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Copper-Catalyzed Intermolecular Difunctionalization of Styrenes with Thiosulfonates and Arylboronic Acids via a Radical Relay Pathway

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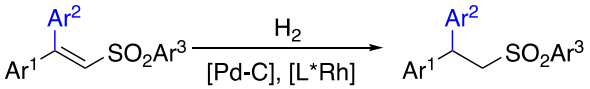
ABSTRACT: A general and practical copper-catalyzed intermolecular difunctionalization strategy of styrenes with methyl thiosulfonates and arylboronic acids has been developed. This method provides an efficient and straightforward avenue to a broad range of 2,2-diarylethylsulfone derivatives from readily available methyl thiosulfonates and commercially available styrene and arylboronic acid derivatives. The diverse substrate scope attests to the high functional group tolerance of this reaction. The mild nature of this protocol make it suitable for late-stage functionalization of bioactive natural products. Mechanistic investigations support the role of sulfonyl radicals and corroborate a copper-catalyzed radical relay pathway.
KEYWORDS: *copper catalysis• radical relay • sulfones • alkenes• difunctionalization*

Sulfones are prevalent scaffolds in natural products,[1] synthetic bioactive molecules,[2] and marketed therapeutics (such as SB-3CT for the treatment of migraine headaches[3] and anti-androgen receptor Casodex 3[4]). In fact, a study of drug likeness analysis found that alkyl aryl sulfones are among the top five drug skeletal fragments.[5] Sulfones also find widespread applications in material science[6] and agricultural industries.[7] They serve as important intermediates in organic synthesis,[8] as exemplified by the well-known Julia–Lythgoe olefination.[9] Therefore, methods for the construction of sulfones have attracted significant attention.

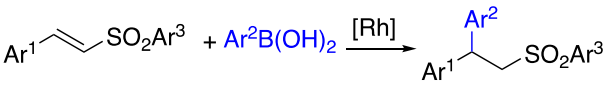
Despite the importance of sulfones in the applications outlined above, 2,2-diarylethylsulfones have received little attention, probably due to a lack of efficient and straightforward synthetic approaches.

Aliphatic sulfones can be prepared from α,β-unsaturated sulfone precursors[10] through hydrogenation, including asymmetric hydrogenations.[11] In 1998, the Ranu group reported the Pd/C-catalyzed hydrogenation of α,β-unsaturated sulfones using ammonium formate.[12] Inspired by this study, an elegant enantioselective rhodium-catalyzed hydrogenation of α,β-unsaturated sulfones was developed by the Hou group in 2019 (Scheme 1a).[13] In this procedure, both the (*E*)- and (*Z*)-isomers gave excellent enantioselectivities leading to opposite configurations of the products. The synthesis of the (*E*)- and (*Z*)-α,β-unsaturated sulfone precursors required 4 steps. In 2004, Lautens and coworkers described a rhodium-catalyzed Heck-type coupling of arylboronic acids with α,β-unsaturated sulfones.[14] By employing a rhodium catalyst bearing an enantioenriched tetrafluorobenzobarrelene-based ligand, an enantioselective 1,4-addition of boronic acids to α,β-unsaturated sulfones was accomplished by Hayashi and his group (Scheme 1b).[15] Here also, the requisite α,β-unsaturated sulfones required several steps to prepare,[15] reducing the overall synthetic efficiency.

a) Hydrogenation: Ranu (1998), Hou (2019)



b) 1,4-Addition: Lautens (2004), Hayashi (2012)



Scheme 1. Previous Synthetic Approaches to 2,2-Diarylethylsulfones

In recent years, copper-catalyzed coupling reactions between *in situ* formed radicals and arylboronic acids have drawn much attention due to copper's low cost, bio-compatibility, and complimentary reactivity to heavier d-block metals.[16] Copper-catalyzed difunctionalization of alkenes represents one of the most powerful and straightforward approaches to rapidly increase molecular complexity, as two chemical bonds are generated in one step.[17] We envisioned that the 2,2-diarylethylsulfones outlined above could be accessed via a three-component process involving the arylsulfonylation of styrenes (Figure 1).

