

# Simple synthesized Mannich bases as ligands in Cu-catalyzed N-arylation of imidazoles in water

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**Abstract** 1,4-Bis(2-hydroxy-5-methoxybenzyl)piperazine and its analogues were used as efficient ligands for CuI-catalyzed N-arylation of imidazoles with aryl halides in water under mild conditions (120 °C for 12 h) with 10 mol% of CuI, 20 mol% of the Mannich base, and two equivalents of KOH or K<sub>2</sub>CO<sub>3</sub> in the presence of 10 mol% phase transfer catalyst (*n*-Bu)<sub>4</sub>NBr. A variety of products were synthesized in moderate to excellent yields using this inexpensive catalytic system.

**Keywords** Catalysis · Water · Ligands · Heterocycles · Arylation

## Introduction

Nitrogen-containing heterocycles such as *N*-arylimidazoles play an important role in the synthesis of a wide range of medicinal [1–4], biological [5], and natural products [6] and *N*-heterocyclic carbene chemistry [7, 8]. Traditionally, this moiety has been prepared by nucleophilic aromatic substitution of activated aryl halides with heterocycles by copper-mediated coupling or via the classical Ullmann-type coupling [6, 9]. In both cases the reactions require harsh conditions (exposure of substrates to high temperature for extended periods of time) and use of high boiling point polar solvents and excess amounts of copper reagents, which lead

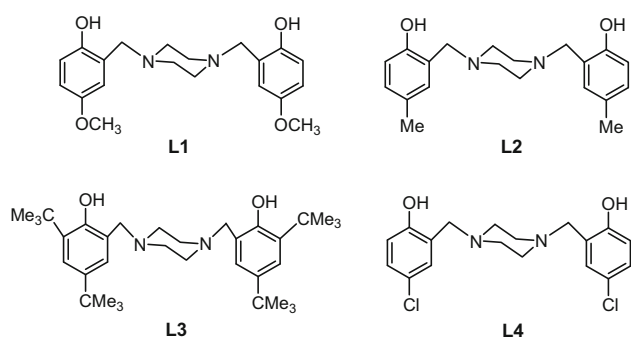
to environmental problems. A breakthrough was made in 1999 by Buchwald et al. who performed such challenging arylation reactions under mild conditions in good yields by use of copper-chelating ligands such as 1,10-phenanthroline [10, 11] and vicinal diamines [12]. In recent years, the development of new ligands for copper-catalyzed cross-coupling protocols has been an area of considerable interest. As a result, a variety of ligands have been screened for the *N*-arylation reaction between aryl halides and imidazoles [13–21]. Despite these successes, efficient ligand-assisted catalytic systems in the aqueous phase are rare [22–24].

Growing concern about pollution from organic solvents has led to the development of more environmentally friendly protocols in organic chemistry. In this context, water has become the solvent of choice to perform many organic transformations because of its properties such as non-toxicity, low cost, and safety [25, 26]. However, the synthesis of organic molecules in water faces challenges such as water tolerance of the catalyst and the associated problems of substrate solubility and reactivity [27]. In this respect, the development of direct metal-catalyzed coupling reactions that utilize less expensive and more sustainable catalysts in water remains an elusive goal in modern organic synthesis.

The Mannich reaction between phenols, formaldehyde, and amines is often a simple, high-yielding reaction that affords Mannich bases (Fig. 1) which are stable, polar compounds and easily form water-soluble metal complexes with copper and iron salts [28]. Recently, Sasmitha et al. [29] developed palladium-catalyzed Suzuki and Heck coupling reactions using the Mannich base **L3** as ligand. However, according to our knowledge, application of these inexpensive Mannich bases in copper-mediated cross-coupling reactions in water has not yet been reported.

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**Fig. 1** Structures of Mannich bases **L1–L4**

## Results and discussion

In this paper, we present an environmentally friendly protocol for N-arylation of imidazoles with aryl halides catalyzed by CuI with Mannich bases as ligands in water. In our initial study, bromobenzene and imidazole were chosen as model substrates for the coupling reaction in water. The standardized protocol was carried out by using imidazole (1.2 equiv), bromobenzene (1 equiv), base (2 equiv), CuI (10 mol%), ligand (20 mol%), and (*n*-Bu)<sub>4</sub>NBr as the phase transfer catalyst (PTC, 10 mol%) in water at 120 °C for 12 h.

