be affected, and whether the selectivity of different oxidation methods would change, when the reactions are carried out in ionic liquid solvents. We are particularly interested in the selectivity of benzylic oxidation: benzylic $-\text{OH}$ vs benzylic $-\text{CH}_2$.

### 3.2 Selection of Oxidation Methods

For our study of the oxidation of alcohols to ketones, we used catalytic methods employing catalysts based on iron tetraphenylporphyrin, on DDQ, and on TEMPO under mild and practical conditions with either molecular oxygen or peroxides as the ultimate oxidant. These catalysts were selected because of literature precedent\textsuperscript{223} and because each one is ultimately regenerated with peroxide or molecular oxygen. Molecular oxygen and peroxides were chosen as ultimate oxidants because they are inexpensive and readily available, thus making the process industrially viable.

The DDQ/NaNO$_2$/O$_2$ combination is one of the catalyst systems that we used to compare benzylic oxidation of $\beta$-O-4 lignin model compounds in IL solvents versus a conventional organic solvent. It was also used by Wang and co-workers\textsuperscript{254} to selectively oxidize benzylic hydroxyl groups. Recently, Westwood’s group\textsuperscript{43} reported that the DDQ/t-BuONO/O$_2$ system promoted the chemo-selective oxidation of the $\beta$-O-4 linkage in model compounds and in lignin.
The ability of benzoquinones to selectively oxidize unsaturated alcohols, including the oxidation of allylic, benzylic, and propargylic alcohols to the corresponding aldehydes and ketones, was first demonstrated by Braude in 1956 with the use of o-chloranil (tetrachloro-1,2-benzoquinone). Under the mild reaction condition that it was used, saturated alcohols were left unaffected.\textsuperscript{255} Four years later, Burn found out that 2,3-dichloro-5,6-dicyano-\textit{p}-quinone (DDQ) was likewise capable of such selectivity, when he was able to oxidize allylic sterols in the presence of saturated alcohols in dioxane or benzene at room temperature.\textsuperscript{256} This work paved the way for the subsequent use of DDQ in selective oxidation of allylic,\textsuperscript{257} benzylic,\textsuperscript{258} and propargylic alcohols,\textsuperscript{259} replicating the role of \textit{o}-chloranil. To date, DDQ has found a wide range of applications in selective oxidation of alcohols\textsuperscript{243,244,260,261} as it enjoys the advantage of having a high oxidation potential ($E^0 = 1.0$ V).\textsuperscript{262} It has been used in selective oxidation of lignin and lignin model compounds as well.\textsuperscript{242,263}

DDQ oxidation of 1-5 was carried out by treating 50 mg of each compound with DDQ (0.1 eq) and NaNO\textsubscript{2} (1.0 eq) separately in three different solvents (DCM, [C\textsubscript{4}C\textsubscript{1}im]Cl, or [P\textsubscript{4444}]Cl), in combination with AcOH, under an O\textsubscript{2} atmosphere (1 atm) at room temperature for 19 h. Oxidation of 6-10 was performed under similar conditions but using 100 mg of each compound and 0.1 eq of NaNO\textsubscript{2} instead of 1.0 eq.

In view of recent successes in the use of TEMPO to oxidize alcohols,\textsuperscript{264-268} lignin model compounds,\textsuperscript{223,269,270} and lignin itself,\textsuperscript{269} we decided to use the TEMPO/NaNO\textsubscript{2}/HCl/NaCl combination to address the question of whether the selectivity of oxidation changes significantly when reactions are carried out in ionic liquids instead of conventional solvents. So far, some of the studies that have employed ILs in TEMPO-
catalyzed oxidations involve immobilization of the catalyst to the IL in order to improve efficiency and facilitate recycling of the catalyst and the IL.\textsuperscript{264,265} Other reports have used ILs as solvent in the oxidation of alcohols to aldehydes and ketones, where a high selectivity for the aldehyde product was noted with primary and benzylic alcohols.\textsuperscript{265,271} An improved selectivity has also been noted in the case of oxidation of allylic alcohols when the IL \([C_4C_1im]Br\) was confined inside the mesochannels of the SBA-supported TEMPO catalyst. It was observed that the catalyst with confined IL exhibited higher selectivities and efficiency compared to one which was not charged with IL.\textsuperscript{266}

Several TEMPO-based catalysts have been investigated, but for this study we used the TEMPO/NaNO\(_2\)/HCl/NaCl combination,\textsuperscript{272,273} which has been observed to efficiently oxidize benzylic alcohol, giving good to excellent results of 75\% to 97\% yield from non-phenolic model compounds.\textsuperscript{223} The phenolic models, however, were converted to insoluble products, presumably polymeric material, thus suggesting a need for protecting the phenolic group prior to using this catalyst for benzylic oxidation.

TEMPO-catalyzed oxidation of 1-5 was carried out by treating 50 mg of each compound with TEMPO (0.15 eq), NaNO\(_2\), (0.25 eq), 36\% aq HCl (0.5 eq), and NaCl (0.5 eq) separately in three different solvents (DCM/[C\(_4\)C\(_1\)im Cl]/ [P\(_{4444}\)]Cl) at room temperature for 19 h. Oxidation of 6 – 10 was carried out under the same conditions, using 100 mg of each compound for starting material.

The third catalyst system that we investigated consists of an iron porphyrin, which has been identified as one of the components of the oxidases that were isolated from ligninolytic cultures of the white rot fungus \textit{Phanerochaete chrysosporium}.\textsuperscript{129,274} In the presence of \(\text{H}_2\text{O}_2\), the enzyme was found to be responsible for natural biodegradation of
Different forms of iron porphyrin catalysts have been employed in investigations. For this particular study, we used tetraphenyl porphyrin iron chloride (TPPFeCl), together with tertrabutyl hydroperoxide (t-BuOOH) as oxidant. When this catalyst system was applied to 2 – 5, the phenolic models were converted to insoluble products, just like when the TEMPO/NaNO₂/HCl/NaCl system was employed. In addition, both the benzylic -OH and benzylic -CH₂ were oxidized. In the current work, we are applying the porphyrin catalyst, this time carrying out the reaction in IL solvent to determine if the selectivity of the benzylic oxidation would improve.

The porphyrin oxidation was carried out by treating 50 mg of each compound with TPPFeCl (0.01 eq) and t-BuOOH (70% aq solution, 2 eq) separately in three different solvents (MeCN/[C₄C₁im]Cl/[P₄4444]Cl) and phosphate buffer (0.1N, pH 3) at room temperature for 14 h. Oxidation of compounds 6 - 10 was done under similar conditions but using 100 mg of each compound and 1 eq t-BuOOH (70% aq soln) instead of 2 eq.

The aforementioned oxidation methods were carried out in a conventional solvent in parallel with oxidations in the ionic liquids 1-butyl-3-methylimidazolium chloride ([C₄C₁im]Cl) and tetrabutylphosphonium chloride ([P₄4444]Cl). Utilization of [C₄C₁im]Cl in the investigation of lignocellulosic biomass has been well documented, while the use of [P₄4444]Cl is based on its higher thermal stability and resistance to oxidation.

The catalytic oxidation of our lignin model compounds was done in two phases. In the first phase, 1 - 5 were used in a preliminary study: 2 - 5 for testing the selectivity of the benzylic oxidations, alcohol vs methylene group, and 1 (the simplest model) for determining how reactivity might be affected as different functionalities are added to the
different models. Once the selectivity of the benzylic oxidations has been established, 6 – 10 were used in the second phase to serve as the final oxidation studies.

3.3 Results and Discussion

The conversion of benzylic hydroxyl groups to ketones in each of the three oxidation reactions described above was confirmed by NMR experiments. For example, $^{13}$C NMR chemical shift for the carbonyl group at 194.5, 197.6, and 195.3 ppm ($6'$, $7'$, $9'$) indicates formation of ketone products from 6, 7, and 9, respectively. The structural assignments were further confirmed by changes in the $^1$H NMR spectra, including complete disappearance of the signal for the $\alpha$-H (multiplets at 5.13-5.06 ppm for 6, at 4.93-4.87 and at 4.63-4.56 ppm for the two diastereomers of 7, and at 4.98-4.93 ppm for 9). In addition, the multiplet signal for the $\beta$-H in each compound changed (to a singlet for 6, to a quartet for 7, and to a doublet of doublets for 9), and shifted downfield to around 5.0 ppm.

3.3.1 DDQ Oxidation

In performing the DDQ oxidation of 1 – 5 (Scheme 3.1, Table 3.1)), we observed that in [C$_4$C$_1$im]Cl and [P$_{4444}$]Cl, the catalyst system selectively oxidized the model compounds at the benzylic -OH group, leaving the benzylic -CH$_2$- group unaffected.

![Scheme 3.1. DDQ oxidation of 1 – 5.](image)

1: $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H$
2: $R_1 = R_2 = R_4 = R_6 = H; R_3 = OH; R_5 = n$-Pr
3: $R_1 = R_3 = R_4 = OCH$_3$; R$_2 = OH; R_4 = CH$_3$; R$_5 = n$-Pr
4: $R_1 = R_2 = OCH$_3$; R$_2 = R_3 = OH; R_4 = CH$_3$; R$_5 = n$-Pr
5: $R_1 = R_2 = R_3 = OCH$_3$; R$_3 = OH; R_4 = CH$_2$OH; R$_5 = n$-Pr

Scheme 3.1. DDQ oxidation of 1 – 5.
Table 3.1. Oxidation of 1 – 5 using DDQ/NaNO₂/O₂.

<table>
<thead>
<tr>
<th>SM&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product&lt;sup&gt;b&lt;/sup&gt; (16)</th>
<th>DCM</th>
<th>[C₄C₁im]Cl</th>
<th>[P₄₄₄₄]Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0% (98%)</td>
<td>0%  (99%)</td>
<td>- (-)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0% (100%)</td>
<td>0%  (98%)</td>
<td>- (-)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12% (52%)</td>
<td>7%  (92%)</td>
<td>trace (0%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>60% (0%)</td>
<td>80% (0%)</td>
<td>56% (0%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>43% (55%)</td>
<td>0%  (95%)</td>
<td>0% (93%)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction was carried out at room temperature for 19 hours using 0.1 eq DDQ, 1.0 eq NaNO₂, 0.2 mL AcOH, and 0.3 mL DCM/0.2g [C₄C₁im]Cl/0.2g [P₄₄₄₄]Cl.  
<sup>b</sup>Yields are for purified, isolated products; (SM) is given in parentheses.

This result is consistent with a report<sup>223</sup> indicating that models with both benzylic -OH and benzylic -CH₂- reacted only at the benzylic -OH when treated with DDQ/NaNO₂/O₂/AcOH. The γ-methyl and hydroxyl methyl groups were also unaffected. We likewise noticed that the phenolic model (4), which was converted to insoluble product when treated with TEMPO/NaNO₂/HCl/NaCl<sup>223</sup> and with TPPFeCl/<i>t</i>-BuOOH,<sup>223</sup> survived the reaction, while the unfunctionalized models 1 and 2 remained unchanged under these experimental conditions. Similar observations were noted in the conventional solvent, except for 5, which was oxidized efficiently in DCM, but was not oxidized fast enough in the IL solvents to be observed under the conditions and the fixed time of the experiment. Oxidation rates for reactions with DDQ were, for the most part, lower in [C₄C₁im]Cl and [P₄₄₄₄]Cl except in the case of the phenolic compound 4, for which oxidation rates were more or less comparable in the two types of solvent. The lower oxidation rate in the IL solvents is most likely due, at least in part, to the high viscosity of [C₄C₁im]Cl and [P₄₄₄₄]Cl.
the ILs (142 cP and 120 cP at 80 °C for [C₄C₁im]Cl and [P₄₄₄₄]Cl, respectively),¹⁴⁷ which hampers mass transport of reactants.

Oxidation of 6 - 10 (Scheme 3.2) in DCM confirmed the preliminary results obtained from reactions of 1 - 5 in terms of selectivity. Under the experimental conditions, functionalized models 7 – 10 were selectively oxidized at the benzylic hydroxyl group, giving corresponding ketone products in moderate yields (27-61%, Table 3.2), but these reactions did not produce the analogous ketone product from the least electron-rich model compound (6). We moved the same combination to [C₄C₁im]Cl and [P₄₄₄₄]Cl and we observed the same selectivity as in DCM, although reaction rates were much lower, again likely due to the high viscosity of the solvents. Additionally, the reaction condition with [P₄₄₄₄]Cl as solvent appeared to be incompatible with substrates bearing unprotected phenolic -OH group.

