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Sc^{3+} (or $HClO_4$) activation of a nonheme Fe^{III}–OOH intermediate for the rapid hydroxylation of cyclohexane and benzene

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ABSTRACT: $[Fe(\beta\text{-BPMCN})(CH_3CN)_2]^{2+}$ (**1**, BPMCN = *N,N'*-bis(pyridyl-2-methyl)-*N,N'*-dimethyl-*trans*-1,2-diaminocyclohexane) is a relatively poor catalyst for cyclohexane oxidation by H_2O_2 and cannot perform benzene hydroxylation. However, addition of Sc^{3+} activates the **1**/H_2O_2 reaction mixture to be able to hydroxylate cyclohexane and benzene within seconds at -40 °C. A metastable $S = ½$ Fe^{III}–(η^1-OOH) intermediate **2** is trapped at -40 °C, which undergoes rapid decay upon addition of Sc^{3+} at rates independent of [substrate] but linearly dependent on [Sc^{3+}]. $HClO_4$ elicits comparable reactivity as Sc^{3+} at the same concentration. We thus postulate that these additives both facilitate O–O bond heterolysis of **2** to form a common highly electrophilic Fe^V=O oxidant (**Ox**) that is comparably reactive to the fastest nonheme high-valent iron-oxo oxidants found to date.

INTRODUCTION

The emergence of nonheme iron enzymes as excellent biocatalysts for C–H bond functionalization[1,2] has spurred the investigation of synthetic nonheme iron catalysts that perform hydrocarbon oxidations with H_2O_2 as the oxidant.[3–5] Spectroscopic and mechanistic studies on some of these synthetic catalysts have provided evidence for an $S = 1/2$ Fe^{III}–OOH intermediate that then undergoes O–O bond heterolysis to generate the actual oxidant. An electrophilic oxoiron(V) species derived therefrom is proposed to be responsible for substrate oxidation.[6–9] For Fe^{II}(TPA) and Fe^{II}(BPMEN) (TPA = tris(pyridyl-2-methyl)amine; BPMEN = *N,N'*-bis(pyridyl-2-methyl)-1,2-diaminoethane), this cleavage is promoted by a proton, delivered by a water or carboxylic acid ligand that is proposed to bind to the iron center *cis* to the HOO moiety. However, $[Fe(\beta\text{-BPMCN})(CH_3CN)_2]^{2+}$ (**1**, Figure 1) shows a reactivity pattern different from the well-studied Fe^{II}(TPA) and Fe^{II}(BPMEN) catalysts, and has previously been found to be a sluggish hydroxylation catalyst with H_2O_2 as the oxidant.[10] We have thus investigated strategies by which to enhance the catalytic performance of **1**.

Extensive work by Fukuzumi and Nam showed that addition of Sc^{3+} and other Lewis acids can significantly enhance the oxidative reactivity of high-valent metal-oxo species, mainly by boosting the rate of electron transfer from substrate to a proposed Lewis-acid adduct of the metal-oxo center, and the electron transfer rate increased with the strength of the Lewis acid.[11,12] In other work, Yin, Goldberg and Collins independently showed Lewis-acid activation of high-valent $Mn(OH)_2$ or Mn(O) centers,.[13–16] while Fukuzumi and Nam subsequently found evidence for the formation of a Sc^{3+}-bound Mn^V(O)(TAML) complex (TAML = tetraamido macrocyclic ligand) with the Lewis acid coordinated to the carbonyl oxygen of the macrocyclic ligand.[17] Similarly, Lau demonstrated activation of polyoxo anions such as chromate, permanganate and ferrate by Lewis acids for the oxidation of C–H bonds.[18–21] In a more recent effort, Lau and coworkers found that Lewis acids could activate $[Os^{VI}(N)(Cl)_4]^-$ by interacting with the nitride ligand to catalyze alkane oxidation with H_2O_2 or ROOH.[22]

More relevant to our effort was the finding that Sc^{3+} and Y^{3+} induce cleavage of the O–O bond in $[Fe^{III}(\eta^2\text{-}O_2)(TMC)]^+$ (TMC = tetramethylcyclam) to form the corresponding oxoiron(IV) complex,[23,24] which led us to explore whether Fe-based intermediates involved in nonheme iron oxidation catalysis with peroxides as oxidants might be similarly activated. We were encouraged by recent papers that demonstrated positive effects of adding Sc^{3+} to metal-catalyzed oxidations at room temperature. Yin and coworkers found that adding Sc^{3+} tripled the olefin epoxidation yield by Fe^{II}(BPMEN)/H_2O_2,[25] while Nodzewska and Watkinson showed that Sc^{3+} accelerated epoxidation rates of electron-deficient styrenes with the $[Mn_2(\mu\text{-}O)_3(TMTACN)_2]^{2+}$/$H_2O_2$ combination (TMTACN = 1,4,7-trimethyl-1,4-7-triazacyclononane).[26] Chatterjee and Paine reported that Sc^{3+} promoted the stoichiometric hydroxylation of cyclohexane in the reaction of a nonheme iron(II)-benzilate complex with O_2.[27] In all these cases, some interaction of Sc^{3+} with the putative metal-based oxidant was postulated, but no direct evidence for such an interaction was demonstrated. In this paper we focus on the sluggish catalyst **1** and report our findings that addition of Sc^{3+} or $HClO_4$ to the **1**/H_2O_2 combination generates a powerful hydroxylating agent. We have trapped a transient $S = ½$ Fe^{III}–(η^1-OOH) intermediate **2** at cryogenic temperatures and demonstrate its activation by interaction with Sc^{3+} or $HClO_4$ to form a species that hydroxylates cyclohexane and benzene at -40 °C within a few seconds.

