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Fe–S Catalyst Generated In Situ from Fe(III)- and $S_3^{\bullet-}$-Promoted Aerobic Oxidation of Terminal Alkenes

Jing-Jing Ai, Bei-Bei Liu, Jian Li, Fei Wang, Cheng-Mi Huang, Weidong Rao, and Shun-Yi Wang*

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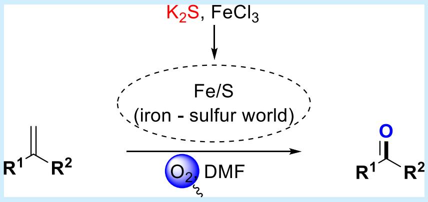
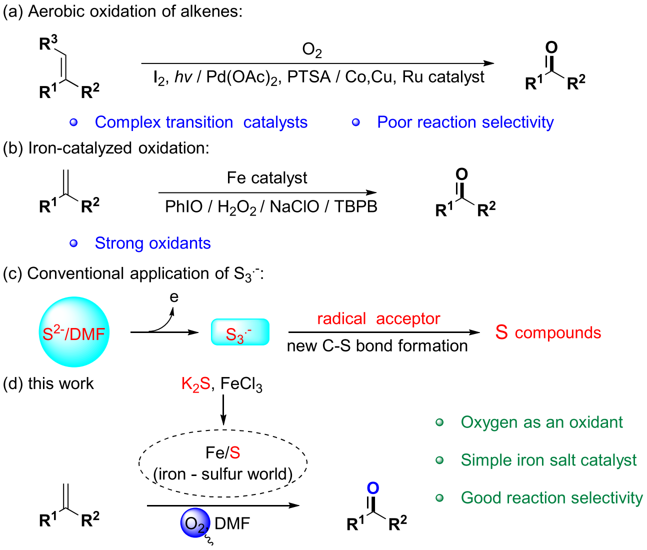
ABSTRACT: An iron–sulfur complex formed by the simple mixture of $FeCl_3$ with $S_3^{\bullet-}$ generated in situ from K_2S is developed and applied to selective aerobic oxidation of terminal alkenes. The reaction was carried out under an atmosphere of O_2 (balloon) and could proceed on a gram scale, expanding the application of $S_3^{\bullet-}$ in organic synthesis. This study also encourages us to explore the application of an Fe–S catalyst in organic reactions.



The selective oxidative cracking of alkenes has a wide range of applications in the fields of organic synthesis, pharmaceuticals, agrochemicals, and materials.[1] For example, it can realize the introduction of oxygen functionalities into molecules, the deprotection of functional groups, and the degradation of macromolecules.[2] Ozonolysis with ozone as an oxidant is still the most used method for this transformation, despite there being many serious safety issues with the method and the high requirements for reaction equipment.[3] In addition, a chemical oxidation with stoichiometric oxidants, for example, $KMnO_4$,[4] OsO_4,[5] $PhIO/HBF_4$,[6] m-CPBA,[7] H_2O_2,[8] and TBHP,[9] has been considered as an effective alternative. However, these reagents are toxic themselves, and a large amount of waste is generated, with some being highly toxic. In recent years, the development of environmentally friendly oxidation protocols is attracting a growing amount of attention,[10] especially methods based on clean oxidants in combination with metal catalysts.[10,11] As an oxidant, molecular oxygen, which has high atomic efficiency and economy, has attracted a great deal of attention (Scheme 1a).[12]

