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Copper-Catalyzed Thiolation of the Di- or Trimethoxybenzene Arene C−H Bond with Disulfides

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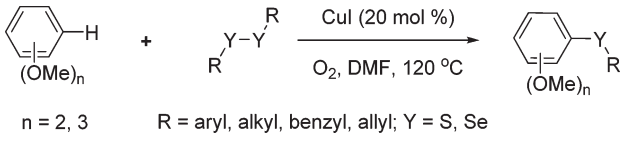
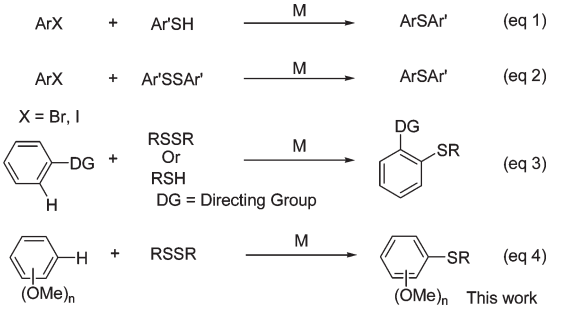


A CuI-catalyzed direct access to sulfides from disulfides via C−H bond cleavage of di- or trimethoxybenzene is described. The procedure utilizes O_2 as a clean and cheap oxidant. Direct selenation of the C−H bond also took place under this procedure. Furthermore, the system enables the use of two RS in $(RS)_2$. Thus, it represents an atom-economical procedure for the synthesis of sulfides and selenides.

Aryl sulfides are a common functionality found in numerous pharmaceutically active compounds and medicinally important natural products.[1] The transition metal-catalyzed cross coupling of ArX (X = Cl, Br, I, OTf, and $B(OH)_2$) and ArSH is a powerful method for the construction of a C−S bond (Scheme 1, eq 1).[2] However, thiols are prone to undergo oxidative S−S coupling reactions, resulting in the undesired formation of disulfides. Moreover, organic sulfur compounds may bind to metal, causing the deactivation of metal catalyst.[3] Employing PhSSPh may solve these drawbacks (Scheme 1, eq 2).[4] Nevertheless, in general, 1 equiv of reductant such as Zn or Mg was added in the reaction of ArX and RSSR, and prefunctionalization is still required for such transformation.

SCHEME 1. Formation of a C−S Bond Catalyzed by Transition Metal



The direct functionalization of a C−H bond is a straightforward transformation in organic synthesis.[5] Among these, much effort has been paid on C−C[6] and C−hetero bonds.[7] However, few examples of the formation of a C−S bond through C−H bond cleavage has been reported before.

In 2006, Yu and co-workers reported a $Cu(OAc)_2$-catalyzed thiolation of the 2-phenylpyridine with PhSH and MeSSMe under oxygen atmosphere (Scheme 1, eq 3).[8] Subsequently,

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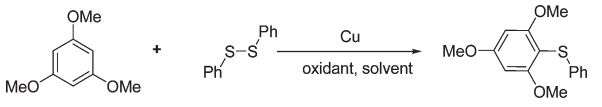
TABLE 1. Screening for the Optimal Conditions[a]



entry	Cu source	oxidant (equiv)	oxidant	yield (%)
1	CuI	oxone (1.0)	DMF	30
2	CuI	$K_2S_2O_8$ (1.0)	DMF	46
3	CuI	$PhI(OAc)_2$ (1.0)	DMF	43
4	CuI	BQ (1.0)	DMF	48
5	CuI	air	DMF	77
6	CuF_2	air	DMF	<5
7	$CuCl_2$	air	DMF	10
8	$CuBr_2$	air	DMF	45
9	CuCl	air	DMF	<5
10	CuBr	air	DMF	70
11	CuI	O_2	DMF	81 (27[b])
12	CuI	O_2	xylene	15
13	CuI	O_2	DMSO	63
14	CuI	O_2	NMP	60
15	CuI	O_2	THF	10
16		O_2	DMF	<5

[a] **1a** (34 mg, 0.2 mmol), PhSSPh **2a** (33 mg, 0.15 mmol), Cu (20 mmol %), oxidant, dry solvent (2 mL), under air, 120 °C, 24 h. [b] Under N_2.

