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Dioxygen-Triggered Oxidative Radical Reaction: Direct Aerobic Difunctionalization of Terminal Alkynes toward β-Keto Sulfones

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Supporting Information

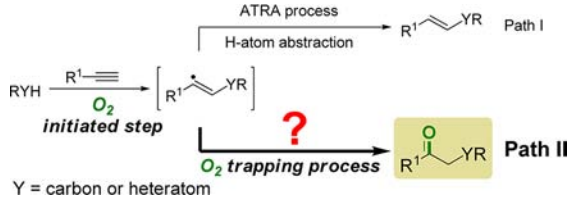
ABSTRACT: An unprecedented dioxygen-triggered oxidative radical process was explored using dioxygen as the solely terminal oxidant, realizing aerobic oxidaitve difunctionalization of terminal alkynes toward β-keto sulfones with high selectivity. Operando IR experiments revealed that pyridine not only acts as a base to successfully surpress ATRA (atom transfer radical addition) process, but also plays a vital role in reducing the activity of sulfinic acids.

Radical chemistry has played great roles in the development of modern organic synthesis. To date, most of the radical reactions are carried out by utilizing precious and/or toxic metal complex such as tin hydride reagents and unfriendly radical initiators including peroxides, diazines, etc.,[1] leading to the difficult purification of the desired products from a large amount of unexpected byproducts and residual catalysts. These disadvantages greatly restrict the application of radical chemistry in the areas of pharmaceutical industry, etc.[1g] Thus, it is challenging to update these traditional methods for green and sustainable organic synthesis.[2]

As a result of its environmental friendliness, cleanliness, and sustainability, radical process using dioxygen as an initiator under metal-free conditions is undoubtedly the ideal and promising route to addressing the aforementioned challenges. In this context, several examples of its use have recently been developed, including hydroacylation of α,β-unsaturated esters,[3] radical addition of Grignard reagents to olefins,[4] autoxidative coupling reactions,[5] oxidative difunctionalization of alkenes,[6] oxidative cleavage of C−C double bonds.[7,8] Despite these advances, radical reactions initiated solely by dioxygen still remain an outstanding challenge. A typical example is the aerobic C−C triple bond functionalization. Up to now, only rare examples have been reported to realize aerobic oxidation of terminal alkynes using transition-metals as catalysts, and the homocoupling of terminal alkynes from the Glaser-Hay coupling can hardly be dodged, which greatly hinders its application in synthetic chemistry.[9,10] Additionally, the major reason for the difficulty of this aerobic transformation is attributed to the fact that the vinyl radical intermediate generated in situ, which belongs to σ radicals, is highly reactive and unstable; thus, it is easier to afford the stable unsaturated alkenes through H-atom abstraction and difficult to be captured by dioxygen.[1e] Because of their high reactivity, these reactions are not always as selective as initially desired and unexpected byproducts are usually generated concurrently. To the best of our knowledge, there have been no reported examples concerning aerobic oxidation of terminal alkynes without assistance of additional initiators or transition-metal catalysts.[11] In this regard, it is desirable to seek exotic radical reactions in this field. Owing to our continuous interest in radical chemistry and dioxygen activation,[12] we report our recent progress in this field.

In principle, H-atom transfer process from the substrate (RYH) to reactive vinyl radical intermediate is the key step to generate stable unsaturated alkenes in Path I (Scheme 1).[1] We

Scheme 1. Dioxygen-Triggered Aerobic Difunctionalization of Terminal Alkynes



envisaged that, if we can establish suitable strategies to suppress the process of H-atom abstraction, the key intermediate, vinyl radical, might be trapped by dioxygen due to its diradical structure. On the basis of this hypothesis, we reasoned that sulfinic acid, which can be easily activated by dioxygen via single electron transfer (SET) and concomitant proton transfer (PT) to produce reactive sulfonyl radical,[7c,13] could be an ideal substrate to achieve this goal. That is because H-atom transfer process can be easily suppressed with the assistance of base to trap the H-proton, and in contrast, the SET and PT process will not be influenced. Furthermore, radical addition to carbon−carbon triple bonds is believed to be the most convenient method to generate the vinyl radical, which could be rapidly and irreversibly trapped via subsequent transformation and thus appears various synthetic possibilities.[1e] Herein, we communicate a novel and convenient protocol of achieving valuable β-keto sulfones using unfunctionalized materials via a dioxygen-triggered radical process.[14]

To probe the feasibility of our proposed assumption, we started our investigation by reacting phenylacetylene (**1a**) with benzenesulfinic acid (**2a**) as the model reaction (Scheme 2).

