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A General Method for the Formation of Aryl−Sulfur Bonds Using Copper(I) Catalysts

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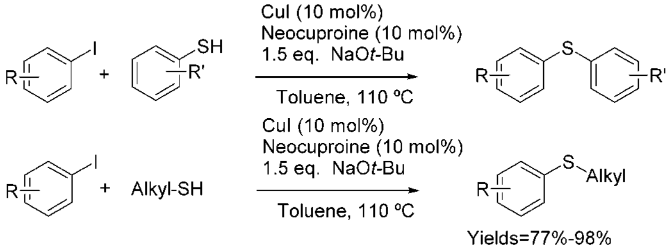
ABSTRACT



We report a mild, palladium-free synthetic protocol for the cross-coupling reaction of aryl iodides and thiols using 10 mol % CuI and 10 mol % neocuproine, with NaOt-Bu as the base, in toluene at 110 °C. Using this protocol, we have shown that a variety of aryl sulfides can be synthesized in excellent yields from readily available iodides and thiols.

Methods for the formation of aryl−sulfur bonds are indispensable tools in synthetic chemistry. Their importance stems from the prevalence of aryl−sulfur bonds in many molecules that are of biological, pharmaceutical and materials interest.[1] Traditional methods for the synthesis of aryl−sulfur bonds often require harsh reaction conditions. For example, coupling of copper thiolates with aryl halides requires polar solvents such as HMPA and temperatures around 200 °C. Reduction of aryl sulfones or aryl sulfoxides requires strong reducing agents such as DIBAL-H or $LiAlH_4$.[2] In 1980, Migita and co-workers first reported the cross-coupling reaction of aryl halides and thiols with $Pd(PPh_3)_4$ as the catalyst and NaO*t*-Bu as the base in polar solvents such as refluxing ethanol or DMSO at 90 °C.[3] However, only few reports have appeared in the literature for the formation of aryl−sulfur bonds using transition metal catalysts (Pd(0) or Ni(0)) since Migita's report.[4] This is in sharp contrast to the volume of literature that exists for the formation of aryl−nitrogen and aryl−oxygen bonds. Following Hartwig's

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[1] (a) Jones, D. N. *Comprehensive Organic Chemistry*; Barton, D. H., Ollis, D. W., Eds.; Pergamon: New York, 1979; Vol. 3. (b) Tiecco, M. *Synthesis-Stuttgart* **1988**, 749−759. (c) Rayner, C. M. *Contemp. Org. Synth.* **1996**, *3*, 499−533. (d) Baird, C. P.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1973−2003. (e) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 641−667. (f) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 835−871. (g) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 335−354. (h) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019−2022 and references therein.

[2] (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456. (b) Yamamoto, T.; Sekine, Y. *Can. J. Chem.* **1984**, *62*, 1544−1547. (c) Hickman, R. J. S.; Christie, B. J.; Guy, R. W.; White, T. J. *Aust. J. Chem.* **1985**, *38*, 899−904. (d) Van Bierbeek, A.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 6283−6286. Also see ref 1.

[3] (a) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.-i.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385−1389. (b) Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3657−3658.

[4] (a) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205−3220. (b) Rane, A. M.; Miranda, E. I.; Soderquist, J. A. *Tetrahedron Lett.* **1994**, *35*, 3225−3226. (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860. (d) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598−11599. (e) Baranano, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937−2938. (f) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205−9219. (g) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1995**, *36*, 4133−4136. (h) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D.; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606−9607. (i) Schöpfer, U.; Schlapbach, A. *Tetrahedron* **2001**, *57*, 3069−3073.

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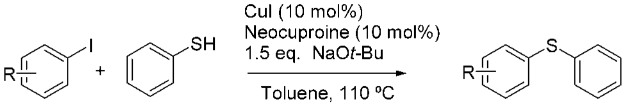
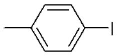
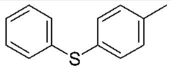
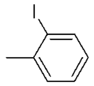
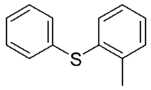
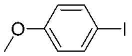
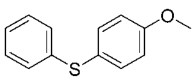
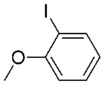
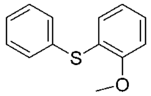
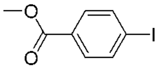
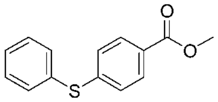
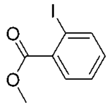
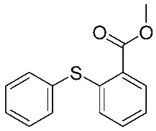
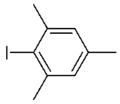
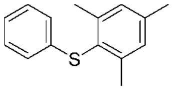
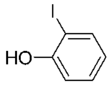
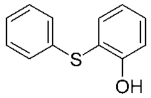
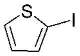
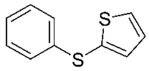
mechanistic studies[4c−f] on the reductive elimination of palladium(II) arylthiolate complexes with chelating phosphines, in 1996, Zheng and co-workers reported the first general palladium-based protocol for the synthesis of aryl sulfides from aryl triflates.[4h] More recently, in 2001, Schöpfer and Schlapbach reported a general palladium-catalyzed method for the synthesis of aryl sulfides from aryl iodides, in toluene, using DPEPhos as the ligand.[4i] In this report, we present a palladium-free general method for the formation of aryl−sulfur bonds from aryl iodides using catalytic amounts of copper iodide and neocuproine (2,9-dimethyl-1,10-phenanthroline).[5]

