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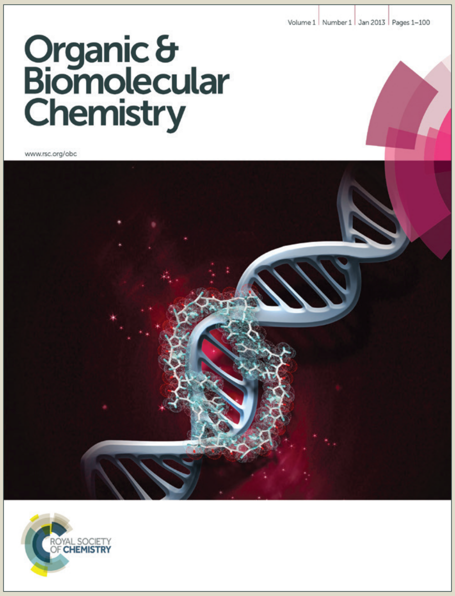

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ARTICLE TYPE

Iron-catalyzed direct difunctionalization of alkenes with dioxygen and sulfinic acids: a highly efficient and green approach to β-ketosulfones†

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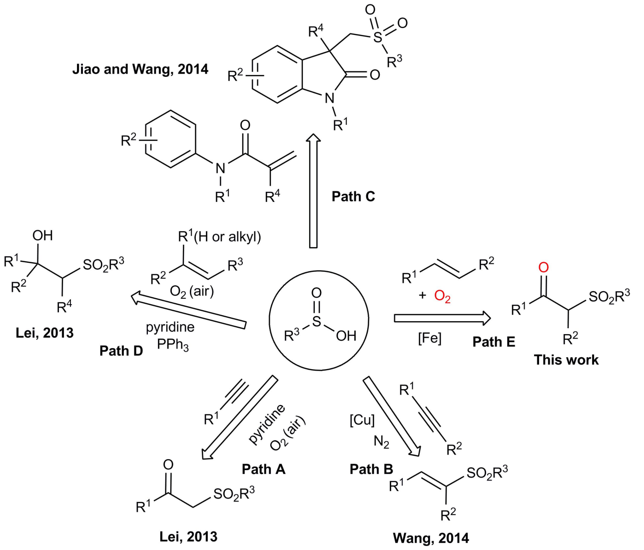
A novel iron-catalyzed direct difunctionalization of alkenes with sulfinic acids and dioxygen for the synthesis of β-ketosulfones has been developed under mild conditions. The present protocol, which utilizes inexpensive iron salt as the catalyst, readily available benzenesulfinic acids as the sulfonylating reagents, and dioxygen as the oxidant and oxygen source, provides a cost-effective and environmentally benign approach to access various β-ketosulfones.

As an important class of biological molecules, sulfone-containing organic compounds are widely used in the organic synthesis, materials, and pharmaceuticals.[1] The introduction of sulfone functionality into organic frameworks via C-S bond formation has thereby drawn great attentions of chemists in view of their important biological properties and widespread synthetic applications.[2] In the past few decades, various functionalized sulfonyl precursors such as sulfonyl halides,[3] sulfonyl selenides,[4] sulfonyl cyanides,[5] sulfonylazides,[6] sulfonyl hydrazides,[7] thiophenols,[8] sulfinates[9] and dimethyl sulfoxide[10] have emerged for the synthesis of organic sulfone compounds. Nevertheless, most sulfonylation reactions usually suffer from low atom-efficiency, relatively complex reaction conditions, stoichiometric amount of oxidants such as TBHP, H_2O_2, $K_2S_2O_8$, copper(II), manganese(III) and cerium(IV) salts, and undesired side-products.[3-9] The development of convenient, efficient, atom-economic, and, especially, environmentally-benign methods using simple sulfonylating agents to access sulfone-containing compounds still remains a highly desirable but challenging task in the modern organic chemistry.

