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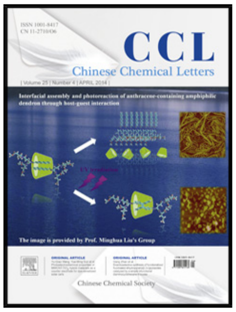

Title: Copper-catalyzed *N*-arylation of 2-arylindoles with aryl halides

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Graphical Abstract

Copper-catalyzed *N*-arylation of 2-arylindoles with aryl halides

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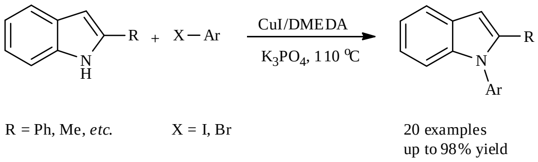

Air-stable CuI combined with the DMEDA ligand can efficiently catalyze the *N*-arylation of 2-arylindoles with aryl iodides and aryl bromides in good to excellent yields (up to 98%). The aryl halides bearing electron-rich or electron-deficient functional groups can be well tolerated under this mild reaction conditions.

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Original article

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ABSTRACT

10 mol% CuI combined with the DMEDA ligand can efficiently catalyze the *N*-arylation of 2-arylindoles with aryl iodides and aryl bromides in good to excellent yields. The aryl halides bearing electron-rich or electron-deficient functional groups can be well tolerated under this mild reaction conditions.

1. Introduction

During the past ten years significant advances have been achieved in the development of C-N cross-coupling reactions [1-4]. In the presence of several transition metal catalysts (Cu, Pd, Ni, *etc.*), various nitrogen-containing compounds, such as pharmaceuticals, agrochemicals and other functional molecules, could be efficiently prepared. In terms of the cost and toxicity, the copper-catalyzed Ullmann-type C-N coupling reaction represents one of the most desirable methods to prepare the numerous *N*-containing molecules in chemical industry [2]. The pioneering work has established the fact that ligands are crucial in the copper-catalyzed C-N coupling reactions [1].

The indole-containing compounds are among the most important and ubiquitous heterocyclic frameworks in nature. Copper-catalyzed *N*-arylation of nitrogen heterocycles with aryl halides have been developed with various ligands. In 2002, Buchwald first found that the diamine ligands were efficient for copper catalyzed *N*-arylation of simple indoles [5-7]. In 2004, Taillefer developed Chxn-Py-Al-copper complex for the C-N coupling reactions [8]. Subsequently, many useful ligands, such as L-proline [9], 1,1'-binaphthyl-2,2'-diamine [10], benzotriazole [11], 2-(2'-pyridyl)benzimidazole [12], 8-hydroxyquinalidine [13], tetrazole-1-acetic acid [14] and 4,7-dipyrrolidinyl-1,10-phenanthroline [15], were developed for promoting the copper-catalyzed *N*-arylation of indoles and other nitrogen heterocycles with aryl halides. Recently, we have been focusing on the preparation of *N*-containing heterocycles based on cheap and green catalyst systems (Cu-based catalysts) *via* C-N cross-coupling reactions (Scheme 1, c). Other elegant catalytic [16-21] or non-catalytic [22-25] methods were developed for the facile synthesis of substituted indoles. Recently, Lutz Ackermann and coworkers [26-27] developed a one-pot substituted indole synthesis base on Pd/Cu catalysis (Scheme 1, a). Katz and coworkers [28] reported an interesting strong base mediated benzodipyrrole syntheses from diethynyldifluorobenzenes (Scheme 1, b). To the best of our knowledge, there are limited examples for the *N*-arylation of 2-arylindoles and its derivatives *via* Cu-catalysis. Herein, we reported our results on the copper-catalyzed *N*-arylation of arylindoles with aryl halides in the presence of the DMEDA ligand with excellent yields under mild conditions.

2. Experimental

Reagents were obtained commercially and used as received. Solvents were purified and dried by standard methods. Toluene was dried and distilled from sodium/benzophenone immediately prior to use under a nitrogen atmosphere. Unless noted otherwise, all other compounds have been reported in the literatures or are commercially available. All reactions were performed in oven-dried glassware. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates. Flash chromatography columns were packed with 200-300 mesh silica gel. ^{1}H NMR and ^{13}C NMR data were recorded in $CDCl_3$ solutions with Varian Mercury (300 MHz) spectrometers

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using tetramethylsilane (TMS) as an internal standard. Analytical gas chromatography (GC) was performed using an Aglient 6890 Gas Chromatography fitted with a flame ionization detector.

