

A General and Efficient Copper Catalyst for the Amidation of Aryl Halides and the *N*-Arylation of Nitrogen Heterocycles

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During the past few years significant advances have occurred in the development of cross-coupling methodology; some of these have emanated from our own labs. Of particular interest has been the acquisition of the ability to utilize inexpensive aryl chlorides.¹ This represents a partial solution to a long-standing problem in organometallic chemistry and catalysis. By far, however, the largest application of cross-coupling chemistry, particularly C–N bond-forming processes, occurs in the medicinal and discovery groups of pharmaceutical companies and in academic laboratories. For the vast majority of these cases the scope, experimental ease, and reliability of a method is much more important than whether aryl chlorides can be used rather than aryl bromides or aryl iodides. Despite significant improvements,² the scope of cross-coupling methodology to form aryl and heteroaryl C–N bonds lags that of analogous C–C bond-forming processes such as Suzuki, Stille, and Negishi coupling reactions.³ There are many reasons for these limitations, including the sensitivity of many functional groups to the combination of amine and base required in C–N coupling protocols. Substrates that contain certain functional groups have proven to be persistently problematic. Of the functional groups that are incompatible with the Pd-catalyzed amination methodology, the most important are probably 1° and 2° amides.⁴ Another problematic situation is when there is a free OH or NH directly bound to the aromatic ring that contains the halide or sulfonate.⁵ While some progress has been made in the *N*-arylation of heterocycles and amination of heterocyclic halides, the scope has been quite limited.⁶ Moreover, as the cost of Pd remains at \$600–700/ounce, less costly alternatives become more desirable.⁷ In this paper we describe a vastly enhanced version of the venerable Goldberg reaction, the copper-catalyzed amidation of aryl and heteroaryl halides. We also describe the application of this catalyst system to the *N*-arylation of a variety of heterocycles and other nitrogenous substrates.

Both Ullmann coupling processes^{8,9} and the related Goldberg coupling reaction¹⁰ have a long history of utility in academic and

industrial laboratories. While the importance of such reactions cannot be overstated, the necessity to use high temperatures, highly polar solvents, and often large amounts of copper reagents have prevented these reactions from being employed to their full potential. We have previously disclosed Ullmann-type methodology for the *N*-arylation of imidazoles¹¹ and for the formation of diaryl ethers.¹² Both of these used 1,10-phenanthroline/(CuOTf)₂·benzene with various additives. This led us to examine the efficiency of other chelating nitrogen ligands in copper-catalyzed carbon–heteroatom bond forming processes. We show here that the combination of air stable CuI and racemic *trans*-1,2-cyclohexanediamine (**1a**) in the presence of K₃PO₄, K₂CO₃, Cs₂CO₃, or NaOt-Bu comprises an extremely efficient and general catalyst system for the *N*-amidation of aryl and heteroaryl iodides and bromides and the *N*-arylation of a number of heterocycles. Preliminary studies with this catalyst also show that it is even capable of the amidation of unactivated aryl chlorides. Moreover, we show for the first time to our knowledge that a Goldberg reaction can be carried out at room temperature.

As shown in Table 1, lactams, primary amides, and formamides derived from primary amines and acetanilide can be coupled to a variety of aryl iodides. In general, 1 mol % of air-stable CuI in combination with 10 mol % of inexpensive racemic *trans*-cyclohexanediamine **1a** is sufficient to obtain a high yield after 23 h at 110 °C in the presence of K₃PO₄. In some cases, the commercial mixture of the *cis* and *trans* diastereomers of 1,2-cyclohexanediamine could be used with comparable results (entry **2h**). While the time for each reaction has not been optimized, we have found that in some cases the reactions are nearly complete (~90%) after 1 h. Of particular interest are entries **2a** (2° amide),¹³ **2b** (free NH₂), and **2c** (free NH₂ in nitrogen nucleophile) in which substrates not compatible with the Pd-catalyzed methodology are transformed in high yield. As can be seen in entries **2d–f** the presence of strongly electron-donating substituents at the ortho or para position has no deleterious effects. In the case of **2f**, the reaction has been carried out with 0.2 mol % CuI (S/C = 500) and proceeds in 98% yield. *N*-BOC aniline can also be arylated in virtually quantitative yield. As shown for case **2i**, the reaction of benzamide and 3,5-dimethyliodobenzene proceeds in high yield at room temperature using 5 mol % of CuI.

