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Thiyl Radical Promoted Chemo- and Regioselective Oxidation of C=C Bonds by Molecular Oxygen via Iron Catalysis

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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The first example of thiyl radical promoted ligand-free iron-catalyzed oxidative cleavage of alkenes by molecular oxygen (1 atm) has been developed. The reaction proceeds under mild reaction conditions with high efficiency and high chemo- and regioselectivity. It features a broad substrate scope and excellent functional group compatibility, enabling a facile access to valuable molecules for application in medicinal chemistry. Preliminary mechanistic studies reveal that a vital intermediate dioxetane might be involved in the reaction and thiyl radical plays a synergistic role in facilitating the selective oxidation of C=C bond.

Introduction

The development of highly selective, environmentally friendly, and sustainable systems for selective chemical transformations are among the most important goals in fundamental researches as well as potential-industrial applications.[1] The oxidative cleavage of alkenes to carbonyl derivatives plays a role of paramount importance in synthetic organic chemistry, owing to the versatility of the carbonyl group,[2] which can allow late-stage diversification of complex molecules via derivatization of the C=C bonds.[3] Moreover, alkenes are ideal sources for the preparation of carbonyl derivatives due to their diversity and both natural and industrial abundance.[4] Despite simplicity of the transformation, mild and highly selective protocols for oxidative cleavage of alkenes with excellent functional group compatibility are still in great demand. The classical approaches for this strategy typically suffer from (i) generation of stoichiometric waste from the oxidants, such as $KMnO_4$, OsO_4, oxone, TBHP, $NaIO_4$, and $PhIO/HBF_4$;[5] and (ii) low chemo- and regioselectivity, along with the concomitant low efficiency and poor functional group tolerance owing to the strongly oxidative properties of the typical oxidants. A more attractive strategy utilizes ozone as the oxidant, which generates only molecular oxygen as a byproduct. However, this strategy cannot be widely applied due to the toxicity and associated safety issues associated with ozone.[6] Therefore, a protocol for the oxidative cleavage of alkenes using safe and environmentally friendly oxidants is highly appealing. Molecular oxygen is an ideal oxidant in terms of availability, cost, and safety.[7-8]

Very recently, a significant photocatalytic method for oxidative cleavage of C=C bonds has been reported by Wang and co-workers, in which terminal and internal alkenes could convert into the corresponding aldehydes and ketones in moderate to excellent yields via an olefin-disulfide charge-transfer complex.[9] Due to their abundance, low toxicity and cost, the use of iron-based catalysts has become more attractive, leading to a renewed interest in this area.[10-11] To date, however, iron-catalyzed methods for the oxidative cleavage of C=C bonds using molecular oxygen have been rare.[12] A protocol involving carbonyl derivatives and other oxidation products was reported by the Demessie group, where the control of chemoselectivity was regulated by the pressure of O_2 in the presence of N_2.[12a] Iron-based heterogeneous systems could also cleave C=C bonds to access the corresponding ketones, albeit in poor to moderate yields under high pressure of O_2.[12b-d] Thus far, these iron-catalyzed oxidative cleavage reactions have generally suffered from low chemo- and regioselectivity, low efficiency, and poor functional-group tolerance. In addition, the competing formation of other oxidation products, including diols, epoxides, allylic alcohols have generally been observed (Scheme 1).[12a,12e,13] Recently, Xiao and coworkers described a method to achieve the oxidation of styrene derivatives to the corresponding carbonyls using an unusual bisimidazoline ligand which is not commercially available nor readily accessible. This catalytic system suffered from a propensity for alkene migration, leading to poor regioselectivity in some cases.[12f] Till now, the issue of highly regioselective cleavage of C=C bonds has not been fully exploited. Thus, we hope to develop a more general catalytic system for the highly selective cleavage of C=C bonds, making a complementarity with previous methods. Herein, we describe a homogenous catalytic system for ligand-free iron-catalyzed oxidation of alkenes to carbonyl compounds using cheap, commercially

