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Mono/Dual Amination of Phenols with Amines in Water

Wanyi Liang,[§] Feng Xie,[§] Zhihai Yang, Zheng Zeng, Chuanjiang Xia, Yibiao Li, Zhongzhi Zhu,* and Xiuwen Chen*

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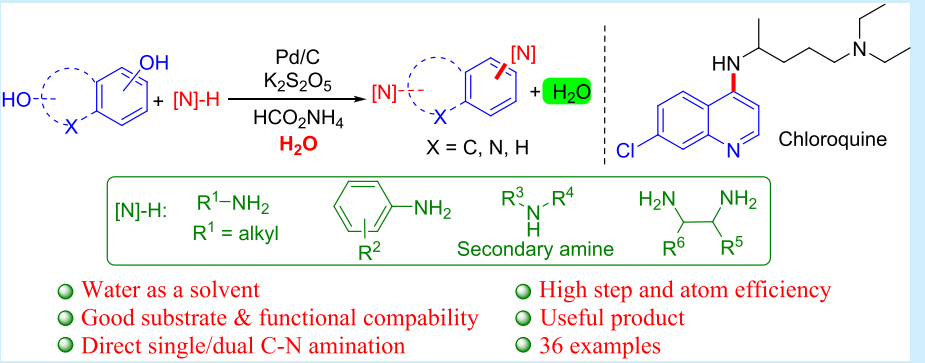


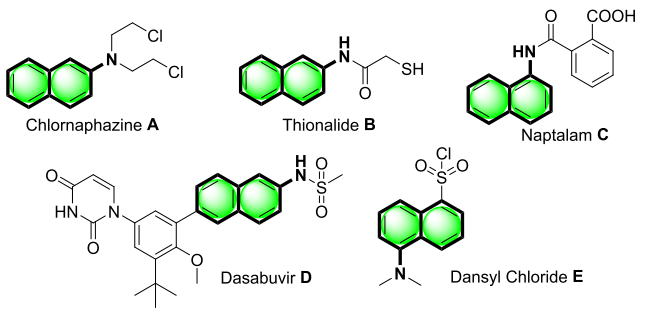
ABSTRACT: We herein describe a practical direct amination of phenols through a palladium-catalyzed hydrogen-transfer-mediated activation method to synthesize the secondary and tertiary amines. In this conversion, environmentally friendly water and inexpensive ammonium formate were used as solvent and reductant, respectively. A range of amines, including aliphatic amines, aniline, secondary amines, and diamines, could be coupled effectively by this method to achieve mono/dual amination and cyclization of phenols. This study not only provides a green and mild strategy for the synthesis of secondary and tertiary naphthylamines but also expands the synthesis of chloroquine in organic chemistry.

Aromatic amines are important structural motifs and intermediates because of their wide distribution in materials[1] and bioactive molecules.[2] Examples include the anticancer drug chlornaphazine (**A**),[3] depositing enrichment agent thionalide (**B**),[4] the pesticide naptalam (**C**),[5] the antiviral agent dasabuvir (**D**),[6] and fluorescence labeling reagent dansyl chloride (**E**)[7] (Scheme 1).

The rapid construction of aromatic amines in a green manner is an important research topic in organic and medicinal chemistry. C–N bond formation is among the most efficient strategies for constructing aryl amines.[8] Most C–N bond reactions are examples of Buchwald–Hartwig coupling or Ullmann-type aminations, wherein aryl halides are frequently utilized as electrophiles to couple with amines (Scheme 2a).[9] However, the prefunctionalization of aryl halides, as well as the production of halide byproducts, limits the utility of these protocols.

The chemistry of phenolic compounds has attracted continued interest over the past two centuries.[10] Therefore, the use of phenols instead of haloarenes is in great demand but is still challenging. C–N bond construction by hydrogen transfer has become a powerful tool in organic chemistry.[11] Recently, a palladium catalyst system for the direct cross-coupling of phenols with anilines was reported by the Li group.[12] Furthermore, there is also some progress on the hydrogenative amination, which allowed facile construction of cyclohexylamines from phenols.[13] Despite these advances, the utilization of ammonium formate as cost-effective reductant and eco-friendly water as solvent to achieve mono/dual

