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Regio- and Stereoselective Oxysulfonylation of Allenes

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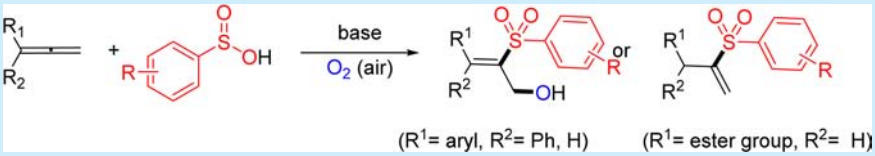
Supporting Information



ABSTRACT: A highly regio- and stereoselective oxysulfonylation of allenes was developed that provided direct access to 2-sulfonyl allylic alcohols in good yields. By means of dioxygen activation, selective difunctionlization of allenes could be successfully achieved under mild metal-free conditions. Preliminary mechanistic investigation disclosed that this transformation probably goes through a radical process.

Allenes, which contain the interesting and special functional groups of two cumulative carbon−carbon double bonds, have been widely used in the synthesis of complicated natural products[1] as well as pharmacologically active compounds.[2] However, due to the diverse possibilities of reactive sites in allenes, challenges still remain in controlling the reaction selectivity.[3] In 2014, two research groups, Ma[4] and Kanai,[5] independently used TEMPO as an oxygen source to build the C−O bond when allenes were used as substrates. In 2015, Liu's group[6] also reported a copper-catalyzed trifluoromethylazidation and trifluoromethylthiocyanation of allenes. However, highly regio- and stereoselective oxysulfonylation of allenes has not yet been achieved.

Radicals exist widely in nature, and radical reactions have also been proven to be powerful tools in modern organic synthesis.[7] Although radical reactions have been fully developed and widely utilized in various organic synthesis for a quite long time, challenges still remain in this area. Among them, appropriate radical initiators and good reaction selectivity might be the key aspects. However, toxic transition metals were often used as radical initiators or oxidants in these reactions, thus making these transformations not environmentally friendly. On the other hand, molecular oxygen, which could be easily photosynthesized by green plants, exists widely in nature. Among those molecular oxygen involved organic transformations, dioxygen activation has now been extensively studied for its high reactivity and amity to the environment.[8] Therefore, introducing dioxygen activation into selective oxysulfonylation of allenes would be quite charming and significant, which will also broaden the scope of allene chemistry. Herein, we report a highly regio- and stereoselective oxysulfonylation of allenes through dioxygen activation under mild metal-free conditions. Basically, as a green oxidizer, dioxygen bears evident advantages over toxic metal salts and complex organic reagents for its sustainability and atom efficiency. On the other hand, primary alcohols were generated in this transformation. Notably, it is quite uncommon in similar dioxygen-involved reactions, in which aldehydes or ketones were usually the dominant products.[9]

Our study was initiated with the reaction between phenylallene (**1a**) and benzenesulfinic acid (**2a**) as the starting materials with DCE (1,2-dichloroethane) as the solvent at room temperature. As a result, complex product mixtures were generated presumably due to the high reactivity of the substrates. Based on our previous finding that base could help eliminate byproducts,[10] pyridine was added into this reaction system. Notably, oxysulfonylation product **3aa** was predominantly formed with high selectivity. Furthermore, single X-ray diffraction measurement of the acylated product confirmed the accurate product structure (Scheme 1).[11]

Afterward, the influence of different kinds of bases to the reaction was investigated thoroughly. As seen in Table 1, base played a crucial role in terms of selectivity and chemical yield (Table 1, entry 1 vs entries 2−6), among which pyridine demonstrated the best reactivity (Table 1, entry 6). Increasing or decreasing the amount of pyridine (Table 1, entries 7 and 8) afforded slightly decreased yields. Screening the solvent for the reaction conditions, DCE was found to be the best, which might be explained partly by the solubility of the reactants in different solvents (see Table S1). Due to the auto-oxidation and disproportionation of benzenesulfinic acid itself,[12] reactant **2a** is usually used with excess amount. Therefore, the ratio of **1a**/**2a** was also tested. Initially, a ratio of **1a**/**2a** 1:5 was employed. When the ratio decreased to 1:4, a slightly decreased yield of 59% was obtained (Table 1, entry 9), suggesting that

