

Lignin-Model Chemistry

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Palladium-Catalyzed Formal Cross-Coupling of Diaryl Ethers with Amines: Slicing the 4-O-5 Linkage in Lignin Models

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Abstract: Lignin is the second most abundant organic matter on Earth, and is an underutilized renewable source for valuable aromatic chemicals. For future sustainable production of aromatic compounds, it is highly desirable to convert lignin into value-added platform chemicals instead of using fossil-based resources. Lignins are aromatic polymers linked by three types of ether bonds (α -O-4, β -O-4, and 4-O-5 linkages) and other C–C bonds. Among the ether bonds, the bond dissociation energy of the 4-O-5 linkage is the highest and the most challenging to cleave. To date, 4-O-5 ether linkage model compounds have been cleaved to obtain phenol, cyclohexane, cyclohexanone, and cyclohexanol. The first example of direct formal cross-coupling of diaryl ether 4-O-5 linkage models with amines is reported, in which dual C(Ar)–O bond cleavages form valuable nitrogen-containing derivatives.

Lignin, the most recalcitrant of the three components of lignocellulosic biomass,^[1] accounts for roughly 30% of the organic carbon on Earth.^[2] To date, lignin has been treated as a waste product in the pulp and paper industry, and is mostly burned to recover its thermochemical energy. Lignin has the potential to provide one of the few renewable sources of aromatic chemicals in the future.^[3] Consequently, valorization of lignin is becoming more and more important for social, economic, and resource sustainability.^[4] Structurally, lignin is a complex polyphenolic substance containing a large number of C–O ether bonds (including α -O-4, β -O-4, and 4-O-5 linkages; Figure 1).^[5] Therefore, cleavage of C–O ether bonds in lignin is a crucial step for the degradation and valorization of lignin biomass to obtain biofuels and commercial chemicals,^[6] and is challenging because of the strength and stability of these ether linkages.^[1a,7] 2-Phenylethyl phenyl ether, benzyl phenyl ether, and diphenyl ether are commonly selected as model compounds for the cleavage of β -O-4, α -O-4, and 4-O-5 linkages, respectively.^[8] Among these three types of C–O ether bonds, the bond dissociation energy (BDE) of the diphenyl ether bond of 4-O-5 (BDE = 314 kJ mol⁻¹) is much

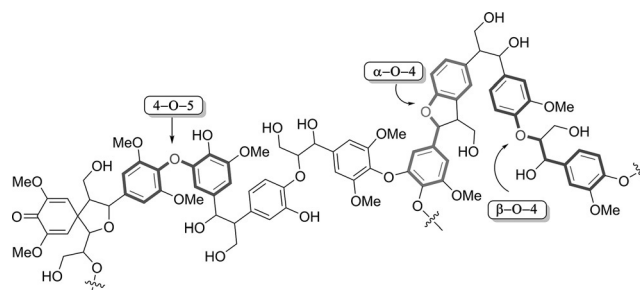
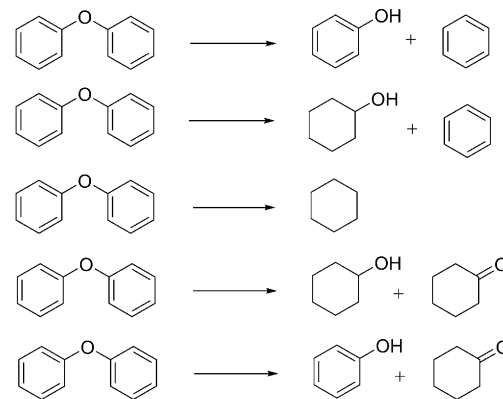


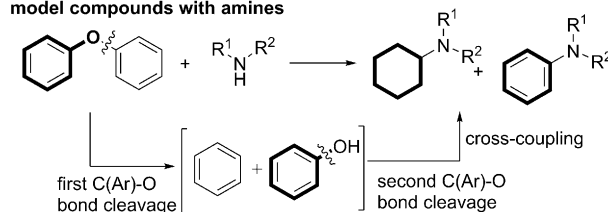
Figure 1. Common ether linkages in lignins.

