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Ligand-free CuCl-catalyzed C–N bond formation in aqueous media

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ABSTRACT

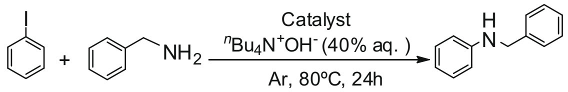
CuCl-catalyzed N-arylation of alkyl amines and N-heterocycles with substituted aryl iodides and bromides can be carried out in 40% $^n\mathrm{Bu_4N^+OH^-}$ aqueous solution without any ligands.

Transition-metal-catalyzed formation of C–N bond is considered to be an important strategy that finds wide applications in the synthesis of many substances such as drugs, materials, and natural products.[1] Among the few metals that are able to perform such transformations, copper stands out as a convenient alternative to palladium catalysts, because copper salts are often cheap and environmentally benign. Several published reviews have detailed the recent progress of copper-catalyzed C–N coupling reactions.[2,3] However, ligands must be applied in most successful examples. Although some ligand-free copper-catalyzed N-arylation reactions have been reported, they showed high substrate limitation.[4] Reactions in aqueous media are of great interest for large-scale industrial processes for economic and safety reasons. These procedures have already been adopted successfully which replace partially or fully organic solvents by water in copper-catalyzed N-arylation reactions.[5]

From the standpoint of green chemistry, the development of more environmentally benign reaction media, such as water, in place of organic solvents would be desirable.[6] To accord further with the demand of green chemistry, herein we report a simple protocol of CuCl-catalyzed formation of C–N bond in aqueous media without any ligands. To the best of our knowledge, thus far there has been only one reported example of N-arylation in aqueous media in the absence of ligands in which active copper is used as a catalyst in the condition of microwave irradiation.[7]

We reported previously a method constructed C–N bond with $\mathrm{Me_4N^+OH^-}$ as a base in organic solvent.[8] No product was observed with water as a solvent in this protocol. Inspired by this experimental result we wonder whether water can be used as a solvent by the alternative of base. $\mathrm{Et_4N^+OH^-}$ and $^n\mathrm{Bu_4N^+OH^-}$ were applied in the reaction of iodobenzene with benzylamine catalyzed by $\mathrm{Cu_2O}$ for this purpose. To our delight, N-benzylaniline was formed in more than 90% GC-yields mediated by $^n\mathrm{Bu_4N^+OH^-}$ (Table 1, entry 3). Encouraged by this finding, a brief search of other reaction conditions was carried out after finding the best aqueous media. The results are listed in Table 1. A series of copper catalysts were screened extensively. $\mathrm{Cu_2O}$, CuI, CuBr, $\mathrm{Cu(OAc)_2}$, $\mathrm{CuBr_2}$, and $\mathrm{CuSO_4}$ were found to be inferior to CuCl as catalysts for the C–N coupling reaction (Table 1, entries 3–9). No reaction was observed without any copper source (Table 1, entry 10). The yields of product decreased when reducing or elevating reaction temperatures (Table

Table 1
Cu/ligand-free catalyzed N-arylation of benzylamine and iodobenzene in water[a]



Entry	Amount of catalyst (mol %)	T/°C	Yield[b] (%)
1	$\mathrm{Cu_2O}$ (5)	80	—[c]
2	$\mathrm{Cu_2O}$ (5)	80	26[d]
3	$\mathrm{Cu_2O}$ (5)	80	91
4	CuI (5)	80	70
5	CuBr (5)	80	44
6	**CuCl (5)**	**80**	**99**
7	$\mathrm{Cu(OAc)_2}$ (5)	80	78
8	$\mathrm{CuBr_2}$ (5)	80	83
9	$\mathrm{CuSO_4}$ (5)	80	90
10	—	80	—
11	CuCl (5)	90	82
12	CuCl (5)	70	67
13	CuCl (2)	80	87
14	CuCl (1)	80	84
15	CuCl (5)	80	22[e]

[a] Reaction conditions: iodobenzene (1 mmol), benzylamine (1.5 mmol), and base (1 mL)in the presence of Cu catalyst at 80 °C under Ar atmosphere for 24 h.
[b] GC yield.
[c] 1 mL $\mathrm{Me_4N^+OH^-}$ (40% aq) is used.
[d] 1 mL $\mathrm{Et_4N^+OH^-}$ (40% aq) is used.
[e] In air.

