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Isolation of Functionalized Phenolic Monomers through Selective Oxidation and C–O Bond Cleavage of the β-O-4 Linkages in Lignin**

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Abstract: *Functionalized phenolic monomers have been generated and isolated from an organosolv lignin through a two-step depolymerization process. Chemoselective catalytic oxidation of β-O-4 linkages promoted by the DDQ/tBuONO/O_2 system was achieved in model compounds, including polymeric models and in real lignin. The oxidized β-O-4 linkages were then cleaved on reaction with zinc. Compared to many existing methods, this protocol, which can be achieved in one pot, is highly selective, giving rise to a simple mixture of products that can be readily purified to give pure compounds. The functionality present in these products makes them potentially valuable building blocks.*

Technologies to produce chemicals and fuels from renewable bioresources are the focus of intense studies.[1] This is due to the falling reserves and rising costs of fossil fuels. In this context, lignocellulosic biomass, which contains cellulose, hemicellulose, and lignin, is considered an important resource.[2] While technologies for the production of ethanol derived from the cellulosic component are already in commercial operation,[3] processes for the valorization of lignin are limited.[4] This constitutes a significant drawback for a biorefinery where the valorization of all the biomass is necessary for economic viability in the absence of subsidies.[4] In addition, despite lignin being a major by-product of the pulp and paper industry,[5] only 1–2% is used to deliver commercial products with most being burnt as a low value fuel. Lignin valorization has therefore become an important challenge that has yet to be solved. The major hurdle to the production of biorenewable chemicals from lignin is the selective depolymerization of this recalcitrant material to useable monomers. It is for this reason that new chemical procedures are needed.

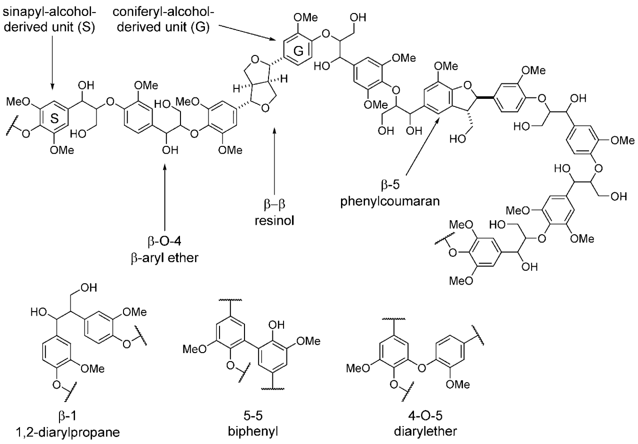


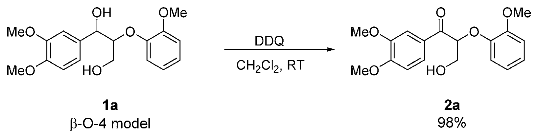
Figure 1. A structural representation of a typical hardwood lignin showing the most common lignin linkages. The β-O-4 linkage is the most abundant and is known to be present in both *threo* and *erythro* forms in lignin. The relative stereochemistry of the β–β and β–5 linkages is shown.

In almost all lignins the β-O-4 unit is the most abundant structural unit, with smaller amounts of β–β, β–5, and other minor linkages (Figure 1).[6] Recently, the selective oxidation of the β-O-4 linkage in lignin combined with a second chemical treatment has been suggested as a method of achieving the selective depolymerization of lignin.[7] Here we report a novel and practical method that achieves puts this strategy into practice.

Our initial studies focused on the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as a benzylic oxidant for lignin, follow on from our recently reported use of this reagent to modify the β–β linkage in kraft lignin.[8] DDQ exhibits excellent selectivity in oxidizing benzylic and allylic alcohols and has been used catalytically in the presence of molecular oxygen and a suitable co-oxidant.[9]

Encouragingly, the reaction of the β-O-4 model linkage (**1a**) with a stoichiometric amount of DDQ in dichloromethane at room temperature led to the formation of ketone **2a** in excellent yield, with complete selectivity for the oxidation of the secondary benzyl alcohol over the primary alcohol (Scheme 1).