To develop the arylsulfonylation of styrenes, three crucial requirements would need to be satisfied (Figure 1). First, a sulfonyl radical source that is compatible with the catalyst and intermediates in the arylsulfonylation would need to be identified.[18] Second, the competitive two-component coupling between sulfonyl radicals and boronic acids would need to be minimized (see byproduct **1**, Figure 1).[19] Finally, an appropriate oxidant for the selective oxidation of Cu(I) to Cu(II) must be chosen that would not oxidize other reactive intermediates (such as oxidize a punitive benzyl radical to the

corresponding cation, leading to byproducts **2**,[10a] **3**,[20] or **4**,[21] Figure 1).

The choice of sulfonyl radical source is important to develop user-friendly general methods to make C–S bonds. Several commonly used sulfonyl radical sources suffer from drawbacks that decrease their attractiveness. For instance, sulfonyl chlorides require expensive silver salts to trap chloride and prevent its undesired radical background additions.[22] The activation of sulfonyl hydrazides usually employ high temperatures, and the release of nitrogen gas raises safety concerns.[23] For our difunctionalization of styrenes to afford 2,2-diarylethylsulfone scaffolds, methyl thiosulfonates were chosen as the sulfonyl radical source.[24] Methyl thiosulfonates are readily available, odorless, and safe. Herein, we report an unprecedented copper-catalyzed intermolecular difunctionalization of styrenes with methyl thiosulfonates and arylboronic acids to afford 2,2-diarylethylsulfones (Figure 1). Our copper-catalyzed difunctionalization reaction features: (a) commercially available styrenes and arylboronic acids and readily available methyl thiosulfonates as starting materials; (b) cheap and abundant copper catalysts; and (c) mild reaction conditions with broad functional group compatibility. It represents an efficient and streamlined method to synthesize 2,2-diarylethylsulfone scaffolds.

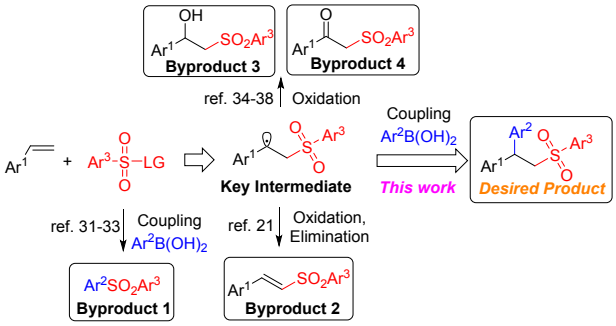
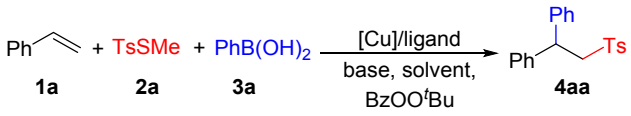


Figure 1. Synthesis of 2,2-Diarylsulfones via a Difunctionalization of Styrenes Strategy and the Potential Challenges

For the reaction optimization, we chose styrene (**1a**), *S*-methyl 4-methylbenzenesulfonothioate (**2a**) and phenylboronic acid (**3a**) as the model substrates. When 2.0 equiv K_2CO_3 was used as base, 2.0 equiv BzOO^{t}Bu as oxidant, 10 mol % $Cu(OTf)_2$ and 15 mol % 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbbpy) as the catalyst at 50 °C in acetone, the desired product **4aa** was isolated in 34% AY (AY = assay yield, determined by ^{1}H NMR integration of the crude product against an internal standard, Table 1, entry 1). Encouraged by this result, three additional bases ($NaHCO_3$, Cs_2CO_3, and $KHCO_3$) were examined. These experiments revealed that $KHCO_3$ was the top choice, generating **4aa** in 48% AY (Table 1, entry 4 vs. entries 1–3). Thus, $KHCO_3$ was used for further optimization. Three additional copper salts [CuBr, $Cu(NCCH_3)_4PF_6$, and CuI] were surveyed (Table 1, entries 5–7). The yield of **4aa** increased to 60% when CuI was utilized (Table 1, entry 7). In subsequent solvent screens, *N,N*-dimethylformamide (DMF) led to formation of **4aa** in 63% yield. This reaction also resulted in the formation of 20% AY of 4-tolyl phenyl sulfone (**4aa'**) from the two-component coupling side reaction between **2a** and **3a** (Table 1, entry 8). Formation of 4-tolyl phenyl sulfone (**4aa'**) was not observed in the prior experiments in acetone (entries 1–7). This observation inspired us to turn to mix solvents with DMF and acetone (Table 1, entries 9–11). When the volume ratio of acetone to DMF was 6 : 1, 74% AY of **4aa** was obtained (Table 1, entry 10). In contrast, an acetone to DMF ratio of 8 : 1, furnished the product in 66% AY (Table 1, entry 11). Upon decreasing the temperature from 50 to 40 °C, **4aa** was formed in 82% AY and 80% isolated yield (Table 1, entry 12). When the reaction was carried out at room temperature, the AY dropped to 48% (Table 1, entry 13). We next examine the catalyst loading. When reducing the catalyst loading to 5 mol % (Table 1, entry 14) the AY dropped to 72%. Thus, subsequent reactions were conducted with 10 mol % copper.