stronger than the aliphatic ether bonds of α -O-4 (BDE = 218 kJ mol⁻¹) and β -O-4 (BDE = 289 kJ mol⁻¹).^[9] Thus, while the cleavage of C–O aliphatic ether bonds (α -O-4 and β -O-4 linkages) by oxidation,^[10] reduction,^[11] hydrolysis/solvolytic,^[3a,12] and other transformations,^[13] has been reported widely, cleavage of the diphenyl ether bond (4-O-5 linkage) is the most challenging. This challenge—cleaving the most difficult diphenyl ether C–O bond (4-O-5 linkage) by hydrogenolysis to form phenol and benzene—was overcome by Hartwig and coworkers.^[8b,c,f] Since that milestone, important progress has been made in the cleavage of diaryl ether bonds

(a) Catalytic reduction and cleavage of 4-O-5 linkage model compounds



(b) This work: catalytic direct formal cross-coupling of 4-O-5 linkage model compounds with amines



Scheme 1. Strategies for cleavage of lignin 4-O-5 linkage model compounds.

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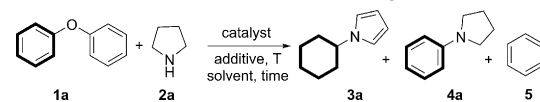
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to form small molecules; including phenol and benzene,^[14] cyclohexanol,^[8d] cyclohexane,^[8e,15] cyclohexanol and cyclohexanone,^[8g] and cyclohexanone and phenol^[8b] (Scheme 1a). It is desirable to generate structural motifs directly from diaryl ethers; and especially those that contain nitrogen, which is a feature shared by >90% of leading pharmaceutical agents.^[16]

Recently, our group reported a palladium-catalyzed formal cross-coupling of phenols with amine to form amine derivatives using a hydrogen-borrowing strategy.^[17] Inspired by this strategy, we contemplated the possibility of directly cleaving the most challenging C(Ar)–O bond of diphenyl ethers to produce nitrogen-containing products via an in-situ-generated phenol intermediate (Scheme 1b). Herein we report, for the first time, a palladium-catalyzed direct conversion of biaryl ethers into amine derivatives by dual C(Ar)–O bond cleavages. The amine derivatives are important building blocks for pharmaceuticals, fine chemicals, and electronic materials.^[18]

Diphenyl ether was used as a model compound for the 4-O-5 linkage of lignin within our investigation. The diphenyl ether was reacted with pyrrolidine with Pd/C (20 mol%) as catalyst in toluene at 160 °C under argon atmosphere for 24 h using sodium formate as a hydride source. Fortunately, the desired nitrogen-containing compound, 1-cyclohexyl-1H-pyrrole was detected by ¹H NMR spectroscopy in 18% yield with 26% conversion (Table 1, entry 1). Encouraged by this result, other palladium catalysts were examined for this transformation; lower conversion or no product was obtained when Pd(PPh₃)₂Cl₂ and Pd(OAc)₂ were used as catalysts (Table 1, entries 2–3). To our delight, higher conversion (35%) and yield (22%) were obtained when Pd(OH)₂/C was used as a catalyst (Table 1, entry 4). Various additives, such as Lewis acids and bases, failed to produce any of the desired coupling products, with only small amounts of starting material being converted (Table 1, entries 5–8). The reaction showed a strong dependence on the solvent, among which *o*-, *m*-, and *p*-xylenes were more effective than toluene (Table 1, entries 9–11). It is interesting to note that the substitution position of xylene is important to this transformation. The highest yield (48%) and highest conversion (71%) were obtained when *m*-xylene was used as solvent (Table 1, entry 10). More polar solvents,

Table 1: Evaluation of various conditions for 4-O-5 bond cleavage.^[a]



