

Article

Direct Sulfoxidation of Aromatic Methyl Thioethers with Aryl Halides by Copper-Catalyzed C(sp³)–H Bond Activation

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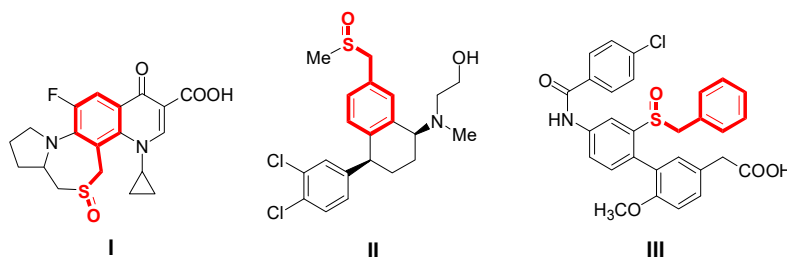


Abstract: A copper-catalyzed direct sulfoxidation reaction by C(sp³)–H bond activation has been developed. Starting from simple aromatic methyl thioethers with aryl halides, versatile biologically-active arylbenzylsulfoxide derivatives were efficiently synthesized in good to high yields under mild conditions. This new methodology provides an economical approach toward C(sp³)–C(sp²) bond formation.

Keywords: copper-catalyzed; direct sulfoxidation; C(sp³)–H bond activation; aromatic methyl thioethers; arylbenzylsulfoxide derivatives

1. Introduction

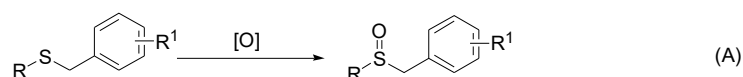
Benzylsulfoxide derivatives are the most privileged scaffolds in natural biological products [1], pharmaceutical chemistry [2], and functionalized materials [3]. In particular, benzylsulfoxide derivatives exhibit a wide range of biological properties, such as anti-bacterial activity (Scheme 1I) [4], anti-cancer activity (Scheme 1II) [5], and HIV inhibition (Scheme 1III) [6].



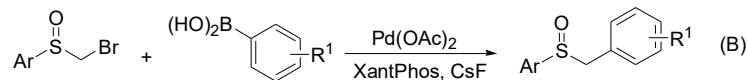
Scheme 1. Important biological benzylsulfoxide derivatives.

The most common synthetic method for benzylsulfoxide derivatives is sulfide oxidation, as illustrated in Scheme 2A [7]. The strong oxidizing agents and reactive organolithium contribute to the wide use of this method, although its scope is limited. Benzylsulfoxides have also been successfully obtained by Pd-catalyzed Suzuki cross-coupling (Scheme 2B) [8]. In 2013, Walsh et al. reported a more efficient synthesis route for benzylsulfoxides with a greater atom economy [9]. This is the first example of the direct arylation of methyl sulfoxides. However, these methods lack sufficient practicality for the synthesis of benzylsulfoxides because of their high substrate requirements and limited catalyst compatibility. Therefore, the development of an efficient and less stringent reaction route for the synthesis of benzylsulfoxides remains highly desirable.

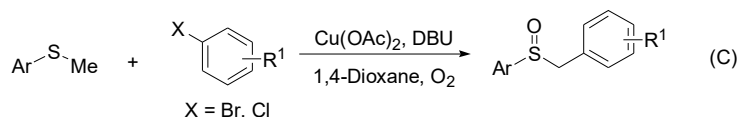
i) Oxidation of Sulfides



ii) Suzuki Coupling



iii) This work !



Scheme 2. Previous sulfoxide synthesis approaches.

The activation of the C–H bond is considered as one of the most useful C–C bond formation strategies [10]. However, many studies have demonstrated that, compared with the C(sp²)–H bond functionalization reactions, the application of C(sp³)–H bond functionalization reactions remains a challenge in this field [11], as the reactions of C(sp³)–H bond functionalization require harsher conditions and activated systems [12]. Given the present challenges, the development of more efficient and environmentally-friendly chemical processes for drug discovery is required [13]. Herein, we report on a novel copper-catalyzed direct sulfoxidation reaction by the activation of the C(sp³)–H bond (Scheme 2C). This method can provide a simple and convenient route to biologically-active benzylsulfinylbenzene compounds.

2. Results

At first, as shown in Table 1, the reaction conditions were screened based on the model reaction of thioanisole **1a** with bromobenzene **2a** (Table 1). The Cu(II) salts displayed a high catalytic activity in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (entries 1–6). In addition, Cu(OAc)₂ exhibited superior catalytic efficiency over all of the examined copper catalysts (entry 6). These results indicated that DBU was the optimal base (entry 12), which produced the product **3a** with an 87% yield. It was also noted that the product yield was decreased when the reaction temperature was less or greater than 110 °C (entries 13 and 14). Thus, the optimum reaction condition was determined as the **1a** and **2a** ratio of 1:1.2 in the presence of Cu(OAc)₂ (10 mol%) and DBU (2 equiv) in 1,4-dioxane (3 mL) at 110 °C for 10 h (Table 1, entry 12).

