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Selective Depolymerisation of γ -Oxidised Lignin via NHC Catalysed Redox Esterification

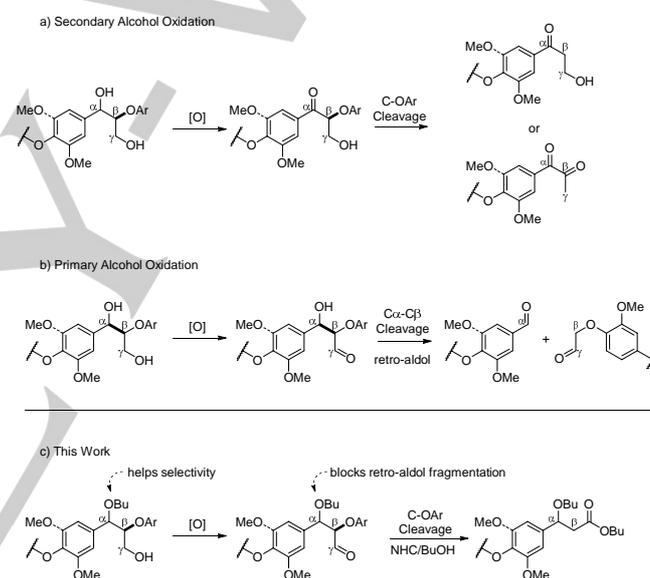
Ganyuan Xiao, Christopher S. Lancefield* and Nicholas J. Westwood*

Abstract: The development of new catalytic methods for the processing of lignocellulose-derived renewable feedstocks continues to gain momentum, despite the considerable challenges associated with the use of complex biopolymers such as lignin. Here, we report a new two-step depolymerisation method for lignin involving primary alcohol oxidation followed by a NHC-mediated redox esterification-depolymerisation step. The process takes advantage of the inherent structure of the β -aryl ether units present in the specific type of lignin that was used (butanosolv) and delivers 4 novel aromatic monomers which retain the C₃ side chain present in the lignin subunits. The utility of the major product is assessed suggesting that rapid access to a wide range of interesting chemical could be achieved from this renewable building block.

Lignocellulosic biorefineries, which do not utilise food crops, have received a great deal of attention in recent years. This is driven by the fact that they are potential sources of renewable sugars that can be used as platform molecules in a renewable chemical industry. A major co-product from such biorefineries is lignin, an aromatic biopolymer which accounts for around 15-30 wt% of the initial feedstocks.^[1] Furthermore, improvements in the efficiency of pulp and paper mills, coupled with the advent of new lignin isolation processes,^[2-4] has resulted in the increased production of industrial kraft lignin. As a result, there has been a renewed interest in the isolation and valorisation of different types of lignin. Various different strategies are currently being explored to achieve this by many different research groups,^[5] with one significant approach being via depolymerisation of the lignin to give aromatic monomers which could function as renewable aromatic feedstocks for a future chemical industry.

Owing to the heterogenous structure of lignin, the production of defined sets of aromatic compounds that can be readily purified is particularly challenging. One general approach that has recently been exploited to achieve this involves a two-step process; the first step being a selective oxidation of either the secondary benzylic (Scheme 1a)^[6-11] or primary alcohols^[12-14] (Scheme 1b) in the most abundant β -aryl ether (β -O-4) linkage in lignin. This activates the lignin towards controlled depolymerisation in a second step (Schemes 1a and 1b). Due to the fact that these processes require two suitably cleavable β -aryl ether units to be next to each other to release one monomer, a key requisite for their success is the presence of large amounts of β -aryl ether linkages in the starting lignin.^[15,16] Unfortunately, even though β -aryl ether linkages are the most abundant linkage in native lignins, they are also the most chemically labile and therefore frequently become depleted during the lignin isolation (pretreatment) process.^[1]

As a result, new pretreatment methods have been developed which feature *in situ* stabilisation strategies to preserve β -aryl ether units, at the same time as providing high quality carbohydrate streams.^[17] We have recently reported on the use of n-butanol (BuOH) as a pretreatment solvent (butanosolv) for this purpose.^[18] This process provides butanosolv lignins in high yield and with relatively high β -aryl ether content, but in contrast to native lignins which have an -OH at the α -position of the β -aryl ether unit, they display extensive incorporation of BuOH at this position. This significantly modifies the properties of the lignin, for example making them much more soluble in many common organic solvents, and therefore opens up new possibilities for (catalytic) chemical transformations.



