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Asymmetric Epoxidation with H_2O_2 by Manipulating the Electronic Properties of Non-heme Iron Catalysts

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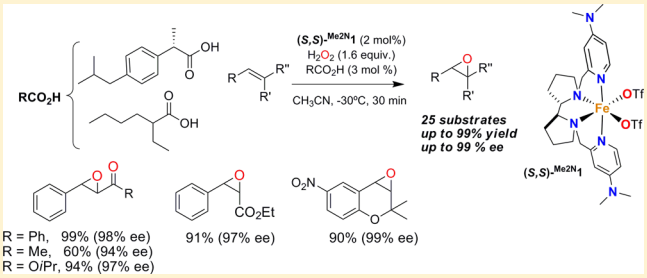
Supporting Information

ABSTRACT: A non-heme iron complex that catalyzes highly enantioselective epoxidation of olefins with H_2O_2 is described. Improvement of enantiomeric excesses is attained by the use of catalytic amounts of carboxylic acid additives. Electronic effects imposed by the ligand on the iron center are shown to synergistically cooperate with catalytic amounts of carboxylic acids in promoting efficient O−O cleavage and creating highly chemo- and enantioselective epoxidizing species which provide a broad range of epoxides in synthetically valuable yields and short reaction times.

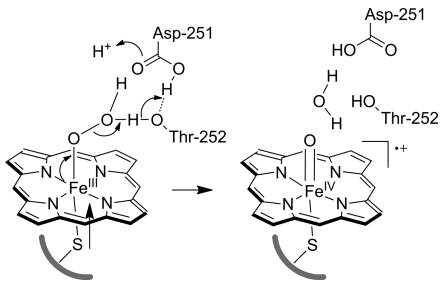


INTRODUCTION

Inspired by oxidations taking place at oxygenases, the combination of iron-based catalysts and hydrogen peroxide is an attractive approach for developing oxidation methods because of availability, low cost, and low toxicity considerations.[1] A particularly appealing transformation for this strategy is asymmetric epoxidation due to its pivotal role in modern organic synthesis.[2] Given its importance, asymmetric epoxidation has been actively pursued, and some excellent metal-based catalytic methods are well established.[2a−c] However, iron-catalyzed asymmetric epoxidations that employ H_2O_2 and provide product yields and stereoselectivities amenable for preparative purposes remain scarce and limited in substrate scope, mainly because of the intrinsic complexities of Fe−H_2O_2 reactions.[1f,g,3−5] While mononuclear iron (hydro)peroxide species are common intermediates in heme and non-heme oxygenases,[6,7] in the absence of the elaborate machinery provided by enzymatic sites, the rich redox chemistry of iron and hydrogen peroxide poses serious problems for controlling the crucial O−O bond cleavage event. Basic concepts and strategies need to be developed for mastering this reaction such that metal-based oxidants susceptible to engage in selective oxygen atom transfer reactions are generated, thus avoiding Fenton-type processes and nonproductive peroxide disproportionation reactions. As a matter of fact, two recent reports of iron catalyzed asymmetric epoxidation bypass this problem by using peracetic acid and iodosylbenzene as alternative oxidants.[5]

Cytochromes P450 (Cyt-P450) constitute a paradigmatic example where the powerful electron-donating properties of the apical thiolate and the H-accepting character of a nearby threonine residue assist the O−O cleavage step of ferric hydroperoxide species via the so-called "push−pull" effect (Scheme 1).[7] In addition, the dianionic and redox noninnocent nature of the porphyrin ligand alleviates positive charge from the iron center and provides stabilization of the high valent ferryl species (compound I) responsible for substrate oxidation.

Scheme 1. Schematic Diagram of the Push−Pull Effect in Assisting O−O Breakage in P450 To Form Ferryl Species Compound I



Herein we show that electronic effects resembling those operating in Cyt-P450 can be used to design excellent non-heme iron epoxidation catalysts that make an efficient use of H_2O_2 to afford epoxides with excellent yields and enantioselectivities in short reaction times. Synergistic operation of metal, a powerful electron-donating ligand, and a carboxylic acid co-ligand allows an efficient heterolytic O−O bond cleavage and relative stabilization of the electrophilic high-valent iron−oxo species, finally leading to stereoselective oxygen atom transfer. Useful insight for further catalyst development and expansion of substrate scope is disclosed.

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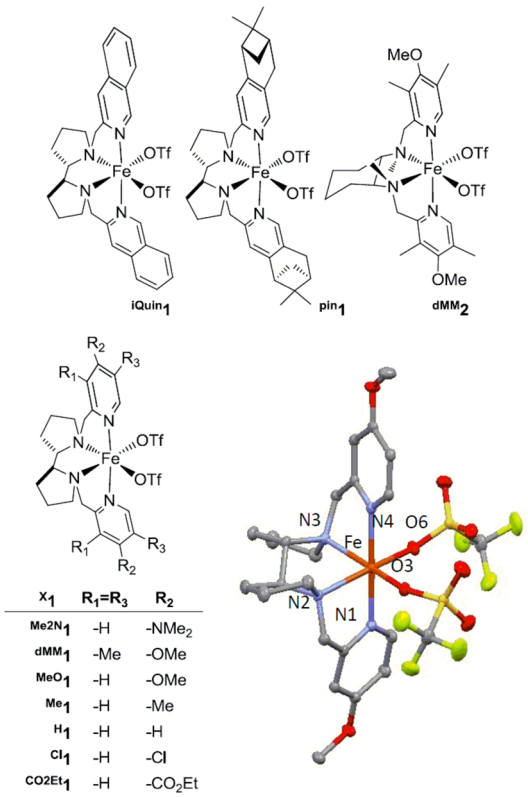
RESULTS AND DISCUSSION