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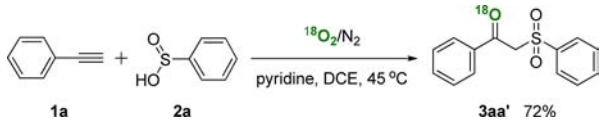
Scheme 2. O^{18} Isotope Labeling Experiment



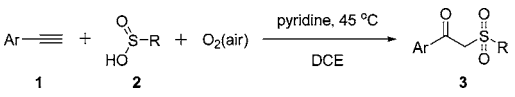
On the basis of our hypothesis, the feasibility of this strategy relies on the selectivity after the initial radical addition step, and the oxidation process under metal-free conditions has very few reports, whereas ATRA (atom transfer radical addition) process has been well studied.[1] Not surprisingly, the reaction gave a complex result when we directly treated **1a** with **2a** in dichloroethane (DCE) at 45 °C under air conditions. Large amounts of unexpected byproducts were formed, presumably due to the ATRA process that was favored under present conditions, which led to the very poor selectivity. Subsequently, we chose pyridine as a base to inhibit the possible ATRA process based on our initial assumption, and we found that the expected 1-phenyl-2-(phenylsulfonyl)ethanone (**3aa**) could be isolated in 28% yields with high selectivity and no other byproducts including homocoupling of **1a** and vinyl sulfone generated through H-atom abstraction process were observed. After a series of further screening conditions, we found that bases and the concentration of dioxygen have significant impact on the efficiency of this transformation; pyridine and air were proved as the best choice (for details, see Supporting Information (SI), Table S1). Finally, **1a** with 5-fold **2a** in the presence of pyridine and air at 45 °C using DCE as the solvent was screened as the optimized aerobic reaction conditions.

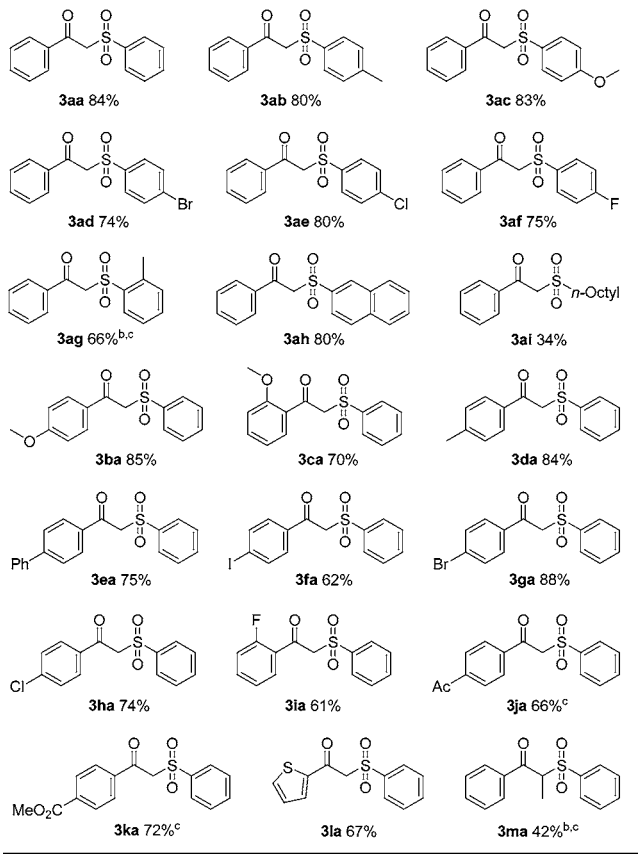
Furthermore, the reaction between **1a** and **2a** in the presence of $^{18}O_2/N_2$ afforded the ^{18}O-labeled product **3aa′** in 72% yield (Scheme 2), demonstrating the carbonyl oxygen atom of the β-keto sulfone originated from dioxygen as our initial assumption.

Subsequently, having optimized the reaction conditions, we then investigated the scope of the reaction with respect to **1a** and different sulfinic acids. As can be seen in Table 1, a variety of aryl sulfinic acids, bearing either electron-donating groups (R = OMe, Me) or electron-withdrawing groups (R = F, Cl, Br) on the aryl ring, reacted smoothly with phenylacetylene, affording the corresponding β-keto sulfones **3aa**−**3af** in good to excellent yield. The sterically hindered *ortho*-methyl substituted benzenesulfinic acid gave the corresponding **3ag** in 66% yield. Moreover, 2-naphthylsulfinic acid was also effective to give the corresponding desired product **3ah** in good yield (80%). Notably, Br, Cl and F substituents can be tolerated in this reaction, thereby, facilitating further modifications at halogenated positions (**3ad**−**3af**). Most importantly, aliphatic sulfinic acid, as a case study of *n*-octylsulfinic acid, was also a suitable substrate for this reaction, giving the desired product **3ai** in moderate yield.