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Scheme 1. Single-Crystal X-ray Structure of the Acylated Product

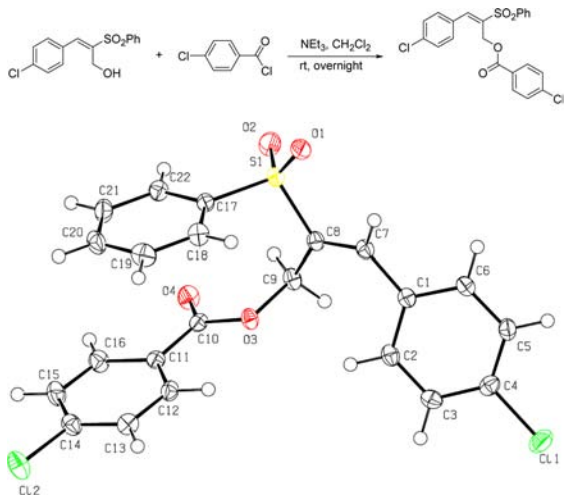
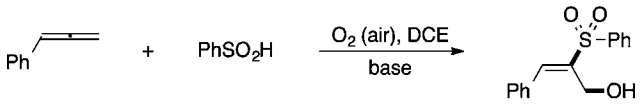


Table 1. Survey of the Reaction Conditions[a]



1a **2a** **3aa**

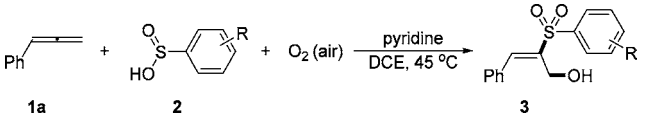
entry	base	ratio (**1a**:**2a**)	temp (°C)	yield[b] (%)
1		1:5	45	complex
2	Et_3N	1:5	45	76
3	DBU	1:5	45	20
4	Et_2NH	1:5	45	50
5	LiOH	1:5	45	32
6	pyridine	1:5	45	79
7	pyridine	1:5	45	71[c]
8	pyridine	1:5	45	60[d]
9	pyridine	1:4	45	59[e]
10	pyridine	1:5	rt	50
11	pyridine	1:5	60	20
12	pyridine	1:5	45	complex[f]
13	pyridine	1:5	45	trace[g]

[a]Unless otherwise specified, all reactions were carried out using **1a** (0.2 mmol), **2a** (1.0 mmol), and base (0.7 mmol) in DCE (4.0 mL) at 45 °C for 1.5 h under 1 atm of air (balloon). [b]Yield of isolated product. [c]Pyridine (0.6 mmol). [d]Pyridine (0.8 mmol). [e]Pyridine (0.56 mmol). [f]Under O_2. [g]Under N_2.

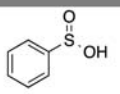
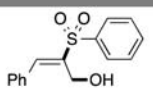
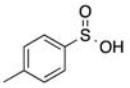
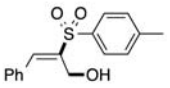
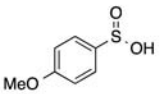
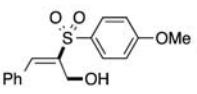
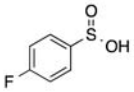
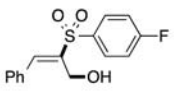
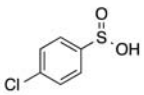
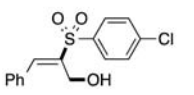
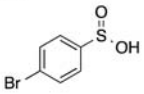
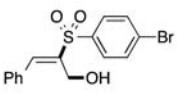
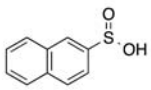
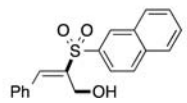
benzenesulfinic acid might also act as a reductant more than a reactant during the reaction. Moreover, the concentration of dioxygen had a great influence on the reaction. When the reaction was carried out under dioxygen atmosphere instead of air, it turned generated a complex product mixture (Table 1, entry 12), while only a trace amount of product was obtained when the reaction was under nitrogen atmosphere (Table 1, entry 13). In addition, both an increase and a decrease of reaction temperature resulted in poor yields (Table 1, entries 10 and 11). Therefore, the best reaction conditions were determined to be 0.2 mmol of **1a**, 1.0 mmol of **2a**, and 0.7 mmol of pyridine in DCE at 45 °C for 1.5 h under air atmosphere.