Synthesis and Characterization of the Catalysts. Selected iron complexes containing aminopyridine tetradentate ligands are emerging as powerful oxidation catalysts.[8−10] Among these, the family of bipyrrolidine based complexes $[Fe^{II}(CF_3SO_3)_2(^{X}PDP)]$ (^{X}**1**) (X = Me_2N, dMM, MeO, Me, H, Cl, CO_2Et, Scheme 2, see the Supporting Information for aspects of the family of complexes with general formula $[Fe^{II}(CF_3SO_3)_2(^{X}PDP)]$ (^{X}**1**). Iron centers adopt a distorted octahedral coordination geometry. Four coordination sites are occupied by nitrogen atoms of the tetradentate ligand, and the two remaining sites contain oxygen atoms from the triflate groups. These are in *cis*-relative position and in the same coordination plane as the two bipyrrolidine nitrogen atoms. The two pyridine rings bind *trans* to each other. Fe−N/O distances are between 2.1 and 2.2 Å and are indicative of a high spin ferrous center.[12] When dissolved in CD_3CN or CD_2Cl_2 the full set of complexes retain a common C_2-symmetric *cis-α* topological geometry, with the iron center in the high spin state, as evidenced in their ^{1}H NMR spectra by the number of signals, their relative integration and the large spectral window (200 to −20 ppm) corresponding to paramagnetic molecules (see the Supporting Information for details).

Scheme 2. Schematic Diagram of the Iron Complexes Studied[a]



[a]The bottom right shows an ORTEP diagram of the single-crystal X-ray determined structure of ^{MeO}**1**.

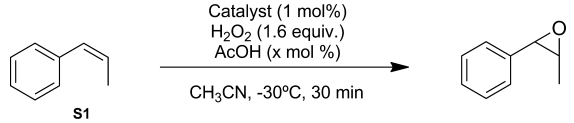
experimental details), was identified as a particularly promising platform to evaluate putative electronic effects in catalytic asymmetric epoxidation, owing to the excellent performance of ^{H}**1** in C−H[10] and C=C[4e,8e] oxidation reactions. In epoxidation reactions, ^{H}**1** in combination with H_2O_2 and acetic acid (1.1 equiv with respect to substrate) has been previously shown to elicit good yields but moderate enantioselectivities (16−62% ee).[4e] Structurally related $[Fe^{II}(CF_3SO_3)_2(^{iQuin}PDP)]$ (^{iQuin}**1**), $[Fe^{II}(CF_3SO_3)_2(^{Pin}PDP)]$ (^{Pin}**1**), and $[Fe^{II}(CF_3SO_3)_2(^{dMM}MCP)]$ (^{dMM}**2**) (Scheme 2) were also prepared in the present work, and their reactivity was studied and compared to ^{X}**1**.

Preparation of the complexes involved straightforward reaction of the corresponding tetradentate ligand and $[Fe(CF_3SO_3)_2(CH_3CN)_2]$ in acetonitrile solution. Removal of the solvent under vacuum and recrystallization by ether diffusion into CH_2Cl_2 solutions yielded the desired complexes as crystalline materials (see the Supporting Information for details). The X-ray structures of ^{H}**1** and ^{Pin}**1** have been previously described.[10a,11] An ORTEP diagram of ^{MeO}**1** is shown in Scheme 2 and serves to illustrate the basic structural

Catalytic epoxidation activity. *Impact of the catalyst in product yield and stereoselectivity.* Epoxidation of *cis-β*-methylstyrene (**S1**) was taken as a model reaction. H_2O_2 (1.6 equiv) was delivered by syringe pump to an acetonitrile solution at −30 °C containing AcOH (140 mol %), catalyst (1−2 mol %) and substrate (see Table 1) under air.

Moderate yield (38%) and enantioselectivity (21% ee) is obtained with the simplest catalyst of the series, ^{H}**1** (Table 1, entry 1). When electron-withdrawing groups are introduced at the *para* position (R2) of the pyridine (Table 1, entries 2−3), both yield and selectivity experience erosion, but they became very much improved in the presence of electron-donating