Traditional copper-mediated reactions suffer from drawbacks such as high reaction temperatures, the use of copper salts in greater than stoichiometric amounts, sensitivity to functional groups on the aryl halide, and irreproducibility.[2a] Yet, they remain as the reactions of choice in large- and industrial-scale syntheses.[8d,e] In the past five years, there has been a resurgence in interest in developing mild synthetic methods based on copper-based catalysts as an alternative to palladium(0) catalysts for the formation of aryl−carbon and aryl−heteroatom bonds. In this regard, our group,[6] Buchwald's group,[7] and others[8] have reported copper-based methods for the formation of aryl−carbon, aryl−nitrogen, and aryl−oxygen bonds. In addition to being simple and mild, these protocols also accommodate substrates that do not undergo coupling by palladium catalysis.[9] Moreover, in comparison to palladium, copper-based catalysts are quite attractive from an economic standpoint. We now extend the utility of copper-based catalysts for the formation of aryl−sulfur bonds through the cross-coupling reaction between aryl iodides and thiols.

We first chose to study the efficacy of copper(I)-based catalysts in the cross-coupling reaction between iodobenzene and thiophenol, in toluene, using Cu(phenanthroline)(PPh_3)Br and Cu(neocuproine)(PPh_3)Br complexes. We had previously shown the utility of these complexes in the formation of aryl−acetylene, aryl−nitrogen, and aryl−oxygen bonds.[6b,c] Our initial choice of base was Cs_2CO_3. We based this choice on observations by Buchwald, Snieckus, and our group that Cs_2CO_3 was essential in copper-based protocols for the formation of aryl−oxygen bonds. In 24 h, although we observed the formation of diphenyl sulfide by GC analyses, the overall conversion was less than 50%. When we replaced Cs_2CO_3 with NaO*t*-Bu, we observed complete consumption of the starting materials when Cu(neocuproine)(PPh_3)Br was the catalyst. However, if Cu(phenanthroline)(PPh_3)Br was used as the catalyst, GC traces showed the presence of starting materials in trace amounts in the same time period. Trace amounts of starting materials were also observed if KO*t*-Bu was used as the base. Diphenyl sulfide was formed only in trace amounts if bromobenzene was used indicating that the reaction was selective to iodides.

Table 1. Reactions of Aryl Iodides with Thiophenol



Entry	Aryl Iodide	Product	Isolated Yield (%)
1			94
2			96
3			96
4			95
5			84
6			81
7			97
8			81
9			91

As a part of our control experiments, we replaced Cu(neocuproine)(PPh_3)Br with 10 mol % CuI, CuI/neocuproine, or CuCl/neocuproine as the catalyst. We found that CuI/neocuproine was as effective as Cu(neocuproine)(PPh_3)Br. However, only a trace amount of diphenyl sulfide was observed if CuI alone was used as the catalyst. This indicated that neocuproine was essential for acceleration of the reaction. Also, GC traces indicated the presence of starting

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(5) Kiplin Guy and co-workers have reported a palladium-free method for the coupling of mercaptans with aryl boronic acids using $Cu(OAc)_2$. See ref 1f.

(6) (a) Gujadhur, R.; Venkataraman, D. *Synth. Commun.* **2001**, *31*, 2865−2879. (b) Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791−4793. (c) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315−4317.

(7) (a) Marcoux, J. F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539−10540. (b) Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657−2660. (c) Klapars, A.; Antilla, J. C.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729. (d) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803−3805. (e) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581−584. (f) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973−976. (g) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269−272.

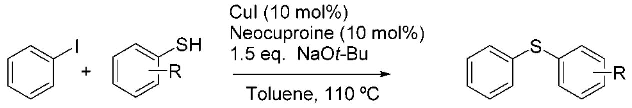
(8) (a) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312−2313. (b) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459−12467. (c) Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986−2987. (d) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670−674. (e) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043−5051.

(9) See refs 6b and 7c,f,g for examples.

materials if CuCl/neocuproine was the catalyst. While we found that K_3PO_4 was as effective as KO*t*Bu, other bases such as triethylamine and K_2CO_3 were ineffective in the coupling of iodobenzene with thiophenol. On the basis of these aforementioned observations, we decided to use CuI (10 mol %)/neocuproine (10 mol %) as the catalyst, NaO*t*-Bu as the base, and toluene as the solvent as a standard protocol for the formation of aryl−sulfur bonds.

