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Palladium-Catalyzed Synthesis of *N*-Cyclohexyl Anilines from Phenols with Hydrazine or Hydroxylamine via N-N/O Cleavage

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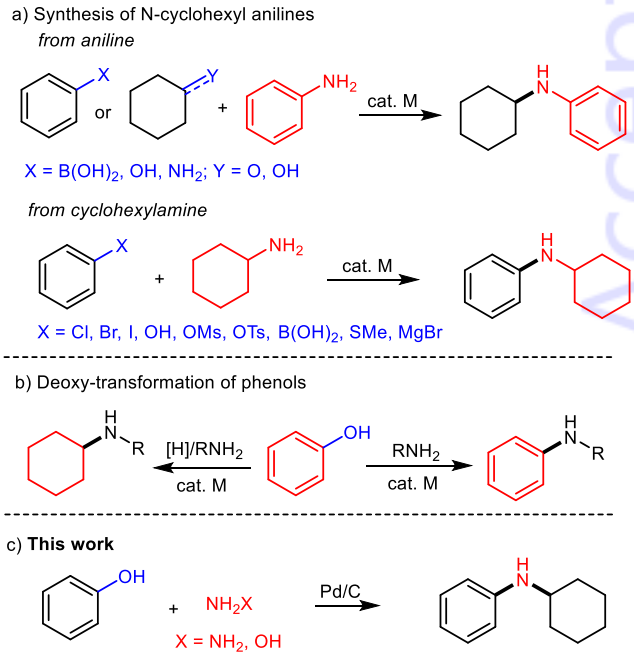
Abstract: Direct access to amines from biomass-based phenols via deoxygenative transformation remains greatly challenging in organic synthesis. Herein, we present a palladium-catalyzed deoxygenative amination of phenols (and their benzyl ether) with hydrazine as nitrogen source. The hydroxylamine/formic acid can be substituted for hydrazine in some cases. This deoxyamination features the involvement of a complex C-O bond and N-N/O bond-cleavage process and allows for the construction of *N*-substituted cyclohexyl anilines from an array of phenols by finely controlling the reaction conditions in moderate to good yields.

Keywords: Phenols; Amines; Deoxygenation; N-N/O cleavage; Hydrazine; Palladium

Arylamines serve as important structural units in pharmaceuticals, pigments and functional materials.[1] They are also versatile intermediates in numerous transformations[2] such as C-halo (the Sandmeyer and Schiemann reactions) or C-N (the Buchwald-Hartwig, the Chan-Lam and the Ullmann reactions) bond formations. Very recently, *N*-cyclohexyl anilines have been used as ligand to promote dehydrogenative transformations,[3] and as antioxidant in food chemistry.[4] To date, a series of elegant methods for the synthesis of *N*-cyclohexyl anilines have been developed, which can be divided into two categories (Scheme 1, a): one involves the use of anilines as amino source,[5] with coupling partners including arylboronic acids,[6] phenols,[7] anilines,[8] cyclohexanones[9] or cyclohexanols;[10] and the other relates to the use of cyclohexylamines as precursors, with coupling partners covering various aryl sources such as haloarenes,[11] phenol[12] and its derivatives,[13] arylboronic acids[6] and aryl Grignard reagents.[14] However, most of these methods require the prefunctionalization, thereby decreasing the total reaction efficiency. Phenols are abundant and naturally occurring motifs in renewable lignocellulosic biomass, and are important precursors of aryl or cyclohexyl groups (Scheme 1, b).[15] In 2015, our group developed a Pd-catalyzed reductive coupling of phenols with amines using sodium formate as a convenient hydrogen source to produce anilines or cyclohexylamines.[7,12] Later, Taddei accomplished this transformation in a flow reactor.[8] In 2016, Beller reported a Pd-catalyzed deoxygenative coupling of phenols or aryl ethers to generate alkylated cyclohexylamines with Lewis acid $Hf(OTf)_4$ as co-catalyst under molecular H_2,[16] and Fu's group further investigated *N*-cyclohexylation of amines with phenols using Al_2O_3 supported palladium hydride (PdH_x) catalyst.[17]