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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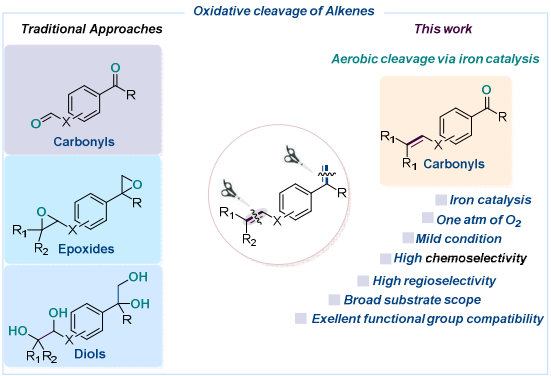
available compounds, bismuththiol (0.3$/g) and 1,1'-bis(diphenylphosphino)ferrocene (dppf) as catalysts under one atmosphere of O_2. This protocol features high chemo- and regioselectivity, high efficiency and excellent functional group compatibility.



Scheme 1 Strategies for the oxidative cleavage of alkenes

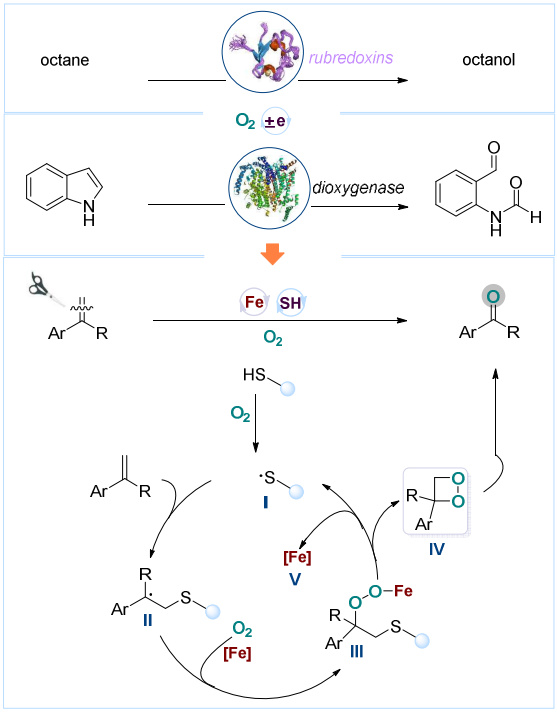
In previous works,[12f,12h,13b] a dioxetane was considered as a plausible intermediate in the oxidative cleavage pathway, which would decompose to give the desired carbonyl product. Therefore, lowering the kinetic barrier to dioxetane formation is critical to improve the chemo- and regioselectivity of this oxidative cleavage reaction. It is known that thiyl radicals, which can be easily generated via a single-electron-transfer (SET) process,[14] will undergo reversible addition to double bonds, generating a reactive carbon-centered radical, which could be intercepted towards the desired cycloaddition products.[14] It is also widely known that in biological systems, iron-containing enzymes can initiate oxidation reactions by SET, such as rubredoxins (iron-sulfur proteins), heme and nonheme oxygenases which can selectively oxidize alkenes to carbonyl compounds.[16]

Design plan

Wang reported that a thiyl radical would generate through the olefin-disulfide charge-transfer complex under visible-light (*vide supra*).[9] Hence, we envisioned a thiyl radical could be initiated by oxygen[8i] or an iron catalyst (for details, see Supporting Information), providing both the selectivity and reactivity in the transformation of the key dioxetane intermediate. The detailed mechanistic description of this transformation is shown in Scheme 2. We proposed that a thiyl radical could be produced, and then the addition to a C=C bond by the thiyl radical produces the intermediate **II**, which would be subsequently trapped by oxygen and iron species and generate an active intermediate **III**. The critical intermediate dioxetane **IV** would be delivered when the thiyl radical and iron species departs from **III**. Finally, the desired ketone would be produced via the collapse of dioxetane.

Results and discussion

To test this hypothesis, we initiated our study by subjecting 2-phenyl-1-propene **1a** to 1 atm of O_2 in the presence of various thiols and iron catalysts. Cysteine was firstly tested since it appears in many iron-sulfur proteins and is known to facilitate the SET process.[17] Gratifyingly, we found that acetophenone was produced in 32% yield when $Fe(ClO_4)_2$ was used (Table 1, entry 1). Other iron sources, such as $FeCl_2$, $FeBr_2$, and $Fe(acac)_3$



Scheme 2 Proposed mechanism for oxidative cleavage of alkenes via the synergy of thiyl radicals and iron catalysis

furnished **1** in less than 10% yields. Switching the thiol from cysteine to ethyl mercaptoacetate **S2** gave the corresponding ketone in a promising 44% yield (Table 1, entry 2). Given ferrocene's propensity to undergo SET,[18] we employed ferrocene **Fe1** in the reaction, which demonstrated promising catalytic efficiency (Table 1, entry 3).

