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Report

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Copper-catalyzed aerobic oxidative cleavage of unstrained carbon-carbon bonds of 1,1-disubstituted alkenes with sulfonyl hydrazides

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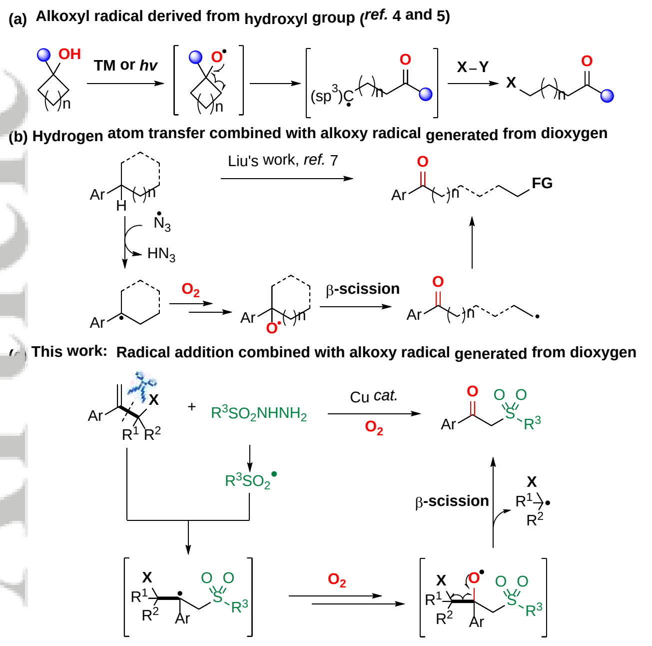
Summary of main observation and conclusion Alkoxy radical-mediated carbon-carbon bond cleavages have emerged as a powerful strategy to complement traditional ionic-type transformations. However, carbon-carbon cleavage reaction triggered by alkoxy radical intermediate derived from the combination of alkyl radical and dioxygen, is scarce and underdeveloped. Herein, we report alkoxy radical, which was generated from alkyl radical and dioxygen, mediated selective cleavage of unstrained carbon-carbon bond for the oxysulfonylation of 1,1-disubstituted alkenes, providing facile access to a variety of valuable *β*-keto sulfones. Mechanistic experiments indicated alkoxy radical intermediate that underwent subsequent regioselective *β*-scission might be involved in the reaction and preliminary computational studies were conducted to provide a detailed explanation on the regioselectivity of the C-C bond cleavage. Notably, the strategy was successfully applied for constructing uneasily obtained architecturally intriguing molecules.

Background and Originality Content

Catalytic and selective cleavage of carbon-carbon bonds, which would provide a complementarily powerful strategy to organic transformation, remains less explored and underdeveloped in organic chemistry due to the difficulties associated with discriminating the carbon-hydrogen and carbon-carbon bonds and thermodynamically stability of C-C σ bond in organic molecules.[1] In order to conquer the above challenges, the well-developed C-C bond cleavage reactions usually depend on specific substrates bearing strained rings, chelation-assisted groups or electron-withdrawing groups to polarize the C-C bonds.[2] Thus, the development of a general and more efficient strategy for selective C-C bond cleavage remains highly desirable. With the rapid development of radical chemistry, a wide range of reactions involving selective C-C bond cleavage by a radical process has emerged as an interesting strategy for the preparation of value-added compounds.[3] In particular, great progress has been achieved in alkoxy radical initiated *β*-scission for the ring-opening functionalization of cycloalkanols to furnish more valuable products (Scheme 1a). For example, transition metal-catalyzed[4] or photocatalytic[5] alkoxy radical-mediated ring-opening functionalization of cycloalkanols has made great achievements. In those works, the key alkoxy radical intermediates generate from the hydroxyl groups of the substrates. The direct use of dioxygen as oxygen source for constructing hydroxyl or carbonyl groups in oxygen-containing organic frameworks has been achieved via radical processes in the past several years.[6] We wondered whether alkoxy radical, which has been applied in the selective C-C bond cleavage, could be generated from the reaction between alkyl radical and dioxygen. The realization of the hypothesis could provide a powerful strategy for selective C-C bond cleavage and building highly valuable compounds. While our manuscript was under preparation, an example of the combination of hydrogen atom transfer (HAT) with alkoxyl radical, derived from alkyl radical capturing dioxygen, for the diverse functionalization of C-C bond adjacent to arene was reported by Liu's group (Scheme 1b)[7].