Fe_4S_4 clusters such as [2Fe-2S], [3Fe-4S], and [4Fe-4S] clusters widely exist in various proteins with important biological activities, which are clarified in bioinorganic chemistry.[13] Much attention have been paid to the iron–sulfur protein structures to understand their bioactivities;[14] however, the application of iron–sulfur clusters or iron–sulfur protein (Figure 1) in organic reactions[15] has not been well studied. It is more desirable to develop a simple protocol for the preparation of iron–sulfur clusters or complexes and apply them in organic reactions. In addition to the Fe_4S_4 clusters, iron-containing compounds have been widely used as catalysts because of their high iron content, low toxicity, low cost, and easy availability. However, all of the catalysts reported so far require an oxidant that is more active than molecular oxygen (Scheme 1b). For example, when an iron–salon complex promoted the oxidation of alkenes in low yields, an excess of H_2O_2 was needed.[16] In the presence of pyridine-carboxylic acids, a simple Fe(II) salt can selectively oxidize alkenes to aldehydes with PhIO as the oxidant and to acetal using H_2O_2.[17] A heterogeneous iron catalyst was reported, which catalyzed the oxidation of styrene by H_2O_2 with very good selectivity; however, the yield was low.[18]

Scheme 1. Selective Oxidation of Terminal Alkenes via (a) a Coventional Oxidation Method, (b) Iron-Catalyzed Oxidation, (c) a Conventional Application of $S_3^{\bullet-}$, and (d) This Work



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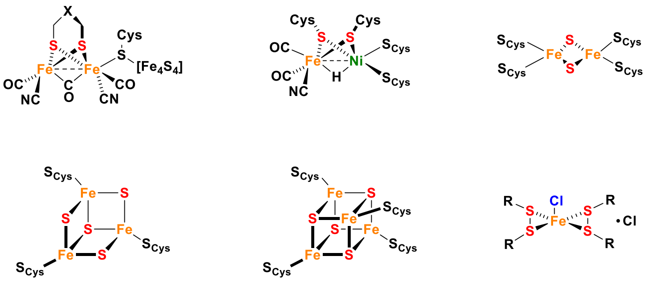
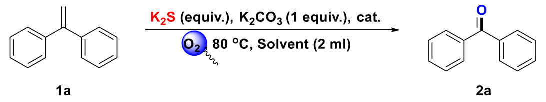


Figure 1. Fe–S cluster and Fe–S compelx catalyst.

$S_3^{\bullet-}$ was discovered more than 40 years ago and can be easily formed by the reaction of elemental sulfur with KOH in DMF at room temperature.[19] Recently, applications of $S_3^{\bullet-}$ species for the synthesis of organic compounds have gradually increased, but almost all of them are used in the synthesis of organic sulfur compounds (Scheme 1c).[20] The new applications in the conversion of other functional groups involving $S_3^{\bullet-}$ have not yet been reported. It is well-known that iron–sulfur proteins can be used as beneficial redox catalysts involving electron transfer.[21] Encouraged by research about the "iron–sulfur world" hypothesis,[21a] we hypothesize that a system similar to iron–sulfur protein can accelerate the selective aerobic oxidation of terminal alkenes. Herein, we demonstrate an iron–sulfur complex, formed by the selective aerobic oxidation of terminal alkenes to carbonyl compounds (Scheme 1d) with a simple mixture of $FeCl_3$ with $S_3^{\bullet-}$ generated in situ from K_2S, promoted the reaction.

Initially, ethene-1,1-diyldibenzene **1a** was treated with K_2S (2.0 equiv), K_2CO_3 (1.0 equiv), and $FeCl_3$ (20 mol %) in DMF at 80 °C for 8 h. From this reaction, benzophenone **2a** was formed in 91% yield (Table 1, entry 1). To improve the efficiency, we tried other diffirent catalysts, changed the amount of catalyst, and found that $FeCl_3$ (20 mol %) has the best catalytic effect (Table 1, entries 2–6). Next, DMSO and DMA were tried as the reaction medium, but the effect on the reaction is not as good as that of DMF (entries 7 and 8). In addition, changing the temperature and the amount of K_2S cannot improve the yield (Table 1, entries 9–12). Intriguingly, when K_2CO_3 was removed from the reaction mixture, the yield increased to 99% (Table 1, entry 13). Finally, we want to find the optimal reaction time (Table 1, entry 14). When the reaction time was decreased to 12 h, the material remained, and the target product was obtained with an isolated yield of 86%. After a series of optimizations of the conditions, the optimized reaction conditions were obtained: ethene-1,1-diyldibenzene **1a** (0.3 mmol), K_2S (0.6 mmol), and $FeCl_3$ (20 mol %) in DMF (2 mL) at 80 °C for 14 h.

