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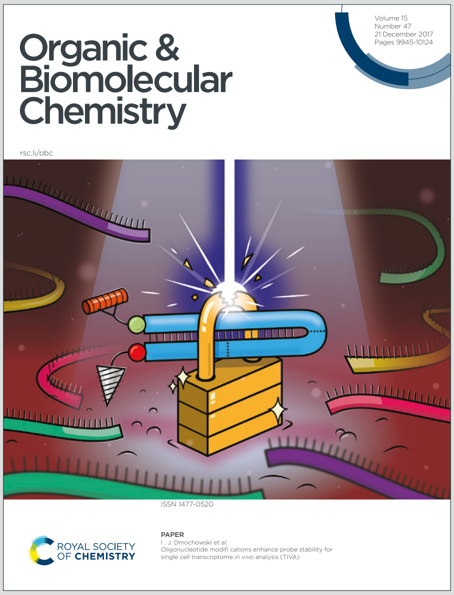

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Cleavage of Lignin Model Compounds and Lignin^{ox} using Aqueous Oxalic Acid

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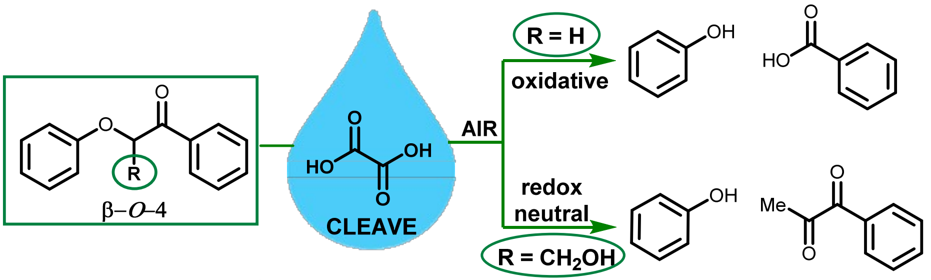

× Organic solvent
× Metals
× Hazardous reagents

✓ Water as solvent
✓ Bio-based oxalic acid
✓ Atmospheric pressure

Abstract

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Aqueous oxalic acid cleaves oxidised β-*O*-4 lignin model compounds by two distinct mechanisms that is dependent on the presence of the hydroxymethyl substituent. Various β-*O*-4 phenoxyacetophenones that do not contain the hydroxymethyl substituent undergo oxidative cleavage upon exposure to aqueous oxalic acid in the presence of air, likely through concerted ring opening of a dioxetane intermediate to give the corresponding benzoic acid and phenyl formate. Importantly, detrimental side reactions arising from singlet oxygen and hydroperoxy radicals (from both O_2 and oxalic acid) are minimal when the cleavage is run under air compared to neat oxygen. When oxidised β-*O*-4 lignin model compounds bearing the hydroxymethyl group are cleaved by aqueous oxalic acid, the resulting diketone and phenol products arise from a redox neutral cleavage that is analogous to the formic acid-sodium formate mediated lignin cleavage process reported by Stahl. Aqueous oxalic acid also cleaves lignin itself, with oxidised milled wood lignin (MWL^{ox}) from *Pinus radiata* giving a 14% yield of ethyl acetate soluble aromatics with good selectivity for vanillin. Aqueous oxalic acid appears to be a promising lignin cleavage system given the benign, bio-based reagents, absence of metals and organic solvents and a simple extraction procedure that enables oxalic acid recycling.

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Introduction

The vast majority of carbon-based chemicals manufactured within the global chemical industry are derived from finite fossil reserves[1]. A sustainable alternative to current practise will involve biorefineries processing renewable biomass into valuable base chemicals that can replace those currently sourced from non-renewable resources[1-3]. The main feedstock in these biorefineries will be lignocellulosic biomass (dry plant matter) that consists of cellulose (35-50%), hemicellulose (20-35%) and lignin (10-25%)[4]. Lignin, an excellent potential source of bio-based aromatic compounds, is a robust, amorphous biopolymer made up of phenylpropanoid units randomly linked via several distinct C-O and C-C crosslinks that render the biopolymer resistant to depolymerisation (Figure 1)[3, 5-13]. The most abundant linkage within lignin is the β-*O*-4 alkyl aryl ether (*ca* 50% of linkages in both soft and hardwood), efficient cleavage of which is vital its depolymerisation[8, 12, 14-21].

