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CuCl-catalyzed formation of C–N bond with a soluble base

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ABSTRACT

Tetramethylammonium hydroxide was used as a base instead of a traditional inorganic base in this copper-catalyzed system and some satisfactory results were obtained. Various functional groups were compatible under this reaction condition.

In recent years, many significant improvements in the formation of carbon–nitrogen bond catalyzed by transition-metals have been achieved.[1] Much attention has been paid on Pd-catalyzed arylation of amines in the past decades.[2] However, the drawbacks of Pd-catalyst systems such as high cost and toxicity are obvious. These drawbacks limit their massive applications for industrial scales. The use of a cheaper metal instead of Pd provides an attractive alternative. Due to the low price and environmental benignity, copper-catalyzed C–N coupling reactions are particularly attractive.[3] Several published reviews have detailed the recent progress of copper-catalyzed C–N coupling reactions.[3,4]

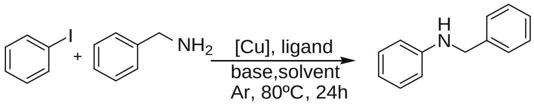
In most reported methods, inorganic solid bases are used as base in the C–N cross-coupling reaction while they are not usually soluble or soluble partially in reaction system, which makes the utilized efficiency of base reduce drastically. To the best of our knowledge, thus far there has been only one reported example of N-arylation with tetraethylammonium carbonate, a soluble base, as base. But, only N-arylation of imidazoles has been achieved.[5] Therefore, it is necessary and important to expand the scope of amines used as nucleophiles in this reaction system with a soluble base. Herein, we report a novel method to construct C–N bond mediated by tetramethylammonium hydroxide.

In our initial experiment, iodobenzene (1 equiv) was treated with benzylamine (1.5 equiv) in DMSO at 80 °C for 24 h with Cu_2O (0.1 equiv)/L1 (0.1 equiv) and $(CH_3)_4N^+OH^-$ (2 equiv). To our delight, *N*-benzylaniline was formed in more than 80% yields. Encouraged by this finding, different reaction conditions were tried. The results are listed in Table 1.

Bases influenced the progress of the reaction greatly. Moderate yields were obtained when $(Et_4N^+)_2CO_3{}^{2-}$, K_2CO_3, Cs_2CO_3, KOH, and K_3PO_4 were used. A high yield was obtained only when $(CH_3)_4N^+OH^-$ was used (Table 1, entries 1–5). Subsequently, several ligands L1–L5 were investigated for this coupling reaction

Table 1

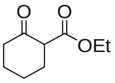
Optimization of reaction conditions for Cu-catalyzed N-arylation of benzylamine with iodobenzene



Entry	[Cu]	Ligand	Base	Solvent	Yield[a,b] (%)
1	Cu_2O	L1	$(CH_3)_4N^+OH^-$	DMSO	86
2	Cu_2O	L1	$(Et_4N^+)_2CO_3^{2-}$	DMSO	31
3	Cu_2O	L1	KOH	DMSO	19
4	Cu_2O	L1	K_3PO_4	DMSO	18
5	Cu_2O	L1	Cs_2CO_3	DMSO	17
6	Cu_2O	L1	K_2CO_3	DMSO	52
7	Cu_2O	L2	$(CH_3)_4N^+OH^-$	DMSO	61
8	Cu_2O	L3	$(CH_3)_4N^+OH^-$	DMSO	17
9	Cu_2O	L4	$(CH_3)_4N^+OH^-$	DMSO	25
10	Cu_2O	L5	$(CH_3)_4N^+OH^-$	DMSO	29
11	Cu_2O	L1	$(CH_3)_4N^+OH^-$	DMF	19
12	Cu_2O	L1	$(CH_3)_4N^+OH^-$	Dioxane	72
13	Cu_2O	L1	$(CH_3)_4N^+OH^-$	Isopropanol	49
14	Cu_2O	L1	$(CH_3)_4N^+OH^-$	Toluene	Trace
15	Cu_2O	L1	$(CH_3)_4N^+OH^-$	H_2O	Trace
16	$CuBr_2$	L1	$(CH_3)_4N^+OH^-$	DMSO	17
17	CuO	L1	$(CH_3)_4N^+OH^-$	DMSO	15
18	CuCl	L1	$(CH_3)_4N^+OH^-$	DMSO	91
19	$CuSO_4$	L1	$(CH_3)_4N^+OH^-$	DMSO	44
20	$Cu(Ac)_2$	L1	$(CH_3)_4N^+OH^-$	DMSO	81
21	CuI	L1	$(CH_3)_4N^+OH^-$	DMSO	72

[a] Reaction conditions: Iodobenzene 1.0 mmol; benzylamine 1.5 mmol; copper source 0.1 mmol; ligand 0.1 mmol; solvent 1 mL; base 2 mmol; temperature 80 °C; 24 h.