In a series of control experiments, Cu(I), dtbbpy and $KHCO_3$ were demonstrated to be essential for the catalytic reaction. No desired product was observed in the absence of any of these components (Table 1, entries 15–17). Therefore, the optimized conditions were: 10 mol % CuI and 15 mol% dtbbpy as the catalyst, styrene (**1a**) as the limiting reagent, 2.0 equiv of thiosulfonate (**2a**), 2.5 equiv of **3a**, 2.5 equiv of $KHCO_3$, and 3.0 equiv BzOO^{t}Bu as both oxidant and radical initiator in a mix solvent of acetone and DMF (6 : 1 volume ratio) at 40 °C for 12 h (for additional screening results, see SI).

Table 1. Optimization of the Copper-Catalyzed Difunctionalization of Styrene with 2a and 3a[a]



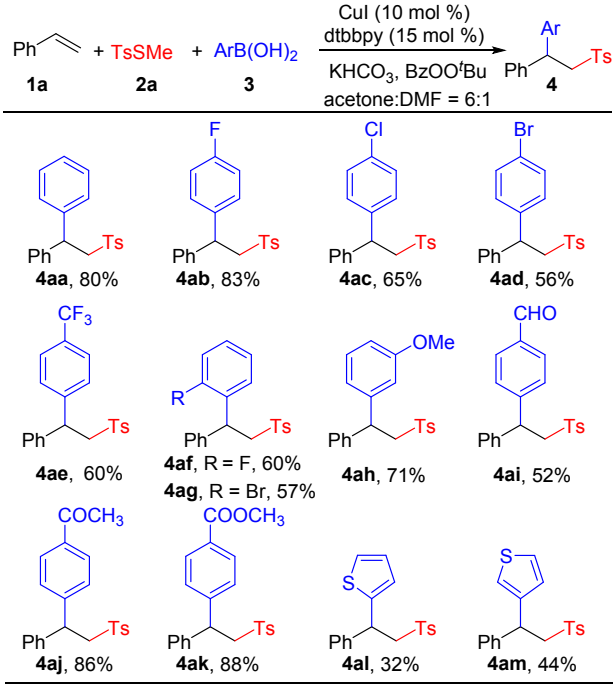
entry	catalyst	base	solvent	T/ °C	**4aa** (AY[b]/%)
1[c]	$Cu(OTf)_2$	K_2CO_3	acetone	50	34
2[c]	$Cu(OTf)_2$	$NaHCO_3$	acetone	50	17
3[c]	$Cu(OTf)_2$	Cs_2CO_3	acetone	50	N.P
4[c]	$Cu(OTf)_2$	$KHCO_3$	acetone	50	48
5[c]	CuBr	$KHCO_3$	acetone	50	trace
6[c]	$Cu(CH_3CN)_4PF_6$	$KHCO_3$	acetone	50	40
7[c]	CuI	$KHCO_3$	acetone	50	60
8	CuI	$KHCO_3$	DMF	50	63
9	CuI	$KHCO_3$	acetone : DMF = 4:1[d]	50	68
10	CuI	$KHCO_3$	acetone : DMF = 6:1[d]	50	74
11	CuI	$KHCO_3$	acetone : DMF = 8:1[d]	50	66
12	CuI	$KHCO_3$	acetone : DMF = 6:1[d]	40	82(80[e])
13	CuI	$KHCO_3$	acetone :	R.T	48

			DMF = 6:1 [d]		
14[f]	CuI	$KHCO_3$	acetone : DMF = 6:1 [d]	40	72
15[g]	CuI	$KHCO_3$	Acetone :DMF = 6:1 [d]	40	trace
16	-	$KHCO_3$	acetone : DMF = 6:1 [d]	40	N.P
17	CuI	-	acetone : DMF = 6:1 [d]	40	N.P

