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Copper-Catalyzed N-Arylation of Imidazoles and Benzimidazoles

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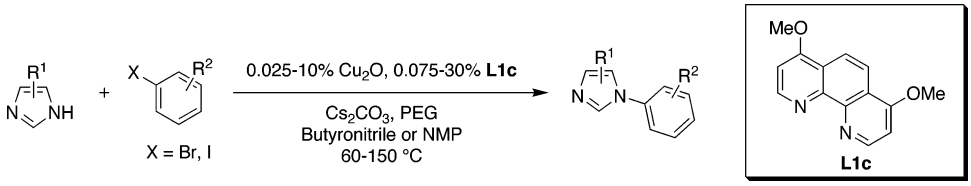
Received April 17, 2007



4,7-Dimethoxy-1,10-phenanthroline (**L1c**) was found to be an efficient ligand for the copper-catalyzed N-arylation of imidazoles and benzimidazoles with both aryl iodides and bromides under mild conditions. Further optimization of the system has revealed that the addition of poly(ethylene glycol) accelerates this reaction. A variety of hindered and functionalized imidazoles, benzimidazoles, and aryl halides were transformed in good to excellent yields. Heteroaryl halides were also coupled in moderate to good yields. We also present the results obtained from a series of coupling reactions, which directly compare the use of **L1c** with other recently reported ligands.

Introduction

N-Aryl imidazoles and benzimidazoles are found in many biologically active compounds.[1] Although traditional preparations of these moieties, including nucleophilic aromatic substitution of an activated aryl halide and copper-mediated coupling of the heterocycle with an aryl iodide, can give access to a wide variety of N-arylated products, these methods suffer from significant limitations. In the former case, the scope of the reaction is confined to the use of aryl halides possessing strongly electron-withdrawing substituents. In the latter case, the range of functional groups tolerated by the long-established Ullmann reaction is severely restricted by the harsh conditions often required (exposure of substrates to high temperatures, typically 150−200 °C, for extended periods of time using stoichiometric quantities of a copper compound).[2]

In recent years, mild transition metal-catalyzed cross-coupling of aryl halides with N−H heterocycles[3−4] has complemented the traditional preparations of these structures. Despite the continued development of hindered biaryl monophosphines[5] and other ligands[3] for improved Pd-catalyzed C−N bond-forming reactions, no Pd-based catalysts display a good generality for the N-arylation of imidazoles. Thus, Cu-based catalysts have continued to provide the most effective systems for the N-arylation of imidazoles.[4] Although the Cu-mediated N-arylation of imidazoles and benzimidazoles has been ac-

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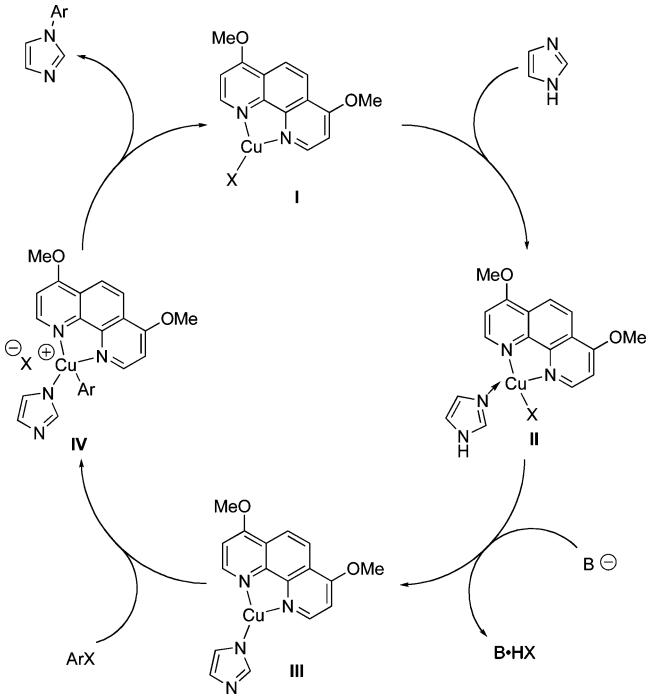
10.1021/jo070807a CCC: $37.00
Published on Web 07/11/2007

complished using aryllead triacetate,[6] arylboronic acid,[7] triarylbismuth,[8] hypervalent aryl siloxane,[9] diaryl iodonium salt,[10] and arylstannane[11] reagents, these methods generally require the use of toxic and/or unstable reagents that can be difficult to prepare. Furthermore, in many cases, only one of the multiple aryl groups is transferred to the heterocycle. In contrast, the use of more stable and readily available aryl halides as the electrophilic coupling partner resolves these issues.

In our previous report, 5 mol% bis-[copper (I) triflate]benzene [$(CuOTf)_2$·PhH] was shown to facilitate the coupling of imidazole with aryl iodides under moderate conditions (100% 1,10-phenanthroline, **L1a**/10% dba/Cs_2CO_3/xylenes/110−125 °C/24−48 h).[12] However, the scope of the catalyst system was limited to the coupling of unhindered imidazoles with unhindered aryl iodides. The use of air-sensitive $(CuOTf)_2$·PhH as the precatalyst required the use of inconvenient glove box techniques for reaction setup. The need for stoichiometric quantities of the 1,10-phenanthroline ligand and long reaction times were also undesirable.

Subsequently, we have developed effective ligands and catalyst systems for the Cu-catalyzed coupling of aryl iodides and bromides with a variety of N−H containing azoles; however, little progress was made with respect to the N-arylation of imidazoles.[13] While reports by other groups have disclosed the use of salicylaldoxime derivatives,[14a] amino acid derivatives,[14b−c] *N*,*N*′-dimethylethylenediamine derivatives (DMEDA),[14d] ligands first reported for C−N couplings by us,[13c−e] 4,7-dichloro-1,10-phenanthroline,[14e] 8-hydroxyquinoline,[14f] aminoarenethiol,[14g] oxime-phosphine oxides,[14h] phosphoamidites,[14i] 1,10-phenanthroline,[14j] fluoroapetite,[14k] and 2-aminopyrimidinediols[14l] as supporting ligands in the Cu-catalyzed N-arylation of imidazoles with aryl iodides, very few examples of the coupling of imidazoles with aryl bromides or of even moderately hindered substrates (e.g., a 2-substituted imidazole or a 2-substituted aryl halide) were disclosed until our recent paper.[15] Furthermore, the use of heteroaryl halides and 4(5)-substituted imidazoles has not been reported. Herein, we describe a full account of our recent work, which significantly expands the substrate scope for the coupling of imidazoles and benzimidazoles with aryl halides. We also present results of a study in which we compare our results with other recently reported catalyst systems.

