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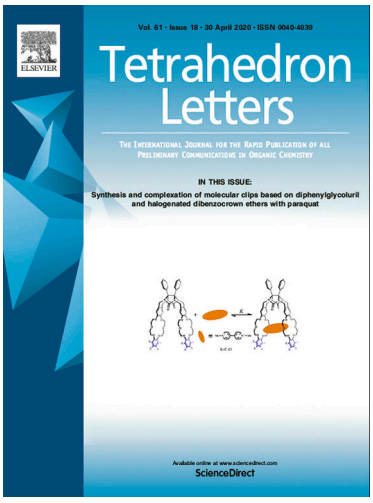

Copper-Mediated C−H Thiolation of (Hetero)Arenes Using Weakly Coordinating Directing Group

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Graphical Abstract

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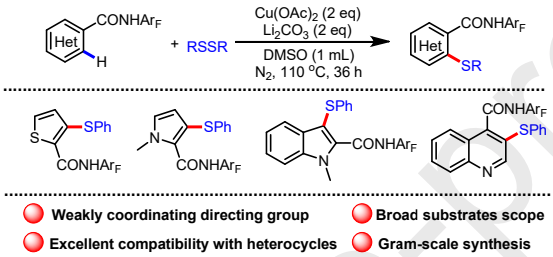

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Copper-Mediated C−H Thiolation of (Hetero)Arenes Using Weakly Coordinating Directing Group

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ABSTRACT

We have developed a copper-mediated C–H thiolation of (hetero)arenes by using monodentate amide as weakly coordinating directing group. This protocol features excellent functional group tolerance and shows satisfactory compatibility with various heterocycles, such as indole, pyrrole, imidazole, pyridine, thiophene and quinoline. The robust nature of this protocol renders that it has potential value in the synthetic application.

Aryl thioethers are important structural motifs in natural products, materials and pharmaceuticals.[1] For instance, Perazine is an antipsychotic drug used in restoring the balance of certain natural substances of brain.[2] Vortioxetine as an atypical antipsychotic and antidepressant can be used for the treatment of major depressive disorder (MDD) in adults.[3] Axitinib is a selective second-generation tyrosine kinase inhibitor of vascular endothelial growth factor receptors.[4] Therefore, the development of efficient synthetic methods for aromatic sulfides are of great value.

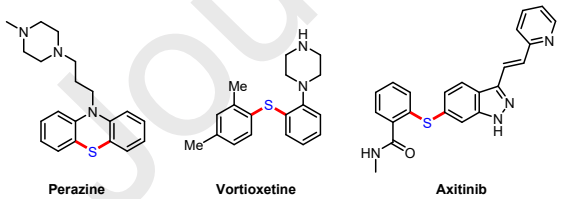
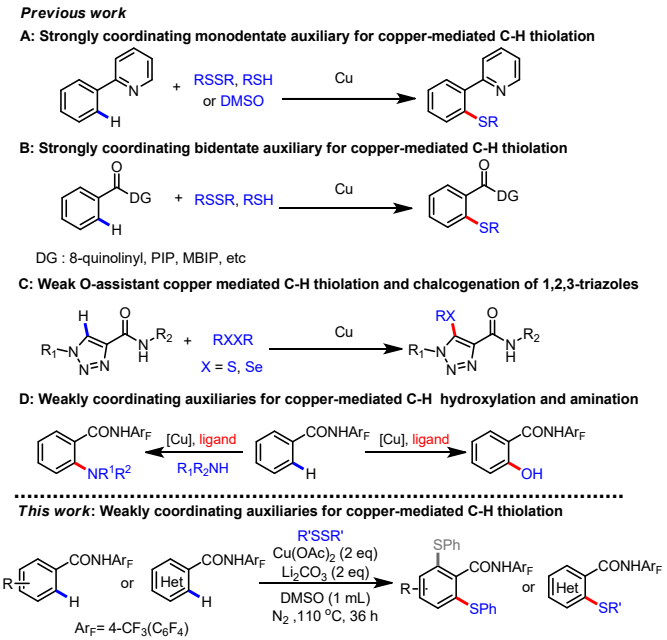


Figure 1 Examples of drug molecules containing aromatic sulfide

In recent years, transition metal such as Ru,[5] Rh,[6] Pd,[7] Ni[8] and Co[9] catalyzed C−H activation has become an efficient way to synthesize thioethers. Especially, directing-group-assisted copper -catalyzed or -mediated C−H thiolation has attracted considerable attentions due to the earth-abundant and low-toxic copper catalysts.[10] In 2006, Yu and co-workers reported the first copper-mediated pyridine-directed C−H thiolation by using PhSH and MeSSMe as thioether source (Scheme 1A).[11] In 2010,



