

Copper-catalyzed direct oxysulfonylation of alkenes with dioxygen and sulfonylhydrazides leading to β -ketosulfones†

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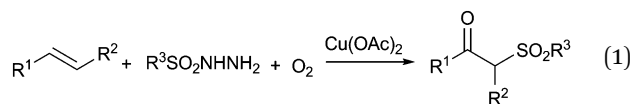
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The first copper-catalyzed oxysulfonylation reaction of alkenes with dioxygen and sulfonylhydrazides for the construction of β -ketosulfones has been developed under mild conditions without any ligand or additive.

Dioxygen is an environmentally benign and cost-effective oxidant and oxygen source in synthetic chemistry. From a “green and sustainable chemistry” perspective, direct oxidative functionalization of organic molecules with dioxygen is one of the most ideal strategies for constructing oxygen-containing compounds.¹ On the other hand, alkenes as versatile and readily available building blocks have been extensively used in organic synthesis. Particularly, transition-metal-catalyzed oxidative difunctionalization of alkenes with dioxygen such as dioxygenation,² amino-oxygenation,³ oxyalkylation,⁴ and oxyphosphorylation⁵ has become a powerful methodology for the construction of oxygenated compounds. Despite some structurally sophisticated products that these methods offer, the development of new protocols for direct oxyfunctionalization of alkenes with dioxygen to access diversely and useful compounds remains highly challenging. Recently, Jiao and co-workers described a catalyst-controlled selective synthesis of alcohols, ketones, and diketones *via* direct oxyfunctionalization of alkenes with dioxygen and arylhydrazides.⁶ Here, we report a novel copper catalyzed direct oxysulfonylation of alkenes with dioxygen and sulfonylhydrazides towards β -ketosulfones, in which C–S and C=O bonds can be formed in a single operation (eqn (1)).



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β -Ketosulfones are an important class of oxygen-containing and extremely versatile compounds in organic chemistry, which strongly attracts synthetic pursuit of chemists due to their interesting biological properties⁷ and widespread synthetic applications for the synthesis of natural products⁸ and various important organic compounds such as disubstituted acetylenes, allenes, vinyl-sulfones, ketones, polyfunctionalized 4*H*-pyrans, and optically active β -hydroxysulfones.⁹ In light of their widespread utilities, considerable efforts have been devoted towards the synthesis of β -ketosulfones. Generally, β -ketosulfones are prepared by the alkylation of metallic arene sulfinates with α -halo-ketones or α -tosyloxy ketones;¹⁰ the acylation of alkyl sulfones with acid chlorides, esters or *N*-acylbenzotriazoles;¹¹ and the oxidation of β -ketosulfides or β -hydroxysulfones with stoichiometric inorganic oxidants.¹² Alternative methods such as the reaction of diazo sulfones with aldehydes,¹³ IBX/I₂-mediated reaction of sodium arenesulfinates with alkenes,¹⁴ and the reaction of sulfonyl chlorides with arylacetylenes¹⁵ have also been developed. However, most of them suffer from some limitations such as the need for multistep processes to prepare starting materials, relatively complicated or harsh reaction conditions, and undesired byproducts. Therefore, there is still a great demand for the development of more mild, convenient and, especially, green and sustainable approaches to produce β -ketosulfones.

Very recently, Lei *et al.* reported an aerobic oxidative difunctionalization of alkynes towards β -ketosulfones in the presence of 4 equiv. pyridine.¹⁶ However, when alkenes were employed as the precursors under similar reaction conditions, the only products obtained are β -hydroxysulfones.¹⁷ The present method of copper-catalyzed oxysulfonylation of alkenes to β -ketosulfones can be conveniently and efficiently realized under mild and environmentally benign conditions without any ligand or additive, in which the side-products are water and nitrogen.

Initially, under an oxygen atmosphere, styrene **1a** and phenyl-sulfonohydrazide **2a** were chosen as model substrates to optimize the reaction conditions. The oxysulfonylation reaction was very sluggish in the absence of catalyst in EtOH (Table 1, entry 1). Furthermore, various metal catalysts such as Pd, Fe, Ag, Ru, Co, Zn, In, and Cu salts were investigated to improve the reaction efficiency (Table 1, entries 2–8 and ESI.†). Among the above

Table 1 Oxysulfonation of alkene to give β -ketosulfones under various conditions^a

