



## ORIGINAL ARTICLE

# L-cysteine as sustainable and effective sulfur source in the synthesis of diaryl sulfides and heteroarene thiols



Yan Xiao<sup>a,1</sup>, Xiangling Pu<sup>a,1</sup>, Fuqing Lu<sup>a</sup>, Yanmin Wang<sup>a</sup>, Yongnan Xu<sup>a</sup>, Hui Zhang<sup>a,\*</sup>, Yajun Liu<sup>b,\*</sup>

<sup>a</sup> School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Wenhua Road 103, Shenyang 110016, China

<sup>b</sup> School of Life and Pharmaceutical Sciences, Dalian University of Technology, Dagong Road 2, Panjin 124221, China

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## KEYWORDS

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**Abstract** L-cysteine, a natural and essential amino acid, was employed as novel sulfur source in the synthesis of symmetrical diaryl sulfides from a variety of aryl iodides in moderate to excellent yields. A tandem three steps' reactions including C(sp<sup>2</sup>)-S bond formation, C(sp<sup>3</sup>)-S bond cleavage and another C(sp<sup>2</sup>)-S bond formation were proposed to be involved in this conversion. This protocol was featured by broad substrate scope and good functional group tolerance. In addition, heteroarenes including benzothiazoles and benzoxazoles were successfully converted into the corresponding heteroarene thiols using L-cysteine as C-H mercaptalization reagent.

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## 1. Introduction

By virtue of the versatile reactivity of sulfur atom, sulfur containing compounds represent a large family of chemicals and widespread in nature and possess various interesting biological activities (Kharasch and Arora, 1976; Milito et al., 2019; Francioso et al., 2020). They also have fundamental application in medicines (Scott and Njardarson,

2018; Zhao et al., 2019), materials (Lim et al., 2015; Mutlu et al., 2019), pesticides (Devendar and Yang, 2017), and so on. As low-valence sulfur compounds, aryl sulfides and aryl thiols are useful substrates for the synthesis of oxidized derivatives such as sulfoxides and sulfones (Rayner, 1995; Chu et al., 2021). Aryl sulfides and aryl thiols are commonly synthesized from aryl halides and arenes with a sulfur source reagent. Common sulfur sources converting aryl halides to aryl sulfides and thiols include elementary sulfur, sodium sulfide, sodium hyposulfide, aliphatic thiols, etc (Liu et al., 2017). In case of other substrates such as  $\alpha$ -perfluoroalkyl ketones, sodium sulfinates or arylsulfonyl chlorides are also effective sulfur sources (Chu et al., 2020). Although many synthetic methods for aryl sulfides and aryl thiols have been developed, some of these sulfur sources suffer from several drawbacks such as easily inflammable (e.g., elementary sulfur), instable (e.g., sodium sulfide), smelly (e.g., thiol). Moreover, excess use of non-natural sulfur sources may give rise to environmental and safety issues. In this regards, the upsurge of the concepts of green chemistry led us to pursue a natural biomass as sustainable and safe sulfur source for the synthesis of sulfur containing compounds.

\* Corresponding authors.

E-mail addresses: zh19683@163.com (H. Zhang), yjliu85@dlut.edu.cn (Y. Liu).

<sup>1</sup> These authors contribute equally to this work.

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$\alpha$ -Amino acids are a class of small molecules of great importance in living organisms. They are not only basic units for constructing proteins, but also indispensable precursors for the synthesis of fatty acid, glucose and nucleotides through enzyme catalyzed complex biotransformations, such as the well-known tricarboxylic acid cycle and gluconeogenesis pathway. Since  $\alpha$ -amino acids are non-toxic and readily available from biomass feedstock, it is very attractive to use them to replace traditional chemical reagents in organic synthesis (Kamanna, 2021). L-Cysteine is a fundamental sulfur source in the biosynthesis of sulfur containing endogenous active substances, such as signal molecules  $H_2S$  and  $SO_2$ , in the human body (Stipanuk, 1986; Paul et al., 2018). The biosynthesis of natural products such as antibiotics lincomycin A and sulfur containing amino acid ergothioneine in microorganisms also requires L-cysteines as sulfur source (Erdelmeier et al., 2012; Zhang, et al., 2018). L-cysteine is frequently used as sulfur source for the synthesis of inorganic nanomaterials such as Tin sulfide films, SnS nanocrystals and CdS nanowires (Gai et al., 2008; Polivtseva et al., 2016). However, the examples using L-cysteine as sulfur source in organic synthesis are still rare. In 2012, the Erdelmeier group (2012) reported a one-pot synthesis of ergothioneine from brominated imidazoles using L-cysteine as sulfur source (Fig. 1a). Treating 2-bromoimidazole with L-cysteine afforded a L-cysteine conjugate, the  $C(sp^3)$ -S bond of which was cleaved to provide ergothioneine in the presence of 3-mercaptopropionic acid. Inspired by the examples above, we started to investigate the possibility of applying L-cysteine as sulfur source in the transition metal catalyzed C-S coupling reaction for the synthesis of sulfur containing compounds. Herein, as a continuous work on the development of the synthetic methodology for sulfur containing compounds (Liu et al., 2015; Xue et al., 2017; Xiao et al., 2019), we report a successful application of L-cysteine as effective sulfur source in the synthesis of copper salts mediated symmetrical diaryl sulfides and heteroarene thiols from aryl halides and heteroarenes, respectively (Fig. 1b).

