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A Highly Efficient Cu-Catalyzed S-Transfer Reaction: From Amine to Sulfide

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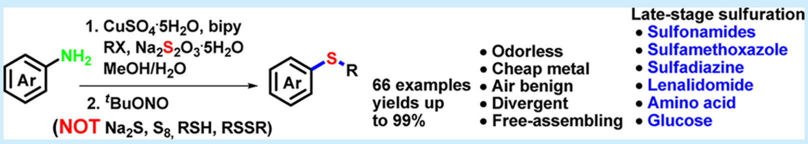
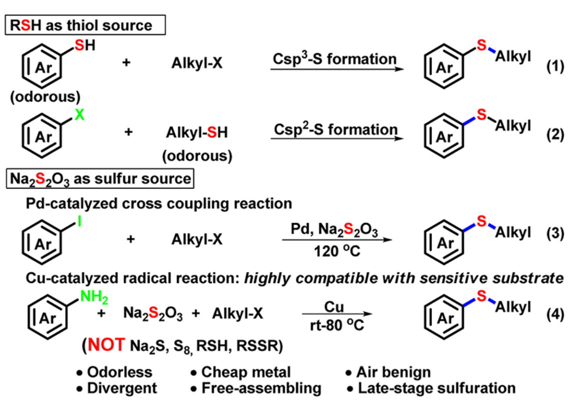
Supporting Information



ABSTRACT: A highly efficient Cu-catalyzed dual C−S bonds formation reaction, proceeding in alcohol and water under air, is reported, in which inodorous stable $Na_2S_2O_3$ is used as a sulfurating reagent. This powerful strategy provides a practical and efficient approach to construct thioethers, using readily available aromatic amines and alkyl halides as starting materials. Sensitive and synthetic useful functional groups could be tolerated. Furthermore, pharmaceuticals, glucose, an amino acid, and a chiral ligand are successfully furnished by this late-stage sulfuration strategy.

Carbon−sulfur bond formation[1] is of strategic importance in synthetic programs since thioether fragments widely exist in pharmaceuticals,[2] materials,[3] and even kinds of food.[4] Furthermore, thioether derivatives in different oxidative states, e.g., sulfone and sulfoxide, show divergent functions and potencies as well.[2] Large amounts of research being conducted and an enormous pharmaceutical market demand indicate that highly effective and broadly tolerant C−S bond constructing methods and late-stage sulfuration techniques are urgently desired. Traditionally, some aryl alkyl thioethers could be synthesized through thiol alkylation[5] (Scheme 1, eq 1). Since the first transition metal catalyzed thiol arylation (eq 2) developed by Migita[6a] in 1980, different catalysts, such as Pd,[6b−i] Cu,[6j−m] Fe,[6n−q] Rh,[6r] Ni,[6s] In,[6t] and Co,[6u] were tested to form sp^2 C−S bonds. Despite this progress, there are still some drawbacks in applications, such as odorous and expensive thiols, unavoidable over-oxidation, and sensitive substrate incompatibility.

Scheme 1. Strategies for Constructing Aryl-S-Alkyl Compounds



To overcome the problems mentioned above, our group[1a,7a,b] and Boehringer Ingelheim Pharmaceutials[7c] have developed novel sulfur transfer methods using $Na_2S_2O_3$ as a sulfurating reagent. The corresponding Pd-catalyzed sulfuration, which used aryl halides as starting materials,[7b] has been achieved (Scheme 1, eq 3). Meanwhile, we have been trying to implement the late-stage sulfuration strategy in the modification of bioactive[7b] and critical functional compounds. Aryl amines widely exist in significant pharmaceuticals[2b] and pesticides[8] and could be used in various conversions,[9] which make the transformation from amine to sulfide important and promising for drug discovery. Herein, we report an odorless, divergent, and practical dual C−S bonds formation reaction that is convenient among aromatic amines, alkyl halides, and $Na_2S_2O_3$ (eq 4).