β-Ketosulfones are widely applied in the synthesis of natural products, pharmaceuticals and agrochemicals and exhibit interesting biological properties,[8] great efforts have hence been devoted for the synthesis of the compounds with various sulfonylating agents.[9] In particular, a variety of methods based on the oxysulfonylation of alkenes with sulfonylhydrazides have been developed to access β-ketosulfones. For example, Wang's[8a] group has proposed copper-catalyzed synthesis of *β*-ketosulfones starting from alkenes with oxygen. Alternatively, Zhang's group has reported metal-free aerobic oxidative synthesis of *β*-ketosulfones[8d]. Recently, visible-light-promoted aerobic oxidative difunctionalization of alkenes for the construction of *β*-ketosulfones has been disclosed by Wang and Zhu's groups.[10] Despite the above achievements, there is still a great demand for the development of alternative strategies to access *β*-ketosulfones in synthetic chemistry. 1,1-Disubstituted alkenes served as powerful building blocks in organic synthesis.[11] However, as a result of the challenges associated with the selective C-C bond cleavage of unstrained C-C bonds of 1,1-disubstituted alkenes, oxysulfonylation of 1,1-disubstituted alkenes with oxygen affording corresponding *β*-ketosulfones has not yet been described in literature. Inspired by the alkoxy radical-mediated C-C cleavage, herein, we report copper-catalyzed aerobic oxidative carbon-carbon cleavage of simple unstrained 1,1-disubstituted alkenes without the assistance of directing group for constructing *β*-ketosulfones *via* O-centered alkoxy radical *in situ* generated from alkyl radical and oxygen (Scheme 1c).

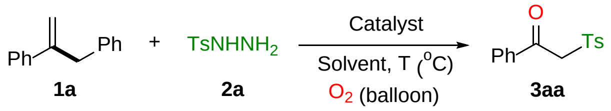
Scheme 1 Alkoxy radical-mediated regioselective C-C bond cleavage *via β*-scission



Results and Discussion

Our studies commenced with *α*-benzylstyene **1a** and *p*-toluenesulfonyl hydrazide **2a** as the model substrates using cuprous iodide (CuI) as catalyst under O_2 atmosphere, and acetonitrile loaded with some water was used as the solvent, in which water was employed to increase the solubility of compound **2a**. To our delight, the selective carbon-carbon bond cleavage of substrate **2a** was observed, affording the desired product **3aa** in 30% yield (Table 1, entry 1). After screening of the catalysts, it was found that $Cu(OTf)_2$ was the ideal catalyst, leading to the desired product in 86% yield while other copper salts gave lower yields (entries 2-6). Then, different solvents, such as THF, DME, DMSO, and NMP loaded with water were examined, acetonitrile was still the best choice (entries 7-10). After the solvent screening, the impact of the amount of water on the reaction was investigated, it was found that when $MeCN/H_2O$ (9:1, V/V) was used as the solvent, the optimal 93% yield was obtained (entries 11-15). Next, no better yield was obtained when the reaction temperature was decreased or increased (entries 16 and 17). Finally, control experiments revealed that oxygen or copper catalyst was crucial to the success of the reaction (entries 18-20).

