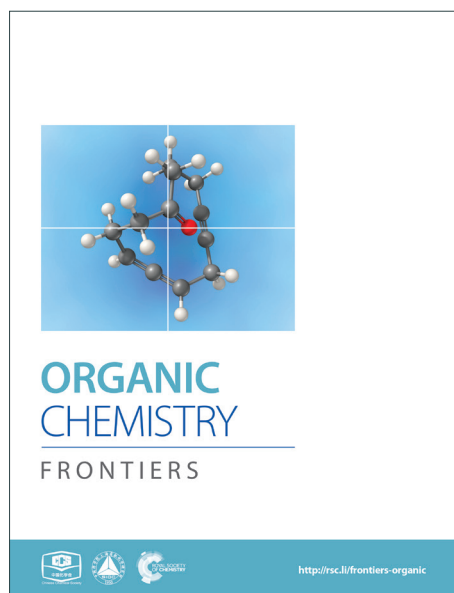
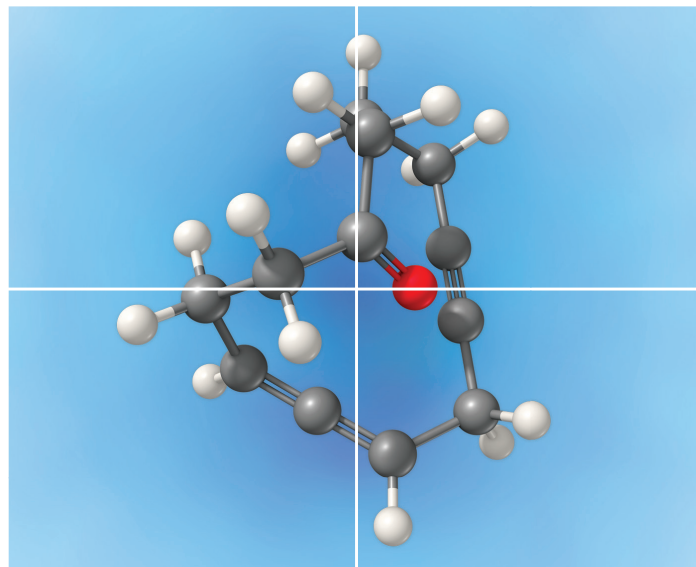


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## Copper-catalyzed direct decarboxylative hydrosulfonylation of aryl propiolic acids with sulfonylhydrazides leading to vinylsulfones

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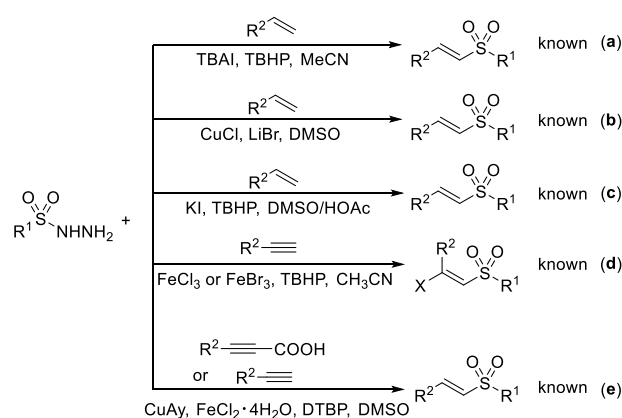
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A simple and facile protocol for copper-catalyzed direct decarboxylative hydrosulfonylation of aryl propiolic acids with sulfonylhydrazides was developed, establishing an attractive approach to (E)-vinylsulfones under base-free conditions. Remarkable features of this reaction include using simple copper catalyst in air and good tolerance aromatic and aliphatic sulfonylhydrazides.

