

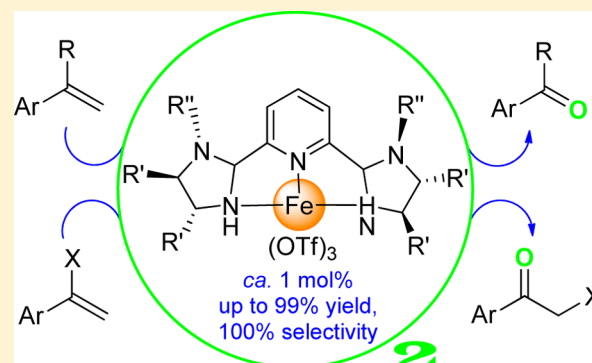
Green and Efficient: Iron-Catalyzed Selective Oxidation of Olefins to Carbonyls with O₂

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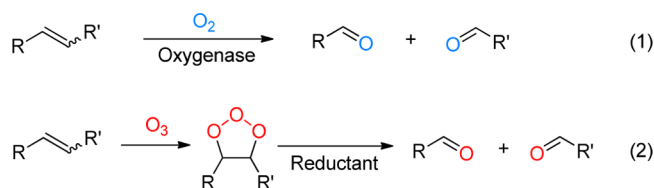
S Supporting Information

ABSTRACT: A mild and operationally simple iron-catalyzed protocol for the selective aerobic oxidation of aromatic olefins to carbonyl compounds is described. Catalyzed by a Fe(III) species bearing a pyridine bisimidazoline ligand at 1 atm of O₂, α - and β -substituted styrenes were cleaved to afford benzaldehydes and aromatic ketones generally in high yields with excellent chemo-selectivity and very good functional group tolerance, including those containing radical-sensitive groups. With α -halo-substituted styrenes, the oxidation took place with concomitant halide migration to afford α -halo acetophenones. Various observations have been made, pointing to a mechanism in which both molecular oxygen and the olefinic substrate coordinate to the iron center, leading to the formation of a dioxetane intermediate, which collapses to give the carbonyl product.



INTRODUCTION

Heme and nonheme enzymes capable of activating dioxygen can serve as versatile catalyst for a wide spectrum of reactions. Apart from selectively oxidizing CH bonds in complex substrates, such enzymes can selectively cleave aromatic,¹ olefinic² or aliphatic³ C–C bonds in organic molecules with concomitant incorporation of oxygen functionalities into the final products. As a matter of fact, such natural aerobic cleavages constitute one of the most significant transformations in biological processes. In particular, heme and nonheme oxygenases can oxidize olefins to carbonyl compounds under mild conditions with exquisite selectivity (eq 1).² To mimic the



oxidation ability of iron-based enzymes, numerous iron complexes have been designed and synthesized.⁴ However, none appears to catalyze the selective oxidative cleavage of olefinic C=C double bonds under an atmosphere of O₂.

Oxidative scission of alkenes into carbonyls is a widely practiced transformation in synthetic chemistry. It allows the incorporation of oxygen functionalities into molecules, functional group deprotection, and degradation of large molecules, such as those derived from biomass.⁵ Not surprisingly, it has been used in the synthesis of a great number of pharmaceutical and bioactive compounds in both academia and industry.⁶

What might be surprising is that until today, this transformation is still practiced most often with ozonolysis,^{5,6a,c,7} despite the serious, well-known safety issues associated with the use of ozone as oxidant,^{5a,8} the high cost of special equipment, and the large amount of waste generated during the work-up (eq 2). This is because there are few other methods that are more effective in terms of selectivity, yield, and cleanness. Thus, while stoichiometric oxidants, such as *meta*-chloroperoxybenzoic acid,⁹ PhIO/HBF₄,¹⁰ KMnO₄, CrO₂Cl₂ or OsO₄, can be used for selectively cleaving olefins into carbonyl compounds, large amounts of waste are encountered, with some being highly toxic.

In recent years, the development of environmentally benign oxidation protocols is gaining growing interest,^{11,4a} with methods based on metal catalysts in combination with clean oxidants being highly sought after.^{11,12} In particular, the development of cheap metal catalysts capable of activating molecular oxygen is of upmost interest, due to the high atom efficiency and process economy associated with such catalysts. Oxidative cleavage of olefins into carbonyls is no exception, and significant efforts have been made toward the design of new methods to allow O₂ to be used as oxidant.^{11b,13} Thus, under a high temperature and oxygen pressure, Pd(OAc)₂ was found to cleave olefins into carbonyls in water in the presence of additives.¹⁴ And under visible light irradiation, a Pt(II) polypyridyl complex was found to promote the aerobic oxidation of aminopent-3-en-2-ones to diketones, affording 1,2-acyl migration in the presence of an alcohol.¹⁵ Cheaper

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cobalt-based catalysts enabled the scission of styrenes under mild aerobic conditions; however, a low selectivity was achieved due to the formation of undesired diols¹⁶ or radical-derived byproducts.¹⁷ More easily available copper salts also catalyzed the aerobic cleavage of electron-rich enamines and enol ethers and styrene under electrocatalytic conditions.¹⁸ Applying forcing conditions, Mn-tetraphenyl porphyrines could oxidatively cleave styrene with modest chemoselectivity.¹⁹ Interestingly, the aerobic oxidation of styrenes could also be carried out by using an organocatalyst, *N*-hydroxyphthalimide, albeit with a high catalyst loading (10%).²⁰

The use of iron-based catalysts has been actively pursued, given the abundance of iron, its low toxicity and the remarkable ability of heme and nonheme oxygenases in cleaving C=C double bonds.² However, the catalysts reported so far all necessitate oxidants more active than molecular oxygen (Figure 1).

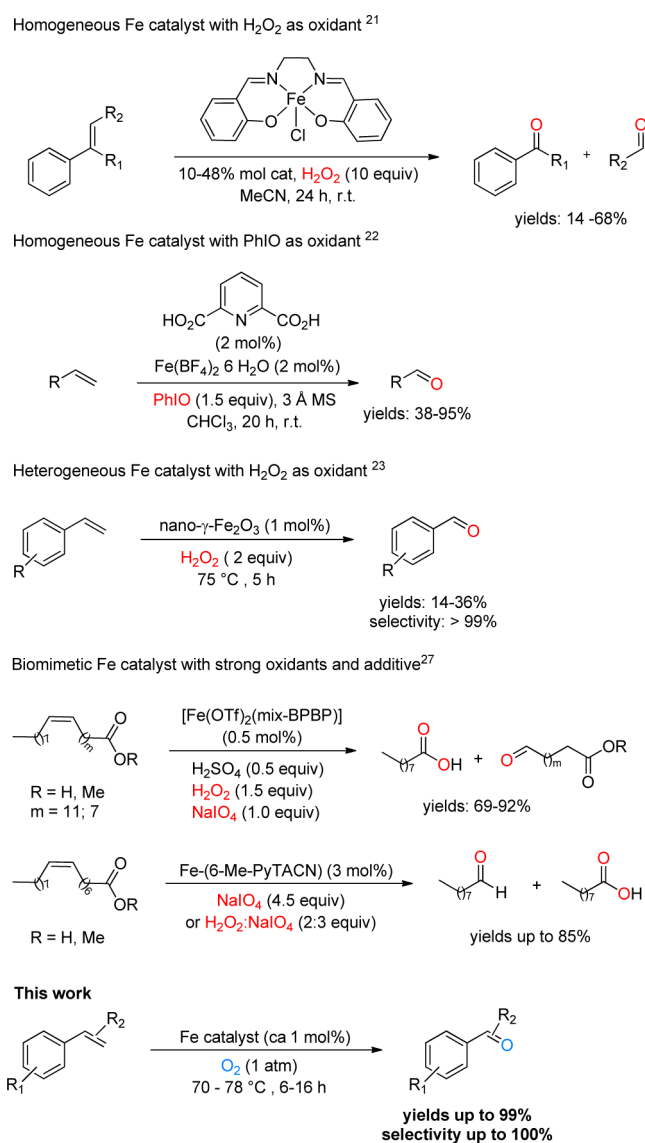


Figure 1. Iron-catalyzed oxidative cleavage of olefins.