SCHEME 1. Possible Catalytic Cycle



Results and Discussion

Method Development and Mechanistic Considerations. Our initial investigations of the coupling of 2-iodotoluene with imidazole demonstrated that 4,7-dimethoxy-1,10-phenanthroline (**L1c**)[16] in combination with $(CuOTf)_2$·PhH and Cs_2CO_3 in CH_3CN provided an improved catalyst system for this transformation relative to those previously reported. As compared to that derived from **L1a**, the enhanced reactivity of the catalyst system based on Cu(I)-**L1c** can be attributed to the increased σ-donating ability of the ligand, as evidenced by the difference in acidities of the corresponding conjugate acids of the free phenanthrolines (pK_a **L1a**-H^+ = 4.86 and pK_a **L1c**-H^+ = 6.45).[17] The more electron-rich ligand should stabilize the presumed Cu(III) intermediate (Scheme 1, **IV**) and lower the oxidation potential for the Cu(I)-Cu(III) redox pair, thus accelerating the rate limiting aryl halide activation.[18]

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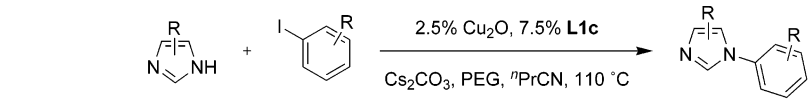
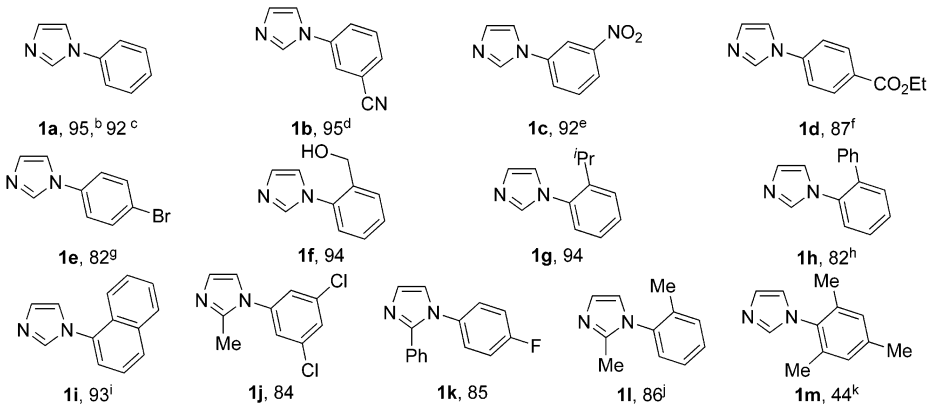
TABLE 1. Coupling of Imidazoles with Aryl Iodides[a]





[a] General reaction conditions: 1.2 mmol of imidazole, 1.0 mmol of ArX, 0.025 mmol of Cu_2O, 0.075 mmol of **L1c**, 1.4 mmol of Cs_2CO_3, 200 mg of PEG, and 0.25−1.0 mL of butyronitrile under Ar or N_2 atmosphere at 110 °C for 24−48 h. [b] 12 mmol of imidazole, 10 mmol of ArI, 14 mmol of Cs_2CO_3, 0.0025 mmol of Cu_2O, 0.0075 mmol of **L1c**, 2.0 g of PEG, and 2.5 mL of butyrontile. [c] Reaction run in NMP for 3 h. [d] Reaction run at 80 °C in MeCN. [e] Reaction run at 90 °C. [f] Reaction run at 80 °C in MeCN with 3 Å molecular sieves. [g] 1.2 mmol of ArI, 1.0 mmol of imidazole; 6:1 ratio of iodo-/bromo-substituted arene. [h] 0.05 mmol of Cu_2O and 0.15 mmol of **L1c**, 120 °C. [i] Reaction run in NMP with no PEG. [j] Reaction run in NMP at 150 °C. [k] Reaction run in DMSO at 150 °C.

Recent reports also have demonstrated that increasing the solubility of the base can accelerate metal-catalyzed amination reactions of aryl halides. As cetyltrimethylammonium bromide has been used as a phase transfer catalyst (PTC) in Pd-catalyzed amination reactions[19] and as tetraethylammonium carbonate (TEAC) has been used as a base in the Cu-catalyzed amination reactions[14f] of aryl halides, we attempted to employ tetraalkylammonium salts in our own system. While the use of these reagents did provide increased reaction rates, product yields were low due to alkylation of the starting imidazole. Further, TEAC decomposed under the reaction conditions to give NEt_3 and CO_2, which were detected by GCMS and by bubbling the gas produced through 1 M HCl. The problems associated with TEAC could be alleviated while maintaining faster reaction rates by using non-tetraalkylammonium solid−liquid phase transfer catalysts in combination with Cs_2CO_3.[20] The key choice of poly(ethylene glycol) (PEG) as an additive allowed for the use of inexpensive and stable copper salts (e.g., Cu_2O, CuI) as precatalysts, as opposed to air- and moisture-sensitive copper complexes, such as $[CuOTf]_2$·PhH.[21]

The use of PEG as a solid−liquid phase transfer catalyst increases the solubility of the carbonate in organic media, increasing the rate of reaction by 10−30%.[22] Without added PEG, the observed reactivity of our system in nitrile solvents is in the order MeCN > EtCN > *n*-PrCN at 110 °C—opposite the trend of their boiling points in the same series—suggesting that the relative insolubility of Cs_2CO_3, or a polar Cu complex (Scheme 1), in less polar solvents retards the reaction. With the use of PEG, reactions carried out in these three solvents proceed at comparable rates at 110 °C.[23] However, using PEG as a solvent was less effective, possibly due to poor mass transport in the highly viscous solvent. While most of the chemistry described herein generally uses either butyronitrile or NMP, it is also important to note that reactions using the PEG/Cs_2CO_3 combination also show rate enhancements in solvents such as MeCN, EtCN, DMF, DMA, and DMSO, although reactions using these other solvents tend to be slower than those conducted in butyronirile or NMP. In addition, this imidazole N-arylation process is moderately tolerant of water, as evidenced by the fact that our typical procedure involves weighing out a hygroscopic base (Cs_2CO_3) in the air with no protection from ambient moisture. Moreover, by using 2.5−10% Cu_2O as the precatalyst, we are necessarily producing water.[24]

Substrate Scope. Using the catalyst system based on **L1c**, we explored the scope of the reaction with unhindered aryl iodides (Table 1). Using a catalyst loading of only 0.05% Cu, we were able to N-arylate imidazole with iodobenzene in 48 h at 110 °C (**1a**). To the best of our knowledge, no Cu-based system for C−N bond formation has previously been reported to achieve as many as 2000 turnovers. The reactions of aryl iodides possessing ester and nitrile groups were inefficient under

(19) Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479.

(20) 18-Crown-6 has been used to accelerate the coupling of diarylamines with aryl iodides using Cu (stoichiometric)/K_2CO_3/*o*-dichlorobenzene/reflux: Gauthier, S.; Fréchet, J. M. J. *Synthesis* **1987**, 383.