Recently, sulfinic acids as simple, stable and readily available solid sulfonylating source have been empolyed for constructing sulfone-containing compounds via functionation of alkynes or alkenes with high atom-efficiency.[11-15] In 2013, Lei and co-workers reported an elegant work for the aerobic oxidaitve synthesis of β-ketosulfones from alkynes and sulfinic acids in the presence of pyridine (Scheme 1, Path A).[11] Copper-catalyzed direct hydrosulfonylation of alkynes with arylsulfinic acids was achieved in our group for the construction of (*E*)-vinyl sulfones with a high atom economy [12] (Scheme 1, path B). Very recently, Jiao et al[13] and our group[14] presented independently the arylsulfonylation of activated alkenes with sulfinic acids to access sulfonated oxindoles (Scheme 1, path C). Also, Lei's group[15] reported a aerobic oxysulfonylation of alkenes with arylsulfinic acids leading to β-hydroxysulfones in the presence of stoichiometric amounts of pyridine and PPh_3 (Scheme 1, path D). To the best of our knowledge, however, there is no example describing the direct aerobic oxidative difunctionalization of alkenes catalyzed by eco-friendly iron salt using sulfinic acids as sulfonylating reagents to access β-ketosulfones, the key structural motifs of many natural products, biological active molecules, clinical pharmaceuticals and synthetic intermediates.[16]



Scheme 1. Methods for the synthesis of sulfone-containing compounds from sulfinic acids.

With continuous efforts to the copper-catalyzed synthesis of sulfone-containing organic compounds,[12,17] here, we report alternatively a more atom-economic and highly efficient iron-catalyzed direct oxysulfonylation of alkenes with sulfinic acids towards β-ketosulfones via cascade C–S and C=O bond formation simply by using dioxgyen as the oxidant and oxygen source (Scheme 1, path E). The present synthesis methodology provides a desirably convenient and green approach to a diverse range of β-ketosulfones in moderate to excellent yields with high-atom efficiency and the sole byproduct of water.

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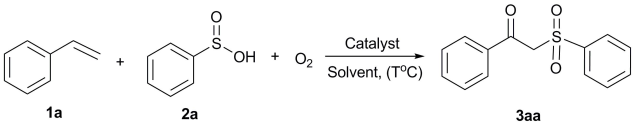
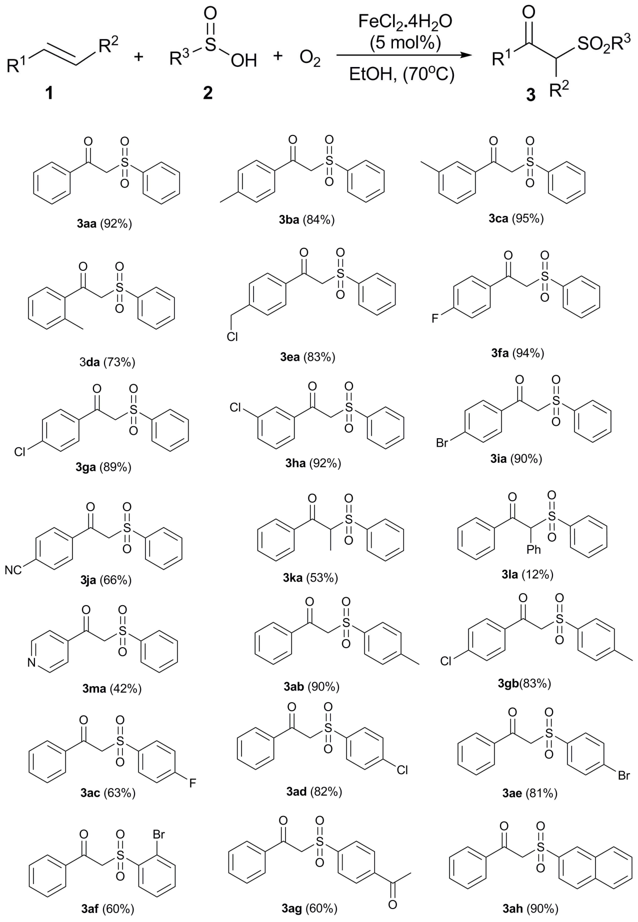
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Yield (%)[b]
1	$Cu(OAc)_2$	EtOH	47
2	CuBr	EtOH	41
3	$CuBr_2$	EtOH	47
4	$CuCl_2$	EtOH	53
5	CuI	EtOH	61
6	$Cu(OTf)_2$	EtOH	49
7	$Fe(NO_3)_3$	EtOH	41
8	$Fe(acac)_2$	EtOH	60
9	$FeSO_4$	EtOH	72
10	$FeBr_3$	EtOH	77
11	$\mathbf{FeCl_2\cdot 4H_2O}$	**EtOH**	**92**
12	$FeCl_2\cdot 4H_2O$	MeOH	67
13	$FeCl_2\cdot 4H_2O$	1,4-dioxane	trace
14	$FeCl_2\cdot 4H_2O$	THF	87
15	$FeCl_2\cdot 4H_2O$	DME	59
16	$FeCl_2\cdot 4H_2O$	DMSO	61
17	$FeCl_2\cdot 4H_2O$	DMF	35
18	$FeCl_2\cdot 4H_2O$	CH_3CN	50
19	$FeCl_2\cdot 4H_2O$	Toluene	33
20	$FeCl_2\cdot 4H_2O$	H_2O	36
21	$FeCl_2\cdot 4H_2O$	EtOH	47[c]
22	$FeCl_2\cdot 4H_2O$	EtOH	54[d]
23	$FeCl_2\cdot 4H_2O$	EtOH	88[e]
24	--	EtOH	42
25	$FeCl_2\cdot 4H_2O$	EtOH	trace[f]

