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2,6-Bis(2-methylhydrazine-1-carbonyl)pyridine 1-oxide as an Efficient Ligand for Copper-Catalyzed C–N Coupling Reaction in Water

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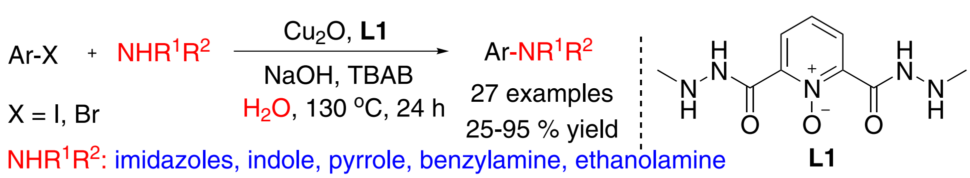
Abstract

Cu_2O/2,6-bis(2-methylhydrazine-1-carbonyl)pyridine 1-oxide was found to be an efficiently catalytic system for the N-arylation of imidazole, indole, benzimidazole, pyrrole, benzylamine and ethanolamine with aryl iodides and bromides by using NaOH as base in the presence of 20 mol% $(n\text{-}Bu)_4NBr$, and water as solvent at 130 °C in 24 h, and giving the N-arylated products in moderate to excellent yields.

Graphical Abstract



Keywords Ligand · C–N coupling · Aryl halides · Copper catalyst · Water

1 Introduction

The works of copper-catalyzed formation of C–N bond have made great progress after the pioneering works of Ullmann and Goldberg and have become one of the most powerful integrated strategies for building nitrogen-containing intermediates, which exist in natural products, pharmaceuticals and pesticides [1, 2]. However, several drawbacks of Ullmann-type coupling reactions, including stoichiometric amounts of copper reagents, high reaction temperature, extended reaction time and narrow functional-group tolerance, limited its applications. Over the past decade, significant improvements have been achieved to improve its efficiency and selectivity by using various ligands, such as 1,2-diamines, amino acid, diols, imines, ß-diketones and others [3–7]. While significant progress has been made in the transformation described above, it is still highly desirable to develop an easily accessible, economical and environmentally friendly solution for this type of reactions.

In spite of advances of organic transformations using organic solvents, its drawbacks can't be ignored, including healthy problems, violating the principle of environmental friendliness. In terms of the requirements of green chemistry, various environmentally benign reaction media have been used as substitutes such as water, supercritical fluids and ionic liquids [8]. Obviously, water is the most attractive one because of its inimitable characters of nontoxic, cheap, and readily available [9, 10]. Therefore, during recent years, water has been successfully employed as a highly desirable solvents for organic transformations [10–14], of which copper-based amination of aryl halides in aqueous media or even in pure water has also been established [8, 15–24].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10562-018-2321-8) contains supplementary material, which is available to authorized users.

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Previously, we have designed and synthesized a novel series of 2-(hydrazinecarbonyl)pyridine *N*-oxides [25, 26] and its structural analogues [27] as ligands for copper-catalyzed N-arylation of nitrogen nucleophiles in water (Scheme 1). The results indicated that the *N*-oxide/anionic phenolate and acylhydrazine moieties of the ligands were the active sites, which might coordinate with the copper ion as the catalytic center in these catalytic systems. However, because of the relatively narrow substrate scopes of these examples mentioned above, we therefore set out to look for an improved catalyst system for this transformation. Herein, we optimized and designed 2,6-bis(2-methylhydrazine-1-carbonyl)pyridine 1-oxides as the ligands for C–N coupling reaction in water.

2 Results and Discussion

To evaluate the catalytic efficiency of the catalyst, imidazole and iodobenzene were chosen as model substrates for the coupling reaction in water. The standardized protocol was carried out by using imidazole (1.5 equiv.), iodobenzene (1 equiv.), base (2 equiv.), Cu source (10 mol%), and ligand (20 mol%) in water at 120 °C for 12 h. The results are shown in Table 1.

