JOC*Note*

N-Hydroxyimides as Efficient Ligands for the Copper-Catalyzed N-Arylation of Pyrrole, Imidazole, and Indole

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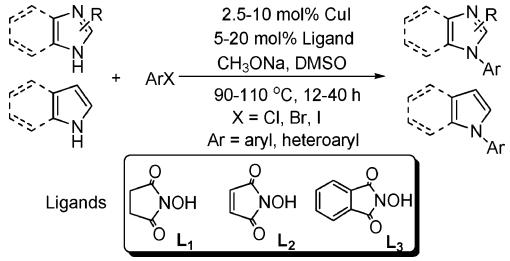

An experimentally simple, efficient, and inexpensive catalyst system was developed for the N-arylation of pyrroles, indoles, and imidazole with aryl and heteroaryl iodides, bromides, and chlorides by applying CuI as catalyst, *N*-hydroxysuccinimide (L_1), *N*-hydroxymaleimide (L_2), or *N*-hydroxyphthalimide (L_3) as ligand, CH_3ONa as base, and DMSO as solvent. A variety of functional groups are tolerated in the reaction, including those that are not compatible with Pd-catalyzed amidation methodology.

Nitrogen-containing heterocycles such as *N*-arylpyrroles, *N*-arylindoles, and *N*-arylimidazoles are an important class of compounds that are ubiquitous in numerous natural products and biologically active pharmaceuticals.[1] The copper-catalyzed Ullmann−Goldberg coupling is a traditional method for the introduction of amine functionality with use of aromatic halides.[2]

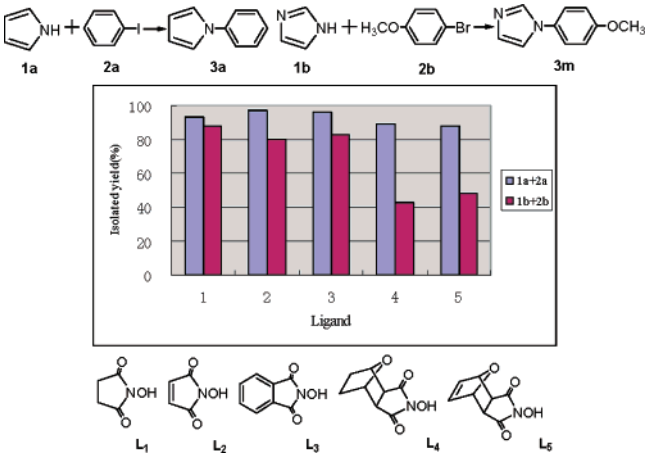

FIGURE 1. Effect of various ligands on the efficiency of the aryl amidation reaction. The reaction of **1a** + **2a** was performed with 5 mol % of CuI, 10 mol % of ligand. 1.0 equiv of **1a** and **2a**, and 1.5 equiv of CH_3ONa in DMSO at 90 °C for 12 h. The reaction of **1b** + **2b** was performed with 10 mol % of CuI, 20 mol % of ligand, 1.0 equiv of **1b** and **2b**, and 1.5 equiv of CH_3ONa in DMSO at 110 °C for 40 h.

However, the harsh reaction conditions such as high temperatures (125−220 °C), the requirement of a stoichiometric amount of copper catalyst, and the low to moderate yields have undoubtedly prevented these reactions from being employed to their full potential. Thus, the development of a mild as well as highly efficient method for constructing *N*-arylazole units has been received increasing interest. Recently, several Pd-catalyzed C−N formation methods have been discovered for the cross-coupling of aryl halides with N−H heterocycles by using some sterically hindered phosphine ligands under relatively mild conditions.[3] Notably, the economic attractiveness of copper has led to a resurgence of interest in the Ullmann-type coupling reaction since Buchwald discovered the copper-catalyzed N-arylation of heterocycles with aryl halides in the presence of diamine ligands.[4] Indeed, some efficient ligands have been disclosed in these coupling reactions, including amino acids,[5] diamines,[4] diimines,[6] aminoarenethiolate,[7] phosphine ligands,[8]

