Efficient Iron/Copper Cocatalyzed N-Arylation of Arylamines with Bromoarenes

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Abstract: $Fe(acac)_3$ and $Cu(OAc)_2 \cdot H_2O$ were found to effectively promote the C–N cross-coupling reaction in the presence of K_2CO_3 as the base. A series of diaryl amine with different substituents can be synthesized in moderate to good yields. This efficient and economic method is attractive for applications on an industrial scale.

Key words: catalysis, iron, copper, diaryl amine

Diaryl amines are prevalent functional units in compounds that are of numerous drugs, materials, and natural products.[1] Therefore, considerable effort has been made in the development of efficient strategies for their constructions. The transition-metal-catalyzed cross-coupling of anilines and aryl halides is one of the most powerful and straightforward methods for the preparation of diaryl amines. During the past years, significant improvements have been achieved in the copper-catalyzed Ullmann reactions[2,3] and the palladium-catalyzed Buchwald–Hartwig reactions.[4,5] But these reactions often require stoichiometric amounts of copper reagents or ligands to promote the reactions. So it is a major goal for organic synthesis to develop less expensive and environmentally more benign catalysts. Iron salts are inexpensive, relatively less toxic, and more environmentally benign in comparison to other transition metals. Following the pioneering work by Tamura and Kochi,[6] the iron salt catalyzed C–N bond-forming reaction is an alternative and promising strategy.[7] However, to our knowledge, the use of iron complexes associated with other metals to form diaryl amine product is rare.[8] Recently, Fu and co-workers[8a] developed an iron/copper cooperative catalysis for N-arylation process of aromatic amines by using the $FeCl_3$, CuO, and rac-BINOL as the catalyst system. Liu and co-workers[8b] disclosed a novel and versatile arylation protocol involving the use of Fe_2O_3, $Cu(acac)_2$, and Cs_2CO_3 under microwave irradiation. However, the yield of N-arylation of aryl iodide with aryl amines was low. Apparently, an effective method of N-arylation of arylamines is still to be found. Herein, we reported C–N cross-coupling reactions of arylamines with bromoarenes based on simple and inexpensive $Fe(acac)_3$, $Cu(OAc)_2 \cdot H_2O$, and K_2CO_3 (Scheme 1). A variety of useful functional groups were tolerated, and moderate to good yields of the diaryl amine products were obtained. The catalyst system was also suitable for the cross-coupling of heteroarylamines with aryl bromides.

Table 1 Optimization of Reaction Conditions[a]

Entry	Fe source	Cu source	Base	Yield (%)[b]
1	$Fe(acac)_3$	CuI	Cs_2CO_3	55
2	$Fe(acac)_3$	CuI	K_2CO_3	60
3	$Fe(acac)_3$	CuI	Et_3N	0
4	$Fe(acac)_3$	CuI	K_3PO_4	58
5	$Fe(acac)_3$	$CuSO_4 \cdot 5H_2O$	K_2CO_3	55
6	$Fe(acac)_3$	$Cu(OAc)_2 \cdot H_2O$	K_2CO_3	66
7	$Fe(acac)_3$	Cu	K_2CO_3	45
8	$Fe(acac)_3$	–	K_2CO_3	0
9	$Fe(NO_3)_3 \cdot 9H_2O$	$Cu(OAc)_2 \cdot H_2O$	K_2CO_3	0
10	Fe_2O_3	$Cu(OAc)_2 \cdot H_2O$	K_2CO_3	10
11	–	$Cu(OAc)_2 \cdot H_2O$	K_2CO_3	6
12	$Fe(acac)_3$	$Cu(OAc)_2 \cdot H_2O$	K_2CO_3	75[c]
13	$Fe(acac)_3$	$Cu(OAc)_2 \cdot H_2O$	K_2CO_3	89[d]
14	–	$Cu(acac)_2$	K_2CO_3	37[e]
15	acac	$Cu(OAc)_2 \cdot H_2O$	K_2CO_3	15[f] 52[g] 58[h]
16	acac	$Cu(acac)_2$	K_2CO_3	53[i] 58[j]

[a] The reaction was performed with bromobenzene (0.5 mmol), *p*-toluidine (0.75 mmol), Fe source (10 mol%), Cu source (10 mol%), and base (1.0 mmol) in DMF (0.8 mL) at 135 °C for 20 h.

[b] Isolated yield based on **1a**.

