LETTER

Formic–acid–induced depolymerization of oxidized lignin to aromatics

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Lignin is a heterogeneous aromatic biopolymer that accounts for nearly 30% of the organic carbon on Earth[1] and is one of the few renewable sources of aromatic chemicals[2]. As the most recalcitrant of the three components of lignocellulosic biomass (cellulose, hemicellulose and lignin)[3], lignin has been treated as a waste product in the pulp and paper industry, where it is burned to supply energy and recover pulping chemicals in the operation of paper mills[4]. Extraction of higher value from lignin is increasingly recognized as being crucial to the economic viability of integrated biorefineries[5,6]. Depolymerization is an important starting point for many lignin valorization strategies, because it could generate valuable aromatic chemicals and/or provide a source of low-molecular-mass feedstocks suitable for downstream processing[7]. Commercial precedents show that certain types of lignin (lignosulphonates) may be converted into vanillin and other marketable products[8,9], but new technologies are needed to enhance the lignin value chain. The complex, irregular structure of lignin complicates chemical conversion efforts, and known depolymerization methods typically afford ill-defined products in low yields (that is, less than 10–20wt%)[2,10,11]. Here we describe a method for the depolymerization of oxidized lignin under mild conditions in aqueous formic acid that results in more than 60wt% yield of low-molecular-mass aromatics. We present the discovery of this facile C–O cleavage method, its application to aspen lignin depolymerization, and mechanistic insights into the reaction. The broader implications of these results for lignin conversion and biomass refining are also considered.

Lignin is biosynthesized from a relatively small number of phenylpropanoid building blocks that contribute to recurring structural elements in this otherwise complex polymeric material. One of the most common motifs is the 'β-O-4' alkyl–aryl ether linkage between aromatic rings[2], which features a secondary benzylic alcohol at the Cα position and a primary aliphatic alcohol at the Cγ position (Fig. 1). Fundamental

studies of wood pulp delignification in the context of paper production have shown that oxidation of the Cα alcohol to a ketone (for example by using stoichiometric Mn or Cr oxide reagents) facilitates the removal of lignin from cellulose, apparently by promoting cleavage of the β-O-4 linkage[12,13]. This concept has not been applied to the production of low-molecular-mass aromatics from lignin. Several groups, including our own, have probed the reactions of oxidized lignin model compounds, such as **2** (Fig. 1b), with varying degrees of success[12,14–21]. The recent development of a method for the chemoselective aerobic oxidation of Cα alcohols to ketones in native lignin, which achieved ~90% conversion to 'lignin^{ox}'[14], enables direct investigation of the reactivity of oxidized lignin. (Oxidative transformations of lignin and lignin model compounds have been the focus of extensive study and are summarized in refs 2, 20, 21. Primary references associated with this work are compiled in Supplementary Information.)

We observed previously that the oxidized lignin model **2** reacts with alkaline hydrogen peroxide to yield the aromatic monomers veratric acid (88% yield) and guaiacol (42%)[14]. The instability of the guaiacol under the reaction conditions prompted us to consider reductive cleavage methods. The reactivity of **2** was tested in the presence of different reducing metals, including zinc, aluminium, magnesium, iron and manganese, in aqueous formic acid at 110 °C (Fig. 2a). Four different major products were identified from these reaction conditions. In the presence of zinc, **2** afforded small amounts of the O-formylated product **3** (6%), together with good yields of the aryl ethyl ketone reductive cleavage product **4** (76%) and guaiacol (69%) (Fig. 2a, entry 1). When the reaction was performed with metal sources other than Zn (Fig. 2a, entries 2–5), the diketone product **5** was observed instead of **4**. Good yields of **5** (74%) and guaiacol (63%) were obtained from the reaction with manganese. Numerous other conditions were tested with these metal sources (see Supplementary Table 1); however, no further improvement in the product yields was observed. For example, substantially lower
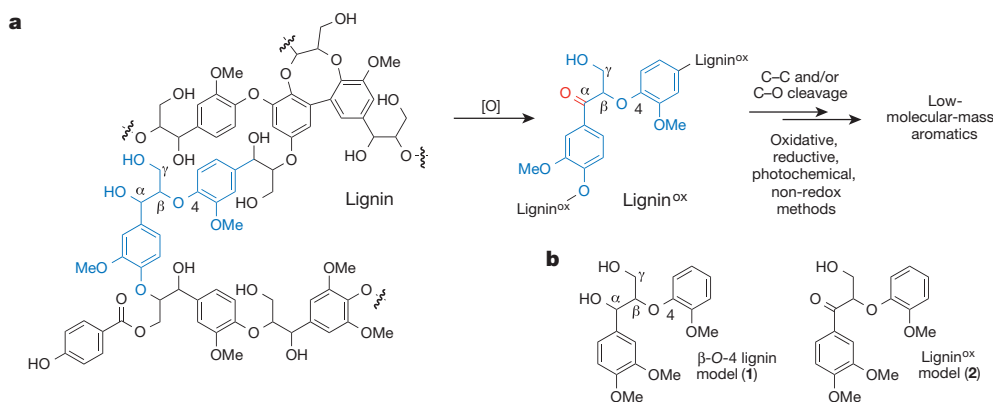

