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Dehydrogenative α-Oxygenation of Ethers with an Iron Catalyst

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S Supporting Information

ABSTRACT: Selective α-oxidation of ethers under aerobic conditions is a long-pursued transformation; however, a green and efficient catalytic version of this reaction remains challenging. Herein, we report a new family of iron catalysts capable of promoting chemoselective α-oxidation of a range of ethers with excellent mass balance and high turnover numbers under 1 atm of O_2 with no need for any additives. Unlike metalloenzymes and related biomimetics, the catalyst produces H_2 as the only byproduct. Mechanistic investigations provide evidence for an unexpected two-step reaction pathway, which involves dehydrogenative incorporation of O_2 into the ether to give a peroxobisether intermediate followed by cleavage of the peroxy bond to form two ester molecules, releasing stoichiometric H_2 gas in each step. The operational simplicity and environmental friendliness of this methodology affords a useful alternative for performing oxidation, while the unique ability of the catalyst in oxygenating a substrate via dehydrogenation points to a new direction for understanding metalloenzymes and designing new biomimetic catalysts.
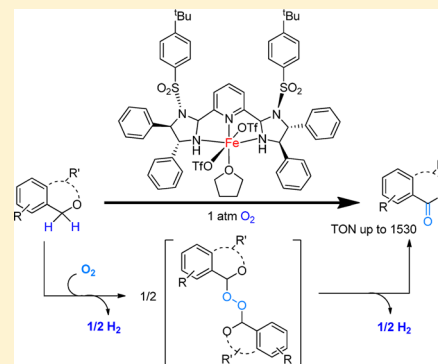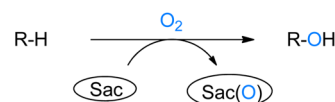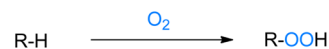
INTRODUCTION

Catalytic selective oxidation of organic chemicals is identified as the most important area to impact the future chemical industry.[1] Nature has mastered the art of oxidation using metalloenzymes, which are capable of selectively oxidizing various substrates with O_2 under mild conditions. Depending on the oxygenases used, different modes of O_2 activation are possible, leading to the insertion of one or both oxygen atoms of O_2 into a C−H bond (Figure 1). For instance, mono-oxygenases operate by inducing the cleavage of the O−O bond at the metal center to form a highly electrophilic iron-oxo species, through which an alkane can be oxidized into an alcohol, releasing water as the byproduct.[2] Inspired by nature, a great variety of iron and copper-based biomimetic catalysts have been designed to replicate and expand naturally occurring oxidations.[3] However, these biomimetic catalysts generally require the use of more expensive H_2O_2 as oxidant to generate the high valent $Fe^{IV}=O$ or $Fe^VO(OH)$ species.[3]

Although dioxygen is the most desired oxidant in oxidation chemistry,[1−4] its activation for catalytic oxidations by synthetic iron complexes has proven a significant challenge. Only a few examples have been reported so far, and they usually rely on the use of additives.[5,6] For instance, the Gif-type systems[7] and macrocyclic Fe^{II} complexes[8] can catalyze the oxidation of alkanes in the presence of a reductant, while some Fe^{III} salts[9] and biomimetic Fe^{III} complexes[10] selectively mono-oxidize organic substrates with the aid of a sacrificial substrate. Photoassisted activation of dioxygen has also been explored.[11] Thus, the design of well-defined iron complexes as potential catalysts for selective oxidation using O_2 under additive-free conditions remains challenging. This is particularly the case for substrates bearing electron-rich functionalities,[12] such as ethers,

GENERAL MODE OF OXIDATION WITH MONOOXYGENASES

$$R\text{-}H \ + \ 2H^+ \ + \ 2e^- \ \xrightarrow{O_2} \ R\text{-}OH \ + \ H_2O$$
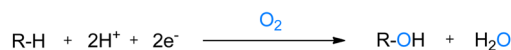
GENERAL MODES OF OXIDATION WITH DIOXYGENASES

$$R\text{-}H \ \xrightarrow{O_2} \ R\text{-}OOH$$

$$\begin{array}{c}R\\ \diagdown \\ R'\end{array} \ + \ 2H^+ \ + \ 2e^- \ \xrightarrow{O_2} \ \begin{array}{c}R \quad OH\\ \diagup\diagdown\\ R' \quad OH\end{array}$$

$$R\text{-}H \ \xrightarrow[\substack{Sac \quad Sac(O)}]{O_2} \ R\text{-}OH$$

Sac: Sacrificial substrate

THIS WORK

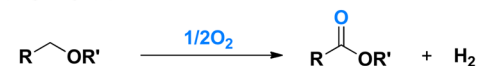$$R\diagdown OR' \ \xrightarrow{1/2 O_2} \ R\text{-}C(=O)\text{-}OR' \ + \ H_2$$

Figure 1. Modes of selective oxidation of organic substrates.

where poor chemoselectivity,[13−17] poor substrate scope,[3c,16−22] and harsh oxidizing conditions[13,15,18] are usually encountered.
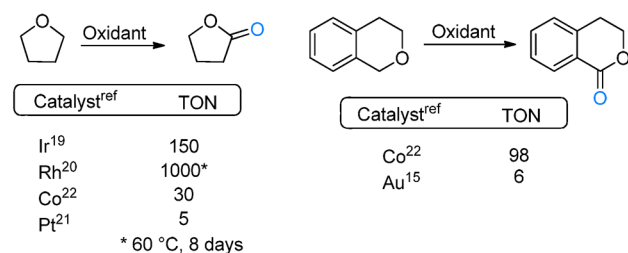
α-Oxidation of ethers to esters is an attractive transformation, due to their applications in the synthesis of complex natural

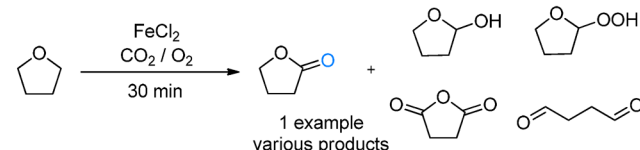products and biologically active molecules.[23] Stoichiometric amounts of metal oxides, such as RuO_4,[13] CrO_3,[18] and permanganates,[24] were early attempted for this transformation. More modern methodologies are based on catalytic metal complexes of Ru[14] and Au[15] using stoichiometric strong oxidants. Greener aerobic oxidation has been attempted with catalysts based on Ir,[19] Rh,[20] Pt,[21] Co,[22] and Cu complexes;[16] however, they all display limited efficiencies, poor mass balance, limited scope, and poor functional group tolerance, while requiring additives (Figure 2A). Surprisingly somehow, the use

