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Evaluating Gold and Selenium Chemistry for Selective Transformations of Lignin Model Compounds

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Abstract. Applications of gold and selenium chemistry are reported as novel approaches to promote lignin depolymerization into more valuable chemicals via selective oxidation reactions (alcohol oxidations and Baeyer-Villiger reactions). In this study, we proposed two different oxidative methodologies using Au/SiO₂ and phenylseleninic acid resin (PAR) as stable and reusable catalysts to promote selective transformations of the β -O-4 linkage of lignin model compounds. After evaluating the catalytic systems under batch conditions, they were both applied in a packed-bed reactor for continuous flow operations. By using Au/SiO2 as a catalyst under flow conditions, ketones were efficiently obtained (up to 86% conversion) from the oxidation of alcohols with a residence time (t_R) of 30 min. In the case of Baeyer-Villiger oxidations catalyzed by phenylseleninic acid resin, the corresponding esters were obtained in up to 91% conversion ($t_R = 30$ min). Both systems efficiently catalyzed the conversion of the lignin model compounds.

Keywords: Lignin; Selectivity; Gold; Selenium.

In recent years, scientists as well as governmental and non-governmental organizations noted the urgency for the development of new strategies to reduce the impact of using nonrenewable carbon resources.^[1] From this perspective, biomass, which is mainly from lignocellulosic softwood, gained attention as a feedstock for biofuels and fine chemicals based on lignin valorization.^[2] Lignin is a biopolymer present in the cell walls of plant that is composed of interconnected aromatic monomers.[3] The most common interconnections are the β -O-4 (β -aryl ethers) bonds between benzylic and aliphatic alcohols, and C_{α} - C_{β} or C_1 - C_{α} bonds, present in *p*-coumaryl, coniferyl and sinapyl alcohols.^[4] Various processes have been developed to extract lignin from the biomass feedstock, including kraft and organosolv processes.^[5,6] Several strategies have been reported for the cracking of the β -O-4 (β -aryl ethers), C_{α} -C_{\beta}

and C_1 - $C_{\alpha}(\alpha-1)$ linkages in lignin.^[7] Some of theses methods involve environmentally friendly approaches, including mild conditions, photocatalysis, metal-free catalysis, and biocatalysis.^[8-12]

Among the chemical transformations employed for lignin depolymerization, oxidation reactions have become common methods for producing a wide range of aromatic compounds.^[13] Lignin transformations can lead to phenols, carboxylic acids, aldehydes, ethers, esters and ketones.^[14] Esters can be produced by esterification reactions or oxidation of C_{β} - C_{γ} and β -1 linkages.^[15]

Considering the chemical structure of lignin, we decided to focus on the reactivity of the β -O-4linkage, specifically the benzylic alcohol moiety. A 3-step approach to break the lignin up into shorter fragments was proposed (Scheme 1).



Scheme 1. β -O-4-type lignin structure^[4] and strategies proposed herein.

According to our approach, an alcohol oxidation catalyzed by gold can produce ketones, which go on

to serve as substrates for Baeyer-Villiger oxidations catalyzed by selenium compounds. Finally, after hydrolysis of the corresponding esters, we would be able to produce lignin fragments containing alcohols and carboxylic acids.

Despite the known applications of gold nanoparticles in the synthesis of carbonyl compounds via alcohol oxidations,^[16] different molecular targets, including lignin, could be challenging for gold chemistry.

After the seminal study by Prati and Rossi^[16i] involving gold nanoparticles supported on carbon for the oxidation of alcohols, several advances have been described in the literature. In recent years, gold nanoparticles have also been used for C–C crosscoupling reactions, cycloadditions, hydrosilyation, etc.^[16j]

Our approach to lignin transformations also requires a Baeyer-Villiger oxidation, and a literature survey revealed that Grieco *et al.*^[17] described the use of benzeneperoxyseleninic acid as oxidizing agent for this reaction. Hydrogen peroxide can be used to regenerate the active selenium species for the Baeyer-Villiger reaction.