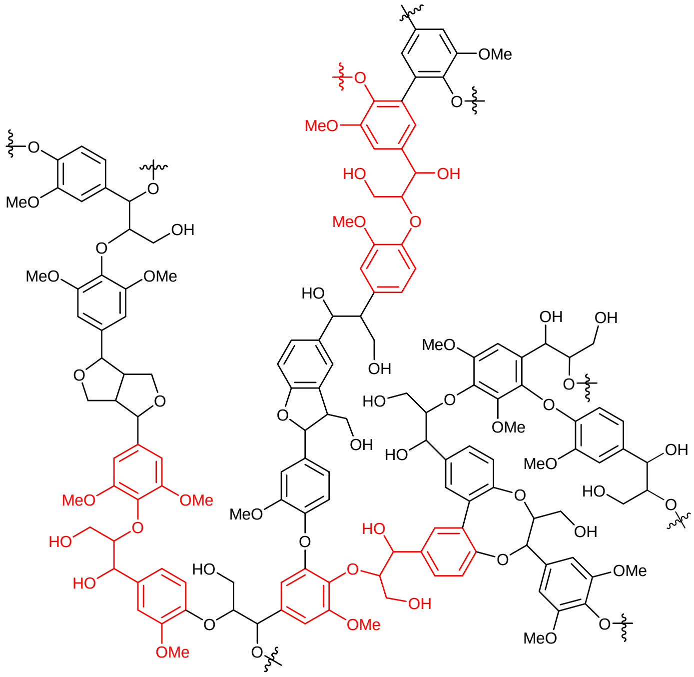

Figure 1: Representative lignin structure highlighting β-*O*-4 aryl ether linkage (red).

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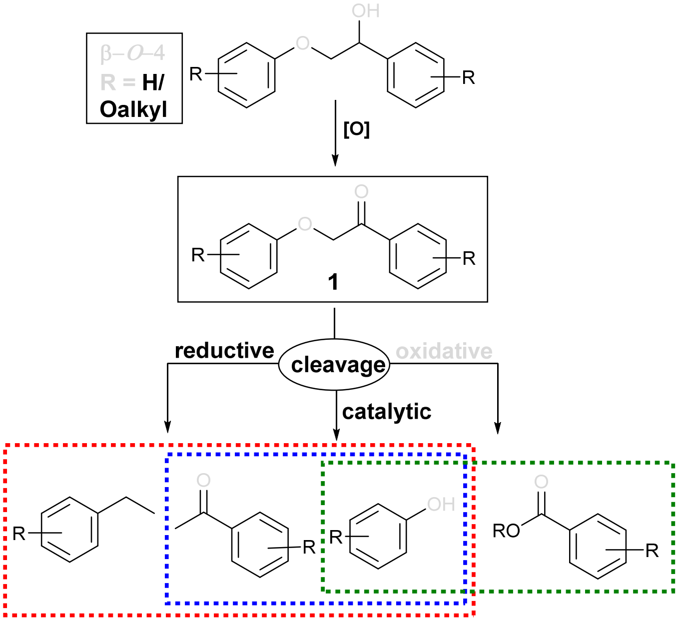
A common strategy for cleavage of the β-*O*-4 linkage involves an initial oxidation to give the β-*O*-4 phenoxyacetophenone **1**, and subsequent C-O bond scission[17, 18, 21]. The oxidation step results in a decrease in the dissociation enthalpy of the C-O aryl ether bond, allowing for more mild cleavage conditions to be subsequently employed[22]. Existing methods for the cleavage of oxidised β-*O*-4 phenoxyacetophenone system **1** include a variety of reductive[23-29], oxidative[30-40] and catalytic processes[41-50] that yield different aromatic cleavage products depending on conditions used (Scheme 1).



Scheme 1: Oxidation of the β-*O*-4 linkage and cleavage of the resulting β-*O*-4 phenoxyacetophenone under reductive[23-29], oxidative[30-40] and catalytic conditions[41-50].

Many of the cleavage methods outlined in Scheme 1 use organic solvents[23, 25, 30, 32, 37, 38, 44-48], including acetonitrile[27, 36, 41-43, 50], *n*-hexanes[26] toluene[31] and ethyl acetate[24] that present environmental and safety concerns, particularly on large scale[51]. Existing reductive cleavage methods require flammable hydrogen gas[23-27], often at high pressure[24, 26, 28] and temperature

(150-275 °C)[23-28], in the presence of transition-metal catalysts[23-29]. Catalytic approaches use a range of transition-metal photocatalysts[41, 42, 44-46, 50], porous organic frameworks[43] and catalysts based on palladium[47]. Current oxidative procedures[30-40] require transition-metal catalysts[30-32, 36, 40] and can feature undesirable additives such as H_3PO_4[33] and $BF_3 \cdot OEt_2$[30].

A valuable addition to the existing methods outlined in Scheme 1 would be a cheap, robust cleavage protocol that is mediated by air[40] at atmospheric pressure and free from both organic solvent and metals. Our preliminary proposal towards this goal is shown in Scheme 2. The diacid oxalic acid would mediate the enolisation of the phenoxyacetophenone system **2** under aqueous conditions to give **3** that upon reaction with the oxygen present in air would undergo C-O bond cleavage[30-39] to the corresponding phenol (**4**) and benzoic acid (**5**). Oxalic acid is a good candidate for large scale lignin depolymerisation as it is a low cost, water soluble crystalline solid that is stable at room temperature[52, 53]. It is fully biodegradable, natural compound that is industrially manufactured through the oxidation of carbohydrates from biorenewable feedstocks such as sugar, reclaimed starch and molasses, with a world-wide manufacturing capacity currently in excess 150,000 tonnes per annum[52]. A recent report detailing the production of oxalic acid by hydrogenation of carbon dioxide emphasises its potential as a readily accessible, biobased reagent for future industrial processes[54]. Furthermore, the fractionation of lignocellulosic biomass into hemicellulose sugars, cellulose pulp and lignin using the oxalic acid-based OrganoCat process further highlights the potential of oxalic acid in biomass processing[55, 56].