Selective DDQ-catalyzed oxidation of benzylic alcohols can proceed through different routes including by hydride transfer (Fig 3.1)²⁵⁴,²⁵⁹,²⁸⁰ and through rapid series of steps involving transfer of electrons and protons, at some point forming radical cation of the substrate.²⁸¹ In the hydride transfer mechanism, reaction rate correlates principally with stability of the resulting intermediate carbocation.²⁸² This is consistent with the observed high reactivity of the functionalized models where electron-rich substituents are present in the phenyl ring, in conjugation with the benzylic alcohol group.
Scheme 3.2. DDQ oxidation of 6 – 10.

Table 3.2. Oxidation of 6 - 10 using DDQ/NaNO₂/O₂.

<table>
<thead>
<tr>
<th>SM</th>
<th>Product b (17)</th>
<th>DCM</th>
<th>[C₄C₅im]Cl</th>
<th>[P₄₄₄₄]Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0% (93%)</td>
<td>0% (96%)</td>
<td>0% (95%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>61% (38%)</td>
<td>10% (60%)</td>
<td>7% (85%)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>57% (2%)</td>
<td>6% (93%)</td>
<td>0% (0)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>27% (65%)</td>
<td>5% (89%)</td>
<td>Trace (75%)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>48% (0%)</td>
<td>1% (67%)</td>
<td>0% (0%)</td>
<td></td>
</tr>
</tbody>
</table>

a Reactions were carried out for 19 hours using 0.1eq DDQ and 0.1eq NaNO₂.
b Yields are for purified, isolated products. Recovered starting material is given in parentheses.

Figure 3.1. Proposed catalytic cycle for DDQ aerobic oxidation.
3.3.2 TEMPO Oxidation

When we applied the TEMPO/NaNO$_2$/O$_2$ catalyst system, first to 1 - 5 (Scheme 3.3, Table 3.3), then later to 6 - 10 (Scheme 3.4, Table 3.4), we obtained moderate to excellent yields from the functionalized, nonphenolic models (2 - 3, 5 - 7, and 9) in DCM. In [C$_4$C$_1$im]Cl and [P$_{4444}$]Cl however, oxidation rates were so low that conversion, for the most part, was not observed within the standard 19-hour reaction time.

![Scheme 3.3. TEMPO oxidation of 1 – 5.](image)

**Table 3.3. Oxidation of 1 - 5 using TEMPO/NaNO$_2$/O$_2$.**

<table>
<thead>
<tr>
<th>SM$^a$</th>
<th>Product$^b$ (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DCM</td>
</tr>
<tr>
<td>1</td>
<td>0% (99%)</td>
</tr>
<tr>
<td>2</td>
<td>94% (0%)</td>
</tr>
<tr>
<td>3</td>
<td>84% (0%)</td>
</tr>
<tr>
<td>4</td>
<td>7% (48%)</td>
</tr>
<tr>
<td>5</td>
<td>82% (0%)</td>
</tr>
</tbody>
</table>

$^a$Reaction was carried out at room temperature for 19 hours using 0.15 eq TEMPO, 0.25 eq NaNO$_2$, 0.5 eq 36% aq HCl, 0.5 eq NaCl, and 0.3 mL DCM/0.2g [C$_4$C$_1$im]Cl /0.2g [P$_{4444}$]Cl.

$^b$Yields are for purified, isolated products; recovered starting material (SM) is given in parentheses.
Scheme 3.4. TEMPO oxidation of 6 – 10.

Table 3.4. Oxidation of 6, 7, and 9 using TEMPO/NaNO₂/O₂.

<table>
<thead>
<tr>
<th>SM</th>
<th>Product(^{(17)})</th>
<th>DCM</th>
<th>[C₄C₁im]Cl</th>
<th>[P₄444]Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>96% (0%)</td>
<td>Trace (98%)</td>
<td>Trace (93%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>88% (0%)</td>
<td>0% 90%)</td>
<td>0% (75%)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>53% (0%)</td>
<td>0% (53%)</td>
<td>0% (80%)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Reactions were carried out for 19 hours using 0.15eq TEMPO and 0.25eq NaNO₂.

\(^b\)Yields are for purified, isolated products. Recovered starting material is given in parentheses.

TEMPO oxidation of alcohols could be slowed down in ILs as a result of the latter’s high viscosity.\(^{283}\) To address the viscosity issue in the use of ILs, the TEMPO oxidation of 2 was performed at elevated temperature (75 °C) using the same concentration of reagents as we used at room temperature. Unexpectedly, a significant decrease in reaction rate was observed at elevated temperature. This may be due to the fact that oxoammonium salts (like TEMPO\(^+\), Fig. 3.2) are unstable and tend to decompose in the presence of water at 25 °C.\(^{284}\) The presence of a small amount of water in concentrated HCl solution and possibly in [C₄C₁im]Cl may have caused partial decomposition of TEMPO\(^+\). As the active form of the TEMPO catalyst, its decomposition is a possible reason for the observed
decrease in reaction rate at elevated temperature. This decomposition of oxoammonium salts can be prevented by ensuring that water is kept out when performing TEMPO oxidation at elevated temperature. The solubility of O₂, which understandably decreases at elevated temperatures, may be a contributing factor, too.

Figure 3.2. Proposed catalytic cycle for TEMPO-catalyzed oxidation of an alcohol.²⁷³,²⁸⁵

We noticed that the TEMPO catalyst system is not compatible with the lignin models that have free phenolic hydroxyl groups, such as compounds 4, 8, and 10. We suspect that the starting material, the products, or both suffer phenolic oxidative coupling, which can occur in processes where free radical species are present.

TEMPO-catalyzed oxidation has been proposed to involve an activated oxoammonium cation (TEMPO⁺) as the oxidizing derivative.²⁷³,²⁸⁶ It oxidizes alcohol into an aldehyde or ketone and, in the process, gets reduced to a hydroxyl amine (TEMPOH). TEMPOH is then oxidized back to TEMPO by oxygen, thus completing the catalytic cycle.
Activation of TEMPO occurs through a one-electron transfer to NOCl, which is formed through another cycle involving the secondary oxidant NaNO₂ (Fig. 3.2).\textsuperscript{285} NaNO₂ supplies NO that reacts with O₂ forming NO₂ which, in the presence of HCl, is converted to NOCl.

### 3.3.3 TPPFeCl Oxidation

Of the three catalyst systems that we have investigated, the TPPFeCl/\textit{t}-BuOOH combination differs from the others in two ways: 1) in chemo-selectivity, and 2) in reactivity. The TPPFeCl catalyst system exhibits a different chemo-selectivity compared to DDQ and TEMPO. When applied to 1 - 5, aside from oxidizing the benzylic -OH, it also oxidized the benzylic -CH₂-, giving three oxidation products (Scheme 3.5): 16, which was oxidized at the benzylic -OH only; 18, which was oxidized at the benzylic -CH₂- only; and 19, which was oxidized at both benzylic positions.

![Scheme 3.5. TPPFeCl oxidation of 1 – 5.](image-url)
Table 3.5 Oxidation of 1 - 5 using TPPFeCl/\(t\)-BuOOH

<table>
<thead>
<tr>
<th>SM(^a)</th>
<th>Solvent</th>
<th>Product(^b)</th>
<th>16</th>
<th>18</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>70% (89%)</td>
<td>9%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>[C(_4)C(_1)im]Cl</td>
<td>11% (85%)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>[P(_{4444})]Cl</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>41% (36%)</td>
<td>8%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>[C(_4)C(_1)im]Cl</td>
<td>40% (30%)</td>
<td>9%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[P(_{4444})]Cl</td>
<td>44% (26%)</td>
<td>10%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>3(^c)</td>
<td>MeCN</td>
<td>30% (35%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>[C(_4)C(_1)im]Cl</td>
<td>21% (70%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>[P(_{4444})]Cl</td>
<td>0% (0%)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>0% (0%)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>[C(_4)C(_1)im]Cl</td>
<td>0% (0%)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>[P(_{4444})]Cl</td>
<td>0% (0%)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>36% (46%)</td>
<td>13%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>[C(_4)C(_1)im]Cl</td>
<td>34% (51%)</td>
<td>0%</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>[P(_{4444})]Cl</td>
<td>23% (59%)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(^a\)Reaction was carried out at room temperature for 14 hours using 0.03 eq TPPFeCl, 2 eq \(t\)-BuOOH, 1.5 mL phosphate buffer pH3, and 0.5 mL MeCN/0.2 g [C\(_4\)C\(_1\)im]Cl/[P\(_{4444}\)]Cl
\(^b\)Yields are for purified, isolated product; recovered starting material(SM) is given in parentheses
\(^c\)Products 18 and 19 were not purified

These three porphyrin oxidation products (16, 18, and 19) were observed specifically for models 2 and 5 (Table 3.5), where 16 was observed to be the predominant product in all three solvents, reflecting preferential oxidation of the benzylic C-OH over the benzylic -CH\(_2\)- group. Table 3.5 shows that in the porphyrin oxidation of 2 and 5, oxidation of the benzylic C-OH (40-44\% yield for 2; 23-36\% for 5) generally occurs faster than that of the benzylic -CH\(_2\) - (8-10\% yield for 2; 0-13\% for 5) in all three solvents. This observation is consistent with bond dissociation energies (BDE), indicating that the C-H bond in benzylic alcohol is weaker than that in a benzylic alkyl
group: average of 347.5 kJ/mol in 4-MeOC₆H₄CH₂OH and 360 kJ/mol in 4-MeOC₆H₄CH₂CH₃. The doubly oxidized product – oxidized at both benzylic positions – was isolated at 9-18% yield for 2 and 3-14% yield for 5.

As noted in the preceding paragraph, 16 was also the predominant product in the porphyrin oxidation of 2 and 5 in [C₄C₁im]Cl and [P₄₄₄₄]Cl, indicating that selectivity was preserved when the oxidation was transferred to these solvents. In the case of 5, product 18 was not observed at all in the reactions performed in [C₄C₁im]Cl and [P₄₄₄₄]Cl, indicating that the selectivity of the porphyrin benzylic oxidation has been improved when the reaction was carried out in said solvents.

The porphyrin catalyst system also exhibits a different reactivity in [C₄C₁im]Cl and [P₄₄₄₄]Cl. Unlike in DDQ and TEMPO oxidations where the rates of benzylic C-OH oxidation are much slower in the IL solvents, the rates under porphyrin catalysis are more or less similar in all three solvents, for both 1 - 5 and 6 - 10 (Tables 3.5 and 3.6), which is a welcome improvement.

Scheme 3.6. TPPFeCl oxidation of 6 - 10.
Table 3.6. Oxidation of 6, 7, and 9 using TPPFeCl/t-BuOOH.

<table>
<thead>
<tr>
<th>SM\textsuperscript{a}</th>
<th>Product\textsuperscript{b} (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MeCN</td>
</tr>
<tr>
<td>6</td>
<td>41% (58%)</td>
</tr>
<tr>
<td>7</td>
<td>22% (68%)</td>
</tr>
<tr>
<td>9</td>
<td>38% (55%)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reactions were carried out for 14 hours using 0.01 eq TPPFeCl and 1 eq t-BuOOH.
\textsuperscript{b}Yields are for purified, isolated products. Recovered starting material is given in parentheses.

As in TEMPO-based systems, the porphyrin catalyst system is not compatible with model compounds having unprotected phenol group as these compounds are converted into insoluble products, presumably through polymerization. This is not really surprising considering that the formation of lignin from monolignols is believed to proceed starting with the formation of stabilized phenoxy radicals at the 4-OH position as shown in Fig 1.5. Then the phenoxy radicals couple to form dilignols. The growth of a dilignol into a polymer takes place at the phenolic end of the growing oligomer which is converted into a stabilized phenoxy radical each time it adds a monolignol. If this is indeed the case, then that it is possible that despite its abundance, most of the phenolic OH in lignin are not free as they are tied up in linkages. Thus, the aforementioned observation on the conversion of the phenolic models to insoluble products - possibly through polymerization, as discussed above, suggests the need to protect phenolic groups if the TEMPO and porphyrin catalyst systems are to be used to oxidize the benzylic alcohols in model compounds.

A proposed mechanism for porphyrin - catalyzed oxidation of lignin/alcohol is shown in Fig. 3.3. Peroxide oxidizes iron(III) porphyrin to Fe(IV) porphyrin cation radical complex (2) which then performs a one-electron oxidation on the lignin/alcohol which
reduces it to porphyrin complex (3). Porphyrin complex (3) performs another one-electron oxidation of lignin/alcohol, restoring it to its starting state porphyrin complex (1).