The N-N bond cleavage of hydrazines has recently been utilized as a strategy for the formation of C-N



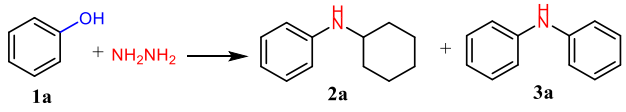
Scheme 1. Approaches to access *N*-cyclohexyl anilines.

bond through the transition-metal-catalyzed C-H bond functionalization.[18] Indeed, it has earlier been documented that hydrazines served as a nitrogen source with carbonyl compounds to prepare amines via catalytically hydrogenative N-N cleavage.[19] Yet to our knowledge, there seems to be no report regarding the synthesis of amines from phenols with hydrazine via the cleavage of C-O and N-N bonds. Herein, we present an efficient palladium-catalyzed direct deoxygenative coupling of phenols with hydrazine or hydroxylamine as nitrogen atom source via C-O bond and N-N/O bond cleavages (Scheme 1, c).

The initial exploration of this deoxygenative amination was carried out using phenol **1a** and hydrazine monohydrate as coupling partners in the presence of Pd/C as the catalyst and HCO_2Na as the hydride donor source. We are delighted to obtain 51% yield of *N*-cyclohexyl aniline **2a** only with trace amount of **3a** (Table 1, entry 1). Other hydrazine sources such as its THF solution (1.0 M), its hydrate, mono or dihydrochloride, and sulfate were also attempted (Table 1, entries 2-6). It was found that all other hydrazine reagents tested delivered lower yields compared with the monohydrate. Then, the solvent effect was tested. The reaction performed in THF gave higher yield than in 1,4-dioxane (Table 1, entries 7 *vs* 8), but still slightly lower than in toluene. When water was used as the solvent, it resulted in only a trace amount of the product (Table 1, entry 9). Changing the amount of Pd/C or using a different Pd/C catalyst (5 wt% Pd loading) could not improve the reaction yields (Table 1, entries 10-12). The yield of **2a** stayed nearly constant while **3a** was formed in 9% yield when the reaction was conducted at 140 °C (Table 1, entry 14). Further elevating the temperature to 160 °C decreased the yield of **2a** but generated more **3a** (Table 1, entry 15). It was found that the reaction was much influenced by the amount of HCO_2Na. Optimization at 160 °C indicated that 2.0 equivalent of HCO_2Na gave higher yield of **2a** (Table 1, entry 16-18). Changing the reaction temperature to 150 °C improved the yield slightly (Table 1, entry 19). Changing the TFA amount to 1.0 equiv gave a better yield (90%) (Table 1, entries 20 *vs* 21). Thus, the optimal reaction conditions were established as follows: phenols (1.0 equiv) reacted with hydrazine monohydrate (0.75 equiv) in the presence of Pd/C (10 wt% Pd loading, 0.1 equiv) as the catalyst, HCO_2Na (2.0 equiv) as a reductive reagent, and TFA (1.0 equiv) as an additive in toluene (0.2 M) at 150 °C under argon for 24 h, providing the 90% yield (85% isolated yield) of *N*-cyclohexyl aniline **2a**.

With the optimized reaction conditions in hand, we set out to investigate the scope of the phenols. Generally speaking, less hindered phenols such as cresols proceeded smoothly under the standard conditions, furnishing their corresponding *cis/trans* isomeric products in good yields (Table 2, entries 2-4). *Para*-and *meta*-ethylphenol **1e** and **1f** delivered the corresponding desired amines **2e** and **2f** in

Table 1 Optimization of the reaction conditions.[a]



