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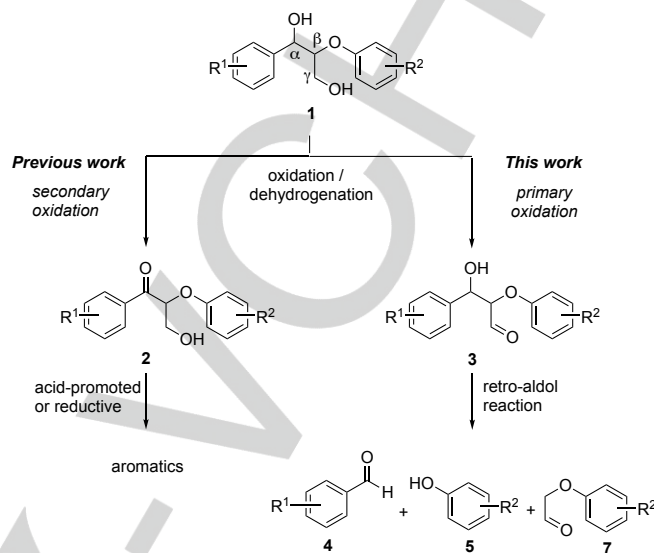
Organocatalytic Chemoselective Primary Alcohol Oxidation and Subsequent Cleavage of Lignin Model Compounds and Lignin

Saumya Dabral,^[a] José G. Hernández,^[a] Paul C. J. Kamer,^{*[b]} Carsten Bolm^{*[a]}

Abstract: A one-pot two-step degradation of lignin β -O-4 model compounds initiated by preferred oxidation of the primary over the secondary hydroxyl groups with a TEMPO/DAIB system has been developed. The oxidised products are then cleaved by proline-catalysed retro-aldol reactions. This degradation methodology produces simple aromatics in good yields from lignin model compounds at room temperature with an extension to organosolv beech wood lignin **L1** resulting in known cleavage products.

Lignin is the largest natural reservoir of aromatics and the second most abundant biopolymer representing 30% of non-fossil organic carbon on earth. Paper and pulp industries are major producers of industrial lignin, which occurs as a waste by-product during wood-processing.^[1] Although lignin has been used for obtaining low-added-value materials such as dispersing or binding agents,^[1a] the majority of it is burnt.^[1] Recently, more and more research is focused on generating valuable co-products (energy, chemicals and fuels) of high market value from this renewable raw material.^[1,2] At the same time, these efforts are intended to decrease the existing dependence on fossil-based raw materials and hence help to reduce carbon footprints.^[3]

The variety of interconnecting bonds of the various building blocks in lignin offer many possibilities for the production of bulk chemicals and functional materials. In our group, the cleavage of lignin at β -O-4 linkages has been of prime focus, because these bonds are most dominant in the three-dimensional biopolymer varying from 45% to 60% depending on the wood type.^[4] However, due to the undefined amorphous nature of lignin, which mainly consists of methoxylated aryl propane units, those degradation studies have been challenging.^[1,2,4] In most of the cases, an initial application of lignin model compounds^[5] proved useful for gaining a better understanding of the chemical transformations taking place on the structurally complex lignin. Recently, various groups reported on lignin depolymerization studies that were initiated by oxidative ketone formations in β -O-4 units.^[6] DFT calculations revealed that such processes weakened the connected C_r-O linkages by ~14 kcal/mol (Scheme 1),^[7] thereby facilitating subsequent bond cleavage reactions. Exemplified are such transformations by the works of Stahl and Westwood, who independently described their two-step depolymerisation pathways through alcohol oxidations using catalytic amounts of AcNH-TEMPO (TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl), combined with inorganic acids^[6b]

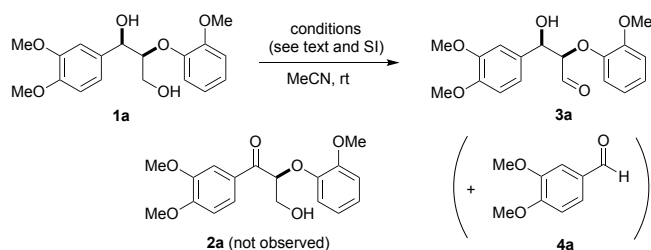


Scheme 1. Oxidations of lignin β -O-4 model compounds **1**.

