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Formal Direct Cross-Coupling of Phenols with Amines

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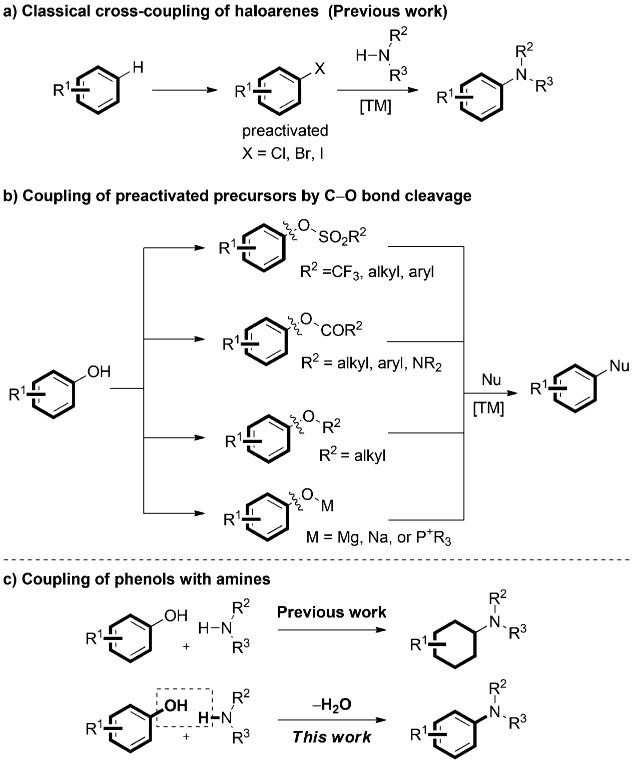
Abstract: *The transition-metal-catalyzed amination of aryl halides has been the most powerful method for the formation of aryl amines over the past decades. Phenols are regarded as ideal alternatives to aryl halides as coupling partners in cross-couplings. An efficient palladium-catalyzed formal cross-coupling of phenols with various amines and anilines has now been developed. A variety of substituted phenols were compatible with the standard reaction conditions. Secondary and tertiary aryl amines could thus be synthesized in moderate to excellent yields.*

Aryl amines are ubiquitous building blocks for various organic molecules and electronic materials and among the most prevalent structural motifs in pharmaceutical agents.[1] As a consequence, continuing efforts have been devoted to developing new and effective approaches for the formation of aryl amines.[2] Transition-metal-catalyzed amination reactions, such as Chan–Lam amination,[3] intermolecular hydroamination,[4] and oxidative aromatization,[5] are examples of modern methods for aryl amine synthesis.[6] Among the various methods, the most prominent reactions are the Buchwald–Hartwig coupling[7] and Ullmann-type aminations,[8] in which aryl halides are frequently used as electrophiles and coupled with amines (Scheme 1 a). However, the need of pre-synthesizing the aryl halides and the generation of unwanted halide waste are drawbacks of the aryl halide based strategies.



Scheme 1. Formal cross-coupling of phenols with amines.

On the other hand, phenols (mostly in their polymeric forms in lignin and coal) are the second most prevalent naturally occurring structural units of renewable biomass on the planet, and have the same oxidation state as haloarenes.[9] Therefore, the direct coupling of phenols, instead of haloarenes, has long been a synthetic aspiration and great scientific challenge. However, phenols have 1) a very reactive hydroxy group and 2) a C–O bond with a high dissociation energy owing to p–π conjugation. In recent years, great achievements have been made in developing coupling reactions of phenols by catalytic C–O bond cleavage by first transforming them into more active derivatives,[10] which include 1) aryl sulfonates[11] (e.g., triflates, tosylates, mesylates, and sulfamates), 2) aryl esters or aryl carbamate derivatives,[12] 3) aryl alkyl ethers,[13] and 4) phenolic salts[14] (Scheme 1 b). Undoubtedly, taking into account the atom and step economy, the development of a direct cross-coupling with non-preactivated phenols would be highly desirable.