Table 1. Epoxidation of S1 Using Different Iron Complexes[a]



entry	catalyst	AcOH (x mol %)	conv (yield, %)	ee (%)
1	^{H}**1**	140	61 (38)	21
2	^{Cl}**1**	140	57 (33)	15
3	^{CO2Et}**1**	140	44 (22)	19
4	^{Me}**1**	140	44 (27)	31
5	^{MeO}**1**	140	64 (37)	39
6	^{dMM}**1**	**140**	97 (81)	40
7	^{Me2N}**1**	**140**	**100 (82)**	**60**
8[b]	^{Me2N}**1**	**140**	**100 (85)**	**61**
9	^{pin}**1**[c]	140	89 (69)	30
10	^{iQuin}**1**	140	80 (46)	20
11	^{dMM}**2**	**140**	82 (55)	32
12	^{Me2N}**1**	**3**	**100 (87)**	**62**
13	^{Me2N}**1**	0	45 (20)	46
14	^{H}**1**	3	49 (26)	19
15	^{Cl}**1**	3	32 (15)	16
16	^{CO2Et}**1**	3	31 (13)	21
17	^{Me}**1**	3	31 (17)	30
18	^{MeO}**1**	3	38 (26)	38
19[b]	^{dMM}**1**	3	82 (67)	38
20	^{pin}**1**[c]	3	53 (41)	30
21	^{iQuin}**1**	3	34 (15)	19

[a]Product yields, substrate conversions and ee's were determined by GC (see the Supporting Information for further details). Unless stated, catalysts employed have (*S,S*) chirality at the bipyrrolidine moiety. [b]2 mol % catalyst, H_2O_2 (1.6 equiv). [c](*R,R*)-Catalyst was employed.

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substituents (Table 1, entries 4−8). Among the series of catalysts tested, excellent epoxide yield and moderate enantioselectivity were obtained with complex ^{Me2N}**1** (82% yield and 60% ee, Table 1, entry 7), which contains strongly donating NMe_2 groups in the pyridines, and a further slight improvement in epoxide yield (85%) and enantioselectivity (61% ee) can be gained by using 2 mol % of catalyst (entry 8). On the other hand, catalysts containing more elaborate pyridine derivatives such as ^{iQuin}**1** and ^{Pin}**1** (Scheme 2) give more modest yields (46−69%) and enantioselectivities (20−30% ee, entries 10 and 9). For comparison, catalyst ^{dMM}**2** elicits reduced ee's (entry 11); thus, the bipyrrolidine backbone is better than the cyclohexyldiamine backbone for eliciting optimum stereoselectivity. Finally, control experiments showed that the ^{Me2N}PDP ligand alone is not an epoxidation catalyst and also that the simple addition of 4-(dimethylamino)pyridine (DMAP) inhibits the epoxidation activity of ^{H}**1**.

Therefore, from the results collected in Table 1 (entries 1−11), it can be concluded that yields and stereoselectivities of the epoxidation reactions appear to be strongly and systematically dependent on the electron-donating nature of the pyridine of the ligand, and ^{dMM}**1** and ^{Me2N}**1** are identified as the best catalysts of the series.

Impact of the Carboxylic Acid Loading Required for Efficient Catalytic Activity. Acetic acid has been previously shown to play a key positive role in enhancing yields and chemoselectivity in iron-catalyzed epoxidation reactions.[8a] Because of that, further studies were conducted to investigate the role of carboxylic acids (CAs) in the current reactions. Most remarkably, by using ^{Me2N}**1** (2 mol %) the amount of acetic acid could be lowered down to only 1.5 equiv with respect to the iron catalyst, and these conditions even slightly improved yield and ee's (Table 1, compare entry 12 with entries 7 and 8). However, in the absence of acetic acid, both yields and stereoselectivities experience a substantial decrease (Table 1, entry 13). Most remarkably, a perusal of Table 1 shows that only ^{Me2N}1 has the ability to efficiently operate at nearly stoichiometric acid concentration. For the rest of the catalysts (Table 1, entries 14−21), the use of 1.5 equiv of acetic acid has a small effect on ee's (<2% ee), but substrate conversions and epoxide yields were substantially smaller than in analogous reactions run with 140 equiv of acetic acid (entries 1−11).

Along the same vein, the effect of the carboxylic acid loading on the chemoselectivity toward epoxidation of the reactions is also dependent on the nature of the catalysts (Table 1). Catalysts that contain the most electron-rich pyridines within the series retain their chemoselectivity when low CA loadings are employed. These include ^{Me2N}**1** but also ^{pin}**1**, ^{dMM}**1**, and ^{MeO}**1**. On the other hand, ^{H}**1**, ^{Me}**1**, ^{Cl}**1**, ^{iQuin}**1**, and ^{CO2Et}**1** lose chemoselectivity at low CA loadings, even though the latter reactions proceed under a priori more favorable conditions for selectivity since lower substrate conversions are obtained. Therefore, the ^{Me2N}**1**, ^{pin}**1**, ^{dMM}**1**, and ^{MeO}**1** catalysts appear to generate more selective oxidizing species.

In conclusion, ^{Me2N}**1** exhibits a unique ability to operate as a remarkably efficient and selective epoxidation catalyst employing H_2O_2 as oxidant and low CA concentration, reflecting an unusual ability to activate and channel H_2O_2 reactivity toward selective epoxidizing species.

Optimization of the Catalytic Activity with Regard to Amount and Identity of the Carboxylic Acid. Further optimization took advantage of a recent report by Lyakin et al. showing an improvement in epoxidation stereoselectivities by using different CA additives (up to 86% ee for chalcone).[4e] However, the large acid loading required for efficient operation (0.5−1.4 equiv with respect to the substrate) in common iron systems limits the diversity of CAs that could be employed. Instead, since ^{Me2N}**1** requires only 1.5 equiv with respect to the catalyst, rapid screening of different CAs differing in the electronic and spatial properties could be tested with the aim of improving the enantioselectivity without requiring extensive catalyst preparation. This approach was then further pursued by taking the epoxidation of **S1** as a model reaction (Table 2).

