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DABCO-promoted diaryl thioether formation by metal-catalyzed coupling of sodium sulfinates and aryl iodides

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Abstract: A scalable catalytic synthesis method using commodity chemicals for constructing diaryl thioethers directly from sodium arylsulfonates and iodoarenes is reported in this study. In the presence of CuO or other copper salts such as Cu(OAc)₂ as well as palladium catalysts, DABCO demonstrated to be essential to promote this transformation. Various iodoarenes and aryl sulfonates were examined and demonstrated the viability of this method. The mechanistic study showed that radical reactions occurred, while DABCO *N*-oxide radical can be observed by mass spectrometry. A plausible catalytic mechanism involving DABCO is also discussed, suggesting synergistic reduction of sulfinate by Cu(II) and DABCO is the key step of this coupling reaction.

Keywords: catalysis; radical reactions; cross-coupling; thioethers; DABCO

Thioethers are one of the important pharmacophores commonly existing in natural products, pharmaceuticals and bioactive compounds (Figure 1).^[1] The application of thioethers in organic materials has also been explored.^[2] Generally, the preparation of thioethers are widely performed via transition metal-catalyzed cross-coupling reactions between thiols and aryl or alkyl halides.^{[3],[4],[5]} However, the disadvantages of using thiols in large quantities in industry, such as strong and repulsive odors, irritation to skins, permanent organ damage and even death upon long-term exposure, urge chemists to find more convenient or less hazardous methods for thioether formation.

Other methods that do not rely on thiols as reagents have already been explored. However, some reactive starting materials or reagents had to be used. Arylsulfonyl hydrazide had been approved to be an effective sulfenylating reagent in recent years, sulfonyl hydrazides could react with aryl iodides^[6] or boronic acids^[7] to form various thioethers. Additionally, arylsulfonyl chloride^[8] and sulfenyl chloride^[9] were also developed for the synthesis of thioethers via carbon-sulfur cross-coupling reaction, despite these thiol surrogates being unstable or needing special reaction conditions. Finding more general and stable sulfenylating reagents is still a meaningful and important approach.

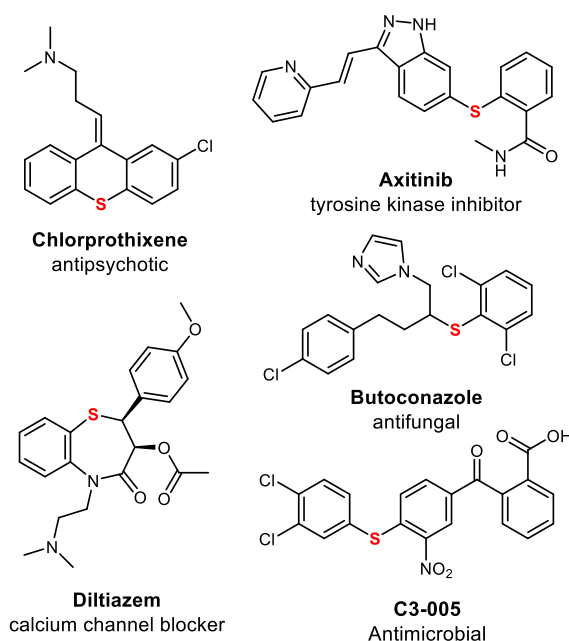
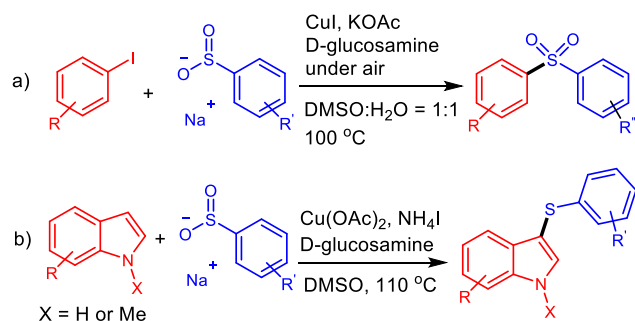


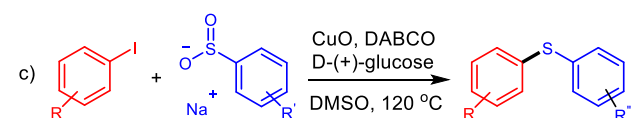
Figure 1. Representative thioether-containing drugs and bioactive compounds.