We began our study by examining the reaction between 4-methoxy aniline and benzyl chloride in the presence of $Na_2S_2O_3{\cdot}5H_2O$ (Table 1). After the examination of different transition metals, copper was found to be the only active catalyst species for this transformation (entries 1−5). In view of the efficiency and selectivity, $Na_2S_2O_3{\cdot}5H_2O$, an alkyl chloride, a catalyst, a ligand, and MeOH/H_2O were stirred at 80 °C for 2 h and then cooled to 0 °C. After aniline and ^tBuONO were added, the mixture was stirred at rt for 10 h, which results in a 20% yield (entry 7). When the temperature was raised to 80 °C, the desired product was afforded in 45% yield (entry 9). Different ligands were estimated, in which 2,2′-bipyridine (L3) was found to be the best choice

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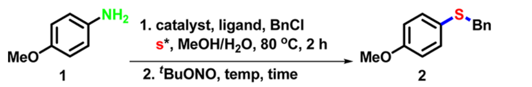
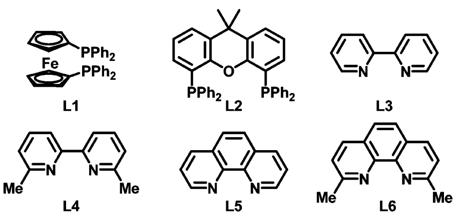
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	ligand	s*	t (°C)	time (h)	yield (%)[b]
1	$PdCl_2(PPh_3)_2$	-	$Na_2S_2O_3{\cdot}5H_2O$	rt	10	0[c]
2	AgOAc	-	$Na_2S_2O_3{\cdot}5H_2O$	rt	10	0[c]
3	$Fe(acac)_3$	-	$Na_2S_2O_3{\cdot}5H_2O$	rt	10	0[c]
4	CuCl	-	$Na_2S_2O_3{\cdot}5H_2O$	rt	10	5[c]
5	$CuSO_4{\cdot}5H_2O$	-	$Na_2S_2O_3{\cdot}5H_2O$	rt	10	9[c]
6	-	-	$Na_2S_2O_3{\cdot}5H_2O$	rt	10	0[c]
7	$CuSO_4{\cdot}5H_2O$	-	$Na_2S_2O_3{\cdot}5H_2O$	rt	10	20
8	$CuSO_4{\cdot}5H_2O$	-	$Na_2S_2O_3{\cdot}5H_2O$	60	10	42
9	$CuSO_4{\cdot}5H_2O$	-	$Na_2S_2O_3{\cdot}5H_2O$	80	10	45
10	$CuSO_4{\cdot}5H_2O$	L1	$Na_2S_2O_3{\cdot}5H_2O$	80	10	41
11	$CuSO_4{\cdot}5H_2O$	L2	$Na_2S_2O_3{\cdot}5H_2O$	80	10	24
12	$CuSO_4{\cdot}5H_2O$	L3	$Na_2S_2O_3{\cdot}5H_2O$	80	10	60
13	$CuSO_4{\cdot}5H_2O$	L4	$Na_2S_2O_3{\cdot}5H_2O$	80	10	47
14	$CuSO_4{\cdot}5H_2O$	L5	$Na_2S_2O_3{\cdot}5H_2O$	80	10	59
15	$CuSO_4{\cdot}5H_2O$	L6	$Na_2S_2O_3{\cdot}5H_2O$	80	10	41
16	$CuSO_4{\cdot}5H_2O$	L3	$Na_2S_2O_3{\cdot}5H_2O$	80	4.5	90
17	***$CuSO_4{\cdot}5H_2O$***	***L3***	***$Na_2S_2O_3{\cdot}5H_2O$***	***80***	***4.5***	***99***[d]
18	$CuSO_4{\cdot}5H_2O$	L3	$Na_2S_2O_3{\cdot}5H_2O$	80	4.5	68[e]
19	$CuSO_4{\cdot}5H_2O$	L3	$Na_2S{\cdot}9H_2O$	80	4.5	0
20	$CuSO_4{\cdot}5H_2O$	L3	S_8	80	4.5	0
21	$CuSO_4{\cdot}5H_2O$	L3	BnSH	80	4.5	0[f]
22	$CuSO_4{\cdot}5H_2O$	L3	BnSSBn	80	4.5	0[f]