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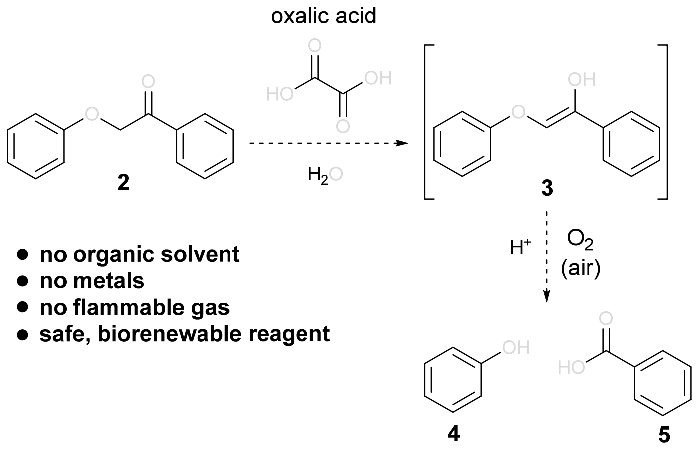

Scheme 2: Proposed metal and organic solvent-free oxidative cleavage of the β-*O*-4 linkage

Results and Discussion

We set out to examine the proposal in Scheme 2 and began by subjecting the β-*O*-4 model **6** to aqueous oxalic acid in the presence of air (Table 1). Treating the model **6** with a 0.02 M aqueous solution of oxalic acid at 100 °C gave trace amounts of *p*-anisic acid (**7**) (entry 1). Increasing the concentration of oxalic acid to 1 M and 2 M did not improve the yield of the cleavage product **7** (entry 2 and 3). Gradually increasing the concentration of oxalic acid (3-16 M) increased the yield of **7** to 73%, also resulting in the isolation of guaiacol (**8**) in all cases (entries 4-7). The instability of guaiacol (**8**) under oxidative conditions[30, 57, 58] explains the low yield in this instance. When no oxalic acid was present, only trace amounts of **7** were observed, clearly indicating oxalic acid is vital for the cleavage reaction (entry 8). When the cleavage was conducted under nitrogen gas, the reaction stalled after 24 h, indicating that the oxidative conditions were indeed essential for efficient cleavage (entry 9). However, when the cleavage reaction was run under an oxygen atmosphere, the yield of *p*-anisic acid (**7**) greatly reduced and *p*-acetanisole (**9**) was formed (entry 10). This unexpected result suggested there was more than one mechanism operating in this process. Indeed, the oxidative cleavage of β-*O*-4 linkages mediated by O_2 has been proposed to occur through singlet oxygen[59], radical intermediates[30,

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[32, 33, 36] or direct reaction with oxygen[34]. In order to decipher the mechanism(s) underpinning this cleavage reaction, a detailed mechanistic study was performed. First, the singlet oxygen generator Rose Bengal[60] was added to the cleavage reaction under an oxygen atmosphere in under ambient light conditions and in the presence of a desk lamp (entries 11-12). These conditions slightly reduced the yield of **7**, but led to a slight increase in yield of *p*-acetanisole (**9**)[59]. When Rose Bengal was added to reaction under air, the cleavage was significantly inhibited (entry 13). The combination of these results indicate that the formation of **9** is likely occurring through a singlet oxygen mediated process that is most prevalent when a pure oxygen atmosphere is present. Next, in order to determine if the formation of **7** and **8** proceeded through a radical pathway, the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)[34] was added to the reaction under an air atmosphere, which led to no significant effect on the yield (entries 7 vs 14). This suggests that the formation of **7** and **8** does not occur via a radical mediated process; indeed, the addition of TEMPO under an oxygen atmosphere led to an increased yield of *p*-anisic acid (**7**) in a much faster reaction time (entry 15). This result is likely due to the quenching of hydroperoxy radicals[30, 32, 33, 36] photolytically formed under an oxygen atmosphere that are otherwise detrimental to the cleavage reaction (entries 10 v 15). Next, we set out to investigate if oxalic acid, which is known to undergo degradation in the presence of oxygen and light to produce hydrogen peroxide (and hence hydroperoxy radicals) and carbon dioxide[61], was detrimental to the reaction. Thus, the cleavage reaction was conducted in the dark, and in the presence of a desk lamp, to hinder and promote H_2O_2 production from oxalic acid, respectively. When the cleavage was run in the dark, the yield of *p*-anisic acid (**7**) was significantly increased compared to ambient light conditions (entries 10 and 16) and only trace amounts of *p*-acetanisole (**9**) were observed. When a desk lamp was shone onto the reaction, a reduced yield of *p*-anisic acid (**7**) was observed that was more in agreement with the initial surprising result (entries 10 and 17). These results infer that oxalic acid undergoes a light-O_2

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mediated degradation into hydrogen peroxide and hydroperoxy radicals[61] that are detrimental to the cleavage, and that this process is most noticeable when the reaction is run under an oxygen atmosphere. Indeed, when hydrogen peroxide was added under controlled conditions, the yield of **7** was significantly reduced (entry 18). Based on all of the data in Table 1, it is interesting to note that running this cleavage under neat oxygen leads to undesired side reactions and the lower oxygen content in air is actually beneficial for this process.