Sodium sulfinate is a stable sulfur-containing reagent without volatility and repulsive odors. Ideally, using sodium sulfonates as sulfur donors to construct thioethers is an attractive aim. Recently, a report demonstrated that aryl sulfones could be synthesized from aryl halides and sodium sulfonates by a copper-catalyzed cross-coupling reaction (Scheme 1a).^[10] Moreover, cross coupling reactions for the C3-sulfenylation of indoles using sodium sulfonates have also been reported (Scheme 1b).^[11] These results encouraged us to develop a novel and more general method to construct thioethers using sodium sulfonates as a convenient type of sulfur surrogates (Scheme 1c).

Previous works:



Our work:



Scheme 1. Synthesis of diarylsulfones or 3-arylthioindoles from sodium arylsulfonates.

4-iodotoluene **1a** was chosen as a model substrate to avoid the problem of volatility of iodobenzene.^[12] Sodium benzenesulfinate **2a** was used as the coupling partner. The original reaction conditions with copper catalysts and D-glucosamine as ligand in DMSO for synthesizing aryl sulfones (Scheme 1a) and indolyl thioethers (Scheme 1b) have been used. However, only trace of thioether coupling product was observed under the conditions of sulfone formation (Table 1, entry 1) and encouragingly, 2% of thioether **3** could be isolated with copper acetate as the catalyst (Table 1, entry 2). With copper acetate as the catalyst, different acids and bases were screened, and only bases led to the product (Table 1, entries 3-9), in which DMAP started to provide a promising yield of 28% in the initial screen. We extended the screen to other amine bases and found that DABCO significantly improve the product yield to 55% (Table 1, entries 5-7). Effectively, Polyzos and co-workers reported a visible light photocatalytic method for thioether formation from aryl iodides and disulfide, and DABCO served as single electron donor in the photocatalytic cycle.^[13] Subsequently, DABCO was chosen as the base and various catalysts including commonly used iron catalysts (Table 1, entries 10-12), nickel catalysts (Table 1, entries 13-15) and palladium catalysts (Table 1, entries 16-18) were screened. Iron and nickel catalysts did not lead to favorable results, while palladium catalysts generally conducted to very good yields of thioether product **3** with the highest one is 70% catalyzed by tris(dibenzylideneacetone)dipalladium(0).

Table 1. Optimization of the reaction conditions (Catalysts and bases)^{a)}

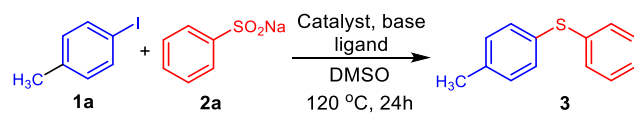


Entry	Catalyst	Base	Temp. (°C)	Yield (%) ^{b)}
1	CuI	KOAc	100	trace
2	Cu(OAc) ₂	NH ₄ I	110	2
3	Cu(OAc) ₂	Cs ₂ CO ₃	120	3
4	Cu(OAc) ₂	Na ₂ CO ₃	120	4
5	Cu(OAc) ₂	NaHCO ₃	120	17
6	Cu(OAc) ₂	DMAP	120	28
7	Cu(OAc) ₂	DABCO	120	55
8	Cu(OAc) ₂	DBU	120	2
9	Cu(OAc) ₂	DIPEA	120	10
10	FeS	DABCO	120	2
11	FeCl ₂	DABCO	120	5
12	Fe(SO ₃ CF ₃) ₂	DABCO	120	5
13	Ni(dppf)Cl ₂ ^{c)}	DABCO	120	6
14	Ni(COD) ₂ ^{d)}	DABCO	120	5
15	NiCl ₂	DABCO	120	4
16	Pd ₂ (dba) ₃ •CHCl ₃ ^{e)}	DABCO	120	70
17	PdCl ₂ (PPh ₃) ₂	DABCO	120	43
18	PdCl ₂ (dtbpf) ^{f)}	DABCO	120	66

^{a)} Reaction conditions: 4-Iodotoluene (0.6 mmol), sodium benzenesulfinate (1.8 mmol), catalyst (0.12 mmol), ligand (0.12 mmol), DABCO (1.2 mmol), DMSO (2 mL). ^{b)} Isolated yield. ^{c)} dppf = 1,1'-bis(diphenylphosphino)ferrocene. ^{d)} COD = 1,5-cyclooctadiene. ^{e)} dba = dibenzylideneacetone. ^{f)} dtbpf = 1,1'-bis(di-tert-butylphosphino)ferrocene.