Inspired by the very interesting results with gold and selenium chemistry, we developed a study focused on the transformations of lignin in which both methodologies could be applied either under batch or continuous flow conditions.^[18]

Initially, we synthesized Au nanoparticles from the reduction of AuCl4 (aq) with ascorbic acid.[19] SEM images (Figure S1) of the Au nanoparticles revealed that they were monodisperse, 20 nm in diameter, and spherical in shape. Since our approach involves the use of gold nanoparticles in a packed-bed reactor for a continuous flow application, we decided to immobilize these nanoparticles in an inert and inexpensive material, SiO₂. Au/SiO₂ particles were prepared via the immobilization of Au nanoparticles onto SiO₂ (pore size 22 Å, 800 m² g⁻¹). The loading of Au on Au/SiO₂ was determined by ICP-OES and was found to be 0.252% (%w/w). The Au/SiO₂ particles were also characterized by SEM (Figure S2) and XRD (Figure S3) analyses. The SEM results showed a uniform dispersion of Au NPs over SiO₂ support.

After the preparation of Au/SiO_2 materials, the next step was the evaluation of their catalytic activity towards the oxidation of 1-(4-methoxyphenyl) ethanol (**1a**) to the corresponding ketone (**2a**). For the optimization study, alcohol **1a** was subjected to different oxidants and organic solvents (THF, MTBE, dioxane, acetone, DMF and MeOH) for appropriate times (2, 4, 8 and 24 h) (Table 1).

The reaction using THF as the solvent and O_2 as the oxidant (Table 1, Entry 1) afforded 1-(4methoxyphenyl)ethanone (**2a**) in 26% after 2 h. By extending the reaction time to 4, 8 and 24 h, increases in the conversion were observed (to 42, 87 and 92% conversion, respectively; Table 1, Entries 2-4). However, instead of using a gaseous oxidant (O_2) we decided to evaluate an aqueous solution of H_2O_2 . Fortunately, the alcohol oxidation with peroxide gave the ketone in >99% conversion (Table 1, Entry 5). According to the proposed reaction mechanism, the oxidant participates in the regeneration of the catalytic gold surface once the gold-hydride species (Au-H) is formed (Scheme 2).

Table 1. Oxidation of 1-(4-methoxyphenyl)ethanol (1a)using Au/SiO_2 as catalyst under batch conditions.

MeO 1a		Au/SiO ₂ (4 mol%) solvent, KOH oxidant, rt		Meo 2a		
Entry ^{a)}	Solvent	Oxidant	t (h)	Conv (%) ^{b)}		
1	THF	O ₂	2	26		
2	THF	O_2	4	42		
3	THF	O_2	8	87		
4	THF	O_2	24	92		
5	THF	H_2O_2	2	>99		
6	MTBE	H_2O_2	2	97		
7	Dioxane	H_2O_2	2	63		
8	Acetone	H_2O_2	2	35		
9	DMF	H_2O_2	2	35		
10	DMSO	H_2O_2	2	10		
11	MeOH	H_2O_2	2	36		
12 ^{c)}	THF	-	2	10		
13 ^{d)}	THF	-	2	n.r.		
14 ^{e)}	THF	H_2O_2	2	n.r.		

^{a)} *Reaction conditions:* **1a** (1 mmol), solvent (2 mL), oxidant [O₂ (atmospheric pressure) or $H_2O_{2 (aq.)}$ (aq. 30%, 40 mmol)], KOH (1 mmol), Au/SiO₂ (80 mg/ 4 mol %) and room temperature. ^{b)} Conversions were calculated based on GC-MS analysis (none byproduct was observed). ^{c)} Without H_2O_2 . ^{d)} Without H_2O_2 and Au/SiO₂. ^{e)} Without Au/SiO₂. n.r. = no reaction was observed.

A solvent screen was also performed, and MTBE, dioxane, acetone, DMF, DMSO and MeOH were tested (Table 1, Entries 6-11). Despite the good results with all these solvents, the best results were achieved with MTBE and THF (97-99% conv, Table 1, Entries 5 and 6). Additional reactions were carried out in the absence of catalyst and H_2O_2 (aq.) (Table 1, Entries 12-14), and the results indicated that both components are essential to the oxidation of the alcohol.

