DOI: 10.1002/cctc.201402825

Selective Aerobic Benzylic Alcohol Oxidation of Lignin Model Compounds: Route to Aryl Ketones

Monali Dawange, Maxim V. Galkin, and Joseph S. M. Samec*[a]

A mild and chemoselective oxidation of the α-alcohol in β-O-4′-ethanoaryl and β-O-4′-glycerolaryl ethers has been developed. The benzylic alcohols were selectively dehydrogenated to the corresponding ketones in 60–93 % yield. A one-pot selective route to aryl ethyl ketones was performed. The catalytic system comprises recyclable heterogeneous palladium, mild reaction conditions, green solvents, and oxygen in air as oxidant. Catalytic amounts of a coordinating polyol were found pivotal for an efficient aerobic oxidation.

Lignocellulosic biomass is one of the most attractive renewable feedstocks for producing chemicals and fuels.[1] Lignin is a biopolymer that represents a major component of nonedible biomass. Rational utilization of this resource requires simple, highly efficient, selective, and preferably catalytic chemical transformations. The chemical structure of the lignin polymer is complex, in which the β-O-4′-glycerolaryl ether linkage represents the most common repeating monomeric unit (Figure 1).[1a,2]

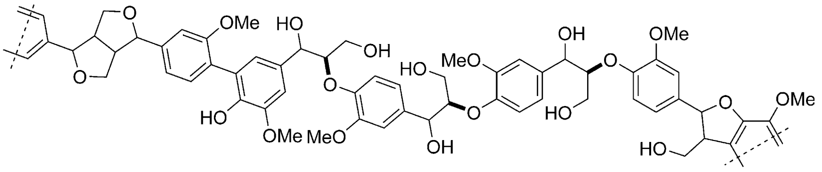
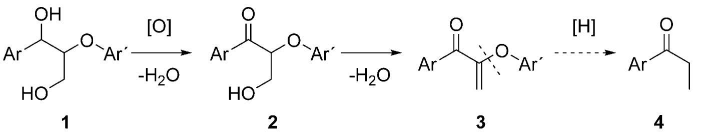


Figure 1. Structure of a lignin fragment. The β-O-4′-glycerolaryl ether linkage is highlighted.

Both reductive and oxidative methodologies to promote reactivity of the β-O-4′-glycerolaryl ether linkage have been reported.[1,3] Methods for oxidation of lignin and its model compounds have been the focus of extensive investigations.[4] Many of the current methods proceed via a C–C bond cleavage that leads to degradation of the propylbenzene skeleton. Usually such methods result in benzoic acids, phenolic aldehydes, or different quinone derivatives as products.[4,5] In certain applications, such as vanillin production, a C–C bond cleavage is desired. In other applications, conservation of the alkyl chain to selectively generate the aryl ethyl ketone is preferred. Such substrates are valuable starting materials in fine chemical industries.[1] Selective oxidation of the secondary alcohol without C–C bond cleavage for phenolic models is still a major challenge in lignin chemistry (Scheme 1).[5] We only found one report that describes the transformation of advanced lignin model compounds (**1**) to the corresponding ketones (**2**) (Scheme 1), for which addition of strong acids was required.[5] However, due to C–C bond cleavage, poor selectivity was obtained.

Recently, we reported a Pd/C-catalyzed transfer hydrogenolysis of lignin model compounds by addition of ammonium formate and formic acid as a hydrogen source to reductively cleave the β-O-4′-ethanoaryl ether linkage.[6] We showed that an initial rate-limiting dehydrogenation generated a ketone intermediate that underwent a fast hydrogenolysis of the β-O-4′-ethanoaryl ether linkage to give aryl ethyl ketone and phenol. No reactivity was observed for the more challenging β-O-4′-glycerolaryl ether under similar reaction conditions. When the reaction time, temperature, and amount of reducing agent were increased, an unselective reaction to yield a mixture of 3-aryl propanol and aryl propane took place (Scheme 2).



Scheme 1. Strategy for selective degradation of lignin to generate **4**.