Scheme 1. Representative Compounds with a Naphthylamine Framework



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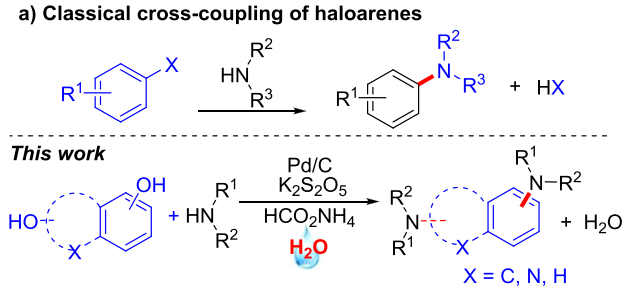
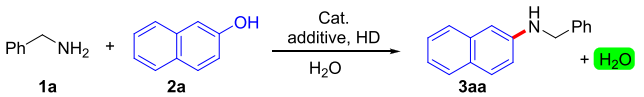
Scheme 2. Methods for Direct Amine Arylations



amination and cyclization of phenols remains unexplored. Owing to our ongoing interest in hydrogen-transfer reactions,[14] we recently reported an *N*-arylation transformation in which indoline reactants were treated as hydrogen donors through hydrogen-transfer-mediated activation.[15] Inspired by this work, here we report a green and efficient approach to synthesize aryl amines from phenols and amines via a direct aqueous hydrogen-transfer coupling.

Initially, the reaction of benzylamine (**1a**) and 2-naphthol (**2a**) was selected as a model system to screen effective parameters. Using $NaBH_4$ as hydride source and toluene as solvent, additives including *t*-BuOK, $NaHSO_3$, $NaOCH_3$, $Na_2S_2O_5$, and $K_2S_2O_5$ were examined under N_2 at 120 °C (entries 1–5). $K_2S_2O_5$ afforded a higher yield of product **3aa** (61%) compared with other additives. Pd/C was the best catalyst among the palladium catalysts evaluated (Table 1, entries 6–8). The reaction yield was greatly reduced when no hydrogen source was used (entry 9). Next, several hydrogen sources were examined in combination with $K_2S_2O_5$; it was found that the product was obtained in 73% yield when HCO_2NH_4 was used as an alternative hydrogen source (Table 1, entries 10–13). Altering the reaction temperature (80, 100, and 140 °C) had no obvious effect on the yield (Table 1, entry 14), which established the optimal conditions.

Table 1. Screening Conditions[a]

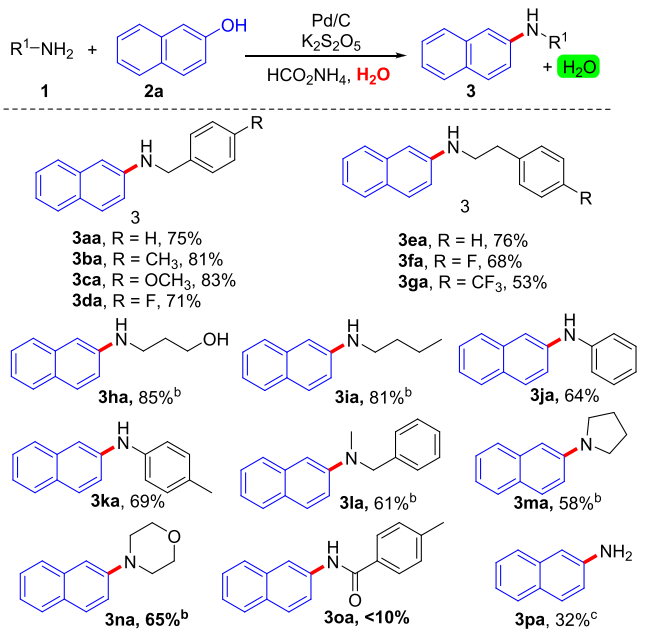


entry	cat. (5 mol %)	additive (50 mol %)	HD	3aa, yield[b] (%)
1	Pd/C	*t*-BuOK	$NaBH_4$	trace
2	Pd/C	$NaHSO_3$	$NaBH_4$	34
3	Pd/C	$NaOCH_3$	$NaBH_4$	29
4	Pd/C	$Na_2S_2O_5$	$NaBH_4$	57
5	Pd/C	$K_2S_2O_5$	$NaBH_4$	61
6	$PdCl_2$	$K_2S_2O_5$	$NaBH_4$	18
7	$Pd(PPh_3)_4$	$K_2S_2O_5$	$NaBH_4$	
8	$Pd(dba)_2$	$K_2S_2O_5$	$NaBH_4$	27
9	Pd/C	$K_2S_2O_5$		19
10	Pd/C	$K_2S_2O_5$	2-propanol	21
11	Pd/C	$K_2S_2O_5$	HCO_2H	44
12	Pd/C	$K_2S_2O_5$	HCOONa	62
13	Pd/C	$K_2S_2O_5$	HCO_2NH_4	(68, 73, 71)[c]
14	Pd/C	$K_2S_2O_5$	HCO_2NH_4	(74, 76, 63)[d]

