Lignin Valorization

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Ruthenium-Catalyzed C–C Bond Cleavage in Lignin Model Substrates**

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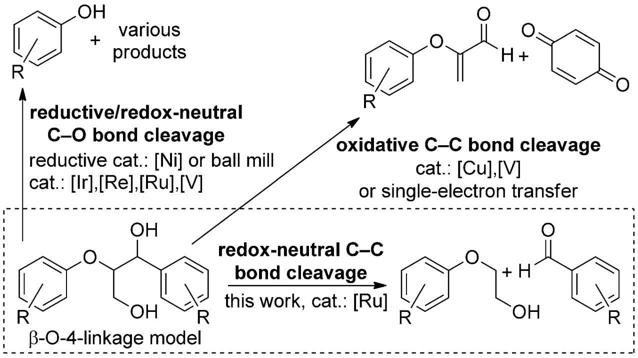
Abstract: *Ruthenium–triphos complexes exhibited unprecedented catalytic activity and selectivity in the redox-neutral C–C bond cleavage of the β-O-4 lignin linkage of 1,3-dilignol model compounds. A mechanistic pathway involving a dehydrogenation-initiated retro-aldol reaction for the C–C bond cleavage was proposed in line with experimental data and DFT calculations.*

Depleting fossil resources demand the development of innovative catalytic concepts for the effective conversion of renewable lignocellulosic feedstock into chemicals and transportation fuels.[1,2] Although the valorization of the carbohydrate components of the lignocellulose raw material has greatly advanced in recent years,[3] the catalytic conversion of lignin still presents a major challenge. The use of the lignin fraction of biomass is currently largely restricted to its caloric value through incineration; consequently, roughly one-third of lignocellulose remains chemically unexploited.[4] The difficulties for catalytic valorization concepts are predominantly related to the recalcitrant polymer structure of lignin, with its complex connectivity through relatively stable C–O and C–C linkages.[4a] Within this multifaceted network the most abundant unit is the β-O-4 linkage, represented by the dilignol model structure in Scheme 1.[4,5] Hence, the efficient catalytic cleavage of this specific linkage could pave the way for selective lignin depolymerization and utilization.

Owing to their tunable reactivity and the accessibility of the polymer for molecular catalysts, homogeneous catalysts hold great potential for the selective fragmentation of lignin.[4b] Several reductive,[6] oxidative,[7,8] and redox-neutral methods[9] for the cleavage of the β-O-4 linkage in lignin model compounds have been reported recently (Scheme 1). The cleavage of C–C bonds is so far limited to oxidative procedures and radical pathways.[7e,h,8] The C–O bond cleavage of dilignol model compounds has been achieved in a redox-neutral fashion, for example, by Toste and co-workers with vanadium catalysts,[9e,f] by Kühn, Cokoja, and co-workers with rhenium catalysts,[9b] and by Stephenson and co-workers by iridium photocatalysis.[9a]



Scheme 1. Selective fragmentation of models of the β-O-4 lignin linkage (see text for details).

The research groups of Bergman and Ellman initially reported such a C–O bond cleavage in 2-aryloxyethanols, the elementary analogue of the β-O-4 motif, by intramolecular transfer hydrogenolysis with a catalyst formed in situ from $[Ru(CO)(H)_2(PPh_3)_3]$ and xantphos.[9c] Later, James and co-workers elucidated the mechanistic aspects of this catalyst system, including a substrate-dependent deactivation pathway for more complex dilignol models that limits the substrate scope of this catalyst.[9d]

Recently, we and others have shown that ruthenium complexes with triphos-type phosphine ligands are highly active catalysts for the hydrogenation of challenging substrates.[10] In the course of our studies, these systems were also found to exhibit very high activity for the C–O bond cleavage of 2-aryloxyethanols through intramolecular hydrogen transfer.[11] Herein, we report that these complexes effectively catalyze unprecedented redox-neutral C–C bond cleavage[12–14] in more elaborate dilignol model compounds incorporating a 1,3-diol functionality. A hydrogen-transfer-initiated retro-aldol mechanism[12,13] is proposed to account for this novel pathway for the disintegration of linkages found abundantly in lignin.