examples of intramolecular C−S bond forming 2-substituted benzothiazoles through C−H functionalization were demonstrated by Doi and Batey, respectively.[9] Recently, Dong and co-workers described the Pd-catalyzed direct sulfonylation of a 2-phenylpyridine C−H bond with $ArSO_2Cl$.[10] In 2009, Fukuzawa and co-workers demonstrated a copper-catalyzed direct thiolation of a benzoxazole C−H bond with diaryl disulfides and aryl thiols.[11] Recently, Li and co-workers disclosed iron-catalyzed sulfenylation of an indole C−H bond with diaryl disulfides, whereas a catalytic amount of iodine was supplied to promote the reaction.[12] Very recently, Qing reported a Cu(II)-mediated reaction of an aryl C−H bond with DMSO to *ortho*-substituted methylthiolation.[13] However, a heteroatom, which mostly acted as a chelation group, is essential for the aforementioned transformations. Herein, we report a nonchelation-assisted Cu-catalyzed thiolation of the di- or trimethoxybenzene arene C−H bond with ArSSAr (Scheme 1, eq 4).

We initially tested the thiolation of 1,3,5-trimethoxybenzene with PhSSPh. To our delight, phenylthiolation could take place in the presence of CuI (20 mol %) in DMF with Oxone as oxidant. The choice of oxidant was essential to the reaction (Table 1, entries 1−4). Intriguingly, the yield dramatically increased to 77% with air as the sole oxidant in DMF (Table 1, entry 5). Further studies revealed the use of other coppers as catalysts resulted in lower yields (Table 1, entries 6−10). Gratifyingly, the system enables the use of two RS in $(RS)_2$. Under an O_2 atmosphere, the yield increased to 81%, while under N_2, only 27% of the desired product was isolated (Table 1, entry 11). These results indicated the oxygen may be served as the terminal oxidant for the reaction. Among the solvents tested, DMF was the best (Table 1, entries 12−15). No product was detected in the absence of copper (Table 1, entry 16). Notably, the reaction conducted on a 10 mmol scale formed the thiolation product in an acceptable 70% yield. The employment of cheap copper as catalyst and O_2 as clean oxidant significantly improved the practicality of this C−H functionalization reaction.

Having identified the optimal reaction conditions, the scope of RSSR was investigated, as shown in Table 2. As expected, a series of functional groups on the phenyl ring of disulfides, such as methoxy, bromo, fluoro, chloro, nitro, and methoxycarbonyl, were well-tolerated under this procedure, providing the thiolation products in moderate to good yields (Table 2, **3b**, **3c**, **3d**, **3e**, **3f**, **3i**, **3j**, **3q**). Generally, the electron-withdrawing groups on the phenyl ring of ArSSAr were beneficial to the reaction (Table 2, **3i** and **3j**). The hindrance on the phenyl ring of disulfides had quite a limited effect on the yield of the reaction. For example, the *ortho*-substituted substrate **2g** delivered a 60% yield of **3g**, while **3f** was isolated in 62% yield. Importantly, the halo groups on the phenyl ring of disulfides survived in the procedure (Table 2, **3d**, **3e**, **3f**, and **3g**). It is notable that halo products could be easily further manipulated. Particularly, when PhSeSePh was subjected to the procedure, the monoselenation product **3o** was isolated in 70% yield, along with 30% of the diselenation product **3p**. Fortunately, the benzyl and allyl groups were compatible with the conditions (Table 2, **3k** and **3m**), albeit the thiolation products were isolated in low yields. It is also noteworthy that 1,2-di(benzo[*d*]thiazol-2-yl)disulfane **3n** could provide the thiolation product in good yield with prolonged reaction time. Furthermore, the alkyl ester **2*l*** was a good reaction partner, providing the corresponding product in 71% yield (Table 2, **3l**). Disappointingly, MeSSMe did not work under the current condition.

Next, the thiolations of other electron-rich arene C−H bonds by PhSSPh were presented in Chart 1. **3s** and **3r** were formed in moderate yields, respectively. No regioisomeric products were observed by GC-MS and ^1H NMR spectroscopy. Disappointingly, other methoxybenzene substrates failed to work under the standard reaction conditions.