Recently, we have reported a palladium-catalyzed reductive coupling of phenols with anilines to afford cyclohexylamines by a reduction/condensation/reduction pathway (Scheme 1 c).[15] Inspired by the "hydrogen-borrowing strategy" for converting alcohols into amines[16] and oxidative aromatization,[5] we hypothesized that if we could temporarily generate a small amount of the ketone form from phenol, the conversion of the C–O bond into a C–N bond with amines and subsequent dehydrogenative aromatization to form the desired aryl amine should be feasible. Herein, we present a highly efficient, palladium-catalyzed formal direct cross-coupling of phenols with various amines and anilines through a tandem reduction/condensation/dehydrogenation process (Scheme 1 c).[17]

Based on our previous work, we first used phenol and *para*-toluidine to optimize the reaction conditions. We found that a higher temperature (120 °C), a smaller amount of

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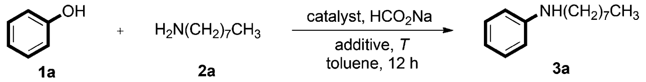
sodium formate (1.5 equiv), and acid additives were advantageous to form the aryl amine product. However, the formation of cyclohexylamine side products could not be avoided (see the Supporting Information, Table S1). Fortunately, when aliphatic amines were used to replace toluidine, the corresponding products could be obtained in good yields without any cyclohexylamine side products. Based on these results, the reaction of phenol (**1a**) with *n*-octylamine (**2a**) was chosen as the model reaction, and a variety of factors, including acid, base, catalyst, ligand, solvent, oxidant, and temperature, were evaluated. To our delight, the reaction gave the desired coupling product in 52% yield when Pd/C was used as the catalyst with sodium formate as the temporary hydrogen source (Table 1, entry 1). Then, various additives, such as acids and bases, were evaluated, and trifluoroacetic acid gave the best results (entries 2–8). Others palladium catalysts were also tested, but only Pd(OH)$_2$/C afforded the desired product in moderate yield (entries 9–12). A control experiment showed that sodium formate was essential to the transformation (entry 13). Subsequently, the effects of the ligand, solvent, and oxidant were also explored, which did not lead to any improvements (see Table S5–S7). With a slight excess of *n*-octylamine, the product yield was further improved to 81% (entry 15). Finally, by changing the reaction temperature to 140°C, the desired product was obtained in 86% yield (yield of isolated product: 81%; entries 16–18).

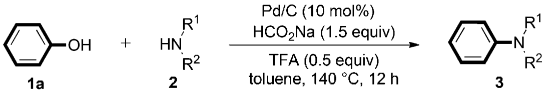
Table 1: Optimization of the reaction conditions.[a]

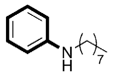


Entry	Catalyst	Additive	T [°C]	Yield[b] [%]
1	Pd/C	–	120	52
2	Pd/C	ZnCl$_2$	120	n.p.
3	Pd/C	HOAc	120	8
4	Pd/C	PhCOOH	120	60
5	Pd/C	TFA	120	65
6	Pd/C	NaO*t*Bu	120	47
7	Pd/C	Na$_2$CO$_3$	120	50
8	Pd/C	DABCO	120	36
9[c]	Pd(OH)$_2$/C	TFA	120	50
10	[PdCl$_2$(dtbpf)]	TFA	120	n.p.
11	Pd(NO$_3$)$_2$·2H$_2$O	TFA	120	n.p.
12	[Pd(acac)$_2$]	TFA	120	trace
13[d]	Pd/C	TFA	120	n.r.
14[e]	Pd/C	TFA	120	73
15[f]	Pd/C	TFA	120	81
16[f]	Pd/C	TFA	130	84
17[f]	**Pd/C**	**TFA**	**140**	**86 (81)**
18[f]	Pd/C	TFA	150	86