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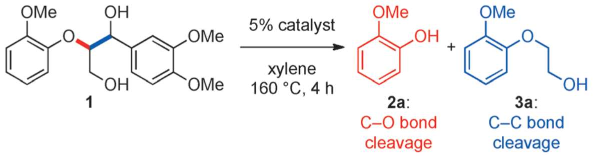
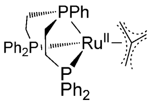
Table 1: C–O and C–C bond cleavage of **1**.[a,b]

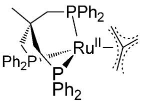


Entry	Precursor	Yield of **2a** [%][c]	Yield of **3a** [%][c]
1	**I**	28	4
2	**II**	14	21
3	**III**	5	24
4	**IV**	26	15
5	**V**	4	66

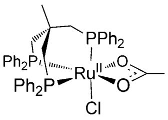
[a] Only the products containing the phenolic ring are shown. For a complete list of products from the reactions, see the Supporting Information. [b] Reaction conditions: **1** (0.1 mmol), *ortho*-xylene (0.5 mL). [c] The yield was determined by GC with dodecane as an internal standard.



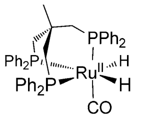
I (**L1**: bdepp)



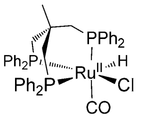
II (**L2**: triphos)



III (**L2**)

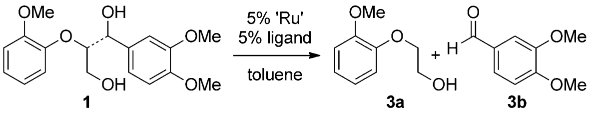


IV (**L2**)



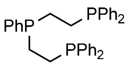
V (**L2**)

Table 2: Ligand screening for the selective C–C bond cleavage of **1**.[a,b]

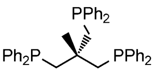


Entry	Ligand	T [°C]	t [h]	Yield of **3a** [%][c]	Yield of **3b** [%][c]
1	none	140	4	3	8
2	**L3**	140	4	2	2
3	**L4**	140	4	6	8
4	**L1**	140	4	31	26
5	**L2**	140	4	64	64
6	**L2**	160[d]	4	77	75
7	**L2**	160[d]	1	70	69

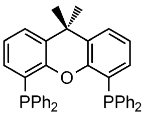
[a] For a complete list of products from the reactions, see the Supporting Information. [b] Reaction conditions: [Ru(Cl)(H)(PPh$_3$)$_3$] (5 mol%), **1** (0.1 mmol), toluene (0.5 mL); the catalyst/**L** mixture was preheated for 2 h at 140 °C. [c] The yield was determined by GC with dodecane as an internal standard. [d] The reaction was carried out with *ortho*-xylene (0.5 mL) as the solvent.