Entry	Catalyst	Solvent	Yield ^b (%)
1	—	EtOH	25
2	CuI	EtOH	60
3	CuBr ₂	EtOH	64
4	CuBr	EtOH	58
5	CuCl	EtOH	59
6	CuCl ₂	EtOH	60
7	Cu(OTf) ₂	EtOH	56
8	Cu(OAc)₂	EtOH	70
9	Cu(OAc) ₂	CH ₃ OH (reflux)	62
10	Cu(OAc) ₂	^t BuOH	64
11	Cu(OAc) ₂	DMSO	28
12	Cu(OAc) ₂	DMF	41
13	Cu(OAc) ₂	CH ₃ CN	32
14	Cu(OAc) ₂	H ₂ O	0
15	Cu(OAc) ₂ /Et ₃ N	EtOH	48 ^c
16	Cu(OAc) ₂ /pyridine	EtOH	59 ^c
17	Cu(OAc) ₂ /PPh ₃	EtOH	60 ^d
18	Cu(OAc) ₂ /1,10-phenanthroline	EtOH	70 ^d
19	Cu(OAc) ₂ , air	EtOH	57 ^e
20	Cu(OAc) ₂ , N ₂	EtOH	0 ^f

^a Reaction conditions: **1a** (0.75 mmol), **2a** (0.5 mmol), catalyst (5 mol%), solvent (3 mL), 70 °C, O₂ (balloon), 20 h. ^b Isolated yields based on **2a**. ^c Bases (0.5 mmol). ^d Ligand (20 mol%). ^e Under air. ^f Under N₂.

metal salts examined, copper salts especially Cu(OAc)₂ was found to be the most effective catalyst to give product **3aa** in 70% yield (Table 1, entry 8). The screening of a range of solvents showed that EtOH was the optimal reaction medium (Table 1, entries 8–14). The addition of bases or ligands did not improve the reaction efficiency (Table 1, entries 15–18). Notably, the target product could also be obtained in 57% yield even under an air atmosphere (Table 1, entry 19). No desired product was observed in the absence of O₂, confirming the necessity of dioxygen for this oxysulfonation reaction (Table 1, entry 20).

Under the optimized conditions, the scope and limitations of this new reaction were investigated and some results are summarized in Table 2. Generally, reactions of aromatic alkenes containing electron-donating or electron-withdrawing groups with phenylsulfonohydrazide proceeded efficiently and provided the corresponding products in moderate to good yields. A wide range of functionalities such as halogen, cyano, and chloromethyl groups were compatible with this reaction leading to the products **3fa–3ja**, which could be used for further transformations. 2-Vinylnaphthalene was also tolerated to afford the product **3ka** in 53% yield. Notably, an internal aromatic alkene such as (*E*)-prop-1-enylbenzene could also be used in the reaction to give the expected β -ketosulfone **3la** in 61% yield. Nevertheless, when an aliphatic alkene such as 1-octene and an activated alkene such as ethyl acrylate were used as the substrates, none of the desired products were obtained. With respect to sulfonohydrazides, in addition to **2a**, various arylsulfonohydrazides bearing both electron-donating groups (R = Me, OMe) and electron-withdrawing groups (R = F, Cl, Br) could also be smoothly transformed to the corresponding β -ketosulfones (**3ab–3af**) in moderate to good yields.

In order to elucidate the origin of the carbonyl oxygen atom of β -ketosulfones, ¹⁸O labeling experiments were performed.

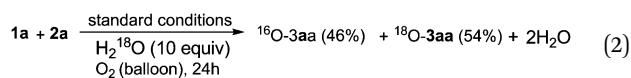
Table 2 Results for the reaction of the oxysulfonation of alkenes^{a,b}

1	2	3

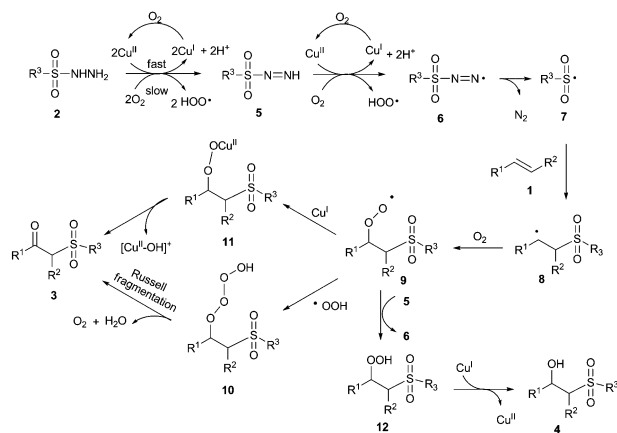
^a Reaction conditions: **1** (0.75 mmol), **2** (0.5 mmol), Cu(OAc)₂ (5 mol%), EtOH (3 mL), O₂ (balloon), 20 h. ^b Isolated yields based on **2**.

The present reaction would generate 2 equiv. H₂O under standard conditions. It is not clear, however, whether O-incorporation of the product results from O₂ or H₂O (formed during the reaction). Therefore, the isotope labeling experiments using O₂/H₂¹⁸O (10 equiv.) and ¹⁸O₂/H₂O (10 equiv.) were conducted. Initially, it was thought that the carbonyl group of ketones possibly undergoes exchange of the oxygen atom with water *via* the hydrate in the presence of Lewis- or Brønsted-acids.¹⁸ Indeed, when ¹⁶O-**3aa** was stirred with Cu(OAc)₂ in the presence of H₂¹⁸O (10 equiv.) under the standard conditions for 20 h, 50% ¹⁸O-labeled **3aa** was observed (HRMS; see ESI[†]).