Entry	Catalyst	Additive	Solvent	Conv. [%]	3a ^[b] [%]	4a ^[b] [%]	5 ^[c] [%]
1	Pd/C		toluene	26	18	6	–
2	Pd(PPh ₃) ₂ Cl ₂		toluene	13	n.p.	n.p.	–
3	Pd(OAc) ₂		toluene	12	n.p.	n.p.	–
4	Pd(OH) ₂ /C		toluene	35	22	5	–
5	Pd(OH) ₂ /C	AlCl ₃	toluene	22	n.p.	n.p.	–
6	Pd(OH) ₂ /C	CF ₃ CO ₂ H	toluene	5	n.p.	n.p.	–
7	Pd(OH) ₂ /C	DBU	toluene	14	n.p.	n.p.	–
8	Pd(OH) ₂ /C	Cs ₂ CO ₃	toluene	8	n.p.	n.p.	–
9	Pd(OH) ₂ /C		<i>o</i> -xylene	60	30	22	–
10	Pd(OH) ₂ /C		<i>m</i> -xylene	71	48	20	–
11	Pd(OH) ₂ /C		<i>p</i> -xylene	62	20	19	–
12	Pd(OH) ₂ /C		1,4-dioxane	11	n.p.	n.p.	–
13	Pd(OH) ₂ /C		H ₂ O	20	trace	n.p.	–
14	Pd(OH) ₂ /C	H ₂ O (5 μL)	<i>m</i> -xylene	85	47	26	–
15	Pd(OH) ₂ /C	H ₂ O (10 μL)	<i>m</i> -xylene	81	52	25	–
16	Pd(OH) ₂ /C	H ₂ O (15 μL)	<i>m</i> -xylene	65	42	18	–
17 ^[d]	Pd(OH) ₂ /C	H ₂ O (10 μL)	<i>m</i> -xylene	88	39	23	–
18 ^[e]	Pd(OH) ₂ /C	H ₂ O (10 μL)	<i>m</i> -xylene	90	57	25	–
19 ^[f]	Pd(OH) ₂ /C	H ₂ O (10 μL)	<i>m</i> -xylene	82	36	20	–
20 ^[e,g]	Pd(OH) ₂ /C	H ₂ O (10 μL)	<i>m</i> -xylene	93	66	18	–
21 ^[e,h]	Pd(OH) ₂ /C	H ₂ O (10 μL)	<i>m</i> -xylene	92	62	17	–
22 ^[e,g,i]	Pd(OH) ₂ /C	H ₂ O (10 μL)	<i>m</i> -xylene	65	22	13	–
23 ^[e,g,i]	Pd(OH) ₂ /C	H ₂ O (10 μL)	<i>m</i> -xylene	99	70	22	–
24 ^[e,g,k]	Pd(OH) ₂ /C	H ₂ O (10 μL)	<i>m</i> -xylene	99	71	24	–
25 ^[e,g,l]	Pd(OH) ₂ /C	H ₂ O (10 μL)	<i>m</i> -xylene	99	77	15	82
26 ^[e,g,i,m]	Pd(OH) ₂ /C	H ₂ O (10 μL)	<i>m</i> -xylene	>99	83 (79)	13 (11)	83
27 ^[e,g,i,n]	Pd(OH) ₂ /C	H ₂ O (10 μL)	<i>m</i> -xylene	93	68	10	78

[a] General conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), catalyst (20 mol%), HCO₂Na (1 equiv), additive (0.5 equiv), and solvent (1 mL) at 160 °C for 24 h under argon atmosphere. [b] Yields were determined by ¹H NMR spectroscopy with nitromethane as an internal standard; isolated yields in brackets. [c] The yields of benzene and cyclohexane were determined by GC-MS. [d] Pyrrolidine (0.3 mmol). [e] Pyrrolidine (0.7 mmol). [f] Pyrrolidine (0.9 mmol). [g] Air (1 mL) was added. [h] Air (2 mL) was added. [i] Pd(OH)₂/C (10 mol%). [j] Pd(OH)₂/C (30 mol%). [k] Pd(OH)₂/C (40 mol%). [l] NaBH₄ was used instead of sodium formate. [m] NaBH₄ (1.5 equiv). [n] H₂ (1 atm) was used instead of argon atmosphere, in the absence of sodium formate. Key: 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), no product (n.p.).