Before extending our studies to catalytic procedures, we were mindful of the fact that while lignin model compounds, such as **1a**, are soluble in a broad range of solvents that are



Scheme 1. Selective benzylic oxidation of β-O-4 model compound **1a**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

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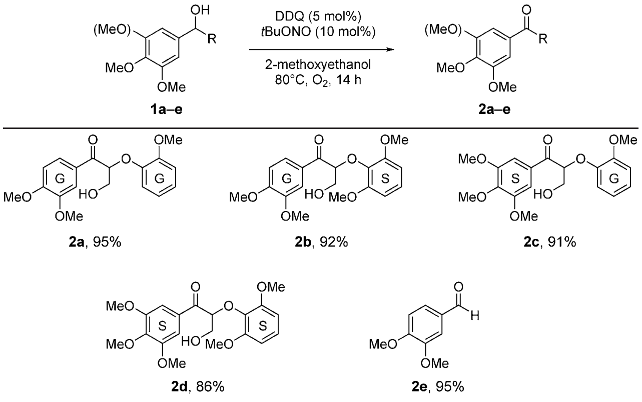
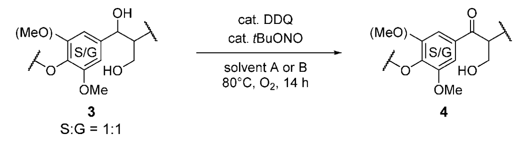
commonly used in catalytic DDQ chemistry, such as chlorobenzene,[9a] toluene,[9b] and acetic acid,[9d] lignin is not. For this reason it was necessary to identify a reaction solvent that was both suitable for catalytic DDQ reactions and effective at solubilizing lignin. A literature survey identified one promising solvent, 2-methoxyethanol.[9a,10] The catalytic aerobic oxidation of lignin models **1a–e** in 2-methoxyethanol was therefore attempted (Table 1). The models were chosen based on their resemblance to linkages found in both hard and softwood lignins representing structures derived from coniferyl and sinapyl alcohol coupling and cross-coupling reactions (**1a–d**).[11] The DDQ/*t*BuONO/O_2 catalytic system with 2-methoxyethanol as the reaction solvent showed excellent selectivity and reactivity in the oxidation of the benzylic alcohol in **1a–d**. The expected ketones were isolated in good to excellent yields in all cases (**2a–d**). The catalytic system also showed excellent reactivity toward veratryl alcohol (**1e**) giving **2e** in a comparable yield to that recently reported using aerobic 4-AcNH-TEMPO oxidation conditions.[7a]

Table 1: Selective catalytic benzylic oxidation of lignin β-O-4 models.



Unlike **1a–d**, lignin is a polymeric substrate that possesses both a secondary and tertiary[12] structure in solution, which both affect linkage reactivity. Therefore, a more relevant polymeric β-O-4 model was investigated. Despite the clear advantages of using model lignin polymers, they are rarely used, with only one reported example, to the best of our knowledge.[13] Challenges inherent in their preparation are probably the cause of their limited use. However, by modification of a reported route,[14] we were able to prepare a β-O-4-containing polymer in just three steps from vanillin and syringaldehyde (see the Supporting Information for details). This polymer, which contained equal proportions of S and G units to mimic a β-O-4-rich hardwood lignin, was used in the DDQ-catalyzed oxidation with reaction conversion being assessed by semiquantitative 2D-HSQC NMR experiments (see Figures S1–S3 for analysis and Scheme S1 for synthesis of authentic compounds to aid NMR assignment). The polymer was initially treated under identical conditions to those used for the monomer studies (Table 2, entry 1). While the catalytic oxidation still proceeded, the conversion was lower than observed with substrates **1a–e** (Table 1). This observation suggested that the polymer was, as expected, a more challenging substrate to oxidize. As a result, the reaction conditions were optimized further. Increasing the DDQ loading to 10 mol% (Table 2, entry 2) and addition of 1,2-dimethoxyethane as a nonprotic cosolvent markedly improved conversions (Table 2, entries 3 and 4). In order to achieve almost complete oxidation, the loading of DDQ and *t*BuONO had to be increased to 20 mol% (Table 2, entry 6). The beneficial effect of the cosolvent in this reaction may in part be explained by an increase in the effective lifetime of DDQ under these conditions. It is interesting to note that in this polymer, G units were oxidized more readily than S units, consistent with the reaction proceeding through a benzylic cation.

Table 2: Selective catalytic benzylic oxidation of a lignin β-O-4 model polymer.