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0040-4039/$ - see front matter Crown Copyright © 2009 Published by Elsevier Ltd. All rights reserved.
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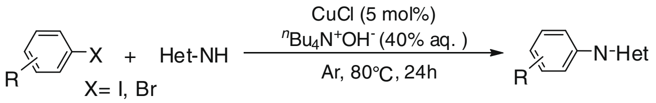
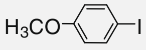
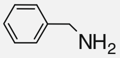
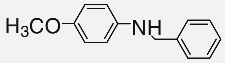
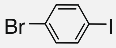
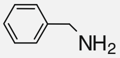
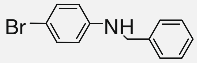
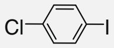
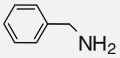
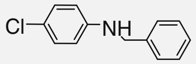
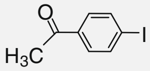
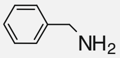
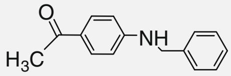
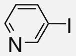
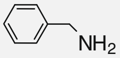
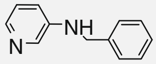
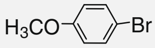
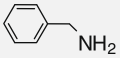
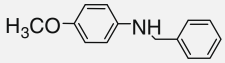
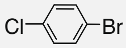
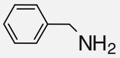
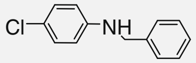
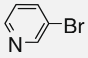
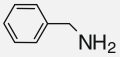
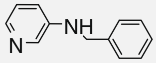
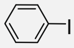
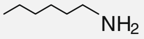
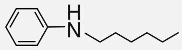
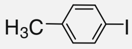
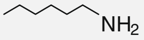
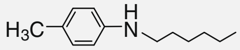
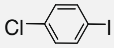
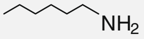
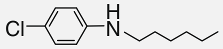
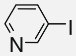
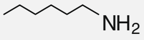
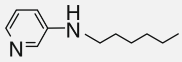
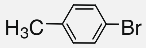
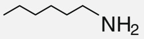
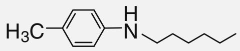
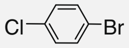
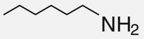
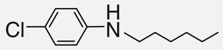
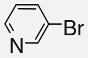
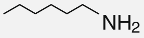
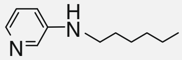
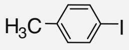
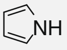
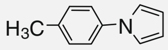
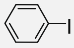
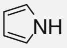
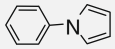
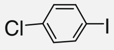
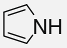
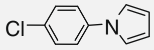
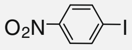
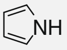
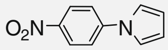
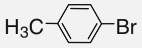
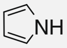
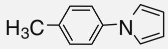
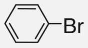
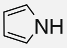
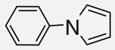
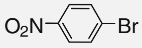
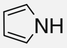
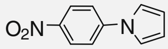
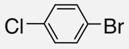
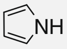
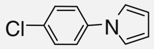
Table 2

CuCl/ligand-free catalyzed N-arylation of aryl halides with N-heterocyclic compounds and alkyl amines in water[a]



Entry	Aryl halide	Het-NH	Product	Yield[b] (%)
1				96
2				80
3				83
4				81
5				80
6				76
7				71
8				61
9				77
10				86
11				72
12				75
13				64
14				62
15				70
16				63
17				86
18				72
19				50
20				51
21				65
22				43
23				57

[a] Reaction conditions: aryl halide (1 mmol), N-heterocyclic compound or alkyl amine (1.5 mmol), ^{n}Bu$_4$N$^+$OH$^-$ (40% aq) (1 mL), and CuCl (0.05 mmol) at 80 °C under Ar atmosphere for 24 h.

[b] Yields are given for isolated products.