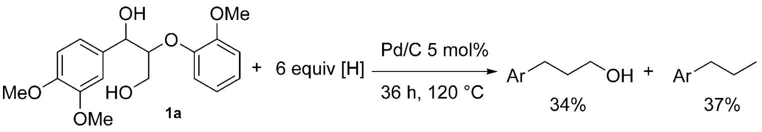
Here, we report a mild and selective oxidation of the benzylic alcohol in lignin model compounds. Stopping the reaction at the benzylic oxidation opens up the possibility to obtain the aryl ethyl ketone in a one-pot procedure (Scheme 1). These compounds are highly valuable as substrates for fine chemicals synthesis (Scheme 3). For example, Chiba and Loh's group recently reported oxidative amide formation by using **2** as starting material.[7] Plietker's and Shim's groups reported an α-alkylation of **4**.[8] Other conceivable reactions include: Baeyer–Villiger oxidation, reductive amination, reduction to alcohol, Mannich reaction, aldol condensation, and the Grignard reaction (Scheme 3).

The addition of catalytic amounts of sodium borohydride and excess of base has been reported to prevent deactivation

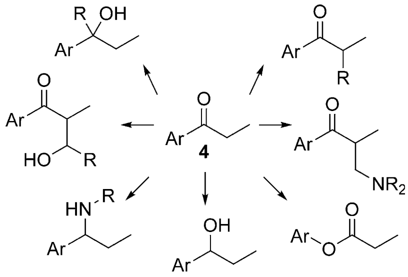
---

[a] *M. Dawange, M. V. Galkin, Dr. J. S. M. Samec*
Department of Chemistry, BMC
Uppsala University
Husargatan 3, 751 23, Uppsala (Sweden)
E-mail: joseph.samec@kemi.uu.se

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201402825.



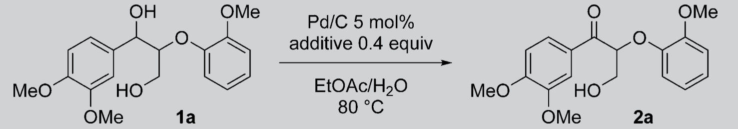
Scheme 2. Previously reported method yielded low selectivity and no ketone.



Scheme 3. Ketone **4** from lignin as a versatile starting material for the synthesis of fine chemicals.

of palladium.[9] However, metal hydrides are not convenient in large-scale productions.[10] Initial attempts to selectively oxidize the benzyl alcohol in lignin model compound **1 a** by Pd/C (see the Supporting Information) with addition of sodium borohydride led to marginally better results compared to the blank reaction without additives (Table 1, entries 9–10). Ammonium formate also gave poor selectivity in the oxidation reaction in which C–O bond cleavage was observed (Table 1, entry 8).[6] On using alcohols, the conversions increased to above 50% of the desired product (Table 1, entries 1–7). The best result was obtained with glucose in which **1 a** was selectively dehydrogenated to yield **2 a** in 68% yield (Table 1, entry 1). An optimum of 40 mol% of glucose was found; increased or decreased levels of glucose gave poorer results. Attempts to perform the reaction in either an inert or oxygen atmosphere were unsuccessful (see the Supporting Information). The reaction could be performed in environmentally friendly solvents such as ethyl acetate, ethanol, cyclopentyl methyl ether, or 2-methyltetrahydrofuran together with water to give **2 a** in a good yield. Notably, the procedure did not require the addition of acids or bases as in earlier reports.[5,9] Performing the reactions in ethyl acetate gave higher selectivity with lignin models than in ethanol. In ethanol, both the dehydrogenation and the C–O bond cleavage were accelerated to give lower selectivity. Another advantage of using ethyl acetate was that the product was easier to isolate from the reaction mixture (i.e., recycling). Performing the reaction in the absence of water gave low reactivity. A plausible explanation is that water facilitated the dissolution of glucose. Notably, this mild dehydrogenation methodology was applied to a variety of primary and secondary alcohols to generate the corresponding aldehydes and ketones in good to excellent yield within minutes (see the Supporting Information). These reactions were performed in ethanol and water, with no side reactions observed.

