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Iridium-catalysed primary alcohol oxidation and hydrogen shuttling for the depolymerisation of lignin†

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Lignin is a potentially abundant renewable resource for the production of aromatic chemicals, however its selective depolymerisation is challenging. Here, we report a new catalytic system for the depolymerisation of lignin to novel, non-phenolic monoaromatic products based on the selective β-O-4 primary alcohol dehydrogenation with a Cp*Ir-bipyridonate catalyst complex under basic conditions. We show that this system is capable of promoting the depolymerisation of model compounds and isolated lignins *via* a sequence of selective primary alcohol dehydrogenation, retro-aldol (C_α–C_β) bond cleavage and *in situ* stabilisation of the aldehyde products by transfer (de)hydrogenation to alcohols and carboxylic acids. This method was found to give good to excellent yields of cleavage products with both etherified and free-phenolic lignin model compounds and could be applied to real lignin to generate a range of novel non-phenolic monomers including diols and di-acids. We additionally show, by using the same catalyst in a convergent, one-pot procedure, that these products can be selectively channelled towards a single di-acid product, giving much simpler product mixtures as a result.

Lignin is the most abundant natural source of renewable aromatic carbon on earth and is now well recognised as a feedstock with great potential for the future production of biobased aromatic chemicals.[1–3] One of the keys to achieving lignin valorisation will be the development of new methods capable of selectively depolymerising this material to monoaromatic chemicals which can then either be directly used in chemical applications or undergo further upgrading to bulk or fine chemicals. Achieving this has, however, proved challenging for a number of reasons. For example, the lignin structure

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is highly complex and heterogeneous, depending strongly on both the botanical origin and, if isolated, the fractionation method used.[2,4] Furthermore, lignin and its derived monomers have a tendency to undergo re-polymerisation reactions which can severely impact the success of many depolymerisation approaches.[5,6]

Recently, a number of methods have been developed which overcome some of these key challenges. One general approach has been to carry out the lignin depolymerisation reaction *in situ* during the lignocellulosic pretreatment process, so called 'lignin-first' approaches.[7–12] In this way, the most deleterious lignin recondensation reactions, which occur during other pretreatment and lignin isolation processes, are avoided as released reactive lignin fragments are immediately converted to more stable compounds. Despite significant recent progress[13–17] there are currently no 'lignin-first' biorefineries in commercial operation and so the valorisation of isolated lignins, such as those being produced now, by depolymerisation still warrants attention. Furthermore, new pretreatment processes are being developed which allow access to high quality, high β-O-4 content lignins which are much more amenable to further upgrading than most of the current generation technical lignins.[18–23]
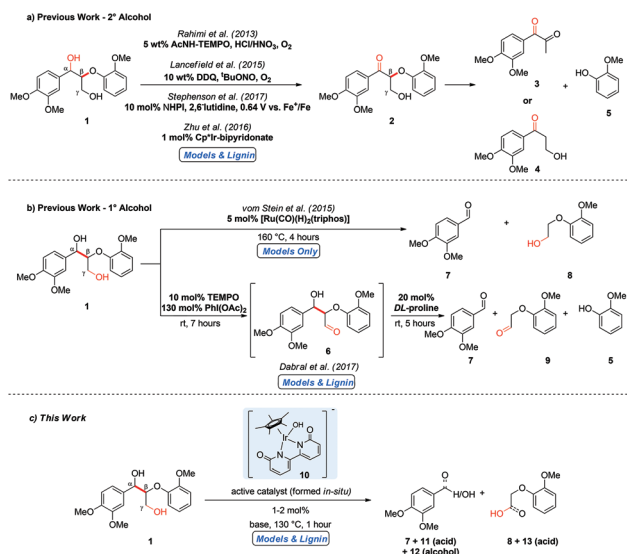
In this respect, depolymerisation processes which again make use of *in situ* stabilisation of reactive intermediates[5,6,24,25] and two-step selective lignin oxidation-depolymerisation strategies[26–30] (Scheme 1a) have proved very effective for producing monoaromatic products from isolated lignins. Most of these depolymerisation methods target cleavage of the β-aryl ether (C–O) bonds in the most abundant β-O-4 linkages, generating phenolic monomers as the major products. However, by targeting alternative depolymerisation pathways (*i.e.* C–C cleavage) it may be possible to improve lignin-derived product structure and functional group diversity, allowing, for example, the production of non-phenolic compounds directly from lignin. Indeed, methods which target an alternative cleavage of the β-O-4 linkages by scission of the C_α–C_β bond for lignin depolymerisation have recently gained interest. For example, Vom Stein *et al.* reported a Ru-triphos system capable