Examples are seen in an iron-salen complex, which promoted the oxidation of styrenes in low yields using an excess of H₂O₂.²¹ Simple Fe(II) salts in the presence of pyridinecarboxylic acids allowed the selective oxidation of styrenes to acetals

with H₂O₂ as oxidant and to aldehydes using PhIO.²² A heterogeneous iron catalyst, which catalyzed the cleavage of styrenes by H₂O₂ with very good selectivity but low yields, was also reported.²³ Biomimetic iron complexes bearing multi-dentate *N*-donor ligands have been widely applied to olefin epoxidation,²⁴ *cis*-hydroxylation²⁵ and to a less degree allylic oxidation,²⁶ using H₂O₂ as oxidant. However, the use of such catalysts for the oxidative cleavage of olefins is less explored, with the oxidative cleavage of fatty acids using strong oxidants and additives being the only example in the literature.²⁷

Clearly, while there is a strong incentive to replace ozone for olefin cleavage, none of the catalysts reported to date are able to offer an efficient, benign alternative, i.e., using O₂ with high product selectivity under mild conditions. In a very recent review on metal-catalyzed C=C double bond cleavage, it was remarked that, "In order to find alternatives for ozone, it is important that the selectivity towards the cleavage products is high. Common side reactions such as epoxidation, dihydroxylation or allylic oxidation should be prevented, and this still remains a challenge."¹³ Overoxidation to carboxylic acids and/or esters can further erode the selectivity.¹³

We have recently developed a family of Fe(II)-pyridine bis-sulfonamide catalyst (Fe(II)-PyBisulidine), which allows for the α -oxygenation of ethers under aerobic conditions with excellent chemoselectivity under mild conditions.²⁸ Further study has revealed that the oxidation proceeds via an unprecedented dehydrogenative-oxygenation mechanism, with oxygen displacing H₂. Herein we disclose a new protocol for the selective cleavage of styrenes into aldehydes or ketones using closely related Fe(III)-PyBisulidine catalysts. The protocol features excellent chemoselectivity and functional group tolerance, O₂ as oxidant, and mild, additive-free conditions. As with our previous study, no freely diffusing radicals appear to be involved in the reaction. Instead, the iron-catalyzed oxidative cleavage appears to be triggered off by olefin and O₂ coordination to the iron center followed by the formation of a dioxetane intermediate.

RESULTS AND DISCUSSION

1. Fe(OTf)₃-L1-Catalyzed Aerobic Cleavage of Styrenes. To start our investigation, the sterically nonencumbered and slightly electron-rich 4-methylstyrene **1a** was chosen as model substrate. No oxidative cleavage was observed when **1a** was exposed to a catalytic amount of Fe(OTf)₂ in the presence of the ligand **L1** (Figure 2) under an aerobic atmosphere in

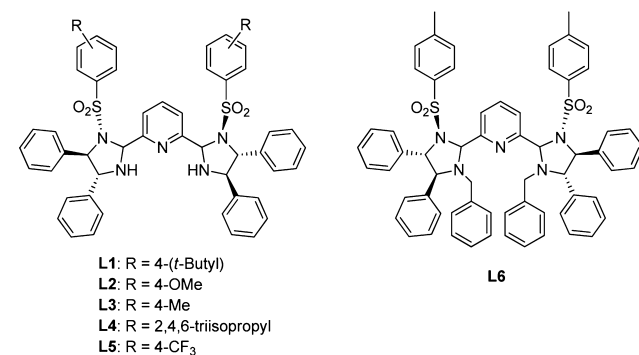
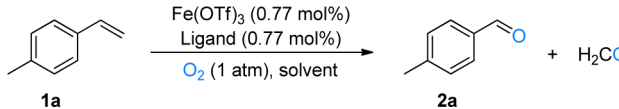


Figure 2. PyBisulidine ligands used in this study.

dichloromethane (DCM) (Table 1, entry 1). **L1** is known to react readily with Fe(OTf)₂, affording the structurally

Table 1. Screening Conditions for the Aerobic C=C Cleavage of 4-Methylstyrene^a


entry	catalyst	solvent	temp/°C	conversion/% ^b
1	Fe(OTf) ₂ -L1	DCM	40	N.R.
2	Fe(OTf) ₃ -L1	DCM	40	18
3	Fe(OTf) ₃ -L1	DCE	40	11
4	Fe(OTf) ₃ -L1	DCE	60	61
5	Fe(OTf) ₃ -L1	DCE	65	78
6	Fe(OTf) ₃ -L1	DCE	70	99
7 ^c	Fe(OTf) ₃ -L1	DCE	70	73
8 ^d	Fe(OTf) ₃ -L1	DCE	70	49
9 ^e	Fe(OTf) ₃	DCE	70	–
10	Fe(OTf) ₃ -L2	DCE	70	84
11	Fe(OTf) ₃ -L3	DCE	70	82
12	Fe(OTf) ₃ -L4	DCE	70	60
13	Fe(OTf) ₃ -L5	DCE	70	51
14	Fe(OTf) ₃ -L6	DCE	70	N.R.
15	Fe(OTf) ₃ -L1	CHCl ₃	70	37
16	Fe(OTf) ₃ -L1	Ph-H	70	20
17	Fe(OTf) ₃ -L1	MeCN	70	N.R.
18	Fe(OTf) ₃ -L1	iPrOH	70	N.R.
19 ^f	Fe(OTf) ₃ -L1	DCE	70	34
20 ^g	Fe(OTf) ₃ -L1	DCE	70	99
21 ^h	Fe(OTf) ₃ -L1	DCE	70	99

^aReaction conditions: Fe(OTf)₃ (2.9 mg, 5.76 × 10⁻³ mmol; 0.77 mol%) and ligand (5.3 mg, 5.78 × 10⁻³ mmol; 0.75 mol%) in solvent (0.5 mL), stirred at 35 °C for 1 h. Then substrate (0.75 mmol) was added and the reaction stirred at a given temperature under O₂ (1 atm) for 6 h. ^bConversion to **2a**, determined by ¹H NMR. N.R. = no reaction. ^cReaction run in 0.6 mL of solvent. ^dReaction run in 0.8 mL of solvent. ^eFull substrate decomposition. ^fThe amount of **L1** decreased with **L1/Fe** = 0.5. No starting material was observed in the ¹H NMR of the crude reaction but significant substrate decomposition was observed. ^gThe amount of **L1** increased with **L1/Fe** = 2.0. ^hThe amount of **L1** increased with **L1/Fe** = 3.0.

characterized [FeL1(THF)(OTf)₂] in THF.²⁸ However, replacement of the iron salt with the stronger Lewis acid Fe(OTf)₃²⁹ cleanly furnished the aldehyde product **2a** and formaldehyde, albeit in low yield (entry 2). This might not be surprising, as Fe(OTf)₃ is known to be more active in activating olefins than Fe(OTf)₂.³⁰ Using the Fe(OTf)₃-**L1** combination as catalyst, the conversion of **1a** to **2a** increased gradually by raising the reaction temperature in dichloroethane (DCE), with full conversion achieved at 70 °C in 6 h (entry 6). It must be noted that complete decomposition of **1a** was observed when Fe(OTf)₃ alone was used as catalyst (entry 9), highlighting the critical role of the ligand in controlling the activity and selectivity of the Fe(III) center in the aerobic cleavage. This is further seen in the reactions where the ligands **L2–L6** (Figure 2) were attempted (entries 10–14). While the relatively electron-rich **L2–L4** led to good conversions, the electron-deficient **L5** showed poor performance and the sterically demanding **L6**, which unlike **L1–L5** contains no NH protons (also see below), was found totally inactive (entry 14). Among the solvents examined, DCE was found the most suitable (entries 15–18), especially at high substrate concentrations (entries 6–8).