Figure 3.3. Structure of TPPFeCl (left) and proposed catalytic cycle for TPPFeCl oxidation (right).288-290

Hydrogen atom abstraction from the benzylic C-H bond is the slow step in the proposed mechanism for the porphyrin-catalyzed oxidation of both the C-OH and -CH₂-groups. For this oxidation, an iron-oxo intermediate is believed to abstract a hydrogen atom from the substrate. In the case of C-OH oxidation, this step results in the formation of an α-hydroxycarbinyl radical, which subsequently transfers an electron and a proton to the oxidant to yield the corresponding carbonyl product.²⁹⁰ For the -CH₂- group oxidation, formation of the carbon radical is followed by oxygen rebound (alkyl rebound in some reports) forming an alcohol,²⁸⁹ which may be oxidized further to a carbonyl compound.
Considering the much higher viscosity of ILs compared to traditional organic solvents, it is interesting to note that 1-10 exhibit comparable reactivity for porphyrin oxidation in the two solvent types. It is possible that the amount of water present in the pH3 buffer, and in the 70% \( t \)-BuOOH that was used as oxidant, has rendered the three reaction mixtures largely aqueous, hence the similarity in reactivity. In order to determine if the presence of water has any effect on the porphyrin-mediated oxidation under aqueous condition, we conducted parallel oxidation experiments on 2, omitting the pH3 buffer and using tert-butylhydroperoxide in decane instead of 70% aqueous solution (Table 3.7). We noticed that under non-aqueous conditions, the conversion to products decreased in all solvents. Moreover, product 18 was obtained only in trace amount in [C\(_4\)C\(_1\)im]Cl and not obtained at all in [P\(_{4\,4\,4\,4}\)]Cl, indicating an improved benzylic oxidation selectivity in these IL solvents.

Table 3.7. Porphyrin oxidation of 2 in non-aqueous solution.

<table>
<thead>
<tr>
<th>Product ( a )</th>
<th>MeCN</th>
<th>[C(_4)C(_1)im]Cl</th>
<th>[P(_{4,4,4,4})]Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>14%</td>
<td>11% (56%)</td>
<td>12% (34%)</td>
</tr>
<tr>
<td>18</td>
<td>1%</td>
<td>trace</td>
<td>0%</td>
</tr>
<tr>
<td>19</td>
<td>3%</td>
<td>1%</td>
<td>2%</td>
</tr>
</tbody>
</table>

\( a \)Yields are for purified, isolated product; recovered starting material(SM) is given in parentheses

At this point, it has become evident that the presence of water may play a significant role in the porphyrin-catalyzed oxidation, because dramatic decreases in yields were obtained in going from aqueous to non-aqueous conditions. This may primarily be due to the elimination of the pH 3 reaction conditions, but the water component of the reagents might have a significant effect as well. For example, it has been shown that water
contributes to the enhanced reaction rate in acetonitrile when the aqueous buffer is used.\textsuperscript{291}

In the proposed mechanism for porphyrin oxidation, it is believed that H atom transfer from a C-H bond to an O-centered radical involves a polar transition state (TS) in which a negative charge develops on the oxygen center while a positive charge is acquired by the incipient carbon radical.\textsuperscript{292-294} As such, hydrogen bonding interactions with water molecules may stabilize the polar TS more than it stabilizes the reactants, causing the free energy of activation to decrease in the slow step.

The low conversion and yields under non-aqueous conditions described above may possibly be due in part to the high viscosity of the IL reaction mixtures. Low reaction rates in some reactions carried out in ILs have been attributed to the high viscosity of the solvent.\textsuperscript{295,296} In these reactions, significant rate enhancement was achieved when a co-solvent was added, decreasing the viscosity of the reaction medium.

So far, a beneficial outcome that has been gained in transferring the catalytic benzylic oxidation to IL solvents is an improved selectivity, as illustrated in the use of porphyrin catalyst. Again, this may be due to high solvent viscosity which, among other things, has been shown to produce solvent cage effects.\textsuperscript{297-299} It has been observed that as the viscosity increases, the solvent cage lifetime increases, affording trapped reactive species more time to recombine.\textsuperscript{299,300} It is possible while within the cage, radical intermediates in this oxidation react with the iron-oxo species again, thus re-forming the starting material. When this re-formed starting material re-enters the catalytic cycle, a hydrogen atom would most likely be abstracted from the benzylic -OH (PhCHOH: BDE 347 kJ/mole) rather than from the benzylic -CH\(_2\)- (PhCH\(_2\)-: BDE 360 kJ/mole). The overall result is an enhanced preference for the formation of either the C-OH oxidation
product (A) or the diketone product (C) or both, at the expense of the -CH₂- oxidation product (B).

In view of overall low conversion and yield in IL solvents, optimization experiments were performed using DDQ oxidation of 8 in [C₄C₁im]Cl as a test case (Table 8). When higher concentrations were used (by decreasing the volume of the solvent), the yield increased, as expected, from 6% to 24%. When higher temperatures were used, however, no improvement in yield was noted. Unfortunately, the reaction temperature could not be increased significantly above 120 °C, as [C₄C₁im]Cl has been shown to start decomposing at about 140 °C. Finally, the reaction was run for a longer period of time, but no improvement in yields was observed. It is possible that under the reaction condition, the amount of O₂ available for the reaction is limited.

Table 3.8. Optimization of DDQ Oxidation in [C₄C₁im]Cl.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcOH (mL)</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
<td>0.4</td>
<td>0.2</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>[C₄C₁im]Cl (g)</td>
<td>3.78</td>
<td>0.4</td>
<td>0.2</td>
<td>3.78</td>
<td>1.9</td>
<td>1.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Temp (°C)</td>
<td>rt</td>
<td>rt</td>
<td>rt</td>
<td>50</td>
<td>100</td>
<td>120</td>
<td>rt</td>
</tr>
<tr>
<td>% Yield</td>
<td>6</td>
<td>24</td>
<td>23</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>% SM recovered</td>
<td>93</td>
<td>69</td>
<td>69</td>
<td>93</td>
<td>61</td>
<td>66</td>
<td>40</td>
</tr>
</tbody>
</table>

3.4 Conclusions

The DDQ/NaNO₂/O₂ catalyst system selectively oxidized the benzylic hydroxyl group of the functionalized models (both phenolic and non-phenolic) in the conventional
solvent and in the ionic liquid [C₄C₁im]Cl. Under these conditions, the compounds with unprotected phenolic groups (4, 8, and 10) were not lost to polymerization in either the conventional solvent or ionic liquid [C₄C₁im]Cl. In the IL [P₄₄₄₄]Cl, only model compounds 4 and 7 were oxidized fast enough to be observed under the reaction conditions. The aerobic TEMPO/NaNO₂ system effectively oxidized the benzylic hydroxyl group in the non-phenolic models with good to excellent yields in the conventional solvent, but in ionic liquids, we find that this reaction was very slow and, as was the case in conventional solvent, unprotected phenolic groups were not tolerated. The TPPFeCl/\(t\)-BuOOH combination selectively oxidized the benzylic C-OH group in the non-phenolic lignin model compounds, in both conventional and ionic liquid solvents. In the case of the non-phenolic, ring alkylated compounds 2 and 5, the catalyst system oxidized both the benzylic -CH₂ and C- OH groups in both types of solvents, but in the ionic liquid solvents there was an increased selectivity for oxidation of the benzylic C-OH. Under these conditions, phenolic models 4, 8, and 10 were consumed but no identifiable, chromatographically mobile products were obtained, as in the case of TEMPO oxidation, and we believe that oxidation of these compounds results in insoluble polymeric products.

Oxidation rates were often lower in ionic liquids than in conventional solvents, as indicated by lower conversion in a standard reaction time, likely due in part to the higher viscosity of ionic liquids. Using the DDQ/NaNO₂ system, it was shown that oxidation in [C₄C₁im]Cl could be enhanced by increasing the concentration of the reaction mixture, as expected, although the reduction in rate could not be overcome by increasing the temperature. In the case of the iron porphyrin-mediated oxidation in ILs, the oxidation rate
was significantly higher under aqueous, relative to non-aqueous conditions, suggesting a possible role of water (as a co-solvent) in enhancing the rate of this oxidation.

Of particular significance was the observed increase in selectivity of the benzylic carbon towards alcohol (compared to methylene group) oxidation when the reaction was carried out in ionic liquid solvents. This selectivity is indicated by a change in the product distribution in the oxidation of 2 and 5 using the TPPFeCl/\textit{t}-BuOOH system as catalyst. In the ionic liquid solvents, the product where both the C-OH and -CH₂ groups were oxidized was significantly enhanced in 2 and 5 and then in 5, the product where only the -CH₂ group was oxidized was not observed at all.

Considering their capacity to dissolve lignin, ionic liquids have characteristics that make them obvious candidates as solvents in reactions on lignin (including deconstruction, by any chemical method). The use of an ionic liquid appears to enhance selectivity in some cases – as exemplified by porphyrin oxidation – and to provide a medium where both phenolic and nonphenolic compounds can be oxidized, like when DDQ is used, but reaction rates drop significantly. Hence, additional optimization work will be needed in order to identify solvent/reagent combinations, possibly including the addition of a co-solvent, that can produce efficient deconstruction of lignin.

3.5 Experimental Section

3.5.1 Synthesis of Ionic Liquid solvents

The [C₄C₁im]Cl and [P₄₄₄₄]Cl used in this study were prepared by Robert B. Pace III. The preparation is included here for completeness of the experimental section.
3.5.1.1 **Synthesis of [C$_4$C$_1$im]Cl$^{228}$**

1-Chlorobutane (116.6 g, 1.26 mol) was slowly added to 1-methyl imidazole (94.00 g, 1145.0 mmol). Stirring was maintained throughout. The solution was then heated to 50 °C and allowed to stir at this temperature for 3 days. The resulting mixture was then purified by subjecting it to rotary evaporation for three eight-hour periods at less than 10 mbar. The bath temperature was initially set to 50 °C, then increased to 60 °C, and then to 75 °C, during the subsequent intervals. Finally, the IL was evacuated on a schlenk apparatus at 75 °C and less than 1 mbar of pressure for 5 days, yielding a viscous, pale yellow liquid, which is pure (other than a trace of water) as observed in NMR.

3.5.1.2 **Synthesis of [P$_{4444}$]Cl$^{228}$**

1-Chlorobutane (69.86 g, 754.7 mmol) was added via cannula to tributyl phosphine (162.76 g, 611.2 mmol) under an atmosphere of dry nitrogen. Stirring was maintained throughout. The solution was then heated to 50 °C and allowed to stir at this temperature for 3 days. The resulting mixture was purified by subjecting it to rotary evaporation for three eight-hour periods at less than 10 mbar. The bath temperature was initially set to 70 °C, then increased to 80 °C, then to 95 °C, during the subsequent intervals. Finally, the IL was evacuated on a schlenk apparatus at 150 °C and less than 1 mbar of pressure for 5 days, yielding a waxy, white solid at room temperature, which is pure (other than a trace of water) as observed in NMR.
3.5.2 Oxidation of β-O-4 lignin model compounds

3.5.2.1 Oxidation with DDQ/NaNO2/O2

**Oxidation of model 3:** Mixtures of 3 (30 mg, 0.083 mmol), DDQ (1.9 mg, 0.0083 mmol), NaNO2 (5.9 mg, 0.083 mmol), and acetic acid (0.20 mL) in three different solvents [1.8 mL CH2Cl2 (A), 0.20 g [C4C1im]Cl (B), and 0.20 g [P4444]Cl (C)] were stirred under an O2 atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with ethyl acetate (3 x 10 mL) and each set of combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO4. After evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:3) to give 3A (16 mg, 0.080 mmol, 52%) and 16A (3.6 mg, 0.010 mmol, 12%); 3B (27 mg, 0.075 mmol, 92%) and 16B (2 mg, 0.006 mmol, 7%); and 16C (trace).

**Oxidation of model 4:** Mixtures of 4 (30 mg, 0.087 mmol), DDQ (2.0 mg, 0.0088 mmol), NaNO2 (6.0 mg, 0.087 mmol), and acetic acid (0.12 mL) in three different solvents [1.2 mL CH2Cl2 (A), 0.13 g [C4C1im]Cl (B), and 0.13 g [P4444]Cl (C)] were stirred under an O2 atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with ethyl acetate (3 x 10 mL) and each set of combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO4. After evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:3) to give 16A (18 mg, 0.050 mmol, 60%); 16B (24 mg, 0.070 mmol, 80%); and 16C (17 mg, 0.050 mmol, 56%).

**Oxidation of model 5:** Mixtures of 5 (43.3 mg, 0.115 mmol), DDQ (3.0 mg, 0.012 mmol), NaNO2 (8.0 mg, 0.11 mmol), and acetic acid (0.20 mL) in three
different solvents [1.8 mL CH₂Cl₂ (A), 0.20 g [C₄C¹im]Cl (B), and 0.20 g [P₄₄₄₄]Cl (C)] were stirred under an O₂ atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with ethyl acetate (3 x 10 mL) and each set of combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO₄. After evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:3) to give 5A (24 mg, 0.064 mmol, 55%) and 16A (18 mg, 0.050 mmol, 43%); 5B (41 mg, 0.11 mmol, 95%); and 5C (40 mg, 0.11 mmol, 93%).