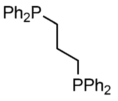
L1: bdepp



L2: triphos



L3: xantphos

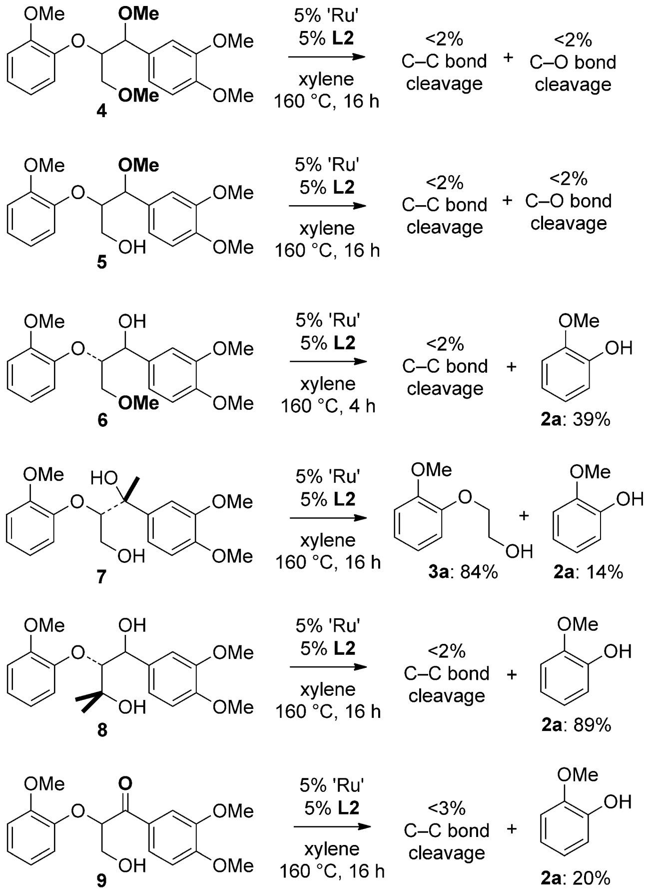


L4: dppp

In initial experiments we investigated the activity of Ru complexes bearing tripodal phosphine ligands in the transformation of the complex lignin model substrate **1** (Table 1). In line with previous findings,[11] [Ru(bdepp)(tmm)] (**I**) catalyzed the C–O bond cleavage to give a mixture of guaiacol (**2a**) and several products formed from the complementary part of the substrate in moderate yield (see the Supporting Information). Also, small amounts of alcohol **3a** and 3,4-dimethoxybenzaldehyde (**3b**) were detected (Table 1, entry 1). The formation of these products can be rationalized formally by intramolecular hydrogen-atom transfer, associated, however, with C–C bond cleavage rather than C–O bond hydrogenolysis. C–C bond cleavage became the major pathway with the catalyst [Ru(tmm)(triphos)] (**II**)[11] to give product **3a** in 21% yield (Table 1, entry 2). Further screening of complexes containing the triphos ligand revealed a strong influence of the catalyst precursor. The acetate complex **III**[15] gave product **3a** in a similar yield of 24% (Table 1, entry 3), whereas the use of [Ru(CO)(H)$_2$(triphos)] (**IV**)[16] resulted in only moderate activity for both C–O and C–C cleavage in **1** (Table 1, entry 4). Finally, the use of [Ru(CO)(Cl)(H)(triphos)] (**V**)[17] afforded the C–C bond-cleavage product **3a** in 66% yield, whereas the C–O bond-cleavage product **2a** was only detected in 4% yield (Table 1, entry 5).

As the ruthenium hydrido chloride precursor provided a promising lead structure for the redox-neutral selective C–C bond cleavage of **1**, catalyst systems formed in situ from [Ru(Cl)(H)(PPh$_3$)$_3$] in combination with selected phosphine ligands were investigated next (Table 2). The triphenylphosphine complex alone showed almost no activity (Table 2, entry 1). The addition of the bidentate ligands xantphos (**L3**; Table 2, entry 2) and DPPP (**L4**; entry 3) did not significantly improve catalytic performance, and only minor amounts of the C–C bond-cleavage products were observed. The use of [Ru(Cl)(H)(PPh$_3$)$_3$] and the tridentate ligand bdepp (**L1**) gave **3a** and **3b** in moderate yield (Table 2, entry 4). Gratifyingly, the catalyst formed in situ from [Ru(Cl)(H)(PPh$_3$)$_3$] and triphos (**L2**) already showed high activity at 140 °C, with products **3a** and **3b** formed in 64% yield (Table 2, entry 5). When this catalytic system was used at 160 °C, the C–C cleavage products **3a** and **3b** were obtained in (76 ± 1)% yield after 4 h, and 70% after 1 h (Table 2, entries 6 and 7, respectively). These results demonstrate again the catalytic potential of triphos–Ru complexes in challenging H-transfer processes at high temperature.

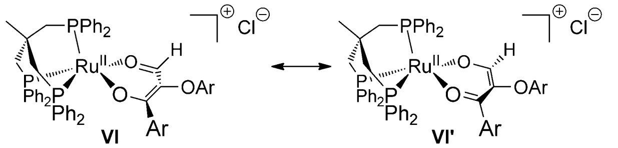
To identify the position of the H-transfer that initiates the C–C bond cleavage, we studied derivatives of compound **1** as substrates (Scheme 2). When the bis(methyl ether) substrate **4** or the secondary methyl ether substrate **5** was used, the C–O and C–C bond-cleavage products were each observed in less than 2% yield. The reaction of substrate **6**, incorporating a secondary hydroxy and a primary methyl ether group, gave the C–O bond-cleavage product **2a** in 39% yield. This C–O bond-cleavage activity is reminiscent of the reactivity of our catalyst system towards 2-phenoxy-1-phenylethan-1-ol.[11] Overall, the reactivity of our catalyst towards substrates **4**–**6** indicates that both hydroxy functionalities need to be present for C–C bond fragmentation to occur, whereas the C–O bond-cleavage pathway requires only the secondary alcohol group. The results with substrates **7** and **8** finally prove that the primary alcohol group[18] is essential to initiate the desired C–C bond cleavage. In substrate **7** containing a primary and a tertiary alcohol group, the C–C bond was cleaved smoothly,