Figure 1 | Lignin structure and strategies for depolymerization.
a, Representative structure of a fragment of poplar (including aspen) lignin, highlighting a β-O-4 unit, together with the strategy for lignin conversion to low-molecular-mass aromatics by chemoselective alcohol oxidation, followed by C–C and/or C–O cleavage. b, Structure of β-O-4 model compounds **1** and **2**.

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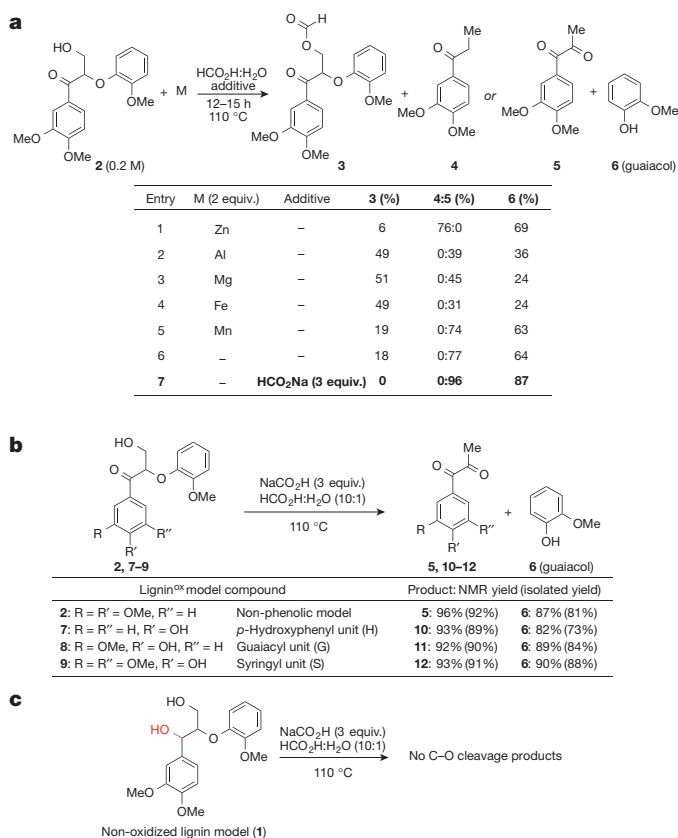
Figure 2 | C–O cleavage of lignin model compounds with formic acid.
a, Cleavage products obtained from the treatment of lignin[ox] model compound **2** in formic acid with and without reducing metals (M). Yields shown in the table were determined by ^{1}H NMR spectroscopy, using hexamethyldisiloxane as the internal standard. **b**, Cleavage of different lignin[ox] model compounds in the presence of formic acid and sodium formate. **c**, Control reaction with the non-oxidized lignin model compound **1** under the formic acid/formate cleavage conditions.

yields were obtained with organic solvents (ethanol, γ-valerolactone or toluene) or on replacement of formic acid with another acid source (acetic acid, HCl or H_2SO_4).

The conversion of **2** into the diketone product **5** is a redox-neutral process. We therefore tested the reaction in the absence of a reducing metal, and products **5** and **6** were obtained in yields comparable to the best results obtained with a stoichiometric metal source (Fig. 2a, entry 6). Even better yields of **5** and **6** resulted (96% and 87%, respectively) when 3 equivalents of sodium formate were included in the reaction mixture (Fig. 2a, entry 7). These conditions proved to be effective with several other lignin[ox] model compounds, including those derived from *p*-hydroxyphenyl (H)-, guaiacyl (G)- and syringyl (S)-type lignin units **7–9** (Fig. 2b). The Cα ketone is crucial to the success of the reaction: no cleavage products were observed when the non-oxidized model compound **1** was subjected to the formic acid/formate reaction conditions (Fig. 2c).

