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# 4,7-Dimethoxy-1,10-phenanthroline: An Excellent Ligand for the Cu-Catalyzed *N*-Arylation of Imidazoles

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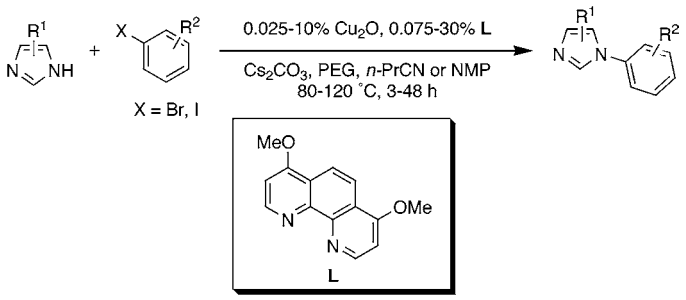
## ABSTRACT




**4,7-Dimethoxy-1,10-phenanthroline (L) was found to be an efficient ligand for the copper-catalyzed *N*-arylation of imidazole with aryl iodides and bromides under mild conditions. A variety of hindered and functionalized imidazoles and aryl halides were transformed in good to excellent yields.**

*N*-Aryl imidazoles are structural motifs found in many biologically active compounds.[1] Traditionally, this moiety has been prepared by nucleophilic aromatic substitution of an activated aryl halide and by copper-mediated coupling of the heterocycle with an aryl iodide. In the former case, the scope of the reaction is limited to those targets that can be assembled from aryl halides bearing strongly electron-withdrawing substituents. In the latter case, the utility of the classical Ullmann reaction has been limited by the harsh conditions often required (exposure of substrates to high temperatures, typically 150−200 °C, for extended periods of time using stoichiometric copper).[2] Because of these shortcomings, newer and milder transition-metal-catalyzed approaches have been pursued.[3,4]

Despite the recent development of Pd-catalyzed C−N bond-forming reactions, these new methods have yet to become general for the *N*-arylation of imidazoles.[3] In contrast, recent modifications to the Ullmann coupling have allowed this reaction to maintain its longstanding grasp on the synthesis of *N*-arylated imidazoles.[4]

Stoichiometric reagents that can be employed for the Cu-mediated *N*-arylation of imidazoles include (a) aryllead triacetates,[5] (b) arylboronic acids,[6] (c) triarylbismuths,[7] (d) hypervalent aryl siloxanes,[8] (e) diaryl iodonium salts,[9] and (f) arylstannanes.[10] A major drawback of the methods that employ these reagents is the use of toxic and/or unstable reagents that can be difficult to access. Furthermore, in some cases, only one of multiple aryl groups is transferred to the heterocycle. The use of aryl halides as the electrophilic coupling partner resolves many of these issues.

We have previously reported that 10 mol % of copper (I) triflate facilitates the coupling of imidazole with aryl iodides under moderate conditions (100% 1,10-phenanthroline/10% dba/$Cs_2CO_3$/xylenes/110−125 °C/24−48 h).[11] However, the scope of the process was primarily limited to the coupling of unhindered imidazoles with unhindered aryl iodides. Aryl bromides did react, though sluggishly. Other drawbacks of this method include long reaction times and the use of both air-sensitive $(CuOTf)_2$·PhH and stoichiometric quantities of 1,10-phenanthroline.

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Recently, we have developed effective systems for the Cu-catalyzed coupling of aryl iodides and bromides with cyclic secondary alkylamines,[12a,b] amides,[12c,d,f] indoles,[12d,e] pyrroles,[12f,g] pyrazoles, indazoles, and triazoles.[12g] Despite these protocols that could be carried out under mild conditions for the *N*-arylation of a number of nitrogen heterocycles through the use of *N*,*N*′-dimethylethylenediamine-based ligands, little progress in our own work had been made for the coupling of imidazoles.[12g]

Subsequent reports by other groups have disclosed the use of salicylaldoxime derivatives,[13a] amino acid derivatives,[13b,c] DMEDA,[13d] 4,7-dichloro-1,10-phenanthroline,[13e] and 8-hydroxyquinoline,[13f] aminoarenethiol,[13g] and oxime-phosphine oxides[13h] as ligands in the Cu-catalyzed *N*-arylation of imidazoles with aryl halides. However, very few examples of the coupling of imidazoles with aryl bromides or of a hindered substrate (either a 2- or 4-substituted imidazole or a 2-substituted aryl halide) have been disclosed. Herein, we describe our recent work, which significantly expands the substrate scope for the coupling of imidazoles with aryl halides.