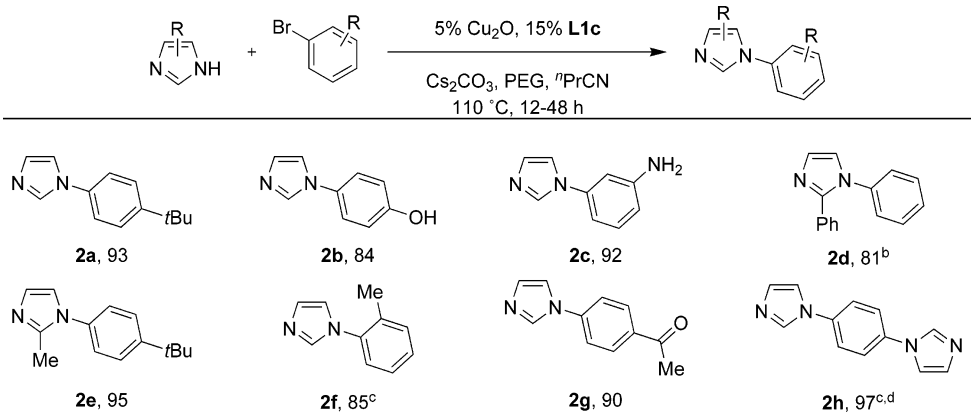
(21) Recent examples of the use of PEG as a solvent in transition metal-catalyzed processes include: (a) Nobre, S. M.; Wolke, S. I.; da Rosa, R. G.; Monteiro, A. L. *Tetrahedron Lett.* **2004**, *45*, 6527. (b) Reed, N. N.; Dickerson, T. J.; Boldt, G. E.; Janda, K. D. *J. Org Chem.* **2005**, *70*, 1728. (c) Svennebring, A.; Garg, N.; Nilsson, P.; Hallberg, A.; Larhed, M. *J. Org. Chem.* **2005**, *70*, 4720. (d) Liu, L.; Zhang, Y.; Wang, Y. *J. Org. Chem.* **2005**, *70*, 6122. (e) Wang, L.; Zhang, Y.; Liu, L.; Wang, Y. *J. Org. Chem.* **2006**, *71*, 1284.

(22) This phenomenon is likely similar to the recently reported use of the more soluble carbonate base, TEAC, in which the amount of the base in solution increases due to the enhanced "greasiness" of the cation.[14f]

(23) Increased rates involving acetonitrile and propionitrile may be partially due to the elevation of the boiling points of these solvents.

(24) Addition of small quantities of water to accelerate solid/liquid phase-transfer catalysis processes is well-documented. See: (a) Albanese, D.; Landini, D.; Maia, A.; Penso, M. *Ind. Eng. Chem. Res.* **2001**, *40*, 2396. (b) Yadav, G. D.; Jadhav, Y. B. *Langmuir* **2002**, *18*, 5595.

TABLE 2. Couplings of Imidazoles with Aryl Bromides[a]



[a] Reaction conditions: 1.2 mmol of imidazole, 1.0 mmol of ArX, 0.05 mmol of Cu_2O, 0.15 mmol of **L1c**, 1.4 mmol of Cs_2CO_3, 200 mg of PEG, and 0.25−1.0 mL of butyronitrile under Ar at 110 °C for 24−48 h. [b] 0.10 mmol of Cu_2O and 0.30 mmol of **L1c** at 120 °C. [c] Reaction run in NMP. [d] 1.0 equiv of ArBr and 2.4 equiv of imidazole with 2.8 equiv of Cs_2CO_3.

the standard conditions, due to the partial hydrolysis of the ester to benzoic acid and of the nitrile to benzamide. However, by lowering the reaction temperatures to 80−90 °C, excellent yields of the N-arylated products could be obtained (**1b**,**d**). Aryl iodides were selectively coupled in the presence of substrates containing aryl bromides, chlorides, and fluorides (**1e**,**j**,**k**). Electron-rich, -neutral, and -deficient aryl iodides all provided products in good to excellent yields. The coupling of hindered substrate combinations could also be accomplished using this catalyst system; 2-alkyl and 2-aryl imidazoles (**1j**−**l**) and ortho-substituted aryl iodides (**1f**−**i**) were effectively converted to product. The coupling of more hindered substrate combinations (**1l**−**m**) could be accomplished at higher reaction temperatures (150 °C). In the combination of imidazole with mesityl iodide, mesitylene from the reduction of the aryl iodide was the major side product. At this point, we do not fully understand the mechanism of the reduction pathway, although we speculate that it might involve a radical pathway.

Aryl bromides were also successfully coupled under our reaction conditions (Table 2). Higher quantities of catalyst and longer reaction times, however, were often necessary to provide good yields of product. The combination of 2-substituted imidazoles with aryl bromides provided N-arylated products in good yields (**2d**,**e**). Additionally, the coupling of imidazole and 2-bromotoluene can be accomplished in good yield (**2f**). Further, imidazole can be selectively arylated in the presence of a free -OH or $-NH_2$ group (**2b**,**c**). This selectivity is particularly interesting, as 1,10-phenanthroline derivatives have also been reported as ligands in the Cu-catalyzed syntheses of aryl ethers and aryl amines from aryl halides.[25]

Butyronitrile was employed as a solvent for many of the reactions described because it is relatively volatile, nonpolar, and easy to remove from products as compared to the higher boiling point solvents such as DMF, DMSO, and NMP. However, in some cases, the use of NMP as the solvent provided faster reactions. For example, we found that we were able to arylate imidazole with iodobenzene in excellent yields in 3 h with 5% Cu in NMP (**1a**), while the same reaction required 4 h using butyronitrile. More difficult cases, including reactions of hindered aryl halides and 2-substituted imidazoles, also reacted more efficiently using NMP (**1i**,**l**, **2f**,**h**, and **3d**). The rate enhancement using NMP can be seen in Figures 1−4.

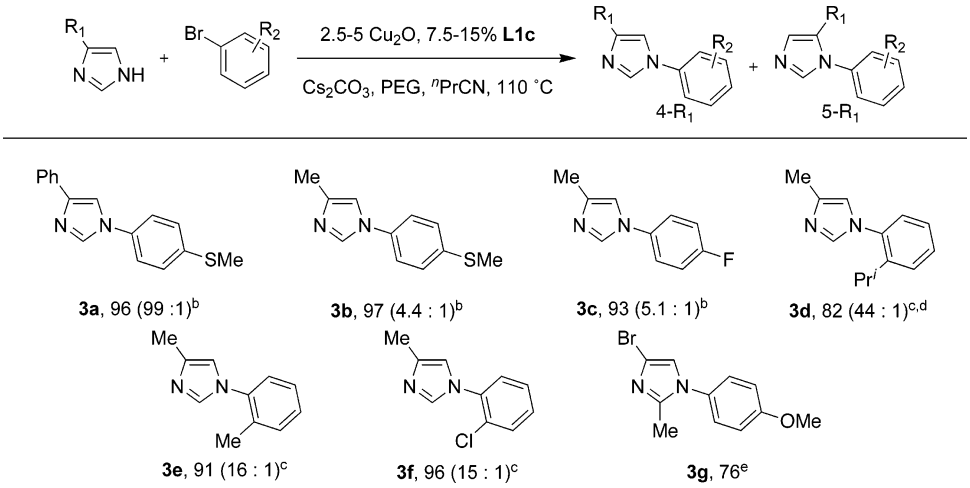
The reactions of 4(5)-substituted imidazoles with aryl halides showed varying degrees of regioselectivity, with the preferential formation of 4-substituted imidazoles (Table 3).[26] With 4-phenyl imidazole, the 1,4-diarylimidazole was the exclusive product observed (**3a**). Reactions of 4-methyl imidazoles with aryl bromides lacking an ortho-substituent showed similar selectivity for the formation of 1-aryl-4-alkyl imidazoles similar to that previously observed (**3b**,**c**).[12] As in the study conducted by Collman et al. on the coupling of 4-substituted imidazoles with aryl boronic acids,[26] the preferential selectivity for the 4-regioisomer over the 5-regioisomer is likely due to the greater steric interactions when the substituent R_1 resides at the 5-position as compared to the 4-position either prior to aryl halide activation (Scheme 2, **V** to **VI**) or upon activation of the aryl halide (**VII** to **VIII**). In contrast, reactions of 4(5)-methylimidazole with ortho-substituted aryl halides provided the 4-regioisomer with significantly better selectivity (**3d**−**f**). This increase in regioselectivity when using a hindered aryl halide likely arises due to the additional unfavorable steric interaction between the group ortho to the halide (R_2) and R_1 when R_1 is situated in the 5-position (**IX**) as opposed to the 4-position (**X**). The reaction of 4-bromo-2-methylimidazole with 4-iodoanisole provided 4-bromo-1-(4-methoxyphenyl)-2-methyl-1*H*-imidazole as the major product (**3g**). Formation of the 5-bromo-1-(4-methoxyphenyl)-2-methyl isomer was not detected by GC or ^{1}H NMR techniques. In this case, the selectivity is likely dictated by the increased steric effects that exist in the Cu (III) intermediate when the large bromide-substituent resides at the 5-position (**XI**) relative to the 4-position (**XII**).