or DDQ^[6g] followed by acid promoted or reductive C_r-O bond cleavage reactions (Scheme 1, left).^[6d,6g] Both routes proceeded through common ketonic species such as **2** resulting from the oxidation of secondary hydroxyl group at the benzylic position of **1**. However, attempts to address the oxidation of primary hydroxyl group of **1** have only been met with limited success.^[8-10] Realising that this process would lead to intermediates such as **3** prone for retro-aldol reactions, providing cleavage products **4**, **5** and **7** (Scheme 1, right), we felt motivated to explore this less studied alternative. Herein we report the success of the approach and a proof-of-principle study for a transition metal-free (organocatalytic) lignin degradation process.^[11] Lately iodine has been gaining considerable attention as a cheap and environmentally benign element of choice for a variety of catalytic chemical transformations. Around 16% of the iodine produced yearly is utilised in various industrial catalytic processes.^[12] In particular, hypervalent iodine reagents such as (diacetoxy)iodobenzene [PhI(OAc)₂, DAIB] are versatile and environmental safe polyvalent iodine reagents used as mild and selective oxidants.^[12,13] Following this idea, we were intrigued by the fact that DAIB in combination with TEMPO enables the selective catalytic oxidation of primary hydroxyl groups in the presence of secondary ones.^[13] Applying this system to lignin was foreseen to open new synthetic opportunities. To test this hypothesis, we focused our attention on the chemoselective oxidation of the γ -hydroxyl group present in the lignin model compound *erythro* dilignol **1a** (Scheme 2). Neither with TEMPO (1.0 equiv) nor with DAIB (1.3 equiv) alone a considerable conversion of **1a** was observed after 24 h of stirring in acetonitrile at ambient temperature. Combining both the reagents, however, led to a significant increase in the activity. With 0.3 equiv of TEMPO and 1.3 equiv of DAIB a 56% conversion of **1a** was observed after only 3 h at room temperature providing aldehyde **3a** in 43% yield.^[14]

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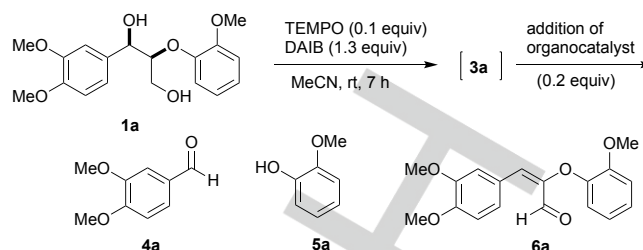


- TEMPO (1 equiv) or DAIB (1.3 equiv): no conv. of **1a** (24 h)
- TEMPO (0.3 equiv) + DAIB (1.3 equiv): 56% conv. of **1a** (3 h), 43% of **3a** and traces of **4a**
- optimal conditions:
TEMPO (0.1 equiv), DAIB (1.3 equiv): >99% conv. of **1a** (7 h), 78% of **3a** and 14% of **4a**

Scheme 2. Chemoselective oxidation of lignin β -O-4 model compound **1a**.^[13]

To our delight ketone **2a** was not observed confirming the high chemoselectivity of the oxidation. Apparently, the primary hydroxyl group of **1a** had been oxidised with great preference over the secondary one.^[13] Trace quantities of veratraldehyde (**4a**) were detected as by-products, which were presumably formed by the retro-aldol reaction of **3a** catalysed by the AcOH developed in situ from DAIB.^[15] Further adjustments of the reaction parameters finally led to the optimal reaction conditions,^[16] which involved the use of 0.1 equiv of TEMPO and 1.3 equiv of DAIB in acetonitrile for 7 h at room temperature.

Next, we focused on the aforementioned retro-aldol step with the goal to find a readily available organocatalyst, which could directly be included into a one-pot reaction sequence starting with the previously developed chemoselective oxidation of lignin β -O-4 model compounds **1**. Again, *erythro* dilignol **1a** was selected as a representative starting material. To our delight, simple DL-proline proved applicable here, effectively catalysing the cleavage of **3a**, which had been generated in-situ from **1a** before (Scheme 3).^[17] Thus, adding 0.2 equiv of DL-proline into the reaction mixture obtained under the preceding oxidation conditions followed by stirring for 5 h at ambient temperature afforded veratraldehyde (**4a**) and guaiacol (**5a**) in 70% and 26% yields respectively, over two steps. Additionally, 5% of elimination product **6a** was isolated by column chromatography Using the methyl ester of DL-proline as catalysts slowed down the retro-aldol reaction and favoured the formation of elimination product **6a**.