The reactions of aryl bromides are detailed in Table 2. The reactions are conducted under conditions similar to those in Table 1, except that K₂CO₃ is used as the base in some cases and often 5–10 mol % CuI is required. As can be seen, a variety of heteroaryl bromides are excellent substrates, including both 2- and 3-bromothiophene, the latter a substrate only moderately

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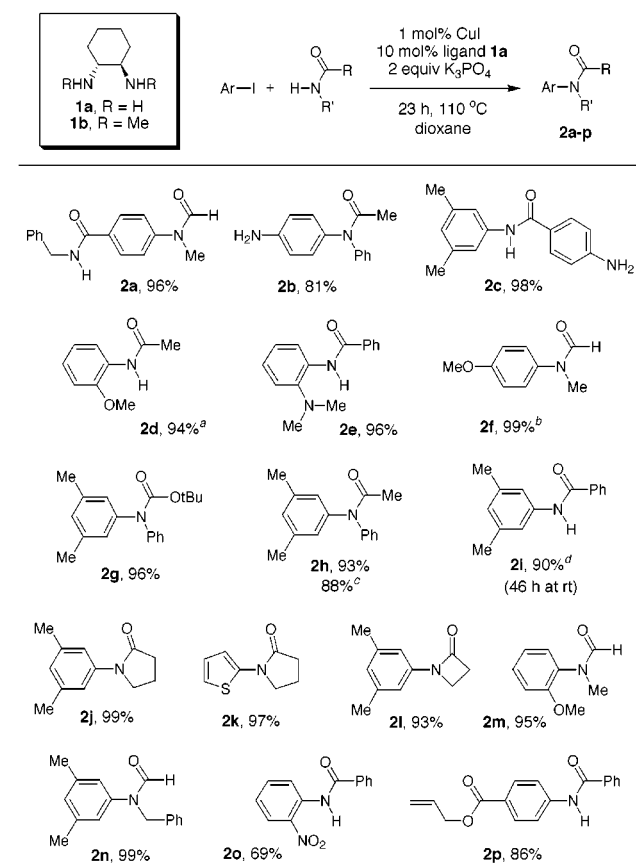
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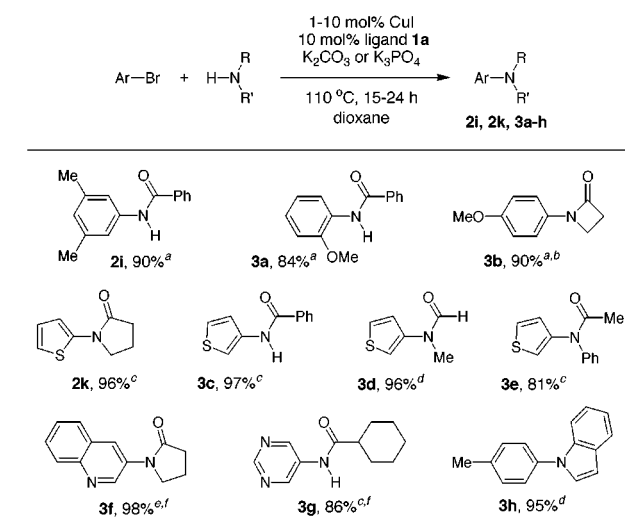
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(13) Generally, *N*-alkylformamides react much faster than other acyclic *N*-alkylamides. This accounts for the chemoselective formation of **2a**.