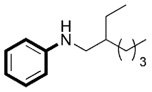
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (10 mol%), HCO$_2$Na (1.5 equiv), and an additive (0.5 equiv) in toluene (1 mL) for 12 h under argon atmosphere. [b] Yields were determined by GC analysis with mesitylene as the internal standard; yields of isolated products are given in parentheses. [c] 20 wt% Pd(OH)$_2$/C. [d] Without HCO$_2$Na. [e] **2a** (0.24 mmol) was used. [f] **2a** (0.28 mmol) was used. acac = acetylacetonate, DABCO = 1,4-diazabicyclo[2.2.2]octane, dtbpf = 1,1′-bis(di-*tert*-butylphosphino)ferrocene, n.p. = no product, n.r. = no reaction, TFA = trifluoroacetic acid.

Table 2: Palladium-catalyzed coupling of phenols with amines.[a]

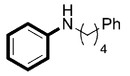




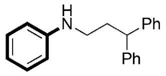
3a 81%



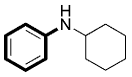
3b 78%



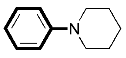
3c 62%



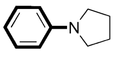
3d 55%



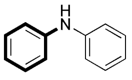
3e 85%
78%[b]



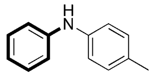
3f 68%



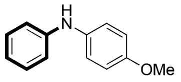
3g 63%



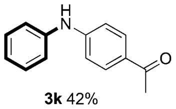
3h 46%[c]



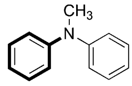
3i 56%[c]



3j 74%[c]



3k 42%



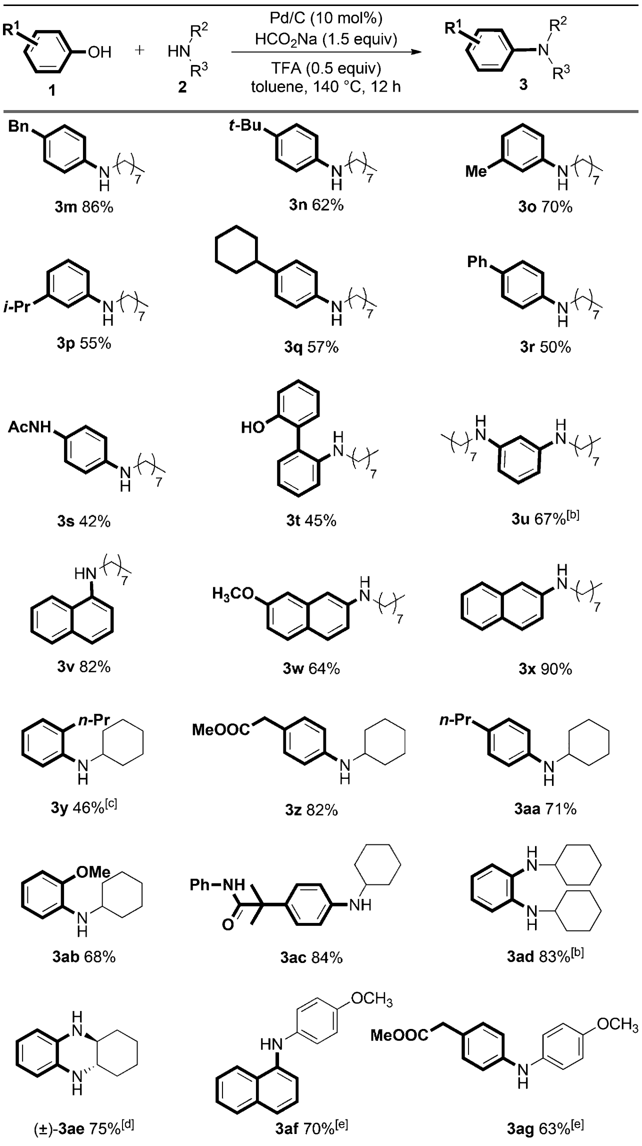
3l 40%[c]

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.28 mmol), Pd/C (10 mol%), HCO$_2$Na (1.5 equiv), and TFA (0.5 equiv) in toluene (1 mL) for 12 h under an argon atmosphere; yields of isolated products are given. [b] 4-Chlorophenol was used as the substrate. [c] 24 h.