Scheme 1 Examples of lignin depolymerisation strategies utilising (a) secondary alcohol[26,27,29,34] and (b) primary alcohol[31,32] oxidation to activate the β-O-4 linkage towards cleavage compared to (c) this work.

Fig. 1 Iridium bipyridine and bipyridonate complexes active in alcohol dehydrogenation and ketone/aldehyde hydrogenation reactions in organic and aqueous solvents.

of cleaving this bond in lignin model compounds such as **1**[31] whilst Dabral *et al.* reported a two-step organocatalytic approach working with model compounds and real lignin (Scheme 1b).[32] In the former case, the reaction is overall redox neutral, proceeding through a hydrogen-transfer initiated retro-aldol pathway, with **7** and **8** being the main products. In the latter case, a stoichiometric co-oxidant such as PhI(OAc)$_2$ (or a polymer supported version), together with 10 mol% TEMPO is required to generate intermediate aldehyde **6**, to which 20 mol% proline is then added catalysing the retro-aldol reaction to give **7** and **9**. However, due to the ability of proline to further catalyse the decomposition of **9**, this process actually gives phenol **5** as the second major product. Model reactions with phenolic substrates were found to give complex reaction products due to non-selective oxidation reactions, limiting the scope of this reaction to etherified units. Additionally, Sannami *et al.* have shown that the primary alcohol moiety in β-O-4 models can be selectively oxidised to carboxylic acids, without C–C bond cleavage, under TEMPO-mediated electro-oxidation conditions.[33]

Here we report a new approach using a highly efficient iridium-based catalytic system for the oxidant-free cleavage of the C$_α$–C$_β$ bond in β-O-4 lignin model compounds and real lignin (Scheme 1c), with *in situ* stabilisation of the resulting aldehyde products through (de)hydrogenation to the corresponding alcohols and carboxylic acids. Additionally, the relatively low catalyst loadings, short reaction times, absence of stoichiometric oxidants and water tolerance set our system apart from previous examples.

Due to the complexity of developing any new reaction directly on lignin, we decided to start our investigations using full, dimeric lignin model compounds (*e.g.* **1**) which provide many of the same structural and chemical features as lignin
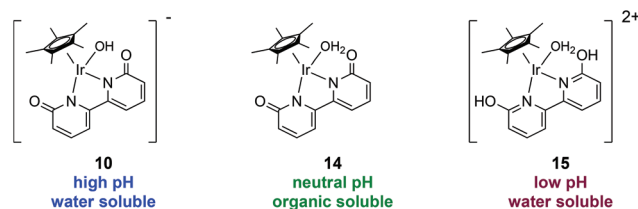
but allow for significantly more straightforward analysis to be carried out. We were, however, aware from the outset that the approach would have to translate to real lignin meaning, in particular, that the solvent chosen must be able to dissolve lignin and the catalyst should, ideally, be water and air tolerant. With this in mind the Cp*Ir based catalysts bearing bipyridonate (**10** and **14**) or 6,6′-dihydroxy-2,2′-bipyridine ligands (**15**) (Fig. 1) were identified as promising candidates for primary alcohol dehydrogenation. These catalysts are capable of performing (acceptor less) alcohol dehydrogenation and ketone/aldehyde hydrogenation reactions in organic (**14**) and/or aqueous (**10** and **15**) solvents,[35–38] and **14** has previously been shown to be active towards acceptorless *secondary* alcohol dehydrogenation of lignin and lignin model compounds[34] (Scheme 1a). In general, these catalysts have been found not to be capable of producing aldehydes from aliphatic primary alcohols due to preferential re-hydrogenation of the products. Nevertheless, if the aldehyde intermediates can be intercepted, *e.g.* during lactone formation, good reactivity can be achieved.[39] Furthermore, Fujita *et al.* have shown that anionic complex **10**, which can be formed from (inactive) **14** or **15** at high pH (pH 7.6–13) displays excellent activity in the dehydrogenation of methanol to hydrogen and CO$_2$, suggesting a high pH can be used to increase reactivity towards primary alcohols.[40]