Table 1. Influence of additives on oxidation of **1 a**.[a]



Entry	Additive	**2 a** [%]
1	glucose	68
2	sorbitol	56
3	2-propanol	53
4	sucrose	52
5	pinacol	50
6	glycerol	48
7	ethylene glycol	42
8	$HCOONH_4$	41
9	$NaBH_4$	36
10	–	18

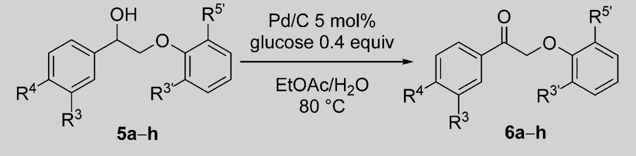
[a] Reaction conditions: 0.4 equiv additive, 0.05 equiv Pd/C (5 wt%), EtOAc/H_2O (4:1), 80 °C, 12 h.

Pd/C-catalyzed aerobic oxidation of benzylic alcohols in lignin model compounds was subsequently investigated. β-O-4′-Ethanolaryl ethers, which mimic lignin from different sources, were chosen as model substrates to investigate the scope of the reaction.[3c] Model **5 a**, with no methoxy substitution of the aryl, is the major component in for example, switchgrass. Substitution of the hydrogen atoms in the aryl group by one methoxy group in the $R^{3'}$ position (**5 f**) corresponds to the predominant lignin substitution pattern in softwood and, by two methoxy groups in the $R^{3'}$ and $R^{5'}$ positions (**5 g**), to the lignin substitution pattern in hardwood, for example, birch and eucalyptus. Gratifyingly, selective oxidation gave the corresponding products in 83–94% isolated yield (Table 2). No degradation of the C–O or C–C bonds was observed. Interestingly, the substitution pattern of the aryl did not affect the yield or selectivity to generate the desired ketone. Highly substituted **5 g** was transformed in a high yield (Table 2, entry 7). This compound has previously proved difficult to transform by transition metal catalysis.[3c] Lignin model compound **5 h** with a free phenolic group also underwent selective dehydrogenation to generate the corresponding ketone **6 h** in a good yield. Unprotected phenols have been reported to be cumbersome to transform.[4a,b,5]

Lignin model compounds with the γ-alcohol motif represent the native lignin structure. These β-O-4′-glycerolaryl ethers models have previously showed low or no reactivity in transition-metal-catalyzed reactions.[6,11] Gratifyingly, the β-O-4′-glycerolaryl ethers underwent selective benzylic oxidation to generate ketones **7 a–d** in moderate to good yields (Table 3). Compounds containing free phenol (**7 c**) also showed good reactivity and selectivity.

To demonstrate the feasibility of the selective dehydrogenation, β-O-4′-glycerolaryl ether **1 a** was converted to aryl ethyl ketone **4 a** in a one-pot procedure (Scheme 4). Performing an aerobic oxidation with Pd/C in an ethyl acetate and water mixture for 12 h at 80 °C gave **2 a**. Addition of base led to dehydration intermediate **3**. This intermediate was re-

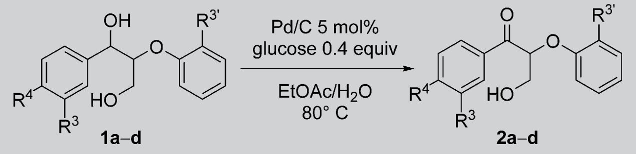
Table 2. Oxidation of various 2-aryloxy-1-arylethanols.[a]



Entry	Substrate	R^3	R^4	$R^{3'}$	$R^{5'}$	*t* [h]	Yield[b] [%]
1	**5a**	H	H	H	H	3	83
2	**5b**	H	OMe	H	H	3	87
3	**5c**	H	H	OMe	H	4	89
4	**5d**	H	OMe	OMe	H	24	89
5	**5e**	OMe	OMe	H	H	36	85
6	**5f**	OMe	OMe	OMe	H	10	93
7	**5g**	OMe	OMe	OMe	OMe	36	93
8	**5h**	OMe	OH	OMe	H	36	89