With the optimized reaction conditions in hand, the substrate scope was explored. As shown in Table 2, different amines reacted efficiently with phenol. Various alkyl aryl amines were obtained in good to high yields in all cases (Table 2; **3a**–**3d**). The use of the sterically hindered amine cyclohexylamine also led to the corresponding product in high yield (**3e**). The reaction of cyclic secondary amines with phenol under the optimized standard conditions furnished the corresponding tertiary aniline derivatives also in good yields (**3f** and **3g**). Various anilines bearing electron-withdrawing or electron-donating groups were all suitable substrates for this transformation, and the corresponding products were obtained in moderate to good yields (**3h**–**3k**). A tertiary aniline was obtained in moderate yield by reacting a secondary aniline with phenol (**3l**). As expected, the corresponding dechlorinated aryl amine was obtained when 4-chlorophenol was used as the substrate (**3e**).

On the other hand, as shown in Table 3, different phenols reacted with *n*-octylamine (**3m**–**3x**), cyclohexylamine (**3y**–**3ad**), and *para*-methoxyaniline (**3af** and **3ag**) to give the corresponding cross-coupling products in moderate to high yields. The presence of a substituent in the *para* or *meta* position of the phenol does not have a significant effect on the reaction (**3m**–**3s**), nor does a substituent group in the *ortho* position (**3t**). When biphenol was used as the starting material, only one C–N bond formation was observed whereas two C–N bonds were formed when resorcinol was employed (**3t** vs. **3u**). Different naphthols also worked well under the standard conditions, and the corresponding products were obtained in good to excellent yields (**3v**–**3x**).

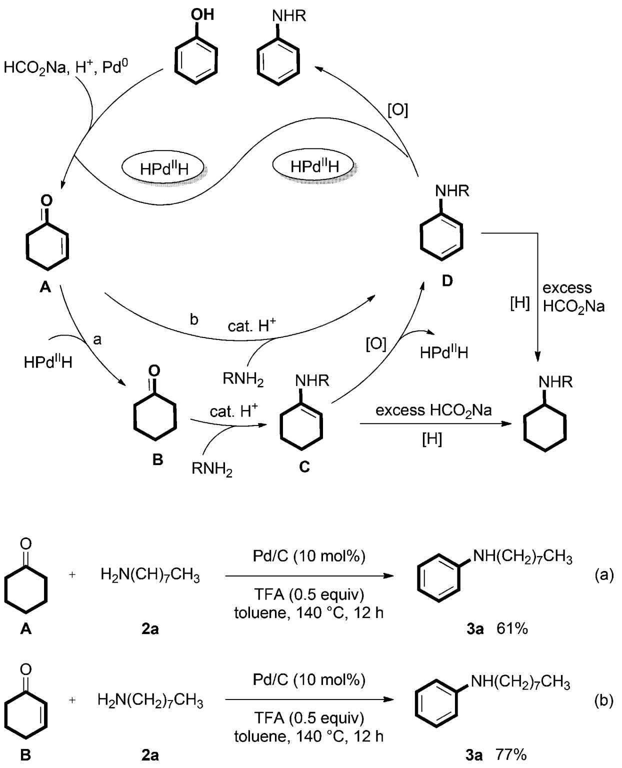
Table 3: Reactions of various substituted phenols and amines.[a]



3m 86%
3n 62%
3o 70%
3p 55%
3q 57%
3r 50%
3s 42%
3t 45%
3u 67%[b]
3v 82%
3w 64%
3x 90%
3y 46%[c]
3z 82%
3aa 71%
3ab 68%
3ac 84%
3ad 83%[b]
(±)-3ae 75%[d]
3af 70%[e]
3ag 63%[e]

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.28 mmol), Pd/C (10 mol%), HCO_2Na (1.5 equiv), and TFA (0.5 equiv) in toluene (1 mL) for 12 h under argon atmosphere; yields of isolated products are given. [b] **2** (0.48 mmol). [c] 2-Allylphenol was used as the substrate. [d] Catechol and *trans*-1,2-diaminocyclohexane were used as the substrates. [e] 24 h.

