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The Ru-Catalyzed Alkylative Dearyloxylation of L-type 2-Aryloxyethanols

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Lignin is a natural occurring biopolymer, which, along with cellulose and hemicellulose, is a major component of wooden plants. Cellulose is an important feedstock for the production of paper, whereas lignin accumulates in large amounts as side product during this process. To date, lignin has received only little attention as a starting material for the production of bulk chemicals and fuels.[1] A small amount of the produced lignin is used for the synthesis of dispersing agents or is burned for the generation of energy and syngas (CO/H_2). Owing to its unique structure, as the only biomaterial consisting mostly of aromatic subunits (Figure 1), lignin is considered to play an important role as a renewable resource for the sustainable production of fuels and chemicals containing aromatic groups in the future.[2]

The activation and functionalization of intrinsically non-reactive chemical bonds like C–H,[3] but also C–C[4] and C–O bonds[5–9] remains one of the challenging tasks of transition metal catalysis. Recently, Bergman and Ellman,[9a] and later on Leitner and Klankermayer[9b] described the ruthenium-catalyzed C-O cleavage of 2-aryloxy-1-arylethanol derivatives which mimic the β-O-4 linkage within the lignin framework. This type of linkage represents the most present junction of the single monomers within the lignin structure (Figure 1). The cleavage of 2-phenoxy-1-phenylethanol proceeded in the presence of a combination of $RuH_2CO(PPh_3)_3$ and Ph-XANTPHOS or Ru(cod)(methallyl)$_2$ and TRIPHOS under redox neutral conditions and might be regarded as an intramolecular version of a so called "hydrogen autotransfer" process (Figure 2).[10–12]

Herein, we present the use of a range of simple and readily available ruthenium catalysts which are not only able to cleave the β-C-O linkage in different lignin model compounds but also allow for a direct sequential alkylation of the resulting acetophenone derivatives using alcohols as alkylating agents (Figure 2).[13] The combination of two independent catalytic hydrogen-autotransfer steps generates new structural motifs with formation of water as the only byproduct.

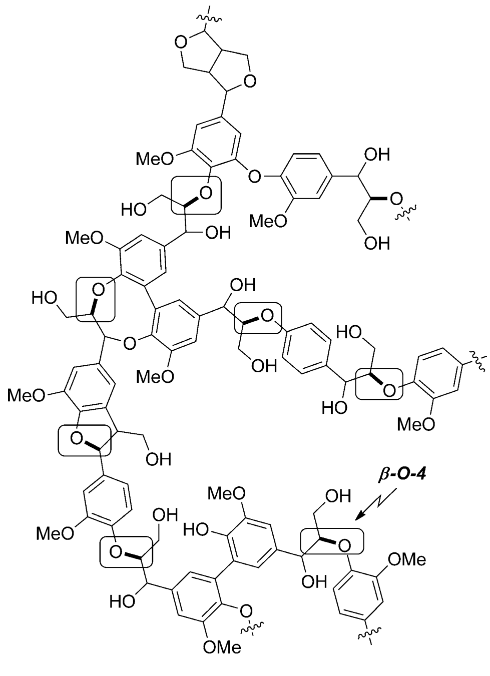

Figure 1. Substructures found in lignin.