Table 1. Optimization of the Reaction Conditions[a]

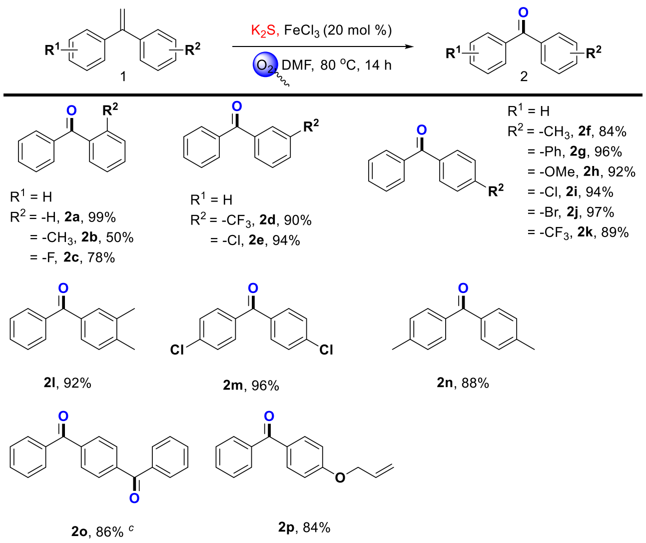


entry	catalyst (mol %)	temp (°C)	K_2S (equiv)	yield (%)[b]
1	$FeCl_3$ (20)	80	2.0	91
2	$Fe(OAc)_2$ (20)	80	2.0	84
3	$Cu(OAc)_2$ (20)	80	2.0	trace
4	$FeCl_3$ (10)	80	2.0	84
5	$FeCl_3$ (5)	80	2.0	37
6	–	80	2.0	trace
7[c]	$FeCl_3$ (20)	80	2.0	83
8[d]	$FeCl_3$ (20)	80	2.0	51
9	$FeCl_3$ (20)	60	2.0	70
10	$FeCl_3$ (20)	100	2.0	88
11	$FeCl_3$ (20)	80	1.0	38
12	$FeCl_3$ (20)	80	–	NR
13[e]	$FeCl_3$ (20)	80	2.0	99
14[f]	$FeCl_3$ (20)	80	2.0	86

[a]Raction conditions: **1a** (0.30 mmol), K_2S (0.60 mmol), catalyst (20 mol %), K_2CO_3 (0.3 mmol), solvent (2 mL), O_2 (1 atm), 14 h. [b]Isolation yields. [c]The solvent is DMA. [d]The solvent is DMSO. [e]Without K_2CO_3. [f]Time of 12 h.

With the optimal reaction conditions in hand, the substrate scope for the synthesis of **2** was investigated. First, we investigated the reaction activity of 1,1-diarylethylene substrates. The results summarized in Scheme 2 show that **1** with just one electron-donating group (EDG) such as methyl, phenyl, or methoxy or an electron-withdrawing group (EWD) such as chloro, bromo, or trifluoromethyl at the *para* or *meta* positions took part in this reaction, smoothly affording **2d–2k** in good yields. However, when there is a substituent in the *ortho* position, the yield is significantly reduced, and target products **2b** and **2c** are obtained in moderate yields. In addition, when there are two substituents on the substrate, whether the substituents are on the same benzene ring or on two benzene rings, the target product (**2l–2n**) can be obtained with yields of 88–96%. To our delight, 1,4-bis(1-phenylvinyl)-benzene can be converted into target product **2o** in 86% yield under the action of K_2S and $FeCl_3$. Notably, when there are two kinds of alkenes in the reactants, they can selectively oxidize aryl-substituted alkenes. For example, 1-(allyloxy)-4-(1-phenylvinyl)benzene can selectively afford target product **2p** in a good yield of 84%.