Owing to the high volatility of thiol catalysts used, an unpleasant smell was produced during the operation of this reaction; to further improve this procedure, various solid thiols were investigated (Table 1, entries 4-5). We were pleased to find that heteroaromatic thiol, bismuththiol **S4** could promote this reaction, leading to moderate yield (Table 1, entry 5). Furthermore, bismuththiol **S4** could improve the reaction efficiency and 67% yield was obtained using acetylferrocene **Fe2** (Table 1, entry 6). Encouraged by these results, several ferrocene-based catalysts with different electronic properties were evaluated (Table 1, entries 6-8). The best result, 81% isolated yield was obtained (Table 1, entry 8) when 1,1'-Bis(diphenylphosphino)ferrocene **Fe4**, which has been extensively used as a ligand in cross-coupling reactions, was employed. Control experiments revealed the necessity of both thiol and iron species. Only trace amount of desired product was observed in the absence of thiol (Table 1, entry 9). Some

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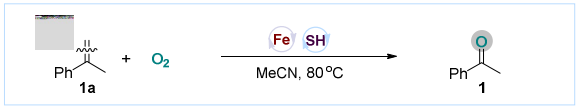
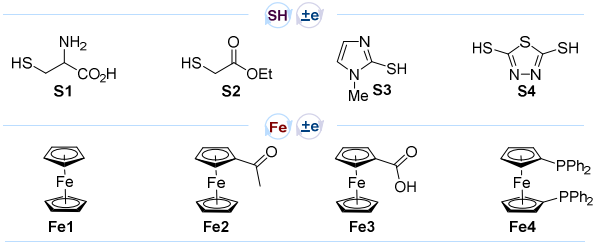
of the iron catalysts, such as ferrocene **Fe1**, $Fe(ClO_4)_2$ could afford acetophenone in the absence of thiols, but in low yield with the concomitant formation of unidentifiable compounds (Table 1, entries 10-12). These results suggest that this reaction is indeed catalyzed by iron catalyst and the thiol might play a synergistic role in facilitating the selective oxidation of C=C bonds.

Table 1 Representative results for the optimization of the iron-catalyzed selective oxidation of 2-Phenyl-1-Propene **1a**[a]



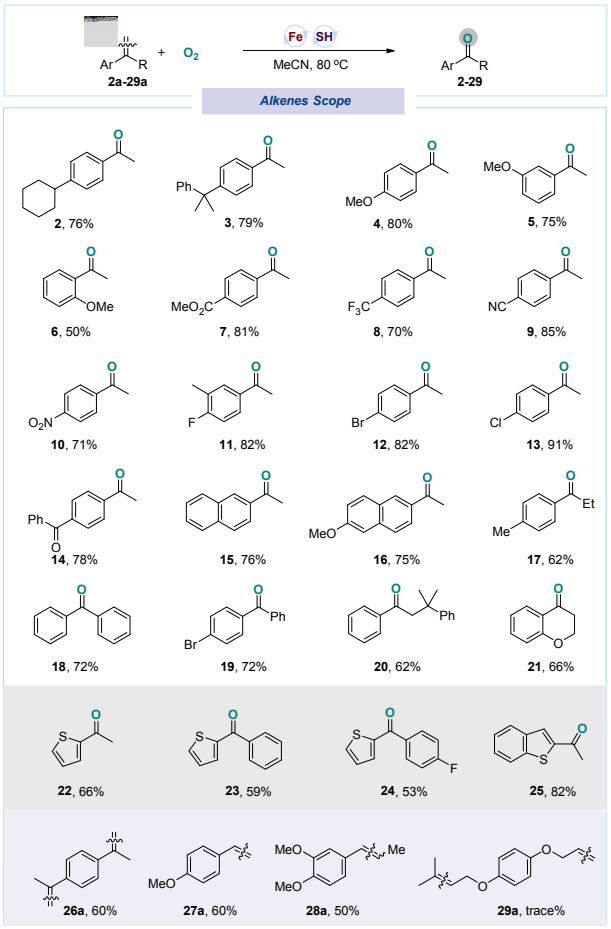
Entry	Thiol (10 mol%)	[Fe] (10 mol%)	Yield[b]
1	**S1**	$Fe(ClO_4)_2$	32%
2	**S2**	$Fe(ClO_4)_2$	44%
3	**S2**	**Fe1**	44%
4	**S3**	**Fe1**	25%
5	**S4**	**Fe1**	45%
6	**S4**	**Fe2**	67%
7	**S4**	**Fe3**	64%
8	**S4**	**Fe4**	85% (81%)
9		**Fe4**	trace
10		**Fe1**	29%
11		$Fe(ClO_4)_2$	15%
12		$Fe(acac)_3$	trace