[c] Conditions: Fe source (10 mol%), Cu source (20 mol%).

[d] Conditions: Fe source (20 mol%), Cu source (20 mol%).

[e] Conditions: Cu source (20 mol%).

[f] Conditions: acac = acetylacetonate (20 mol%), Cu source (20 mol%).

[g] Conditions: acac (40 mol%), Cu source (20 mol%).

[h] Conditions: acac (60 mol%), Cu source (20 mol%).

[i] Conditions: acac (10 mol%), $Cu(acac)_2$ (20 mol%), K_2CO_3 (2 equiv).

[j] Conditions: acac (10 mol%), $Cu(acac)_2$ (20 mol%), K_2CO_3 (3 equiv).

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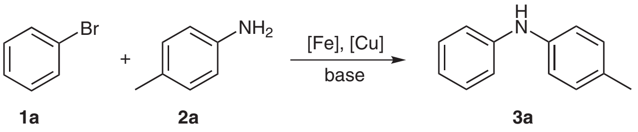
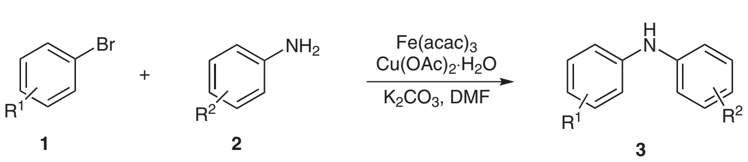


Scheme 1

In our initial study, the reaction between aryl bromoarene (**1a**) and *p*-toluidine (**2a**) was chosen as a model for the coupling reaction. As shown in Table 1, a series of experiments were carried out to evaluate the ability of various iron sources, Cu sources, and bases for the N-arylation process. By investigating into the base system, no product was obtained when Et_3N was used as the base (Table 1, entry 3). Moderate yields were obtained when K_3PO_4, K_2CO_3, or Cs_2CO_3 was used as the base (Table 1, entries 1, 2, and 4). So the inexpensive K_2CO_3 was used in experiments to investigate the effect of iron sources and copper sources on the coupling reaction. $Cu(OAc)_2{\cdot}H_2O$ and $Fe(acac)_3$ was found to be the best combination to catalyze this reaction (Table 1, entries 2 and 5–15). Other iron sources $Fe(NO_3)_3{\cdot}9H_2O$ or Fe_2O_3 together with $Cu(OAc)_2{\cdot}H_2O$ gave no product or the product in poor yield, respectively (Table 1, entries 9 and 10), while copper sources $CuSO_4{\cdot}5H_2O$ and Cu power gave the product in moderate yields (Table 1, entries 5 and 7). Subsequently, a blank test was performed with only an iron source (no copper source) and showed that the arylation did not proceed at all (Table 1, entry 8). Low yield of diaryl amine was obtained when using the copper source in the absence of the iron salt (Table 1, entries 11 and 14). When the ligand acac (acetylacetonate) was added instead of $Fe(acac)_3$, we only got the product at low yields (Table 1, entry 15). And when $Cu(acac)_2$ was used in combination with acac, the product was obtained in moderate yield. We then increased the amount of the base from 2 to 3 equivalents but with little improvement in yield (Table 1, entry 16). Finally, it was concluded that the optimal conditions for the diaryl amines involved the use of $Fe(acac)_3$, $Cu(OAc)_2{\cdot}H_2O$, and K_2CO_3 in DMF at 135 °C.

Table 2 $Fe(acac)_3/Cu(OAc)_2{\cdot}H_2O$-Catalyzed C–N Cross-Coupling of Various Anilines and Aryl Bromoarenes[a]



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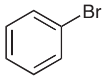
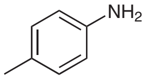
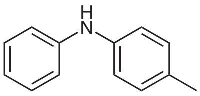
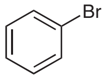
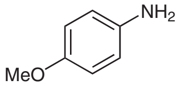
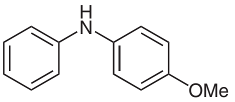
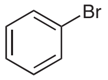
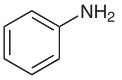
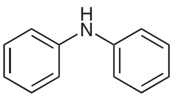
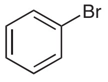
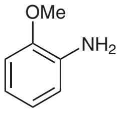
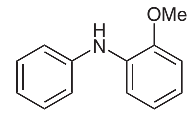
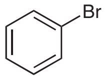
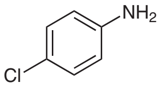
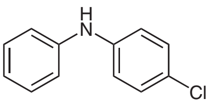
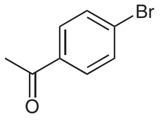
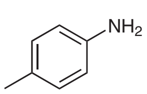
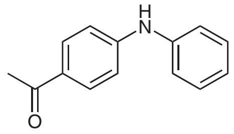
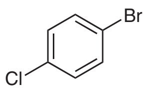
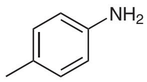
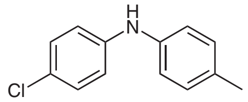
1				89
2				91
3				65
4				87
5				44
6				85
7				84