[a] Reaction conditions: **1a** (0. 5 mmol), **2a** (1 mmol), catalyst (5 mol %), solvent (2 mL), O_2 (balloon), 16. [b] Isolated yields based on **1a**. [c] catalyst (1 mol %). [d] catalyst (2 mol %). [e] catalyst (10 mol %). [f] N_2.

Table 2 Results for iron-catalyzed difunctionalization of alkenes with dioxygen and sulfinic acids[ab.]

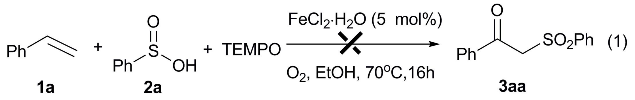


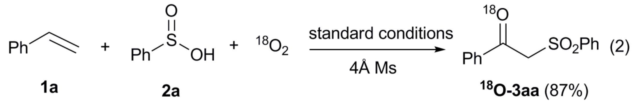
[a] Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), $FeCl_2\cdot 4H_2O$ (5 mol %), EtOH (2 mL), 16-24 h, O_2 (balloon). [b] Isolated yields based on **1**.

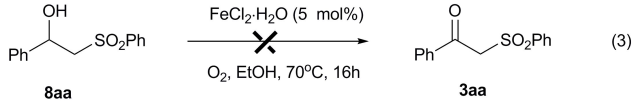
For purpose of comparison to the copper-catalyzed oxysulfonylation of alkenes with sulfonylhydrazides,[16] initially, the reactions of styrene **1a** and benzenesulfinic acid **2a** catalyzed by various Cu salts (5 mol%) were performed in EtOH at 70°C under dioxygen. Low to moderate yields were obtained for the desired products (Table 1, entries 1-6). Instead, iron salts were introduced as the catalysts into these reactions. To our delight, significantly improved reaction efficiencies were obtained, and $FeCl_2\cdot 4H_2O$ was found to be the best catalyst to afford the desired product **3aa** in 92% yield (Table 1, entries 7-11). Furthermore, a range of reaction solvents were screened, with EtOH being the superior for the formation of product **3aa** (Table 1, entries 12-20). The effects of catalyst loadings were also examined and 5 mol% of catalyst was found to the best choice (Table 1, entries 21-23). Notably, the desired product could be obtained in 42% yield when the reaction was conducted in the absence of catalyst (Table 1, entry 24). In contrast, only a trace amount of **3aa** was detected when the reaction occurred in the absence of dioxygen. It indicates that dioxygen could play the key role in the formation of β-ketosulfone (Table 1, entry 25).