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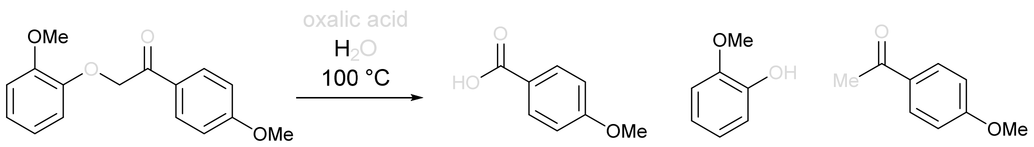
Table 1: Oxidative Cleavage of β-*O*-4 Model **6**



6 **7** **3** **9**

Entry	**Oxalic acid**[a] **(molL^{-1})**	**Time (h)**	**Atmosphere**	**Additive**	**Desk Lamp (42W)**	**Product and yield**
1	0.02	120	air	-	-	**7** (trace)
2	1	96	air	-	-	**7** (trace)
3	2	48	air	-	-	**7** (trace)
4	3	24	air	-	-	**7** (20%), **8** (11%)
5	4	24	air	-	-	**7** (29%), **8** (11%)
6	8	24	air	-	-	**7** (53%), **8** (18%)
7	**16**[b]	**24**	**air**	**-**	**-**	**7** (73%), **8** (10%)
8	-	120	air	-	-	**7** (trace)[c]
9	16	24	N_2	-	-	**7** (15%)[d]
10	16	10	O_2	-	-	**7** (29%), **9** (5%)
11	16	24	O_2	Rose Bengal	-	**7** (16%), **8** (25%), **9** (9%)
12	16	24	O_2	Rose Bengal	Yes	**7** (20%), **8** (20%), **9** (8%)
13	16	24	air	Rose Bengal	-	**7** (4%), **8** (8%)
14	16	30	air	TEMPO	-	**7** (68%), **8** (11%)
15	16	6.5	O_2	TEMPO	-	**7** (80%), **8** (9%)
16	16	22	O_2	-	DARK	**7** (80%), **9** (trace)
17	16	24	O_2	-	Yes	**7** (44%), **9** (trace)
18	16	24	Air	H_2O_2	DARK	**7** (36%), **8** (6%)

[a] Oxalic acid dihydrate; [b] 16 molL^{-1} = 21 equivalents; [c] reaction abandoned after 5 days with only trace amounts of **7** observed; [d] reaction stalled with no further cleavage occurring.

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Based on the study outlined in Table 1 ruling out both singlet oxygen and radical mediated cleavage mechanisms when air is used, we proceeded to develop a plausible mechanistic scenario for the formation of **7** and **8** from model **6**. We initially set out to investigate if the mechanism was akin to that reported by Han, who identified the intermediate glyoxal **10** during the oxidative cleavage of 2-phenoxyacetophenone (**2**) into phenol (**4**) and benzoic acid (**5**) catalysed by the ionic liquid [OMIm][OAc] (Scheme 3, **A**)[34]. Attempts to synthesise the putative glyoxal intermediate **11** from both *p*-acetanisole (**9**) and 2-hydroxy-4'-methoxyacetophenone (**12**) using a variety of oxidative conditions[62-67] led to only *p*-anisic acid (**7**), presumably resulting from the decarboxylation of the intermediate glyoxal **11** (Scheme 3, **B**). The facile nature of this decarboxylation under oxidative conditions implies that glyoxal **11** could be an intermediate in this cleavage reaction; however, when the putative glyoxylic acid intermediate **13** (also proposed by Han, Scheme 3, **A**) was subjected to our cleavage conditions, *p*-anisic acid (**7**) was not formed, inferring the cleavage (ie, the formation of **7** from **6**) does not proceed via a glyoxylic acid intermediate **13**.

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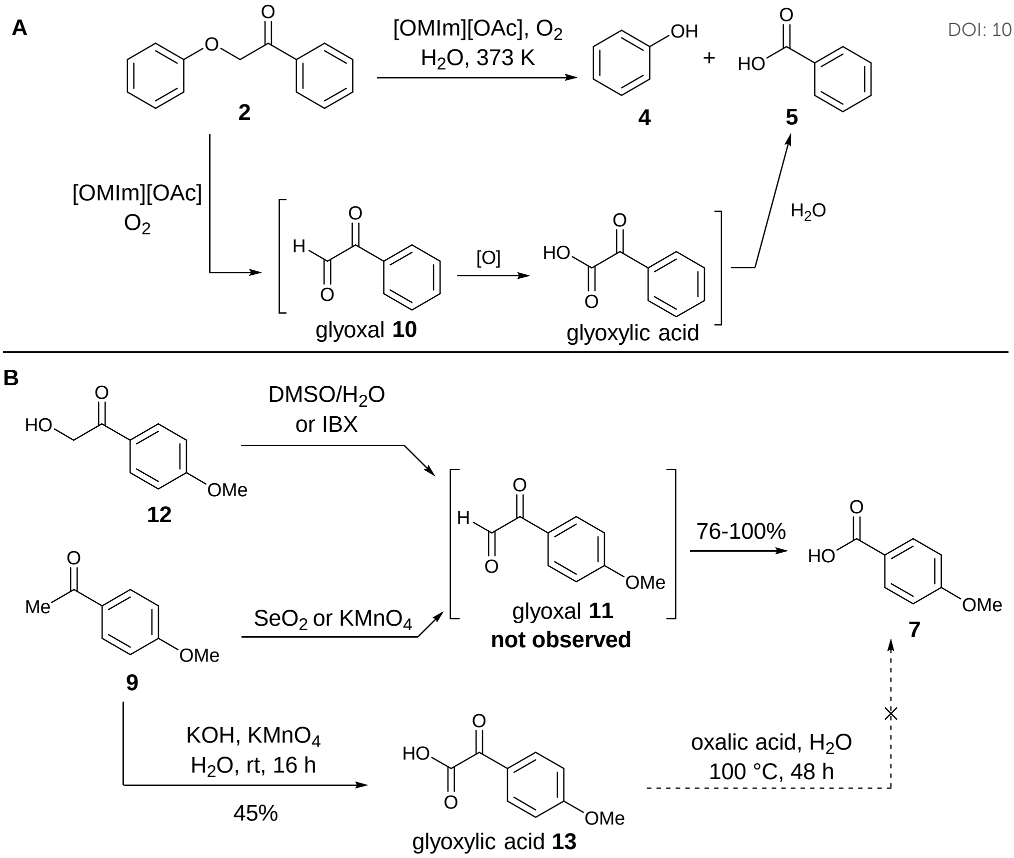