More experiments were carried out to gain preliminary insight into the mechanism of catalytic procedure. The product **3a** could be gained in 40% yield catalyzed by 1 mol % of PhSCu in DMF under O_2 at 120 °C for 72 h (Scheme 2, eq 1), while the stoichiometric reaction of 1,3,5-trimethoxybenzene and PhSCu catalyzed by Cu(I) in DMF under O_2 at 120 °C for 36 h produced **3a** in 65% yield (Scheme 2, eq 2). This result indicated that PhSCu may serve as an intermediate in the catalytic cycle. The lack of reactivity with PhSCu under N_2 suggested that the oxygen was necessary for the thiolation reaction (Scheme 2, eqs 1 and 2). Furthermore, when 4-iodoanisole was submitted to our catalytic system, no corresponding thioether product was found (Scheme 2, eq 3), which ruled out the possibility of an in situ iodination followed by a conventional sulfide formation pathway. Furthermore, the radical inhibitors including 2,6-di-*tert*-butyl-4-methylphenol (BHT, 2 mol %) and 2,2,6,6-tetramethylpiperidinooxy (TEMPO, 2 mol %) were subjected to the standard procedure, however, the product **3a** were isolated in 70% and 75% yields, respectively. Thus, a radical-mediated mechanism was also excluded.

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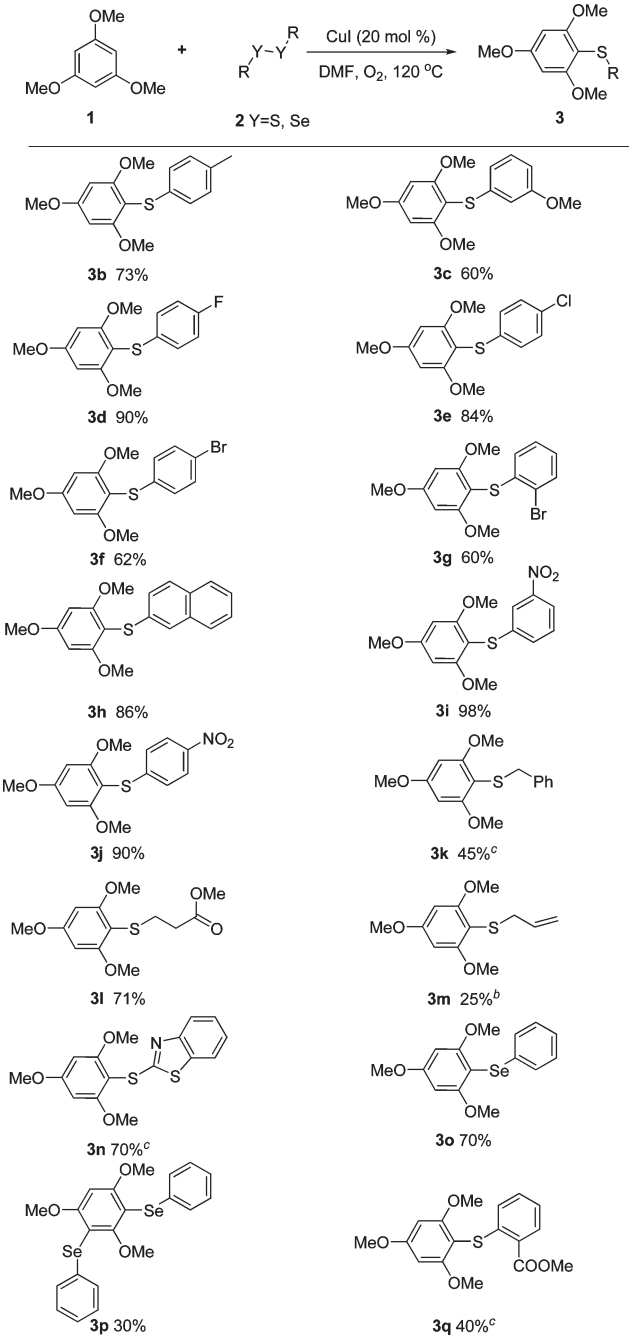
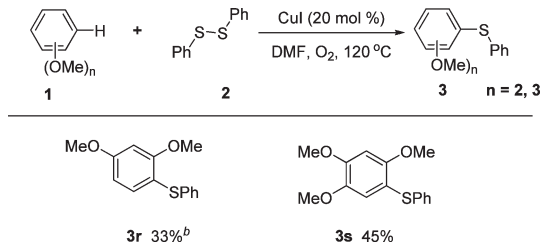
TABLE 2. CuI-Catalyzed Thiolation of the 1,3,5-Trimethoxybenzene C−H Bond[a]



[a]**1a** (34 mg, 0.2 mmol), RSSR **2a** (0.15 mmol), CuI (8 mg, 20 mol %), dry DMF (2 mL), under O_2, 120 °C, 24 h. [b]RSSR **2a** (0.2 mmol). [c]RSSR **2a** (0.2 mmol), 48 h.