Our initial investigations of the coupling of 2-iodotoluene with imidazole demonstrated that 4,7-dimethoxy-1,10-phenanthroline (**L**) in combination with $(CuOTf)_2 \cdot PhH$ and $Cs_2CO_3$ in $CH_3CN$ provided an improved catalyst system for this transformation. As tetraethylammonium carbonate (TEAC) had been recently shown to increase reaction rates in the Cu-catalyzed *N*-arylation of imidazoles and benzimidazoles,[13f] we attempted to employ this base in our system. However, yields of *N*-*o*-tolyl imidazole were low due to *N*-alkylation of the imidazole. This problem could be alleviated while maintaining increased reaction rates by using poly(ethylene glycol)[14] (PEG) as a solid−liquid phase-transfer catalyst with $Cs_2CO_3$ as base.[15] Furthermore, with PEG as an additive, we were able to use a wider variety of inexpensive and stable copper precursors (e.g., $Cu_2O$, CuI) and polar aprotic solvents (e.g., $CH_3CN$, EtCN, *n*-PrCN, DMF, DMSO, NMP) to effect the desired transformation.

Using the catalyst system based on **L**, we first explored the scope of the reaction with *m*- and *p*-substituted aryl halides (Table 1). We found that we were able to arylate imidazole with iodobenzene in excellent yields in 3 h with 5% Cu at 110 °C in NMP and in 48 h with 0.05% Cu in *n*-PrCN (entry 1). To the best of our knowledge, no Cu-based system for C−N bond formation has previously been reported to achieve 2000 turnovers. The reactions of aryl bromides possessing ester and nitrile groups were inefficient under the standard conditions because of the partial hydrolysis of the ester to benzoic acid and of the nitrile to amide. However, by using lower reaction temperatures (80−90 °C) with aryl iodide substrates, excellent yields of the ester- and nitrile-bearing *N*-arylated products could be obtained (entries 2 and 4). We were able to exploit the intrinsic reactivity differences of aryl halides in Cu-catalyzed amination reactions ($I > Br \gg Cl > F$),[2,4] to couple aryl iodides selectively in the presence of substrates containing aryl bromides, chlorides, and fluorides (entries 7, 10, and 15). Electron-rich, -neutral, and -deficient aryl iodides all provide products

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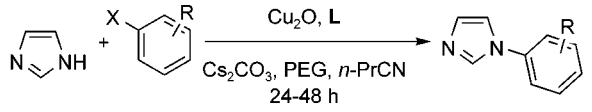
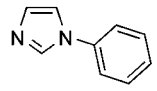
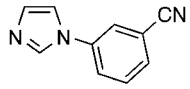
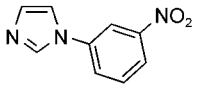
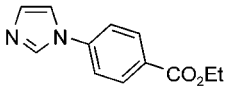
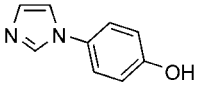
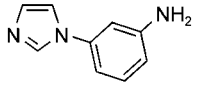
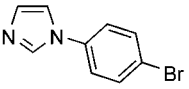
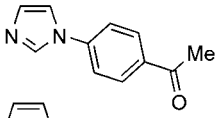
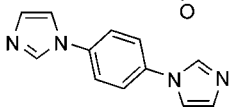
**Table 1.** Cu-Catalyzed Coupling of Unhindered Aryl Halides with Imidazole[a]



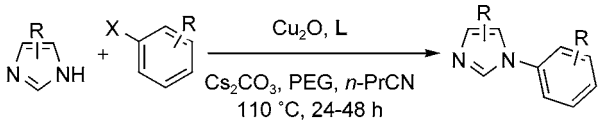

| entry | product | X | % Cu / % **L** | yield (%) |
|---|---|---|---|---|
| 1 |  | I | 0.05/0.075 | 95 |
| | | | 5/7.5 | 92[b,c] |
| 2 |  | I | 5/7.5 | 95[d,e] |
| 3 |  | I | 5/7.5 | 92[f] |
| 4 |  | I | 5/7.5 | 87[d,e,g] |
| 5 |  | Br | 10/15 | 84 |
| 6 |  | Br | 10/15 | 92 |
| 7 |  | I | 5/7.5 | 82[h] |
| 8 |  | Br | 10/15 | 90 |
| 9 |  | Br | 10/15 | 97[c] |

