Efficient Ligand-Free Copper-Catalyzed Arylation of Aliphatic Amines

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Abstract: An efficient and practical protocol has been developed for the cross-coupling of alkyl amines and aryl iodides under ligand-free copper(I) iodide catalyzed conditions. A variety of alkyl amines undergo the catalytic system to afford the N-arylated products in moderate to good yields (up to 93%).

Key words: ligand-free, copper, aliphatic amines, N-arylation

Transition-metal-catalyzed cross-coupling reactions of amines with aryl halides has emerged as one of the most powerful strategy for the formation of C-N bonds in organic synthesis. In particular, the intense demand for the synthesis of N-arylated amines has been fueled by their applications as key synthons in natural products, pharmaceuticals, and in materials research.¹ Among the various strategies developed to date, the copper-catalyzed Ullmann-type coupling reaction has proven to be a convenient and versatile method for rapidly accessing arylated amines. Important developments made on the Ullmanntype C-N cross-coupling reactions mostly involve widening the scope of such reactions in terms of substrate tolerance, copper loading, and practicality of the reaction conditions.² Generally, this goal is achieved via the addition of suitable mono- or bidentate ligands such as phosphines,³ diols,⁴ diketones,⁵ amino acids,⁶ 1,10phenanthroline derivatives,⁷ oxalyldihydrazone,⁸ salicylamides,⁹ and phosphoramidites¹⁰ to increase the yield and generality of the reaction. Critical to the success of these strategies is the need for the presence of an assisting ligand in the reaction protocols.

Although significant progress has been achieved on the aforementioned transformation, there still remains a need to develop economical and sustainable protocols that operate under environmentally friendly conditions.¹¹ In this respect, ligand-free Ullmann-type coupling protocols remain underdeveloped. Correa and Bolm have reported a ligand-free Cu₂O catalytic system for the cross-coupling of aryl iodides with sulfoximines and nitrogen heterocyles.¹² Hu demonstrated the N-arylation of azoles using copper powder without additional ligand.¹³ Xu reported the reusable ligand-free Cu₂O for N-arylation of nitrogen-containing heterocycles with aryl halides.¹⁴ Rossi demonstrated N-arylation of indole with aryl iodides under base-free and ligand-free conditions using CuOAc.¹⁵ Chan de-

veloped successful protocols for the cross-coupling of nitrogen heterocycles and aryl halides under ligand-free conditions using Cu(I) halide salts.¹⁶ Van Koten also reported an efficient protocol for the coupling of various nitrogen nucleophiles with aryl halides under coppercatalyzed ligand-free conditions.¹⁷ However, the protocol requires a high reaction temperature, and a limited substrate range of aliphatic amines was tested under the catalytic conditions. Punniyamurthy demonstrated crosscoupling of a variety of amines with iodobenzene using CuO nanoparticles¹⁸. Wolf has developed a Cu₂O coupling procedure for the amination of aryl halides with various alkyl amines under ligand-free conditions which necessitated the use of the strong base sodium tert-butoxide.¹⁹ In this paper, we report a ligand-free copper-catalyzed system for the cross-coupling of aryl iodides with a wide variety of aliphatic and cyclic amines.