With the best reaction conditions in hand, we then explored the substrate scope. Notably, arylsulfinic acid derivatives with different substituents at the 4-position of the phenyl ring could react smoothly with **1a** to afford the desired products in moderate to good yields (Table 2). Generally, electron-neutral

Table 2. Substrate Scope of the Reaction[a]



1a **2** **3**

entry	2a	3	yield (%)[b]
1		 (**3aa**)	79
2		 (**3ab**)	80
3		 (**3ac**)	74
4		 (**3ad**)	57
5		 (**3ae**)	63
6		 (**3af**)	49(63[c])
7		 (**3ag**)	79

[a]Unless otherwise specified, all reactions were carried out using **1a** (0.2 mmol), **2** (1.0 mmol), and pyridine (0.7 mmol) in DCE (4.0 mL) at 45 °C for 1.5 h under 1 atm of air (balloon). [b]Yield of isolated product. [c]65 °C.

and electron-rich arylsulfinic acids demonstrated better reactivity over electron-poor arylsulfinic acids in terms of chemical yields (Table 2, entries 1–3 vs entries 4–6). On the other hand, arylsulfinic acids with halogen substituents such as F, Cl, and Br could be well tolerated in this reaction (Table 2, entries 4–6), which allows for more diverse transformations of these types of products. For bromo-substituted benzenesulfinic acid, only 49% yield of the corresponding product was obtained after the reaction, which could be further increased to 63% with an elevated temperature (Table 2, entry 6). Additionally, naphthalene-2-sulfinic acid also proved to be an excellent reaction partner with **1a**, generating the desired product in 79% yield (Table 2, entry 7).

Next, various allenes were also examined under the optimized conditions, and the results are listed in Table 3. Typical functional groups, such as alkyl, alkoxy, fluoro, chloro, and bromo moieties, were well tolerated under the optimized conditions, affording the corresponding products in moderate to good yields (Table 3, entries 1–6). Notably, when 1,1-phenyl-substituted allene (Table 3, entry 7) was introduced into this reaction, a diverse tetrasubstituted alkene could be obtained in one step. In addition, besides aryl-substituted allenes, ester group substituted allenes could also survive under

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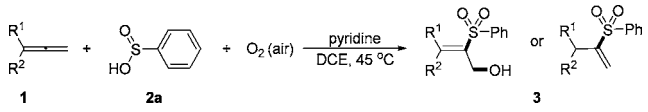
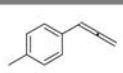
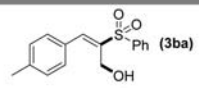
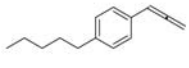
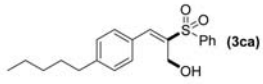
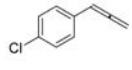
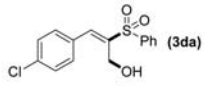
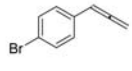
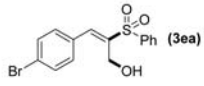
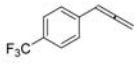
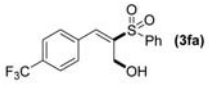
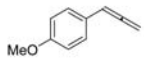
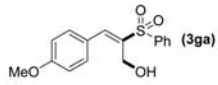
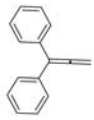
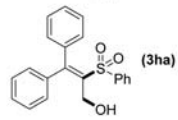
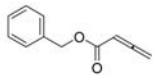
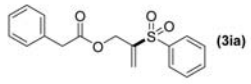
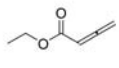
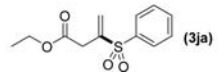
Table 3. Substrate Scope of the Reaction[a]



