

Evidence of a Sole Oxygen Atom Transfer Agent in Asymmetric Epoxidations with Fe-pdp Catalysts

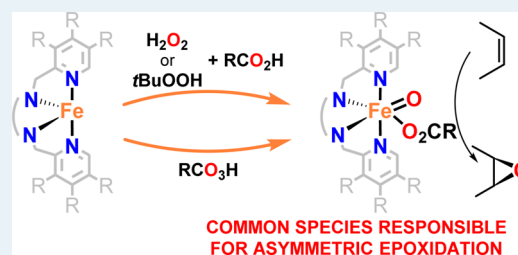
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Supporting Information

ABSTRACT: Iron complexes with chiral tetradentate ligands based on the pdp scaffold (pdp = *N,N'*-bis(2-pyridylmethyl)-2,2'-bipyridine) are efficient and versatile catalysts for the highly enantioselective epoxidation of a wide range of olefins. The nature of the species responsible for oxygen atom transfer to the olefin in these reactions is under debate. In order to investigate this question, the enantioselectivity of the epoxidation reaction has been used as a mechanistic probe. The enantioselectivities obtained under different reaction conditions for two iron catalysts (*S,S*)-[Fe(CF₃SO₃)₂(^{Me2N}pdp)] ((*S,S*)^{Me2N}1Fe) and (*S,S*)-[Fe(CF₃SO₃)₂(^{dMM}pdp)] ((*S,S*)^{dMM}1Fe) have been analyzed. Reactions were performed with a series of peracids, and enantioselectivities of these reactions were compared with those obtained by combining peroxides and carboxylic acids. This analysis provides conclusive experimental evidence that the same oxidant is responsible for the asymmetric epoxidation reaction in both scenarios. The study also provides insight into the nature of the oxygen atom transfer species, as well as its mechanism of formation, offering a rational guide for defining catalytic systems with more versatile structures and improved selectivity.

KEYWORDS: epoxidation, iron, high valent, peracid, enantioselectivity



INTRODUCTION

The selective oxidations of alkane and alkene moieties are important reactions in bulk and fine chemistry and are in continuous demand for novel methodologies that render novel or improved selectivities.¹ In that regard, nature provides inspiration for the design of metal catalysts that enable the achievement of these goals.² Along this vein, non-heme iron-dependent oxygenases have become paradigmatic motifs to develop iron-based oxidation catalysts.³ Interestingly, the availability and low toxicity of iron compounds make their use appealing from a sustainability perspective.⁴ Understanding the fundamental aspects of the chemistry of these catalysts is important because it should allow the rational design of novel generations exhibiting tailored selectivity or improved activity. Furthermore, this knowledge may also help in the comprehension of the enzymatic oxidations.^{3d,5}

Iron coordination complexes bearing tetradentate aminopyridine ligands constitute a privileged platform for performing efficient and selective C–H and C=C oxidation reactions.^{3b,6} Using hydrogen peroxide as oxidant, regioselective and stereoretentive C–H hydroxylation,⁷ syn-dihydroxylation,⁸ and enantioselective epoxidation⁹ have been achieved, strongly suggesting that these reactions do not involve freely diffusing hydroxyl radicals, but instead metal-based oxidants.^{3c,10} Elucidation of the reaction mechanisms that operate in these reactions has been proven challenging because the active species are extraordinarily reactive and rarely accumulate in solution, making their characterization and direct reactivity interrogation very difficult. A common strategy in order to unravel mechanistic details has

been to use selected substrates that can provide information upon analysis of the oxidation products.^{3d,10a}