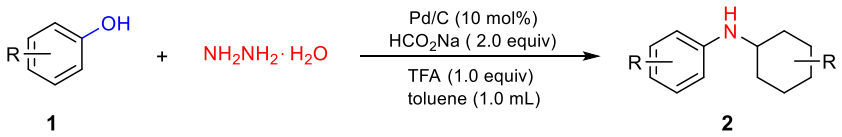
1a 2a 3a

Entry	Hydrazine	Solvent	Temp. [°C]	Yield[%] 2a	3a
1	$N_2H_4{\cdot}H_2O$	toluene	120	51	trace
2[b]	N_2H_4	toluene	120	20	0
3	N_2H_4 hydrate	toluene	120	45	5
4	$N_2H_4{\cdot}HCl$	toluene	120	4	0
5	$N_2H_4{\cdot}2HCl$	toluene	120	4	0
6	$N_2H_4{\cdot}H_2SO_4$	toluene	120	38	0
7	$N_2H_4{\cdot}H_2O$	THF	120	49	0
8	$N_2H_4{\cdot}H_2O$	1,4-dioxane	120	5	0
9	$N_2H_4{\cdot}H_2O$	H_2O	120	6	0
10[c]	$N_2H_4{\cdot}H_2O$	toluene	120	11	0
11[d]	$N_2H_4{\cdot}H_2O$	toluene	120	44	1
12[e]	$N_2H_4{\cdot}H_2O$	toluene	120	23	1
13	$N_2H_4{\cdot}H_2O$	toluene	110	20	0
14	$N_2H_4{\cdot}H_2O$	toluene	140	52	9
15	$N_2H_4{\cdot}H_2O$	toluene	160	48	18
16[f]	$N_2H_4{\cdot}H_2O$	toluene	160	56	22
17[g]	$N_2H_4{\cdot}H_2O$	toluene	160	70	12
18[h]	$N_2H_4{\cdot}H_2O$	toluene	160	56	25
19[g]	$N_2H_4{\cdot}H_2O$	toluene	150	75	10
20[g] [i]	$N_2H_4{\cdot}H_2O$	toluene	150	90	5
21[g] [j]	$N_2H_4{\cdot}H_2O$	toluene	150	81	7

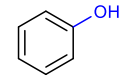
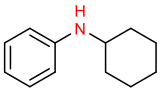
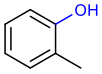
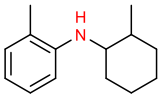
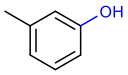
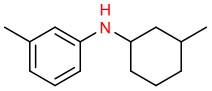
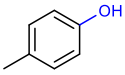
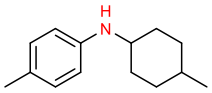
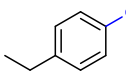
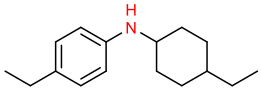
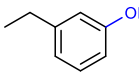
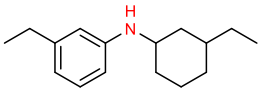
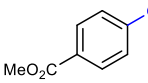
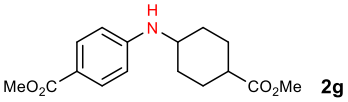
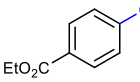
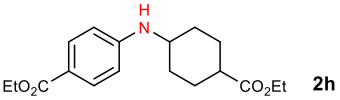
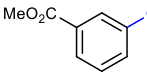
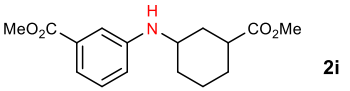
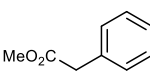
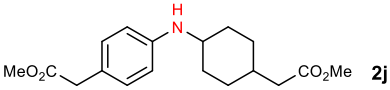
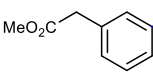
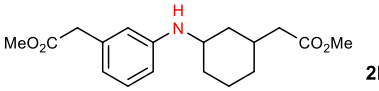
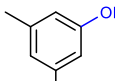
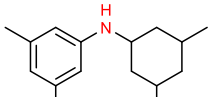
[a] Reaction conditions: phenol (0.2 mmol), Pd/C (10 wt% loading) (10 mol%), hydrazine (0.75 equiv), HCO_2Na (3.0 equiv), TFA(7.5 µL, 0.5 equiv) in solvent (1.0 mL) under Ar for 24 h unless otherwise stated. [b] N_2H_4 in THF (1.0 M). [c] Pd/C (10 wt% loading) (5 mol%). [d] Pd/C (10 wt% loading) (20 mol%). [e] Pd/C (5 wt% loading) (10 mol%). [f] HCO_2Na (2.5 equiv). [g] HCO_2Na (2.0 equiv). [h] HCO_2Na (1.5 equiv). [i] TFA (15 µL, 1.0 equiv). [j] TFA (22 µL, 1.5 equiv). Yields are calculated based on ^1H NMR spectra data.

