JOC Note

Simple Copper Salt-Catalyzed N-Arylation of Nitrogen-Containing Heterocycles with Aryl and Heteroaryl Halides

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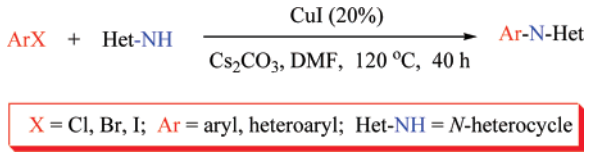
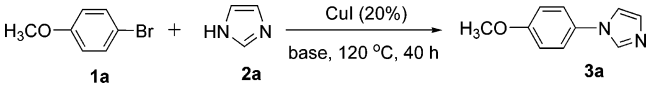


Relatively mild and highly efficient CuI-catalyzed N-arylation procedures for nitrogen-containing heterocycles (e.g., imidazoles, benzimidazoles, pyrroles, pyrazoles, indoles, triazoles, etc.) with aryl and heteroaryl halides have been developed. The protocols can be performed easily and tolerate a number of functional groups, such as ester, nitrile, nitro, ketone, free hydroxyl, and free primary amine on the aryl halide.

N-Arylimidazoles, *N*-arylpyrroles, *N*-arylpyrazoles, *N*-arylindoles, and *N*-aryltriazoles have received great attention in a variety of fields throughout the chemical, pharmaceutical, and material sciences.[1] Traditionally, these *N*-arylazoles have been synthesized via S_NAr (nucleophilic aromatic substitution) of N-containing heterocycles with electron-deficient aryl halides[2] or via the classical Ullmann-type coupling with aryl halides.[3]

TABLE 1. Some Representative Results from the Screening of Reaction Conditions for the N-Arylation of Imidazole with 4-Bromoanisole[a]



1a 2a 3a

entry	imidazole (mmol)	solvent	base	yield[b] (%)
1	1.6	DMF	Cs_2CO_3	86
2	1.4	DMF	Cs_2CO_3	89
3	1.2	DMF	Cs_2CO_3	78
4	1.0	DMF	Cs_2CO_3	45
5	1.4	none	Cs_2CO_3	72
6	1.4	DMSO	Cs_2CO_3	71
7	1.4	toluene	Cs_2CO_3	*c*
8	1.4	*n*-butanol	Cs_2CO_3	74
9	1.4	DMF	KOH	48
10	1.4	DMF	NaOH	44
11	1.4	DMF	K_2CO_3	63
12	1.4	DMF	K_3PO_4	44

[a] Reaction conditions: **1a** (1.0 mmol), base (2.0 mmol) in the presence of CuI (0.2 mmol) in 2.0 mL of solvent at 120 °C under N_2 atmosphere. [b] Isolated yields (average of two runs). [c] Little coupling product was determined.

These well-known reactions, however, generally suffer from several limitations: (i) high reaction temperatures (often 150 °C or as high as 200 °C), (ii) the use of stoichiometric amounts of copper reagents, (iii) moderate yields, and (iv) poor substrate generality. It is therefore not surprising that great efforts have been directed toward the development of a mild as well as highly efficient method for constructing *N*-arylazole units.[4,5] Recently, Buchwald[6] and Taillefer[7] have discovered and developed the copper catalytic path for N-arylation of nitrogen-containing heterocycles with aryl halides in the presence of N- and O-based ligands under relatively mild conditions, which has led to a resurgence of interest in Ullmann-type coupling reactions due to the economic attractiveness of copper.[8] Quite recently, our laboratory has also presented highly efficient CuI-catalyzed N-arylation procedures for N-containing heterocycles with aryl and heteroaryl bromides or chlorides through the use of (*S*)-pyrrolidinylmethylimidazole ligands.[9]

Recently, we have developed the CuCl-catalyzed N-arylation of imidazole with arylboronic acids in protic solvents in the