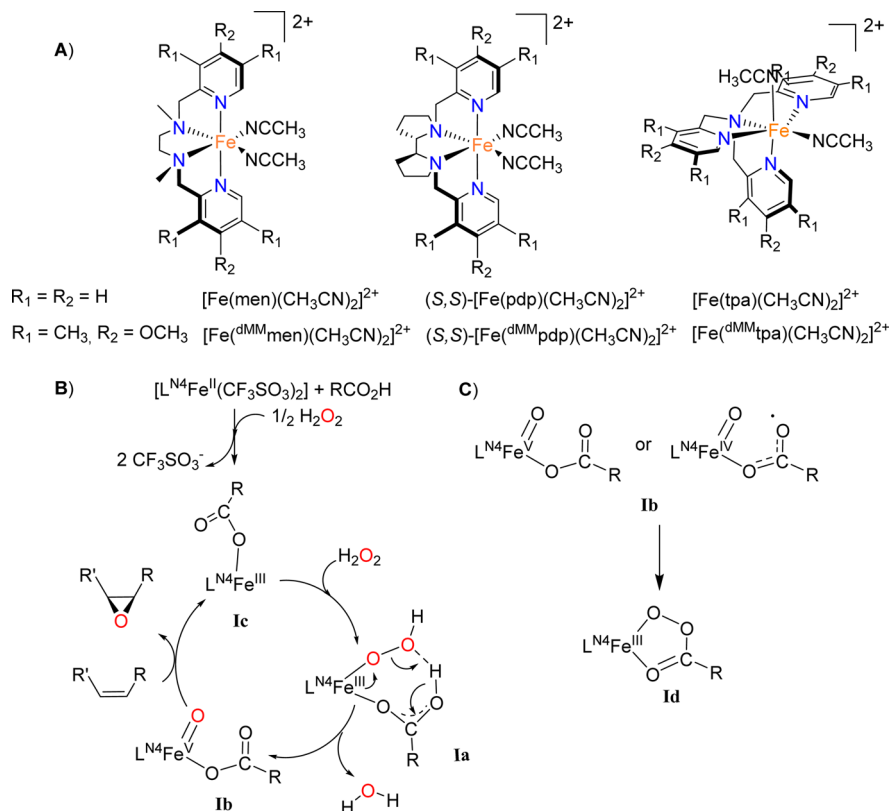
In landmark works by Jacobsen, White, and co-workers it was shown that by addition of acetic acid the activity and selectivity of these catalysts is substantially improved in epoxidation¹¹ and C–H oxidation reactions,^{7d} thus enabling their use as tools for organic synthesis. Que and co-workers provided for the first time a mechanistic proposal to rationalize the positive role of acetic acid (Scheme 1).¹² Reaction of the mononuclear ferrous complexes [Fe(L^{N4})(CH₃CN)₂]²⁺ (L^{N4} = men or tpa, men = *N,N'*-dimethyl-*N,N'*-bis(2-methylpyridine), tpa = tris(2-methylpyridyl)amine) with excess hydrogen peroxide entails initial formation of a ferric hydroperoxide species (Fe^{III}(OOH)(CH₃CO₂H), **Ia** in Scheme 1) that then undergoes heterolytic O–O cleavage, resulting in the formation of a highly electrophilic Fe^V(O)(OCOCH₃) species (**Ib** in Scheme 1), which is then responsible for the oxidation of an alkane or alkene moiety. Acetic acid, ligated to the ferric center in a *cis* relative position with respect to the peroxide site, critically assists the O–O cleavage. Chiral catalysts related to [Fe(pdp)(CH₃CN)₂]²⁺ are presumed to follow analogous paths. Mechanistic studies on these systems performed by at least two different research groups have concluded that hydrogen peroxide and alkyl peroxides produce the common Fe^V(O)(OCOCH₃) species **Ib**,

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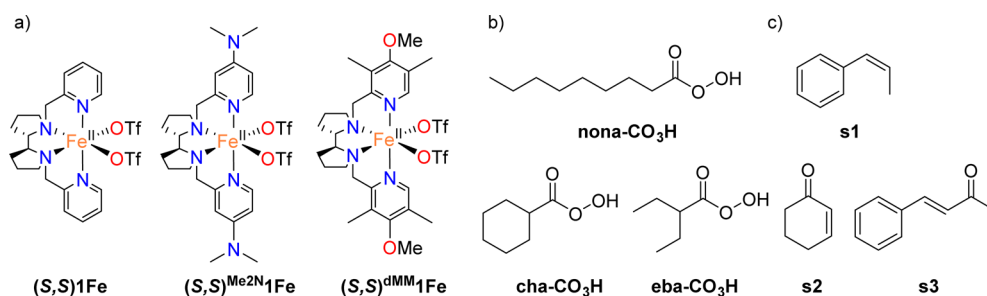
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Scheme 1. (A) Schematic Diagram of Representative Iron Catalysts ($[\text{Fe}(\text{L}^{\text{N}4})(\text{CH}_3\text{CN})_2]^{2+}$) Bearing Strong Field Tetradentate Ligands Discussed in This Work, (B) Original Mechanistic Scheme Proposed by Que et al. for the Carboxylic Acid Assisted O–O Cleavage, and (C) Conversion of High-Valent **Ib** To Give Ferric Peracoxylate Species **Id**^a



^a $\text{L}^{\text{N}4}$ stands for a tetradentate aminopyridine ligand.

Scheme 2. (a) Schematic Diagram of Catalysts $(S,S)\text{1Fe}$, $(S,S)^{\text{Me}2\text{N}}\text{1Fe}$, and $(S,S)^{\text{dMM}}\text{1Fe}$, (b) Uncommon Organic Peroxides, and (c) Substrates Employed in This Work



presumably via the same O–O lysis pathway.^{9f,13} The exact nature of this high-valent oxoiron **Ib** formed after the O–O cleavage is still under debate.^{9g,13,14} Computational analysis by Shaik and co-workers has suggested that it may be best described as a $[\text{Fe}^{\text{IV}}(\text{O})(\text{O})(\text{O})\text{C}(\text{O})\text{R}]^{2+}$ species, which rapidly evolves toward its ferric peracetate electromer (**Id** in Scheme 1) that is then the reactive species.¹⁵ Alternatively, O–O bond cleavage in species **Id** has been proposed to be the rate-determining step for catalysts with electron-rich ligands $\text{L}^{\text{N}4} = \text{dMM}^{\text{pdp}}, \text{dMM}^{\text{tpa}}, \text{dMM}^{\text{men}}$ (Scheme 1).¹⁶ The obvious consequence of this mechanistic scenario is that peracids can also be valid oxidants in order to generate species **Ib**.

