



Mechanistic Study of Diaryl Ether Bond Cleavage during Palladium-Catalyzed Lignin Hydrogenolysis

Yanding Li,^[a, b, g] Steven D. Karlen,^[b, c] Benginur Demir,^[b, d] Hoon Kim,^[b, c] Jeremy Luterbacher,^[e] James A. Dumesic,^[b, d] Shannon S. Stahl,^[b, f] and John Ralph^{*[a, b, c]}



Hydrogenolysis has emerged as one of the most effective means of converting polymeric lignin into monoaromatic fragments of value. Reported yields may be higher than for other methods and can exceed the theoretical yields estimated from measures of the content of lignin's most readily cleaved alkyl-aryl ether bonds in β -ether units. The high yields suggest that other units in lignin are being cleaved. Diaryl ether units are important units in lignin, and their cleavage has been examined previously using simple model compounds, such as di-

phenyl ether. Herein, the hydrogenolysis of model compounds that closely resemble the native lignin 4-O-5 diaryl ether units was analyzed. The results provided unexpected insights into the reactivity and partial cleavage of these compounds. The models and lignin polymer produced not only monomers, but also unusual 1,3,5-*meta*-substituted aromatics that appear to be diagnostic for the presence and the cleavage of the 4-O-5 diaryl ether unit in lignin.

Introduction

Lignin is the most abundant aromatic resource for the replacement of fossil-derived products.^[1–3] Hydrogenolysis or reductive catalytic fractionation (RCF) of lignin is one of the most promising methods for lignin valorization.^[4–6] High-yield aromatic monomers are obtained by catalytic alkyl-O-aryl (β -O-4) bond hydrogenolysis.^[7–9] The cleavage of this bond has been widely studied because β -O-4 units represent the dominant interunit linkage in native lignins, and hydrogenolysis reactions have been studied mechanistically by using prototypical β -O-4 model compounds.^[10–12] It is generally assumed that the reductive cleavage of lignin cannot proceed whenever there is a linkage other than a β -ether; however, the high yields of monomers (> 50%) reported under various catalytic conditions^[13–20] suggest that the cleavage of other linkages may contribute to monomer formation.

Other linkages in the native lignin can be divided into two groups, C–C linkages (including β -5, β - β , β -1, and 5-5) and C–O diaryl ether (4-O-5) linkages (Figure 1 A). The presence of 4-O-5-linked lignin units was first proposed by Freudenberg et al., based on observed diaryl ether products from permanganate oxidation of spruce wood,^[21] and further supported by the isolation of similarly linked dimers from the hydrogenolysis of Japanese larch compression wood.^[22] The presence of free-phenolic 4-O-5 units in native gymnosperm lignin (as modeled in Figure 1 A) was recently confirmed by 2D NMR spectroscopy,^[23,24] the traditionally accepted role of 4-O-5 units in polymer branching is now being questioned owing to the lack of evidence for their etherified counterparts. It has been shown that 4-O-5-linked moieties would be released from larger polymer fragments by hydrogenolysis of the more abundant β -ether units^[22,25] and may therefore limit the degree of lignin

[a] Dr. Y. Li, Prof. J. Ralph
Department of Biological Systems Engineering
University of Wisconsin-Madison
Madison, WI 53706 (USA)
E-mail: jralph@wisc.edu

[b] Dr. Y. Li, Dr. S. D. Karlen, Dr. B. Demir, Dr. H. Kim, Prof. J. A. Dumesic,
Prof. S. S. Stahl, Prof. J. Ralph
DOE Great Lakes Bioenergy Research Center
Madison, WI 53726 (USA)

[c] Dr. S. D. Karlen, Dr. H. Kim, Prof. J. Ralph
Department of Biochemistry
University of Wisconsin-Madison
Madison, WI 53706 (USA)

[d] Dr. B. Demir, Prof. J. A. Dumesic
Department of Chemical and Biological Engineering
University of Wisconsin-Madison
Madison, WI 53706 (USA)

[e] Prof. J. Luterbacher
Institute of Chemical Sciences and Engineering
École Polytechnique Fédérale de Lausanne
Route Cantonale, 1015 Lausanne (Switzerland)

[f] Prof. S. S. Stahl
Department of Chemistry
University of Wisconsin-Madison
Madison, WI 53706 (USA)

[g] Dr. Y. Li
Current address:
Department of Chemical Engineering
Massachusetts Institute of Technology
Cambridge, MA 02142 (USA)

Supporting Information and the ORCID identification number(s) for the author(s) of this article can be found under:
<https://doi.org/10.1002/cssc.202000753>.

This publication is part of a Special Issue focusing on "Lignin Valorization: From Theory to Practice". Please visit the issue at <http://doi.org/10.1002/cssc.v13.17>