We noticed that certain criteria were necessary for efficient and selective epoxidation activity. First, poor activity was observed when a strong acid such as CF_3CO_2H was used (entry 1). In addition, the use of sodium acetate instead of acetic acid resulted in very small epoxide yields (entry 2). The combination of the two observations indicates that both the carboxylate moiety and the proton are important for optimized epoxidation activity. Improved performance both in terms of epoxide yield and enantioselectivity with regard to acetic acid can be gained with the use of a number of aliphatic carboxylic acids (Table 2, entries 3−8). Of these, as also shown by Lyakin et al., racemic 2-ethylhexanoic acid (2-eha) provides relatively high ee's (80% ee, entry 8). Chiral carboxylic acids could be also tested, leading to the discovery that the combination of *S*-Ibuprofen (*S*-ibp) with ^{Me2N}**1** affords the epoxide with high yield and good enantioselectivity (97% yield, 86% ee, entry 9). Interestingly, use of (***R,R***)-^{Me2N}**1** in combination with *S*-ibuprofen resulted in smaller enantioselectivity (63% ee, entry 10) indicating that the high stereoselection requires proper matching of the chirality of the complex with that of the acid. Analogous results were obtained when other chiral carboxylic acids were tested (entries 11−16); for example, *S*-Naproxen provides the epoxide with 77% and 66% ee's when ^{NMe2}**1** and (***R,R***)-^{Me2N}**1** are employed (entries 10 and 11), respectively. Unfortunately, examples of quite versatile families of chiral carboxylic acids such as amino acids and chiral phosphoric acids (entries 17 and 18) proved incompatible with this system.

Substrate Scope. Substrate scope was then explored under optimized conditions (Table 3), using *S*-ibp and 2-eha as the carboxylic acids of choice.

For both carboxylic acids, good yields and excellent enantioselectivities were obtained with *cis*-cinnamic esters (**S2**, Table 3, entries 2 and 3), an amide derivative (**S3**, Table 3, entries 4 and 5), and with electron-deficient chromenes (Table 3, entries 6−9). We conclude that this catalyst constitutes a rare example of an iron-based system which effectively epoxidizes *cis*-aromatic substrates with high enantioselectivity.[13] On the other hand, *trans*-β-methylstyrene (**S6**) and the terminal aromatic olefin α-methyl styrene (**S7**) were epoxidized with modest chemoselectivity and only low ee's (entries 10−13). Further scope of the catalyst includes the epoxidation of aromatic enones. Initial experiments employing *S*-ibuprofen as a coligand did elicit good stereoselectivities in the epoxidation of chalcone, but only moderate yields (entry 14). However, excellent yields (99%) and stereoselectivitives (98% ee) were obtained in the epoxidation of chalcone when employing 2-eha (Table 3, entry 15, **S8**), which are the highest reported for an iron-based system.[1f,4] Introduction of electron-donating (**S9**) or electron-withdrawing (**S10** and **S11**) groups in the aromatic rings retains the excellent performance (Table 3, entries 16−18). Most interestingly, *trans*-cinnamic esters (**S13**-**S16**) are also a suitable family of substrates and are epoxidized with excellent yields and selectivities (entries 20−

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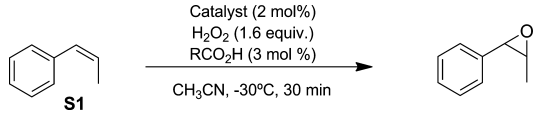
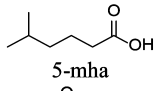
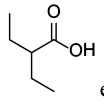
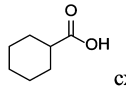
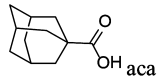
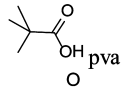
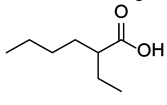
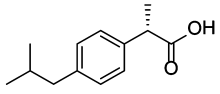
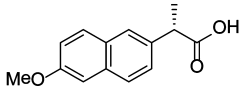
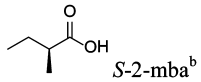
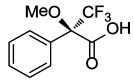
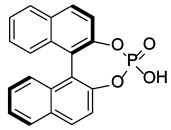
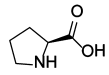
Table 2. Asymmetric Epoxidation of S1 Using Different Carboxylic Acids Using Catalyst ^{Me2N}1[a]



Entry	RCO_2H	Conv.(yield) (%)	ee (%)
1	CF_3CO_2H	37(13)	36
2	AcONa	26(6)	58
3	 5-mha	100(81)	64
4	 eba	100(88)	80
5	 cxa	100(76)	67
6	 aca	100(91)	73
7	 pva	100(73)	76
8	 2-eha	100(86)	80
9	 **S-Ibuprofen**	**100(97)**	**86**
10	*S*-Ibuprofen[b]	100(87)	63
11	 *S*-Naproxen	100(97)	77
12	*S*-Naproxen[b]	100(87)	66
13	 *S*-2-mba[b]	100(84)	74
14	*S*-2-mba	100(84)	76
15	 *R-Mosher's acid*[b]	62(42)	58
16	*R-Mosher's acid*	60(36)	63
17		-	-
18		-	-