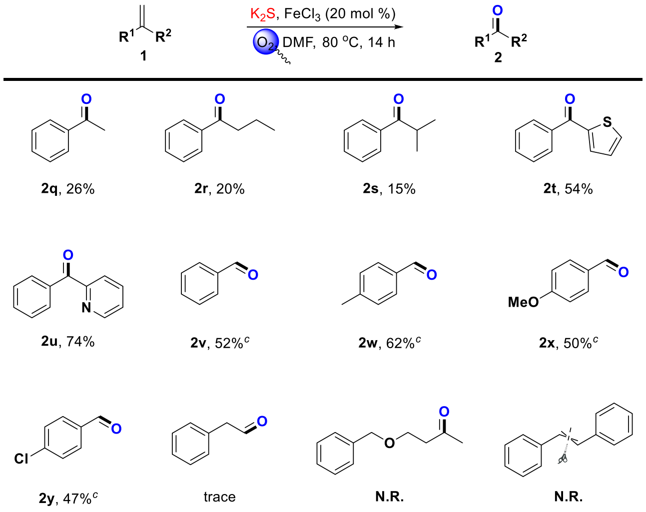
Scheme 2. Substrate Scope of 1,1-Diaryl-Substituted Alkenes[a–c]



[a]Raction conditions: **1** (0.30 mmol), K_2S (0.60 mmol), $FeCl_3$ (20 mol %), DMF (2 mL), O_2 (1 atm), 80 °C, 14 h. [b]Isolated yields. [c]**1** (0.30 mmol), K_2S (1.20 mmol), $FeCl_3$ (40 mol %), DMF (2 mL), O_2 (1 atm), 80 °C, 14 h.

Next, other substituted alkenes have also been studied, and the results are listed in Scheme 3. First, when 1,1-arylalkyl-substituted alkenes were used as substrates, the effect on the

Scheme 3. Substrate Scope of Disulfides[a−c]



[a]Raction conditions: **1** (0.30 mmol), K_2S (0.60 mmol), $FeCl_3$ (20 mol %), DMF (2 mL), O_2 (1 atm), 80 °C, 14 h. [b]Isolated yields. [c]GC yields.

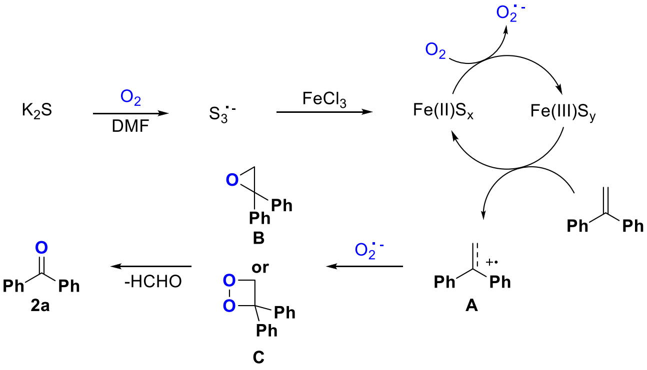
reaction is obviously worse, and we can obtain the target products (**2q**−**2s**) in only 15−26% yields. Next, 2-(1-phenylvinyl)thiophene and 2-(1-phenylvinyl)pyridine can be converted into the corresponding target products **2t** and **2u** in 54% and 74% yields, respectively. In addition, different styrene compounds (**2v**−**2y**) were used for the transformation, and the conversion rates were known to be 47−62%. Further study showed that the alkenes without an aryl substitution and 1,2-diphenylethene do not react smoothly.