## 2. Material and methods

### 2.1. Chemical reagents

The chemical reagents were purchased from commercial suppliers, and used without further purification.

### 2.2. Structure characterization

The chemical structure of all synthesized compounds was determined by nuclear magnetic resonance (NMR) spec-

troscopy and mass spectroscopy. The purity of isolated products was greater than 95%. NMR spectra were recorded at 600 MHz on a Bruker DMX- 600 spectrometer with  $CDCl_3$  (7.26 ppm) or  $DMSO-d_6$  (2.50 ppm) as the solvent and tetramethylsilane was used as internal standard. Spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants are reported in hertz (Hz). Mass spectra of heteroarene thiols were recorded by GC-MS on QP2010 Ultra (Shimadzu, Japan). Mass spectra of heteroarene thiols were recorded by a UPLC-ESI-MS/MS system. The UPLC-ESI-MS/MS system consisted of an Acquity UPLC system (Waters Corp., MA, USA) coupled to a QTRAP 6500 Plus mass spectrometer (Sciex, Toronto, Canada) equipped with a TurboIonSpray source. Analyst Software 1.6.3 was used for data acquisition and data processing.

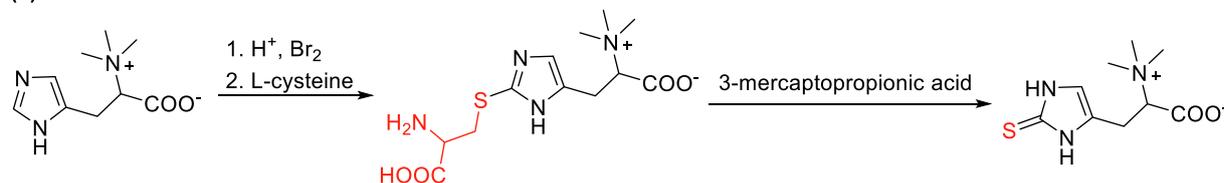
### 2.3. General procedure for the synthesis of diaryl sulfides

To a solution of aryl iodide (0.5 mmol) in DMSO /DMF (1.5 mL, v/v = 4/1) in a Schlenk tube, was added L-cysteine (30.3 mg, 0.25 mmol), potassium hydroxide (84.2 mg, 1.5 mmol) and cuprous iodide (95.2 mg, 0.5 mmol). The tube was vacuumed, and backfilled with argon three times consecutively. The reaction mixture was stirred at 120 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate three times. The organic layers were combined, washed with water and brine, dried over anhydrous magnesium sulfate and condensed in vacuum. The crude product was further purified by silica column chromatography using petroleum ether/ethyl acetate as eluent. The reported yields were isolated yields.

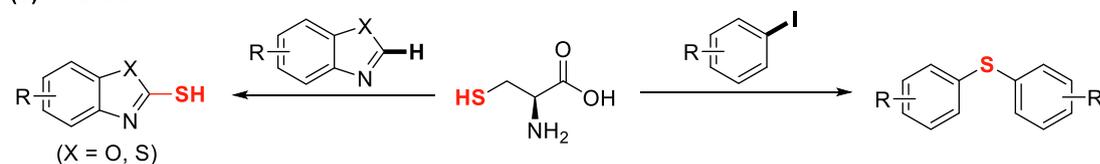
### 2.4. General procedure for the synthesis of heteroarene thiols

To a solution of heteroarenes (0.5 mmol) in DMSO (2 mL) in a Schlenk tube, was added L-cysteine (121.0 mg, 1 mmol), potassium hydroxide (140.0 mg, 2.5 mmol) and copper sulfide (47.5 mg, 0.5 mmol). The tube was vacuumed, and backfilled with argon three times consecutively. The reaction mixture was stirred at 140 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with water and the pH

#### (a) Previous work



#### (b) This work



- L-cysteine as sustainable sulfur source
- Single step conversion
- Wide substrate scope

Fig. 1 L-cysteine as sulfur source in organic synthesis.

was adjusted to 3 with 5% HCl. The resulted mixture was extracted with ethyl acetate three times. The organic layers were combined, washed with water and brine, dried over anhydrous magnesium sulfate and condensed in vacuum. The crude product was further purified by silica column chromatography using petroleum ether/ethyl acetate as eluent. The reported yields were isolated yields.