organocatalyst	3a [%]	4a [%]	5a [%]	6a [%]
DL-proline	---	70	26	5
DL-proline methyl ester	40	23	5	14
pyrrolidine	---	25	10	58

Scheme 3. One-pot chemoselective oxidation of **1a** followed by organocatalytic retro-aldol reaction of **3a**.^[16]

The latter product was formed predominantly, when the more basic pyrrolidine was applied instead of DL-proline (Scheme 3).^[17] To understand the overall reaction pathway, the progress of the reaction for **1a** was monitored by ¹H-NMR and gas chromatography-mass spectrometry (GC-MS) under the optimised reaction conditions (Figure 1). The reaction profile showed a good correlation between the consumption of **1a** (black line) and the formation of **3a** (grey line), reaching its maximum values (conv. of **1a** = >99%, yield of **3a** = 79%) after 7 h. Additionally, the formation of veratraldehyde (**4a**) (grey dash) was traced from the start of the reaction, which resulted in a 16% yield after the first 7 h. Thereafter the addition of DL-proline led to a spontaneous retro-aldol cleavage of **3a**. The yield of (**4a**) increased to 50% after the first hour of addition and plateaued out at 80% within the next 5 h. A combined analysis of the reaction mixture also led to the detection of the retro-aldol product 2-(2-methoxyphenoxy) acetaldehyde (**7a**) (black dash), which followed a pattern similar to **4a** and resulted in a 10% yield after 7 h. This reactive acetaldehyde derivative proved unstable under column chromatographic conditions and was thus quantified by GC with respect to the internal standard *n*-octadecane (see ESI sections 7 and 8 for details).

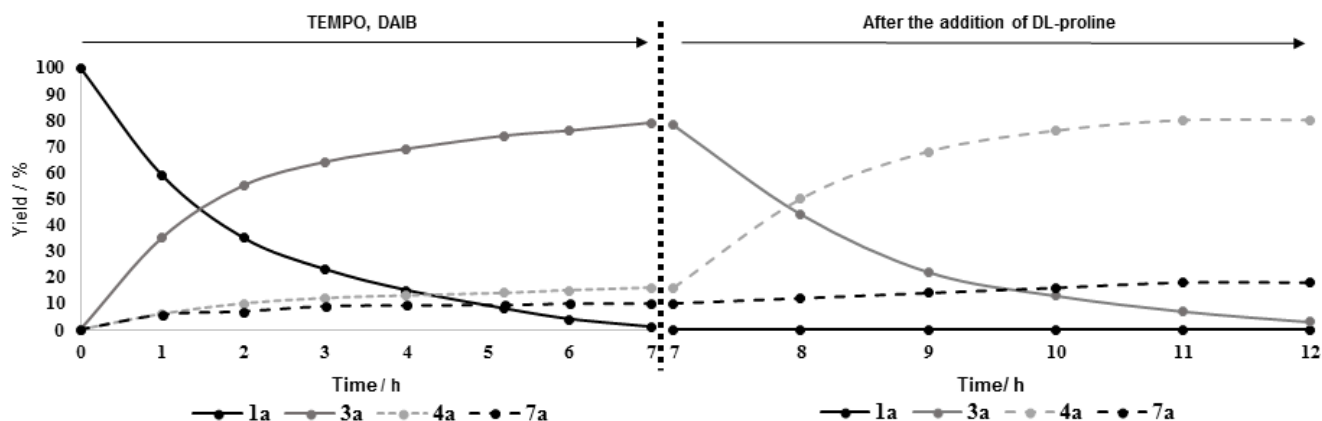


Figure 1. Reaction profile for the one-pot two-step chemoselective oxidation of lignin β -O-4 model compound **1a** (0.250 mmol) under optimised reaction conditions.