[a]Yields, conversions and ee's were determined by chiral GC (see the Supporting Information for details): 5-mha, 5-methylhexanoic acid; eba, ethylbutyric acid; cha, cyclohexanoic acid; aca, adamantane carboxylic acid; pva, pivalic acid; 2-eha, 2-ethylhexanoic acid; *S*-2-mba, *S*-methylbutyric acid. [b]Reaction with (*R,R*)-^{Me2N}**1**

23, ee's 91−97%), and the same applies to an alkylstyrylketone **S17** (entry 24, 94% ee). The amide derivative **S18** is epoxidized

Table 3. Substrate Scope on the Optimized Asymmetric Epoxidation[a]

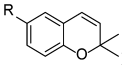
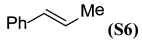
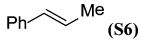
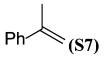
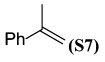
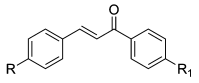
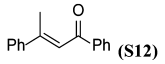
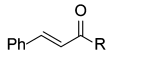
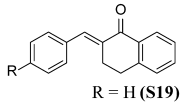
Entry	Substrate	CA	Conv.(Epox. Isol. Yield, %)	ee (%)
1	R = Me (**S1**)	*S*-ibp	100(97)[b]	86
2[c]	R = CO_2Et (**S2**)	*S*-ibp	91	97
3	R = CO_2Et (**S2**)	2-eha	81	95
4[c]	R = C(O)N(OMe)(Me) (**S3**)	*S*-ibp	84	96
5	R = C(O)N(OMe)(Me) (**S3**)	2-eha	78	95
6	 R= CN (**S4**)	*S*-ibp	100(85)[d]	98(3*R*,4*R*)
7	R= CN (**S4**)	2-eha	95	99(3*R*,4*R*)
8	R = NO_2(**S5**)	*S*-ibp	100(90)[d]	99(3*R*,4*R*)
9	R = NO_2(**S5**)	2-eha	97	99(3*R*,4*R*)
10	 (**S6**)	*S*-ibp	48(21)[b]	7
11	 (**S6**)	2-eha	53(32)[b]	19
12	 (**S7**)	*S*-ibp	100(67)[b]	45
13	 (**S7**)	2-eha	82(47)[b]	31
14	 R = R_1 = H (**S8**)	*S*-ibp	57(38)	90
15	R = R_1 = H (**S8**)	2-eha	99	98(2*R*,3*S*)
16	R = Me = R_1 = H (**S9**)	2-eha	95	97(2*R*,3*S*)
17	R = Cl= R_1 = H (**S10**)	2-eha	97	97(2*R*,3*S*)
18	R = H= R_1 = CF_3 (**S11**)	2-eha	94	97(2*R*,3*S*)
19	 (**S12**)	2-eha	69	47
20	 R = OMe (**S13**)	2-eha	66	91(2*R*,3*S*)
21	R = OEt (**S14**)	2-eha	91	91
22	R = O*i*Pr (**S15**)	2-eha	94	97(2*R*,3*S*)
23	R = OBz (**S16**)	2-eha	94	96
24	R = Me (**S17**)	2-eha	60	94
25	R = N(OMe)(Me) (**S18**)	2-eha	95	99
26	 R = H (**S19**)	2-eha	94	90(2*R*,3*S*)

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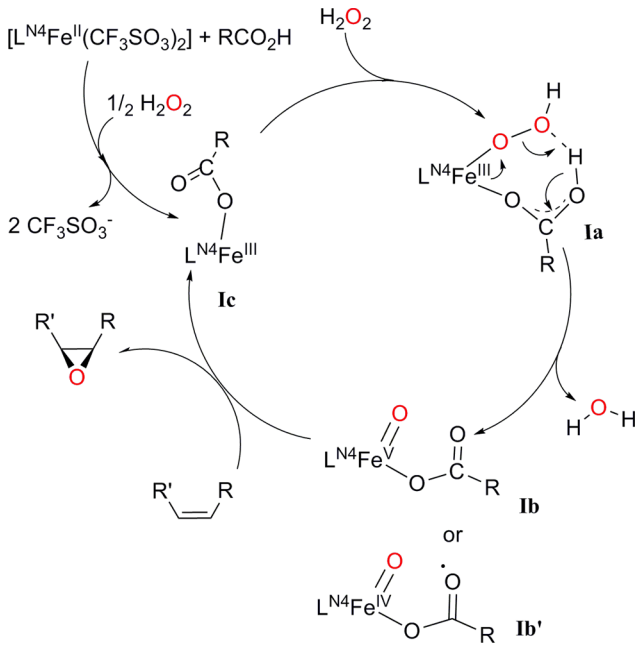
Table 3. continued

Entry	Substrate	CA	Conv.(Epox. Isol. Yield, %)	ee (%)
27	R = Me (**S20**)	2-eha	97	97(2*R*,3*S*)
28	R = F (**S21**)	2-eha	96	97(2*R*,3*S*)
29	R = *t*Bu (**S22**)	2-eha	96	95
30[e]	 (**S23**)	2-eha	100(99)[b]	84 (*R*)
31[e]	 (**S24**)	2-eha	92(79)[b]	87
32[e]	 (**S25**)	2-eha	94(79)[b]	80