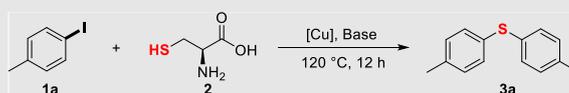
### 3. Results and discussion

#### 3.1. Synthesis of diaryl sulfides using L-cysteine as sulfur source

Conventionally, symmetrical diaryl sulfides are prepared by transition metal catalyzed C-S coupling reaction of aryl halides with sulfur source including elemental sulfur, thiourea, Na<sub>2</sub>S KSCN, dithiooxamide and ethanedithiol (Ke et al., 2011; Li et al., 2011; Chen et al., 2012; Li et al., 2012; Kamal et al., 2013; Firouzabadi et al., 2015; Hajipour and Jajarmi, 2016; Yousofvand et al., 2018; Xie et al., 2020; Tamoradi et al., 2020; Ashraf et al., 2020a; Ashraf et al., 2020b; Yarmohammadi et al., 2021; Samanta et al., 2021). In order to assess the feasibility of the C-S coupling reaction using L-cysteine as sulfur source, L-cysteine was applied in the synthesis of symmetrical diaryl sulfide. 4-Iodotoluene (**1a**, 0.5 mmol) was treated with L-cysteine at 120 °C in DMSO in the presence of KOH as base. Although no reaction was observed in the absence of copper salt, we were delighted to see that 78% yield of the corresponding diaryl sulfide **3a** was obtained when 1 equiv. of CuI was added in the reaction system (Entries 1–2,

Table 1). Besides diaryl sulfide, 11% yield of 4-methylbenzenethiol was obtained as byproduct (Entry 2, Table 1). A screening of solvents revealed that DMF gave a low yield of diaryl sulfide but no 4-methylbenzenethiol was observed (Entry 3, Table 1). We speculated that DMSO was more effective than DMF in initiating the thiolation of **1a** with L-cysteine to give 4-methylbenzenethiol as intermediate, while DMF was able to accelerate the C-S coupling reaction of 4-methylbenzenethiol and 4-iodotoluene to afford final product diaryl sulfide **3a**. In fact, many previous reports have revealed DMF was more effective than DMSO in the C-S cross coupling reactions of aryl halides and aryl thiols. [Hajipour, et al., 2014; Venkanna et al., 2014; Jiang et al., 2017] Thus, in order to reduce the production of 4-methylbenzenethiol and improve the yield of diaryl sulfide, a mixture solvent of DMSO and DMF was investigated (Entries 4–6, Table 1). DMSO/DMF (4/1) was the most effective for this conversion as 99% yield of **3a** was obtained. Further increasing the proportion of DMF in the solvent lowered the reaction conversion rate. The yield decreased either at lower temperature or at lower loading of copper salt (Entry 5, Table 1). Generally, cuprous salts exhibited higher efficiency than cupric salts to promote this transformation (Entries 7–13, Table 1). Cupric salts including CuCl<sub>2</sub>, CuSO<sub>4</sub>, CuS, Cu(OAc)<sub>2</sub>, Cu(NO<sub>3</sub>)<sub>2</sub> and Cu(OH)<sub>2</sub> provided lower yields. Screening of bases revealed that KOH was the most effective base in this conversion (Entries 14–18, Table 1). A variety of different bases, such as NaOH, Ca(OH)<sub>2</sub>, LiOH·H<sub>2</sub>O, K<sub>2</sub>CO<sub>3</sub> and NaOAc, afforded lower yields than KOH. In summary, the optimized

**Table 1** Condition screening for the synthesis of diaryl sulfides using L-cysteine as sulfur source.<sup>[a]</sup>



Entry	[Cu]	Base	Solvent	Yield (%) <sup>[b]</sup>
1	none	KOH	DMSO	ND
2	CuI	KOH	DMSO	78
3	CuI	KOH	DMF	14
4	CuI	KOH	DMSO/DMF(10/1)	87
5	CuI	KOH	DMSO/DMF(4/1)	99 (51 <sup>[c]</sup> , 73 <sup>[d]</sup> )
6	CuI	KOH	DMSO/DMF(2/1)	89
7	CuCl	KOH	DMSO/DMF(4/1)	78
8	CuCl <sub>2</sub>	KOH	DMSO/DMF(4/1)	30
9	CuSO <sub>4</sub>	KOH	DMSO/DMF(4/1)	60
10	CuS	KOH	DMSO/DMF(4/1)	74
11	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	KOH	DMSO/DMF(4/1)	46
12	Cu(NO <sub>3</sub> ) <sub>2</sub>	KOH	DMSO/DMF(4/1)	43
13	Cu(OH) <sub>2</sub>	KOH	DMSO/DMF(4/1)	30
14	CuI	NaOH	DMSO/DMF(4/1)	49
15	CuI	Ca(OH) <sub>2</sub>	DMSO/DMF(4/1)	76
16	CuI	LiOH·H <sub>2</sub> O	DMSO/DMF(4/1)	68
17	CuI	K <sub>2</sub> CO <sub>3</sub>	DMSO/DMF(4/1)	53
18	CuI	NaOAc	DMSO/DMF(4/1)	42