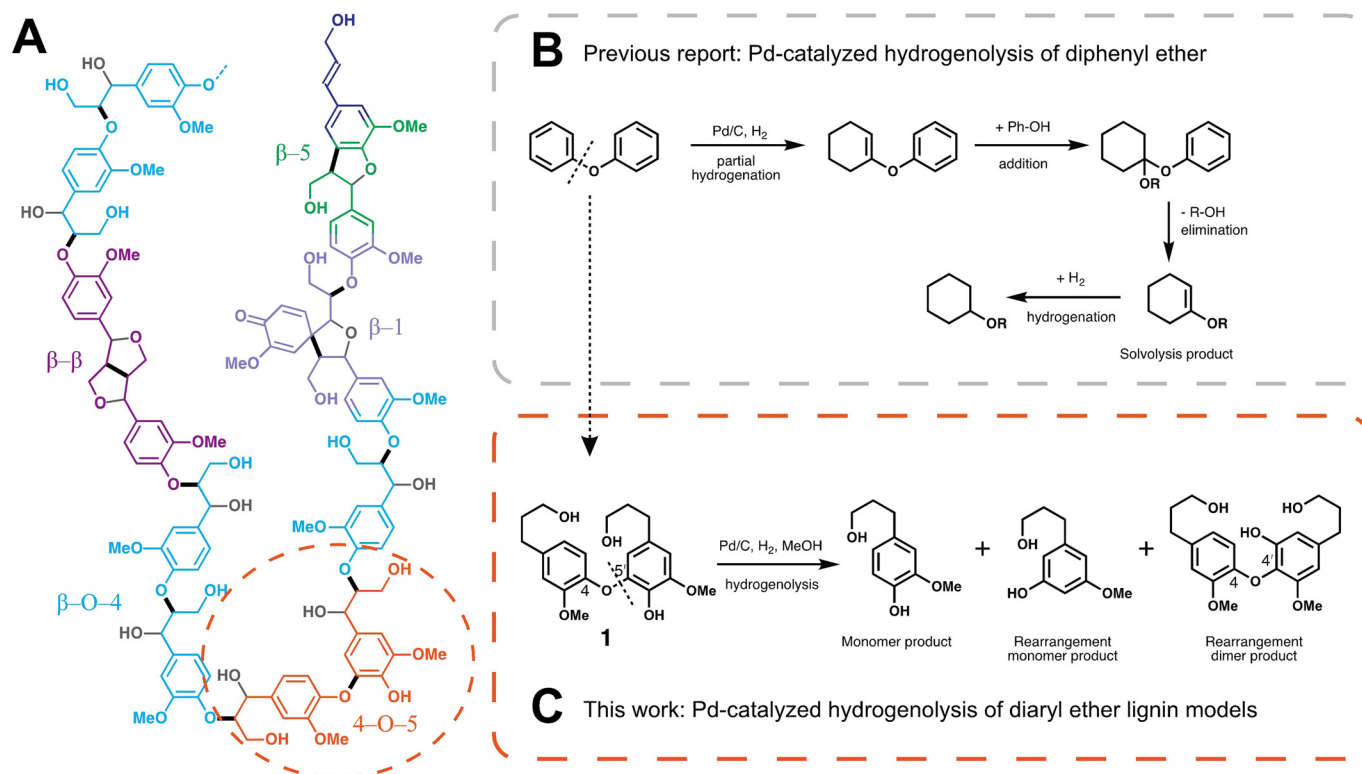


Figure 1. A) A gymnosperm lignin model highlighting the free-phenolic 4-O-5 diaryl ether unit. B) A proposed Pd-catalyzed diphenyl ether hydrogenolysis reaction pathway.^[27] C) Pd-catalyzed diaryl ether hydrogenolysis reaction products from model **1** discovered in this work.

depolymerization, but whether such units are cleaved remains unclear.

Diaryl ether cleavage may play an important role in decreasing the molecular weight of lignin beyond that possible from currently known cleavage pathways and could contribute to the high yields of monomers from such processes. Previous studies of the mechanism of palladium-catalyzed reactions of diaryl ethers with hydrogen have been limited to very simple, commercially available model compounds, such as diphenyl ether. Recent studies of Pd-catalyzed hydrogenolysis of diphenyl ether suggests that the reaction starts by partial hydrogenation of one of the phenyl rings to give an enol ether. Subsequent addition of a nucleophilic solvent (e.g., water or alcohol) converts the enol ether to a ketal that can react further to release phenol and (partially) saturated cleavage products (Figure 1 B).^[26–29]

The Pd-catalyzed hydrogenolysis of lignin does not typically generate cyclohexanes or other arene hydrogenation products, so we hypothesized that the hydrogenolytic scission of 4-O-5 units in lignin might differ from the reactivity observed with diphenyl ether. To test this hypothesis, it was necessary to design and synthesize new and more representative model compounds and evaluate their reactivity under the hydrogenolysis conditions. In this work, several archetypal 4-O-5 lignin models, from dimers to tetramers, that closely resemble the authentic structures present in native gymnosperm lignin, were synthesized (see Figure 1 A, C).^[30] Hydrogenolysis of these compounds led to the expected monomers derived from O-5-

bond scission, but novel unexpected aromatic products were also obtained, corresponding to apparent rearrangement of the phenolic group (Figure 1 C). Evidence for this rearrangement product was also detected from hydrogenolysis of gymnosperm lignin. The phenolic group of the 4-O-5 units is proposed to play a crucial role in the cleavage of diaryl ether linkages in lignin.

Results and Discussion

Model compound design and synthesis

To initiate this study, model compounds were designed to represent the authentic 4-O-5 diaryl ether units in native lignin, in addition to the diaryl ether fragments that have been proposed as products of lignin hydrogenolysis studies (1–6, Figure 2).^[22,25] The first dimeric model we targeted was 4-O-5'-di-[7,8-dihydroconiferyl] alcohol (**1**), which represents a logical product of hydrogenolysis of various β -ether bonds (β -O-4, 4-O- β , or free-phenolic) connecting a 4-O-5 unit into the lignin (see Figure 1 A).^[30] 4-O-5'-Dipropylguaiaicol (**2**) is a closely related structure lacking the γ -hydroxy groups and has also been implicated as a lignin hydrogenolysis product.^[22,25] 4-O-5'-Divanillyl alcohol (**3**) and vanillyl alcohol-4-O-5'-[7,8-dihydroconiferyl] alcohol (**4**) were selected to investigate the reactivity of lignin-like benzylic alcohols and their potential influence on diaryl ether cleavage. Native 4-O-5 units are formed through coupling reactions between pre-formed lignin oligomers, and,