A. Oxidation of ethers

Catalyst[ref]	TON
Ir[19]	150
Rh[20]	1000*
Co[22]	30
Pt[21]	5

* 60 °C, 8 days

Catalyst[ref]	TON
Co[22]	98
Au[15]	6

B. Oxidation of ethers with O_2 catalyzed by iron

1 example
various products

C. Oxidation of ethers with H_2O_2 catalyzed by iron

(S,S)-Fe(PDP) (15 mol%)
AcOH (1.5 equiv)
H_2O_2 (3.6 equiv)
MeCN, 25°C, 30 min

(1.0 mmol)
n = 1,2

n = 1, 41% yield, TON = 3
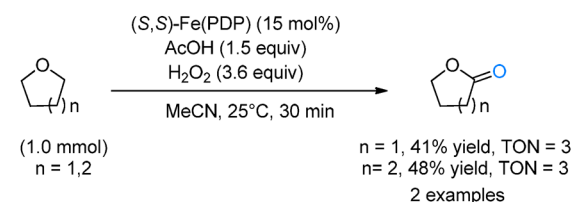n = 2, 48% yield, TON = 3
2 examples

**Figure 2.** Literature examples of ether oxidation.

of cheaper and environmentally friendly iron catalysts for the oxidation of ethers is limited to the example of a $FeCl_2$-catalyzed oxidation of THF under CO_2/O_2 atmosphere, which yields a variety of species (Figure 2B),[17] and that of a biomimetic (S,S)-Fe(PDP) catalyst, which oxidizes THF and THP in preparative yields with H_2O_2/AcOH[3c] (Figure 2C). Although a turnover number (TON) of 3 was initially achieved with the latter due to the large amount of catalyst used (15 mol %), higher efficiencies have been subsequently reported with the Fe-(PDP) and structurally related biomimetic catalysts.[25]

Considering the limitations of the reported catalysts and the appeal of an iron catalyst, we started a program to investigate new ligand designs, aiming for more efficient iron-catalyzed aerobic oxidations. Herein, we disclose a novel family of iron catalysts bearing pyridine bissulfonylimidazolidine ligands, and their application in the α-oxidation of ethers under 1 atm of O_2 and additive-free-conditions with high chemoselectivity and excellent mass balance. We also reveal that the oxidation appears to proceed via an unprecedented dehydrogenative–oxygenation mechanism, with H_2 released as the sole byproduct (Figure 1).

■ RESULTS AND DISCUSSION

1. Synthesis of PyBisulidine Ligands. The application of tetradentate N-donor ligands for biomimetic oxidations has been extensively studied either as porphyrin type skeletons or as nonhaem designs.[3] However, tridentate N-donor ligands are less explored, and their application is surprisingly limited mainly to olefin epoxidation.[26] Recently, a novel pyridine bisimidazoline (PyBidine) ligand was reported and exploited in Cu-catalyzed [3+2] cycloadditions[27] and Mannich reactions.[28] Inspired by the bulky, flexible PyBidine skeleton and the influence of electron-withdrawing groups of ligands on iron-catalyzed oxidation,[29] we hypothesized that sulfonylation of the PyBidine moieties could give rise to a new family of ligands with interesting coordinating properties, which might confer facilely tunable Lewis acidity onto or steric hindrance around the iron, enhance the ability of iron for O_2 activation, and allow for better catalytic activity and selectivity.

An ample variety of sulfonylated PyBidine ligands, PyBisulidines, were synthesized with excellent yields by simple condensation of pyridine-2,6-dicarboxaldehyde with sulfonyl diamine derivatives under catalytic acidic conditions (eq 1).

(1)

L1: R = 4-*tert*-Butyl
L2: R = 4-OMe
L3: R = 4-Me
L4: R = 4-CF_3
L5: R = 2,4,6-triisopropyl
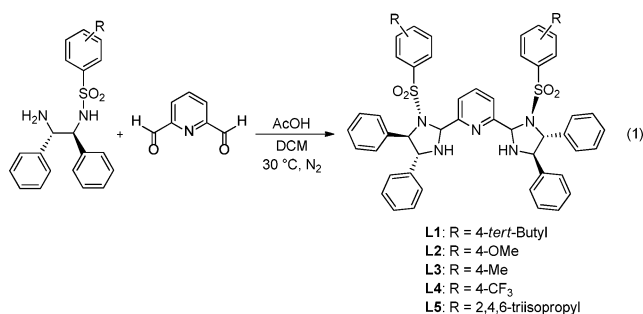
Reacting **L1** with $Fe(OTf)_2$ in THF led to a THF-ligated complex $[FeL1(THF)(OTf)_2]$, the structure of which has been determined by X-ray diffraction (Figure 3). The complex shows a distorted octahedral geometry with two axial OTf ligands and an equatorial THF. Although surrounded by the sterically demanding **L1**, the Fe–O3 distance of 2.042 Å is considerably shorter than those found in the iron porphyrin [Fe(TPP)-$(THF)_2$]-type complexes and other iron–THF species,[30,31] suggesting a highly electrophilic Fe^{II} center.

2. $Fe(OTf)_2$–L1-Catalyzed Aerobic Oxidation of THF Substrates. When investigating possible catalytic reactions with the complex synthesized, small amounts of γ-butyrolactone were detected in the bright orange THF solution of $[FeL1(THF)(OTf)_2]$. Prompted by this observation, we set out to explore this complex as a potential catalyst for aerobic oxidation of THF. Exposing a stirred THF solution of the complex to 1 atm of O_2 indeed led to the isolation of γ-butyrolactone, with a TON of 98 in 24 h at 40 °C. Subsequent optimization of the reaction conditions with the in situ prepared catalyst, which behaved similarly to $[FeL1(THF)-(OTf)_2]$, raised the TON to 312 at 60 °C. The TON increased to 412 in a prolonged time of 48 h (Table 1, entries 1,2). Control experiments showed that no reaction occurred in the absence of **L1**, $Fe(OTf)_2$, or O_2, showing that the three components are indispensable for the oxidation (see the Supporting Information).

Further optimization revealed that modification of the ligand structure resulted in the most significant oscillations in the catalytic activity. The PyBisulidine ligands exhibited the highest
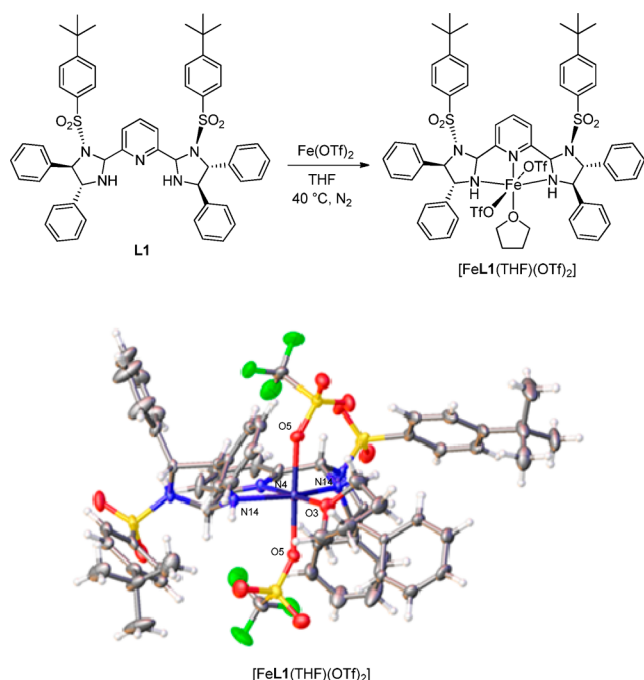
L1