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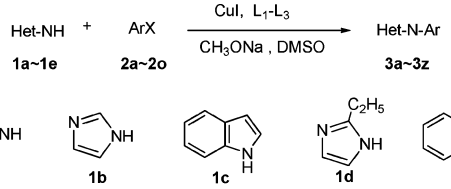
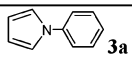
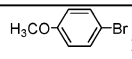
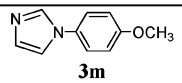
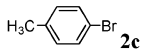
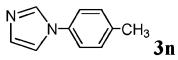
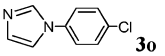
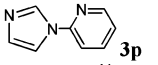
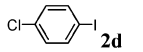
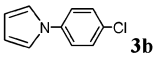
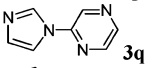
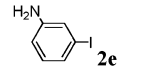
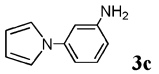
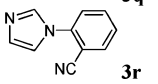
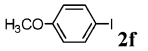
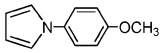
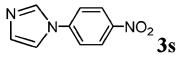
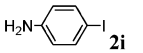
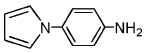
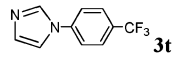
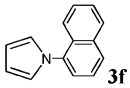
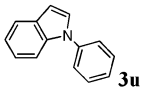
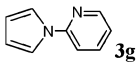
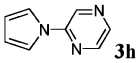
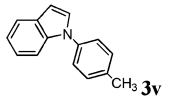
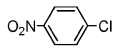
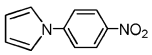
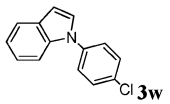
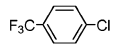
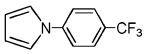
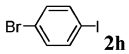
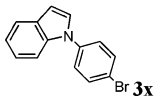
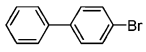
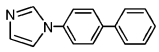
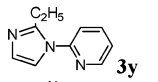
TABLE 1. Copper *N*-Hydroxyimides-Catalyzed N-Arylation of *N*-H Heterocycles[a]



entry	ArX	product	L[d]	(°C/h)	yield[b]	entry	ArX	product	L	(°C/h)	yield
1	 **2a**	 **3a**	L_3	90/12	96	16	 **2b**	 **3m**	L_1	110/40	88
2	**2a**	**3a**	L_2	90/12	97	17	 **2c**	 **3n**	L_3	110/40	73
3[c]	**2a**	**3a**	L_2	90/12	75	18	**2d**	 **3o**	L_2	90/12	98
4	**2a**	**3a**	_	90/12	trace	19	**2k**	 **3p**	L_1	110/24	96
5	 **2d**	 **3b**	L_3	90/12	95	20	**2l**	 **3q**	L_3	110/24	94
6	 **2e**	 **3c**	L_1	90/12	92	21	 **2m**	 **3r**	L_3	110/24	52
7	 **2f**	 **3d**	L_2	90/12	93	22	**2n**	 **3s**	L_3	110/40	62
8	 **2i**	 **3e**	L_1	90/12	98	23	**2o**	 **3t**	L_2	110/40	48
9	 **2j**	 **3f**	L_1	90/12	98	24	**2a**	 **3u**	L_1	90/12	97
10	 **2k**	 **3g**	L_1	110/24	96	25	**2a**	**3u**	L_3	90/12	94
11	 **2l**	 **3h**	L_3	110/24	90	26	**2c**	 **3v**	L_1	110/24	48
12	 **2n**	 **3i**	L_2	110/40	45	27	**2d**	 **3w**	L_3	90/12	99
13	 **2o**	 **3j**	L_2	110/40	45	28	 **2h**	 **3x**	L_1	90/12	86
14	 **2g**	 **3k**	L_1	110/40	82	29	**2k**	 **3y**	L_3	110/24	92
15	**2a**	**3l**	L_1	90/12	98	30	**2k**	**3z**	L_1	110/24	68

[a] Reaction conditions: ArX (1.5 mmol), Het-NH (1.5 mmol), CH_3ONa (1.5 equiv), DMSO (4 mL); X = I, with CuI (5 mol %)/ligand (10 mol %); X = Br or Cl, with CuI (10mol%)/ligand (20 mol %). [b] Isolated yield. [c] Performed with 2.5 mol % of CuI and 5 mol % of L_2. [d] Ligands L_1, L_2, and L_3 were chosen at random.