The vinyl sulfone derivatives as versatile building blocks or key structural motifs have wide applications in various organic transformations, pharmaceutical intermediates, biologically active compounds and material sciences.<sup>1</sup> Over the past several decades, various classic synthetic routes to the vinyl sulfone skeleton have been developed such as Knoevenagel condensation,<sup>2</sup> Wittig reaction,<sup>3</sup> and Horner–Emmons reaction,<sup>4</sup> although suffering from the Z/E mixture isomers of vinyl sulfones. To cope with the drawback and limitation, the direct cross-coupling of the sulfonyl derivative (e.g., RSO<sub>2</sub>Cl and RSO<sub>2</sub>NHNH<sub>2</sub>) with an alkene source (e.g., alkene or alkyne) has emerged as robust and reliable tools for the synthesis of vinyl sulfones and drawn much attention within recent years (Scheme 1).<sup>5</sup> Especially, sulfonyl hydrazides are not sensitive to air and moisture, easy to prepare and store, and more importantly, their byproducts: i.e., nitrogen and water, are environmentally benign to nature. Therefore, many research efforts have been devoted to the use of sulfonyl hydrazides as a sulfonyl source.<sup>5a-d</sup> The pioneering work of this type of coupling belongs to Li, who reported the first cross-coupling of 4-methylbenzenesulfonylhydrazide with styrene in MeCN under metal-free conditions in 2012, albeit affording the vinyl sulfone in a relatively low yield (31%) (Scheme 1a).<sup>5a</sup> Subsequently, Jiang et al. described a copper-catalyzed version of styrene with 4-methylbenzenesulfonylhydrazide in DMSO using LiBr as the additive



Scheme 1 Catalytic synthesis of vinylsulfones starting from sulfonylhydrazides.

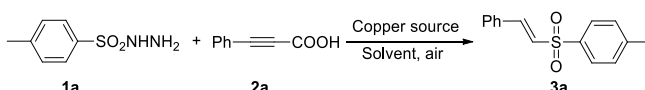
in 2014, and vinyl sulfones could be generated in a high yield (Scheme 1b).<sup>5c</sup> Remarkably, Lei developed another facile and elegant synthesis of vinyl sulfones via the iodine-catalyzed reaction of styrene and 4-methylbenzenesulfonylhydrazide in the absence of any metal catalysts (Scheme 1c).<sup>5d</sup> Moreover, Xu established a simple and efficient approach to vinyl sulfones by iron-catalyzed chlorosulfonylation addition using terminal alkynes as an alternative alkene source (Scheme 1d).<sup>5b</sup>

Aryl propiolic acids are usually solid-state without pungent smell and easy to prepare, store, and transport.<sup>6</sup> Just recently, Mao developed a Cu/Fe co-catalyzed sulfonylation of aromatic propiolic acids with sulfonyl hydrazides using DTBP as an oxidant via a combined decarboxylative and dehydrazine process, which was not suitable for aliphatic sulfonylhydrazides (Scheme 1e).<sup>5e</sup> And our research interest is to demonstrate a simple and environmental synthesis of vinyl sulfones through the copper-catalyzed direct decarboxylative coupling of aryl propiolic acids with sulfonyl hydrazides using environmentally benign oxidant. And we envisioned to develop another reaction pattern of aryl propiolic acids with sulfonylhydrazides, possibly in a different hydrosulfonylation process.

The initial optimization process of decarboxylative coupling of 4-methylbenzenesulfonylhydrazide (**1a**) with phenylpropionic acid (**2a**) was investigated, and the results are displayed in Table 1. After the effect of various copper catalysts was checked, we found that

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† Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

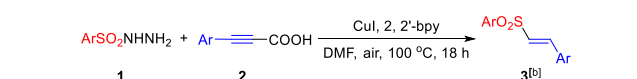
**Table 1** Optimization of the reaction conditions<sup>[a]</sup>