Table 1. One-pot two-step degradation of β -O-4 lignin model compounds.^[16]

Entry	Substrate	Cleavage products [Yield] ^[a]		
1	 1a	 4a 76% (70%)	 5a 40% (26%)	 7a 20%
2	 1b	 4a 74% (67%)	 5a 42% (20%)	 7a 19%
3	 1c	 4b 70% (59%)	 5a 35% (12%)	 7a 14%
4	 1d	 4c 79% (68%)	 5a 46% (28%)	 7a 18%
5	 1e	 4a 73% (60%)	 5b 29% (16%)	 7b 32%
6	 1f	 4d 24% (15%)	 5a 17% (5%)	 7a 6%

[a] Quantifications done by gas chromatography with respect to *n*-octadecane as an internal standard. Values within the parenthesis are obtained after column chromatography and are based on an average of two runs.

Moreover, stirring a solution of **7a** and DL-proline in MeCN at room temperature resulted in the formation of guaiacol (**5a**) in 69% GC yield after 1 h (see ESI section 8.2.8). This asserts the low stability of aldehyde **7a** and the reduced yields observed, in comparison to **4a**, after the addition of DL-proline during the second half of the reaction profile (see Figure 1).

Besides the above-mentioned products, minor oxidative by-products from veratraldehyde (**4a**) and guaiacol (**5a**) were also observed (see ESI Table S6 for details).^[18]

With the aim of exploring the generality of the organocatalytic primary alcohol hydroxyl oxidation/retro-aldol approach, analogous cleavage reactions were performed with other β -O-4

