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Cleavage/cross-coupling strategy for converting β-O-4 linkage lignin model compounds into high valued benzyl amines *via* dual C–O bond cleavage

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ABSTRACT

Lignin is the most recalcitrant of the three components of lignocellulosic biomass. The strength and stability of the linkages have long been a great challenge for the degradation and valorization of lignin biomass to obtain bio-fuels and commercial chemicals. Up to now, the selective cleavage of C–O linkages of lignin to afford chemicals contains only C, H and O atoms. Our group has developed a cleavage/cross-coupling strategy for converting 4-O-5 linkage lignin model compounds into high value-added compounds. Herein, we present a palladium-catalyzed cleavage/cross-coupling of the β-O-4 lignin model compounds with amines *via* dual C–O bond cleavage for the preparation of benzyl amine compounds and phenols.

Conversion of renewable biomass to chemicals and fuels is becoming an ideal way to build a sustainable development due to the gradual depletion of fossil resources and environmental pollution concerns [1–5]. Lignocelluloses (cellulose, hemicellulose and lignin) are the most representative biomass resources [6]. Among them, due to the complexity of lignin structure, the utilization of lignin is the most challenge [7,8]. Until now, lignin has been discarded as a waste product of the pulp and paper industry, and is generally burned to supply thermal energy. From the perspective of sustainable development, lignin is a unique candidate for the sustainable production of organic aromatic molecules [9–11]. The development of effective methods to access valuable chemicals from lignin is not only highly desirable but also challenging. More recently, some impressive achievements have been made. The selective cleavages of C–O or C–C linkages to obtain oxygen-containing compounds (phenols [12–14], ketone [15,16], acids [17,18] and aldehydes [19–21]) and alkane (cycloalkanes [22,23], alkene [24] and other small molecules compounds [25]) have been reported (Scheme 1a). However, these transformations typically afford chemicals containing only C, H, and O atoms. For converting lignin to high value-added compounds, cross-coupling reaction of lignin and its model compounds is highly desirable.

Nitrogen-containing compounds are important organic building block for synthetic dyes, pharmaceuticals and polyurethane precursors, which are usually generated from non-renewable fossil resource [26–29]. For sustainable development of resource and society, synthesis of nitrogen-containing compounds from renewable biomass is highly desirable. Toward to this aim, our group has developed a cleavage/cross-coupling strategy for converting lignin 4-O-5 linkage model compounds to high value-added nitrogen-containing compounds *via* dual C–O bond cleavage (Scheme 1b) [30,31]. Due to the continuing interest of our research group on the degradation and valorization of renewable lignin and its model compounds [32–42], it is also advantageous to use the cleavage/cross-coupling strategy to convert other lignin linkage to high value-added compounds. Meanwhile, considering that the β-O-4 structural motifs are the most abundant in all the linkages of lignin [43–47], its efficient cleavage is of great significance to the degradation of lignins. Herein, we present a palladium-catalyzed direct cross-coupling of the β-O-4 lignin model compounds with amines *via* dual C–O bond cleavages for the preparation of benzyl amine compounds and phenols (Scheme 1c). Very recently, Li and co-workers reported similar method during the preparation of the current report [48].

Initially, we started our investigation using β-O-4 model compound **1a** and 1-heptanamine **2a** as model substrates to optimize the reaction conditions. Several palladium catalysts were examined using toluene as the solvent (Table 1, entries 1-3). When the reac-

