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Copper-catalyzed N-arylation and aerobic oxidative C–H/C–H coupling: one-pot synthesis of indoloimidazoquinoline derivatives†

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Meng Wang,[ab] Yunhe Jin,[a] Haijun Yang,[a] Hua Fu*[ac] and Liming Hu*[b]

A novel and efficient copper-catalyzed one-pot synthesis of indoloimidazoquinoline derivatives has been developed. The protocol uses the readily available substituted 2-(2-bromophenyl)-1*H*-indoles, imidazole and benzoimidazoles as the starting materials, inexpensive CuBr as the catalyst, air as the terminal oxidant, and the procedure underwent a sequential copper-catalyzed intermolecular N-arylation and an aerobic oxidative intramolecular C–H/C–H coupling.

The synthesis of nitrogen heterocycles is an important goal in organic synthesis because they occur widely in various natural products and biologically active molecules,[1] and have been assigned as privileged structures in drug development.[2] The traditional methods for the synthesis of *N*-heterocycles usually need precursors with the appropriate functional groups. Recently, there have been great advances in C–H functionalization[3] that make it possible and economical for the construction of *N*-heterocycles through C–H functionalization. For example carbazoles,[4] indazoles,[5] *N*-methoxylactams,[6] benzimidazoles,[7] and indolines,[8] were synthesized by the transition metal-catalyzed aerobic oxidation of C–H bonds using molecular oxygen as the oxidant,[9] for which expensive palladium-, rhodium-, and ruthenium-based catalysts are usually required. During the past decade, copper-catalyzed cross-coupling reactions have attracted attention because of the low cost and the low toxicity of the copper-catalysts,[10] and some efficient syntheses of heterocycles through copper-catalyzed aerobic oxidation have been developed by us[11] and other groups.[12] However, the synthesis of *N*-heterocycles *via* a copper-catalyzed C–H/C–H coupling still remains limited.

On the other hand, indole derivatives are used as receptor antagonists,[13a,b] antihypertensive[13c] and antibiotic angents.[13d] Imidazoquinoline derivatives also show a wide range of biological activities.[14] For example, they are used as anxiolytic,[15a] antifungal/antibacterial,[15b] antineoplastic,[15c] anticancer agents,[15d] and as DNA intercalators.[15e] However, the synthesis and biological function of *N*-fused heterocycles of indole and imidazoquinoline motifs and indoloimidazoquinolines (Fig. 1), have not been reported thus far. In this communication, we report a novel and efficient method for the synthesis of indoloimidazoquinoline derivatives through a sequential copper-catalyzed N-arylation and aerobic oxidative C–H/C–H coupling. As shown in Fig. 1, our strategy for the copper-catalyzed one-pot synthesis of indoloimidazoquinolines is divided into the following two-step process: the copper-catalyzed N-arylation of imidazole derivatives with 2-(2-bromophenyl)-1*H*-indoles under a nitrogen atmosphere, and an aerobic oxidative intramolecular C–H/C–H coupling, leading to the target products.

At first, 2-(2-bromophenyl)-1*H*-indole (**1a**) and imidazole (**2a**) were chosen as the model substrates to optimize the reaction conditions including the catalysts, ligands, bases, solvents and temperature for the N-arylation (*the first step*) and acids for the C–H/C–H coupling (*the second step*). As shown in Table 1, the N-arylation was performed by using CuBr as the catalyst,

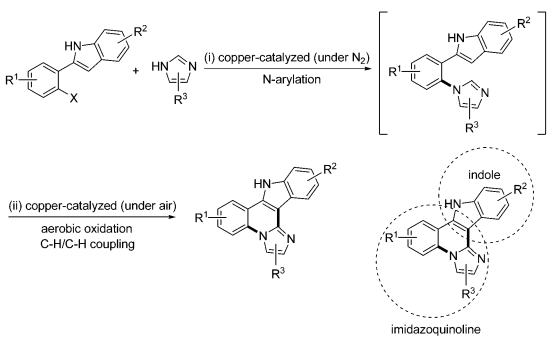


Fig. 1 Our strategy for the copper-catalyzed one-pot synthesis of indoloimidazoquinoline derivatives (*N*-fused heterocycles of indole and imidazoquinoline motifs).

