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An Efficient Copper Catalyst for the Formation of Sulfones from Sulfinic Acid Salts and Aryl Iodides

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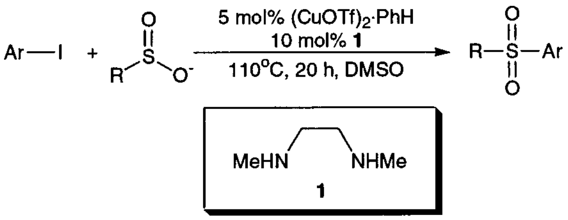
ABSTRACT



A novel copper-catalyzed method for the coupling of sulfinic acid salts and aryl iodides is described. A variety of methyl and diaryl sulfones have been formed in excellent yields.

Aryl sulfones are important compounds in the practice of medicinal chemistry. The functional group is found in numerous drugs, including the recently developed selective COX-2 inhibitor Vioxx.[1] The common methods for preparing these sulfones include the oxidation of sulfides[2] or the sulfonylation of arenes using aryl sulfonyl halides or aryl sulfonic acids in the presence of a strong acid catalyst.[3] Though these methods are attractive for their simplicity, they are incompatible with numerous functional groups, including olefins, amines, and some nitrogen heterocycles.

A metal-mediated cross-coupling of sulfinic acid salts with aryl halides would represent a mild alternative to these conditions. Indeed, there has been a report by Suzuki wherein aryl iodides were treated with 1.6 equiv of an aryl sulfinate and 1.5 equiv of CuI in DMF at 110 °C to yield diaryl sulfones.[4,5] The use of stoichiometric amounts of copper complicates the workup of large-scale reactions.

In contrast to the development of catalytic C−O and C−N bond-forming technology,[6] there have been fewer reports on transition metal-catalyzed C−S bond formation.[7] The major-

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ity of these reports, which have focused on the formation of aryl sulfides, employ Pd(0) or Ni(0) as catalysts. A recent report from Venkataraman, however, achieves the coupling of aliphatic and aromatic thiols with aryl iodides using a Cu(I)-based catalyst.[7a] Inspired by recent reports from the Buchwald group[6b−f] using copper/diamine systems for Ullmann-type processes, we sought to develop a method for the coupling of sulfinic acid salts and aryl halides.

Using the reaction of 1-iodonaphthalene and sodium methanesulfinate as a test reaction, we screened a number of copper salts, diamine ligands, solvents, and reaction temperatures. Since our study involved the coupling of the anionic sulfinate, rather than a neutral species, the addition of a base was not required. After screening several Cu(I) salts in combination with various diamine ligands (Figure 1), we were pleased to find that 5 mol % $(CuOTf)_2{\cdot}PhH$ and 10 mol % *N*,*N*′-dimethylethylene-diamine (**1**) led to complete conversion in DMSO after 20 h at 110 °C. Racemic *trans*-1,2-cyclohexanediamine also proved to be an effective ligand for this transformation.

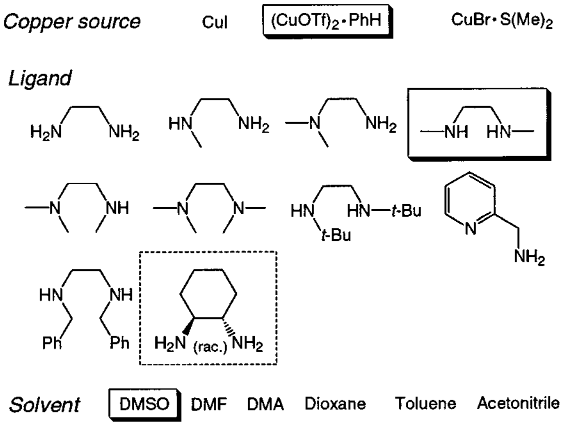
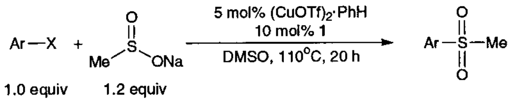
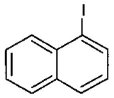
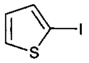
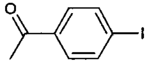
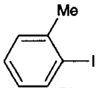
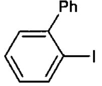
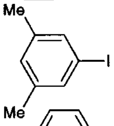
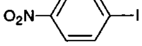
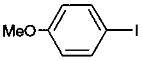
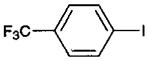
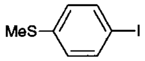
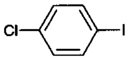
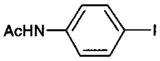
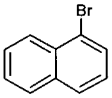


Figure 1. Cu(I) salts, diamine ligands, and solvents screened for catalysis efficiency.

