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Efficient C–S cross coupling catalyzed by Cu_2O

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

[a] School of Chemical Engineering, Hefei University of Technology, Hefei 230009, China
[b] Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

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ABSTRACT

A protocol for the copper-catalyzed C–S bond formation between aryl, alkyl, or heteroaryl thiols and aryl or heteroaryl halides is reported. The reaction is catalyzed by Cu_2O which shows the highest catalytic activity with ethyl 2-oxocyclohexanecarboxylate ligand in DMSO at 80 °C. The corresponding coupling products are obtained with good to excellent yields under relatively mild reaction conditions with good chemoselectivity and functional group tolerance.

The formation of the C–S bond is indispensable in synthetic chemistry. Their importance stems from the prevalence of this bond in many pharmaceutical compounds and from the utility of aryl sulfides as intermediates in organic synthesis.[1] Traditional methods for the formation of C–S bond involved condensation of aryl halides with thiols requiring strongly basic and harsh reaction conditions.[2] To overcome these difficulties, considerable attention has been focused on the development of transition metal-catalyzed coupling of thiols with aryl halides. Palladium-,[3] copper-,[4] nickel-,[5] cobalt-,[6] and iron-based[7] catalytic systems have been reported for this purpose. The high cost and air sensitivity of Pd catalyst systems and tedious procedures for the preparation of ligands restrict their applications in large-scale processes. On the other hand, Cu-mediated coupling reactions sometimes require some expensive Cu salts and the water-free conditions. Hence, there is a need for improved procedures for this important reaction in organic chemistry. As an ongoing research of exploring the less expensive Cu salts for this coupling reaction,[4h] we reported here that cheap and readily available Cu_2O catalyzes efficiently the C–S cross-coupling of aryl, alkyl, and heteroaryl thiols with aryl and heteroaryl halides in excellent yields. During the preparation of this article, Bao and co-workers[8] had reported that the system Cu_2O/ethyl 2-oxocyclohexanecarboxylate can catalyze Ullmann-type reaction of vinyl bromides and chlorides with imidazole and benzimidazole.

In the first stage of the study, we tried to seek the optimal ligand from compounds **1**–**8** for the reaction of the model substrate *p*-methyl benzenethiol with iodobenzene with Cu_2O as the catalyst. The reactions promoted by *N*,*N*-type ligands **7** and **8** gave low yields, although **7** was often used as an excellent ligand for the C–N coupling.[9] *O*,*O*-type ligands **3**, **4**, **5**, and **6** were also tested, and moderate results were achieved. Interestingly, the reactions gave different results when ligands **1** and **2** were used, where only ethyl group of **1** was changed into methyl group of **2**. Finally, a control experiment without any ligand was carried out, and low yield was obtained under the similar condition. From the above descriptions, ligand **1** was chosen for further investigation.

A brief search of other reaction conditions was carried out after finding the best ligand. The reaction with Cs_2CO_3 was superior to that using KOH, K_2CO_3, and K_3PO_4. Then, the effect of solvent was evaluated. Dioxane and toluene were not suitable as solvents. DMSO performed as the best solvent. DMF gave fair results, but was not as good as DMSO. The copper sources were also found to have remarkable effects on the reaction. CuO and $Cu(OAc)_2$ were not suitable as copper sources. CuI, CuBr, CuCl, $CuSO_4$, and $CuBr_2$ were found to be inferior to Cu_2O as catalysts for the C–S coupling reaction. No reaction was observed without any copper source. The