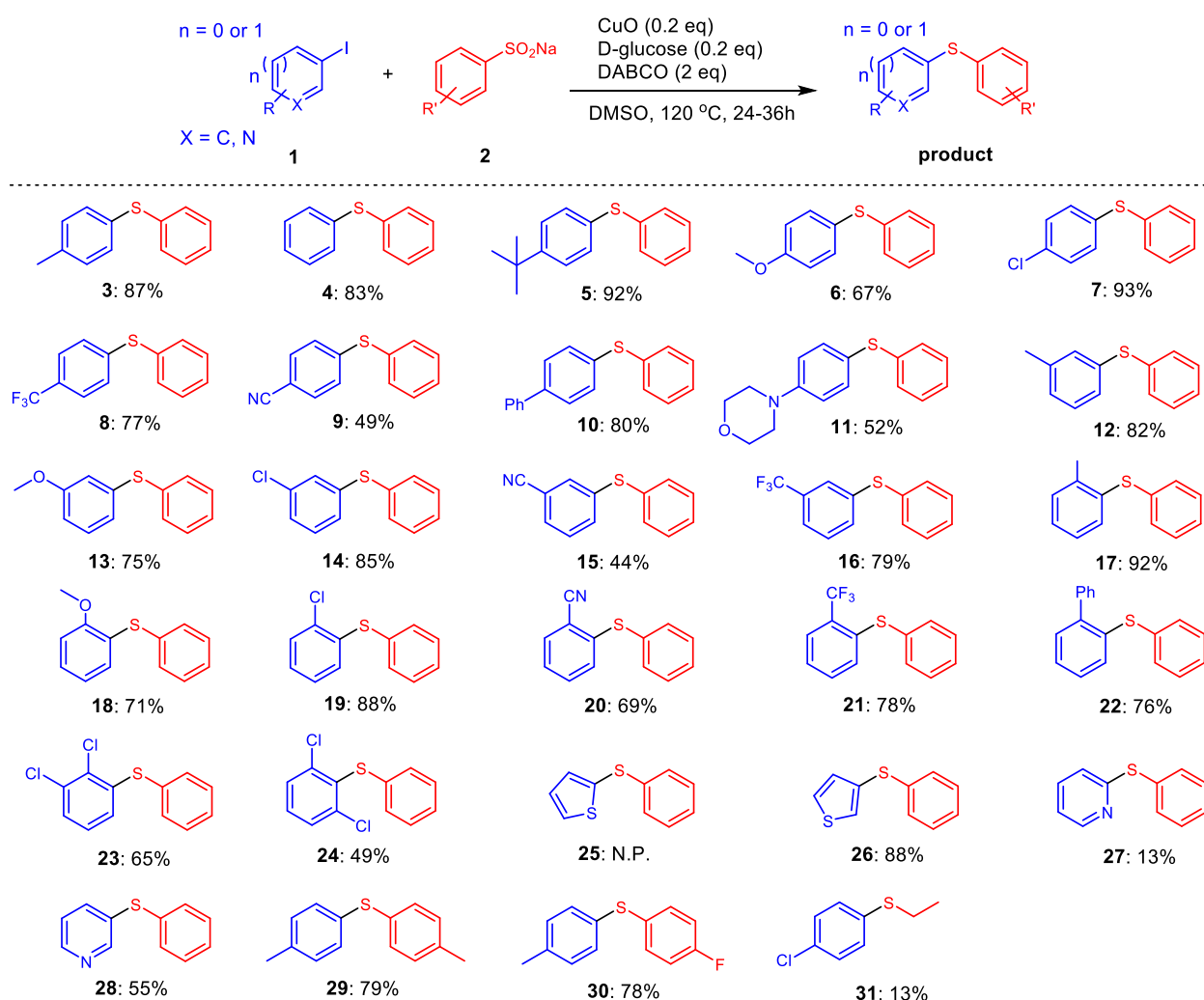
Consequently, we screened diverse copper catalysts using DABCO as the amine base (Table 2, entries 1-8). The yield of product **3** was further increased to 73% when Cu(OAc)₂ was replaced by CuO (Table 2, entry 2). Additionally, diverse ligands were screened when CuO was used as the catalyst and it seemed that only *N,O*- and *N,N*-bidentate ligands furnished the thioether product except 1,2-dimethylethylenediamine (DMEDA) (Table 2, entries 9-12). Thioether **3** could be obtained using D-glucose as ligand with a yield of 70% (Table 2, entry 9), slightly inferior to the reaction conditions using D-Glucosamine (Table 2, entry 2). We were inclined to keep using D-glucose as the ligand for this reaction because of its accessibility and low cost. Finally, we optimized the reaction conditions: the quantity of benzenesulfinate **2a** has been explored (Table 2, entries 13-14). 4 equivalents of **2a** achieved the highest yield of 93% (Table 2, entry 13), while the yield of **3** decreased to 48% when only 2 equivalents of **2a** were added (Table 2, entry 14). Ligand such as D-glucose was able to significantly increase the reaction yield (Table 2, entry 15), while DABCO base was necessary for this reaction, otherwise the yield of thioether **3** dropped dramatically to 13% (Table 2, entry 16).