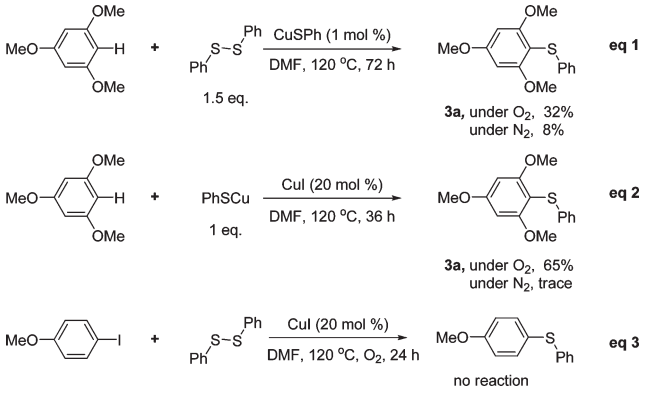
Upon the basis of the experimental results, the plausible pathway for the thiolation reaction was outlined in Scheme 3.[11] Step i involves the cuprate of the trimethoxybenzene C−H bond to afford intermediate **A**. In step ii, the ArCu(I) species **A** reacts with diphenyl disulfide to afford the product **3a** and PhSCu(I) **B**. Then, in step iii, intermediate **B** takes place with 1,3,5-trimethoxybenzene under O_2 to form ArCu(II)SPh intermediate **C**. Finally, the reductive elimination of the Cu(II) complex **C** affords the product **3a** and Cu(0), which is oxidized to Cu(I) by O_2.

CHART 1. CuI-Catalyzed Thiolation of the 1,2,4-Tri- and 1,3-Dimethoxybenzene C−H Bond[a]

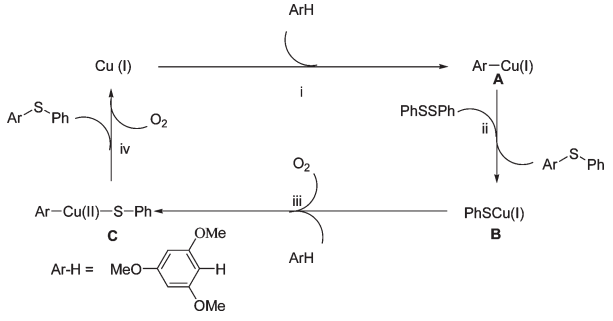


[a]Reagents and conditions: **1a** (0.2 mmol), PhSSPh **2a** (33 mg, 0.2 mmol), CuI (8 mg, 20 mmol %), dry DMF (2 mL), under O_2, 120 °C, 24 h. [b]48 h.

SCHEME 2. Preliminary Mechanism Study



SCHEME 3. Plausible Mechanism



In conclusion, we have demonstrated an efficient Cu-catalyzed thiolation of electron-rich arene C−H bonds with diphenyl disulfide and diselenide. The employment of cheap copper as catalyst and O_2 as clean oxidant significantly improved the practicality of this C−H functionalization reaction. As such, the reaction provides a convenient and atom-economical method for the synthesis of sulfides and selenides

Experimental Section

General Procedure for Thiolation of the Corresponding Subtrates. Under oxygen atmosphere, a reaction tube was charged with 1,3,5-trimethoxybenzene (34 mg, 0.2 mmol), RSSR (0.15 mmol), CuI (8 mg, 20 mol %), and dry DMF (2 mL). The mixture was stirred at 120 °C for 24 h. After the completion of the reaction, as monitored by TLC, the solvent

was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (300−400 mesh) with petroleum ether−EtOAc as eluent to give the desired product.

Phenyl(2,4,6-trimethoxyphenyl)sulfane (3a):[14] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18−7.13 (m, 2H), 7.05−7.00 (m, 3H), 6.22 (s, 2H), 3.87 (s, 3H), 3.80 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.9, 162.5, 138.7, 128.5, 125.6, 124.3, 100.0, 91.2, 56.3, 55.5.

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Supporting Information Available: Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.