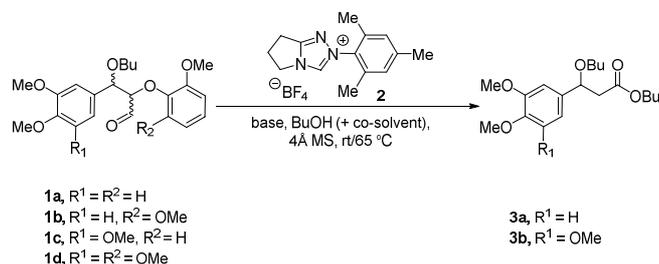
Scheme 1. Previously reported two-step oxidative approaches to lignin depolymerisation via a) secondary^[6-11] or b) primary alcohol^[12-14] oxidation of native type β -aryl ether linkages lignin compared to this work c) employing selective oxidation and NHC catalysis for the depolymerisation of butanosolv lignin β -aryl ether linkages.

Inspired by previous pioneering work on the oxidation of the primary alcohol in lignin by Bolm et al.^[12] and the NHC catalysed redox-esterification of α -phenoxyaldehydes by Smith et al.,^[19] we proposed a new two-step depolymerisation route for butanosolv lignins (Figure 1c). We believed that the incorporation of BuOH into the β -aryl ethers would be key to achieving this selective transformation as it not only simplifies the selectivity challenges in alcohol oxidation, but also prevents the usually observed retro-aldol C α -C β fragmentation pathway following conversion of the primary alcohol to the aldehyde.^[12,20]

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Table 1. Optimisation of NHC catalysed redox esterification and cleavage of butanosolv lignin β -aryl ether γ -aldehyde models.



Entry	Model	2 (mol%)	Co-solvent ^[a]	Base ^[b]	Temp. (°C)	Time (hrs)	Yield of 3 (%) ^[c]
1	1a	20	DCM	Cs ₂ CO ₃	25	24	69
2	1a	20	DCM	K ₂ CO ₃	25	24	0
3	1a	20	DCM	NEt ₃ ^[d]	25	24	30
4	1a	20	THF	Cs ₂ CO ₃	25	24	66
5	1a	20	THF	Cs ₂ CO ₃	65	6	86
6	1a	20	THF	Cs ₂ CO ₃	65	24	91
7	1a	10	THF	Cs ₂ CO ₃	65	6	43
8	1a	10	THF	Cs ₂ CO ₃	65	24	45
9	1b	20	THF	Cs ₂ CO ₃	65	6	93
10	1c	20	THF	Cs ₂ CO ₃	65	6	92 (3b)
11	1d	20	THF	Cs ₂ CO ₃	65	6	90 (3b)
12	1a	20	-	Cs ₂ CO ₃	65	24	81

[a] BuOH:co-solvent = 3:1 [b] Pre-catalyst **2**:Base = 1:0.9 [c] Isolated yields [d] 1 equivalent was used See Table S1-S4 for more detailed optimisation studies.

We started our investigations with the synthesis of a series of oxidised dimeric model compounds (**1a-d**) (Scheme S1) which represent the different types of units that would be found in oxidised soft or hardwood butanosolv lignins (lignin ^{γ -ox}). The NHC catalysed redox-esterification step was then investigated using **1a-d** and a previously reported triazolium based pre-catalyst **2**.^[19] Typically, in these types of reactions the aryloxy leaving group rebounds, undergoing acylation by the acyl azolium intermediate, regenerating the NHC catalyst (Scheme S2). In the case of lignin, this approach would result in rearrangement but not depolymerisation of the polymeric chains, therefore we proposed the use of an alcohol co-solvent (BuOH) which would out-compete the phenoxy leaving group for acylation by the acyl azolium intermediate resulting in depolymerisation of the lignin and the release of monomeric compounds (Scheme S3).