Consistent with this mechanistic scenario, we have observed that enantioselective epoxidation of *cis*- β -methylstyrene (**s1**, Scheme 2c) with the electron-rich catalyst $(S,S)\text{-}[\text{Fe}(\text{CF}_3\text{SO}_3)_2(\text{Me}_2\text{N}^{\text{pdp}})]$ ($(S,S)^{\text{Me}2\text{N}}\text{1Fe}$) (Scheme 2a) produces the

corresponding epoxide with absolute retention of configuration and with the same level of enantioselectivity ($61 \pm 1\%$ ee) when three different oxidants are employed: $\text{H}_2\text{O}_2/\text{CH}_3\text{CO}_2\text{H}$, *t*BuOOH (TBHP)/ $\text{CH}_3\text{CO}_2\text{H}$, and peracetic acid ($\text{CH}_3\text{CO}_3\text{H}$).^{9f} These observations led us to conclude that there is a common and unique oxidant in these reactions and therefore peracids also form the $\text{Fe}^{\text{V}}(\text{O})(\text{O})\text{C}(\text{O})\text{R}$ oxidizing species **Ib**. A cautious note at this point must be exercised, because direct detection of the common oxidizing species (presumably **Ib**) has not been obtained so far.

In contrast, in a recent work by Talsi, Bryliakov, and co-workers it was proposed that different mechanistic paths are followed when peracids ($\text{RC}(\text{O})\text{OOH}$) or peroxides in the presence of carboxylic acids are employed in catalytic epoxidation with $(S,S)\text{-}[\text{Fe}(\text{CF}_3\text{SO}_3)_2(\text{pdp})]$ and $(S,S)\text{-}[\text{Fe}(\text{dMM}^{\text{pdp}})(\mu\text{-OH})_2]^{4+}$.¹³ In their mechanistic proposal, the reaction with peracids

generates a ferric peracetate intermediate (**Id** in Scheme 1) that shows distinctive selectivity properties in comparison with the ferryl oxidant **Ib** formed in reactions with peroxides assisted by carboxylic acids (RC(O)OH).¹³ This proposal is based in two elements: (a) changes in the *cis*-/*trans*-stilbene to epoxide ratio in the epoxidation of *cis*-stilbene (from 48 with peroxides/carboxylic acid to 83 with peracids, determined by ¹H NMR) and (b) the observation that reactions with H₂O₂/ethylhexanoic acid (eha) and TBHP/eha produce epoxides with the same enantioselectivity (81 ± 1 ee for *trans*-chalcone), distinct from that obtained when CH₃CO₃H/eha is employed as oxidant (67% ee). Since ee values in these reactions are not the same, it was concluded that the active species must be different.

Therefore, the exact nature of the active species formed in iron-catalyzed enantioselective epoxidations with this class of catalysts remains under debate, with species **Ib,d** being regarded as putative oxidants. Herein, a mechanistic study to address this dilemma is described. In order to respond to this question, the enantioselectivity of the epoxidation reaction has been used as a mechanistic probe. The enantiomeric excess obtained under different reaction conditions for the two iron catalysts (S,S)-[Fe(CF₃SO₃)₂(^{Me2N}pdp)] ((S,S)^{Me2N}1Fe) and (S,S)-[Fe(CF₃SO₃)₂(^{dMM}pdp)] ((S,S)^{dMM}1Fe) (Scheme 2a) has been analyzed. Representative reactions with (S,S)-[Fe(CF₃SO₃)₂(pdp)] ((S,S)1Fe) are also collected in the Supporting Information. Reactions were performed with a series of peracids, and enantioselectivities of these reactions were compared with those obtained with peroxides (H₂O₂ and TBHP) combined with carboxylic acids.

The use of different peracids constitutes the key and novel aspect of this study, because it provides conclusive experimental evidence that these oxidants form the same oxygen atom transfer species as those formed when peroxides and carboxylic acids are employed as oxidants. By helping to define the nature of the oxygen species and its mechanism of formation, the study provides a rational guide for defining structurally more versatile and improved catalytic systems.

RESULTS AND DISCUSSION

The enantiomeric excess obtained in the catalytic epoxidation of olefins employing iron catalysts (S,S)^{Me2N}1Fe and (S,S)^{dMM}1Fe (Scheme 2a) has been analyzed. Three different substrates were studied: *cis*- β -methylstyrene (**s1**), 1-cyclohexenone (**s2**), and benzalacetone (**s3**) (Scheme 2c). Reactions were performed with different oxidants, including H₂O₂, TBHP, and a series of peracids including linear alkane chains (CH₃CO₃H and nonanoic peracid (nona-CO₃H)), 2-alkyl-branched peracids (ethyl butyl peracid (eba-CO₃H), and cyclohexane carboxylic peracid (cha-CO₃H)) and an aromatic peracid, *m*-chloroperbenzoic acid (*m*CPBA) (Scheme 2b). All of the reactions were performed at 0 °C, adding the oxidant (1.2 equiv) diluted in acetonitrile via syringe pump during 30 min to an acetonitrile solution containing the catalyst (2 mol %) and the substrate. Afterward an internal standard was added and the reaction was rapidly subjected to workup (filtration through a silica plug, which then was washed with AcOEt) and analyzed by GC or ¹H NMR and HPLC. Blank experiments confirmed that epoxidation does not take place under these specific conditions.