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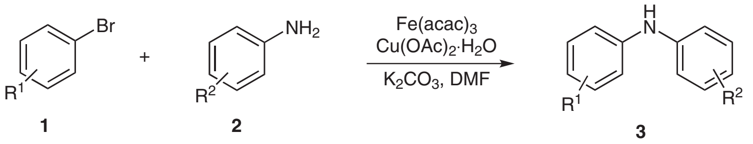
Table 2 Fe(acac)$_3$/Cu(OAc)$_2$·H$_2$O-Catalyzed C–N Cross-Coupling of Various Anilines and Aryl Bromoarenes[a] (continued)



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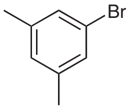
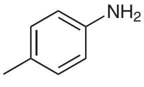
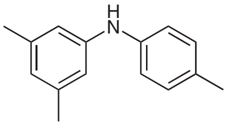
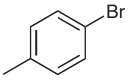
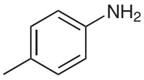
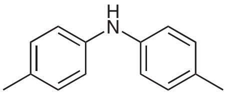
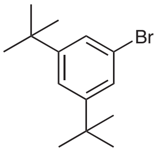
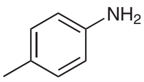
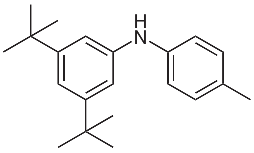
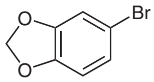
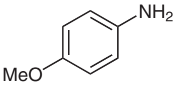
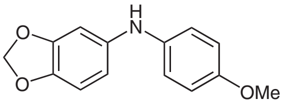
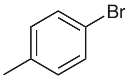
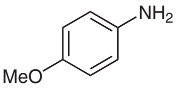
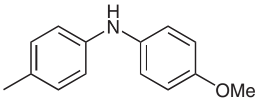
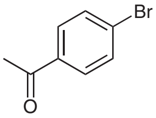
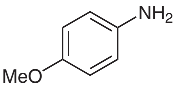
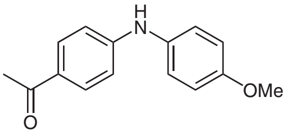
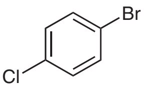
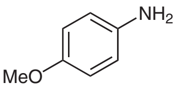
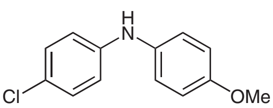
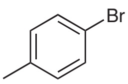
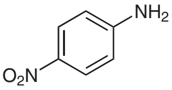
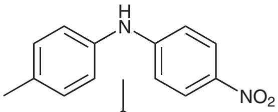
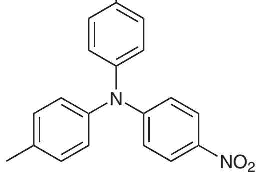
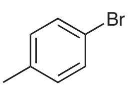
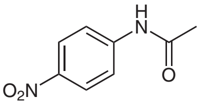
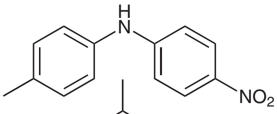
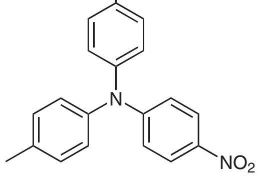
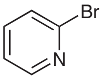
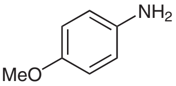
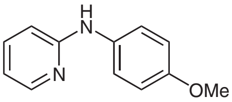
8				74
9				85
10				73
11				67
12				92
13				82
14				90
15			 	56 21
16			 	52 21
17				64