RESULTS AND DISCUSSION

Effect of Sc(OTf)$_3$ on the reactivity of 1/H_2O_2. The oxidation of cyclohexane using **1** and 90% H_2O_2 (10 eq relative to **1**) in CH_3CN at 20 °C affords 0.5 eq cyclohexanol and 0.6 eq cyclohexanone as products (Figure 1 and Table 1). The apparent stoichiometric oxidation of cyclohexane and the low alcohol-to-ketone ratio (A/K) of 0.8 together indicate an unpromising catalyst/oxidant combination. These values do not change much upon addition of 2 eq Al^{3+}, Y^{3+}, Yb^{3+}, or Zn^{2+} relative to **1** (Figure S1), but treatment with 2 eq Sc^{3+} elicits a 10-fold increase in both the cyclohexanol yield and the A/K ratio (Figure 1). This observation can be rationalized by noting that H_2O_2 solutions contain water, and Lewis acidic metal salts such as $Al(OTf)_3$ and $Zn(OTf)_2$ are known to react with water and decompose. However, $Sc(OTf)_3$ is a relatively stable Lewis acid in water and a much stronger Lewis acid than the other water-stable Lewis acids tried like $Y(OTf)_3$ and $Yb(OTf)_3$.[12,28] The increase in the alcohol TON (turnover number) is dependent on [Sc^{3+}] and this effect starts to plateau at ca. 2 eq Sc^{3+}. These results suggest that addition of Sc^{3+} changes the nature of the active oxidant formed in the reaction (Figure 1).

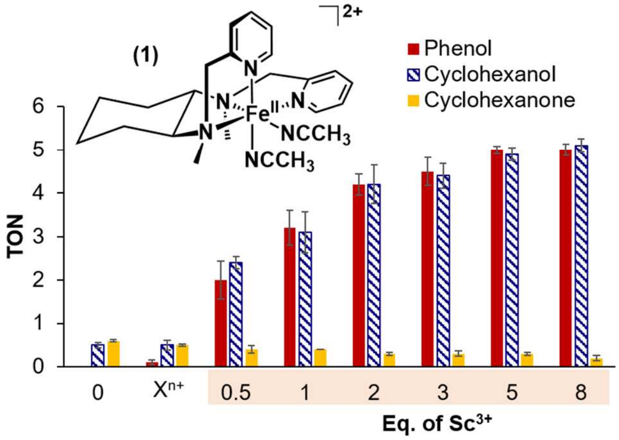


Figure 1. Yields in the hydroxylation of C_6H_6 (100 eq relative to **1**) or c-C_6H_{12} (1000 eq) by **1** (0.7 mM) and 10 eq 90% H_2O_2 in CH_3CN at 20 °C under air as a function of [Sc^{3+}]. X^{n+} reflects the averaged results from adding 2 eq Al^{3+}, Y^{3+}, Yb^{3+}, or Zn^{2+} (for individual results see Figure S1). (90% H_2O_2 was used as oxidant to minimize Lewis-acid deactivation by water present in the H_2O_2 solution.)

In the presence of Sc^{3+}, 50% of H_2O_2 can be converted into products versus only 11% conversion in the absence of Sc^{3+} (Figure 1). The high alcohol-to-ketone ratio (A/K) of 14 found for the Sc-activated reaction indicates that the alkyl radical generated after the initial H-atom abstraction must be short-lived and immediately rebounds to the oxygen attached to the metal center, which is also consistent with the absence of any significant effect of O_2 on the product TONs (Tables 1 and S1). The competitive oxidation of c-C_6H_{12} and c-C_6D_{12} in the presence of Sc^{3+} shows a product kinetic isotope effect (PKIE) of 2.5(2) versus 5(1) in the absence of Sc^{3+} (Table 1), suggesting the generation of a more powerful oxidant in the presence of Sc^{3+}. Taken together, the high A/K ratio, the absence of a significant effect of O_2 and a PKIE ≥ 2 point to a metal-based oxidant that forms in the presence of Sc^{3+}.

Table 1: Hydroxylation of c-C_6H_{12} and C_6H_6 by **1**/H_2O_2[a]

	TON alcohol (A)	TON ketone (K)	A/K[b]	PKIE[c]	% H_2O_2 converted[d]	TON PhOH (P)
no Sc^{3+}	0.5(1)	0.6(1)	0.8	5(1)	11	0
2000 eq AcOH	2.0(1)	0.4(1)	5	4.2(4)	24	0
2 eq Sc^{3+}	4.2(4)	0.3(1)	14	2.5(2)	45	4.2(2)
2 eq $HClO_4$	4.0(2)	0.1(1)	40	2.0(1)	40	4.0(3)

[a] All reactions were performed at room temperature under air; TON (Turnover Number) = moles of product/moles of **1**. [b] A/K = TON alcohol/TON ketone. [c] PKIE = kinetic isotope effect based on yields of cyclohexanol and cyclohexanol-d_{11} (For PKIE experiments, H_2O_2 was added by syringe pump). [d] % conversion of H_2O_2 = (A + K)/H_2O_2 x 100 for c-C_6H_{12} oxidation.