These results provided the basis for testing the reactivity of authentic lignin polymer. Aspen is a representative hardwood, and a sample of native aspen lignin was isolated and determined to have a ratio of S:G subunits of 2.2:1 on the basis of two-dimensional heteronuclear single quantum coherence NMR analysis (see Supplementary Fig. 1)[22]. After treatment of this material under the aerobic conditions described previously[14], the oxidized lignin was subjected to the formic acid/sodium formate reaction conditions at 110 °C. The amount of sodium formate added to the reaction mixture was estimated from the mass of the lignin sample to provide about 3 equivalents of formate per S/G aromatic subunit. The formic acid was evaporated after 24 h, and the residue was extracted

with ethyl acetate. A soluble fraction, corresponding to 61.2wt% of the original lignin, was obtained, together with an insoluble fraction that accounted for 29.7wt% of the lignin (Fig. 3a). Acetylation of the insoluble material and analysis by gel-permeation chromatography revealed a significant decrease in molecular mass relative to the initial lignin polymer (Fig. 3b). The soluble fraction, containing the majority of the lignin-derived mass, was analysed by high-resolution mass spectrometry coupled with liquid chromatography (LC–MS) to identify and quantify the products of the reaction (Fig. 3c and Supplementary Table 2). Product identities were confirmed by comparison with authentic samples obtained commercially or synthesized independently (see Supplementary Information for details).

Overall, more than 52% of the original lignin was converted to well-defined aromatic compounds (Fig. 3c). Syringyl and guaiacyl-derived diketones, directly analogous to those observed in the model study (compare Fig. 2b), are two of the major depolymerization products (19.8%). The S:G diketone ratio (2:1) is very similar to the S:G monomer composition in the lignin. Additional syringyl and guaiacyl-derived aromatics (for example, syringaldehyde and vanillin) account for most of the remaining product mass, together with *p*-hydroxybenzoic acid (4%), which is probably derived from *p*-hydroxybenzoic esters present in aspen (and other poplar) lignins[23]. A full listing of characterized products is provided in Supplementary Table 2.

An attempt to use unoxidized lignin in the reaction resulted in only 7.2wt% yield of low-molecular-mass aromatics. The products that are observed probably arise from the small amount of Cα ketones present in native lignin (evident from two-dimensional NMR spectroscopy). This
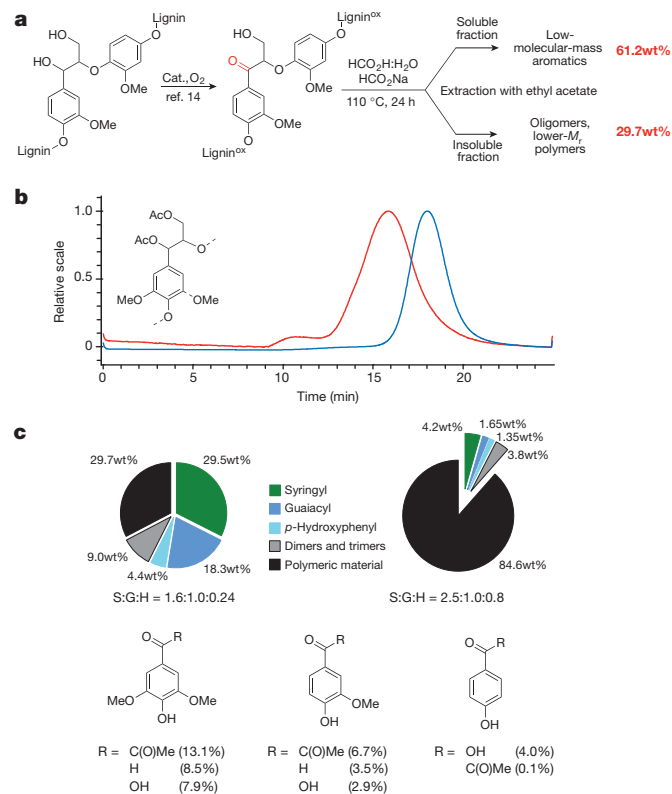