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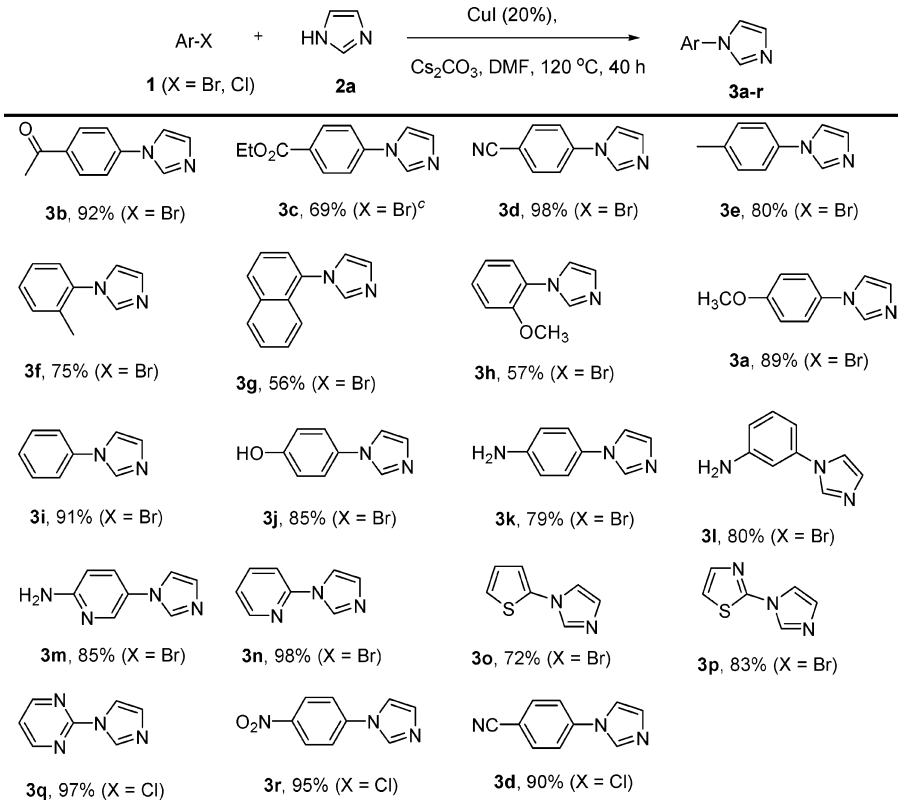
TABLE 2. Catalytic N-Arylation of Imidazole with Aryl and Heteroaryl Halides by CuI[a,b]



[a] Reaction conditions: **1** (1.0 mmol), **2a** (1.4 mmol), 2.0 mmol of Cs_2CO_3 in the presence of 20 mol % of CuI in 2.0 mL of DMF at 120 ± 5 °C under N_2 atmosphere. [b] Isolated yields (average of two runs) based on **1**. [c] 100 mg activated 4 Å molecular sieves.

absence of an additional chelating ligand.[10] Thus, it was a natural extension for us to explore new simple copper salt catalytic systems for preparing *N*-arylimidazoles through the coupling reactions of aryl halides, which are more easily available and less expensive than the corresponding organometal reagents.[11] In this study, we surprisingly found that a catalytic amount of air-stable CuI could promote the cross-couplings of a number of nitrogen-containing heterocycles with various aryl and heteroaryl halides under relatively mild conditions when the heterocycle is in excess in relation to the aryl halide, which constitutes very practical, general, and highly efficient processes for the synthesis of *N*-arylazoles.

Despite significant progress in the Cu-catalyzed N-arylation of nitrogen heterocycles with aryl halides, only a few reports have appeared describing the couplings of imidazoles with aryl bromides or of functional substrates or of hindered substrates.[7−9] The majority of aryl halides investigated to date, already limited in examples, are aryl iodides.[6b,c,8a,d,g] In some cases with respect to aryl bromides, the electron-withdrawing groups and/or higher reaction temperatures even have to be required.[8d,f,j] We therefore chose to focus initial studies on the cross-couplings of imidazole through the use of CuI without the assistance of an additional chelating ligand.

It was determined during a preliminary survey of reaction conditions using 4-bromoanisole (**1a**) and imidazole (**2a**) as model arylating agents shown in Table 1. We found that the amount of imidazole was crucial to the outcome of the reaction, and the catalytic performance proved to be improved by increasing the quantity of nitrogen-containing heterocycle, which