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv), **3a** (2.5 equiv), base (2.5 equiv), $BzOO^tBu$ (3.0 equiv), copper catalyst (10 mol %), dtbbpy (15 mol %), acetone (0.6 mL) and DMF (0.1 mL), 40 °C for 12 h. [b]AY = Assay yield, determined by ^1H NMR analysis of the crude reaction mixtures using 0.1 mmol CH_2Br_2 (7.0 μL) as internal standard. [c]**3a** (2.0 equiv), $KHCO_3$ (2.0 equiv), $BzOO^tBu$ (2.0 equiv) and solvent (1.0 mL). [d]Volume ratio. [e]Isolated yield. [f]CuI (5 mol %), dtbbpy (7.5 mol %). [g]Without dtbbpy.

With the optimized conditions in hand, we evaluated the substrate scope of arylboronic acids in the three-component coupling reaction to generate 2,2-diarylethylsulfones. As shown in Table 2, the parent phenylboronic acid gave the product **4aa** in 80% yield. Arylboronic acids with electronegative or electron-withdrawing groups reacted smoothly with **1a** and **2a** to give the target products **4ab**, **4ac**, **4ad** and **4ae** in 56–83% yields. Likewise, *ortho*- and *meta*-substituted phenylboronic acids furnished the products **4af–h** in 57–71% yield. Of note, arylboronic acids possessing aldehyde (**3i**), ketone (**3j**) and ester (**3k**), provided **4ai-k** in 52–88% yields. Heterocycles are important in medicinal chemistry, but often challenging to install.[25] When 2-thiophenyl and 3-thiophenyl boronic acids were employed, **4al** and **4am** were generated from **1a** and **2a** under our standard reaction conditions in 32 and 44% yields, respectively.

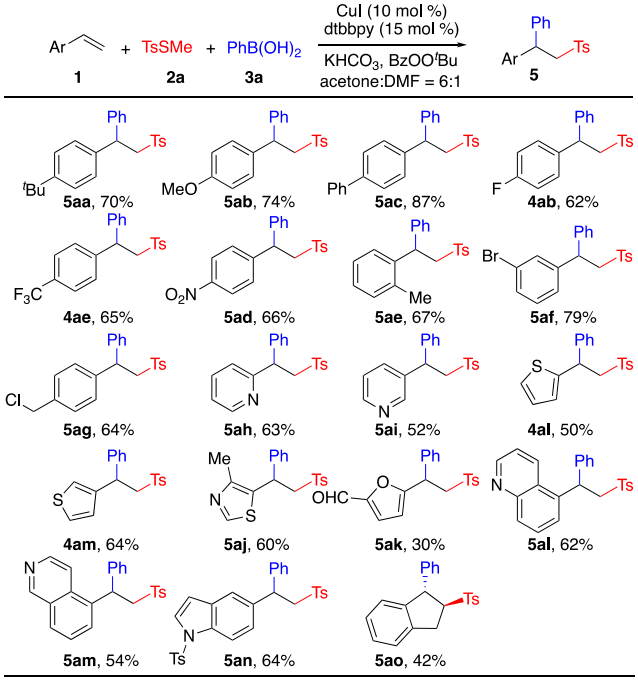
Table 2. Substrate Scope of Arylboronic Acids in the Copper-Catalyzed Difunctionalization with 1a and 2a[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv), **3** (2.5 equiv), $KHCO_3$ (2.5 equiv), $BzOO^tBu$ (3.0 equiv), CuI (10 mol %), dtbbpy (15 mol %), acetone (0.6 mL) and DMF (0.1 mL), 40 °C for 12 h.