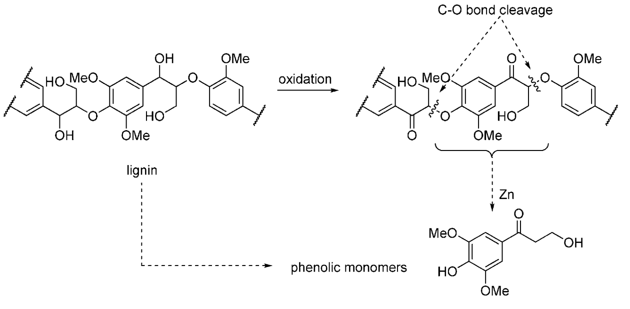


Entry	DDQ [mol%]	*t*BuONO [mol%]	Solvent system[a]	Conversion [%][b] total	G	S
1	5	10	A	50	64	35
2	10	10	A	74	83	64
3	5	10	B	69	81	57
4	10	10	B	91	100	82
5	15	15	B	97	100	94
6	20	20	B	99	100	98

[a] A = 2-methoxyethanol, B = 2-methoxyethanol/1,2-dimethoxyethane (2:3). [b] Conversions were determined by comparison of the integrals of the aromatic cross-peaks characteristic of oxidized and unoxidized structures in the 2D HSQC NMR. Error analysis indicated the standard deviation for these measurements was less than 0.05. See the Supporting Information for more information.

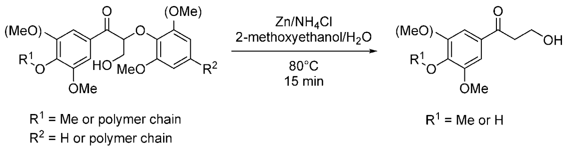
Having developed a working catalytic oxidation method, our investigation turned to the selective degradation of the oxidized β-O-4 structure. Zinc is a versatile reductant, in particular, it is an excellent reagent for the conversion of acyloin derivatives to ketones.[15] If an analogous reaction could be carried out on oxidized β-O-4 linkages in lignin, depolymerization could be achieved to produce phenolic monomers (Scheme 2).

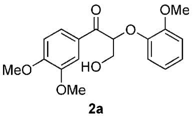
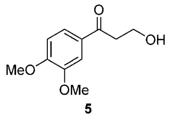
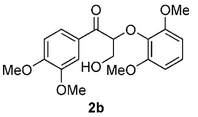
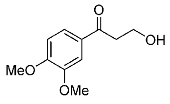
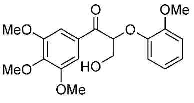
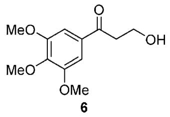
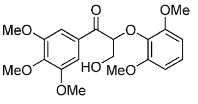
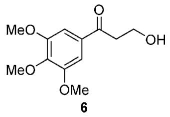
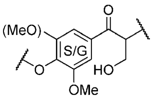
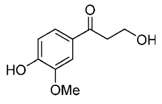
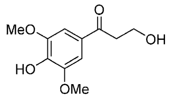
When the oxidized model compounds **2a–d** were treated with an excess amount of zinc in the presence of NH_4Cl, the



Scheme 2. Strategy for the production of phenolic monomers from lignin.

Table 3: C–O bond cleavage of oxidized β-O-4 model compounds **2a–d** and **4**.



Substrate	Product	Yield[a] [%]
 **2a**	 **5**	88 (92)[b]
 **2b**	 **5**	84
 **2c**	 **6**	81
 **2d**	 **6**	90
 **4**	 **7**	27
	 **8**	23

[a] Yields of isolated products. [b] Yield of the isolated product from a one-pot reaction.[16]

corresponding ketones (**5** or **6**) were isolated in good yields (Table 3). This reaction also required no prior purification of the substrate **2** to achieve high yields of **5** or **6**. For example, when run as a one-pot oxidation/cleavage protocol, isolated compound **5** was obtained in 92% yield from **1a**. When this procedure was applied to the oxidized β-O-4 polymer model **4**, the two phenolic monomers **7** and **8** were isolated in approximately equal, reasonable yields, indicating high levels of C–O bond cleavage.

Next, we turned our focus to the use of real lignin as a substrate. A dioxasolv process was used to extract lignin from Birch sawdust (*Betula pendula*). This involved a mild-acid-catalyzed organosolv process using 0.2 N HCl in 90% dioxane. The isolated lignin was rich in syringyl units and contained a high proportion of β-O-4 linkages, smaller amounts of the β–β linkage, and only just detectable amounts of the β–5 linkage (Figure 2A). Oxidation under the optimized catalytic DDQ conditions described in Table 2 proceeded smoothly to give an oxidized lignin in which the appearance of the desired alpha ketone β-O-4 structure could be readily identified in the 2D HSQC NMR spectrum (Figure 2B). No special drying of our lignin or solvents was required prior to this transformation.