Scheme 2. Reactivity of [Ru(Cl)(H)(PPh$_3$)$_3$]/triphos towards analogues of substrate **1**. The dotted bonds denote the bonds that are broken. Reaction conditions: [Ru(Cl)(H)(PPh$_3$)$_3$] (5 mol%), substrate (0.1 mmol), *ortho*-xylene (0.5 mL); the catalyst/**L** mixture was preheated for 2 h at 140°C. For a complete list of products from the reactions, see the Supporting Information.

whereas exclusively C–O bond-cleavage products were obtained from substrate **8**, in which the C–H position of the primary alcohol was blocked. Finally, the use of ketone substrate **9**[19] gave only traces of C–C and some C–O bond-fragmentation products. These results led to the conclusion that 1) the secondary hydroxy group is required for both the C–C and the C–O bond cleavage to occur, and 2) the primary alcohol group is essential for access to the C–C bond-cleavage pathway.

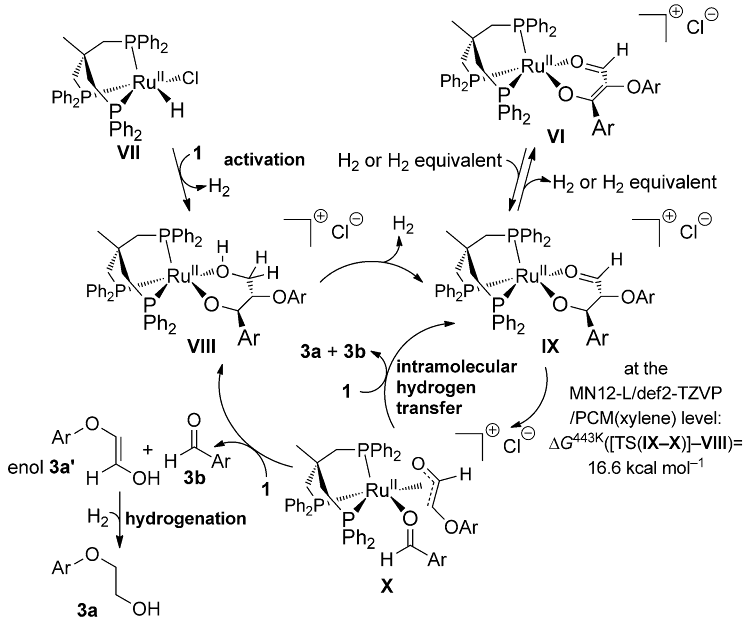
The important role of dehydrogenation at the primary alcohol functionality was further corroborated by the characterization of complex **VI** in solution after catalysis by multinuclear NMR spectroscopy (Scheme 3; see also the Supporting Information). When the [Ru(Cl)(H)(PPh$_3$)$_3$]/triphos system was used, complex **VI** could be assigned as a major reaction product alongside dimeric [(triphos)Ru(μ-Cl)$_3$Ru(triphos)]Cl,[20] PPh$_3$, and unreacted triphos ligand. The latter complex is inactive for the C–C bond cleavage of **1**. Consistently, **VI** was also formed in the catalytic C–C cleavage of **1** with [Ru(CO)(Cl)(H)(triphos)] (**V**) as the catalyst. This result strongly supports the hypothesis that **VI** is a resting state of the Ru–triphos system for the catalytic C–C bond-cleavage of **1**. The formation of complex **VI** by the dehydrogenation of diol **1** is well in line with the known dehydrogenation activity of related Ru catalysts.[21] In contrast to the catalytically inactive six-coordinated xantphos–diol–Ru complexes reported by the James research group,[9d] the Ru center of complex **VI** is five-coordinated, thus providing a vacant coordination site. This feature may at least in part explain the catalytic activity of the triphos system.



Scheme 3. Ru complex obtained after the reaction.

On the basis of the observed complex **VI** and the substrate specificity depicted in Scheme 2, a combined hydrogen-transfer/retro-aldol mechanism[22–24] can be proposed to account for the C–C bond cleavage (Scheme 4). Activation of precatalyst **VII** by the association of substrate **1** could result in complex **VIII**. Dehydrogenation of **VIII** subsequently gives **IX**, followed by retro-aldol-type C–C bond cleavage[25,26] to form **X**. The reaction of **X** with substrate **1** regenerates complex **VIII** with the liberation of aldehyde **3b** and enol **3a′**, which can be hydrogenated under the reaction conditions to give **3a**. Alternatively, intramolecular hydrogen transfer may also enable the formation of **3a** and **3b**, thus regenerating **IX** directly.