moderate yields, respectively (Table 2, entries 5 & 6), while *ortho*-ethylphenol is an ineffective substrate. Unfortunately, other phenols with bulky alkyl groups such as *iso*-propyl, *tert*-butyl are sluggish under the optimal conditions. These results suggested that the deoxyamination efficiency depends greatly on the steric property of substituents on the phenols. To our surprise, however, hydroxylbenzoates could proceed well in such a transformation. For example, methyl *para*-hydroxylbenzoate **1g** was successfully converted into its corresponding *cis/trans* amines **2g** in 78% total yield. The bulky ethyl ester **1h** also gave the desired products **2h** in 80% total yield. However, the much bulkier phenyl *para*-hydroxylbenzoate was found to be partially cleaved with phenol being detected. When the ester group was anchored on the *meta* position, the reaction worked well, and afforded a 72% total yield of the *N*-cyclohexylamines **2i** (Table 2, entry 9). However, when the methyl, ethyl or phenyl salicylates were used instead, negative results were obtained. Likewise, the hydroxylphenylacetates showed comparable

Table 2. Pd-catalyzed deoxygenative amination of phenols with hydrazine monohydrate as N source.[a]



1 **2**

Entry	Substrate	Product	*cis/trans*	Yield (%)
1	 **1a**	 **2a**	–	85
2	 **1b**	 **2b**	0.56:1	83
3	 **1c**	 **2c**	1.6:1	75
4	 **1d**	 **2d**	1.5:1	83
5	 **1e**	 **2e**	1:1	65
6	 **1f**	 **2f**	0.85:1	53
7	 **1g**	 **2g**	0.56:1	78
8	 **1h**	 **2h**	0.55:1	80
9	 **1i**	 **2i**	1.1:1	72
10	 **1j**	 **2j**	1:1	75
11	 **1k**	 **2k**	0.82:1	66
12	 **1l**	 **2l**	0.28:0.57:1	65

[a] Reaction conditions: phenol (0.2 mmol), $NH_2NH_2 \cdot H_2O$ (8 µL, 0.15 mmol), Pd/C (10 mol% Pd), HCO_2Na (27.2 mg, 0.4 mmol), TFA (15 µL, 0.2 mmol), toluene (1 mL) under Ar at 150 °C. Yields were for isolated *cis/trans* mixtures. The ratio was determined by ^1H NMR analysis of the crude products.

reactivities to the benzoate analogues. For instance, methyl *para*- and *meta*-hydroxylphenylacetates **1j** and **1k** reacted with hydrazine to successfully provide the desired amines **2j** and **2k**, respectively, but the efficiency slightly decreased (Table 2, entries 10 & 11). The o*rtho*-hydroxylphenylacetate analogues gave complex mixtures, along with the formation of the cyclization product benzofuran-2(3*H*)-one. It is worthwhile to note that, in all cases of the esters, no hydrazination or amidation of the ester group occurred under the current conditions. Furthermore, pure *cis*- and *trans*-isomers of these secondary amines except **2f** could be isolated readily by chromatography method, and individually