Scheme 3: **A**) Han's proposed mechanism[34], **B**) Investigation of key intermediates **11** and **13**

Based on all the results accumulated thus far, a plausible mechanistic scenario for the oxidative, oxalic acid-mediated cleavage can be proposed (Scheme 4). An initial acid mediated enolisation of **6** occurs to give **14**; reaction with molecular oxygen generates an unstable dioxetane intermediate **15** that could potentially fragment via two pathways[68]. In pathway A, ring opening of **15** gives hydroperoxide **16** which, after reduction to alcohol **17** (potentially mediated by oxalic acid[69]), proceeds through an acid-mediated C-O bond cleavage to yield guaiacol (**8**) and glyoxal **11**. Attack of water, subsequent loss of formic acid to anisaldehyde (**18**) and oxidation would give *p*-anisic acid (**7**)[70]. Alternatively, in pathway B, dioxetane **15** undergoes C-C bond cleavage through a concerted ring opening[71] to give *p*-anisic (**7**) and phenyl formate **19**, the later undergoing facile cleavage the under acidic reaction conditions[72] to give guaiacol (**8**). In a control experiment, anisaldehyde (**18**) did not convert into *p*-anisic

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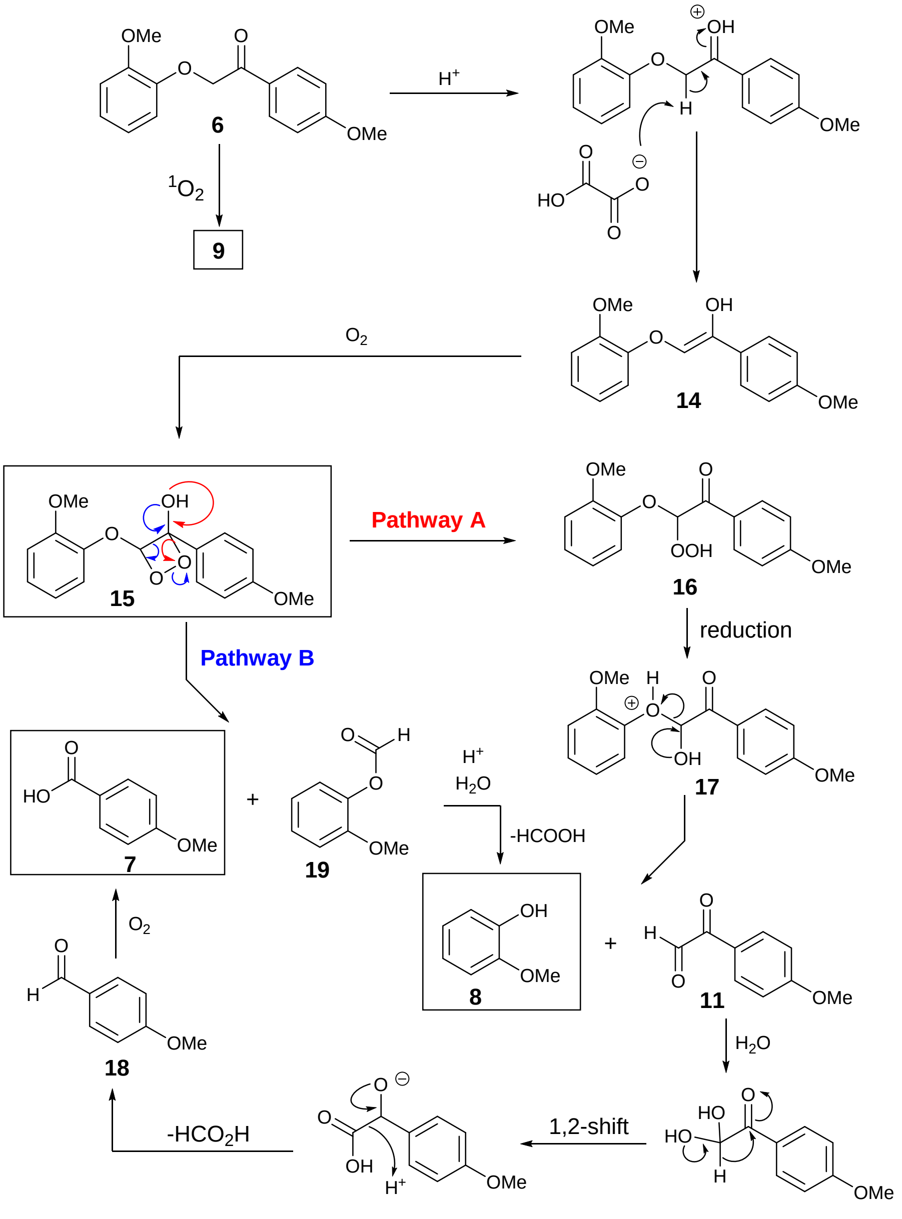
acid (**7**) under the cleavage conditions, suggesting pathway B is operating. The formation of *p*-acetanisole (**9**) is likely a result of singlet oxygen induced C-O bond cleavage, which has been reported to proceed via initial reaction of singlet oxygen with the acetophenone ring in **6**[59].