[a]Unless stated, reaction conditions are as follow: ^{Me2N}**1** (2 mol %), H_2O_2 (1.6 equiv), and CA (3 mol %) in CH_3CN at −30 °C during 30 min. Yields refer to isolated yields of pure epoxide. ee's and configuration were determined by chiral GC and HPLC (see the Supporting Information for details). [b]Epoxide yields and substrate conversions determined by GC. [c]5 mol % catalyst, and 3 equiv of H_2O_2. [d]Epoxide yields and substrate conversions determined by ^{1}H NMR. [e]Reaction conditions: ^{dMM}**1** (1 mol %), H_2O_2 (1.2 equiv), and 2-eha (140 mol %) in CH_3CN at −30 °C during 30 min.

Scheme 3. Original Mechanistic Scheme Proposed by Que et al. for the Carboxylic Acid Assisted O−O Cleavage[15]



with outstanding enantioselectivity (entry 25, 99% ee). Epoxidation of trisubstituted aromatic enones was also accomplished with varying outcomes. α-Methyl-substituted chalcone **S12** yielded moderate ee's (entry 19, 47% ee), but the cyclic enones **S19**−**S22** (Table 3, entries 26−29) were epoxidized with excellent yield (94−97%) and enantioselectivity (90−97% ee).

Encouraged by the results in the epoxidation of aromatic enones, we turned our attention to the challenging cyclic aliphatic enones.[14] Initial epoxidation reactions using catalyst ^{Me2N}**1** provided poor yields (12%) and moderate enantioselectivity (76% ee) in the epoxidation of 2-cyclohexen-1-one (**S23**). The poor performance of ^{Me2N}**1** in the epoxidation of these cyclic enones is most likely due to the rapid deactivation of this catalyst that occurs when the substrate is not rapidly oxidized under the standard oxidation conditions. Competitive epoxidation of chalcone (**S8**) and cyclic enone (**S23**) with ^{Me2N}**1** indeed shows that the former is epoxidized preferentially (ratio of epoxides >10:1) over the later. Instead, ^{dMM}**1** is more tolerant to the oxidative conditions, giving improved yields and ee's in the epoxidation of 2-cyclohexen-1-one (**S23**), (Table 3, entry 30, 99% yield, 84% ee) and 2-cyclopenten-1- one (**S24**) (Table 3, entry 31, 79% yield, 87% ee), albeit 140 mol % of 2-eha coligand was required. Trisubstituted aliphatic cyclic enones were also convenient substrates for the system and were epoxidized with good yields and enantioselectivity (Table 3, entry 32, 79% yield, 80% ee). In conclusion, these catalysts exhibit a very remarkable broad substrate scope, which is substantially more extended than any other iron based system described so far.

Mechanistic Studies. *Precedents.* The positive role of acetic acid in iron-catalyzed oxidations has been documented for some years,[8a] but mechanistic interpretation has not been provided until recently.[15] The original mechanism proposed by Que and co-workers for the Fe-catalyzed AcOH-assisted epoxidation of olefins with H_2O_2 involves the intermediacy of oxocarboxylate−iron(V) species (**Ib**, Scheme 3) as the oxygen atom delivering agent. Species **Ib** is formed via acid-assisted heterolytic cleavage of the O−O bond in a Fe^{III}(OOH)-(HOAc) (**Ia**) precursor.[15] Experimental spectroscopic evidence in favor of this mechanistic scenario has been also recently provided by Talsi, Bryliakov, and co-workers,[16] and further computational support for the formation and oxidative competence of these species has been built by Rajaraman et al. in a study of the *ortho*-hydroxylation of aromatic compounds by non-heme Fe complexes.[17]

On the other hand, Shaik, Que, et al. have recently proposed on the basis of DFT analyses that the carboxylate may play a role as a redox noninnocent ligand, sharing one electron with the iron site.[18] The electronic structure of this intermediate (**Ib**′, Scheme 3) will bear obvious similarities with that of compound I in P450.[7]

The mechanistic picture that emerges from analyzing the reactivity of ^{Me2N}**1** is in good agreement with that originally proposed by Que et al. This mechanistic scheme provides a rationale for the efficient H_2O_2 activation mediated by ^{Me2N}**1** and for the origin of the high stereoselectivity observed for this catalyst.

Mechanistic Studies into the Nature of the Oxidizing Species. Insight into the O-delivering species could be deduced by comparing the epoxidation of **S1** with catalyst ^{Me2N}**1** and acetic acid as co-ligand but employing different oxidants including H_2O_2, ^{t}BuOOH, and peracetic acid (Table SI.1, Supporting Information). Substrate conversion and epoxide yields are dependent on the oxidant, 32% conversion and 20% epoxide yield for ^{t}BuOOH and 85% conversion and 63% epoxide yield for peracetic acid, to compare with quantitative conversion and 87% epoxide yield with H_2O_2. But the most significant aspect with regard to the nature of the O-delivering species is that the enantiomeric excess in the corresponding epoxide is virtually the same (61 ± 1% ee) when any of the three different oxidants are employed. Particularly interesting is the observation that ^{t}BuOOH is also a competent oxidant to engage in an enantioselective epoxidation because, unlike in the