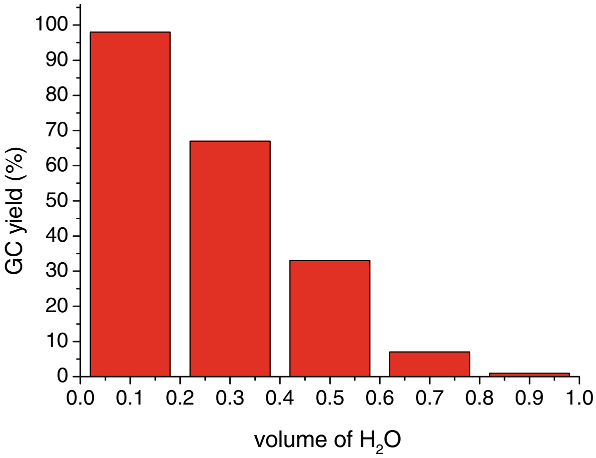

Figure 1. Effect of H_2O on the cross-coupling reaction of PhI and *p*-Me-C_6H_4SH. The volume sum of H_2O and DMSO is equal to 1 ml.

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[*] Corresponding authors. Tel./fax: +86 551 3607476 (Y.F.).
E-mail address: fuyao@ustc.edu.cn (Y. Fu).

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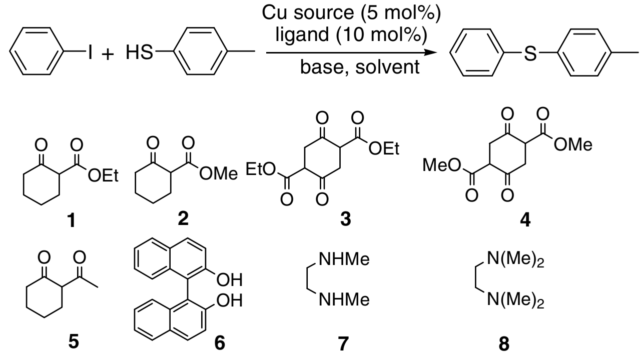
Table 1
Copper-catalyzed coupling of *p*-methyl benzenethiol with iodobenzene[a]



Entry	Cu source	Ligand	Base	Solvent	Yield[b] (%)
1	Cu_2O	**1**	Cs_2CO_3	DMSO	98
2	Cu_2O	**2**	Cs_2CO_3	DMSO	85
3	Cu_2O	**3**	Cs_2CO_3	DMSO	76
4	Cu_2O	**4**	Cs_2CO_3	DMSO	76
5	Cu_2O	**5**	Cs_2CO_3	DMSO	78
6	Cu_2O	**6**	Cs_2CO_3	DMSO	63
7	Cu_2O	**7**	Cs_2CO_3	DMSO	53
8	Cu_2O	**8**	Cs_2CO_3	DMSO	33
9	Cu_2O	–	Cs_2CO_3	DMSO	54
10	Cu_2O	**1**	K_2CO_3	DMSO	75
11	Cu_2O	**1**	K_3PO_4	DMSO	84
12	Cu_2O	**1**	KOH	DMSO	76
13	Cu_2O	**1**	Cs_2CO_3	DMF	85
14	Cu_2O	**1**	Cs_2CO_3	Dioxane	42
15	Cu_2O	**1**	Cs_2CO_3	Toluene	22
16	CuI	**1**	Cs_2CO_3	DMSO	66
17	CuBr	**1**	Cs_2CO_3	DMSO	39
18	CuCl	**1**	Cs_2CO_3	DMSO	50
19	$Cu(OAc)_2$	**1**	Cs_2CO_3	DMSO	18
20	$CuSO_4$	**1**	Cs_2CO_3	DMSO	65
21	$CuBr_2$	**1**	Cs_2CO_3	DMSO	86
22	CuO	**1**	Cs_2CO_3	DMSO	2
23	–	**1**	Cs_2CO_3	DMSO	0
24[c]	Cu_2O	**1**	Cs_2CO_3	DMSO	25
25[d]	Cu_2O	**1**	Cs_2CO_3	DMSO	98
26[e]	Cu_2O	**1**	Cs_2CO_3	DMSO	90

[a] General reaction conditions: iodobenzene (1.0 mmol), *p*-methyl benzenethiol (1.1 mmol), Cu catalyst (0.05 mmol), ligand (0.1 mmol), and Cs_2CO_3 (2 mmol) in indicated solvent (1.0 ml) at 80 °C under Ar for 20 h.