Interestingly, the **1**/H_2O_2/Sc^{3+} combination can also catalyze benzene hydroxylation, affording phenol in amounts comparable to cyclohexanol in cyclohexane oxidation (Figure 1). Benzene hydroxylation is observed only when Sc^{3+} is present with as much as 5 TON or 50% conversion of H_2O_2 into phenol (Figure 1), a yield comparable to or better than the other iron systems reported so far under similar conditions (Table S2). As found for cyclohexane hydroxylation, the phenol yield depends on [Sc^{3+}] and begins to plateau at ~2 eq Sc^{3+} w.r.t **1** (Figure 1). No over-oxidation products are found, unlike for other catalytic systems in which p-benzoquinone and/or catechol were observed as byproducts.[9,29,30] The oxidant formed is also able to attack electron-poor benzene derivatives such as bromobenzene, trifluoromethylbenzene, nitrobenzene (Figure S2), and even 1-chloro-2-nitrobenzene. For nitrobenzene, 3-nitrophenol and 2-nitrophenol products are obtained, with respective TONs of 1.1(1) and 0.5(1). These results point to the formation of a powerful and highly electrophilic oxidant. An inverse KIE of 0.9 is found from GC-MS analysis based on product peak intensity ratios in the oxidation of a 1:1 mixture of C_6H_6 and C_6D_6. Such values are typically found for electrophilic aromatic substitution reactions,[31] implicating a metal-based electrophilic oxidant, rather than a radical-based oxidant for which the KIE is typically greater than 1.[30,32,33]

Despite being quite different transformations, cyclohexane and benzene oxidation by **1**/H_2O_2/Sc^{3+} show a similar dependence on [Sc^{3+}] (Figure 1), allowing the comparison of the two distinct and relatively difficult reactions. Competitive oxidation of cyclohexane and benzene shows the oxidation of the latter to be favored by 10:1 on a per mole basis (Figure 2). On the other hand, oxidation of a 1:1 mixture of cyclohexane and nitrobenzene shows cyclohexane oxidation to be favored 3:1 over that of nitrobenzene. These comparisons give rise to a reactivity order of benzene > cyclohexane > nitrobenzene and, to the best of our knowledge, represent a unique opportunity for such a reactivity comparison for a first-row transition metal oxidation catalyst.

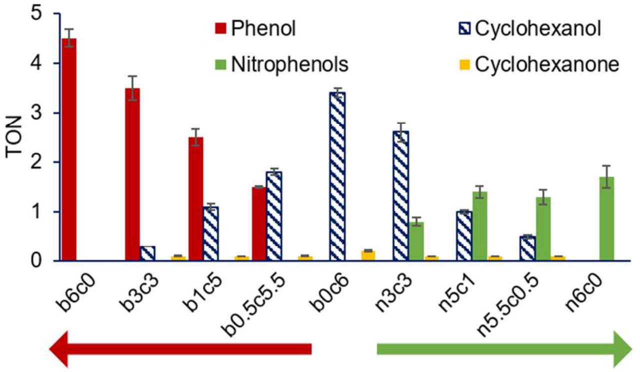


Figure 2. Competitive hydroxylations of cyclohexane (**c**) and benzene (**b**, left) or nitrobenzene (**n**, right) with 0.7 mM **1**, 10 eq H_2O_2, 2 eq Sc^{3+} and 600 eq total substrate. The numbers on the x-axis represent the substrate ratio in the competition experiments.

Effect of HOAc and $HClO_4$ on the reactivity of 1/H_2O_2. In our previous work with **1** and olefins, we showed that addition of 2000 eq HOAc to **1**/H_2O_2 switched its reactivity preference from *cis*-dihydroxylation of electron-poor olefins to epoxidation of electron-rich olefins, involving formation of a putative $Fe^{V}(O)(OAc)$ oxidant.[34] Here, we found that addition of 2000 eq HOAc to **1**/H_2O_2 only doubled the amount of cyclohexanol from cyclohexane but did not convert benzene to phenol (see Table 1). Additionally, the PKIE observed for HOAc addition is quite similar to the value observed without additive but different from that obtained in the presence of Sc^{3+} (Table 1). These results suggest that the oxidant produced by adding HOAc is less effective and quite distinct from that formed with Sc^{3+}.

We have also investigated replacing Sc^{3+} with $HClO_4$ and found $HClO_4$ to have the same effect as Sc^{3+} on **1**-catalyzed oxidations (Table 1). At the same concentration as Sc^{3+}, $HClO_4$ affords similar yields of cyclohexanol and phenol (Figure 3). Furthermore, essentially the same PKIE value is found for cyclohexane oxidation by **1**/H_2O_2/$HClO_4$ as **1**/H_2O_2/Sc^{3+}, showing comparable selectivity for attacking the cyclohexane C–H over C–D bonds. Additionally, addition of Sc^{3+} or $HClO_4$ affects the lifetime of intermediate **2** similarly (*vide infra*). These results together suggest the formation of a common oxidant for $HClO_4$ and Sc^{3+}. In preliminary experiments, we have found that adding HNO_3 or H_2SO_4 instead of $HClO_4$ to the **1**/H_2O_2/benzene mixture also leads to formation of **3** but either at a slower rate than $HClO_4$ or at a lower spectroscopic yield of **3**, respectively. This reactivty difference may derive from the higher pKa's of these acids and/or possible interactions of the NO_3^- or SO_4^{2-} counteranion with the active oxidant. The acid dependence will be further investigated in subsequent efforts.