It can be seen from Table 1 that the CuI–**L1** combination successfully promoted the coupling reaction in a yield around 90% in water. The catalytic efficiency of the other Mannich ligands was also evaluated in the same reaction system (Table 1, entries 2–4). The more beneficial and inexpensive ligand **L1** was chosen for further reactions. Table 1 also shows that more than one equivalent of base is needed for the reaction to take place. In the presence of two equivalents of an inorganic base, KOH or K<sub>2</sub>CO<sub>3</sub>, 90 or 68% yield of the N-arylation product was obtained. Only a trace amount of product was found when organic bases such as triethylamine and pyridine were used (Table 1, entries 9 and 10). The more effective and inexpensive KOH was chosen for further reactions. Meanwhile, the control experiments showed that the presence of CuI was indispensable and Mannich base ligand and PTC were beneficial for the coupling. No product was detected in the absence of CuI; only 28% yield was obtained by using CuI as catalyst in the absence of any ligand; in the absence of the PTC only 81% yield was obtained (Table 1, entries 5–7). Furthermore, temperatures lower than 120 °C decrease the reaction rate and conversion (Table 1, entry 11). In summary, the optimal conditions for the N-arylation process consist of the combination of CuI (10 mol%), Mannich base **L1** (20 mol%), PTC (10 mol%), and KOH (2 equiv) at 120 °C for 12 h in water.

In order to evaluate the scope of the process with respect to the aryl halides, a variety of substituted aryl iodides and

**Table 1** Results of N-arylation of imidazole with bromobenzene

Entry	Cu source	Ligand	Base	Yield <sup>a</sup> (%)
1	CuI	<b>L1</b>	KOH	90
2	CuI	<b>L2</b>	KOH	85
3	CuI	<b>L3</b>	KOH	92
4	CuI	<b>L4</b>	KOH	83
5	CuI	<b>L1</b>	KOH	81 <sup>b</sup>
6	CuI		KOH	28
7		<b>L1</b>	KOH	0
8	CuI	<b>L1</b>	K <sub>2</sub> CO <sub>3</sub>	68
9	CuI	<b>L1</b>	Et <sub>3</sub> N	<5
10	CuI	<b>L1</b>	Pyridine	<5
11	CuI	<b>L1</b>	KOH	78 <sup>c</sup>
12	CuI	<b>L1</b>	KOH	69 <sup>d</sup>
13	CuI	<b>L1</b>	KOH	72 <sup>e</sup>

Unless otherwise noted, the reaction was carried out with imidazole (2.40 mmol), bromobenzene (2.00 mmol), KOH (4.00 mmol), CuI (10 mol%), **L1** (20 mol%), and PTC (10 mol%) in 2 cm<sup>3</sup> water at 120 °C for 12 h

<sup>a</sup> Yield calculated by GC

<sup>b</sup> Without PTC

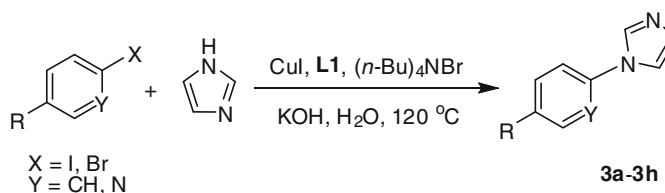
<sup>c</sup> The reaction temperature was 100 °C

<sup>d</sup> The reaction was performed with CuI (5 mol%) and **L1** (10 mol%)

<sup>e</sup> The reaction was performed with KOH (3.00 mmol)

bromides were tested under the optimized reaction conditions using imidazole as model substrate. The results are shown in Table 2.

The results indicate clearly that the reaction of imidazole with aryl iodides provided slightly superior yields than those with aryl bromides employed as arylating agents. Most of the substituted aryl iodides and electron-deficient aryl bromides afford N-arylimidazole products in water with excellent yields ranging from 78 to 93% (Table 2, entries 1–7). However, the arylation of electron-rich aryl bromides resulted in lower yields (47–64%) even with prolonged reaction time (24 h, Table 2, entries 8–11). It is noteworthy that the present protocol could tolerate many functional groups. Imidazole could be selectively arylated in the presence of a free amino or hydroxyl group (Table 2, entries 9 and 10). However, when *p*-nitroiodobenzene was used as arylating agent, hydrolysis took place in the presence of KOH. Use of K<sub>2</sub>CO<sub>3</sub> instead of KOH as base led to the formation of the desired N-arylation product in 93% yield (Table 2, entry 3). When 4-chlorobromobenzene was used as the