Gratifyingly, our initial investigations proved very encouraging. Reaction of **1a** with 20 mol% **2** and 18 mol% Cs₂CO₃ in BuOH/DCM (3:1) provided the intended cleavage product **3a** in 69% yield (Table 1, entry 1). Changing the base to

either K₂CO₃ (entry 2) or NEt₃ (entry 3) proved detrimental to the yield, however changing the solvent to the non-halogenated, higher boiling point and potentially biomass derived THF was well tolerated (entry 4). Increasing the reaction temperature to 65 °C allowed the reaction time to be reduced from 24 to 6 hours (entries 5 and 6) but decreasing the catalyst loading resulted in a significant drop in yield (entry 7), even after extended reaction times (entry 8). Extending these reaction conditions to the other model compounds **1b-1d** showed that the methodology was generally applicable, with excellent yields of **3a** or **3b** being obtained in all cases (entries 9-11). We also found that the reaction proceeded smoothly in 100% BuOH (entry 12) indicating that THF was not necessary but is advantageous for eventual lignin solubility. The conversion was also still excellent using 100% DCM as the solvent but, in the absence of BuOH, a more complex product mixture was obtained consisting predominantly of rebound products (Scheme S4).^[21]

With optimised conditions identified for the NHC catalysed cleavage of model compounds **1a-1d**, we turned our focus to the depolymerisation of a real lignin substrate. Thus, a beech butanosolv lignin was prepared according to previous reports^[18] and the oxidation of the primary alcohol groups to aldehydes in the β -aryl ether linkages was attempted using the biphasic TEMPO/NCS catalytic system developed by Einhorn *et al.*^[22] In contrast to our previous reports on the direct TEMPO-catalysed oxidation of this alcohol to carboxylic acids,^[23] attempts to perform this reaction on the butanosolv lignin failed to provide the expected aldehyde product. Reasoning that this was likely due to competing and complicating oxidation of the abundant phenol groups in lignin, we selectively methylated them using the MeI/TBAF protocol reported by Lu and Ralph.^[24] Once methylated (Figure 1A), the lignin could be smoothly oxidised to give the intended aldehyde, which was characterised by HSQC NMR (Figure 1B). With the desired lignin ^{γ -ox} aldehyde in hand, we transferred the optimal reaction conditions identified for the NHC-catalysed reaction in our model studies to this substrate. These also proved successful on lignin, with complete disappearance of signals associated with β -aryl ether γ -aldehyde units and the appearance of new signals consistent with formation of the intended cleavage products (Figure 1C) being observed in the HSQC NMR spectrum obtained on analysis of the crude reaction mixture. Additionally, cross peaks for resinol (β - β) units were clearly observed in all the spectra (c.f. Figures 1A and 1B with 1C), indicating that they are preserved during the oxidation-depolymerisation sequence. Subsequent purification of the crude products by column chromatography gave **3a**, **3b** and **3c** as an inseparable mixture (0.6wt%, 1.2wt% and 0.6wt% yields respectively based on quantitative ¹H NMR analysis) and **3d** (2.6wt%) (Scheme 2) providing us with a new set of lignin-derived monomeric aromatic building blocks. It is interesting to note that **3a** and **3b** are generated only from (methylated) terminal β -aryl ether units, while **3c** and **3d** derive from internal units that have required two sequential β -aryl ether cleavages to be released. Based on semi-quantitative analysis of the HSQC NMR data (Figure 1b), which can be used as a guide but should not be viewed as quantitative, we estimate that β -aryl ether γ -aldehydes are present at a level of approximately 22 per 100 C₉ units. Thus, assuming a polymer of infinite length,

the maximum molar yield of monomers arising from the selective cleavage of such units would be approximately 5wt%, or about 6wt% accounting for incorporation of BuOH.^[15,16] This suggests that our depolymerisation method is actually rather efficient at releasing the potentially available monomers from the lignin polymer, although the overall yield (5wt%) appears moderate.