2-aminopyrimidine-4,6-diol,[9] hydroxyquinoline,[10] (*S*)-pyrrolidinylmethylimidazoles,[11] 4,7-dimethoxy-1,10-phenanthroline,[12] 2-oxocyclohexanecarboxylate,[13] and benzotriazole.[14] While many significant results have been achieved for the copper-

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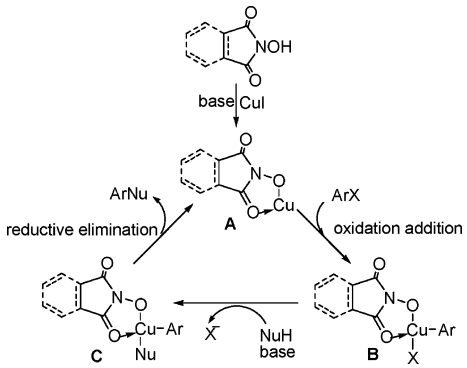
catalyzed N-arylation of a variety of nitrogen-containing heterocycles through the use of those ligands mentioned above, the applications of these Ullmann methods might be limited to a certain degree by the high expense, unavailability, or specificity of the ligands. It was also noted that the successful arylation methods for each of the major classes of nitrogren heterocycles such as imidazoles, pyrroles, indoles, etc. have been scarcely reported.[4,12−14] Therefore, more efficient, versatile, and facile ligands for these coupling reactions under relatively milder conditions are still in demand. Herein we report our preliminary investigations on the use of *N*-hydroxysuccinimide (L_1), *N*-hydroxymaleimide (L_2), and *N*-hydroxyphthalimide (L_3) as efficient ligands for the copper-catalyzed N-arylation of nitrogen-containing heterocycles.

Initially, a set of ligands was screened for the comparison models of pyrrole (**1a**) with iodobenzene(**2a**) and imidazole (**1b**) with 4-bromoanisole (**2b**). As shown in Figure 1, both reactions presented similar trends with respect to the structure of ligands L_1−L_5. Possibly, the steric hindrance of ligands has a negative effect on the catalytic behavior; ligands L_4 and L_5 are evidently less favorable than ligands L_1, L_2, and L_3 for the arylation of **1b** with **2b**. However, all ligands have been found to be available for the coupling of **1a** with **2a** under the specified conditions, especially, the easily prepared and also commercially available ligands L_1, L_2, and L_3 were recommended in most cases. In our reaction system, it was observed clearly that base plays a very important role in the transformation. With an increase in the basicity, K_2CO_3, K_3PO_4, and CH_3ONa led to sharply ascending coupling. efficiency. The reaction does not work in some cases if CH_3ONa is replaced with a weaker base such as K_2CO_3. A copper source applied as an alternative catalyst precursor has been tested; the readily available copper salts such as CuI, CuBr, CuCl, or $CuBr_2$ afforded a satisfactory result in the arylation of **1a** with **2a**, in agreement with the previously reported results that copper compounds in various oxidation states are catalytically active and presumably are transformed into the same active catalyst under the reaction conditions.[15] For the less reactive aryl halides, bromo- and chloro-substituted aromatic compounds, CuI turned out to give the best results. Therefore, CuI was chosen as the catalyst precursor for subsequent experiments. While 5 mol % of CuI and 10 mol % of ligand were employed in the presence of 1.5 equiv of CH_3ONa, typical solvents such as THF, toluene, DMF, and DMSO were investigated, and we found that the polar solvents are more favorable for the catalytic reaction. Consequently, DMSO was chosen as the reaction media for the C−N coupling reaction.

From Table 1, we can discern that the coupling reactions tolerated a wide scope of functional groups, including nitrile (entry 21), and NH_2 (entries 6 and 8). The selective Ullmann-type C−N formation of N−H heterocycles with aryl iodides containing a free NH_2 is particularly interesting, since substrates (**2e** and **2i**) are not compatible with the Pd-catalyzed methodology. Therefore, this result implicated the possibility that the selectivity of formation the C−N bond could be accomplished simply by choosing a Pd- or Cu-based catalyst system. The high selectivity was also observed in the amidation of aryl iodides containing another halide group such as bromine or chlorine (entries 5, 18, 27, and 28).