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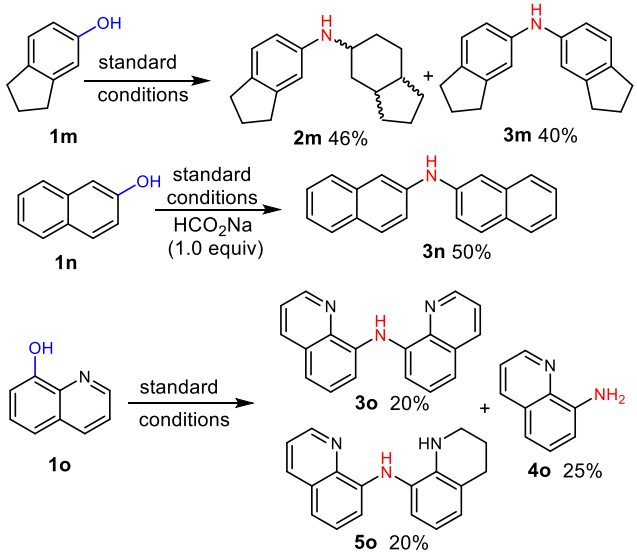
characterized by NMR and MS analysis (see Supporting Information). Besides mono substituted phenols, disubstituted analogues are also suitable for this protocol. The use of 3,5-dimethylphenol **1l** gave rise to its corresponding amines **2l** in 65% total yield with three stereo-isomers, the two major of which were purified by preparative thin layer chromatography.

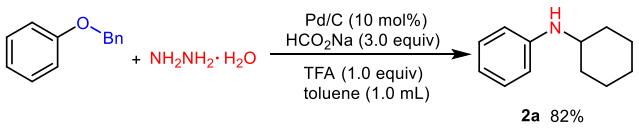
As expected, dehalo reduction occurs under "hydrogenation conditions". When 3-fluorophenol was used as a substrate, the C-F bond was completely cleaved and phenol was obtained as main product, except with traces of *N*-cyclohexyl aniline and *N*,*N*-diphenylamime being detected by GC-MS analysis. *Ortho*- or *para*-methoxylphenol suffered from partial demethoxygenation, producing a complex mixture containing its desired amines, while the *meta*-analogue underwent complete C-OMe cleavage, yielding mainly *N*-cyclohexyl aniline.

In addition, phenols such as **1m**, **1n** and **1o** were also studied (Scheme 2). Subjecting phenol **1m** (5-indanol) to the standard conditions produced 46% of **2m** (*cis/trans* isomeric mixture) and 40% of **3m**. 2-Naphthanol **1n** was reactive enough for such transformation to generate a complex mixture under standard conditions. After reducing the amount of sodium formate to 1.0 equivalent, diaryl amine **3n** was obtained in 50% yield. Interestingly, 8-hydroxyquinoline **1o** underwent the transformation smoothly, furnishing three aminoquinolines in a total isolated yield of 65%. Here it is noteworthy that the products di(quinolin-8-yl) amine **3o** and 8-amino-1,2,3,4-tetrahydroquinoline **5o** are potential polydentate ligands for catalysis chemistry.

The aryl ethers are more abundant structural units in biomass resources such as lignin. We hope this chemistry can be applied to these model ethers. When benzyl phenyl ether was subjected to this protocol, *N*-cyclohexyl aniline was obtained in 82% yield, as phenol delivered (Scheme 3).

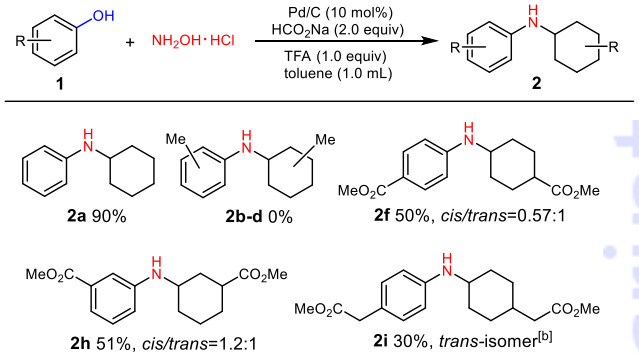


Scheme 2. Other examples.