[b] GC yield.

[c] The reaction was carried out at 60 °C.

[d] The reaction was carried out at 100 °C.

[e] The reaction was carried out in air.

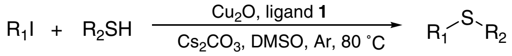
yield of product drastically decreased when reducing the reaction temperature, while the yield of product remain the same with higher reaction temperatures. In addition, the yield of product reduced only slightly even when the reaction was carried out in air. Therefore, the optimized conditions employed 5 mol % of Cu_2O, 10 mol % of ligand **1**, and 2 equiv of Cs_2CO_3 in DMSO at 80 °C under argon.

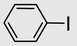
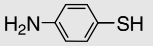
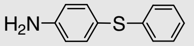
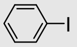
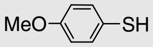
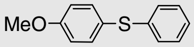
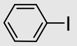
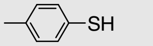
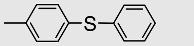
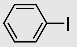
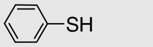
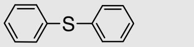
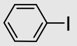
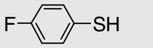
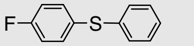
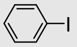
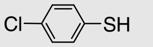
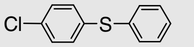
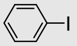
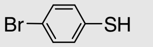
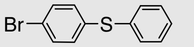
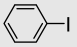
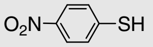
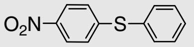
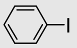
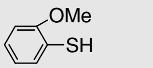
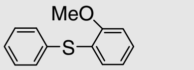
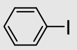
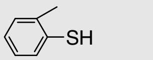
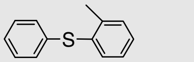
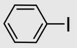
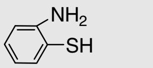
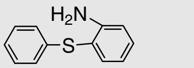
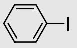
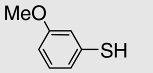
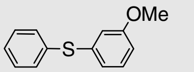
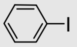
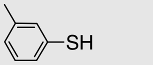
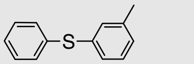
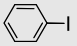
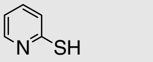
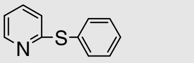
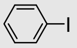
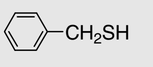
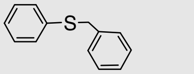
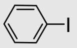
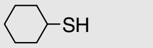
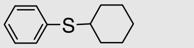
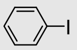
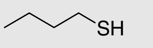
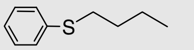
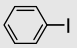
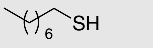
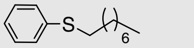
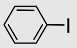
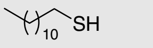
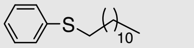
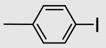
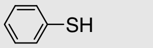
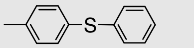
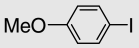
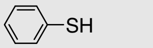
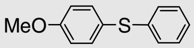
Next, in order to further simplify the procedure, we explored the effect of water on the reaction under the optimized conditions as shown in Figure 1. Small amount of water had no impact on the reaction (volume of H_2O = 0.1 ml). However, the yield of product decreased when more water was added. No reaction was observed in water.

According to these findings, all materials used in the experiments need not be dry and can be used directly, which can drastically reduce the cost and time of the reaction. This is important for application to large-scale processes (see Table 1).