[a]Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv), O_2 (1 atm), [Fe] (0.03 mmol, 0.1 equiv), thiol (0.03 mmol, 0.1 equiv), MeCN (0.5 mL), 80 °C, 15 h. [b]Determined by ^1H NMR using mesitylene as an internal standard. The isolated yield is shown in parentheses.

With the optimized reaction conditions in hand, we examined the scope of this iron-catalyzed oxidative cleavage reaction. As shown in Table 2, when α-alkyl aryl ethylenes were used as substrates, the reaction proceeded smoothly, delivering the corresponding products in good to excellent yields. Functional groups, such as methoxy, halides, nitro, cyano, alkoxycarbonyl, carbonyl, and trifluoromethyl were well-tolerated. Alkenes bearing alkyl group, led to the desired products in 76-79% yields (**2**-**3**). Both electron-rich and electron-poor alkenes proceeded smoothly without loss of efficiency, furnishing the corresponding ketones in good to excellent yields (**4**-**10**, 50-85%). The alkenes containing a strong electron-donating group methoxy were excellent substrates, and the transformations with **4a**-**5a** proceeded in 75-80% yields. The efficiency of this reaction was somewhat reduced in the case of **6a** bearing an ortho-substituent on the aromatic ring. Notably, this reaction was not only limited to α-methyl aryl ethylenes. Substrates **17a**-**21a** with bulky substituents were also well-tolerated, producing the ketones in 62-72% yields. In addition, products **17**, **20** were formed in good yields with no observed products deriving from olefin isomerization, in contrast to previously-described methods.[11f] Asymmetric diaryl ketones are multifaceted compounds in organic chemistry, which are usually prepared from C–H arylation of aldehydes.[19] Further, good yields were obtained, when 1,1-diaryl alkenes were examined (**18a**, **19a**, **23a**, **24a**), showing that our protocol is an excellent alternative strategy to access asymmetric diaryl ketones. Most remarkably, naphthalene derivatives (**15a**, **16a**) and heterocyclic alkenes (**22a**-**25a**) were also suitable substrates, affording the corresponding products in moderate to excellent yields (75-76%, 53-82%, respectively). This is in a sharp contrast to previous results,[12f] in which the substrates bearing a bulky naphthyl group or a heterocyclic ring proceeded only in low efficiency due to the steric and coordination effect between the substrates and the catalyst.

Table 2 Scope of the iron-catalyzed oxidative cleavage of alkenes[a]



[a]Reaction conditions: alkenes (0.3 mmol, 1.0 equiv), O_2 (1 atm), 1,1'-bis(diphenylphosphino)ferrocene (0.03 mmol, 0.1 equiv), bismuththiol (0.03 mmol, 0.1 equiv), MeCN (0.5 mL), 80 °C, 15 h.