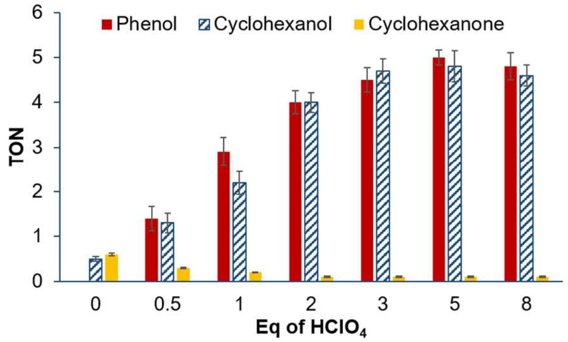


Figure 3. Yields in the hydroxylation of C_6H_6 (100 eq relative to **1**) or c-C_6H_{12} (1000 eq) by **1** (0.7 mM) and 10 eq 90% H_2O_2 in CH_3CN at 20 °C under air as a function of [$HClO_4$].

Characterization of the $[Fe^{III}(\beta\text{-BPMCN})(OOH)]^{2+}$ intermediate 2. To gain insight into this chemistry of **1**/H_2O_2 with Sc^{3+} or $HClO_4$, the reaction of **1** with H_2O_2 was initially investigated in the absence of Sc^{3+} and $HClO_4$ at -40 °C in CH_3CN. A transient purple intermediate, **2**, is observed with a λ_{max} at 545 nm, an EPR signal with g = 2.22, 2.17, and 1.96, and a resonance Raman spectrum with bands at 613 and 802 cm^{-1} assigned to Fe–O and O–O vibrations, respectively (Figure 4 and S3). Taken together, all the spectroscopic evidence characterizes **2** as a low-spin (S = ½) Fe^{III}–η^1-OOH intermediate, based on literature precedents (Table S3).[35,36] The corresponding $[(TPA)Fe^{III}–OOH]^{2+}$ species has been implicated as the precursor to the electrophilic oxidant responsible for Fe(TPA)-catalyzed alkane hydroxylation and olefin epoxidation and *cis*-dihydroxylation.[6–8] However, despite their spectroscopic similarities, **2** is much less reactive than its TPA analog[6,10] and requires activation by Sc^{3+} or $HClO_4$ to carry out electrophilic oxidations.

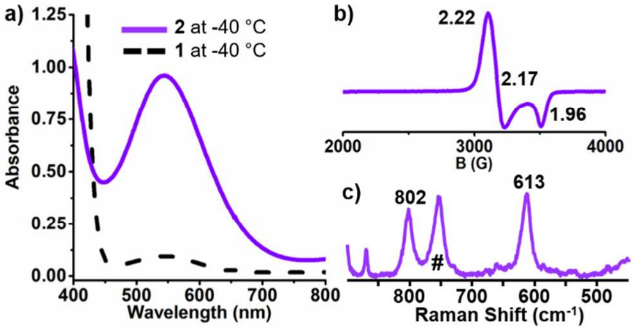


Figure 4. (a) UV-vis spectrum of **2** formed at -40 °C in CH_3CN from 1 mM **1** and 20 eq H_2O_2; (b) X-band EPR spec-

trum of **2** obtained at 40 dB at 2 K; (c) resonance Raman spectrum of **2** formed with 2.5 mM **1** and 20 eq H_2O_2 at -30 °C (λ_{exc} 561 nm).

Kinetic analysis of the reaction of 2 with Sc^{3+} or $HClO_4$ in the presence of benzene and cyclohexane. Upon addition of excess H_2O_2 to **1** in the presence of cyclohexane, **2** forms and reaches a pseudo-steady-state phase and then decays over the course of 90 min at -40 °C (Figure S4a). However, addition of Sc^{3+} to this mixture upon maximum accumulation of **2** accelerates the decay of **2** by a 1000-fold (Figures 5b (green) and S4b). Similarly, **2** accumulates upon addition of H_2O_2 in the presence of benzene within the same time period as for cyclohexane. However, addition of Sc^{3+} to **2** in the presence of benzene instead of cyclohexane generates an intense blue chromophore characteristic of an Fe^{III}-phenolate species **3** (λ_{max} 620 nm),[37] which is conveniently monitored at 800 nm where there is no contribution from **2** (Figures 5a and 5b). No formation of **3** was observed until Sc^{3+} was added to the reaction mixture containing benzene (Figure 5b). These observations concur with the catalytic results for **1**/H_2O_2 where phenol is formed only in the presence of Sc^{3+} (Table 1).