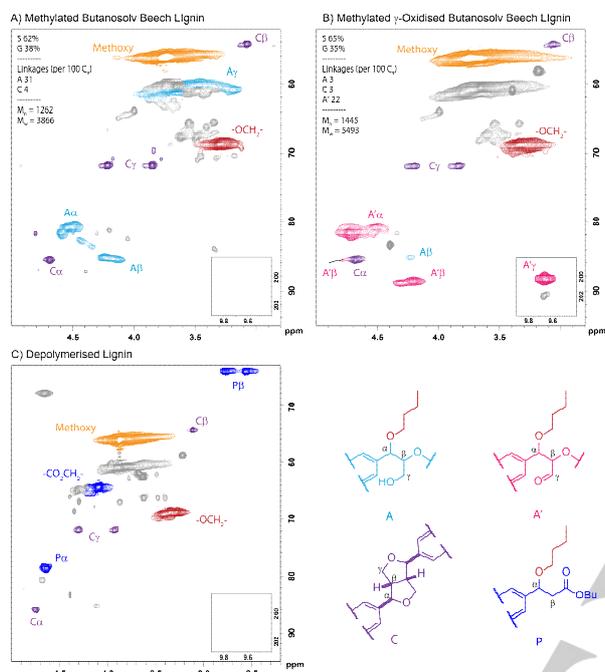
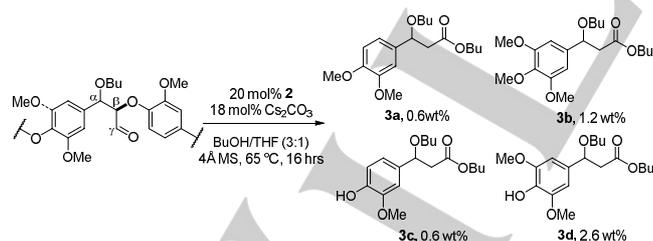


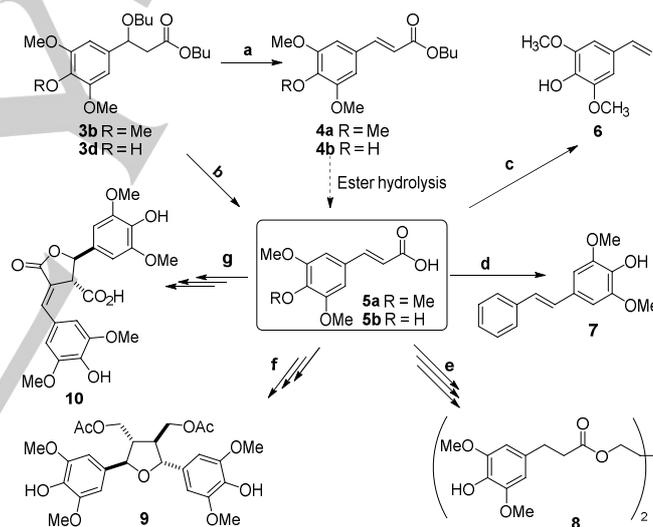
Figure 1. Lignin 2D HSQC NMR spectra at each stage of the depolymerisation process. A) Phenol methylated beech butanosolv lignin. B) Beech butanosolv lignin^{γ-ox} aldehyde. C) Crude mixture of depolymerised products after NHC mediated redox esterification-depolymerisation. Full spectra are available in Figures S3-S5. Whilst no apparent change in total β-O-4 content was observed after oxidation as assessed by integration of the corresponding 2D HSQC spectra.^[21]



Scheme 2. Depolymerisation of beech butanosolv lignin^{γ-ox}. Given the requirement for monomer production from lignin via approaches of this type required that there are two adjacent β-O-4 units, the yields of **3a**, **3b**, **3c** and **3d** could alternatively be stated as 10wt%, 20wt%, 10wt% and 43wt% respectively, based on a theoretical monomer yield of ~5 mol% or ~6wt% accounting for butanol incorporation.^[15,16]

To demonstrate the potential utility of the produced monomers, the transformation of **3b** and **3d** to their respective cinnamate ester derivatives was investigated. We found this could be achieved in near quantitative yield by heating the

compounds with a catalytic amount of methanesulfonic acid in toluene for just 10 minutes giving **4a** or **4b** at the same time as releasing one equivalent of the BuOH that was introduced into the lignin during the pretreatment process (Scheme 3 (reaction a) and Figures S1 and S2). Alternatively, direct conversion of **3d** to sinapic acid (**5b**) was achieved under basic conditions (Schemes 3 (reaction b) and S8). Similar compounds such as *p*-coumaric and ferulic acid can be obtained directly by alkaline hydrolysis of herbaceous biomasses or lignins,^[25–28] however sinapic acid derivatives cannot be isolated in the same way. Thus, our methodology provides a complimentary way of accessing derivatives of these versatile renewable aromatic building blocks. To highlight the potential value further a selection of interesting transformations reported in the literature involving **5b** are also summarised in Scheme 3. For example, NHC-catalysed decarboxylation of **5b** gives 4-vinylsyringol **6** (Scheme 3 (reaction c)) a potent antimutagenic compound,^[29,30] whilst palladium catalysed decarboxylative coupling with arylboronic acids gives stilbenes such as **7** (Scheme 3 (reaction d)).^[31] **5b** can also serve as the starting point for the synthesis of more complex molecules such as the potential antioxidant dimer **8** and structures **9** and **10**.^[32–34]