<sup>[a]</sup> Reaction conditions: 4-iodotoluene (0.5 mmol), L-cysteine (0.5 equiv.), [Cu] (1 equiv.), base (3 equiv.), solvent (1.5 mL), 120 °C, 12 h, under Argon;

<sup>[b]</sup> Isolated yields; ND: not detected;

<sup>[c]</sup> 0.5 equiv. of CuI;

<sup>[d]</sup> 110 °C.

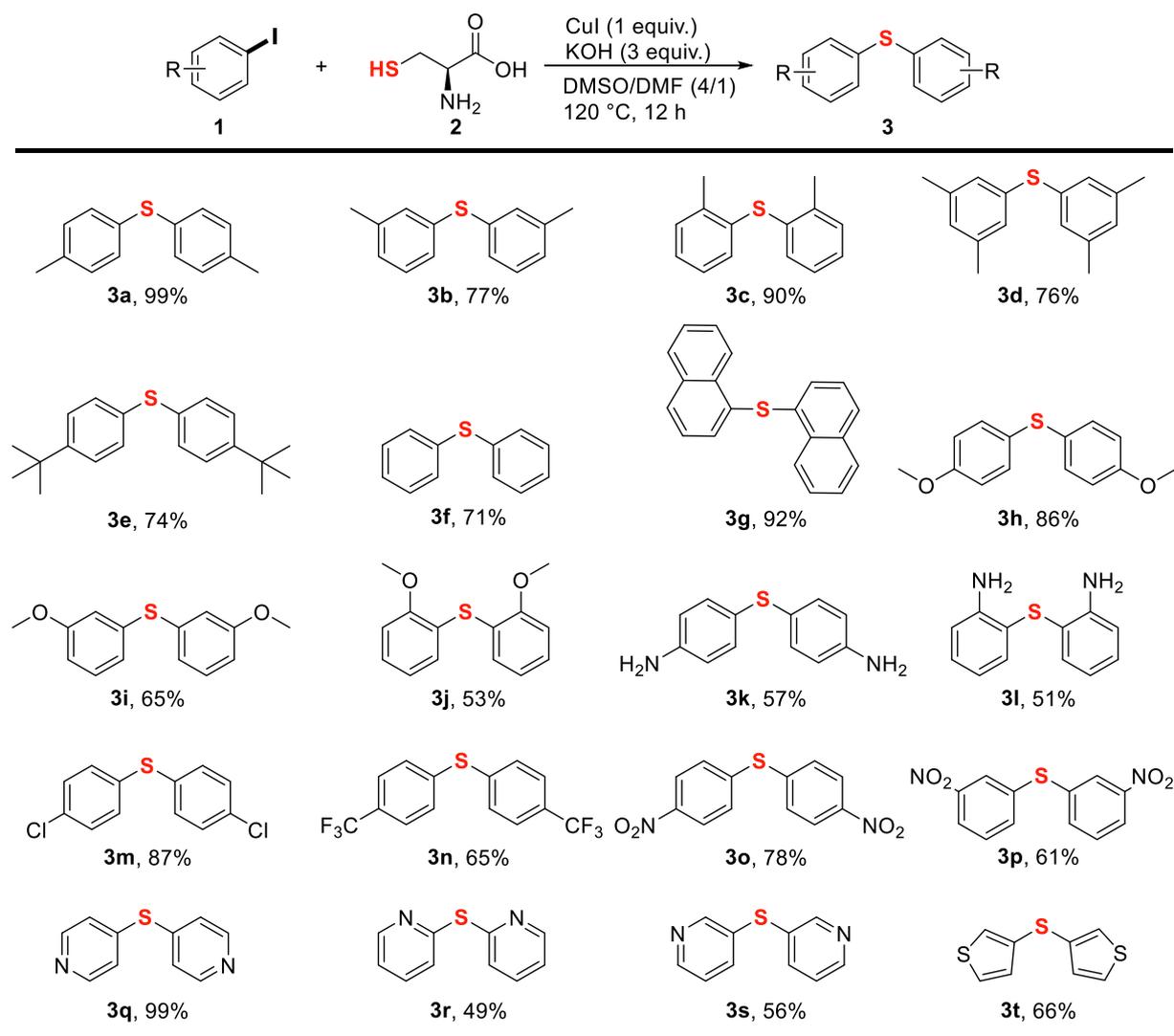
condition for this conversion is as follows: 4-iodotoluene (0.5 mmol), L-cysteine (0.5 equiv.), CuI (1 equiv.), KOH (3 equiv.), DMSO/DMF (v/v = 4/1, 1.5 mL), 120 °C, 12 h.