Between the two ligands used, **L1** exhibited much higher catalytic ability than **L0** (entries 1 and 2). As the better ligand was determined, we next examined copper sources, and CuCl, Cu_2O, CuO combined with **L1** afforded the N-arylated product in good yields of 70, 75, and 73% respectively (entries 4, 5, and 7). Control experiment certificated that copper catalyst of the reaction mixture was essential (entry 9). The following screening of various bases, including NaOH, KOH, K_2CO_3, K_3PO_4 and Cs_2CO_3, indicated that NaOH to be the best one in 75% yield (entries 5 and 10–13). Furthermore, temperatures lower than 120 °C resulted in inferior product yield while dramatically increased the yield when temperatures higher than 130 °C and prolong the reaction time to 24 h (entries 14–16). Decreasing the loading of ligand resulted in lower yields (entry 17). In summary, the optimal conditions for the N-arylation process in water consist of the combination of Cu_2O (10 mol%), NaOH (2 equiv.), **L1** (20 mol%), TBAB (20 mol%) at 130 °C for 24 h without the protection of inert gas.

In order to explore the scope of the application of the catalytic system, a variety of functionalized aryl iodides and bromides were aminated with nitrogen nucleophiles in water under the optimized reaction conditions, and the results were demonstrated in Tables 2 and 3. As shown in Table 2, to our delight, most of the nitrogen-containing heterocycle and amines with aryl iodides reacted well to afford the corresponding products in moderate to excellent yields (38–95%). Electron-donating groups seemed to be more beneficial than electron-withdrawing groups for these catalytic system. No obvious electronic effects were observed for *para*- and *meta*-substituted aryl iodides, however, steric hindrance of *ortho*-substituents resulted in a lower reactivity and afforded lower yield (entry 4). The amination of heteroaryl iodides, including dibenzothiophene (entry 10) and quinoline (entries 11, 14 and 17), proved to be successful. Notably, the coupling of aryl iodides with other N-containing nucleophiles, such as indole, benzimidazole, pyrrole, and benzylamine, did

Scheme 1 Previous works and this work

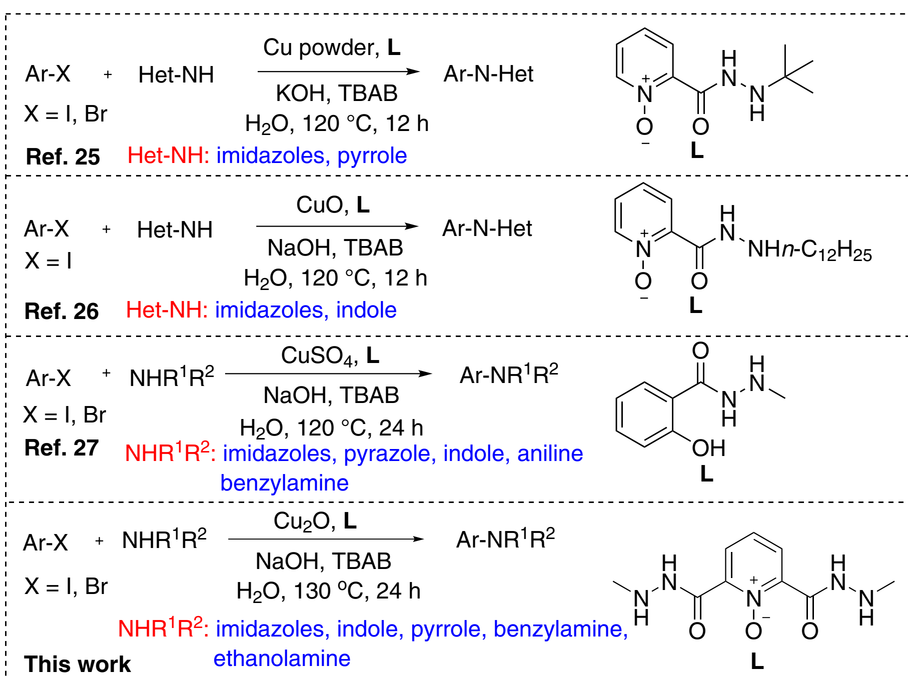
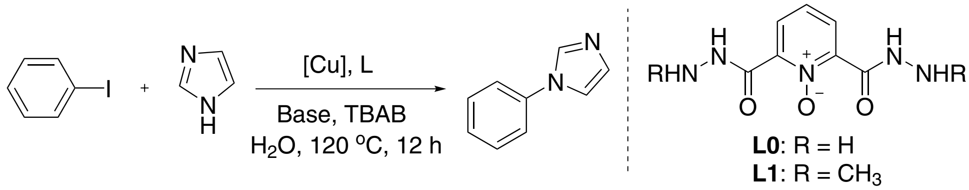


