Ligand-Free C–S Bond Formation Catalyzed by Copper(I) Oxide

Hua-Jian Xu,[a] Xiao-Yang Zhao,[a] Yao Fu,*[b] Yi-Si Feng*[a]

[a] School of Chemical Engineering, Hefei University of Technology, Hefei, 230009, P. R. of China
[b] Department of Chemistry, University of Science and Technology of China, Hefei 230026, P. R. of China
Fax +86(551)3607476; E-mail: fuyao@ustc.edu.cn

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Abstract: An efficient ligand-free Cu_2O-catalyzed C–S bond-formation reaction was developed. A large number of diaryl sulfides and alkylaryl sulfides could be rapidly assembled using this new reaction protocol.

Key words: copper(I) oxide, ligand-free, C–S coupling, iodides, thiols

Transition-metal-catalyzed C–S bond formation is an important reaction in synthetic organic chemistry because aryl sulfides and their sulfone derivatives are of great significance to the pharmaceutical and material industry.[1] Several metals such as palladium-,[2] copper-,[3] nickel-,[4] cobalt-,[5] and iron-based[6] catalytic systems have been reported for this purpose. Among these proceeding methods, copper-catalyzed C–S cross-coupling has attracted more attentions because copper is much less expensive and toxic than palladium and nickel, and the reaction conditions are relatively milder, which can be applied in large-scale industrial process.

The traditional Cu-mediated couplings between thiols and aryl halides require the use of copper salts in greater than stoichiometric amounts, polar solvents such as HMPA, and high temperatures around 200 °C.[7] In 2002, Venkataraman et al. reported a Cu-catalyzed protocol for the coupling between aryl iodides and thiols using 10 mol% CuI and 10 mol% neocuproine, with NaO*t*-Bu as the base, in toluene at 110 °C.[8] Subsequently, examples of other attractive copper-catalyzed processes have been reported, mainly using copper salts as the metal source together with a suitable ligand.[3]

However, ligand-free C–S coupling is much less studied. Till recently, several research results were reported. For examples, Ranu et al. reported microassisted and ligand-free Cu-nanoparticle-catalyzed (20 mol%) aryl–sulfur bond formation with K_2CO_3 as the base and DMF as solvent;[9a] Punniyamurthy et al. reported ligand-free CuO-nanoparticle-catalyzed (1.26 mol%) C–S cross-coupling of thiols with iodobenzene with KOH as base and DMSO as solvent;[9b] van Koten et al. reported ligand-free CuI-catalyzed C–S coupling of aryl iodides and thiols with K_2CO_3 as the base and NMP as solvent.[9c]

As an ongoing research of exploring the less expensive Cu salts, more simple and ligand-free process for this coupling reaction, we reported here that readily available Cu_2O could catalyze efficiently the C–S cross-coupling of aryl, alkyl, and heteroaryl thiols with aryl and heteroaryl iodides in excellent yields without any ligands.

We firstly studied the reaction of the model substrate benzenethiol with iodobenzene (Scheme 1).

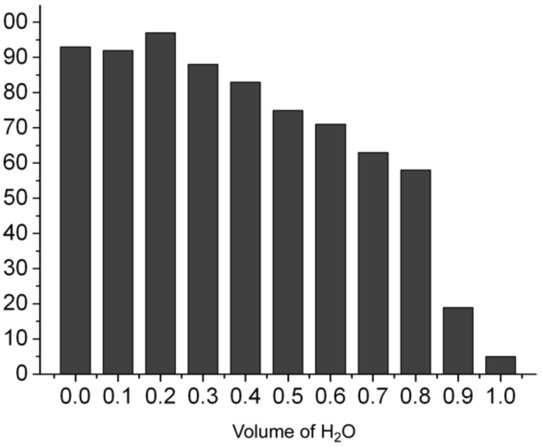
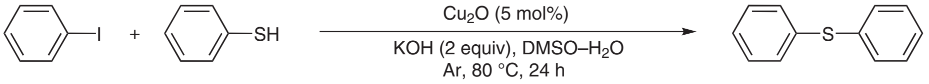


Figure 1 Effect of H_2O on the cross-coupling reaction of PhI and PhSH. The volume sum of DMSO and H_2O is equal to 1 mL