Aryl bromides and chlorides react more slowly than aryl iodides and typically require 10 mol % of CuI and 20 mol % of ligand and heating at 110 °C for 24−40 h. By using the catalyst system based on one ligand of L_1, L_2, and L_3, the coupling reaction of aryl bromides such as 4-bromobiphenyl (**2g**), 4-bromoanisole (**2b**), and 4-methylbromobenzene (**2c**) with *N*-H heterocycles could be conducted with the corresponding products in 82%, 96%, and 73% yields, respectively (entries 14, 16, and 17 in Table 1). It should be pointed out that the heteroaryl bromide (**2k**) was an excellent coupling partner with pyrroles **1a** and imidazoles **1b** under the standard reaction conditions (entries 10, 19, 29, and 30 in Table 1). Encouraged by these results, the less reactive 2-chloropyrazine (**2I**) was then treated with pyrroles **1a** and imidazoles **1b** (entries 12 and 20 in Table 1), and gave the coupling products in 90% and 94% yields. Unfortunately, the arylation reactions with aryl chlorides containing electron-withdrawing groups such as **2n**, **20**, and **2m** gave unsatisfied yields (entries 12, 13, and 21−23 in Table 1). With respect to the reactivity order for *N*-H heterocycles, pyrrole and imidazole are more reactive partners than indole.

SCHEME 1. Proposed Mechanism for the Coupling Reaction



As described in Scheme 1, we have formulated a possible mechanism for the copper-catalyzed N-arylation of pyrrole, imidazole, and indole based on the previously reported mechanism.[9,14,16] The chelating CuI with *N*-hydroxyimide formed a five-membered reactive species **A**, and the subsequent oxidative addition of the chelating with aryl halides led to the intermediate **B**. In the presence of base, *N*-H heterocycles reacted with **B** readily to afford complex **C**, which undergoes reductive elimination to provide the desired product and regenerate the reactive species **A**.

In summary, we have disclosed a set of *N*-hydroxyimide compounds for promoting the arylation of *N*-H heterocycles with aryl halides in the presence of CuI as catalyst, CH_3ONa as base, and DMSO as solvent at 90−110 °C. The practical benefits of *N*-hydroxyimide accelerated amidation methodology were contributed to their easy preparation and commercial availability. A wider scope of nitrogen-containing heterocycles such as pyrroles, indoles, and imidazole has been arylated efficiently. Particularly, our protocols could tolerate an array of functional groups such as nitrile, nitro, and free primary amine on the aryl halides. Overall, we believe that the present catalyst system could provide an excellent complement to the Pd- or Cu-catalyzed methods that have already been utilized in a number of applications, and is of great importance to research and development in the pharmaceutical industry.

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Experimental Section

General Procedure for the Arylation of Nitrogen-Containing Heterocycles with Halides. To a solution of CH_3ONa (3.0 mmol) in DMSO (3 mL) was added CuI (19 mg, 0.1 mmol) and ligand (0.2 mmol). After stirring at room temperature for 30 min, a mixture of halide (2.0 mmol) and nitrogen-containing heterocycle (2.0 mmol) in 2 mL of DMSO was added to the flask, and the reaction mixture was stirred at the indicated temperature for the corresponding reaction time. The mixture was cooled to room temperature, 10 mL of water was added, and the resulting suspension was extracted with ethyl acetate (4 × 10 mL). The extraction was dried over $MgSO_4$, then concentrated and purified by column chromatography on silica gel to provide the desired products.

4-(1*H*-Pyrrol-1-yl)benzenamine (3e): pale yellow solid, mp 86−87 °C (uncorrected); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.21 (d, J = 8.8 Hz, 2H), 7.02−7.01 (t, J = 1.6, 2.4 Hz, 2H), 6.75−6.73(d, J = 8.8 Hz, 2H), 6.35−6.34 (t, J = 1.6, 2.4 Hz, 2H), 3.69 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 132.8, 122.3, 119.7, 115.7, 109.6; LRMS (EI, 20 eV) m/z (%) 158 (M^+, 100). Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.75; H, 6.43; N, 17.53.

2-(1*H*-Imidazol-1-yl)pyridine (3p): pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27−8.26 (m, 1H), 8.20 (s, 1H), 7.63−7.61 (m, 1H), 7.48 (s, 1H), 7.17−7.15 (d, J = 8.0 Hz, 1H), 7.05−7.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 138.9, 134.8, 130.4, 121.9, 116.0, 112.1; LRMS (EI, 20 eV) m/z (%) 145 (M^+, 100). Anal. Calcd for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.35; H, 4.74; N, 28.85.

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Supporting Information Available: Analytical data, spectra (^{1}H NMR and ^{13}C NMR) for products, and typical experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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