Unless stated, reaction conditions for peracids are catalyst (2 mol %) and peracid (1.2 equiv) in 1 mL of CH₃CN at 0 °C for 30 min. Reaction conditions for peroxides are catalyst (2 mol %), peroxide (1.2 equiv), and carboxylic acids (1.1 equiv)

in 1 mL of CH₃CN at 0 °C for 30 min. Epoxide yields, substrate conversions, and enantioselectivities were determined by GC for *cis*- β -methylstyrene and 2-cyclohexenone. In the case of benzalacetone epoxide yields and substrate conversions were determined by ¹H NMR and the enantioselectivities by HPLC with an IC column.

Results from this collection of reactions with catalysts (S,S)^{Me2N}1Fe and (S,S)^{dMM}1Fe are shown in Table 1, while those corresponding to (S,S)1Fe are collected as Supporting Information. Data in Table 1 show that the combination of the three parameters (catalyst, substrate, and oxidant) produced a set of reactions where the enantioselectivity ranges from 9 to 89% ee. This broad range highlights the sensitivity of the enantioselectivity to these parameters.

For each catalyst and substrate, epoxidation with H₂O₂ and TBHP were studied first in the absence of a carboxylic acid (rows 1 and 2 for (S,S)^{Me2N}1Fe and 20 and 21 for (S,S)^{dMM}1Fe). Then a series of 30 triads (**T1–T30**, Table 1) of catalytic epoxidation experiments were performed and ee values compared under identical experimental conditions (reaction time and temperature). Each of the 30 triads entailed including (a) H₂O₂/RCO₂H, (b) TBHP/RCO₂H, and (c) RCO₃H, where R = methyl, nonyl, cyclohexadienyl, 2-ethylbutyl, *m*-chlorobenzoyl. In line with previous reports, conditions a and b are accepted to form a Fe^V(O)(O₂CR) (**Ib**) species that is then responsible for the stereoselective oxygen atom transfer.^{9f,13} The exhibited enantioselectivity is therefore compared with the enantioselectivity of the species formed in the reactions with the corresponding peracid. Results collected in Table 1 show that each of the parameters chosen has a sizable impact in enantioselectivity;

Dependence on the Catalyst and Substrate. Irrespective of the reaction conditions and for a given oxidant, epoxidation of **s1** and **s3** with (S,S)^{Me2N}1Fe proceeds with higher ee values (20–30 ee points) in comparison with those for (S,S)^{dMM}1Fe, while the opposite occurs systematically (approximately 10 points of ee) in the epoxidation of **s2** (compare each of the rows 1–5 in Table 1 with the same rows in Table 2). Epoxidation of **s1** with (S,S)1Fe provides epoxides with the lowest ee values of the series (see the Supporting Information). We have previously observed a systematic improvement in ee values when the electron-donating character of the pyridine rings of the ligands is increased.^{9f} We reasoned that this dependence reflects the systematic effect of the electron-donating properties of the ligand in modulating the electrophilicity of the iron–oxo species responsible for the oxygen atom transfer. The change in relative enantioselectivity observed for **s2** is unexpected and indicates that some additional, unidentified factor is contributing to the enantioselectivity.

Dependence on the Oxidant. Irrespective of the catalyst, the reaction with H₂O₂ or TBHP in the absence of a carboxylic acid usually showed moderate activities and enantioselectivities (entries 1, 2, 18, and 19 in Table 1); however, the addition of aliphatic carboxylic acids enhanced the activities and enantioselectivities for all of the substrates and catalysts (for H₂O₂ entries 3, 6, 9, 12, and 15 and for TBHP entries 4, 7, 10, 13 and 16). Addition of *m*-chlorobenzoic acid (*m*CBA), has an opposite effect, as lower enantioselectivities were obtained. Moreover, as expected, the use of bulky carboxylic acids, containing α -alkyl substituents, gave improved enantioselectivities for both catalysts. As a general trend, irrespective of the catalyst and substrate, the enantioselectivity is regularly

Table 1. Asymmetric Epoxidation of **s1**–**s3** Employing (*S,S*)^{Me2N}1Fe and (*S,S*)^{dMM}1Fe and Different Oxidants