Scheme 4: Proposed mechanism of oxidative oxalic acid-mediated cleavage of **6**

With a plausible mechanism established, the optimised cleavage conditions were examined on a number of other β-*O*-4 lignin model compounds (**20-25**, Table 2). These conditions proved to be successful, with good to moderate yields of the corresponding carboxylic acid cleavage products obtained in all instances. Moreover, this procedure does not require traditional

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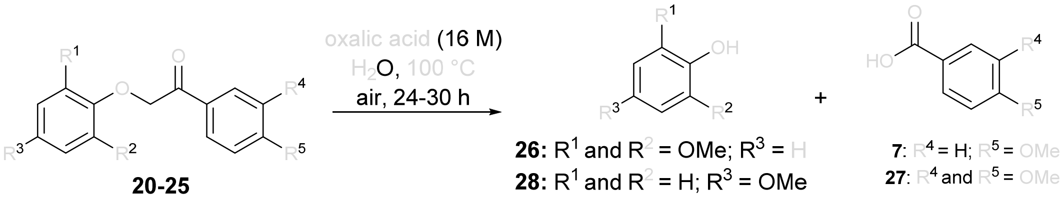
extraction based work-up procedures. Upon cooling, oxalic acid dihydrate crystallises from the reaction mixture, and the desired cleavage products can be simply washed with ethyl acetate from the resultant crystals. The residual oxalic acid can be reused in the cleavage three times with no reduction in yield (see supporting information).

Table 2: Cleavage of phenoxyacetophenone lignin model compounds with aqueous oxalic acid



Lignin^{ox} Model Compounds	Product(s) and yield	
20: R^1=R^2=R^5=OMe; R^3=R^4=H	-	**7** (67%)
21: R^3=R^5=OMe; R^1=R^2=R^4=H	**26** (10%)	**7** (60%)
22: R^3=R^4=R^5=OMe; R^1=R^2=H	-	**27** (85%)
23: R^5=OMe; R^1=R^2=R^3=R^4=H	-	**7** (27%)
24: R^2=R^4=R^5=OMe; R^1=R^3=H	-	**27** (57%)
25: R^1=R^2=R^4=R^5=OMe; R^3=H	**28** (22%)	**27** (37%)

With the successful cleavage of phenoxyacetophenone models **20-25** achieved, we anticipated that the same conditions could also cleave oxidised β-*O*-4 models of type **29** bearing a hydroxymethyl substituent (Scheme 5). Based on Stahl's pioneering, redox neutral cleavage of lignin models using sodium formate-formic acid,[53, 73] we anticipated an initial oxalylation of **29** would lead to **30**. Upon E1H-3c4e[74] elimination of **30** to enol **31**, tautomerisation and hydrolysis would deliver diketone **32** and phenol **4**.

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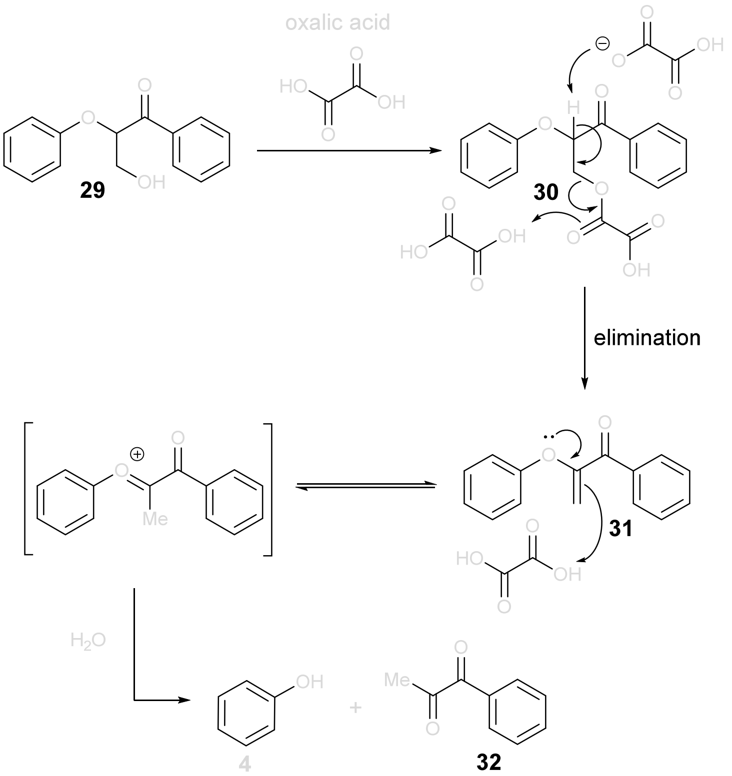