Moderate to high yields were achieved when various phenols reacted with cyclohexylamine (**3y**–**3ad**). For a phenol bearing an allyl group at the *ortho* position, the product was formed in moderate yield with reduction of the allyl group to a propyl group (**3y**). Furthermore, 4-propylphenol and 2-methoxyphenol (as the most prevalent structural units in lignin) provided the products in good yield (**3aa** and **3ab**). It is noteworthy that the corresponding product was obtained in high yield without ester–amide exchange when the substrate included an ester group (**3z**). A double C−N bond formation occurred in high yield when catechol was reacted with cyclohexylamine (**3ad**). A nitrogen-containing heterocycle was formed when catechol and 1,2-diaminocyclohexane were used as the substrates (**3ae**). Good yields were also achieved when phenol derivatives reacted with *para*-methoxyaniline (**3af** and **3ag**).



Scheme 2. Tentative mechanism for the reaction between phenol and amines.

A tentative mechanism for this novel coupling reaction is shown in Scheme 2. Initially, sodium formate reacts with the palladium catalyst to generate the $HPd^{II}H$ species.[18] Subsequently, reduction of phenol generates intermediate **A**, which undergoes further reduction immediately followed by dehydration with the amine to give intermediate **C**.[19] Substoichiometric amounts of acid can accelerate the condensation of cyclohexanone and the amine. A sequential dehydrogenation process of intermediate **C** leads to intermediate **D**, which is similar to a mechanism proposed by Liu et al. (path a).[18] Alternatively, it is also possible that dehydration of intermediate **A** with the amine gives intermediate **D** (path b). Finally, the second dehydrogenation of intermediate **D**, a process similar to the first dehydrogenation, results in the aryl amine products and regenerates the $HPd^{II}H$ species. When a large excess of sodium formate is used, intermediates **C** and **D** can be reduced to cyclohexylamine derivatives, the products obtained in our previous work.[15] Further control experiments suggest that both cyclohexanone or cyclohexenone could be the reaction intermediates, as good yields were obtained when they were used as the starting materials under the standard reaction conditions (Scheme 2 a, b).

In conclusion, we have developed a highly efficient direct coupling of phenols with various amines and anilines catalyzed by palladium. Both primary and secondary amines are suitable substrates for this novel coupling process. A wide range of important phenols and phenolic lignin model compounds, such as 4-propylphenol and 2-methoxyphenol, could be coupled efficiently. Compared to the formation of cyclohexylamines, a higher temperature, a substoichiometric amount of sodium formate, a catalytic amount of acid, and aliphatic amines are beneficial to the generation of aryl amines. This work unlocks unprecedented opportunities for synthetic strategies for directly coupling phenol. The various substituted anilines generated in this work have many applications in the synthesis of natural products, medicines, dyes, and electronic materials. Investigations regarding the scope and application of this catalytic process and further mechanistic studies are currently in progress.

Experimental Section

An oven-dried screw-cap test tube was charged with a magnetic stir bar, Pd/C (10 wt%, 21.2 mg, 10 mol% based on Pd content) and sodium formate (20.4 mg, 0.3 mmol). The tube was then evacuated and backfilled with argon. The evacuation/backfilling sequence was repeated two additional times. Under a counter-flow of argon, a solution of the phenol (0.2 mmol) and the amine (0.28 mmol) in toluene (1 mL) was added, followed by the addition of trifluoroacetic acid (8 μL, 0.1 mmol) by syringe. The tube was placed in a preheated oil bath at 140 °C, and the mixture was stirred vigorously for 12 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 column chromatography to give the desired aryl amine.

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Keywords: aryl amines · dehydrogenation · hydrogen borrowing · palladium · phenols

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