With the optimized condition in hand, substrate scopes with various aryl iodides as well as heteroaryl iodides have been studied (Fig. 2). Generally, the C-S coupling reaction of (hetero)aryl iodides and L-cysteine afforded the corresponding symmetrical diaryl sulfides (**3a–3t**) in a good yield. The variation of methyl group at *para*, *meta* and *ortho*-positions gave a yield of 99%, 77% and 90%, respectively. 3,5-Dimethyl and 4-*tert*-butyl substituted iodobenzenes gave moderate yields of diaryl sulfides. Simple iodobenzene and 1-iodonaphthalene were also smoothly converted into the corresponding diaryl sulfides. Although methoxy group of iodoanisole was slightly demethylated under the optimized condition, moderate to good yields of diaryl sulfides **3h**, **3i** and **3j** were obtained. Iodoanilines afforded relatively low yields, because intermolecular C-N coupling reaction also occurred under the optimized condition (Wang et al., 2010). Electron-deficient iodobenzenes bearing chloro, trifluoromethyl and nitro group were con-

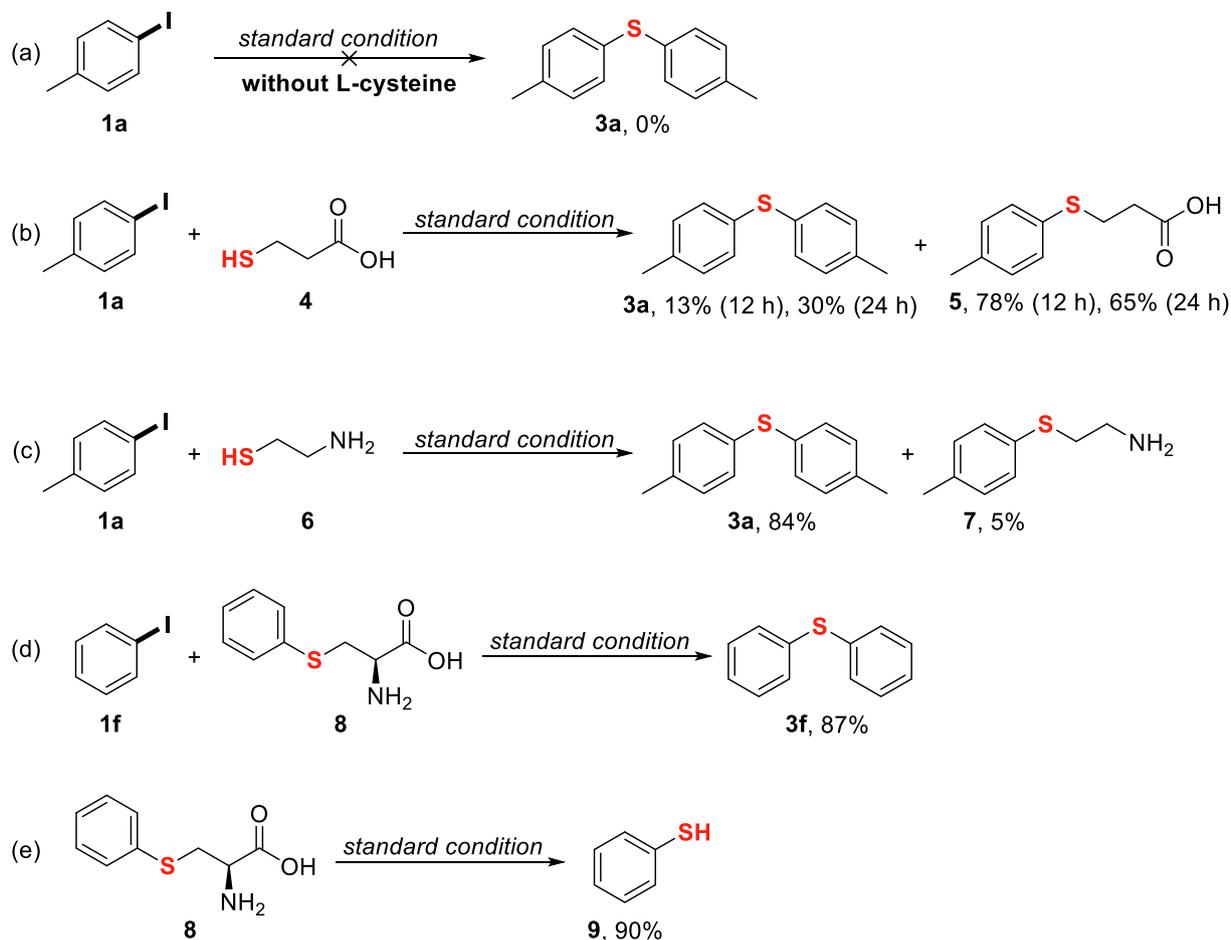
verted into diaryl sulfides in acceptable yields. Several heteroaryl iodides were further tested. Treating iodopyridines and iodothiophene with L-cysteine under the standard condition successfully afforded the corresponding diheteroaryl sulfides. Unfortunately, when aryl bromides and chlorides were employed, very low yields were obtained even at harsher conditions.

