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COMMUNICATION

A highly efficient Cu-catalyst system for *N*-arylation of azoles in water†

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6,7-Dihydroquinolin-8(5*H*)-one oxime (L3) was found to serve as a superior ligand for the CuI-catalyzed *N*-arylation of imidazoles with aryl iodides, bromides, and electron-deficient chlorides in water. Moreover, the CuI/L3 catalyst system enabled the coupling reactions to take place smoothly with high yields under a low catalyst loading (0.1–1 mol% CuI and 0.2–2 mol% L3).

N-Arylazoles are important building blocks in numerous agrochemicals, pharmaceuticals, biological active compounds, and *N*-heterocyclic carbene chemistry.[1,2] Traditional synthetic methods for these compounds[3] often suffer from several drawbacks such as harsh reaction conditions (>200 °C), the use of stoichiometric amounts of copper reagents, and low functional-group tolerance. Recently, Buchwald *et al.*[4] and Taillefer *et al.*[5] found several *N*- and *O*-based chelators which were highly efficient ligands for the copper-catalyzed *N*-arylation of azoles. After the discovery of these ligands, different mono- and bidentate ligands have been reported to promote the Cu-catalyzed *N*-arylation of azoles under milder conditions.[6] Nevertheless, there is still a need to explore efficient catalytic systems, especially the simple and eco-friendly catalytic systems.[6j,7]

As we all know, water is the most economical and eco-friendly media in the world,[8] and the wide use of *N*-arylazoles in many fields have stimulated much interest into the development of new methods for their synthesis in water. Recently, Zhou *et al.*[9] and Fu *et al.*[10] reported several efficient ligands for the copper-catalyzed *N*-arylation of imidazoles with aryl iodides and activated aryl bromides in water. Wan *et al.* developed a Cu-additive system for the coupling reactions of imidazoles with aryl iodides and bromides in good yields in water, but in which the three component catalyst system of 5 mol% CuO, 50 mol% oxalyldihydrazide, and 100 mol% hexane-2,5-dione was essential.[11] Thus, the coupling of electron-rich aryl bromides and aryl chlorides with imidazoles in water remains problematic work for the Cu-catalyst system.

On the other hand, oximes have been found to be efficient ligands for the Cu-catalyzed C–C, C–N, and C–O bond formation (Fig. 1, **L1** and **L4**),[5a,b,10,12] but the conformationally constrained 6,7-dihydroquinolin-8(5*H*)-one oxime (Fig. 1, **L3**) has never been reported as a ligand. Herein, we wish to report 6,7-dihydroquinolin-8(5*H*)-one oxime, one of the commercially available oximes, as an excellent ligand for the Cu-catalyzed *N*-arylation of azoles with aryl iodides, bromides, and electron-deficient chlorides in water. This protocol contains several advantages: (1) water, an environmentally benign solvent, is used in place of volatile organic solvents; (2) the coupling reactions could take place with low catalyst loading (0.1 mol% CuI and 0.2 mol% ligand for aryl iodides; 1 mol% CuI and 2 mol% ligand for aryl bromides); (3) the catalyst system worked well for aryl iodides, bromides, and electronic-withdrawing aryl chlorides with good to excellent yields; (4) NaOH, a more inexpensive base, is used for the coupling reaction.

Initially, we chose the coupling of bromobenzene with imidazole in water under a low catalyst loading (1 mol% CuI and 2 mol% Ligand) to identify the efficiency of various oximes (Fig. 1). To our delight, **L3** afforded the highest yield (95%) under the specified conditions. Using **L3** as ligand, the potential catalytic efficiency of several other copper salts was

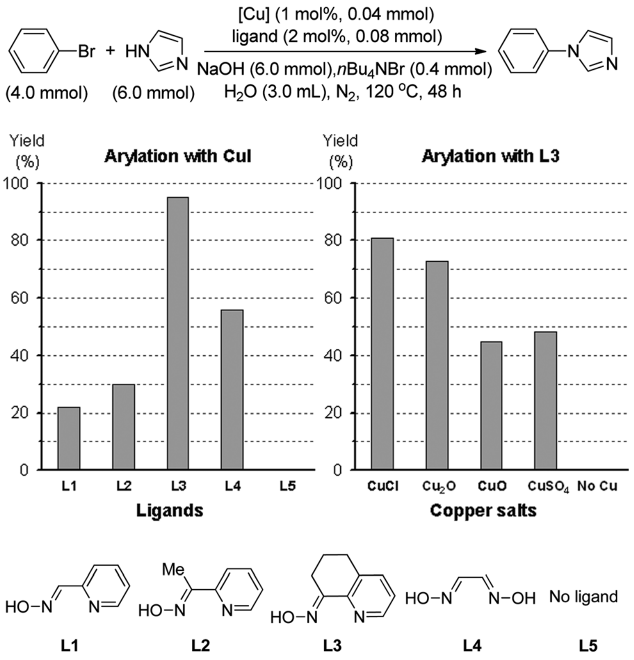

Fig. 1 Effect of ligands and copper salts on the efficiency of the *N*-arylation of imidazole.