Next, a wide array of thioanisoles **1** and bromobenzenes **2** were subjected to this reaction, and provided the products with good to excellent yields (Table 2). Thioanisoles bearing an electron-donating group (Me and MeO) demonstrated better activity than those bearing an electron-withdrawing group (Cl, Br, and CF₃). Bromobenzenes **2**, bearing an electron-withdrawing group, also demonstrated better activity than those bearing an electron-donating group. It was notable that the very strong electron-withdrawing effect of the trifluoromethyl group was still obtained with a 71% yield (entry 10) of the corresponding product **3n**.

Furthermore, other aromatic methyl thioethers **1** with aryl chlorides **4** also successfully provided the corresponding products (Table 3). Naphthalene-2-thiol displayed a moderate reactivity with chlorobenzene, with an 86% yield (entry 6). However, this reaction did not take place for thioanisoles **1**, which bear the electron-deficient group substitutes CF₃ and NO₂.

Table 1. Optimization of the reaction conditions ^a.

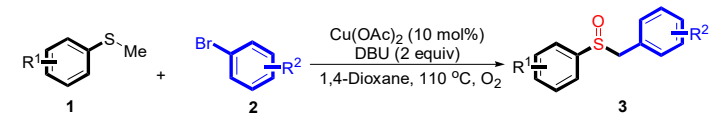
Entry	Catalyst	Base	1a:2a	3a [%] ^b
1	CuBr	DBU	1:1	nr
2	CuCO ₃	DBU	1:1	37
3	CuSO ₄	DBU	1:1	45
4	CuCl ₂	DBU	1:1	40
5	CuBr ₂	DBU	1:1	56
6	Cu(OAc) ₂	DBU	1:1	78
7	Cu(OAc) ₂	Imidazole	1:1.2	31
8	Cu(OAc) ₂	Piperidine	1:1.2	66
9	Cu(OAc) ₂	<i>N,N</i> -dimethylaniline	1:1.2	51
10	Cu(OAc) ₂	tri- <i>n</i> -propylamine	1:1.2	nr
11	Cu(OAc) ₂	DABCO ^h	1:1.2	55
12	Cu(OAc) ₂	DBU	1:1.2	87
13	Cu(OAc) ₂	DBU	1:1.2	69 ^c
14	Cu(OAc) ₂	DBU	1:1.2	76 ^d
15	Cu(OAc) ₂	DBU	1:1.2	74 ^e
16	Cu(OAc) ₂	DBU	1:1.2	5 ^f
17	Cu(OAc) ₂	DBU	1:1.2	0 ^g

^a Unless otherwise noted, reaction conditions were **1a** (0.5 mmol), **2a** (0.5 mmol), copper salt (10 mol%), base (2 equiv), 1,4-dioxane (3 mL), 110 °C for 10 h. ^b Isolated yield. ^c At 100 °C. ^d At 120 °C. ^e In CHCl₃. ^f In dimethylformamide (DMF). ^g Absence of the Cu(OAc)₂. ^h 1,4-Diazabicyclo[2.2.2]octane

Table 2. Copper-catalyzed sulfoxidation of thioanisoles **1** with bromobenzenes **2** ^a.

Entry	1	2	3	Yield ^b (Yield ^c)
1				87 (83)
2				83 (80)
3				84 (81)
4				93 (92)
5				88 (87)

Table 2. Cont.

				
Entry	1	2	3	Yield ^b (Yield ^c)
6				90 (81)
7				87 (83)
8				81 (80)
9				85 (79)
10				80 (77)
11				75 (70)
12				79 (74)
13				74 (69)
14				72 (65)

^a Unless otherwise noted, reaction conditions were **1** (0.5 mmol), **2** (0.6 mmol), Cu(OAc)₂ (10 mol%), DBU (2 equiv), 1,4-dioxane (3 mL), 110 °C for 10 h. ^b Isolated yield. ^c Reaction conditions were **1** (0.1 mol), **2** (0.12 mmol), Cu(OAc)₂ (10 mol%), DBU (2 equiv), 1,4-dioxane (3 mL), 110 °C for 10 h.

Table 3. Copper-catalyzed sulfoxidation of aromatic methyl thioethers **1** with aryl chlorides **4** ^a.