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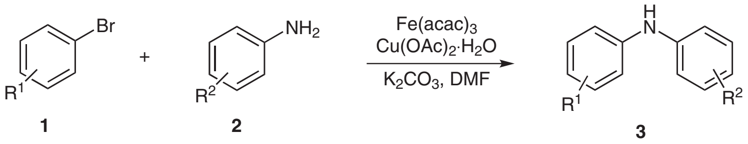
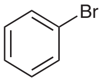
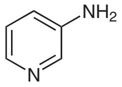
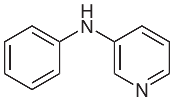
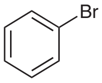
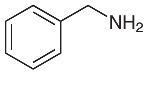
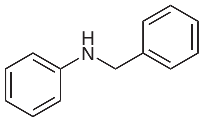
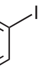
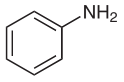
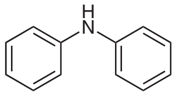
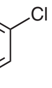
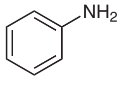
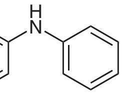
Table 2 Fe(acac)$_3$/Cu(OAc)$_2$·H$_2$O-Catalyzed C–N Cross-Coupling of Various Anilines and Aryl Bromoarenes[a] (continued)



Entry	Substrate **1**	Substrate **2**	Product **3**	Yield (%)[b]
18				78
19				78
20				92
21				0

[a] The reaction was performed with aryl bromoarenes (0.5 mmol), anilines (0.75 mmol), K$_2$CO$_3$ (1.0 mmol), Fe(acac)$_3$ (20 mol%), Cu(OAc)$_2$·H$_2$O (20 mol%) in DMF (0.8 mL) at 135 °C for 20 h.

[b] Isolated yield based on aryl bromoarenes.

Under the optimized conditions, we set out to study the effect of substituent for the coupling reactions which involved various aryl bromides and aryl amines (Table 2). Firstly, the reaction of substituted arylamines with aryl bromoarene were studied. 4-Methyl-, 4-methoxy-, 2-methoxy-, and 4-chloroaniline underwent reaction with bromobenzene to give products in 44–91% yields (Table 2, entries 1–5). These reactions indicated that arylamines having electron-donating groups showed greater reactivity in comparison to those with electron-withdrawing groups (Table 2, entries 1, 2, 4 and 5). The steric hindrance of anilines also exerted some effect on this reaction as indicated from the reaction of 4-methoxyaniline, and 2-methoxyaniline gave high yields with bromoarenes (Table 2, entries 2 and 4). As for bromoarenes, electron-neutral (Table 2, entries 6, 7, 13, and 14) and electron-rich ones (Table 2, entries 8–12) offered the desired products in good yields. The reaction of 4-nitroaniline with 1-bromo-4-methylbenzene provided the target product in moderate yield together with a significant quantity of triarylamine (Table 2, entry 15). Because of the basic conditions and the reaction temperature of 135 °C, the acetyl group of *N*-(4-nitrophenyl)acetamide was cleaved to provide the above products (Table 2, entry 16). We were pleased to note the reaction conditions were also suitable for the cross-coupling of pyridin-3-amine and phenylmethanamine with bromobenzene (Table 2, entries 18 and 19), and 2-bromopyridine with 4-methoxyaniline could also give the product in moderate yield (Table 2, entry 17). Additionally, phenyl iodide was found to be more efficient than phenyl bromide while phenyl chloride failed to offer the amination product (Table 2, entries 20 and 21).

These reaction conditions were also suitable for the cross-coupling of heteroarylamines with aryl bromides. A variety of substituted aryl bromides were tested under the optimized reaction conditions with imidazole, which afforded the corresponding coupling products in excellent yields (Table 3, entries 1–3). Hence, imidazole derivatives 1*H*-imidazole-4-carboxylic acid and ethyl 1*H*-imidazole-4-carboxylate reacted with 1-bromo-4-methylbenzene to give the products in good to moderate yields (Table 3, entries 4 and 5). Furthermore, triazole, pyrazole, and indole underwent reaction to provide coupling products in 61–93% yields (Table 3, entries 6–8).

In summary, we have demonstrated an efficient iron/copper-catalyzed N-arylation of arylamines with aryl bromoarenes. From a synthesis point of view, a series of diaryl amines was obtained in moderate to good yields. Due to the relatively low cost and commercial availability of the metal salts and inorganic base, the reaction was very convenient and could be easily applied on an industrial scale.