Entry	Catalyst	Solvent	Ligand	Yield <sup>[b]</sup>
1	CuCl	DMF	-	28%
2	CuBr	DMF	-	51%
3	CuI	DMF	-	57%
4 <sup>[c]</sup>	Cu <sub>2</sub> O	DMF	-	25%
5	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	DMF	-	36%
6	CuI	DMSO	-	41%
7	CuI	Dioxane	-	25%
8	CuI	<i>p</i> -xylene	-	21%
9	CuI	DMF	2, 2'-bpy	85%
10	-	DMF	-	< 5%
11 <sup>[d]</sup>	CuI	DMF	2, 2'-bpy	87%
12 <sup>[e]</sup>	CuI	DMF	2, 2'-bpy	64%
13 <sup>[f]</sup>	CuI	DMF	2, 2'-bpy	< 5%

<sup>[a]</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (10 mol%) and base (0.4 mmol) in solvent (1 mL) at 100 °C under air for 18 h. <sup>[b]</sup> Isolated yield. <sup>[c]</sup> Under 5 mol% of Cu<sub>2</sub>O catalyst loading. <sup>[d]</sup> At 120 °C. <sup>[e]</sup> At 80 °C. <sup>[f]</sup> Under a nitrogen atmosphere.

10 mol% of CuI gave the best result, affording the vinylsulfone product in a moderate yield of 57% under air in DMF (Table 1, entry 3); CuCl, CuBr, Cu<sub>2</sub>O and Cu(OAc)<sub>2</sub>·H<sub>2</sub>O also showed catalytic activity, generating the desired product in relatively lower yields of 25–51% (Table 1, entries 1–2, 4–5); other copper species such as CuCl<sub>2</sub>, CuBr<sub>2</sub> and CuF<sub>2</sub>·2H<sub>2</sub>O could not facilitate the reaction (see ESI). Then, other solvents (e.g., DMA, THF, toluene, DMSO, dioxane, and *p*-xylene) were also examined, and among them, the desired product could be obtained in DMSO, dioxane and *p*-xylene in yields of 41%, 25% and 21%, respectively (Table 1, entries 6–8). Moreover, ligand effect played an important role in this hydrosulfonation process, and notably, 2,2'-bpy (2,2'-bipyridine) exhibited excellent activity affording the desired product in a high yield of 85% (Table 1, entry 9). However, other nitrogen ligands such as pyridine, phen (1,10-phenanthroline), DMEDA (N,N'-dimethyl-1,2-ethanediamine) did not showed any catalytic activity (see ESI). Finally, some controlling experiments were also explored. For example, when the reaction was performed under copper-free conditions, we almost did not get the desired product **3a** (Table 1, entry 10). when the reaction temperature was increased to 120 °C or decreased to 80 °C, no much better results were observed and the coupling product were afforded in 87% and 64%, respectively (Table 1, entries 11 and 12). If the reaction was performed under a nitrogen atmosphere instead of air, only a trace of desired product could be received (Table 1, entry 13).

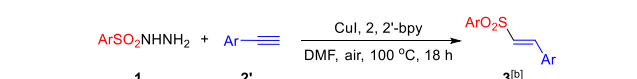
Under the optimized reaction conditions, the substrate scope was then explored and the results are summarized in Tables 2 and 3. Generally, either arylsulfonylhydrazides or alkynes possessing an electron-donating group at the benzene ring would be beneficial for this coupling reaction, while the substrates bearing an electron-withdrawing group at the benzene ring would lead to the coupling products in slightly lower yields. For example, arylsulfonylhydrazides possessing an electron-donating group such as alkyl and alkoxy group would accelerate the reaction process, generating the products in excellent yields (**3a–3c**). The neutral

**Table 2** Decarboxylative hydrosulfonylation of aryl propiolic acids or terminal alkynes with sulfonylhydrazides<sup>[a]</sup>