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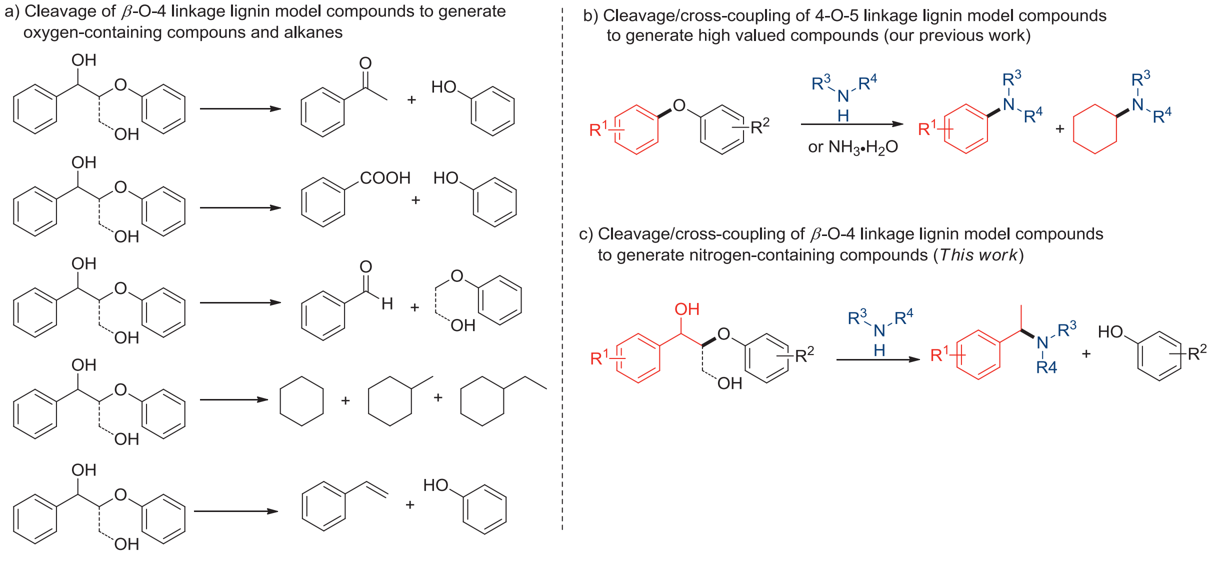
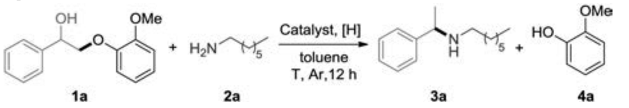


Scheme 1. Cleavage strategy *vs.* cleavage/cross-coupling strategy for valorization of lignin model compounds.

Table 1
Optimization of the reaction conditions.[a]



Entry	Catalyst	[H] (equiv.)	T(°C)	Yield (%)[b]	
				3a	4a
1	Pd/C	HCO_2Na	150	67	93
2	$Pd(OH)_2/C$	HCO_2Na	150	43	61
3	Pd/Al_2O_3	HCO_2Na	150	8	23
4	Pd/C (in air)	HCO_2Na	150	39	82
5	/	HCO_2Na	150	n.d.	n.d.
6	Pd/C	/	150	trace	42
7	Pd/C	HCO_2H	150	trace	91
8	Pd/C	HCO_2NH_4	150	trace	67
9	Pd/C	$NaBH_4$	150	trace	56
10	Pd/C	Isopropanol	150	n.d.	60
11	Pd/C	H_2 (1 atm)	150	trace	66
12	Pd/C	HCO_2Na (2.0)	150	53	93
13	Pd/C	HCO_2Na (4.0)	150	84	>95
14	Pd/C	HCO_2Na (5.0)	150	87	>95
15[c]	Pd/C	HCO_2Na (5.0)	150	89	>95
16[d]	Pd/C	HCO_2Na (5.0)	150	95	>95
17[e]	Pd/C	HCO_2Na (5.0)	150	67	60
18[d]	Pd/C	HCO_2Na (5.0)	160	91	92
19[d]	Pd/C	HCO_2Na (5.0)	130	64	76
20[d]	Pd/C	HCO_2Na (5.0)	110	40	80
21[d,f]	Pd/C	HCO_2Na (5.0)	150	80	83

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), Pd/C (10 mol%, 10 wt%) and HCO_2Na (3.0 equiv.) in toluene (1.0 mL) was heated under argon atmosphere for 12 h.

[b] Yields were determined by ^1H NMR spectroscopy using dibromomethane as an internal standard.

[c] **2a** (0.375 mmol).

[d] **2a** (0.5 mmol).