Representative procedure for the synthesis of 1,2-diphenylindole (**3a**): A 10 mL Schlenk tube was charged with 2-phenylindole **1a** (193.2 mg, 1.0 mmol), CuI (10 mol%, 19.0 mg, 0.1 mmol) and K_3PO_4 (424 mg, 2.0 mmol). The Schlenk tube was evacuated and filled with N_2 (this procedure was repeated three times), and then toluene (2.0 mL), DMEDA (20 mol%, 17.6 mg, 0.2 mmol) and iodobenzene **2a** (244.8 mg, 1.2 mmol) were added. The resulting mixture was stirred at 110 ^{o}C for 24 h. After cooling to room temperature, the reaction mixture was quenched and extracted with ethyl acetate (10 mL × 3). The organic extracts were combined, dried over Na_2SO_4 and concentrated under reduced pressure, and then purified by silica gel chromatograph (petroleum ether) to yield the desired product as a white solid (245.1mg, 91% yield). The data of compounds **3a-q** can be found in Supporting information.

3. Results and discussion

The C-N coupling reaction between 2-phenylindole (**1a**) and iodobenzene (**2a**) was selected as the model reaction to explore the suitable reaction conditions (Table 1). Commonly used and air-stable copper salt CuI was chosen as the catalyst and several other reaction parameters, such as ligand, base and solvent were carefully optimized. Using anhydrous K_3PO_4 (2 equiv.) as the base and toluene as the solvent, a series of bidentate *N*-containing ligands were tested. In the absence of any ligands, CuI (10 mol%) could not independently promote the conversion of 2-phenylindole (**1a**) after 24 h at 110 ^{o}C (Table 1, entry 1). The use of ethylenediamine (EDA) led to a 55% yield of the desired *N*-arylation product (**3a**) (Table 1, entry 2). When *N,N'*-dimethylethylenediamine (DMEDA) was used, a 100% conversion of **1a** was observed and a 96% yield of the desired *N*-arylation product (**3a**) was obtained (Table 1, entry 3). However, the use of tetramethyl substituted ethylenediamine (TMEDA) resulted in no consumption of **1a** (Table 1, entry 4). Presumably, the increased level of substitution at nitrogen leads to reduced binding capacity. Other commonly used ligands, such as cyclohexane-1,2-diamine (CHDA), 2,2'-bipyridine (bipy), 1,10-phenanthroline (phen) and L-proline were also examined but all offered poor to moderate yields of **3a** (Table 1, entries 5-8). 8-Hydroxyquinoline (quinolin-8-ol) showed inferior efficiency as well (Table 1, entry 9). The preliminary results showed that the combination of air stable CuI (10 mol%) and DMEDA (20 mol%) appeared to be an efficient catalyst system for the *N*-arylation of 2-phenylindole (**1a**) with aryl iodides (**2**). Base is also crucial for this transformation. K_3PO_4 was the most efficient among the tested bases (Table 1, entries 11-14), and other tested strong bases (*t*-BuOK, *t*-BuONa and *t*-BuOLi) produced no or lower conversion (Table 1, entries 12-14). Amongst all tested solvents, toluene is a superior solvent to others (dioxane and DMF) (Table 1, entries 15 and 16). It required 24 h to complete conversion of **1a**, while a shorter reaction time (12 h) led to a 66% yield of **3a** (Table 1, entry 10). Moreover, ligandless reaction conditions [16-17] were also examined for this reaction (Table 1, entries 17 and 18), the results showed that using 20 mol% CuI as catalyst and DMF as solvent, no reaction was observed in the presence of K_3PO_4 or Cs_2CO_3.

With the optimized reaction conditions in hand, the substrate scope of the *N*-arylation of 2-arylindole (**1**) with aryl halides (**2**) was studied and the results were shown in Table 2. Electron-rich and electron-deficient aryl iodides reacted smoothly with 2-phenylindole (**1a**) and offered good to excellent yields in most cases. 1-Iodo-4-methylbenzene (**2b**) and 1-iodo-4-methylbenzene (**2c**) reacted with 2-phenylindole (**1a**) to generate the corresponding *N*-arylation products (**3b** and **3c**) in 90% and 87% yield, respectively. 1-Iodo-4-methoxybenzene (**2e**) and 1-iodo-3-methoxybenzene (**2f**) reacted well with 2-phenylindole (**1a**) and produced the corresponding *N*-arylation products (**3e** and **3f**) in 84% and 87% yield, respectively. Notably, aryl iodides bearing *ortho*-substituents (Me, OMe and Cl) reacted sluggishly and no or lower conversions were observed (**3d**, **3g** and **3j**), which might be attributable to the influence of steric hindrance. The reactions of 1-fluoro-4-iodobenzene and 1-chloro-4-iodobenzene gave 75% and 74% yield (**3h** and **3i**), respectively. Electron-deficient aryl iodide bearing ester group was also favored in this system and produced the corresponding *N*-arylation product (**3m**) in 80% yield. Other aryl iodides, such as 1-butyl-4-iodobenzene and 4-iodo-1,2-dimethylbenzene can be efficiently coupled with 2-phenylindole (**1a**) and gave the coupling products in 94% and 86% yield (**3k** and **3l**), respectively. Under the standard reaction conditions, the Cu-catalyzed *N*-arylation of other substituted indoles were examined as well. Carbazole and 2-methylindole can undergo the C-N coupling smoothly and afforded the corresponding *N*-arylation products (**3n** and **3o**) in 98% and 94% yield, respectively. Moreover, 2-(4-fluorophenyl)-indole and 2-(4-chlorophenyl)-indole were also suitable under the same reaction conditions and afforded the *N*-arylation products (**3p** and **3q**) in 81% and 86% yield, respectively.