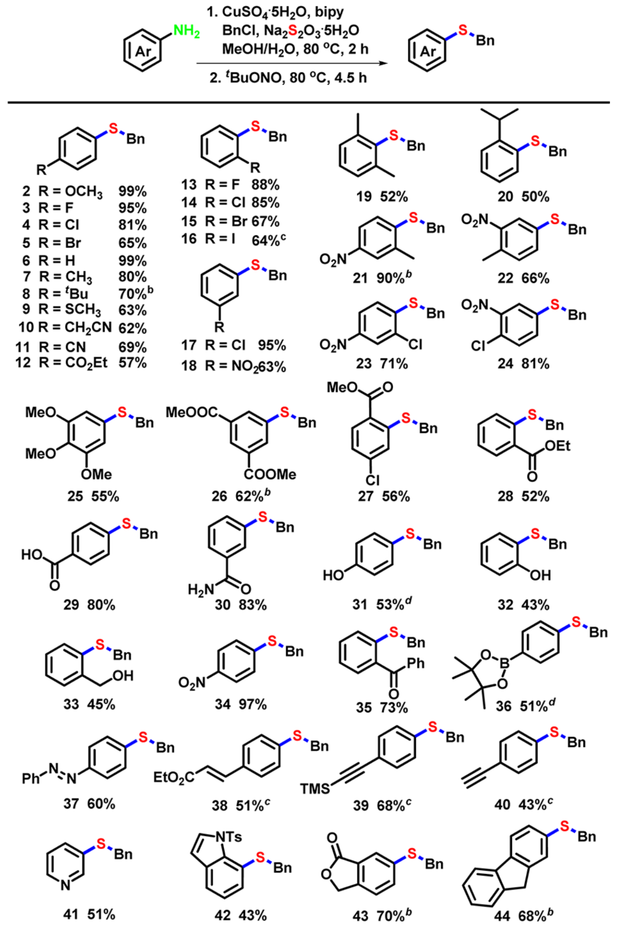
[a]General procedure: To a Schlenk tube were added, $Na_2S_2O_3{\cdot}5H_2O$ (1.0 mmol), alkyl chloride (1.0 mmol), catalyst (0.02 mmol), ligand (0.02 mmol), and $MeOH/H_2O$ (1 mL/1 mL). The mixture was stirred at 80 °C for 2 h, then cooled to 0 °C. After aniline (0.2 mmol) and ^{t}BuONO (0.3 mmol) were added, the mixture was stirred at room temperature for 10 min, then at a certain temperature for appointed time. [b]Isolated yields. [c]All compounds were added in one step. [d]BnCl (1.4 mmol), $Na_2S_2O_3{\cdot}5H_2O$ (1.4 mmol). [e]$CuSO_4{\cdot}5H_2O$, bipy were added in step 2. [f]Without BnCl.



giving a 60% yield (entries 10−15). Following the transversion through GC/MS, a reaction time of 4.5 h was found to be the peak point (entry 16). The yield was further promoted to 99% by increasing the amount of BnCl and $Na_2S_2O_3$ to 7 equiv (entry 17). Yet, when the catalyst and ligand were added in step 2, the yield decreased to 68% (entry 18). Remarkably, other S-sources, such as Na_2S, S_8, BnSH, and BnSSBn (entries 19−22), could not afford the transformation, showing the irreplaceability of $Na_2S_2O_3$ in this system.