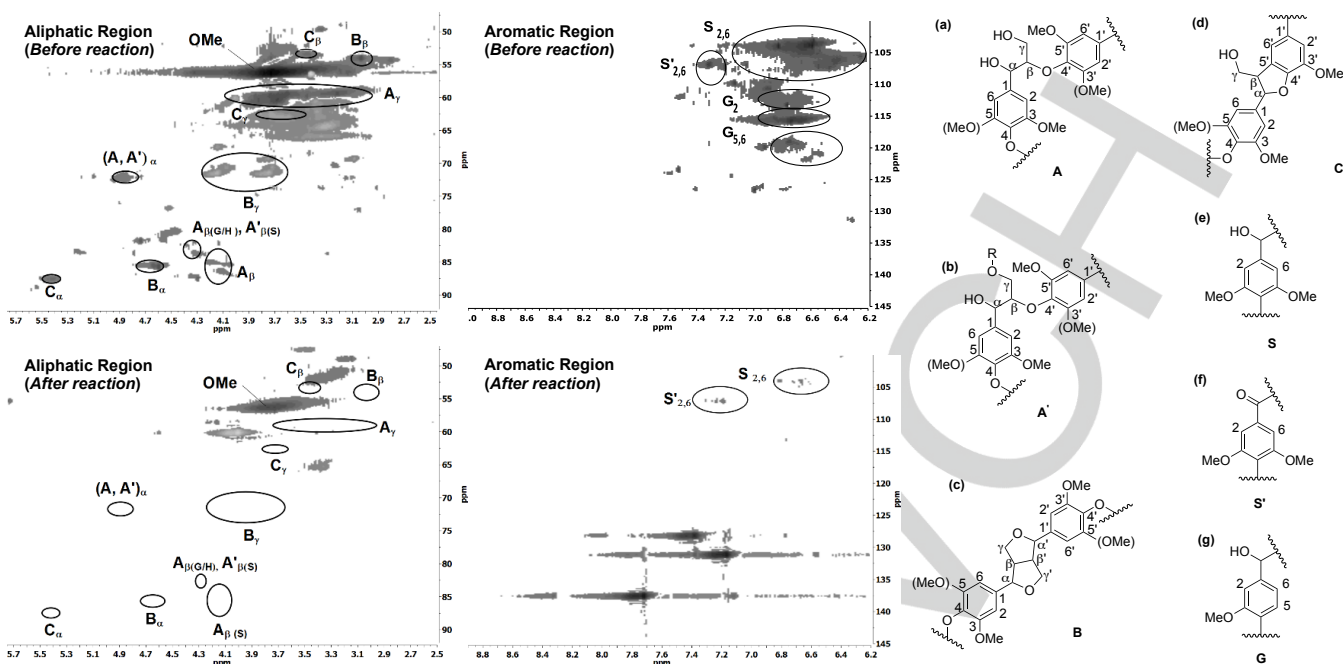


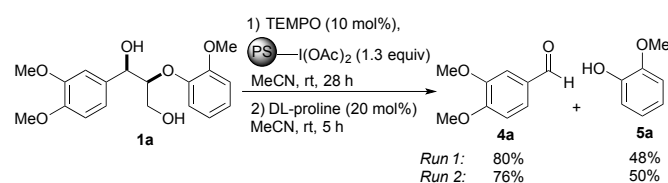
Figure 2. 2D HSQC NMR spectra (in DMSO- d_6) of beech wood lignin (L1): top: before the reaction; bottom: after the two-step degradation reaction; (a) β -O-4 aryl ether linkages with a free-OH at the γ -carbon; (b) β -O-4 aryl ether linkages with acetylated and/or *p*-hydroxybenzoated -OH at γ -carbon; (c) resinol substructures formed by β - β -, α -O- γ -, and γ -O- α' -linkages; (d) phenylcoumaran substructures formed by β -5- and α -O-4-linkages; (e) syringyl units; (f) syringyl unit with oxidised benzylic position; (g) guaiacyl units.

lignin model compounds having primary and secondary hydroxyl groups but varying in the ratios of guaiacyl (G) and syringyl (S) aromatic nuclei and their *erythro* and *threo* stereostructures (Table 1).^[19] Also for those substrates the TEMPO/DAIB system showed excellent selectivity towards the oxidation of the primary hydroxyl groups of **1a-f**. Furthermore, the subsequent addition of DL-proline catalysed the retro-aldol cleavage reaction in all the cases. Table 1 shows the yields for the resulting benzaldehyde derivatives **4** along with the expected methoxyphenols **5** and 2-aryloxyacetaldehydes **7** (component counterparts). The low yields for products **7** and **5** after column purification can be attributed to their low stability and volatile nature, respectively. In general, all model compounds showed high degradations and essentially full conversions (>98%) of **1** were observed after the organocatalytic two-step reaction sequence. *Threo* dilignol **1b** showed a similar reactivity as its *erythro* counterpart **1a** affording veratraldehyde (**4a**) in 67% yield after column chromatography (Table 1, entries 1 and 2). Also, model compounds **1c-e** varying in sterics and substitution pattern at the arenes reacted smoothly, under similar reaction conditions, leading to the corresponding aldehydes and methoxyphenol derivatives in good yields (Table 1, entries 3-5). For instance, cleavage of dilignol **1c** with a (methylenedioxy) phenyl-capped arene provided **4b** in 59% yield after purification along with the detection of 14% of **7a** and 35% of guaiacol (**5a**) by GC (Table 1, entry 3). Furthermore, the presence of the trioxxygenated S-type nuclei in **1d** had no effect on the overall reaction time, and the expected 3,4,5-trimethoxybenzaldehyde (**4c**) was isolated in 68% yield (see ESI 7; Table 1, entry 4). Substrate **1e** with bulkier *ortho*-substituents at the arene however required a longer reaction time, and finally afforded the aldehydes **4a** in 60% yield (see ESI 7; Table 1, entry 5).

Applying G-type model compound **1f** with a free phenolic hydroxyl group as substrate led to a high conversion of the starting material,^[20] with the formation of **4d** and **5a** in 24% and 17% GC yields respectively (Table 1, entry 6; for details on product distribution see ESI 8.2.6).

Substituting DAIB by its immobilised variant poly[4-(diacetoxyiodo)-styrene]^[13e,f] and performing the TEMPO catalysis for 28 h at ambient temperature resulted in the degradation of model compound **1a** to a mixture of **4a** and **5a** in 80% and 48% yield respectively, under otherwise identical reaction conditions (Scheme 4). Pleasantly, using the recycled iodine reagent in a second run gave almost identical product yields (**4a**: 76%, **5a**: 50%).^[21]

The success of the sequential organocatalytic oxidative degradation strategy on lignin model compounds encouraged us to test its applicability on the cleavage of an organosolv beech wood lignin (L1) sample following the one-pot procedure. Based on the 2D HSQC analysis of the first step, the oxidation of the lignin sample resulted in a reduction of C-H signals with a corresponding increase in the carbonyl content typical for aldehydes ($\delta = 9.5$ – 10.0 and 175 – 200 ppm) (ESI, Figure S18). Furthermore, two new cross-peaks at $\delta = 5.5/70.0$ and $5.0/87.0$ ppm were observed after the primary oxidation step that could correspond to the shifted



Scheme 4. Two-step degradation of **1a** using TEMPO/immobilized DAIB catalytic system.