[FeL1(THF)(OTf)$_2$]

[FeL1(THF)(OTf)$_2$]

Figure 3. Formation of the THF-ligated $[\text{FeL1}(\text{THF})(\text{OTf})_2]$ complex, and its X-ray structure. Selected interatomic distances [Å] and angles [deg]: Fe1−O3 2.042(3), Fe1−O5 2.157(2), Fe1−N4 2.117(3), Fe1−N14 2.252(2), N14−Fe1−N14 151.24(12), N4−Fe1−N14 75.62(6), O3−Fe1−N14 104.38(6), O3−Fe1−O5 88.73(6).
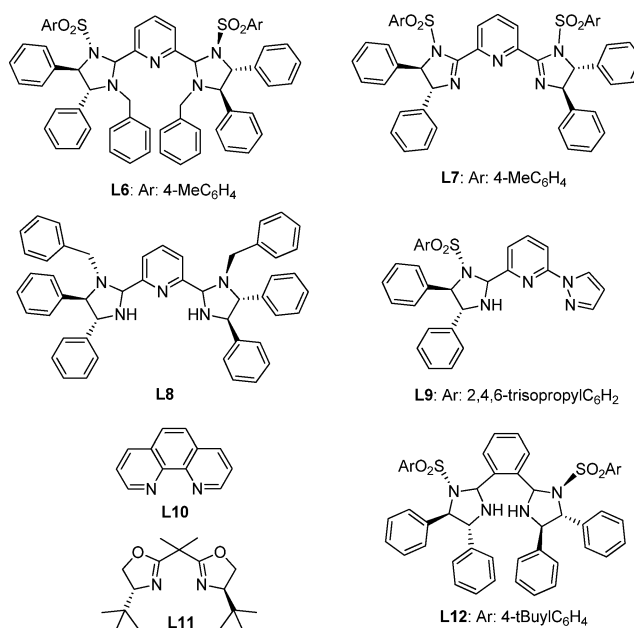
Table 1. Effect of Ligands on the Iron-Catalyzed Aerobic α-Oxidation of THF[a]

entry	ligand	butyrolactone/TON[b]
1	L1	312
2[c]	L1	412
3	L2	283
4	L3	207
5	L4	194
6	L5	121
7	L6	NR
8[d]	L7	20
9	L8	50
10	L9	NR
11	L10	NR
12	L11	NR
13	L12	NR

[a]Reaction conditions: distilled THF (2.0 mL), in situ prepared Fe(OTf)$_2$−ligand complex (5.65 × 10^{-3} mmol, 0.02 mol %), O$_2$ (1 atm) at 60 °C, 24 h. [b]TON refers to mmol of product per mmol of catalyst. [c]Reaction run for 48 h. [d]Tetrahydrofuran hydroperoxide was obtained as the major product, with peroxide/lactone = 4/1.

efficiency, especially when electron-donating groups were present in the sulfonyl moiety (Table 1, entries 1−6). Nonetheless, replacement of **L1** with the more electron-rich but much more sterically demanding **L5** resulted in a 2.5-fold reduction in the TON (Table 1, entry 6), and the sterically very congested **L6**, in which the NH proton is replaced with a
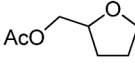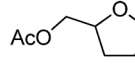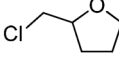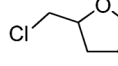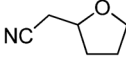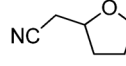
benzyl group, afforded no activity at all (entry 7), indicating that both electronic and steric effects are important factors in modulating the catalyst activity. Using the conjugated **L7** as ligand, which bears no NH proton, resulted in a significant TON reduction and lower selectivity; the undesired autoxidation product tetrahydrofuran α-hydroperoxide was observed as the major product (entry 8). Additionally, replacement of **L1** with the previously reported PyBidine ligand **L8** significantly lowered the catalytic activity, showing the beneficial effect of the sulfonyl group (entry 9). Still further, the asymmetric ligand **L9** and bidentate ligands **L10**−**L12** were all found inactive (entries 10−13). Finally, the Fe(OTf)$_2$−**L1**-catalyzed aerobic oxidation of THF was found compatible with arene solvents, whereas halogenated or donor solvents were found very detrimental for the catalyst activity (see the Supporting Information).

L6: Ar: 4-MeC$_6$H$_4$

L7: Ar: 4-MeC$_6$H$_4$

L8

L9: Ar: 2,4,6-trisopropylC$_6$H$_2$

L10

L11

L12: Ar: 4-tBuylC$_6$H$_4$

Although the conversion of the aerobic oxidation of **1a** was low, it should be noted that 2.3 mmol of γ-butyrolactone was isolated from a one-step reaction (Table 2, entry 1). Moreover, α-substituted γ-butyrolactones were also obtained from THF-type substrates with good chemoselectivity, mass balance, and functional group tolerance (Table 2; also see below). In addition, the oxidation with Fe(OTf)$_2$−**L1** is easy to conduct, with the starting substrate and the lactone product being easily separable, and it may still be possible to increase the conversion further (see below). The resulting substituted γ-butyrolactones are widely used in synthetic chemistry[32] and are common motifs in pharmaceutical[33] and natural[23c,34] products, and biomass processing.[35] To the best of our knowledge, this is the first catalyst in the literature that allows access to such functionalized compounds via aerobic oxidation. An exception is seen in **2b**, which can be obtained via a rhodium catalyzed oxidation, albeit with lower efficiency, harsher conditions, and longer reaction times (TON of 150 in a 7 day reaction under CO$_2$/O$_2$ pressure).[20]

3. Oxidation of Isochromans. To evaluate the applicability of the Fe(OTf)$_2$−**L1**-catalyzed oxidation of ethers, we next investigated the α-oxidation of substituted isochromans. The resulting products, isochromanones, are common motifs in natural products and bioactive molecules.[23b,36] To our delight,

Table 2. Fe(OTf)$_2$−L1-Catalyzed Aerobic Oxidation of THF Substrates[a]

Fe(OTf)$_2$-**L1** (5.6 x 10^{-3} mmol), O$_2$ (1 atm), 60 °C, 48 h

1a-e → 2a-e

Entry	Substrate (rsm%[b])	Lactone (TON[c], mmol)
1	1a (87%)	2a (412, 2.33)
2	1b (88%)	2b (371, 2.10)
3	1c (87%)	2c (133, 0.75)
4	1d (90%)	2d (123, 0.70)
5	1e (93%)	2e (94, 0.53)
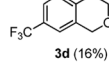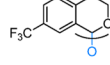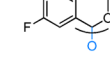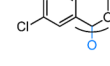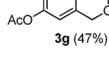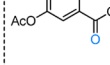
[a]Reaction conditions: substrate (2.0 mL), Fe(OTf)$_2$ (2.0 mg, 5.65 × 10^{-3} mmol), **L1** (5 mg, 5.65 × 10^{-3} mmol), O$_2$ (1 atm) at 60 °C, 48 h. [b]rsm: recovered starting material (unoxidized). [c]TON refers to mmol of isolated product per mmol of catalyst.