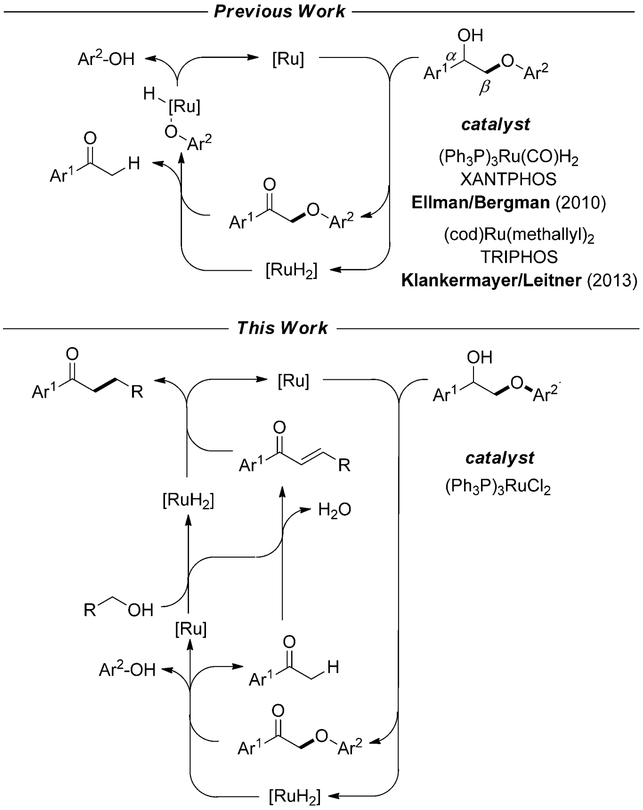

Figure 2. Ru-catalyzed dearyloxylation and Ru-catalyzed alkylative dearyloxylation.

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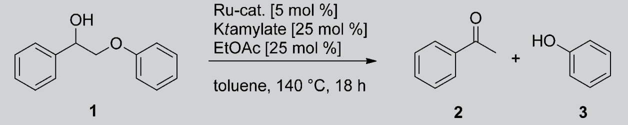
During our investigation regarding the use of (NNNN)(P)Ru complexes as catalyst for reactions based on ruthenium hydride mechanisms,[14] we found that the simple ruthenium complex $(Ph_3P)_3RuCl_2$ efficiently cleaves the β-C–O bond in 2-phenoxy-1-phenylethanol **1** after activation of the precatalyst with K*t*amylate (entry 2, Table 1). The presence of a catalytic amount of ethyl acetate proved to be essential for an efficient catalytic turn over (entry 3, Table 1). In the absence of a catalyst the C-O cleavage did not take place under thermal conditions and only a small of amount of phenol **2** and trace amounts of acetophenone **3** were formed (entry 1, Table 1). Besides $(Ph_3P)_3RuCl_2$ a range of other ruthenium complexes gave the cleavage products in good to high yields (entries 4–10, Table 1).

Table 1. Ru-catalyzed C-O cleavage of 2-phenoxy-1-phenylethanol **1**.

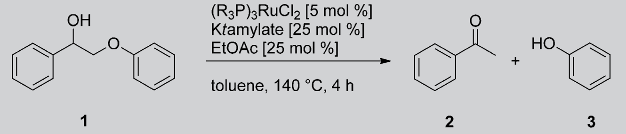


Entry[a]	Catalyst	Yield **2** [%][b]	Yield **3** [%][b]
1	–	2	13
2	$(PPh_3)_3RuCl_2$	94	94
3	$(PPh_3)_3RuCl_2$[c]	23	27
4	$[Ru(p\text{-cymene})Cl_2]_2$	70	70
5	$[Ru(p\text{-cymene})Cl_2]_2/PPh_3$	80	81
6	$(Ph_3P)_3Ru(OAc)_2$	80	89
7	$(Ph_3P)_3Ru(OAc)_2$[c]	53	47
8	$(dmso)_4RuCl_2$	52	58
9	$(PPh_3)_4RuH_2$	80	99
10	$RuHCl(CO)(PPh_3)_3$	79	75

[a] All reactions were carried out in a closed Schlenk tube under N_2 atmosphere with 2-phenoxy-1-phenylethanol **1** (0.125 mmol), catalyst (5 mol%), K*t*amylate (25 mol%) and EtOAc (25 mol%) in toluene (0.25 mL). [b] Determined by GC analysis using dodecane as internal standard. [c] Without EtOAc.

Based on $(Ph_3P)_3RuCl_2$, which showed the highest catalytic activity in the C–O cleavage of 2-phenoxy-1-phenylethanol **1**, the influence of monodentate phosphine ligands in complexes of the kind $(R_3P)_3RuCl_2$ was further investigated. Complexes containing more electron donating phosphines showed improved reactivity (entries 2 and 3, Table 2), whereas the use of a more electron deficient phosphine ligand lead to a decrease of the yield of the cleavage products (entry 4, Table 2). The presence of mixed aryl-alkyl-phosphines proved to be less effective than the presence triaryl-substituted phosphines (entry 5, Table 2).

Table 2. Ru-catalyzed C-O cleavage of 2-phenoxy-1-phenylethanol **1** - phosphine effect.