As *N*-heteroaryl imidazoles are interesting targets in drug discovery and medicinal chemistry,[27] the coupling of imidazoles with unactivated heteroaryl bromides and iodides was examined (Table 4). Generally, isolated yields for reactions of imidazoles

(25) (a) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (b) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973. (c) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978.

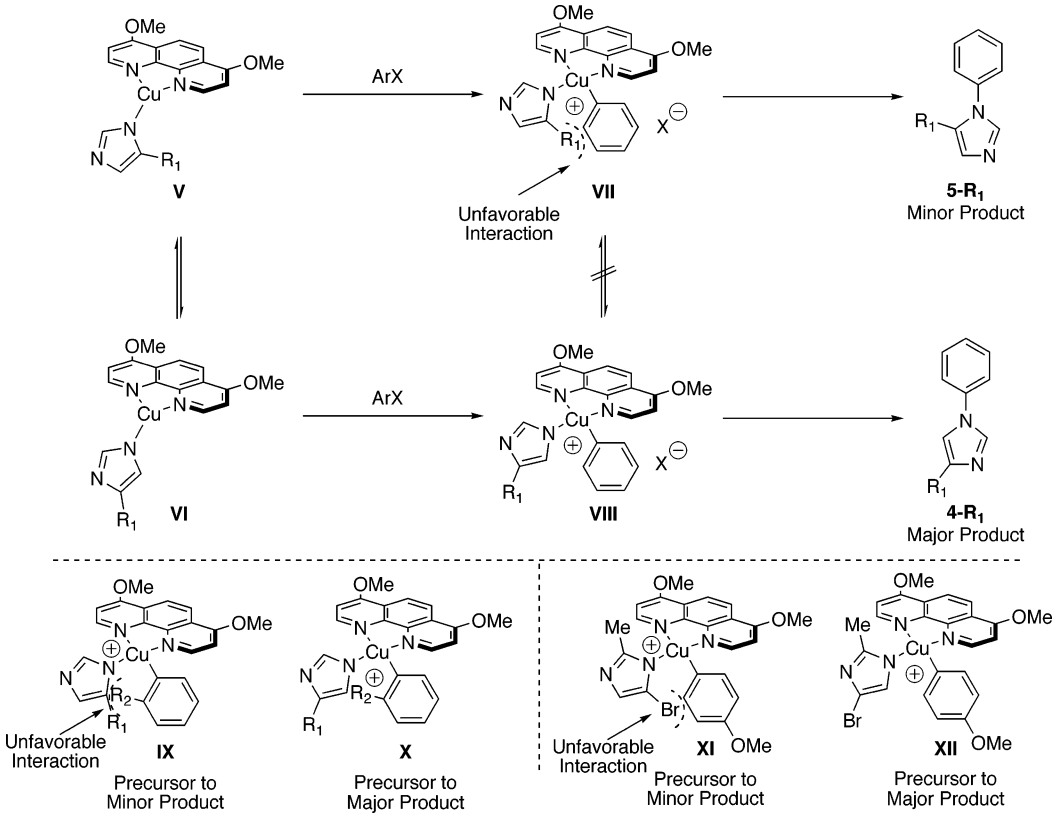
(26) Increased selectivity for the preferential formation of the 4-substituted *N*-aryl imidazole over the 5-regioisomer, due to increased steric effects, has also been observed in the Cu-catalyzed coupling of 4(5)-substituted imidazoles with aryl boronic acids. See: Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 7892.

TABLE 3. Coupling of 4(5)-Substituted Imidazoles[a,b]



[a] 4-R_1: 5-R_1 selectivity is reported in parentheses and was determined by GC analyses of the crude reaction mixtures and/or ^{1}H NMR spectra of the pure products. [b] Reaction conditions for ArBr: 1.2 mmol of imidazole, 1.0 mmol of ArBr, 0.05 mmol of Cu_2O, 0.15 mmol of **L1c**, 1.4 mmol of Cs_2CO_3, 200 mg of PEG, and 0.25−1.0 mL of butyronitrile under Ar atmosphere at 110 °C for 24−30 h. Isolated yields reported. [c] Reaction conditions for ArI: 1.2 mmol of imidazole, 1.0 mmol of ArI, 0.025 mmol of Cu_2O, and 0.075 mmol of **L1c**, with ArI. [d] NMP used as solvent. GC yield reported. [e] 1.2 mmol of ArI, 1.0 mmol of imidazole, no PEG, 0.05 mmol of CuI, and 0.075 mmol of **L1c** in 0.5 mL of MeCN. Only one regioisomeric bromide was detected by GC and ^{1}H NMR.

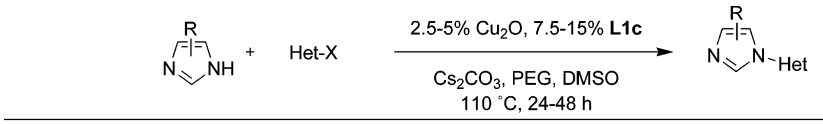
SCHEME 2. Consideration of Steric Effects in Reactions of 4(5)-Substituted Imidazoles

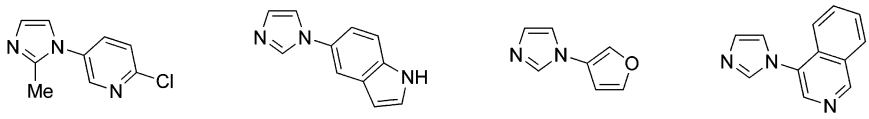


with heteroaryl iodides and bromides were slightly lower than those with simple aryl halides due to the formation of the reduced heteroarene as a byproduct.[28] In some cases, the use of DMSO as a solvent caused an increase in the yield of the desired product and decreased the quantity of the dehalogenated byproduct.