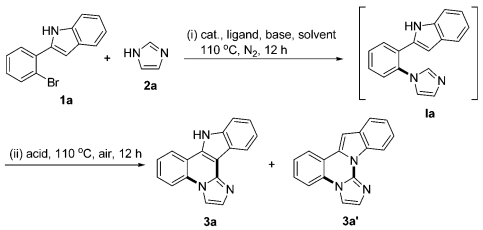
[a]*Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China. E-mail: fuhua@mail.tsinghua.edu.cn*

[b]*College of Life Sciences and Bioengineering, Beijing University of Technology, Beijing 100124, P. R. China. E-mail: huliming@bjut.edu.cn*

[c]*Key Laboratory of Chemical Biology (Guangdong Province), Graduate School of Shenzhen, Tsinghua University, Shenzhen 518057, P. R. China*

† Electronic supplementary information (ESI) available: General procedure for synthesis, characterization data, and ^{1}H and ^{13}C NMR spectra of compounds **3a–q**. See DOI: 10.1039/c3ra40999f

Table 1 Copper-catalyzed one-pot reaction of 2-(2-bromophenyl)-1*H*-indole (**1a**) with imidazole (**2a**): optimization of conditions[a]



Entry	Catalyst	Ligand	Base	Acid	Yield (**3a**) (%)[b]	Yield (**3a′**) (%)[b]
1	CuBr	DMEDA	Cs_2CO_3	—	3	4
2	CuBr	DMEDA	Cs_2CO_3	PivOH	78	9
3	CuI	DMEDA	Cs_2CO_3	PivOH	54	9
4	CuCl	DMEDA	Cs_2CO_3	PivOH	15	5
5	Cu_2O	DMEDA	Cs_2CO_3	PivOH	73	15
6	$Cu(OAc)_2$	DMEDA	Cs_2CO_3	PivOH	44	5
7	CuBr	DMEDA	Cs_2CO_3	AcOH	75	8
8	CuBr	DMEDA	Cs_2CO_3	TFA	Trace	Trace
9	CuBr	DMEDA	K_2CO_3	PivOH	24	3
10	CuBr	DMEDA	K_3PO_4	PivOH	45	4
11	CuBr	L-Proline	Cs_2CO_3	PivOH	77	10
12	**CuBr**	**1,10-phen**	**Cs_2CO_3**	**PivOH**	**80**	**11**
13	CuBr	PA	Cs_2CO_3	PivOH	16	3
14[c]	CuBr	phen	Cs_2CO_3	PivOH	Trace	Trace
15[d]	CuBr	phen	Cs_2CO_3	PivOH	66	7
16[e]	CuBr	phen	Cs_2CO_3	PivOH	73	9
17[f]	CuBr	phen	Cs_2CO_3	PivOH	Trace	Trace

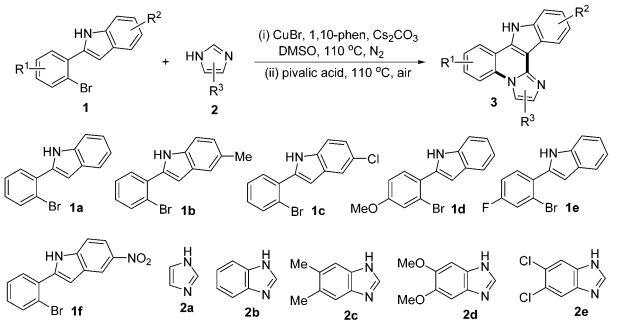
[a] Reaction conditions: 2-(2-bromophenyl)-1*H*-indole (**1a**) (0.25 mmol), imidazole (**2a**) (0.5 mmol), catalyst (0.05 mmol), ligand (0.1 mmol), base (0.5 mmol), DMSO for entries 1–15 (1.5 mL), acid (1.75 mmol), reaction temperature for entries 1–13, 16 and 17 (110 °C) under nitrogen atmosphere for the first step, under air for the second step. [b] Isolated yield. [c] Reaction temperature (80 °C). [d] Reaction temperature (130 °C). [e] Using *N*,*N*-dimethylformamide (DMF) (1.5 mL) as the solvent. [f] Using 1,4-dioxane (1.5 mL) as the solvent. PivOH = pivalic acid. AcOH = acetic acid. TFA = trifluoroacetic acid. DMEDA = dimethylethylenediamine. phen = 1,10-phenanthroline. PA = pipecolic acid.