Building on this, we believed these catalysts would serve as a good starting point for our work, leading us to propose a new catalytic approach for the depolymerisation of lignin consisting of anionic iridium complex **10** in a 1,4-dioxane/water solution, at pH ~11. These conditions were designed to (1) efficiently dissolve lignin, (2) promote primary over secondary alcohol dehydrogenation, (3) catalyse the retro-aldol reaction
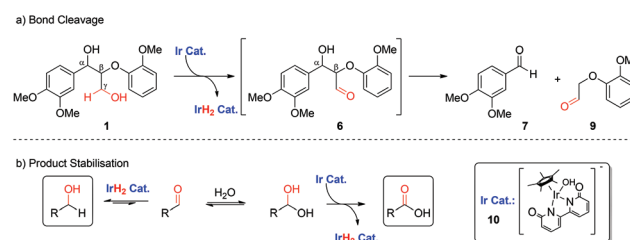
Scheme 2 Proposed route for iridium catalysed β-O-4 cleavage and product stabilisation.

Table 1 Results of the iridium catalysed cleavage of β-O-4 lignin model compounds

1: R^1 = Me, R^2 = H
18: R^1 = R^2 = H
19: R^1 = Me, R^2 = OMe

| Entry | Model | Pre-catalyst to **10** | | Base (eq.) | Conversion (%) | Product yields (%) | | | | | | |
		Structure	mol%			A1	A2	A3	Total A	B1	B2	Total B
1	**1**	**14**	1	1	84	23	43	12	78	56	20	76
2	**1**	**14**	2	1	100	28	31	26	85	70	25	95
3	**1**	**14**	2	0	5	0	0	0	0	0	0	0
4	**1**	**14**	2	0.2	58	12	28	13	53	41	15	56
5	**1**	**14**	2	0.5	96	25	38	24	87	67	28	95
6[a]	**1**	**14**	1	1	34	4	5	6	15	7	0	7
7[b]	**1**	**14**	1	1	79	14	11	23	48	37	12	49
8	**1**	**16 + 17**	2	1	100	13	33	33	79	46	42	88
9	**1**	**17**	2	1	21	0	2	0	2	0	0	0
10	**18**	**16 + 17**	2	1	100	0	67	1	69[c]	38	44	82
11	**19**	**16 + 17**	2	1	70	8	22	19	49	31	10	41

[a] In 100% 1,4-dioxane. [b] In 100% H$_2$O. [c] Including 1% 4-methylguaiacol. Conversions and yields determined by quantitative ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Every effort has been made to ensure the accuracy of these measurements however small errors (*ca.* <5%) are expected. Blank reaction runs with **A1–3** and **B1–2**, in the absence of catalyst, indicated that all the products are stable under the reaction conditions. See Tables S1–5 for more extensive optimisation studies and Fig. S1–3 for time course profiles.

of **6** to give **7** and **9** (Scheme 2a) and (4) provide *in situ* product stabilisation (Scheme 2b).

Gratifyingly, our initial reaction of the etherified dimeric lignin model compound **1** with 1 mol% of catalyst **14**, which generates **10** *in situ*, in a 1:1 mixture of 1,4-dioxane/water using 1 equivalent of Na$_2$CO$_3$ as base in a closed system, resulted in 79% conversion of **1** after 1 h at 130 °C (Table 1, entry 1). Quantitative ^{1}H NMR analysis of the reaction mixture

revealed five main products, all resulting from the intended primary alcohol dehydrogenation/retro-aldol pathway. For the A ring, the expected benzaldehyde product (**A2**) was formed in 41% yield, together with benzyl alcohol **A1** and benzoic acid **A3** in 19% and 18% yields respectively. Following the reaction with respect to time (Fig. S1–3†) suggested that **A2** is gradually converted to **A1** and **A3** during the reaction (Fig. S2†). Indeed, a control reaction using only **A2** as a substrate revealed that