Table 2. Optimization of the reaction conditions (Cu catalysts and ligands)^{a)}



Entry	Catalyst	Ligand	Base	Yield (%) ^{b)}	15 ^{d)} 16 ^{d)}	CuO CuO	/ D-Glucose	DABCO /	33 13
1	Cu(OAc) ₂	GlcN ^{c)}	DABCO	55	a) Reaction conditions: 4-Iodobenzene (0.6 mmol), sodium benzenesulfinate (1.8 mmol), catalyst (0.12 mmol), ligand (0.12 mmol), DABCO (1.2 mmol), DMSO (2 mL). ^{b)} Isolated yield. ^{c)} GlcN: D-Glucosamine. ^{d)} 2.4 mmol 2a was added. ^{e)} 1.2 mmol 2a was added.				
2	CuO	GlcN	DABCO	73					
3	CuBr ₂	GlcN	DABCO	42					
4	CuCl ₂	GlcN	DABCO	57					
5	Cu(SO ₃ CF ₃) ₂	GlcN	DABCO	59					
6	CuCl	GlcN	DABCO	58					
7	CuBr	GlcN	DABCO	36					
8	CuI	GlcN	DABCO	60					
9	CuO	D-Glucose	DABCO	70					
10	CuO	L-Proline	DABCO	42					
11	CuO	DMEDA	DABCO	trace					
12	CuO	TMEDA	DABCO	40					
13 ^{d)}	CuO	D-Glucose	DABCO	93					
14 ^{e)}	CuO	D-Glucose	DABCO	48					

With the optimized conditions in hand, we examined the scope of this cross-coupling reaction. Various substituents at the *para* position of iodobenzene were tested. Alkyl and aryl-substituted iodobenzenes were able to be transformed to the corresponding thioether products **3**, **5** and **10** and **22** with excellent yields of 80-92%, similar to iodobenzene **4**.



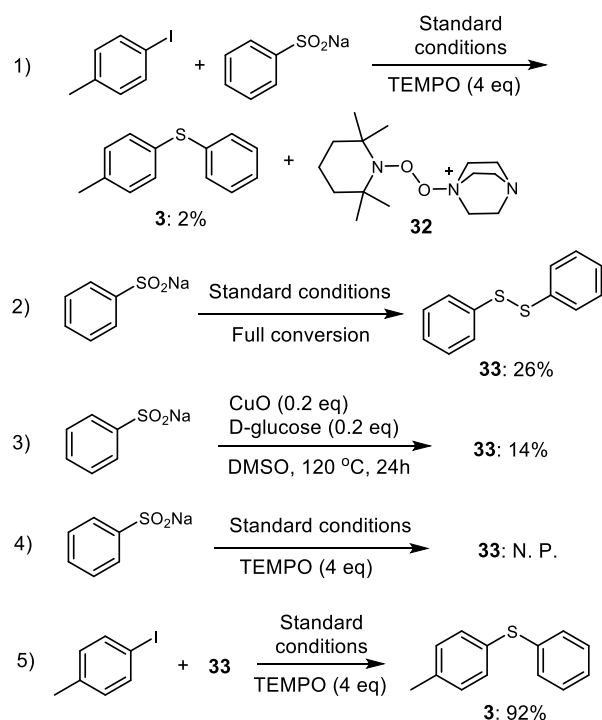
Scheme 2. Synthesis of thioethers.