A yield of 93% (GC) of product was obtained without water in the reaction system, a yield of 92% (GC) of product was gained when DMSO–H_2O (volume ratio = 9:1) was used as solvent for this model reaction, the best yield (97%, GC) of product was obtained when volume ratio of DMSO–H_2O was 4:1, and no reaction was observed without Cu_2O. In order to make the reaction more environmentally benign, we tried to add more water into the reaction system. The effect of water on this reaction is shown in



Scheme 1

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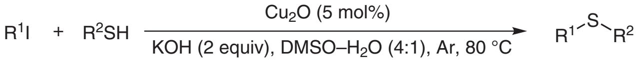
Figure 1. The yield of product decreased with more water adding. Only 5% yield (GC) of product was obtained in pure water. Therefore, the optimized conditions employed 5 mol% of Cu_2O, 2 equivalents of KOH in 1 mL DMSO–H_2O (volume ratio = 4:1) at 80 °C under argon.

Next, we screened a range of commercially available aryl and heteroaryl iodides and aryl, alkyl, and heteroaryl thiols to explore the scope of the C–S coupling reaction. As shown in Table 1,[10] the coupling of different thiols with aryl and heteroaryl iodide moieties was successful, leading to the desired products in excellent yields (60–96%).[11] The protocol could tolerate electron-withdrawing and -donating functional groups and also to the presence of functional groups at the *ortho* position of the aryl iodide or thiol (entries 9–11 and 27, 28). Heteroaryl iodides (entries 30, 31) and heteroaryl thiols (entry 14) were also applied to this coupling reaction. Hence, the scope of our protocol was quite broad.

Table 1 The C–S Cross-Coupling Reaction of Aryl and Heteroaryl Iodides with Aryl, Alkyl, and Heteroaryl Thiols[a]



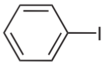
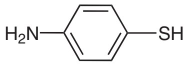
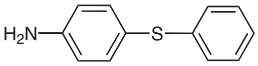
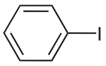
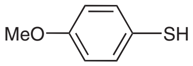
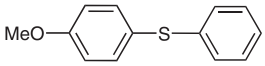
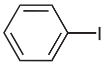
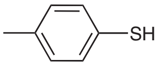
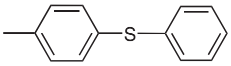
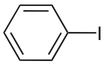
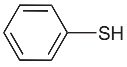
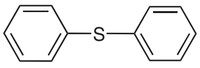
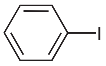
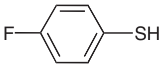
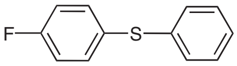
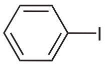
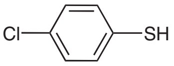
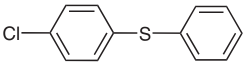
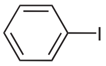
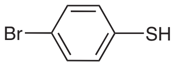
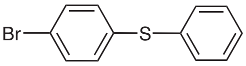
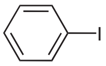
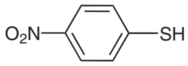
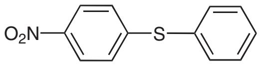
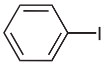
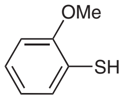
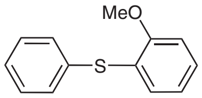
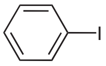
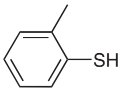
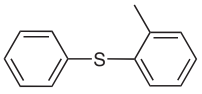
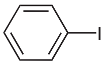
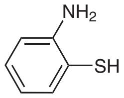
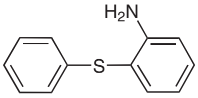
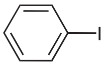
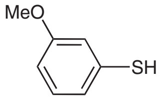
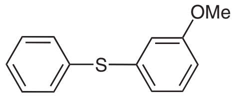
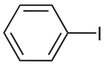
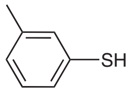
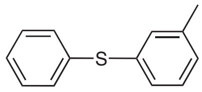
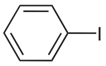
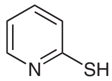
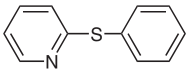
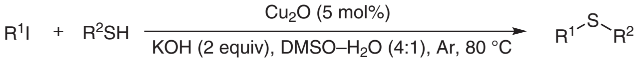
Entry	Aryl iodides	Thiols	Product	Isolated yield (%)
1				88
2				93
3				92
4				90
5				87
6				95
7				91
8				60
9				89
10				87
11				76
12				86
13				85
14				86