Because the methyl sulfone group is found in many therapeutic agents, we focused most of our efforts on showing the generality of the coupling procedure with sodium methanesulfinate. As shown in Table 1, using the optimized conditions described above, various methyl sulfones were formed in excellent yield.[8] A wide variety of functional groups are tolerated by these conditions, including ketones, nitro groups, and heterocycles. Of particular note is entry 10, whose synthesis using standard oxidative procedures would require a tedious multistep sequence. As well, the hindered 2-iodotoluene and 2-iodobiphenyl (entries 4 and 5) proceeded quite well, although a longer reaction time was required for the latter iodide. The reaction of 4-iodoacetanilide (entry 12) exhibits a low yield, possibly due to oligomerization of the aryl iodide.[9] Like many other copper-catalyzed methodologies for aryl−heteroatom bond

Table 1. Formation of Methyl Sulfones[a]



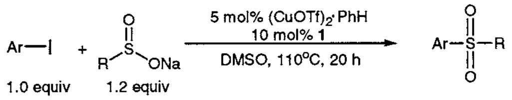
entry	aryl halide	% yield[b]
1		96
2		63
3		73
4		76
5		75[c]
6		91
7		85[d]
8		86
9		83
10		90
11		78[e]
12		27[f]
13		24

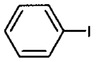
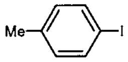
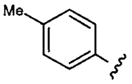
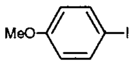
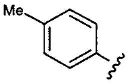
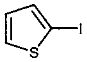
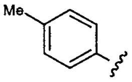
[a] All reactions were 1 M in DMSO. [b] Yield of sulfone of >95% purity as determined by ^1H NMR. [c] Reaction time of 64 h. The 20 h reaction afforded a 55% yield with 29% recovered iodide. [d] Product consists of a 12:1 ratio of desired product to 1,4-bis(methylsulfonyl)benzene. [e] Product consists of a 24:1 ratio of desired product to 1,4-bis(methylsulfonyl)benzene. [f] 2.0 equiv sulfinate was used.

I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205−9219. (h) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1995**, *36*, 4133−4136. (i) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D.; Volante, R. P. *J Org. Chem.* **1998**, *63*, 9606−9607. (j) Schopfer, U.; Schlaobach, A. *Tetrahedron* **2001**, *57*, 3096−3073.

(8) **Typical Experimental Procedure.** To a sealable tube equipped with an 8 × 1.5 mm stir bar was added 0.05 mmol of $(CuOTf)_2{\cdot}PhH$, 1.20 mmol of the sodium sulfinate, and 1.00 mmol of the aryl iodide under an air atmosphere. The aperture of the tube was then covered with a rubber septum, and a nitrogen atmosphere was established. *N*,*N*′-Dimethylethylenediamine (0.10 mmol) and anhydrous DMSO (1 mL) were added via syringe. The septum was then replaced by a Teflon-coated screw cap, and the reaction vessel was placed in a 110 °C oil bath. After stirring for approximately 20 h, the reaction mixture was allowed to cool to room temperature, diluted with 10 mL of ethyl acetate, and filtered through a pad of silica gel. The filtrate was washed with water (2 × 20 mL) and brine (1 × 20 mL), dried over Na_2SO_4, filtered through silica gel, and concentrated. In some cases, further purification by flash column chromatography was required to obtain a pure product. In all cases, the yields reported in the publication represent the isolated yield of products of >95% purity as determined by ^1H NMR.

Table 2. Formation of Diaryl Sulfones[a]



entry	aryl iodide	R	% yield[b]
1		Ph	70[c]
2			70
3			75[d]
4			43

[a] All reactions were 1 M in DMSO. [b] Isolated yield, from aryl halide, of sulfone of >95% purity as determined by ^{1}H NMR. [c] 1.6 equiv sulfinate was used. [d] Reaction time of 48 h.

formation, the present method does not achieve full conversion of aryl bromides. For example, the reaction of 1-bromonaphthalene with sodium methanesulfinate affords only a 24% yield of the desired product (entry 13).

As diaryl sulfones are also compounds of interest, a few examples using two commercially available sulfinic acid salts were performed, giving satisfactory yields, as described in Table 2. These examples in particular demonstrate the superiority of the present method for forming diaryl sulfones to that using stoichiometric amounts of CuI, which generally gives lower yields.[4]

While sulfinic acid salts have a limited commercial availability, recent advances in our laboratories have led to the development of a mild, convenient synthesis of sulfinic acid salts, which will expand the scope of the methodology described here.[10]

In summary, we have developed an efficient copper-catalyzed one-step transformation of aryl iodides and sulfinic acid salts into methyl and diaryl sulfones. We are currently examining the extension of this methodology to include aryl bromides.

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Supporting Information Available: Experimental procedures and characterization data (^{1}H and ^{13}C NMR, MS, and mp) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) As the conditions for the coupling of sulfinic acid salts and aryl iodides reported here are similar to those for the amidation of aryl iodides (ref 6f), we suspect that these two reactions are in competition in the case of Table 1, entry 12.

(10) Baskin, J. M.; Wang, Z. *Tetrahedron Lett.* **2002** *43*, 8479−8483.