Table 3. Fe(OTf)$_2$−L1-Catalyzed Aerobic Oxidation of Isochromans[a]

Fe(OTf)$_2$-**L1** (5.6 x 10^{-3} mmol), O$_2$ (1 atm), 60 °C, 16 h

3a-h → 4a-h + 5a-h

Entry	Substrate (rsm%[b])	Yield (%)[c]	Isochromanone (TON[d], yield%[e])	1,1'-Oxidi-isochroman (TON[d], yield%[e])
1	3a (60%)	40%	4a. 844; 30%	5a. 281; 10%
2	3b (71%)	24%	4b. 573	5b. N.D.
3	3c (61%)	38%	4c. 668; 28%	5c. 239; 10%
4	3d (16%)	82%	4d. 1173; 67%	5d. 262; 15%
5	3e (30%)	70%	4e. 1256; 54%	5e. 372; 16%
6	3f (46%)	54%	4f. 902; 42%	5f. 251; 12%
7[f]	3g (47%)	52%	4g. 552; 40%	5g. 166; 12%
8	3h (64%)	35%	4h. 597; 25%	5h. 238; 10%

[a]Reaction conditions: substrate (2.0 mL), Fe(OTf)$_2$ (5.65 × 10^{-3} mmol), **L1** (5.65 × 10^{-3} mmol), O$_2$ (1 atm) at 60 °C, 16 h. [b]rsm: recovered starting material (unoxidized). [c]Isolated yield of both oxidized products. [d]TON refers to mmol of isolated product per mmol of catalyst. [e]Isolated yield of the individual product. [f]Substrate (1.5 g) was added to a C$_6$H$_6$ (0.5 mL) solution of in situ formed Fe(OTf)$_2$−**L1** (0.02 mol %) by heating at 35 °C for 1 h.

isochroman was oxidized with a 40% total yield, affording isochromanone with a TON of 844 in an overnight reaction (Table 3, entry 1). Isochroman-1-ol was not detected under this reaction condition; however, the unusual ether byproduct **5** was generated in low yield (also see below). The catalyst operates with high chemoselectivity even in the presence of tertiary benzyl or O-alkyl substituents with no sign of tertiary alcohol byproduct formation (entries 1−3). This selectivity is further manifested when **3a** was reacted for 5 days under the same conditions, which afforded **4a** and **5a** in about the same isolated yields with no overoxidation being observed (see the Supporting Information). The reactions also proceeded with excellent mass balance with no substrate decomposition, and the unreacted starting material was easily recovered.

Although the presence of substituents in the alkyl ring barely affects the reaction yields, substitution in the aromatic ring revealed a dramatic electronic effect, with electron-withdrawing groups inducing higher TONs and electron-donating groups exerting the opposite effect (entries 4−8). In particular, the trifluoromethyl- and fluorine-substituted **4d** and **4e** were isolated in over 1000 TON (6.63 and 7.09 mmol isolated, respectively). This appears to suggest the involvement of proton transfer in the turnover limiting step.

Very electron-rich isochromans can also be oxidized (Table 4). Although the TONs were reduced, very good mass balance was again demonstrated, allowing for full recovery of the unreacted starting material. Thus, the protected form of the natural product aurocitrine[37] was isolated in 5% yield (0.36

mmol) in a single-step reaction (Table 4, entry 4), indicating the potential applicability of our catalyst in natural product synthesis. Additionally, the scope of the reaction can be extended to a thiophene derivative, although the yield was low (Table 4, entry 2). To the best of our knowledge, this is the first iron catalyst capable of selectively oxidizing such electron-rich substrates to isochromanones.

Although biomimetic iron complexes catalyze the oxidation of ethers with H$_2$O$_2$ under acidic conditions, electron-rich aryl alkanes are decomposed.[3c,12] Among stoichiometric oxidants, ceric ammonium nitrate (CAN) oxidizes electron-rich isochromans under mild conditions, albeit with poor chemoselectivity.[38] SeO$_2$ can oxidize electron-rich isochromans in low yields through tedious procedures that require harsh reaction conditions.[39] Toxic CrO$_3$ can be used under milder conditions;[39] however, the reactions are substrate dependent.[18] Indeed, when the substrate **3l** was treated with a stoichiometric amount of CrO$_3$, the quinone product **3m** was obtained predominantly, with only traces of the desired isochromanone **4l** obtained (eq 2). Oxidation of p-dimethoxybenzene moieties

Table 4. Fe(OTf)₂−L1-Catalyzed Aerobic Oxidation of Electron-Rich Isochromans[a]

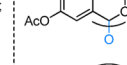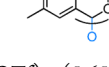| Entry	Substrate (rsm%[b])	Product (**TON**[c], yield %)
1	3i (82%)	4i. *388*; 18%
2	3j (82%)	4j. *454*; 18%
3[d]	3k (92%)	4k. *109*; 8%
4[d]	3l (95%)	4l. *63*; 5%

[a]Reaction conditions: substrate (2.0 mL), Fe(OTf)₂ (5.65 × 10⁻³ mmol), **L1** (5.65 × 10⁻³ mmol), O₂ (1 atm) at 60 °C, 16 h. [b]rsm: recovered starting material (unoxidized). [c]TON refers to mmol of isolated product per mmol of catalyst. [d]Substrate (1.5 g) was added to a C₆H₆ (0.5 mL) solution of in situ formed Fe(OTf)₂−**L1** (0.02 mol %) by heating at 35 °C for 1 h.

to quinones is often encountered when using stoichiometric oxidants, such as CAN,[40] MnO₂,[41] or hypervalent iodine.[42]

$$(2)$$
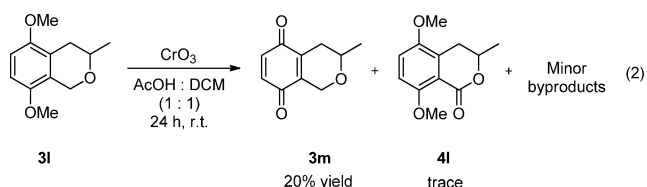
4. Oxidation of Phthalans. Having showed the viability of the catalyst in oxidizing isochromans, we turned the attention to the oxidation of phthalans to phthalides, important building blocks for more complex chemicals, such as dyes,[43] natural oils,[44] fungicides,[45] and biologically active compounds[46] (Table 5). A similar strong electronic effect was observed for these substrates, with higher yields obtained for substrates containing electron-withdrawing groups. Interestingly, this electronic effect can now be harnessed to direct the regioselectivity of the oxidation. Thus, with a strong *meta* directing effect ($\sigma_m = 0.34$ vs $\sigma_p = 0.06$), the fluorine substitute induced exclusive oxidation of the *meta* methylene unit to afford the ester **7a** in 60% isolated yield and 1533 TON. Similarly, dihydrofuro[3,4]-pyridines were regioselectively oxidized at the *ortho* or *meta* position, leading to azaphthalide skeletons of pharmaceutical and other industrial interest (Table 5, entries 5,6).[47] The higher

Table 5. Fe(OTf)₂−L1-Catalyzed Regioselective Aerobic Oxidation of Phthalans[a]

Entry	Substrate (rsm%[b])	Product (**TON**[c], yield %)
1	6a (40%)	7a. *1533*; 60%
2	6b (49%)	7b. *1164*; 51%
3	6c (60%)	7c. *711*; 40%
4	6d (83%)	7d. *500*; 17%
5	6e (48%)	7e. *1517*; 52%
6	6f (81%)	7f. *555*; 19%

[a]Reaction conditions: substrate (2.0 mL), Fe(OTf)₂ (5.65 × 10⁻³ mmol), **L1** (5.65 × 10⁻³ mmol), O₂ (1 atm) at 60 °C, 16 h. [b]rsm: recovered starting material (unoxidized). [c]TON refers to mmol of isolated product per mmol of catalyst.