In our initial study, benzylamine and iodobenzene were chosen as model substrates for the N-arylation reaction. Under ligand-free conditions, the reaction of benzylamine (1 equiv) with iodobenzene (2 equiv), Cu_2O (10 mol%) as catalyst, and Cs₂CO₃ in toluene gave a moderate yield of 54% (Table 1, entry 1). Encouraged by this result, optimization studies were initiated to evaluate the efficiency of various copper sources for the arylation reaction. Among the various copper salts screened (entries 1-5), CuI proved to be the best copper catalyst (entry 5), affording the N-arylated product in a good yield of 70%. To rule out the possibility that catalysis was assisted by other contaminants that might be present in the system, control experiments revealed that no product was obtained in the absence of the copper source (entry 6). Next, we probed the solvent effect using a series of commonly used organic solvents and water as reaction medium. In this study, DMF was found to be the solvent of choice which gave the product in an excellent yield of 93% (entry 8). Lower yields were obtained in the case of toluene (entry 5) and acetonitrile (entry 7) as the system solvent. A moderate yield was also achieved when water was used as the only reaction medium for the reaction (entry 9). Further experiments revealed that the nature of the bases has a pronounced impact on the process. The choice of Cs_2CO_3 as the base plays an important role for this coupling reaction, as K₂CO₃, KOH, and K₃PO₄ were evaluated and shown to be ineffective (entries 10–12). In summary, the optimized conditions for our ligand-free copper-catalyzed crosscoupling reactions use CuI (10 mol%) and Cs_2CO_3 (2 equiv) in DMF at 135 °C for 24 hours. It is noteworthy

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that the cross-coupling reaction is water-tolerant as shown by the fact that product **3a** was obtained in a good yield of 71% (entry 14) when the reaction was carried out in a mixture of DMF and water (7.5:1).

To establish the generality of this protocol, a variety of functionalized aryl halides was coupled with benzylamine under the optimized conditions. The results are shown in Table 2. In general, good to excellent yields were obtained regardless of the electronic nature of the substituent for aryl iodides. Aryl halides with ortho substitution are not significantly hampered in the cross-coupling reaction, affording the products in good yields (Table 2, entries 2 and 3), and no significant electronic effects were observed for meta-substituted (entries 4-6) and para-substituted (entries 7-11) aryl iodides. However, the use of bromobenzene and 4-bromoanisole as coupling partners gave only trace amounts of the products (entries 12 and 13). This difference in reactivity of the halide substituent in the electrophilic counterpart confers high chemoselectivity to the catalytic process whereby coupling only takes place on the carbon with the iodo substituent in the presence of other halide groups (entries 8–10).

In order to expand the scope of the ligand-free CuI-catalyzed amination, we carried out cross-coupling reactions between a series of aliphatic nitrogen nucleophiles and iodobenzene. As revealed by the data in Table 3, several amine substrates can be arylated under the ligand-free catalytic conditions. A variety of linear and branched aliphatic primary amines afforded the products in good yields ranging from 60–78% (entries 1–5). The arylation of a representative cyclic primary amine, cyclohexylamine also gave the arylated product with a good yield of 63% (entry 6). Moreover, cyclic secondary amines such as pyrrolidine, morpholine, and piperazine also gave the corresponding *N*-phenyl derivatives in good yields (entries 7– 9). **Table 1** Optimization Studies of Ligand-Free Copper-Catalyzed

 Cross-Coupling of Benzylamine and Iodobenzene^a



Entry	[Cu] source	Base	Solvent	Yield (%) ^b
1	Cu ₂ O	Cs ₂ CO ₃	toluene	54
2	CuO	Cs ₂ CO ₃	toluene	0
3	CuCl	Cs ₂ CO ₃	toluene	trace
4	CuBr	Cs ₂ CO ₃	toluene	66
5	CuI	Cs ₂ CO ₃	toluene	70
6	-	Cs ₂ CO ₃	toluene	0
7	CuI	Cs ₂ CO ₃	MeCN	62
8	CuI	Cs ₂ CO ₃	DMF	93
9	CuI	Cs ₂ CO ₃	H_2O	50
10	CuI	K ₂ CO ₃	DMF	14
11	CuI	КОН	DMF	trace
12	CuI	K ₃ PO ₄	DMF	33
13	CuI	Cs ₂ CO ₃	DMF	80 ^c
14	CuI	Cs ₂ CO ₃	DMF	71 ^d

 a The reaction was carried out with benzylamine (1.47 mmol), iodobenzene (2.94 mmol), base (2.94 mmol), Cu source (10 mol%), solvent (0.75 mL) at 135 $^\circ C$ for 24 h.

^b Isolated yield after column chromatography.