Table 1 Optimization of the reaction conditions.[a]

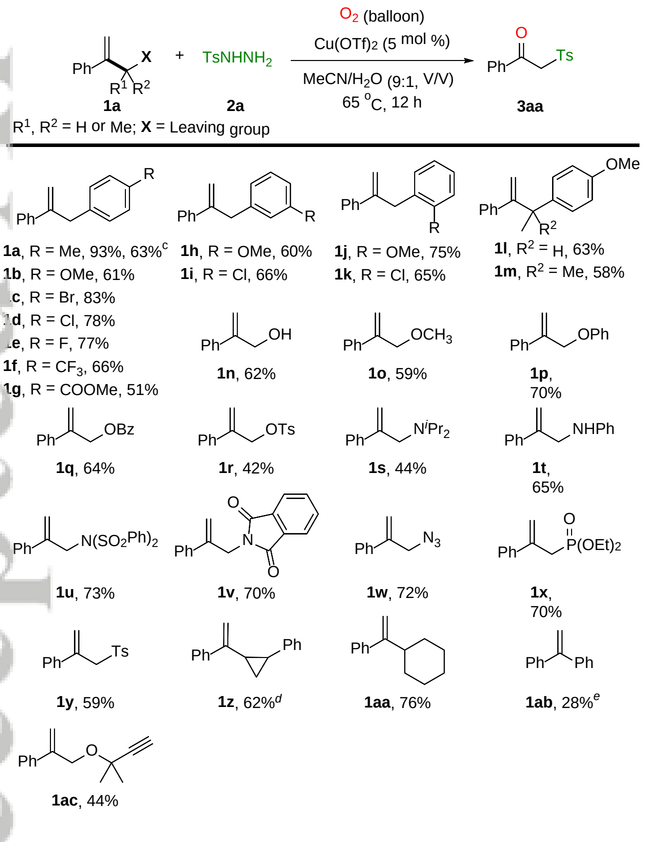


Entry	Catalyst	Solvent	**3aa** (%)[b]
1	CuI	$MeCN/H_2O$ (5:1)	30[c]
2	CuI	$MeCN/H_2O$ (5:1)	52
3	Cu_2O	$MeCN/H_2O$ (5:1)	46
4	$CuBr_2$	$MeCN/H_2O$ (5:1)	55
5	$Cu(OAc)_2$	$MeCN/H_2O$ (5:1)	79
6	$Cu(OTf)_2$	$MeCN/H_2O$ (5:1)	86
7	$Cu(OTf)_2$	THF/H_2O (5:1)	44
8	$Cu(OTf)_2$	DME/H_2O (5:1)	76
9	$Cu(OTf)_2$	$DMSO/H_2O$ (5:1)	58
10	$Cu(OTf)_2$	NMP/H_2O (5:1)	33
11	$Cu(OTf)_2$	$MeCN/H_2O$ (3:1)	51
12	$Cu(OTf)_2$	$MeCN/H_2O$ (7:1)	89
13	**$Cu(OTf)_2$**	**$MeCN/H_2O$ (9:1)**	**93**
14	$Cu(OTf)_2$	$MeCN/H_2O$ (11:1)	92
15	$Cu(OTf)_2$	MeCN	51
16	$Cu(OTf)_2$	$MeCN/H_2O$ (9:1)	54[d]
17	$Cu(OTf)_2$	$MeCN/H_2O$ (9:1)	46[e]
18	$Cu(OTf)_2$	$MeCN/H_2O$ (9:1)	31[f]
19	$Cu(OTf)_2$	$MeCN/H_2O$ (9:1)	0[g]
20	—	$MeCN/H_2O$ (9:1)	26[h]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), Catalyst (5 mol %), Solvent (2 mL), 65 °C, 12 h, O_2 (balloon). [b] Isolated yield based on **1a**. [c] Catalyst (2 mol %), 40 °C, 7 h. [d] 50 °C. [e] 80 °C. [f] Air (balloon). [g] N_2 (balloon). [h] 24 h.

