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Efficient ligand-free copper-catalyzed C–S cross-coupling of thiols with aryl iodides using KF/Al_2O_3 as base

Yi-Si Feng [a,b], Yuan-Yuan Li [a], Lin Tang [a], Wei Wu [a], Hua-Jian Xu [a,b,*]

[a] School of Chemical Engineering, Hefei University of Technology, Hefei 230009, PR China
[b] Anhui Key Laboratory of Controllable Chemical Reaction & Material Chemical Engineering, Hefei 230009, PR China

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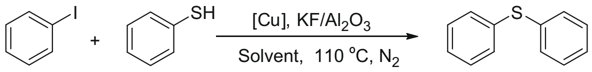
ABSTRACT

We report a mild, convenient, environmentally friendly, and ligand-free synthetic protocol for the cross-coupling reaction of aryl iodides and thiols using 10 mol % CuI with KF/Al_2O_3 as the base, in DMF 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.

The formation of C(aryl)–S bonds represents a key step in the synthesis of many molecules that are of biological, pharmaceutical, and material interest.[1] However, traditional methods for the synthesis of aryl-sulfur bonds often require harsh reaction conditions[2] such as high temperature, the usual requirement of stoichiometric amounts of copper reagents, long reaction times, and low yields. The development of transition metal-catalyzed coupling has overcome these difficulties to a great extent. On the other hand, modern transition-metal (palladium,[3] nickel,[4] copper,[5] cobalt,[6] iron,[7] and indium[8]) in combination with appropriate ligands for catalyzed cross-coupling reactions of aryl halides with thiols enable the synthesis of aryl sulfides in good yields under milder reaction conditions. However, the high cost and air sensitivity of Pd catalysts and often tedious procedure for the preparation of ligands restrict their applications in large-scale processes. On the other hand, in general, Co and Ni catalysts are associated with toxicity. Thus, development of alternative inexpensive, ligand-free, non-air sensitive catalysts for this useful reaction is highly desirable in the context of environmental and industrial concerns.

The selection of the correct base is crucial for the success of C–S coupling processes. This is particularly true with respect to functional group tolerance and reaction rate. Nevertheless, in almost all documented methods, Cs_2CO_3, NaO*t*Bu, KO*t*Bu, K_2CO_3, and K_3PO_4 were chosen as bases. In fact, these bases with high sensitivity to moisture reduce their capability as bases in moisture sensitive reactions. Solid base has enjoyed growing attention due to its environmentally friendly nature and unique properties. Of a variety of solid bases, KF/Al_2O_3 is a typical example. It has been employed as an effective base in a variety of organic reactions, many of which are staples of synthetic organic chemistry.[9] On the other hand, KF/Al_2O_3 is a mild base that is effective for a wide range of substrates of coupling reactions and it has been applied extensively in Suzuki reaction[10] and C–N and C–O bond formation.[11] However, the application in the formation of C(aryl)–S bond has not been explored. Herein, we will fill this gap with our developed protocol.

Table 1
Optimization of reaction condition[a]



Entry	[Cu]	Solvent	Time (h)	Yield[b] (%)
1	**CuI**	**DMF**	**8**	**99**
2	CuBr	DMF	8	76
3	CuCl	DMF	8	76
4	Cu_2O	DMF	8	93
5	CuO	DMF	8	87
6	$CuBr_2$	DMF	8	67
7	$CuSO_4$	DMF	8	49
8	$Cu(OAc)_2$	DMF	8	73
9	CuI	DMF	8	25[c]
10	CuI	DMF	6	94
11	CuI	DMF	4	91
12	CuI	DMF	2	74
13	CuI	DMSO	8	95
14	CuI	Dioxane	8	40[c]
15	CuI	Toluene	8	3[c]
16	CuI	DMF	8	50[d]
17	–	DMF	8	5

[a] General reaction conditions: iodobenzene (1.0 mmol), thiophenol (1.2 mmol), Cu catalyst (0.1 mmol), and 2.5 equiv KF/Al_2O_3 as base in DMF (2.5 ml) at 110 °C under N_2 for 8 h.
[b] GC yield.
[c] The reaction was carried out at 80 °C.
[d] The reaction was carried out in air.

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[*] Corresponding author.
E-mail address: hjxu@ustc.edu (H.-J. Xu).