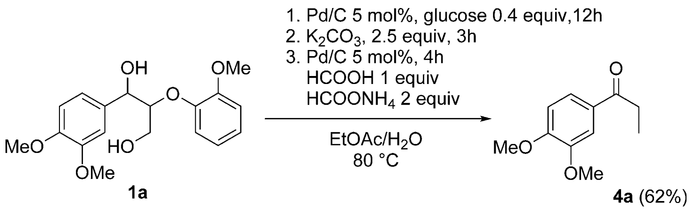
[a] Reaction conditions: 0.4 equiv glucose, 0.05 equiv Pd/C (5 wt%), EtOAc/H_2O (4:1), 80 °C. [b] Average isolated yield of the corresponding ketone based on two duplicate experiments.

Table 3. Oxidation of various β-O-4′-glycerolaryl ethers.



Entry	Substrate	R^3	R^4	$R^{3'}$	*t* [h]	Yield[a] [%]
1	**1a**	OMe	OMe	OMe	12	68
2	**1b**	H	OMe	OMe	12	81
3	**1c**	OMe	OH	OMe	48	60
4	**1d**	H	H	H	24	64

[a] Average isolated yield of the corresponding ketone based on two duplicate experiments.



Scheme 4. Selective benzylic oxidation followed by β-O-4′-bond cleavage.

duced and cleaved by utilizing the same batch of Pd/C (regenerated) and water by addition of formic acid and ammonium formate to yield the aryl ethyl ketone **4a** in 62% yield.

The role of the additive was investigated. Our initial hypothesis was that the alcohol could act as a mild hydrogen donor to prevent over-oxidation of Pd/C as previously reported for aerobic oxidation of benzylic alcohols in the presence of sodium borohydride.[9] A couple of experiments were performed to probe the role of the polyol. After the dehydrogenation of **1a** to **2a**, the glucose additive was studied. Surprisingly, no oxidation of sugar was observed. However, small amounts of oxidation could be difficult to observe because of the different forms of glucose. The same investigation of the sugar derivative was also performed on the reaction with sorbitol as additive. In this case, oxidized sugars would be easily detected. However, no traces of the oxidized sugar derivatives were observed after dehydrogenation of **1a**. An alternative explanation is that the alcohol/polyol stabilizes palladium to prevent palladium from aggregation.[12] The results from above would support such a role. The dehydrogenation of **1a** in the presence of pinacol gave a 50% conversion to **2a** (Table 1, entry 5). Thus, pinacol that could coordinate to palladium but could not act as a hydrogen donor gave similar conversions to other polyols. These results support that the role of glucose is to stabilize palladium on the support. Other research groups have observed similar role of polyols or other ligands in heterogeneous palladium catalysis.[12]

In our previous studies we used Pd/C with different additives to transform benzyl alcohols, lignin model compounds, and lignin itself.[13] Notably, the effect of the additive is fundamental to the reactivity. Formic acid alone promotes a disproportionation reaction of the benzyl alcohol in both benzyl alcohols and lignin models. Use of formate instead of formic acid gives C–O bond cleavage in different β-O-4′-ethanolaryl ether lignin models. This reaction also starts with an initial dehydrogenation. However, in the presence of formate a reductive cleavage of the weaker C–O ether bond[14] occurs in a fast subsequent reaction step. Notably, the more challenging β-O-4′-glycerolaryl ethers models were not reactive at 80 °C. To achieve reactivity, the oil bath was heated to 120 °C and an overstoichiometric amount of hydrogen donor was required. Under those reaction conditions no aryl ethyl ketone was formed. In the present study we complement the reactivity of Pd/C and lignin model compounds to a selective dehydrogenation reaction for lignin model compounds. The role of the additive is to maintain the palladium activity only in the dehydrogenation reaction. This way, the aryl ethyl ketone can be prepared selectively under mild reaction conditions.