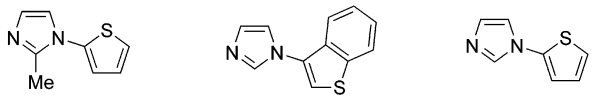
Useful selectivity was observed in the reaction of imidazole with 2-chloro-5-iodopyridine, a substrate activated at the 2-position for uncatalyzed S_nAr. In this case, the Cu-catalyzed substitution occurred predominantly at the iodide to provide **4a** in good yield. In the coupling of 5-iodoindole with imidaozle (**4b**), the *N*-heteroaryl imidazole was isolated in good yield, with trace amounts of *N*-aryl indole formed as a side product.[29] This selectivity likely arises from the more rapid transmetallation of imidazole with Cu(I) through the sp^2-hybridized lone pair electrons as compared to the case of indole, where coordination

TABLE 4. Couplings of Heteroaryl Halides





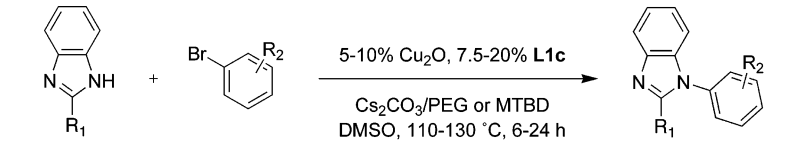
4a, 76 (X = I)[a] **4b**, 83 (X = I)[c] **4c**, 60 (X = Br)[b] **4d**, 85 (X = Br)[b]

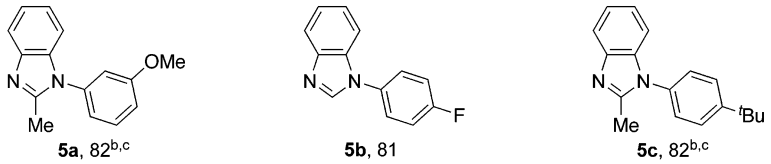


4e, 70 (X = I)[a] **4f**, 79 (X = Br)[b] **4g,** 83 (X = I)[a]

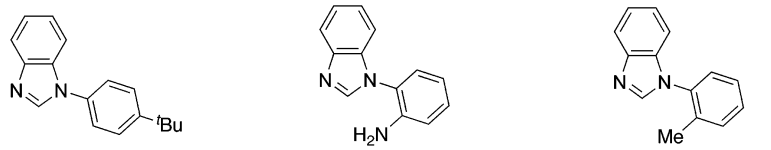
[a] Reaction conditions for ArI: 1.0 mmol of imidazole, 1.2 mmol of ArI, 0.025 mmol of Cu_2O, 0.075 mmol of **L1c**, 1.4 mmol of Cs_2CO_3, 200 mg of PEG, and 0.5 mL of DMSO under Ar at 110 °C for 12−24 h. [b] Reaction conditions for ArBr: 1.0 mmol of imidazole, 1.2 mmol of ArBr, 0.05 mmol of Cu_2O, 0.15 mmol of **L1c**, 1.4 mmol of Cs_2CO_3, 200 mg of PEG, and 0.5 mL of DMSO under Ar at 110 °C for 24−48 h. [c] 1.2 mmol of imidazole, 1.0 mmol of ArI, 0.025 mmol of Cu_2O, 0.075 mmol of **L1c**, 1.4 mmol of Cs_2CO_3, and 0.5 mL of butyronitrile under Ar at 110 °C for 16 h.

TABLE 5. Coupling of Benzimidazoles with Aryl Bromides[a]





5a, 82[b,c] **5b**, 81 **5c**, 82[b,c]



5d, 98 **5e**, 71 **5f**, 78[c,d]

[a] General reaction conditions: 1.2 mmol of benzimidazole, 1.0 mmol of ArBr, 0.10 mmol of Cu_2O, 0.20 mmol of **L1c**, 1.4 mmol of Cs_2CO_3, 200 mg of PEG, and 0.5 mL of DMSO under Ar or N_2 atmosphere at 110 °C for 24 h. [b] MTBD used as base. [c] Reaction run at 130 °C for 24 h. [d] 0.05 mmol of Cu_2O and 0.15 mmol of **L1c**.

of the p-hybridized lone pair electrons results in a partial loss of aromaticity. Imidazoles were also successfully combined with a variety of heteroaryl halides including 3-halofuran (**4c**), 3-haloisoquinoline (**4d**), 2-halothiazole (**4e**), 2-halothiophene (**4f**,**h**),[30] and a 3-halobenzothiophene (**4g**).

The use of DMSO and **L1c** also permits the successful coupling of benzimidazoles to unactivated aryl bromides (Table 5), which until recently[14f] had previously been limited to aryl iodides and unhindered aryl bromides using Cu-catalyzed methodology.[12,13g,14] As seen previously, substrates containing a free anilino-NH_2 groups (**5e**) were good substrates under our conditions. ortho-Substituted aryl bromides, as well as 2-substituted benzimidazoles, were successfully used as partners (**5a**,**c**,**e**,**f**). In some cases, the use of 7-methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene (MTBD) as a base provided better yields than the Cs_2CO_3/PEG combination (**5a**,**c**).[31]

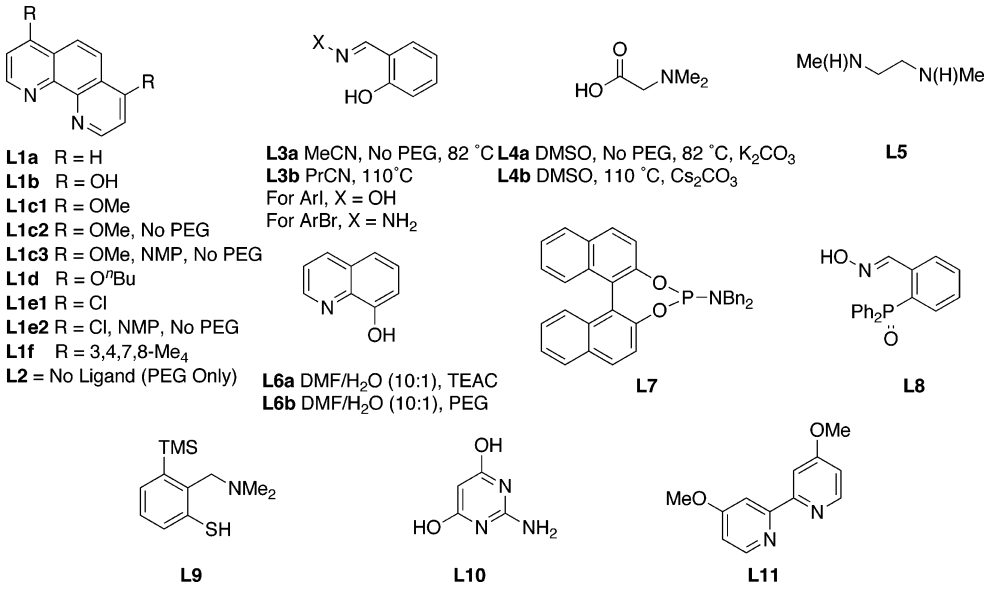
(27) Representative examples: (a) Maekawa, T.; Sakai, N.; Tawada, H.; Murase, K.; Hazama, M.; Sugiyama, Y.; Momose, Y. *Chem. Pharm Bull*. **2003**, *51*, 565. (b) Hoffmann-La Roche Inc. Heteroaryl-Substituted Imidazole Derivatives. U.S. Patent 20,040,254,179, December 16, 2004. (c) Smithkline Beecham Corporation. Thiophene Compounds. WO/014899 A1, February 19, 2004. (d) Chen, P.; Doweyko, A. M.; Norris, D.; Gu, H. H.; Spergel, S. H.; Das, J.; Moquin, R. V.; Lin, J.; Wityak, J.; Iwanowicz, E. J.; McIntyre, K. W.; Shuster, D. J.; Behnia, K.; Chong, S.; de Fex, H.; Pang, S.; Pitt, S.; Shen, D. R.; Thrall, S.; Stanley, P.; Kocy, O. R.; Witmer, M. R.; Kanner, S. B.; Schieven, G. L.; Barrish, J. C. *J. Med. Chem*. **2004**, *47*, 4517.