Table 2 Results of the iridium catalysed depolymerisation of softwood lignins

| Entry | Lignin[a] | Solvent | Pre-catalyst (wt% of **17**)[b] | Time (h) | Product yields[c] (wt%) | | | | | | | | | | |
					A1	A2	A3	A4	L1	L2	L3	L4	L5	L6	Total
1	EL	Dioxane/water	5	1	0.02	1.1	0.12	0.15	0.53	0.07	0.44	0.42	0.05	0.89	3.8
2	EL	Dioxane/water	1.5	1	0.01	0.38	0.04	0.05	0.01	0.00	0.03	0.00	0.01	0.12	0.7
3	EL	Dioxane/water	5	2	0.03	1.0	0.15	0.36	0.34	0.15	0.44	0.46	0.06	0.77	3.8
4	EL	Diglyme/water	5	2	0.03	0.82	0.10	0.58	0.44	0.09	0.39	0.34	0.05	0.58	3.4
5	EL	water	5	2	0.00	0.00	0.17	0.42	0.00	0.00	0.22	0.00	0.10	0.42	1.5
6	Dioxasolv	Dioxane/water	5	2	0.04	1.4	0.13	0.56	0.34	0.11	0.54	0.58	0.05	0.84	4.6
7[d]	Dioxasolv	Dioxane/water	5	1 + 16	0.00	1.4	0.54	0.28	0.00	0.19	0.01	0.00	0.01	2.4	4.8
8[e]	Dioxasolv	Dioxane/water	5	1 + 16	0.00	0.00	0.55	0.18	0.00	0.11	0.00	0.00	0.00	1.8	2.7

[a] EL = enzyme lignin, dioxasolv = lignin extracted with dioxane/water (8:2), 0.1 M HCl, 1 hour, reflux. [b] 5 wt% of **17** corresponds to ~2 mol% loading of Ir based on total lignin. 1.5 wt% corresponding to ~2 mol% loading of Ir based on β-O-4 content. [c] From GC-FID analysis of silylated products using 1,3,5-trimethoxybenzene as internal standard and experimentally determined response factors. [d] Crude reaction mixture further refluxed open to air for 16 h. [e] Crude reaction mixture concentrated, redissolved in the same volume of water and refluxed open to air for 16 h.

this is indeed the case and that this is due to the action of the catalyst, rather than base-catalysed disproportionation reactions.[41] Furthermore, two products were identified as originating from the B ring, namely primary alcohol **B1** and acid **B2**, which were formed in 63% and 22% yields respectively. The high yields of B ring fragments and lack of any observable B ring aldehydes, or aldol products, suggests that these aldehydes are short lived species and never present in appreciable quantities.

Increasing the catalyst loading to 2 mol% improved conversion to 100% after 1 h, with an accompanied improvement in the total yields of the A and B ring fragments to 85% and 95%, respectively (entry 2). Sufficient base was found to be vital for good activity, with at least 0.5 equivalents of Na_2CO_3 being required (entries 3–5). Additional experiments showed that the exact nature of the base was less important with other soluble carbonates and sodium hydroxide also being suitable (Table S1†). In contrast, the solvent mixture was found to be very important, with reduced activity and selectivity observed in either water or 1,4-dioxane alone (entries 6 and 7).