such as dioxane and water, were less effective (Table 1, entries 12–13). A small amount of water (10 μL) was found to be beneficial to this reaction (Table 1, entry 15), whereas a higher or lower amount of water resulted in a lower yield (Table 1, entries 14 and 16). The ratio of pyrrolidine and diphenyl ether at 3.5: 1 appeared to be optimal for this reaction (Table 1, entries 17–19). The amount of air was also important for both the yield and the conversion. A higher yield (66%) and higher conversion (93%) were achieved when air (1 mL) was added to this reaction system (Table 1, entry 20). Further increasing the amount of air (2 mL) decreased the yield slightly (Table 1, entry 21). Decreasing the amount of Pd(OH)₂/C to 10%, both the yield and the conversion were reduced significantly (Table 1, entry 22). No improvement in yield was observed when increasing the amount of catalyst; and almost the same yields were observed with 30 or 40 mol% Pd(OH)₂/C (Table 1, entries 23–24). For economic reasons, we chose the amount of 30 mol% Pd(OH)₂/C as the optimal conditions for the following

optimization process. A much better result (77% yield, 99% conversion) was obtained when NaBH₄ was used as an alternative hydride source (Table 1, entry 25). Further increasing the amount of NaBH₄ gave the best result in 83% yield (Table 1, entry 26). When 1 atm H₂ was used, instead of NaBH₄ and argon atmosphere, a lower yield and conversion were observed (Table 1, entry 27). The optimization experiments are detailed in the Supporting Information.

With the optimized reaction conditions in hand, the substrate scope was explored with 3.5 equiv of pyrrolidine at 160 °C under argon (with air (1 mL) and water (10 μL)) using 30 mol % of Pd(OH)₂/C as the catalyst and 1.5 equiv of sodium borohydride as the hydride source in *m*-xylene (1 mL) for 24 h. As shown in Table 2, symmetrical diaryl ether reacted with pyrrolidine in good to excellent conversions and moderate to excellent yields (Table 2, entries 1–8). Diaryl ethers bearing electron-donating and -withdrawing groups at different positions were all effective for the transformation. Notably, with a strong electron-donating methoxy group substituted at different positions (*ortho*-, *meta*-, or *para*-) of diphenyl ether, the same major product 1-cyclohexylpyrrole (**3a**) was obtained with demethoxylation at the same time, and the minor product 1-phenylpyrrolidine (**4a**) was also obtained with demethoxylation (Table 2, entries 4–6). The corresponding products were obtained in good total yield without ester–amide exchange when the substrate contained an ester group (Table 2, entry 7). When fluorine-containing diphenyl ether was used, defluorination products were obtained with excellent conversion and high total yield (Table 2, entry 8). For all substrates, the corresponding arenes were obtained with good to high yields (Table 2, entries 1–8).

Non-symmetrical diaryl ethers were used to investigate the regioselectivity of the reactions (Table 3). We found that nitrogen-containing products were obtained with high total yields (71–74%), excellent conversions (>99%), and highly regioselective cleavage of the C(Ar)–O bond with only a small difference in the substitution of the phenyl ring (Table 3, entries 1–2). Similar excellent total yields (88–93%), excellent conversions (>99%), and regioselective cleavage of the C(Ar)–O bond were observed for compound **1k**, **1l**, and **1m** as starting materials (Table 3, entries 3–5).

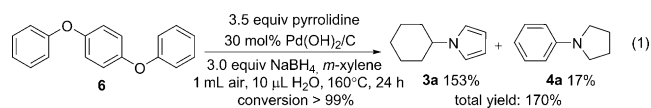
To further investigate the scope of this catalytic system, oligomeric phenylene oxide **6** containing four C(Ar)–O bonds was tested under the standard reaction conditions with increasing sodium borohydride, up to 3.0 equiv; 1-cyclohexyl-1*H*-pyrrole (**3a**) and 1-phenylpyrrolidine (**4a**) were obtained in high total yields (170%) and with excellent conversion (>99%) [Eq. (1)].

To further exploit the potential of this method, different amines were examined in cross-coupling reactions with diphenyl ether (Table 4). The optimized conditions were

Table 2: Direct formal cross-coupling of symmetrical diaryl ether with pyrrolidine.^[a]

Entry	Substrate	Conv. [%]	Products		
1		> 99			
2		> 99			
3		> 99			
4		68			
5		75			
6		70			
7		86			
8		> 99			