We next explored the scope of the reaction between a set of functionalized alkynes and benzenesulfinic acid **2a**. As shown in Table 1, a range of alkynes, with either electron-rich or electron-poor substituents on aromatic ring, were viable in this transformation. Electron-donating aryl alkynes (**3ba**, **3da**) displayed higher reactivity than those bearing electron-withdrawing groups (**3ja**, **3ka**). *ortho*-Methoxyl substituted phenylacetylene was found to marginally affect the efficiency of this reaction, providing the desired product **3ca** in 70% yield. Notably, halo substituents including F, Cl, Br were proved to be well tolerated under the standard reaction conditions (**3ga**−**3ia**). Even aryl iodides remained intact after reaction and

Table 1. Substrate Scope of Aerobic Difunctionalization of Terminal Alkynes[a]





[a]Unless otherwise specified, all reactions were carried out using **1** (0.20 mmol), **2** (1.0 mmol), and pyridine (0.82 mmol) in DCE (2.0 mL) at 45 °C for 4 h under 1 atm of air (balloon). Isolated yield. [b]**2** (1.2 mmol) and pyridine (0.98 mmol) were employed. [c]$CHCl_3$ (2.0 mL).

product **3fa** was isolated in moderate yield. These results are significant since aryl halides, in particular for Br and I, are reactive and, thus, are difficult to be retained in many transition metal participated or organocatalytic reactions,[15] which offer opportunities for further functionalization. Most importantly, aryl alkynes with carbonyl groups such as ketone and ester substituents on phenyl ring were also compatible reaction substrates, affording the corresponding products (**3ja**, **3ka**) in good yields, which are difficult to be prepared by other methods. The heterocyclic alkynes which usually are sensitive to oxidative conditions, as exemplified by 2-ethynylthiophene, could also serve as suitable reaction partner in this protocol and gave the desired product **3la** in 67% yield. Internal alkyne, as an example of prop-1-ynylbenzene, was also mendable to this protocol, although exhibiting relatively low reactivity and affording the expected **3ma** in moderate yield.[16]

Additionally, radical trapping experiments were also conducted by employing 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,4-di-*tert*-butyl-4-methylphenol (BHT) to elucidate whether the reaction involves radical species.[3,5] The reactions were found to be mostly inhibited by TEMPO and BHT (see SI).

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To further investigate the mechanism in detail, we investigated these reactions using operando IR to monitor the reaction of **1a** with **2b** under the optimized conditions. As can be seen from the kinetic profiles of relative absorbance (ConcIRT vs time) for individual species in Figure 1A, the

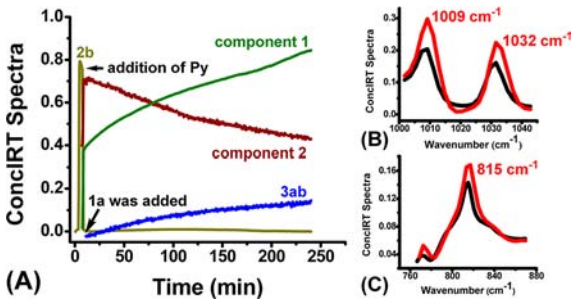


Figure 1. (A) The 2D-Kinetic profile of the reaction of *p*-toluenesulfinic acid **2b** (2.0 mmol), pyridine (1.64 mmol), and **1a** (0.4 mmol) added to $CHCl_3$ (4.0 mL) at 45 °C in succession; the reaction was monitored by operando IR. (B) ConcIRT spectra of the new component **1** (black curve) and authentic sample (pyridinium *p*-toluenesulfonate, red curve). (C) ConcIRT spectra of the new component **2** (black curve) and authentic sample (pyridinium *p*-toluenesulfinate, red curve).

absorbance of **2b** dropped to baseline as soon as pyridine was added. In the meantime, a new component **2** was formed immediately. This component was assigned to be pyridinium *p*-toluenesulfinate when compared with authentic sample (Figure 1C). When **1a** was added, the pyridinium *p*-toluenesulfinate was consumed as the product **3ab** generated from the reaction. Besides the formation of **3ab**, another formation of new component **1** was observed accordingly. From authentic sample (Figure 1B), this component was assigned as pyridinium *p*-toluenesulfonate.

Additionally, to acquire further understanding of the effect of the pyridine in this reaction, autoxidation of *p*-toluenesulfinic acid (**2b**) was also monitored by in situ IR in the presence or absence of pyridine. The kinetic profiles in Figure 2 clearly