With the optimal conditions in hand (Table 1, entry 13), we subsequently evaluated the generality of the radical-induced C-C cleavage reaction for oxysulfonylation of different kinds of 1,1-disubstituted alkenes. As illustrated in Table 2, a diverse array of styrenes bearing different groups at *α*-position could undergo C-C bond cleavage with high selectivity. The substrates with different functional groups at *para*-, *meta*- and *ortho*-position of benzyls, including methyl (**1a**), methoxyl (**1b**, **1h**, and **1j**), halogens (**1c**-**1e**, **1i** and **1k**), trifluoromethyl (**1f**), all reacted well. We next turned our attention to examine the compatibility of substrates with various functional groups attached to the *α*-carbon atom. Pleasingly, a broad range of functional groups had no significant effect on the radical-induced C-C bond cleavage process. As also shown in Table 2, various heteroatom-containing functional groups, such as hydroxyl (**1n**), methoxyl (**1o**), phenoxyl (**1p**), acyloxyl (**1q**), sulfonyloxyl (**1r**), amino (**1s**-**1v**), azido (**1w**), phosphonyl (**1x**) and sulfonyl (**1y**), are tolerated well, affording the desired product *via* C-C bond cleavage in 42-73% yields, demonstrating the flexibility of the current method. Notably, moderate yields could also be obtained with styrenes bearing tertiary-carbon (**1z** and **1aa**). In addition, C(sp^2)-C(sp^2) bond resided in 1,1-diphenyl-ethylene **1ab** could also be selectively cleaved albeit in relatively lower yield, which might be attributed to different reactivity of substrate **1ab** and higher bond energy of C(sp^2)-C(sp^2) bond than C(sp^2)-C(sp^3) bond in the alkoxy radical intermediate. Additionally, the substrate **1ac** containing C-C triple bond was also compatible in the reaction. Taken together, the selectivity of the carbon-carbon cleavage could be controlled in a selective manner by substituents on the alkenes. Besides, a gram-scale model reaction was carried out to afford the product **3aa** in 63% isolated yield, demonstrating the practicality and scalability of the present method (see SI for more details). Notably, X, leaving as a substituted carbon radical, might transform into oxygenated products with oxygen, coupling products with another radical, or some unidentified products after the reaction.

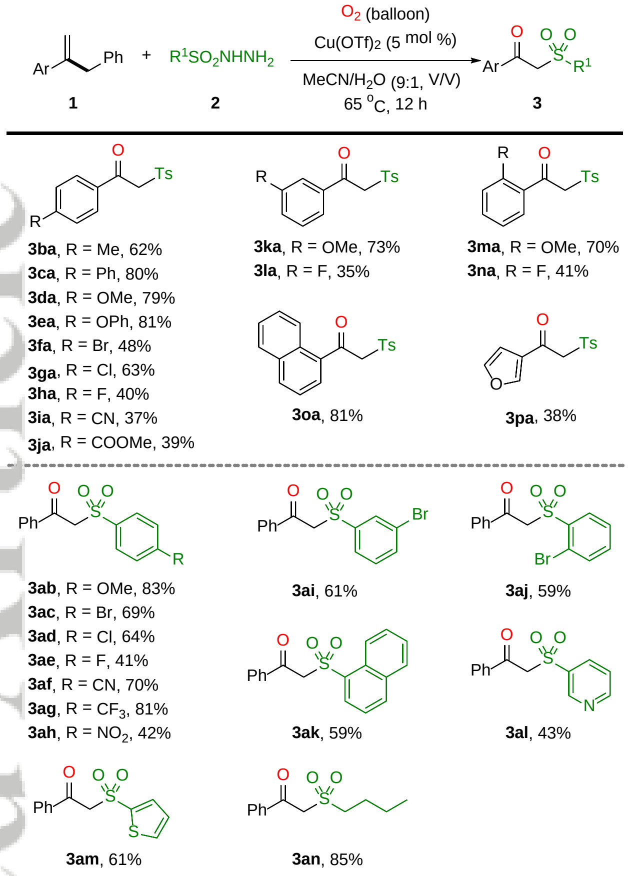
Table 2 Substrate scope of 1,1-disubstituted alkenes.[a,b]



[a] **1** (0.5 mmol), **2** (1.0 mmol), Cu(OTf)$_2$ (5 mol %), MeCN/H$_2$O (9:1, 2 mL), 65 °C, 12 h, O$_2$ (balloon). [b] Isolated yields based on **1**. [c] Performed at 6 mmol scale of **1a**. [c] When R^1, R^2, X = H, *β*-hydroxysulfone was obtained in 66%. [d] Ring-opening products were identified by LC-HRMS. [e] Two byproducts acetophenone and (2-tosylethene-1,1-diyl)dibenzene were isolated and confirmed by NMR spectra.