### 3.2. The formation of diaryl sulfide underwent a multiple C-S bond formation and cleavage process

In order to investigate the plausible mechanism of L-cysteine as sulfur source and the effect of amino group and carboxylic group of L-cysteine involved in this developed protocol for the synthesis of symmetrical diaryl sulfides, several control experiments were carried out. In the absence of L-cysteine, **3a** was not observed in the reaction mixture, suggesting that the sulfur atom in **3a** was derived from L-cysteine (Fig. 3a). Treating 4-iodotoluene (**1a**) with 3-mercaptopropionic acid (**4**) under standard condition predominately afforded sulfide **5** in 78%



**Fig. 2** Substrate scope of the synthesis of diaryl sulfides. Reaction conditions: iodobenzenes (0.5 mmol), L-cysteine (0.5 equiv.), CuI (1 equiv.), KOH (3 equiv.), DMSO/DMF (v/v = 4/1, 1.5 mL), 120 °C, 12 h; Isolated yields were presented.



**Fig. 3** Control experiments. Standard reaction conditions: CuI (1 equiv.), KOH (3 equiv.), DMSO/DMF (v/v = 4/1, 1.5 mL), 120 °C, 12 h; 0.5 equiv. of sulfur sources **4** and **6** were used in (b) and (c), respectively; 1 equiv. of **8** was used in (d).

yield, along with the production of **3a** in 13% yield after 12 h. It should be noted that, when the reaction time was extended to 24 h, the yield of **3a** increased to 30% and the yield of **5** decreased to 65%, suggesting a slow conversion from **5** into **3a** (Fig. 3b). The reaction of 4-iodotoluene (**1a**) with 2-aminoethanethiol (**6**) gave 84% yield of **3a**, 5% yield of 2-(p-tolylthio)ethan-1-amine (**7**) (Fig. 3c). It was obvious that L-cysteine was a better sulfur source than either 3-mercaptopropionic acid or 2-aminoethanethiol. On the other hand, these results indicated that the aryl alkyl sulfide may be formed as an intermediate from aryl iodide and L-cysteine, and then reacted with another molecule of aryl iodide to yield diaryl sulfide. In order to verify this hypotheses, commercially available S-phenyl L-cysteine (**8**) was used to react with iodobenzene (**1f**) and, as expected, this reaction gave 87% yield of diaryl sulfide **3f** (Fig. 3d). Furthermore, we found that **8** was converted into benzenethiol **9** in 90% yield under standard condition, indicating that diaryl sulfide **3f** was formed through C-S coupling reaction of **9** and another molecule of **1f** (Fig. 3e).

Based on these results of control reactions, taking iodobenzene (**1f**) as example, a plausible reaction pathway involving double C(sp<sup>2</sup>)-S bond formations and a C(sp<sup>3</sup>)-S bond cleavage was proposed as Fig. 4. Like common copper catalyzed C-S coupling reactions, oxidative addition occurred between **1f** and copper salt afforded a copper complex, and the subse-

quent ligand exchange by L-cysteine and final reductive elimination completed the first C(sp<sup>2</sup>)-S bond formation to provide thioether **8**. [Deng et al., 2004] Intermediate **8** was then converted into benzenethiol **9** via C(sp<sup>3</sup>)-S bond cleavage, which was initiated through an intramolecular nucleophilic attack by the terminal amine and carboxylate under basic condition (Johnston et al., 1986). Amino group and carboxylic group possibly have synergistic effect on promoting the C(sp<sup>3</sup>)-S cleavage as both **4** and **6** exhibited less efficiency than L-cysteine in this conversion. Benzenethiol **9** was further coupled with another molecule of **1f** to afford the final diaryl sulfide **3f** through the second C(sp<sup>2</sup>)-S bond formation.