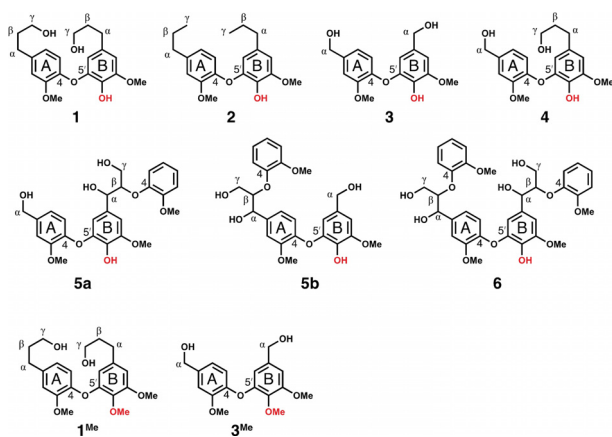


Figure 2. Diaryl ether 4-O-5 model compounds employed in this study.

therefore, 4-O-5 units in plants are at least tetrameric structures.^[30,31] This insight prompted us to prepare extended 4-O-5 model compounds, including the isomeric trimer model compounds **5a** and **5b** and the tetrameric model **6**, which incorporates two β -O-4 dimer units linked by the diaryl ether. Compound **6** is the most sophisticated model prepared to date for the 4-O-5 structure in native gymnosperm lignin. The native 4-O-5 units that have been characterized in the plant cell wall feature a free phenol,^[23,24,30] as reflected in models **1–6**; however, the corresponding methylated analogues **1^{Me}** and **3^{Me}** were prepared to assess the role of the phenolic-OH group on the hydrogenolysis reactivity.

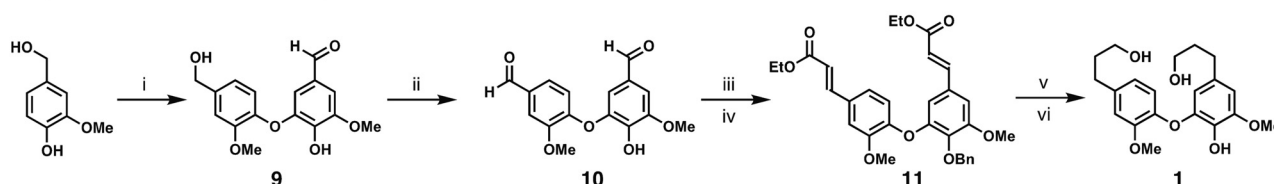
Radical coupling reactions were used to prepare the diaryl ether fragments of the targeted 4-O-5 model compounds (Figure 3A and Scheme S1 in the Supporting Information).^[32] Ag_2O

was used to promote oxidative dimerization of vanillyl alcohol to generate vanillyl alcohol-(4-O-5'-)vanillin (**9**), which was isolated in 30% yield following crystallization.^[24,32] Subsequent sidechain oxidation, olefination, and hydrogenation steps led to the desired model compound **1**, bearing two hydroxypropyl sidechains (Figure 3A). The dialdehyde **10** was an effective precursor to the trimeric model compounds **5a/5b** (Figure 2, obtained as an inseparable mixture) and tetrameric model **6**, through single or double enolate addition to the aldehyde intermediate **13** followed by reduction and debenzylation (Figure 3B).^[33] Access to the diaryl ether core of the 4-O-5' model **2** was achieved through a biomimetic oxidative coupling reaction of propylguaiacol promoted by horseradish peroxidase and H_2O_2 .^[34] This reaction and synthetic steps leading to the other model compounds are elaborated in the Supporting Information (Scheme S1).

Hydrogenolysis of lignin model compounds

The use of a Pd/C catalyst in methanol is among the most effective methods for lignin hydrogenolysis, producing high monomer yields with guaiacylpropanol and syringylpropanol as the major lignin depolymerization products.^[13–20] Such hydrogenolysis conditions were used to probe the reactivity of the 4-O-5 model compounds shown in Figure 2. The dimeric model **1** was subjected to the hydrogenolysis conditions for 3 h (Figure 4), upon which approximately 40% scission of the O-5'-bond occurred to yield two equivalents of the corresponding monomeric guaiacylpropanol (**15**). The possible 4-O scission products, 1,3-substituted and 1,3,4,5-substituted monomers, were not detected among the products. Additional cleavage products included sidechain-truncated mono-

A Synthesis of Model 4-O-5 Compound 1



B Synthesis of Model 4-O-5 Compound 6

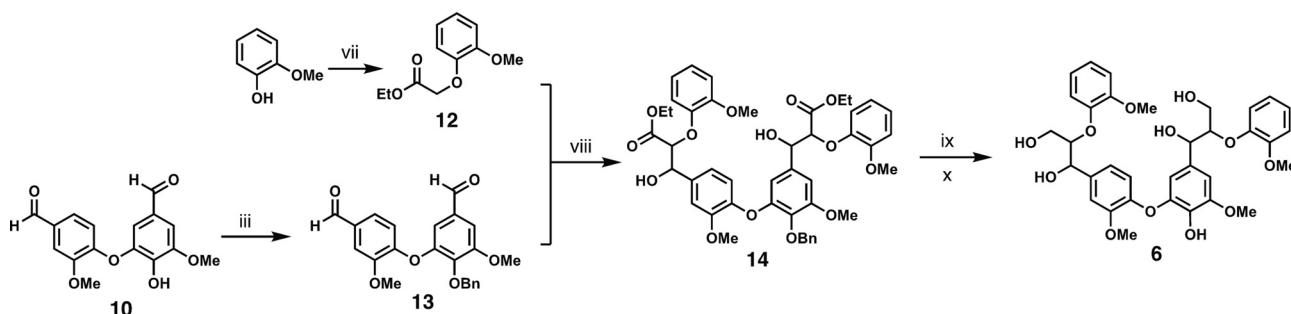


Figure 3. Synthetic pathways for the preparation of 4-O-5 model compounds **1** (A) and **6** (B). (i) Ag_2O , acetone, 30%; (ii) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), THF, 95%; (iii) BnBr , K_2CO_3 , KI, DMF, 99%; (iv) triethyl phosphonoacetate, NaH, THF, 90%; (v) diisobutylaluminum hydride (DIBAL-H), THF, 91%; (vi) H_2 , Pd/C, MeOH, 99%; (vii) ethyl chloroacetate, K_2CO_3 , KI, acetone, 99%; (viii) lithium diisopropylamide (LDA), THF, -78°C , 90%; (ix) NaBH_4 , MeOH, 99%; (x) H_2 , Pd/C, MeOH, 99%.