Having demonstrated the powerful capability of the method in the radical-initiated carbon-carbon bond cleavage of diverse 1,1-disubstituted alkenes, the scope of the substitutes on the arenes was investigated. As illustrated in Table 3, the substrates bearing electron-donating (**3ba**, **3da**-**3ea**) or electron-withdrawing (**3ha**-**3ja**) groups at the *para*-position of phenyls all underwent the reaction smoothly. The substrates with methoxyl (**3ka** and **3ma**) or fluoride (**3la** and **3na**) substituted at *meta*- or *ortho*-position could also afford the desired products *via* selective C-C cleavage. Substrates containing naphthyl (**3oa**) or furyl (**3pa**) could also be applied to the transformation. Furthermore, the generality of the method with respect to the sulfonyl hydrazide coupling partner was explored using *α*-benzylstrene **1a** as the substrate. Aryl sulfonyl hydrazides containing methoxyl (**3ab**), halogen (**3ac**-**3ae**, **3la**, and **3na**), cyano (**3ia**), trifluoromethyl (**3ag**) or nitro (**3ah**) substituents were compatible. Additionally, 2-naphthyl, 3-pyridyl and 2-thienyl sulfonyl hydrazides (**3ak**-**3am**) reacted under the optimized conditions to afford the products in moderate yields. Finally, alkyl sulfonyl hydrazide (**3an**) could also undergo high-yielding coupling with the model substrate **1a**, which was possibly due to the fact that alkyl sulfonyl hydrazide could be more easily oxidized to alkyl radical but also alkyl sulfonyl radical was more reactive than aryl sulfonyl radical.

Table 3 Substrate scope of *α*-benzyl substituted styrenes and sulfonyl hydrazides.[a,b]