**Oxidation of model 7:** Mixtures of 7 (100 mg, 0.314 mmol), DDQ (7.1 mg, 0.031 mmol), NaNO₂ (2.2 mg, 0.031 mmol), and acetic acid (0.40 mL) in three different solvents [3.6 mL CH₂Cl₂ (A), 3.78 g [C₄C¹im]Cl (B), and 3.24 g [P₄₄₄₄]Cl (C)] were stirred under an O₂ atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with ethyl acetate (3 x 10 mL) and each set of combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO₄. After evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:3) to give 7A (38 mg, 0.12 mmol, 38%) and 17A (60 mg, 0.19 mmol, 61%); 7B (60 mg, 0.19 mmol, 60%) and 17B (10 mg, 0.032 mmol, 10%); and 7C (85 mg, 0.27 mmol, 85%) and 17C (7 mg, 0.02 mmol, 7%).

**Oxidation of model 8:** Mixtures of 8 (100 mg, 0.329 mmol), DDQ (7.5 mg, 0.033 mmol), NaNO₂ (2.3 mg, 0.033 mmol), and acetic acid (0.40 mL) in three different solvents [3.6 mL CH₂Cl₂ (A), 3.78 g [C₄C¹im]Cl (B), and 3.24 g [P₄₄₄₄]Cl (C)] were stirred under an O₂ atmosphere (1 atm) at 25 °C for 19 h. The mixtures were
extracted separately with ethyl acetate (3 x 10 mL) and each set of combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO₄. After evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:3) to give 8A (1.9 mg, 0.0060 mmol, 2%), 17A (57 mg, 0.19 mmol, 57%); 8B (93 mg, 0.31 mmol, 93%) and 17B (5.6 mg, 0.019 mmol, 6%).

**Oxidation of model 9:** Mixtures of 9 (100 mg, 0.300 mmol), DDQ (6.8 mg, 0.030 mmol), NaNO₂ (2.1 mg, 0.030 mmol), and acetic acid (0.40 mL) in three different solvents [3.6 mL CH₂Cl₂ (A), 3.78 g [C₄C₁im]Cl (B), and 3.24 g [P₄444]Cl (C)] were stirred under an O₂ atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with ethyl acetate (3 x 10 mL) and each set of combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO₄. After evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:1) to give 9A (65 mg, 0.20 mmol, 65%), 17A (27 mg, 0.080 mmol, 27%); 9B (89 mg, 0.27 mmol, 89%) and 17B (4.7 mg, 0.014 mmol, 5%); and 9C (75 mg, 0.22 mmol, 75%) and 17C (trace).

**Oxidation of model 10:** Mixtures of 10 (100 mg, 0.313 mmol), DDQ (7.1 mg, 0.031 mmol), NaNO₂ (2.2 mg, 0.031 mmol), and acetic acid (0.40 mL) in three different solvents [3.6 mL CH₂Cl₂ (A), 3.78 g [C₄C₁im]Cl (B), and 3.24 g [P₄444]Cl (C)] were stirred under an O₂ atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with ethyl acetate (3 x 10 mL) and each set of combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO₄. After evaporating the solvent under vacuum, each of the resulting residues was subjected
to column chromatography on silica gel (EtOAc:hexanes 1:1) to give 17A (47 mg, 0.15 mmol, 48%); 10B (67 mg, 0.21 mmol, 67%) and 17B (1.3 mg, 0.0040 mmol, 1%). ¹H NMR (400 MHz, CDCl₃): δ 7.75 (dd, J₁=8.4, J₂=2.0 Hz, 1H), δ 7.69 (dd, J₁=8.5, J₂=2.0 Hz, 1H), δ 7.57 (d, J=2.0 Hz, 1H), δ 6.94 (d, J=8.3 Hz, 1H) δ 6.87-6.75 (m, 4H), δ 5.43 (dd, J₁=6.4, J₂=4.1 Hz, 1H), δ 4.17-4.03 (m, 2H), δ 3.9 (s, 3H), δ 3.73 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 195.2, 154.6, 154.4, 151.2, 146.8, 127.6, 124.2, 116.6, 114.8, 114.1, 110.7, 81.8, 63.5, 56.1, 55.7. GC-MS m/z (relative intensity): 300(M⁺-18, 2.0), 288(34), 165(0.5), 151(100), 137(9), 123(14), 108(4), 92(4), 77(6), 65(3), 52(3). HRMS (ESI) m/z [M+H]⁺ calcd for C₁₇H₁₉O₆ 319.1176, found 319.1176.

3.5.2.2 Oxidation with TEMPO/NaNO₂/O₂

Oxidation of model 2.²²³ Mixtures of 2 (50 mg, 0.20 mmol), TEMPO (8.0 mg, 0.050 mmol), NaNO₂ (12 mg, 0.17 mmol), 36% aq HCl (6.0 μL, 0.20 mmol), and NaCl (10 mg 0.17 mmol) in three different solvents [0.30 mL CH₂Cl₂ (A), 0.25 g [C₄C₁im]Cl (B), and 0.25 g [P₄₄₄₄]Cl (C)] were stirred under an O₂ atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with dichloromethane (3 x 10 mL) and each set of combined extracts was washed successively with 30% aq. Na₂S₂O₃ solution, saturated aq. NaHCO₃ solution, and water. The extracts were dried separately over MgSO₄ and after evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:5) to give 16A (47 mg, 0.18 mmol, 94%); 2B (46 mg, 0.18 mmol, 92%), 16B (1.5 mg, 0.0060 mmol, 3%) and 2C (45 mg, 0.18 mmol, 90%), 16C (2 mg, 0.008 mmol, 4%).
Oxidation of model 3: Mixtures of 3 (30 mg, 0.083 mmol), TEMPO (2.0 mg, 0.012 mmol), NaNO₂ (1.5 mg, 0.021 mmol), 36% aq HCl (2.0 μL, 0.042 mmol), and NaCl (2.5 mg 0.042 mmol) in three different solvents [1.0 mL CH₂Cl₂ (A), 0.20 g [C₆C₁₇im]Cl (B), and 0.20 g [P₄₄₄₄]Cl (C)] were stirred under an O₂ atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with dichloromethane (3 x 10 mL) and each set of combined extracts was washed successively with 30% aq. Na₂S₂O₃ solution, saturated aq. NaHCO₃ solution, and water. The extracts were dried separately over MgSO₄ and after evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:5) to give 16A (25 mg, 0.070 mmol, 84%); 3B (22 mg, 0.060 mmol, 74%); and 3C (24 mg, 0.070 mmol, 80%).

Oxidation of model 4: Mixtures of 4 (30 mg, 0.087 mmol), TEMPO (3.9 mg, 0.024 mmol), NaNO₂ (2.8 mg, 0.038 mmol), 36% aq HCl (3.0 μL, 0.23 mmol), and NaCl (4.7 mg 0.080 mmol) in three different solvents [0.60 mL CH₂Cl₂ (A), 0.63 g [C₆C₁₇im]Cl (B), and 0.54 g [P₄₄₄₄]Cl (C)] were stirred under an O₂ atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with dichloromethane (3 x 10 mL) and each set of combined extracts was washed successively with 30% aq. Na₂S₂O₃ solution, saturated aq. NaHCO₃ solution, and water. The extracts were dried separately over MgSO₄ and after evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:5) to give 4A (14 mg, 0.042 mmol, 48%) and 16A (2 mg, 0.006 mmol, 7%); 4B (27 mg, 0.080 mmol, 90%); and 4C (15 mg, 0.040 mmol, 50%).

Oxidation of model 5: Mixtures of 5 (60 mg, 0.16 mmol), TEMPO (7.7 mg, 0.024 mmol), NaNO₂ (2.8 mg, 0.038 mmol), 36% aq HCl (3.0 μL, 0.23 mmol), and NaCl (4.7 mg 0.080 mmol) in three different solvents [0.60 mL CH₂Cl₂ (A), 0.63 g [C₆C₁₇im]Cl (B), and 0.54 g [P₄₄₄₄]Cl (C)] were stirred under an O₂ atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with dichloromethane (3 x 10 mL) and each set of combined extracts was washed successively with 30% aq. Na₂S₂O₃ solution, saturated aq. NaHCO₃ solution, and water. The extracts were dried separately over MgSO₄ and after evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:5) to give 5A (14 mg, 0.042 mmol, 48%) and 5B (27 mg, 0.080 mmol, 90%).
mg, 0.048 mmol), NaNO₂ (5.5 mg, 0.080 mmol), 36% aq HCl (5.0 μL, 0.16 mmol), and NaCl (9.4 mg 0.16 mmol) in three different solvents [0.60 mL CH₂Cl₂ (A), 0.63 g [C₄Cim]Cl (B), and 0.54 g [P₄₄₄₄]Cl (C)] were stirred under an O₂ atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with dichloromethane (3 x 10 mL) and each set of combined extracts was washed successively with 30% aq. Na₂S₂O₃ solution, saturated aq. NaHCO₃ solution, and water. The extracts were dried separately over MgSO₄ and after evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:5) to give 16A (49 mg, 0.13 mmol, 82%); 5B (53 mg, 0.14 mmol, 88%), 16B (5.2 mg, 0.014 mmol, 9%) and 5C (30 mg, 0.080 mmol, 50%), 16C (26 mg, 0.070 mmol, 44%).

Oxidation of model 6: Mixtures of 6 (100 mg, 0.461 mmol), TEMPO (11 mg, 0.070 mmol), NaNO₂ (8.1 mg, 0.12 mmol), 36% aq HCl (7.0 μL, 0.23 mmol), and NaCl (13.7 mg 0.234 mmol) in three different solvents [0.60 mL CH₂Cl₂ (A), 0.63 g [C₄Cim]Cl (B), and 0.54 g [P₄₄₄₄]Cl (C)] were stirred under an O₂ atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with dichloromethane (3 x 10 mL) and each set of combined extracts was washed successively with 30% aq. Na₂S₂O₃ solution, saturated aq. NaHCO₃ solution, and water. The extracts were dried separately over MgSO₄ and after evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:5) to give 17A (95 mg, 0.45 mmol, 96%); 6B (98 mg, 0.46 mmol, 98%), 17B (trace) and 6C (93 mg, 0.43 mmol, 93%), 17C (trace).
Oxidation of model 7: Mixtures of 7 (100 mg, 0.314 mmol), TEMPO (7.5 mg, 0.047 mmol), NaNO₂ (5.4 mg, 0.078 mmol), 36% aq HCl (5.0 μL, 0.16 mmol), and NaCl (9.2 mg, 0.16 mmol) in three different solvents [0.60 mL CH₂Cl₂ (A), 0.63 g [C₄C₁im]Cl (B), and 0.54 g [P₄₄₄₄]Cl (C)] were stirred under an O₂ atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with dichloromethane (3 x 10 mL) and each set of combined extracts was washed successively with 30% aq. Na₂S₂O₃ solution, saturated aq. NaHCO₃ solution, and water. The extracts were dried separately over MgSO₄ and after evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:3) to give 17A (87 mg, 0.27 mmol, 88%); 7B (90 mg, 0.28 mmol, 90%) and 7C (75 mg, 0.24 mmol, 75%).

Oxidation of model 9: Mixtures of 9 (100 mg, 0.300 mmol), TEMPO (7.2 mg, 0.045 mmol), NaNO₂ (5.2 mg, 0.075 mmol), 36% aq HCl (5.0 μL, 0.15 mmol), and NaCl (8.8 mg, 0.15 mmol) in three different solvents [0.60 mL CH₂Cl₂ (A), 0.63 g [C₄C₁im]Cl (B), and 0.54 g [P₄₄₄₄]Cl (C)] were stirred under an O₂ atmosphere (1 atm) at 25 °C for 19 h. The mixtures were extracted separately with dichloromethane (3 x 10 mL) and each set of combined extracts was washed successively with 30% aq. Na₂S₂O₃ solution, saturated aq. NaHCO₃ solution, and water. The extracts were dried separately over MgSO₄ and after evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:1) to give 17A (52 mg, 0.16 mmol, 53%); 9B (53 mg, 0.16 mmol, 53%) and 9C (80 mg, 0.24 mmol, 80%).
3.5.2.3 Oxidation with TPPFeCl

**Oxidation of model 1:** Mixtures of 1 (50 mg, 0.25 mmol), TPPFeCl (6.0 mg, 0.0025 mmol), t-BuOOH (70% aq solution, 15 μL, 0.25 mmol), and 0.1N phosphate buffer, pH 3 (1.5 mL) in three different solvents [0.50 mL CH₃CN (A), 0.20 g [C₄C¹im]Cl (B), and 0.20 g [P₄₄₄₄]Cl (C)] were stirred at 25 °C for 14 h. The mixtures were extracted separately with EtOAc (3 x 5 mL) and each set of combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO₄. After evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:9) to give 1A (48 mg, 0.24 mmol, 89%) and 16A (3.8 mg, 0.018 mmol, 7%); 1B (47 mg, 0.24 mmol, 87%) and 16B (4.8 mg, 0.020 mmol, 9%); 1C (45 mg, 0.23 mmol, 85%) and 16C (5.9 mg, 0.030 mmol, 11%).