**Table 2** *N*-Arylation of imidazole with aryl halides catalyzed by Cu/**L1**/PTC in water

Entry	ArX	Product	Yield <sup>a</sup> (%)
1			<b>3a</b> 90
2			<b>3b</b> 78
3			<b>3c</b> 93 <sup>c</sup>
4			<b>3a</b> 85
5			<b>3c</b> 87
6			<b>3d</b> 83
7			<b>3e</b> 85
8			<b>3b</b> 47
9			<b>3f</b> 62 <sup>b</sup>
10			<b>3g</b> 60 <sup>b</sup>
11			<b>3h</b> 64 <sup>b</sup>

<sup>a</sup> Isolated yield after column chromatography

<sup>b</sup> Reaction time was 24 h

<sup>c</sup> K<sub>2</sub>CO<sub>3</sub> as the base

electrophilic counterpart, the reaction showed high chemoselectivity, and only the bromo functionality reacted (Table 2, entry 6).

To expand the scope of this protocol further, this new catalytic system was applied to a variety of nitrogen heterocycles. In order to get better yields, the reaction time was extended to 24 h and the results are shown in Table 3.

To our delight, most of the nitrogen nucleophiles such as pyrrole, indole, and benzimidazole were found to be effective nucleophilic counterparts for the coupling process, affording the corresponding coupling products in excellent yields (82–92%). Notably, the sterically hindered 2-methylimidazole could undergo selective *N*-arylation with 2-bromopyridine to afford the corresponding coupling product in 81% yield (Table 3, entry 6).

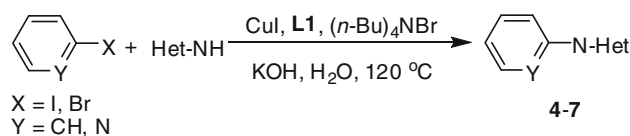
In summary, we have developed a simple, practical, and efficient protocol for the *N*-arylation of imidazoles with aryl halides promoted by a ligand-assisted copper catalyst

in water. This method avoids the use of toxic organic solvents and precludes the need for stringent inert conditions. The ligand **L1** could easily be synthesized via Mannich reaction from inexpensive starting materials.

## Experimental

All reagents unless otherwise stated were purchased from commercial suppliers and used without further purification. Column chromatography was carried out with silica gel (200–300 mesh). Thin-layer chromatography was carried out using silica gel GF254 plates. <sup>1</sup>H NMR spectra were recorded on Bruker DPX (300 or 400 MHz) with CDCl<sub>3</sub> as solvent. Chemical shifts are reported in ppm using TMS as internal standard. Gas chromatography mass spectra (GC/MS) were recorded on an Agilent Technologies 6890 N instrument with an Agilent 5973 N mass detector (EI) and

**Table 3** N-Arylation of nitrogen heterocycles with aryl halides catalyzed by CuI/L1/PTC in water



Entry	Het-NH	ArX	Product	Yield <sup>a</sup> (%)
1				<b>4</b> 92
2				85
3				<b>5</b> 90
4				82
5				<b>6</b> 90
6				<b>7</b> 81

<sup>a</sup> Isolated yield after column chromatography

an HP5-MS 30 m × 0.25 mm capillary apolar column (Stationary phase: 5% diphenyldimethylpolysiloxane film, 0.25 μm). GC/MS method: initial temperature 100 °C, initial time 2 min, ramp 10 °C/min until 250 °C then held for 20 min.

#### Synthesis of Mannich bases LI–L4

The Mannich bases were synthesized according to Refs. [28, 29].

#### General procedure for the N-arylation of nitrogen nucleophiles

Imidazole (163.4 mg, 2.40 mmol), 38.1 mg CuI (0.20 mmol), 143.4 mg 1,4-bis(2-hydroxy-5-methoxybenzyl) piperazine (0.40 mmol), aryl halide (2.00 mmol), 225 mg KOH (4.0 mmol), 64.4 mg (*n*-Bu)<sub>4</sub>NBr (0.20 mmol), and 2 cm<sup>3</sup> water were put into a Teflon septum screw-capped tube and then sealed in the air. The reaction mixture was stirred at 120 °C for 12 h. After cooling to room temperature, ethyl acetate (3 × 1 cm<sup>3</sup>) was added to extract the coupling product and results were determined by GC. The pure N-arylated product was obtained by column

chromatography on silica gel. All products were known and characterized by <sup>1</sup>H NMR spectroscopy, the data were found to be identical with those reported in the literature [13–24, 30–34].

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