[a]Reaction conditions: **1a** (0.45 mmol), HD (1 equiv), **2a** (0.3 mmol), Pd catalyst (5 mol %), temperature (120 °C), and additive (50 mol %) in water (1.0 mL) for 16 h, N_2. [b]Isolated yield. [c]HCO_2NH_4 (1, 2, and 4 equiv). [d]Yields achieved at temperatures of 140, 100, and 80 °C, respectively.

Having establishing the reaction conditions, different amine substrates were evaluated (Scheme 3). Different amines **1** reacted with 2-naphthol (**2a**) with high efficiency. Electron-donating groups on the phenyl ring of the benzylamines resulted in relatively high yields (81–83%, **3ba–3ca**) compared with the substituent-free (75%, **3aa**) and fluoride-substituted (71%, **3da**) substrates. In these cases, the nucleophilicity of the corresponding benzylamines was enhanced by the increased electron density, which improved the condensation process in this transformation. Similarly, phenylethylamines (**1e–1g**) performed effective coupling to produce desired products **3ea–3ga**. Alkyl amines 3-amino-propanol and butylamine reacted smoothly with 2-naphthol, providing **3ha** and **3ia** in 85% and 81% yields, respectively. Compounds **3ja** and **3ka** were obtained in moderate yields when aniline and *p*-toluidine were employed to react with 2-naphthol. In addition, we found that this amination methodology is suitable for use with secondary amines and 2-naphthol, and we successfully synthesized a variety of 2-dialkylamino-naphthalenes (**3la–3na**). The reaction of **2a** with 4-methylbenzamide afforded naphthylamine **3oa** in a very low yield. Pleasingly, desired product **3pa** was detected when NH_3 was applied under these reaction conditions.

Scheme 3. Substrate Scope of Amines[a]



[a]Standard conditions: **1** (0.45 mmol), **2** (0.3 mmol), HCO_2NH_4 (2 equiv), Pd/C (5 mol %), and additive (0.15 mol) in water (1.0 mL) at 100 °C for 16 h, N_2. [b]**1** (0.9 mmol, 3 equiv). [c]5 bar of NH_3.

We next explored the reactions of different amines **1** with different phenols **2**, producing arylamines **3ab–3bh** in 46%–81% isolated yields (Scheme 4). Electron-donating groups on the naphthols led to higher yields compared with electron-withdrawing groups (**3ab–3ac**). Both α-naphthol and phenol were evaluated to produce arylamines **3ad–3ie** in moderate yields. Gratifyingly, benzylamine **3af** was obtained in 58% yield when using 2-hydroxyanthracene as substrate. Finally, the scope of heterocyclic phenols was investigated, such as indol-5-

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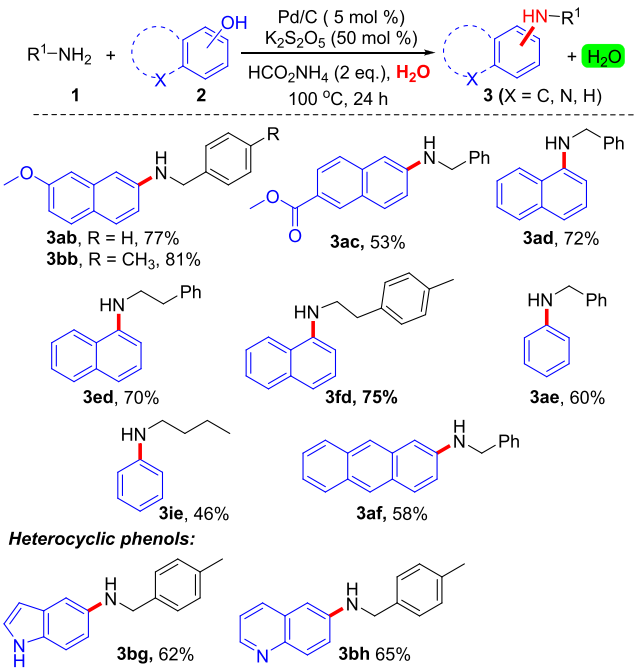
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 4. Substrate Scope[a]