### 3.3. Synthesis of heteroarene thiols using L-cysteine as sulfur source

C-H mercaptalization with a proper thiosurrogate represents an attractive way to prepare heteroarene thiols from heteroarenes. Several thiosurrogates such as elementary sulfur and aliphatic dithiols were reported to convert benzothiazoles and benzoxazoles into the corresponding heteroarene thiols (Popov et al., 2009; Yan et al., 2017; Xiao et al., 2019). In order to test whether L-cysteine is a usable sulfur source in C-H mercaptalization, we next tried to apply L-cysteine in the synthesis of heteroarene thiols. Benzothiazole (**11a**) was

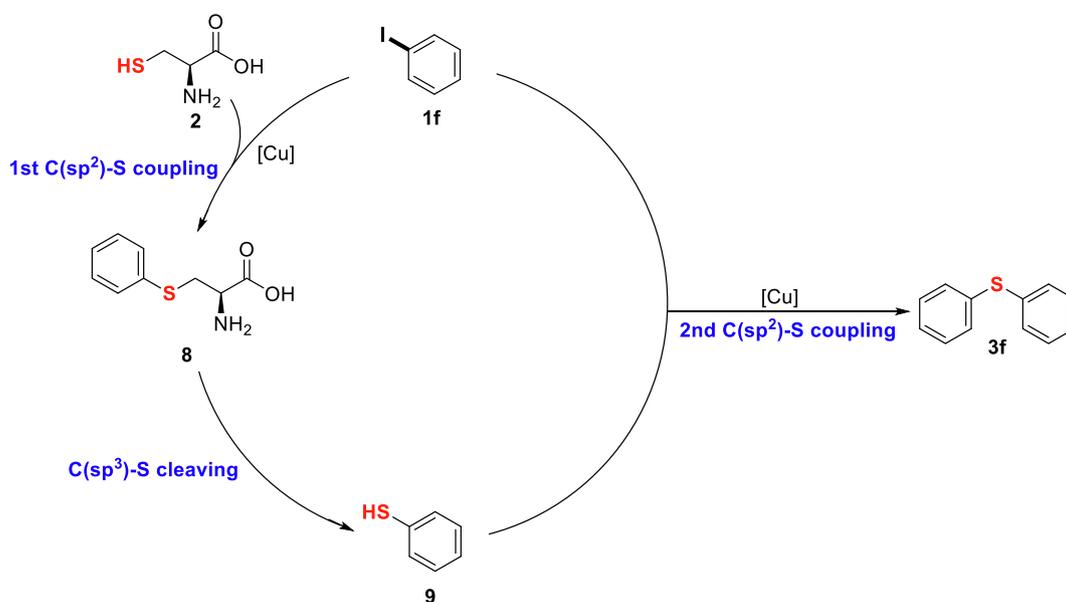
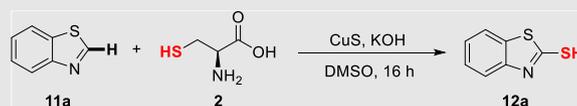


Fig. 4 Plausible reaction pathway.

used as a model substrate and treated with L-cysteine in the presence of copper salt and base in DMSO. Preliminary condition screening revealed that CuS was effective in promoting this C-H mercaptalization reaction. As shown in Table 2, both copper salt and L-cysteine were indispensable for this conversion (Entries 1–2, Table 2). With loading 1 equiv. of CuI and 1 equiv. of L-cysteine, 46% yield of 2-mercaptobenzothiazole (**12a**) was obtained, indicating that L-cysteine functioned as thiol source in this conversion (Entry 3, Table 2). A screening of copper salts revealed that CuS was the most effective in this conversion (Entries 4–6, Table 2). Considering that CuS was significantly more effective than other copper salts, it is possible that CuS provided additional sulfur source in the mercaptal-

ization of benzothiazole. Reducing the loading amount of CuS significantly decreased the yields (Entries 7–8, Table 2). Further increasing the amount of L-cysteine to 2 equiv. improved the yield to 84%, along with the recovery of 10% of benzothiazole (Entry 9, Table 2). It is noteworthy that no byproduct was found by TLC in these reactions. Further condition screening revealed that either less loading amount of KOH or lowering the reaction temperature led to the lower yields (Entries 10–11, Table 2). Therefore, the optimized condition for C-H mercaptalization of benzothiazole was as follows: benzothiazole (0.5 mmol), L-cysteine (2 equiv.), KOH (5 equiv.), CuS (1 equiv.), DMSO (2 mL), 140 °C, 16 h, under argon.