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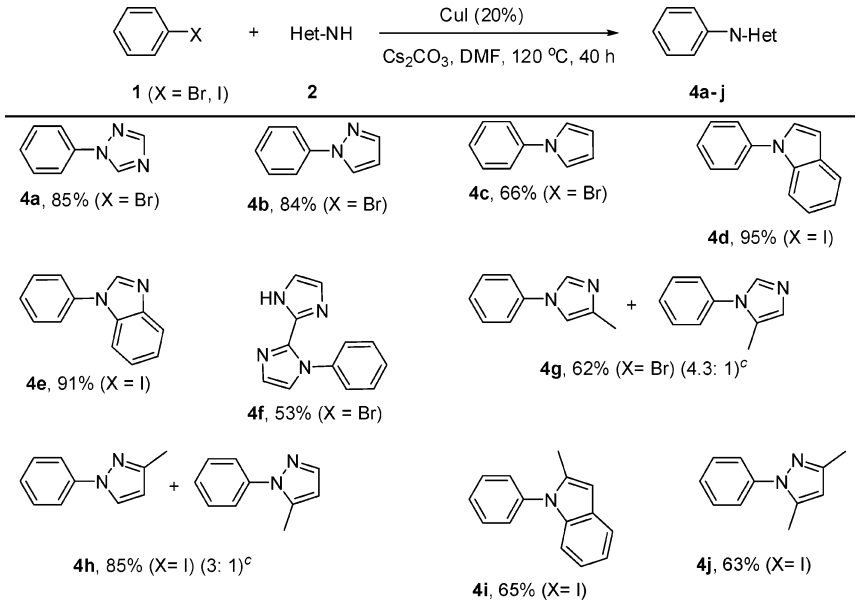
(11) Relatively mild conditions have been achieved by the use of other types of cross-coupling reagents in place of aryl halides as substrates, such as aryllead triacetates, aryl siloxanes, triphenylbismuths, arylstannanes, diaryliodonium salts, or, recently, arylboronic acids. However, these methods generally require additional steps to transform aryl halides into the corresponding organometal reagents and thus are limited by the high cost and poor availability of functionalized substrates. In addition, the synthesis of some reagents may involve the use of highly toxic materials and/or unstable reagents.

TABLE 3. Catalytic N-Arylation of Azoles with Aryl Halides by CuI[a,b]



[a] Reaction conditions: see Table 2. [b] Isolated yields (average of two runs) based on **1**. [c] The regioselectivity was determined by GC−mass analysis and is described in parentheses.

shows a clear maximum at 1.4 equiv of imidazole (compare entries 1−4). While 20 mol % of CuI was employed in the presence of 2 equiv of Cs_2CO_3, a series of reaction solvents (e.g., toluene, *n*-butanol, DMF, and DMSO) were also investigated (entries 2, 6−8). Among the solvents tested, DMF was clearly the best choice, and DMSO and *n*-butanol provided slightly low yields while the use of toluene delivered little desired coupling product. These results suggest that imidazole and/or the solvent itself might possibly act as the ligand(s) for the copper. Subsequently, we surprisingly found that this coupling reaction could give the corresponding product in good yield (72%) without addition of any solvent, which excludes the possibility of the solvent as a ligand (entry 5). It is also noteworthy that imidazoles as well as other nitrogen heterocycles themselves have proved to be outstanding classes of ligands, being capable of forming a broad variety of metal complexes that are able to catalyze a great number of reactions.[9] It is therefore reasonable to assume that this procedure could be extended to other nitrogen-containing heterocycles for the synthesis of *N*-arylazoles. After screening a variety of bases (e.g., KOH, NaOH, K_2CO_3, K_3PO_4, and Cs_2CO_3), we found that Cs_2CO_3 gave the best result of 89% yield in DMF (compare entries 2, 9−12).

With optimized conditions now in hand, we explored the scope of the coupling reactions of aryl and heteroaryl halides with imidazole in the presence of 20 mol % of CuI and 2 equiv of Cs_2CO_3 in DMF at 120 °C under N_2, and the results are summarized in Table 2. We were delighted to find that the catalytic system was able to tolerate a broad range of aryl bromides (e.g., electron-rich, electron-deficient, electron-neutral, sterically hindered, and functionalized bromoarenes, **3a**−**l**). Notably, our catalyst system could facilitate the coupling reactions with regard to electron-rich aryl halides, although transition-metal-catalyzed reactions involving these electron-rich arylating agents are traditionally less straightforward (**3a**, **3h**, **3j**−**l**). In addition, Ullmann-type condensations are generally sensitive to steric hindrance near the halogen atom, and there are rare examples describing the Cu-catalyzed couplings of imidazole with sterically hindered aryl halides. Our catalytic system could be applied to N-arylation of imidazole with *ortho*- or pseudo-*ortho*-substituted aryl bromides (**3f**−**h**). It is noteworthy that the N-arylation of imidazole could be performed without problems on 10 mmol scales.