We next turned our attention to the substrate scope of styrenes in the three-component difunctionalization with **2a** and **3a**. Overall, this method proved general with respect to the styrenes, providing access to a wide range of 2,2-diarylethylsulfones (Table 3). Styrenes with electron-donating groups, such as *para*-^{t}Bu, -OMe or -Ph were well tolerated, providing **5aa-c** in 70–87% yields. Styrenes bearing electron-withdrawing 4-F, 4-CF_3, and 4-NO_2 (**1e–g**) were good coupling partners, delivering the desired products **4ab**, **4ae** and **5ad** in 62–66% yields. When sterically hindered 2-methyl styrene (**1h**) was utilized as the coupling partner, the corresponding product **5ae** was afforded in 65% yield. In addition, *meta*-bromostyrene (**1i**) exhibited good reactivity generating the expected product **5af** in 79% yield. 1-(Chloromethyl)-4-vinylbenzene is a substrate that would react rapidly with any anionic sulfur-based nucleophiles. This substrate was suitable for the multicomponent reaction, affording **5ag** in 64% yield, leaving the *para*-chloromethyl group for further modification. As noted earlier, heterocycles are important in medicinal chemistry.[25] Our catalytic protocol proved applicable to a variety of heterocyclic styrene derivatives.[2] Pyridyl (**1k**, **1l**), thiophenyl (**1m**, **1n**), furanyl (**1p**), quinolonyl (**1q**), isoquinolonyl (**1r**), and indolyl (**1s**) alkenes furnished the desired 2,2-diarylethylsulfones (**5ah-l**, **4al-m**, and **5aj-n**) in 30–64% yields. The internal styrene derivative, indene (**1t**), was successfully applied to this transformation, delivering the corresponding *trans*-sulfone product **5ao** as a single diastereomer in 42% yield.

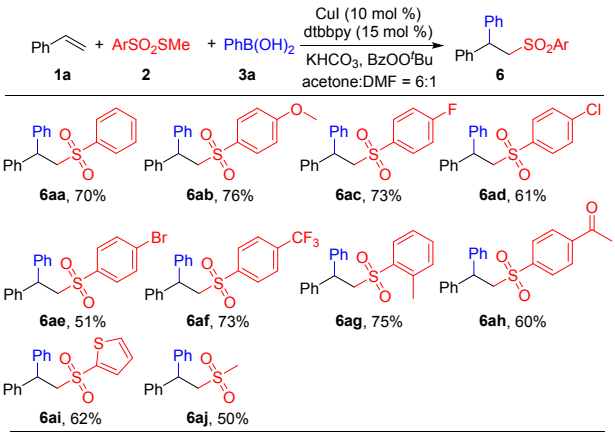
Table 3. Substrate Scope of Styrenes in Copper-Catalyzed Difunctionalization with 2a and 3a[a]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (2.0 equiv), **3a** (2.5 equiv), $KHCO_3$ (2.5 equiv), BzOO^{t}Bu (3.0 equiv), CuI (10 mol %), dtbbpy (15 mol %), acetone (0.6 mL) and DMF (0.1 mL), 40 °C for 12 h.

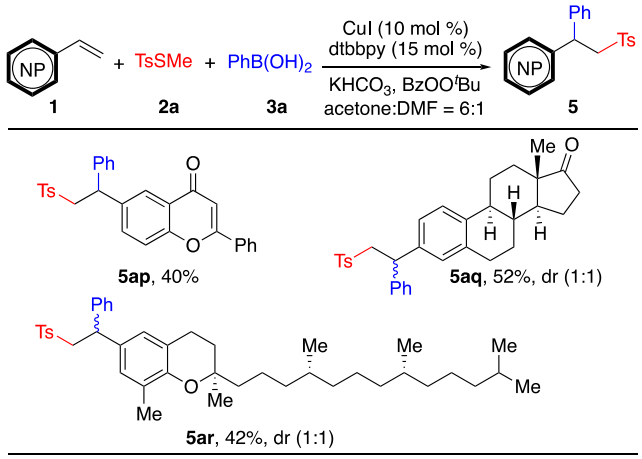
The generality of methyl thiosulfonates in copper-catalyzed difunctionalization with **1a** and **3a** was next investigated (Table 4). The parent 2,2-diphenylethyl phenyl sulfone (**6aa**) was generated in 70% yield. The electron-donating 4-methoxy substituent exerts a negligible effect on the outcome of the transformation, affording **6ab** in 76% yield. Aryl thiosulfonates with electronegative or electron-withdrawing groups, such as 4-F, 4-Cl, 4-Br and 4-CF_3, coupled under the standard conditions, providing **6ac**–**6af** in 51–73% yields. Using sterically demanding 2-methyl thiosulfonate (**2h**) as coupling partner in the difunctionalization led to formation of **6ag** in 75% yield. An acetyl group on the phenyl sulfone (**2i**) was tolerated owing to the mild reaction conditions, furnishing the product **6ah** in 60% yield. 2,2-Diphenylethyl 2-thiophenyl sulfone (**6ai**), a heteroaryl sulfone, was produced in 62% yield. It is noteworthy that methyl thiosulfonate **2j**, an example of an alkyl thiosulfonate, also exhibited good reactivity in the copper-catalyzed difunctionalization with **1a** and **3a**, providing **6aj** in 50% yield under the optimized conditions.