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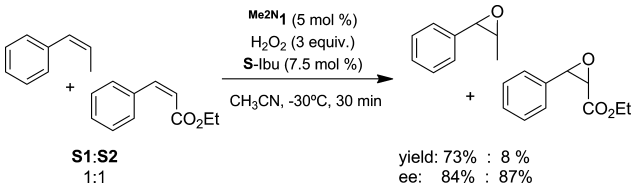
present reactions, its combination with non-heme iron complexes has been shown to produce unselective free-diffusing radical reactions initiated by homolytic O−O cleavage of $Fe^{III}(OO^tBu)$ intermediates.[19] The ability of ^{Me2N}**1** to avoid this free-radical reactivity and engage in metal-centered stereoselective chemistry is therefore notable. Enantiomeric excesses are quite sensitive indicators of the differences in energy between the transition states associated with the oxygen atom transfer reaction, leading to the two enantiomeric epoxides, and are usually finely dependent on the nature of the reagents. Because of that, the observation of virtually identical ee's strongly suggests that oxygen atom transfer is performed by the same species, irrespective of the oxidant, discarding iron-peroxides such as **Ia** as possible oxidants. This conclusion is in agreement with recent studies by Nam et al. showing that ferric hydroperoxide and alkyl peroxide species are sluggish oxygen atom transfer agents.[20] Furthermore, since enantioselection is affected by both the nature and the chirality of the carboxylic acid, it could be deduced that the latter remains as a ligand in the oxygen delivering species.

Evidence in favor of the implication of an electrophilic oxidant species is derived from a competitive epoxidation of **S1** and ethyl *cis*-cinnamic ester **S2**. Epoxidation of the most electron-rich alkene **S1** (Scheme 4) is favored roughly 9 times

Scheme 4. Competitive Epoxidation Experiment of Substrates S1 and S2

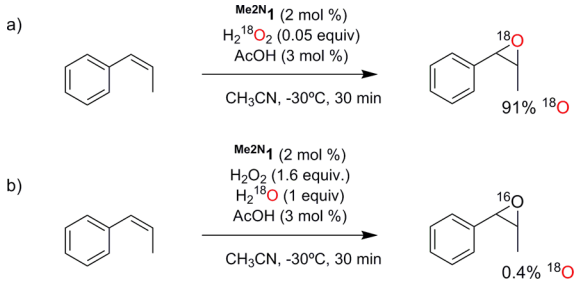


with regard to **S2**. This result is also significant because it provides solid evidence against epoxidation taking place though a nucleophilic Weitz−Scheffer-type epoxidation mechanism.[2e,21]

The sum of these observations, namely the identical enantioselectivity irrespective of the oxidant, as well as the electrophilic character of the oxidizing species, in combination with the literature precedents for poor oxygen atom transfer reactivity of iron peroxides thus provides experimental evidence that O−O breakage in ^{Me2N}**1** precedes formation of the oxidizing species. The cleavage of the O−O bond in iron peroxide species can occur through homolysis or heterolysis. Homolysis is discarded in the present case because it implies formation of poorly selective hydroxyl radicals and oxo-iron(IV) species, which are relatively modest O-atom transfer agents.[22] Therefore, heterolysis must be the operating path, leading to an electrophilic $Fe^{V}(O)(O_2CR)$ species (**Ib**, Scheme 3), which is then responsible for the O-atom transfer.

Isotopic analyses were also employed as mechanistic tools (Scheme 5) and conform to the same mechanistic picture, providing insight into the mechanism of O−O lysis. Epoxidation of **S1** with ^{Me2N}**1** using $H_2{}^{18}O_2$ (90% ^{18}O enrichment) as oxidant provided the corresponding epoxide 91(±1)% ^{18}O-labeled (Scheme 5a), and virtually no ^{18}O was incorporated (0.4(±1)%) when $H_2{}^{16}O_2/H_2{}^{18}O$ was used (Scheme 5b), indicating that the oxidant is the source of oxygen atoms incorporated into the epoxide and also that oxygen from water is not incorporated. This isotopic pattern

Scheme 5. Isotopic Analysis Studies[a]



[a] $H_2{}^{18}O_2$ reagent is a 2% solution in $H_2{}^{16}O$.

argues against the implication of a water-assisted O−O lysis that results in $Fe^{V}(O)(OH)$ species[8b,22] and instead points toward the carboxylic acid mediated pathway that leads to **Ib**, in line with the previous proposals.[15,16]

On the basis of these mechanistic considerations, the ability of ^{Me2N}**1** to efficiently and selectively operate at low CA loadings most likely indicates that the heterolytic cleavage of the O−O bond in $Fe^{III}(OOH)(HOAc)$ (**Ia**) to form $Fe^{V}(O)(O_2CR)$ (**Ib**) is exceptionally facilitated for this catalyst. We propose that the mechanism of O−O cleavage in this case is facilitated by the assistance of a proton of the carboxylic acid (pull effect, as early proposed by Que et al.) and also by a push effect exerted by the powerful electron donating character of the dimethyl amino pyridine ligand. This synergistic operation may then provide an efficient channel for controlling the O−O cleavage event and prevent from otherwise energetically competitive alternative paths. Interestingly, this scenario bears a strong resemblance to that operating in the mechanism of formation of Cpd I in Cyt P450 (Scheme 1).[7]