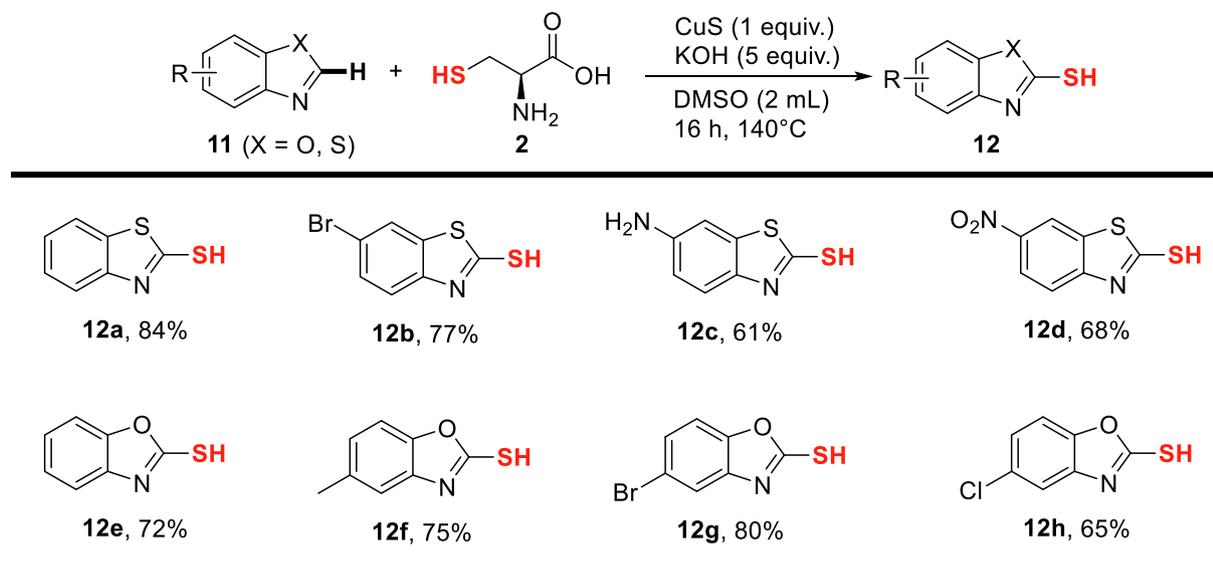
Table 2 Condition screening for C-H mercaptalization of benzothiazole with L-cysteine.<sup>[a]</sup>



Entry	[Cu] (equiv.)	L-cysteine (equiv.)	Bases (equiv.)	Temp (°C)	Yield <sup>[b]</sup> (%)
1	–	1	KOH (5)	140	ND
2	CuI (1)	–	KOH (5)	140	ND
3	CuI (1)	1	KOH (5)	140	46
4	CuSO <sub>4</sub> (1)	1	KOH (5)	140	27
5	CuO (1)	1	KOH (5)	140	35
6	CuS (1)	1	KOH (5)	140	62
7	CuS (0.5)	1	KOH (5)	140	49
8	CuS (0.1)	1	KOH (5)	140	7
9	CuS (1)	2	KOH (5)	140	84
10	CuS (1)	2	KOH (3)	140	64
11	CuS (1)	2	KOH (5)	130	44

<sup>[a]</sup> Reaction conditions: benzothiazole (0.5 mmol), DMSO (2 mL), 140 °C, 16 h, under argon;

<sup>[b]</sup> Isolated yields; ND: not detected.



**Fig. 5** Substrate scope of the synthesis of heteroarene thiols. Reaction conditions: benzothiazole or benzoxazole (0.5 mmol), L-cysteine (2 equiv.), KOH (5 equiv.), CuS (1 equiv.), DMSO (2 mL), 140 °C, 16 h, under argon; Isolated yields were presented.

The substrate scope was further broadened by using benzothiazoles and benzoxazoles bearing a variety of functional groups (Fig. 5). Using L-cysteine as sulfur source, all benzothiazoles and benzoxazoles were successfully converted into the corresponding thiolated products in satisfying yields. Functional groups including halides, amino and nitro groups were well compatible with this reaction system.

#### 4. Conclusion

In conclusion, we employed L-cysteine as sulfur source and developed novel C-S coupling strategies for the synthesis of symmetrical diaryl sulfides from aryl halides. Brief mechanistic study revealed that a tandem C(sp<sup>2</sup>)-S coupling and C(sp<sup>3</sup>)-S cleaving reactions were possibly involved in this conversion. In addition, we also successfully applied L-cysteine in the C-H mercaptalization of benzothiazoles and benzoxazoles. Since L-cysteine is an attractive choice of sulfur source because of the safety and sustainability, more synthetic applications of L-cysteine in the preparation of sulfur containing compounds could be expected in the future.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.arabjc.2022.103896>.

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