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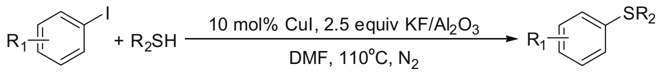
Table 2
The C–S cross-coupling reaction of aryl iodides with thiols using KF/Al_2O_3 as base[a]



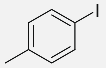
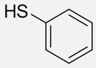
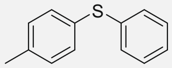
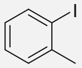
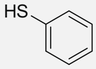
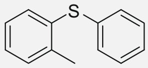
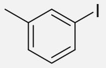
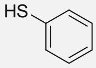
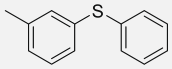
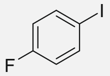
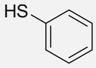
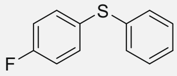
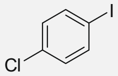
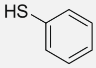
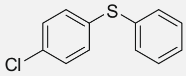
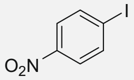
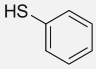
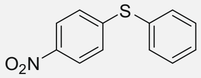
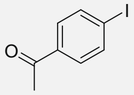
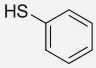
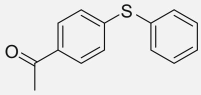
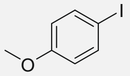
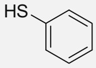
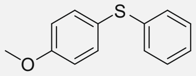
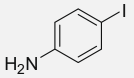
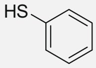
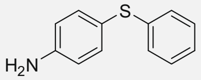
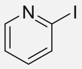
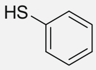
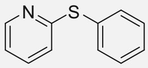
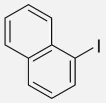
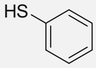
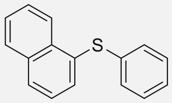
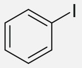
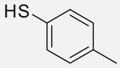
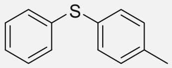
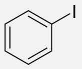
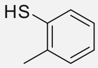
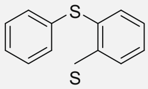
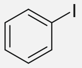
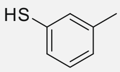
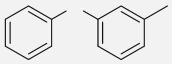
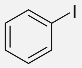
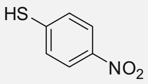
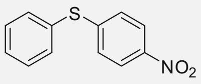
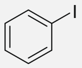
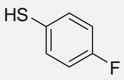
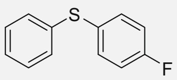
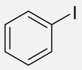
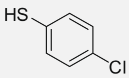
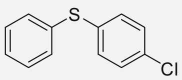
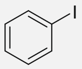
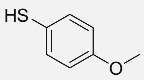
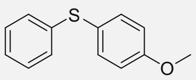
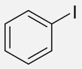
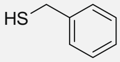
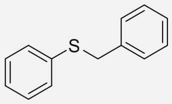
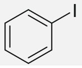
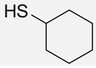
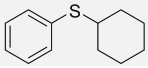
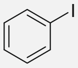
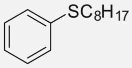
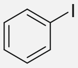
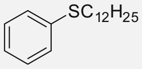
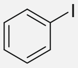
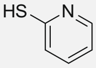
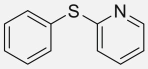
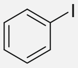
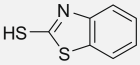
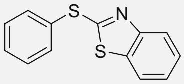
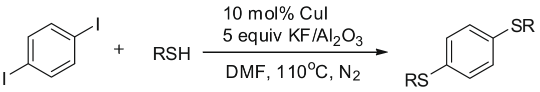
Entry	ArI	R_2SH	Product	Yield[b] (%)
1				87
2				60
3				78
4				93
5				99
6				94
7				70
8				91
9				83
10				85
11				99
12				97
13				91
14				86
15				62
16				92
17				87
18				88
19				92
20				43

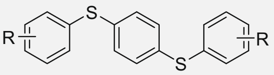
Table 2 (*continued*)

Entry	ArI	R_2SH	Product	Yield[b] (%)
21		n-$C_8H_{17}SH$		95
22		n-$C_{12}H_{25}SH$		75
23				57
24				64

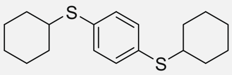
[a] Reaction conditions: aryl iodide (1 mmol), thiol (1.2 mmol), CuI (0.10 mmol), and KF/Al_2O_3 (2.5 mmol) in DMF at 110 °C under N_2 for 8 h.
[b] Isolated yield.

Table 3
One-pot fashion synthesis of disulfide with thiols and 1,4-diiodobenzene[a]





R = H, 79%[a]
R = p-Me, 83%[a]
R = m-Me, 82%[a]



65%[a]

[a] Yield of the isolated product.

The subject of this study was the development of a novel, simple C–S cross-coupling methodology incorporating the use of commercially available KF/Al_2O_3 without any ligand. In the first stage of the study we focused on the reaction of thiophenol with iodobenzene. A variety of experimental conditions were examined (see Table 1). The highest yield (99%) was obtained when 10 mol % CuI was used as the catalyst, 2.5 equiv KF/Al_2O_3 as the base, and DMF as the solvent (Table 1, entry 1). Other copper compounds including CuBr, CuCl, Cu_2O, CuO, $CuBr_2$, $CuSO_4$, and $Cu(OAc)_2$ provided lower yields (Table 1, entries 2–8). The control experiment showed that the corresponding product with only 25% yield was obtained when the model reaction was performed at 80 °C (Table 1, entry 9). The yield of the product with 94%, 91%, and 74% was observed when the reaction times were shortened, respectively, to 6 h, 4 h, and 2 h (Table 1, entries 10–12). DMF was found to be the best solvent while DMSO, dioxane, and toluene caused lower yields (Table 1, entries 1, 13–15). In addition, the yield of the product was reduced to 50% when the reaction was carried out in air (Table 1, entry 16). Therefore, the optimized conditions employed 10 mol % CuI and 2.5 equiv KF/Al_2O_3 in DMF at 110 °C under N_2. We also found that when KF/Al_2O_3 was used in CuI-catalyzed reactions of C–N and C–O bond formation, 1,10-phenanthroline or *N*,*N*-dibenzylethylenediamine as ligand was accompanied. But, simplicity of no ligand and less reaction time could be achieved in our protocol compared with other documented methods.