[b] Isolated yields.



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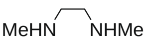

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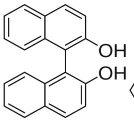

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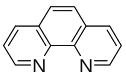

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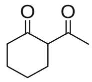

L5

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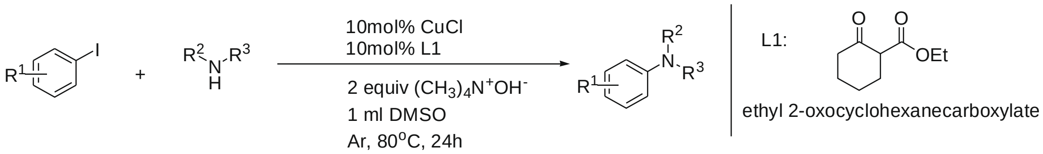
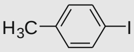
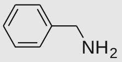
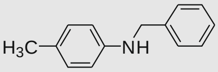
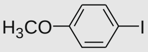
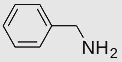
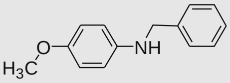
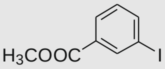
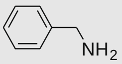
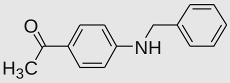
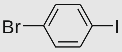
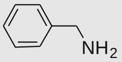
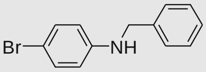
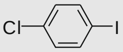
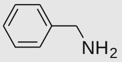
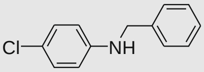
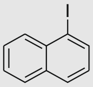
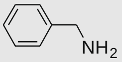
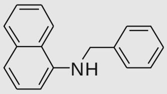
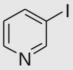
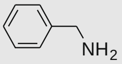
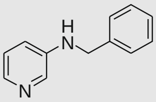
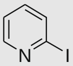
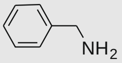
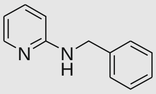
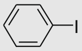
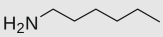
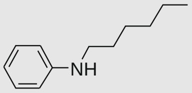
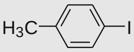
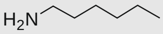
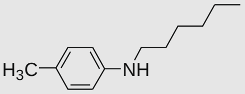
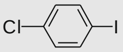
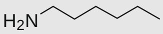
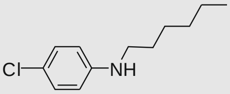
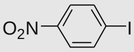
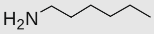
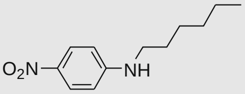
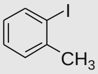
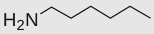
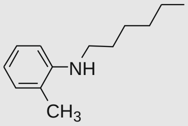
Table 2

CuCl/ L1-catalyzed N-arylation of alkyl amines and N-heterocycles with aryl iodides in the presence of $(CH_3)_4N^+OH^-$[a]



Entry	Aryl iodides	Amines	Product	Yield[b] (%)
1				80
2				70
3				74
4				86
5				78
6				68
7				65
8				72
9				87
10				74
11				81
12				68
13				56

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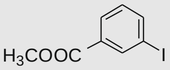
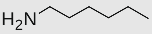
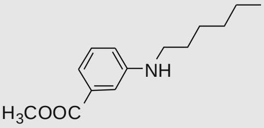
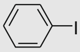
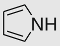
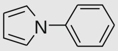
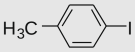
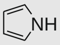
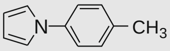
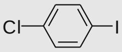
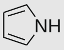
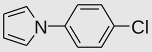
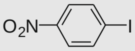
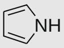
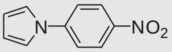
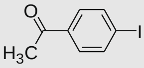
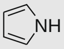
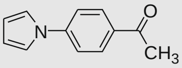
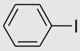
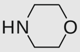
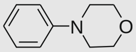
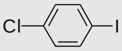
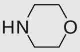
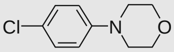
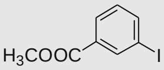
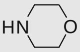
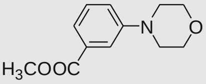
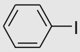
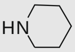
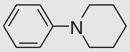
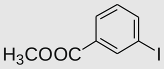
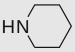
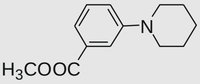
14				59
15				90
16				86
17				83
18				74
19				78
20				77
21				72
22				67
23				82
24				70