Interestingly, we found that simple addition of the catalyst components 6,6′-dihydroxy-2,2′-bipyridine (**16**) and $[Cp*IrCl_2]_2$ (**17**) to the reaction mixture resulted in an active system with similar activity to the preformed pre-catalyst complex **14** (entry 8). This indicates that the active catalyst complex **10** readily forms under these reaction conditions and, to the best of our knowledge, this is the first example of such *in situ* preparation of these catalysts. This proposal was supported by the fact that omission of ligand **16** resulted in greatly reduced activity (entry 9). Encouragingly, we also found that this system can effectively cleave phenolic model **18**, which, as mentioned previously, was found to be a challenging substrate for organocatalytic approaches[32] with totals yield of 69% and 82% of the A and B ring products, respectively. Interestingly, in this case, whilst phenolic **A2** (vanillin) was formed in good yield of 67%, only relatively small amounts of benzoic acid **A3** was formed (1%), whilst no benzyl alcohol **A1** was observed. Instead, small amounts of 4-methylguaiacol (1%, see **A4**, Table 2 for structure) could be detected, which we believe arises from phenolic **A1**, *via* reduction of an intermediate quinone methide formed under the reaction conditions due to the high pH. One explanation for the relatively low yields of **A1** (or **A4**) and **A3**, compared to the neutral products obtained from the etherified model compound substrates, is that phenolic aldehyde **A2** will be deprotonated under the reaction conditions. This results in a delocalised negative charge on the phenolic aldehyde and, therefore, an electrostatic repulsion will exist between this substrate and the anionic catalyst complex **10**, potentially lowering the reactivity. Finally, model compound **19** with a sterically bulkier syringyl B ring was tested. This model gave similar products but displayed somewhat reduced overall reactivity compared to **1** (entry 11), consistent with the increased steric demands of this substrate.

Having successfully developed and applied our catalytic system on model compounds, producing excellent yields of up to 87% and 95% respectively of A and B ring products, we
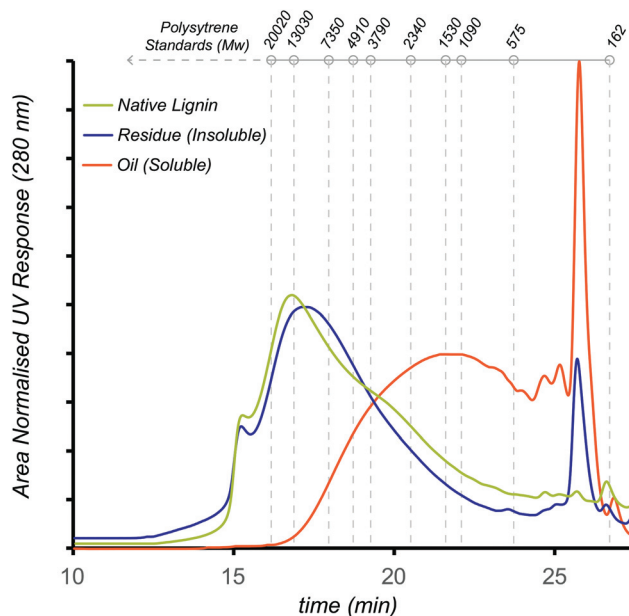

Fig. 2 GPC analysis of softwood enzyme lignin before (green, M_w = 8326, M_n = 1303) and after reaction: residue (blue, M_w = 9615, M_n = 1308) and oil (orange, M_w = 1698, M_n = 612). The yield of residue was 18 wt% from which an oil yield of 82 wt% was calculated (by difference). Elution times for polystyrene standards (grey) are added for reference.