Table 1. Copper-Catalyzed Amidation of Aryl Iodides^a

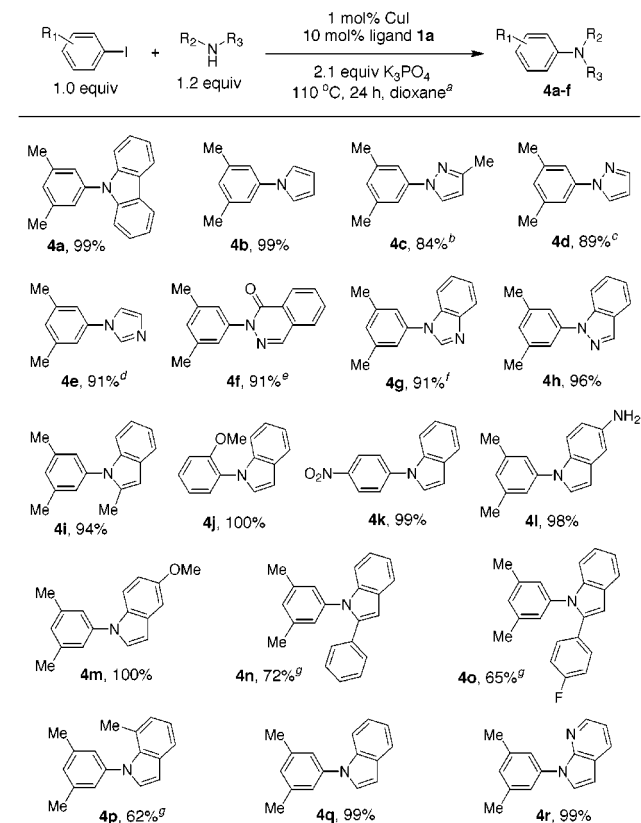
^a Reaction performed at 90 °C. ^b With 0.2 mol % CuI and 5 mol % ligand **1a**. ^c With a mixture of cis and trans isomers of ligand **1a**. ^d With 5 mol % CuI, 10 mol % ligand **6e**, and 2 equiv Cs₂CO₃ at room temperature for 46 h. ^e Yields refer to the average of two isolated yields of >95% purity as determined by GC and ¹H NMR.

Table 2. Reactions of Aryl Bromides with Amides and Indoles^a

^a With 1 mol % CuI. ^b With 10 mol % ligand **1b**. ^c With 10 mol % CuI. ^d With 5 mol % CuI. ^e With 2 mol % CuI at 120 °C and 2 M in diglyme. ^f With 10 mol % *N,N*-dimethylethylenediamine. ^g Yields refer to the average of two isolated yields of >95% purity as determined by GC and ¹H NMR.

amenable to Pd-catalyzed amination.¹⁴ Additionally, 3-bromoquinoline and 5-bromopyrimidine are efficiently transformed.

While some progress has been made in the *N*-arylation of nitrogen heterocycles, the scope of these with respect to either

Table 3. *N*-Arylation of Nitrogen Heterocycles^h

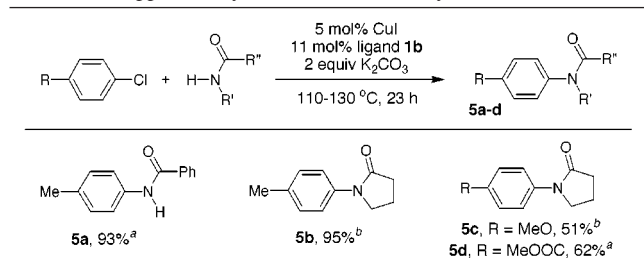
^a All reactions 1 M in dioxane unless otherwise noted. ^b With K₂CO₃ as base and 2 M in dioxane. ^c With K₂CO₃ as base. ^d With 5 mol % CuI, 10 mol % 1,10-phenanthroline, Cs₂CO₃ as base, and 2 M in dioxane. ^e With 3 mol % CuI, Cs₂CO₃ as base, and 2 M in dioxane. ^f With 10 mol % CuI, 20 mol % 1,10-phenanthroline, Cs₂CO₃ as base, and 2 M in DMF. ^g Reaction time of 48 h and 2 M in dioxane. ^h Yields refer to the average of two isolated yields of >95% purity as determined by GC and ¹H NMR.

heterocycle or aryl halide (or sulfonate) substrates has been modest in most instances.^{6,15} As is shown in Table 3, pyrazoles (**4c,d**), indazole (**4h**), 7-azaindole (**4r**), and phthalazinone (**4f**) can be efficiently transformed. This is in addition to indoles (including 2-aryl and 7-alkyl), pyrrole (**4b**), and carbazole (**4a**). Noteworthy is that we are able to prepare *N*-(2-methoxyphenyl)indole **4j** in high yield, an accomplishment not reported with the analogous Pd chemistry, and that competitive C-arylation is not observed. Although we previously reported the Cu-catalyzed arylation of benzimidazole and imidazole,¹¹ we have developed an improved procedure for these heterocycles that obviates the need of the air-sensitive CuOTf.