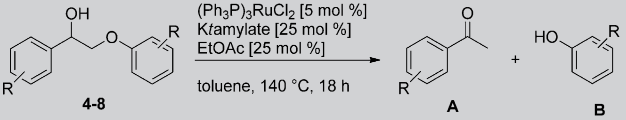
Entry[a]	Phosphine R_3P	Yield **2** [%][b]	Yield **3** [%][b]
1	Ph_3P	68	74
2	$(p\text{-MeC}_6H_4)_3P$	78	85
3	$(p\text{-MeOC}_6H_4)_3P$	72	84
4	$(p\text{-FC}_6H_4)_3P$	26	20
5	Ph_2CyP	47	47

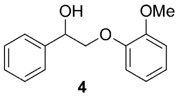
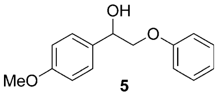
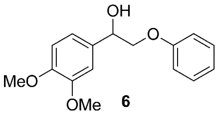
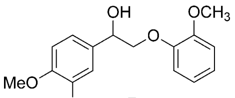
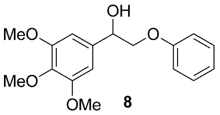
[a] All reactions were carried out in a closed Schlenk tube under N_2 atmosphere with 2-phenoxy-1-phenylethanol **1** (0.125 mmol), catalyst (5 mol%), K*t*amylate (25 mol%) and EtOAc (25 mol%) in toluene (0.25 mL). [b] Determined by GC analysis using dodecane as internal standard.

With $(Ph_3P)_3RuCl_2$, as one of the most reactive and most readily available catalysts containing the cheapest phosphine ligand, a range of lignin model compounds were subjected to the established reaction conditions. Substrates **4**–**8** derived from the three monolignols coumaryl-, coniferyl-, and sinapyl-alcohol underwent clean C–O cleavage reactions and the corresponding products could be obtained in good to excellent yields (Table 3). The reaction of these substrates can be considered as chemoselective as the β-alkyl-aryl-ether bond is cleaved in the presence of one or more methyl-aryl-ether bonds.

With this system in hand, we were wondering whether the coupling of two H_2-autotransfer processes would be possible. $(Ph_3P)_3RuCl_2$ is known to catalyze the direct alkylation of ke-

Table 3. Ru-catalyzed cleavage of different lignin model compounds.

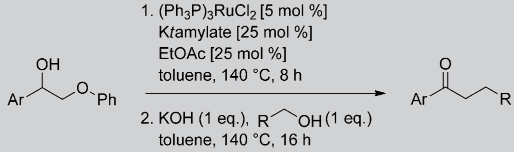


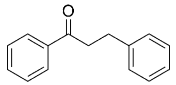
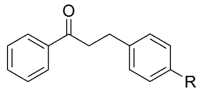
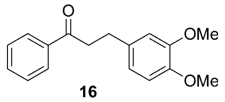
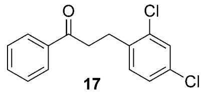
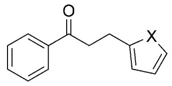
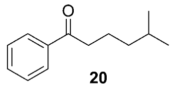
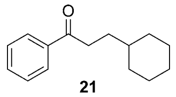
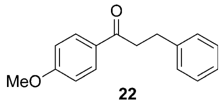
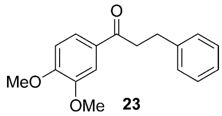
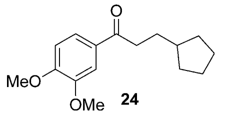
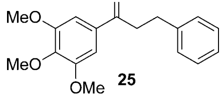
Entry[a]	Substrate	Yield **A** [%][b]	Yield **B** [%][b]
1	 **4**	**2** 59	**9** 53
2	 **5**	**10** 62	**3** 82
3	 **6**	**11** 98[c]	**3** 98
4	 **7**	**11** 81[c]	**9** 62
5	 **8**	**12** 68[c]	**3** 65

[a] All reactions were carried out in a closed Schlenk tube under N_2 atmosphere with substrate **4**–**8** (0.25 mmol), $(Ph_3P)_3RuCl_2$ (5 mol%), K*t*amylate (25 mol%), EtOAc (25 mol%) in toluene (0.5 mL) at 140 °C for 18 h. [b] Determined by GC analysis using dodecane as internal standard. [c] Isolated yield.

tones with alcohols.[13a] Hence, after the dearyloxylation of **1** was completed benzyl alcohol and a stoichiometric amount of KOH was added to the reaction mixture. Gratifyingly, after heating for another 16 h the benzylated acetophenone **13** could be obtained in 71 % overall yield (entry 1, Table 4). In this type of ruthenium catalyzed sequential C-O cleavage/α-alkylation reaction we were able to convert different lignin model compounds to the corresponding alkylated acteophenone derivatives with a range of benzylic-, heterobenzylic-, and aliphatic alcohols (Table 4).