In the reactions above, the catalyst was *in situ* generated from the ligand and Fe(OTf)₃. It is worth noting that while

increasing the **L1/Fe** ratio did not affect the conversion or the selectivity of the reaction (entries 6, 20, and 21), a deficit of ligand resulted in a significantly lower conversion and a loss of selectivity due to the decomposition of **1a** (entry 19). Given the bulkiness of **L1** which would render less likely the coordination of two ligands to one iron center, this is consistent with the active catalyst bearing one **L1** per iron center. Indeed, reacting **L1** with Fe(OTf)₃ in DCE led to an isolable mononuclear compound, [FeL1(OTf)₃], according to the elemental, Nano-ESI-MS, and IR analysis (see the Supporting Information (SI)), and this compound showed the same activity and selectivity as the *in situ* generated species in the oxidation of **1a**. Attempts to crystallize the iron complex in various solvent mixtures were unsuccessful, although its structure may be expected to be similar to that of [FeL1(THF)(OTf)₂].²⁸

With the optimal reaction conditions in hand, a variety of styrenes were subjected to the Fe(OTf)₃-**L1**-catalyzed aerobic cleavage, where the catalyst was *in situ* formed. As can be seen from Table 2, the corresponding aldehydes were obtained in good to excellent yields at a low catalyst loading of 0.77 mol%. The catalyst tolerated the presence of both electron-withdrawing (**1c–1f**) and relatively electron-donating (**1a**, **1i**, **1j**) substituents in the *para*- and *meta*-positions of the aromatic region. More sterically demanding *ortho*-substituted styrenes (**1k–1n**), including remarkably the 2,6-dichloro-substituted **1n**, were also oxidized, although longer reaction times were needed for obtaining the desired aldehydes in preparative yields. This most likely results from the substrate C=C bond being less accessible for coordination to the iron center, which seems essential for the reaction to occur (*vide infra*). However, the aerobic cleavage of substrates incorporating bulky aromatics (**1o**, **1p**) proceeded with more moderate yields. This is probably due to steric clashes between the substrate and the bulky ligand **L1**, and particularly those coming from the naphthyl or phenyl group of these substrates and the imidazoline moiety of **L1**. One phenyl and the *tert*-butylphenyl units on each of the imidazoline rings point to the way of olefin coordination to the Fe(III) (see the X-ray structure of [FeL1(THF)(OTf)₂]²⁸ and last part of section 6).

It is noted that these aerobic reactions proceeded cleanly, furnishing the aldehyde products with high selectivity with no over oxidation to the carboxylic acid observed. Competing formation of other oxidation products, such as diols, epoxides or allylic alcohols or solvent decomposition, was not observed either. Formaldehyde was the only additional product detected during the oxidation, suggesting the incorporation of one O₂ molecule per olefin substrate (also see below).

2. Aerobic Cleavage of α -Substituted Styrenes. The aerobic cleavage of α -substituted styrenes was expected to afford ketones and next investigated (Table 3). Delightfully, α -methylstyrenes (**3a–3e**), including a 2-fluoro-substituted one (entry 5), were oxidatively cleaved in good yields, again at a low catalyst loading (1.15 mol%). For these reactions, the bulkier **L4** afforded somehow slightly higher yields than **L1** when combined with Fe(OTf)₃ and so was chosen as the ligand. For example, **4a** was obtained in 68% yield when using Fe(OTf)₃-**L1** under otherwise the same conditions. Substrate **3f** bearing a pyridine ring was also oxidized, albeit with low yield. In addition, the aerobic cleavage proceeded with similarly good yields when the methyl group was replaced with bulkier alkyl cycles (**3g–3i**). Of particular note is the clean cleavage of **3g**, suggesting no formation of radicals in the olefin during the oxidation (*vide infra*). Styrenes bearing very sterically demanding α -substituents (**3j**, **3k**) were also well tolerated by

Table 2. Aerobic C=C Cleavage of Styrenes Catalyzed by Fe(OTf)₃-L1^a

Entry	Substrate (rsm% ^b)	Product (isol. yield%)	Entry	Substrate (rsm% ^b)	Product (isol. yield%)
1	1a	2a (96%)	10	1j (20%)	2j (78%)
2	1b (21%)	2b (77%)	11	1k ^c (2%)	2k (95%)
3	1c (20%)	2c (79%)	12	1l ^c (2%)	2l (96%)
4	1d (11%)	2d (87%)	13	1m ^c (19%)	2m (79%)
5	1e (21%)	2e (78%)	14	1n ^c (40%)	2n (58%)
6	1f (9%)	2f (90%)	15	1o (64%)	2o (30%)
7	1g (5%)	2g (93%)	16	1p (40%)	2p (57%)
8	1h (25%)	2h (75%)			
9	1i (4%)	2i (95%)			

^aReaction conditions: Fe(OTf)₃ (2.9 mg; 5.76 × 10⁻³ mmol), L1 (5.3 mg; 5.78 × 10⁻³ mmol), in DCE (0.5 mL), stirred at 35 °C for 1 h. Then substrate (0.75 mmol) was added and the reaction heated to 70 °C for 6 h under O₂ (1 atm). ^bRecovered starting material. ^cReaction run for 24 h at 70 °C.

the iron catalyst, affording bulky ketones in preparative yields. Significantly, substrate **3k** incorporating a norbornene ring was transformed to **4k** selectively with no oxidation of the aliphatic C=C bond or ring cleavage being observed. In addition, styrenes bearing a halo substituent in the aliphatic chain (**3l**, **3m**) were also oxidized cleanly, resulting in the selective formation of the ketone products with no undesired dehalogenation taking place. The potential usefulness of this green, aerobic transformation in synthetic chemistry is further exemplified in the selective oxidation of 1,1-diaryl alkenes to unsymmetrical diaryl ketones of industrial significance.³¹ These results appear to suggest that the catalyst is far more tolerant of steric interactions arising from α substitution than those from substitution on the phenyl ring of styrene, presumably reflecting how the olefin approaches the iron center (*vide infra*).

3. Aerobic Cleavage of β -Substituted Styrenes. Next we focused our attention on the aerobic fragmentation of β -substituted styrenes, in which the C=C double bond is less accessible (Table 4). *trans*- β -Methylstyrene **5a** was oxidatively cleaved into benzaldehyde and acetaldehyde with excellent yield under the catalysis of Fe(OTf)₃-L1. From a synthetic perspective, the oxidation of a commercial *cis/trans* mixture of methyl isoeugenol **5b** is interesting, **6b** being formed in a preparative yield and excellent chemoselectivity with no other reactions being detected under the reaction conditions. However, when a *cis/trans* mixture of isoeugenol **5c** was subjected to the reaction conditions, the dimeric γ -diisoeugenol was obtained quantitatively at a catalyst loading as low as 0.75 mol%. Although diisoeugenol dimers have attracted great interest in drug design,³² to the best of our knowledge, there are

Table 3. Fe(OTf)₃-L4-Catalyzed Aerobic C=C Cleavage of α -Substituted Styrenes^a

Entry	Substrate (<i>rsm</i> % ^b)	Product (isol. yield%)	Entry	Substrate (<i>rsm</i> % ^b)	Product (isol. yield%)
1	3a (12%)	4a (87%)	9	3i (25%)	4i (73%)
2	3b (15%)	4b (85%)	10	3j ^c (42%)	4j (54%)
3	3c (16%)	4c (83%)	11	3k ^c (20%)	4k (78%)
4	3d ^c (1%)	4d (98%)	12	3l ^c (5%)	4l (92%)
5	3e ^c (2%)	4e (97%)	13	3m ^c (7%)	4m (91%)
6	3f (54%)	4f (20%)	14	3n (4%)	4n (95%)
7	3g (10%)	4g (87%)	15	3o (36%)	4o (63%)
8	3h (45%)	4h (54%)	16	3p (43%)	4p (56%)

^aReaction conditions: Fe(OTf)₃ (2.9 mg; 5.76 × 10⁻³ mmol), L4 (5.4 mg; 5.78 × 10⁻³ mmol), stirred at 35 °C for 1 h. Then the substrate (0.5 mmol) was added and the reaction stirred under O₂ (1 atm) at 75 °C for 8 h. ^bRecovered starting material. The poor mass balance in the case of 3f was due to its decomposition during the reaction. ^cReaction run for 24 h at 75 °C.

only a few methods for its selective preparation, with all requiring high catalysts loadings and/or toxic or hazardous reagents.^{32,33} Thus, the iron-catalyzed dimerization appears to be an efficient and greener alternative for selectively synthesizing γ -diisoeugenol.