Entry	Yield <sup>[b]</sup>
<b>3a</b>	85%
<b>3b</b>	78%
<b>3c</b>	90%
<b>3d</b>	76%
<b>3e</b>	67%
<b>3f</b>	51%
<b>3g</b>	57%
<b>3h</b>	67%
<b>3i</b>	43%
<b>3j</b>	36%
<b>3k</b>	65%
<b>3l</b>	72%
<b>3m</b>	89%
<b>3n</b>	73%
<b>3o</b>	55%
<b>3p</b>	60%
<b>3q</b>	45%
<b>3s</b>	55%
<b>3t</b>	64%
<b>3v</b>	55%

<sup>[a]</sup> Reaction conditions: sulfonylhydrazide **1** (0.2 mmol), aryl propiolic acid **2** (10 mol%), 2, 2'-bpy (10 mol%), DMF (1.0 ml) at 100 °C under air for 18 h. <sup>[b]</sup> Isolated yield based on the amount of sulfonylhydrazide.

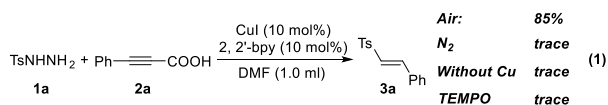
arylsulfonylhydrazides were well tolerated in this reaction, affording the corresponding products in good yields (**3d–3e**).

**Table 3** Decarboxylative hydrosulfonylation of terminal alkynes with sulfonylhydrazides<sup>[a]</sup>


Entry	Yield <sup>[b]</sup>
<b>3a</b>	77%
<b>3b</b>	71%
<b>3c</b>	80%
<b>3d</b>	65%
<b>3g</b>	35%
<b>3j</b>	35%
<b>3m</b>	72%
<b>3r</b>	51%
<b>3s</b>	50%
<b>3t</b>	60%
<b>3u</b>	41%
<b>3v</b>	53%

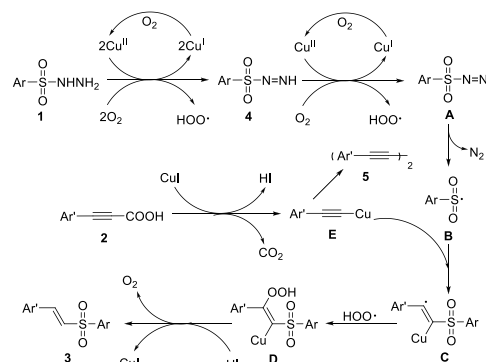
<sup>[a]</sup> Reaction conditions: sulfonylhydrazide **1** (0.2 mmol), terminal alkyne **2'** (0.24 mmol), CuI (10 mol%), 2, 2'-bpy (10 mol%), DMF (1.0 ml) at 100 °C under air for 18 h. <sup>[b]</sup> Isolated yield based on the amount of sulfonylhydrazide.

Various electron-withdrawing groups such as halogen atoms and  $\text{CF}_3$  were also suitable to this process, albeit delivering the corresponding vinylsulfones in relatively lower to moderate yields (**3f-3j**). Similarly, aryl propiolic acids or terminal alkynes bearing an electron-donating groups such as  $n\text{Bu}$ ,  $\text{OBn}$  methoxy and methyl group at the benzene ring also afford the corresponding products in moderate to excellent yields (**3k-3q**). The steric effect played an important role in this reaction, and arylpropionic acid bearing an ortho-methyl or  $\text{OBn}$  group lead to evident decrease of reaction yields (**3o-3q**). Moreover, an alkyne possessing an electron-withdrawing bromo atom could also give the product in a moderate yield of 51% (**3r**). Finally, the reaction of aliphatic sulfonylhydrazides with aryl propiolic acids or terminal alkynes was also performed, and the corresponding vinylsulfone products were obtained in moderate yields (**3s-3v**). The molecular structure of the vinylsulfone product (**3b**) was unambiguously determined by the single crystal X-ray diffraction study.<sup>7</sup>



In order to understand the mechanism of the transformations, a number of controlling experiments were carried out to gain more insights into the mechanism (eq (1)). When the decarboxylative hydrosulfonylation of phenylpropionic acid **2a** with 4-methylbenzenesulfonylhydrazide **1a** was performed under a nitrogen atmosphere instead of under air, only trace amount of desired product **3a** could be observed; when the reaction was performed under copper-free conditions, the reaction could not occur at all, which indicates that the copper species and oxygen are essential to the reaction. The addition of radical scavenger TEMPO could dramatically inhibit the formation of **3a**, demonstrating that a radical process may be involved in this reaction.