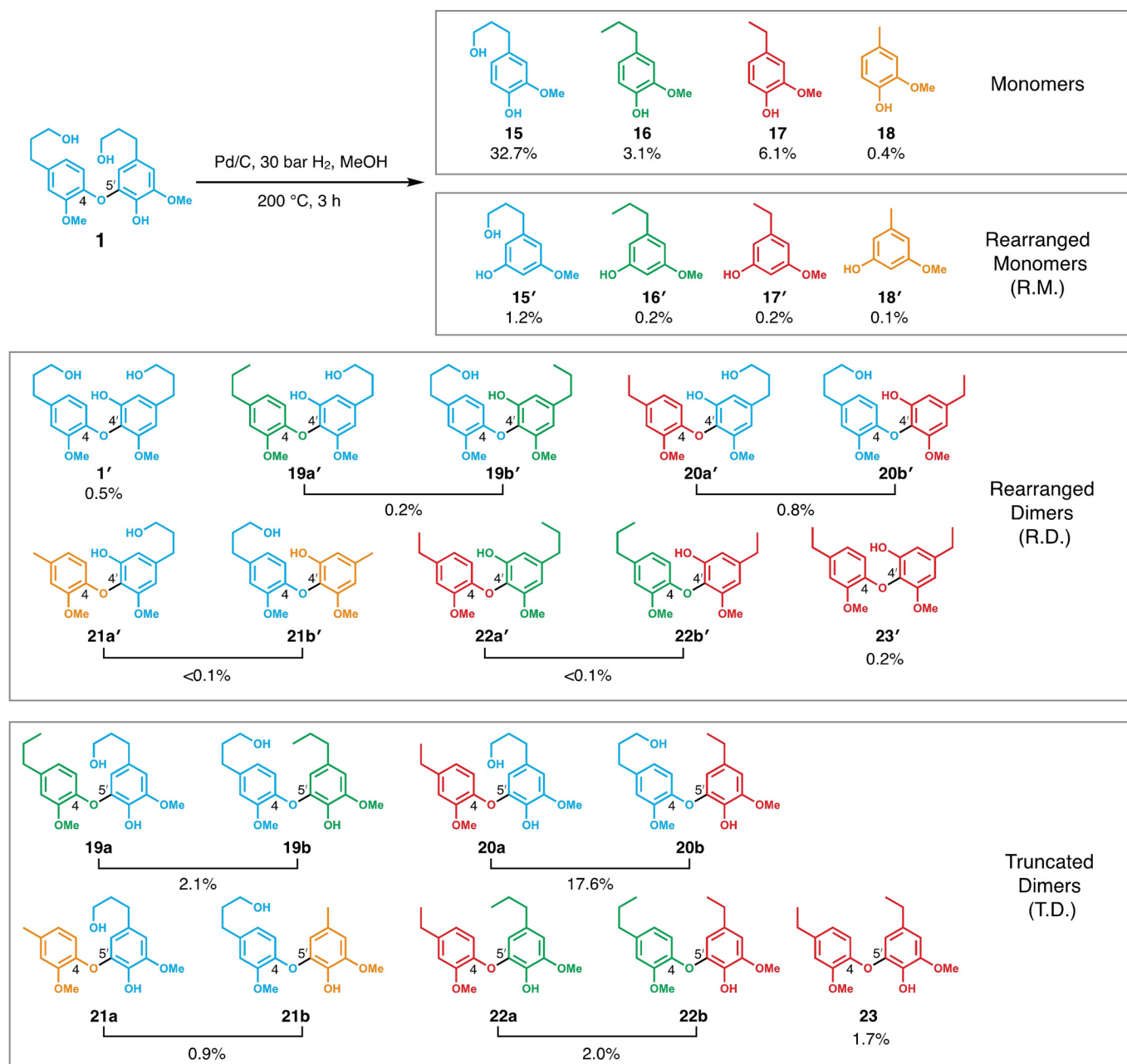
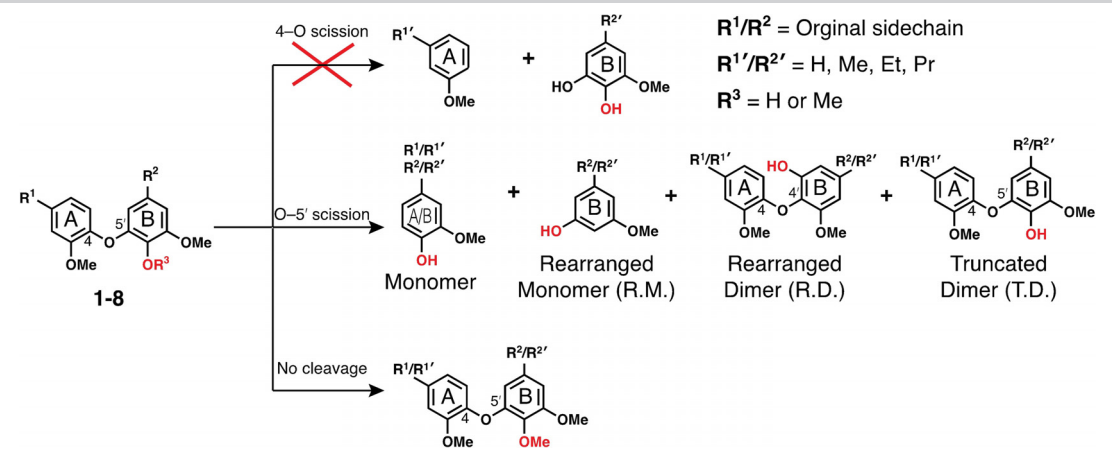