Substrate **26a** possessing two styrenyl unsaturated bonds exhibited good reactivity, delivering the desired compound (**26**)

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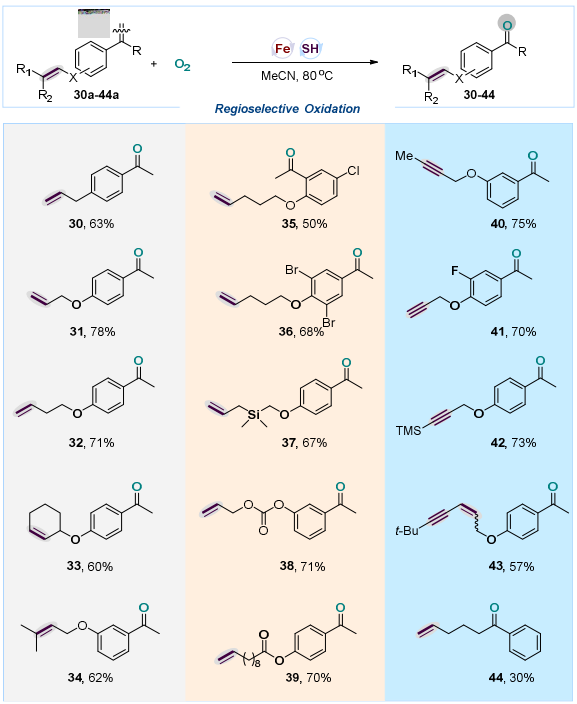
in 60% yield. It should be addressed that electron-rich styrene derivative 4-methoxystyrene (**27a**) produced the desired product in a moderate yield. Interestingly, substrate **28a** containing a less accessible, internal C=C bond also proceeded well. Moreover, we observed that aliphatic alkenes (**29a**) were not reactive, leading only to trace amount of the cleavage product, likely owing to the equilibrium of the thiyl/olefin addition reaction favoring the *S*-centered radical. This result encouraged us to further investigate the regioselectivity of this transformation (*vide infra*).

To evaluate the regioselectivity of this transformation, we subjected substrates containing multiple-unsaturated bonds to the optimized reaction conditions (Table 3). Moderate to excellent yields of the desired compounds were obtained without over-oxidation. Notably, we found that in these substrates bearing multiple unsaturated bonds as substrates, the oxidative cleavage preferred the conjugated π-extended backbones, yielding the mono-oxidized products with high efficiency (**30**-**43**, 50%-78% yields). The high selectivity of this transformation could be accredited to the new generated π-extended carbon-centered radical is more stable than the unconjugated carbon-centered radical. This transformation could also tolerate a wide range of functional groups on the side chains. Base-sensitive groups, such alkoxycarbonyl, trimethylsilyl, allylsilyl, and carbonate were amenable to this protocol. Substrate (**30a**) containing an allyl group on the aromatic ring provided the corresponding product **30** in 63% yield. In contrast, with a double bond tethered to the α-alkyl substituent, the substrate reacted with low efficiency, yielding 30% yield of **44** under the standard conditions. The low efficiency was likely due to intramolecular radical cyclization.

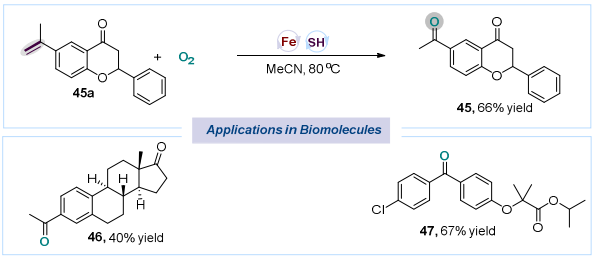
Table 3 Scope of the Iron-Catalyzed Regioselective Oxidative Cleavage of Alkenes[a]



[a]Reaction conditions: alkenes (0.3 mmol, 1.0 equiv), O_2 (1 atm), 1,1'-bis(diphenylphosphino)ferrocene (0.03 mmol, 0.1 equiv), bismuththiol (0.03 mmol, 0.1 equiv), MeCN (0.5 mL), 80 °C, 15 h.

Substrate possessing an allyloxy group was also tolerated, furnishing **31** in good yield (78%). Furthermore, substrates with prolonged carbon chains could proceed well, yielding the ketones (**32**, **35**, **36**, **39**) in 50-71% yields. Multi-substituted olefins could also be tolerated, as the substrates were converted to the desired compounds (**33**, **34**) in moderate yields (60-62%) without loss of selectivity. Interestingly, alkenes bearing alkynyl group were excellent substrates, furnishing the corresponding products (**40**-**43**) in 57-75% yields. It is noteworthy that **43a** bearing a conjugated unsaturated bond system also proceeded well. These results demonstrate excellent regioselectivity inherent to this thiyl radical-mediated approach, which is complementary to the traditional approaches.[5-6]