[e] **2a** (0.75 mmol).

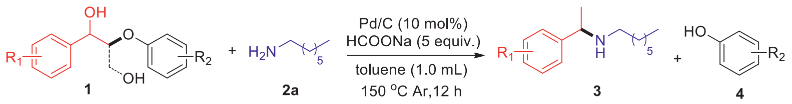
[f] Pd/C (5 mol%).

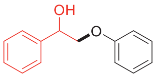
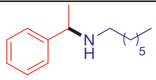
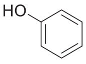
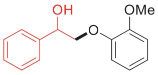
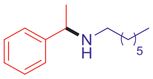
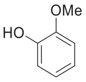
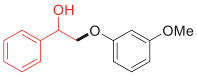
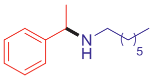
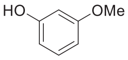
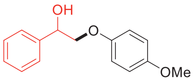
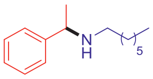
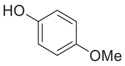
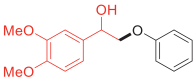
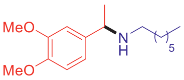
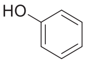
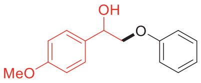
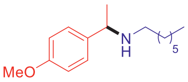
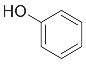
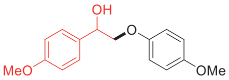
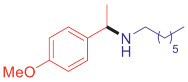
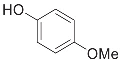
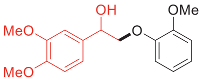
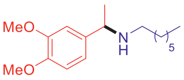
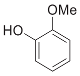
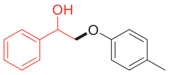
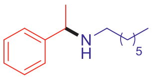
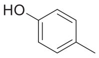
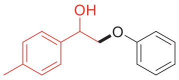
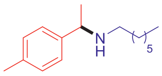
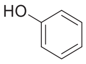
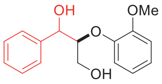
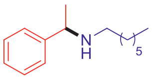
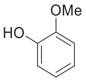
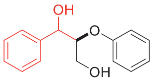
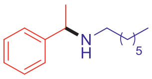
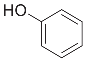
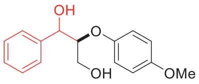
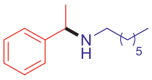
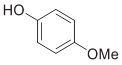
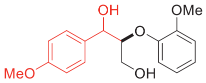
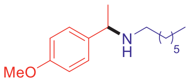
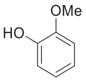
tion was performed in the presence of Pd/C (10 mol%), HCO_2Na (3 equiv.), cross-coupling product **3a** and phenol **4a** were obtained in 67% and 93% yield, respectively (entry 1). Other palladium catalysts, such as $Pd(OH)_2/C$ and Pd/Al_2O_3 showed lower catalytic activity than Pd/C (entries 2 and 3). When the reaction was explored under air atmosphere, the yield was slightly decreased (entry 4). As expected, the reaction did not occur without the catalyst (entry 5). When the reaction was performed in the absence of hydrogen donor, the yield of **4a** was reduced to 42%, with cross-coupling product **3a** being only a trace amount together with a large amount of unreduced imine product (entry 6). A variety of hydrogen sources (HCO_2H, HCO_2NH_4, $NaBH_4$, isopropanol and H_2) were investigated, giving lower yield than HCO_2Na (entries 7–11). Adjusting the amount of HCO_2Na, we found that a lower yield was obtained when it was reduced to 2 equiv. (entry 12). On the contrary, the best yield (87% and 95%) was obtained when the amount of HCO_2Na was increased to 5 equiv. (entry14). Increasing the amount of **2a** to 2 equiv. gave the highest yields (entry 16). Further increasing the amount of **2a** led to a lower yield (entry 17). The yield of **3a** and **4a** did not increase when the temperature was raised or lowered (entries 18–20). Adjusting the loading of the catalyst led to lower yields (entry 21) (see Supporting information for details).