Electron-donating groups at the *para* position decreased the yields to 52-67% (**6** and **11**), while some electron-withdrawing groups did not demonstrate obvious influence on the reactivity to provide the respective yields of 77% and 93% from the reactions

of 4-Cl and 4-CF₃ benzene (**7** and **8**), except 4-CN substituted iodobenzene, which was obtained with a yield of 49% (**9**). Substituents at the *ortho* (**12** – **16**) or *meta* position (**17** – **22**) of iodobenzene demonstrated a similar trend on the reactivity-substituents

relationship as at the *para* position. The best results were obtained with 2-Me iodobenzene (**17**, 92% yield) and 2-Cl benzene (**19**, 88% yield).

Polysubstituted iodobenzenes were also competent partners in this transformation. 2,3-Di-Cl iodobenzene led to a slightly inferior yield of the desired diaryl thioether (**23**, 65%), while 2,6-di-Cl iodobenzene significantly affected the yield of the product to 49%, probably due to steric hindrance (**24**). Heteroaryl compounds were also tested. 3-Iodothiophene and 3-iodopyridine were transformed to the corresponding products with good to moderate yields (**26**, 88% and **28**, 55%), while an iodine atom at the C2-position of heteroaromatic rings drastically diminished the yields (**25** and **27**). Finally, diverse benzenesulfonates were examined. Both 4-Me or 4-F benzenesulfonates could be converted to the thioether products in ~80% yields (**29** and **30**). Additionally, an attempt using sodium ethanesulfinate demonstrated that this coupling reaction for aryl alkyl thioethers could be performed (**31**) although with a lower yield.



Scheme 3. Control experiments.

In order to support a plausible mechanism of this reaction, a series of control experiments were conducted. When 4 equivalents of TEMPO as the radical trapping reagent were added to the standard reaction conditions, the yield of thioether **3** decreased

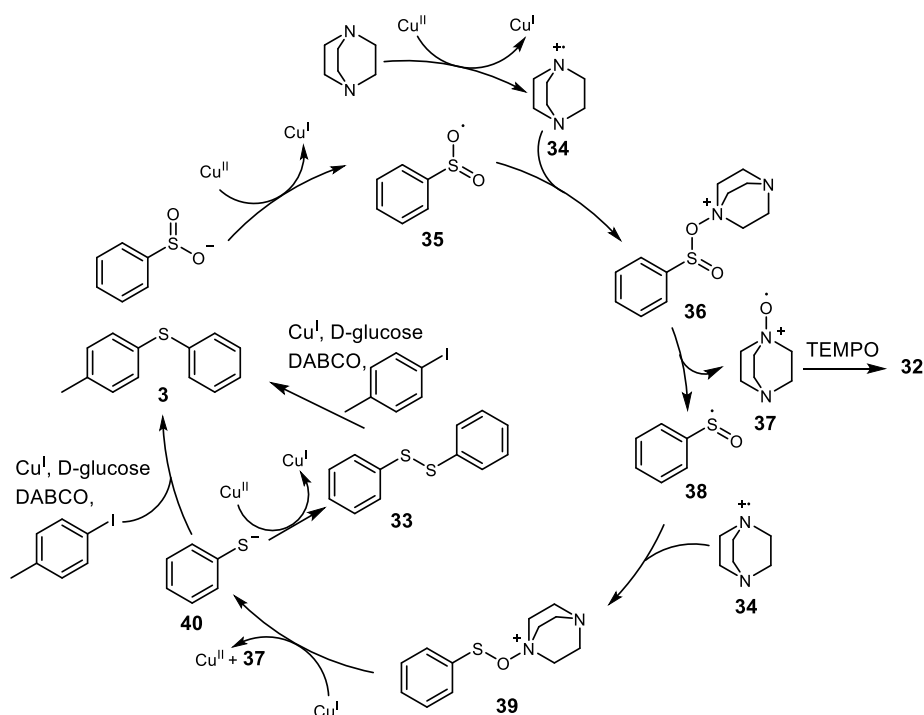
dramatically to 2%. The result suggested that a radical reaction might mechanistically occurred. The reaction mixture was further examined using mass spectrometry (Scheme 3, entry 1 and Figure S1), and peroxide **32** was detected suggesting DABCO *N*-oxide radical **37** might be involved in the reaction. NEW REF [14]

14: For a related peroxide suggested by ESI-MS, see: J.-H. Xu, W.-B. Wu, J. Wu, *Org. Lett.* **2019**, *21*, 5321-5325.