Using our protocol, we were able to couple thiophenol with electron-rich and electron-poor aryl iodides in excellent yields (Table 1). Furthermore, we successfully coupled a variety of readily available thiophenols with iodobenzene in excellent yields (Table 2). We were pleased to note that our protocol can also be used to couple sterically hindered thiophenols such as 2,6-dimethylthiophenol with iodobenzene in 95% yield (entry 7, Table 2). Moreover, our protocol can also be extended to couple aryl halides with alkyl thiols in excellent yields (Table 3).

Table 2. Reactions of Iodobenzene with Readily Available Thiophenols



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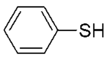
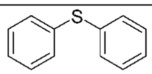
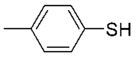
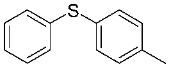
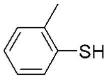
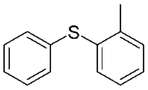
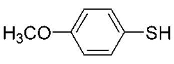
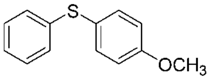
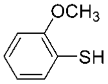
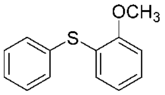
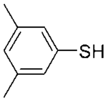
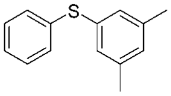
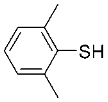
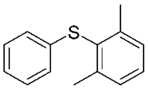
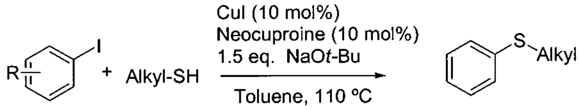
1			98
2			97
3			95
4			95
5			94
6			97
7			95

The only other report that we are aware of that deals with the coupling of unactivated aryl iodides and thiols in the presence of a catalytic amount of copper(I), in refluxing toluene, was reported by Palomo and co-workers in 2000.[10] This protocol, however, calls for the use of expensive Schwesinger's Phosphazene bases such as P_2-Et.[11] Moreover, this procedure was not shown to couple aryl iodides with alkyl thiols.

Table 3. Reactions of Aryl Iodides with Readily Available Alkyl Thiols



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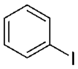
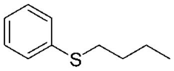
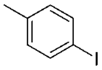
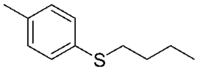
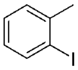
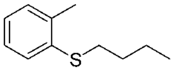
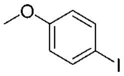
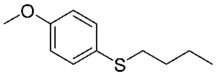
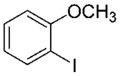
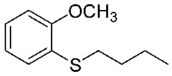
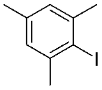
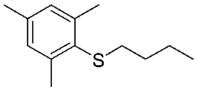
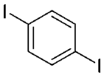
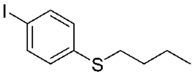
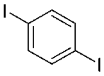
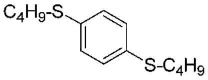
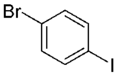
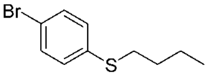
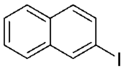
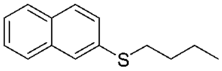
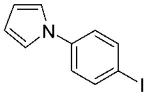
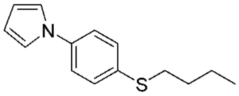
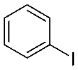
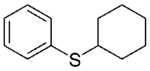
1			95
2			94
3			93
4			95
5			84
6			98
7			88
8			98
9			92
10			95
11			95
12			77

In summary, we have reported a general synthetic protocol for the formation of aryl−sulfur bonds, using copper(I) catalysts. In this protocol, we recommend the use of 10 mol % CuI, 10 mol % neocuproine, NaO*t*-Bu as the base, and toluene as the solvent. In cases where NaO*t*-Bu cannot be used, we recommend the use of K_3PO_4. Our protocol is palladium-free and avoids the use of expensive and/or air-sensitive ligands. We are in the process of expanding the scope of these reactions and studying their mechanistic aspects and will be reporting on them shortly.

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(10) Palomo, C.; Oiarbide, M.; Lopez, R.; Gomez-Bengoa, E. *Tetrahedron Lett.* **2000**, *41*, 1283−1286. Snieckus and co-workers (ref 7c) have reported the coupling of activated aryliodides such as *o*-iodobenzamides and *o*-iodosulfonamides with thiophenols using $Cu(CH_3CN)_4PF_6$ as a catalyst.

(11) Schwesinger's Phosphazene bases are readily available from Aldrich. The cost of P_2-Et is $260.00 for 5 mL.

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Supporting Information Available: Synthetic procedures and characterization data for products listed in Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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