cat. (2 mol%)
Oxidant (1,2 equiv.)
RCO₂H (1.1 equiv.)
CH₃CN, 0°C, 30 min

	Cat	Oxidant	Additive	s1		s2		s3	
				Conv/ yield (%)	ee (%)	Conv/ yield (%)	ee (%)	Conv/ yield (%)	ee (%)
1	Me ^{2N} 1Fe	H ₂ O ₂	-	57/34	43	8/2	36	25/23	64
2	Me ^{2N} 1Fe	TBHP	-	56/30	46	9/2	41	24/22	60
					T1	T6		T11	
3	Me ^{2N} 1Fe	H ₂ O ₂	<i>m</i> CBA	100/61	34	-	-	34/31	64
4	Me ^{2N} 1Fe	TBHP	<i>m</i> CBA	100/68	37	-	-	46/33	64
5	Me ^{2N} 1Fe	<i>m</i> CPBA	-	78/66	35	-	-	41/32	60
					T2	T7		T12	
6	Me ^{2N} 1Fe	H ₂ O ₂	CH ₃ CO ₂ H	100/74	53	82/36	50	85/66	65
7	Me ^{2N} 1Fe	TBHP	CH ₃ CO ₂ H	100/77	54	35/15	47	38/29	66
8	Me ^{2N} 1Fe	CH ₃ CO ₃ H	-	100/59	54	69/36	49	72/41	63
					T3	T8		T13	
9	Me ^{2N} 1Fe	H ₂ O ₂	nona-CO ₂ H	100/75	61	40/21	54	55/51	74
10	Me ^{2N} 1Fe	TBHP	nona-CO ₂ H	100/67	61	20/8	53	56/38	74
11	Me ^{2N} 1Fe	nona-CO ₃ H	-	100/52	62	24/9	52	64/59	70
					T4	T9		T14	
12	Me ^{2N} 1Fe	H ₂ O ₂	cha-CO ₂ H	100/73	61	82/38	57	58/52	77
13	Me ^{2N} 1Fe	TBHP	cha-CO ₂ H	100/75	62	14/4	56	66/56	77
14	Me ^{2N} 1Fe	cha-CO ₃ H	-	71/57	61	11/6	55	63/59	74
					T5	T10		T15	
15	Me ^{2N} 1Fe	H ₂ O ₂	eba-CO ₂ H	100/69	73	96/35	67	76/68	88
16	Me ^{2N} 1Fe	TBHP	eba-CO ₂ H	100/73	74	19/4	67	85/66	89
17	Me ^{2N} 1Fe	eba-CO ₃ H	-	76/46	74	30/19	68	55/49	88
					T16	T21		T26	
18	d ^{MM} 1Fe	H ₂ O ₂	-	93/49	28	100/66	62	53/40	32
19	d ^{MM} 1Fe	TBHP	-	54/19	27	58/35	66	20/17	33
					T17	T22		T27	
20	d ^{MM} 1Fe	H ₂ O ₂	<i>m</i> CBA	67/35	9	-	-	32/28	35
21	d ^{MM} 1Fe	TBHP	<i>m</i> CBA	64/24	10	-	-	27/22	36
22	d ^{MM} 1Fe	<i>m</i> CPBA	-	56/30	10	-	-	33/20	36
23	d ^{MM} 1Fe	H ₂ O ₂	CH ₃ CO ₂ H	100/59	33	100/61	64	100/72	35
24	d ^{MM} 1Fe	TBHP	CH ₃ CO ₂ H	100/44	32	100/52	65	100/64	37
25	d ^{MM} 1Fe	CH ₃ CO ₃ H	-	100/61	34	89/39	63	79/53	37

Table 1. continued

Cat	Oxidant	Additive	s1		s2		s3		
			Conv/ yield (%)	ee (%)	Conv/ yield (%)	ee (%)	Conv/ yield (%)	ee (%)	
				T18		T23		T28	
26	^{dMM} 1Fe	H ₂ O ₂	nona-CO ₂ H	100/90	32	99/70	66	100/69	43
27	^{dMM} 1Fe	TBHP	nona-CO ₂ H	100/68	33	100/48	68	100/58	43
28	^{dMM} 1Fe	nona-CO ₃ H	-	68/35	35	76/21	69	64/50	43
				T19		T24		T29	
29	^{dMM} 1Fe	H ₂ O ₂	cha-CO ₂ H	100/49	37	100/65	68	100/70	50
30	^{dMM} 1Fe	TBHP	cha-CO ₂ H	100/48	35	92/43	69	100/62	51
31	^{dMM} 1Fe	cha-CO ₃ H	-	62/45	38	53/11	72	60/46	53
				T20		T25		T30	
32	^{dMM} 1Fe	H ₂ O ₂	eba-CO ₂ H	85/47	49	100/62	77	100/63	64
33	^{dMM} 1Fe	TBHP	eba-CO ₂ H	100/68	44	100/42	78	85/66	64
34	^{dMM} 1Fe	eba-CO ₃ H	-	62/46	46	44/11	76	45/40	65

Table 2. Epoxidation of s1 with Peroxyethylbutyric Acid in the Presence of Different Amounts of Acetic Acid

cat.	oxidant	RCO ₂ H (x equiv.)	conv/yield (%)	ee (%)	
1	Me ₂ N ¹ Fe	eba-CO ₃ H	CH ₃ CO ₂ H (1.5)	53/32	74
2	Me ₂ N ¹ Fe	eba-CO ₃ H	CH ₃ CO ₂ H (5)	55/29	75
3	Me ₂ N ¹ Fe	eba-CO ₃ H	CH ₃ CO ₂ H (10)	54/22	73
4	Me ₂ N ¹ Fe	eba-CO ₃ H	CH ₃ CO ₂ H (50)	50/18	71
5	Me ₂ N ¹ Fe	eba-CO ₃ H	mCBA (10)	75/55	68
6	Me ₂ N ¹ Fe	mCPBA	eba (10)	100/53	44

^aUnless stated, the reaction conditions are (S,S)^{Me2N}1Fe (2 mol %), peracid (1.2 equiv), and carboxylic acid (x equiv) in 1 mL of CH₃CN at 0 °C for 30 min. Epoxide yields, substrate conversions, and enantioselectivities were determined by GC.