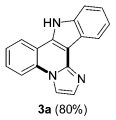
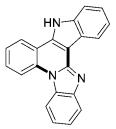
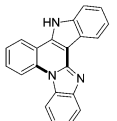
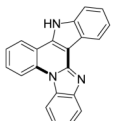
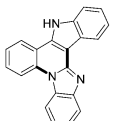
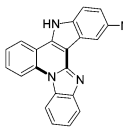
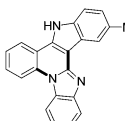
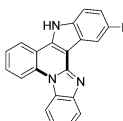
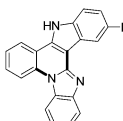
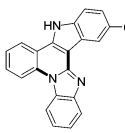
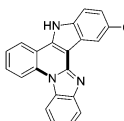
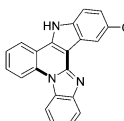
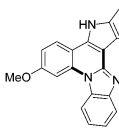
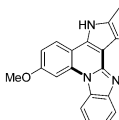
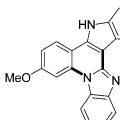
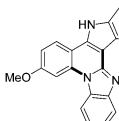
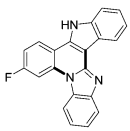
dimethylethylenediamine (DMEDA) as the ligand and 2 equivalents of Cs_2CO_3 as the base, in DMSO at 110 °C for 12 h under N_2. The C–H/C–H coupling was carried out at 110 °C for 12 h under air without the addition of an acid, and the one-pot two-step reactions provided a small amount of two products **3a** and **3a′** (entry 1). When 7 equivalents of pivalic acid was added for the second step reaction, the yield of **3a** increased to 78% with **3a′** (9% yield) also isolated (entry 2). Other copper catalysts were tested, and they were inferior to CuBr (*versus* entries 3–6). When acetic acid was used in the second step, instead of pivalic acid, a 75% yield of **3a** was provided (entry 7). Only a trace amount of **3a** was observed when trifluoroacetic acid was added (entry 8). When K_2CO_3 and K_3PO_4 were used as the base in the first step N-arylation, lower yields were observed (entries 9 and 10). L-Proline, 1,10-phenanthroline and pipecolic acid were used as the ligands (entries 11–13), and 1,10-phenanthroline afforded the highest yield (compare entries 2 and 11–13). We varied the temperature, and 110 °C was suitable (compare entries 12, 14 and 15). DMF (entry 16) or 1,4-dioxane (entry 17) replaced DMSO as the solvent, and no better result was found. Therefore, the optimal conditions for the copper-catalyzed one-pot synthesis of indoloimidazoquinoline derivatives are as follows: CuBr as the catalyst, 1,10-phenanthroline as the ligand and Cs_2CO_3 as the base, in DMSO at 110 °C for 12 h under N_2 for the N-arylation (*the first step*); 7 equivalents of pivalic acid was used in the resulting solution, at 110 °C for 12 h under air for the C–H/C–H coupling (*the second step*).

As is shown in Table 2, the scope of the copper-catalyzed one-pot synthesis of indoloimidazoquinoline derivatives was investigated, and the substrates that were examined provided moderate to good yields of products. For substituted 2-(2-bromophenyl)-1*H*-indoles (**1a–1f**), their various electronic characteristics did not obviously affect the product yields. For substituted benzoimidazoles, the substrates containing electron-withdrawing groups provided higher yields than those containing neutral, or electron-donating groups. The reactions in Table 2 could tolerate some functional groups, including an ether (**3d**, **3h**, **3l–p**), C–Cl (**3e**, **3j–l** and **3p**), C–F bond (**3q**).

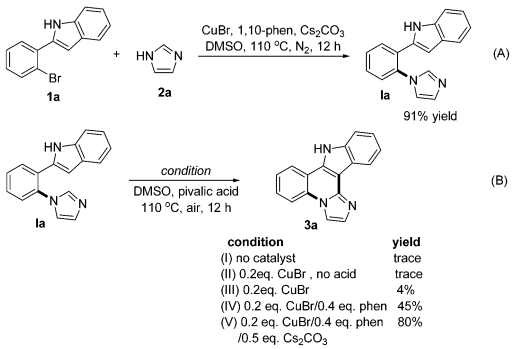
As is shown in Scheme 1, some control experiments were performed in order to explore the reaction mechanism for the synthesis of indoloimidazoquinoline derivatives. The copper-catalyzed coupling of 2-(2-bromophenyl)-1*H*-indole (**1a**) with imidazole (**2a**) under N_2 provided the N-arylation product (**Ia**) in a 91% yield (see Scheme 1A). We attempted the copper-catalyzed aerobic oxidative intramolecular C–H/C–H coupling of isolated **Ia** under various conditions (Scheme 1B). Only a trace amount of the target product was observed in the absence of a copper-catalyst (condition (I) in Scheme 1B). The copper-catalyzed reaction did not work in the absence of pivalic acid (condition (II) in Scheme 1B). A low yield (4%) was provided in the presence of pivalic acid

