Cobalt-Catalyzed Oxidation of the β-O-4 Bond in Lignin and Lignin Model Compounds

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ABSTRACT: In this work we demonstrate the use of Co(acac)₃ in combination with N-hydroxyphthalimide as an oxidant for the selective α-oxidation of the representative β-O-4 linkages in lignin model compounds. The oxidation reaction proceeds under mild conditions at 80 °C using 1,4-dioxane as the solvent and an oxygen atmosphere. The prior α-oxidation in the β-O-4 linkage of the lignin polymer is known to result in an easier cleavage of the adjacent C−O and C−C bonds because of a decrease in bond stability. Finally, the conditions were successfully transferred to kraft- and organosolv-lignin samples as proven by 2D-NMR (HSQC) experiments and gel permeation chromatography measurements.

INTRODUCTION

The valorization of biomass has become increasingly important in various fields including the production of specialized materials and fuels as well as in a biorefinery approach—producing bulk and fine chemicals from renewable substrates. In this context, a promising resource is lignocellulosic biomass, which is the most abundant raw material on earth. It can be obtained as a waste material from, for example, the food production sector or directly harvested, which could potentially be in conflict with agricultural areas. Lignocellulosic biomass is composed of three main components—cellulose, hemicellulose, and lignin. The latter one—lignin—is an amorphous macromolecule, which in nature gives rigidity and protection to plants. It holds exceptionally high oxygen-to-carbon ratios, thus making it interesting for the synthesis of oxygenated chemical compounds. The chemical structure of native lignin is highly complex and varies with the plant type, its geographical origin, and age. Consequently, the analytical investigation of lignin is a challenging task. To avoid this complexity, the majority of recent studies makes use of lignin model compounds containing representative binding motifs of the real lignin structure (Figure 1). Here, the β-O-4 lignin motif is commonly addressed as it is the most abundant one in the polymer itself.

Various approaches for the depolymerization of lignin and lignin model compounds are known. They can be reductive or employ redox-neutral catalysis, acid- or base-catalysis, and oxidative catalysis. For oxidative transformations, it was found that α-oxidation of the secondary alcohol group in the β-O-4 motif in lignin or in similar lignin model compounds decreased the bond strength of the neighboring C−C and C−O bonds. Stephenson and co-workers validated this observation by density functional theory calculations with...
respect to the cleavage of adjacent C−O bond in β-O-4 model systems (Scheme 1). Along the same lines, Samec and co-workers utilized Pd/C and glucose in EtOAc/H₂O mixtures for benzylic oxidations and showed that the catalytic cleavage of β-O-4 model compounds was facilitated. A two-step oxidative cleavage of simple monolignol-type β-O-4 lignin model compounds employing VOSO₄/TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxyl) in acetonitrile or methanol for the preoxidation step was reported by Wang et al., and Bolm and co-workers employed HO-TEMPO under mechanochemical conditions for the oxidation of the secondary hydroxyl group of β-O-4 lignin model compounds, thereby facilitating the cleavage of the interconnecting bonds in lignin to lead to a range of useful fine chemicals.

Here, we describe the selective oxidation of dilignol-type β-O-4 lignin model compounds and two lignin samples using a cobalt salt in combination with N-hydroxyphthalimide (NHPI) and oxygen to yield the respective ketones.

**RESULTS AND DISCUSSION**

Our initial experiments for the Co-catalyzed oxidation involved the use of β-O-4 lignin model compound erythro-dilignol 1a, which can easily be obtained on a large scale in diastereomerically pure form. The first reactions were performed in analogy to the work by Ishii using acetic acid as the solvent at 100 °C and 1 atm of dioxygen (Supporting Information, Table S1, entry 1). However, these conditions only led to a mixture of the primary- and secondary acetylation products of 1a. A thorough solvent screening revealed 1,4-dioxane as the solvent of choice, delivering 63% of the corresponding ketone 2a and 4% of the cleavage product 3a as determined by high-performance liquid chromatography (HPLC) analysis (Table 1, entries 1−3, and Supporting Information).

Following these initial results, the time course of the reaction together with the selectivity and activity at various temperatures was investigated (Supporting Information, Table S1, entries 27−33). By performing the catalysis in a glass autoclave instead of a reaction vessel, the oxygen pressure could be increased to 5 bar, allowing for lowering the reaction temperature to 80 °C without affecting the product yield (Table 1, entry 4). On a 1 mmol scale, isolation of the...
products by column chromatography yielded 2a in 68%, 3a in 7%, and cleavage product 4 in 4%.