[a] Reaction conditions: diaryl ether (0.2 mmol), pyrrolidine (0.7 mmol), Pd(OH)₂/C (30 mol %), and NaBH₄ (0.3 mmol) in *m*-xylene (1 mL). All reactions were carried out at 160 °C in a sealed tube under argon (with air (1 mL) and H₂O (10 mL)) for 24 h; yields of isolated products are provided; conversions were determined by ¹H NMR spectroscopy with nitromethane as an internal standard. [b] The *cis/trans* (isomer) ratio was determined by crude ¹H NMR spectroscopy. [c] Yields of benzene and cyclohexane were determined by GC-MS; a small peak of cyclohexane overlapped with a large peak of benzene. [d] Yield was determined by GC-MS; no methylcyclohexane was detected. [e] Yield was determined by GC-MS; no cyclohexylmethyl ether was detected. [f] Yield of isolated product. Methyl cyclohexanecarboxylate (52%) was obtained.



obtained by elevating the reaction temperature to 150 °C, with 3.5 equiv of amines under argon using 30 mol % of Pd(OH)₂/C as the catalyst and 1.25 equiv of sodium borohydride as the hydride source in toluene (0.5 mL, with water (10 μL)) for 24 h (see the Supporting Information for details). As shown in Table 4, diphenyl ether reacted with different amines in high to excellent conversion, to generate the corresponding anilines and cyclohexyl amines^[19] in high to excellent total yields. Piperidine reacted very well with diphenyl ether, generating phenyl piperidine **7b** and cyclohexyl piperidine **8b** in high conversion and excellent total yield (Table 4, entry 1). Piperidine bearing methyl groups at different positions (2-, 3-, or 4-) were all effective for the

Table 3: Direct formal cross-coupling of unsymmetrical diaryl ether with pyrrolidine.^[a]

Entry	Substrate	Conv. [%]	Products
1		> 99	 <i>cis/trans</i> ^[b] =1:2.4
2		> 99	 <i>cis/trans</i> ^[b] =2.2:1
3		> 99	
4		> 99	 <i>cis/trans</i> ^[b] =1:2.9
5		> 99	

[a] Reaction conditions: diaryl ether (0.2 mmol), pyrrolidine (0.7 mmol), Pd(OH)₂/C (30 mol%), and NaBH₄ (0.3 mmol) in *m*-xylene (1 mL). All reactions were carried out at 160°C in a sealed tube under argon with air (1 mL) and H₂O (10 mL) for 24 h; yields of isolated products provided; conversions determined by ¹H NMR spectroscopy with nitromethane as an internal standard. [b] The *cis/trans* (isomer) ratio was determined by crude ¹H NMR spectroscopy. [c] 1-Cyclohexyl-1*H*-pyrrole (10%) and toluene (9%) were also obtained. [d] 1-Cyclohexyl-1*H*-pyrrole (14%) and toluene (10%) were also obtained. [e] Yield of isolated product; 1,2,3,4-tetrahydronaphthalene (77%) was also obtained. [f] Yield of isolated product; 1,2,3,4-tetrahydronaphthalene (75%) was also obtained. [g] Yield of isolated product; cyclohexylbenzene (85%) was also obtained.

transformation (Table 4, entries 2–4). Excellent conversion and high yield were also obtained with linear primary amine **2f** (Table 4, entry 5). Cyclopentylamine (**2g**) also reacted smoothly with diphenyl ether to afford the corresponding products in high yields (Table 4, entry 6). Likewise, aryl amines also reacted with diphenyl ether efficiently (Table 4, entries 7–8). Despite bearing two methyl groups at the 2- and 6-positions, the sterically hindered 2,4,6-trimethylaniline reacted smoothly (Table 4, entry 8).

To explore the reaction mechanism, diphenyl ether was examined without amine under the standard reaction conditions (Figure 2a). Phenol (**9**), cyclohexanone (**10**), benzene (**5**), and a trace amount of cyclohexane were detected by GC-MS. The total yields of phenol (**9**) and cyclohexanone (**10**) were almost the same as the total yields of benzene (**5**) and cyclohexane. To further investigate the potential pathway of C(Ar)–O cleavage, cyclohexenyl phenyl ether (**12**), which was proposed as a partial hydrogenation intermediate in the literature,^[8g,h,20] was explored under the standard reaction conditions (Scheme 2a). The direct C=C bond hydrogenation products cyclohexenyl phenyl ether (**11**, 65%) and dicyclohexenyl ether (**13**, 16%) were obtained as major products with only a small amount of the cross-coupling product **3a** (10%). These results suggest that the C(Ar)–O bond was cleaved during the Pd(OH)₂/C catalyzed hydrogenolysis of