C–H and C–H₂ groups post primary-alcohol-oxidation step. Furthermore, the aliphatic and aromatic regions in the 2D-NMR HSQC spectra both before and after the one-pot two-step degradation (reaction of lignin sample **L1**) are also depicted in figure 2.²² As revealed by the disappearance of their characteristic signals, several interconnecting bonds including the β -O-4 linkages contained in substructures **A** and **A'**, the resinol units **B**, and phenylcoumaran substructure **C** were cleaved following the two-step degradation strategy. Since the exact structural modifications after the two-step cleavage reaction could not be specified by the NMR technique, the reaction mixture was analysed by gel permeation chromatography (GPC) to determine the post degradation change in the molecular weights of lignin **L1**. Figure 3 shows the mass distribution for the organosolv lignin **L1** (top) and the corresponding elugram (bottom). A double shift in the mass maximum of the treated sample **L1** towards lower molecular weights was observed (grey line). The maximum mass value in the original **L1** sample at 3537 Dalton (black line) was significantly reduced by 29% and 41%. In addition, a broad peak having initially a mass maximum at approximately 10206 Dalton showed a decrease of 32% after the cleavage. Most importantly, the absence of peaks at higher molecular weights after the reaction, greater than the original **L1** sample, precluded the possibility of lignin re-polymerisation under the cleavage reaction conditions. In addition to this, the organic fraction, which accounted to 15 wt% of the starting lignin **L1** was also analysed by GC-MS. This confirmed the presence of low-molecular monomeric aromatics such as 0.3 wt% guaiacol, 2.5 wt% syringaldehyde and 1.1 wt% vanillin, with respect to the starting lignin sample, which are typical products found in the cleavage reactions of hardwood lignin (see ESI for details).

In conclusion, we developed an organocatalytic one pot two-step degradation strategy for lignin β -O-4 model compounds and representative lignin sample **L1** at room temperature.^[23] In contrast to the prevalent oxidations of the benzylic secondary hydroxyl groups, the reaction sequence is initiated by a TEMPO-catalysed DAIB oxidation addressing the primary hydroxyl units. For this step, also a recyclable polymer-bound oxidant can be applied. Proline-catalysed retro-aldol reactions then lead to lignin degradations by various C–C bond cleavages as confirmed by 2D NMR (HSQC), GPC, GC-MS. analysis. We realise that for applying this proof-of principle approach on an industrially relevant scale, the reagent amounts are high and the production of monoaromatic products low. Consequently, our future efforts will be directed towards the screening and optimisation of reliable lignin samples obtained from different upstream processes along with increasing the overall efficiency of the process in terms of both oxidation as well as the subsequent base cleavage reaction. In this context, based on our preliminary results with immobilised DAIB variant, an important advancement would be to develop a chemoselective catalytic primary hydroxyl oxidation using supported oxidants in a flow reactor system.

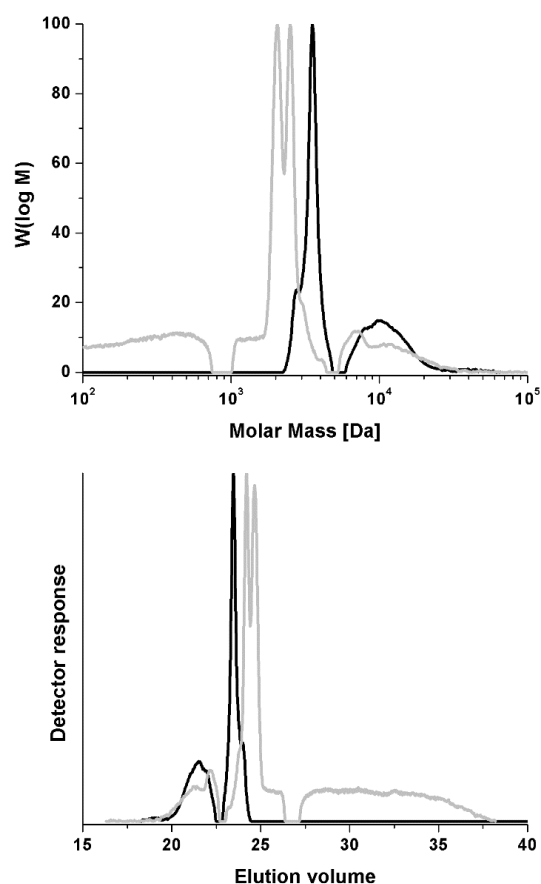


Figure 3. GPC measurements of the ethanosolv beech wood lignin sample before (black) and after the treatment (grey). The mass values acquired are relative with respect to the external calibrations with polystyrene sulfonate standards.