Table 4. Substrate Scope of Thiosulfonates in Copper-Catalyzed Difunctionalization with 1a and 3a[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2** (2.0 equiv), **3a** (2.5 equiv), $KHCO_3$ (2.5 equiv), BzOO^{t}Bu (3.0 equiv), CuI (10 mol %), dtbbpy (15 mol %), acetone (0.6 mL) and DMF (0.1 mL), 40 °C for 12 h.

To explore the potential synthetic utility of our method, late-stage functionalization of bioactive natural products was conducted. Alkenes bearing cromaril, estrone and tocol, three well known bioactive natural products, proceeded smoothly under the optimized reaction conditions to provide **5ap**, **5aq**, and **5ar** in synthetically useful yields (40–52%) (Scheme 2).

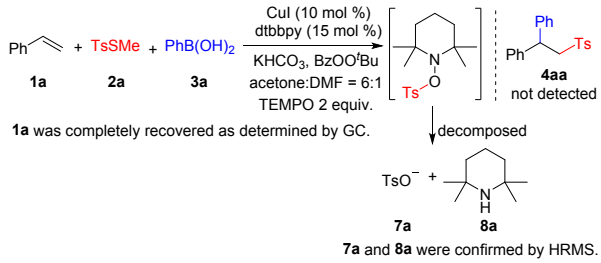


Scheme 2. Late-Stage Functionalization of Natural Products Based on Copper-Catalyzed Difunctionalization of Styrenes with 2a and 3a

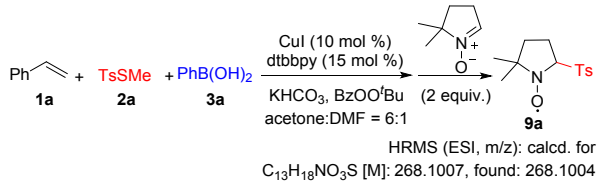
Several experiments to probe the mechanism of this catalytic transformation were performed (Scheme 3). First, when 2 equiv of radical scavenger 2,2,6,6-tetramethylpiperidinyl-1-oxide (TEMPO) was added to the reaction under otherwise standard conditions, the formation of product **4aa** was inhibited and **1a** was recovered in near quantitative assay yield, as determined by GC (Scheme 3a). Both *p*-methyl benzene sulfonate anion (**7a**) and 2,2,6,6-tetramethylpiperidine (**8a**) were detected in the reaction mixture via HRMS analysis (see Scheme S1). Based on these observations, we speculate that TEMPO captured the sulfonyl radical, which was followed by reduction to **7a** and **8a**. These results are consistent with a radical pathway. When 2.0 equiv of the spin trap 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) was added to the model reaction, the formation of **9a** was

confirmed by HRMS (Scheme 3b) and electron paramagnetic resonance spectroscopy (EPR) (Scheme 3c). This result supports the intermediacy of the sulfonyl radical in this process (Scheme 3b). In addition, a series of UV–vis experiments was performed to probe the oxidation states of the copper catalyst (Scheme 3d). When copper(I) iodide was mixed together with dtbbpy ligand, the UV absorption of Cu(I) complex is ca. 431 nm (Scheme 3d). However, the UV band shifted to 703 nm when copper(I) iodide and dtbbpy were mixed together with BzOO^{t}Bu, which is consistent with the d-d transition of Cu(II) species.[26] To verify the existence of Cu(II) species, the solution of CuI, dtbbpy and BzOO^{t}Bu was monitored by EPR, which clearly exhibited signals for a Cu(II) species (see Figure S1 in the SI). When the reaction mixture was monitored by UV, the copper absorption is approximately 684 nm, which was attributed to a Cu(II) species as the catalyst resting state.