Table 1 Screening reaction conditions for N-arylation of imidazole with iodobenzene



Entry	[Cu]	Ligand	Base	Yield (%)[a]
1	Cu	**L0**	NaOH	40
2	Cu	**L1**	NaOH	56
3	CuI	**L1**	NaOH	61
4	CuCl	**L1**	NaOH	70
5	Cu_2O	**L1**	NaOH	75
6	$Cu(OAc)_2$	**L1**	NaOH	64
7	CuO	**L1**	NaOH	73
8	$CuSO_4$	**L1**	NaOH	68
9	–	**L1**	NaOH	trace
10	Cu_2O	**L1**	KOH	67
11	Cu_2O	**L1**	K_2CO_3	25
12	Cu_2O	**L1**	K_3PO_4	40
13	Cu_2O	**L1**	Cs_2CO_3	10
14[b]	Cu_2O	**L1**	NaOH	72
15[c]	Cu_2O	**L1**	NaOH	81
16[c,d]	Cu_2O	**L1**	NaOH	95
17[c,d,e]	Cu_2O	**L1**	NaOH	78

Reaction conditions iodobenzene (0.5 mmol), imidazole (0.75 mmol), [Cu] (10 mol %), **L** (20 mol %), TBAB (20 mol %), base (1 mmol), H_2O (1 mL), 120 °C, 12 h

[a]Isolated yield

[b]Reaction temperature: 100 °C

[c]Reaction temperature: 130 °C

[d]Reaction time: 24 h

[e]0 mol % of **L1**

occur smoothly (entries 12–18). Interestingly, the reaction was highly chemoselective; for example, reaction of ethanolamine only gave the N-arylated product under present conditions (entry 19). As a result of lower activity of aryl bromides than that of iodides, the coupling reaction of aryl bromides provided slightly lower yields (Table 3, entries 1–5), and fortunately, heteroaryl bromides also coupled with imidazole to give the corresponding products in moderate yields (Table 3, entries 6–8).

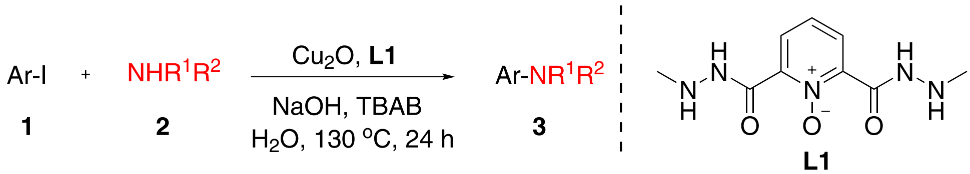
A large scale synthesis was performed by taking 5 mmol of iodobenzene and 7.5 mmol of imidazole in 10 mL of H_2O at 130 °C for 24 h, and the reaction proceeded without any difficulty to obtain *N*-aryl product **3a** in 89% yield (Scheme 2).

A proposed mechanism for the present coupling reaction is shown in Scheme 3. In the presence of NaOH, Cu_2O might react with **L1** to afford Cu(I) complex **I**, in which the strong electron-donating ability of the ligand could make this complex very active toward the oxidative addition with an aryl halide. The oxidation addition of **I** with aryl halides provided Cu(III) complex **II**, which might interacts with nitrogenous heterocycle to form **III**. Reductive elimination of **III** led to the coupling products and regenerated the catalytic species **I**.

3 Conclusions

In summary, this effort has led to the identification of 2,6-bis(2-methylhydrazine-1-carbonyl)pyridine 1-oxide as an ideal ligand for promoting copper-catalyzed Ullmann-type coupling reactions of aryl halides with nitrogen nucleophiles in water. The protocol demonstrated broad substrate scopes with good isolated yields. Further studies of this

Table 2 Cu-catalyzed N-arylation of nitrogen nucleophiles with aryl iodides using 2,6-bis(2-methylhydrazine-1-carbonyl)pyridine 1-oxide as ligand in water