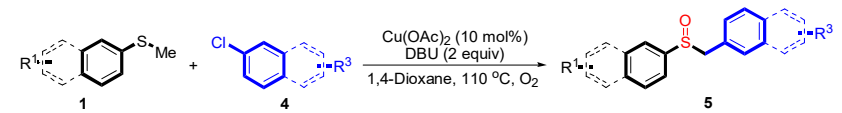
				
Entry	1	4	5	Yield ^b (Yield ^c)
1				79 (70)

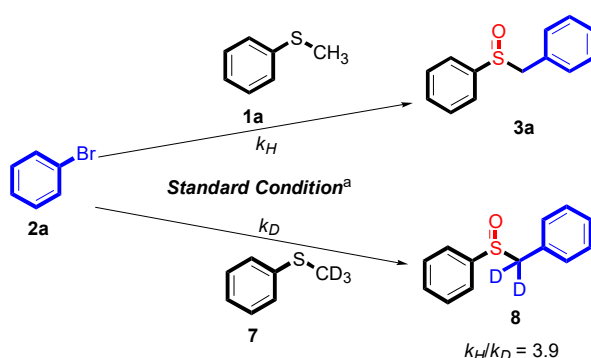
Table 3. Cont.

Entry	1	4	5	Yield ^b (Yield ^c)
2				87 (79)
3				63 (54)
4				90 (82)
5				81(76)
6				86 (78)

^a Unless otherwise noted, reaction conditions were **1** (0.5 mmol), **4** (0.6 mmol), Cu(OAc)₂ (10 mol%), DBU (2 equiv), 1,4-dioxane (3 mL), 110 °C for 10 h. ^b Isolated yield. ^c Reaction conditions were **1** (0.1 mol), **2** (0.12 mmol), Cu(OAc)₂ (10 mol%), DBU (2 equiv), 1,4-dioxane (3 mL), 110 °C for 10 h.

3. Discussion

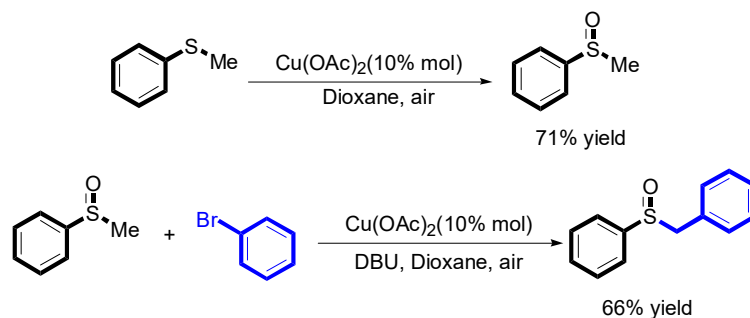
To obtain preliminary data for the reaction mechanism study, some additional reactions were conducted according to Scheme 3. The kinetic deuterium isotope effects [14] observed in the control experiments ($k_H/k_D = 3.9$) were consistent with the C–H cleavage, being the rate-limiting step (see Supplementary Materials).



^a reactions conditions were **1** (0.5 mmol), **2** (0.6 mmol), Cu(OAc)₂ (10 mol%), DBU (2 equiv), 1,4-dioxane(3 mL), in O₂, 110 °C for 10 h.

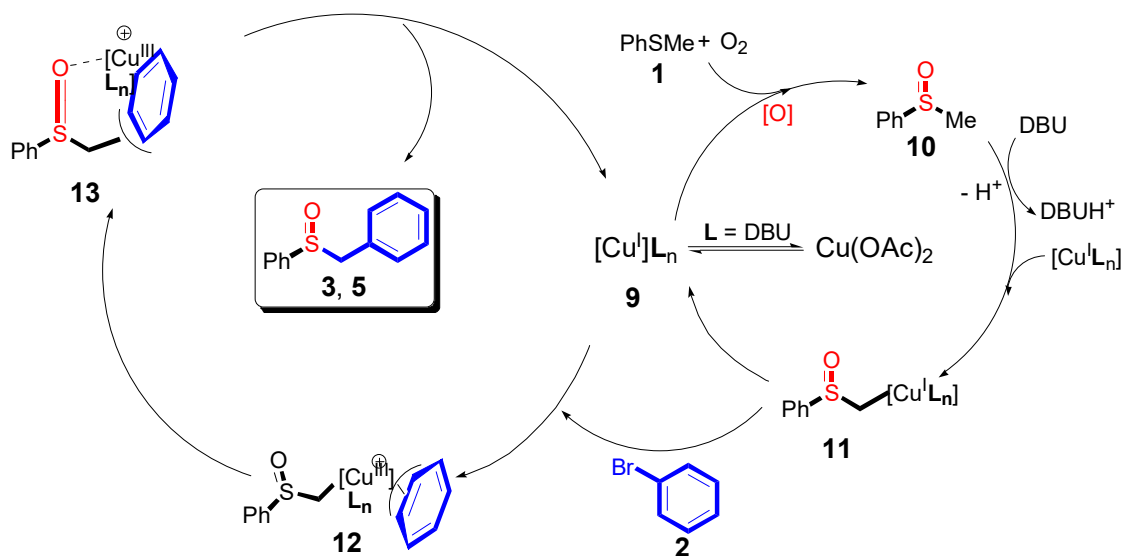
Scheme 3. The kinetic deuterium isotope effects.