Table 4: Direct formal cross-coupling of diphenyl ether with amines.^[a]

Entry	Substrate	Conv. [%]	Products
1		> 99	
2		> 99	
3		> 99	
4		> 99	
5		> 99	
6		> 99	
7		> 99	
8		> 89	

[a] Reaction conditions: diaryl ether (0.2 mmol), amines (0.7 mmol), Pd(OH)₂/C (30 mol%), and NaBH₄ (0.25 mmol) in toluene (0.5 mL). All reactions were carried out at 150°C in a sealed tube under argon with H₂O (10 mL) for 24 h; yields of isolated products provided; conversions determined by ¹H NMR spectroscopy with nitromethane as an internal standard. [b] Yields of benzene and cyclohexane were determined by GC-MS; a small peak from cyclohexane overlapped with a large peak from benzene.

diphenyl ether under our standard conditions, to form phenol and benzene instead of hydrolysis of compound **12**. The phenol can be reduced to form cyclohexanone.^[21] The reaction of phenol (**9**) and cyclohexanone (**10**) proceeded well under the standard conditions (Scheme 2b,c) to give *N*-cyclohexylpyrrole (**3a**) and *N*-phenylpyrrolidine (**4a**) in high total yields (99% and 97%, respectively), suggesting that they may be intermediates in the conversion of diphenyl ether. *N*-Cyclohexylpyrrolidine (**14**) was also explored under standard reaction conditions; oxidative aromatization products **3a** and **4a** were also obtained with high total yields (Scheme 2d). Cross-coupling of diphenyl ether with pyrrolidine was subsequently investigated within different reaction periods under the standard conditions (Figure 2b). The nitrogen-containing products (*N*-cyclohexylpyrrolidine and *N*-cyclohexylpyrrole) and hydrocarbon products (benzene and cyclohexane) were formed in an approximately 1:1 ratio. The results indicated that one Ar–O bond was reductively

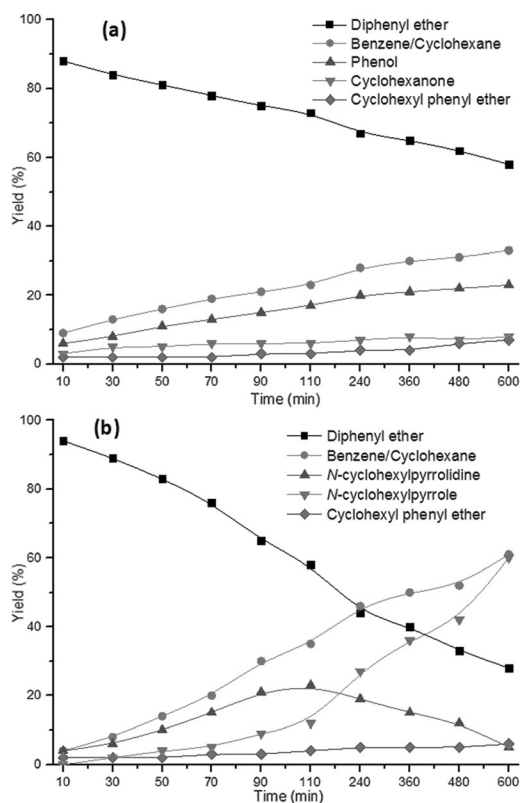
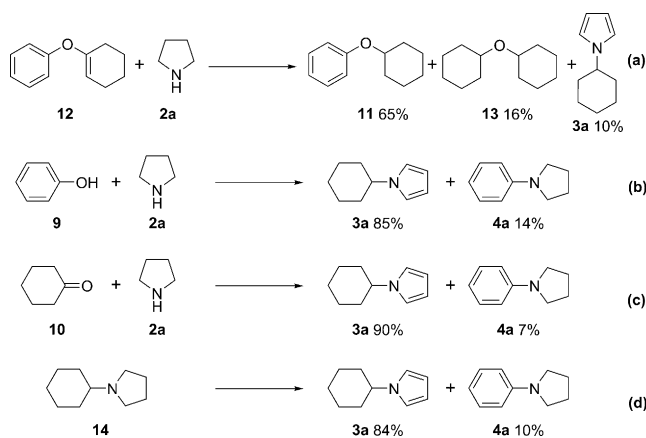


Figure 2. Product distributions versus time for the reaction of diphenyl ether a) without amine and b) with amine under standard reaction conditions.

cleaved to form benzene and cyclohexane and the remaining fragment predominantly became phenol and cyclohexanone. This rationale is also in agreement with the results in Figure 2a. Subsequently, the phenol and cyclohexanone were transformed into the nitrogen-containing products (*N*-cyclohexylpyrrolidine and *N*-cyclohexylpyrrole).