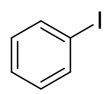
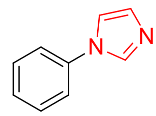
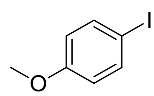
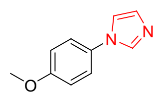
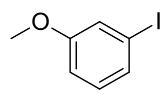
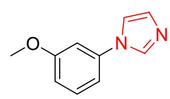
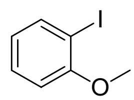
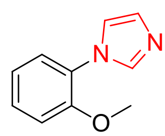
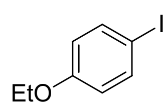
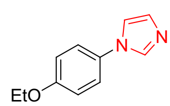
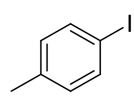
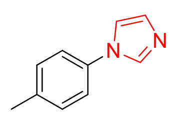
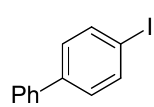
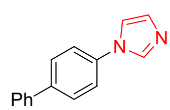
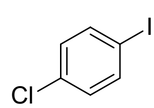
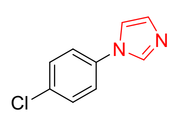
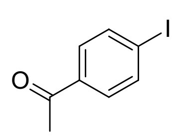
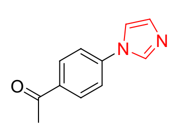
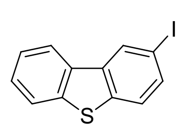
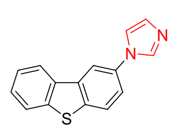
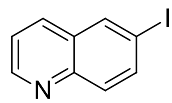
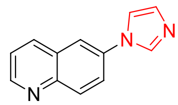
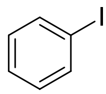
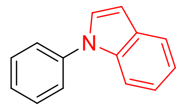
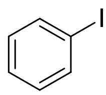
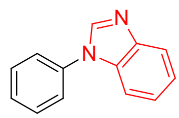
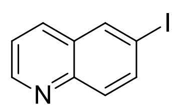
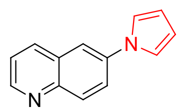
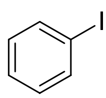
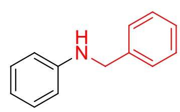
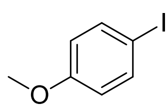
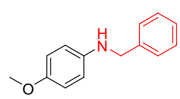
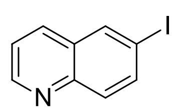
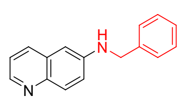
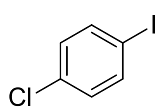
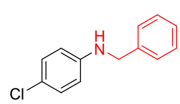
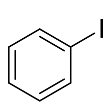
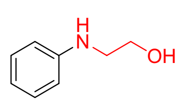
Entry	Ar-X	Product		Yield (%)[a]
1			**3a**	95
2			**3b**	92
3			**3c**	87
4			**3d**	48
5			**3e**	90
6			**3f**	71
7			**3g**	60
8			**3h**	89
9			**3i**	77
10[b]			**3j**	40

Table 2 (continued)

Entry	Ar-X	Product		Yield (%)[a]
11			**3k**	95
12			**3l**	60
13			**3m**	38
14			**3n**	70
15[c]			**3o**	60
16[c]			**3p**	67
17[c]			**3q**	80
18[c]			**3r**	50
19[c]			**3s**	61

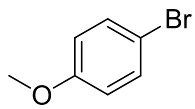
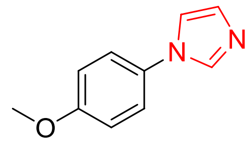
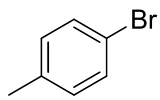
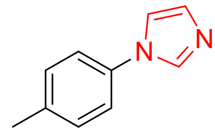
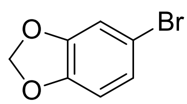
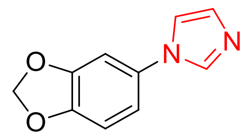
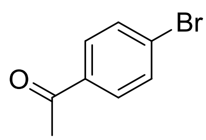
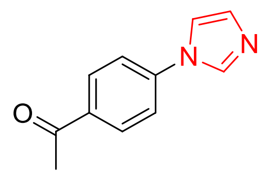
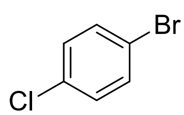
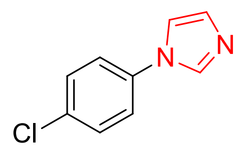
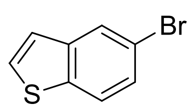
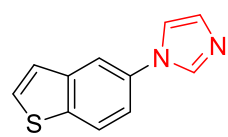
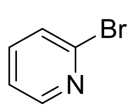
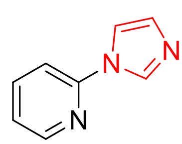
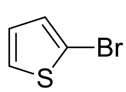
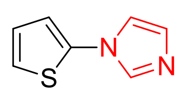
Reaction conditions ArI (0.5 mmol), R^1R^2NH (0.75 mmol), Cu_2O (0.05 mmol), **L1** (20 mol %), TBAB (20 mol %), NaOH (1 mmol), H_2O (1 mL), 130 °C, 24 h