turned our attention towards real lignin. Treatment of a softwood enzyme lignin with approximately 2 mol% (based on total lignin)[42] *in situ* formed catalyst (from 2.6 wt% **16** and 5 wt% **17**) resulted in the production of a lignin oil (82 wt%) which had a significantly lower molecular weight than the starting lignin (oil M_w = 1698, M_n = 612 *vs.* enzyme lignin M_w = 8326, M_n = 1303), as determined by GPC analysis (Fig. 2). Additionally, a small amount of extracting solvent insoluble (EtOAc/MeCN, 1:1), higher molecular weight material (18 wt%) was also recovered from the reaction. Detailed 2D HSQC NMR analysis of these fractions revealed major structural changes had occurred in the lignin (Fig. 3). Analysis of the linkage region (Fig. 3A–C) showed that cross peaks corresponding to β-O-4 units (**A**) had almost completely disappeared following the reaction and new cross peaks consistent with both types of expected cleavage products were present. For example, cross peaks for phenoxyethanol (**PE**), phenoxy acetic acid (**PA**) and benzyl alcohol (**BAlc**) groups (*cf.* A and B rings products from model compounds) were all clearly visible. Additionally, analysis of the aromatic regions (Fig. 3D–E) showed the presence of new cross peaks which could be assigned to the formation of benzaldehyde (**BAld**) and benzoic acid (**BA**) groups, all completely in line with the chemistry seen for the model compounds. Of the other lignin linkages, phenylcoumaran (β-5) units (**B**) were also almost completely absent in the lignin products, indicating that these units are also processed by our catalytic system, whilst resinol (β–β) units (**C**) appeared to be relatively inert, presumably because they possess no free alcohol groups. Cinnamyl alcohol
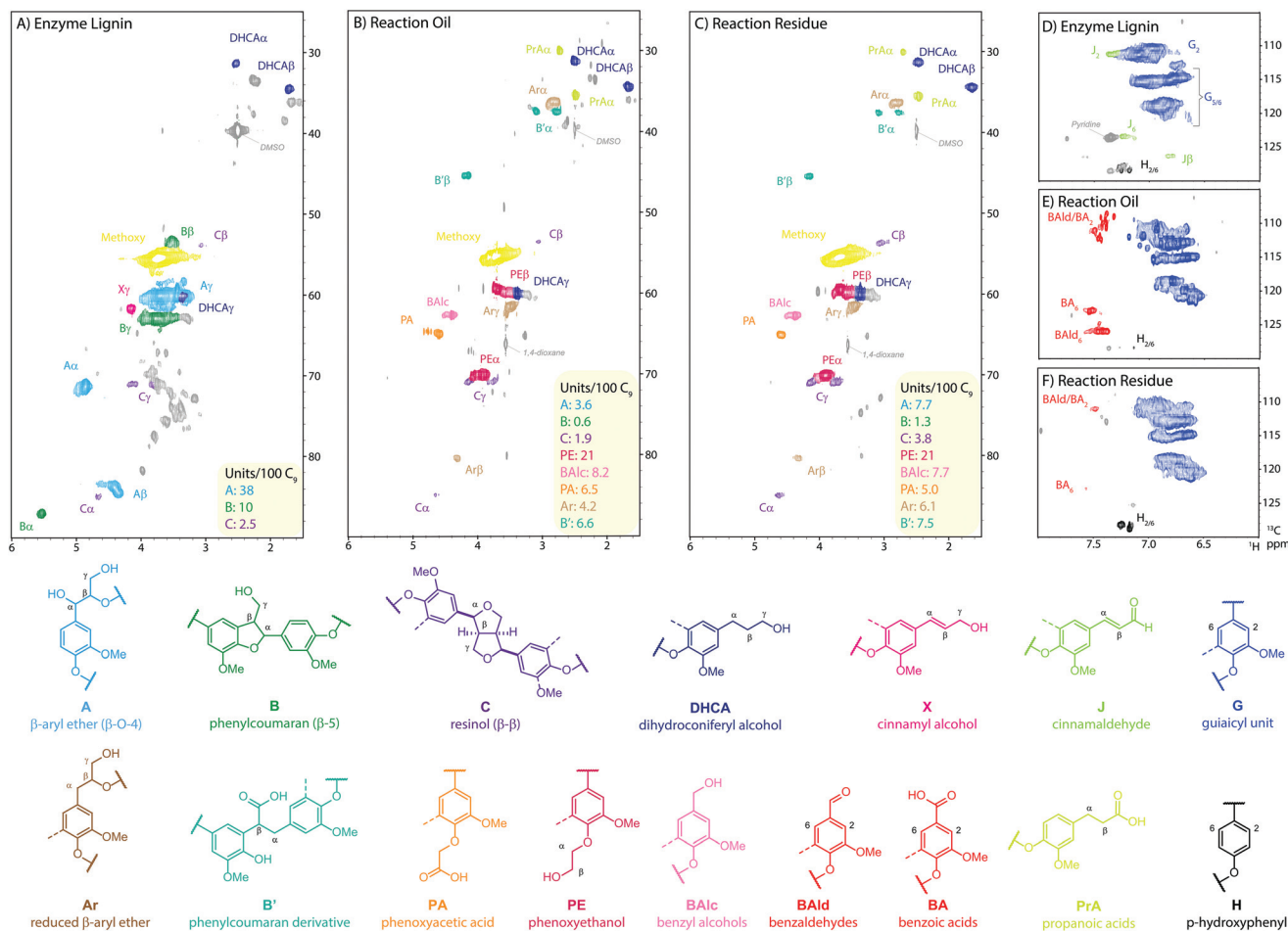
Fig. 3 ¹H–¹³C HSQC NMR analysis of the linkage (A–C) and aromatic regions (D–F) of softwood enzyme lignin (A and D), reaction oil (B and E) and residue (C and F). Contours are colour coded and labelled to match the assigned structures as shown. Reaction conditions: ~2 mol% cat. (5 wt% [Cp*IrCl₂]₂, 2.6 wt% 6,6′-dihydroxy-2,2′-bipyridine), 1,4-dioxane/water (1:1), Na₂CO₃, 130 °C, 1 hour (Table 2, entry 1). Unit quantities were estimated based on volume integrals of the characteristic cross peaks for each unit relative to the total integral for the aromatic G and H cross peaks. These values are intended for qualitative comparisons and are not rigorously quantitative. For the enzyme lignin this analysis gave identical results to using only the G₂ and H₂/₆ cross peaks, *i.e.* the per 100 C₉ values were equivalent, hence the use of this descriptor was maintained but may not strictly be correct. See Fig. S4† for HSQC-TOCSY analysis, and Fig. S5–6† for more detailed assignment of **B′**, **PrA** and **Ar** units.