**Oxidation of model 2:** Mixtures of 2 (50 mg, 0.19 mmol), TPPFeCl (5.0 mg, 0.0050 mmol), t-BuOOH (70% aq solution, 27 μL, 0.47 mmol), and 0.1N phosphate buffer, pH 3 (1.5 mL) in three different solvents [0.50 mL CH₃CN (A), 0.20 g [C₄C¹im]Cl (B), and 0.20 g [P₄₄₄₄]Cl (C)] were stirred at 25 °C for 14 h. The mixtures were extracted separately with EtOAc (3 x 5 mL) and each set of combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO₄. After evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:9) to give 2A (18 mg, 0.070 mmol, 36%), 16A (20 mg, 0.080 mmol, 41%), 18A (4.2 mg, 0.016 mmol, 8%), and 19A (4.7 mg, 0.017 mmol, 9%); 2B (15 mg, 0.060 mmol, 30%), 16B (20 mg, 0.080 mmol, 40%), 18B (4.7 mg, 0.017 mmol, 9%), and 19B (8.9 mg, 0.033 mmol, 17%); 2C (13 mg, 0.050 mmol, 26%), 16C (22 mg, 0.090 mmol, 44%), 18C (5.3 mg, 0.019 mmol, 10%), and 19C (9.4 mg, 0.035 mmol, 18%).
Oxidation of model 3: Mixtures of 3 (30 mg, 0.083 mmol), TPPFeCl (2.3 mg, 0.0025 mmol), t-BuOOH (70% aq solution, 24 μL, 0.17 mmol), and 0.1N phosphate buffer, pH 3 (1 mL) in three different solvents [0.40 mL CH₃CN (A), 0.20 g [C₄Cl₁im]Cl (B), and 0.20 g [P₄₄₄₄]Cl (C)] were stirred at 25 ºC for 14 h. The mixtures were extracted separately with EtOAc (3 x 5 mL) and each set of combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO₄. After evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:9) to give 3A (10 mg, 0.029 mmol, 35%), 16A (9 mg, 0.02 mmol, 30%); 3B (21 mg, 0.060 mmol, 70%), 16B (6.3 mg, 0.017 mmol, 21%).

Oxidation of model 5: Mixtures of 5 (70 mg, 0.19 mmol), TPPFeCl (6.0 mg, 0.0060 mmol), t-BuOOH (70% aq solution, 51 μL, 0.37 mmol), and 0.1N phosphate buffer, pH 3 (2 mL) in three different solvents [0.60 mL CH₃CN (A), 0.30 g [C₄Cl₁im]Cl (B), and 0.30 g [P₄₄₄₄]Cl (C)] were stirred at 25 ºC for 14 h. The mixtures were extracted separately with ethyl acetate (3 x 10 mL) and each set of combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO₄. After evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:CH₂Cl₂ 1:14) to give 5A (32 mg, 0.085 mmol, 46%), 16A (25 mg, 0.070 mmol, 36%), 18A (9.4 mg, 0.024 mmol, 13%), and 19A (2.1 mg, 0.0050 mmol, 3%); 5B(36 mg, 0.090 mmol, 51%), 16B (24 mg, 0.060 mmol, 34%) and 19B (8.7 mg, 0.023 mmol, 12%); 5C (41 mg, 0.11 mmol, 59%), 16C (16 mg, 0.040 mmol, 23%) and 19C (10 mg, 0.026 mmol, 14%).

Oxidation of model 6: Mixtures of 6 (100 mg, 0.470 mmol), TPPFeCl (4.3 mg, 0.0047 mmol), t-BuOOH (70% aq solution, 64 μL, 0.47 mmol), and 0.1N phosphate buffer,
pH 3 (3 mL) in three different solvents [1.0 mL CH₃CN (A), 1.05 g [C₄C₁im]Cl (B), and 0.90 g [P₄₄₄₄]Cl (C)] were stirred at 25 °C for 14 h. The mixtures were extracted separately with EtOAc (3 x 10 mL) and each set of combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO₄. After evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:5) to give 6A (58 mg, 0.27 mmol, 58%) and 17A (40 mg, 0.19 mmol, 41%); 6B (67 mg, 0.31 mmol, 67%) and 17B (28 mg, 0.13 mmol, 28 %) and 6C (50 mg, 0.23 mmol, 50%) and 17C (46 mg, 0.22 mmol, 47 %).

**Oxidation of model 7:** Mixtures of 7 (100 mg, 0.310 mmol), TPPFeCl (2.9 mg, 0.0031 mmol), t-BuOOH (70% aq solution, 43 μL, 0.31 mmol), and 0.1N phosphate buffer, pH 3 (3 mL) in three different solvents [1.0 mL CH₃CN (A), 1.05 g [C₄C₁im]Cl (B), and 0.90 g [P₄₄₄₄]Cl (C)] were stirred at 25 °C for 14 h. The mixtures were extracted separately with ethyl acetate (3 x 10 mL) and each set of combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO₄. After evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:3) to give 7A (68 mg, 0.22 mmol, 68%) and 16A (22 mg, 0.070 mmol, 22%); 7B (72 mg, 0.23 mmol, 72%) and 16B (9.4 mg, 0.030 mmol, 9.5%); and 7C (58 mg, 0.18 mmol, 58%) and 16C (25 mg, 0.080 mmol, 25%).

**Oxidation of model 9:** Mixtures of 9 (100 mg, 0.470 mmol), TPPFeCl (4.3 mg, 0.0047 mmol), t-BuOOH (70% aq solution, 64 μL, 0.47 mmol), and 0.1N phosphate buffer, pH 3 (3 mL) in three different solvents [1.0 mL CH₃CN (A), 1.05 g [C₄C₁im]Cl (B), and 0.90 g [P₄₄₄₄]Cl (C)] were stirred at 25 °C for 14 h. The mixtures were extracted separately with ethyl acetate (3 x 10 mL) and each set of
combined extracts was washed with saturated aq. NaCl solution, then dried over MgSO₄. After evaporating the solvent under vacuum, each of the resulting residues was subjected to column chromatography on silica gel (EtOAc:hexanes 1:5) to give 9A (55 mg, 0.16 mmol, 55%) and 17A (37 mg, 0.11 mmol, 38%); 9B (69 mg, 0.21 mmol, 69%) and 17B (22 mg, 0.070 mmol; 22%) and 9C (64 mg, 0.19 mmol, 64%) and 17C (30 mg, 0.090 mmol, 30%). ¹H NMR (400 MHz, CDCl₃): δ 7.75 (dd, J₁=8.4, J₂=2.0 Hz, 1H), δ 7.57 (d, J=2.0 Hz, 1H), δ 6.88 (d, J=8.5 Hz, 1H), δ 6.87-6.75 (m, 4H), δ 5.43 (dd, J₁=6.1, J₂=4.2 Hz, 1H), δ 4.17-4.04 (m, 2H), δ 3.94 (s, 3H), δ 3.89 (s, 3H), δ 3.73 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 195.3, 154.6, 154.1, 151.4, 149.2, 127.9, 123.6, 116.6, 114.8, 110.8, 110.1, 82.0, 63.6, 56.1, 55.9, 55.6. GC-MS m/z (relative intensity): 314(M⁺-18, 1.0), 302(25), 284(1.0), 207(0.5), 165(100), 151(8), 137(5), 123(5), 107(5), 92(4), 77(7), 65(2), 51(2). HRMS (ESI) m/z [M+H]⁺ calcd for C₁₈H₂₁O₆ 333.1333, found 333.1332.
Chapter 4. OXIDATIVE DEPOLYMERIZATION OF KRAFT LIGNIN

Note: This chapter was taken from the following papers:
1) Yao, S. G.; Meier, M. S.; Pace, R. III B.; Crocker, M. A comparison of the oxidation of lignin model compounds in conventional and ionic liquid solvents and application to the oxidation of lignin. RSC Adv., 2016, 6, 104742.
2) Yao, S. G.; Mobley, J. K.; Meier, M. S.; Ralph, J.; Crocker, M.; Parkin, S.; Selegue, J., Mechanochemical treatment facilitates two-step oxidative depolymerization. (Just submitted to ACS for publication)

4.1 Introduction

As pointed out in Chapter 1, lignin is an abundant renewable resource but which needs to be depolymerized if it were to be of greater and more valuable applications. Lignin depolymerization is certainly a challenging endeavor, and great efforts have been put in by different groups, achieving different levels of limited success. Numerous options are available in depolymerizing lignin, depending on the intended purpose for the end products. Our group opted for an oxidative approach from which we aim to derive functionalized aromatic compounds either for direct application and use, or for further conversion into bulk and fine aromatic chemicals. In this chapter, we describe our oxidative approach to lignin depolymerization and highlight the preliminary considerations we looked into in an effort to overcome the challenges that are associated with the process.

4.2 Oxidation of Indulin Kraft Lignin With TPPFeCl: Conventional vs Ionic Liquid Solvent

As mentioned previously (Section 3.1.3) iron porphyrin complexes have been identified components of the oxidases that are present in the white rot fungus Phanerochaete chrysosporium which is accountable for the natural biodegradation of lignin. Several biomimetic studies have employed different forms of porphyrin catalysts to
mimic ligninase in the oxidation of lignin and lignin model compounds. In addition, iron porphyrin oxidation of lignin model compounds in ionic liquid has also been studied, and recently, an ionic liquid tagged porphyrin, designed for oxidation of lignin, has been synthesized and tested on a lignin model compound.

In the current work, porphyrin was selected as catalyst in studying the oxidation of lignin in the ionic liquids [C₄C₁im]Cl /[P₄444]Cl based on the observed similarity in oxidation rates of lignin model compounds in MeCN and in the ionic liquids. Oxidation of Kraft lignin was carried out by treating the polymer with TPPFeCl and t-BuOOH (70% aq solution) separately in three different solvents ( MeCN/[C₄C₁im]Cl /[P₄444]Cl) and phosphate buffer (0.1N, pH 3) at room temperature for 14 h. The goal is to compare porphyrin oxidation of lignin in MeCN and in the ILs [C₄C₁im]Cl and [P₄444]Cl.

4.3 Oxidation of Indulin Kraft Lignin With PPFeeCl: The Effect of Mechanochemical Treatment

The first step in lignin utilization is isolation of the polymer from lignocellulosic biomass. This process typically involves pretreatment, usually including milling which powderizes the raw biomass, reducing the particle size to 0.8 mm or less, and helps maximize the amount of extracted lignin. In general, the more extensive the milling, the more lignin can be extracted from the biomass. However, mechanical treatment of the biomass is known to significantly alter the chemical composition of the lignin. This includes a decrease in molecular weight and polydispersity, as well as an increase in the carbonyl functionality and cleavage of aryl ether (β-O-4) linkages, with an accompanying increase in phenolic OH content. When applied in the presence of hydroxide ion (e.g. NaOH), mechanical treatment facilitates depolymerization of lignin.
into oligomers and monomers, degradation of lignin and wood into lower molecular weight fragments, as well as depolymerization of cellulose and hemicellulose into monomeric carbohydrates. Mechanical treatment has also proven to make cellulose more accessible to enzymatic hydrolysis and fermentation, due to decreased particle size and loosened cellulose fiber structure. However, due to the associated cost - basically arising from the high-energy requirement in reducing particle size, milling is not recommended for use as a stand-alone pretreatment approach, but can be combined with other methods including chemical and physicochemical procedures.

An example of a combined pretreatment approach is the mechanochemical method. This process typically involves solvent-free reactions in the solid state and is often performed in ball mills where reactant mixtures can be efficiently mixed and subjected to significant energy input.

In this work, we apply a mechanochemical method as a strategy to promote lignin depolymerization. Specifically, we employ mechanochemical treatment as a preliminary step to porphyrin lignin oxidation which is the first step in our two-oxidation step approach to lignin depolymerization.