The mechanism of this reaction likely involves three main steps (Scheme 2). Initially, alkoxide is generated from the base, and then it is adsorbed on the gold surface to afford species **B**. In the second step, β -hydride elimination affords the corresponding ketone and gold-hydride species (Au-H, species **C**). Finally, Au-H is oxidized by the presence of an oxidant (by H₂O₂ or O₂) to regenerate the catalytic gold surface (species **A**).^[20]



Scheme 2. Proposed mechanism for alcohol oxidation catalyzed by Au/SiO₂.^[20]

Table 2. Oxidation of 1-(4-methoxyphenyl)ethanol (1a) using Au/SiO₂ as the catalyst and H_2O_2 (aq.) under continuous flow conditions.



^{a)} *Reaction conditions:* **1a** (12 mmol L⁻¹); $H_2O_{2 (aq.)}$ (30% aq., 4-400 equiv); KOH (12 mmol L⁻¹); t_R 30 min; Au/SiO₂ particles (460 mg) were packed into stainless-steel tube (PBR: 1/4 in. × 4.6 mm × 5 cm; reactor volume with Au/SiO₂: 0.5 mL); Continuous flow operation for 1.5 h, 3 h (Entries 6 and 9) or 8 h (Entry 7). ^{b)} Conversions were determined by GC-MS at the end of each t_R (no byproduct was observed). ^{c)} t_R 60 min. ^{d)} A Celite pad (380 mg) and a BPR (back pressure regulator: 100 psi) were attached to the system. n.p. = Not performed (The injection pump shut off due to clogging).

Aiming to enhance the Au catalyst recycling, we designed a packed-bed reactor that can be used in continuous flow mode (Table 2). The Au/SiO_2 particles were confined into a packed-bed reactor

(PBR) (1/4 in. $\times 4.6$ mm $\times 5$ cm; reactor volume with particles: 0.5 mL). The oxidation of 1-(4-methoxyphenyl)ethanol (**1a**) was chosen as model reaction for the optimization of the continuous flow conditions (Table 2).

As shown in Table 2, Entry 1-4, various attempts to run the reaction using different conditions were not successful, since the injection pump shut off due to clogging. We used silica (SiO_2) as the support material, and a high pressure was generated due to the large amount of water in the reaction mixture. Fortunately, the fluidic system worked very well when methanol was employed as the solvent. In addition, the amount of H₂O_{2 (aq)} was decreased along with the concomitant decrease in the amount of water (Table 2, Entry 5). The reaction was carried out at 40 °C with 30 min of residence time, and the ketone was prepared in 57% conversion. When the residence time was increased to 60 min, higher product formation was observed (75% conv; Table 2, Entry 6). When a back pressure regulator (100 psi) was attached to the system, higher ketone formation was obtained (77% conv) in a shorter residence time (Table 2, Entry 7). When the continuous production of **2a** was maintained for 8 h, no decrease in catalytic activity was observed. Finally, another attempt to further decrease the amount of $H_2O_{2(aq)}$ (4 equiv) was not effective (Table 2, Entry 10 and 11).

From this set of experiments, we were able to identify suitable reaction conditions for other substrates, namely, benzylic alcohols **1b-d** (Table 3).

Table 3. Substrates for alcohol oxidation catalyzed by Au/SiO₂ particles under continuous flow conditions.



^{a)} *Reaction conditions:* Substrates **1b-d** (12 mmol L⁻¹ in MeOH); $H_2O_{2(aq.)}(30\% \text{ aq., }40 \text{ equiv})$; KOH (12 mmol L⁻¹); $t_R = 30 \text{ min; }40 \text{ °C}$; Continuous flow operation for 8 h; Au/SiO₂ (460 mg) was packed into stainless-steel tube (1/4 in. × 4.6 mm × 5 cm; reactor volume with beads: 0.5 mL); Celite pad (380 mg); and BPR (100 psi). ^{b)} Conversions were determined by GC-MS and ¹H NMR analysis, and at the end of the t_R no byproduct was observed.