With the optimized reaction conditions in hand, we explored the substrate scope of various lignin β-O-4 model compounds (Table 2). The simplest model compounds 2-phenoxy-1-phenylethan-1-ol (**1b**) was successfully cleaved and cross-coupled with 1-heptanamine to generate desired products **3a** and **4b** in high yields (entry 1). A methoxy group substituted on different positions (*ortho*-, *para*- and *meta*-position) of the phenyl ring (phenolic part) has no effect, obtaining the corresponding products with good to high yields (entries 2–4). Methoxyl group substituted on both aromatic rings or another aromatic ring (left part) also successfully reacted to form the desired products (entries 5-8). Aromatics (**1i** and **1j**) with a weak electron-donating methyl substituent were used in the reaction, generating targeted products in moderate to high yields (entries 9 and 10). Model compounds with hydroxymethyl substituent on β-position was the most similar to lignin, which was also successfully cleaved by the ether bond to form C-C bond cleavage products (entries 11–14, **3a** and **3c**) and phenols (**4a**, **4b** and **4d**). The C-C bond cleavage may be the result of a retro-aldol process when the benzyl alcohol part was oxidized to the corresponding ketone by palladium catalyst.

We also investigated the scope of various amines for this cleavage/cross-coupling reaction (Table 3). First, the transformation of lignin β-O-4 model compounds **1a** with different primary amines was tested, delightfully, obtaining good to excellent yields for all these primary amines (Table 3, entries 1–10). It is interesting to note that the use of cyclopropylmethylamine as substrate did not generate any three-membered rings opening product under the palladium-catalyzed reductive condition (entry 3). Trifluoromethyl group also remained intact in the product without fur-

Table 2
Cleavage/cross-coupling of lignin β-O-4 model compounds with 1-heptanamine.[a]



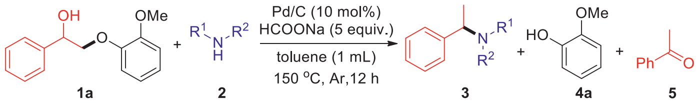
Entry	1		Yield **3** (%)		Yield **4** (%)	
1		**1b**		**3a**, 80		**4b**, 84
2		**1a**		**3a**, 90		**4a**, 91
3[b]		**1c**		**3a**, 55		**4c**, 53
4		**1d**		**3a**, 73		**4d**, 57
5		**1e**		**3b**, 52		**4b**, 61
6		**1f**		**3c**, 71		**4b**, 62
7		**1g**		**3c**, 53		**4d**, 57
8		**1h**		**3b**, 81		**4a**, 90
9		**1i**		**3a**, 52		**4e**, 76
10		**1j**		**3d**, 51		**4b**, 58
11[c]		**1k**		**3a**, 56		**4a**, 79
12[b]		**1l**		**3a**, 41		**4b**, 62%
13[d]		**1m**		**3a**, 58		**4d**, 82%
14[d]		**1n**		**3c**, 40		**4a**, 65

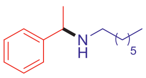
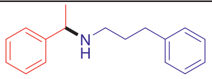
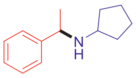
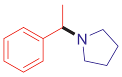
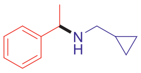
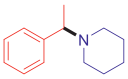
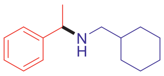
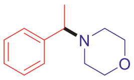
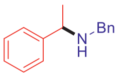
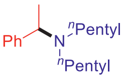
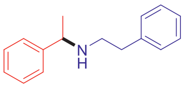
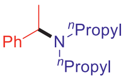
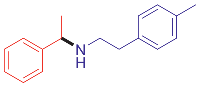
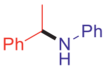
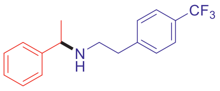
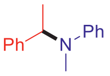
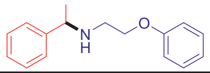
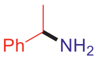
[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), Pd/C (10 mol%) and HCO_2Na (5.0 equiv.) in toluene (1.0 mL) were heated at 150 °C under argon atmosphere for 12 h; isolated yields were given.
[b] HCO_2Na (7.0 equiv.).
[c] HCO_2Na (2.0 equiv.).
[d] HCO_2Na (1.5 equiv.).