increasing in the order H₂O₂/mCBA (row 3) ≈ TBHP/mCBA (row 4) ≈ mCPBA (row 5) > H₂O₂ (row 1) ≈ TBHP (row 2) > H₂O₂/CH₃CO₂H (row 6) ≈ TBHP/CH₃CO₂H (row 7) ≈ CH₃CO₃H (row 8) > H₂O₂/nona-CO₂H (row 9) ≈ TBHP/nona-CO₂H (row 10) ≈ nona-CO₃H (row 11) > H₂O₂/cha-CO₂H (row 12) ≈ TBHP/cha-CO₂H (row 13) > cha-CO₃H (row 14) > H₂O₂/eba-CO₂H (row 15) ≈ TBHP/eba-CO₂H (row 16) ≈ eba-CO₃H (row 17) (see the Supporting Information for a graphical diagram). Of note, depending on the catalyst and substrate, the choice of oxidant has an impact of 25–40 ee points from the least (rows 3–5) to the most (rows 15–17) enantioselective. This dependence highlights the sensitivity of this parameter, which makes it particularly suitable as a mechanistic probe.

A particular aspect that deserves comment is the lack of epoxidation of cyclic enone s2 when mCPBA and

peroxides/mCBA are employed as oxidants (entries 6 and 21 in Table 1). In these reactions, a dark blue color is rapidly observed, suggestive of the hydroxylation of the aromatic ring of mCBA, forming phenolate-bound ferric species, as described for related aminopyridine iron catalysts.^{16a,17} We conclude that in these reactions intramolecular oxidation of the carboxylic acid is favored over oxidation of the electron-poor substrate. Instead, epoxidation of s1 and s3 appears to be faster than the self-hydroxylation reaction.

However, the most remarkable aspect that emerges from the reactions collected in Table 1 is that for both (S,S)^{Me2N}1Fe and (S,S)^{dMM}1Fe catalysts, irrespective of the substrate, virtually the same enantioselectivity (±2% ee difference) was obtained when a peracid (RCO₃H) was used instead of a combination of a peroxide (H₂O₂ or TBHP) and the corresponding carboxylic acid (RCO₂H). For example, epoxidation of s1 with AcOOH, H₂O₂/CH₃CO₂H, and TBHP/CH₃CO₂H all showed enantioselectivities of 53 ± 1% (T2, entries 6–8) for catalyst (S,S)^{Me2N}1Fe and 33 ± 1% for catalyst (S,S)^{dMM}1Fe (T17, entries 23–25). Likewise, epoxidations of s1 with the branched ethyl hexanoic peracid, H₂O₂/ethyl hexanoic acid (eha), and TBHP/eha proceed with 74 ± 1% (T5) and 47 ± 35% ee (T20) with catalysts (S,S)^{Me2N}1Fe and (S,S)^{dMM}1Fe, respectively. The same trend was observed for the two catalysts, using four different alkyl peracids and mCPBA. Although it was not studied with the same level of detail, (S,S)1Fe exhibits the same behavior, as shown by the data collected in the Supporting Information.

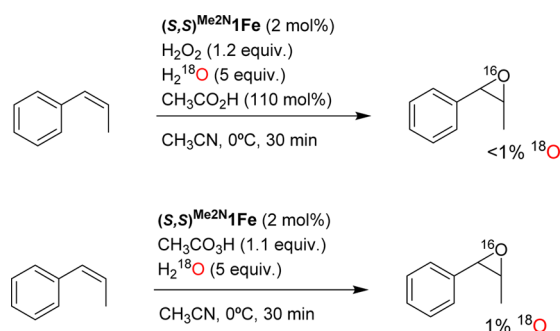
The common enantioselectivity measured in the reactions of each of the 30 triads, with values that range from 9 ± 1% ee (T16, for the oxidation of s1) to 89 ± 1% ee (T15, for epoxidation of s3), constitutes unambiguous evidence that each triad entails a common oxidizing species, presumably Fe^V(O)-(O₂CR) (Ib). The important consequence that emerges from this analysis is that the putative ferryl species Fe^V(O)(O₂CR) (Ib) are also formed in reactions with peracids, but in this case without the aid of an external carboxylic acid.

It is also important to notice that the substrate conversion and epoxide yield of the reactions are highly dependent on the particular reaction conditions, although a major side product cannot be identified in any case. Most remarkably, reactions belonging to the same triad can differ substantially in these parameters, despite the fact that they still share a common enantioselectivity in the epoxidation reaction. This observation indicates that side oxidation reactions do not contribute to the asymmetric epoxidation reaction to any detectable extent. Importantly, it raises a cautious note with regard to the analysis of other selectivity parameters that are not necessarily connected to the asymmetric epoxidation reaction and that may be sensibly affected by side reactivity.

Considering that $\text{Fe}^{\text{V}}(\text{O})(\text{O}_2\text{CR})$ (**1b**) is the only species responsible for the asymmetric oxygen atom transfer in these reactions, we studied the possible exchange of the oxo ligand with water molecules and the incorporation of external carboxylic acids as carboxylate ligands in $\text{Fe}^{\text{V}}(\text{O})(\text{O}_2\text{CR})$ (**1b**) in reactions where peracids are used as oxidants.