Styrenes bearing longer chains at the β -position also underwent the aerobic cleavage under the catalysis of Fe(OTf)₃-L1 (entries 4–6). When substrate 5d bearing an allyl ether functionality was subjected to the reaction, benzaldehyde was generated in low yield. Surprisingly, cinnamaldehyde was also isolated as a result of C–O and C–H bond cleavage. However, the substrates 5e and 5f, bearing terminal alkene and alkyne functionalities, respectively, were primarily cleaved at the styrene C=C bond to

give benzaldehyde and the corresponding unsaturated ethers, with no competing oxidation of the terminal multiple bonds. Cinnamaldehyde was isolated again as the only byproduct in these two reactions, with 17% and 7% yield, respectively.

4. Aerobic Oxygenation of Vinyl Halides with Concomitant Halogen Migration. Encouraged by the ample substrate scope realized with the Fe(III)-PyBisulidine catalysts, we also explored the oxidative cleavage of vinyl halides. When 7a was subjected to the oxidation catalyzed by Fe(OTf)₃-L1 in DCE, 8a was formed cleanly accompanied by, surprisingly, the migration of the bromide to the β carbon, with no formation of formaldehyde (Figure 3).

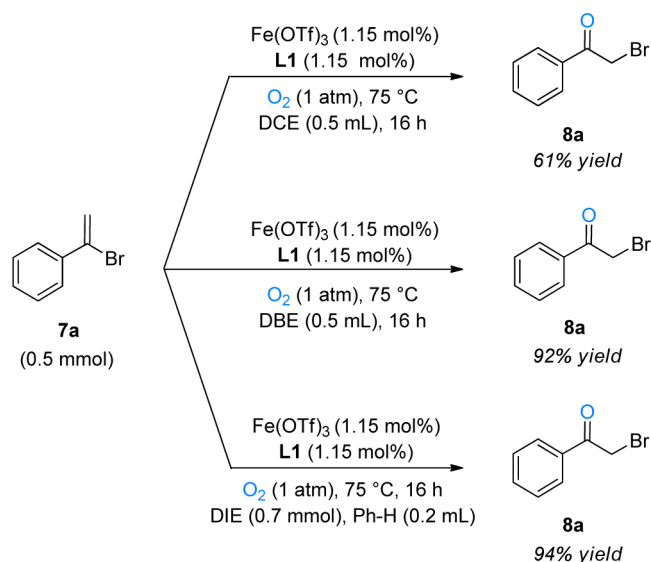
Table 4. Fe(OTf)₃-L1-Catalyzed Aerobic C=C Cleavage of β -Substituted Styrenes^a

Entry	Substrate (<i>rsm</i> ^g)	Products (isol. yield%)
1		(96%)
2		(68%)
3		(>99%)
4		(20%) (20%)
5		(45%) (40%) ^d
6		(42%) (32%) ^d

^aReaction conditions: Fe(OTf)₃ (2.9 mg; 5.76×10^{-3} mmol), L1 (5.3 mg; 5.78×10^{-3} mmol), stirred at 35 °C for 1 h. Then the substrate (0.5 mmol) was added and the reaction stirred under O₂ (1 atm) at 78 °C for 16 h. Yield refers to isolated yield. ^bReaction run with 0.75 mmol substrate. ^cReaction run with 0.4 mmol substrate at 72 °C. ^dNMR conversion.

Interestingly, the solvent DCE may have participated in the oxygenation, as a small amount of seemingly 2,3-dichlorosuccinaldehyde was detected by NMR (see the SI). In line with this, **8a** was obtained in a higher yield of 92% when DCE was replaced with 1,2-dibromoethane (DBE) as the reaction solvent, again with possible formation of 2,3-dibromosuccinaldehyde (Figure 3). Furthermore, diiodoethane (DIE) was co-oxidized to 2-iodoethanol when subjected to the oxidation of **7a** in the presence of the iron catalyst (see the SI). This reaction afforded **8a** in an excellent isolated yield of 94%. As no solvent oxidation was observed in the absence of **7a**, the halogenated solvent is likely to be involved and oxidized in the process of **7a** being converted to **8a**, taking up the other oxygen atom of O₂, with the higher yield in DBE and DIE probably reflecting the weaker C–Br and C–I bonds. How this happens remains an open question, however.

Due to the synthetic relevance of phenacyl halides as precursors to optically active compounds of pharmaceutical interest, such as styrene oxides,³⁴ the scope of this reaction was explored (Table 5). Vinyl bromides bearing electron-withdrawing (**7b–7d**) and electron-donating substituents (**7e**) were all oxidized to the corresponding phenacyl bromides with good yields, especially when DBE was used as solvent. Moreover, the

**Figure 3.** Conversion of a vinyl bromide into phenacyl bromide with solvent participation.

reaction could be expanded to styrenes bearing either a weaker C–I (**7f**) or stronger C–Cl (**7g**, **7h**) bond. In these cases, partial dehalogenation was observed when the oxidation was carried out in DCE, resulting in relatively lower yields. The acetophenone byproducts, resulting from the dehalogenation, were isolated in 20–25% yields. However, higher yields of the desired phenacyl halides were obtained in DBE, with almost dehalogenation being observed (yield ca. 5%). Prompted by the interest in converting vinyl halides into α -haloketones, such transformation has been attempted in the presence of stoichiometric strong oxidants.³⁵ To the best of our knowledge, an oxidation method using O₂ has not been reported thus far.

Encouraged by the efficiency of the halogen migration, we explored whether a similar sequential oxygenation–nucleophilic migration could be attempted with olefins bearing nucleophiles different from halogens. Interestingly, styrenes incorporating good leaving groups (**7i–7l**) were hydrolyzed to acetophenone in good yields in either DCE or DBE. In contrast, vinyl ethers (**7m**, **7n**) bearing a strongly nucleophilic but poorly leaving alkoxy group afforded ester products when subjected to the oxidation reaction in DCE. These results suggest that both the nucleophilicity and leaving ability of the migrating nucleophiles are important for the tandem reaction to occur. In addition, β -bromostyrenes **7o** and **7p** were found inert toward the oxidation, even in the presence of Ph₂S as an additive (*vide infra*). The oxidation pattern displayed by **7a** and its analogues has considerable implication to the mechanism of the iron-catalyzed oxidative olefin cleavage in question and is discussed below.

5. Comparison with Ozonolysis. As mentioned early, oxidative cleavage of olefins with ozone is a widely used transformation for converting aliphatic and aromatic olefins into carbonyls and/or carboxylic acids.^{5,6a,c,7} A comparison with the current protocol serves to highlight the cons and pros of each method. In ozonolysis, primary olefins like styrene lead to an ozonide (Figure 4), from which two different modes of cleavage are possible with the zwitterionic species trappable with a nucleophile.^{36,37} Take the ozonolysis of styrene as an example. At a low temperature of –70 °C, the reaction was early reported to proceed in good yield and with good mass balance; however, several products were obtained.^{36a} At a higher temperature in aprotic

Table 5. Fe(OTf)₃-L1-Catalyzed Aerobic Oxidation of Vinyl Halides with Halogen Migration^a

Reaction scheme: $\text{7b-n} \xrightarrow[\text{O}_2 (1 \text{ atm}), 75 \text{ }^\circ\text{C}, 16 \text{ h}]{\text{Fe(OTf)}_3 (1.15 \text{ mol}\%), \text{L1} (1.15 \text{ mol}\%)} \text{8b-n}$