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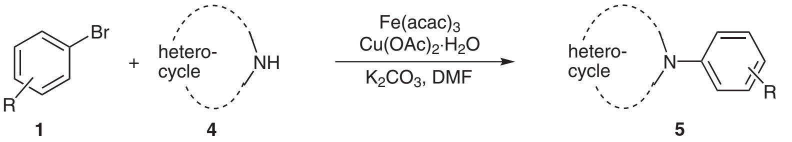
Table 3 Fe(acac)$_3$/Cu(OAc)$_2$·H$_2$O-Catalyzed C–N Cross-Coupling of Heteroarylamines and Aryl Bromoarenes[a]



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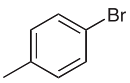
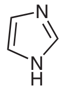
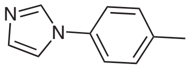
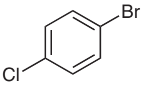
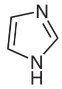
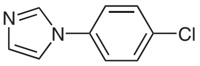
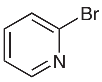
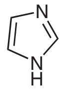
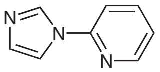
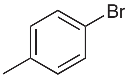
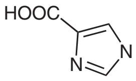
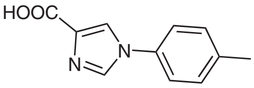
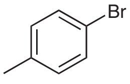
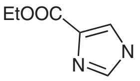
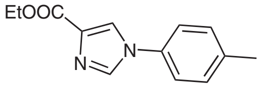
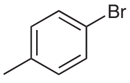
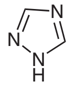
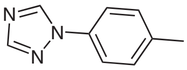
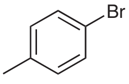
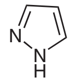
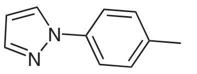
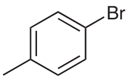
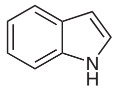
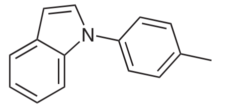
1				98
2				92
3				95
4				82
5[9]				52
6				81
7				93
8				61

[a] The reaction was performed with aryl bromoarenes (0.5 mmol), heteroarylamines (0.75 mmol), K$_2$CO$_3$ (1.0 mmol), Fe(acac)$_3$ (20 mol%), Cu(OAc)$_2$·H$_2$O (20 mol%) in DMF (0.8 mL) at 135 °C for 20 h.

[b] Isolated yield based on aryl bromoarenes.

Acknowledgment

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(9) **General Procedure for the Synthesis of Diaryl Ethers**
A Schlenk tube equipped with a magnetic stir bar was charged with *p*-toluidine (**2a**, 0.75 mmol, 80 mg), K_2CO_3 (138 mg, 1 mmol), $Fe(acac)_3$ (34.4 mg, 20 mo%), and $Cu(OAc)_2·H_2O$ (20 mg, 20 mol%). Under a nitrogen atmosphere, bromobenzene (**1a**, 0.5 mmol, 78.0 mg) was added followed by dry DMF (0.8 mL). The reaction mixture was then heated in an oil bath of 135 °C. After being stirred at this temperature for 20 h, the mixture was cooled to r.t. and diluted with Et_2O. The resulting suspension was directly filtered through a pad of Celite, the filtrate was concentrated, and the crude mixtures were purified by column chromatography on silica gel using PE–EtOAc solvent mixture as the eluent.

4-Methyl-*N*-phenylaniline (3a)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (t, *J* = 7.7 Hz, 2 H), 7.07 (d, *J* = 8.3 Hz, 2 H), 6.94–7.00 (m, 4 H), 6.87 (t, *J* = 7.3 Hz, 1 H), 5.58 (br s, 1 H), 2.29 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.35, 140.68, 131.34, 130.30, 129.75, 120.71, 119.31, 117.26, 21.15. HRMS (EI$^+$): *m/z* calcd for $C_{13}H_{13}N$ [M$^+$]: 183.1048; found: 183.1051.

Ethyl 1-*p*-Tolyl-1*H*-imidazole-4-carboxylate (Table 3, Entry 5)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (s, 1 H), 7.82 (s, 1 H), 7.30 (s, 4 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 2.42 (s, 3 H), 1.41 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.25, 138.99, 136.77, 135.30, 134.50, 131.02, 124.56, 122.02, 61.17, 21.481, 14.87. HRMS (EI$^+$): *m/z* calcd for $C_{13}H_{14}N_2O_2$ [M$^+$]: 230.1055; found: 230.1058.

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