When sodium benzenesulfinate was treated with standard reaction system, disulfide **33** was isolated with only a yield of 26% even the conversion was complete (Scheme 3, entry 2), suggesting that disulfide intermediate formation may not be the major mechanism of this reaction.

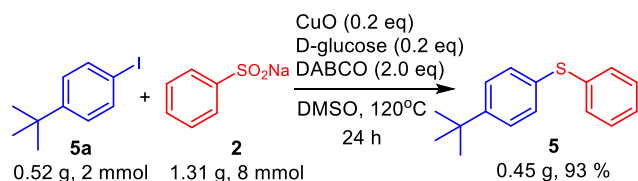
When DABCO was absent from the reaction, the yield of disulfide **33** further decreased to 14% (Scheme 3, entry 3), indicating DABCO plays an important role for disulfide formation. When 4 equivalents of TEMPO were added into the standard reaction conditions, no disulfide **33** was detected (Scheme 3, entry 4). In summary, the results of these three reactions demonstrated that **33** was formed *via* the radical pathway, and DABCO promoted the process. Finally, 4-iodotoluene and **33** reacted under standard conditions in the presence of 4 equivalents of TEMPO, and **3** was formed with 92% yield (Scheme 3, entry 5). The results suggest that the CuO-catalyzed cross-coupling between 4-iodotoluene **1a** and disulfide **33** follows a canonical mechanism for such Cu-catalyzed C-S bond formation, without the intervention of radical species.

Based on the above results, a plausible mechanism was proposed as shown in Scheme 4. DABCO radical cation **34** can be formed by copper(II) oxidation.^[14] The copper(II) oxidation would also transform sodium benzenesulfinate to provide benzenesulfinate radical **35**, which consequently adds to **34** to form DABCO-sulfinate **36**. After DABCO *N*-oxide radical **37** leaves,^[15] the reduced sulfinyl radical **38** reacts again with **34** furnishes DABCO-sulfanolate **39**. By oxidation of copper(I), thiolate **40** is obtained and undergo a coupling reaction with 4-iodotoluene to provide the final diaryl thioether product **3**. In the presence of thiolate **40**, the formation of disulfide **33** can be formed spontaneously as an intermediate (Scheme 3, entry 2), **33** could continuously react with 4-iodotoluene to give thioether **3** (Scheme 3, entry 5).



Scheme 4. Proposed mechanism.

A scale up reaction has been set up using 0.52 g (2 mmol) of 4-*t*-butyl iodobenzene as the reactant, 4 equivalent of sodium benzenesulfinate was added to the reaction together with copper oxide (0.2 eq.), D-glucose (0.2 eq.) and DABCO (2.0 eq.) using DMSO as the solvent. The reaction was stirred at 120 °C for 24 hours to provide the desired product **5** with a yield of 93% (Scheme 5).



Scheme 5. Scale up reaction of the thioether formation.

In summary, we developed a novel and convenient catalytic method for synthesizing thioethers promoted by DABCO. The thioether can be formed directly from the coupling reaction of sodium arylsulfinate and iodoarene. The reaction scope demonstrated the potential for synthesizing diverse diaryl thioethers and even aryl alkyl ethers, and no highly reactive reducing agent is needed.

The mechanism study suggested a radical pathway by forming a DABCO *N*-oxide radical species from affordable sodium sulfinites rather than commonly

used thiols or disulfides. The potential application of our method can be expected.

Experimental Section

To a stirred solution of sodium sulfinate **2** (1.31 g, 8.0 mmol), CuO (31.8 mg, 0.4 mmol), D-glucose (72.1 mg, 0.4 mmol) and DABCO (0.45 g, 4.0 mmol) in DMSO (10 mL) in sealed tube, was dropwise added 1-(*t*-butyl)-4-iodobenzene **5a** (0.52 g, 2.0 mmol). The solution was heated at 120 °C for 24 hours and monitored by thin layer chromatography. The reaction mixture was cooled to room temperature and added ethyl acetate (10 mL) to dilute, then the resulting mixture was filtered through diatomite and washed using ethyl acetate (5 mL) for three times. The filtrate was diluted with water (20 mL), isolating and collecting the organic layer, and the inorganic layer was extracted with ethyl acetate (5 mL) for another two times. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography on silica gel (pure hexane) provided **5** (0.45 g) as a colorless oil.

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