1 2a 3

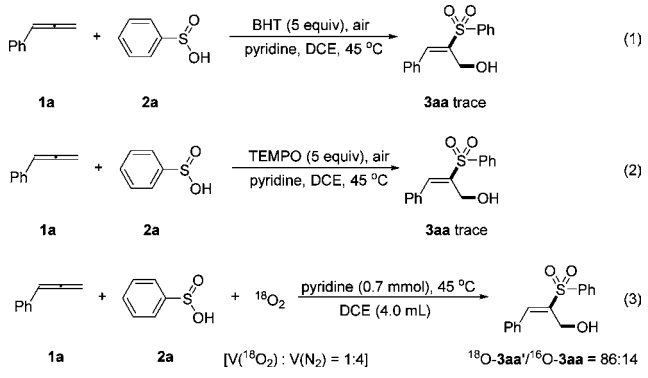
entry	2a	3	yield (%)[b]
1		 (3ba)	65
2		 (3ca)	72[c]
3		 (3da)	82[c]
4		 (3ea)	85
5		 (3fa)	45
6		 (3ga)	50
7		 (3ha)	21
8		 (3ia)	23
9		 (3ja)	34

[a]Unless otherwise specified, all reactions were carried out using **1** (0.2 mmol), **2a** (1.0 mmol), and pyridine (0.7 mmol) in DCE (4.0 mL) at 45 °C for 1.5 h under 1 atm of air (balloon). [b]Yield of isolated product. [c]Reaction time: 2 h.

the standard conditions, in which terminal alkene products were generated instead (Table 3, entries 8 and 9).

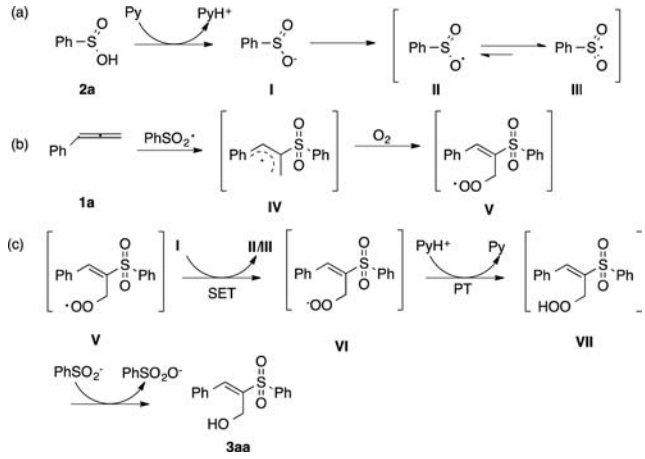
In order to gain insights into the reaction mechanism, radical-trapping experiments were first conducted to elucidate the reaction type (Scheme 2). BHT (2,6-di-*tert*-butyl-4-methylphenol) was employed under the standard reaction conditions. The desired reaction was completely inhibited (eq 1). When TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was used as a radical-trapping agent, the same result was achieved (eq 2). These two results indicated that this transformation is likely to involve a radical process. Afterward, an ^{18}O isotope labeling experiment was carried out (eq 3). The reaction between **1a** and **2a** under $^{18}O_2$ afforded the ^{18}O-labeled product **3aa′** in 86% isotopic purity. Further $H_2{}^{18}O$ labeling experiments supported this result (see the SI for more details). These results demonstrated that O_2 took part into this reaction and was transformed into the final product.

Scheme 2. Radical-Trapping Experiments and $^{18}O_2$ Isotope-Labeling Experiment



Although the detailed mechanism remains to be elucidated, a tentative reaction mechanism was proposed (Scheme 3).

Scheme 3. Proposed Mechanism



Initially, benzenesulfinic acid was quickly transformed into sulfonyl anion **I** in the presence of pyridine. Subsequently, the pathway was triggered by the autoxidation of **I** with dioxygen via a single-electron-transfer (SET) process, affording an oxygen-centered radical **II** which could resonate with sulfonyl radical **III**. Thereafter, the addition of sulfonyl radical to allene produced the reactive allyl radical **IV**, which could be trapped by dioxygen under the present conditions and formed intermediate **V**. Afterward, the intermediate **V** went through the SET and PT process successively with **I** and pyridinium, generating **II**/**III** and affording peroxide **VII**. Finally, **VII** underwent subsequent reduction by benzenesulfinic acid and generated **3aa**.

In conclusion, we have developed a unique approach for the highly selective oxysulfonylation of allenes under metal-free conditions, providing a direct access to allylic alcohols with satisfactory yields. Different kinds of arylsulfinic acids and allenes could be well tolerated. Preliminary mechanistic studies disclosed that a radical process was probably involved in this transformation. Isotopic labeling experiment demonstrated that O_2 was activated and transformed into the final product. Ongoing research including further mechanistic details and application of this reaction is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01575.

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Experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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