Under the optimized conditions, we investigated the sulfurating reaction with multifarious aryl amines. The results in Table 2 showed the great functional group tolerance of the protocol. Generally, the aniline derivatives, bearing both electron-withdrawing and -donating groups in ortho-, meta-, or para- positions of the amino group, afford moderate to excellent yields (**2**−**18**). Halogen atoms are well tolerated, amazingly for iodine (**16**), which should be highly reactive in coupling and radical reactions. Notably, more sterically hindered groups, such as 2,6-dimethyl and 2-isopropyl, could afford the desired products (**19**, **20**). Di- or multisubstituted thioethers could also be obtained through this transformation (**21**−**27**), especially for strongly electron-donating (**25**) and strongly electron-withdrawing (**26**) anilines. Remarkably, substrates containing active hydrogen, such as carboxyl acid (**29**), amide (**30**), and hydroxyl (**31**−**33**), could be tolerated, which is a big challenge in many coupling reactions. Moreover, sensitive coupling precursors such as Bpin (**36**) and diazo (**37**), Michael addition precursor (**38**), and Cu-sensitive terminal alkyne (**40**) as well as compounds bearing pyridine (**41**), indole (**42**), benzoheterocycle (**43**), and a benzo fused ring (**44**) could be transformed by this method as well.

Table 2. Diversity of Aryl Amines for Sulfuration[a]

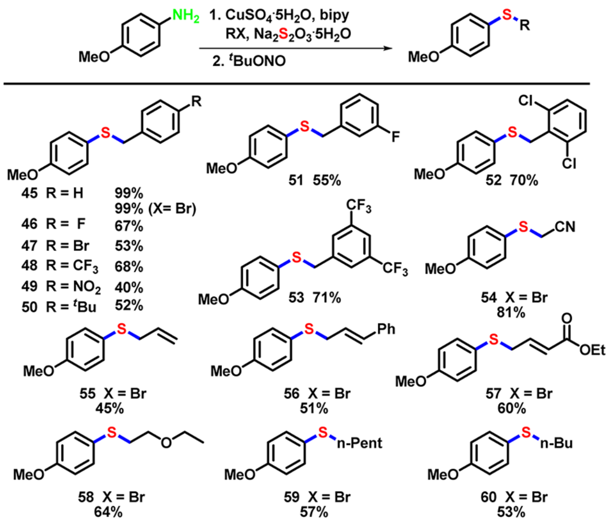


[a]Standard conditions. Isolated yields are shown. [b]Step 2, 80 °C, 24 h. [c]Step 2, rt, 24 h. [d]Step 2, rt, 4.5 h.

After the high tolerance of aryl amine derivatives was demonstrated, the diversity of alkyl halide partners for sulfuration was examined. As shown in Table 3, in general, benzylic halides with electron-withdrawing and -donating groups in different positions could produce moderate to excellent yields (**45**−**53**). Other activated halides, e.g., bromo acetonitrile (**54**), allyl bromide (**55**), cinnamyl bromide (**56**), and 4-bromocrotonic ethyl ester (**57**), could be a sulfurating partner as well. Satisfactory results could also be achieved by using unactivated alkyl halides (**58**−**60**).