Entry	Substrate (<i>rsm</i> %)	Products (isol. yield %)	Entry	Substrate (<i>rsm</i> %)	Products (isol. yield %)
1	 7b (33% ^b ; 20% ^c)	 8b (65% ^b ; 78% ^c)	7	 7h ^f (25% ^b ; 19% ^c)	 8h (50% ^b ; 70% ^c)
2	 7c	 8c (97% ^b)	8	 7i (R = Ph; 25% ^b) 7j (R = Me; 20% ^b)	 8i (R = Ph; 70% ^b) 8j (R = Me; 76% ^b)
3	 7d (22% ^b ; 10% ^c)	 8d (75% ^b ; 89% ^c)	9	 7k (R = H; 38% ^b) 7l (R = Me; 27% ^b)	 8k (R = H; 62% ^b) 8l (R = Me; 73% ^b)
4	 7e	 8e (99% ^b)	10	 7m ^g (12% ^b)	 8m (76% ^b)
5	 7f ^d (24% ^b ; 20% ^c)	 8f (50% ^b ; 70% ^c)	11	 7n (20% ^b)	 8n (78% ^b)
6	 7g ^e (22% ^b ; 20% ^c)	 8g (50% ^b ; 70% ^c)			

8m' 7o 7p

^aReaction conditions: Fe(OTf)₃ (2.9 mg; 5.76 × 10⁻³ mmol), L1 (5.3 mg; 5.78 × 10⁻³ mmol) in DCE (0.5 mL), stirred at 35 °C for 1 h. Then substrate (0.5 mmol) was added and stirred under O₂ (1 atm) at 75 °C for 16 h. Yield refers to isolated yield. ^bReactions run in DCE (0.5 mL). ^cReactions run in DBE (0.5 mL). ^dAcetophenone was obtained as byproduct in a 5% isolated yield in DBE and in a 24% in DCE. ^eAcetophenone was obtained as byproduct in a 6% isolated yield in DBE solution and in 25% in DCE. ^fAcetophenone was obtained as byproduct in a 7% isolated yield in DBE and in 23% in DCE. ^gCompound 8m' was obtained as byproduct in 10% isolated yield.

solvents, much poorer mass balance and yield were achieved, although in a mixture of CCl₄ and MeOH at 35 °C the yield of benzaldehyde increased to 41% (Figure 4).^{36b} Higher carbonyl yields (70–100%) have been achieved when the ozonolysis was run in an organic solvent–water mixture (H₂O₂ being the byproduct) or in a flow reactor.³⁸ In comparison, our catalytic system afforded benzaldehydes generally with high isolated yield under simpler, safer conditions with very high chemoselectivity and mass balance. However, under the conditions explored the Fe(III)-L1/L4 catalyst does not promote the oxidation of aliphatic olefins.

6. Mechanistic Observations. Involvement of Radical Species. To gain some insight into the reaction mechanism, the possible formation of radical species was first investigated. Initially, the aerobic cleavage of 1b under the catalysis of Fe(OTf)₃-L1 was performed in the presence of radical trapping

reagents (Figure 5). As the reaction was fully inhibited in the presence of a trapping reagent, such as BHT and *p*-benzoquinone, formation of radical intermediates seemed plausible. However, the possibility that the inhibition may stem from the catalyst being deactivated by interacting with the trapping agent cannot be discarded,²⁸ as only partial inhibition occurred in the presence of BrCCl₃ (Figure 5a). Moreover, the presence of the radical initiator benzoyl peroxide did not alter the oxidative cleavage of 1b or induce the formation of other products, suggesting that freely diffusing carbon-based radicals are not generated during the oxidation reaction (Figure 5b). Indeed, catalytic oxidation of styrenes that proceeds via benzyl radical intermediates¹⁶ generates polymerization or dimer byproducts; however, polymers and dimer byproducts were not observed in the Fe(OTf)₃-L1-catalyzed oxidations. In addition, catalysts that initiate radical species are substantially less

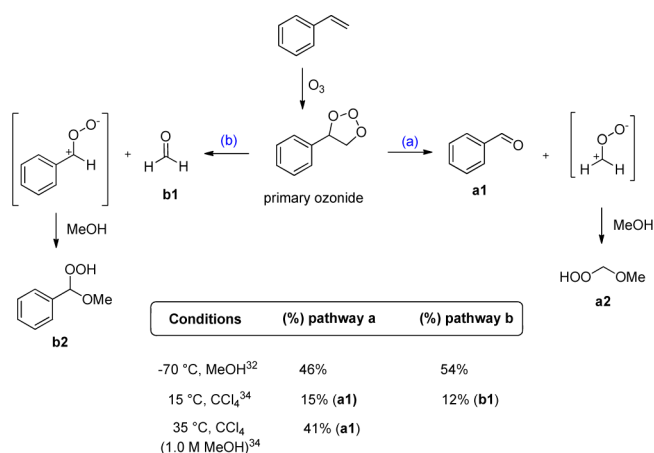


Figure 4. Selectivity in an ozone-mediated cleavage of styrene.

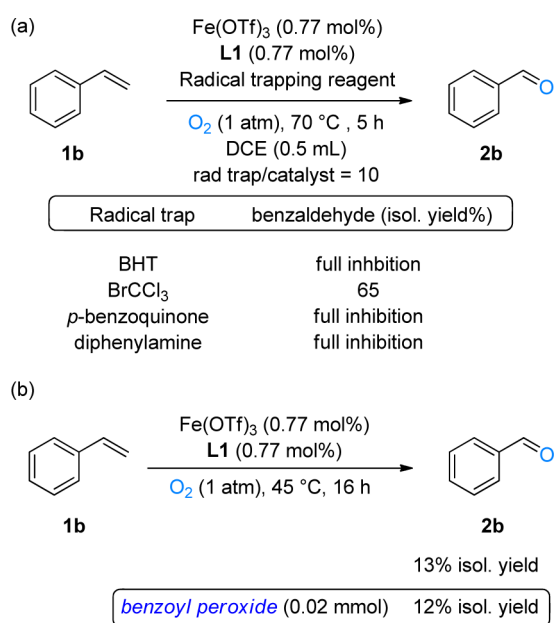


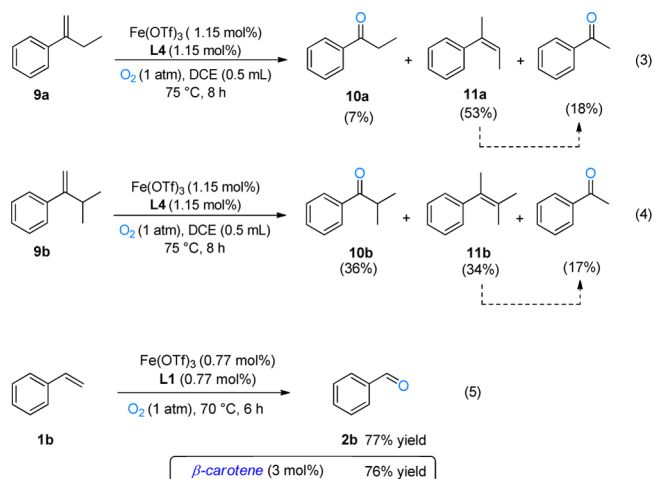
Figure 5. Experiments suggesting no formation of freely diffusing radicals. For these experiments and subsequent mechanistic studies, yields refer to isolated yields unless otherwise stated.

efficient or inactive toward the oxidation of electron-deficient styrenes.^{13,16,17} In contrast, the Fe(OTf)₃-L1 catalyst promotes the oxidation of both electron-rich and -deficient styrenes with high yields (Table 2).

Further evidence against the involvement of freely diffusing radical species is seen in the chemoselective aerobic cleavage of **3g** to the corresponding ketone in 87% isolated yield (Table 3, entry 7). Had radical species been involved in the oxidation of this *pseudo-π* compound, a cyclopropylbenzyl radical would be generated and expected to undergo fast ring-opening rearrangements at the reaction temperature of 75 °C ($k = 3.6 \times 10^5 \text{ s}^{-1}$ at 22 °C).³⁹ Thus, while the formation of radical intermediates, particularly those of very short lifetime, cannot be discarded, we may conclude that freely diffusing carbon-based radicals are not likely to be generated during the aerobic cleavage.