Table 4. Ru-catalyzed sequential C-O cleavage/α-alkylation.



Entry[a]	Substrate	Product	Yield [%][b]
1	Ar = C_6H_5 **1**	 **13**	71
	Ar = C_6H_5 **1**		
2		R = OMe **14**	43
3		Cl **15**	51
4	Ar = C_6H_5 **1**	 **16**	58
5	Ar = C_6H_5 **1**	 **17**	47
	Ar = C_6H_5 **1**		
6		X = O **18**	40
7		S **19**	40
8	Ar = C_6H_5 **1**	 **20**	47
9	Ar = C_6H_5 **1**	 **21**	53
10	Ar = 4-MeO-C_6H_5 **5**	 **22**	44
11	Ar = 3,4-MeO-C_6H_5 **6**	 **23**	53
12	Ar = 3,4-MeO-C_6H_5 **6**	 **24**	53
13	Ar = 3,4,5-MeO-C_6H_5 **8**	 **25**	37

[a] All reactions were carried out in a closed Schlenk tube under N_2 atmosphere with substrate **1**, **5**, **6** or **8** (0.25 mmol), $(Ph_3P)_3RuCl_2$ (5 mol %), K*t*amylate (25 mol %), EtOAc (25 mol %) in toluene (0.5 mL) at 140 °C for 8 h, then KOH (0.25 mmol) and alcohol (0.25 mmol) for another 16 h. [b] Isolated yield.

The selective cleavage of β-aryloxy groups is one of the most promising strategies in lignin chemistry. Herein, we disclosed a study in which $(Ph_3P)_3RuCl_2$ was employed as a commercially available catalyst for the selective C–O-bond cleavage in different 2-aryloxy-1-phenylethanols. The corresponding acetophenones were obtained in good to excellent yields. The coupling of two hydrogen-autotransfer processes of dearyloxylation and subsequent dehydrative α-alkylation using primary alcohols allowed for the alkylative dearyloxylation of various lignin-type model compounds. Future work along these lines is currently underway.

Experimental Section

General procedure for the Ru-catalyzed C-O cleavage of lignin model compounds

KO*t*Am (36 μL, 0.063 mmol) was added to a solution of $(Ph_3P)_3RuCl_2$ (12 mg, 0.013 mmol) in toluene (0.5 mL). Then ethyl acetate (6.2 μL, 0.063) and substrate **1** or **4**–**8** (0.250 mmol) were added. The Schlenk tube was sealed and the reaction mixture was stirred at 140 °C for 18 h. After cooling to room temperature dodecane (30 μL, 0.125 mmol) was added and an aliquot of the reaction mixture was filtered over silica and analyzed by gas chromatography. Products were identified by comparison with an original sample. Acetophenones **11** and **12** were isolated by flash column chromatography.

General procedure for the Ru-catalyzed sequential C-O cleavage/α-alkylation of lignin model compounds

KO*t*Am (36 μL, 0.063 mmol) was added to a solution of $(Ph_3P)_3RuCl_2$ (12 mg, 0.013 mmol) in toluene (0.5 mL). Then ethyl acetate (6.2 μL, 0.063) and substrate **1**, **5**, **6** or **8** (0.250 mmol) were added. The Schlenk tube was sealed and the reaction mixture was stirred at 140 °C for 8 h. After cooling to room temperature KOH (14 mg, 0.25 mmol) and the corresponding alcohol (0.25 mmol) was added. The reaction mixture was stirred for another 16 h at 140 °C. Products were isolated by flash column chromatography.

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Keywords: catalysis · C–O-bond · hydrogenation · lignin · ruthenium

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