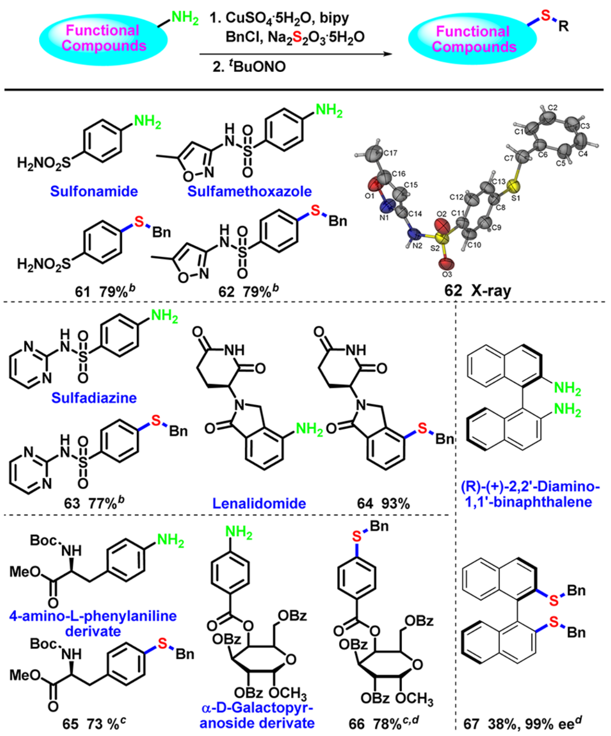
Late-stage modification[10] was considered as a valuable method for screening drugs and constructing complex materials. Herein, we present the late-stage sulfuration of functional aryl amines through this protocol (Table 4). Sulfonamides[11] show a broad spectrum of antimicrobial properties and exhibit much activity against Gram positive and Gram negative bacteria. Among these, sulfonamide, sulfamethoxazole, and sulfadiazine were converted to thiol ether analogues from amine substrates (**61**−**63**) in good

Table 3. Diversity of Alkyl Halides for Sulfuration[a]



[a]Standard conditions. Isolated yields are shown.

Table 4. Late-Stage Sulfuration of Functional Aryl Amines[a]

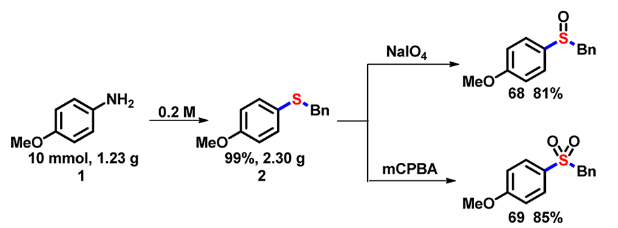


[a]Standard conditions, isolated yields are shown. [b]$CuSO_4{\cdot}5H_2O$ (0.1 mmol), bipy (0.1 mmol), step 2, 80 °C, 24 h. [c]$CuSO_4{\cdot}5H_2O$ (0.1 mmol), bipy (0.1 mmol). [d]0.1 mmol scale.

yields. **62** was confirmed by X-ray crystallography analysis.[12] Lenalidomide[13] could significantly improve overall survival in myeloma, which exhibits excellent reactivity producing thiol analogue compound **64** in 93% yield. Glucose and amino acid functional structures as essential components in a living body could also be tolerated in our system and give desired products in good yields (**65**, **66**), which show the potential of this reaction in a bioorthogonal reaction.[14] A chiral aryl diamine ligand could also be transferred into 2,2′-bis(benzylthio)-1,1′-binaphthalene (**67**) without racemation, providing a convenient route to construct corresponding chiral sulfur ligands.

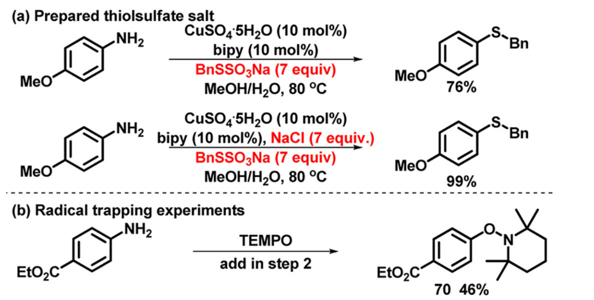
Showing the efficiency and practicability further, 4-methoxyaniline was reacted on the gram scale to generate the desired product **2** in 99% yield in a higher concentration. Furthermore, the sulfide **2** could be easily transformed to sulfoxide **67** and sulfone **68** by tuning the oxidants (Scheme 2).