We have also begun studies on the *N*-arylation of aryl chlorides as shown in Table 4. These reactions are carried out neat, using an excess (4 equiv) of the aryl chloride as solvent. We have been able to carry these out at significantly lower temperatures than

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Table 4. Copper-Catalyzed Amidation of Aryl Chlorides^c

^a At 110 °C. ^b At 130 °C. ^c Yields refer to the average of two isolated yields of >95% purity as determined by GC and ¹H NMR.

previously possible¹⁶ using 5 mol % CuI and 11 mol % of the *N,N'*-dimethyl ligand **1b**. Thus, at 110 °C the reaction of *p*-chlorotoluene with benzamide occurs in 23 h in 93% yield. The corresponding reaction with pyrrolidinone proceeds in 95% yield at 130 °C.

In addition to those results described above, the chemistry (with **1a** or 1,10-phenanthroline as ligand) can be used for the *N*-arylation of *N*-BOC hydrazide¹⁷ and benzophenone hydrazone¹⁸ (Table 5). Moreover, *trans*-cyclohexanediamine **1a** can be selectively mono-*N*-arylated in moderate yield.^{19,20} These results, which complement those seen in Pd chemistry,²¹ should allow the preparation of *N,N'*-diarylcyclohexanediamines with two

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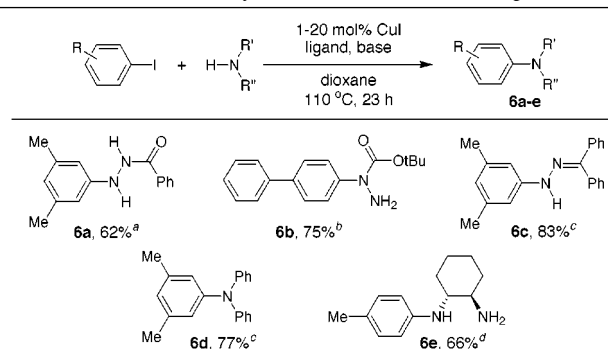
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(19) *N*-Arylation of the diamine (usually <1% with respect to the aryl halide although up to 10% in some cases involving aryl bromides) was also observed in the reactions where **1a** was used as the ligand. Diamine **1b** is less susceptible to *N*-arylation and <1% arylation of the ligand was observed even in the amidation of aryl bromides. Except for the entry **2i** in Table 1, the monoarylated diamines were found to be less catalytically active than diamine **1a**.

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Table 5. Reactions of Aryl Iodides with Other Nucleophiles^c

^a With 1 mol % CuI, 10 mol % ligand **1a**, and 2 equiv of K₂CO₃.

^b With 5 mol % of CuI, 10 mol % of 1,10-phenanthroline, and 1.4 equiv of Cs₂CO₃.

^c With 1 mol % CuI, 10 mol % ligand **1a**, and 1.5 equiv of NaOtBu. ^d Reaction was performed using 4-bromotoluene, 20 mol % CuI, and 2 equiv of K₃PO₄.

^e Yields refer to the average of two isolated yields of >95% purity as determined by GC and ¹H NMR.

different aryl groups. This has important implications for the preparation of non-*C*₂-symmetric diamine ligands.

In summary, we have developed an extremely general, experimentally simple, and inexpensive catalyst system for the amidation of aryl halides and the *N*-arylation of a wide variety of heterocycles. We believe that this catalyst system provides an excellent complement to the Pd-catalyzed methodology that has already been utilized in a number of applications. Efforts to expand the utility of the method in combination with mechanistic studies are in progress in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for all unknown compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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