TON observed for **6e** than **6f** is consistent with a stronger inductive effect by the nitrogen on the *ortho* methylene. In the case of the heavier halogens, their significantly stronger *para* directing effect ($\sigma_m = 0.37$ for Cl and 0.39 for Br vs $\sigma_p = 0.23$ for both) and larger size might result in the observed *para* oxidation (Table 5, entries 2,3). These results, together with those above, demonstrate that the Fe(OTf)₂−**L1**-catalyzed aerobic oxidation of ethers allows for the production of valuable lactone products at the gram scale under green, mild, and operationally simple conditions, thus addressing to a certain degree the challenges facing the design of chemoselective and stable homogeneous iron catalysts for selective oxidation on a commercial scale.[1,3a,48]

5. Product Inhibition and Catalyst Reuse. While Fe(OTf)₂−**L1** showed high chemoselectivity and TONs, the oxidations above generally displayed relatively low conversions. In an attempt to increase the efficiency of the Fe(OTf)₂−**L1**-catalyzed aerobic oxidations, higher catalyst loadings were tested. However, no significant improvement was observed in the oxidation of **1a** or **3a** when the catalyst loading was increased under otherwise the same conditions (see the Supporting Information). Further experiments revealed, surprisingly somehow, that the loss of catalytic activity at a

certain level of conversion results from product inhibition, rather than catalyst decomposition. Thus, in the presence of the ester product **4a** (30%, chosen according to the yield obtained under the normal conditions; see Table 3, entry 1), the Fe(OTf)$_2$−**L1**-catalyzed oxidation of **3a** afforded only 6% of additional **4a** (eq 3), in stark contrast with the isolated yield of
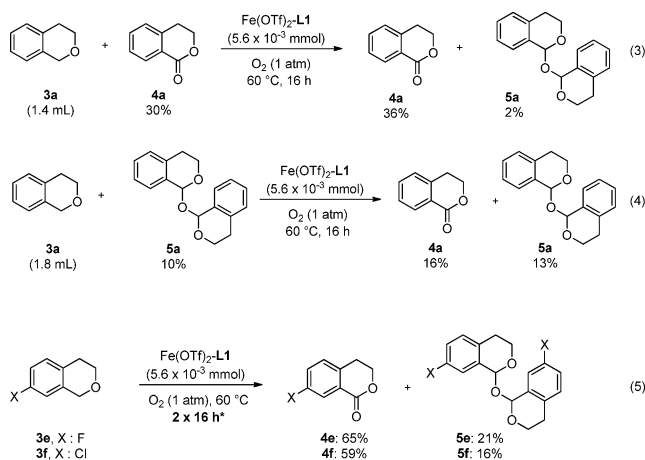
4a shown in Table 3. The oxidation was also inhibited by the ether byproduct **5a** (eq 4). Most likely, the inhibition arises from the carbonyl coordination in the case of **4a**, or the ether chelation in the case of **5a**, to the iron center, preventing the coordination of **3a** and hence its oxidation. This is in line with the detrimental effect exerted by coordinating solvents mentioned above.

Realizing the inhibition effect of product, it became possible to increase the overall yield of the oxidation with Fe(OTf)$_2$−**L1**, particularly when the product could be readily separated from the reaction mixture. This is demonstrated in the oxidation of isochromans **3e** and **3f** (eq 5). After the initial oxidation under the same conditions as those in Table 3, the resulting solid products were removed, enabling the oxidation to continue for another 16 h to give **4e** and **4f** in a total isolated yield of 65% (1503 TON) and 59% (1282 TON), respectively, with no product overoxidation (see the Supporting Information). These results highlight the robustness of the iron catalyst and point to a strategy for addressing the conversion issue in question, that is, run the oxidation in a continuous flow reactor.
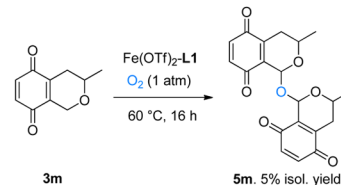
6. Mechanistic Investigations. *Involvement of Radical Species.* The high chemoselectivity, unusual tolerance to electron-rich groups, and strong electronic effect observed suggest that the Fe(OTf)$_2$−**L1**-catalyzed oxidation of ethers may proceed by a mechanism different from the one involving an electrophilic iron-oxo species or autoxidation mechanism. Indeed, no alcohol products were detected even in conditions of limited O$_2$ in the reactions presented (see the Supporting Information), which contrasts with the initial methylene oxidation to alcohol and subsequent over-oxidation to its ketone form observed in the methylene oxidation with H$_2$O$_2$ using the biomimetic Fe(PDP) catalyst.[3c] To gain insight into these observations, preliminary mechanistic investigations were performed. As such oxidation reactions often involve radical intermediates, we first examined the Fe(OTf)$_2$−**L1**-catalyzed oxidation of ethers in the presence of a radical trapping reagent. Isochroman was selected as a model substrate as no uncontrolled autoxidation occurred upon addition of a radical trapping agent, 2,6-di^{t}butyl-4-methylphenol (BHT), BrCCl$_3$,

TEMPO, or *para*-benzoquinone.[49] Addition of any of these reagents inhibited the formation of both isochromanone and 1,1′-oxidiisochroman with the former being more adversely affected (Figure 4A). However, no adducts resulting from the
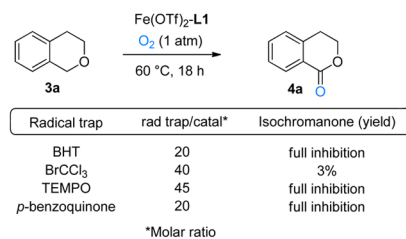
Figure 4. Experiments indicating no formation of freely diffusing radicals during the oxidation.

substrate and the radical trap were observed, such as 1-isochromanol or 1-bromoisochroman. Similarly, no products commonly derived from radicals[50] were observed when 3-methyl-3,4-dihydro-1*H*-isochromene-5,8-dione was subjected to the oxidation (Figure 4B).