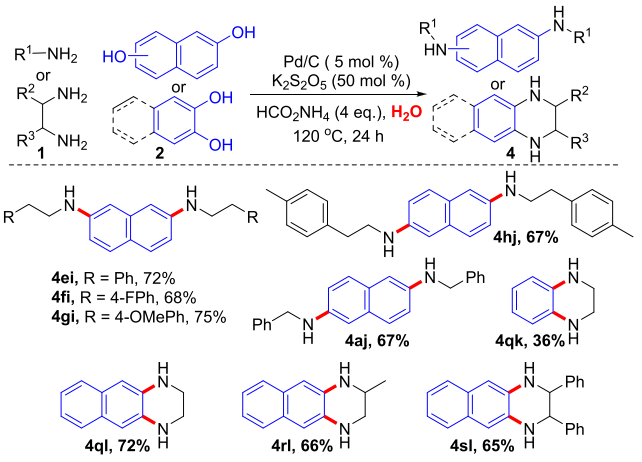


[a]Standard conditions: **1** (0.45 mmol), **2** (0.3 mmol), HCO_2NH_4 (2 equiv), Pd/C (5 mol %), and $K_2S_2O_5$ (0.5 equiv) in water (1.0 mL) at 100 °C for 16 h.

ol and quinolin-6-ol, affording the aminoindole and aminoquinoline target products in moderate yields.

To further evaluate the synthetic utility, this catalytic system was applied to the direct deamination of phenols. 1,6-Dihydroxynaphthalene, 2,7-dihydroxynaphthalene, and 2,6-dihydroxynaphthalene were examined, affording the corresponding diamination products in 67%−75% yields (**4ei**−**4aj**). Interestingly, the reactions of 2,3-diamines (**1q**, **1r**, and **1s**) with 2,3-dihydroxynaphthalene **2** (**2k**, **2l**) were tested, giving the cyclization products (**4qk**−**4sl**) (Scheme 5).

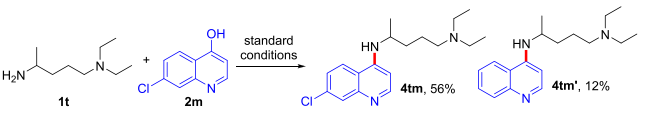
Scheme 5. Dual Amination and Cyclization of Dihydroxynaphthalene[a]



[a]Standard conditions: **1** (0.9 mmol), **2** (0.3 mmol), HCO_2NH_4 (2 equiv), Pd/C (5 mol %), and $K_2S_2O_5$ (0.5 equiv) in water (1.0 mL) at 100 °C for 16 h.

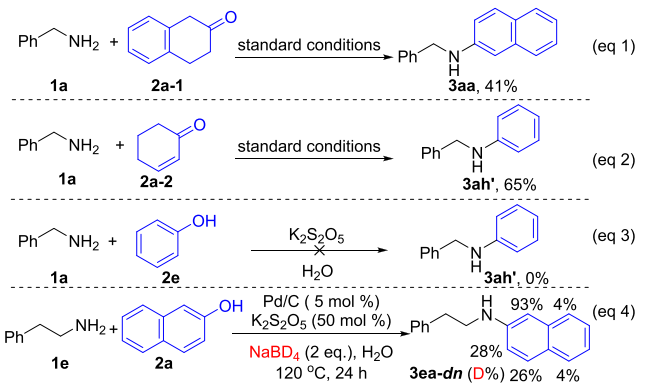
We were interested in elucidating the utility of our synthetic methods. Chloroquine phosphate, a broadly used antimalarial drug, has been shown to have apparent efficacy and acceptable safety against COVID-19.[16] Therefore, we selected 2-amino-5-diethylaminopentane (**1t**) and 7-chloroquinolin-4-ol (**2m**) as substrates under standard conditions to obtain the target product **4tm** and dechlorinated product **4tm′** (see the SI), providing a new synthetic route to access chloroquine derivatives (Scheme 6).