The experimentally observed complex **VI** serves in our proposed mechanism as an off-cycle resting state that is

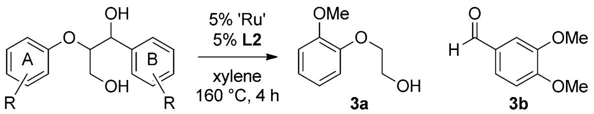


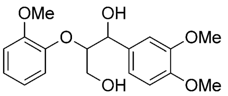
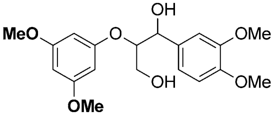
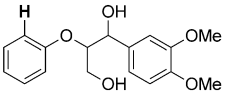
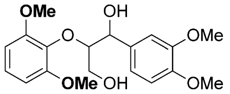
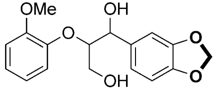
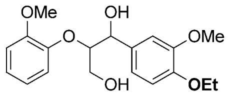
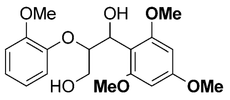
Scheme 4. Proposed hydrogen-transfer-based retro-aldol mechanism for the C–C bond cleavage.[22]

connected to the ruthenium alkoxide **IX** by hydrogenation/dehydrogenation. All three intermediates of the cycle **VIII–X** were found as stationary points on the energetic hyperface by DFT calculations, with **VIII** being the most stable component (see the Supporting Information for details). The energetic difference between **VIII** and the transition state for the crucial C–C bond-cleavage step, TS[**IX**–**X**], was determined to be only 16.6 kcal mol^{-1}. Although our current results cannot distinguish between the inter- and intramolecular hydrogen-transfer paths for the formation of **3a**, this energy difference indicates that the overall catalytic cycle may well be feasible under the given reaction conditions. Albeit alternative pathways invoving dehydration cannot be excluded, the experimental and computational data provide a coherent picture at this stage.

Finally, the effect of substitution of the aromatic rings A and B on the C–C bond-cleavage reaction was systematically evaluated by using the catalyst prepared in situ with **L2** (Table 3). The substitution pattern of ring A had only a moderate effect on the yield of **3b** (**10**: 86 %, **1**: 75 %, **11**: 63 %; Table 3, entries 1–3) unless significant steric constraint was induced with the two *ortho* methoxy groups in substrate **12**, in which case the yield of **3b** was only 26 % (entry 4). Similarly, substituents on ring A only had a small effect on the formation of **3a** (**13**: 94 %, **1**: 77 %, **14**: 75 %; Table 3, entries 1, 5, and 6). However, the use of substrate **15** with methoxy groups in the 2-, 4-, and 6-positions of ring B gave **3a** in only 14 % yield, presumably because of steric hindrance (Table 3, entry 7). Our results indicate that the [Ru(Cl)(H)-$(PPh_3)_3$]/triphos catalyst is tolerant of various substitution patterns of the aromatic rings in the model compounds of the β-O-4 linkage of lignin, which is an important feature considering the diversity of functionalized aryl rings present in lignin.

Table 3: Reactivity of [Ru(Cl)(H)$(PPh_3)_3$]/triphos towards substrates with various aryl substitution patterns.[a,b]



Entry	Substrate		Yield of **3a** [%][c]	Yield of **3b** [%][c]
1		**1**	77	75
variation of fragment A:				
2		**10**	–	86
3		**11**	–	63
4		**12**	–	26
variation of fragment B:				
5		**13**	94	–
6		**14**	75	–
7		**15**	14	–

[a] For a complete list of products from the reactions, see the Supporting Information. [b] Reaction conditions: [Ru(Cl)(H)$(PPh_3)_3$] (5 mol %), substrate (0.1 mmol), *ortho*-xylene (0.5 mL); the catalyst/**L** mixture was preheated for 2 h at 140 °C. [c] The yield of fragment **3a** or **3b** was determined by GC with dodecane as an internal standard.

In conclusion, we have described a novel ruthenium-catalyzed redox-neutral C–C bond cleavage of 1,3-diol lignin model compounds that mimic the important β-O-4 linkage. A mechanistic pathway involving a dehydrogenation-initiated retro-aldol reaction for the C–C-bond cleavage was proposed in line with experimental data and DFT calculations. Our Ru–triphos-based system is one of the first homogeneous catalysts that display this reactivity[12] and is by far the most selective known to date. Application of the catalytic protocol for C–C bond formation[27] is currently under investigation in our laboratories.

Keywords: C–C bond cleavage · cleavage reactions · homogeneous catalysis · lignin · ruthenium complexes

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