Figure 4. Product distribution from **1** after hydrogenolysis for 3 h. Reaction conditions: models (20 mg), dimethoxybenzene (10 mg, internal standard), 5% Pd/C (10 mg), methanol (20 mL), 30 bar H₂, 200 °C. Products were purified and characterized by ultra-high-performance liquid chromatography-quadrupole time-of-flight (UHPLC-QTOF) high-resolution MS (Table S1 in the Supporting Information). Yields were determined by GC-flame ionization detection (FID) following trimethylsilane (TMS) derivatization (Table 1).

mers **16–18**, reflecting C–C (or just C_γ–OH) bond cleavage under the hydrogenolysis conditions, and unprecedented 1,3,5-*meta*-substituted “rearranged monomers” (R.M.) **15'–18'**, which have not been noted previously from hydrogenolysis reactions. The rearrangement process evident in the latter monomers was also evident in “rearranged dimers” (R.D.) **1'** and **19'–23'**, which correspond to 4-O-4'-linked dimers. Significant quantities of sidechain-truncated dimers (T.D.) **19–23** were observed, again reflecting C–C (or just C_γ–OH) bond cleavage of the hydroxypropyl sidechains in starting material **1**.

Each of the model compounds depicted in Figure 2 was subjected to the same hydrogenolysis conditions, and the products were analyzed after 3 and 15 h reaction times. The results of these reactions are summarized in Table 1. Overall, higher monomer yields, arising from O-5'-bond cleavage, were observed from the longer (15 h) reactions, in addition to higher yields of the rearranged and truncated products, R.M., R.D., and T.D. No sidechain truncation products were observed with model compound **2**, indicating that C–C cleavage of the sidechain requires the γ-hydroxy group. Comparing the reactions of **1** and **2** indicates that the ether cleavage rate of **1** may be

Table 1. Conversion and product yields of 4-O-5 lignin model hydrogenolysis.


1-8

4-O scission

O-5' scission

No cleavage

R^1/R^2 = Original sidechain
 $R^1'/R^{2'}$ = H, Me, Et, Pr
 R^3 = H or Me

Monomer

Rearranged Monomer (R.M.)

Rearranged Dimer (R.D.)

Truncated Dimer (T.D.)

Model	t [h]	Conversion [%]	Monomer ^[b] ($R^1 + R^{1'}$) [%]	R.M. ($R^2 + R^{2'}$) [%]	R.D. ($R^{1/2} + R^{1/2'}$) [%]	T.D. [%]
1	3	70	42 (33 + 9)	2 (1.2 + 0.5)	2 (0.5 + 1.2)	24
	15	95	55 (41 + 14)	6 (5 + 1)	5 (2 + 3)	29
2	3	38	29	4	5	0
	15	77	51	15	11	0
3	3	99	20 (0 + 20)	1 (0 + 1)	6 (0 + 6)	73
	15	100	31 (0 + 31)	9 (0 + 9)	10 (0 + 10)	50
4	3	100	22 (11 + 11)	1 (1.1 + 0.1)	3 (1.6 + 1.4)	71
	15	100	25 (15 + 9)	5 (5 + 0.2)	9 (0 + 9)	64
5a/5b ^[a]	3	100	34 (11 + 23)	3 (0 + 3)	4 (0 + 4)	59
	15	100	39 (14 + 25)	5 (0 + 5)	6 (0 + 6)	50
6 ^[a]	3	100	38 (23 + 15)	8 (3 + 5)	4 (2 + 2)	50
	15	100	45 (32 + 13)	10 (3 + 7)	7 (3 + 4)	38
1 ^{Me}	3	1	0	0	0	1
	15	4	0	0	0	4
3 ^{Me}	3	91	0	0	0	91
	15	100	0	0	0	100

[a] Monomer yield: moles of product monomers/(2 × moles of the starting material) × 100%. [b] β-O-4 cleavage product guaiacol not counted as part of the monomer yield.

faster than that of **2** at the beginning of the reaction. However, as the reaction time increased, the diaryl ether cleavage rate of **1** diminished, whereas the cleavage rate of **2** remained steady after 15 h. These observations seem to suggest that sidechain truncation of **1** causes a decrease in the reaction rate. Compound **2** showed the highest yield of the rearrangement products (R.M. and R.D.) among all models.

The results from model compound **3** indicates that, in contrast to γ -hydroxy groups, benzylic alcohols do not facilitate diaryl ether cleavage. The monomer yield from **3** was less than 30% after 15 h, which was significantly lower than the monomer yields from **1** or **2**. However, the conversion of **3** was very high owing to C–O cleavage of the benzylic alcohol, resulting in high yields of truncated products.

The reaction of **4**, which features two different sidechains, revealed that the rearrangement reaction only occurred on the phenolic B-ring of the dimer because R.M. were observed predominantly with 2 or 3 carbon atoms on the sidechain. These products can only arise from the hydroxypropyl sidechain moiety of the B-ring. Similar to the reaction of **3**, **4** also underwent significant sidechain truncation of the hydroxymethyl group of the A-ring. The overall monomer yields from reactions of the benzylic alcohol models **3** and **4** were significantly

lower than those of the hydroxypropyl models **1**. These observations could be rationalized by rapid hydrogenolysis of the benzyl alcohols, which removes the ability of the hydroxy groups to anchor the substrate to the catalyst surface.

The product distributions from **5a/5b** and **6** were similar, albeit much more complex than those from the dimeric models. Not only were monomers and dimers identified (including sidechain-truncated products), but also some trimers without full cleavage of their β -O-4 bonds. Similar to observations made in some previous studies on lignin hydrogenolysis,^[11,12] once the α -hydroxy group on the β -O-4 dimer moiety was removed by hydrogenolysis, the retained β -O-4 moiety did not undergo ether cleavage. After 15 h, the total monomer yields from both **5** and **6** were lower than those from **1** and **2**, suggesting that the rate of diaryl ether cleavage slowed down once sidechain truncation took place. These results are consistent with observations made from the reactions of the dimeric models.