After the best reaction condition was set, we firstly screened a range of commercially available aryl and heteroaryl iodides and aryl, alkyl, and heteroaryl thiols to explore the scope of the C–S

Table 2
The C–S cross-coupling reaction of aryl iodides with thiols[a]



Entry	Aryl iodides	Thiols	Product	Isolated yield (%)
1				86
2				95
3				93
4				96
5				90
6				95
7				93
8				51
9				92
10				90
11				81
12				93
13				90
14				76
15				89
16				82
17				73
18				71
19				70
20				91
21				92

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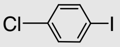
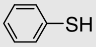
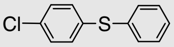
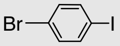
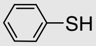
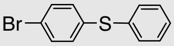
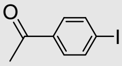
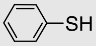
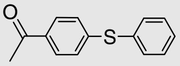
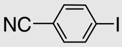
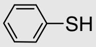
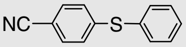
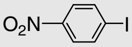
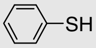
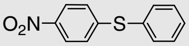
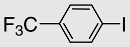
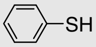
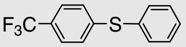
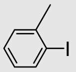
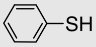
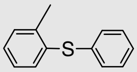
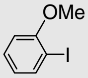
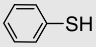
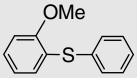
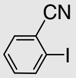
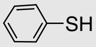
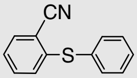
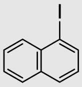
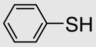
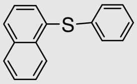
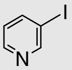
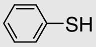
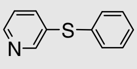
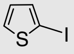
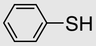
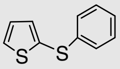
22				90
23				87
24				93
25				91
26				95
27				96
28				86
29				83
30				90
31				93
32				91
33				90

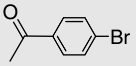
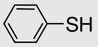
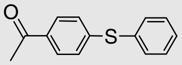
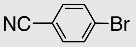
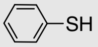
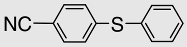
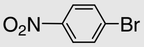
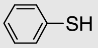
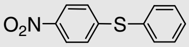
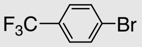
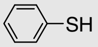
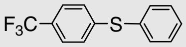
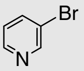
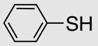
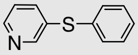
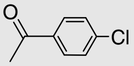
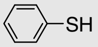
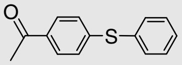
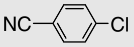
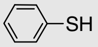
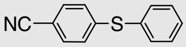
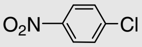
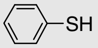
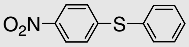
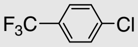
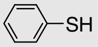
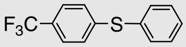
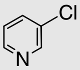
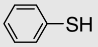
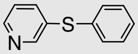
[a] Reaction conditions: aryl iodide (1 mmol), thiol (1.1 mmol), Cu_2O (0.05 mmol), ligand 1 (0.1 mmol), and Cs_2CO_3 (2 mmol) in DMSO (1 ml) at 80 °C under Ar for 20 h.

Table 3

The C–S cross-coupling reaction of aryl halides with thiophenol[a]

$$\mathrm{RX} + \mathrm{PhSH} \xrightarrow[\mathrm{Cs_2CO_3,\ DMSO,\ Ar,\ 80\ ^\circ C}]{\mathrm{Cu_2O,\ ligand}\ \mathbf{1}} \mathrm{R{-}S{-}Ph}$$

X= Br, Cl

Entry	Aryl halides	Thiols	Product	Isolated yield (%)
1				61
2				67
3				90[b]
4				85
5				85
6				52
7				53
8				82
9				71
10				77

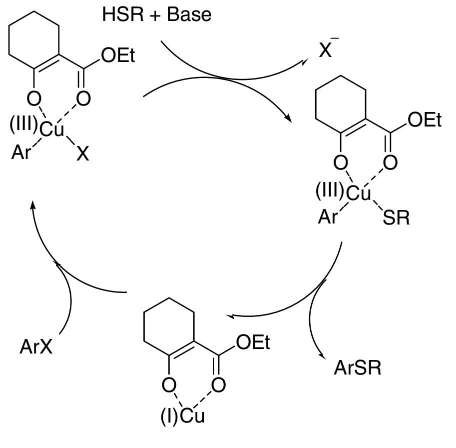
[a] Reaction conditions: arylhalide (1 mmol), thiol (1.1 mmol), Cu_2O (0.05 mmol, ligand **1** (0.1 mmol), and Cs_2CO_3 (2 mmol) in DMSO (1 ml) at 80 °C under Ar for 24 h.