Scheme 5: Proposed oxalic acid-mediated cleavage of oxidised hydroxymethyl model **29** based on the work of Stahl

The oxalic acid conditions proved to be successful on a variety of oxidised hydroxymethyl β-*O*-4 models **33-38**, with good to excellent yields of the diketones **39-40** isolated in all examples (Table 3). Variable yields of the phenol component **26**, **28** and **8** were also observed, in line with their reported instability under acidic conditions. The isolation of diketones **39-40** and phenols **26**, **28** and **8** infers that the cleavage is occurring by an analogous redox neutral mechanism reported previously.[57, 74]

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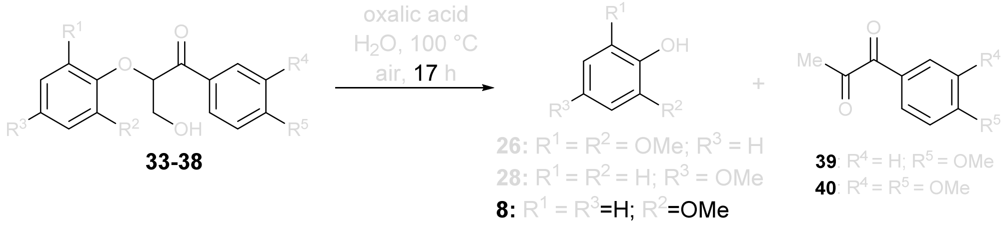
Table 3: Cleavage of oxidised hydroxymethyl containing β-*O*-4 models with aqueous oxalic acid.



Lignin^{ox} Model Compounds	**Product(s) and yield**	
33: R^1=R^2=R^5=OMe; R^3=R^4=H	**26** (100 %)	**39** (91 %)
34: R^3=R^5=OMe; R^1=R^2=R^4=H	**28** (27 %)	**39** (98 %)
35: R^3=R^4=R^5=OMe; R^1=R^2=H	-	**40** (86 %)
36: R^2=R^4=R^5=OMe; R^1=R^3=H	**8** (22 %)	**40** (54 %)
37: R^1=R^2=R^4=R^5=OMe; R^3=H	**26** (39 %)	**40** (54 %)
38: R^2=R^5=OMe; R^1=R^3=R^4=H	**8** (70 %)	**39** (100%)

With the cleavage of several β-*O*-4 model systems successfully developed, the depolymerisation of lignin was investigated. Milled wood lignin (MWL) from *Pinus radiata,* the fast growing tree at the core of the New Zealand forestry industry[75], was pre-washed with ethyl acetate and subjected to the oxalic acid cleavage conditions, which resulted in a 4 wt% yield of ethyl acetate soluble aromatics, along with an insoluble char-like by-product. ^{1}H HSQC NMR of the char showed the disappearance of key lignin linkages, indicating the depolymerisation of the biopolymer, albeit in poor yield (Figure 2, A vs B). The cleavage was subsequently examined on oxidised *Pinus radiata* MWL (MWL^{ox}). Oxidation of the MWL using DDQ[22] was successful, as shown through the disappearance of C-Hα along with the corresponding appearance of the ketone structure in A` in the ^{1}H HSQC NMR (Figure 2, A vs C). Subsequent cleavage of the pre-washed MWL^{ox} under our optimised conditions gave a 14 wt% yield of ethyl acetate soluble aromatics, along with char. The loss of key linkages evident

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by ^{1}H HSQC NMR analysis demonstrated successful depolymerisation (Figure 2, C vs D). The ^{1}H NMR of the soluble fraction from MWL^{ox} showed the cleavage had proceeded with good selectivity, with vanillin identified as the major product (Figure 2, E), as supported by GC-MS analysis (see supporting information). The production of vanillin from the cleavage of the MWL^{ox} is interesting. Vanillin may form upon formylation of guaiacol by the formic acid produced during the cleavage (see Scheme 4). Additionally, the oxidation step proposed in Scheme 4 (**18** --> **7**) may not operate on the real biopolymer system, instead resulting in vanillin.