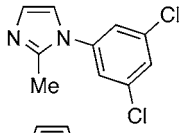
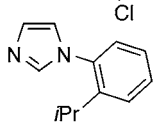
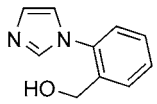
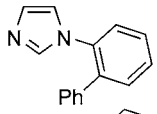
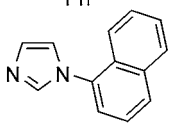
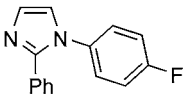
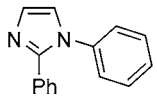
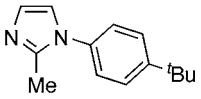
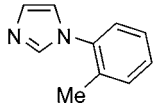
[a] General reaction conditions: 1.2 mmol of imidazole, 1.0 mmol of ArX, 1.4 mmol of $Cs_2CO_3$, 200 mg of PEG, 0.25−1.0 mL of butyronitrile under Ar or $N_2$ atmosphere at 110 °C. [b] 3 h. [c] NMP used as solvent. [d] MeCN used as solvent. [e] 80 °C. [f] 90 °C. [g] 100 mg flame-activated 3 Å molecular sieves. [h] 6:1 Ratio of iodo-/bromo-substituted arenes.

in good to excellent yields. Imidazole can be selectively arylated in the presence of a free −OH or $-NH_2$ group (entries 5, 6, and 12). This is particularly interesting as 1,-10-phenanthroline derivatives have also been reported as ligands in the Cu-catalyzed syntheses of aryl ethers and arylamines from aryl halides.[16]

Because the Cu-catalyzed coupling imidazoles with aryl halides employing hindered substrates are rare, we decided to examine the expansion of the scope of this coupling further by utilizing our Cu/**L**-based system in reactions of hindered imidazoles and with hindered aryl halides (Table 2). We were pleased to discover that 2-methyl- and 2-phenyl-substituted

**Table 2.** Cu-Catalyzed Coupling of Hindered Imidazole−Aryl Halide Combinations[a]




| entry | product | X | % Cu / % **L** | yield (%) |
|---|---|---|---|---|
| 10 |  | I | 5/7.5 | 84 |
| 11 |  | I | 5/7.5 | 94 |
| 12 |  | I | 5/7.5 | 94 |
| 13 |  | I | 10/15 | 82[c] |
| 14 |  | I | 10/15 | 93[b,d] |
| 15 |  | I | 5/7.5 | 85 |
| 16 |  | Br | 20/30 | 92[c] |
| 17 |  | Br | 10/15 | 95 |
| 18 |  | Br | 10/15 | 85[d] |

[a] General reaction conditions: 1.2 mmol of imidazole, 1.0 mmol of ArX, 1.4 mmol of $Cs_2CO_3$, 200 mg of PEG, 0.25−1.0 mL of butyronitrile under Ar or $N_2$ atmosphere at 110 °C. [b] No PEG. [c] 120 °C. [d] NMP used as solvent.

imidazoles could be coupled with aryl iodides and bromides in good to excellent yields (entries 10, 15−17).[17] This system could also be successfully applied to imidazole *N*-arylation with *o*-substituted aryl halides. In this way, good yields of *N*-aryl imidazoles were obtained using 2-alkyl and 2-phenyl iodobenzene (entries 11−13, 18).[18] The coupling of 1-io-

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(17) The coupling of 2-methylimidazole with 4-iodoanisole proceeds to 65% conversion in 48 h (10% $(CuOTf)_2$·PhH/10% dba/100% 1,10-phenanthroline/xylenes/125 °C/48 h).[11] The coupling of 2-methylimidazole with 5-bromo-*m*-xylene (10% CuI, 10% 8-hydroxyquinoline/TEAC/10:1 DMF/$H_2O$/ 130 °C/ 16 h) yields 64% of *N*-aryl imidazole.[13f]

donaphthalene could also be accomplished using this improved catalyst system (entry 14).

In conclusion, we have described a new electron-rich 1,-10-phenanthroline ligand for the Cu-catalyzed *N*-arylation of imidazoles with aryl iodides and bromides. This system not only is capable of coupling hindered substrate combinations but also operates under conditions mild enough to tolerate a wide array of functional groups. A detailed comparison of ligands commonly used for Cu-catalyzed imidazole arylation will subsequently be reported as part of a full paper.

(18) The coupling of 1-bromo-2,4-dimethoxy-benzene with imidazole gives 62% yield (10% CuI/40% L-proline/$K_2CO_3$/DMSO/110 °C/40 h).[13c] The coupling of imidazole with 2-bromotoluene (10% CuI, 10% 8-hydroxy quinoline/TEAC/10:1 DMF/$H_2O$/ 130 °C/16 h) yields 46% of *N*-*o*-tolyl imidazole.[13f] The coupling of 2-iodotoluene with imidazole gives 92% yield (5% $Cu_2O$/20% Salox/$Cs_2CO_3$/$CH_3CN$/82 °C/36 h).[13a]

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**Supporting Information Available:** Experimental procedures and characterization data for all new and known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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