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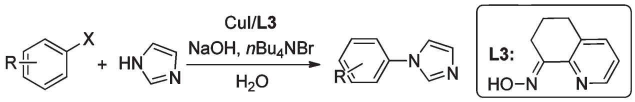
Table 1 Cu/**L3**-catalyzed *N*-arylation of imidazole with aryl and heteroaryl halides in water[a]



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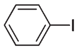
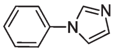
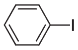
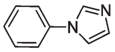
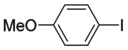
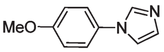
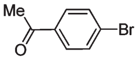
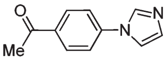
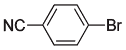
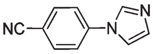
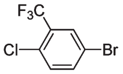
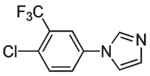
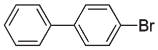
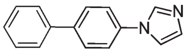
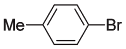
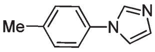
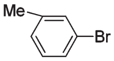
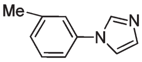
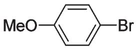
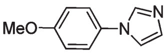
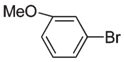
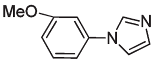
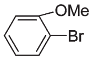
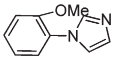
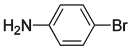
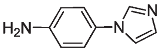
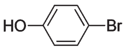
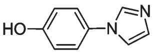
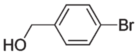
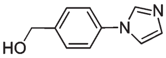
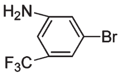
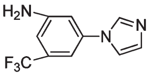
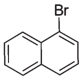
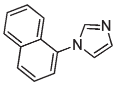
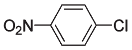
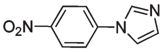
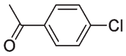
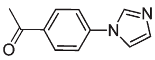
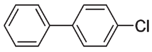
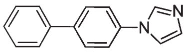
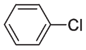
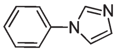
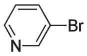
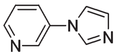
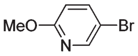
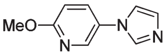
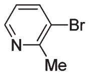
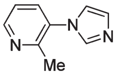
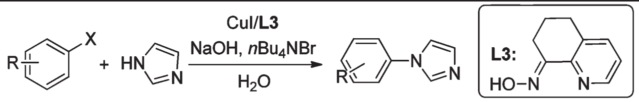
1			95
2			90[c]
3			93
4			94
5			95
6			93
7			91
8			90
9			87
10			83
11			90
12			61
13			78
14			82[d]
15			79
16			80
17			92
18			69[e] 21[f] 0[g]
19			40[e]
20			33[e]
21			0
22			94
23			90
24			72

Table 1 *(Contd.)*



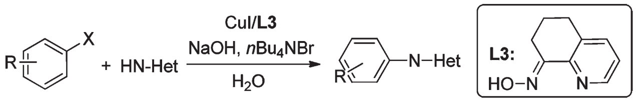
[a] Reaction conditions: Ar–X (4.0 mmol), imidazole (6.0 mmol), CuI (1 mol%), **L3** (2 mol%), $n\mathrm{Bu_4NBr}$ (10 mol%), NaOH (6.0 mmol), H_2O (3.0 mL), 120 °C, under N_2, 48 h. [b] Isolated yield. [c] CuI (0.1 mol%), **L3** (0.2 mol%). [d] NaOH (10 mmol). [e] CuI (5.0 mol%), **L3** (10 mol%), 130 °C. [f] Without **L3**. [g] Without CuI and **L3**.

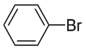
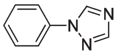
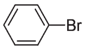
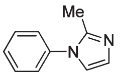
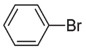
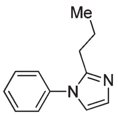
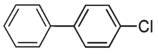
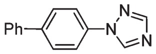
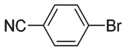
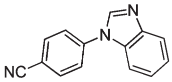
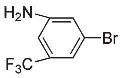
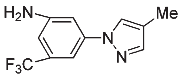
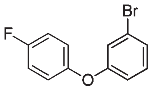
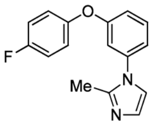
subsequently evaluated (Fig. 1). The results showed that copper compounds in I oxidation states were more catalytically active and CuI gave the best result. Control experiments revealed that no product was isolated in the absence of either the ligand or the copper salt. In addition, a 63% yield of 1-phenyl-1*H*-imidazole was achieved without $n\mathrm{Bu_4NBr}$. Thus, the combination of 1 mol % CuI, 2 mol% **L3**, 10 mol% $\mathrm{nBu_4NBr}$, and 150 mol% NaOH in water was chosen as the optimal conditions for further exploration.