In conclusion, we have demonstrated the selective oxidation of benzylic alcohols in lignin model compounds to the corresponding ketones without C–O or C–C cleavage or γ-alcohol dehydrogenation. Selective dehydrogenation of the benzylic alcohol in lignin model compounds is a straightforward route to aryl ethyl ketones and this is demonstrated here. The key to success is the addition of catalytic amounts of glucose, for example, to inhibit catalyst deactivation. We propose that the role of the polyol is to stabilize the palladium, thus preventing it from aggregation. The utilization of mild reaction conditions, air as an oxidant, and recyclable Pd/C in green solvents makes this procedure interesting from economic and environmental perspectives.

Experimental Section

General procedure for oxidation of benzylic alcohols to corresponding carbonyl compounds: To a suspension of Pd/C (16 mg, 7.5 μmol) in H_2O (0.6 mL), glucose (11 mg, 0.06 mmol), substrate

(0.15 mmol), and EtOAc (2.4 mL) were added. The reaction mixture was heated to 80 °C in air in a reflux condenser. The progress of reaction was monitored by using TLC on silica gel. After completion, the reaction mixture was cooled to RT and the organic phase decanted and filtered through a Celite pad by using EtOAc (10 mL) as eluent and concentrated in vacuo to give a crude oil. The oil was purified by column chromatography.

Acknowledgements

We thank the Swedish Energy Agency for financial support. M.D. thanks Erasmus Mundus for financial support.

Keywords: biomass valorization · heterogeneous catalysis · lignin · oxidation · palladium

[1] a) J. Zakzeski, P. C. A. Bruijnincx, A. L. Jongerius, B. M. Weckhuysen, *Chem. Rev.* **2010**, *110*, 3552 – 3599; b) J. J. Bozell, J. E. Holladay, D. Johnson, J. F. White, *Top Value Added Candidates from Biomass, Vol. 2*, Pacific Northwest National Laboratory, Richland, WA, **2007**, pp. 42 – 47; c) A. Corma, S. Iborra, A. Velty, *Chem. Rev.* **2007**, *107*, 2411 – 2502; d) G. W. Huber, S. Iborra, A. Corma, *Chem. Rev.* **2006**, *106*, 4044 – 4098.

[2] a) R. Vanholme, B. Demedts, K. Morreel, J. Ralph, W. Boerjan, *Plant Physiol.* **2010**, *153*, 895 – 905; b) Á. T. Martínez, J. Rencoret, G. Marques, A. Gutierrez, D. Ibarra, J. Jimenez-Barbero, J. C. del Río, *Phytochemistry* **2008**, *69*, 2831 – 2843; c) W. Ibrahim, K. Lundquist, *Acta Chem. Scand.* **1994**, *48*, 149 – 151.

[3] a) H. Lange, S. Decina, C. Crestini, *Eur. Polym. J.* **2013**, *49*, 1151 – 1173; b) C. Crestini, M. Crucianelli, M. Orlandi, R. Saladino, *Catal. Today* **2010**, *156*, 8 – 22; c) J. M. Nichols, L. M. Bishop, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2010**, *132*, 12554 – 12555.

[4] a) J. M. W. Chan, S. Bauer, H. Sorek, S. Sreekumar, K. Wang, F. D. Toste, *ACS Catal.* **2013**, *3*, 1369 – 1377; b) S. Son, F. D. Toste, *Angew. Chem. Int. Ed.* **2010**, *49*, 3791 – 3794; *Angew. Chem.* **2010**, *122*, 3879 – 3882; c) J. Zhang, H. Deng, L. Lin, *Molecules* **2009**, *14*, 2747 – 2757; d) W. Partenheimer, *Adv. Synth. Catal.* **2009**, *351*, 456 – 466; e) C. Crestini, M. C. Caponi, D. S. Argyropoulos, R. Saladino, *Bioorg. Med. Chem.* **2006**, *14*, 5292 – 5302; f) W. A. Herrmann, T. Weskamp, J. P. Zoller, R. W. Fischer, *J. Mol. Catal. A* **2000**, *153*, 49 – 52; g) F. Cui, D. Dolphin, *Bioorg. Med. Chem.* **1995**, *3*, 471 – 477; h) F. Cui, T. Wijesekera, D. Dolphin, *J. Biotechnol.* **1993**, *30*, 15 – 26.