Mechanistic Insights in the O-Atom Transfer Reaction. *Stereospecificity and Linear Free Energy Correlation.* Remarkably, epoxidation with the present iron-based catalysts is stereospecific and takes place with stereoretention even in the cases of substrates that can easily undergo epimerization during epoxidation with other reagents. For example, epoxidation of **S1** and of the sterically congested disubstituted *β*,*β*′-enone **S12** yields a single diastereomer. This indicates that oxygen atom transfer occurs through concerted formation of the two new C−O bonds, or alternatively, sequential C−O bond formation occurs very fast, without scrambling. That constitutes a difference with respect to Mn-salen systems,[24] and Weitz−Scheffer-type epoxidations, where some degree of epimerization takes place.[2e,21]

Finally, this mechanistic scenario provides a rational mechanistic frame for understanding the electronic effects of the catalysts in the enantioselectivity. A plot of the log (ee) (ratio of enantiomers) corresponding to chiral induction in epoxidation of **S8** as a function of the Hammett parameter of the X group in ^{X}**1** (Figure 1) shows a linear correlation. The enantioselectivity ranges from 51% to 90% ee for epoxidation of **S8** with the series of ^{X}**1** complexes, which corresponds to a notable improvement in selectivity of $\Delta\Delta G^{\ddagger} \sim 1.0$ kcal·mol^{-1}. The same analysis was done for substrates **S1**, **S4**, and **S13**, showing analogous correlations. The consistent linear nature of the Hammett correlation for four different substrates strongly suggests that this linear free energy relationship is general and has mainly an electronic origin which can be straightforwardly analyzed with the previously proposed mechanistic frame (Scheme 3). As the ligand becomes more electron rich, the

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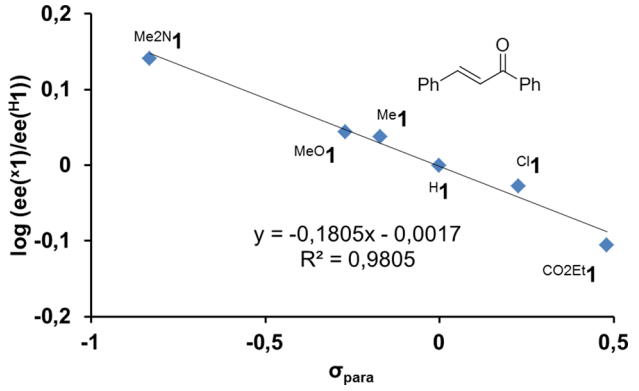

Figure 1. Hammett analysis of stereoselectivity as a function of catalyst employed in the epoxidation of **S8** (for analogous analysis with **S1**, **S4** and **S13**, see Figures SI.1 and SI.2 (Supporting Information)). Catalyst ^{x}**1** (1 mol %), AcOH (140 mol %), and H_2O_2 (1.2 equiv) in CH_3CN at 0 °C. Hammett's values are taken from ref 25.

electrophilicity of the metal−oxo species is attenuated, and the transition state is displaced toward a more product-like complex, characterized by a tighter substrate/metal−oxo species, with more specific nonbonding interactions. However, electron-poorer systems result in a more electrophilic and less discriminatory oxidant, exhibiting lower stereochemical differentiation.[27a] This scenario indeed finds precedent in Mn-salen epoxidation systems,[27] but its application in non-heme iron chemistry is, to the best of our knowledge, unprecedented. It is important to mention that manipulation of the electronic properties of heme ferryl species has been used to modulate the chemoselectivity of their oxidation reactions,[28] but translation into asymmetric oxidations has not been described so far.

CONCLUSION AND FUTURE REMARKS

In conclusion, the present work illustrates how electronic effects can be used as powerful tools for controlling the activation of H_2O_2 and O-atom transfer in non-porphyrinic iron complexes, leading to excellent catalysts for highly asymmetric epoxidation of olefins with H_2O_2. Efficient activation of H_2O_2 is proposed to occur via facile heterolytic O−O bond cleavage in electron-rich iron complexes. Although the exact details by which this reaction is exceptionally facilitated by ^{Me2N}**1** remain to be clarified, a resemblance to the so-called push−pull effect operating in P450 can be drawn.[7] Even more exciting analogies could be also suggested between the well-established redox active non-innocent nature of porphyrins[7,29] and dimethylaminopyridine ligands,[30] and how these electronic structures may facilitate stabilization of highly electrophilic high oxidation states. From a more synthetic perspective, this work provides directions for future rational design of catalysts, fine tuning of enantioselection, and expanding substrate scope, without the need for elaborate catalyst development, but by taking advantage of cooperative catalysis effects between aminopyridine and carboxylic acid ligands. Expansion of substrate scope, extension toward other oxygen atom transfer reactions, and clarification of the reaction intermediates involved in these reactions are currently being explored.

ASSOCIATED CONTENT

Supporting Information

Experimental details for the preparation and characterization of ligands and metal complexes. Experimental details of catalytic reactions and spectroscopic data for product characterization. X-ray data for ^{MeO}**1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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