To examine further the possible formation of radicals, the aerobic oxidation of isochroman was conducted in the presence of a radical initiator, benzoyl peroxide (Luperox),[51] at 35 °C. The presence of the initiator did not affect the oxidation of isochroman to isochromanone (16% in its presence vs 17% in its absence); however, a small amount of radical-derived isochroman hydroperoxide **8** (ca. 2%) was detected (Figure 4C). Notably, the hydroperoxide product gained significance in the absence of **L1** and became the sole product when the catalyst was omitted (see also the Supporting Information). Formation of the oxidation dimer **5a** was also observed in the presence of the Fe(OTf)$_2$−**L1** catalyst (see also Table 3). Although no clear evidence of the mechanism of its formation has been obtained, it is likely that **5a** is formed via a

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dx.doi.org/10.1021/ja502167h | *J. Am. Chem. Soc.* 2014, 136, 8350−8360

competitive, Fe(OTf)$_2$–**L1**-catalyzed process. Its formation via catalytic aerobic oxidation has not been reported; however, exposure of **3a** to stoichiometric[52] or radical[53] oxidants resulted in the formation of **5a**.

The ability of benzoyl peroxide to initiate radical reactions with such ethereal substrates is also seen in the reaction of the radical clock (±)-*trans*-(2-methoxymethyl)cyclopyl)benzene,[54] which underwent rapid ring-opening when exposed to a small amount of benzoyl peroxide under 1 atm of O$_2$ (Figure 4D). In sharp contrast, no reaction occurred when the radical initiator was replaced with Fe(OTf)$_2$–**L1**. The lack of reaction in the case of the iron catalyst is probably due to the steric bulkiness of the radical clock, which prevents its coordination to the iron center (see the Supporting Information, where a sterically demanding ether is shown to be equally inactive; also see below). Taken together, these observations suggest that while radicals may be generated in the Fe(OTf)$_2$–**L1**-catalyzed oxidation, freely diffusing carbon or oxygen-based radicals are not involved.

Identification of a Peroxide Intermediate. Further probing of the isochroman oxidation revealed a peroxy intermediate. Thus, when the oxidation was stopped after 1 h reaction, 1,1′-peroxydiisochroman **12**[55] was detected, apart from the expected isochromanone **4a** and the 1,1′-oxidiisochroman byproduct **5a** (Figure 5). Importantly, the peroxy species disappeared,
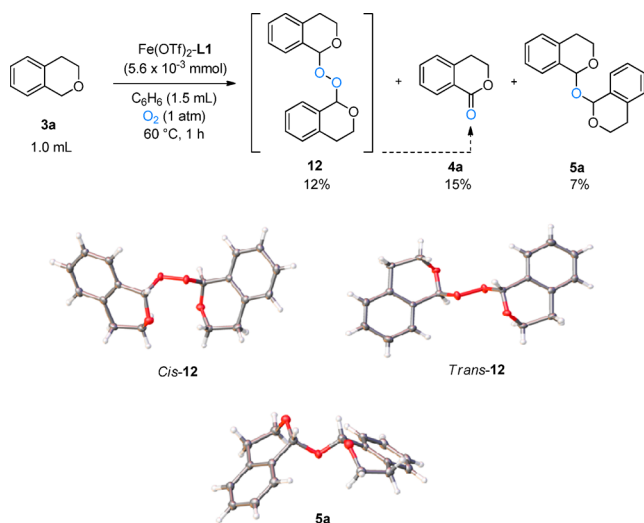

Figure 5. Identification of a peroxide intermediate during the oxidation of isochroman, and the X-ray structures of the peroxide intermediate and the 1,1′-oxidiisochroman byproduct (cis and trans refer to the positioning of the two ether oxygen atoms in **12**).

accompanied by an increase in the yield of **4a**, following further reacting overnight (see the Supporting Information). X-ray crystallographic analysis of the isolated mixture confirmed the structure of 1,1′-peroxydiisochroman **12** existing in two conformational isomers and that of 1,1′-oxidiisochroman **5a** (Figure 5). These observations suggest that Fe(OTf)$_2$–**L1** is capable of catalyzing rapid and selective formation of 1,1′-peroxyisochroman, from which the isochromanone results.

To gain more evidence of the intermediacy of **12**, an isolated mixture of **12** and **5a** (1.0:0.6 molar ratio) was exposed to a catalytic amount of Fe(OTf)$_2$–**L1** at 45 °C (eq 6). Crude ^{1}H NMR spectra revealed a clean reaction in which the peroxide **12** was fully converted into 2 equiv of isochromanone **4a** under an O$_2$ atmosphere, whereas 1,1′-oxidiisochroman **5a** remained
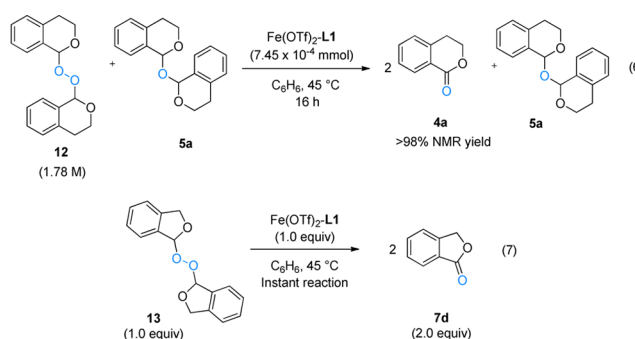
intact, establishing the intermediacy of the peroxide to isochromanone. Apparently, the oxy species is not involved in the formation of the ester product. To our surprise, this clean transformation of **12** to **4a** was also observed under a N$_2$ atmosphere; however, no reaction occurred in the absence of the iron catalyst. Interestingly, the reaction was not affected by the addition of either an excess of a radical inhibitor *para*-benzoquinone or the radical initiator benzoyl peroxide (see the Supporting Information), indicating that no radical species are involved at this stage of the isochroman oxidation. The presence of isochroman did not affect this transformation either (see the Supporting Information), nor was isochroman oxidized under the N$_2$ atmosphere, reinforcing that the oxidation of isochroman to the peroxide **12** involves O$_2$ while the conversion of **12** to the ester does not.