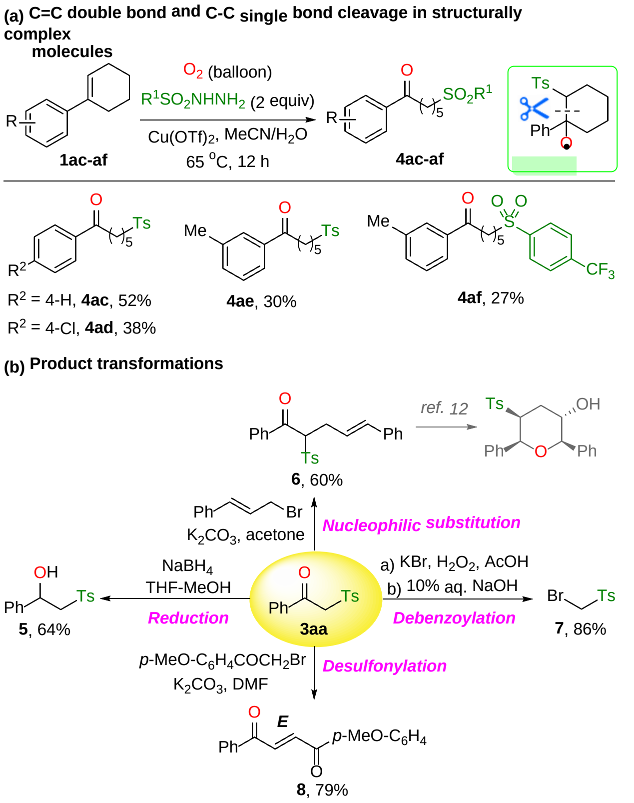


3ba, R = Me, 62%
3ca, R = Ph, 80%
3da, R = OMe, 79%
3ea, R = OPh, 81%
3fa, R = Br, 48%
3ga, R = Cl, 63%
3ha, R = F, 40%
3ia, R = CN, 37%
3ja, R = COOMe, 39%
3ka, R = OMe, 73%
3la, R = F, 35%
3ma, R = OMe, 70%
3na, R = F, 41%
3oa, 81%
3pa, 38%
3ab, R = OMe, 83%
3ac, R = Br, 69%
3ad, R = Cl, 64%
3ae, R = F, 41%
3af, R = CN, 70%
3ag, R = CF_3, 81%
3ah, R = NO_2, 42%
3ai, 61%
3aj, 59%
3ak, 59%
3al, 43%
3am, 61%
3an, 85%

[a] **1** (0.5 mmol), **2** (1.0 mmol), $Cu(OTf)_2$ (5 mol %), $MeCN/H_2O$ (9:1, 2 mL), 65 °C, 12 h, O_2 (balloon). [b] Isolated yields based on **1**.

To validate the potential applicability of the strategy, aryl substituted cyclohexenes **1ac-af** were subjected to the standard reaction conditions, and they could undergo carbon-carbon cleavage smoothly to furnish structurally interesting products **4ac-af** (Scheme 2a). Particularly, an intriguing C=C double bond cleavage occurred in the reaction which could be hardly achieved by other methods. Then, the utility of the method was further confirmed by facile derivatization of the product **3aa** (Scheme 2). For example, the keto group of the product could be easily reduced to generate *β*-hydroxysulfone **5**. Intermolecular nucleophilic substitution between *β*-ketone sulfone and cinnamyl bromide provided the mono-C-cinnamylation product **6**, which could be stereoselectively transformed into sulfonyl tetrahydropyrans *via* sequential reduction, epoxidation, and ring-closure[12]. Moreover, *α*-bromomethyl sulfone **7** could also be achieved in moderate yield *via* mono-bromination and base-induced chemoselective cleavage.[13] Furthermore, the combination of the *β*-keto sulfone with *α*-bromo ketone formed an extremely valuable unsymmetric 1,4-enedione **8** with complete *E* selectivity[14]. The success of these experiments indicate that the protocol could constitute a potentially useful strategy for further functionalization of the commodity chemicals.

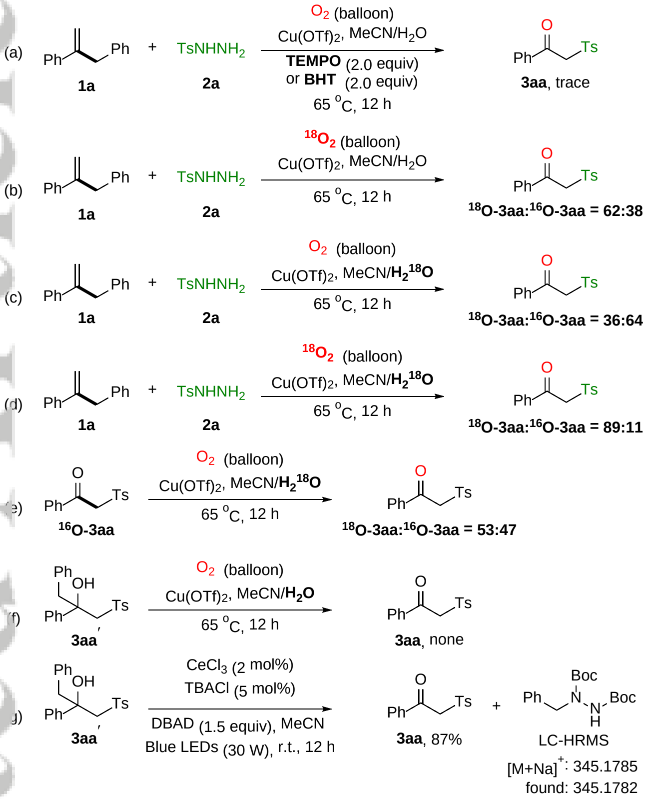
Scheme 2 Synthetic applications of the reaction.