On the basis of these experimental results and previous reports, a plausible mechanism for direct decarboxylative hydrosulfonylation of aryl propiolic acids with arylsulfonylhydrazides leading to vinylsulfone is illustrated in Scheme 3. Initially, the  $\text{Cu(I)}$  catalyst was oxidized to  $\text{Cu(II)}$  species in the presence of oxygen in air. The Arylsulfonylhydrazide **1** was oxidized to (arylsulfonyl)diazene **4** by  $\text{Cu(II)}$  species formed in situ and  $\text{O}_2$  to release a hydrogen peroxide radical. In this way, (arylsulfonyl)diazene **4** was further oxidized to an active azo radical intermediate **A**. This oxidation of an arylsulfonylhydrazide **1** into an azo radical **A** proceeds with an assist of a  $\text{Cu(II)}$  species in the air, which is quite different from the Mao and Zhang's version of  $\text{Fe(II)/Cu(II)}$  species in the presence of DTBP.<sup>5e</sup> Then, the intermediate **A** was transferred to a sulfonyl radical **B** with the release of a molecular nitrogen via single electron transfer process. Then, the sulfonyl radical **B** reacted with alkynylcopper(I) intermediate **E** generated from aryl propiolic acid **2** and copper(I) iodide to afford an active intermediate radical **C**. The active intermediate **C** coupled with hydrogen peroxide radical to form the copper (I) intermediate **D**. In the presence of HI, the copper(I) intermediate **D** was decomposed to the vinylsulfone product **3**, along with the regeneration of a molecular oxygen and  $\text{CuI}$  to fulfill the catalytic cycle. Note that the homocoupling of



Scheme 2. Proposed Mechanism.

alkynylcopper(I) intermediate **E** could occur to afford diyne **5** as a byproduct.

In conclusion, we have developed a copper-catalyzed direct decarboxylative hydrosulfonylation of aryl propiolic acids with sulfonylhydrazides, providing a new and convenient route to (E)-vinylsulfone. This reaction features simple catalytic system and good tolerance of substrates including aliphatic sulfonylhydrazides. Moreover, the decarboxylative hydrosulfonylation shows highly regio and stereo-selectivity, generating (E)-vinylsulfone as the only product.

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- 7 CCDC 1059933 (**3b**).† Crystal data for compound **3b**:  
12  $C_{15}H_{14}O_3S$ ,  $M = 274.32$ , Triclinic,  $a = 8.5030(6) \text{ \AA}$ ,  $\alpha =$   
13  $76.750(5)^\circ$ ,  $b = 10.6762(5) \text{ \AA}$ ,  $\beta = 81.107(5)^\circ$ ,  $c = 15.8607(10)$   
14  $\text{ \AA}$ ,  $\gamma = 88.437(5)^\circ$ ,  $V = 1384.60(15) \text{ \AA}^3$ ,  $T = 291.15 \text{ K}$ , space  
15 group =  $P\bar{1}$ ,  $Z = 4$ , number of reflections = 9993, Independent  
16 reflections = 4932,  $[R(\text{int}) = 0.0186]$ , Final  $R$  indices  $[I > 2\sigma(I)]$   
17  $R_1 = 0.0630$ ,  $wR_2 = 0.1737$ ,  $R$  indices (all data)  $R_1 = 0.0743$ ,  
18  $wR_2 = 0.1857$ .