Scheme 2. Gram Scale and Synthetic Transformations

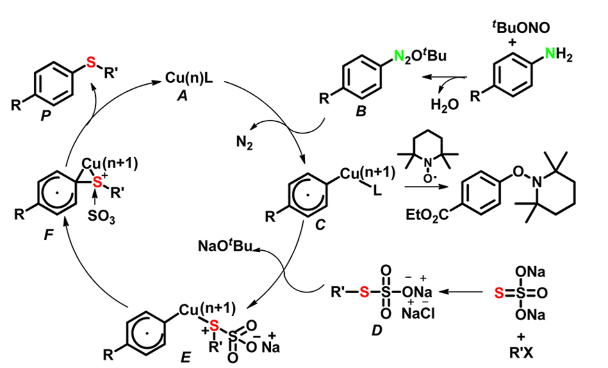


To explore the reaction mechanism, first, benzyl thiosulfate, which was prepared by BnCl and $Na_2S_2O_3$, was used in this reaction and a 76% yield was obtained (Scheme 3a). By adding additional NaCl, the yield was back to 99%, which showed that the salt played a role in this system (see Supporting Information (SI)). Second, a radical trapping experiment was performed (Scheme 3). Compound **70** was obtained in 46% yield when TEMPO was added after the addition of ^{t}BuONO. These results indicated that a Cu-catalyzed aryl radical species existed in this system. Meanwhile, the reaction could not proceed without $CuSO_4$ (Table 1, entry 6). It means that copper behaved critically in the combination of the aryl radical and the unique sulfur species, which contrasted with Na_2S, S_8, BnSH, and BnSSBn (Table 1, entries 18−21). On the basis of the above results, we proposed that the Cu-catalyzed thiolation reaction may proceed through the mechanism in Scheme 4. The arene diazonium **B**, which was generated in situ from aryl amine and *tert*-butyl nitrite,

Scheme 3. Control Experiments



Scheme 4. Proposed Mechanism



produced Cu-intermediate **C** through oxidative addition with Cu(I).[15] On the other hand, alkyl halide and $Na_2S_2O_3$ generated special sulfurating reagent **D**.[7b] Then the ligands exchange between **C** and **D** affording the Cu-intermediate **E**, which could convert to intermediate **F** through releasing SO_3. During this step, the electron-withdrawing effect of the sulfonic acid group weakened the strong coordinating properties from sulfur to copper, which makes a difference from other sulfur sources. The product emerged through reductive elimination of **F**, which was accelerated by the dissociation of SO_3. Cu(I) regenerated in this process.

In summary, we have developed a cheap metal catalyzed sulfur transfer reaction, which could be realized by free assembly between aryl amines, alkyl halides, and $Na_2S_2O_3$ in alcohol and H_2O under air. As a novel sulfur source, $Na_2S_2O_3$ shows its irreplaceability in this system. In contrast with organic thiols and thiophenols, its intrinsic properties helped us accomplish this S-atom transfer reaction efficiently and practicably. This reaction functions under mild conditions, and various useful functional groups are well tolerated. Most importantly, it possesses an inspiring capability in functional compounds decoration. This powerful late-stage sulfuration strategy will be bringing about further profound applications in medicinal chemistry and chemical biological studies. Further study on the mechanism and additional applications is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure, NMR spectra, and X-ray and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) CCDC-983614 (**62**): $C_{17}H_{16}N_2O_3S_2$, MW = 360.44, monoclinic, space group $P2_1/n$, final R indices $[I > 2\sigma(I)]$, $R_1 = 0.0418$, $wR_2 = 0.0983$, R indices (all data), $R_1 = 0.0593$, $wR_2 = 0.1102$, $a = 10.7362(5)$ Å, $b = 14.1883(7)$ Å, $c = 12.3716(6)$ Å, $\alpha = 90°$, $\beta = 108.855(2)°$, $\gamma = 90°$, $V = 1783.4(2)$ Å^3, $Z = 4$, Reflections collected/unique: 20355/3132 ($R_{(int)} = 0.0437$). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/ci.

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