Scheme 3. Reductive amination of benzyl phenyl ether with hydrazine monohydrate.

Table 3. The use of hydroxylamine as N source.[a]

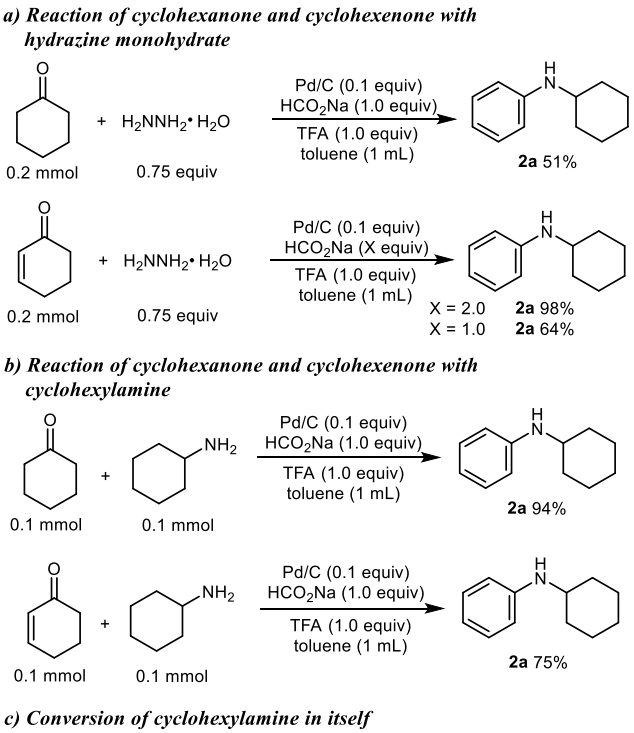


[a]Conditions: phenol (0.2 mmol), $NH_2OH{\cdot}HCl$ (0.15 mmol). Yields and *cis/trans* ratio were determined by ^1H NMR analysis of the crude product, using 1,3,5-trimethoxybenzene as an internal standard.[b]The *cis*-isomer overlapped with other peaks in either $CDCl_3$ or CD_3OD.

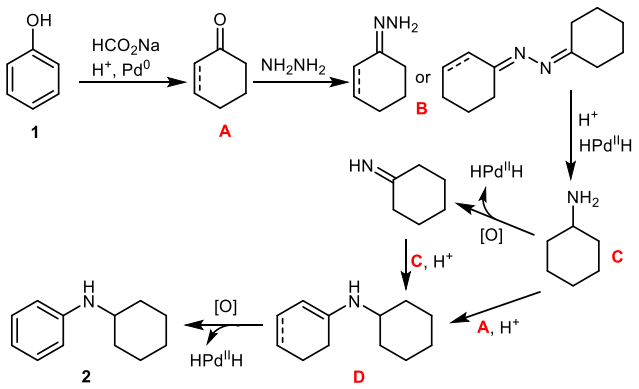
Hydroxylamine and its derivatives have been extensively utilized as amino source in the reductive amination and C-H amidation through an N-O bond-cleavage step.[20] We are curious about the possibility of using hydroxylamine in this deoxyamination. When using hydroxylamine hydrochloride/formate in lieu of the hydrazine, the reaction of phenol **1a** resulted in the formation of **2a** in excellent yield of 90%, but cresols **1b-d** are ineffective under the same conditions (Table 3). Surprisingly, both hydroxylbenzoates and hydroxylphenylacetate gave moderate yields. The catalyst recycling experiment was also performed; unfortunately, the NMR yield significantly dropped from 90% to 16% with the recycled Pd/C as the catalyst under the optimized conditions using phenol as the substrate.