By running the reactions with a $t_R = 30$ min at 40 °C, the mono-alcohols 1-(4-(benzyloxy)phenyl)ethanol (**1b**) and 1-(4-(benzyloxy)phenyl)-2-phenylethanol (1c)were oxidized to the corresponding ketone in 80 and 51% conv, respectively (Entries 1 and 2, Table 3). In addition, when substrate 1-(4-(benzyloxy)phenyl)-2phenyl-propane-1,3-diol (1d) was submitted to continuous flow oxidation, ketone 2d was prepared in 68% conv. Notably, only the benzylic alcohol moiety was oxidized, which indicates the oxidation is highly selective.

Due to concerns about gold leaching during continuous flow operation, we analyzed the reaction effluent by ICP-OES. The results are illustrated in Table S1, and showed that there is no significant loss of Au from the Au/SiO₂ during the continuous flow operation.

After preparing the ketones by the Au-catalyzed alcohol oxidations, we turned our attention to the Baeyer-Villiger oxidation using selenium species as oxidizing agents.^[17] We also envisioned a packed-bed reactor loaded with solid catalyst for the oxidation reaction, i.e., phenylseleninic acid resin (PAR) (Scheme 3).



Scheme 3. Proposed mechanism/system for the Baeyer-Villiger oxidation of lignin model ketones with PAR.

Phenylseleninic acid resin (PAR) was prepared from poly(styrene-co-divinylbenzene) (4) and *n*dibutyl diselenide (Scheme 4). Commercially available resin 4 was treated with *n*-BuLi, and *n*dibutyl diselenide [(*n*-Bu)Se₂] was added, resulting in the *n*-butylselenide resin (5). Then, 5 was oxidized to phenylseleninic acid by $H_2O_{2 (aq.)}$.^[20] The loading of selenium was evaluated by acid-base titration with NaOH, and was found to be 1.42 ± 0.05 mmol g⁻¹.^[21,22]



Scheme 4. Preparation of the PAR catalyst.

With the phenylseleninic acid resin in hand, we then used it as a catalyst for the Baeyer-Villiger oxidation under batch conditions (Table 4). Considering the presence of phenylselenyl moieties on the PAR, we also decided to test diphenyl diselenide, which is a commercially available selenium compound.

Table 4. Baeyer-Villiger oxidation of 4-methoxyacetophenone employing $(PhSe)_2^{a}$ and PAR^{b} as catalysts.

MeO 2a Se Catalyst OH NeO 2a Solvent, rt, 4h MeO 3a 6a Hydrolysis										
Entry	Solvent	Oxidant	Se	Conv (%) ^{e)}						
			Catalyst	3a	6a	_				
1	CH_2Cl_2	TBHP	(PhSe) ₂	-	-					
2	CH_2Cl_2	UHP	(PhSe) ₂	2	-					
3	CH_2Cl_2	H ₂ O _{2 (aq.)}	(PhSe) ₂	4	-					
4	THF	TBHP	(PhSe) ₂	-						
5	THF	UHP	(PhSe) ₂	5	-					
6	THF	H ₂ O _{2 (aq.)}	(PhSe) ₂	89	-					
7	MeOH	TBHP	(PhSe) ₂	-	-					
8	MeOH	UHP	(PhSe) ₂	-	-					
9	MeOH	$H_2O_{2 (aq.)}$	(PhSe) ₂	94	-					
10 ^{c)}	MeOH	H_2O_2 (aq.)	PAR	35	23					
11 ^{c),d)}	MeOH	H_2O_2 (aq.)	PAR	38	24					

^{a)} *Reaction conditions:* **2a** (0.5 mmol); oxidant (2 mmol); (PhSe)₂ (0.025 mmol); solvent (3 mL). ^{b)} *Reaction conditions:* **2a** (0.5 mmol); H₂O₂ (30% aq., 5 mmol); PAR (50 mg); MeOH (3 mL). ^{c)} PAR was recycled three times. ^{d)} 30 °C. ^{e)} Conversions were determined based on GC-MC analysis (no byproduct was observed).