We applied mechanochemical treatment to Indulin AT kraft lignin (KL) by ball milling in the presence of potassium hydroxide and toluene. Toluene was added as it has been found to help with vibratory ball milling by preventing the milled material from adhering around the steel ball. We monitored changes in the structure of the lignin using IR and HSQC NMR spectroscopies.
4.4 The Two-Oxidation Step Lignin Depolymerization: The Effect of Mechanochemical Treatment

Overall, we sought to determine how the addition of mechanochemical pretreatment step affects the success of our two-step oxidative approach to lignin depolymerization. The method consists of initial oxidation of the benzylic hydroxyl groups to carbonyl groups using the TPPFeCl/t-BuOOH catalyst system. This is followed by Baeyer-Villiger (BV) oxidation of ketones to esters with HCOOH/H₂O₂, and the esters then hydrolyze in situ to carboxylic acids and phenols (Scheme 4.1).²²³

Scheme 4.1. Reaction sequence for two-oxidation step lignin depolymerization.

4.5 Results and Discussion

4.5.1 Oxidation of Indulin Kraft Lignin With TPPFeCl: Conventional vs Ionic Liquid Solvent

Initial results, based on KBr-FTIR absorption spectra from the porphyrin oxidation of Kraft lignin separately in MeCN, [C₄C₁im]Cl and [P₄₄₄₄]Cl, showed evidence of lignin oxidation in both the conventional and ionic liquid solvents, as shown by the appearance of additional absorption bands/shoulders in the carbonyl region, ~1707-1713 cm⁻¹, coupled
with an increase in intensity of the absorption bands in the same region (Fig.4.1). These new bands fall within the range of the spectral window where lignin carbonyl bands have been observed.\textsuperscript{324-339}

![Figure 4.1. IR spectra of kraft lignin before and after oxidation with TPPFeCl/t-BuOOH in different solvents. The carbonyl region is shown with an arrow.](image)

Additional results, based on \textsuperscript{1}H NMR experiment showed a signal at around 7.8 ppm (Fig. 4.2) in the post-oxidation spectra of oxidation reactions carried out in ILs. A similar signal was also observed in the \textsuperscript{1}H NMR spectrum of the Swern-oxidized model compound 3 (Appendix A ), indicating that lignin has indeed been oxidized, as what FTIR data showed. Specifically, the \textsuperscript{1}H NMR at about 7.8 ppm is indicative of benzylic OH group
oxidation to ketone as observed in the Swern oxidation of 3. This signal was not observed, though, in the post-oxidation spectrum in the conventional solvent, possibly due to the lower solubility of lignin in this solvent. We were not able to observe evidence of lignin oxidation in either solvent by $^{13}$C or HSQC NMR spectroscopy. It’s possible that the extent of oxidation is not sufficient to show in these low-sensitivity measurements.

![Image of NMR spectra](image_url)

Figure 4.2. $^1$H NMR spectra of Kraft lignin before and after oxidation with TPPFeCl/\text{-}BuOOH in different solvents. Resonances at 7.8 ppm (circled) are consistent with the formation of benzylic ketones.

### 4.5.2 Mechanochemical Treatment of Indulin Kraft Lignin

Mechanical treatment is one of the most commonly used pretreatment methods in the processing of biomass.$^{176,340}$ Pretreatment is done to activate the material being processed for the chemical interactions that would follow. Mechanical treatment, which is usually done by grinding or milling, reduces particle size and increases the available surface area of the treated material. This process can increase the reactivity of the treated material by ten times or even more.$^{341}$ One of the known beneficial effects of mechanical
treatment of biomass is the loosening of cellulose fibrillary structure which makes it more accessible to enzymatic hydrolysis and fermentation.\textsuperscript{210,320-322} In addition, it has been shown that mechanical treatment of biomass significantly alters the chemical composition of lignin, including a decrease in molecular weight\textsuperscript{315} and polydispersity,\textsuperscript{316} as well as an increase in the carbonyl functionality\textsuperscript{315} and cleavage of aryl ether (\(\beta\)-O-4) linkages,\textsuperscript{212,317-319} with an accompanying increase in phenolic-OH content.\textsuperscript{316}

Recently, Ikeda and his co-workers\textsuperscript{317} studied the effect of ball milling on lignin structure. They observed that dry vibratory ball milling under a nitrogen atmosphere caused substantial structural changes in lignin, including some condensation reactions, whereas vibratory ball milling in toluene had little effect on lignin structure.

The use of alkali is another common pretreatment method for biomass processing.\textsuperscript{176} It has also been used in the depolymerization of lignin (Section 1.2.2). In a recent study, Kleine and his co-workers\textsuperscript{212} combined the two pretreatments discussed above (ball milling and use of alkali such as NaOH and KOH) and designed a base-assisted ball milling process as a possible mechanochemical technique of degrading lignin and wood. The procedure is solvent-free which eliminates concerns about solubility. They observed that bonds in lignin were cleaved, providing fragments of lower molecular weight and cellulose and hemicellulose were hydrolyzed to sugar monomers.

In a more recent study, Brittain \textit{et al.}\textsuperscript{220} applied a similar mechanochemical method to depolymerize lignin. They observed that ball milling with alkali depolymerizes lignin but that the amount of monomer products is limited by condensation reactions. However, they found that addition of methanol quenches the reactive intermediates that tend to undergo condensation, and thus prevents condensation reactions from taking place. In
addition, they found that increasing the moisture content by the addition of a small amount of water could also increase formation of monomers by enhancing base-catalyzed hydrolysis of lignin. The major monomer products they obtained include phenol, guaiacol, and syringol in a maximum total monomer yield of about 42%, as quantified by LC-MS.

In the current work, we applied mechanochemical method by ball milling lignin with KOH and toluene in hope that additional bonds in the polymer would be cleaved and that new sites for oxidation would emerge.

After 1-2 days of ball milling, significant growth was observed in the IR spectral band of the ball milled Kraft lignin (KLBM) at 1715-1700 cm\(^{-1}\), indicating an increase in the carbonyl functionality. When a sample of KLBM was stirred with NaBH\(_4\), a decrease in intensity of the above-mentioned spectral band was observed, consistent with the behavior of the carbonyl functionality (Fig. 4.3). A well-defined peak is still visible at around 1715 cm\(^{-1}\) after borohydride reduction, possibly because the reaction mixture requires longer stirring with the reductant.
Fig. 4.3 IR spectra of KL, of ball-milled KL (KLBM), and of the NaBH₄ reduction product.

4.5.3 Effect of Mechanochemical Treatment on Porphyrin Oxidation of Lignin

In order to determine how the mechanochemical treatment affects the efficiency of catalytic oxidation of lignin benzylic hydroxyl groups, both KLBM and KL were oxidized with the TPPFeCl₃/t-BuOOH catalyst system. This was carried out by stirring TPPFeCl₃, t-BuOOH (70% aqueous), phosphate buffer (pH 3), and MeCN for 26 h at room temperature (Scheme 4.2).²²³
Scheme 4.2. Porphyrin oxidation, the first oxidation step towards lignin depolymerization, converts Cα hydroxyl groups to ketones.

We followed the progress of oxidation by measuring IR spectra at several time intervals. After 19 h of reaction time, we observed that the intensity of the carbonyl spectral band for KL (1722 cm\(^{-1}\)) almost doubled, while that for KLBM (1731 cm\(^{-1}\)) roughly tripled in intensity (Fig. 4.4). After stirring overnight (\textit{ca.} 26 h), the carbonyl spectral band intensity for KLBM (1731 cm\(^{-1}\)) increased very little, suggesting that the maximum extent of oxidation under these conditions had been reached. While the carbonyl band intensity for KL (1729 cm\(^{-1}\)) nearly tripled at this same time relative to that of the starting material, the intensity remained somewhat lower than observed in KLBM at 19 h of reaction time, reflecting the lower reactivity of KL compared to KLBM.
In order to confirm that lignin has indeed been oxidized, we treated both the porphyrin-oxidized KL and KLBM with NaBH₄. To our satisfaction, the carbonyl absorption band at around 1730 cm⁻¹ decreased significantly in intensity for both lignin samples, demonstrating that the oxidation reaction had been reverted by borohydride reduction (Fig. 4.5).

Figure 4.4. IR spectra on parallel porphyrin oxidation of KLBM and KL.
The effects of mechanochemical treatment of KL and the oxidation of lignin are clearly demonstrated in the aforementioned IR experiments (Fig. 4.3, Fig. 4.4, and Fig. 4.7). All these IR spectra show that the intensity of the carbonyl absorption band at around 1700 cm\(^{-1}\) had increased significantly after ball milling. Moreover, it is shown in Fig. 4.4 that the ball milled KL had exhibited a higher reactivity towards porphyrin oxidation than the KL that was not ball milled. Finally, Fig. 4.5 shows that the porphyrin-oxidized KL and KLBM had been reverted by borohydride reduction, demonstrating that said lignin samples had indeed been oxidized.

We then performed HSQC NMR experiments to examine changes in the lignin after mechanochemical treatment and after subsequent porphyrin oxidation. The
resulting spectra was divided into aliphatic (~ < 6 ppm) and aromatic (~ > 6 ppm) regions. The aliphatic region is where lignin units with their characteristic inter-unit linkages are typically profiled, including β-O-4, β-5 and β-β. Changes in the cross-peaks representing these linkages - like a decrease in peak size, or better yet, complete disappearance of peaks - are indicative of lignin degradation. On the other hand, the aromatic region provides insight on possible oxidation of the α-carbon, the effect of which is observed in the aromatic ring. Here we expect to be able to observe cross-peaks representing the aromatic protons of guaiacyl (G), the predominant monolignol comprising Kraft lignin. Again, partial or complete disappearance of G proton cross-peaks and replacement with proton peaks for oxidized guaiacyl (G’) provide direct evidence of lignin oxidation.

Fig. 4.6 (Frames I-VII) shows the aliphatic region HSQC spectra of lignin samples before and after ball milling, porphyrin oxidation, and borohydride reduction. Shown right below are the structures of the oxidized and unoxidized forms of the lignin linkages mentioned in the preceding paragraph for reference.
Figure 4.6. Lignin linkages profiled in the HSQC spectra aliphatic region of the different lignin samples.

Note: All the HSQC spectra shown in Figures 4.6 and 4.7 were obtained for us by Dr. Justin Mobley, using the NMR facility at the University of Wisconsin, Madison, WI, with the approval and consent of Dr. John Ralph.
I. Indulin AT Kraft Lignin

II. Ball Milled Indulin AT Kraft Lignin
Frame I in Fig. 4.6 shows the HSQC spectrum for KL, where units characterized by linkages including β-O-4 (A), β-5 (B), and β-β (C) are visible. Similar units are also evident in KLBM (Frame II). After porphyrin oxidation (Frames III and IV), the cross-peaks representing the aforementioned units were of noticeably lower intensity (in most cases completely absent), suggesting that nearly all of the aliphatic alcohols, or at least all of the benzylic ones, present in KL had been oxidized. Indeed, the absence of a cross-peak representing Aβ of the β-O-4 unit suggests that the peak at ca. 4.9/71 ($\delta_H/\delta_C$, Frames III and IV of figure 4.6) does not represent Aα but rather some unknown structure.
III. Porphyrin-Oxidized Indulin AT Kraft Lignin

IV. Porphyrin-Oxidized Ball Milled Indulin AT Kraft Lignin
Frames V and VI in Fig. 4.6 show the aliphatic region spectra for the porphyrin-oxidized KL and KLBM, respectively, after stirring with NaBH₄. To our delight, some of the cross-peaks for the normal units reappeared in the HSQC spectra and the cross-peaks representing the oxidized units were gone. These changes in the cross-peaks in the aliphatic region of the HSQC spectra (before and after porphyrin oxidation (Frames III and IV), as well as after subsequent treatment with NaBH₄ (Frames V and VI), are consistent with oxidation of lignin by the porphyrin catalyst, and demonstrate that such oxidation can be reverted, to a significant extent, by borohydride reduction.

V. NaBH₄-Reduced Porphyrin-Oxidized Indulin AT Kraft Lignin
VI. NaBH₄-Reduced Porphyrin-Oxidized Ball Milled Indulin AT Kraft

VII. NaBH₄-Reduced Ball Milled Indulin AT Kraft Lignin
Porphyrin-oxidized KLBM was likewise stirred with NaBH₄ (Frame VII,) after which the cross-peaks for the different linkages noticeably became smaller, compared to those in KLBM, consistent with results of IR experiment (Fig. 4.3) showing an enhancement of carbonyl functionality in KL after ball milling.

Fig. 4.7 (Frames I'-VII') shows the corresponding aromatic region HSQC spectra of the different lignin samples described above. The structures of the compounds represented by the cross-peaks in the spectra are shown below.