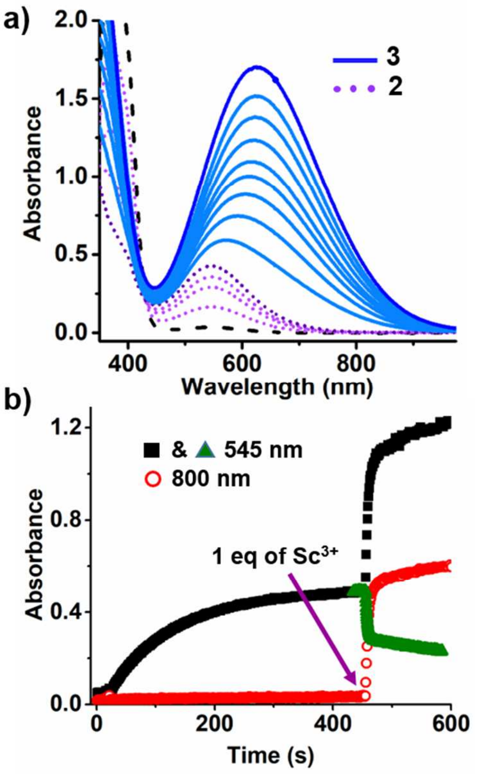


Figure 5. (a) Spectral changes in the visible region upon reaction of 0.5 mM **1** (dashed black line) in CH_3CN at -40 °C with 20 eq H_2O_2 to form **2** (dotted purple lines). Formation of **3** is observed upon subsequent addition of 1 eq $Sc^{3+}$to **2** (solid blue lines). (b) Time traces monitoring nearly instantaneous changes in absorbance at 545 and 800 nm after addition of 1 eq Sc^{3+}. ■: 545 nm and ○: 800 nm in the presence of C_6H_6; ▲: 545 nm in the presence of C_6H_{12}.

Very interestingly, upon addition of Sc^{3+} to **2**, the rate of **3** formation in the presence of benzene matches the decay rate of **2** in the presence of cyclohexane (Figure 5b and 6). At the same concentration as Sc^{3+}, $HClO_4$ causes **2** to decay (in the presence of cyclohexane) or **3** to form (in the presence of benzene) at essentially the same rates as Sc^{3+} (Figure S5 and Table S4), supporting our earlier inference that Sc^{3+} and $HClO_4$ activate **2** in a similar fashion to form a common active oxidant. Importantly, the rates of **2** decay and **3** formation both increase as a function of $[Sc^{3+}]/[HClO_4]$ (Figure 6b and Figure S5) but do not depend on either [cyclohexane] or [benzene] (Table S4). Taken together, these observations suggest that **2** is not the actual oxidant, but instead interacts with $Sc^{3+}/HClO_4$ to form **Ox**, the species responsible for substrate oxidation, and the substrate oxidation step must be faster than the oxidant forming step.

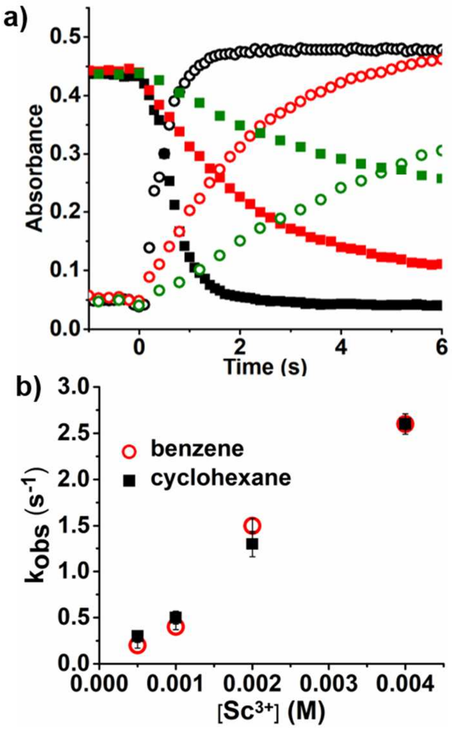


Figure 6. (a) Time traces monitoring decay of **2** at 545 nm in the presence of 185 eq cyclohexane (■) and formation of **3** at 800 nm with 100 eq benzene (○) showing the effect of increasing $[Sc^{3+}]$ (green: 1 eq; red: 2 eq; black: 8 eq Sc^{3+}). (b) $[Sc^{3+}]$ dependence of k_{obs} for **2** decay with cyclohexane as substrate (■) or **3** formation (○) with benzene as substrate. Data for the effect of $HClO_4$ addition are shown in Figure S5.

Addition of Sc^{3+} or $HClO_4$ allows **1**/H_2O_2 to perform previously unachievable reactions, such as aromatic hydroxylations, as well as accelerates the reaction step responsible for the formation of the active oxidant. Fe^{III}–OOH intermediates have also been trapped for other nonheme iron catalysts and found to serve as precursors to the actual oxidant in their reactions, where the step to form the actual oxidant can be accelerated by addition of water/acids (Table 2). For $[Fe^{III}(TPA)(OOH)]^{2+}$, we showed that it underwent water-assisted O–O bond cleavage to generate an epoxidation agent,[8] wherein substitution of H_2O with D_2O resulted in a 2.5-fold decrease in the rates of intermediate decay and epoxide product formation. Addition of 200 eq HOAc increased the reaction rate about 100-fold.[38] Similarly, Rybak-Akimova concluded that for Fe^{II}(BPMEN)/H_2O_2 the observed Fe^{III}-OOH intermediate serves as precursor to the actual oxidant.[9] Hydroxylation of benzene to form Fe^{III}-OPh occurs at a [benzene]-independent rate of 0.03 s^{-1} at 20 °C, which increases to 0.5 s^{-1} with 1 eq HOAc. Serrano-Plana et al. found $[Fe^{III}(PyNMe_3)(OOH)]^{2+}$ to be quite unreactive but could be activated by adding 1.1 eq HOTf to generate an oxidant capable of hydroxylating cyclohexane.[39] When adjusted to a common temperature of -40 °C, the decay rate constants of these (L)Fe^{III}–OOH species increase in the order: L = BPMEN,[9] TPA,[8] BPMEN + 1 eq HOAc,[9] $PyNMe_3$ + 1.1 eq HOTf,[39] TPA + 200 eq HOAc,[38] and β-BPMCN + 1-8 eq Sc^{3+} or $HClO_4$) (Table 2). This comparison places the **1**/H_2O_2/(Sc^{3+} or $HClO_4$) combination among the fastest in the conversion of an Fe^{III}-OOH intermediate into a highly reactive oxidant for oxidation catalysis.