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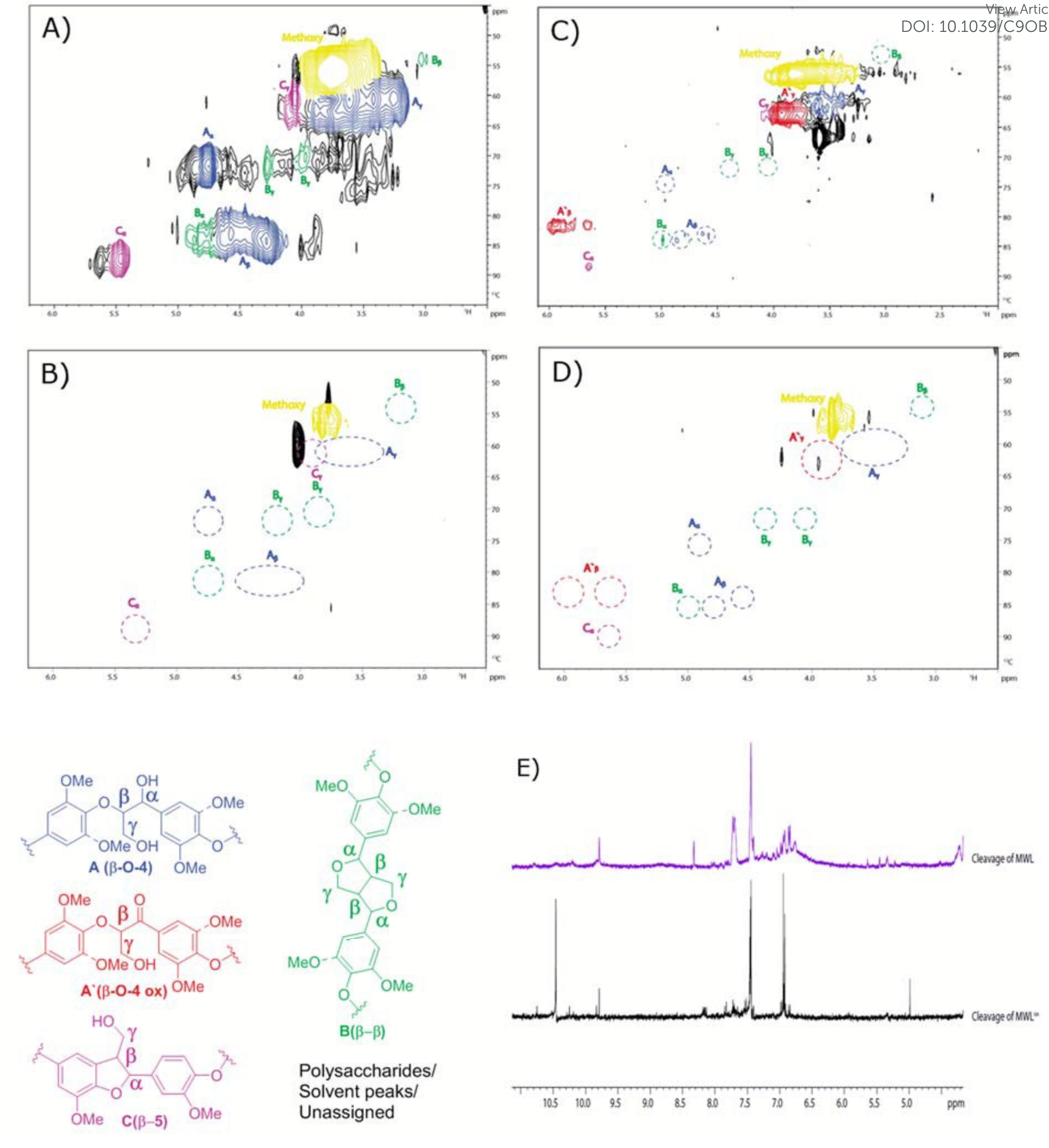

Figure 2: Partial 2D HSQC NMR spectra (DMSO-d_6) of: **A)** *Pinus radiata* MWL; **B)** *Pinus radiata* MWL after oxalic acid mediated cleavage; **C)** oxidised *Pinus radiata* MWL; **D)** oxidised *Pinus radiata* MWL after oxalic acid mediated cleavage. Cross peaks are colour coded to corresponding key lignin linkages. Reaction conditions: MWL or MWL^{ox}, oxalic acid (16 M), air, 100 °C, 4 h; **E)** Partial ^{1}H NMR spectra (DMSO-d_6) of the ethyl acetate soluble fraction from the cleavage of MWL (top) versus MWL^{ox} (bottom). Relevant GPC traces are available in the supporting information

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Conclusions

The hydroxymethyl substituent on β-*O*-4 lignin models dictates the mechanism by which they undergo cleavage in aqueous oxalic acid. β-*O*-4 models that do not contain the hydroxymethyl substituent undergo oxidative cleavage in the presence of air, whereas models bearing the hydroxymethyl group undergo a redox neutral cleavage that is analogous to the formic acid-sodium formate cleavage process reported by Stahl.[52,68] It was also shown that aqueous oxalic acid cleaves oxidised milled wood lignin (MWL^{ox}) from New Zealand *Pinus radiata* to give a 14% yield of ethyl acetate soluble aromatics with good selectivity for vanillin. Advantages of this cleavage procedure include; (i) the use of benign reagents, oxalic acid and water, with air as the oxidant; (ii) the absence of any metals and organic solvents; (iii) a simple extraction procedure that enables oxalic acid recycling. Examination of these cleavage conditions on various lignin biopolymers are currently underway in our laboratory.

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