(**X**) and cinnamaldehyde (**J**) end groups were also absent in the products but dihydroconiferyl alcohol groups (**DHCA**) were still present. A number of additional new cross peaks were also identified in the HSQC spectra which we could assign to products from other minor reaction pathways in lignin. For example, reduced β-O-4 units (**Ar**), phenylcoumaran derivatives (**B′**) and arylpropanoic acid groups (**PrA**) were all present in the products. The formation of all these units can be readily explained based on the interplay of (de)hydrogenation and base catalysis during the reaction (Scheme 3). For the **Ar** units, we propose that the most likely route for their formation is *via* reduction of intermediate enal structures (Scheme 3a), however direct formation and reduction of β-O-4 derived quinone methides, without any oxidation step, is another possible route. For **B′** units, we believe the most likely route for their formation involves an initial double dehydrogenation of the β-5 unit, followed by base-catalysed ring opening[43] and sub-

sequent hydrogenation of the conjugated double bond (Scheme 3b). This was proposed over the potentially competing aldehyde pathway based on the absence of any detectable B″ units in the products (Scheme 3b). A general reaction pathway for the conversion of primary alcohols to acids (*e.g.* DHCA to PrA groups), *via* hydration of intermediate aldehydes, is also shown based on previous proposals for related iridium catalyst complexes (Scheme 3c).[44]

GC-FID analysis of the reaction mixture showed that all the expected monomeric products were present in the lignin oil to different degrees (Table 2, entry 1). Additionally, we could group these products into those obtained from β-O-4 end groups (**A1–4**), requiring only a single bond cleavage to be released, and those obtained from internal units (**L1–6**), requiring the cleavage of two adjacent β-O-4 linkages to be released. Overall the total yield of identified monomeric products was 3.8 wt%, with the most abundant products being
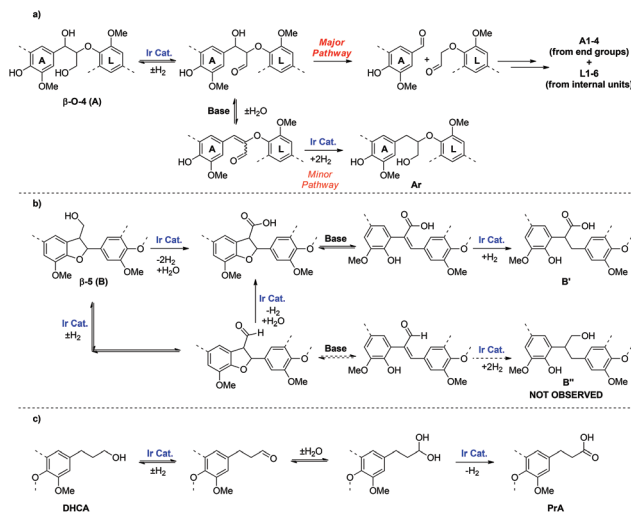
Scheme 3 Proposed routes for iridium catalysed processing of some of the major units in lignin. (a) β-O-4 (b) β-5 and (c) dihydrocinnamyl alcohol units.