Based on the experimental results, a tentative mechanism for the cross-coupling reaction is proposed in Figure 3. Firstly, NaBH_4 reacts with the $\text{Pd}(\text{OH})_2/\text{C}$ catalyst to form the $\text{HPd}^{\text{II}}\text{H}$ species. Subsequently, hydrogenolysis of diphenyl



Scheme 2. Control experiments performed under standard conditions.

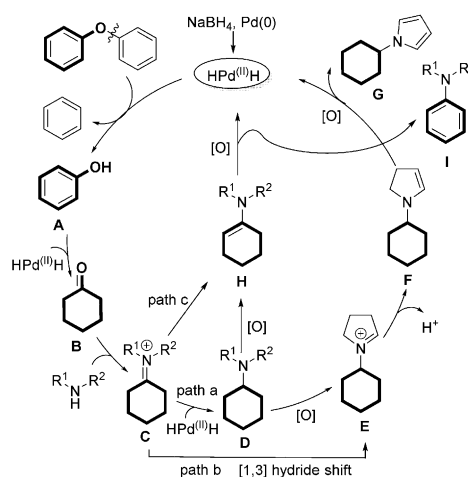


Figure 3. Proposed reaction pathway for cross-coupling of diaryl ethers with amines.

ether generates phenol **A** by C(Ar)–O bond cleavage, which is further reduced by $\text{HPd}^{\text{II}}\text{H}$ species to form cyclohexanone **B**.^[17a,19] Intermediate **B** reacts with amine to form iminium intermediate **C**, which is reduced to form compound **D** (path a), and **D** is subsequently oxidized to generate intermediate **E** or **H**. Intermediate **E**, upon losing H^+ , tautomerizes to form enamine **F**. Finally, enamine **F** is oxidatively aromatized to form the product pyrrole **G**, as well as regenerating the $\text{HPd}^{\text{II}}\text{H}$ species. Another intermediate **H** undergoes oxidative aromatization to form product **I** and regenerates the $\text{HPd}^{\text{II}}\text{H}$ species. It is also possible that intermediate **C** can undergo a [1,3] hydride shift to generate intermediate **E** (path b).^[22] Furthermore, a small portion of intermediate **C** can tautomerize to form enamine **H** (path c).

In conclusion, we have developed a novel, direct cross-coupling of diaryl ethers with amines by dual C(Ar)–O bond cleavage. The 4-O-5 linkage lignin models can be converted into amine derivatives directly and efficiently. This research illustrated potential applications for converting renewable lignin biomass to value-added nitrogen-containing chemicals. Further research into obtaining high-value chemicals from lignin biomass feedstock is in progress.

Experimental Section

General procedure for the coupling of diaryl ether with pyrrolidine: a 20 mL oven-dried vial was charged with a magnetic stirrer bar, $\text{Pd}(\text{OH})_2/\text{C}$ (42 mg, 30 mol % based on Pd contents), and NaBH_4 (12 mg, 0.3 mmol). The tube was then evacuated and backfilled with argon. The evacuation/backfill sequence was repeated two additional times. *m*-Xylene (1 mL), diphenyl ether (0.2 mmol), and pyrrolidine (0.7 mmol) were added by syringe, followed by the addition of H_2O (10 μL) and air (1 mL) by syringe. The tube was placed in a preheated oil bath at 160 °C and the mixture was stirred under an argon atmosphere for 24 h. The reaction mixture was cooled to room temperature and filtered through a pad of silica gel. The filtrate was concentrated and the resulting residue was purified by preparative thin layer chromatography to give *N*-cyclohexylpyrrole and phenylpyrrolidine.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amines · C–O bond cleavage · cross-coupling · diaryl ethers · lignin

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