Figure 4.7. Lignin units represented in the HSQC spectra aromatic region of the different lignin samples.
I'. Indulin AT Kraft Lignin

II'. Ball Milled Indulin AT Kraft Lignin
The cross-peaks at 6-8 ppm/110-140 ppm (δH/δC, Frames I’-VII’ of figure 4.7) represent the aromatic protons of the unoxidized (G) and oxidized (G’) forms of guaiacyl. It will be noted that the oxidized form of guaiacyl units (G’: G’2, G’5, and especially G’6) are nearly absent in the spectrum of the unmodified KL (Frame I’), but are noticeably present in that for KLBM (Frame II’). This indicates that partial oxidation of KL had occurred during ball milling. After porphyrin oxidation (Frames III’ and IV’), the cross-peaks corresponding to unoxidized guaiacyl (G) units became smaller, while those corresponding to oxidized guaiacyl units (G’, especially G’6), became significantly larger, as is consistent with nearly complete oxidation of the α-carbons.
III’. Porphyrin-Oxidized Indulin AT Kraft Lignin

IV’. Porphyrin-Oxidized Ball Milled Indulin AT Kraft Lignin
Then, after treatment with NaBH₄ (Frames V’ and VI’), most of the signals for oxidized guaiacyl (G’) had disappeared, indicating that those units had been reduced back to normal guaiacyl (G) units, lending support to the observation of porphyrin oxidation of lignin, and at the same time re-affirming that such oxidation can easily be reversed by borohydride reduction.

V’. NaBH₄-Reduced Porphyrin-Oxidized Indulin AT Kraft Lignin
VI'. NaBH₄-Reduced Porphyrin-Oxidized Ball Milled Indulin AT Kraft

VII'. NaBH₄-Reduced Ball Milled Indulin AT Kraft Lignin
Frame VII’ of Fig. 4.7 shows the aromatic region HSQC spectrum of KLBM after borohydride reduction. Clearly, all the peaks for the oxidized guaiacyl (G’) had disappeared.

4.5.4 Effect of mechanochemical treatment on Baeyer-Villiger reaction

Next we investigated the effect of the mechanochemical pretreatment on the outcome of the Baeyer-Villiger (BV) oxidation step of our two-step oxidative lignin depolymerization method (Scheme 4.3). This was done to determine if mechanochemical treatment results in a more efficient oxidative deconstruction of lignin.

Scheme 4.3. Baeyer-Villiger oxidation, the second oxidation step, further oxidizes the Cα ketone to an ester and cleaves the Cα-Cβ bond through hydrolysis of the resulting ester.

As a starting point, we looked at the extent of Cα oxidation of the lignin samples at the beginning of the BV oxidation. As shown in Fig. 4.8, the intensity of the carbonyl absorption band of KL (around 1700 cm⁻¹) is low to start with, the intensities of those
bands in Porp-KL and Porp-KLBM (1735 cm⁻¹ and 1725 cm⁻¹, respectively) are much higher, while that of KLBM (1715 cm⁻¹) is somewhere in between. An excess amount of oxidant was used in the oxidation of KL in order to see if the more heavily oxidized KL produced better yields of monomer products than Porp-KLBM, even without mechanochemical treatment.

Figure 4.8. IR Spectra of the starting materials used in BV oxidation: absorption band frequency in cm⁻¹ enclosed in parentheses.

The lignin samples (KL, KLBM, Porp-KL and Porp-KLBM) were subjected to BV oxidation by heating with formic acid and hydrogen peroxide at 50°C for 70 h. After oxidation, each reaction mixture was treated with BF₃•OEt₂ and methanol to esterify any carboxylic acids that had been formed, then extracted with water and with ethyl acetate. The water-soluble fractions were back-extracted with ethyl acetate and
thus, four fractions were produced from each BV reaction mixture: material that is only water soluble, material that is both water and ethyl acetate soluble, material that is only soluble in ethyl acetate, and insoluble material. The amount of material in each fraction is given in Table 4.1.

Table 4.1. Fractionation of Baeyer-Villiger oxidation mixtures by solubility.

<table>
<thead>
<tr>
<th>Sample</th>
<th>$\text{H}_2\text{O}$</th>
<th>$\text{H}_2\text{O} &amp; \text{EtOAc}$</th>
<th>EtOAc</th>
<th>Insoluble</th>
</tr>
</thead>
<tbody>
<tr>
<td>KL</td>
<td>31%</td>
<td>20%</td>
<td>0.2%</td>
<td>46%</td>
</tr>
<tr>
<td>KLBM</td>
<td>38%</td>
<td>17%</td>
<td>2%</td>
<td>42%</td>
</tr>
<tr>
<td>Porp-KL</td>
<td>65%</td>
<td>19%</td>
<td>7%</td>
<td>12%</td>
</tr>
<tr>
<td>Porp-KLBM</td>
<td>44%</td>
<td>19%</td>
<td>6%</td>
<td>32%</td>
</tr>
</tbody>
</table>

The amount of the water-soluble fraction (Table 4.1 column 1, presumably small, polar molecules) obtained from the product mixtures correlates with the degree of Cα oxidation at the start of the BV oxidation. Analysis of the material that was soluble in both water and ethyl acetate (column 2) was revealing. From each of these samples we were able to isolate two compounds (Fig. 4.9), one of which was readily identified as methyl vanillate ($\text{1}$). The other was identified by NMR spectroscopy and X-ray crystallography as methyl 5-carbomethoxyvanillate ($\text{2}$). The yields of $\text{1}$ and $\text{2}$, isolated from the reaction mixtures, are shown in Table 2. The rest of the material in these fractions is likely to be dimeric/trimeric/oligomeric products.$^{342}$
Compounds 1 and 2 are similar to monomer products that have previously been identified from transformed lignin. Indeed, Villar obtained vanillin and vanillic acid from alkaline oxidation of softwood lignin, and syringaldehyde and syringic acid were also obtained from hardwood lignin. Under acidic oxidation conditions, Werhan detected vanillin and 1 as major products, along with methyldehydroabietate and five additional monomers, one of which was believed to be 2. Assmann adopted Werhan’s acidic oxidation procedure for a supercritical extraction study and recovered similar monomer products to Werhan.

Table 4.2. Yields of 1 and 2.

<table>
<thead>
<tr>
<th>BV Sample</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>KL</td>
<td>1.5%</td>
<td>0.2%</td>
</tr>
<tr>
<td>KLBM</td>
<td>2.2%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Porp-KL</td>
<td>2%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Porp-KLBM</td>
<td>7.8%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

Compound 2 appears to be an electrophilic substitution product of 1. When pure 1 was subjected to Baeyer-Villiger oxidation conditions (HCO₂H, H₂O₂), a small amount of 2 was detected. The presence of the vanillic acid moiety is evident in the aromatic region of the HSQC spectra (Fig 4.5 Frames A’ to F-1’). The absence of these signals in F2’ suggests that any free vanillic acid had been washed out in the basic
reaction mixture.

As shown by the results in Tables 4.1 and 4.2, all the lignin samples we investigated underwent depolymerization to some extent, including the as-received lignin KL (1.7%). This yield is consistent with the presence of carbonyl functionality in Kraft lignin, as reported previously.\textsuperscript{345,346} For KLBM and Porp-KL, total yields of 1 and 2 are the same, suggesting that mechanochemical treatment and porphyrin oxidation have more or less the same effect on the efficiency of the two-step lignin depolymerization process. However, the significantly higher total yield of 1 and 2 (10%) obtained from Porp-KLBM is quite noticeable, because at the start of the BV step this sample showed a lower initial extent of C\textsubscript{a} oxidation than Porp KL, yet produced significantly more monomeric products. These results demonstrate what appears to be a synergistic positive effect of mechanochemical treatment and porphyrin oxidation on the overall lignin depolymerization. In a large and complex molecule like lignin, a high degree of C\textsubscript{a} oxidation is not sufficient for the BV reaction to efficiently produce monomeric products. Reduced particle size brought about by mechanochemical treatment, or potentially mechanical shearing of the polymer itself, significantly improved the efficiency of the two-oxidation step lignin depolymerization.

4.6 Conclusions

The TPPFeCl/\text{}-BuOOH catalyst system brought about partial oxidation of Kraft lignin in conventional (MeCN) and ionic liquid ([C\textsubscript{4}C\textsubscript{1}im]Cl and [P\textsubscript{4444}]Cl) solvents. The extent of oxidation was enough to be observable in a KBr-FTIR experiment but not
enough to be detected in the less sensitive HSQC technique. In the ionic liquid solvents, the extent of oxidation was sufficient to be seen under \(^1\)H NMR experiment.

Mechanochemical treatment with KOH and toluene resulted in an increase in the carbonyl content in Indulin AT Kraft lignin, as shown by a growth in the absorption band at 1715-1700 cm\(^{-1}\) in the IR spectra of KLBM. Treatment of KLBM with NaBH\(_4\) caused a decrease in intensity of the carbonyl absorption band, consistent with reduction of the carbonyl functionality and demonstrates that oxidation of lignin is reversible.

The enhanced carbonyl content and presumably the reduced particle size of lignin brought about by mechanochemical treatment, or potentially mechanical shearing of the polymer itself, improved the efficiency of two-step oxidative depolymerization, as demonstrated by HSQC NMR experiments and by isolation of monomeric products. Lignin linkage degradation was promoted through a first oxidation step using the TPPFeCl/\(t\)-BuOOH catalyst system, while depolymerization to aromatic monomers was achieved via Baeyer-Villiger oxidation.

## 4.7 Experimental Section

Ball milling was done at 25 Hz in a RETSCH Ball Mill model MM2 equipped with a 1-cm diameter stainless steel ball. IR spectra were measured in KBr pellets.

**Mechanochemical treatment of KL to form KLBM**

Kraft lignin was ball milled with KOH (KL/KOH = 2:1 w/w) and toluene (enough to cover the steel ball) at 25 Hz for 2-3 days. The ball milled lignin was dispersed in water, then acidified with 0.2M HCl until precipitation of lignin took place. The precipitated lignin was recovered by vacuum filtration, washed with deionized
water until the washings were pH neutral, and then dried in a vacuum oven overnight at 80 °C.

**Reduction of KLBM**

To a solution of KLBM in 1% NaOH was added NaBH₄ (KLBM/NaBH₄ = 1:2 w/w) and the resulting mixture was stirred overnight at room temperature. The excess NaBH₄ was quenched with 0.2M HCl and the reduced KLBM was filtered, washed with deionized water until the washings were pH neutral, and then dried in a vacuum oven overnight at 80 °C.

**Oxidation with TPPFeCl/t-BuOOH**

A mixture consisting of 26 mg TPPFeCl, 10 mL t-BuOOH, 30 mL phosphate buffer (pH 3), and 10 mL MeCN for every 1 gram of lignin was stirred at room temperature for 4-5 days. The mixture was acidified with 0.2 M HCl until precipitation occurred. The precipitated, oxidized lignin was recovered by vacuum filtration, washed with deionized water until the washings were pH neutral, and then dried in a vacuum oven overnight at 80 °C.

**Baeyer-Villiger oxidation**

A mixture consisting of 2 mL HCOOH (95%), 3.4 mL H₂O₂ (30%), and 2.7 mL H₂O for every 1 g of lignin was stirred at 50 °C for 70 hours. Deionized water was added until the pH was ~4. The resulting mixture was filtered by gravity filtration. The water-soluble and water-insoluble fractions were each extracted separately with EtOAc (3 x 30 mL). The residue from each fraction was filtered by gravity filtration, washed with EtOAc, then dried in a vacuum oven overnight.
EtOAc-soluble and water-soluble fractions were derivatized by heating with 200 µL BF$_3$•OEt$_2$ and 20 mL MeOH for every mmol substrate (computed based on theoretical methyl vanillate yield) at 100 °C for 6h.$^{42}$ After evaporating to dryness, water was added and the resulting mixture was extracted with EtOAc (3 x 30mL). The EtOAc solvent was evaporated under vacuum and the residue was subjected to column chromatography on silica gel (EtOH:hexanes 1:10) to give products 1 and 2: BV-1 (1.5%, 0.2% = 1.7%); BV-2 (2.2%, 0.5% = 2.7%); BV-3 (2%, 0.6% = 2.6%); BV-4 (7.8%, 2.2% = 10%).
CHAPTER 5. SUMMARY, CONCLUDING REMARKS, AND FUTURE DIRECTIONS

5.1 Summary

In this work, we presented our studies on the catalytic oxidation of β-O-4 lignin model compounds and the potential for application of this approach to the depolymerization of lignin. The oxidation tactic involves the catalytic oxidation of benzylic alcohols in lignin, followed by further oxidizing the resulting ketones to esters that can then be hydrolyzed to small molecule fragments of the original lignin. Two aspects of the oxidation and depolymerization reactions were investigated in this current work: 1) the effect of the solvent; and 2) the effect of mechanochemical pretreatment.