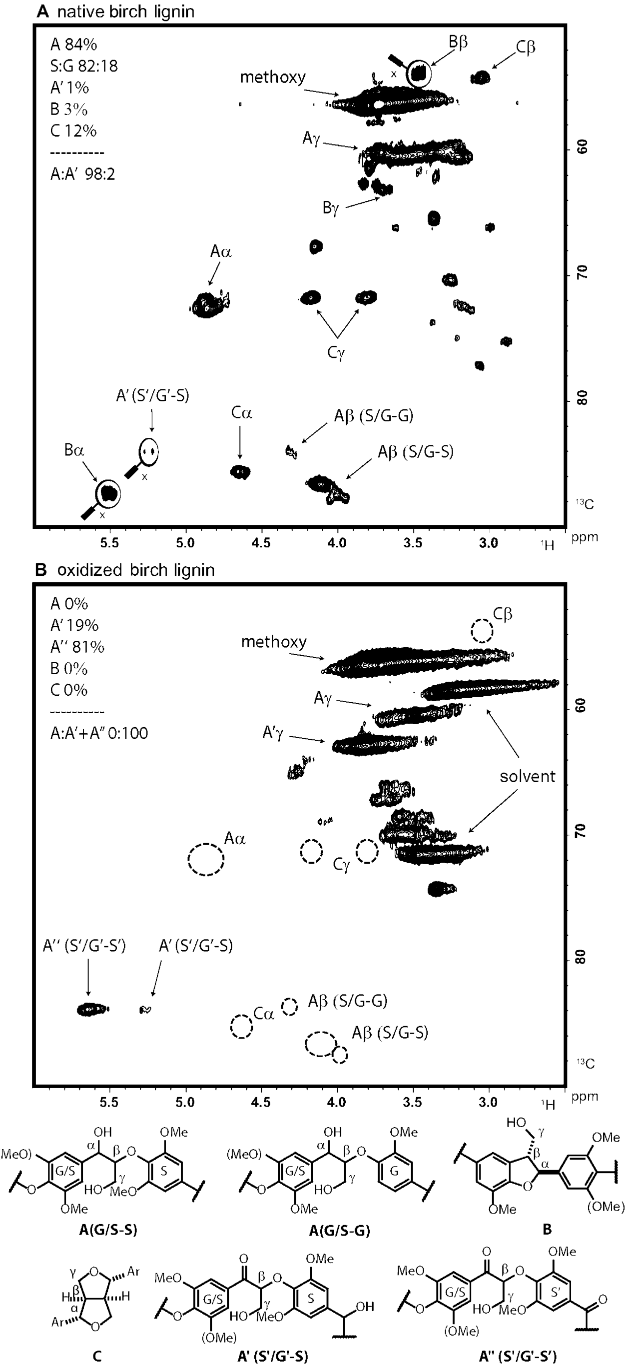
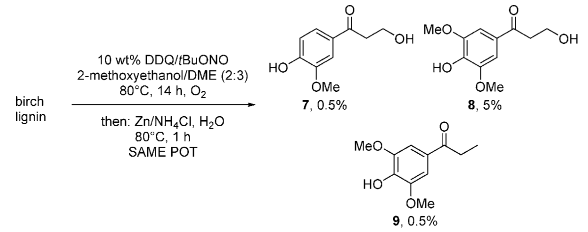


Figure 2. Partial 2D HSQC NMR spectra of dioxasolv Birch lignin in [D$_6$]DMSO before (A) and after (B) treatment with our catalytic oxidation system (10 wt% DDQ, 4.4 wt% *t*BuONO). The relative volume integrals of characteristic peaks are given. Cross-peaks for the β-5 (B) and oxidized β-O-4 (A′) structures in native birch lignin have been magnified to make them visible. Standard deviations for the integral values; native lignin = 0.06, $n = 39$, oxidized lignin = 0.10, $n = 15$ (see the Supporting Information for more details). For issues relating to the processing of the β–β linkage, see Ref. [8] and for structural assignment of A′ and A″, see Figure S5.