Table 1 The C–S Cross-Coupling Reaction of Aryl and Heteroaryl Iodides with Aryl, Alkyl, and Heteroaryl Thiols[a] (continued)



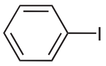
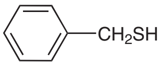
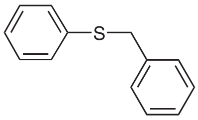
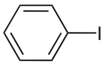
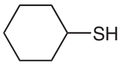
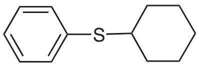
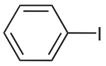
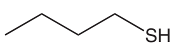
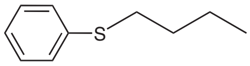
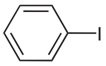
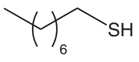
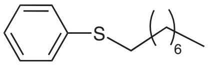
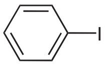
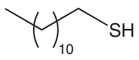
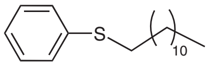
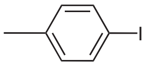
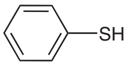
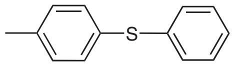
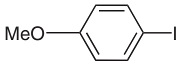
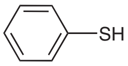
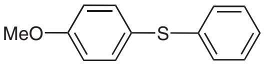
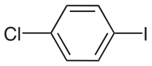
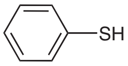
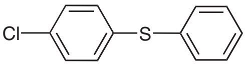
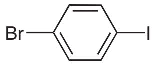
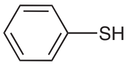
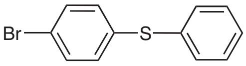
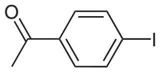
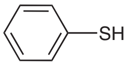
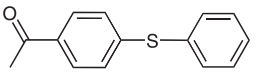
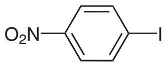
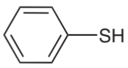
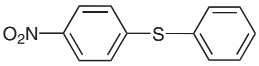
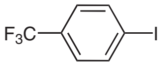
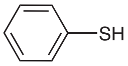
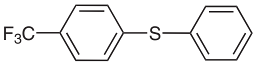
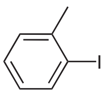
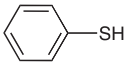
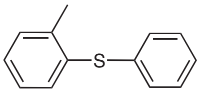
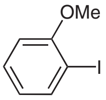
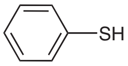
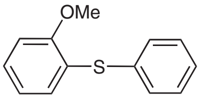
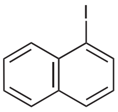
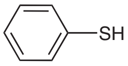
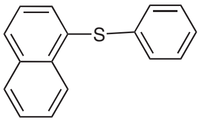
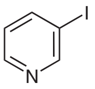
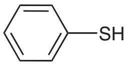
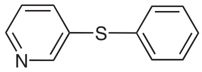
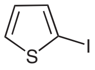
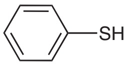
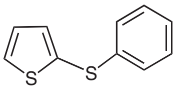
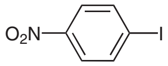
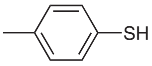
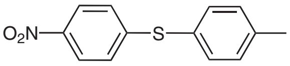
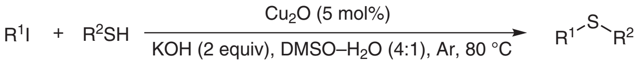
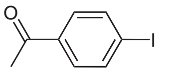
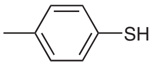
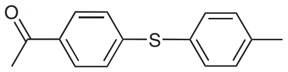
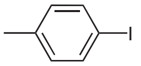
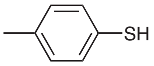
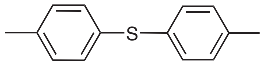
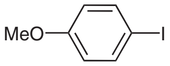
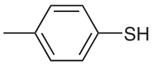
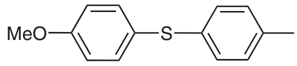
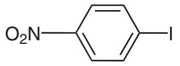
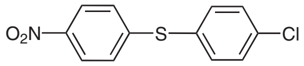
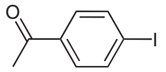
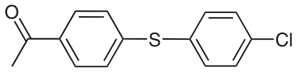
Entry	Aryl iodides	Thiols	Product	Isolated yield (%)
15				85
16				82
17				79
18				75
19				70
20				89
21				91
22				91
23				85
24				95
25				96
26				95
27				90
28				83
29				86
30				91
31				91
32				95