As summarized in Table 1, the optimized conditions were then applied to a wide range of substituted aryl iodides, bromides, and chlorides. The results showed that excellent yields were obtained for the coupling of aryl iodides with imidazole (Table 1, entries 1–3). Also, we were pleased to find that only 0.1 mol% CuI and 0.2 mol% **L3** could successfully arylate imidazole with iodobenzene in 90% isolated yields (Table 1, entry 2). It is worth noting that no Cu–ligand system for C–N bond formation in water has previously been reported to achieve 1000 turnovers. Various aryl bromides, including electron-rich, electron-neutral and electron-deficient aryl bromides, were coupled with imidazole in excellent yields (Table 1, entries 4–17). Of particular note, electron-rich aryl bromides have been considered as highly challenging substrates for the Cu-catalysed *N*-arylation of imidazoles in water.[9,10] The CuI/**L3** system was found to effectively arylate imidazole with electron-rich aryl bromides in water with 1 mol% CuI and 2 mol% **L3** (Table 1, entries 8–15). Furthermore, various functional groups, such as ketones, nitriles, free amines, and free hydroxyls were well tolerated with satisfactory yields under the optimal conditions (Table 1, entries 4, 5, 13–16).

Attempts to use electron-deficient aryl chlorides to couple with imidazole under catalyst loadings of 5 mol% CuI and 10 mol% **L3** in water were successful and gave the desired products in moderate yields (Table 1, entries 18–20). To the best of our knowledge, there are no previous examples of the Cu-catalyzed synthesis of *N*-arylimidazoles directly from aryl chlorides in water.[13] While 1-chloro-4-nitrobenzene coupled with imidazole, without **L3** or both CuI and **L3**, the yield was dramatically reduced to 21% and 0%, respectively (Table 1, entry 18). However, when chlorobenzene was used as the substrate, no coupling products were isolated (Table 1, entry 21). Moreover, the reactions of various bromopyridines with imidazole were

Table 2 Cu/**L3**-catalyzed *N*-arylation of azoles with aryl halides[a]



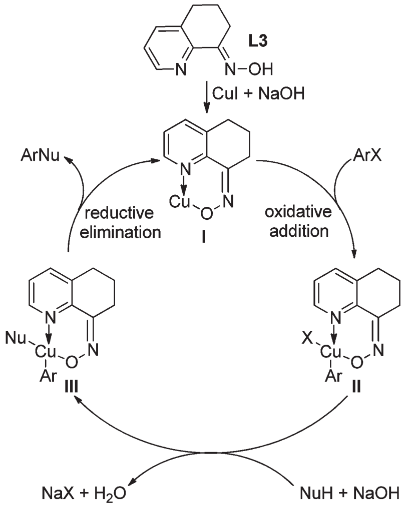
Entry	Ar–X	Product	Yield[b] (%)
1			90
2			77
3			68
4			33[c]
5			86
6			83
7			75

[a] Reaction conditions: Ar–X (4.0 mmol), imidazole (6.0 mmol), CuI (1 mol%), **L3** (2 mol%), NaOH (6.0 mmol), $n\mathrm{Bu_4NBr}$ (10 mol%), H_2O (3.0 mL), 120 °C, under N_2, 48 h. [b] Isolated yield. [c] CuI (5.0 mol%), **L3** (10 mol%), 130 °C.

also performed with great success. Almost all the bromopyridines coupled with imidazole in excellent yields in water (Table 1, entries 22–24).

To further expand the substrate scope of this methodology, the CuI/**L3** system was explored with other nitrogen-containing heterocycles. As listed in Table 2, a variety of five-membered azoles such as 1,2,4-triazole, benzimidazole, and pyrazole coupled with kinds of aryl halides to afford the corresponding products in moderate to excellent yields under the optimal conditions (Table 2). The sterically hindered 2-methylimidazole and 2-propylimidazole coupled with aryl bromides in good yields (Table 2, entries 2, 3, and 7). *N*-arylation of benzimidazole and 4-methyl-1*H*-pyrazole with aryl bromides bearing a nitrile and a free amino group could successfully take place to assemble the corresponding products in yields of 86% and 83%, respectively (Table 2, entries 5–6).

Based on previous literature reports,[4e,5b,6e] a possible mechanism of the Cu/**L3**-catalyzed *N*-arylation of *N*–H heterocycles is proposed in Scheme 1. The chelating Cu(I) with **L3** formed a six-member reactive species **I**, and the subsequent oxidative addition of **I** with aryl halides produced the transient $\mathrm{Cu^{III}}$ species **II**. In the presence of base, the intermediate **II** was nucleophilic substituted by *N*–H heterocycles to afford intermediate **III**, followed by reductive elimination readily to provide the coupling product and regenerate the active Cu(I) species **I**.



Scheme 1 Proposed mechanism.

In summary, we have developed an excellent copper catalytic system for the arylation of *N*–H heterocycles with 6,7-dihydroquinolin-8(5*H*)-one oxime as ligand in water. This *N*-arylation process takes place under a low catalyst loading (0.1–5 mol% CuI) and avoids the use of expensive bases. Overall, we believe that this economical, general, and highly efficient method could provide an attractive complement to the Cu-catalyzed synthesis of *N*-arylazoles.

Acknowledgements

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