Table 2. Rates of decay of Fe^{III}–OOH intermediates at -40 °C, except where noted.

Iron complex + additive	k_{obs} (s^{-1})	Ref
Fe^{III}(BPMEN)(OOH) (20 °C)[a]	0.03	9
Fe^{III}(BPMEN)(OOH) + 1 eq HOAc (20 °C)[a]	0.5	9
Fe^{III}(TPA)(OOH)[b]	0.002	8
Fe^{III}(TPA)(OOH) + 200 eq HOAc	0.17	38
$Fe^{III}(PyNMe_3)$(OOH) + 1.1 eq HOTf[c]	0.02	39
Fe^{III}(β-BPMCN)(OOH) + 1-8 eq Sc^{3+}/H^+ [d]	0.3–2.6	This work

[a] In the presence of benzene. [b] In the presence of 1-octene. [c] $PyNMe_3$ = 3,6,9-trimethyl-3,6,9-triaza-1(2,6)-pyridinacyclodecaphane. [d] In the presence of cyclohexane or benzene.

We also compare the oxidant generated by the **1**/H_2O_2/Sc^{3+} combination with a number of high-valent nonheme iron-oxo species that have been characterized and shown to directly hydroxylate cyclohexane (Table 3). For the latter complexes, their reactivity is reflected by the magnitude of their second order rate constants measured at -40 °C. Unlike these complexes, **Ox**, the oxidant from our $[Fe^{II}$(β-BPMCN)$(OTf)_2$/(Sc^{3+} or $HClO_4$) system cannot be observed, because its formation upon decay of **2** is slower than the actual substrate oxidation step. Nevertheless, a comparison of the rate of **2** decay to the cyclohexane oxidation rates from the examples in the literature would still be informative, and these data are collected in Table 3. With 1 eq Sc^{3+} or $HClO_4$, **2** decays to form the active oxidant at 0.3 s^{-1}, which is significantly faster than the oxidation rates of 1 M cyclohexane by $[Fe^V(O)(TAML)]^-$ and $[Fe^{III}(13\text{-}TMC)(OIAr)]^{2+}$ (which could be considered to be a 'masked Fe^V(O)' species), but comparable to those of the oxoiron(IV) complexes, *S* = 1 $[Fe^{IV}(O)(Me_3NTB)]^{2+}$ and *S* = 2 $[Fe^{IV}(O)(TQA)]^{2+}$, and $[Fe^{IV}(O)(TDCPP)]^+$ (a synthetic analog for Compound I).[40–43] The decay rate of **2** is 10-fold slower than that of the fastest cyclohexane oxidation rate reported thus far, which is found for the putative $[Fe^V(O)(O_2CR)(PyNMe_3)]^{2+}$ oxidant generated from the reaction of $[Fe^{II}(PyNMe_3)(OTf)_2]$ with excess peracid;[44,45] however increasing the amount of added Sc^{3+} or $HClO_4$ to 8 eq makes the rates of the two systems comparable. Interestingly, the fastest rates in this series match, or perhaps even exceed, the 13 s^{-1} rate for oxidation of the C3-H bond of taurine by the *S* = 2 Fe^{IV}=O intermediate of taurine dioxygenase at 5 °C, after correction for the 45° temperature difference.[46] Thus, the **1**/H_2O_2/(Sc^{3+} or $HClO_4$) combination can generate a highly reactive oxidant for the hydroxylation of challenging hydrocarbon substrates like cyclohexane and benzene.

Table 3. Cyclohexane oxidation rates by high-valent nonheme iron species at -40 °C.

	k_2 ($M^{-1}s^{-1}$)	Ref
$[Fe^V(O)(TAML)]^-$	0.00026	40
$[Fe^{III}(13\text{-}TMC)(OIAr)]^{2+}$	0.011	41
$[Fe^{IV}(O)(TDCPP)]^+$	0.11	42
S = 1 $[Fe^{IV}(O)(Me_3NTB)]^{2+}$	0.25	42
S = 2 $[Fe^{IV}(O)(TQA)]^{2+}$	0.37	43
$[Fe^V(O)(O_2CR)(PyNMe_3)]^{2+}$	2.8	44
$[Fe^{III}(β\text{-}BPMCN)(OOH)]^{2+}$ (**2**) + 1 – 8 eq Sc^{3+} or $HClO_4$	k_{obs} (s^{-1}) = 0.3-2.6	This work

Abbreviations used: TAML = tetraaza macrocyclic ligand; H_2TDCPP = *meso*-tetrakis(2,6-dichlorophenyl)porphin; 13-TMC = 1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclotridecane; Me_3NTB = tris(benzimidazolyl-2-methyl)-amine; TQA = tris(quinolyl-2-methyl)amine.