[b] Only 8% yield of the corresponding product was obtained without Cu_2O and ligand **1** under the similar reaction condition.

coupling reaction. As shown in Table 2,[10] the coupling of different thiols with aryl and heteroaryl iodide moieties was successful, leading to the desired products in excellent yields. The protocol is tolerant to electron-withdrawing and -donating functional groups and also to the presence of a functional group in the *ortho*-position of the aryl iodide or thiol (entries 9–11 and 28–30). Heteroaryl iodides (entries 32 and 33) and heteroaryl thiols (entry 14) were also applied to this coupling reaction. The coupling reaction is also very chemoselective. Aryl iodides coupled with thiols without affecting fluoro, chloro and bromo groups present in the aryl ring (entries 5–7, 22 and 23). Moreover, the reaction showed interesting chemoselectivity for the thiol. For instance, in entries 1 and 11 C–S coupling was preferred in the presence of an $-NH_2$ group.

Next, we investigated the reactivities of diverse aryl (or heteroaryl) bromides and chlorides. Both aryl bromides and chlorides with electron-donating groups or without any substituents could not react with thiophenol, while aryl bromides and chlorides with electron-withdrawing groups could react with thiophenol to give moderate yields. 3-Bromopyridene and 3-chloropyridene also could be applied to this coupling reaction and satisfactory yields were obtained. The results are summarized in Table 3.

On the basis of these observations and by reference to the literature,[11] we propose that these reactions proceed by oxidative addition followed by reductive elimination. The results from the



Scheme 1.

present study are consistent with the mechanism in which a four-coordinated Cu(III) intermediate is involved (see Scheme 1). According to the mechanism, the role of the ethyl 2-oxocyclohexanecarboxylate ligand in the reaction is either to promote the oxidative addition of ArX to the Cu(I) species or to stabilize the Cu(III) intermediate.

In conclusion, we have described an efficient modified protocol for C–S cross-coupling of aryl, alkyl, and heteroaryl thiols with aryl and heteroaryl iodides, bromides, and chlorides using cheap and available Cu_2O as the catalyst. This catalytic procedure offers general applicability and simplicity, avoiding the use of expensive Cu salts and the use of dry starting materials. Because of these interesting features, we believe that the newly developed protocol can be applied to large-scale synthesis of aromatic thioethers.

Acknowledgments

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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 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. TLC was carried out with 0.2 mm thick silica gel 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 salt (0.05 mmol), inorganic base (2 mmol), and solid substrate, if present. Then liquid reagents (aryl or heteroaryl halide, 1 mmol; thiol, 1.1 mmol), ligand (0.1 mmol), and 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 the time listed in Tables 1–3. The resulting suspension was cooled to room temperature and filtered through a pad of filter paper with the help of 10 ml of ethyl acetate. The filtrate was concentrated and the residue was purifiled by silica gel chromatography.
    (4-Methoxyphenyl) phenyl sulfane (entry 2, Table 2): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 3H), 6.98 (d, J = 8.7 Hz, 2H), 7.17-7.21(m, 5H), 7.40 (d, J = 9.0 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.2, 115.0, 124.2, 125.7, 128.2, 128.9, 135.3, 138.6, 159.8 ppm. HRMS m/z: 216.0613 (216.0609 calcd for $C_{13}H_{12}OS$).
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