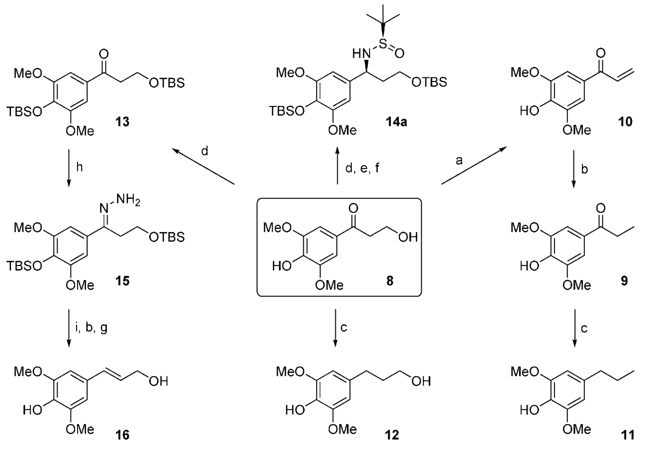
Application of the cleavage method using zinc to the oxidized lignin followed by extraction and purification gave isolated compound **8** in 5 wt% yield, together with minor amounts of **7** and **9**[16] (Scheme 3). The catalytic oxidation and



Scheme 3. Depolymerization of lignin to phenolic monomers. DME = 1,2-dimethoxyethane.

depolymerization of lignin could also be conducted in one pot with no impact on the yield of **8**. A key advantage of our lignin depolymerization method is the retention of functional groups in the major phenolic product **8**, as these groups are frequently lost in other lignin depolymerization processes.[13,17] Future studies will focus on integrating methods to recover and recycle both the organic solvents used and the solubilized zinc salts in the aqueous waste stream. The environmental and cost implications of using a halogenated organic catalyst, such as DDQ, will also be assessed. Optimizing these and other factors may enable this promising initial reaction sequence to be developed into a large-scale process.

To assess whether **8** is of potential relevance to the valorization of lignin, several chemical transformations starting from **8** were assessed (Scheme 4).[18] Products from these reactions include potentially polymerizable monomer **10**,[19] from which propiophenone **9** and syringylpropane **11**[20] could be accessed, dihydrosinapyl alcohol **12** and β-amino acid precursor **14a**.[21–23] A recent report has shown that **12** can be produced as a mixture with other phenolic monomers through bimetallic hydrogenolysis of organosolv lignin in water.[17a]



Scheme 4. Synthetic conversion of phenolic monomer **8** to various chemical compounds. Reaction conditions: a) PPh_3, DDQ, NBu_4I, DBU, CH_2Cl_2, RT, 4 h, 78%; b) Zn dust, AcOH, RT, 12 h, 63% for **9**; c) $NaBH_3CN$, $BF_3{\cdot}OEt_2$, RT, 12 h, 89% for **11**, 82% for **12**; d) TBS-Cl, DMAP, imidazole, DMF, RT, 1 h, 94%; e) (*R*)-*tert*-butyl sulfinamide, $Ti(OEt)_4$, PhMe, 100 °C, 12 h, 60%; f) L-selectride, THF, −20 °C→RT, 4 h, 80%; g) TBAF, THF, 3Å M.S., RT, 2 h, 63%; h) $H_2NNH_2{\cdot}H_2O$, 100 °C, 12 h, 82%; i) I_2, Et_2O, 0 °C, 30 min, 51%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP = 4-dimethylaminopyridine; DMF = *N*,*N*-dimethylformamide; M.S. = molecular sieves; TBAF = tetra-*n*-butylammonium fluoride; TBS = *tert*-butyldimethylsilyl.

Finally, **8** was converted to the monolignol sinapyl alcohol **16**, which is known to possess anti-inflammatory and antinociceptive activity,[24] and which is a potential substrate for a wide range of chemical transformations that could add complexity and hence value.[25]

In summary, we report the depolymerization of birch lignin leading to the isolation of a pure phenolic monomer **8** as the major product in a 5 wt% yield. To the best of our knowledge, this is the first time that compounds such as **8** (and **7**) have been isolated as the major products in the depolymerization of lignin. Our one-pot method involves an initial aerobic catalytic oxidation of the β-O-4 linkages in lignin followed by zinc-mediated cleavage of the C-OAryl bond. The method reported here was developed through the use of simple model compounds and more complex β-O-4 model polymers. This strategy has allowed us to observe, for the first time, a clear difference in reactivity between simple and polymeric models, which is of potential importance in the development of future methods for lignin valorization. We also demonstrate that **8**, a compound not readily obtainable from lignin by other methods, is a useful starting point for subsequent synthetic sequences aimed at delivering valuable products from this recalcitrant, but highly abundant renewable biopolymer.

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Keywords: biomass · depolymerization · lignin · oxidation · renewable chemicals

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