[a]Isolated yield

[b]Reaction time: 36 h

[c]NHR^1R^2 (1.5 mmol)

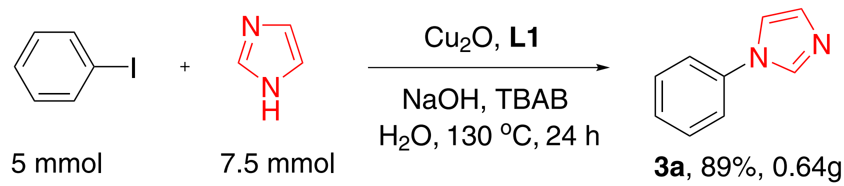
Table 3 Cu-catalyzed N-arylation of imidazole with aryl bromides using 2,6-bis(2-methylhydrazine-1-carbonyl) pyridine 1-oxide as ligand in water

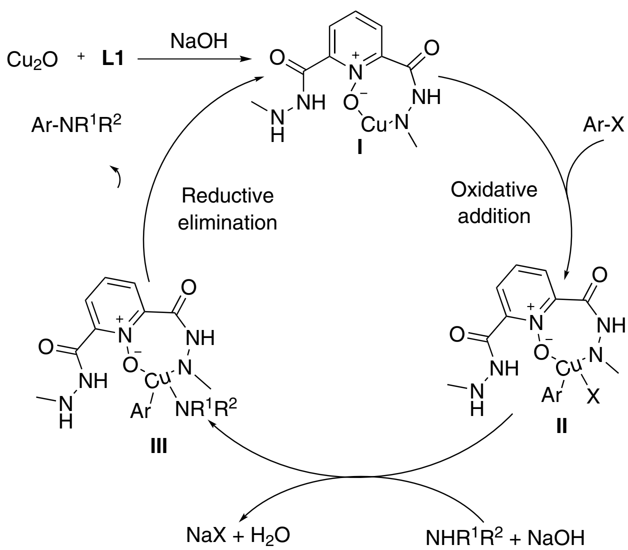
Entry	Ar–Br	Product		Yield (%)[a]
1			**3b**	50
2			**3f**	25
3			**3t**	48
4			**3i**	67
5			**3h**	53
6			**3u**	67
7			**3v**	71
8			**3w**	28

Reaction conditions ArI (0.5 mmol), Het-NH (0.75 mmol), Cu_2O (0.05 mmol), **L1** (20 mol %), TBAB (20 mol %), NaOH (1 mmol), H_2O (1 mL), 130 °C, 24 h

[a]Isolated yield

Scheme 2 Large-scale reaction of N-arylation of imidazole with iodobenzene in water





Scheme 3 Proposed mechanism

catalytic process are currently underway in our lab, and will be reported in due course.

3.1 Experimental Section

3.1.1 General Methods

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Column chromatography was performed with silica gel (200–300 mesh) purchased from Qingdao Haiyang Chemical Co. Ltd. Thin-layer chromatography was carried out with Merck silica gel GF_{254} plates and visualized by exposure to UV light (254 nm). All derivatives are characterized by ^{1}H NMR and ^{13}C NMR and GC-MS, which were compared with the previously reported data. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded at room temperature on a Bruker Avance III HD 400 instrument at 400 and 100 MHz, respectively. Mass spectra were recorded on GC-MS (Agilent 7890A/5975C) instrument under EI model. Electrospray ionization high-resolution mass spectra (ESI–HRMS) were recorded on a Thermo Scientific LTQ Orbitrap XL high-resolution mass spectrometer.

3.1.2 General Procedure for the Synthesis of 3a–3w

A 25 mL Schlenk tube was charged with Cu_2O (0.05 mmol), ArX (0.5 mmol), NHR^1R^2 (0.75 mmol), NaOH (1 mmol), TBAB (0.1 mmol), **L1** (0.1 mmol) and water (1 mL). The mixture was stirred at 130 °C for 24 h. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatograph on silica gel (ethyl acetate/petroleum ether as the eluent) to provide the target products **3a–3w**.

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