Absence of Singlet Oxygen. As reactions between olefins and singlet oxygen, which can be generated from O₂, light and a photosensitizer, are well known to give oxidative cleavage products,⁴⁰ we next investigated the differences between the

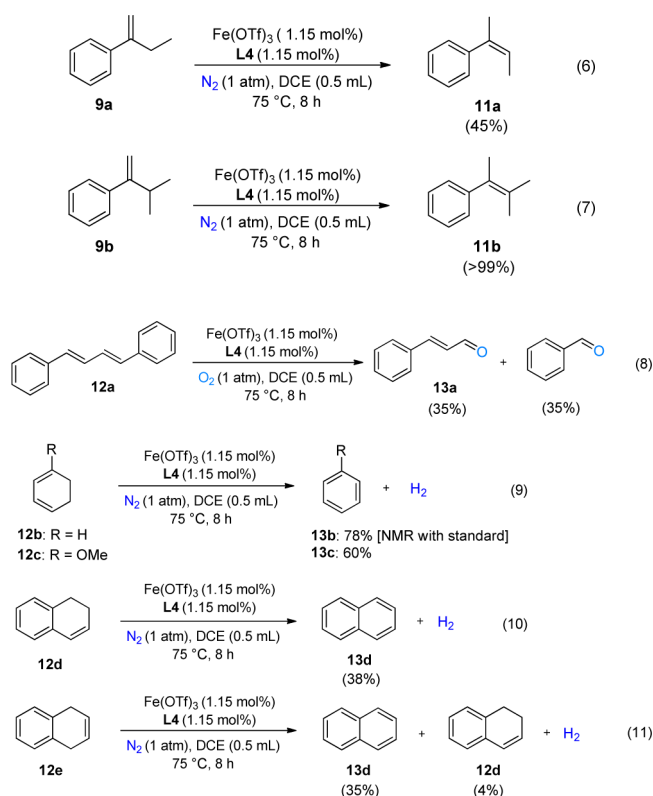
¹O₂ participated and the Fe(OTf)₃-L4-catalyzed aerobic cleavages of olefins. The 1,3-addition of singlet oxygen to olefins possessing at least one allylic hydrogen is known to afford mainly allylic hydroperoxides.⁴¹ However, when α -allylic styrenes **9a** and **9b** possessing allylic hydrogens were subjected to the Fe(OTf)₃-L4-catalyzed reaction, the carbonyl compounds **10a** and **10b** were obtained, with no allylic hydroperoxides being detected (eqs 3 and 4). The same is true with



the substrates **3g–3k** (Table 3). Furthermore, while ¹O₂ reacts preferentially with electron-rich olefins to furnish dioxetan species that can readily cleave, affording carbonyl compounds,⁴² Fe(OTf)₃-L1 promotes the aerobic cleavage of both electron-deficient and -rich styrenes with high yields (Table 2). Still further, allylic hydroperoxides were reported as main products from the ¹O₂ mediated cleavage of cyclopropyl-substituted olefins^{43,44} and the photooxidation of **3g** furnished a distribution of products with **4g** being obtained as a minor product;⁴⁵ in contrast, the Fe(OTf)₃-L4-catalyzed oxidation of **3g** afforded **4g** as the sole reaction product (Table 3). Additionally, the introduction of β -carotene,^{17a} an inhibitor of ¹O₂, did not affect the oxidation of styrene **1b** to benzaldehyde (eq 5). Taken together, these observations indicate that the iron-catalyzed aerobic cleavage of olefins does not involve the catalytic formation of singlet oxygen.

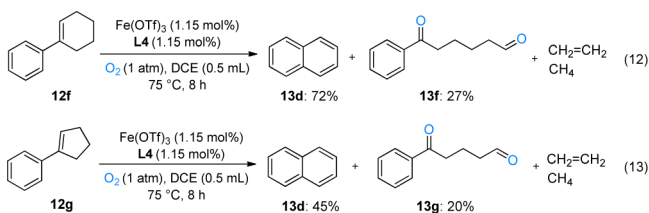
Interestingly, competing C=C bond isomerization was observed in the oxidation of **9a** and **9b**, with the acetophenone derived from the isomerized olefins **11a** and **11b** (eqs 3 and 4). Indeed, under an inert atmosphere the iron catalyst furnished the isomerization products exclusively⁴⁶ (eqs 6 and 7). Since this isomerization almost certainly involves the initial coordination of the olefin to the iron center,⁴⁷ it is very likely, as in the case of ether oxidation,²⁸ that olefin coordination occurs during the aerobic cleavage (also see below).

Dehydrogenation of Dienes. Singlet oxygen is known to readily undergo 1,4-addition to dienes to yield endoperoxides; although depending on the substrate and/or reaction conditions subsequent rearrangements have been reported.⁴⁸ Partly driven by the desire to further exclude the possibility of ¹O₂ involvement in our protocol and partly by that to mimic the ability of dioxygenases to cleave conjugated C=C bonds, we also examined the oxidative cleavage of diene substrates. Delightfully, the *trans*-diene **12a** was oxidatively cleaved into cinnamaldehyde and benzaldehyde when exposed to O₂ in the presence of Fe(OTf)₃-L4 (eq 8), forming no other products. In stark contrast, *cis*-dienes **12b** and **12c** were dehydrogenated to arene products, releasing H₂ under an inert atmosphere



(eq 9). While $\text{Fe}(\text{OTf})_2\text{-L1}$ catalyzes oxygenative dehydrogenation of etheral substrates under aerobic conditions,²⁸ it is clear that the $\text{Fe}(\text{OTf})_3\text{-L4}$ complex is capable of promoting the direct dehydrogenation of partially oxidized hydrocarbons. This is further seen in the dihydronaphthalenes **12d** and **12e**, which afforded naphthalene in low yields when treated with $\text{Fe}(\text{OTf})_3\text{-L4}$ under N_2 (eqs 10 and 11). Interestingly, traces of **12d** were detected during the dehydrogenation of **12e**, suggesting an initial isomerization of the substrate followed by direct dehydrogenation⁴⁹ of the relatively weak allylic CH bond in **12d** (~85 kcal/mol).⁵⁰ By way of comparison, the reaction of **12d** with singlet oxygen initially afforded the allylic hydroperoxide, which loses H_2O_2 to yield naphthalene,⁵¹ while that of **12e** gave rise to a distribution of products including naphthalene and a hydroperoxide.⁵²

Of further interest is the oxidation of 1-phenyl-1-cycloalkenes, which afforded allylic hydroperoxides in photo-oxidation.⁵³ Exposure of **12f** and **12g** to $\text{Fe}(\text{OTf})_3\text{-L4}$ under O_2 furnished, much to our surprise, naphthalene as the major product (eqs 12 and 13). The expected acyclic dicarbonyl **13f**

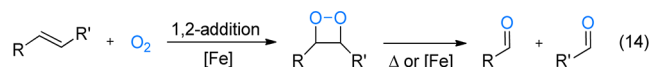


and **13g** were obtained in lower yields. Interestingly, ethene and small amounts of methane were also identified by GC (see the SI), showing that the iron catalyst is capable of extensive C–C and C–H bond cleavages.

It should be noted, however, that **12f** and **12g** underwent no reaction in the absence of O_2 or the iron catalyst (see the SI).

Although the mechanism for the formation of naphthalene is unclear, rearrangements of olefinic substrates in the presence of singlet oxygen are well known and often lead to unexpected products.⁵⁴

Dioxetane as Possible Key Intermediate. Dioxetanes, which can be readily formed from the reaction of $^1\text{O}_2$ with electron-rich olefins,⁴² are well known to undergo C–C cleavage to afford two carbonyl products. Although singlet oxygen does not appear to be generated in the iron-catalyzed oxidation in question, the results shown in Tables 2–4 points to dioxetane being a possible key intermediate under the iron catalysis. An iron-catalyzed 1,2-addition of O_2 to the olefinic substrates could lead to the formation of the dioxetane (eq 14).



