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Copper-Catalyzed Halogen Exchange in Aryl Halides: An Aromatic Finkelstein Reaction

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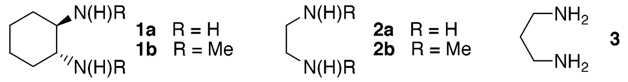
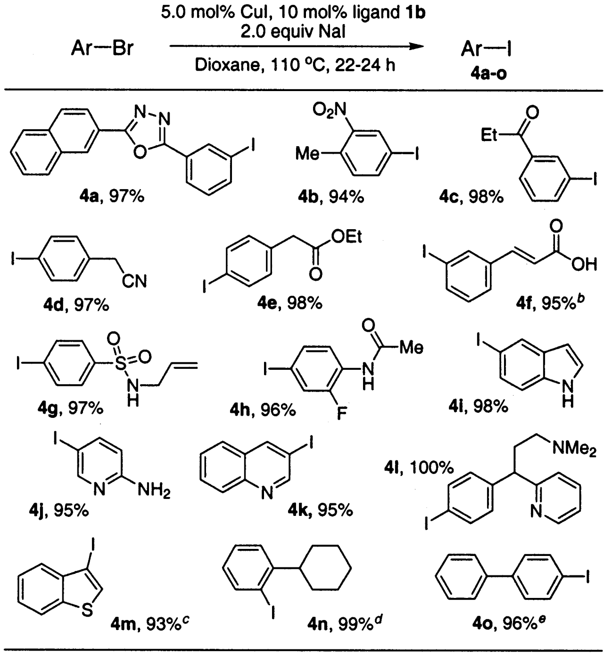
Aryl halides are widely used in organic synthesis to form carbon−carbon and carbon−heteroatom bonds in transition metal-catalyzed processes such as the Heck-, Stille-, Suzuki-, and Ullmann-type coupling reactions. In these reactions, aryl bromides and chlorides are usually less reactive than the corresponding aryl iodides.[1] In addition, ^{125}I-radiolabeled aryl iodides find an important application in pharmacokinetic studies.[2] Unfortunately, preparation of functionalized aryl iodides may be difficult.[3] One of the common preparative methods is nickel- or copper-catalyzed conversion of the more available aryl bromides into aryl iodides. This method suffers from significant limitations; for example, the nickel-catalyzed halogen exchange usually results in poor yields, incomplete conversion of aryl halides, and is accompanied by formation of biaryl side products. Furthermore, the reaction may require a stoichiometric amount of the nickel reagent.[4] The related copper-catalyzed process is limited by the harsh reaction conditions. It traditionally requires high temperatures (>150 °C), polar solvents (DMF or HMPA), and multiple equivalents of copper(I) iodide, which may present a waste disposal problem if the reaction is performed on a large scale.[5]



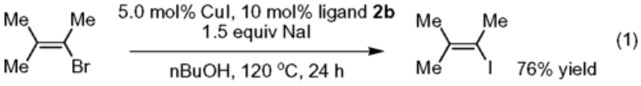
During our studies on the copper-catalyzed coupling of aryl bromides with amides and nitrogen heterocycles using the diamine ligands **1**−**2**,[6] minor amounts of aryl iodides corresponding to halogen exchange in the aryl bromide were occasionally detected. This fortuitous observation led to the discovery that 1,2- and 1,3-diamine ligands such as **1**−**3** strongly accelerate the copper-catalyzed halogen exchange reaction, the ligand **1b** being the most active.[7] Reaction conditions employing 5 mol % of CuI, 10 mol % of **1b**, and 2 equiv of NaI in dioxane at 110 °C typically provide ca. 99% conversion of an aryl bromide into the corresponding aryl iodide (Table 1).[8] For comparison, less than 1% yield (by GC) of the aryl iodide is observed if ligand **1b** is omitted. A variety of polar functional groups are tolerated including an aliphatic ester and nitrile (entries **4d** and **4e**). A carboxylic acid (entry **4f**) can be employed provided that hexamethyldisilazane is included in the reaction mixture to derivatize the carboxylic acid as the more soluble TMS ester, which can be readily cleaved during workup of the reaction. Interestingly, N−H containing substrates such as sulfonamide **4g**, amide **4h**, and indole **4i** are also tolerated, and no N-arylation is observed. Presumably, the lack of a strong base in the reaction mixture prevents the N-arylation reaction. As evidenced by the examples in Table 1, heteroaryl iodides can be prepared by this method; in other cases the presence of numerous heterocyclic moieties causes no problems. The halogen exchange reaction is sensitive to steric hindrance in the aryl bromide. Thus, formation of **4n** requires 40 h at 130 °C. As exemplified by entry **4o**, very inexpensive diamine ligands such as **3** can be used instead of **1b**, although a higher reaction temperature (130 °C) is then required.[9] Solvents other than dioxane can be employed including *n*-pentanol (entries **4n** and **4o**) and an *m*-xylene/diglyme mixture (entry **4m**).

Table 1. The Scope of the Copper-Catalyzed Conversion of Aryl Bromides into Aryl Iodides[a]



[a] Isolated yields (average of two runs); >95% purity as determined by GC and ^{1}H NMR. [b] With 1.0 equiv of hexamethyldisilazane. [c] Performed in 4:1 *m*-xylene/diglyme solvent mixture at 130 °C for 22 h. [d] Performed in *n*-pentanol at 130 °C for 40 h. [e] With 10 mol % of ligand **3** in *n*-pentanol at 130 °C for 22 h.

Initial experiments indicate that the current method can also be extended to halogen exchange in vinyl halides (eq 1).