[a] Reaction conditions: aryl iodides 1.0 mmol; amines 1.5 mmol; CuCl 0.1 mmol; L1 0.1 mmol; DMSO 1 mL; $(CH_3)_4N^+OH^-$ 2 mmol; 80 °C; 24 h.

[b] Isolated yields.

and L1 gave the best result (entries 1, 6–9). Solvents also played an important role in this reaction. The experimental results suggested that DMSO was the best solvent among the screened ones, such as DMF, dioxane, toluene, and H_2O (Table 1, entries 1, 10–14). Other copper compounds (CuI, $CuSO_4$, $Cu(OAc)_2$, CuO, $CuBr_2$, and CuCl) were also evaluated. To our delight, CuCl gave a better yield even than Cu_2O (entries 1, 15–20).

With the optimum condition in hand, N-arylations of alkyl amines and N-heterocycles with substituted aryl iodides were examined to evaluate the scope and the generality of this catalytic system. The results are summarized in Table 2.[6]

We were delighted to find that the N-arylation of benzylamine with a variety of aryl iodides proceeded smoothly to give the corresponding products in good yields (65–86%) (Table 2, entries 1–8). Aliphatic amines also performed very well with 56–87% yields (Table 2, entries 9–14). Subsequently, other N-heterocycles, such as pyrrole, morpholine, and piperidine were also tested as the substrates. The reactions also appeared to work well (Table 2, entries 15–24). We discovered that the N-arylation reactions of amides with *p*-substituted aryl halides were easier than with *o*-substituted ones (Table 2, entries 10 and 13).

In conclusion, $(CH_3)_4N^+OH^-$ was found to be an efficient soluble base for the CuCl-catalyzed N-arylation of amines with aryl iodides. The development of an effective catalytic system for the coupling of amines and aryl iodides is still far from being satisfied. The further work of the mechanism of the reactions and the applications of this catalytic system are ongoing in our laboratory.

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6. *General experimental procedure.* All reagents and solvents, except the soluble base-$(CH_3)_4N^+OH^-$, were pure analytical grade materials purchased from commercial sources and were used without further purification. The soluble base, $(CH_3)_4N^+OH^-$, was dissolved in pure water and frozen at −10 °C for 24 h till they were turned into solid. Then, the base was put into lyophilizer and was dried for 8 h. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 300 MHz instrument with TMS as internal standard. TLC was carried out with 0.2 mm thick silica gel plates (GF254). The columns were hand packed with Silica Gel 60 (200–300). All reactions were carried out in a Schlenk tube equipped with a magnetic stir bar under Ar atmosphere. A Schlenk tube was charged with Cu salt (0.1 mmol), base (2 mmol), ligand (0.1 mmol), and solvent (1 ml) 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 resulting suspension was cooled to room temperature and filtered through a pad of filter paper with the help of 10 ml of ethyl acetate. The filtrate was concentrated and the residue was purified by silica gel chromatography.*N*-benzyl-4-methoxyaniline (entry 2, Table 2). ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.36–7.25 (5H, m), 6.79 (2H, d, J = 8.4 Hz), 6.65 (2H, d, J = 8.4 Hz), 4.28 (2H, s), 3.74 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$): 152.4, 142.5, 139.8, 128.7, 127.6, 127.3, 115.1, 114.3, 55.9, 49.4 ppm. HRMS *m/z*: 213.1154 (213.1160 calcd for $C_{14}H_{15}NO$).1-*p*-Tolyl-1H-pyrrole (entry 16, Table 2). ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.29–7.19 (4H, m), 7.05 (2H, d, J = 1.5 Hz), 6.33 (2H, d, J = 1.5 Hz), 2.36 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$): 138.6, 135.3, 130.1, 120.5, 119.4, 110.1, 20.8 ppm. HRMS *m/z*: 157.0891 (157.0903 calcd for $C_{11}H_{11}N$).