ther reduction (entry 7). In addition, secondary amines such as pyrrolidine, piperidine and morpholine also successfully coupled to afford the corresponding product (**3n**, **3o** and **3p**) with good to high yields (entries 11–13). When benzylamine, acyclic secondary amines (such as dipentylamine and dipropylamine) and anilines (such as aniline and *N*-methylaniline) subjected to the C-O ether bond cleavage, phenols **4a** was obtained with high yields (83%-93%) (entries 5 and 14–17). However, the corresponding cross-coupling products amines were generated in lower yields (0–32%) instead of acetophenone (**5**) with moderate to good yields. Inorganic nitrogen resource, ammonia, was used instead of organic amines, generating C-O ether bond cleavage product acetophenone (**5**) and guaiacol (**4a**) in lower yields (entry 18).

To investigate the reaction mechanism, a series of control experiments were carried out. Methyl ether compounds **6** and tertiary alcohol **7** did not generate the desired product, indicating that the hydrogen of hydroxyl and benzyl position was very important, which benefited the reaction *via* dehydrogenation to give

Table 3
Cleavage/cross-coupling of lignin β-O-4 model compound **1a** with amines.[a]



Entry	Yield **3** (%)	Yield **4a/5** (%)	Entry	Yield **3** (%)	Yield **4a/5** (%)
1	 **3a**, 89	91	10	 **3m**, 70	82
2	 **3e**, 75	92	11[c]	 **3n**, 67	72
3	 **3f**, 62	77	12	 **3o**, 73	84
4	 **3g**, 65	70	13[d]	 **3p**, 63	88
5[b]	 **3h**, 52	93/51	14[b]	 **3q**, n.d.	88/58
6	 **3i**, 71	82	15[b]	 **3r**, n.d	85/69
7	 **3j**, 71	82	16[b]	 **3s**, 11	91/67
8	 **3k**, 67	88	17[b]	 **3t**, 23	83/59
9	 **3l**, 70	81	18[b,e]	 **3u**, n.d.	31/19

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), Pd/C (10 mol%) and HCO_2Na (5.0 equiv.) in toluene (1.0 mL) were heated at 150 ºC under argon atmosphere for 12 h; isolated yields were given.
[b] Yields were determined by ^1H NMR spectroscopy using dibromomethane as an internal standard.
[c] HCO_2Na (3.0 equiv.), 130 ºC.
[d] HCO_2Na (3.0 equiv.)
[e] $NH_3\cdot H_2O$ (2.0 equiv.) was used instead of amine **2**.