Lowering the reaction temperature from 80 to 60 °C led to a drop in catalytic activity, as expected following along the lines of reaction kinetics, where a certain activation energy is necessary (Table 1, entry 5). At 135 °C, the formation of cleavage product 3a (29% at full conversion) was favored and only 2% of ketone 2a was formed (Table 1, entry 6). Here, it needs to be mentioned that a complete change in product selectivity was observed, which could be explained with an increased activation barrier for the bond cleavage toward compound 3a. Under the given reaction conditions, this barrier can only be reached at higher temperatures.

Extending the reaction time from 16 to 24 h had only a minor effect on the product yields (2a: 67%, 3a: 9%; Table 1, entry 7). Along the same lines, a decrease in reaction time to 2 h led to only 3% of the oxidation product 2a at a conversion of 7% (Table 1, entry 8). Hence, a 16 h period was chosen for the subsequent optimization.

Next, the effects of other catalysts were studied. Two representative examples are shown in Table 1. Both Co(NO₃)₂ (entry 11) and Co(OAc)₂ (entry 12) showed reduced activity toward the α-oxidation product 2a, which underlined the importance of the Co(III) species for the activation of the NHPI–O₂ system. Similarly, experiments with iron and copper salts led to a decrease in both substrate conversion and product formation (for details see Supporting Information).

When the reactions were performed in air, under an argon atmosphere, in the absence of Co(acac)₃, or without NHPI, the activity of the system was strongly reduced to yield ketone 2a in <10% (Table 1, entries 13–16). Noteworthy to mention is that α-oxidation of 1a toward ketone 2a also took place when Co(acac)₃ was omitted. However in that case, a stoichiometric amount of NHPI was required in combination with molecular oxygen.

No oxidation products were observed when 2 equiv of TEMPO was added, underlining the relevance of the most probably formed phthalimide-N-oxyl (PINO) radical derived from Co(acac)₃, NHPI, and O₂. Additionally, using ketone 2a

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**Table 2. Oxidation of Various β-O-4 Lignin Model Compounds with Co–NHPI**

| Entry | Model compound | Product | Yield [%] |
|-------|----------------|---------|-----------|
| 1     | ![Image](image1.png) | ![Image](image2.png) | 68        |
| 2     | ![Image](image3.png) | ![Image](image4.png) | 58        |
| 3     | ![Image](image5.png) | ![Image](image6.png) | 63        |
| 4     | ![Image](image7.png) | ![Image](image8.png) | 56        |
| 5     | ![Image](image9.png) | ![Image](image10.png) | 0         |
| 6     | ![Image](image11.png) | ![Image](image12.png) | 72        |
| 7     | ![Image](image13.png) | ![Image](image14.png) | 48        |
| 8     | ![Image](image15.png) | ![Image](image16.png) | 0         |

“Reaction conditions: 1 (1.0 mmol), Co(acac)₃ (0.01 mmol, 1 mol %), NHPI (0.1 mmol, 10 mol %), dioxane (4 mL), O₂ (5 bar), 80 °C, and 16 h and yields (after column chromatography and given in mole basis).
as the substrate under the optimized conditions led to a 27% conversion and the formation of 3a in 8% yield. This result was interpreted as evidence for the intermediacy of ketone 2a in the generation of 3a and 4 instead of a direct conversion of dilignol 1a into such products.

With the optimized conditions in hand, lignin β-O-4 model compounds 1b–h with different substitution patterns and representing the higher steric demands present in the lignin biopolymer were employed (Table 2). Compared to dilignol erythro-1a, its diastereomer threo-1b reacted slightly less efficient providing 58% of ketone 2a highlighting the small but detectable impact of the changed steric environment (entry 1 vs entry 2). Also monolignol model compound 1c and dilignols 1d and 1f with more electron-rich and sterically demanding substituents reacted well leading to the corresponding ketones in yields of 63, 56, and 72%, respectively (Table 2, entries 3, 4, and 6). In comparison, model compound 1g with a 2,6-dimethoxy-substituted phenolic ether moiety showed a lower activity giving the respective ketone 2e in only 48% yield (Table 2, entry 7). Presumably, the benzylic position became too crowded leading to an inefficient oxidation of the secondary hydroxyl group by the bulky PINO radical.