1, entries 11 and 12). In addition, the yield of product reduced drastically to 22% when the reaction was carried out in air (Table 1, entry 15). The yields of product were 87% and 84%, respectively, when the amount of catalyst CuCl was reduced to 2 mol % and 1 mol % (Table 1, entries 13 and 14). In summary, the optimal results were obtained when amine (1.5 equiv) and aryl halide (1.0 equiv) were allowed to react with 5 mol % of CuCl stirred in 40% aq ^{n}Bu$_4$N$^+$OH$^-$ at 80 °C under argon for 24 h.

With this optimized procedure in hand, we explored the general scope of the reaction and screened N-arylations of alkyl amines and N-heterocycles with substituted aryl iodides.[9] As shown in Table 2, the coupling of alkyl amines and aryl iodides with electron-withdrawing and electron-donating functional groups all gave more than 60% yield. We discovered that the N-arylation reactions of alkyl amines with aryl iodides including electron-donating substituents were better than those with electron-withdrawing ones

(Table 2, entries 1–4). The reactions of N-heterocycles with aryl iodide moieties (Table 2, entries 16–19) and of alkyl amine with heteroaryl iodide (Table 2, entry 5 and 12) were successful in the protocol, leading to the desired products in good yields. On the basis of the successful examples, the coupling reactions of alkyl amines with aryl bromides (Table 2, entries 6–8, 13–15, and 20–23) were also explored and moderate yields were obtained. However, to our disappointment, the N-arylations of alkyl amines and N-heterocycles with aryl chlorides were not observed in the present protocol.[10]

In conclusion, we developed a practical and simple protocol for the N-arylations of amines with differently substituted aryl halides. The aqueous $^{n}Bu_4N^{+}OH^{-}$ was used as a base and as a solvent which plays the role of a phase transfer catalyst (PTC). The results obtained were better than those of $Me_4N^{+}OH^{-}$ and $Et_4N^{+}OH^{-}$ in the same reaction conditions. The versatility, convenient operation, and environmental friendliness of this procedure make it easily transferrable to industrial applications.

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9. *General experimental procedure*. A Schlenk tube was charged with Cu salt (0.1 mmol) and solid substrate, if present, evacuated, and backfilled with argon three times. Then, liquid reagents (aryl halides or alkyl amines and N-heterocycles), 40% aq base solutions (1 mL) were added under Ar. The reaction vessel was closed and placed under stirring in a preheated oil bath at 80 °C. The reaction mixture was stirred for 24 h. The mixture was cooled to room temperature and partitioned between ethyl acetate and aq HCl, the organic layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography to provide the desired product. Selected spectral and analytical data for *N-Benzyl-4-methoxybenzenamine* (Table 2, entries 1 and 6): ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.36–7.26 (m, 5H), 6.78 (d, J = 8.4 Hz, 2H), 6.63 (d, J = 8.4 Hz, 2H), 4.29 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 152.4, 142.5, 139.8, 128.7, 127.6, 127.3, 115.1, 114.3, 55.9, 49.4. HRMS calcd $C_{14}H_{15}NO$: 213.1154. Found: 213.1160. *N-Hexyl-4-methylbenzenamine* (Table 2, entries 10 and 13): ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 6.97 (d, J = 8.1 Hz, 2H), 6.53 (d, J = 8.4 Hz, 2H), 3.07 (t, J = 7.0 Hz, 3H), 2.22 (s, 3H), 1.61 (m, 2H), 1.37 (m, 6H), 0.91 (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 146.2, 129.7, 126.5, 113.1, 44.6, 31.7, 30.9, 29.6, 26.9, 22.7, 20.4, 14.1. HRMS calcd $C_{13}H_{21}N$: 191.1674. Found: 191.1678. *1-p-tolyl-1H-pyrrole* (Table 2, entries 16 and 20): ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.29–7.20 (m, 4H), 7.05 (d, J = 1.5 Hz, 2H), 6.33 (d, J = 1.5 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 138.6, 135.3, 130.1, 120.5, 119.4, 110.1, 20.8. HRMS calcd $C_{11}H_{11}N$: 157.0891. Found: 157.0895.
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