Hydrogenolysis of the methyl-protected, non-phenolic, models **1^{Me}** and **3^{Me}** (Figure 2) revealed that no monomers derived from diaryl ether cleavage nor rearrangement products were formed (Figures S9 and 10 in the Supporting Information). The only reactivity observed was extensive hydrogenolysis of the

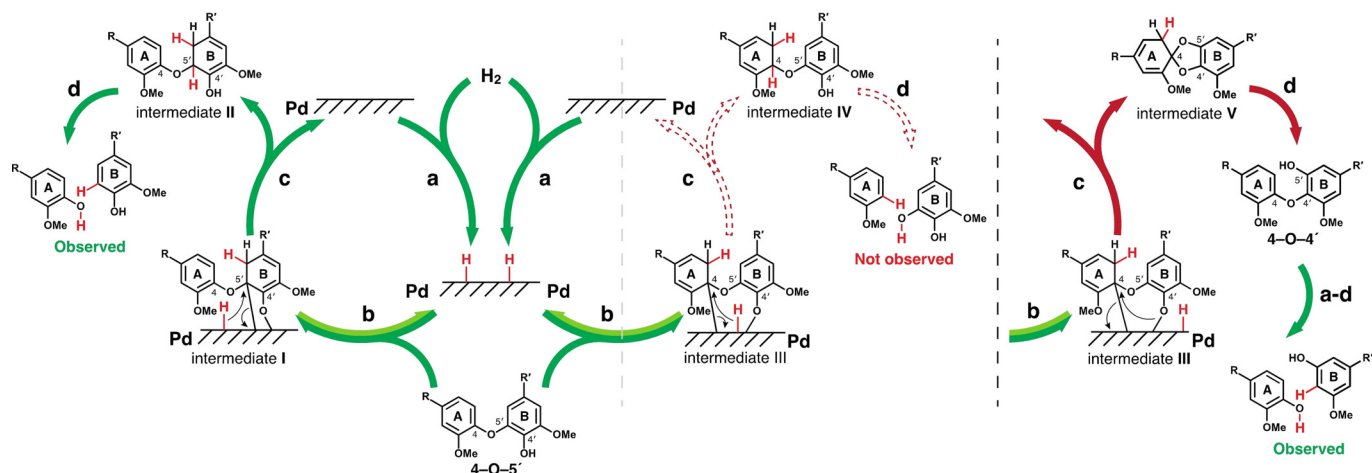


Figure 5. Proposed palladium-catalyzed ether bond cleavage and rearrangement of 4-O-5 lignin models under hydrogenolytic conditions: a) dissociative adsorption; b) insertion and coordination; c) reductive elimination; d) E1 elimination. Based on the products observed experimentally (see main text), we conclude that the best mechanistic rationale is via the solid arrow pathways.

benzylic alcohol of 3^{Me} and a low level of sidechain truncation from 1^{Me} (<5%). These results highlight the important role of the phenol in promoting diaryl ether cleavage and in the formation of the rearrangement products.

The reactions of **1** and 1^{Me} in $[D_4]\text{MeOH}$ were performed to probe the possibility of methanolysis reactions, which have been observed in hydrogenolysis reactions of the simple diphenyl ether model compound. No $-\text{OCD}_3$ -substituted products were detected under our reaction conditions (Figure S11 in the Supporting Information), showing that methanolysis did not occur in these more relevantly substituted 4-O-5 lignin models.

The relevance of the reactivity of model compounds **1–6** (Table 1) to hydrogenolysis reactions of native lignin was tested by subjecting extract-free gymnosperm (pine) cell wall material to the hydrogenolysis reaction conditions. The previously unreported rearranged monomer **15'** (Figure 4) was identified by matching its electron-ionization (EI)-MS mass-fragmentation pattern and GC-MS retention time with the authentic compound from the above model reactions (Figure S12 in the Supporting Information). This result establishes **15'** as a fingerprint marker, both for the existence of diaryl ethers themselves in lignin and for their (partial) cleavage to monomers, and highlights the value of using lignin model complexes that closely resemble their native structures in lignin.

Proposed mechanism for diaryl ether cleavage and rearrangement

As the results from the methylated models demonstrate, the phenolic-OH group is crucial in the diaryl ether cleavage mechanism. Recent DFT work demonstrates that a phenolic group can form a Pd–O bond on the catalyst surface, and this bonding was suggested to play an essential role in the dissociative adsorption of phenol onto a Pd(111) surface.^[35] We hypothesize that such a Pd–O bond is also crucial to facilitate the cleavage of 4-O-5 units in lignin. The following proposed

mechanism accounts for the key observations made herein. Hydrogenolysis reaction mechanisms begin with dissociative adsorption of H_2 onto the palladium catalyst surface, generating surface-bound hydrogen atoms (Figure 5, step a).^[36] Reaction of a C5'–C6' bond with the Pd–H species will partially saturate the B-ring (intermediate I), with the regiochemistry for addition of Pd–H to the aromatic ring rationalized similarly to Markovnikov's rule for charged species. The Pd–O bond could help stabilize the substrate on the catalyst surface via a Pd-coordinated intermediate (intermediate I). Migration of a second hydrogen atom to the palladium-B-ring complex will release the partially hydrogenated product (intermediate II) and regenerate the Pd catalyst. An elimination reaction from intermediate II will cleave the ether bond to generate monomeric products while rearomatizing the B-ring. The products of this hydrogenolysis pathway are two identical 1,3,4-substituted monomers, as observed in the reactions described above.