Moreover, when the similar peroxide **13**, which could be isolated (see below), was subjected to a stoichiometric reaction with Fe(OTf)$_2$–**L1**, phthalide **7d** was rapidly and exclusively generated (eq 7), providing unequivocal evidence for the intermediacy of the peroxide species in the Fe(OTf)$_2$–**L1**-catalyzed oxidation of ethers to lactones. To the best of our knowledge, the catalytic conversion of a peroxide, such as **12**, to 2 equiv of an ester like **4a** is unprecedented. Mixtures of the peroxide **12** and isochroman hydroperoxide **8** can be generated from the autoxidation of **3a** under prolonged aerobic exposition (4 weeks)[56] or pressurized O$_2$ atmosphere (5 bar) for shorter times (48 h).[55]

Evidence of H$_2$ Gas Release. Further study into how the oxidation proceeds revealed, much to our surprise, that the oxidation is accompanied by release of H$_2$, forming no H$_2$O. Thus, quantitative GC analysis established the stoichiometric formation of H$_2$ in the Fe(OTf)$_2$–**L1**-catalyzed oxidation of phthalan to phthalide, and showed that the H$_2$ formation took place in each individual step, that is, oxidation to afford the peroxide and its subsequent conversion to phthalide (Figure 6). In line with this observation, quantitative analysis with ^{1}H NMR showed that no water was formed in the oxidation of phthalan to phthalide (see the Supporting Information). Isolation of **13** was possible by running the catalytic oxidation in a C$_6$H$_6$ solution and at lower temperature than in Table 3. These results indicate that unlike common enzymatic
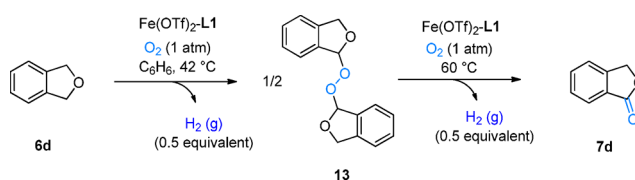

Figure 6. H$_2$ gas formation in the oxidation of phthalan.

oxidations, the oxidation in question proceeds via an unusual, sequential dehydrogenative oxygenation process. In fact, to the best of our knowledge, there appears to be no literature report of oxygenation coupled with dehydrogenation in enzymatic or biomimetic catalysis.

Isotope Labeling. Still further, oxygen isotope labeling experiments indicate that the initial formation of the peroxide involves no cleavage of the O−O bond in O_2. Thus, the oxidation of phthalan to 1,1′-peroxybis(1,3-dihydroisobenzo-furan) with a mixture of $^{18}O_2$ and $^{16}O_2$ afforded $^{16}O−^{16}O$ and $^{18}O−^{18}O$ containing peroxides; however, no crossover $^{16}O−^{18}O$ peroxy species were detected in the MS analysis (eq 8). The preservation of the O−O bond in the formation of the peroxide suggests that an iron-oxo intermediate is not involved in the oxidation mediated by $Fe(OTf)_2−L1$.
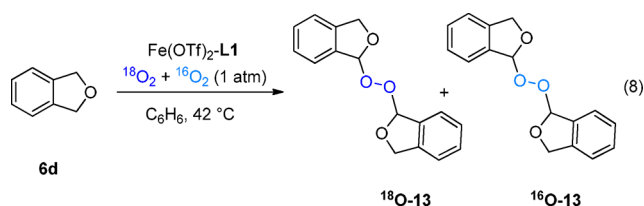
The cleavage of the peroxide **13** to give off H_2 (Figures 6 and 7) could involve a Fe−H hydride intermediate. Likewise, a Fe−
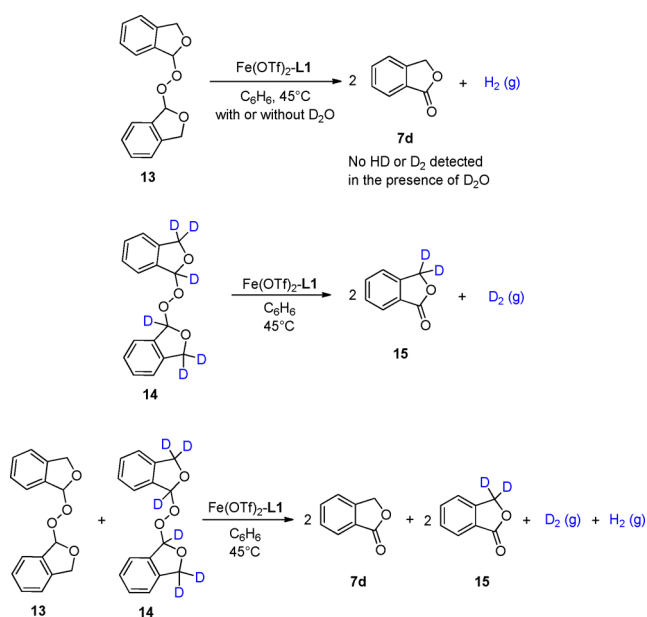
Figure 7. Deuterium labeling experiments revealing no HD or D_2 formation in the dehydrogenation of **13** in the presence of D_2O, and no HD formation in the reaction of a mixture of **13** and **14** (see the Supporting Information for details).

D deuteride may form in the case of the deuterium-labeled peroxide **14**, which afforded D_2. If so, it is likely that the iron hydride may undergo H−D exchange with D_2O. However, no HD or D_2 formation was observed when the oxidation of **13** to **7d** was performed in the presence of D_2O (Figure 7). We note that no HD or D_2 formation was reported either during the dehydrogenative pyrolysis of hydroxyalkyl peroxides.[57] The reaction was proposed to occur via a radical-cage mechanism, in which radical recombination is much faster than its combination with solvent molecules.[57]

To gain further insight into the conversion of the peroxide intermediate to the ester product, a mixture of peroxides **13** and **14** was exposed to the $Fe(OTf)_2−L1$ catalyst (Figure 7). GC−MS monitoring of the reaction revealed the exclusive formation of H_2 and D_2, suggesting that the cleavage of the peroxide is likely to occur within the coordination sphere of the iron center, involving no free alkoxide ion or free alkoxy radical in the solution (see below).

Suggested Mechanism. The results above point to the $Fe(OTf)_2−L1$-catalyzed α-oxidation of ethers following an unprecedented tandem dehydrogenative−oxygenation process involving the formation of a peroxide intermediate, and the peroxide cleavage appears to be the turnover-limiting step of the catalytic process (Figure 8). Although the formation of the
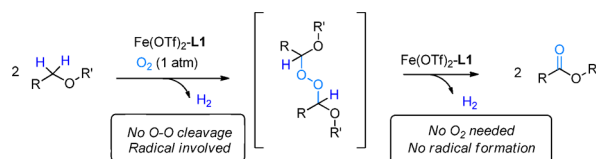
Figure 8. $Fe(OTf)_2−L1$-catalyzed α-oxidation of ethers via a tandem dehydrogenative−oxygenation process.

peroxide intermediate is unclear mechanistically, the preservation of the O−O bond in the peroxide intermediate and the absence of water formation rule out the formation of an iron-oxo species. Its formation via an autoxidation reaction is not in agreement with the chemoselectivity observed and radical trapping experiments either. Iron-induced CH activation of the ethereal substrate followed by O_2 attack appears also unlikely[21] due to instability of metalated ethers and the easy formation of cleavage products,[58] which contradicts with the excellent mass balance observed. Although CH activation of ethers via the classic β-hydrogen (α to the oxygen) elimination following the ether coordination to a metal is known,[59] the ethers under the conditions employed here undergo no hydrogen elimination or exchange in the absence of O_2, thus ruling out the possibility of an anaerobic CH activation process initiated by iron. The generation of oxonium ions from ethereal substrates under catalytic conditions also seems improbable. These ions can be easily trapped by nucleophiles;[52a] however, no lactol formation was observed when the isochroman **3a** was oxidized in the presence of H_2O or D_2O.