R^2 = 4-H, **4ac**, 52%
R^2 = 4-Cl, **4ad**, 38%
4ae, 30%
4af, 27%
6, 60%
5, 64%
7, 86%
8, 79%

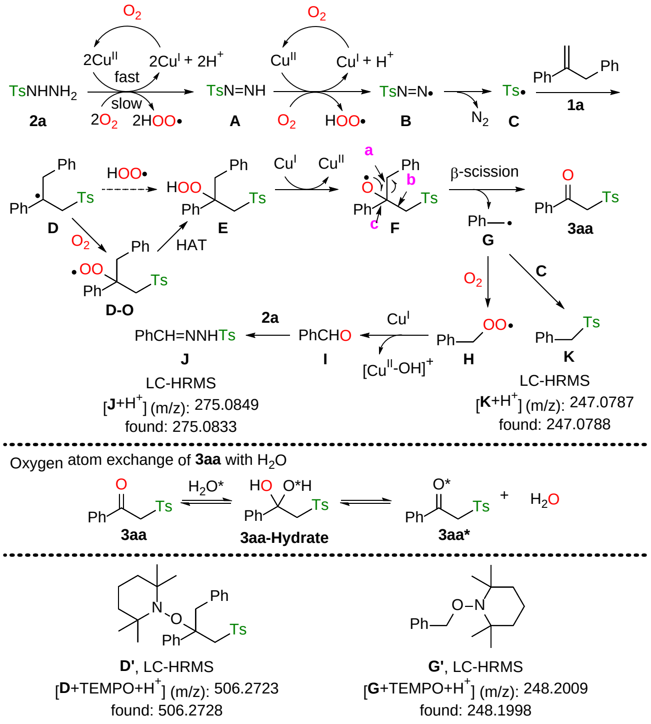
A final set of studies focused on the detailed mechanism of the reaction. As shown in Scheme 3, the model reaction was completely suppressed when radical scavenger 2,2,6,6-tetramethyl-piperidinyloxyl (TEMPO) or butylated hydroxytoluene (BHT) was added into the reaction system (Scheme 3a), indicating that a radical process might be involved in the present cleavage reaction. Subsequently, isotope-labeling experiments were performed under $^{18}O_2$ or in $H_2{}^{18}O$ to get a more in-depth understanding of the pivotal role of dioxygen in the transformation. When the model reaction was conducted under $^{18}O_2$ atmosphere, 62% of ^{18}O-labeled product **3aa** was detected in HR-MS spectra (Scheme 3b, and see SI). Upon performing the reaction in the presence of $H_2{}^{18}O$, 36% of ^{18}O-labeled product **3aa** was detected in HR-MS spectra (Scheme 3c, and see SI). And, when the model reaction was conducted under both ^{18}O-labeled $H_2{}^{18}O$ and $^{18}O_2$, 89% of ^{18}O-labeled product **3aa** was detected. Moreover, oxygen exchange between the product ^{16}O-**3aa** and $H_2{}^{18}O$ *via* the hydrate was observed by the oxygen scrambling experiment under the standard conditions (Scheme 3d, and see SI).[8a] The combination of the above results provided strong support for the carbonyl oxygen originating from dioxygen. Besides, when substrate **3aa′** was subjected to the standard reactions, no corresponding product was detected, precluding the possibility that **3aa’** was the key intermediate in the reaction (Scheme 3e). Furthermore, when **3aa’** was transformed into alkoxy radical-mediated by cerium photocatalysis,[5f] the product **3aa** was obtained smoothly, providing the evidence that an alkoxy radical mediated *β*-scission process might be involved in the reaction (Scheme 3f).

Scheme 3 Mechanistic studies.