In the first place catalytic epoxidation of **s1** with $(S,S)\text{Me}_2\text{N}_1\text{Fe}$ catalyst and either $\text{H}_2\text{O}_2/\text{CH}_3\text{CO}_2\text{H}$ or $\text{CH}_3\text{CO}_3\text{H}$ as oxidant in the presence of labeled H_2^{18}O (Scheme 3) showed only

Scheme 3. Isotopic Studies with Different Oxidants in the Epoxidation of **s1 with $\text{Me}_2\text{N}_1\text{Fe}$**



a trace amount (<1%) of ^{18}O incorporation into the epoxide. We conclude that the oxo group does not exchange with water molecules under the catalytic oxidation conditions employed.

In the second place, in order to study the possible incorporation of an external carboxylate ligand into the active species in reactions with peracids, two sets of experiments were performed.

Catalytic epoxidations of **s1** with catalyst $(S,S)\text{Me}_2\text{N}_1\text{Fe}$ and $\text{eba-CO}_3\text{H}$ as oxidant were conducted in the presence of different amounts of acetic acid (1.5–50 equiv with respect to the catalyst, Table 2, entries 1–4). It could be seen that this addition translates into only small changes in ee values (from 74 to 71% ee).

On the other hand, the addition of *m*CBA (10 equiv) to the catalytic epoxidation of **s1** with catalyst $(S,S)\text{Me}_2\text{N}_1\text{Fe}$ and $\text{eba-CO}_3\text{H}$ as oxidant causes a more significant erosion in ee values (from 74 to 68% ee, entry 5 in Table 2), while in the complementary experiment the addition of *eba* (10 equiv) to a catalytic epoxidation with *m*CPBA produces a significant improvement in ee values (from 35 to 44% ee, entry 6 in Table 2).

These observations strongly suggest that an external carboxylate ligand can be incorporated into **1b**, although it only occurs to a limited extent. We conclude that reactions with peracids form **1b** mainly via a mechanism distinct from that occurring with peroxides. The carboxylic acid assisted path, if present, will be a minor path. Alternatively, carboxylic acids may be incorporated in **1b** via a carboxylate ligand exchange.¹⁸

DISCUSSION

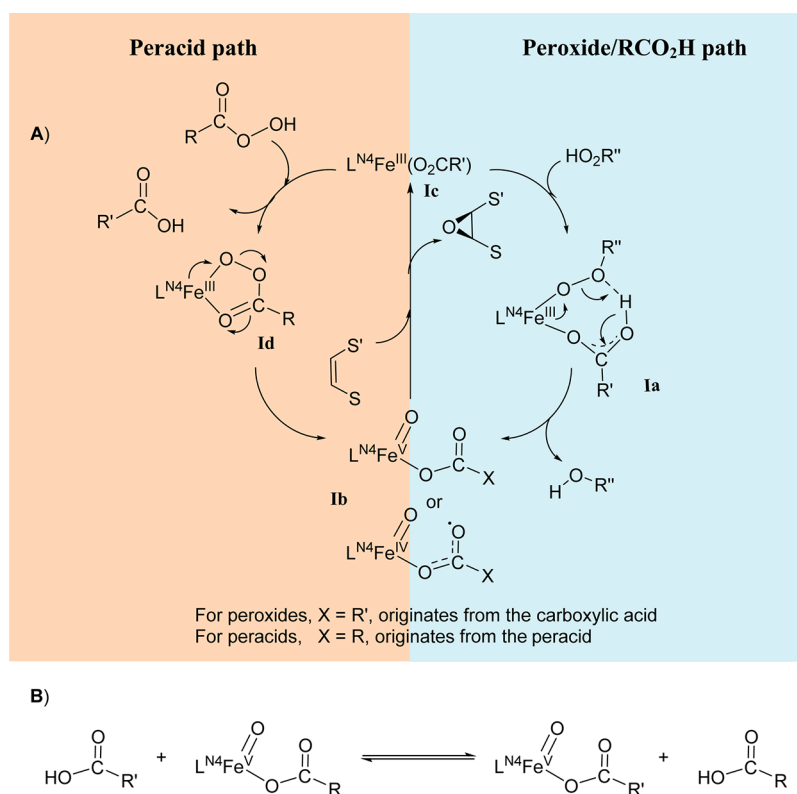
The results described herein constitute unambiguous evidence that the active species for the asymmetric epoxidation of olefins by non-heme iron complexes $(S,S)\text{1Fe}$, $(S,S)\text{Me}_2\text{N}_1\text{Fe}$, and $(S,S)\text{dMM}_1\text{Fe}$ is the same when peroxides (assisted by carboxylic acids) or peracids are employed as oxidants. The reaction mechanism operating when peroxides are used in combination with carboxylic acids is currently accepted to entail formation of the $\text{Fe}^{\text{V}}(\text{O})(\text{O}_2\text{CR})$ species **1b** via a carboxylic acid assisted path.^{9f,12,13} In this mechanism, the carboxylate ligand originates from the carboxylic acid that assists the heterolytic O–O cleavage of a ferric–hydroperoxo moiety. The data shown herein provide strong evidence that peracids generate the same active species, tentatively assigned to $\text{Fe}^{\text{V}}(\text{O})(\text{O}_2\text{CR})$ (**1b**). However, in this scenario (Scheme 4a) the carboxylate ligand originates mainly from the alkyl peracid itself, and external assistance of a carboxylic acid is unnecessary. Presumably, reaction of the alkyl peracid with the iron catalysts results in the formation of a ferric peracetate species (**1d**, Scheme 4a), where the peracid binds the iron center in a chelate mode via the carbonyl oxygen and a terminal peroxide atom¹⁶ and then undergoes rate-determining O–O cleavage. This proposal is congruent with previous reports,¹⁶ where low-spin ferric peracetate species (**1d**) have proven kinetically incompetent for reacting with olefinic substrates and where rate-determining O–O cleavage is proposed to result in the formation of a higher valent electromer ($\text{Fe}^{\text{V}}(\text{O})(\text{O}_2\text{CR})$ (or $\text{Fe}^{\text{IV}}(\text{O})(\bullet\text{O}_2\text{CR}')$) species (**1b**), which is the final oxygen atom transfer agent. The lack of participation of a carboxylic acid in the O–O cleavage may be a consequence of (i) the lack of available binding sites at the iron center in **1d**, (ii) a facilitated O–O lysis by the electron-withdrawing character (pull effect) of the peracid carbonyl moiety, or a combination of both.