Attempts to isolate any possible intermediate from the aerobic cleavage of **1b** were unsuccessful, probably because dioxetanes are thermally sensitive and can be cleaved even in the presence of traces of metals⁵⁵ and silica.⁵⁶ It has been reported that dioxetanes resulting from the 1,2-addition of $^1\text{O}_2$ to olefins can react with diphenyl sulfide, furnishing ketone type products.⁵⁷ This is due to the diphenyl sulfide being capable of rapidly reacting with dioxetanes while being inert toward endoperoxides, hydroperoxides, and singlet oxygen.⁵⁷ Bearing this in mind, we envisioned that if the oxidation of a vinyl bromide under the iron catalysis proceeds via a dioxetane intermediate, the migration of the bromide to afford a phenacyl bromide could be assisted with diphenyl sulfide, as shown in Figure 6. As noted above, **8a** was obtained in 61% yield as the

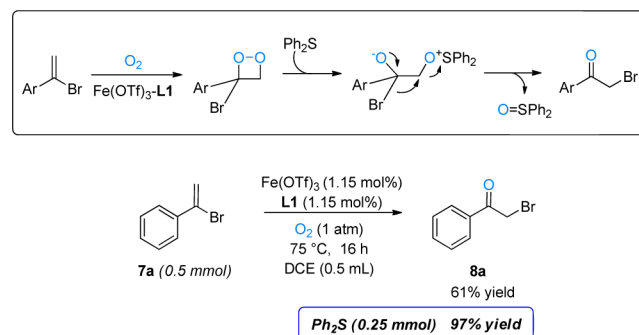
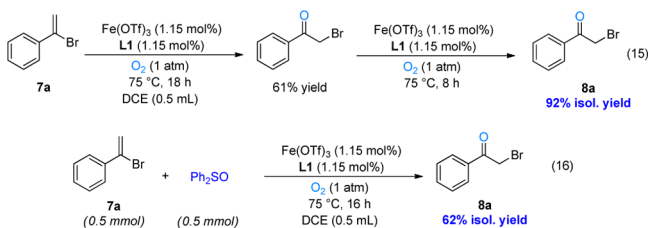


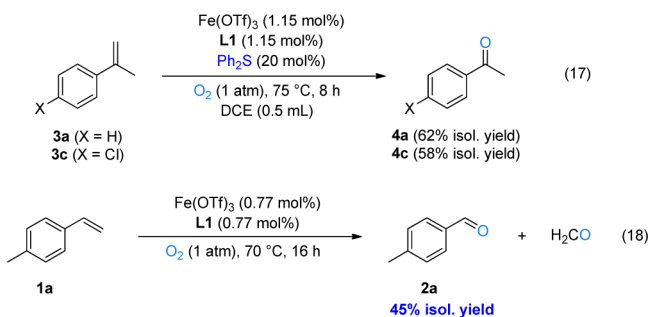
Figure 6. Diphenyl sulfide-assisted conversion of vinyl bromide to arylacyl bromide, supporting the formation of a dioxetane intermediate.

sole product of **7a** under aerobic atmosphere in the presence of $\text{Fe}(\text{OTf})_3\text{-L1}$ (Figure 3). Significantly, addition of diphenyl sulfide to the catalytic reaction increased the yield of **8a** to 97%, supporting the notion that dioxetane intermediates are involved in the iron-catalyzed oxidation reaction (Figure 6).

The decomposition of the unstable dioxetane intermediate is expected to be facile, i.e. not turnover limiting. This raises an interesting question as to how the addition of Ph_2S gives rise to a higher product yield. It appears that the lower yields in its absence results from catalyst deactivation. This hypothesis is supported by the significant increase in the yield of the oxidation of **7a** from 61% to 92% upon the addition of a second portion of $\text{Fe}(\text{OTf})_3\text{-L1}$ (eq 15). As mentioned above, solvent molecules participated in the oxidation of vinyl halides (Table S), probably yielding highly reactive species, such as



2,3-dihalosuccinaldehydes, which may poison the catalyst. In contrast, the Ph_2SO byproduct generated during the oxygenation of vinyl halides in the presence of Ph_2S does not exert any detrimental effect on the catalyst. This is evident in the oxygenation of **7a** in the presence of 1.0 equiv of Ph_2SO , affording **8a** in 62% yields in 16 h (eq 16) (cf. Figure 6). In addition, Ph_2S does not promote the oxidation of normal styrenes. In fact, introducing Ph_2S to the $\text{Fe}(\text{OTf})_3$ -**L1**-catalyzed oxygenation of **3a** and **3c** resulted in a reduction in the yield of **4a** and **4c** (eq 17) (cf. Table 3), probably due to its



competitive coordination to the iron center. Thus, the promoting effect of the sulfide additive (Figure 6) can be attributed to its ability in facilitating the nucleophilic migration step, as hypothesized above. Solvent molecules may play a similar role but may lead to byproducts poisonous to the catalyst, resulting in lower yields.

Further support for the dioxetane intermediate is seen in the oxygenation of neat *p*-methylstyrene **1a** promoted by $\text{Fe}(\text{OTf})_3$ -**L1**. With no solvent or additive used, the reaction afforded **2a** in 45% isolated yield after 8 h, with some substrate degradation taking place due to the *in situ* formation of the $\text{Fe}(\text{OTf})_3$ -**L1** in neat **1a** (eq 18). Paraformaldehyde was also accumulated as a white solid in the reaction tube and was found to be the only byproduct.

Suggested Reaction Mechanism. The results presented above point toward that the $\text{Fe}(\text{OTf})_3$ -**L1**/**L4**-catalyzed oxygenation of olefins initially affords a labile dioxetane intermediate, which is followed by its iron-mediated or thermal cleavage to furnish the carbonyl compounds. The formation of the peroxide intermediate is unclear mechanistically; however, its formation via 1,2-addition of $^1\text{O}_2$ is not in agreement with the observations aforementioned. Formation of the dioxetane via a radical pathway also seems unlikely, as no byproducts derived from benzyl radicals were observed and no ring-opening of pseudo- π -group substituted styrenes was observed.

Alternatively, the formation of the dioxetane intermediate could be seen as a result of the formation of a radical cation followed by its subsequent reaction with O_2 .^{17b} To probe this possibility, the oxidation of **1b** was carried out in the presence of halide anions, which are known to react with the radical cations.^{17b} However, competitive formation of phenacyl halides was not observed when an excess of Cl^- or Br^- donors

was introduced during the $\text{Fe}(\text{OTf})_3$ -**L1**-catalyzed oxidation, which furnished benzaldehyde and formaldehyde exclusively (Figure 7). In addition, the oxidative cleavage of **1a** and **1f**

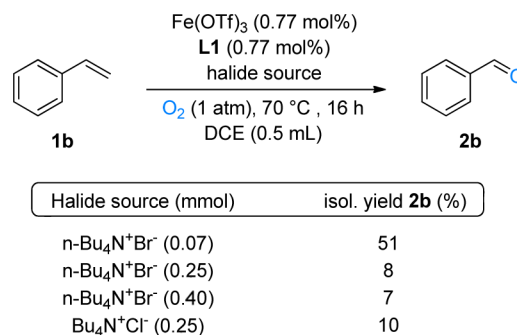


Figure 7. Effect of halides on the oxidative cleavage of styrene, indicating no formation of radical cations.

appears to proceed in a similar rate (Figure 8), which disagrees with the styrene being converted into a cation.

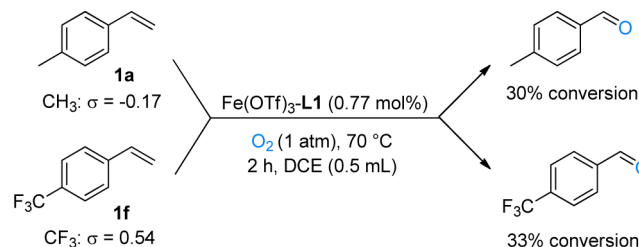


Figure 8. Oxidative cleavage of styrenes bearing electron-donating and -withdrawing substituents. Reaction conditions: $\text{Fe}(\text{OTf})_3$ (2.9 mg; 5.76×10^{-3} mmol) and **L1** (5.3 mg; 5.78×10^{-3} mmol) in DCE (0.5 mL), stirred at 35 °C for 1 h. Then the substrate (0.75 mmol) was added and the reaction stirred under O_2 (1 atm) at 70 °C for 2 h after the substrate addition at 35 °C.