After the optimized reaction conditions were determined, we first screened a range of commercially available thiophenols with a variety of aryl iodides. The corresponding products were obtained in moderate to excellent yields (43–99%) (Table 2, entries 1–11).[12] We discovered that the S-arylation reactions of thiophenol with *p*-substituted aryl halides were easier than those with *o*-substituted and *m*-substituted aryl halides (Table 2, entries 1–3). It is observed that electron-donating substituents in the aryl iodides (Table 2, entries 7–9) decreased the yields of the products. Furthermore, we successfully coupled a variety of readily available aryl thiols with iodobenzene in good yields. (Table 2, entries 12–18). As expected, the tolerance of the catalytic system on aryl thiols counterpart was not remarkable. The reactivity of the substrates with electron-withdrawing groups was similar to that with electron-donating groups (Table 2, entries 15–18). We managed to obtain the desired coupling product of aliphatic thiols with aryl iodide in good yields for the synthesis of phenyl alkyl sulfide (Table 2, entries 19–22). We also extended the scope of thiol substrates to heterocyclic thiols and desired that the coupling products were also successfully observed in good yields (Table 2, entries 23 and 24).

We next turned our attention to apply this protocol to the procedure of disulfide. Four thiols and 1,4-diiodobenzene (see Table 3, entries 1–4) were examined. It is interesting to note that the two iodide groups in 1,4-diiodobenzene can participate in the C–S coupling reaction in a one-pot fashion. The yields are around 65–83%, which are good enough for many synthetic applications.

In conclusion, the use of KF/Al_2O_3 as a solid base[13] in copper-catalyzed S-arylation of aryl and alkyl thiols with aryl iodide reactions offers a convenient, environmentally benign, ligand-free, and efficient alternative. We believe that the application to KF/Al_2O_3 will provide new way to a wide array of organic reactions.

Acknowledgment

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12. *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, respectively, in $CDCl_3$ on a 300 MHz and 75 MHz instrument with TMS as internal standard. 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 N_2 atmosphere.
    A Schlenk tube was charged with CuI (0.1 mmol, 19 mg), KF/Al_2O_3 (2.5 equiv, 390 mg), and solid substrate, if present. Then liquid reagents (aryl or heteroaryl halide, 1 mmol; thiol, 1.2 mmol), and solvent (2.5 ml) were added under N_2. The reaction vessel was closed and placed under stirring in a preheated oil bath at 110 °C. The reaction mixture was stirred for 8 h. 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 purified by silica gel chromatography.
    (a) 1,4-Bis(phenylthio)benzene (Table 3, entry 1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.33 (m, 5H), 7.31 (s, 2H), 7.27 (d, $J = 4.0$ Hz, 2.1, 2H), 7.24 (d, $J = 9.8$ Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.12, 131.57, 131.28, 129.41, 127.50; (b) 1,4-Bis(*m*-toluenelthio)benzene (Table 3, entry 2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.12 (m, 9H), 7.07 (d, $J = 7.1$ Hz, 2H), 2.32 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.31, 135.13, 134.80, 132.29, 131.92, 131.13, 129.26, 128.79, 128.45, 21.42; (c) 1,4-Bis(*p*-toluenethio)benzene (Table 3, entry 3): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.22 (m, 4H), 7.13 (d, $J = 6.5$ Hz, 7H), 2.34 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.91, 135.56, 132.45, 131.12, 130.32, 21.26; (d) 1,4-Bis(cyclohexylthio)benzene (Table 3, entry 4): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 4H), 3.22–2.93 (m, 2H), 1.98 (d, $J = 10.4$ Hz, 4H), 1.77 (d, $J = 5.2$ Hz, 4H), 1.62 (d, $J = 6.5$ Hz, 2H), 1.47–1.07 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.75, 132.11, 46.74, 33.45, 26.02, 25.70–25.52; (e) 1,4-Bis(octylthio) benzene (Table 3, entry 5): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23 (s, 4H), 2.88 (t, $J = 7.3$ Hz, 4H), 1.63 (m, $J = 6.8$ Hz, 4H), 1.40–1.26 (br m, 20H), 0.88 (t, $J = 6.4$ Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.62, 129.85, 34.25, 32.50, 29.32, 29.29, 29.50, 22.84, 14.27.
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