(28) Significant reduction in the Cu-catalyzed amination of heteroaryl halides has been observed. See: Arterburn, J. B.; Pannala, M.; Gonzalez, A. M. *Tetrahedron Lett.* **2001**, *42*, 1475.

(29) The Cu-catalyzed N-arylation of indole under mild conditions has been previously reported by our group.[13e]

(30) 2-Aminothiophenes are unstable in air oxidation and decompose readily upon exposure to air. See: Lu, Z.; Twieg, R. J. *Tetrahedron* **2005**, *61*, 903.

TABLE 6. Ligands Reported for Cu-Catalyzed N-Arylation of Imidazoles



Comparison of Ligands Commonly Employed for N-Arylation of Imidazoles. After most of our work for this paper was finished, several catalyst systems were reported for the N-arylation of imidazoles and benzimidazoles (Table 6).[14−15] To evaluate our new catalyst system in light of those previously published, we decided to undertake a study to compare our system not only with those that had been previously reported for this coupling but also with other 1,10-phenanthroline derivatives. While ligands **L1a**, **L1b**, **L1c**, **L2**−**L6**, and **L10** are commercially available, **L7**−**9** are only accessible through multiple step sequences. Furthermore, the harsh conditions necessary for the use of **L9**,**10** (145−160 °C) suggest that at the time of the report, these ligands were useful only in specific circumstances. For this reason, we focused the following study on **L1**−**L6**. **L11** was also examined to assess the significance of ligand rigidity for this transformation. Importantly, no reaction was observed for control reactions in which no ligand or PEG was added.

Case 1: Aryl Bromide, No Issues of Steric Hindrance. To examine a process in which steric hindrance was not a significant factor, the reaction of 4-*t*-butylbromobenzene with imidazole was conducted (eq 1). Of the catalysts examined, only systems derived from the 4,7-disubstituted-1,10-phenanthrolines and **L6** (with PEG/Cs_2CO_3 instead of TEAC) provided reasonable results (>60% GC yield). Of these, the use of **L1c** provided a nearly quantitative yield of *N*-aryl product, followed by **L1e** and **L1b** (86 and 76% GC yields, respectively).

Case 2: Aryl Iodide, 2-Substituted Imidazole. The efficient N-arylation of 2-substituted imidazoles had not been achieved prior to our earlier paper.[15,32] The reaction of 4-*n*-butyliodobenzene with 2-methylimidazole was chosen to probe the sensitivity of each catalytic system to substitution on the nucleophile (eq 2). Only catalyst systems based on 4,7-disubstituted-1,10-phenanthrolines (**L1b**−**e**), **L6**, and **L11** were effective for this transformation. Of those mentioned, **L1b**, **L1c**, and **L6b** provided slightly better yields (>95% GC yield) of product than did **L1e** (86−88% GC yield). All other ligands were ineffective for this transformation within a reasonable time period (<20% GC yield).

Case 3: Hindered Aryl Bromide with Imidazole. The very few examples of Cu-catalyzed reactions of ortho-substituted aryl bromides with imidazole require high temperatures and/or long reaction times.[14b,f,l] We, therefore, chose to examine the reaction of 2-bromotoluene with imidazole (eq 3). The majority of the ligands screened provided similarly efficacious catalysts (40−60% GC yield). The use of **L1e** provided a slightly higher yield of product (66%). Only the use of dimethoxy **L1c** and **L6** as ligands provided synthetically useful yields (83−85% GC yield, respectively) using PEG/Cs_2CO_3. However, using **L6** and TEAC as the base, 15% of the aryl bromide was lost.

Case 4: Hindered Aryl Iodide with 4(5)-Substituted Imidazole. To explore the effect of the ligand employed on the regioselectivity of the coupling process, 4-methylimidazole was combined with 2-isopropyliodobenzene (eq 4). Systems based on most ligands provided low catalytic activity (<40% GC yield) and moderate selectivity in favor of the 4-regioisomer. Reactions utilizing **L1b** and **L1e** provided reasonable reaction efficiencies (51−62% GC yield) with excellent selectivity for the 4-alkyl imidazole (30−42:1). Once again, the use of **L1c** provided the best result, giving an 82% GC yield with a selectivity of 37:1 in favor of the 4-methyl regioisomer.

Summary of Ligand Comparisons Screens. In general, **L1c** outperformed other 1,10-phenanthrolines lacking heteroatoms in the 4- and 7-positions **(L1a** and **L1f)**. The catalyst derived from anionic 4,7-dihydroxy derivative **L1b** showed a higher reactivity than unsubstituted **L1a** but was generally less active than that with **L1c**. This may be due to the relative insolubility of **L1b** in the solvents employed. Interestingly, **L1c** outperformed 4,7-dibutoxy-1,10-phenanthroline (**L1d**),[33] which we had postulated might be a better ligand due to its increased solubility.

(31) MTBD previously has been used as a soluble base for the Pd-catalyzed amination of aryl nonaflates using microwave irradiation. Tundel, R. E.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2006**, *71*, 430.

(32) Coupling of 2-methylimidazole with 4-iodoanisole proceeds to 65% conversion in 48 h (10% $(CuOTf)_2$·PhH/10% dba/100% **L1a**/xylenes/125 °C/48 h).[12] Coupling of 2-methylimidazole with 5-bromo-*m*-xylene (10% CuI, 10% **L6**/TEAC/10:1 DMF/H_2O/130 °C, 16 h) yields 64% of *N*-aryl imidazole.[14f]

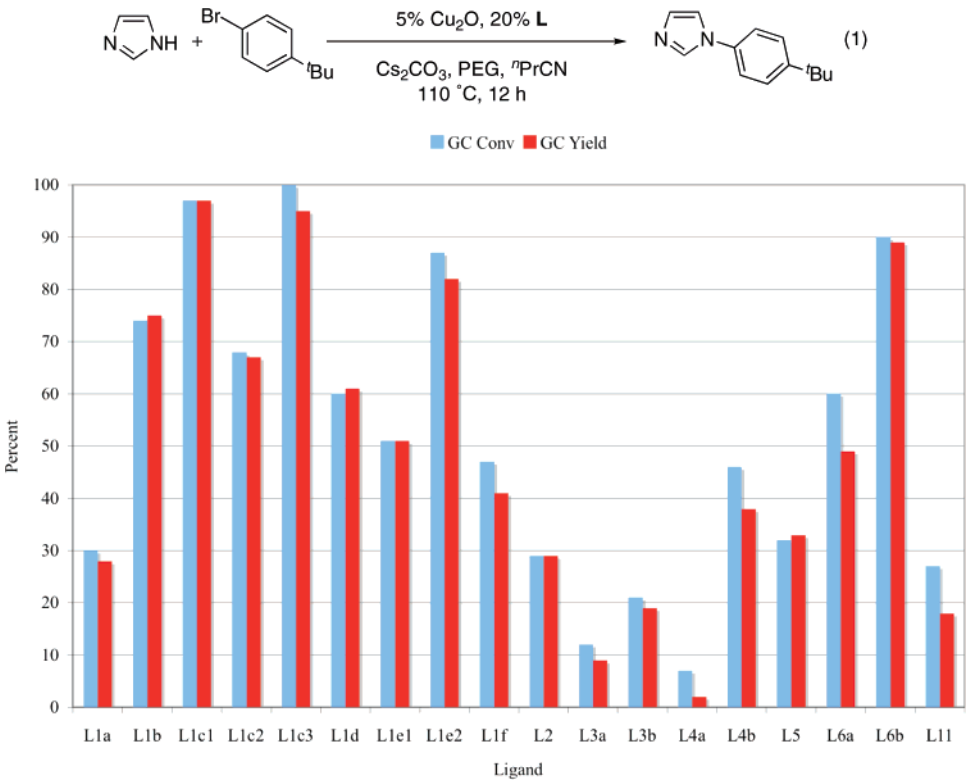


FIGURE 1. Reaction of imidazole with 4-*t*-butylbromobenzene.