vanillin (**A2**), **L1**, **L3**, **L4** and **L6**. To put this into perspective, based on a β-O-4 content of 38 per 100 C_9 units and a degree of (C5) condensation of 34% for softwood lignin,[45] the estimated theoretical maximum yield of β-O-4 derived monomers from this softwood lignin is approximately 9.5 wt%.[46,47] Moreover, products such as **L1–6** have not previously been reported from lignin, meaning this system allows us to expand the scope of lignin depolymerisation reactions into new classes of structurally interesting compounds. For example, **L3** has previously been investigated for the synthesis of bio-based polyesters,[48] and it is easy to imagine similar uses for many of these compounds as bio-renewable aromatic buildings blocks.

Replacing the 1,4-dioxane solvent with diglyme was well tolerated (entry 4), however omitting the organic solvent altogether severely reduced monomer yields (entry 5), consistent with our model studies. Interestingly, based on HSQC NMR analysis, this appears to be due to a switch in selectivity to unproductive reaction pathways for the β-O-4 linkages and concomitant low monomer yields, rather than poor catalyst activity (Fig. S7†). We also tested our system on a dioxasolv (organosolv) lignin that also had a high β-O-4 content (entry 6).[49] This lignin performed slightly better in the reaction, giving improved yields of the same monomeric products compared to the enzyme lignin. In particular, the small increase in yield is predominantly due to an increase in the amount of end group derived vanillin (**L2**). Given the rather large range of products generated in this reaction, we considered whether it would be possible to further process the products so that they converge to a single product, **L6** in this case. Indeed, we found that simply further refluxing the crude mixture of products open to air for 16 h, led to a significant convergence of the products giving **L6** as the major product in an improved 2.4 wt% yield (entry 7), with a con-

current disappearance or significant reduction in the yields of most of the other products (**L1–5**). The selectivity towards **L6** could be further enhanced by performing the second reflux step in 100% water, although overall lower yields were obtained (entry 8). It should be noted that these are not extensively optimised conditions, however they do nicely demonstrate an ability to tune and simplify the complex mixtures of products obtained directly from lignin depolymerisation reactions.

Conclusions

A new catalytic system for the cleavage of the β-O-4 linkages in model compounds and real lignin has been developed using an anionic Cp*Ir-bypyridonate complex. In contrast to previous secondary alcohol oxidation-lignin activation strategies, in this work, we targeted primary alcohol oxidation as an activation strategy, thus opening lignin depolymerisation pathways via cleavage of the C_α–C_β bond in the β-O-4 linkages, rather than the more common β-aryl ether (C–O) pathway. In model compounds this approach proved very selective for primary over secondary alcohol oxidation. Translating this chemistry to actual lignin proved effective, allowing us to demonstrate the production of non-phenolic monomers directly from lignin, setting our C–C bond cleavage method and products apart from other methods. The major products include bifunctional monoaromatic compounds containing carboxylic acid and/or alcohol groups, potentially making them useful building blocks. Furthermore, through the use of detailed 2D HSQC NMR analysis we have shown that resinol units are inert under our conditions, whilst phenylcoumarans are processed to novel ring opened, oxidised products. We have also shown through a simple, two-step, one pot, one catalyst reaction procedure that the initially rather complex mixtures of products obtained from lignin can be channelled towards a single set of carboxylic acid products. The approach demonstrated here opens up a new portfolio of lignin-derived monoaromatic products, thus diversifying the potential product slate for this key biorefinery component.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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42 To calculate the approximate stoichiometry of the reaction we assumed a lignin monomer unit mass of ~180 which gave a catalyst loading of 4.4 wt% based on **17** which we rounded to 5 wt% for convenience. A similar calculation using only the β-O-4 content of 38 per 100 C_9 units gave a loading of 1.68 wt% which we rounded to 1.5 wt%.

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