The inherent value of this selective alkene cleavage protocol was further demonstrated by its applicability to bio-relevant compounds. As such, flavanone- and estrone-derived alkenes underwent this C=C bond cleavage smoothly, delivering the desired products (**45**, **46**) in reasonable to good yields (66% and 40%, respectively). We could easily prepare fenofibrate **47**, a pharmaceutical that is mainly used to reduce cholesterol levels in people at risk of cardiovascular disease, from the analogous olefin precursor in 67% yield. This late-stage cleavage strategy could provide a versatile method to access valuable molecules in medicinal chemistry. To demonstrate the practicality of this transformation, the acetophenone **1** could be synthesized on a 25g scale, and was obtained in 62% yield.



Scheme 3 Synthesis of Biologically Active Compounds via Oxidative Cleavage of Alkenes

Mechanism studies

To gain further insight into the mechanism of this oxidative alkene cleavage reaction, a radical clock experiment was carried out. Instead of ring opening product, compound **48** was obtained in 65% yield when (1-cyclopropylvinyl)benzene was subjected to the standard reaction conditions. Furthermore, to probe whether a free radical really exists in this reaction, EPR studies of this reaction were conducted using phenyl tert-butyl nitrone (PBN) as a spin-trapping agent, and demonstrated that a free radical was involved in this reaction (for details, see the Supporting Information).[12f]

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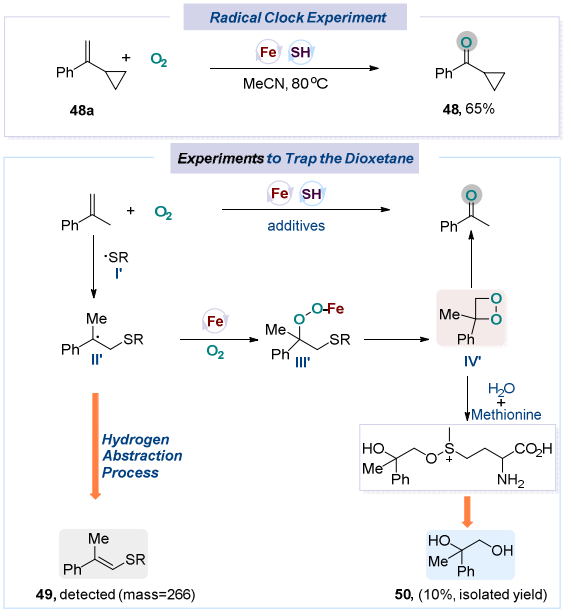
Additionally, we observed trace amount of vinyl thioether **49** on LC-MS; we speculate that compound **49** was produced from intermediate **II'** via a hydrogen abstraction process. So far, we have not been able to directly observe the key intermediate dioxetane owing to its instability. Inspired by Wang's work, we were pleased to observe that diol **50** was successfully isolated when the reaction was performed in the presence of stoichiometric amount of methionine and water.[9, 20] These results suggest that the proposed mechanism illustrated in Scheme 2 is reasonable. Continued studies are ongoing in our laboratory to further elucidate the mechanism of this reaction, including direct observation of key intermediates.



Scheme 4 Mechanistic Studies

Conclusions

In conclusion, we have developed the first example of oxidative cleavage of alkenes to carbonyl compounds via an iron/thiol dual catalytic system. The reaction proceeds under mild conditions at one atm of O_2 with high chemo- and regioselectivity and broad substrate scope, as well as excellent functional group compatibility. A notable feature of this method is its compatibility for late-stage oxidation of bioactive compounds in good yields, providing good opportunities for applications in drug discovery and development. Preliminary mechanistic studies suggest that a dioxetane intermediate might be involved in this reaction, and both iron and thiyl radical play important roles in the catalytic cycle. Further studies to expand this novel transformation are undergoing in our lab and the results will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support from National Natural Science Foundation of China (Nos. 21572027, Nos. 21801029) 100 Talent Plan from Chongqing University (0247001104405). We thank Prof. Xingang Zhang (Shanghai Institute of Organic Chemistry), Dr. Gang Li (Princeton University) and Dr. Jeffrey M. Lipshultz (Princeton University) for helpful discussions.

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DOI: 10.1039/C8GC02369G

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