In the first phase of this investigation, we moved the oxidation of lignin model compounds from conventional solvents earlier studied in our group, to ionic liquids, in an effort to determine if such liquids are useful in lignin depolymerization. We performed oxidation reactions in the ionic liquids 1-butyl-3-methylimidazolium chloride ([C₄C₁im]Cl) and tetrabutylphosphonium chloride ([P₄444]Cl) in parallel with the same oxidations carried out in the corresponding conventional solvents. Oxidation catalysts included aerobic DDQ/NaNO₂, aerobic TEMPO/NaNO₂, and TPPFeCl/t-BuOOH systems.

We observed that reaction rates were often lower in ionic liquids than in conventional solvents, as indicated by lower conversion in a standard reaction time. This could partly be due to the higher viscosity of ionic liquids. Of particular significance is the observed increase in selectivity of the benzylic carbon towards oxidation (C-OH vs C-H) when the reaction was carried out in ionic liquid solvents.
For the oxidation of lignin in ionic liquids, we chose to employ the TPPFeCl/t-BuOOH catalyst system, based on the observation that among the three catalyst systems studied, it is with the porphyrin catalyst where conversion rates in the ionic liquid solvents are more or less comparable with those in the conventional solvent. When applied to Kraft lignin, partial oxidation of the polymer was observed in both the conventional and ionic liquid solvents, as shown by FTIR experiments, although the extent of oxidation was not enough to be detected by the (less sensitive) HSQC NMR technique. In the IL solvents, nevertheless, the extent of oxidation was sufficient to be seen in $^1$H NMR experiments.

Next, we turned to another potential way to help with depolymerizing lignin. This time we incorporated into our depolymerization procedure a mechanochemical step by ball milling the lignin sample with an alkali (KOH), before we carried out the porphyrin oxidation.

Through FTIR analysis we were able to show that mechanochemical pretreatment facilitates lignin oxidation. The carbonyl content of the lignin sample was enhanced when the lignin sample was ball milled, and when subsequently subjected to porphyrin oxidation, milled lignin demonstrated faster and higher degree of conversion, compared to an untreated lignin sample.

In an effort to observe a more complete picture of the changes in the lignin after mechanochemical pretreatment and subsequent porphyrin oxidation, we performed HSQC NMR experiments. After milling and oxidation with TPPFeCl/tBUOOH, degradation of lignin linkages was clearly observed by the nearly complete disappearance of cross-peaks corresponding to certain linkages ($\beta$-O-4, $\beta$-5 and $\beta$-$\beta$) in
the aliphatic region. Other explicit signs of oxidation were evident in the aromatic region. Cross-peaks associated with the oxidized form of guaiacyl (G’) showed up after ball milling and more so after porphyrin oxidation. At the same time, cross-peaks corresponding to the un-oxidized form (G) became less prominent after ball milling and almost completely disappeared after porphyrin oxidation. In addition, the signals for the oxidized guaiacyl (G’) was practically gone after mixing the porphyrin oxidized samples with NaBH₄, consistent with IR based conclusion on porphyrin oxidation’s reversibility.

Ultimately, we were interested to find out to what extent mechanochemical pretreatment helps with depolymerizing lignin. After the encouraging results we had observed on the first oxidation step, we were inclined to believe that these positive results would carry over to the second oxidation step. To our delight, we achieved a significant step toward the goal of transforming lignin into monomers. After Baeyer-Villiger oxidation and derivatization of the product mixture, we identified methyl vanillate as the main product, along with methyl 5-carbomethoxyvanillate as a minor product. The latter, which was identified by NMR spectroscopy and X-ray crystallography, is apparently a substitution product of methyl vanillate. These monomers were isolated in a combined yield of roughly 10%. It is important to note that the combination of mechanochemical pretreatment and porphyrin oxidation produced a synergistic effect, possibly due to reduced particle size brought about by mechanochemical pretreatment, or possibly due to mechanical shearing of the polymer itself, thus significantly improving the efficiency of the two-oxidation step depolymerization.
5.2 Concluding remarks and future directions

Lignin is a readily available material that has potential to be a renewable, non-petroleum source for fuels and chemicals. However, utilization of lignin for these purposes requires cost-effective methods for depolymerization and production of small molecules. Among others, the reductive approach, which gives less oxygenated compounds, is recommended if the goal is to produce biofuel from lignin, while the oxidative route works better if the desired value-added products are aromatic monomer compounds.

Because of their unusual ability to dissolve lignin, ionic liquids are obvious candidates as solvents for reactions and processing of lignin, including depolymerization by any chemical method. The use of an ionic liquid appears to enhance selectivity in some cases, as shown by porphyrin oxidation, and to provide a medium where both phenolic and nonphenolic compounds can be oxidized, as shown in our DDQ results. However, reaction rates drop significantly due to the inherently high viscosity of these solvents. Hence, additional optimization work will be needed in order to identify solvent/reagent combinations, possibly including the addition of a co-solvent, that produce efficient depolymerization of lignin.

Milling, including ball milling, is a time-honored approach to materials processing. It reduces particle size indicating that mechanic processing can break bonds, particularly in large molecules (Section 1.4.2). Chemical methods to break β-O-4 linkages in lignin are known, too (Section 1.2.2 and 1.2.3). We looked at using these methods together, because if the two methods break different bonds, then it is likely that we will end up closer to the goal of breaking many linkages.
Despite the progress reported in this dissertation, the goal of a low-cost, zero waste method for conversion of lignin into high-value small molecules remains elusive. Future studies may be directed at developing ways to cleave lignin at some of the other linkages, including $\beta$-1 and $\beta$-5. Moreover, further studies can be performed on the aqueous and insoluble fractions arising from the aforementioned depolymerization process to determine if the remaining materials in those fractions, presumably dimers/trimers/oligomers, can be further cleaved at some other positions like the $\beta$-1 and $\beta$-5 to give additional monomer products.

The mechanochemical treatment facilitated two-oxidation step depolymerization, involving porphyrin oxidation followed by Baeyer-Villiger oxidation, has been shown in this work to have achieved a certain level of success in cleaving lignin, presumably at the $\beta$-O-4 linkage, to produce monomers.
APPENDIX A. Supporting Information for Chapter 2

$^1$H NMR and $^{13}$C NMR spectra of 6 in CDCl$_3$
$^1$H NMR and $^{13}$C NMR spectra of 7 in CDCl₃
$^1$H NMR and $^{13}$C NMR spectra of 8 in CDCl$_3$
$^1$H NMR and $^{13}$C NMR spectra of 9 in CDCl$_3$
$^1$H NMR and $^{13}$C NMR spectra of 10 in CDCl$_3$
$^{1}H$ NMR and $^{13}C$ NMR spectra of 14 in CDCl$_3$
$^{1}H$ NMR and $^{13}C$ NMR spectra of 15 in CDCl$_3$
$^{1}H$ NMR and $^{13}C$ NMR spectra of Swern product 2' in CDCl$_3$
$^1$H NMR and $^{13}$C NMR spectra of Swern product 3' in CDCl$_3$
$^1$H NMR and $^{13}$C NMR spectra of Swern product 4' in CDCl$_3$
$^{1}$H NMR and $^{13}$C NMR spectra of Swern product 5' in CDCl$_3$
$^1$H NMR and $^{13}$C NMR spectra of Swern product 11' in CDCl$_3$
$^1$H NMR and $^{13}$C NMR spectra of TEMPO/TPPFeCl product 6' in CDCl$_3$
$^{1}$H NMR and $^{13}$C NMR spectra of DDQ/TEMPO/TPPFeCl product 7' in CDCl$_3$
Appendix B. Supporting Information for Chapter 3

$^1$H NMR and $^{13}$C NMR spectra of DDQ product 8' in CDCl$_3$
$^{1}H$ NMR and $^{13}C$ NMR spectra of DDQ/TEMPO/TPPFeCl product 9' in CDCl$_3$
$^1$H NMR and $^{13}$C NMR spectra of DDQ product 10' in CDCl$_3$
$^1$H NMR spectrum of Kraft Lignin in DMSO-d$_6$

$^1$H NMR spectrum of Kraft lignin in DMSO-d$_6$: post-oxidation in MeCN
$^1$H NMR spectrum of Kraft lignin post-oxidation in $[\text{C}_4\text{C}_1\text{im}]\text{Cl}$

$^1$H NMR spectrum of Kraft lignin in DMSO-d$_6$: post-oxidation in P$_{4444}\text{Cl}$
ATR-FTIR spectrum of Kraft lignin

ATR-FTIR spectrum of Kraft lignin post-oxidation in MeCN
ATR-FTIR spectrum of Kraft lignin post-oxidation in $[\text{C}_4\text{C}_{1\text{im}}]\text{Cl}$

ATR-FTIR spectrum of Kraft lignin post-oxidation in P4444 Cl
IR spectra of kraft lignin before and after oxidation with TPPFeCl/t-BuOOH in different solvents.
### Table 1. Crystal data and structure refinement for x17063.

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<th>Property</th>
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<td>Refinement method</td>
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Data / restraints / parameters  3392 / 1 / 315

Goodness-of-fit on $F^2$  1.091

Final $R$ indices [$I > 2\sigma(I)$]  $R1 = 0.0430$, $wR2 = 0.0852$

$R$ indices (all data)  $R1 = 0.0594$, $wR2 = 0.0935$

Absolute structure parameter  0.01(19)

Extinction coefficient  n/a

Largest diff. peak and hole  0.162 and -0.170 e.A$^{-3}$

**Table 2.** Atomic coordinates (x 10$^4$) and equivalent isotropic displacement parameters (Å$^2$ x 10$^3$) for x17063. U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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Table 3. Bond lengths [Å] and angles [deg] for x17063.

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C(6B)-O(6B)-C(11B) 116.7(3)
O(1B)-C(1B)-C(2B) 122.5(3)
O(1B)-C(1B)-C(6B) 117.3(3)
C(2B)-C(1B)-C(6B) 120.2(3)
C(1B)-C(2B)-C(3B) 119.1(3)
C(1B)-C(2B)-C(7B) 120.0(3)
C(3B)-C(2B)-C(7B) 121.0(3)
C(4B)-C(3B)-C(2B) 120.3(3)
C(4B)-C(3B)-H(3BA) 119.9
C(2B)-C(3B)-H(3BA) 119.9
C(3B)-C(4B)-C(5B) 120.3(3)
C(3B)-C(4B)-C(9B) 117.1(3)
C(5B)-C(4B)-C(9B) 122.6(3)
C(6B)-C(5B)-C(4B) 120.2(3)
Table 4. Anisotropic displacement parameters (Å² x 10³) for x17063. The anisotropic displacement factor exponent takes the form: -2 π² \[ h² a^*² U11 + ... + 2 h k a^* b^* U12 \]

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<th>U33</th>
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Table 5. Hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($A^2 \times 10^3$) for x17063.

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<th>x</th>
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<th>z</th>
<th>U(eq)</th>
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Table 6. Torsion angles [deg] for x17063.

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Table 7. Hydrogen bonds for x17063 [Å and deg.].

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<th>d(H...A)</th>
<th>d(D...A)</th>
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Symmetry transformations used to generate equivalent atoms: #1 -x+1/2,y-1,z+1/2  #2 x,y+1,z

X-ray diffraction data were collected at 150.0(5) K on a Bruker-Nonius X8 Proteum diffractometer with graded-multilayer focused CuK(α) x-rays. Raw data were integrated, scaled, merged and corrected for Lorentz-polarization effects using the APEX2 package. Corrections for absorption were applied using SADABS. The structure was solved by direct methods and refined against F² by weighted full-matrix least-squares. Hydrogen atoms were found in difference maps but subsequently placed at calculated positions and refined using a riding model. Non-hydrogen atoms were refined with anisotropic displacement parameters. The final structure model was checked using an R-tensor and by Platon/check CIF. Atomic scattering factors were taken from the International Tables for Crystallography.
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Spring 2015 – Fall 2017

University of Kentucky Teaching Assistantship
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Publications
Yao, S. G.; Pace, R. B. III; Crocker, Mark; Meier, M. S., A comparison of the oxidation of lignin model compounds in conventional and ionic liquid solvents and application to the oxidation of lignin. *RSC Advances*. **2016**, 6, 104742-104753.


Yao, S. G.; Mobley, J. K.; Meier, M. S.; Ralph, J.; Crocker, M.; Parkin, S., Selegue, J., Mechanochemical treatment facilitates two-step oxidative depolymerization. (Just submitted to ACS for publication)