In line with previous observations,15,19 model compound 1e proved unreactive and neither conversion nor product formation was observed (Table 2, entry 5). Apparently, the presence of the free phenolic hydroxyl group hampered the hydroxyl group oxidation, allowing a full recovery of the starting material. Overall, these observations were rather surprising considering that catalytic oxidations of this type of phenolic lignin model compounds often lead to further polymerization reactions. To our surprise, the same was true for dilignol 1h (Table 2, entry 8), which had previously been converted to guaiacol and methoxy benzoquinone under mechanochemical treatment using HO-TEMPO (Table 2, entry 8).15

After having established an overview on the reactivity of the Co-catalyzed reaction system on lignin model compounds, the optimized reaction conditions were applied on samples of the lignin biopolymer. Here, a kraft-lignin sample (A) and an organosolv-lignin sample (B) were tested. In each experiment, the sample size of the respective lignin source was 200 mg to ensure an adequate concentration for the analytical investigations. Although the catalyst composition remained the same (1 wt % of Co(acac)₃ and 20 wt % of NHPI), the solvent amount was relatively increased (to 4 mL) to guarantee a full dissolution of the biopolymer.

First, two-dimensional (2D) NMR heteronuclear single quantum coherence (HSQC) analysis was performed on the corresponding lignin samples before and after the reaction. Therefore, the unreacted lignin samples were directly dissolved in DMSO-d₆ whereas for the other samples, the solvent (1,4-dioxane) was first removed in vacuo. Using the 2D NMR assignments by Sun and co-workers, the signals of the aliphatic ether region (1H NMR: 2.0−6.0 ppm, 13C NMR: 42.0−92.0 ppm) were compared for the native samples and those obtained after the cobalt catalysis.20

Figure 2 displays this aliphatic ether region of the organosolv-lignin sample B. Apparently, both the resinol (Ba,β,γ) and phenylcoumaran linkages (Ca,β,γ) have remained mostly unaffected by the oxidative transformation. However, an evident reduction in signal intensity for the Aα signal of the β-O-4 linkages is visible, which is in accord with the expected oxidation of the secondary hydroxyl groups of this linkage in the lignin polymer. Moreover, the respective signals for the oxidized β-O-4 linkage AO can be observed in the spectrum after the reaction with values of 5.23 ppm (1H NMR) and 83.3 ppm (13C NMR). Unfortunately, the 2D NMR HSQC spectrum of the kraft-Lignin sample A (see Supporting Information) does not show this characteristic signal, which indicates that either no or only partial oxidation of the β-O-4 linkages occurred.

Second, gel permeation chromatography (GPC) measurements were performed for both lignin samples A and B (see Supporting Information, Figures S7–S12). The respective elution volumes were calibrated with different standards bearing fixed molecular weight distributions. Figure 3 shows...
the molecular mass distribution for the organosolv-lignin sample B; here, three main regions can be identified. For both the kraft- and the organosolv-lignin samples, no significant changes of the molecular weight maxima (between 3000 and 3500 Da) were observed. Only differences around 50 Da are visible, when the specific area is enlarged (Supporting Information Figures S9 and S12). In addition, both samples showed a molecular weight $M_n$ area of around 10 000–20 000 Da before and after the reaction with Co(acac)$_3$/NHPI. However, these high molecular mass regions seem to strongly decrease in signal intensity after the reaction. These findings are in line with the model compound studies because only minor amounts of C–O and C–C bond cleavage products could be observed. Along those lines, the small peaks at around 100 Da in the GPC spectra could refer to the cleavage of terminal β-O-4 bonds in very minor quantities but could also stem from remaining amounts of NHPI or dioxane.

**CONCLUSIONS**

In summary, a simple system for the oxidation of lignin and lignin β-O-4 model compounds was developed. As demonstrated for the lignin model compound dilignol 1a, the optimized reaction conditions involved the use of a combination of 1 mol % of Co(acac)$_3$ and 10 mol % of NHPI under a dioxygen pressure of 5 bar in 1,4-dioxane at 80 °C for 16 h. Under these conditions, oxidation of the benzylic hydroxyl group of a range of β-O-4 model compounds occurred, affording the corresponding ketones 2 in good yields. Alternative oxidations of the primary hydroxyl groups present in the substrates were not observed.

Model compound 1e having a phenolic hydroxyl substituent remained unreactive and was fully recovered. Although this result was disappointing, it must not be considered as a serious drawback for the devised catalysis because such phenolic fragments are mostly present in the terminal segments of the lignin polymer, thereby representing only a small fraction of the entire polymer.

During the conversion of dilignol 1a, small quantities of 3,4-dimethoxybenzoic acid (3a) and 1-(3,4-dimethoxyphenyl)-3-hydroxypropan-1-one (4) were identified. Most likely, these products stem from a consecutive cleavage of ketone 2a, which indicates that a subsequent decomposition of the β-O-4 linkages by altering the catalytic conditions might be possible.