Another possible hydrogenolysis cycle could involve hydrogen addition to the A-ring, resulting in the formation of the Pd-coordinated intermediate III. Addition of the second hydrogen atom to this intermediate would release the partially saturated A-ring product (intermediate IV), and subsequent elimination would cleave the aryl ether bond and form two different monomers with 1,3,4,5- and 1,3-substitution patterns. These products were not detected experimentally, however, suggesting that the pathway in green is favored. Nevertheless, a variant of this secondary pathway provides a rationale for the unique rearrangement products observed in this study. As noted above, the reaction of **4** shows that rearrangement products arise only from the B-ring. In a modification of the mechanism, intermediate III could undergo rearrangement, rather than addition of a second hydrogen atom. Intramolecular addition of the Pd-coordinated phenoxide onto the B-ring can give the spirocyclic cyclohexadiene (intermediate V). Formation of the new C4–O bond could arise from rotation of the B-ring to orient parallel to the Pd surface, leading to orbital overlap between the C4 and O atoms. This process is the re-

verse of an ether bond-scission step described in a recent DFT calculation.^[37] An elimination reaction involving ring-opening of the 5-membered dioxalane ring will rearomatize the A-ring and either generate the 4-O-4' rearrangement product or regenerate the 4-O-5' starting material, depending on which C4–O bond is cleaved in intermediate **V**. The 4-O-4' products can then enter the ether cleavage cycle (green cycle, step a–d) to afford the 1,3,4- and the novel 1,3,5-substituted (rearrangement) products observed in our study.

The largest differences between our proposed reaction pathways and those reported previously for 4-O-5 cleavage are the lack of aromatic ring hydrogenation to cyclohexane derivatives and the accommodation of novel rearrangement products that have not been previously considered. The experimental results and mechanistic proposals implicate various roles for the phenolic group in the 4-O-5 models and lignin units. By binding to the catalyst surface, the phenol can contribute to low-energy surface-mediated reaction steps, facilitate addition of the surface-bound hydrogen atoms to the aromatic ring, and provide a pathway for the previously unknown rearrangement products. Overall, this study shows that the hydrogenolysis and diaryl ether cleavage of authentic 4-O-5 lignin models is strikingly different from the reaction pathways observed for diphenyl ether (i.e., arene hydrogenation and ether-cleavage through methanolysis), which is the principal model used previously to probe pathways for hydrogenolysis of diaryl ether bonds in lignin.

Conclusions

Lignin hydrogenolysis, either on lignins resulting from mild biomass pretreatment processes or on the native lignins in biomass as part of the pretreatment itself (i.e., on processes designated as “lignin-first” approaches)^[38,39] remains a promising method to deliver a small range of valuable phenolic commodity-chemical monomers from the complex polymer. Although certain mechanistic details regarding hydrogenolysis mechanisms may be gained from the study of simplified (commercially available) model compounds, the analysis of substitutions present in real lignin and their influence on reaction pathways necessitates the deployment of realistic models for informative insight into lignin reactivity. We have reevaluated the hydrogenolytic reaction mechanisms with 4-O-5-linked model compounds that incorporate structural features that closely resemble the authentic lignin structures, or products anticipated from cleaving β -ether units in the usual way. Our results provide experimental evidence for the participation of the phenolic group and the influence of sidechain substituents on 4-O-5 diaryl ether cleavage under Pd-catalyzed lignin hydrogenolysis conditions. A plausible mechanism has been offered to rationalize the unprecedented rearrangement products obtained from the reactions. The confirmation of the rearrangement monomer from the hydrogenolysis products of pine cell wall suggests that 4-O-5-bond cleavage follows a similar reaction mechanism in real lignins, highlighting the importance of using structurally accurate model compounds.

Acknowledgements

Funding for YL, JL, and JR was provided by the Swiss National Science Foundation (Synergia) grant # CRS115_180258. Funding for SK, BD, HK, JD, SS, and JR was provided by DOE Great Lakes Bioenergy Research Center (DOE BER Office of Science DE-SC0018409). The laboratory and the instrumentation (NMR and MS) were also supported by DOE Great Lakes Bioenergy Research Center (DOE BER Office of Science DE-SC0018409) in related work.

Conflict of interest

The authors declare no conflict of interest.