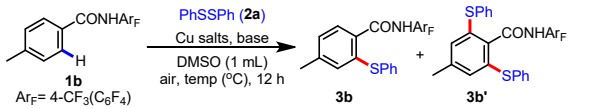
Sscheme 1 Directing groups for copper-catalyzed or -mediated C–H thiolation of (hetero)arenes

Qing and co-workers developed copper-mediated C−H thiomethylation of 2-phenylpyridine, in which DMSO was used as the thiomethylation reagent.[12] In 2012, Daugulis developed 8-aminoquinoline as the removable bidentate directing group to achieve the copper-promoted C−H thiolation (Scheme 1B).[13] Subsequently, Shi developed 2-(pyridin-2-yl) isopropyl-amine

(PIP by thiolation of (hetero)arenes with disulfides[14a] and S_8.[14b] Assisted by 2-aminalkylbenzimidazole (MBIP) as directing group, Song reported copper-mediated C−H thiolation of arenes and olefins.[15] Recently, Ackermann developed a copper-catalyzed highly regioselective C−H thiolation of indoles (C2 position) and indolines (C7 position).[16] Very recently, our group disclosed a Cu-mediated room-temperature C−H thiolation of arenes by using ethylene sulfide as the thiolation reagent.[17]

Despite those undisputable advances, strongly coordinating directing groups are often required in the reaction. Copper catalyzed or mediated C–H thiolation *via* weakly coordinating directing group is rare, possibly due to relatively low catalytic activity and the irreversible coordination of copper catalyst with sulfur compounds.[18] In 2016, Ackermann and coworkers achieved copper mediated C−H thiolation and chalcogenation of 1,2,3-triazoles *via* weak O-assistance (Scheme 1C).[19] Previously, our group reported copper mediated *ortho*-hydroxylation and amination of arenes by utilizing a weakly coordinating monodentate directing group (Scheme 1D).[20] In this work, we reported a copper-mediated C−H thiolation of (hetero)arenes by weakly coordinating directing group.

Table 1 Optimization of the reaction conditions[a]



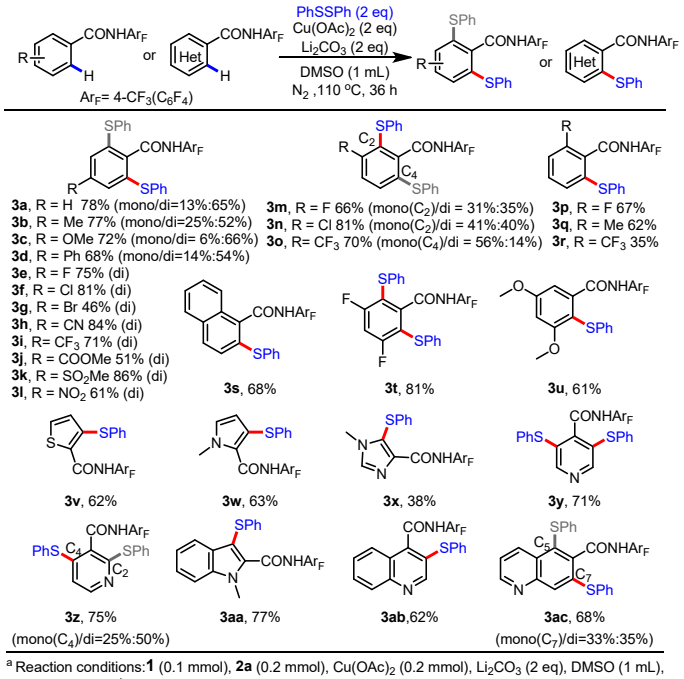
Entry	Cu salts (x eq)	base (2 eq)	temp (°C)	yield (%) [mono+di][b]
1	$Cu(OAc)_2$ (1.0)	CsOAc	100	28 (25:3)
2	CuO (1.0)	CsOAc	100	0
3	CuOAc (1.0)	CsOAc	100	14 (13:1)
4	$Cu(OAc)_2$ (1.0)	/	100	0
5	$Cu(OAc)_2$ (1.0)	K_3PO_4	100	16 (11:5)
6	$Cu(OAc)_2$ (1.0)	Na_2CO_3	100	33 (25:8)
7	$Cu(OAc)_2$ (1.0)	Li_2CO_3	100	48 (31:17)
8	$Cu(OAc)_2$ (1.0)	Li_2CO_3	90	34 (17:17)
9	$Cu(OAc)_2$ (1.0)	Li_2CO_3	110	57 (22:35)
10	$Cu(OAc)_2$ (1.0)	Li_2CO_3	120	55 (22:33)
11[c]	$Cu(OAc)_2$ (1.0)	Li_2CO_3	110	ND
12[d]	$Cu(OAc)_2$ (1.0)	Li_2CO_3	110	65 (34:31)
13[d]	$Cu(OAc)_2$ (0)	Li_2CO_3	110	ND
14[d]	$Cu(OAc)_2$ (0.3)	Li_2CO_3	110	25 (20:5)
15[d]	$Cu(OAc)_2$ (2.0)	Li_2CO_3	110	76 (43:33)
16[d,e]	$Cu(OAc)_2$ (2.0)	Li_2CO_3	110	79 (33:46)
17[d,f]	$Cu(OAc)_2$ (2.0)	Li_2CO_3	110	78 (25:53)
18[d,f]	$Cu(OAc)_2$ (2.0)	Li_2CO_3	110	77 (25:52)[h]
19[d,g]	$Cu(OAc)_2$ (2.0)	Li_2CO_3	110	74 (22:52)