Table 2 Copper-catalyzed one-pot synthesis of indoloimidazoquinoline derivatives *via* a sequential N-arylation and aerobic oxidative C–H/C–H coupling[ab]



3 (Yield)		
 3a (80%)	 3b (67%)	 3c (84%)
 3d (61%)	 3e (89%)	 3f (66%)
 3g (81%)	 3h (34%)	 3i (85%)
 3j (87%)	 3k (88%)	 3l (62%)
 3m (79%)	 3n (81%)	 3o (66%)
 3p (90%)	 3q (45%)	

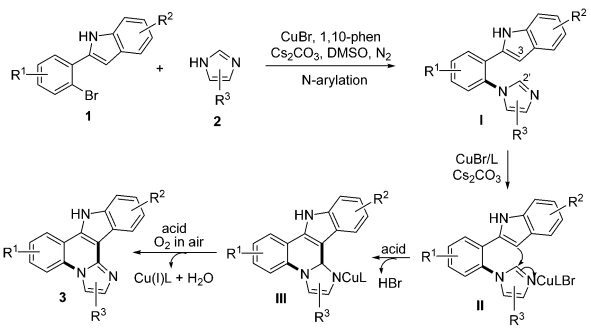
[a] Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), CuBr (0.05 mmol), 1,10-phen (0.1 mmol), Cs_2CO_3 (0.5 mmol), DMSO (1.5 mL), pivalic acid (1.75 mmol) and reaction temperature 110 °C, (for both the two-step reactions). Reaction time 12 h and under nitrogen atmosphere for the first step; reaction time 12 h and under air for the second step. [b] Isolated yield.



Scheme 1 (A) Copper-catalyzed coupling of 2-(2-bromophenyl)-1*H*-indole (**1a**) with imidazole (**2a**) under N_2 leading to the N-arylation product (**Ia**); (B) copper-catalyzed aerobic oxidative intramolecular C–H/C–H coupling of **Ia** under air providing **3a** under various conditions.

(condition (III) in Scheme 1B). When 0.4 equivalents of 1,10-phen were added as the ligand, the yield increased to 45% (condition (IV) in Scheme 1B). A high yield (80%) was obtained in the presence of 0.5 equivalents of Cs_2CO_3 (condition (V) in Scheme 1B). Therefore, a possible mechanism for the synthesis of the indoloimidazoquinoline derivatives is suggested in Scheme 2. The coupling of substituted 2-(2-bromophenyl)-1*H*-indole (**1**) with imidazole derivative (**2**) initially affords the N-arylation product (**I**) under copper catalysis. The coordination of CuBr with the imidazole moiety in **I** gives complex **II**, and the addition of the 3-CH in the indole group to the 2′-C of the imidazole provides **III**. The oxidation of **III** leads to the target product (**3**), freeing the Cu(I) catalyst.

In summary, we have developed a novel, efficient and practical copper-catalyzed one-pot method for the synthesis of indoloimidazoquinoline derivatives. The protocol uses readily available substituted 2-(2-bromophenyl)-1*H*-indoles and imidazoles as the starting materials, cheap CuBr–1,10-phenanthroline as the catalyst system, and economical and environmentally friendly air as the terminal oxidant. The corresponding indoloimidazoquinoline derivatives were prepared in moderate to good yields. The one-pot two-step reactions underwent a sequential copper-catalyzed Ullmann-type N-arylation and an aerobic oxidative C–H/C–H coupling, and this convenient and efficient method for the



Scheme 2 Possible mechanism for the copper-catalyzed synthesis of indoloimidazoquinoline derivatives.

synthesis of *N*-heterocycles may attract much attention from academic and industrial researchers.

Acknowledgements

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