^c The reaction was performed with benzylamine (2.94 mmol) and iodobenzene (1.47 mmol).

 $^{\rm d}$ The reaction was performed with a mixture of DMF and $\rm H_2O~(7.5:1)$ as solvent.

Table 2 N-Arylation of Benzylamine with Aryl Halides Catalyzed by Ligand-Free CuI in DMF^a



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 Table 2
 N-Arylation of Benzylamine with Aryl Halides Catalyzed by Ligand-Free CuI in DMF^a (continued)

 \wedge

	NH ₂ + R X	$\begin{array}{c} Cul (10 \text{ mol}\%) \\ \hline Cs_2CO_3 \\ \hline DMF, 135 \ ^{\circ}C \\ 24 \text{ h} \end{array} \xrightarrow{N} H$	∑ <u>R</u>	
Entry	ArX	Product		Yield (%) ^b
3			3c	53
4		NH NH	3d	74°
5		N H CI	3e	84
6		N CF3	3f	82
7	I—————————————————————————————————————	N N OMe	3g	66°
8	I	N H	3h	84
9	I-CI	CI H	3i	90
10	I—————————————————————————————————————	N H Br	3ј	88
11		CF ₃	3k	60
12	Br	N N	3a	trace
13	Br-OMe	OMe	3g	trace

^a The reaction was carried out with benzylamine (1.47 mmol), aryl halides (2.94 mmol), Cs_2CO_3 (2.94 mmol), CuI (10 mol%), DMF (0.75 mL) at 135 °C for 24 h.

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^b Isolated yield after column chromatography.

^c The reaction was performed with CuI (20 mol%).

Table 3 N-Arylation of Amines with Iodobenzene Catalyzed by Ligand-Free CuI in DMF^a

Cul (20 mol%)

R^1 NH + $\langle R^2$	Cs₂CÒ₃ (2 equív) → DMF, 135 °C 24 h	R ¹ R ² N		
Entry	Amine	Product		Yield (%) ^b
1	NH ₂	N N N N N N N N N N N N N N N N N N N	4a	75
2	NH ₂		4b	62
3	MeO NH ₂	MeO	4c	72
4	NH ₂		4d	78
5	NH ₂	L H	4e	60
6			4f	63
7	NH		4g	82
8	0 NH		4h	64
9	Ph—NNH	Ph-N_N-	4i	75

^a The reaction was carried out with amines (1.47 mmol), iodobenzene (2.94 mmol), Cs₂CO₃ (2.94 mmol), CuI (20 mol%), DMF (0.75 mL) at 135 °C for 24 h.

^b Isolated yield after column chromatography.

In summary, we have developed a versatile, operationally simple, and practical ligand-free CuI-catalyzed cross-coupling protocol for the arylation of various aliphatic nitrogen nucleophiles with differently substituted aryl iodides. In most instances, the N-arylated derivatives are obtained in good to excellent yields. This renders the current approach an attractive alternative to access various N-arylated aliphatic amines²⁰ and will also provide a valuable platform for chemists who are interested in large-scale applications. Exploration of this ligand-free Cu catalytic system to other cross-coupling is ongoing.

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- (20) Representative Procedure for N-Arylation of Aliphatic Amines
 - A mixture of CuI (Sigma-Aldrich, 99.99% purity, 0.147 mmol), Cs_2CO_3 (2.94 mmol) was dissolved in (0.75 mL) DMF, the aryl halide (2.94 mmol), and the aliphatic amine (1.47 mmol) were added, and the mixture was stirred under air in a closed system at 135 °C for 24 h. The heterogeneous mixture was then cooled to r.t. and diluted with CH_2Cl_2 . The resulting solution was directly filtered through a pad of Celite and the solvent removed under reduced pressure. The crude product was purified by silica gel column chromatography to afford the N-arylated product. The identity and purity of products was confirmed by ¹H NMR and ¹³C NMR spectroscopic analysis.

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