Considering the coordination mode of $[FeL1(THF)(OTf)_2]$ and particularly the short Fe−O3 (THF) distance (Figure 3), we hypothesized that under the reaction conditions, the iron complex may coordinate to one or two ethereal substrates. Exposure to O_2 atmosphere would easily result in the formation of a Fe^{III} superoxo species **16** in a fashion similar to that with metalloenzymes[3a] and related biomimetics.[60] The Fe^{III} super-oxo species could initiate the cleavage of the α-CH bond of the Fe-bound ether substrate; hydrogen atom transfer to the Fe^{III} center followed by, or concurrent with, the attack of the superoxo radical at the α carbon leads to a radical-ligated $Fe^{III}−$H hydride or a tight hydride−radical pair **17** (Figure 9). From the species **17**, a second hydrogen atom transfer and radical combination afford **12** and a $Fe^{IV}−(H)_2$ dihydride, which undergoes reductive elimination to give off H_2. This hypothetic mechanism is consistent with the presence of radical species, the high chemoselectivity of the oxidation, and the strong electronic as well as steric bias manifested in the substrate scope. Support for the mechanism is also found in the
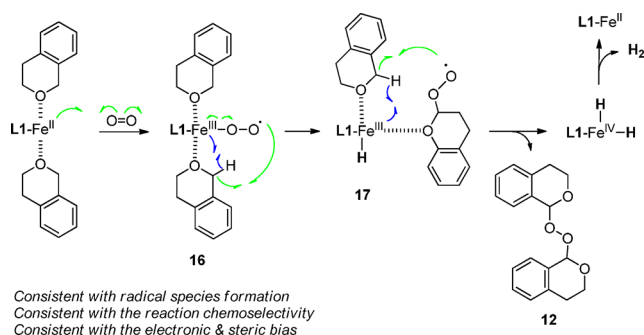
Figure 9. Postulated formation of the peroxide intermediate.

literature. In particular, hydrogen transfer from a sp³ carbon α to oxygen followed by the formation of Fe^{IV}–H hydride–radical pair has been suggested for the coupling of alcohols with alkenes.[61] Many transition metals, including Fe^{IV}, are known to form metal–dihydride and metal–dihydrogen complexes, from which hydrogen release can occur.[62]

The cleavage of the peroxy bond to form the ester product could proceed via the oxidative addition of the peroxide on the Fe center followed by β-hydrogen abstraction, giving off H$_2$ (Figure 10). It is known that some metal complexes can
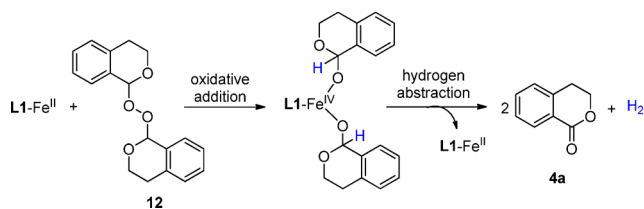

Figure 10. Conversion of **12** to **4a** via a hypothetic oxidative addition–hydrogen abstraction sequence.

undergo oxidative addition of peroxides ROOR, resulting in cleavage of the O–O bond.[63] This cleavage may involve polar addition of the RO–OR bond to a metal center generating a M$^+$–OR cation and a RO$^-$ anion, or concerted nonpolar addition of the peroxide bond to give two M–OR bonds, or a radical mechanism giving rise to a M$^\bullet$–OR and a RO$^\bullet$ radical.[63a] Because the oxidation with Fe(OTf)$_2$–**L1** leads to no formation of HD (Figure 7), readily takes place in nonpolar solvents such as benzene, and the catalytic conversion of **12** to **4a** is insensitive to radical inhibitors, the oxidative addition of the peroxide to the iron catalyst is likely to proceed via the concerted pathway.

Bearing in mind the observations made with the isotope labeling, the dehydrogenation step shown in Figure 10 may involve consecutive β-hydrogen migration to the iron followed by fast reductive elimination to release H$_2$. Literature examples are known of hydrogen abstract from iron-alkoxo species, leading to dehydrogenation including release of H$_2$, in catalysis by both metal complexes and enzymes.[64] In addition, under pyrolytic conditions, hydroxyl[65] and bis-hydroxyalkyl[66] peroxides can give off hydrogen gas.

On the basis of these mechanistic investigations, a catalytic cycle involving the inner-sphere formation of a peroxide intermediate via the attack of an iron-superoxo radical at coordinated ethers is postulated (Figure 11). Subsequent conversion of the isolable peroxide intermediate to the ester product may proceed through a concerted oxidative addition–
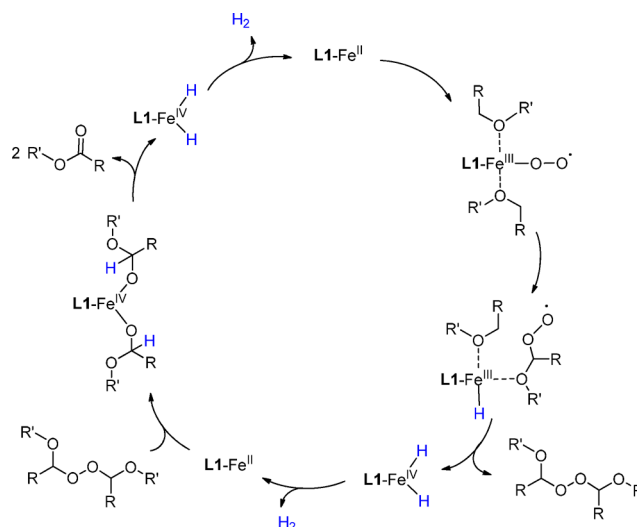

Figure 11. Proposed catalytic cycle for the Fe(OTf)$_2$–**L1**-catalyzed aerobic oxidation of ethers to esters.

hydrogen abstraction sequence. The release of H$_2$ is likely to be a result of fast reductive elimination of hydrides at a Fe^{IV} center.

■ CONCLUSION

This Article reports a well-defined iron catalyst capable of promoting selective oxidation of aromatic ethers to afford valuable γ-butyrolactones, isochromanones, and phthalides under 1 atm of O$_2$ with high TONs, excellent mass balance, and significantly improved functional group tolerance. Although the conversions remain to be improved, considerable amounts of product can be isolated in a one-step reaction, with the substrates easily recovered. An unusual mechanism involving dehydrogenation without initial metal-centered O–O cleavage appears in operation, which may inspire new thinking in understanding and mimicking iron-based mono and dioxygenases. We note, however, that the details of the reaction mechanism are yet to be delineated, in particular those concerning the formation of the peroxide and its transformation into the ester accompanied by H$_2$ release.

■ ASSOCIATED CONTENT

S Supporting Information

Experimental procedures, and ligands and products characterization data including ¹H and ¹³C NMR spectra and detailed mechanistic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

experiments. We also thank Dr. Weijun Tang, Dinesh Talwar, and Zhijun Wang for helpful discussions. A GB patent on the catalysts reported is pending (application ref 1321025.7).

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