As shown in Entries 1-3 of Table 4, the use of diphenyl diselenide as a pre-catalyst for the Baeyer-Villiger oxidation in CH₂Cl₂ was not efficient even when using different oxidants, including *t*-butyl hydroperoxide (TBHP), urea-hydrogen peroxide (UHP) or H₂O_{2 (aq.)}. However, the reactions in THF and MeOH with H₂O_{2 (aq.)} as the oxidant showed good conversions (89 and 94%, respectively) (Entries 6 and 9, Table 4). In fact, the water solubility of these solvents (THF and MeOH) had a positive effect on the oxidation reaction since that facilitates the interactions of all chemicals, which was not observed in the reaction with dichloromethane, a highly hydrophobic solvent.

Based on these results, we evaluated the activity of the phenylseleninic acid resin in the oxidation of **2** using H_2O_2 (aq.) with methanol as the solvent. The Baeyer-Villiger oxidation was efficient (58% conv, Table 4, entry 10); however, 4-methoxy-phenol (**6a**) was also produced from the hydrolysis of ester **3a**. Considering our lignin transformation approach (Scheme 1), the ester hydrolysis under the Baeyer-Villiger oxidation conditions is not an issue since the alcohol is our desired fragment. In addition, by treating this crude mixture (Table 4, entry 10) with a K₂CO₃/methanolic solution for 30 min, the ester was completely hydrolyzed into the corresponding phenol (**6a**). Furthermore, a slight increase in the temperature did not provide a significant increase in the conversion (Entry 11, Table 4). A recycling study was performed with the phenylseleninic acid resin, which revealed the PAR maintained excellent activity even after reuse (Entries 10 and 11, Table 4).

The apparatus for the Baeyer-Villiger oxidation under continuous flow operation was very similar to what was used in the oxidation study (previous section). A packed-bed reactor (stainless steel tubing: 1/4 in \times 4.6 mm \times 5 cm; reactor volume with PAR: 0.5 mL) was loaded with PAR (570 mg).

The Baeyer-Villiger oxidation of 4methoxyacetophenone (2a) was chosen for evaluating some parameters under continuous flow operation (Table 5).

Different ratios between 2a and H_2O_2 (aq.) were studied, including 1:2 (Entry 3, Table 5), 1:5 (Entry 4, Table 5) and 1:10 (Entries 1 and 2, Table 5). The residence time (t_R) was also evaluated (15 min (Entries 2-4, Table 5) and 30 min (Entry 1, Table 5)).

Table5.Baeyer-Villigeroxidationof4-methoxyacetophenone(2a)usingPARundercontinuousflow conditions.



^{a)} *Reaction conditions:* **2a** (20 mmol L⁻¹) and H₂O_{2 aq.} (30% aq.; ^{b)} 200 mmol L⁻¹; ^{c)} 40 mmol L⁻¹; ^{d)} 100 mmol L⁻¹) in MeOH; Continuous flow operation for 1.5 h or 12 h (Entry 2); PAR (570 mg) was packed into stainless-steel tube (1/4 in. × 4.6 mm × 5 cm; reactor volume with PAR: 0.5 mL); BPR (100 psi). ^{e)} Conversions were determined based on GC-MS analysis at the end of each t_R . ^{f)} Byproducts were identified as quinones.

As shown in Table 5, a reaction with a $t_R = 30$ min afforded the desired products (**3a** and **6a**) in high conversion (91%, Entry 1, Table 5). However, we also observed the formation of quinones, which are from the over-oxidation of the phenolic products.^[23] Fortunately, the formation of these by-products was suppressed by using a lower concentration of the oxidant and a shorter residence time. By decreasing the t_R (15 min), the conversions to **3a** and **6a** were not affected, but the conversions to the undesired products were decreased (Entries 1 and 2, Table 5). The oxidation of **2a** with $H_2O_{2 (aq.)}(1:10)$ with a $t_R = 15$ min showed good product formation with low over-oxidation (Entry 2, Table 5, conv = 77%).

These reaction conditions were applied in the Baeyer-Villiger oxidation of the ketonic lignin analogues (**2b-d**) (Table 6).

Table 6. Baeyer-Villiger oxidation of lignin model ketonesemploying phenylseleninic acid resin in a flow system.