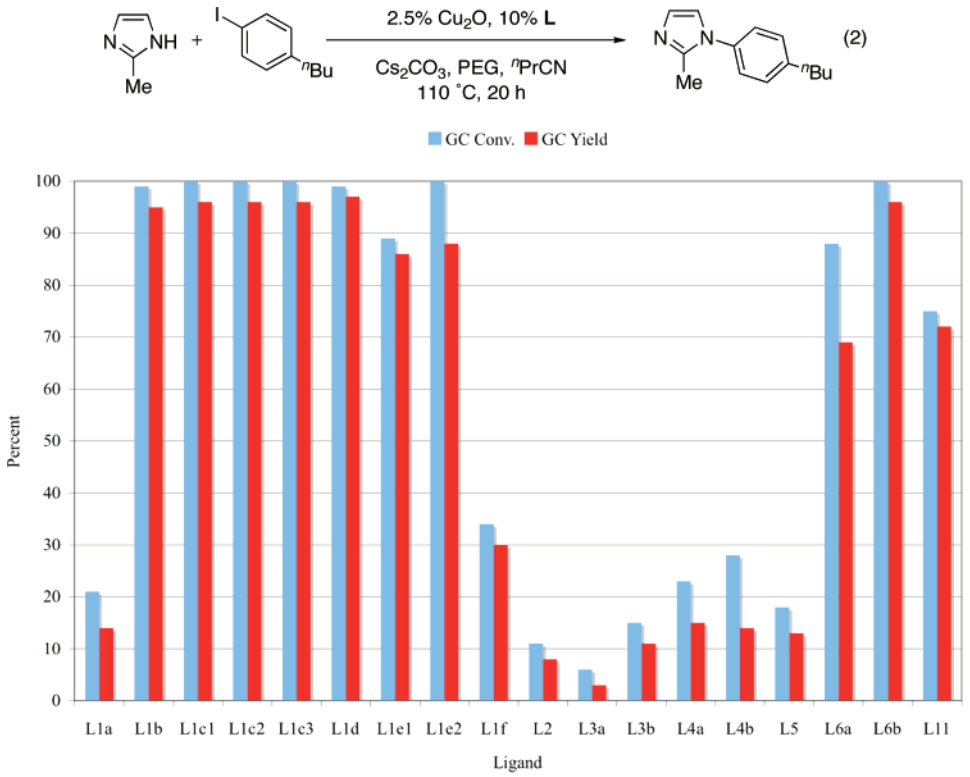


FIGURE 2. Reaction of 2-methylimidazole with 4-*n*-butyliodobenzene.

Reactions using chlorinated **L1e** as a ligand demonstrated good conversion to product, which we found surprising considering the electron-deficient nature of the ligand as compared to the methoxy counterpart. However, using **L1e**, reisolation of the ligand at the end of the reaction showed that the chlorides had been displaced at the 4- and 7-positions by a mixture of both residual water and imidazole. Thus, using the Cu/**L1e** combina-

(33) 4,7-Diethoxy-1,10-phenanthroline was also found to be more effective than **L1d** but less effective than **L1c** for this transformation.

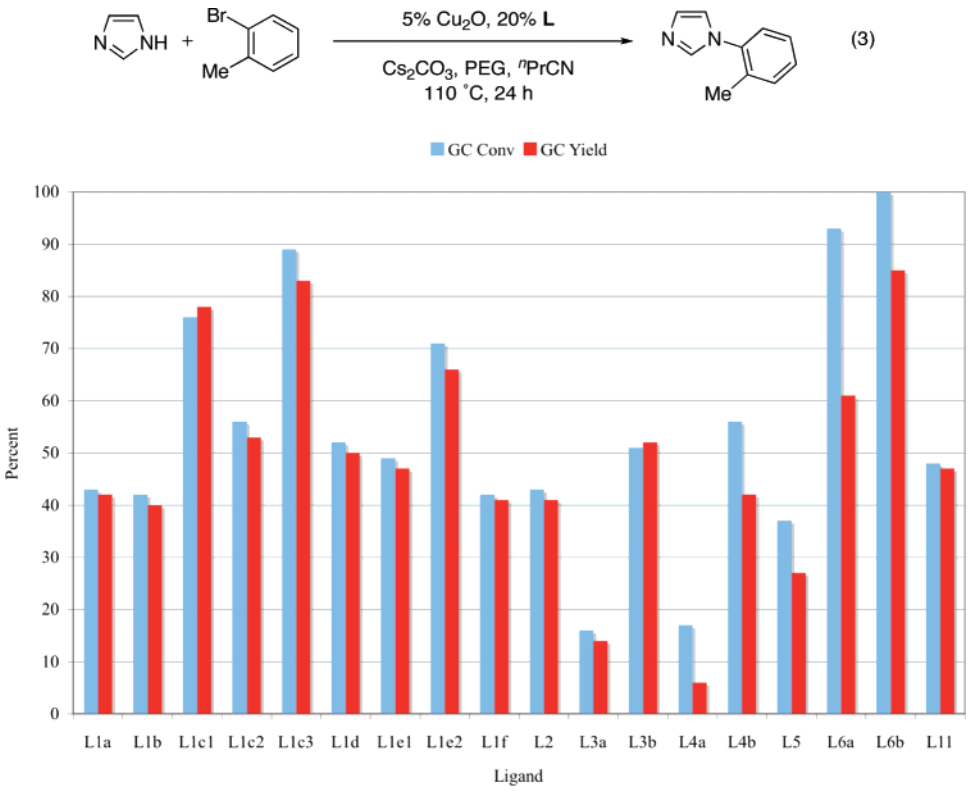


FIGURE 3. Reaction of imidazole with 2-bromotoluene.