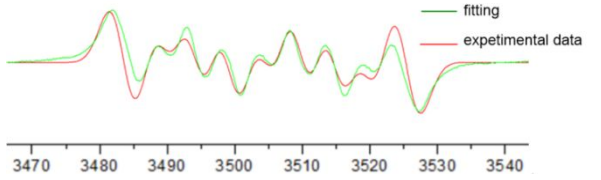
a) Radical trapping experiments with TEMPO



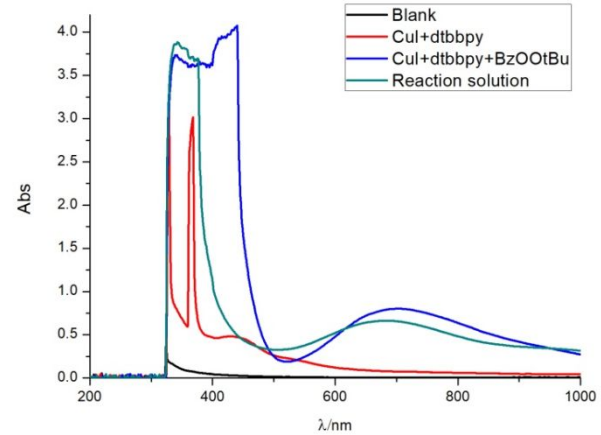
b) EPR studies with DMPO



c) EPR spectra of **9a** (the fitting data and experimental data)



d) UV-Vis spectra studies



Scheme 3. Control Experiments to Probe the Reaction Mechanism

Based on the experimental results above, and related literature reports,[16c] a plausible reaction mechanism is illustrated (Figure 2). CuI binds the ligand dtbbpy to give (dtbbpy)CuI (**A**), which reacts with BzOO^{t}Bu to generate the copper(II) complex **B**, and •OCMe$_3$ (**E**).[27] Then •OCMe$_3$ (**E**) abstracts hydrogen from DMF to generate the formyl radical **F**.[28] A radical relay process between **2a** and the formyl radical **F** affords sulfonyl radical (**G**), and generates the thiocarbamate, which was formed in 72% AY by ^{1}H NMR spectroscopy (and fully characterized, see SI for details). Ts• (**G**) undergoes addition to styrene **1a**, generating the benzyl radical **H**. Meanwhile, the Cu(II) complex **B** reacts with arylboronic acid **3a** via transmetallation to form the aryl copper(II) species **C**, which then undergoes oxidative trapping with the benzylic radical **H** to afford a reactive Cu(III) intermediate **D**.[29] Complex **D** undergoes reductive elimination to furnish **4aa** and regenerate the copper(I) species **A** to close the catalytic cycle. As mentioned earlier, the reaction forming **5ag**, containing a benzylic chloromethyl group, suggests that anionic sulfur species are unlikely to be intermediates in this process. Anionic sulfur compounds undergo rapid S_N2 reactions with benzyl chloride derivatives.

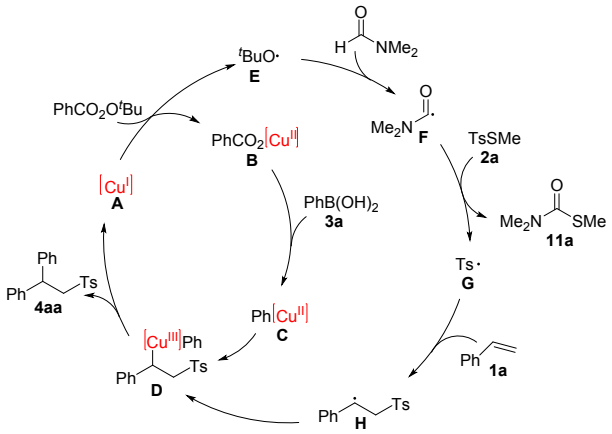


Figure 2. Proposed Mechanism of Copper-Catalyzed Difunctionalization of Styrenes

In summary, a novel copper-catalyzed intermolecular difunctionalization of styrenes with arylboronic acids and methyl thiosulfonates has been developed. A variety of styrenes, methyl thiosulfonates and arylboronic acids were compatible with the catalytic conditions, resulting in rapid access to 2,2-diarylethylsulfone derivatives in a one-pot procedure. Key to success of this three component coupling hinges on the use of methyl thiosulfonates as sulfonyl radical source, which suppress the direct arylation of sulfonyl radical with arylboronic acids when reactions are conducted in acetone/DMF solvent systems. Importantly, owing to mild reaction conditions, our method is suited for the late-stage functionalization of complex natural products. The mechanistic studies point toward a sulfonyl radical initialized radical relay pathway. The development of enantioselective version of the strategy described herein is currently ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Detailed experimental procedures, characterization data, and NMR spectra of new compounds (PDF).

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Notes

The authors declare no competing financial interest.

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