Once the O–O bond has been broken, high-valent species **1b** do not exchange the oxo ligand with exogenous water molecules to a detectable extent. Exchange of the oxo ligand with water molecules is usually regarded as evidence for the presence of high valent iron–oxo species,¹⁹ but recent studies where water exchange with well-defined iron(IV)–oxo species has been kinetically analyzed have shown that the reactions are slow and can become negligible when the iron center does not contain labile sites.²⁰ The lack of detectable water exchange likely arises from the short lifetime of **1b**.

On the other hand, **1b** species can incorporate external carboxylate ligands into their structure, albeit to a limited extent. This incorporation can be detected in cases where the difference in ee values between the two putative species $\text{Fe}^{\text{V}}(\text{O})(\text{O}_2\text{CR})$ and $\text{Fe}^{\text{V}}(\text{O})(\text{O}_2\text{CR}')$ is large. For example, catalytic epoxidations of **s1** with $(S,S)\text{Me}_2\text{N}_1\text{Fe}$ produce epoxides with very different enantioenrichment when *m*CPBA or $\text{eba-CO}_3\text{H}$ is employed as oxidant (from 34 to 73% ee), and the exchange becomes evident (Table 2, entries 5 and 6). However, this incorporation may be difficult to observe in cases where the difference is not as large (for example, in the reactions with $\text{eba-CO}_3\text{H}$ in the presence of acetic acid, Table 2, entries 1–4). The rather minor incorporation of external carboxylate moieties into species **1b** may indicate that the carboxylic acid assisted O–O cleavage path is operative (although to a very minor extent) in reactions with peracids. Alternatively, ligand exchange in **1b** with the carboxylic acid takes place (Scheme 4b) to some small extent, presumably because of the short lifetime of **1b**.

This conclusion has obvious consequences in the design of catalytic oxidation systems based on these types of iron complexes.

Scheme 4. (A) Reaction Mechanism for the Formation of High-Valent Species Ib from Peroxides and Peracids and (B) Carboxylate Exchange



Carboxylic acids can be envisioned as valuable partners to modulate the structure of the oxygen atom species in reactions where peroxides are used as oxidants. In these reactions, the corresponding carboxylate is incorporated as a ligand effectively defining the structure of the oxygen atom transfer species. However, an analogous effect cannot be expected, or at least is very much limited, in reactions where peracids are employed as oxidants.

CONCLUSION

In conclusion, asymmetric epoxidation of olefins with strong field bipyrrolidine-based tetradentate ligands takes place via a common oxidizing species when either peroxides (in combination with a carboxylic acid) or peracids are employed as oxidants. The sum of the experimental data strongly suggests that the putative oxidant is a $\text{Fe}^{\text{V}}(\text{O})(\text{O}_2\text{CR})$ (or $\text{Fe}^{\text{IV}}(\text{O})(^*\text{O}_2\text{CR})$) **Ib** species. Isomerically related ferric peracetate complexes appear not to contribute to a significant extent to the epoxidation reaction. The origin of the carboxylate ligand in **Ib** depends on the nature of the oxidant, which in turn determines the particular mechanism of O–O lysis from the corresponding ferric precursor. Ferric peroxides require a carboxylic acid assisted cleavage, while ferric peracetate molecules mainly undergo acid unassisted O–O lysis. The high reactivity of **Ib** limits its ability to engage in ligand exchange reactions with water and carboxylic acid moieties. However, the carboxylic acid assistance to the O–O cleavage reaction of peroxides offers an excellent tool to introduce structural versatility in the oxidizing species, without the need to engage in laborious ligand design and synthesis protocols. This versatility constitutes a unique and powerful tool to further develop the scope of these systems.

Finally, while this study has been focused on two catalysts based on the PDP scaffold, it is very likely that a common scenario applies to other iron catalysts with strong-field tetradentate aminopyridine ligands, which often share common mechanisms of O–O cleavage in reactions with peroxides.^{3d,21} However, caution must be exercised when considering catalysts with different ligand denticity and nuclearity or those with weak-field ligands,²² because these factors influence in a dramatic manner the reaction mechanisms.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b01184.

Experimental procedures and GC and HPLC spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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