Scheme 3. Conversion of selected lignin depolymerisation products to cinnamate-type esters and acids and examples of literature conversions of sinapic acid (**5b**). Reaction conditions: This work: a) MsOH, *d*₈-toluene, 90 °C, 10 min, 93% (**4a**), 91% (**4b**); b) KO^tBu, *i*-PrOH, 120 °C, 24 h, 96% (**5a**), 94% (**5b**); Literature reports using **5b**: c) 1-Ethyl-3-methyl imidazolium acetate, DMSO, 100 °C, 60 min, 100%^[29,30]; d) Phenylboronic acid, Pd(acac)₂, Cu(OAc)₂, LiOAc, DMF, 60 °C, 8 h, 89%^[31]; e) (i): HCl, EtOH, reflux, 2d; (ii): H₂, Pd/C, EtOAc, 10 °C, 45 min; (iii) 1,4-Butanediol, CAL-B, 75 °C, 4–72 h, 87%^[32]; f) (i): Horseradish peroxidase–H₂O₂, aq. acetone; (ii) acetic anhydride/pyridine; (iii) bromine, NH₄OAc, AcOH, 50 °C, 6 h; (iv) AcCl–MeOH, 16 h; (v) Pd/C–Et₃N, H₂, MeOH, 2d, 80%; (vi) DIBAL-H, toluene, 2 h; (vii) pyrrolidine, 3 min^[33]; g) (i) FeCl₃, EtOH, RT., 1h; (ii) 1N NaOH, RT., 5 min, 62%^[34].

In summary, several different elegant methods have previously been reported for the selective oxidation and depolymerisation of lignins, either via the oxidation of the secondary or primary alcohols. Here we have demonstrated, for the first time, that the same general approach can be used for the selective depolymerisation of butanosolv lignins, that contain

high degrees of α -butoxylation in their β -aryl ether linkages. This feature, which precludes the use of previously reported methodologies, is key for enabling, the facile oxidation of the primary alcohols after phenol methylation. This provides a relatively stable β -aryl ether γ -aldehyde containing lignin (lignin^{γ-ox}) which can be depolymerised selectively in the presence of BuOH using an NHC catalyst generated from **2**. The resulting monomeric ester products could be purified by column chromatography, giving **3d** as the major compound from a beech butanosolv lignin. This biomass derived aromatic monomer, which has not previously been obtained from lignin, was shown to be efficiently converted into cinnamic acid derivatives opening the door to a wide range of useful chemical transformations and the production of high value products.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

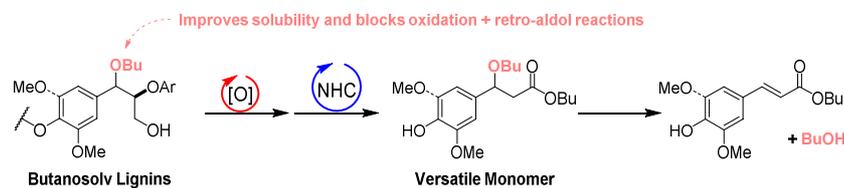
Keywords: lignin • oxidation • NHC catalysis • biomass conversion • butanol

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Layout 2:

COMMUNICATION



Ganyuan Xiao, Christopher S. Lancefield* and Nicholas J. Westwood*

Page No. – Page No.
Selective Depolymerisation of γ -Oxidised Lignin via NHC Catalysed Redox Esterification

Selective Lignin Depolymerisation: Using butanosolv lignins with high degrees of butanol incorporation at the α -position of the β -aryl ether units facilitates oxidation of the primary alcohols to stable aldehydes. Subsequent, depolymerisation via an NHC catalysed redox esterification process is demonstrated which yields selectively synthetically versatile aromatic monomers.