Mechanistic insights and the nature of Ox. ^{18}O-labeling experiments have been shown to be the key to shedding mechanistic light on the action of oxygenases since 1955,[47–50] and have also proven useful in providing insight into the nature of the oxidants formed upon O–O cleavage of Fe^{III}–OOH intermediates in bio-inspired metal-catalyzed reactions.[6,7,51] For the well-studied Fe(BPMEN) and Fe(TPA) catalysts, the accumulated evidence supports the rate determining H_2O-assisted cleavage of the O–O bond of the *cis*-$H_2\mathbf{O}$–Fe^{III}–OOH intermediate to form an (H**O**)–Fe^V=O oxidant. Oxo-hydroxo tautomerism rationalizes the observed partial incorporation of ^{18}O from added $H_2{}^{18}O$ into the oxidation products (Table 4).[6–9]

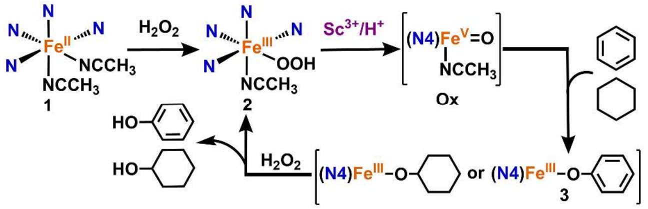
For the case of **1**/H_2O_2 in the absence of additives, ^{18}O from $H_2{}^{18}O$ is partially incorporated into the products. However a significant fraction of the O-atom incorporated into the products is derived from O_2, unlike for Fe(TPA) and Fe(BPMEN) (Table 4).[10] The observed incorporation of an O-atom from O_2 suggests that the alkyl radical formed after initial hydrogen atom abstraction by the iron oxidant is sufficiently long lived to be captured by O_2. In contrast, no ^{18}O-incorporation from added $H_2{}^{18}O$ into the cyclohexanol and phenol products is observed in the **1**-catalyzed oxidation of cyclohexane and benzene in the presence of Sc^{3+} or $HClO_4$, which is confirmed by complementary experiments with a 10% aqueous solution of $H_2{}^{18}O_2$ showing essentially quantitative ^{18}O-label incorporation into the cyclohexanol and phenol products in the Sc^{3+} experiments (Table 4). Furthermore, the absence of O-atom incorporation from O_2 in the presence of Sc^{3+} indicates the formation of short-lived alkyl radicals that undergo fast rebound, as we deduced from the reactivity studies mentioned earlier. These results thereby exclude the H_2O-assisted mechanism associated with the Fe^{II}(TPA) and Fe^{II}(BPMEN) catalysts[6,7] to account for the labeling results observed for the **1**/H_2O_2/(Sc^{3+} or $HClO_4$) system.

Table 4: Percentage of ^{18}O-incorporation into products from the oxidation of cyclohexane and benzene[a]

	$H_2{}^{18}O_2$	$H_2{}^{18}O$	Ref
Cyclohexanol			
Fe^{II}(β-BPMCN) + Sc^{3+}	97	1	This work
Fe^{II}(β-BPMCN)	34	10	10
Fe^{II}(TPA)	70	27	6
Fe^{II}(BPMEN)	84	18	6
Phenol			
Fe^{II}(β-BPMCN) + Sc^{3+}	99	2	This work
Fe^{II}(BPMEN)	81	22	9

[a] All experiments reported in this work were performed in the presence of air. The percentage incorporation values were calculated based on the ^{18}O-content of the reagents. The $H_2{}^{18}O_2$ labeling experiments were performed with 10% $H_2{}^{18}O_2$. The larger amount of H_2O present in 10% $H_2{}^{18}O_2$ relative to that in 90% $H_2{}^{16}O_2$ reduced the product yield by 50% but the effect of Sc^{3+} is still present (Figure S6).

Instead, we propose the mechanism shown in Scheme 1, which rationalizes the similar reactivity patterns observed upon addition of Sc^{3+} or $HClO_4$, the equivalent kinetic effects of adding Sc^{3+} or $HClO_4$ to **2** and the ^{18}O-labeling results. Both these additives facilitate O–O bond heterolysis in the Fe^{III}-OOH intermediate **2** to form a distinct and highly electrophilic oxidant **Ox** that hydroxylates cyclohexane and benzene at high rates. As the hydroxide formed in this cleavage combines with Sc^{3+} or the proton from $HClO_4$, the nascent Fe^{V}=O center in this case no longer has a bound hydroxide, which should make it much more electrophilic than the proposed Fe^{V}(O)(OH) oxidant associated with the water-assisted mechanism. This mechanism parallels that proposed by Serrano-Plana *et al.* for the activation of $[Fe^{III}(PyNMe_3)(OOH)]^{2+}$ by strong acid,[39] which is supported by DFT calculations. Furthermore, in contrast to **Ox**, the presence of the anionic acetate ligand in the putative Fe^{V}(O)(OAc) oxidant formed from **1**/H_2O_2 in the presence of HOAc presumably reduces the electrophilicity of the Fe^{V}(O) unit, rationalizing its inability to perform benzene hydroxylation.



Scheme 1. Proposed mechanism for the effect of Sc^{3+} or $HClO_4$ in cyclohexane and benzene hydroxylation by **1**/H_2O_2.