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Keywords: lignin • organocatalysis • alcohol oxidation • one-pot • retro-aldol • C_α–C-bond cleavage

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- [14] Aldehyde **3a** was unstable to column chromatography. The formation of **3a** was therefore monitored by ¹H NMR spectroscopy of the crude reaction mixture using the signals for the α,β protons as indicators. The structural assignment was further confirmed by reduction of **3a** with NaBD₄ to give **1a-D**. For details, see Supporting Information (Fig. S1). The conversion of **1a** and the yields of **2a** and **4a** presented in Scheme 2 were determined by ¹H NMR with 1,4-dinitrobenzene as internal standard.
- [15] A chemoselective TEMPO/DAIB oxidation of **1a** with in the presence of 2 equiv of AcOH led to the formation of **3a** and **4** in 68% and 24% yield, respectively, thereby confirming the role of AcOH in the retro-aldol reaction of **3a**. For details, see Supporting Information (Table S1, entry 11).
- [16] See Tables S1 and S2 in the Supporting Information.
- [17] For the results of the catalyst screening, see Table S3 in the Supporting Information.
- [18] Guaiacol (**5a**) reacted with DAIB (1.0 equiv) and TEMPO (0.1 equiv) leading to a mixture of products (see ESI 8.2.7). These results were in agreement with the reported investigations on DAIB-assisted oxidations of **5a** to benzoquinone derivatives. For details, see: a) S. Quideau, L. Pouységu, D. Deffieux, A. Ozanne, J. Gagnepain, I. Fabre, M. Oxoby, *ARKIVOC* **2003**, *6*, 106–119; b) T. -C. Kao, G. J. Chuang, C. C. Liao, *Angew. Chem.* **2008**, *120*, 7435–7437; *Angew. Chem. Int. Ed.* **2008**, *47*, 7325–7327; c) S. Y. Gao, S. K. Chittimalla, G. J. Chuang, C. -C Liao, *J. Org. Chem.* **2009**, *74*, 1632–1639; d) T. Dohi, T. Nakae, N. Takenaga, T. Uchiyama, K. I. Fukushima, H. Fujioka, Y. Kita, *Synthesis* **2012**, *44*, 1183–1189; e) S. K. Chittimalla, R. Kuppusamy, N. Akavaram, *Synlett* **2015**, *26*, 613–618; f) S. K. Chittimalla, C. Bandi, *Tetrahedron Lett.* **2016**, *57*, 15–19.
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- [21] The supported catalyst was regenerated as follows: A peracetic acid solution was prepared by the dropwise addition of 30% H₂O₂ (2.0 mL) to Ac₂O (6 mL) at 0 °C. The solution was slowly warmed to room temperature and stirred overnight. Then, this solution was

added to the recovered poly(4-iodostyrene) (220 mg, 0.325 mmol). The reaction was stirred at 50 °C overnight. The resultant mixture was precipitated with diethyl ether and filtered to give poly[4-(diacetoxyiodo)styrene] (300 mg) as a light yellow powder.

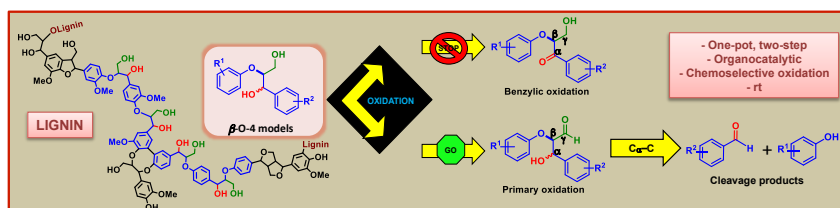
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**Organocatalytic Chemoselective
Primary Alcohol Oxidation and
Subsequent Cleavage of Lignin Model
Compounds and Lignin**



Text for Table of Contents

Follow your primary intuition! An unprecedented route for the degradation of lignin model compounds and lignin has been developed, via catalytic oxidation of the primary hydroxyl groups in β -O-4 lignin units by a TEMPO/DAIB system. This unique pathway widens the scope of the existing strategies in the area of lignin depolymerization.