To probe the mechanism of this chemistry, possible intermediates instead of phenol were used for a series of control experiments. For instance, the use of cyclohexanone and cyclohexenone reacting with hydrazine can lead to the formation of the desired amine **2a** in moderate to excellent yields (Scheme 4, a). Noteworthy, under standard conditions, 2-cyclohexenone gave a quantitative yield. When both ketones reacted with cyclohexylamine under the standard conditions in the presence of 1.0 equiv of HCO_2Na, the amine **2a** was obtained in 94% and 75% yields, respectively (Scheme 4, b). Interestingly, cyclohexylamine can dimerize to form the desired product **2a** under modified standard conditions either with or without HCO_2Na (Scheme 4, c). Furthermore, when using the hydrazone or azine for this transformation, the desired amine can also be obtained, albeit in moderate yields (Scheme 4, d). All these experimental results indicated that all the

intermediates tested in the control experiments, such as cyclohexanone, cyclohexenone, cyclohexylamine and even hydrazone or azine are likely involved in the present transformation.



Scheme 4. Control experiments.



Scheme 5. Proposed mechanism.

Based on these results and previous literatures,[7, 12, 21] a possible mechanism was proposed (Scheme 5).[22] Firstly, phenol **1** was reduced to cyclohexanone or cyclohexenone **A**, which then condensed with hydrazine to form hydrazone or azine **B**. The intermediate **B** was further reduced to access the key intermediate cyclohexylamine **C**. Then **C** reacted with **A** to generate **D**, subsequently giving the desired amine **2** via dehydrogenation. Alternatively, **C** reacted with the imine derived from itself to produce the target amine **2**.

In summary, we have disclosed the catalytic deoxgenative amination of phenols with hydrazine as N source using commercial Pd/C. Benzyl phenyl ether is suitable for this amination, and hydroxylamine/formic acid is an alternative to hydrazine in some cases. This chemistry involves a complex C-O bond and N-N or N-O bond-cleavage process and enables access to a variety of *N*-substituted cyclohexyl anilines from lignin-derived phenols. In most cases, the *cis-/trans*-isomer can be isolated using flash chromatography. These amines have various applications in pharmaceuticals, pigments and functional materials. Further deoxygenative transformations of biomass are under way in our lab.

Experimental Section

General procedure for the palladium-catalyzed synthesis of *N*-cyclohexyl anilines

An oven-dried screw cap test tube was charged with a magnetic stir-bar, phenol **1** (0.2 mmol), Pd/C (10 wt%, 21.2 mg, 10 mol% based on Pd content) and sodium formate (27.2 mg, 0.4 mmol). The tube was then evacuated and backfilled with argon for three times. Toluene (1 mL, pretreated by three cycles of evacuation-refill with argon), hydrazine monohydrate (8 μL, 0.15 mmol), TFA (15 μL, 0.2 mmol) were sequentially added by syringe under argon flow. Then the tube was screwed and placed in a preheated oil bath at 150 °C with vigorous stirring for 24 h. The reaction system was cooled to room temperature and filtered through the pad of silica gel. The filtrate was concentrated and the resulting residue was purified via the column chromatography using hexane: ethyl acetate (20:1-4:1) as eluent.

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[22] The proton involvement plays a key role in this transformation. From **1** to **A**, the proton helped generate the HPdH species; from **B** to **C**, the proton promoted the cleavage of N-N bond via the protonation process; from **C** to **D**, the proton facilitated the condensation process to get the enamine **D**.

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UPDATE

Palladium-Catalyzed Synthesis of *N*-Cyclohexyl Anilines from Phenols with Hydrazine or Hydroxylamine via N-N/O Cleavage

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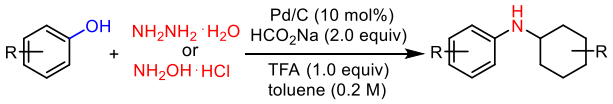

phenols being both aryl and cyclohexyl sources
hydrazine or hydroxylamine being N source
C-O bond and N-N/O bond cleavages in one-pot