Scheme 6. Synthetic Application



With the aim of investigating the reaction mechanism, several control experiments were performed (Scheme 7). First,

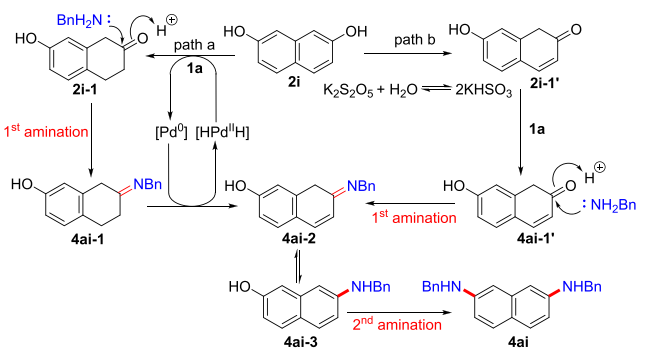
Scheme 7. Control Experiments



cyclohexanone and cyclohexenone were used instead of phenols, reacting smoothly with benzylamine to afford **3aa** and **3ah′** in 41% and 65% yields, respectively (eqs 1 and 2), indicating that **2a-1** and **2a-2** are reaction intermediates. In another reaction to further understand the mechanism, in the presence of $K_2S_2O_5$ (0.5 equiv) and no hydride source in water (1.0 mL) at 100 °C, benzylamine and phenol failed to give the target product (eq 3). Further, the deuterium-labeling experiment of $NaBD_4$ with **2a** led to **3ea-dn** deuterated on the naphthalene ring, which suggested that hydrogen transfer occurred from $NaBD_4$ to 2-naphthol **2a** (eq 4).

We proposed a possible reaction pathway for this hydrogen-transfer amination (Scheme 8). To begin with, HCO_2NH_4

Scheme 8. Plausible Reaction Pathways



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Org. Lett. XXXX, XXX, XXX−XXX

reacts with the palladium catalyst to generate an active $HPd^{II}H$ species. Next, 2-naphthol is hydrogenated to give ketone **2i-1**, regenerating the palladium catalyst. In the presence of $K_2S_2O_5$, intermediate **2i-1** performs the first amination with benzylamine (**1a**) to give key intermediate **4ai-1**. Then, the dehydrogenation of **4ai-1** produces intermediate **4ai-2** and releases the $[HPd^{II}H]$ species (see path a). Finally, tautomer **4ai-3** undergoes a second amination to form the final product **4ai**. Moreover, $K_2S_2O_5$ is crucial for product formation (see path b) because using $K_2S_2O_5$ as the sole additive resulted in only a small amount of amination product (see the SI). The addition of $K_2S_2O_5$ and H_2O enables the formation of a cyclohexenone intermediate from naphthol under these conditions.

In summary, we have developed a simple, green, and highly efficient direct mono/dual amination and cyclization using a hydrogen-transfer strategy. Various phenols and amines were evaluated using inexpensive HCO_2NH_4 as reductant in water, providing green and mild access to secondary/tertiary naphthylamines and chloroquine with different functionalities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02924.

Experimental procedures and copies of NMR spectra for all products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Zhongzhi Zhu − *School of Biotechnology and Health Sciences, Wuyi University, Jiangmen 529020, China*; Email: chenxiuwen2010@126.com

Xiuwen Chen − *School of Biotechnology and Health Sciences, Wuyi University, Jiangmen 529020, China*; orcid.org/0000-0003-3301-6730; Email: wyuchemzzz@126.com

Authors

Wanyi Liang − *School of Biotechnology and Health Sciences, Wuyi University, Jiangmen 529020, China*

Feng Xie − *School of Biotechnology and Health Sciences, Wuyi University, Jiangmen 529020, China*

Zhihai Yang − *School of Biotechnology and Health Sciences, Wuyi University, Jiangmen 529020, China*

Zheng Zeng − *Affiliated Hospital of Guilin Medical University, Guilin 541001, China*

Chuanjiang Xia − *School of Biotechnology and Health Sciences, Wuyi University, Jiangmen 529020, China*

Yibiao Li − *School of Biotechnology and Health Sciences, Wuyi University, Jiangmen 529020, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02924

Author Contributions

[§]W.L. and F.X. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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