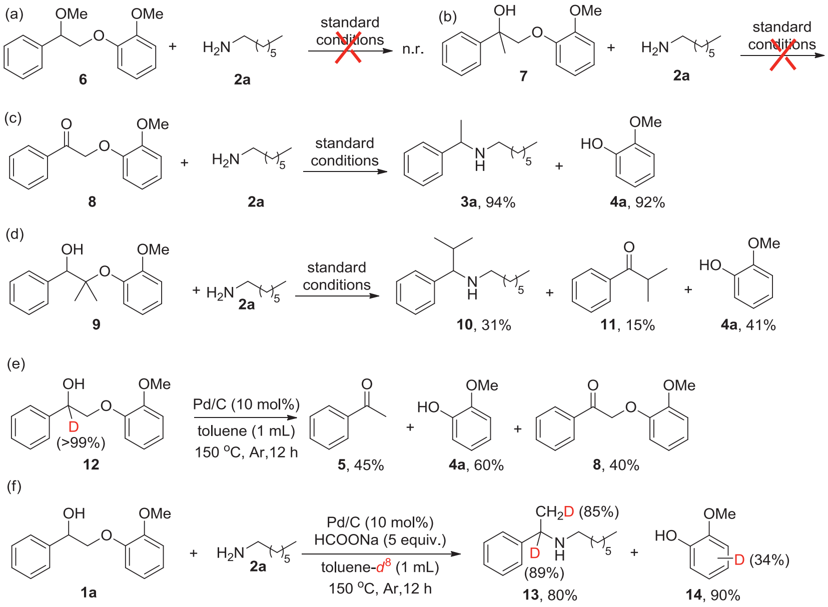
a ketone intermediate (Schemes 2a and b). When we used the ketone **8**, mimicking the possible intermediate under standard conditions, the cross-coupling product and phenol were obtained with excellent yields (Scheme 2c). This result demonstrated that the ketone was the intermediate for this transformation. To further investigate the cleavage of the ether bond *via* enol or enamine, *beta*-dimethyl substituted compound **9** was used for this transformation under standard conditions, cross-coupling product **10** (31% yield), C–O bond cleavage product **11** (15% yield) and phenol **4a** (41% yield) were obtained (Scheme 2d). This information excluded C–O bond cleavage *via* enol or enamine process. *alpha* D-isotope labelling compound **12** was then chosen as substrate for investigating the whereabouts of D atom (Scheme 2e). The result showed that no D atom was incorporated into the product. Based on our previous work [42], we propose that D atom might exchange with solvent. Therefore, we used deuterated toluene-d^8 as a solvent. It was found that there was D atom in the product, indicating that the deuterium atoms in toluene participated in the reaction and was transferred to the amination product and guaiacol.

According to the above experimental results, a possible mechanism for the cleavage/cross-coupling reaction of lignin model compound with amine is proposed in Scheme 3. The alcohol **A** is dehydrogenatively oxidized by palladium to generate ketone intermediate **B** and simultaneously form palladium hydrogen species. The ketone **B** may condense with amine to generate imine **C**. Next, palladium inserts into the C-O bonds of the ketone **B** or imine **C** *via* *O*-oriented or *N*-oriented process to form intermediate **D** or **E**. Finally, the intermediate **D** or **E** is reduced by a hydrogen source to obtain phenol **H**, and ketone **F** or imine **G**, as well as regenerates palladium catalyst. The ketone **F** is condensed with amine and reduced by palladium hydrogen species to obtain the cross-coupling product **J**. The imine **G** is also reduced to generate product **J**.

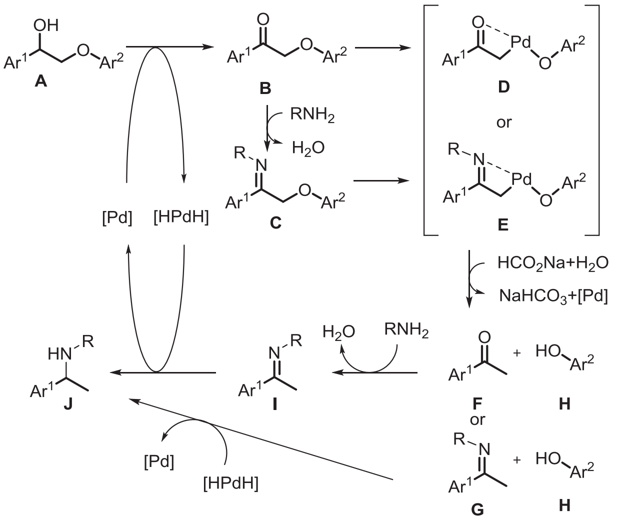
In summary, we have developed cleavage/cross-coupling strategy for converting β-O-4 linkage lignin model compounds to high valued benzyl amines via dual C–O bond cleavage and cross coupling reaction. The lignin β-O-4 model compounds can be directly converted into nitrogen-containing aromatic compounds and phenols. This method provides a novel avenue in the exploitation of novel sustainable feedstocks for chemical production and represents a particularly difficult transformation. Further efforts will be made to apply the present strategy to obtain high-valued chemicals from natural lignins.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



Scheme 2. Control experiments.



Scheme 3. Proposed reaction pathways for cross-coupling of lignin β-O-4 model compound with amines.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.08.125.

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