Aryl bromides were tested under the standard reaction conditions (10 mol% CuI/20 mol% DMEDA) and a 62% yield of the coupled product was obtained after 24 h. When the less reactive Ph-Cl was tested, lower conversion was observed with 20 mol% CuI catalyst at elevated temperature (120 ^{o}C) after 36 h (Table 2, **3a**). Considering the modest outcome of the less reactive aryl bromides, 20 mol% CuI and 40 mol% DMEDA was employed to promote the reactions and good yields (80%-84%) of the corresponding *N*-arylation products (**3a**, **3b** and **3e**) were achieved (Scheme 2).

4. Conclusion

In conclusion, we have developed a simple and efficient method for the synthesis of substituted indoles using cheap CuI as the catalyst and DMEDA as the ligand. Electron-rich and electron-deficient aryl iodides and aryl bromides all can afford the corresponding *N*-arylation products with 2-arylindole in good to excellent yields under mild reaction conditions. Further investigation on promoting the conversion of aryl halides bearing *ortho*-substituents will be reported in due course.

Acknowledgments

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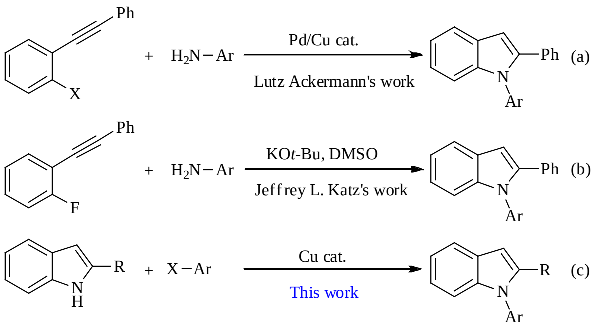
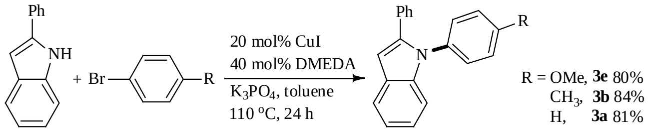


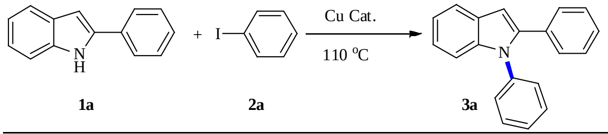
Scheme 1. Methods for the preparation of 1,2-arylindoles.



Scheme 2. *N*-Arylation of 2-phenylindole with aryl bromides.

Table 1

Reaction conditions for C-N coupling. [a]



1a **2a** **3a**

Entry	[Cat.] (mol%)	Ligand	Base	Solvent	Time (h)	Yield (%)[b]
1	CuI (10)	none	K_3PO_4	Toluene	24	<5
2	CuI (10)	EDA	K_3PO_4	Toluene	24	55
3	CuI (10)	DMEDA	K_3PO_4	Toluene	24	96 (91[c])
4	CuI (10)	TMEDA	K_3PO_4	Toluene	24	<5
5	CuI (10)	CHDA	K_3PO_4	Toluene	24	42
6	CuI (10)	Bipy	K_3PO_4	Toluene	24	60
7	CuI (10)	Phen	K_3PO_4	Toluene	24	65
8	CuI (10)	L-proline	K_3PO_4	Toluene	24	27
9	CuI (10)	Quinolin-8-ol	K_3PO_4	Toluene	24	20
10	CuI (10)	DMEDA	K_3PO_4	Toluene	12	66
11	CuI (10)	DMEDA	K_2CO_3	Toluene	24	68
12	CuI (10)	DMEDA	*t*-BuOK	Toluene	24	<5
13	CuI (10)	DMEDA	*t*-BuONa	Toluene	24	8
14	CuI (10)	DMEDA	*t*-BuOLi	Toluene	24	33
15	CuI (10)	DMEDA	K_3PO_4	Dioxane	24	84
16	CuI (10)	DMEDA	K_3PO_4	DMF	24	0
17[d]	CuI (20)	none	K_3PO_4	DMF	24	0
18[d]	CuI (20)	none	Cs_2CO_3	DMF	24	<5