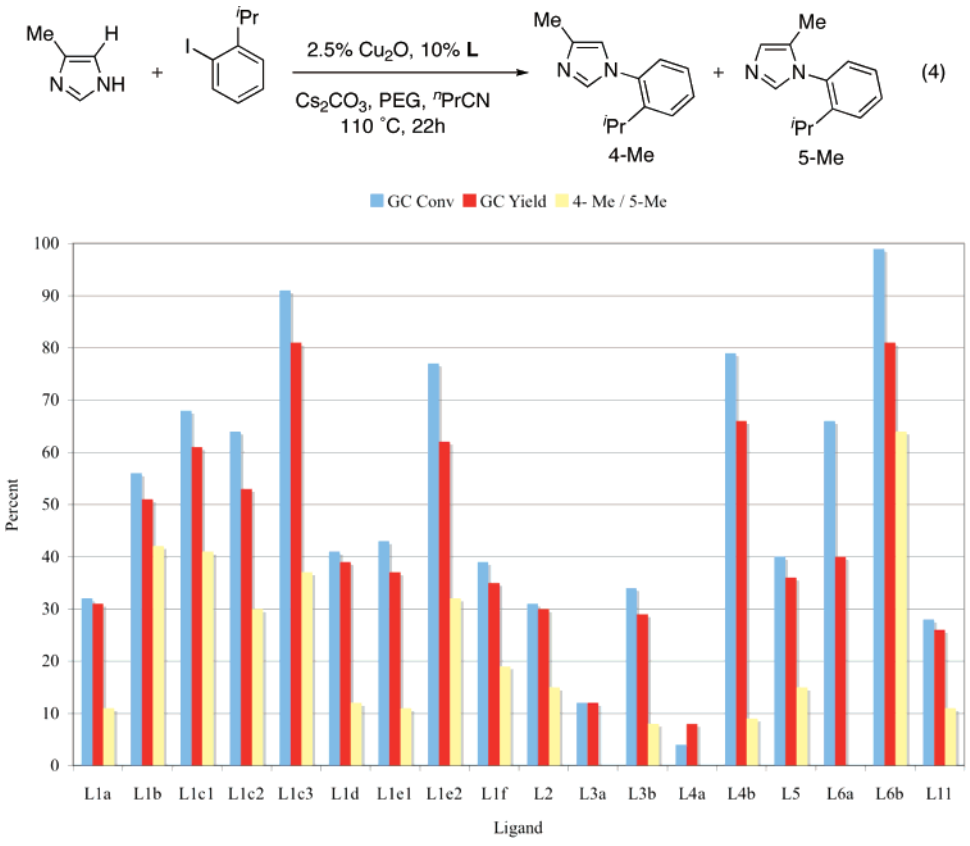


FIGURE 4. Reaction of 4-methylimidazole with 2-isopropyliodobenzene.

tion, it is unclear as to the nature of the actual ligand in the active catalyst. The increased efficiency of catalysts based on **L1c** relative to **L11** demonstrated the significance of the rigid phenanthroline backbone over the 2,2′-bipyridine structure, which

contains conformational freedom about the biaryl bond. While catalysts using ligands **L3**−**L5** demonstrated sluggish reactivity with more challenging imidazole/aryl halide substrate combinations under the reported conditions,[14a−d] their use with the PEG/Cs_2CO_3 conditions described here provided higher conversions and yields. The effect of PEG can be further seen as the Cu_2O/PEG combination, **L2** (without a N-containing ligand), which provided similar reactivity as when unsubstituted 1,10-phenantholine (**L1a**) was used as the ligand. The use of **L6** as a ligand for these reactions provided high reactivity; however, the use of TEAC as a base provided low yields as previously mentioned in this text. Using **L6**, the use of PEG/Cs_2CO_3 instead of TEAC as the base provided higher yields of *N*-aryl imidazoles due to the formation of multiple byproducts due to three processes: (1) reduction of the aryl halide, (2) O-arylation of the ligand, and (3) N-alkylation of imidazole by the tetraalkylammonium cation. Because of their low cost, many of these systems might still be attractive for the coupling of more facile substrate combinations; however, there are significant limitations to the scope of imidazoles and aryl halides that can be effectively coupled by these systems as compared to **L1c**.

Conclusion

In conclusion, we have demonstrated the utility of 4,7-dimethoxy-1,10-phenanthroline as an excellent ligand for the Cu-catalyzed arylation of imidazoles and benzimidazoles with aryl and heteroaryl iodides and bromides in combination with PEG and Cs_2CO_3. Not only is our system the most general reported to date, it also allows for the cross-coupling of hindered substrate combinations. The mild conditions employed also manifest a high functional group tolerance.

Experimental Section

General Procedure for Tables 1−5. An oven-dried screw-capped test tube was charged with Cu_2O, **L1c**, imidazole, aryl halide (if solid), PEG, Cs_2CO_3, and a magnetic stir bar, and the reaction vessel was fitted with a rubber septum. The vessel was evacuated and back-filled with argon or nitrogen, and this sequence was repeated an additional time. Aryl halide (if liquid) and solvent were then added successively. The reaction tube was sealed and stirred in a pre-heated oil bath for the designated time period. The reaction mixture was cooled to room temperature, diluted with dichloromethane (15 mL), and filtered through a plug of celite, eluting with additional dichloromethane (20 mL). The filtrate was concentrated, and the resulting residue was purified by flash chromatography using a mixture of hexane and ethyl acetate to provide the desired product. Representative examples are as follows.

1-(3,5-Dichloro-phenyl)-2-methyl-1*H*-imidazole (1j). The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 1,3-dichloro-5-iodobenzene (273 mg, 1.00 mmol), and 2-methylimidazole (100 mg, 1.2 mmol) with butyronitrile (0.5 mL) as solvent for 24 h at 110 °C. Chromatographic purification (hexane/ethyl acetate 1:3) provided the title compound as white needles (194 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.44 (t, 1H, J = 1.8 Hz), 7.23 (d, 2H, J = 1.9 Hz), 7.05 (d, 1H, J = 1.2 Hz), 6.99, (d, 1H, J = 1.2 Hz), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 135.8, 128.5, 128.4, 124.1, 14.0. IR (KBr disc, cm^{-1}) 1534, 1501, 1463, 1451, 1405, 1305, 1176, 1143, 1115, 1099, 985, 850, 781. Anal. Calcd for $C_{10}H_8N_2Cl_2$: C 52.89, H 3.55. Found: C 52.95, H 3.44. mp 122−125 °C.

4-Imidazol-1-yl-isoquinoline (4d). The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-bromoisoquinoline (250 mg, 1.2 mmol), and imidazole (68 mg, 1.00 mmol) with DMSO (0.5 mL) as solvent for 24 h at 110 °C. Chromatographic purification (ethyl acetate/hexane 3:1) provided the *N*-aryl product as clear crystals (165 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (d, 1H, 0.9 Hz), 8.48 (s, 1H), 8.08 (m, 1H), 7.78−7.62, (m, 4H), 7.30 (bs, 1H), 7.25 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 139.6, 138.2, 132.1, 131.9, 130.2, 129.2, 128.8, 128.4, 127.9, 121.5, 121.2. IR (KBr disc, cm^{-1}) 1589, 1508, 1491, 1406, 1307, 1107, 1078, 1038, 942, 913, 782, 660. Anal. Calcd for $C_{12}H_9N_3$: C 73.43 H 4.65. Found: C 73.43, H 4.63. mp 67−71 °C.

Acknowledgment. We thank the National Institutes of Health (GM58160) for financial support for this project. We are grateful to Merck, Amgen, and Boehringer-Ingelheim for additional unrestricted support. We also thank Dr. Alex Shafir for providing **L1c**. The Varian NMR instruments used for this publication were paid for by the NSF (CHE 9808061 and DBI 9729592). E.D.K. thanks MIT UROP for funding.

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.

JO070807A