We also did the two controlled experiments (Scheme 4). The results showed that both of the two reactions proceeded smoothly.



Scheme 4. The two controlled experiments.

The results suggested that the sulfoxidation product originating from the thioanisoles was followed by the copper-catalyzed oxidation in the presence of oxygen [15]. Based on these results, we proposed a possible reaction mechanism, as seen in Scheme 5. At the beginning of the reaction, the ligand coordination process of $\text{Cu}(\text{OAc})_2$ and DBU generated intermediate **9**. After that, intermediate **10** was followed by the ligand exchange step with DBU [16,17]. Then, intermediate **10** was converted to intermediate **11** by the oxidation addition step. Copper p-benzyl intermediates were previously observed to serve as synthetic intermediates. Next, intermediate **12** was provided from intermediate **11** via copper p-benzyl coordination, which generated a Cu species **13**. Through the reductive elimination step, intermediate **13** generated the desired product of benzylsulfoxide derivatives, and concomitantly formed intermediate **9**, which re-entered the catalytic cycle.



Scheme 5. A possible mechanism for copper-catalyzed direct sulfoxidation.

4. Materials and Methods

4.1. Materials

All reagents used in the experiment were obtained from commercial sources and used without further purification. Solvents for chromatography were of technical grade and distilled prior to use. Solvent mixtures were understood as volume/volume. Chemical yields refer to pure isolated substances. Catalysts were purchased from Alfa Aesar (analytical reagent, Tianjin, China). Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with an F-254 indicator (Spectrum, USA), visualized by irradiation with UV light. The Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker AVANCE III-400 spectrometer (Bruker, Germany) at 400 MHz and 100 MHz for ^1H and ^{13}C NMR in CDCl_3 , respectively. The NMR chemical shift was reported in ppm relative to

7.26 and 77 ppm of CDCl_3 as the standards of ^1H and ^{13}C NMR, respectively. The mass spectra were performed on a Bruker Esquire 3000 plus mass spectrometer (Bruker, Germany) equipped with an Electron Spray Ionization (ESI) interface and ion trap analyzer. The Electron Spray Ionization High Resolution Mass Spectrometry (ESI-HRMS) was tested on a Bruker 7-tesla Fourier Transform Mass Spectrometry (FT-ICR MS) equipped with an electrospray source.

4.2. General Synthesis Methods of 3a–5f

A solution of methylsulfanylbenezene **1a** (0.5 mmol, 62.1 mg), bromobenzene **2a** (0.6 mmol, 94.2 mg), $\text{Cu}(\text{OAc})_2$ (10 mol%, 9.1 mg), and DBU (2 equiv, 152.2 mg) in 1,4-dioxane (3 mL) was stirred under air. After being stirred at 110 °C for 10 h, it was cooled to room temperature. Then, the reaction mixture was quenched with saturated salt water (10 mL). Next, the solution was extracted with ethyl acetate (3×10 mL), and then washed with saturated Na_2CO_3 solution. The organic layers were combined and dried by Na_2SO_4 and concentrated in vacuo. The pure product benzylsulfinylbenzene **3a** (94.1 mg, 87% yield) was afforded by flash column chromatography on silica gel (cyclohexane/ethyl acetate = 5:1).

5. Conclusions

In conclusion, we reported on a copper-catalyzed $\text{C}(\text{sp}^3)\text{--H}$ bond direct sulfoxidation reaction. Starting from sample aromatic methyl thioethers with aryl halides, versatile biologically-active arylbenzylsulfoxide derivatives were synthesized in good to high yields under a moderate condition. This one-step transformation to a synthetically valuable internal benzylsulfoxide scaffold was realized for the first time with high efficiency. The reaction mechanism was studied by kinetic deuterium isotope labeling experiments. This present reaction provides a high efficiency approach to the formation of $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ bonds.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4344/9/1/105/s1>.

Author Contributions: Conceptualization, R.X.; methodology, Y.Z.; formal analysis, F.X.; and Writing—Original Draft preparation, S.T.

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Conflicts of Interest: The authors declare no conflict of interest.

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