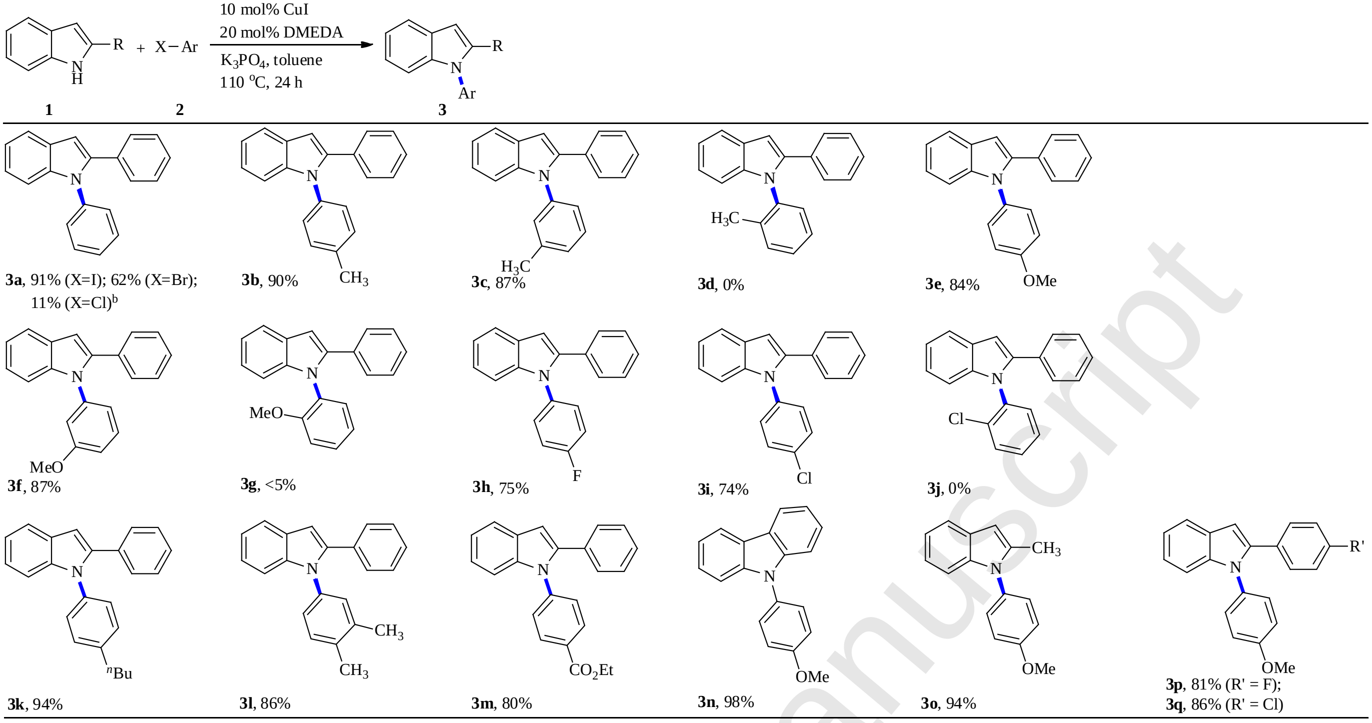
[a] Unless otherwise noted, the reaction was carried out with **1a** (1.0 mmol), **2a** (1.2 mmol), CuI (0.10 mmol), ligand (0.20 mmol), base (2.0 mmol), solvent (2.0 mL), 110 °C, under nitrogen atmosphere.

[b] Yield was determined by GC analysis.

[c] Isolated yield.

[d] The reaction was carried out with **1a** (1.4 mmol) and **2a** (1.0 mmol).

Table 2
Substrates scope for *N*-arylation of 2-arylindole.[a]



3a, 91% (X=I); 62% (X=Br); 11% (X=Cl)[b]
3b, 90%
3c, 87%
3d, 0%
3e, 84%
3f, 87%
3g, <5%
3h, 75%
3i, 74%
3j, 0%
3k, 94%
3l, 86%
3m, 80%
3n, 98%
3o, 94%
3p, 81% (R' = F);
3q, 86% (R' = Cl)

[a] The reaction was carried out with **1** (1.0 mmol), **2** (1.2 mmol), CuI (0.10 mmol), DMEDA (0.20 mmol), K$_3$PO$_4$ (2.0 mmol), toluene (2.0 mL), 110 ^{o}C, under nitrogen atmosphere.

[b] CuI (0.20 mmol), DMEDA (0.40 mmol), K$_3$PO$_4$ (2.0 mmol), toluene (2.0 mL), 120 ^{o}C, 36 h.