[a] Reaction conditions:**1b** (0.1 mmol), **2a** (0.2 mmol), Cu salts, base (0.2 mmol), DMSO (1 mL), air, 12 h. [b] Yield was determined by ^1H NMR analysis of crude reaction mixture using CH_2Br_2 as the internal standard. [c] O_2 atmosphere. [d] N_2 atmosphere. [e] 24 h. [f] 36 h. [g] 48 h. [h] Isolated yield.

We commenced our studies by selecting substrate **1b** and phenyl disulfide **2a** as the model substrates. We initially treated substrate **1b** with 2 equiv. of **2a**, 1 equiv. of $Cu(OAc)_2$ and 2 equiv. of CsOAc in DMSO at 100 °C for 12 h, giving the target product in 28% with a 25/3 mono- to di-thiolation ratio (Table 1, entry 1). Then we screened other copper catalysts, and $Cu(OAc)_2$ gave the best results (entry 2, 3). Base is essential in the reaction, and no desired product could be obtained in the absence of base (entry 4-increasing the temperature to 110 °C (entry 8-10). When the reaction was carried out under N_2 atmosphere, 65% yield of desired product could be obtained (entry 12). Unexpectedly, all the raw materials were decomposed and no desired product could be observed under O_2 conditions (entry 11). When we increased loading of copper catalyst to 2 equiv., the yield could be improved to 76% (entry 13-15). Prolonged reaction time could slightly improve the yield with higher di- to mono-thiolation ratio (Entry 16-19).

With the optimal conditions in hand, we proceeded to explore the substrate scope of benzamide derivatives. As shown in Table 2, our protocol appeared to be very general with respect to the substituents in benzamide **1** (**1a-1r**). Electron-rich OMe, Ph-substituted arenes gave the corresponding products in 72% and 68% yields respectively (**3c**, **3d**). Electron-deficient arenes bearing halogen, cyano, trifluoromethyl, ester, sulfonyl and nitryl group could be thiolated smoothly under the standard conditions, obtaining the corresponding products in moderated to good yields (**3e-3o**). When the *ortho*-position was substituted by fluorine, methyl and trifluoromethyl, the yields decreased to 35-67%, possibly due to the steric hindrance (**3p-3r**). 1-Naphthylbenzamide afforded mono-thiolation product **3s** in 68% yields (**3s**). Compared to 3, 5-dimethoxyl benzamide, 3, 5-difluoro benzamide gave higher selectivity of di-thiolation product perhaps due to the small size of the fluorine atom (**3t**, **3u**). To our delight, this protocol could be compatible with heterocycles including thiophene, pyrrole, imidazole and indole derivatives, furnishing the desired thiolated products in moderate to good yields (**3v**, **3w**, **3x**, **3aa**). Substrates containing strongly coordinated pyridine and quinoline could also be thiolated in good yields (**3y**, **3z**, **3ab**, **3ac**).