To evaluate the application of this oxidation reaction, we scaled up the template reaction to 10 mmol and obtained 1.7 g of target product **2a** in 95% yield (see the Supporting Information for more details). The reaction was allowed to proceed under argon conditions, and it was found that the reaction did not occur (see the Supporting Information for more details). Because epoxide **B** is suspected to be an intermediate in the reaction, **B** is allowed to react under standard conditions. Expectedly, target product **2a** can be obtained with a separation yield of 64%.

To gain some insight into the mechanism of the reaction, an electron paramagnetic resonance (EPR) experiment was carried out (see the Supporting Information for more details). At room temperature, strong free radical signals can be observed in the system, which indicates that the reaction may involve free radicals. To our delight, a strong single EPR signal (g = 2.027) that is very similar to the reported $S_3^{\bullet-}$ detected by the DMF solution of $Na_2S{\cdot}9H_2O$ and elemental sulfur at room temperature can be detected in the DMF solution of K_2S.[17a] However, the signal changed after the addition of $FeCl_3$ to a new signal (g = 2.348). A significant Fe(III) signal can be detected in the DMF solution of $FeCl_3$, and the addition of K_2S will make the signal disappear. We speculate that K_2S may combine with Fe(III) to form a Fe−S complex to promote the reaction. We use *N*-methylindole as a formaldehyde trapping agent and obtain **2a** in 97% yield and **3a** in 26% yield, indicating that formaldehyde may be formed in the reaction system (see the Supporting Information for more details).

On the basis of the experimental results presented above and literature reports, a plausible reaction mechanism is proposed in Scheme 4. $S_3^{\bullet-}$ generated in situ from K_2S reacts with $FeCl_3$ to produce divalent iron−sulfur complex Fe(II)S_x. Subsequently, Fe(II)$_x$S$_y$ promotes the conversion of oxygen (O_2) into superoxide anion radical ($O_2^{\bullet-}$) with the formation of a trivalent iron−sulfur complex Fe(III)S_y. The oxidation of 1,1-diphenylethylene generated by Fe(III)S_y gives radical cation intermediate **A** and regenerates Fe(II)S_x. Then, a cycloaddition between $O_2^{\bullet-}$ and radical cation intermediate **A** affords an epoxide intermediate **B** or dioxetane **C**. The subsequent C−C bond cleavage of **B** or **C** gives the desired product **2a**.[22]

Scheme 4. Proposed Mechanism



In summary, a selective oxidation reaction of terminal olefins promoted by $S_3^{\bullet-}$ catalyzed by Fe(III) is discovered. The reaction is carried out under an oxygen atmosphere and can be carried out in units of grams, thereby providing a convenient and practical method for converting terminal olefins into carbonyl compounds and expanding the application of $S_3^{\bullet-}$ in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01408.

Detailed experimental procedures and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Shun-Yi Wang − *Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science & Collaborative Innovation Center of Suzhou Nano Science and Technology, Soochow University, Suzhou 215123, China*; orcid.org/0000-0002-8985-8753; Email: shunyi@suda.edu.cn

Authors

Jing-Jing Ai − *Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science & Collaborative Innovation Center of Suzhou Nano Science and Technology, Soochow University, Suzhou 215123, China*

Bei-Bei Liu − *Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science & Collaborative Innovation Center of Suzhou Nano Science and Technology, Soochow University, Suzhou 215123, China*

Jian Li − *Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science & Collaborative Innovation Center of*

Suzhou Nano Science and Technology, Soochow University, Suzhou 215123, China

Fei Wang − *Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science & Collaborative Innovation Center of Suzhou Nano Science and Technology, Soochow University, Suzhou 215123, China*

Cheng-Mi Huang − *Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science & Collaborative Innovation Center of Suzhou Nano Science and Technology, Soochow University, Suzhou 215123, China*

Weidong Rao − *Key Laboratory of Biomass-based Green Fuels and Chemicals, College of Chemical Engineering, Nanjing Forestry University, Nanjing 210037, China;* orcid.org/0000-0002-6088-7278

Complete contact information is available at:
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Notes

The authors declare no competing financial interest.

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