Figure 3 | Depolymerization of aspen lignin with formic acid.
a, Depolymerization of oxidized aspen lignin. **b**, Gel-permeation chromatography of the insoluble fraction from depolymerization (29.7wt%) (blue trace) compared with that of native lignin (red trace). For the insoluble fraction of depolymerized lignin, $M_w/M_n = 1.08$ and $M_n = 4,600$ Da; for native lignin, $M_w/M_n = 1.18$ and $M_n = 10,800$ Da. **c**, Identification, quantification and distribution of products obtained from the depolymerization of oxidized lignin (upper left) compared with those from native lignin (upper right). Bottom: major depolymerization products from oxidized lignin. For a full product listing see Supplementary Table 2.

result demonstrates the importance of Cα oxidation in promoting lignin depolymerization and provides strong motivation to develop improved lignin oxidation methods suitable for large-scale application. The Cα benzylic alcohol in lignin is activated electronically relative to the Cγ primary alcohol, and our previous study showed that numerous classes of oxidants promote the chemoselective oxidation of the Cα alcohol[14]. These observations bode well for the development of improved oxidation methods.

Mechanistic insights into the depolymerization process were obtained from additional studies of model compound **2**. Reaction time-course data, obtained by ^{1}H NMR spectroscopy, revealed that **2** converts quickly into the alcohol formylation product **3**, followed by a slower conversion of **3** into products **5** and **6** (Fig. 4a, b). Conversion of **2** into **3** is rapid, even at room temperature (Fig. 4c). Direct investigation of the reaction of **3** revealed a small steady-state concentration of the aryl vinyl ether intermediate **13** during the formation of diketone product **5** (Fig. 4d). Independent testing of **13** confirmed that this intermediate is consumed more rapidly than the overall conversion of **3** into **5** (Fig. 4e). A large deuterium kinetic isotope effect, observed when the independent reaction rates of **2** and **2**-d_1 were compared ($k_H/k_D = 9.3 \pm 0.2$; Fig. 4f), indicates that the elimination of formic acid from **3** is the rate-limiting step in the transformation. This kinetic isotope effect is larger than the semi-classical limit associated with the cleavage of a C–H bond, but it aligns with a previous study providing evidence for proton tunnelling in concerted E2 elimination reactions[24].

Overall, the sequence is a redox-neutral process that results in no net consumption of formic acid (Fig. 4g). This feature distinguishes the present approach from other lignin conversion methods that employ formic acid as a source of H_2 in transfer hydrogenation/hydrogenolysis reactions with heterogeneous catalysts (see, for example, refs 25, 26). According to the mechanism in Fig. 4g, the beneficial effect of lignin oxidation may be attributed to the ability of the benzylic carbonyl group to polarize the C–H bond and lower the barrier for the rate-limiting E2 elimination reaction. Both the increased C–H acidity and orbital overlap between the carbonyl C=O π system and the developing π bond of the alkene are expected to contribute to a lower barrier for this step. The mechanism also accounts for the beneficial effect of using a 'buffered' reaction medium, containing both formate and formic acid (compare Fig. 2a, entries 6 and 7). The rate-limiting elimination step in Fig. 4g is proposed to involve both a base (formate) to remove the proton and an acid (formic acid) to assist in the loss of the formate as a leaving group.