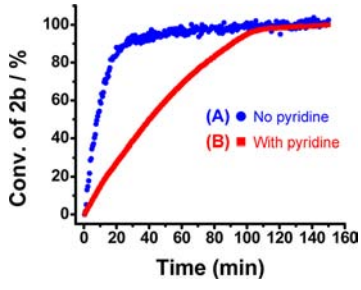
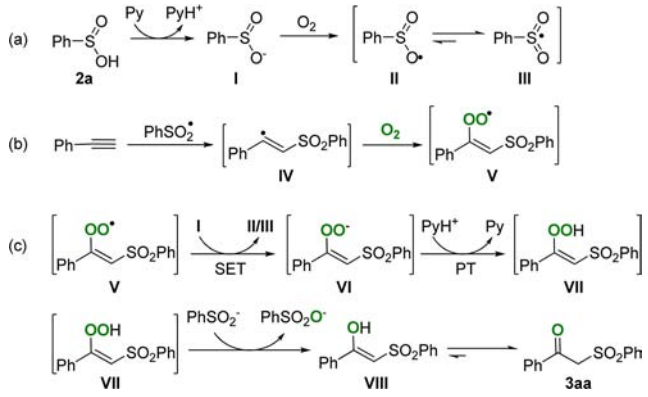


Figure 2. Kinetic profiles of the autoxidation of **2b** monitored by in situ IR under different conditions: (A) **2b** (0.5 mmol) in $CHCl_3$ (4.0 mL) at 45 °C, monitored by **2b**; (B) **2b** (0.5 mmol), pyridine (0.41 mmol) in $CHCl_3$ (4.0 mL) at 45 °C, monitored by pyridinium *p*-toluenesulfonate.

show that the existence of pyridine prolongs the reaction time of autoxidation of **2b**, which means that the role of the pyridine as a base is to reduce the reactivity and obviate the accelerated oxygenation of the sulfinic acids.

On the basis of the results described above and previous studies,[7c,13] a proposed reaction pathway is depicted in Scheme 3. Initially, benzenesulfinic acid is quickly transformed into

Scheme 3. Proposed Mechanism



sulfinyl anion **I** in the presence of pyridine. Subsequently, the pathway was triggered by the autoxidation of **I** with dioxygen via single electron transfer (SET) process, affording an oxygen-centered radical **II** which could resonate with sulfonyl radical **III**. Thereafter, sulfonyl radical addition to alkynes produces the reactive vinyl radical **IV**, which could be trapped by dioxygen under present conditions and forms intermediate **V**. Afterward, the intermediate **V** goes through SET and PT process successively with **I** and pyridinium, generating **II**/**III** and affording peroxide **VII**. Finally, **VII** undergoes subsequent reduction by benzenesulfinic acid, produces **VIII**, which isomerizes and furnishs **3aa**.

On the basis of the speculation, besides the desired product **3ab** from the reaction of **1a**, **2b** and O_2, we posited that *p*-toluenesulfonic acid should be the other reaction product. In fact, from Figure 1, we did identify the formation of pyridinium *p*-toluenesulfonate from the reaction mixture. However, from Figure 2, we knew pyridinium *p*-toluenesulfonate could also be generated from an autoxidation of **2b** and O_2. Actually, the autoxidation of **2b** had been also reported to form sulfonate, although there is less detailed kinetic investigation.[17] To clarify whether the sulfonate generated from autoxidation or from the oxidative radical reaction of **1a**, **2b**, and O_2, the in situ IR investigations were further conducted, and the results were shown in the Figure 3. It was clear that the formation of pyridinium *p*-toluenesulfonate from the oxidative difunctionalization of **1a**, **2b**, and O_2 was faster than the autoxidation of **2b** with O_2. This result indicated that the embodied oxygen atom (at least parts of) of pyridinium *p*-toluenesulfonate from pyridinium *p*-toluenesulfinate was not directly from O_2, but from one of the intermediates of the oxidative radical reaction.

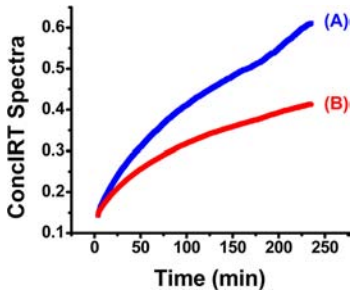


Figure 3. Kinetic profiles of the pyridinium *p*-toluenesulfonate monitored by in situ IR under different conditions: (A) **2b** (2.0 mmol), pyridine (1.64 mmol), and **1a** (0.4 mmol) in $CHCl_3$ (4.0 mL) at 45 °C; (B) autoxidation of **2b** under same conditions without **1a**.

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This could serve as an evidence to support the reaction pathway shown in Scheme 3, step c.

In conclusion, we have developed an environmentally challenging dioxygen-triggered oxidative radical process using dioxygen as the only oxidant, and offered an unprecedented sustainable radical method for highly selective synthesis of valuable β-keto sulfones via aerobic difunctionalization of terminal alkynes. Notably, this reaction exhibits a wide range of functional-groups tolerance. Preliminary mechanism revealed that a radical process is involved, and pyridine not only acts as a base to successfully suppress ATRA (atom transfer radical addition) process, but also plays vital roles in reducing the activity of sulfinic acids. The unique transformation holds significant potential for the applications to a series of novel organic reactions. Our further efforts in this area are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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