Keywords: biorefinery · catalysis · diaryl ether · lignin · mechanism

- [1] R. Rinaldi, R. Jastrzebshi, M. T. Clough, J. Ralph, M. Kennema, P. C. A. Bruijninx, B. M. Weckhuysen, *Angew. Chem. Int. Ed.* **2016**, *55*, 8164–8215; *Angew. Chem.* **2016**, *128*, 8296–8354.
- [2] A. Rahimi, A. Ulbrich, J. J. Coon, S. S. Stahl, *Nature* **2014**, *515*, 249–252.
- [3] E. M. Anderson, M. L. Stone, R. Katahira, M. Reed, G. T. Beckham, Y. Román-Leshkov, *Joule* **2017**, *1*, 613–622.
- [4] L. Shuai, M. T. Amiri, Y. M. Questell-Santiago, F. Héroguel, Y. Li, H. Kim, R. Meilan, C. Chapple, J. Ralph, J. S. Luterbacher, *Science* **2016**, *354*, 329–333.
- [5] W. Schutyser, T. Renders, S. Van den Bosch, S.-F. Koelewijn, G. T. Beckham, B. F. Sels, *Chem. Soc. Rev.* **2018**, *47*, 852–908.
- [6] Z. Sun, B. Fridrich, A. de Santi, S. Elangovan, K. Barta, *Chem. Rev.* **2018**, *118*, 614–678.
- [7] C. Z. Li, X. C. Zhao, A. Q. Wang, G. W. Huber, T. Zhang, *Chem. Rev.* **2015**, *115*, 11559–11624.
- [8] E. Furimsky, *Appl. Catal. A* **2000**, *199*, 147–190.
- [9] J. He, C. Zhao, J. A. Lercher, *J. Am. Chem. Soc.* **2012**, *134*, 20768–20775.
- [10] E. M. Anderson, M. L. Stone, M. J. Hülsey, G. T. Beckham, Y. Román-Leshkov, *ACS Sustainable Chem. Eng.* **2018**, *6*, 7951–7959.
- [11] Y. Li, B. Demir, L. M. Vázquez Ramos, M. Chen, J. A. Dumesic, J. Ralph, *Green Chem.* **2019**, *21*, 3561–3572.
- [12] H. Li, G. Song, *ACS Catal.* **2019**, *9*, 4054–4064.
- [13] Q. Song, F. Wang, J. Cai, Y. Wang, J. Zhang, W. Yu, J. Xu, *Energy Environ. Sci.* **2013**, *6*, 994–1007.
- [14] C. Li, M. Zheng, A. Wang, T. Zhang, *Energy Environ. Sci.* **2012**, *5*, 6383–6390.
- [15] I. Klein, C. Marcum, H. Kenttämä, M. M. Abu-Omar, *Green Chem.* **2016**, *18*, 2399–2405.
- [16] X. Huang, O. M. M. Gonzalez, J. Zhu, T. I. Korányi, M. D. Boot, E. J. M. Hensen, *Green Chem.* **2017**, *19*, 175–187.
- [17] M. V. Galkin, J. S. M. Samec, *ChemSusChem* **2014**, *7*, 2154–2158.
- [18] Y. Li, L. Shuai, H. Kim, A. H. Motagamwala, J. K. Mobley, F. Yue, Y. Tobimatsu, D. Havkin-Frenkel, F. Chen, R. A. Dixon, J. S. Luterbacher, J. A. Dumesic, J. Ralph, *Sci. Adv.* **2018**, *4*, eaau2968.
- [19] W. Lan, M. Talebi Amiri, C. M. Hunston, J. S. Luterbacher, *Angew. Chem. Int. Ed.* **2018**, *57*, 1356–1360; *Angew. Chem.* **2018**, *130*, 1370–1374.
- [20] S. Van den Bosch, W. Schutyser, S. F. Koelewijn, T. Renders, C. M. Courtin, B. F. Sels, *Chem. Commun.* **2015**, *51*, 13158–13161.
- [21] K. Freudenberg, C. L. Chen, *Chem. Ber.* **1967**, *100*, 3683–3688.
- [22] S. Yasuda, A. Sakakibara, *Mokuzai Gakkaishi (Journal of the Japan Wood Research Society)* **1977**, *23*, 383–387, <http://www.jwrs.org/english/journals/mkz-toce/mkze-23/#08>.
- [23] F. Yue, F. Lu, S. Ralph, J. Ralph, *Biomacromolecules* **2016**, *17*, 1909–1920.
- [24] Y. Li, T. Akiyama, T. Yokoyama, Y. Matsumoto, *Biomacromolecules* **2016**, *17*, 1921–1929.

- [25] S. Van den Bosch, W. Schutyser, R. Vanholme, T. Driessen, S.-F. Koelewijn, T. Renders, B. De Meester, W. J. J. Huijgen, W. Dehaen, C. M. Courtin, B. Lagrain, W. Boerjan, B. F. Sels, *Energy Environ. Sci.* **2015**, *8*, 1748–1763.
- [26] M. Wang, H. Shi, D. M. Camaioni, J. A. Lercher, *Angew. Chem. Int. Ed.* **2017**, *56*, 2110–2114; *Angew. Chem.* **2017**, *129*, 2142–2146.
- [27] M. Wang, O. Y. Gutiérrez, D. M. Camaioni, J. A. Lercher, *Angew. Chem. Int. Ed.* **2018**, *57*, 3747–3751; *Angew. Chem.* **2018**, *130*, 3809–3813.
- [28] H. Zeng, D. Cao, Z. Qiu, C. J. Li, *Angew. Chem. Int. Ed.* **2018**, *57*, 3752–3757; *Angew. Chem.* **2018**, *130*, 3814–3819.
- [29] D. Cao, H. Zeng, C.-J. Li, *ACS Catal.* **2018**, *8*, 8873–8878.
- [30] J. Ralph, C. Lapierre, W. Boerjan, *Curr. Opin. Biotechnol.* **2019**, *56*, 240–249.
- [31] W. Boerjan, J. Ralph, M. Baucher, *Annu. Rev. Plant Biol.* **2003**, *54*, 519–546.
- [32] J. Ralph, S. Quideau, J. H. Grabber, R. D. Hatfield, *J. Chem. Soc. Perkin Trans. 1* **1994**, 3485–3498.
- [33] F. Nakatsubo, K. Sato, T. Higuchi, *Holzforschung* **1975**, *29*, 165–168.
- [34] F. Yue, F. Lu, M. Regner, R. Sun, J. Ralph, *ChemSusChem* **2017**, *10*, 830–835.
- [35] G. Li, J. Han, H. Wang, X. Zhu, Q. Ge, *ACS Catal.* **2015**, *5*, 2009–2016.
- [36] T. Mitsui, M. K. Rose, E. Fomin, D. F. Ogletree, M. Salmeron, *Nature* **2003**, *422*, 705.
- [37] J. Lu, M. Wang, X. Zhang, A. Heyden, F. Wang, *ACS Catal.* **2016**, *6*, 5589–5598.
- [38] T. Renders, G. Van den Bossche, T. Vangeel, K. Van Aelst, B. Sels, *Curr. Opin. Biotechnol.* **2019**, *56*, 193–201.
- [39] T. Renders, E. Cooreman, S. Van den Bosch, W. Schutyser, S.-F. Koelewijn, T. Vangeel, A. Deneyer, G. Van den Bossche, C. Courtin, B. Sels, *Green Chem.* **2018**, *20*, 4607–4619.

Manuscript received: March 23, 2020

Accepted manuscript online: March 23, 2020

Version of record online: April 20, 2020