The overall yield of structurally identified, monomeric aromatics obtained here is the highest reported so far for lignin depolymerization[2,10,11]. Although some of the products obtained from this process have direct commercial value (for example vanillin and syringaldehyde)[27,28], the more important result may be the generation of a stream of soluble aromatic
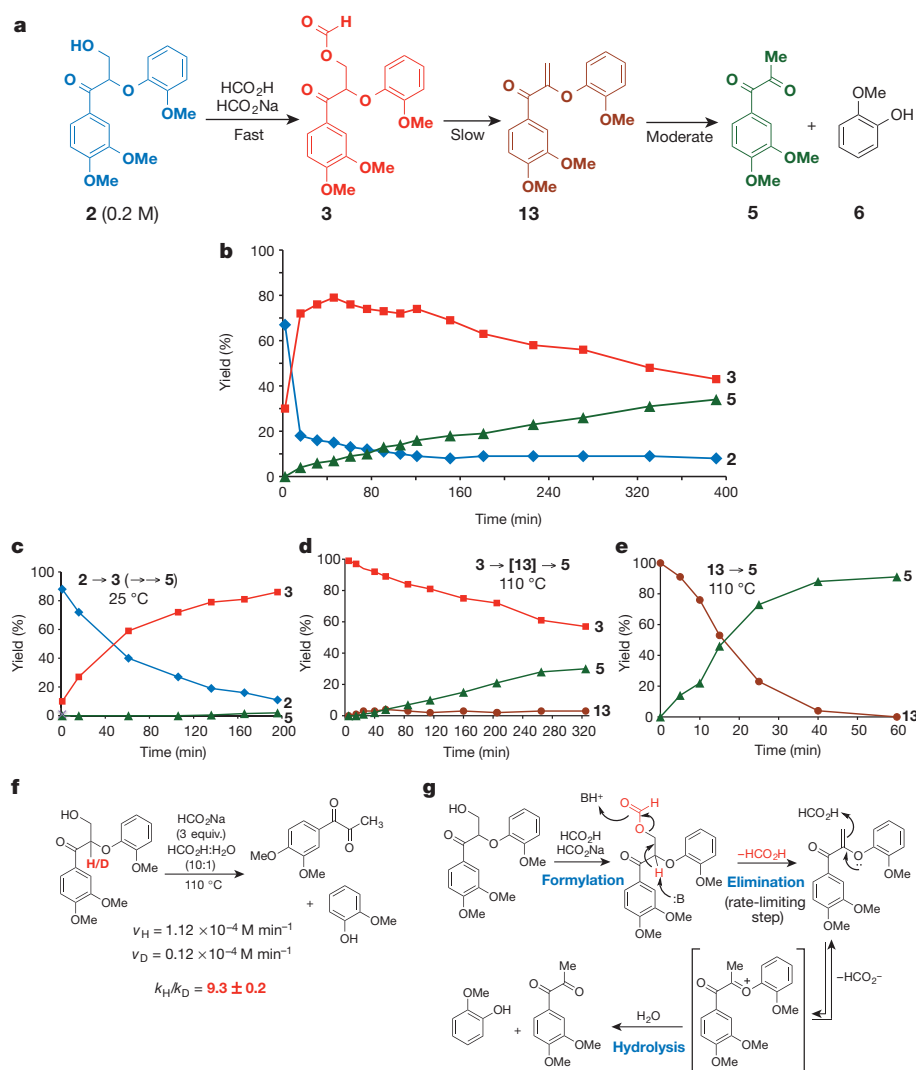

Figure 4 | Mechanistic study of C–O cleavage in 2. a, b, Different intermediates (**a**) and overall time course of the reaction **2**→**3**→[**13**]→**5** at 110 °C (**b**). **c–e,** Time courses of formylation of **2** at 25 °C (**c**), elimination of formic acid from **3** at 110 °C (**d**), and hydrolysis of aryl vinyl ether **13** at 110 °C (**e**). **f,** Kinetic isotope effect for cleavage of the oxidized model compound **2**. **g,** Proposed mechanism for C–O cleavage.

feedstocks for further upgrading. For example, low-molecular-mass feedstocks should reduce coking and char formation, enhance conversions and facilitate product separations in processes with heterogeneous catalysts (such as hydrogenation, hydrogenolysis, decarbonylation and decarboxylation). The syringyl, guaiacyl and *p*-hydroxyphenyl aromatic products arise directly from the monomeric composition of the lignin, and their yields correlate closely with the quantity of β-*O*-4 linkages present in the original lignin. These observations highlight the importance of developing chemical conversion technologies for S-, G- and H-derived aromatics and suggest that plants containing lignin with high β-*O*-4 content (as much as 85% has been observed[29]) could be particularly appealing feedstocks for biomass valorization. This work further draws attention to biomass separation methods. Since the inception of the pulp and paper industry, biomass separation methods have emphasized the production of high-purity cellulose. Most existing process conditions, ranging from the classic kraft pulping to modern organosolvolysis methods, significantly modify or damage the lignin and lead to a significant decrease or complete loss of β-*O*-4 structural units. Biomass separation methods that deliver both high-purity sugar and native-type lignin streams, such as a recent γ-valerolactone-based process[30], could gain a competitive advantage in biorefining applications.

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Supplementary Information is available in the online version of the paper.

Author Contributions A.R. and S.S.S. conceived the idea for the lignin depolymerisation. A.R. performed the chemical reactions of lignin and lignin model compounds, including NMR spectroscopic characterization of the products. A.U. and J.J.C. designed the analytical approach to characterize the lignin depolymerization products. A.U. performed LC/MS analysis. A.R. and S.S.S. wrote the manuscript in consultation with A.U. and J.J.C.

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