Table 1 The C–S Cross-Coupling Reaction of Aryl and Heteroaryl Iodides with Aryl, Alkyl, and Heteroaryl Thiols[a] (continued)



Entry	Aryl iodides	Thiols	Product	Isolated yield (%)
33				91
34				87
35				93
36				95
37				90

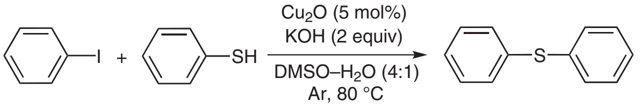
[a] Reaction conditions: aryl iodide (1 mmol), thiol (1.1 mmol), Cu_2O (0.05 mmol), KOH (2 mmol) in DMSO (0.8 mL) and H_2O (0.2 mL) at 80 °C under Ar for 24 h.

The catalyst was found to be recyclable without loss of activity (Table 2). After the reaction of benzenethiol with iodobenzene had reached completion, the catalyst was recovered from the reaction mixture by centrifugation and reused up to three times. Only a slight decrease in catalytic activity was observed.

Compared with the previous reports,[9] our protocol provided a more efficient synthetic route of C–S bond formation: (a) Cu_2O is cheaper than other copper salts and producing cost is reduced; (b) the amount of organic solvent used was less, which will make the reaction system more environmentally benign and safe.

In summary, an efficient Cu_2O-catalyzed C–S bond-forming reaction of aryl and heteroaryl iodides with aryl, alkyl, and heteroaryl thiols was developed. This catalytic procedure offers general applicability and simplicity, avoiding the expensive and time-consuming preparation of copper salts and suitable ligands. We believe that this protocol can be applied to large-scale industrial process.

Table 2 Recycling of Cu_2O



Run	Catalyst recovery (%)	Isolated yield (%)
1[a]	95	86
2[b]	87	80
3[b]	75	68

[a] Aryl iodide (1 mmol), thiol (1.1 mmol), Cu_2O (0.05 mmol), KOH (2 mmol) in DMSO (0.8 mL) and H_2O (0.2 mL) at 80 °C under Ar for 24 h.

[b] The recovered catalyst was used under identical reaction conditions to those for the first run.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(10) **General Experimental Procedure**
All reagents and solvents were pure analytical-grade materials purchased from commercial sources and were used without further purification. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 300 MHz instrument with TMS as internal standard. High-resolution mass spectra (HRMS) were determined on a Micromass GCT-MS mass spectrometer. Thin-layer chromatography was carried out with 0.2 mm thick SiO_2 plates (GF254). The columns were hand packed with silica gel 60 (200–300). All reactions were carried out in a Schlenk tube equipped with a magnetic stir bar under Ar atmosphere. A Schlenk tube was charged with Cu_2O (0.05 mmol), KOH (2 mmol) and solid substrate, if present. Then, liquid reagents (aryl or heteroaryl halide, 1 mmol; thiol, 1.1 mmol), solvent (1 mL) were added under Ar. The reaction vessel was closed and placed under stirring in a preheated oil bath at 80 °C. The reaction mixture was stirred for 24 h. The resulting suspension was cooled to r.t. and filtered through a pad of filter paper with the help of EtOAc (10 mL). The filtrate was concentrated and the residue was purified by silica gel chromatography.
(4-Methoxyphenyl)phenylsulfane (Entry 2, Table 1)
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.78$ (s, 3 H), 6.98 (d, $J = 8.7$ Hz, 2 H), 7.17–7.21 (m, 5 H), 7.40 (d, $J = 9.0$ Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 55.2$, 115.0, 124.2, 125.7, 128.2, 128.9, 135.3, 138.6, 159.8 ppm. HRMS: *m/z* calcd for $C_{13}H_{12}OS$: 216.0609; found: 216.0613.
Phenyl(*p*-tolyl)sulfane (entry 20, Table 1)
^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.31$ (s, 3 H), 7.09–7.29 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.1$, 126.4, 129.0, 129.8, 130.1, 131.4, 132.3, 137.2, 137.5 ppm. HRMS: *m/z* calcd for $C_{13}H_{12}S$: 200.0660; found: 200.0652.

(11) No Cu was found in pure diphenylsulfane (entry 4, Table 1) with X-radial fluorescence-spectrum determining.