Interestingly, the data in Figure 7 also showed that an increase in the amount of the halide source did not lead to the formation of phenacyl halides; rather, it strongly inhibited the oxidation reaction. This is in line with the proposition that the oxidation proceeds via olefin coordination, which is expected to be hampered in the presence of coordinatively competing halide anions.

To gain more evidence of the potential coordination of the olefin to the iron catalyst, styrene **1b** was added to a DCE solution of the $\text{Fe}(\text{OTf})_3$ -**L1** catalyst (**1b**/ Fe = 1:1) and was stirred. The initial dark red solution of the catalyst evolved to dark brown after exposure to the olefin for 1 h at 50 °C but turned red again when cooled down to ambient temperature (see the SI). Upon removal of the solvent *in vacuo*, the resulting dark red solid revealed almost no shifts in the styrene IR absorption bands. These observations indicate that the olefin is coordinating to the iron catalyst; however, the coordination is weak and temperature dependent.

As mentioned at the beginning, reacting $\text{Fe}(\text{OTf})_3$ with **L1** in DCE led to $[\text{FeL1}(\text{OTf})_3]$, which is expected to be structurally similar to $[\text{FeL1}(\text{THF})(\text{OTf})_2]$,^{28,58} with the triflates completing the octahedral geometry. Subjecting the isolated compound to Nano-ESI-MS analysis revealed the presence of the expected $[\text{FeL1}(\text{OTf})_2]^+$ as well as $[\text{Fe}(\text{L1-H})(\text{OTf})]^+$ and $[\text{Fe}(\text{L1-H})]^{2+}$ (see the SI), where **L1-H** denotes the monodeprotonated form

of ligand **L1**. The identification of the latter two species is interesting, as it indicates that the acidic proton of **L1** could be deprotonated under the reaction conditions, turning **L1** into an amido ligand, the lone pair of which could stabilize iron at higher oxidation states.

Taking together the observations made above, a mechanism is tentatively suggested, which involves the coordination of the olefin and oxygen to the iron center followed by the formation of the dioxetane intermediate (Figure 9). Reaction of the olefin

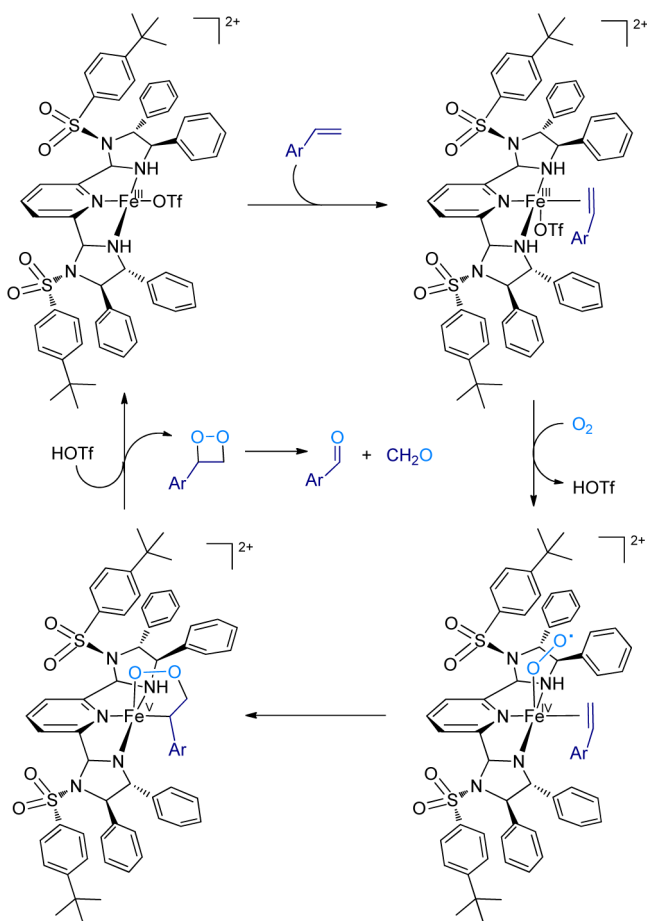


Figure 9. Postulated mechanism for the Fe(III)-**L1**-catalyzed oxidative cleavage of styrenes.

with $[\text{FeL1}(\text{OTf})_2]^+$, resulting from triflate dissociation in $[\text{FeL1}(\text{OTf})_3]$, leads to the formation of an Fe(III)-alkene intermediate. Alternatively, the species may be formed from $[\text{FeL1}(\text{OTf})_2]^+$ or $[\text{FeL1}(\text{OTf})_3]$. Activation of oxygen by the Fe(III) leads to an Fe-superoxo radical, accompanied by deprotonation of **L1** by the triflate as a result of increased Lewis acidity of the iron. On the basis of the X-ray structure of $[\text{FeL1}(\text{THF})(\text{OTf})_2]$,²⁸ the olefin substrate may bond to the Fe(III) at the equatorial position, while the sterically less demanding O_2 coordinates axially. This mode of coordination appears to explain why the *p*-phenyl-substituted styrene is less reactive (Table 2): the phenyl would clash with the sulfonyl moiety of **L1** when the olefin approaches the iron center. The superoxo radical is proposed to undergo radical cyclization with the coordinated olefin, affording a five-membered peroxometallacycle. The latter collapses via reductive elimination to give the dioxetane, which is expected to decompose readily to afford the carbonyl products. Peroxometallacycles are often

invoked in the mechanism of C–C cleavage by iron-based dioxygenases^{2g,3a} and have been isolated in the cases of other metals.⁵⁹ Such a mechanism resembles the aerobic cleavages performed by some dioxygenases, such as tryptophan pyrrolase,⁶⁰ which is known to cleave the C=C bond of the pyrrole ring in tryptophan, probably via the formation of a ternary complex in which both molecular oxygen and the substrate coordinate to the metalloenzyme.⁶¹

The mechanism features some unusual iron species,⁵⁸ such as the presumed Fe(IV)-superoxo and Fe(V) metallacycle, which are rare. There are literature examples of Fe(V) complexes in which the iron is stabilized by special ligands.⁶² In the current case, stabilization of these high valent iron species may be possible through π -donation of the amido ligand lone pair. The inability of **L6** in promoting the oxidation could partly stem from the lack of the acidic hydrogen in the ligand (Table 1). It must be stressed, however, that before more insightful evidence emerges, the proposed mechanism remains largely speculative.

CONCLUSION

In summary, this paper reports a facile, environmentally friendly new method for the selective oxidation of aromatic olefins. Under the catalysis of $\text{Fe}(\text{OTf})_3$ -PyBisulidine, both α - and β -substituted styrenes were cleaved to afford carbonyl compounds at 1 atm of O_2 with high efficiency, chemoselectivity, and functional group tolerance. In the case of α -halo styrenes, migration of the halogen occurred, affording α -halo acetophenones. However, olefin isomerization and competing dehydrogenation were encountered in some instances. In comparison with the widely practiced ozonolysis, our protocol is easier, safer, greener, and more economic to use. Under the conditions developed so far, the catalyst is, however, ineffective toward aliphatic olefins. On the basis of various observations, a mechanism involving the coordination of the olefin and oxygen to the iron center seems in operation, which gives rise to a dioxetane intermediate and subsequently the cleavage products. However, further studies are needed to substantiate or discard the proposed mechanism, bearing in mind that the observations made thus far have only excluded some mechanistic possibilities.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, products characterization data including ^1H and ^{13}C NMR spectra, and detailed mechanistic data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03956.

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Notes

The authors declare no competing financial interest.

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