Table 2 Scope of benzamide substrates[a,b]

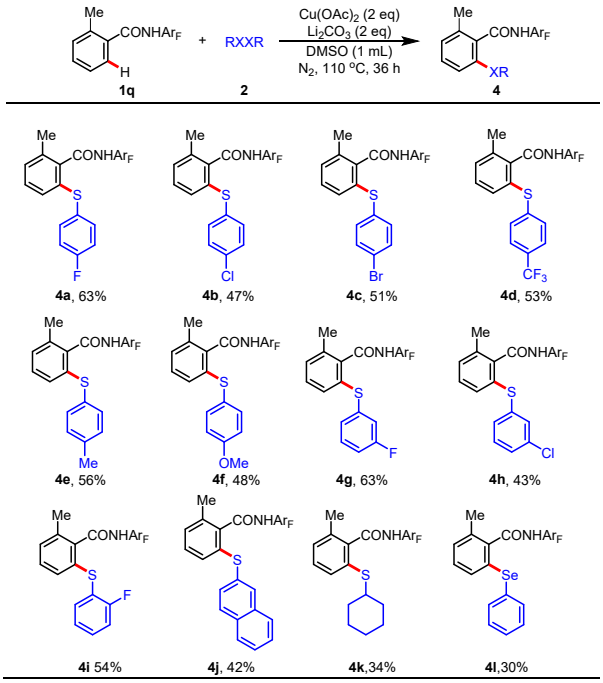


[a] Reaction conditions:**1** (0.1 mmol), **2a** (0.2 mmol), $Cu(OAc)_2$ (0.2 mmol), Li_2CO_3 (2 eq), DMSO (1 mL), N_2, 110 °C, 36 h. [b] Isolated yield.

Next, we investigated the scope of disulfides. As shown in Table 3, 1,2-diphenyl disulfide containing various substituents, including methyl, methoxy, trifluoromethyl, fluoro, chloro, and

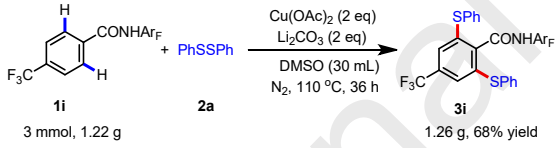
bror ght moderate yields (**4a**-**4i**). Dialkyl disulfide could be also compatible under the standard conditions, albeit in lower yields (**4k**). As analogues of disulfides, diphenyl diselenide was reactive and provided the desired product in acceptable yields (**4l**).

Table 3 Scope of disulfides[a]



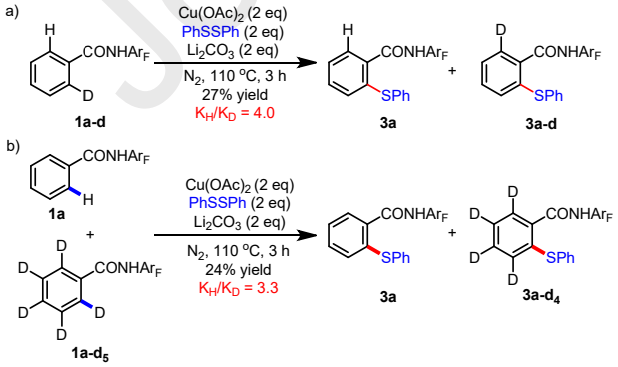
[a] Reaction conditions:**1q** (0.1 mmol), **2** (0.2 mmol), $Cu(OAc)_2$ (0.2 mmol), Li_2CO_3 (2 eq), DMSO (1 mL), N_2, 110 °C, 36 h. [b] Isolated yield.

To showcase the synthetic utility of this protocol, the C−H thiolation of substrate **1i** with disulfide **2a** was carried out on gram scale under the standard conditions, providing the corresponding product **3i** in 68% yield (Scheme 2).



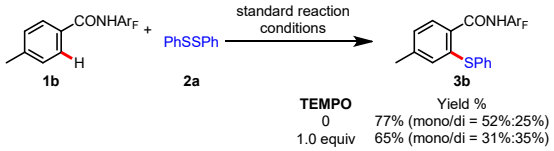
Scheme 2 Gram-scale synthesis

For better understanding of the mechanism of copper-mediated C–H thiolation of arenes, intra- and intermolecular kinetic isotope effects experiments were carried out. Significant isotope effects (4.0 and 3.3) suggested that C−H cleavage could be involved the rate-limiting step (Scheme 3).



Scheme 3 Kinetic isotope effects

In addition, the addition of 1 equiv. TEMPO had only a slight not involve radical process (Scheme 4).



Scheme 4 The effect of TEMPO

In summary, we have developed copper-mediated C–H thiolation of benzoic acid derivatives by employing monodentate amide as weakly coordinating directing group. This protocol has high functional group tolerance, and a variety of heterocycles including indole, pyrrole, imidazole, pyridine, thiophene and quinoline could be compatible in the reaction. KIE experiments indicated that C−H cleavage could be involved the rate-limiting step.

Acknowledgments

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Highlight:

- Weakly coordinating directing group
- Broad substrates scope
- Excellent compatibility with heterocycles
- Gram-scale synthesis

Declaration of interests

competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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