Based on the above observations, LC-HRMS analysis (see SI for information) and previous reports[6b, 8a], a plausible mechanism for the present transformation is described in Scheme 4. Initially, a sulfonyl radical would be formed from sulfonyl hydrazide **2a** *via* intermediate **A** and **B** with the release of N_2. The sulfonyl radical would attack the double bond of alkene **1a** to provide the alkyl radical intermediate **D**, which captures an O_2 to deliver peroxide radical intermediate **D-O**. Subsequently, the intermediate **D-O** might undergo hydrogen atom transfer (HAT) giving rise to intermediate **E**. Also, intermediate **E** might be formed through the coupling between alkyl radical intermediate **D** with peroxyl radical (•OOH) generated form oxygen. Then, the single electron transfer (SET) between intermediate **E** and Cu(I) results in alkoxy radical **F**. Eventually, highly selective *β*-scission of the carbon-carbon of the intermediate **F** would lead to the final product **3aa** along with the benzyl radical **G**,[15] which could react with oxygen or sulfonyl radical **C** leading to the corresponding aldehyde **I** and radical-radical coupling molecule **K**. Notably, the oxygen atom of carbonyl group of **3aa** could undergo reversible oxygen atom exchange with water. In addition, benzaldehyde hydrazone **J**, compound **K**, TEMPO-trapped compounds **D'** and **G'** were detected through LC-HRMS analysis of the ongoing reaction mixture, which validates the existence of radicals **D** and **G**, providing further evidence for the reaction mechanism. Importantly, preliminary computational studies indicated that the C-C bond cleavage of position **a** of alkoxy radical **F** was more thermodynamically favorable than *β*-scission of position **b** and **c** due to the much lower energetic barrier of the transition state (See SI for more information).

Scheme 4 Possible reaction mechanism.



Conclusions

In summary, we have successfully developed an aerobic copper-catalyzed radical-initiated selective cleavage of unstrained carbon-carbon bond for the oxysulfonylation of 1,1-disubstituted alkenes. The protocol features excellent chemo- and regio-selectivities, good functional group tolerance, broad substrate scope, high yields and could be readily extended to reconstruct structurally complex molecules. Notably, the alkoxy radicals involved in the reaction are generated from alkyl radicals and dioxygen. We anticipate that the present protocol would be beneficial to the development of alkoxy radical-mediated regioselective carbon-carbon bond cleavage with dioxygen for the construction of structurally more complex products that are difficult to access by other approaches. Further studies on the nature of alkoxy radical are undergoing in our laboratory.

Experimental

Cu(OTf)$_2$ (9 mg, 5 mol%) was added to a mixture of 1,1-disubstituted alkene **1** (0.5 mmol), sulfonyl hydrazide **2** (1.0 mmol), and MeCN/H$_2$O (2 mL, 9/1) in a 25 mL round-bottomed flask at room temperature under O$_2$ (balloon). The reaction vessel was allowed to stir at 65 °C for 12 h. Upon completion of the reaction, the resulting mixture was concentrated under vacuum and the residue was purified by flash column chromatography using petroleum ether/ethyl acetate (v/v 10:1 to 1:1) to provide the desired product.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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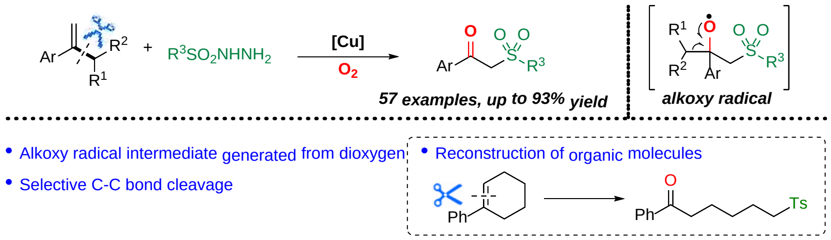
Copper-catalyzed aerobic oxidative cleavage of unstrained carbon-carbon bonds of 1,1-disubstituted alkenes with sulfonyl hydrazides



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Herein, we report alkoxy radical, which was generated from alkyl radical and dioxygen, mediated selective cleavage of unstrained carbon-carbon bond for the oxysulfonylation of 1,1-disubstituted alkenes, providing facile access to a variety of valuable β-keto sulfones. Importantly, the strategy was successfully applied for constructing uneasily obtained architecturally intriguing molecules.