When the reaction of **1a** with **2a** was performed in the presence of H₂¹⁸O (10 equiv.) under the standard conditions for 20 h, 54% ¹⁸O-**3aa** and 46% ¹⁶O-**3aa** products were detected (eqn (2), HRMS, see ESI[†]). If the carbonyl oxygen atom of β -ketosulfones originates from H₂¹⁸O, about 83% ¹⁸O-**3aa** should be obtained theoretically, since the quantity of H₂¹⁸O is at least five times that of H₂O (formed during the reaction). However, the experimental results demonstrated that 46% ¹⁶O-**3aa** and 54% ¹⁸O-**3aa** were obtained in the present reaction system. The combination of this result and oxygen scrambling experiments revealed that the carbonyl oxygen atom of β -ketosulfones originated from O₂. The existence of 54% ¹⁸O-**3aa** could be explained by the oxygen scrambling reaction between the ¹⁶O-**3aa** and H₂¹⁸O.

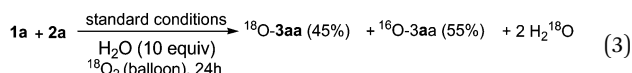


Further control experiments showed that 45% ¹⁸O-**3aa** and 55% ¹⁶O-**3aa** were detected when the reaction of **1a** with **2a** was

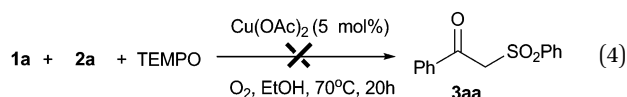


Scheme 1 Postulated reaction pathway.

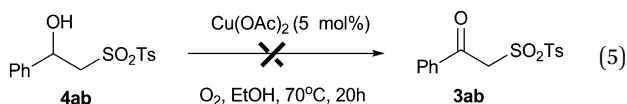
performed in the presence of H₂O (10 equiv.) under ¹⁸O₂ (eqn (3), HRMS, see ESI[†]). The combination of this result and oxygen scrambling experiments also clearly indicated that the carbonyl oxygen atom of the β-ketosulfones originated from dioxygen.



It is known that radical species are formed from hydrazide compounds *via* the generation of diazenes in the presence of transition metals or dioxygen.¹⁹ Therefore, a radical pathway was also supposed to be involved in this reaction. Radical trapping experiments supported this assumption. As shown in eqn (4), when TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, a well known radical-capturing species) was added to the reaction system, the oxysulfonylation reaction was completely suppressed, indicating that this reaction presumably involves a radical process.



Furthermore, β-hydroxysulfone **4ab** could be isolated from the reaction system of **1a** with *p*-toluenesulfonylhydrazide **2b**. However, the desired product **3ab** was not obtained when **4ab** was treated under the standard conditions (eqn (5)), suggesting that **4ab** might not be an intermediate in this reaction.



Based on the above experiments and previous reports especially the recent work of Jiao,^{6,19–21} a postulated reaction pathway is described in Scheme 1. Initially, the sulfonyl radical **7** and [•]OOH species were generated from **2** and dioxygen with the release of N₂ *via* single electron transfer and the deprotonation process.^{6,19} The transformations occurred faster when high-oxidation-value metal salts such as Cu^{II} species were employed.⁶ Then, the sulfonyl radical **7** selectively added to alkene **1** leading to alkyl radical **8**, which interacted with O₂ to afford peroxy radical **9**. Finally, **9** coupled with the [•]OOH species to form a monoalkyl tetroxide **10**, which decomposed to give the product **3**,

along with the generation of dioxygen and water *via* Russell fragmentation.^{6,20} In contrast, product **3** was also formed *via* intermediate **11** followed by the elimination of [Cu^{II}-OH]⁺ due to the low concentration of the hydroperoxide radical in the Cu-catalytic system.^{6,21} The side product **4** might be produced by the reduction of the hydroperoxide **12**, which was generated from **9** *via* the abstraction of a H atom from the strong H-donor **5**.⁶

In conclusion, we have developed an unprecedented copper-catalyzed direct oxysulfonylation of alkenes with dioxygen and sulfonylhydrazides to access β-ketosulfones. Isotope labeling and radical capture experiments suggested that the carbonyl oxygen atom of β-ketosulfones originated from O₂ and a radical pathway might be involved. Taking into account the following desirable features, such as operation simplicity, cheap catalysts, readily-available materials, as well as mild and environmentally benign conditions, this novel catalytic system provides a highly attractive approach to produce β-ketosulfones. Studies of the detailed mechanism of this process and its application are underway.

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