Finally, the optimized reaction conditions were applied in the oxidation of two different lignin samples: kraft-lignin A and organosolv-lignin B. Here, the oxidation of the secondary hydroxyl group in the β-O-4 linkages was identified by 2D NMR analysis. The signals for the other structural motifs remained mostly unchanged. GPC analysis showed a constant molecular mass maximum in both lignin samples. Only a small signal at lower masses was observed, which is in accordance with the formation of minor amounts of cleavage products in the model compound studies.

**EXPERIMENTAL SECTION**

**Materials and Methods.** The used reagents were acquired from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was dried by distillation over Solvona (sodium on molecular sieves) in the presence of benzophenone. Dichloromethane (DCM), MeOH, EtOAc, and dioxane were purified by distillation over boiling chips. Thin-layer chromatography (TLC) analysis was performed using Merck silica gel 60 F254 TLC plates. Flash column chromatography was carried out with silica gel 60 (35–70 mesh). Catalytic reactions were carried out in a Büchi “tinyclave steel” type 1/25 mL autoclave. Kraft-lignin sample A was directly purchased from sigma-Aldrich (CAS: 8068-05-1), whereas lignin sample B was supplied by the “Fraunhofer-Zentrum für Chemisch-Biotechnologische Prozesse” (CBP) Leuna, Germany, using the organosol method.

NMR spectra were recorded on a Varian Inova 400 (¹H NMR: 400 MHz, ¹³C NMR: 101 MHz) or an Agilent VNMRS 600 (¹H NMR: 600 MHz, ¹³C NMR: 151 MHz) spectrometer. Mass spectra were recorded on a Finnigan SSQ 7000 spectrometer (ELCI) and high-resolution mass spectrometry spectra were recorded on a Finnigan MAT 95 spectrometer (ESI).

HPLC measurements were conducted on an Agilent Infinity 1260 HPLC apparatus using an Agilent Eclipse XDB-C18 (4.6 mm i.d. × 250 mm, 5 μm) column. H$_2$O/MeOH (60:40) was employed as the eluent and a flow rate of 1.0 mL/min was used.

GPC measurements were performed on an ECO Sec System apparatus (HLC-8320GPC) from TOSOH-Bioscience LLC Company with one precolumn PSS Suprema (50 × 8 mm, 100 Å) and three PSS Suprema (300 × 8 mm, 100 Å) columns. A Na$_2$HPO$_4$ buffer solution (pH 12) with 0.5 g of polyethylene glycol 6000 was used as the solvent, and the signals were detected with an ECO Sec RI detector.

**General Procedure for the Catalytic Oxidation of β-O-4 Lignin Model Compounds.** The model compound 1a–h (1.00 mmol, 1 equiv), Co(acac)$_3$ (3.6 mg, 0.01 mmol, 1 mol %), and N-hydroxyphthalimide (16.4 mg, 0.10 mmol, 10 mol %) were added into a 25 mL glass autoclave equipped with a magnetic stirring bar followed by the addition of 1,4-dioxane (4 mL). Next, the autoclave was charged with 5 bar of O$_2$ and the reaction mixture was stirred at 80 °C for 16 h and subsequently cooled to room temperature. Next, a 1 M HCl solution (20 mL) was added and the mixture was extracted with DCM (3 × 20 mL). The combined organic layers were washed with an aqueous 1 M HCl solution (20 mL), brine (20 mL), and water (20 mL). Drying over MgSO$_4$ and evaporation under reduced pressure afforded the crude material that was further purified by standard column chromatography over silica (DCM/MeOH gradient: 100:0.5 to 100:5).
General Procedure for the Catalytic Oxidation of β-O-4 Bonds in Lignin Samples. Lignin sample A or B (200 mg), Co(acac)\textsubscript{2} (2.0 mg, 1 wt %) and N-hydroxysuccinimide (40 mg, 20 wt %) were added into a 25 mL glass autoclave equipped with a magnetic stirring bar. Subsequently, 1,4-dioxane (4 mL) was added. Next, the autoclave was charged with 5 bar of O\textsubscript{2} and the reaction mixture was then stirred in an oil bath at 80 °C for 16 h. At the end of the reaction time, the autoclave was taken out of the oil bath and cooled to room temperature. The remaining pressure was released and the autoclave opened. For GPC measurements, the solvent was removed under reduced pressure and the solid residue was directly processed under the GPC conditions (see Supporting Information). The respective 2D NMR HSQC measurements were performed in DMSO-\textsubscript{d\textsubscript{4}} after the removal of the reaction solvent under reduced pressure.

ASSOCIATED CONTENT

Supporting Information

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Notes

The authors declare no competing financial interest.

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