With the optimized conditions in hand, the scope of the reaction with respect to various alkenes and sulfinic acids were investigated (Table 2). Generally, aromatic alkenes containing electron-donating or withdrawing groups on the aryl rings were also suitable for this process, with the corresponding products in moderate to good yields (**3aa-3ja**). Also, functional groups such as halogen, chloromethyl, and cyano groups (**3ea-3ka**) were all well tolerated, which corresponding products could be applied in further modifications. It is noteworthy that internal alkenes such as (*E*)-prop-1-enylbenzene and (*E*)-1,2-diphenylethene) could be compatible with this protocol, with the desired products (**3ka** and **3la**) in 53% and 12% yields, respectively. Heteroaromatic alkene (i.e., 4-vinylpyridine) could also be used in the reaction to give the product **3ma** in 42% yield. Moreover, investigations of different arylsulfinic acids showed that the substrates bearing with electron-rich and electron-deficient groups were all suitable for this reaction to give the corresponding products in good yields (**3ab-3ag**). Notably, the transformation could be sterically dependent, as confirmed by the moderate yield obtained when 2-bromobenzenesulfinic acid was employed as the substrate (**3af**). Interestingly, naphthalene-2-sulfinic acid could be used in the reaction to give the desired product **3ah** in 90% yield.

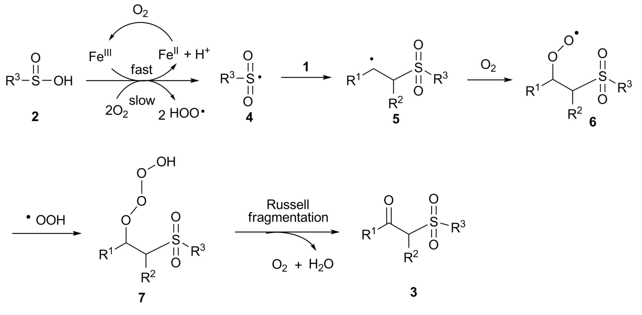
To gain further insights into this reaction, several control experiments were conducted as shown in eqns 1-3. It is well known that sulfonyl radical species are easily formed from sulfinic acids in the presence of dioxygen or transition metals.[10-14] Therefore, a radical pathway might also be involved in this reaction system. As shown in eqn (1), when TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, a well-known radical scavenger) was added into the reaction system, the present reaction was completely inhibited. Accordingly, this transformation reaction is thought to involve a radical pathway. Furthermore, ^{18}O-labeling experiment was performed to elucidate the origination of the carbonyl oxygen atom of β-ketosulfones. Considering that H_2O would be formed in the present reaction system to exert the possible effect on the judgement of the origin of carbonyl oxygen atom of β-ketosulfone, 4 Å MS was added into the reaction of **1a** and **2a** under $^{18}O_2$ to eliminate water generated in the this reaction system. As demonstrated in eqn (2), the experimental result showed that the carbonyl oxygen atom of β-ketosulfone came from dioxygen (HRMS spectrum see ESI.†). In addition, when the reaction with β-hydroxysulfone **8aa** was performed under the standard conditions, the desired product **3aa** could not be obtained (eqn (3)), indicating that β-hydroxysulfone might not be an intermediate in the present reaction system.







Although the detailed reaction mechanism is still unclear at the present stage, on the basis of above observations and previous studies,[11-15,17,18] a tentative reaction pathway is proposed as shown in Scheme 2. Firstly, the sulfonyl radical **4** could be easily produced via the single electron transfer (SET) and deprotonation process in the presence of iron salt and dioxgyen.[11-15] Subsequently, the sulfonyl radical addition to alkene **1** gives the alkyl radical **5**, which is captured by dioxygen to generate peroxy radical **6**. Next, peroxy radical **6** interacted with $^{\bullet}OOH$ to form monoalkyl tetroxide intermediate **7**, which would be decomposed into product **3** with the release of dioxygen and water.[17,18]



Scheme 2. Possible reaction pathway.

In conclusion, we have successfully developed a simple and efficient iron-catalyzed oxidative synthesis of β-ketosulfones via direct difunctionalization of alkenes with sulfinic acids and dioxygen. Taking into account the combination of advantages, such as readily available starting materials, cheap catalyst, operation simplicity, high atom efficiency, clean reaction byproduct (water), and environmently-benign conditions, this synthesis system is expected to provide an alternative and green approach to a series of β-ketosulfones. Further studies of the detailed reaction mechanism and the synthetic application are ongoing.

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