Substrates that contain certain functional groups have proven to be persistently problematic in the N-arylation of imidazoles. To our delight, our catalytic system could almost exclusively undergo the selective N-arylation of 4-bromophenol, 4-bromoaniline, 3-bromoaniline, and 2-amino-5-bromopyridine to afford the corresponding *N*-arylimidazoles (**3j**−**m**) in good yields, avoiding the competition from the formation of diaryl ethers and diarylamines.[4,8n,s,12,13] On the other hand, our protocol could also tolerate a number of functional groups, such as ester, nitrile, ketone, and nitro, although these functional groups themselves might be decomposed at higher temperatures, for example, the partial hydrolysis of the ester to benzoic acid and of the nitrile to amide (**3b**−**d**,**r**).[8k,n] Thus, our protocol has offered a new addition for the synthesis of highly functionalized azoles.

Preliminary results suggest that the current system could be applicable to aryl chlorides to a less extent (**3d**,**q**−**r**). Further exploration revealed that some heteroaryl halides were compatible with these reaction conditions, giving satisfactory yields of 72−98% (**3m**−**q**).[8c,j,14] Notably, we run the control reactions of aryl chlorides bearing strong electron-withdrawing groups (e.g., 4-chlorobenzonitrile and 4-chloronitrobenzene) and activated heteroaryl bromides and halides (2-bromopyridine, 2-bromothiazole, 2-chloropyrimidine) in the absence of Cu and found

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that the desired coupling reactions did not occur under our standard conditions.

The development of chemistry that could emanate from a single method for each of the major classes of nitrogen-containing heterocycles has been seriously inhibited so far. In an endeavor to expand the scope of the methodology, we found that our new catalytic system was also suitable for other π-electron-rich nitrogen heterocycles (e.g., pyrroles, pyrazoles, indazoles, imidazoles, triazoles, etc.; Table 3). It is worth noting that these optimized conditions could be applied to the N-arylation of other imidazole derivatives. For example, the coupling reaction of 1*H*-benzimidazole with iodobenzene afforded the corresponding N-arylated product in 91% yield (**4e**, Table 3). The hindered 2-(1*H*-imidazol-2-yl)-1*H*-imidazole could be selectively monoarylated with bromobenzene in 53% yield (**4f**, Table 3). The coupling of 4-methyl-1*H*-imidazole with bromobenzene gave a mixture of regioisomers of 1-aryl-4-methyl imidazole and 1-aryl-5-methyl imidazole, which stems from the two possible imidazole tautomers on the NH position (**4g**, Table 3). As demonstrated by Collman[15] and Buchwald,[8t] the major product is the 4-regioisomer because the substituent at the 4-position of imidazole is more geometrically favored than that situated in the 5-position during the formation of the intermediate. Similarly, the coupling of 3-methyl-1*H*-pyrazole with iodobenzene afforded a mixture of regioisomers with the preferential selectivity for the 3-regioisomer (**4h**, Table 3).[7a] To our delight, the sterically hindered heterocycles such as 2-methyl-1*H*-indole and 3,5-dimethyl-1*H*-pyrazole could also work with iodobenzene using our new method (**4i**−**j**, Table 3).

In summary, we have developed relatively mild and highly efficient CuI-catalyzed N-arylation procedures for nitrogen-containing heterocycles with aryl and heteroaryl halides. The system is effective for aryl bromides and, to a less extent, for aryl chlorides. Particularly noteworthy is the fact that our protocols could tolerate a number of functional groups, such as ester, nitrile, nitro, ketone, free hydroxyl, and free primary amine, on the aryl halide. In addition, the procedures could be performed easily. This work should find wide application among synthetic and medicinal chemists in industry and academics.

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Experimental Section

General Procedure for the Catalytic N-Arylation of Nitrogen-Containing Heterocycles with Aryl Halides. To a flame-dried Schlenk test tube with a magnetic stirring bar was charged CuI (38.2 mg, 0.2 mmol), Cs_2CO_3 (0.65 g, 2.0 mmol), nitrogen-containing heterocycle (1.4 mmol), aryl or heteroaryl halide (1.0 mmol), and DMF (2 mL) under N_2. A rubber septum was replaced with a glass stopper, and the system was then evacuated twice and back filled with N_2. The reaction mixture was stirred for 30 min at room temperature, and then heated at 120 °C for 40 h. The reaction mixture was then cooled to ambient temperature, diluted with 2−3 mL of ethyl acetate, filtered through a plug of silica gel, and washed with 10−20 mL of ethyl acetate. The combined organic extracts were concentrated, and the resulting residue was purified by column chromatography on silica gel to provide the desired product.

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Supporting Information Available: Detailed experimental procedures for the synthesis of *N*-arylazoles, characterizational NMR spectral data (^{1}H and ^{13}C) of *N*-arylazoles, and copies of ^{1}H and ^{13}C NMR spectra for compounds **3a**−**r** and **4a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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