[5] A. Rahimi, A. Azarpira, H. Kim, J. Ralph, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 6415 – 6418.

[6] M. V. Galkin, S. Sawadjoon, V. Rohde, M. Dawange, J. S. M. Samec, *ChemCatChem* **2014**, *6*, 179 – 184.

[7] J. Zhang, Y. Liu, S. Chiba, T.-P. Loh, *Chem. Commun.* **2013**, *49*, 11439 – 11441.

[8] a) D. Weickmann, B. Plietker, *ChemCatChem* **2013**, *5*, 2170 – 2173; b) C. S. Cho, B. T. Kim, M. J. Lee, T.-J. Kim, S. C. Shim, *Angew. Chem. Int. Ed.* **2001**, *40*, 958 – 960; *Angew. Chem.* **2001**, *113*, 984 – 986.

[9] a) G. An, H. Ahn, K. A. De Castro, H. Rhee, *Synthesis* **2010**, *3*, 477 – 485; b) G. An, M. Lim, K.-S. Chun, H. Rhee, *Synthesis* **2007**, *1*, 95 – 98.

[10] Z. C. Çelik, B. Z. Can, M. M. Kocakerim, *J. Hazard. Mater.* **2008**, *152*, 415 – 422.

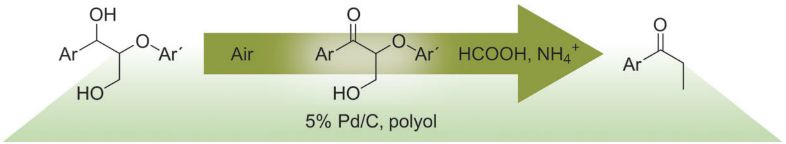
[11] A. Wu, B. O. Patrick, E. Chung, B. R. James, *Dalton Trans.* **2012**, *41*, 11093 – 11106.

[12] a) F. Coccia, L. Tonucci, N. d'Alessandro, P. D'Ambrosio, M. Bressan, *Inorg. Chim. Acta* **2013**, *399*, 12 – 18; b) F. Coccia, L. Tonucci, D. Bosco, M. Bressan, N. d'Alessandro, *Green Chem.* **2012**, *14*, 1073 – 1078; M. Mifsud, K. V. Parkhomenko, I. W. C. E. Arends, R. A. Sheldon, *Tetrahedron* **2010**, *66*, 1040 – 1044; c) T. Mallat, A. Baiker, *Chem. Rev.* **2004**, *104*, 3037 – 3058.

[13] a) S. Sawadjoon, A. Lundstedt, J. S. M. Samec, *ACS Catal.* **2013**, *3*, 635 – 642; b) M. V. Galkin, J. S. M. Samec, *ChemSusChem* **2014**, *7*, 2154 – 2158.

[14] a) J. M. Younker, A. Beste, A. C. Buchanan III., *ChemPhysChem* **2011**, *12*, 3556 – 3565; b) S. Kim, S. C. Chmely, M. R. Nimlos, Y. J. Bomble, T. D. Foust, R. S. Paton, G. T. Beckham, *J. Phys. Chem. Lett.* **2011**, *2*, 2846 – 2852.

Received: October 15, 2014



The ligninator: A mild and chemoselective oxidation of the α-alcohol in β-O-4′ lignin model compounds is developed. The benzylic alcohols are selectively dehydrogenated to the corresponding ketones in 60–93% yield. A one-pot selective route to aryl ethyl ketones is performed. The catalytic system comprises recyclable heterogeneous palladium, mild reaction conditions, green solvents, and oxygen in air as oxidant.

*M. Dawange, M. V. Galkin, J. S. M. Samec**

■■–■■

Selective Aerobic Benzylic Alcohol Oxidation of Lignin Model Compounds: Route to Aryl Ketones