^{a)} *Reaction conditions:* **2b-d** (20 mmol L⁻¹) and H₂O₂ (aq. 30%; 200 mmol L⁻¹) in MeOH; Continuous flow operation for 8 h with a $t_R = 15$ min; PAR (570 mg) was packed into stainless-steel tube (1/4 in. × 4.6 mm × 5 cm; reactor volume with PAR: 0.5 mL); and BPR (100 psi). ^{b)} Conversions were determined by GC-MS and ¹H NMR analysis at the end of t_R (no byproduct was observed). ^{c)} 1- (4-(Benzyloxy)phenyl)-2-phenoxyprop-2-en-1-one (**9**) was obtained as the sole product. ^{d)} This reaction was performed under batch condition. n.d.: Not detected.

The oxidation reaction of 4-benzyloxyacetophenone (**2b**) at rt with a $t_R = 15$ min afforded the corresponding ester (**3b**) and 4-benzyloxyphenol (**6b**), which is from the hydrolysis of the ester (71% conv, Table 6, entry 1). Notably, no undesired overoxidation products were observed.

A similar reaction profile was also observed for the Baeyer-Villiger oxidation of 1-(4-(benzyloxy)phenyl)-2-phenoxyethanone (**2c**), which gave the ester 4-(benzyloxy)phenyl-2-phenoxyacetate (**3c**) and 4-benzyloxyphenol (**6b**) (86% conv, Entry 2, Table 6). On the other hand, when 1-(4-(benzyloxy)phenyl)-3-hydroxy-2-phenoxy-propan-1-one (**2d**) was used as the substrate, the desired product was not observed (Entry 3, Table 6); the dehydration product, 1-(4-(benzyloxy)phenyl)-2-phenoxyprop-2-en-1-one (**9**) was identified as the sole product. We proposed that the substrate (**2d**), which is a β -hydroxy ketone, undergoes an elimination reaction to afford corresponding unsaturated ketone **9**.

Despite the unexpected formation of α,β unsaturated ketone **9**, we decided to submit ketone **9** to Baeyer-Villiger oxidation under batch conditions (Entry 10, Table 4), and the corresponding esters (25% conv, as a mixture of regioisomers) were observed. Considering our lignin depolymerization approach, the α,β -unsaturated ketones can be further oxidized to the corresponding esters and then hydrolyzed to alcohols and carboxylic acids as initially proposed.

In summary, two selective oxidation processes for lignin model molecules were developed using supported catalysts (Au/SiO2 and phenylseleninic acid resin) and an inexpensive oxidant, H₂O₂. The Au/SiO₂ catalyst showed high efficiency for the oxidation of alcohols (up to >99% conv). The PAR catalyst also showed high efficiency for Baeyer-Villiger oxidation (up to 91% conv). Both reactions were carried out under batch and continuous flow conditions using different forms of the catalysts (different gold and selenium species). In the case of the immobilized catalysts, Au/SiO₂ and PAR could be reused several times with high efficiency under continuous flow conditions. We believe that the effective catalysts from the developed methodologies will aid in the understanding of the reactivities and properties of the lignin β -O-4 linkages.

Experimental Section

General procedure for the oxidation of alcohols under continuous flow conditions

A packed-bed reactor, a stainless-steel tube (1/4 in x 4.6 mm x 5 cm), was loaded with Au/SiO₂ (460 mg). The reactor volume with beads was 583 μ L. The alcohols (**1b-d**) (12 mmolL⁻¹), H₂O₂ (40 equiv) and KOH (12 mmolL⁻¹) in MeOH were loaded into a syringe. The reactions were carried out at appropriate flow rates to obtain the desired residence time (See tables). Then, the reaction effluent was collected in a 10-mL vial.

General procedure for the Baeyer-Villiger oxidation under continuous flow conditions

A packed-bed reactor, a stainless-steel tube (1/4 in x 4.6 mm x 5 cm), was loaded with PAR (570 mg). The reactor volume with beads was 573 μ L. The ketones (**2b-d**) (12 mmol L⁻¹) and H₂O₂ (aq. 30%, see tables) in MeOH were loaded into a syringe. The reactions were carried out at appropriate flow rates to obtain the desired residence time (See tables). Then, the reaction effluent was collected in a 10-mL vial.

The remaining procedures, flow equipment, and analytical data for all compounds are given in the Supporting Information.

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