SUMMARY

In summary, we have shown that addition of a redox-inactive strong Lewis acid like $Sc(OTf)_3$ or a Brønsted acid like $HClO_4$ to the reaction mixture of the nonheme iron catalyst **1** and H_2O_2 leads to the formation of a highly electrophilic oxidant capable of hydroxylating cyclohexane and benzene with comparable catalytic efficiency, a combination of transformations rarely observed for synthetic nonheme iron catalysts.[3,4,36] This highly reactive species compares well in C–H bond cleaving ability with the fastest nonheme iron-oxo oxidants reported thus far (Table 3). Catalyst **1** is unique as the nature of the active oxidant that is formed can be tuned by various additives to perform four distinct reactions. The *cis*-dihydroxylation of electron-deficient C=C bonds in the absence of any additive and the epoxidation of electron-rich C=C bonds in the presence of acetic acid have been reported previously.[10,34] In this paper, we demonstrate its ability to hydroxylate benzene and cyclohexane within seconds at -40 °C upon addition of Sc^{3+} or $HClO_4$ and identify a new route for accessing a powerful electrophilic oxidant in this fascinating landscape of high-valent nonheme oxoiron oxidants.

EXPERIMENTAL SECTION

Materials and Instrumentation. All materials were purchased from Sigma-Aldrich and used as received unless noted otherwise. $H_2{}^{18}O$ (97% ^{18}O-enriched) and $H_2{}^{18}O_2$ (90% ^{18}O-enriched, 10% solution in $H_2{}^{16}O$) were obtained from Berry & Associates-ICON Isotopes. Cyclohexane, benzene and nitrobenzene were passed through alumina and silica gel before the reactions. 90% H_2O_2 was obtained from FMC Corporation. ***Caution***: 90% H_2O_2 is potentially explosive and should be handled with proper safety precautions.[52,53] The ligand BPMCN and the complex $[Fe^{II}$(β-BPMCN)]$(OTf)_2$ were synthesized according to previously published procedures.[10,54]

Product analyses were performed on a Perkin-Elmer Sigma 3 gas chromatograph (AT-1701 column) with a flame-ionization detector. GC mass spectral analyses were performed on a HP 6890 GC (HP-5 column) using an Agilent 5973 mass detector. For chemical ionization analyses, NH_3/CH_4 (4%) was used as the ionization gas. UV-visible absorption spectra were recorded on a HP8453A diode array spectrometer equipped with a cryostat from Unisoku, Scientific Instruments (Osaka, Japan). Resonance Raman spectra were obtained at -30 °C with excitation at 561 nm (100 mW at source, Cobolt Lasers) through the sample in a flat bottom NMR tube using a 90° backscattering arrangement (parallel to the slit direction). The collimated Raman scattering was collected using two Plano convex lenses (f = 12 cm, placed at an appropriate distance) through appropriate long pass edge filters (Semrock) into an Acton AM-506M3 monochromator equipped with a Princeton Instruments ACTON PyLON LN/CCD-1340x400 detector. The detector was cooled to -120 °C prior to the experiments. Spectral calibration was performed using the Raman spectrum of acetonitrile/toluene 50:50 (v:v).[55] Each spectrum was accumulated, typically 60 times with 1 s acquisition time, resulting in a total acquisition time of 1 min per spectrum. The collected data was processed using Spekwin32,[56] and a multi-point baseline correction was performed for all spectra. X-band EPR spectra were recorded on a Bruker Elexsys E-500 spectrometer equipped with an Oxford ESR 910 liquid helium cryostat and an Oxford temperature controller.

Reaction conditions. All experiments reported in this work were performed in the presence of air. In a typical reaction, 70 μL of a 0.2 M H_2O_2 solution (diluted from 90% H_2O_2/H_2O solution) in CH_3CN (10 eq H_2O_2 relative to **1**$(OTf)_2$) was added all at once to a vigorously stirred CH_3CN solution (1.93 mL) containing the iron catalyst **1**$(OTf)_2$, the substrate and $Sc(OTf)_3$ or $HClO_4$ and stirred for 30 min at room temperature. The final concentration of the iron catalyst in the reaction mixture was 0.7 mM with 1000 eq cyclohexane/ 100 eq benzene/ 600 eq nitrobenzene and 0.5–8 eq $Sc(OTf)_3$ or $HClO_4$. After the reaction was over, 0.1 mL 1-methylimidazole and 1 mL acetic anhydride were added to the reaction solution to esterify the alcohol/phenol. An internal standard (naphthalene) was added after this and then the products were extracted into CH_3Cl and the solution was then subjected to GC and/or GC-MS analysis. In experiments with $H_2{}^{18}O_2$, 10 eq or 70 μL of a 0.2 M $H_2{}^{18}O_2$ solution (diluted from the 10% $H_2{}^{18}O_2/H_2O$ solution) relative to **1**$(OTf)_2$ was added instead of H_2O_2. In experiments with $H_2{}^{18}O$, 68 μL of a 3.5-M $H_2{}^{18}O$ solution in CH_3CN (170 eq $H_2{}^{18}O$ relative to **1**$(OTf)_2$, which is about the same amount of H_2O that would be introduced from a 10% H_2O_2 solution) was added to the reaction mixture before adding H_2O_2.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge via the internet at http://pubs.acs.org.

Additional data and experimental details (PDF)

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Notes

The authors declare no competing financial interests.

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