The copper-catalyzed halogen exchange in aryl halides is an equilibrium reaction in which the position of the equilibrium is influenced by the solubility difference of the halide salts, in analogy to the Finkelstein reaction (halogen exchange in alkyl halides). For example, NaI in dioxane or *n*-butanol provides higher equilibrium conversion (99.5%) of 5-bromo-*m*-xylene into 5-iodo-*m*-xylene than either NaI or KI in DMF, which have been historically recom-

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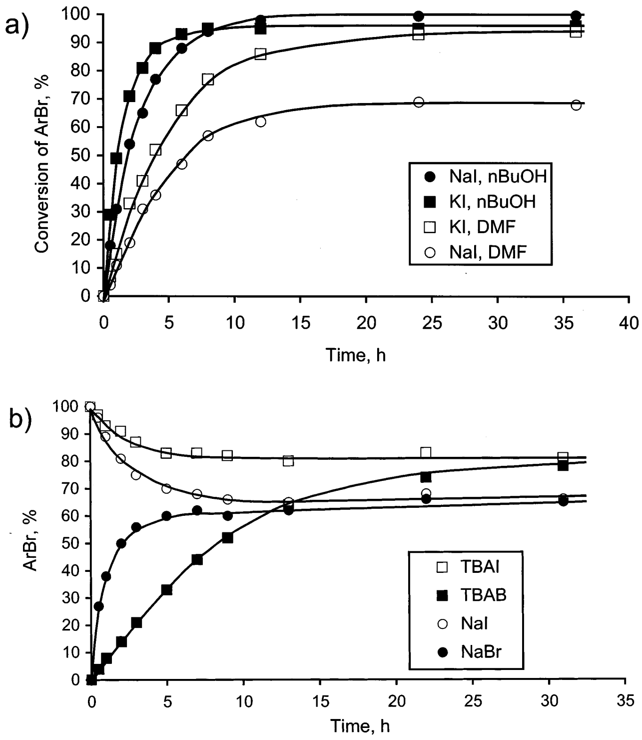

Figure 1. (a) Conversion of 5-bromo-*m*-xylene into 5-iodo-*m*-xylene using NaI or KI in *n*-BuOH or DMF as solvents. Performed with 5.0 mol % CuI, 10 mol % ligand **1b**, 1.0 equiv of aryl bromide, and 2.0 equiv of the iodide salt at 110 °C. (b) Conversion of 5-bromo-*m*-xylene into 5-iodo-*m*-xylene using NaI or TBAI (tetrabutylammonium iodide), and the reverse reaction using NaBr or TBAB (tetrabutylammonium bromide). Performed with 5.0 mol % CuI, 10 mol % ligand **1b**, 1.0 equiv of aryl halide, and 1.0 equiv of the halide salt in DMF at 110 °C.

mended for the copper-catalyzed halogen exchange (Figure 1a).[1a] The rate of the halogen exchange exhibits an interesting dependence on the total concentration of the halide salts in the solution. Thus, NaI in DMF is the only combination in Figure 1a that gives a homogeneous solution initially, and it also provides the lowest rate. This is further emphasized by Figure 1b, where the completely soluble tetrabutylammonium halides provide lower rates of halogen exchange (in either direction) than sodium halides, which give heterogeneous reaction mixtures. We speculate that a high concentration of the halide salts in the solution inhibits the desired halogen exchange reaction via formation of poorly reactive halocuprate complexes.[10]Nevertheless, there seems to exist an optimal range of the halide concentrations because the halogen exchange reaction is sluggish in nonpolar solvents such as toluene and xylene that dissolve the iodide salt only sparingly. In those cases, solubilizing additives, such as diglyme, can be of great benefit (Figure 2). While neither pure *m*-xylene nor diglyme is well-suited as a solvent, the use of a mixture of 5−60% diglyme in *m*-xylene gives excellent results. Thus, the success of the current method relies on a combination of multiple factors, most importantly, on the proper choice of the ligand, solvent, and halide salt.

In conclusion, we have developed a new method for the conversion of aryl, heteroaryl, and vinyl bromides into the corresponding iodides utilizing a catalyst system comprising CuI and a 1,2- or 1,3-diamine ligand. Efforts to expand the reaction scope and to apply it in various problems are in progress in our laboratory.

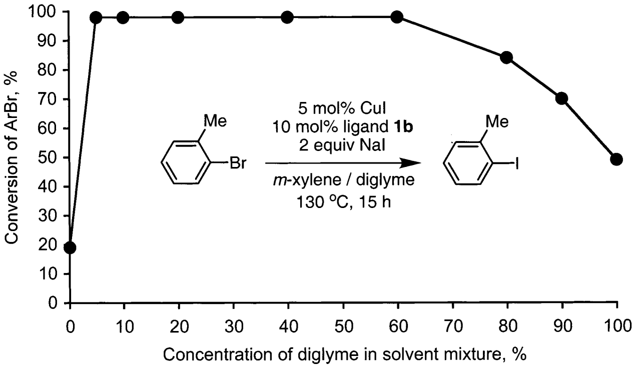

Figure 2. The halogen exchange reaction performed in a *m*-xylene/diglyme solvent mixture of variable composition.

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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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(7) The following conversions of 5-bromo-*m*-xylene into 5-iodo-*m*-xylene were observed after 22 h at 110 °C in dioxane using 2.0 equiv of NaI, 5.0 mol % of CuI, and 10 mol % of a ligand: **1a**, 77%; **1b**, 99.3%; **2a**, 73%; **2b**, 98%; **3**, 72%; 1,10-phenanthroline, 6%; no ligand, $<0.1\%$.

(8) Aryl chlorides react more slowly than aryl bromides. A 35% conversion (GC) of 4-chlorotoluene into 4-iodotoluene was observed after 24 h at 130 °C.

(9) In a control experiment, only 1% yield (by GC) of **4o** was observed if ligand **3** was omitted.

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